

Cu-catalyzed Selective Cascade sp^3 C-H Bonds Oxidative Functionlization towards Isoxazoline Derivatives

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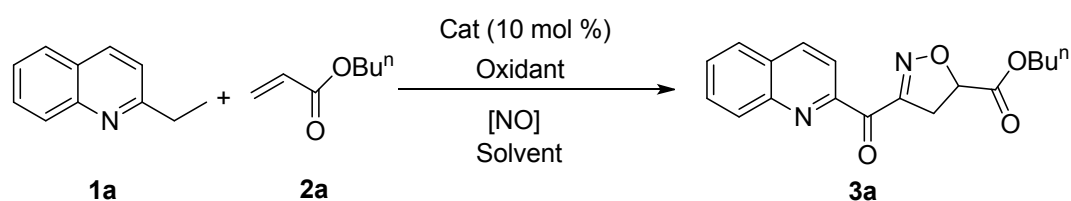
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1. General information

^1H and ^{13}C NMR spectra were recorded on a Bruker advance III 400 spectrometer in CDCl_3 with TMS as internal standard. ^{19}F NMR was recorded on the same instrument. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), Coupling constants, J , are reported in hertz. IR spectra were recorded on a Nexus 670 FT-IR spectrometer and only major peaks are reported in cm^{-1} . Mass spectra were measured using Bruker microTOF-Q II. The starting materials were purchased from Aldrich, Acros Organics, J&K Chemicals or TCI and used without further purification. Solvents were dried and purified according to the procedure from "Purification of Laboratory Chemicals book". Column chromatography was carried out on silica gel (particle size 200-400 mesh ASTM).

2. Reaction conditions screening^[a]



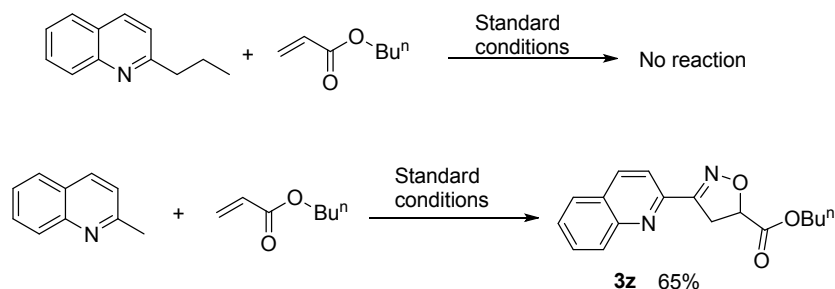
Entry	Cat.	Oxidant	[NO]	Solvent	Yield of 3a [%] ^[b,c]
1	CuCl ₂	PhI(OAc) ₂	KNO ₃	DMF	0
2	CuCl ₂	BQ	KNO ₃	DMF	0
3	CuCl ₂	TBHP	KNO ₃	DMF	0
4	CuCl ₂	Select-F	KNO ₃	DMF	21
5	CuCl ₂	K ₂ S ₂ O ₈	KNO ₃	DMF	63
6	CuCl	K ₂ S ₂ O ₈	KNO ₃	DMF	65
7	CuBr	K ₂ S ₂ O ₈	KNO ₃	DMF	71
8	Sc(OTf) ₃	K ₂ S ₂ O ₈	KNO ₃	DMF	0
9	AlCl ₃	K ₂ S ₂ O ₈	KNO ₃	DMF	0
10	Zn(OTf) ₂	K ₂ S ₂ O ₈	KNO ₃	DMF	0
11	Fe(acac) ₂	K ₂ S ₂ O ₈	KNO ₃	DMF	24
12	CuBr	K ₂ S ₂ O ₈	KNO ₃	DMF	72 ^[d]
13	CuBr	K ₂ S ₂ O ₈	KNO ₃	DMF	76
14	CuBr	K ₂ S ₂ O ₈	KNO ₂	DMF	0
15	CuBr	K ₂ S ₂ O ₈	NaNO ₃	DMF	74
16	CuBr	K ₂ S ₂ O ₈	NH ₄ NO ₃	DMF	37
17	CuBr	K ₂ S ₂ O ₈	AgNO ₃	DMF	0
18	CuBr	K ₂ S ₂ O ₈	KNO ₃	DMSO	42
19	CuBr	K ₂ S ₂ O ₈	KNO ₃	THF	0
20	CuBr	K ₂ S ₂ O ₈	KNO ₃	DCE	0
21	CuBr	K ₂ S ₂ O ₈	KNO ₃	Toluene	0
22	CuBr	K ₂ S ₂ O ₈	KNO ₃	CH ₃ CN	43
23	CuBr	K ₂ S ₂ O ₈	KNO ₃	DMF/CH ₃ CN=10:1	82 ^[e]
24	---	K ₂ S ₂ O ₈	KNO ₃	DMF	0

[a] Reaction was carried out with Cu (10 mol %), oxidant (2.5 equiv), [NO] (6.0 equiv), 2-ethylquinoline **1a** (0.2mmol), butyl acrylate **2a** (0.6 mmol) in solvent (2.0 ml) at 80 °C for 24 h. [b] Isolated yield. [c] Entries 1-9 were performed in a closed tube under air and entries 11-20 were performed in an open tube. [d] Reaction was performed under O₂. [e] DMF/CH₃CN=2ml/0.2ml.

3. General procedures:

In a schlenk tube, 2-ethylquinoline **1a** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), $K_2S_2O_8$ (0.75 mmol), KNO_3 (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3 mL) were added. The mixture was allowed to stir at 80°C for 24 hr with the tube open to air. After substrate was consumed (monitored by TLC), the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (4*10 mL) and H_2O . The organic layers were combined, dried with $MgSO_4$. The residue was purified by column chromatography (EtOAc /petroleum ether=10/1) to give the product **3a**.

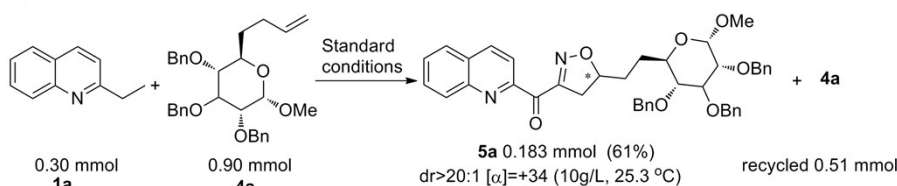
4. Other 2-substituted quinolines scope



5. Synthetic application

5.1 High selective synthesis of isoxazoline-linked carbohydrates

a) High selective synthesis of isoxazoline-linked carbohydrates



b) Gram-scale reaction



In a schlenk tube, 2-ethylquinoline **1a** (0.30 mmol), carbohydrates **4a** (0.9 mmol), CuBr (0.03 mmol), $K_2S_2O_8$ (0.75 mmol), KNO_3 (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3 mL) were added. After the mixture was stirred at 80°C for 20 hours with the tube open to air, the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (5*10 mL) and H_2O . Organic layers were combined, dried with $MgSO_4$. The residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the product **5a**, and the big part of excess carbohydrates **4a** was recycled (0.51 mmol).

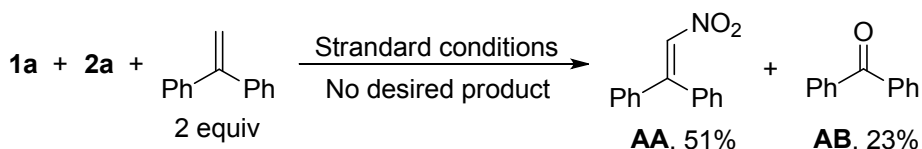
5.2 Gram-scale reaction



In a 100 ml round-bottom flask, 2-ethylquinoline **1a** (8.0 mmol, 1.26g), butyl acrylate **2a** (2.4 mmol, 3.07g), CuBr (0.8 mmol), K₂S₂O₈ (20 mmol), KNO₃ (48 mmol) were added. Then, anhydrous DMF (60 mL) and acetonitrile (6 mL) were added. After the mixture was stirred at 80°C for 24 hours with the tube open to air, the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (2*150 mL) and H₂O (150 mL). Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the product **3a** (5.28 mmol, 1.73g, 66 %).

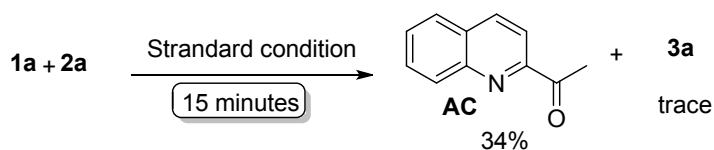
6. Mechanism experiments

6.1. Radical trapping experiments

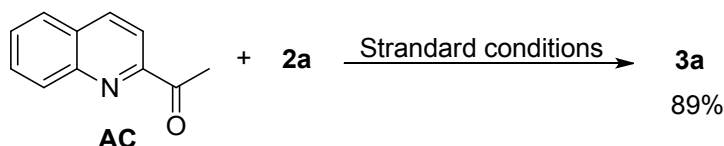


In a schlenk tube, 2-ethylquinoline **1a** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added, then 1, 1-Diphenylethylene (0.60 mmol) was added to the system. After stirred at 80°C for 4 hours, the reaction was completed (TLC). Then it was cooled to room temperature, extracted by EtOAc (3*10 mL) and H₂O. The organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (petroleum ether/EtOAc=50/1) to give the (2-nitroethene-1, 1-diyl)dibenzene **AA** (51%) and benzophenone **BB** (23%). No desired product was formed under this condition.

6.2. Control experiments

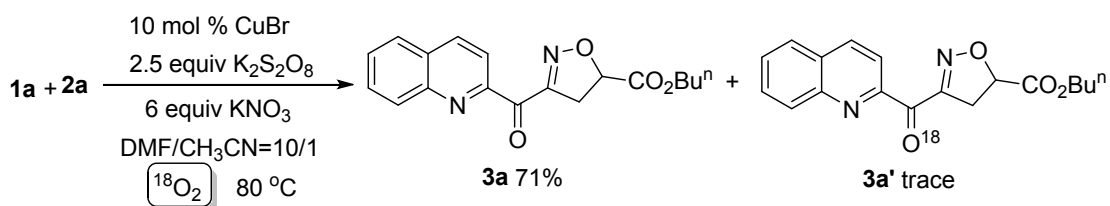


In a schlenk tube, 2-ethylquinoline **1a** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added. The mixture was allowed to stir at 80°C for 15 minutes with the tube open to air. Then the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (3*10 mL) and H₂O. Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (EtOAc/petroleum ether=20/1) to give the product **AC** in 34 % yield combined with trace amount of **3a**.



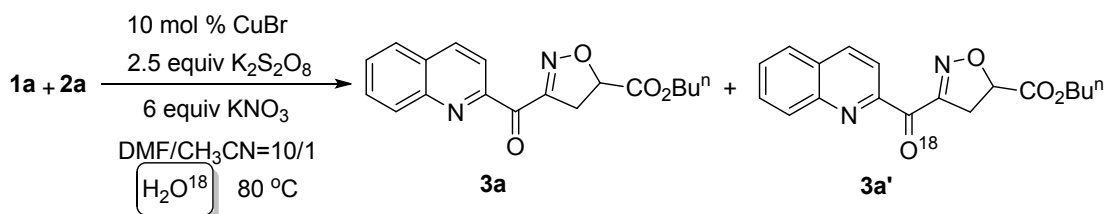
In a schlenk tube, 1-(quinolin-2-yl)ethanone **AC** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added. The mixture was allowed to stir at 80°C for 24 hr with the tube open to air. Then the reaction was cooled to room temperature, and the mixture is extracted by EtOAc (3*10 mL) and H₂O. Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (EtOAc /petroleum ether=101/1) to give the product **3a** in 89 % yield.

6.3. $^{18}\text{O}_2$ labeling experiment



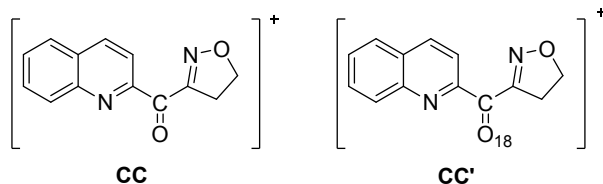
In a schlenk tube, 2-ethylquinoline **1a** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), $\text{K}_2\text{S}_2\text{O}_8$ (0.75 mmol), KNO_3 (1.80 mmol) were added, anhydrous DMF (3 mL) and acetonitrile (0.3 mL) were added, the tube was degassed and charged with ^{18}O (three times). The mixture was allowed to stir at 80°C for 24 hours, then the reaction was cooled to room temperature and extracted by EtOAc (3*10 mL) and H_2O . The organic were combined, dried with MgSO_4 . The residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the product, and product was analyzed by chromatography-mass spectrometry to identify the percentage of **3a'**. This result indicated that molecular oxygen was not the oxygen source of the carbonyl group

6.4. H_2O^{18} labeling experiment

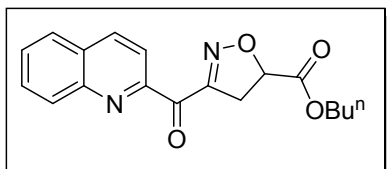


Equivalent of H_2O^{18} (equiv)	0	1	2	3	4	5	7	9
Total yield (3a + 3a')	81.4%	81.9%	76.6%	69.0%	57.8%	54.5%	33.1%	29.9%
Percentage of 3a' [3a' /(3a + 3a')]	0%	7.7%	11.1%	13.4%	15.4%	18.3%	24.5%	28.7%

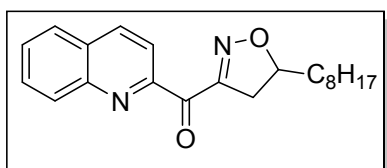
In eight different schlenk tubes, 2-ethylquinoline **1a** (0.30 mmol), butyl acrylate **2a** (0.9 mmol), CuBr (0.03 mmol), $\text{K}_2\text{S}_2\text{O}_8$ (0.75 mmol), KNO_3 (1.80 mmol), anhydrous DMF (3 mL) and acetonitrile (0.3 mL) were added to every tube, then different equivalents of H_2O^{18} (0, 1, 2, 3, 4, 5, 7, 9,) were added to the different tubes and allowed to stir at 80°C for 24 hours, then every reactions were extracted by EtOAc (3*10 mL) and H_2O . The organic were combined, dried with MgSO_4 . The every residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the corresponding products, and products were analyzed by chromatography-mass spectrometry to identify the percentage of **3a'** (We used the debris samples of **CC** and **CC'** as the standard to set up the ration). This result indicated that that H_2O might serve as a small part of the oxygen source for the carbonyl group.



