Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis of kinase inhibitors containing a pentafluorosulfanyl moiety.

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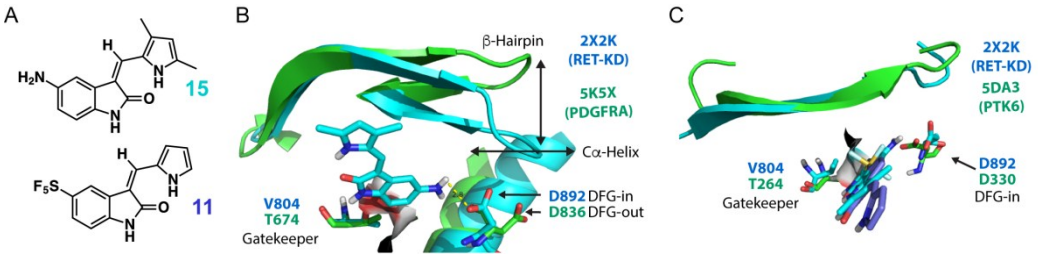


Figure S1. Structural studies comparing binding modes of methylidene indolinone-based kinase inhibitors **11** and **15** (A) with active and inactive kinase domains. Compound **15** (A) was co-crystallised with RET kinase domain (B, PDB: 2X2K) forcing a "DFG-in" kinase conformation. This **15**-bound RET conformation was aligned with the PDGFRA crystal structure (B, PDB: 5K5X) revealing gross conformational shifts around the ATP-binding pocket, particularly between the RET and PDGFRA b-hairpin and Ca-helix (B), and compared to RET, the PDGFRA DFG catalytic-motif aspartic acid is pointing outside of the ATP-binding pocket; evidence for an inactive kinase conformation. Compound **11** displayed the greatest potency in the series against PDGFRA, a receptor tyrosine kinase containing a threonine gatekeeper. RET has a valine gatekeeper, and thus PTK6 (C, PDB: 5DA3), a non-receptor tyrosine kinase containing a threonine gatekeeper, was selected for docking studies with compound **10** - **11** (Fig. 5, main article) to ascertain the molecular determinants for the superior potency of **11** vs **10**. The alignment between 15-bound RET and **11**-docked PTK6 (C) reveals very similar binding modes between compounds **11** and **15** and an agreement in PTK6 and RET kinase conformation, both in the active state.

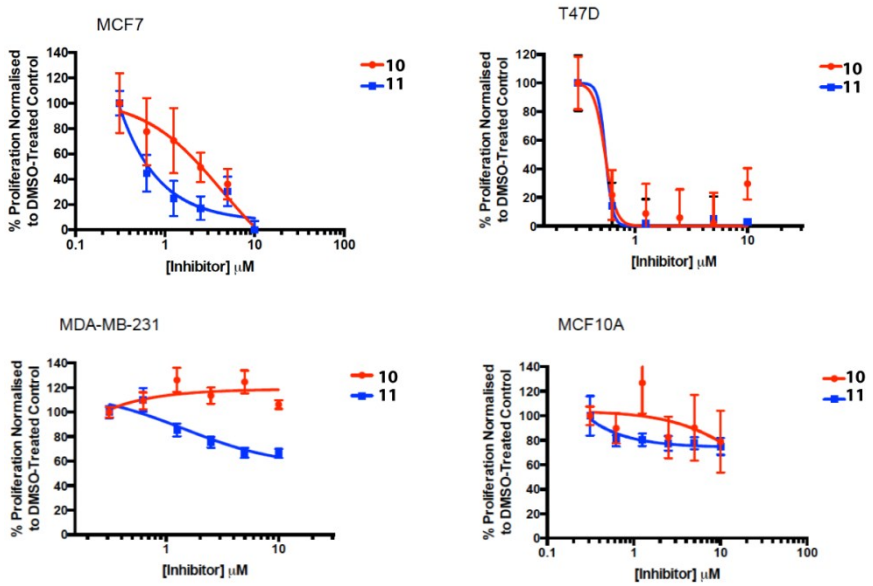
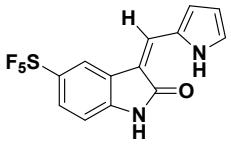
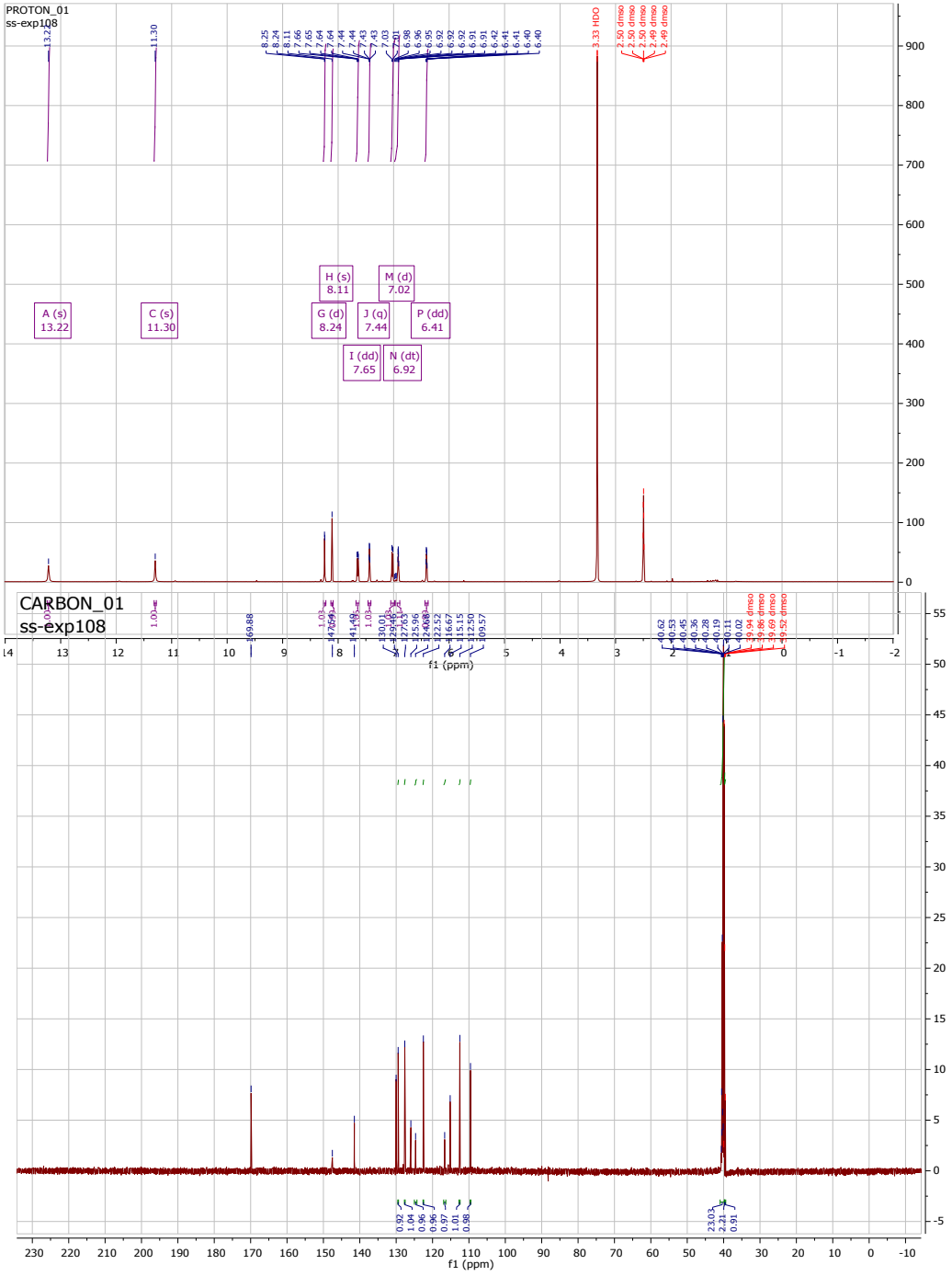


