Electronic Supplementary Material (ESI) for ChemComm.

Selective Chlorination of Iminosydnones for Fast Release of Amide, Urea and Sulfonamide-Containing Drugs

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I. Materials and equipments

***Reactants and solvents**:*

Unless otherwise noted, all reactions were carried out in oven-dried glassware.
Commercially available chemicals were purchased from from ABCR, Acros Organics, Sigma-Aldrich, Alfa Aesar, Combi-Blocks, Carbolution, Fluorochem, and TCI Europe and used as received unless otherwise stated. The following solvents were dried by distillation over the drying agents indicated in parentheses: THF (Sodium), Dichloromethane (CaH_2). Additional anhydrous solvents were purchased from Acros Organics, SigmaAldrich, Alfa Aesar and stored over molecular sieves under an argon atmosphere.
*t*BuOCl (**5**) was prepared according to the literature[1].

***Purifications**:*

Flash chromatography were performed on silica gel (Merck Kieselgel 60, grading 40-63 µm) or using automate Combiflash® Rf Teledyne ISCO with pre-packed column RediSep® Rf (grading 35-70 µm).

Analysis:

Reactions were monitored by TLC carried out on silica 0,25 mm (60 F254, Merck) using UV light as visualizing agent. For staining, the TLC plates were dipped into a solution basic aqueous permanganate (1 g $KMnO_4$, 6 g K_2CO_3 and 0.1 g KOH in 100 mL H_2O) and developed with a heat gun.

Nuclear Magnetic Resonance (NMR) Spectroscopy: ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) were measured on a Brucker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m).

Electrospray mass spectra were obtained using an ESI-Quadripole autopurify, Waters (pump: 2545, mass: ZQ2000) mass Spectrometer.
LC-MS spectra were recorded on a Waters Acquity UPLC® equipped PDA eλ Detector and SQ Detector 2, mobile phase A: H_2O + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid.
Hight resolution mass spectroscopy of the final compounds were determined using a Xevo® G2-XS QTof.

Infrared spectra (IR) were obtained on a Perkin Elmer UATR TWO FTIR spectrophotometer and are reported as wavelength numbers (cm^{-1}).
Melting points (Mp) were obtained on a BÜCHI Melting Point B-545 and are reported in °C.
Absorbances were measured on a Molecular Device SpectraMax® M5e.

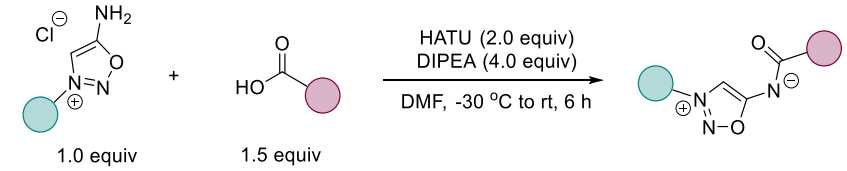
[1] M. J. Mintz and C. Walling, *Org. Synth.* **1969**, *49*, 9.

II. Synthetic Procedure and Analytical Data

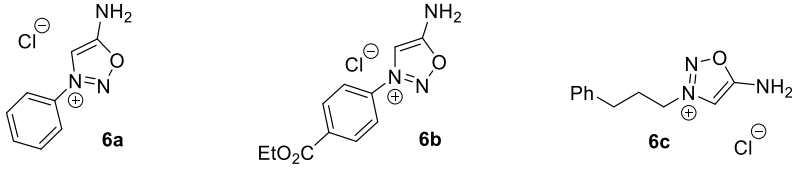
1. Procedure and analytical data of iminosydnone precursors

The synthesis of iminosydnones **6a**, **6b**, **IS6**, **IS7**, **IS8**, **IS9**, **IS10**, **IS14**, **IS16** and **IS17** were previously described by our group and others.[2]

General procedure A : amide coupling of iminosydnones substrates



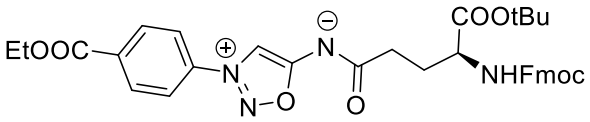
iminosydnone salt involved:



To a solution of iminosydnone salt (1.0 equiv.) in DMF (0.3 M) was added carboxylic acid (1.5 equiv.) followed by HATU (2.0 equiv.). The reaction was stirred at room temperature for 20 min before cooled to -30 °C. DIPEA (4.0 equiv.) was added and the mixture was warmed to room temperature and stirred during 6 hours. A saturated NH_4Cl aqueous solution (15 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). Organic layers were combined, dried over $MgSO_4$ and filtered. Solvents were evaporated under vacuum and the crude was purified by flash chromatography (heptane/ethyl acetate) on silica gel to give the desired product.

[2] For compounds **6a**, **IS7** and **IS16**, see: M. Riomet, E. Decuypere, K. Porte, S. Bernard, L. Plougastel, S. Kolodych, D. Audisio, F. Taran, *Chem. Eur. J.* **2018**, *24*, 8535–8541; for compounds **6b** and **IS17** see: Z. Shao, W. Liu, H. Tao, F. Liu, R. Zeng, P. A. Champagne, Y. Cao, K. N. Houk, Y. Liang, *Chem. Commun.* **2018**, *54*, 14089-14092; for compounds **IS6**, **IS9**, **IS10** and **IS14** see: M. Riomet, K. Porte, L. Madegard, P. Thuéry, D. Audisio, F. Taran, *Org. Lett.* **2020**, *22*, 2403–2408; for compound **IS8**, see: S. Bernard, D. Audisio, M. Riomet, S. Bregant, A. Sallustrau, L. Plougastel, E. Decuypere, S. Gabillet, R. Arun Kumar, J. Elyian, M. Nguyet Trinh, O.Koniev, A. Wagner, S.Kolodych and Frédéric Taran, *Angew. Chem. Int. Ed.* **2017**, *56*, 15612–15616.

IS1
(S)-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoyl)(3-(4-(propionyloxy)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

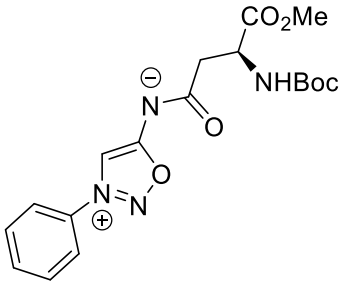


$C_{35}H_{36}N_4O_8$
MW: 640 g.mol^{-1}
Yield: 63%
Yellow foam

The product was obtained following the General Procedure A using iminosydnone **6b** (89.2 mg, 0.33 mmol, 1.0 equiv.), Fmoc-Glu-OtBu (210 mg, 0.50 mmol, 1.5 equiv.), HATU (213 mg, 0.66 mmol, 2.0 equiv.) and DIPEA (170 mg, 1.33 mmol, 4.0 equiv.) to give the desired product in 63% yield (132 mg, 0.21 mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.68 (s, 1H), 8.28 – 8.20 (m, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.63 (dd, *J* = 6.9, 5.1 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.23 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.29 (d, *J* = 7.1 Hz, 2H), 4.19 – 4.12 (m, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.21 (dt, *J* = 12.7, 7.5 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.46 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H).*The free N-H is not visible in the H-NMR.*
^{13}C NMR (100 MHz, MeOD) δ 182.3, 174.9, 173.2, 166.0, 158.6, 145.2 (2C), 142.5, 142.5 (2C), 138.1, 135.9, 132.4 (2C), 128.8 (2C), 128.1 (2C), 126.2 (2C), 123.5 (2C), 120.9 (2C), 82.8, 68.0, 63.0, 55.9, 36.8, 28.6, 28.3 (3C), 28.2, 14.5.
LCMS (ESI) *m/z* $[M+H]^+$ 641.7
IR (neat, cm^{-1}) : 2980, 1712, 1626, 1543, 1478, 1449, 1368, 1346, 1274, 1153.
HRMS (ESI) *m/z* calcd for $C_{35}H_{36}N_4O_8$ $[M+H]^+$: 641,2606 found 641,2612.

IS2
(S)-(3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide



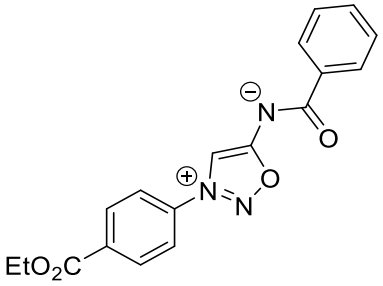
$C_{18}H_{22}N_4O_6$
MW: 390 g.mol^{-1}
Yield: 81%
Yellow solid

The product was obtained following the General Procedure A using iminosydnone **6a** (200 mg, 1.0 mmol, 1.0 equiv.), acid Boc-L-Asp-OMe (375 mg, 1.5 mmol, 1.5 equiv.), HATU (770 mg, 2.0 mmol, 2.0 equiv.) and DIPEA (523 mg, 4.1 mmol, 4.0 equiv.) to give the desired product in 81% yield (320 mg, 0.82 mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.69 (s, 1H), 8.04 – 7.98 (m, 2H), 7.84 – 7.69 (m, 3H), 4.57 (t, *J* = 5.7 Hz, 1H), 3.72 (s, 3H), 2.93 (t, *J* = 6.1 Hz, 2H), 1.44 (s, 9H). *The free N-H is not visible in the H-NMR.*

^{13}C NMR (100 MHz, MeOD) δ 179.4, 174.8, 174.2, 157.8, 135.3, 134.5, 131.6 (2C), 123.4 (2C), 107.2, 80.7, 52.8, 52.2, 42.1, 28.7 (3C).
LCMS (ESI) *m/z* $[M+H]^+$ 391.5.
IR (neat, cm^{-1}) : 2953, 1697, 1623, 1540, 1469, 1359, 1294, 1160, 841, 761, 557.
HRMS (ESI) m/z calcd for $C_{18}H_{22}N_4O_6$ $[M+H]^+$: 391.1612 . found 391.1619.

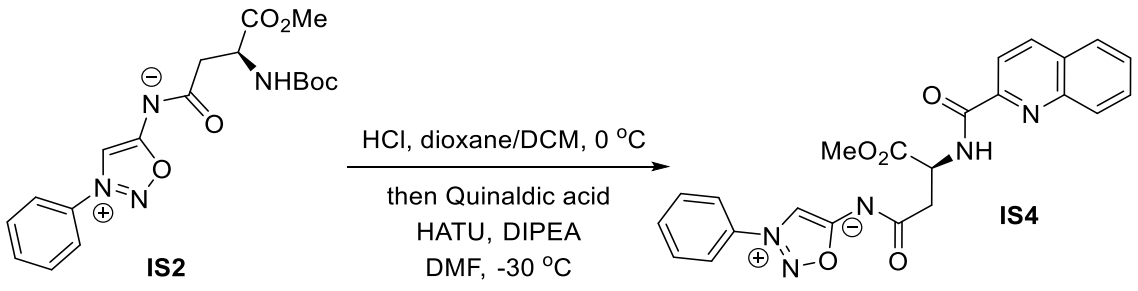
IS3
Benzoyl(3-(4-(ethoxycarbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide



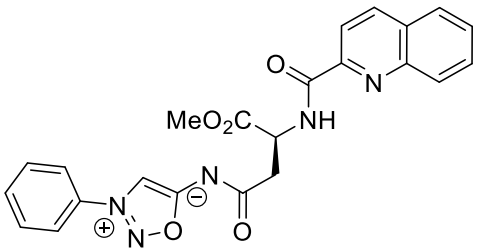
$C_{18}H_{15}N_3O_4$
MW: 337 g.mol^{-1}
Yield: 50%
Yellow solid

The product was obtained following the General Procedure A using iminosydnone **6b** (108 mg, 0.4 mmol, 1.0 equiv.), benzoic acid (73 mg, 0.6 mmol, 1.5 equiv.), HATU (305 mg, 0.8 mmol, 2.0 equiv.) and DIPEA (272 mg, 1.6 mmol, 4.0 equiv.) to give the desired product in 50% yield (68 mg, 0.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.33 – 8.25 (m, 4H), 7.98 – 7.91 (m, 2H), 7.52 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 174.5, 164.5, 136.9, 136.8, 135.0, 131.9 (2C), 131.9, 129.7 (2C), 128.2 (2C), 121.7 (2C), 104.7, 62.2, 14.4.
LCMS (ESI) *m/z* $[M+H]^+$ 338.4.
IR (cm^{-1}) : 3195, 1720, 1631, 1580, 1552, 1439, 1321, 1295, 1275, 1105, 970, 856, 770, 735, 689.
HRMS (ESI) *m/z* calcd for $C_{18}H_{15}N_3O_4$ $[M+H]^+$: 338.1135 ; found: 338.1143.



IS4
(S)-(4-methoxy-4-oxo-3-(quinoline-2-carboxamido)butanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide

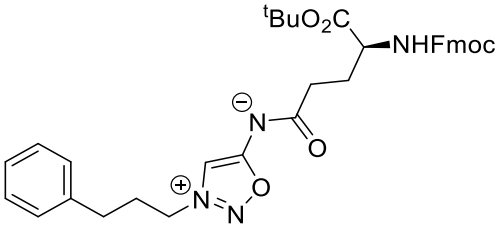


$C_{23}H_{19}N_5O_5$
MW: 445 g.mol^{-1}
Yield: 54%
Yellow solid

To the solution of **IS2** (156 mg, 0.4 mmol, 1 equiv.) in DCM (8 mL) at 0 °C, a solution of HCl (4.0 M, 8 mL) in dioxane was added dropwise. The reaction was stirred at 0 °C for 2 hours before being concentrated under *vacuum*. The residue was then dissolved in DMF (10 mL). Quinaldic acid (104 mg, 0.6 mmol, 1.5 equiv.) was added followed by HATU (258 mg, 0.8 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 20 min before cooled to -30 °C. DIPEA (0.782 mL, 1.6 mmol, 4.0 equiv.) was added and the mixture was warmed to room temperature and stirred during 6 hours. A saturated NH_4Cl aqueous solution (15 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). Organic layers were combined, dried over $MgSO_4$ and filtered. Solvents were evaporated under vacuum and the crude product was purified by flash chromatography (heptane/ethyl acetate) on silica gel to give the desired product **IS4** in 54% yield over two steps (96 mg, 0.22 mmol)**.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 7.4 Hz, 1H), 8.53 (s, 1H), 8.27 (d, *J* = 0.9 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.56 (m, 8H), 5.13 (dt, *J* = 7.4, 5.1 Hz, 1H), 3.67 (s, 3H), 3.27 (ddd, *J* = 56.9, 16.4, 5.1 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 174.3, 172.0, 164.5, 149.8, 146.7, 137.3, 133.8, 133.4, 130.7 (2C), 130.3, 129.9, 129.4, 127.9, 127.7, 121.6 (2C), 118.9, 104.9, 52.8, 51.9, 37.2.
LCMS (ESI) *m/z* $[M+H]^+$ 446.5.
HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_5O_5$ $[M+H]^+$ 446,1459; found: 446,1465.
IR (neat, cm^{-1}) 3381, 3133, 1734, 1674, 1630, 1556, 1498, 1470, 1367, 1316, 1215, 1186.

IS5
(S)-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoyl)(3-(3-phenylpropyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

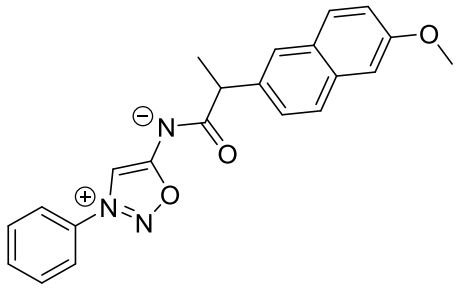


$C_{35}H_{38}N_4O_6$
MW: 610 g.mol^{-1}
Yield: 95%
White solid

The product was obtained following the General Procedure A using iminosydnone **6c** (115 mg, 0.48 mmol, 1.0 equiv.), Fmoc-Glu-O^{t}Bu (306 mg, 0.72 mmol, 1.5 equiv.), HATU (365 mg, 0.96 mmol, 2.0 equiv.) and DIPEA (279 mg, 2.16 mmol, 4.5 equiv.) to give the desired product in 95% yield (278 mg, 0.46 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.27 (m, 4H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 2H), 5.96 (d, *J* = 7.8 Hz, 1H), 4.44 – 4.27 (m, 5H), 4.21 (t, *J* = 7.3 Hz, 1H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.67 – 2.56 (m, 2H), 2.34 (dd, *J* = 14.4, 7.2 Hz, 2H), 2.28 – 2.20 (m, 1H), 2.09 (dt, *J* = 14.3, 7.2 Hz, 1H), 1.48 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 173.8, 171.6, 156.1, 144.0, 141.2 (2C), 138.4, 128.9 (2C), 128.4 (2C), 127.6 (2C), 127.1 (2C), 127.0 (2C), 125.3 (2C), 119.9 (2C), 105.8, 82.0, 67.0, 54.5, 52.7, 47.2, 38.6, 36.0, 32.0, 30.1, 28.0 (3C).
LCMS (ESI) *m/z* $[M+H]^+$ 611.8.
IR (cm^{-1}) : 3295, 2975, 1717, 1626, 1551, 1449, 1400, 1368, 1330, 1247, 1152, 1104, 1081, 1050, 956, 845, 759, 740, 700, 645, 621, 559, 539.
HRMS (ESI) *m/z* calcd for $C_{35}H_{38}N_4O_6$ $[M+H]^+$: 611.2864 ; found: 611.2874.

IS11
(2-(6-methoxynaphthalen-2-yl)propanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide

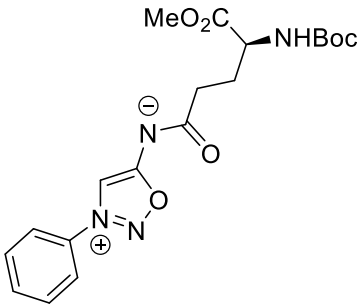


$C_{22}H_{19}N_3O_3$
MW: 373 g.mol^{-1}
Yield: Quant.
Yellow solid

The product was obtained following the General Procedure A using iminosydnone **6a** (50 mg, 0.25 mmol, 1.0 equiv.), DL-naproxen (87 mg, 0.38 mmol, 1.5 equiv.), HATU (184 mg, 0.51 mmol, 2.0 equiv.) and DIPEA (131 mg, 1.0 mmol, 4.0 equiv.) to give the desired product in 99% yield (94 mg, 0.25 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.79 – 7.71 (m, 3H), 7.68 (dd, *J* = 8.1, 5.6 Hz, 3H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.54 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.11 – 7.06 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 1H), 3.88 (s, 3H), 1.63 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 174.2, 157.4, 138.1, 133.9, 133.6, 133.2, 130.7 (2C), 129.4, 129.2, 127.0, 126.9, 126.1, 121.6 (2C), 118.6, 105.7, 104.5, 55.4, 50.1, 19.0.
LCMS (ESI) *m/z* $[M+H]^+$ 374.9.
IR (cm^{-1}) : 2934, 1731, 1605, 1548, 1470, 1391, 1359, 1265, 1230, 1214, 1175, 1081, 1028, 970, 927, 842, 764, 686, 558, 478.
HRMS (ESI) *m/z* calcd for $C_{22}H_{19}N_3O_3$ $[M+H]^+$: 374.1499 ; found: 374.1505.

IS12a
(S)-(4-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide

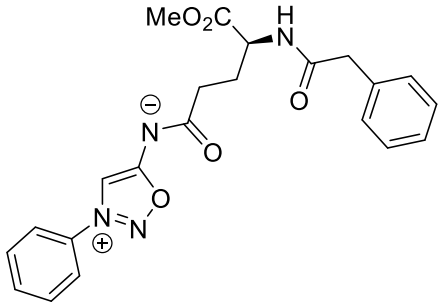


$C_{19}H_{24}N_4O_6$
MW: 404 g.mol^{-1}
Yield: 29%
Yellow solid

IS6a (647 mg, 3.3 mmol, 1.0 equiv.) was dissolved in DMF (65 mL) and Boc-L-glutamic acid a-methyl-ester (1.31 g, 5.0 mmol, 1.5 equiv.) was added followed by HATU (2.35 g, 7.2 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 20 min before cooled to -20 °C. DIPEA (1.70 g, 2.18 mL, 13.2 mmol, 4.0 equiv.) was added and the mixture was warmed to room temperature and stirred for 6 hours. A NH_4Cl solution was added and the mixture was extracted with EtOAc. Organic layers were combined and evaporated to give the crude product, which was purified by chromatographic column to give the desired product as a yellow solid in 29% yield (386.6 mg, 0.96 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.45 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.77 – 7.63 (m, 3H), 5.43 (d, *J* = 8.0 Hz, 1H), 4.36 (dd, *J* = 13.1, 8.0 Hz, 1H), 3.73 (s, 3H), 2.67 – 2.55 (m, 2H), 2.22 (m, 1H), 2.03 (m, 1H), 1.42 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 173.8, 173.4, 155.6, 133.9, 133.4, 130.8 (2C), 121.7 (2C), 104.5, 79.8, 53.5, 52.4, 36.0, 28.5 (3C), 28.4.
LCMS (ESI) *m/z* $[M+H]^+$ 405.4
IR (cm^{-1}) : 2925, 1735, 1698, 1625, 1541, 1470, 1361, 1162, 839, 738, 557.
HRMS (ESI) m/z calcd for $C_{19}H_{24}N_4O_6$ [M+H]+: 405.1774 ; found 405.1776.

IS12
(S)-(5-methoxy-5-oxo-4-(2-phenylacetamido)pentanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide



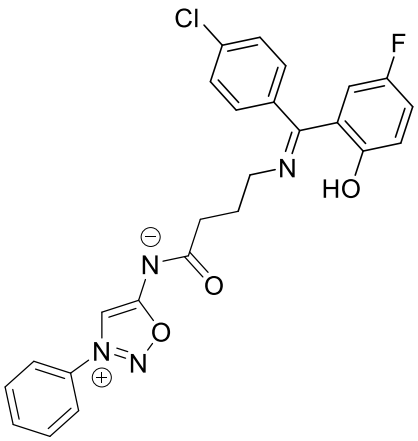
$C_{22}H_{22}N_4O_5$
MW: 422 g.mol^{-1}
Yield: 9%
Yellow solid

To a solution of **IS12a** (333 mg, 0.83 mmol, 1.0 equiv.) in DCM (15 mL) was added HCl (4 M in dioxane, 15 mL) and the mixture was stirred overnight and evaporated. The product was redissolved in THF (5 mL) and a saturated aqueous solution of sodium carbonate (4 mL) was added at 0 °C. Phenyl acetyl chloride (192 mg, 1.24 mmol, 1.5 equiv.) was added slowly and the reaction was stirred for 3 hours until completion. The mixture was evaporated and the residue was dissolved in ethyl acetate and

washed with a saturated aqueous solution of sodium carbonate to give the desired product in 9% yield (31 mg, 0,074 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.84 – 7.78 (m, 2H), 7.77 – 7.65 (m, 3H), 7.28 (d, *J* = 4.4 Hz, 3H), 7.23 – 7.17 (m, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 4.59 (td, *J* = 7.8, 5.0 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 2H), 2.63 – 2.46 (m, 2H), 2.19 (m, 1H), 2.04 (m, 1H). *The free N-H is not visible in the H-NMR.*
^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 173.7, 172.8, 171.1, 135.0, 133.9, 133.4, 130.8 (2C), 129.6 (2C), 128.9 (2C), 127.1, 121.7 (2C), 104.5, 52.6, 52.4, 43.6, 36.0, 27.3.
LCMS (ESI) *m/z* $[M+H]^+$ 423.3

IS13
(E)-(4-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)butanoyl)(3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide

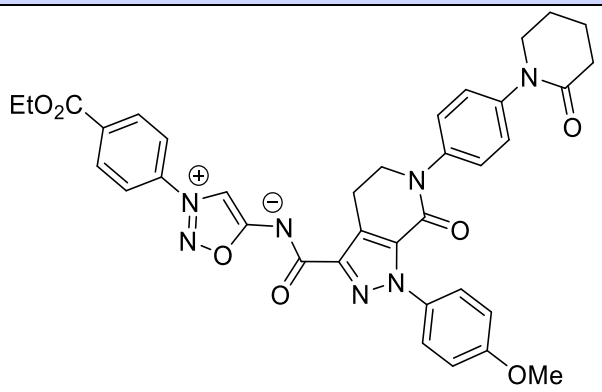


$C_{25}H_{20}ClFN_4O_3$
MW: 478 g.mol^{-1}
Yield: 46%
Yellow solid

The product was obtained following the General Procedure A using iminosydnone **6a** (66 mg, 0.34 mmol, 1.0 equiv.), progabide acid (169 mg, 0.50 mmol, 1.5 equiv.), HATU (216 mg, 0.67 mmol, 2.0 equiv.) and DIPEA (174 mg, 1.35 mmol, 4.0 equiv.) to give the desired product with 46% yield (73 mg, 0.15 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.79 (dd, *J* = 7.3, 1.8 Hz, 2H), 7.77 – 7.64 (m, 3H), 7.50 – 7.44 (m, 2H), 7.22 – 7.15 (m, 2H), 6.93 (td, *J* = 8.5, 2.9 Hz, 1H), 6.85 (dd, *J* = 8.9, 4.8 Hz, 1H), 6.43 (dd, *J* = 9.7, 2.8 Hz, 1H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.10 (p, *J* = 7.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 173.7, 172.2, 159.3, 154.4 (d, $^1J_{C\text{-}F}$ = 235.0 Hz), 135.4, 134.0, 133.3, 131.9, 130.7 (2C), 129.3 (2C), 129.0 (2C), 121.7 (2C), 119.6 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 119.3 (d, $^4J_{C\text{-}F}$ = 5.7 Hz), 118.8 (d, $^3J_{C\text{-}F}$ = 7.2 Hz), 116.5 (d, $^2J_{C\text{-}F}$ = 24.3 Hz), 104.3, 51.8, 38.0, 27.1.
LCMS (ESI) *m/z* $[M+H]^+$ 479.3.
IR (cm^{-1}) : 2941, 1614, 1543, 1490, 1470, 1361, 1256, 1175, 1090, 1016, 844, 765, 684, 558.
HRMS (ESI) *m/z* calcd for $C_{25}H_{20}ClFN_4O_3$ $[M+H]^+$: 479.1281 ; found: 479.1286.

IS15
(3-(4-(ethoxycarbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)(1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonyl)amide



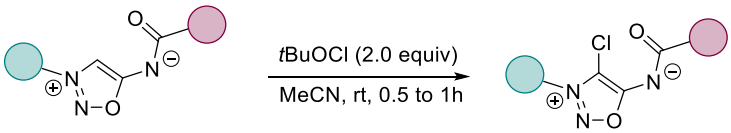
$C_{36}H_{33}N_7O_7$
MW: 675 g.mol^{-1}
Yield: 46%
Yellow solid

The product was obtained following the General Procedure A using iminosydnone **6b** (66 mg, 0.25 mmol, 1.0 equiv.), Apixaban (169 mg, 0.37 mmol, 1.5 equiv.), HATU (186 mg, 0.49 mmol, 2.0 equiv.) and DIPEA (127 mg, 0.98 mmol, 4.0 equiv.) to give the desired product with 46% yield (76 mg, 0.11 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.36 – 8.29 (m, 2H), 7.95 (m, 2H), 7.53 – 7.49 (m, 2H), 7.35 (m, 2H), 7.26 (m, 2H), 6.89 – 6.86 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 3H), 3.57 (t, *J* = 4.8 Hz, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 2.55 (m, 2H), 1.96 – 1.88 (m, 4H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.3, 169.8, 164.5, 159.6, 157.8, 145.1, 141.3, 140.4, 136.7, 135.1, 133.1, 132.9, 131.9 (2C), 127.2 (2C), 126.8 (2C), 126.7, 126.3 (2C), 121.8 (2C), 113.5 (2C), 105.1, 62.2, 55.6, 51.7, 51.3, 32.9, 23.6, 22.3, 21.5, 14.4.
LCMS (ESI) *m/z* $[M+H]^+$ 676.6.

2. Procedure and analytical data for chlorination of iminosydnones

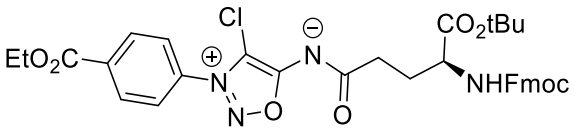
General procedure B: chlorination of iminosydnone substrates



To a solution of iminosydnone (1.0 equiv) in MeCN (0.5 M) was added *t*BuOCl (2.0 equiv). The mixture was stirred at room temperature. The reaction was followed by LCMS. Once the reaction has reached completion (ca. 0.5 to 1 hour), the solvent was evaporated under reduced pressure to give the crude product. The crude product was then purified by chromatographic column on gel to give the desired Cl-imsyd. product (heptane/ethyl acetate). The product of chlorination being not so stable in system, quick work up and purification are essential.

Attention: Safety precautions
*t*BuOCl is known to be unstable when exposed to intense light. To avoid vigorous decomposition, this reagent should be handled only in dim light and should not be heated above its boiling point or be exposed to rubber.

IS1'
(S)-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoyl)(4-chloro-3-(4-(propionyloxy)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

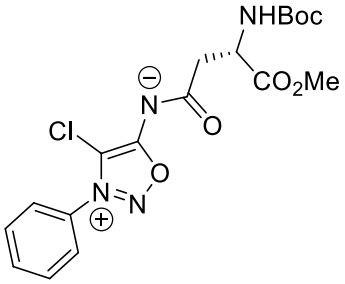


$C_{35}H_{35}ClN_4O_8$
MW: 675 g.mol^{-1}
Yield: 83%
Orange oil

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS1** (35 mg, 55 µmol, 1 equiv.) and *t*BuOCl (6.8 µL, 60 µmol, 1.1 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as an orange oil in 83% yield (30 mg, 44 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.71 (dd, *J* = 22.6, 8.0 Hz, 4H), 7.61 (dd, *J* = 7.3, 3.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.34 – 7.27 (m, 2H), 5.81 (d, *J* = 8.1 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.41 – 4.28 (m, 3H), 4.22 (t, *J* = 7.2 Hz, 1H), 2.77 – 2.57 (m, 2H), 2.29 (dt, *J* = 13.9, 7.2 Hz, 1H), 2.12 (td, *J* = 14.7, 7.9 Hz, 1H), 1.49 (s, 9H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 171.7, 164.5, 163.0, 156.2, 144.1 (2C), 141.4 (2C), 135.1, 134.9, 131.6 (2C), 127.7 (2C), 127.2 (2C), 125.4 (2C), 124.9 (2C), 120.0 (2C), 105.8, 82.1, 67.1, 62.3, 54.6, 47.3, 36.2, 28.2 (3C), 28.1, 14.4.
LCMS (ESI) *m/z* $[M+H]^+$ 675.5.
IR (cm^{-1}) : 2934, 1615, 1470, 1372, 1237, 1155, 1096, 976, 860, 764, 629.
HRMS (ESI) *m/z* calcd for $C_{35}H_{35}ClN_4O_8$ $[M+H]^+$: 675.2216; found: 675.2216.

IS2'
(S)-(3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoyl)(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)amide

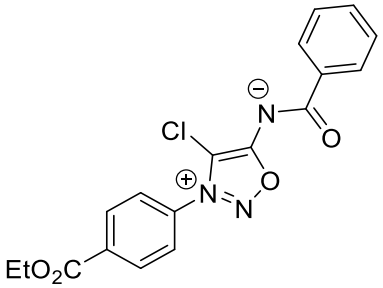


$C_{18}H_{21}ClN_4O_6$
MW: 425 g.mol^{-1}
Yield: 81%
Yellow solid

The product was obtained using general procedure A from the non-chlorinated iminosydnone substrate **IS2** (75 mg, 192 µmol, 1 equiv.) and *t*BuOCl (44.0 µL, 384 µmol, 2 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as yellow solid in 81% yield (66 mg, 156 µmol).

^{1}H NMR (400 MHz, MeOD) δ 7.87 – 7.80 (m, 3H), 7.79 – 7.73 (m, 2H), 4.59 (t, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 3.01 – 2.90 (m, 2H), 1.44 (s, 9H). *The free N-H is not visible in the H-NMR.*
^{13}C NMR (100 MHz, MeOD) δ 179.1, 174.1, 166.0, 157.8, 134.5, 133.3, 131.4 (2C), 126.4 (2C), 109.4, 80.7, 52.8, 52.2, 42.5, 28.7 (3C).
LCMS (ESI) *m/z* $[M+H]^+$ 425.6.
HRMS (ESI) *m/z* calcd for $C_{18}H_{21}ClN_4O_6[M+H]^+$: 425.1222; found: 425.1224.
IR (cm^{-1}) : 3425, 2978,1704,1581, 1495, 1379, 1209, 1162, 1059, 1027, 843, 765, 689, 558.

IS3'
Benzoyl(4-chloro-3-(4-(ethoxycarbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide



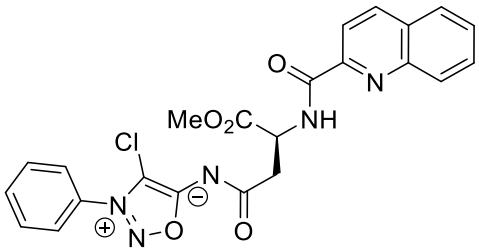
$C_{18}H_{14}ClN_3O_4$
MW: 372 g.mol^{-1}
Yield: 99%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS3** (32.3 mg, 96 µmol, 1 equiv.) and *t*BuOCl (40 µL, 354 µmol, 3.7 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 3/7) to afford the desired product as a yellow solid in 99% yield (35.4 mg, 96 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.35 (m, 2H), 8.33 – 8.28 (m, 2H), 7.83 – 7.75 (m, 2H), 7.54 – 7.42 (m, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 164.5, 164.0, 136.7, 136.6, 135.1, 132.1, 131.7 (2C), 130.0 (2C), 128.2 (2C), 125.0 (2C), 106.3, 62.3, 14.4.
LCMS (ESI) *m/z* $[M+H]^+$ 372.2.

IR (cm^{-1}) : 2930, 1716, 1639, 1438, 1311, 1358, 1278, 1220, 1164, 1107, 1050, 1015, 913, 769, 715.
HRMS (ESI) *m/z* calcd for $C_{18}H_{14}ClN_3O_4$ $[M+H]^+$: 372.0746; found: 372.0789.

IS4'
(S)-(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(4-methoxy-4-oxo-3-(quinoline-2-carboxamido)butanoyl)amide

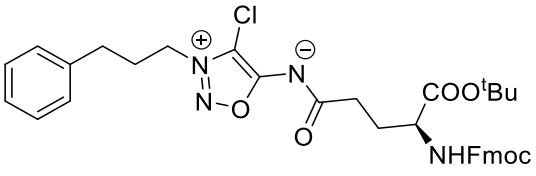


$C_{23}H_{18}ClN_5O_5$
MW: 479 g.mol^{-1}
Yield: 85%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS4** (59.0 mg, 132 µmol, 1 equiv.) and *t*BuOCl (30.0 µL, 265 µmol, 2 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 4/6) to afford the desired product as a yellow solid in 85% yield (53 mg, 112 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 8.9 Hz, 1H), 8.28 (d, *J* = 1.2 Hz, 2H), 8.17 – 8.10 (m, 1H), 7.85 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.76 – 7.61 (m, 6H), 7.58 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 5.21 (dt, *J* = 9.0, 4.5 Hz, 1H), 3.79 (s, 3H), 3.42 (dd, *J* = 17.2, 4.8 Hz, 1H), 3.17 (dd, *J* = 17.2, 4.3 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 172.1, 164.4, 163.6, 149.5, 146.6, 137.3, 133.3, 131.8, 130.4 (2C), 130.1, 129.9, 129.3, 127.9, 127.6, 124.7 (2C), 119.0, 106.2, 52.6, 49.4, 41.8.
LCMS (ESI) *m/z* $[M+H]^+$ 480.7.
IR (cm^{-1}) : 3386, 2924, 1744, 1673, 1583, 1498, 137, 1204, 1061, 845, 769, 698.
HRMS (ESI) *m/z* calcd for $C_{23}H_{18}ClN_5O_5$ $[M+H]^+$: 480.1075; found: 480.1078.

IS5'
(S)-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoyl)(3-(3-phenylpropyl)-1,2,3-oxadiazol-3-ium-5-yl)amide



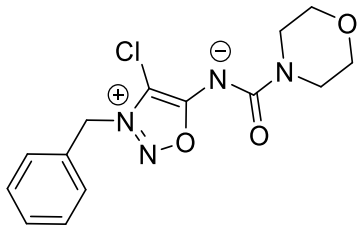
$C_{35}H_{37}ClN_4O_6$
MW: 644 g.mol^{-1}
Yield: 42%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS5** (85 mg, 139 µmol, 1 equiv.) and *t*BuOCl (35 µL, 306 µmol, 2.2 equiv.). The crude product was purified by column chromatography (SiO_2, 100% EtOAc) to afford the desired product as a yellow solid in 42% yield (38 mg, 58 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.65 – 7.56 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (q, *J* = 6.7 Hz, 4H), 7.16 (d, *J* = 7.2 Hz, 2H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.38 (t, *J* = 7.3 Hz, 2H), 4.31 (dd, *J* = 17.6, 7.4 Hz, 2H), 4.21 (t, *J* = 7.2 Hz, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.62 (dd, *J* = 16.4, 7.6 Hz, 2H), 2.38 – 2.29 (m, 2H), 2.28 – 2.20 (m, 1H), 2.10 (dd, *J* = 14.7, 7.6 Hz, 1H), 2.00 – 1.85 (m, 2H), 1.48 (s, 9H).
The product is not stable enough in solvent to afford a ^{13}C NMR spectrum.

LCMS (ESI) *m/z* $[M+H]^+$ 645.8.
IR (cm^{-1}) : 2977, 2929, 1715, 1589, 1450, 1395, 1154, 1044, 842, 744, 557.
HRMS (ESI) *m/z* calcd for $C_{35}H_{37}ClN_4O_6$ $[M+H]^+$: 645.2474; found: 645.2471.

IS6'
(3-benzyl-4-chloro-1,2,3-oxadiazol-3-ium-5-yl)(morpholine-4-carbonyl)amide

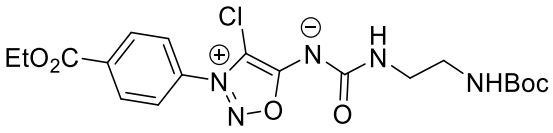


$C_{14}H_{15}ClN_4O_3$
MW: 322 $g.mol^{-1}$
Yield: 65%
White solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS6** (17.5 mg, 61 µmol, 1 equiv.) and *t*BuOCl (27.5 µL, 243 µmol, 4 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/MeOH, 9/1) to afford the desired product as a white solid in 65% yield (12 mg, 40 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 5H), 5.47 – 5.42 (m, 2H), 3.70-3.58 (m, 8H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 158.9, 130.3, 129.9, 129.6 (2C), 128.9 (2C), 102.4, 67.1 (2C), 55.2, 46.1, 43.1.
IR (cm^{-1}) : 2854, 1635, 1454, 1414, 1275, 1236, 1179, 1113, 1026, 852, 713, 517
LCMS (ESI) *m/z* $[M+H]^+$ 324.
HRMS (ESI) *m/z* calcd for $C_{14}H_{15}ClN_4O_3$ $[M+H]^+$: 323.0905; found: 323.0905.

IS7'
((tert-butoxycarbonyl)glycyl)(4-chloro-3-(4-(propionyloxy)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

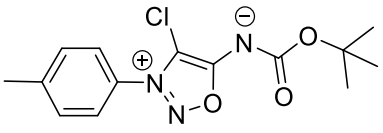


$C_{19}H_{24}ClN_5O_6$
MW: 453 $g.mol^{-1}$
Yield: 80%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS7** (92 mg, 219 µmol, 1 equiv.) and *t*BuOCl (60 µL, 526 µmol, 2.4 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as a yellow solid in 80% yield (82 mg, 175 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 5.60 (s, 1H), 5.01 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.39 – 3.29 (m, 2H), 3.24 (d, *J* = 5.4 Hz, 2H), 1.41 – 1.34 (m, 12H).
The product is not stable enough in solvent to afford a ^{13}C NMR spectrum.
LCMS (ESI) *m/z* $[M+H]^+$ 454.8.
IR (cm^{-1}) : 2934, 1615, 1470, 1372, 1237, 1155, 1096, 976, 860, 764, 629.
HRMS (ESI) *m/z* calcd for $C_{19}H_{24}ClN_5O_6$ $[M+H]^+$: 454.1488 ; found: 454.1493.

IS8'
(tert-butoxycarbonyl)(4-chloro-3-(p-tolyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

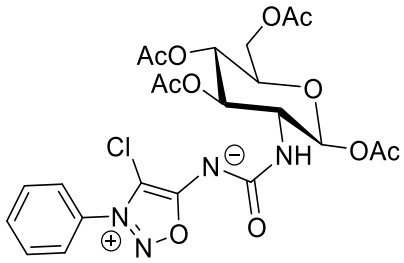


$C_{14}H_{16}ClN_3O_3$
MW: 309 g.mol^{-1}
Yield: 61%
White solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS8** (30.0 mg, 109 µmol, 1 equiv.) and *t*BuOCl (24.7 µL, 218 µmol, 2 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as a white solid in 61% yield (27 mg, 66 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 2.47 (s, 3H), 1.52 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 158.4, 144.0, 130.8 (2C), 126.2, 124.4 (2C), 79.8, 28.2 (3C), 21.5.
The C_4 of the iminosydnone is not visible in C-NMR (too low signal).
IR (cm^{-1}) : 2976, 2927, 1749, 1668, 1621, 1509, 1452, 1366, 1283, 1220, 1146, 1050, 1028, 879, 820, 577, 525.
HRMS (ESI) *m/z* calcd for $C_{14}H_{16}ClN_3O_3$ $[M+H]^+$: 310.0959 ; found: 310.0964.

IS9'
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(((2S,3R,4R,5S,6R)-2,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-3-yl)carbamoyl)amide

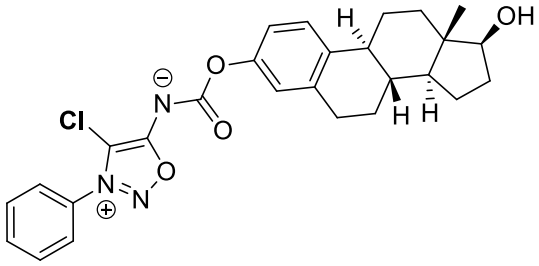


$C_{23}H_{25}ClN_4O_{11}$
MW: 568 g.mol^{-1}
Yield: 88%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS9** (59.0 mg, 110 µmol, 1 equiv.) and *t*BuOCl (30.0 µL, 265 µmol, 2.4 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 2/8) to afford the desired product as a yellow solid in 88% yield (55 mg, 97 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.55 (m, 5H), 5.80 (d, *J* = 8.8 Hz, 1H), 5.45 – 5.24 (m, 2H), 5.12 (t, *J* = 9.6 Hz, 1H), 4.28 (dd, *J* = 12.4, 4.6 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.85 (ddd, *J* = 10.0, 4.5, 2.1 Hz, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.7, 169.5, 169.5, 161.8, 159.1, 133.0, 132.0, 130.3 (2C), 124.7 (2C), 103.5, 92.7, 72.7, 72.6, 68.3, 61.8, 54.0, 21.0, 20.8, 20.7, 20.6.
LCMS (ESI) *m/z* $[M+H]^+$ 569.5.
HRMS (ESI) *m/z* calcd for $C_{23}H_{25}ClN_4O_{11}$ $[M+H]^+$: 569.1281; found: 569.1281.
IR (cm^{-1}) : 2968, 1748, 1645, 1505, 1368, 1222, 1073, 1043, 906, 772, 691.