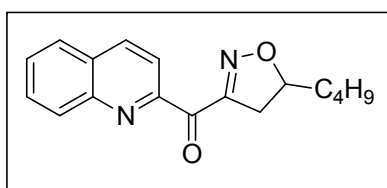
7. Characterization of the Products



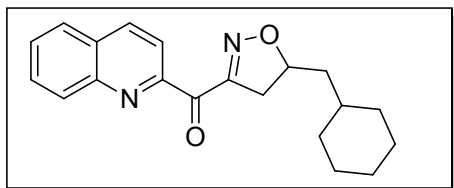
butyl 3-(quinoline-2-carbonyl)-4,5-dihydroisoxazole-5-carboxylate 3a : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.32 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 5.28 (t, $J = 9.6$ Hz, 1H), 4.24 (t, $J = 9.6$ Hz, 2H), 3.86 (d, $J = 9.6$ Hz, 2H), 1.69 (m, 2H), 1.40 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ : 185.66, 169.13, 156.48, 152.54, 147.18, 137.09, 130.71, 130.33, 129.36, 128.98, 127.57, 120.08, 79.62, 65.96, 38.72, 30.38, 19.02, 18.93, 13.57. HRMS calc. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$, 327.1339; found, 327.1335.



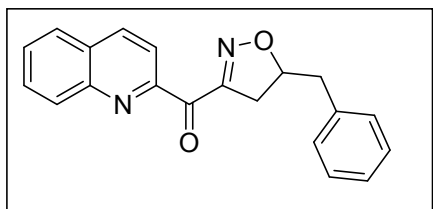
(5-octyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3b : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.80-7.76 (m, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 4.91-4.83 (m, 1H), 3.54 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.15 (dd, $J = 8.8$ Hz, $J = 17.6$ Hz, 1H), 1.90-1.81 (m, 1H), 1.74-1.62 (m, 1H), 1.54-1.39 (m, 12H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.96, 157.50, 153.27, 147.31, 136.93, 130.77, 130.22, 129.26, 128.70, 127.55, 120.39, 84.23, 38.95, 35.14, 31.79, 29.40, 29.33, 29.15, 25.25, 22.61, 14.05. HRMS calc. for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 339.2067; found, 339.2063.



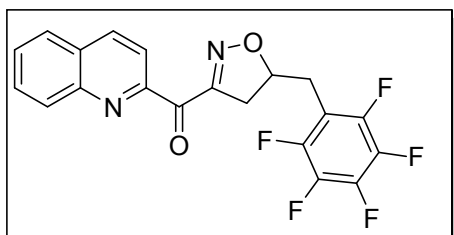
(5-butyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3c : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.31 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.81-7.77 (m, 1H), 7.68-7.64 (m, 1H), 4.92-4.84 (m, 1H), 3.54 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.16 (dd, $J = 8.8$ Hz, $J = 17.2$ Hz, 1H), 1.91-1.82 (m, 1H), 1.73-1.65 (m, 1H), 1.55-1.35 (m, 4H), 0.94 (t, $J = 6.8$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.91, 157.46, 153.18, 147.23, 136.91, 130.69, 130.20, 129.19, 128.68, 127.52, 120.37, 84.19, 38.87, 34.78, 27.31, 22.39, 13.89. HRMS calc. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 283.1441; found, 283.1438.



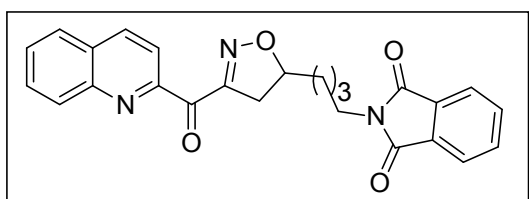
(5-(cyclohexylmethyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3d : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (d, $J = 8.8$ Hz, 1H), 8.25 (d, $J = 8.8$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.80-7.76 (m, 1H), 7.67-7.63 (m, 1H), 5.00-4.94 (m, 1H), 3.56 (dd, $J = 10.4$ Hz, $J = 17.2$ Hz, 1H), 3.12 (dd, $J = 8.8$ Hz, $J = 17.2$ Hz, 1H), 1.86-1.54 (m, 6H), 1.53-1.49 (m, 2H), 1.33-1.15 (m, 3H), 1.04-0.94 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.87, 157.52, 153.18, 147.22, 136.88, 130.88, 130.27, 129.17, 128.64, 127.80, 120.35, 82.37, 42.93, 38.52, 34.55, 33.38, 32.87, 26.30, 26.05, 26.03. HRMS calc. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 323.1754; found, 323.1758.



(5-benzyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3e : Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.29 (d, $J = 9.6$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.78 (m, 1H), 7.65 (m, 1H), 7.28 (m, 5H), 5.13 (m, 1H), 3.49 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.27 (dd, $J = 8.4$ Hz, $J = 17.6$ Hz, 1H), 3.19 (dd, $J = 6.0$ Hz, $J = 14.0$ Hz, 1H), 2.99 (dd, $J = 6.4$ Hz, $J = 14.0$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.71, 157.42, 153.06, 147.23, 136.97, 136.10, 130.69, 130.26, 129.40, 129.31, 129.25, 128.75, 128.65, 127.54, 126.91, 120.34. HRMS calc. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 317.1286; found, 317.1282.

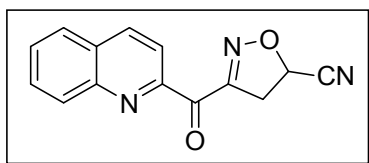


(5-((perfluorophenyl)methyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3f : White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.33 (d, $J = 8.8$ Hz, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.83-7.78 (m, 1H), 7.70-7.66 (m, 1H), 5.15-5.07 (m, 1H), 3.65 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.37 (dd, $J = 7.2$ Hz, $J = 17.6$ Hz, 1H), 3.23 (dd, $J = 7.6$ Hz, $J = 14.0$ Hz, 1H), 3.10 (dd, $J = 6.0$ Hz, $J = 14.4$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.36, 157.12, 152.75, 147.20, 145.44 (dm, $J = 246.0$ Hz), 140.35 (dm, $J = 251.0$ Hz), 137.52 (dm, $J = 244.0$ Hz), 137.12, 130.69, 130.37, 129.37, 128.97, 127.60, 120.10, 109.98-109.57 (m), 81.11, 39.46, 27.90. ^{19}F NMR (367 MHz, CDCl_3) δ : -142.0 (m, 2F), -155.3 (t, $J = 18.5$ Hz 1F), -161.8 (m, 2F). HRMS calc. for $\text{C}_{20}\text{H}_{11}\text{F}_5\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 407.0813; found, 407.0808.



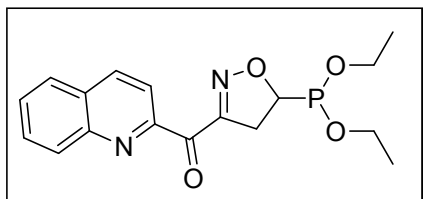
mixed with trace amount of impurities.

2-(2-(3-(quinoline-2-carbonyl)-4,5-dihydroisoxazol-5-yl)ethyl)isoindoline-1,3-dione 3h : Yellow oil. Selected ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (d, $J = 8.8$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 7.88-7.76 (m, 4H), 7.71-7.63 (m, 3H), 4.91-4.83 (m, 1H), 3.74-3.71 (m, 2H), 3.56 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.16 (dd, $J = 8.4$ Hz, $J = 17.2$ Hz, 1H), 1.95-1.86 (m, 1H), 1.84-1.73 (m, 3H), 1.64-1.55 (m, 1H), 1.53-1.43 (m, 1H). Selected ^{13}C NMR (400 MHz, CDCl_3) δ : 186.76, 168.33, 157.41, 153.10, 147.18, 136.92, 133.85, 131.97, 130.67, 130.20, 129.19, 128.68, 127.50, 123.13, 120.32, 83.70, 39.00, 37.52, 34.58, 28.23, 22.56. HRMS calc. for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$) $^+$, 428.1605; found, 428.1606.

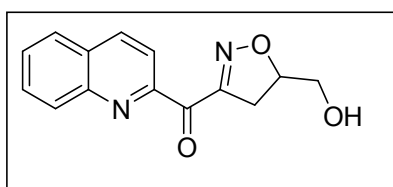


3-(quinoline-2-carbonyl)-4,5-dihydroisoxazole-5-carbonitrile 3i : Red oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.36 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.85-7.81 (m, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 5.48 (dd, $J = 7.6$ Hz, $J = 10.4$ Hz, 1H), 4.11-3.99 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ : 184.69, 156.30, 151.87, 147.12, 137.51,

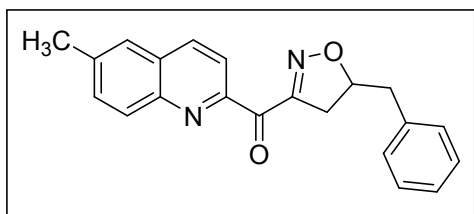
130.69, 129.67, 129.51, 127.73, 119.69, 116.20, 67.64, 41.61. HRMS calc. for $C_{14}H_9N_3O_2$ ($M+H$)⁺, 252.0768; found, 252.0765.



diethyl (3-(quinoline-2-carbonyl)-4,5-dihydroisoxazol-5-yl)phosphonite 3j : Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.32 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.82-7.77 (m, 1H), 7.69-7.65 (m, 1H), 5.04-4.98 (m, 1H), 4.34-4.24 (m, 4H), 3.89 (dd, *J* = 11.2 Hz, *J* = 23.6 Hz, 2H), 1.41-1.37 (m, 6H). ¹³C NMR (400 MHz, CDCl₃) δ: 185.67, 156.83, 156.77, 152.49, 147.13, 137.05, 130.65, 130.29, 129.32, 128.96, 127.54, 119.95, 77.76, 76.08, 63.62, 63.56, 63.39, 63.32, 37.46, 16.43, 16.37. ³¹P NMR (162 MHz, CDCl₃) : 17.11. HRMS calc. for $C_{17}H_{19}N_2O_5P$ ($M+H$)⁺, 363.1104; found, 363.1100.

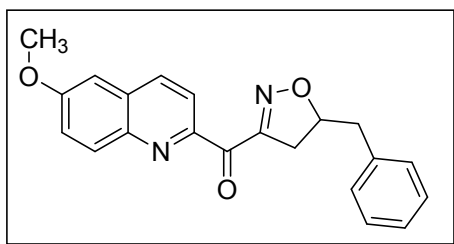


(5-(hydroxymethyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3k : Red oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.31 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.81-7.77 (m, 1H), 7.68-7.64 (m, 1H), 5.04-4.97 (m, 1H), 3.95 (dd, *J* = 2.8 Hz, *J* = 12.4 Hz, 1H), 3.75 (dd, *J* = 4.8 Hz, *J* = 12.4 Hz, 1H), 3.57 (dd, *J* = 11.2 Hz, *J* = 17.2 Hz, 1H), 3.46 (dd, *J* = 8.4 Hz, *J* = 17.2 Hz, 1H), 2.61 (br, 1H). ¹³C NMR (400 MHz, CDCl₃) δ: 188.45, 157.81, 152.33, 147.13, 137.15, 130.58, 130.39, 129.22, 128.89, 127.60, 120.11, 83.76, 63.44, 35.64. HRMS calc. for $C_{14}H_{12}N_2O_3$ ($M+H$)⁺, 257.0921; found, 257.0919.

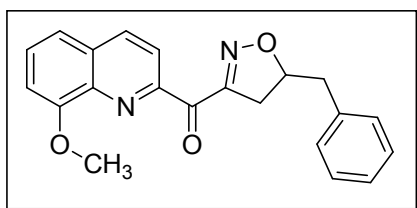


(5-benzyl-4,5-dihydroisoxazol-3-yl)(6-methylquinolin-2-yl)methanone 3l : Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.18 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.61-7.59 (m, 2H), 7.28-7.24 (m, 5H), 5.15-5.07 (m, 1H), 3.48 (dd, *J* = 11.2 Hz, *J* = 17.6 Hz, 1H), 3.27 (dd, *J* = 8.4 Hz, *J* = 17.6 Hz, 1H), 3.18 (dd, *J* = 6.4 Hz, *J* = 14.0 Hz, 1H), 2.97 (dd, *J* = 7.2 Hz, *J* = 14.0 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ: 186.59, 157.43, 152.14, 145.84, 139.18, 136.13,

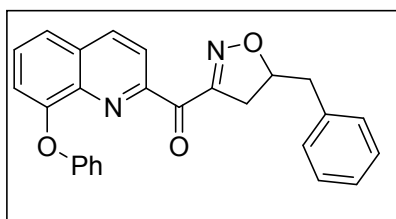
132.65, 130.32, 129.39, 129.36, 128.62, 126.87, 126.32, 120.47, 84.12, 40.83, 38.63, 21.77.
HRMS calc. for $C_{21}H_{18}N_2O_2$ ($M+H$)⁺, 331.1441; found, 331.1437.



(5-benzyl-4,5-dihydroisoxazol-3-yl)(6-methoxyquinolin-2-yl)methanone 3m : Yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.15-8.10 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 7.33-7.24 (m, 5H), 7.08 (d, *J* = 2.8 Hz, 1H), 5.15-5.07 (m, 1H), 3.95 (s, 3H), 3.49 (dd, *J* = 10.8 Hz, *J* = 17.6 Hz, 1H), 3.28 (dd, *J* = 8.0 Hz, *J* = 17.6 Hz, 1H), 3.18 (dd, *J* = 6.0 Hz, *J* = 13.6 Hz, 1H), 2.98 (dd, *J* = 6.8 Hz, *J* = 14.0 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ: 186.28, 159.61, 157.44, 150.56, 143.40, 136.17, 135.27, 132.25, 130.84, 129.39, 128.62, 126.86, 123.47, 120.98, 104.61, 84.00, 55.61, 40.83, 38.82. HRMS calc. for $C_{21}H_{18}N_2O_2(M+H)^+$, 347.1390; found, 347.1386.



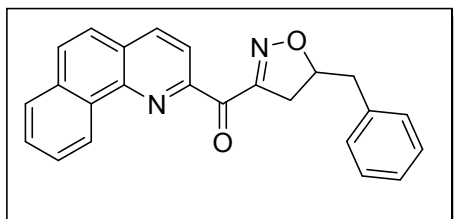
(5-benzyl-4,5-dihydroisoxazol-3-yl)(8-methoxyquinolin-2-yl)methanone 3n : Yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.24 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.34-7.23 (m, 5H), 7.07 (d, *J* = 7.6 Hz, 1H), 5.14-5.06 (m, 1H), 4.05 (s, 3H), 3.49 (dd, *J* = 10.8 Hz, *J* = 17.6 Hz, 1H), 3.30 (dd, *J* = 8.4 Hz, *J* = 17.6 Hz, 1H), 3.20 (dd, *J* = 6.0 Hz, *J* = 13.6 Hz, 1H), 2.97 (dd, *J* = 7.2 Hz, *J* = 14.0 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ: 186.31, 157.47, 156.16, 151.70, 139.15, 136.72, 136.19, 130.38, 129.31, 129.28, 128.54, 126.77, 120.68, 119.09, 108.28, 84.19, 56.04, 40.80, 38.65. HRMS calc. for $C_{21}H_{18}N_2O_3$ ($M+H$)⁺, 347.1390; found, 347.1386.



