Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A facile synthesis of oroidin and its congeners through imidazo[1, 2-*a*]pyrimidine chemistry

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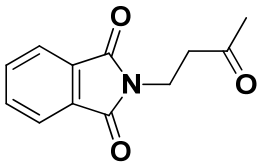
Supporting Information

General Information. All reactions were carried out in flame-dried glassware. Anhydrous THF, diethyl ether, dichloromethane, DMSO solvents were purchased from Aldrich and used directly. Thin-layer chromatography (TLC) was carried out on Silicycle F254 precoated, glass silica gel plates which were visualized with either ultraviolet light or stained with PMA. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AC (Tecmag DSPECT-F12 data acquisition system) spectrometer. Chemical shifts are reported in ppm with reference to tetramethylsilane [^{1}H-NMR: $CDCl_3$ (0.00 δ)] or residual protio solvent signals [^{1}H-NMR: CDCl3 (7.26 δ); ^{13}C-NMR: $CDCl_3$ (77.27 δ)]. Signal patterns are indicated as br (broad peak); s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). Infrared spectral data were obtained using Perkin-Elmer Spectrum 100 FT-IR spectrometer with diamond ATR accessory as thin film. HRMS data was obtained on Q-Tof instrument using ESI mode (University of Illinois, SCS, Mass Spectrometry Lab).

2-(3-oxobutyl)isoindoline-1,3-dione (15)



To a well-stirred suspension of phthalimide 147.00 g (1 mol) and of 3-buten-2-one 70.00 g (1 mol) in 1000 mL of EtOAc was added a freshly prepared NaOEt solution, prepared from 1.15g (0.05 mol) of sodium in 200 mL of anhydrous EtOH, under a N_2 atmosphere. After 2 h stirring at ambient temperature, the mixture was refluxed until an almost clear solution was obtained and refluxing was continued for an additional 2 h. The reaction mixture was cooled to room temperature and water (1L) was added. The precipitated solid was filtered off and washed with water (3 x 100 mL) and dried under reduced pressure to give the title compound **15** as a white crystalline solid (195 g, 90 %).

Melting Point: 108.5-110 ^{o}C (lit.[1] M. P = 111 ^{o}C)

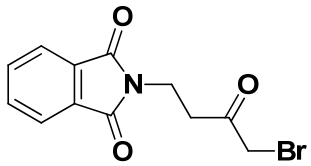
IR (Diamond-ATR, neat): νmax: 1771, 1717, 1437, 1395, 1305, 1040, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.62-7.96 (m, 4H), 3.96 (t, J = 7.0 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 2.22 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 206.2, 168.3, 134.3, 127.1, 123.5, 41.8, 33.3, 30.3.

1. Viscontini, M.; Kaiser, W.; Leidner, H. A. *Helv. Chim. Acta* **1965,** *48*, 1221-5

2-(4-bromo-3-oxobutyl) isoindoline-1,3-dione (16)



To a solution of 2-(3-oxobutyl) isoindole-1,3-dione **15** (114.00 g, 0.5 mol) in methanol (500 mL) was added bromine (88.00 g, 0.55 mol) drop wise at 0°C; the reaction mixture was stirred at the same temperature for 30 min and then at room temperature for 15 h. To the resulting clear solution was added concentrated sulfuric acid (10 M; 100 mL) and the resulting mixture was stirred at rt for 24 h. The precipitated solid was filtered and dried in vacuum to afford compound **16** (82 g, 52%) as a white solid. The yields were improved to 82% by following the modification of *Org. Process Res. Dev.* **2012**, *16*, 704−709.

Melting point: 120-124°C (lit.[2] M. P = 119-120 °C)

IR (Diamond-ATR, neat): vmax: 1770, 1706, 1437, 1378, 1327, 1086, 1002, 875, 713, 530 cm^{-1}.

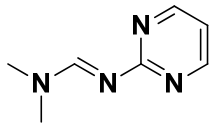
^{1}H NMR ($CDCl_3$): δ 7.60-7.96 (m, 4H), 4.04 (t, J = 7.3 Hz, 2H), 3.92 (s, 2H), 3.21 (t, J = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ 200.0, 178.0, 134.6, 123.8, 38.4, 33.5.

MS (ESI): $[M + H]^+$ 214 (**MP**: 120-122.4 °C).

2. Jones, R. G. *J. Am. Chem. Soc*. **1950**, *72*, 4526-9

(E)-*N*,*N*-dimethyl-*N'*-(pyrimidin-2-yl)formimidamide (11)[3]



To a solution of 2-aminopyrimidine (100.00 g, 1.05 mol) in toluene (600 mL) was added dimethylformamide dimethylacetal (141 mL, 1.05 mol) dropwise and the resulting mixture was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and the solvent was evaporated to give (175, 98%) of the amidine **11** as a white solid.

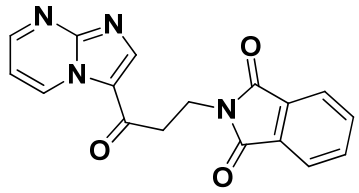
Melting point: 150-152°C

^{1}H NMR ($CDCl_3$): δ 8.64 (s, 1H), 8.48 (d, J = 4. 8 Hz, 2H), 6.95 (t, J = 4.8 Hz, 1H), 3.0 (s, 3H) 3.0 (s, 3H).;

^{13}C NMR ($CDCl_3$): δ 158.3, 114.8, 111.4, 41.1, 35.1.

3. Podergajs, S.; Stanovnik, B.; Tisler, M. *Synthesis*, **1984**, 263.

2-(3-(imidazo[1,2-a]pyrimidin-3-yl)-3-oxopropyl)isoindoline-1,3-dione (19)



A mixture of *N,N*-dimethyl-*N*-pyrimidylformamidine **11** (25.00 g, 0.16 mol) and 2-(4-bromo-3-oxobutyl)isoindoline-1,3-dione **16** (49.29 g, 0.16 mol) in ethanol (60 ml) was stirred under reflux for 2 h. The mixture was cooled to room temperature. The resulting precipitate was collected by filtration and washed with cold ethanol (3 x 30 mL) to give compound **19** as a pale white solid (37.31 g, 70%).

Melting point: 220-225 °C

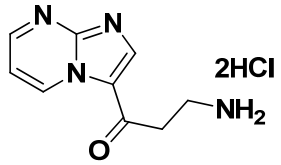
IR (Diamond-ATR, neat): vmax: 3039, 2974, 2039, 1683, 1639, 1520, 1403, 1360, 1152, 840, 768, cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.87 (dd, J = 6.8, 2.0 Hz, 1H), 8.80 (dd, J = 4.1, 2.0 Hz, 1H), 8.52 (s, 1H), 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.72 (dd, J = 5.4, 3.1 Hz, 2H), 7.26 (s, 1H), 7.18 (dd, J = 6.8, 4.1 Hz, 1H), 4.18 (t, J = 7.0 Hz, 2H), 3.39 (t, J = 7.0 Hz, 2H).

^{13}CNMR ($CDCl_3$): δ 200.3, 187.8, 168.3, 154.2, 143.2, 138.0, 136.8, 134.3, 132.1, 123.6, 111.8, 37.6, 33.7.

HRMS (ESI+) *m/z* calc. for $[C_{17}H_{12}N_4O_3+H^+]$+: 321.0981, obsd.: 321.0988.

3-amino-1-(imidazo[1,2-a]pyrimidin-3-yl)propan-1-one hydrochloride (20)



Compound **19** (30.00 g, 0.09 mol) was dissolved in 6N hydrochloric acid (125 ml) and the reaction mixture was heated at reflux for 24 h. After completion, reaction mixture was cooled to room temperature and solid phthalic acid was filtered. The filtrate was extracted with dichloromethane and the aqueous layer was concentrated under reduced pressure and the residue was recrystalised using ethanol to gave **20** as a brown solid (20.15 g, 81 %).

Melting point: 206-210 °C

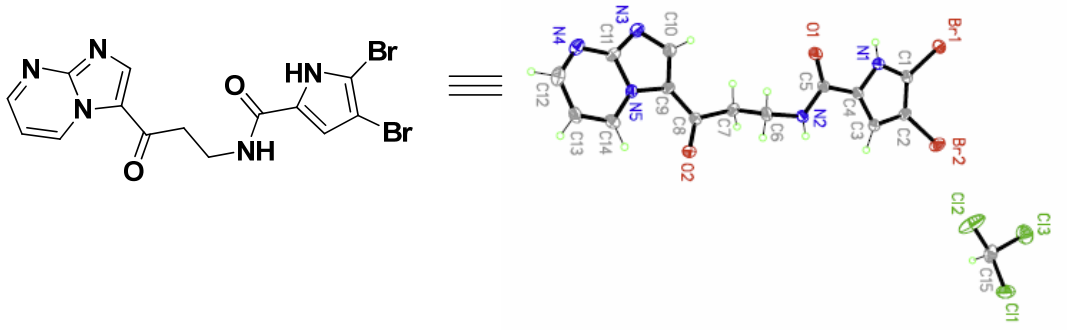
IR (Diamond-ATR, neat): νmax: 3102, 2961, 1775, 1696, 1633, 1514, 1394, 1169, 997, 941, 805, 720 cm^{-1}.

^{1}H NMR (D_2O): δ 10.00 (dd, J = 6.9, 1.5 Hz 1H), 9.12 (dd, J = 4.2, 1.5 Hz, 1H), 9.06 (s, 1H), 7.80 (dd, J = 4.2, 6.9 Hz, 1H), 3.57 (t, J = 6.2 Hz, 2H), 3.47 (t, J = 6.2 Hz, 2H).