IS10'
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)((((8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)carbonyl)amide

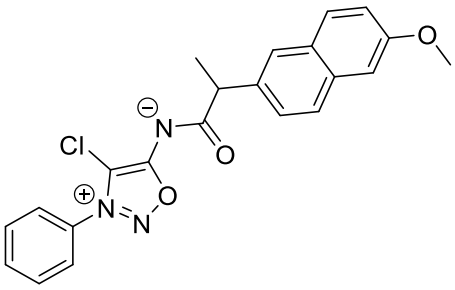


$C_{27}H_{28}ClN_3O_4$
MW: 493 g.mol^{-1}
Yield: 84%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS10** (23.0 mg, 50 µmol, 1 equiv.) and *t*BuOCl (9.0 µL, 80 µmol, 1.6 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as a yellow solid in 84% yield (21 mg, 42 µmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.82 – 7.76 (m, 1H), 7.76 – 7.66 (m, 4H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 3.74 – 3.66 (m, 1H), 2.93 – 2.82 (m, 2H), 2.39 – 2.32 (m, 1H), 2.25 (td, *J* = 11.1, 4.1 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.97 – 1.87 (m, 2H), 1.76 – 1.66 (m, 1H), 1.57 – 1.50 (m, 2H), 1.49 – 1.47 (m, 1H), 1.45 (m, 1H), 1.41 – 1.37 (m, 1H), 1.37 – 1.33 (m, 1H), 1.33 – 1.29 (m, 1H), 1.26 – 1.18 (m, 1H), 0.78 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2) δ 164.9, 158.1, 150.2, 138.7, 138.1, 133.9, 132.4, 131.0 (2C), 126.6, 125.3 (2C), 122.3, 119.4, 106.3, 82.3, 50.7, 44.8, 43.8, 39.2, 37.3, 31.1, 30.2, 27.7, 26.9, 23.7, 11.4.
LCMS (ESI) *m/z* $[M+H]^+$ 495.1.
HRMS (ESI) *m/z* calcd for $C_{27}H_{28}ClN_3O_4[M+H]^+$: 494.1841; found: 494.1841.
IR (cm^{-1}) : 2922, 1682, 1626, 1493, 1378, 1205, 1156, 1067, 767.

IS11'
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(2-(6-methoxynaphthalen-2-yl)propanoyl)amide



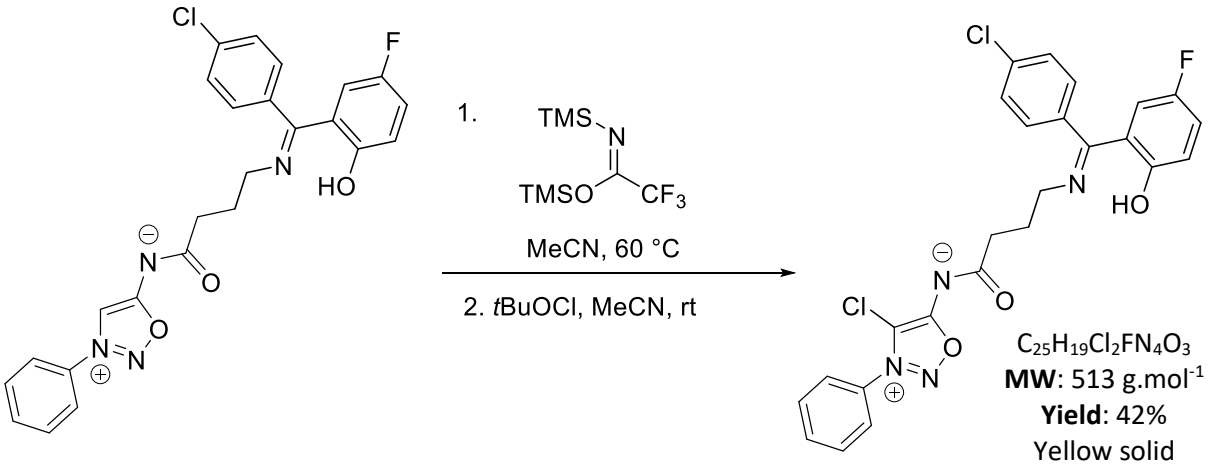
$C_{22}H_{18}ClN_3O_3$
MW: 407 g.mol^{-1}
Yield: 65%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS11** (80.0 mg, 214 µmol, 1 equiv.) and *t*BuOCl (48.5 µL, 428 µmol, 2 equiv.). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 1/1) to afford the desired product as a yellow solid in 65% yield (57 mg, 139 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.80 – 7.68 (m, 5H), 7.65 (t, *J* = 7.4 Hz, 3H), 7.24 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 1H), 4.00 (s, 3H), 1.63 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 173.8, 152.3, 138.8, 133.8, 133.4, 131.0, 130.8 (2C), 129.8, 128.2, 128.0, 126.5, 123.7, 121.7 (2C), 116.8, 113.8, 104.8, 57.1, 49.8, 18.9.

IR (cm^{-1}) : 2924, 1635, 1599, 1545, 1468, 1357, 1274, 1176, 1070, 965, 847, 752, 558
LCMS (ESI) ***m/z*** $[M+H]^+$ 409.0.
HRMS (ESI) ***m/z*** calcd for $C_{22}H_{18}ClN_3O_3$ $[M+H]^+$: 408.1109; found: 408.1109.

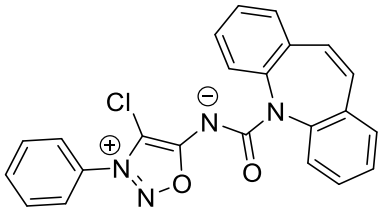
IS13'
(E)-(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(4-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)butanoyl)amide



A solution of substrate **IS13** (60 mg, 0.126 mmol, 1.0 equiv.) in dry MeCN (0.5 mL) was stirred under inert atmosphere. Then trimethylsilyl 2,2,2-trifluoro-*N*-(trimethylsilyl)acetimidate (50 µL, 0.188 mmol, 1.5 equiv.) was added to the reaction dropwise at room temperature. Then the reaction was heated to 60 °C and stirred overnight. After removing the solvent under reduced pressure, the afforded crude product was used in the following step without further purification.
The TMS protected substrate was dissolved in 8 mL MeCN, then *t*BuOCl (29 µL, 0.252 mmol, 2.0 equiv.) was added in one portion. The reaction was stirred at room temperature. The reaction was stopped after 45 mins. The solvent was evaporated under reduced pressure to give the crude product. Then the crude product was treated with HCl dioxane solution (1.0 M, 5.0 equiv) in MeCN for overnight. The reaction was concentrated and purified by column chromatography gave the desired 4-Cl-imSyd in 42% yield (35 mg, 0.053 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (ddd, *J* = 6.2, 3.8, 1.4 Hz, 1H), 7.73 – 7.61 (m, 4H), 7.54 – 7.46 (m, 2H), 7.21 – 7.15 (m, 2H), 6.98 (ddd, *J* = 9.0, 7.9, 3.1 Hz, 1H), 6.90 (dd, *J* = 9.0, 4.8 Hz, 1H), 6.43 (dd, *J* = 9.7, 3.1 Hz, 1H), 3.42 (t, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.10 (p, *J* = 7.1 Hz, 2H). *The free O-H is not visible in the H-NMR.*
The product is not stable enough in solvent to afford a ^{13}C NMR spectrum.
LCMS (ESI) ***m/z*** $[M+H]^+$ 514.6.
HRMS (ESI) ***m/z*** calcd for $C_{25}H_{19}Cl_2FN_4O_3$ $[M+H]^+$: 513.0897; found: 513.0898.

IS12'
(S)-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(tert-butoxy)-5-oxopentanoyl)(4-chloro-3-(4-(propionyloxy)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

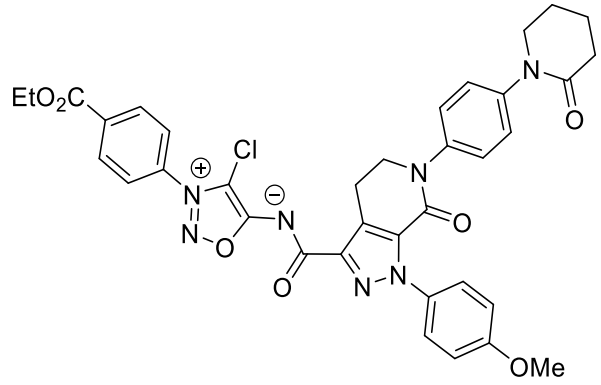


$C_{23}H_{15}ClN_4O_2$
MW: 414 g.mol^{-1}
Yield: 80%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS14** (28.7 mg) and *t*BuOCl (18 µL). The crude product was purified by column chromatography (SiO_2, Hept/EtOAc, 6/4 to 100% EtOAc) to afford the desired product as an orange oil in 80% yield (25 mg, 60 µmol).

^{1}H NMR (400 MHz, MeOD) δ 7.82 – 7.65 (m, 5H), 7.51 – 7.26 (m, 8H), 6.97 (d, *J* = 1.6 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 158.8, 142.1, 141.2, 134.4, 134.2, 132.9 (2C), 132.2, 130.9, 130.3 (2C), 129.7, 129.2, 129.2, 129.0, 128.8, 128.4, 127.0, 126.7, 124.7 (2C), 104.0.
LCMS (ESI) *m/z* $[M+H]^+$ 415.9.
IR (cm^{-1}) : 2934, 1615, 1470, 1372, 1237, 1155, 1096, 976, 860, 764, 629.
HRMS (ESI) *m/z* calcd for $C_{23}H_{15}ClN_4O_2$ $[M+H]^+$: 415.0956; found: 415.0958.

IS14'
(4-chloro-3-(4-(ethoxycarbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)(1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonyl)amide



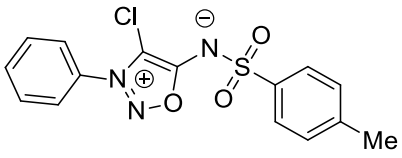
$C_{36}H_{32}ClN_7O_7$
MW: 709 g.mol^{-1}
Yield: 59%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS15** (33.0 mg) and *t*BuOCl (9.0 µL). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as a yellow solid in 59% yield (35 mg, 49 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.33 (m, 2H), 7.81 – 7.75 (m, 2H), 7.54 – 7.49 (m, 2H), 7.38 – 7.34 (m, 2H), 7.25 – 7.23 (m, 2H), 6.91 – 6.88 (m, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.80 (s, 3H), 3.59 (t, *J* = 5.3 Hz, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.55 (t, *J* = 5.5 Hz, 2H), 1.94 – 1.91 (m, 4H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.9, 164.6, 164.5, 159.7, 157.8, 144.8, 141.3, 140.3, 135.2, 134.9, 133.1, 133.0, 131.7 (2C), 127.2 (2C), 127.1, 126.9, 126.8 (2C), 126.3 (2C), 125.0 (2C), 113.6 (2C), 62.3, 55.6, 51.8, 51.3, 33.0, 23.6, 22.2, 21.5, 14.4.
LCMS (ESI) ***m/z*** $[M+H]^+$ 711.3.
IR (cm^{-1}) : 2924, 1602, 1514, 1372, 1279, 1249, 1024, 837.
HRMS (ESI) ***m/z*** calcd for $C_{36}H_{32}ClN_7O_7$ $[M+H]^+$: 710.2125; found: 710.2138.

IS15'
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(tosyl)amide

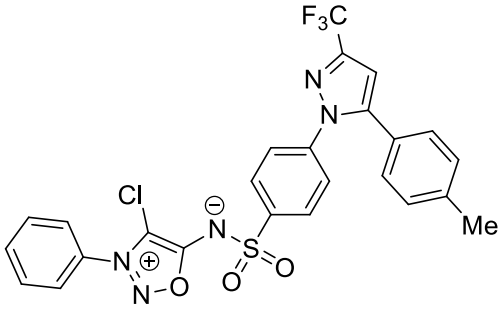


$C_{15}H_{12}ClN_3O_3S$
MW: 349 $g.mol^{-1}$
Yield: 90%
Yellow solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS16** (17.0 mg) and *t*BuOCl (12.0 µL). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 6/4) to afford the desired product as a yellow solid in 90% yield (17 mg, 49 µmol).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.98 – 7.74 (m, 7H), 7.38 (d, *J* = 7.6 Hz, 2H), 2.42 (s, 3H).
^{13}C NMR (100 MHz, Acetone-d_6) δ 161.2, 143.4, 141.4, 134.1, 133.0, 131.2 (2C), 130.1 (2C), 127.8 (2C), 126.4 (2C), 106.8, 21.4.
LCMS (ESI) ***m/z*** $[M+H]^+$ 350.4.
HRMS (ESI) ***m/z*** calcd for $C_{15}H_{12}ClN_3O_3S$ $[M+H]^+$: 350.0361; found: 350.0361.
IR (cm^{-1}) : 3073, 2926, 1614, 1467, 1370, 1301, 1289, 1150, 1091, 1007, 932, 858, 765, 688, 660, 610, 551.

IS16'
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)((4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)sulfonyl)amide

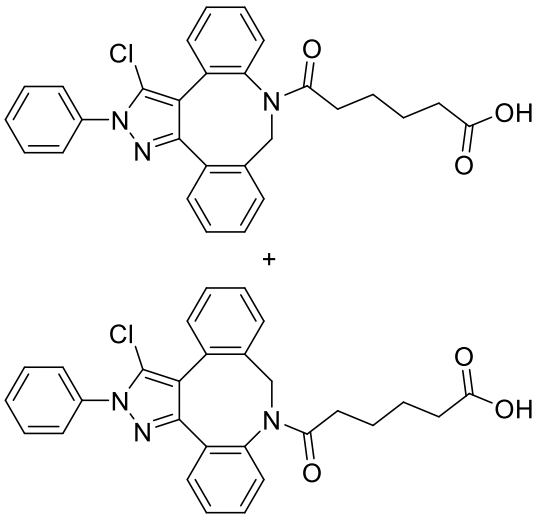


$C_{25}H_{17}ClF_3N_5O_3S$
MW: 559 g.mol^{-1}
Yield: 77%
White solid

The product was obtained using general procedure **B** from the non-chlorinated iminosydnone substrate **IS17** (16.0 mg) and *t*BuOCl (6.5 µL). The crude product was purified by column chromatography (SiO_2, EtOAc/Hept, 3/7) to afford the desired product as an white solid in 77% yield (13 mg, 23 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.80 – 7.76 (m, 1H), 7.70 (t, *J* = 7.7 Hz, 2H), 7.61 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.15 (dd, *J* = 22.4, 8.1 Hz, 4H), 6.74 (s, 1H), 2.38 (s, 3H).
^{13}C NMR (100 MHz, CD_2Cl_2) δ 161.2, 145.9, 144.1 (q, J_{C-F} = 38.1 Hz), 142.9, 142.3, 140.4, 134.1, 132.0, 131.1 (2C), 130.2 (2C), 129.3 (2C), 128.8 (2C), 126.7 (q, J_{C-F} = 227.6 Hz), 126.3, 125.9 (2C), 125.2 (2C), 122.4, 106.5, 21.6.
LCMS (ESI) *m/z* $[M+H]^+$ 561.2.
IR (cm^{-1}) : 2934, 1615, 1470, 1372, 1237, 1155, 1096, 976, 860, 764, 629.
HRMS (ESI) *m/z* calcd for $C_{25}H_{17}ClF_3N_5O_3S$ $[M+H]^+$: 560.0765; found: 560.0759.

Pyrazole
(4-chloro-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)((4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)sulfonyl)amide



$C_{28}H_{24}ClN_3O_3$
MW: 485 g.mol^{-1}
Yield: 52%
Pink sticky solid

IS9' (14.3 mg, 25 µmols, 1 equiv.) was dissolved in DCM (0.5 mL) and DBCO-COOH (9.2 mg, 28 µmols, 1.1 equiv.) was added under stirring at room temperature. The reaction was left under stirring during 2 hours before being concentrated under reduced pressure. The reaction was quantitative according

to NMR analysis of the crude. The crude mixture was then purified by supercritical fluid chromatography to obtain a mixture of two regioisomers of the desired pyrazole product as a purple sticky solid in 52% yield (6.3 mg, 13 µmols).
SFC Conditions: Column TORUS DEA 250x19 mm; 4.6 µm.
Elution system:

Min	CO_2	MeOH
0	95%	5%
1	95%	5%
10	50%	50%

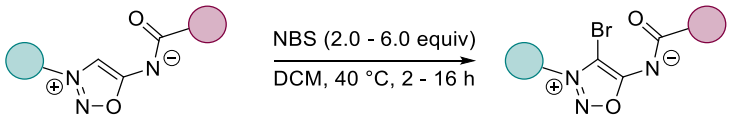
Flow = 70 mL/min.
BPR = 120 bar.

Since the purified product is a mixture of regioisomers, the following characterization report all the peaks for both isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (t, *J* = 8.3 Hz, 2H), 7.52 (dd, *J* = 24.0, 8.4 Hz, 3H), 7.42 (dd, *J* = 15.0, 6.9 Hz, 3H), 7.34 (dd, *J* = 22.1, 5.5 Hz, 1H), 7.26 (s, 1H), 7.20 (dd, *J* = 19.6, 5.3 Hz, 3H), 6.08 (dd, *J* = 75.0, 16.1 Hz, 1H), 4.42 (dd, *J* = 16.0, 6.1 Hz, 1H), 2.19 (s, 2H), 1.90 – 1.63 (m, 2H), 1.46 (s, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 172.5, 151.8, 140.8, 140.4, 138.1, 134.8, 134.7, 133.6, 132.5, 132.2, 131.8, 130.8, 130.4, 130.2, 129.9, 129.7, 129.6, 129.4, 129.1 (2C), 129.1, 128.9, 128.7, 128.6, 128.5, 128.0 (2C), 128.0 (2C), 127.3, 127.2, 125.2 (2C), 125.0 (2C), 124.2, 117.0, 52.5, 52.3, 33.6, 33.5, 30.9, 24.3.
LCMS (ESI) *m/z* $[M+H]^+$ 486.2.
IR (cm^{-1}) : 3062, 2926, 2248, 1657, 1499, 1398, 1356, 908, 761, 727, 693.
HRMS (ESI) *m/z* calcd for $C_{28}H_{24}ClN_3O_3$ $[M+H]^+$: 486.1584; found: 486.1582.

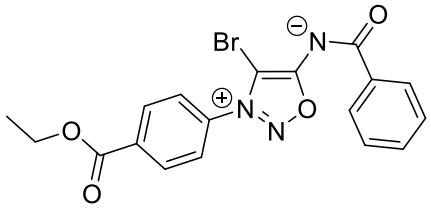
3. Procedure and analytical data for bromination of iminosydnones

General procedure C: Bromination of iminosydnone substrates



To a solution of iminosydnone (1.0 equiv.) in DCM (0.5 M) was added NBS (2.0 – 6.0 equiv.). The mixture was stirred at 40 °C. The reaction was followed by LCMS. Once the reaction has reached completion (ca. 2 to 16 hours), the solvent was evaporated under reduced pressure to give the crude product. The crude product was then purified by chromatographic column to give the desired Br-iminosydnone product (heptane/ethyl acetate).

IS3''
Benzoyl(4-bromo-3-(4-(ethoxycarbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-yl)amide

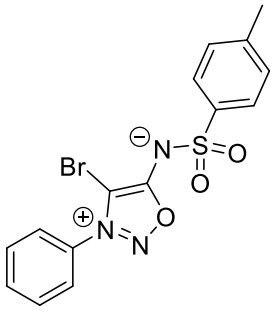


$C_{18}H_{14}BrN_3O_4$
MW: 415 g.mol^{-1}
Yield: 65%
White solid

The product was obtained using general procedure **C** from iminosydnone **IS3** (9 mg) and NBS (28 mg). The crude product was purified by chromatographic column (SiO_2, EtOAc/Hept, 3/7) to afford the desired product as a white solid in 65% yield (7.2 mg, 17 µmols).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 18.6, 8.0 Hz, 4H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.47 (dt, *J* = 27.6, 7.5 Hz, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 165.7, 164.6, 136.8, 136.0, 135.1, 132.0, 131.6 (2C), 130.0 (2C), 128.2 (2C), 125.3 (2C), 92.6, 62.3, 14.4.
LCMS (ESI) *m/z* $[M+H]^+$ 416.
IR (cm^{-1}) : 2928, 1710, 1582, 1346, 1313, 1275, 1215, 1172, 1107, 1014, 866, 770, 715, 672.
HRMS (ESI) *m/z* calcd for $C_{18}H_{14}BrN_3O_4$ $[M+H]^+$: 416.0246; found: 416.0244.

IS15''
(4-bromo-3-phenyl-1,2,3-oxadiazol-3-ium-5-yl)(tosyl)amide

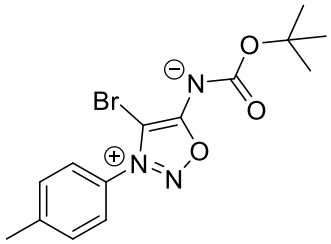


$C_{15}H_{12}BrN_3O_3S$
MW: 393 g.mol^{-1}
Yield: 75%
White solid

The product was obtained using general procedure **C** from iminosydnone **IS15** (50 mg) and NBS (113 mg). The crude product was purified by chromatographic column (SiO_2, EtOAc/Hept, 3/7) to afford the desired product as a white solid in 75% yield (46.9 mg, 119 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H), 7.77 – 7.73 (m, 1H), 7.70 – 7.65 (m, 2H), 7.60 – 7.55 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 143.1, 139.3, 133.5, 132.6, 130.5 (2C), 129.4 (2C), 127.5 (2C), 125.0 (2C), 91.1, 21.7.
LCMS (ESI) *m/z* $[M+H]^+$ 394.
IR (cm^{-1}) : 2926, 1602, 1464, 1361, 1285, 1146, 1088, 1005, 910, 854, 814, 764, 723, 686, 657, 603, 548.
HRMS (ESI) *m/z* calcd for $C_{15}H_{12}BrN_3O_3S$ $[M+H]^+$: 393.9861; found: 393.9858.

IS8''
(4-bromo-3-(p-tolyl)-1,2,3-oxadiazol-3-ium-5-yl)(tert-butoxycarbonyl)amide



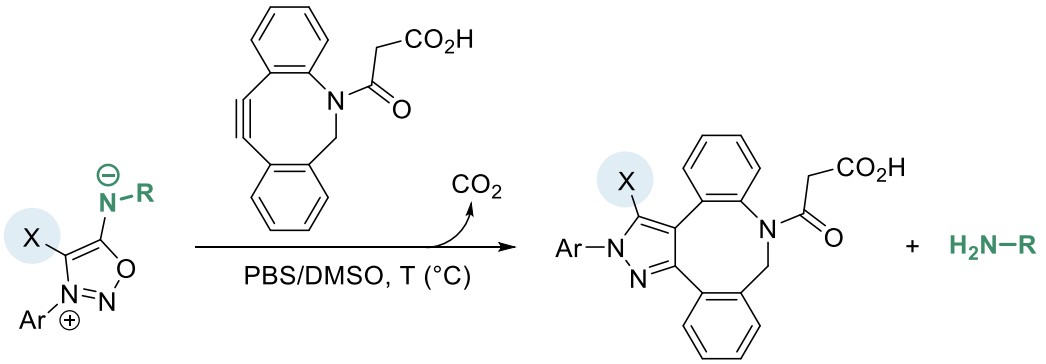
$C_{14}H_{16}BrN_3O_3$
MW: 353 g.mol^{-1}
Yield: 90%
White solid

The product was obtained using general procedure **C** from iminosydnone substrate **IS8** (50 mg) and NBS (64.7 mg). The crude product was purified by chromatographic column (SiO_2, EtOAc/Hept, 3/7) to afford the desired product as a white solid in 90% yield (57.9 mg, 163 µmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 2.50 (s, 3H), 1.55 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 158.6, 144.1, 130.8 (2C), 130.5, 124.8 (2C), 90.7, 79.9, 28.3 (3C), 21.7.
LCMS (ESI) *m/z* $[M+H]^+$ 356.
IR (cm^{-1}) : 2976, 2931, 1614, 1454, 1366, 1288, 1208, 1148, 1052, 823, 735.
HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BrN_3O_3$ $[M+H]^+$: 354.0453; found: 354.0450.

III. Kinetic data for Iminosydnone/Cyclooctyne cycloaddition

Reactions were followed by measuring the decrease of the maximum absorbance signal of iminosydnone at different wavelengths after addition of DBCO-acid.



X = Cl, Br

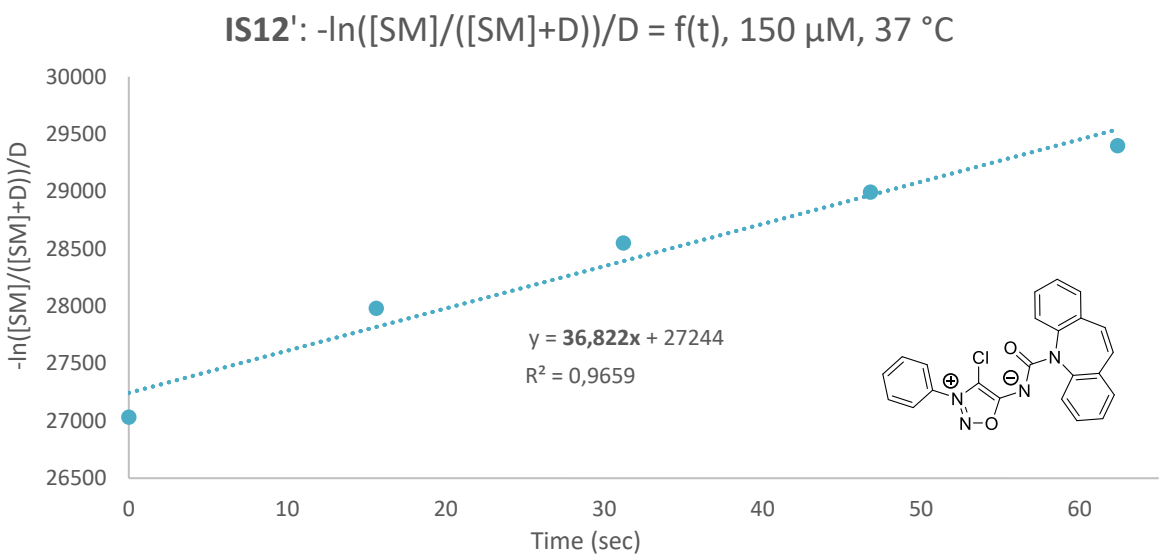
Reactions of iminosydnone pro-drug with DBCO were carried out in PBS/DMSO (8:2) mixtures at 37 °C, under stirring, at 150 µM concentration of iminosydnones and 225 µM concentration of DBCO using the following procedure.

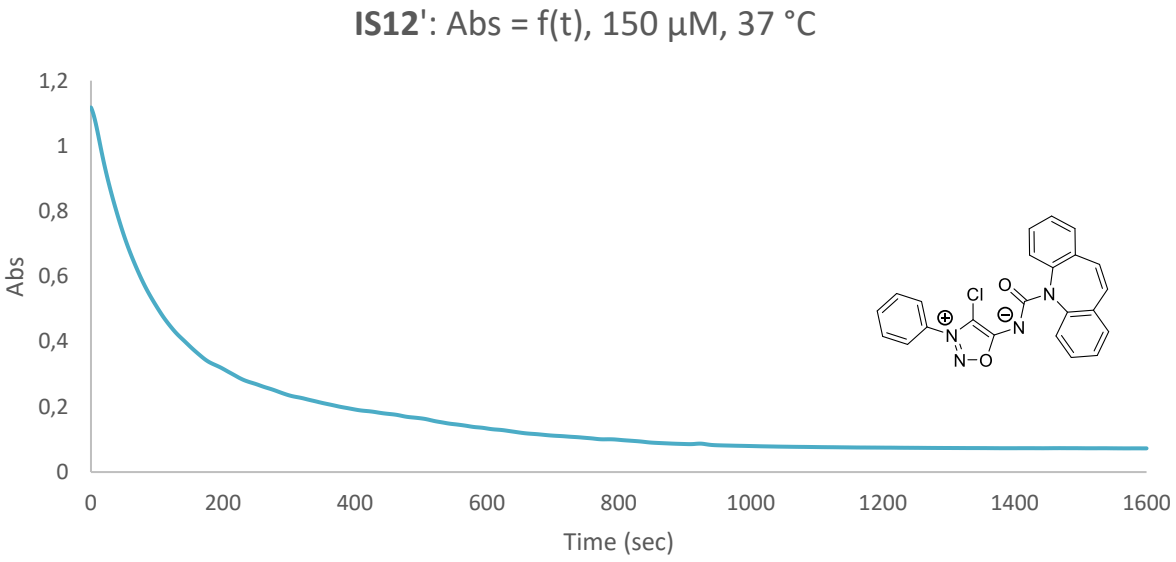
To 1594 µL of phosphate buffered saline (PBS, 10 mM) was added 372 µL of DMSO and 10 µL of the solution of iminosydnone (30 mM in DMSO) . Absorbance spectrum of the solution was measured to identify the λ_{max} of the compound. Kinetic measurement was then started upon addition of 25 µL of DBCO-COOH (18 mM in DMSO).

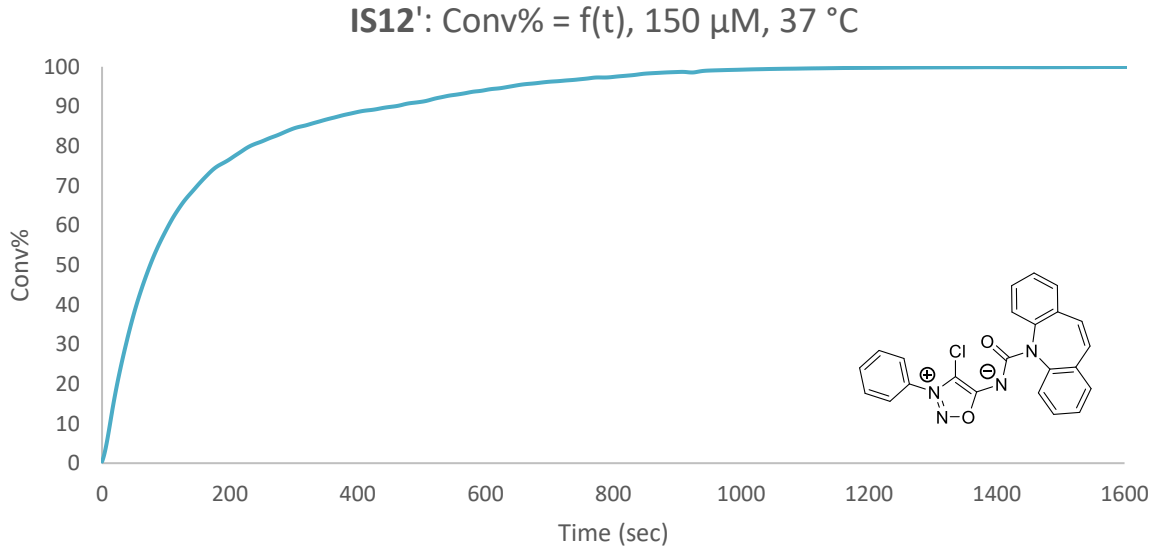
Second order reaction rate was determined by plotting ln([A]/[B])/([A] – [B]) versus time between 0% to 10% of conversion and analyzing by linear regression (**Equation S1**). Second order rate constant corresponds to the determined slope.

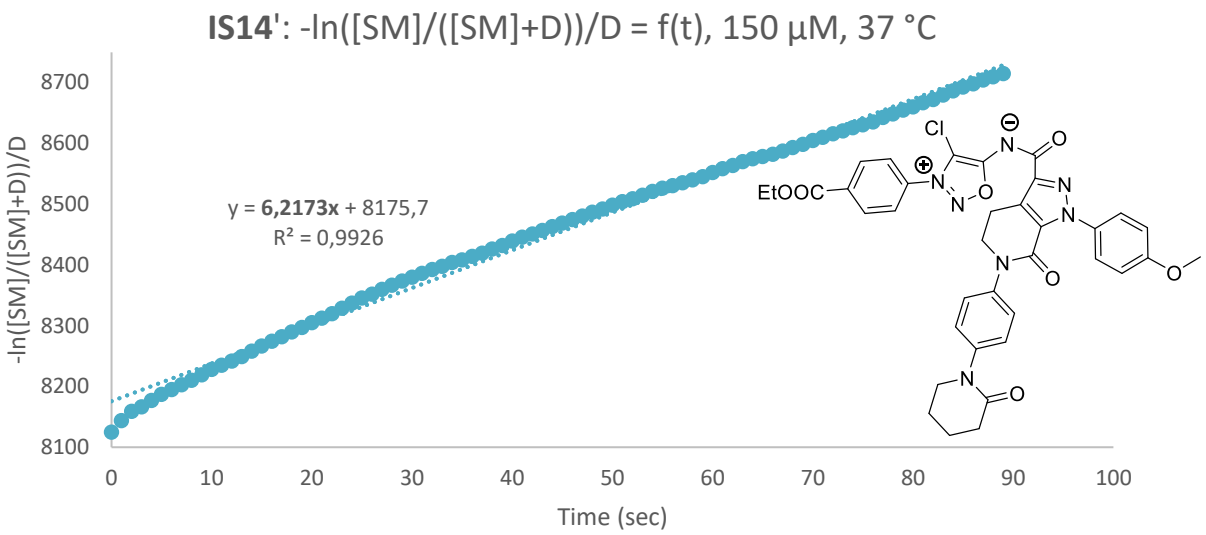
$$\frac{ln(\frac{[A]}{[B]})}{[A]-[B]} = kt + const$$

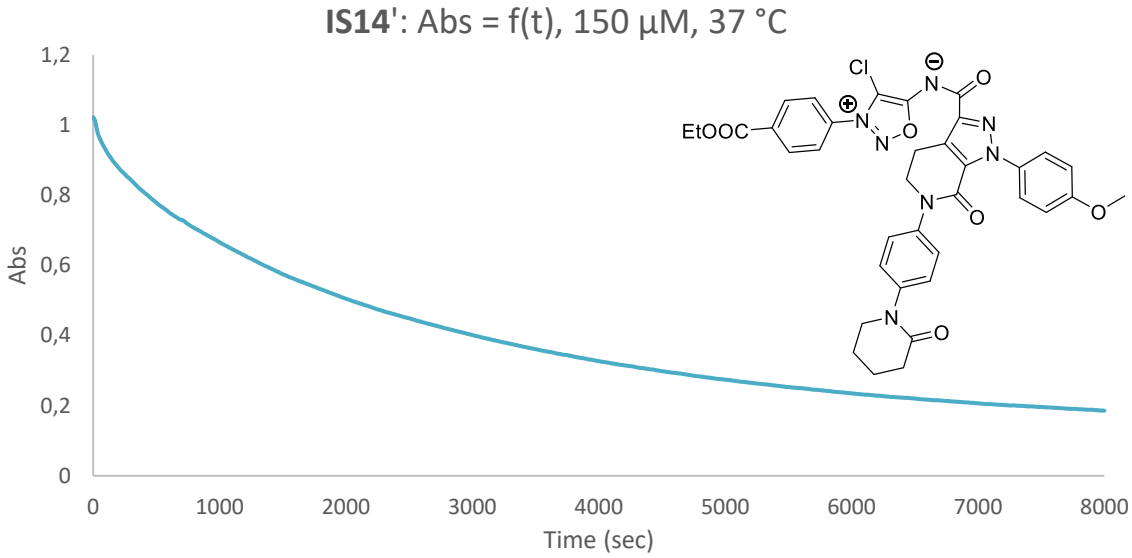
Equation S1. [A] – concentration of iminosydnones (M); [B] – concentration of DBCO (M); t – reaction time (sec); k – reaction rate ($M^{-1}\cdot sec^{-1}$).

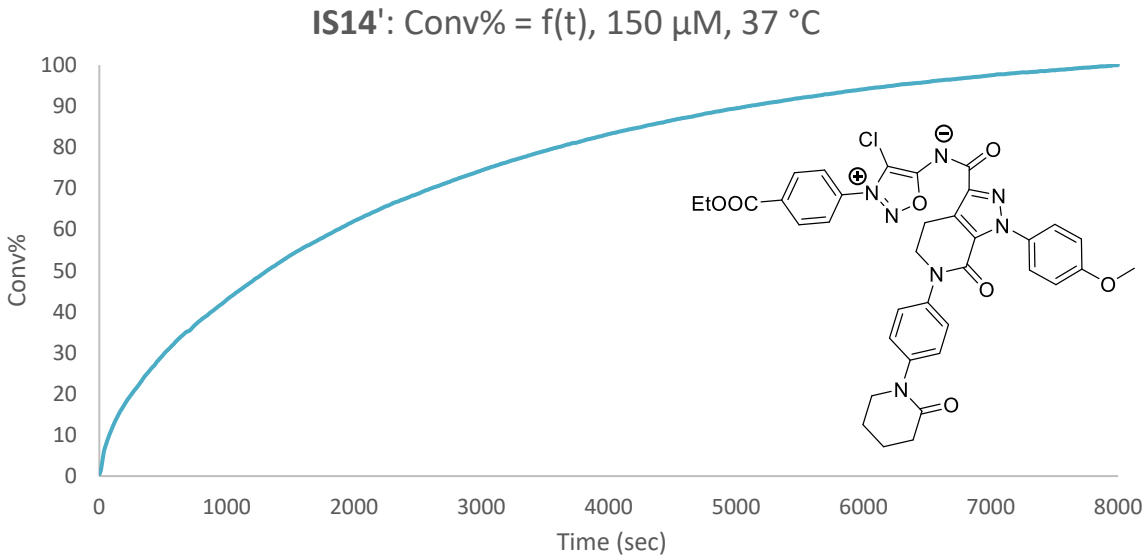

IS12': -ln([SM]/([SM]+D))/D = f(t), 150 µM, 37 °C
-ln([SM]/([SM]+D))/D
30000
29500
29000
28500
28000
27500
27000
26500
0
10
20
30
40
50
60
Time (sec)
y = 36,822x + 27244
R² = 0,9659


IS12': Abs = f(t), 150 µM, 37 °C
Abs
1,2
1
0,8
0,6
0,4
0,2
0
0
200
400
600
800
1000
1200
1400
1600
Time (sec)

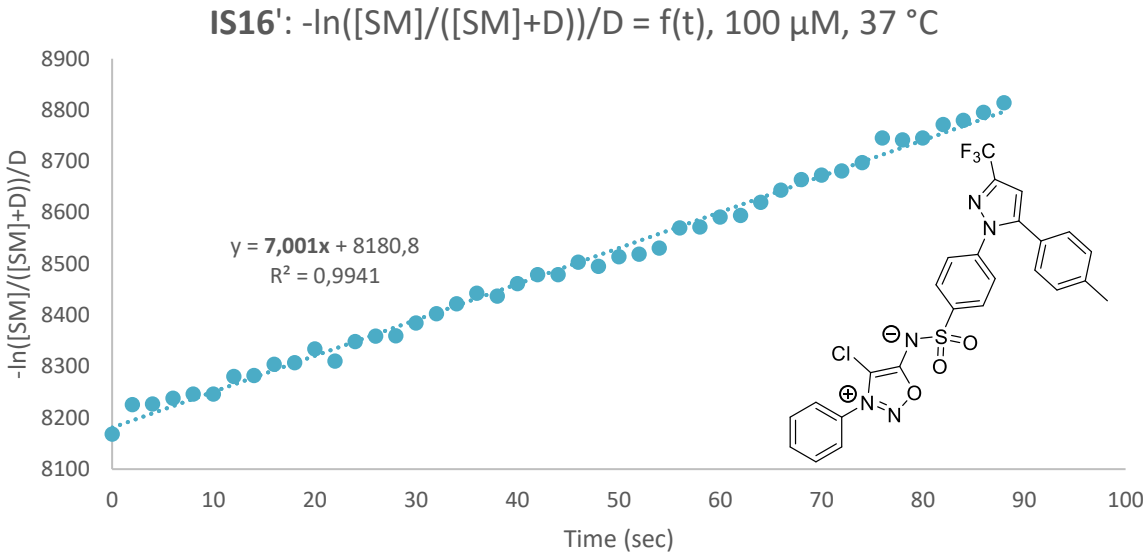

IS12': Conv% = f(t), 150 µM, 37 °C
Conv%
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1000
1200
1400
1600
Time (sec)

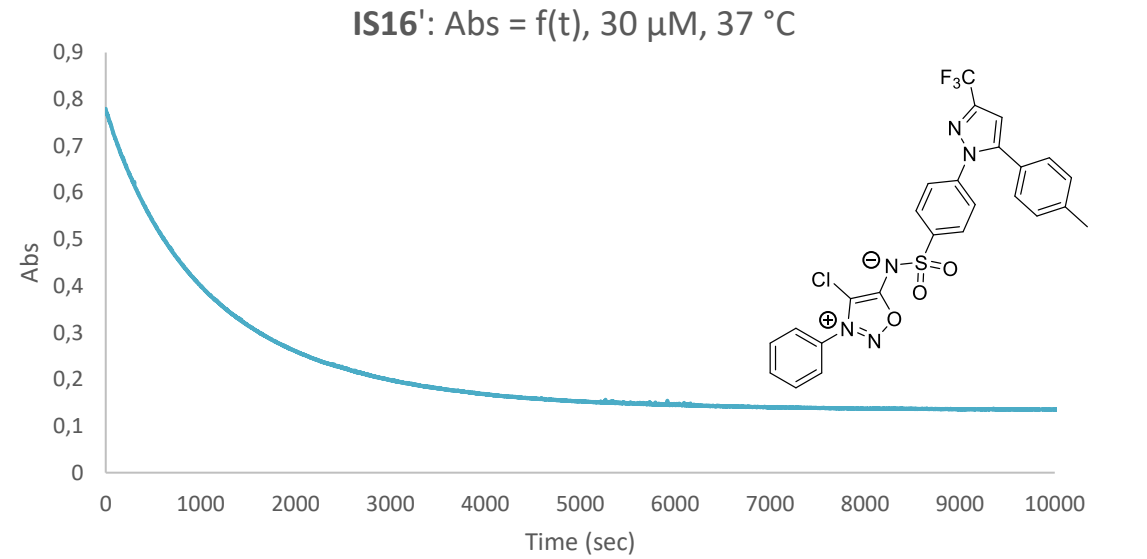

IS14': -ln([SM]/([SM]+D))/D = f(t), 150 µM, 37 °C
-ln([SM]/([SM]+D))/D
y = 6,2173x + 8175,7
R² = 0,9926
Time (sec)

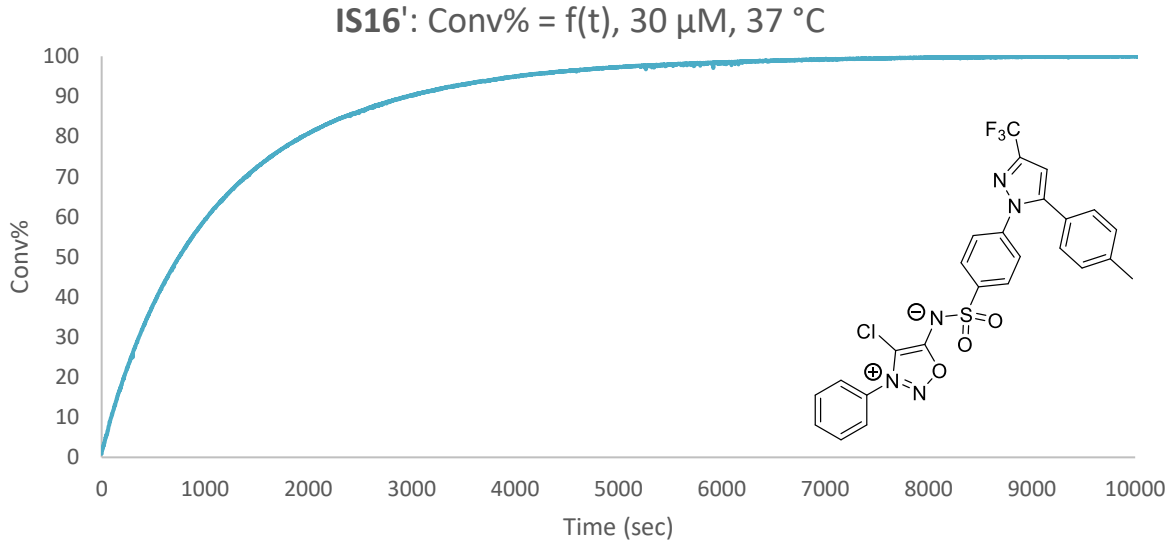

IS14': Abs = f(t), 150 µM, 37 °C
Abs
Time (sec)


IS14': Conv% = f(t), 150 µM, 37 °C
Conv%
Time (sec)

Due to problem of solubility, reaction was carried out at 100 µM of iminosydnone, 150µM of DBCO in PBS/DMSO (5:5) for compound **IS16'**.







