

Supporting Information

Iodine-Mediated Cascade Amination Enables One-pot Access to Antimicrobial Indole-Embedded Dihydropyrazoles

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1. Chemistry

General Experimental Methods

All the chemicals and solvents (anhydrous) were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out under an argon atmosphere unless otherwise noted. Column chromatography was performed using Silica gel (100-200 mesh), and a hexane-ethyl acetate mixture was used for elution. NMR spectra were recorded at 500 (^1H) and 126 (^{13}C) MHz on a Bruker ASCENDTM spectrometer by using CDCl_3 as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) for ^1H NMR spectra are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of CDCl_3 (δ 7.27, singlet). Coupling constants (J) are given in Hertz (Hz), and multiplicities were represented as s, d, t, q, m, and dd for singlet, doublet, triplet, quartet, multiplet, and doublet of a doublet, respectively. Chemical shifts (δ) for ^{13}C NMR are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of CDCl_3 (δ 77.03, triplet). Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Infrared spectra were recorded with a Bruker Alpha-T FT-IR spectrometer. Mass spectra were recorded under HRMS (ESI-Orbitrap) using Thermo Scientific Exactive mass spectrometer. Melting points were determined on a Buchi melting point apparatus and were uncorrected.

1.1. Procedure for synthesis of (*E*)-chalcones ¹

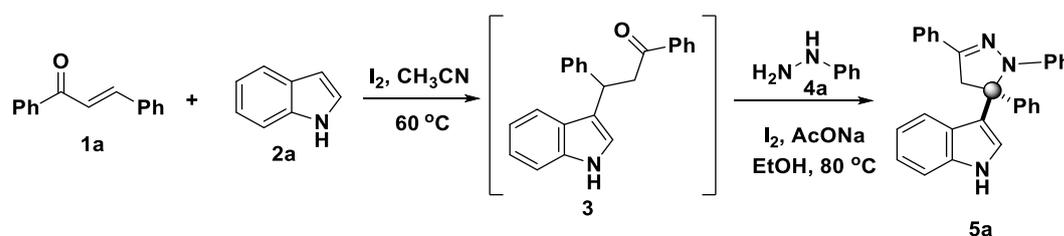
One equivalent of arylaldehyde or heteroarylaldehyde is added to the solution of one equivalent of acetophenone in ethanol. 10% aqueous solution of NaOH was added drop wise to the mixture at 0 °C, which resulted in precipitation. The mixture was then stirred for 30 min, filtered, washed with cold methanol, and dried to yield 60 - 90% solid compound.

1.2. Procedure for synthesis of Indoly dihydropyrazole

A mixture of chalcone (52 mg, 1 equiv), indole (1 equiv), and I_2 (10 mol%) was added to a Schlenk tube containing acetonitrile (2 mL). The reaction mixture was stirred at 55–60 °C until complete consumption of the starting materials, as monitored by TLC. The solvent was then removed *in vacuo*. To the resulting residue were added phenylhydrazine hydrochloride (1.5 equiv), iodine (0.5 equiv),

NaOAc (0.5 equiv), and ethanol (2 mL), and the mixture was stirred at 80 °C until completion of the reaction (TLC monitoring). The reaction mixture was then extracted with ethyl acetate and washed successively with an aqueous sodium thiosulfate solution and brine. The organic layer was dried over anhydrous Na₂SO₄, and the solvent was evaporated *in vacuo*. Purification of the residue by column chromatography using hexane/ethyl acetate as eluents afforded the desired products.

1.3. Table 1: Optimization table^a



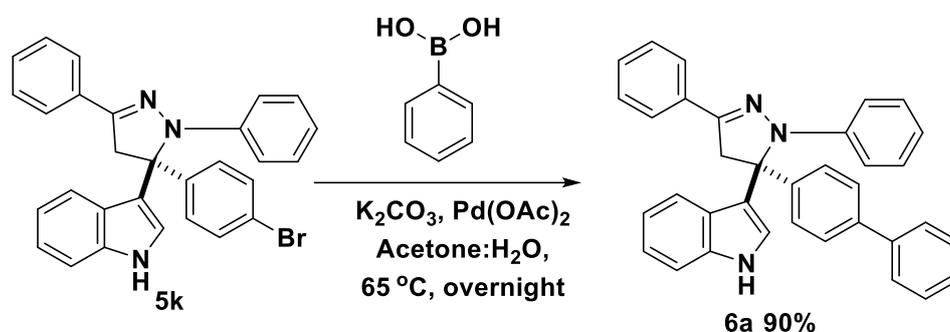
entry	4a (equiv.)	I ₂ source	Base	Solvent	Temp.	yield ^b
1	1	I ₂ (20 mol%)	AcONa(0.25)	EtOH	80 °C	30%
2	1	I ₂ (0.5 equiv.)	AcONa(0.25)	EtOH	80 °C	48%
3	1.5	I ₂ (0.5 equiv.)	AcONa(0.25)	EtOH	80 °C	58%
4	2	I ₂ (0.5 equiv.)	AcONa(0.25)	EtOH	80 °C	50%
5	2.5	I ₂ (0.5 equiv.)	AcONa(0.25)	EtOH	80 °C	54%
6	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	EtOH	80 °C	72%
7	1.5	-	-	EtOH	80 °C	NA
8	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	EtOH	reflux	62%
9	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	MeOH	80 °C	21%
10	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	tBuOH	80 °C	11%
11	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	DMF	80 °C	20%
12	1.5	I ₂ (0.5 equiv.)	AcONa(0.5)	DMSO	80 °C	18%
13	1.5	NaI (0.5 equiv.)	AcONa(0.5)	EtOH	80 °C	28%
14	1.5	KI (0.5 equiv.)	AcONa(0.5)	EtOH	80 °C	28%
15	1.5	PIDA(0.5 equiv.)	AcONa(0.5)	EtOH	80 °C	36%
16	1.5	I ₂ (0.5 equiv.)	AcOK(0.5)	EtOH	80 °C	46%
17	1.5	I ₂ (0.5 equiv.)	K ₂ CO ₃ (0.5)	EtOH	80 °C	11%
18	1.5	I ₂ (0.5 equiv.)	K ₃ PO ₄ (0.5)	EtOH	80 °C	trace

^a Unless otherwise specified, all the reactions are conducted with 1 equiv., 0.25mmol of 1a, and 2a phenylhydrazine, iodine and base in a solvent. ^b isolated yields. NA (Not appeared)

1.4. Procedure for synthesis of 3-(5-([1,1'-biphenyl]-4-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ba)²

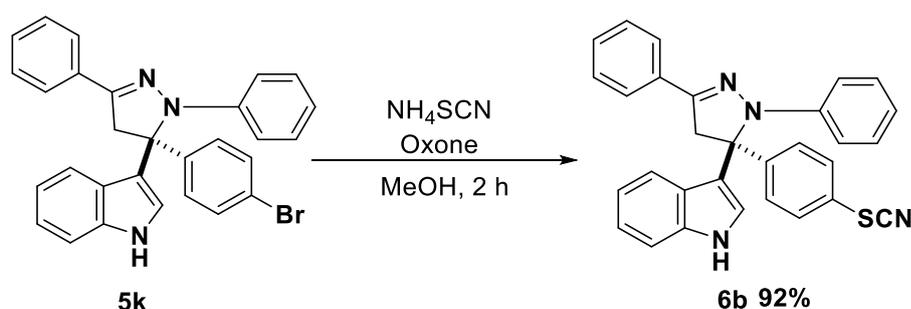
A mixture of compound **5k** (30 mg, 0.06 mmol), phenyl boronic acid (7.3 mg, 0.06 mmol) and K₂CO₃ (16.5 mg, 0.12 mmol) were charged into a schlenk tube. The reaction tube was equipped with a septum and sealed up. Then, it is evacuated and backfilled with Argon, followed by the addition of acetone: water (1 mL: 1 mL). The reaction mixture was heated to 65 °C (oil bath). A solution of Pd(OAc)₂ (2

mol%, 0.23 mg, 0.001 mmol) in acetone was added to the above reaction mixture and continued stirring at 65 °C overnight. The crude product was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried with Na₂SO₄; the solvent was removed in vacuo. The product **6a** (27 mg, 90%) was isolated as a yellow solid by column chromatography (silica gel: 100-200 mesh) using ethyl acetate: hexane (12:88) as the eluent.



1.5. Procedure for the synthesis of -3-(1,3-diphenyl-5-(4-thiocyanatophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (**5bb**)

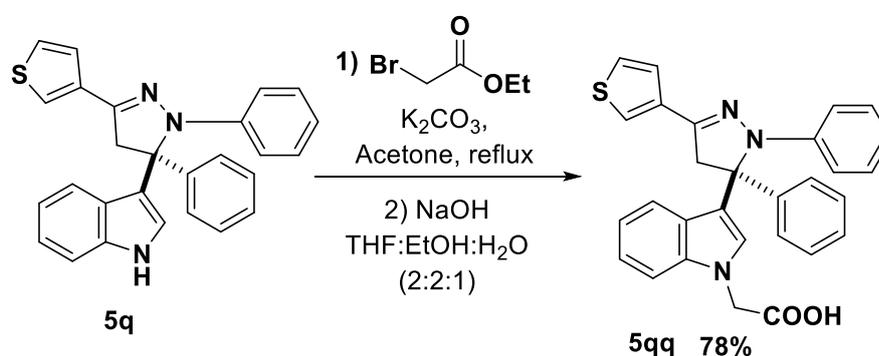
A solution of **5k** (30 mg, 0.06mmol), and ammonium thiocyanate (9 mg, 0.12mmol) in 2mL of methanol was treated with oxone (18 mg, 0.12mmol), allowed to stir at room temperature until completion of the reaction, monitored by TLC, it was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried with Na₂SO₄; the solvent was removed in vacuo. The product **6b** (26 mg, 92%) was isolated as a yellow solid by column chromatography (silica gel: 100-200 mesh) using ethyl acetate: hexane (12:88) as the eluent.



1.6. Procedure for the synthesis of 2-(3-(1,5-diphenyl-3-(thiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indol-1-yl)acetic acid (**5qq**)

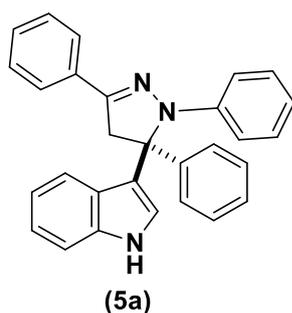
To a solution of **5q** (30 mg, 0.06 mmol) in acetone (3 mL) was added K₂CO₃ (16 mg, 0.12mmol) and ethyl bromoacetate (0.009 mL, 0.09 mmol). The mixture was heated to reflux overnight and concentrated under reduced pressure. H₂O (100 mL) was added to the residue, and the resulting mixture was extracted with EtOAc (2 x 100 mL). The organic layers were combined and washed with 1M aqueous HCl (50 mL), saturated aqueous NaHCO₃ (50 mL) and brine (2 x 100 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product as

a light brown oil that was used immediately in the next step. To a solution of the crude product obtained from the previous step (assuming quantitative yield, 10.0 mmol) in a 50 mL THF:EtOH:H₂O mixed solvent system (2:2:1) was added NaOH (600 mg, 15 mmol). The resulting mixture was stirred at room temperature overnight. Then the mixture was acidified with 1 M aqueous HCl to pH 2 and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried with Na₂SO₄, filtered and concentrated under reduced pressure to give the crude material, which was taken up in 2 M aqueous NaOH to pH 11 and CH₂Cl₂ (30 mL) then washed with CH₂Cl₂ (30 mL). The aqueous phase was acidified again with conc. HCl to pH 2 and extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product **5qq** (26 mg, 78%) was isolated as a yellow solid by column chromatography (silica gel: 100-200 mesh) using ethyl methanol:chloroform (5:95) as the eluent.



1.7. Characterization data of products (5a-5qq)

3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5a)



Yield: 74 mg, 72 % as a yellow solid

IR (neat, cm⁻¹): 3316, 3046, 2822, 1717, 1584, 1567, 1489, 1452, 1389, 1327, 1131, 744, 696.

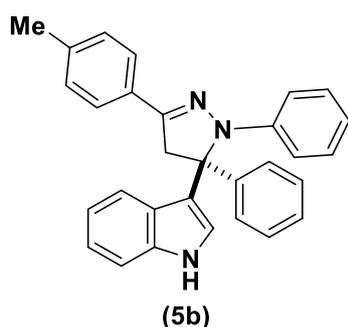
Mp: 86-87 °C

¹H NMR (500 MHz, CDCl₃): δ 7.92(s, 1H), 7.64(d, *J* = 7.6 Hz, 2H), 7.52(d, *J* = 7.9 Hz, 1H), 7.26-7.18(m, 6H), 7.13-7.0(m, 7H), 6.79(s, 1H), 6.69-6.62(t, *J* = 7.1 Hz, 1H), 5.12(d, *J* = 4.4 Hz, 1H), 4.72(d, *J* = 4.3 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 147.9, 144.2, 141.6, 136.6, 132.4, 129.2, 128.3, 128.2, 127.7, 126.3, 125.2, 127.7, 126.3, 125.8, 122.5, 122.4, 120.0, 118.9, 118.8, 115.3, 111.5, 73.2, 53.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₂₉H₂₄N₃, M+H]⁺ : 414.1970; Found: 414.1969.

3-(1,5-diphenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5b)



Yield: 74 mg, 70% as light-yellow solid

IR (neat, cm^{-1}): 3417, 3065, 2938, 1718, 1587, 1562, 1489, 1453, 1388, 1378, 1130, 741, 693.

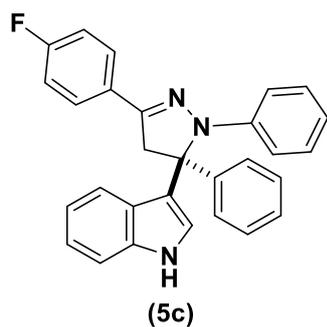
Mp: 118-119 °C

^1H NMR (500 MHz, CDCl_3): δ 7.91 (s, 1H) 7.54 (t, $J = 7.8$ Hz, 3H), 7.26 (m, 5H), 7.21 (m, 1H), 7.15 (d, $J = 7.0$ Hz, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.08 (d, $J = 7.4$ Hz, 1H), 7.05 (d, $J = 7.7$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 7.8$ Hz, 2H), 6.80 (s, 1H), 6.68 (t, $J = 7.1$ Hz, 1H), 5.10 (d, $J = 4.5$ Hz, 1H), 4.71 (d, $J = 4.5$ Hz, 1H), 2.17 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 148.1, 144.4, 141.7, 138.2, 136.6, 129.6, 129.2, 129.0, 128.9, 127.6, 126.2, 125.8, 122.4, 122.4, 120.0, 118.9, 118.7, 115.4, 113.1, 111.4, 53.8, 21.3.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{30}\text{H}_{26}\text{N}_3, \text{M}+\text{H}]^+$: 428.2127; Found: 428.2118.

3-(3-(4-fluorophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5c)



Yield: 77mg, 72 % as a yellow gummy solid

IR (neat, cm^{-1}): 3436, 3045, 2938, 1797, 1697, 1556, 1499, 1455, 1389, 1328, 1140, 735, 663.

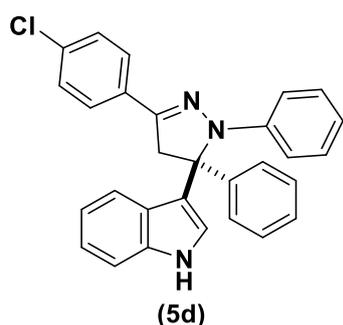
^1H NMR (500 MHz, CDCl_3): δ 7.97(s, 1H), 7.64(d, $J = 7.6$ Hz, 2H), 7.50(d, $J = 7.9$ Hz, 1H), 7.25(d, $J = 7.9$ Hz, 1H), 7.19-7.16 (m, 2H), 7.13-7.08 (m, 5H), 7.05 (d, $J = 7.5$ Hz, 1H), 7.10 (d, $J = 8.2$ Hz, 2H), 6.95-6.90 (t, $J = 8.5$ Hz, 2H), 6.82 (s, 1H), 6.71-6.68(t, $J = 7.2$ Hz, 1H), 5.10 (d, $J = 4.7$ Hz, 1H), 4.69 (d, $J = 4.7$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.8, 144.1, 137.4, 137.3, 136.6, 132.3, 129.0, 128.3, 128.2, 127.5, 127.4, 126.2, 125.7, 122.5, 122.4, 120.1, 119.1, 118.7, 116.2, 116.0, 115.1, 113.2, 111.4, 53.7.

^{19}F NMR (371 MHz, CDCl_3) δ 105.54 (s, 1F)

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{FN}_3, \text{M}+\text{H}]^+$: 432.1876; Found: 432.1870.

3-(3-(4-chlorophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5d)



Yield: 82mg, 74% as a light-yellow gummy solid

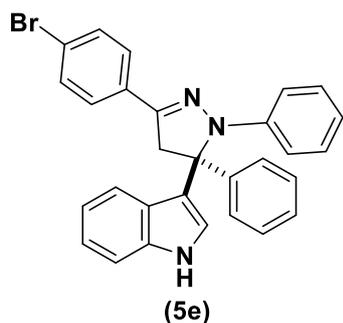
IR (neat, cm^{-1}): 3421, 3059, 1596, 1554, 1496, 1452, 1095, 833, 744, 694.

^1H NMR (500 MHz, CDCl_3): δ 8.01 (s, 1H), 7.62-7.59 (m, 2H), 7.50 (d, $J = 7.9\text{Hz}$, 1H), 7.29- 7.25 (m, 3H), 7.25 (d, $J = 7.5\text{Hz}$, 3H), 7.16 - 7.14 (m, 1H), 7.11 - 7.08 (t, $J = 7.6\text{Hz}$, 2H), 7.05 (d, $J = 7.7\text{Hz}$, 1H), 7.01 (d, $J = 8.3\text{Hz}$, 2H), 6.85 (s, 1H), 6.83 - 6.79 (t, $J = 7.2\text{Hz}$, 2H), 6.70 - 6.67 (t, $J = 8.4\text{Hz}$, 1H), 5.13 (d, $J = 4.9\text{Hz}$, 1H), 4.70 (d, $J = 4.9\text{Hz}$, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 144.2, 141.6, 136.6, 129.2, 129.0, 128.0, 128.0, 127.7, 125.8, 125.7, 122.6, 122.4, 120.1, 119.0, 118.8, 115.4, 115.2, 115.1, 113.2, 111.5, 73.3, 53.9.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{ClN}_3, \text{M}+\text{H}]^+$: 448.1581; Found: 448.1579.

3-(3-(4-bromophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5e)



Yield: 88mg, 72% as a yellow gummy solid

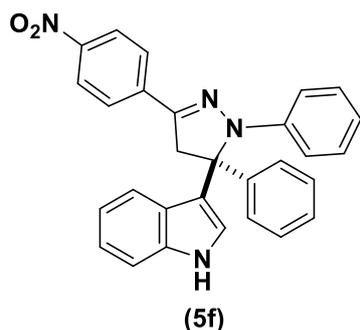
IR (neat, cm^{-1}): 3418, 3049, 2928, 1728, 1599, 1542, 1489, 1459, 1388, 1318, 1130, 748, 683.

^1H NMR (500 MHz, CDCl_3): δ 8.01 (s, 1H), 7.64 (d, $J = 7.0$ Hz, 2H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 1H), 7.16 (s, 2H), 7.15 - 7.10 (m, 5H), 7.07 - 7.04 (t, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 8.2$ Hz, 2H), 6.87 (s, 1H), 6.73 - 6.70 (t, $J = 7.2$ Hz, 1H), 5.10 (d, $J = 4.9$ Hz, 1H), 4.70 (d, $J = 4.9$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.9, 144.0, 140.2, 136.6, 133.4, 132.2, 129.4, 129.0, 128.3, 128.3, 127.2, 126.3, 125.7, 122.6, 122.4, 120.1, 119.2, 118.7, 115.1, 113.3, 111.5, 72.6, 53.7.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{BrN}_3, \text{M}+\text{H}]^+$: 492.1075; Found: 492.1068.

3-(3-(4-nitrophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5f)



Yield: 76mg, 67% as orange-yellow gummy solid

IR (neat, cm^{-1}): 3403, 3062, 1691, 1597, 1516, 1494, 1338, 1248, 1108, 1022, 749, 695.

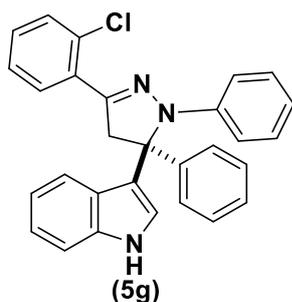
^1H NMR (500 MHz, CDCl_3): δ 8.08 (s, 1H), 7.98 (d, $J = 8.3\text{Hz}$, 2H), 7.76 (d, $J = 8.4\text{Hz}$, 2H), 7.49 (d, $J = 7.9\text{Hz}$, 1H), 7.34 - 7.28 (m, 4H), 7.22 (d, $J = 7.6\text{Hz}$, 3H), 7.15 - 7.12 (m, 2H), 7.08 (d, $J =$

8.3Hz, 3H), 6.90 (s, 1H), 6.79 - 6.76(t, J =Hz, 1H), 5.25 (d, J = 5.0Hz, 1H), 4.75 (d, J = 5.0Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 145.2, 143.2, 140.9, 138.9, 136.7, 129.4, 129.1, 128.0, 126.3, 125.6, 123.7, 122.8, 122.3, 120.3, 120.2, 118.6, 114.7, 113.8, 111.6, 73.7, 53.3.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{N}_4\text{O}_2, \text{M}+\text{H}]^+$: 459.1821; Found: 459.1819.

3-(3-(2-chlorophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5g)



Yield: 81mg, 73% as a light-yellow gummy solid

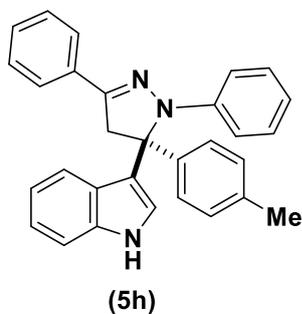
IR (neat, cm^{-1}): 3413, 3347, 2926, 1707, 1595, 1497, 1426, 1098, 881, 744, 692.

^1H NMR (500 MHz, CDCl_3): δ 8.04 (s, 3H), 7.65 (d, J = 7.6 Hz, 6H), 7.50 (d, J = 8.1 Hz, 4H), 7.30 (d, J = 8.0 Hz, 6H), 7.23 (s, 5H), 7.20 - 7.16 (m, 2H), 7.15 - 7.11 (m, 6H), 7.07 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 6.89 (s, 1H), 6.73 (t, J = 7.0Hz, 1H), 5.09 (d, J = 4.9 Hz, 3H), 4.72 (d, J = 4.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.9, 144.0, 140.2, 136.6, 133.4, 132.2, 129.4, 129.0, 128.3, 128.3, 127.2, 126.3, 122.6, 122.4, 120.1, 119.2, 118.7, 113.3, 111.5, 72.6, 53.7.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{ClN}_3, \text{M}+\text{H}]^+$: 448.1581; Found: 448.1578.

3-(1,3-diphenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5h)



Yield: 81mg, 70% as a yellow solid

IR (neat, cm^{-1}): 3416, 3055, 2926, 1708, 1596, 1552, 1498, 1454, 1388, 1318, 1130, 745, 693.

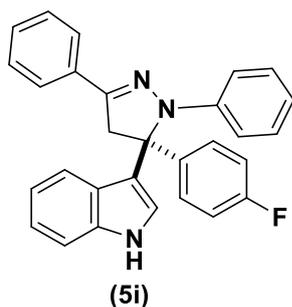
Mp: 125-126 °C

^1H NMR (500 MHz, CDCl_3): δ 7.98 (s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.14 - 7.11 (m, 6H), 7.09 - 7.05 (m, 5H), 7.03 (d, J = 8.2 Hz, 2H), 6.86 (s, 1H), 6.69 - 6.66 (t, J = 7.1 Hz, 1H), 5.12 (d, J = 4.4 Hz, 1H), 4.72 (d, J = 4.4 Hz, 1H), 2.25 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.8, 144.2, 138.7, 137.3, 136.6, 132.5, 129.8, 128.9, 128.3, 128.1, 126.2, 125.8, 125.7, 122.4, 122.4, 120.0, 118.9, 118.8, 115.4, 113.2, 111.4, 72.9, 53.7, 21.1.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{30}\text{H}_{26}\text{N}_3, \text{M}+\text{H}]^+$: 428.2127; Found: 428.2118.

3-(5-(4-fluorophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5i)



Yield: 77 mg, 72% as a light-yellow gummy solid

IR (neat, cm⁻¹): 3432, 3052, 2949, 1788, 1691, 1585, 1482, 1463, 1373, 1316, 1133, 745, 693.

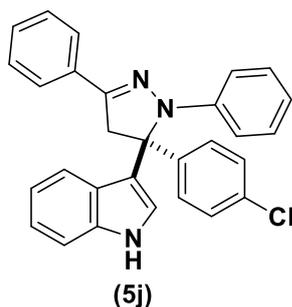
¹H NMR (500 MHz, CDCl₃): δ 7.98 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.20 - 7.14 (m, 4H), 7.13 - 7.09 (m, 4H), 7.07 - 7.04 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.96 - 6.93 (t, *J* = 8.5 Hz, 2H), 6.86 (s, 1H), 6.72 - 6.69 (t, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 4.7 Hz, 1H), 4.70 (d, *J* = 4.7 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 147.9, 144.1, 136.6, 132.3, 129.0, 128.3, 128.2, 127.5, 127.4, 126.3, 122.5, 122.4, 120.1, 119.1, 118.7, 116.2, 116.0, 115.1, 113.2, 111.5, 72.6, 53.7.

¹⁹F NMR (371 MHz, CDCl₃) δ 109.05 (s, 1F)

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₂₉H₂₃FN₃, M+H]⁺ : 432.1876; Found: 432.1869.

3-(5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5j)



Yield: 82 mg, 74% as a light-yellow gummy solid

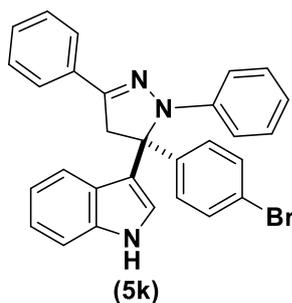
IR (neat, cm⁻¹): 3419, 3342, 2930, 1716, 1584, 1489, 1434, 1096, 871, 731, 662.

¹H NMR (500 MHz, CDCl₃): δ 7.98 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 - 7.09 (m, 8H), 7.07 - 7.04 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 1H), 6.72 - 6.70 (t, *J* = 7.1 Hz, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 4.70 (d, *J* = 4.8 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 147.9, 144.0, 140.2, 136.6, 133.4, 132.2, 129.4, 129.0, 128.3, 128.3, 127.2, 126.3, 125.7, 122.6, 122.4, 120.1, 119.2, 118.7, 115.1, 113.3, 111.5, 53.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₂₉H₂₃ClN₃, M+H]⁺ : 448.1581; Found: 448.1589.

3-(5-(4-bromophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5k)



Yield: 88mg, 72 % as a yellow solid

IR (neat, cm⁻¹): 3411, 3058, 2928, 1706, 1595, 1495, 1452, 1388, 1361, 1129, 1010, 744, 693.

Mp: 117-118 °C

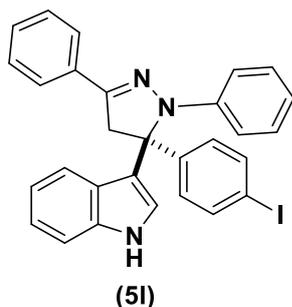
¹H NMR (500 MHz, CDCl₃): δ 8.02 (s, 1H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.17 - 7.08 (m, 8H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.2 Hz,

2H), 6.86 (s, 1H), 6.72 (t, $J = 7.2$ Hz, 1H), 5.09 (d, $J = 4.9$ Hz, 1H), 4.70 (d, $J = 4.8$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.9, 144.0, 140.7, 136.6, 132.3, 132.2, 129.0, 128.3, 128.3, 127.6, 126.3, 125.7, 122.5, 122.4, 121.5, 120.1, 119.2, 118.7, 115.0, 113.3, 111.5, 72.7, 53.7.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{BrN}_3, \text{M}+\text{H}]^+$: 492.1075; Found: 492.1068.

3-(5-(4-iodophenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5l)



Yield: 71mg, 67% as a light-yellow gummy solid

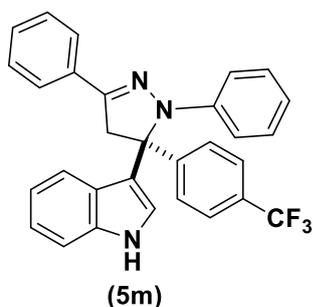
IR (neat, cm^{-1}): 3417, 2922, 1707, 1597, 1497, 1454, 1387, 1360, 1320, 1128, 743, 696.

^1H NMR (500 MHz, CDCl_3): δ 8.01 (s, 1H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.60 (s, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.18 - 7.11 (m, 7H), 7.07 - 7.04 (t, $J = 7.5$ Hz, 1H), 7.01 (d, $J = 8.6$ Hz, 3H), 6.89 (s, 1H), 6.74 - 6.71 (t, $J = 7.2$ Hz, 1H), 5.05 (d, $J = 5.1$ Hz, 1H), 4.72 (d, $J = 5.0$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 148.0, 144.3, 141.7, 138.2, 136.6, 129.6, 129.2, 129.0, 128.9, 127.6, 126.2, 125.8, 122.4, 122.4, 120.0, 118.9, 118.7, 115.4, 113.1, 111.4, 77.2, 77.0, 76.7, 73.1, 53.7.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{IN}_3, \text{M}+\text{H}]^+$: 540.0937; Found: 540.0928.

3-(1,3-diphenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5m)



Yield: 52mg, 45 % as a yellow gummy solid

IR (neat, cm^{-1}): 3319, 3062, 2923, 2853, 1708, 1597, 1454, 1323, 1125, 1068, 847, 745, 695.

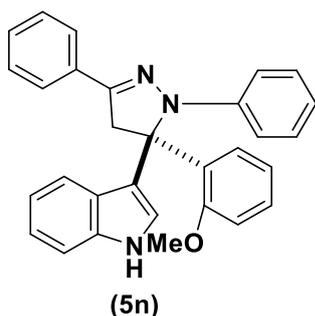
^1H NMR (500 MHz, CDCl_3): δ 8.04 (s, 1H), 7.65 (d, $J = 6.8$ Hz, 2H), 7.55 (d, $J = 7.9$ Hz, 3H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.28 (s, 3H), 7.16 - 7.08 (m, 5H), 7.00 (d, $J = 8.0$ Hz, 2H), 6.91 (s, 1H), 6.74 - 6.71 (t, $J = 7.2$ Hz, 1H), 5.20 (d, $J = 4.8$ Hz, 1H), 4.72 (d, $J = 4.7$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.6, 146.0, 144.1, 141.7, 141.4, 129.2, 128.9, 128.3, 128.2, 127.7, 126.2, 125.7, 124.1, 119.1, 113.3, 77.2, 77.0, 76.7, 73.3, 53.6.

^{19}F NMR (371 MHz, CDCl_3) δ 62.85 (s, 1F)

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{30}\text{H}_{23}\text{F}_3\text{N}_3, \text{M}+\text{H}]^+$: 482.1844; Found: 482.1839.

3-(5-(2-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5n)



Yield: 72mg, 69 % as a yellow solid

IR (neat, cm⁻¹): 3415, 3058, 2928, 1707, 1596, 1495, 1459, 1244, 1104, 1206, 747, 694.

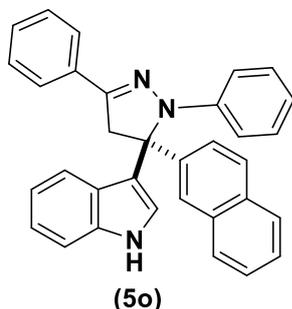
Mp: 115-116 °C

¹H NMR (500 MHz, CDCl₃): δ 7.95 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.07 (m, 7H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 6.75 - 6.72 (t, *J* = 7.5 Hz, 1H), 6.68 - 6.65 (t, *J* = 7.2 Hz, 1H), 5.51 (d, *J* = 2.5 Hz, 1H), 4.65 (d, *J* = 2.7 Hz, 1H), 3.79 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 149.2, 144.1, 136.4, 129.0, 128.6, 128.2, 128.0, 127.9, 126.9, 126.2, 122.5, 122.1, 121.4, 120.8, 119.5, 119.2, 118.4, 115.5, 112.8, 111.2, 110.6, 77.2, 77.0, 76.7, 67.1, 55.1, 51.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃O, M+H]⁺ : 444.2076; Found: 444.2068.

3-(5-(naphthalen-2-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5o)



Yield: 88mg, 72 % as a yellow solid

IR (neat, cm⁻¹): 3439, 3407, 1706, 1594, 1497, 1454, 1389, 1360, 1130, 744, 692.

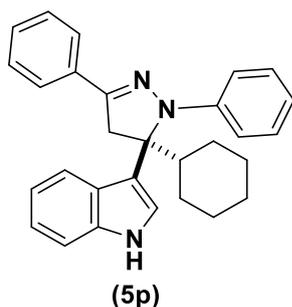
Mp: 115-116 °C

¹H NMR (500 MHz, CDCl₃): δ 8.01 (s, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.62 (s, 1H), 7.59 - 7.56 (t, *J* = 7.0 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 3H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 3H), 7.07 (d, *J* = 8.8 Hz, 3H), 6.90 (s, 1H), 6.81 - 6.78 (t, *J* = 7.2 Hz, 1H), 6.72 - 6.69 (t, *J* = 7.2 Hz, 1H), 5.19 (d, *J* = 4.6 Hz, 1H), 4.79 (d, *J* = 4.5 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 140.6, 129.3, 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 127.3, 127.0, 126.3, 126.2, 126.2, 122.4, 122.4, 120.1, 118.9, 118.9, 113.2, 112.7, 111.4, 72.9, 53.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₃H₂₆N₃, M+H]⁺ : 464.2127; Found: 464.2120.

3-(5-cyclohexyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5p)



Yield: 69mg, 65 % as Yellow foam

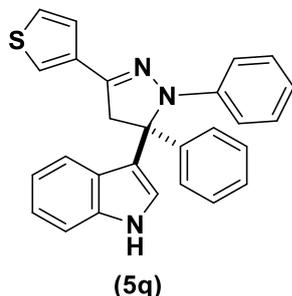
IR (neat, cm^{-1}): 3397, 3349, 2925, 2853, 1708, 1595, 1496, 1450, 1361, 1227, 745, 695.

^1H NMR (500 MHz, CDCl_3): δ 7.93 (s, 1H), 7.67 (d, $J = 7.5$ Hz, 2H), 7.61 (d, $J = 7.7$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.17 - 7.11 (m, 5H), 7.10 - 7.09 (m, 3H), 7.05 (d, $J = 7.1$ Hz, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 4.65 (s, 1H), 4.17 (s, 1H), 1.99 (d, $J = 11.3$ Hz, 1H), 1.80 (d, $J = 12.5$ Hz, 2H), 1.67 (d, $J = 11.6$ Hz, 2H), 1.59 (s, 3H), 1.54 (d, $J = 11.9$ Hz, 2H), 1.43 (d, $J = 12.3$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 149.2, 144.2, 136.5, 132.4, 129.1, 128.3, 127.9, 126.1, 125.6, 122.5, 122.2, 119.8, 118.6, 118.3, 115.8, 113.3, 111.3, 77.2, 77.0, 76.7, 73.5, 43.2, 39.0, 28.9, 26.4, 26.3, 26.1, 25.9.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{30}\text{N}_3, \text{M}+\text{H}]^+$: 420.2440; Found: 420.2436.

3-(1,5-diphenyl-3-(thiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5q)



Yield: 82mg, 80 % as a yellow solid

IR (neat, cm^{-1}): 3419, 2915, 2862, 1735, 1579, 1489, 1431, 1380, 1102, 739, 669.

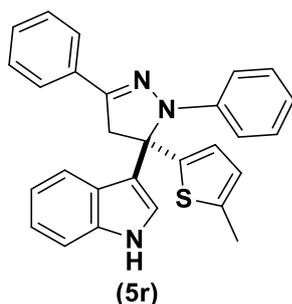
Mp: 91-92 $^{\circ}\text{C}$

^1H NMR (500 MHz, CDCl_3): δ 8.03 (s, 1H), 7.53 (d, $J = 5.1$ Hz, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 7.0$ Hz, 2H), 7.21 (d, $J = 7.4$ Hz, 3H), 7.15 - 7.120 (m, 2H), 7.09 (d, $J = 7.7$ Hz, 2H), 7.05 (s, 1H), 7.02 (d, $J = 7.9$ Hz, 2H), 6.91 (s, 1H), 6.70 - 6.68 (t, $J = 7.1$ Hz, 1H), 5.09 (d, $J = 5.9$ Hz, 1H), 4.65 (d, $J = 5.9$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 145.2, 144.6, 141.9, 129.1, 128.9, 127.6, 126.3, 125.8, 125.4, 123.0, 122.5, 122.4, 120.1, 118.9, 113.3, 111.4, 73.1, 55.1.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{27}\text{H}_{22}\text{N}_3\text{S}, \text{M}+\text{H}]^+$: 420.1534; Found: 420.1526.

3-(5-(5-methylthiophen-2-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5r)



Yield: 81mg, 78 % as a yellow solid

IR (neat, cm^{-1}): 3418, 2925, 2855, 1705, 1597, 1498, 1455, 1388, 1122, 747, 696.

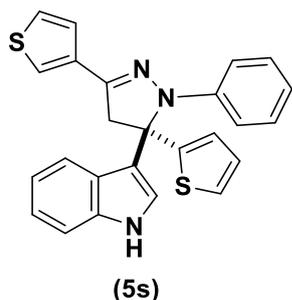
Mp: 89-90 °C

^1H NMR (500 MHz, CDCl_3): δ 8.01 (s, 1H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.17 - 7.14 (m, 5H), 7.12 - 7.06 (m, 4H), 6.89 (d, $J = 9.3$ Hz, 3H), 6.75 (t, $J = 7.0$ Hz, 1H), 5.40 (d, $J = 3.9$ Hz, 1H), 4.89 (d, $J = 3.9$ Hz, 1H), 2.10 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 148.2, 144.8, 144.4, 144.3, 141.4, 136.6, 132.3, 128.9, 128.3, 127.1, 126.3, 124.8, 124.3, 122.5, 120.1, 119.4, 118.8, 114.6, 113.6, 111.4, 68.9, 54.0, 30.9.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{28}\text{H}_{24}\text{N}_3\text{S}, \text{M}+\text{H}]^+$: 434.1691; Found: 434.1689.

3-(1-phenyl-5-(thiophen-2-yl)-3-(thiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5s)



Yield: 60mg, 56 % as a light-yellow gummy solid, (inseparable mixtures)

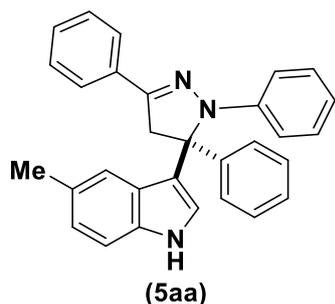
IR (neat, cm^{-1}): 3426, 2919, 2862, 1713, 1589, 1478, 1450, 1376, 1134, 794, 695.

^1H NMR (500 MHz, CDCl_3): δ 8.15 (s, 12H), 7.63 (d, $J = 6.6$ Hz, 2H), 7.57 (d, $J = 7.6$ Hz, 2H), 7.52 (d, $J = 6.6$ Hz, 4H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.32 - 7.26 (m, 15H), 7.18 (s, 3H), 7.10 (dd, $J = 20.5, 8.4$ Hz, 16H), 6.97 (d, $J = 7.8$ Hz, 2H), 6.88 (d, $J = 7.8$ Hz, 3H), 6.83 (s, 2H), 6.74 (t, $J = 7.1$ Hz, 1H), 5.17 (d, $J = 3.9$ Hz, 1H), 4.70 (d, $J = 3.5$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 151.6, 140.3, 139.6, 136.0, 135.1, 133.1, 131.8, 130.5, 129.1, 128.4, 128.2, 127.7, 126.7, 126.3, 125.4, 124.1, 122.3, 120.0, 119.9, 118.4, 113.9, 113.2, 111.1, 72.8, 53.7.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{25}\text{H}_{20}\text{N}_3\text{S}_2, \text{M}+\text{H}]^+$: 426.1099; Found: 426.1090.

5-methyl-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5aa)



Yield: 72mg, 60 % as a yellow gummy solid

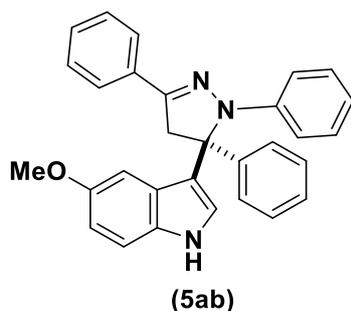
IR (neat, cm⁻¹): 3422, 3365, 2824, 1793, 1590, 1483, 1470, 1220, 1139, 752, 690.

¹H NMR (500 MHz, CDCl₃): δ 7.87 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 3H), 7.15 – 7.08 (m, 6H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.81 (s, 1H), 6.70 - 6.67 (t, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 4.7 Hz, 1H), 4.71 (d, *J* = 4.7 Hz, 1H), 2.38 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 147.8, 144.2, 138.7, 137.3, 136.6, 132.5, 129.8, 128.9, 128.3, 128.1, 126.2, 125.7, 122.4, 122.4, 120.0, 118.9, 118.8, 113.2, 111.4, 72.9, 53.7, 21.1.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃, M+H]⁺ : 428.2127; Found: 428.2120.

5-methoxy-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ab)



Yield: 85mg, 72 % as a yellow gummy solid

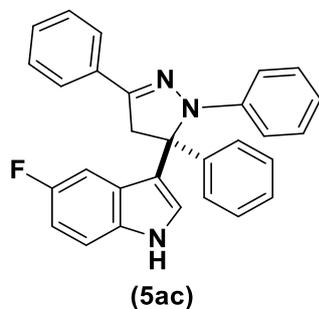
IR (neat, cm⁻¹): 3407, 3340, 2927, 1708, 1596, 1495, 1450, 1217, 1131, 754, 695.

¹H NMR (500 MHz, CDCl₃): δ 7.90 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.28 – 7.24 (m, 4H), 7.22 (d, *J* = 6.2 Hz, 1H), 7.16 – 7.12 (m, 4H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 18.0 Hz, 2H), 6.76 (s, 1H), 6.70 - 6.67 (t, *J* = 7.0 Hz, 1H), 5.15 (d, *J* = 4.6 Hz, 1H), 4.69 (d, *J* = 4.6 Hz, 1H), 3.52 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 154.3, 147.6, 144.3, 141.9, 129.2, 129.0, 128.3, 128.1, 127.7, 126.3, 125.7, 122.8, 119.0, 113.0, 112.9, 112.2, 100.2, 72.9, 55.5, 54.0.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃O, M+H]⁺ : 444.2076; Found: 444.2062.

5-fluoro-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ac)



Yield: 60mg, 58 % as a yellow gummy solid

IR (neat, cm⁻¹): 3441, 3162, 2831, 1780, 1691, 1589, 1452, 1491, 1361, 1327, 1029, 737, 683.

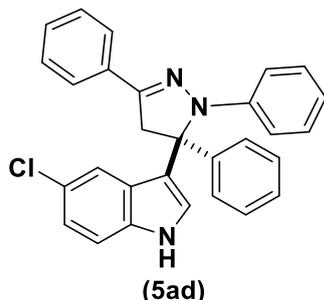
¹H NMR (500 MHz, CDCl₃): δ 8.01 (s, 1H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.29 - 7.26 (m, 3H), 7.23 (d, *J* = 7.1 Hz, 7H), 7.15 (d, *J* = 7.1 Hz, 6H), 7.12 - 7.09 (m, 6H), 7.03 (d, *J* = 7.8 Hz, 5H), 6.91 (d, *J* = 10.3 Hz, 4H), 6.71 - 6.68 (t, *J* = 7.1 Hz, 3H), 5.10 (d, *J* = 2.9 Hz, 2H), 4.67 (d, *J* = 3.0 Hz, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 147.5, 144.1, 133.1, 132.3, 129.9, 129.2, 128.9, 128.3, 128.2, 127.7, 126.2, 125.7, 124.1, 119.0, 113.3, 112.1, 112.0, 111.0, 110.8, 103.7, 73.3, 53.5.

