Supporting Information

Rh(III)-Catalyzed Redox-Neutral C–H Activation/Annulation of Oxadiazolones with Sulfoxonium Ylides to access oxadiazoloisoquinolinone

Pothapragada SK Prabhakar Ganesh,[‡a] Eswaran Kamaraj,[‡b] Vairaperumal Veeramani,[c] Rajaram Rajmohan,*[d] Muthuraja Perumal,*[d]

[a] Department of Chemistry, Indian Institute of Science Education and Research (IISER), Tirupati, 517 507, India.

[b] Department of Chemistry, Yeungnam University, Gyeongsan 38541, Republic of Korea.

[c] Organic Chemistry Division, Syngene International Limited, Bangalore, Karnataka, 560 099, India,

[d] School of Chemical Engineering, Yeungnam University, Gyeongsan 38541, Republic of Korea.

E-mail: pmuthuraja.chem@yu.ac.kr ; rajmohanau@yu.ac.kr

TABLE OF CONTENTS

1.0 General remarks

All chemicals were obtained from commercial sources and were used as received unless otherwise noted. All the required anhydrous solvents were purchased from Sigma Aldrich. Reactions were monitored using precoated Aluminum supported silica gel 60 F254 TLC (thin layer chromatography) plates (Merck) and are visualized by UV light at 254 nm. All the final products were purified using column chromatography (100-200 mesh silica gel purchased from Merck). 1H NMR (400 MHz), 19F NMR (376 MHz), and ^{13}C NMR (100 MHz) spectra were recorded on the Bruker AVANCE NEO 400 MHz spectrometer. Deuterated chloroform, DMSO-d6 were used as solvents, and Chemical shifts (δ) for ^{1}H and ^{13}C-NMR spectra are given in ppm relative to tetramethylsilane (TMS) [δ 7.27 for 1H (chloroform-d), δ 77.0 for 13C (chloroform-d); δ 2.50 for 1H (DMSO- d6), δ 39.52 for 13C (DMSO-d6)], ^{19}F-NMR spectra are not externally calibrated and chemical shifts are given relative to CCl3F as received from automatic data processing. Abbreviations used in the NMR follow-up experiments: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; dd, doublet of doublet; m, multiplet. High resolution mass spectra (HRMS) were obtained from Orbitrap Elite HybridIon Trap-Orbitrap (Thermofischer scientific, Newington, NH, USA) Mass Spectrometer in electrospray ionization mode (ESI+) and Agilent Bio-QTOF-6545XT high resolution mass spectrometer in electrospray ionization mode (ESI+). X-ray data for the compound was collected on a Bruker D8 VENTURE diffractometer instrument with an IμS 3.0 Mo source (λ = 0.7107 Å) and a PHOTON-III C28 detector.

Sulfoxonium ylides[1] (**2a**-**2p)**, and 1,2,4-oxadiazol-5(2H)-one[2] (**1a-1k)** were prepared according to the literature procedures.

Table S1: Sulfoxonium ylides

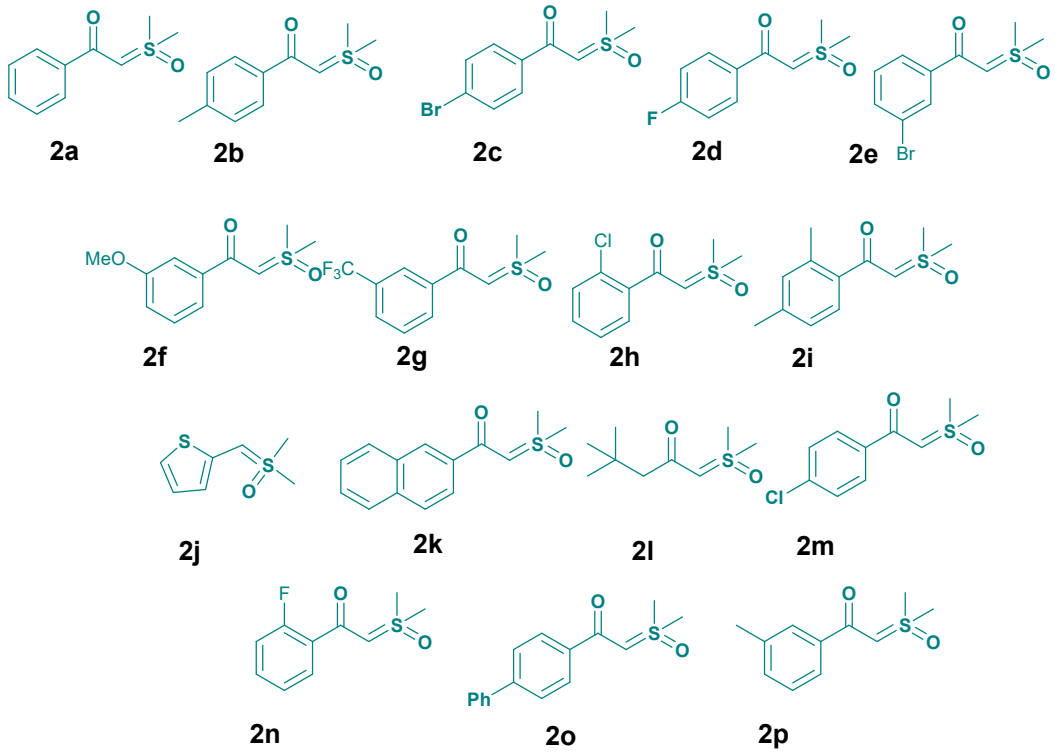
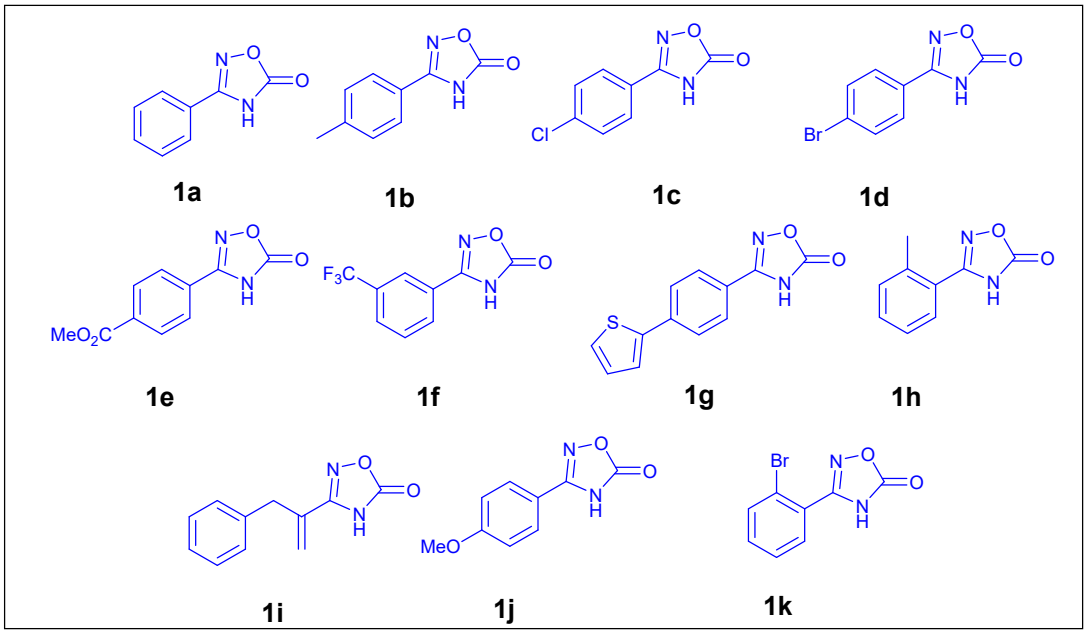


Table S2: Synthesized 1,2,4-oxadiazol-5(2H)-one



2 Experimental section

2.0 General procedure for the synthesis of compound 3a

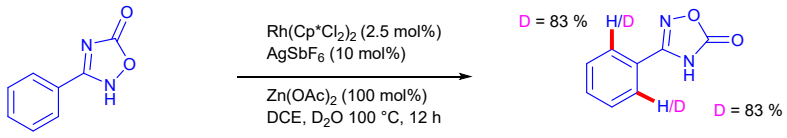
In a 10-mL screw cap reaction vial, 3-(*p*-tolyl)-1,2,4-oxadiazol-5(4H)-one **1b** (18.0 mg, 0.1 mmol), phenyl sulfoxonium ylide **2a** (43.2 mg, 0.22 mmol), zinc acetate (18.3 mg, 0.1 mmol), $[RhCp^*Cl_2]_2$ (1.23 mg, 2 mol%), $Agsbf_6$ (6.9 mg, 20 mol%), and 1.0 mL DCE were added. Then the reaction mixture was sealed with a screw cap after flushing with nitrogen and placed in oil bath at 100 °C. The reaction mixture was stirred at the same temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through a short silica gel bed (100-200 mesh), and concentrated under vacuum. The crude product was purified on a flash column chromatography using hexane/ethyl acetate (8:2) to afford the desired product **3a** in 30.12 mg, 73% yield.

2.1 Representative 4 mmol scale synthesis of (3a)

In a 25-mL screw cap reaction vial, 3-(*p*-tolyl)-1,2,4-oxadiazol-5(4H)-one **1b** (180 mg, 1.0 mmol), phenyl sulfoxonium ylide **1a** (432 mg, 2.2 mmol), zinc acetate (183 mg, 1.0 mmol), $[RhCp^*Cl_2]_2$ (12.3 mg, 2 mol%), $Agsbf_6$ (69 mg, 20 mol%), and 10 mL DCE were added. Then the reaction mixture was sealed with a screw cap after flushing with nitrogen and placed in oil bath at 100 °C. The reaction mixture was stirred at the same temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through a short silica gel bed (100-200 mesh), and concentrated under vacuum. The crude product was purified on a flash column chromatography using hexane/ethyl acetate (8:2) to afford the desired product **3a** in 284.4 mg, 69% yield.

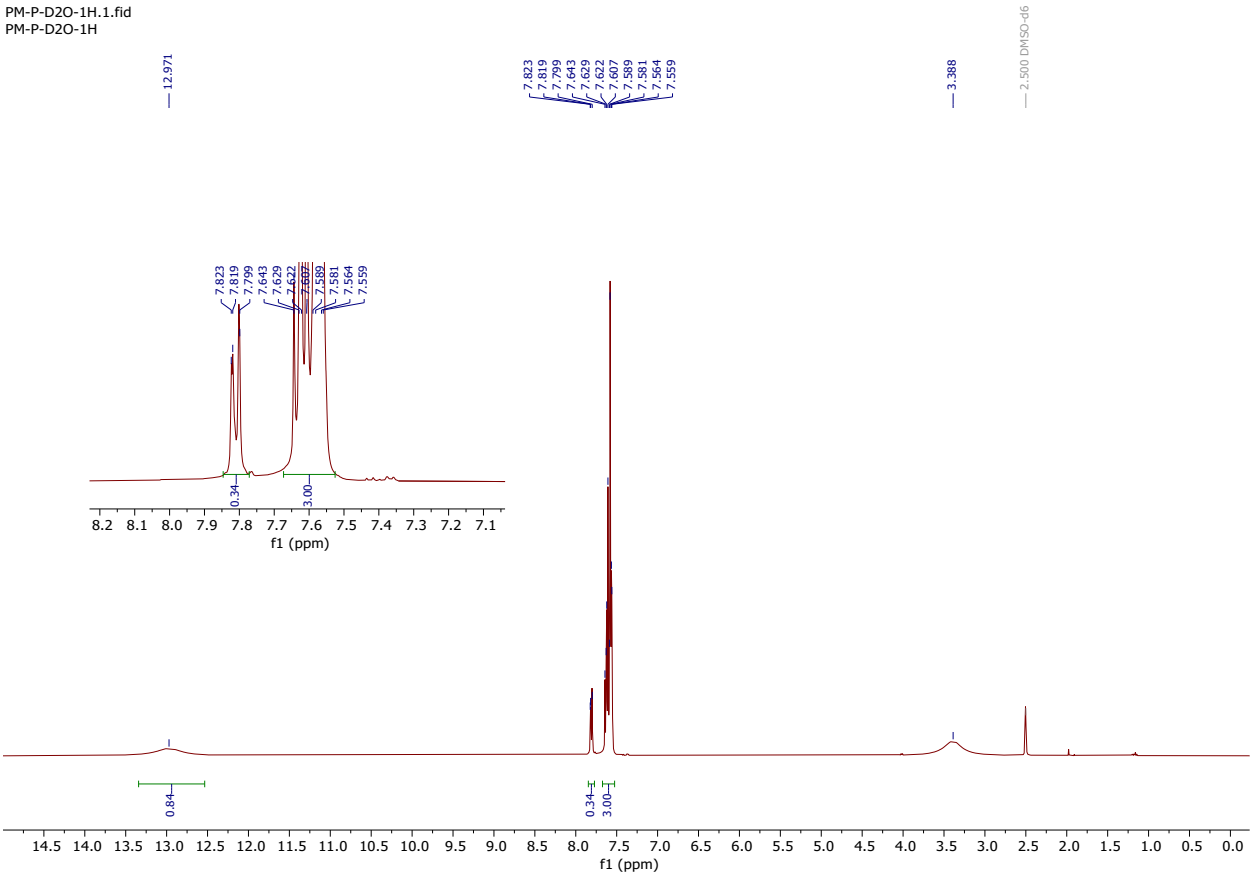
3.0 Control experiments:

Deuterium incorporation studies

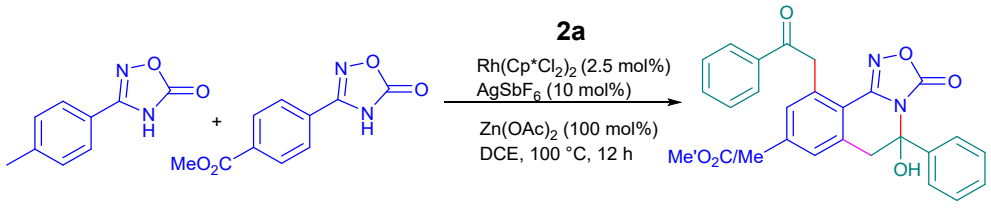


1a **1a/1a-D**

In a 10-mL screw cap reaction vial, 3-(*p*-tolyl)-1,2,4-oxadiazol-5(4H)-one **2a** (18.0 mg, 0.1 mmol), zinc acetate (18.3 mg, 0.1 mmol), $[RhCp^*Cl_2]_2$ (1.23 mg, 2 mol%), $Agsbf_6$ (6.9 mg, 20 mol%), D_2O (40.06 mg, 2.0 mmol), and 1.0 mL DCE were added. Then the reaction mixture was sealed with a screw cap after flushing with nitrogen and placed in oil bath at 100 °C. The reaction mixture was stirred at the same temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through a short silica gel bed (100-200 mesh), and concentrated under vacuum. The crude product was purified on a flash column chromatography using hexane/ethyl acetate (8:2) to afford the desired deuterio **1a-D** in 12.14 mg, 74% yield. The incorporation of deuterium was calculated from ^1H NMR spectrum.



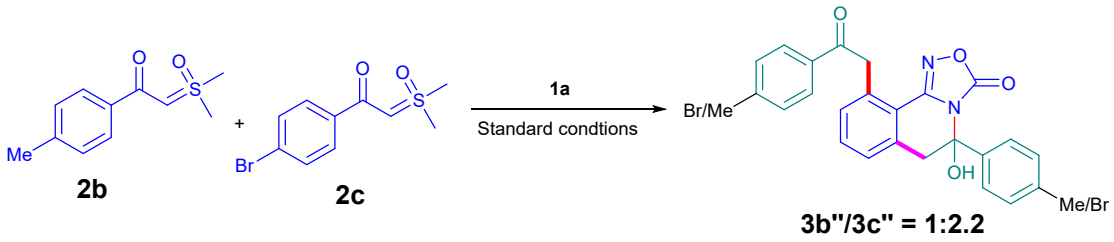
3.1 Competitive experiment between the oxadiazolone



1b **1e** **4b''/4e'' = 1:2**

In a 10-mL screw cap reaction vial, 3-(p-tolyl)-1,2,4-oxadiazol-5(4H)-one **1b** (8.8 mg, 0.05 mmol), methyl 4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzoate **1e** (11.0 mg, 0.05 mmol), phenyl sulfoxonium ylide **1a** (43.2 mg, 0.22 mmol), zinc acetate (18.3 mg, 0.1 mmol), $[RhCp^*Cl_2]_2$ (1.23 mg, 2 mol%), $Agsbf_6$ (6.9 mg, 20 mol%), and 1.0 mL DCE were added. Then the reaction mixture was sealed with a screw cap after flushing with nitrogen and placed in oil bath at 100 °C. The reaction mixture was stirred at the same temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through a short silica gel bed (100-200 mesh), and concentrated under vacuum. The crude product was purified on a flash column chromatography using hexane/ethyl acetate (8:2) to afford the desired product **4b''/4e''** in 1:2 ratio

3.2 Competitive experiment between the sulfoxonium ylide

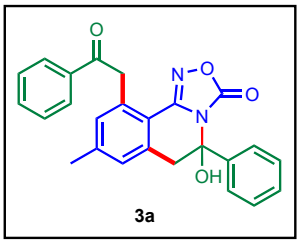


2b **2c** **3b''/3c'' = 1:2.2**

In a 10-mL screw cap reaction vial, 4-methyl-phenyl sulfoxonium ylide **2b** (46.26 mg, 2.2 mmol), 4-methyl-phenyl sulfoxonium ylide **2c** (60.53 mg, 2.2 mmol), 3-phenyl-1,2,4-oxadiazol-5(4H)-one **1a** (8.10 mg, 0.05 mmol), phenyl sulfoxonium ylide **1a** (43.2 mg, 0.22 mmol), zinc acetate (18.3 mg, 0.1 mmol), $[RhCp^*Cl_2]_2$ (1.23 mg, 2 mol%), $Agsbf_6$ (6.9 mg, 20 mol%), and 1.0 mL DCE were added. Then the reaction mixture was sealed with a screw cap after flushing with nitrogen and placed in oil bath at 100 °C. The reaction mixture was stirred at the same temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through a short silica gel bed (100-200 mesh), and concentrated under vacuum. The crude product was purified on a flash column chromatography using hexane/ethyl acetate (8:2) to afford the desired product **3b''/3c''** in 1:2.2 ratio

4.0 Characterization Data

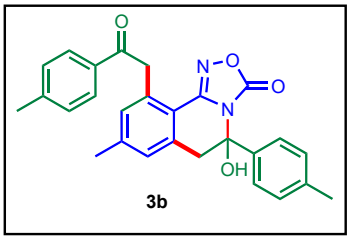
5-Hydroxy-8-methyl-10-(2-oxo-2-phenylethyl)-5-phenyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3a)



3a

Yield (0.1 mmol scale, 30.10 mg, 73%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 186-187 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.29 (m, 5H), 7.03 (s, 1H), 6.92 (s, 1H), 5.14 (s, 1H), 4.93 (d, *J* = 17.6 Hz, 1H), 4.68 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.38 (d, *J* = 16.0 Hz, 1H), 2.31 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.0, 157.2, 154.6, 143.3, 140.3, 137.0, 135.0, 134.3, 133.3, 132.8, 129.3, 129.0, 129.0, 128.7, 128.3, 124.8, 116.8, 86.2, 45.5, 45.1, 21.5; **HR-MS** (ESI) m/z calcd for $C_{25}H_{21}N_2O_4^+$ [M+H$^+$] 413.1496, found 413.1496.

