



Supplementary material: Direct ring fluorination of 3-substituted 5-(1,3-dioxane) acetal isoxazoles: application to the formal synthesis of a bioactive fluorinated isoxazole

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Not yet published

1. General information

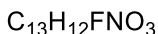
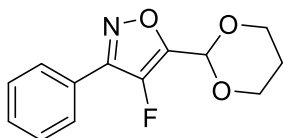
All air and/or water sensitive reactions were carried out under an argon atmosphere. THF and Et₂O were dried over alumina columns in a solvent purification apparatus (Innovative technology). Select-fluor was purchased from Strem and NFSI from Fluorochem. Reactions were monitored by thin layer chromatography carried out on precoated silica gel plates (Merck 60F254) and revealed with either an ultra-violet lamp ($\lambda = 254$ nm) or a potassium permanganate solution. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using a Bruker AC 400 (400 MHz) or Bruker Avance NEO 500 MHz (471 MHz). The chemical shifts are expressed in parts per million (ppm) referenced to

residual chloroform (7.26 ppm). Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constants and integration. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Bruker AC 400 (101 MHz) or Bruker Avance NEO 500 MHz (126 MHz). Fluorine-19 nuclear magnetic resonance (¹⁹F NMR) spectra were recorded using a Bruker AC 400 (376 MHz) or Bruker Avance NEO 500 MHz (471 MHz). The chemical shifts are expressed in parts per million (ppm) relative to the centre line of the triplet at 77.16 ppm for CDCl₃. High resolution mass spectrometric (HRMS) analyses were measured on Agilent 6546 LC/QTOF at Chimie ParisTech. Mass spectra (Chemical ionization, NH₃ or Electrospray) were recorded at Chimie ParisTech.

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2. General method for the preparation of fluorinated isoxaoles 2a-2k

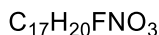
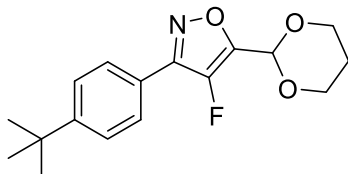
2.1. 5-(1,3-Dioxan-2-yl)-4-fluoro-3-phenylisoxazole (2a)



Molecular Weight: 249.24

Colorless oil: 85 mg, 75%; ^1H NMR (400 MHz, CDCl_3) δ 7.90–7.82 (m, 2H), 7.51–7.44 (m, 3H), 5.85 (d, $J = 0.8$ Hz, 1H), 4.34–4.26 (m, 2H), 4.06–3.95 (m, 2H), 2.36–2.23 (m, 1H), 1.57–1.48 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -177.53. ^{13}C NMR (101 MHz, CDCl_3) δ 153.0 (d, $^3J_{\text{CF}} = 10.4$ Hz), 151.6 (d, $^2J_{\text{CF}} = 20.9$ Hz), 142.2 (d, $^1J_{\text{CF}} = 261.4$ Hz), 130.7, 129.1 (2C), 127.2 (d, $^4J_{\text{CF}} = 3.1$ Hz, 2C), 126.5 (d, $^4J_{\text{CF}} = 3.6$ Hz), 94.2 (d, $^4J_{\text{CF}} = 2.9$ Hz), 67.5 (2C), 25.6. HRMS (APCI) m/z : $[\text{M}]^+$ Calcd. for $\text{C}_{13}\text{H}_{12}\text{FNO}_3$ 249.0801; Found 249.0802.

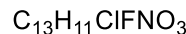
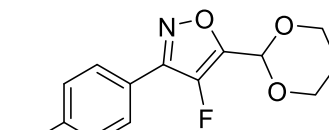
2.2. 3-(4-(tert-Butyl)phenyl)-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (2b)



Molecular Weight: 305.35

Yellow oil: 63 mg, 69%; ^1H NMR (400 MHz, CDCl_3) δ 7.83–7.76 (m, 2H), 7.53–7.47 (m, 2H), 5.84 (d, $J = 1.0$ Hz, 1H), 4.33–4.26 (m, 2H), 4.04–3.95 (m, 2H), 2.36–2.23 (m, 1H), 1.56–1.51 (m, 1H), 1.35 (s, 9H). ^{19}F NMR (376 MHz, CDCl_3) δ -177.56. ^{13}C NMR (101 MHz, CDCl_3) δ 154.0, 152.9 (d, $^3J_{\text{CF}} = 10.5$ Hz), 151.4 (d, $^2J_{\text{CF}} = 20.8$ Hz), 142.2 (d, $^1J_{\text{CF}} = 261.3$ Hz), 127.0 (d, $^4J_{\text{CF}} = 3.0$ Hz, 2C), 126.1 (2C), 123.6 (d, $^4J_{\text{CF}} = 3.6$ Hz), 94.2 (d, $^4J_{\text{CF}} = 2.9$ Hz), 67.5 (2C), 35.0, 31.3 (3C), 25.6. Mass (CI/ NH_3): $m/z = 306$ $[\text{M} + \text{H}]^+$.

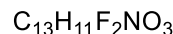
2.3. 3-(4-Chlorophenyl)-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (2c)



Molecular Weight: 283.68

Yellow solid: 73 mg, 68%; ^1H NMR (400 MHz, CDCl_3) δ 7.83–7.78 (m, 2H), 7.48–7.43 (m, 2H), 5.84 (d, $J = 0.9$ Hz, 1H), 4.33–4.24 (m, 2H), 4.05–3.92 (m, 2H), 2.36–2.22 (m, 1H), 1.57–1.49 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -177.37. ^{13}C NMR (101 MHz, CDCl_3) δ 152.1 (d, $^3J_{\text{CF}} = 6.8$ Hz), 151.9 (d, $^2J_{\text{CF}} = 17.3$ Hz), 142.0 (d, $^1J_{\text{CF}} = 261.5$ Hz), 136.9, 129.5 (2C), 128.5 (d, $^4J_{\text{CF}} = 3.3$ Hz, 2C), 125.0 (d, $^4J_{\text{CF}} = 3.7$ Hz), 94.1 (d, $^4J_{\text{CF}} = 2.9$ Hz), 67.5 (2C), 25.6. Mass (CI/ NH_3): $m/z = 284$ $[\text{M} + \text{H}]^+$.

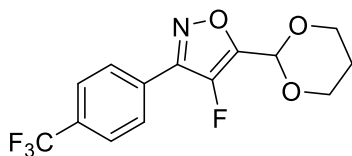
2.4. 5-(1,3-Dioxan-2-yl)-4-fluoro-3-(4-fluorophenyl)isoxazole (2d)



Molecular Weight: 267,23

Yellow oil: 74 mg, 70%; ^1H NMR (400 MHz, CDCl_3) δ 7.91–7.81 (m, 2H), 7.22–7.11 (m, 2H), 5.84 (d, $J = 0.9$ Hz, 1H), 4.34–4.26 (m, 2H), 4.05–3.94 (m, 2H), 2.37–2.22 (m, 1H), 1.57–1.48 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.14, -177.71. ^{13}C NMR (101 MHz, CDCl_3) δ 164.2 (d, $^1J_{\text{CF}} = 251.1$ Hz), 152.1 (d, $^3J_{\text{CF}} = 10.4$ Hz), 151.8 (d, $^2J_{\text{CF}} = 20.8$ Hz), 142.0 (d, $^1J_{\text{CF}} = 261.2$ Hz), 129.3 (dd, $^3J_{\text{CF}} + ^4J_{\text{CF}} = 8.5, 3.3$ Hz, 2C), 122.7 (t, $^4J_{\text{CF}} = 3.3$ Hz), 116.3 (d, $^2J_{\text{CF}} = 22.0$ Hz, 2C), 94.1 (d, $^4J_{\text{CF}} = 3.0$ Hz), 67.5 (2C), 25.6. HRMS (APCI) m/z : $[\text{M}]^+$ Calcd. for $\text{C}_{13}\text{H}_{11}\text{F}_2\text{NO}_3$ 267.0707; Found 267.0711.

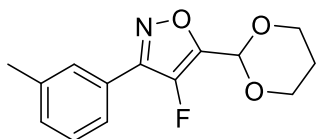
2.5. 5-(1,3-Dioxan-2-yl)-4-fluoro-3-(4-(trifluoromethyl)phenyl)isoxazole (**2e**)



$C_{14}H_{11}F_4NO_3$
Molecular Weight: 317.24

Yellow solid: 66 mg, 63%; 1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, $J = 8.5$ Hz, 2H), 7.75 (d, $J = 8.2$ Hz, 2H), 5.86 (d, $J = 0.8$ Hz, 1H), 4.34–4.27 (m, 2H), 4.06–3.96 (m, 2H), 2.37–2.24 (m, 1H), 1.57–1.50 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.05, -177.26. ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (d, $^2J_{CF} = 20.7$ Hz), 151.9 (d, $^3J_{CF} = 10.3$ Hz), 142.2 (d, $^1J_{CF} = 261.9$ Hz), 132.5 (q, $^2J_{CF} = 32.7$ Hz), 130.0, 127.6 (d, $^4J_{CF} = 3.3$ Hz, 2C), 126.1 (d, $^4J_{CF} = 3.6$ Hz, 2C), 123.9 (q, $^1J_{CF} = 274.3$ Hz), 94.1 (d, $^4J_{CF} = 2.9$ Hz), 67.6 (2C), 25.6. HRMS (APCI) m/z : $[M]^+$ Calcd. for $C_{14}H_{11}F_4NO_3$ 317.0675; Found 317.0675.

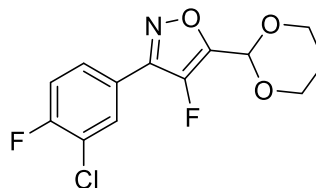
2.6. 5-(1,3-Dioxan-2-yl)-4-fluoro-3-(*m*-tolyl)isoxazole (**2f**)



$C_{14}H_{14}FNO_3$
Molecular Weight: 263,27

Yellow oil: 68 mg, 63%; 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 5.85 (d, $J = 1.0$ Hz, 1H), 4.33–4.26 (m, 2H), 4.04–3.95 (m, 2H), 2.41 (s, 3H), 2.36–2.22 (m, 1H), 1.57–1.47 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -177.43. ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (d, $^3J_{CF} = 10.5$ Hz), 151.5 (d, $^2J_{CF} = 20.9$ Hz), 142.2 (d, $^1J_{CF} = 261.3$ Hz), 138.9, 131.5, 130.0, 127.7 (d, $^4J_{CF} = 2.5$ Hz), 126.4 (d, $^4J_{CF} = 3.6$ Hz), 124.4 (d, $^4J_{CF} = 3.5$ Hz), 94.2 (d, $^4J_{CF} = 3.0$ Hz) 67.5 (2C), 25.6, 21.5. Mass (CI/ NH_3): $m/z = 264$ $[M + H]^+$.

