Atroposelective Desymmetrization of Resorcinol-Bearing Quinazolinones via Cu-Catalyzed C–O Bond Formation

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Supporting Information

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General Reaction Considerations

Room temperature is considered 20-23 °C. All reactions were performed under regular conditions unless otherwise stated. All reactions were magnetically stirred and elevated temperatures were reported as the temperature of the surrounding oil bath. Reactions were monitored by thin layer chromatography (TLC) [EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness)], by crude UPLCMS analysis of a worked up aliquot or by crude ^{1}H-NMR analysis of a worked up aliquot. TLC visualization was performed under a UV lamp or $KMnO_4$/CAM stain developed with heat. Solvent evaporation was conducted by rotary evaporation at the appropriate temperature and pressure. All normal phase flash column chromatography was conducted using silica gel 60 Å (32–63 microns). Reversed phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 µm silica) or SNAP Ultra C18 (HP Sphere, 25 µm silica) cartridge. All reported yields reflect spectroscopically (^{1}H-NMR) pure material unless otherwise stated.

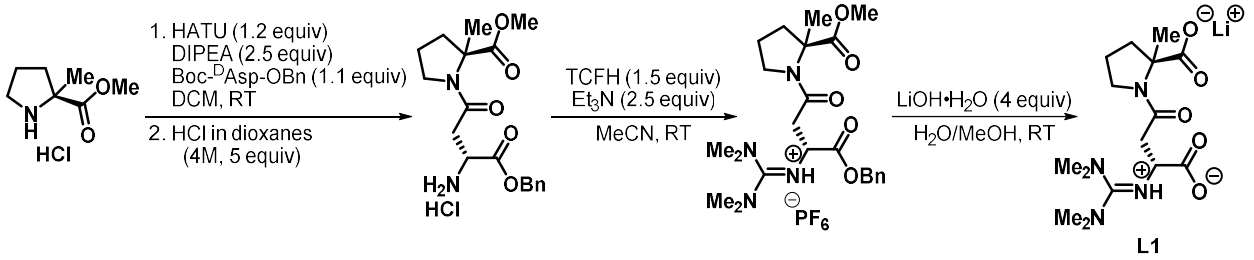
Materials

Unless stated otherwise, all reagents were used as received. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), and Toluene (PhMe) were dried over alumina and dispensed under argon via a Seca solvent purification system by GlassContour. Trimethyl benzene-1,3,5-tricarboxylate was crushed into a fine powder by a mortar and pestle, dried overnight *in vacuo* and stored in a desiccator.

Analysis

Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-*d* ($CDCl_3$), dimethylsulfoxide-d_6 (DMSO-d_6), methanol-d_4 (CD_3OD), and dichloromethane-*d*2 (CD_2Cl_2) were purchased from Cambridge Isotopes and used as received. DMSO-d_6/CD_3OD ampules were used immediately upon opening. NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Measurements were carried out at 23 °C and chemical shifts (δ) are reported as parts per million (ppm). The solvent resonance was used as the internal standard for ^{1}H-NMR (chloroform at 7.26 ppm, methanol at 3.31 ppm, and DMSO at 2.50 ppm) and ^{13}C-NMR (chloroform at 77.0 ppm, methanol at 49.0 ppm, and DMSO at 39.5 ppm). The *J* values are reported in hertz (Hz) and multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m) and broad (br). Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 µm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization S4 (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select ν_{max} are reported in cm^{-1}. Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 25 °C and reported as follows: $[\alpha]\frac{temp}{\lambda}$, concentration (c, in g/100 mL), and solvent. Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (210 nm and 230 nm) and columns (chiral supports, 5 µm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.

Synthesis of L1:

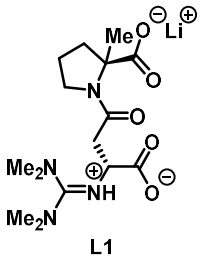


Peptide Coupling: To a flask containing α-Me-Pro-OMe•HCl (1 equiv), was added a solution of Boc-^{D}Asp-OBn (1.1 equiv), HATU (1.2 equiv), and DIPEA (2.5 equiv) in DCM (0.2 M), dropwise. The reaction was stirred at room temperature overnight. Upon complete conversion (via LCMS), the solution was quenched with 10% (w/v) aqueous citric acid and extracted with DCM (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*.

Deprotection: The crude peptide dimer was treated with 4 M HCl in 1,4-dioxane (5 equiv). The solution was stirred at room temperature and was monitored with LCMS. Upon complete conversion, the crude mixture was concentrated *in vacuo*.

Guanidinylation: To a solution of the crude deprotected dimer (1 equiv) in MeCN (0.5 M) was added TCFH (1.5 equiv) and Et_3N (2.5 equiv) sequentially. Upon complete conversion (via LCMS) the solution was quenched with 10% (w/v) aqueous citric acid and extracted with DCM (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The reaction was purified exclusively via reversed-phase chromatography using the indicated mobile phase (KP-C18-HS column).

Hydrolysis: To a solution of the guanidinylated dimer (1 equiv) in H_2O/MeOH (0.5 M), LiOH•H_2O (4 equiv) was added. The reaction was allowed to stir at room temperature overnight. Upon full conversion, the crude mixture was purified exclusively via reversed-phase chromatography using the indicated mobile phase (KP-C18-HS column). Note: Multiple chromatography runs was required to remove $LiPF_6$ salt.



Lithium (*S*)-1-((*R*)-3-((bis(dimethylamino)methylene)ammonio)-3-carboxylatopropanoyl)-2-methylpyrrolidine-2-carboxylate

Prepared according to synthesis of **L1** with an overall yield of 24%. **L1** was purified using reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) and was obtained as an off-white solid. Note: The ligand elutes at 100% H_2O, however, it has a propensity to streak during purification.

^{1}H NMR (400 MHz, CD_3OD) δ 4.23 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.56 (m, 1H), 3.29 (p, *J* = 1.7 Hz, 2H), 3.00 (s, 6H), 2.91 (m, 6H), 2.79 (m, 1H), 2.22 – 2.11 (m, 2H), 1.97 (m, 2H), 1.84 (m, 1H), 1.52 (s, 3H).

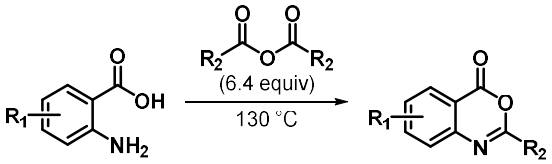
^{13}C NMR (101 MHz, CD_3OD) δ 180.0, 176.2, 167.8, 162.6, 68.3, 56.5, 48.2, 39.5, 38.6, 38.5, 37.8, 23.2, 21.3.

IR (neat film, cm^{-1}) 3389, 2496, 2363, 2337, 2189, 2162, 2020, 1975, 1615, 1396.

HRMS (ESI) $[M+H]^+$ calculated 343.1981 m/z (found 343.1978 m/z for $C_{15}H_{27}N_4O_5$).

General procedure for the synthesis of quinazolinones:

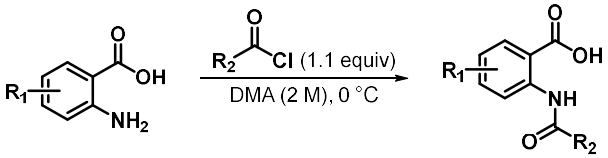
General procedure 1A (GP1A):



The desired benzoxazin-4-one was prepared following the literature procedure.[1]

The anthranilic acid (1.0 equiv) was added to an oven-dried sealed (thick-walled) flask equipped with a magnetic stir bar. The solid was suspended in anhydride (6.4 equiv), sealed tightly, and submerged into an oil bath at 130 ºC. The cloudy suspension quickly became a homogeneous solution, which was allowed to stir at 130 °C overnight. The reaction solution was allowed to cool to room temperature, and the contents of the sealed tube were transferred to a round bottom flask washing with DCM. The benzoxazin-4-one was concentrated *in vacuo* and was used without further purification assuming quantitative yield.

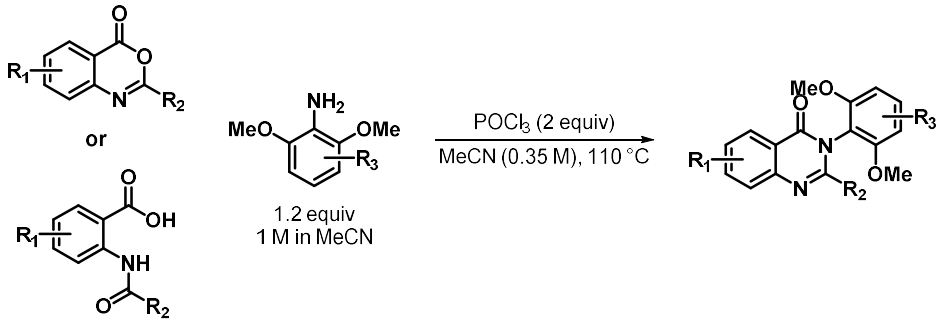
General procedure 1B (GP1B):



The desired *N*-acyl anthranilic acid was prepared following the literature procedure.[1]

The anthranilic acid (1 equiv) was dissolved in *N*,*N*-dimethylacetamide (2 M) in a round bottom flask equipped with a magnetic stir bar. The solution was cooled to 0 °C, and the acid chloride (1.1 equiv) was added slowly to the stirring solution at 0 ºC. The solution was allowed to stir for 4 h at 0 ºC before being poured into ice water. The resulting suspension was filtered, and the collected solid was dried *in vacuo* to yield *N*-acyl anthranilic acid.

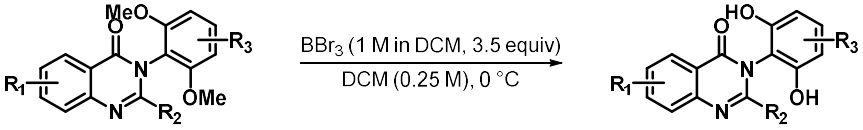
General procedure 2 (GP2):



The desired quinazolinone was prepared following a modified literature procedure.[2]

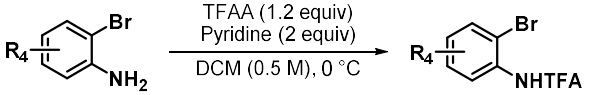
The benzoxazin-4-one (1.0 equiv) or *N*-acyl anthranilic acid (1.0 equiv) was added to an oven dried sealed (thick-walled) flask equipped with a magnetic stir bar. MeCN (0.35 M) and $POCl_3$ (2 equiv) were added sequentially. The aniline (1.2 equiv, 1 M in MeCN) was added to the flask, sealed tightly and submerged into an oil bath at 110 ºC overnight. The reaction was allowed to cool to room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$/IPA (3:1) (2x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The reaction was purified via Si gel flash chromatography using the indicated mobile phase, followed by reversed-phase chromatography using the indicated mobile phase (KP-C18-HS column).

General procedure 3 (GP3):



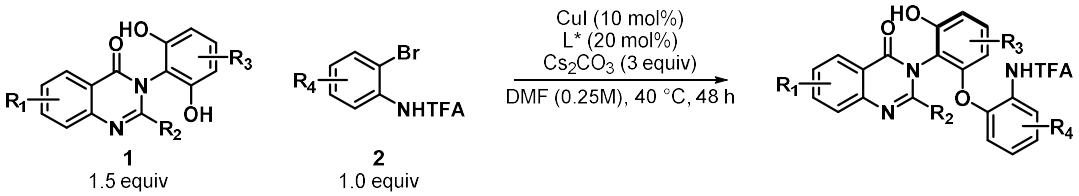
To a flame dried round bottom flask under argon atmosphere, quinazolinone (1 equiv) was added. DCM (0.25 M) was added and the solution was cooled to 0 °C. BBr_3 (1 M in DCM, 3.5 equiv) was added dropwise and the reaction was stirred overnight. The reaction was quenched with cold water at 0 °C and extracted with $CHCl_3$/IPA (3:1) (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The reaction was purified exclusively via reversed-phase chromatography using the indicated mobile phase (KP-C18-HS column).

General Procedure 4 (GP4):



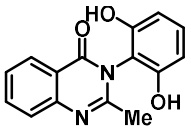
The bromooaniline (1 equiv) was added to a round bottom flask equipped with a magnetic stir bar. DCM (0.5 M) was added and the solution was cooled to 0 °C. Pyridine (2 equiv) and TFAA (1.2 equiv) were added sequentially. The reaction was stirred for 3 hours at room temperature. The reaction was quenched with cold water and extracted with DCM (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The trifluoroacetamides were purified via Si gel flash column chromatography using the indicated mobile phase.

General procedure 5 (GP5):



To a flame dried two dram vial under argon atmosphere, quinazolinone **1** (1.5 equiv), trifluoroacetamide **2** (1 equiv), CuI (10 mol%), ligand (20 mol%), and Cs_2CO_3 (3 equiv) were added. DMF (0.25 M) was added and a Teflon lined screw cap was fitted. The vial was sealed with Teflon tape and placed in a preheated oil bath at the indicated temperature and time. The reaction was quenched with 1 M HCl and extracted with $CHCl_3$/IPA (3:1) (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered through a plug of silica gel using $CHCl_3$/IPA and concentrated *in vacuo*. The pure products were obtained via silica gel flash column chromatography using the indicated mobile phase.

Quinazolinones:



3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (1a)

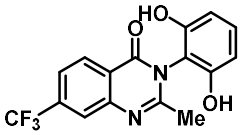
Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 67%. The quinazolinone was purified by flash column chromatography using hexanes:EtOAc (2:1 v:v) during **GP2** and reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) during **GP3** and was obtained as an off-white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.81 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 161.9, 156.9, 153.9, 147.3, 134.4, 130.3, 126.3, 126.3, 125.6, 120.4, 112.5, 106.8, 21.1.

IR (neat film, cm^{-1}) 3252, 1663, 1608, 1473, 1431, 1383, 1356, 1262, 1022.

HRMS (ESI) $[M+H]^+$ calculated 269.0921 m/z (found 269.0930 m/z for $C_{15}H_{13}N_2O_3$).



3-(2,6-dihydroxyphenyl)-2-methyl-7-(trifluoromethyl)quinazolin-4(3*H*)-one (1b)

Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 24%. The quinazolinone was purified by flash column chromatography using hexanes:EtOAc (1:1 v:v) during **GP2** and reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) during **GP3** and was obtained as an off-white solid.

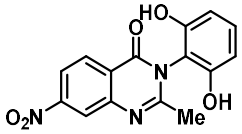
^{1}H NMR (600 MHz, CD_3OD) δ 8.36 (d, *J* = 8.3 Hz, 1H), 7.91 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 161.0, 158.7, 153.8, 147.5, 135.5 (q, *J* = 32.8 Hz), 130.5, 127.9, 123.6 (q, *J* = 272.2 Hz), 123.2 (q, *J* = 4.1 Hz), 123.1, 122.0 (q, *J* = 3.4 Hz), 112.2, 106.9, 21.4.

^{19}F NMR (376 MHz, CD_3OD) δ -64.7.

IR (neat film, cm^{-1}) 3253, 1674, 1607, 1475, 1441, 1384, 1321, 1277, 1172, 1131, 1069, 1022.

HRMS (ESI) $[M+H]^+$ calculated 337.0795 m/z (found 337.0802 m/z for $C_{16}H_{11}F_3N_2O_3$).



3-(2,6-dihydroxyphenyl)-2-methyl-7-nitroquinazolin-4(3*H*)-one (1c)

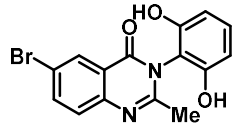
Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 29%. The quinazolinone was purified by flash column chromatography using hexanes:EtOAc (1:1 v:v) during **GP2** and reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) during **GP3** and was obtained as an off-white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, *J* = 2.2 Hz, 1H), 8.38 (d, *J* = 8.8 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.15 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 160.6, 159.3, 153.7, 151.8, 148.0, 130.6, 128.5, 124.6, 121.2, 119.7, 112.1, 106.9, 21.4.

IR (neat film, cm^{-1}) 3420, 3262, 1678, 1607, 1534, 1475, 1349, 1030.

HRMS (ESI) $[M+H]^+$ calculated 314.0771 m/z (found 314.0783 m/z for $C_{15}H_{11}N_3O_5$).



6-bromo-3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (1d)

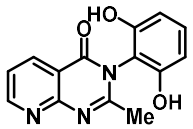
Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 19%. The quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (10:10:1 v:v:v) during **GP2** and sequentially reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) and triturated with MeOH during **GP3** and was obtained as a light brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 2H), 8.13 (d, *J* = 2.4 Hz, 1H), 7.94 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.07 (t, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 2H), 2.11 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 159.9, 157.0, 154.3, 146.9, 137.7, 130.6, 129.5, 128.7, 122.7, 118.9, 112.9, 107.4, 22.9.

IR (neat film, cm^{-1}) 3270, 1669, 1610, 1471, 1379, 1355, 1281, 1031.

HRMS (ESI) $[M+H]^+$ calculated 347.0026 m/z (found 347.0031 m/z for $C_{15}H_{12}BrN_2O_3$).



3-(2,6-dihydroxyphenyl)-2-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (1e)

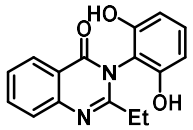
Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 39%. The quinazolinone was purified by sequential flash column chromatography using reversed-phase [H_2O/MeOH (0% to 100%)] and DCM:acetone (4:1 v:v) during **GP2** and reversed-phase flash column chromatography using H_2O/MeOH during **GP3** and was obtained as a light green solid.

^{1}H NMR (400 MHz, CD_3OD) δ 9.01 – 8.84 (m, 1H), 8.69 – 8.52 (m, 1H), 7.62 – 7.48 (m, 1H), 7.15 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 161.9, 160.8, 157.3, 155.5, 153.8, 136.6, 130.6, 122.1, 115.8, 112.0, 106.8, 21.5.

IR (neat film, cm^{-1}) 3250, 1674, 1594, 1474, 1441, 1382, 1352, 1288, 1258, 1031.

HRMS (ESI) $[M+H]^+$ calculated 270.0873 m/z (found 270.0882 m/z for $C_{14}H_{11}N_3O_3$).



3-(2,6-dihydroxyphenyl)-2-ethylquinazolin-4(3*H*)-one (1f)

Prepared according to **GP1A**, **GP2**, and **GP3** with an overall yield of 59%. The quinazolinone was filtered through a Si gel plug with EtOAc during **GP2** and reversed-phase flash column chromatography using H_2O/MeOH (0% to 100%) during **GP3** and was obtained as an off-white solid.

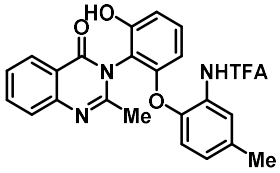
^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.81 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.48 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.13 (t, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 162.2, 160.3, 154.0, 147.6, 134.3, 130.2, 126.2, 126.1, 126.0, 120.4, 112.2, 106.8, 27.9, 10.0.

IR (neat film, cm^{-1}) 3252, 2962, 1663, 1611, 1473, 1377, 1026, 776.

HRMS (ESI) $[M+H]^+$ calculated 283.1077 m/z (found 283.1089 m/z for $C_{16}H_{14}N_2O_3$).

Arylated Quinazolinones:



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-5-methylphenyl)acetamide (3a)

Prepared according to **GP5** using *N*-(2-bromo-5-methylphenyl)-2,2,2-trifluoroacetamide (56.4 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (80.4 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:1:1 v:v:v) and was obtained as a white solid (55 mg, 0.12 mmol, 59%).

Scale up: To a flame dried 50 mL pressure flask under argon atmosphere, *N*-(2-bromo-5-methylphenyl)-2,2,2-trifluoroacetamide (564 mg, 2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (804 mg, 3 mmol), CuI (38 mg, 0.2 mmol), ligand (140 mg, 0.3 mmol), and Cs_2CO_3 (1.95 g, 6.0 mmol) were added. DMF (8 mL) was added and a Teflon lined screw cap was fitted. The vial was sealed with Teflon tape and placed in a preheated oil bath at at 40 ºC for 72 hours. The reaction was quenched with 1 M HCl and extracted with $CHCl_3$/IPA (3:1) (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered through a plug of silica gel using $CHCl_3$/IPA and concentrated *in vacuo*. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:1:1 v:v:v) and was obtained as a white solid (516 mg, 1.1 mmol, 55%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.46 (s, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 161.8, 156.2, 155.8 (q, *J* = 37.8 Hz), 154.3, 153.7, 147.2, 145.6, 135.0, 134.7, 130.5, 128.3, 126.5, 126.4, 125.9, 125.8, 120.4, 120.1, 115.9 (q, *J* = 287.5 Hz), 114.8, 110.7, 106.9, 21.2, 19.4.

^{19}F NMR (376 MHz, CD_3OD) δ -76.8.

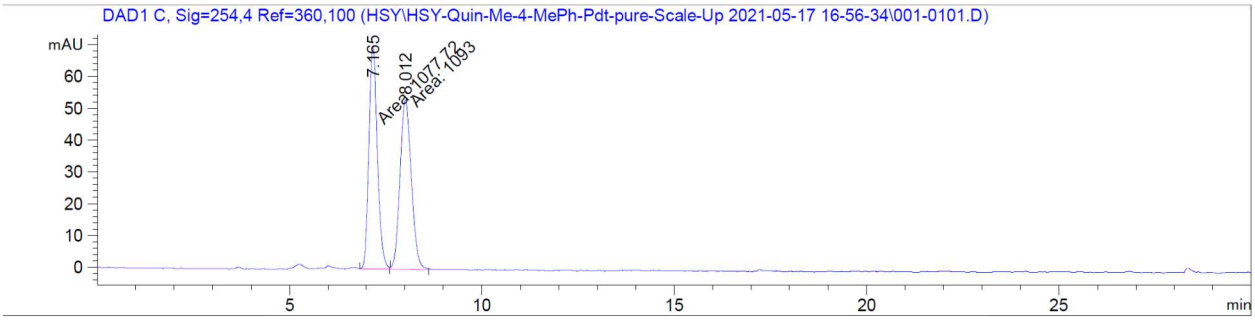
IR (neat film, cm^{-1}) 3253, 2947, 2834, 1728, 1672, 1607, 1469, 1267, 1210, 1162, 1018.

$[\alpha]_{589}^{20}$ +38.24 (c = 0.5, MeOH).

HRMS (ESI) $[M+H]^+$ calculated 470.1322 m/z (found 470.1329 m/z for $C_{24}H_{19}F_3N_3O_4$).

HPLC (AD-H, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 7.1 min (major), 8.0 min (minor)

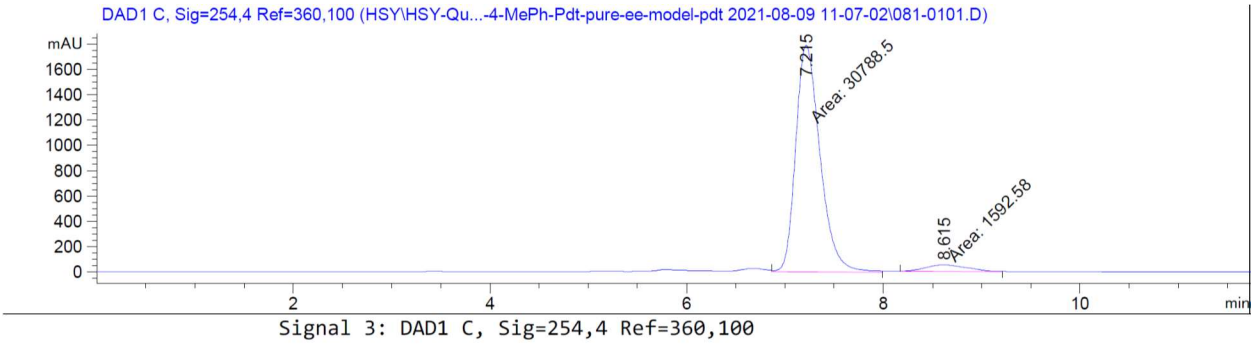
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.165	MM	0.2560	1077.71680	70.17303	49.6479
2	8.012	MM	0.3414	1093.00159	53.35354	50.3521
Totals :				2170.71838	123.52658	

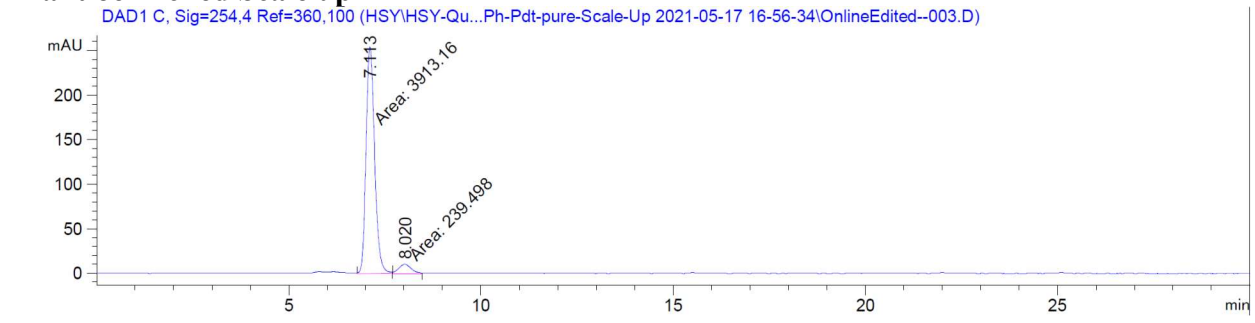
Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.215	MM	0.2861	3.07885e4	1793.27087	95.0818
2	8.615	MM	0.4976	1592.58264	53.34053	4.9182

Enantioenriched Scale up



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.113	MM	0.2563	3913.15698	254.44354	94.2326
2	8.020	MM	0.3771	239.49825	10.58506	5.7674
Totals :				4152.65523	265.02860	

2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)phenyl)acetamide (3b)

Prepared according to **GP5** using *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (80.4 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:0.5:1 v:v:v) and was obtained as a white solid (49 mg, 0.11 mmol, 54%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.16 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.78 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.50 – 7.41 (m, 1H), 7.31 – 7.21 (m, 2H), 7.21 – 7.09 (m, 2H), 6.79 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.39 (dd, *J* = 8.4, 1.1 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 161.8, 156.2, 155.8 (q, *J* = 37.7, 37.2 Hz), 154.4, 153.5, 148.1, 147.2, 134.7, 130.6, 127.8, 126.7, 126.5, 126.4, 125.8, 125.7, 124.6, 120.4, 120.0, 115.9 (q, *J* = 287.5 Hz), 115.0, 111.0, 107.4, 21.2.

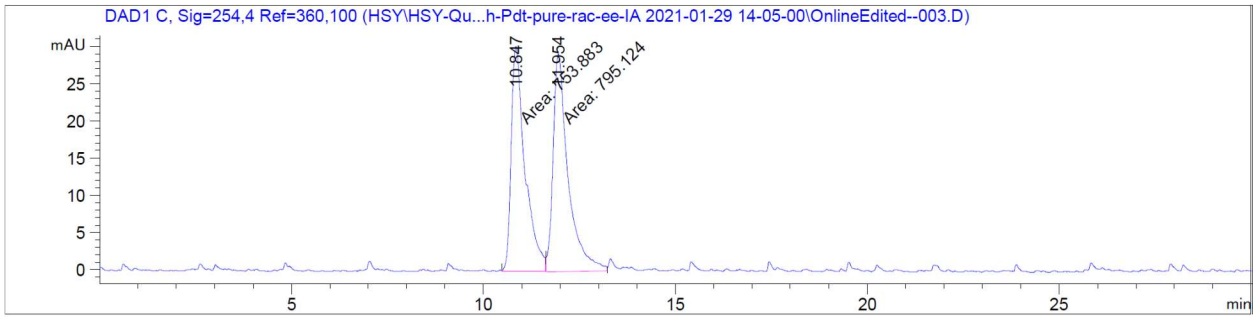
^{19}F NMR (376 MHz, CD_3OD) δ -76.7.

IR (neat, cm^{-1}) 3250, 2946, 1728, 1671, 1605. 1470, 1459, 1259, 1209, 1152, 1105, 1018, 769.

HRMS (ESI) $[M+H]^+$ calculated 456.1166 m/z (found 456.1170 m/z for $C_{23}H_{17}F_3N_3O_4$).

HPLC (IA, ethanol/*n*-hexane = 5/95, flow rate = 1.0 mL/min, l = 254 nm) tR = 10.9 min (minor), 11.9 min (major)

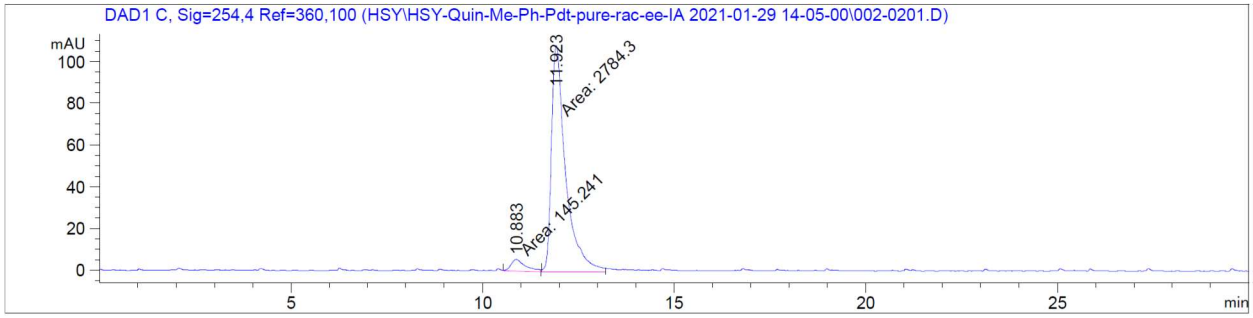
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

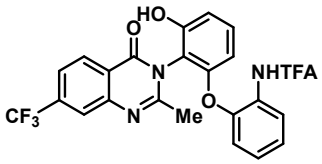
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.847	MM	0.4159	753.88342	30.21387	48.6688
2	11.954	MM	0.4530	795.12408	29.25619	51.3312
Totals :				1549.00751	59.47005	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.883	MM	0.4381	145.24062	5.52484	4.9578
2	11.923	MM	0.4283	2784.29736	108.34653	95.0422
Totals :				2929.53798	113.87138	



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxo-7-(trifluoromethyl)quinazolin-3(4*H*)-yl)phenoxy)phenyl)acetamide (3c)

Prepared according to **GP5** using *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methyl-7-(trifluoromethyl)quinazolin-4(3*H*)-one (100.9 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash

column chromatography using hexanes:DCM:acetone (3:1:1 v:v:v) and was obtained as a white solid (65 mg, 0.124 mmol, 62%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.32 (d, *J* = 8.2 Hz, 1H), 7.90 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.36 – 7.22 (m, 2H), 7.20 – 7.10 (m, 2H), 6.81 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.41 (dd, *J* = 8.4, 0.9 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 160.9, 157.8, 155.8 (q, *J* = 37.7 Hz), 154.3, 153.3, 148.2, 147.4, 135.7 (q, *J* = 32.6 Hz), 130.8, 128.0, 127.9, 126.6, 125.8, 124.6, 123.5 (q, *J* = 272.2 Hz), 123.3 (q, *J* = 4.1 Hz), 122.7, 122.2 (q, *J* = 3.4 Hz), 120.2, 115.9 (q, *J* = 287.5 Hz), 114.8, 111.1, 107.5, 21.5.

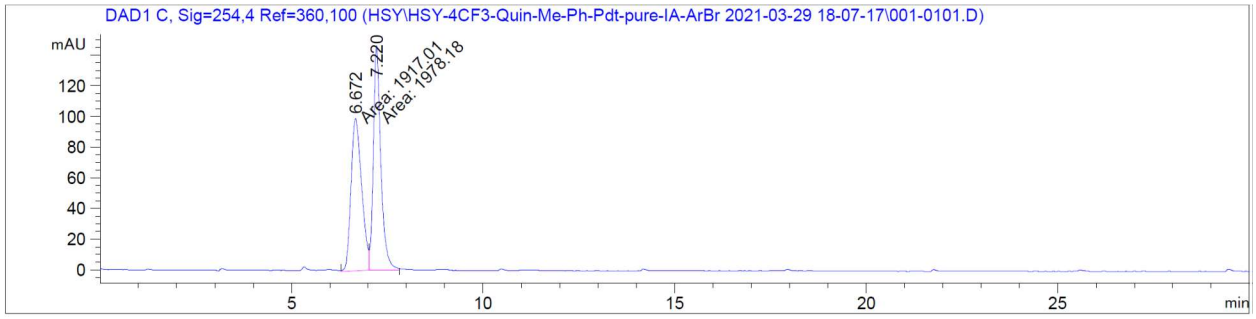
^{19}F NMR (376 MHz, CD_3OD) δ -64.7, -76.7.

IR (neat film, cm^{-1}) 3254, 1730, 1682, 1606, 1546, 1471, 1321, 1262, 1213, 1162, 1067, 1018.

HRMS (ESI) $[M+H]^+$ calculated 524.1040 m/z (found 524.1047 m/z for $C_{24}H_{16}F_6N_3O_4$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 6.7 min (minor), 87.2 min (major)

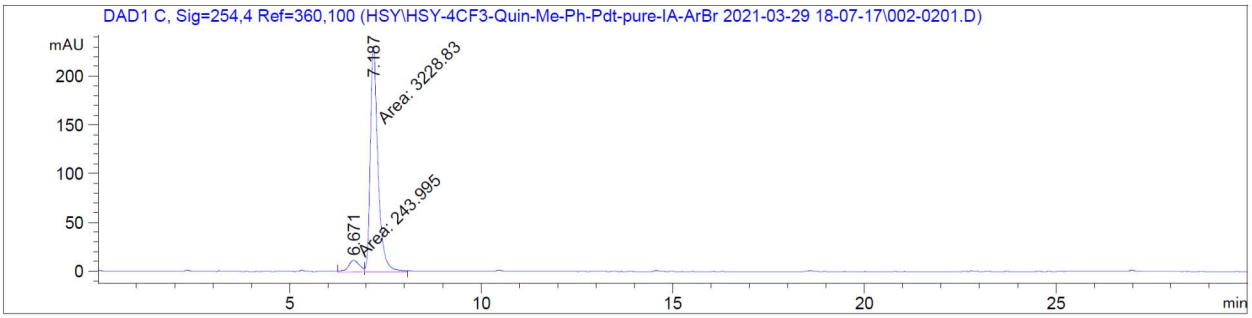
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

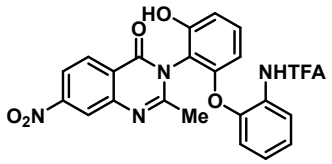
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.672	MM	0.3224	1917.01477	99.11428	49.2148
2	7.220	MM	0.2257	1978.18445	146.07533	50.7852
Totals :				3895.19922	245.18961	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.671	MM	0.3363	243.99524	12.09381	7.0258
2	7.187	MM	0.2328	3228.83496	231.14221	92.9742
Totals :				3472.83020	243.23602	



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-7-nitro-4-oxoquinazolin-3(4*H*)-yl)phenoxy)phenyl)acetamide (3d)

Prepared according to **GP5** using *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methyl-7-nitroquinazolin-4(3*H*)-one (94.0 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (1:4:0.1 v:v:v) and was obtained as an off-white solid (51 mg, 0.102 mmol, 51%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.40 (d, *J* = 2.2 Hz, 1H), 8.33 (d, *J* = 8.7 Hz, 1H), 8.20 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.17 (td, *J* = 7.8, 1.4 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.42 (dd, *J* = 8.4, 1.1 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 160.5, 158.4, 155.8 (q, *J* = 37.7 Hz), 154.3, 153.2, 151.8, 148.2, 147.9, 130.9, 128.5, 127.9, 126.5, 125.8, 124.6, 124.3, 121.4, 120.1, 119.9, 115.9 (q, *J* = 287.5 Hz), 114.7, 111.1, 107.6, 21.5.

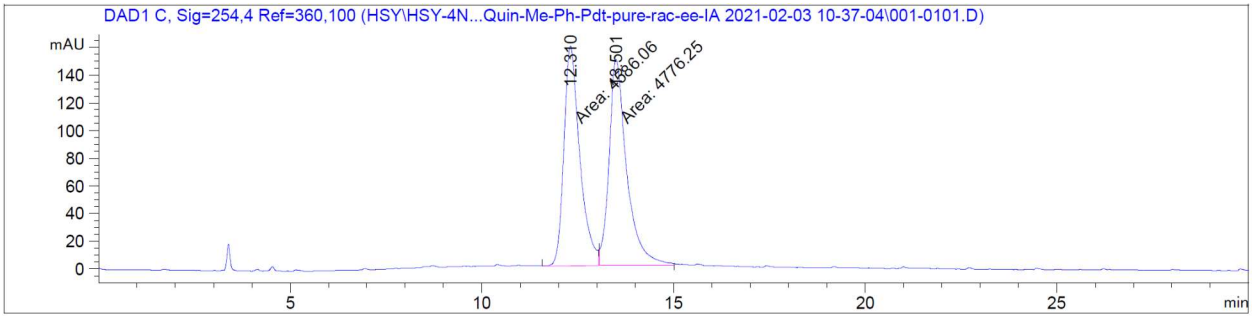
^{19}F NMR (376 MHz, CD_3OD) δ -76.8.