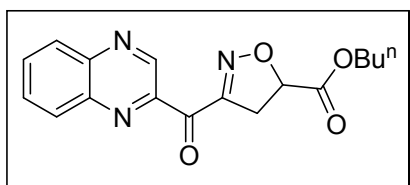
mixed with trace amount of impurities.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(8-phenoxyquinolin-2-yl)methanone 3o : Yellow oil. Selected ¹H NMR (400 MHz, CDCl₃) δ: 8.33 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.62 (d,

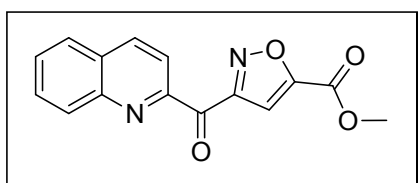
$J = 8.4$ Hz, 1H), 7.61-7.54 (m, 1H), 7.35-7.31 (m, 2H), 7.29-7.20 (m, 6H), 7.13-7.06 (m, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 5.01-4.93 (m, 1H), 3.40 (dd, $J = 10.4$ Hz, $J = 17.6$ Hz, 1H), 3.24 (dd, $J = 8.4$ Hz, $J = 17.6$ Hz, 1H), 3.09 (dd, $J = 8.4$ Hz, $J = 14.0$ Hz, 1H), 2.85 (dd, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H). Selected ^{13}C NMR (400 MHz, CDCl_3) δ : 186.07, 157.29, 154.19, 152.44, 139.90, 137.16, 136.33, 130.85, 129.74, 129.34, 129.24, 128.56, 126.76, 123.61, 122.46, 120.51, 119.09, 117.34, 84.50, 40.85, 39.38. HRMS calc. for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$, 409.1547; found, 409.15443.



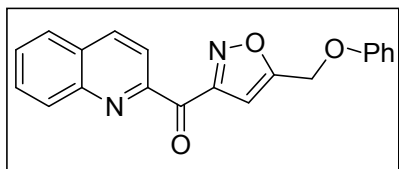
benzo[h]quinolin-2-yl(5-benzyl-4,5-dihydroisoxazol-3-yl)methanone 3p : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 9.02 (d, $J = 8.4$ Hz, 1H), 8.62 (t, $J = 2.4$ Hz, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 8.06-7.99 (m, 3H), 7.93 (d, $J = 6.8$ Hz, 1H), 7.72-7.67 (m, 2H), 7.35-7.24 (m, 5H), 5.17-5.05 (m, 1H), 3.51 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.28 (dd, $J = 8.0$ Hz, $J = 17.6$ Hz, 1H), 3.19 (dd, $J = 6.0$ Hz, $J = 14.0$ Hz, 1H), 2.99 (dd, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.30, 157.52, 152.17, 147.50, 136.09, 132.43, 131.79, 131.41, 129.41, 128.93, 128.78, 128.65, 128.45, 128.39, 127.42, 127.31, 126.91, 123.29, 121.39, 84.19, 40.84, 38.54. HRMS calc. for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 367.1441; found, 367.1437.



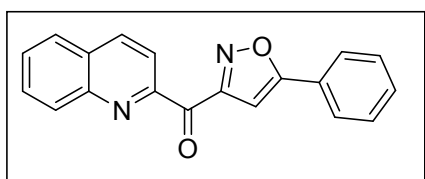
butyl 3-(quinoxaline-2-carbonyl)-4,5-dihydroisoxazole-5-carboxylate 3r : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 9.46 (s, 1H), 8.27-8.25 (m, 1H), 8.20-8.18 (m, 1H), 7.95-7.86 (m, 2H), 5.30 (dd, $J = 9.2$ Hz, $J = 10.8$ Hz, 1H), 4.25 (t, $J = 6.4$ Hz, 2H), 3.82-3.73 (m, 2H), 1.73-1.66 (m, 2H), 1.46-1.37 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ : 184.68, 168.80, 156.35, 147.01, 144.23, 143.61, 141.15, 132.65, 131.05, 130.75, 129.33, 79.97, 66.14, 37.76, 30.40, 18.96, 13.60. HRMS calc. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$) $^+$, 328.1292; found, 328.1296.



methyl 3-(quinoline-2-carbonyl)isoxazole-5-carboxylate 3u : Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (d, $J = 8.8$ Hz, 1H), 8.29-8.23 (m, 2H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.86 (s, 1H), 7.85-7.81 (m, 1H), 7.31-7.69 (m, 1H), 4.04 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ : 184.04, 160.92, 160.47, 156.89, 152.07, 147.10, 137.46, 130.77, 130.53, 129.65, 129.49, 127.72, 119.66, 111.87, 53.06. HRMS calc. for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$, 283.0713; found, 283.0710.

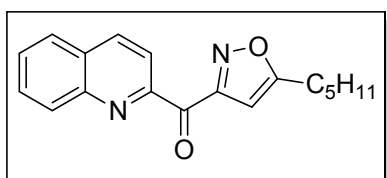


(5-(phenoxyethyl)isoxazol-3-yl)(quinolin-2-yl)methanone 3v: Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.35 (d, $J = 8.4$ Hz, 1H), 8.25-8.21 (m, 2H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.82-7.78 (m, 1H), 7.70-7.66 (m, 1H), 7.35-7.35 (m, 2H), 7.22 (s, 1H), 7.05-7.00 (m, 3H), 5.28 (d, $J = 0.4$ Hz, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ : 185.13, 168.64, 160.75, 157.60, 152.49, 147.14, 137.28, 130.78, 130.37, 129.67, 129.52, 129.21, 127.66, 121.95, 119.93, 114.78, 105.64, 61.09. HRMS calc. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$, 331.1077; found, 331.1076.



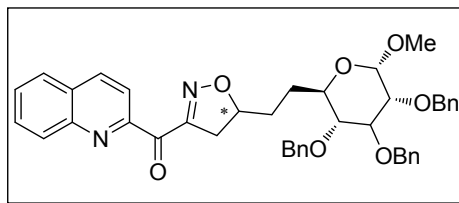
mixed with small amount of impurities.

(5-phenylisoxazol-3-yl)(quinolin-2-yl)methanone 3w : Yellow oil. Selected ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (d, $J = 8.4$ Hz, 1H), 8.30 (dd, $J = 2.0$ Hz, $J = 8.4$ Hz, 2H), 7.93-7.88 (m, 3H), 7.84-7.80 (m, 1H), 7.72-7.68 (m, 1H), 7.54-7.47 (m, 3H), 7.38 (s, 1H). Selected ^{13}C NMR (400 MHz, CDCl_3) δ : 185.57, 170.71, 161.38, 152.76, 147.27, 137.28, 130.89, 130.59, 130.38, 129.56, 129.17, 129.10, 127.69, 126.00, 120.15, 101.46. HRMS calc. for $\text{C}_{19}\text{H}_{12}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 301.0972; found, 301.0969.



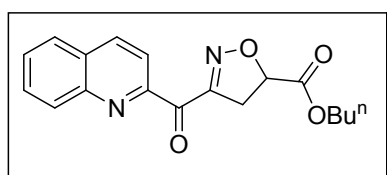
(5-pentylisoxazol-3-yl)(quinolin-2-yl)methanone 3x : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.35 (d, $J = 8.8$ Hz, 1H), 8.26 (t, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.83-7.79 (m, 1H), 7.70-7.66 (m, 1H), 6.83 (s, 1H), 2.88 (t, $J = 7.6$ Hz, 2H), 1.83-1.76 (m, 2H), 1.46-1.34 (m, 4H),

0.93 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ : 185.91, 174.64, 160.84, 152.94, 147.27, 137.19, 130.86, 130.29, 129.50, 129.04, 127.65, 120.19, 102.74, 31.18, 27.14, 26.67, 22.25, 13.88. MS (ESI) ($\text{M}+\text{H}$) $^+$: 294.9. HRMS calc. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$, 295.1441; found, 295.1438.

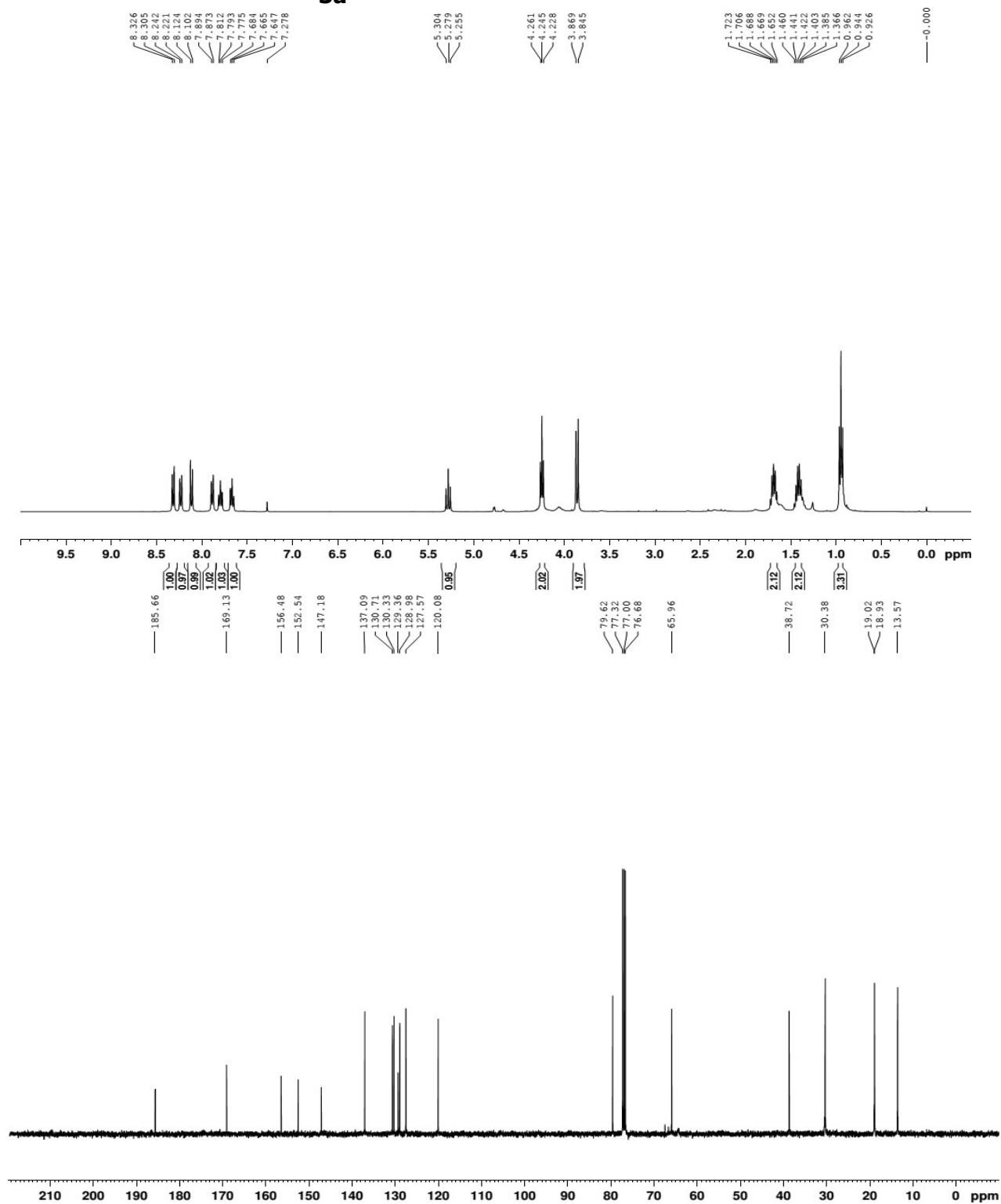


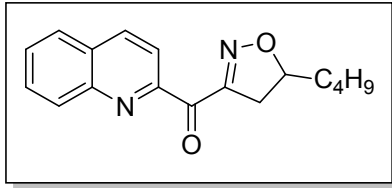
quinolin-2-yl(5-(((3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H- pyran-2- yl)methoxy)methyl)-4,5-dihydroisoxazol-3-yl)methanone 5a : Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.29-8.21 (m, 2H), 8.07 (dd, $J = 2.4$ Hz, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.78-7.73 (m, 1H), 7.65-7.61 (m, 1H), 7.36-7.30 (m, 6H), 7.28-7.24 (m, 9H), 5.00 (d, $J = 10.8$ Hz, 1H), 4.91 (d, $J = 10.8$ Hz, 1H), 4.82 (t, $J = 12.0$ Hz, 3H), 4.68-4.61 (m, 2H), 4.54 (d, $J = 3.2$ Hz, 1H), 3.98 (t, $J = 9.2$ Hz, 1H), 3.62 (t, $J = 8.8$ Hz, 1H), 3.53-3.34 (m, 2H), 3.33 (s, 3H), 3.21 (t, $J = 9.2$ Hz, 1H), 3.14-3.05 (m, 1H), 2.01-1.92 (m, 1H), 1.89-1.80 (m, 1H), 1.69-1.40 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ : 186.76, 157.31, 153.06, 147.17, 138.57, 138.00, 137.98, 136.89, 130.65, 130.64, 130.17, 129.15, 128.66, 128.36, 128.31, 128.01, 127.98, 127.91, 127.82, 127.73, 127.54, 127.48, 120.27, 120.25, 97.73, 97.70, 83.84, 83.74, 81.93, 81.41, 80.00, 75.66, 75.15, 75.12, 73.22, 69.64, 69.59, 55.02, 38.92, 38.85, 31.02, 30.95, 27.26, 27.00. HRMS calc. for $\text{C}_{42}\text{H}_{41}\text{N}_2\text{O}_7$ ($\text{M}+\text{Na}$) $^+$, 709.2891; found, 709.2884.