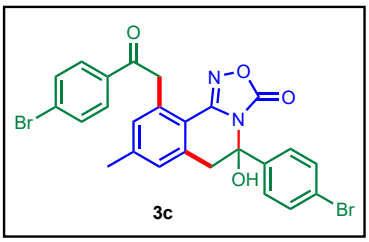
5-Hydroxy-8-methyl-10-(2-oxo-2-(*p*-tolyl)ethyl)-5-(*p*-tolyl)-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3b)



3b

Yield (0.1 mmol scale, 33.92 mg, 77%); light brown solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 196-198 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.4 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.74 (m, 1H), 4.83 (d, *J* = 17.0 Hz, 1H), 4.59 (d, *J* = 17.0 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.34 (d, *J* = 16.0 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.9, 157.2, 154.6, 143.1, 140.3, 138.8, 137.0, 135.1, 134.3, 134.0, 132.7, 130.0, 128.9, 128.7, 125.4, 121.7, 116.8, 86.22, 45.49, 45.04, 21.52, 21.47, 21.44.
δ 204.01, 177.82, 174.88, 159.85, 152.49, 138.43, 135.54, 129.27, 127.64, 125.99, 124.53, 124.31, 114.79, 55.67, 44.21, 41.59, 37.67, 29.95. **HR-MS** (ESI) m/z calcd for $C_{27}H_{25}N_2O_4^+$ [M+H$^+$] 441.1809, found 441.1800.

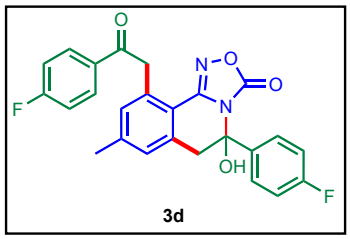
5-(4-bromophenyl)-10-(2-(4-bromophenyl)-2-oxoethyl)-5-hydroxy-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3c)



3c

Yield (0.1 mmol scale, 35.97 mg, 66%); brown solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 186-197 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H), 6.93 (s, 1H), 5.19 (s, 1H), 4.90 (d, *J* = 17.6 Hz, 1H), 4.57 (d, *J* = 17.6 Hz, 1H), 3.67 (d, *J* = 16.0 Hz, 1H), 3.32 (d, *J* = 16.0 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 196.0, 157.1, 154.4, 143.7, 139.4, 135.7, 134.8, 134.1, 133.0, 132.2, 132.1, 129.9, 129.8, 129.2, 128.6, 126.7, 123.7, 116.7, 85.9, 45.4, 45.0, 21.6.
HR-MS (ESI) m/z calcd for $C_{25}H_{19}Br_2N_2O_4^+$ [M+H$^+$] 571.9706, found 571.9701.

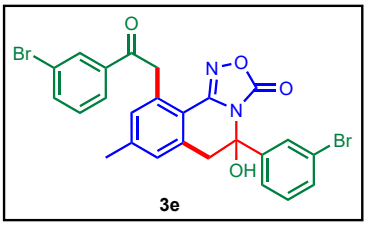
5-(4-Fluorophenyl)-10-(2-(4-fluorophenyl)-2-oxoethyl)-5-hydroxy-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3d)



3d

Yield (0.1 mmol scale, 29.60 mg, 66%); off white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 229-231 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.19 (t, *J* = 8.8 Hz, 2H), 7.08 – 7.00 (m, 3H), 6.93 (s, 1H), 5.14 (s, 1H), 4.93 (d, *J* = 17.6 Hz, 1H), 4.59 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.33 (d, *J* = 16.0 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 167.2(d, $^{1}J_{C-F}$ = 253.1 Hz), 164.4(d, $^{1}J_{C-F}$ = 247.4 Hz), 157.2, 154.5, 143.6, 136.3(d, $^{4}J_{C-F}$ = 3.2 Hz), 134.5, 134.2, 133.5(d, $^{4}J_{C-F}$ = 3.2 Hz), 132.9, 131.0(d, $^{3}J_{C-F}$ = 9.3 Hz), 129.1, 126.9(d, $^{3}J_{C-F}$ = 8.5 Hz), 116.8, 116.1(d, $^{2}J_{C-F}$ = 21.7 Hz), 116.0(d, $^{2}J_{C-F}$ = 21.7 Hz), 85.9, 45.4, 45.2, 21.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -104.91, -112.36.**HR-MS** (ESI) m/z calcd for $C_{25}H_{19}F_2N_2O_4^+$ [M+H$^+$] 449.1307, found 449.1302.

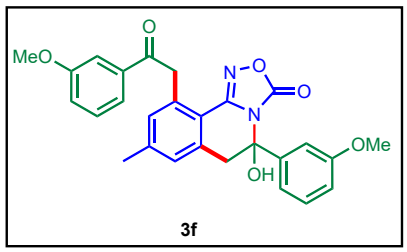
5-(3-Bromophenyl)-10-(2-(3-bromophenyl)-2-oxoethyl)-5-hydroxy-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3e)



3e

Yield (0.1 mmol scale, 31.36 mg, 55%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 196-198 °C; **^{1}H NMR** (600 MHz, Chloroform-*d*) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.60 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 5.22 (s, 1H), 4.88 (d, *J* = 17.4 Hz, 1H), 4.61 (d, *J* = 17.4 Hz, 1H), 3.67 (d, *J* = 16.2 Hz, 1H), 3.35 (d, *J* = 16.2 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.6, 157.0, 154.3, 143.7, 142.6, 138.7, 136.2, 134.6, 134.0, 133.0, 132.5, 131.3, 130.5, 130.4, 129.2, 128.3, 126.9, 123.5, 123.3, 123.1, 116.7, 85.4, 45.6, 45.1, 21.6. **HR-MS** (ESI) m/z calcd for $C_{25}H_{19}Br_2N_2O_4^+$ [M+H$^+$] 571.9706, found 571.9711.

5-Hydroxy-5-(3-methoxyphenyl)-10-(2-(3-methoxyphenyl)-2-oxoethyl)-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3f)

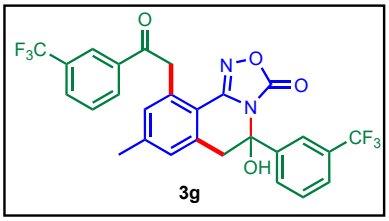


3f

Yield (0.1 mmol scale, 37.32 mg, 79%); white solid; (hexane/ethyl acetate = 7.5:2.5, V/V). Melting point: 193-195 °C; **^{1}H NMR** (600 MHz, Chloroform-*d*) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.59 (s, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.19 (dd, *J* = 7.6, 3.2 Hz, 1H), 7.06 (s, 1H), 6.96 (s, 1H), 6.93 – 6.84 (m, 3H), 5.16 (s, 1H), 4.93 (d, *J* = 17.5 Hz, 1H), 4.69 (d, *J* = 17.6 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.73 (d, *J* = 15.9 Hz, 1H), 3.41 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H).**^{13}C NMR** (100 MHz,

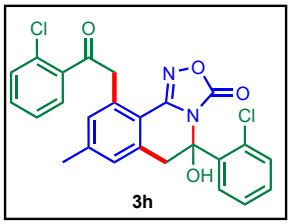
$CDCl_3$) δ 196.7, 160.0, 159.9, 157.2, 154.5, 143.3, 142.1, 138.4, 135.1, 134.3, 132.8, 130.1, 129.7, 129.0, 120.9, 119.6, 117.0, 116.8, 114.8, 112.7, 110.6, 86.09, 55.5, 55.4, 45.6, 45.0, 21.5. **HR-MS** (ESI) m/z calcd for $C_{27}H_{25}N_2O_6^+$ [M+H$^+$] 473.1707, found 324. 473.1702.

5-Hydroxy-8-methyl-10-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-5-(3-(trifluoromethyl)phenyl)-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3g)



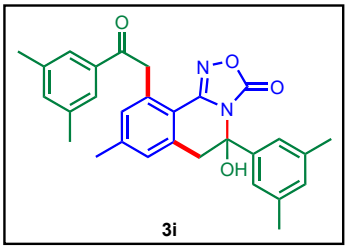
Yield (0.1 mmol scale, 27.97 mg, 51%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 183-185 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.07 (s, 1H), 6.97 (s, 1H), 5.28 (s, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 4.65 (d, *J* = 17.6 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.38 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.6, 156.8, 154.2, 143.7, 141.3, 137.4, 134.3, 133.8, 133.0, 132.0(q, J_{C-F} = 32.5 Hz), 131.4, 130.8(q, J_{C-F} = 32.5 Hz), 129.8(q, J_{C-F} = 3.7 Hz), 129.4, 129.2, 128.1, 127.8(q, J_{C-F} = 270.7 Hz), 126.2(q, J_{C-F} = 3.6 Hz), 125.0(q, J_{C-F} = 3.6 Hz), 121.1(q, J_{C-F} = 3.6 Hz), 116.5, 85.4, 45.5, 45.1, 21.4. **HR-MS** (ESI) m/z calcd for $C_{27}H_{19}F_6N_2O_4^+$ [M+H$^+$] 549.1244, found 549.1238.

5-(2-Chlorophenyl)-10-(2-(2-chlorophenyl)-2-oxoethyl)-5-hydroxy-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3h)



Yield (0.1 mmol scale, 30.80 mg, 64%); light brown solid; (hexane/ethyl acetate = 8:2 V/V). Melting point: 161-163 °C; **^{1}H NMR** (600 MHz, Chloroform-*d*) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 1.9 Hz, 1H), 7.95 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.59 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 2.0 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.10 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.05 (s, 1H), 6.95 (s, 1H), 5.18 (s, 1H), 4.89 (d, *J* = 17.6 Hz, 1H), 4.62 (d, *J* = 17.6 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.36 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.7, 157.0, 154.4, 143.7, 142.4, 138.5, 135.2, 135.1, 134.6, 134.0, 133.3, 133.0, 130.3, 130.1, 129.6, 129.2, 128.4, 126.4, 125.4, 123.0, 116.7, 85.6, 21.6. **HR-MS** (ESI) m/z calcd for $C_{25}H_{19}Cl_2N_2O_4^+$ [M+H$^+$] 481.0716, found 481.0700.

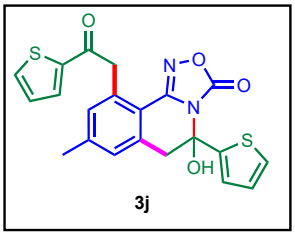
5-(3,5-Dimethylphenyl)-10-(2-(3,5-dimethylphenyl)-2-oxoethyl)-5-hydroxy-8-methyl-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3i)



Yield (0.1 mmol scale, 36.54 mg, 81%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 186-188 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.00 (s, 1H), 6.96 (s, 1H), 6.91 (s, 3H), 5.02 (s, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 4.59 (d, *J* = 17.6 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.0 Hz, 1H), 2.42 (s, 6H), 2.32 (s, 4H), 2.30 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.0, 157.4,

154.8, 143.1, 140.3, 138.6, 138.3, 137.2, 135.31, 134.9, 134.4, 132.7, 131.0, 128.9, 126.0, 122.6, 116.9, 86.3, 45.6, 45.0, 21.5, 21.4, 21.4. **HR-MS** (ESI) m/z calcd for $C_{29}H_{29}N_2O_4^+$ [M+H$^+$] 469.2122, found 469.2122.

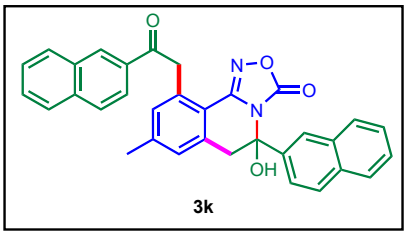
5-Hydroxy-8-methyl-10-(2-oxo-2-(thiophen-2-yl)ethyl)-5-(thiophen-2-yl)-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3j)



3j

Yield (0.1 mmol scale, 27.16 mg, 64%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 180-182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.4 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.74 (m, 1H), 4.83 (d, *J* = 17.0 Hz, 1H), 4.59 (d, *J* = 17.0 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.34 (d, *J* = 16.0 Hz, 1H), 2.36 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 156.9, 154.2, 143.6, 142.5, 138.6, 136.1, 134.5, 133.9, 132.5, 131.2, 130.4, 129.1, 126.7, 123.4, 123.2, 116.6, 85.4, 45.5, 44.9, 21.5. **HR-MS** (ESI) m/z calcd for $C_{21}H_{17}N_2O_4S_2^+$ [M+H$^+$] 425.0624, found 425.0616.

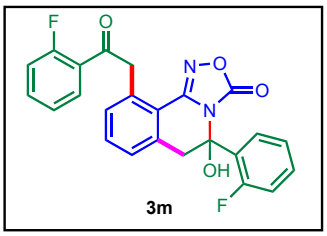
5-Hydroxy-8-methyl-5-(naphthalen-2-yl)-10-(2-(naphthalen-2-yl)-2-oxoethyl)-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3k)



3k

Yield (0.1 mmol scale, 39.98 mg, 78%); off white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 198-200 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (t, *J* = 7.2 Hz, 3H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.67 – 7.56 (m, 3H), 7.54 – 7.47 (m, 3H), 7.07 (s, 1H), 6.90 (s, 1H), 5.25 (s, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 4.78 (d, *J* = 17.6 Hz, 1H), 3.80 (d, *J* = 16.0 Hz, 1H), 3.47 (d, *J* = 16.0 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.8, 157.4, 154.9, 143.4, 137.4, 135.9, 135.2, 134.5, 134.4, 133.5, 132.9, 132.9, 132.7, 130.0, 129.8, 129.3, 129.1, 128.9, 128.6, 128.6, 127.9, 127.6, 127.0, 126.9, 126.8, 124.4, 124.1, 122.4, 117.1, 86.6, 45.6, 45.1, 21.5. **HR-MS** (ESI) m/z calcd for $C_{33}H_{25}N_2O_4^+$ [M+H$^+$] 513.1809, found 513.1801.

5-(2-Fluorophenyl)-10-(2-(2-fluorophenyl)-2-oxoethyl)-5-hydroxy-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3m)

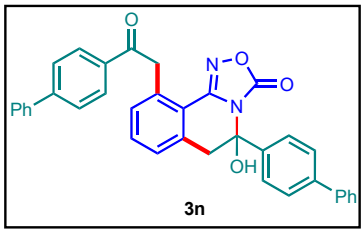


3m

Yield (0.1 mmol scale, 32.15 mg, 74%); off white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 182-184 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7. Hz, 1H), 7.88 – 7.76 (m, 2H), 7.63 – 7.53 (m, 2H), 7.46 – 7.38 (m, 2H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.12 (td, *J* = 8.4, 2.4 Hz, 1H), 5.45 (s, 1H), 5.03 (d, *J* = 17.6 Hz, 1H), 4.79 (d, *J* = 17.6 Hz, 1H), 3.79 (d, *J* = 16.0 Hz, 1H), 3.52 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.8, 164.27 (d, $^1J_{C-F}$ = 246.4

Hz), 164.22 (d, $^{1}J_{C-F}$ = 246.4 Hz), 157.0, 154.3, 142.7 (d, $^{3}J_{C-F}$ = 6.6 Hz), 138.9 (d, $^{3}J_{C-F}$ = 6.4 Hz), 134.8, 134.2, 132.8, 132.1, 130.7 (d, $^{3}J_{C-F}$ = 7.9 Hz), 130.5 (d, $^{3}J_{C-F}$ = 7.9 Hz), 129.5, 126.1, 124.1 (d, $^{4}J_{C-F}$ = 2.9 Hz), 120.64, 120.4, 119.4, 116.6 (d, $^{2}J_{C-F}$ = 21.0 Hz), 115.2 (d, $^{1}J_{C-F}$ = 22.2 Hz), 112.7 (d, $^{2}J_{C-F}$ = 23.6 Hz), 85.6, 45.8, 45.2. **HR-MS** (ESI) m/z calcd for $C_{24}H_{17}F_2N_2O_4^+$ [M+H$^+$] 435.1151, found 435.1144.