^{13}C NMR (D_2O + DMSO-D_6): 190.1, 161.3, 146.3, 140.7, 133.6, 122.6, 117.4, 37.4, 35.4.

HRMS (ESI+) *m/z* calc. for $[C_9H_{10}N_4O+H^+]+$: 191.0933, obsd.: 191.0933

4,5-dibromo-*N*-(3-(imidazo[1,2-a]pyrimidin-2-yl)-3-oxopropyl)-1H-pyrrole-2-carboxamide (21a)



To a solution of **19** (2.00 g, 10 mmol) in anhydrous DMF (10 ml), anhydrous sodium carbonate (5.10 g, 0.05 mol) was added and the reaction mixture was stirred for 10 min and dibromopyrrolyl trichloroacetone **20a** (5.63 g, 0.015 mol) was added and reaction mixture was stirred at 55 °C for 2h. After completion of the reaction (monitored by TLC) solvent was removed under reduced pressure. The residue was purified by flash chromatography using methanol:dichloromethane (1:9) as eluent to obtain compound **21a** ((2.4 g, 55 %).

Melting point: 195-200 °C

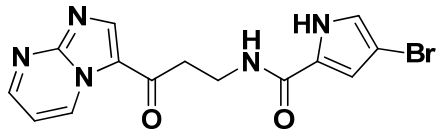
IR (Diamond-ATR, neat): vmax: 3227, 1628, 1522, 1408, 1325, 1181, 767, 733 cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 12.68 (s, 1H), 9.79 (dd, J = 6.0, 2.1 Hz, 1H), 8.82 (dd, J = 4.2, 2.1 Hz, 1H), 8.76 (s, 1H), 8.23 (t, J = 5.4 Hz, 1H), 7.38 (dd, J = 6.0, 4.2 Hz, 1H), 6.86 (s, 1H), 3.60 (q, J = 6.6 Hz, 2H), 3.20 (t, J = 6.6 Hz, 2H).

^{13}CNMR (DMSO-D_6): δ 188.7, 158.9, 153.8, 150.5, 144.3, 136.4, 128.0, 121.7, 112.5, 111.7, 104.5, 97.7, 38.7, 34.9.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{11}N_5O_2Br_2$+H^+]: 439.9359, obsd.: 439.9358.

4-bromo-*N*-(3-(imidazo[1,2-a]pyrimidin-2-yl)-3-oxopropyl)-1H-pyrrole-2-carboxamide (21b)



To a solution of **19** (2.00 g, 10 mmol) in anhydrous DMF (10 ml), anhydrous sodium carbonate (5.10 g, 0.05 mol) was added and the reaction mixture was stirred for 10 min and monobromopyrrolyl trichloroacetone **20b** (4.43 g, 0.015 mol) was added and reaction mixture was stirred at 55 °C for 2h. After completion of reaction (TLC) solvent was removed rotary evaporation under reduced pressure. The residue was purified by flash column chromatography using methanol:dichloromethane (1:9) as eluent to obtain condensed compound **21b** (2.02 g, 55%).

Melting point: 205-210 °C

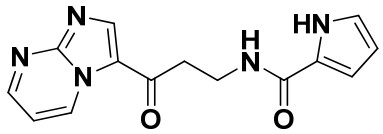
IR (Diamond-ATR, neat): vmax: 3124, 2940, 1628, 1522, 1408, 1325, 1178, 974, 773 cm^{-1}.

^{1}H NMR (DMSO-D_6): 11.83 (s, 1H), 9.79 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.83 (dd, *J* = 4.2, 2.0 Hz, 1H), 8.77 (s, 1H), 8.23 (t, *J* = 5.4 Hz, 2H), 7.40 (dd, *J* = 6.8, 4.2 Hz, 1H), 6.96 (s, 1H), 6.79 (s, 1H), 3.62 (q, *J* = 6.4 Hz, 2H), 3.22 (t, *J* = 6.4 Hz, 2H).

^{13}CNMR (DMSO-D_6): δ 189.0, 160.8, 153.8, 150.5, 144.3, 136.4, 126.1, 121.2, 111.7, 109.8, 108.5, 94.9, 39.1, 34.9.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{12}N_5O_2Br+H^+$]: 362.0247, obsd.: 362.0253.

_N_-(3-(imidazo[1,2-a]pyrimidin-2-yl)-3-oxopropyl)-1H-pyrrole-2-carboxamide (21c)



To a solution of **19** (2.00 g, 10.15 mmol) in anhydrous DMF (10 ml), anhydrous sodium carbonate (5.10 g, 0.05 mol) was added and the reaction mixture was stirred for 10 min and pyrrolyl trichloroacetone **20c** (3.22 g, 0.015 mol) was added and reaction mixture was stirred at 55 °C for 2h. After completion of reaction (TLC) solvent was removed by rotary evaporation under reduced pressure. The residue was purified by flash chromatography using methanol:dichloromethane as eluent to obtain condensed compound **21c** (1.43 g, 50 %).

Melting point: 220-225 °C

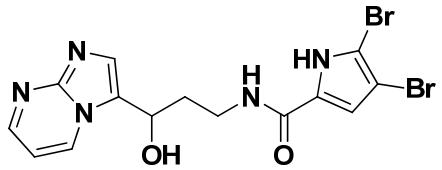
IR (Diamond-ATR, neat): vmax: 3039, 2975, 2698, 2040, 1652, 1634, 1520, 1403, 1350, 1152, 826, 769 cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 11.43 (s, 1H), 9.78 (dd, J = 6.8, 2.0 Hz, 1H), 8.82 (dd, J = 4.2, 2.0 Hz, 1H), 8.77 (s, 1H), 8.14 (t, J = 5.5 Hz, 1H), 7.39 (dd, J = 6.8, 4.3 Hz, 1H), 6.83 (dd, J = 2.1, 3.9 Hz, 1H), 6.70 (dd, J = 2.1, 4.8, 1H), 6.04 (dd, J = 2.4, 5.7 Hz, 1H), 4.16 (q, J = 6.4 Hz, 2H), 3.75 (t, J = 6.4 Hz, 2H).

^{13}CNMR (DMSO-D_6): δ 189.1, 160.8, 153.9, 150.6, 144.3, 136.5, 126.1, 121.8, 121.3, 111.8, 109.9, 108.5, 39.1, 35.0.

HRMS (ESI+) *m/z* calc. for [$C_{14}H_{13}N_5O_2$+H^+]: 284.1155, obsd.: 284.1147.

4,5-dibromo-*N*-(3-hydroxy-3-(imidazo[1,2-a]pyrimidin-2-yl)propyl)-1H-pyrrole-2-carboxamide (22a)



To a well stirred solution of keto compound **21a** (0.50 g, 1.76 mmol) in THF:H_2O (9:1) 15 mL was added $NaBH_4$ (0.032 g, 0.88 mmol) portion wise at 0 °C and the reaction mixture was continue to stir at room temp. After completion of reaction (30 min), it was quenched using acetic acid. The pH was adjusted to 6.5 with acetic acid and the solvent was removed by rotary evaporation under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2) eluting with dichloromethane:methanol (1:9) to deliver the hydroxyl compound **22a** (0.42 g, 85%).

Melting point: 200-204 °C

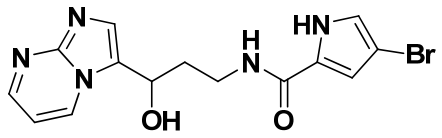
IR (Diamond-ATR, neat): vmax: 3228, 1630, 1614, 1520, 1403, 1327, 1135, 921, 773 cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 12.69 (s, 1H), 8.86 (dd, J = 6.8, 1.9 Hz, 1H), 8.55 (dd, J = 4.0, 1.9 Hz, 1H), 8.20 (t, J = 5.4 Hz, 1H), 7.70 (s, 1H), 7.09 (dd, J = 6.8, 4.0 Hz, 1H), 6.90 (s, 1H), 5.53 (d, J = 6.0 Hz, 1H), 5.02 (q, J = 6.3 Hz, 1H), 3.37 (q, J = 5.5 Hz, 2H), 2.09-2.21 (m, 2H).

^{13}CNMR (DMSO-D_6): 159.0, 149.6, 148.1, 133.9, 131.2, 128.1, 125.5, 112.4, 108.3, 104.4, 97.7, 61.3, 35.7, 34.4.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{13}N_5O_2Br_2$+H^+]: 441.9505, obsd.: 441.9514.

4-bromo-*N*-(3-hydroxy-3-(imidazo[1,2-*a*]pyrimidin-2-yl)propyl)-1H-pyrrole-2-carboxamide (22b)



To a well stirred solution of keto compound **21b** (0.5 g, 1.37 mmol) in THF:H_2O (9:1) 15 mL was added $NaBH_4$ (0.025g, 0.68 mmol) portionwise at 0 ^oC and the reaction mixture was continued to stir at room temp. After completion of reaction (30 min), it was quenched using acetic acid. The pH was adjusted to 6.5 and solvent was removed by rotary evaporation under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with dichloromethane:methanol (1:9) to deliver the hydroxyl compound **22b** (0.41g, 82%).

Melting point: 201-205 °C

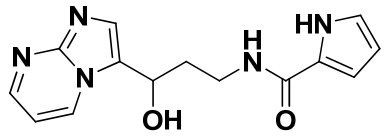
IR (Diamond-ATR, neat): vmax: 3228, 2948, 1604, 1561, 1516, 1403, 1327, 1135, 921, 773 cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 11.85 (s, 1H), 8.88 (dd, J = 6.8, 1.9 Hz, 1H), 8.55 (dd, J = 4.0, 1.9 Hz, 1H), 8.20 (t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.08 (dd, J = 6.8, 4.0 Hz, 1H), 6.97 (d, J = 1.5 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 5.54 (d, J = 7.5 Hz, 1H), 5.00 – 5.04 (m, 1H), 3.38 (q, J = 6.6 Hz, 2H), 2.08 – 2.22 (m, 2H).

