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Oxidative Regioselective Amination of Chromones Exposes Potent Inhibitors of Hedgehog Signaling Pathway

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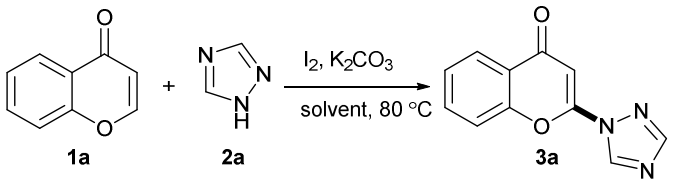
General information:

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade. Petroleum ether (bp: 40-60°C) was used for column chromatography and thin layer chromatography. Dry solvents were purified by the Solvent Purification System M-BRAUN Glovebox Technology SPS-800. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualised by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Solvent mixtures are understood as volume/volume.

^{1}H-NMR and ^{13}C-NMR were recorded on Bruker DRX300 (300 MHz), Bruker DRX400 (400 MHz), DRX500 (500 MHz) and INOVA500 (500 MHz) spectrometer in $CDCl_3$, DMF-D_7, Acetone-D_6, $(CD_3)_2SO$, CD_2Cl_2. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz). Mass spectra was recorded on gas chromatograph (HP 6890) with mass detector (HP 5973), coupled to a J&W fused silica GC column (GC column: stationary phase DB-5ms, 25 m × 0.202 mm× 0.33 µm) using the program (acquisition time: 3 min, Initial temperature: 50 °C, Initial time: 1 min, Rate of temperature increasing: 40 °C/min, Final temperature: 300 °C, Final time: 15 min) or on a HPLC-MS system from HP Agilent 1100 series binary pump together with a reversed-phase HPLC column (CC250/4 Nucleosil 120-5 C4 by Macherey-Nagel, flow 1.0 mL/min, from 90% A to 100% B over 15 min; A = 0.1% HCOOH in H_2O, B = 0.1% HCOOH in CH_3CN). High resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm × 1 mm × 1.9 µm). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1})

Optimization of reaction conditions



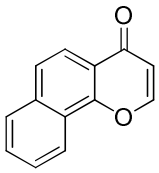
1a 2a 3a

Entry	Solvent	I_2 (equiv)	**2a** (equiv)	Time [h]	Yield [%][b]
1	Dioxane	1.5	2.0	24	5
2	DME	1.5	2.0	24	57
3	CH_3CN	1.5	2.0	24	50
4	*t*-AmOH	1.5	2.0	24	38
5	EtOAc	1.5	2.0	24	29
6	Toluene	1.5	2.0	24	n.d.
7	DCE	1.5	2.0	24	n.d.
8	THF	1.5	2.0	24	30
9	**DMF**	**1.5**	**2.0**	**17**	**78**
10	DMF	1.1	2.0	17	25
11	DMF	1.3	2.0	17	68
12	DMF	1.8	2.0	17	52
13	DMF	2.0	2.0	17	15
14[c]	DMF	1.5	2.0	24	traces
15[d]	DMF	1.5	2.0	24	traces
16	DMF	1.5	1.5	24	63
17	DMF	1.5	2.5	10	76
18	DMF	1.5	3.0	10	72
19	DMF	-	2.0	24	n.d.
20[e]	DMF	1.5	2.0	24	n.d.

[a] Conditions: **1a** (1 equiv.), **2a** (1.5 - 3 equiv.), I_2, anhydrous K_2CO_3 (5 equiv), in solvent (0.2M). [b] Isolated yields [c] Using Br_2 instead of I_2 [d] Using *N*-iodosuccinimide instead of I_2. [e] Without K_2CO_3. DMF = *N*,*N*-dimethylformamide, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxy ethane, *t*-AmOH = *tert*-amyl alcohol, THF = tetrahydrofuran, n.d. = not determined.

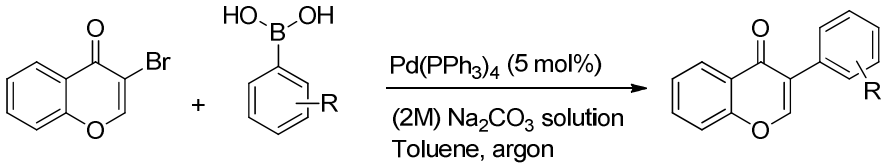
We began our studies using chromone (**1a**) and 1,2,4-triazole (**2a**) with molecular iodine as oxidant and a base such as K_2CO_3 in 1,4-dioxane (entry 1). However, under these conditions the cross-coupled product **3a** was obtained in only 5% yield. To our delight, formation of the desired product **3a** increased to 57% when 1,2-dimethoxyethane was used as the solvent (entry 2). Acetonitrile also gave product **3a** in 50% yield (entry 3). Other solvents such as *tert*-amyl alcohol, THF and EtOAc offered poor yields (entries 1-9). Almost no conversion was detected using toluene or DCE as solvent. Gratifyingly, when the reaction was conducted in DMF, the product yield raised to 78%. Afterwards, we optimized the amount of oxidant (entries 9-13). It was observed that the optimal loading of molecular iodine is important in order to get a high yield of **3a**. The best yield (78%) was archived using 1.5 equiv of iodine. Increase in iodine loading led to over-iodinated products and reduction of desired product amount. It is notable that the application of other electrophilic sources such as bromine or *N*-iodosuccinimide instead of molecular iodine did not lead to **3a** (entries 14, 15). Next, we examined the optimal loading of **2a**. We found that two or more equivalents of **2a** allowed the best conversion (entries 9, 16-18). In the control experiments it was found that in absence of iodine or potassium carbonate there was no product formation (entries 19, 20). It was interesting to observe that even though it was possible to form mixtures of several regioisomeric products; selective formation of only one isomer was observed.

Analytical data of chromones:

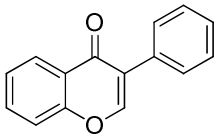


Prepared according to literature known procedure. [1] The analytical data was identical with the reported literature.

Procedure for the synthesis of isoflavones:[2]

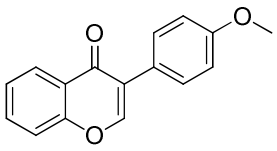


3-Bromochromone (0.5 mmol), phenylboronic acid (1.5 mmol) and (2M) Na_2CO_3 solution were taken in toluene (3 mL) in a 25 mL round bottom flask. The solvent was purged with argon for 30 min to remove the dissolved oxygen from solvent. Then $Pd(PPh_3)_4$ (0.025 mmol) was added to the reaction mixture and it was refluxed for 18-24 h. After completion of the reaction, it was allowed to come to room temperature. The reaction mixture was extracted with ethyl acetate, washed with water, brine and dried over anhydrous $MgSO_4$. Purified by normal silica gel column chromatography (20-30% ethyl acetate/pet. Ether) to afford the corresponding isoflavones in 70-85% isolated yield.



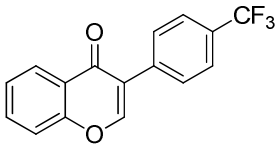
3-Phenyl-4*H*-chromen-4-one[3]

Prepared according to general procedure. The analytical data was identical with the reported literature.



3-(4-Methoxyphenyl)-4*H*-chromen-4-one[4]

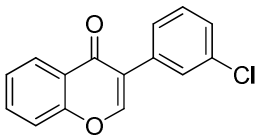
Prepared according to general procedure. The analytical data was identical with the reported literature.



3-(4-(Trifluoromethyl)phenyl)-4*H*-chromen-4-one

Prepared according to general procedure.

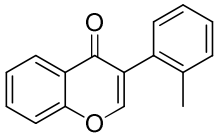
Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.8 Hz, 1H), 8.07 (s, 1H), 7.79 – 7.65 (m, 5H), 7.59 – 7.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.97, 156.31, 153.64, 135.69, 134.11, 129.36, 126.55, 125.72, 125.58 (q, *J* = 3.7 Hz), 124.49 (d, *J* = 16.9 Hz), 118.26.



3-(3-Chlorophenyl)-4*H*-chromen-4-one

Prepared according to general procedure.

Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.04 (s, 1H), 7.74 – 7.66 (m, 1H), 7.58 (s, 1H), 7.54-7.41 (m, 3H), 7.40 – 7.29 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.03, 156.26, 153.48, 134.45, 134.00, 133.68, 129.85, 129.06, 128.43, 127.22, 126.51, 125.61, 124.53, 124.35, 118.22.

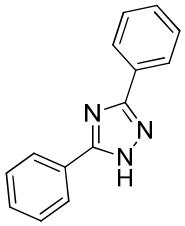


3-(*o*-Tolyl)-4*H*-chromen-4-one[5]

Prepared according to general procedure. The analytical data was identical with the reported literature.

Procedure for the synthesis of 3,5-disubstituted 1,2,4-triazoles:[6]

A mixture of nitrile (3 mmol), hydrazide (1 mmol), and anhydrous K_2CO_3 (0.5 mmol) were taken in 2 mL of nBuOH and heated in sealed tube at 150 °C for 3-16h. Once reaction finished reaction mixture was filtered, concentrated and purified by silica gel column chromatography with 30-40% EtOAc/Pet. Ether eluent.



3,5-Diphenyl-1*H*-1,2,4-triazole

White solid; ^{1}H NMR (400 MHz, MeOH-D_4) δ 8.07 (d, *J* = 6.6 Hz, 4H), 7.58 – 7.42 (m, 6H); ^{13}C NMR (101 MHz, MeOH-D_4) δ 131.07, 129.97, 127.59.

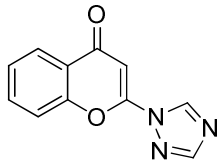
General procedure for the coupling between chromones and azoles:

Procedure A:

Chromone (0.2 mmol) and triazole (0.4 mmol) were dissolved in a 4 mL screw-capped vial with 1 mL of anhydrous DMF. Then molecular iodine (0.3 mmol), followed by anhydrous K_2CO_3 were added at room temperature. The reaction mixture was stirred at 80 °C for 2-20h. The reaction mixture was quenched with saturated solution of sodium thiosulphate and extracted with dichloromethane, washed with water, brine, dried over anhydrous Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the pure product.

Procedure B:

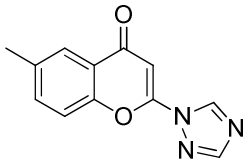
Chromone (0.2 mmol) and triazole (0.22 mmol) were dissolved in a 4 mL screw-capped vial with 1 mL of anhydrous DMF. Then molecular iodine (0.3 mmol) was added at room temperature and the reaction mixture was stirred at 80 °C for 12 h. Azole (0.4-0.8 mmol) followed by anhydrous K_2CO_3 were added to the reaction mixture and the reaction was continued for 3-14 h. Then the reaction mixture was quenched with saturated solution of sodium thiosulphate and extracted with dichloromethane, washed with water, brine, dried over anhydrous Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the pure product.



2-(1*H*-1,2,4-Triazol-1-yl)-4*H*-chromen-4-one [7], **3a**

Prepared by following general procedure A.

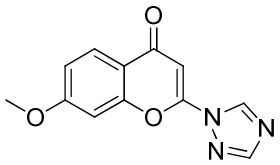
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.18 (s, 1H), 7.80 – 7.73 (m, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.73, 154.16, 154.09, 153.03, 142.14, 134.58, 126.54, 126.38, 123.81, 117.66, 98.32; FT-IR: $\tilde{\nu}$ = 3105, 2923, 1631, 1572, 1510, 1462, 1421, 1401, 1366, 1281, 1240, 1151, 1065, 1018 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{11}H_8O_2N_3$: 214.06110 found: 214.06118.



6-Methyl-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3b

Prepared by following general procedure A.

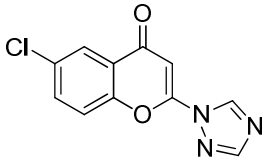
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.17 (s, 1H), 8.01 (d, *J* = 1.1 Hz, 1H), 7.55 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.92, 154.01, 152.96, 152.39, 142.17, 136.71, 135.68, 125.78, 123.41, 117.38, 98.16, 21.09; FT-IR: $\tilde{\nu}$ = 3079, 2921, 1629, 1583, 1506, 1483, 1437, 1410, 1360, 1270, 1243, 1227, 1119 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}O_2N_3$: 228.07675 found: 228.07684.



6-Methoxy-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3c

Prepared by following general procedure A using triazole in 3 equiv.

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.17 (s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.82 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.15, 164.78, 155.91, 154.04, 152.83, 142.10, 127.74, 117.55, 115.15, 100.64, 98.34, 56.19; FT-IR: $\tilde{\nu}$ = 3086, 2923, 1654, 1631, 1611, 1571, 1512, 1467, 1438, 1409, 1353, 1285, 1264, 1231, 1164, 1130, 1082, 1062 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}O_3N_3$: 244.07167 found: 244.07165.

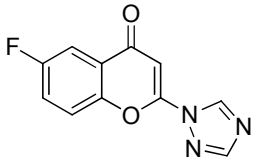


6-Chloro-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3e

Prepared by following general procedure A.

White solid; ^{1}H NMR (400 MHz, DMF-D_7) δ 9.63 (s, 1H), 8.53 (s, 1H), 8.05 (d, *J* = 2.5 Hz, 1H), 8.01 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (101 MHz, DMF-D_7) δ 176.24, 154.58, 154.16, 153.18, 144.71, 134.99, 131.53, 125.01, 124.59, 121.02, 97.24; FT-IR: $\tilde{\nu}$ = 3089, 2923, 1655, 1606, 1569, 1509, 1435, 1409, 1361, 1275,

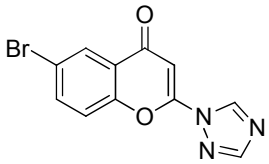
1224, 1062 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{11}H_7O_2N_3{}^{35}Cl$: 248.02213 found: 248.02225; $[M+H]^+$ $C_{11}H_7O_2N_3{}^{37}Cl$: 250.01918 found: 250.01894.



6-Fluoro-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3f

Prepared by following general procedure A.

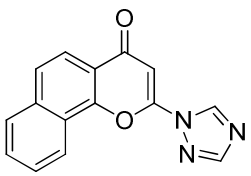
White solid; ^1H NMR (400 MHz, DMF-D_7) δ 9.63 (s, 1H), 8.53 (s, 1H), 7.93 (dd, *J* = 9.1, 4.3 Hz, 1H), 7.90 – 7.77 (m, 2H), 6.77 (s, 1H); ^{13}C NMR (101 MHz, DMF-D_7) δ 176.63, 160.26 (d, *J* = 245.4 Hz), 154.54, 154.19, 150.93 (d, *J* = 1.3 Hz), 144.59, 125.17 (d, *J* = 7.3 Hz), 122.92 (d, *J* = 25.8 Hz), 121.34 (d, *J* = 8.6 Hz), 110.32 (d, *J* = 24.3 Hz), 96.71; FT-IR: $\tilde{\nu}$ = 3089, 1655, 1621, 1587, 1511, 1475, 1413, 1363, 1335, 1277, 1224, 1126, 1064 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{11}H_7O_2N_3F$: 232.05168 found: 232.05172.



6-Bromo-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3d

Prepared by following general procedure A.

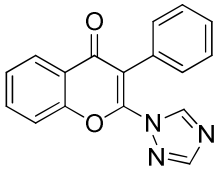
White solid; ^1H NMR (400 MHz, DMF-D7) δ 9.63 (s, 1H), 8.53 (s, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 8.13 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 6.79 (s, 1H); ^{13}C NMR (101 MHz, DMF-D7) δ 176.11, 154.59, 154.15, 153.62, 144.63, 137.80, 127.75, 125.37, 121.21, 119.21, 97.32; FT-IR: $\tilde{\nu}$ = 3091, 1654, 1603, 1567, 1508, 1461, 1435, 1410, 1360, 1321, 1275, 1222, 1122, 1064 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{11}H_7O_2N_3{}^{79}Br$: 291.97162 found: 291.97151; $[M+H]^+$ $C_{11}H_7O_2N_3{}^{81}Br$: 293.96957 found: 293.96941.



2-(1*H*-1,2,4-Triazol-1-yl)-4*H*-benzo[*h*]chromen-4-one, 3g

Prepared by following general procedure A.

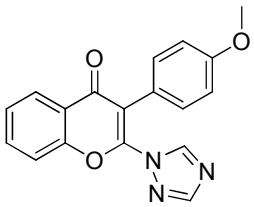
White solid; ^{1}H NMR (400 MHz, DMF-D_7) δ 9.95 (s, 1H), 8.97 (d, *J* = 7.7 Hz, 1H), 8.56 (s, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.10 (s, 2H), 7.96 – 7.81 (m, 2H), 6.91 (s, 1H); ^{13}C NMR (101 MHz, DMF-D_7) δ 177.18, 154.46, 153.82, 151.90, 144.71, 136.50, 130.19, 128.63, 128.19, 126.65, 123.67, 123.08, 120.35, 120.24, 98.53; FT-IR: $\tilde{\nu}$ = 3118, 3083, 1650, 1624, 1505, 1467, 1442, 1411, 1377, 1346, 1293, 1223, 1160, 1136, 1119, 1086 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{10}O_2N_3$: 264.07675 found: 264.07666.



3-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3h

Prepared by following general procedure A.

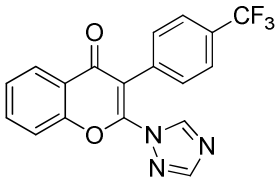
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.81 – 7.73 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.23-7.15 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.16, 154.55, 153.05, 149.63, 145.34, 134.86, 129.94, 129.48, 129.12, 129.07, 126.80, 126.40, 123.36, 118.19, 117.94; FT-IR: $\tilde{\nu}$ = 3122, 1645, 1614, 1576, 1501, 1466, 1424, 1380, 1347, 1289, 1271, 1241, 1209, 1174, 1150, 1126, 1110 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{12}O_2N_3$: 290.09240 found: 290.09242.



3-(4-Methoxyphenyl)-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3j

Prepared by following general procedure A.

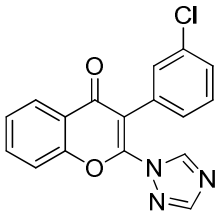
Light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 7.56 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 7.13 – 7.08 (m, 2H), 6.91 – 6.84 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 177.34, 160.00, 154.41, 152.91, 149.34, 145.34, 134.72, 131.08, 126.67, 126.24, 123.20, 121.23, 118.09, 117.59, 114.61, 55.32; FT-IR: $\tilde{\nu}$ = 2959, 1644, 1607, 1578, 1510, 1465, 1422, 1381, 1348, 1293, 1271, 1239, 1218, 1175, 1125, 1109, 1058, 1032 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{14}O_3N_3$: 320.10297 found: 320.10318.



2-(1*H*-1,2,4-Triazol-1-yl)-3-(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one, 3l

Prepared by following general procedure A.

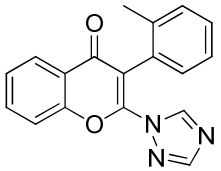
White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.10 (s, 1H), 8.06 (s, 1H), 7.83-7.77(m, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.60-7.57 (m, 1H), 7.55 – 7.50 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.72 , 154.39 , 153.28, 149.76 , 144.93, 135.14, 133.39 , 130.89 (q, *J* = 32.6 Hz), 130.51, 126.72 (d, *J* = 13.0 Hz), 125.79 (q, *J* = 3.8 Hz), 125.01, 123.11, 122.85, 118.12 , 116.62; FT-IR: $\tilde{\nu}$ = 3120, 1643, 1613, 1579, 1503, 1468, 1422, 1381, 1330, 1291, 1273, 1241, 1124, 1106, 1071 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{11}O_2N_3F_3$: 358.07979 found: 358.07989.



3-(3-Chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)-4H-chromen-4-one, 3k

Prepared by following general procedure A.

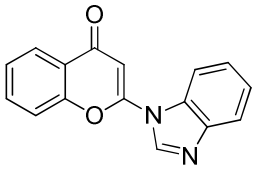
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 2H), 7.83 – 7.73 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.22 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.76, 154.32, 153.16, 149.65, 145.07, 135.04, 134.77, 131.17, 130.17, 130.12, 129.16, 128.00, 126.68, 126.56, 123.05, 118.11, 116.55; FT-IR: $\tilde{\nu}$ = 3121, 3065, 1641, 1611, 1595, 1572, 1502, 1464, 1432, 1414, 1378, 1347, 1289, 1273, 1241, 1217, 1172, 1151, 1119, 1083, 1058 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{11}O_2N_3{}^{35}Cl$: 324.05343 found: 324.05371; $[M+H]^+$ $C_{17}H_{11}O_2N_3{}^{37}Cl$: 326.05048 found: 326.05067.



3-(*o*-Tolyl)-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, 3i

Prepared by following general procedure A.

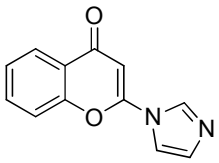
Light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.82-7.76 (m, 1H), 7.63 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 7.3, 1.2 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.20 (ddd, *J* = 7.3, 4.5, 1.2 Hz, 1H), 7.08 – 7.04 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.00, 154.59, 152.89, 149.72, 144.88, 137.54, 134.78, 130.89, 130.15, 129.52, 129.37, 126.71, 126.70, 126.36, 123.06, 118.15, 116.43, 19.73; FT-IR: $\tilde{\nu}$ = 3135, 1631, 1612, 1575, 1501, 1467, 1427, 1383, 1349, 1333, 1272, 1240, 1214, 1175 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{14}O_2N_3$: 304.10805 found: 304.10815.



2-(1*H*-Benzo[d]imidazol-1-yl)-4*H*-chromen-4-one[7], **4g**

Prepared by following general procedure A.

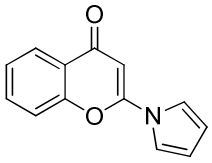
Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.27 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.81 – 7.73 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.41 (m, 3H), 6.60 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.94, 154.63, 153.92, 144.19, 139.95, 134.51, 131.07, 126.44, 126.26, 125.75, 124.97, 123.59, 121.48, 117.73, 112.61, 99.16; FT-IR: $\tilde{\nu}$ = 3106, 1643, 1626, 1607, 1569, 1509, 1451, 1410, 1313, 1234, 1181, 1122 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{11}O_2N_2$: 263.08150 found: 263.08156.



2-(1*H*-imidazol-1-yl)-4*H*-chromen-4-one[7], **4a**

Prepared by following general procedure B.

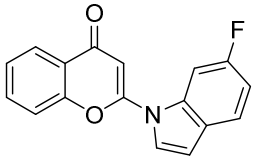
Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.18 (m, 2H), 7.78 – 7.70 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.28 – 7.24 (m, 1H), 6.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.94, 154.35, 153.46, 134.92, 134.52, 131.90, 126.43, 126.13, 123.46, 117.75, 116.03, 97.23; ; FT-IR: $\tilde{\nu}$ = 3117, 1626, 1568, 1462, 1425, 1367, 1304, 1264, 1056 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_9O_2N_2$: 213.06585 found: 213.06587.



2-(1*H*-Pyrrol-1-yl)-4H-chromen-4-one[7], **4e**

Prepared by following general procedure B using pyrrole in 4 equiv.

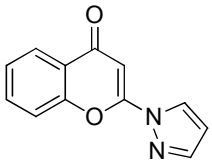
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.36 – 7.30 (m, 2H), 6.47 – 6.40 (m, 2H), 6.34 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.36, 155.97, 154.36, 133.95, 126.05, 125.96, 123.48, 118.39, 117.58, 113.72, 94.88; FT-IR: $\tilde{\nu}$ = 3118, 1620, 1567, 1538, 1486, 1461, 1419, 1388, 1335, 1311, 1276, 1059 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}O_2N$: 212.07061 found: 212.06995.



2-(5-Fluoro-1*H*-indol-1-yl)-4*H*-chromen-4-one, 4f

Prepared by following general procedure B using pyrrole in 3 equiv.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.92 (dd, *J* = 9.1, 4.3 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.60-7.55 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.11 (td, *J* = 9.1, 2.5 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.42 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.14, 159.34 (d, *J* = 240.1 Hz), 156.50, 154.50, 134.00, 131.72 (d, *J* = 10.1 Hz), 126.21, 126.13, 126.05, 125.99, 123.58, 117.48, 114.44 (d, *J* = 9.4 Hz), 112.68 (d, *J* = 25.6 Hz), 108.82 (d, *J* = 4.0 Hz), 107.30 (d, *J* = 23.8 Hz), 97.43; FT-IR: $\tilde{\nu}$ = 3118, 3065, 1620, 1563, 1467, 1446, 1417, 1372, 1341, 1326, 1302, 1267, 1200, 1148, 1124 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{11}O_2NF$: 280.07683 found: 280.07615.

