

Supporting Information

Directed, Palladium(II)-Catalyzed Intermolecular Aminohydroxylation of Alkenes Using a Mild Oxidation System

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Table of Contents

General Information.....	S-2
Experimental Procedures.....	S-2
Alkene Substrate Synthesis.....	S-2
General Procedure for Aminohydroxylation of Alkenes.....	S-3
Oxidant Screens	S-10
Unsuccessful Scope.....	S-11
Procedure for Deprotection of Protecting Group.....	S-11
Additional Mechanistic studies	S-15
References.....	S-18
X-Ray Crystallography.....	S-19
Compound 3a	S-19
Compound 3g	S-25
Mass-Spec Data of Representative Mechanistic Studies.....	S-42
¹ H and ¹³ C NMR Spectra.....	S-48

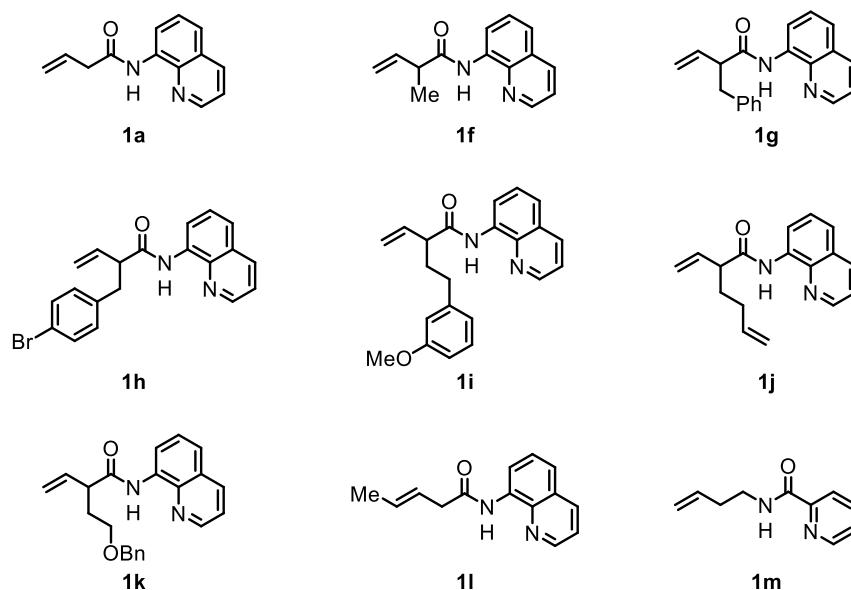
GENERAL INFORMATION

Unless otherwise noted, all materials were used as received from commercial sources without further purification. All chemicals were purchased from Aldrich, Alfa Aesar, Oakwood, and Combi-Blocks. ^1H and ^{13}C spectra were recorded on Bruker DRX-500 and AV-600 instruments. Spectra were internally referenced to SiMe_4 or solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. High-resolution mass spectra (HRMS) for new compounds were recorded on an Agilent LC/MSD TOF mass spectrometer.

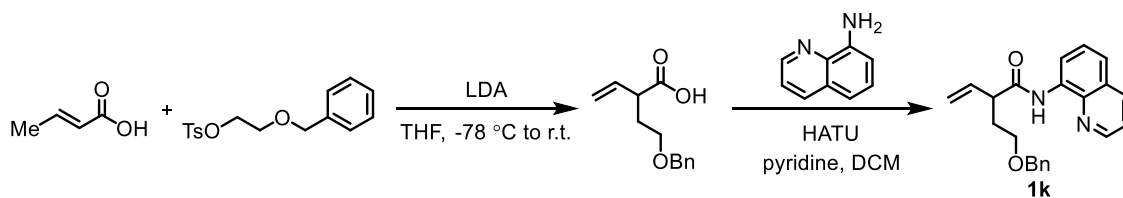
EXPERIMENTAL PROCEDURES

Alkene Substrate Synthesis

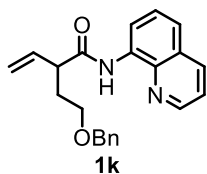
Table S1. Alkene substrates **1a** and **1f–m**.



Alkene substrates **1a**, **1f–j**, **1l** and **1m** were prepared according to literature methods.^{1–6}



Scheme S1: Synthesis of 2-(2-(benzyloxy)ethyl)-*N*-(quinolin-8-yl)but-3-enamide (**1k**).¹



2-(2-(benzyloxy)ethyl)-N-(quinolin-8-yl)but-3-enamide (1k): The title compound was prepared by adapting a literature procedure.¹ To a 100-mL Schlenk flask equipped with a magnetic stir bar was added *n*-BuLi (3.5 mL, 8.8 mmol, 2.5 M in hexanes) under a positive pressure of N₂. The flask was evacuated, and hexanes was removed under gentle stirring to leave an opaque

paste. The flask was filled with N₂ and charged with dry THF (3.2 mL), and the resulting light-yellow solution was submerged in a -78 °C dry ice/acetone bath. Diethylamine (0.92 mL) was added dropwise over 5 min. The resulting solution was warmed to 0 °C for 10 min and recooled to -78 °C. A solution of crotonic acid (344 mg, 4 mmol) in 3.2 mL THF was added dropwise over 5 min, and the reaction was allowed to warm to 0 °C in an ice bath for 45 min. The reaction was cooled again to -78 °C, and a solution of 2-(benzyloxy)ethyl 4-methylbenzenesulfonate (1.2 g, 4 mmol) in THF (8 mL) was added dropwise over 5 min. After 30 min, the solution was warmed to 0 °C. After 4 h at this temperature, the solution was quenched slowly with water (15 mL). The aqueous layer was transferred to a separatory funnel and washed with Et₂O (30 mL, ×2) before being charged back into the Schlenk flask. Phosphoric acid was added dropwise into the vigorously stirring solution at 0 °C until pH = 3. The milky solution was then extracted with EtOAc (60 mL, ×2). The combined organic extracts were washed with brine (30 mL, ×1), dried over Na₂SO₄, concentrated, and carried forward to the next step without further purification. Analysis of the crude ¹H NMR spectrum revealed ~4 mmol of the desired acid (~82% yield). The crude acid (~4 mmol) was charged into a 100-mL round-bottom flask containing 8 mL DCM. 8-Aminoquinoline (580 mg, 4 mmol), pyridine (1.06 mL, 13.7 mmol), and HATU (1.52 g, 4 mmol) were added sequentially, and the reaction was stirred at ambient temperature for 20 h. The deep brown solution was diluted with EtOAc (100 mL), washed with sat. NaHCO₃ (50 mL, ×2) and brine (50 mL, ×1), and purified by column chromatography (15% EtOAc in Hexanes) to afford 865 mg (62.5% yield from crotonic acid) of **1k** as a light-yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 10.03 (s, 1H), 8.83–8.72 (m, 2H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58–7.47 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.38–7.31 (m, 2H), 7.29–7.26 (m, 2H), 7.25–7.21 (m, 1H), 6.03 (ddd, *J* = 17.1, 10.1, 8.7 Hz, 1H), 5.36 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.56–4.45 (m, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 3.50 (q, *J* = 7.7 Hz, 1H), 2.32 (ddt, *J* = 13.7, 7.4, 6.0 Hz, 1H), 1.97 (ddt, *J* = 13.6, 7.4, 6.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 171.84, 148.17, 138.52, 138.38, 136.59, 136.25, 134.52, 128.28, 127.91, 127.68, 127.66, 127.49, 127.36, 121.55, 121.48, 118.15, 116.42, 73.05, 67.57, 49.83, 31.95; HRMS (ESI-TOF) calcd. for C₂₂H₂₃N₂O₂⁺ [M+H]⁺: 347.1754, Found: 347.1753.

General Procedure for Aminohydroxylation of Alkenes

General Procedure: To a 25-mL Schlenk tube equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol), the appropriate nitrogen nucleophile (0.15 mmol), 2,6-dimethylbenzoquinone (0.2 mmol), Pd(OAc)₂ (10 mol %), KHCO₃ (0.1 mmol), and HFIP (0.3 mL). The tube was cooled to a -78 °C in a dry ice/acetone bath until the solvent had frozen, and it was then evacuated and refilled with O₂ using a three-way valve connected to an O₂ balloon (×3). Finally, the tube was sealed and submerged up to the solvent level in an oil bath that was preheated to 100 °C. After a time period of 10–12 h, the reaction tube was allowed cooled to room temperature, and the reaction mixture was filtered through a short plug of silica gel (EtOAc, 25 mL, as eluent). The solvent was removed in *vacuo* to leave a brown residue, which upon purification by preparative TLC, afforded pure product.

Caution! Because the reaction involves heating a sealed vessel under O₂, a blast shield should be used at all times, and after the indicated reaction time, the reaction vessel should be allowed to cool to room temperature behind the blast shield prior to workup.

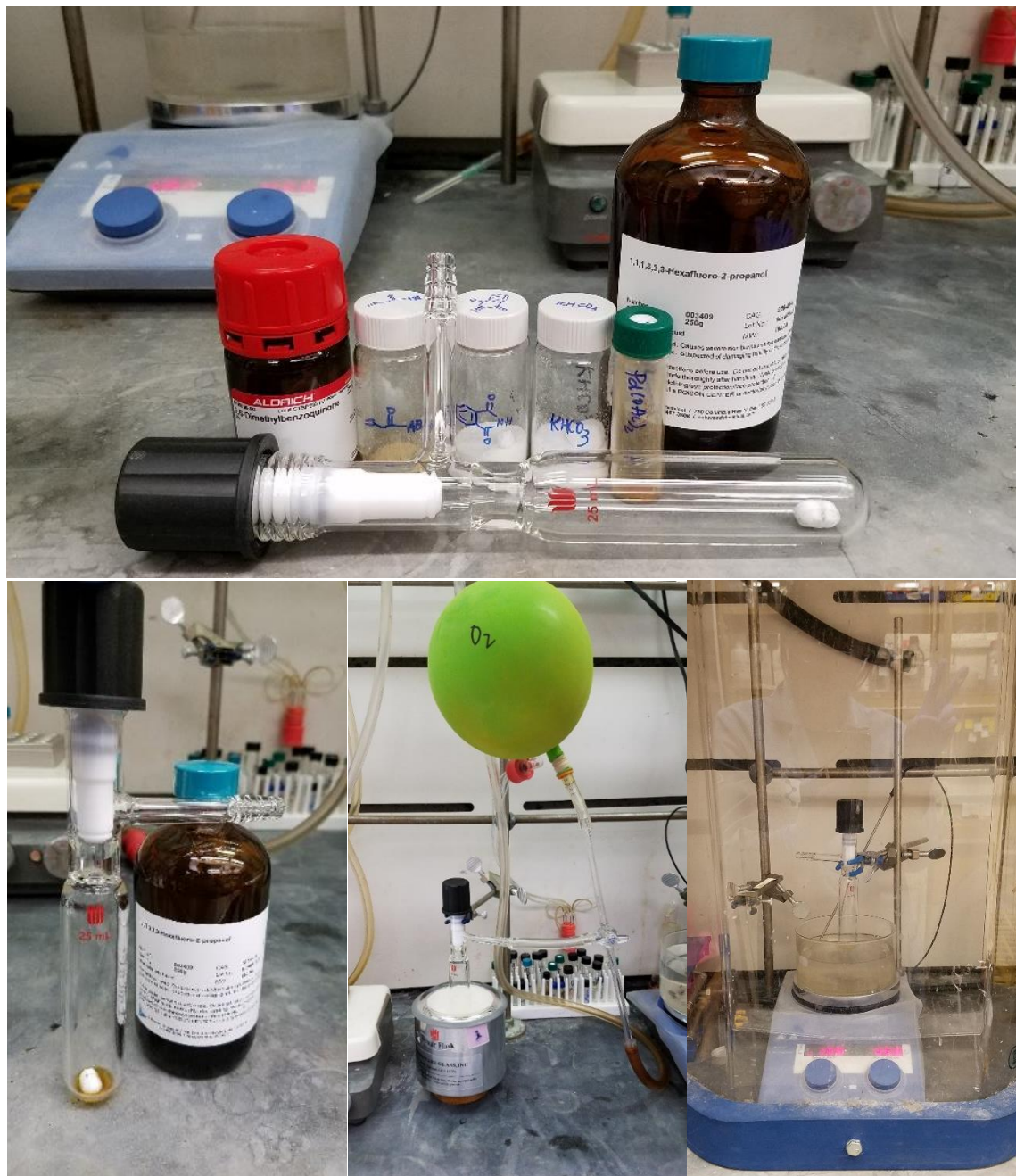
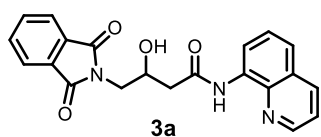
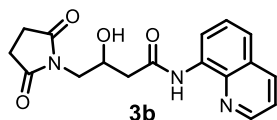


Figure S1: Photographic depiction of reaction setup following general procedure. a) Adding reactants. b) Injecting solvent. c) Degassing and backfilling with oxygen. d) Heating in stir plate behind blast shield.



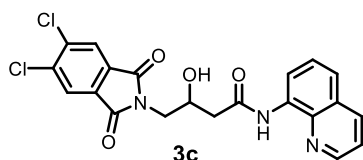
4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide (3a): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as an off-white solid (30.5 mg, 81%

yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.99 (s, 1H), 8.80 (dd, $J = 4.0, 1.8$ Hz, 1H), 8.71 (t, $J = 4.6$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.96–7.82 (m, 2H), 7.82–7.66 (m, 2H), 7.62–7.41 (m, 3H), 4.54 (t, $J = 7.7$ Hz, 1H), 3.99 (dd, $J = 14.0, 6.7$ Hz, 1H), 3.90 (dd, $J = 14.0, 4.8$ Hz, 1H), 2.86 (dd, $J = 15.4, 3.1$ Hz, 1H), 2.77 (dd, $J = 15.6, 8.7$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.95, 168.63, 148.29, 138.34, 136.34, 134.09, 131.96, 127.91, 127.28, 123.45, 121.93, 121.66, 116.91, 77.00, 67.27, 43.17, 41.69; the analytical data were in accordance with literature values.⁶ **X-ray** (single-crystal) Colorless needle crystals of X-ray diffraction quality were obtained by vapor diffusion of pentane into a saturated solution of **3a** in DCM (CCDC 1839335).⁷



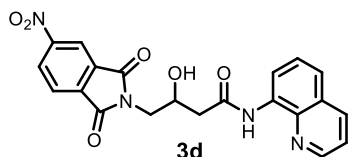
4-(2,5-dioxopyrrolidin-1-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide (3b): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol) and succinimide (14.8 mg, 0.15 mmol) according to the general procedure.

Purification using preparative TLC (1:4 hexane:EtOAc) gave the product as an off-white solid (26.4 mg, 81% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.00 (s, 1H), 8.80 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.75–8.64 (m, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.58–7.47 (m, 2H), 7.45 (dd, $J = 8.3, 4.2$ Hz, 1H), 4.44 (tt, $J = 7.6, 3.7$ Hz, 1H), 4.01 (s, 1H), 3.83 (dd, $J = 13.7, 7.3$ Hz, 1H), 3.70 (dd, $J = 13.7, 4.3$ Hz, 1H), 2.84–2.68 (m, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 178.05, 170.18, 148.73, 138.75, 136.76, 134.44, 128.34, 127.67, 122.38, 122.09, 117.30, 67.12, 44.43, 42.30, 28.60; the analytical data were in accordance with literature values.⁶



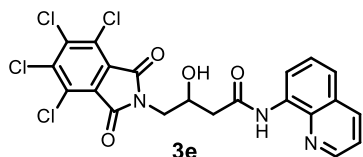
4-(5,6-dichloro-1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide (3c): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol) and 5,6-dichloroisindoline-1,3-dione (32.4 mg, 0.15 mmol) according to the general procedure.

Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as a brown solid (27.0 mg, 61% yield). $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 10.34 (s, 1H), 8.91 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.60 (dd, $J = 7.7, 1.3$ Hz, 1H), 8.39 (dd, $J = 8.3, 1.7$ Hz, 1H), 8.12 (s, 2H), 7.73–7.58 (m, 2H), 7.53 (t, $J = 8.0$ Hz, 1H), 5.51 (d, $J = 5.2$ Hz, 1H), 4.34 (q, $J = 6.4$ Hz, 1H), 3.71 (dd, $J = 13.7, 7.9$ Hz, 1H), 2.82–2.61 (m, 2H); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ 169.42, 166.21, 148.80, 137.91, 137.03, 136.55, 134.55, 131.76, 127.76, 126.89, 125.03, 122.09, 121.69, 116.22, 64.97, 44.14, 42.71; **HRMS** (ESI-TOF) Calcd for $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{N}_3\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 444.0512, found 444.0512.