8. Charts of products

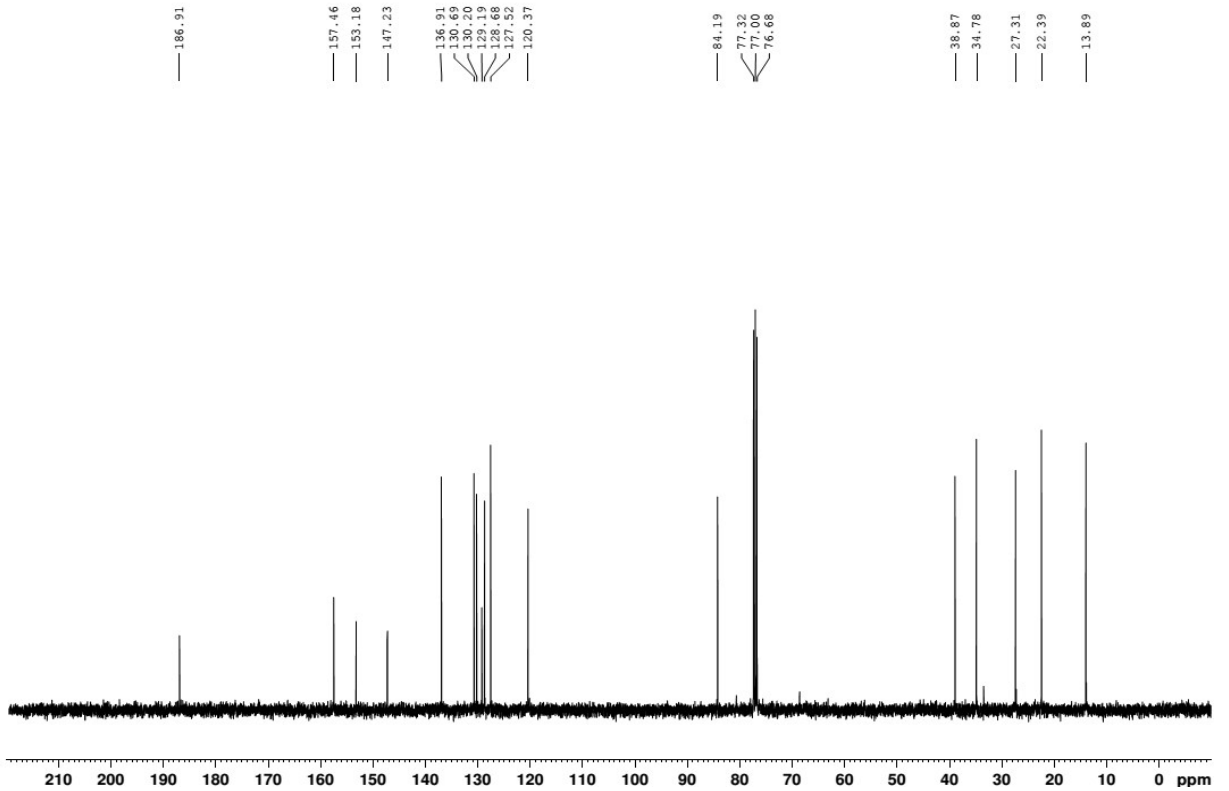
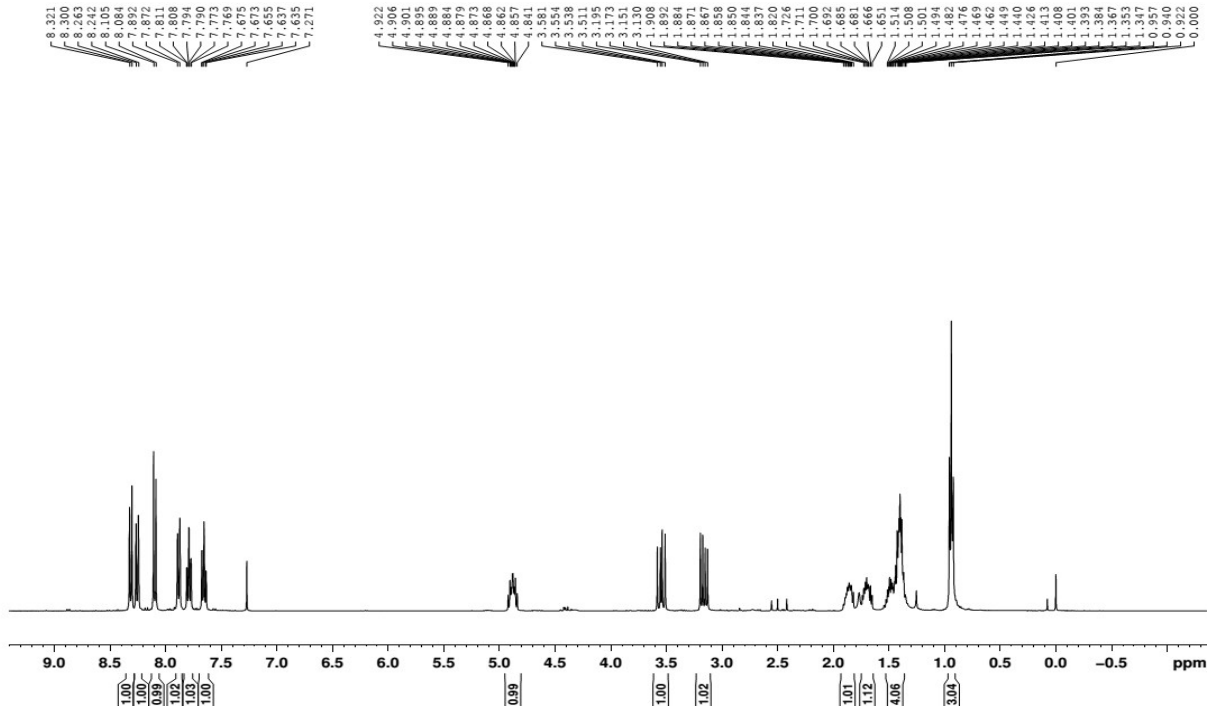


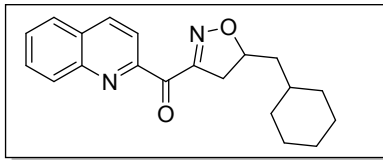
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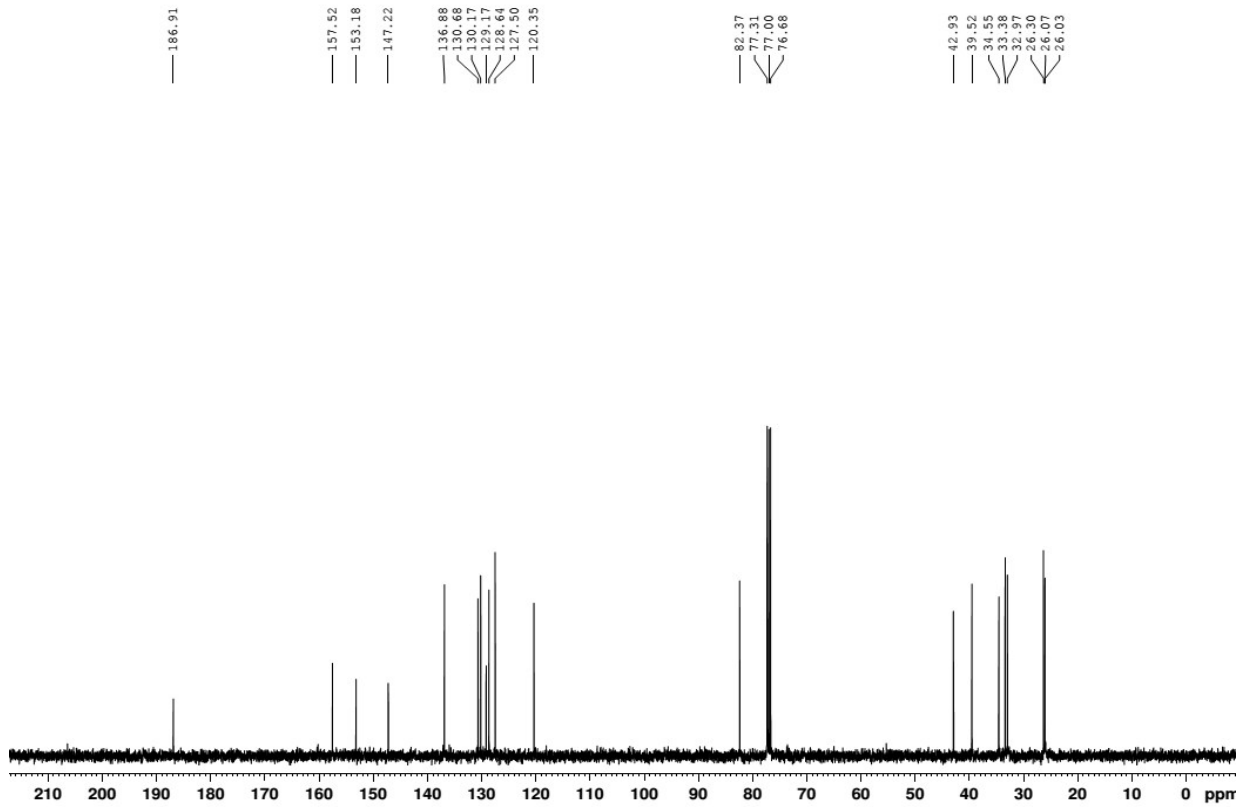
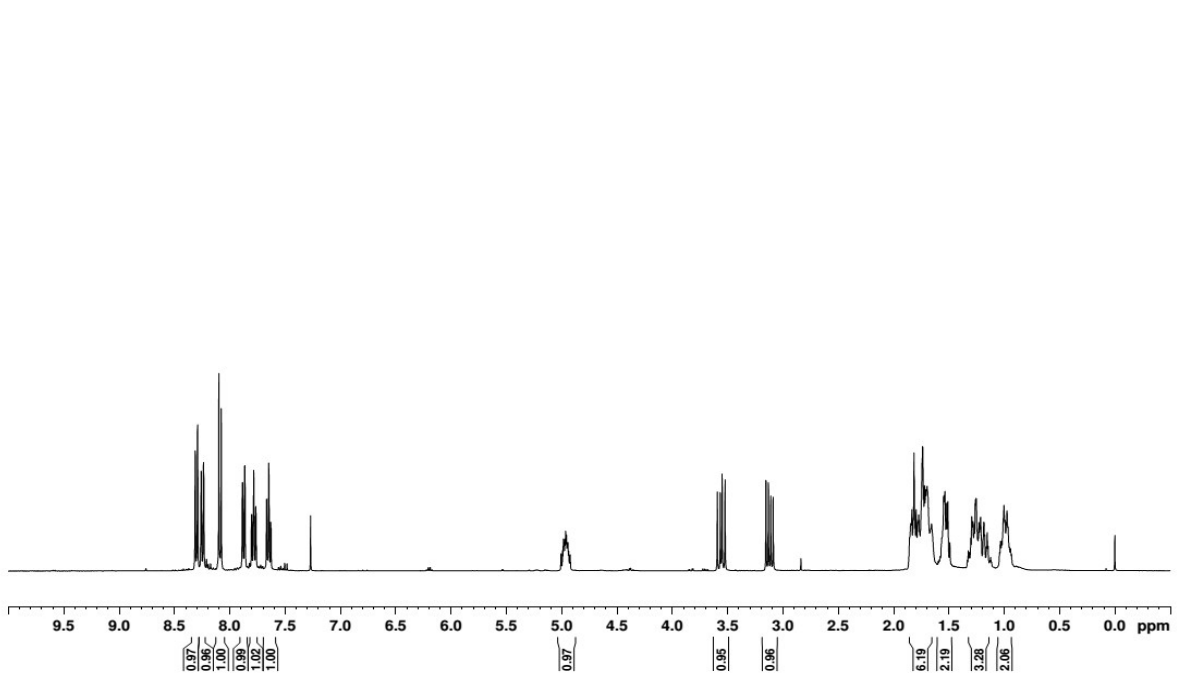
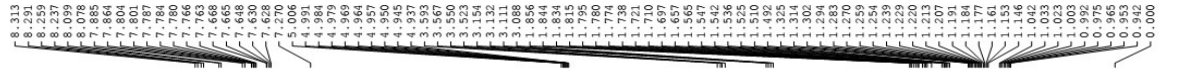


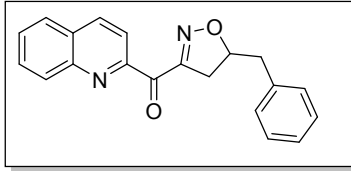
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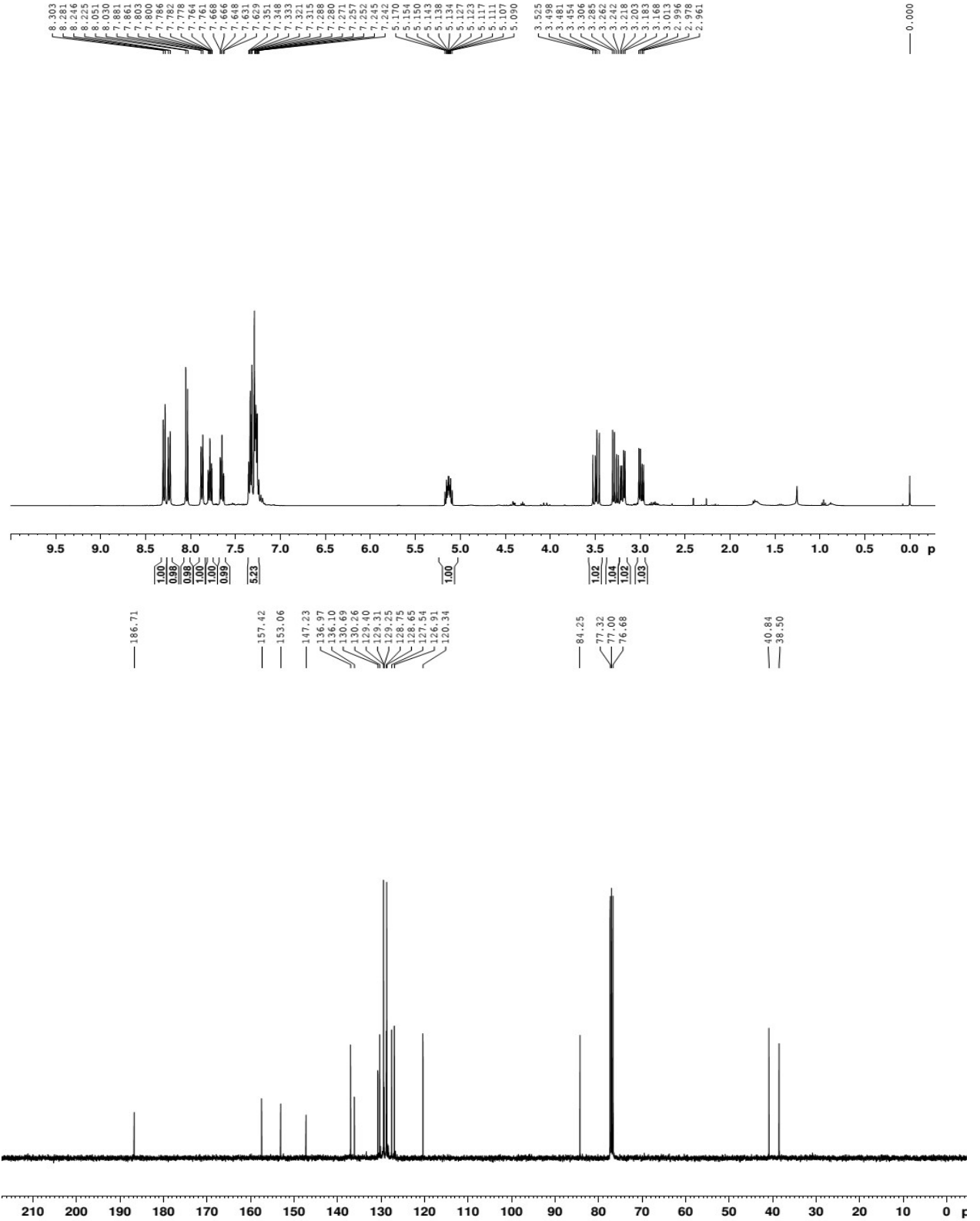