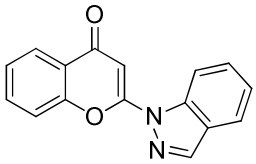


2-(1*H*-pyrazol-1-yl)-4*H*-chromen-4-one[7], **4b**

Prepared by following general procedure B.

Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.19 (m, 2H), 7.83 (d, *J* = 0.9 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.59

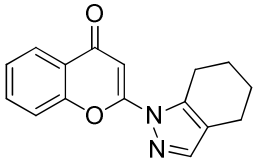
– 6.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.09, 155.40, 154.15, 144.46, 133.98, 127.87, 126.18, 126.02, 123.83, 117.55, 109.76, 96.41; FT-IR: $\tilde{\nu}$ = 3102, 1632, 1528, 1463, 1414, 1395, 1296, 1220, 1125, 1053, 1036 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_9O_2N_2$: 213.06585 found: 213.06594.



2-(1*H*-indazol-1-yl)-4*H*-chromen-4-one[7], **4d**

Prepared by following general procedure B.

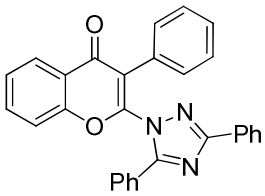
Light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 – 8.21 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.51 – 7.44 (m, 1H), 7.40 – 7.33 (m, 1H), 6.92 (s, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 177.88, 158.10, 154.21, 140.45, 138.75, 133.70, 129.34, 126.63, 126.29, 126.01, 124.08, 124.03, 121.96, 117.38, 113.62, 96.62; FT-IR: $\tilde{\nu}$ = 3093, 3056, 1622, 1606, 1564, 1464, 1413, 1371, 1344, 1267, 1182 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{11}O_2N_2$: 263.08150 found: 263.08153.



2-(4,5,6,7-Tetrahydro-1*H*-indazol-1-yl)-4*H*-chromen-4-one, 4c

Prepared by following general procedure B.

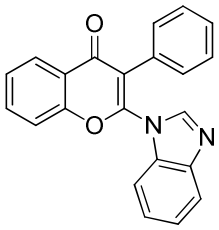
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.86 (s, 1H), 7.69 – 7.62 (m, 1H), 7.51 – 7.37 (m, 2H), 6.74 (s, 1H), 2.75 (t, *J* = 6.3 Hz, 2H), 2.63 (t, *J* = 6.1 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.81 – 1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.02, 155.73, 155.64, 154.13, 133.64, 126.10, 125.75, 124.30, 123.88, 120.99, 117.43, 95.06, 23.78, 23.06, 20.73; FT-IR: $\tilde{\nu}$ = 3089, 2937, 1624, 1569, 1479, 1467, 1418, 1389, 1375, 1329, 1300, 1253, 1206, 1155 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{15}O_2N_2$: 267.11280 found: 267.11230.



2-(3,5-Diphenyl-1*H*-1,2,4-triazol-1-yl)-3-phenyl-4*H*-chromen-4-one, 4k

Prepared by following general procedure A.

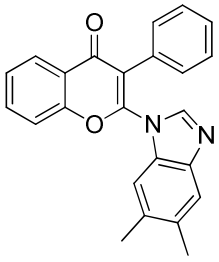
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.27 – 8.19 (m, 2H), 7.83 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.46 (m, 4H), 7.44 – 7.36 (m, 1H), 7.29 – 7.12 (m, 5H), 7.04 (t, *J* = 7.7 Hz, 2H), 6.70 – 6.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.33, 163.44, 157.43, 154.89, 150.75, 134.86, 130.88, 130.24, 129.96, 129.29, 128.83, 128.77, 128.70, 128.23, 128.17, 127.80, 127.09, 126.82, 126.47, 126.32, 123.57, 121.73, 118.56; FT-IR: $\tilde{\nu}$ = 3062, 1652, 1633, 1481, 1461, 1445, 1393, 1371, 1283, 1267, 1219, 1164, 1127, cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{29}H_{20}O_2N_3$: 442.15500 found: 442.15446.



2-(1*H*-benzo[d]imidazol-1-yl)-3-phenyl-4*H*-chromen-4-one, 4h

Prepared by following general procedure A.

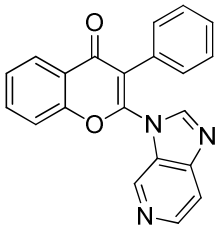
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.67 – 7.60 (m, 2H), 7.59 – 7.48 (m, 2H), 7.41 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 7.21 (dd, *J* = 7.0, 2.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.20, 154.40, 150.72, 142.99, 141.82, 134.58, 132.35, 129.97, 129.76, 129.04, 128.79, 126.84, 126.24, 124.99, 124.21, 123.36, 120.93, 117.69, 117.02, 112.17; FT-IR: $\tilde{\nu}$ = 3058, 1627, 1575, 1496, 1467, 1450, 1395, 1235, cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{15}O_2N_2$: 339.11280 found: 339.11302.



2-(5,6-Dimethyl-1*H*-benzo[*d*]imidazol-1-yl)-3-phenyl-4*H*-chromen-4-one, 4i

Prepared by following general procedure A.

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.77 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.60 – 7.47 (m, 4H), 7.39 (s, 1H), 7.33 – 7.26 (m, 3H), 7.24 – 7.18 (m, 2H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.22, 154.44, 151.04, 141.53, 141.09, 134.46, 134.30, 133.25, 130.88, 130.01, 129.98, 128.95, 128.69, 126.83, 126.13, 123.42, 120.86, 117.70, 116.79, 112.36, 20.70, 20.32; FT-IR: $\tilde{\nu}$ = 2918, 1623, 1573, 1495, 1460, 1396, 1286, 1242, 1221, cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{24}H_{19}O_2N_2$: 367.14410 found: 367.14445.

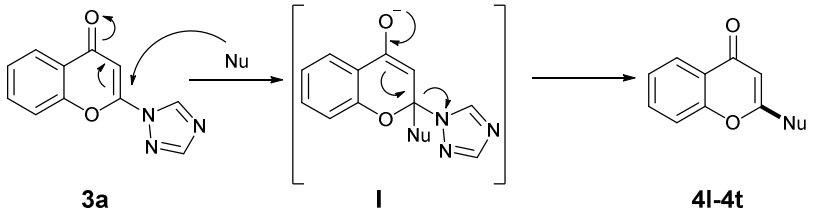


2-(3*H*-Imidazo[4,5-c]pyridin-3-yl)-3-phenyl-4*H*-chromen-4-one, 4j

Prepared by following general procedure A.

Light yellow solid; ^{1}H NMR (400 MHz, Acetone-D6) δ 8.97 (s, 1H), 8.42 (s, 1H), 8.29 – 8.12 (m, 2H), 7.93 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.67 – 7.56 (m, 1H), 7.38 – 7.19 (m, 5H); ^{13}C NMR (101 MHz, Acetone-D6) δ 177.42, 155.61, 150.67, 144.59, 144.46, 143.65, 138.43, 135.56, 131.24, 131.02, 129.15, 129.11, 126.95, 126.81, 124.23, 119.07, 108.40; FT-IR: $\tilde{\nu}$ = 3034, 1624, 1572, 1462, 1397, 1353, 1300, 1177 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{14}O_2N_3$: 340.10805 found: 340.10785.

Possible mechanism of nucleophilic substitution in 3a:



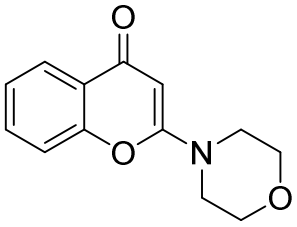
3a **I** **4l-4t**

Discussion:

The nucleophile **Nu** attacks the electrophilic C-2 position of the chromone **3a** to generate the tetrahedral intermediate **I** from which 1,2,4-triazole is eliminated to furnish the substitution product **4**.

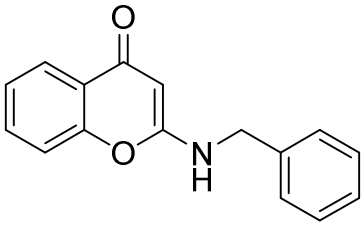
General procedure for the nucleophilic substitution in 3a.

1 equiv of 2-(1*H*-1,2,4-triazol-1-yl)-4*H*-chromen-4-one, **3a** was transfered to a vail followed by the additon of 1 mL of dry DMF. After that 2 equiv of nucleophile was added to the solution followed by the addition of required amount of base and the mixture was heated at mentioned temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with EtOAc (10 mL) and washed 3 times with H_2O (3*10 mL). The organic phase was dried by sodium sulfate and concentrated in vacuo. The pure product was obtained by column chromatography (Ethal acetate/Petroleum Ether).



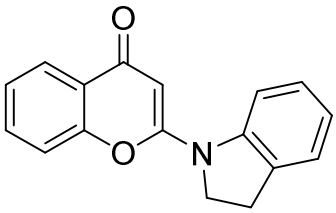
2-Morpholino-4*H*-chromen-4-one, 4l

The product was obtained as colorless solid in 71 % yield by heating the mixture of **3a** (1 equiv) and morpholine (2 equiv) at 80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59-7.55 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 5.68 (s, 1H), 3.83 (t, *J* = 5.05 Hz, 4H), 3.55 (t, *J* = 5.05 Hz, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.89, 162.82, 153.72, 132.73, 125.69, 125.18, 122.47, 116.46, 87.44, 66.11, 44.92 ppm; FT-IR: $\tilde{\nu}$ = 3428, 2919, 2859, 1609, 1550, 1482, 1248 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{13}H_{14}O_3N$: 232.09682 found: 232.09687.



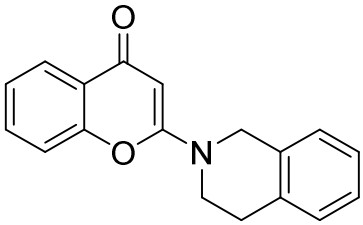
2-(Benzylamino)-4*H*-chromen-4-one, 4m

The product was obtained as colorless solid in 79 % yield by heating the mixture of **3a** (1 equiv) and benzylamine (2 equiv) in DMF at 100°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.57-7.54 (m, 1H), 7.42-7.28 (m, 7H), 5.83 (s, 1H), 4.52 (d, *J* = 5.6 Hz, 2H), 4.31 (brs, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.49, 163.87, 153.58, 136.62, 132.52, 129.03, 128.10, 127.75, 125.60, 125.07, 122.32, 116.45, 86.86, 45.90 ppm; FT-IR: $\tilde{\nu}$ = 3209, 3034, 1600, 1551, 1526, 1461, 1225 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{14}O_2N$: 252.10191 found: 252.10191.



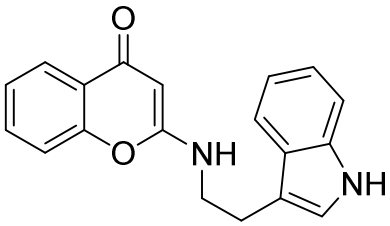
2-(Indolin-1-yl)-4*H*-chromen-4-one, 4n

The product was obtained as yellow solid in 64 % yield by heating the mixture of **3a** (1 equiv) and indoline (2 equiv) with K_2CO_3 (2 equiv) in DMF at 80°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.62 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.42-7.36 (m, 1H), 7.29-7.24 (m, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.73 (s, 1H), 4.02 (t, *J* = 8.5 Hz, 2H), 3.28 (t, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.74, 159.63, 153.88, 141.77, 132.81, 132.22, 128.02, 125.82, 125.62, 125.32, 123.72, 123.06, 116.59, 114.86, 89.65, 49.17, 27.70 ppm; FT-IR: $\tilde{\nu}$ = 3097, 3062, 2928, 1611, 1542, 1460, 1250 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{14}O_2N$: 264.10191 found: 264.10205.



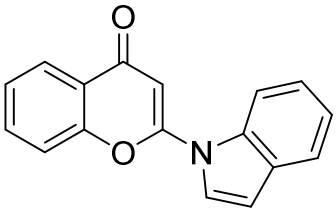
2-(1,2,3,4-Tetrahydroisoquinolin-2(1*H*)-yl)-4*H*-chromen-4-one, 4o

The product was obtained as light yellow oil in 61 % yield by heating the mixture of **3a** (1 equiv) and tetrahydroisoquinoline (2 equiv) with K_2CO_3 (1.1 equiv) in DMF at 80°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.36-7.30 (m, 2H), 7.25-7.19 (m, 4H), 5.70 (s, 1H), 4.66 (s, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 6.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.52, 162.30, 153.77, 134.47, 132.44, 131.91, 128.48, 127.50, 127.00, 126.53, 125.68, 125.01, 122.65, 116.45, 86.92, 77.58, 77.16, 76.74, 46.55, 42.70, 28.56 ppm; FT-IR: $\tilde{\nu}$ = 3027, 2924, 2226, 1610, 1549, 1414, 1242 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N$: 278.11756 found: 278.11747.



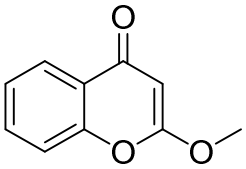
2-((2-(1*H*-Indol-3-yl)ethyl)amino)-4*H*-chromen-4-one, 4q

The product was obtained as light yellow solid in 61 % yield by heating the mixture of **3a** (1 equiv) and tryptamine (2 equiv) with Et_3N (2.2 equiv) in DMF at 80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 8.27(s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.60-7.58 (m, 1H), 7.49-7.45 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24-7.22 (m, 1H), 7.13-7.09 (m, 2H), 7.00 (s, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 6.43 (s, 1H), 3.79-3.78 (m, 2H), 3.10 (t, *J* = 6.6 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.28, 152.29, 136.52, 133.47, 127.07, 125.99, 124.67, 123.19, 122.17, 119.53, 118.30, 116.35, 111.69, 111.46, 77.48, 77.16, 76.84, 42.45, 25.29 ppm; FT-IR: $\tilde{\nu}$ = 3294, 3057, 2923, 1644, 1606, 1559, 1183 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{19}H_{17}O_2N_2$: 305.12845 found: 305.12850.



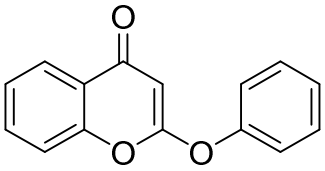
2-(1*H*-Indol-1-yl)-4*H*-chromen-4-one, 4p

The product was obtained as light yellow solid in 68 % yield by heating the mixture of **3a** (1 equiv) and indole (2 equiv) with K_2CO_3 (2 equiv) in DMF at 80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.8, 1.1 Hz 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.75-7.71 (m, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 6.47 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.23, 156.78, 154.56, 134.71, 133.91, 130.86, 126.10, 126.00, 125.95, 124.69, 124.66, 123.61, 123.17, 121.94, 117.53, 113.57, 109.10, 97.51 ppm; FT-IR: $\tilde{\nu}$ = 3115, 3065, 1616, 1560, 1449, 1416, 1337 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{12}O_2N$: 262.08626 found: 262.08622.



2-Methoxy-4*H*-chromen-4-one, 4r

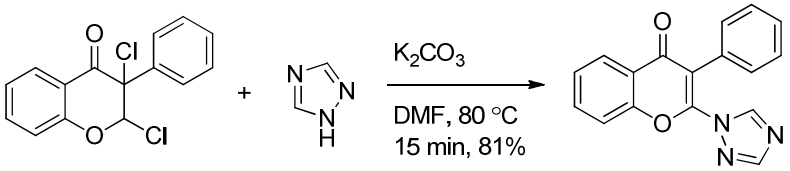
The product was obtained as light yellow solid in 68 % yield by treating **3a** (1 equiv) with $NaOCH_3$ (25% in methanol) at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 1H), 7.66-7.61 (m, 1H), 7.41-7.38 (m, 2H), 5.63 (s, 1H), 3.98 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.48, 168.07, 153.72, 133.49, 125.92, 125.45, 122.89, 117.30, 87.38, 56.54 ppm; FT-IR: $\tilde{\nu}$ = 3075, 2924, 2855, 1653, 1606, 1567, 1387, 1249 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{10}H_9O_3$: 177.05462 found: 177.05431.



2-Phenoxy-4*H*-chromen-4-one, 4s

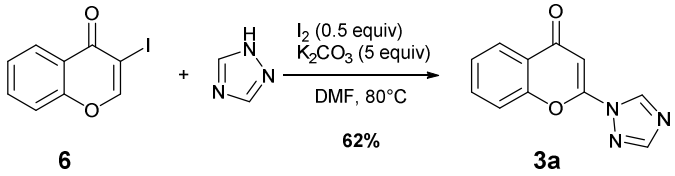
The product was obtained as colorless solid in 58 % yield by heating the mixture of **3a** (1 equiv) and phenol (2 equiv) with K_2CO_3 (2 equiv) in DMF at 80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.50-7.43 (m, 4H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.23-7.20 (m, 2H), 5.63 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.55, 153.87, 151.46, 133.98, 130.58, 127.24, 126.04, 125.91, 120.94, 117.58, 115.60, 115.46, 90.44 ppm; FT-IR: $\tilde{\nu}$ = 3055, 1693, 1605, 1590, 1474, 1398, 1223 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{11}O_3$: 239.07027 found: 239.07023.

Control experiment with 2,3-Dichloro-3-phenylchroman-4-one:



2,3-Dichloro-3-phenylchroman-4-one (0.1 mmol) and triazole (0.2 mmol) were taken in dry DMF (0.5 mL). Then anhydrous K_2CO_3 (0.5 mmol) was added to it and stir it at 80 °C for 15 min. After finishing the reaction, it was cooled to room temperature and directly purified by using normal silica gel column chromatography with 30-40% EtOAc/pet. ether as eluant in 81% yield.

Control experiment with 2-iodochromone 6:



S. No.	I_2 (equiv)	K_2CO_3 (equiv)	Yield (%)
1	0.5	5	62
2	-	5	98

Experimental procedure for the control experiments:

3-Iodochromone **6** (0.05 mmol) and triazole (2 equiv) were taken in dry DMF in a reaction vial. Then anhydrous K_2CO_3 (5 equiv) and I_2 (0.5 equiv) were added to the reaction mixture and stirred at 80°C. The progress of the reaction was monitored by TLC and upon completion the reaction was cooled to rt and directly purified by column chromatography to yield the cross-coupled product **3a** in 62% yield.

3-Iodochromone **6** (0.05 mmol) and triazole (2 equiv) were taken in dry DMF in a reaction vial. Then anhydrous K_2CO_3 (5 equiv) was added to the reaction mixture and stirred at 80°C. The progress of the reaction was monitored by TLC and upon completion the reaction was cooled to rt and directly purified by column chromatography to yield the cross-coupled product **3a** in 98% yield.

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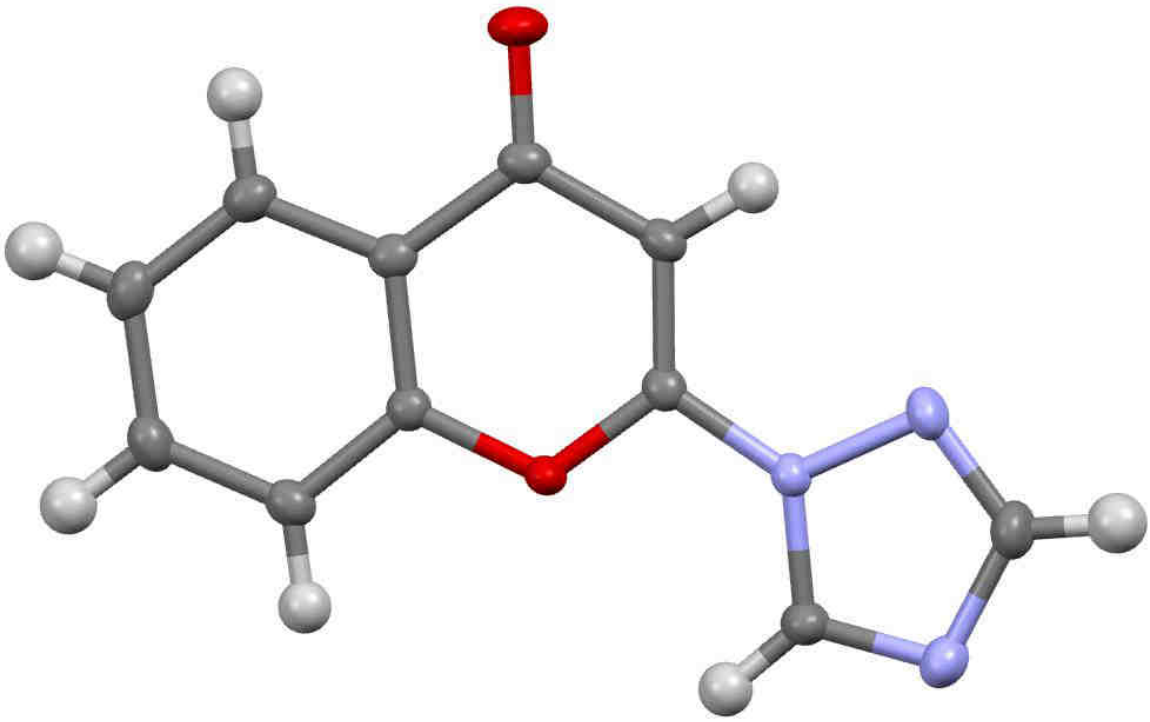

Table 1. Crystal data and structure refinement for **3a** (CCDC 1030687).

Identification code	2370	
Empirical formula	C11 H7 N3 O2	
Formula weight	213.20	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 11.9949(6) Å	α= 90°.
	b = 20.6933(10) Å	β= 90°.
	c = 3.7537(2) Å	γ = 90°.
Volume	931.72(8) $Å^3$	
Z	4	
Density (calculated)	1.520 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	440	
Crystal size	0.50 x 0.20 x 0.10 mm^3	
Theta range for data collection	2.60 to 25.98°.	
Index ranges	-14<=h<=14, -25<=k<=25, -4<=l<=4	

Reflections collected	14473
Independent reflections	1836 [R(int) = 0.0326]
Completeness to theta = 25.98°	99.8 %
Max. and min. transmission	0.9891 and 0.9474
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1836 / 1 / 145
Goodness-of-fit on F^2	1.000
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0656
R indices (all data)	R1 = 0.0272, wR2 = 0.0665
Absolute structure parameter	0.7(11)
Largest diff. peak and hole	0.170 and -0.198 e.$Å^{-3}$

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

	x	y	z	U(eq)
C(1)	10242(1)	2976(1)	4050(4)	19(1)
C(2)	10594(1)	2321(1)	4735(4)	20(1)
C(3)	9798(1)	1819(1)	3588(4)	18(1)
C(4)	9989(1)	1158(1)	4141(4)	22(1)
C(5)	9196(1)	709(1)	3135(4)	25(1)
C(6)	8207(1)	908(1)	1525(4)	24(1)
C(7)	7999(1)	1554(1)	922(4)	21(1)
C(8)	8798(1)	1998(1)	1980(3)	17(1)
C(9)	9266(1)	3089(1)	2411(4)	17(1)
C(10)	7850(1)	3868(1)	174(4)	22(1)
C(11)	8786(1)	4701(1)	1129(5)	27(1)
N(1)	8850(1)	3701(1)	1591(3)	18(1)
N(2)	9468(1)	4246(1)	2222(4)	25(1)
N(3)	7783(1)	4497(1)	-160(4)	27(1)
O(1)	11483(1)	2194(1)	6230(3)	29(1)
O(2)	8544(1)	2639(1)	1300(3)	19(1)

Biological Methods:

The hedgehog signaling inhibition and cell viability

Assay:

For assaying signal transduction through the HH pathway mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the SMO agonist Purmorphamine. During differentiation osteoblast specific genes such as alkaline phosphatase (ALK), which plays an essential role in bone formation, are highly expressed. Activity of ALK can directly be monitored by following substrate hydrolysis yielding a highly luminescent product. Inhibition of the pathway results in reduction of luminescence.[1]

The screening for small molecule inhibitors of the HH pathway was carried out in 384 well format. Shortly, 800 cells per well were seeded and allowed to grow overnight. The next day, compounds were added to a final concentration of 10 µM using the acoustic nanoliter dispenser ECHO 520. After one hour, Purmorphamine was added to a final concentration of 1.5 µM; control cells did not receive Purmorphamine. After four days, the cell culture medium was aspirated and a commercial luminogenic ALK substrate (CDP-Star, Roche) was added. After one hour, luminescence was read. To identify and exclude toxic compounds that also lead to a reduction in the luminescent signal, cell viability measurements were carried out in parallel. The cell viability assay followed the same workflow as the HH assay, except that only 200 cells per well were seeded. Cell culture medium alone served as control for the cell viability assay. For the measurement of cell viability, Cell Titer Glo reagent (Promega) which determines the cellular ATP content was used. Hits were scored as showing at least a 50% reduction in the luminescent signal in the HH assay, and a minimum of 80% cell viability. Dose-response analysis for hit compounds was done using a three-fold dilution curve starting from 30 µM. IC_{50} values were calculated using the Quattro software suite (Quattro Research GmbH).