^{13}CNMR (DMSO-D_6): δ 158.4, 148.3, 146.9, 132.6, 129.9, 125.5, 124.3, 119.8, 110.0, 107.0, 93.6, 60.1, 34.3, 33.2.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{14}N_5O_2Br+H^+$]: 364.0412, obsd.: 364.0409.

_N_-(3-hydroxy-3-(imidazo[1,2-*a*]pyrimidin-2-yl)propyl)-1H-pyrrole-2-carboxamide (22c)



To a well stirred solution of keto compound **21c** (500mg, 1.76 mmol) in THF:H_2O (9:1) 15 mL was added $NaBH_4$ (0.032g, 0.88 mmol) portion wise at 0 °C and the reaction mixture was continued to stir at room temp. After completion of reaction (30 min), it was quenched using acetic acid. The pH was adjusted to 6.5 and solvent was removed by rotary evaporation under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with dichloromethane:methanol (1:9) to deliver the hydroxyl compound **22c** (0.40 g, 80%).

Melting point: 90-95 °C

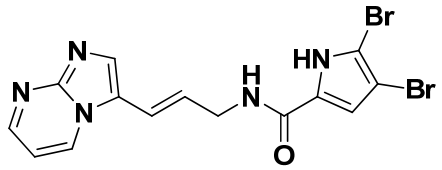
IR (Diamond-ATR, neat): νmax: 3039, 2975, 1635, 1621, 1520, 1403, 1350, 1152, 827, cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 10.82 (s, 1H), 8.27 (dd, J = 6.9, 2.1 Hz, 1H), 7.95 (dd, J = 2.1, 4.2 Hz, 1H), 7.46 (t, J = 5.5 Hz, 1H), 7.11 (s, 1H), 6.48 (dd, J = 6.9, 4.2 Hz, 1H), 6.23 (dd, J = 1.5, 4.7 Hz, 1H), 6.13 (dd, J = 1.5, 2.4 Hz, 1H), 5.46 (dd, J = 2.4, 4.7 Hz, 1H), 4.94 (d, J = 6.3 Hz, 1H), 4.44 (q, J = 6.3 Hz, 1H), 2.78 (q, J = 5.4 Hz, 1H), 1.49 – 1.63 (m, 2H).

^{13}CNMR (DMSO-D_6): δ 154.4, 142.4, 140.4, 126.7, 125.9, 122.1, 117.5, 113.4, 101.3, 100.7, 100.5, 53.9, 27.6, 26.2.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{15}N_5O_2$+H^+]: 286.1295, obsd.: 286.1304.

(*E*)-4,5-dibromo-*N*-(3-(imidazo[1,2-a]pyrimidin-2-yl)allyl)-1H-pyrrole-2-carboxamide (23a)



A solution of compound **22a** (100 mg, 0.226 mmol) in acetic acid (5 mL)was heated at 70 ^{o}C for 8 h. After completion of the reaction acetic acid was removed by rotary evaporation under reduced pressure and the residue was purified by flash column chromatography using methanol:dichloromethane (1:9) as eluent to obtain olefin **23a** (0.053 g, 55%)

Melting point: 185-190 °C

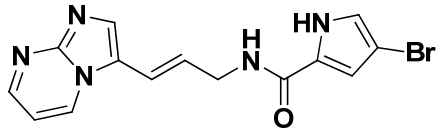
IR (Diamond-ATR, neat): νmax: 3103, 2936, 2851, 1621, 1562, 1509, 1304, 1151, 973, 947, 795, 762 cm^{-1}.

^{1}H NMR (DMSO-D_6): δ 12.76 (s, 1H), 9.08 (dd, J = 6.9, 2.1 Hz, 1H), 8.55 (dd, J = 4.2, 2.1 Hz, 1H), 8.48 (t, J = 5.4 Hz, 1H), 8.06 (s, 1H), 7.16 (dd, J = 6.9, 4.2 Hz, 1H), 7.01 (s, 1H), 6.90 (d, J = 16.0 Hz, 1H), 6.40 (dt, J = 16.0, 5.8 Hz, 1H), 4.08 (t, J = 5.4 Hz, 2H).

^{13}CNMR (DMSO-D_6): δ 158.7, 149.8, 147.7, 133.0, 131.5, 128.1, 127.6, 121.7, 115.4, 112.8, 109.3, 104.7, 97.9, 40.3.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{11}N_5O_2Br_2$+H^+]: 423.9407, obsd.: 423.9409.

(*E*)-4-bromo-*N*-(3-(imidazo[1,2-a]pyrimidin-2-yl)allyl)-1H-pyrrole-2-carboxamide (23b)



A solution of compound **22b** (0.1 g, 0.274 mmol) in acetic acid (5 mL) was heated at 70 ^{o}C for 8 h. After completion of the reaction acetic acid was removed by evaporation under reduced pressure and the crude compound was purified by flash column chromatography using methanol:dichloromethane (1:9) as eluent to obtain olefin **23b** (0.052 g, 55%).

Melting point: 210-214 °C

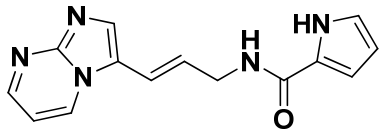
IR (Diamond-ATR, neat): vmax: 3290, 2918, 1629, 1582, 1513, 1434, 11285, 1157, 970, 919, 770, 749 cm^{-1}.

^{1}H NMR (DMSO-D$_6$): δ 11.87 (s, 1H), 9.03 (dd, J = 6.7, 1.5 Hz, 1H), 8.50 (dd, J = 4.0, 1.5 Hz, 1H), 8.42 (t, J = 6.0 Hz, 1H), 8.01 (s, 1H), 7.10 (dd, J = 6.7, 4.0 Hz, 2H), 6.99 (s, 1H), 6.91 (s, 1H), 6.86 (d, J = 16.0 Hz, 1H), 6.38 (dt, J = 16.0, 5.4 Hz, 1H), 4.08 (t, J = 5.4 Hz, 2H).

^{13}CNMR (DMSO-D$_6$): δ 159.4, 149.4, 148.1, 132.8, 132.3, 127.5, 126.7, 121.5, 121.2, 115.5, 111.6, 109.1, 94.9, 40.7.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{13}N_5OBr+H^+$]: 346.0301 obsd.: 346.0303

(*E*)-*N*-(3-(imidazo[1,2-a]pyrimidin-2-yl)allyl)-1H-pyrrole-2-carboxamide (23c)



A solution of compound **22c** (0.350 mmol) in acetic acid (5 mL) was heated at 70 ^{o}C for 8 h. After completion of reaction, acetic acid was removed by evaporation under reduced pressure and compound was purified by using flash chromatography using methanol:dichloromethane (1:9) as eluent to obtain olefin compound **23c** (0.046 g, 50%).

Melting point: 216-220 °C

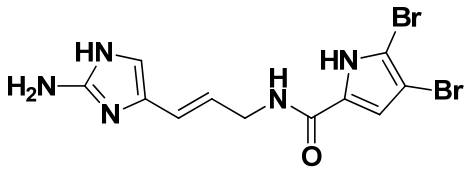
IR (Diamond-ATR, neat): vmax: 3295, 2930, 1632, 1512, 1434, 1170, 1157, 970, 919, 770, 749 cm^{-1}.

^{1}H NMR (DMSO-D$_6$): δ 11.55 (s, 1H), 9.04 (dd, J = 6.9, 2.4 Hz, 1H), 8.52 (dd, J = 4.2, 2.4 Hz, 1H), 8.38 (t, J = 5.7 Hz, 1H), 8.02 (s, 1H), 7.12 (dd, J = 6.9, 4.2 Hz, 1H), 6.77 – 6.92 (m, 1H), 6.40 (dt, J = 15.8, 5.8 Hz, 1H), 6.09 (dd, J = 2.1, 4.2 Hz, 1H), 4.09 (t, J = 5.4 Hz, 2H).

^{13}CNMR (DMSO-D$_6$): 160.5, 149.4, 148.0, 132.8, 132.3, 127.9, 126.2, 121.6, 121.3, 115.4, 110.1, 109.0, 108.5, 40.7.

HRMS (ES+) *m/z* calc. for [$C_{14}H_{13}N_5O$+H^+]: 268.1188, obsd.: 268.1198.

(*E*)-*N*-(3-(2-amino-1H-imidazol-4-yl)allyl)-4,5-dibromo-1H-pyrrole-2-carboxamide (oroidin) (1)



To compound **23a** (0.030 g, 0.071 mmol) was added hydrazine hydrate (3 mL) followed by stirring for 30 min at room temp. After completion of reaction (TLC), hydrazine was removed at rt under reduced pressure in the fume hood. The residue was purified by column chromatography using methanol:dichloromethane:NH_4OH (1:9:0.001) to obtain compound **1** as a white solid (0.017 g, 65%).

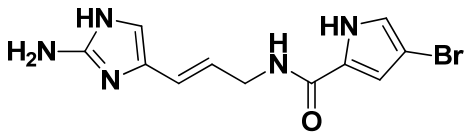
Melting point: 195-199 °C (lit[4]. mp: 202-205 °C)

^{1}H NMR (CD_3OD): δ 6.75 (s, 1H), 6.41 (s, 1H), 6.21 (d, J = 16.1 Hz, 1H), 5.82 (dt, J = 16.1 and 6.3 Hz, 1H), 3.92 (d, J = 6.3 Hz, 1H).