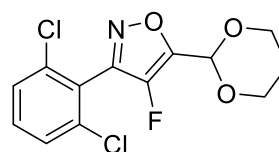
2.7. 3-(3-Chloro-4-fluorophenyl)-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (**2g**)



$C_{13}H_{10}ClF_2NO_3$
Molecular Weight: 301.67

Yellow oil: 46 mg, 44%; 1H NMR (400 MHz, $CDCl_3$) δ 7.93–7.84 (m, $J = 8.9, 7.8, 6.0$ Hz, 1H), 7.10–7.05 (m, 1H), 6.79 (d, $J = 3.8$ Hz, 1H), 5.76 (s, 1H), 4.34–4.24 (m, 2H), 4.01 (dt, $J = 12.2, 2.5$ Hz, 2H), 2.35–2.19 (m, 1H), 1.56–1.46 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.36 (d, $J = 4.9$ Hz), -112.77 (d, $J = 4.9$ Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 159.9 (d, $^1J_{CF} = 252.1$ Hz), 156.7 (d, $^1J_{CF} = 256.2$ Hz), 156.4, 127.2 (dd, $^3J_{CF} + ^4J_{CF} = 9.1, 3.8$ Hz), 114.4 (dd, $^3J_{CF} + ^4J_{CF} = 12.3, 3.8$ Hz), 112.5 (dd, $^2J_{CF} + ^4J_{CF} = 21.4, 3.6$ Hz), 111.0 (t, $^2J_{CF} = 20.9$ Hz), 102.3 (d, $^3J_{CF} = 8.9$ Hz), 94.8, 67.3 (2C), 25.5. Mass (CI/ NH_3): $m/z = 302$ $[M + H]^+$.

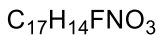
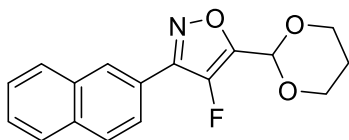
2.8. 3-(2,6-Dichlorophenyl)-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (**2h**)



$C_{13}H_{10}Cl_2FNO_3$
Molecular Weight: 318.13

Colorless oil: 22 mg, 21%; 1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $J = 2.2$ Hz, 1H), 7.42 (d, $J = 0.6$ Hz, 1H), 7.37 (dd, $J = 9.4, 6.4$ Hz, 1H), 5.89 (d, $J = 1.1$ Hz, 1H), 4.36–4.27 (m, 2H), 4.06–3.96 (m, 2H), 2.38–2.20 (m, 1H), 1.56–1.51 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.41. ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (d, $^2J_{CF} = 19.6$ Hz), 151.0 (d, $^2J_{CF} = 14.9$ Hz), 142.1 (d, $^1J_{CF} = 261.3$ Hz), 136.1, 132.1, 128.4 (2C), 124.8, 124.7, 94.2 (d, $^4J_{CF} = 2.9$ Hz), 67.5 (2C), 25.6. Mass (CI/ NH_3): $m/z = 335$ $[M + H]^+$.

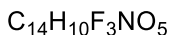
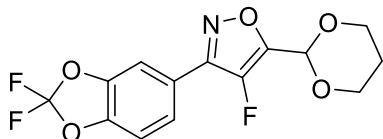
2.9. 5-(1,3-Dioxan-2-yl)-4-fluoro-3-(naphthalen-2-yl)isoxazole (**2i**)



Molecular Weight: 299,30

Colorless oil: 21 mg, 20%; ^1H NMR (400 MHz, CDCl_3) δ 8.36 (s, 1H), 8.02–7.85 (m, 4H), 7.60–7.51 (m, 2H), 5.89 (s, 1H), 4.38–4.28 (m, 2H), 4.03 (td, $J = 12.1, 2.5$ Hz, 2H), 2.43–2.24 (m, 1H), 1.59–1.49 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -177.01. ^{13}C NMR (101 MHz, CDCl_3) δ 153.0 (d, $^3J_{\text{CF}} = 10.1$ Hz), 151.7 (d, $^2J_{\text{CF}} = 20.8$ Hz), 142.4 (d, $^1J_{\text{CF}} = 261.5$ Hz), 133.7 (d, $^2J_{\text{CF}} = 108.0$ Hz), 129.0, 128.9, 128.0, 127.6, 127.53, 127.49, 126.9, 124.0 (d, $^4J_{\text{CF}} = 3.7$ Hz), 123.9 (d, $^4J_{\text{CF}} = 1.3$ Hz), 94.2 (d, $^4J_{\text{CF}} = 2.9$ Hz), 67.6, 25.61 (2C). Mass (CI/ NH_3): $m/z = 300$ [M + H] $^+$.

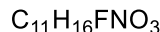
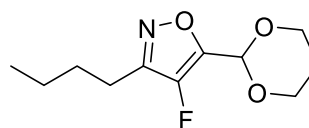
2.10. 3-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (**2j**)



Molecular Weight: 329,23

Pale yellow oil: 63 mg, 60%; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (dd, $J = 8.5, 6.5$ Hz, 1H), 6.98 (dd, $J = 8.5, 0.9$ Hz, 1H), 6.76 (d, $J = 3.5$ Hz, 1H), 5.75 (s, 1H), 4.32–4.24 (m, 2H), 4.06–3.95 (m, 2H), 2.34–2.19 (m, 1H), 1.54–1.47 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -49.29, -136.39. ^{13}C NMR (101 MHz, CDCl_3) δ 169.2, 156.7, 146.6 (d, $^4J_{\text{CF}} = 3.9$ Hz), 143.8 (d, $^1J_{\text{CF}} = 257.2$ Hz), 132.0, 129.5 (d, $^3J_{\text{CF}} = 17.2$ Hz), 124.1, 114.3 (d, $^3J_{\text{CF}} = 9.0$ Hz), 106.1 (d, $^4J_{\text{CF}} = 3.7$ Hz), 102.2 (d, $^3J_{\text{CF}} = 8.0$ Hz), 94.9, 67.4 (2C), 25.6. Mass (CI/ NH_3): $m/z = 329$ [M + H] $^+$.

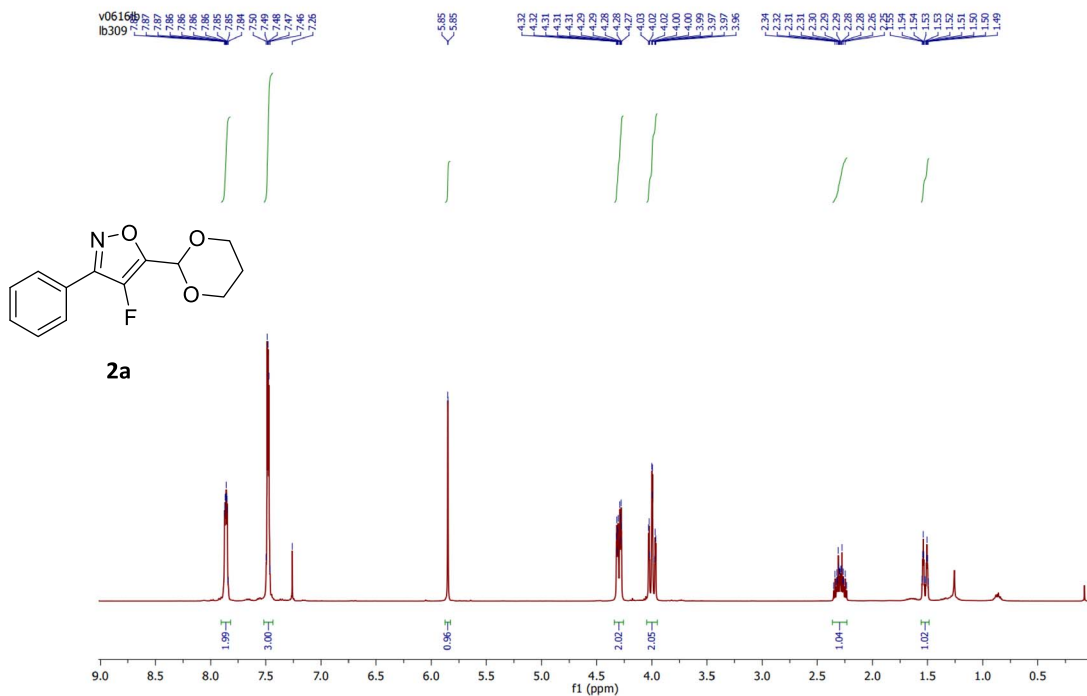
2.11. 3-Butyl-5-(1,3-dioxan-2-yl)-4-fluoroisoxazole (**2k**)



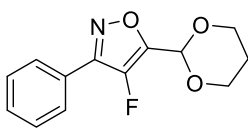
Molecular Weight: 229,25

Colorless oil: 26 mg, 25%; ^1H NMR (400 MHz, CDCl_3) δ 5.76 (d, $J = 1.0$ Hz, 1H), 4.32–4.21 (m, 2H), 4.03–3.91 (m, 2H), 2.68 (t, $J = 7.8$ Hz, 2H), 2.33–2.18 (m, 1H), 1.72–1.62 (m, 2H), 1.53–1.45 (m, 1H), 1.45–1.33 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -180.07. ^{13}C NMR (101 MHz, CDCl_3) δ 155.4 (d, $^2J_{\text{CF}} = 14.8$ Hz), 150.1 (d, $^2J_{\text{CF}} = 19.7$ Hz), 142.7 (d, $^1J_{\text{CF}} = 258.3$ Hz), 94.3 (d, $^4J_{\text{CF}} = 3.0$ Hz), 67.5 (2C), 29.2, 25.6, 23.5 (d, $^4J_{\text{CF}} = 2.5$ Hz), 22.3, 13.7. Mass (CI/ NH_3): $m/z = 230$ [M + H] $^+$.