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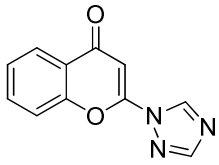
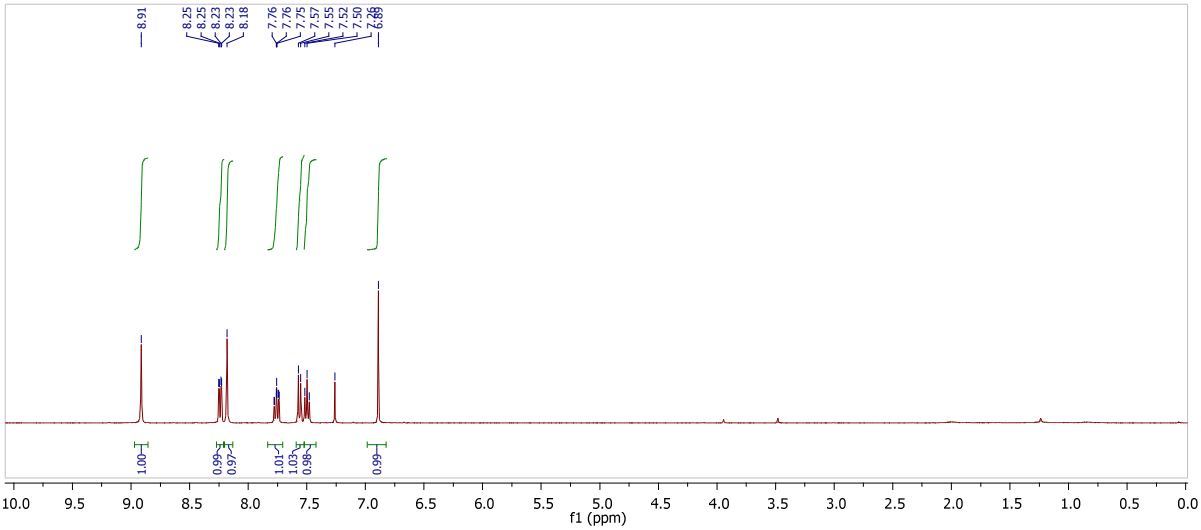


3a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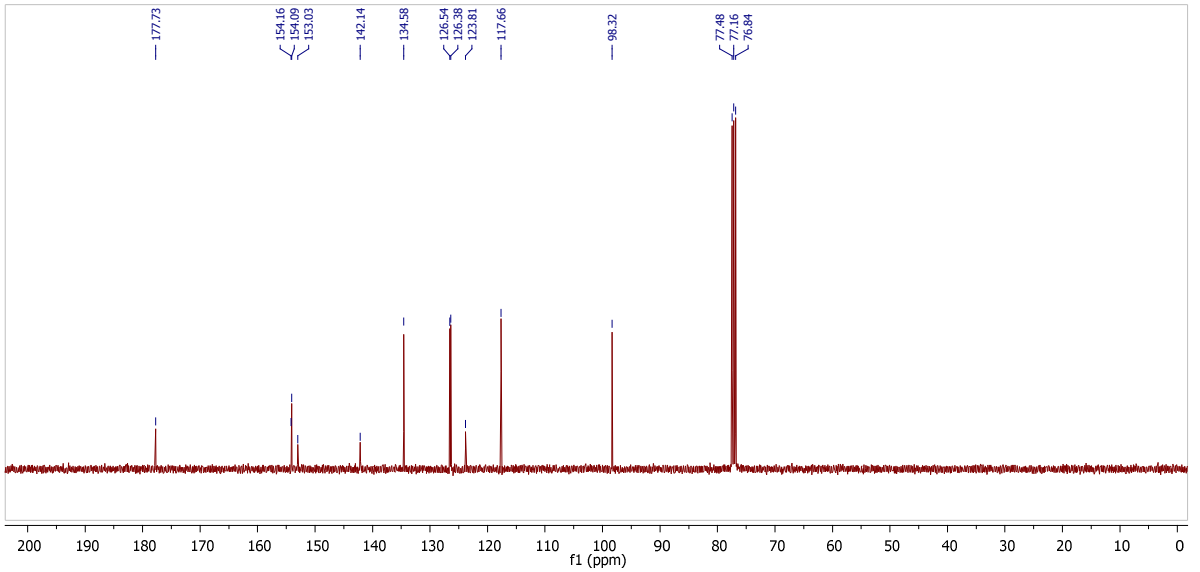
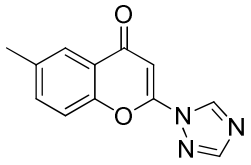
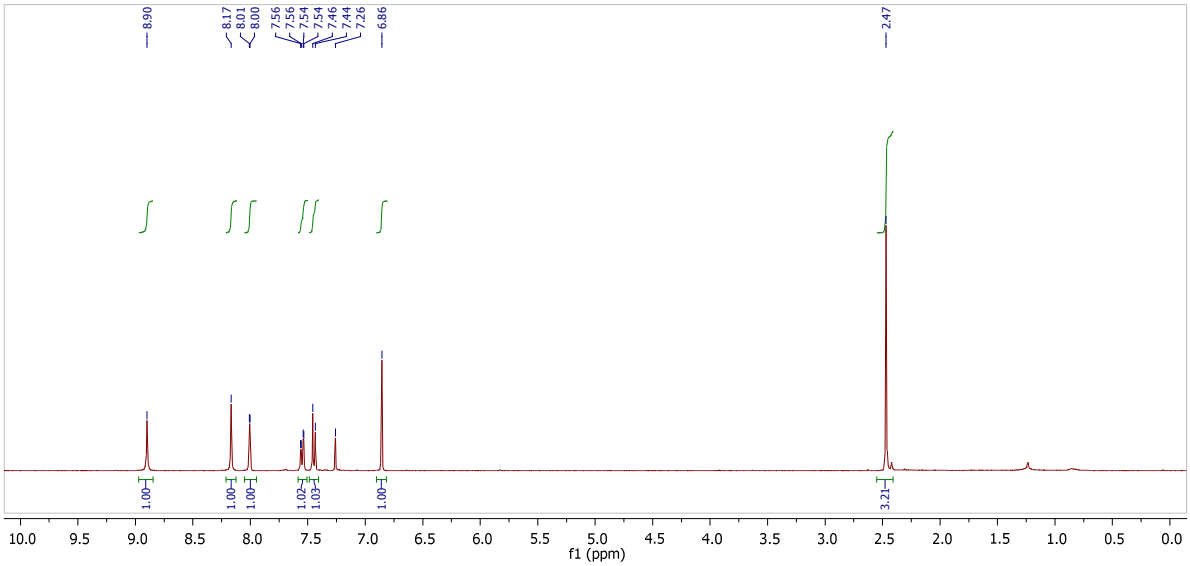
8.25
8.25
8.23
8.23
8.18
7.76
7.76
7.75
7.57
7.55
7.52
7.50
7.26
6.89
1.00
0.99
0.97
1.01
1.03
0.98
0.99
f1 (ppm)


177.73
154.16
154.09
153.03
142.14
134.58
126.54
126.38
123.81
117.66
98.32
77.48
77.16
76.84
f1 (ppm)



3b


8.90
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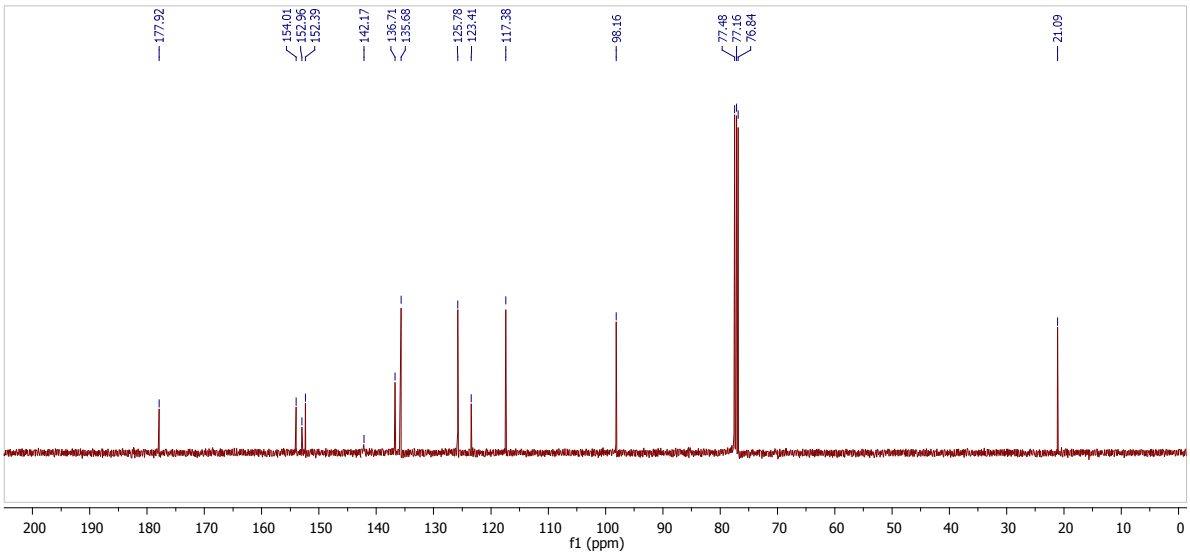
8.00
7.56
7.56
7.54
7.54
7.46
7.44
7.26
6.86
2.47
1.00
1.00
1.00
1.02
1.03
1.00
3.21
f1 (ppm)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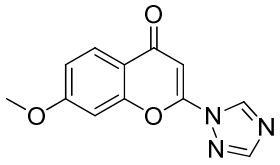
154.01
152.96
152.39
142.17
136.71
135.68
125.78
123.41
117.38
98.16
77.48
77.16
76.84
21.09
f1 (ppm)



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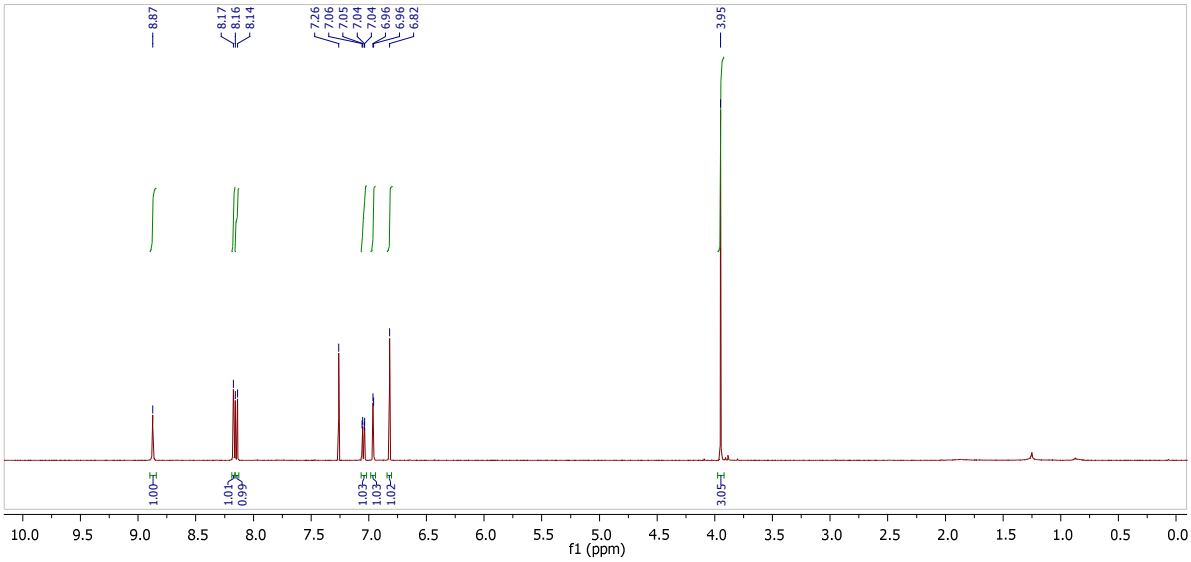
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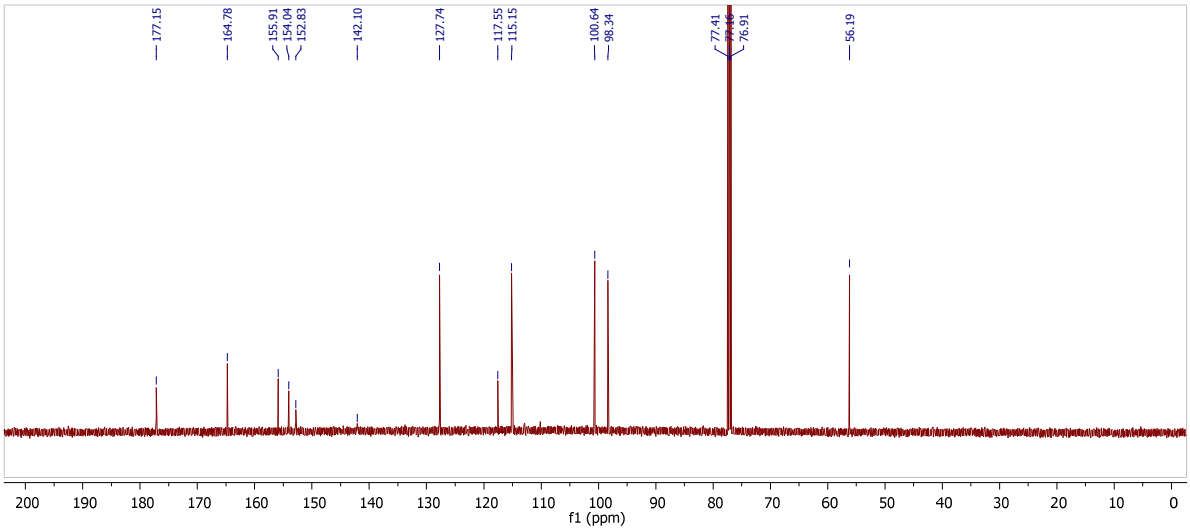
8.17
8.16
8.14
7.26
7.06
7.05
7.04
7.04
6.96
6.96
6.82
3.95
1.00
1.01
0.99
1.03
1.03
1.02
3.05
f1 (ppm)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117.55
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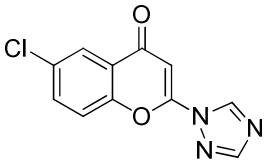
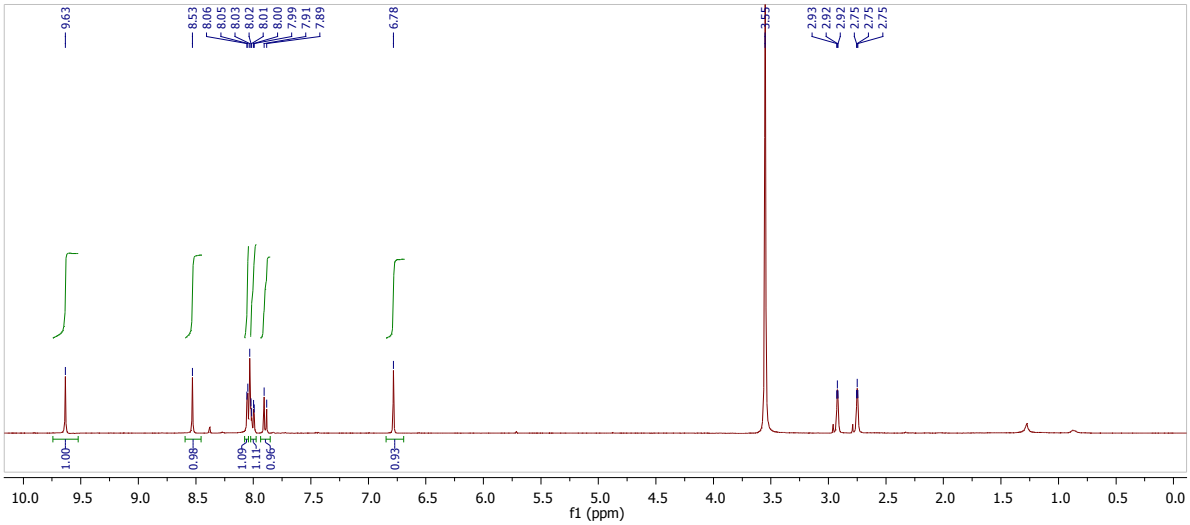
100.64
98.34
77.41
77.16
76.91
56.19
f1 (ppm)


O
Cl
O
N
N
N

3e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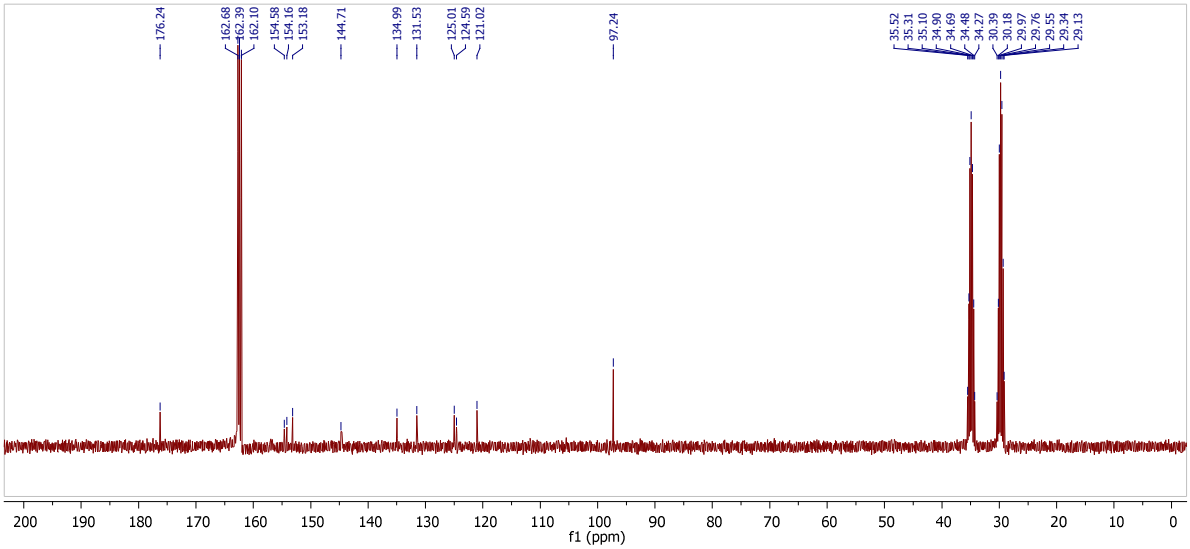
8.03
8.02
8.01
8.00
7.99
7.91
7.89
6.78
3.55
2.93
2.92
2.92
2.75
2.75
2.75
1.00
0.98
1.09
1.11
0.96
0.93
f1 (ppm)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154.16
153.18
144.71
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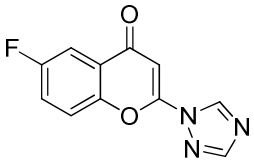
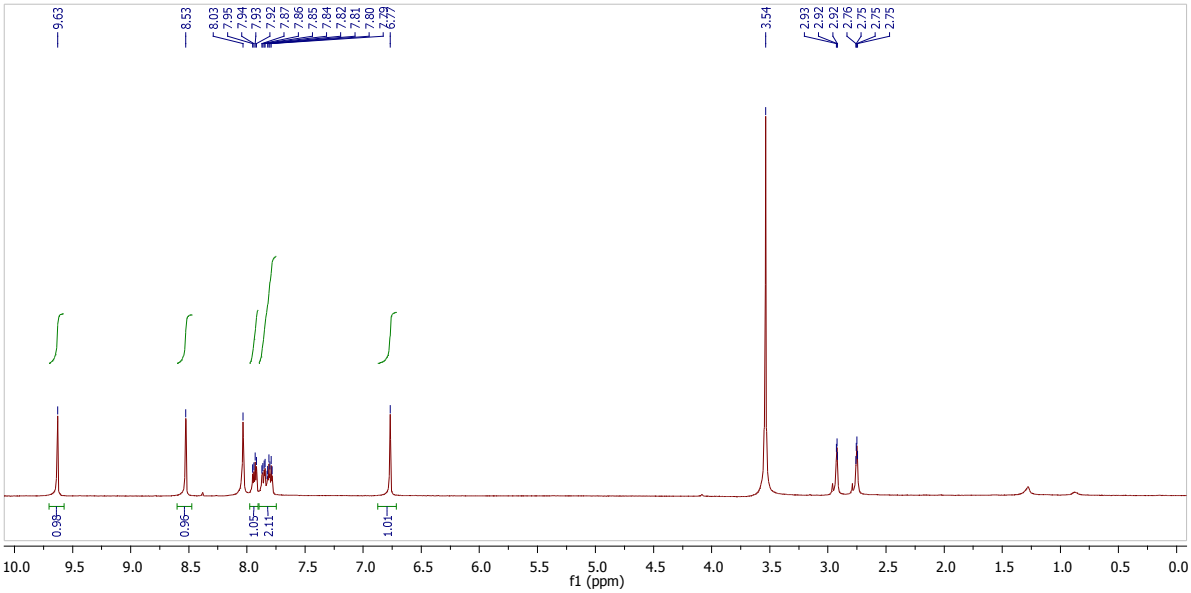
131.53
125.01
124.59
121.02
97.24
35.52
35.31
35.10
34.90
34.69
34.48
34.27
30.39
30.18
29.97
29.76
29.55
29.34
29.13
f1 (ppm)