Figure S2. Proliferation assays. Dose-dependent inhibition of MCF7, T47D MDA-BM-231 and MCF10A cells by compounds **10** and **11**.

Fig S3. NMRs

(*Z*)-3-((1H-Pyrrol-2-yl)methylene-5-pentafluorosulfanylindoline-2-one





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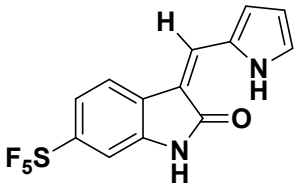

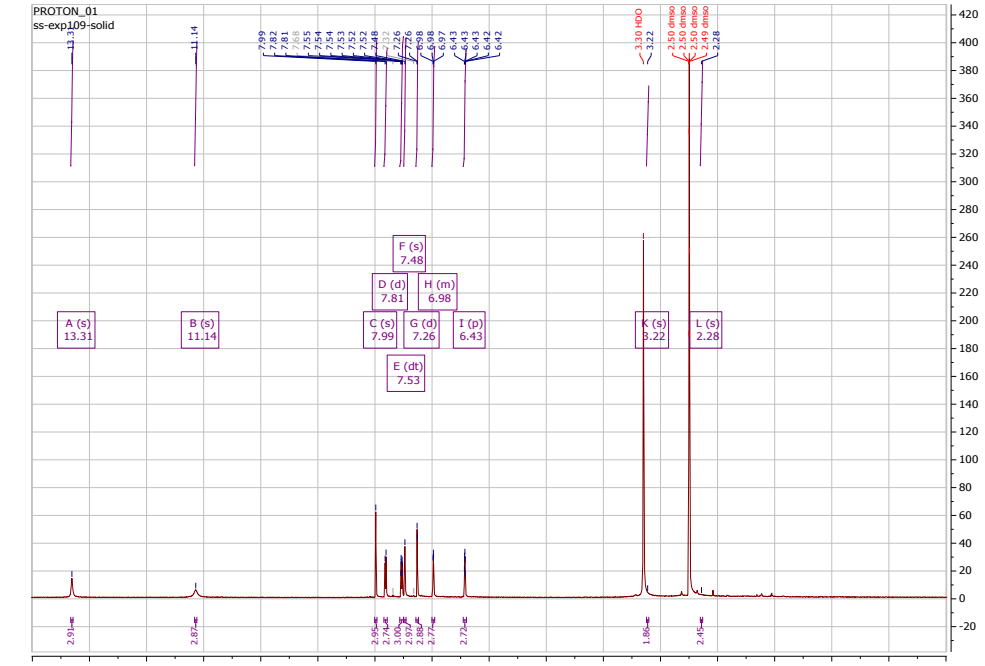

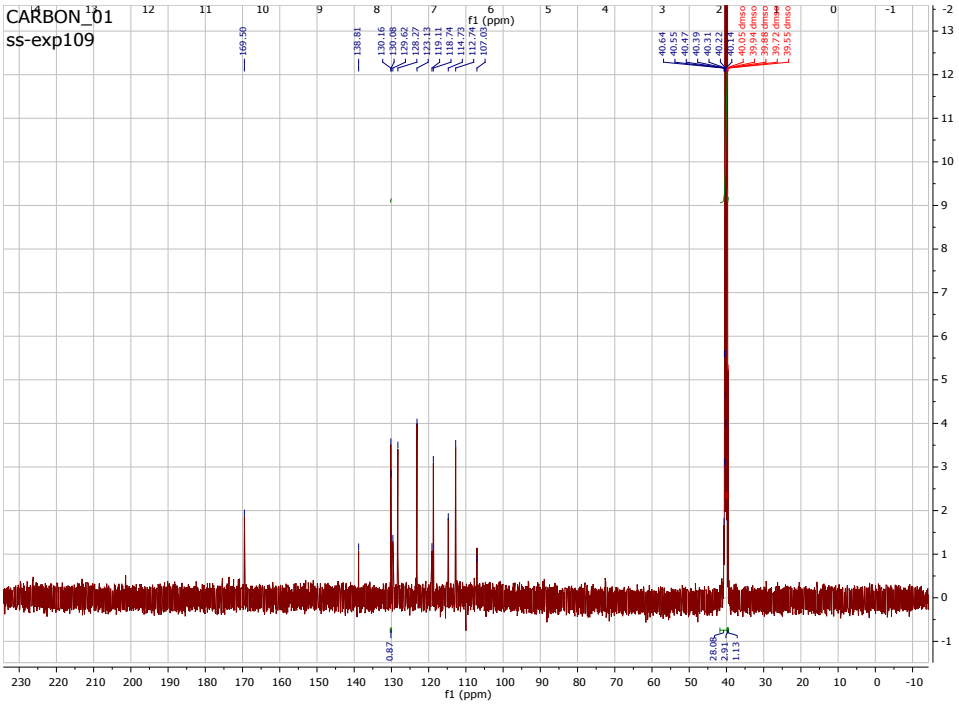

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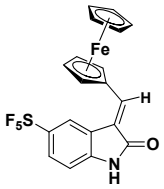

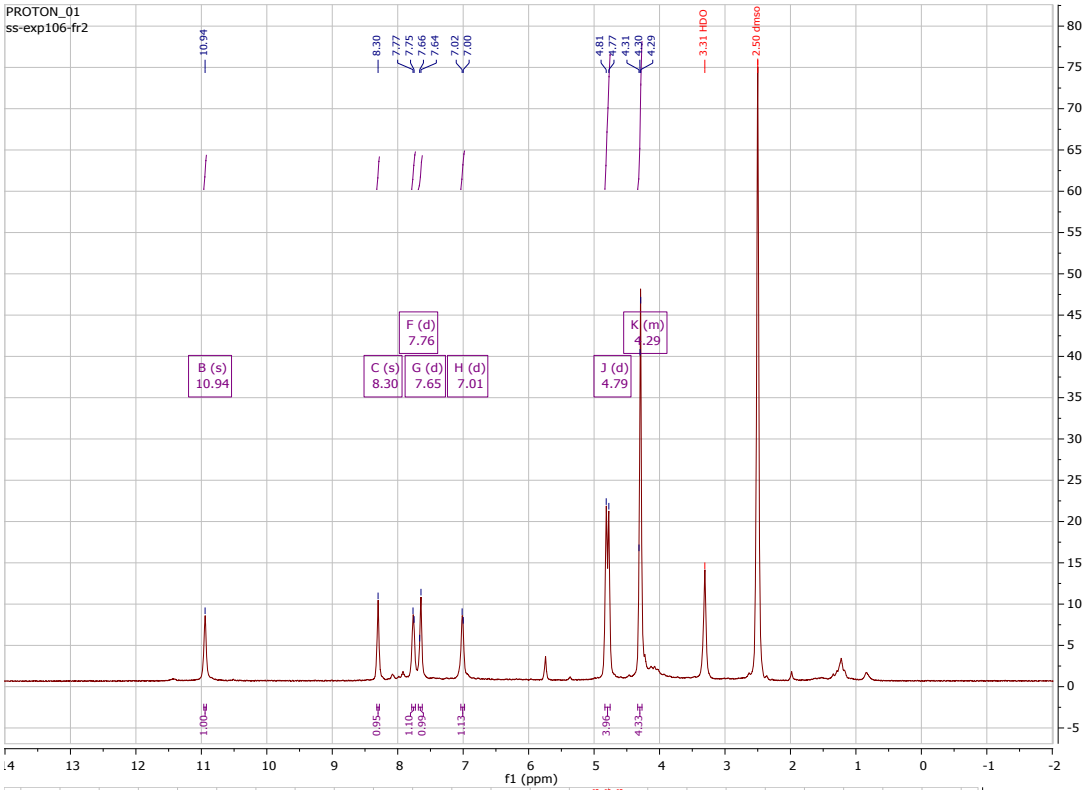

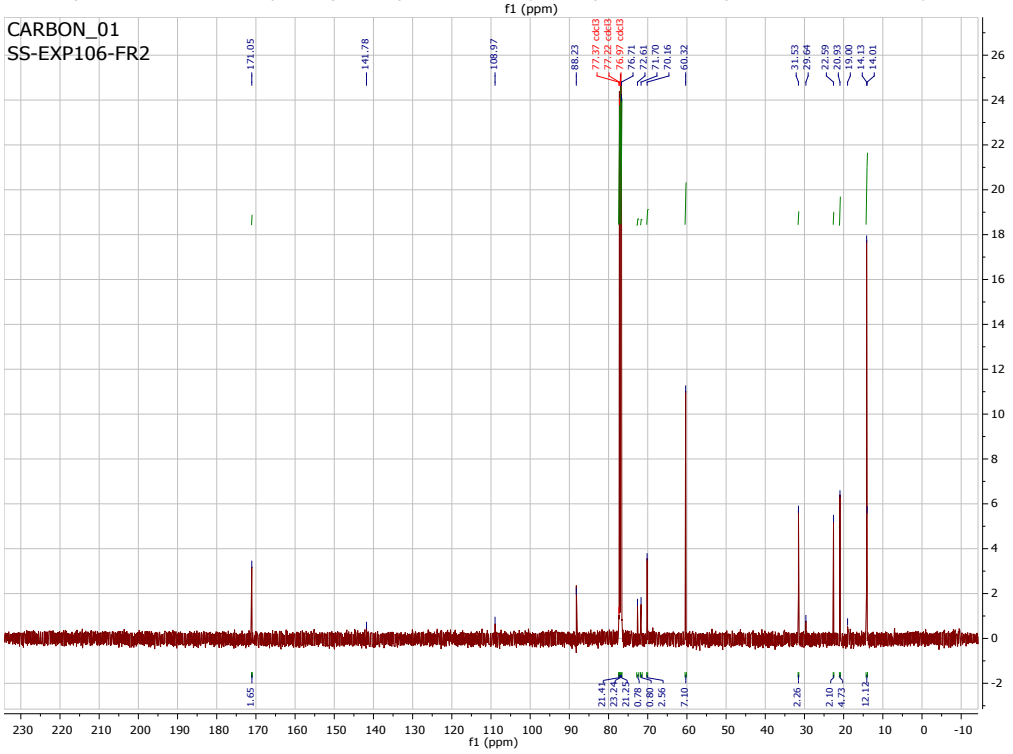

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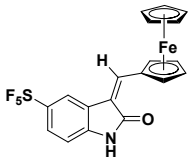