¹⁹F NMR (371 MHz, CDCl₃) δ 121.37 (s, 1F)

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₂₉H₂₃FN₃, M+H]⁺ : 432.1876; Found: 432.1869.

5-chloro-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ad)



Yield: 52mg, 49% as yellow gummy solid

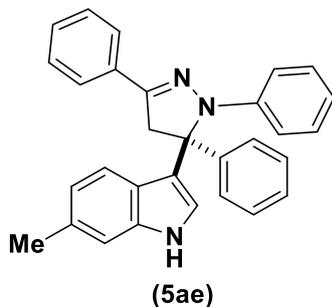
IR (neat, cm⁻¹): 3064, 2926, 2854, 1702, 1598, 1494, 1457, 1255, 1094, 761, 696.

¹H NMR (500 MHz, CDCl₃): δ 8.09 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.47 - 7.44 (t, *J* = 7.7 Hz, 1H), 7.39 - 7.36 (t, *J* = 7.5 Hz, 3H), 7.33 - 7.29 (t, *J* = 7.5 Hz, 1H), 7.28 (s, 1H), 7.20 (d, *J* = 7.3 Hz, 3H), 7.13 (d, *J* = 8.9 Hz, 3H), 7.00 (d, *J* = 8.9 Hz, 3H), 5.15 (d, *J* = 2.6 Hz, 2H), 5.10 (d, *J* = 2.4 Hz, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 147.4, 142.0, 137.5, 133.7, 131.0, 130.1, 129.3, 129.3, 128.9, 128.8, 128.8, 128.4, 128.1, 126.0, 125.8, 124.5, 114.4, 114.3, 83.1, 73.3.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₂₉H₂₃ClN₃, M+H]⁺ : 448.1581; Found: 448.1572.

6-methyl-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ae)



Yield: 60mg, 52% as a light-yellow solid

IR (neat, cm⁻¹): 3406, 3058, 2922, 1707, 1596, 1496, 1448, 1363, 1222, 753, 695.

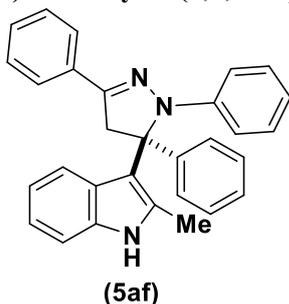
Mp: 116-117 °C

¹H NMR (500 MHz, CDCl₃): δ 7.93 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.29 - 7.24 (m, 5H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.17 - 7.15 (m, 2H), 7.14 - 7.09 (m, 4H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 6.70 - 6.67 (t, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 4.5 Hz, 1H), 4.70 (d, *J* = 4.5 Hz, 1H), 2.33 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 147.8, 144.2, 138.7, 136.6, 132.5, 129.8, 128.9, 128.3, 128.1, 126.2, 125.7, 122.4, 122.4, 120.0, 118.9, 118.8, 115.4, 113.2, 111.4, 72.9, 53.7, 21.1.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃, M+H]⁺ : 428.2127; Found: 428.2120.

(S)-2-methyl-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5af)



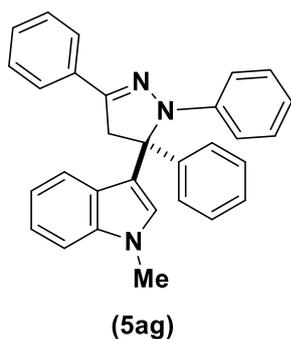
Yield: 28mg, 30% as a light-yellow foam

¹H NMR (500 MHz, CDCl₃): δ 7.83 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 2H), 7.45 - 7.42 (t, 1H), 7.33 (d, *J* = 12.1 Hz, 3H), 7.25 (d, *J* = 6.6 Hz, 4H), 7.12 (d, *J* = 7.2 Hz, 3H), 7.06 (d, *J* = 9.8 Hz, 3H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.73 (s, 1H), 5.05 (s, 1H), 4.97 (s, 1H), 2.33 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 147.5, 143.6, 137.0, 133.8, 133.4, 133.0, 129.2, 129.0, 128.5, 128.4, 128.3, 128.3, 128.0, 127.7, 127.4, 126.1, 125.9, 125.5, 124.8, 121.7, 121.0, 118.4, 113.5, 111.3, 43.3, 36.5, 29.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃, M+H]⁺ : 428.2127; Found: 428.2118.

1-methyl-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ag)



Yield: 74mg, 70% as a brownish-yellow solid

IR (neat, cm⁻¹): 3057, 2925, 2855, 1597, 1497, 1713, 1597, 1497, 1388, 1029, 745, 696.

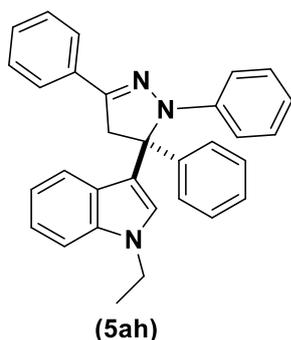
Mp: 81-82 °C

¹H NMR (500 MHz, CDCl₃): δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.37 - 7.34 (m, 1H), 7.28 - 7.22 (m, 6H), 7.13 - 7.08 (m, 4H), 7.04 (d, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 13.6 Hz, 1H), 6.70 - 6.67 (t, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 3.7 Hz, 1H), 4.72 (d, *J* = 3.7 Hz, 1H), 3.60 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 148.0, 144.2, 141.6, 137.4, 129.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.6, 126.9, 126.3, 126.2, 125.9, 125.8, 121.9, 119.5, 118.9, 113.9, 113.1, 109.5, 73.4, 53.5, 32.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃, M+H]⁺ : 428.2127; Found: 428.2119.

1-ethyl-3-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ah)



Yield: 80mg, 72 % as a light-yellow solid

IR (neat, cm⁻¹): 3048, 2916, 2840, 1589, 1490, 1727, 1579, 1492, 1372, 1120, 732, 680.

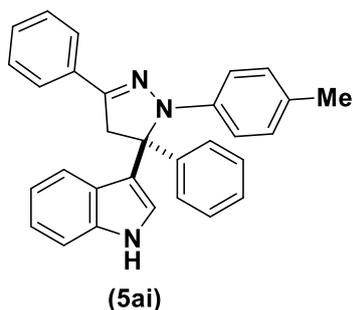
Mp: 85-86 °C

¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.20 (m, 8H), 7.16 - 7.10 (m, 5H), 7.04 (t, *J* = 7.0 Hz, 2H), 6.78 (s, 1H), 6.70 - 6.67 (t, *J* = 7.2 Hz, 1H), 5.14 (d, *J* = 3.6 Hz, 1H), 4.72 (d, *J* = 3.4 Hz, 1H), 4.01 - 3.97 (q, *J* = 14.4, 2H), 1.31 - 1.28 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 148.0, 144.2, 141.6, 136.4, 132.5, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 128.0, 127.6, 126.4, 126.3, 125.8, 125.3, 125.2, 121.8, 119.4, 119.0, 118.8, 113.9, 113.2, 109.6, 73.3, 53.6, 41.0, 15.4.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₁H₂₈N₃, M+H]⁺ : 442.2283; Found: 442.2278.

3-(3,5-diphenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ai)



Yield: 74mg, 71 % as a yellow solid

IR (neat, cm⁻¹): 3657, 3431, 3399, 3291, 2920, 1703, 1612, 1515, 1492, 1452, 1360, 1101, 743, 697.

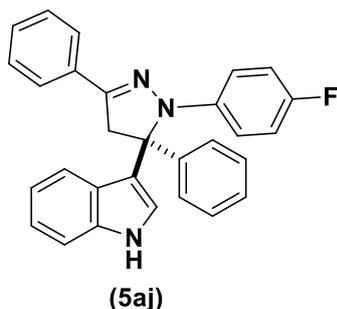
Mp: 110-111 °C

¹H NMR (500 MHz, CDCl₃): δ 8.02 (s, 1H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.30 - 7.20 (m, 6H), 7.13 - 7.09 (m, 4H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 4.8 Hz, 3H), 6.87 (s, 1H), 5.12 (d, *J* = 4.4 Hz, 1H), 4.72 (d, *J* = 4.4 Hz, 1H), 2.15 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 147.6, 141.8, 129.5, 129.1, 128.2, 127.9, 127.6, 126.1, 125.8, 122.4, 120.0, 118.9, 115.4, 113.2, 111.4, 73.3, 53.7, 29.7.

HRMS (ESI-Orbitrap): [M+H]⁺ calcd for [C₃₀H₂₆N₃, M+H]⁺ : 428.2127; Found: 428.2120.

3-(1-(4-fluorophenyl)-3,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5aj)



Yield: 74mg, 69% as a yellow solid

IR (neat, cm⁻¹): 3423, 3059, 2926, 1707, 1605, 1503, 1360, 1219, 1127, 1093, 823, 741, 695.

Mp: 108-109 °C

¹H NMR (500 MHz, CDCl₃): δ 7.95 (s, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.27 - 7.24 (t, *J* = 7.8 Hz, 3H), 7.20 (d, *J* = 7.3 Hz, 3H), 7.15 - 7.09 (m, 4H), 7.05 - 7.02 (t, *J* = 7.5 Hz, 1H),

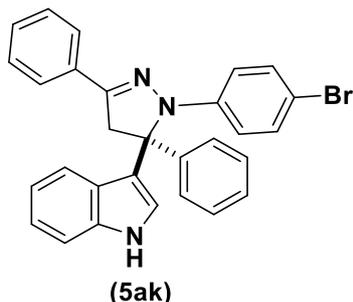
6.95 - 6.93 (m, 2H), 6.84 (s, 1H), 6.80 - 6.77 (t, $J = 8.4$ Hz, 2H), 5.08 (d, $J = 4.7$ Hz, 1H), 4.74 (d, $J = 4.6$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.9, 141.4, 136.6, 132.3, 129.2, 128.3, 128.2, 127.7, 126.2, 125.8, 122.5, 122.3, 120.1, 118.8, 115.5, 115.3, 114.1, 114.1, 111.4, 73.6, 53.9.

^{19}F NMR (371 MHz, CDCl_3) δ 126.15 (s, 1F)

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{FN}_3, \text{M}+\text{H}]^+$: 432.1876; Found: 432.1869.

3-(1-(4-bromophenyl)-3,5-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ak)



Yield: 74mg, 70 % as a yellow solid

IR (neat, cm^{-1}): 3418, 3179, 2951, 1700, 1613, 1592, 1382, 1228, 1139, 1082, 762, 682.

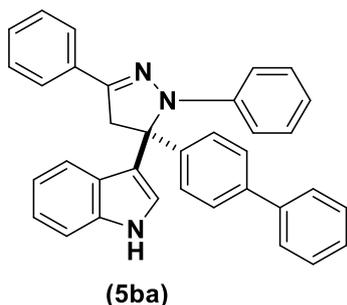
Mp: 105-106 °C

^1H NMR (500 MHz, CDCl_3): δ 7.98 (s, 1H), 7.65 (d, $J = 6.6$ Hz, 4H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.30 - 7.26 (m, 4H), 7.23 - 7.20 (m, 3H), 7.16 (d, $J = 7.5$ Hz, 4H), 7.07 - 7.04 (t, $J = 7.4$ Hz, 2H), 6.90 (s, 1H), 6.88 - 6.86 (m, 2H), 5.10 (d, $J = 4.5$ Hz, 1H), 4.75 (d, $J = 4.5$ Hz, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 148.6, 143.1, 141.0, 136.6, 132.1, 131.7, 129.3, 128.4, 128.3, 127.9, 126.3, 125.7, 122.6, 122.3, 120.1, 118.8, 115.1, 114.8, 115.1, 114.8, 111.5, 110.9, 73.0, 53.0.

HRMS (ESI-Orbitrap): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{29}\text{H}_{23}\text{BrN}_3, \text{M}+\text{H}]^+$: 492.1075; Found: 492.1068.

3-(5-([1,1'-biphenyl]-4-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5ba)



Yield: 88mg, 90 % as a yellow solid

IR (neat, cm^{-1}): 3428, 3416, 1728, 1590, 1499, 1462, 1371, 1381, 1127, 732, 681.

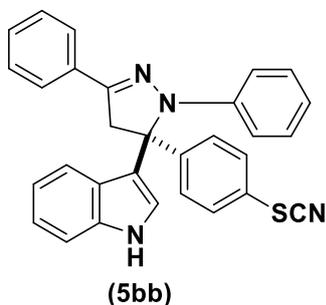
Mp: 116-117 °C

^1H NMR (500 MHz, CDCl_3): δ 8.00 (s, 1H), 7.77 (s, 1H), 7.76 (d, $J = 7.3$ Hz, 2H), 7.70 (d, $J = 5.1$ Hz, 2H), 7.67 (d, $J = 6.3$ Hz, 3H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.39 - 7.36 (t, $J = 8.5$ Hz, 3H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.17 - 7.10 (m, 5H), 7.08 - 7.06 (t, $J = 4.9$ Hz, 4H), 7.04 (d, $J = 7.6$ Hz, 1H), 6.88 (s, 1H), 6.68 - 6.67 (m, 1H), 5.29 (d, $J = 4.9$ Hz, 2H), 4.81 (d, $J = 4.9$ Hz, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 147.9, 144.2, 140.6, 140.9, 136.6, 132.4, 129.3, 129.0, 128.7, 128.6, 128.3, 128.1, 127.9, 127.3, 127.0, 126.3, 126.2, 126.1, 122.5, 122.4, 120.1, 118.9, 115.3, 113.2, 112.7, 111.4, 72.9, 53.7.

HRMS (ESI-Orbitrap): $[M+H]^+$ calcd for $[C_{33}H_{26}N_3, M+H]^+$: 464.2127; Found: 464.2120.

3-(1,3-diphenyl-5-(4-thiocyanatophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indole (5bb)



Yield: 96mg, 92 % as a light-yellow solid

IR (neat, cm^{-1}): 3103, 3025, 2926, 2855, 1731, 1598, 1182, 1127, 745, 697.

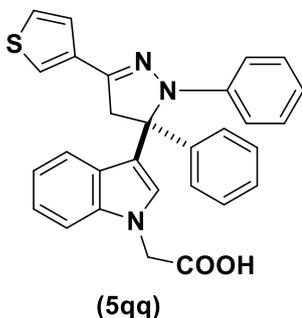
Mp: 112-113 °C

1H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.72 (s, 2H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.50 (d, $J = 7.7$ Hz, 2H), 7.37 (d, $J = 7.7$ Hz, 4H), 7.24 (d, $J = 4.5$ Hz, 4H), 7.16 - 7.13 (t, $J = 7.7$ Hz, 3H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.94 (s, 1H), 5.16 (s, 1H), 4.81 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 145.4, 139.5, 136.6, 134.0, 132.6, 129.0, 128.5, 127.4, 126.6, 122.8, 122.4, 120.3, 118.5, 114.5, 111.6, 72.2, 53.9.

HRMS (ESI-Orbitrap): $[M+H]^+$ calcd for $[C_{30}H_{23}N_4S, M+H]^+$: 471.1643; Found: 471.1639.

2-(3-(1,5-diphenyl-3-(thiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-indol-1-yl)acetic acid (5qq)



Yield: 84mg, 78% as a yellow solid

IR (neat, cm^{-1}): 3402, 3058, 2924, 2155, 1589, 1491, 1394, 1098, 1010, 745, 693.

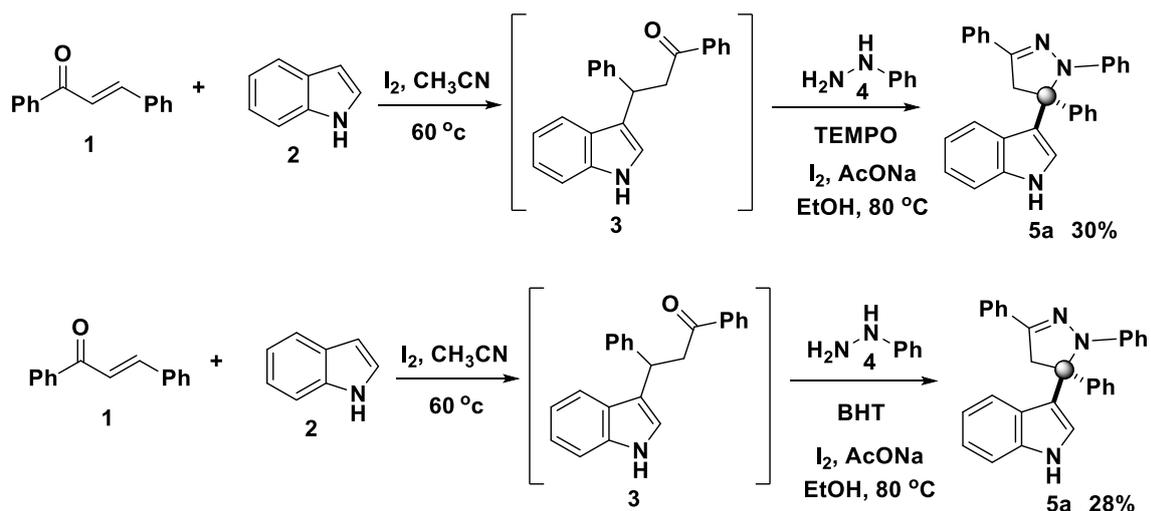
Mp: 118-119 °C

1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, $J = 3.7$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.32 - 7.29 (m, 3H), 7.27 (d, $J = 6.9$ Hz, 3H), 7.23 (d, $J = 12.1$ Hz, 3H), 7.16 - 7.12 (m, 5H), 7.07 (d, $J = 7.9$ Hz, 3H), 6.85 (s, 1H), 6.77 - 6.74 (t, $J = 7.0$ Hz, 1H), 5.16 (d, $J = 5.6$ Hz, 1H), 4.75 (s, 2H), 4.69 (d, $J = 5.6$ Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.15, 145.0, 144.5, 141.8, 137.3, 134.4, 129.1, 128.9, 127.6, 126.3, 125.8, 125.4, 122.7, 120.4, 119.3, 119.0, 115.1, 113.4, 109.3, 73.0, 55.0, 47.3.

HRMS (ESI-Orbitrap): $[M+H]^+$ calcd for $[C_{29}H_{24}N_3O_2S, M+H]^+$: 478.1589; Found: 478.1578.

1.8. Control experiments



2. Crystallization procedure for compound 5e:

In a 5 mL glass vial, 10 mg of **5e** was dissolved in 1 mL of HPLC-grade methanol, followed by the addition of 1 mL of HPLC-grade chloroform. The solution was homogenised by gentle shaking. The sample vial with the solution was then capped and kept undisturbed for slow evaporation at room temperature for 7 days.

3.1. ORTEP diagram of compound 5e:

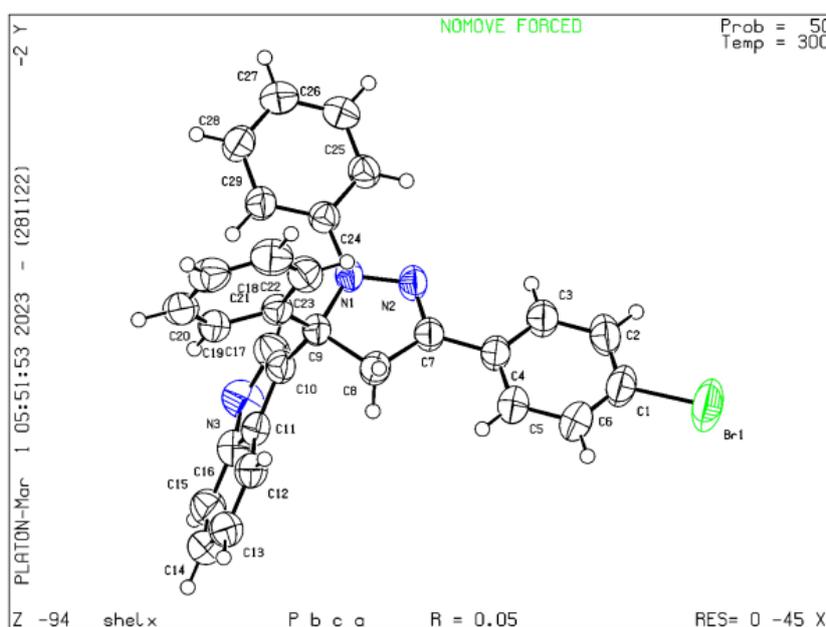


Figure S68 ORTEP drawing of 5e with 50% ellipsoid probability

Table 1. Crystal data and structure refinement for 5e

Identification code	shelx
Empirical formula	C ₂₉ H ₂₂ Br N ₃
Formula weight	492.40
Temperature	300(2) K
Wavelength	1.54178 Å ⁰
Crystal system, space group	Orthorhombic, P b c a
Unit cell dimensions	a = 12.5521(3) Å ⁰ alpha = 90 deg. b = 11.6842(3) Å ⁰ beta = 90 deg. c = 31.6373(7) Å ⁰ gamma = 90 deg.
Volume	4639.97(19) Å ³
Z, Calculated density	8, 1.410 Mg/m ³
Absorption coefficient	2.576 mm ⁻¹
Crystal size	0.163 x 0.055 x 0.052 mm
Theta range for data collection	2.793 to 68.553 deg.
Limiting indices	-15<=h<=15, -14<=k<=14, -38<=l<=38
Reflections collected / unique	103545 / 4259 [R(int) = 0.0643]
Completeness to theta = 67.679	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7531 and 0.6096
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4259 / 0 / 302
Goodness-of-fit on F ²	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0528, wR2 = 0.1324
R indices (all data)	R1 = 0.0727, wR2 = 0.1569
Extinction coefficient	0.00055(10)
Largest diff. peak and hole	0.850 and -0.827 e.Å ⁻³

3. Biology

3.1. *In-vitro* antimicrobial activity

3.1.1. Zone of inhibition

Agar plate diffusion assay was used to evaluate the antimicrobial activity. Twelve different compounds were screened for antimicrobial activity against test organisms, namely, *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*, and fungal strains including *C. albicans* and *C. glabrata*. A quantity of 25 µg/mL of each synthesized compound was added in the wells of nutrient agar

plates (for bacteria) and potato dextrose agar plates (for fungi), seeded with 100 μ L of activated test cultures. The plates were incubated at 37 °C (bacteria) and 30 °C (fungi) under aerobic conditions for 24–48 h, and the clear zones of inhibition around the compounds were measured and compared with the negative control. ^{3,4}

Zone of Inhibition of selected compounds:

Table 2. Zone of inhibitions (mm) was measured by using an agar gel diffusion assay. The results are mean \pm S.D of three replicate experiments at a concentration of 25 μ g/mL. - zone of inhibition not observed.

Zone of Inhibition (mm)						
Compounds	Bacteria				Fungi	
	Gram-negative		Gram-positive		<i>C. albicans</i> (ATCC 24433)	<i>C. glabrata</i> (MTCC3019)
	<i>E. coli</i> (ATCC 10799)	<i>P. aeruginosa</i> (MTCC11778)	<i>B. cereus</i> (MTCC 13343)	<i>S. aureus</i> (ATCC 6538)		
5c	10.66 \pm 0.57	-	11.33 \pm 0.57	9.66 \pm 0.57	14.33 \pm 0.57	14.66 \pm 0.57
5f	10.66 \pm 0.57	-	8.66 \pm 0.57	7.00 \pm 0.57	11.66 \pm 0.57	10.33 \pm 0.57
5i	7.33 \pm 0.57	-	10.00 \pm 0.57	9.66 \pm 0.57	-	13.66 \pm 0.57
5k	7.00 \pm 0.57	-	7.33 \pm 0.57	7.33 \pm 0.57	10.00 \pm 0.57	13.33 \pm 0.57
5o	10.00 \pm 0.57	-	10.00 \pm 0.57	9.66 \pm 0.57	14.00 \pm 0.57	14.66 \pm 0.57
5p	10.00 \pm 0.57	-	7.66 \pm 0.57	8.66 \pm 0.57	10.33 \pm 0.57	14.33 \pm 0.57
5q	8.66 \pm 0.57	-	13.66 \pm 0.57	10.33 \pm 0.57	11.00 \pm 0.57	12.33 \pm 0.57
5s	-	-	8.66 \pm 0.57	6.33 \pm 0.57	9.66 \pm 0.57	9.66 \pm 0.57
5aa	15.33 \pm 0.57	16.33 \pm 0.57	14.66 \pm 0.57	12.33 \pm 0.57	15.66 \pm 0.57	17.33 \pm 0.57
5ab	-	-	7.00 \pm 0.57	-	11.00 \pm 0.57	10.00 \pm 0.57
5ad	8.00 \pm 0.57	-	-	9.66 \pm 0.57	10.00 \pm 0.57	13.33 \pm 0.57
5ah	9.33 \pm 0.57	-	7.66 \pm 0.57	11.66 \pm 0.57	11.00 \pm 0.57	14.33 \pm 0.57
5aj	14.66 \pm 0.57	-	14.00 \pm 0.57	12.00 \pm 0.57	14.66 \pm 0.57	12.66 \pm 0.57

3.1.2. Minimum Inhibition Concentration (MIC), Minimum Bactericidal (MBC), Fungicidal (MFC) Concentration

Materials: Mueller–Hinton agar (MHA), yeast extract, peptone, soluble starch, sodium chloride, resazurin sodium, dextrose, ampicillin sodium salt, ciprofloxacin hydrochloride monohydrate, Hi-Media, Fluconazole Sigma-Aldrich.

Microorganisms and media

The synthesized compounds were tested for *in-vitro* antimicrobial activity against six microbial cultures. Inoculum was prepared by re-suspending the pure loop full of exponentially growing culture on LB agar in 5 ml of sterile saline (0.85%). The newly synthesized compounds were vortexed/sonicated in an ultrasonic bath till dissolved (final concentration of <1% DMSO) and the solution became homogenous. Using a spectrophotometer, the cell density was fixed to 70% transmittance at 530nm (Labman, LMSP UV-1200) which contained 1×10^6 to 5×10^6 cells per mL [4,5]. The *minimum inhibitory concentration* (MIC) values for bacteria was determined in Miller Hilton broth and for yeast antibiotic medium-3 as recommended by CLSI.

Methods:

The anti-microbial activity of the newly synthesized compounds was determined by resazurin-based micro-broth dilution method according to the guidelines of CLSI document M07 and M27-A2 with slight modifications. 10 μ l culture inoculums were added with 180 μ l sterile broths in a sterile flat bottom 96 well plates and 10 μ l of 10 compounds were added to make the final concentration from 0.5-64 μ g/ml in a serial dilution manner. Ampicillin (AMP), ciprofloxacin (CIP), and fluconazole (FLC) were used as standard drugs for gram-positive bacteria, gram-negative bacteria and yeast respectively. The plates were incubated for 24 h at 37°C and after incubation, each of the wells was added with 20 μ L of resazurin solution (0.015%) and allowed to stand for 1 h for colour change. The MIC was defined as the lowest concentration of synthesized compounds/standard drug resulting in persistent blue colour. After determining the MIC, an aliquot of 50 μ l sample was withdrawn from each clear tube up to 8 folds of the MIC and spread onto respective agar plates. Inoculated plates were incubated, and MBC/MFCs were recorded after 36 h. The compound is said to be static if there's growth at eightfold the MIC whose MBC/MFC is not determined (ND). The MBC/MFC was defined as the lowest concentration of each compound that resulted in total inhibition or $\geq 99\%$ inhibition of the growth.

Results of Antimicrobial Activity:

Compound	Concentration in $\mu\text{g/ml}$											
	Bacteria								Fungi			
	Gram negative				Gram positive							
	<i>E. coli</i>		<i>P. aeruginosa</i>		<i>B. subtilis</i>		<i>S. aureus</i>		<i>C. albicans</i>		<i>C. glabrata</i>	
MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MFC	MIC	MFC	
5c	64	ND	64	ND	32	ND	32	ND	32	ND	64	ND
5q	32	ND	64	ND	64	ND	64	ND	64	ND	64	ND
5qq	8	64	4	64	4	64	8	64	4	64	8	ND
5cc	16	ND	32	ND	8	ND	16	ND	16	ND	16	ND
AMP	ND	ND	ND	ND	16	64	16	64	ND		ND	
CIP	8	32	8	32	ND	ND	ND	ND	ND		ND	
FCL	ND	ND	ND	ND	ND	ND	ND	ND	16		ND	

Table 3. Results of the MIC and MFC of newly synthesized compounds along with standard drugas determined by resazurin based micro-broth dilution method and CFU respectively. (AMP: Ampicillin, CIP: Ciprofloxacin, FCL: Flucanazole; ND: Not determined)

3.2. Cytotoxicity evaluation by MTT assay

The cytotoxicity of the compound **5qq** was assessed using the standard colourimetric MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)[8]. This method evaluates cell viability based on the ability of living cells to convert the yellow MTT dye into a blue/purple formazan product through a reduction reaction catalysed by mitochondrial dehydrogenase enzymes. Human liver hepatocellular carcinoma HepG2 cells were seeded into 96-well plates and cultured for 24 hours at 37°C in a humidified atmosphere containing 5% CO₂ to allow cell attachment. Fresh solutions of the test compound were prepared in DMSO at the desired concentrations. The cells were then treated with varying concentrations of this compound, with 2 μL of each DMSO solution added to 200 μL of the final culture volume. Control wells included untreated cells containing 0.5% DMSO (negative control) and wells with medium only (blank control). After 72 hours of exposure to the test compound, 20 μL of MTT solution (4 mg/mL) was added to each well, and the plates were incubated for an additional 4 hours in the CO₂ incubator. Following incubation, the medium was removed, and the resulting formazan crystals were dissolved in 75 μL of DMSO. The plates were then shaken for 30 minutes at room temperature to ensure complete dissolution. The optical density (OD) of each well was measured at a wavelength of 540 nm using a microplate reader, and the percentage of cell growth was calculated. All samples were tested in triplicate[9].

3.3. ADMET calculations

The physicochemical properties, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity), and drug-likeness of the compounds were assessed using the pkCSM online tool. These results provide insights into the pharmacokinetic characteristics of the compounds, aiding in the evaluation of their potential as drug candidates.

Table 4. ADMET Predictions

Values in their respective units 5qq	
Molecular Weight	477.589
Rotatable Bonds	6
Acceptors	5
Donors	1
Surface Area	206.744

Model Name	Predicted Value	
	5qq	Ciprofloxacin
Water solubility (log mol/L)	-3.467	-2.894
Caco2 permeability (log Papp in 10 ⁻⁶ cm/s)	1.174	0.48
Intestinal absorption (human)	96.907	96.331
Skin Permeability (log Kp)	-2.735	-2.734
VDss (human) (log L/kg)	-1.571	-0.241
Fraction unbound (human) (Fu)	0.142	0.654
BBB permeability (log BB)	0.135	-0.562
CNS permeability (log PS)	-1.41	-2.995
CYP2D6 substrate	No	No

CYP3A4 substrate	Yes	No
CYP1A2 inhibitor	Yes	No
CYP2C19 inhibitor	Yes	No
CYP2C9 inhibitor	Yes	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Total Clearance (log ml/min/kg)	0.08	0.633
Renal OCT2 substrate	No	No
AMES toxicity	No	No
Max. tolerated dose (human) (log mg/kg/day)	0.519	0.904
hERG I inhibitor	No	No
hERG II inhibitor	No	No
Oral Rat Acute Toxicity (LD ₅₀) (mol/kg)	2.79	2.819
Skin Sensitisation	No	No
T.Pyriformis toxicity (log µg/L)	0.285	0.285
Minnow toxicity (log mM)	-0.277	1.376