O
F
O
N
N
N

3f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7.93
7.92
7.87
7.86
7.85
7.84
7.82
7.81
7.80
7.79
7.77
3.54
2.93
2.92
2.92
2.76
2.75
2.75
2.75
0.98
0.96
1.05
2.11
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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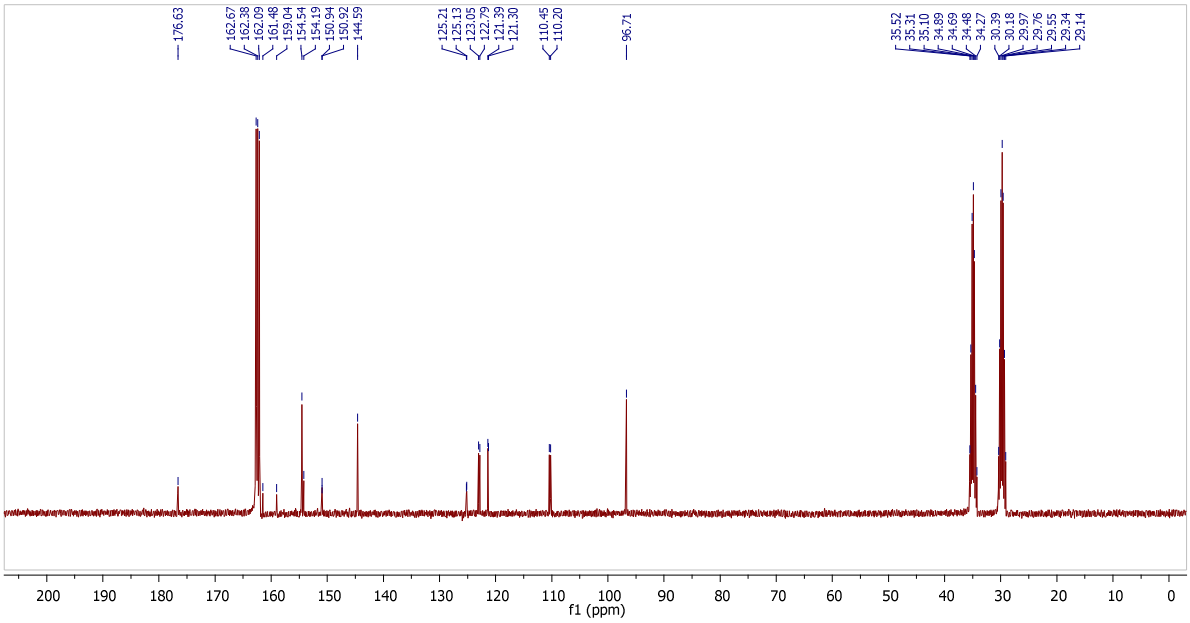
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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162.09
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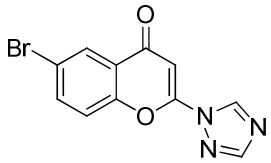
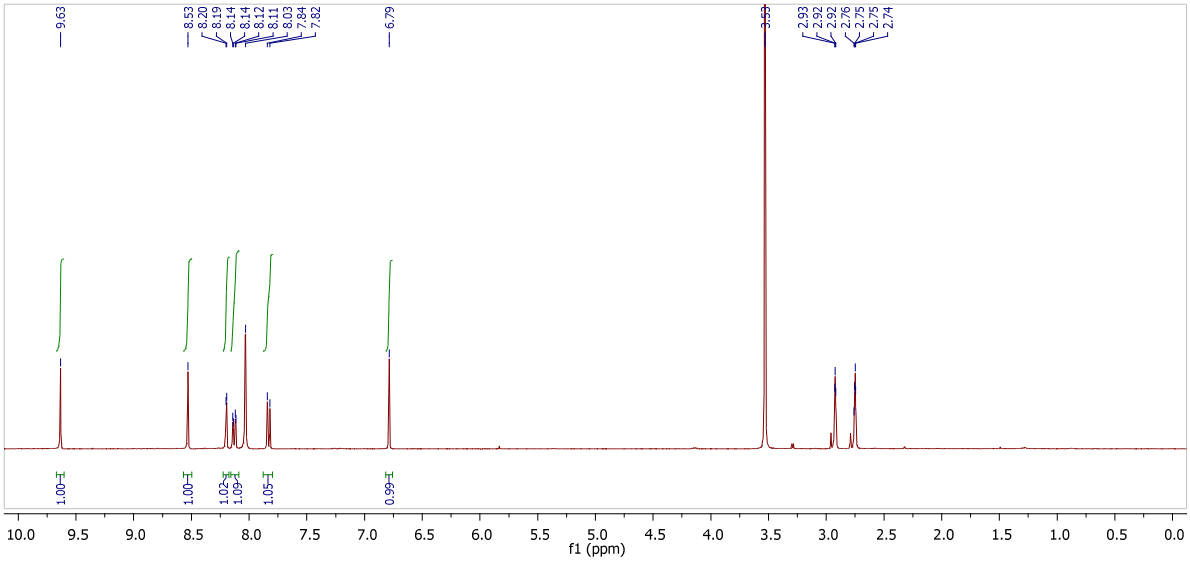
154.54
154.19
150.94
150.92
144.59
125.21
125.13
123.05
122.79
121.39
121.30
110.45
110.20
96.71
35.52
35.31
35.10
34.89
34.69
34.48
34.27
30.39
30.18
29.97
29.76
29.55
29.34
29.14
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Br
O
N
N
N

3d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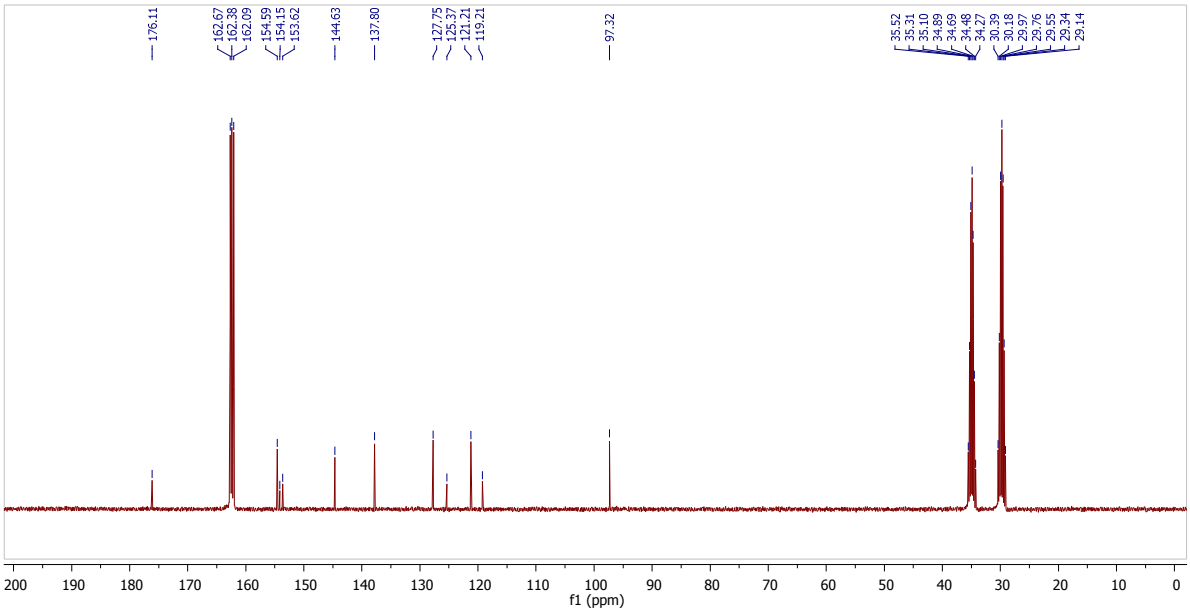
8.53
8.20
8.19
8.14
8.14
8.12
8.11
8.03
7.84
7.82
6.79
3.53
2.93
2.92
2.92
2.76
2.75
2.75
2.74
1.00
1.00
1.02
1.09
1.05
0.99
f1 (ppm)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162.09
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154.15
153.62
144.63
137.80
127.75
125.37
121.21
119.21
97.32
35.52
35.31
35.10
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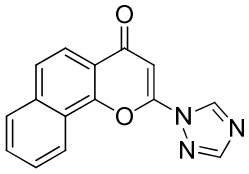
29.76
29.55
29.34
29.14
f1 (ppm)



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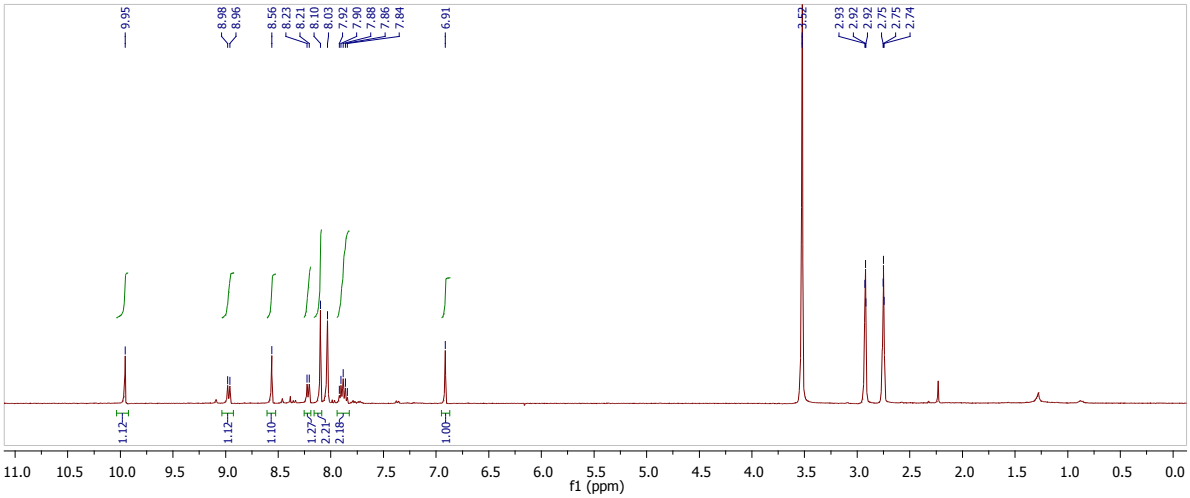
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8.98
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8.56
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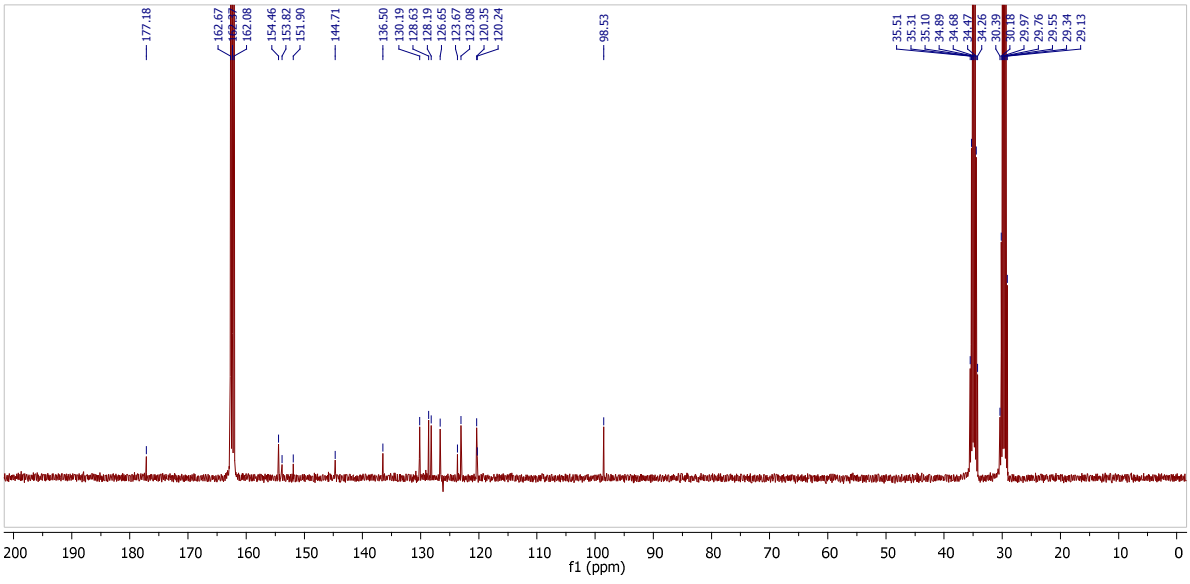
8.21
8.10
8.03
7.92
7.90
7.88
7.86
7.84
6.91
3.52
2.93
2.92
2.92
2.75
2.75
2.74
1.12
1.12
1.10
1.27
2.21
2.18
1.00
f1 (ppm)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144.71
136.50
130.19
128.63
128.19
126.65
123.67
123.08
120.35
120.24
98.53
35.51
35.31
35.10
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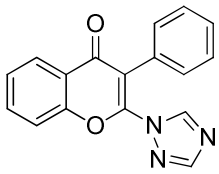
34.26
30.39
30.18
29.97
29.76
29.55
29.34
29.13
f1 (ppm)



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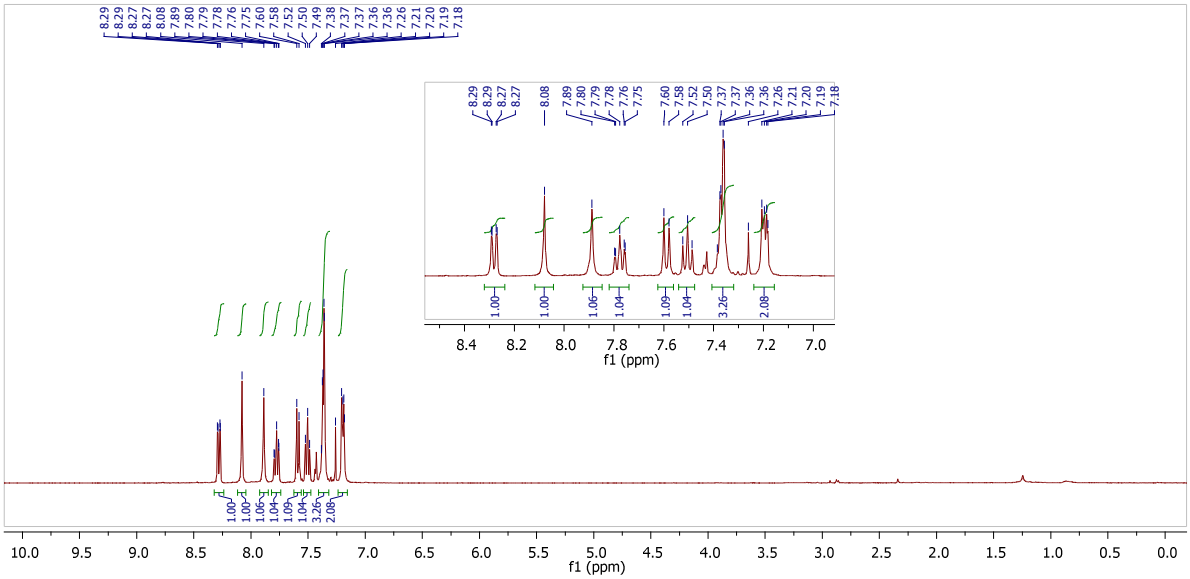
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8.27
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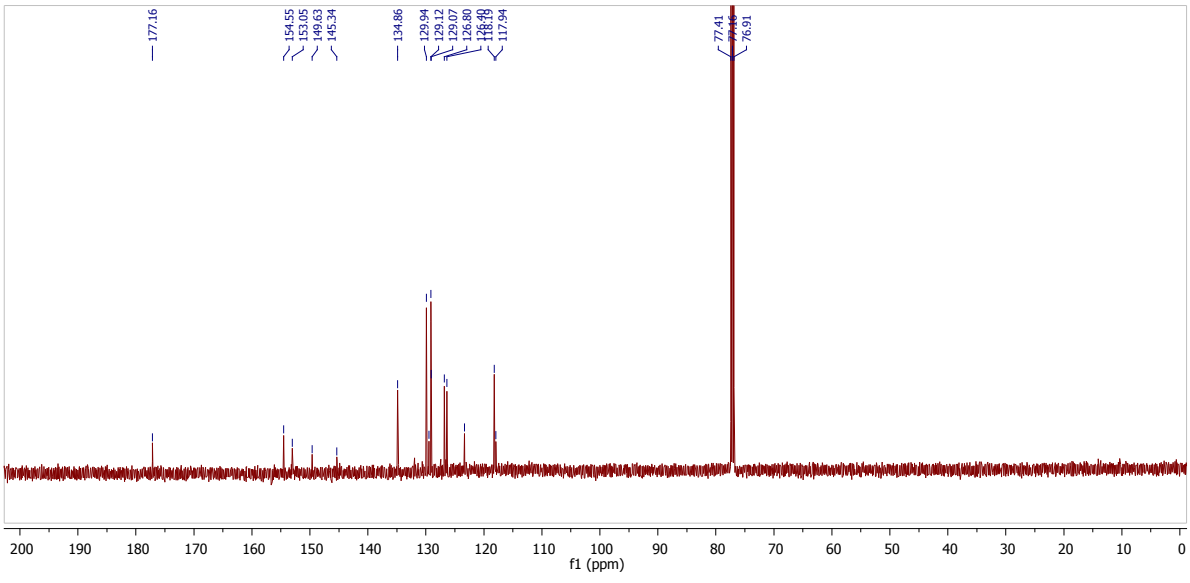
7.80
7.79
7.78
7.76
7.75
7.60
7.58
7.52
7.50
7.37
7.36
7.26
7.21
7.20
7.19
7.18
1.00
1.00
1.06
1.04
1.09
1.04
3.26
2.08
f1 (ppm)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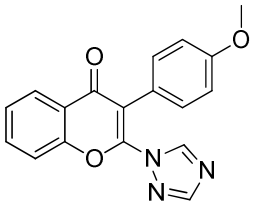
129.12
129.07
126.80
118.19
117.94
77.41
76.91
f1 (ppm)



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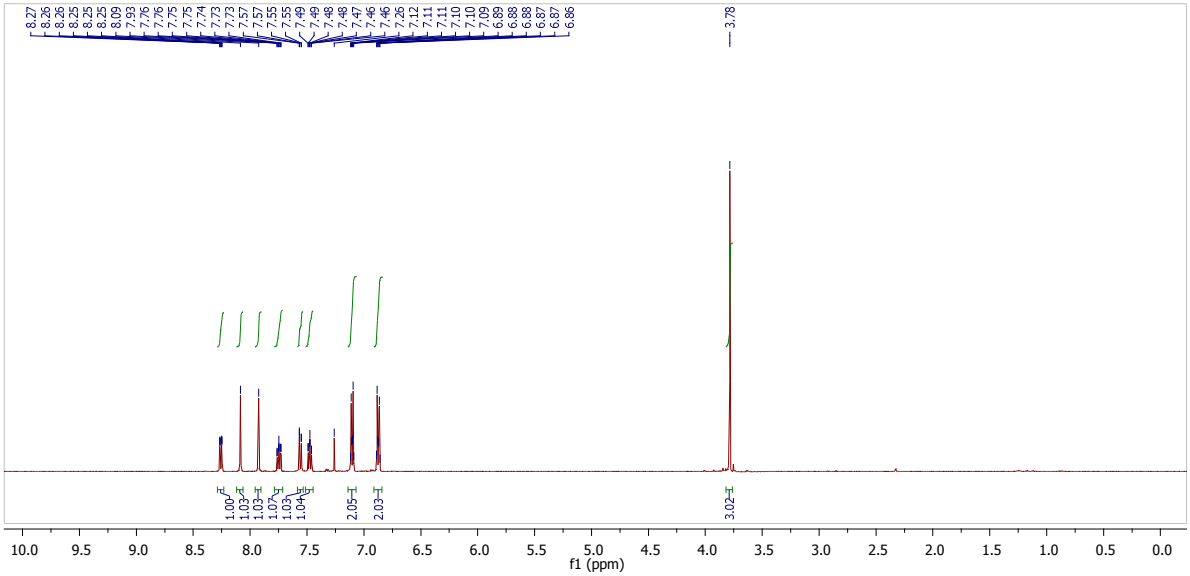
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8.25
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7.76
7.75
7.75
7.74
7.73
7.73
7.57
7.57
7.55
7.55
7.49
7.49
7.48
7.48
7.47
7.46
7.46
7.26
7.12
7.11
7.11
7.10
7.10
7.09
6.89
6.88
6.88
6.87
6.87
6.86
3.78
1.00
1.03
1.03
1.07
1.03
1.04
2.05
2.03
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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1.0
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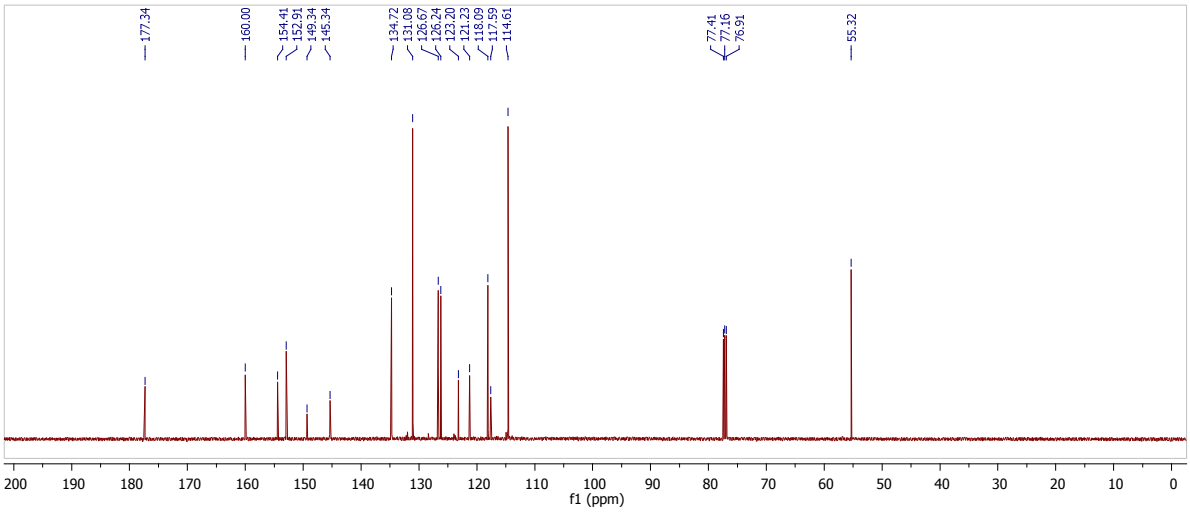
0.0
f1 (ppm)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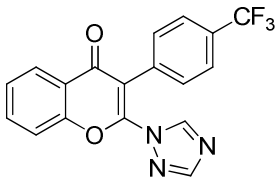
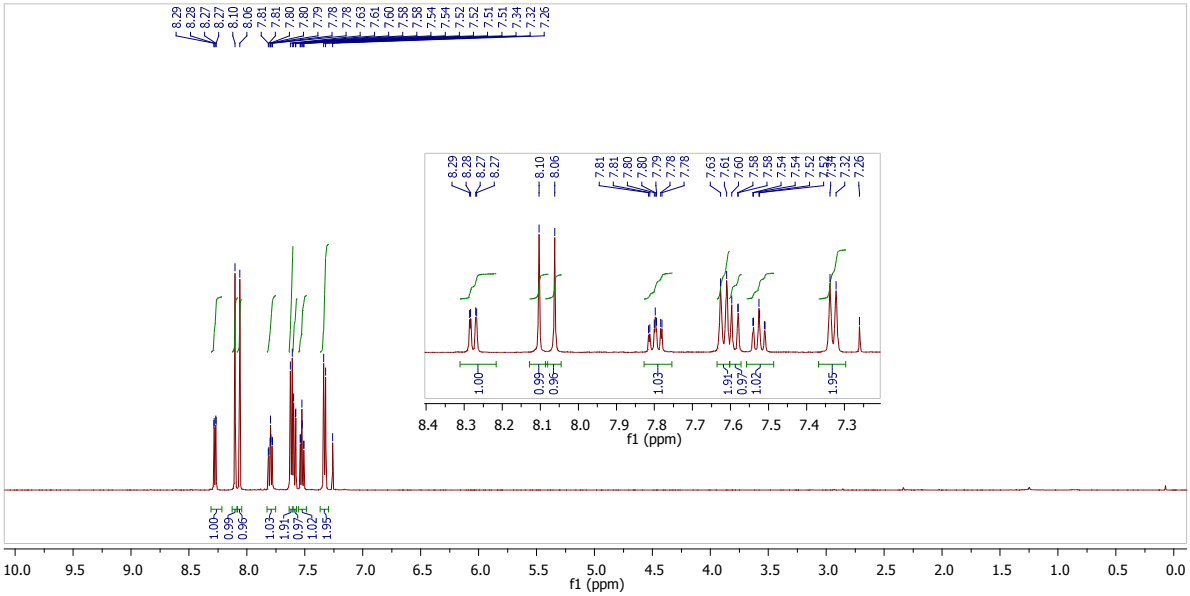
126.24
123.20
121.23
118.09
117.59
114.61
77.41
77.16
76.91
55.32
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
CF3
O
N
N
N