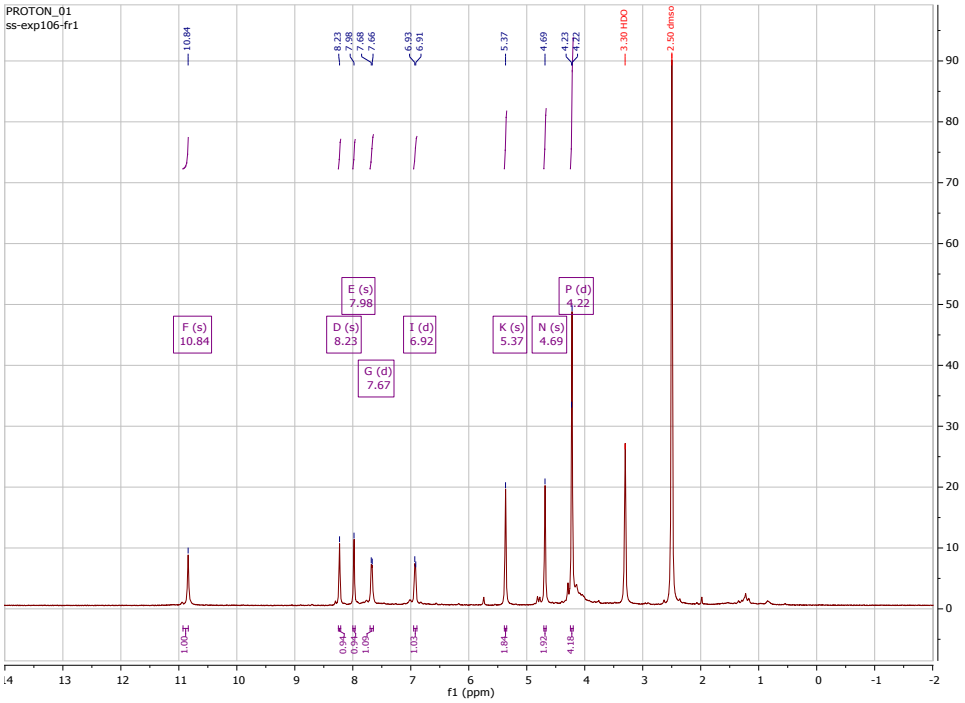

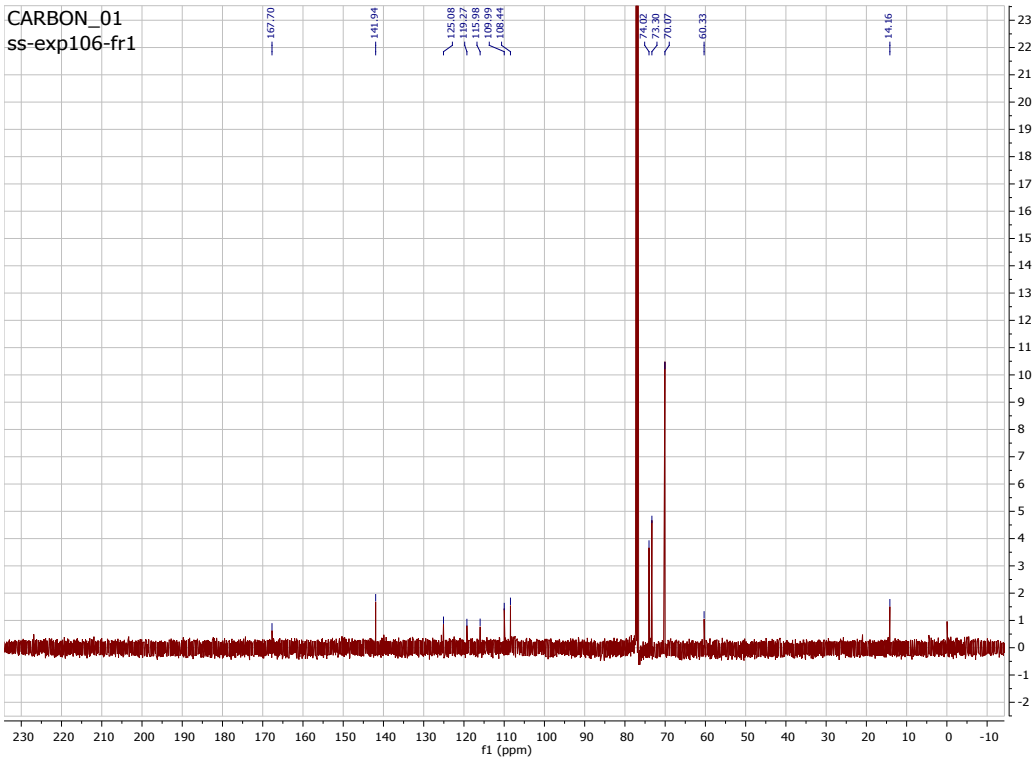

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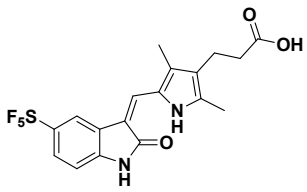