IR (neat film, cm^{-1}) 3265, 2949, 1728, 1682, 1605, 1534, 1471, 1344, 1261, 1017.

HRMS (ESI) $[M+H]^+$ calculated 501.1016 m/z (found 501.1035 m/z for $C_{23}H_{16}F_3N_4O_6$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 12.3 min (minor), 13.5 min (major)

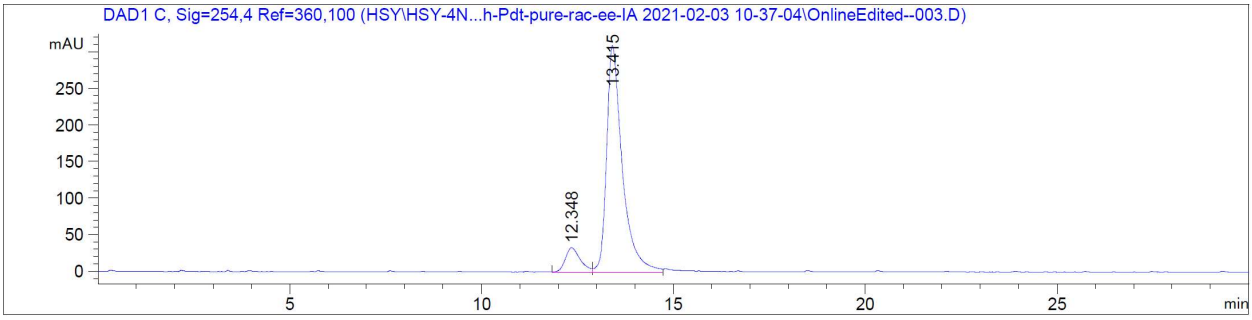
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

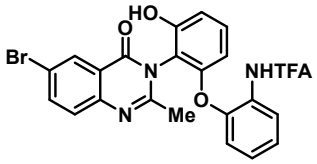
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.310	MM	0.4808	4586.06006	158.97169	48.9843
2	13.501	MM	0.5351	4776.24609	148.75368	51.0157
Totals :				9362.30615	307.72537	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.348	VV	0.4101	907.07922	33.47605	9.3014
2	13.415	VV	0.4188	8845.02344	310.10425	90.6986
Totals :				9752.10266	343.58030	



_N_-(2-(2-(6-bromo-2-methyl-4-oxoquinazolin-3(4_H_)-yl)-3-hydroxyphenoxy)phenyl)-2,2,2-trifluoroacetamide (3e)

Prepared according to **GP5** using _N_-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 6-bromo-3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3_H_)-one (104.2 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:1:1 v:v:v) and was obtained as a white solid (63 mg, 0.118 mmol, 59%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.23 (d, J = 2.3 Hz, 1H), 7.86 (dd, J = 8.7, 2.3 Hz, 1H), 7.61 (dd, J = 8.1, 1.6 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.17 (td, J = 7.7, 1.4 Hz, 1H), 7.13 (dd, J = 8.1, 1.4 Hz, 1H), 6.79 (dd, J = 8.4, 1.1 Hz, 1H), 6.40 (dd, J = 8.5, 1.1 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 160.6, 156.7, 155.8 (q, J = 37.8 Hz), 154.3, 153.3, 148.1, 146.2, 137.6, 130.7, 128.7, 128.1, 127.8, 126.6, 125.7, 124.6, 121.6, 120.2, 119.5, 115.9 (q, J = 287.5 Hz), 114.9, 111.1, 107.5, 21.4.

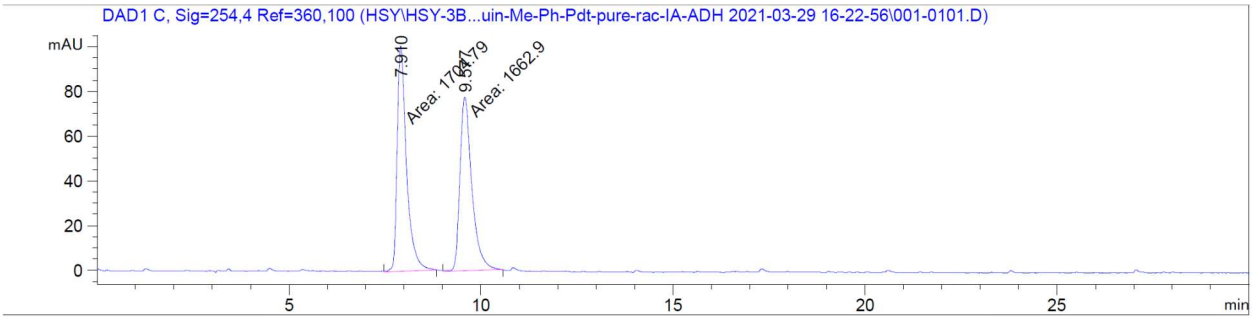
^{19}F NMR (376 MHz, CD_3OD) δ -76.7.

IR (neat film, cm^{-1}) 3255, 2946, 2833, 1728, 1675, 1604, 1470, 1261, 1156, 1018.

HRMS (ESI) $[M+H]^+$ calculated 536.0250 m/z (found 536.0261 m/z for $C_{23}H_{16}BrF_3N_3O_4$).

HPLC (IA, ethanol/_n_-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 7.9 min (minor), 9.5 min (major)

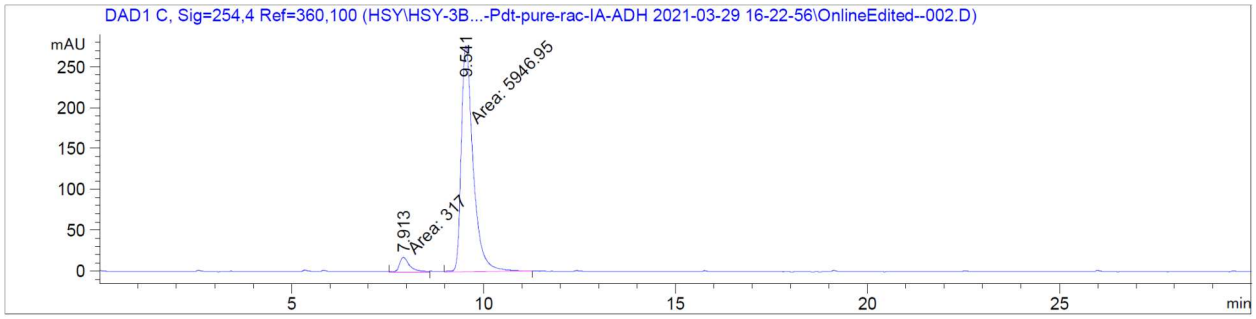
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

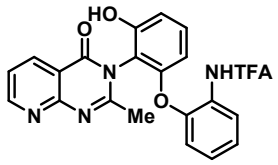
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.910	MM	0.2822	1704.79333	100.69882	50.6220
2	9.577	MM	0.3571	1662.90210	77.60058	49.3780
Totals :				3367.69543	178.29940	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.913	MM	0.2963	316.99979	17.83138	5.0607
2	9.541	MM	0.3583	5946.95166	276.62503	94.9393
Totals :				6263.95145	294.45641	



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxopyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)phenoxy)phenyl)acetamide (3f)

Prepared according to **GP5** using *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (80.8 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using DCM:MeOH (95:5 v:v) and was obtained as a white solid (48 mg, 0.11 mmol, 53%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 11.06 (s, 1H), 9.26 (s, 1H), 8.63 (s, 1H), 8.35 – 7.96 (m, 2H), 7.46 – 7.08 (m, 5H), 7.00 (s, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 2.61 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.7, 160.6, 156.6, 155.2 (q, *J* = 38.3 Hz), 154.6, 153.1, 144.2, 137.7, 131.2, 128.0, 126.7, 125.7, 123.5, 123.4, 121.9, 121.6, 115.6 (q, *J* = 288.3 Hz), 115.3, 113.8, 113.5, 105.7, 23.2.

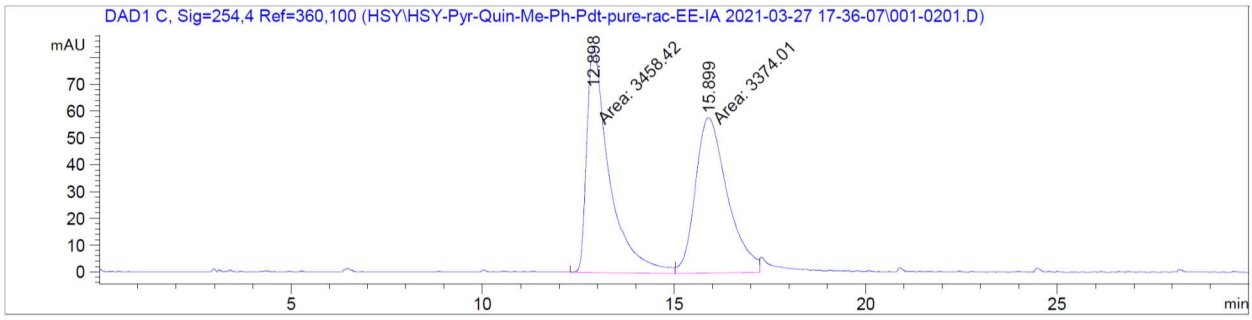
^{19}F NMR (471 MHz, CD_2Cl_2) δ -76.8.

IR (neat film, cm^{-1}) 3248, 3070, 1730, 1681, 1595, 1440, 1259, 1208, 1019.

HRMS (ESI) $[M+H]^+$ calculated 457.1118 m/z (found 457.1130 m/z for $C_{22}H_{16}F_3N_4O_4$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 12.9 min (major), 15.9 min (minor)

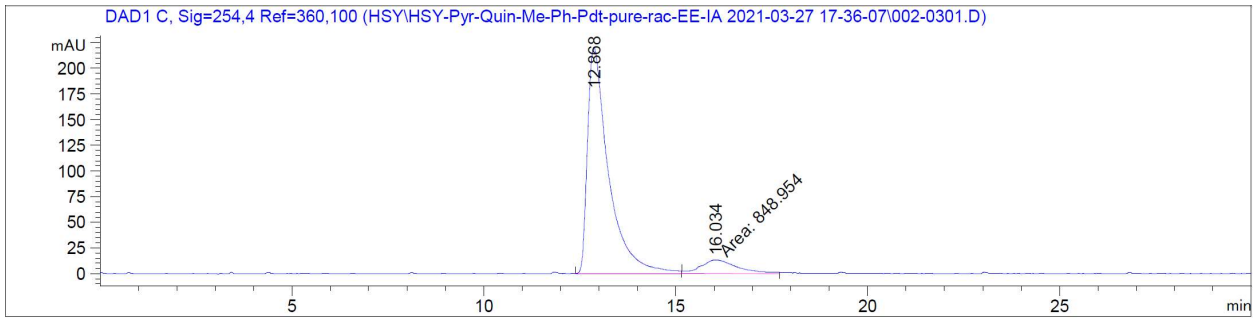
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

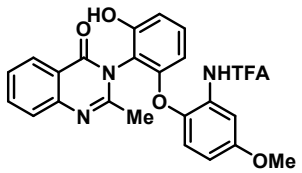
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.898	MM	0.6831	3458.41577	84.38475	50.6177
2	15.899	MM	0.9703	3374.00806	57.95691	49.3823
Totals :				6832.42383	142.34166	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.868	VV	0.5519	8439.99316	220.81288	90.8606
2	16.034	MM	1.0931	848.95392	12.94417	9.1394
Totals :				9288.94708	233.75705	



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-5-methoxyphenyl)acetamide (3g)

Prepared according to **GP5** using *N*-(2-bromo-5-methoxyphenyl)-2,2,2-trifluoroacetamide (59.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (80.5 mg, 0.3 mmol)

at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:1.5:0.75 v:v:v) and was obtained as a white solid (40 mg, 0.082 mmol, 41%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.33 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.78 – 6.70 (m, 1H), 6.24 (d, *J* = 8.3 Hz, 1H), 3.81 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (151 MHz, CD_2Cl_2) δ 161.8, 157.1, 156.3, 155.4 (q, *J* = 38.3 Hz), 154.1, 153.7, 146.6, 137.2, 135.1, 130.9, 129.0, 127.0, 126.9, 125.7, 122.3, 120.1, 115.6 (q, *J* = 288.3 Hz), 113.8, 111.7, 111.2, 108.4, 105.4, 55.7, 22.3.

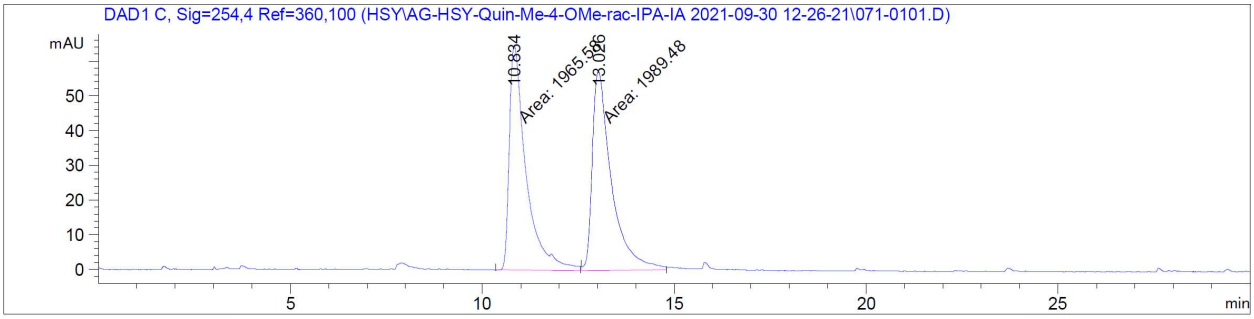
^{19}F NMR (471 MHz, CD_2Cl_2) δ -75.4.

IR (neat film, cm^{-1}) 3251, 2951, 1730, 1673, 1608, 1467, 1209.

HRMS (ESI) $[M+H]^+$ calculated 486.1271 m/z (found 486.1276 m/z for $C_{24}H_{19}F_3N_3O_5$).

HPLC (IA, ethanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, l = 254 nm) tR = 10.8 min (minor), 13.0 min (major)

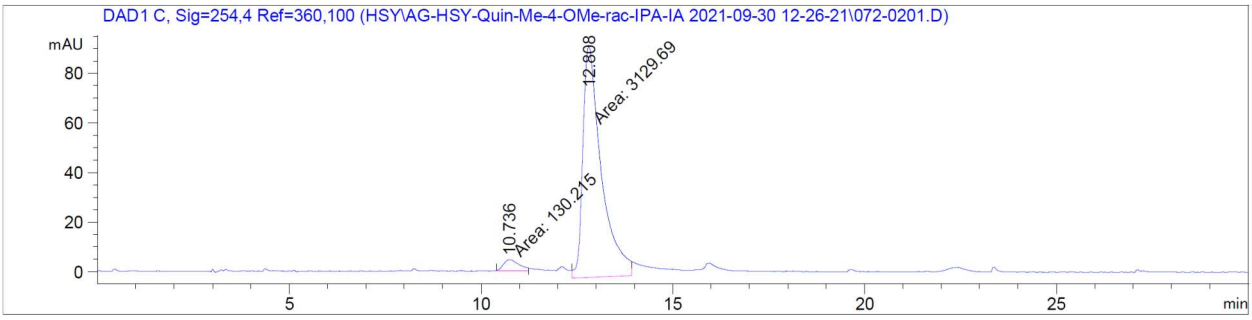
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

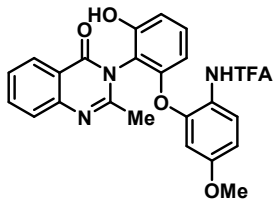
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.834	MM	0.5069	1965.58167	64.63077	49.6978
2	13.026	MM	0.5794	1989.48364	57.22647	50.3022
Totals :				3955.06531	121.85723	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.736	MM	0.4847	130.21454	4.47744	3.9944
2	12.808	MM	0.5597	3129.69165	93.20229	96.0056
Totals :				3259.90619	97.67973	



2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-4-methoxyphenyl)acetamide (3h)

Prepared according to **GP5** using *N*-(2-bromo-4-methoxyphenyl)-2,2,2-trifluoroacetamide (59.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (80.5 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetonitrile (1:1:1 v:v:v) and was obtained as a white solid (53 mg, 0.114 mmol, 57%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.20 – 8.14 (m, 1H), 7.84 – 7.76 (m, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 9.1 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 6.80 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.75 – 6.68 (m, 2H), 6.45 (dd, *J* = 8.4, 1.1 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 161.8, 159.6, 156.2, 156.1 (q, *J* = 37.3 Hz), 154.4, 153.3, 149.7, 147.2, 134.7, 130.6, 127.1, 126.5, 126.4, 125.8, 120.1, 118.9, 117.0 (q, *J* = 287.3 Hz), 115.2, 111.1, 110.1, 107.8, 105.7, 54.7, 21.2.

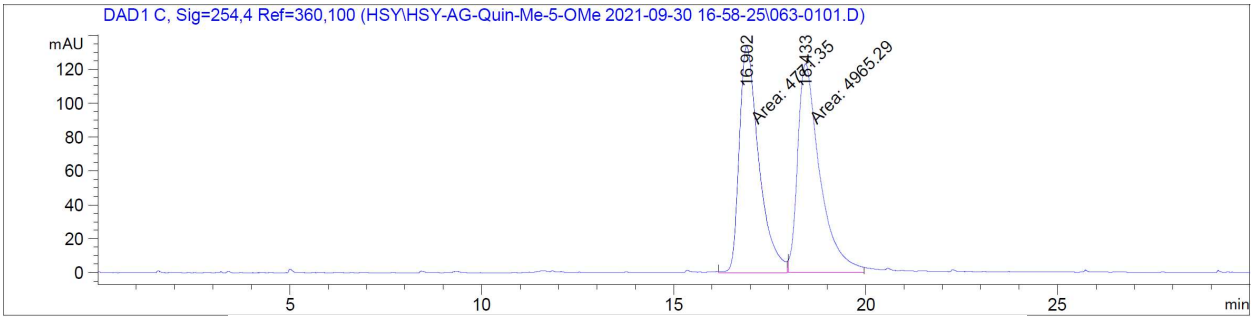
^{19}F NMR (376 MHz, CD_3OD) δ -76.8.

IR (neat film, cm^{-1}) 3302, 2946, 2835, 1717, 1673, 1606, 1547, 1471, 1275, 1158, 1020.

HRMS (ESI) $[M+H]^+$ calculated 486.1271 m/z (found 486.1276 m/z for $C_{24}H_{19}F_3N_3O_5$).

HPLC (IA, ethanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, l = 254 nm) tR = 16.9 min (minor), 18.4 min (major)

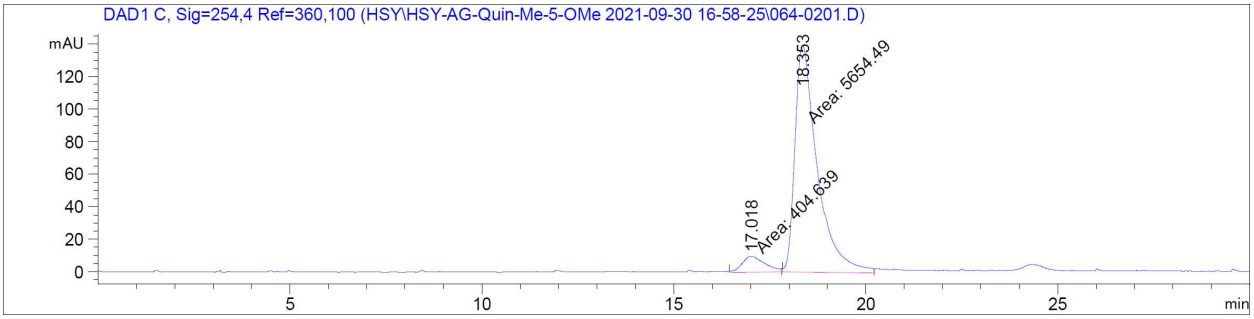
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

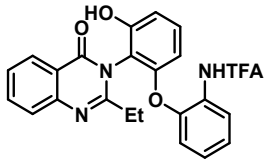
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.902	MM	0.5939	4771.34521	133.90636	49.0040
2	18.433	MM	0.6728	4965.29492	122.99427	50.9960
Totals :				9736.64014	256.90063	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.018	MM	0.6982	404.63861	9.65964	6.6782
2	18.353	MM	0.6768	5654.49316	139.25217	93.3218
Totals :				6059.13177	148.91181	



_N_-(2-(2-(2-ethyl-4-oxoquinazolin-3(4_H_)-yl)-3-hydroxyphenoxy)phenyl)-2,2,2-trifluoroacetamide (3i)

Prepared according to **GP5** using _N_-(2-bromophenyl)-2,2,2-trifluoroacetamide (53.6 mg, 0.2 mmol) and 3-(2,6-dihydroxyphenyl)-2-ethylquinazolin-4(3H)-one (84.7 mg, 0.3 mmol) at 40 ºC for 48 hours. The arylated quinazolinone was purified by flash column chromatography using hexanes:DCM:acetone (3:0.5:1 v:v:v) and was obtained as a white solid (47 mg, 0.1 mmol, 50%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.16 (dd, J = 8.0, 1.5 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 8.0, 1.6 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.29 – 7.22 (m, 2H), 7.17 (td, J = 7.8, 1.4 Hz, 1H), 7.14 (dd, J = 8.2, 1.4 Hz, 1H), 6.78 (dd, J = 8.4, 1.1 Hz, 1H), 6.39 (dd, J = 8.4, 1.1 Hz, 1H), 2.68 – 2.54 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 162.1, 159.4, 155.8 (q, J = 37.7 Hz), 154.4, 153.7, 148.2, 147.5, 134.5, 130.5, 127.8, 126.7, 126.3, 126.3, 125.7, 124.5, 120.4, 120.1, 115.9 (q, J = 287.6 Hz), 114.9, 110.9, 107.4, 27.9, 9.9.

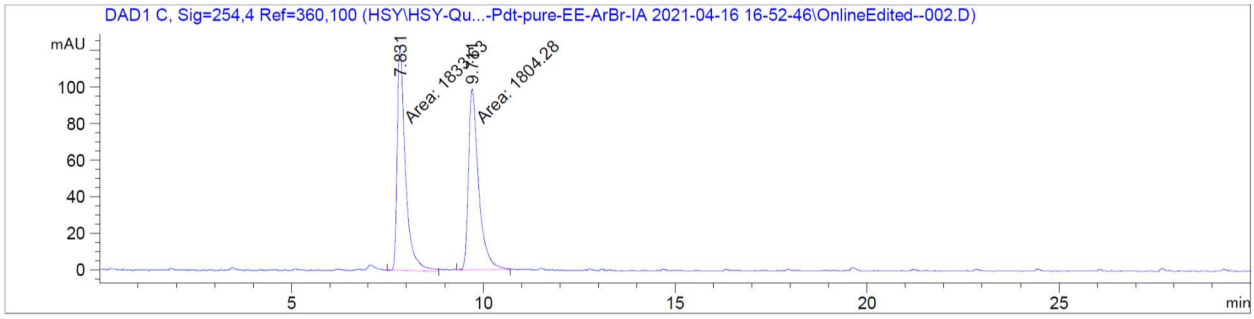
^{19}F NMR (376 MHz, CD_3OD) δ -76.8.

IR (neat film, cm^{-1}) 3247, 3068, 1727, 1667, 1605, 1470, 1285, 1259, 1211, 1154.

HRMS (ESI) $[M+H]^+$ calculated 470.1322 m/z (found 470.1331 m/z for $C_{24}H_{19}F_3N_3O_4$).

HPLC (IA, ethanol/_n_-hexane = 5/95, flow rate = 1.0 mL/min, l = 254 nm) tR = 7.9 min (minor), .95 min (major)

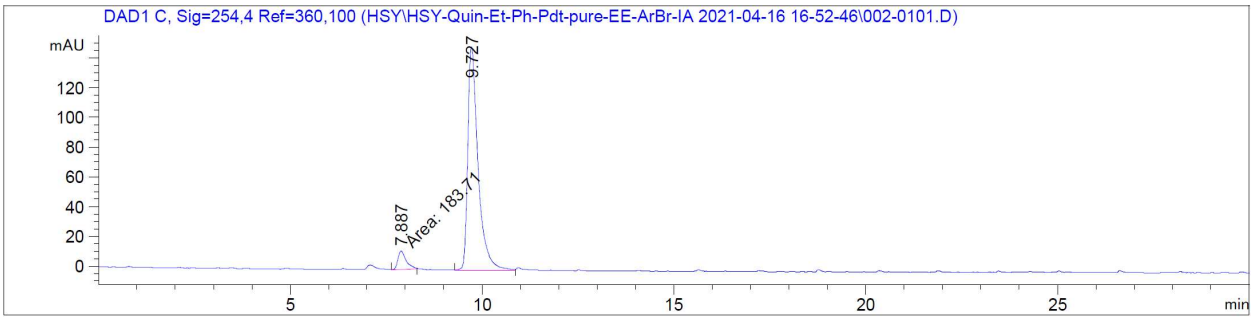
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.831	MM	0.2490	1833.63330	122.74162	50.4034
2	9.711	MM	0.3049	1804.28296	98.61400	49.5966
Totals :				3637.91626	221.35562	

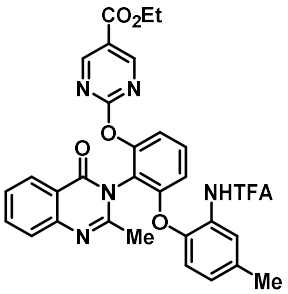
Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.887	MM	0.2485	183.71024	12.31980	6.1358
2	9.727	VV	0.2763	2810.33960	150.16862	93.8642
Totals :				2994.04984	162.48842	

Derivatizations:



Ethyl 2-(3-(4-methyl-2-(2,2,2-trifluoroacetamido)phenoxy)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)phenoxy)pyrimidine-5-carboxylate (4)

To a two dram vial equipped with a magnetic stir bar was added 2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-5-methylphenyl)acetamide (**3a**) (47 mg, 0.1 mmol), Cs_2CO_3 (37 mg, 0.115 mmol), and ethyl 2-chloropyrimidine-5-carboxylate (21 mg, 0.115 mmol). The vial was cooled to 0 ºC and DMF (1 mL) was added. The reaction stirred at 0 ºC for 1 hour before stirring at room temperature for 21 hours. The reaction was then diluted with EtOAc and washed with water (3x) and brine. The crude residue was purified via flash column chromatography using hexanes:DCM:acetone (7:7:1 v:v) to yield **4** as a white solid (58.2 mg, 94% yield).

^{1}H NMR (600 MHz, CD_3OD) δ 8.91 (s, 2H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 165.6, 162.8, 161.1, 161.0, 155.9 (q, *J* = 37.6 Hz), 155.2, 154.1, 149.7, 146.9, 146.0, 135.4, 134.9, 130.8, 128.7, 126.7, 126.5, 126.4, 126.3, 126.0, 120.8, 120.2, 119.6, 117.6, 119.1 – 112.9 (q, *J* = 287.6 Hz), 114.1, 61.4, 21.5, 19.4, 13.0.

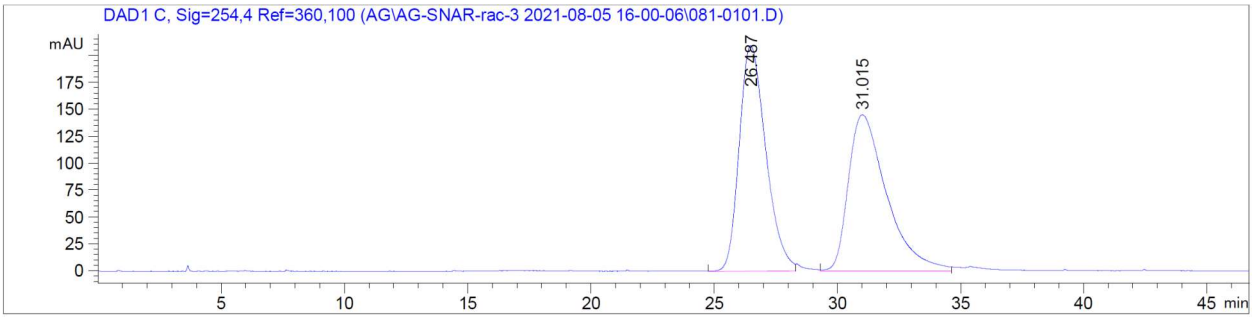
^{19}F NMR (376 MHz, CD_3OD) δ = -76.6.

IR (neat film, cm^{-1}) 3367, 3071, 2972, 1727, 1681, 1606, 1468, 1425, 1284, 1207, 1159, 1017.

HRMS (ESI) $[M+H]^+$ calculated 620.1751 m/z (found 620.1752 m/z for $C_{31}H_{25}F_3N_5O_{6s}$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 254 nm) tR = 25.9 min (major), 31.1 min (minor)

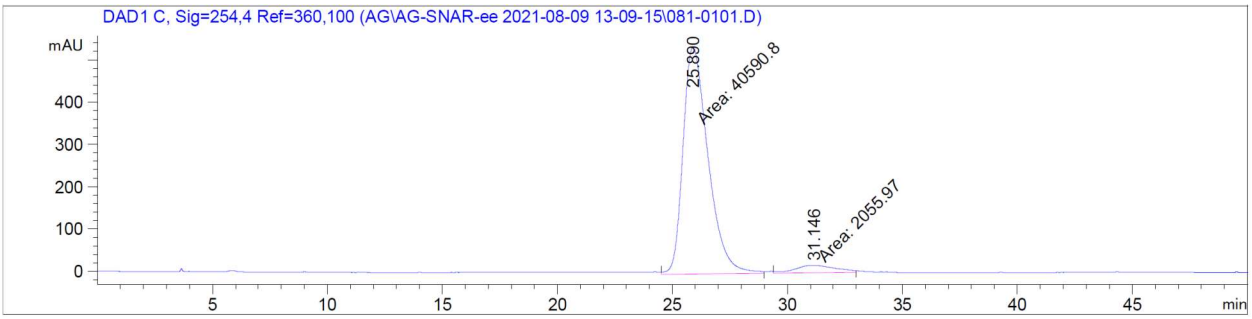
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

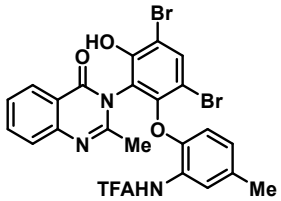
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.487	VV	1.1565	1.57621e4	209.79991	50.0254
2	31.015	VV	1.5568	1.57461e4	145.46889	49.9746
Totals :				3.15081e4	355.26880	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.890	MM	1.2612	4.05908e4	536.39655	95.1791
2	31.146	MM	1.9656	2055.96777	17.43281	4.8209
Totals :				4.26468e4	553.82936	



***N*-(2-(4,6-dibromo-3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-5-methylphenyl)-2,2,2-trifluoroacetamide (5)**

To a two dram vial equipped with a magnetic stir bar was added **3a** (47 mg, 0.1 mmol), DCM (1 mL), and Et_3N (0.001 mL, 0.01 mmol). The solution was cooled to 0 ºC and NBS (36 mg, 0.2

mmol) was added. The reaction was allowed to slowly warm to room temperature over 3 hours at which point it was diluted with DCM and washed with 1 M $HCl_{(aq)}$. The residue was purified via reversed phase chromatography (MeOH:H_2O) to afford **5** as an off white solid (56.4 mg, 90% yield).

^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (s, 1H), 7.97 (s, 1H), 7.79 – 7.69 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.27 (s, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 2.14 (s, 3H). Note: 3H at 2.21 is missing.

^{13}C NMR (126 MHz, CD_3OD) δ 161.3, 155.2 (t, *J* = 37.5 Hz), 154.5, 151.9, 148.4, 146.9, 136.8, 134.7, 133.2, 127.3, 126.5, 126.2, 126.1, 124.6, 123.8, 121.2, 119.8, 115.8 (q, *J* = 287.5 Hz), 115.3, 108.5, 106.7, 19.2. Note: Missing 1C in aliphatic region.

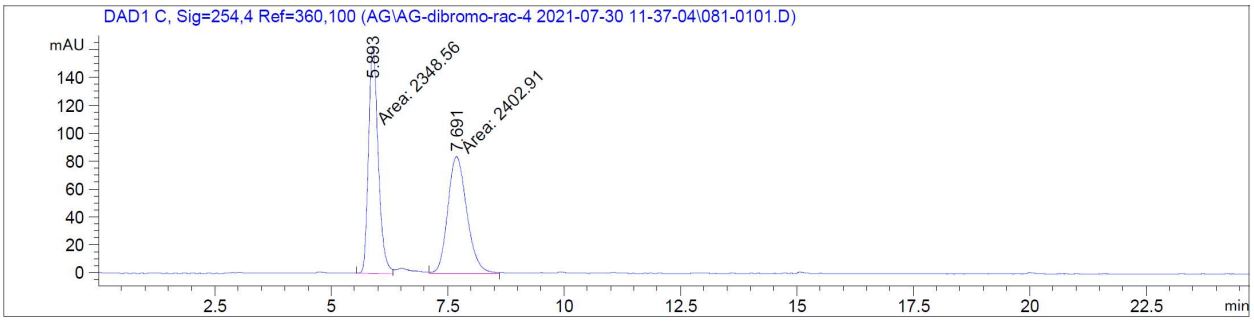
^{19}F NMR (471 MHz, CD_3OD) δ = -76.8.

IR (neat film, cm^{-1}) 3366, 2946, 2834, 1729, 1678, 1606, 1437, 1206, 1020.

HRMS (ESI) $[M+H]^+$ calculated 627.9514 m/z (found 627.9512 m/z for $C_{24}H_{17}Br_2F_3N_3O_4$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 265 nm) tR = 5.9 min (major), 7.7 min (minor)

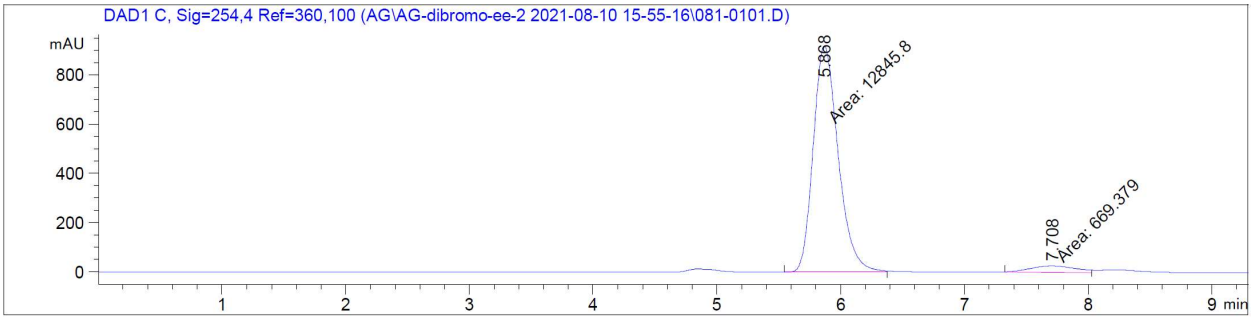
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

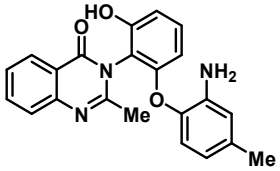
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.893	MM	0.2412	2348.56445	162.31238	49.4282
2	7.691	MM	0.4773	2402.90601	83.89826	50.5718
Totals :				4751.47046	246.21064	

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.868	MM	0.2332	1.28458e4	918.21710	95.0472
2	7.708	MM	0.4260	669.37909	26.18668	4.9528
Totals :				1.35152e4	944.40378	



3-(2-(2-amino-4-methylphenoxy)-6-hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (6)

To a 2-dram vial equipped with a magnetic stir bar was added **3a** (47 mg, 0.1 mmol), K_2CO_3 (28 mg, 0.2 mmol), MeOH (0.5 mL), and water (0.5 mmol). The vial was sealed and heated at 60 ºC for 1 hour before cooling to room temperature. The reaction mixture was diluted with ca. 1 mL water before acidifying with 0.3 mL 1 M $HCl_{(aq)}$. The resulting precipitate was isolated by filtration to yield **6** as a light orange solid (34.4 mg, 92% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.11 (dd, J = 8.0, 1.5 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 8.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.69 (dd, J = 8.3, 0.9 Hz, 1H), 6.54 (s, 1H), 6.36 (d, J = 7.8 Hz, 1H), 6.15 – 6.05 (m, 1H), 2.28 (s, 3H), 2.14 (s, 3H).