^{13}CNMR (CD_3OD): δ 161.6, 151.9, 131.2, 129.0, 122.5, 122.1, 117.2, 114.4, 106.2, 100.0, 42.3.

4. Little, T. L.; Webber S. E. *J. Org. Chem.* **1994**, *59*, 7299–7305

(*E*)-*N*-(3-(2-amino-1H-imidazol-4-yl)allyl)-4-bromo-1H-pyrrole-2-carboxamide (hymenidin) (2)

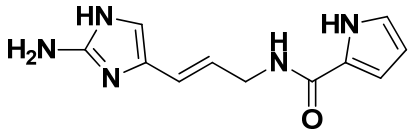


To the compound **23b** (0.020 g, 0.057 mmol) was added hydrazine hydrate (1 mL) and stirred for 10 min with gentle heating at 40-50°C. After completion of reaction (TLC), hydrazine was removed at rt under reduced pressure in the fume hood. The residue was purified by preparative chromatography using methanol:dichloromethane:NH_4OH (1:9:0.001) to obtain compound **2** as a yellowish gummy product (0.010 g, 65%).

^{1}H NMR (CD_3OD**):** δ 6.86 (s, 1H), 6.74 (s, 1H), 6.53 (s, 1H), 6.24 (d, J = 16.3 Hz, 1H), 5.92 (dt, J = 16.3, 6.0 Hz, 1H), 3.97 (d, J = 6.0 Hz, 2H).

^{13}CNMR (CD_3OD): δ 162.8, 152.8, 129.9, 127.91, 124.51, 123.3, 121.1, 115.8, 113.7, 97.9, 42.4.

(*E*)-*N*-(3-(2-amino-1H-imidazol-4-yl)allyl)-1H-pyrrole-2-carboxamide (clathrodin) (3)

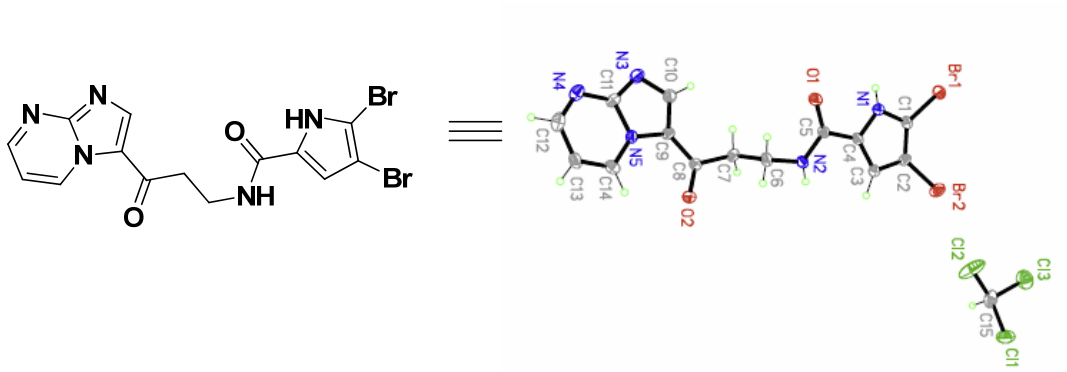


To the compound **23c** (0.016 g, 0.059 mmol) was added hydrazine hydrate (1 mL) followed by stirring for 10 min with gentle heating at 40-50 °C. After completion of reaction (TLC), hydrazine was removed at rt under reduced pressure in the fume hood. The residue was purified by preparative chromatography using methanol:dichloromethane:NH_4OH (1:9:001) to obtain compound **3** as a gummy solid. (0.007 g, 60%).

^{1}H NMR (CD_3OD)**:** δ 6.81 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.50 (s, 1H), 6.21 (d, J = 16.0 Hz, 1H), 6.08 – 6.03 (m, 2H), 5.91 (dt, J = 16.0, 5.4 Hz, 2H), 3.95 (d, J = 5.4 Hz, 2H).

^{13}CNMR (CD_3OD): δ 163.9, 150.6, 129.2, 126.9, 125.4, 123.1, 119.9, 114.7, 111.9, 110.3, 41.9.

X-Ray Structural data for compound 21a



A colorless crystal of RASP15 was mounted on a Cryoloop with Paratone-N oil and data was collected at 100 K on a Bruker APEX CCD system with Mo K alpha radiation. Data corrected for absorption with SADABS and structure solved by direct methods. All non-hydrogen atoms were refined anisotropically by Fourier full matrix least squares. Hydrogen atoms H1N and H2N were found from a Fourier difference map and refined with DFIX set at 0.85(0.02) and all other hydrogen atoms were placed in calculated positions with appropriate riding models.

Highest peak 0.63 at 0.1180 0.8764 0.0825 [0.99 A from CL1]

Deepest hole -0.60 at 0.4048 0.5381 0.2093 [0.88 A from BR1]

Table 1. Crystal data and structure refinement for RASP15. (UMass Dartmouth)

Identification code	rasp15	
Empirical formula	C15 H12 Br2 Cl3 N5 O2	
Formula weight	560.47	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.979(4) Å	□= 90°.
	b = 10.814(4) Å	□= 99.916(5)°.
	c = 16.912(6) Å	□ = 90°.
Volume	1977.8(12) $Å^3$	
Z	4	
Density (calculated)	1.882 Mg/m^3	
Absorption coefficient	4.526 mm^{-1}	
F(000)	1096	
Crystal size	0.25 x 0.15 x 0.10 mm^3	

Crystal color / habit	colorless / block
Theta range for data collection	2.06 to 26.52°.
Index ranges	-13<=h<=7, -8<=k<=13, -19<=l<=21
Reflections collected	13769
Independent reflections	4002 [R(int) = 0.0487]
Completeness to theta = 25.00°	98.3 %
Absorption correction	multi-scan / sadabs
Max. and min. transmission	0.6603 and 0.3975
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4002 / 2 / 250
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.0799
R indices (all data)	R1 = 0.0684, wR2 = 0.0899
Largest diff. peak and hole	0.633 and -0.600 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for RASP15. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	517(4)	1549(4)	3291(3)	19(1)
C(2)	688(4)	2805(4)	3278(3)	21(1)
C(3)	753(4)	3258(4)	4062(3)	20(1)
C(4)	629(4)	2239(4)	4538(3)	18(1)
C(5)	631(4)	2108(4)	5403(3)	17(1)
C(6)	934(4)	3132(4)	6707(3)	23(1)
C(7)	2255(4)	2907(4)	7165(3)	22(1)
C(8)	2339(4)	3287(4)	8032(3)	19(1)
C(9)	2531(4)	2336(4)	8637(3)	19(1)
C(10)	2743(4)	1075(4)	8574(3)	24(1)
C(11)	2790(4)	1381(4)	9837(3)	22(1)
C(12)	2694(4)	2240(4)	11038(3)	28(1)

C(13)	2469(4)	3427(4)	10693(3)	26(1)
C(14)	2413(4)	3565(4)	9896(3)	23(1)
C(15)	1188(5)	7476(5)	668(3)	36(1)
N(1)	484(3)	1206(3)	4055(2)	20(1)
N(2)	891(3)	3127(3)	5846(2)	21(1)
N(3)	2901(4)	500(3)	9296(2)	27(1)
N(4)	2857(3)	1242(3)	10628(2)	27(1)
N(5)	2575(3)	2533(3)	9455(2)	18(1)
O(1)	378(3)	1102(3)	5691(2)	28(1)
O(2)	2203(3)	4378(2)	8198(2)	25(1)
Br(1)	423(1)	400(1)	2456(1)	26(1)
Br(2)	769(1)	3759(1)	2361(1)	31(1)
Cl(1)	284(1)	8811(1)	616(1)	44(1)
Cl(2)	768(2)	6463(1)	1388(1)	67(1)
Cl(3)	1049(1)	6759(1)	-273(1)	48(1)

Table 3. Bond lengths [Å] and angles [°] for RASP15.

C(1)-N(1)	1.350(6)	C(7)-C(8)	1.510(6)
C(1)-C(2)	1.371(5)	C(7)-H(7A)	0.9900
C(1)-Br(1)	1.871(4)	C(7)-H(7B)	0.9900
C(2)-C(3)	1.404(6)	C(8)-O(2)	1.229(5)
C(2)-Br(2)	1.877(4)	C(8)-C(9)	1.441(6)
C(3)-C(4)	1.384(6)	C(9)-C(10)	1.389(5)
C(3)-H(3A)	0.9500	C(9)-N(5)	1.393(5)
C(4)-N(1)	1.376(5)	C(10)-N(3)	1.354(6)
C(4)-C(5)	1.470(6)	C(10)-H(10)	0.9500
C(5)-O(1)	1.243(5)	C(11)-N(4)	1.336(6)
C(5)-N(2)	1.335(5)	C(11)-N(3)	1.341(6)
C(6)-N(2)	1.448(5)	C(11)-N(5)	1.404(5)
C(6)-C(7)	1.541(6)	C(12)-N(4)	1.312(6)
C(6)-H(6A)	0.9900	C(12)-C(13)	1.414(6)
C(6)-H(6B)	0.9900	C(12)-H(12)	0.9500