3l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7.80
7.79
7.78
7.78
7.63
7.61
7.60
7.58
7.58
7.54
7.54
7.52
7.52
7.51
7.51
7.34
7.32
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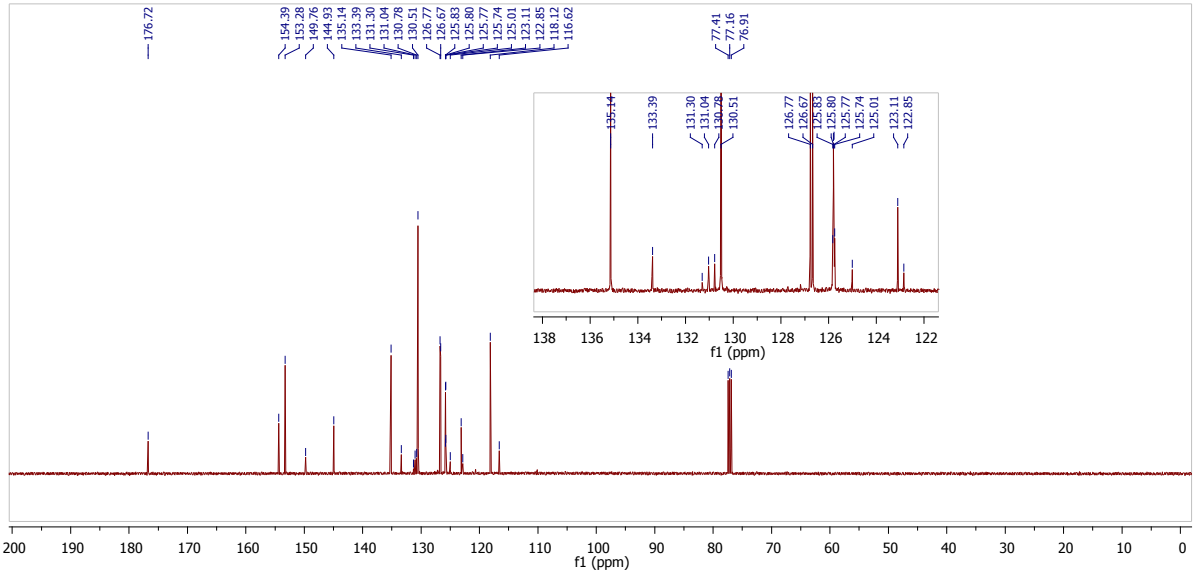
0.96
1.03
1.91
0.97
1.02
1.95
f1 (ppm)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130.51
126.77
126.67
125.83
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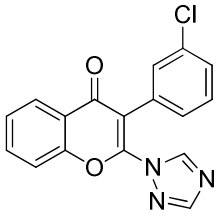
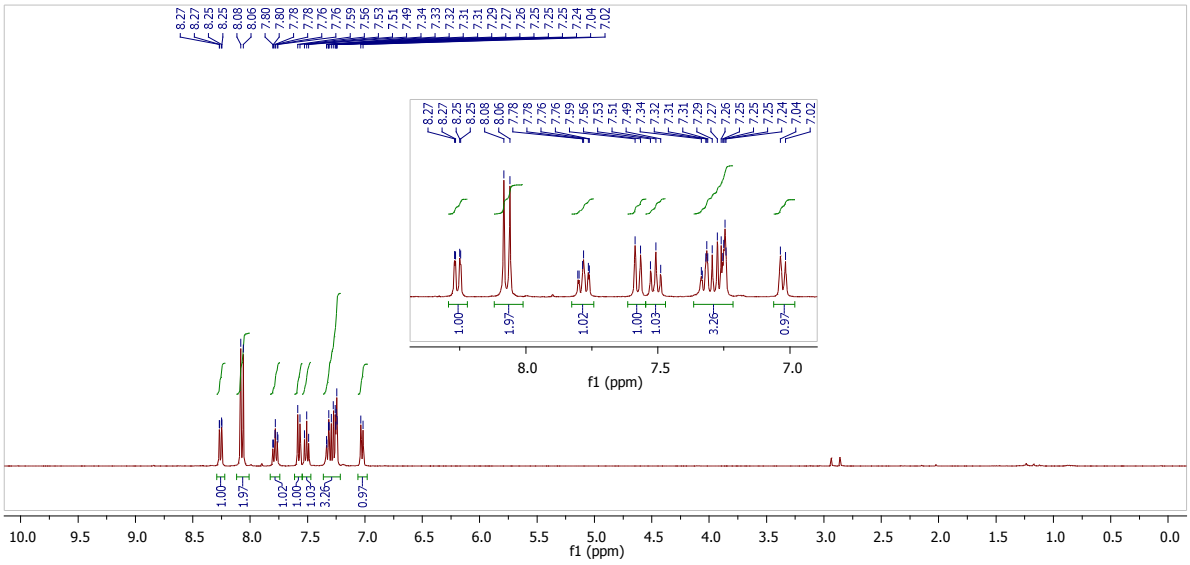
116.62
77.41
77.16
76.91
f1 (ppm)


Cl
O
O
N
N
N

3k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7.76
7.59
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7.29
7.27
7.26
7.25
7.25
7.25
7.24
7.04
7.02
1.00
1.97
1.02
1.00
1.03
3.26
0.97
8.0
7.5
7.0
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
1.5
1.0
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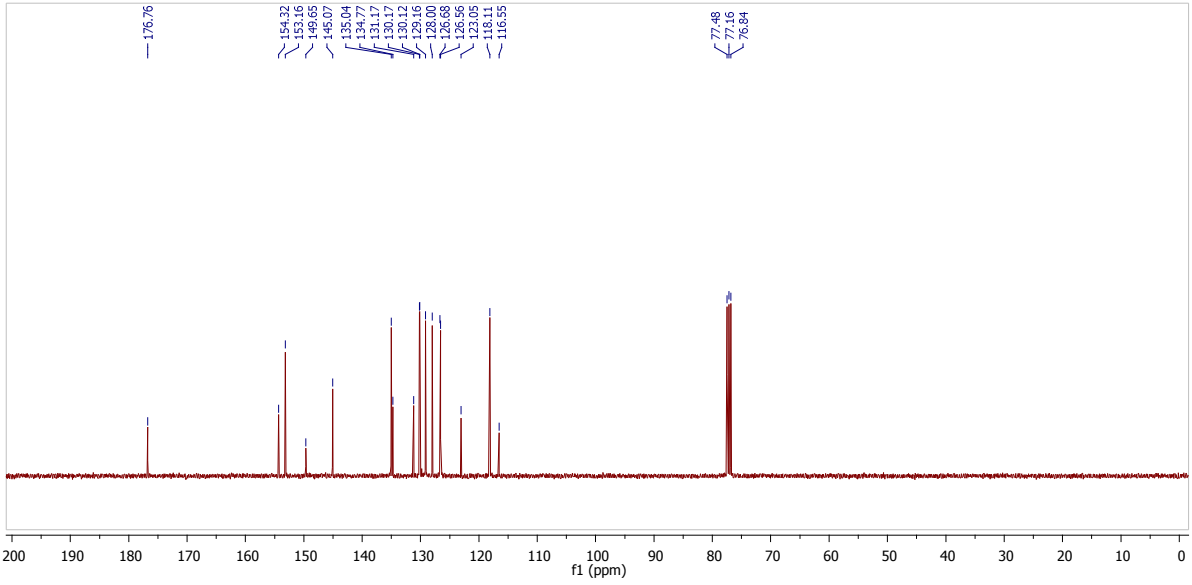
0.0
f1 (ppm)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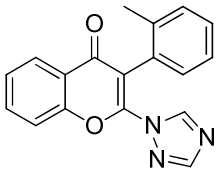
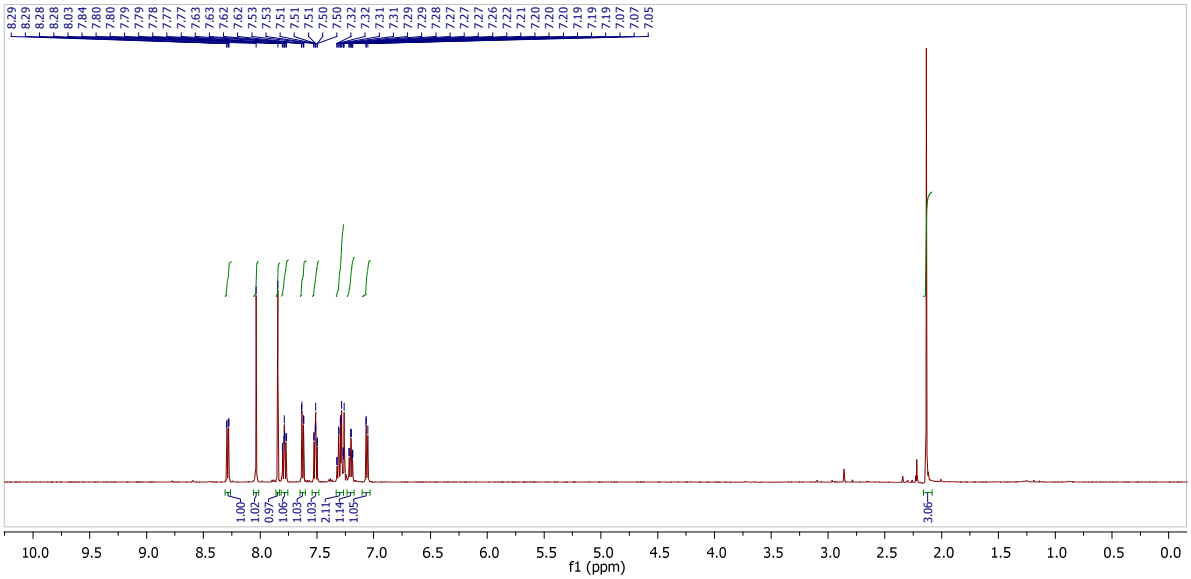
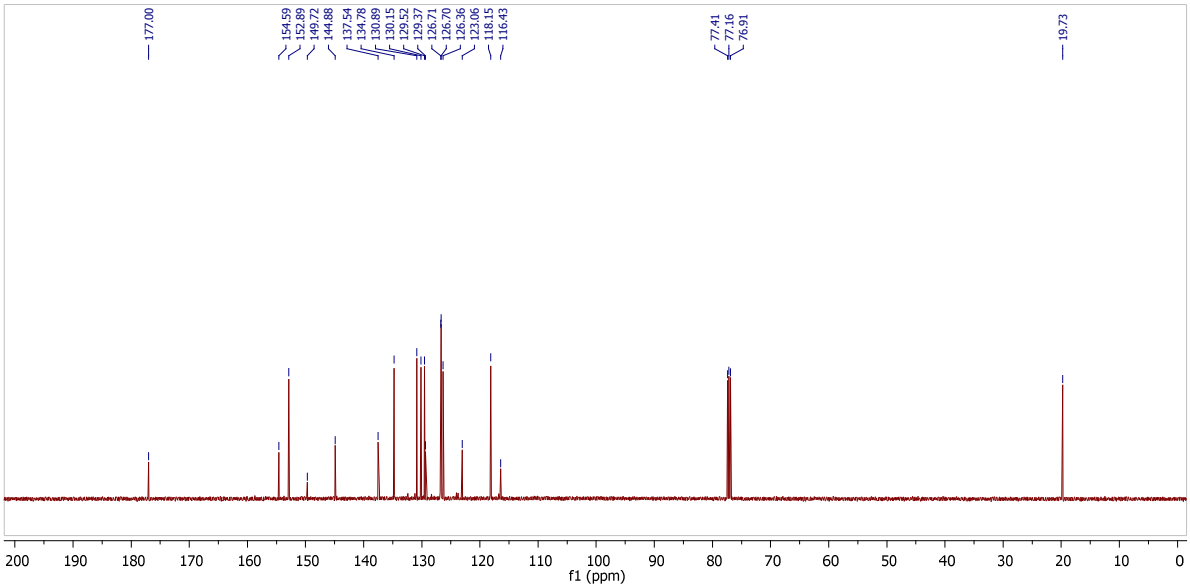
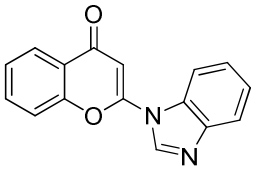
131.17
130.17
130.12
129.16
128.00
126.68
126.56
123.05
118.11
116.55
77.48
77.16
76.84
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



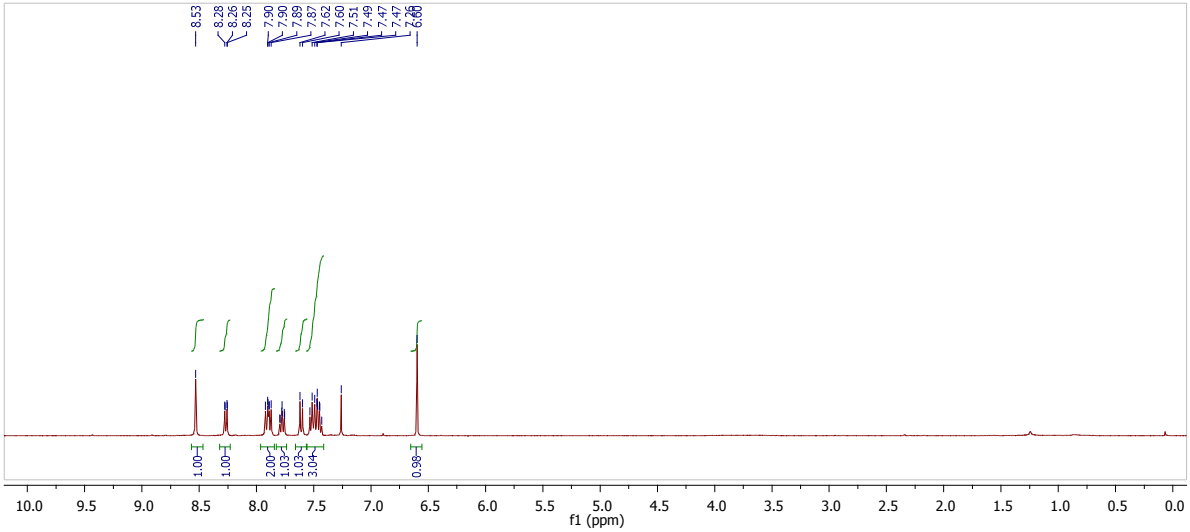
3i







4g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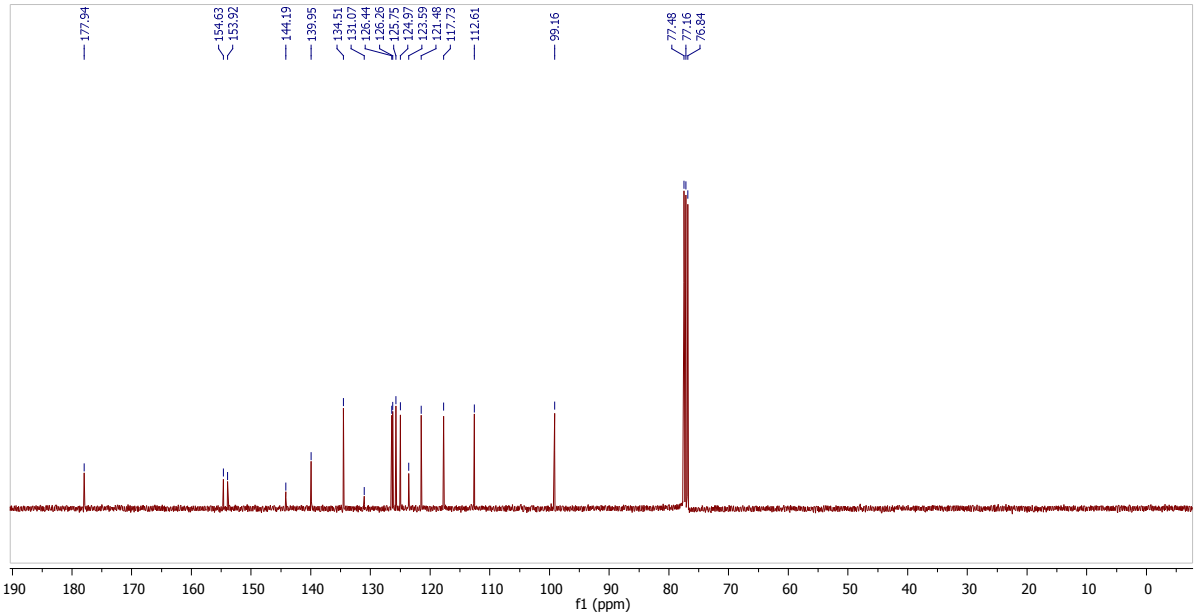
7.89
7.87
7.62
7.60
7.51
7.49
7.47
7.47
7.26
6.80
1.00
1.00
2.00
1.03
1.03
3.04
0.98
f1 (ppm)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117.73
112.61
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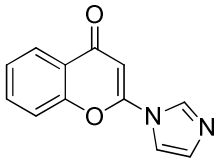
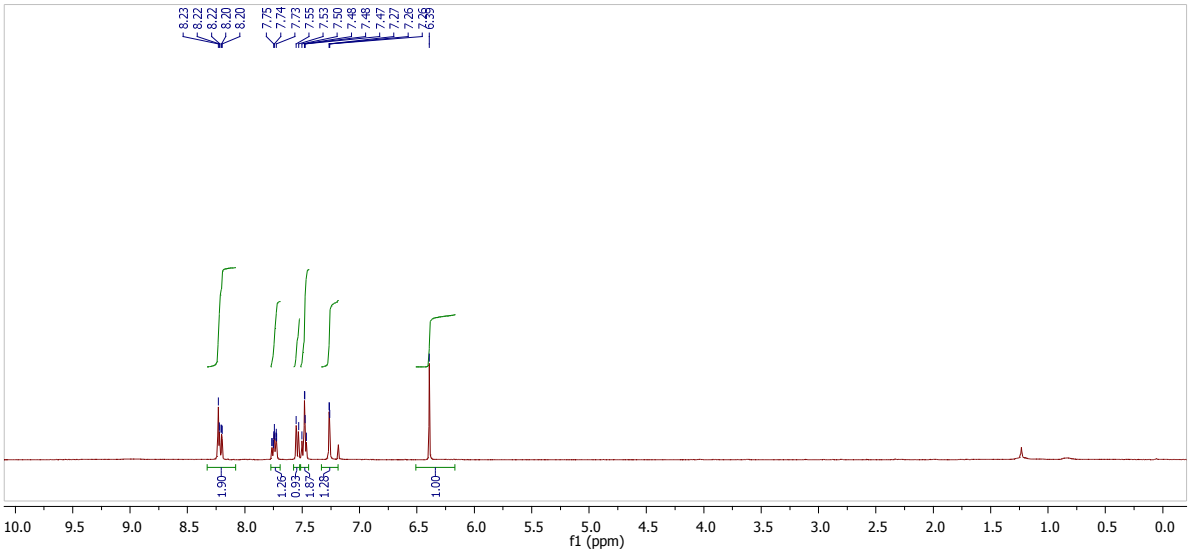
76.84
f1 (ppm)



4a


8.23
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8.22
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8.20
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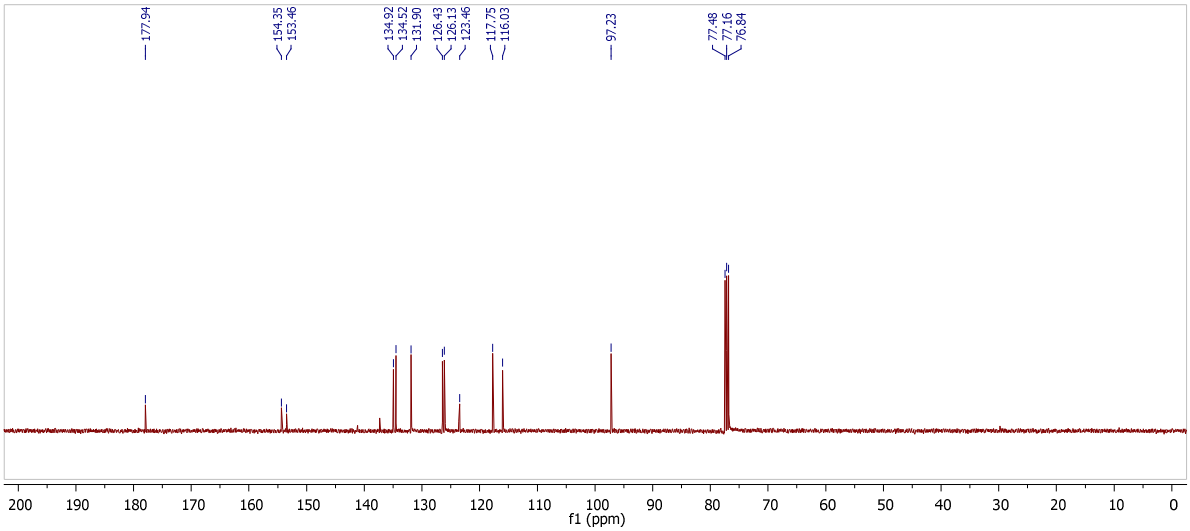
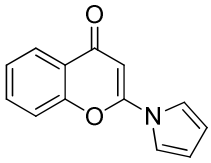
7.73
7.55
7.53
7.50
7.48
7.48
7.47
7.27
7.26
6.99
6.99
1.90
1.26
0.93
1.87
1.28
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


177.94
154.35
153.46
134.92
134.52
131.90
126.43
126.13
123.46
117.75
116.03
97.23
77.48
77.16
76.84
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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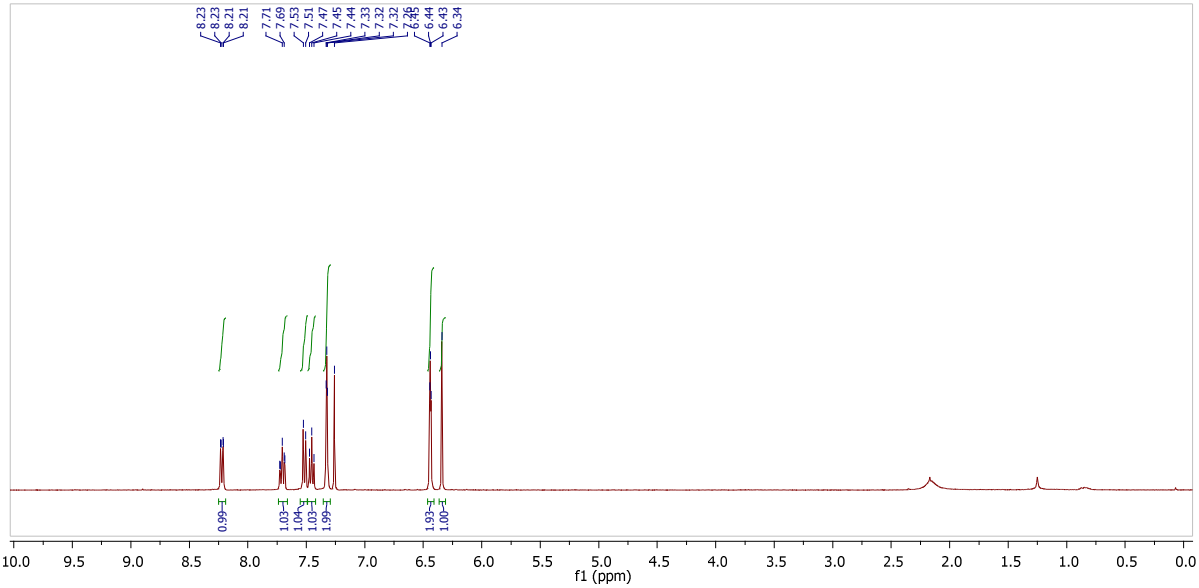
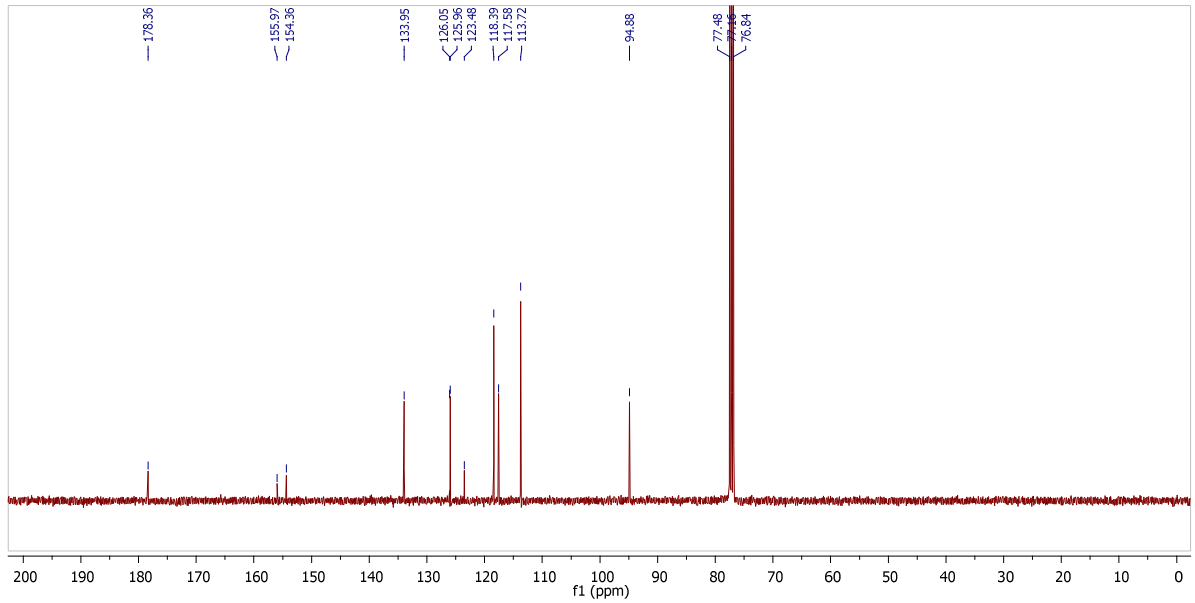
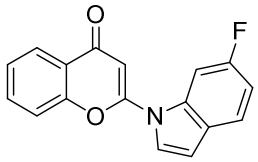
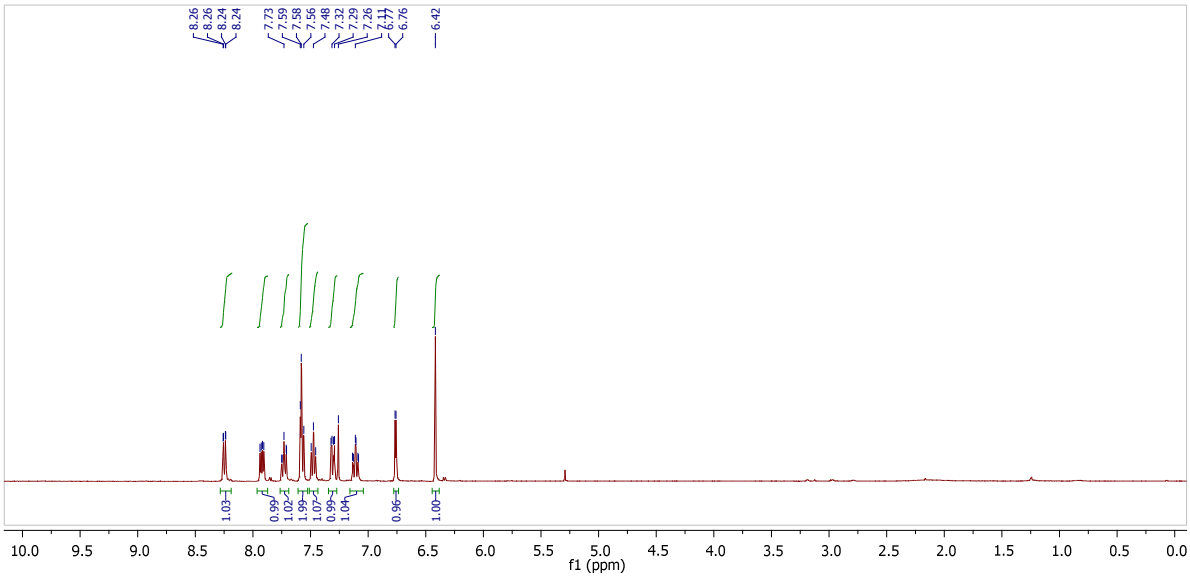
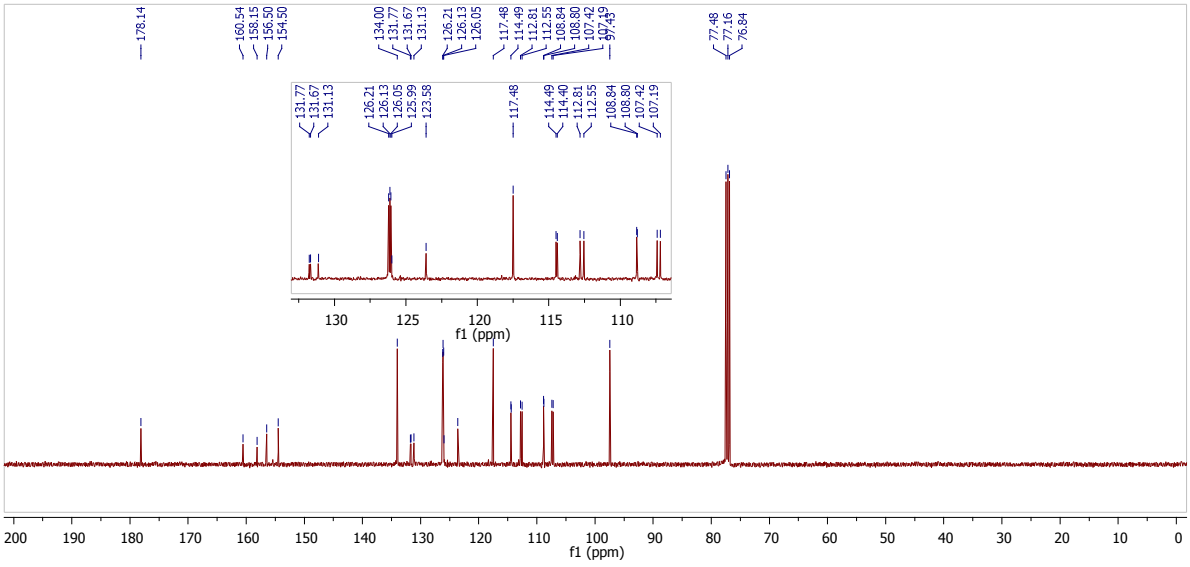