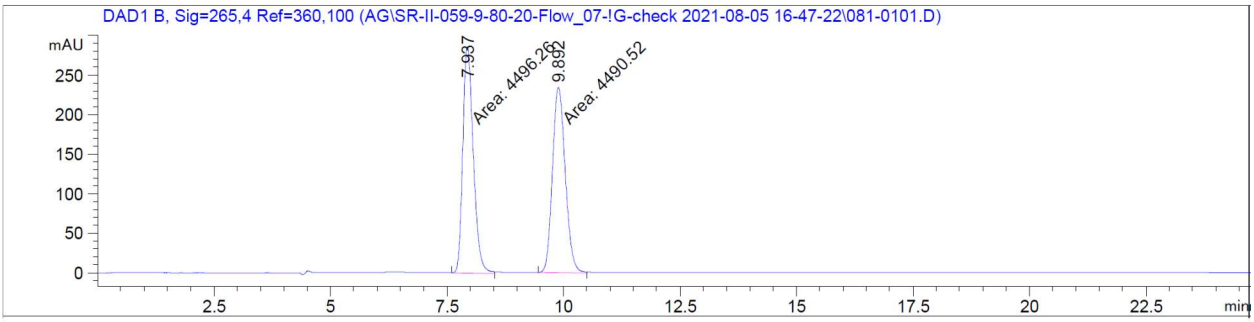
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.4, 155.8, 154.8, 154.4, 147.9, 139.8, 138.1, 135.5, 135.3, 130.8, 127.1, 127.0, 126.8, 122.2, 120.6, 117.8, 117.0, 114.2, 110.4, 105.3, 23.0, 21.2.

IR (neat film, cm^{-1}) 3360, 2945, 2832, 1666, 1606, 1508, 1468, 1349, 1307, 1161, 1118.

HRMS (ESI) $[M+H]^+$ calculated 374.1499 m/z (found 374.1509 m/z for $C_{22}H_{20}N_3O_3$).

HPLC (IA, ethanol/*n*-hexane = 8/92, flow rate = 1.0 mL/min, l = 265 nm) tR = 7.9 min (minor), 9.8 min (major)

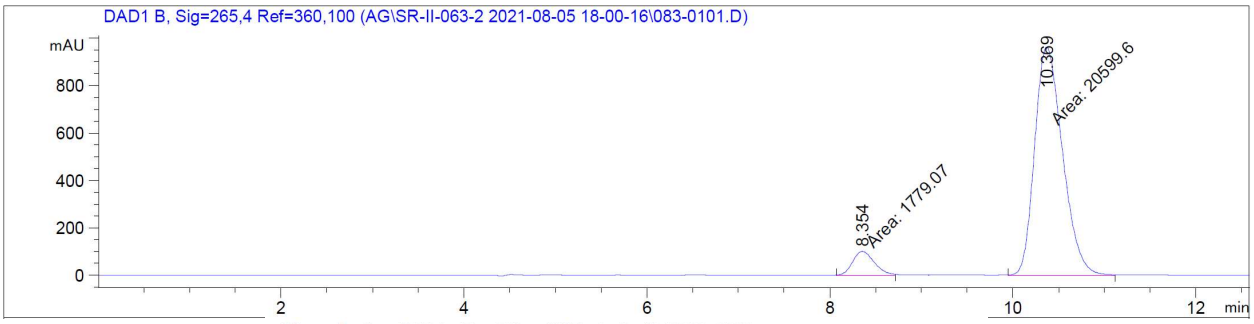
Racemic



Signal 1: DAD1 B, Sig=265,4 Ref=360,100

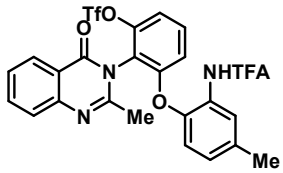
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.937	MM	0.2615	4496.25830	286.55505	50.0319
2	9.892	MM	0.3190	4490.51758	234.59312	49.9681
Totals :				8986.77588	521.14818	

Enantioenriched



Signal 1: DAD1 B, Sig=265,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.354	MM	0.2861	1779.07471	103.63993	7.9498
2	10.369	MM	0.3555	2.05996e4	965.89270	92.0502
Totals :				2.23787e4	1069.53263	



3-(4-methyl-2-(2,2,2-trifluoroacetamido)phenoxy)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)phenyl trifluoromethanesulfonate (7')

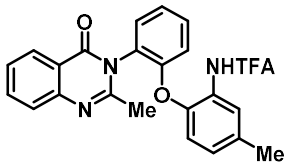
To a flame dried two dram vial equipped with a magnetic stir bar under argon atmosphere was added 2,2,2-trifluoro-*N*-(2-(3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)-5-methylphenyl)acetamide (**3a**) (47 mg, 0.1 mmol), DCM (1 mL) and pyridine (24 µL, 0.3 mmol).

The solution was cooled to 0 ºC and Tf_2O (25 µL, 0.15 mmol) was added dropwise over 5 minutes. The reaction stirred for 1 hour at 0 ºC before an additional portion of Tf_2O (10 µL, 0.06 mmol) was added dropwise. After stirring for an additional hour at 0 ºC, the reaction was quenched by addition of water (1 mL) and DCM (1 mL). The layers were separated and the organic layer was washed with water, dried over Na_2SO_4 and purified via flash chromatography (2% acetone in 1:1 DCM/hexanes) to yield aryl triflate **7'** as a white foam (50.5 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.97 (s, 1H), 7.81 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.28 – 7.23 (m, 1H), 7.09 – 6.98 (m, 2H), 6.86 (dd, *J* = 8.6, 1.1 Hz, 1H), 2.40 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.4, 156.0 (q, *J* = 38.6 Hz), 154.7, 153.3, 147.2, 145.8, 141.7, 136.9, 135.5, 131.7, 127.8, 127.5, 127.5, 127.4, 127.0, 125.1, 121.4, 112.0, 119.8, 118.4 (q, *J* = 320.8 Hz), 116.3, 115.7 (q, *J* = 288.1 Hz), 114.8, 23.0, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -73.6, -75.4.



2,2,2-trifluoro-*N*-(5-methyl-2-(2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)phenyl)acetamide (7)

To a flame dried two dram vial equipped with a magnetic stir bar under argon atmosphere was added aryl triflate (**4'**) (51 mg, 0.084 mmol) $PdCl_2(PPh_3)_2$ (6 mg, 0.008 mmol), dppp (5 mg, 0.013 mmol), anhydrous DMF (0.85 mL), Et_3N (0.12 mL, 0.84 mmol), and formic acid (0.019 mL, 0.5 mmol) before a Teflon lined screw cap was fitted. The vial was sealed with Teflon tape and heated to 60 ºC for 18 hours. The reaction mixture was then diluted with EtOAc, which was washed with 1 M $HCl_{(aq)}$, and water. The crude residue was purified via flash column chromatography using hexanes:EtOAc (7:3 v:v) to yield **7** as a white solid (14.5 mg, 38 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.00 (s, 1H), 7.79 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.48 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.20 (td, *J* = 7.6, 1.3 Hz, 1H), 7.00 (m, 2H), 6.81 (dd, *J* = 8.3, 1.3 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 155.9 (q, *J* = 38.3 Hz), 154.2, 152.9, 147.6, 141.9, 136.2, 135.1, 131.2, 129.5, 127.7, 127.4, 127.4, 127.0, 126.9, 126.5, 124.6, 123.6, 121.6, 120.5, 115.8 (q, *J* = 288.4 Hz), 115.3, 24.4, 21.3.

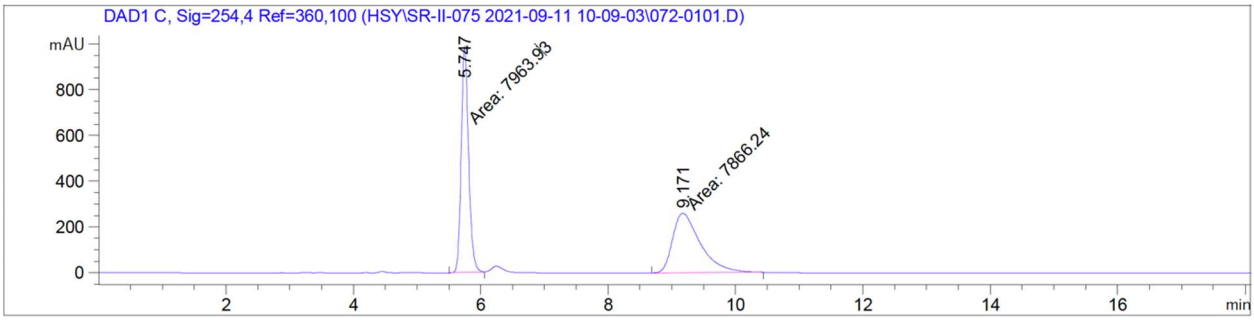
^{19}F NMR (376 MHz, $CDCl_3$) δ = -75.3.

IR (neat film, cm^{-1})3247, 3071, 2925, 1730, 1672, 1607, 1490, 1343, 1267, 1211, 1163.

HRMS (ESI) $[M+H]^+$ calculated 454.1379 m/z (found 454.1369 m/z for $C_{24}H_{19}F_3N_3O_3$).

HPLC (IA, ethanol/*n*-hexane = 15/85, flow rate = 1.0 mL/min, l = 254 nm) tR = 5.7 min (minor), 9.2 min (major)

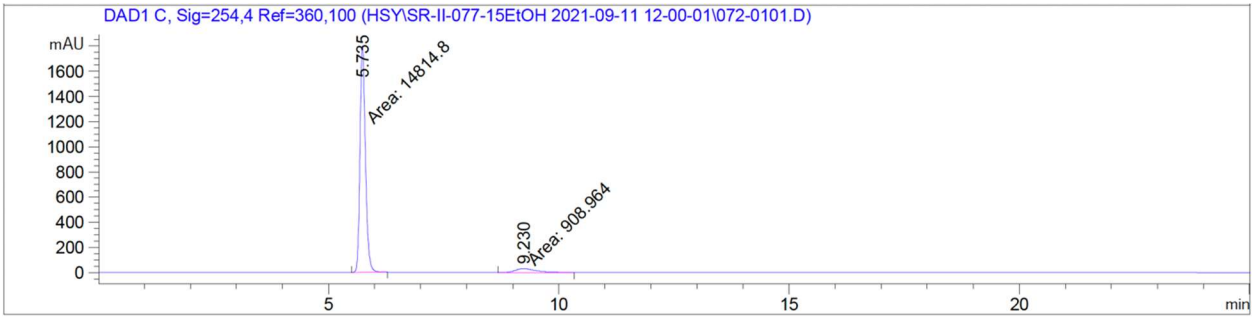
Racemic



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.747	MM	0.1343	7963.92871	988.29980	50.3085
2	9.171	MM	0.5044	7866.24170	259.93979	49.6915

Enantioenriched



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.735	MM	0.1368	1.48148e4	1804.30505	94.2192
2	9.230	MM	0.5138	908.96362	29.48417	5.7808

X-Ray Crystal Structure

Experimental

The crystal was grown via slow diffusion of hexanes into DCM. Note, gentle heating (35 ºC was needed to fully dissolve the product.)

Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007a-21048. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007a-21048 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 007a-21048 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

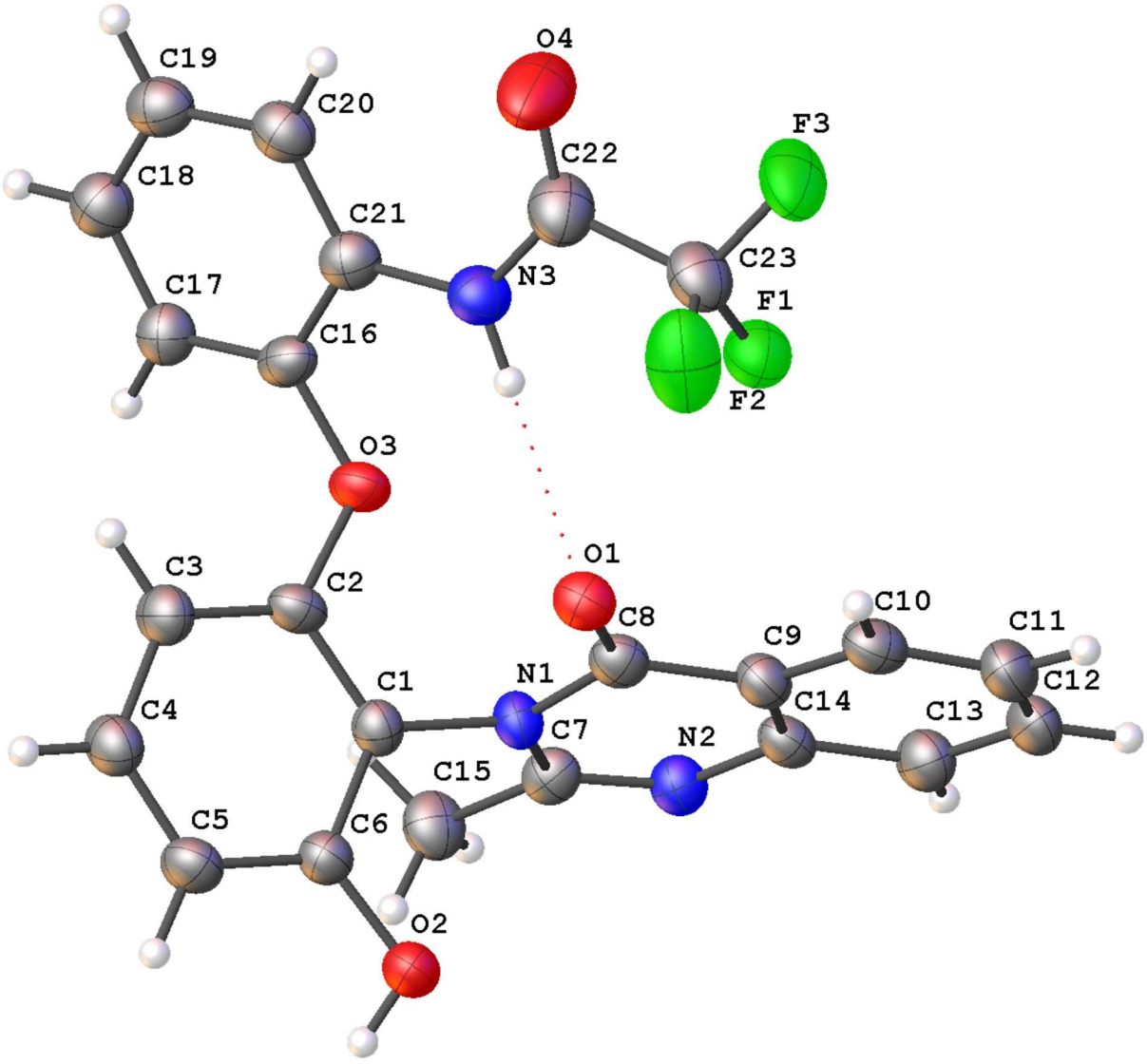


Figure 1. The complete numbering scheme of 007a-21048 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table 1. Crystal data and structure refinement for 007a-21048

Identification code	007a-21048	
Empirical formula	C23 H16 F3 N3 O4	
Formula weight	455.39	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.1852(3) Å	α= 90°.
	b = 11.0182(4) Å	β= 90°.
	c = 20.1500(7) Å	γ = 90°.
Volume	2039.27(12) $Å^3$	
Z	4	
Density (calculated)	1.483 Mg/m^3	
Absorption coefficient	1.041 mm^{-1}	
F(000)	936	
Crystal size	0.200 x 0.200 x 0.080 mm^3	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	4.388 to 66.601°.	
Index ranges	-10<=h<=10, -13<=k<=13, -23<=l<=23	
Reflections collected	73479	
Independent reflections	3604 [R(int) = 0.1814]	
Observed reflections (I > 2sigma(I))	2797	
Completeness to theta = 66.601°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.64670	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	3604 / 0 / 300	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1153	
R indices (all data)	R1 = 0.0731, wR2 = 0.1278	
Absolute structure parameter	0.05(15)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.188 and -0.228 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 007a-21048. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	6272(3)	3730(3)	5794(1)	47(1)
F(2)	7136(4)	5385(3)	5406(2)	71(1)
F(3)	8148(3)	3675(3)	5174(2)	62(1)
O(1)	3971(4)	5403(3)	6141(2)	34(1)
O(2)	457(4)	6946(3)	7002(2)	38(1)
O(3)	1789(4)	4510(3)	5202(2)	34(1)
O(4)	6507(5)	3868(5)	4113(2)	77(2)
N(1)	1718(4)	4908(3)	6527(2)	28(1)
N(2)	1368(4)	3519(4)	7402(2)	33(1)
N(3)	4504(5)	4281(4)	4753(2)	38(1)
C(1)	1084(5)	5770(4)	6076(2)	30(1)
C(2)	1150(5)	5594(4)	5398(2)	31(1)
C(3)	616(6)	6457(4)	4965(2)	36(1)
C(4)	-14(6)	7500(5)	5228(2)	38(1)
C(5)	-104(6)	7686(4)	5901(2)	37(1)
C(6)	463(5)	6828(4)	6334(2)	31(1)
C(7)	842(5)	4207(4)	6938(2)	32(1)
C(8)	3232(5)	4857(4)	6552(2)	32(1)
C(9)	3820(5)	4150(4)	7108(2)	32(1)
C(10)	5309(5)	4181(5)	7250(2)	38(1)
C(11)	5822(6)	3551(5)	7785(2)	42(1)
C(12)	4883(6)	2852(5)	8170(3)	39(1)
C(13)	3423(6)	2826(4)	8037(3)	39(1)
C(14)	2855(5)	3504(4)	7504(2)	32(1)
C(15)	-747(5)	4265(5)	6829(3)	40(1)
C(16)	1935(6)	4276(4)	4526(2)	34(1)
C(17)	745(6)	4095(4)	4122(2)	35(1)
C(18)	961(6)	3813(4)	3459(3)	40(1)
C(19)	2359(6)	3730(5)	3217(3)	40(1)
C(20)	3567(6)	3892(4)	3619(3)	38(1)
C(21)	3358(6)	4153(4)	4289(2)	35(1)

C(22)	5934(6)	4099(5)	4635(3)	48(1)
C(23)	6867(6)	4215(5)	5258(3)	45(1)

Table 3. Bond lengths [Å] and angles [°] for 007a-21048.

F(1)-C(23)	1.323(6)
F(2)-C(23)	1.346(7)
F(3)-C(23)	1.329(6)
O(1)-C(8)	1.228(5)
O(2)-C(6)	1.353(5)
O(2)-H(2)	0.8400
O(3)-C(2)	1.389(5)
O(3)-C(16)	1.392(5)
O(4)-C(22)	1.203(7)
N(1)-C(7)	1.389(6)
N(1)-C(8)	1.393(6)
N(1)-C(1)	1.438(6)
N(2)-C(7)	1.296(6)
N(2)-C(14)	1.381(6)
N(3)-C(22)	1.349(7)
N(3)-C(21)	1.414(7)
N(3)-H(3)	0.8800
C(1)-C(2)	1.381(6)
C(1)-C(6)	1.398(6)
C(2)-C(3)	1.381(7)
C(3)-C(4)	1.392(7)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.373(7)
C(4)-H(4)	0.9500
C(5)-C(6)	1.388(7)
C(5)-H(5)	0.9500
C(7)-C(15)	1.477(7)
C(8)-C(9)	1.466(6)
C(9)-C(14)	1.390(7)
C(9)-C(10)	1.397(7)
C(10)-C(11)	1.366(7)
C(10)-H(10)	0.9500
C(11)-C(12)	1.392(8)
C(11)-H(11)	0.9500

C(12)-C(13)	1.367(8)
C(12)-H(12)	0.9500
C(13)-C(14)	1.408(7)
C(13)-H(13)	0.9500
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-C(17)	1.376(7)
C(16)-C(21)	1.398(7)
C(17)-C(18)	1.388(7)
C(17)-H(17)	0.9500
C(18)-C(19)	1.376(7)
C(18)-H(18)	0.9500
C(19)-C(20)	1.386(7)
C(19)-H(19)	0.9500
C(20)-C(21)	1.394(7)
C(20)-H(20)	0.9500
C(22)-C(23)	1.525(8)

C(6)-O(2)-H(2)	109.5
C(2)-O(3)-C(16)	118.6(4)
C(7)-N(1)-C(8)	122.3(4)
C(7)-N(1)-C(1)	120.7(4)
C(8)-N(1)-C(1)	117.0(4)
C(7)-N(2)-C(14)	118.9(4)
C(22)-N(3)-C(21)	126.4(4)
C(22)-N(3)-H(3)	116.8
C(21)-N(3)-H(3)	116.8
C(2)-C(1)-C(6)	120.1(4)
C(2)-C(1)-N(1)	121.1(4)
C(6)-C(1)-N(1)	118.8(4)
C(3)-C(2)-C(1)	120.9(4)
C(3)-C(2)-O(3)	124.2(4)
C(1)-C(2)-O(3)	114.9(4)
C(2)-C(3)-C(4)	118.3(4)
C(2)-C(3)-H(3A)	120.8

C(4)-C(3)-H(3A)	120.8
C(5)-C(4)-C(3)	121.7(5)
C(5)-C(4)-H(4)	119.2
C(3)-C(4)-H(4)	119.2
C(4)-C(5)-C(6)	119.8(5)
C(4)-C(5)-H(5)	120.1
C(6)-C(5)-H(5)	120.1
O(2)-C(6)-C(5)	124.0(4)
O(2)-C(6)-C(1)	116.9(4)
C(5)-C(6)-C(1)	119.2(4)
N(2)-C(7)-N(1)	122.6(4)
N(2)-C(7)-C(15)	120.1(4)
N(1)-C(7)-C(15)	117.3(4)
O(1)-C(8)-N(1)	120.5(4)
O(1)-C(8)-C(9)	124.8(4)
N(1)-C(8)-C(9)	114.7(4)
C(14)-C(9)-C(10)	121.2(4)
C(14)-C(9)-C(8)	118.4(4)
C(10)-C(9)-C(8)	120.3(4)
C(11)-C(10)-C(9)	119.2(5)
C(11)-C(10)-H(10)	120.4
C(9)-C(10)-H(10)	120.4
C(10)-C(11)-C(12)	120.5(5)
C(10)-C(11)-H(11)	119.8
C(12)-C(11)-H(11)	119.8
C(13)-C(12)-C(11)	120.6(5)
C(13)-C(12)-H(12)	119.7
C(11)-C(12)-H(12)	119.7
C(12)-C(13)-C(14)	120.2(5)
C(12)-C(13)-H(13)	119.9
C(14)-C(13)-H(13)	119.9
N(2)-C(14)-C(9)	122.6(4)
N(2)-C(14)-C(13)	119.1(4)
C(9)-C(14)-C(13)	118.2(4)
C(7)-C(15)-H(15A)	109.5
C(7)-C(15)-H(15B)	109.5

H(15A)-C(15)-H(15B)	109.5
C(7)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(17)-C(16)-O(3)	121.8(4)
C(17)-C(16)-C(21)	121.8(4)
O(3)-C(16)-C(21)	116.2(4)
C(16)-C(17)-C(18)	119.2(5)
C(16)-C(17)-H(17)	120.4
C(18)-C(17)-H(17)	120.4
C(19)-C(18)-C(17)	119.3(5)
C(19)-C(18)-H(18)	120.3
C(17)-C(18)-H(18)	120.3
C(18)-C(19)-C(20)	122.1(5)
C(18)-C(19)-H(19)	119.0
C(20)-C(19)-H(19)	119.0
C(19)-C(20)-C(21)	118.9(5)
C(19)-C(20)-H(20)	120.6
C(21)-C(20)-H(20)	120.6
C(20)-C(21)-C(16)	118.6(5)
C(20)-C(21)-N(3)	123.9(5)
C(16)-C(21)-N(3)	117.5(4)
O(4)-C(22)-N(3)	127.6(5)
O(4)-C(22)-C(23)	119.5(5)
N(3)-C(22)-C(23)	112.9(5)
F(1)-C(23)-F(3)	106.9(4)
F(1)-C(23)-F(2)	106.4(5)
F(3)-C(23)-F(2)	107.1(5)
F(1)-C(23)-C(22)	114.0(4)
F(3)-C(23)-C(22)	110.7(5)
F(2)-C(23)-C(22)	111.4(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 007a-21048. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	42(2)	54(2)	47(2)	3(1)	4(1)	3(1)
F(2)	68(2)	50(2)	94(3)	11(2)	-25(2)	-13(2)
F(3)	34(2)	94(3)	58(2)	14(2)	5(2)	12(2)
O(1)	33(2)	32(2)	38(2)	1(1)	4(2)	-2(2)
O(2)	40(2)	39(2)	35(2)	-4(2)	-2(2)	10(2)
O(3)	41(2)	28(2)	34(2)	-5(1)	3(2)	7(2)
O(4)	43(2)	140(5)	49(3)	-3(3)	9(2)	15(3)
N(1)	25(2)	29(2)	32(2)	5(2)	0(2)	1(2)
N(2)	32(2)	30(2)	37(2)	2(2)	-1(2)	-2(2)
N(3)	34(2)	40(2)	38(2)	-1(2)	3(2)	0(2)
C(1)	30(3)	27(2)	32(2)	2(2)	-2(2)	1(2)
C(2)	31(3)	27(2)	36(2)	-6(2)	2(2)	3(2)
C(3)	42(3)	33(3)	34(2)	5(2)	1(2)	4(2)
C(4)	40(3)	35(3)	39(3)	5(2)	1(2)	5(2)
C(5)	42(3)	30(3)	40(3)	-3(2)	1(2)	5(2)
C(6)	31(3)	30(2)	31(2)	-1(2)	0(2)	2(2)
C(7)	37(3)	26(2)	32(2)	0(2)	0(2)	-3(2)
C(8)	35(3)	27(2)	35(3)	-4(2)	0(2)	0(2)
C(9)	30(3)	32(3)	36(3)	-1(2)	0(2)	4(2)
C(10)	32(3)	38(3)	42(3)	-6(2)	4(2)	2(2)
C(11)	38(3)	46(3)	43(3)	-3(2)	-4(2)	11(3)
C(12)	45(3)	34(3)	39(3)	0(2)	-4(2)	12(2)
C(13)	43(3)	34(3)	39(3)	3(2)	-1(2)	5(2)
C(14)	29(3)	28(2)	38(2)	-4(2)	1(2)	4(2)
C(15)	30(3)	44(3)	46(3)	5(2)	1(2)	-3(2)
C(16)	46(3)	28(2)	27(2)	-1(2)	2(2)	4(2)
C(17)	36(3)	33(3)	37(3)	2(2)	-2(2)	-2(2)
C(18)	43(3)	37(3)	41(3)	2(2)	-1(2)	0(2)
C(19)	48(3)	35(3)	39(3)	0(2)	5(2)	1(2)
C(20)	38(3)	33(3)	43(3)	2(2)	4(2)	1(2)
C(21)	38(3)	31(2)	36(3)	-1(2)	1(2)	-2(2)

C(22)	39(3)	58(4)	48(3)	8(3)	2(3)	-1(3)
C(23)	34(3)	49(3)	52(3)	6(3)	4(3)	2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 007a-21048.

	x	y	z	U(eq)
H(2)	-267	7361	7118	57
H(3)	4261	4502	5158	45
H(3A)	677	6342	4498	44
H(4)	-392	8098	4936	46
H(5)	-553	8399	6069	45
H(10)	5956	4634	6978	45
H(11)	6826	3589	7895	51
H(12)	5259	2389	8529	47
H(13)	2792	2350	8304	47
H(15A)	-1108	5066	6960	60
H(15B)	-1228	3639	7096	60
H(15C)	-958	4128	6358	60
H(17)	-212	4162	4297	43
H(18)	153	3678	3174	48
H(19)	2500	3557	2759	49
H(20)	4522	3827	3441	46

Table 6. Torsion angles [°] for 007a-21048.

C(7)-N(1)-C(1)-C(2)	-111.8(5)
C(8)-N(1)-C(1)-C(2)	71.1(6)
C(7)-N(1)-C(1)-C(6)	71.5(6)
C(8)-N(1)-C(1)-C(6)	-105.6(5)
C(6)-C(1)-C(2)-C(3)	0.4(7)
N(1)-C(1)-C(2)-C(3)	-176.2(4)
C(6)-C(1)-C(2)-O(3)	-179.9(4)
N(1)-C(1)-C(2)-O(3)	3.4(6)
C(16)-O(3)-C(2)-C(3)	1.4(7)
C(16)-O(3)-C(2)-C(1)	-178.2(4)
C(1)-C(2)-C(3)-C(4)	-1.1(7)
O(3)-C(2)-C(3)-C(4)	179.3(4)
C(2)-C(3)-C(4)-C(5)	0.4(8)
C(3)-C(4)-C(5)-C(6)	1.0(8)
C(4)-C(5)-C(6)-O(2)	178.3(5)
C(4)-C(5)-C(6)-C(1)	-1.7(7)
C(2)-C(1)-C(6)-O(2)	-179.0(4)
N(1)-C(1)-C(6)-O(2)	-2.3(6)
C(2)-C(1)-C(6)-C(5)	1.0(7)
N(1)-C(1)-C(6)-C(5)	177.7(4)
C(14)-N(2)-C(7)-N(1)	1.7(7)
C(14)-N(2)-C(7)-C(15)	-178.4(4)
C(8)-N(1)-C(7)-N(2)	4.7(7)
C(1)-N(1)-C(7)-N(2)	-172.2(4)
C(8)-N(1)-C(7)-C(15)	-175.2(4)
C(1)-N(1)-C(7)-C(15)	8.0(6)
C(7)-N(1)-C(8)-O(1)	173.2(4)
C(1)-N(1)-C(8)-O(1)	-9.8(6)
C(7)-N(1)-C(8)-C(9)	-8.7(6)
C(1)-N(1)-C(8)-C(9)	168.3(4)
O(1)-C(8)-C(9)-C(14)	-175.1(5)
N(1)-C(8)-C(9)-C(14)	6.8(6)
O(1)-C(8)-C(9)-C(10)	8.0(7)
N(1)-C(8)-C(9)-C(10)	-170.1(4)

C(14)-C(9)-C(10)-C(11)	0.8(7)
C(8)-C(9)-C(10)-C(11)	177.6(4)
C(9)-C(10)-C(11)-C(12)	2.2(7)
C(10)-C(11)-C(12)-C(13)	-2.8(8)
C(11)-C(12)-C(13)-C(14)	0.3(8)
C(7)-N(2)-C(14)-C(9)	-3.4(7)
C(7)-N(2)-C(14)-C(13)	175.5(4)
C(10)-C(9)-C(14)-N(2)	175.7(5)
C(8)-C(9)-C(14)-N(2)	-1.1(7)
C(10)-C(9)-C(14)-C(13)	-3.2(7)
C(8)-C(9)-C(14)-C(13)	180.0(4)
C(12)-C(13)-C(14)-N(2)	-176.3(5)
C(12)-C(13)-C(14)-C(9)	2.6(7)
C(2)-O(3)-C(16)-C(17)	-66.7(6)
C(2)-O(3)-C(16)-C(21)	117.5(5)
O(3)-C(16)-C(17)-C(18)	-177.3(4)
C(21)-C(16)-C(17)-C(18)	-1.7(7)
C(16)-C(17)-C(18)-C(19)	-0.5(7)
C(17)-C(18)-C(19)-C(20)	1.5(8)
C(18)-C(19)-C(20)-C(21)	-0.3(8)
C(19)-C(20)-C(21)-C(16)	-1.8(7)
C(19)-C(20)-C(21)-N(3)	177.0(5)
C(17)-C(16)-C(21)-C(20)	2.9(7)
O(3)-C(16)-C(21)-C(20)	178.7(4)
C(17)-C(16)-C(21)-N(3)	-176.0(4)
O(3)-C(16)-C(21)-N(3)	-0.2(6)
C(22)-N(3)-C(21)-C(20)	-4.6(8)
C(22)-N(3)-C(21)-C(16)	174.3(5)
C(21)-N(3)-C(22)-O(4)	4.8(10)
C(21)-N(3)-C(22)-C(23)	-175.2(4)
O(4)-C(22)-C(23)-F(1)	-139.9(6)
N(3)-C(22)-C(23)-F(1)	40.1(7)
O(4)-C(22)-C(23)-F(3)	-19.4(8)
N(3)-C(22)-C(23)-F(3)	160.6(5)
O(4)-C(22)-C(23)-F(2)	99.6(7)
N(3)-C(22)-C(23)-F(2)	-80.3(6)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 007a-21048 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...N(2)#1	0.84	1.89	2.693(5)	158.7
N(3)-H(3)...O(1)	0.88	2.23	3.098(5)	167.4

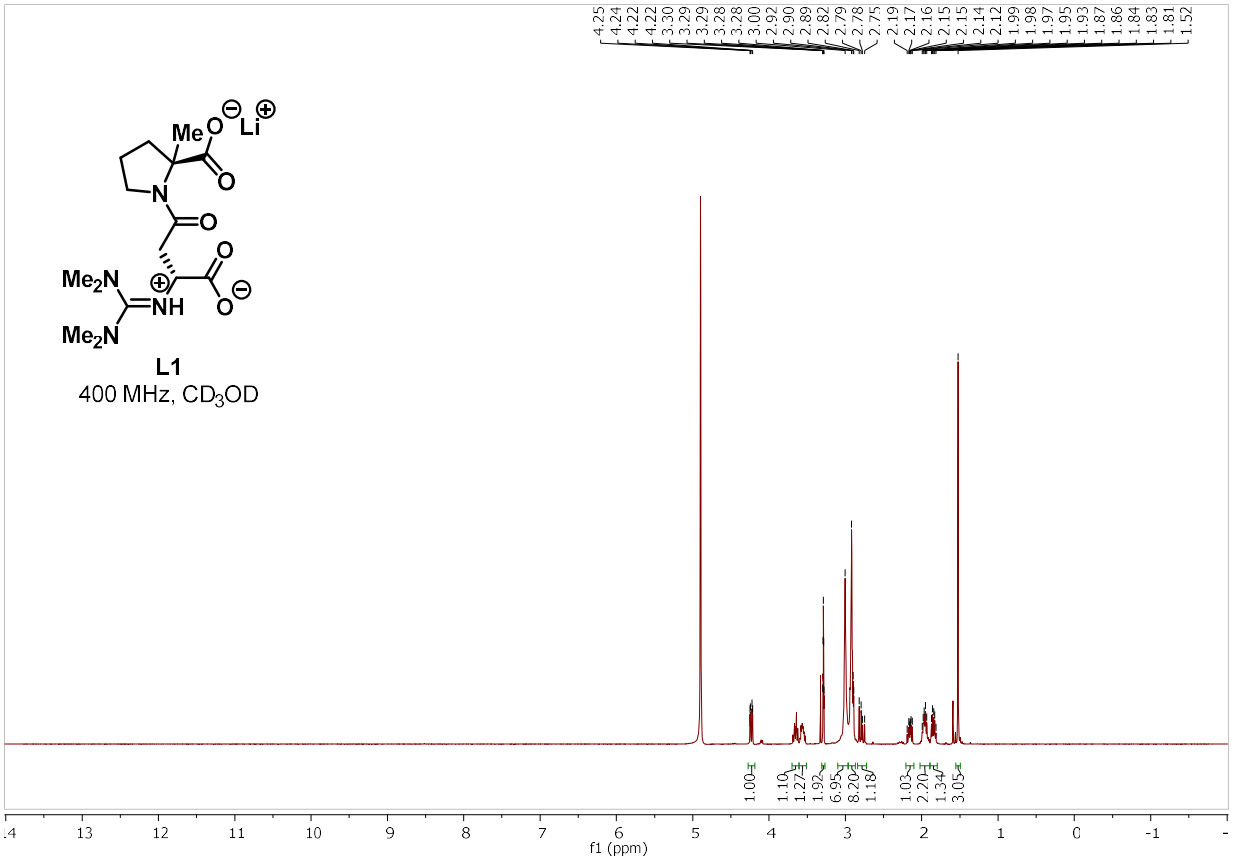
Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+3/2

References:

1. Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. Enantioselective Synthesis of 3 Arylquinazolin-4(3H)-ones via Peptide-Catalyzed Atroposelective Bromination. *J. Am. Chem. Soc.* **2015**, *137*, 12369-12377.