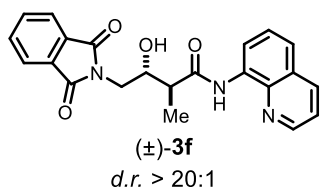
3-hydroxy-4-(5-nitro-1,3-dioxoisindolin-2-yl)-N-(quinolin-8-yl)butanamide (3d): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol) and 5-nitroisindoline-1,3-dione (28.8 mg, 0.15 mmol) according to the general procedure. Purification using

preparative TLC (1.5:1 hexane:EtOAc) gave the product as an off-white solid (21.0 mg, 50% yield). $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 10.36 (s, 1H), 8.91 (dd, $J = 4.3, 1.8$ Hz, 1H), 8.60 (ddd, $J = 8.2, 6.4, 1.7$ Hz, 2H), 8.48–8.34 (m, 2H), 8.10 (d, $J = 8.1$ Hz, 1H), 7.75–7.58 (m, 2H), 7.53 (t, $J = 7.9$ Hz, 1H), 5.54 (d, $J = 5.1$ Hz, 1H), 4.43–4.30 (m, 1H), 3.76 (dd, $J = 13.4, 7.9$ Hz, 1H), 3.67 (dd, $J = 13.7, 4.9$ Hz, 1H), 2.74 (d, $J = 6.3$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ 169.44, 166.43, 166.16, 151.26, 148.80, 137.91, 136.53, 136.49, 134.57, 133.20, 129.40, 127.77, 126.93, 124.34, 122.10, 121.67, 117.61, 116.25, 64.96, 44.31, 42.66; **HRMS** (ESI-TOF) Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_4\text{O}_6^+$ $[\text{M}+\text{H}]^+$ 421.1143, found 421.1144.



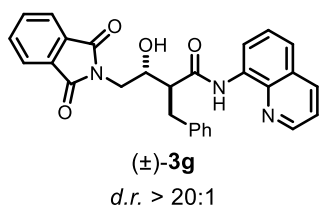
3-hydroxy-*N*-(quinolin-8-yl)-4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanamide (3e): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol) and 4,5,6,7-tetrachloroisindoline-1,3-dione (42.6 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (3:1 to

2:1 hexane:EtOAc) gave the product as an off-white solid (29.6 mg, 58% yield). $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 10.34 (s, 1H), 8.90 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.57 (dd, $J = 7.7, 1.3$ Hz, 1H), 8.38 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.69–7.60 (m, 2H), 7.50 (t, $J = 8.0$ Hz, 1H), 5.54 (d, $J = 5.2$ Hz, 1H), 4.36 (td, $J = 7.2, 3.6$ Hz, 1H), 3.71 (dd, $J = 13.7, 7.6$ Hz, 1H), 3.64 (dd, $J = 13.7, 5.5$ Hz, 1H), 2.72 (d, $J = 6.7$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ 169.35, 163.44, 148.80, 137.96, 137.82, 136.51, 134.48, 128.33, 127.86, 127.73, 126.80, 122.10, 121.66, 116.04, 64.77, 44.26, 42.66; **HRMS** (ESI-TOF) Calcd for $\text{C}_{21}\text{H}_{14}\text{Cl}_4\text{N}_3\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 511.9733, found 511.9732.



4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-2-methyl-*N*-(quinolin-8-yl)butanamide ((±)-3f): The title compound was prepared from (±)-**1f** (22.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as a brown solid (28.7 mg, 74% yield).

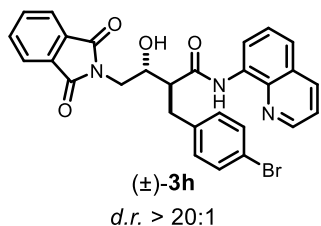
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.05 (s, 1H), 8.81 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.72 (p, $J = 4.6$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.86–7.74 (m, 2H), 7.76–7.60 (m, 2H), 7.56–7.47 (m, 2H), 7.45 (dd, $J = 8.3, 4.2$ Hz, 1H), 4.12 (d, $J = 6.4$ Hz, 1H), 4.07–3.87 (m, 3H), 2.80 (qd, $J = 7.1, 5.1$ Hz, 1H), 1.54 (d, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 173.43, 168.24, 147.86, 138.00, 135.87, 133.60, 133.52, 131.51, 127.44, 126.81, 122.88, 121.47, 121.18, 116.54, 72.23, 44.73, 42.20, 15.37; **HRMS** (ESI-TOF) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 390.1448, found 390.1147.



2-benzyl-4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-*N*-(quinolin-8-yl)butanamide ((±)-3g): The title compound was prepared from (±)-**1g** (30.2 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as an off-white solid (37.2 mg, 80% yield).

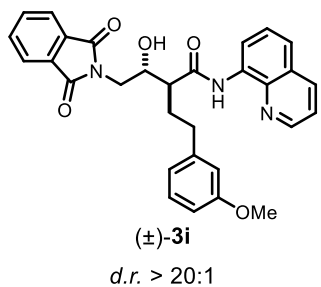
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.91 (s, 1H), 8.74 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.67 (dd, $J = 6.1, 2.9$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.80–7.70 (m, 2H),

7.68–7.61 (m, 2H), 7.52–7.46 (m, 2H), 7.43 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.34–7.27 (m, 2H), 7.24–7.18 (m, 2H), 7.15–7.07 (m, 1H), 4.29 (d, $J = 7.4$ Hz, 1H), 4.13–4.07 (m, 1H), 4.01 (dd, $J = 14.1, 7.9$ Hz, 1H), 3.92 (dd, $J = 14.1, 3.7$ Hz, 1H), 3.27 (qd, $J = 13.7, 7.7$ Hz, 2H), 2.91 (ddd, $J = 8.2, 7.3, 3.4$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 172.26, 168.61, 148.33, 138.27, 137.36, 136.17, 133.97, 133.55, 131.88, 131.66, 130.82, 127.77, 127.10, 123.33, 122.14, 121.63, 120.53, 117.04, 70.93, 52.65, 42.99, 36.10; **HRMS** (ESI-TOF) Calcd for $\text{C}_{28}\text{H}_{24}\text{N}_3\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 466.1761, found 466.1759. **X-ray** (single-crystal) Colorless needle crystals of X-ray diffraction quality were obtained by vapor diffusion of pentane into a saturated solution of **3g** in DCM (CCDC 1839336).⁷



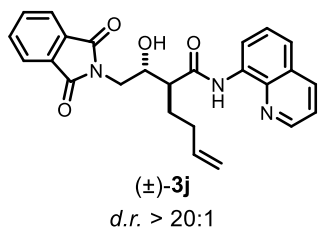
2-(4-bromobenzyl)-4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide ((±)-3h**):** The title compound was prepared from (±)-**1h** (38.0 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as an off-white solid (40.7 mg, 75% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.83 (s, 1H), 8.74 (dd, $J = 4.3, 1.7$ Hz, 1H), 8.63 (dd, $J = 7.0, 2.0$ Hz, 1H), 8.12 (dd,

$J = 8.3, 1.7$ Hz, 1H), 7.80–7.73 (m, 2H), 7.69–7.63 (m, 2H), 7.49 (dt, $J = 9.9, 4.7$ Hz, 2H), 7.46–7.41 (m, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.1$ Hz, 2H), 4.34–4.21 (m, 1H), 4.10 (d, $J = 9.4$ Hz, 1H), 4.02 (dd, $J = 14.1, 7.7$ Hz, 1H), 3.93 (dd, $J = 14.1, 3.7$ Hz, 1H), 3.21 (qd, $J = 13.7, 7.8$ Hz, 2H), 2.86 (ddd, $J = 8.7, 6.8, 3.5$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 172.26, 168.61, 148.33, 138.27, 137.36, 136.17, 133.97, 133.55, 131.88, 131.66, 130.82, 127.77, 127.10, 123.33, 122.14, 121.63, 120.53, 117.04, 70.93, 52.65, 42.99, 36.10; **HRMS** (ESI-TOF) Calcd for $\text{C}_{28}\text{H}_{23}\text{BrN}_3\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 544.0866, found 544.0865.

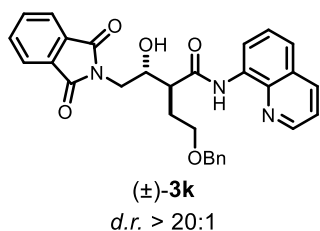


4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-2-(3-methoxyphenethyl)-N-(quinolin-8-yl)butanamide ((±)-3i**):** The title compound was prepared from (±)-**1i** (34.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as an off-white solid (35.2 mg, 69% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.07 (s, 1H), 8.83 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.76 (dd, $J = 6.1, 2.9$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.85–7.73 (m, 2H), 7.73–7.60 (m, 2H), 7.60–

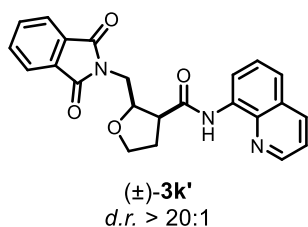
7.42 (m, 3H), 7.14 (t, $J = 7.9$ Hz, 1H), 6.81 (d, $J = 7.6$ Hz, 1H), 6.77 (t, $J = 2.0$ Hz, 1H), 6.69 (dd, $J = 8.2, 2.5$ Hz, 1H), 4.25–4.07 (m, 2H), 3.97 (dd, $J = 14.1, 7.7$ Hz, 1H), 3.88 (dd, $J = 14.1, 3.8$ Hz, 1H), 3.74 (s, 3H), 2.76 (dddd, $J = 22.5, 15.6, 11.5, 6.9$ Hz, 2H), 2.69–2.60 (m, 1H), 2.40 (dtd, $J = 14.7, 9.0, 5.9$ Hz, 1H), 2.25–2.12 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 173.06, 168.58, 159.69, 148.37, 142.56, 138.45, 136.27, 133.93, 133.81, 131.92, 129.41, 127.89, 127.24, 123.30, 122.09, 121.66, 120.84, 117.10, 113.97, 111.65, 71.43, 55.07, 49.96, 43.00, 33.38, 31.87; **HRMS** (ESI-TOF) Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_3\text{O}_5^+$ $[\text{M}+\text{H}]^+$ 510.2023, found 510.2024.



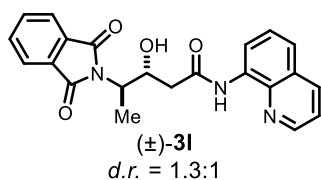
2-(2-(1,3-dioxoisindolin-2-yl)-1-hydroxyethyl)-N-(quinolin-8-yl)hex-5-enamide ((±)-3j**):** The title compound was prepared from (±)-**1j** (26.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as a brown solid (27.1 mg, 63% yield). ¹H NMR (500 MHz, CDCl₃) δ 10.08 (s, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.74 (dd, *J* = 6.4, 2.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.84–7.71 (m, 2H), 7.71–7.59 (m, 2H), 7.56–7.49 (m, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H), 5.09 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.02 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.21–4.05 (m, 2H), 3.98 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.90 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.69 (ddd, *J* = 8.6, 5.5, 3.0 Hz, 1H), 2.30–2.12 (m, 3H), 1.95 (dtd, *J* = 13.2, 8.6, 7.2, 4.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 173.22, 168.58, 148.35, 138.43, 137.35, 136.27, 133.92, 133.80, 131.94, 127.88, 127.23, 123.29, 122.06, 121.65, 117.07, 115.99, 71.46, 49.79, 43.08, 31.35, 29.54; HRMS (ESI-TOF) Calcd for C₂₅H₂₄N₃O₄⁺ [M+H]⁺ 430.1761, found 430.1763.



2-(2-(benzyloxy)ethyl)-4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide ((±)-3k**):** The title compound was prepared from (±)-**1k** (34.6 mg, 0.1 mmol) and phthalimide (26.5 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as an off-white solid (41.4mg, 52% yield). ¹H NMR (500 MHz, CDCl₃) δ 10.27 (s, 1H), 8.76 (dt, *J* = 5.4, 2.4 Hz, 1H), 8.66 (t, *J* = 2.9 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.84–7.72 (m, 2H), 7.72–7.61 (m, 2H), 7.53 (t, *J* = 3.0 Hz, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (d, *J* = 6.6 Hz, 2H), 7.24 (d, *J* = 5.6 Hz, 3H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.12 (q, *J* = 4.7, 3.2 Hz, 1H), 4.03 (dd, *J* = 13.8, 8.4 Hz, 1H), 3.96–3.82 (m, 1H), 3.68 (q, *J* = 5.2 Hz, 1H), 3.60 (t, *J* = 6.1 Hz, 1H), 3.09–2.97 (m, 1H), 2.34 (t, *J* = 12.6 Hz, 1H), 2.26–2.12 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 173.50, 168.51, 148.26, 138.12, 136.30, 136.24, 136.22, 133.86, 132.03, 128.27, 127.91, 127.62, 127.51, 127.27, 123.26, 122.09, 121.63, 117.20, 73.22, 71.71, 67.41, 46.58, 43.00, 30.85; HRMS (ESI-TOF) Calcd for C₃₀H₂₈N₃O₅⁺ [M+H]⁺ 510.2023, found 510.2023.

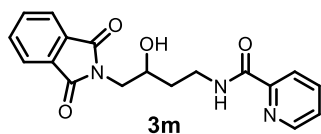


2-((1,3-dioxoisindolin-2-yl)methyl)-N-(quinolin-8-yl)tetrahydrofuran-3-carboxamide ((±)-3k'**):** The title compound was prepared from (±)-**1k** (34.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as a white solid (5.2 mg, 13% yield). ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.77–7.66 (m, 2H), 7.66–7.54 (m, 2H), 7.54–7.38 (m, 3H), 4.56 (q, *J* = 6.1 Hz, 1H), 4.13–3.86 (m, 4H), 3.11 (dt, *J* = 9.0, 7.1 Hz, 1H), 2.50–2.29 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.82, 168.46, 148.27, 138.43, 136.23, 134.22, 133.75, 131.90, 127.83, 127.24, 123.24, 121.70, 121.58, 116.67, 79.74, 68.15, 50.57, 40.43, 30.96; HRMS (ESI-TOF) Calcd for C₂₃H₂₀N₃O₄⁺ [M+H]⁺ 402.1448, found 402.1449.



4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)pentanamide ((±)-3l**):** The title compound was prepared from (±)-**1l** (22.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as a yellow solid (8.9 mg, 23% yield).

This product was isolated as an inseparable 1.3:1 mixture of diastereomers. The reported *d.r.* was determined by ^1H NMR analysis of purified **3l** and is consistent with that of the crude reaction mixture. ^1H NMR (500 MHz, CDCl_3) δ 10.11 (s, 1.3H), 10.05 (s, 1H), 8.79 (dd, $J = 4.2, 1.7$ Hz, 1.3H), 8.77 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.75–8.68 (m, 2.3H), 8.15 (ddd, $J = 8.2, 4.9, 1.7$ Hz, 2.3H), 7.88–7.79 (m, 4.6H), 7.72 (ddd, $J = 5.5, 4.0, 3.0$ Hz, 4.6H), 7.54–7.48 (m, 5.6H), 7.44 (ddd, $J = 8.3, 6.8, 4.2$ Hz, 2.3H), 4.72–4.25 (m, 6.9H), 2.90–2.64 (m, 4.6H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.64, 170.39, 169.67, 169.37, 148.98, 148.92, 139.09, 139.08, 137.02, 137.01, 134.88, 134.88, 134.80, 132.55, 132.47, 128.61, 128.00, 124.13, 124.10, 122.52, 122.29, 117.61, 117.57, 70.69, 70.66, 52.25, 52.20, 42.95, 42.42, 16.16, 14.55; the analytical data were in accordance with literature values.⁶



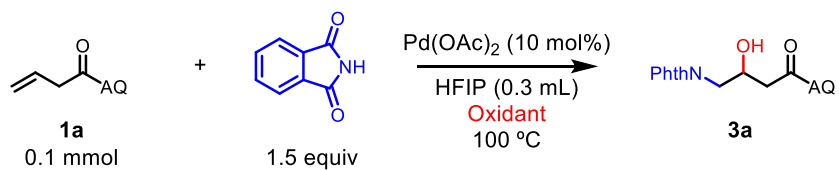
N-(4-(1,3-dioxoisindolin-2-yl)-3-hydroxybutyl)picolinamide (3m): The title compound was prepared from **1m** (17.6 mg, 0.1 mmol) and phthalimide (22 mg, 0.15 mmol) according to the general procedure. Purification using preparative TLC (1:1 hexane:EtOAc)

gave the product as a brown solid (3.4 mg, 10% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.54 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 8.35 (d, $J = 7.6$ Hz, 1H), 8.15 (dt, $J = 7.8, 1.1$ Hz, 1H), 7.92–7.81 (m, 3H), 7.79–7.66 (m, 2H), 7.43 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 4.06 (d, $J = 4.5$ Hz, 1H), 3.95 (dddd, $J = 18.6, 10.4, 8.3, 4.2$ Hz, 2H), 3.85 (dd, $J = 14.0, 7.8$ Hz, 1H), 3.74 (dd, $J = 13.9, 4.0$ Hz, 1H), 3.43 (dq, $J = 14.0, 5.1$ Hz, 1H), 1.84 (dddd, $J = 13.4, 10.4, 5.3, 2.9$ Hz, 1H), 1.71 (ddt, $J = 14.6, 10.5, 4.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.68, 165.59, 149.29, 148.12, 137.38, 133.98, 132.03, 126.34, 123.35, 122.37, 66.97, 43.69, 35.85, 35.27; HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_4^+$ $[M+H]^+$ 340.1292, found 340.1293.