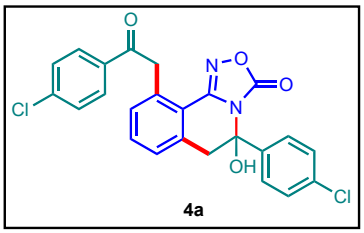
5-([1,1'-biphenyl]-4-yl)-10-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-5-hydroxy-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (3n)



3n

Yield (0.1 mmol scale, 45.70 mg, 83%); off white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 3H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.46 (m, 5H), 7.46 – 7.40 (m, 5H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 17.6 Hz, 1H), 4.76 (d, *J* = 17.6 Hz, 1H), 4.48 (s, 1H), 3.75 (d, *J* = 16.0 Hz, 1H), 3.49 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.7, 161.7, 157.3, 157.1, 154.6, 146.1, 142.2, 140.0, 138.9, 135.7, 135.3, 134.5, 132.6, 132.6, 132.0, 129.4, 129.0, 128.9, 127.8, 127.7, 127.4, 127.1, 126.1, 125.4, 122.6, 119.6, 86.2, 45.8, 45.4. **HR-MS** (ESI) m/z calcd for $C_{36}H_{27}N_2O_4^+$ [M+H$^+$] 551.1965, found 551.1975.

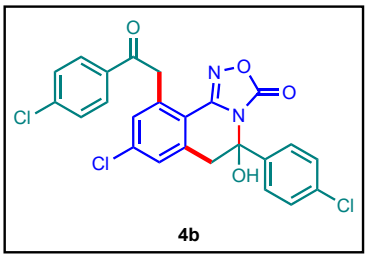
5-(4-Chlorophenyl)-10-(2-(4-chlorophenyl)-2-oxoethyl)-5-hydroxy-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-onedione (4a)



4a

Yield (0.1 mmol scale, 34.11 mg, 79%); off white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 191-193 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.30 – 7.22 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 1H), 5.12 (s, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 4.64 (d, *J* = 17.6 Hz, 1H), 3.72 (d, *J* = 16.0 Hz, 1H), 3.39 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.6, 157.0, 154.4, 139.9, 138.7, 135.5, 135.3, 135.0, 134.2, 132.7, 132.1, 131.6, 129.7, 129.3, 129.1, 129.0, 128.5, 126.4, 119.6, 85.8, 45.6, 45.2. **HR-MS** (ESI) m/z calcd for $C_{24}H_{17}Cl_2N_2O_4^+$ [M+H$^+$] 467.0560, found 467.0566.

8-Chloro-5-(4-chlorophenyl)-10-(2-(4-chlorophenyl)-2-oxoethyl)-5-hydroxy-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (4b)

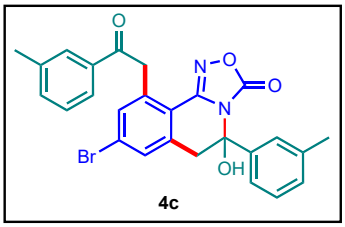


4b

Yield (0.1 mmol scale, 33.11 mg, 66%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 189-190 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 4H), 7.17 (s, 1H), 5.22 (s, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 4.61 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.0, 156.8, 153.9, 140.1, 138.8, 138.4, 136.8,

135.8, 135.7, 135.0, 132.2, 131.6, 129.7, 129.4, 129.2, 129.0, 128.5, 126.4, 118.2, 85.7, 45.4, 45.1. **HR-MS** (ESI) m/z calcd for $C_{24}H_{17}Cl_3N_2O_4^+$ [M+H$^+$] 501.0170, found 501.0162.

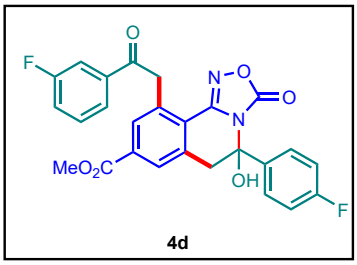
8-bromo-5-hydroxy-10-(2-oxo-2-(*m*-tolyl)ethyl)-5-(m-tolyl)-5,6-dihydro-3H-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (4c)



4c

Yield (0.1 mmol scale, 34.37 mg, 68%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 170-172 °C; 400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.11 (s, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 5.03 (s, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 4.63 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.38 (d, *J* = 16.1 Hz, 1H), 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.1, 157.0, 154.1, 139.9, 139.1, 138.6, 138.4, 137.2, 136.8, 136.1, 134.3, 132.0, 130.4, 129.0, 128.8, 128.7, 128.3, 125.5, 125.4, 121.8, 118.4, 86.2, 45.5, 45.0, 21.6, 21.5. **HR-MS** (ESI) m/z calcd for $C_{26}H_{22}BrN_2O_4^+$[M+H$^+$] 505.0757, found 505.0748.

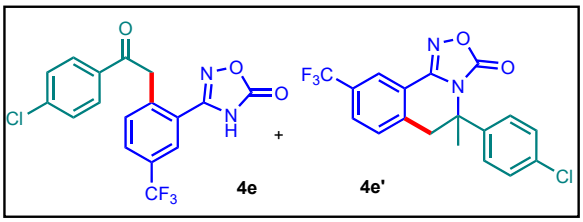
Methyl 5-(4-fluorophenyl)-10-(2-(3-fluorophenyl)-2-oxoethyl)-5-hydroxy-3-oxo-5,6-dihydro-3*H*-[1,2,4]oxadiazolo[3,4-a]isoquinoline-8-carboxylate (4d)



4d

Yield (0.1 mmol scale,35.46, 72%); brown solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 171-172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.90 (s, 1H), 7.79 (s, 1H), 7.31 (dd, *J* = 8.8, 4.8 Hz, 2H), 7.20 (t, *J* = 8.6 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 5.22 (s, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 4.70 (d, *J* = 17.6 Hz, 1H), 3.90 (s, 3H), 3.76 (d, *J* = 16.0 Hz, 1H), 3.47 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.7, 167.3(d, $^{1}J_{C-F}$ = 253.6 Hz), 165.5, 164.5(d, $^{1}J_{C-F}$ = 247.8 Hz), 156.8, 154.0, 135.7(d, $^{4}J_{C-F}$ = 3.2 Hz), 135.5, 134.6, 133.5, 133.2(d, $^{4}J_{C-F}$ = 2.9Hz), 132.8, 131.0(d, $^{3}J_{C-F}$ = 9.3 Hz), 129.3, 127.0(d, $^{3}J_{C-F}$ = 8.4 Hz), 123.5, 116.3(d, $^{2}J_{C-F}$ = 21.6 Hz), 116.0(d, $^{2}J_{C-F}$ = 21.9 Hz), 86.0, 52.8, 45.5, 45.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -104.40, -111.93. **HR-MS** (ESI) m/z calcd for $C_{26}H_{19}F_2NO_6^+$ [M+H$^+$] 493.1206, found 493.1200.

3-(2-(2-(4-Chlorophenyl)-2-oxoethyl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5(4*H*)-one (4e+4e')

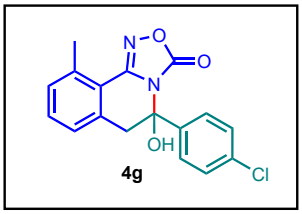


4e 4e'

Yield (0.1 mmol scale, 27.56 mg, 72%); Yellow solid; (hexane/ethyl acetate = 8:2, V/V). **^{1}H NMR** (400 MHz, DMSO-d*6*) δ 12.11 (s, 1H), 7.23 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.2, 3.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.02 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-d*6*) δ 195.3, 159.3, 156.8, 139.6, 138.3, 135.0, 131.1(q, J_{C-F} = 270 Hz), 129.9, 128.9, 128.7,

128.1, 128.0, 127.9(q, J_{C-F} = 3.6 Hz), 127.5(q, J_{C-F} = 3.8 Hz), 125.70, 125.14, 44.2. **^{19}F NMR** (376 MHz, DMSO-d*6*) δ -61.16. **HR-MS** (ESI) m/z calcd for $C_{17}H_{11}ClF_3N_2O_3^+$ [M+H$^+$] 383.0405 found 383.0400.

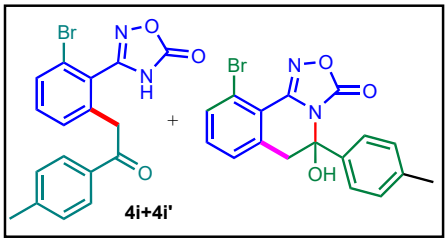
5-(4-Chlorophenyl)-5-hydroxy-10-methyl-5,6-dihydro-3H-[1,2,4]oxadiazolo[3,4-a]isoquinolin-3-one (4g)



4g

Yield (0.1 mmol scale, 25.26 mg, 77%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 178-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.18 (s, 1H), 3.70 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.0 Hz, 1H), 2.70 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 154.8, 139.4, 139.1, 135.5, 133.7, 132.5, 131.3, 129.3, 126.9, 126.2, 118.5, 85.7, 45.0, 22.9. **HR-MS** (ESI) m/z calcd for $C_{17}H_{14}ClN_2O_3^+$ [M+H$^+$] 329.0687, found 329.0681.

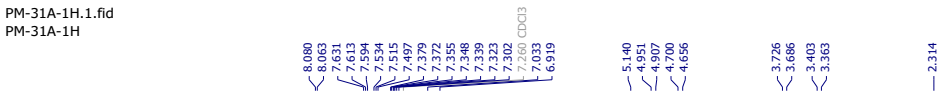
3-(2-Bromo-6-(2-oxo-2-(p-tolyl)ethyl)phenyl)-1,2,4-oxadiazol-5(4H)-one (4i+4i')

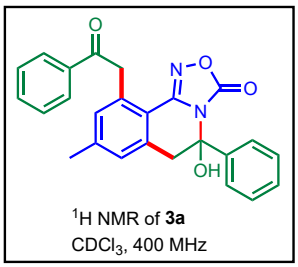


4i+4i'

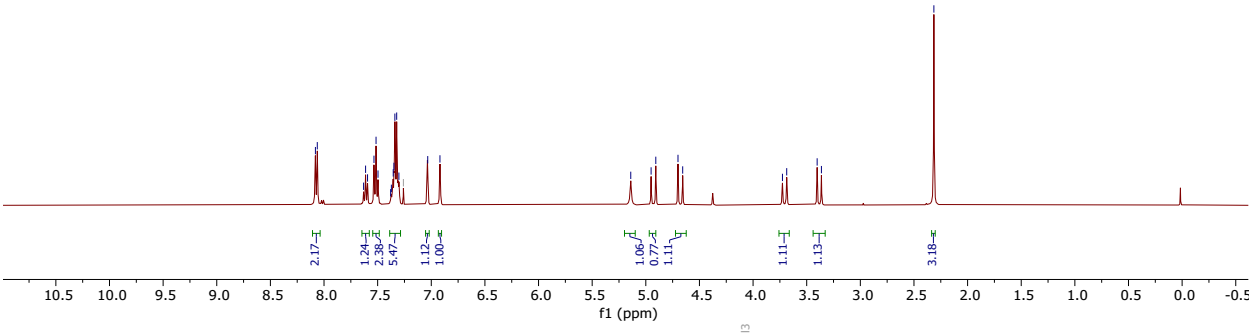
Yield (0.1 mmol scale, 24.63 mg, 66%); white solid; (hexane/ethyl acetate = 8:2, V/V). Melting point: 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.11 (m, 1H), 4.47 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 158.8, 156.0, 139.0, 137.8, 135.8, 135.2, 133.0, 132.4, 130.3, 129.1, 128.9, 125.8, 43.6, 21.4. **HR-MS** (ESI) m/z calcd for $C_{17}H_{14}BrN_2O_3^+$ [M+H$^+$] 374.0182, found 374.0190.

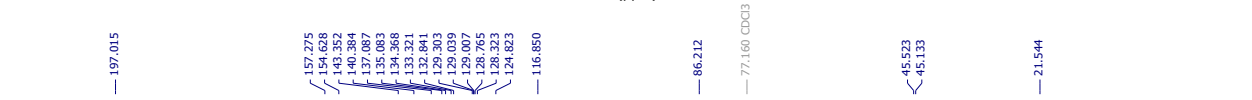
PM-31A-1H.1.fid
PM-31A-1H

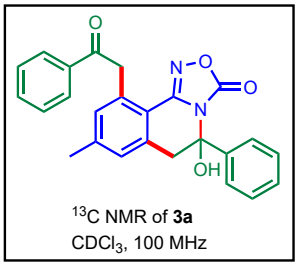




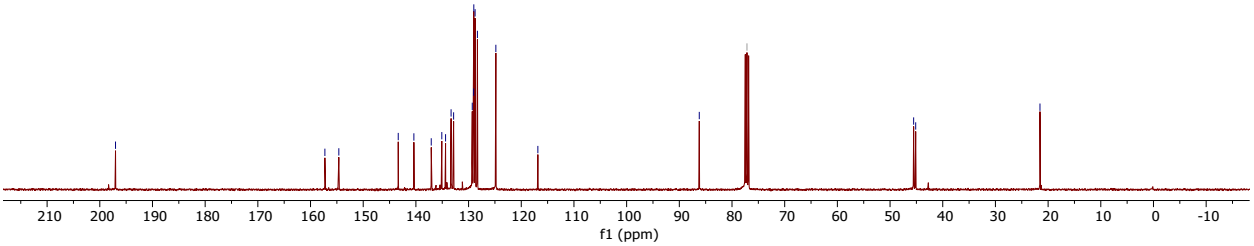
^{1}H NMR of **3a**
$CDCl_3$, 400 MHz





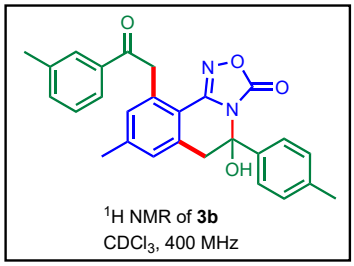


^{13}C NMR of **3a**
$CDCl_3$, 100 MHz

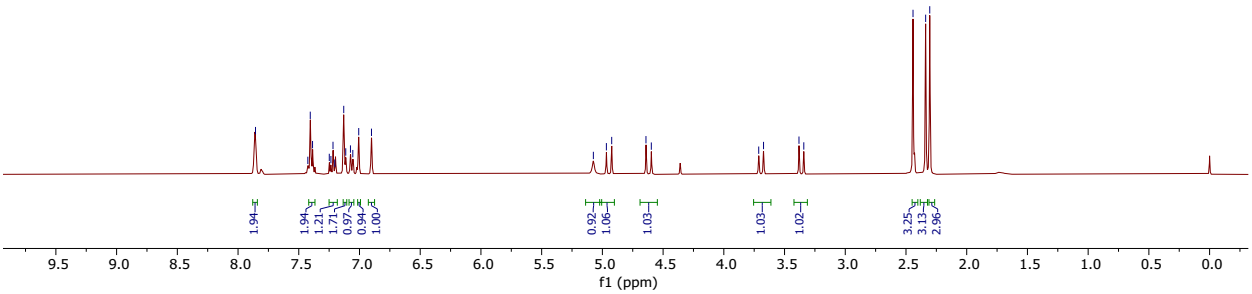


1 (4)/1

7.856
7.425
7.405
7.387
7.249
7.235
7.218
7.203
7.130
7.113
7.074
7.055
7.006
6.901
5.074
4.967
4.923
4.641
4.597
3.713
3.673
3.381
3.341
2.442
2.338
2.304

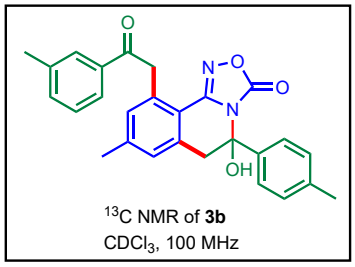


^{1}H NMR of **3b**
$CDCl_3$, 400 MHz

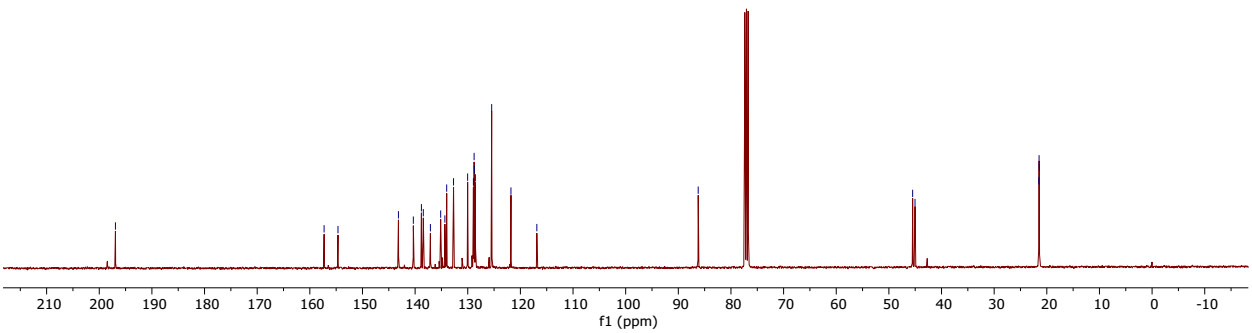


10 (3).20.fid

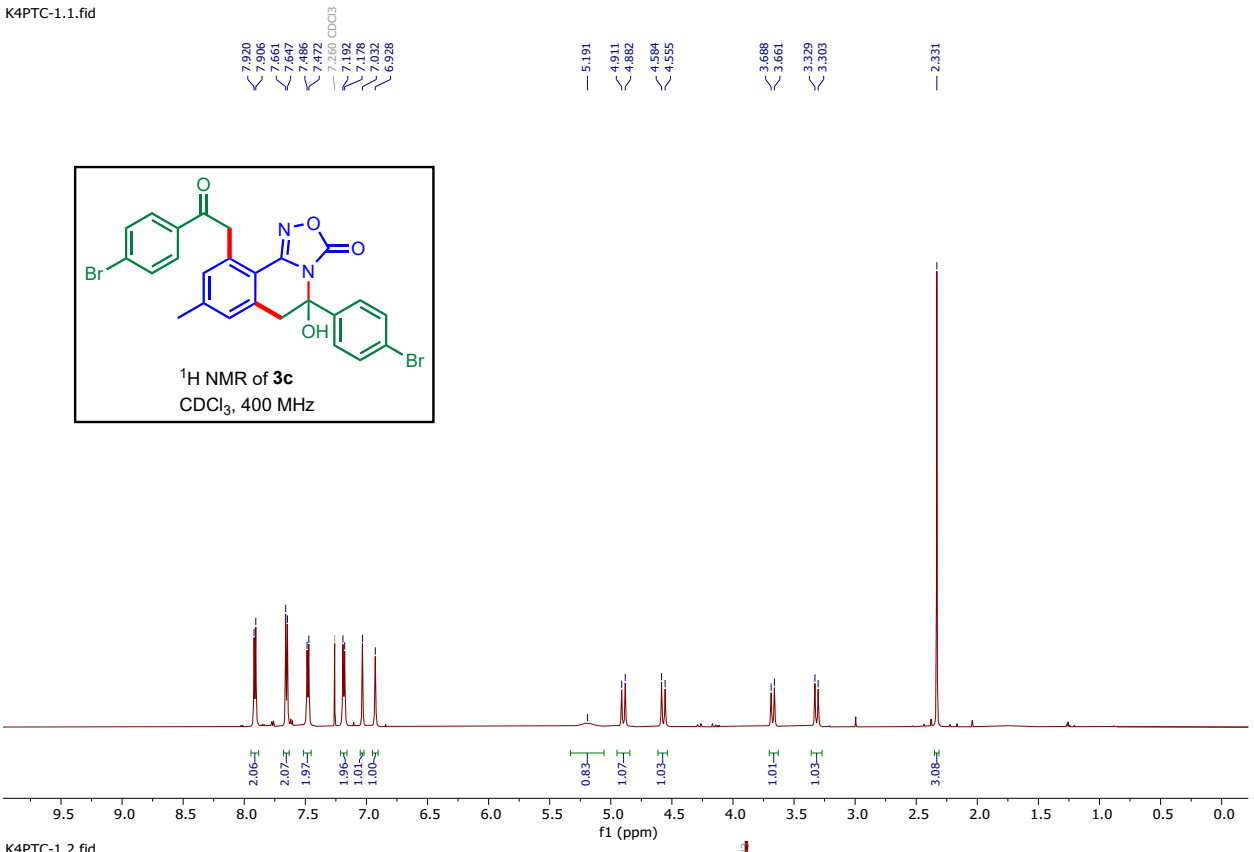
196.929
157.289
154.651
143.168
140.336
138.803
138.444
137.093
135.143
134.346
134.000
132.702
130.021
128.926
128.792
128.734
128.555
125.455
121.793
116.876
86.222
45.486
45.035
21.518
21.468
21.444