4. ^1H and ^{13}C NMR of products

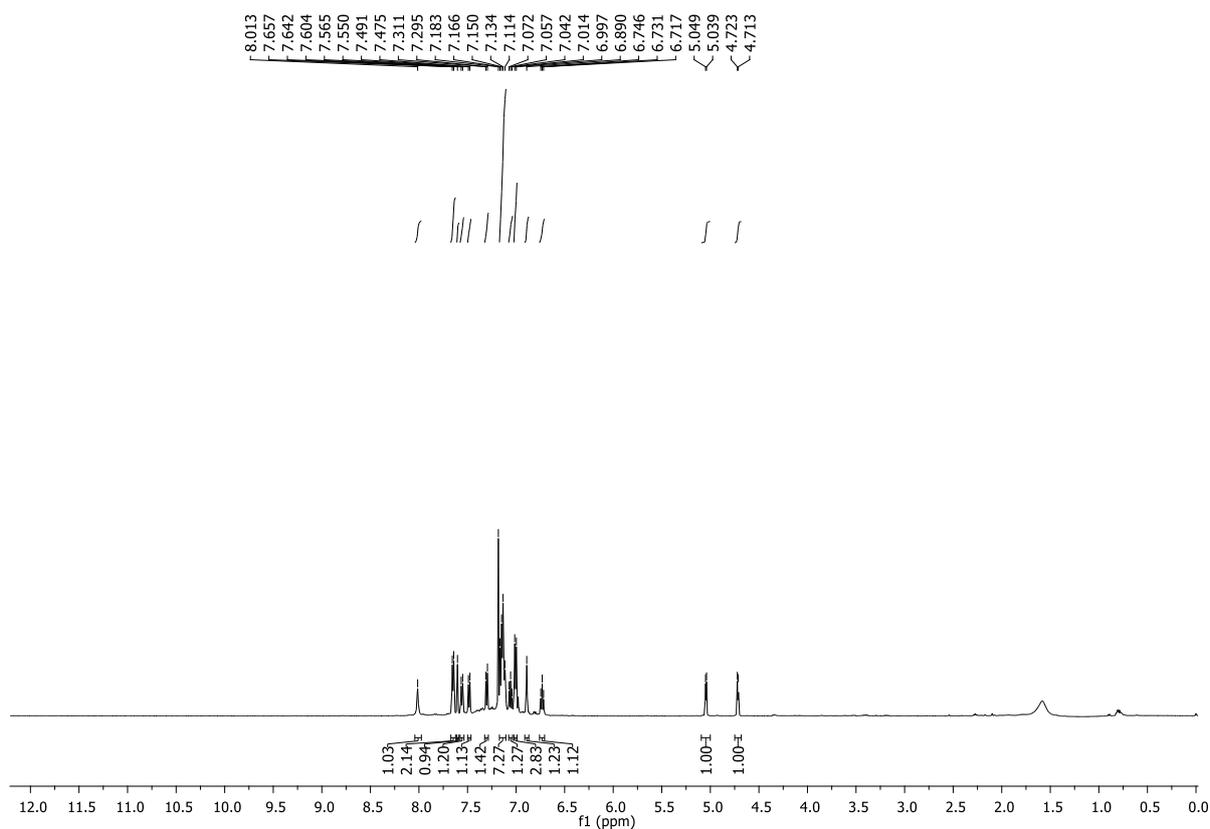


Figure S1. ^1H (500 MHz, CDCl_3) of **5a**

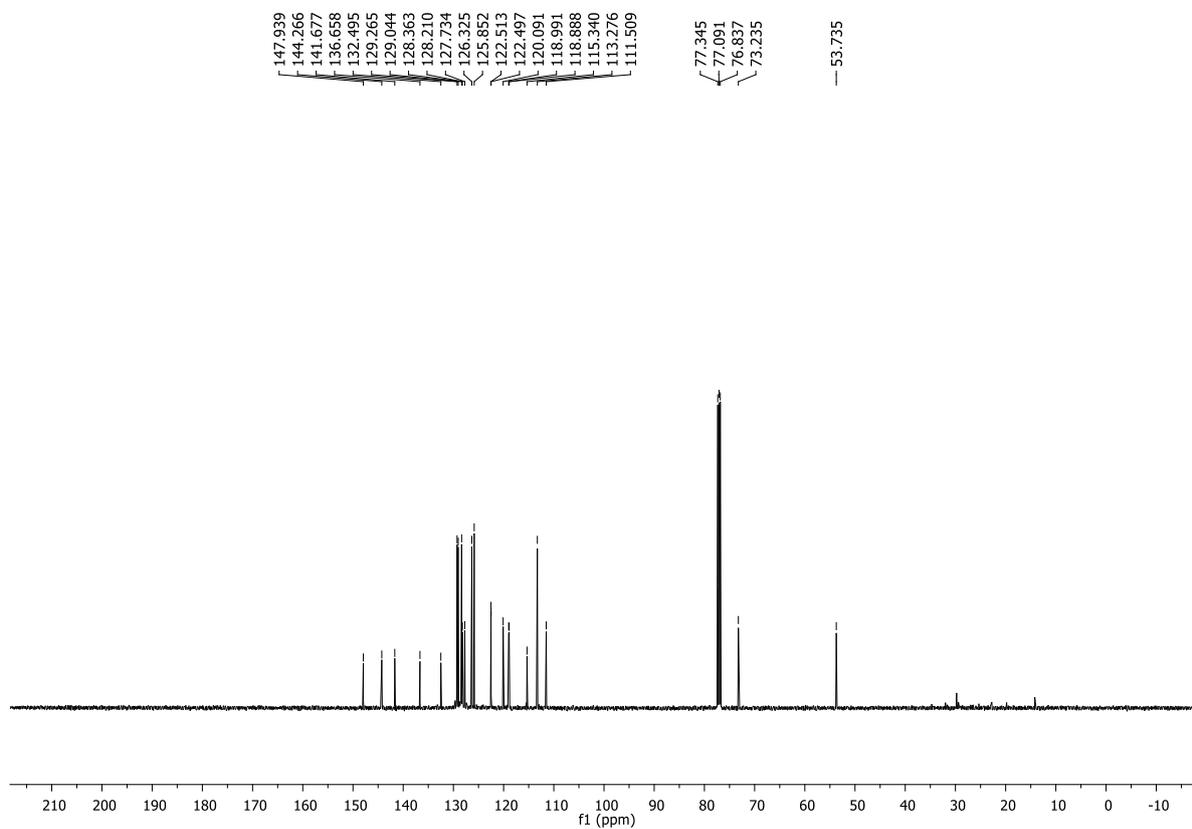


Figure S2. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5a**

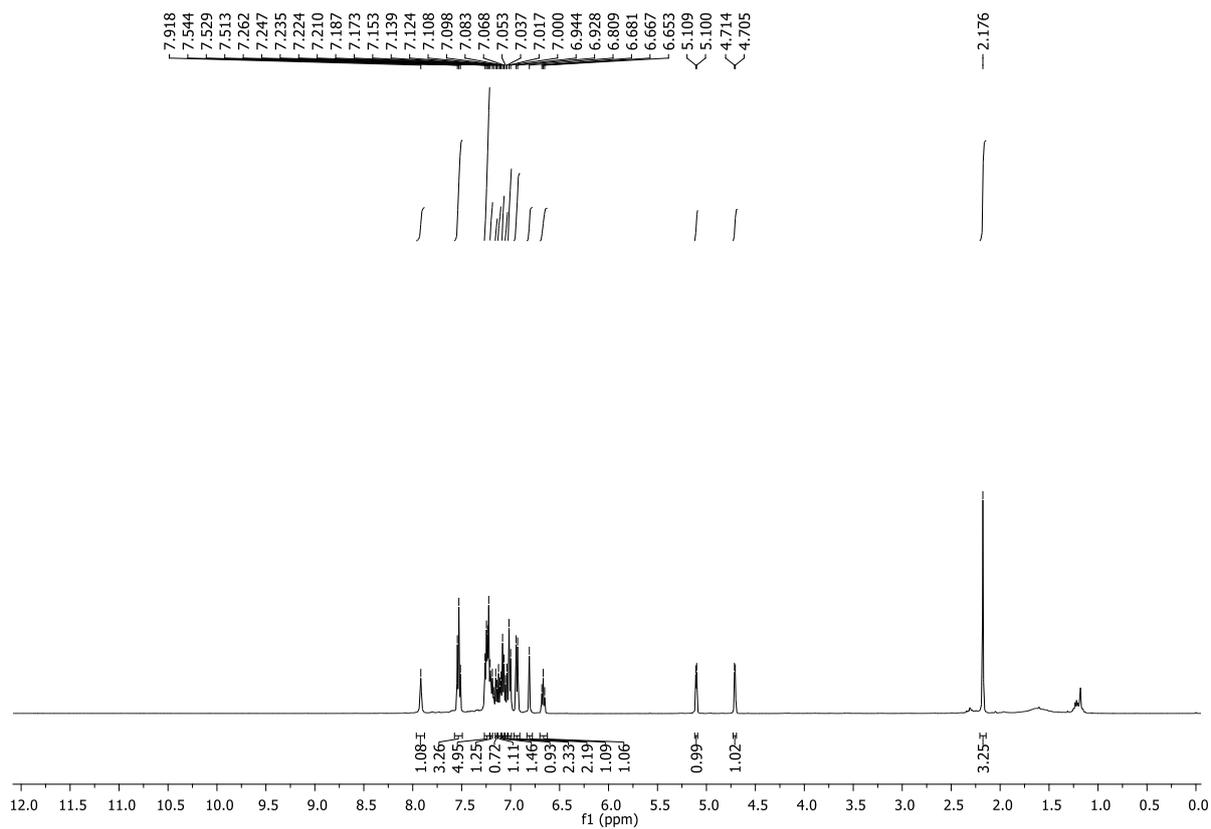


Figure S3. ^1H (500 MHz, CDCl_3) of **5b**

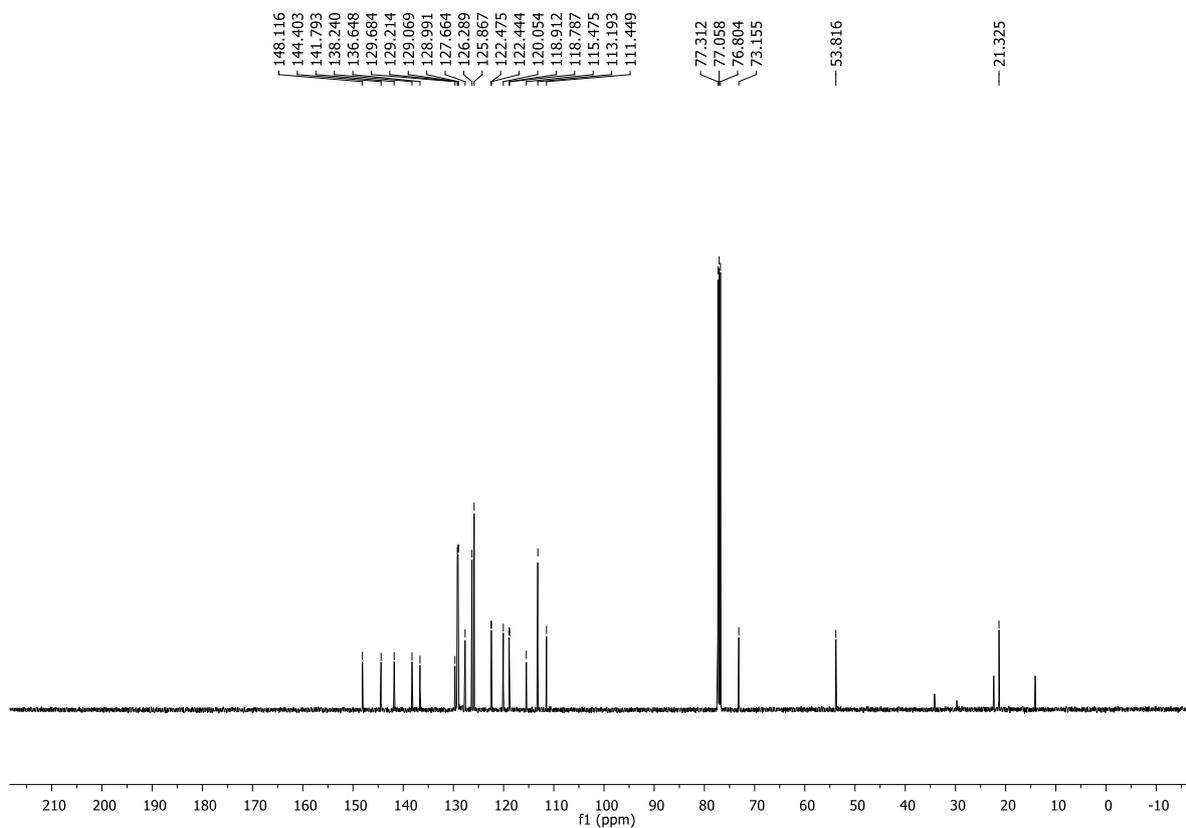


Figure S4. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5b**

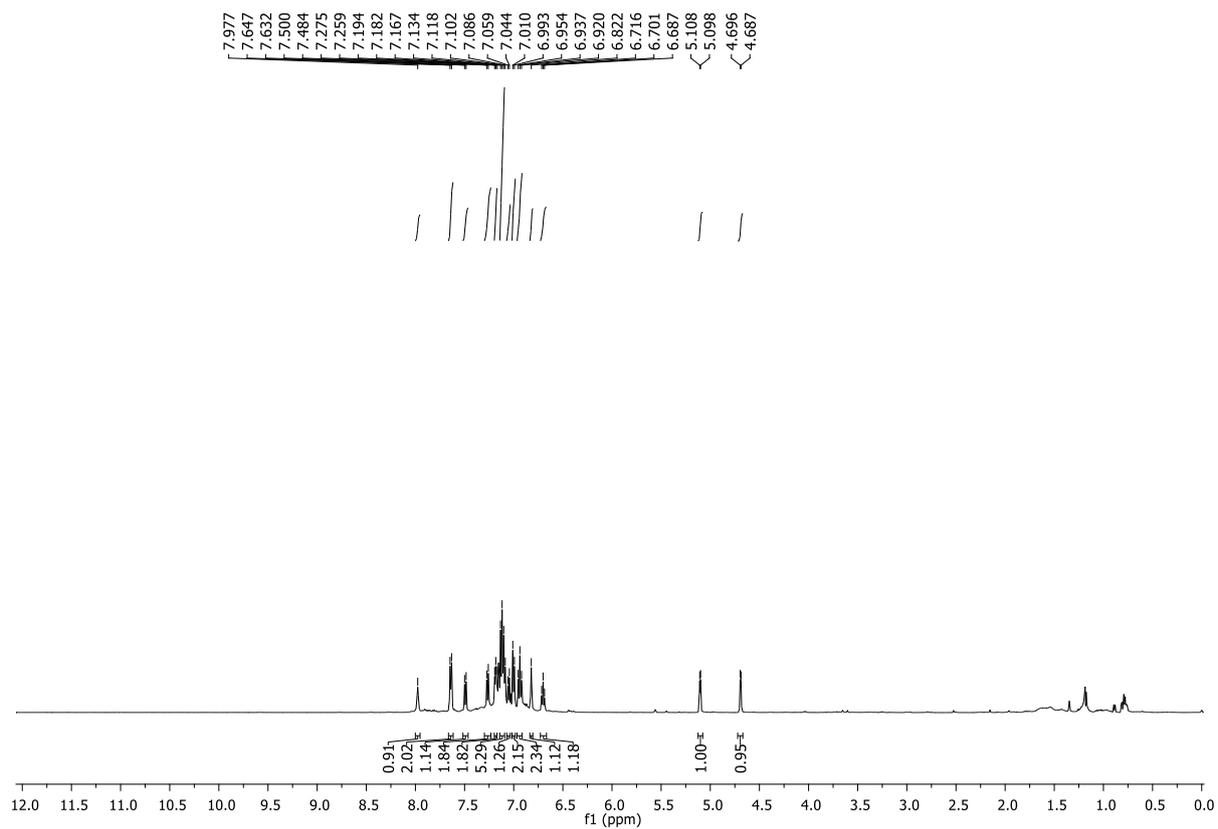


Figure S5. ^1H (500 MHz, CDCl_3) of **5c**

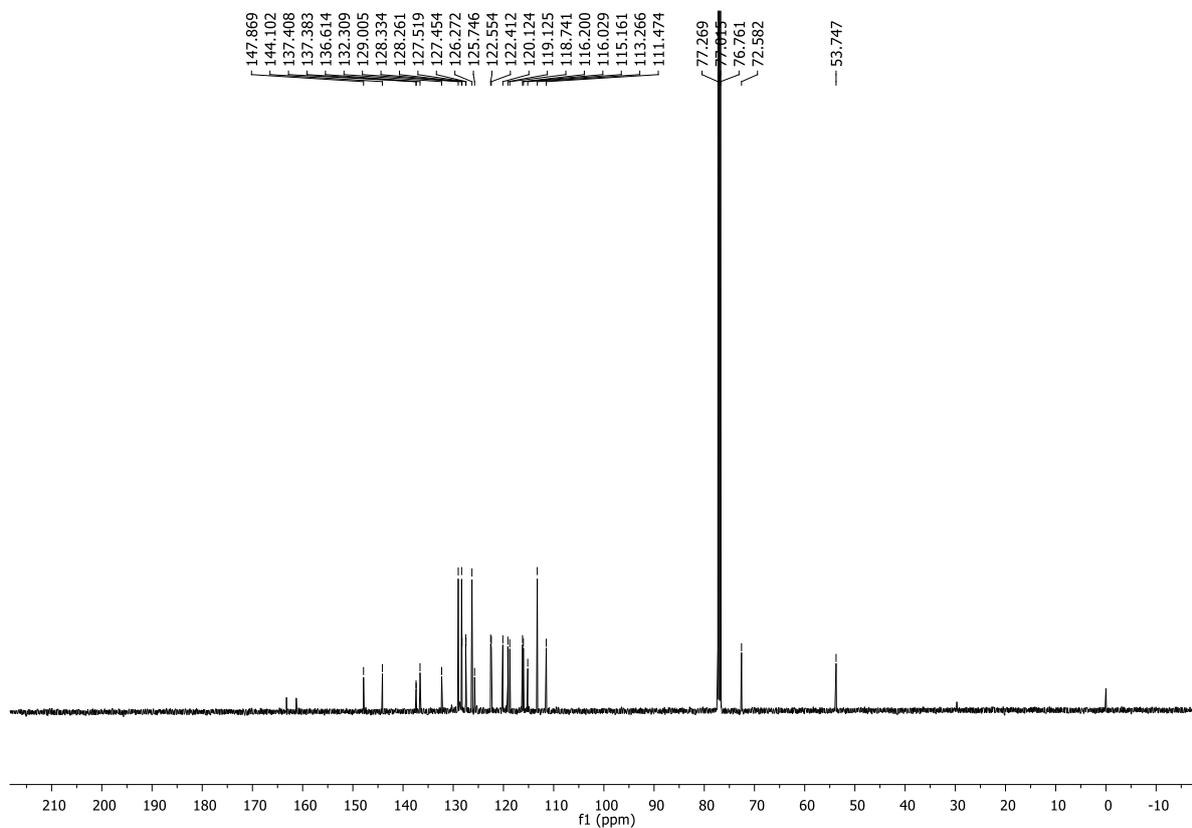


Figure S6. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5c**

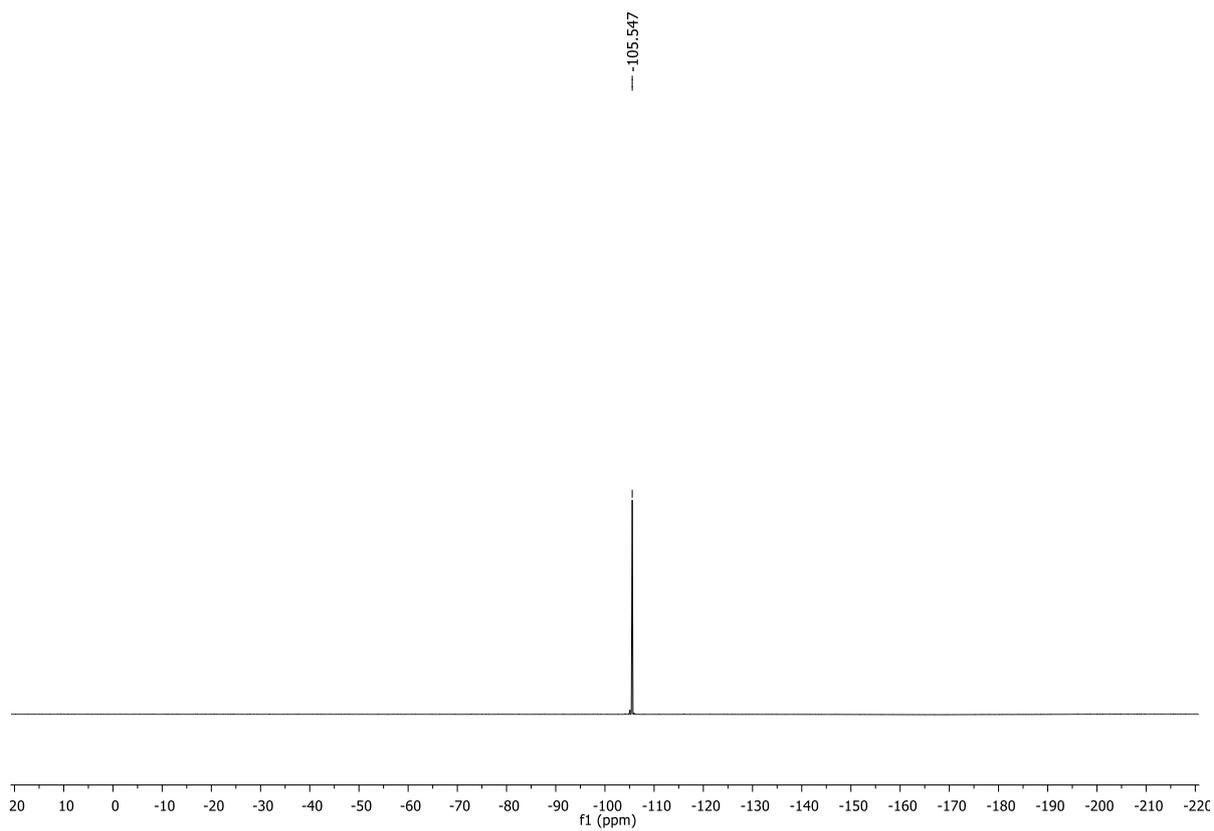


Figure S7. ^{19}F NMR (371 MHz, CDCl_3) of **5c**

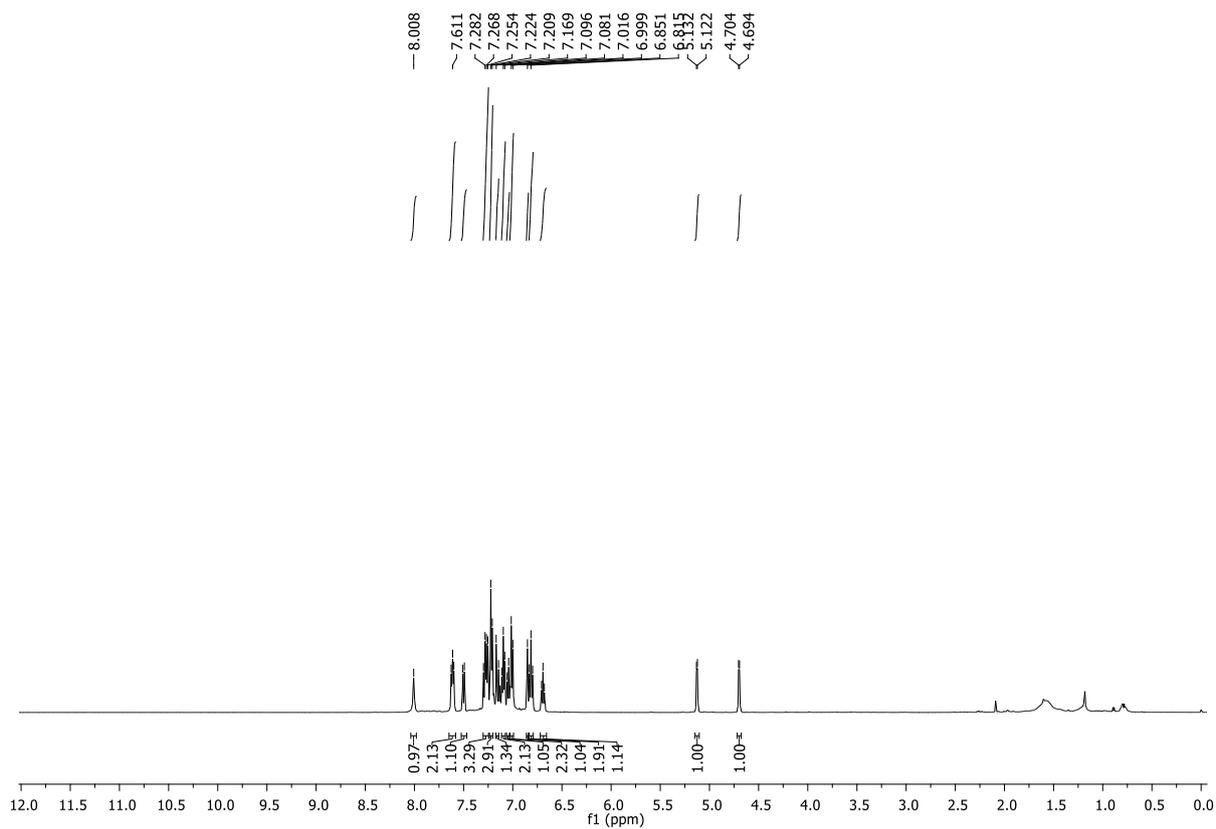


Figure S8. ^1H (500 MHz, CDCl_3) of **5d**

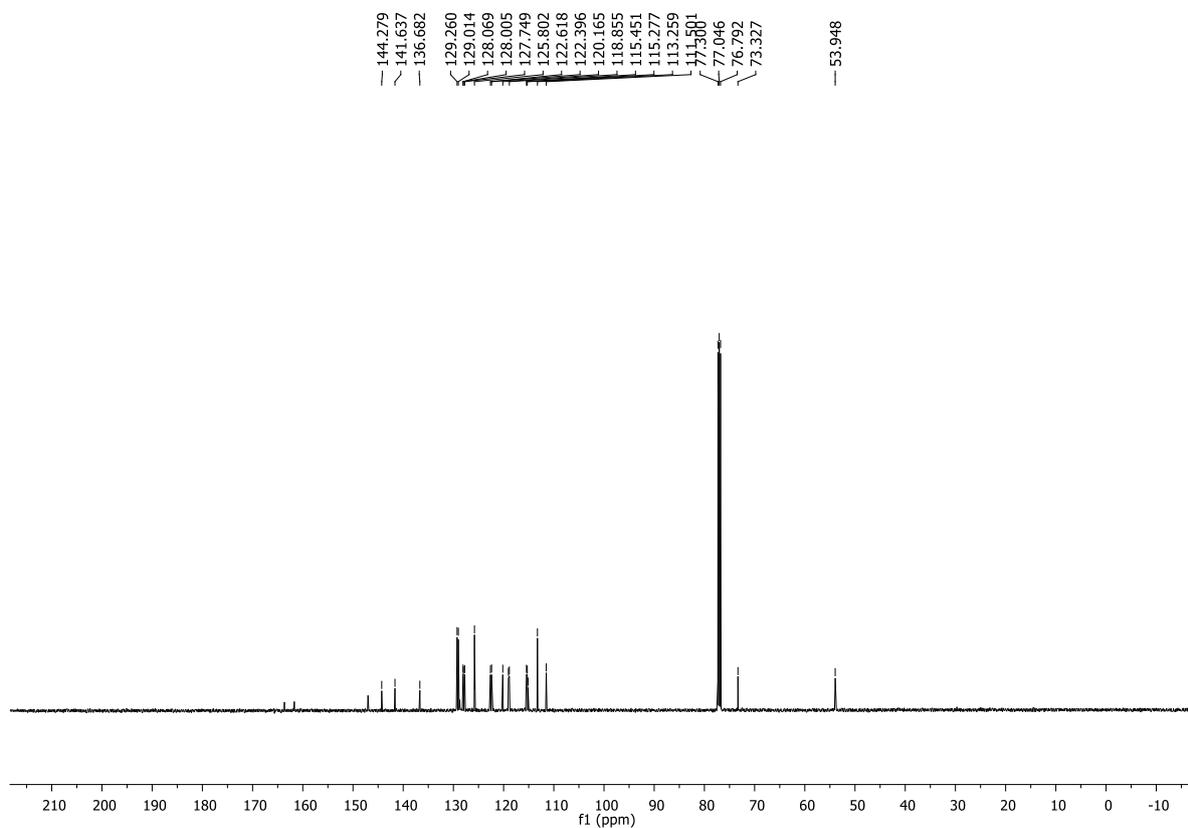


Figure S9. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5d**

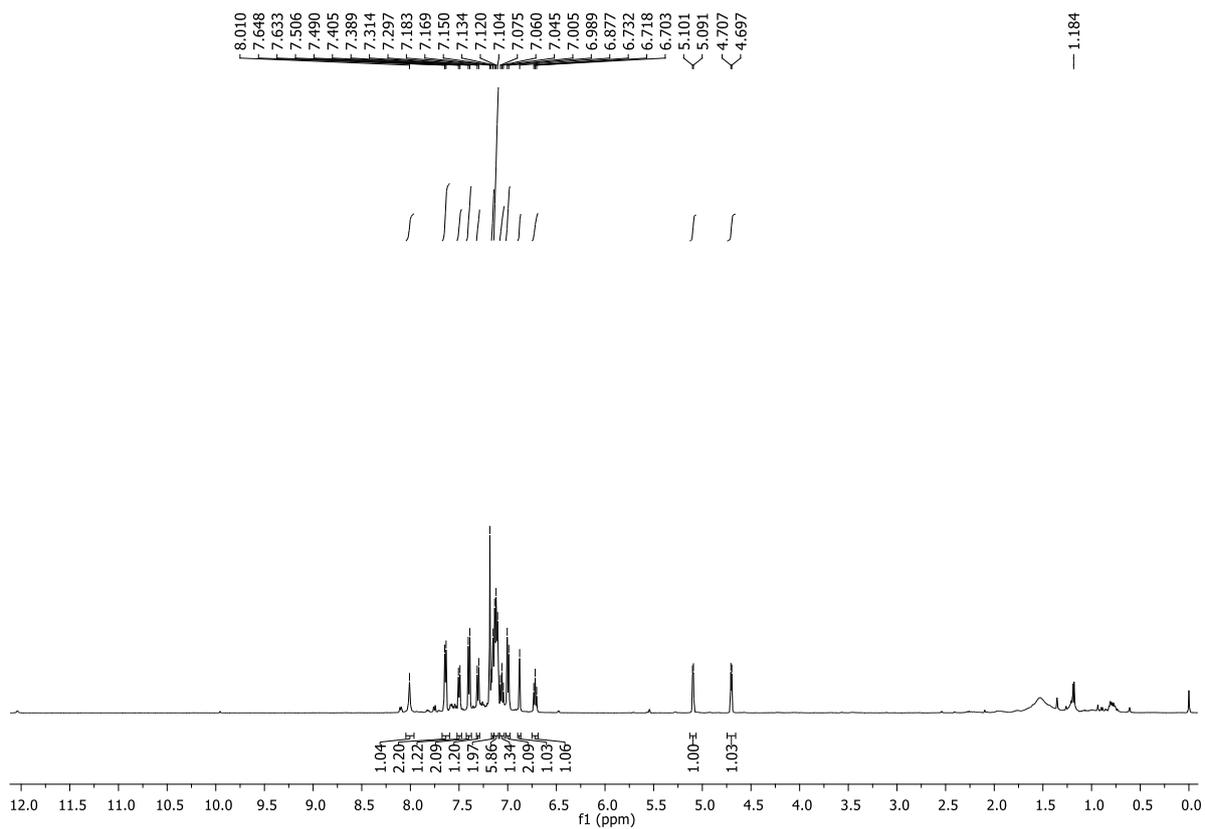


Figure S10. ^1H (500 MHz, CDCl_3) of **5e**

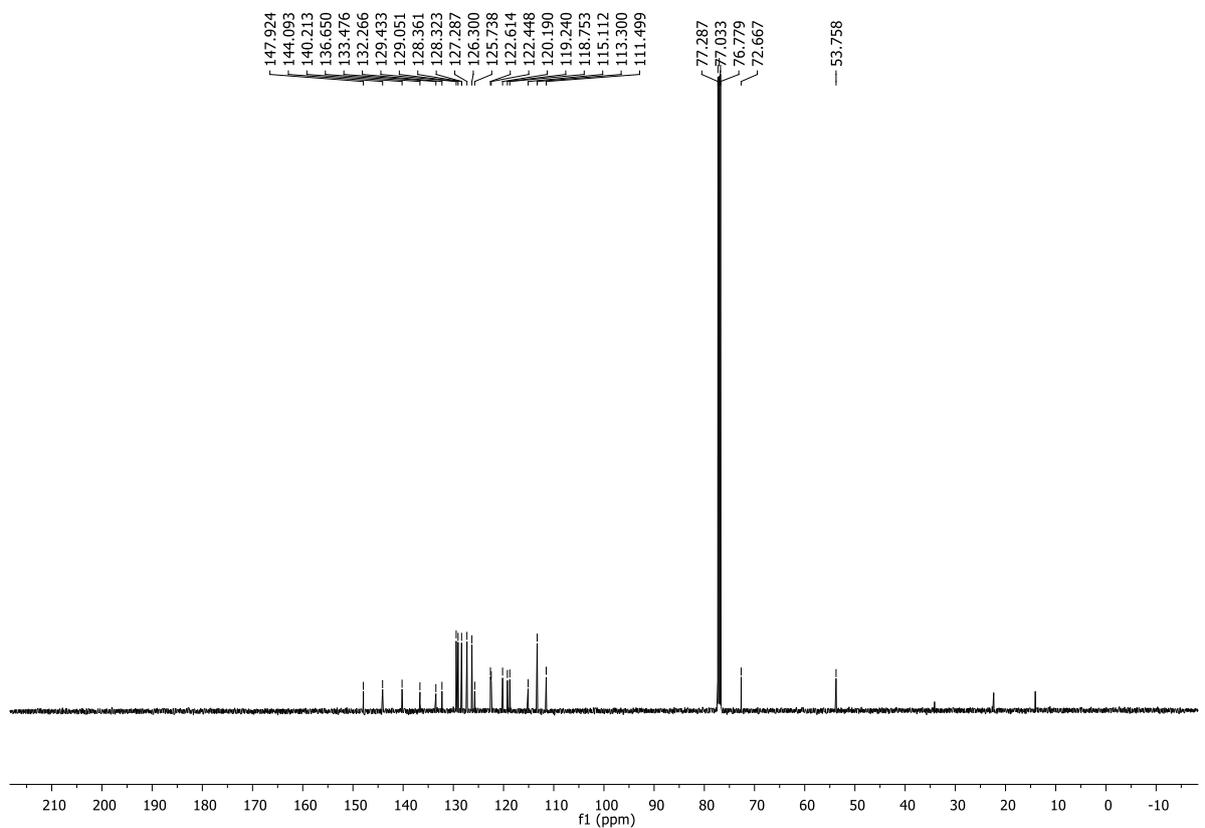


Figure S11. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5e**

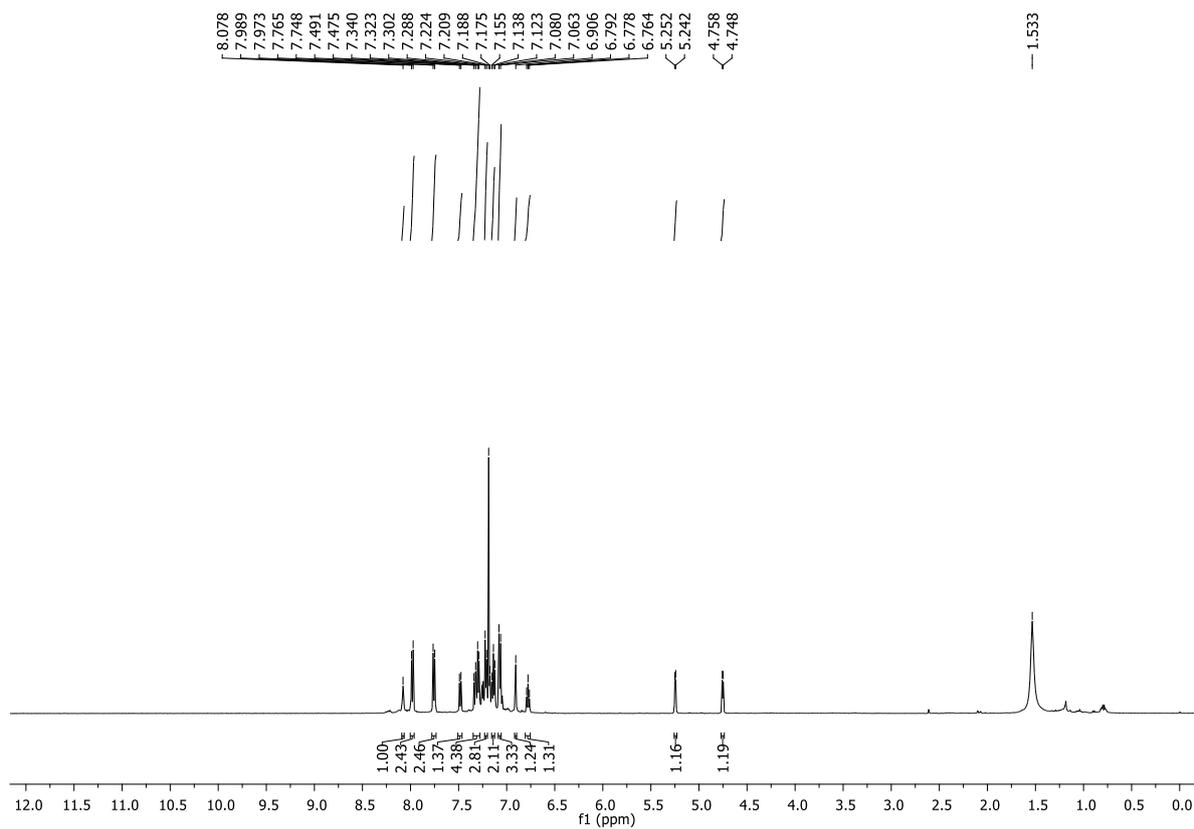


Figure S12. ^1H (500 MHz, CDCl_3) of **5f**

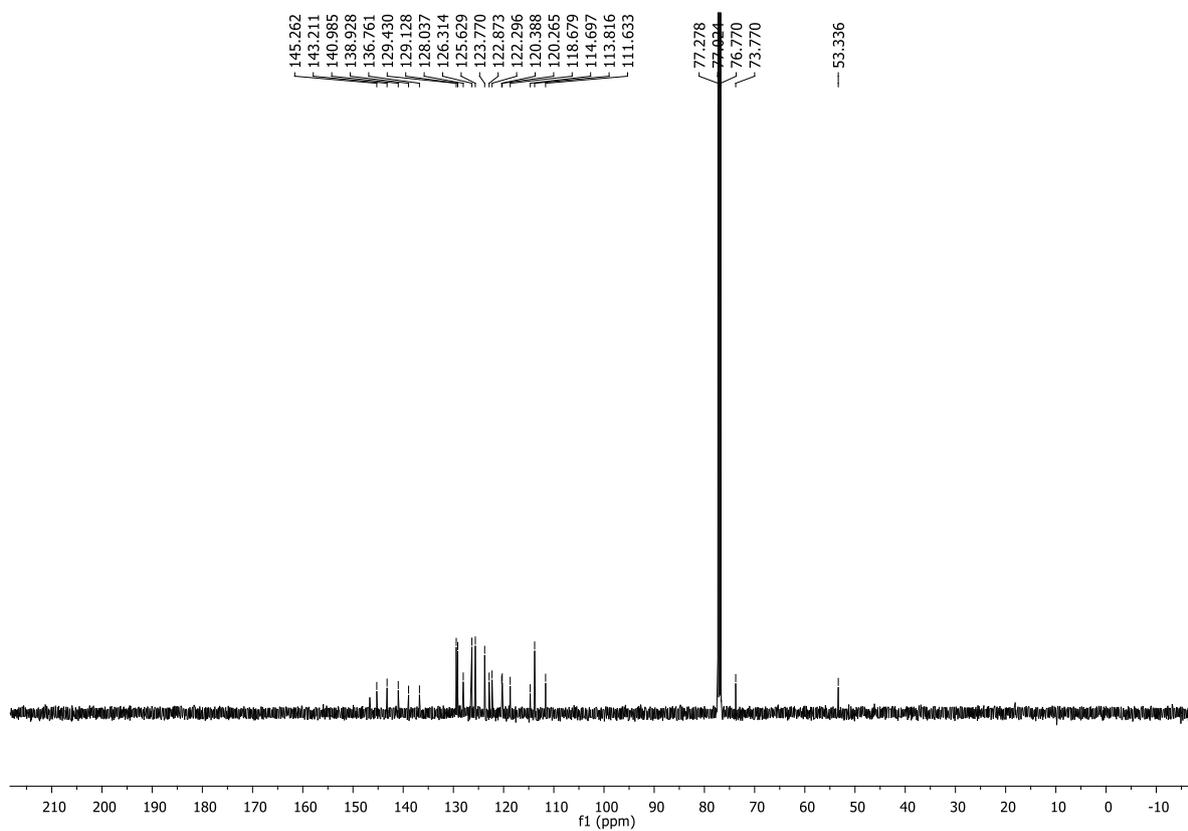


Figure S13. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5f**

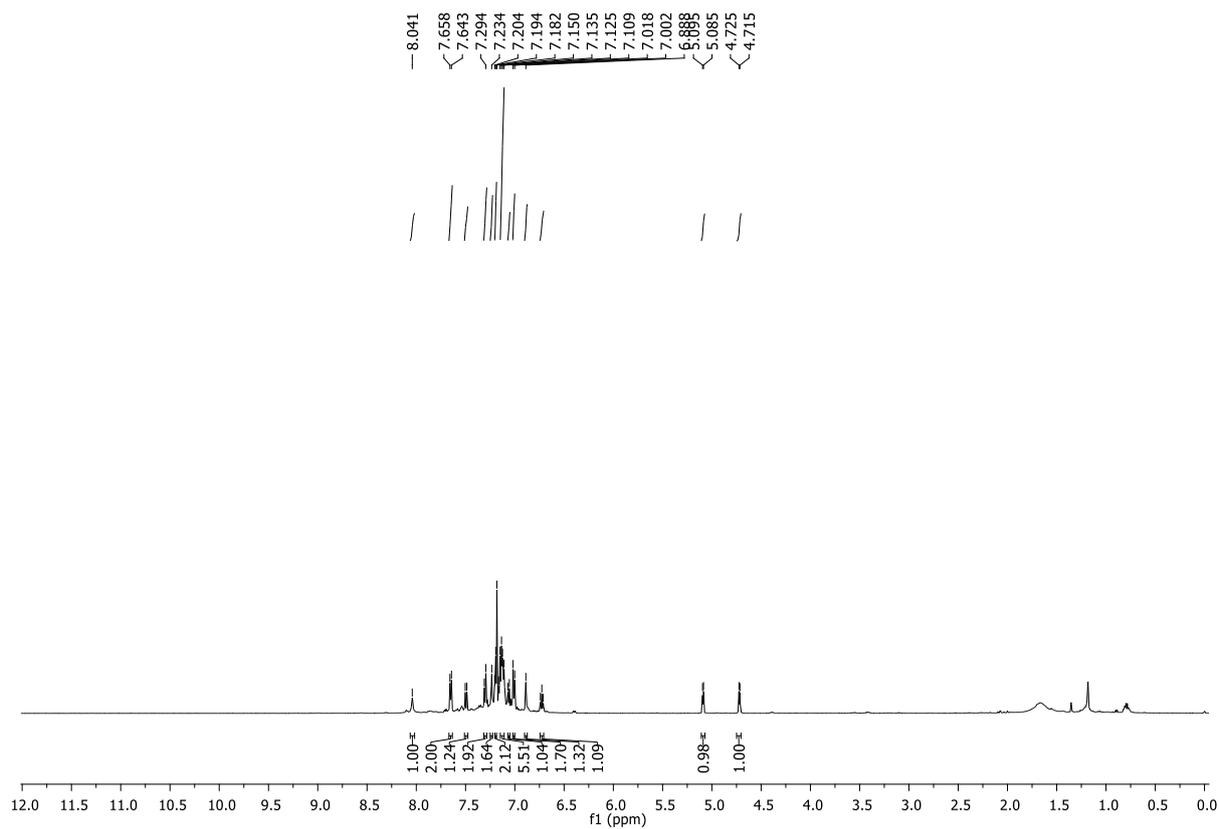


Figure S14. ^1H (500 MHz, CDCl_3) of **5g**

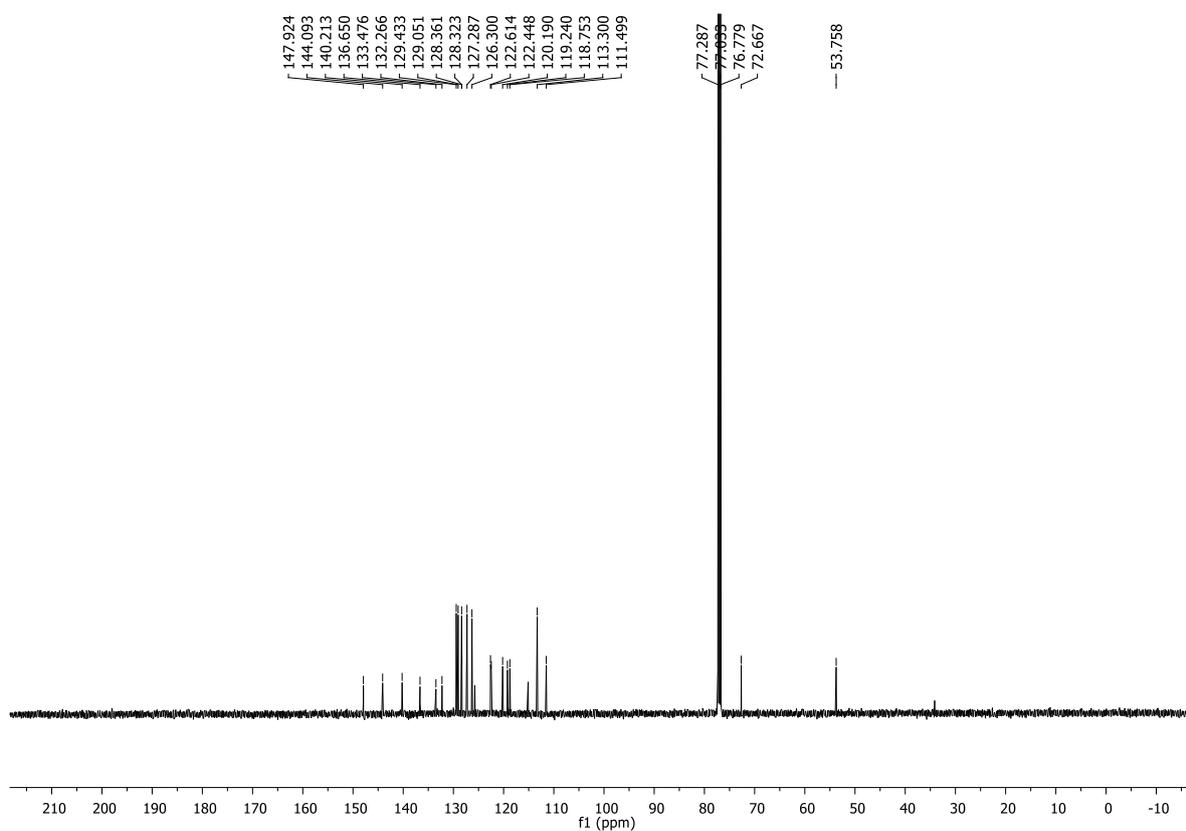