Note on assignment of diastereomeric ratios: The diastereomeric ratios of products **3f–k** and **3l** were determined directly from ^1H NMR spectra of the crude reaction mixtures. In substrates **3f–k**, based on our analysis, only a single product diastereomer could be detected (conservatively reported as >20:1). Trace impurities were detected in the ^1H NMR spectra of the crude reaction mixtures of some of the compounds, but the peaks of these minor byproducts did not appear to correspond to the other potential diastereomer.

Oxidant Screens

Table S2. Oxidant screening. ^a



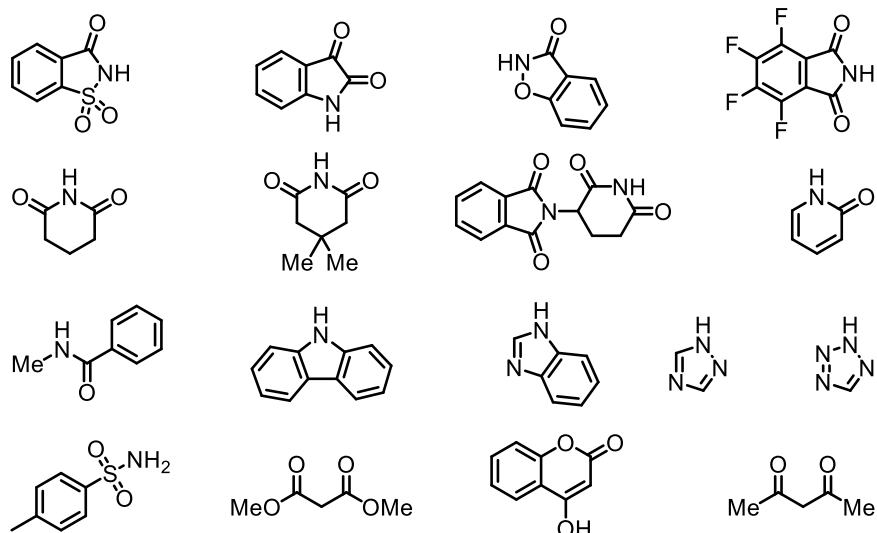
Entry	Oxidant	Atmosphere	1a	3a
1	0.5 equiv DMBQ	O ₂	(31 %)	(45 %)
2	1.5 equiv DMBQ	O ₂	trace	65 %
3	2 equiv DMBQ	O ₂	N.D.	80 %
4	3 equiv DMBQ	O ₂	(5 %)	(48 %)
5	2 equiv DMBQ + 2 equiv DTBP	N ₂	(56 %)	N.D.
6	2 equiv DTBP	N ₂	(15 %)	N.D.
7	2 equiv DTBP	Air	(45 %)	(10 %)
8	--	O ₂	(60 %)	N.D.

^a Values in parenthesis represent yields determined by ¹H NMR analysis of the crude reaction mixture

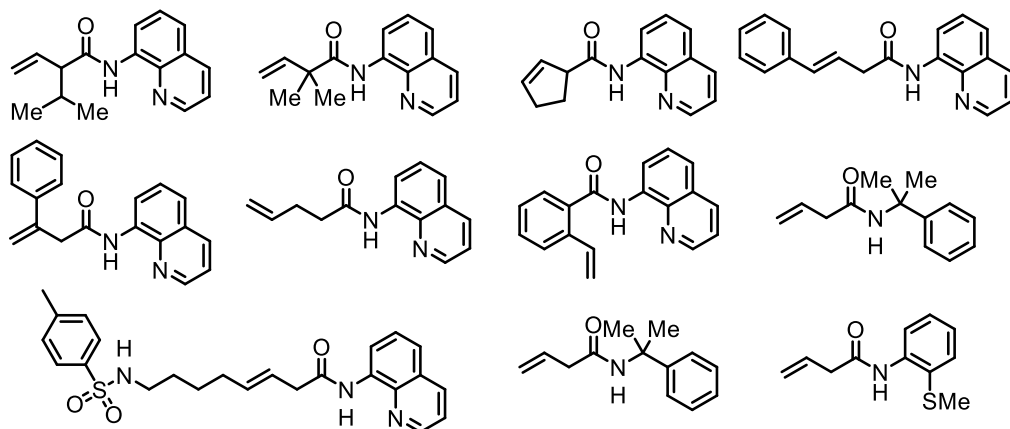
Unsuccessful Scope

Table S3. Unsuccessful nucleophile and alkene scope. ^a

Unsuccessful Nucleophiles

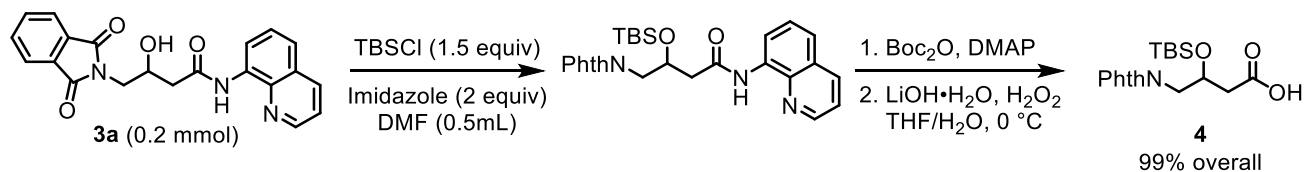


Unsuccessful Alkene Substrates

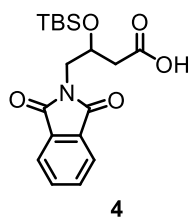


^a The above nucleophiles and alkene substrates gave less than 10% yield.

Deprotection of Protecting Group

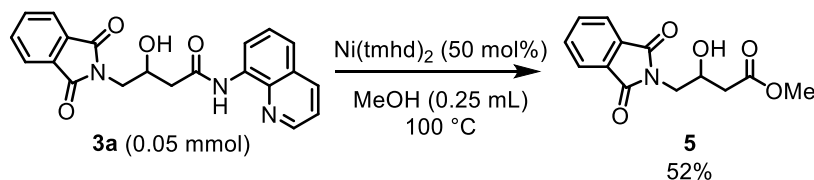


Scheme S2: Deprotection of 8-aminoquinoline protecting group to carboxylic acid.

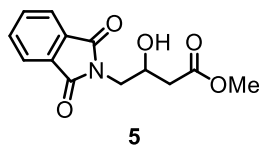


4

4-(1,3-dioxoisindolin-2-yl)-3-hydroxy-N-(quinolin-8-yl)butanamide 3-((tert-butyl)dimethylsilyloxy)-4-(1,3-dioxoisindolin-2-yl)butanoic acid (4): The deprotection was accomplished by adapting a literature procedure.⁸ Compound **3a** (75 mg, 0.2 mmol), TBSCl (46 mg, 1.5 equiv), imidazole (28 mg, 2 equiv) were mixed with 0.5 mL of DMF. The resulting mixture was stirred at room temperature for 16 h, then was concentrated under reduced pressure. Half of the crude mixture by weight was then dissolved in MeCN (1 mL) along with Boc₂O (67 mg, 1.5 equiv) and DMAP (23 mg, 2 equiv). The mixture was stirred for 2 h at 40 °C while being monitored by TLC. Upon completion, the crude reaction mixture was concentrated under reduced pressure. The crude mixture was then dissolved in THF (1.8 mL) and H₂O (0.6 mL) and cooled to 0 °C, followed by addition of 30% hydrogen peroxide (100 μL, 8.8 equiv) and LiOH·H₂O (4.6 mg, 1.1 equiv). The solution was stirred for 2.5 h at 0 °C in an ice bath and was then quenched with 1.5 M aqueous Na₂S₂O₃ (1 mL) while being held at 0 °C. The aqueous phase was acidified to pH = 2 with 10% aqueous HCl and extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (1:1 Hex:EtOAc), affording the product as an off-white solid (36.3 mg, 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.97–7.81 (m, 2H), 7.81–7.68 (m, 2H), 4.46 (p, *J* = 6.1 Hz, 1H), 3.80 (qd, *J* = 13.7, 6.2 Hz, 2H), 2.66–2.45 (m, 2H), 0.85 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 176.17, 168.22, 134.12, 131.94, 123.36, 66.88, 43.34, 40.81, 25.61, 17.81; HRMS (ESI-TOF) Calcd for C₁₈H₂₆NO₅Si⁺ [M+H]⁺ 364.1575, found 364.1574.

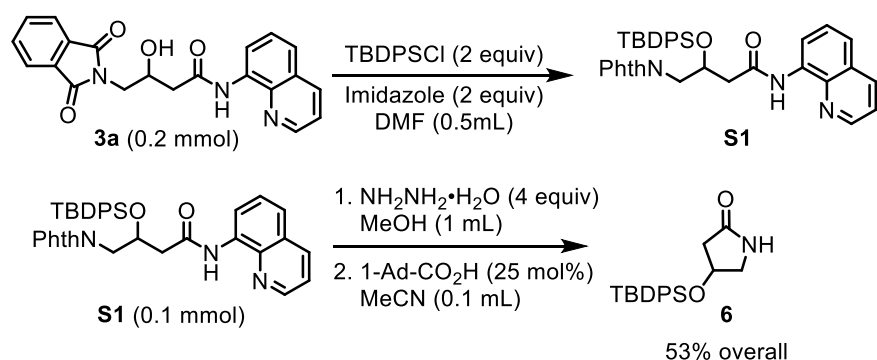


Scheme S3: Deprotection of 8-aminoquinoline protecting group to ester.

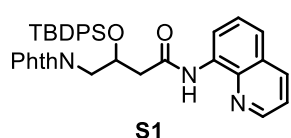


5

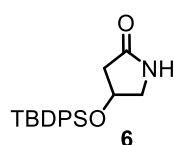
Methyl 4-(1,3-dioxoisindolin-2-yl)-3-hydroxybutanoate (5): The deprotection was accomplished by adapting a literature procedure.⁹ Compound **3a** (18.8 mg, 0.05 mmol) and nickel(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) (10.5 mg, 50 mol %) were stirred in methanol (0.25 mL) at 100 °C for 2 d. The crude mixture was filtered through a short plug of silica and concentrated under reduced vacuum. Purification using preparative TLC (1:1 hexane:EtOAc) gave the product as a white solid (6.8 mg, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.95–7.80 (m, 2H), 7.80–7.65 (m, 2H), 4.37 (tt, *J* = 8.5, 4.2 Hz, 1H), 3.90 (dd, *J* = 14.1, 7.1 Hz, 1H), 3.80 (dd, *J* = 14.1, 4.5 Hz, 1H), 3.72 (s, 3H), 3.22 (d, *J* = 5.0 Hz, 1H), 2.62 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.54 (dd, *J* = 16.6, 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.19, 168.58, 134.16, 131.90, 123.48, 66.63, 51.94, 42.89, 38.80; the analytical data were in accordance with literature values.¹⁰



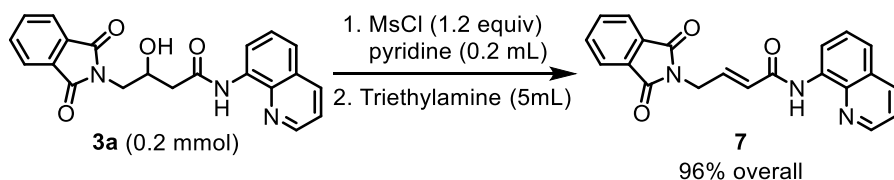
Scheme S4: Deprotection of 8-aminoquinoline protecting group and phthalimide to form β -hydroxy- γ -lactam.



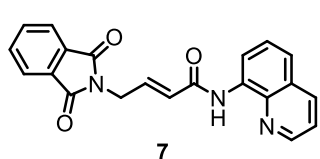
3-((*tert*-butyldiphenylsilyloxy)-4-(1,3-dioxoisindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (S1): Compound **3a** (75 mg, 0.2 mmol), *tert*-Butyl(chloro)diphenylsilane (109 mg, 4 equiv) and imidazole (28 mg, 2 equiv) were stirred in DMF (0.5 mL) at room temperature for 2 d. The crude mixture was concentrated under reduced vacuum, and the resulting residue was purified by flash chromatography (3:1 hexane:EtOAc), providing the product as a yellow solid (119 mg, 97% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.72 (s, 1H), 8.95 (s, 1H), 8.76 (dd, $J = 10.5, 5.9$ Hz, 2H), 8.00–7.54 (m, 11H), 7.38–7.14 (m, 7H), 4.85 (t, $J = 5.8$ Hz, 1H), 3.93 (ddd, $J = 40.0, 13.5, 6.0$ Hz, 2H), 3.06 (qd, $J = 15.2, 5.8$ Hz, 2H), 1.03 (s, 8H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.93, 168.07, 143.28, 136.01, 135.99, 133.57, 133.40, 132.16, 131.44, 130.28, 129.49, 129.36, 127.44, 124.85, 123.11, 122.59, 120.77, 68.40, 43.52, 43.44, 26.94, 19.19; **HRMS** (ESI-TOF) Calcd for $\text{C}_{37}\text{H}_{36}\text{N}_3\text{O}_4\text{Si}^+$ $[\text{M}+\text{H}]^+$ 614.2470, found 614.2473.



4-((*tert*-butyldiphenylsilyloxy)pyrrolidin-2-one (6): The deprotection was accomplished by adapting a literature procedure.^{6, 8} Compound **S2** (61.3 mg, 0.1 mmol) was dissolved in MeOH (1 mL), and hydrazine monoxide (20 mg, 4 equiv) was added dropwise while the reaction was stirred at room temperature. The reaction was allowed to run for 2 d before being filtered through a short plug of Celite. The plug of Celite was washed with MeOH, and the filtrate was concentrated under reduced pressure. The crude product was dissolved in MeCN (0.1 mL) with 1-adamantane carboxylic acid (4.5 mg, 25 mol %), and the reaction was stirred under 120 °C overnight. The reaction vessel was cooled to room temperature, and the reaction mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. Purification of the resulting residue using preparative TLC (1:2 hexane:EtOAc) gave the product as an off-white solid (8.5 mg, 53% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.72–7.59 (m, 4H), 7.49–7.36 (m, 6H), 5.81 (s, 1H), 4.53 (ddd, $J = 10.5, 6.0, 4.0$ Hz, 1H), 3.37 (dd, $J = 10.1, 6.1$ Hz, 1H), 3.28 (dd, $J = 10.1, 3.6$ Hz, 1H), 2.46–2.29 (m, 2H), 1.06 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 176.01, 135.59, 135.54, 133.36, 133.10, 129.99, 129.95, 127.84, 127.81, 68.84, 51.09, 40.02, 26.76, 18.99; the analytical data were in accordance with literature values.¹¹



Scheme S5: Elimination to produce protected trans-4-aminocrotonic acid.