8.23
8.23
8.21
8.21
7.71
7.69
7.53
7.51
7.47
7.45
7.44
7.33
7.32
7.32
6.45
6.44
6.43
6.34
0.99
1.03
1.04
1.03
1.99
1.93
1.00
f1 (ppm)


178.36
155.97
154.36
133.95
126.05
125.96
123.48
118.39
117.58
113.72
94.88
77.48
76.84
f1 (ppm)


O
F
O
N

4f


8.26
8.26
8.24
8.24
7.73
7.59
7.58
7.56
7.48
7.32
7.29
7.26
6.77
6.76
6.42
1.03
0.99
1.02
1.99
1.07
0.99
1.04
0.96
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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160.54
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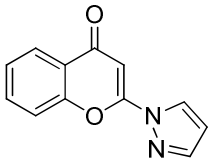
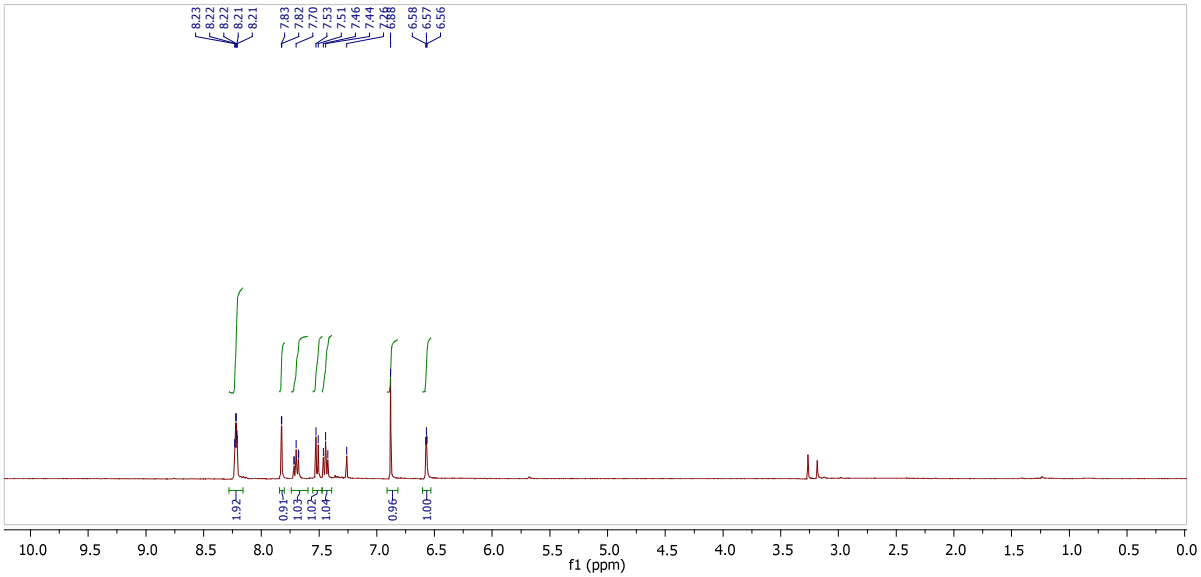
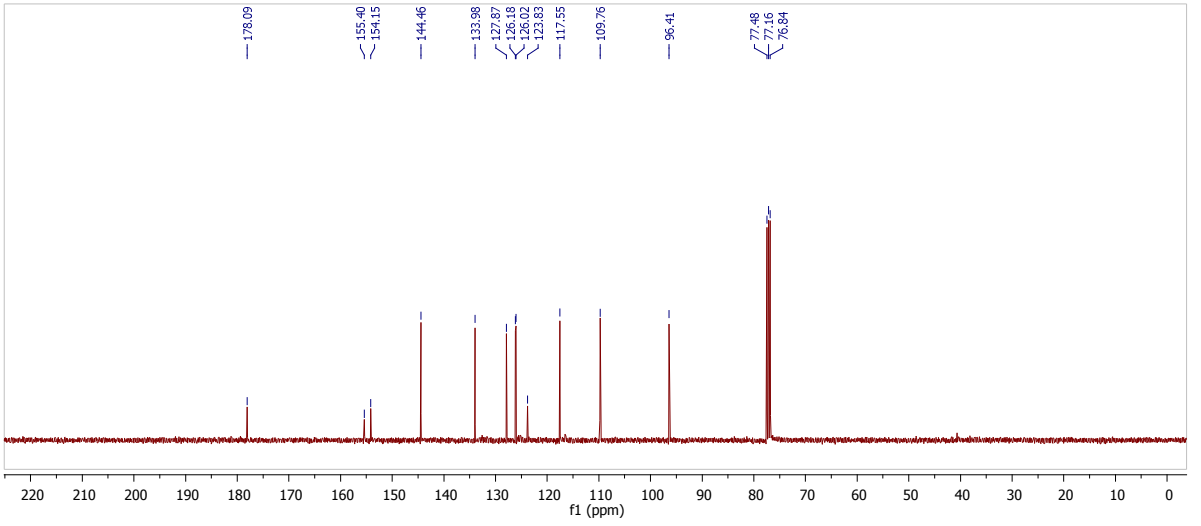
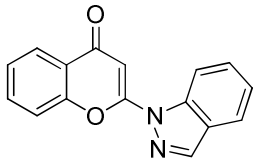
154.50
134.00
131.77
131.67
131.13
126.21
126.13
126.05
117.48
114.49
112.81
112.55
108.84
108.80
107.42
107.19
77.48
77.16
76.84
131.77
131.67
131.13
126.21
126.13
126.05
125.99
123.58
117.48
114.49
114.40
112.81
112.55
108.84
108.80
107.42
107.19
130 125 120 115 110
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



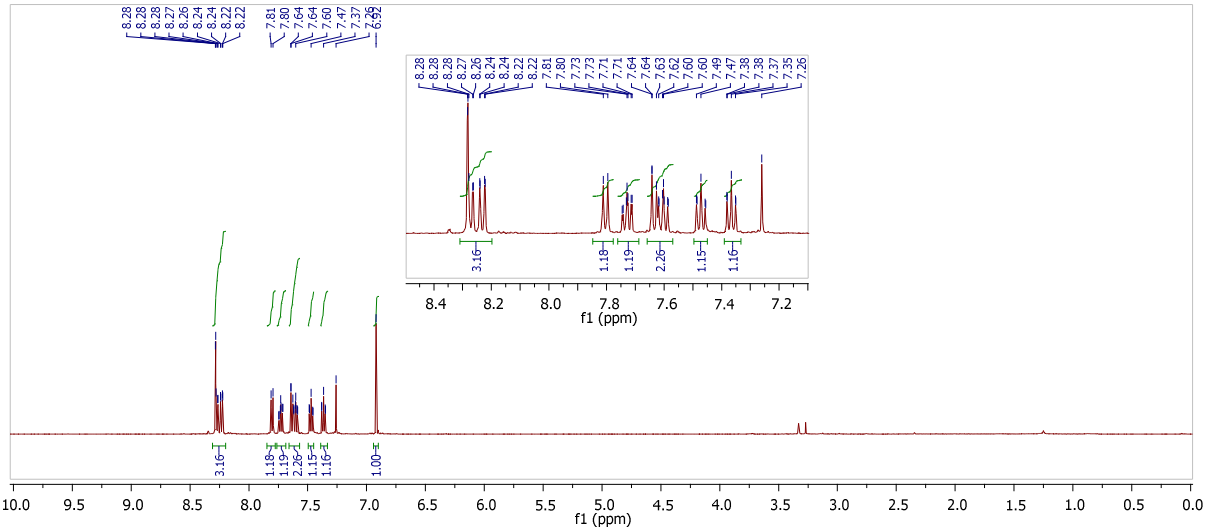
4b

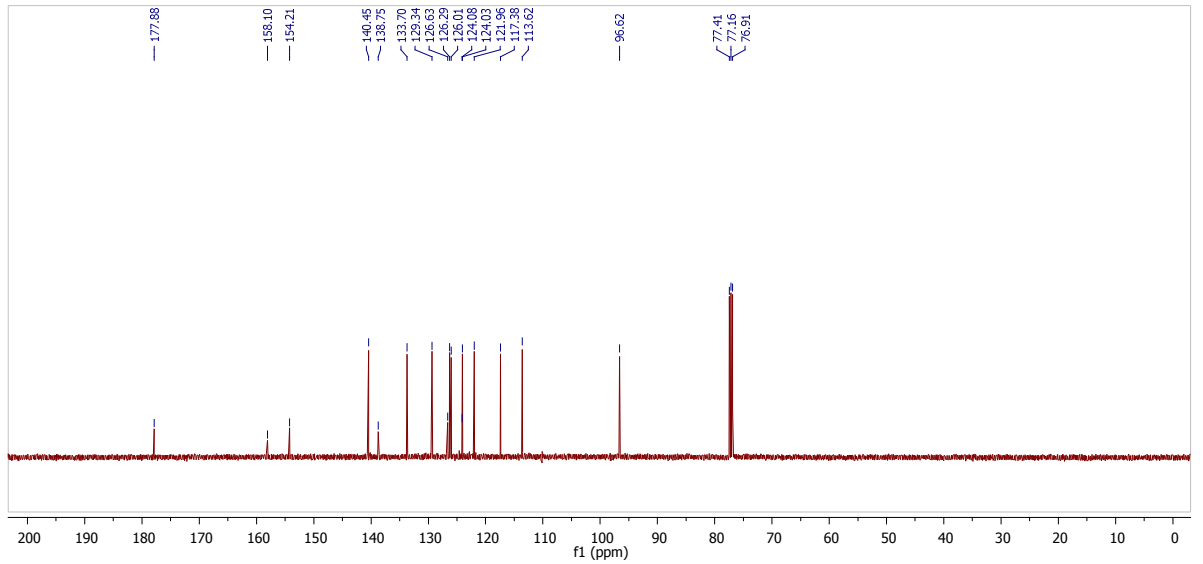

8.23
8.22
8.22
8.21
8.21
7.83
7.82
7.70
7.53
7.51
7.46
7.44
6.58
6.57
6.56
1.92
0.91
1.03
1.02
1.04
0.96
1.00
f1 (ppm)

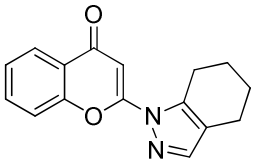

178.09
155.40
154.15
144.46
133.98
127.87
126.18
126.02
123.83
117.55
109.76
96.41
77.48
77.16
76.84
f1 (ppm)



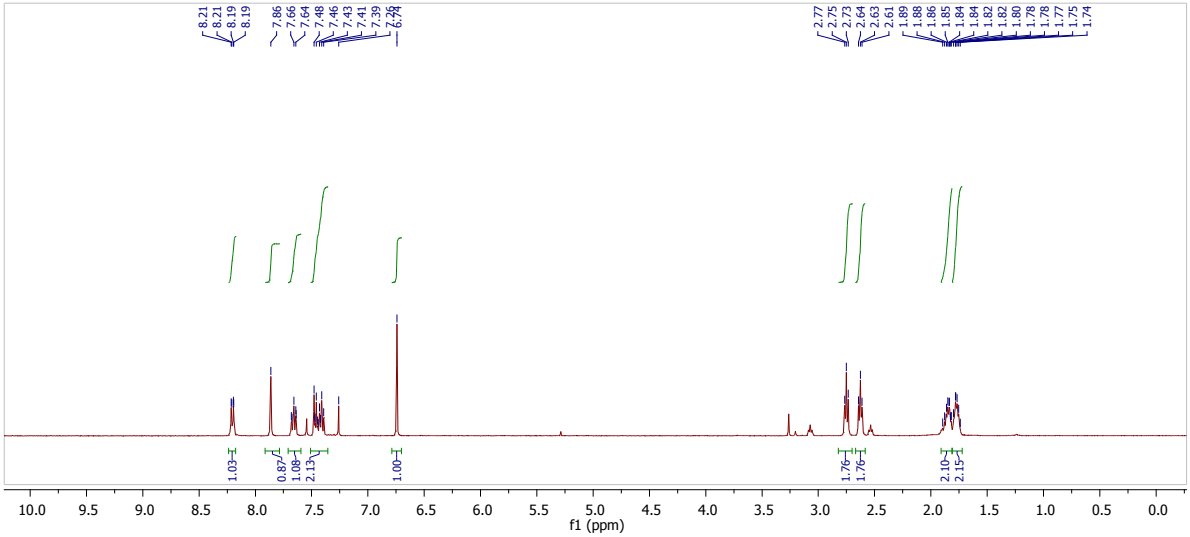
4d







4c


8.21
8.21
8.19
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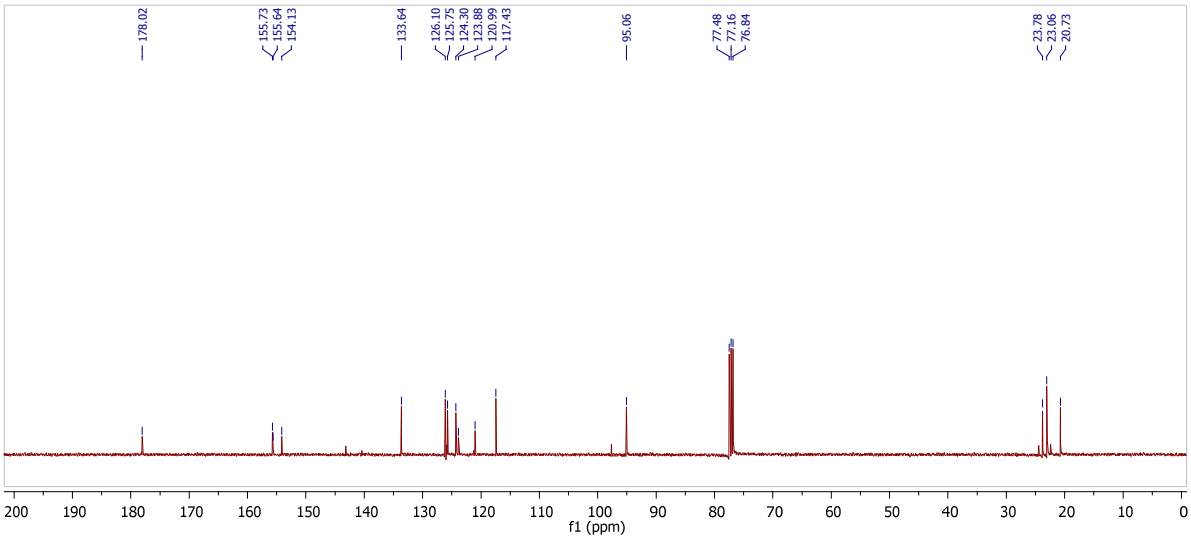
7.66
7.64
7.48
7.46
7.43
7.41
7.39
7.25
6.74
2.77
2.75
2.73
2.64
2.63
2.61
1.89
1.88
1.86
1.85
1.84
1.84
1.82
1.82
1.80
1.78
1.78
1.77
1.75
1.74
1.03
0.87
1.08
2.13
1.00
1.76
1.76
2.10
2.15
f1 (ppm)


178.02
155.73
155.64
154.13
133.64
126.10
125.75
124.30
123.88
120.99
117.43
95.06
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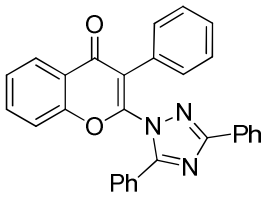
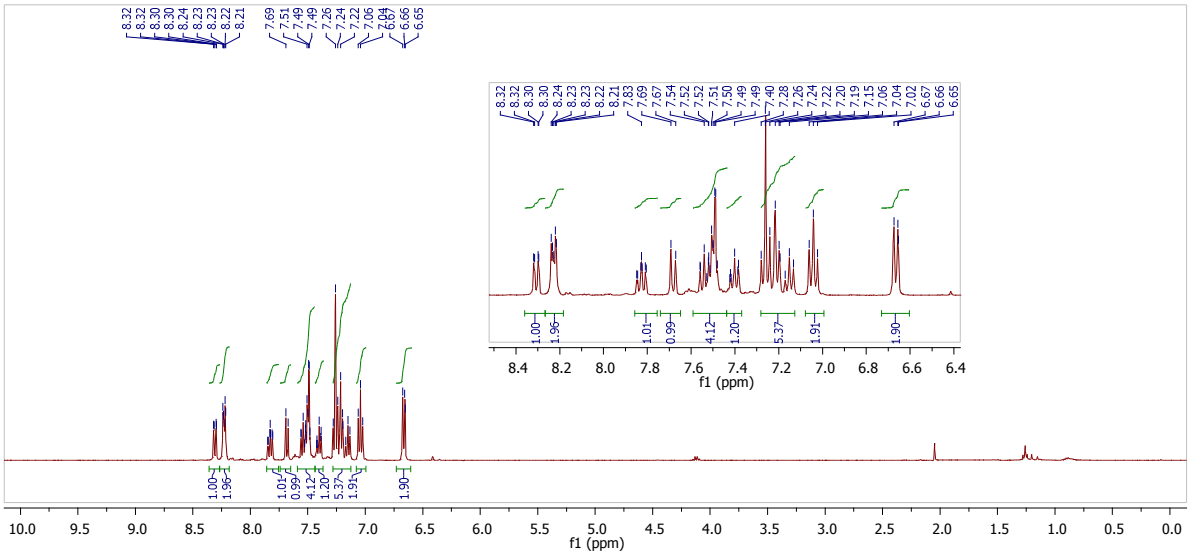
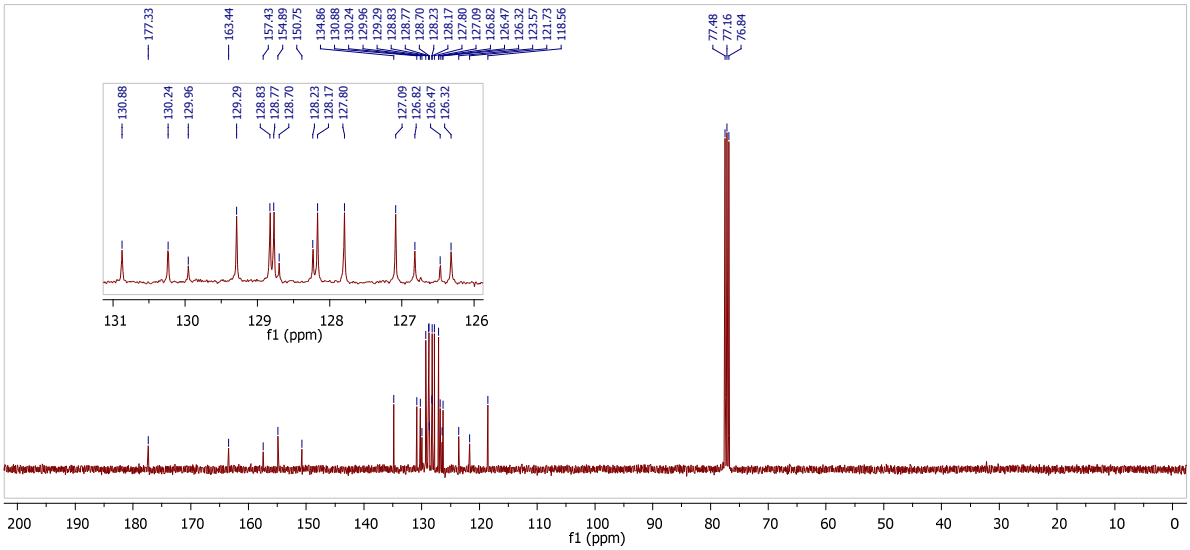
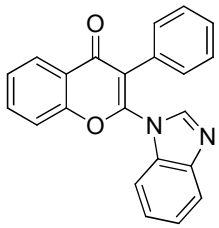
76.84
23.78
23.06
20.73
f1 (ppm)