C(13)-C(14)	1.347(6)	C(15)-Cl(3)	1.754(5)
C(13)-H(13)	0.9500	C(15)-Cl(2)	1.757(5)
C(14)-N(5)	1.370(5)	C(15)-H(15)	1.0000
C(14)-H(14)	0.9500	N(1)-H(1N)	0.840(19)
C(15)-Cl(1)	1.746(5)	N(2)-H(2N)	0.846(19)
N(1)-C(1)-C(2)	108.3(4)	O(1)-C(5)-N(2)	122.8(4)
N(1)-C(1)-Br(1)	122.2(3)	O(1)-C(5)-C(4)	120.8(4)
C(2)-C(1)-Br(1)	129.4(3)	N(2)-C(5)-C(4)	116.3(4)
C(1)-C(2)-C(3)	108.3(4)	N(2)-C(6)-C(7)	111.7(4)
C(1)-C(2)-Br(2)	125.7(3)	N(2)-C(6)-H(6A)	109.3
C(3)-C(2)-Br(2)	125.9(3)	C(7)-C(6)-H(6A)	109.3
C(4)-C(3)-C(2)	106.1(4)	N(2)-C(6)-H(6B)	109.3
C(4)-C(3)-H(3A)	127.0	C(7)-C(6)-H(6B)	109.3
C(2)-C(3)-H(3A)	127.0	H(6A)-C(6)-H(6B)	107.9
N(1)-C(4)-C(3)	108.3(4)	C(8)-C(7)-C(6)	109.9(4)
N(1)-C(4)-C(5)	119.5(4)	C(8)-C(7)-H(7A)	109.7
C(3)-C(4)-C(5)	132.1(4)	C(6)-C(7)-H(7A)	109.7

C(8)-C(7)-H(7B)	109.7	C(13)-C(12)-H(12)	118.0
C(6)-C(7)-H(7B)	109.7	C(14)-C(13)-C(12)	119.2(4)
H(7A)-C(7)-H(7B)	108.2	C(14)-C(13)-H(13)	120.4
O(2)-C(8)-C(9)	122.1(4)	C(12)-C(13)-H(13)	120.4
O(2)-C(8)-C(7)	119.6(4)	C(13)-C(14)-N(5)	117.8(4)
C(9)-C(8)-C(7)	118.2(4)	C(13)-C(14)-H(14)	121.1
C(10)-C(9)-N(5)	104.4(4)	N(5)-C(14)-H(14)	121.1
C(10)-C(9)-C(8)	130.7(4)	Cl(1)-C(15)-Cl(3)	111.1(3)
N(5)-C(9)-C(8)	124.9(4)	Cl(1)-C(15)-Cl(2)	109.6(3)
N(3)-C(10)-C(9)	112.3(4)	Cl(3)-C(15)-Cl(2)	111.1(3)
N(3)-C(10)-H(10)	123.8	Cl(1)-C(15)-H(15)	108.3
C(9)-C(10)-H(10)	123.8	Cl(3)-C(15)-H(15)	108.3
N(4)-C(11)-N(3)	127.4(4)	Cl(2)-C(15)-H(15)	108.3
N(4)-C(11)-N(5)	122.4(4)	C(1)-N(1)-C(4)	109.0(3)
N(3)-C(11)-N(5)	110.2(4)	C(1)-N(1)-H(1N)	128(3)
N(4)-C(12)-C(13)	124.0(4)	C(4)-N(1)-H(1N)	121(3)
N(4)-C(12)-H(12)	118.0	C(5)-N(2)-C(6)	122.3(3)

C(5)-N(2)-H(2N)	119(3)
C(6)-N(2)-H(2N)	116(3)
C(11)-N(3)-C(10)	106.0(4)
C(12)-N(4)-C(11)	116.6(4)
C(14)-N(5)-C(9)	132.8(4)
C(14)-N(5)-C(11)	120.0(4)
C(9)-N(5)-C(11)	107.2(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for RASP15. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(2)	22(2)	16(2)	-3(2)	2(2)	0(2)
C(2)	24(2)	20(2)	19(2)	4(2)	3(2)	-1(2)
C(3)	25(2)	18(2)	17(2)	0(2)	1(2)	-2(2)
C(4)	18(2)	18(2)	17(2)	-4(2)	1(2)	-1(2)
C(5)	17(2)	18(2)	18(2)	-1(2)	4(2)	-4(2)
C(6)	29(3)	24(2)	16(2)	-3(2)	1(2)	-4(2)
C(7)	27(3)	21(2)	17(2)	4(2)	4(2)	0(2)
C(8)	21(2)	17(2)	18(2)	-1(2)	3(2)	0(2)
C(9)	21(2)	19(2)	18(2)	2(2)	4(2)	-1(2)
C(10)	27(3)	21(2)	22(3)	-1(2)	0(2)	6(2)
C(11)	22(2)	21(2)	23(3)	6(2)	5(2)	3(2)
C(12)	24(3)	40(3)	21(3)	4(2)	5(2)	6(2)

C(13)	30(3)	29(2)	19(2)	-8(2)	1(2)	3(2)
C(14)	19(2)	22(2)	27(3)	-5(2)	4(2)	-1(2)
C(15)	25(3)	48(3)	32(3)	7(2)	0(2)	1(2)
N(1)	24(2)	17(2)	18(2)	0(2)	2(2)	-2(2)
N(2)	26(2)	19(2)	16(2)	-1(2)	2(2)	-6(2)
N(3)	37(2)	22(2)	22(2)	2(2)	7(2)	5(2)
N(4)	29(2)	30(2)	23(2)	6(2)	7(2)	5(2)
N(5)	19(2)	19(2)	16(2)	0(2)	3(2)	1(1)
O(1)	41(2)	23(2)	20(2)	1(1)	3(2)	-12(1)
O(2)	35(2)	17(1)	21(2)	0(1)	3(1)	0(1)
Br(1)	36(1)	24(1)	19(1)	-5(1)	4(1)	2(1)
Br(2)	50(1)	25(1)	21(1)	6(1)	11(1)	3(1)
Cl(1)	62(1)	24(1)	46(1)	4(1)	9(1)	-2(1)
Cl(2)	90(1)	52(1)	68(1)	37(1)	40(1)	32(1)
Cl(3)	45(1)	55(1)	44(1)	-11(1)	7(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3)

	x	y	z	U(eq)
H(3A)	860	4094	4232	24
H(6A)	378	2481	6851	28
H(6B)	632	3940	6870	28
H(7A)	2468	2021	7135	26
H(7B)	2853	3393	6914	26
H(10)	2773	665	8082	29
H(12)	2729	2161	11601	34
H(13)	2358	4119	11020	32
H(14)	2267	4351	9648	27
H(15)	2073	7717	844	43
H(1N)	250(40)	530(30)	4220(30)	24
H(2N)	1250(40)	3730(30)	5660(30)	25

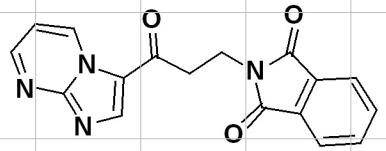
Table 6. Hydrogen bonds for RASP15 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.840(19)	1.91(2)	2.730(5)	165(4)
N(2)-H(2N)...N(3)#2	0.846(19)	2.13(3)	2.917(5)	155(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1 #2 -x+1/2,y+1/2,-z+3/2

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry



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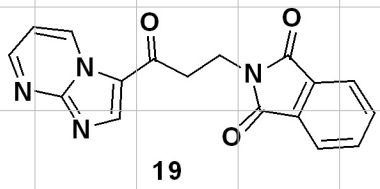

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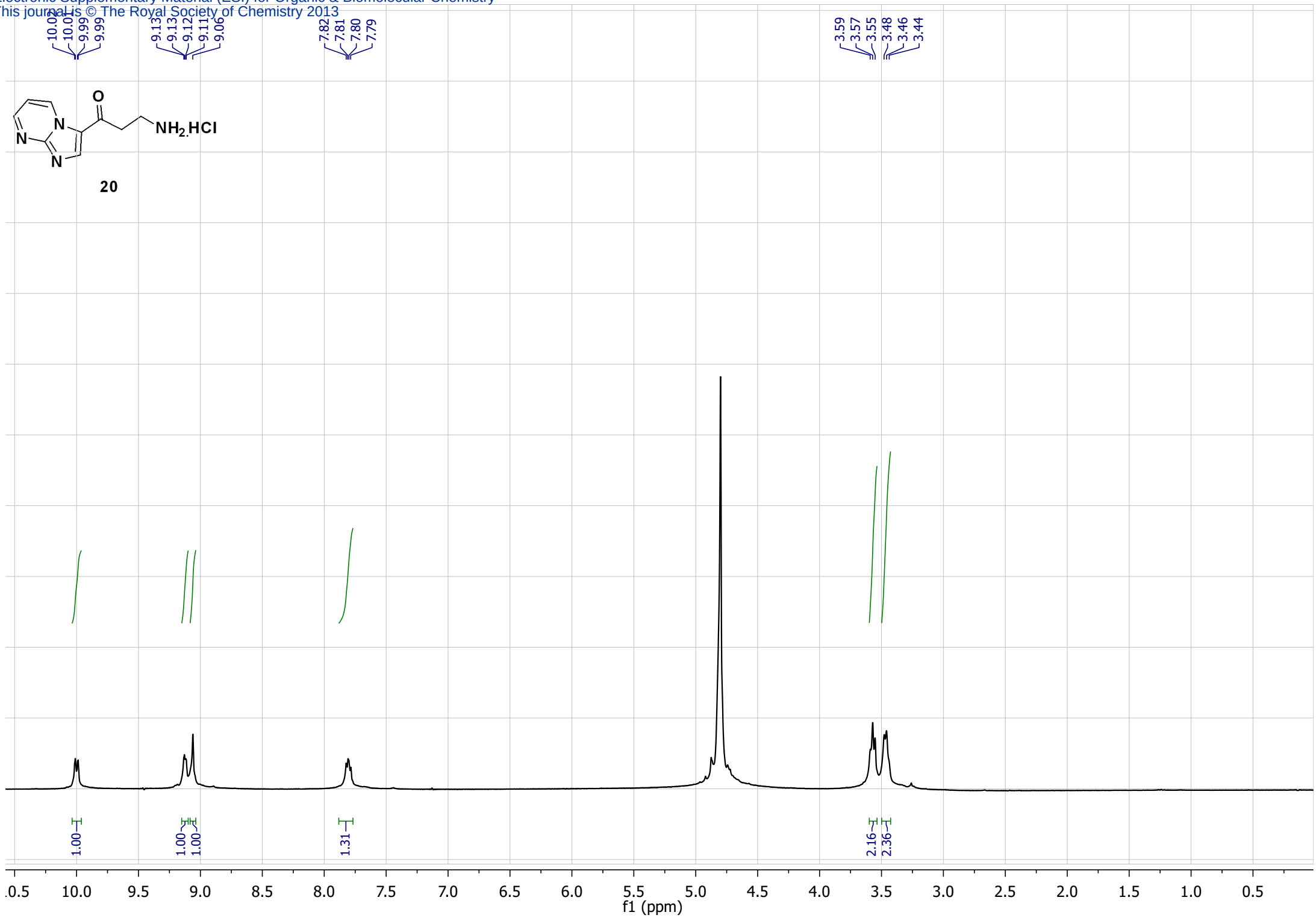