4-((tert-(E)-4-(1,3-dioxoisindolin-2-yl)-N-(quinolin-8-yl)but-2-enamide (7): The deprotection was accomplished by adapting a literature procedure.¹² Compound **3a** (75 mg, 0.2 mmol) and methanesulfonyl chloride (27 mg, 1.2 equiv) were dissolved in pyridine (0.2 mL), and the resulting mixture was stirred at room temperature

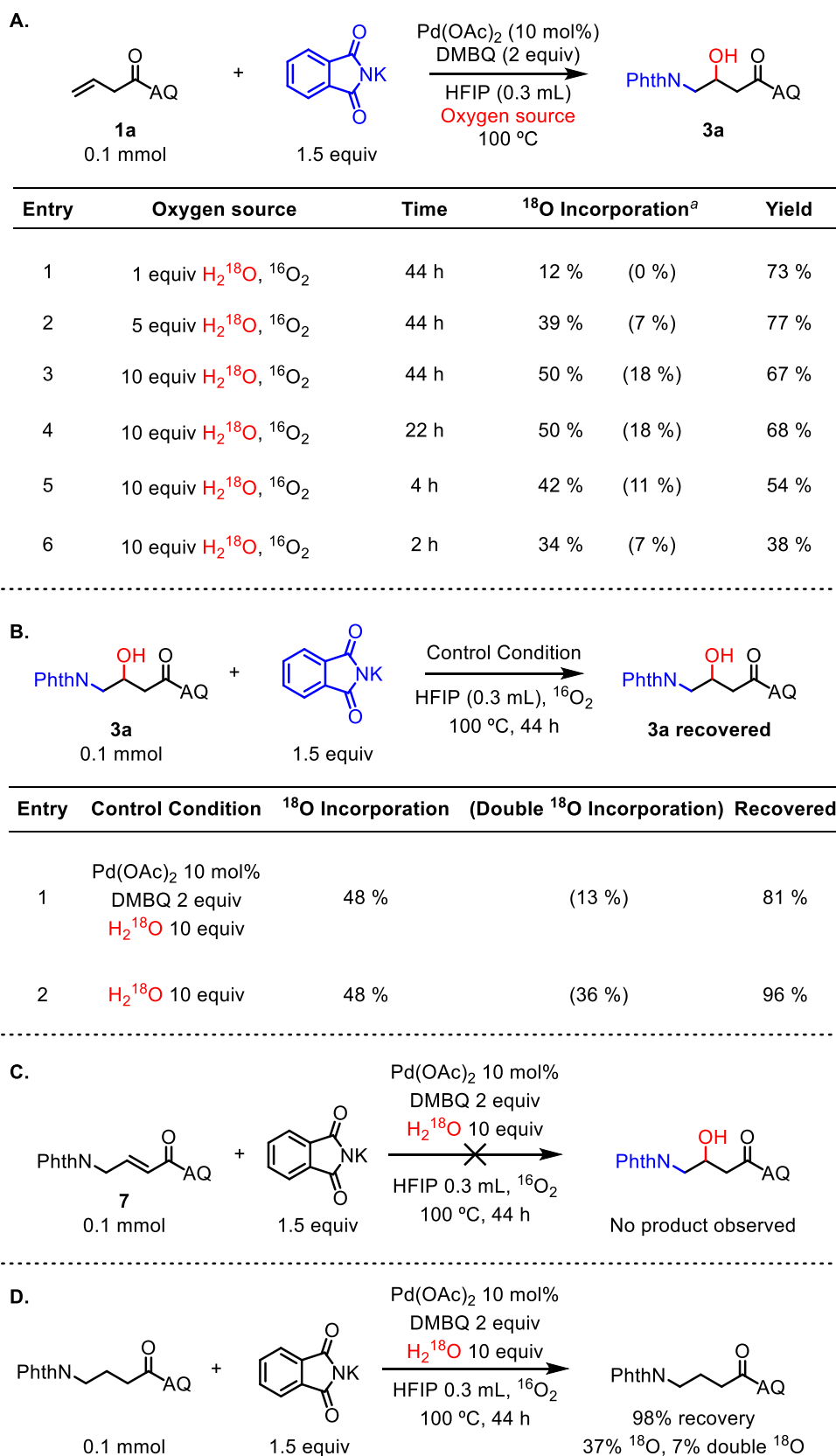
until no starting material was remaining as determined by TLC. Upon completion of the reaction, the reaction mixture was then filtered through a short plug of silica and concentrated under reduced pressure. The crude product was then dissolved in triethylamine (5 mL), and the resulting solution was stirred at 60 °C for 3 d. The reaction mixture was then cooled to room temperature, and the solvent was removed under reduced pressure. Purification using preparative TLC (2:1 hexane:EtOAc) gave the product as an off-white solid (68.8 mg, 96% yield). ¹H NMR (500 MHz, CDCl₃) δ 9.86 (s, 1H), 8.81 (dd, *J* = 7.2, 1.9 Hz, 1H), 8.78 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.94–7.87 (m, 2H), 7.80–7.72 (m, 2H), 7.59–7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.03 (dt, *J* = 15.2, 5.6 Hz, 1H), 6.32 (dt, *J* = 15.2, 1.6 Hz, 1H), 4.54 (dd, *J* = 5.6, 1.7 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 167.61, 162.84, 148.09, 138.36, 137.73, 136.34, 134.26, 134.17, 131.98, 127.86, 127.35, 126.70, 123.49, 121.78, 121.62, 116.88, 38.26; HRMS (ESI-TOF) Calcd for C₂₁H₁₆N₃O₃⁺ [M+H]⁺ 358.1186, found 358.1187.

MECHANISTIC STUDIES

Procedure for mechanistic reactions

Procedure for isotope labeling experiments under $^{16}\text{O}_2$: To a 25-mL Schlenk tube equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol), potassium phthalimide (0.15 mmol), 2,6-dimethylbenzoquinone (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), the appropriate amount of H_2O additive (when applicable), and HFIP (0.3 mL). The tube was cooled to a $-78\text{ }^\circ\text{C}$ dry ice/acetone bath until solvent had frozen, then was evacuated and refilled with oxygen three times. Finally, the tube was sealed and submerged up to the solvent level in an oil bath that was pre-heated to $100\text{ }^\circ\text{C}$. After a time period of 40–46 h, the reaction tube was allowed cooled to room temperature, and the reaction mixture was filtered through a short plug of silica gel (EtOAc, 25 mL, as eluent). The solvent was removed *in vacuo* to leave a brown residue, which upon purification by preparative TLC, afforded pure product.

Procedure for isotope labeling experiment using autoclave: Into an autoclave were added the starting material **1a** (250 mg, 1.18 mmol), potassium phthalimide (334 mg, 1.50 equiv), 2,6-dimethylbenzoquinone (324 mg, 2 equiv), $\text{Pd}(\text{OAc})_2$ (27 mg, 0.10 equiv) and HFIP (3.5 mL). The reaction vessel was pressurized to 30 psi and vented with N_2 ($\times 10$), then was pressurized to 15 psi with O_2 and vented ($\times 3$). The autoclave was finally pressurized with O_2 to 13.5 psi, sealed, and heated to $100\text{ }^\circ\text{C}$ for 43 h. After this time, the reaction vessel was allowed to cool. The system was carefully vented, and the crude reaction mixture, which at this point was a thick gummy black material, was passed through a pad of silica gel. The filtrate was concentrated *in vacuo* and purified by flash column chromatography over silica gel ($\times 2$) (0 to 100% EtOAc in hexanes gradient). The product was isolated as a brown foam.



Scheme S6. Additional mechanistic experiments.

We were curious about the origin of double label incorporation, which we speculated could arise from exchange of *in situ* generated H_2^{18}O with an $\text{C}=\text{O}$ or $\text{C}-\text{OH}$ group of the product. To probe this possibility, we carried out several additional experiments. First, we ran the reaction with different amounts of H_2^{18}O and observed an increase in single and double incorporation as H_2^{18}O stoichiometry increased (Scheme S6A, entries 1–3). Furthermore, using 10 equiv H_2^{18}O we monitored ^{18}O incorporation at various time points and found that both single and double incorporation increased over time (entries 3–6). To directly test whether water could participate in oxygen atom exchange with the aminohydroxylated product, we subjected unlabeled product **3a** to the modified reaction condition with 10 equiv H_2^{18}O and recovered 81% of the product containing 48% single label and 13% doubly label (Scheme S6B, entry 1). Additionally, we were able to obtain labeled product in high recovery yield without adding $\text{Pd}(\text{OAc})_2$ or DMBQ (entry 2), indicating that the catalyst and co-oxidant are not required for the oxygen exchange process.

To rationalize the mechanism for oxygen exchange, we envisioned three potential pathways: (1) a Michael/retro-Michael reaction pathway to exchange the β -alcohol, (2) a nucleophilic substitution pathway of the $\text{C}-\text{OH}$ bond that could involve participation of the Phth $\text{C}=\text{O}$ moiety, and (3) oxygen-atom exchange with a $\text{C}=\text{O}$ group of the product. To investigate the first possibility, we independently prepared the conjugated alkene intermediate that would be formed in the Michael/retro-Michael pathway (**7**) and subjected it to the modified reaction conditions and found that no reaction took place, ruling out the first pathway (Scheme S6C). We then subjected a model compound¹ that did not contain the key $\text{C}-\text{OH}$ bond to the reaction conditions with H_2^{18}O and found oxygen incorporation (Scheme S6D), albeit to a lesser extent than that with the alcohol-containing product (Scheme S6B, entry 2). Based on this data, we were not able to distinguish between pathways 2 or 3, and we believe that both pathways could be active during the reaction process.

We also considered the possibility that after oxidative addition of $^{16}\text{O}_2$ the resulting high-valent intermediate, for instance $[\text{Pd}(\text{IV})(\text{alkyl})(^{16}\text{OH})]$, could undergo OH ligand exchange with $^{18}\text{H}_2\text{O}$ in solution prior to $\text{C}-\text{O}$ reductive elimination, as a means of ^{18}O incorporation using $^{18}\text{H}_2\text{O}$. Though this possibility cannot be fully excluded, we believe the pathways described above are more likely based on the experimental data.

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- (7) CCDC 1839335 and 1839336 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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X-RAY CRYSTALLOGRAPHY

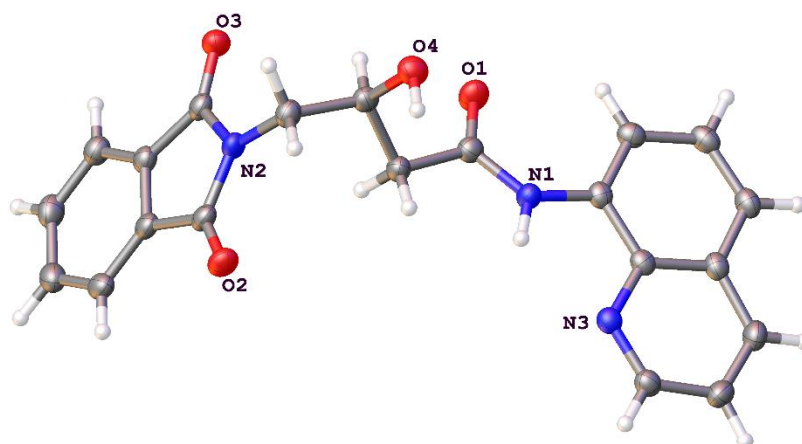


Table S4. Crystal data and structure refinement for **3a**.

Identification code	LZ-03-136-1	
Empirical formula	C ₂₁ H ₁₇ N ₃ O ₄	
Formula weight	375.38	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 5.2465(2) Å	a = 90°.
	b = 36.0755(13) Å	b = 98.580(2)°.
	c = 9.1602(3) Å	g = 90°.
Volume	1714.35(11) Å ³	
Z	4	
Density (calculated)	1.454 Mg/m ³	
Absorption coefficient	0.848 mm ⁻¹	
F(000)	784	
Crystal size	0.27 x 0.1 x 0.08 mm ³	
Theta range for data collection	2.449 to 68.431°.	
Index ranges	-6 ≤ h ≤ 6, -43 ≤ k ≤ 42, -11 ≤ l ≤ 9	
Reflections collected	13002	
Independent reflections	3145 [R(int) = 0.0453]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3201 and 0.2260	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3145 / 1 / 260	
Goodness-of-fit on F ²	1.059	
Final R indices [I > 2σ(I)]	R1 = 0.0460, wR2 = 0.1201	
R indices (all data)	R1 = 0.0501, wR2 = 0.1230	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.752 and -0.232 e.Å ⁻³	

Table S5. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3a**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	8483(3)	6575(1)	1410(2)	34(1)
O(2)	886(3)	6001(1)	5279(2)	33(1)
O(3)	7039(3)	5379(1)	3187(2)	30(1)
O(4)	2537(3)	6221(1)	313(2)	33(1)
N(1)	6070(3)	7072(1)	1866(2)	24(1)
N(2)	3709(3)	5725(1)	3897(2)	25(1)
N(3)	4947(3)	7748(1)	2721(2)	23(1)
C(1)	5553(4)	8409(1)	2786(2)	31(1)
C(2)	7339(4)	8391(1)	1844(2)	30(1)
C(3)	7992(4)	8042(1)	1300(2)	25(1)
C(4)	6772(3)	7726(1)	1801(2)	22(1)
C(5)	7459(3)	7365(1)	1345(2)	22(1)
C(6)	6636(4)	6707(1)	1908(2)	25(1)
C(7)	4842(4)	6462(1)	2638(2)	28(1)
C(8)	4023(4)	6124(1)	1681(2)	25(1)
C(9)	2463(4)	5845(1)	2443(2)	27(1)
C(10)	5871(3)	5494(1)	4142(2)	24(1)
C(11)	6341(4)	5425(1)	5766(2)	25(1)
C(12)	8236(4)	5220(1)	6616(2)	29(1)
C(13)	8195(4)	5210(1)	8134(2)	34(1)
C(14)	4473(4)	5613(1)	6403(2)	26(1)
C(15)	4418(4)	5603(1)	7910(2)	31(1)
C(16)	6330(4)	5396(1)	8774(2)	34(1)
C(17)	2755(4)	5808(1)	5204(2)	26(1)
C(18)	9304(3)	7328(1)	432(2)	25(1)
C(19)	10473(3)	7645(1)	-80(2)	27(1)
C(20)	9843(4)	7995(1)	331(2)	27(1)
C(21)	4387(4)	8079(1)	3175(2)	26(1)

Table S6. Bond lengths [\AA] and angles [$^\circ$] for **3a**.

O(1)-C(6)	1.226(2)	C(13)-H(13)	0.9500
O(2)-C(17)	1.213(2)	C(13)-C(16)	1.387(3)
O(3)-C(10)	1.213(2)	C(14)-C(15)	1.385(3)
O(4)-C(8)	1.417(2)	C(14)-C(17)	1.489(3)
O(4)-H(4)	0.960(17)	C(15)-H(15)	0.9500
N(1)-C(5)	1.408(2)	C(15)-C(16)	1.397(3)
N(1)-C(6)	1.351(2)	C(16)-H(16)	0.9500
N(1)-H(1)	0.91(2)	C(18)-H(18)	0.9500
N(2)-C(9)	1.459(2)	C(18)-C(19)	1.411(3)
N(2)-C(10)	1.398(2)	C(19)-H(19)	0.9500
N(2)-C(17)	1.398(2)	C(19)-C(20)	1.370(3)
N(3)-C(4)	1.369(2)	C(20)-H(20)	0.9500
N(3)-C(21)	1.314(2)	C(21)-H(21)	0.9500
C(1)-H(1A)	0.9500	C(8)-O(4)-H(4)	105.8(16)
C(1)-C(2)	1.367(3)	C(5)-N(1)-H(1)	112.2(15)
C(1)-C(21)	1.408(3)	C(6)-N(1)-C(5)	128.35(16)
C(2)-H(2)	0.9500	C(6)-N(1)-H(1)	118.8(15)
C(2)-C(3)	1.414(3)	C(10)-N(2)-C(9)	124.49(15)
C(3)-C(4)	1.418(2)	C(10)-N(2)-C(17)	112.09(15)
C(3)-C(20)	1.420(3)	C(17)-N(2)-C(9)	123.28(15)
C(4)-C(5)	1.427(3)	C(21)-N(3)-C(4)	117.23(15)
C(5)-C(18)	1.377(3)	C(2)-C(1)-H(1A)	120.6
C(6)-C(7)	1.517(3)	C(2)-C(1)-C(21)	118.89(18)
C(7)-H(7A)	0.9900	C(21)-C(1)-H(1A)	120.6
C(7)-H(7B)	0.9900	C(1)-C(2)-H(2)	120.3
C(7)-C(8)	1.525(3)	C(1)-C(2)-C(3)	119.39(17)
C(8)-H(8)	1.0000	C(3)-C(2)-H(2)	120.3
C(8)-C(9)	1.530(3)	C(2)-C(3)-C(4)	117.19(17)
C(9)-H(9A)	0.9900	C(2)-C(3)-C(20)	123.44(17)
C(9)-H(9B)	0.9900	C(4)-C(3)-C(20)	119.33(17)
C(10)-C(11)	1.492(3)	N(3)-C(4)-C(3)	122.93(16)
C(11)-C(12)	1.383(3)	N(3)-C(4)-C(5)	117.59(15)
C(11)-C(14)	1.390(3)	C(3)-C(4)-C(5)	119.48(16)
C(12)-H(12)	0.9500	N(1)-C(5)-C(4)	114.78(15)
C(12)-C(13)	1.394(3)	C(18)-C(5)-N(1)	125.39(17)