Figure S15. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5g**

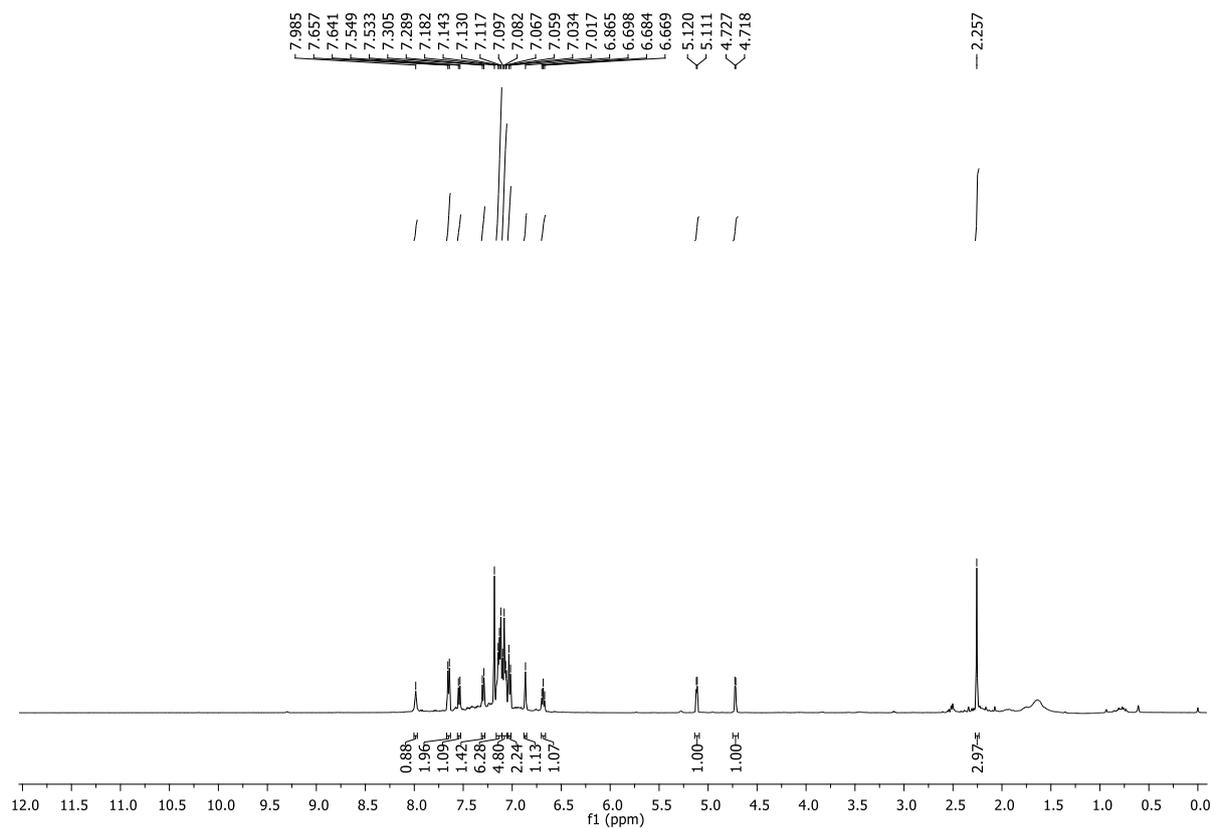


Figure S16. ^1H (500 MHz, CDCl_3) of **5h**

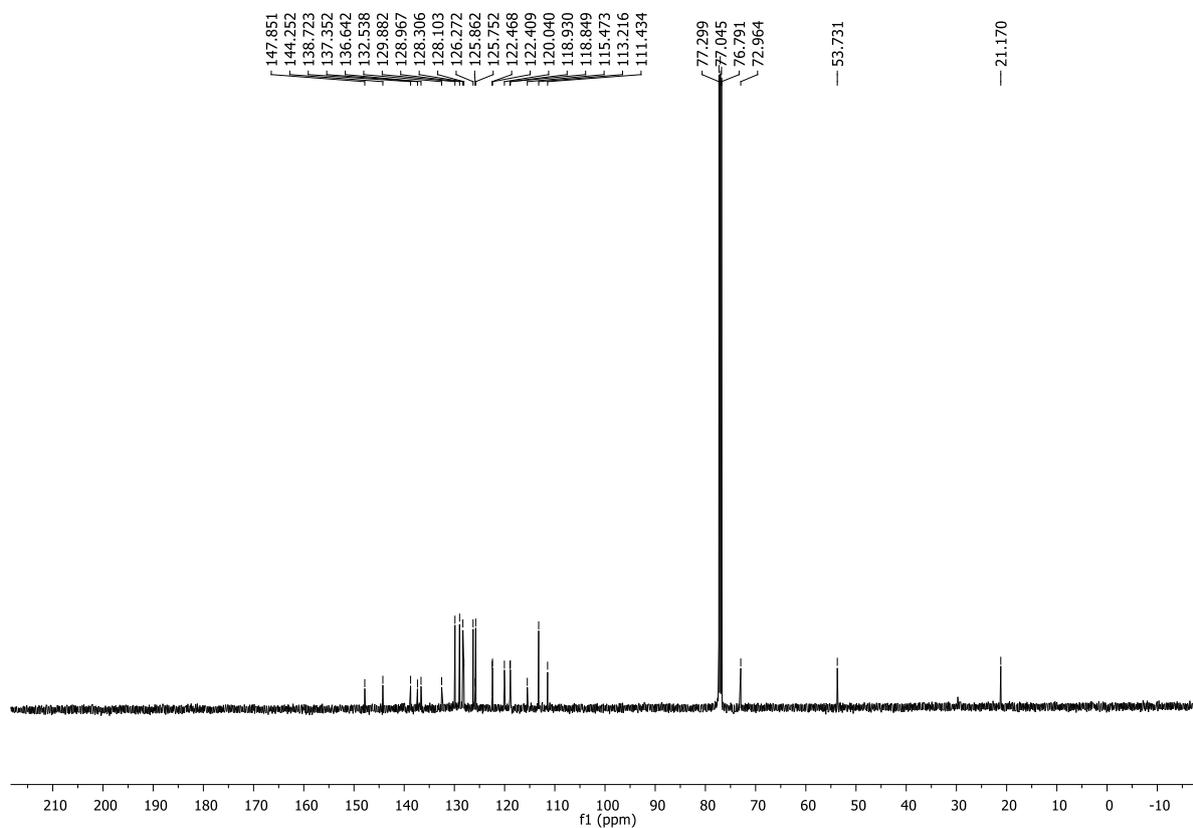


Figure S17. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5h**

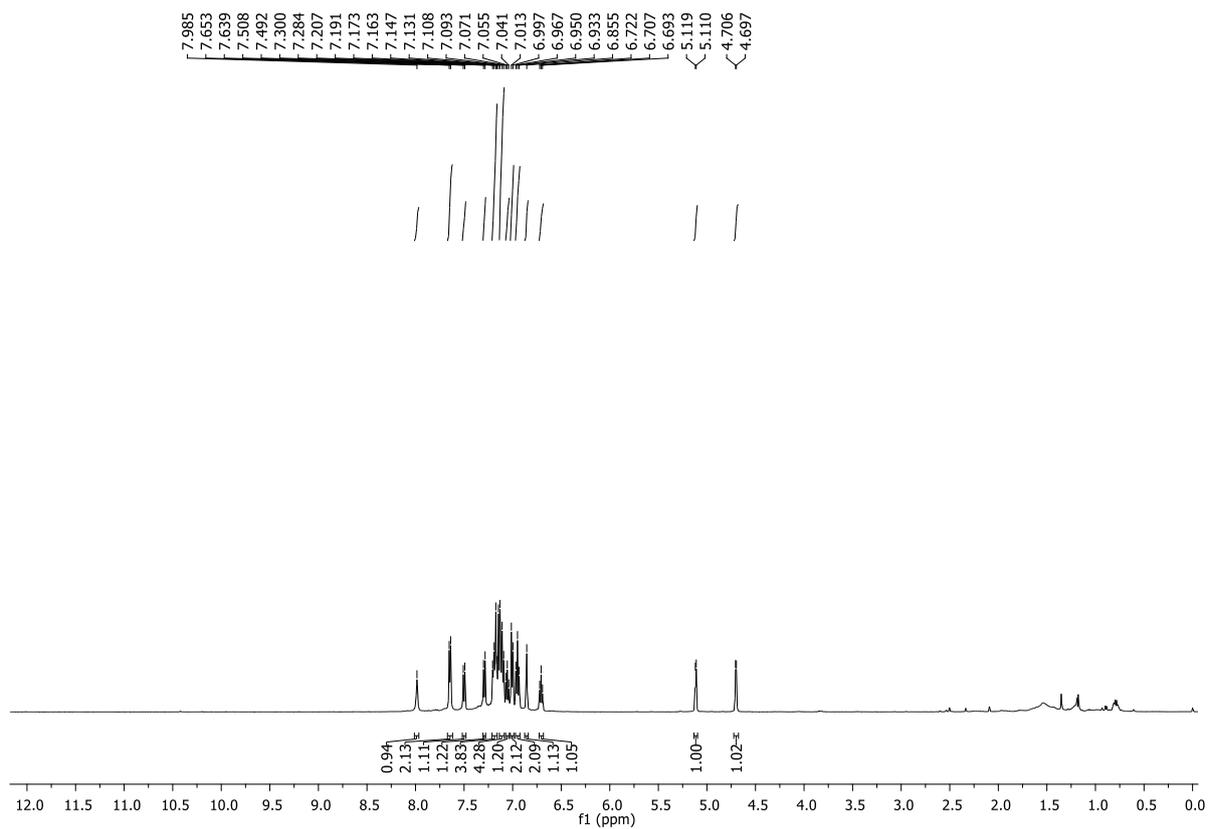


Figure S18. ^1H (500 MHz, CDCl_3) of **5i**

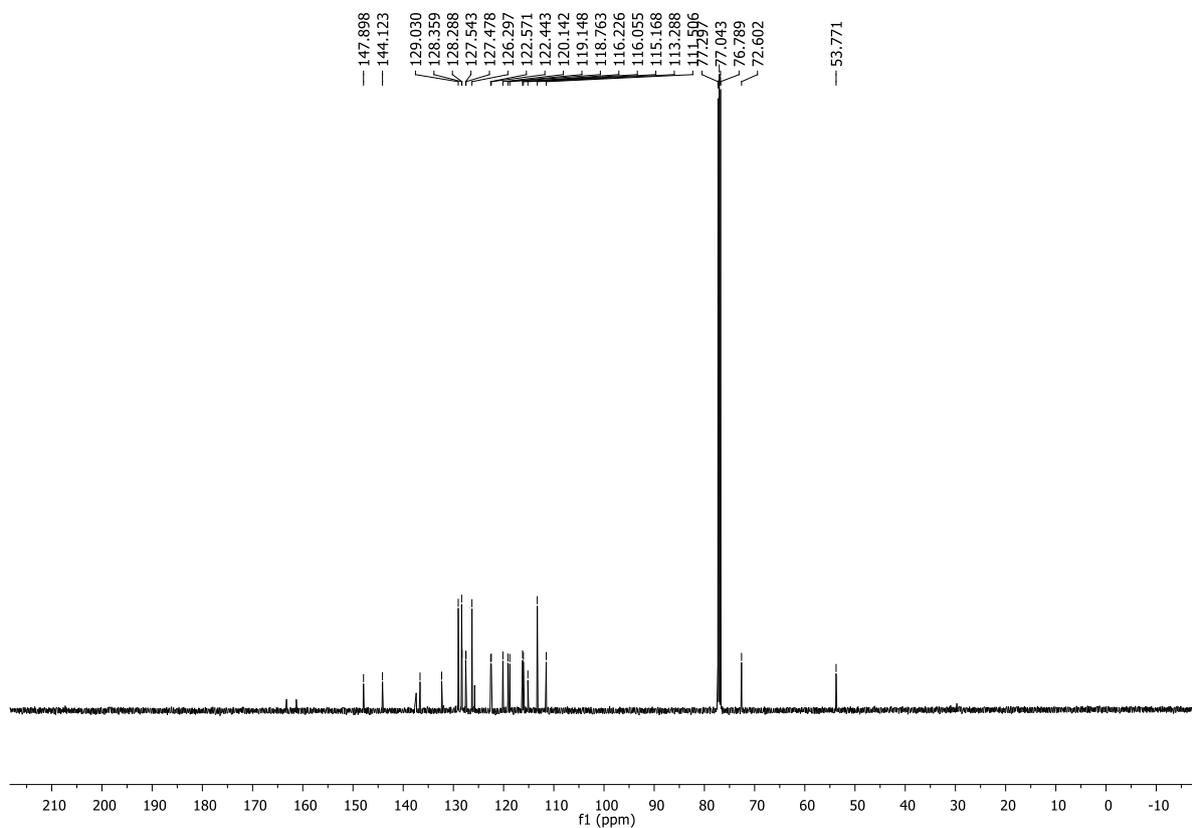


Figure S19. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5i**

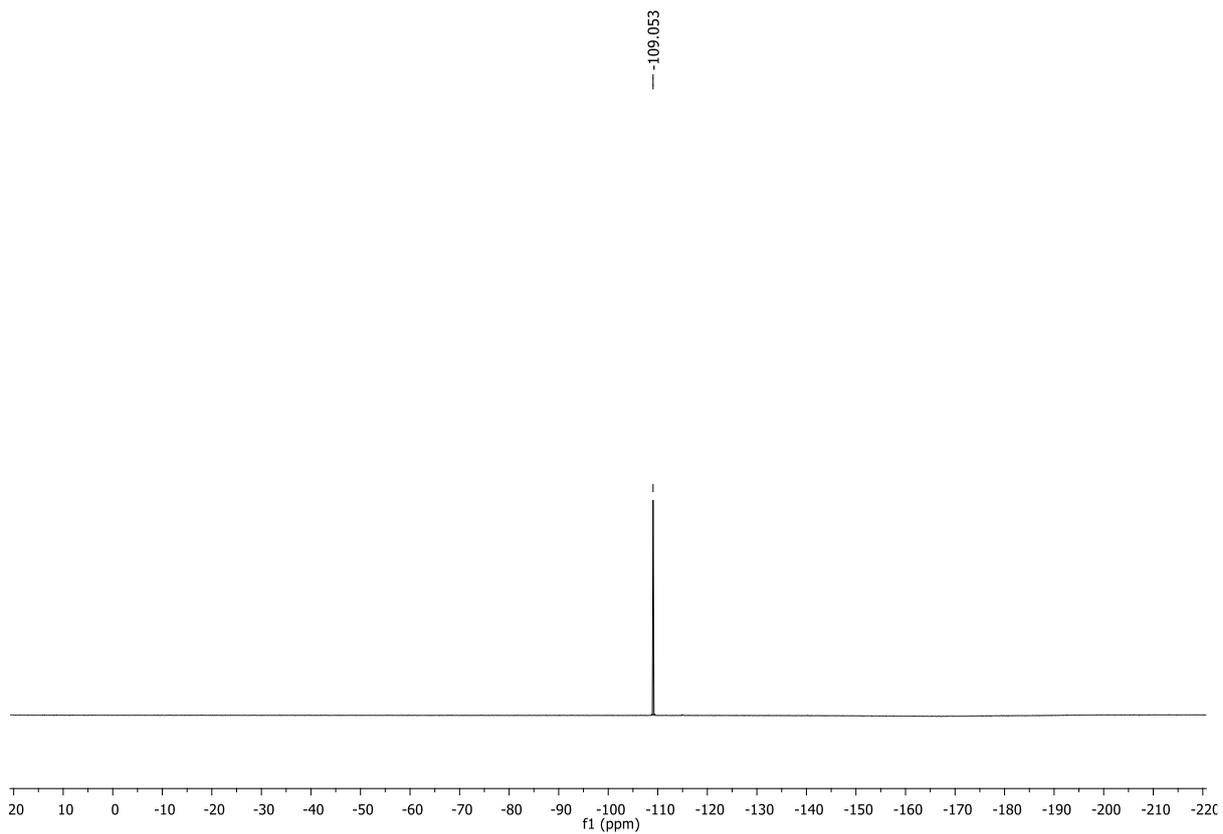


Figure S19. ^{19}F NMR (371 MHz, CDCl_3) of **5i**

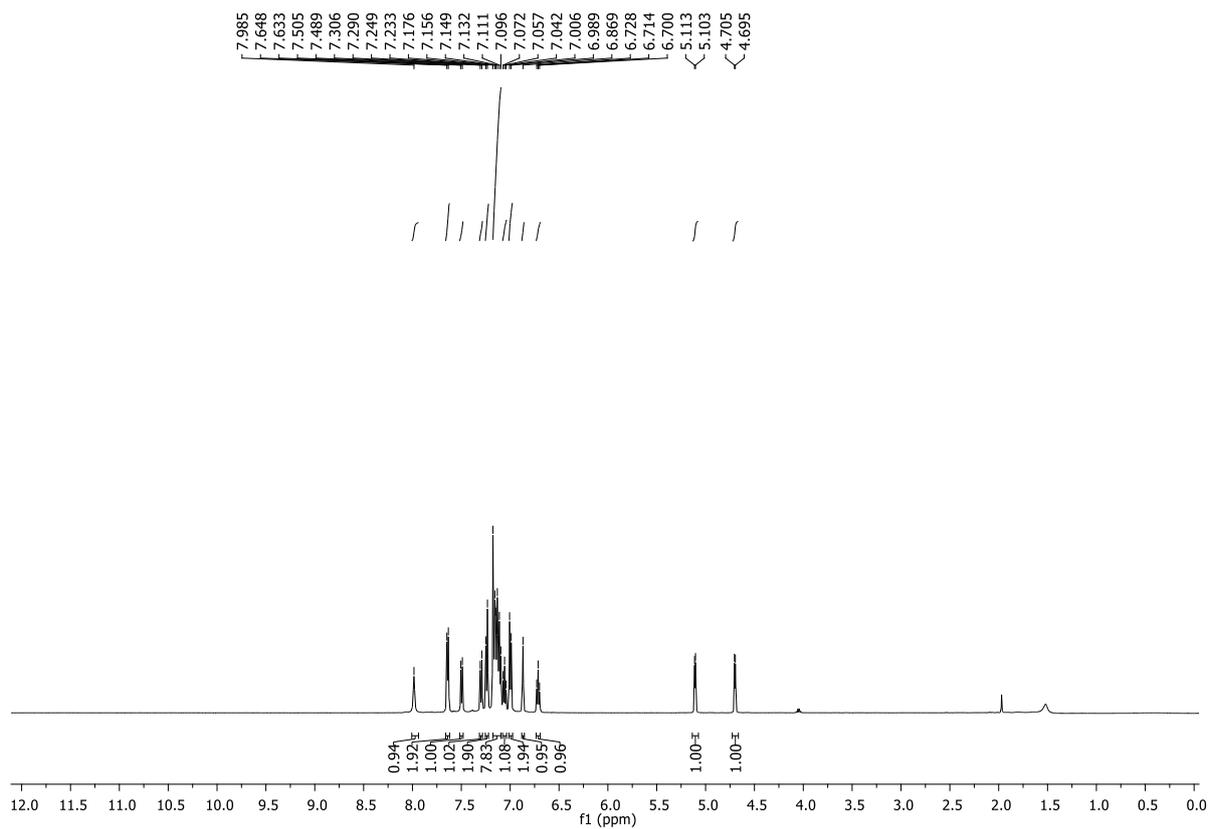


Figure S20. ^1H (500 MHz, CDCl_3) of **5j**

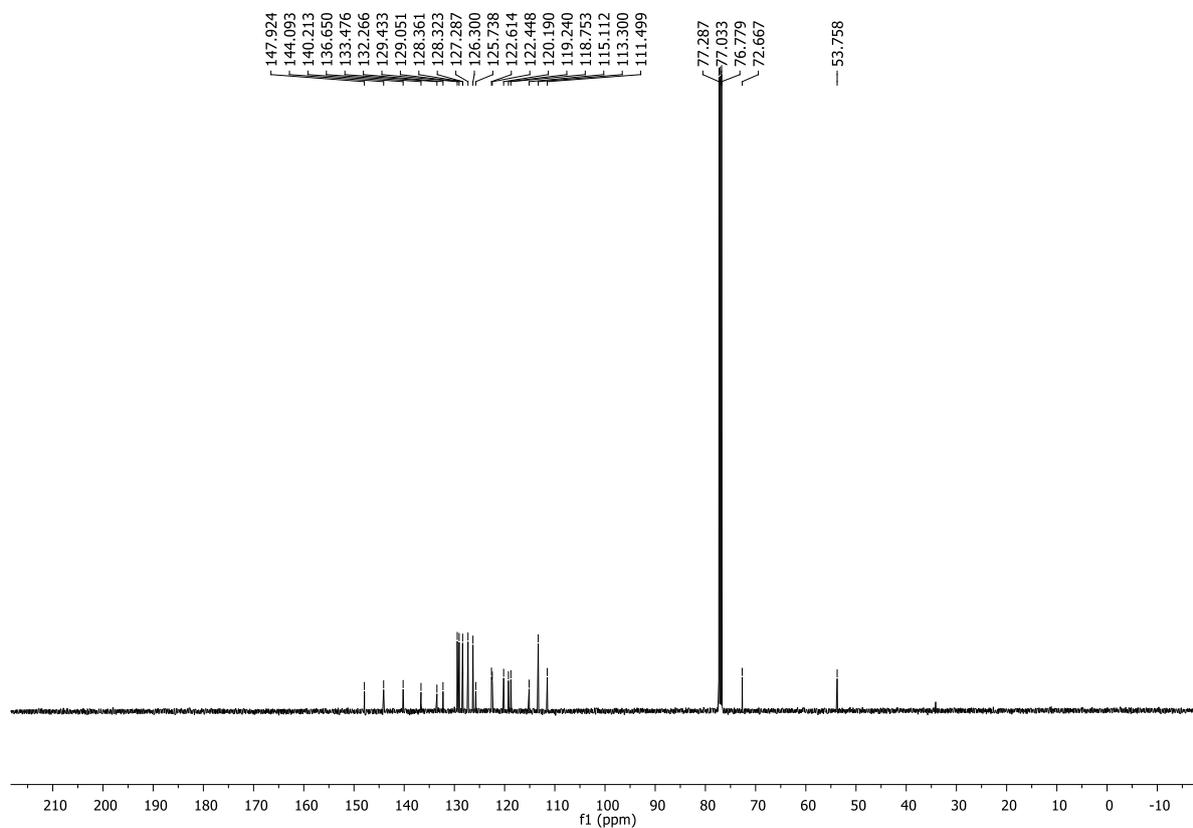


Figure S21. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5j**

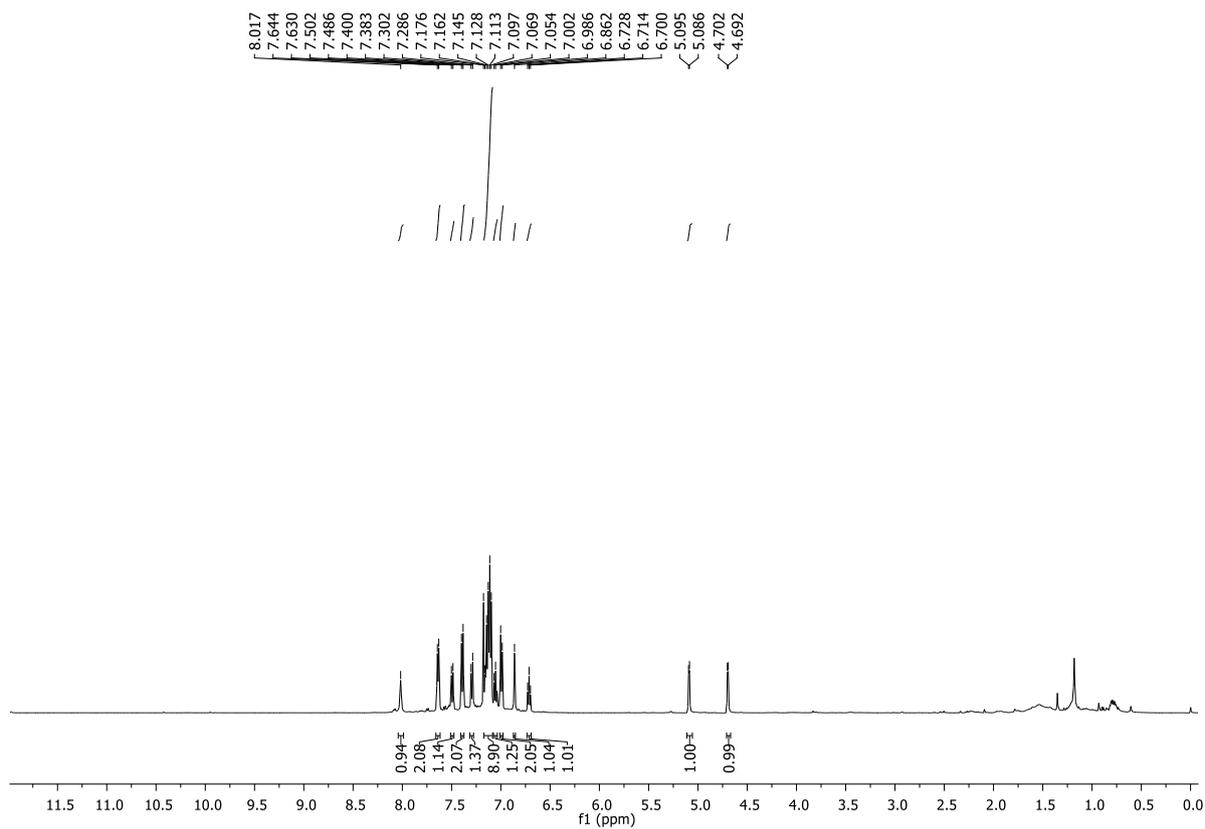


Figure S22. ^1H (500 MHz, CDCl_3) of **5k**

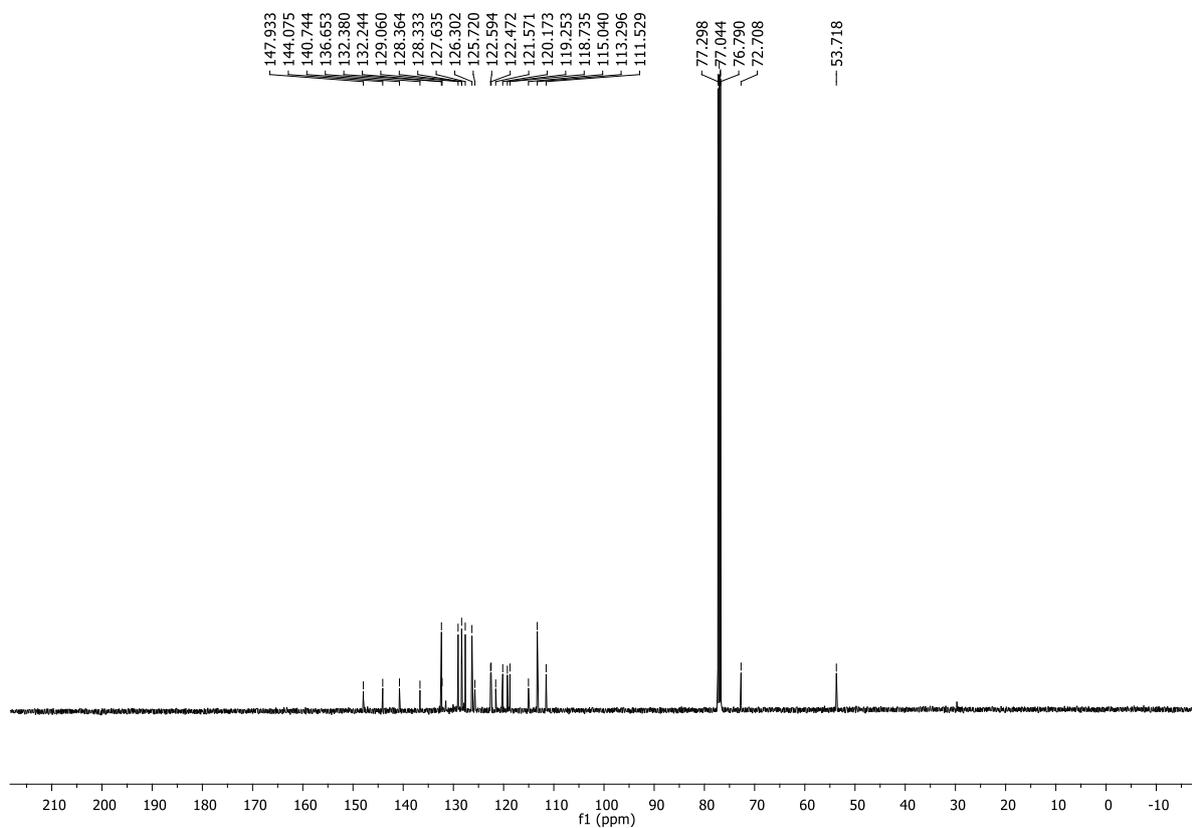


Figure S23. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5k**

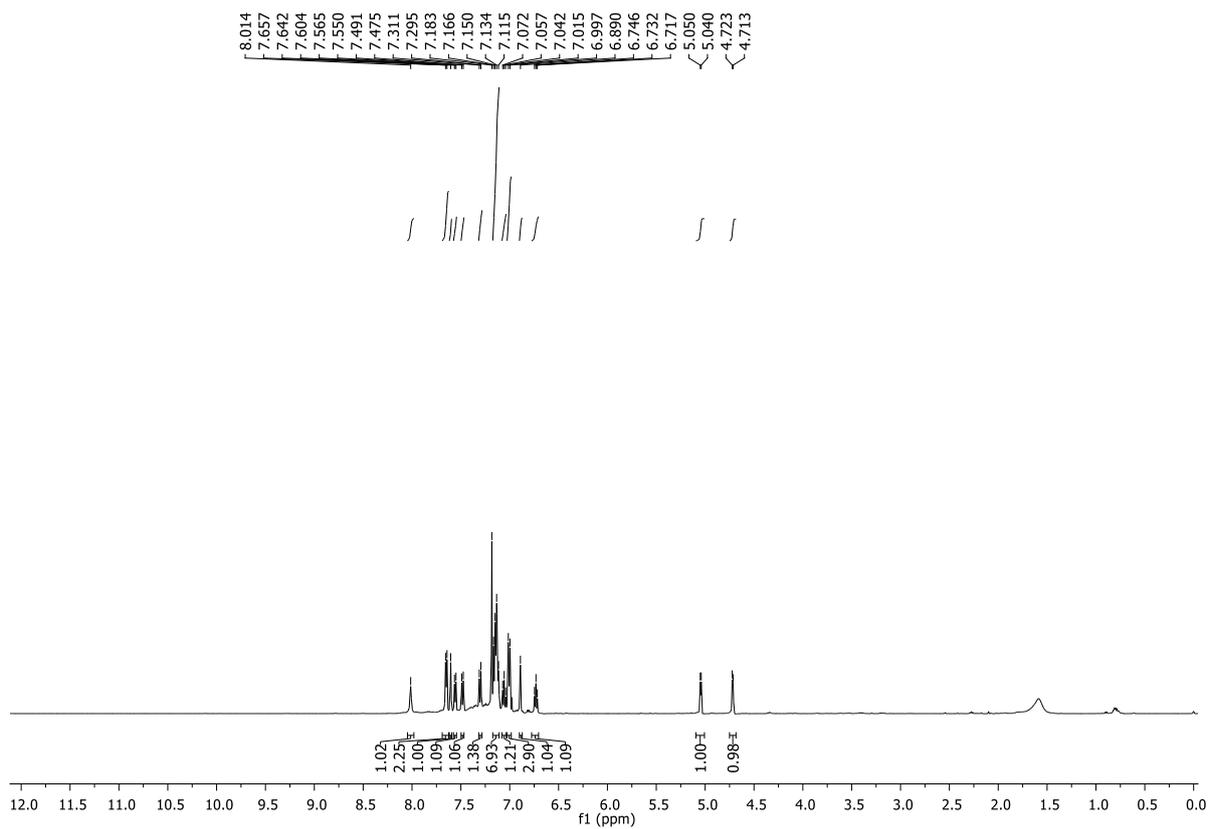


Figure S24. ^1H (500 MHz, CDCl_3) of **51**

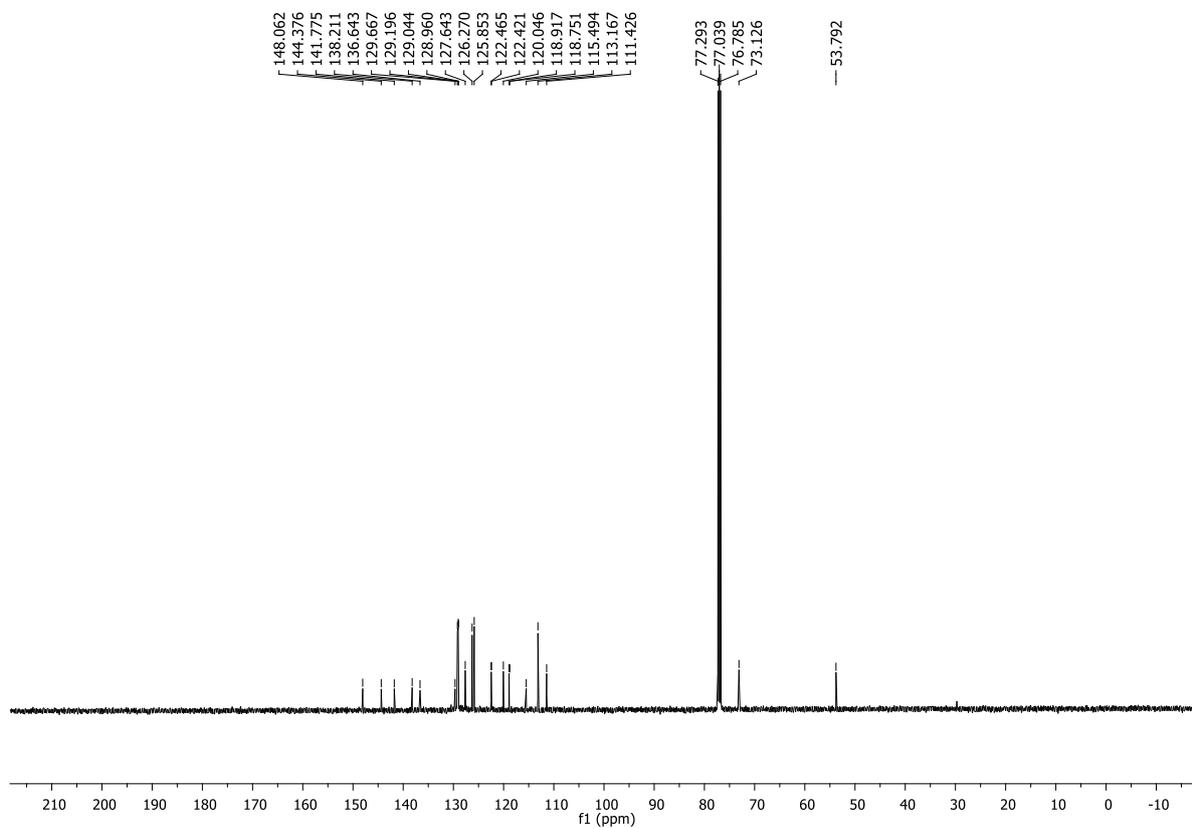


Figure S25. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **51**

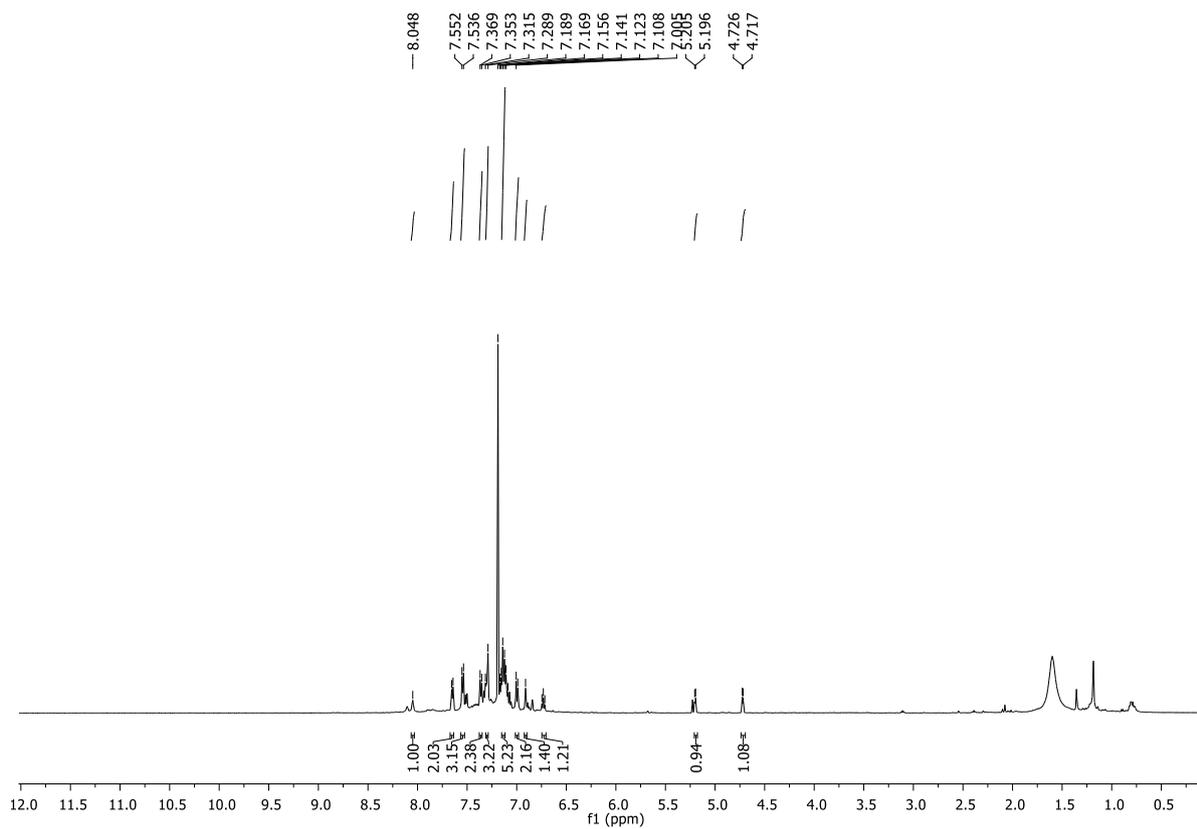


Figure S26. ^1H (500 MHz, CDCl_3) of **5m**

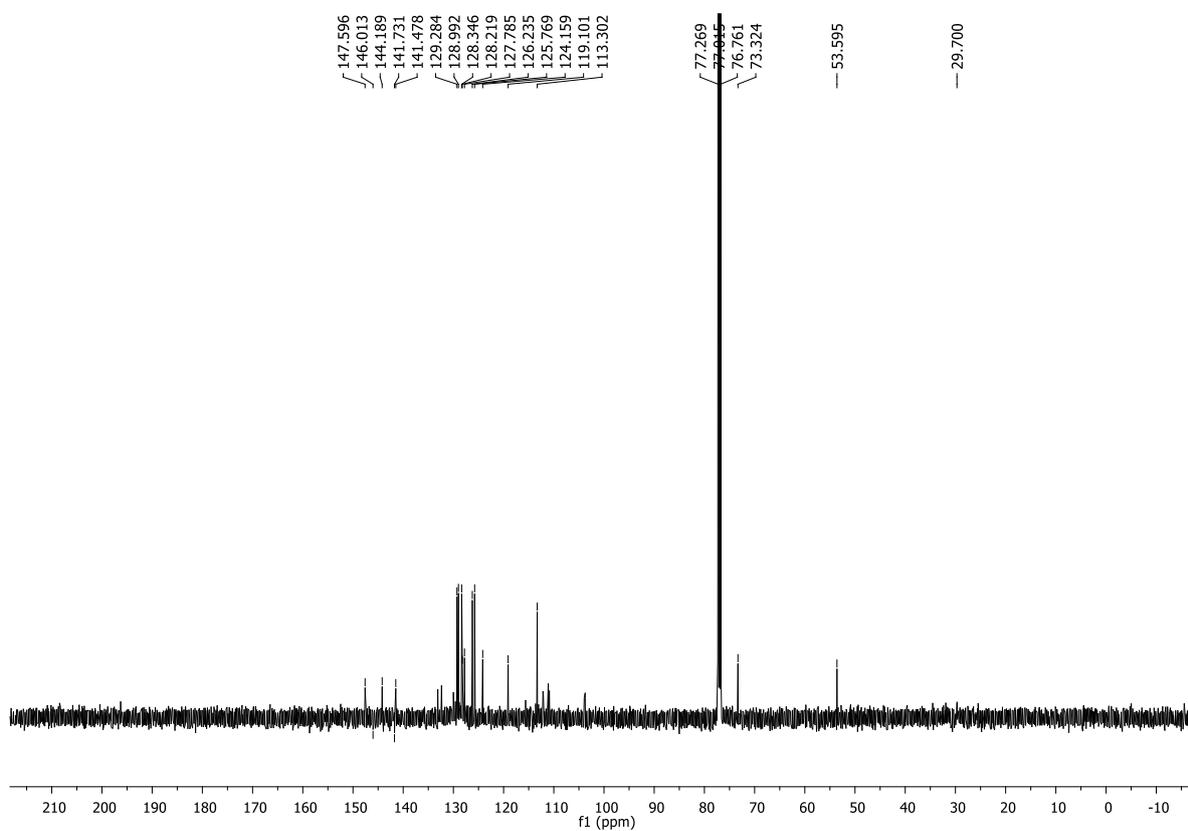


Figure S27. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5m**

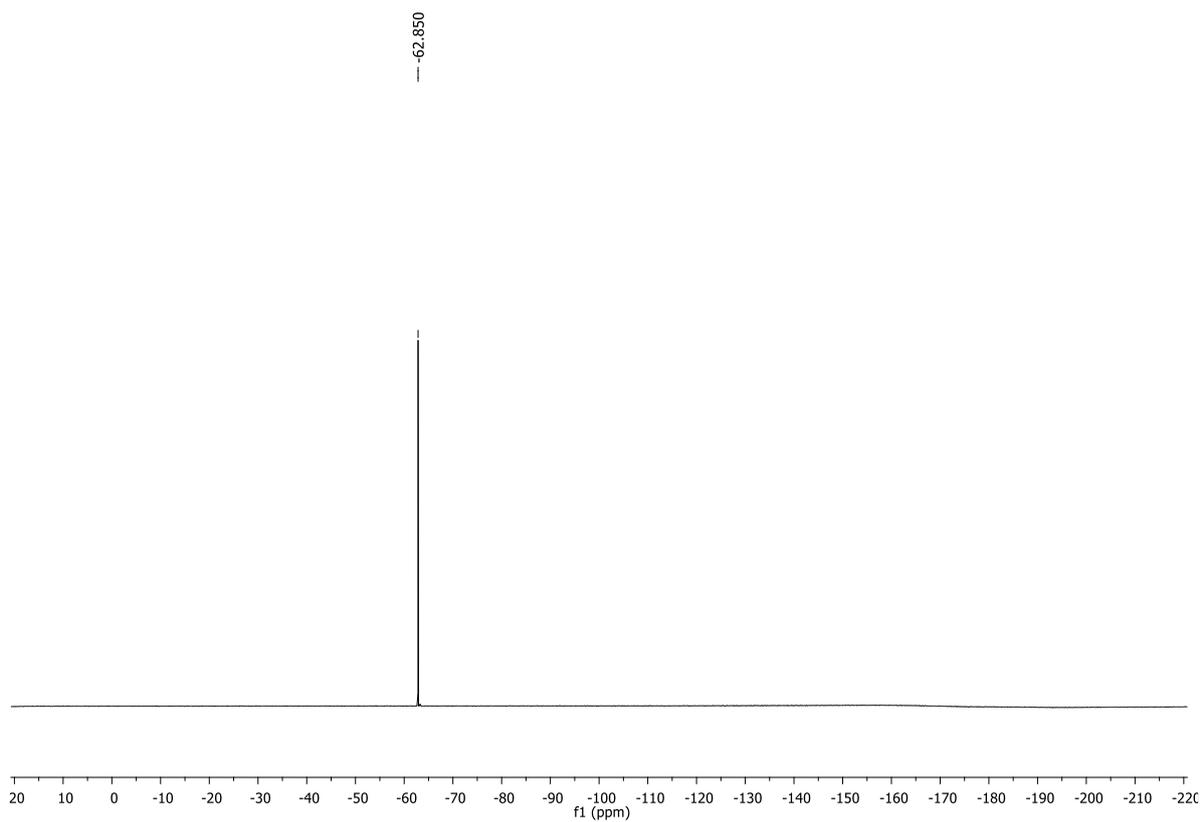


Figure S28. ^{19}F NMR (371 MHz, CDCl_3) of **5m**