2. Schroeder, C. E.; Neuenswander, S. A.; Yao, T.; Aubé, J.; Golden, J. E. One-pot, regiospecific assembly of (E)-benzamidines from δ- and γ-amino acids via an intramolecular aminoquinazolinone rearrangement. *Organic & Biomolecular Chemistry* **2016**, *14*, 3950-3955.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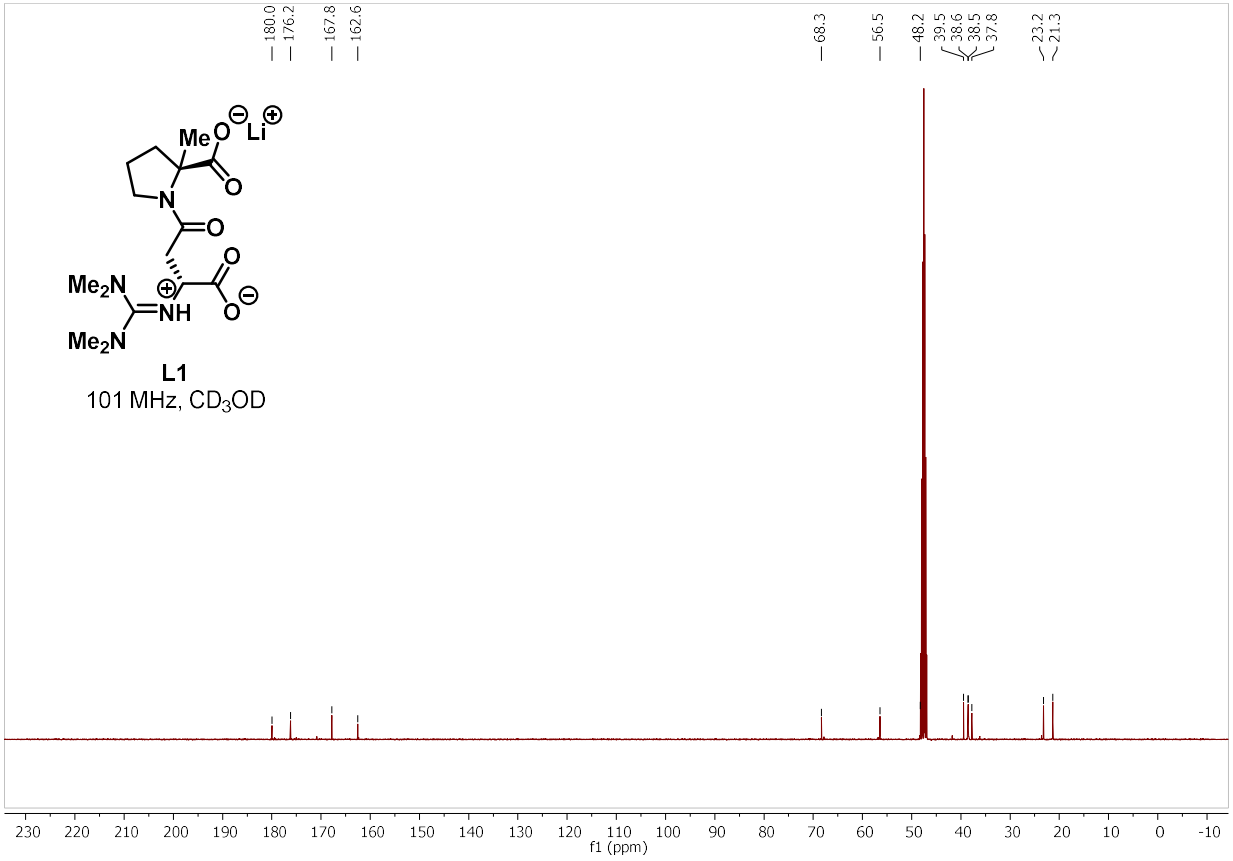
f1 (ppm)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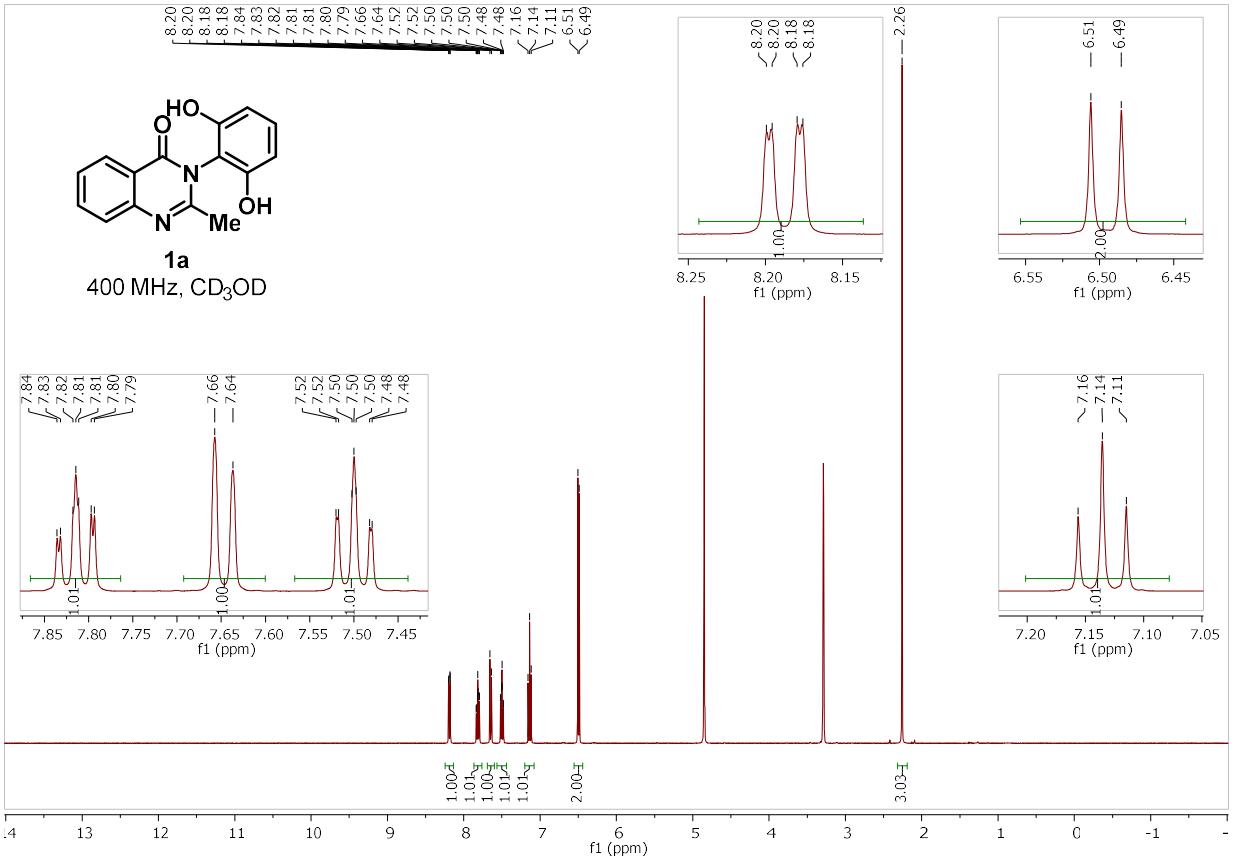
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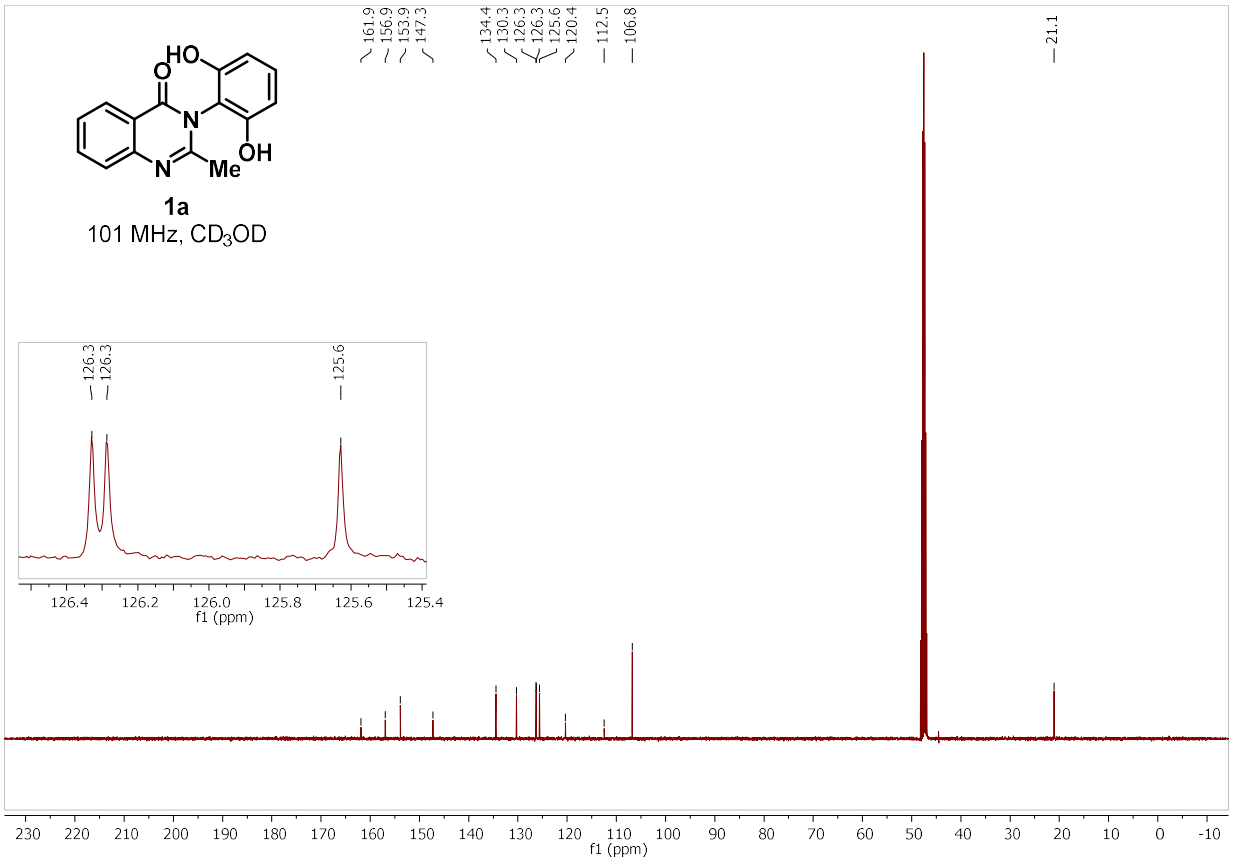
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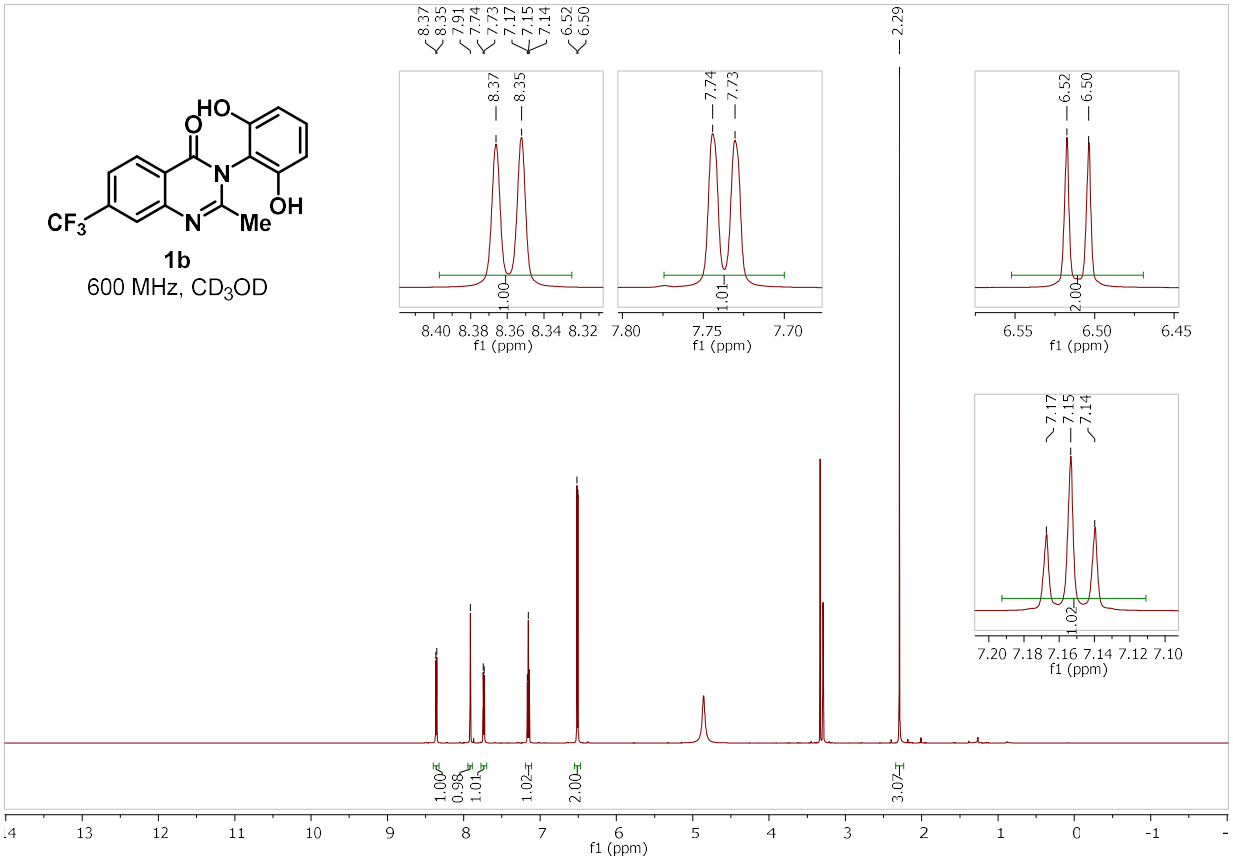
f1 (ppm)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N
Me
OH
CF3
1b
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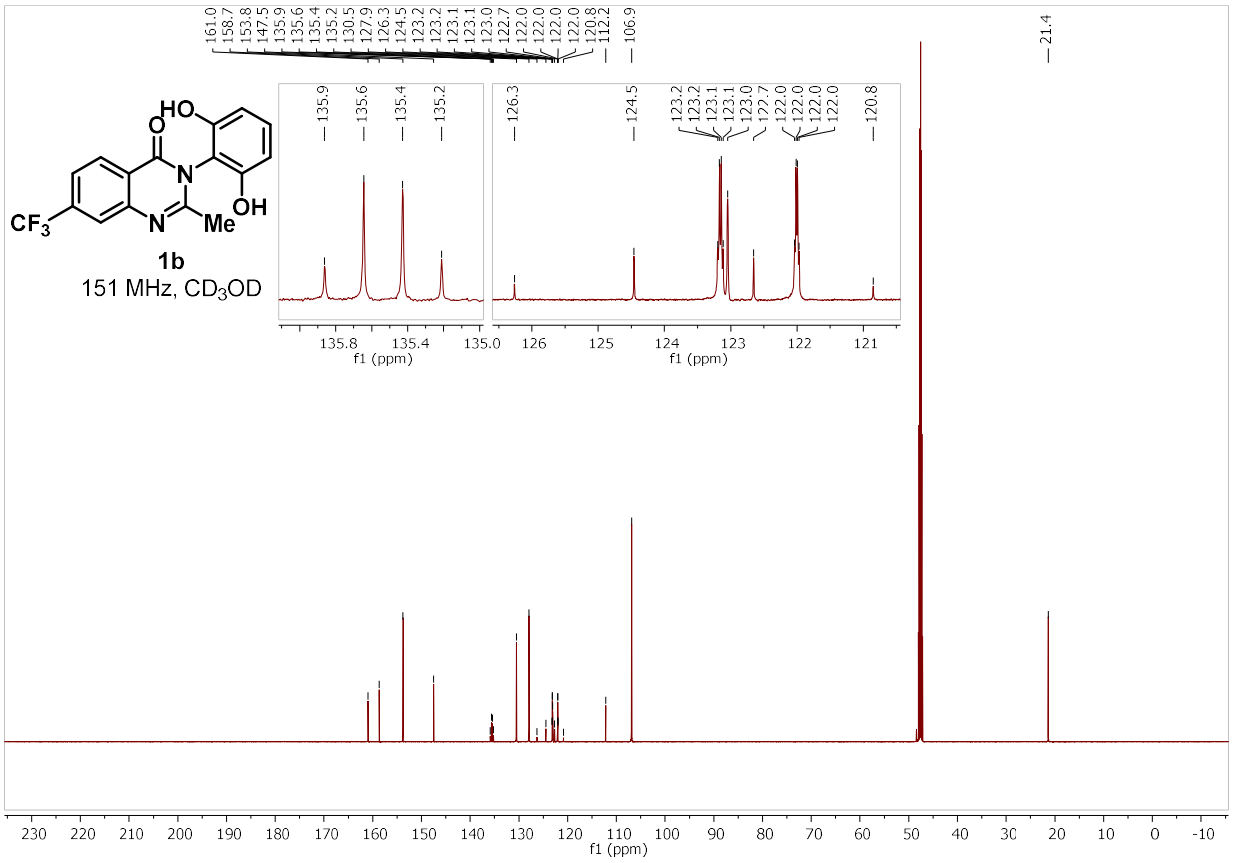
7.14
6.52
6.50
2.29
f1 (ppm)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Me
OH
CF3
1b
151 MHz, CD3OD
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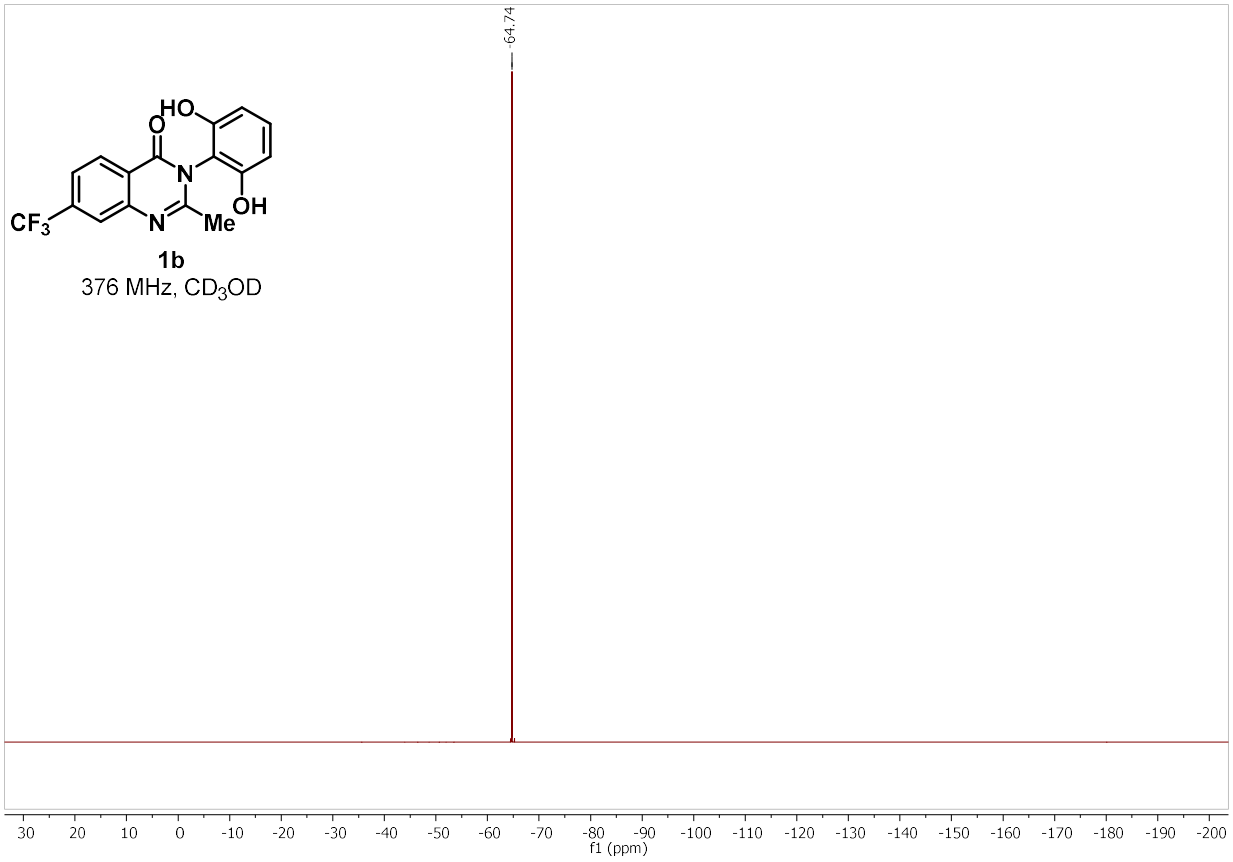
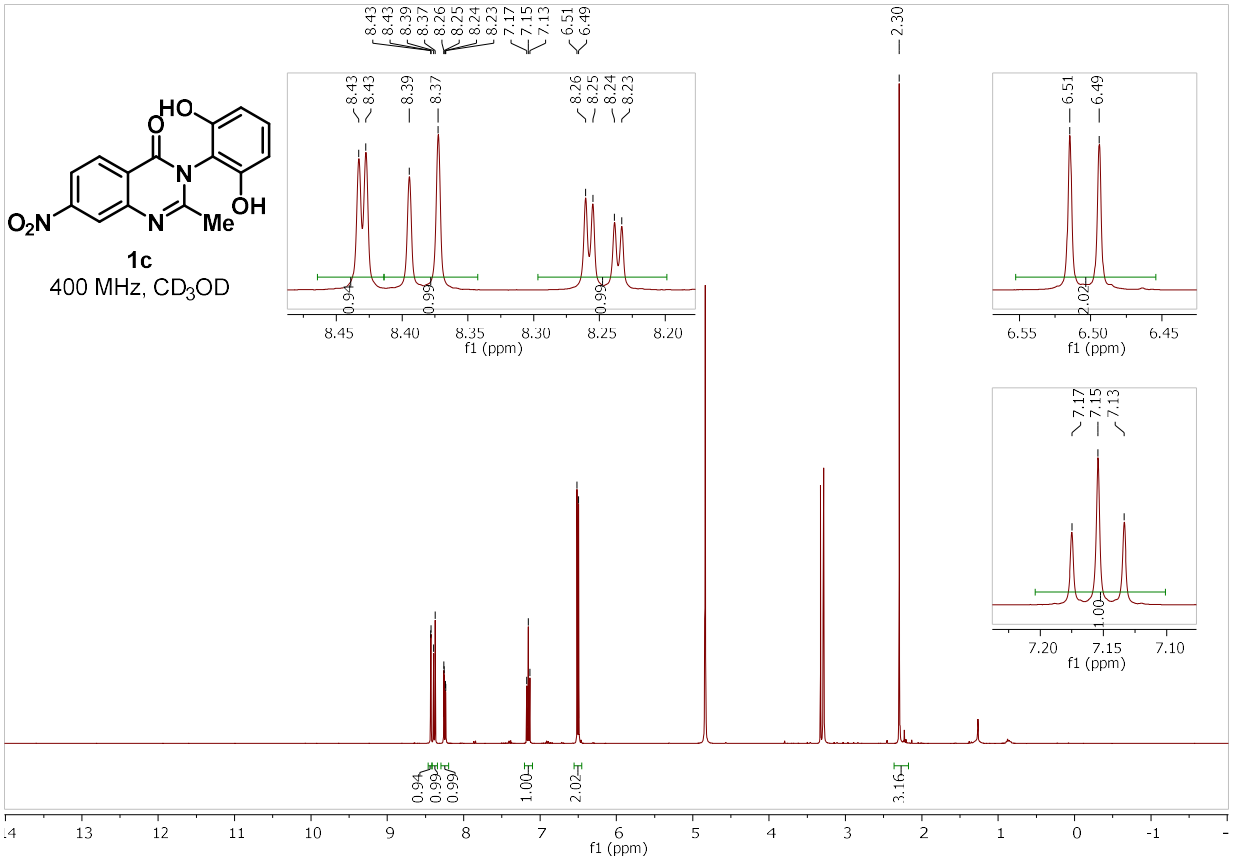
135.9
135.6
135.4
135.2
130.5
127.9
126.3
124.5
123.2
123.1
123.0
122.7
122.0
120.8
112.2
106.9
21.4
f1 (ppm)