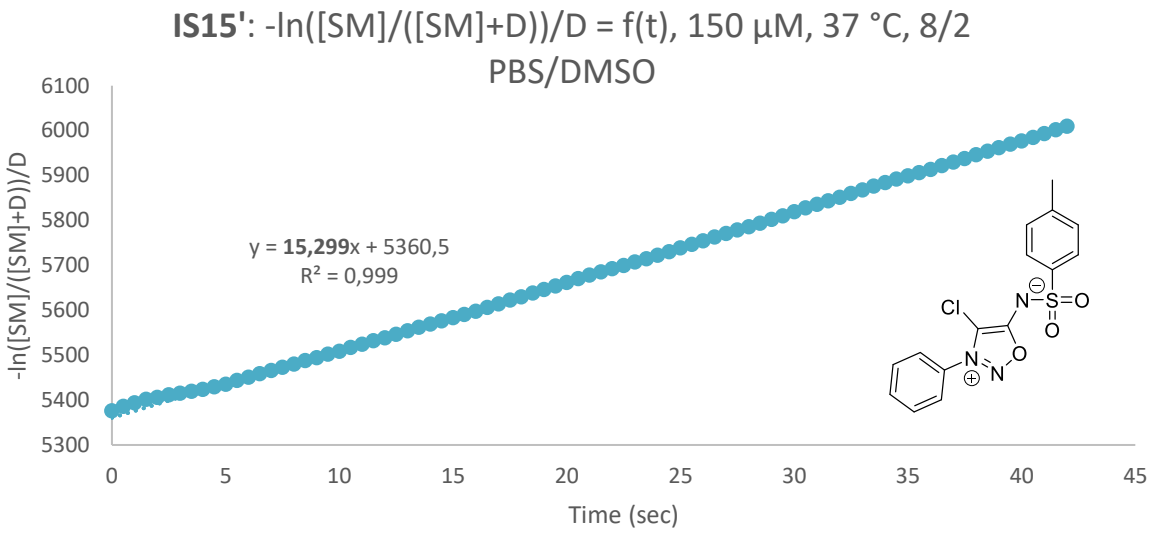
Reactions of iminosydnones with DBCO were either carried out in PBS/DMSO mixtures at physiological pH, under stirring, at 150 µM concentration of iminosydnones and 225 µM concentration of DBCO or at 30 µM concentration of iminosydnones and 45 µM concentration of DBCO using the following procedure.

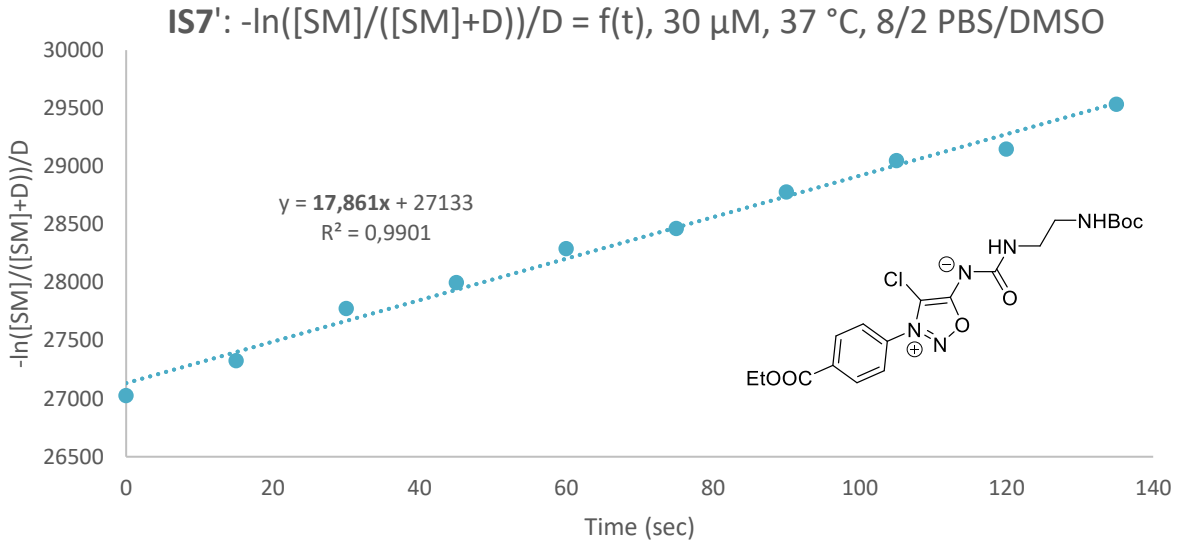
<u>When carried at 150 µM of iminosydnones</u> :

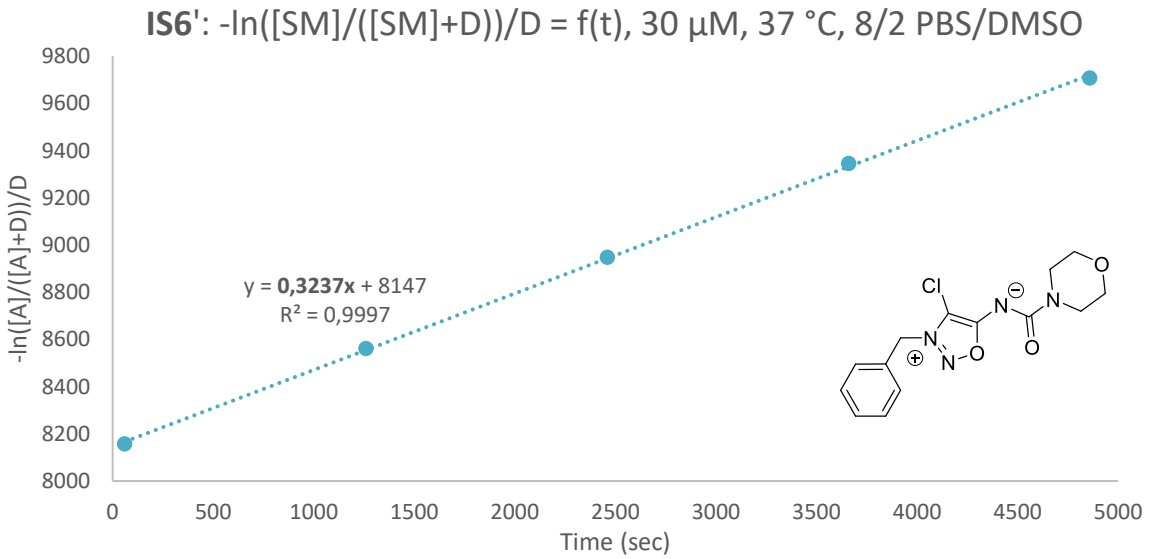
- For 8/2 PBS/DMSO : To 1594 µL of phosphate buffered saline (PBS, 10 mM) was added 372 µL of DMSO and 10 µL of the solution of iminosydnone (30 mM in DMSO) . Absorbance spectrum of the solution was measured to identify the λ_{max} of the compound. Kinetic measurement was then started upon addition of 25 µL of DBCO-COOH (18 mM in DMSO).
- For 5/5 PBS/DMSO : To 1000µL of phosphate buffered saline (PBS, 10 mM) was added 965 µL of DMSO and 10 µL of the solution of iminosydnone (30 mM in DMSO) . Absorbance spectrum of the solution was measured to identify the λ_{max} of the compound. Kinetic measurement was then started upon addition of 25 µL of DBCO-COOH (18 mM in DMSO).

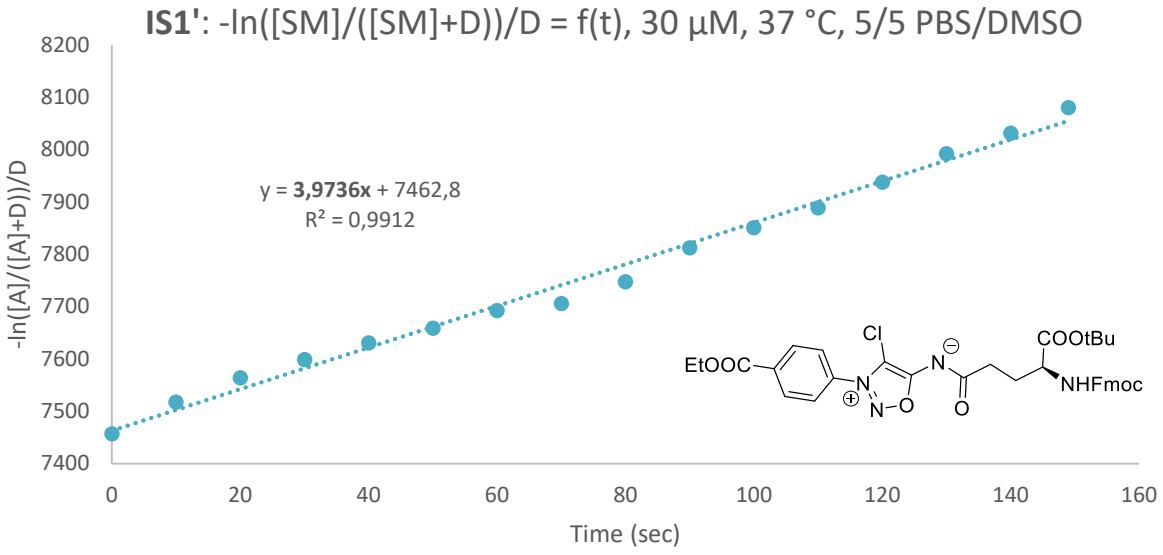
<u>When carried at 30 µM of iminosydnones</u> :

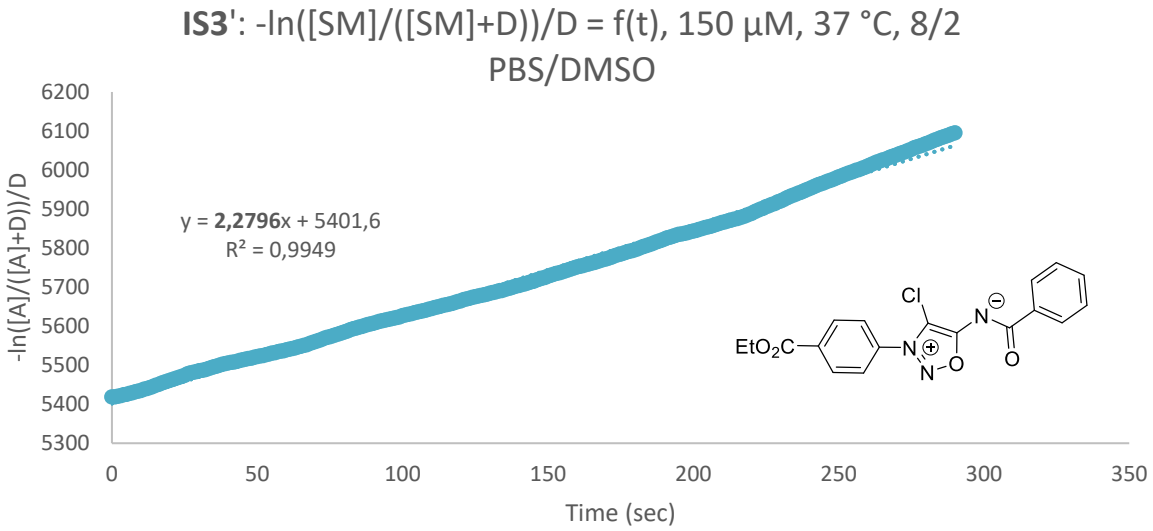
To 797 µL of phosphate buffered saline (PBS, 10 mM) was added 199 µL of DMSO and 3 µL of the solution of iminosydnone (10 mM in DMSO). Absorbance spectrum of the solution was measured to identify the λ_{max} of the compound. Kinetic measurement was then started upon addition of 1 µL of DBCO-COOH (45 mM in DMSO).

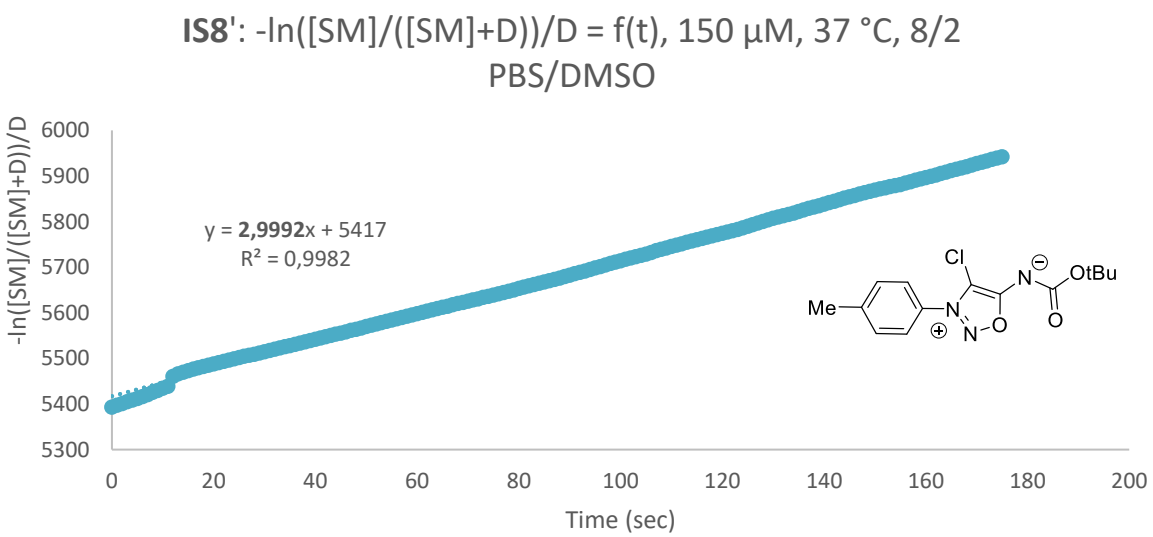

IS15': -ln([SM]/([SM]+D))/D = f(t), 150 µM, 37 °C, 8/2 PBS/DMSO
-ln([SM]/([SM]+D))/D
y = 15,299x + 5360,5
R² = 0,999
Time (sec)

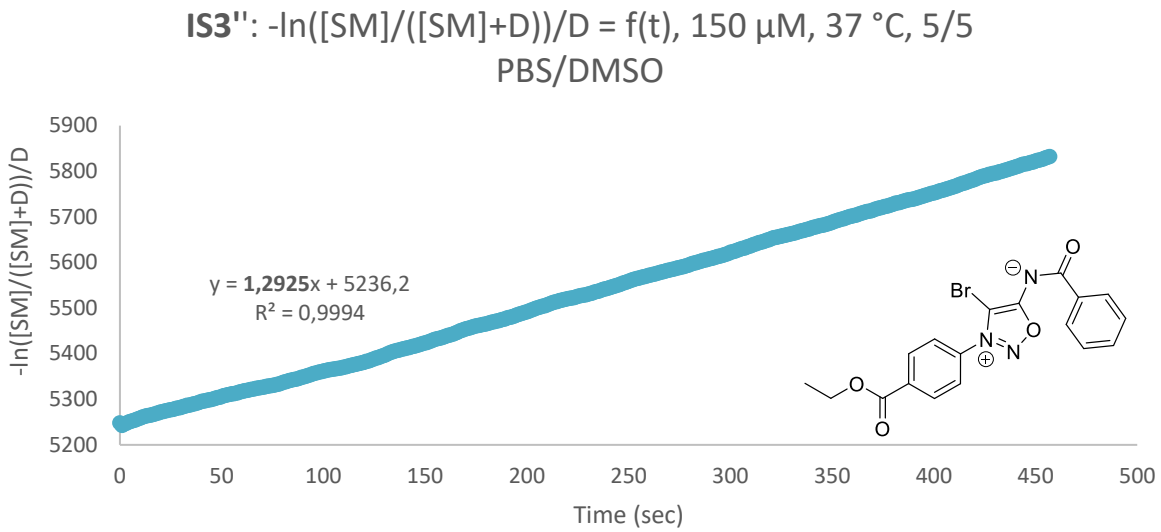

IS7': -ln([SM]/([SM]+D))/D = f(t), 30 µM, 37 °C, 8/2 PBS/DMSO
-ln([SM]/([SM]+D))/D
y = 17,861x + 27133
R² = 0,9901
Time (sec)

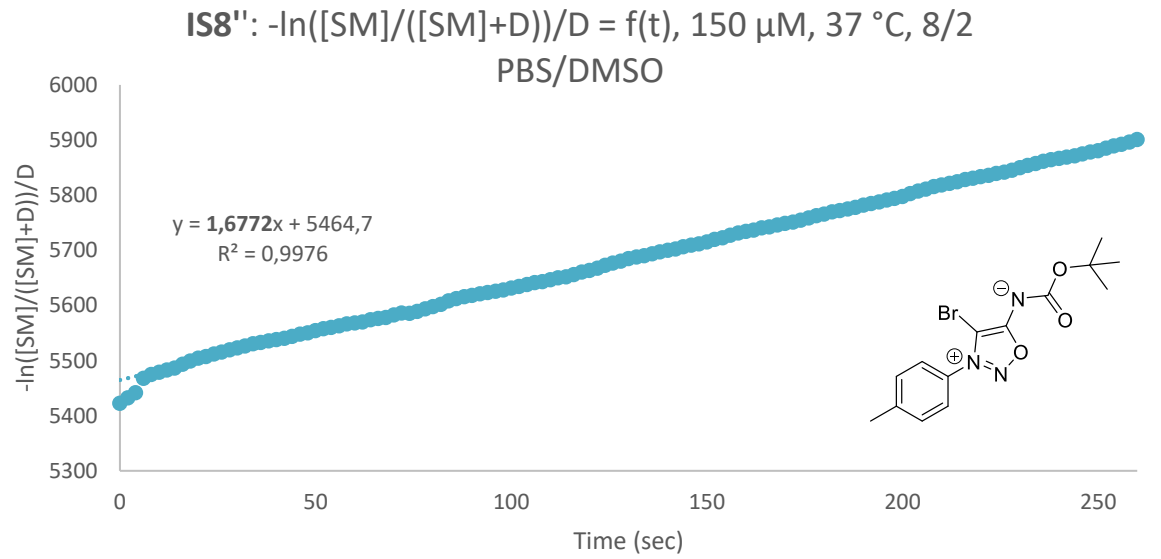

IS6': -ln([SM]/([SM]+D))/D = f(t), 30 µM, 37 °C, 8/2 PBS/DMSO
-ln([A]/([A]+D))/D
y = 0,3237x + 8147
R² = 0,9997
Time (sec)


IS1': -ln([SM]/([SM]+D))/D = f(t), 30 µM, 37 °C, 5/5 PBS/DMSO
y = 3,9736x + 7462,8
R² = 0,9912
-ln([A]/([A]+D))/D
Time (sec)
8200
8100
8000
7900
7800
7700
7600
7500
7400
0
20
40
60
80
100
120
140
160
EtOOC
Cl
N
COOtBu
NHFmoc
O

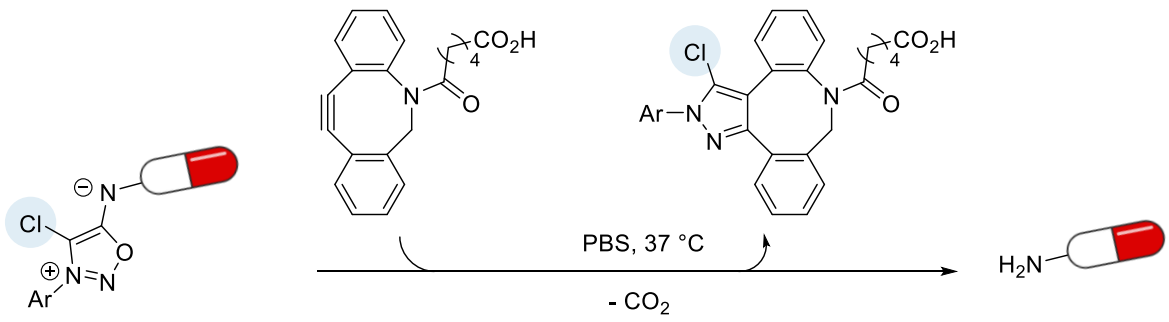

IS3': -ln([SM]/([SM]+D))/D = f(t), 150 µM, 37 °C, 8/2 PBS/DMSO
y = 2,2796x + 5401,6
R² = 0,9949
-ln([A]/([A]+D))/D
Time (sec)
6200
6100
6000
5900
5800
5700
5600
5500
5400
5300
0
50
100
150
200
250
300
350
EtO2C
Cl
N
O


IS8': -ln([SM]/([SM]+D))/D = f(t), 150 µM, 37 °C, 8/2 PBS/DMSO
y = 2,9992x + 5417
R² = 0,9982
-ln([SM]/([SM]+D))/D
Time (sec)
6000
5900
5800
5700
5600
5500
5400
5300
0
20
40
60
80
100
120
140
160
180
200
Me
Cl
N
OtBu
O





<u>Release of drugs upon SPICC reaction:</u>



Reactions of **IS15'** with DBCO was carried out in PBS/DMSO (8:2) at 37 °C, under stirring, at 30 µM concentration of iminosydnone and 45 µM concentration of DBCO using the following

procedure.

In a HPLC vial, the reagents were added in the order listed below (1 mL in total):

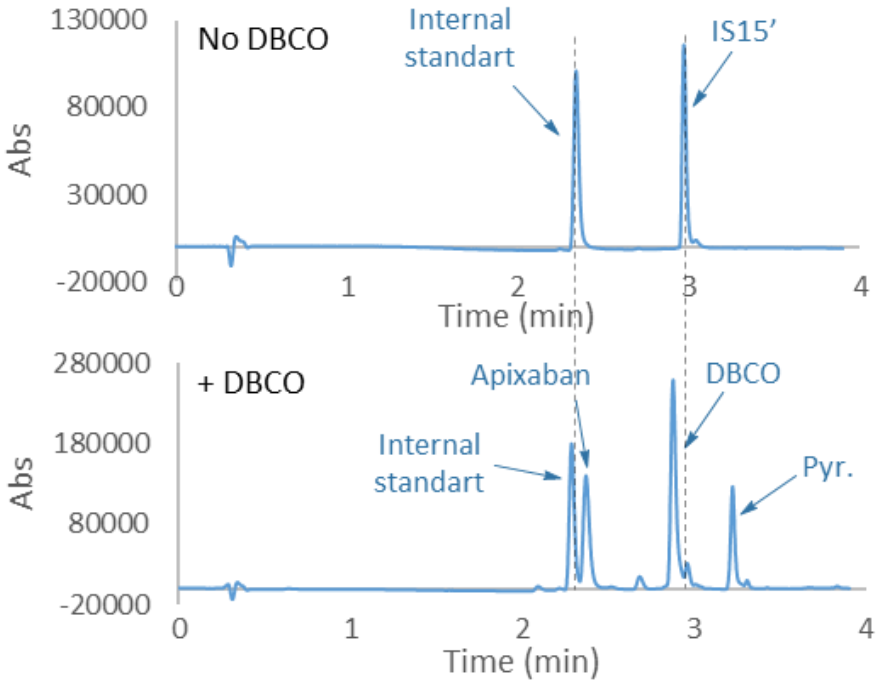
788 µL of PBS (0.01 M), 10 µL of **IS15'** solution (10 mM in DMSO), 1 µL of 3-fluoro-4-nitrophenol as internal standard (at 100 mM in DMSO) and 200 µL of DMSO.

The absorbance spectrum of the solution was first measured to get the T0. Then, 1 µL of the DBCO solution (150 mM in DMSO) was added to the reaction. The reaction was monitored by HPLC after 1 hour of reaction.

Conditions of HPLC eluant:

T = 0 min: 95/05 (H_2O/MeCN)

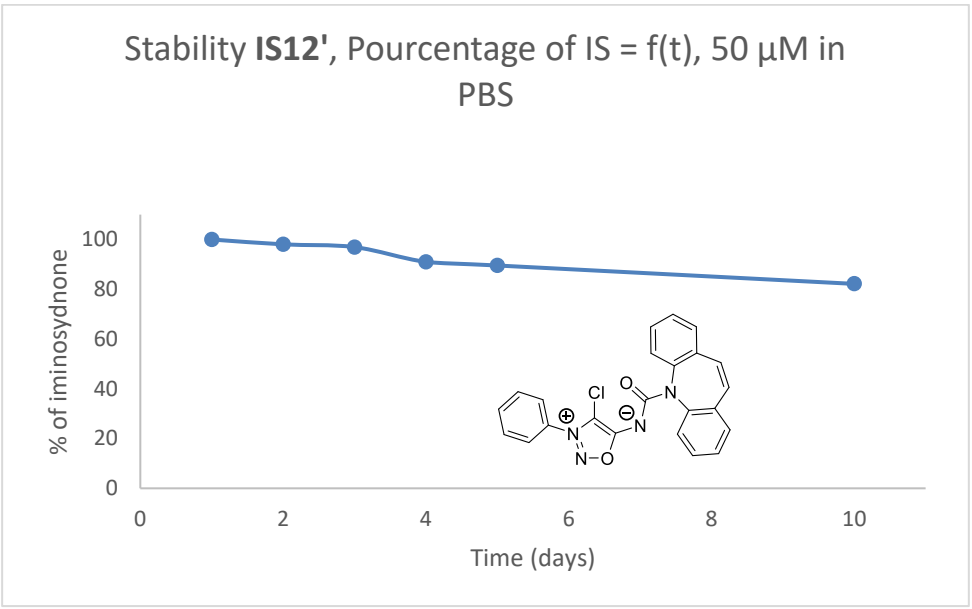
T = 4 min: 100% MeCN

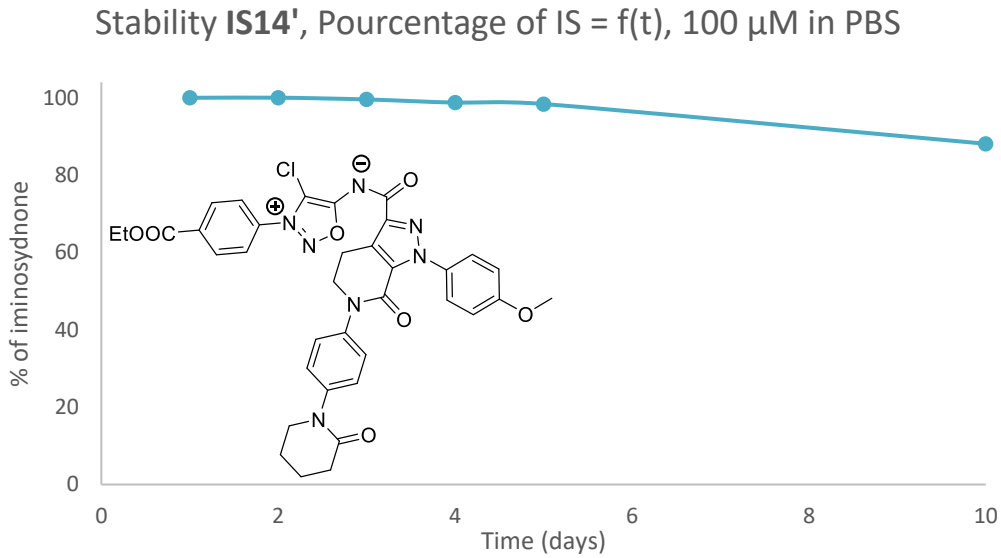


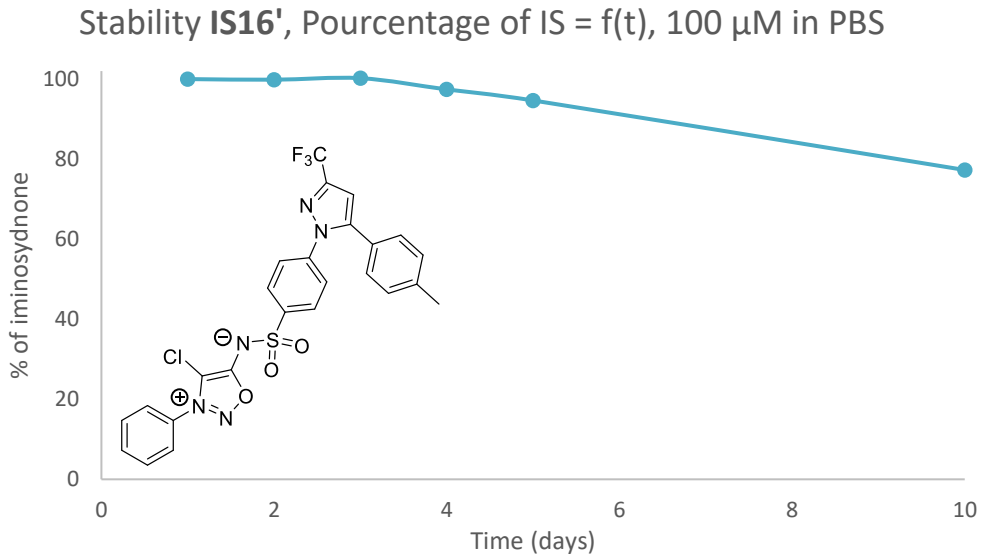
IV. Stability of chlorinated iminosydnones

Stability studies of chlorinated iminosydnone prodrugs were done in phosphate buffer saline solution pH 7.4 with 10% of DMSO at room temperature.

In a HPLC vial, 100 µL of iminosydnone solution at 1 mM in DMSO were added to 899 µL of PBS (0.1 M, pH 7.4). 1 µL of 3-fluoro-4-nitrophenol (at 100 mM in DMSO) was then added as an internal standard.
The solution was stored at room temperature. Quantification of iminosydnone was carried out by HPLC analysis at different time and the percentage of the remaining compound was determined.

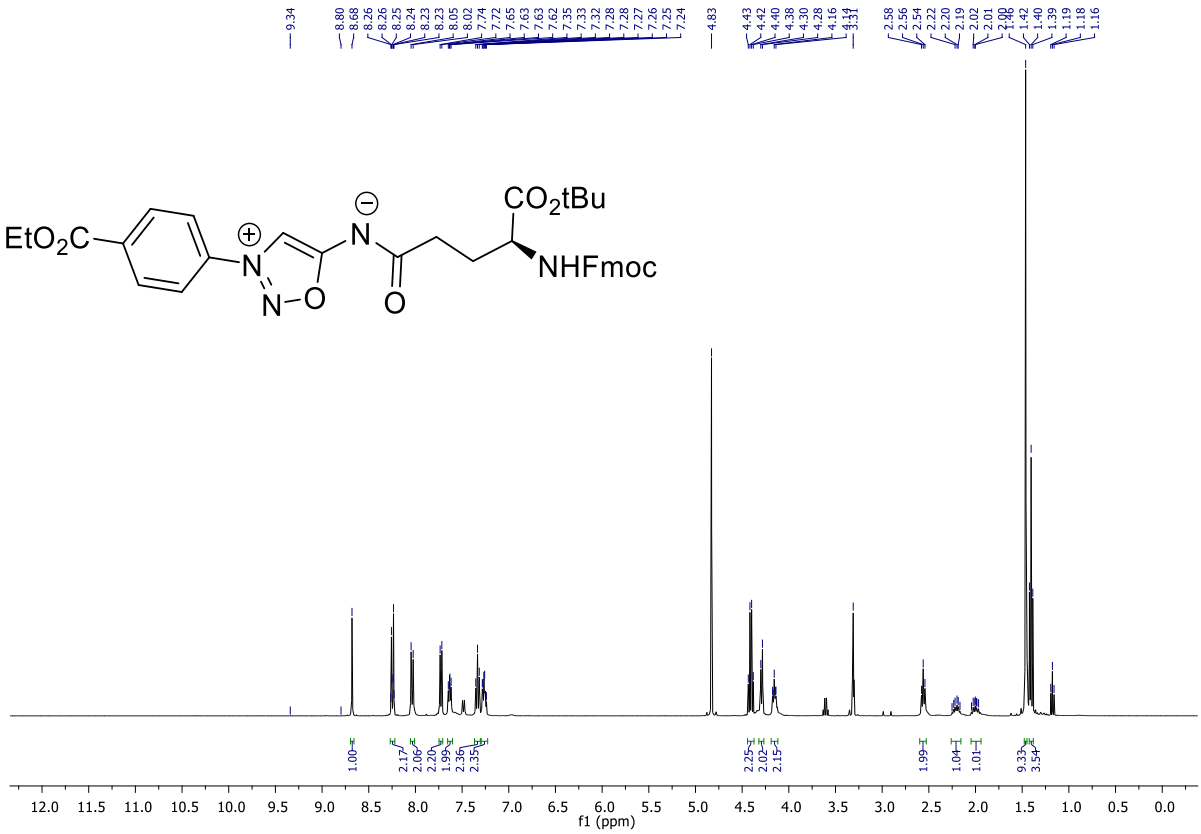




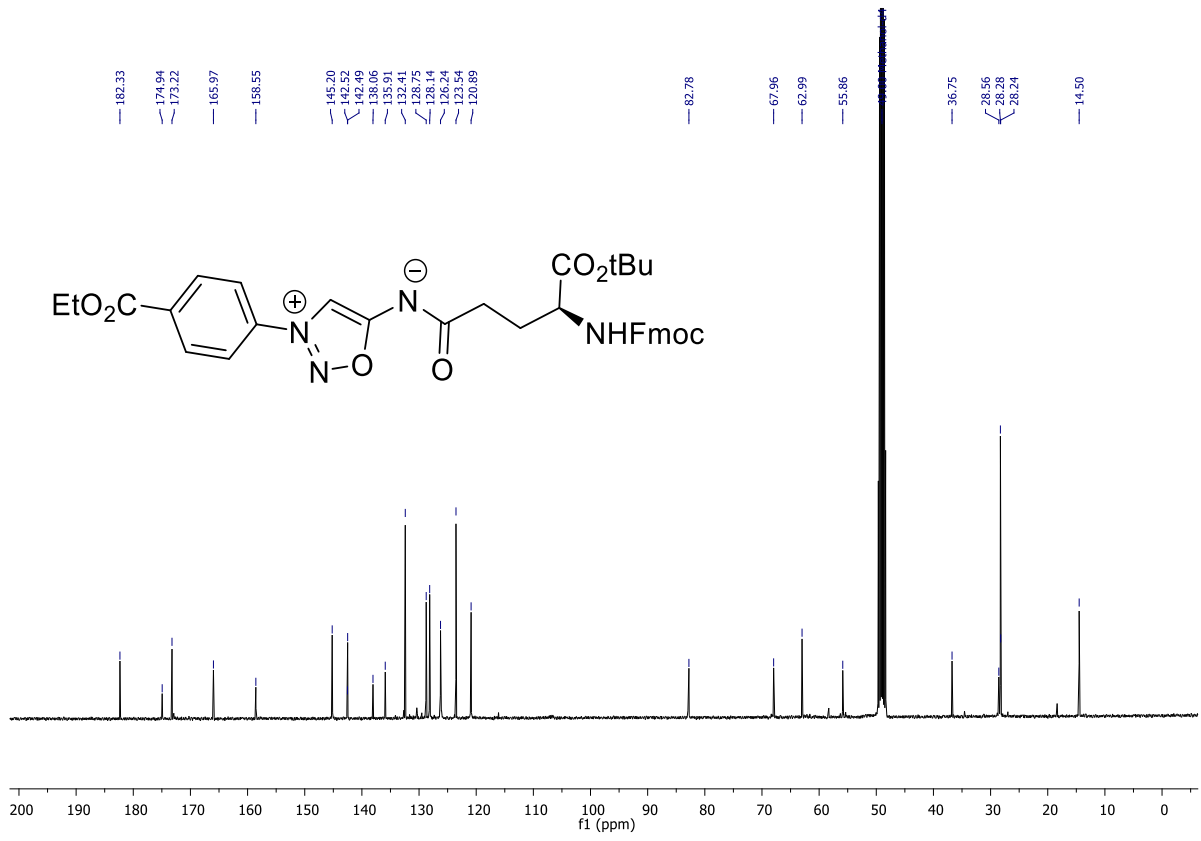

Stability **IS16'**, Pourcentage of IS = f(t), 100 µM in PBS
% of iminosydnone
100
80
60
40
20
0
0
2
4
6
8
10
Time (days)
F3C
N
N
Cl
N
S
O
O
N
N
O

V. NMR Spectra

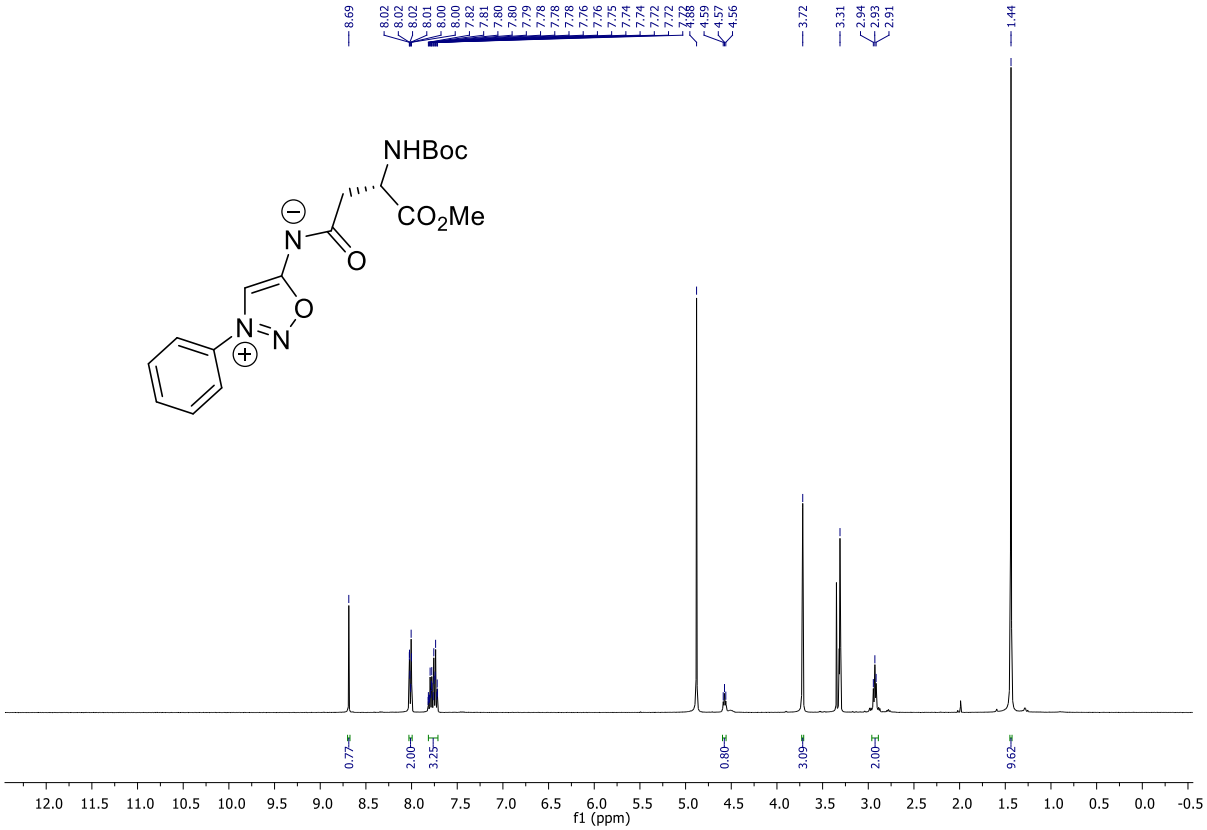
^{1}H NMR (400 MHz, MeOD) (**IS1**)