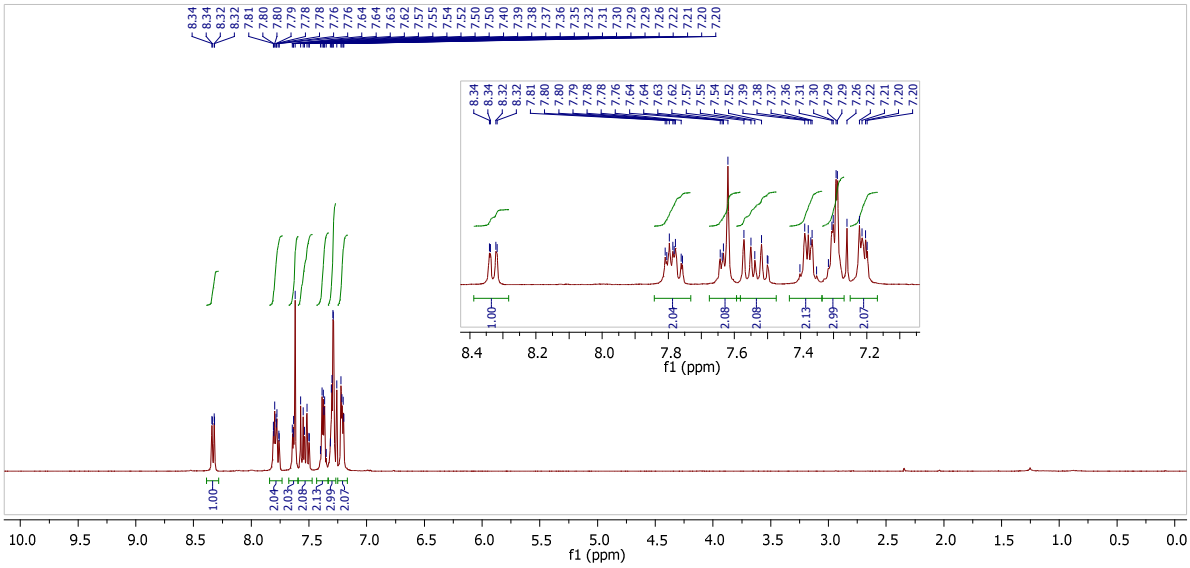
4k

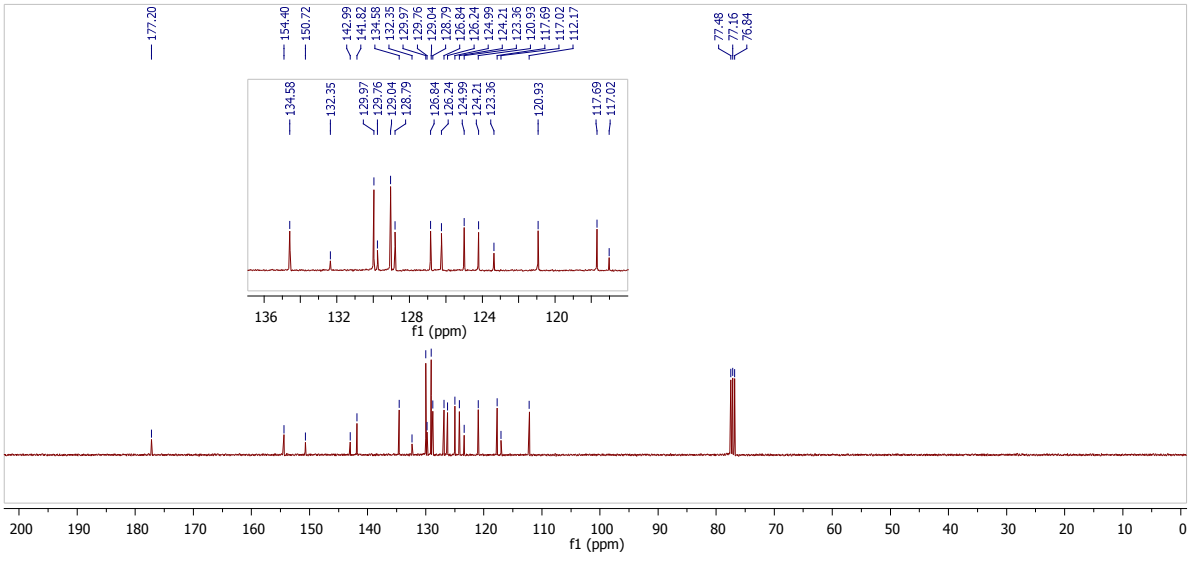


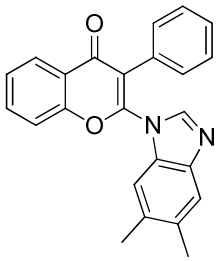




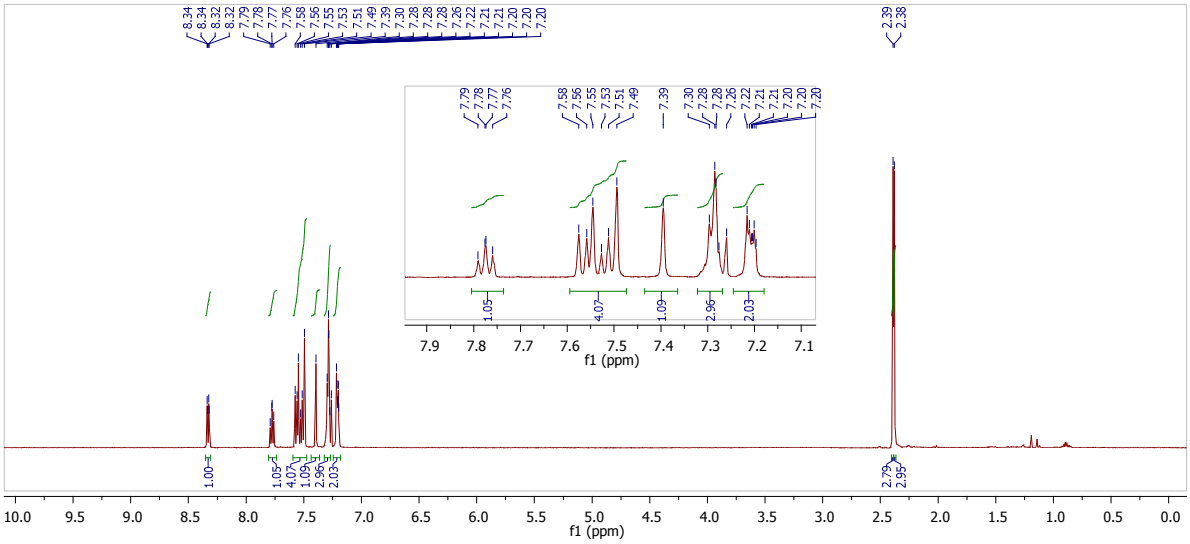
4h

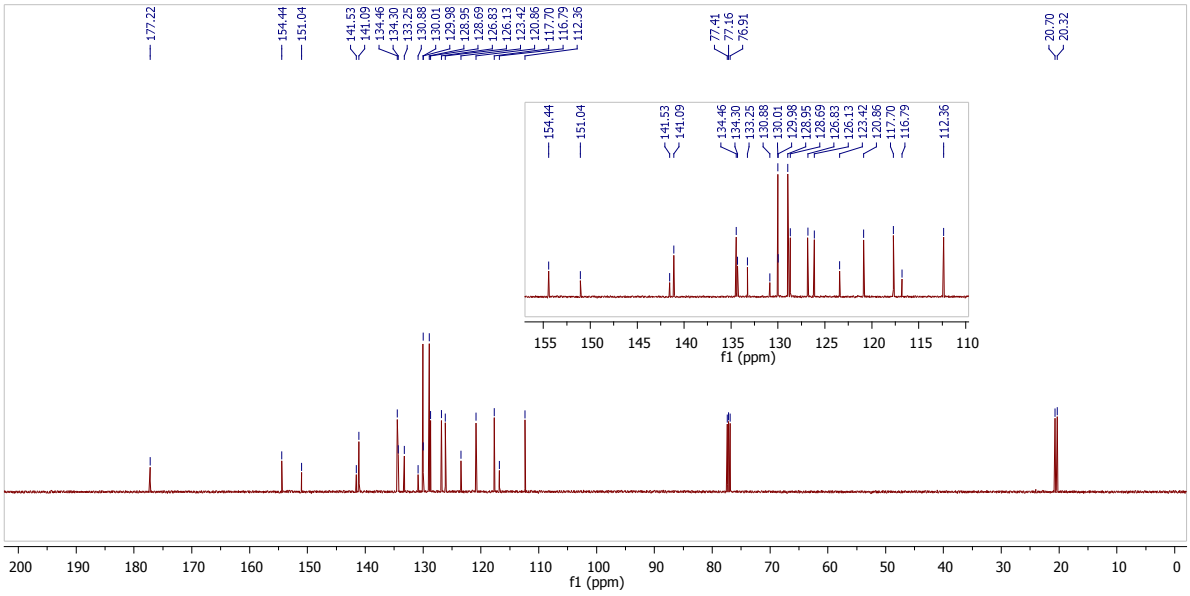


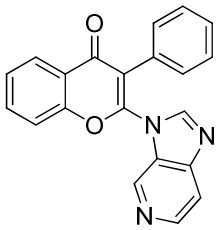




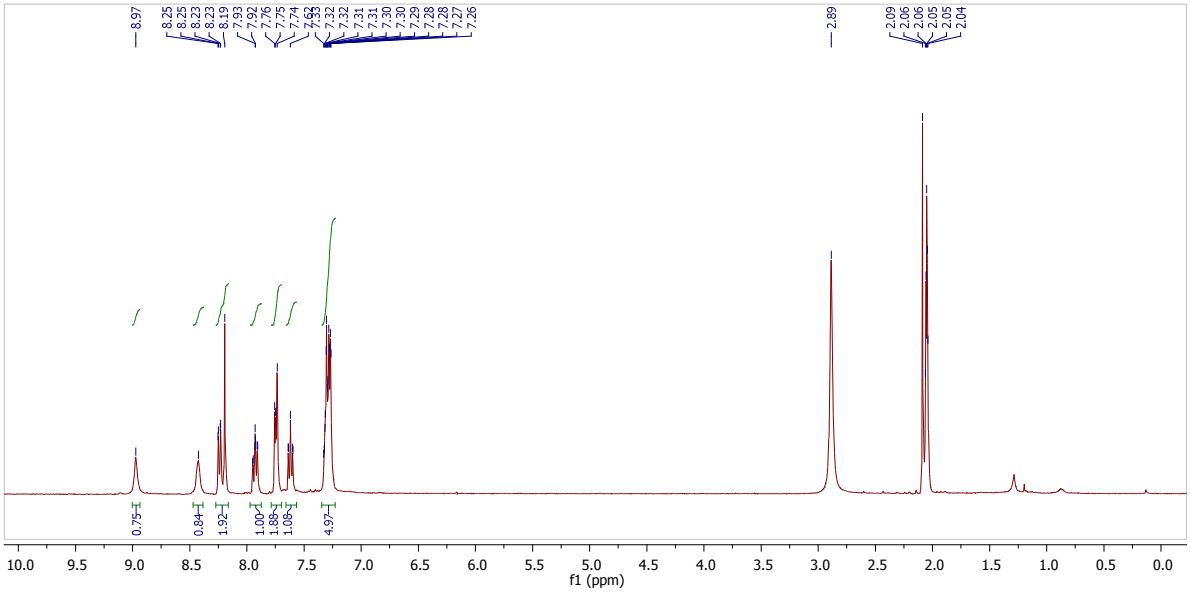
4i







4j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8.25
8.23
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8.19
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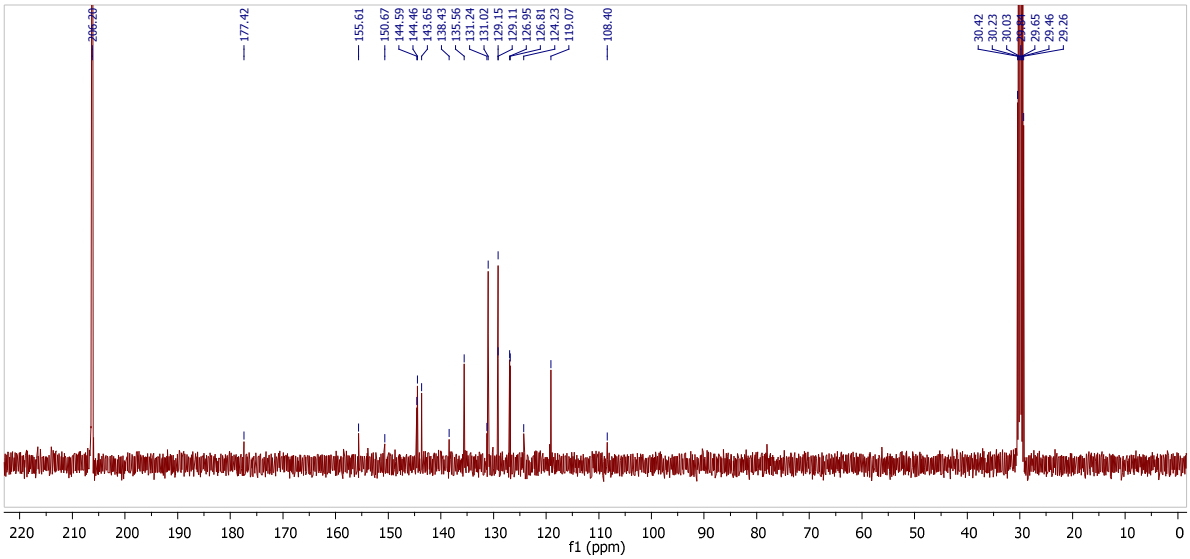
7.92
7.76
7.75
7.74
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.26
2.89
2.09
2.06
2.06
2.05
2.05
2.04
0.75
0.84
1.92
1.00
1.88
1.08
4.97
f1 (ppm)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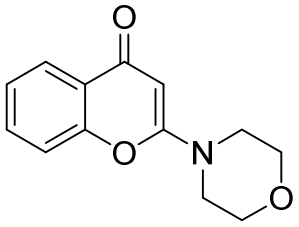
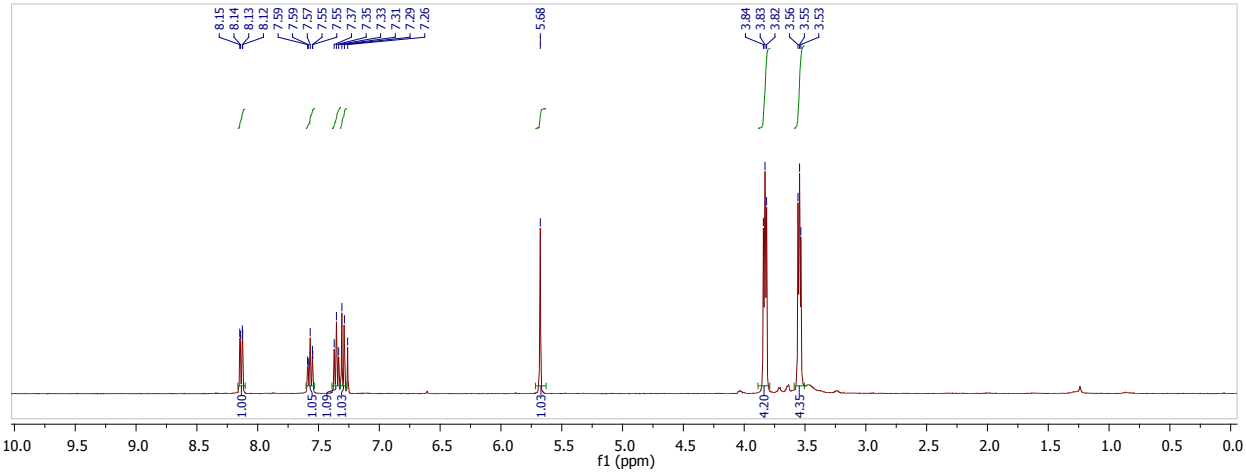
144.46
143.65
138.43
135.56
131.24
131.02
129.15
129.11
126.95
126.81
124.23
119.07
108.40
30.42
30.23
30.03
29.65
29.46
29.26
f1 (ppm)



4l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8.12
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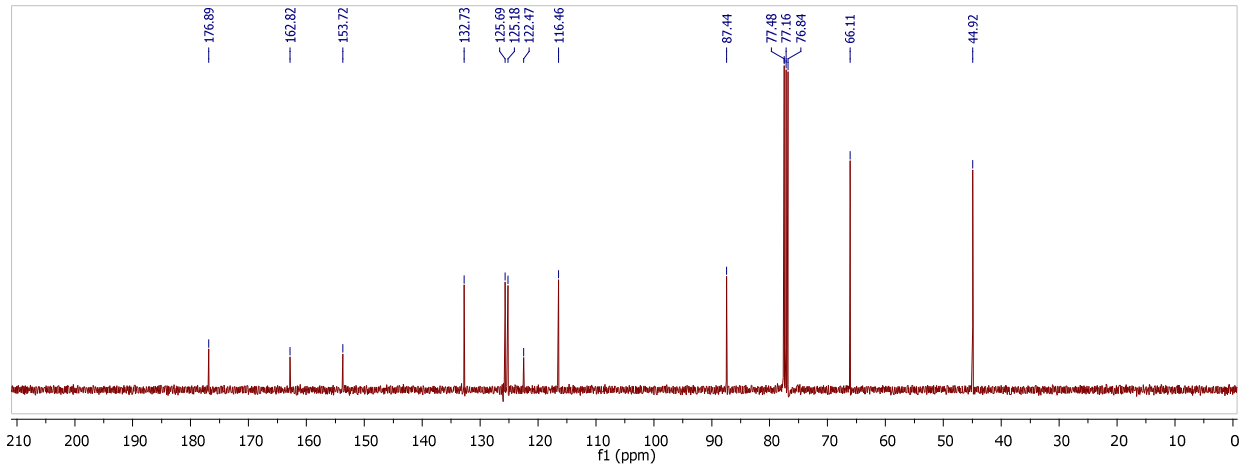
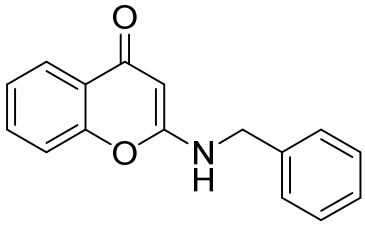
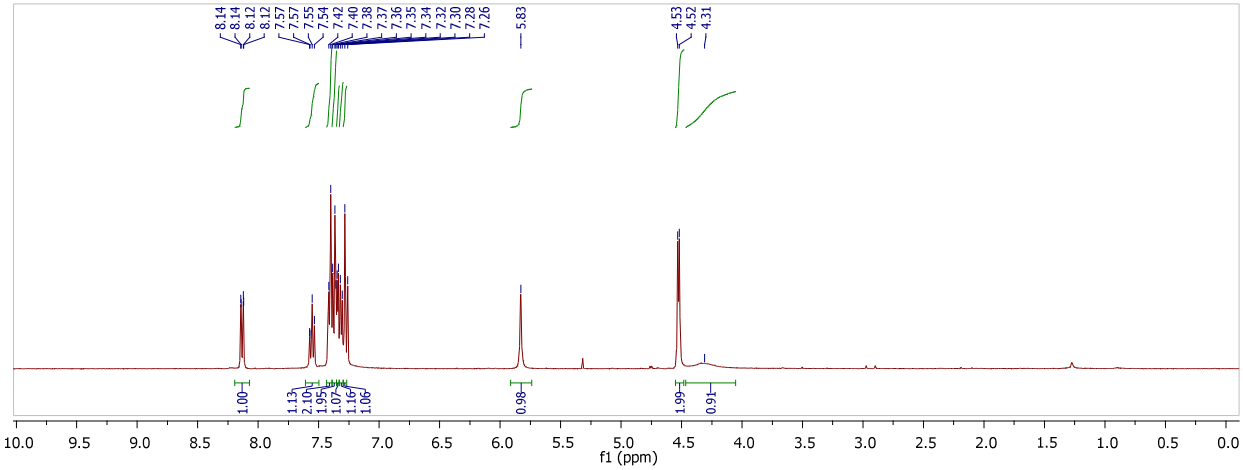
7.59
7.57
7.55
7.55
7.37
7.35
7.33
7.31
7.29
7.26
5.68
3.84
3.83
3.82
3.56
3.55
3.53
1.00
1.05
1.09
1.03
1.03
4.20
4.35
f1 (ppm)


176.89
162.82
153.72
132.73
125.69
125.18
122.47
116.46
87.44
77.48
77.16
76.84
66.11
44.92
f1 (ppm)



4m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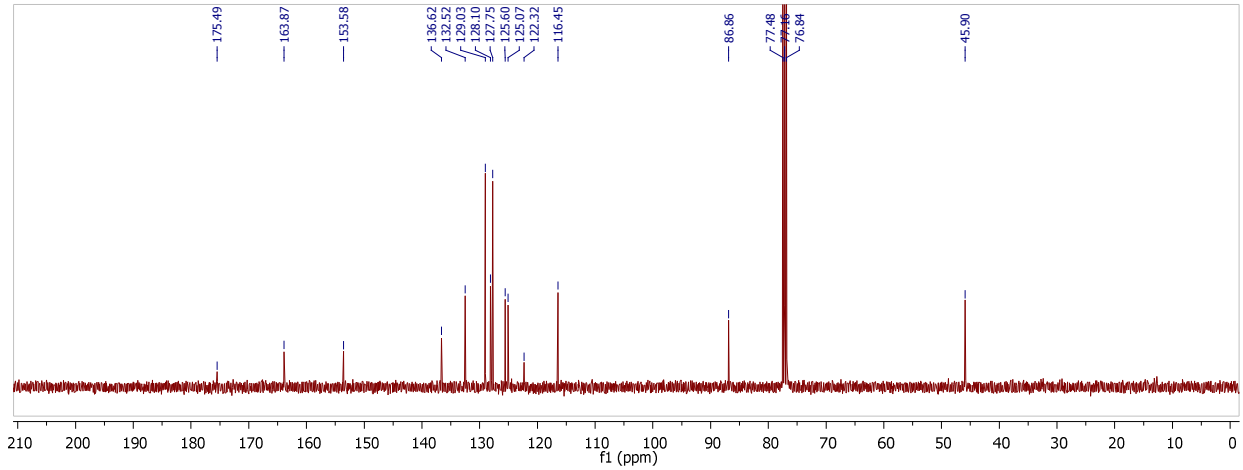
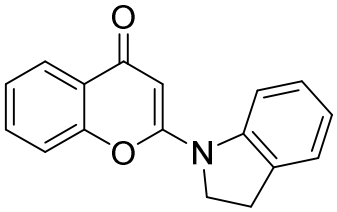
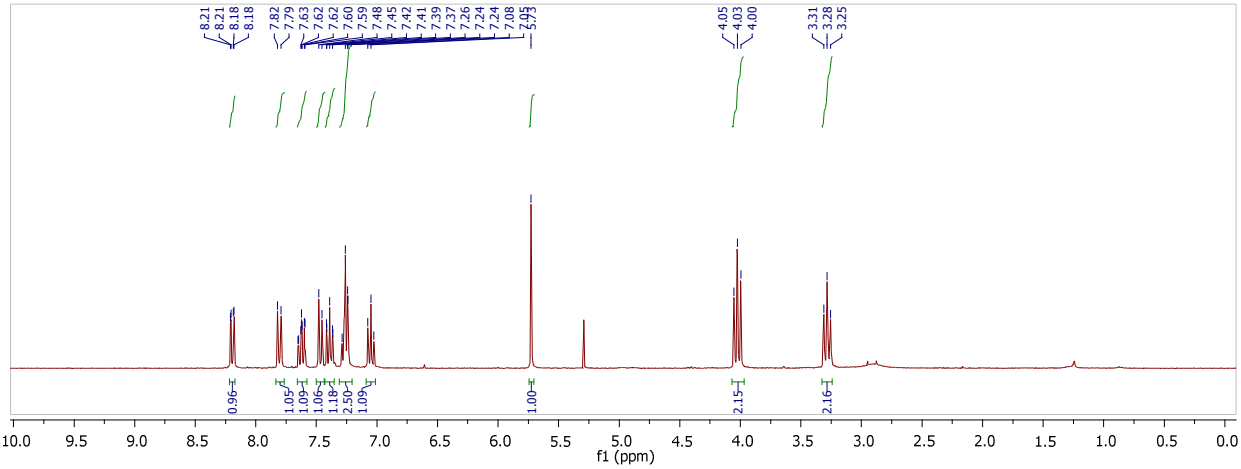
8.14
8.12
8.12
7.57
7.57
7.55
7.54
7.42
7.40
7.38
7.37
7.36
7.35
7.34
7.32
7.30
7.28
7.26
5.83
4.53
4.52
4.31
1.00
1.13
2.10
1.95
1.07
1.16
1.06
0.98
1.99
0.91
f1 (ppm)


175.49
163.87
153.58
136.62
132.52
129.03
128.10
127.75
125.60
125.07
122.32
116.45
86.86
77.48
77.16
76.84
45.90
f1 (ppm)