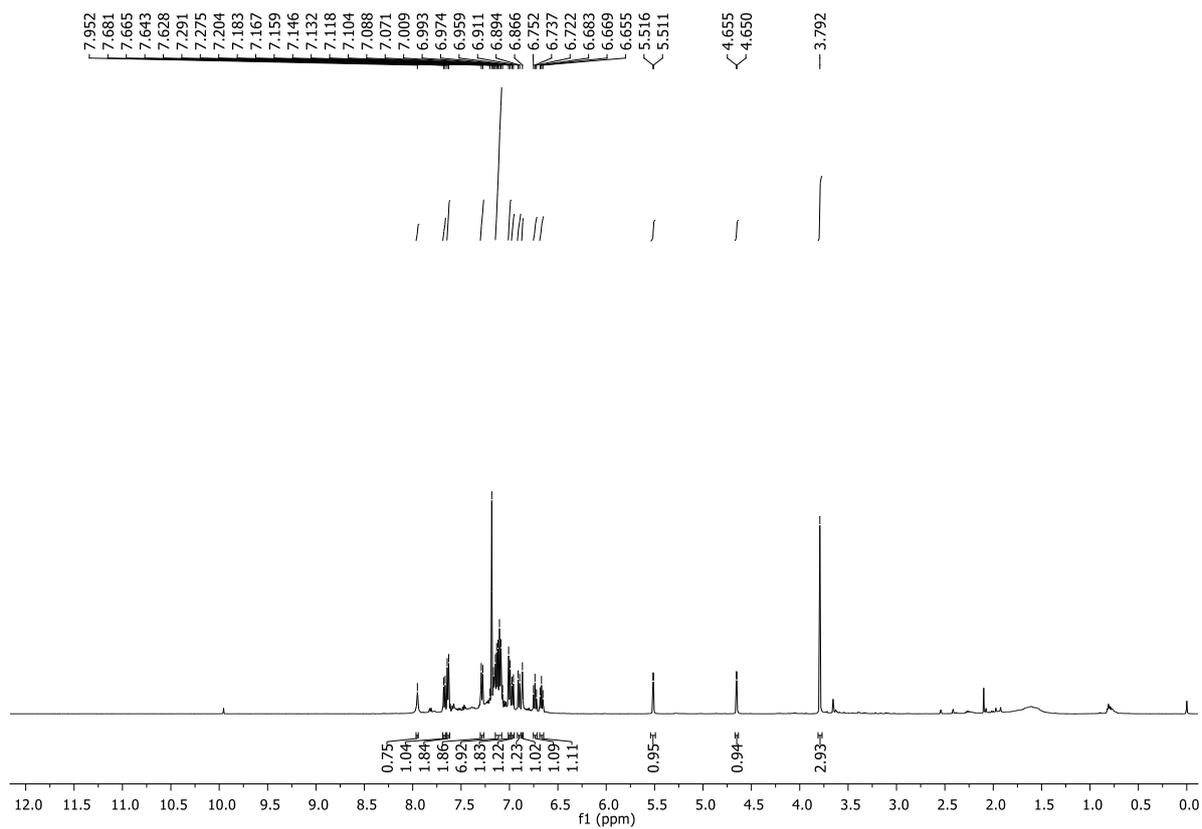


Figure S29. ^1H (500 MHz, CDCl_3) of **5n**

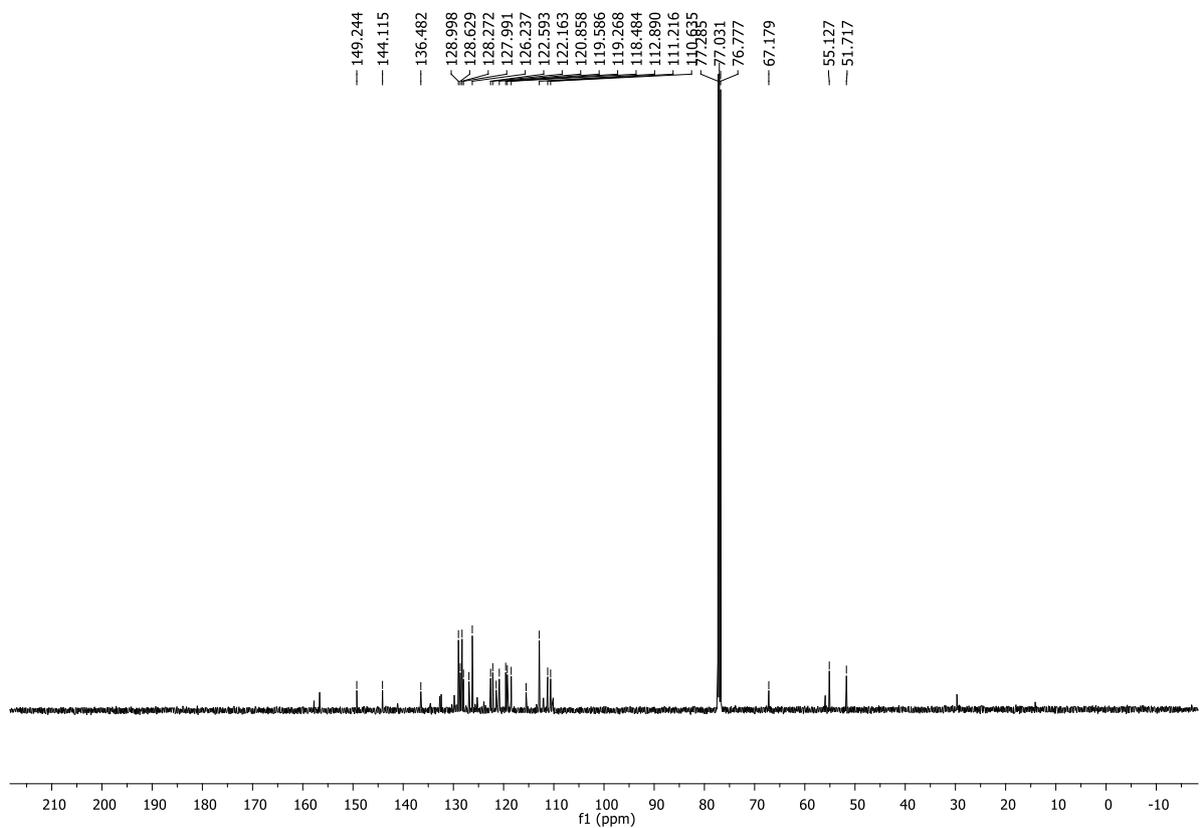


Figure S30. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5n**

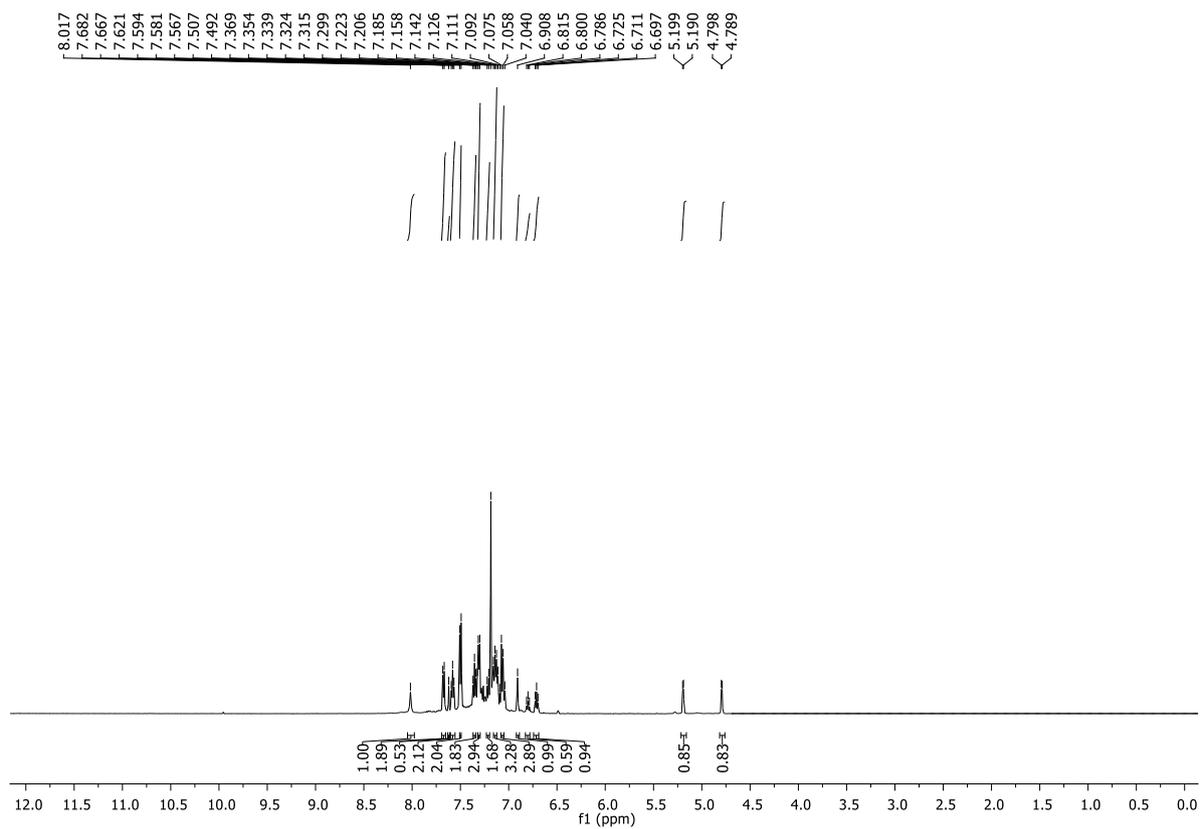


Figure S31. ^1H (500 MHz, CDCl_3) of **50**

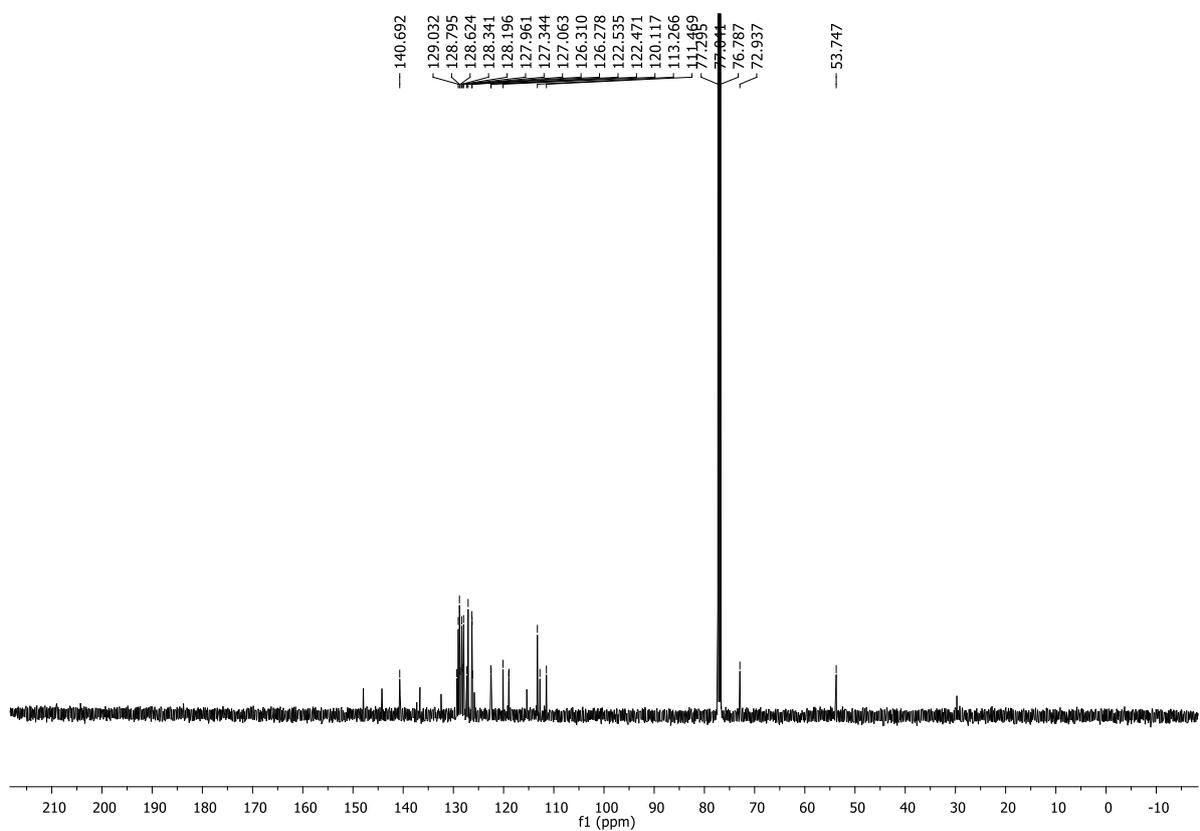


Figure S32. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **50**

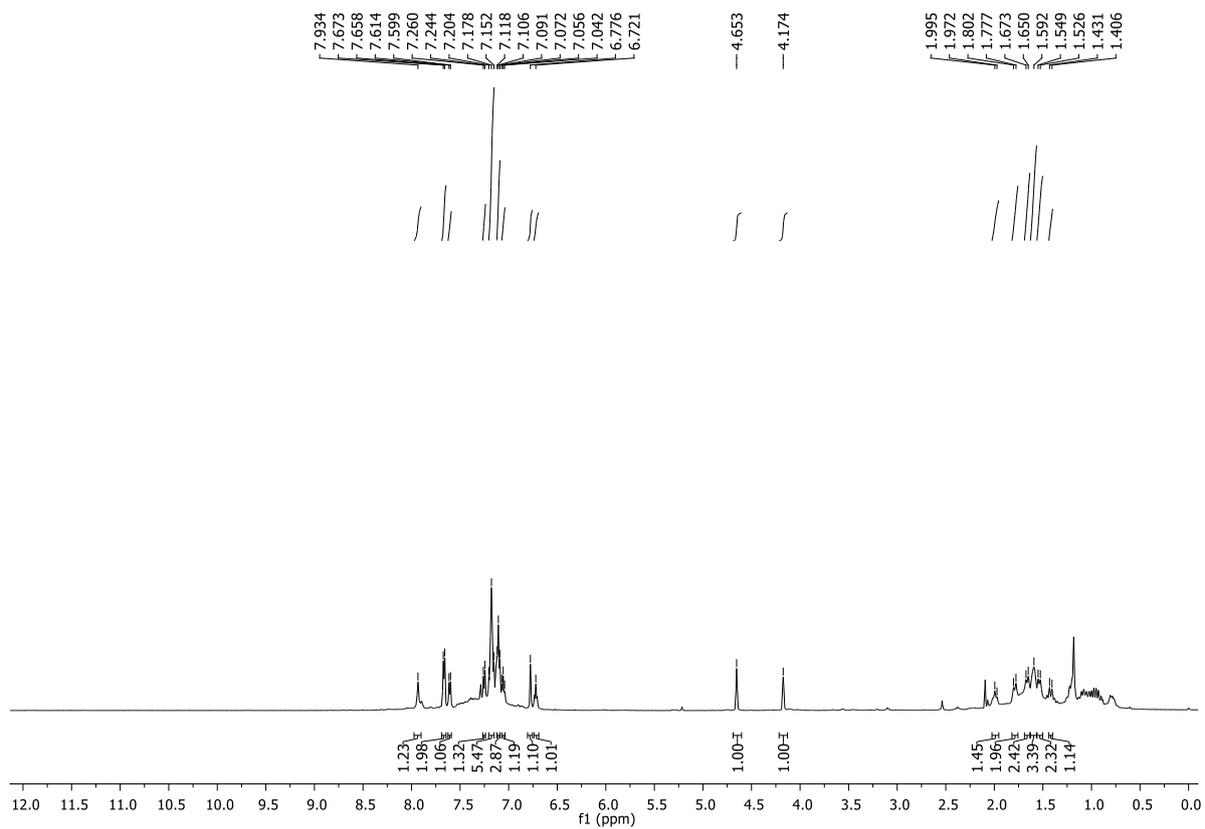


Figure S33. ^1H (500 MHz, CDCl_3) of **5p**

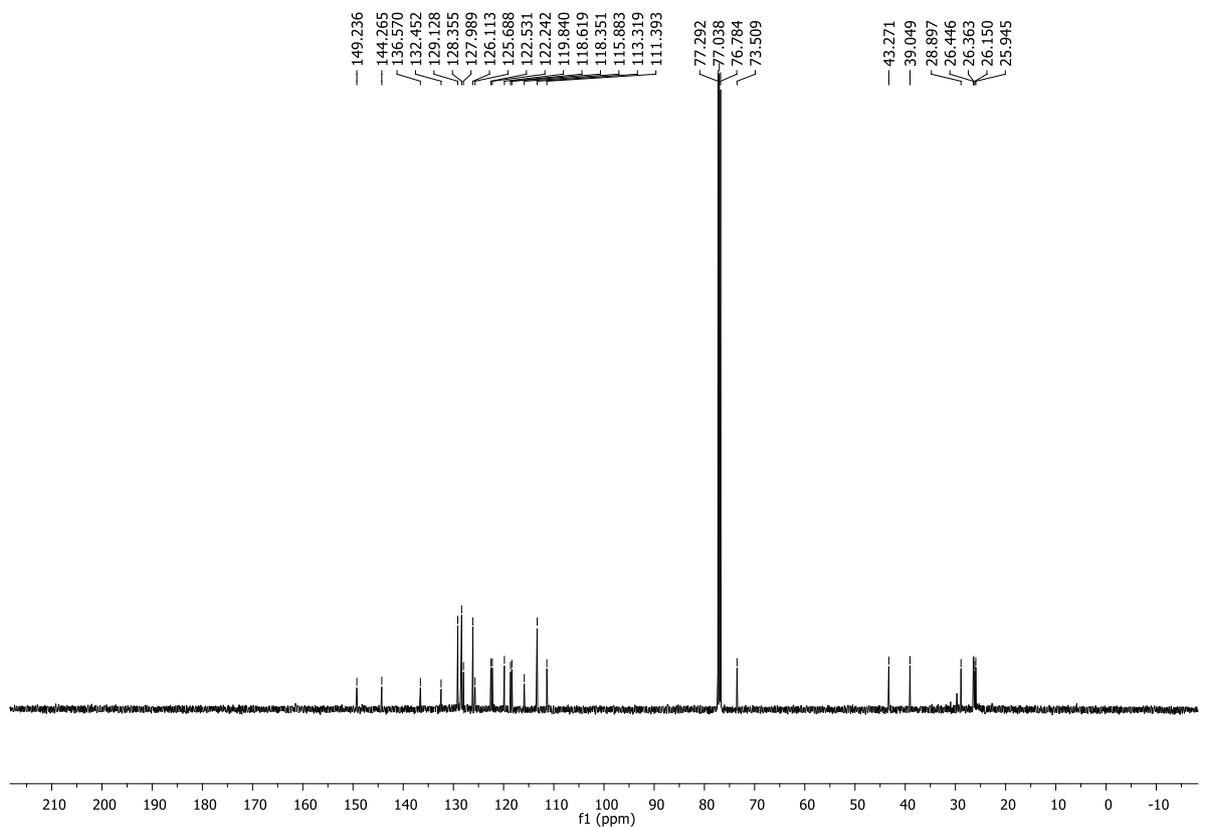


Figure S34. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5p**

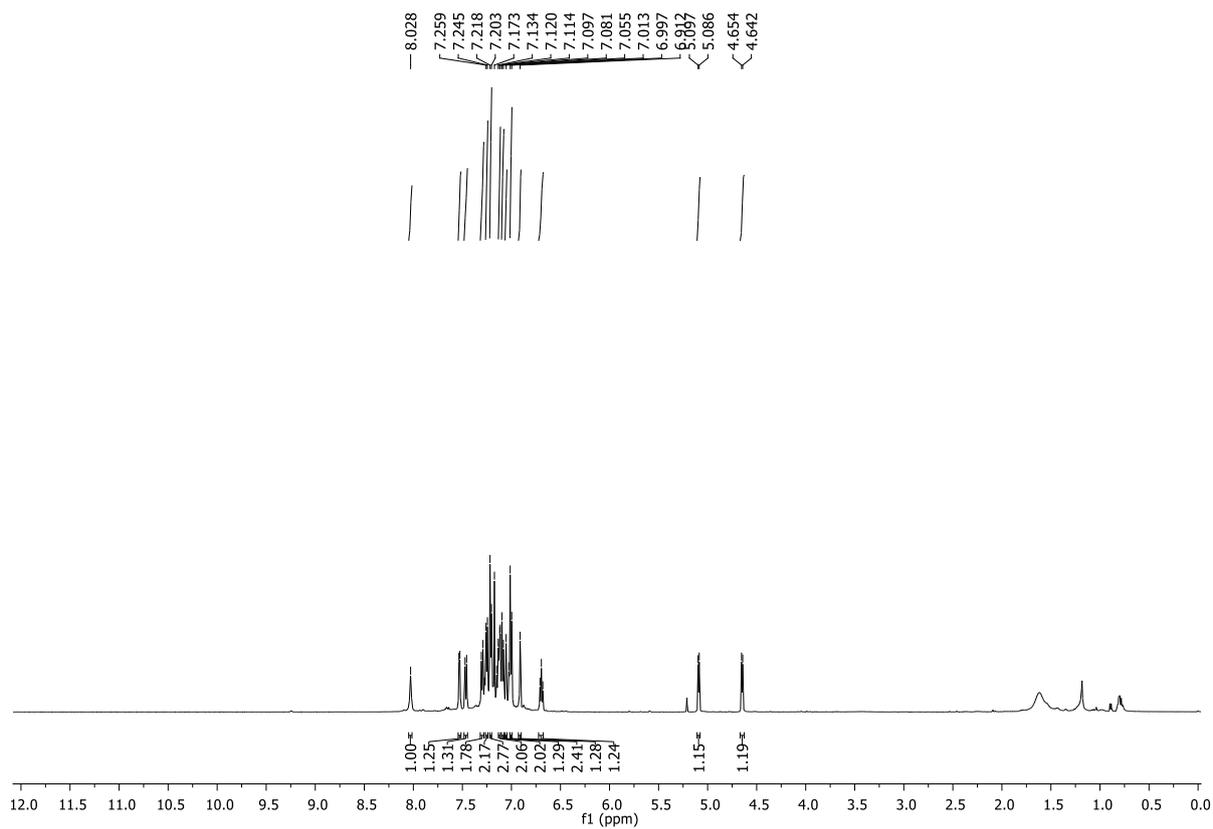


Figure S35. ^1H (500 MHz, CDCl_3) of **5q**

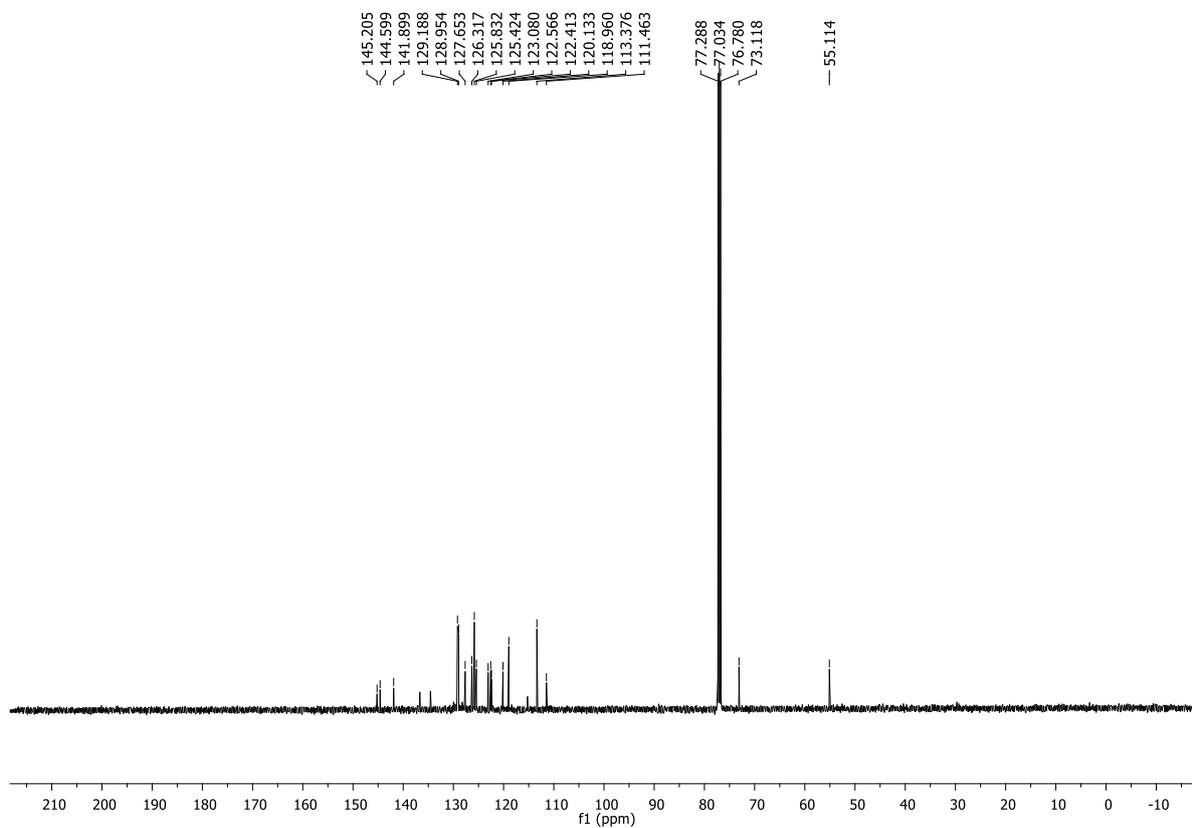


Figure S36. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5q**

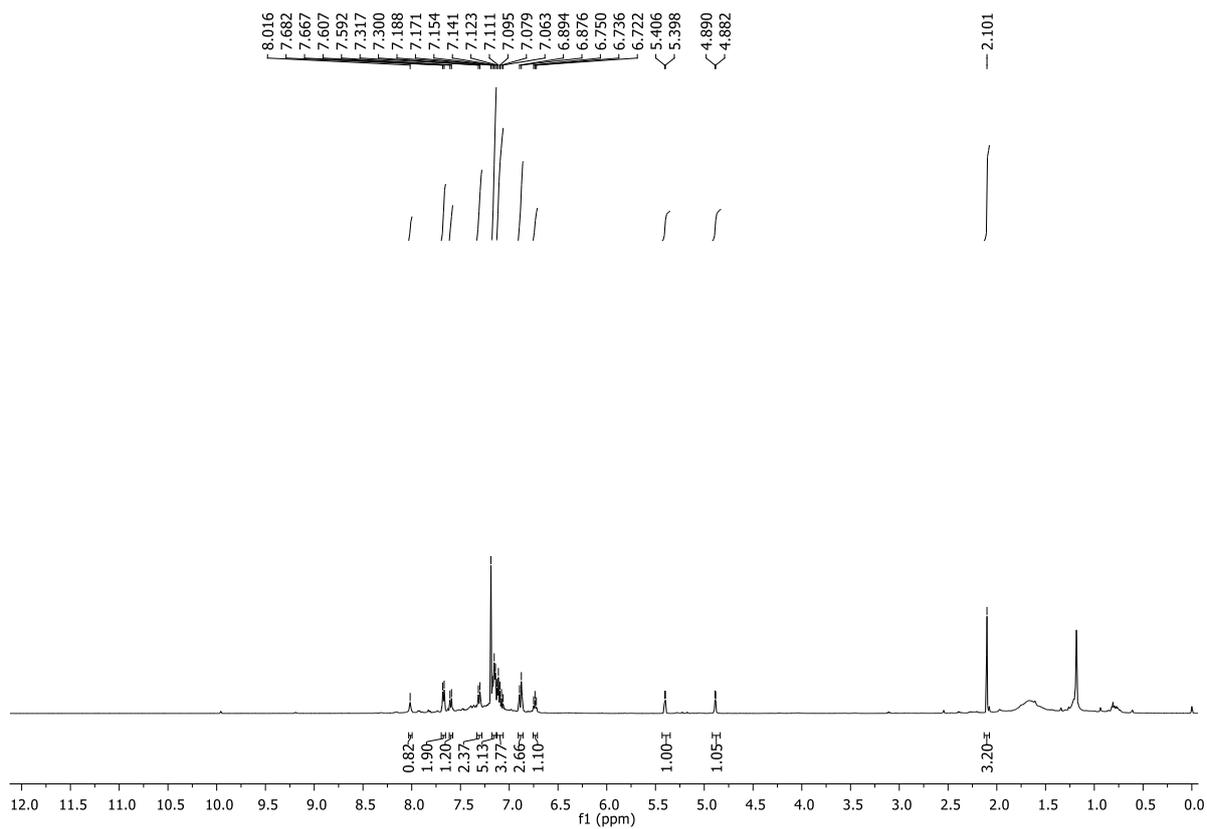


Figure S37. ^1H (500 MHz, CDCl_3) of **5r**

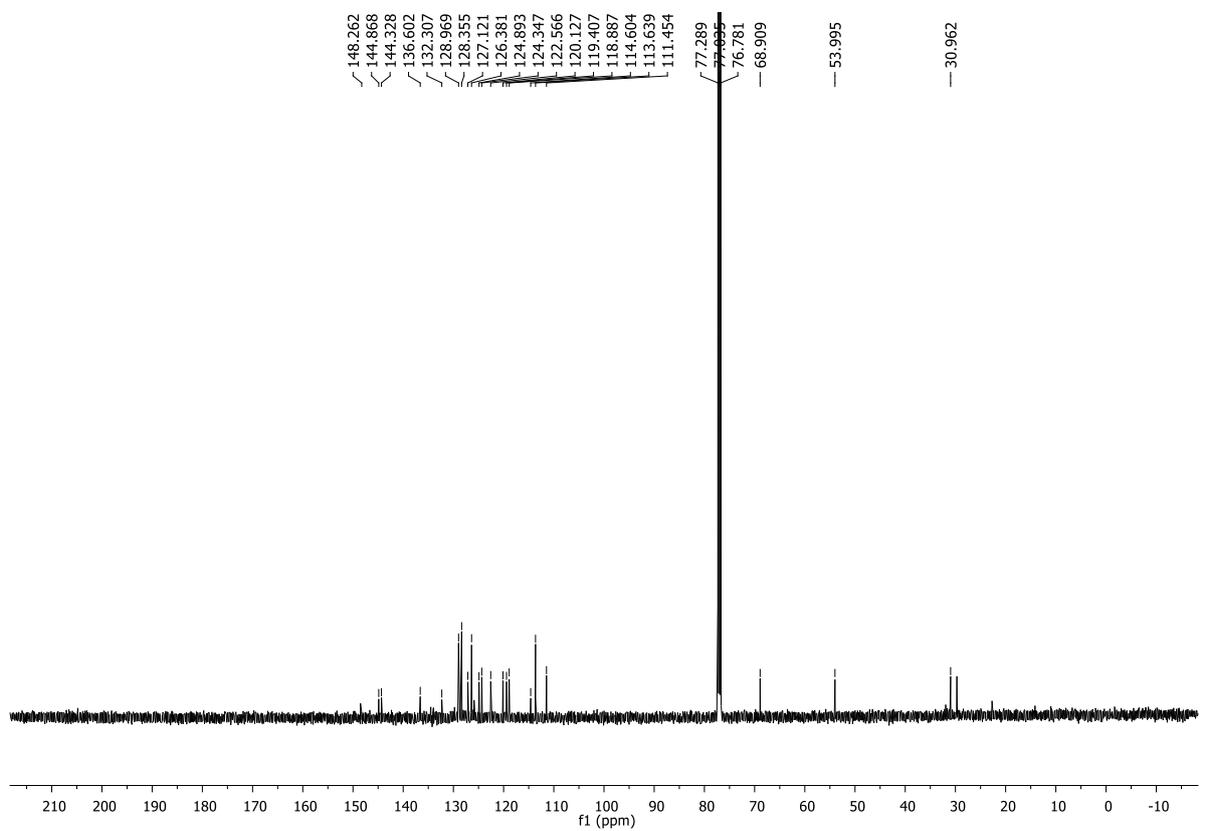


Figure S38. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5r**

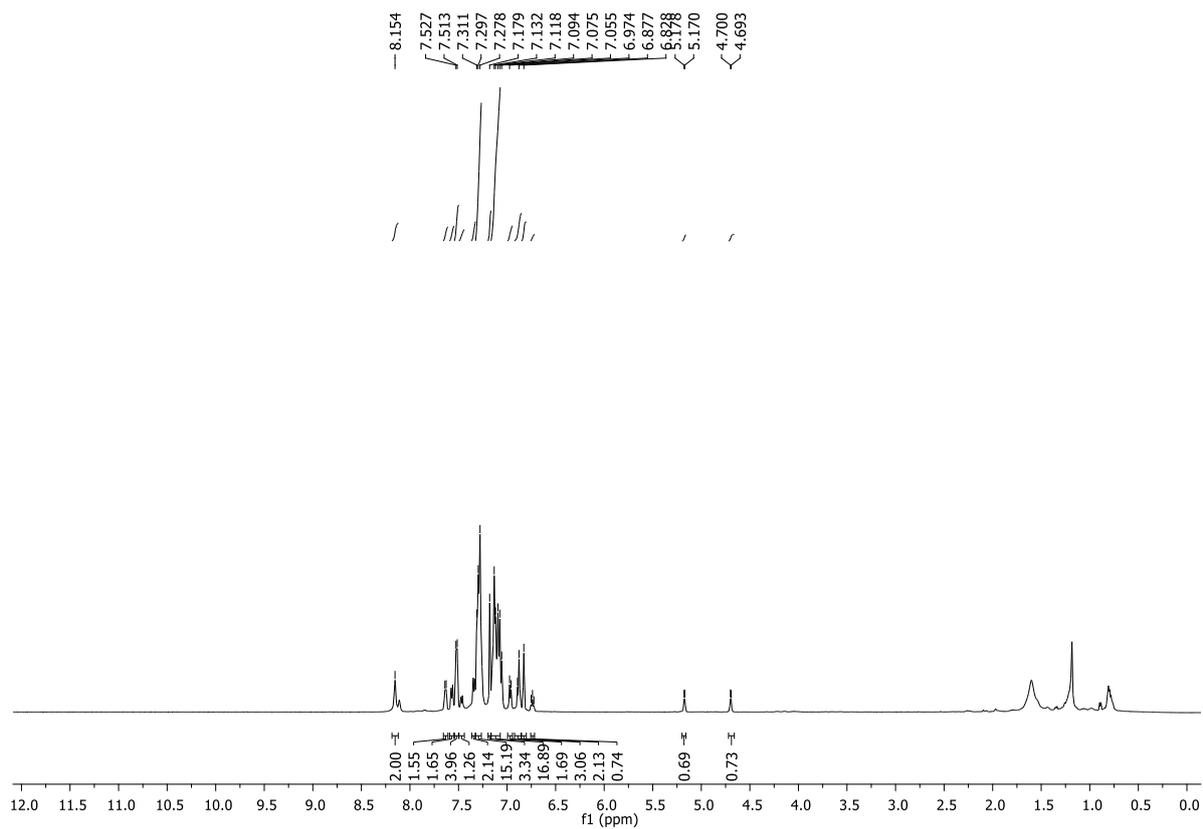


Figure S39. ^1H (500 MHz, CDCl_3) of **5s**

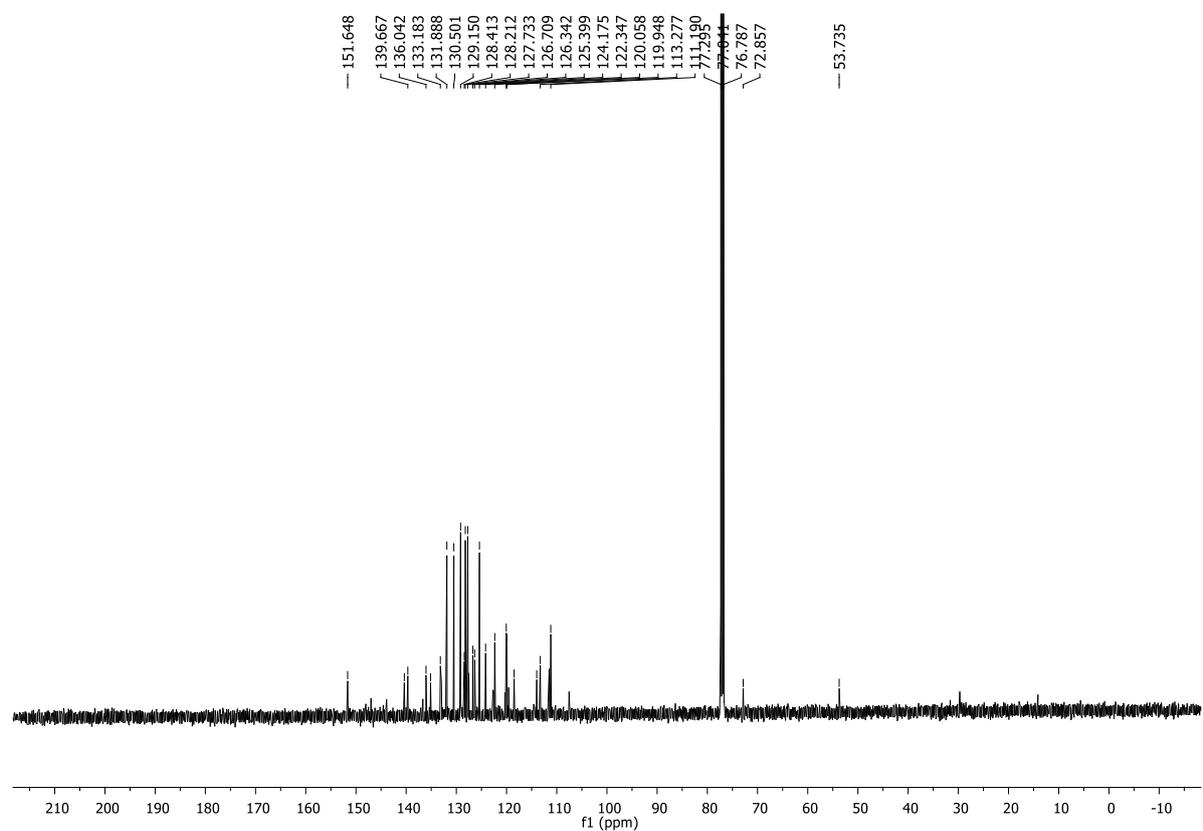


Figure S40. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5s**

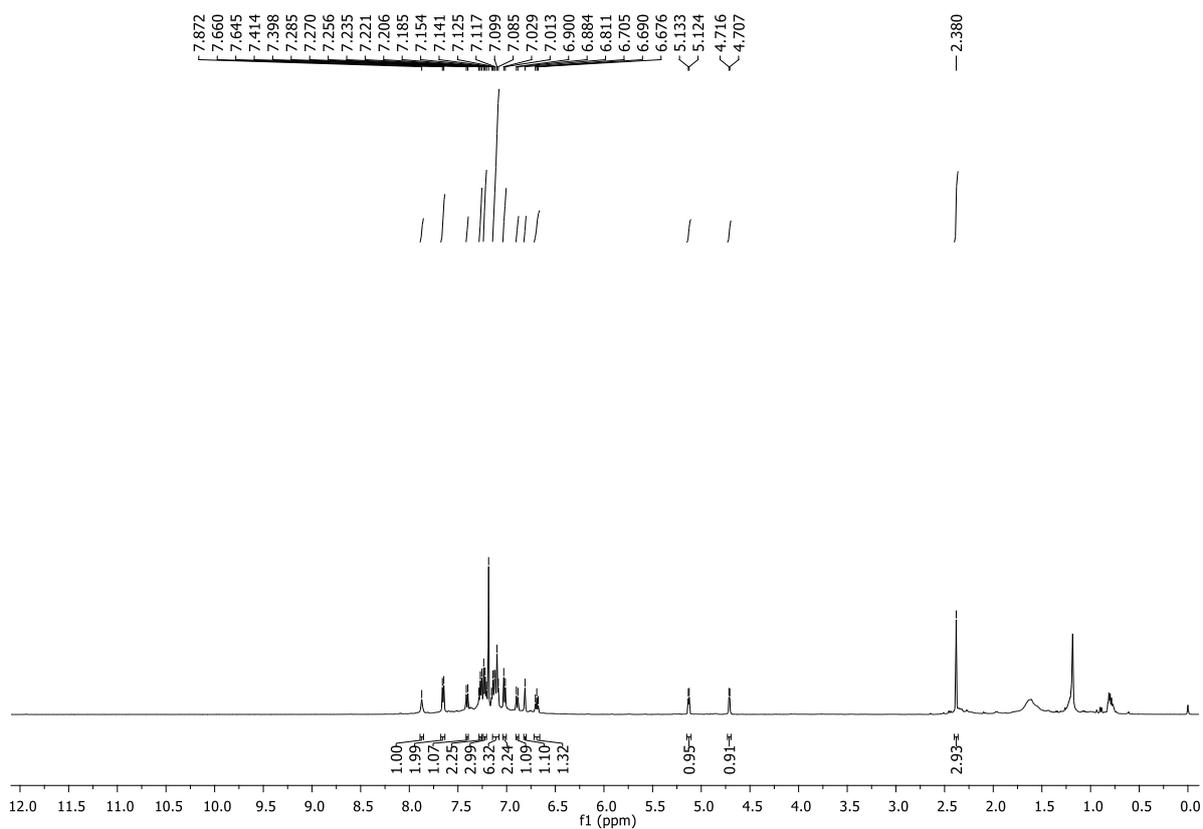


Figure S41. ^1H (500 MHz, CDCl_3) of **5aa**

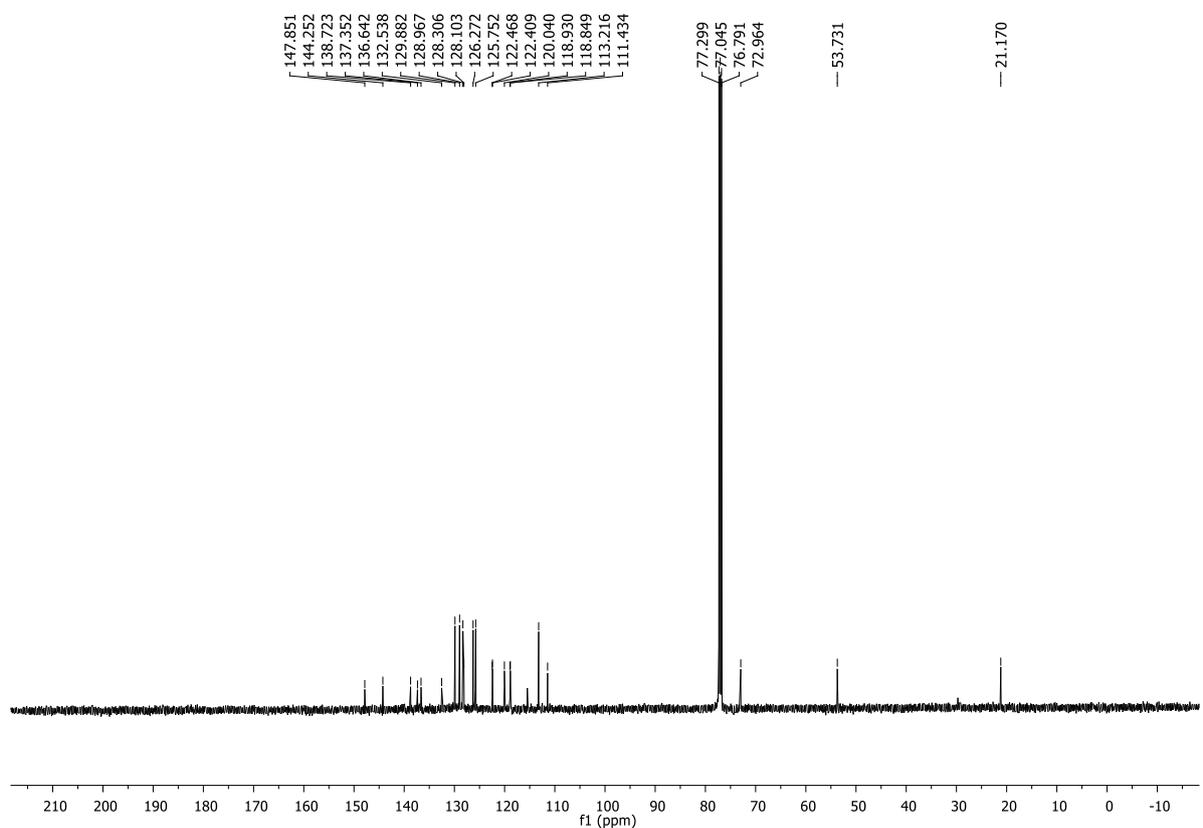


Figure S42. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5aa**

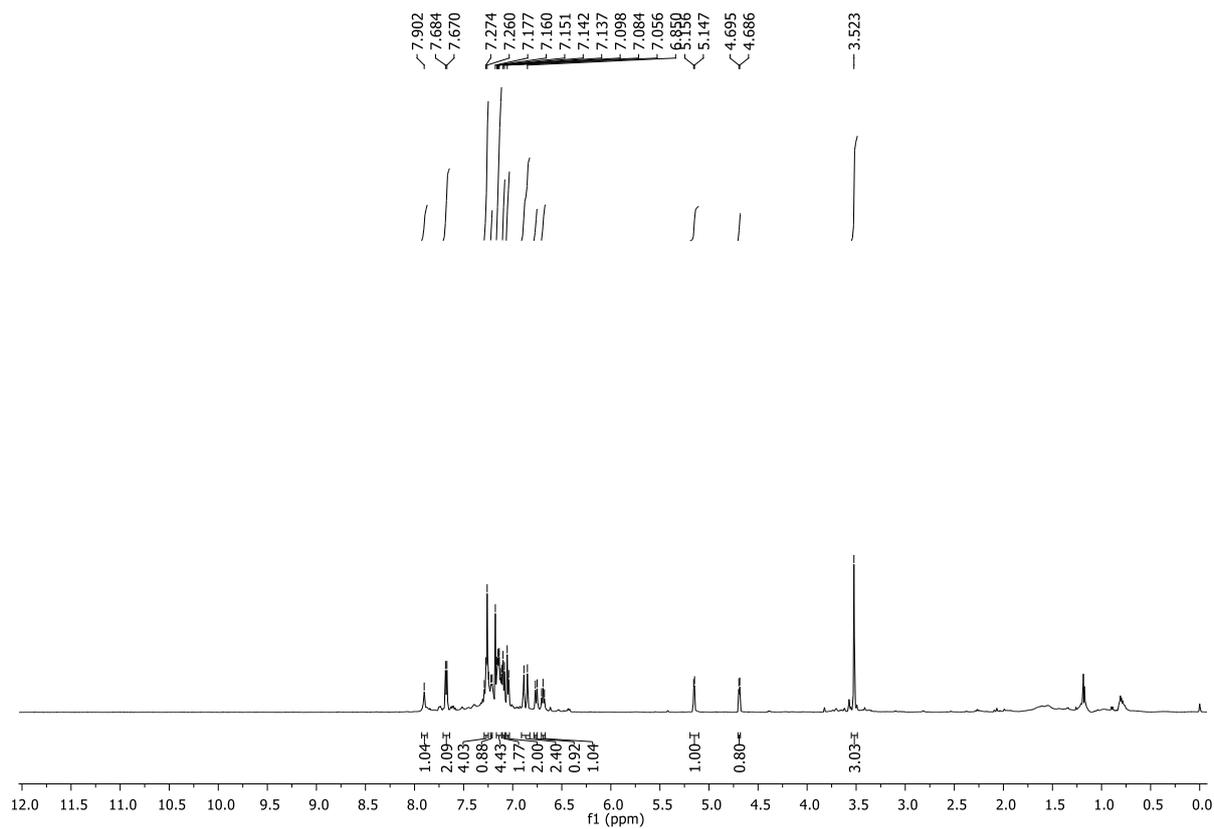