1b

376 MHz, CD_3OD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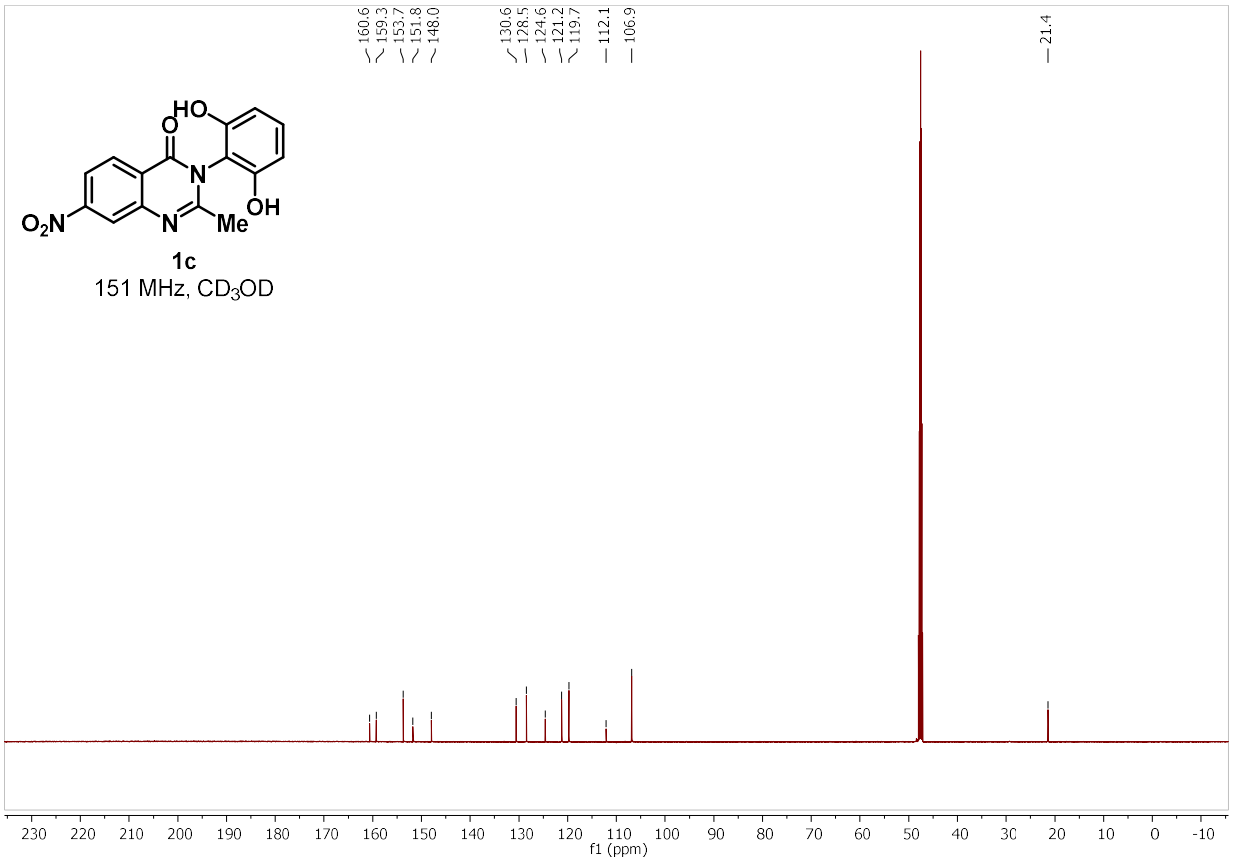
f1 (ppm)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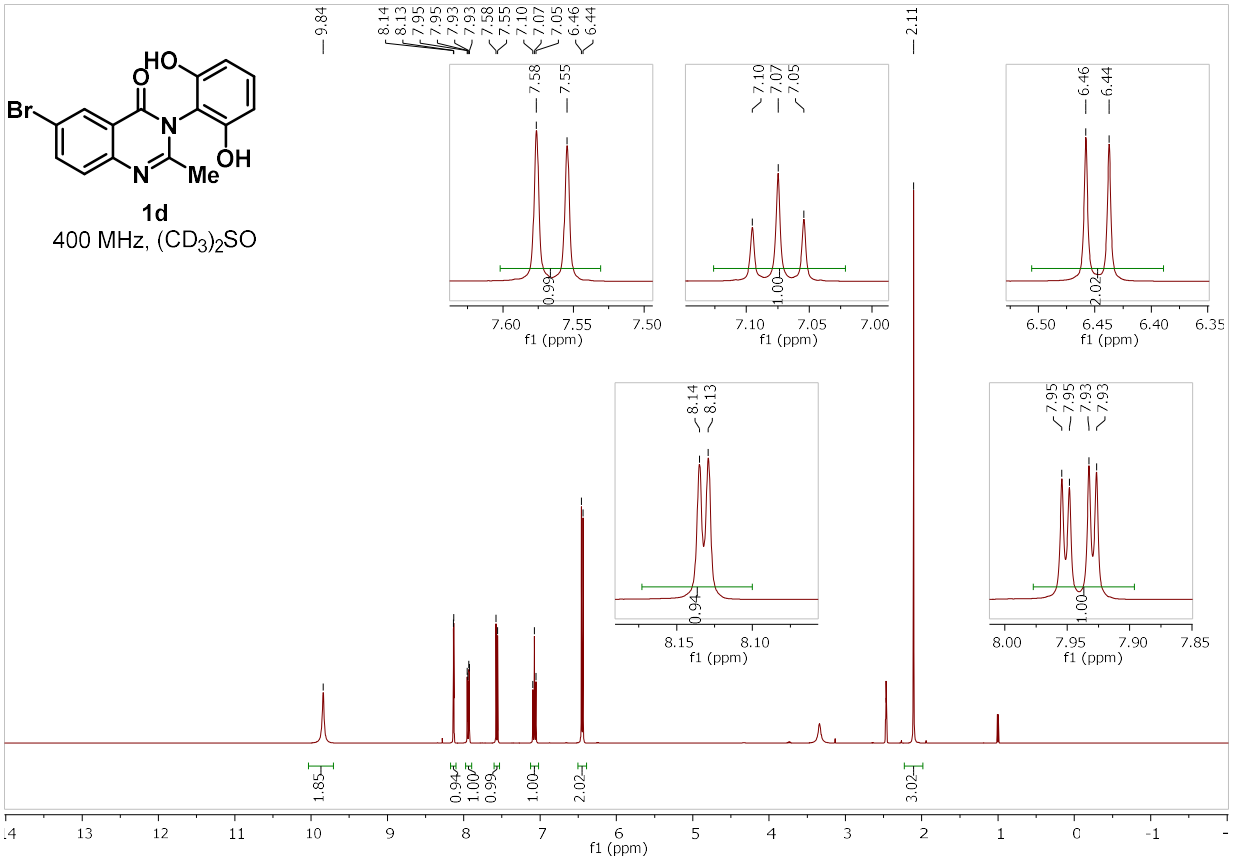
f1 (ppm)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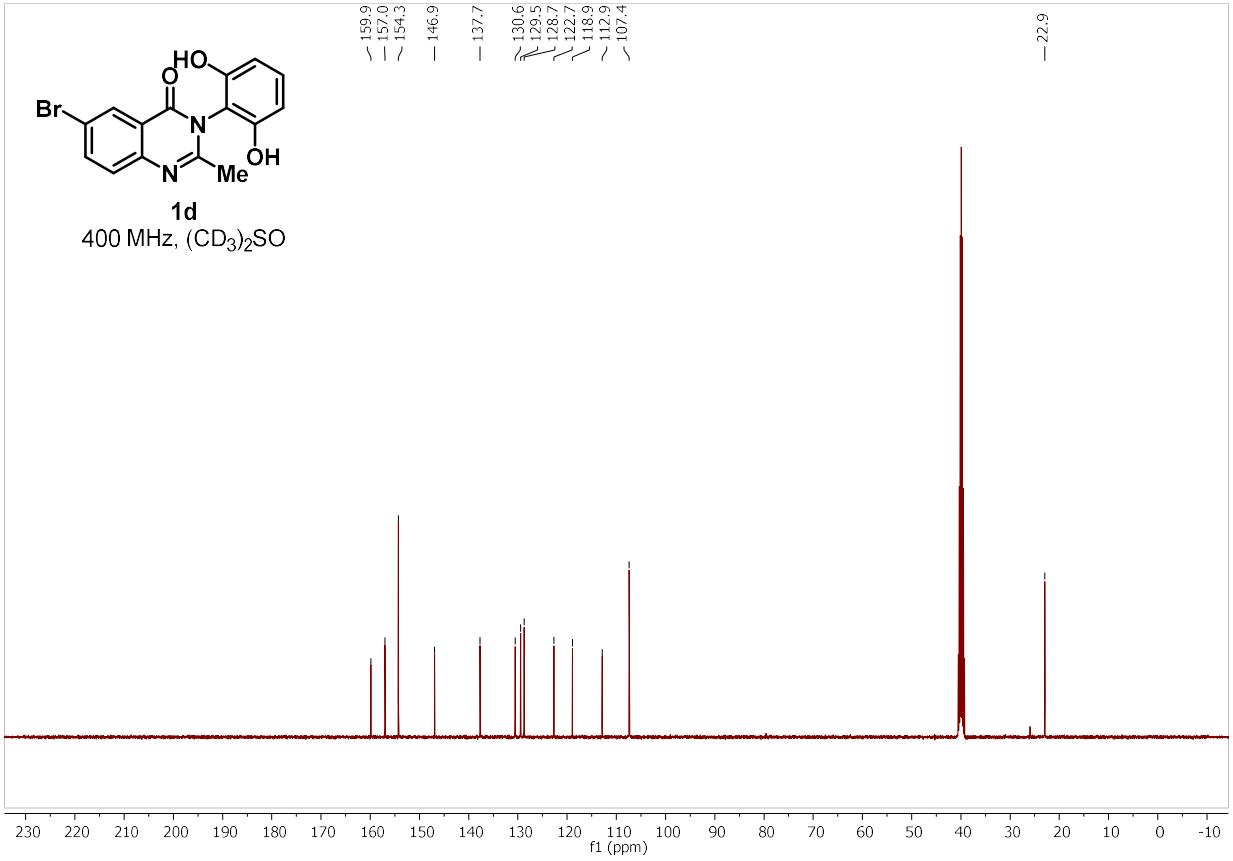
Br
N
OH
N
Me
1d
400 MHz, (CD3)2SO
f1 (ppm)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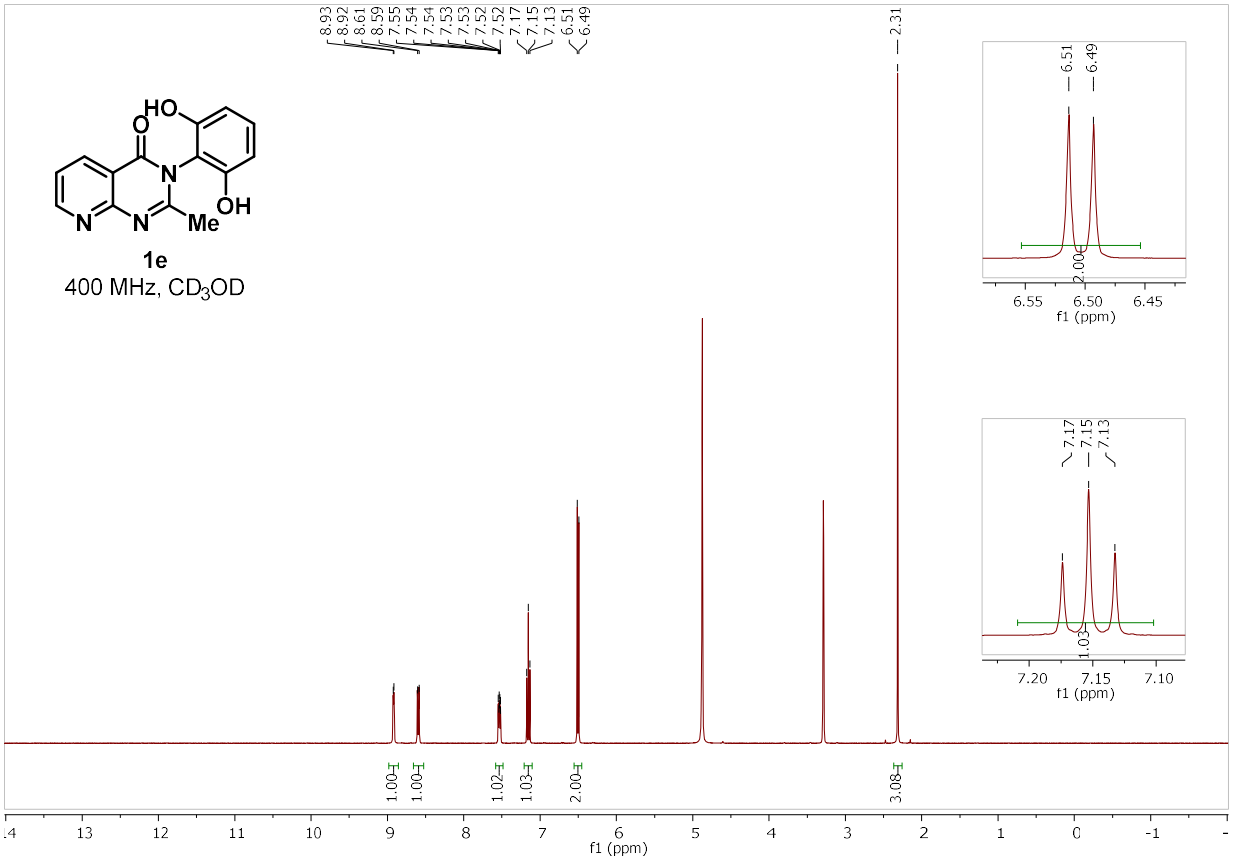
Br
N
OH
N
Me
1d
400 MHz, (CD3)2SO
f1 (ppm)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7.54
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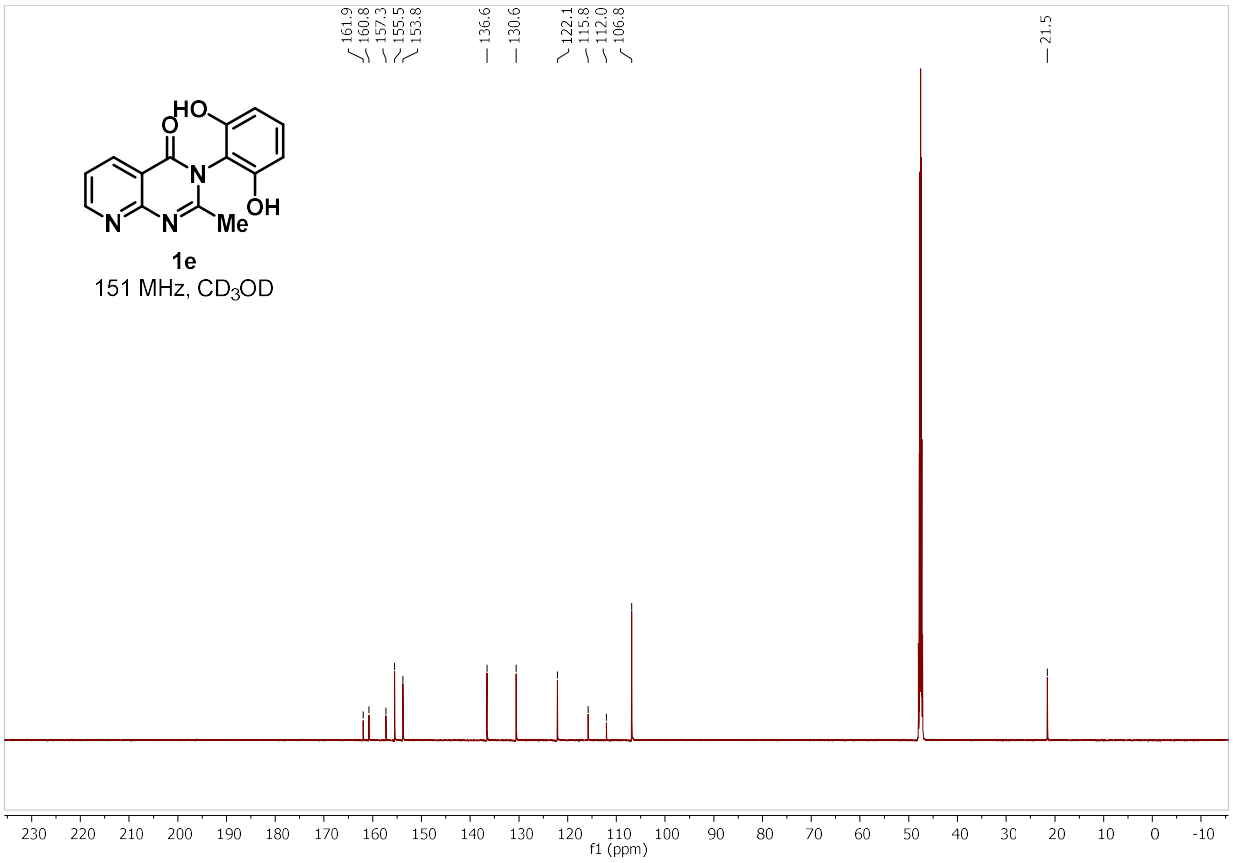
7.53
7.53
7.52
7.52
7.17
7.15
7.13
6.51
6.49
2.31
1.00
1.00
1.02
1.03
2.00
3.08
f1 (ppm)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151 MHz, CD3OD
161.9
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157.3
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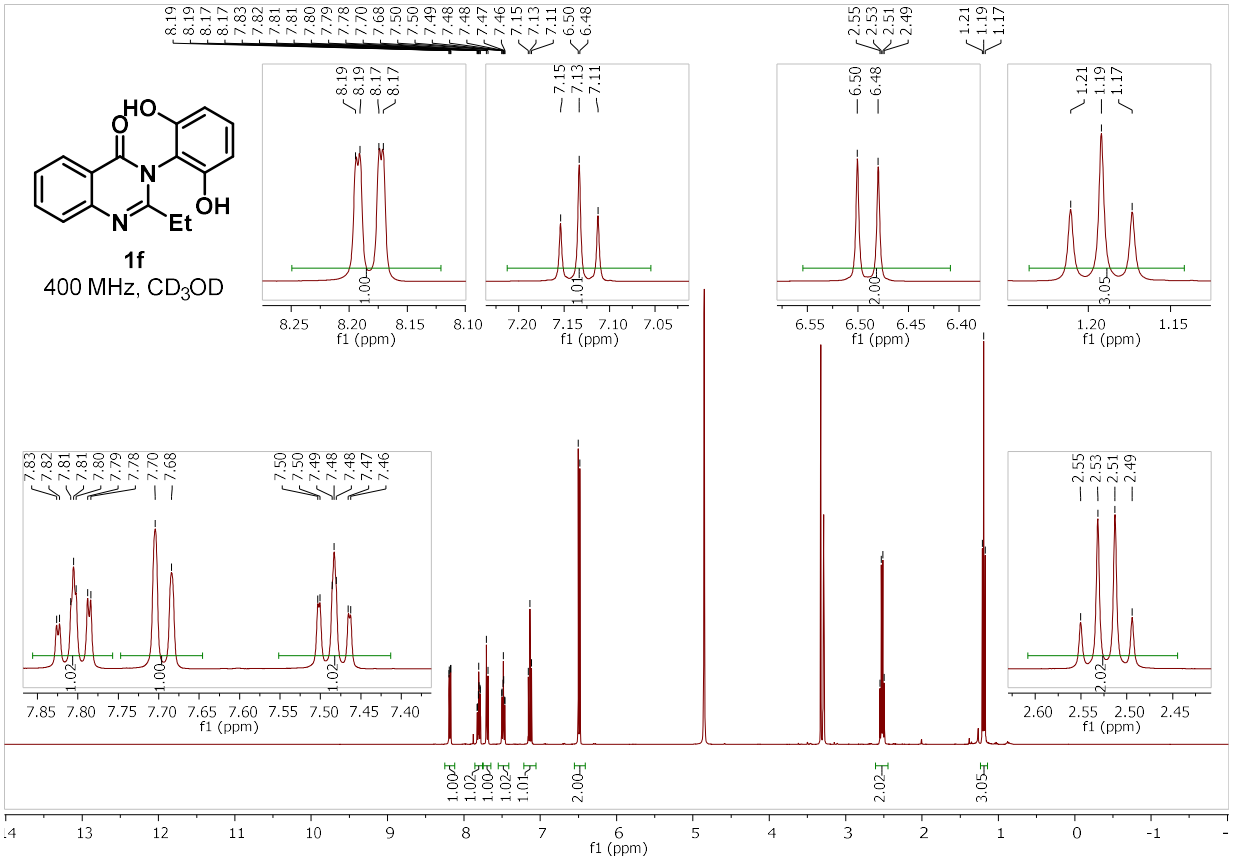
153.8
136.6
130.6
122.1
115.8
112.0
106.8
21.5
f1 (ppm)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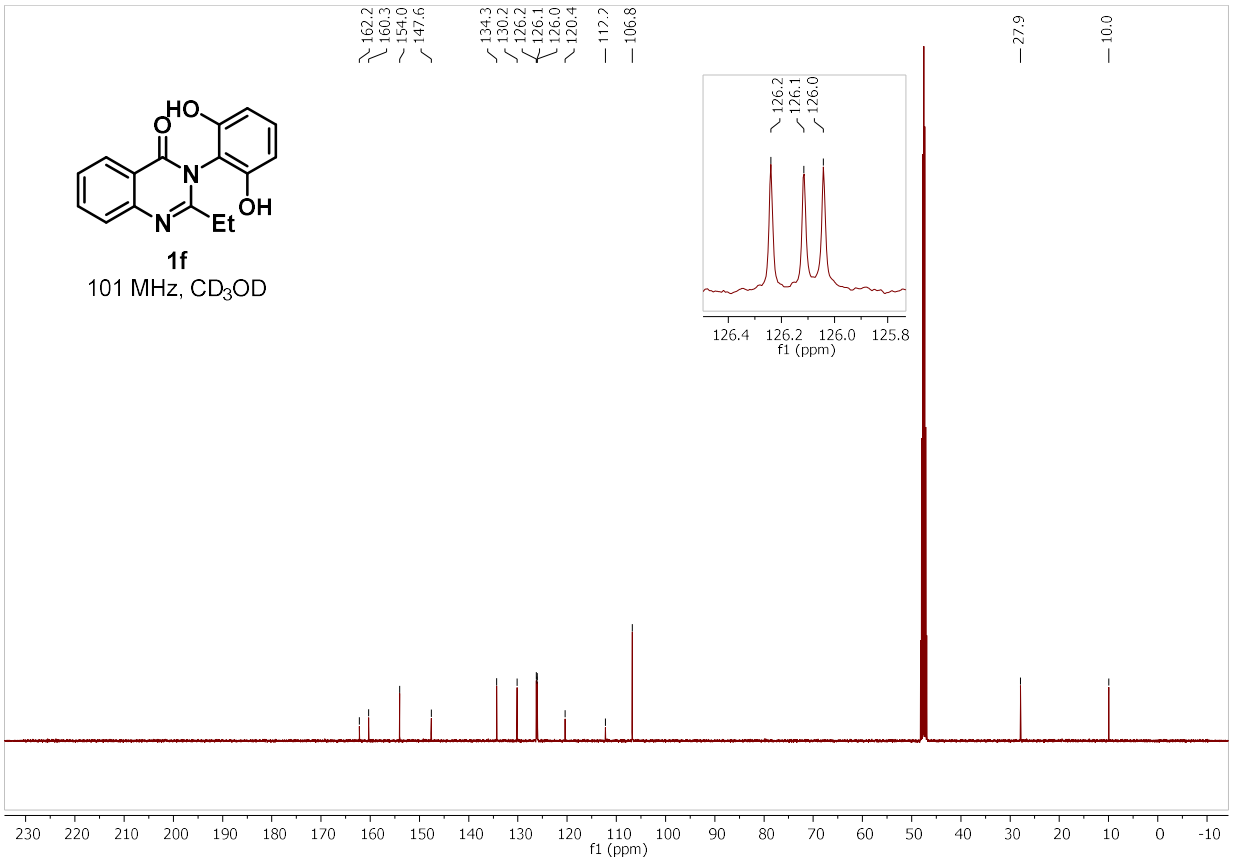
f1 (ppm)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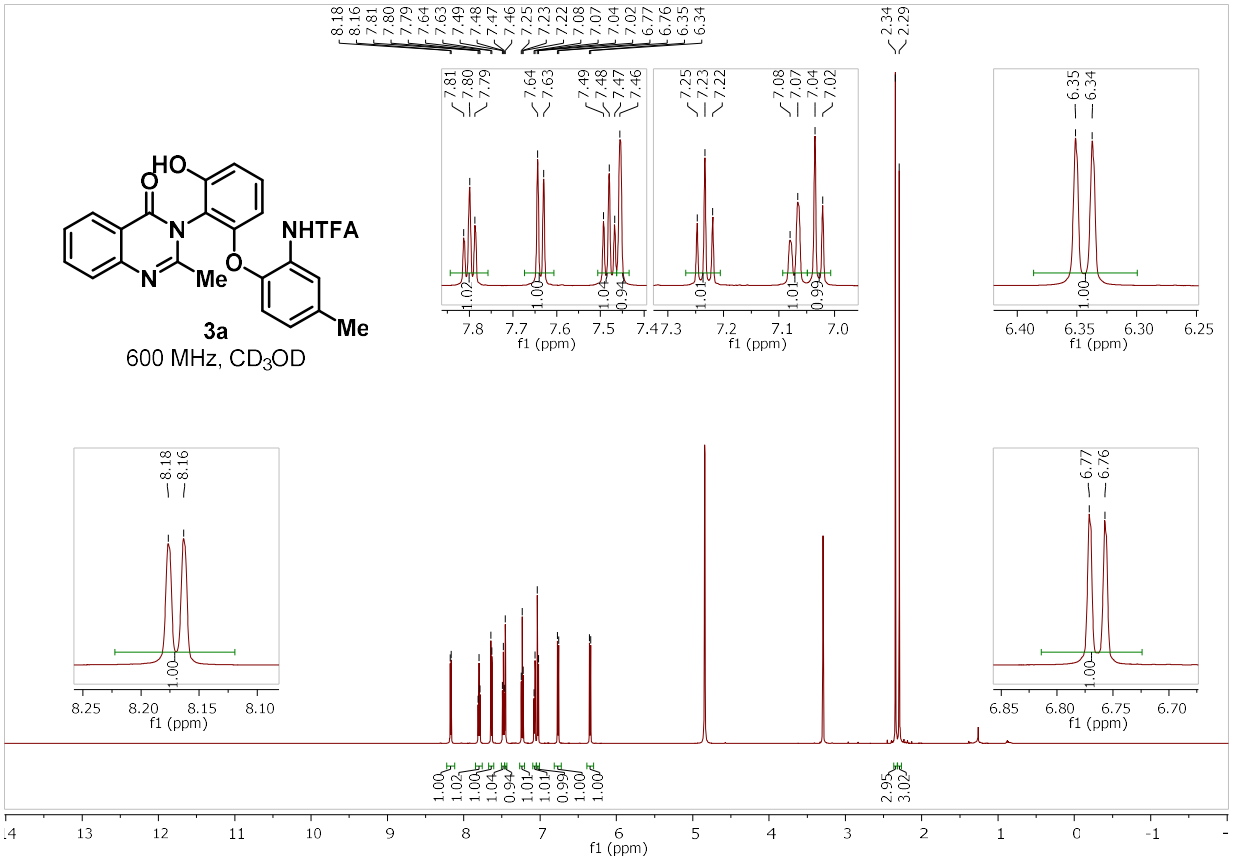
f1 (ppm)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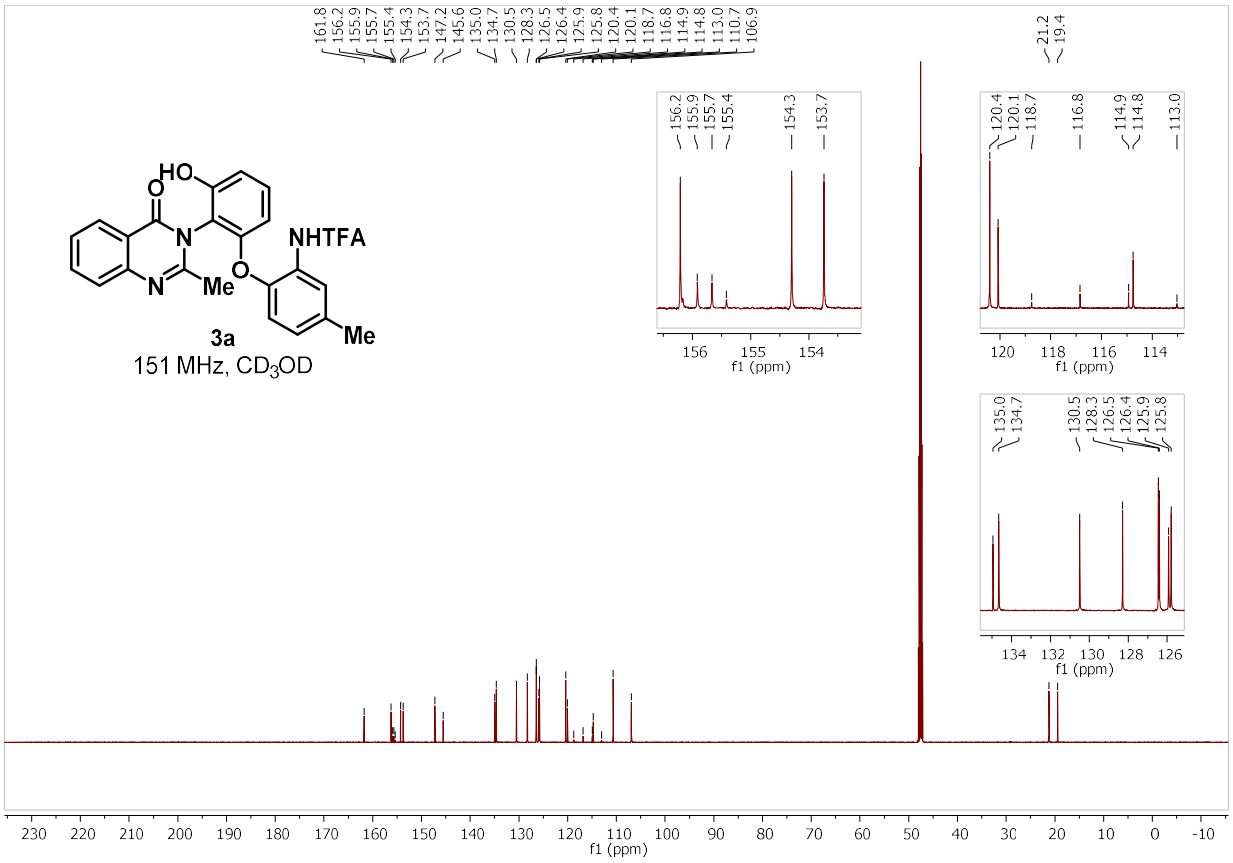
Me
O
NHTFA
Me
3a
600 MHz, CD3OD
f1 (ppm)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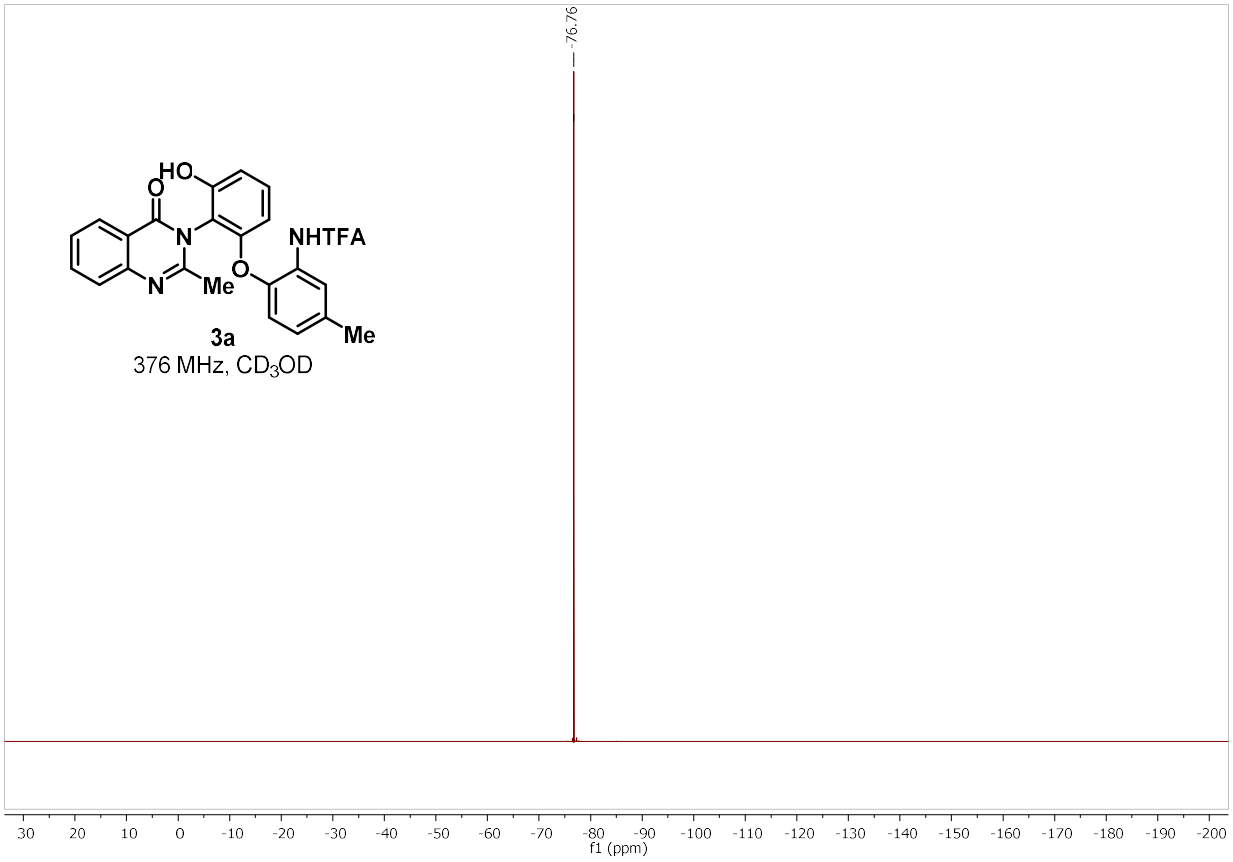
Me
O
NHTFA
Me
3a
151 MHz, CD3OD
f1 (ppm)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N
Me
O
NHTFA
Me
3a
376 MHz, CD3OD
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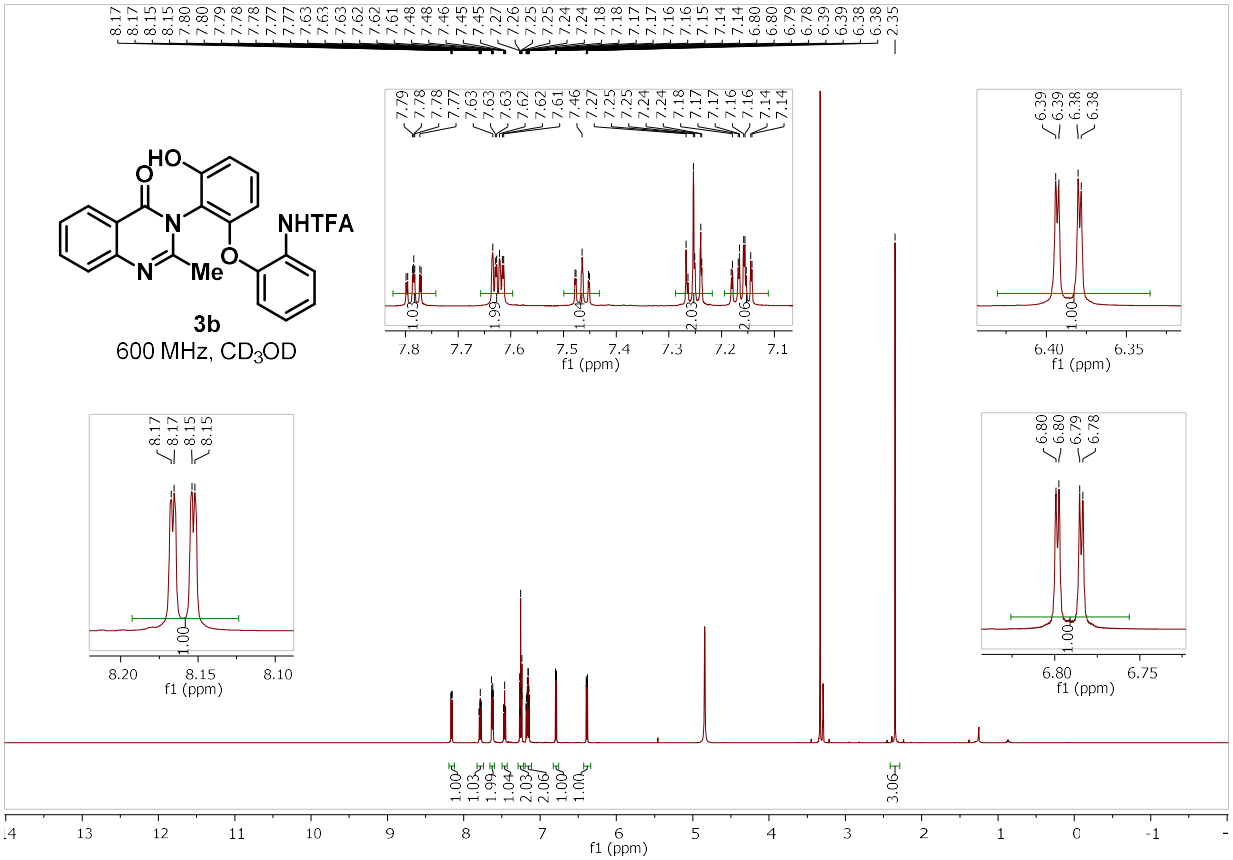
f1 (ppm)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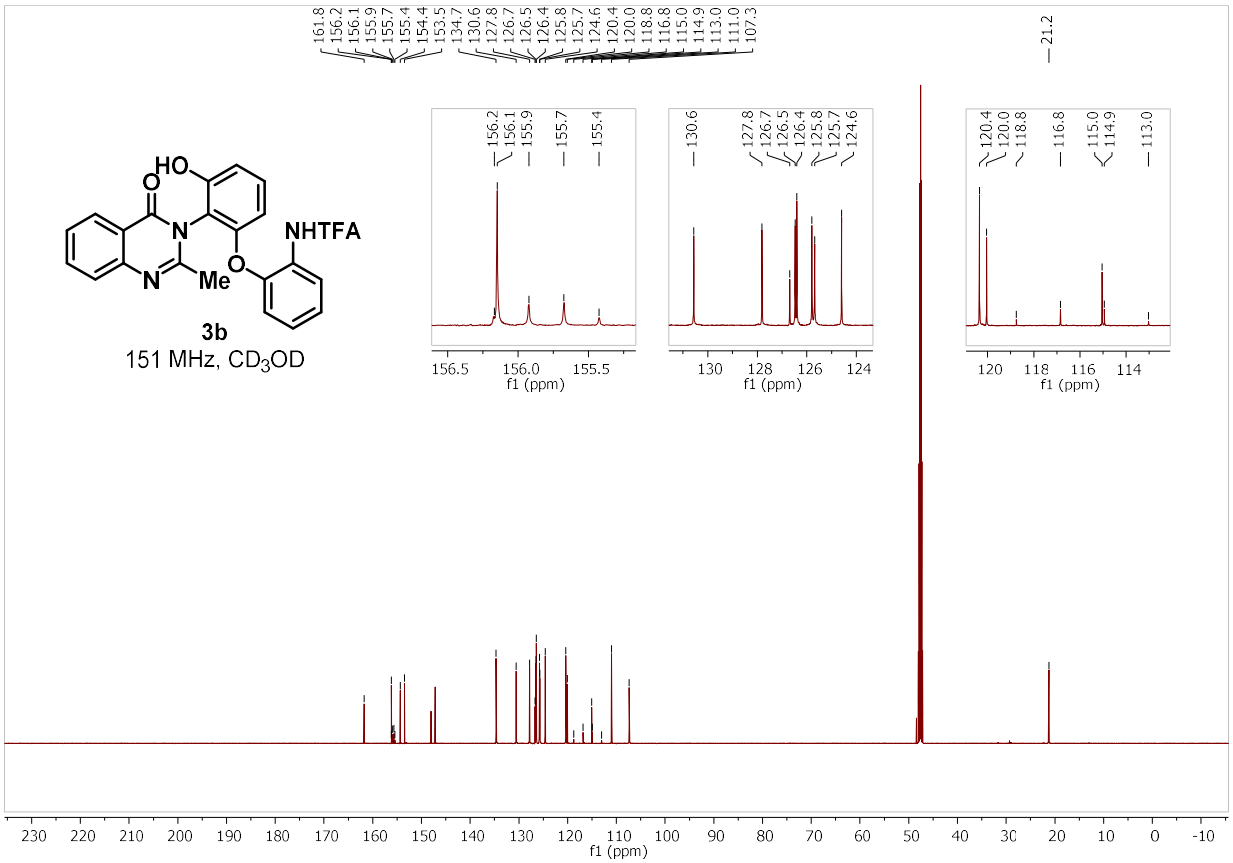
NHTFA
O
N
Me
3b
600 MHz, CD3OD
f1 (ppm)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N
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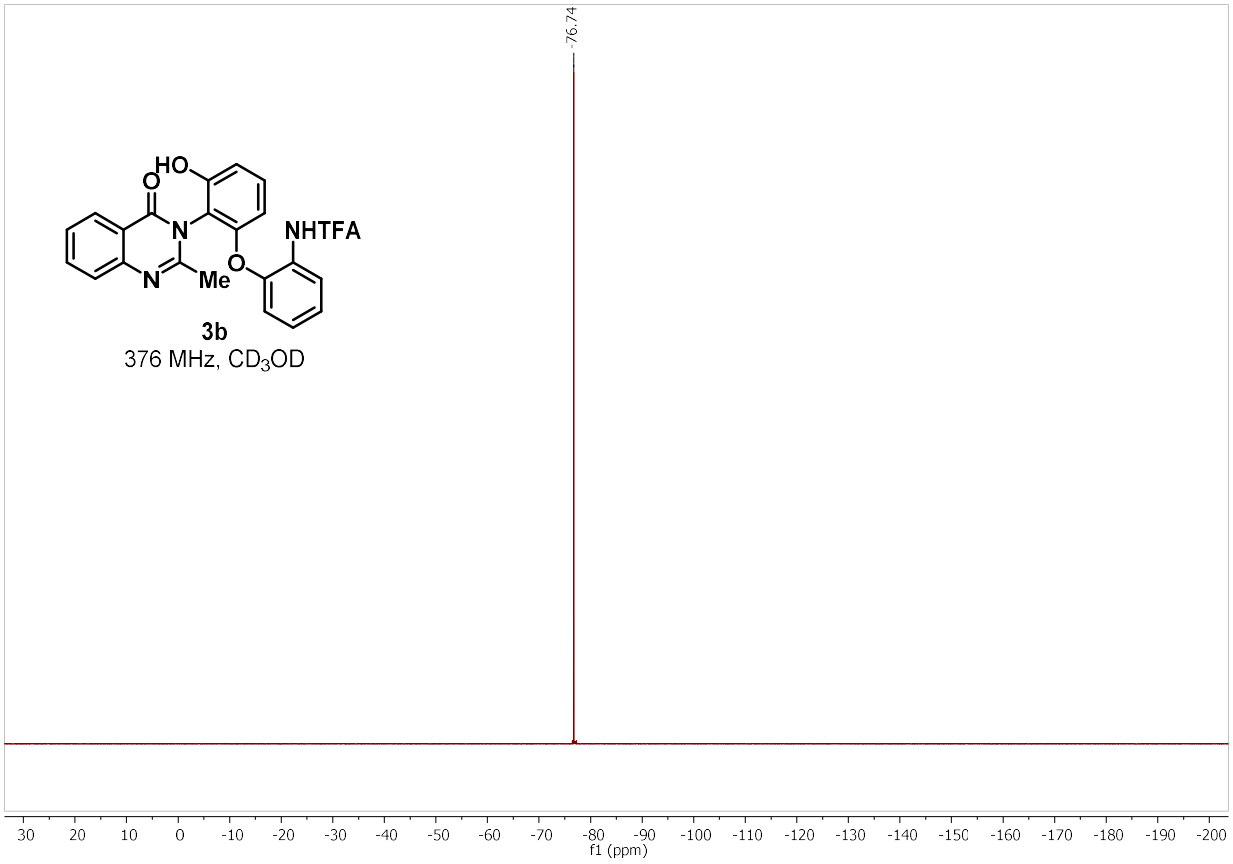
O
N
Me
3b
151 MHz, CD3OD
f1 (ppm)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Me
O
3b
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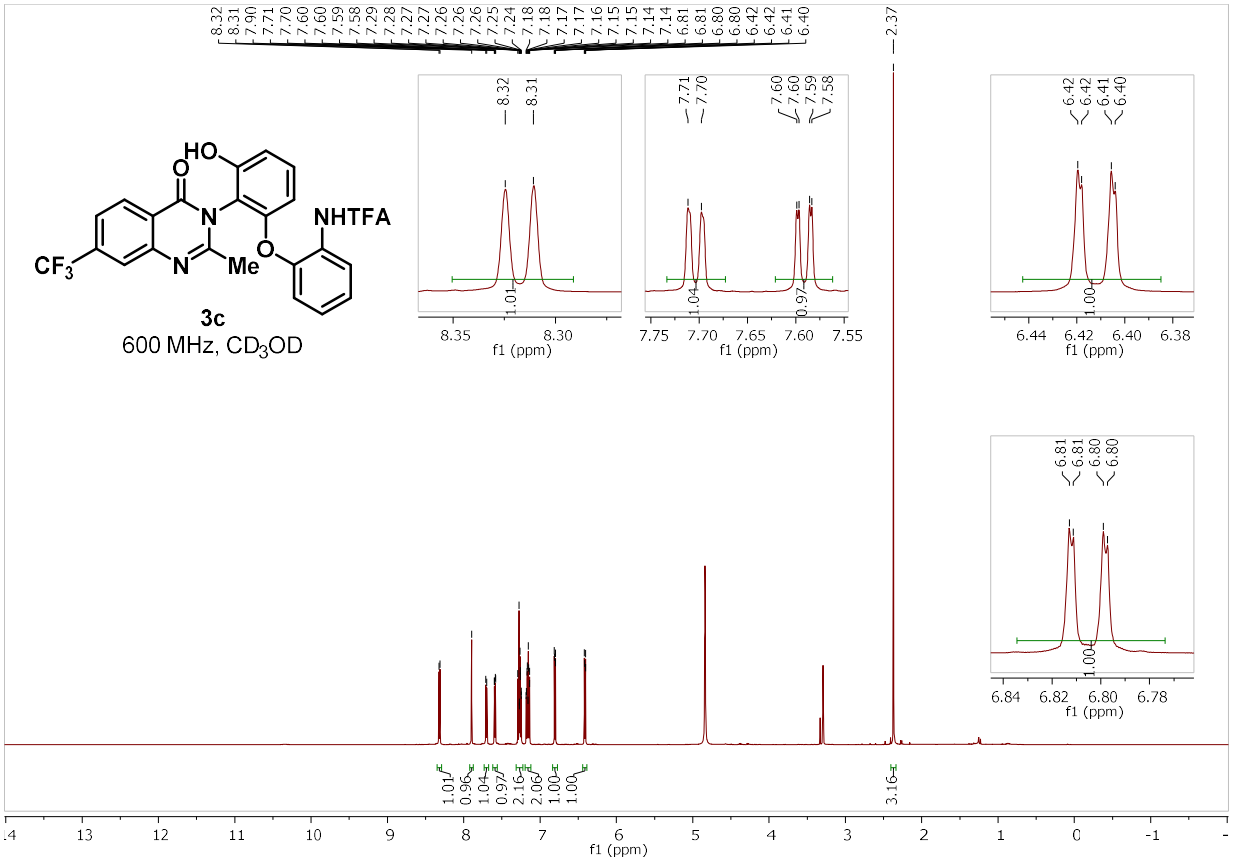
f1 (ppm)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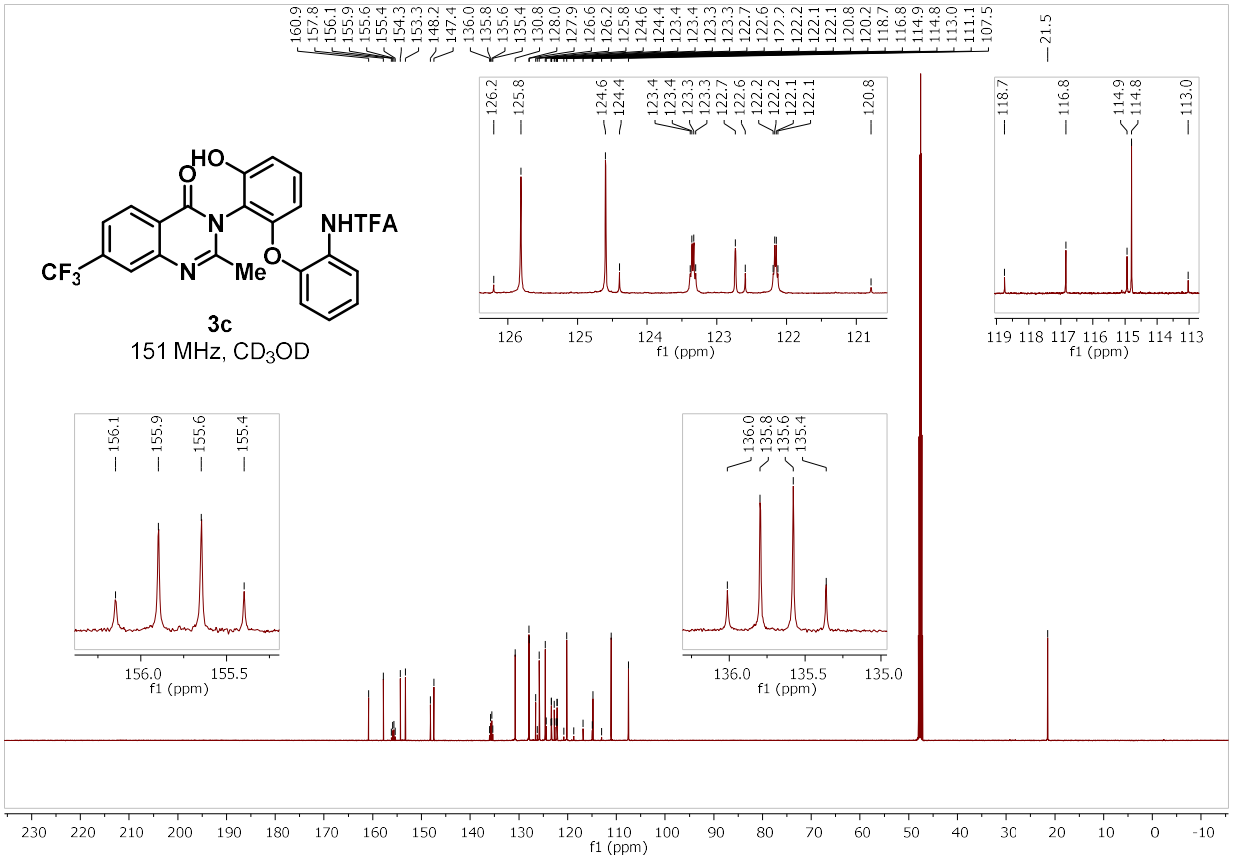
CF3
N
Me
O
3c
600 MHz, CD3OD
f1 (ppm)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Me
O
3c
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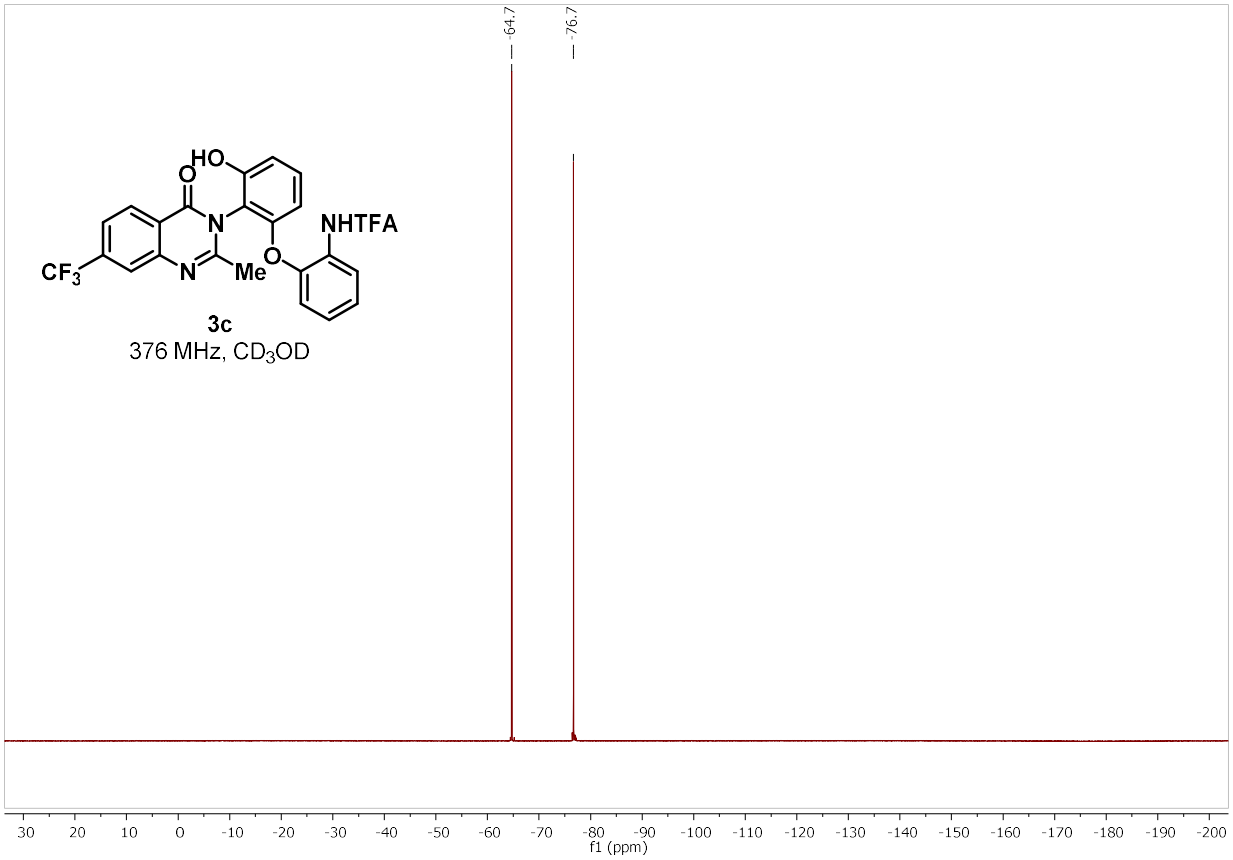
f1 (ppm)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HO
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CF3
N
Me
O
3c
376 MHz, CD3OD
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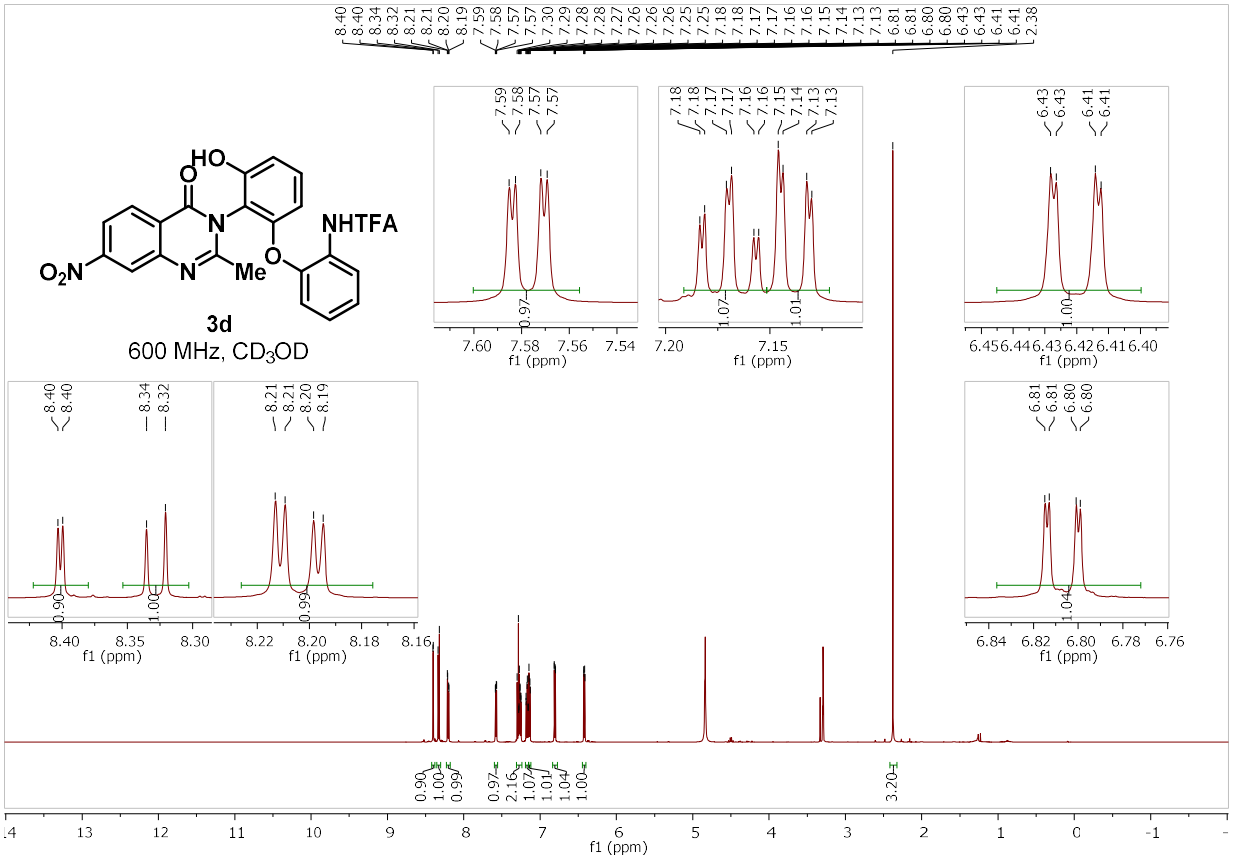
f1 (ppm)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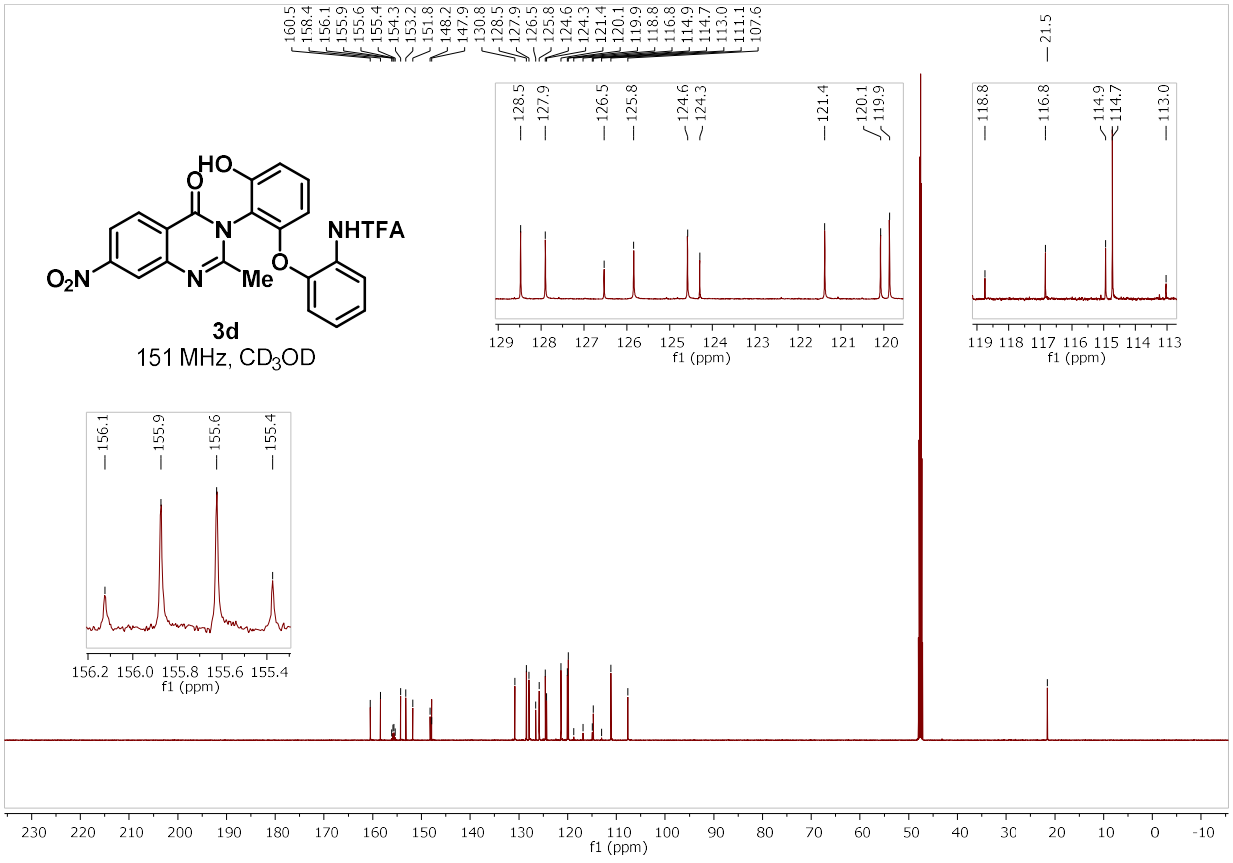
N
Me
O
3d
600 MHz, CD3OD
f1 (ppm)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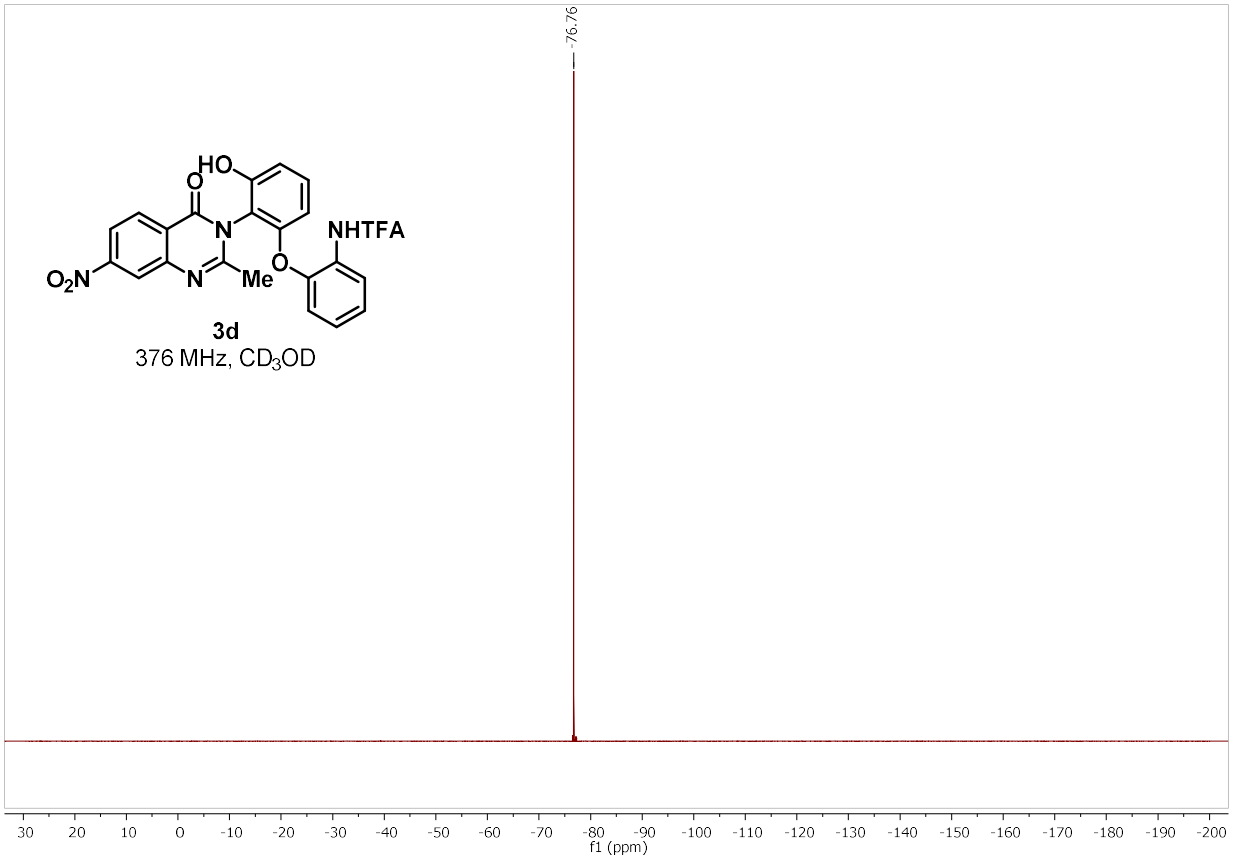
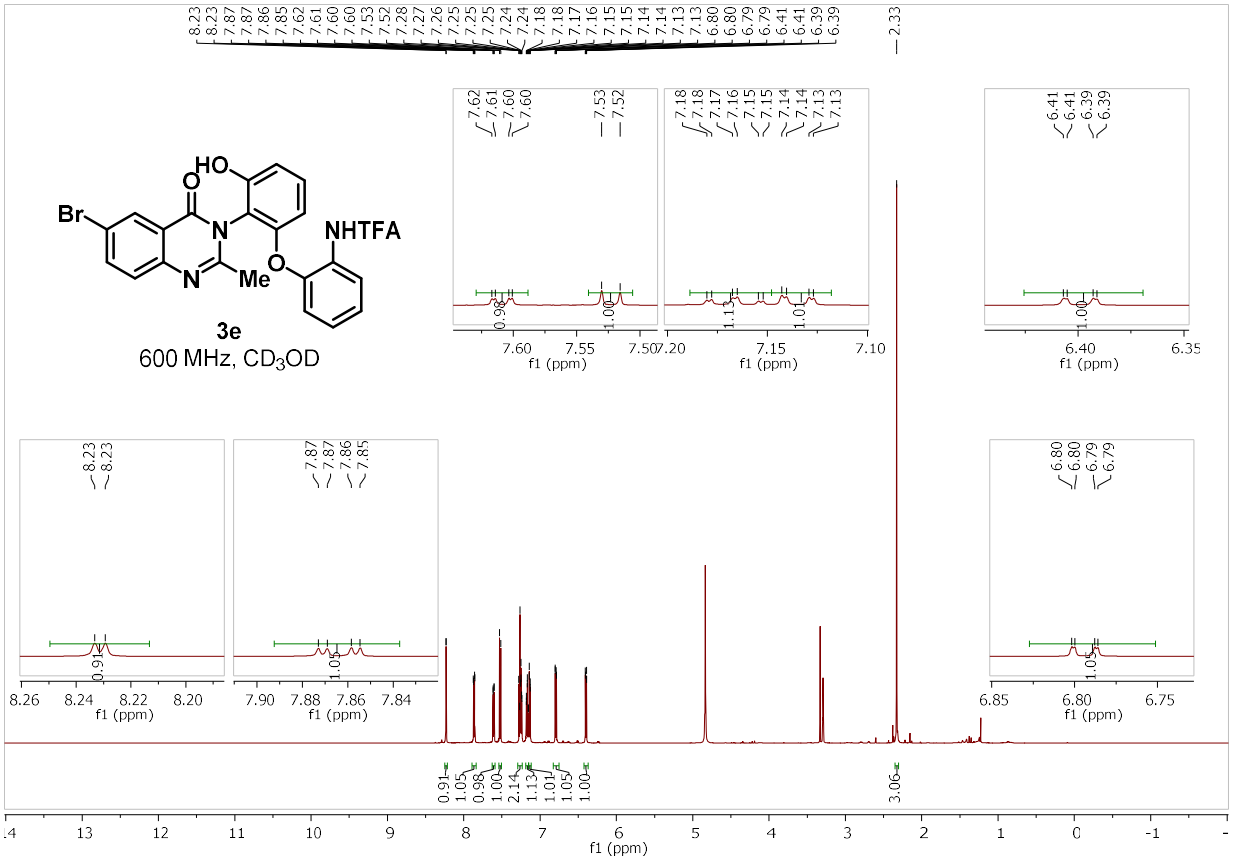
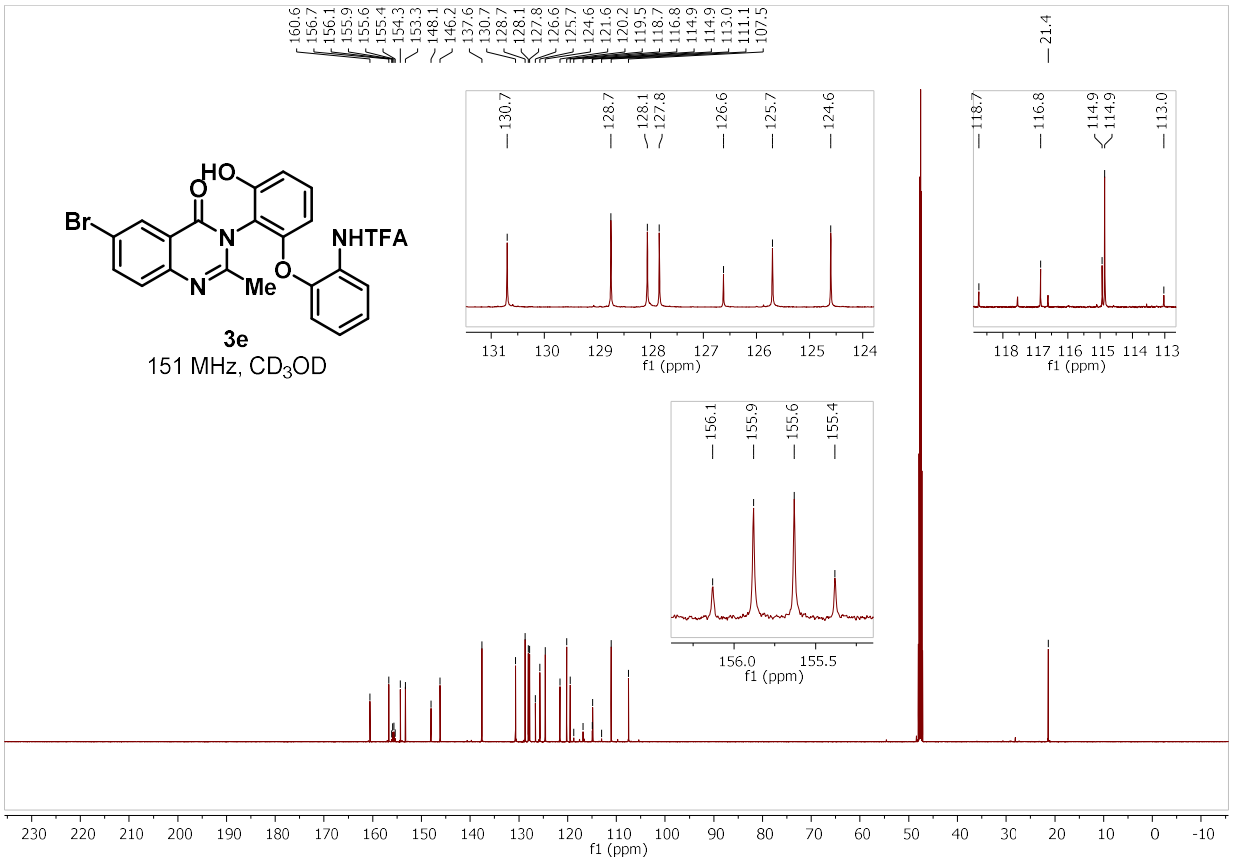
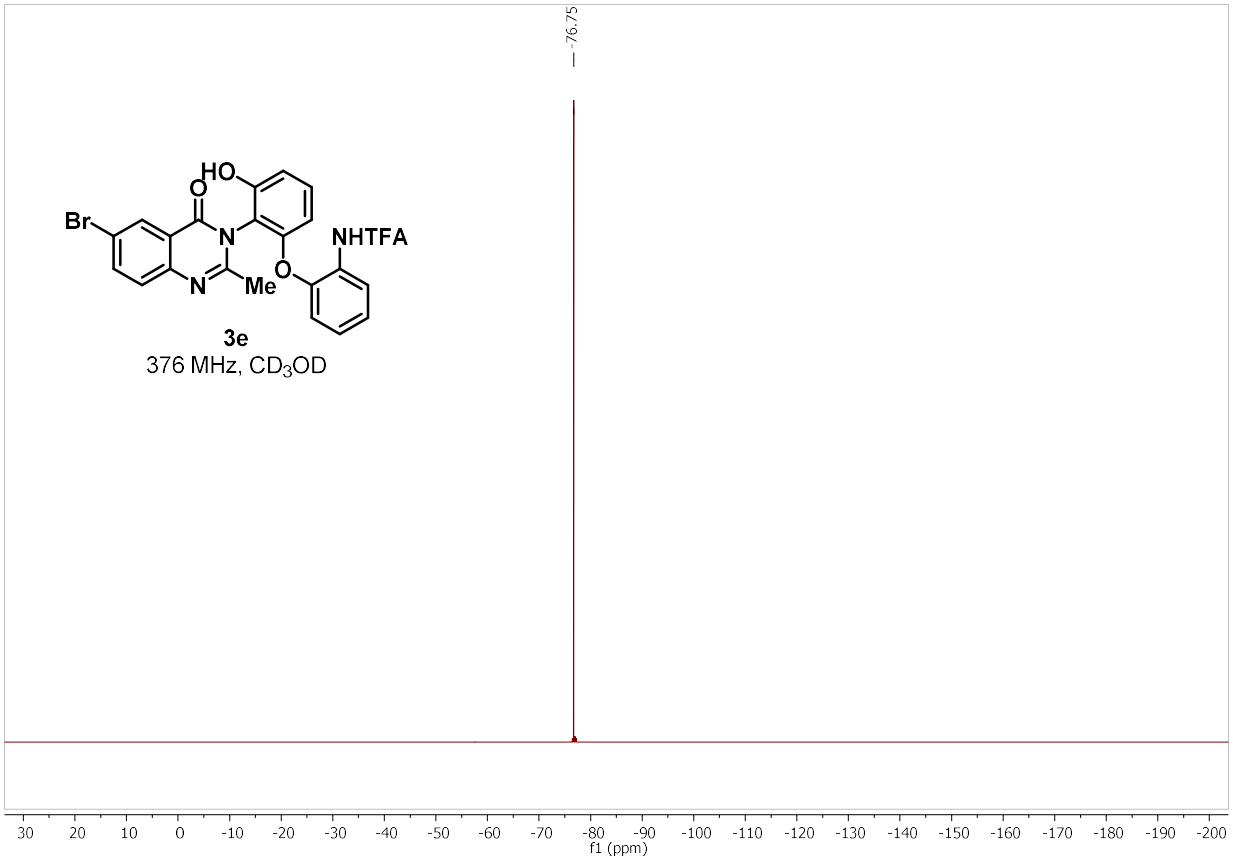
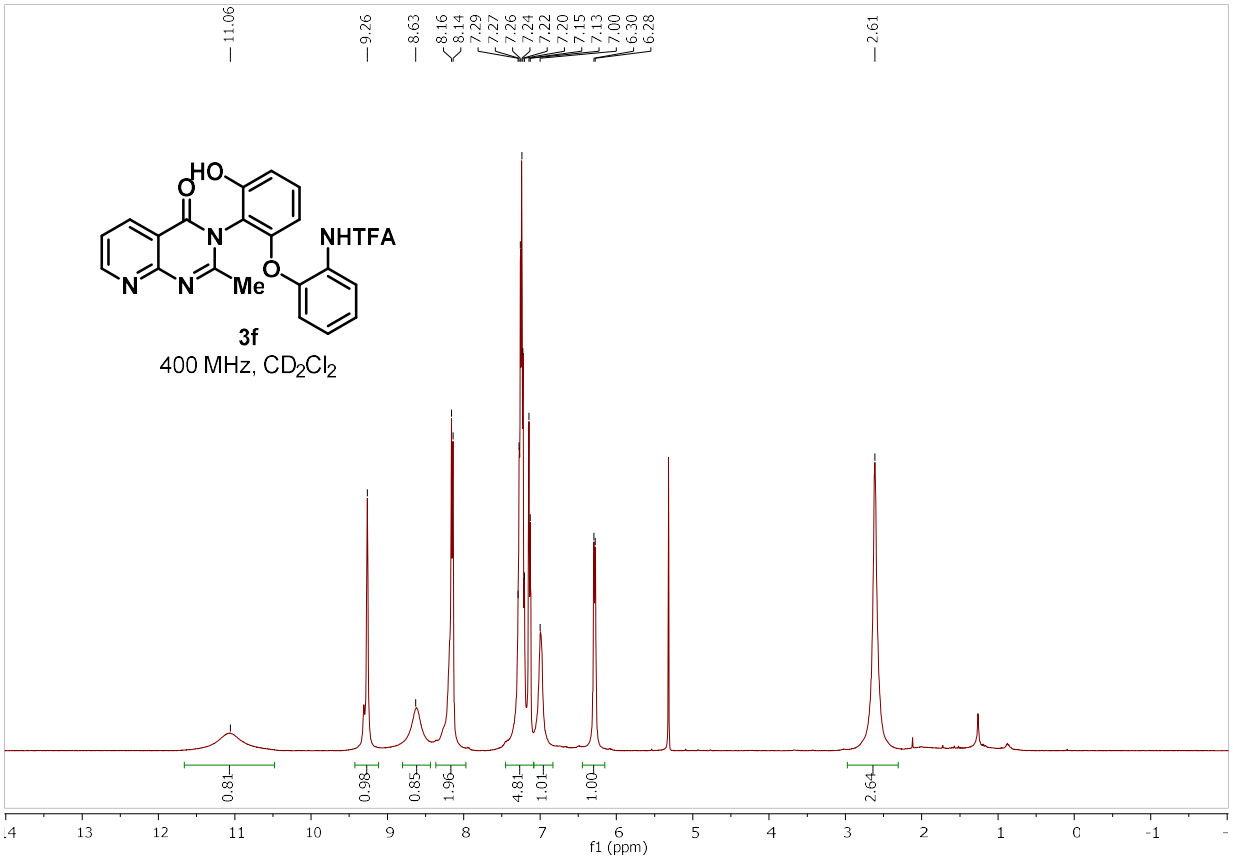
Me
O
3d
151 MHz, CD3OD
f1 (ppm)