C(18)-C(5)-C(4)	119.80(16)	C(11)-C(12)-C(13)	117.19(18)
O(1)-C(6)-N(1)	123.35(17)	C(13)-C(12)-H(12)	121.4
O(1)-C(6)-C(7)	121.03(16)	C(12)-C(13)-H(13)	119.1
N(1)-C(6)-C(7)	115.62(16)	C(16)-C(13)-C(12)	121.79(19)
C(6)-C(7)-H(7A)	109.5	C(16)-C(13)-H(13)	119.1
C(6)-C(7)-H(7B)	109.5	C(11)-C(14)-C(17)	107.94(17)
C(6)-C(7)-C(8)	110.65(15)	C(15)-C(14)-C(11)	121.72(18)
H(7A)-C(7)-H(7B)	108.1	C(15)-C(14)-C(17)	130.34(18)
C(8)-C(7)-H(7A)	109.5	C(14)-C(15)-H(15)	121.3
C(8)-C(7)-H(7B)	109.5	C(14)-C(15)-C(16)	117.33(19)
O(4)-C(8)-C(7)	112.44(15)	C(16)-C(15)-H(15)	121.3
O(4)-C(8)-H(8)	107.9	C(13)-C(16)-C(15)	120.73(19)
O(4)-C(8)-C(9)	107.72(15)	C(13)-C(16)-H(16)	119.6
C(7)-C(8)-H(8)	107.9	C(15)-C(16)-H(16)	119.6
C(7)-C(8)-C(9)	112.83(15)	O(2)-C(17)-N(2)	124.60(18)
C(9)-C(8)-H(8)	107.9	O(2)-C(17)-C(14)	129.41(18)
N(2)-C(9)-C(8)	114.47(15)	N(2)-C(17)-C(14)	105.99(15)
N(2)-C(9)-H(9A)	108.6	C(5)-C(18)-H(18)	119.9
N(2)-C(9)-H(9B)	108.6	C(5)-C(18)-C(19)	120.20(17)
C(8)-C(9)-H(9A)	108.6	C(19)-C(18)-H(18)	119.9
C(8)-C(9)-H(9B)	108.6	C(18)-C(19)-H(19)	119.3
H(9A)-C(9)-H(9B)	107.6	C(20)-C(19)-C(18)	121.33(17)
O(3)-C(10)-N(2)	124.88(18)	C(20)-C(19)-H(19)	119.3
O(3)-C(10)-C(11)	129.53(17)	C(3)-C(20)-H(20)	120.1
N(2)-C(10)-C(11)	105.59(15)	C(19)-C(20)-C(3)	119.83(17)
C(12)-C(11)-C(10)	130.37(17)	C(19)-C(20)-H(20)	120.1
C(12)-C(11)-C(14)	121.23(18)	N(3)-C(21)-C(1)	124.30(18)
C(14)-C(11)-C(10)	108.39(16)	N(3)-C(21)-H(21)	117.8
C(11)-C(12)-H(12)	121.4	C(1)-C(21)-H(21)	117.8

Symmetry transformations used to generate equivalent atoms:

Table S7. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
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O(1)	31(1)	30(1)	45(1)	4(1)	14(1)	8(1)
O(2)	33(1)	27(1)	43(1)	0(1)	14(1)	7(1)
O(3)	32(1)	28(1)	32(1)	1(1)	12(1)	6(1)
O(4)	34(1)	34(1)	31(1)	2(1)	7(1)	6(1)
N(1)	24(1)	21(1)	28(1)	1(1)	8(1)	0(1)
N(2)	27(1)	19(1)	30(1)	4(1)	9(1)	4(1)
N(3)	21(1)	24(1)	23(1)	1(1)	4(1)	0(1)
C(1)	39(1)	23(1)	30(1)	-1(1)	6(1)	2(1)
C(2)	35(1)	23(1)	31(1)	3(1)	6(1)	-4(1)
C(3)	25(1)	27(1)	22(1)	3(1)	2(1)	-3(1)
C(4)	20(1)	26(1)	19(1)	2(1)	2(1)	-1(1)
C(5)	20(1)	24(1)	21(1)	2(1)	1(1)	-1(1)
C(6)	26(1)	24(1)	25(1)	1(1)	4(1)	3(1)
C(7)	35(1)	21(1)	29(1)	2(1)	12(1)	1(1)
C(8)	26(1)	24(1)	27(1)	1(1)	7(1)	4(1)
C(9)	27(1)	23(1)	30(1)	2(1)	5(1)	2(1)
C(10)	25(1)	17(1)	32(1)	2(1)	7(1)	0(1)
C(11)	27(1)	20(1)	30(1)	2(1)	9(1)	-1(1)
C(12)	30(1)	23(1)	34(1)	2(1)	6(1)	1(1)
C(13)	38(1)	28(1)	33(1)	6(1)	0(1)	-1(1)
C(14)	30(1)	16(1)	32(1)	0(1)	10(1)	-2(1)
C(15)	39(1)	22(1)	34(1)	-2(1)	14(1)	-4(1)
C(16)	45(1)	27(1)	30(1)	1(1)	9(1)	-5(1)
C(17)	28(1)	17(1)	35(1)	-1(1)	10(1)	0(1)
C(18)	22(1)	29(1)	23(1)	-1(1)	3(1)	1(1)
C(19)	22(1)	36(1)	23(1)	0(1)	5(1)	-3(1)
C(20)	26(1)	31(1)	25(1)	4(1)	5(1)	-4(1)
C(21)	26(1)	27(1)	25(1)	2(1)	6(1)	3(1)

Table S8. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for **3a**.

	x	y	z	U(eq)
H(1A)	5105	8641	3172	37
H(2)	8135	8610	1558	36
H(7A)	3297	6605	2793	33
H(7B)	5728	6380	3614	33
H(8)	5619	5996	1469	30
H(9A)	778	5957	2547	32
H(9B)	2122	5624	1801	32
H(12)	9512	5090	6183	35
H(13)	9480	5073	8746	40
H(15)	3132	5731	8338	37
H(16)	6352	5383	9811	40
H(18)	9792	7089	146	30
H(19)	11721	7616	-723	32
H(20)	10642	8205	-31	33
H(21)	3113	8097	3807	31
H(1)	4780(50)	7155(6)	2350(30)	33(6)
H(4)	1030(40)	6342(7)	550(30)	50

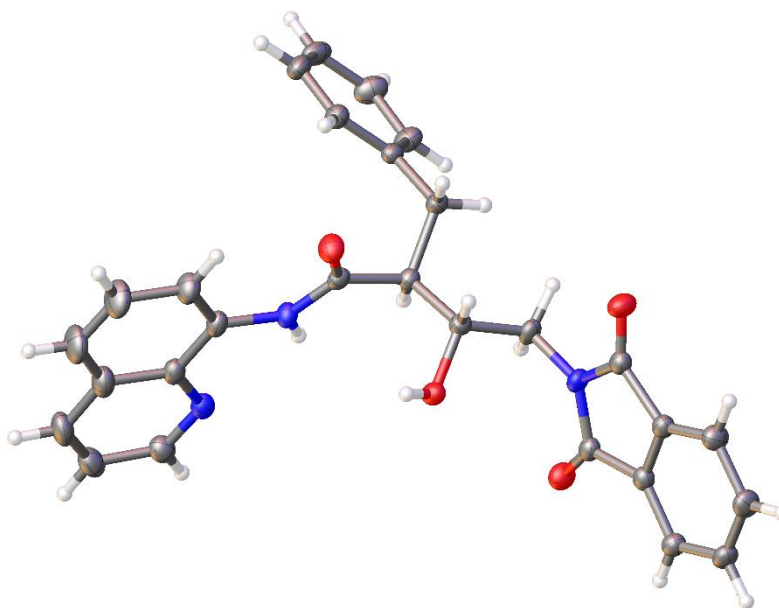


Table S9. Crystal data and structure refinement for **3g**.

Report date	2017-04-27	
Identification code	engle33_sq	
Empirical formula	C ₂₈ H ₂₃ N ₃ O ₄	
Molecular formula	C ₂₈ H ₂₃ N ₃ O ₄	
Formula weight	465.49	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.1657(4) Å	α = 72.1060(10)°.
	b = 12.1843(4) Å	β = 74.3870(10)°.
	c = 19.7995(6) Å	γ = 67.8670(10)°.
Volume	2547.65(14) Å ³	
Z	4	
Density (calculated)	1.214 Mg/m ³	
Absorption coefficient	0.670 mm ⁻¹	
F(000)	976	
Crystal size	0.2 x 0.2 x 0.17 mm ³	
Crystal color, habit	colorless block	
Theta range for data collection	3.983 to 68.318°.	
Index ranges	-14 ≤ h ≤ 14, -14 ≤ k ≤ 13, -23 ≤ l ≤ 23	

Reflections collected	50312
Independent reflections	9190 [R(int) = 0.0435]
Completeness to theta = 67.500°	98.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5210 and 0.4485
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9190 / 0 / 633
Goodness-of-fit on F ²	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0939
R indices (all data)	R1 = 0.0455, wR2 = 0.0993
Extinction coefficient	n/a
Largest diff. peak and hole	0.561 and -0.352 e.Å ⁻³

Table S10. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for **3g**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1827(1)	1831(1)	9331(1)	30(1)
O(2)	3785(1)	2765(1)	7816(1)	24(1)
O(3)	4761(1)	4881(1)	6516(1)	30(1)
O(4)	5062(1)	4462(1)	8841(1)	32(1)
N(1)	782(1)	1608(1)	7129(1)	26(1)
N(2)	1248(1)	2098(1)	8271(1)	23(1)
N(3)	4630(1)	4630(1)	7741(1)	24(1)
C(1)	544(1)	1380(1)	6582(1)	31(1)
C(2)	302(2)	318(2)	6621(1)	37(1)
C(3)	313(2)	-534(2)	7256(1)	39(1)
C(4)	545(1)	-331(1)	7860(1)	34(1)

C(5)	546(2)	-1167(2)	8539(1)	45(1)
C(6)	760(2)	-911(2)	9102(1)	44(1)
C(7)	1004(2)	168(1)	9027(1)	33(1)
C(8)	1022(1)	1001(1)	8376(1)	25(1)
C(9)	783(1)	768(1)	7772(1)	26(1)
C(10)	1618(1)	2455(1)	8735(1)	22(1)
C(11)	1777(1)	3709(1)	8458(1)	21(1)
C(12)	3138(1)	3530(1)	8309(1)	21(1)
C(13)	3357(1)	4753(1)	7967(1)	25(1)
C(14)	1101(1)	4478(1)	9024(1)	24(1)
C(15)	-252(1)	4744(1)	9206(1)	24(1)
C(16)	-764(1)	3928(1)	9732(1)	28(1)
C(17)	-2008(1)	4214(2)	9932(1)	32(1)
C(18)	-2761(1)	5325(2)	9617(1)	34(1)
C(19)	-2265(1)	6141(2)	9091(1)	36(1)
C(20)	-1021(1)	5846(1)	8885(1)	30(1)
C(21)	5223(1)	4709(1)	7026(1)	23(1)
C(22)	6486(1)	4582(1)	7039(1)	23(1)
C(23)	7460(1)	4576(1)	6482(1)	26(1)
C(24)	8534(1)	4476(1)	6655(1)	29(1)
C(25)	8614(1)	4411(2)	7354(1)	32(1)
C(26)	7631(1)	4409(2)	7912(1)	30(1)
C(27)	6574(1)	4484(1)	7739(1)	24(1)
C(28)	5381(1)	4503(1)	8203(1)	24(1)
O(1')	3338(1)	1463(1)	5755(1)	37(1)
O(2')	1514(1)	3699(1)	6710(1)	23(1)

O(3')	828(1)	6423(1)	7154(1)	30(1)
O(4')	470(1)	6241(1)	4950(1)	32(1)
N(1')	4257(1)	206(1)	8230(1)	32(1)
N(2')	3776(1)	1190(1)	6857(1)	25(1)
N(3')	940(1)	6130(1)	6031(1)	22(1)
C(1')	4531(2)	-283(2)	8881(1)	40(1)
C(2')	4641(2)	-1499(2)	9248(1)	48(1)
C(3')	4413(2)	-2210(2)	8928(1)	48(1)
C(4')	4105(1)	-1732(1)	8236(1)	39(1)
C(5')	3864(2)	-2427(2)	7871(1)	51(1)
C(6')	3617(2)	-1939(2)	7194(1)	51(1)
C(7')	3589(1)	-735(2)	6836(1)	38(1)
C(8')	3796(1)	-20(1)	7177(1)	28(1)
C(9')	4055(1)	-510(1)	7894(1)	30(1)
C(10')	3553(1)	1853(1)	6189(1)	25(1)
C(11')	3563(1)	3156(1)	6012(1)	23(1)
C(12')	2246(1)	4011(1)	6032(1)	21(1)
C(13')	2183(1)	5321(1)	5935(1)	24(1)
C(14')	4341(1)	3432(1)	5263(1)	29(1)
C(15')	5633(1)	2596(1)	5219(1)	28(1)
C(16')	6042(2)	1642(2)	4871(1)	57(1)
C(17')	7233(2)	883(2)	4830(1)	68(1)
C(18')	8031(2)	1084(2)	5123(1)	46(1)
C(19')	7632(1)	1995(1)	5484(1)	31(1)
C(20')	6438(1)	2741(1)	5535(1)	28(1)
C(21')	362(1)	6579(1)	6648(1)	24(1)

C(22')	-904(1)	7274(1)	6541(1)	29(1)
C(23')	-1876(2)	7851(2)	6999(1)	44(1)
C(24')	-2981(2)	8362(2)	6764(1)	64(1)
C(25')	-3090(2)	8306(2)	6098(1)	64(1)
C(26')	-2106(2)	7732(2)	5636(1)	45(1)
C(27')	-1014(1)	7221(1)	5873(1)	29(1)
C(28')	178(1)	6494(1)	5534(1)	24(1)

Table S11. Bond lengths [Å] and angles [°] for **3g**.

O(1)-C(10)	1.2250(17)	C(2)-H(2B)	0.9500
O(2)-H(2)	0.8400	C(2)-C(3)	1.362(3)
O(2)-C(12)	1.4255(16)	C(3)-H(3)	0.9500
O(3)-C(21)	1.2117(17)	C(3)-C(4)	1.409(2)
O(4)-C(28)	1.2091(18)	C(4)-C(5)	1.416(3)
N(1)-C(1)	1.321(2)	C(4)-C(9)	1.424(2)
N(1)-C(9)	1.3677(19)	C(5)-H(5)	0.9500
N(2)-H(2A)	0.8800	C(5)-C(6)	1.354(3)
N(2)-C(8)	1.4084(18)	C(6)-H(6)	0.9500
N(2)-C(10)	1.3609(18)	C(6)-C(7)	1.411(2)
N(3)-C(13)	1.4547(17)	C(7)-H(7)	0.9500
N(3)-C(21)	1.3960(18)	C(7)-C(8)	1.375(2)
N(3)-C(28)	1.3974(18)	C(8)-C(9)	1.431(2)
C(1)-H(1)	0.9500	C(10)-C(11)	1.5241(19)
C(1)-C(2)	1.407(2)	C(11)-H(11)	1.0000

C(11)-C(12)	1.5436(18)	C(24)-C(25)	1.390(2)
C(11)-C(14)	1.5425(18)	C(25)-H(25)	0.9500
C(12)-H(12)	1.0000	C(25)-C(26)	1.393(2)
C(12)-C(13)	1.5262(19)	C(26)-H(26)	0.9500
C(13)-H(13A)	0.9900	C(26)-C(27)	1.382(2)
C(13)-H(13B)	0.9900	C(27)-C(28)	1.4902(19)
C(14)-H(14A)	0.9900	O(1')-C(10')	1.2239(18)
C(14)-H(14B)	0.9900	O(2')-H(2')	0.8400
C(14)-C(15)	1.5154(19)	O(2')-C(12')	1.4270(16)
C(15)-C(16)	1.393(2)	O(3')-C(21')	1.2108(17)
C(15)-C(20)	1.390(2)	O(4')-C(28')	1.2132(18)
C(16)-H(16)	0.9500	N(1')-C(1')	1.319(2)
C(16)-C(17)	1.390(2)	N(1')-C(9')	1.367(2)
C(17)-H(17)	0.9500	N(2')-H(2'A)	0.8800
C(17)-C(18)	1.384(2)	N(2')-C(8')	1.4088(19)
C(18)-H(18)	0.9500	N(2')-C(10')	1.3593(19)
C(18)-C(19)	1.383(2)	N(3')-C(13')	1.4607(17)
C(19)-H(19)	0.9500	N(3')-C(21')	1.3949(18)
C(19)-C(20)	1.390(2)	N(3')-C(28')	1.3917(18)
C(20)-H(20)	0.9500	C(1')-H(1')	0.9500
C(21)-C(22)	1.4911(19)	C(1')-C(2')	1.408(3)
C(22)-C(23)	1.384(2)	C(2')-H(2'B)	0.9500
C(22)-C(27)	1.385(2)	C(2')-C(3')	1.355(3)
C(23)-H(23)	0.9500	C(3')-H(3')	0.9500
C(23)-C(24)	1.392(2)	C(3')-C(4')	1.408(3)
C(24)-H(24)	0.9500	C(4')-C(5')	1.415(3)