^{13}C NMR of **3b**
$CDCl_3$, 100 MHz

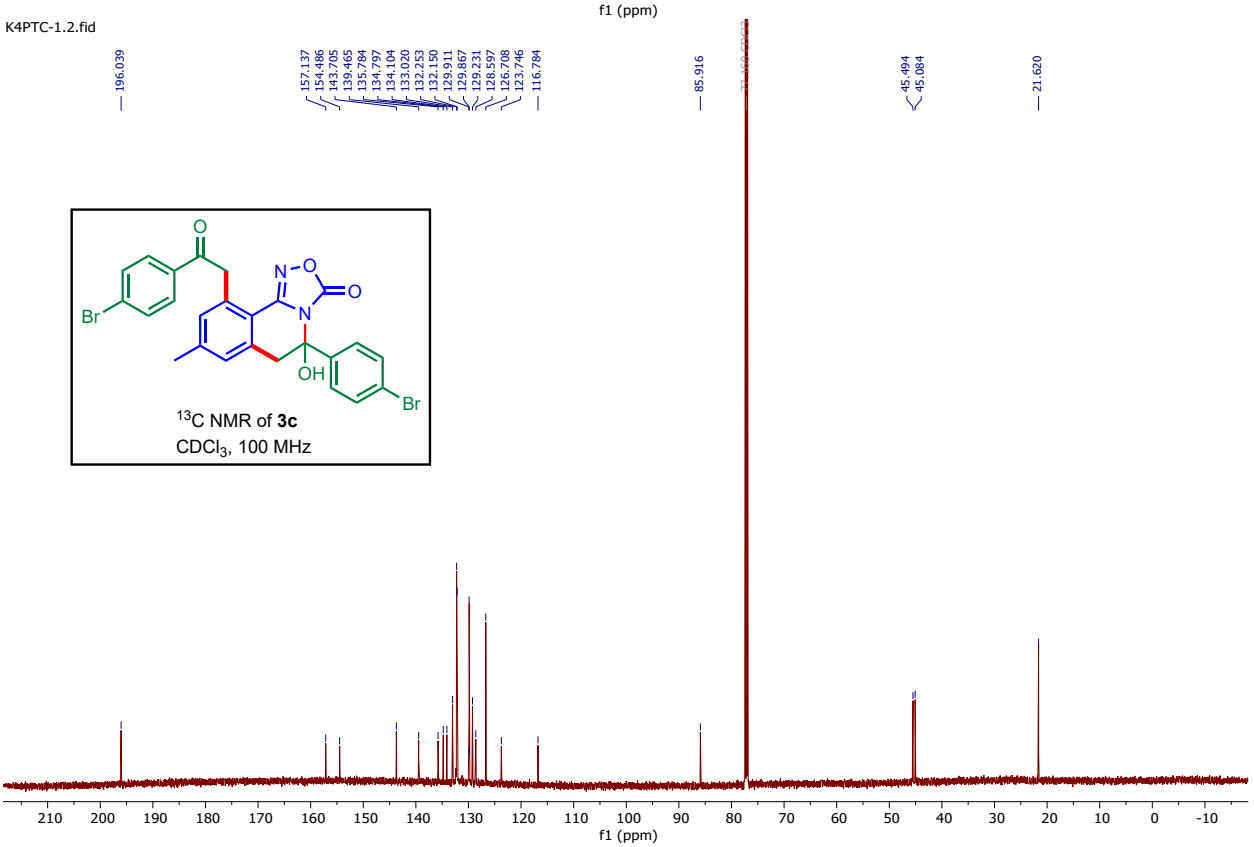


K4PTC-1.1.fid



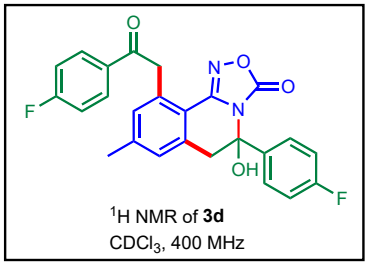
^{1}H NMR of **3c**
$CDCl_3$, 400 MHz

K4PTC-1.2.fid

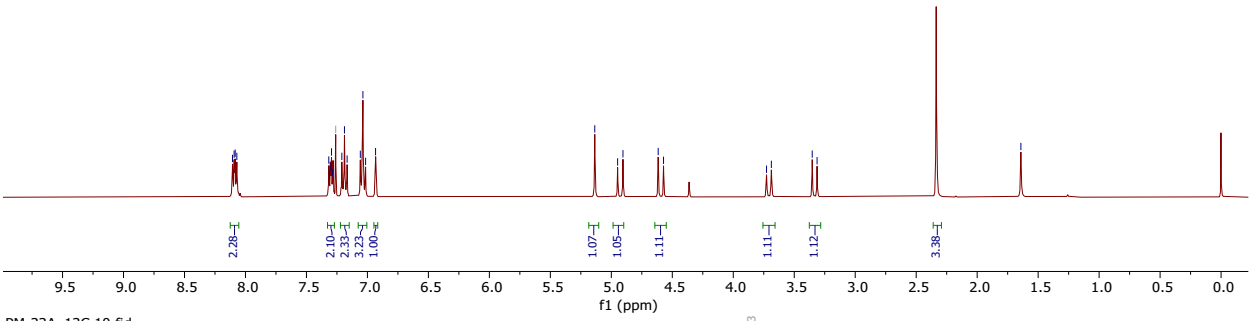


^{13}C NMR of **3c**
$CDCl_3$, 100 MHz

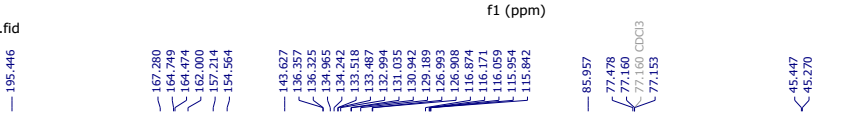
PM-33-A-1H.1.fid
PM-33-A-1H

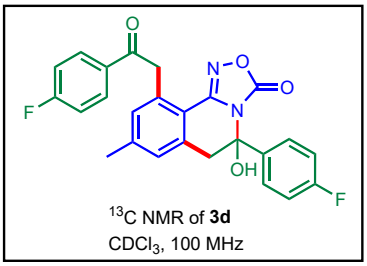


^{1}H NMR of **3d**
$CDCl_3$, 400 MHz



PM-33A_13C.10.fid
PM-33A_13C

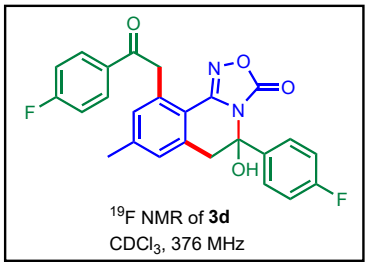




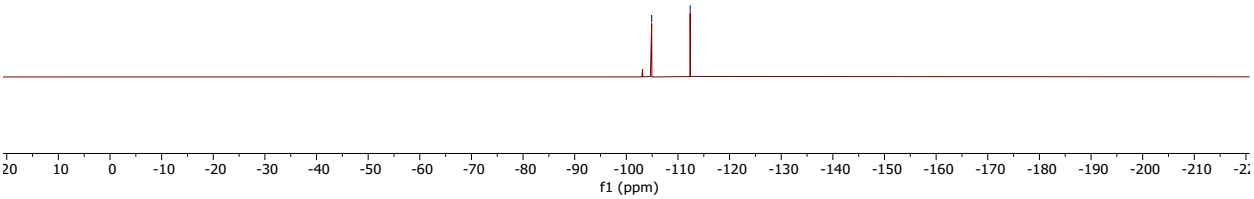
^{13}C NMR of **3d**
$CDCl_3$, 100 MHz

PM-33A_19F.12.fid
PM-33A_19F

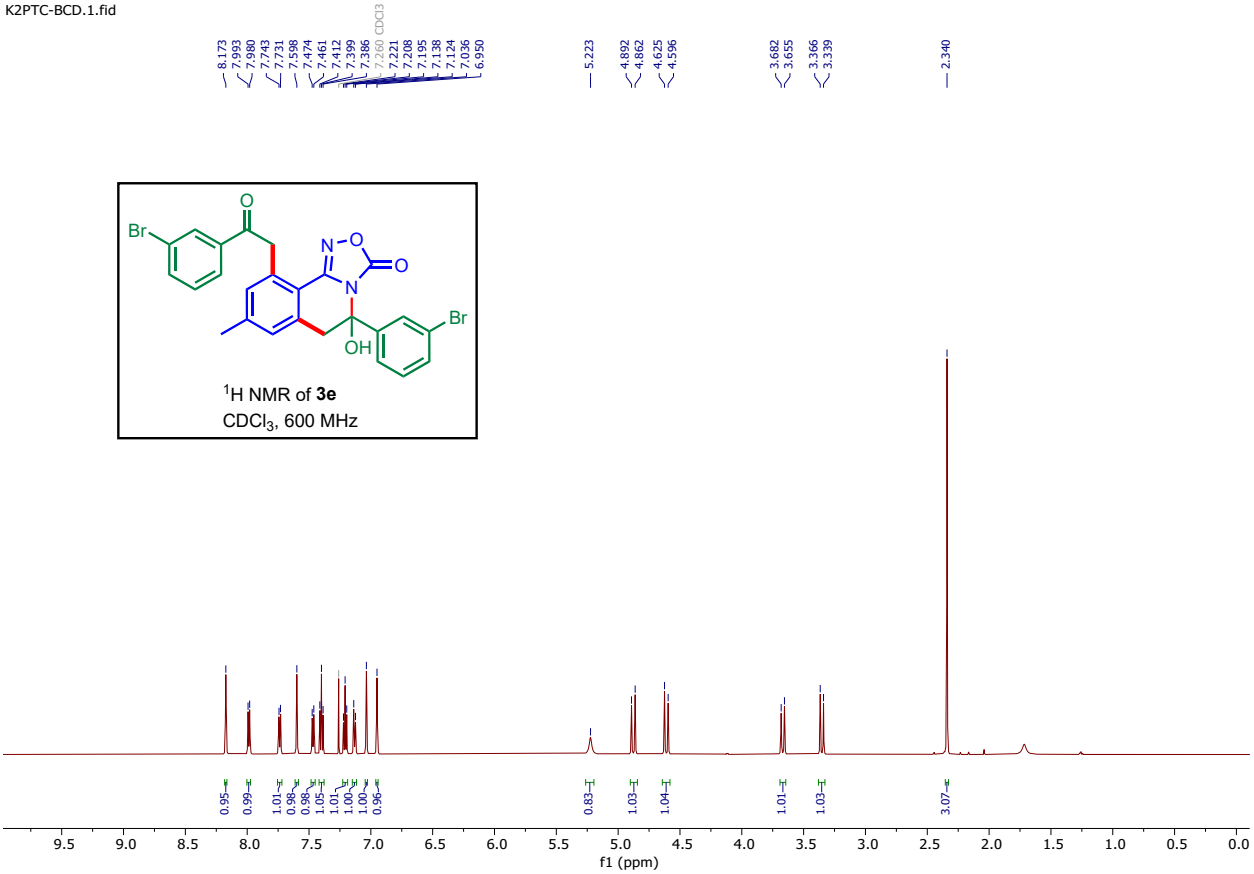
-104.906
-112.361



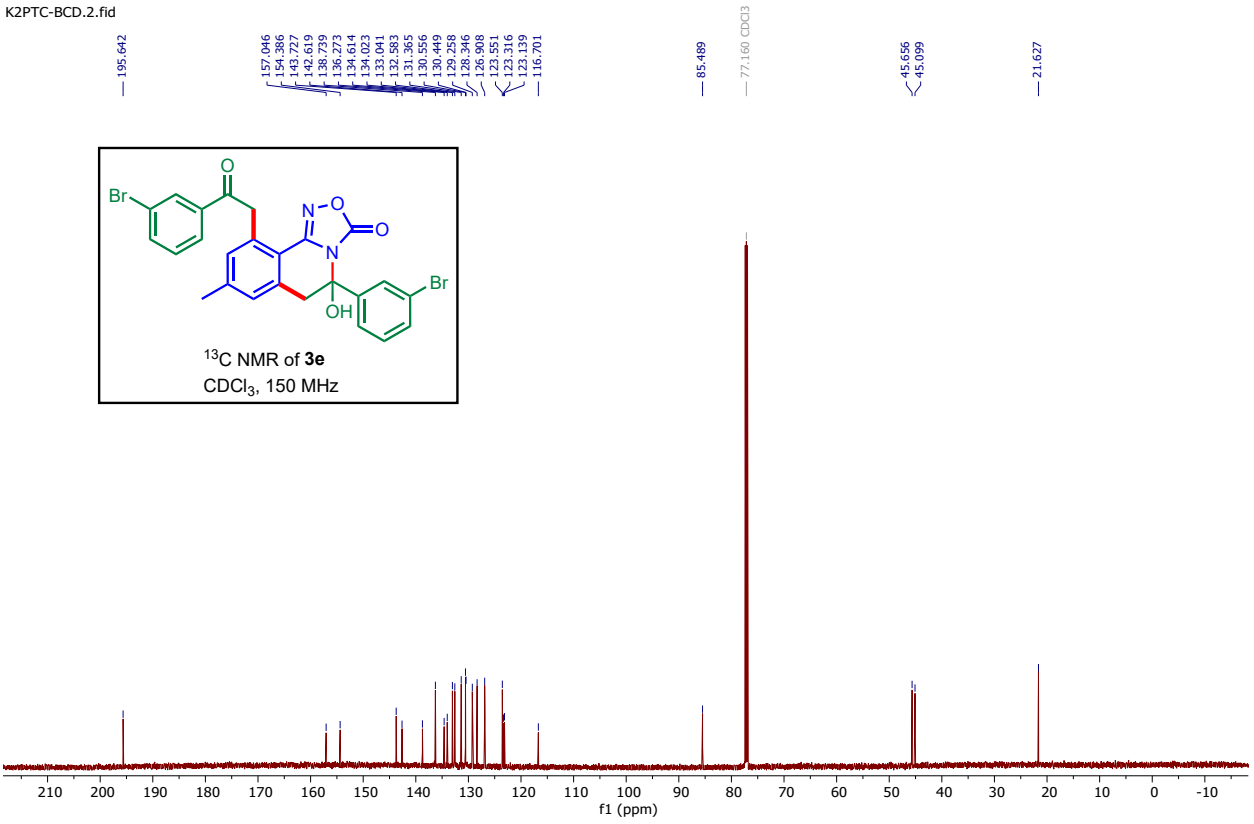
^{19}F NMR of **3d**
$CDCl_3$, 376 MHz



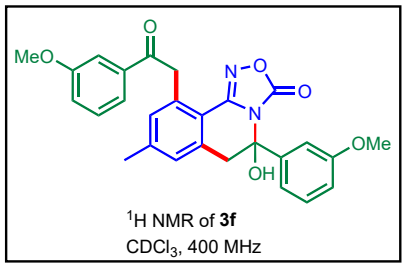
K2PTC-BCD.1.fid



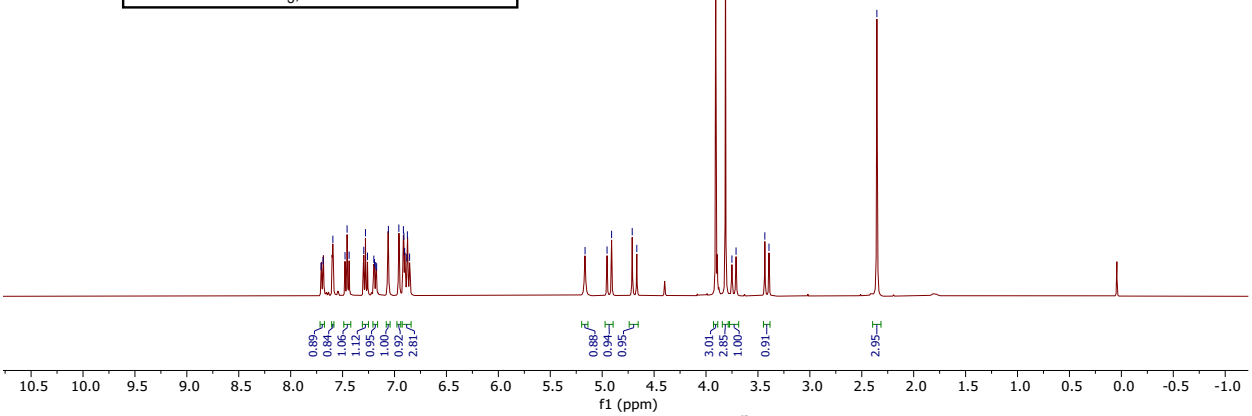
K2PTC-BCD.2.fid



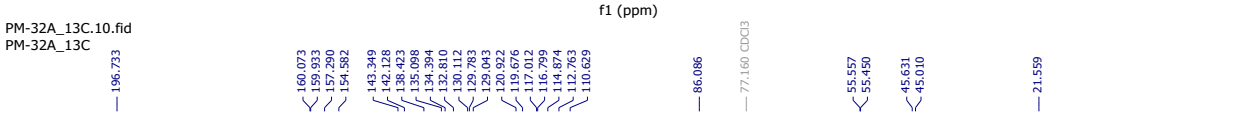
PM-32A-1H.1.fid
PM-32A-1H

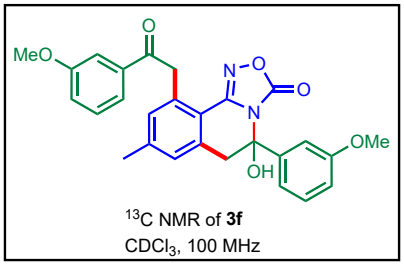


^{1}H NMR of **3f**
$CDCl_3$, 400 MHz

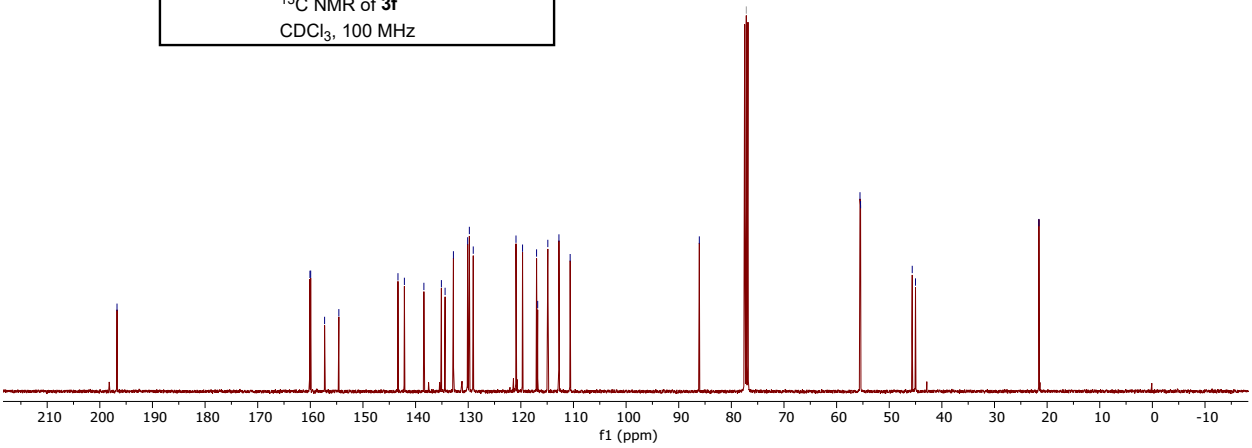