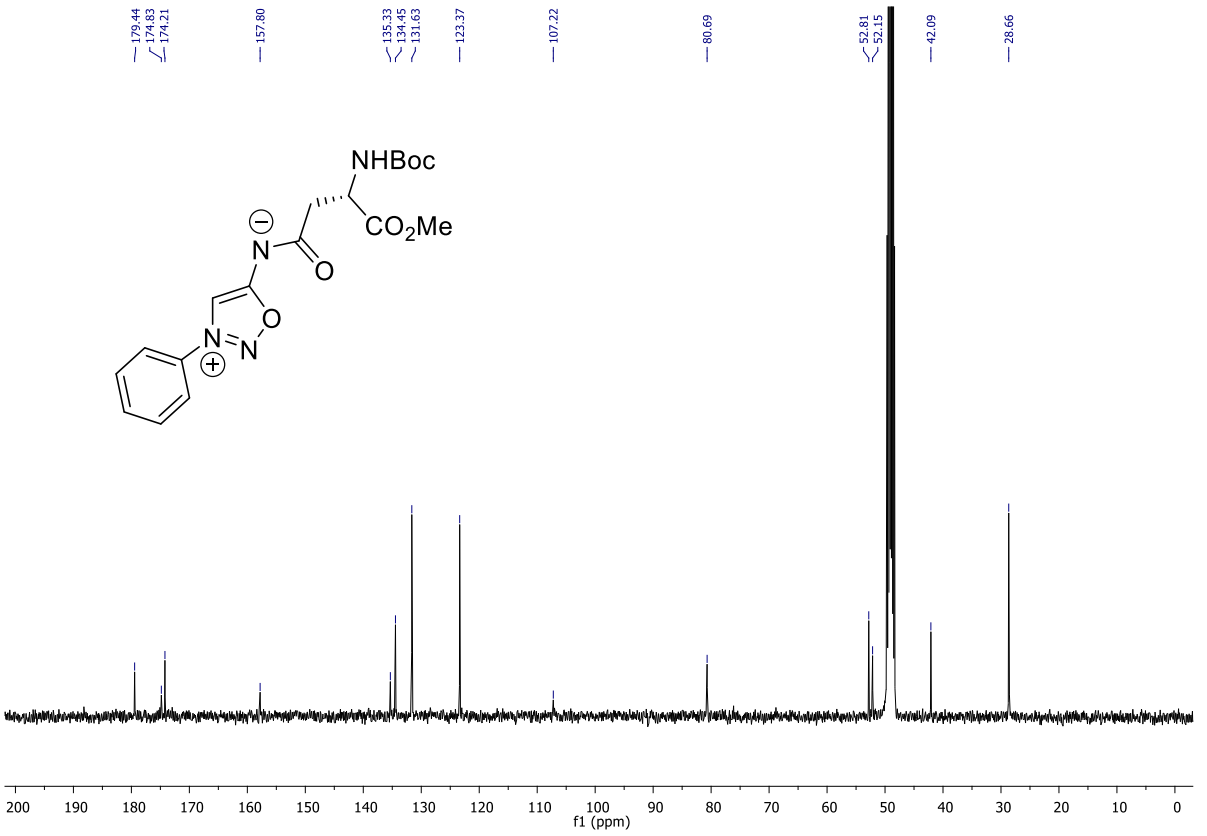
^{13}C NMR (100 MHz, MeOD) (**IS1**)



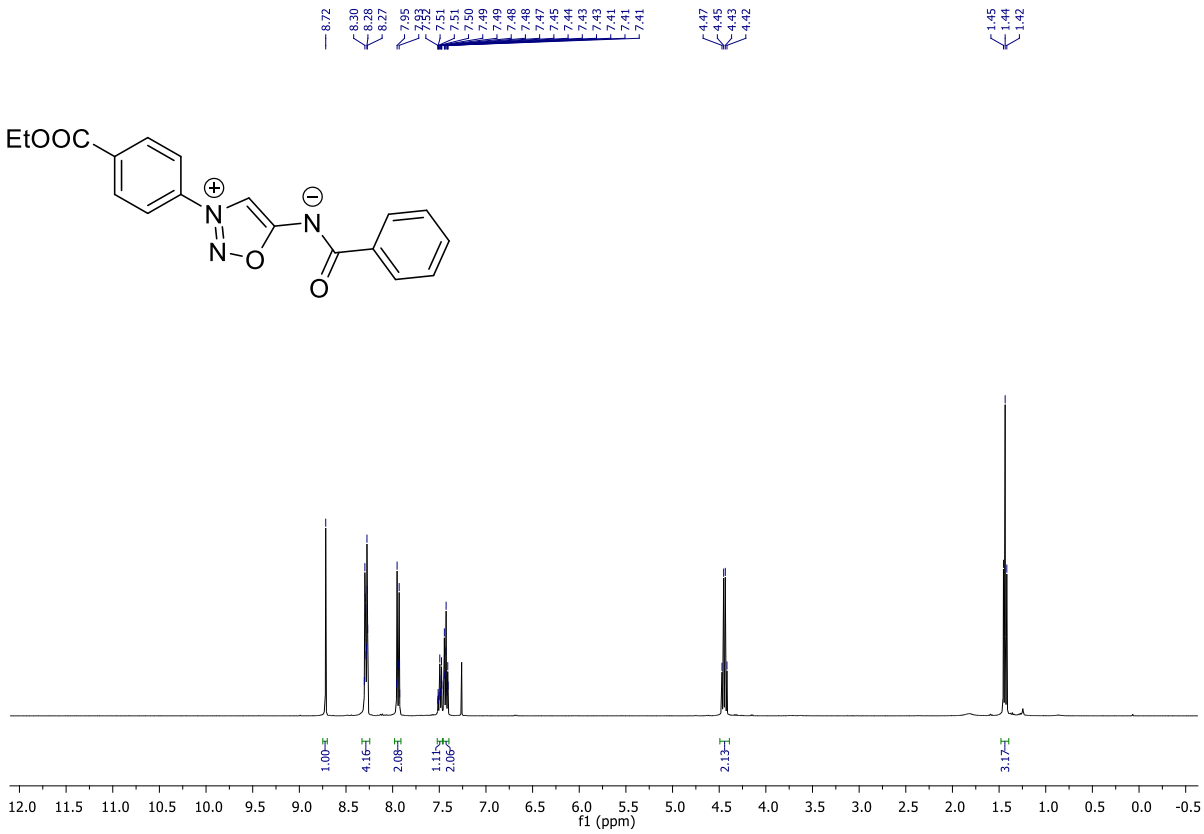
^{1}H NMR (400 MHz, MeOD) **(IS2)**



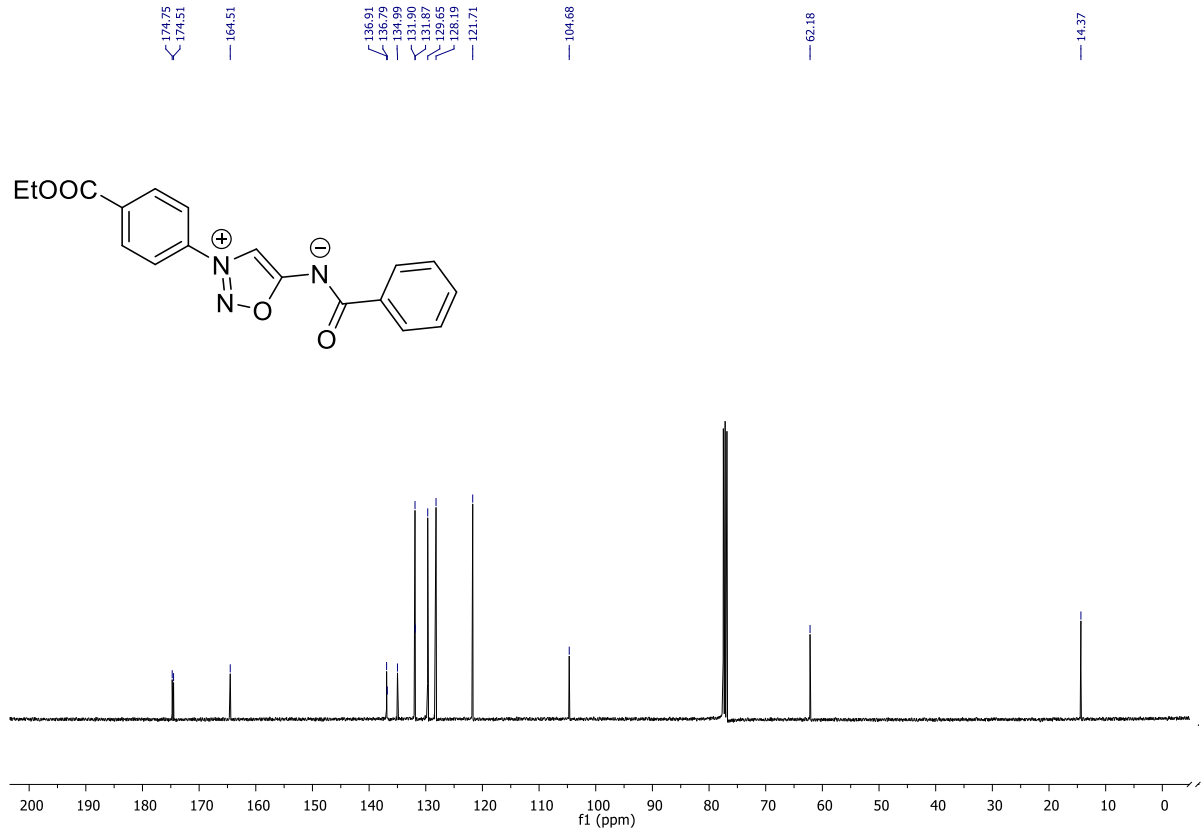
^{13}C NMR (100 MHz, MeOD) (**IS2**)



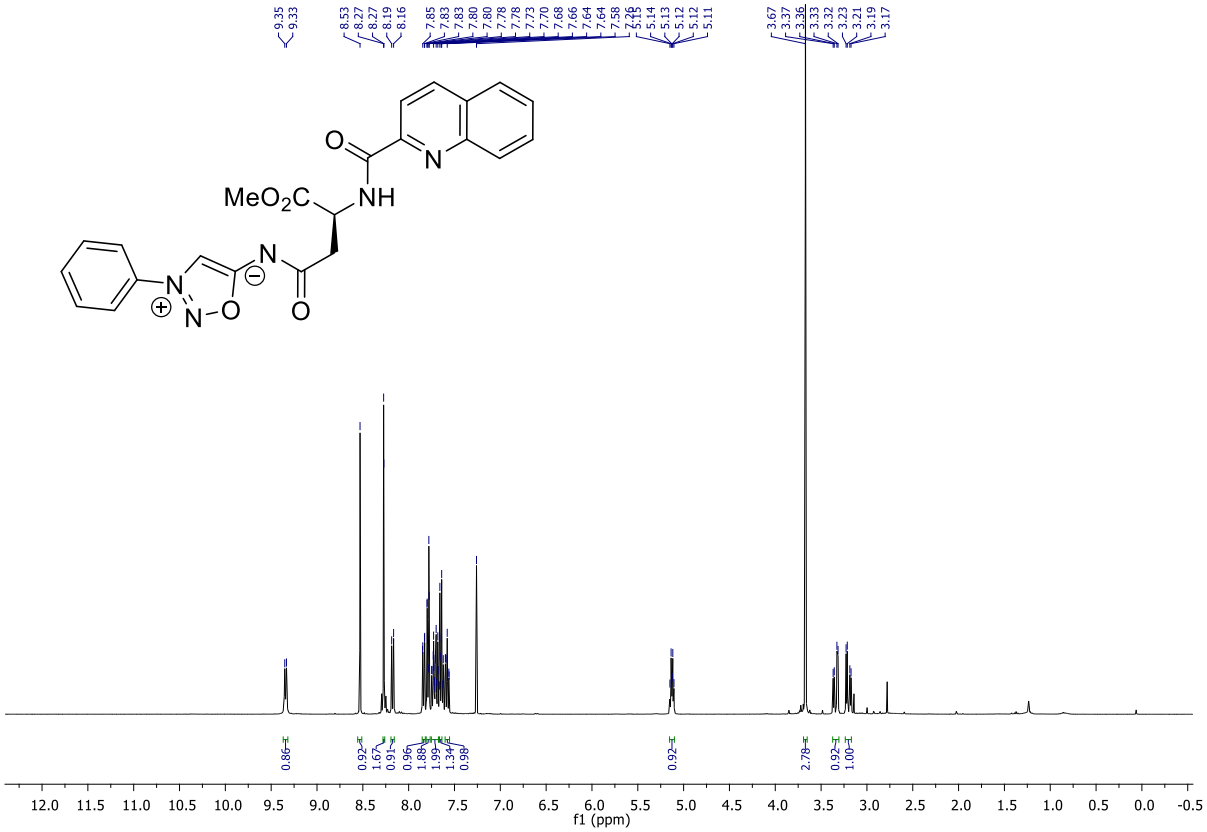
^{1}H NMR (400 MHz, $CDCl_3$) **(IS3)**



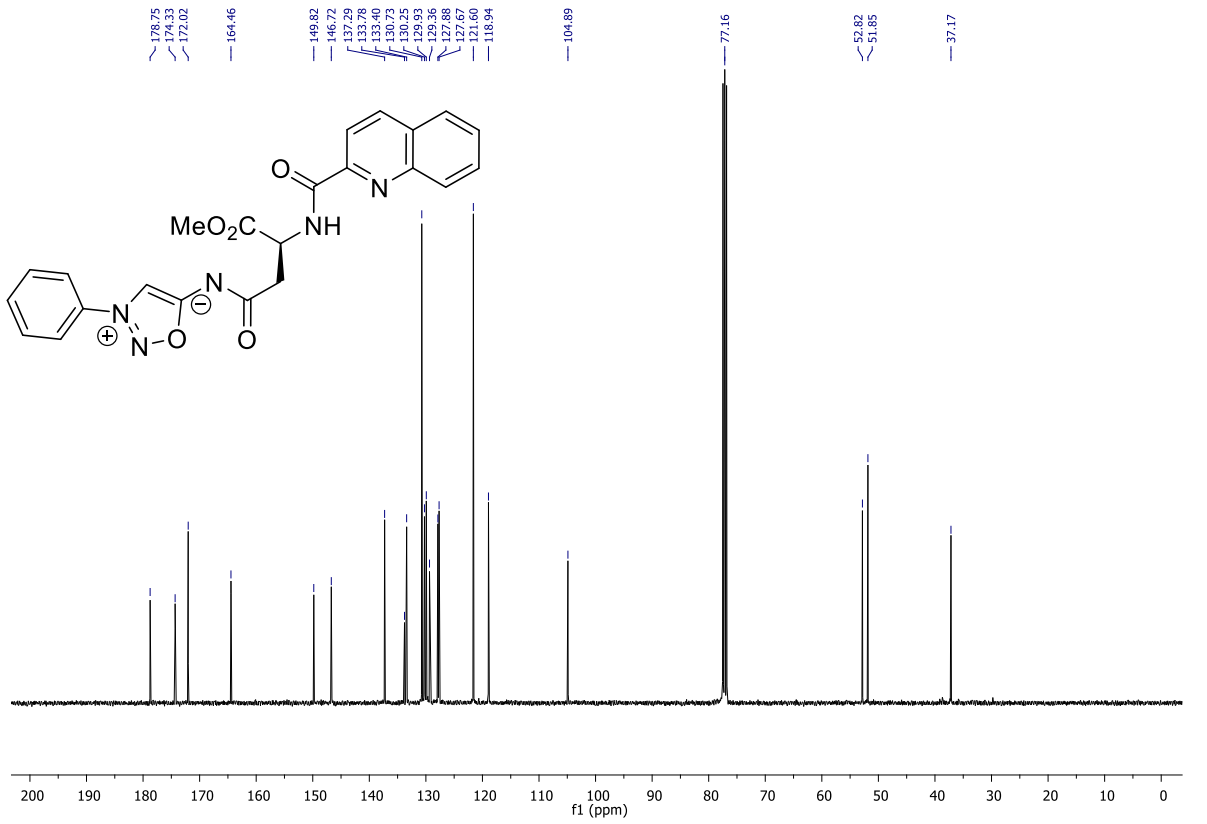
^{13}C NMR (100 MHz, $CDCl_3$) **(IS3)**



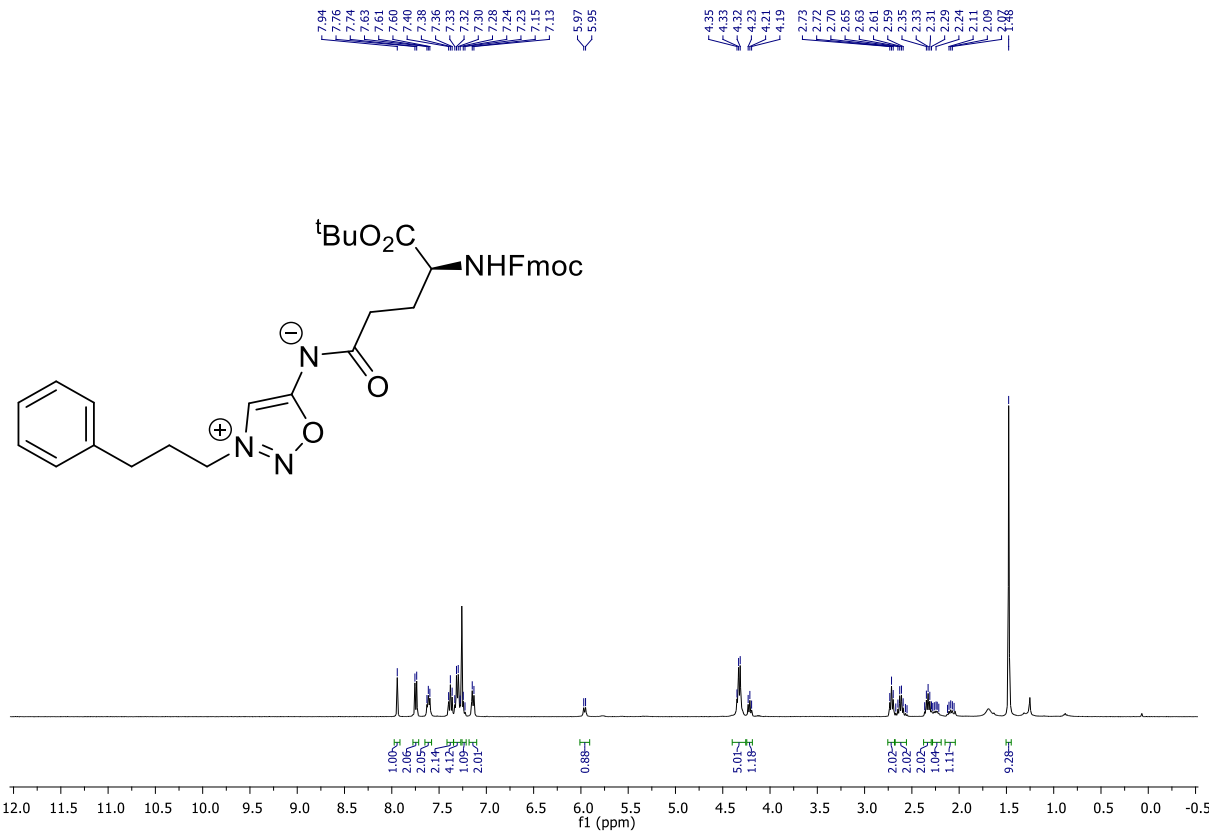
^{1}H NMR (400 MHz, $CDCl_3$) **(IS4)**



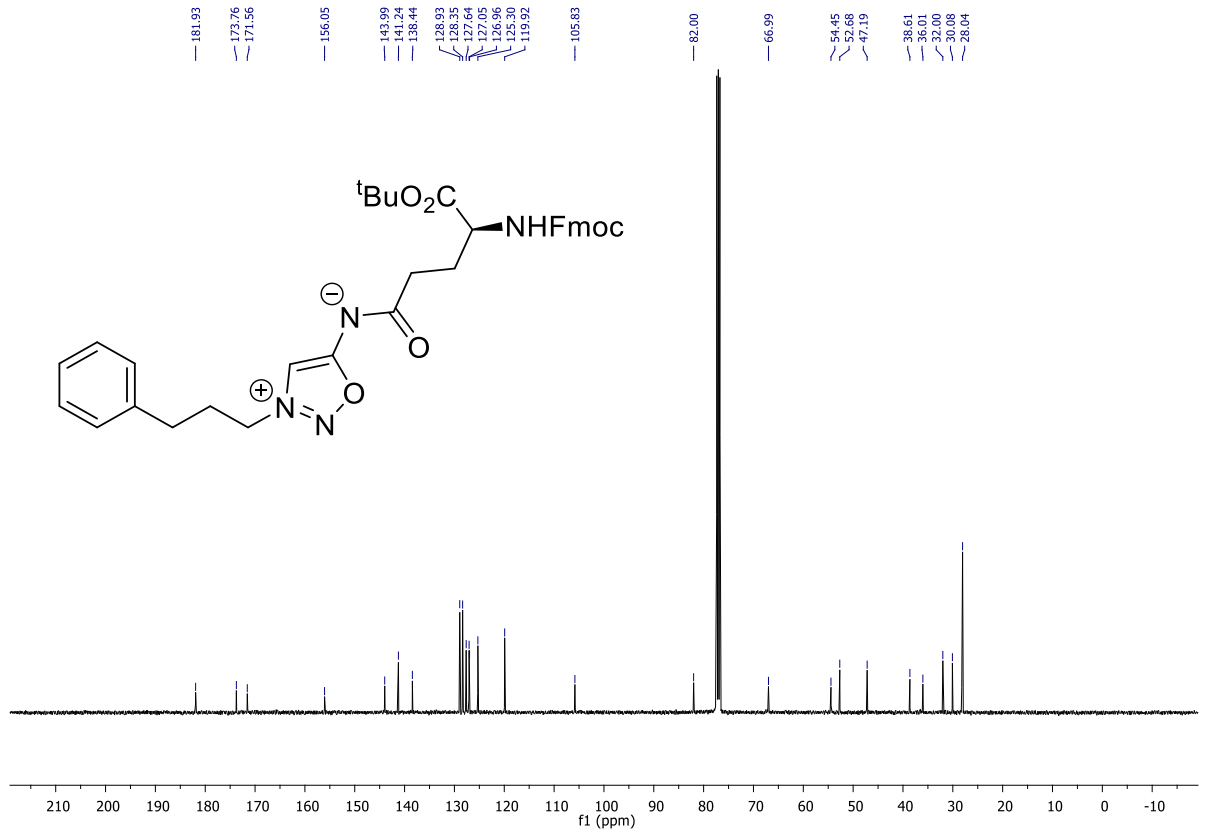
^{13}C NMR (100 MHz, $CDCl_3$) **(IS4)**



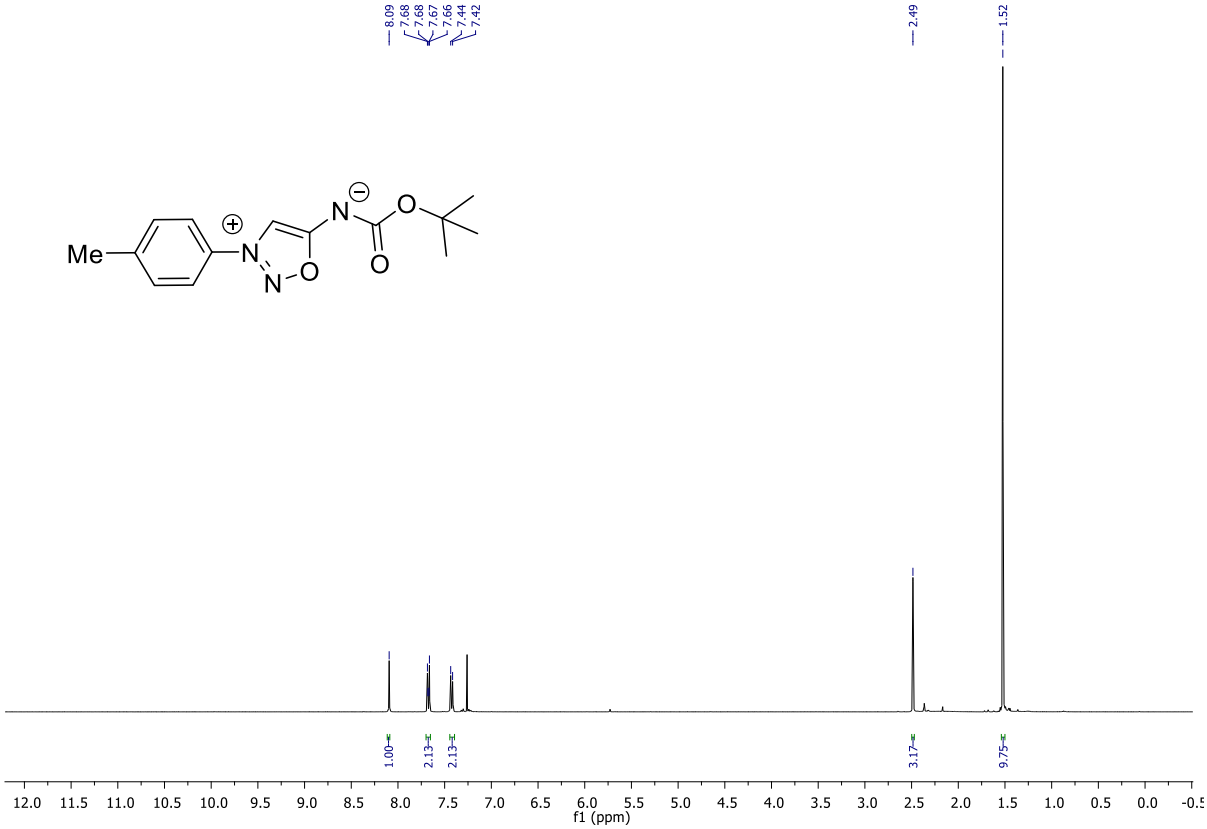
^{1}H NMR (400 MHz, $CDCl_3$) **(IS5)**



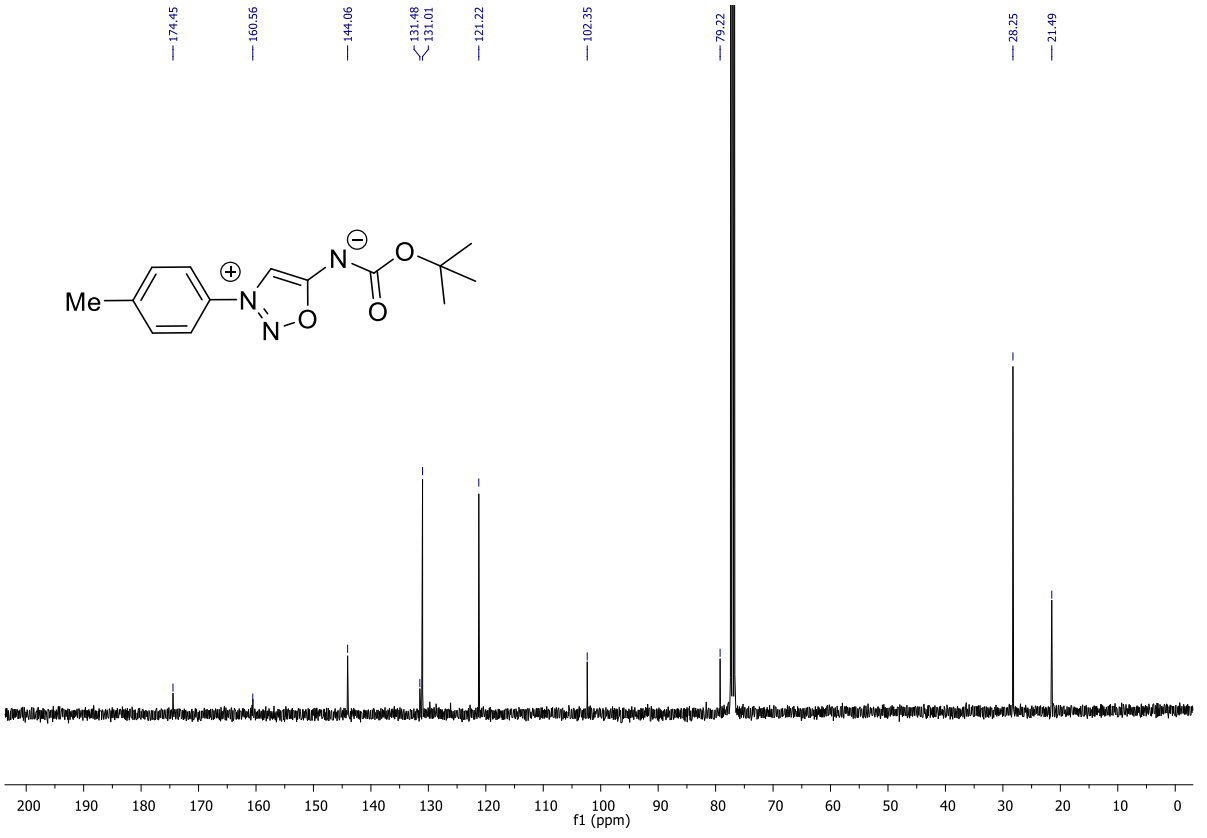
^{13}C NMR (100 MHz, $CDCl_3$) **(IS5)**



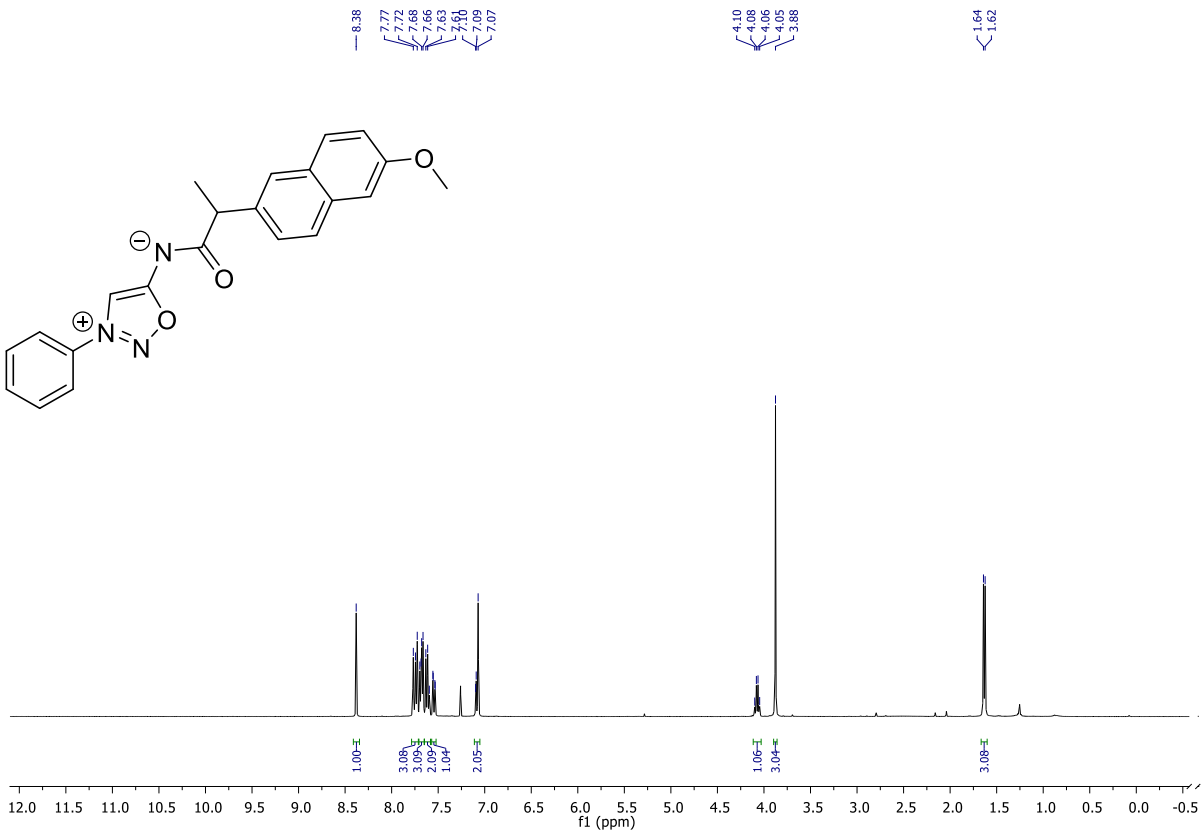
^{1}H NMR (400 MHz, $CDCl_3$) **(IS8)**



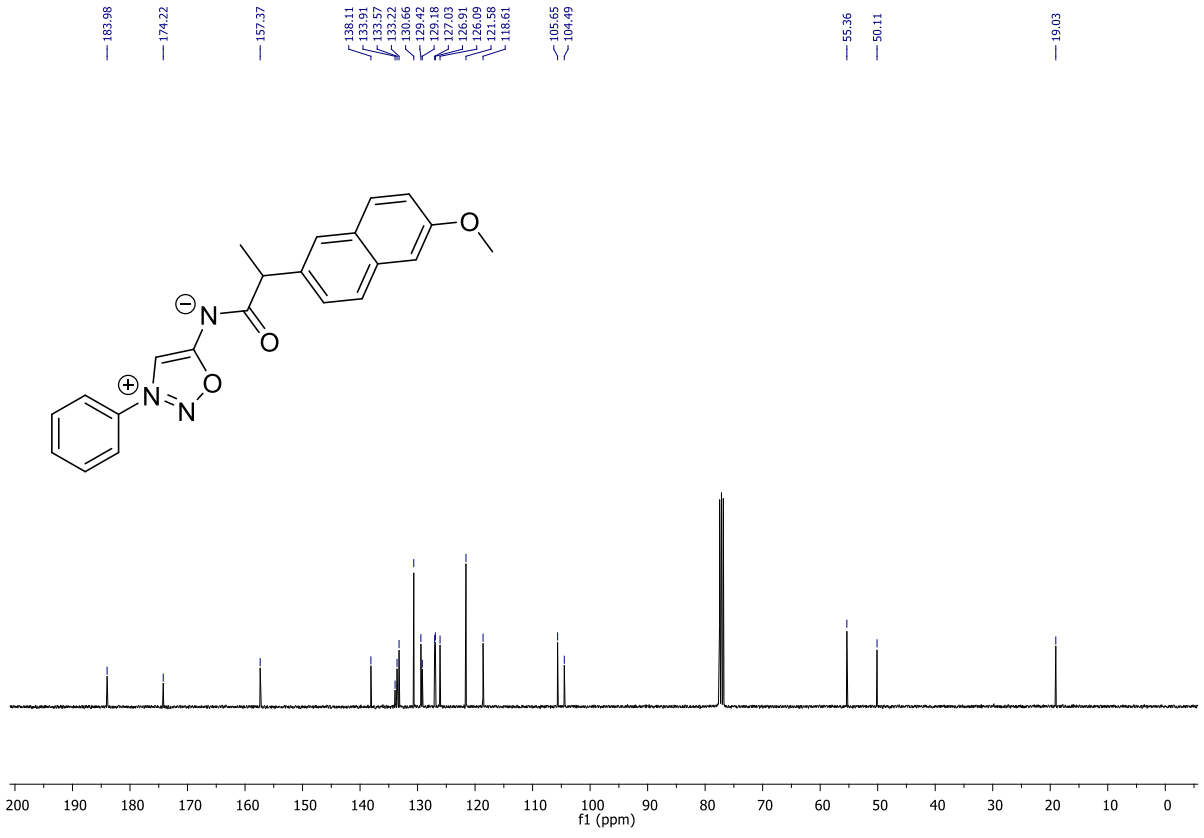
^{13}C NMR (100 MHz, $CDCl_3$) **(IS8)**



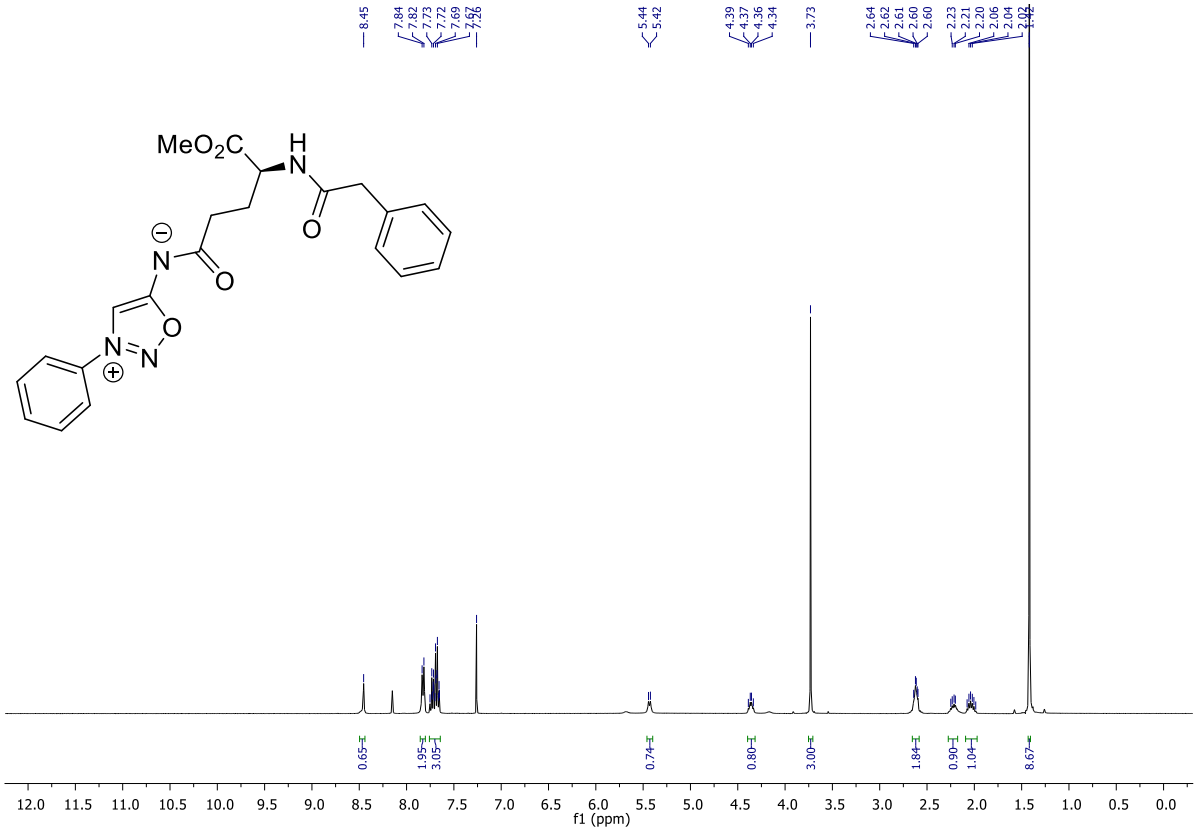
^{1}H NMR (400 MHz, $CDCl_3$) **(IS11)**



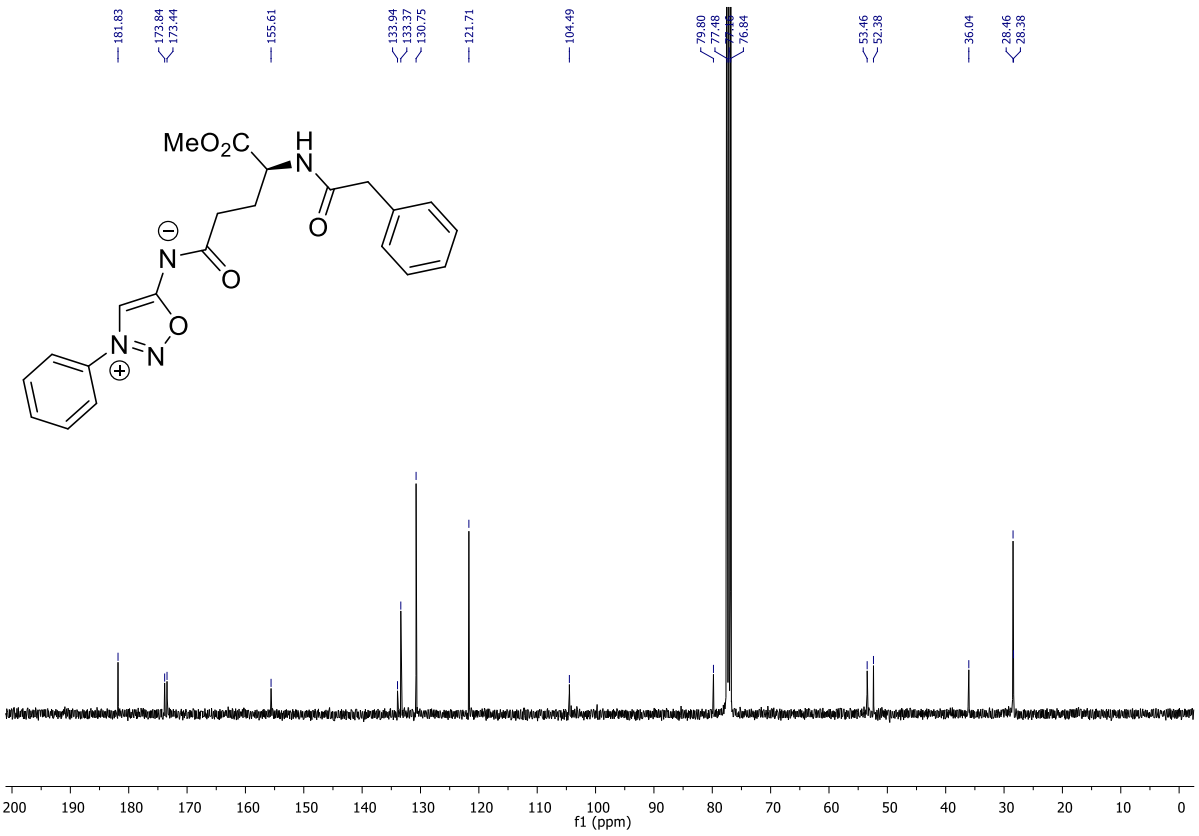
^{13}C NMR (100 MHz, $CDCl_3$) **(IS11)**



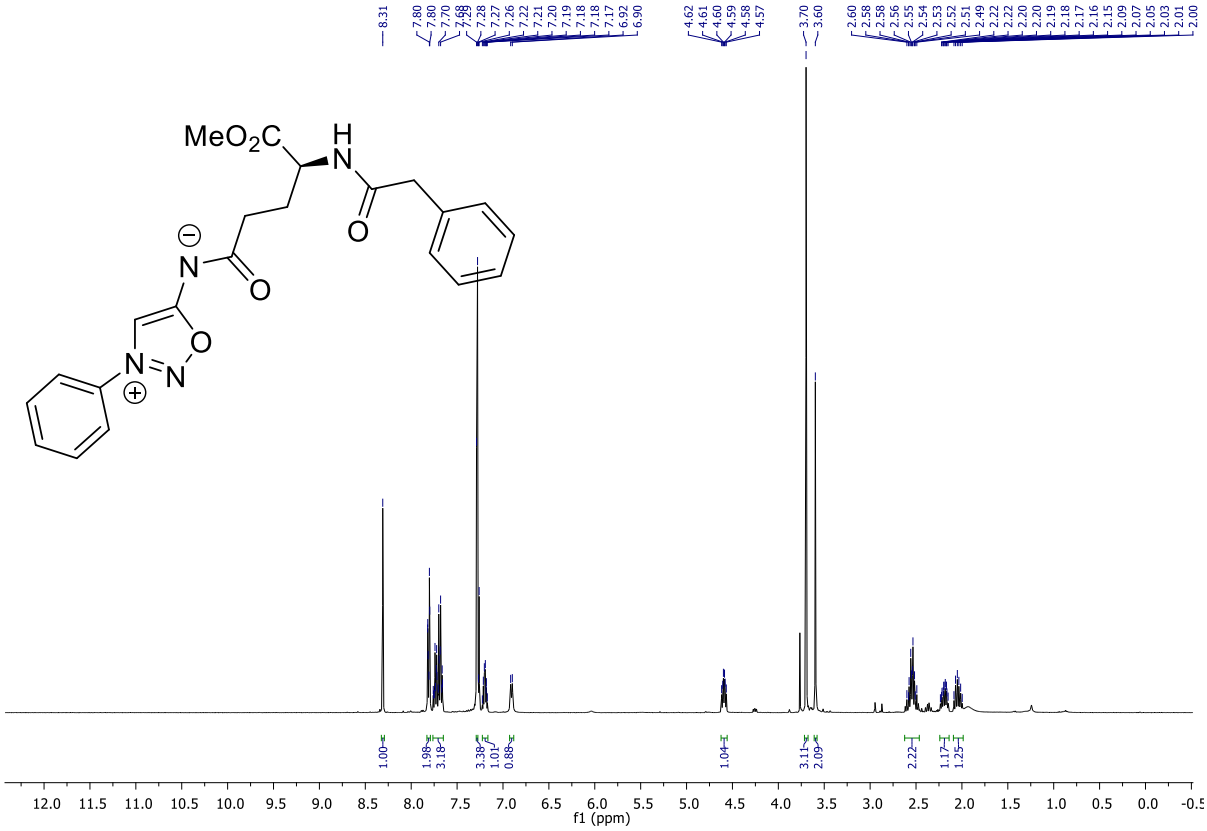
^{1}H NMR (400 MHz, $CDCl_3$) **(IS12a)**