C(4')-C(9')	1.419(2)	C(18')-C(19')	1.368(2)
C(5')-H(5')	0.9500	C(19')-H(19')	0.9500
C(5')-C(6')	1.354(3)	C(19')-C(20')	1.390(2)
C(6')-H(6')	0.9500	C(20')-H(20')	0.9500
C(6')-C(7')	1.412(3)	C(21')-C(22')	1.490(2)
C(7')-H(7')	0.9500	C(22')-C(23')	1.379(2)
C(7')-C(8')	1.377(2)	C(22')-C(27')	1.387(2)
C(8')-C(9')	1.430(2)	C(23')-H(23')	0.9500
C(10')-C(11')	1.522(2)	C(23')-C(24')	1.393(3)
C(11')-H(11')	1.0000	C(24')-H(24')	0.9500
C(11')-C(12')	1.5459(18)	C(24')-C(25')	1.385(3)
C(11')-C(14')	1.544(2)	C(25')-H(25')	0.9500
C(12')-H(12')	1.0000	C(25')-C(26')	1.389(3)
C(12')-C(13')	1.522(2)	C(26')-H(26')	0.9500
C(13')-H(13C)	0.9900	C(26')-C(27')	1.379(2)
C(13')-H(13D)	0.9900	C(27')-C(28')	1.488(2)
C(14')-H(14C)	0.9900		
C(14')-H(14D)	0.9900	C(12)-O(2)-H(2)	109.5
C(14')-C(15')	1.5138(19)	C(1)-N(1)-C(9)	118.07(13)
C(15')-C(16')	1.394(2)	C(8)-N(2)-H(2A)	116.0
C(15')-C(20')	1.382(2)	C(10)-N(2)-H(2A)	116.0
C(16')-H(16')	0.9500	C(10)-N(2)-C(8)	127.98(12)
C(16')-C(17')	1.391(3)	C(21)-N(3)-C(13)	123.75(12)
C(17')-H(17')	0.9500	C(21)-N(3)-C(28)	112.15(11)
C(17')-C(18')	1.381(3)	C(28)-N(3)-C(13)	123.96(12)
C(18')-H(18')	0.9500	N(1)-C(1)-H(1)	118.1

N(1)-C(1)-C(2)	123.88(15)	O(1)-C(10)-N(2)	123.96(13)
C(2)-C(1)-H(1)	118.1	O(1)-C(10)-C(11)	121.04(12)
C(1)-C(2)-H(2B)	120.6	N(2)-C(10)-C(11)	115.00(11)
C(3)-C(2)-C(1)	118.76(15)	C(10)-C(11)-H(11)	109.4
C(3)-C(2)-H(2B)	120.6	C(10)-C(11)-C(12)	107.94(11)
C(2)-C(3)-H(3)	120.1	C(10)-C(11)-C(14)	109.92(11)
C(2)-C(3)-C(4)	119.79(15)	C(12)-C(11)-H(11)	109.4
C(4)-C(3)-H(3)	120.1	C(14)-C(11)-H(11)	109.4
C(3)-C(4)-C(5)	122.71(15)	C(14)-C(11)-C(12)	110.62(11)
C(3)-C(4)-C(9)	117.74(15)	O(2)-C(12)-C(11)	111.30(10)
C(5)-C(4)-C(9)	119.54(15)	O(2)-C(12)-H(12)	109.4
C(4)-C(5)-H(5)	120.1	O(2)-C(12)-C(13)	107.07(11)
C(6)-C(5)-C(4)	119.90(15)	C(11)-C(12)-H(12)	109.4
C(6)-C(5)-H(5)	120.1	C(13)-C(12)-C(11)	110.14(11)
C(5)-C(6)-H(6)	119.2	C(13)-C(12)-H(12)	109.4
C(5)-C(6)-C(7)	121.59(16)	N(3)-C(13)-C(12)	112.74(11)
C(7)-C(6)-H(6)	119.2	N(3)-C(13)-H(13A)	109.0
C(6)-C(7)-H(7)	119.8	N(3)-C(13)-H(13B)	109.0
C(8)-C(7)-C(6)	120.43(15)	C(12)-C(13)-H(13A)	109.0
C(8)-C(7)-H(7)	119.8	C(12)-C(13)-H(13B)	109.0
N(2)-C(8)-C(9)	117.55(12)	H(13A)-C(13)-H(13B)	107.8
C(7)-C(8)-N(2)	122.97(13)	C(11)-C(14)-H(14A)	108.3
C(7)-C(8)-C(9)	119.47(13)	C(11)-C(14)-H(14B)	108.3
N(1)-C(9)-C(4)	121.74(13)	H(14A)-C(14)-H(14B)	107.4
N(1)-C(9)-C(8)	119.20(12)	C(15)-C(14)-C(11)	115.87(11)
C(4)-C(9)-C(8)	119.05(13)	C(15)-C(14)-H(14A)	108.3

C(15)-C(14)-H(14B)	108.3	C(22)-C(23)-C(24)	117.01(13)
C(16)-C(15)-C(14)	121.15(13)	C(24)-C(23)-H(23)	121.5
C(20)-C(15)-C(14)	120.68(12)	C(23)-C(24)-H(24)	119.4
C(20)-C(15)-C(16)	118.05(13)	C(25)-C(24)-C(23)	121.21(13)
C(15)-C(16)-H(16)	119.6	C(25)-C(24)-H(24)	119.4
C(17)-C(16)-C(15)	120.87(14)	C(24)-C(25)-H(25)	119.3
C(17)-C(16)-H(16)	119.6	C(24)-C(25)-C(26)	121.35(13)
C(16)-C(17)-H(17)	119.8	C(26)-C(25)-H(25)	119.3
C(18)-C(17)-C(16)	120.34(14)	C(25)-C(26)-H(26)	121.4
C(18)-C(17)-H(17)	119.8	C(27)-C(26)-C(25)	117.10(14)
C(17)-C(18)-H(18)	120.3	C(27)-C(26)-H(26)	121.4
C(19)-C(18)-C(17)	119.41(14)	C(22)-C(27)-C(28)	108.11(12)
C(19)-C(18)-H(18)	120.3	C(26)-C(27)-C(22)	121.55(13)
C(18)-C(19)-H(19)	119.9	C(26)-C(27)-C(28)	130.33(13)
C(18)-C(19)-C(20)	120.13(15)	O(4)-C(28)-N(3)	124.50(12)
C(20)-C(19)-H(19)	119.9	O(4)-C(28)-C(27)	129.72(13)
C(15)-C(20)-C(19)	121.18(14)	N(3)-C(28)-C(27)	105.75(11)
C(15)-C(20)-H(20)	119.4	C(12')-O(2')-H(2')	109.5
C(19)-C(20)-H(20)	119.4	C(1')-N(1')-C(9')	117.88(14)
O(3)-C(21)-N(3)	125.28(12)	C(8')-N(2')-H(2'A)	116.1
O(3)-C(21)-C(22)	129.11(13)	C(10')-N(2')-H(2'A)	116.1
N(3)-C(21)-C(22)	105.58(11)	C(10')-N(2')-C(8')	127.90(13)
C(23)-C(22)-C(21)	129.89(13)	C(21')-N(3')-C(13')	123.68(11)
C(23)-C(22)-C(27)	121.74(13)	C(28')-N(3')-C(13')	123.96(11)
C(27)-C(22)-C(21)	108.36(12)	C(28')-N(3')-C(21')	112.29(11)
C(22)-C(23)-H(23)	121.5	N(1')-C(1')-H(1')	118.0

N(1')-C(1')-C(2')	124.04(18)	O(1')-C(10')-N(2')	123.94(14)
C(2')-C(1')-H(1')	118.0	O(1')-C(10')-C(11')	121.14(13)
C(1')-C(2')-H(2'B)	120.7	N(2')-C(10')-C(11')	114.92(12)
C(3')-C(2')-C(1')	118.66(18)	C(10')-C(11')-H(11')	109.3
C(3')-C(2')-H(2'B)	120.7	C(10')-C(11')-C(12')	107.95(11)
C(2')-C(3')-H(3')	120.1	C(10')-C(11')-C(14')	109.32(11)
C(2')-C(3')-C(4')	119.71(16)	C(12')-C(11')-H(11')	109.3
C(4')-C(3')-H(3')	120.1	C(14')-C(11')-H(11')	109.3
C(3')-C(4')-C(5')	122.54(16)	C(14')-C(11')-C(12')	111.55(11)
C(3')-C(4')-C(9')	117.99(17)	O(2')-C(12')-C(11')	111.26(11)
C(5')-C(4')-C(9')	119.47(17)	O(2')-C(12')-H(12')	109.5
C(4')-C(5')-H(5')	119.9	O(2')-C(12')-C(13')	106.69(10)
C(6')-C(5')-C(4')	120.25(16)	C(11')-C(12')-H(12')	109.5
C(6')-C(5')-H(5')	119.9	C(13')-C(12')-C(11')	110.48(11)
C(5')-C(6')-H(6')	119.4	C(13')-C(12')-H(12')	109.5
C(5')-C(6')-C(7')	121.30(18)	N(3')-C(13')-C(12')	111.73(11)
C(7')-C(6')-H(6')	119.4	N(3')-C(13')-H(13C)	109.3
C(6')-C(7')-H(7')	119.9	N(3')-C(13')-H(13D)	109.3
C(8')-C(7')-C(6')	120.28(18)	C(12')-C(13')-H(13C)	109.3
C(8')-C(7')-H(7')	119.9	C(12')-C(13')-H(13D)	109.3
N(2')-C(8')-C(9')	116.85(13)	H(13C)-C(13')-H(13D)	107.9
C(7')-C(8')-N(2')	123.50(15)	C(11')-C(14')-H(14C)	109.0
C(7')-C(8')-C(9')	119.65(14)	C(11')-C(14')-H(14D)	109.0
N(1')-C(9')-C(4')	121.65(15)	H(14C)-C(14')-H(14D)	107.8
N(1')-C(9')-C(8')	119.31(13)	C(15')-C(14')-C(11')	113.07(12)
C(4')-C(9')-C(8')	119.04(15)	C(15')-C(14')-H(14C)	109.0

C(15')-C(14')-H(14D)	109.0	C(22')-C(23')-C(24')	116.78(16)
C(16')-C(15')-C(14')	121.10(14)	C(24')-C(23')-H(23')	121.6
C(20')-C(15')-C(14')	120.89(14)	C(23')-C(24')-H(24')	119.3
C(20')-C(15')-C(16')	118.00(14)	C(25')-C(24')-C(23')	121.36(17)
C(15')-C(16')-H(16')	119.7	C(25')-C(24')-H(24')	119.3
C(17')-C(16')-C(15')	120.66(17)	C(24')-C(25')-H(25')	119.2
C(17')-C(16')-H(16')	119.7	C(24')-C(25')-C(26')	121.58(17)
C(16')-C(17')-H(17')	120.0	C(26')-C(25')-H(25')	119.2
C(18')-C(17')-C(16')	120.06(18)	C(25')-C(26')-H(26')	121.6
C(18')-C(17')-H(17')	120.0	C(27')-C(26')-C(25')	116.84(16)
C(17')-C(18')-H(18')	120.1	C(27')-C(26')-H(26')	121.6
C(19')-C(18')-C(17')	119.76(15)	C(22')-C(27')-C(28')	108.13(12)
C(19')-C(18')-H(18')	120.1	C(26')-C(27')-C(22')	121.65(15)
C(18')-C(19')-H(19')	119.9	C(26')-C(27')-C(28')	130.13(15)
C(18')-C(19')-C(20')	120.16(15)	O(4')-C(28')-N(3')	125.02(13)
C(20')-C(19')-H(19')	119.9	O(4')-C(28')-C(27')	129.19(13)
C(15')-C(20')-C(19')	121.27(14)	N(3')-C(28')-C(27')	105.79(12)
C(15')-C(20')-H(20')	119.4		
C(19')-C(20')-H(20')	119.4		
O(3')-C(21')-N(3')	125.58(13)		
O(3')-C(21')-C(22')	128.79(13)		
N(3')-C(21')-C(22')	105.63(11)		
C(23')-C(22')-C(21')	130.01(14)		
C(23')-C(22')-C(27')	121.79(14)		
C(27')-C(22')-C(21')	108.14(12)		
C(22')-C(23')-H(23')	121.6		

Table S12. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3g**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	37(1)	28(1)	25(1)	0(1)	-8(1)	-15(1)
O(2)	24(1)	21(1)	24(1)	-6(1)	0(1)	-8(1)
O(3)	25(1)	37(1)	30(1)	-8(1)	-6(1)	-12(1)
O(4)	28(1)	44(1)	27(1)	-12(1)	2(1)	-15(1)
N(1)	22(1)	26(1)	31(1)	-8(1)	-4(1)	-8(1)
N(2)	25(1)	22(1)	23(1)	-2(1)	-5(1)	-11(1)
N(3)	18(1)	27(1)	28(1)	-8(1)	1(1)	-10(1)
C(1)	27(1)	34(1)	35(1)	-12(1)	-6(1)	-10(1)
C(2)	33(1)	41(1)	45(1)	-21(1)	-8(1)	-13(1)
C(3)	40(1)	32(1)	57(1)	-18(1)	-9(1)	-17(1)
C(4)	33(1)	28(1)	46(1)	-10(1)	-6(1)	-14(1)
C(5)	60(1)	30(1)	54(1)	-4(1)	-12(1)	-27(1)
C(6)	61(1)	32(1)	44(1)	5(1)	-13(1)	-27(1)
C(7)	40(1)	28(1)	34(1)	-2(1)	-6(1)	-18(1)
C(8)	22(1)	22(1)	32(1)	-5(1)	-2(1)	-10(1)
C(9)	21(1)	24(1)	34(1)	-9(1)	-2(1)	-9(1)
C(10)	16(1)	24(1)	23(1)	-5(1)	0(1)	-7(1)
C(11)	19(1)	22(1)	21(1)	-5(1)	-2(1)	-9(1)

C(12)	19(1)	24(1)	22(1)	-7(1)	-2(1)	-7(1)
C(13)	16(1)	27(1)	34(1)	-9(1)	1(1)	-9(1)
C(14)	22(1)	27(1)	24(1)	-9(1)	1(1)	-12(1)
C(15)	23(1)	30(1)	22(1)	-12(1)	1(1)	-12(1)
C(16)	28(1)	29(1)	28(1)	-9(1)	1(1)	-13(1)
C(17)	29(1)	42(1)	29(1)	-12(1)	5(1)	-21(1)
C(18)	21(1)	53(1)	31(1)	-18(1)	2(1)	-14(1)
C(19)	26(1)	43(1)	33(1)	-6(1)	-4(1)	-6(1)
C(20)	26(1)	36(1)	27(1)	-5(1)	0(1)	-12(1)
C(21)	21(1)	21(1)	28(1)	-7(1)	-1(1)	-8(1)
C(22)	20(1)	20(1)	29(1)	-8(1)	-2(1)	-7(1)
C(23)	23(1)	26(1)	28(1)	-9(1)	1(1)	-9(1)
C(24)	20(1)	31(1)	35(1)	-13(1)	4(1)	-9(1)
C(25)	19(1)	39(1)	41(1)	-14(1)	-4(1)	-10(1)
C(26)	24(1)	39(1)	32(1)	-13(1)	-3(1)	-11(1)
C(27)	20(1)	24(1)	29(1)	-10(1)	0(1)	-8(1)
C(28)	22(1)	22(1)	28(1)	-9(1)	-1(1)	-9(1)
O(1')	42(1)	34(1)	43(1)	-17(1)	-16(1)	-7(1)
O(2')	21(1)	25(1)	25(1)	-7(1)	1(1)	-10(1)
O(3')	29(1)	33(1)	28(1)	-10(1)	-8(1)	-6(1)
O(4')	31(1)	38(1)	27(1)	-14(1)	-4(1)	-7(1)
N(1')	26(1)	28(1)	36(1)	-1(1)	-4(1)	-9(1)
N(2')	24(1)	21(1)	34(1)	-9(1)	-6(1)	-7(1)
N(3')	18(1)	22(1)	24(1)	-7(1)	-2(1)	-4(1)
C(1')	35(1)	38(1)	39(1)	3(1)	-7(1)	-11(1)