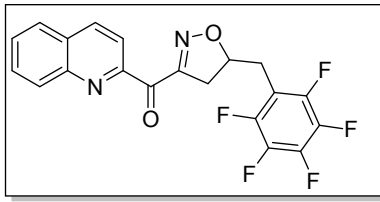
3d



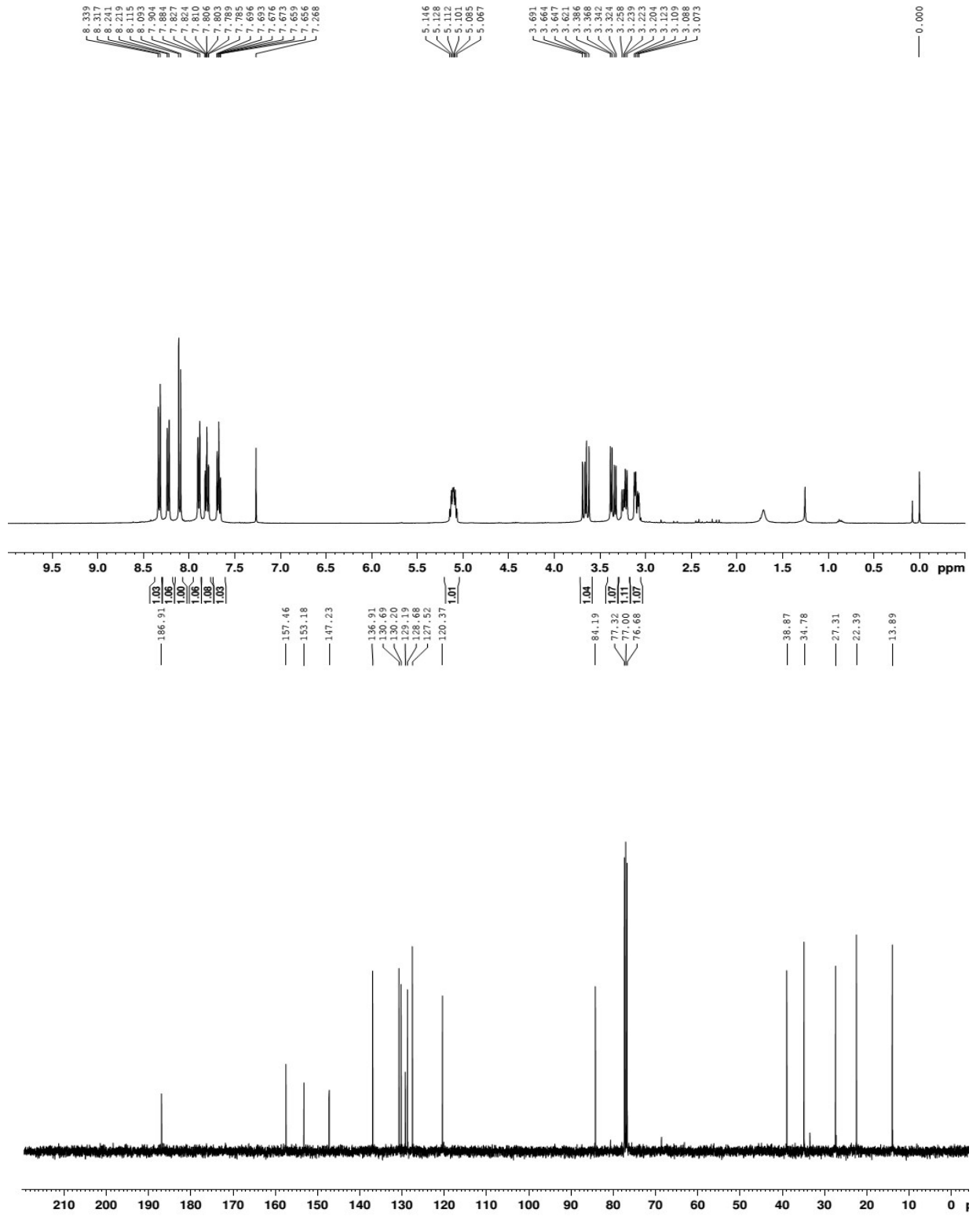


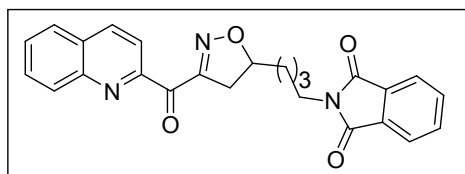
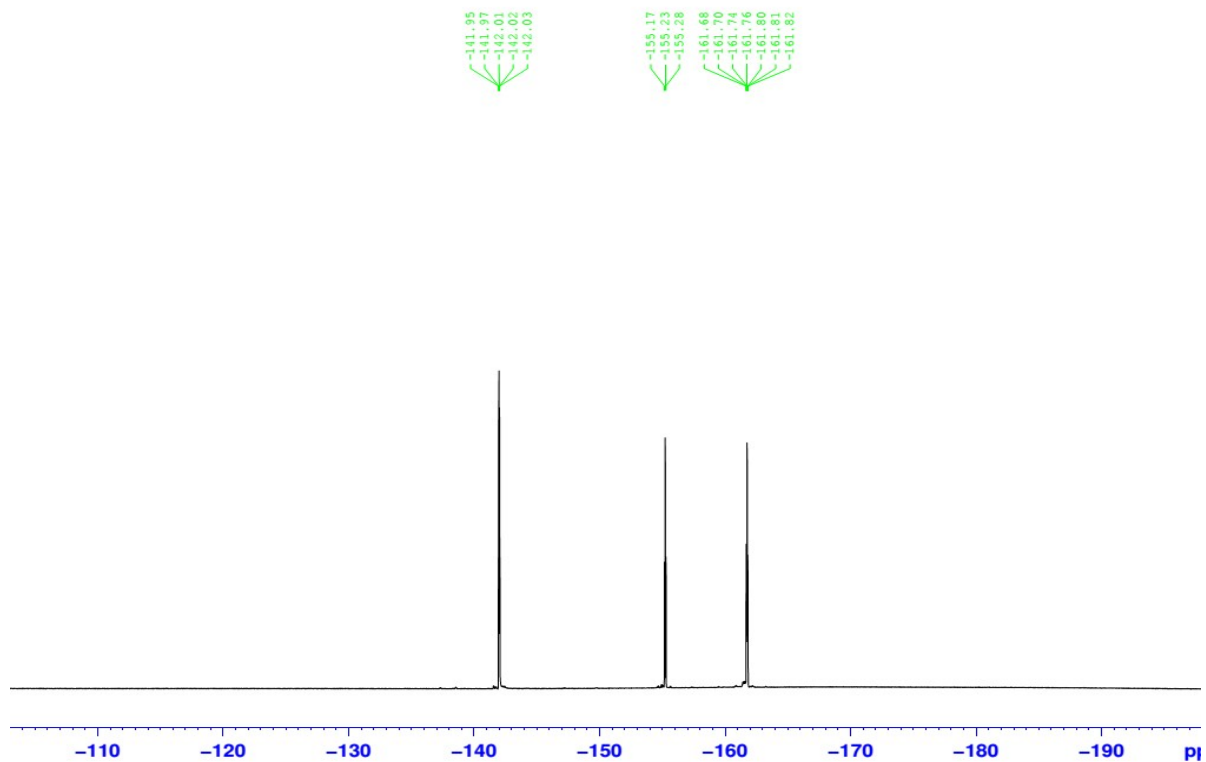
3e



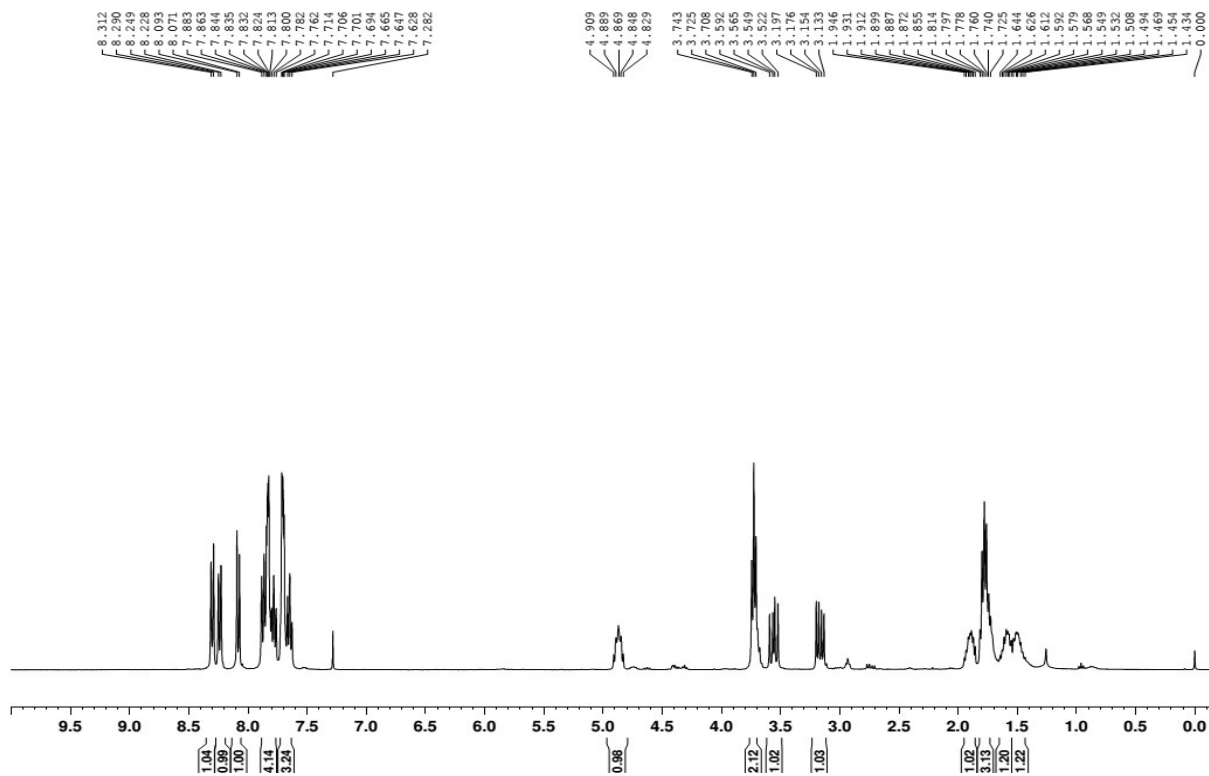


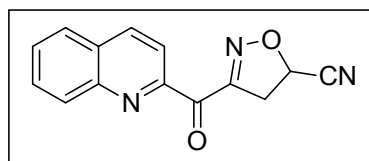
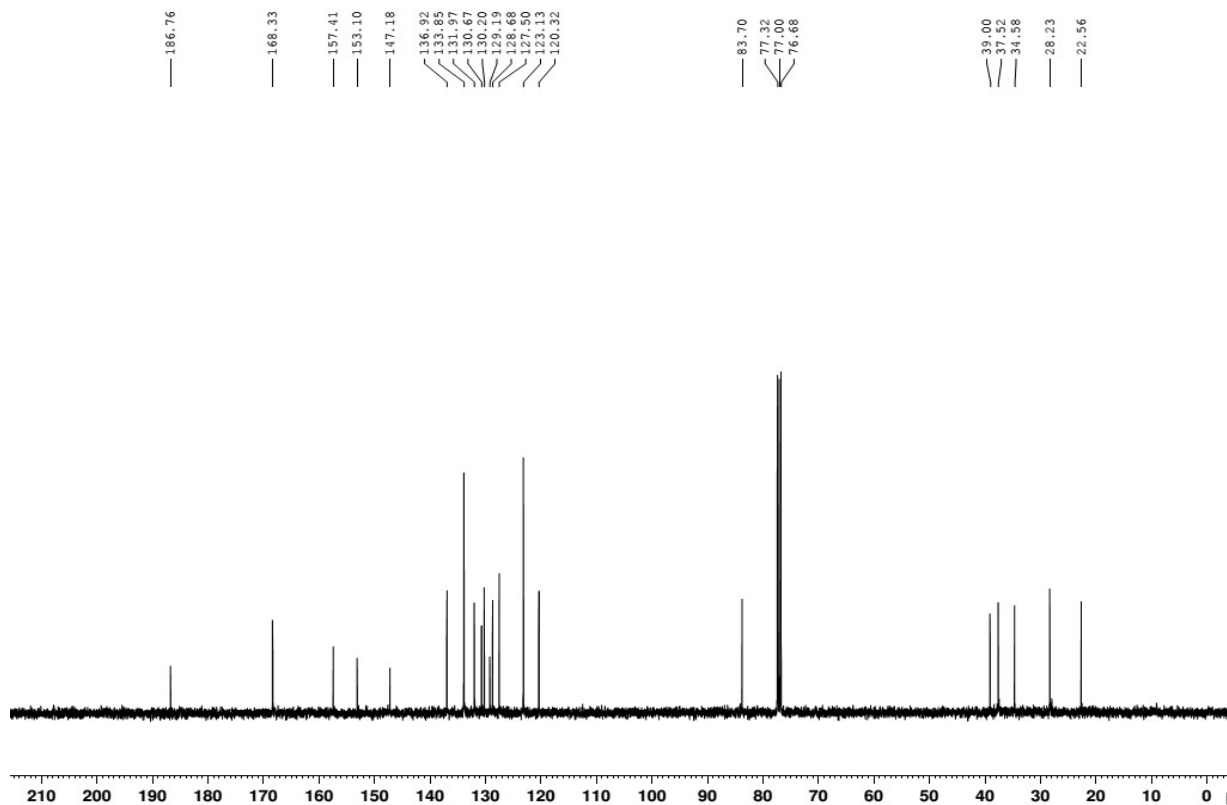
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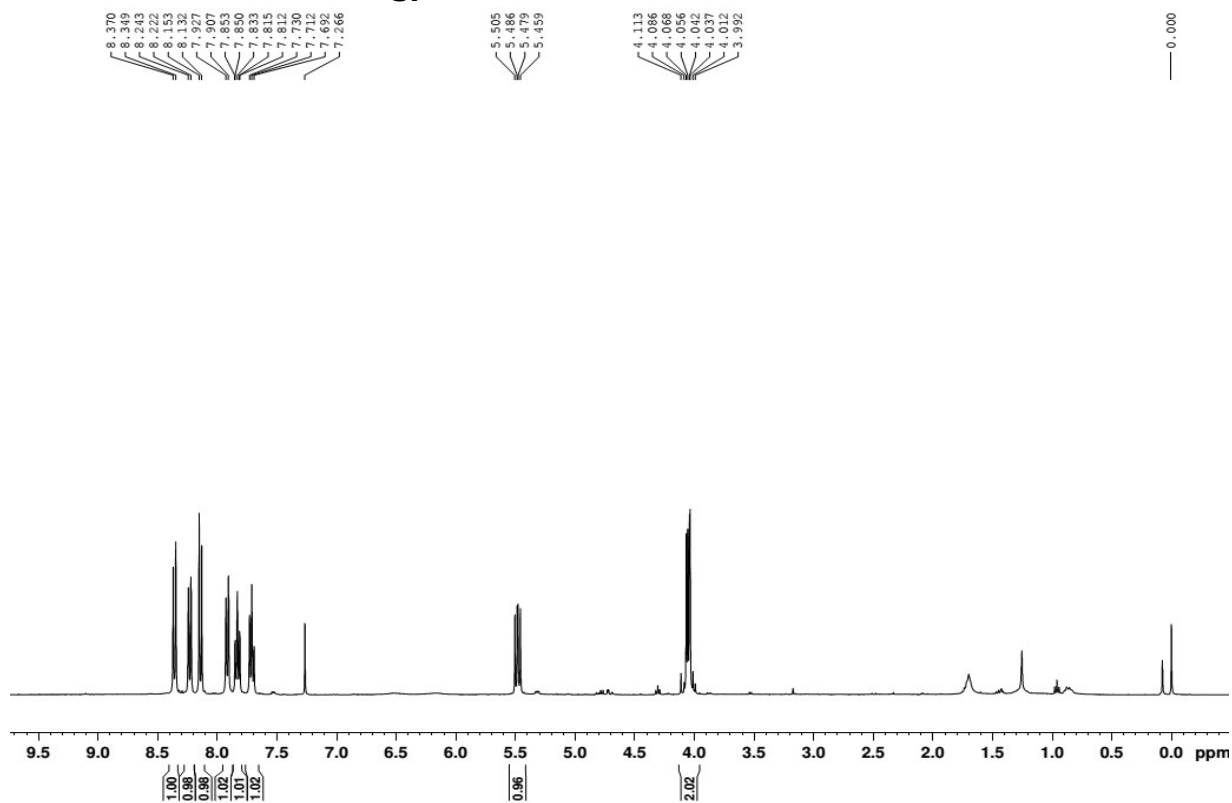