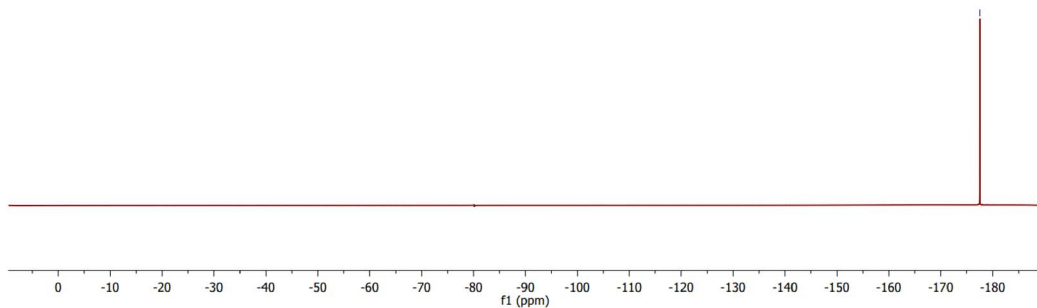
3. NMR spectras of fluorinated isoxaoles 2a-2k

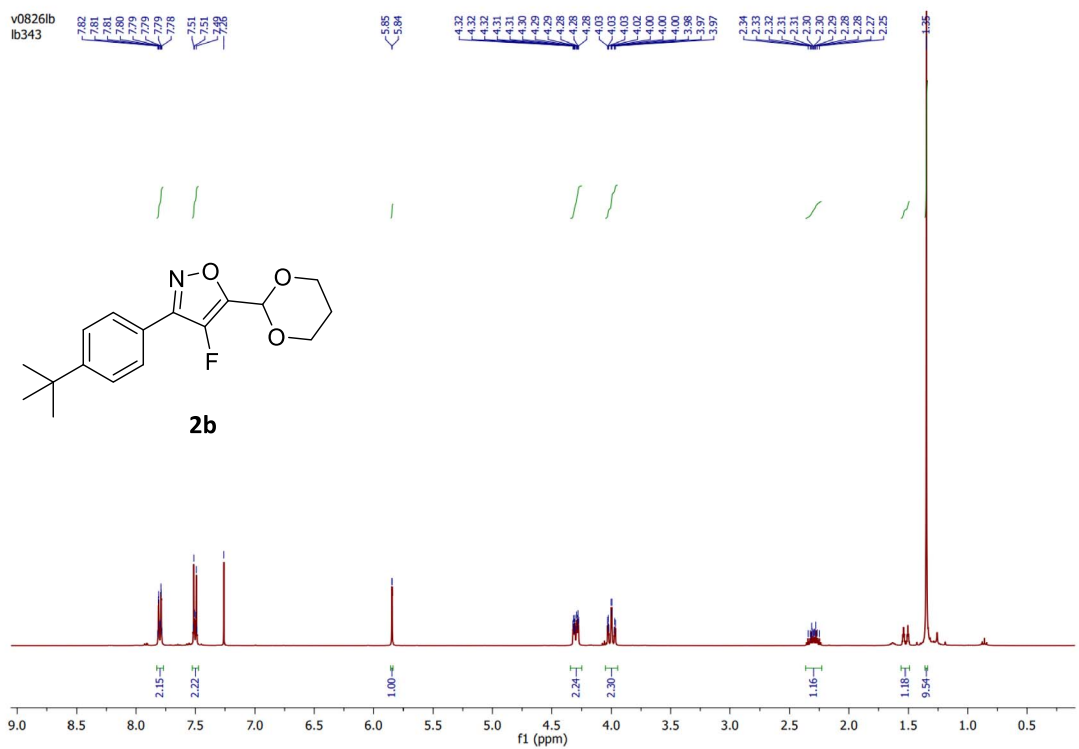
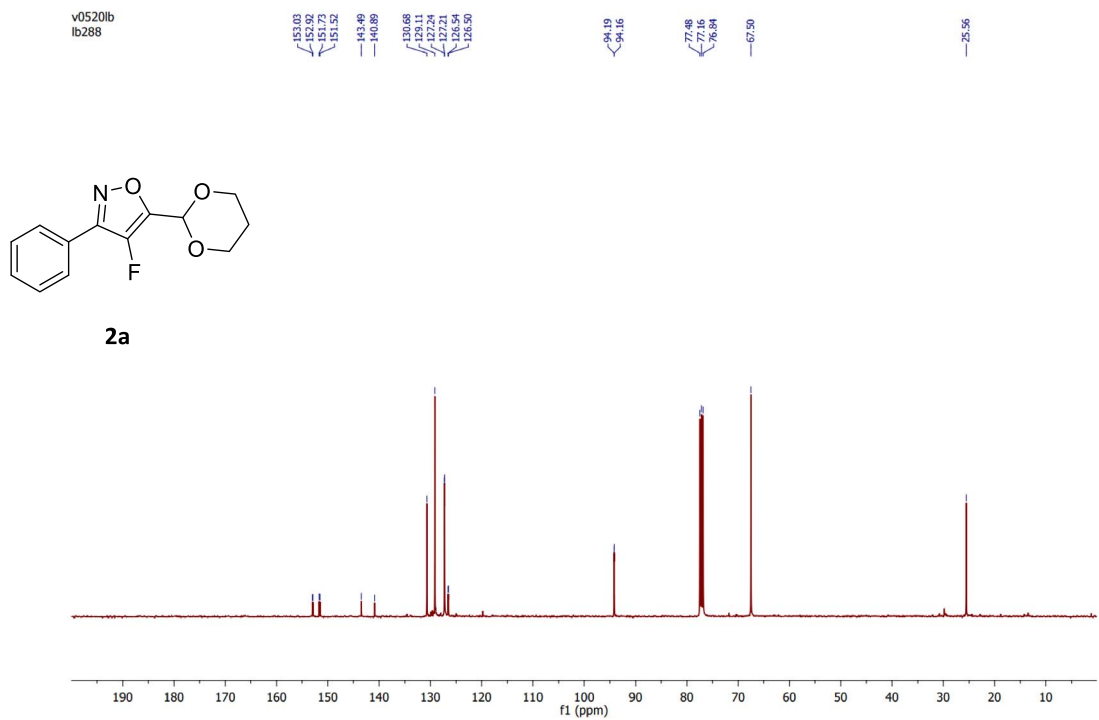


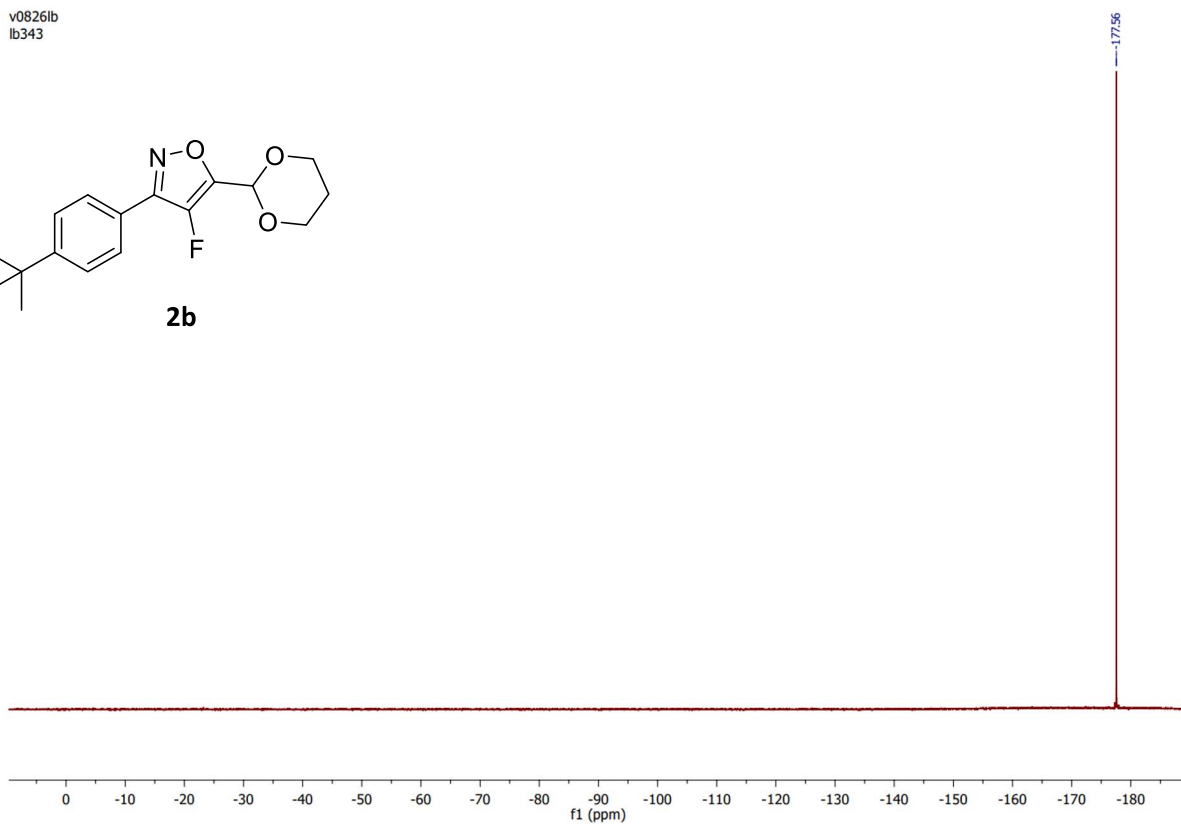
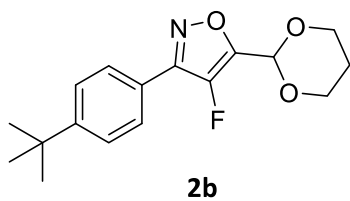
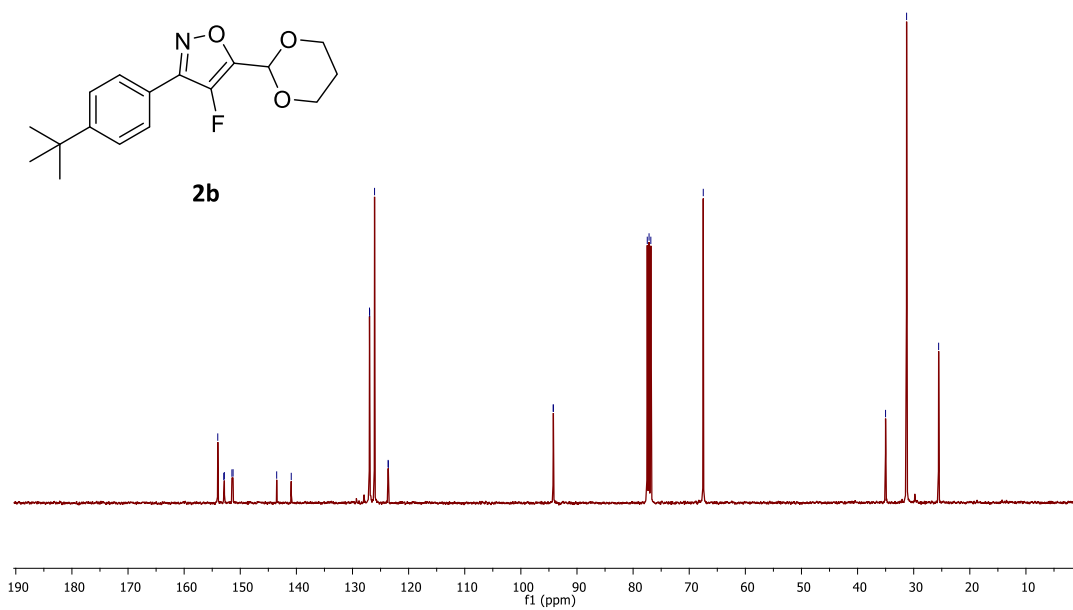
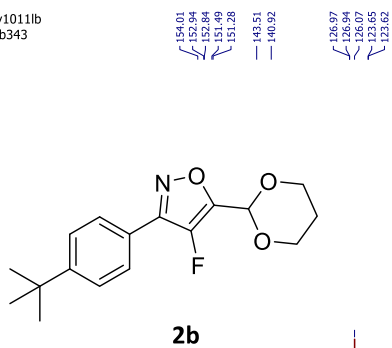
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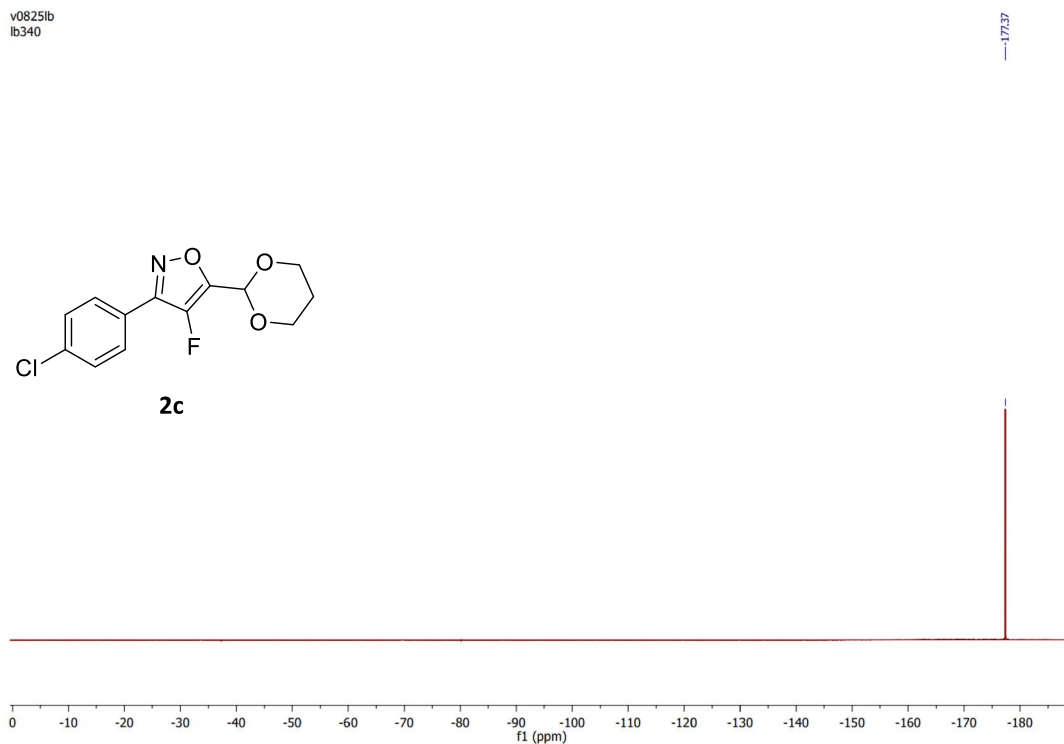
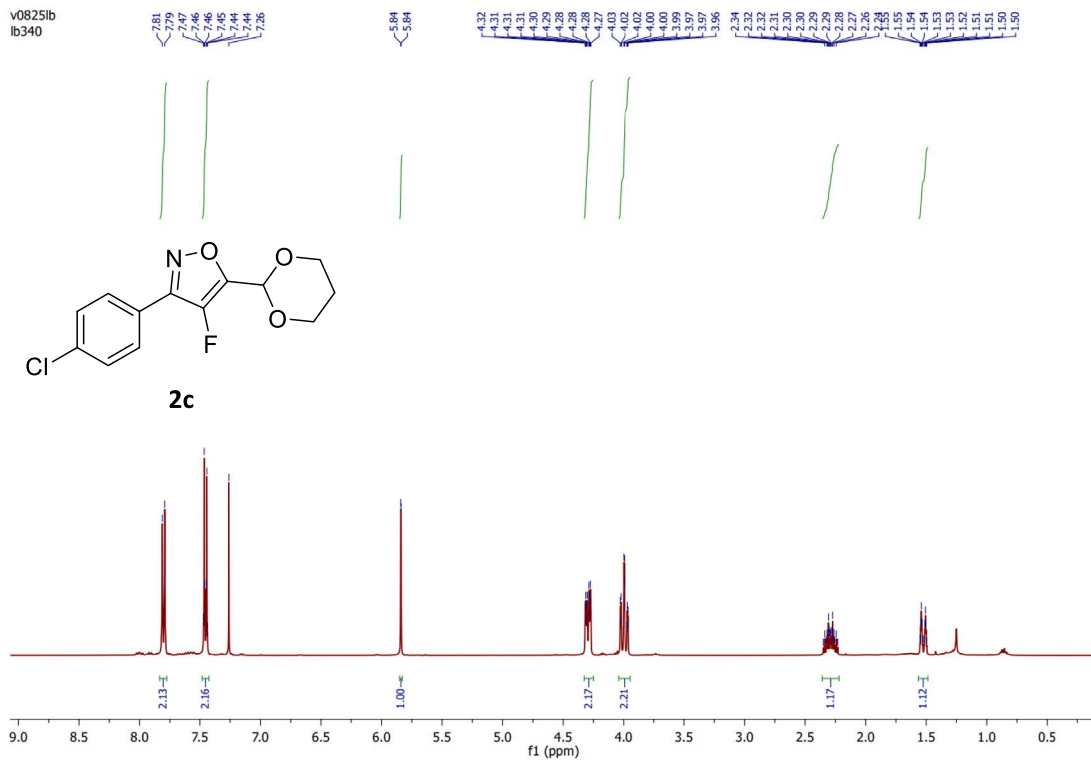