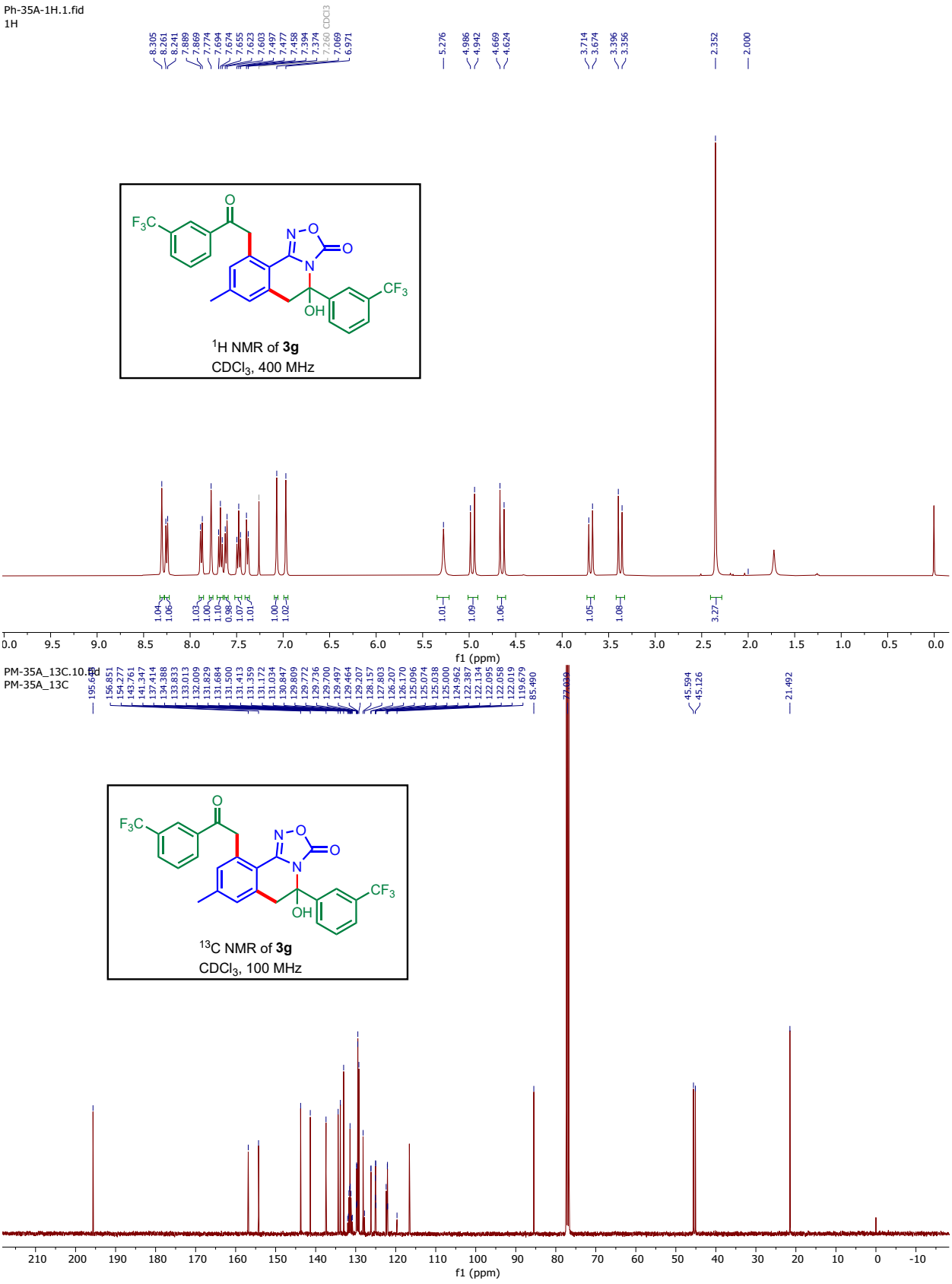
PM-32A_13C.10.fid
PM-32A_13C

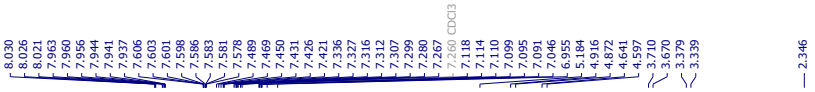


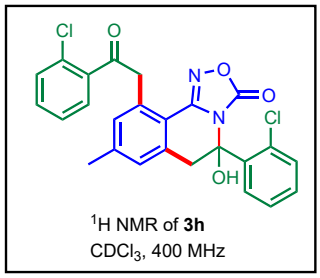


^{13}C NMR of **3f**
$CDCl_3$, 100 MHz

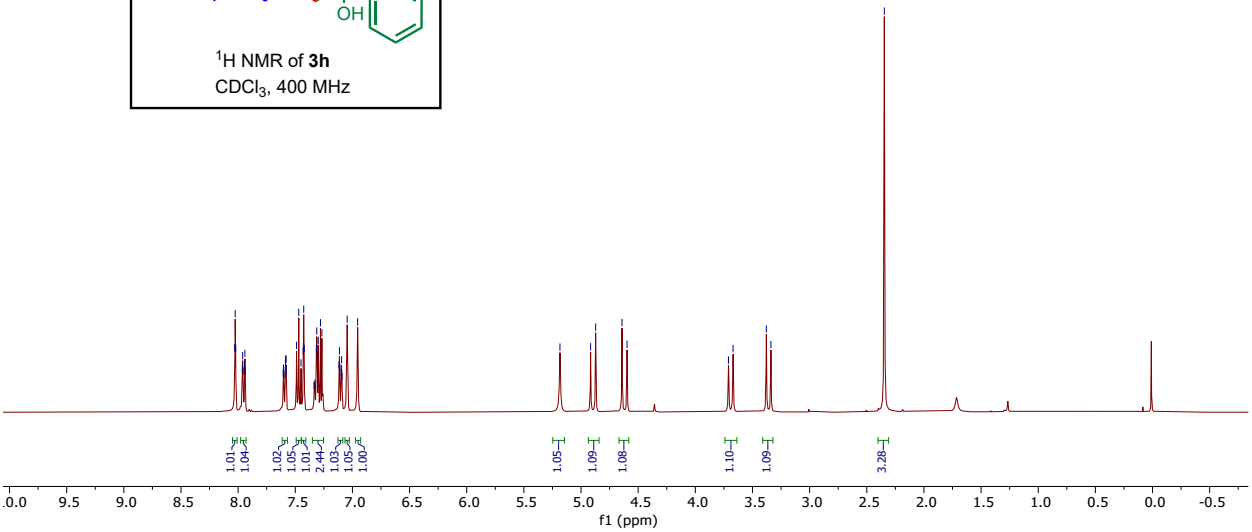


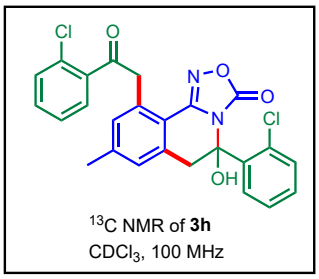

Ph-35A-1H.1.fid
1H
8.305
8.261
8.241
7.889
7.869
7.774
7.694
7.674
7.655
7.623
7.603
7.497
7.477
7.458
7.394
7.374
7.260
CDCl3
7.069
6.971
5.276
4.986
4.942
4.669
4.624
3.714
3.674
3.396
3.356
2.352
2.000
F3C
O
N
O
O
N
CF3
OH
1H NMR of 3g
CDCl3, 400 MHz
1.04
1.06
1.03
1.00
1.10
0.98
1.07
1.01
1.00
1.02
1.01
1.09
1.06
1.05
1.08
3.27
f1 (ppm)
PM-35A_13C.10.fid
PM-35A_13C
195.684
156.851
154.277
143.761
141.347
137.414
134.388
133.833
133.013
132.009
131.829
131.684
131.500
131.413
131.359
131.172
131.034
130.847
129.809
129.772
129.736
129.700
129.497
129.464
129.207
128.157
127.803
126.207
126.170
125.096
125.074
125.038
125.000
124.962
122.387
122.134
122.095
122.058
122.019
119.679
85.490
77.030
45.594
45.126
21.492
F3C
O
N
O
O
N
CF3
OH
13C NMR of 3g
CDCl3, 100 MHz
f1 (ppm)