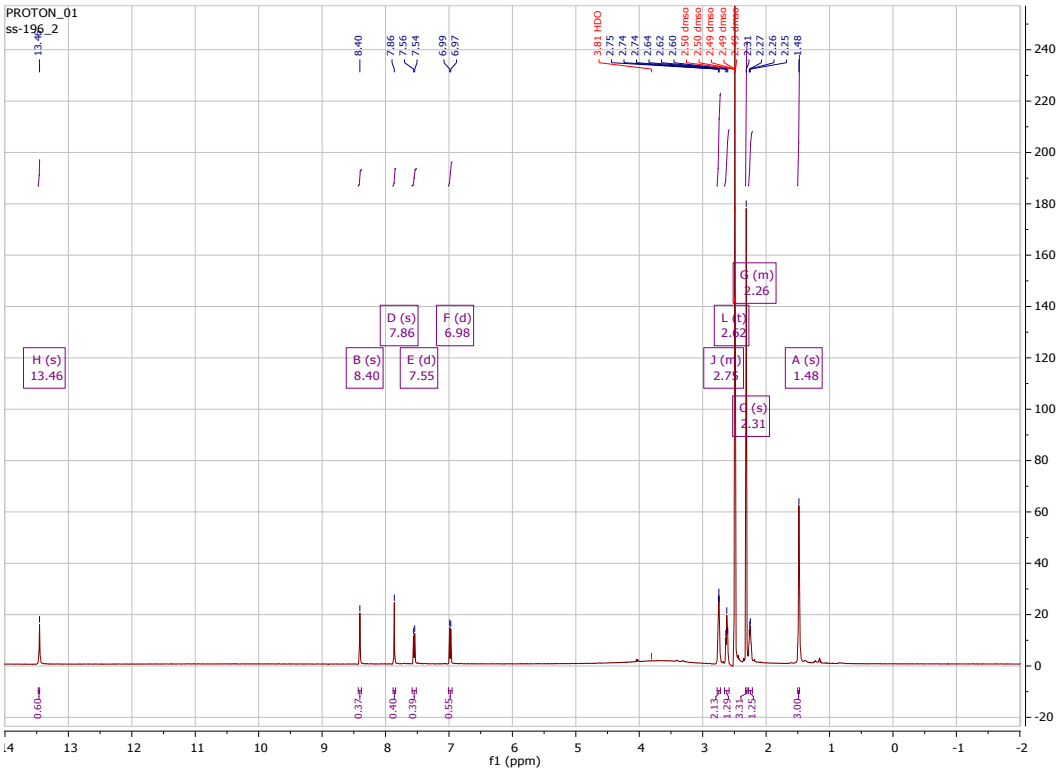

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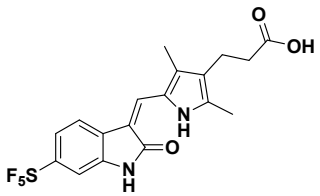
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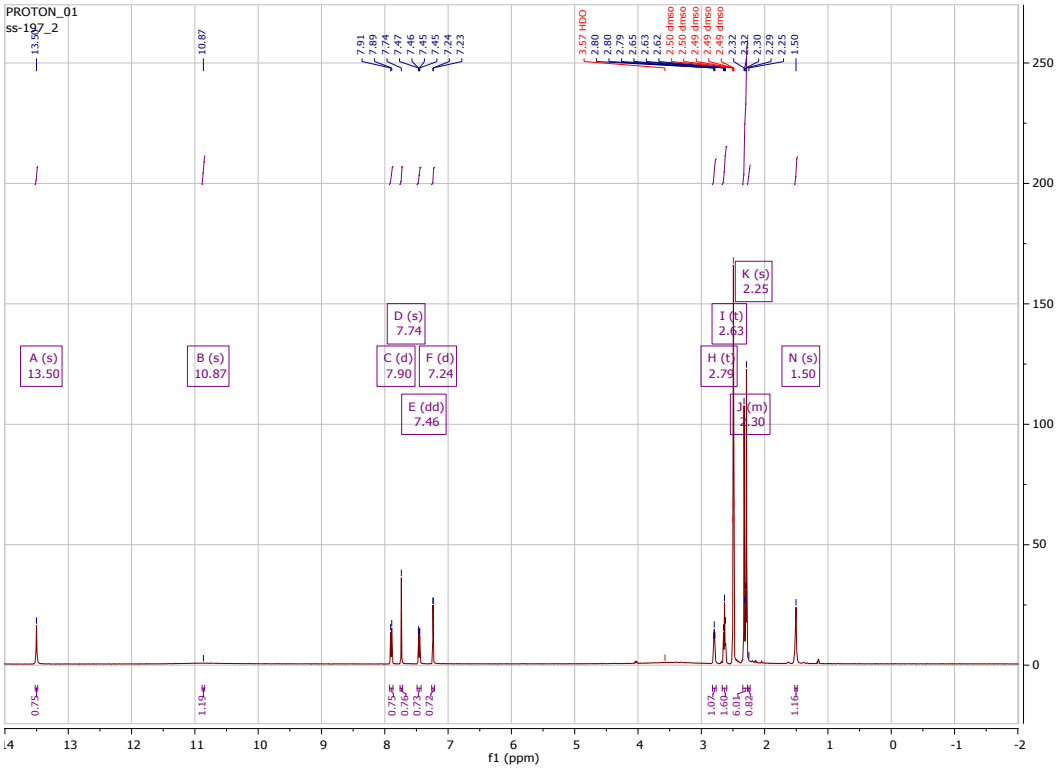
N
H
O
N
H
F5S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B (s)
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C (d)
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D (s)
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E (dd)
7.46
F (d)
7.24
H (t)
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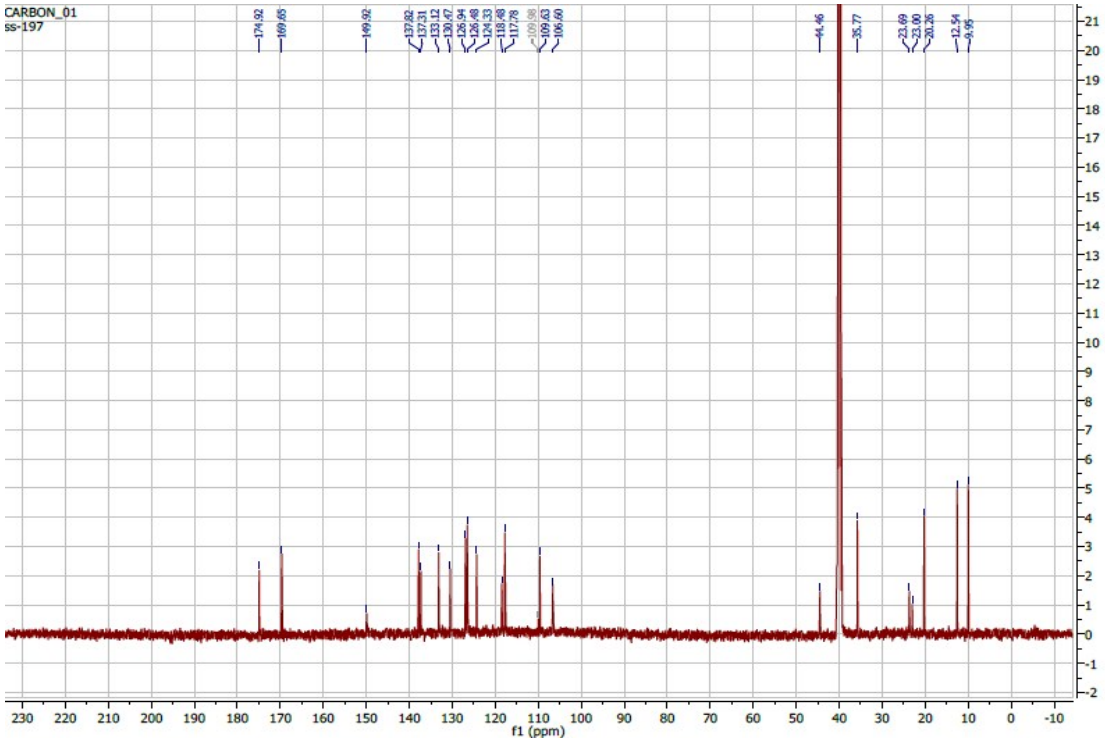
I (t)
2.63
J (m)
2.30
K (s)
2.25
N (s)
1.50
f1 (ppm)