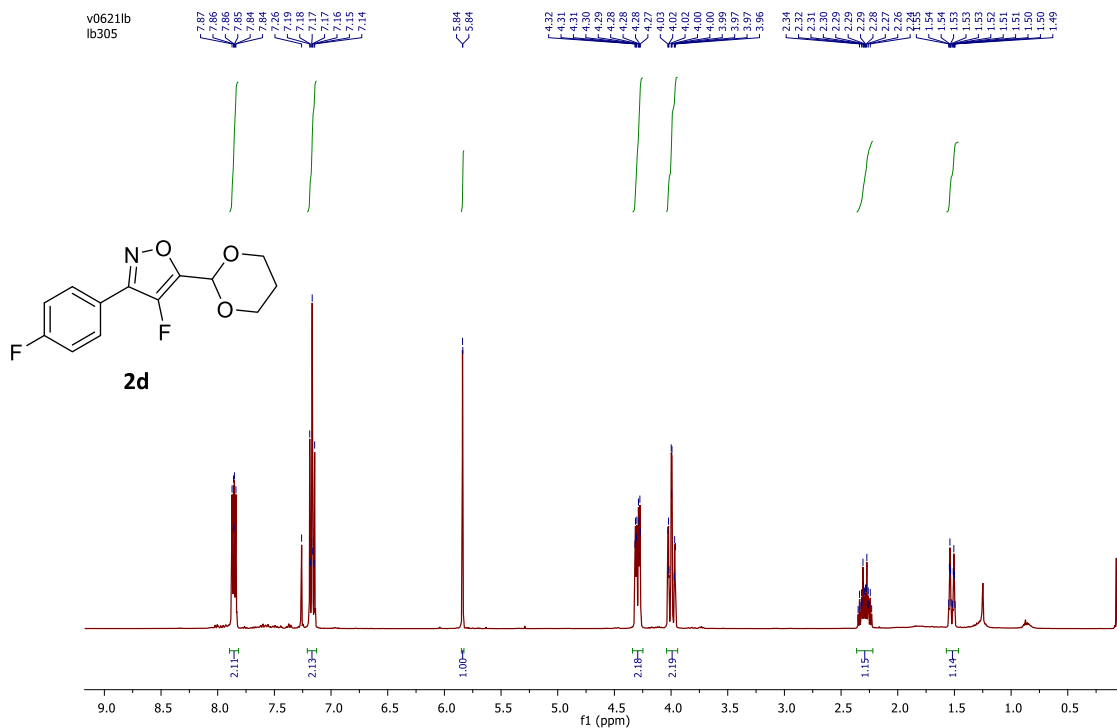
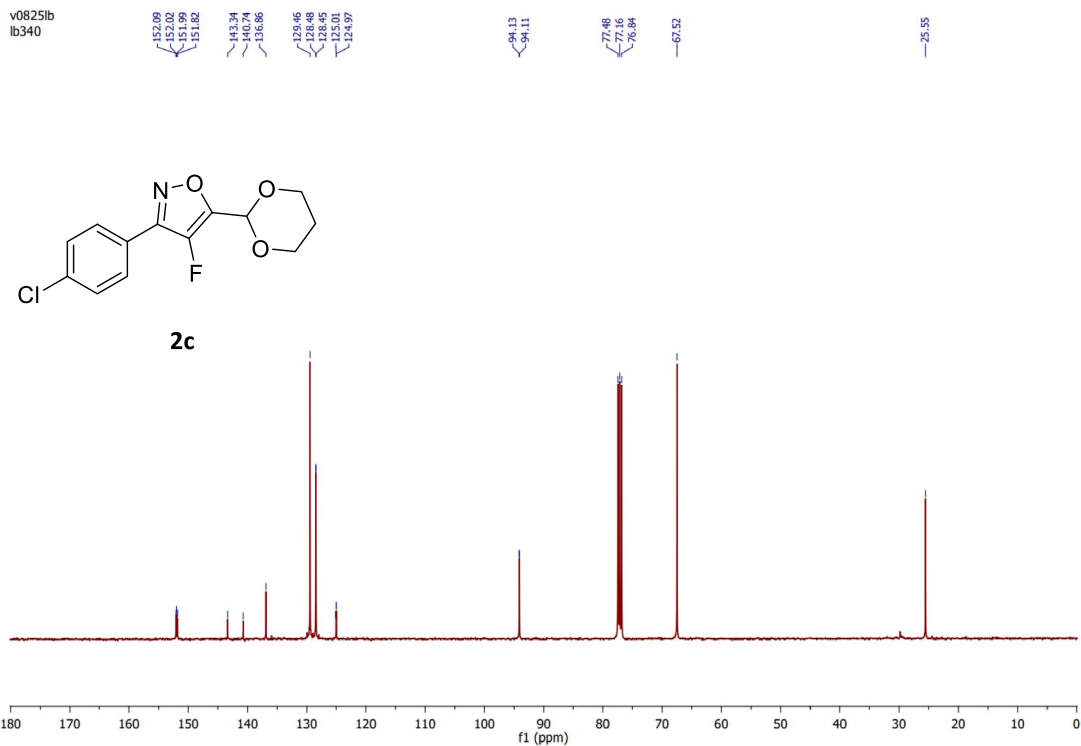
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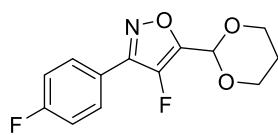
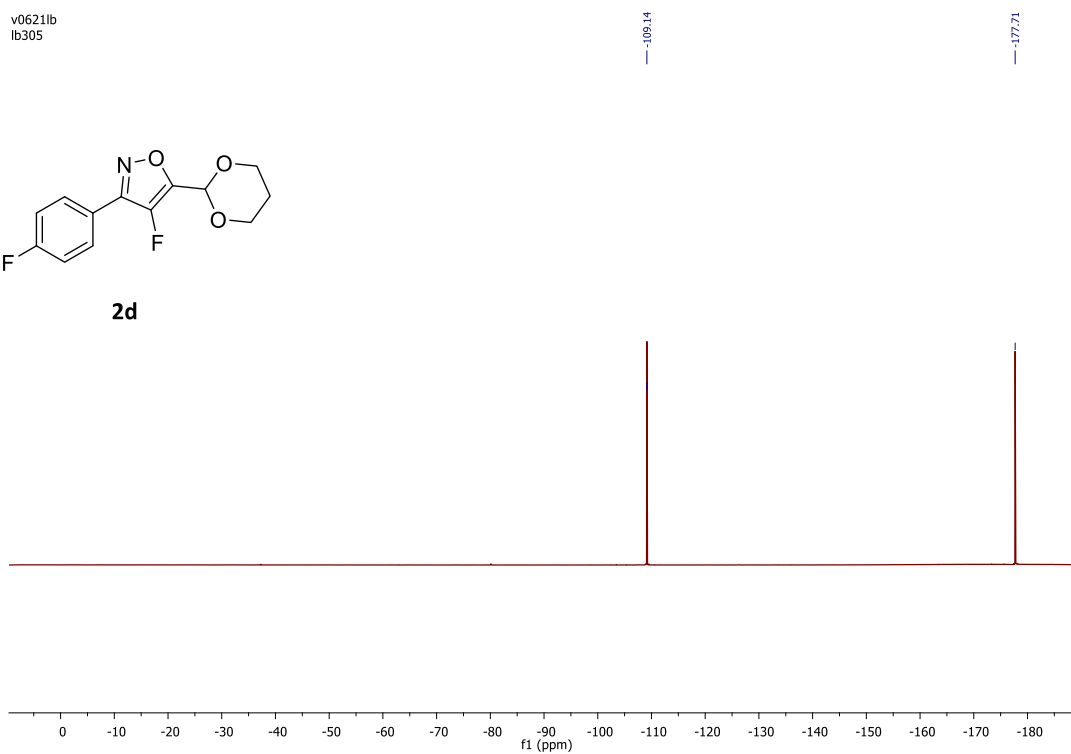
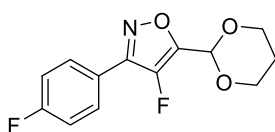
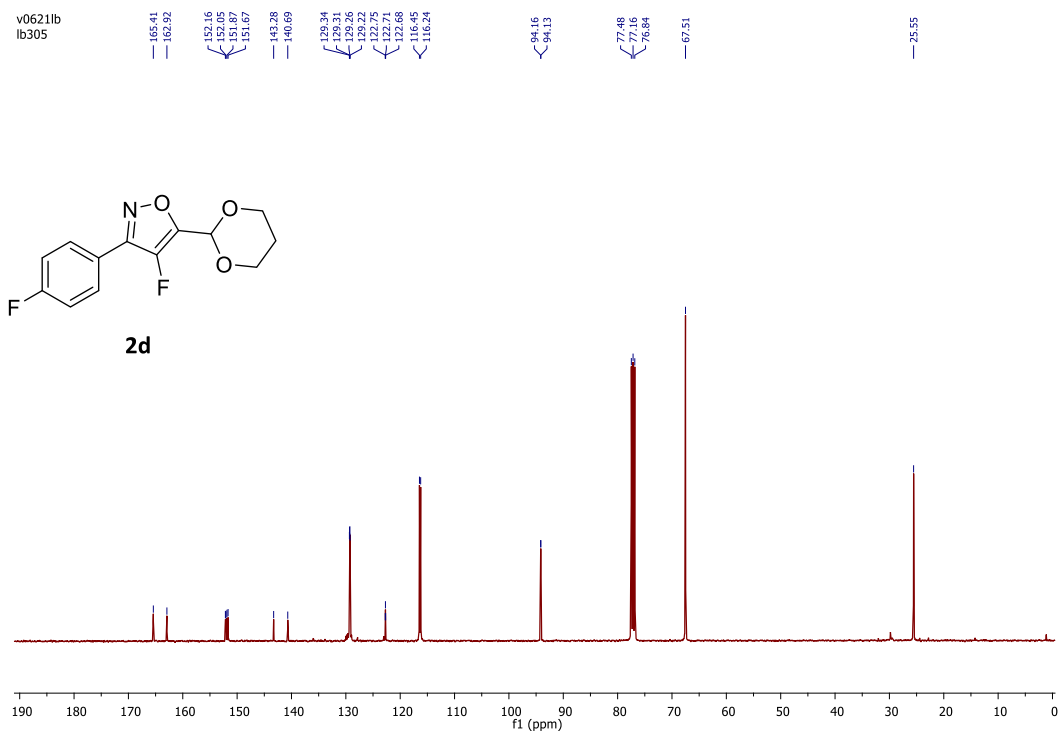