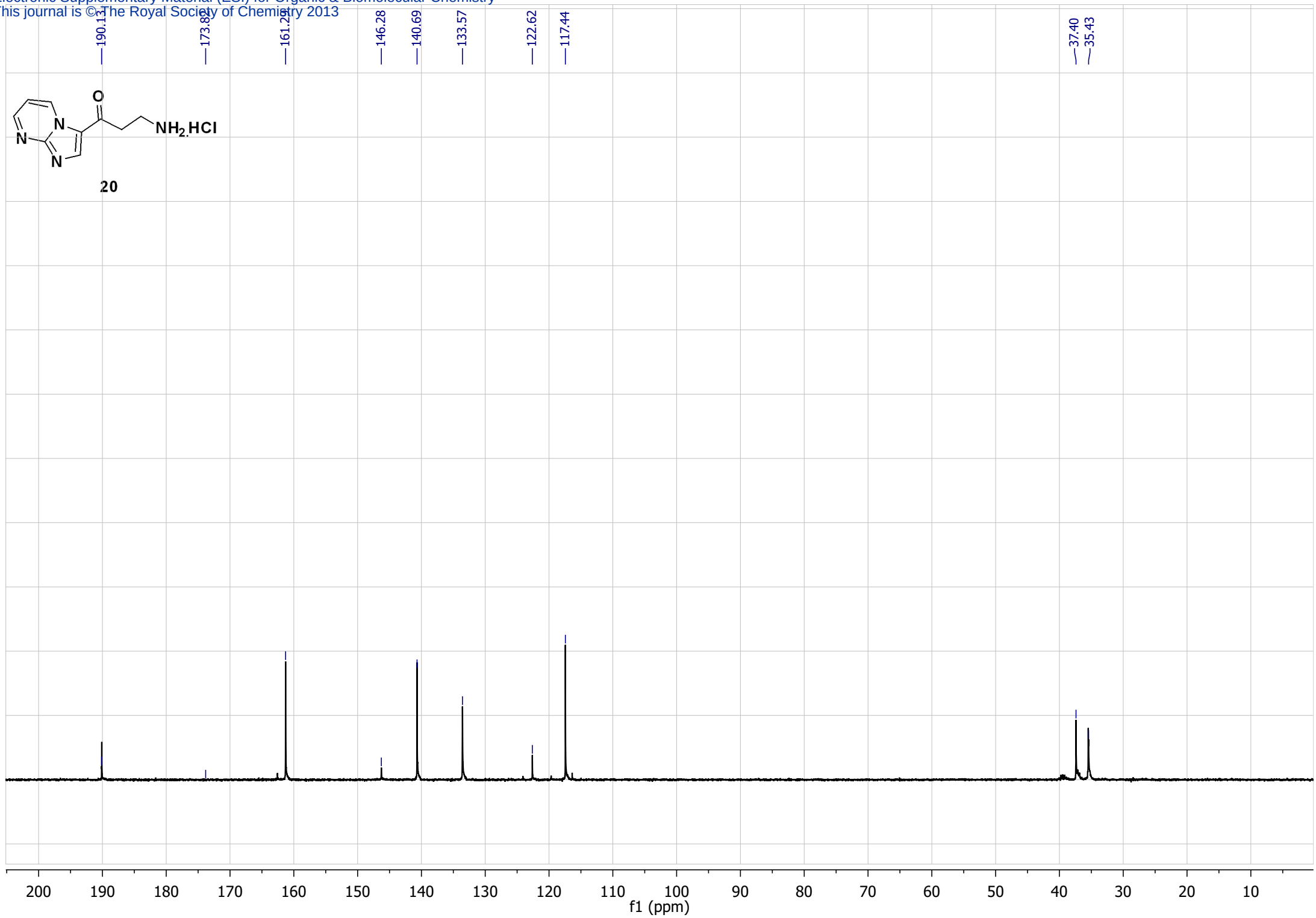

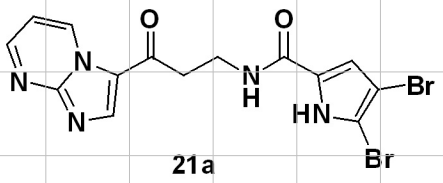

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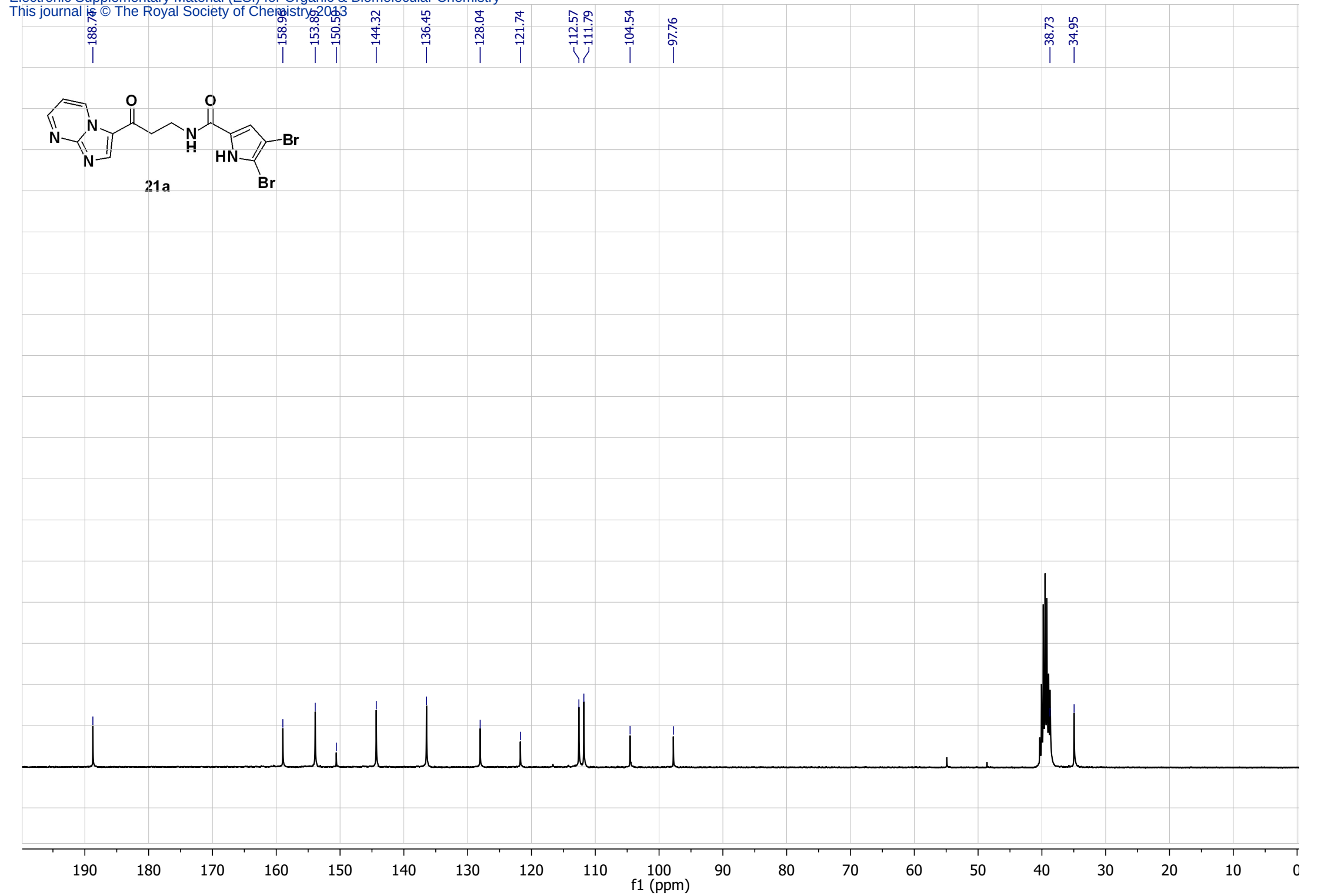

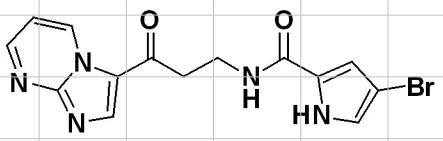

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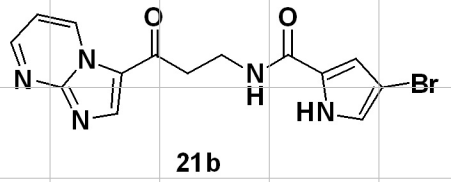