Figure S43. ^1H (500 MHz, CDCl_3) of **5ab**

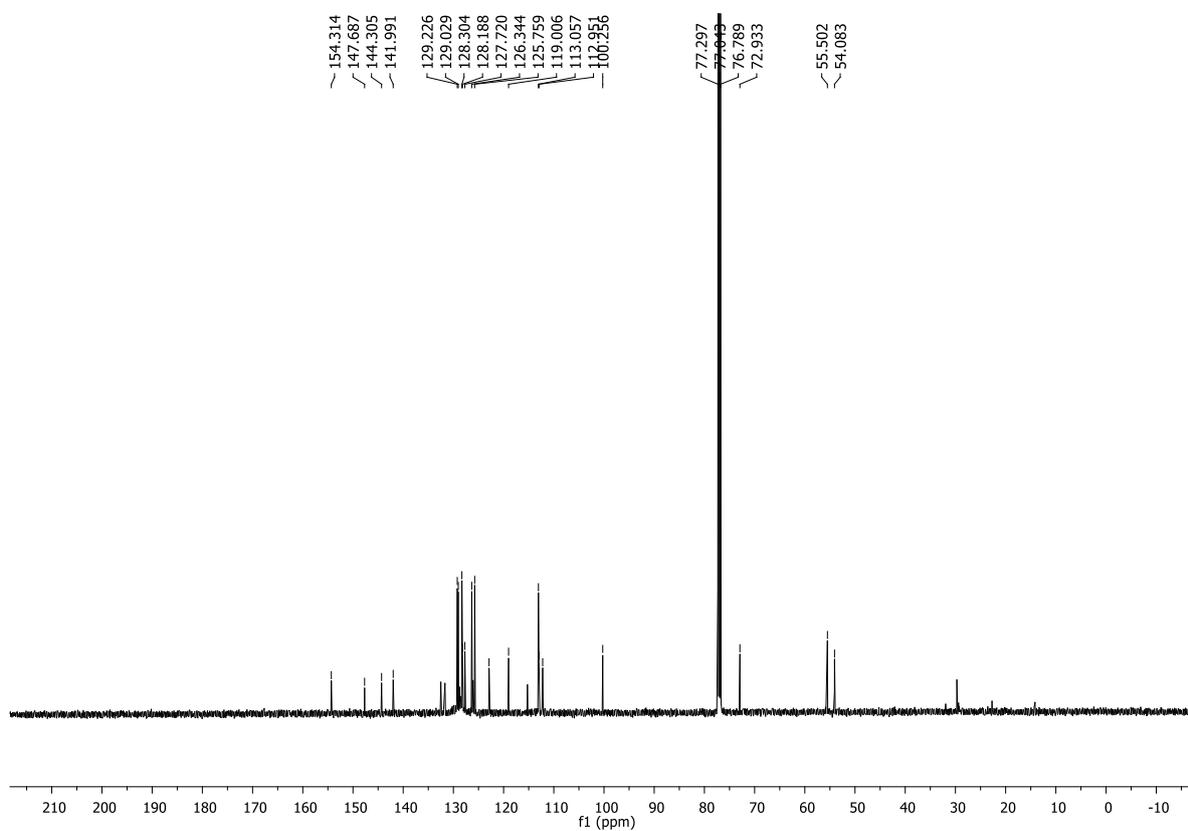


Figure S44. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ab**

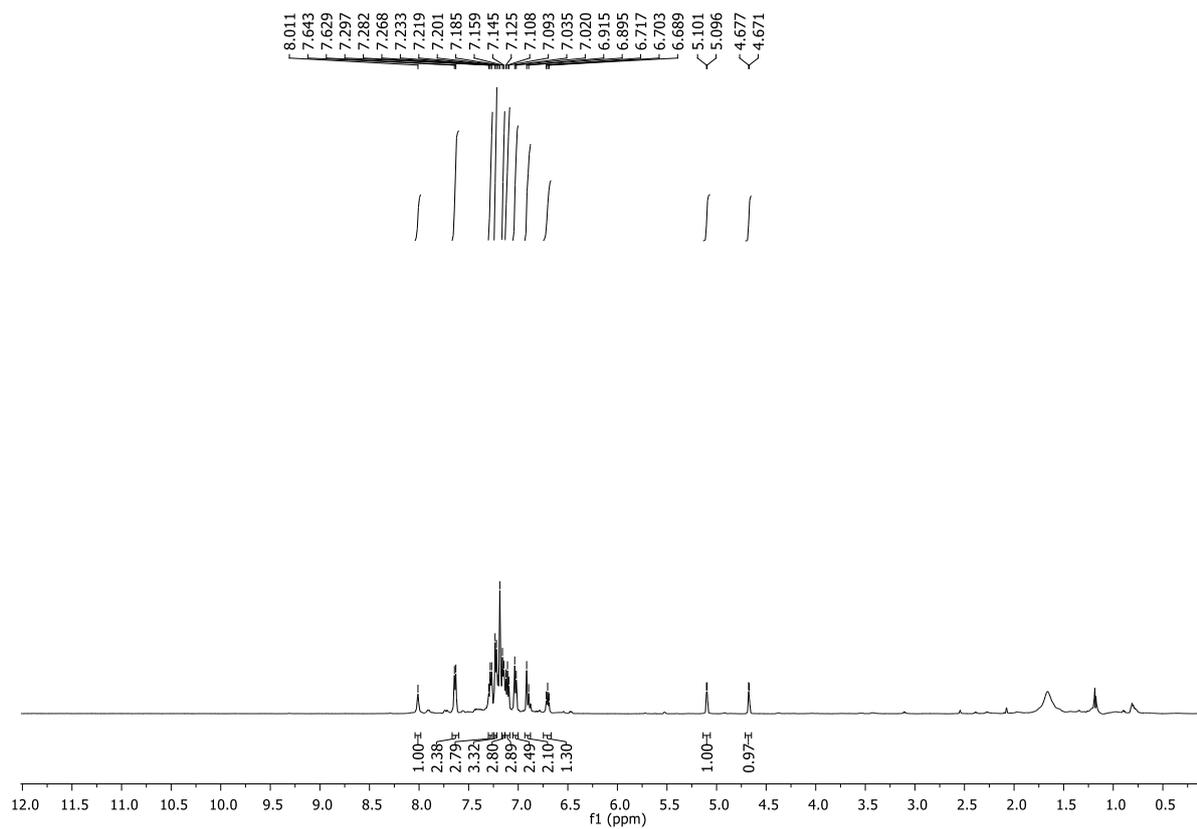


Figure S45. ^1H (500 MHz, CDCl_3) of **5ac**

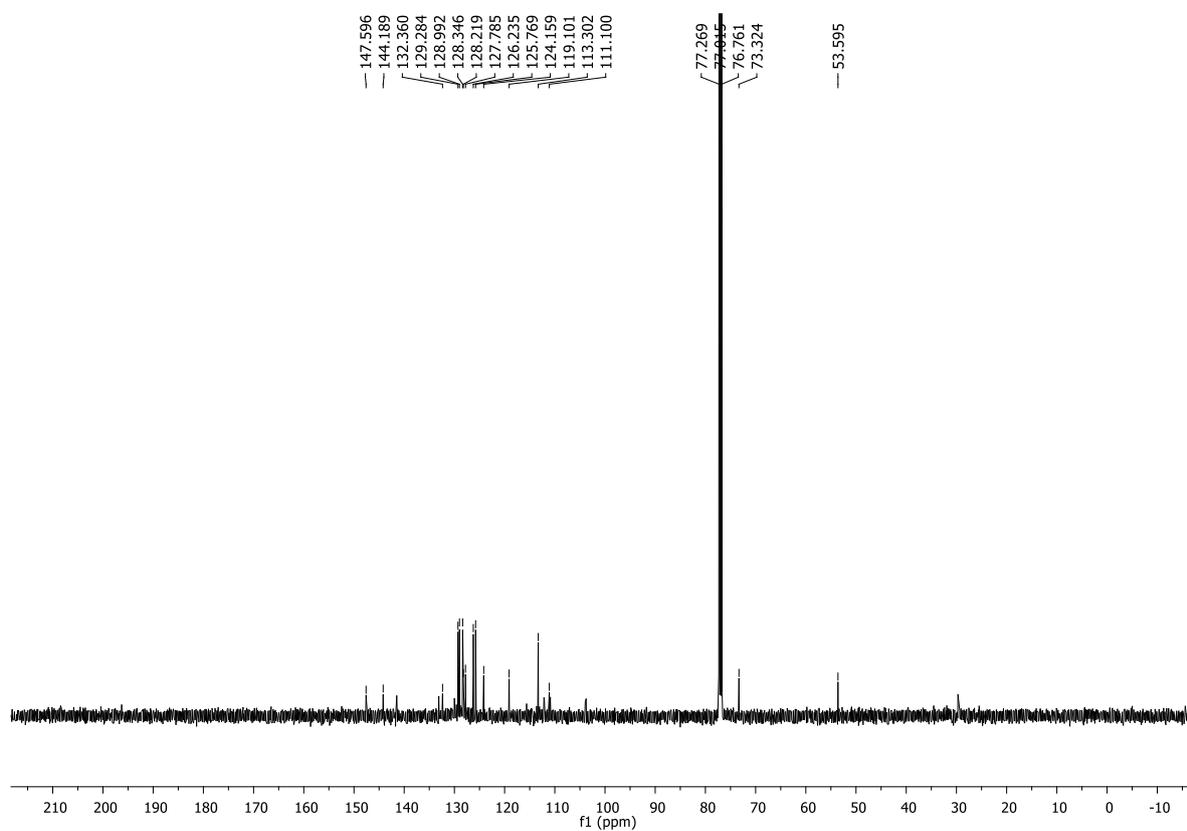


Figure S46. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ac**

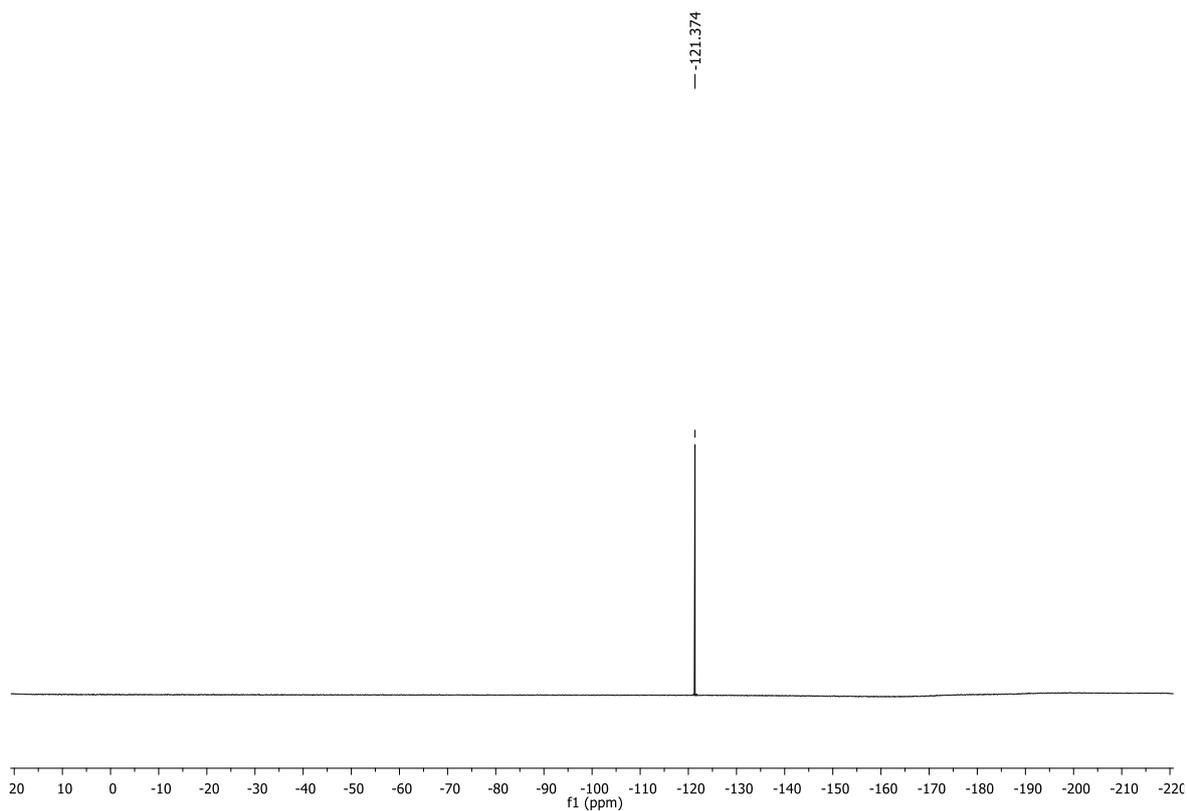


Figure S47. ^{19}F NMR (371 MHz, CDCl_3) of **5ac**

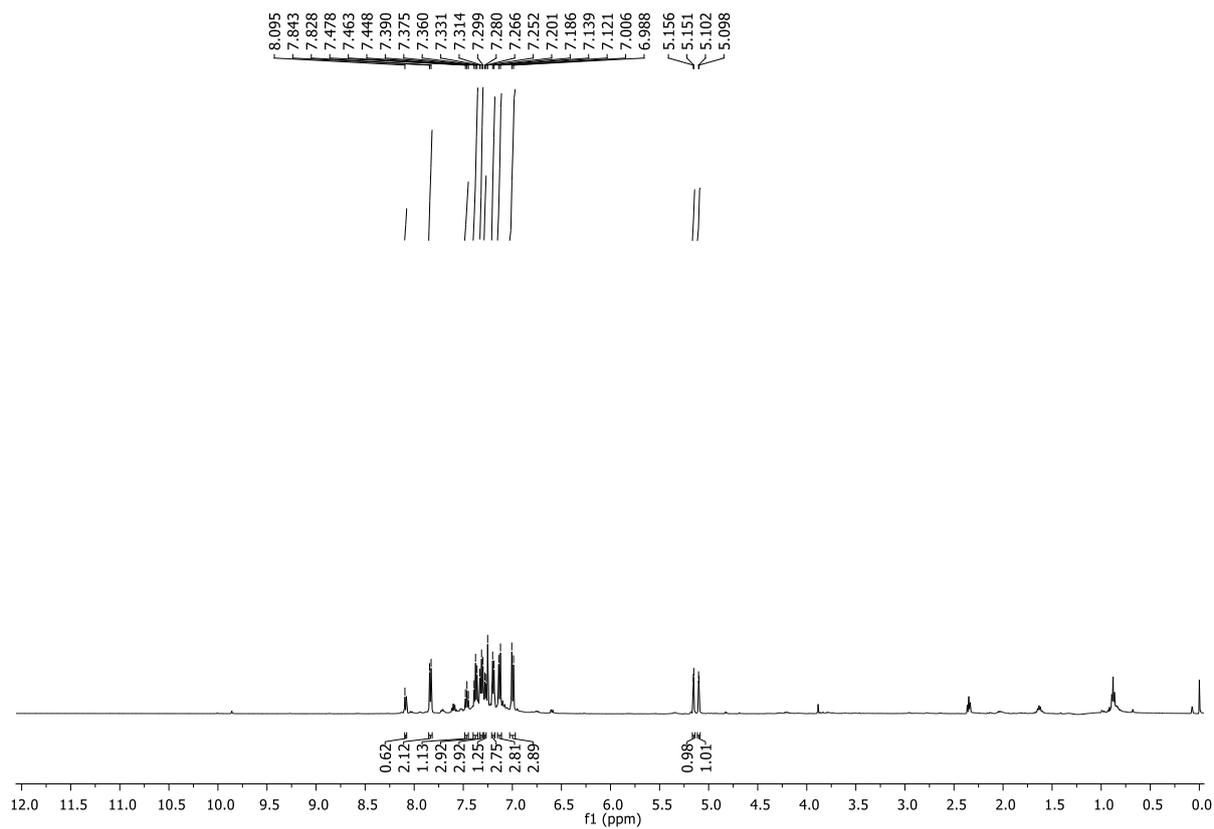


Figure S48. ^1H (500 MHz, CDCl_3) of **5ad**

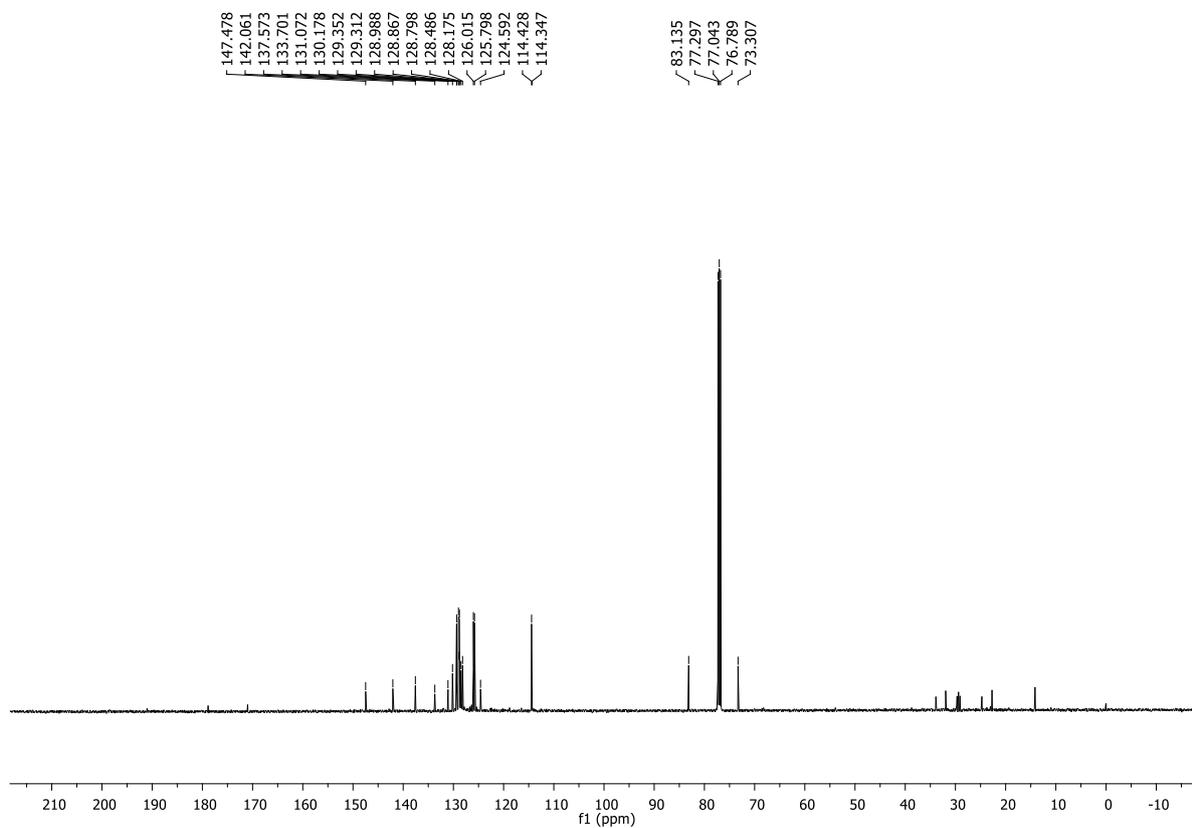


Figure S49. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ad**

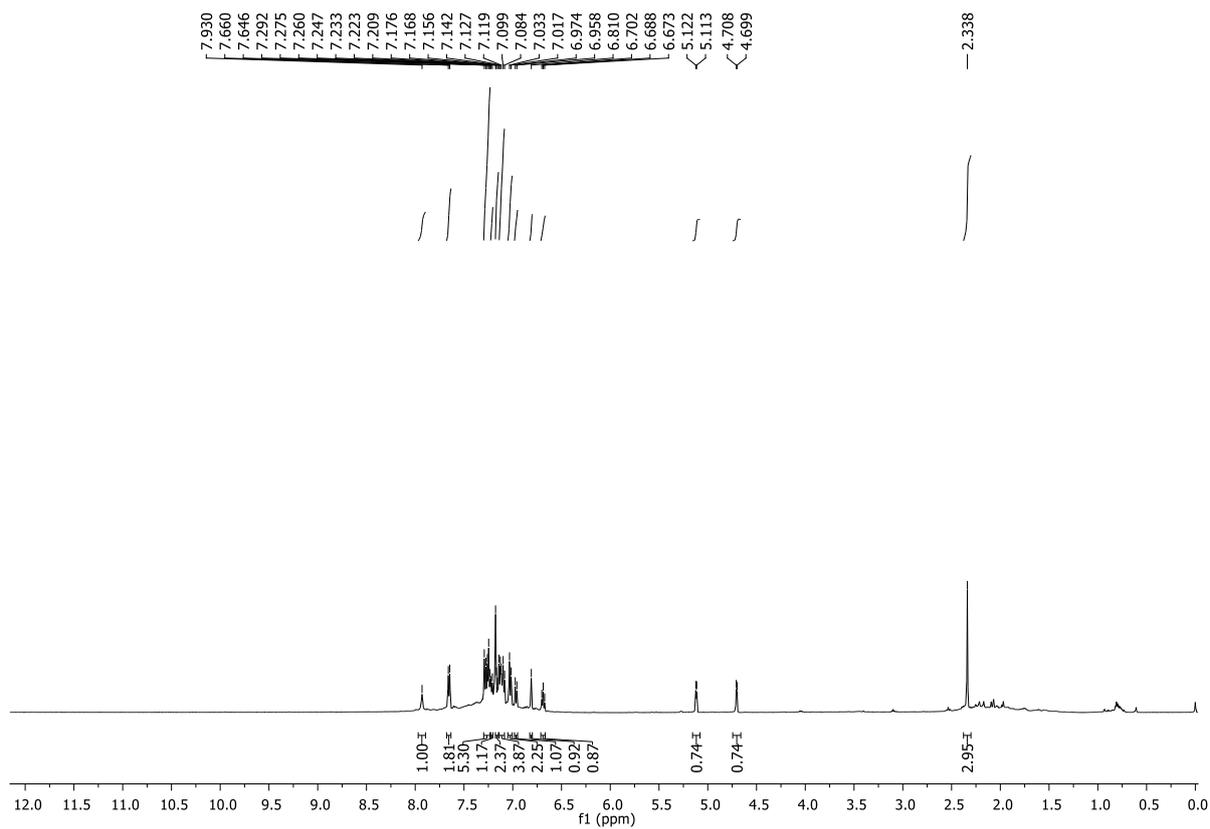


Figure S50. ^1H (500 MHz, CDCl_3) of **5ae**

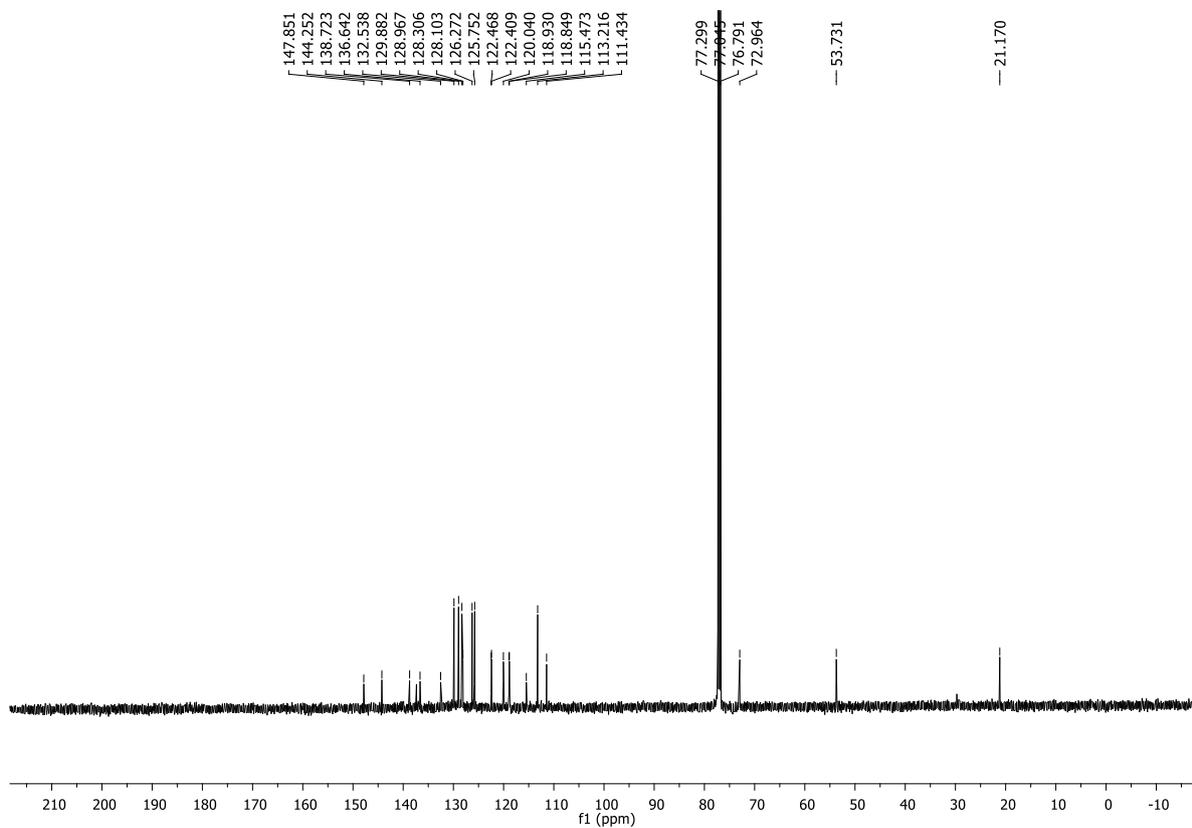


Figure S51. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ae**

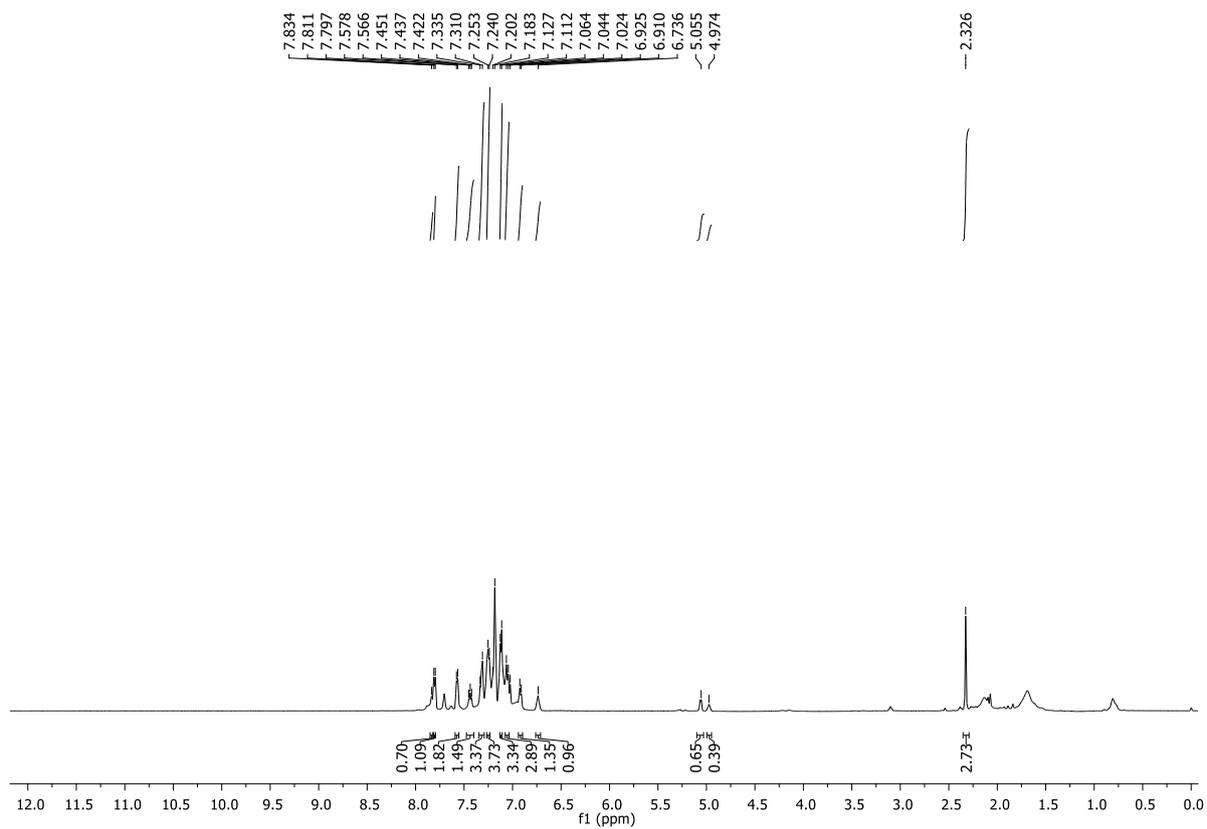


Figure S52. ^1H (500 MHz, CDCl_3) of **5af**

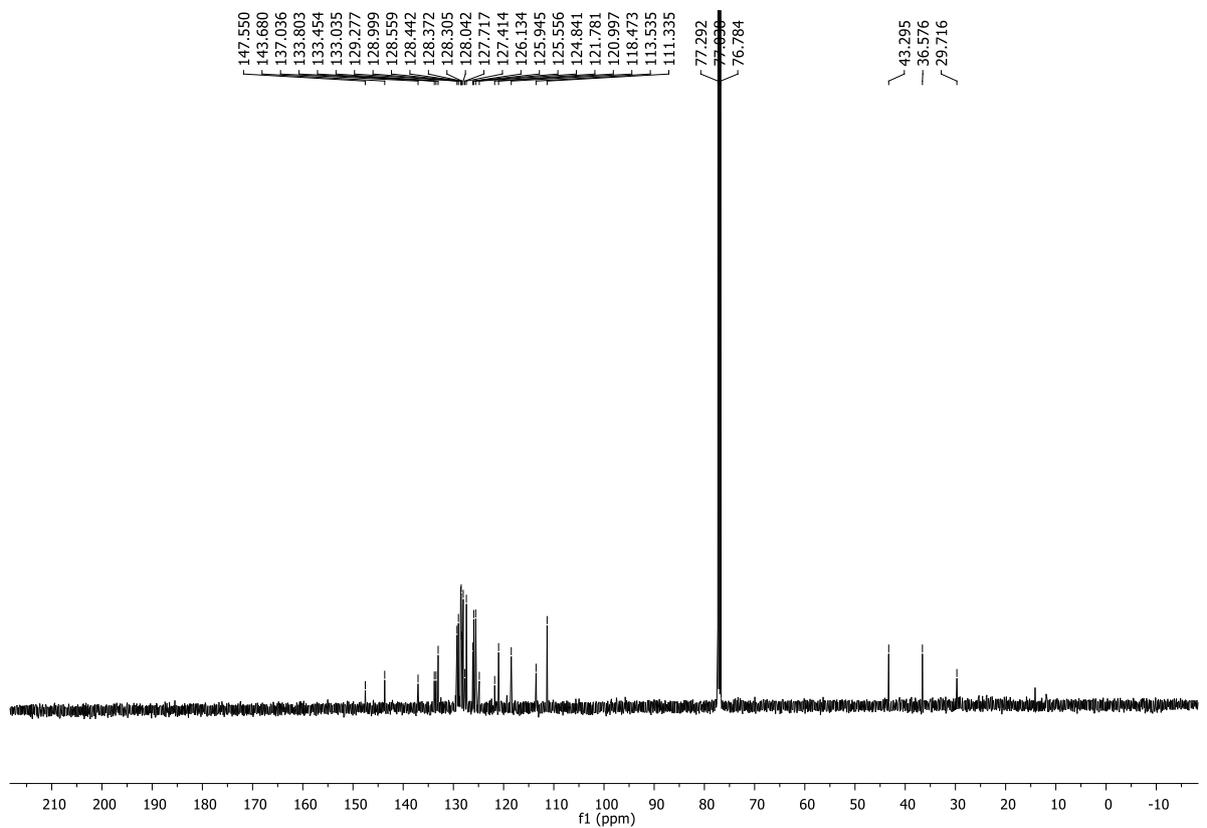


Figure S53. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5af**

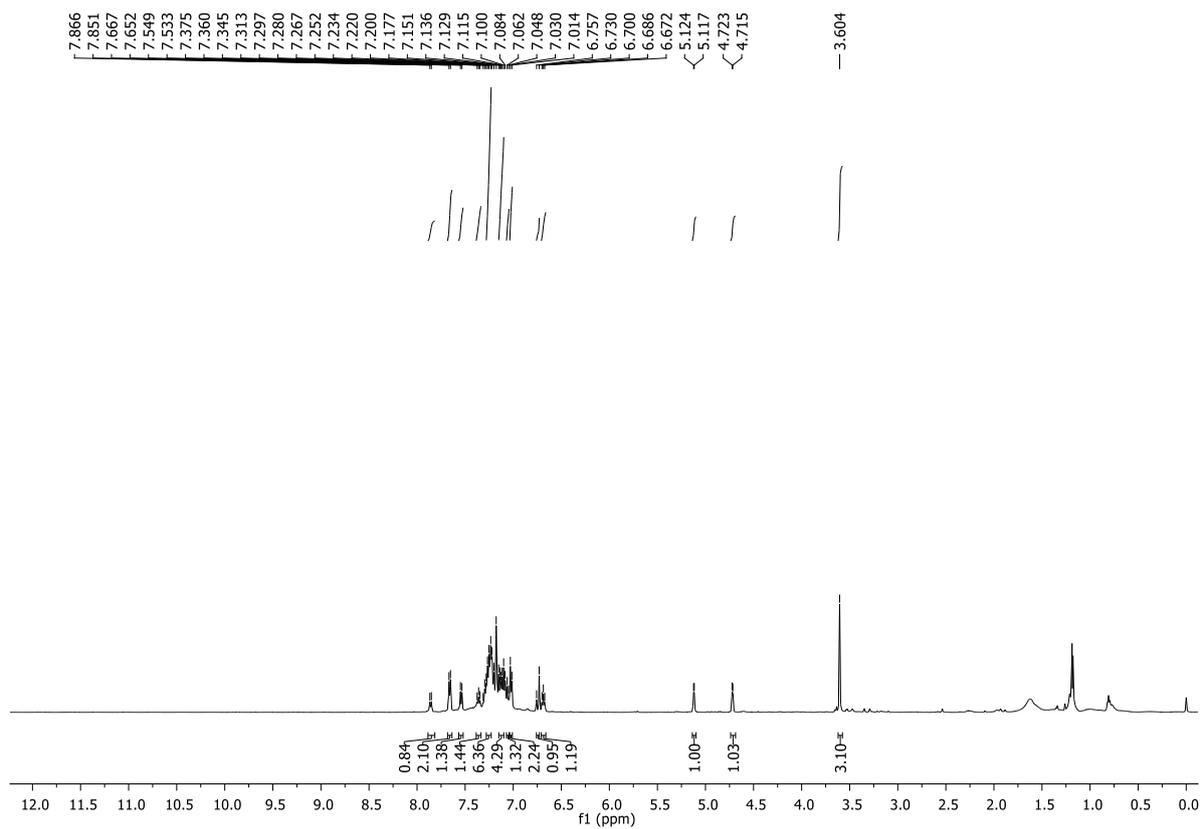


Figure S54. ^1H (500 MHz, CDCl_3) of **5ag**

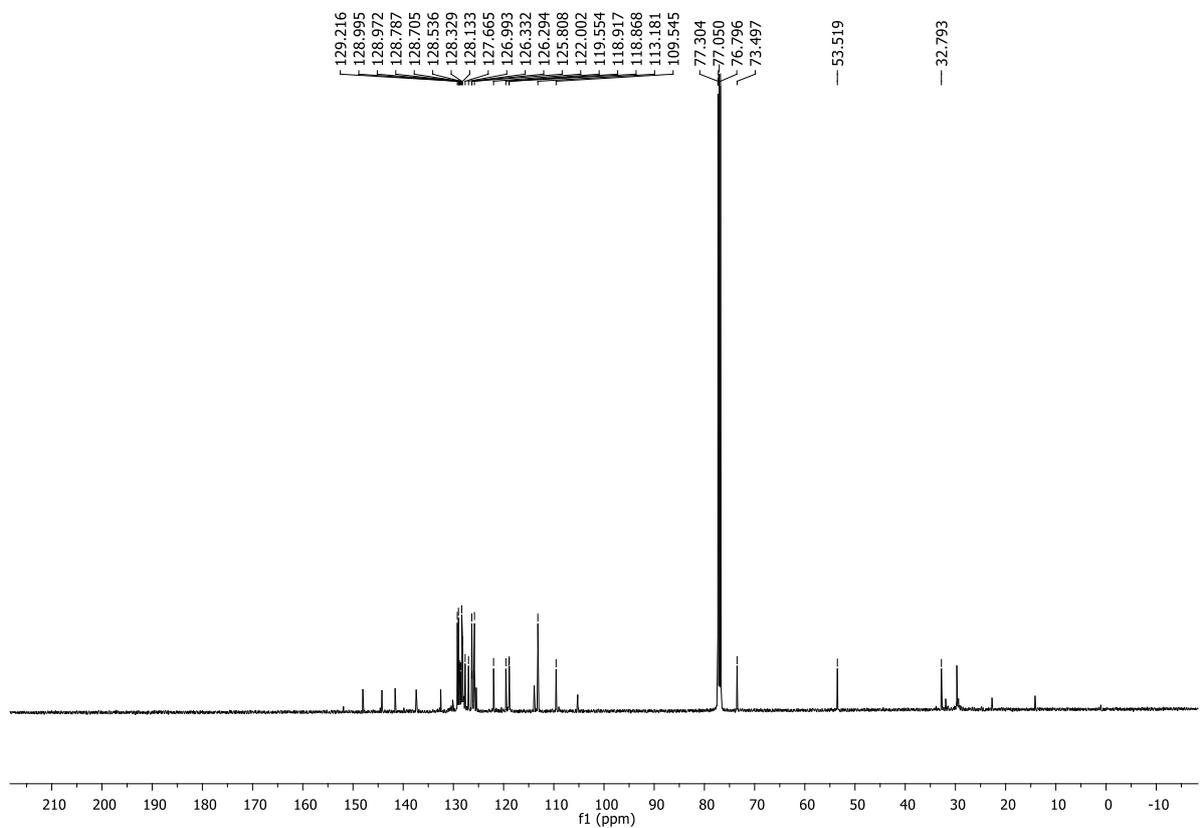


Figure S55. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ag**

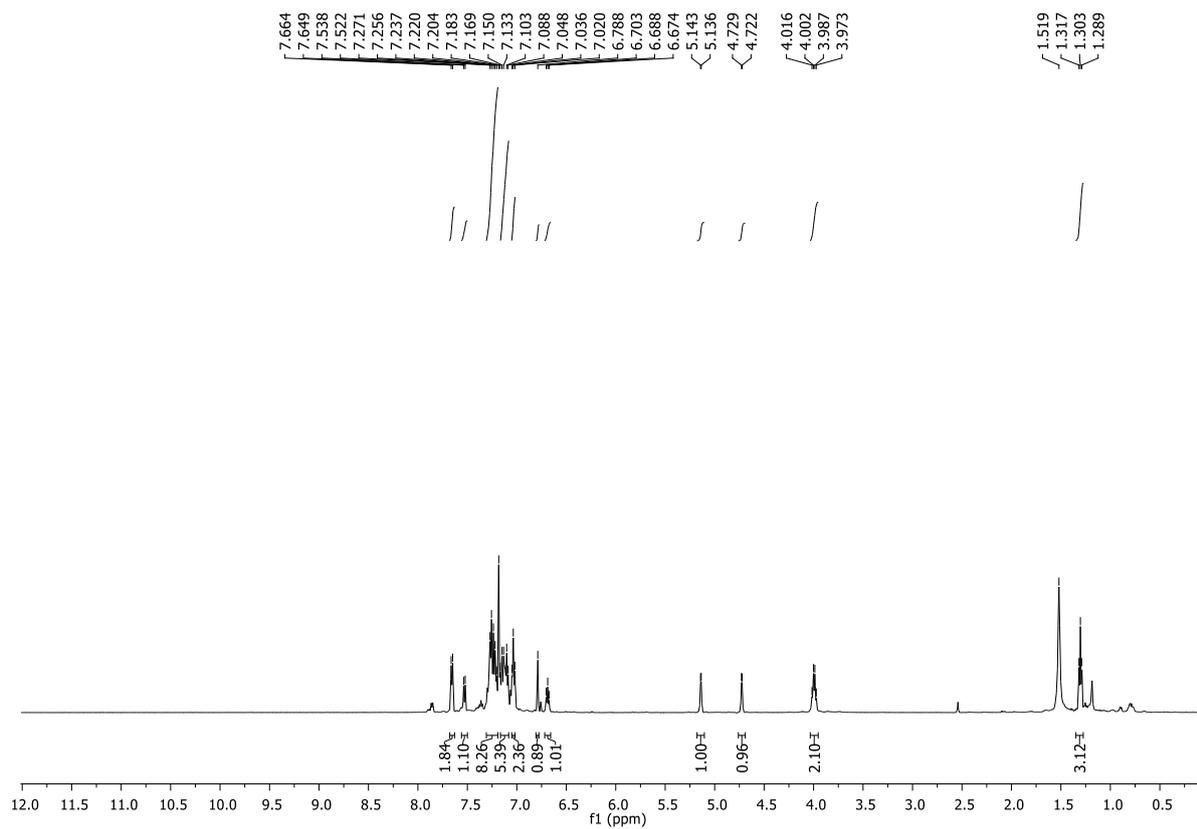


Figure S56. ^1H NMR (500 MHz, CDCl_3) of **5ah**

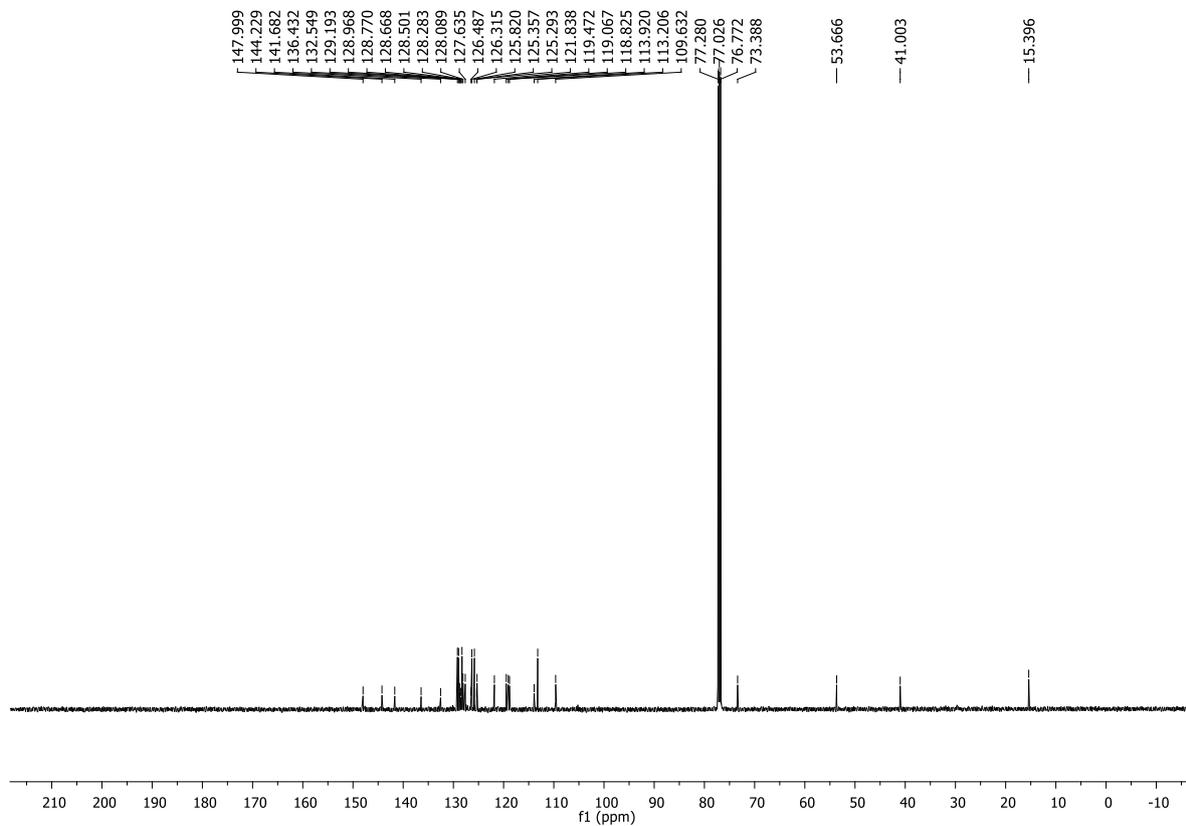


Figure S57. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ah**