CARBON_01
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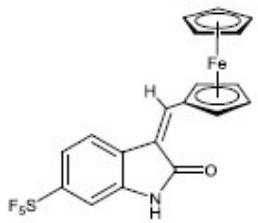
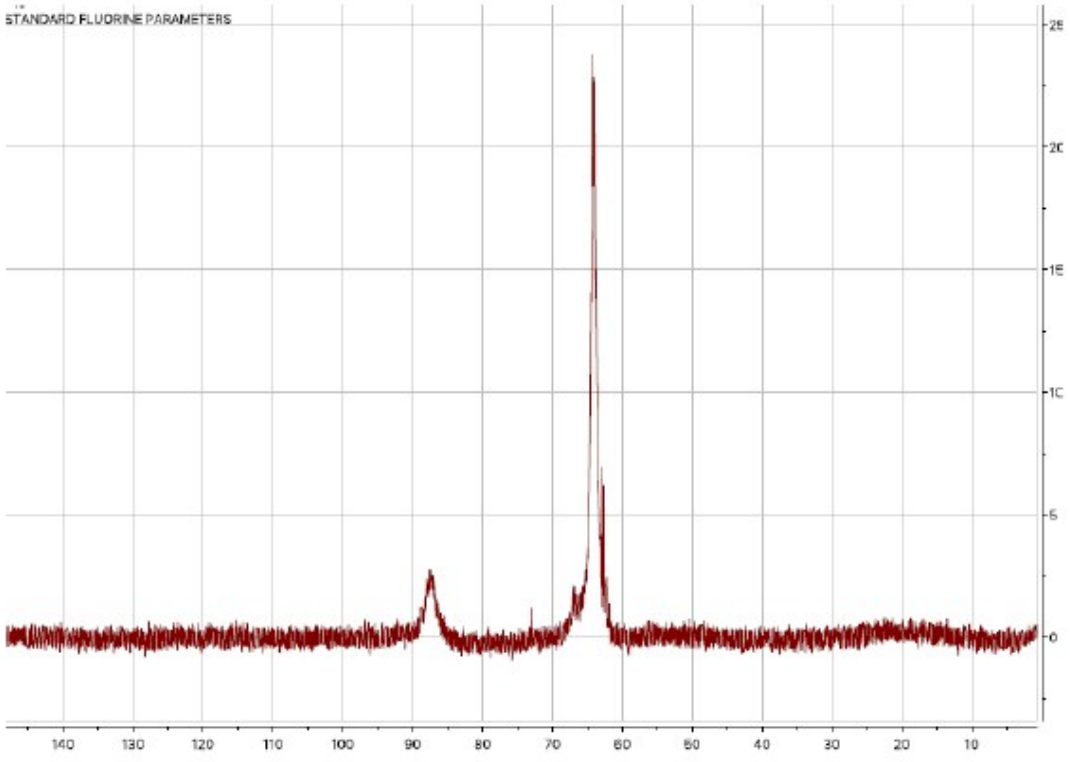
f1 (ppm)