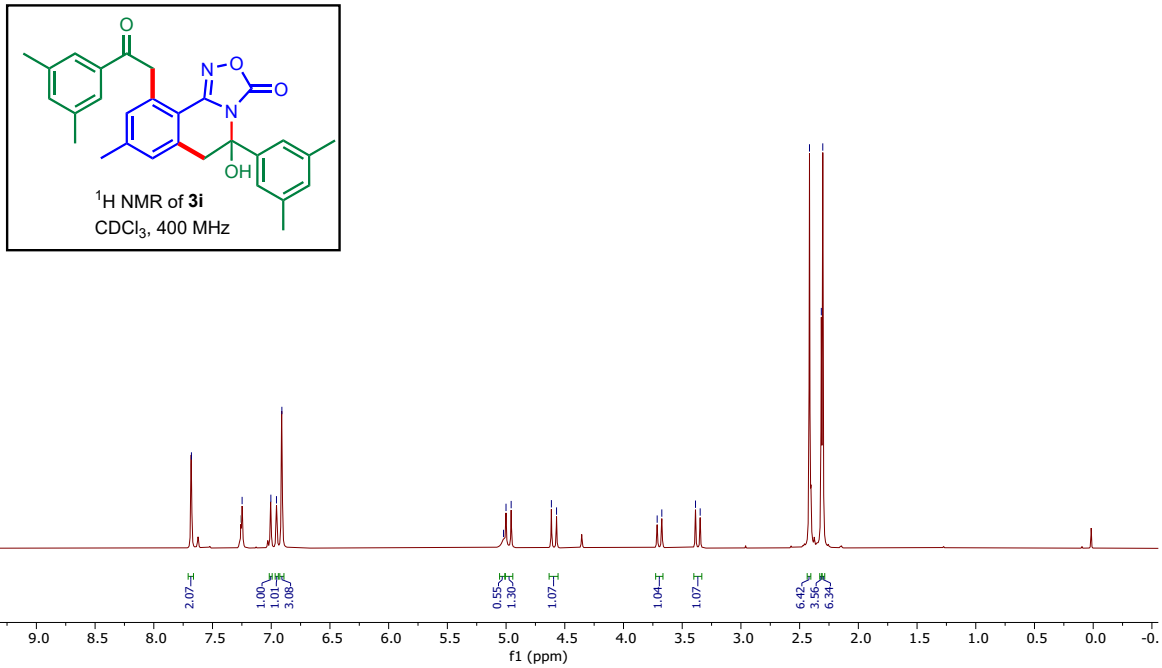
^{1}H NMR of **3h**
$CDCl_3$, 400 MHz



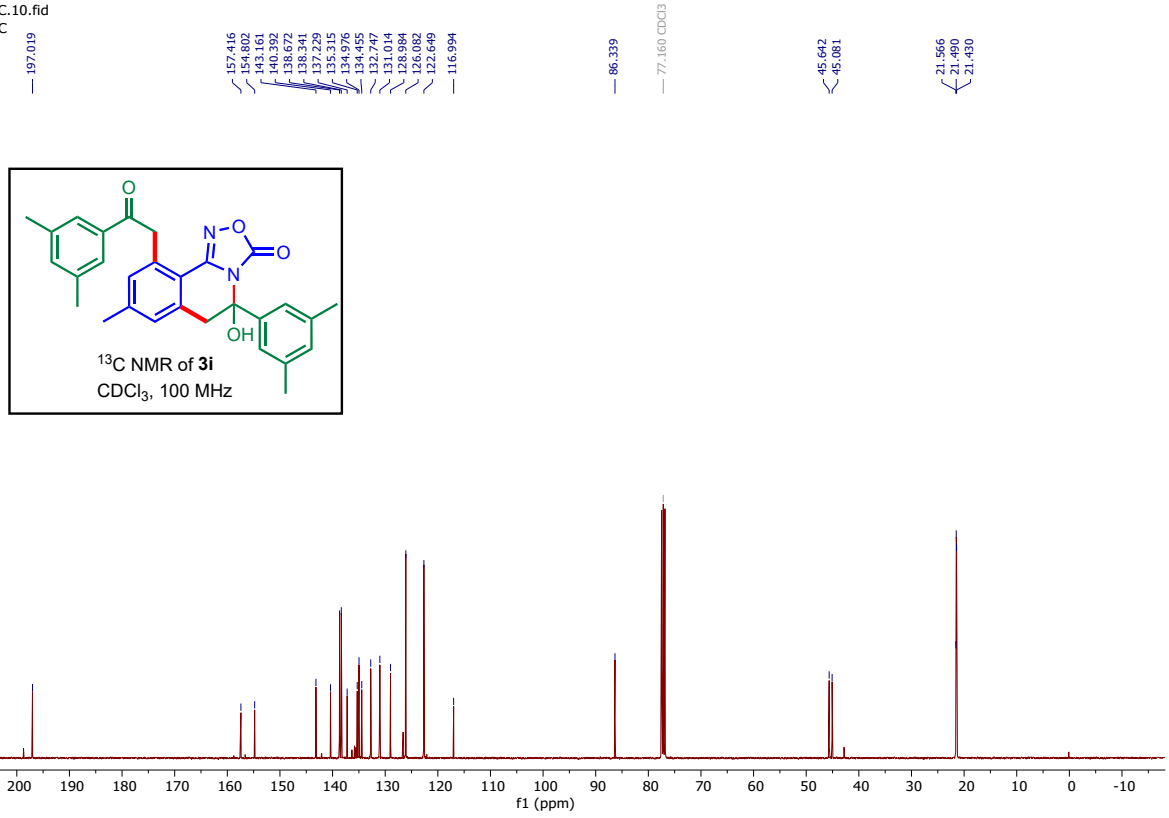


^{13}C NMR of **3h**
$CDCl_3$, 100 MHz

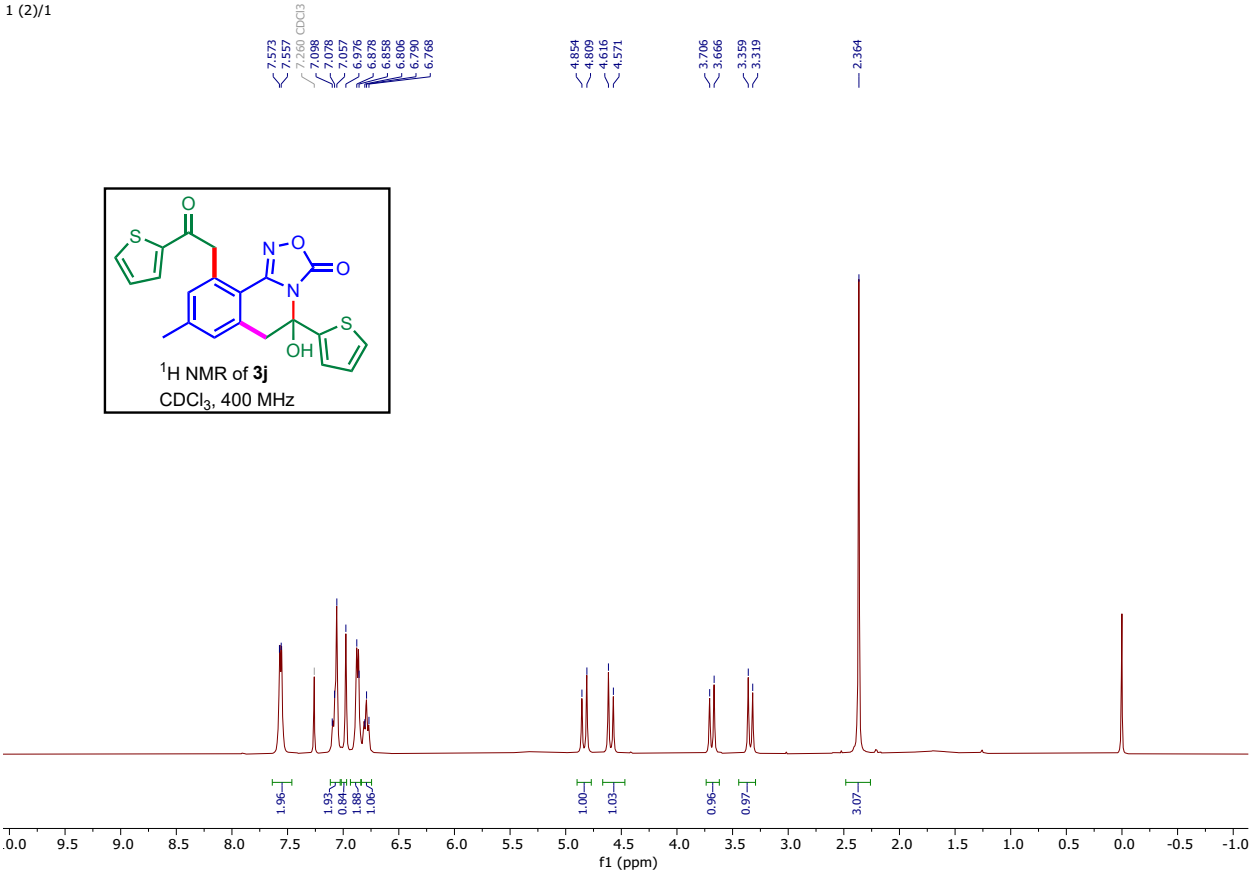
PM-37A-1H.1.fid
PM-37A-1H



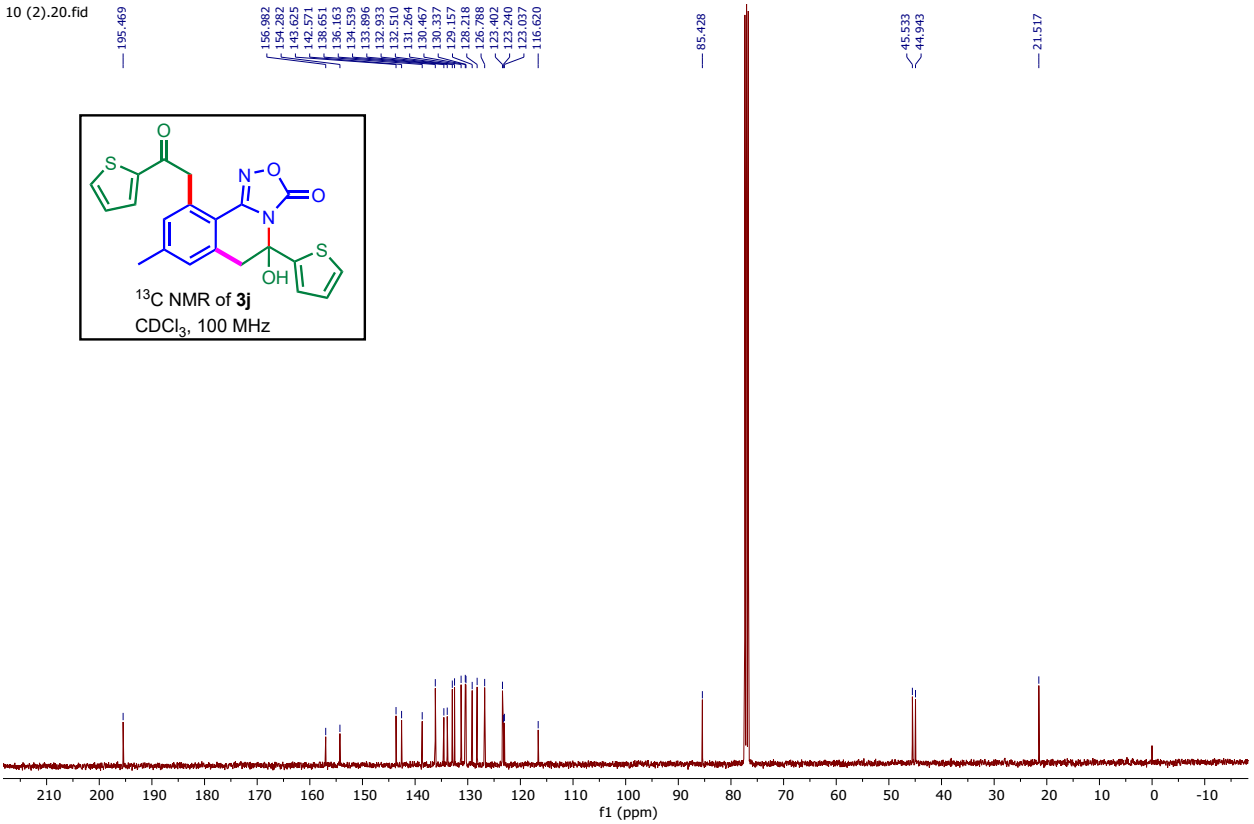
PM-37A_13C.10.fid
PM-37A_13C

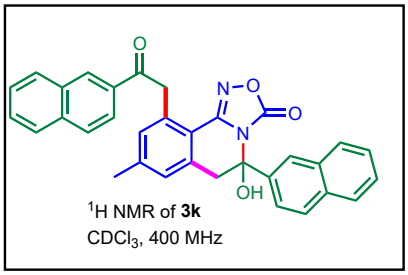


1 (2)/1

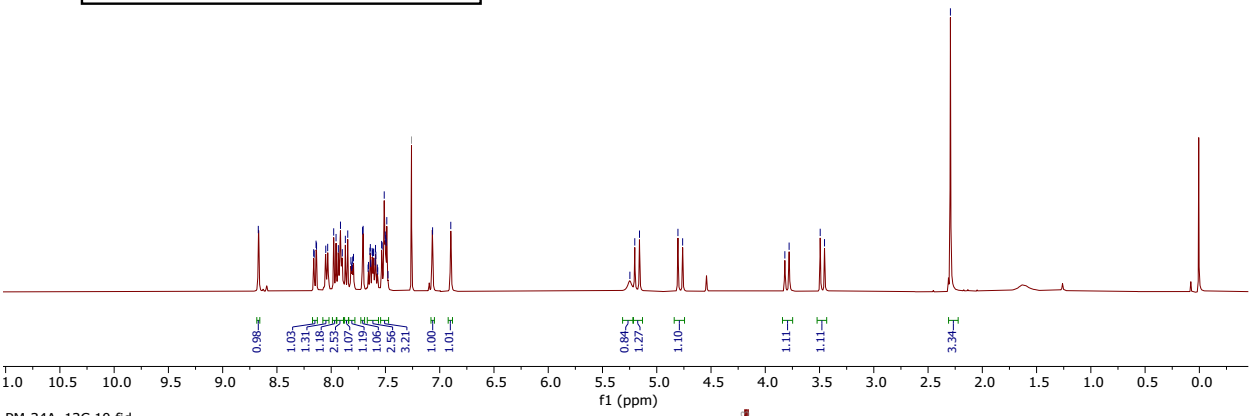


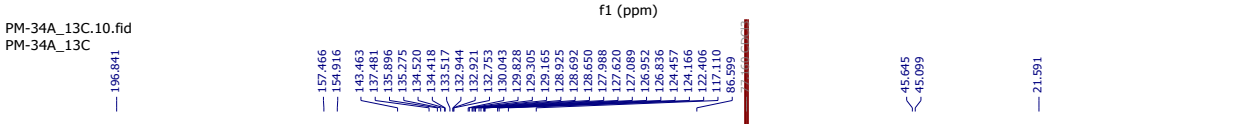
10 (2).20.fid

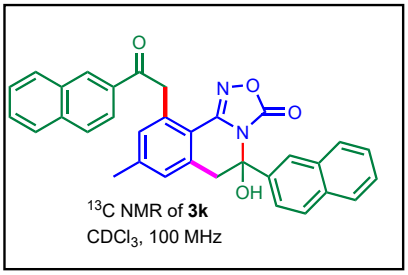




^{1}H NMR of **3k**
$CDCl_3$, 400 MHz

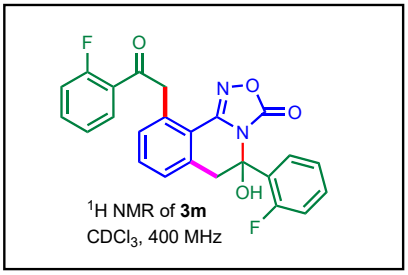




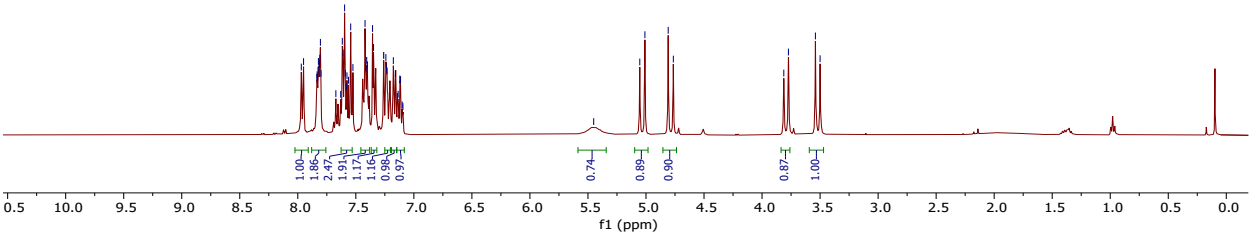


^{13}C NMR of **3k**
$CDCl_3$, 100 MHz

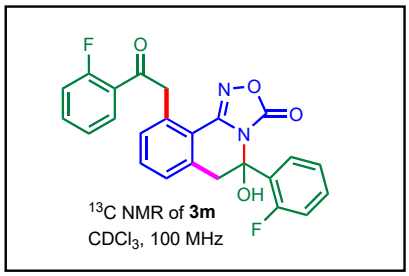
PM-P-16-1H.1.fid
PM-P-16-1H



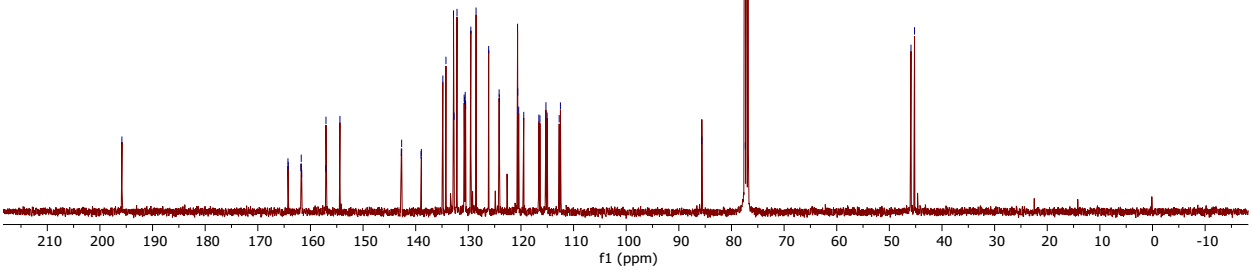
^{1}H NMR of **3m**
$CDCl_3$, 400 MHz



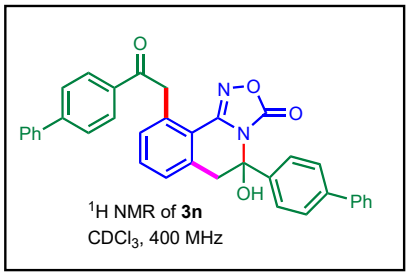
PM-P-16_13C.10.1.1r
PM-P-16_13C



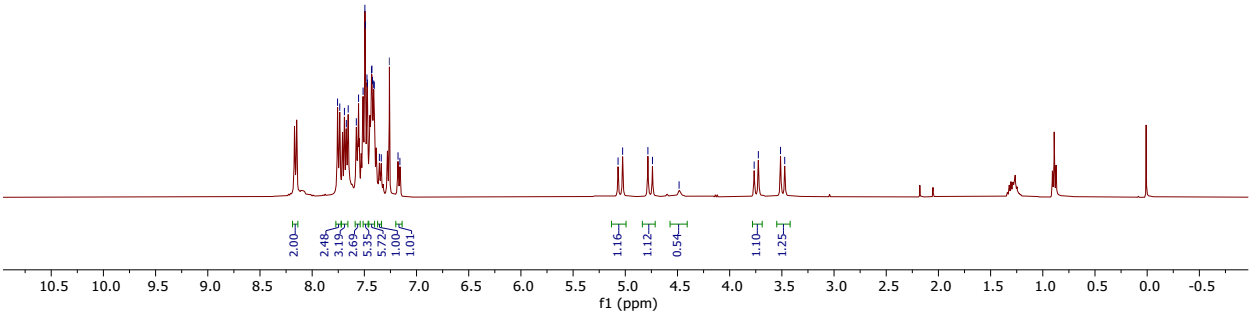
^{13}C NMR of **3m**
$CDCl_3$, 100 MHz



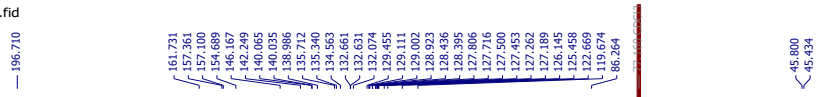
PM-P-17-1H.1.fid
PM-P-17-1H

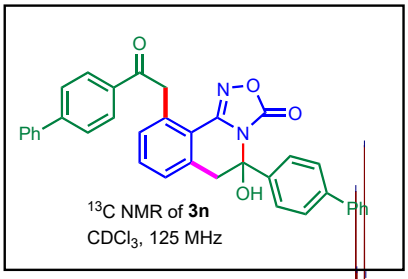


^{1}H NMR of **3n**
$CDCl_3$, 400 MHz



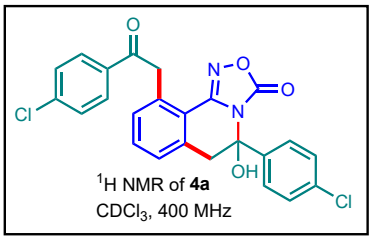
PM-P-17-13C.3.fid