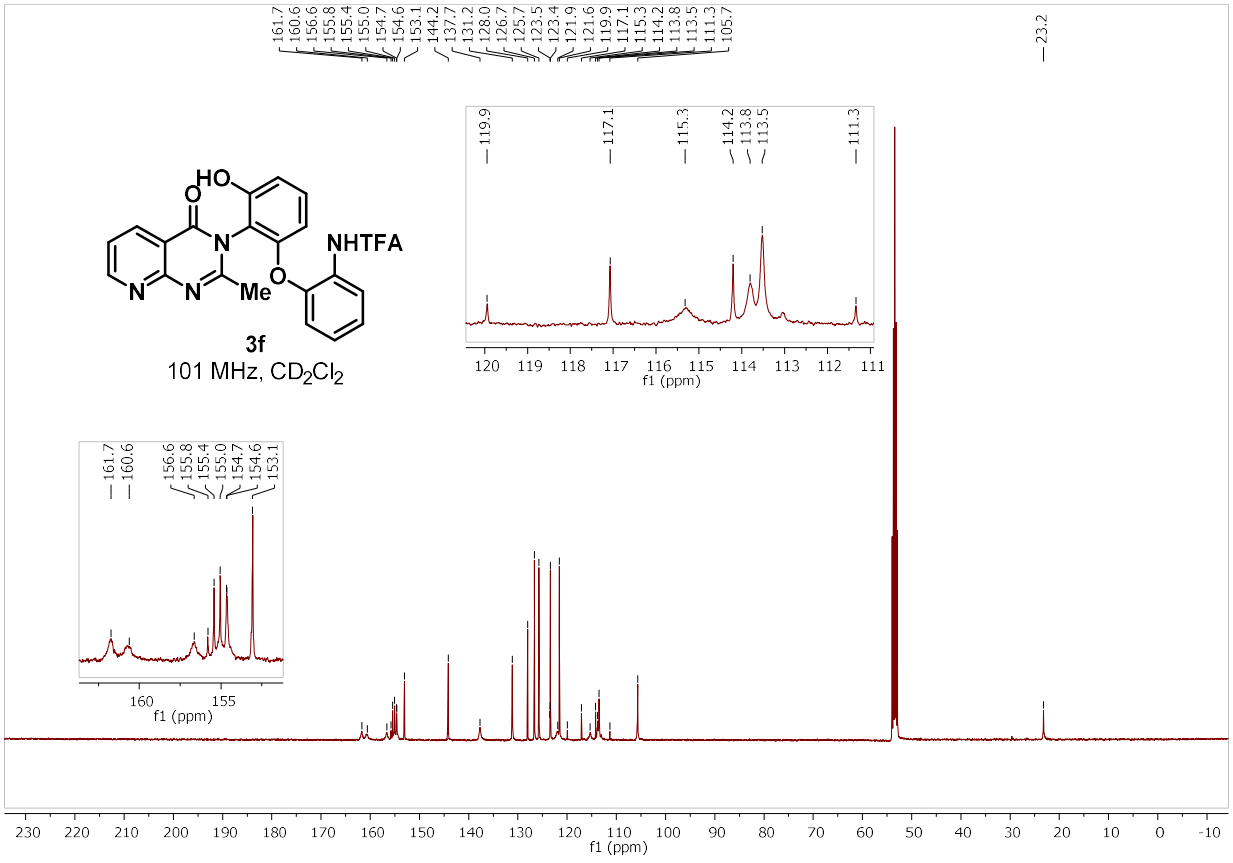

-76.76
HO
O
N
NHTFA
O2N
N
Me
O
3d
376 MHz, CD3OD
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

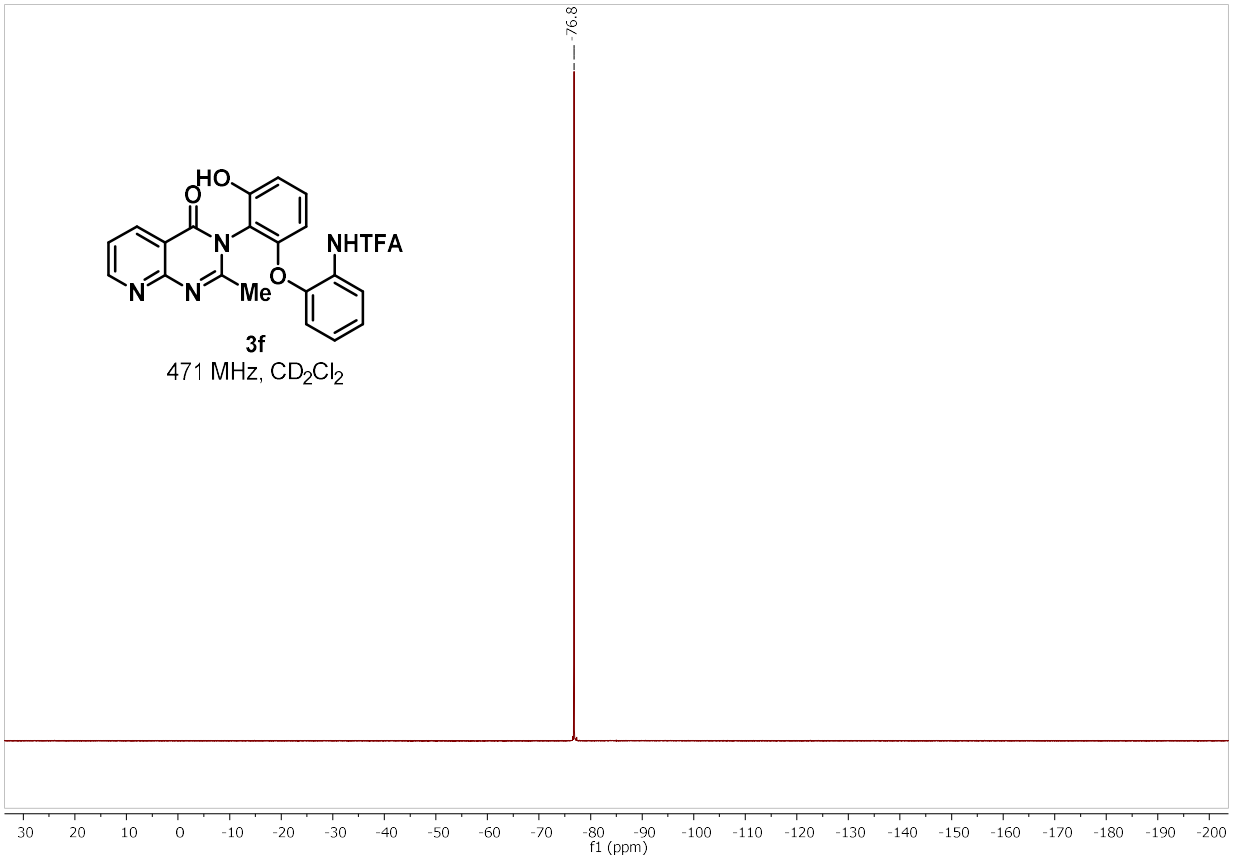

HO
O
Br
N
NHTFA
N
Me
O
3e
600 MHz, CD3OD
f1 (ppm)