Fe
H
O
N
H
F5S

^{19}F: (broad)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80
70
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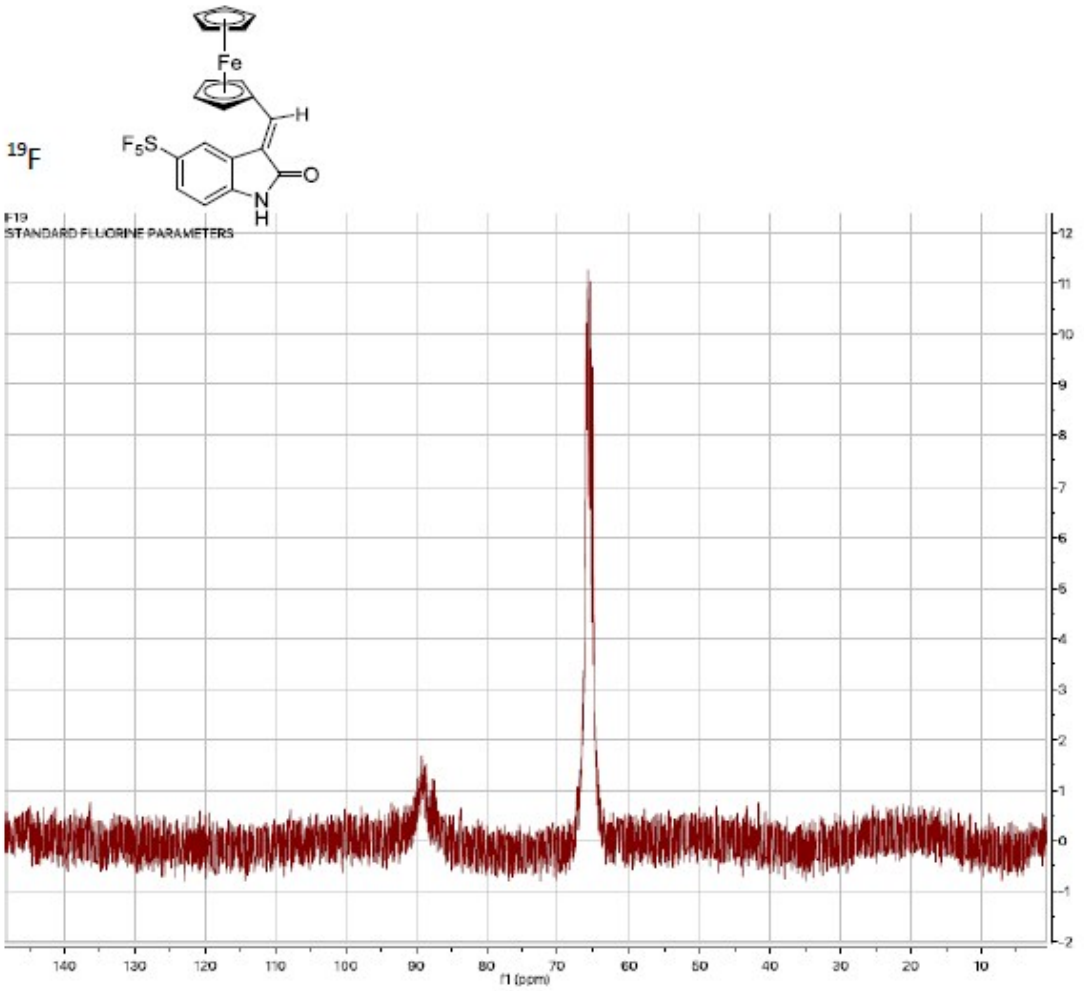
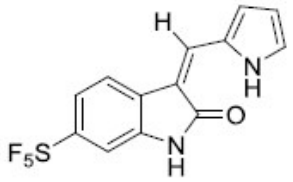
50
40
30
20
10


Fe
H
F5S
O
N
H
19F
F19
STANDARD FLUORINE PARAMETERS
f1 (ppm)

^{19}F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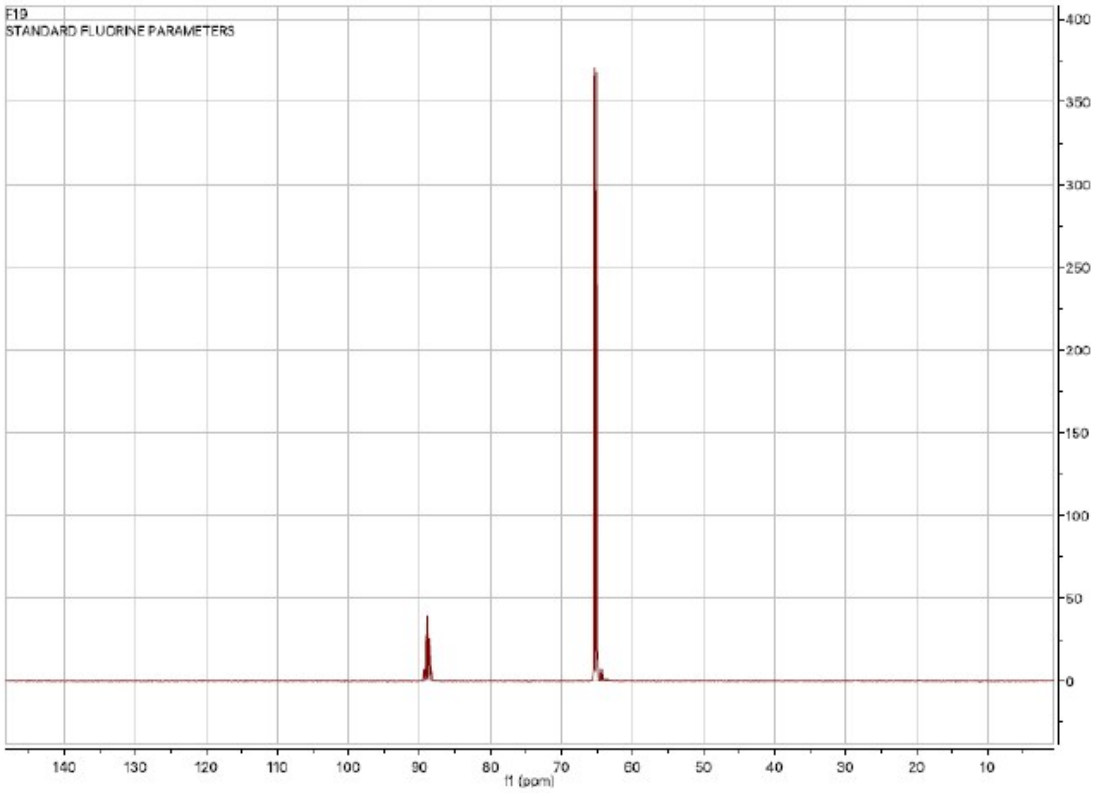
N
H
O
N
H
F5S