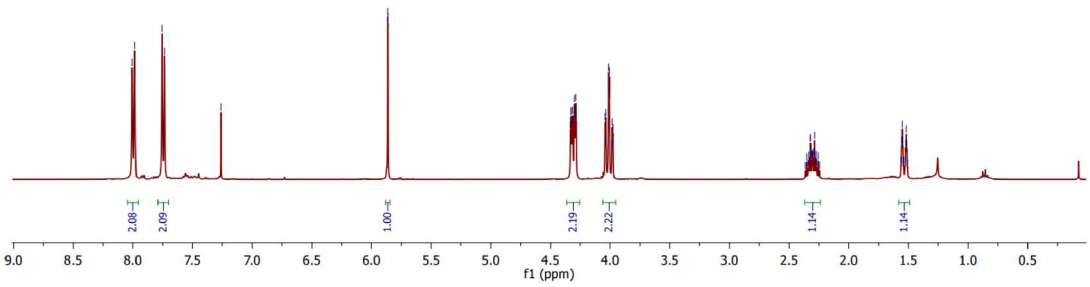
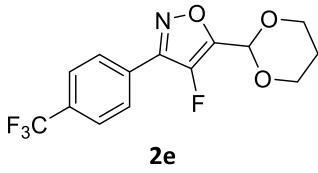
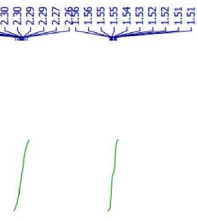
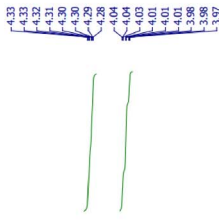
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lb343v1011lb
lb343





v0621lb
lb305**2d**v0621lb
lb305**2d**

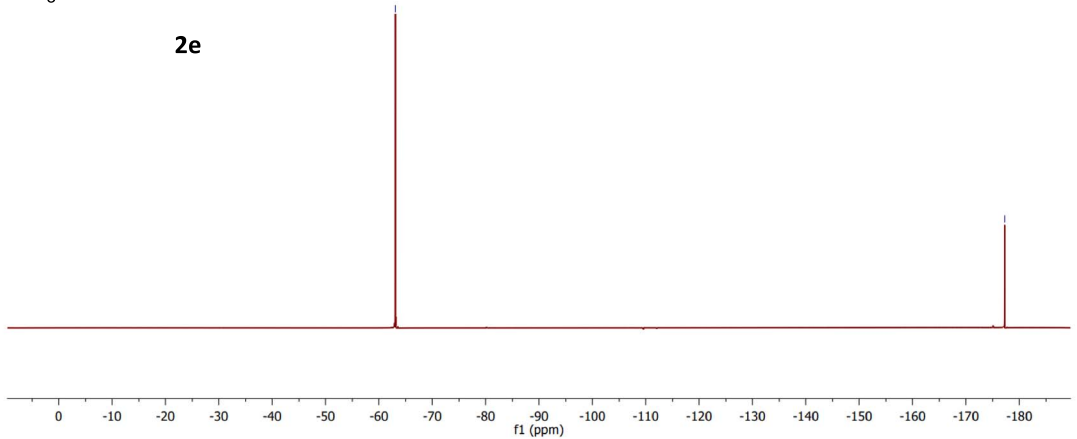
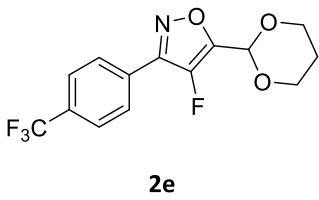
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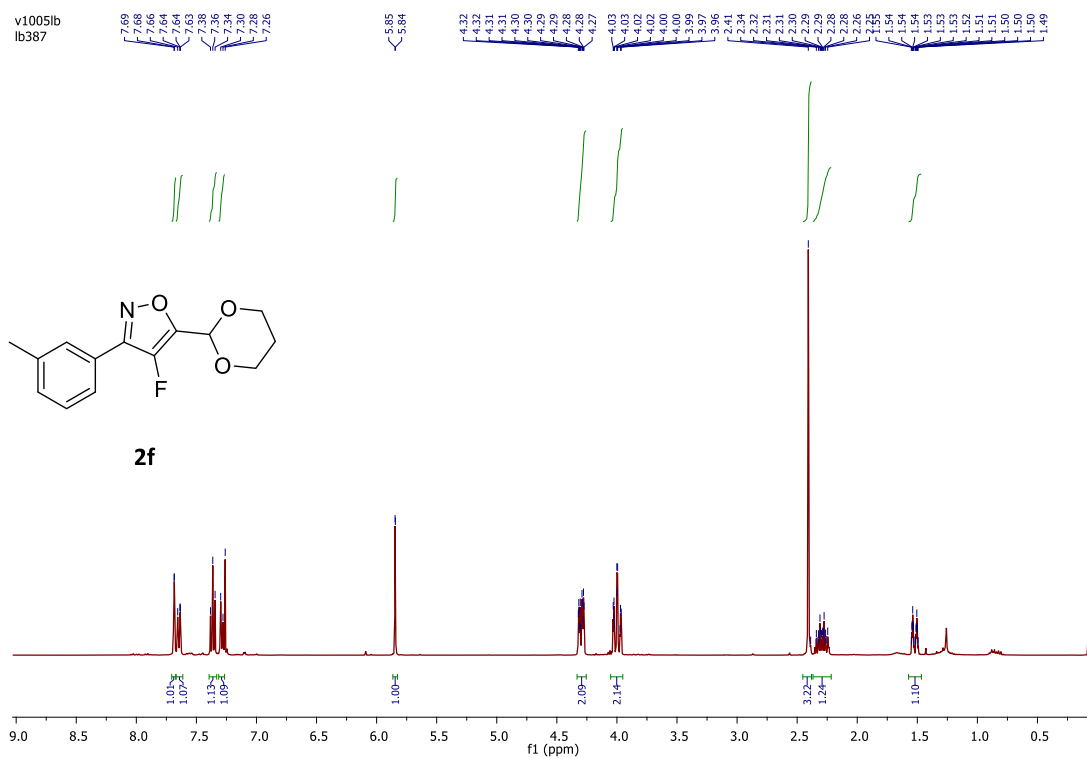
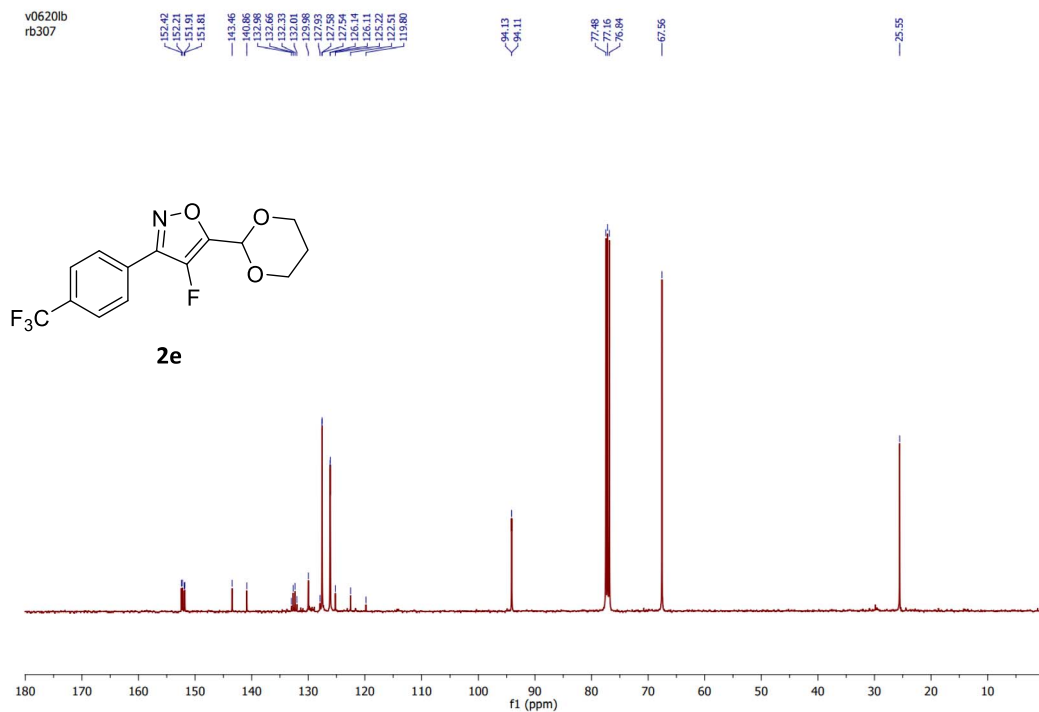