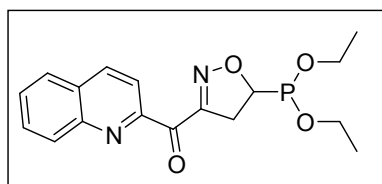
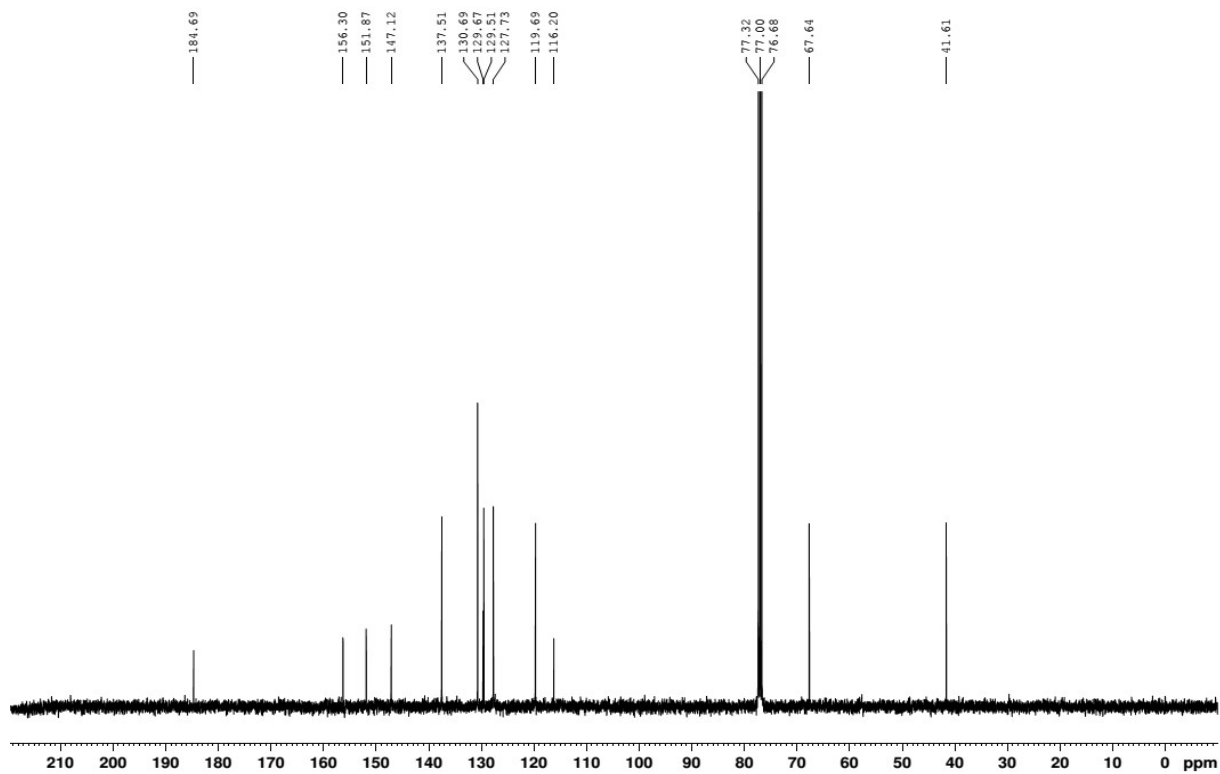
3h mixed with a small amount of impurities.



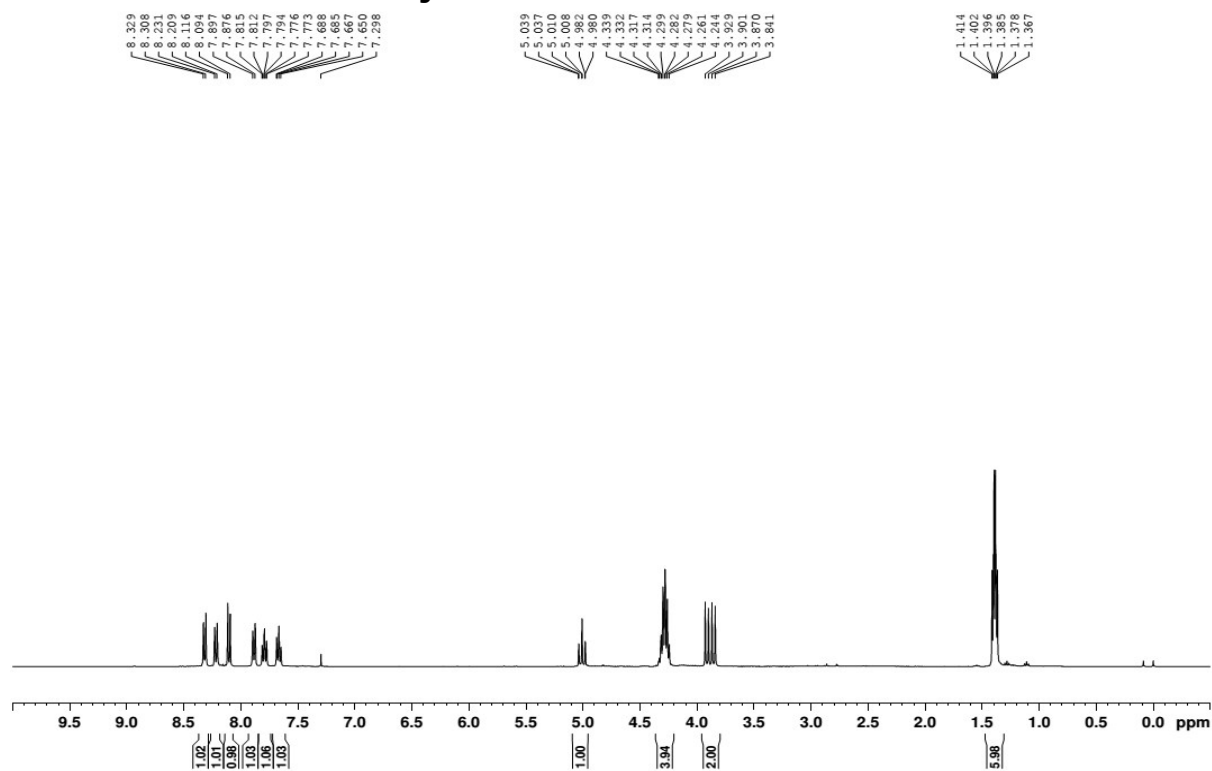


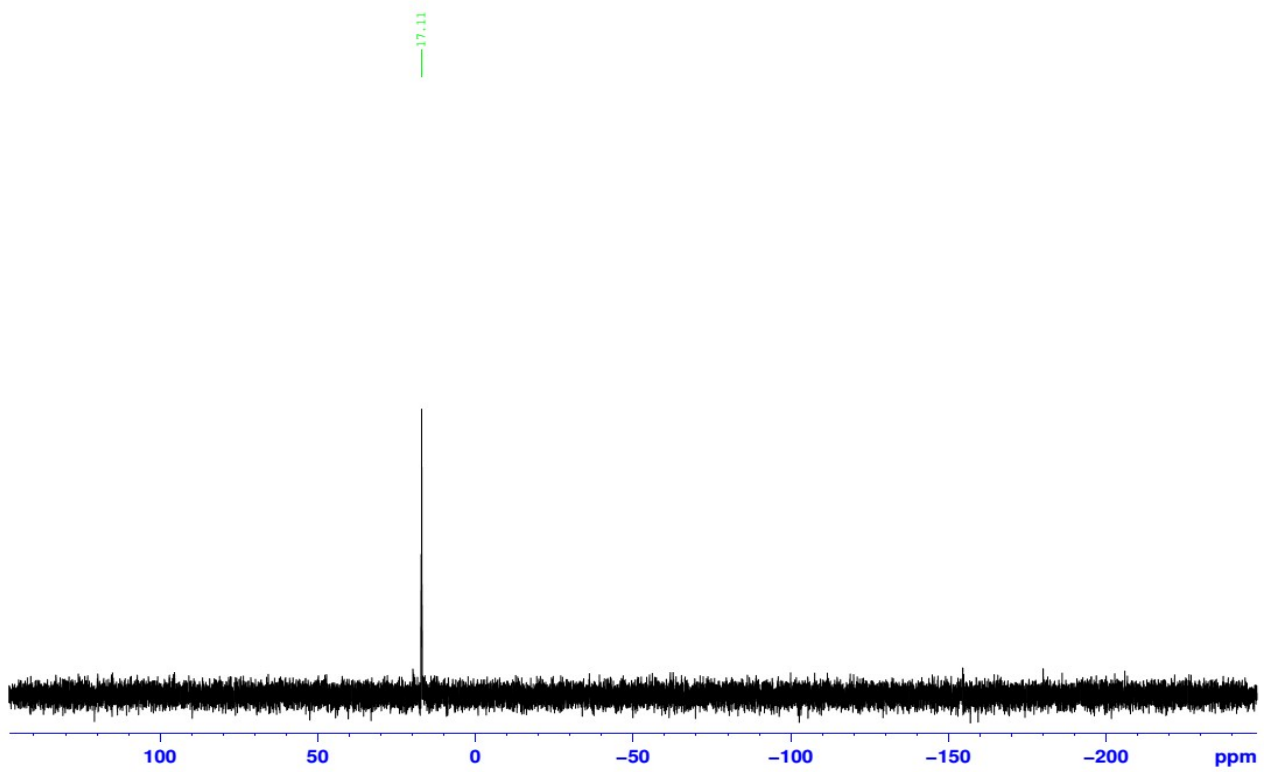
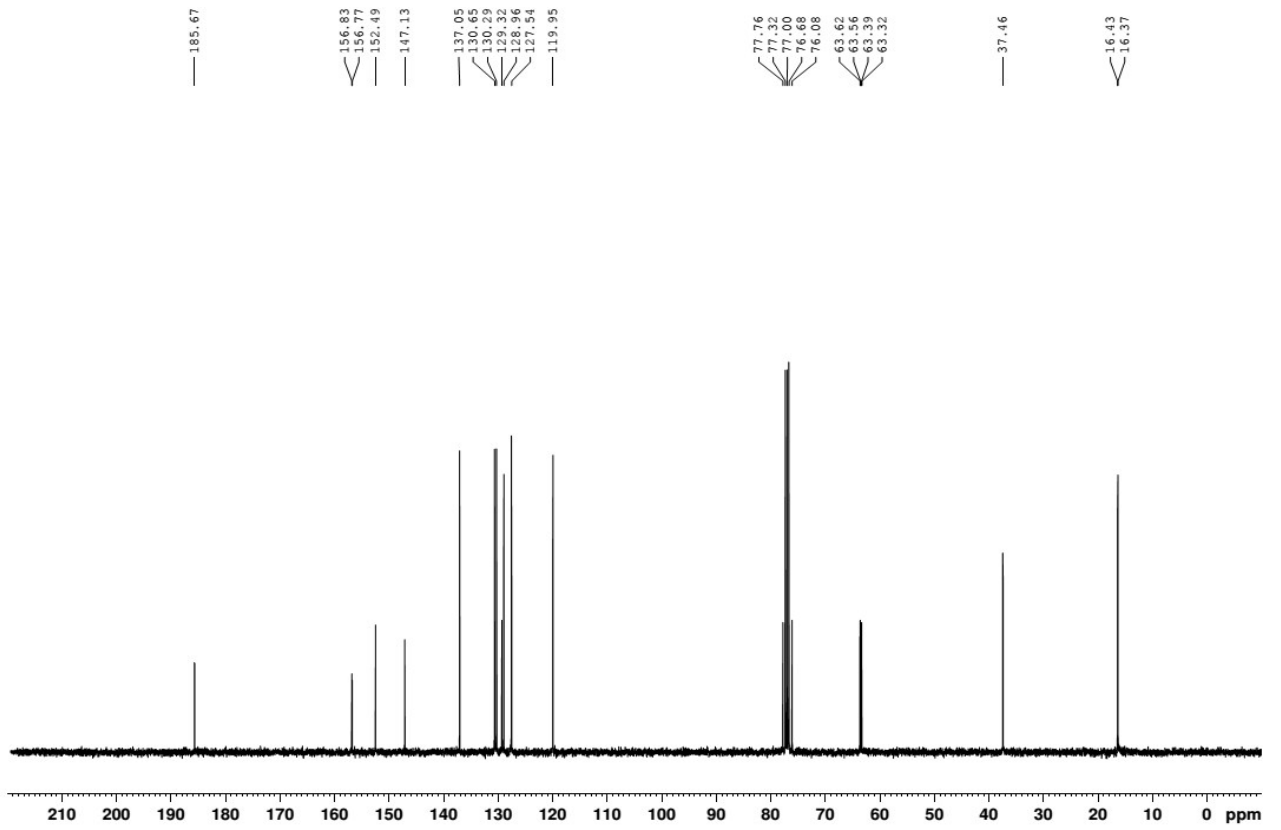
3i