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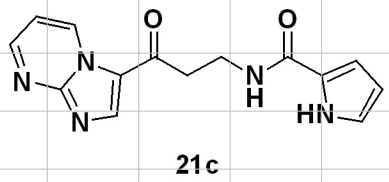

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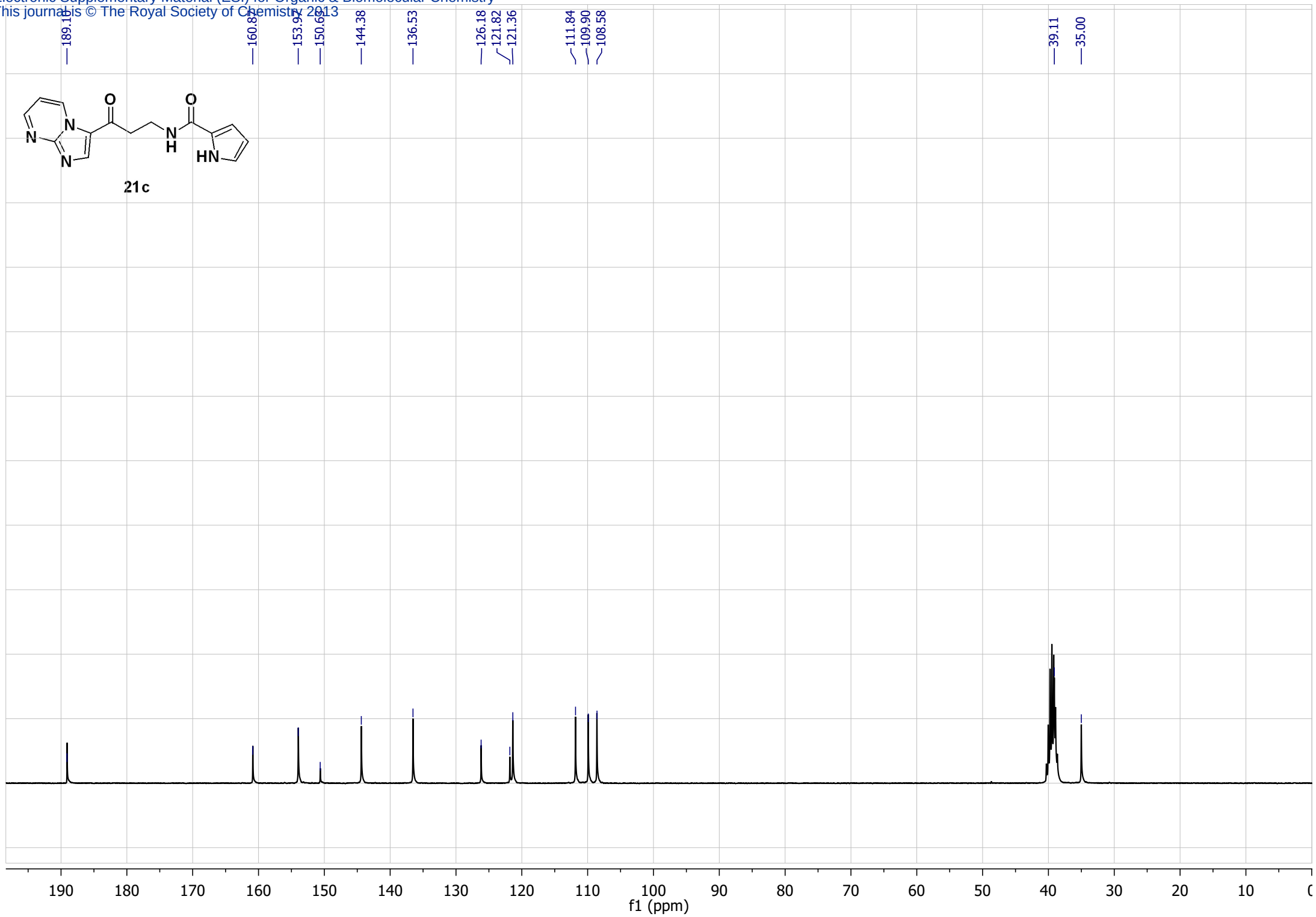