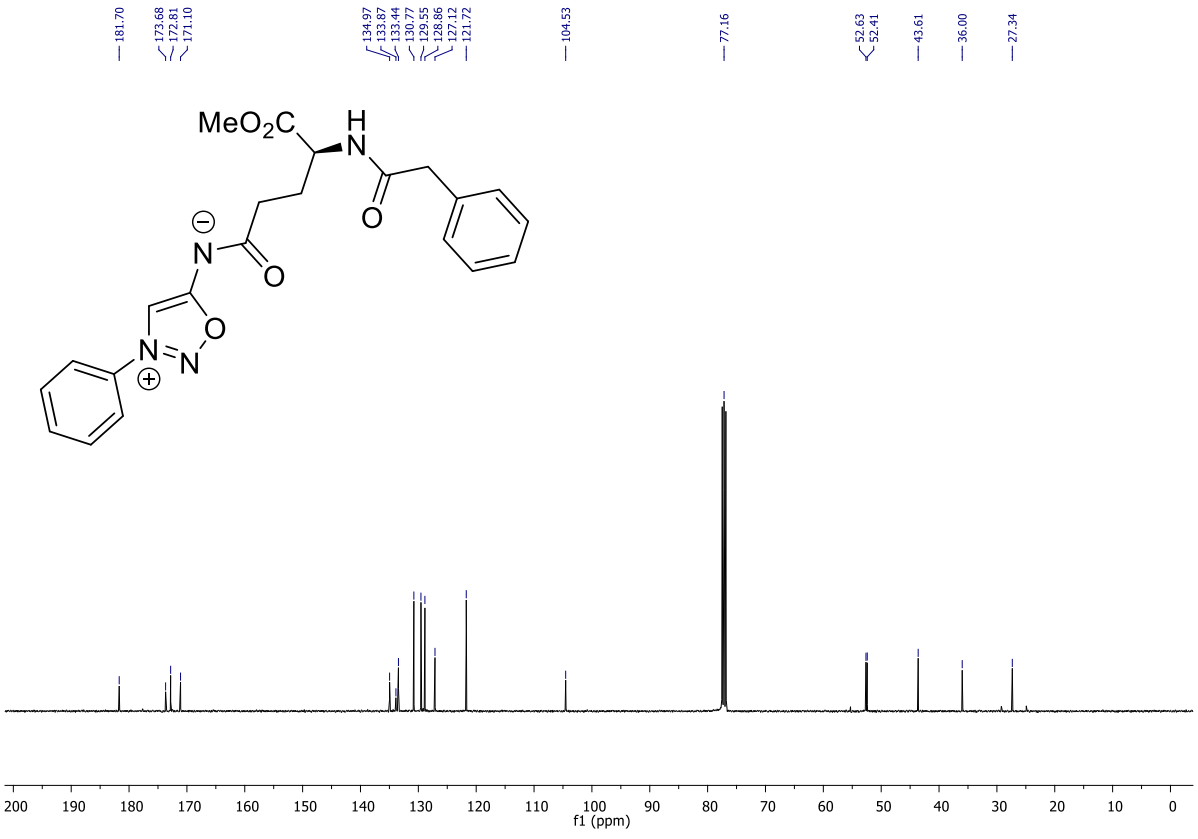
^{13}C NMR (100 MHz, $CDCl_3$) **(IS12a)**



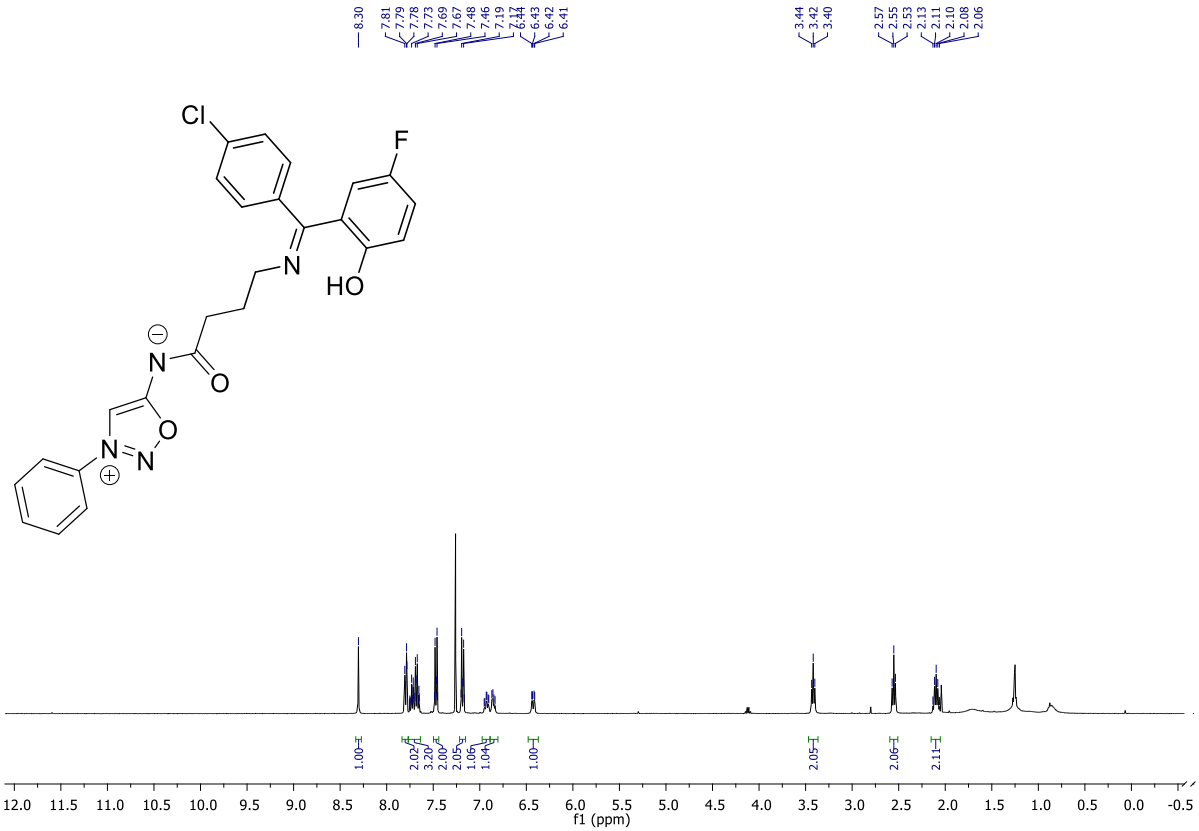
^{1}H NMR (400 MHz, $CDCl_3$) **(IS12)**



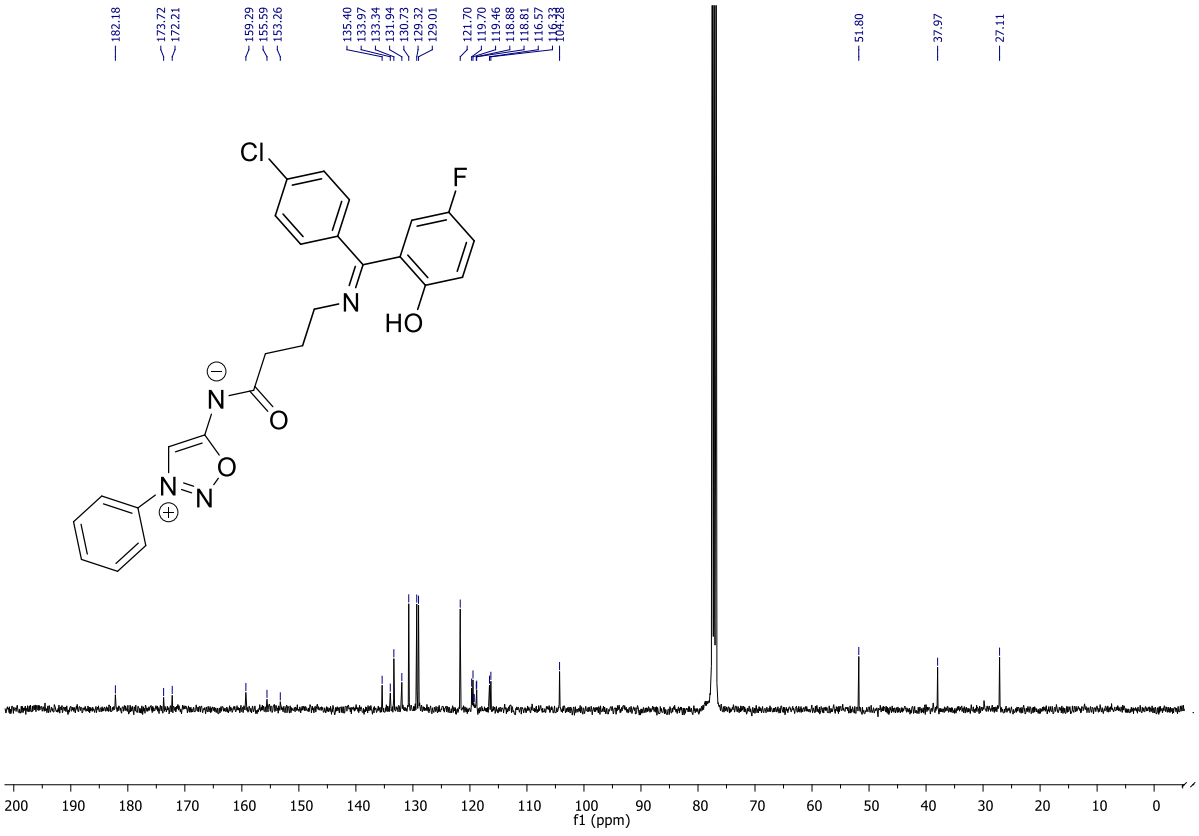
^{13}C NMR (100 MHz, $CDCl_3$) **(IS12)**



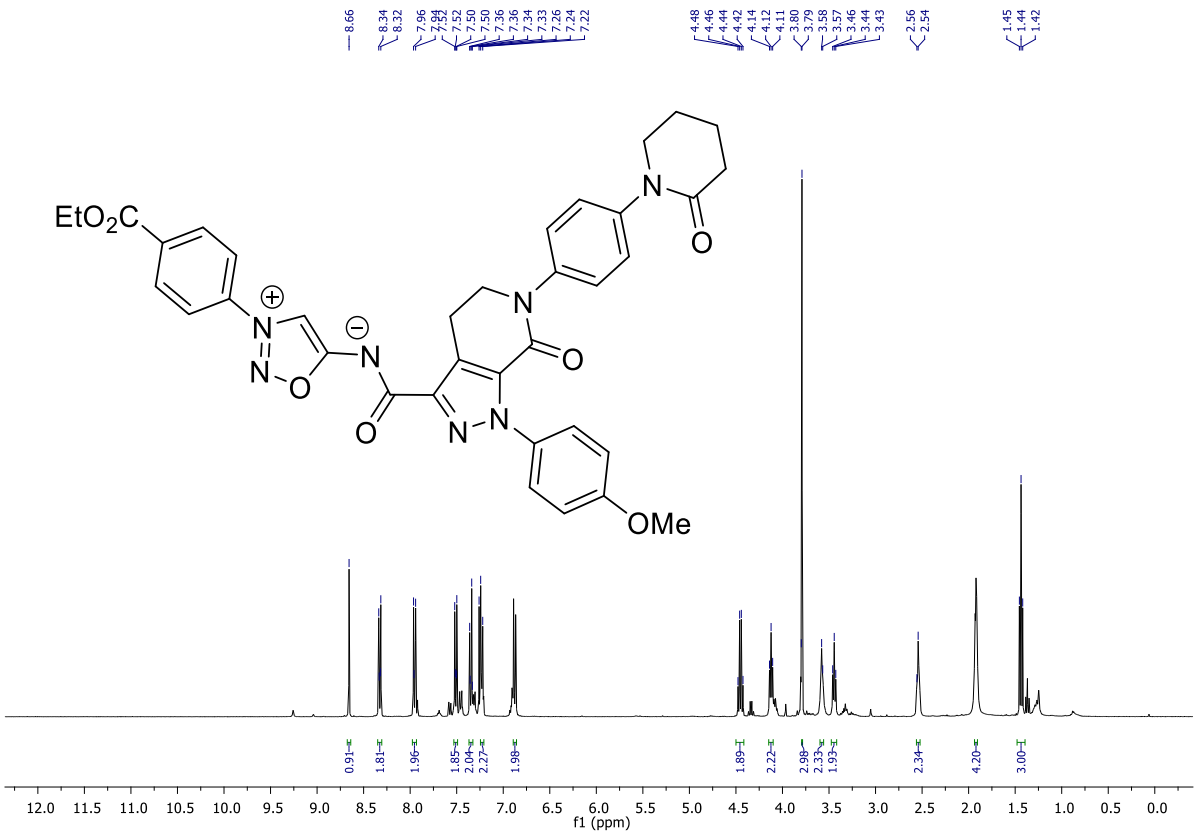
^{1}H NMR (400 MHz, $CDCl_3$) **(IS13)**



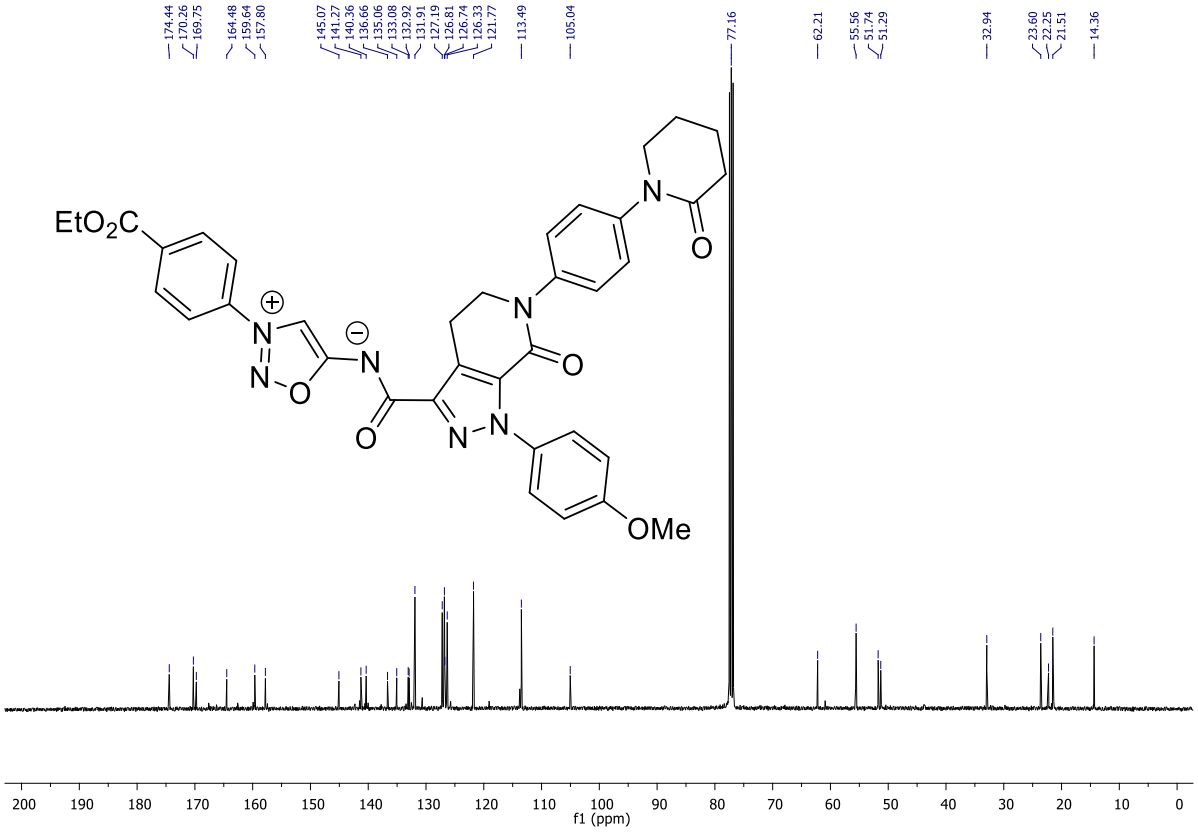
^{13}C NMR (100 MHz, $CDCl_3$) **(IS13)**



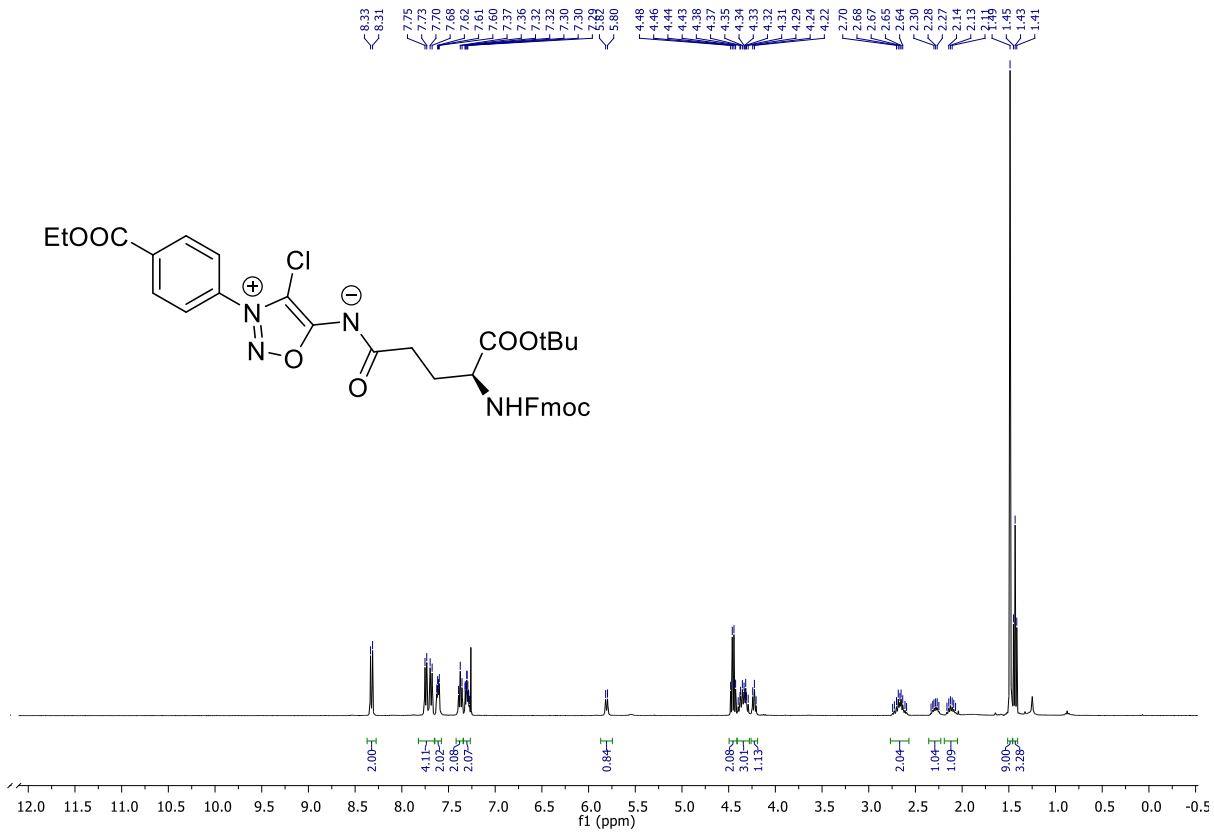
^{1}H NMR (400 MHz, $CDCl_3$) **(IS15)**



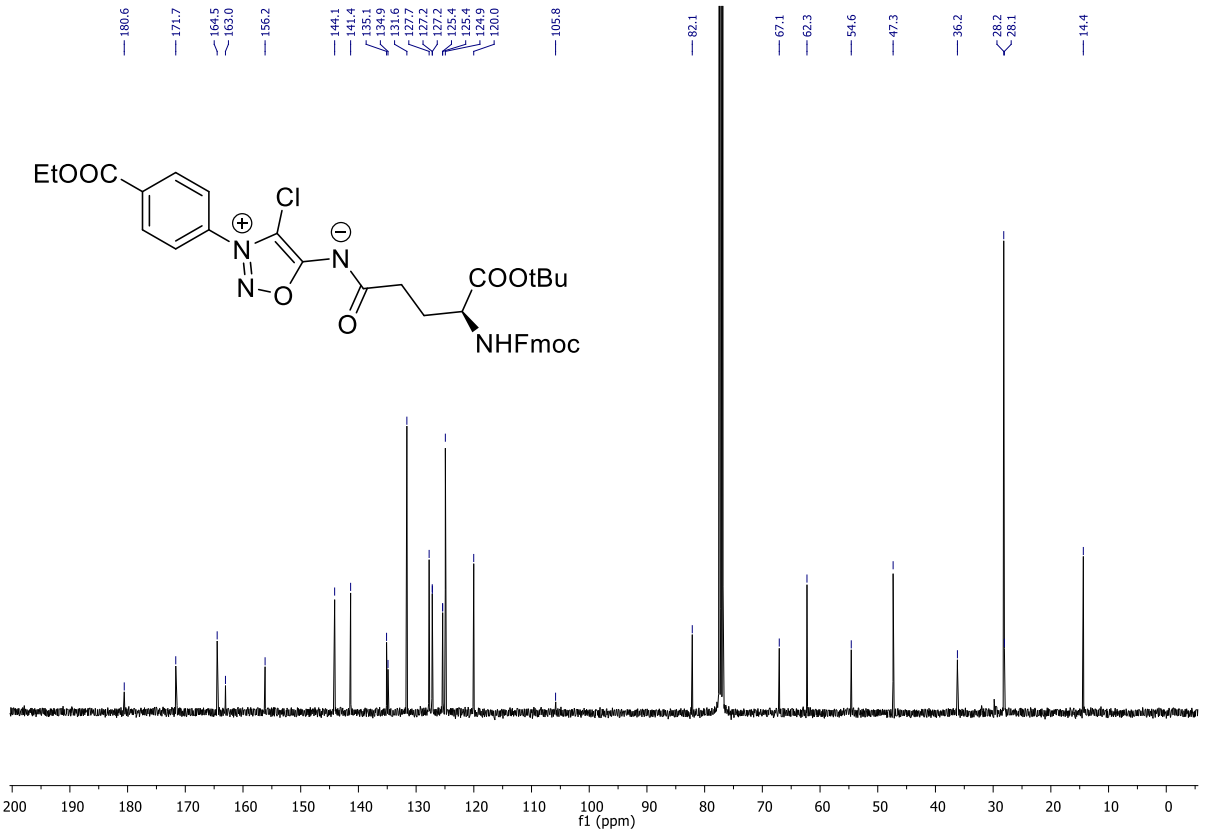
^{13}C NMR (100 MHz, $CDCl_3$) **(IS15)**



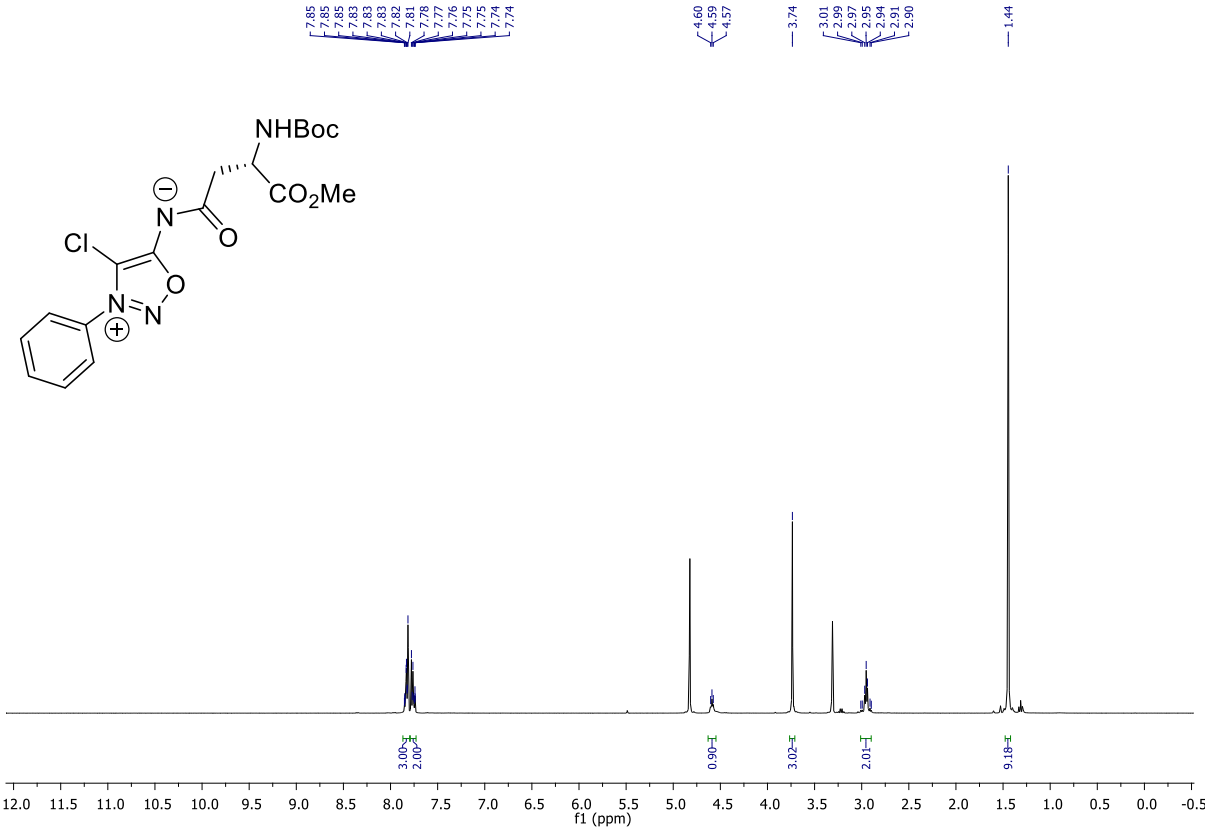
^{1}H NMR (400 MHz, $CDCl_3$) (**IS1'**)



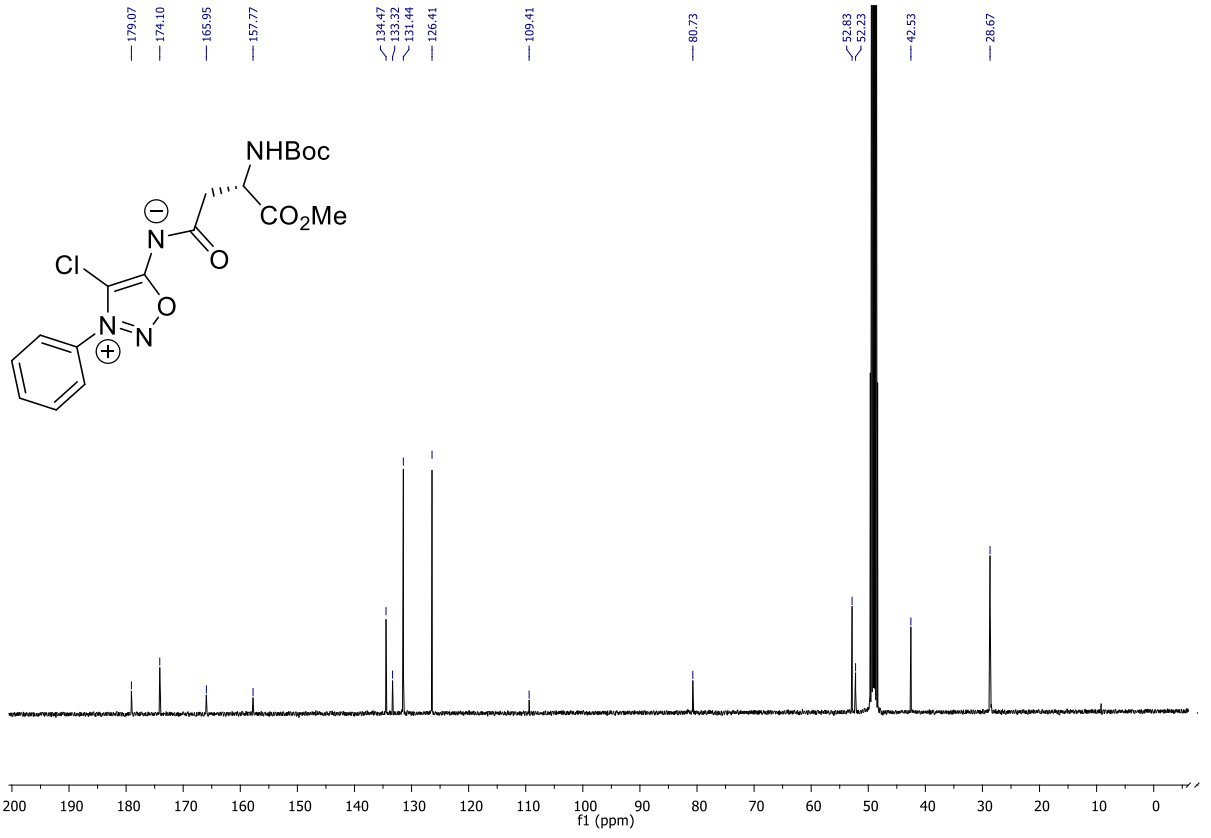
^{13}C NMR (100 MHz, $CDCl_3$) (**IS1'**)



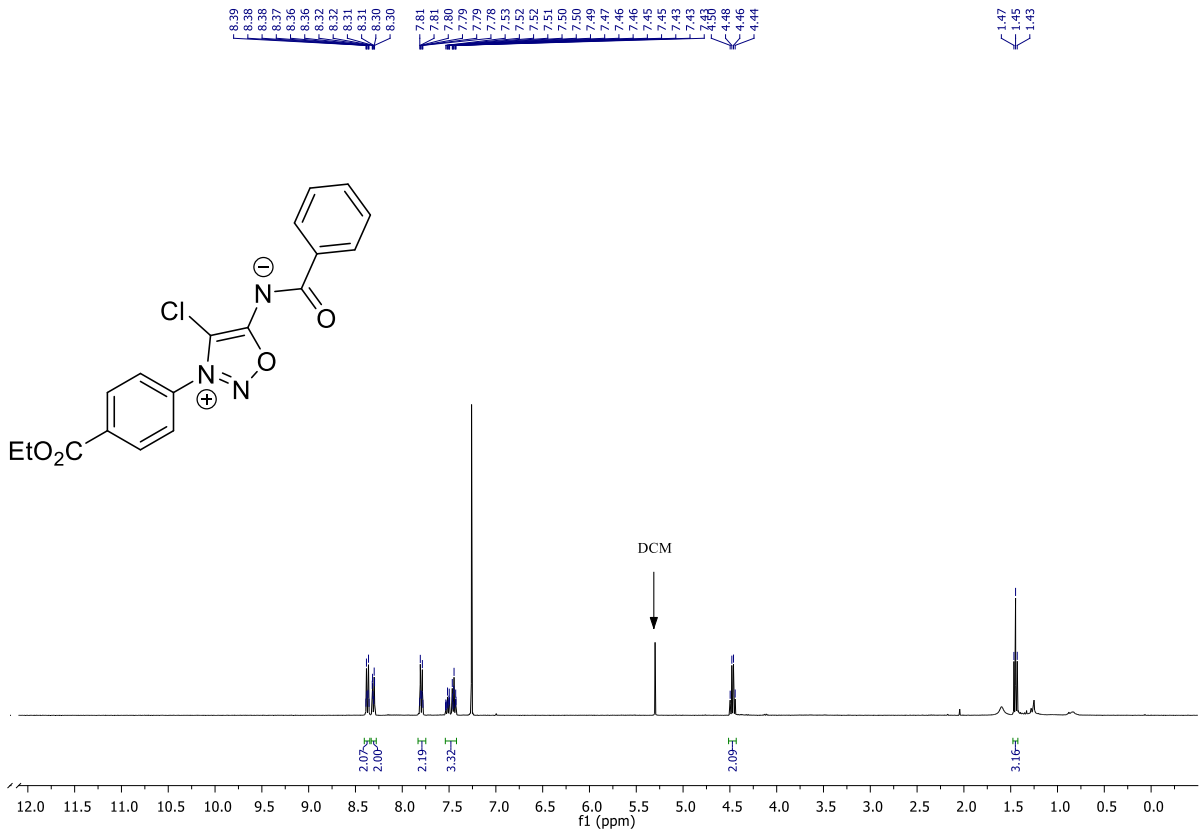
^{1}H NMR (400 MHz, MeOD) (**IS2'**)



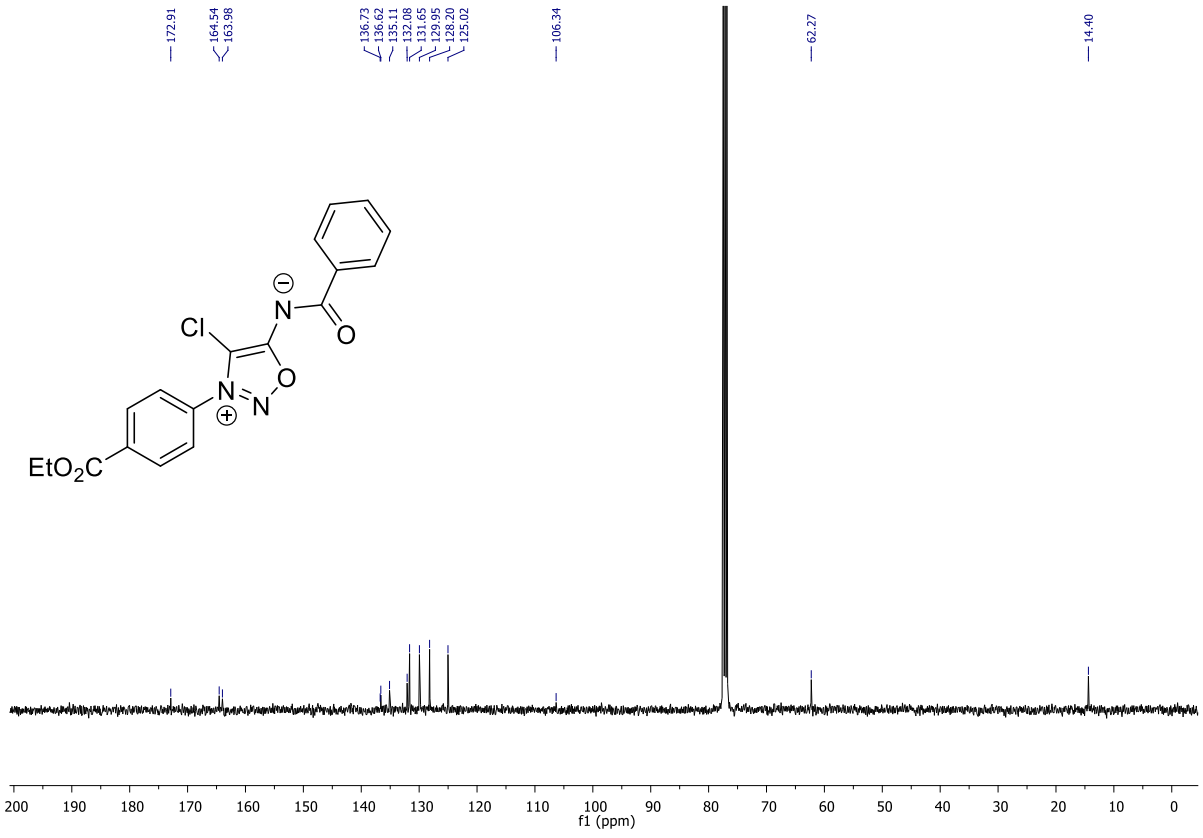
^{13}C NMR (100 MHz, MeOD) (**IS2'**)



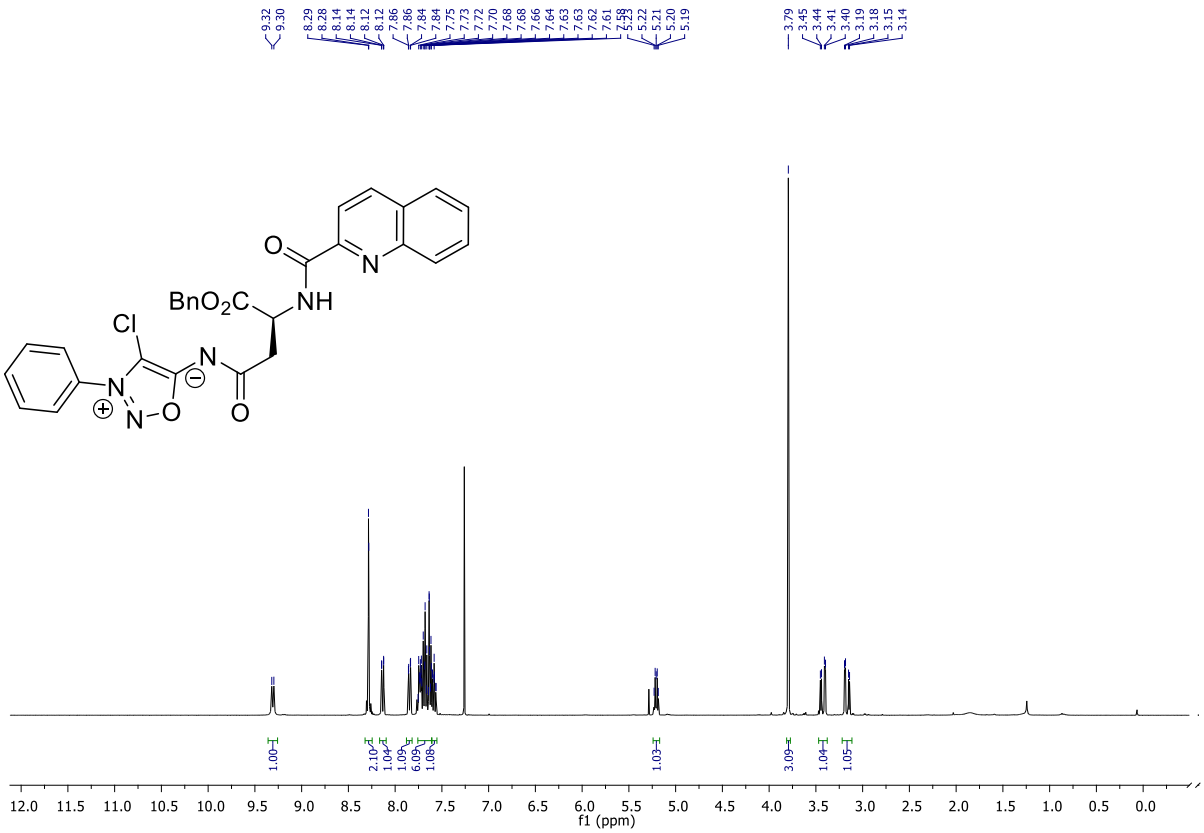
^{1}H NMR (400 MHz, $CDCl_3$) (**IS3'**)



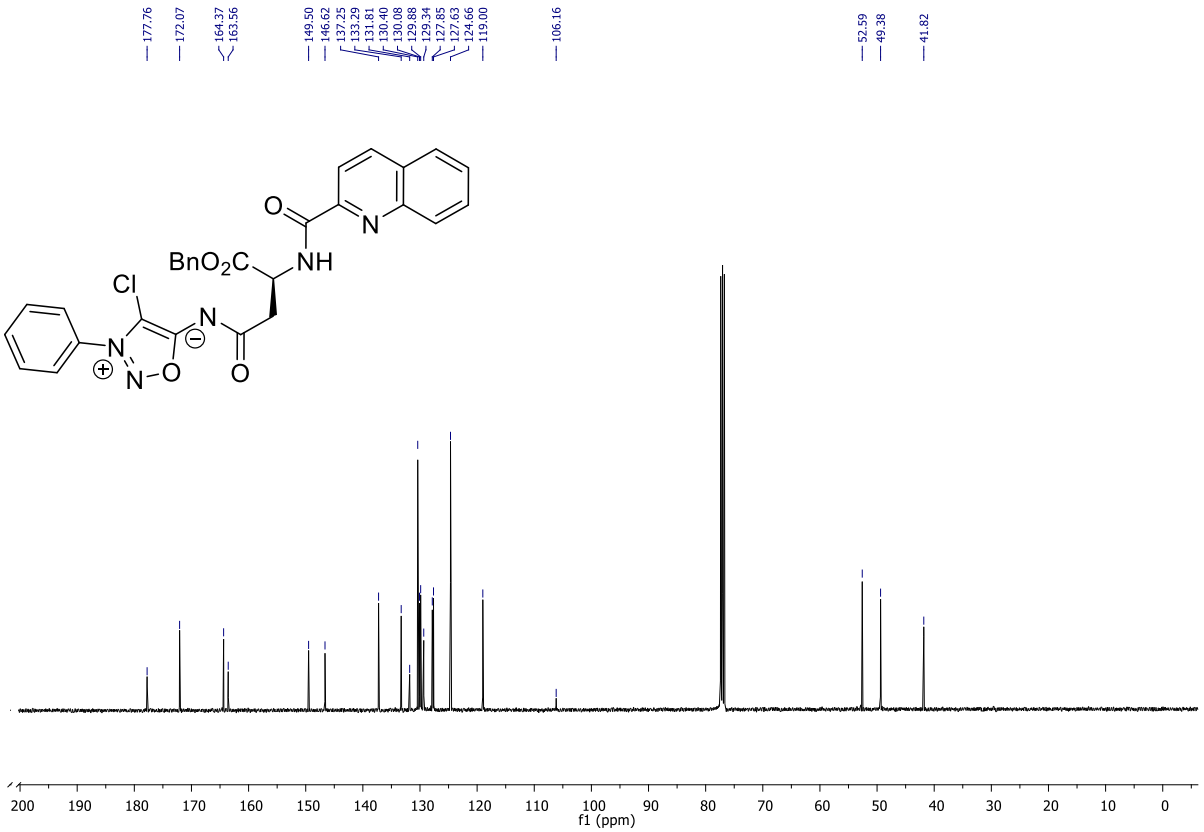
^{13}C NMR (100 MHz, $CDCl_3$) (**IS3'**)