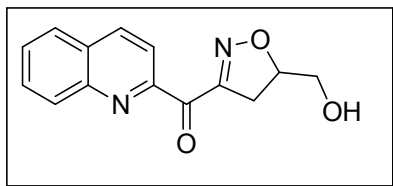




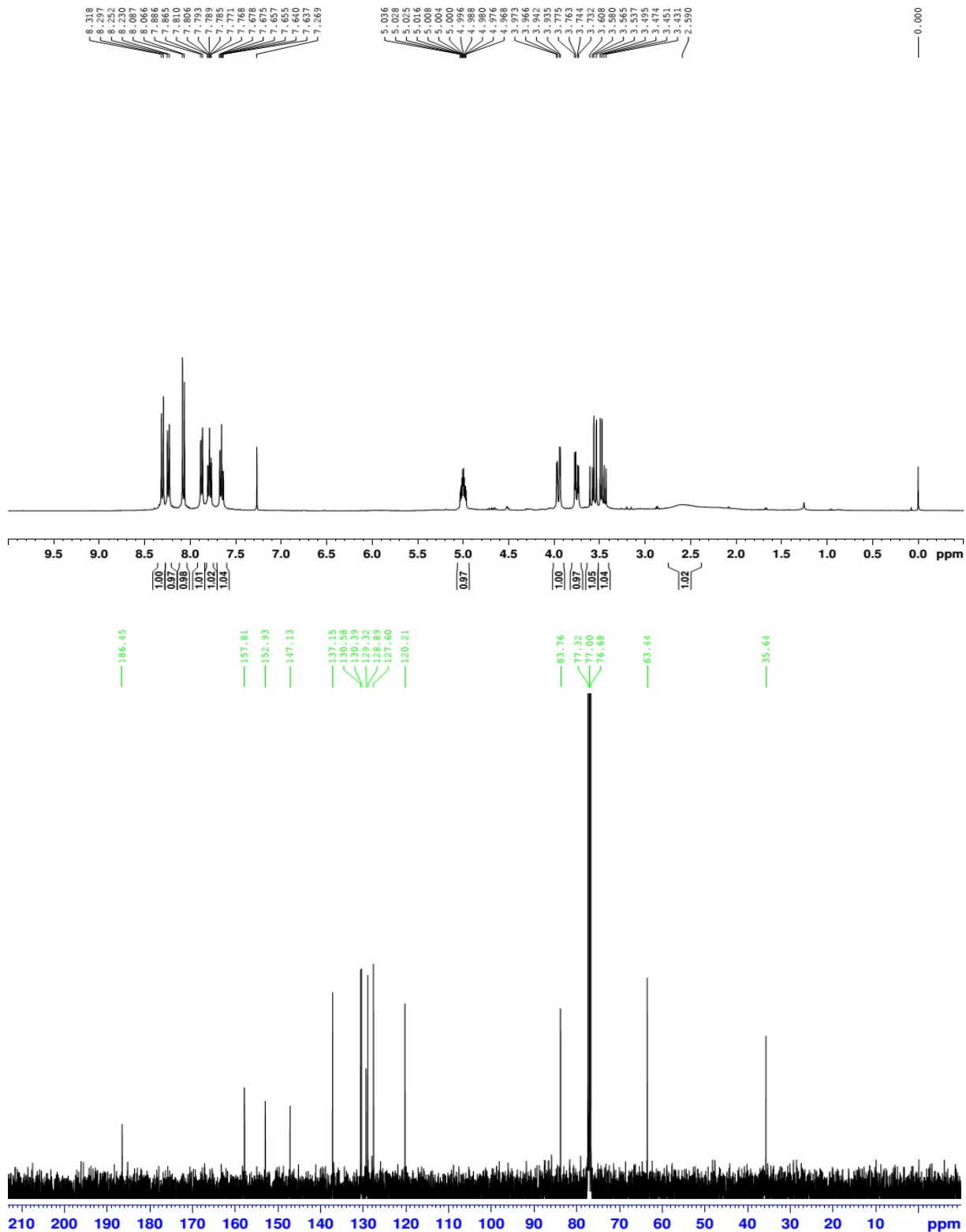
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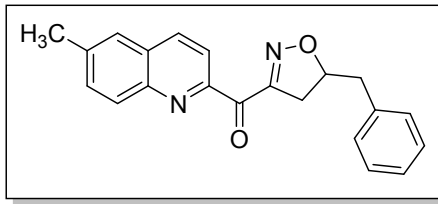




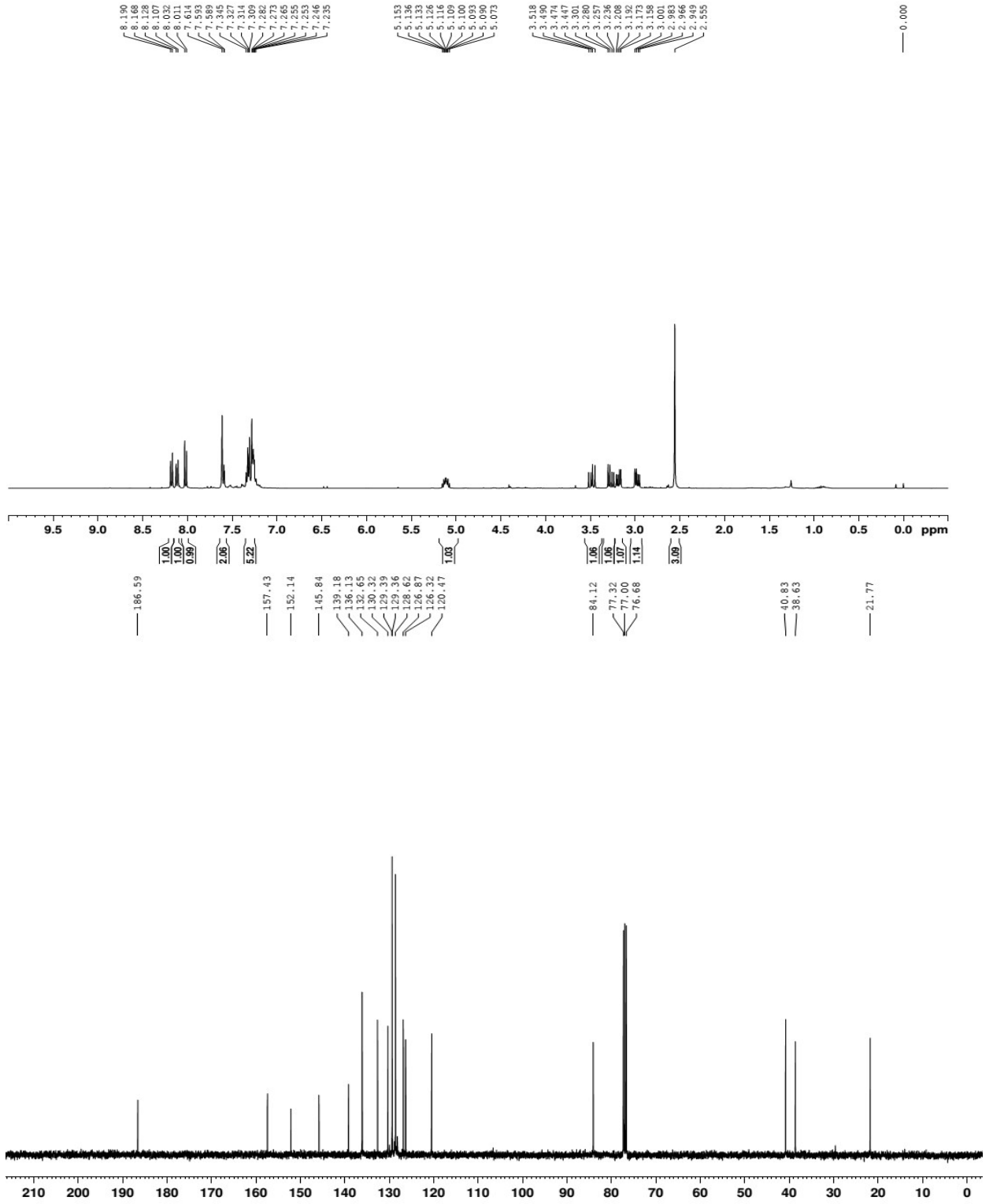


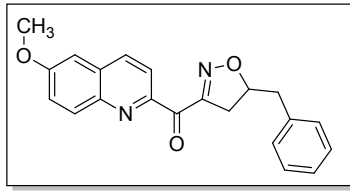
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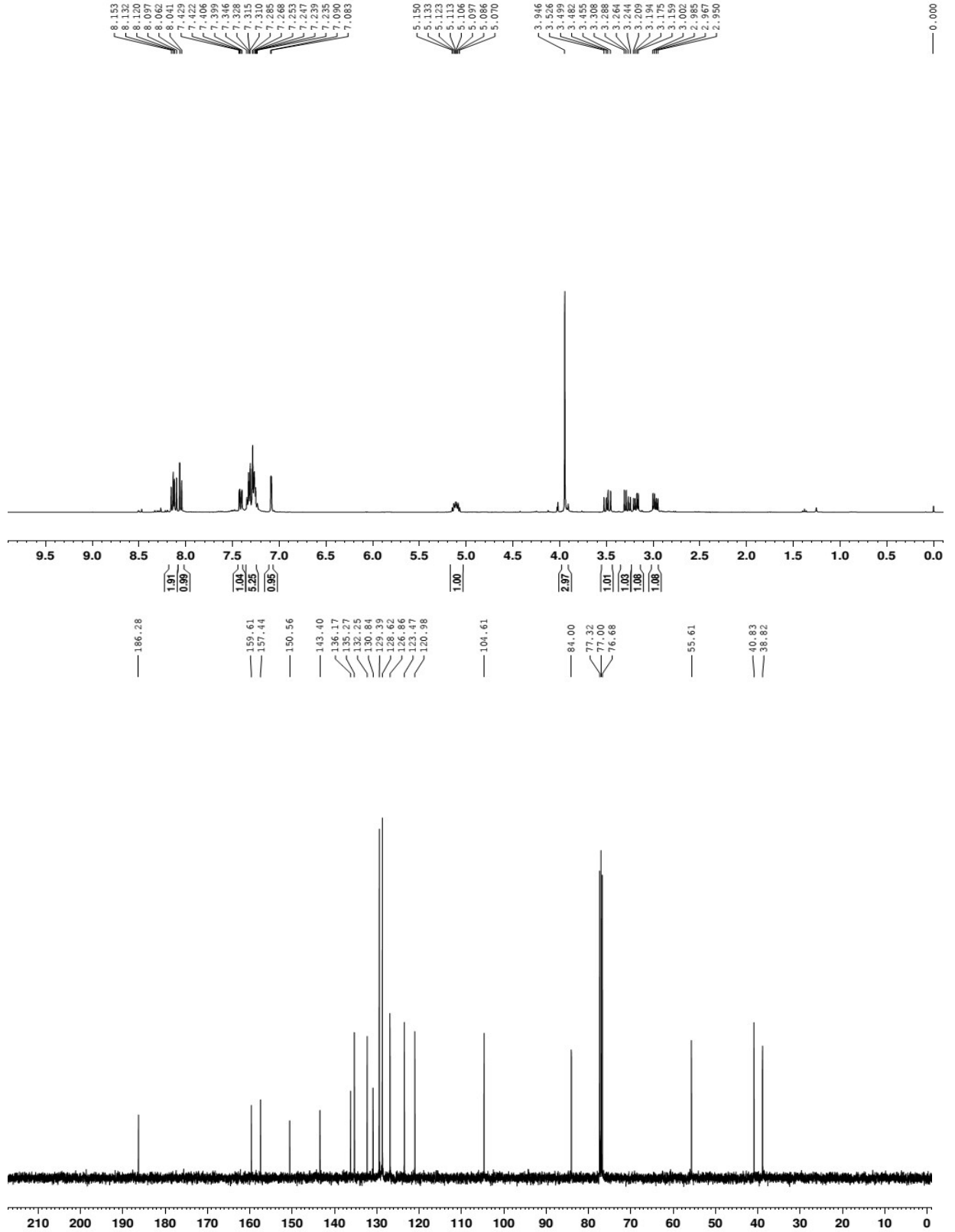


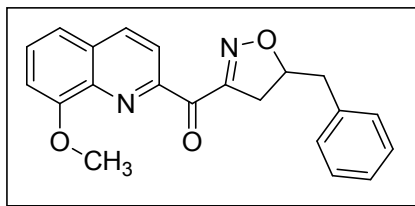
31



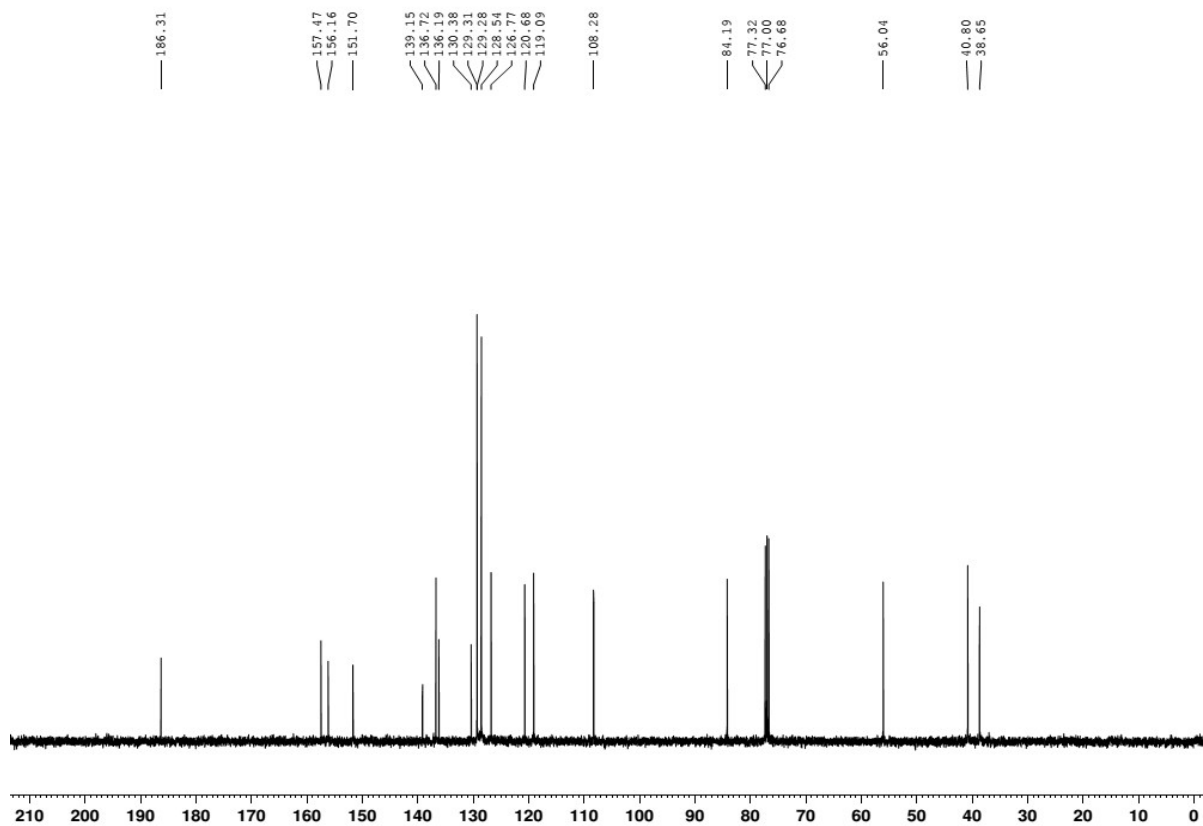
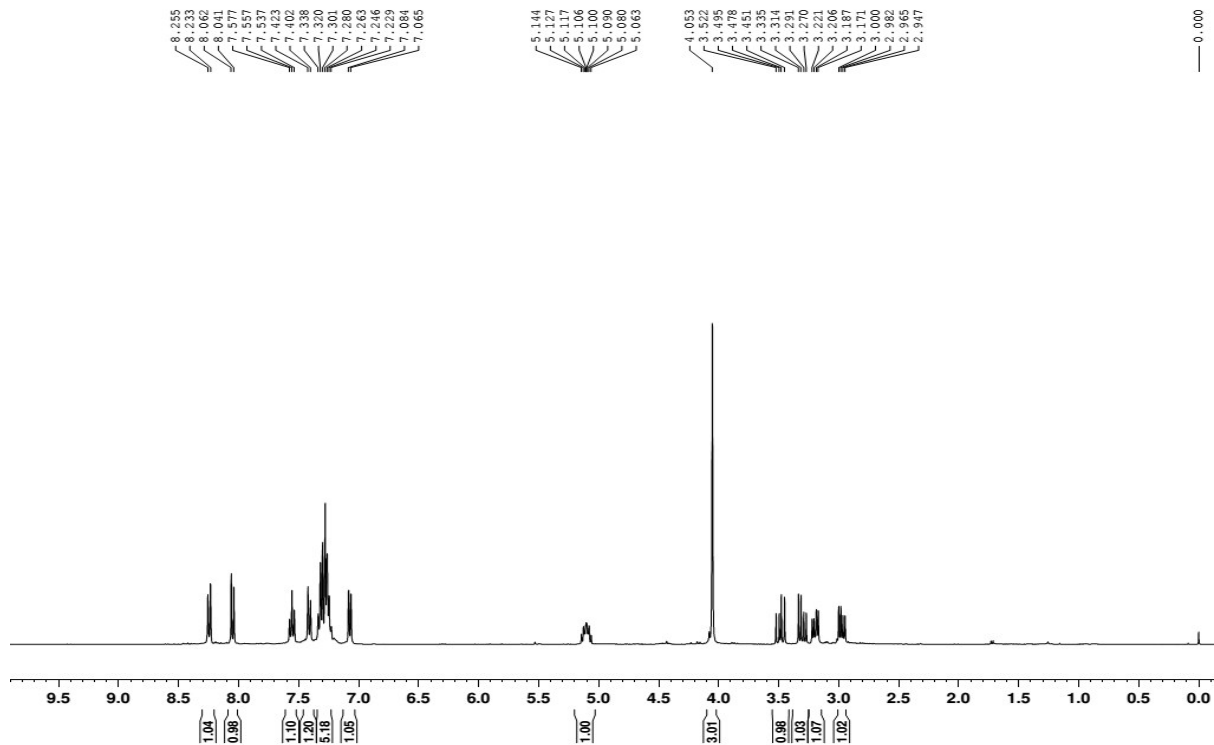