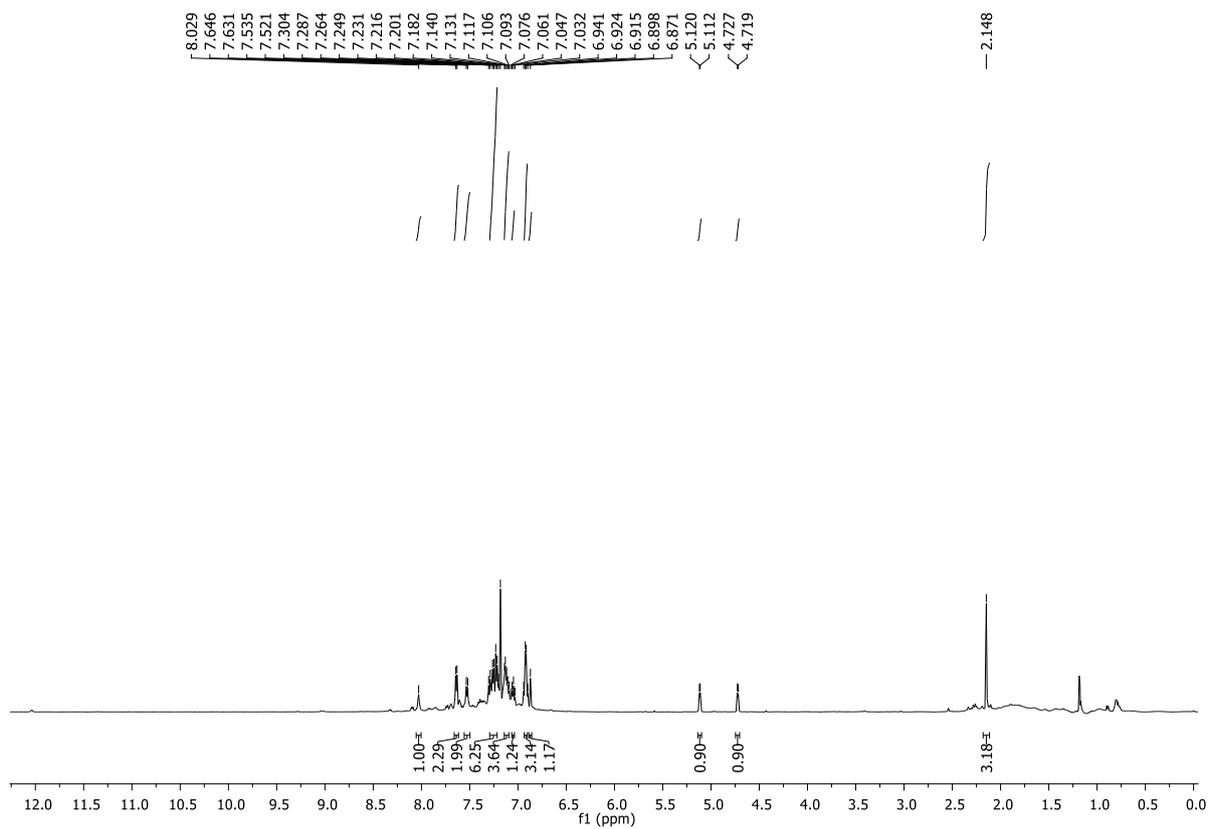


Figure S58. ^1H NMR (500 MHz, CDCl_3) of **5ai**

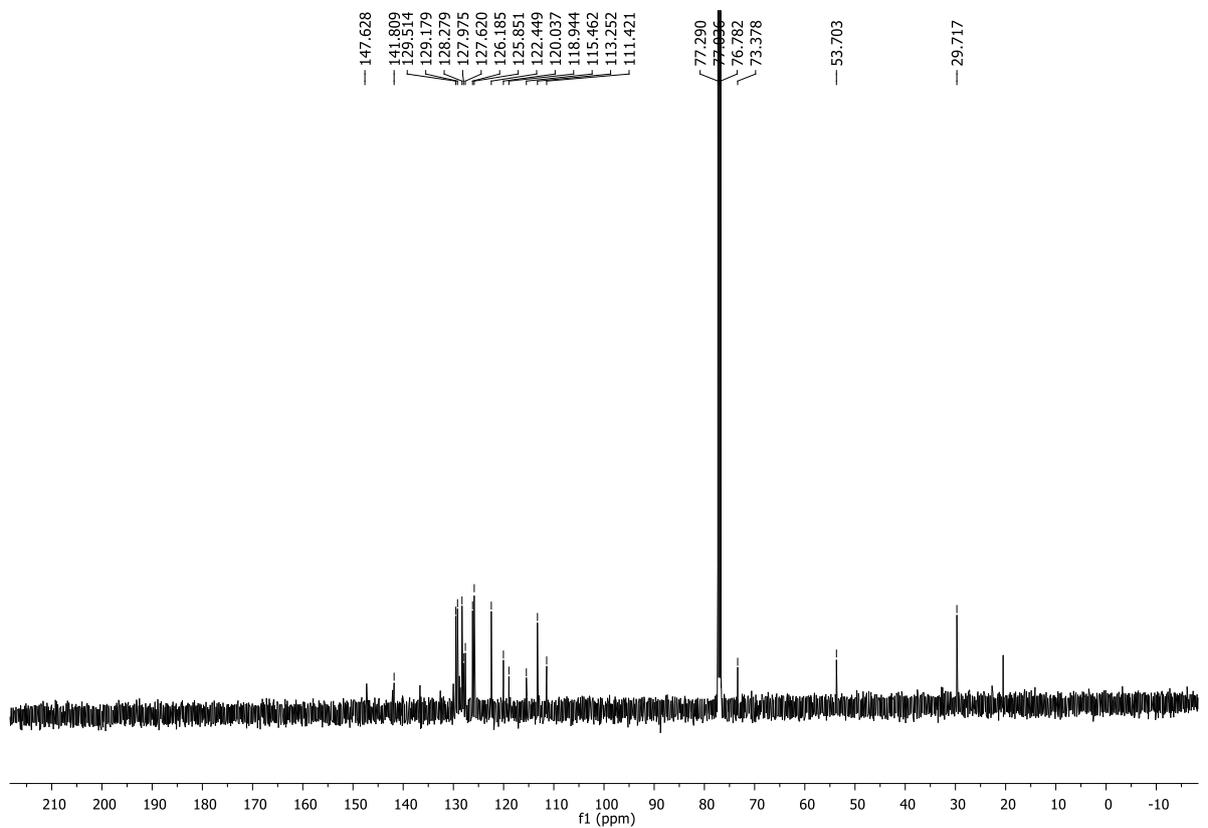


Figure S59. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ai**

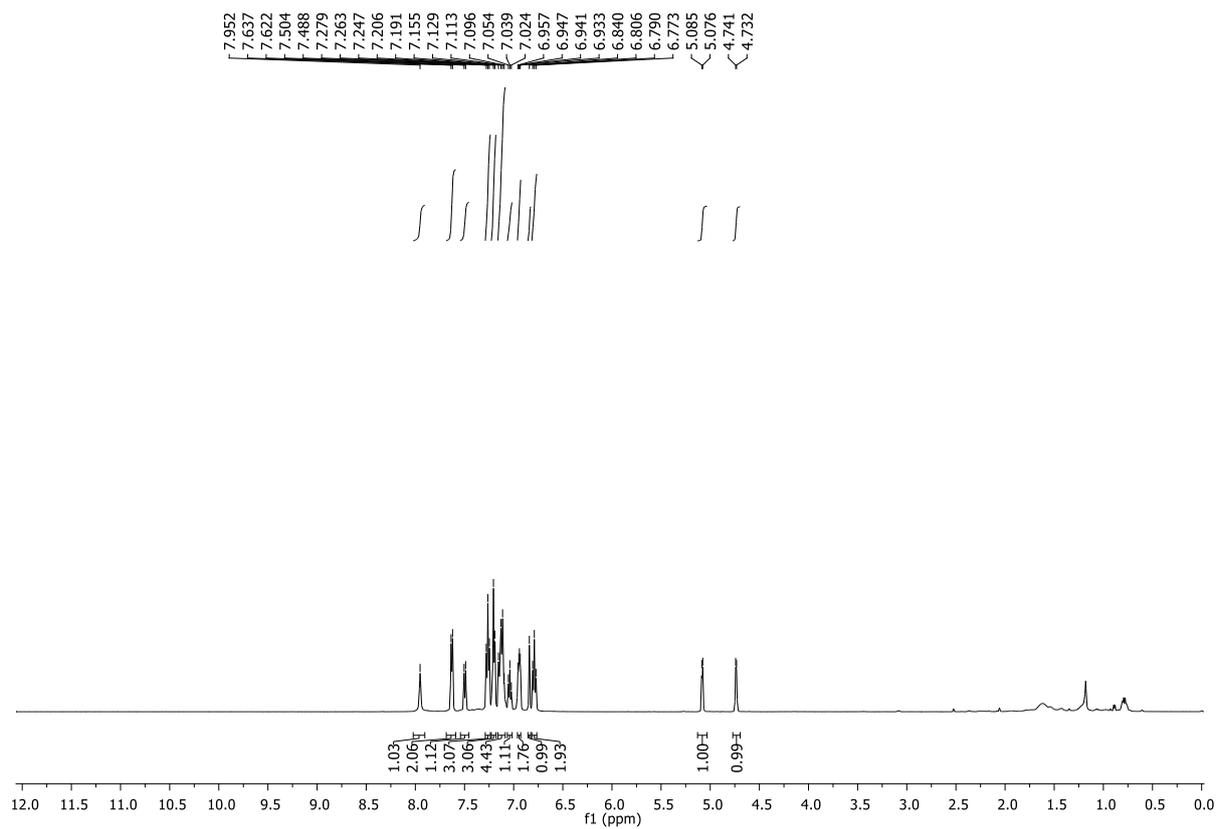


Figure S60. ^1H (500 MHz, CDCl_3) of **5aj**

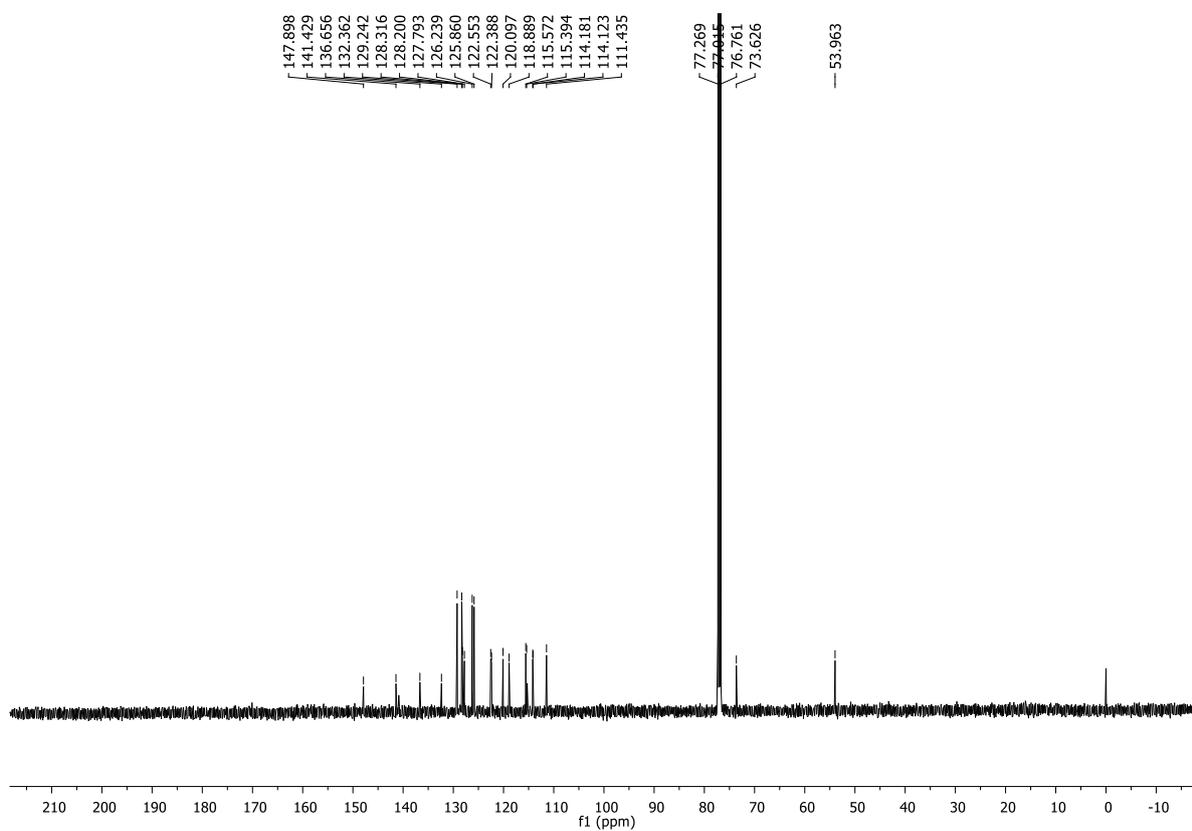


Figure S61. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5aj**

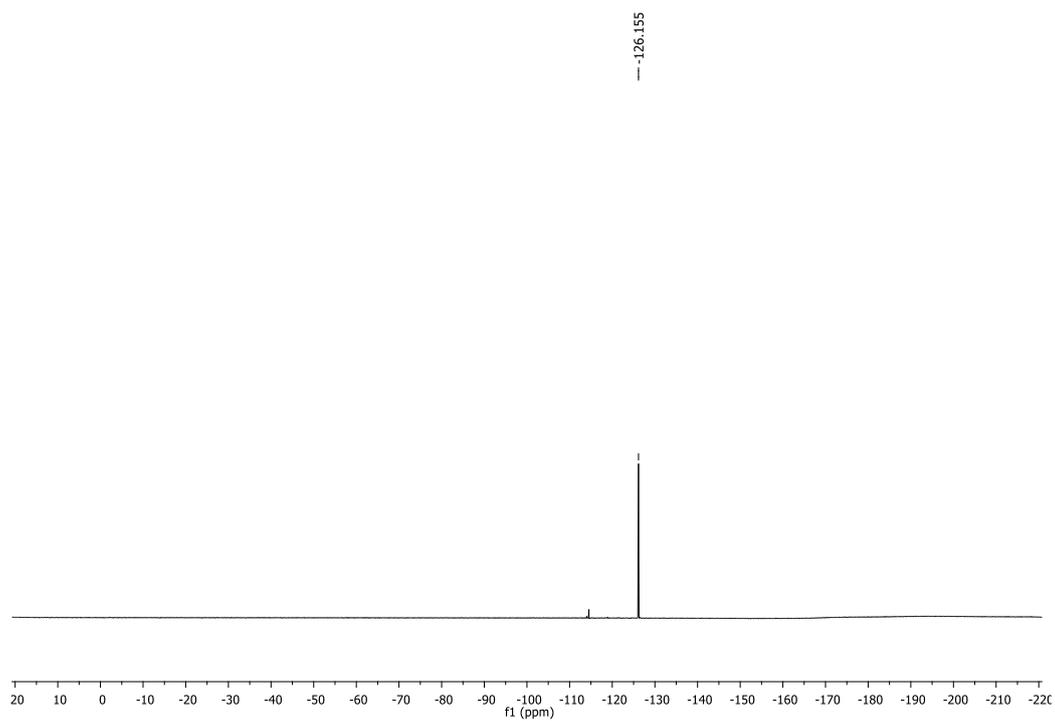


Figure S62. ^{19}F NMR (371 MHz, CDCl_3) of **5aj**

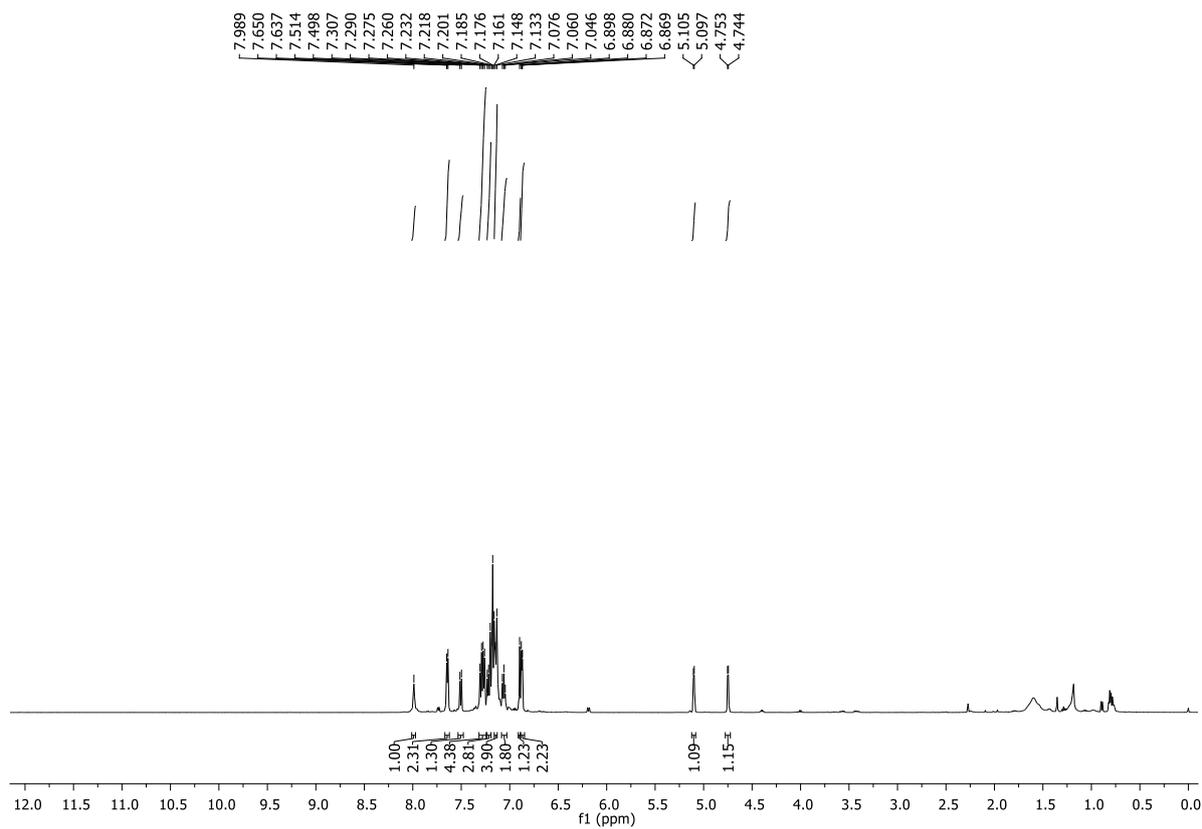


Figure S63. ^1H (500 MHz, CDCl_3) of **5ak**

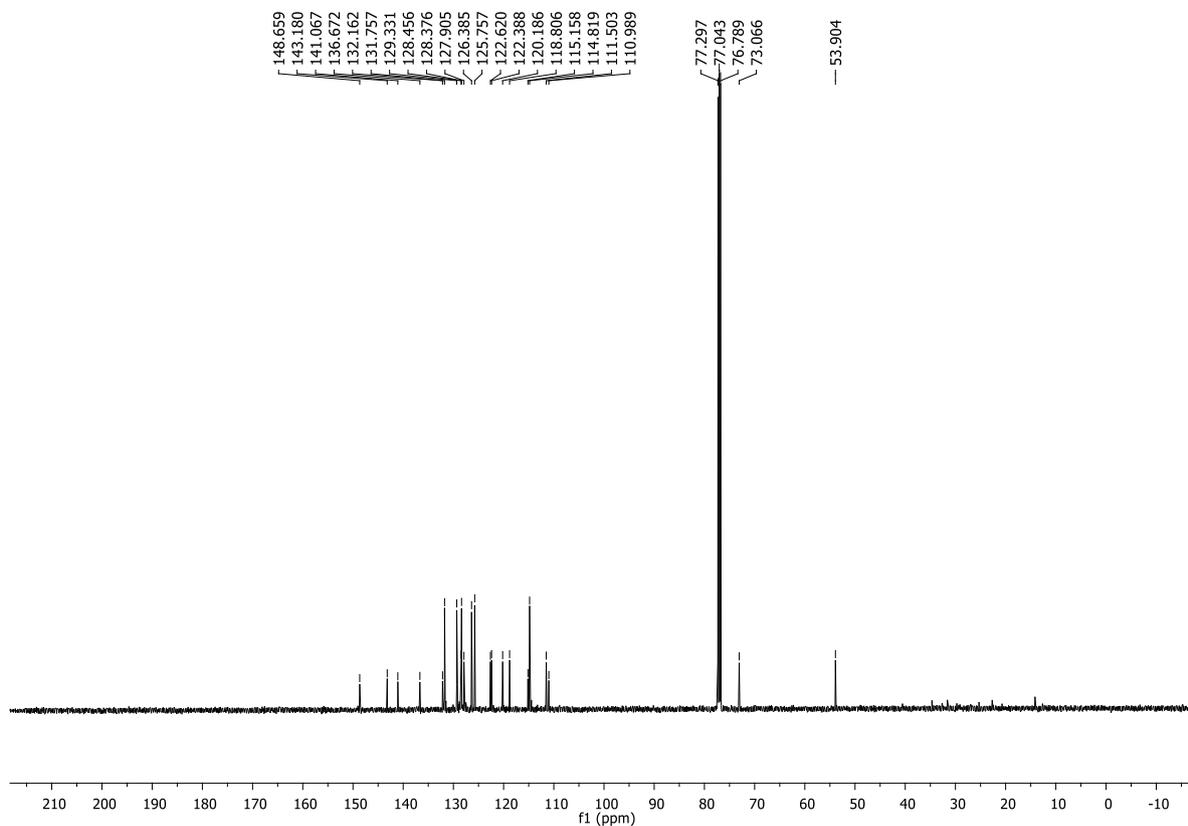


Figure S64. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ak**

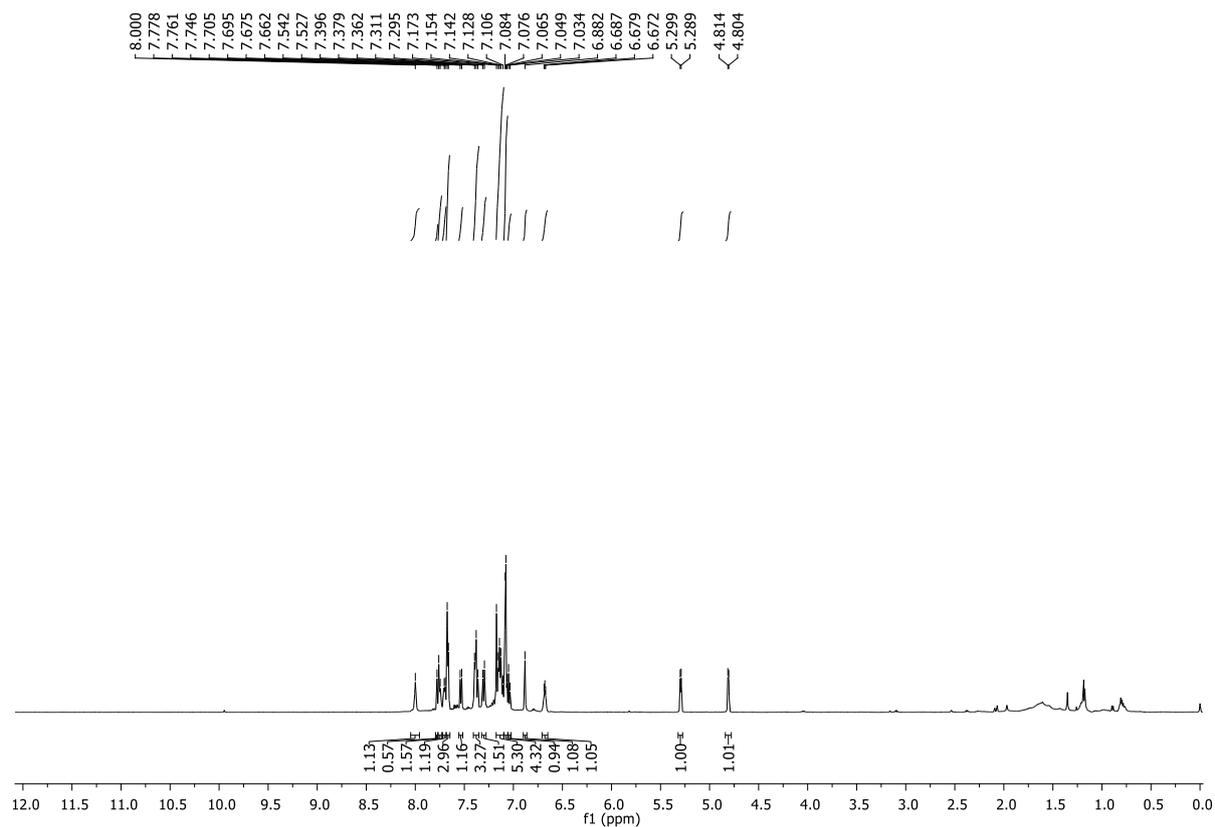


Figure S65. ^1H (500 MHz, CDCl_3) of **5ba**

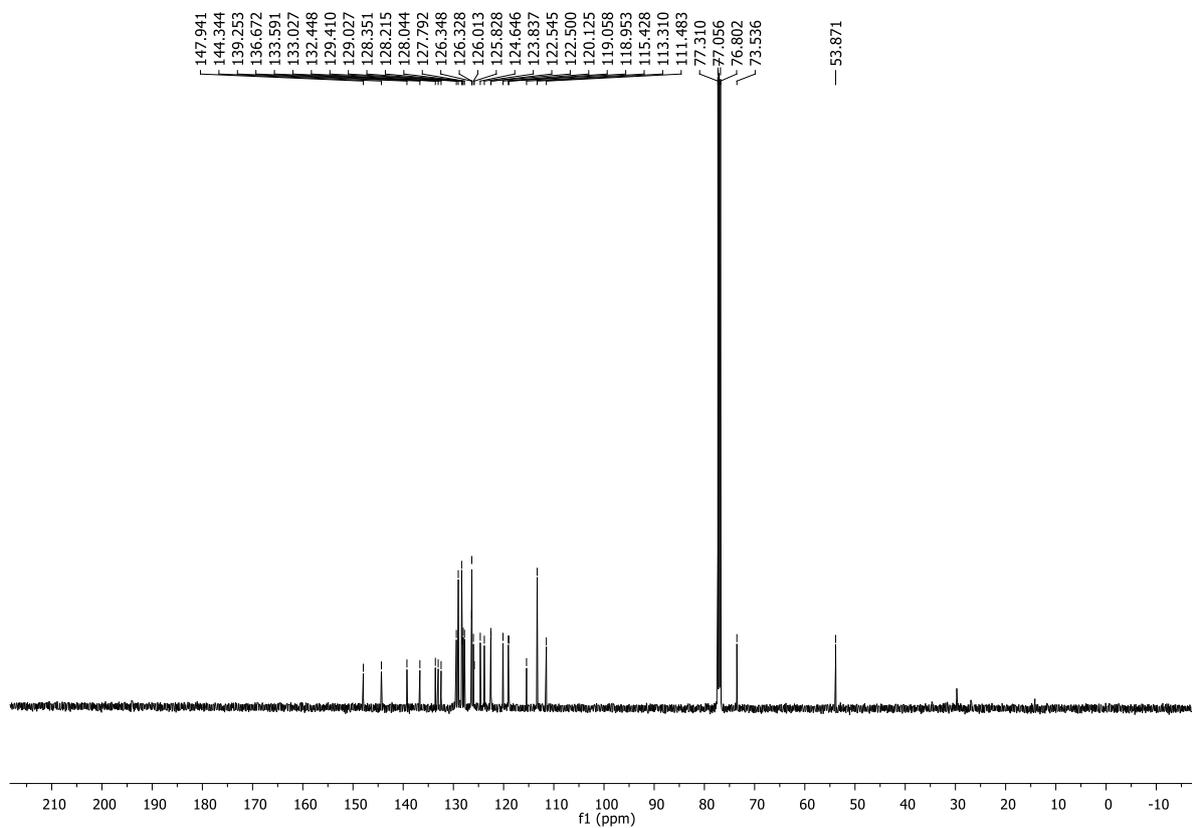


Figure S66. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5ba**

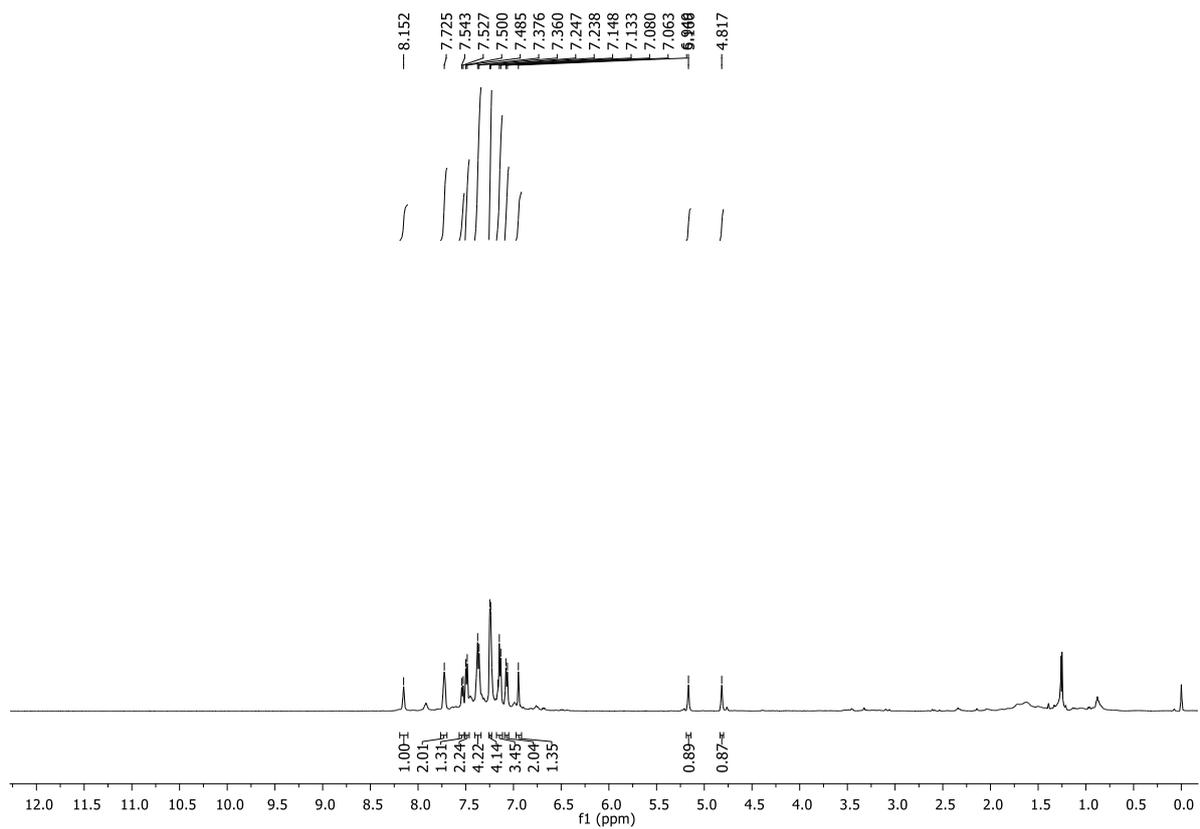


Figure S67. ^1H (500 MHz, CDCl_3) of **5bb**

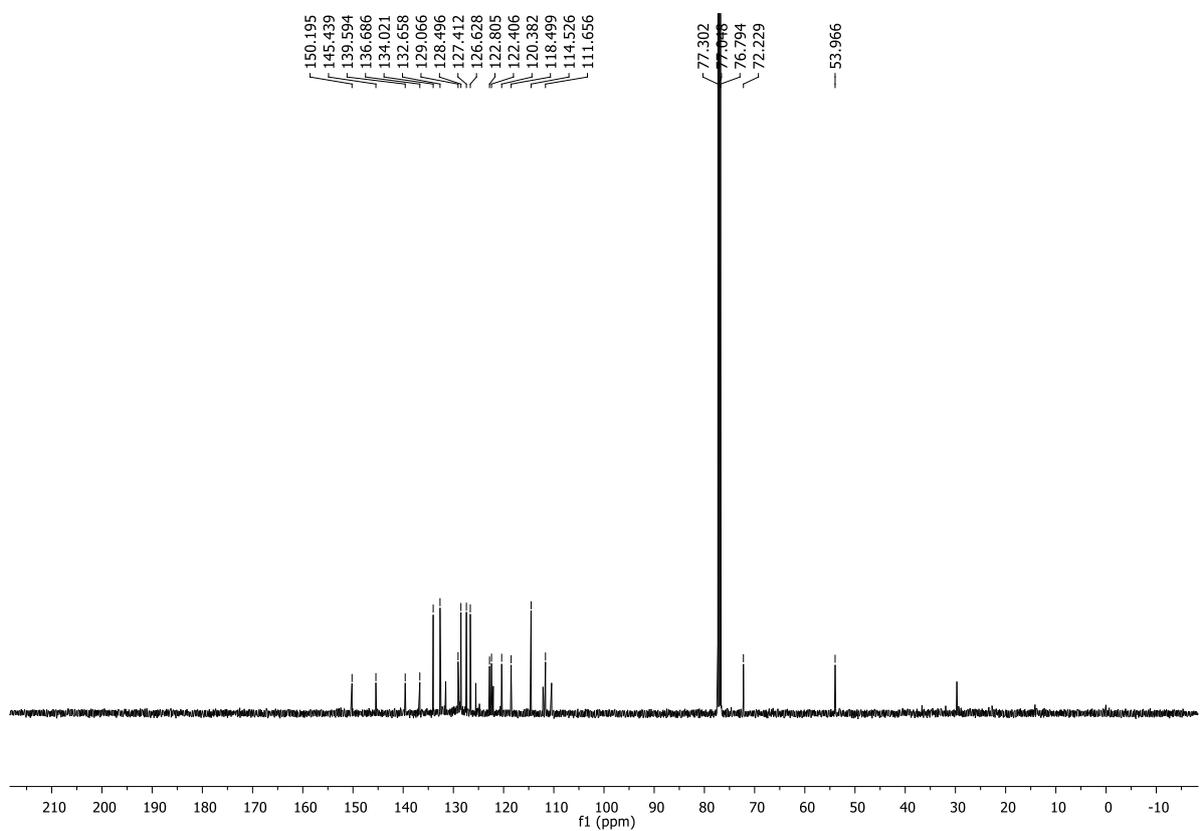


Figure S68. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5bb**

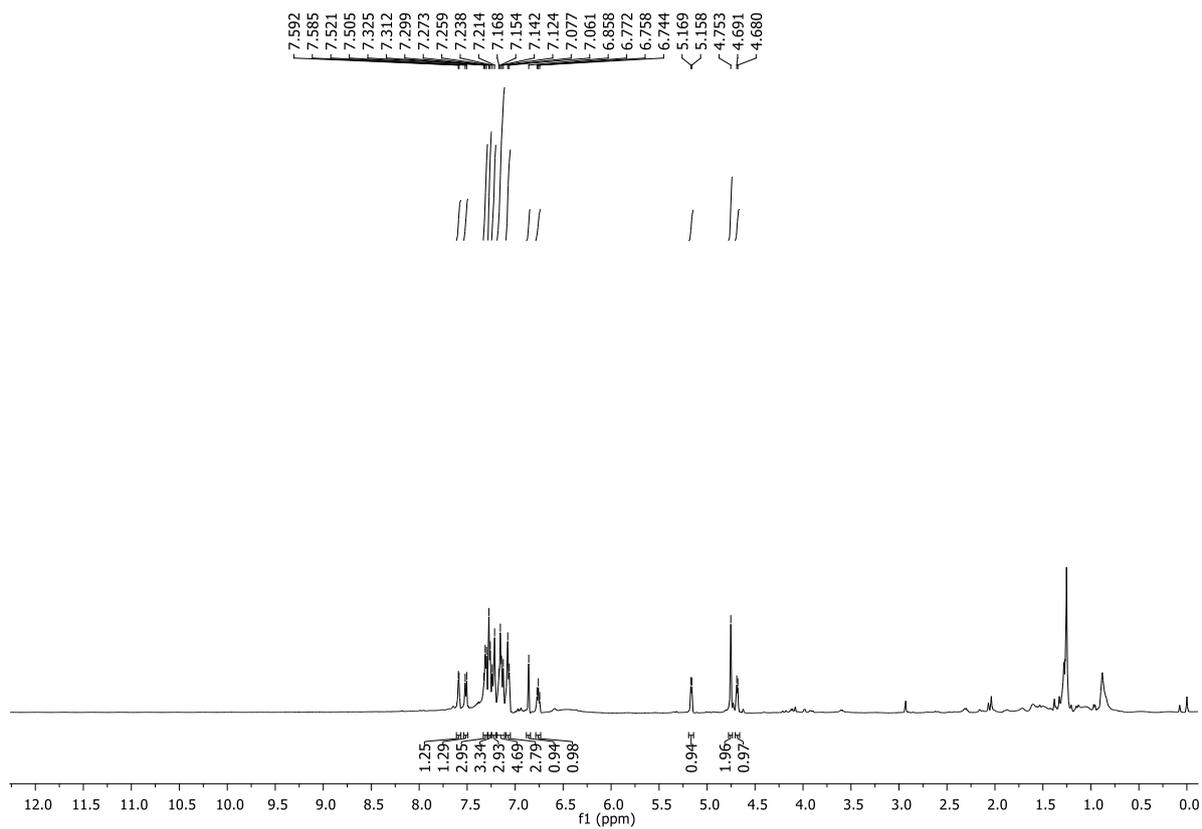


Figure S69. ^1H (500 MHz, CDCl_3) of **5qq**

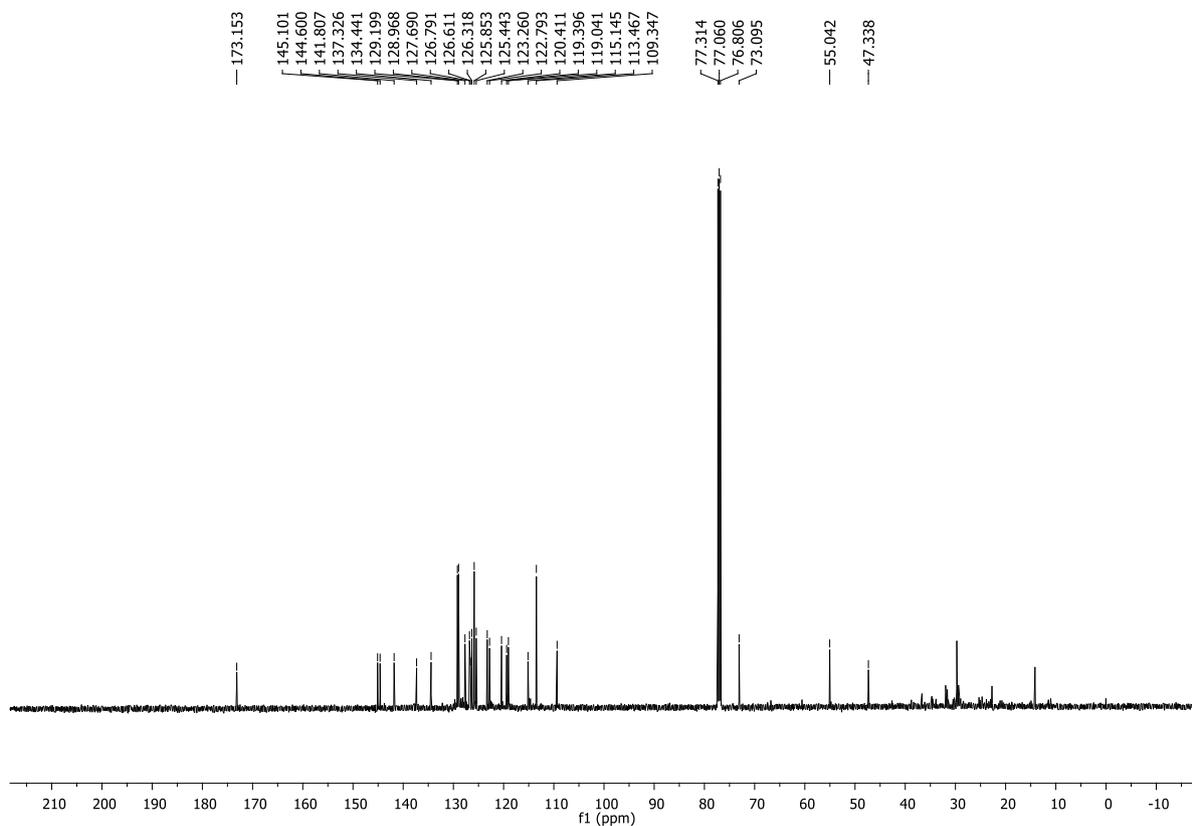
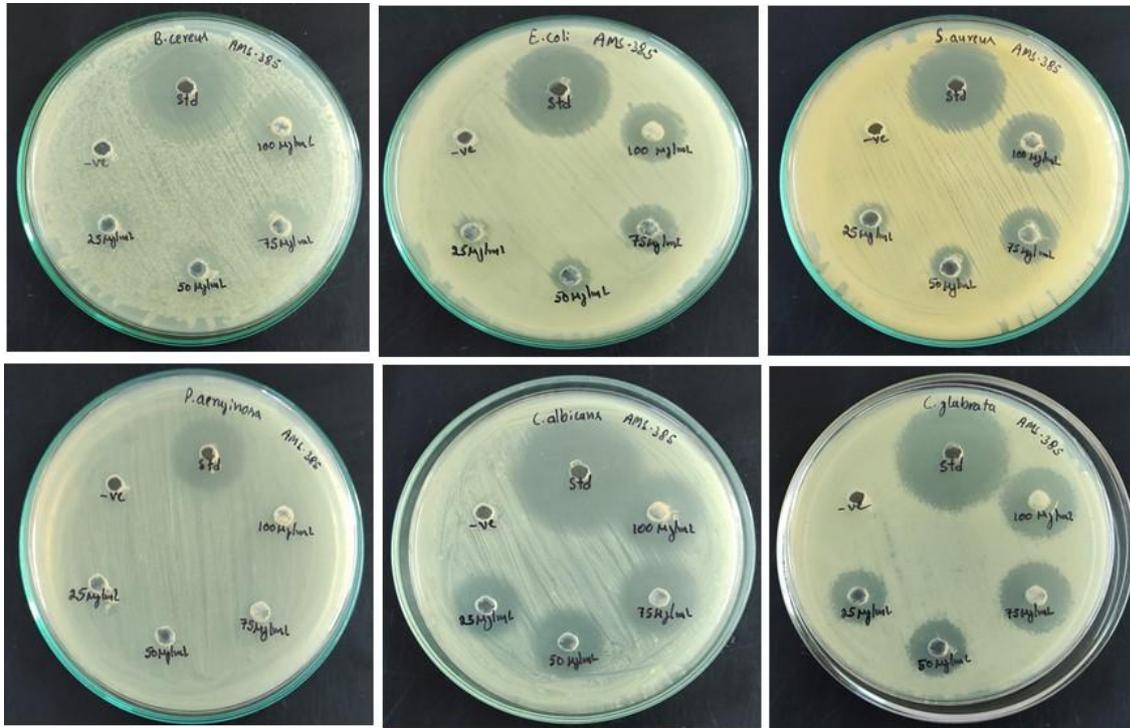


Figure S70. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) of **5qq**

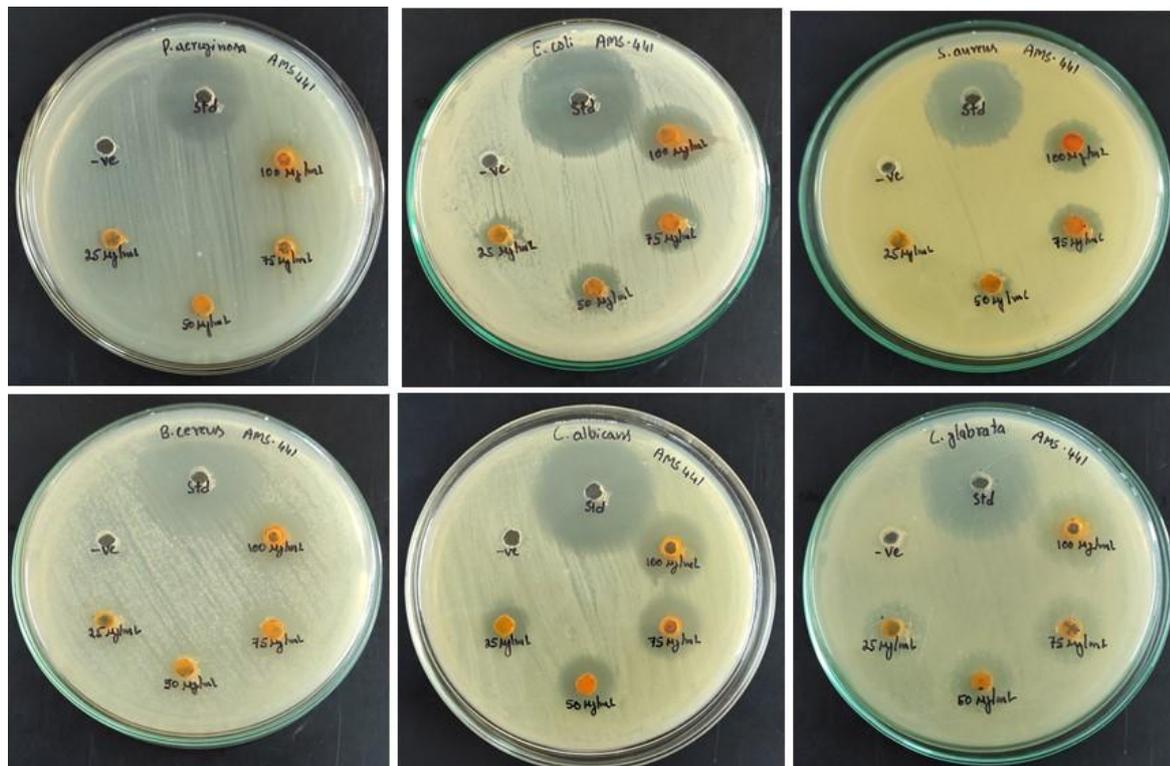
Zone of Inhibition (ZOI) of Compounds

Figures S71.