PM-P-17-13C

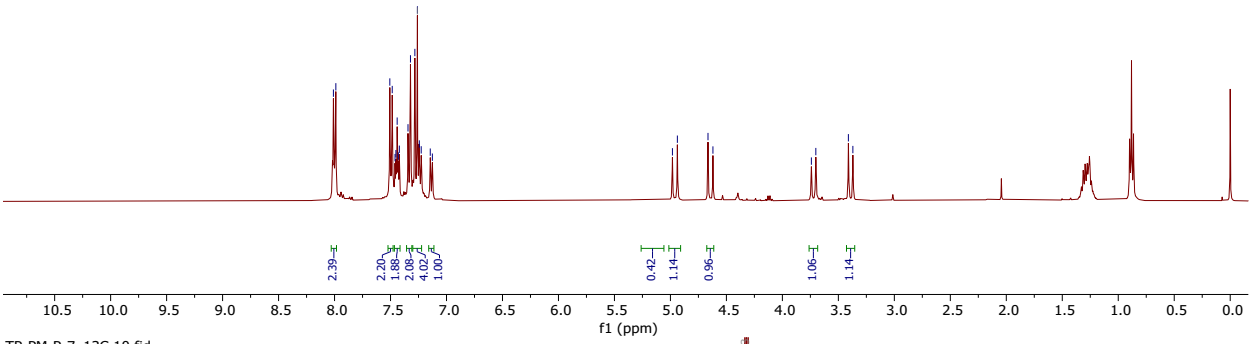




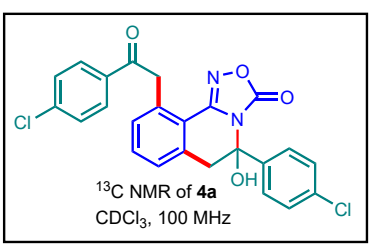
^{13}C NMR of **3n**
$CDCl_3$, 125 MHz

PM-P-7-1H.1.fid
PM-P-7-1H

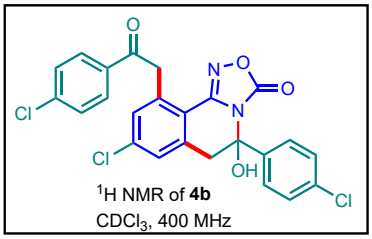




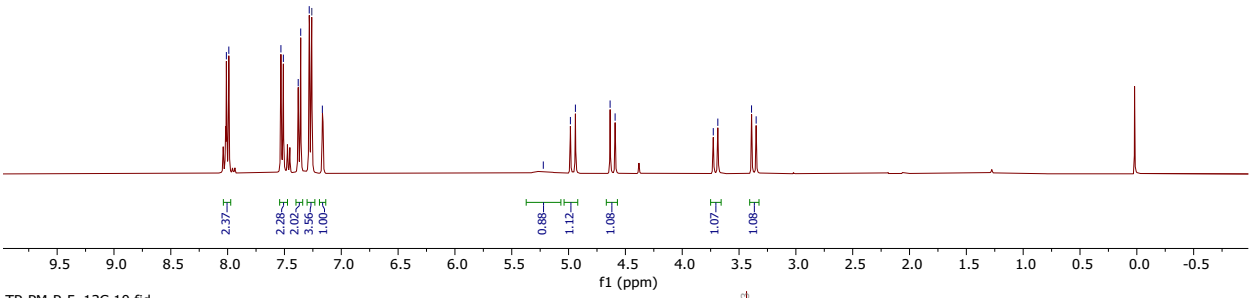
TP-PM-P-7_13C.10.fid
TP-PM-P-7_13C



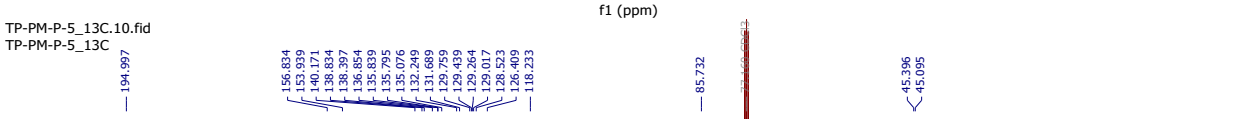
PM-P-5-1H.1.fid
PM-P-5-1H

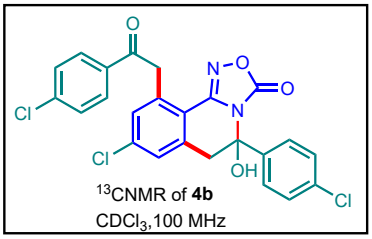


^{1}H NMR of **4b**
$CDCl_3$, 400 MHz

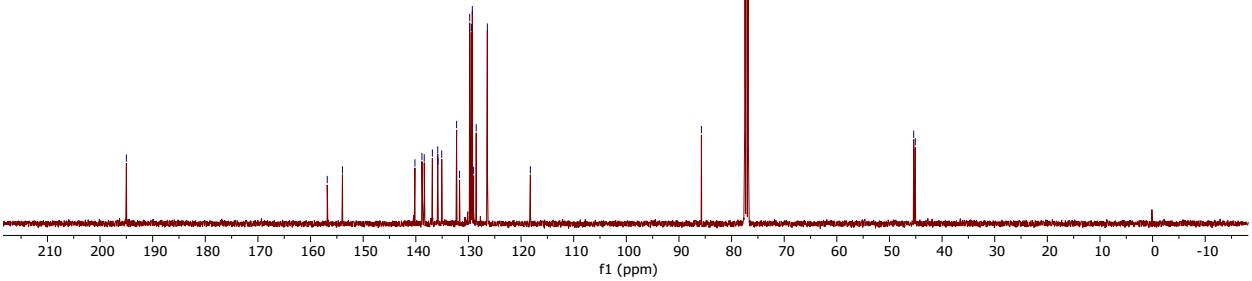


TP-PM-P-5_13C.10.fid
TP-PM-P-5_13C

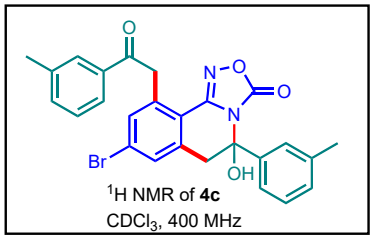




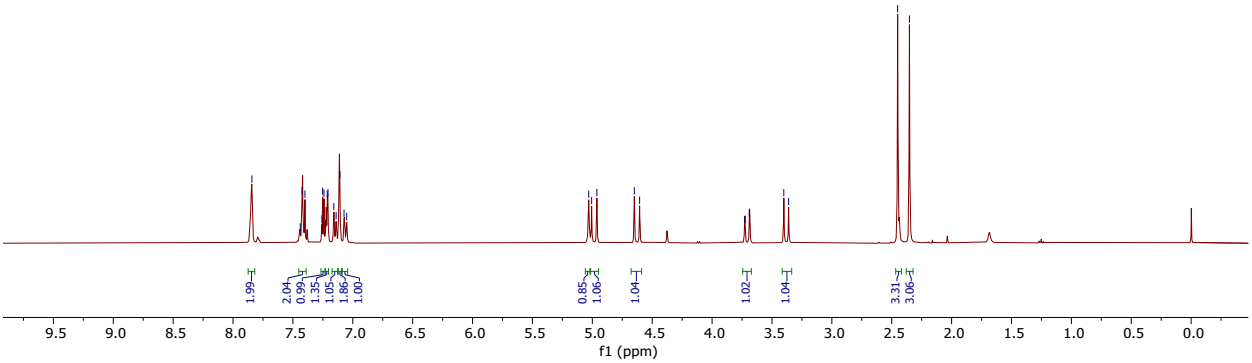
^{13}CNMR of **4b**
$CDCl_3$,100 MHz



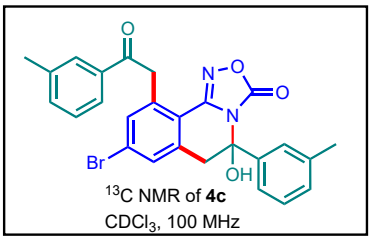
PM-P-15-1H.1.fid
PM-P-15-1H



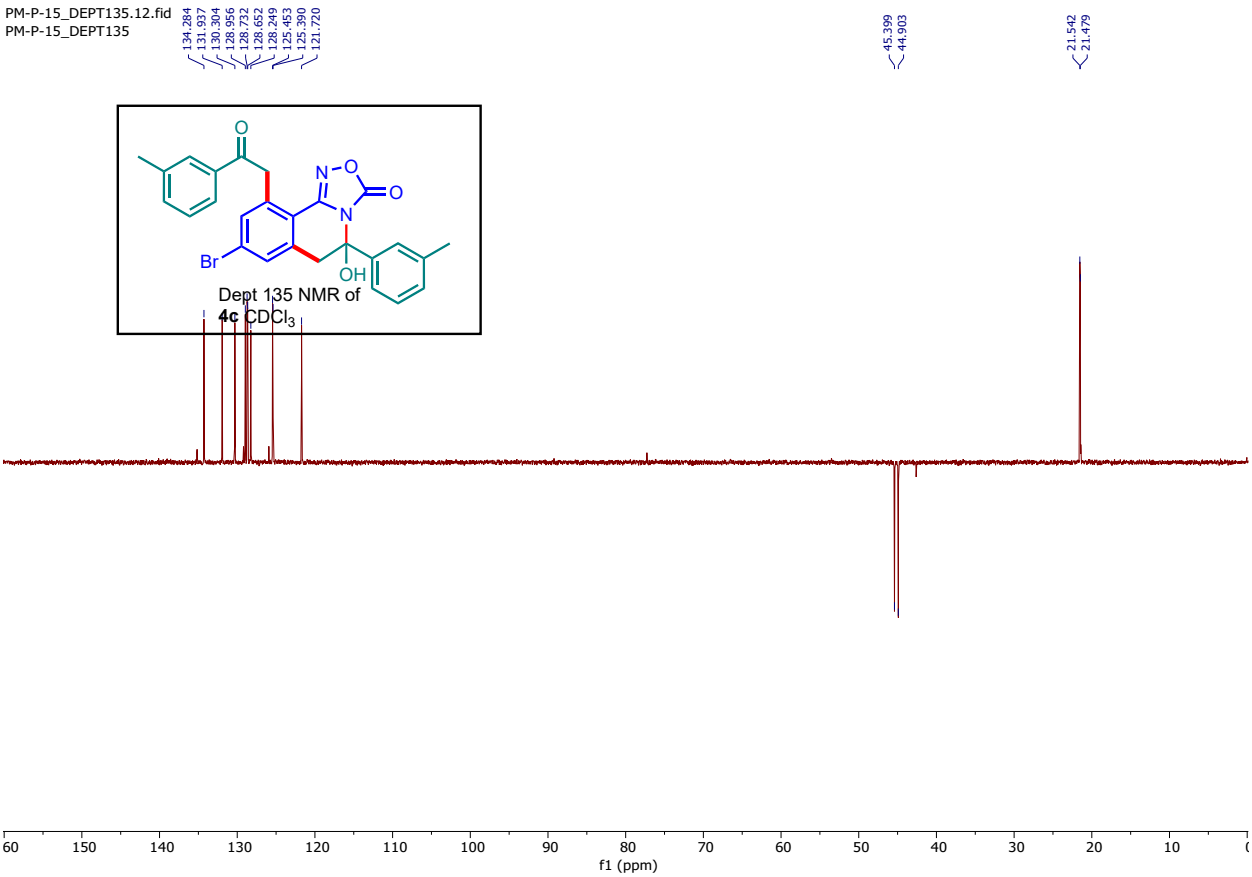
^{1}H NMR of **4c**
$CDCl_3$, 400 MHz



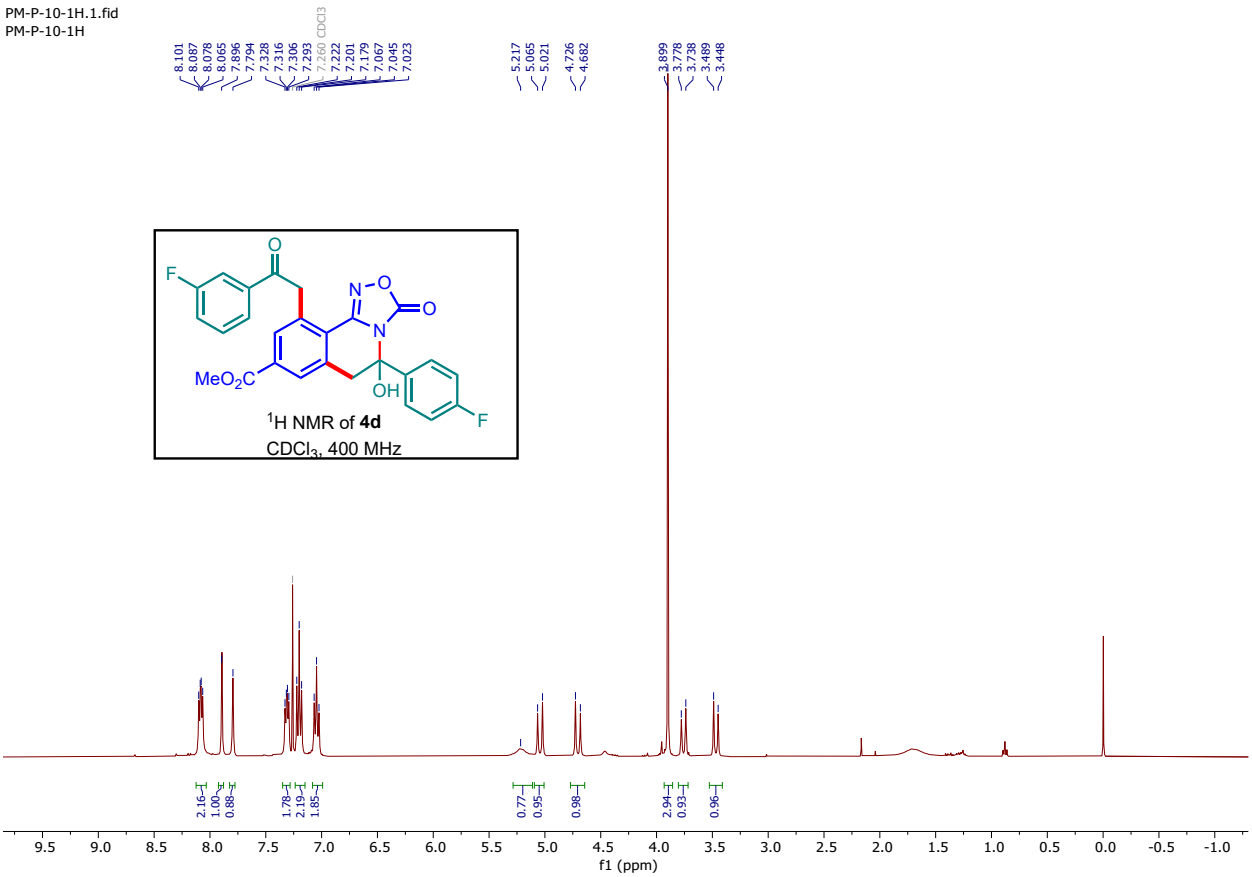
PM-P-15_13C.10.fid
PM-P-15_13C



^{13}C NMR of **4c**
$CDCl_3$, 100 MHz

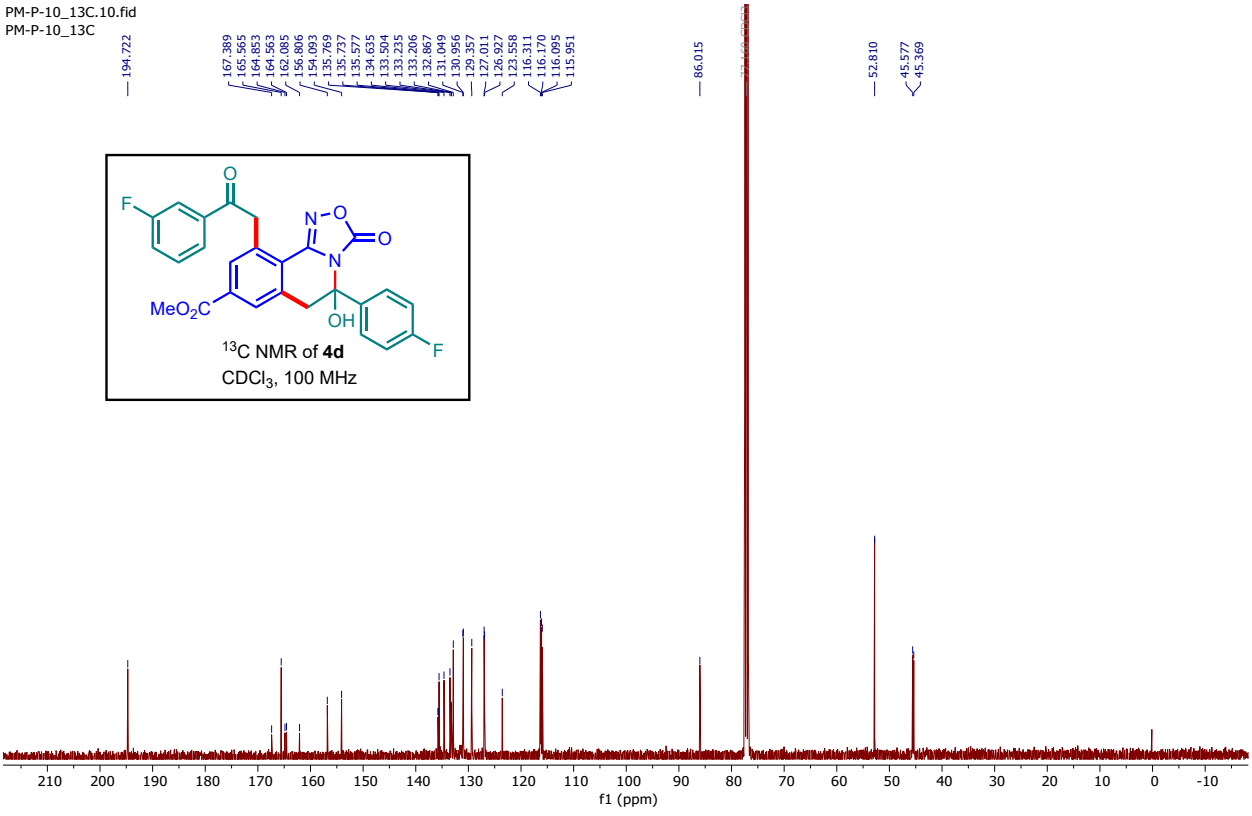

PM-P-15_DEPT135.12.fid
PM-P-15_DEPT135
134.284
131.937
130.304
128.956
128.732
128.652
128.249
125.453
125.390
121.720
45.399
44.903
21.542
21.479
O
N
O
O
N
Br
OH
Dept 135 NMR of
4c CDCl3
60
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