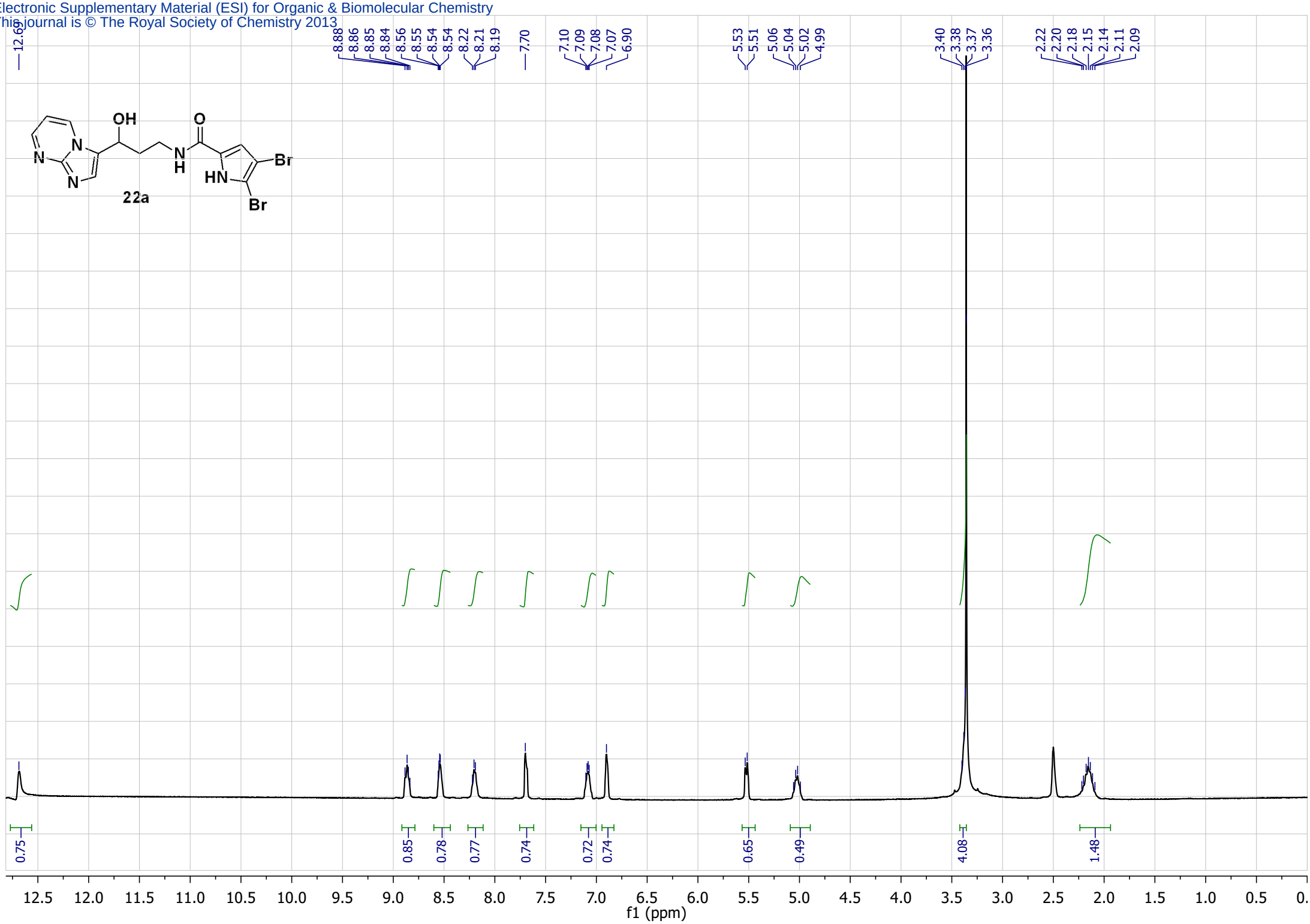

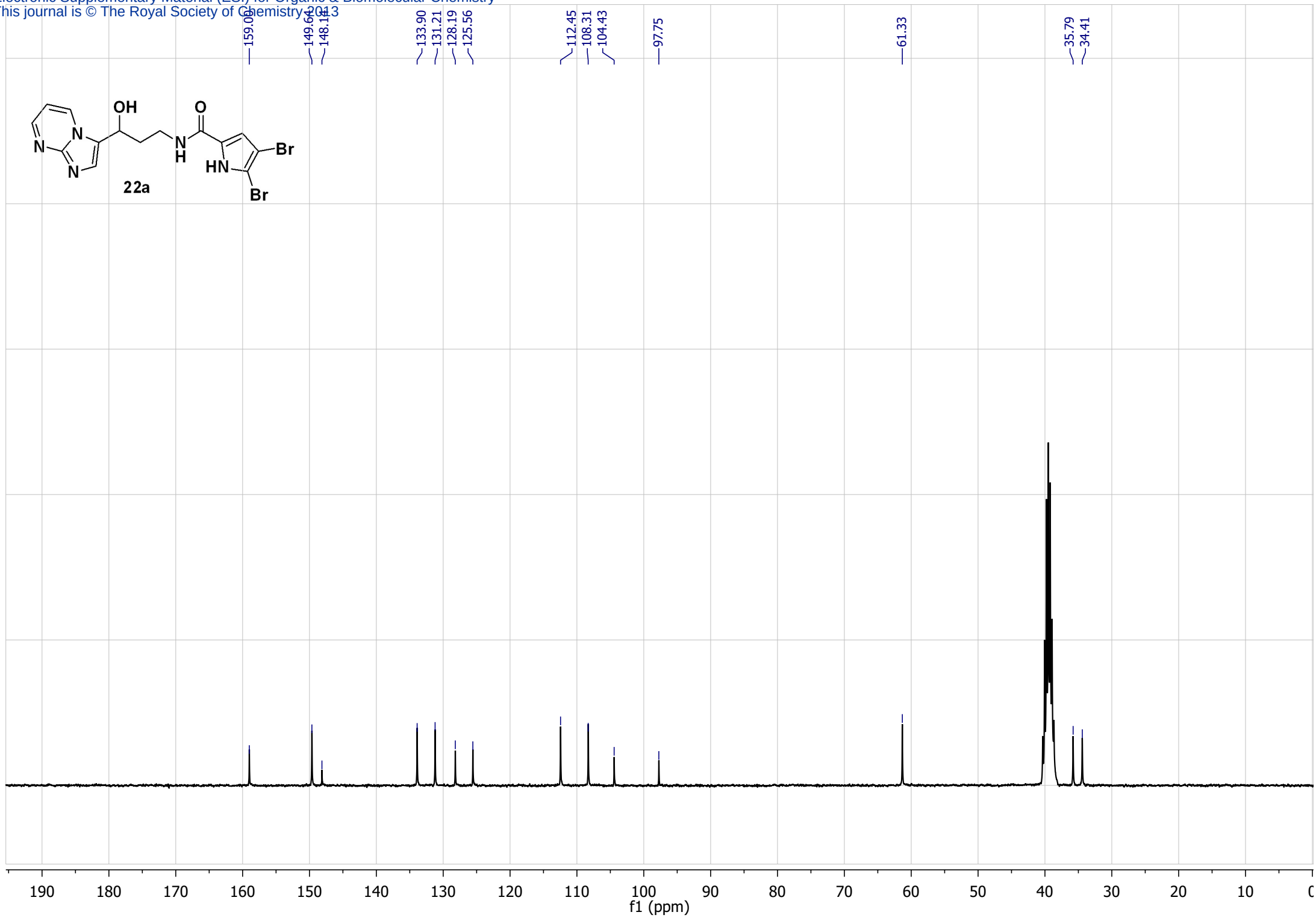

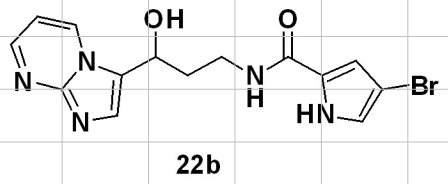

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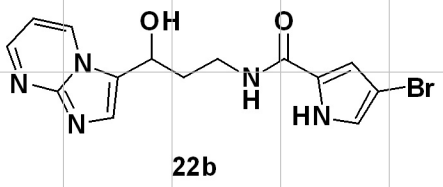

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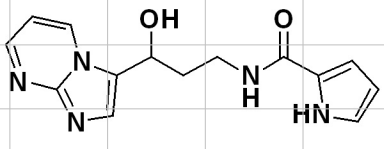

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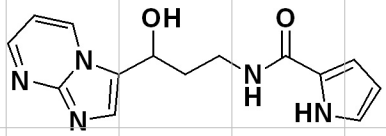

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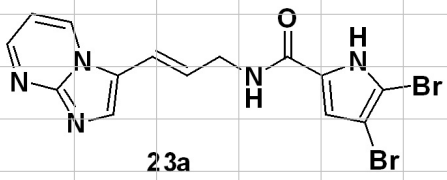

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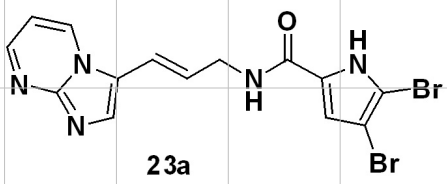

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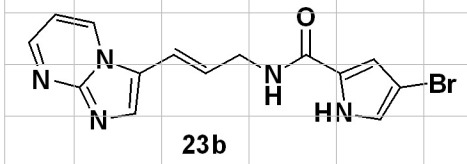

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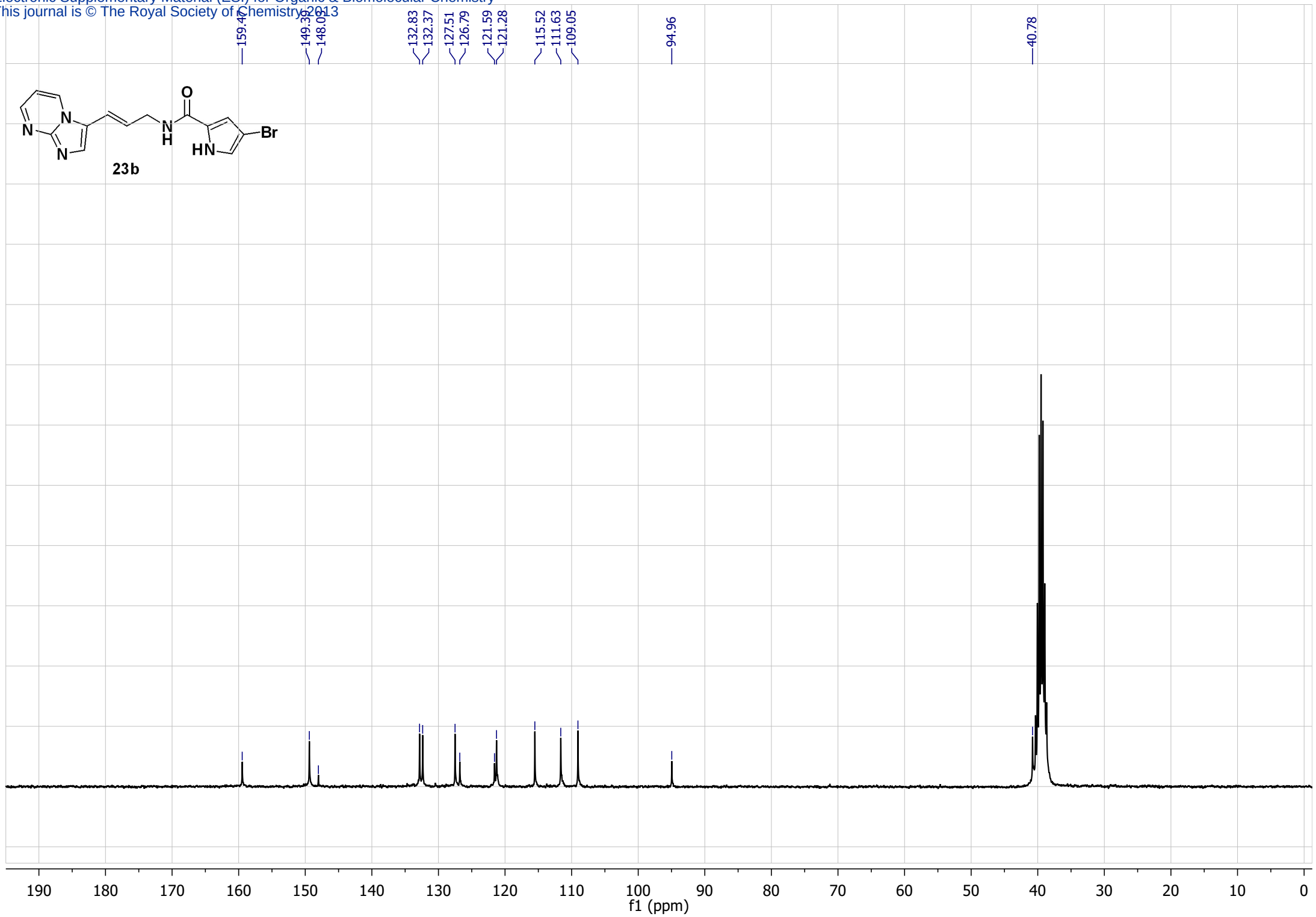

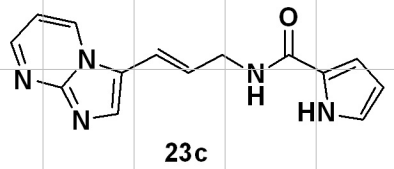

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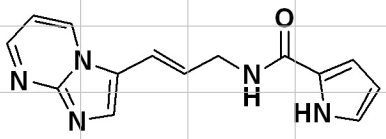

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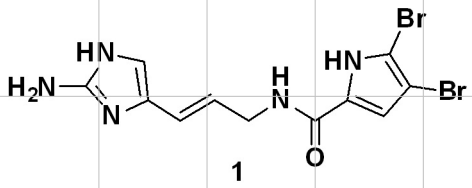

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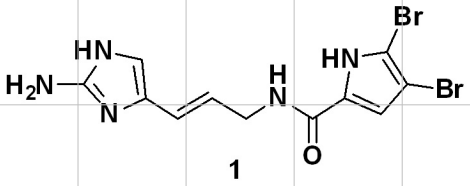

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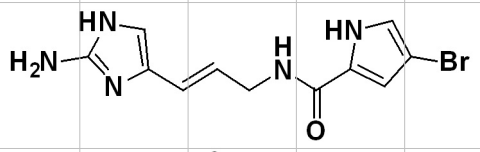

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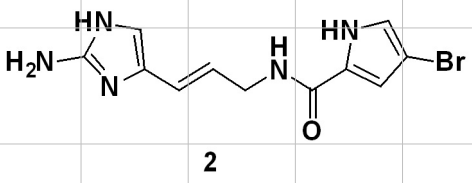

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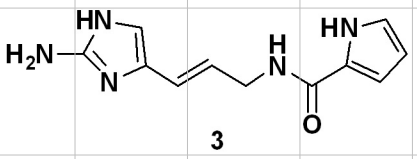

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