C(2')	32(1)	41(1)	49(1)	13(1)	-6(1)	-8(1)
C(3')	26(1)	27(1)	67(1)	12(1)	-3(1)	-5(1)
C(4')	21(1)	21(1)	63(1)	-1(1)	-1(1)	-4(1)
C(5')	35(1)	18(1)	94(2)	-7(1)	-8(1)	-7(1)
C(6')	39(1)	26(1)	93(2)	-22(1)	-11(1)	-9(1)
C(7')	27(1)	26(1)	64(1)	-18(1)	-9(1)	-4(1)
C(8')	16(1)	19(1)	46(1)	-9(1)	-2(1)	-4(1)
C(9')	16(1)	22(1)	47(1)	-5(1)	-1(1)	-4(1)
C(10')	17(1)	26(1)	32(1)	-12(1)	-4(1)	-2(1)
C(11')	18(1)	24(1)	24(1)	-7(1)	-3(1)	-5(1)
C(12')	18(1)	24(1)	21(1)	-6(1)	-2(1)	-6(1)
C(13')	16(1)	23(1)	29(1)	-7(1)	-1(1)	-4(1)
C(14')	21(1)	33(1)	26(1)	-7(1)	-1(1)	-4(1)
C(15')	20(1)	33(1)	25(1)	-8(1)	0(1)	-4(1)
C(16')	29(1)	81(2)	72(1)	-54(1)	-14(1)	4(1)
C(17')	37(1)	84(2)	91(2)	-67(1)	-17(1)	12(1)
C(18')	22(1)	56(1)	55(1)	-28(1)	-7(1)	6(1)
C(19')	22(1)	36(1)	31(1)	-6(1)	-4(1)	-9(1)
C(20')	26(1)	27(1)	30(1)	-8(1)	0(1)	-8(1)
C(21')	22(1)	23(1)	25(1)	-6(1)	-2(1)	-7(1)
C(22')	22(1)	33(1)	31(1)	-10(1)	-3(1)	-5(1)
C(23')	27(1)	60(1)	38(1)	-23(1)	-1(1)	-1(1)
C(24')	24(1)	97(2)	59(1)	-40(1)	0(1)	6(1)
C(25')	21(1)	99(2)	66(1)	-36(1)	-13(1)	5(1)
C(26')	25(1)	63(1)	47(1)	-23(1)	-13(1)	-2(1)

C(27')	21(1)	34(1)	32(1)	-11(1)	-4(1)	-6(1)
C(28')	22(1)	25(1)	27(1)	-7(1)	-3(1)	-8(1)

Table S13. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3g**.

	x	y	z	U(eq)
H(2)	3946	2032	8043	36
H(2A)	1136	2617	7854	27
H(1)	536	1968	6137	37
H(2B)	135	198	6213	44
H(3)	165	-1263	7292	47
H(5)	397	-1906	8601	54
H(6)	745	-1472	9557	53
H(7)	1158	321	9430	40
H(11)	1448	4128	8000	25
H(12)	3456	3160	8772	26
H(13A)	2948	5163	7544	30
H(13B)	2995	5275	8319	30
H(14A)	1438	4050	9473	28
H(14B)	1267	5264	8846	28
H(16)	-257	3166	9956	33
H(17)	-2343	3644	10288	38

H(18)	-3610	5526	9760	40
H(19)	-2775	6904	8870	44
H(20)	-691	6407	8517	36
H(23)	7397	4636	6003	31
H(24)	9227	4452	6288	35
H(25)	9353	4367	7453	38
H(26)	7686	4358	8391	36
H(2')	1353	3076	6729	35
H(2'A)	3927	1562	7122	30
H(1')	4663	216	9117	48
H(2'B)	4870	-1815	9710	57
H(3')	4460	-3026	9171	57
H(5')	3875	-3238	8102	61
H(6')	3459	-2417	6955	61
H(7')	3427	-416	6358	46
H(11')	3915	3255	6384	27
H(12')	1911	3958	5638	26
H(13C)	2603	5354	6289	28
H(13D)	2605	5605	5446	28
H(14C)	3978	3352	4896	35
H(14D)	4333	4285	5148	35
H(16')	5501	1510	4660	68
H(17')	7498	226	4600	81
H(18')	8854	591	5074	55
H(19')	8173	2117	5699	37

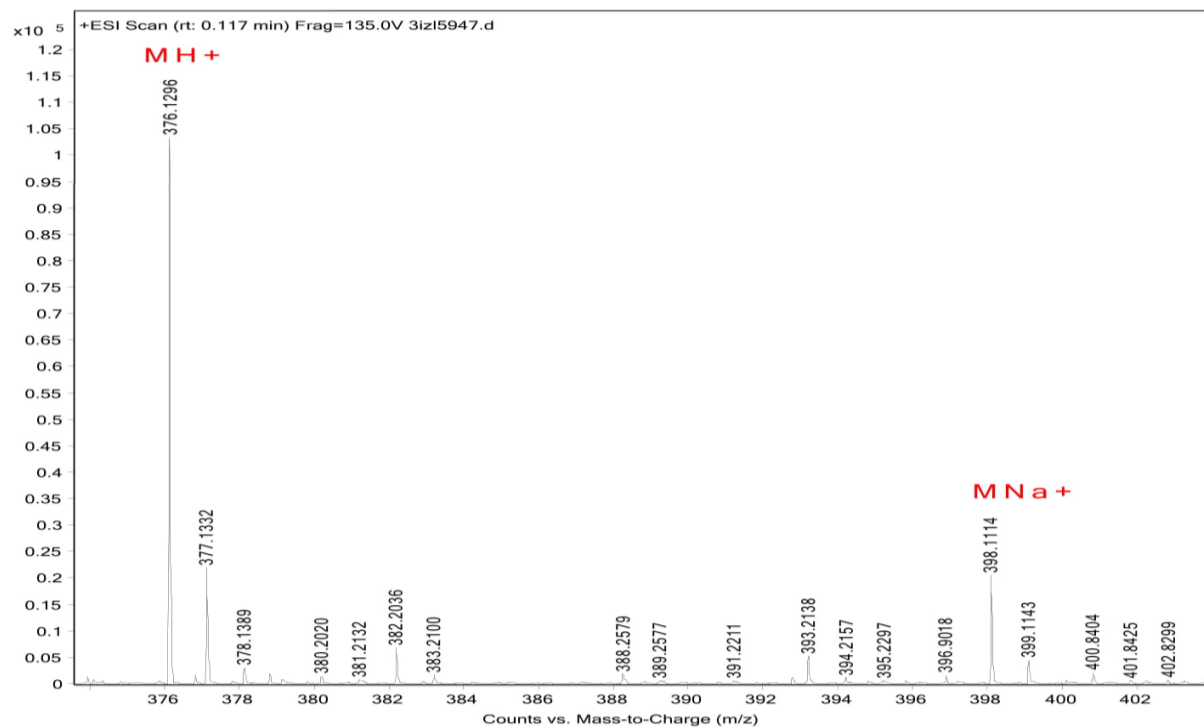
H(20')	6169	3364	5792	34
H(23')	-1795	7897	7453	53
H(24')	-3675	8757	7067	76
H(25')	-3856	8670	5953	77
H(26')	-2180	7694	5180	54

Table S14. Hydrogen bonds for **3g** [Å and °].

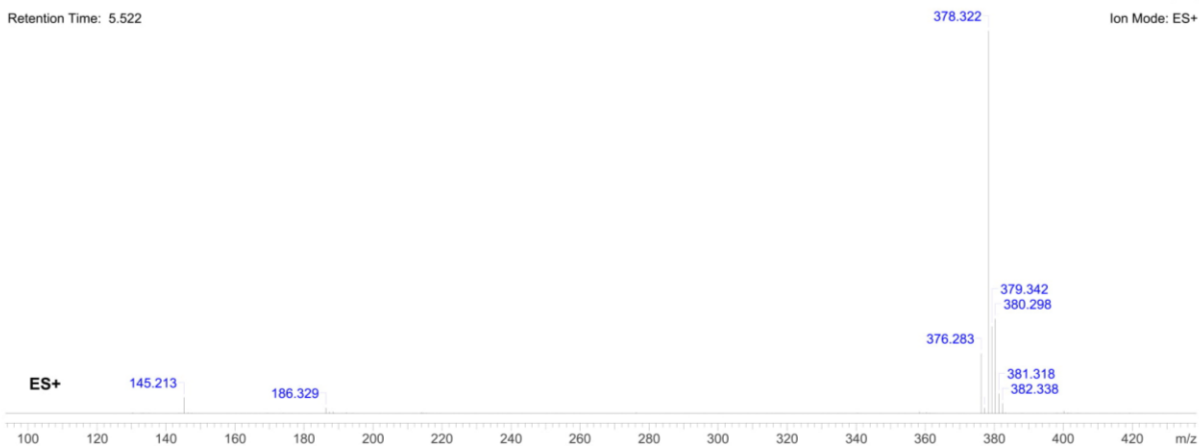
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...N(1')	0.84	2.04	2.8380(16)	158.2
N(2)-H(2A)...O(2')	0.88	2.27	3.1133(15)	161.2
O(2')-H(2')...N(1)	0.84	2.02	2.8249(15)	160.5
N(2')-H(2'A)...O(2)	0.88	2.23	3.0910(15)	164.8

Mass-Spec Data of Representative Mechanistic Studies

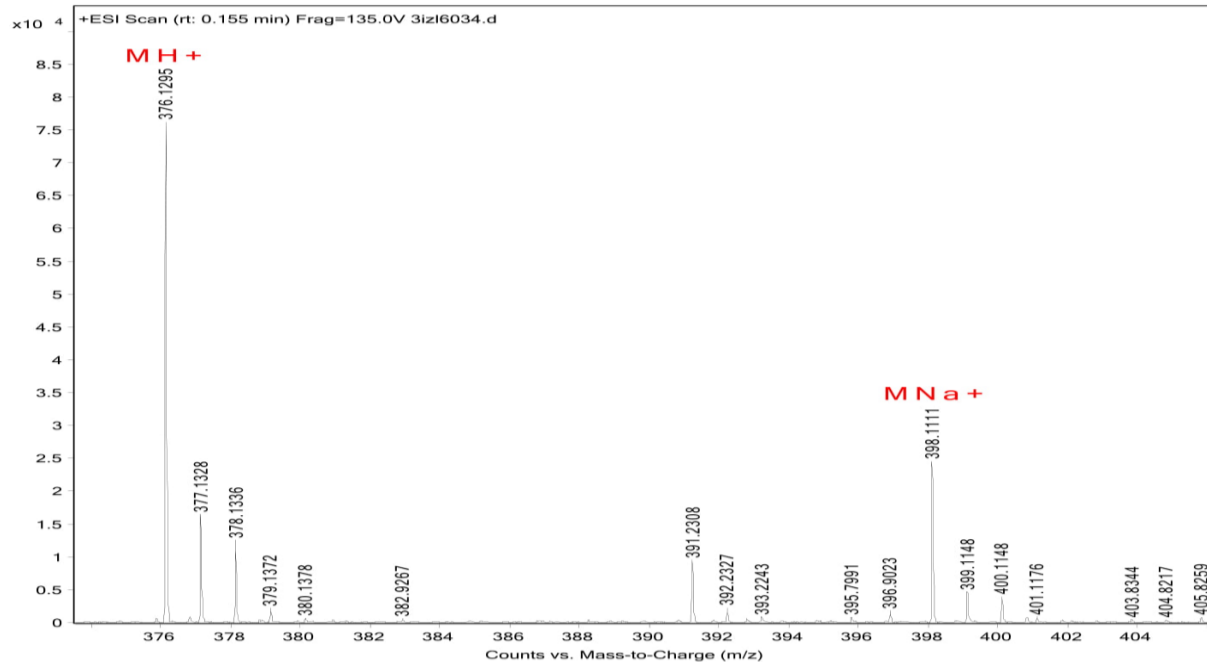
Scheme 4B, entry 1: Standard reaction



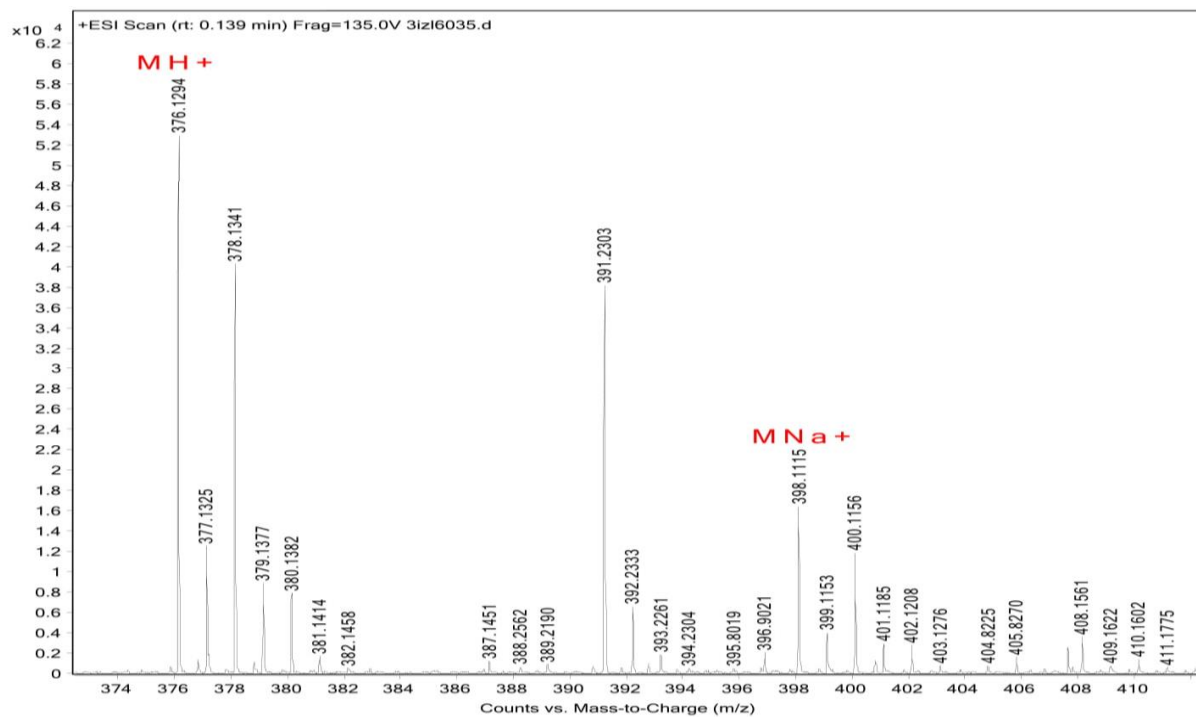
Scheme 4B, entry 2: ¹⁸O₂, 44 hours



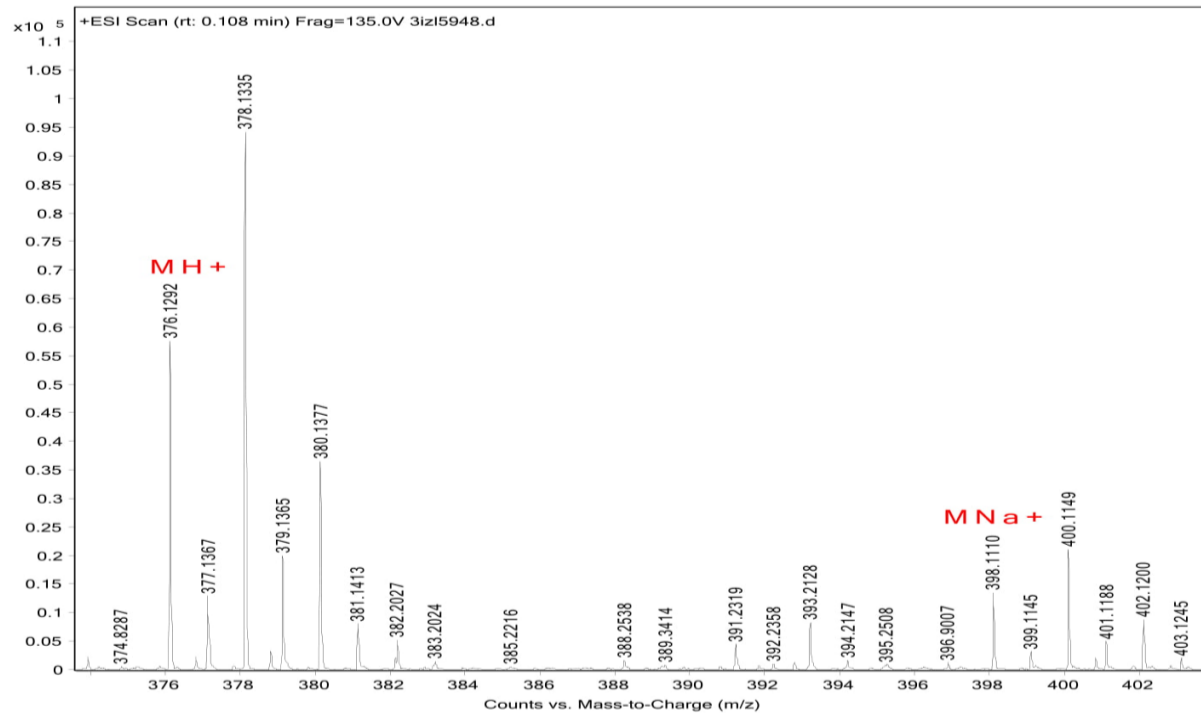
Scheme 4B, entry 3; Scheme S6A, entry 1: 1 equiv H₂¹⁸O, 44 hours