PM-P-10-1H.1.fid
PM-P-10-1H



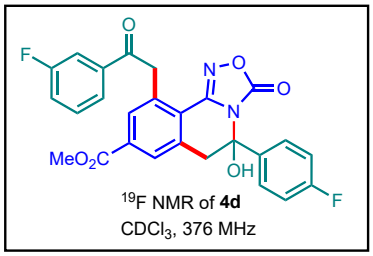
^{1}H NMR of **4d**
$CDCl_3$, 400 MHz

PM-P-10_13C.10.fid
PM-P-10_13C



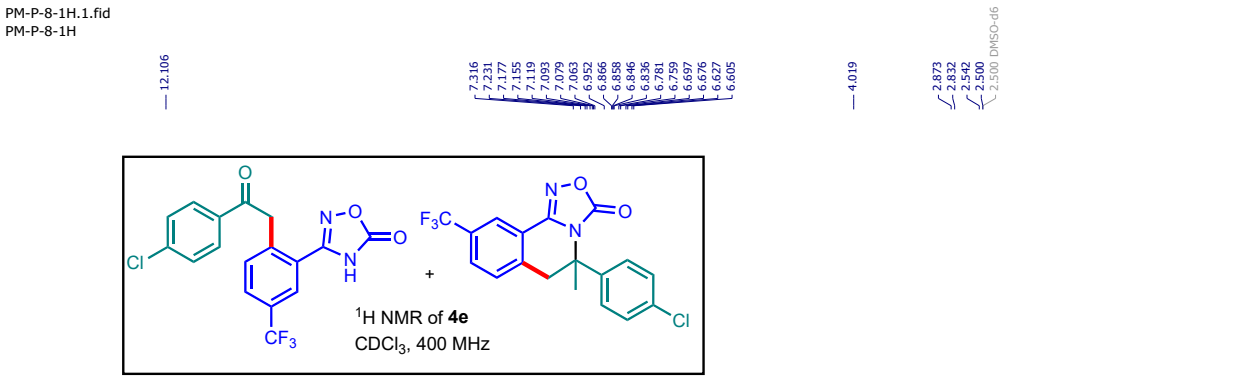
^{13}C NMR of **4d**
$CDCl_3$, 100 MHz

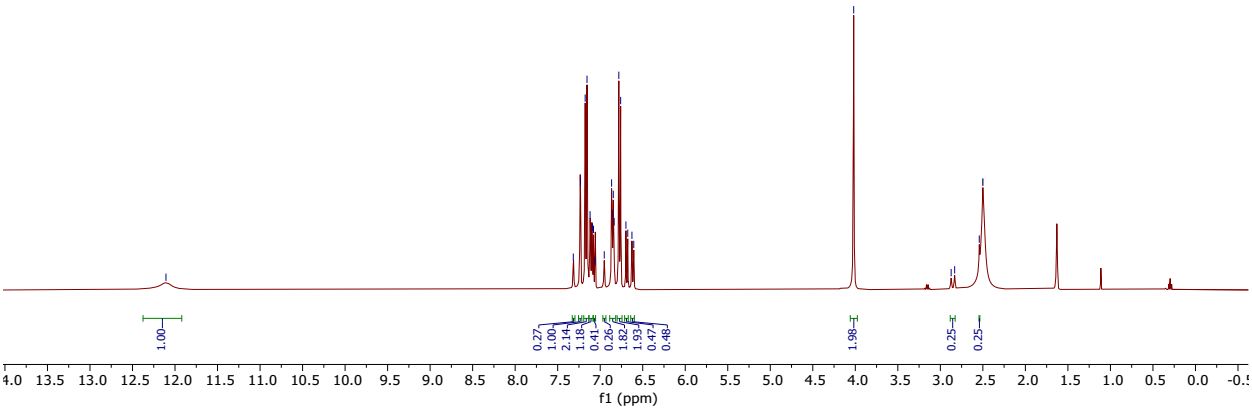
PM-P-10_19F.12.fid
PM-P-10_19F



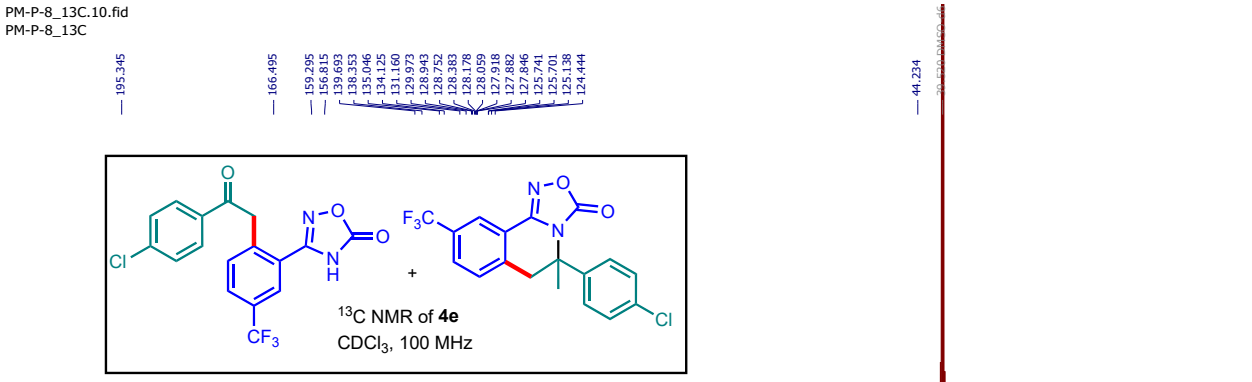
^{19}F NMR of **4d**
$CDCl_3$, 376 MHz

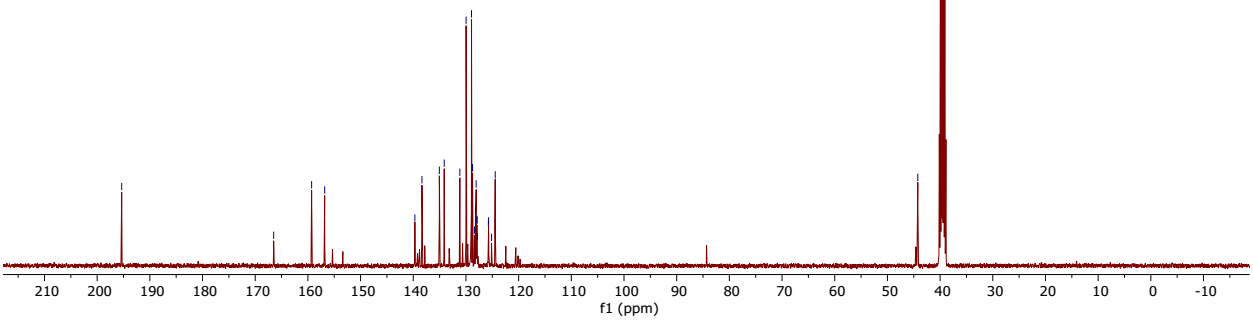
PM-P-8-1H.1.fid
PM-P-8-1H





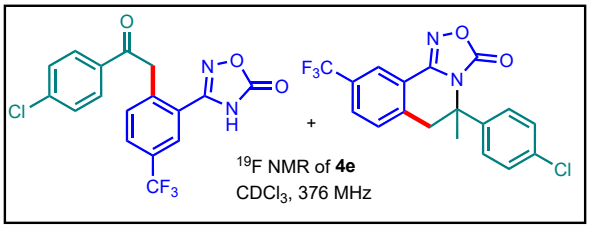
PM-P-8_13C.10.fid
PM-P-8_13C



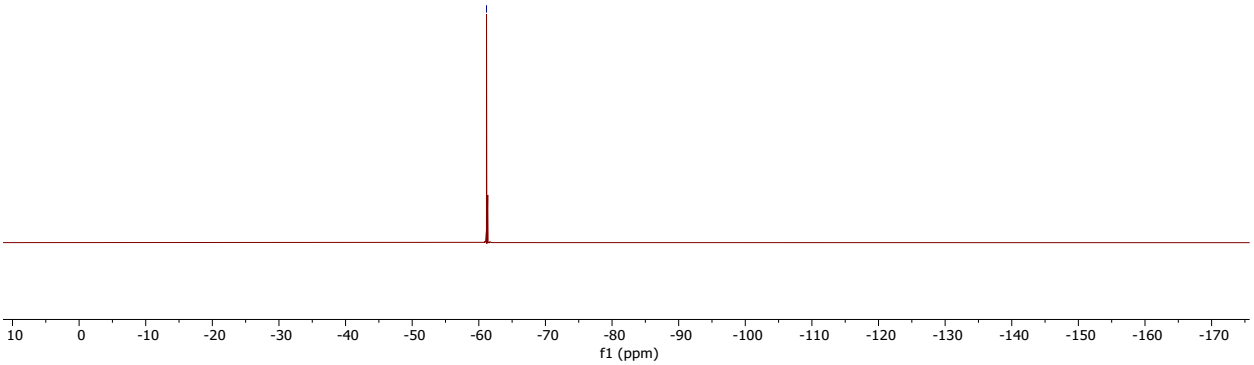


PM-P-8_19F.12.fid
PM-P-8_19F

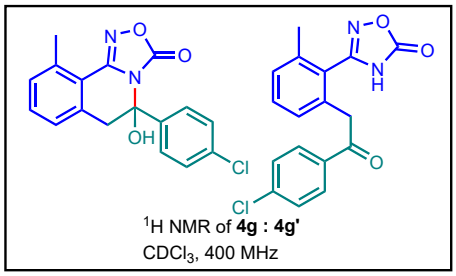
−61.158



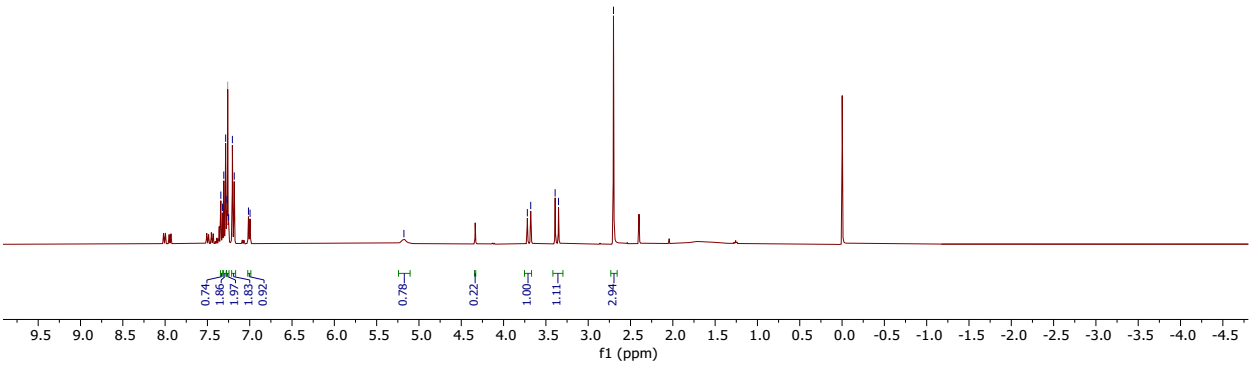
^{19}F NMR of **4e**
$CDCl_3$, 376 MHz



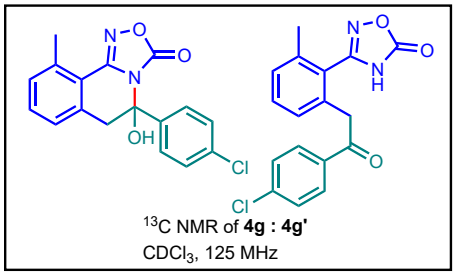
PM-P-11-1H.1.fid
PM-P-11-1H



^{1}H NMR of **4g : 4g'**
$CDCl_3$, 400 MHz

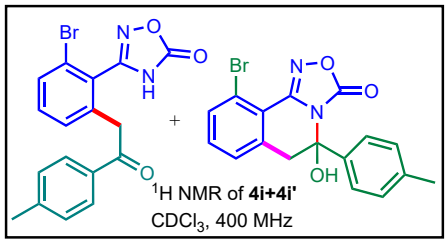


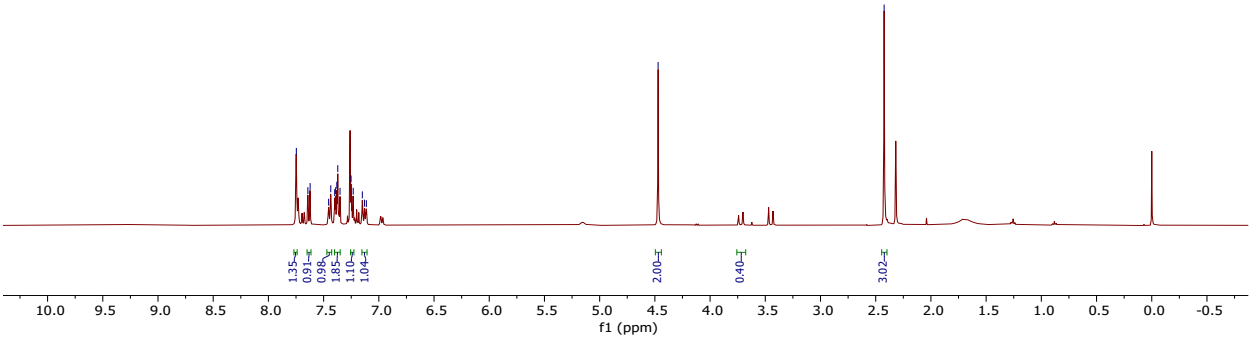
PM-P-11_13C.10.fid
PM-P-11_13C



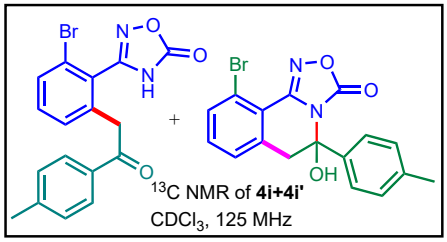
^{13}C NMR of **4g : 4g'**
$CDCl_3$, 125 MHz

PM-P-18-1H.1.1.1r
PM-P-18-1H





PM-P-18-13C.1.fid
PM-P-18-13C



5.1. Experimental procedure for anti-inflammatory activity

The synthesized compound and standard diclofenac sodium were screened for anti-inflammatory activity by inhibiting the albumin denaturation technique with minor modification. The standard drug and compound were dissolved in a minimum quantity of Dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). The final concentration of DMF in all solutions was less than 2.5%. Test Solution (2.5 mL) containing different drug concentrations was mixed with 1 mL of 1 mM Bovine serum albumin solution in phosphate buffer and incubated at 37 °C in an incubator for 10 min. Denaturation was induced by keeping the reaction mixture at 70 °C in a water bath for 10 min. After cooling, the turbidity was measured at 660 nm. The percentage inhibition of denaturation can be calculated from a reference where no drug was added. We noted that each experiment was done in triplicate and an average value was taken. The percentage inhibition of denaturation was calculated using the following formula:

$$\% \text{ of Inhibition} = 100 \times [A_c - A_t / A_c]$$

A_t : Absorbance of test

A_c : Absorbance of control.

5.2 Anti-diabetic activity α-amylase inhibition technique

The antidiabetic activity of the samples was performed using the α-amylase inhibition method. Briefly, Amylase (0.2%) was incubated with and without samples (in 1.5 mL) and standard for 10 min at 25 °C. This experiment was performed in 0.2 M phosphate buffer (pH 6.9). After pre-incubation, the 1% starch solution (0.5 mL) was added and the reaction mixture was incubated for 30 min at 25 °C. To stop the enzymatic reaction, DNSA reagent (0.5 mL) was added as the color reagent and then incubated in a boiling water bath for 90 min. After cooling down to room temperature, 0.5 mL of samples were diluted to 2.5 mL of distilled water and the absorbance was measured at 540 nm using a UV-visible spectrophotometer. The measured absorbance was compared with that of the control experiment. The percentage inhibition was calculated using the given formula.

$$\% \text{ of Inhibition} = 100 \times [A_c - A_t / A_c]$$

A_t: Absorbance of test

A_c: Absorbance of control

Statistical analysis

All experiments were carried out in triplicate. Regressions were made using Sigma-Plot (version 10.0.0.54), except in the case of the spectra graphics, which were made by the spectrofluorimeter software. A T-test was carried out using Rstudio (version 0.99.878) with a significance of $P < 0.05$. Other mathematical operations were carried out using wxMaxima (version 12.04.0).

Table S1. Anti-inflammation activity of the synthesized compounds (3a to 5a)

Concentrations (µg/ml)	Anti-inflammation (% of inhibition)											
	3a	3b	3c	3d	3f	3g	3j	4a	4b	4d	4g	Standard
20	25.43	25.01	24.30	25.63	25.04	24.11	25.41	26.54	25.55	26.01	25.94	25.38
40	31.33	30.30	32.13	33.63	31.99	30.27	31.49	32.50	31.89	31.22	31.61	31.19
80	45.51	45.91	44.44	47.61	46.63	45.58	46.99	47.05	46.51	45.98	45.39	45.56
200	60.53	59.53	58.73	59.23	61.51	59.05	61.83	62.11	61.75	61.59	60.97	60.14
400	75.31	76.35	77.75	76.59	77.56	75.43	77.99	78.15	77.50	84.74	84.37	85.22

Table S2. Anti-diabetic activity of the synthesized compounds

Concentrations (µg/ml)	Anti-diabetic (% of inhibition)											
	3a	3b	3c	3d	3f	3g	3j	4a	4b	4d	4g	Standard
20	20.89	19.81	19.91	20.31	21.43	20.17	19.68	20.39	20.98	21.12	20.89	32.19
40	40.48	38.75	35.41	39.53	41.44	40.48	36.39	41.89	41.47	42.05	41.52	48.92
80	53.27	50.71	48.73	53.31	55.53	52.79	48.54	53.81	54.41	56.31	55.69	62.10
200	70.38	65.51	60.55	65.99	72.83	69.96	67.67	71.67	71.69	73.57	72.57	78.96
400	80.25	75.69	73.31	79.31	82.83	79.39	75.96	81.89	82.85	85.48	83.71	87.19

6.0 References:

S1. P. Muthuraja, M. Saeed Akhtar, P. Gopinath and Y. Rok Lee, *Adv. Synth. Catal.*, 2023, **365**, 4595–4602.

S2. Y. H. Fan, X. Y. Guan, W. P. Li, C. Z. Lin, D. X. Bing, M. Z. Sun, G. Cheng, J. Cao, J. J. Chen and Q. H. Deng, *Org. Chem. Front.*, 2022, **9**, 380–385.