F19
STANDARD FLUORINE PARAMETERS
400
350
300
250
200
150
100
50
0
140
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120
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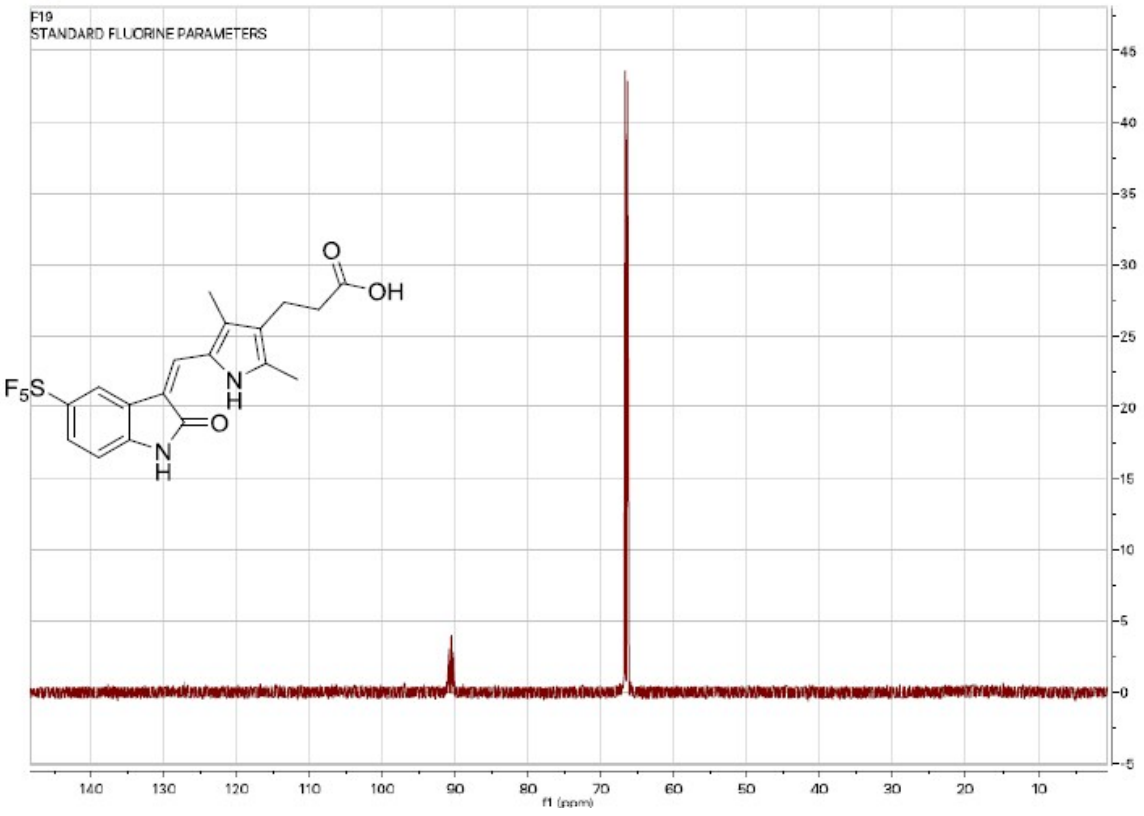
50
40
30
20
10
f1 (ppm)

^{19}F


F19
STANDARD FLUORINE PARAMETERS
O
OH
N
H
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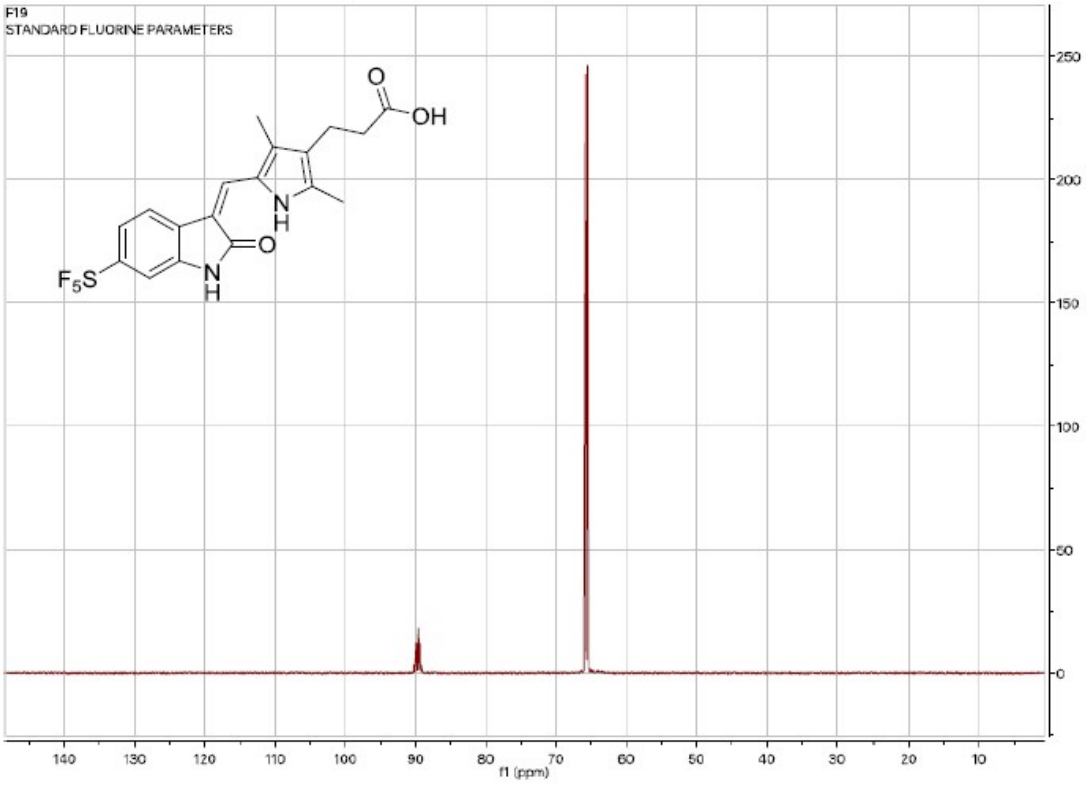
O
N
H
f1 (ppm)

^{19}F


F19
STANDARD FLUORINE PARAMETERS
O
OH
N
H
F5S
O
N
H
f1 (ppm)