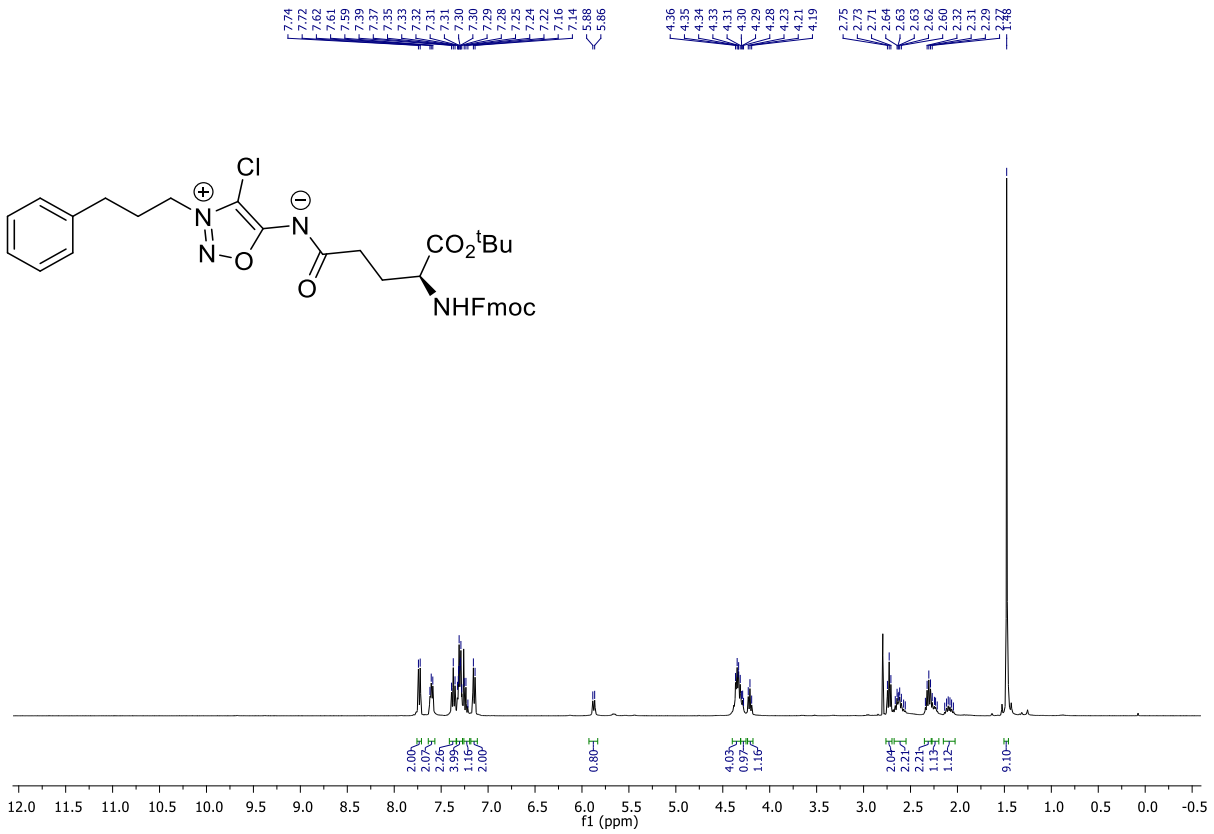
^{1}H NMR (400 MHz, $CDCl_3$) (**IS4'**)



^{13}C NMR (100 MHz, $CDCl_3$) (**IS4'**)

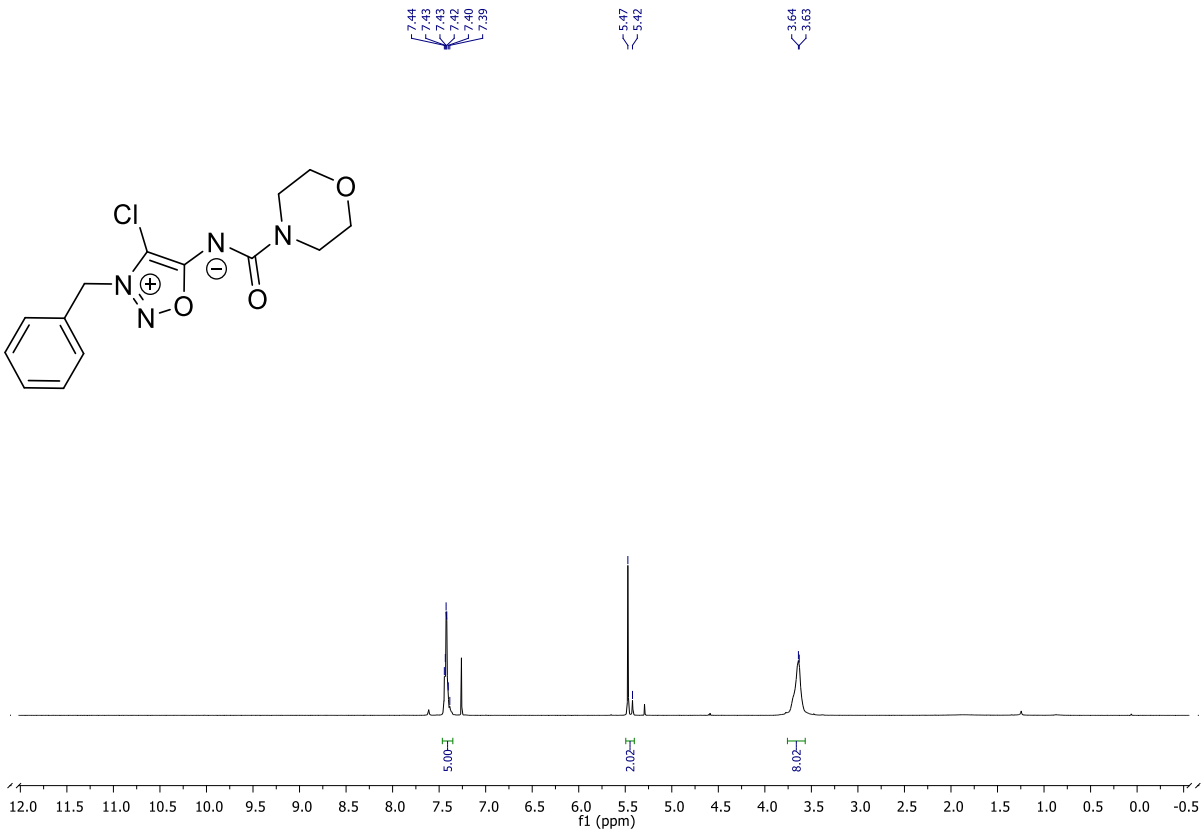


^{1}H NMR (400 MHz, $CDCl_3$) (**IS5'**)

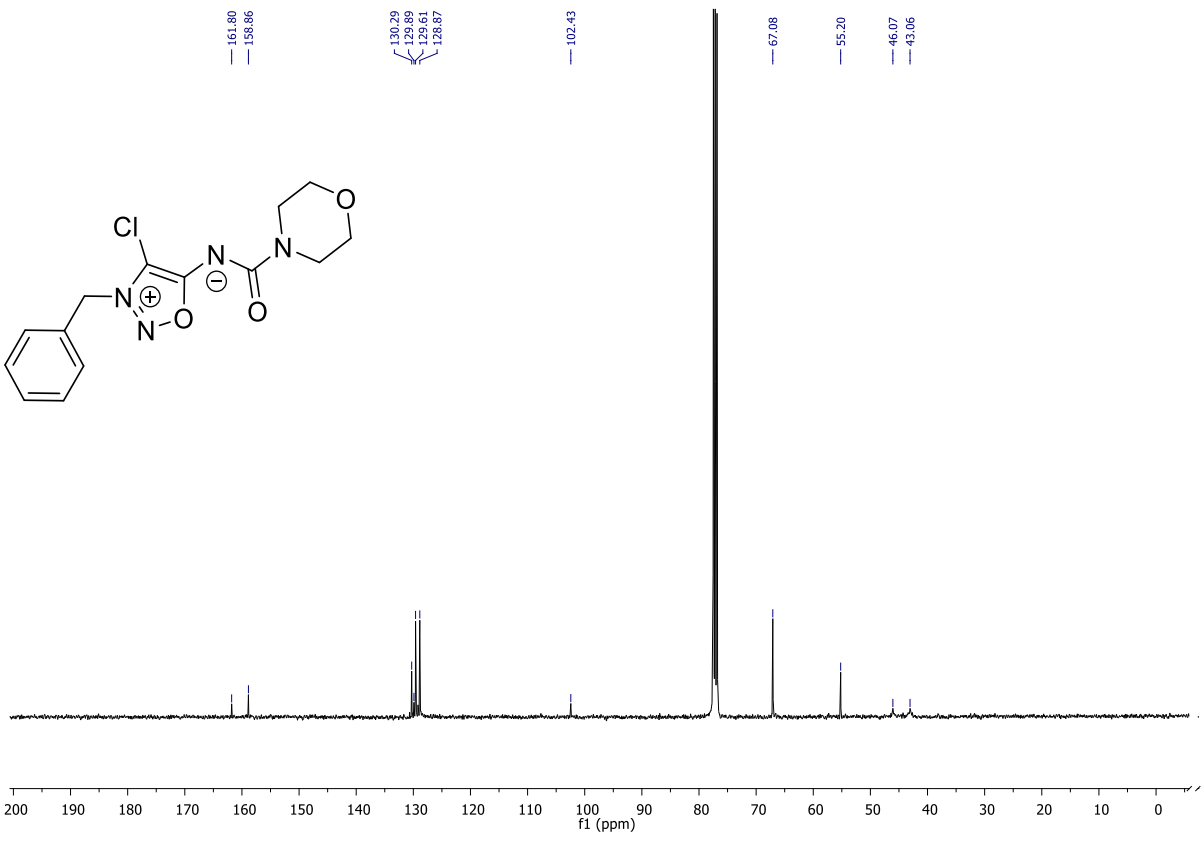


The product is not stable enough in solvent to afford a ^{13}C NMR spectrum.

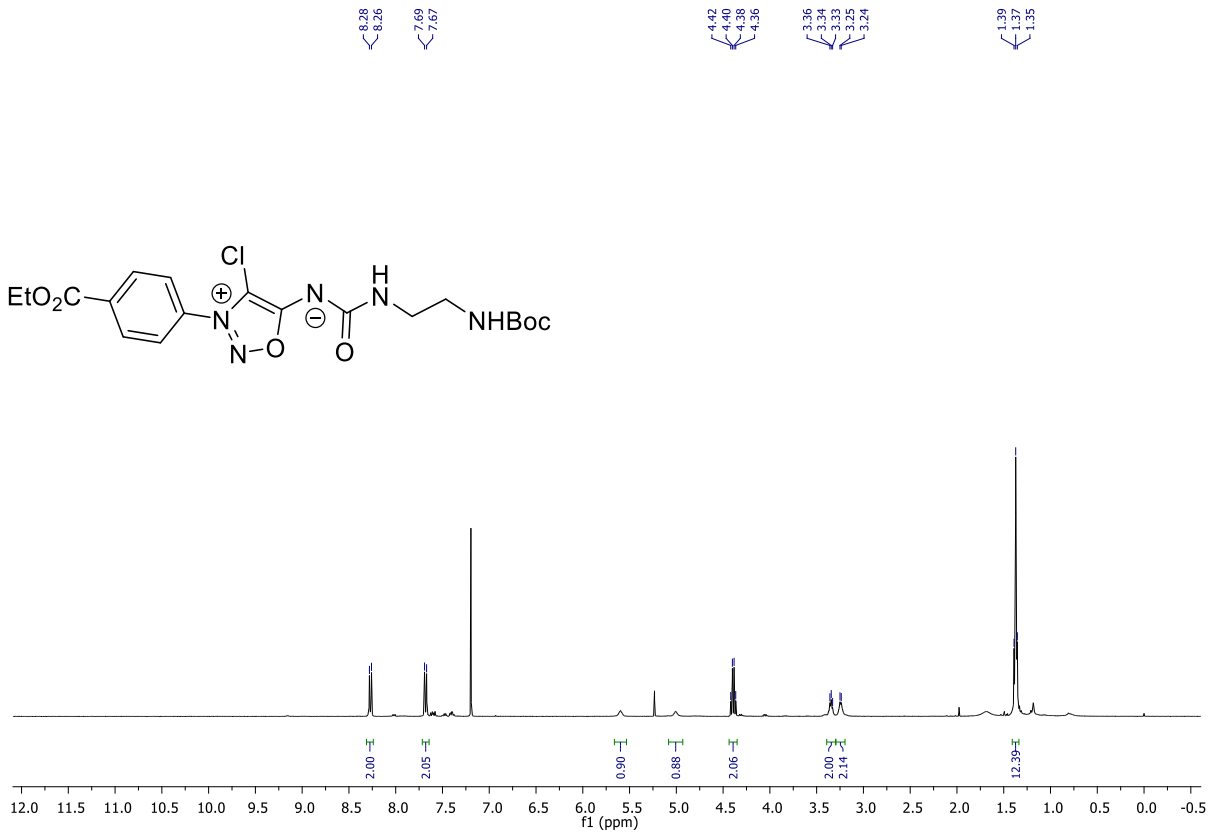
^{1}H NMR (400 MHz, $CDCl_3$) (**IS6'**)



^{13}C NMR (100 MHz, $CDCl_3$) (**IS6'**)

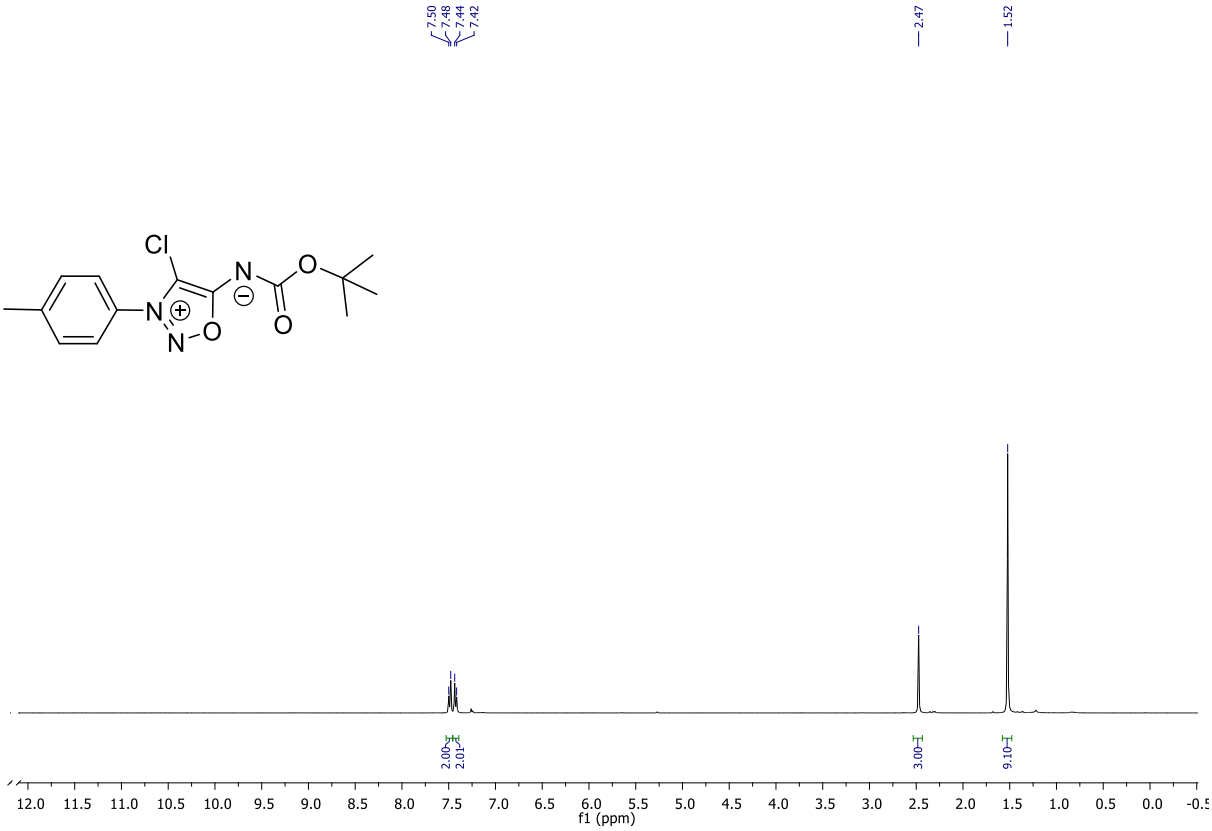


^{1}H NMR (400 MHz, $CDCl_3$) (**IS7'**)

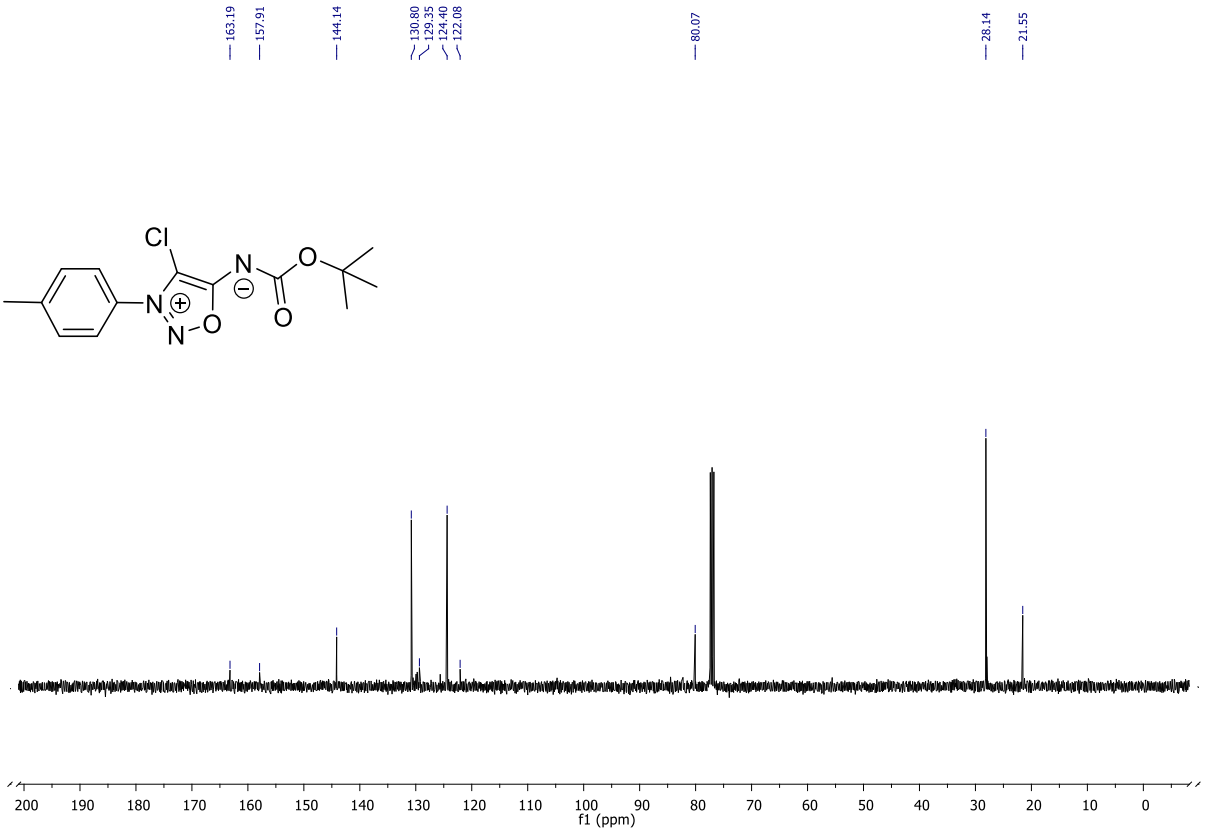


The product is not stable enough in solvent to afford a ^{13}C NMR spectrum.

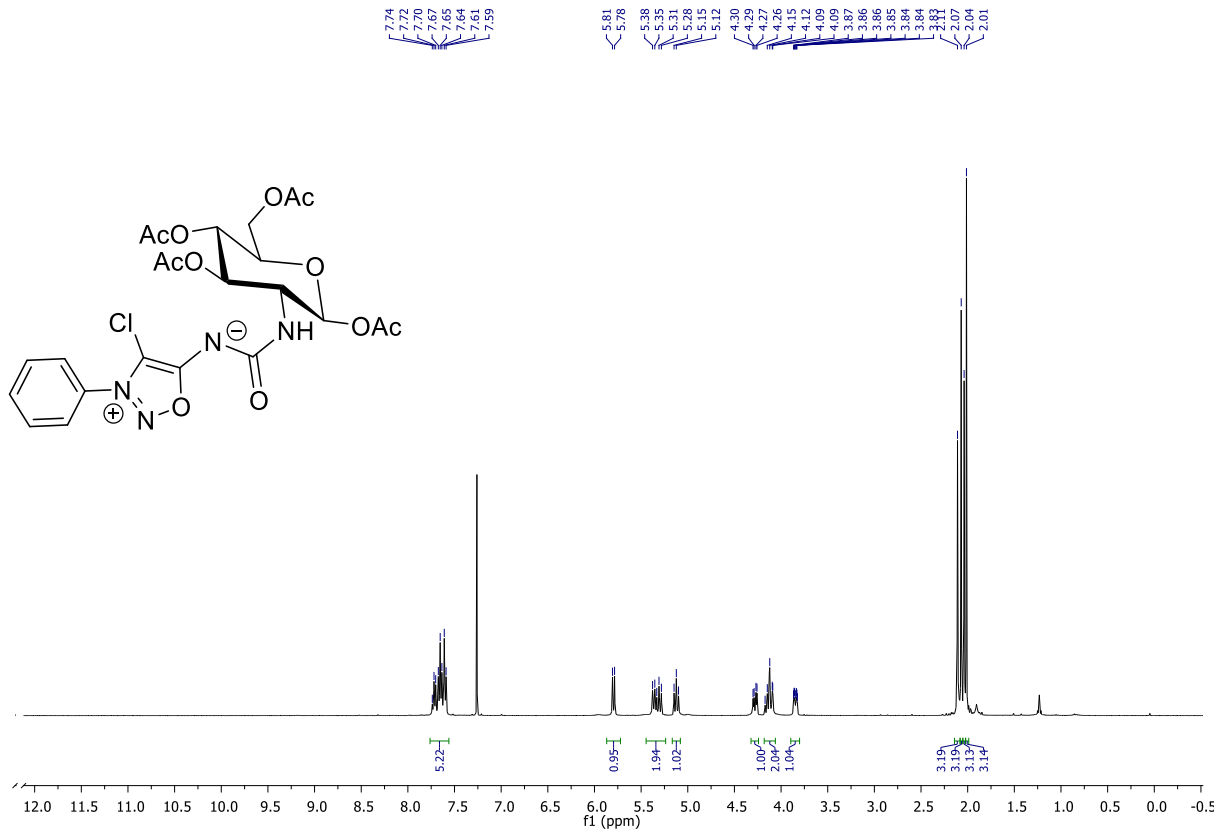
^{1}H NMR (400 MHz, $CDCl_3$) (**IS8'**)



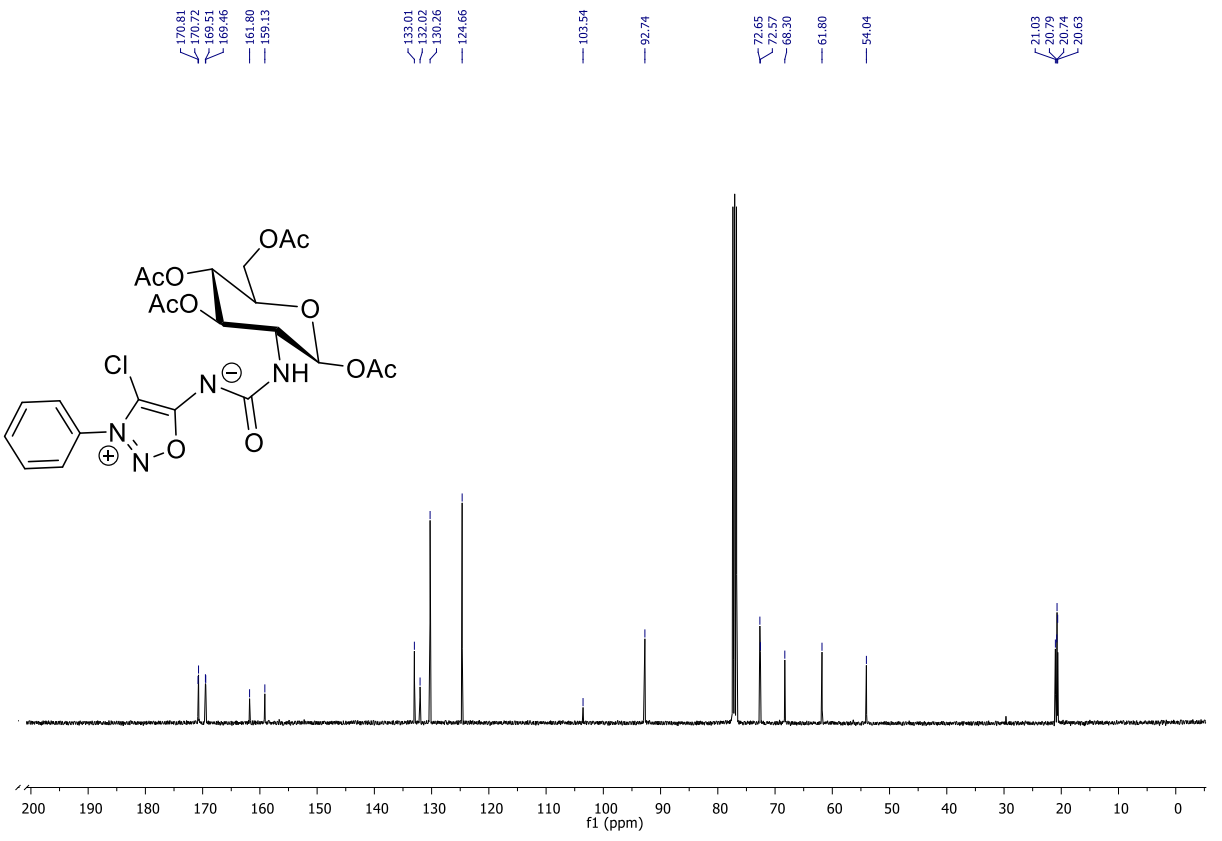
^{13}C NMR (100 MHz, $CDCl_3$) (**IS8'**)



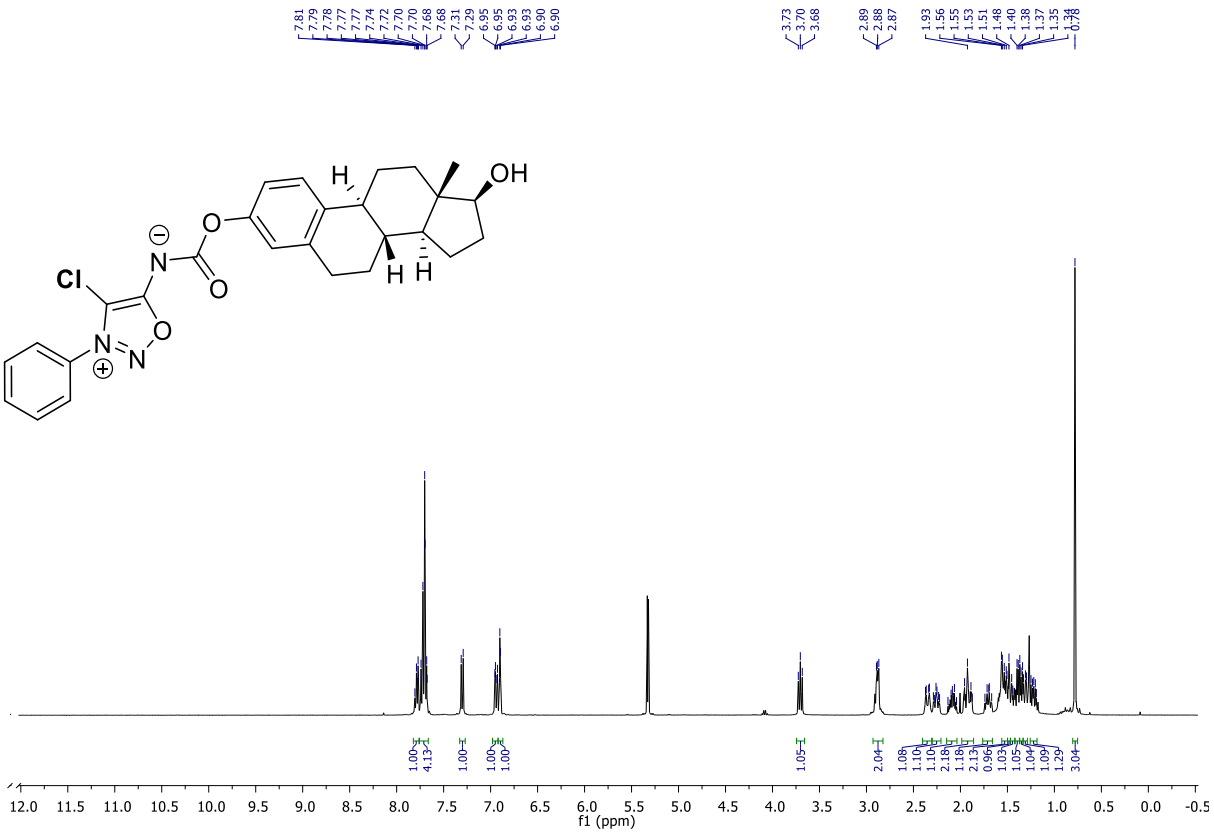
^{1}H NMR (400 MHz, $CDCl_3$) (**IS9'**)



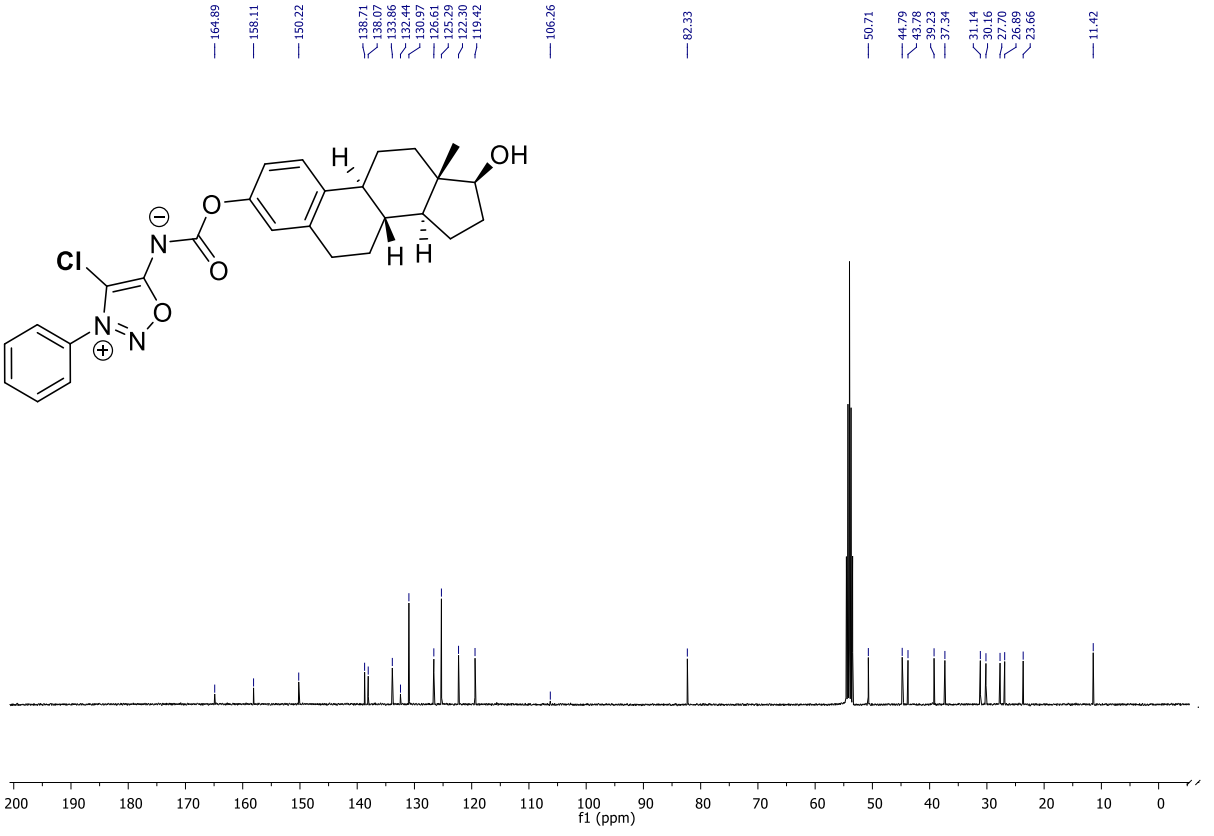
^{13}C NMR (100 MHz, $CDCl_3$) (**IS9'**)



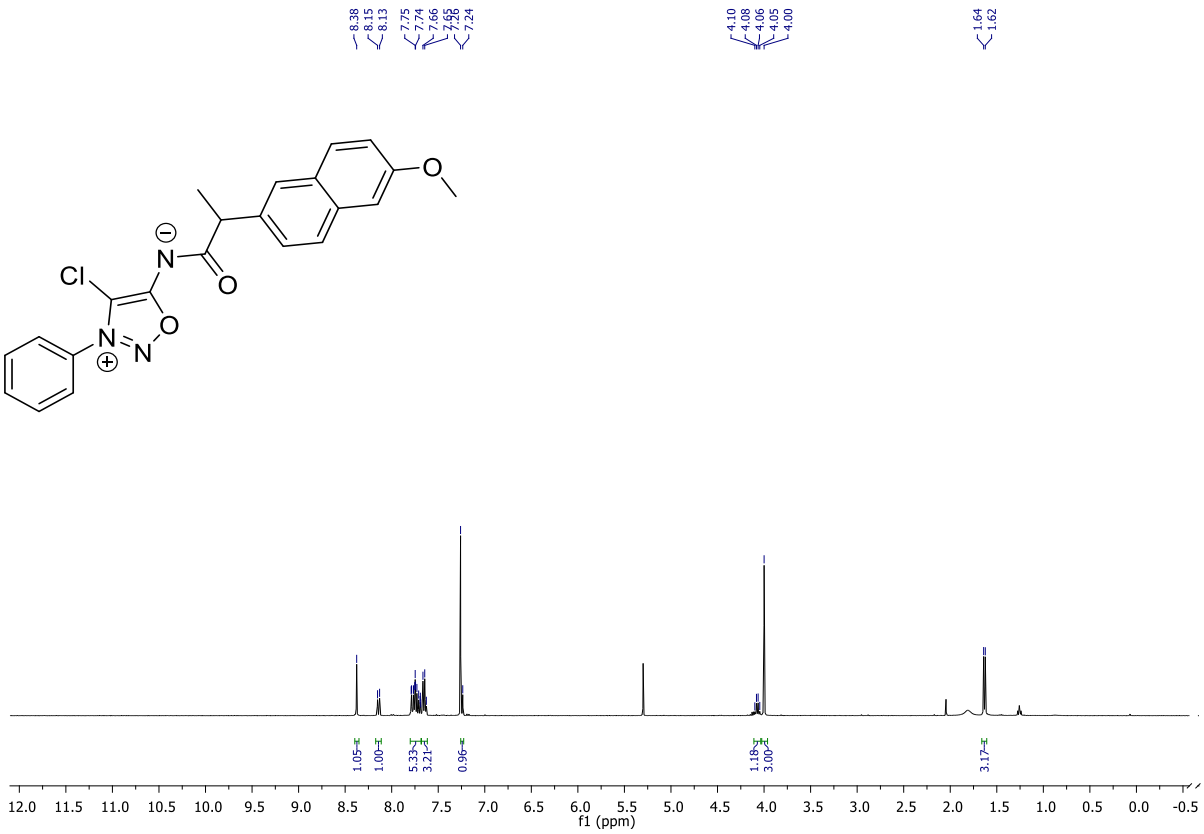
^{1}H NMR (400 MHz, CD_2Cl_2) (**IS10'**)



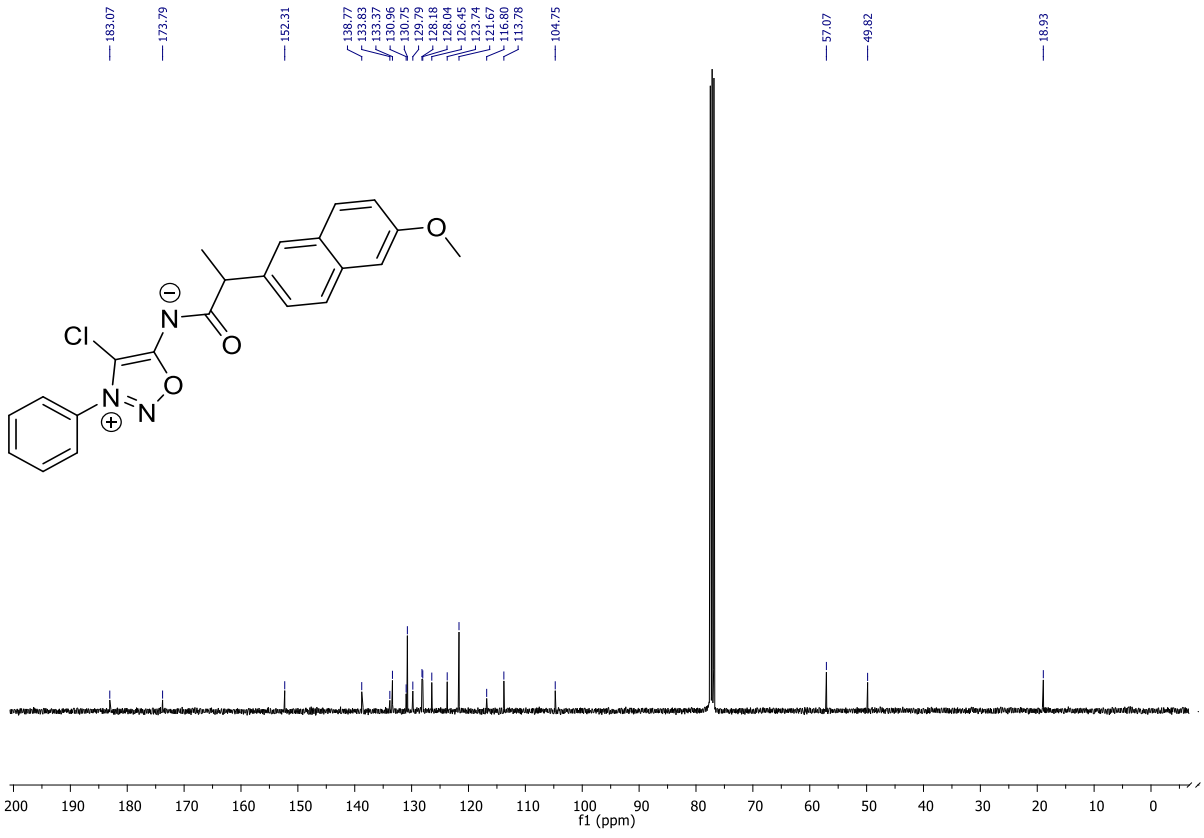
^{13}C NMR (100 MHz, CD_2Cl_2) (**IS10'**)



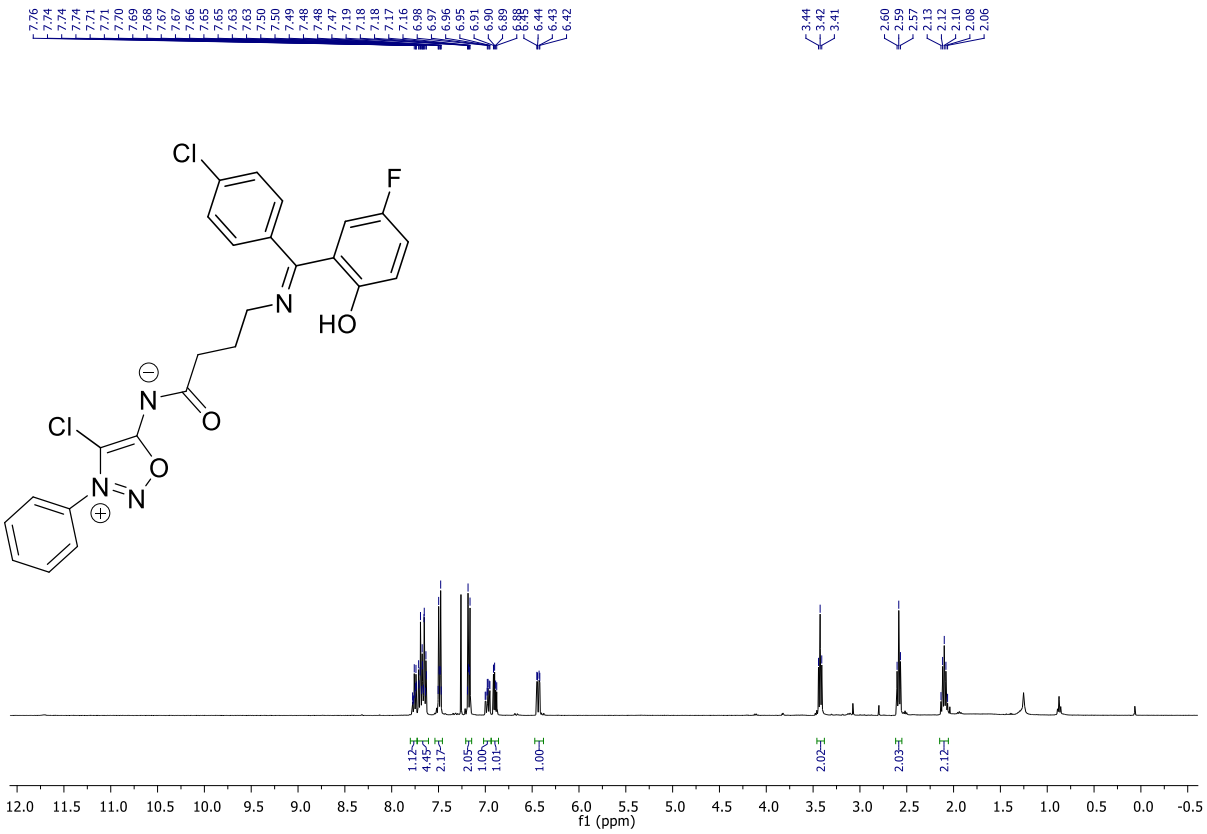
^{1}H NMR (400 MHz, $CDCl_3$) (**IS11'**)



^{13}C NMR (100 MHz, $CDCl_3$) (**IS11'**)

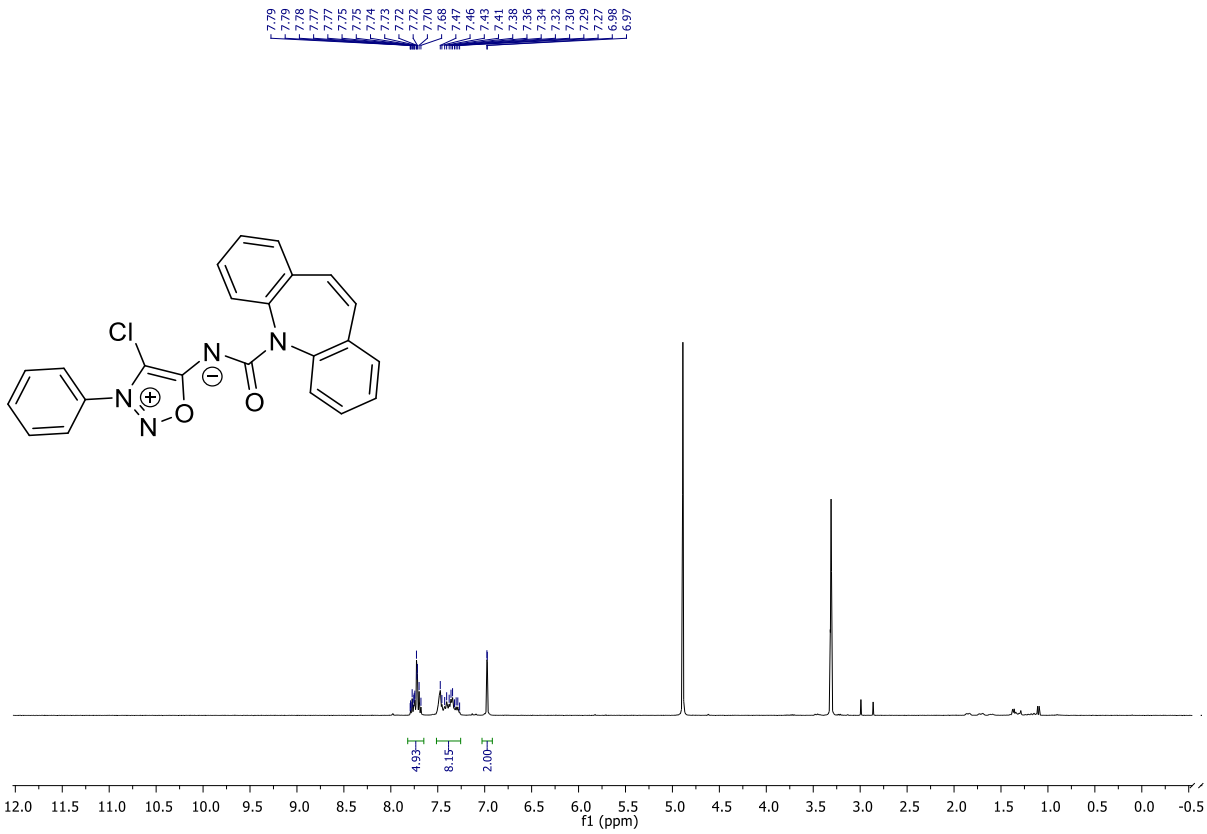


^{1}H NMR (400 MHz, $CDCl_3$) (**IS13'**)

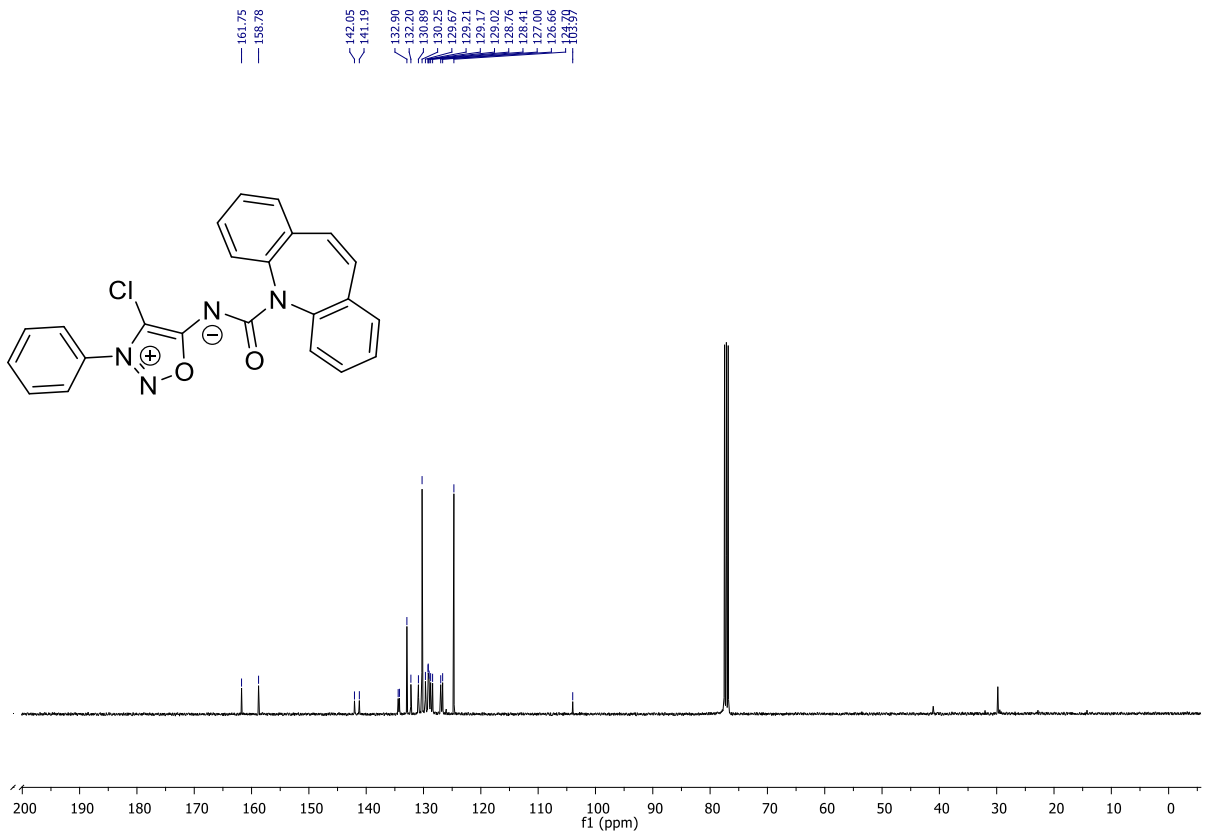


The product is not stable enough to afford a ^{13}C NMR.