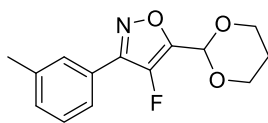
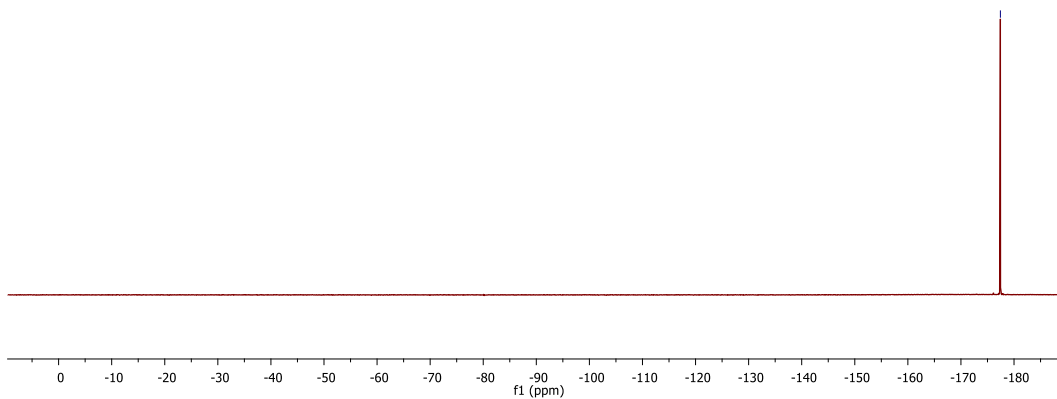
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rb307

-63.05

-177.26





v1005lb
lb387**2f**v1005lb
lb387

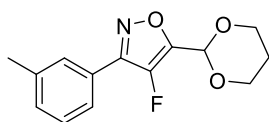
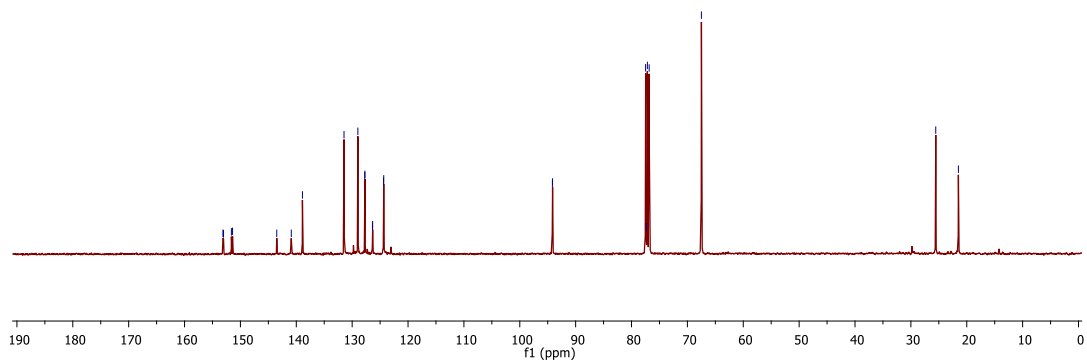
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138.90
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127.72
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126.33
124.38
124.35

94.16
94.13

77.48
77.36
77.16
76.84

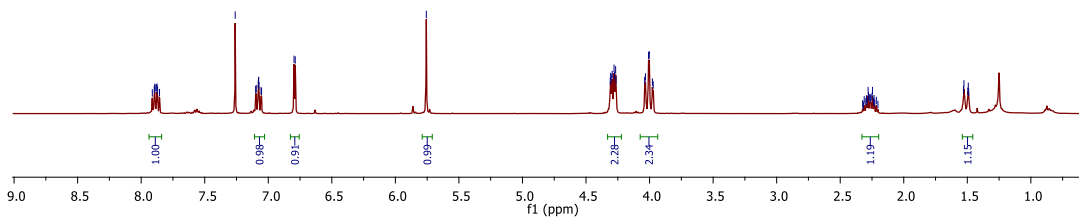
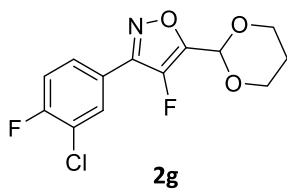
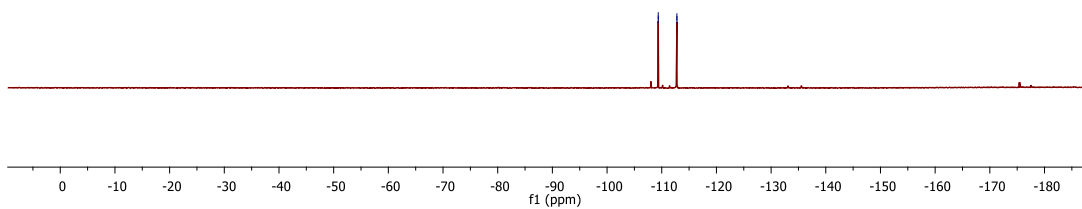
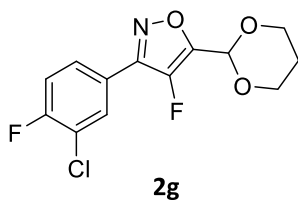
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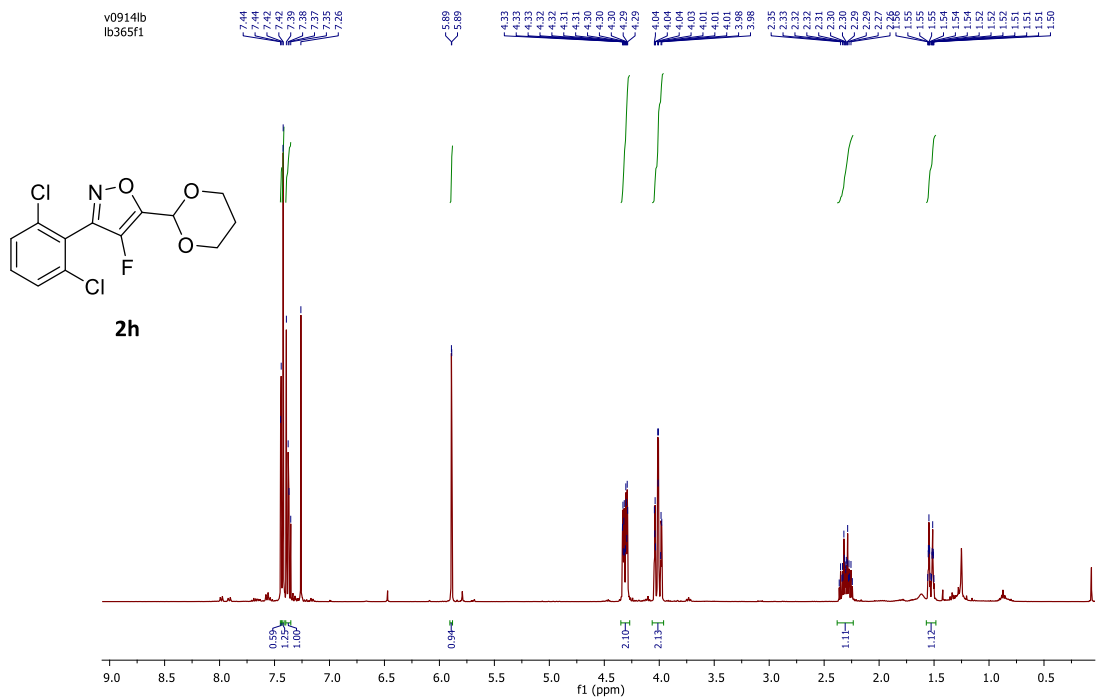
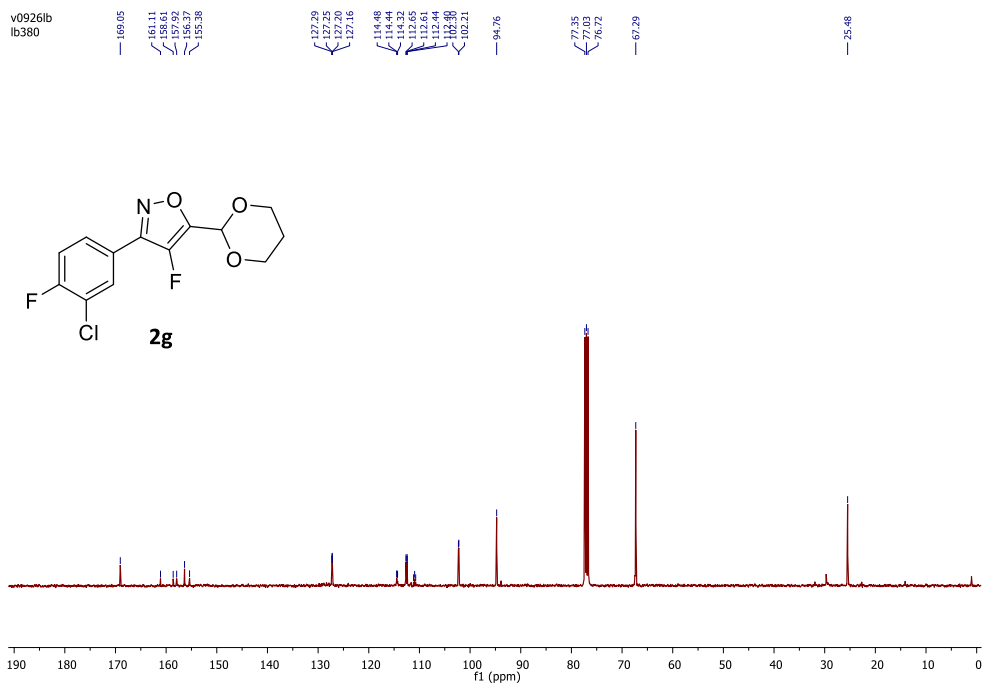
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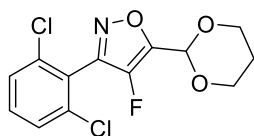
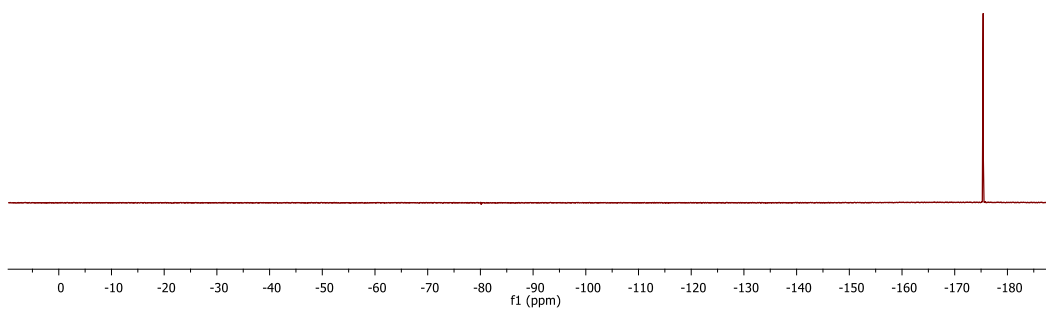
**2f**