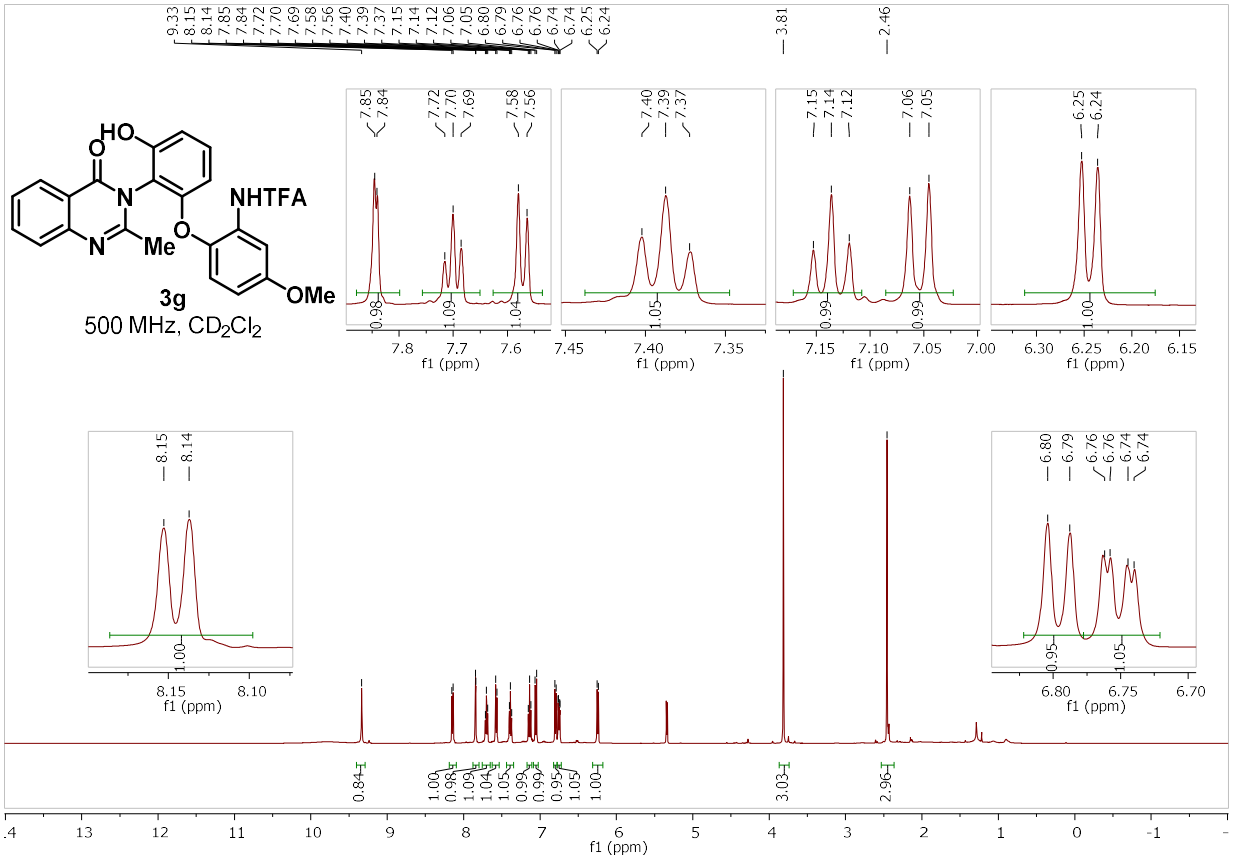

HO
O
Br
N
NHTFA
N
Me
O
3e
151 MHz, CD3OD
f1 (ppm)

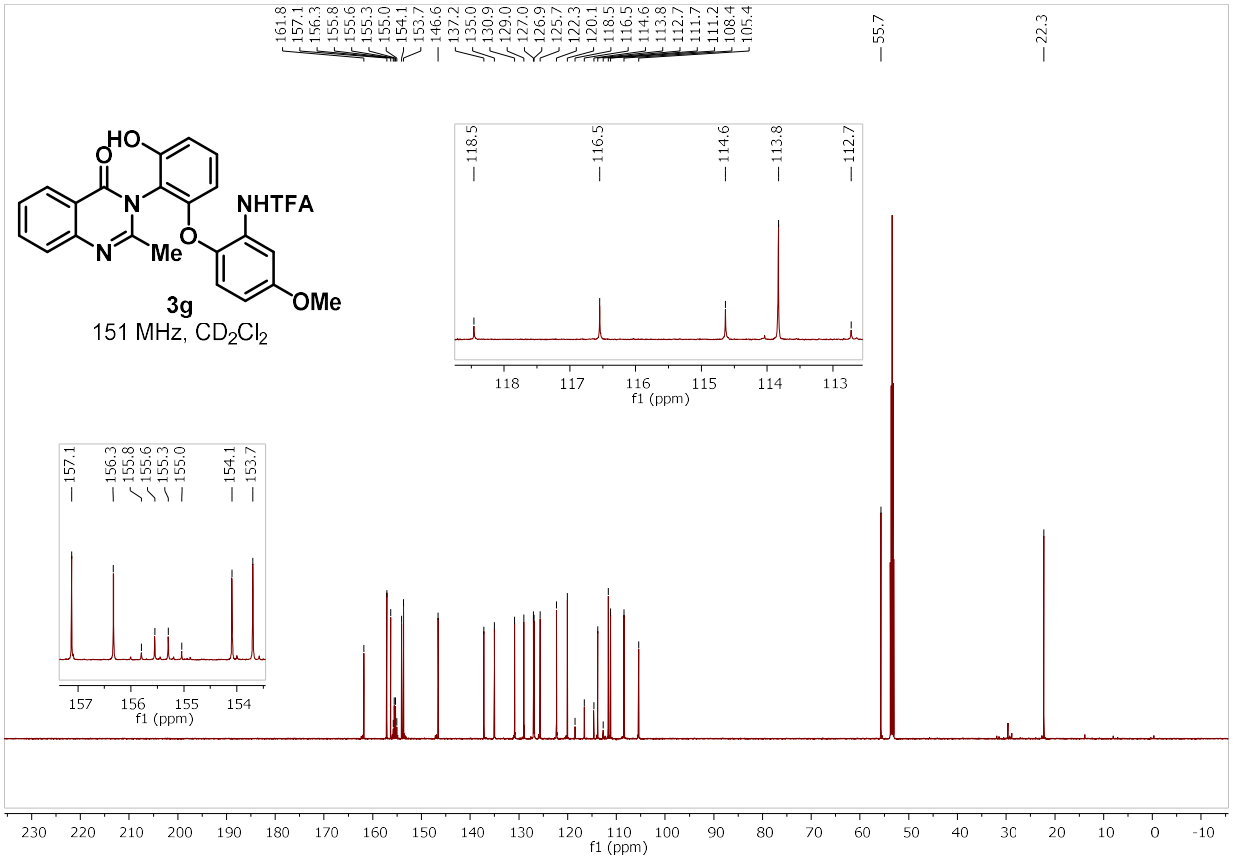

-76.75
HO
O
Br
N
NHTFA
N
Me
O
3e
376 MHz, CD3OD
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

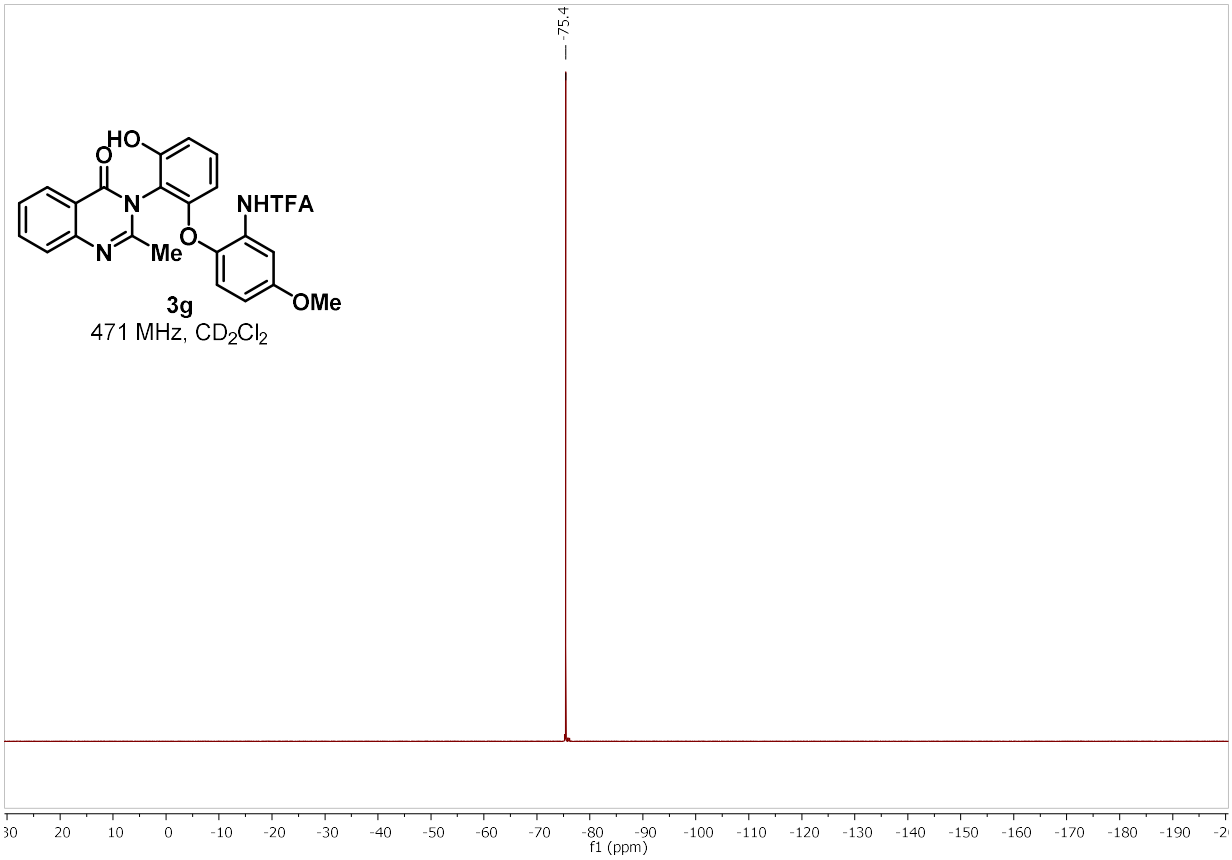

11.06
9.26
8.63
8.16
8.14
7.29
7.27
7.26
7.24
7.22
7.20
7.15
7.13
7.00
6.30
6.28
2.61
HO
O
N
NHTFA
N
N
Me
O
3f
400 MHz, CD2Cl2
0.81
0.98
0.85
1.96
4.81
1.01
1.00
2.64
f1 (ppm)

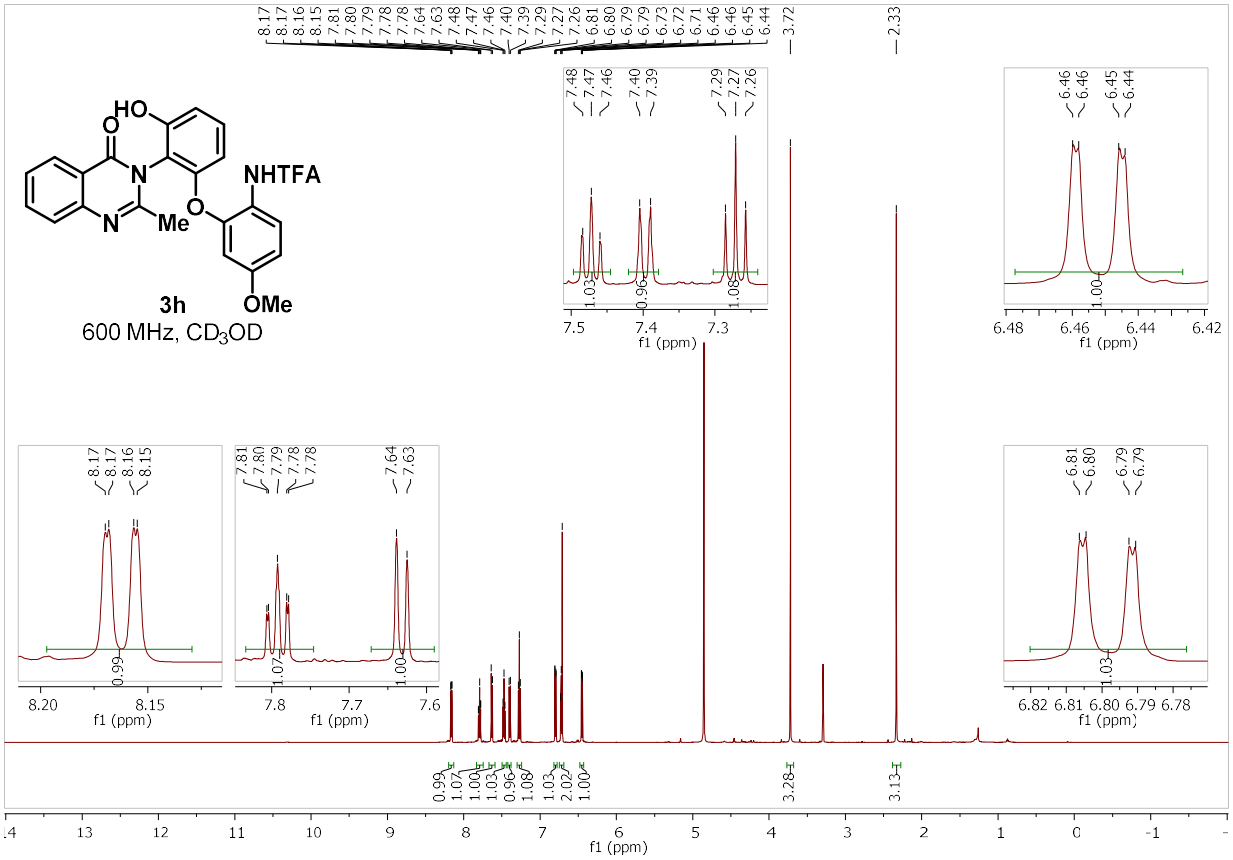

161.7
160.6
156.6
155.8
155.4
155.0
154.7
154.6
153.1
144.2
137.7
131.2
128.0
126.7
125.7
123.5
123.4
121.9
121.6
119.9
117.1
115.3
114.2
113.8
113.5
111.3
105.7
23.2
HO
O
N
NHTFA
N
N
Me
O
3f
101 MHz, CD2Cl2
119.9
117.1
115.3
114.2
113.8
113.5
111.3
f1 (ppm)
161.7
160.6
156.6
155.8
155.4
155.0
154.7
154.6
153.1
f1 (ppm)
f1 (ppm)

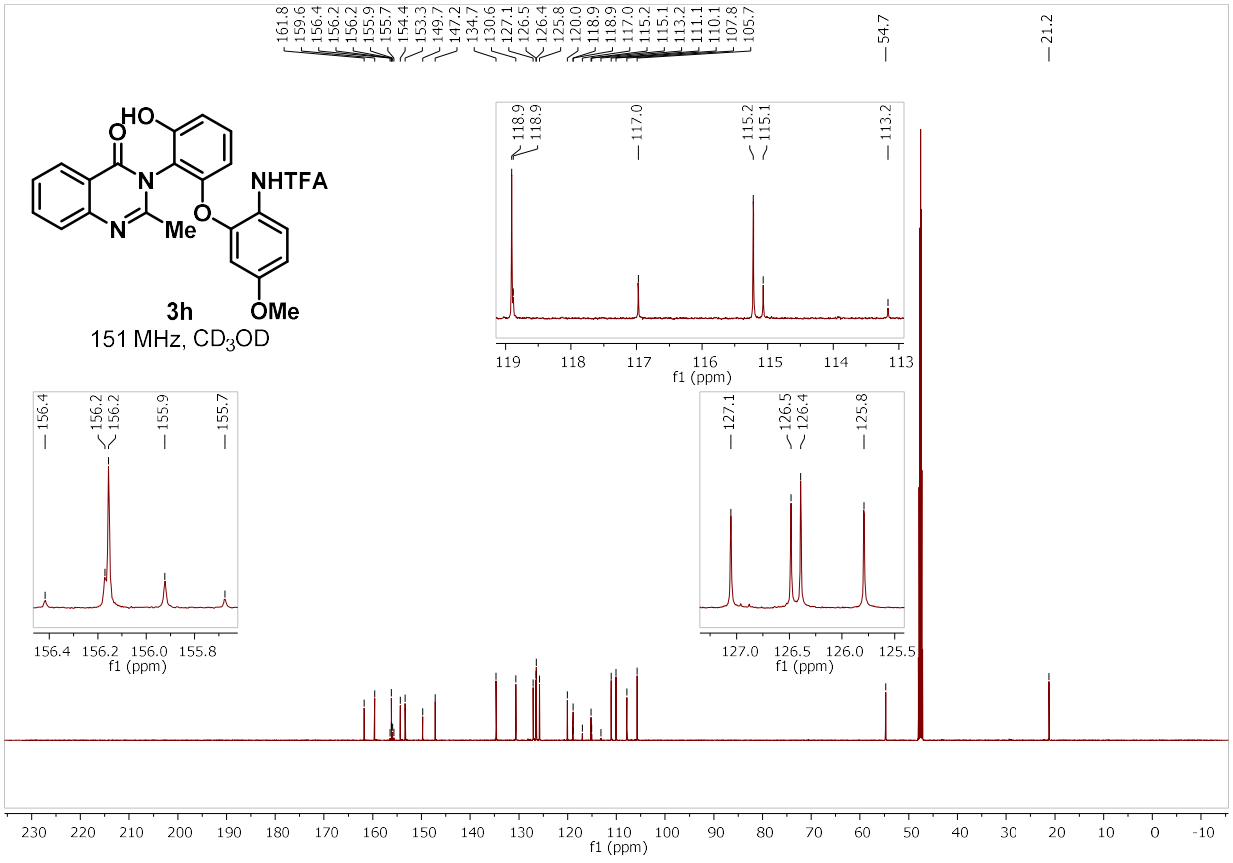

-76.8
HO
O
N
NHTFA
N
N
Me
O
3f
471 MHz, CD2Cl2
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

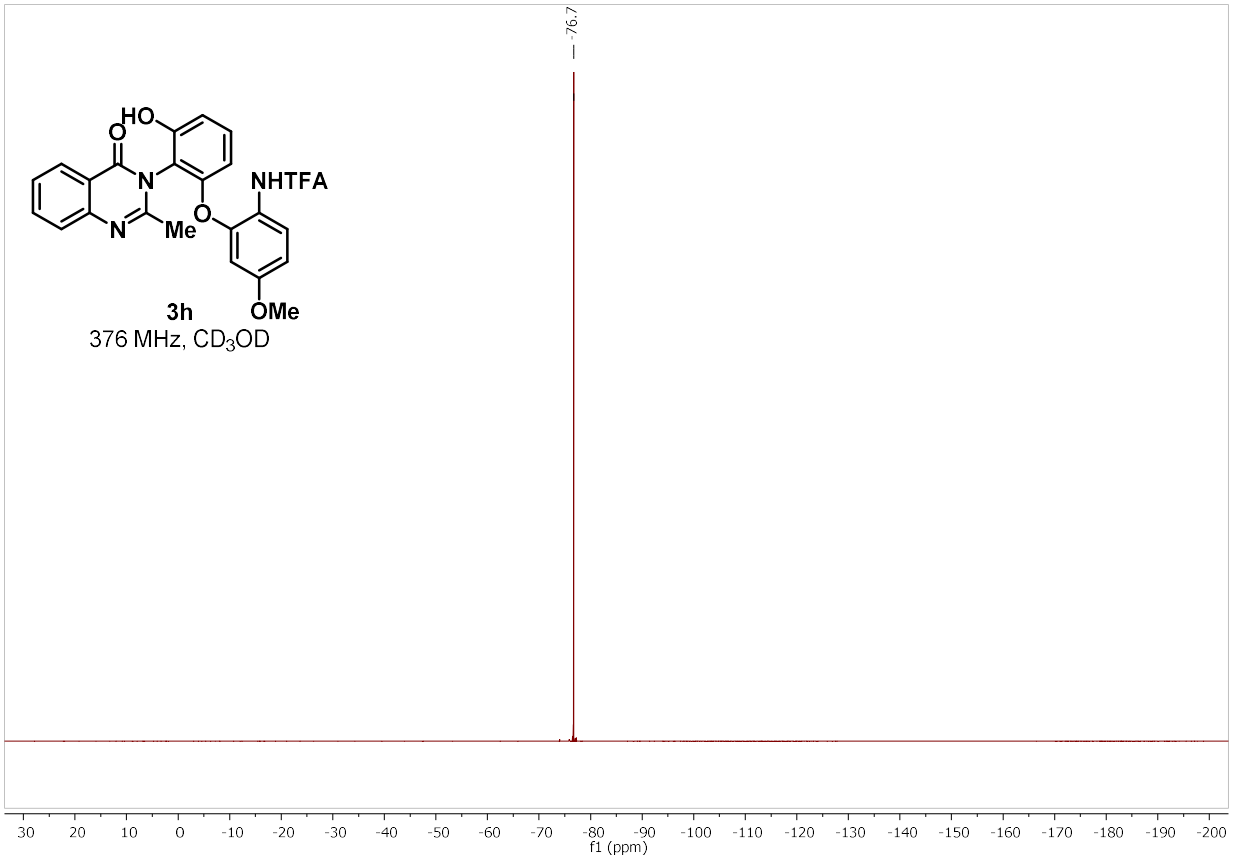

HO
O
N
N
Me
O
NHTFA
OMe
3g
500 MHz, CD2Cl2
f1 (ppm)

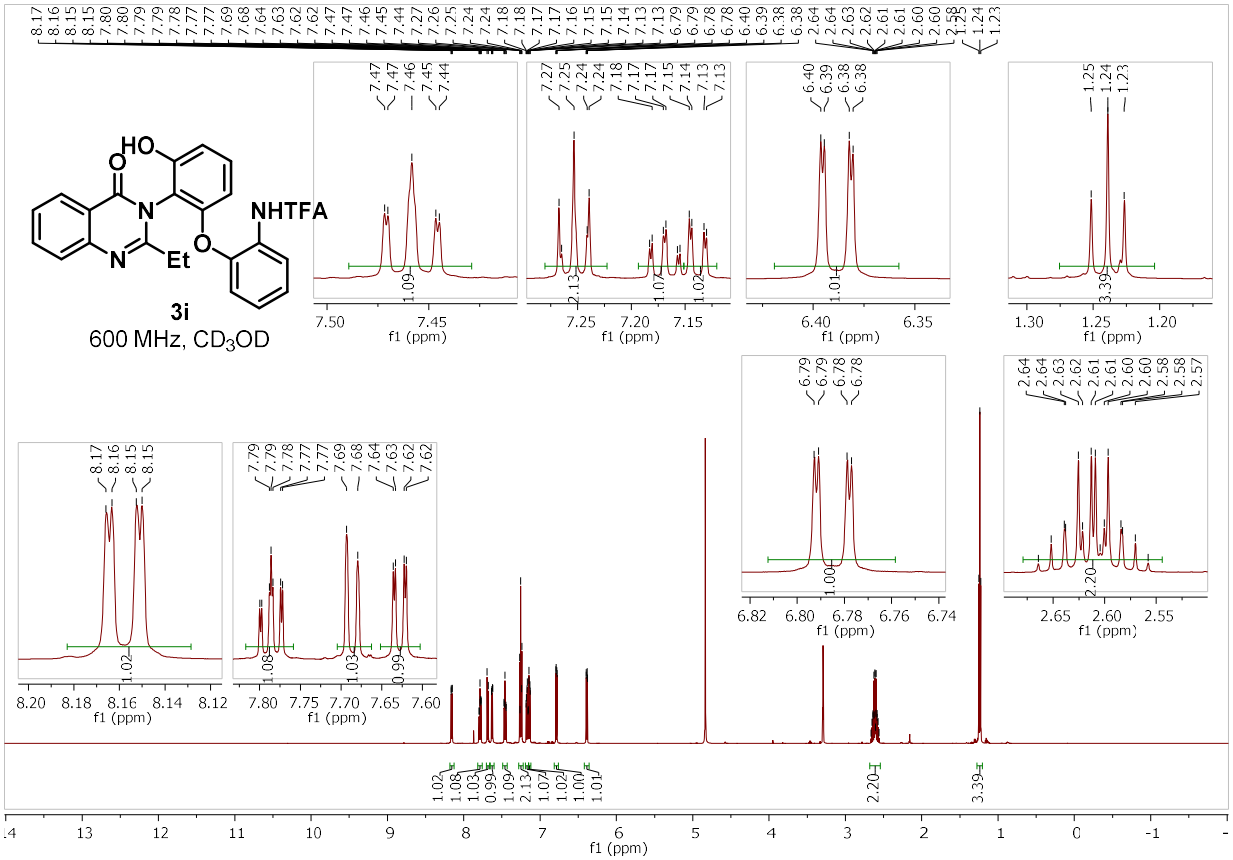

HO
O
N
N
Me
O
NHTFA
OMe
3g
151 MHz, CD2Cl2
f1 (ppm)

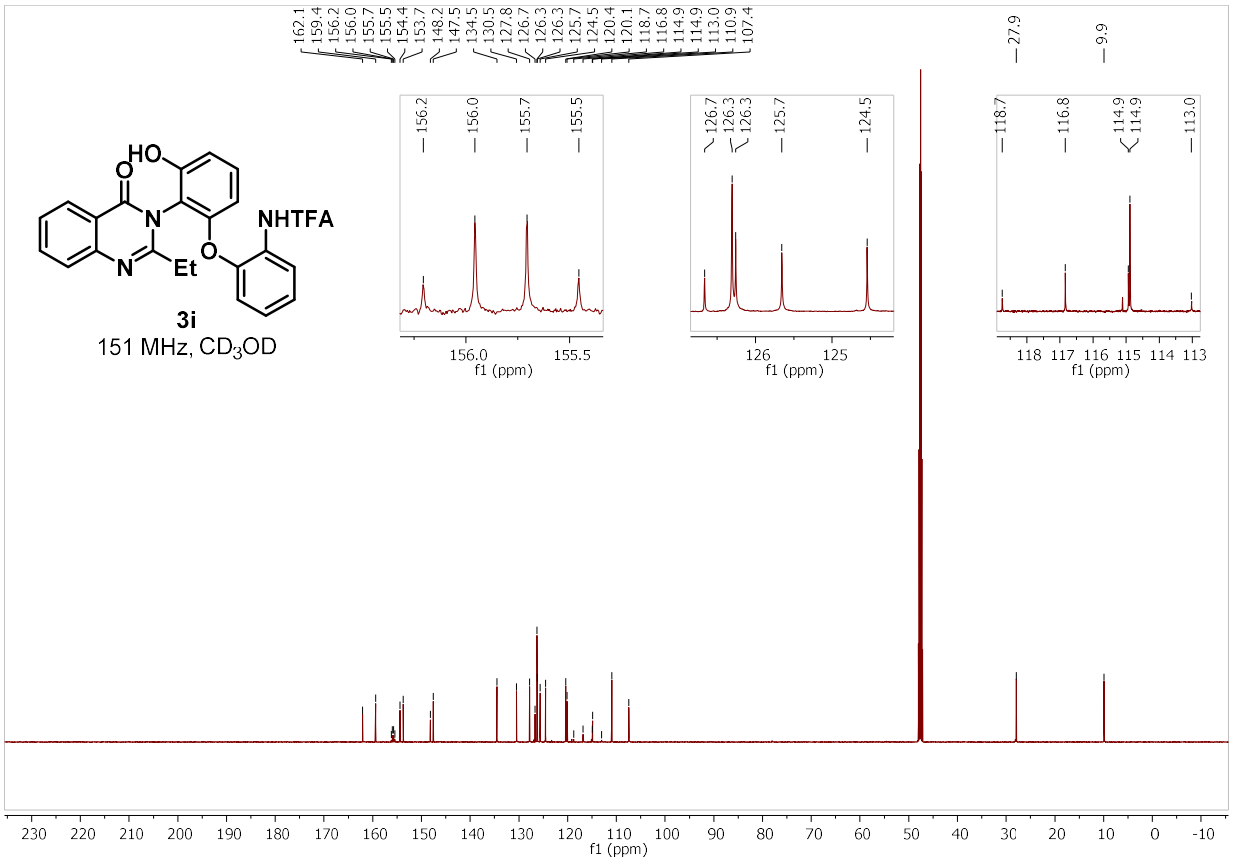

-75.4
HO
O
N
N
Me
O
NHTFA
OMe
3g
471 MHz, CD2Cl2
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

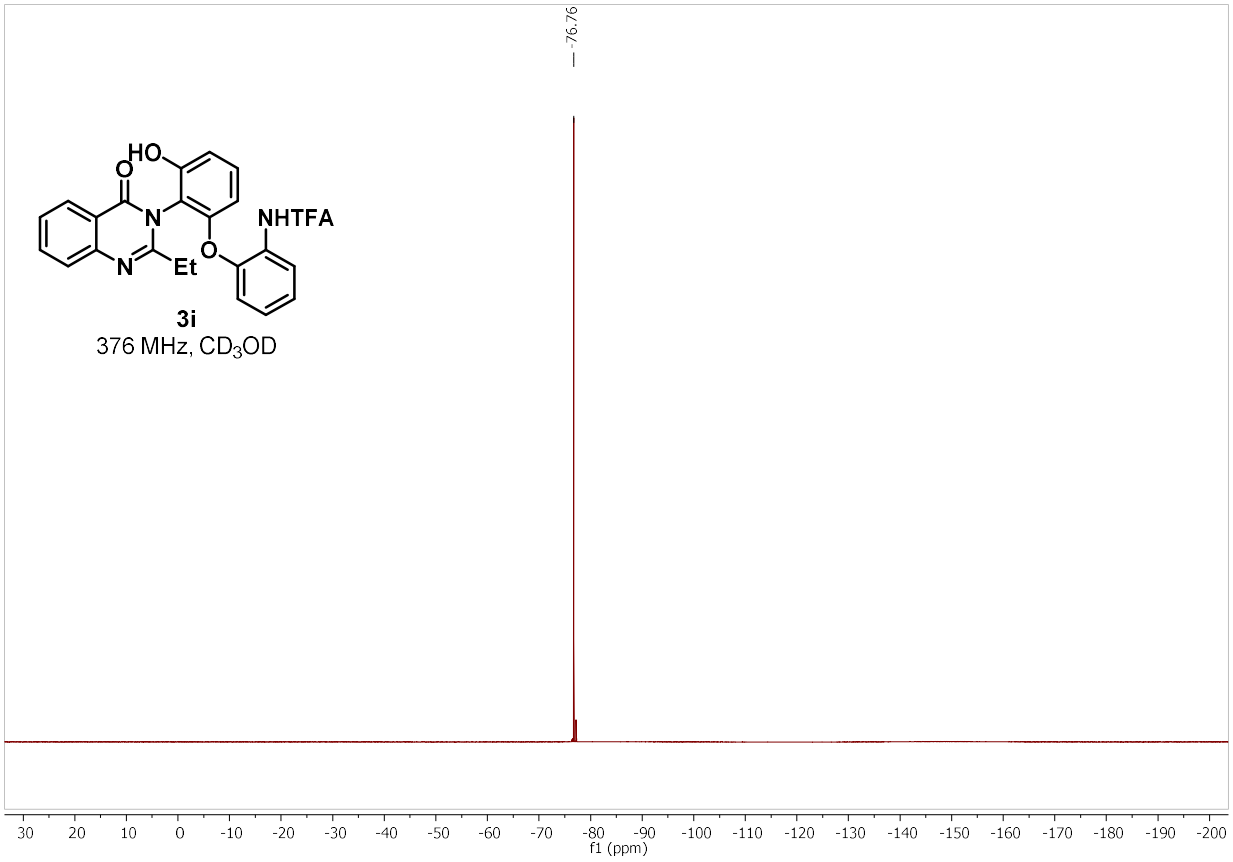

HO
O
N
N
Me
O
NHTFA
OMe
3h
600 MHz, CD3OD
f1 (ppm)

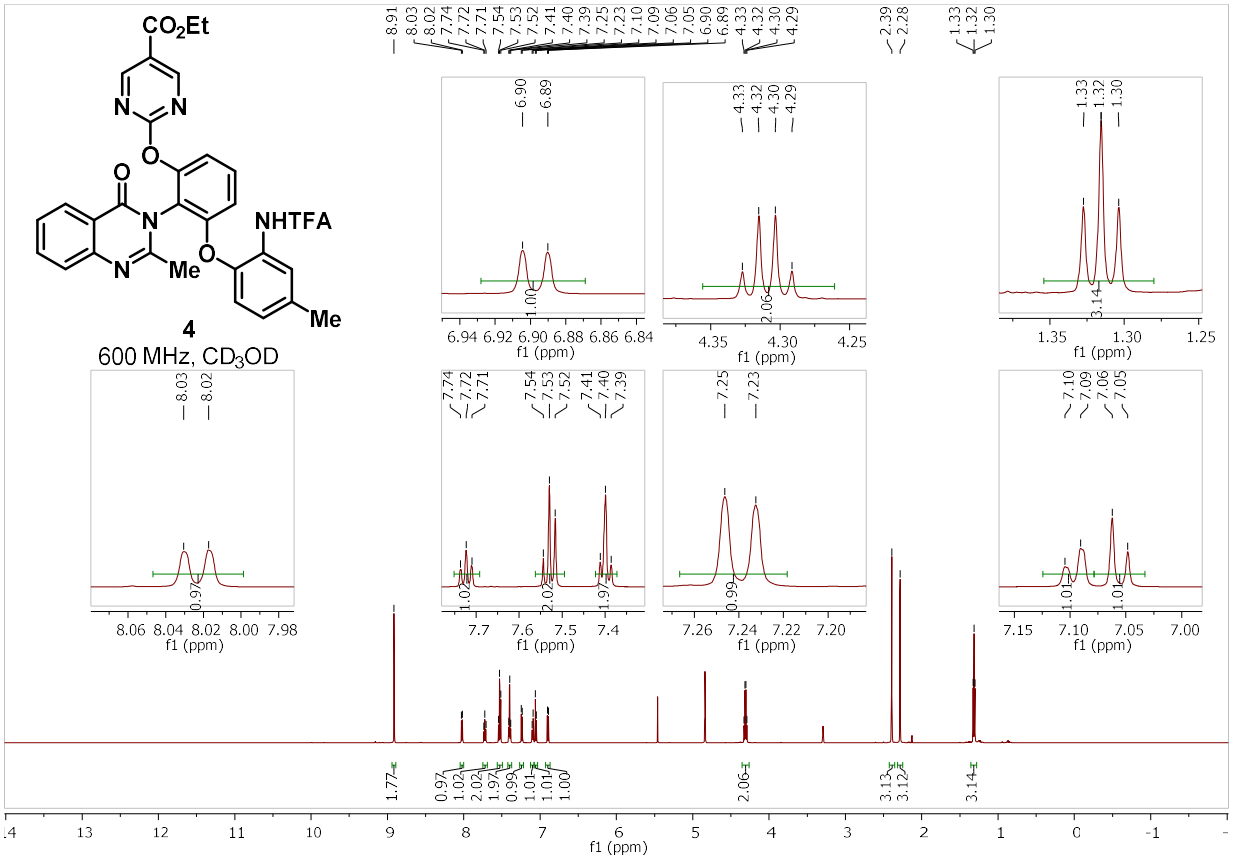

HO
O
N
N
Me
O
NHTFA
OMe
3h
151 MHz, CD3OD
f1 (ppm)

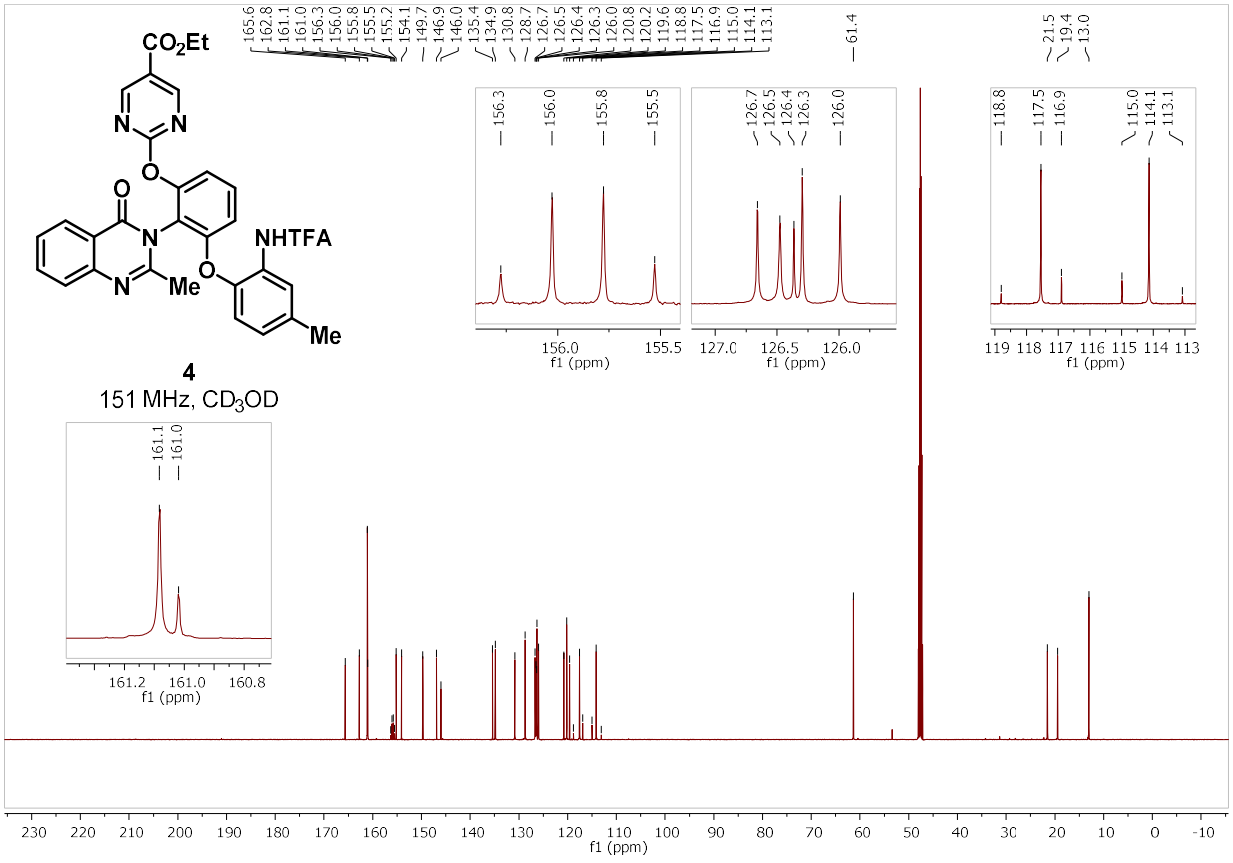

HO
O
N
N
Me
O
NHTFA
OMe
3h
376 MHz, CD3OD
-76.7
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