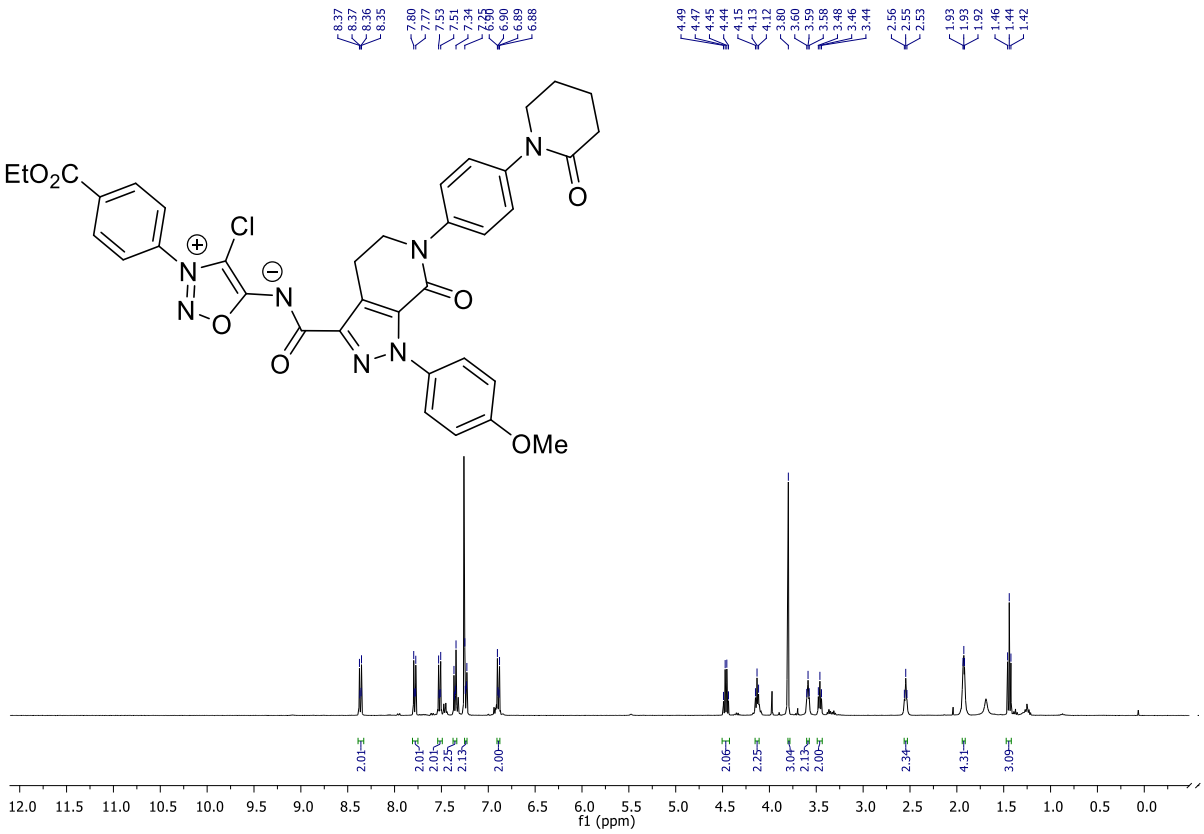
^{1}H NMR (400 MHz, MeOD) (**IS12'**)



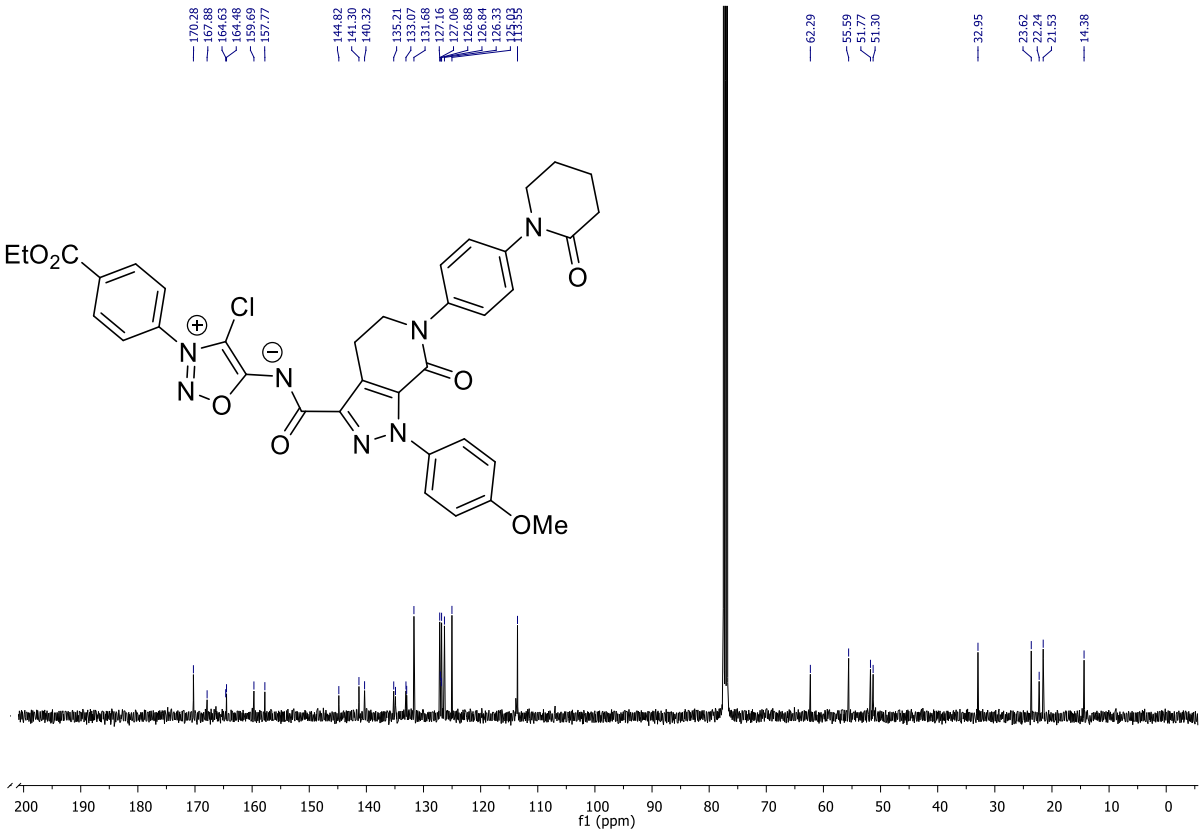
^{13}C NMR (100 MHz, $CDCl_3$) (**IS12'**)



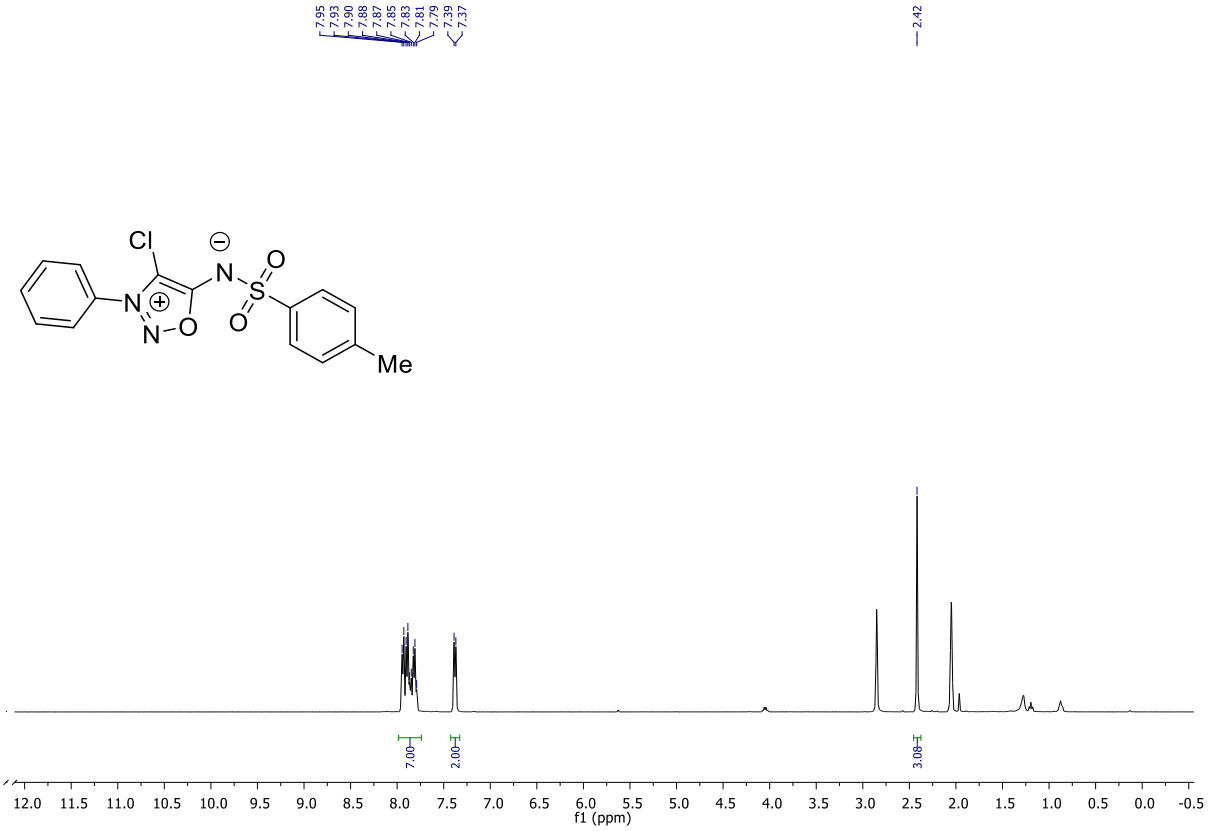
^{1}H NMR (400 MHz, $CDCl_3$) (**IS14'**)



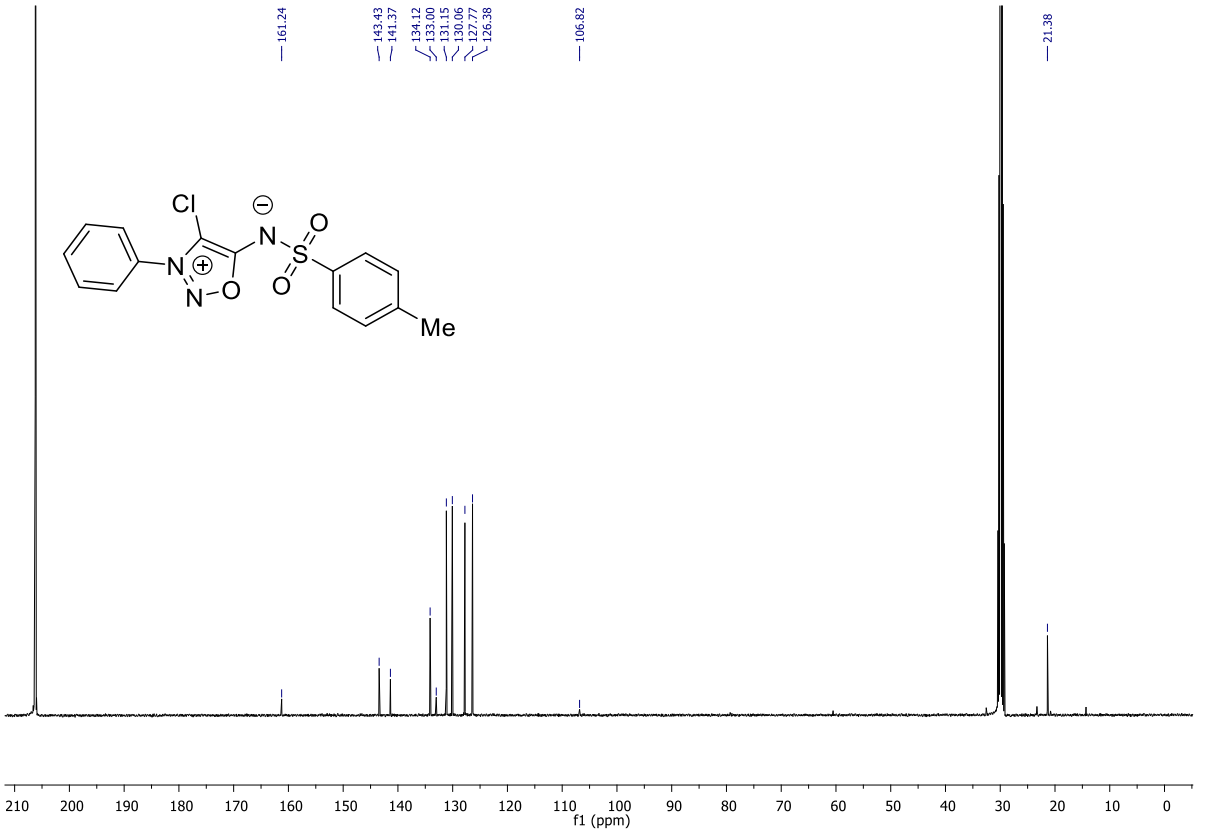
^{13}C NMR (100 MHz, $CDCl_3$) (**IS14'**)



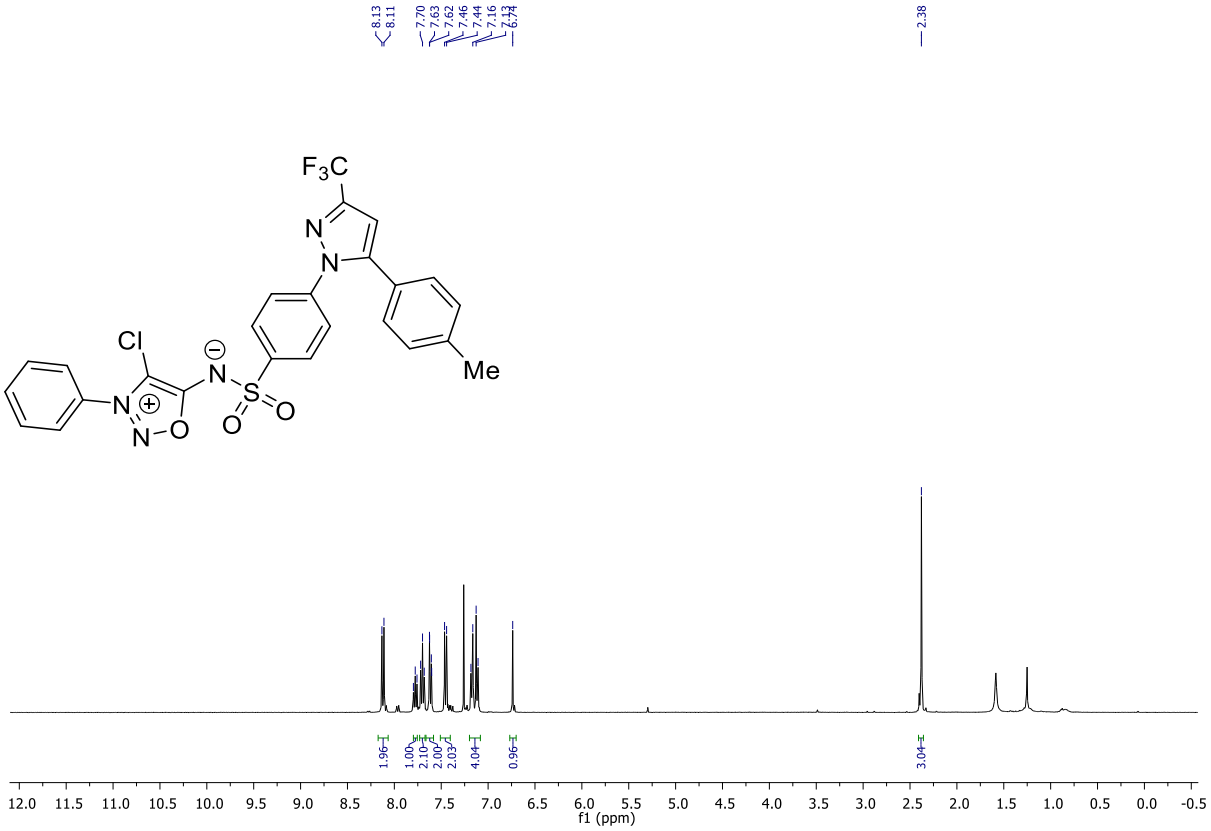
^{1}H NMR (400 MHz, Acetone-d_6) (**IS15'**)



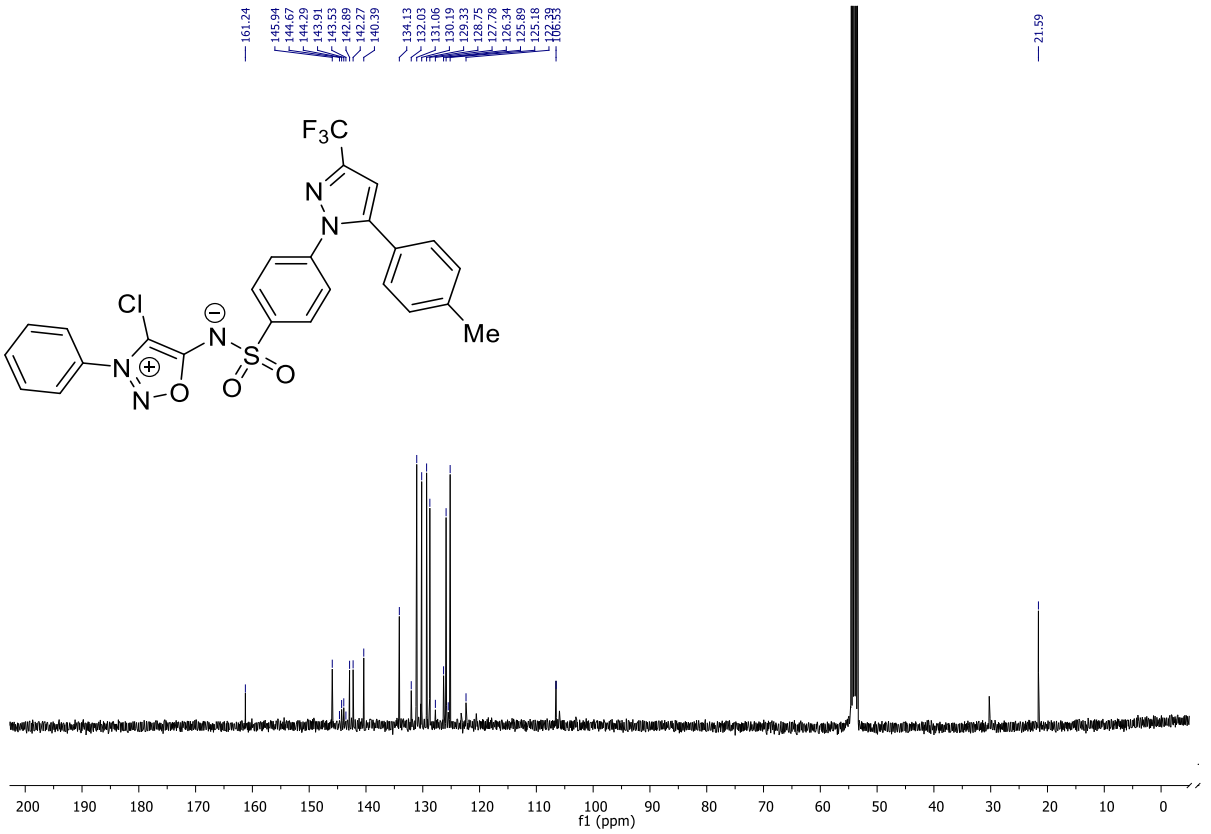
^{13}C NMR (100 MHz, Acetone-d_6) (**IS15'**)



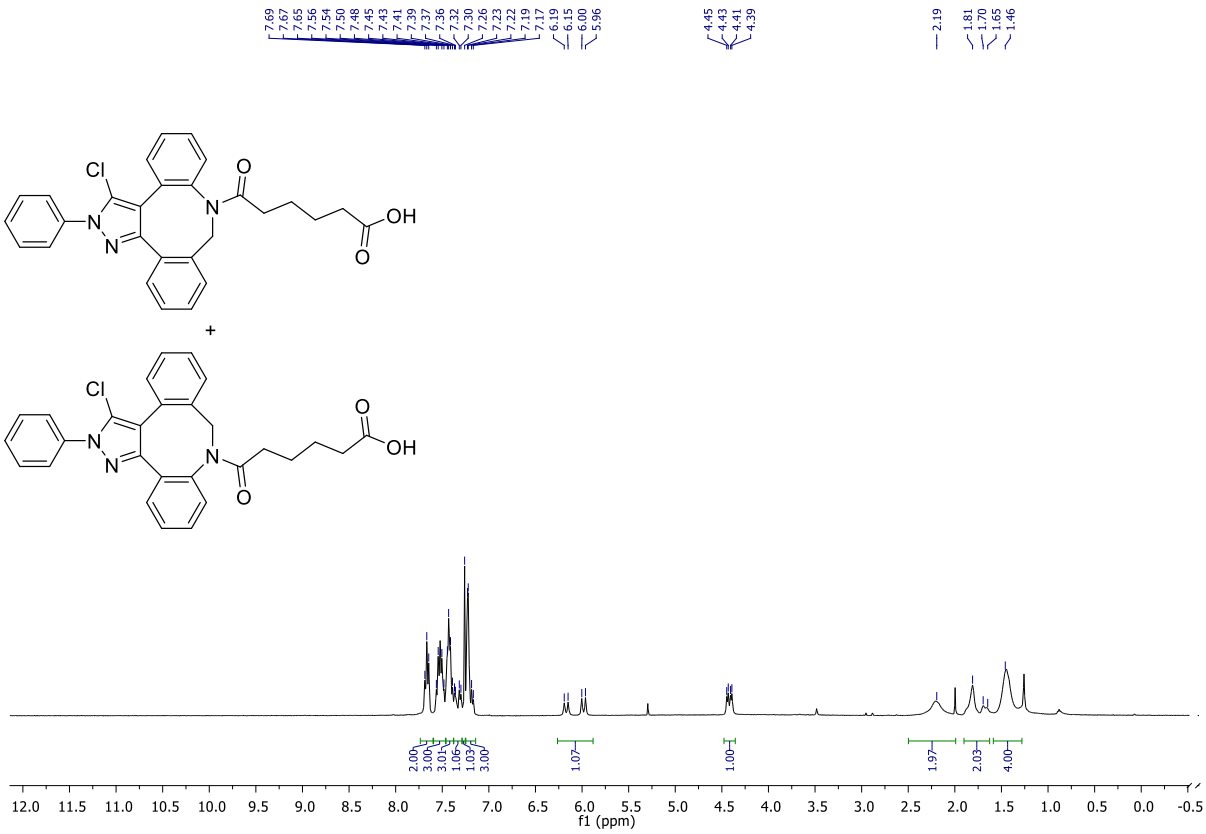
^{1}H NMR (400 MHz, $CDCl_3$) (**IS16'**)



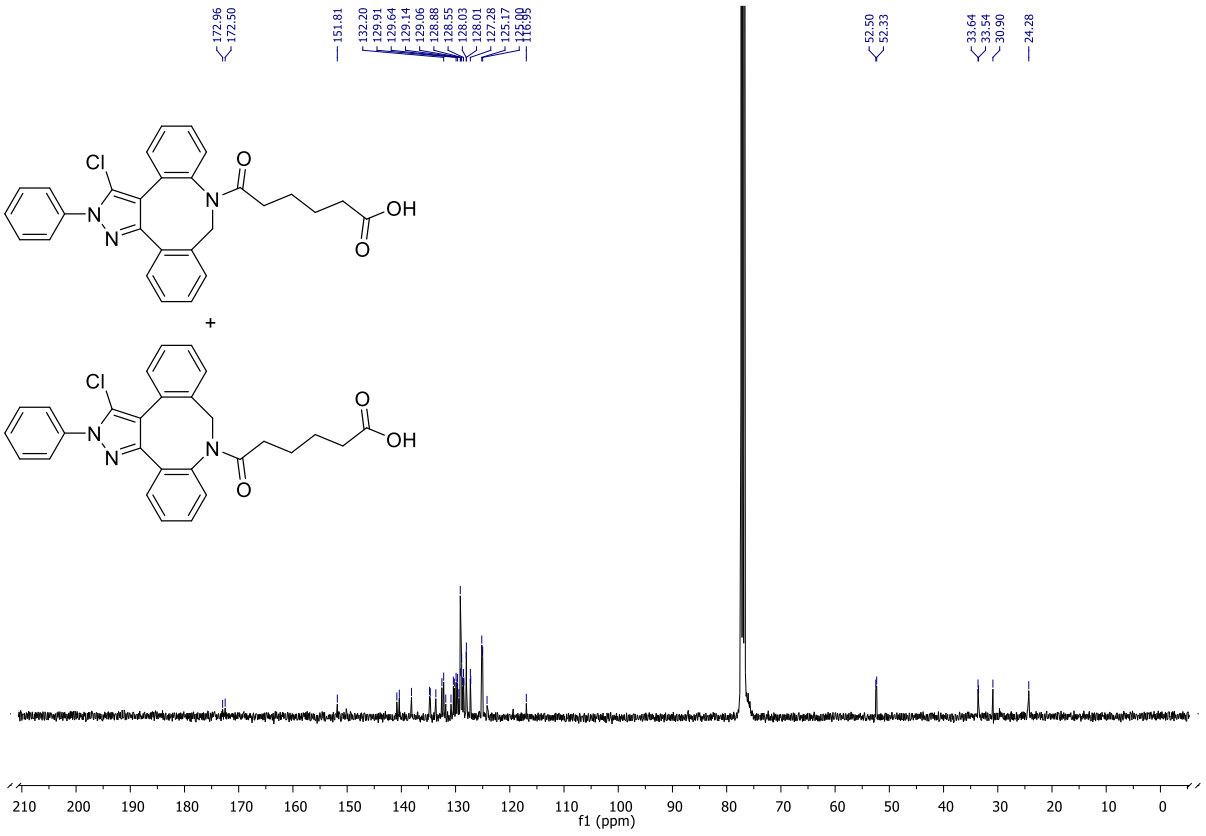
^{13}C NMR (100 MHz, $CDCl_3$) (**IS16'**)



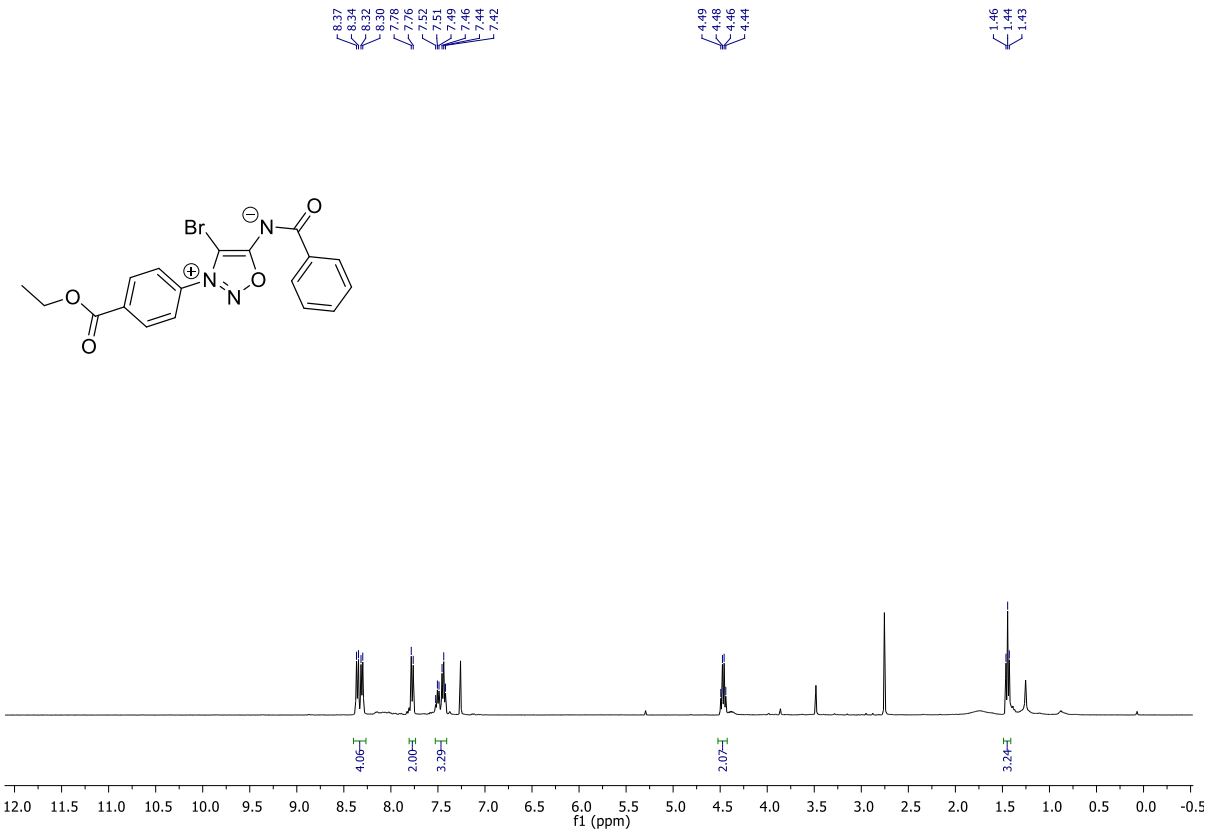
^{1}H NMR (400 MHz, $CDCl_3$) (**Pyrazole**)



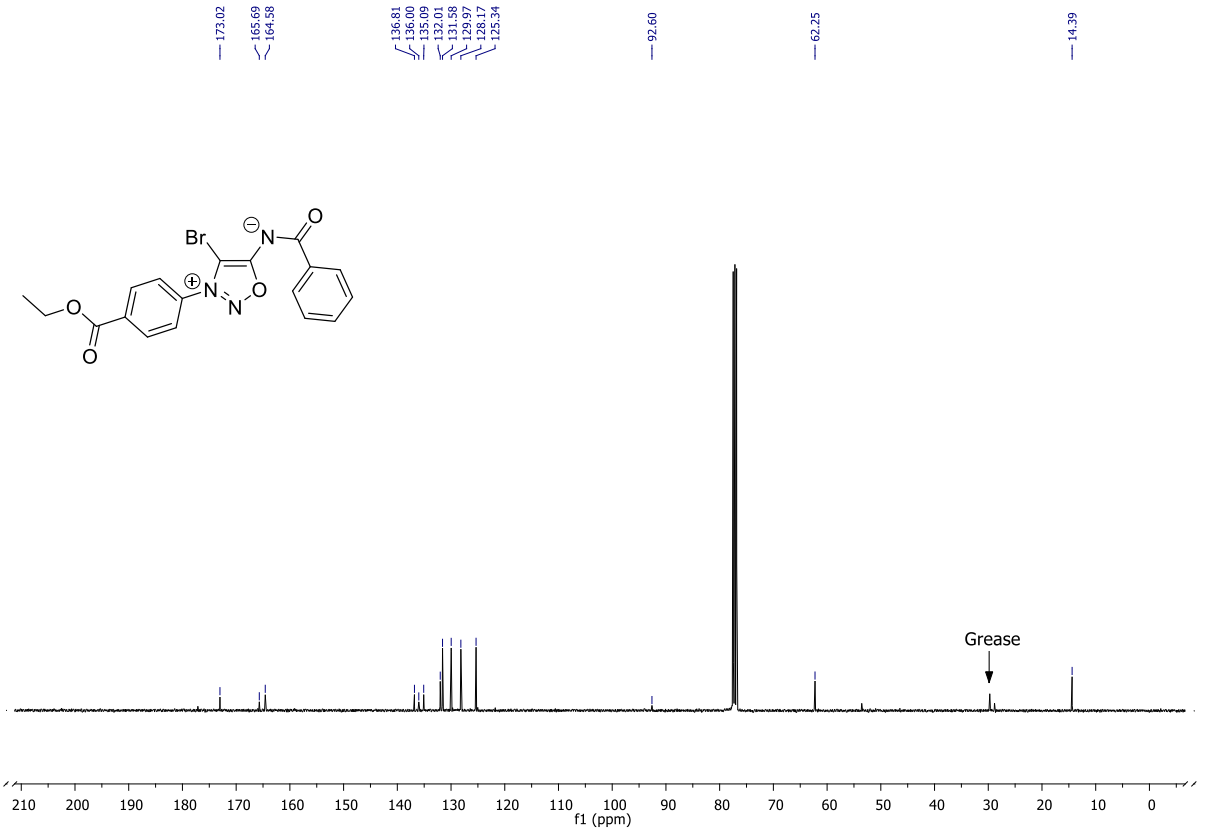
^{13}C NMR (100 MHz, $CDCl_3$) (**Pyrazole**)



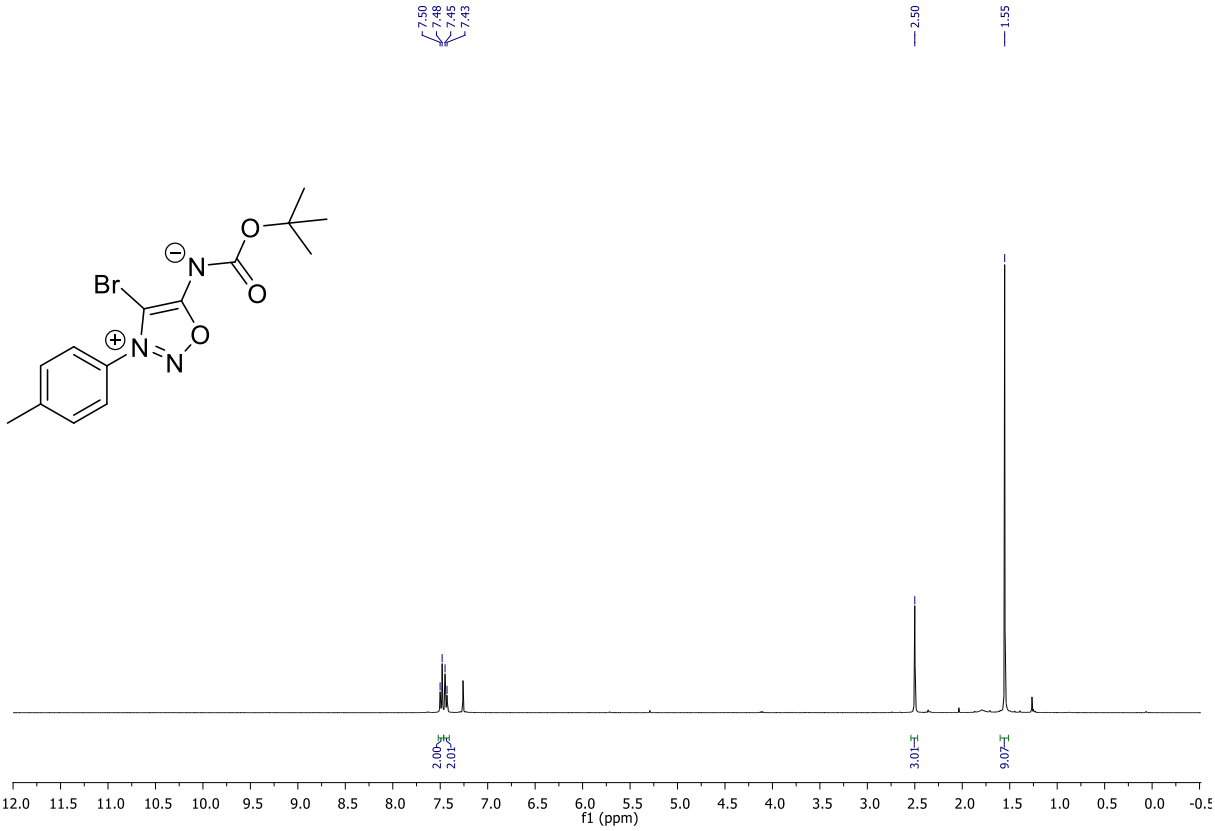
^{1}H NMR (400 MHz, $CDCl_3$) (**IS3''**)