v09261b
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6.79

-5.76

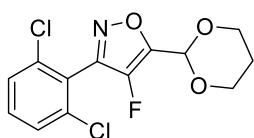
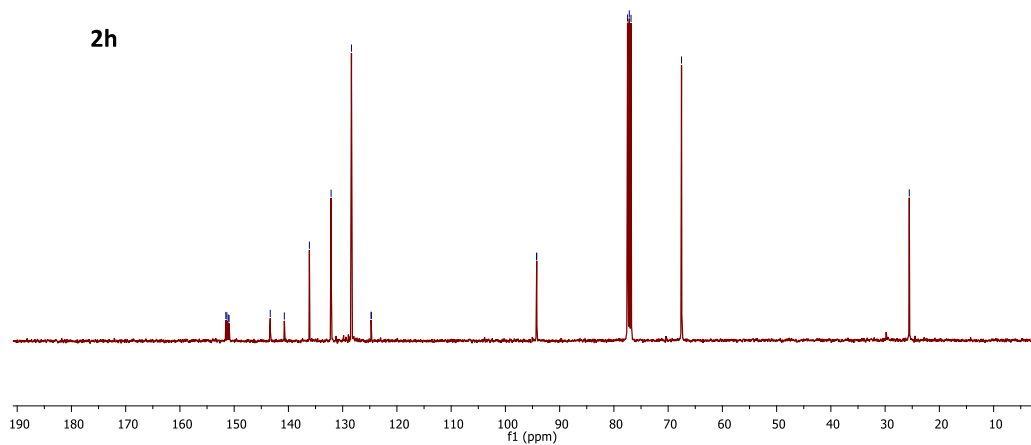
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2.26
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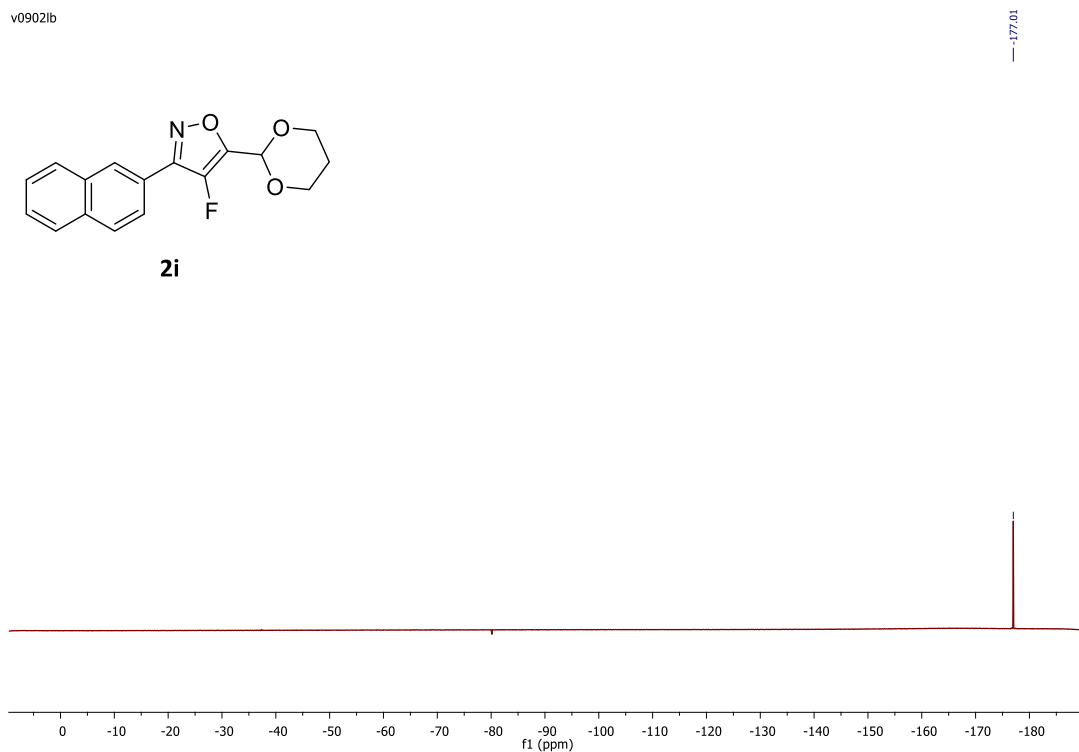
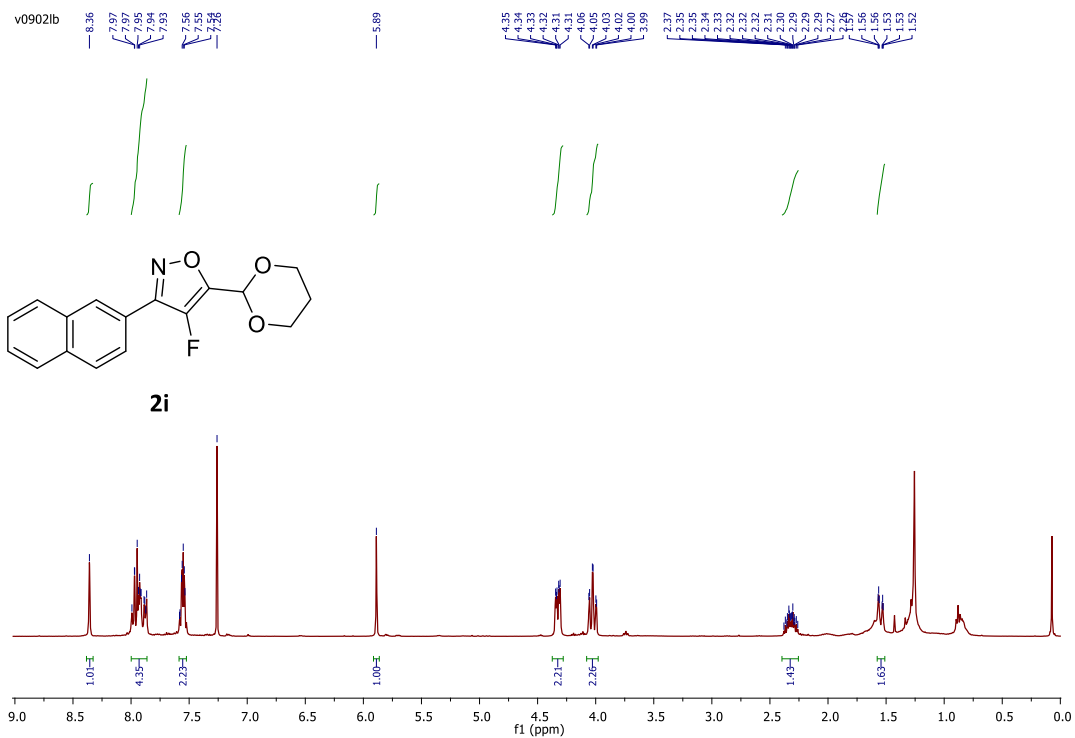