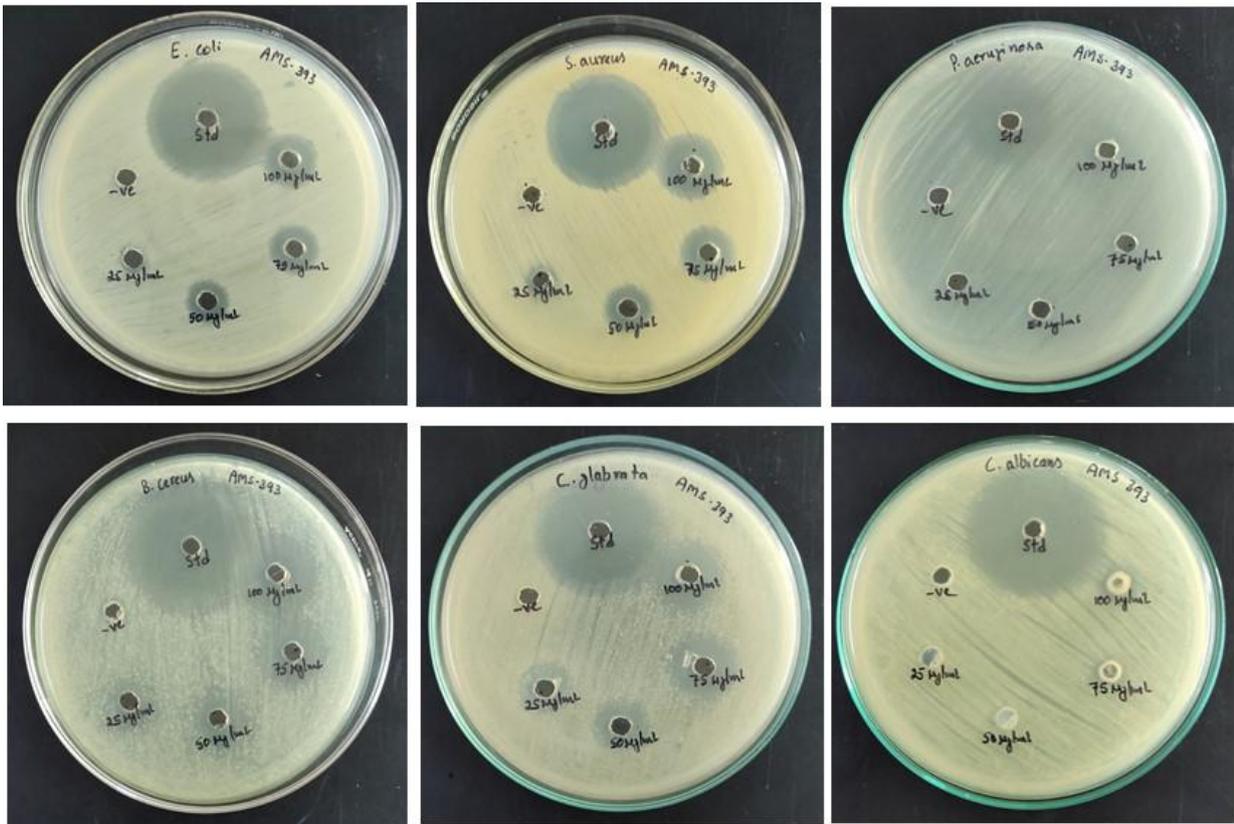
Zone of inhibition of compound 5c



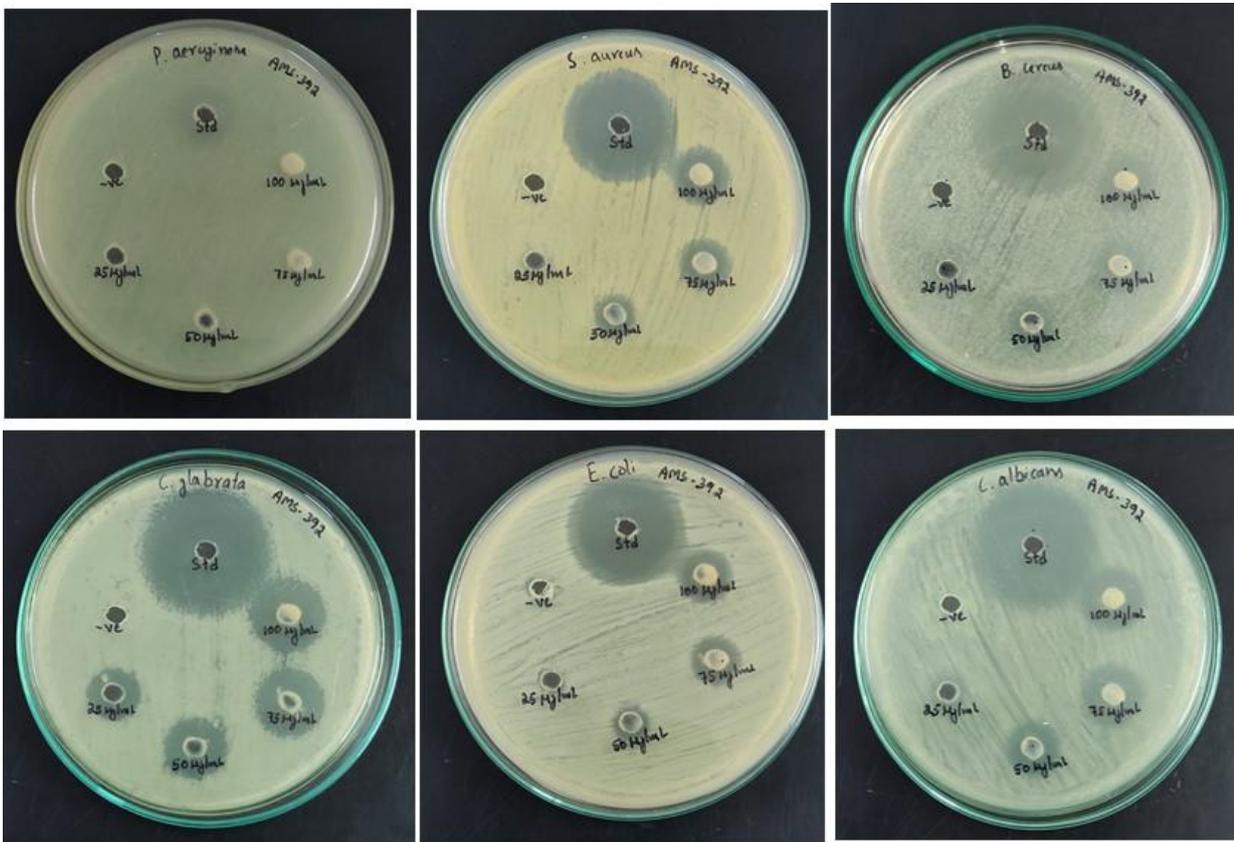
Zone of inhibition of compound 5f



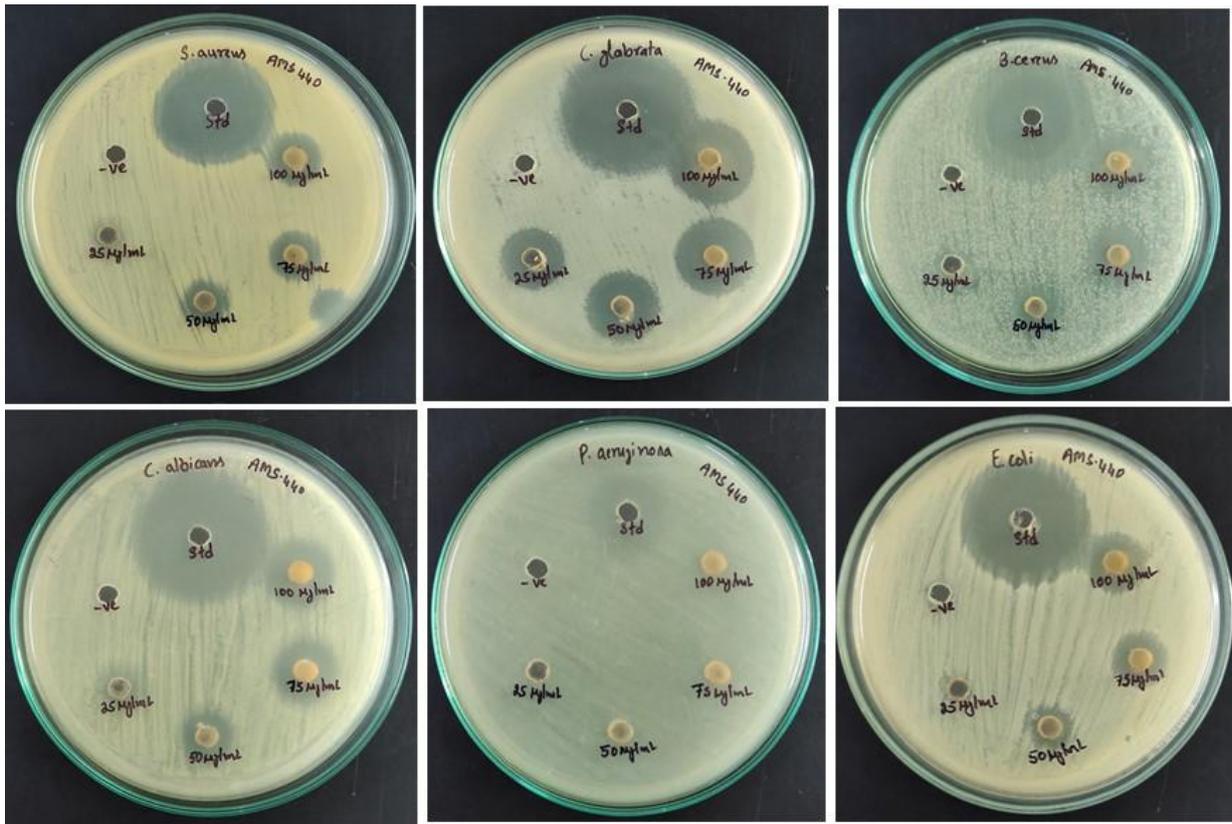
Zone of inhibition of compound 5i



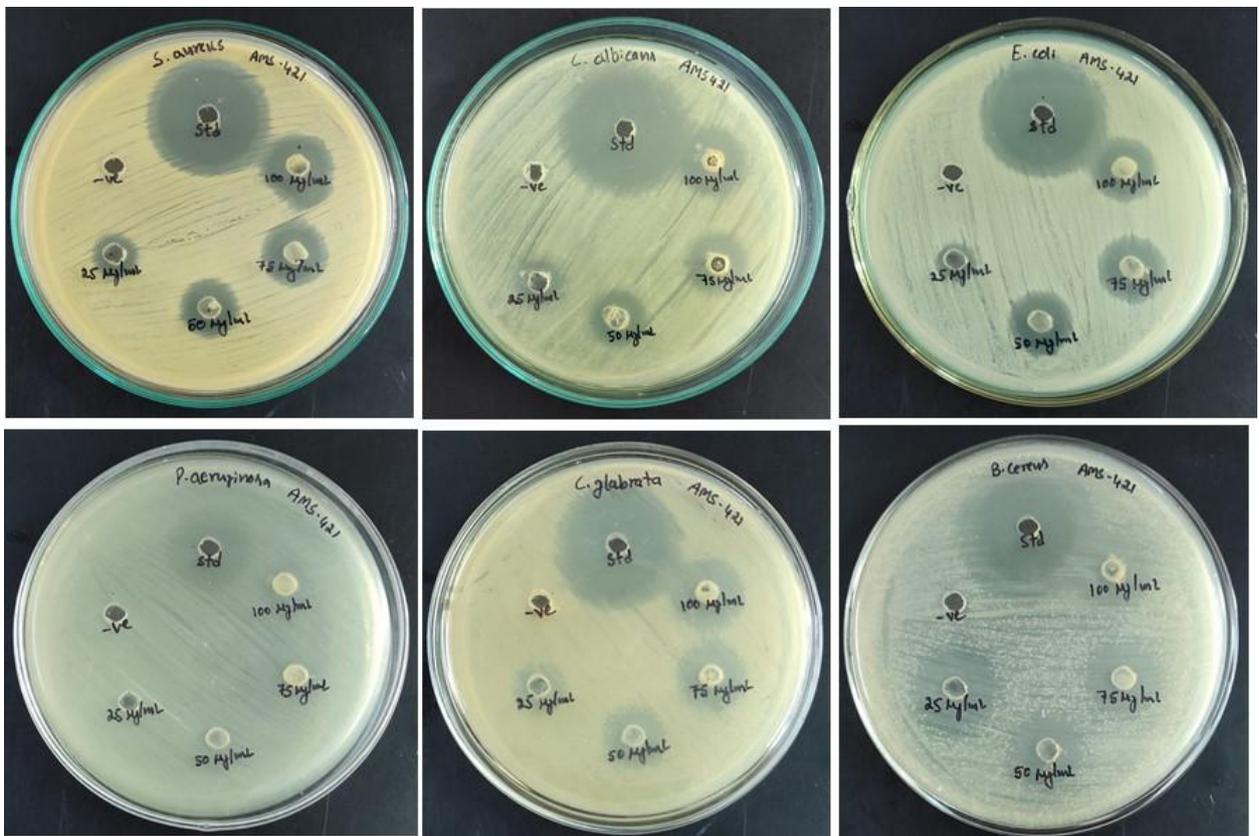
Zone of inhibition of compound 5k



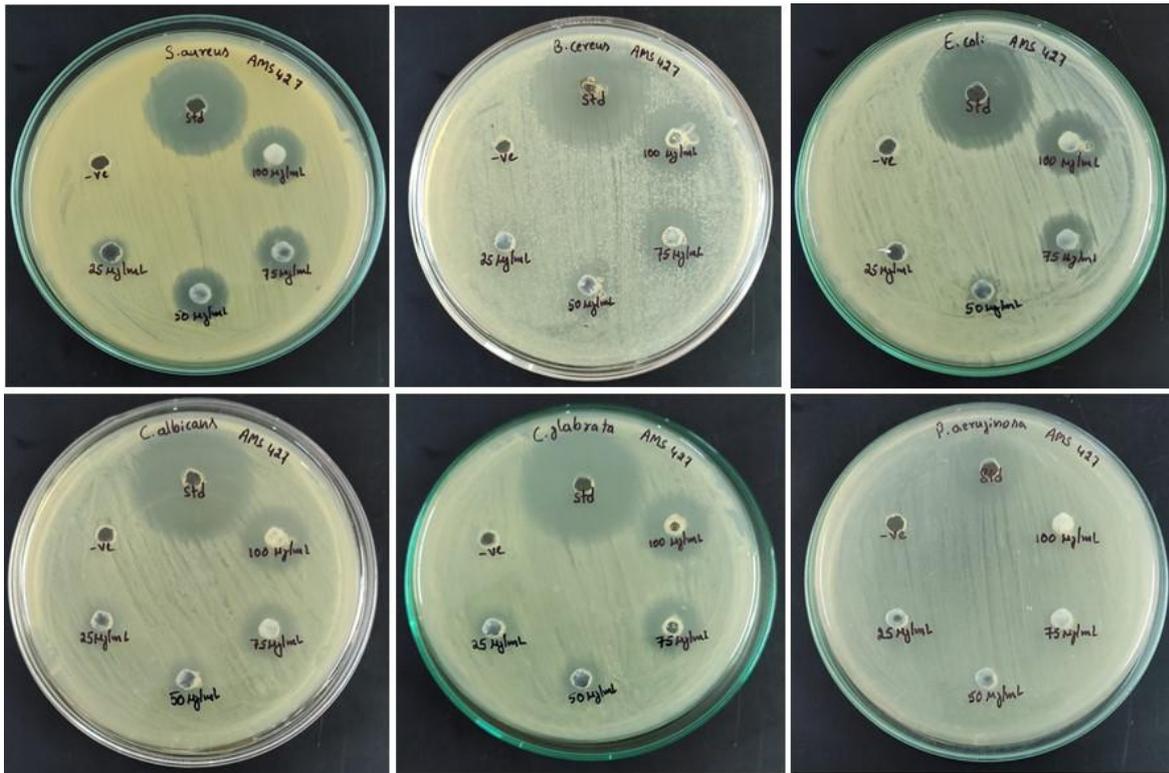
Zone of inhibition of compound 5o



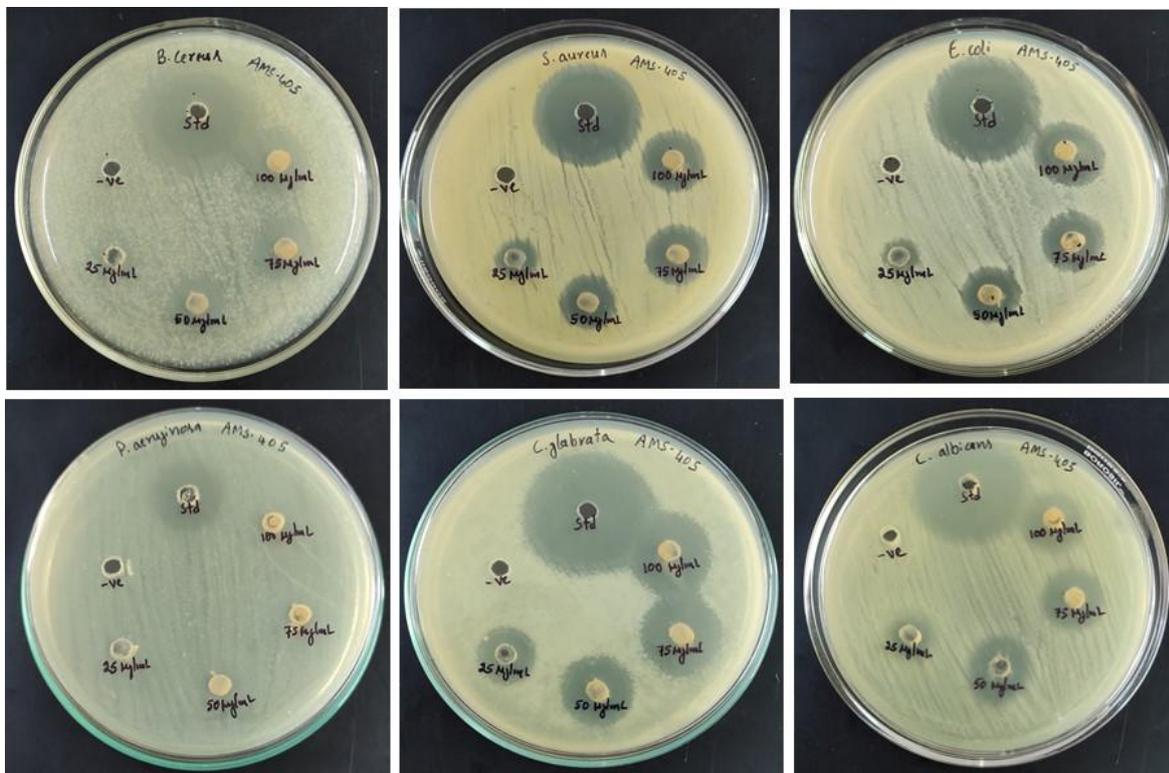
Zone of inhibition of compound 5p



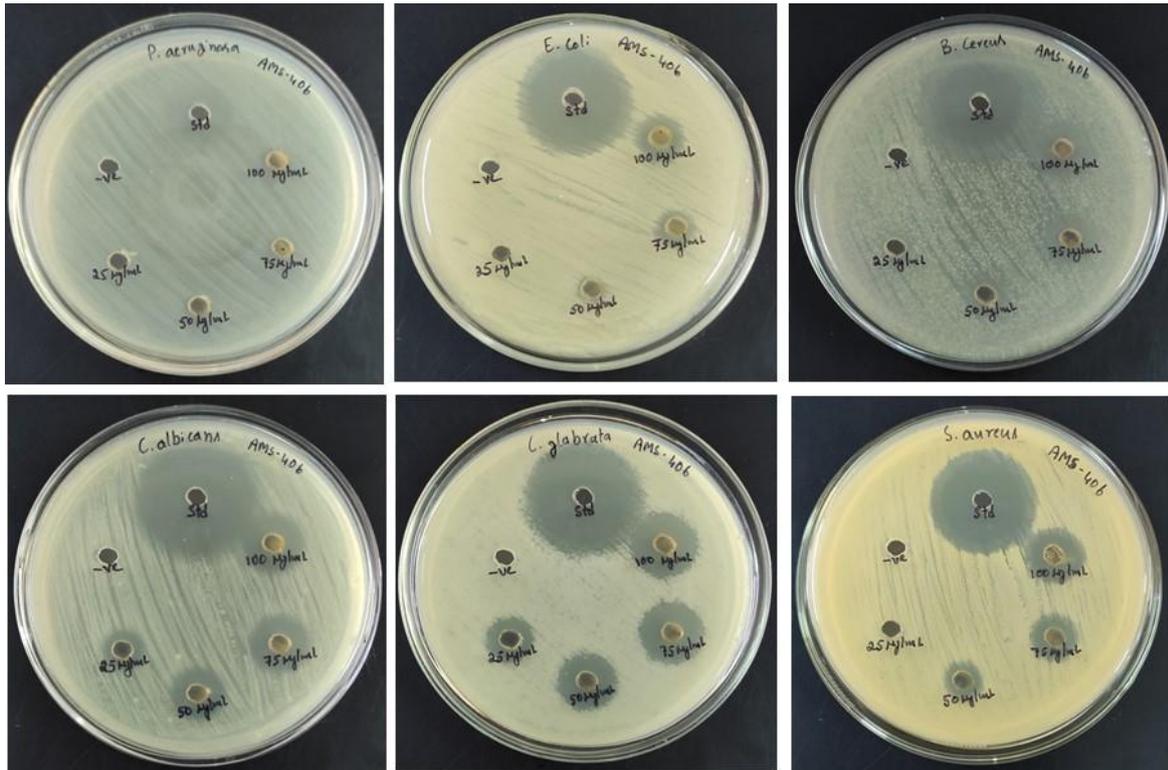
Zone of inhibition of compound 5q



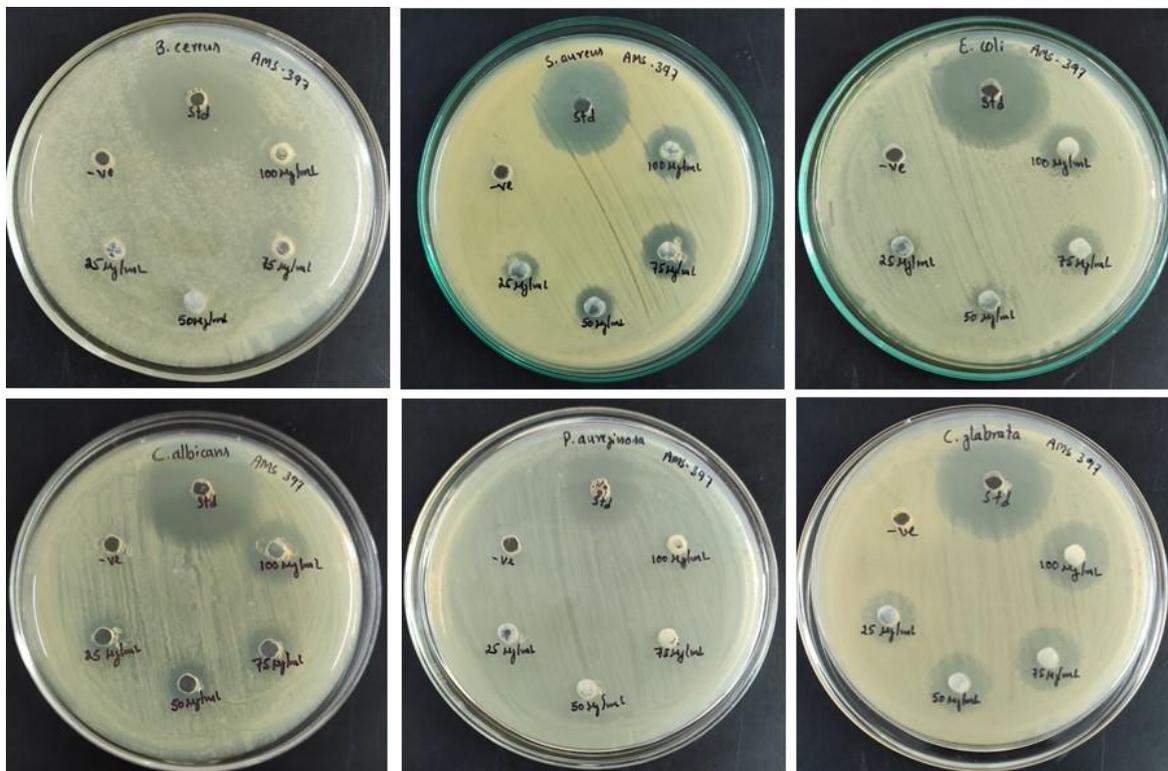
Zone of inhibition of 5s



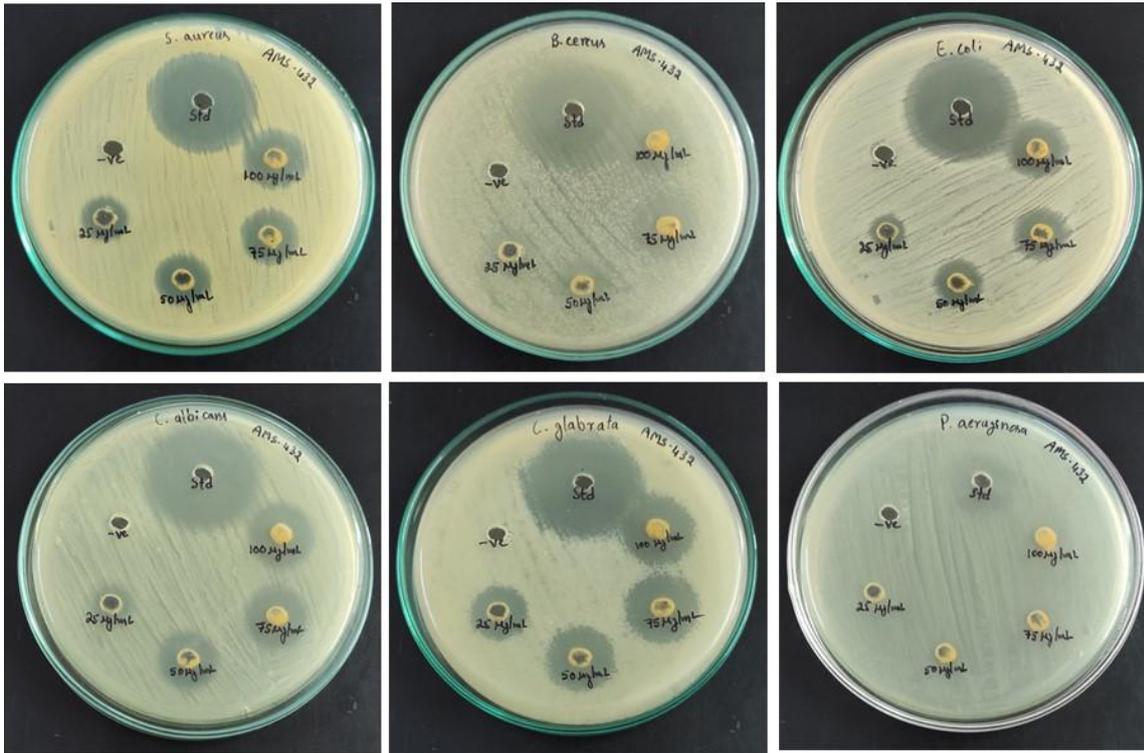
Zone of inhibition of compound 5aa



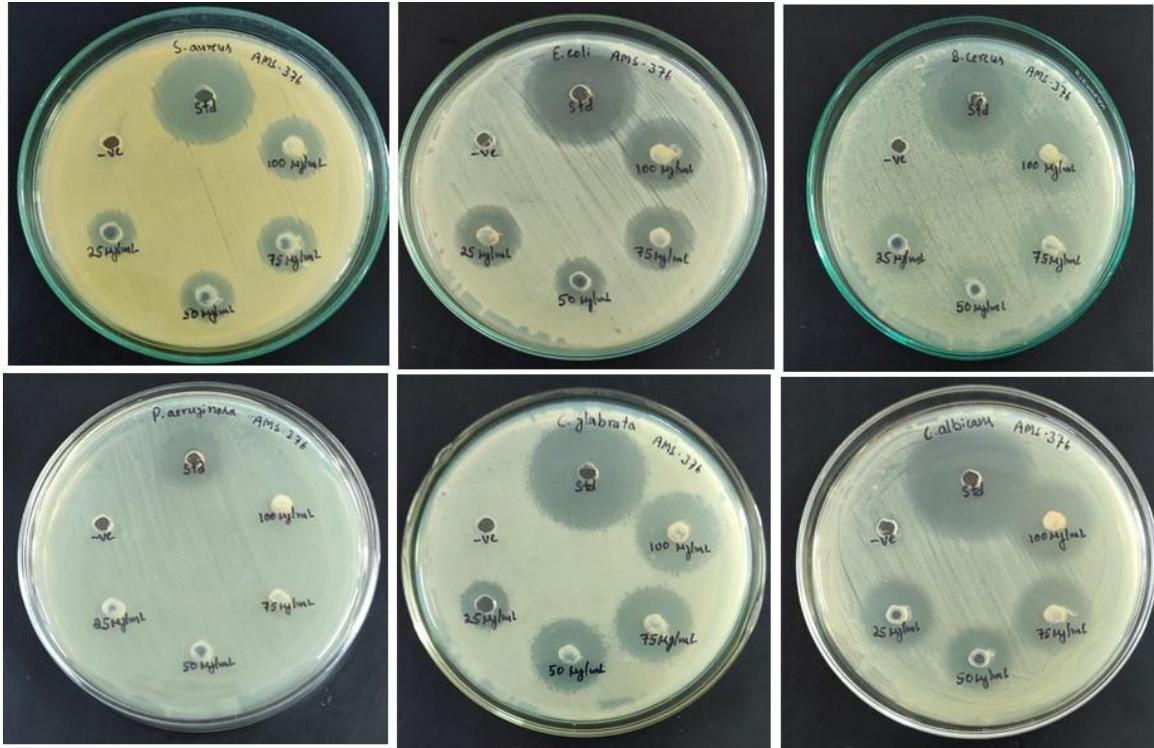
Zone of inhibition of compound 5ab



Zone of inhibition of compound 5ad



Zone of inhibition of compound 5ah



Zone of inhibition of compound 5aj

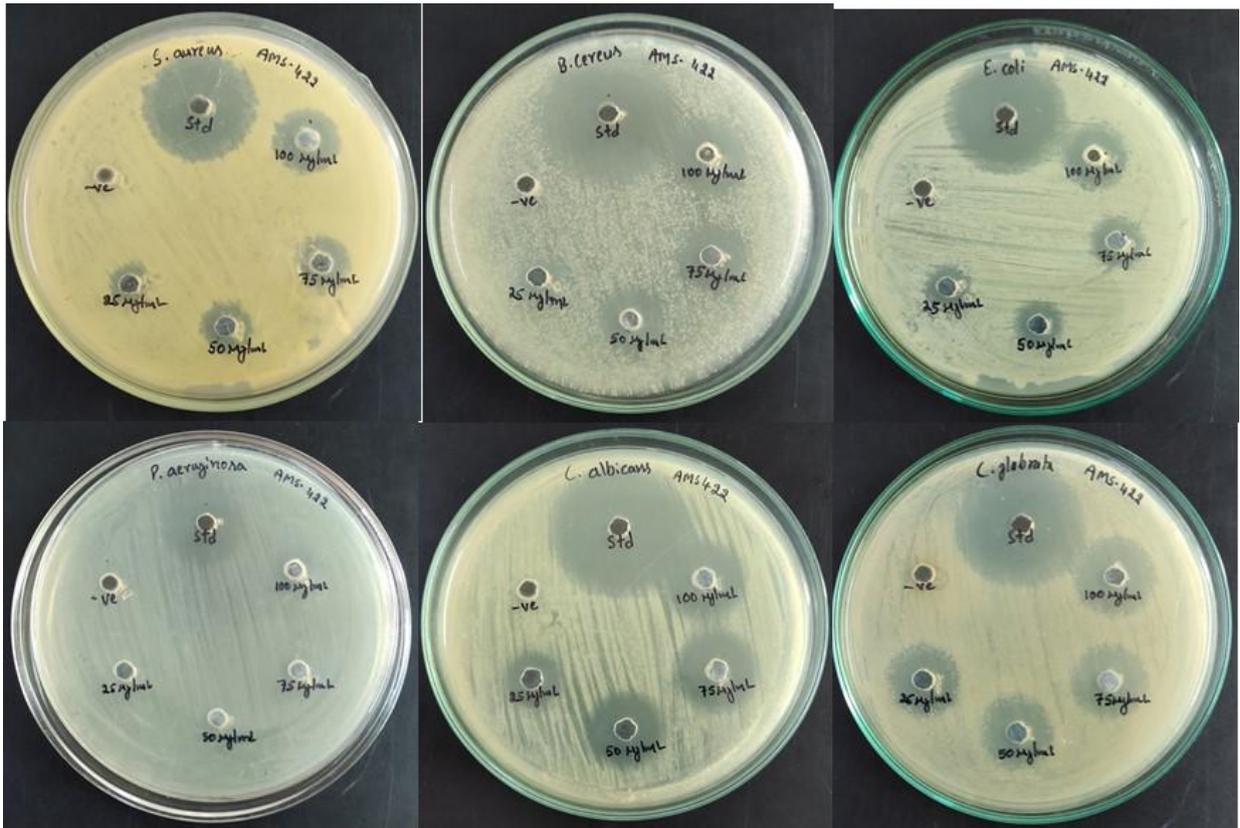
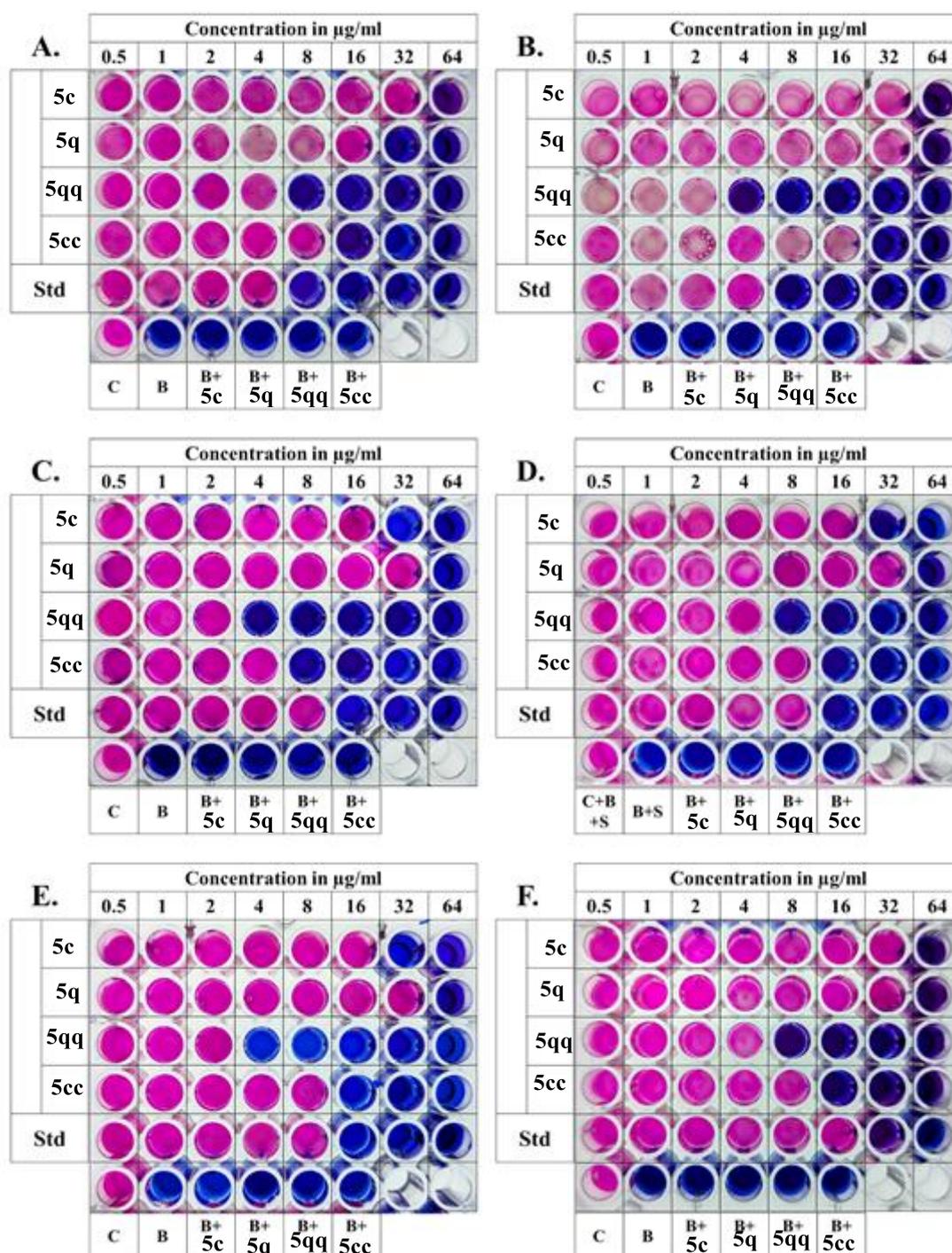


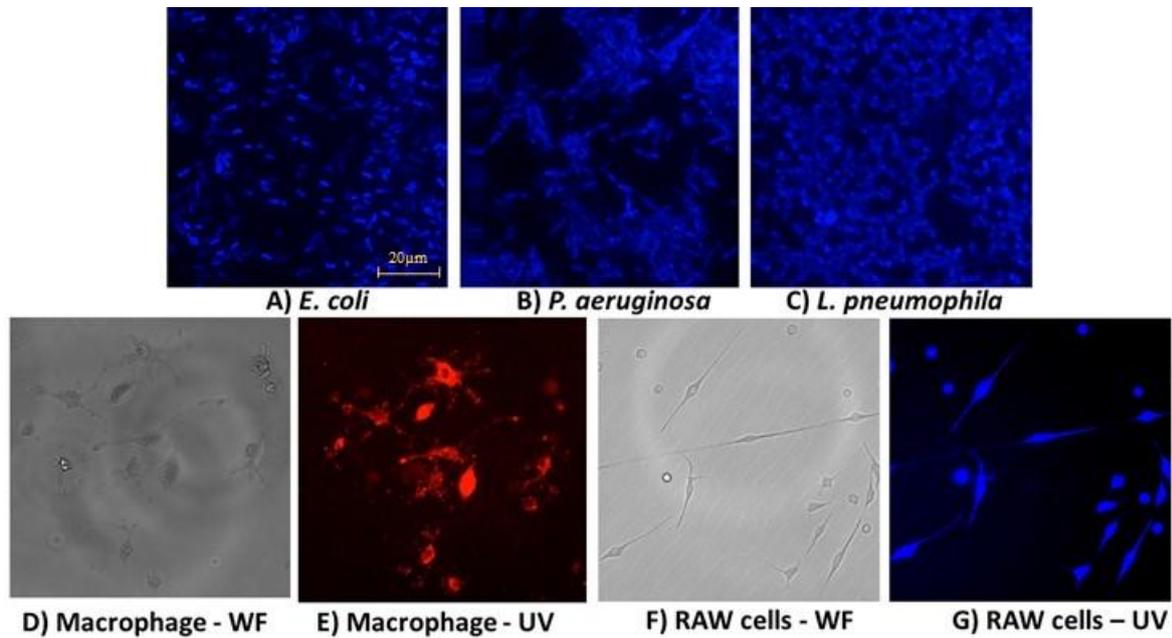
Figure S72. Minimum Inhibition Concentration (MIC) of compounds



Results of MIC of the newly synthesized compounds along with standard drug as determined by resazurin based micro-broth dilution method against A) *Escherichia coli* (ATCC 10799); B) *Pseudomonas aeruginosa* (ATCC 27853); C) *Bacillus subtilis* (MTCC 13343); D) *Staphylococcus aureus* (ATCC 6538); E) *Candida albicans* (ATCC 24433); F) *Candida glabrata*. (B: Broth only; C: Culture inoculated broth)

Fluorescence microscopy analysis

Figure S73.



(A) Bacterial localisation in *E. coli* (B) *P. aeruginosa* (C) *L. pneumophila* (D, E) cell permeability in bone marrow derived macrophages and (F, G) RAW cells (localization and puncta formation is specifically seen in the Macrophages)

Figure S74. Drug target prediction for mammalian proteins

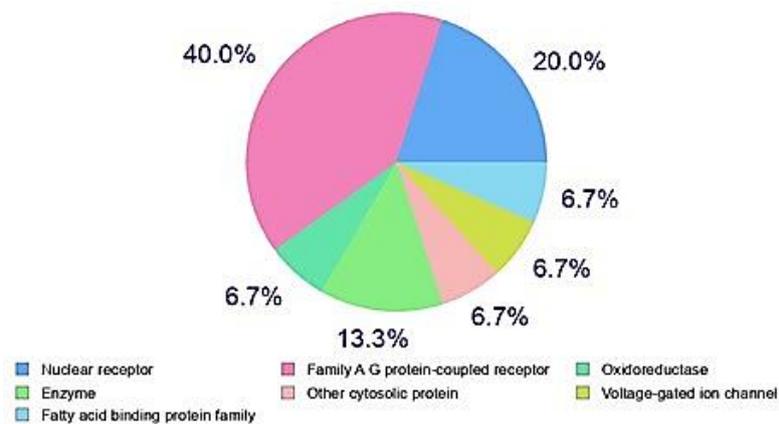
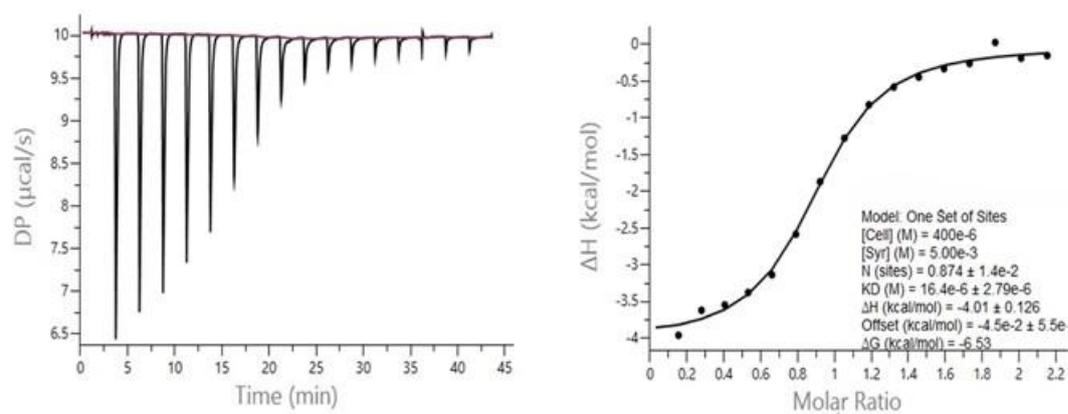
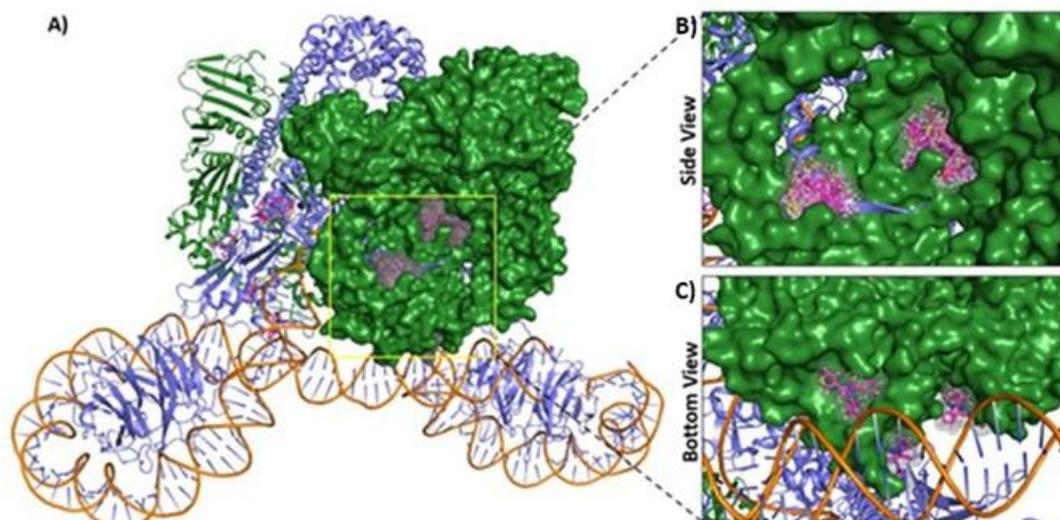


Figure S78. Isothermal titration calorimetry measurements and Molecular Docking



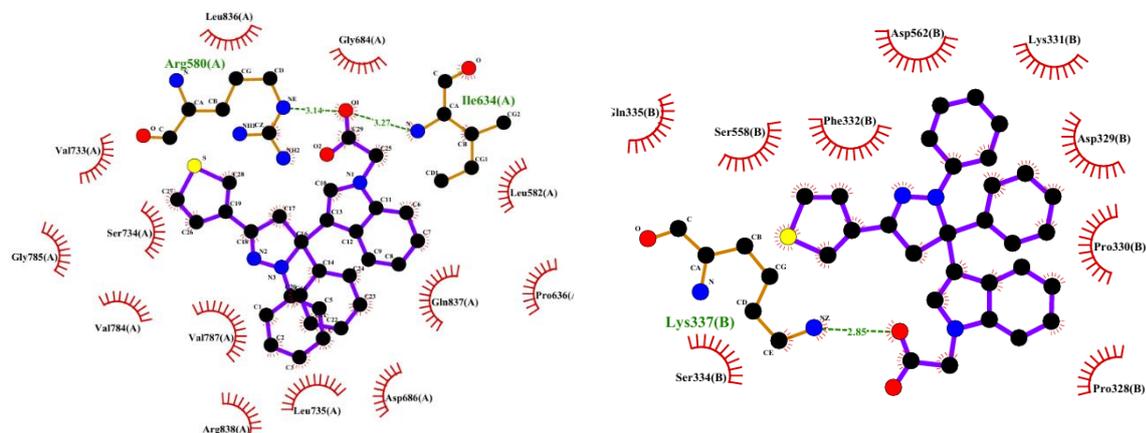
ITC results showing the 5qq interaction with the DNA Gyrase

Figure S79.



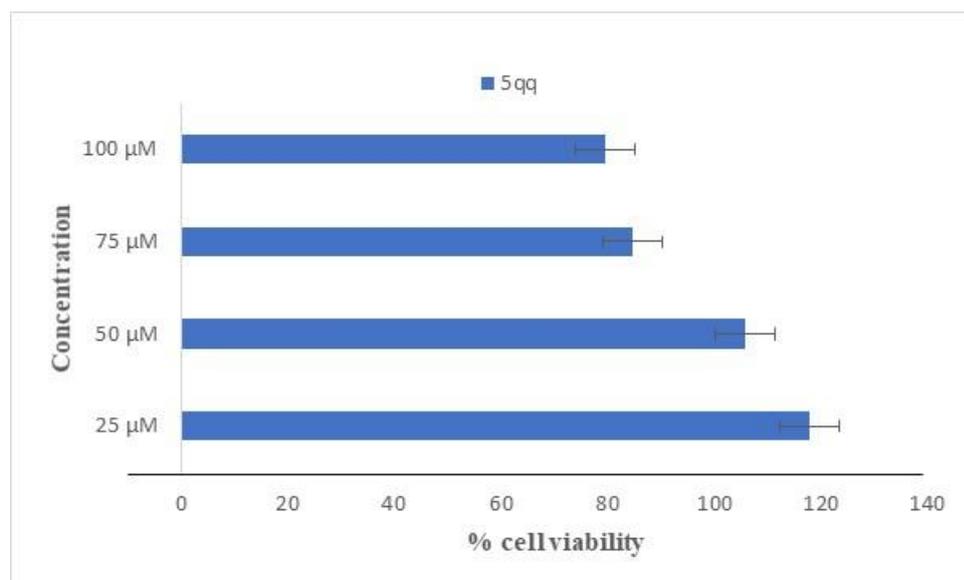
(A) The bound/docked compound **5qq** (pink) with different conformations in the DNA gyrase A and B complex within the active site or catalytic pocket where, DNA gyrase (A site) is shown with a green surface, showing that the **5qq** could effectively bind DNA gyrase in both sites and makes a larger binding interface (**B and C**).

Figure S80.



Ligplot showing the side chain interaction with DNA gyrase A/B complex in two different key interaction sites (Left-Site A and Right-Site B)

Figure S81. % Cell viability



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