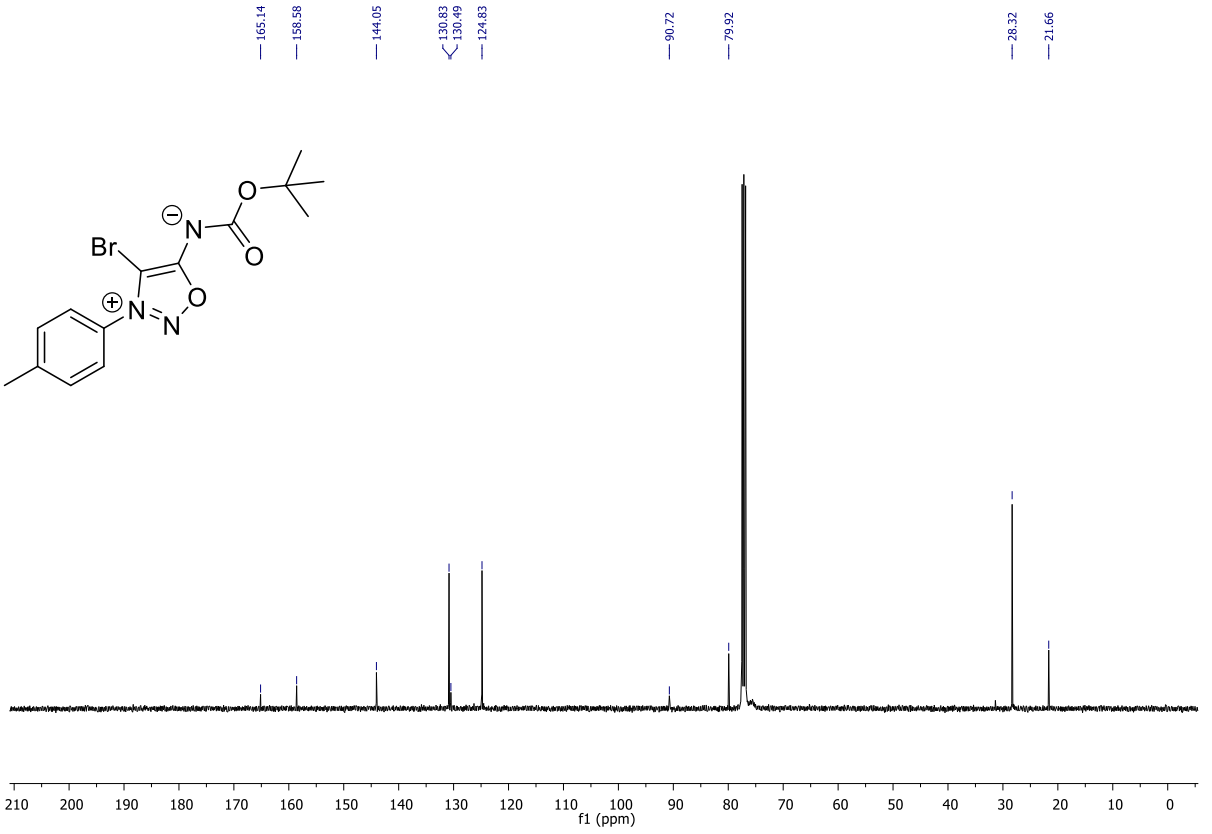
^{13}C NMR (100 MHz, $CDCl_3$) (**IS3''**)



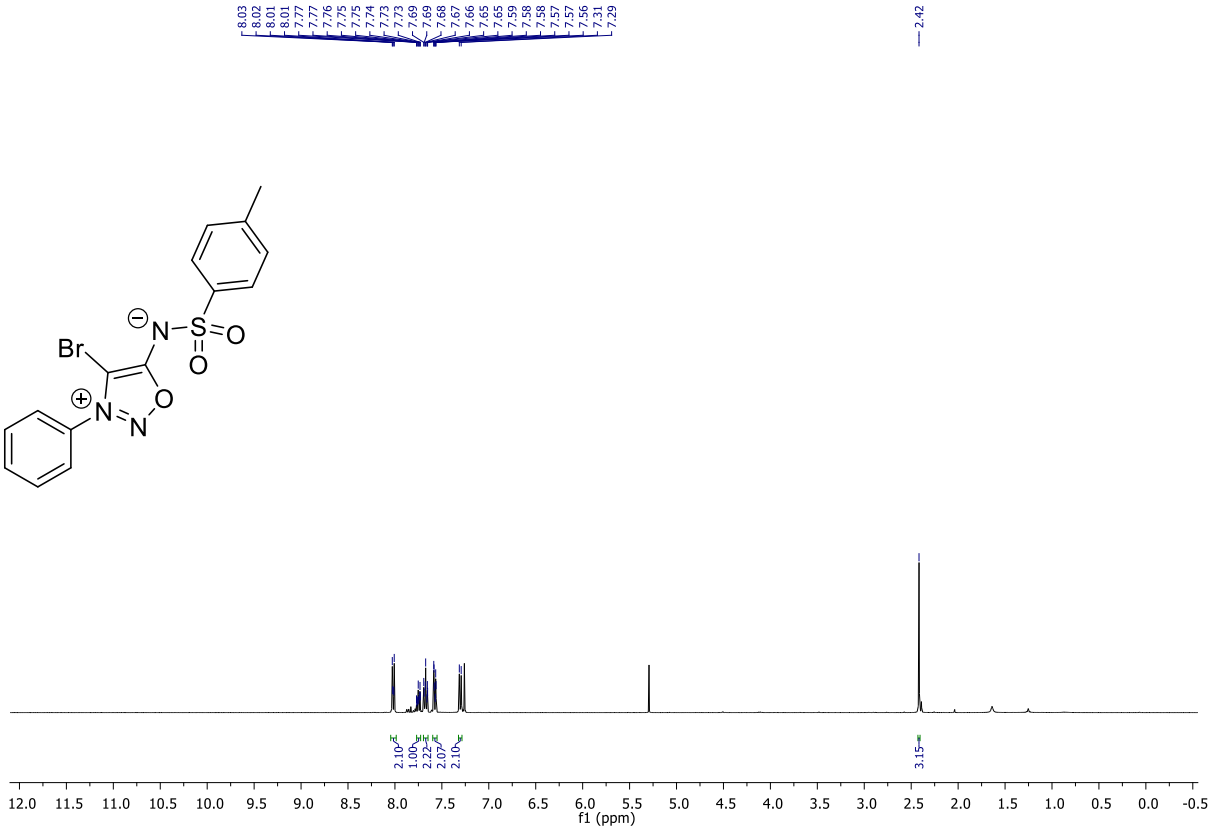
^{1}H NMR (400 MHz, $CDCl_3$) (**IS8''**)



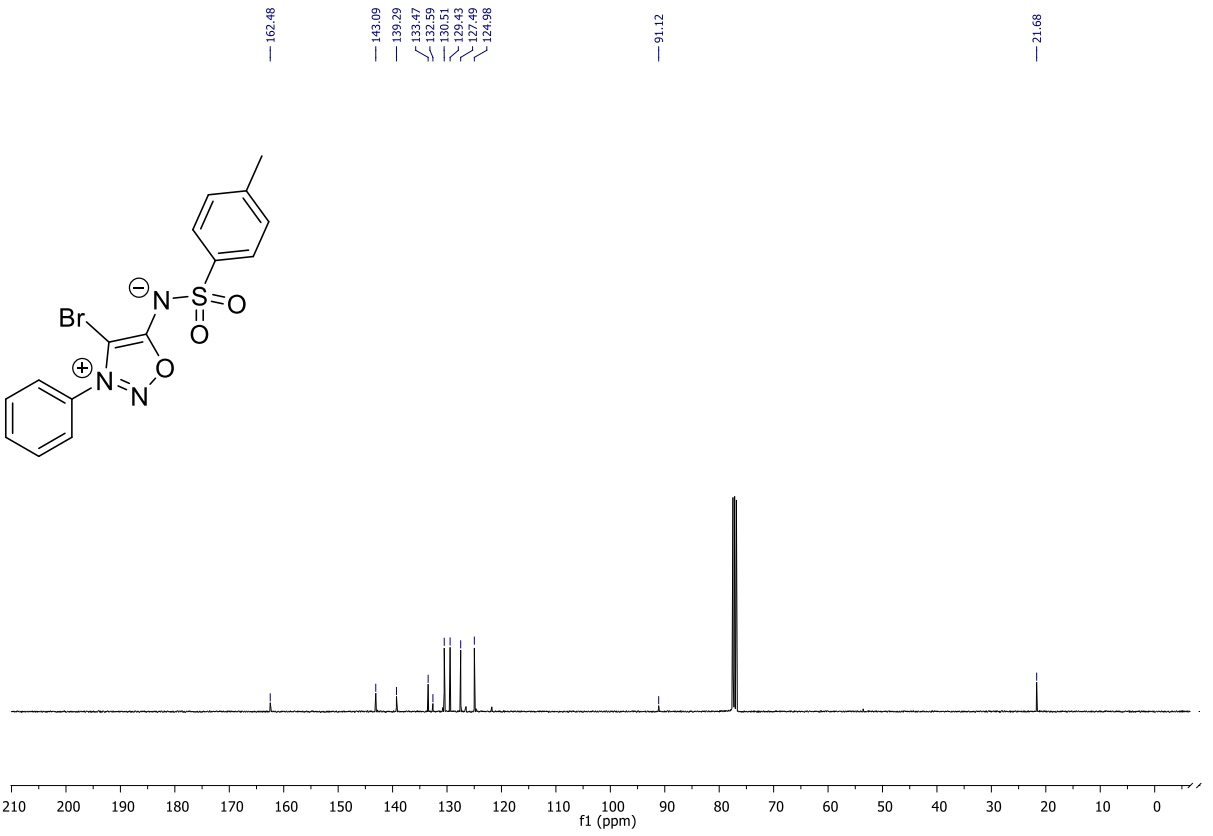
^{13}C NMR (100 MHz, $CDCl_3$) (**IS8''**)



^{1}H NMR (400 MHz, $CDCl_3$) (**IS15''**)



^{13}C NMR (100 MHz, $CDCl_3$) (**IS15''**)



VI. DFT calculations

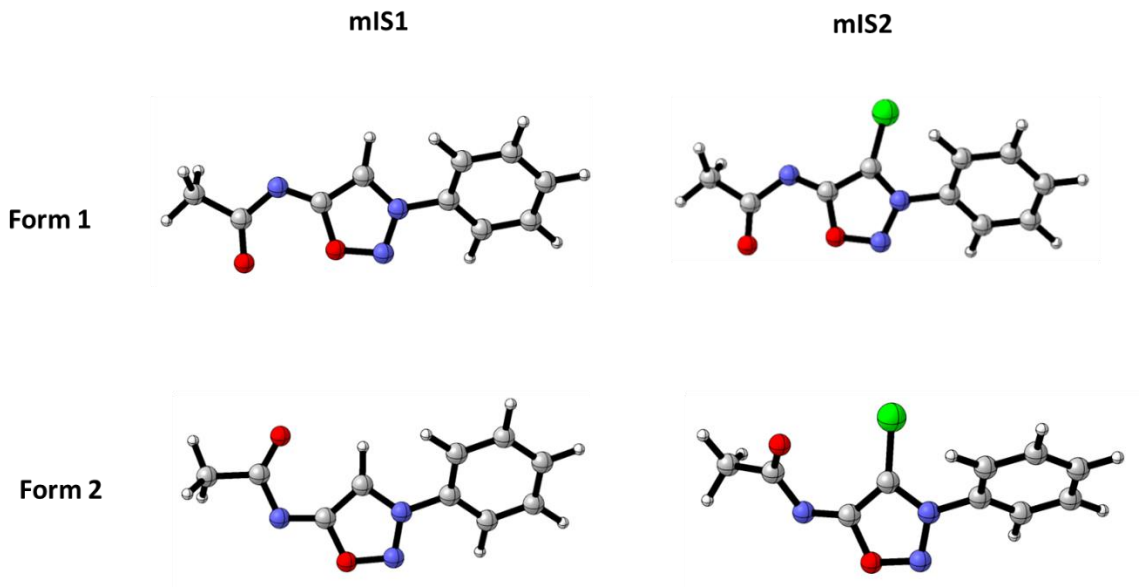
Computational Details

Calculations were performed with the Gaussian 16 package. Geometry optimization of all the minima and transition structures was carried out at the M06-2X level of theory with the 6-31+G(d,p) basis set and the CPCM solvation model for water. The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum or a saddle-point and to obtain its zero-point, enthalpy, and free energy corrections. These corrections were obtained with a standard state of 298 K and 1 atm, using Grimme's quasiharmonic scheme for the treatment of small (<100 cm^{-1}) frequencies,[3] using CYLview 2.0.[4]

Geometry optimization of the model iminosydnone mIS1-2 and DBCO:

For both model iminosydnones, two isomers displaying the amide carbonyl in a different orientation (forms 1 and 2) were considered and their geometries optimized at the M06-2X/6-31+G(d,p)/CPCM(H_2O) level of theory. For **mIS1**, form 2 is 3.5 kcal/mol more stable than form 1, while for **mIS2**, form 1 is more stable by 1.3 kcal/mol.

Optimized geometry of the model iminosydnones:



[3] Grimme, S. *Chem. - Eur. J.* **2012**, *18*, 9955–9964.
[4] CYLview20; Legault, C. Y., Université de Sherbrooke, 2020 (http://www.cylview.org)

Cartesian Coordinates of mIS and DBCO:

mIS1 form 1

C -3.97486 1.29062 -0.35062
C -4.73642 0.20418 0.08048
C -4.11538 -0.98439 0.46599
C -2.72818 -1.09572 0.42791
C -1.99369 0.00228 -0.00780
C -2.58650 1.19673 -0.40218
N -0.55798 -0.10130 -0.05425
N -0.02702 -1.20926 -0.46233
O 1.30406 -1.00542 -0.37526
C 1.58790 0.26121 0.08233
C 0.33190 0.84560 0.29141
N 2.77872 0.77077 0.27306
H -4.45872 2.21137 -0.65665
H -5.81758 0.28420 0.11661
H -4.70864 -1.82575 0.80639
H -2.22358 -2.00347 0.73876
H -1.98268 2.02492 -0.75760
H 0.05536 1.80922 0.68206
C 5.18571 0.80678 0.30046
H 5.22397 1.68817 -0.34569
C 3.91296 0.03433 0.03386
O 3.94659 -1.13418 -0.35733
H 6.05445 0.17578 0.11579
H 5.19561 1.16114 1.33462

mIS1 form 2

C 3.50731 -1.58471 -0.45293
C 4.46418 -0.75651 0.13411
C 4.10294 0.49490 0.63451
C 2.78199 0.92735 0.55615
C 1.84929 0.08261 -0.03685
C 2.18217 -1.16746 -0.54711
N 0.47967 0.51857 -0.12810
N 0.23750 1.75653 -0.40138
O -1.10270 1.85089 -0.39894
C -1.69468 0.64280 -0.13149
C -0.62421 -0.24302 0.04900
N -3.00547 0.62028 -0.10410
H 3.79014 -2.55428 -0.84725
H 5.49480 -1.08779 0.20269
H 4.84672 1.13474 1.09613
H 2.47597 1.88803 0.95458
H 1.43182 -1.79064 -1.02156
H -0.59742 -1.28308 0.31390
C -5.08869 -0.56846 0.17962
H -5.43919 0.15729 0.91836
C -3.57892 -0.59662 0.16715
O -2.95370 -1.64053 0.38491
H -5.48273 -1.55666 0.41416
H -5.45906 -0.24351 -0.79661

mIS2 form 1

C 4.01841 0.64617 0.90338
C 4.74072 -0.14528 0.00893
C 4.08251 -1.02514 -0.85029
C 2.69299 -1.11859 -0.82574
C 2.00087 -0.31731 0.07460
C 2.62925 0.56539 0.94593
N 0.56203 -0.42296 0.11046
N 0.03441 -1.58972 0.32117
O -1.30140 -1.38191 0.27218
C -1.60372 -0.06689 0.03715
C -0.34596 0.55480 -0.06634
N -2.78494 0.47345 -0.07193
H 4.53431 1.32360 1.57449
H 5.82292 -0.07598 -0.01737
H 4.64705 -1.63712 -1.54474
H 2.15521 -1.78665 -1.48937
H 2.05105 1.16100 1.64422
C -5.19442 0.51227 -0.11048
H -5.23575 1.27953 0.66757
C -3.92481 -0.29316 0.03709
O -3.95243 -1.50739 0.23432
H -6.06395 -0.13947 -0.03428
H -5.19661 1.02674 -1.07509
Cl 0.00358 2.16846 -0.42475

mIS2 form 2

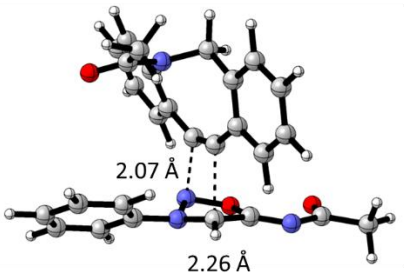
C -3.67547 -1.22351 0.80911
C -4.57763 -0.54732 -0.01397
C -4.16036 0.54165 -0.77910
C -2.83342 0.96258 -0.73143
C -1.95859 0.26974 0.09688
C -2.34597 -0.81653 0.87364
N -0.58673 0.71345 0.16177
N -0.35497 1.95254 0.44984
O 0.98398 2.07115 0.40731
C 1.60079 0.89079 0.08739
C 0.53282 -0.01350 -0.06842
N 2.89491 0.90077 -0.06425
H -4.00554 -2.06530 1.40730
H -5.61190 -0.87132 -0.05821
H -4.86368 1.06292 -1.41871
H -2.47958 1.79924 -1.32365
H -1.63270 -1.31998 1.51761
C 4.99794 -0.23795 -0.41086
H 4.95489 -0.17242 -1.50195
C 3.59518 -0.26362 0.14599
O 3.16321 -1.23565 0.76728
H 5.53589 -1.13888 -0.11817
H 5.52544 0.64889 -0.05142
Cl 0.51032 -1.58638 -0.69037

DBCO model

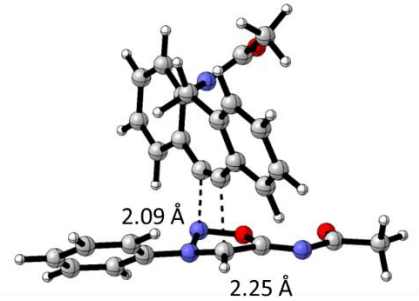
C -0.63546 -1.72895 -0.52545
C 0.57790 -1.77006 -0.48313
C -1.91739 -1.17431 -0.21872
C 1.85665 -1.20533 -0.18549
C -1.84725 -0.03507 0.62135
C 1.79296 0.14909 0.21949
C -0.51743 0.44661 1.18826
N 0.53651 0.84257 0.22100
C -3.03773 0.58954 0.98667
C -4.26850 0.11146 0.53230
C -4.32292 -1.00508 -0.30136
C -3.14794 -1.65083 -0.67835
C 3.08595 -1.87210 -0.20580
C 2.95892 0.80525 0.60235
C 4.18136 0.13573 0.57155
C 4.24535 -1.19890 0.16606
C 0.38688 1.89361 -0.64945
C -0.89874 2.68424 -0.57803
O 1.25799 2.17887 -1.46891
H -0.70576 1.28233 1.86924
H -0.08046 -0.35699 1.78651
H -3.00576 1.46208 1.63436
H -5.18325 0.61373 0.82943
H -5.27929 -1.37413 -0.65670
H -3.17584 -2.52289 -1.32302
H 3.12082 -2.91250 -0.51050
H 2.90221 1.84404 0.91134
H 5.08541 0.65759 0.86744
H 5.19865 -1.71630 0.14670
H -1.18343 2.92693 0.44811
H -0.75232 3.60308 -1.14370
H -1.71623 2.11467 -1.02854

Transition structures (TS) and activation free energies ($\Delta G^{\ddagger}_{water}$) for their reactions with DBCO

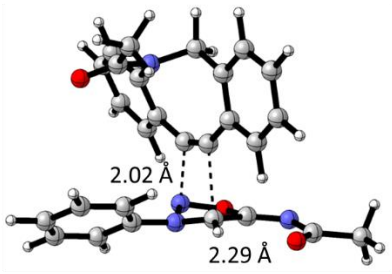
For each iminosydnone, we considered transition structures using both forms 1 and 2 with two conformations of the DBCO model. The resulting structures and activation free energies are shown below. The lowest-energy structures for **mIS1** use form 2, while for **mIS2** they use form 2, reproducing the above results.



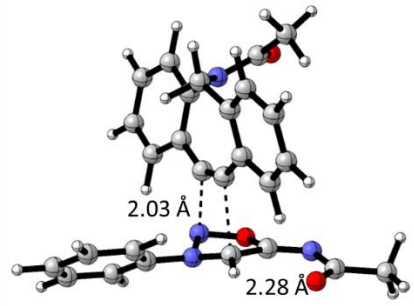
TS_{1a}: $\Delta G^{\ddagger}_{water}$ = 25.4 kcalmol^{-1}



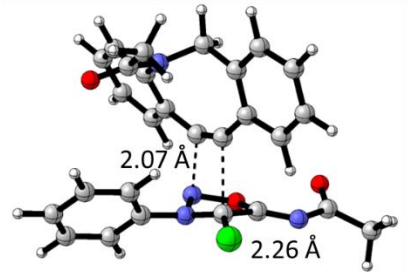
TS_{1b}: $\Delta G^{\ddagger}_{water}$ = 25.5 kcalmol^{-1}



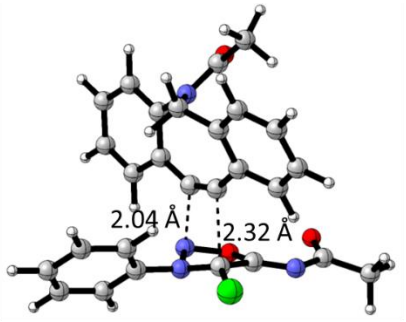
TS_{1c}: $\Delta G^{\ddagger}_{water}$ = 23.0 kcalmol^{-1}



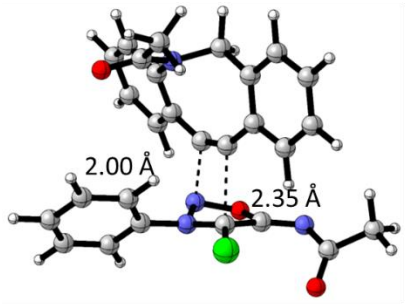
TS_{1d}: $\Delta G^{\ddagger}_{water}$ = 23.0 kcalmol^{-1}



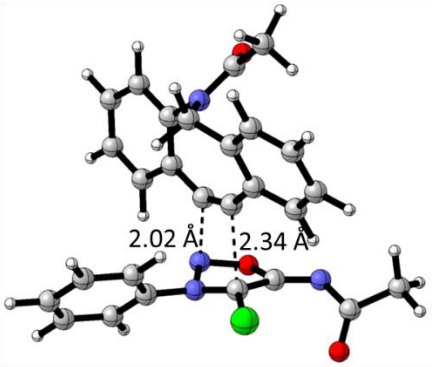
TS_{2a}: $\Delta G^{\ddagger}_{water}$ = 21.2 kcalmol^{-1}



TS_{2b}: $\Delta G^{\ddagger}_{water}$ = 20.5 kcalmol^{-1}



TS_{2c}: $\Delta G^{\ddagger}_{water}$ = 24.2 kcalmol^{-1}



TS_{2d}: $\Delta G^{\ddagger}_{water}$ = 23.4 kcalmol^{-1}

Cartesian coordinates for all TS:

TS_{1a} (mIS1 form 1 conf1)

N -0.62967 -2.03469 -0.99045
N -0.61486 -2.24026 0.32970
O -1.94336 -2.07113 0.70769
C -2.58752 -1.34356 -0.24212
C -1.62108 -1.17594 -1.29496
N -3.80469 -0.90951 -0.21969
C 0.61566 -2.17534 -1.67328
C 1.05473 -1.16145 -2.52204
C 2.27525 -1.32046 -3.17518
C 3.04388 -2.46400 -2.96141
C 2.59260 -3.46122 -2.09467
C 1.36866 -3.32582 -1.44669
C -4.59401 -1.06661 0.91656
C -0.67512 0.40947 0.00749
C -0.00890 -0.31897 0.78602
C -1.01989 1.74497 -0.43246
C 1.08147 -0.45029 1.71970
C -0.30540 2.83762 0.11302
C 2.02625 0.59491 1.74827
C 0.73751 2.64495 1.19421
N 1.84744 1.72108 0.88760
C -0.62095 4.12992 -0.30274
C -1.63097 4.36456 -1.23524
C -2.34295 3.29043 -1.76390
C -2.03797 1.99254 -1.36402
C 1.24560 -1.54026 2.58651
C 3.10992 0.54036 2.61969
C 3.26415 -0.54994 3.47277
C 2.32784 -1.58601 3.45867
C 2.74659 1.91930 -0.12724
C 2.57747 3.15650 -0.97730
O 3.64872 1.11335 -0.35010
H -1.82622 -0.86109 -2.30713
H 0.46804 -0.25830 -2.65810
H 2.62949 -0.53975 -3.83964
H 3.99592 -2.57842 -3.46877
H 3.18920 -4.35171 -1.92916
H 0.99267 -4.09555 -0.78149
H 1.14420 3.62068 1.48000
H 0.24958 2.23462 2.08252
H -0.06706 4.96832 0.11200
H -1.86016 5.37979 -1.54189
H -3.13700 3.45890 -2.48377
H -2.61564 1.16412 -1.75830
H 0.52205 -2.34703 2.56304
H 3.82748 1.35472 2.61849
H 4.11093 -0.58872 4.15003
H 2.44412 -2.43304 4.12663
H 2.37958 4.04946 -0.38025
H 3.49307 3.29333 -1.55067
H 1.73971 3.02240 -1.66799
O -4.24988 -1.64073 1.94205
C -5.96152 -0.44927 0.76511
H -6.47690 -0.90406 -0.08527
H -6.54281 -0.59307 1.67484
H -5.85937 0.61787 0.54920

TS_{1b} (mIS1 form 1 conf2)

N 2.11742 1.43914 -0.10540
N 1.78966 0.89865 -1.28160
O 0.90132 1.81563 -1.83423
C 0.38646 2.58984 -0.84417
C 1.08983 2.18334 0.34425
N -0.53076 3.49471 -0.94090
C 3.05958 0.71494 0.68415
C 2.77272 0.43512 2.01853
C 3.70577 -0.28225 2.76465
C 4.88941 -0.72406 2.17444
C 5.15043 -0.44609 0.83146
C 4.23644 0.28208 0.07596
C -1.17485 3.72877 -2.15300
C -0.25171 0.38044 0.36838
C 0.31077 -0.34250 -0.49158
C -1.22240 0.50634 1.43377
C 0.41274 -1.62133 -1.15318
C -1.76556 -0.68101 1.97510
C -0.59789 -2.56907 -0.88896
C -1.37481 -2.03359 1.42012
N -1.67760 -2.23506 -0.01410
C -2.64631 -0.59408 3.05211
C -3.02342 0.64125 3.57712
C -2.52157 1.81346 3.01354
C -1.62246 1.74573 1.95340
C 1.47357 -1.98069 -1.99852
C -0.53930 -3.83635 -1.46261
C 0.51311 -4.17507 -2.30911
C 1.52019 -3.24578 -2.57398
C -2.94932 -2.22192 -0.53004
C -4.09709 -2.00704 0.42806
O -3.15244 -2.36855 -1.73395
H 1.11859 2.71530 1.28362
H 1.83586 0.75428 2.46420
H 3.49756 -0.50487 3.80550
H 5.60884 -1.28624 2.76028
H 6.07149 -0.78804 0.37210
H 4.42688 0.52185 -0.96468
H -0.29405 -2.16820 1.51829
H -1.85047 -2.82414 2.00943
H -3.05199 -1.50764 3.47969
H -3.71261 0.68653 4.41390
H -2.82336 2.78057 3.40205
H -1.23828 2.65962 1.51111
H 2.25505 -1.25739 -2.19656
H -1.32936 -4.54770 -1.24448
H 0.54919 -5.16346 -2.75527
H 2.34568 -3.50805 -3.22739
H -3.99068 -2.58891 1.34591
H -4.16294 -0.95102 0.70411
H -5.01252 -2.29692 -0.08571
O -0.87528 3.21271 -3.22224
C -2.30132 4.72359 -2.03058
H -2.78631 4.86469 -2.99552
H -3.02615 4.36817 -1.29297
H -1.90851 5.67678 -1.66597

TS_{1c} (mIS1 form 2 conf1)

N	0.67724	2.20487 -0.31423
N	0.25809	2.21023 0.95558
O	1.42767	2.07338 1.68558
C	2.39255	1.53274 0.90021
C	1.79547	1.45253 -0.41056
N	3.53123	1.25549 1.44792
C	-0.32873	2.35474 -1.31559
C	-0.39682	1.44132 -2.36551
C	-1.39475	1.60017 -3.32493
C	-2.31452	2.64253 -3.21729
C	-2.23764	3.53876 -2.14946
C	-1.23753	3.40399 -1.19120
C	4.57392	0.87036 0.61339
C	0.61064	-0.34555 0.36111
C	-0.28559	0.26614 1.00095
C	1.12350	-1.60830 -0.13058
C	-1.58748	0.24003 1.62550
C	0.37234	-2.78383 0.11020
C	-2.43625	-0.83518 1.29884
C	-0.91689	-2.75631 0.90246
N	-1.96679	-1.84535 0.40536
C	0.85723	-4.00682 -0.34946
C	2.06506	-4.09454 -1.04086
C	2.80172	-2.93814 -1.28373
C	2.33293	-1.70702 -0.83271
C	-2.03939	1.21033 2.53170
C	-3.70759	-0.92571 1.85738
C	-4.14703	0.04809 2.75118
C	-3.30825	1.11105 3.09212
C	-2.54151	-1.94002 -0.83454
C	-2.08377	-3.06291 -1.73514
O	-3.39068	-1.13230 -1.20853
H	2.31653	1.29586 -1.34085
H	0.30095	0.61221 -2.42603
H	-1.45927	0.89655 -4.14788
H	-3.09292	2.75659 -3.96424
H	-2.95169	4.35080 -2.06589
H	-1.15205	4.09770 -0.36178
H	-1.31853	-3.77250 0.97446
H	-0.70070	-2.42890 1.92298
H	0.27642	-4.90716 -0.16527
H	2.42295	-5.05852 -1.38732
H	3.74275	-2.98927 -1.82166
H	2.92391	-0.81567 -1.01137
H	-1.39115	2.04057 2.78643
H	-4.34429	-1.76071 1.58252
H	-5.13917	-0.02539 3.18409
H	-3.64559	1.86662 3.79389
H	-1.98003	-4.01090 -1.20307
H	-2.81700	-3.16712 -2.53361
H	-1.11231	-2.81535 -2.17330
O	4.48670	0.74493 -0.60572
C	5.86029	0.61153 1.35068
H	6.64636	0.32915 0.65192
H	6.15183	1.50714 1.90573
H	5.70370	-0.18640 2.08203

TS_{1d} (mIS1 form 2 conf2)

N	-2.43597	-0.09584 -0.57592
N	-1.74131	0.58079 -1.49474
O	-1.28216	-0.40741 -2.35038
C	-1.29713	-1.60391 -1.71172
C	-1.90124	-1.32765 -0.42961
N	-0.83019	-2.62939 -2.34645
C	-3.07594	0.68097 0.43419
C	-2.89553	0.35515 1.77665
C	-3.52719	1.13566 2.74298
C	-4.30499	2.22989 2.36602
C	-4.46078	2.54846 1.01568
C	-3.84994	1.77025 0.03729
C	-1.00894	-3.88368 -1.77486
C	0.08609	-0.37557 0.17011
C	-0.02040	0.72796 -0.42806
C	0.81950	-1.19717 1.11178
C	0.54410	2.02175 -0.74110
C	1.89823	-0.60981 1.81482
C	1.89981	2.23520 -0.42021
C	2.28649	0.83508 1.59388
N	2.64787	1.19301 0.20677
C	2.58608	-1.36589 2.76222
C	2.24558	-2.69419 3.01414
C	1.20074	-3.28082 2.30409
C	0.49074	-2.53601 1.36612
C	-0.18756	3.07386 -1.31353
C	2.50181	3.46305 -0.68087
C	1.76695	4.49330 -1.26172
C	0.42007	4.29789 -1.57121
C	3.71523	0.65628 -0.46634
C	4.56966	-0.35363 0.26274
O	3.96290	0.97399 -1.62831
H	-2.29041	-2.05731 0.26188
H	-2.26410	-0.47911 2.06500
H	-3.39848	0.89214 3.79198
H	-4.78985	2.83566 3.12415
H	-5.06727	3.39811 0.72147
H	-3.97252	1.99010 -1.01795
H	1.44289	1.47897 1.85686
H	3.10913	1.09883 2.26651
H	3.40776	-0.90812 3.30742
H	2.79615	-3.26436 3.75515
H	0.92980	-4.31641 2.48233
H	-0.32512	-3.00144 0.82397
H	-1.23195	2.91937 -1.55498
H	3.54828	3.59853 -0.42702
H	2.24239	5.44731 -1.46424
H	-0.15908	5.10144 -2.01397
H	4.79455	-0.04892 1.28704
H	4.05659	-1.31853 0.30389
H	5.49631	-0.46801 -0.29779
O	-1.53814	-4.08824 -0.68515
C	-0.48461	-5.00591 -2.62959
H	-0.65329	-5.96432 -2.14087
H	-0.98043	-4.98654 -3.60384
H	0.58417	-4.85716 -2.80711

TS_{2a} (mIS2 form 1 conf1)

N 0.58348 2.01306 -0.51792
N 0.50156 2.03862 0.81932
O 1.81318 1.82633 1.24203
C 2.51593 1.23132 0.24817
C 1.59878 1.19482 -0.87003
N 3.74863 0.86642 0.25513
C -0.63383 2.26389 -1.22880
C -1.21639 1.25576 -1.99345
C -2.41721 1.52897 -2.64436
C -3.01874 2.78031 -2.51437
C -2.42484 3.77136 -1.73044
C -1.22079 3.51825 -1.08055
C 4.45178 0.77906 1.45836
C 0.58912 -0.54809 0.29150
C -0.15875 0.14277 1.02934
C 0.96434 -1.85722 -0.19622
C -1.38805 0.24154 1.77855
C 0.10206 -2.94517 0.07549
C -2.37910 -0.72501 1.51128
C -1.11790 -2.78956 0.95927
N -2.10596 -1.76447 0.57026
C 0.44103 -4.21210 -0.39598
C 1.61989 -4.42654 -1.10969
C 2.48424 -3.36065 -1.34992
C 2.15755 -2.08591 -0.89603
C -1.64583 1.23958 2.72909
C -3.60003 -0.67917 2.17901
C -3.84578 0.32024 3.11733
C -2.86501 1.27464 3.39613
C -2.86102 -1.84016 -0.57342
C -2.58024 -2.98985 -1.51228
O -3.71306 -0.99559 -0.83793
H -0.75387 0.27618 -2.06484
H -2.88907 0.75323 -3.23679
H -3.95574 2.98355 -3.02216
H -2.89487 4.74342 -1.62927
H -0.73367 4.27321 -0.47277
H -1.61805 -3.75889 1.05380
H -0.78321 -2.51127 1.96237
H -0.22475 -5.04732 -0.19328
H 1.86399 -5.42230 -1.46499
H 3.41361 -3.51832 -1.88718
H 2.84493 -1.26376 -1.06151
H -0.88546 1.98504 2.93161
H -4.35126 -1.42899 1.95294
H -4.79942 0.35105 3.63388
H -3.05320 2.04970 4.13160
H -2.53559 -3.94967 -0.99228
H -3.37440 -3.01374 -2.25673
H -1.62034 -2.83706 -2.01445
O 3.92895 0.72816 2.56216
C 5.94291 0.70122 1.26351
H 6.28777 1.57905 0.71036
H 6.44593 0.64224 2.22756
H 6.18390 -0.17813 0.65985
Cl 2.06716 0.94356 -2.48438

TS_{2b} (mIS2 form 1 conf2)

N 1.70001 1.64173 0.23006
N 1.06349 1.46140 1.39356
O 1.76084 0.42318 2.00709
C 2.44776 -0.27296 1.07119
C 2.23258 0.46215 -0.15604
N 3.19040 -1.31202 1.22994
C 1.19976 2.69917 -0.59407
C 0.64574 2.41312 -1.84041
C 0.13171 3.46620 -2.59395
C 0.16307 4.76893 -2.09624
C 0.71117 5.03074 -0.83949
C 1.23805 3.99206 -0.07770
C 3.18433 -2.00683 2.44145
C 0.12111 -0.49619 -0.12819
C -0.45106 0.31118 0.64504
C 0.03719 -1.52188 -1.14116
C -1.69287 0.83747 1.16595
C -1.18068 -1.64609 -1.84743
C -2.88270 0.19146 0.76952
C -2.37491 -0.79617 -1.47034
N -2.82786 -0.96391 -0.07084
C -1.26699 -2.56684 -2.89007
C -0.18862 -3.38950 -3.21383
C 0.99249 -3.30539 -2.47727
C 1.10778 -2.37273 -1.45090
C -1.78014 1.97327 1.98517
C -4.11807 0.67994 1.18613
C -4.18946 1.80132 2.00837
C -3.01812 2.44643 2.40671
C -3.28410 -2.15286 0.44271
C -3.36519 -3.34213 -0.48494
O -3.60887 -2.25503 1.62426
H 0.60587 1.39363 -2.21007
H -0.30137 3.26334 -3.56731
H -0.24150 5.58256 -2.68892
H 0.73538 6.04395 -0.45374
H 1.67704 4.16989 0.89825
H -2.12466 0.26310 -1.57793
H -3.20591 -1.00003 -2.15325
H -2.19841 -2.65581 -3.44358
H -0.27751 -4.10311 -4.02635
H 1.82726 -3.95985 -2.70585
H 2.02826 -2.29980 -0.87975
H -0.87068 2.47867 2.28463
H -5.01874 0.16520 0.86715
H -5.15636 2.17208 2.33216
H -3.06822 3.32392 3.04279
H -3.75729 -3.08229 -1.47014
H -2.37182 -3.77865 -0.62096
H -4.01396 -4.07966 -0.01449
O 2.38564 -1.81877 3.34779
C 4.26111 -3.05726 2.51625
H 4.22356 -3.56795 3.47731
H 4.12358 -3.77580 1.70340
H 5.23982 -2.59091 2.37453
Cl 3.16923 0.26897 -1.55875

TS_{2c} (mIS2 form 2 conf1)

N 0.52924 2.12907 0.13079
N 0.10665 1.89383 1.37825
O 1.27259 1.60617 2.07326
C 2.24207 1.19531 1.21054
C 1.64050 1.39321 -0.10166
N 3.32974 0.71837 1.68298
C -0.48031 2.52576 -0.80641
C -0.85368 1.67134 -1.84180
C -1.86665 2.08193 -2.70537
C -2.49398 3.31398 -2.51964
C -2.11391 4.14787 -1.46695
C -1.09755 3.75677 -0.60018
C 4.51433 0.68467 0.95675
C 0.42791 -0.54362 0.44779
C -0.50421 0.01604 1.08235
C 0.98968 -1.76978 -0.07808
C -1.86902 -0.03712 1.55471
C 0.20288 -2.94508 -0.03432
C -2.69485 -1.04403 1.01486
C -1.16918 -2.95528 0.60387
N -2.14373 -1.97663 0.08456
C 0.73469 -4.13899 -0.51817
C 2.02962 -4.20018 -1.03161
C 2.81098 -3.04775 -1.06413
C 2.29161 -1.84614 -0.59222
C -2.40697 0.84727 2.50119
C -4.02593 -1.14843 1.40862
C -4.54976 -0.25866 2.34311
C -3.73624 0.73370 2.89327
C -2.61780 -1.98732 -1.20250
C -2.07188 -3.04205 -2.13603
O -3.44020 -1.15972 -1.58939
H -0.37711 0.70379 -1.96193
H -2.17196 1.42998 -3.51642
H -3.28360 3.62425 -3.19588
H -2.60318 5.10487 -1.32283
H -0.77731 4.38878 0.22128
H -1.59164 -3.96321 0.53728
H -1.06115 -2.72979 1.66832
H 0.12522 -5.03864 -0.48808
H 2.42339 -5.14192 -1.39935
H 3.82333 -3.07963 -1.45358
H 2.91068 -0.95810 -0.61760
H -1.77692 1.62325 2.91886
H -4.64222 -1.92908 0.97433
H -5.58811 -0.34405 2.64588
H -4.13954 1.42288 3.62774
H -2.04708 -4.03296 -1.67715
H -2.70648 -3.06324 -3.02059
H -1.05109 -2.78508 -2.43382
O 4.88064 1.59682 0.22987
C 5.36270 -0.52875 1.23305
H 6.24649 -0.52104 0.59670
H 5.66229 -0.52024 2.28500
H 4.78184 -1.44074 1.06873
Cl 2.42449 1.42961 -1.61230

TS_{2d} (mIS2 form 2 conf2)

N -1.33056 1.86560 -0.42492
N -0.52979 1.71572 -1.48588
O -1.23205 0.85651 -2.31531
C -2.15454 0.16145 -1.59889
C -2.06163 0.73767 -0.26582
N -2.79668 -0.78777 -2.16758
C -0.85365 2.76403 0.58386
C -0.49457 2.28548 1.84258
C 0.01066 3.18885 2.77499
C 0.16340 4.53461 2.44069
C -0.18953 4.98990 1.16952
C -0.70474 4.10251 0.22919
C -4.04195 -1.21879 -1.72772
C -0.07111 -0.48081 -0.09648
C 0.69747 0.32524 -0.67817
C -0.24551 -1.61493 0.78082
C 2.05512 0.72988 -0.97249
C 0.84774 -1.99681 1.59156
C 3.09096 -0.12847 -0.54886
C 2.18152 -1.29439 1.46257
N 2.77853 -1.35768 0.10995
C 0.68294 -3.03389 2.50802
C -0.52472 -3.72379 2.60660
C -1.58496 -3.38438 1.76732
C -1.44614 -2.33289 0.86751
C 2.39353 1.93959 -1.59809
C 4.42238 0.22243 -0.75486
C 4.74322 1.41956 -1.38925
C 3.72603 2.27760 -1.80849
C 3.13711 -2.52941 -0.50916
C 2.93675 -3.82124 0.24729
O 3.59726 -2.53347 -1.64934
H -0.59585 1.23340 2.08714
H 0.29287 2.83522 3.76064
H 0.55997 5.23030 3.17260
H -0.07014 6.03614 0.91046
H -0.99324 4.43178 -0.76340
H 2.06343 -0.23075 1.68774
H 2.88624 -1.70066 2.19526
H 1.51944 -3.31909 3.14111
H -0.63041 -4.53103 3.32377
H -2.52162 -3.92982 1.81755
H -2.27544 -2.06254 0.22393
H 1.60394 2.60889 -1.91519
H 5.20025 -0.45598 -0.41944
H 5.78340 1.68339 -1.54922
H 3.97029 3.21540 -2.29631
H 3.22461 -3.74385 1.29742
H 1.88509 -4.11854 0.20634
H 3.53904 -4.58455 -0.24335
O -4.90095 -0.46156 -1.29849
C -4.28636 -2.69020 -1.93899
H -3.47060 -3.28044 -1.51301
H -5.23796 -2.97943 -1.49550
H -4.30396 -2.89259 -3.01402
Cl -3.15120 0.53171 1.02106

Quasiharmonic-corrected free energies of all structures:

Molecule	G (with Grimme correction) in Hartrees
mIS1 form 1	-700.707867
mIS1 form 2	-700.713499
mIS2 form 1	-1160.273641
mIS2 form 2	-1160.271606
DBCO model	-785.066646
TS 1a	-1485.739604
TS 1b	-1485.739511
TS 1c	-1485.743541
TS 1d	-1485.743529
TS 2a	-1945.306544
TS 2b	-1945.307679
TS 2c	-1945.301638
TS 2d	-1945.302968