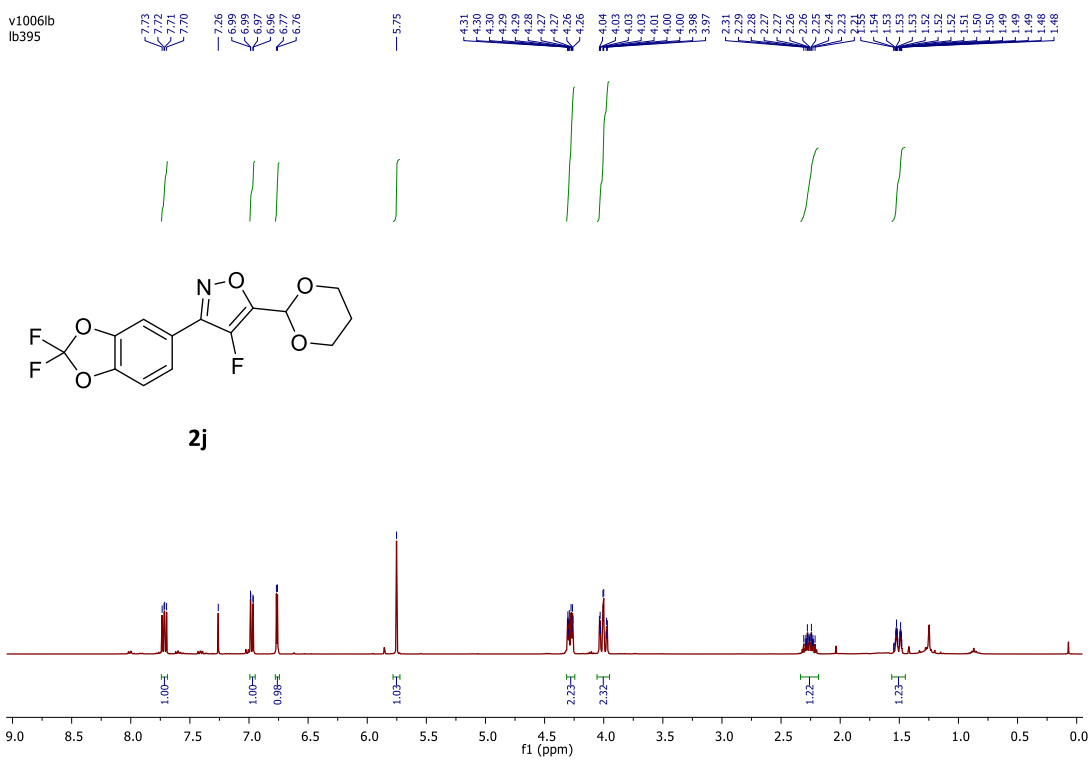
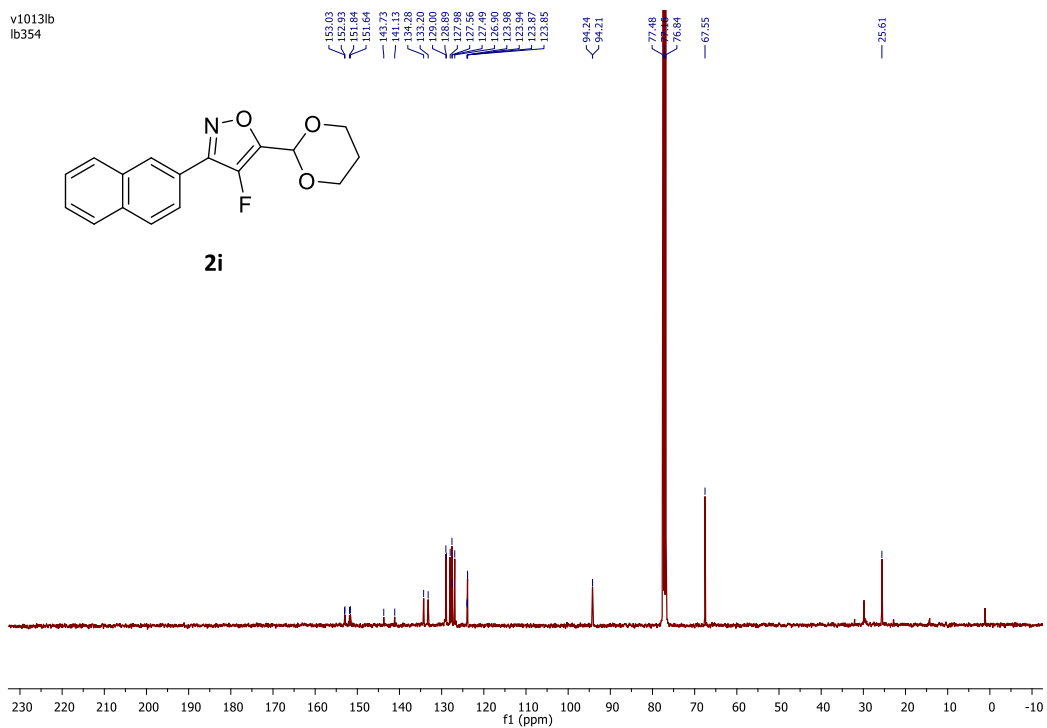
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lb365f1**2h**v0914lb
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77.05
76.84

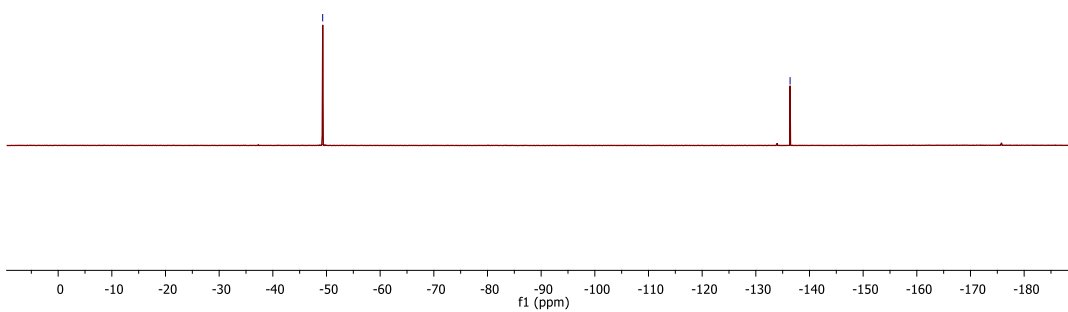
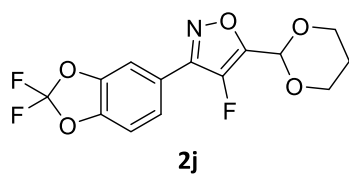
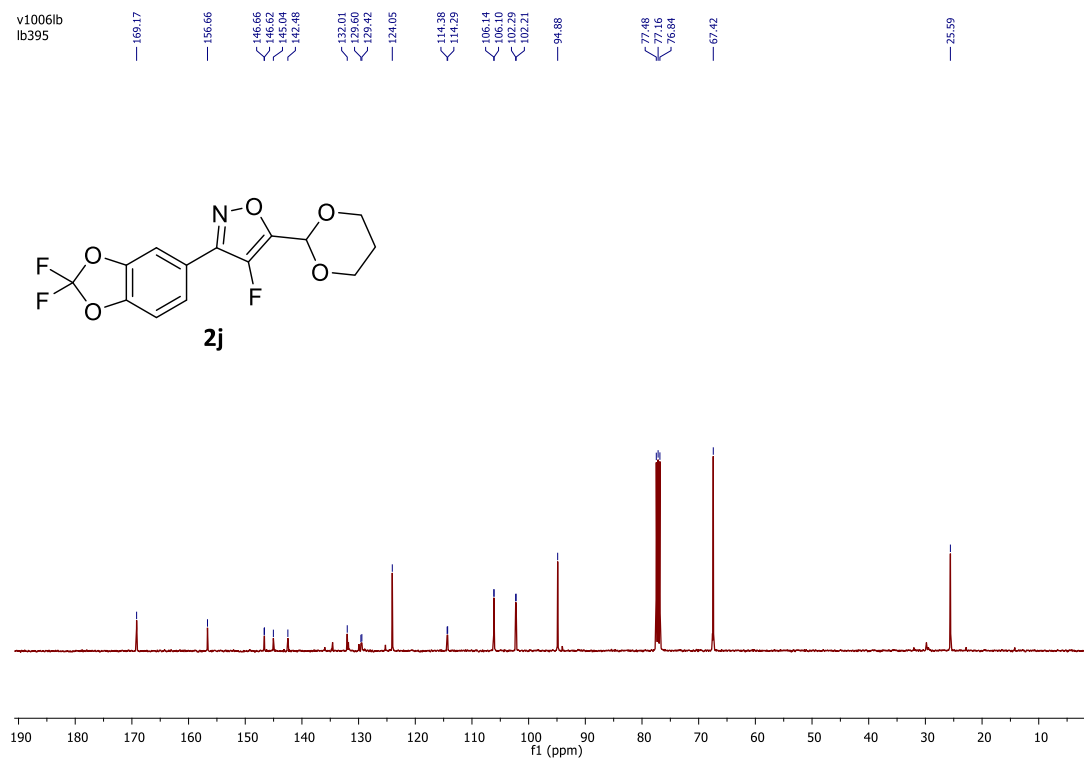
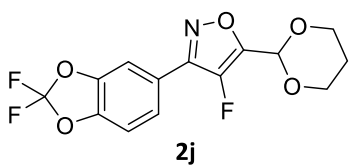
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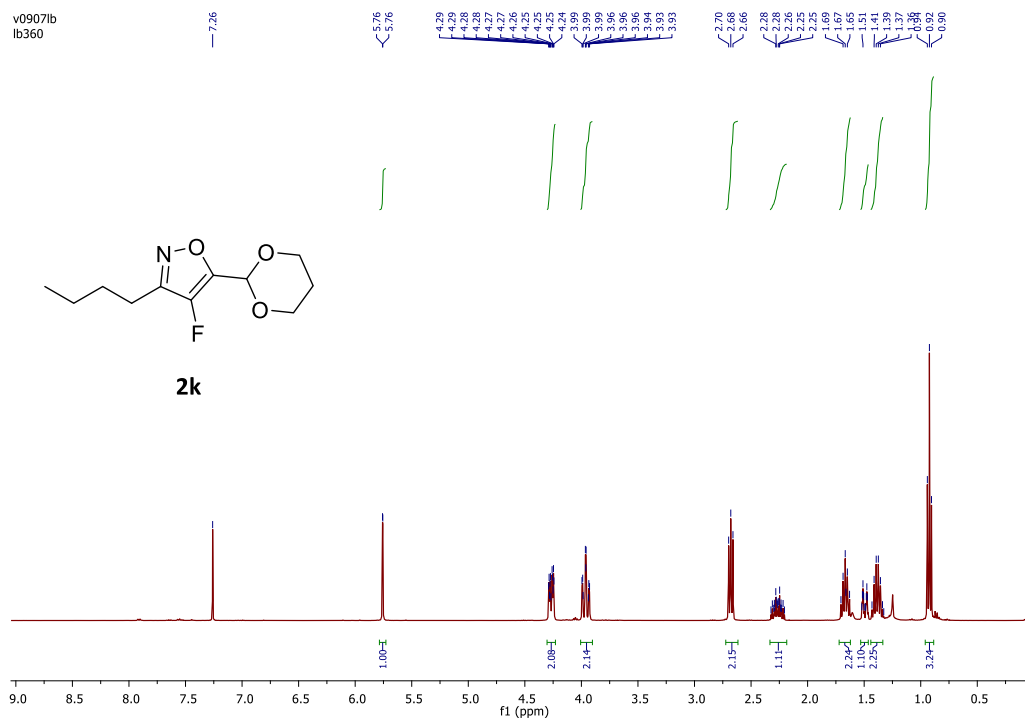
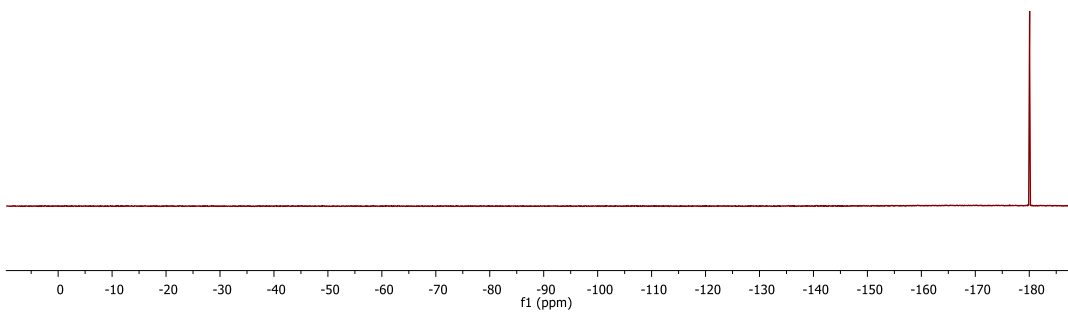
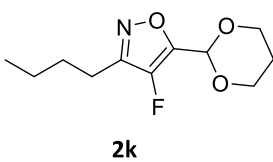
25.95

**2h**





v1006lb
lb395v1006lb
lb395

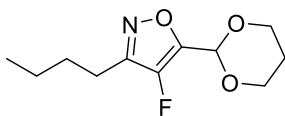
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v09071b
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77.16
76.84

67.49

29.20
25.56
23.53
23.51
22.51

13.73

**2k**