4n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8.21
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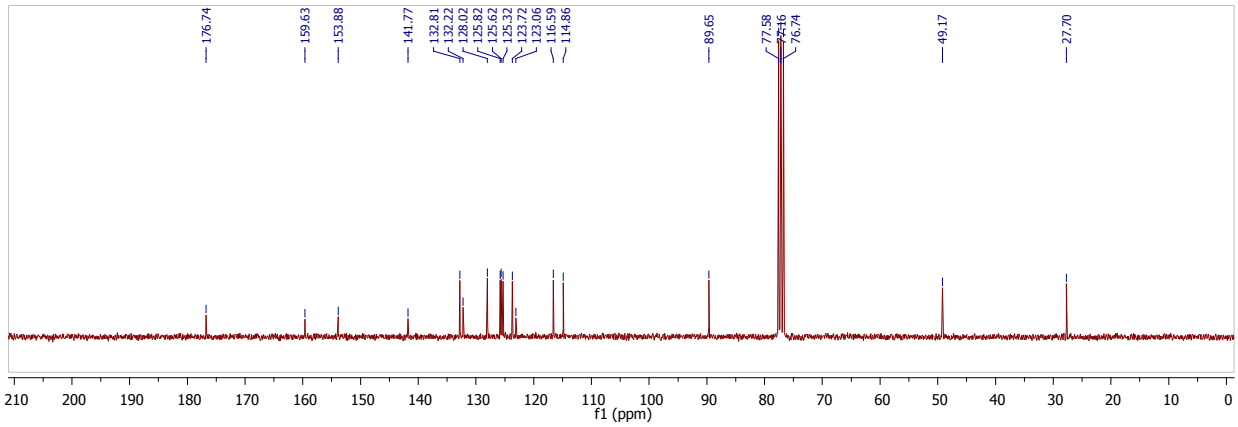
8.18
7.82
7.79
7.63
7.62
7.62
7.60
7.59
7.48
7.45
7.42
7.41
7.39
7.37
7.26
7.24
7.24
7.08
5.93
4.05
4.03
4.00
3.31
3.28
3.25
0.96
1.05
1.09
1.06
1.18
2.50
1.09
1.00
2.15
2.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


176.74
159.63
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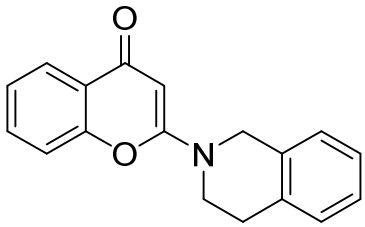
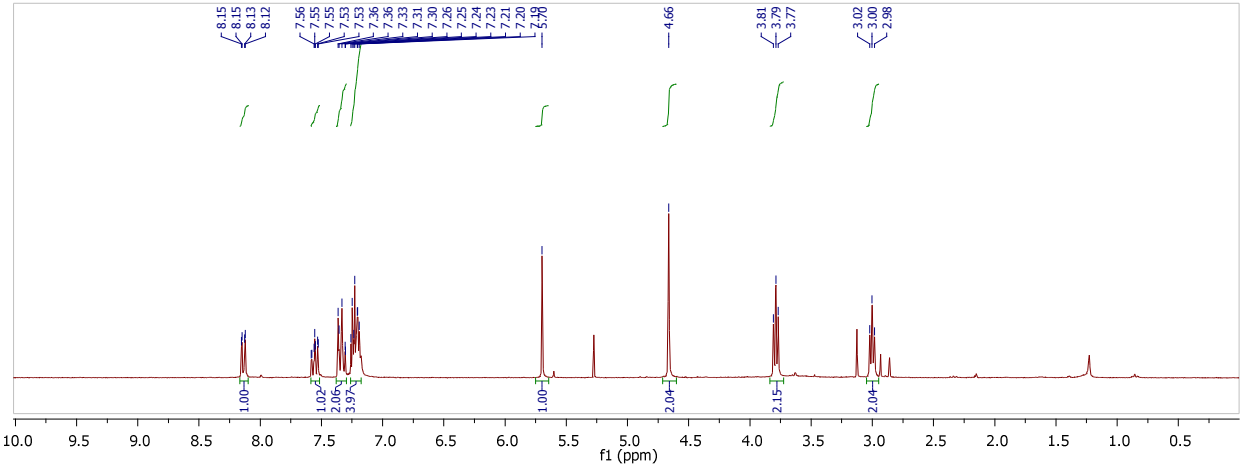
141.77
132.81
132.22
128.02
125.82
125.62
125.32
123.72
123.06
116.59
114.86
89.65
77.58
77.16
76.74
49.17
27.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
N

4o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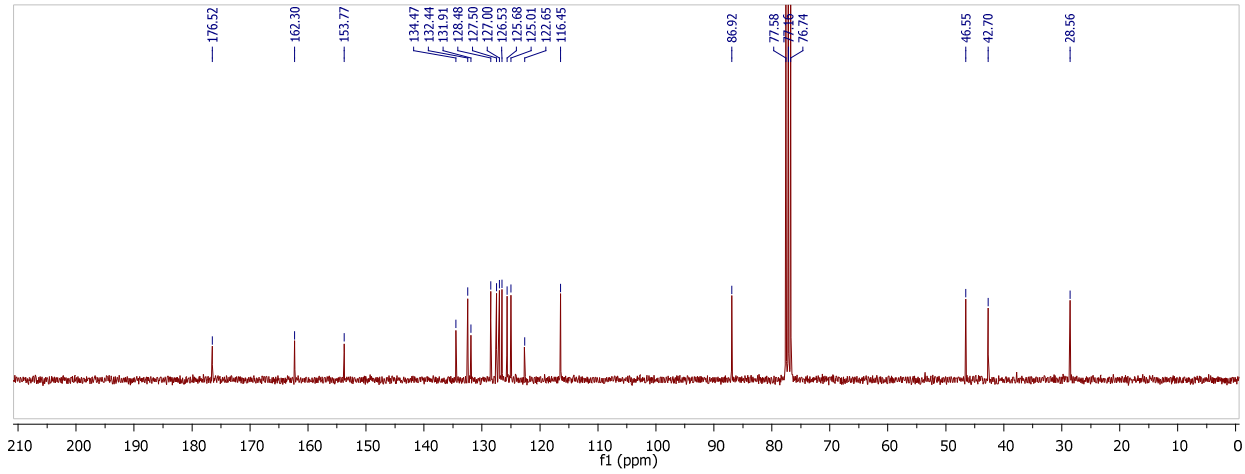
8.15
8.13
8.12
7.56
7.55
7.55
7.53
7.53
7.36
7.36
7.33
7.31
7.30
7.26
7.25
7.24
7.23
7.21
7.20
7.19
5.70
4.66
3.81
3.79
3.77
3.02
3.00
2.98
1.00
1.02
2.06
3.97
1.00
2.04
2.15
2.04
f1 (ppm)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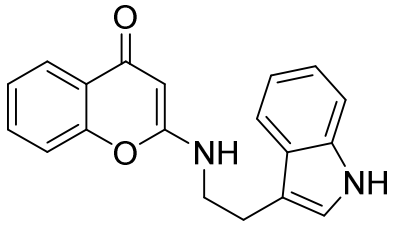
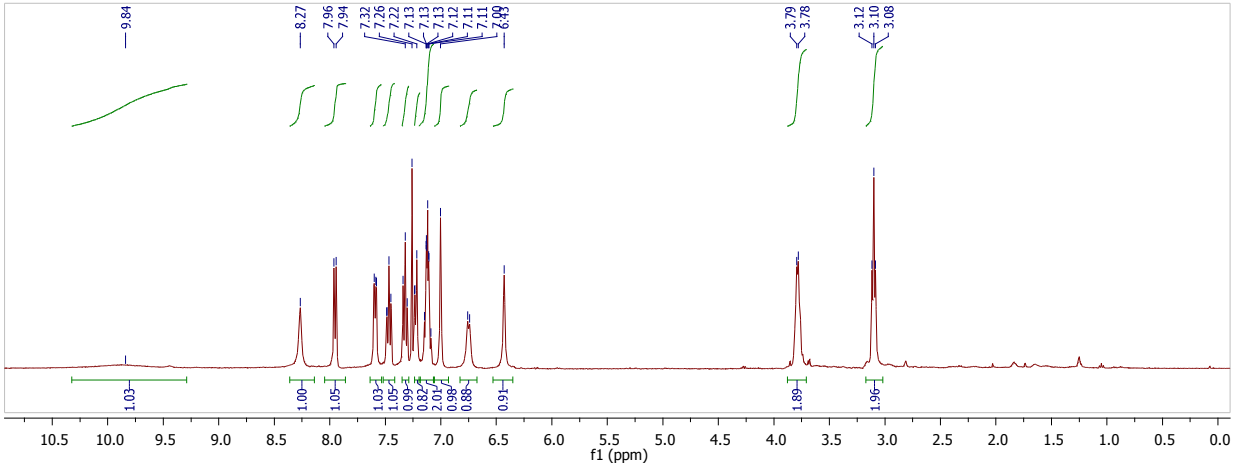
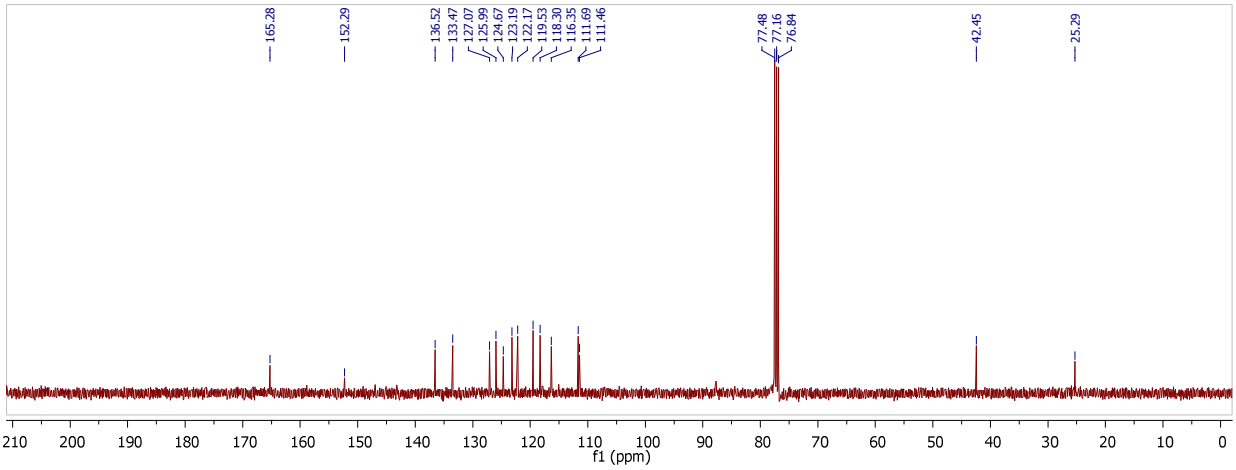
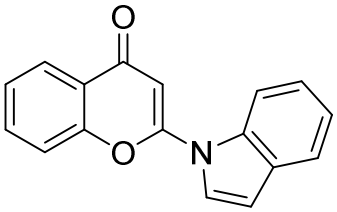
162.30
153.77
134.47
132.44
131.91
128.48
127.50
127.00
126.53
125.68
125.01
122.65
116.45
86.92
77.58
77.16
76.74
46.55
42.70
28.56
f1 (ppm)


O
O
NH
NH

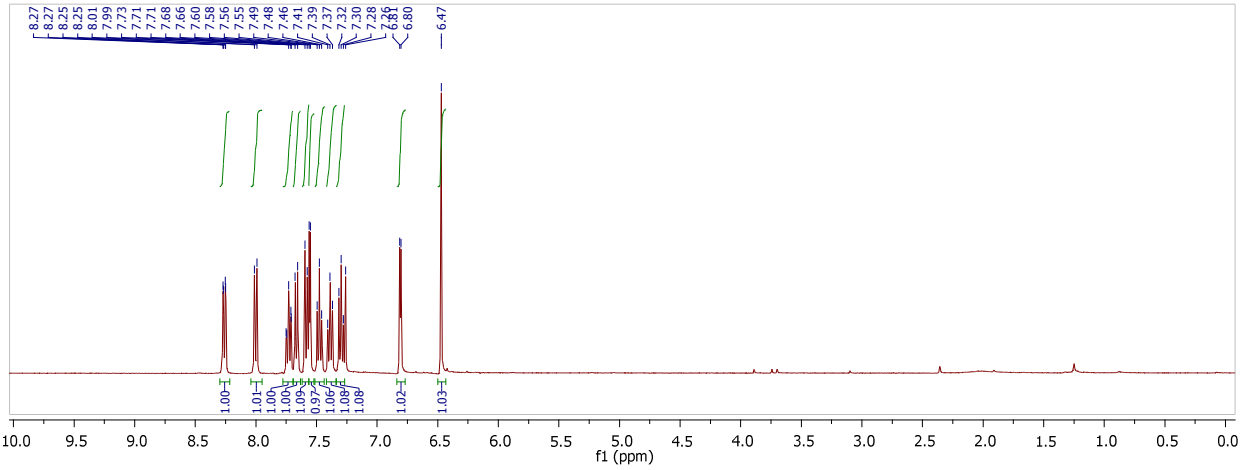
4q

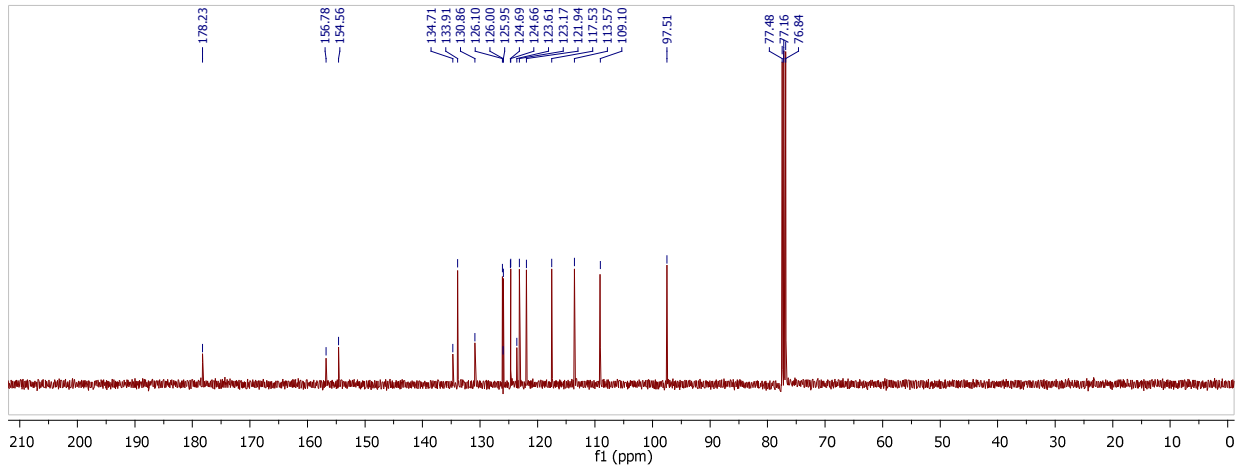

9.84
8.27
7.96
7.94
7.32
7.26
7.22
7.13
7.13
7.13
7.12
7.11
7.11
7.09
6.93
3.79
3.78
3.12
3.10
3.08
1.03
1.00
1.05
1.03
1.05
0.99
0.82
2.01
0.98
0.88
0.91
1.89
1.96
f1 (ppm)

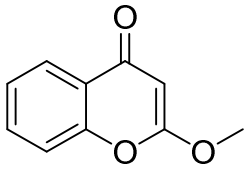

165.28
152.29
136.52
133.47
127.07
125.99
124.67
123.19
122.17
119.53
118.30
116.35
111.69
111.46
77.48
77.16
76.84
42.45
25.29
f1 (ppm)



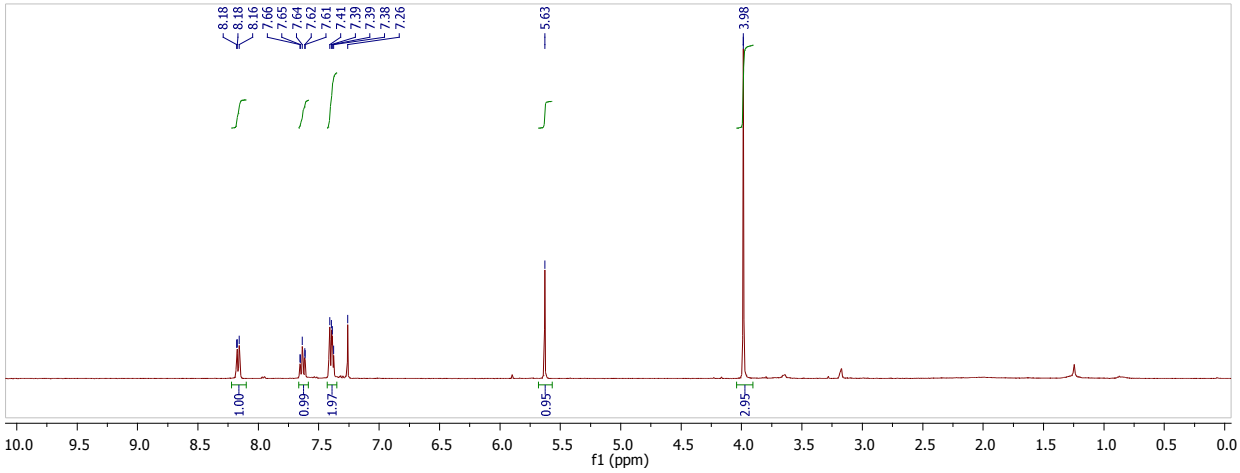
4p

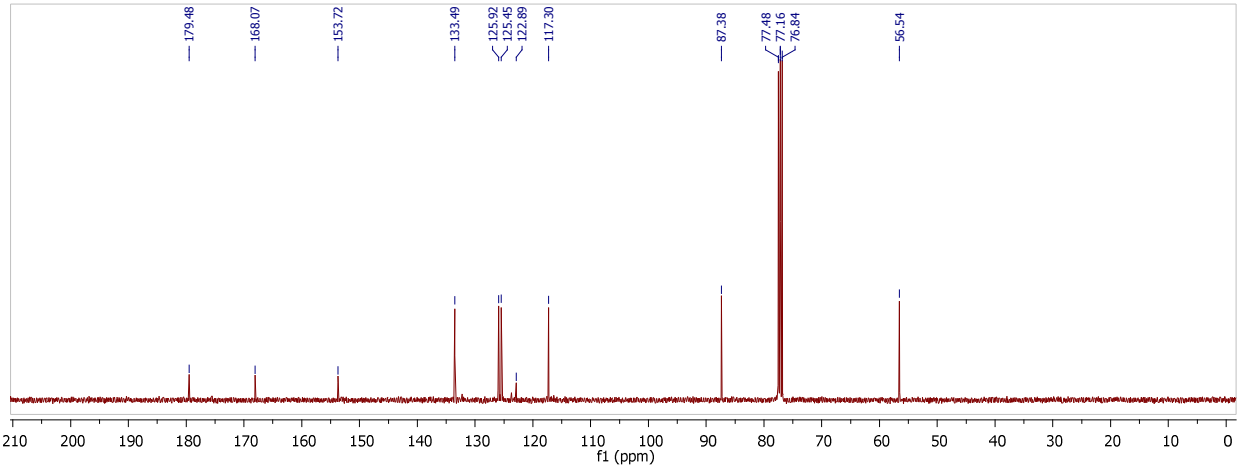

8.27
8.27
8.25
8.25
8.01
7.99
7.73
7.71
7.71
7.68
7.66
7.60
7.58
7.56
7.55
7.49
7.48
7.46
7.41
7.39
7.37
7.32
7.30
7.28
6.80
6.47
1.00
1.01
1.00
1.00
1.09
0.97
1.06
1.08
1.08
1.02
1.03
f1 (ppm)

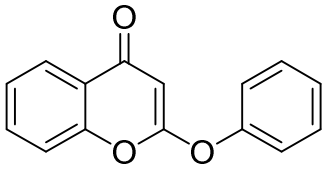

178.23
156.78
154.56
134.71
133.91
130.86
126.10
126.00
125.95
124.69
124.66
123.61
123.17
121.94
117.53
113.57
109.10
97.51
77.48
77.16
76.84
f1 (ppm)



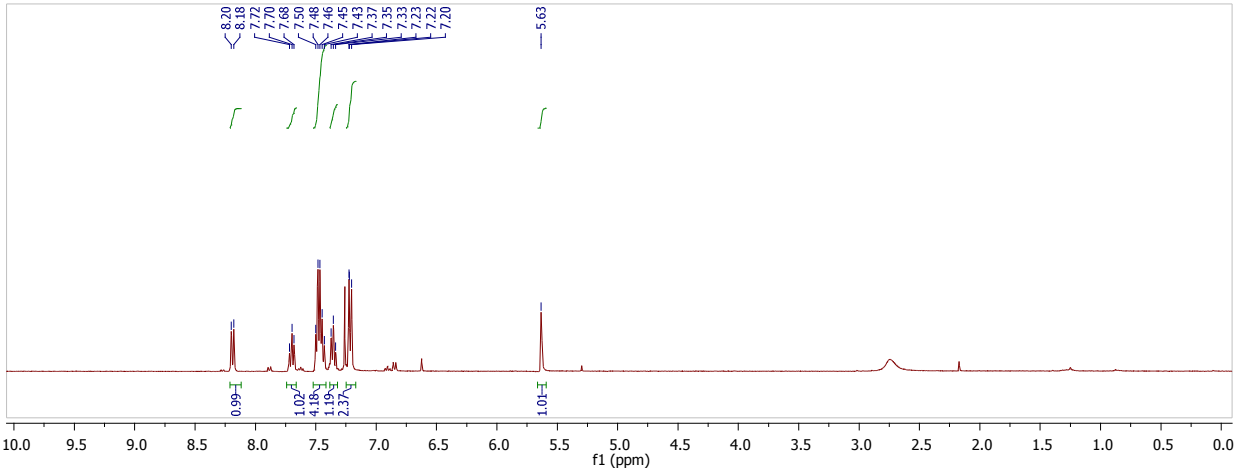
4r

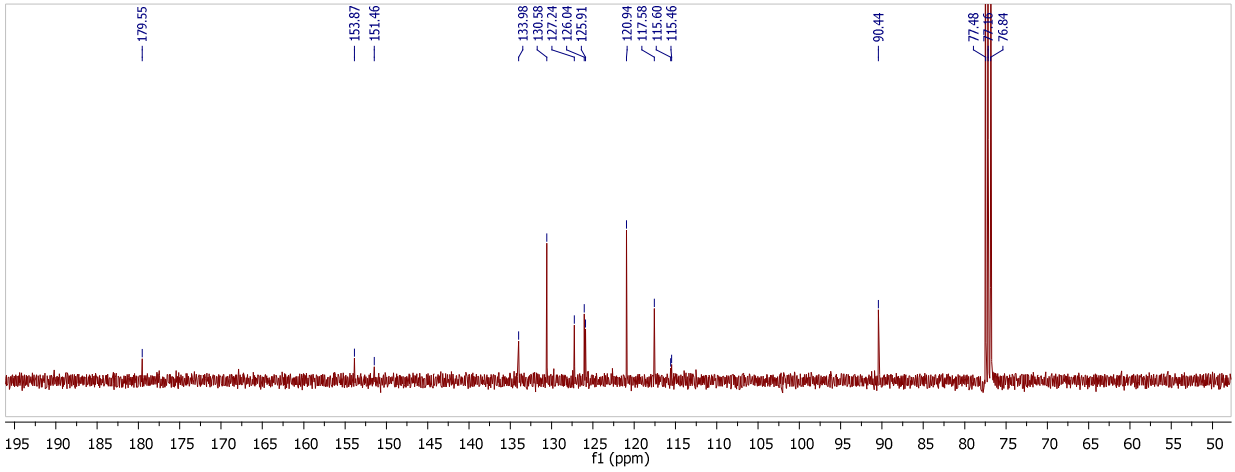

8.18
8.18
8.16
7.66
7.65
7.64
7.62
7.61
7.41
7.39
7.39
7.38
7.26
5.63
3.98
1.00
0.99
1.97
0.95
2.95
f1 (ppm)


179.48
168.07
153.72
133.49
125.92
125.45
122.89
117.30
87.38
77.48
77.16
76.84
56.54
f1 (ppm)



4s


8.20
8.18
7.72
7.70
7.68
7.50
7.48
7.46
7.45
7.43
7.37
7.35
7.33
7.23
7.22
7.20
5.63
0.99
1.02
4.18
1.19
2.37
1.01
f1 (ppm)


179.55
153.87
151.46
133.98
130.58
127.24
126.04
125.91
120.94
117.58
115.60
115.46
90.44
77.48
77.16
76.84
f1 (ppm)