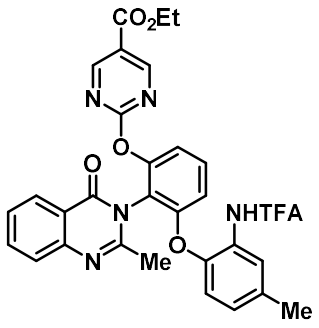

HO
O
N
NHTFA
O
N
Et
3i
600 MHz, CD3OD
f1 (ppm)


HO
O
N
NHTFA
O
N
Et
3i
151 MHz, CD3OD
f1 (ppm)


-76.76
HO
O
N
N
Et
O
NHTFA
3i
376 MHz, CD3OD
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

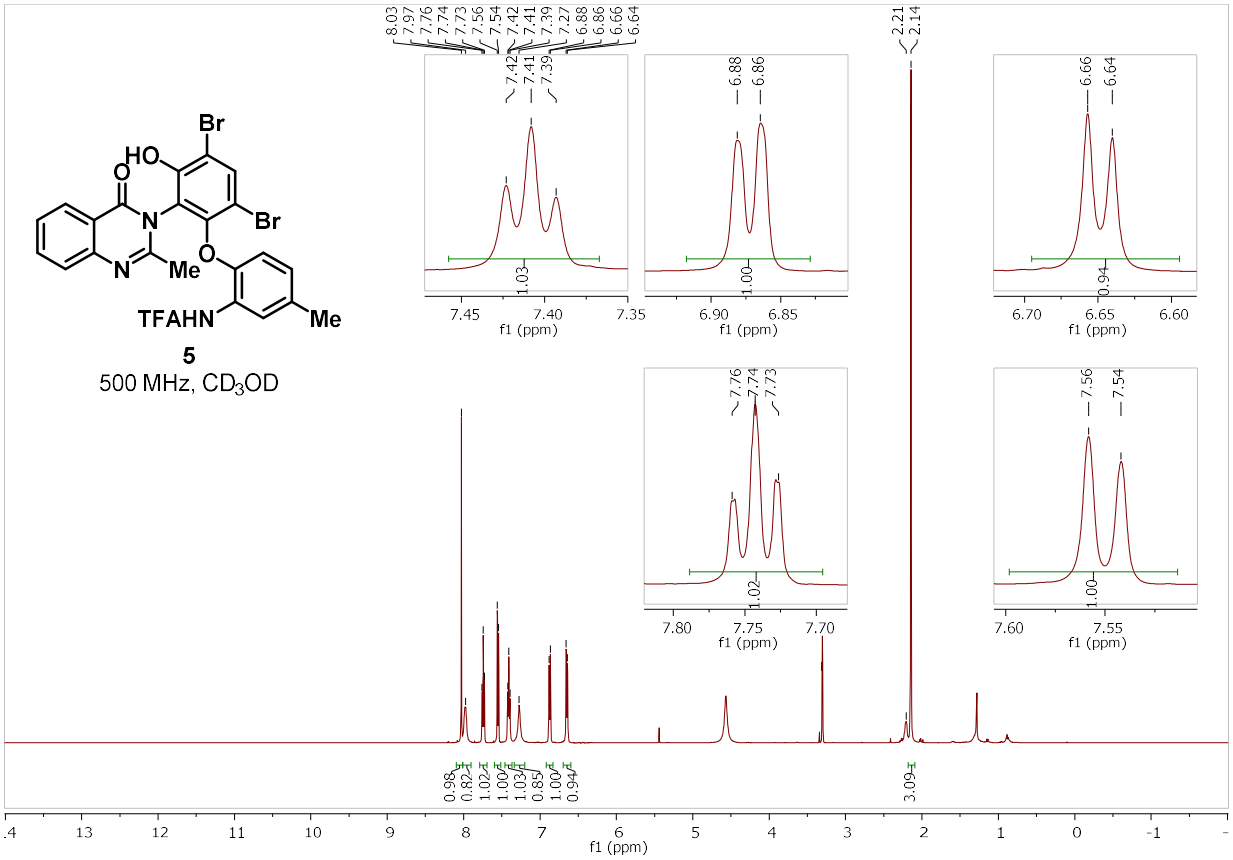

CO2Et
NHTFA
Me
Me
4
600 MHz, CD3OD
f1 (ppm)

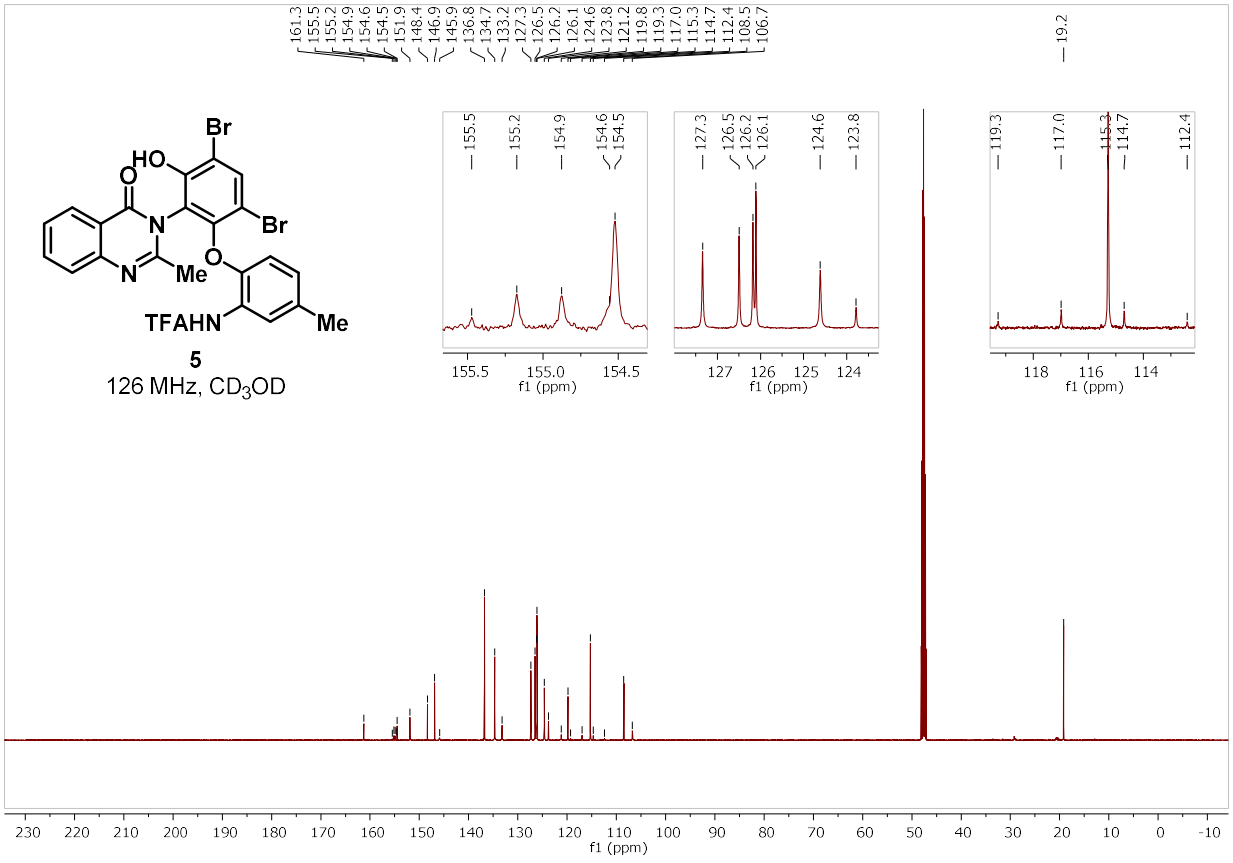

CO2Et
NHTFA
Me
Me
4
151 MHz, CD3OD
f1 (ppm)

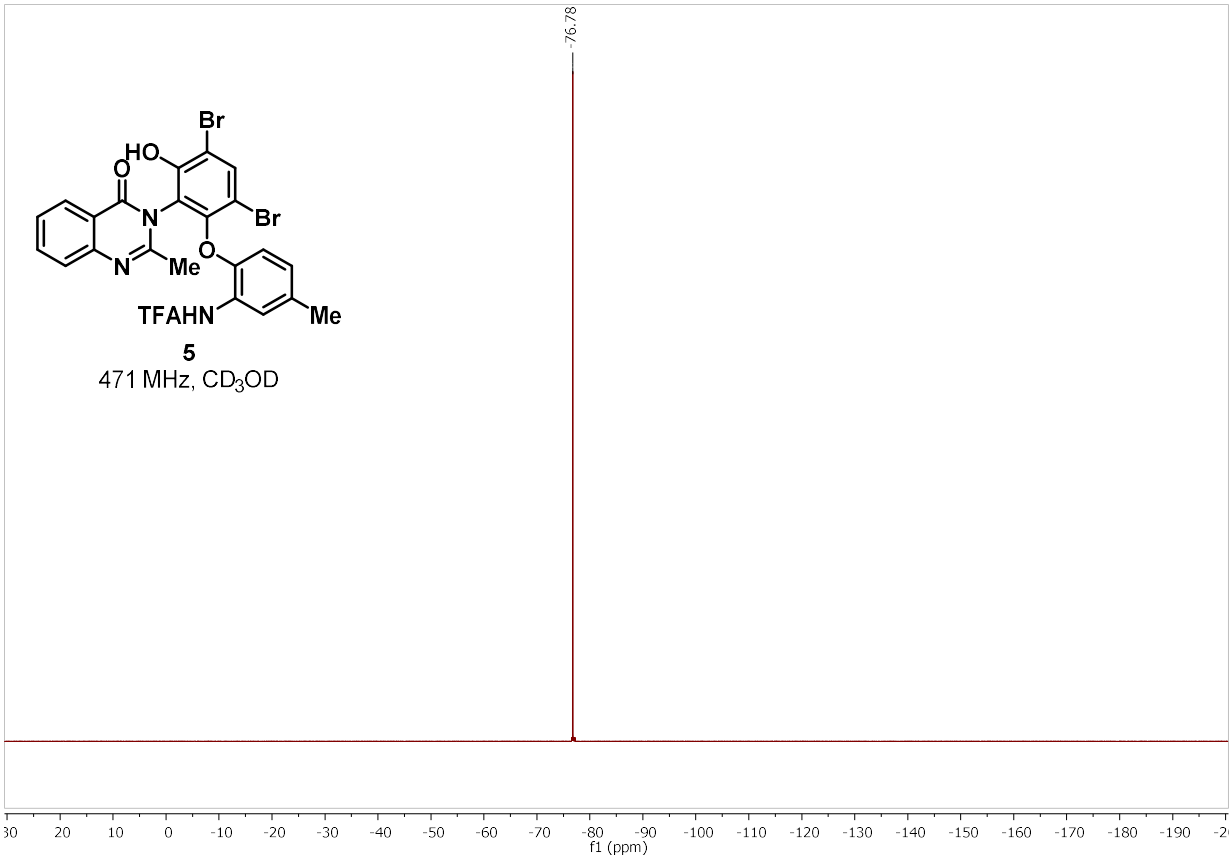


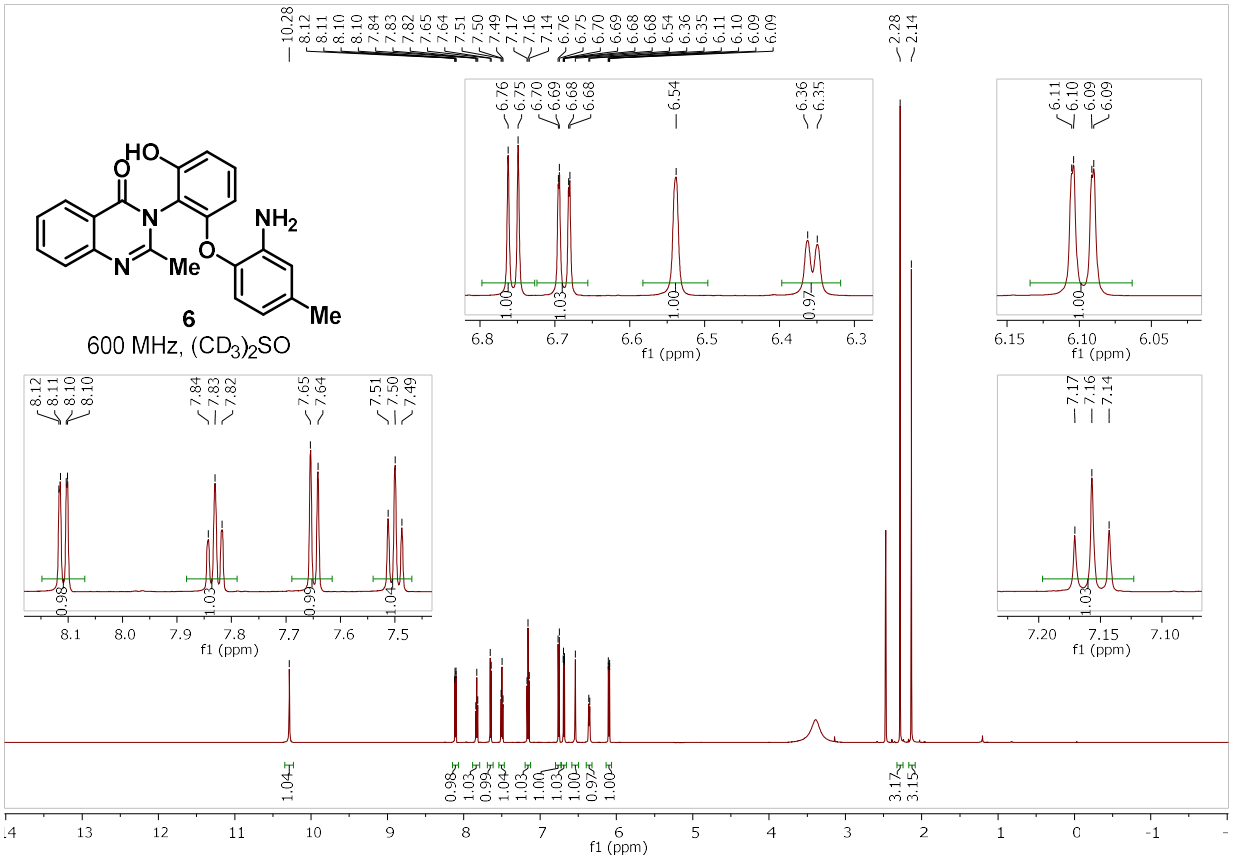
4

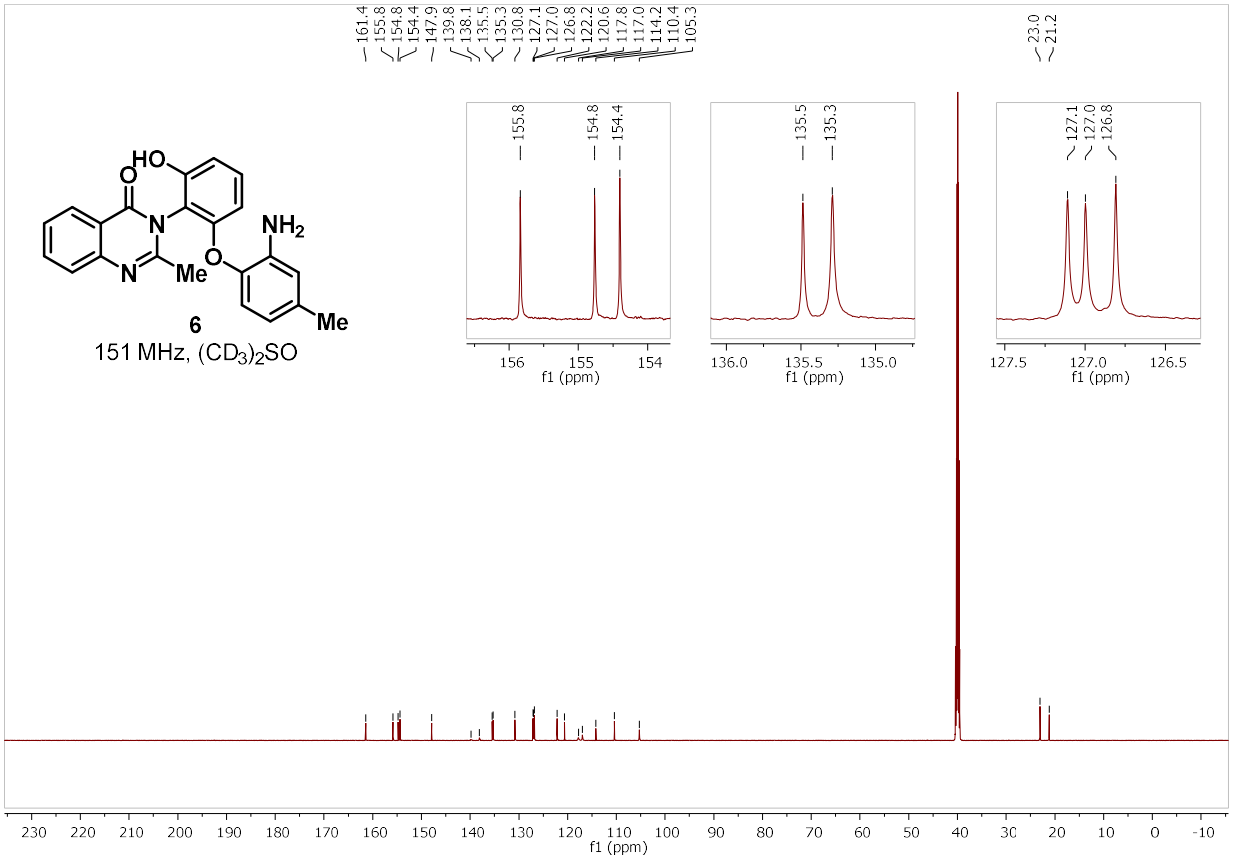
376 MHz, CD_3OD

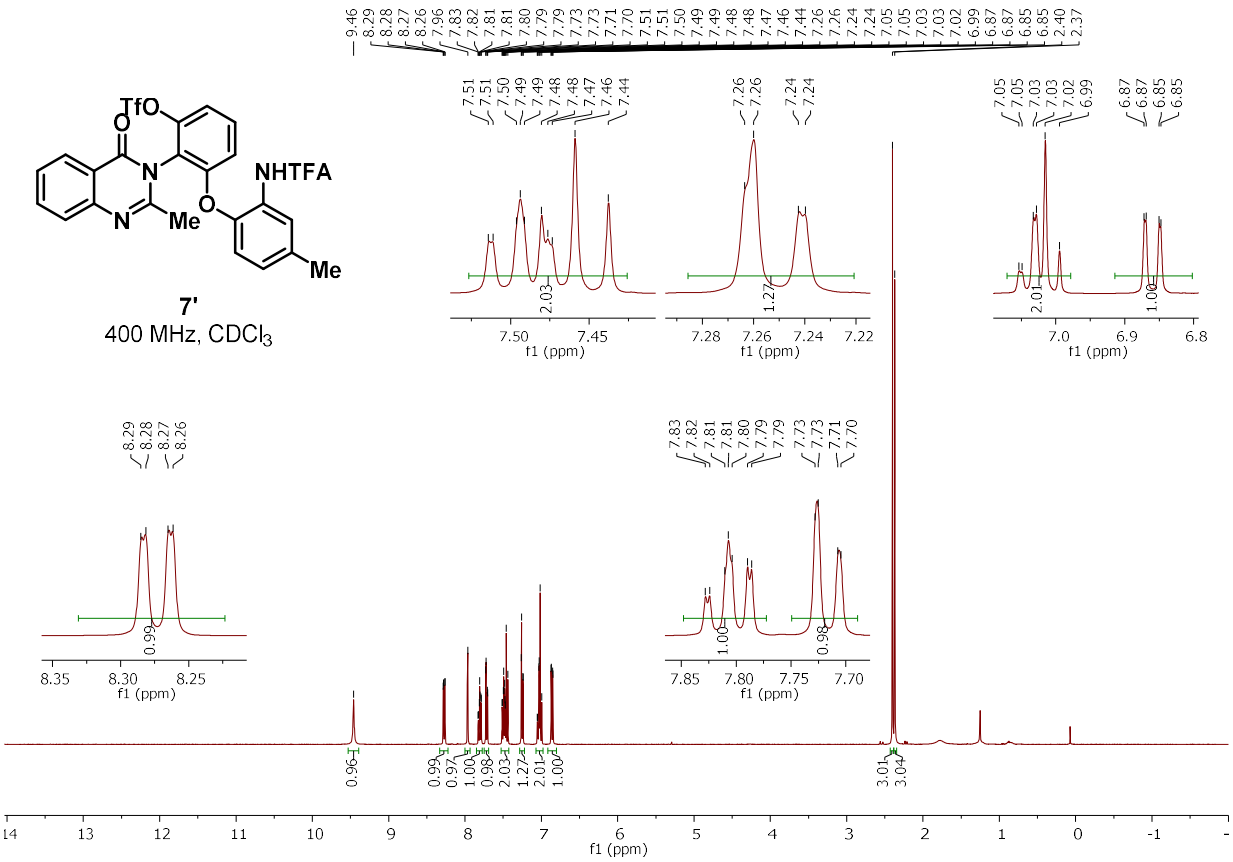

Br
HO
O
N
Br
O
N
Me
TFAHN
Me
5
500 MHz, CD3OD
f1 (ppm)

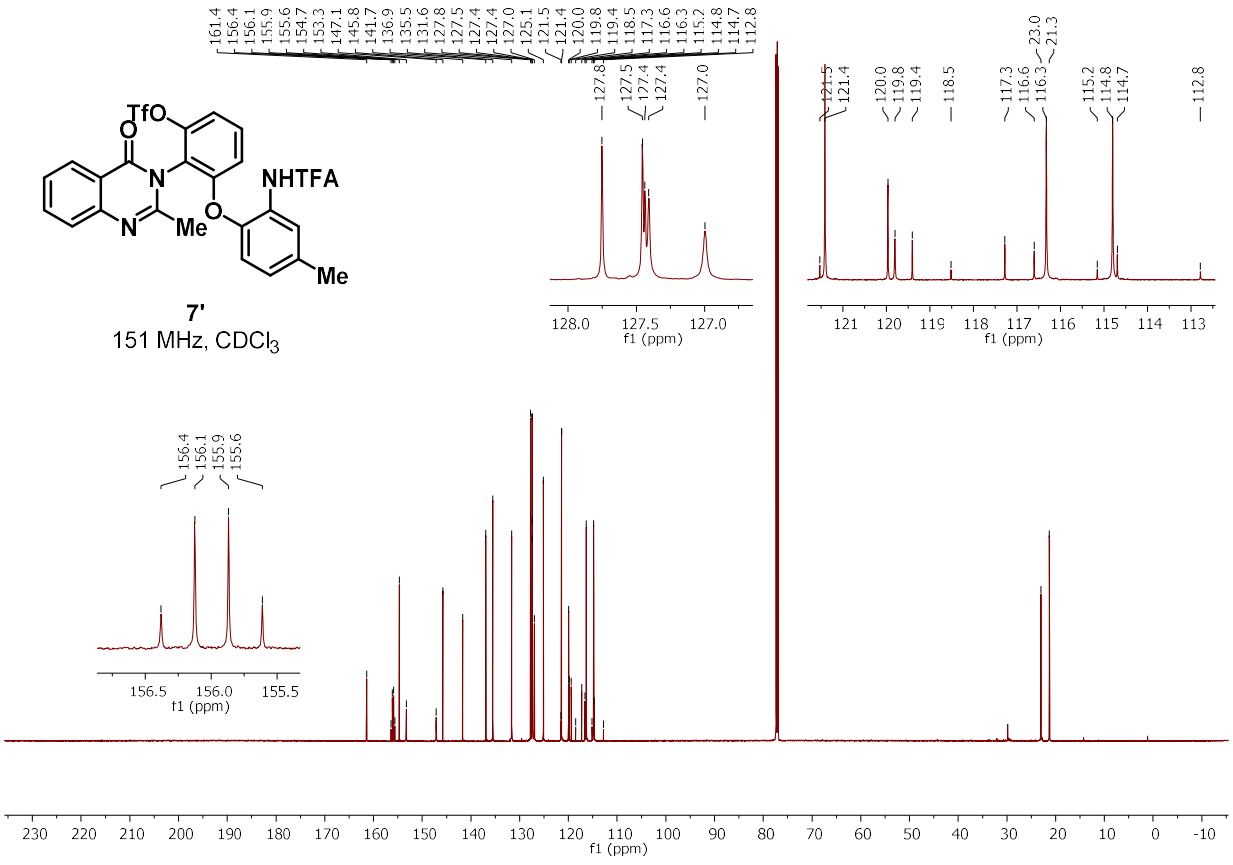

Br
HO
O
N
Br
O
N
Me
TFAHN
Me
5
126 MHz, CD3OD
f1 (ppm)

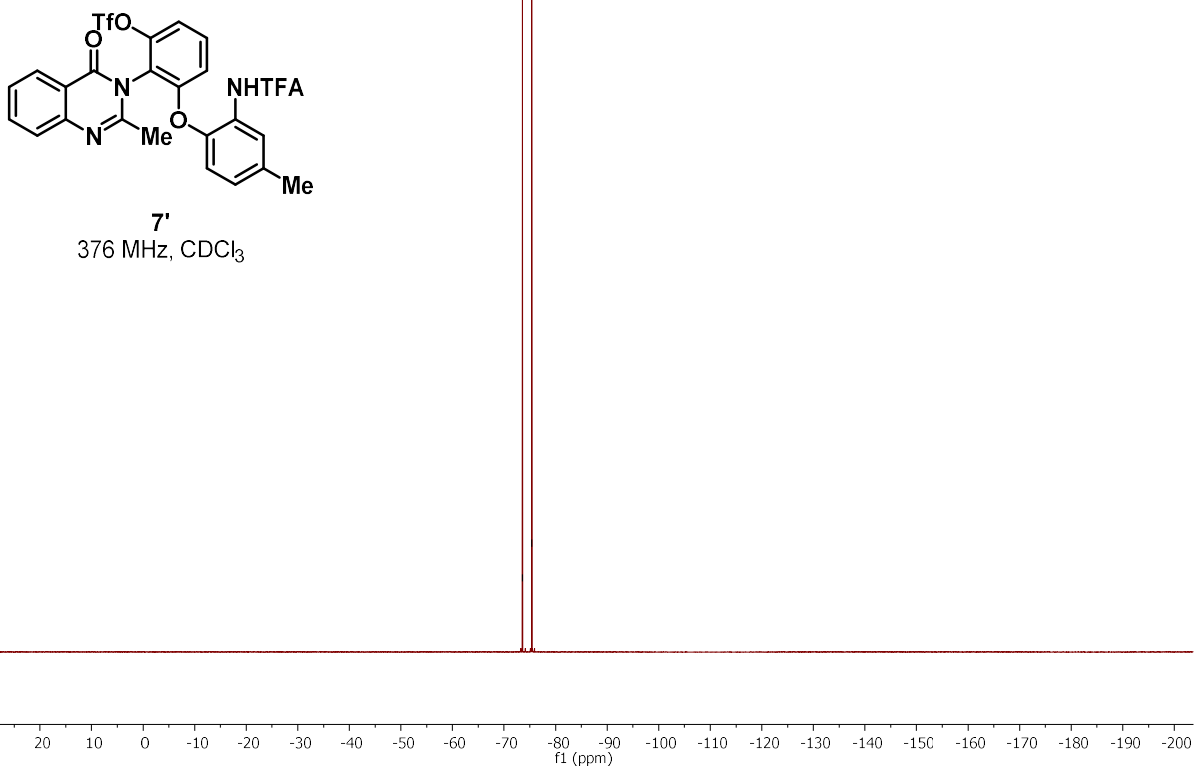

-76.78
Br
HO
O
N
Br
N
Me
O
TFAHN
Me
5
471 MHz, CD3OD
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


HO
O
N
N
Me
O
NH2
Me
6
600 MHz, (CD3)2SO
f1 (ppm)

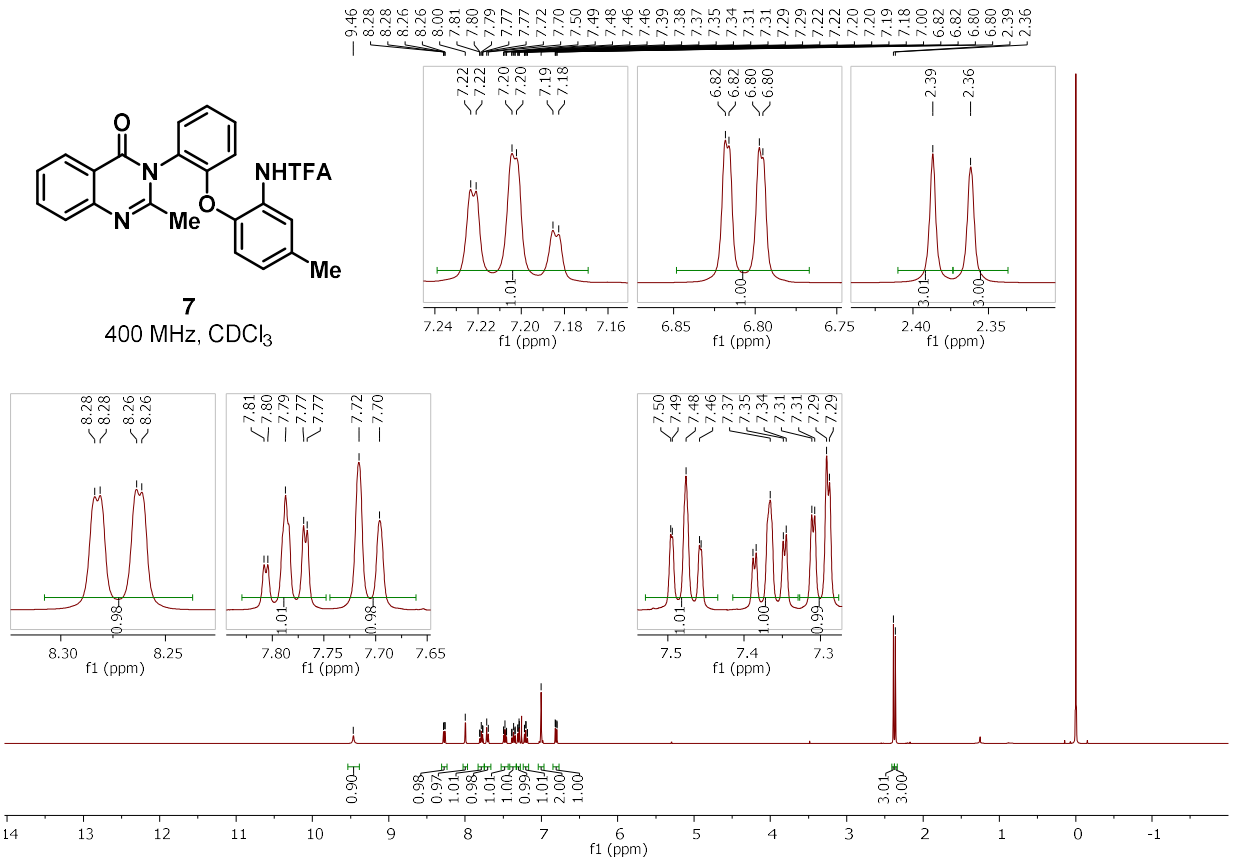

HO
O
N
N
Me
O
NH2
Me
6
151 MHz, (CD3)2SO
f1 (ppm)

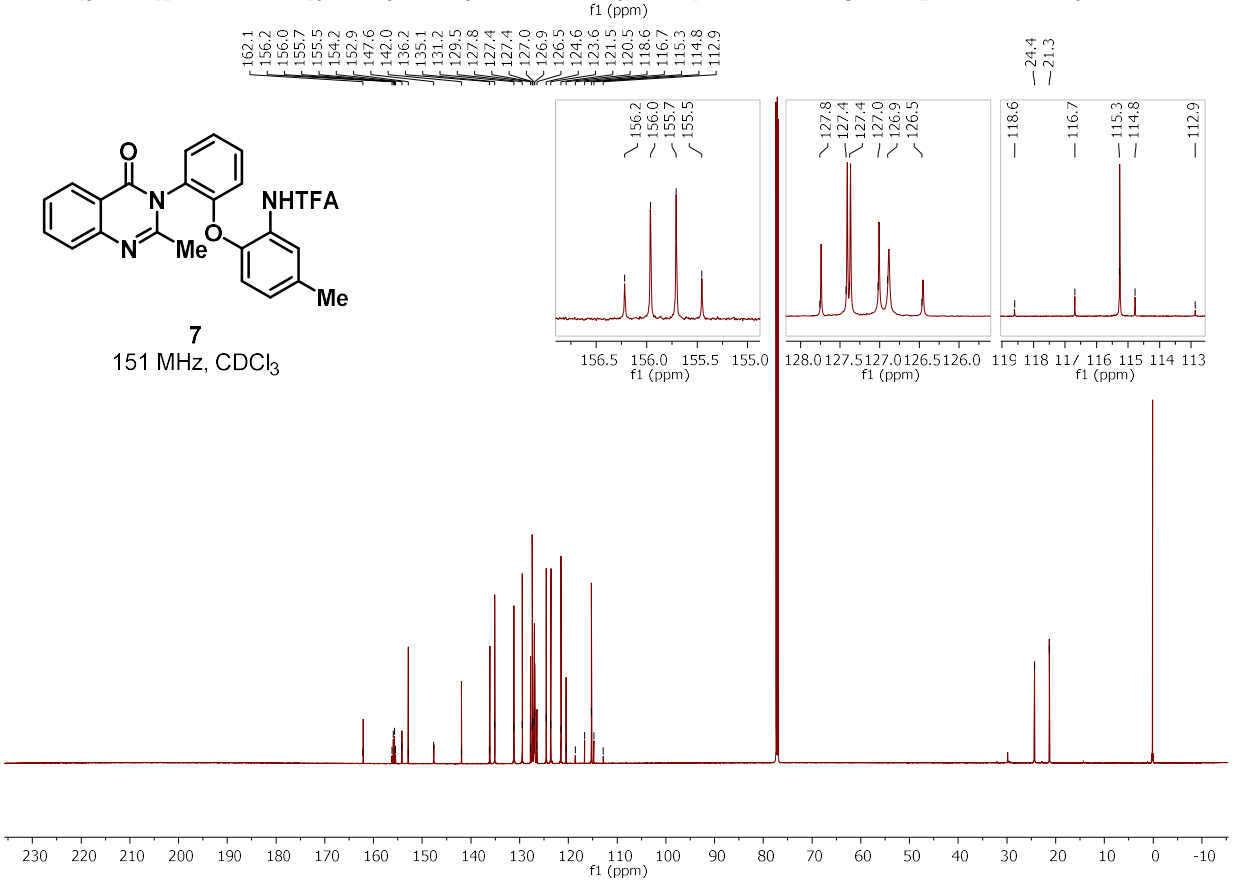

TfO
NHTFA
Me
Me
7'
400 MHz, CDCl3
f1 (ppm)

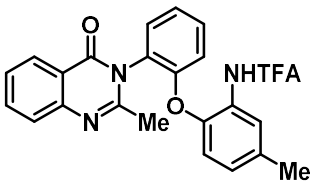

TfO
NHTFA
Me
Me
7'
151 MHz, CDCl3
f1 (ppm)



7'
376 MHz, $CDCl_3$


NHTFA
Me
Me
7
400 MHz, CDCl3
f1 (ppm)


NHTFA
Me
Me
7
151 MHz, CDCl3
f1 (ppm)



7
376 MHz, $CDCl_3$