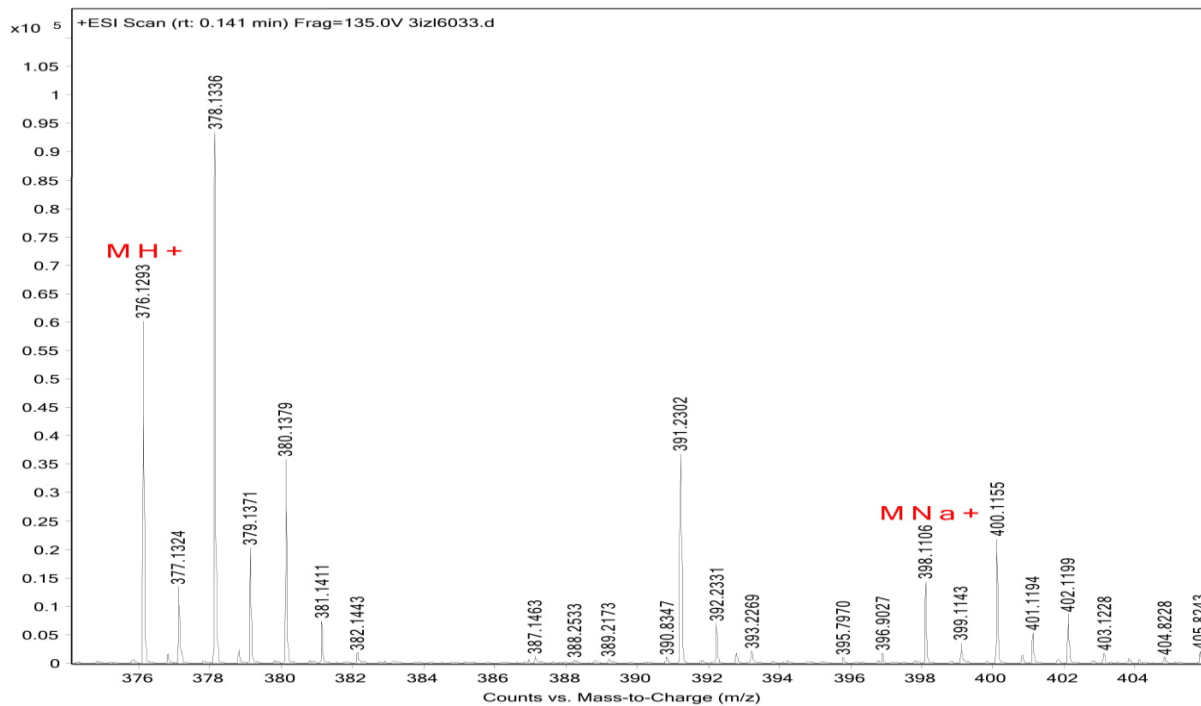
Scheme S6A, entry 2: 5 equiv H₂¹⁸O, 44 hours



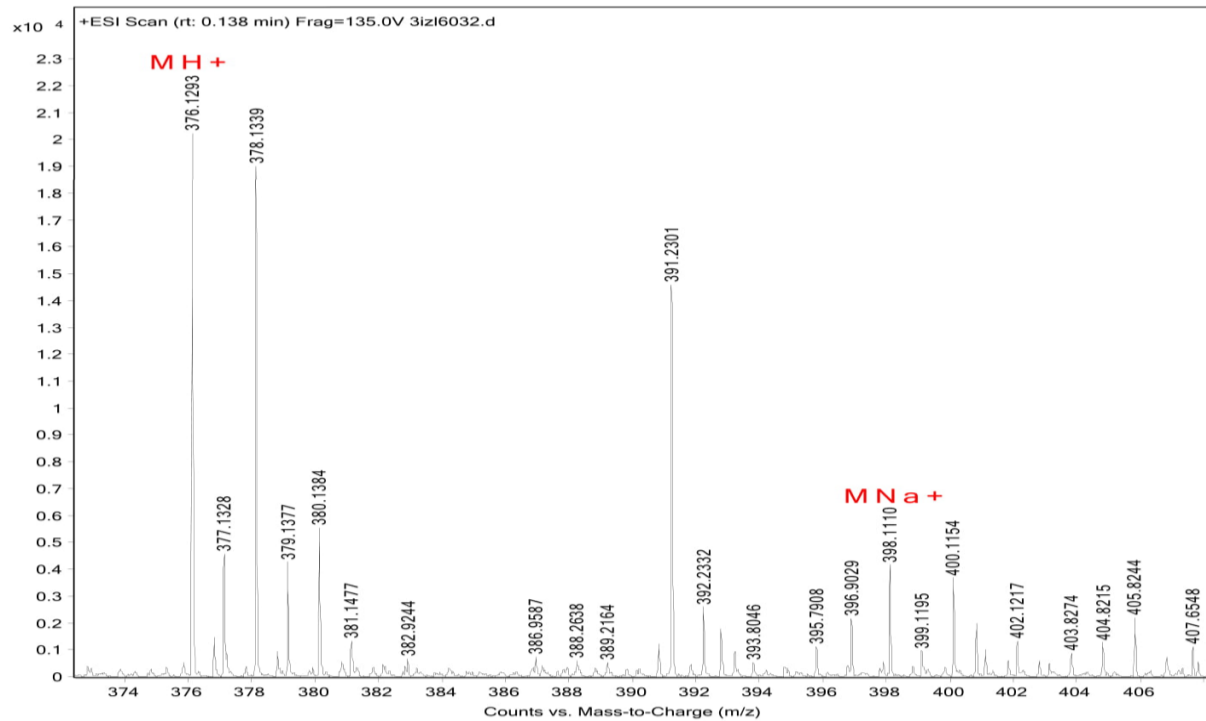
Scheme S6A, entry 3: 10 equiv H₂¹⁸O, 44 hours



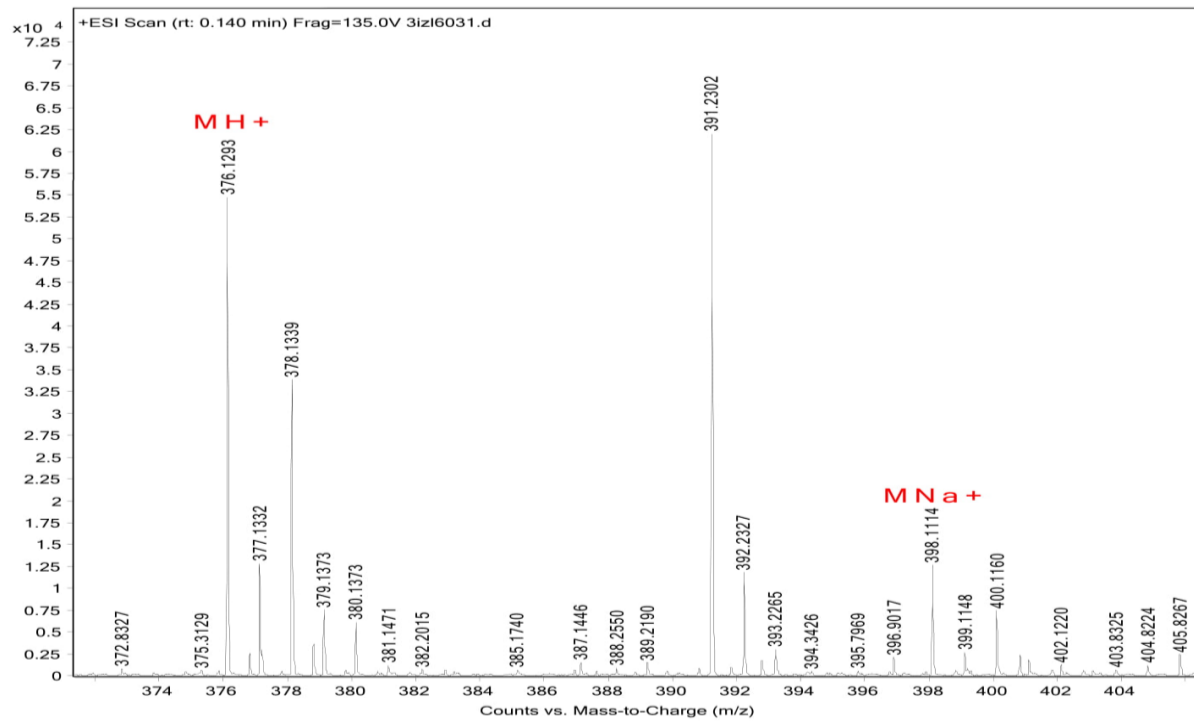
Scheme S6A, entry 4: 10 equiv H₂¹⁸O, 22 hours



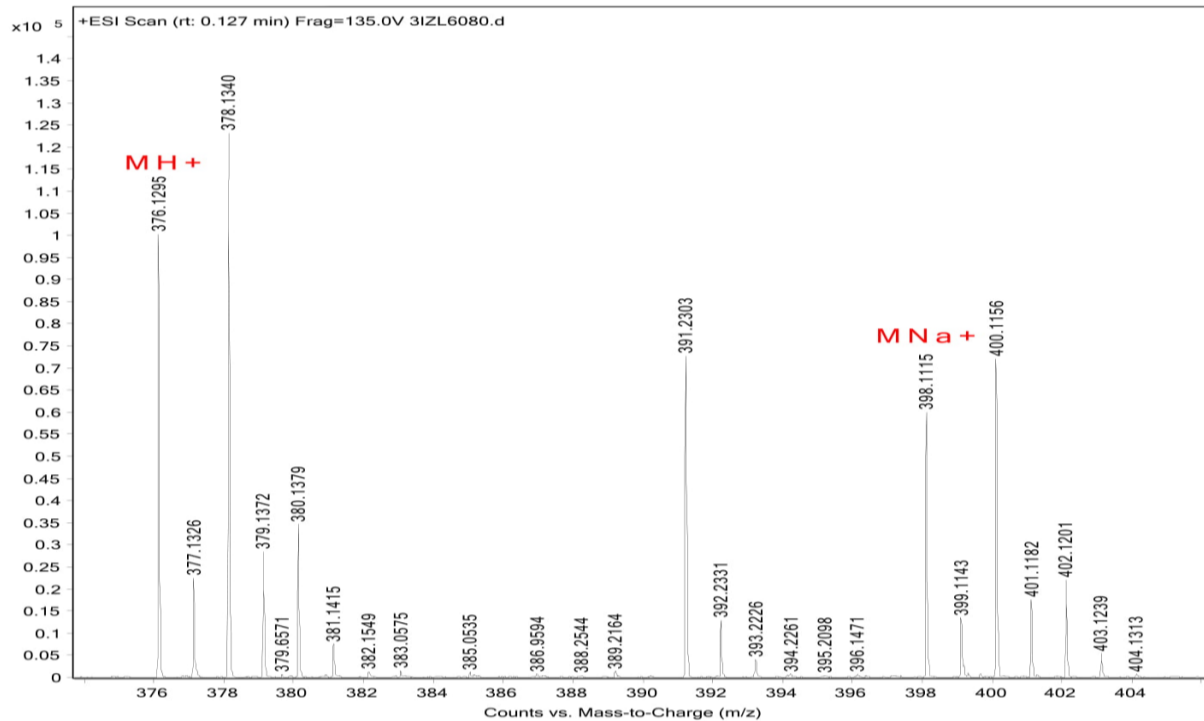
Scheme S6A, entry 5: 10 equiv H₂¹⁸O, 4 hours



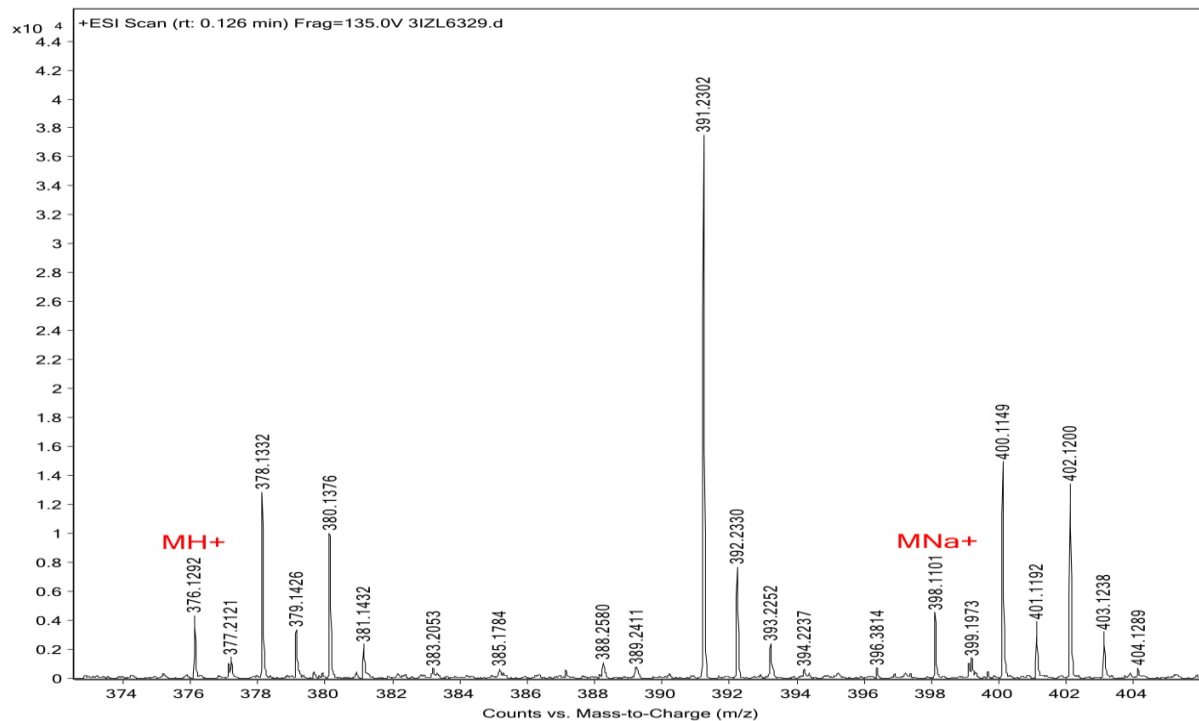
Scheme S6A, entry 6: 10 equiv H₂¹⁸O, 2 hours



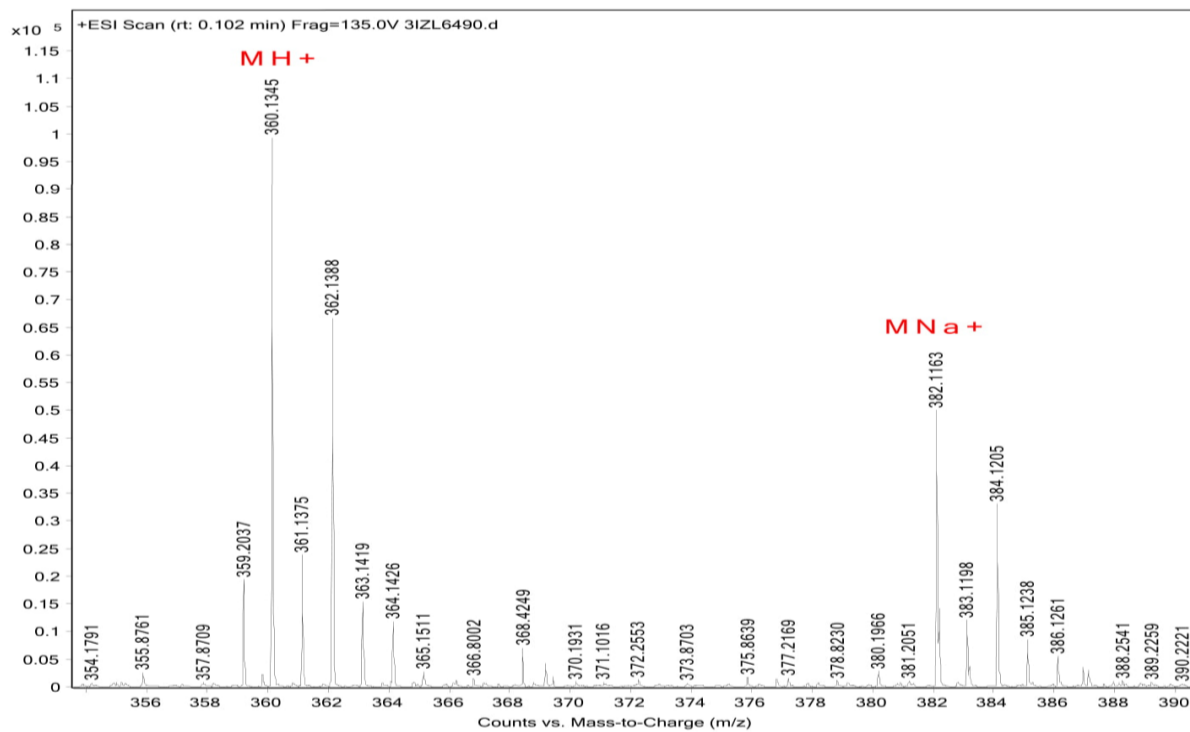
Scheme S6B, entry 1



Scheme S6B, entry 2



Scheme S6D:



^1H and ^{13}C NMR Spectra