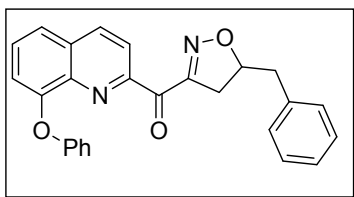
3m



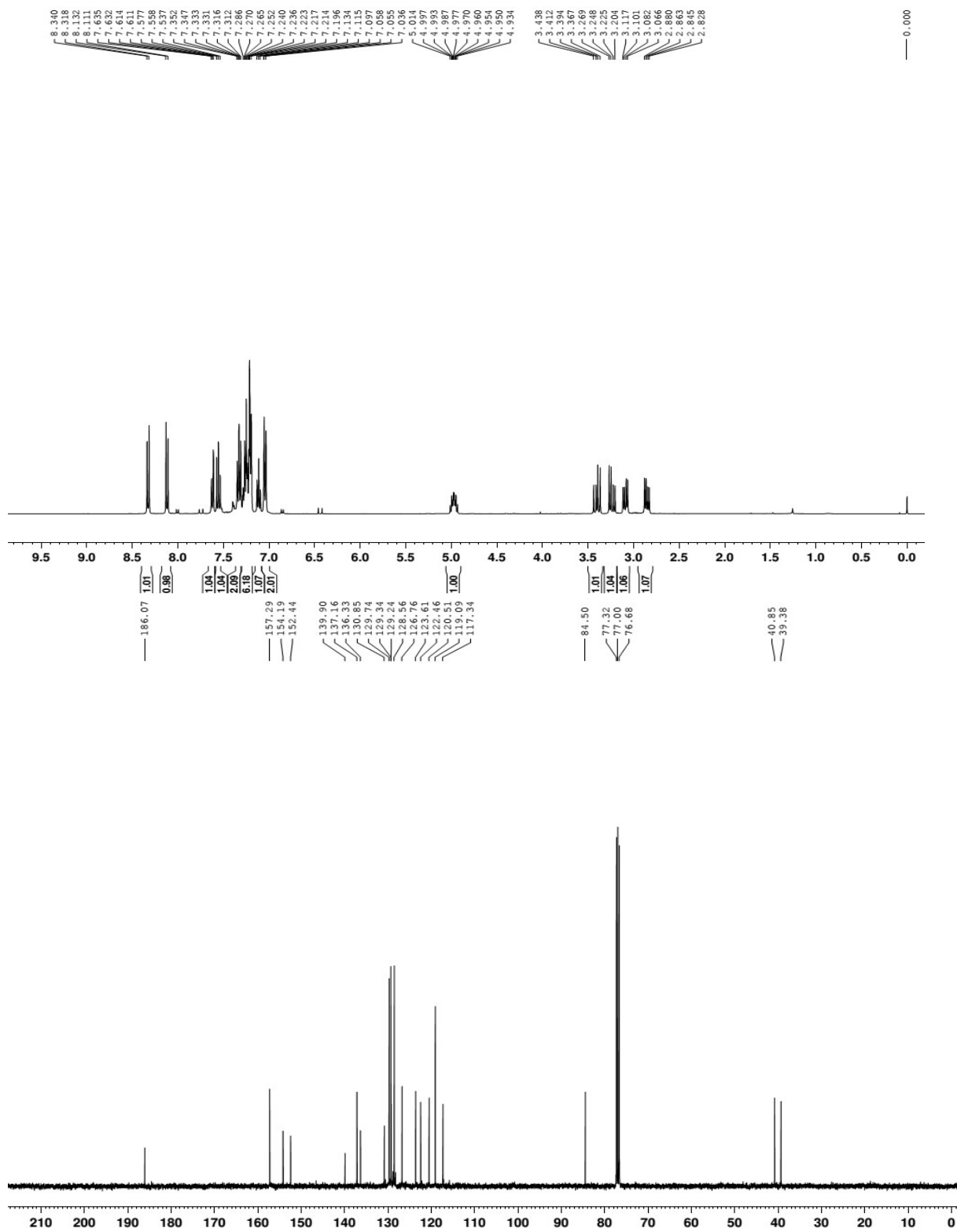


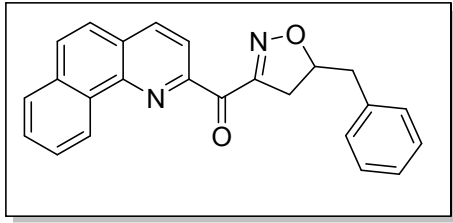
3n



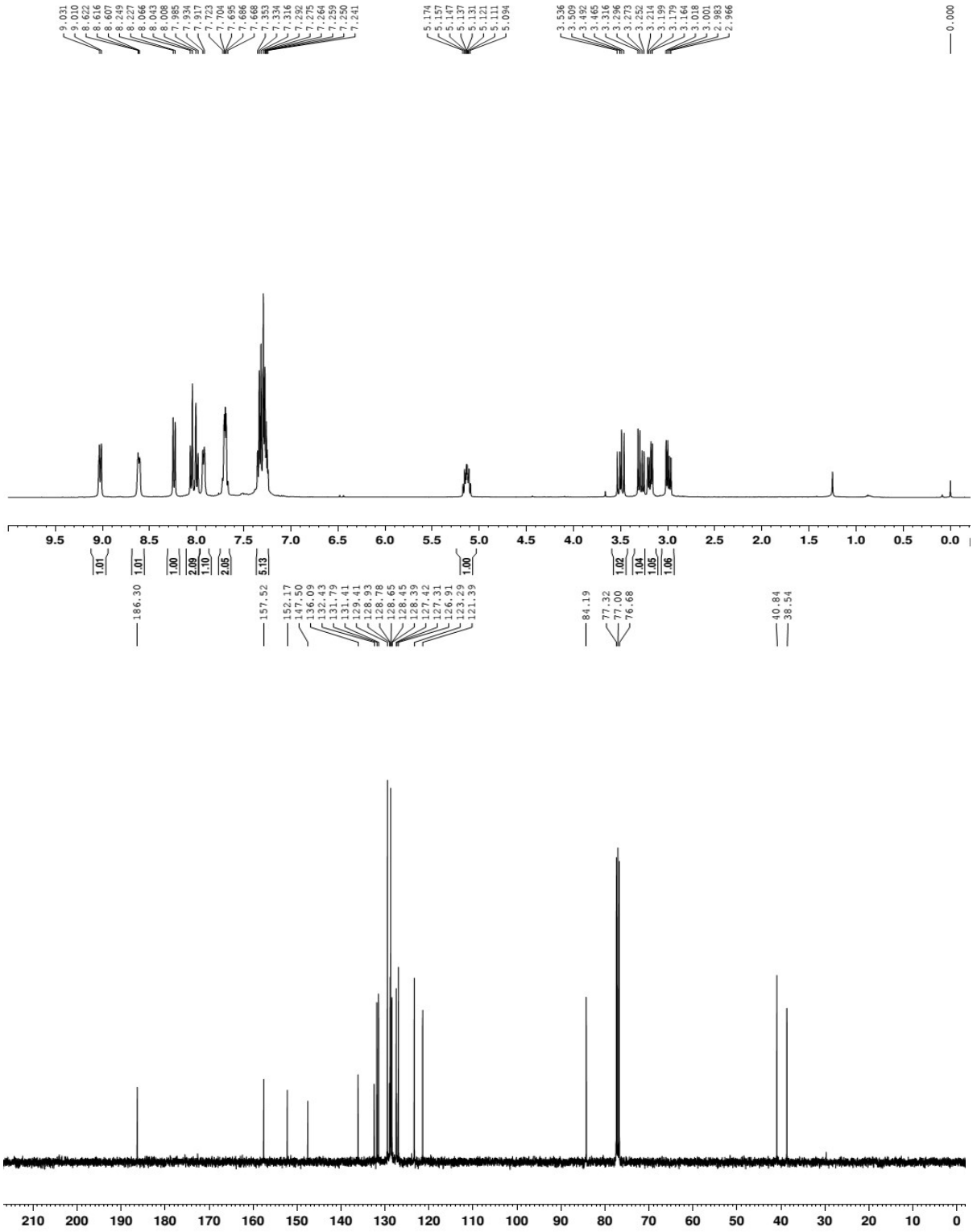


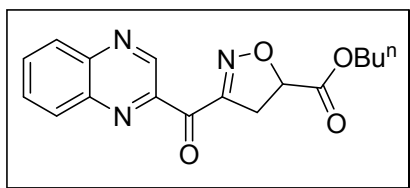
30 mixed with trace amount of impurities.



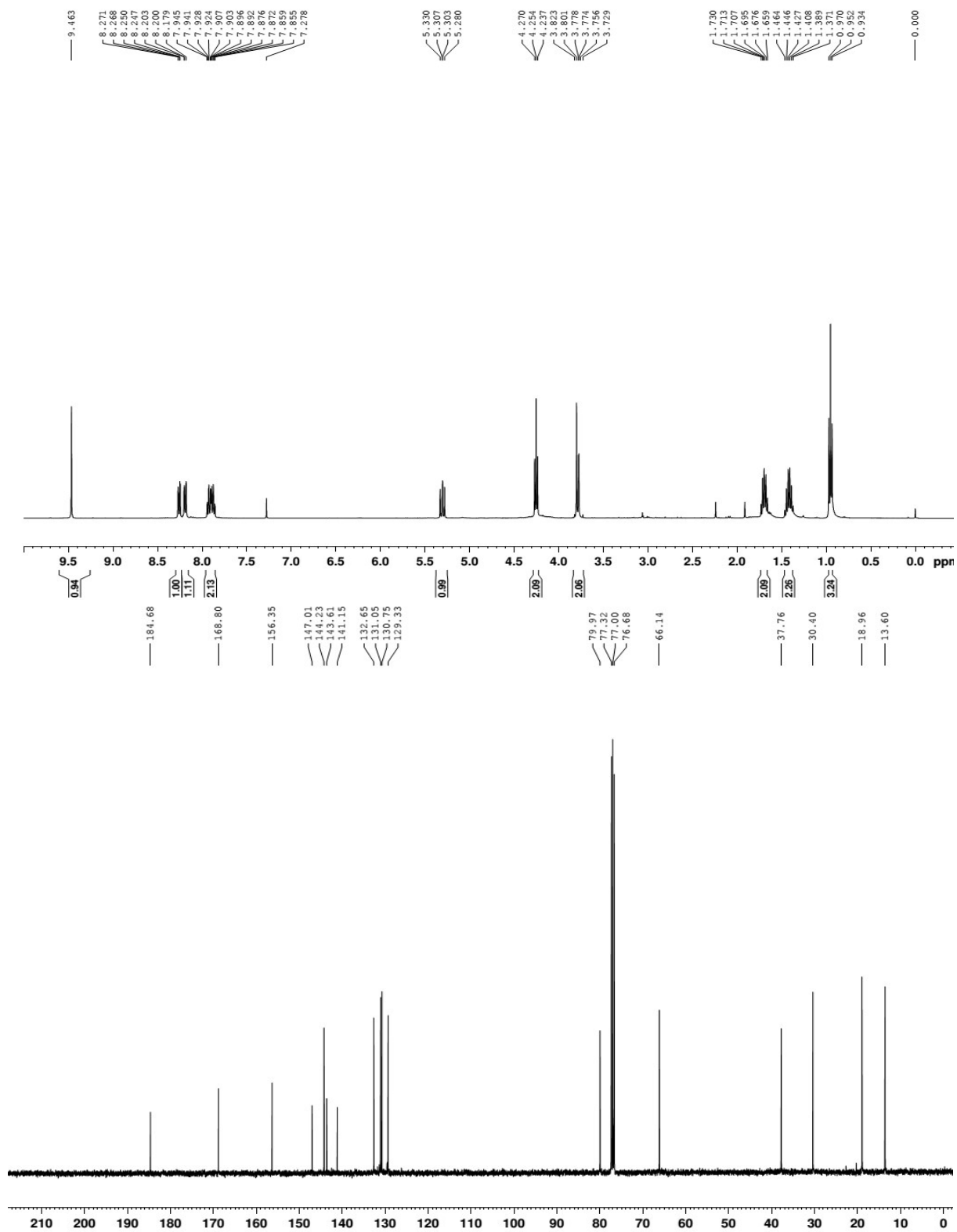


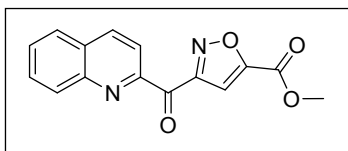
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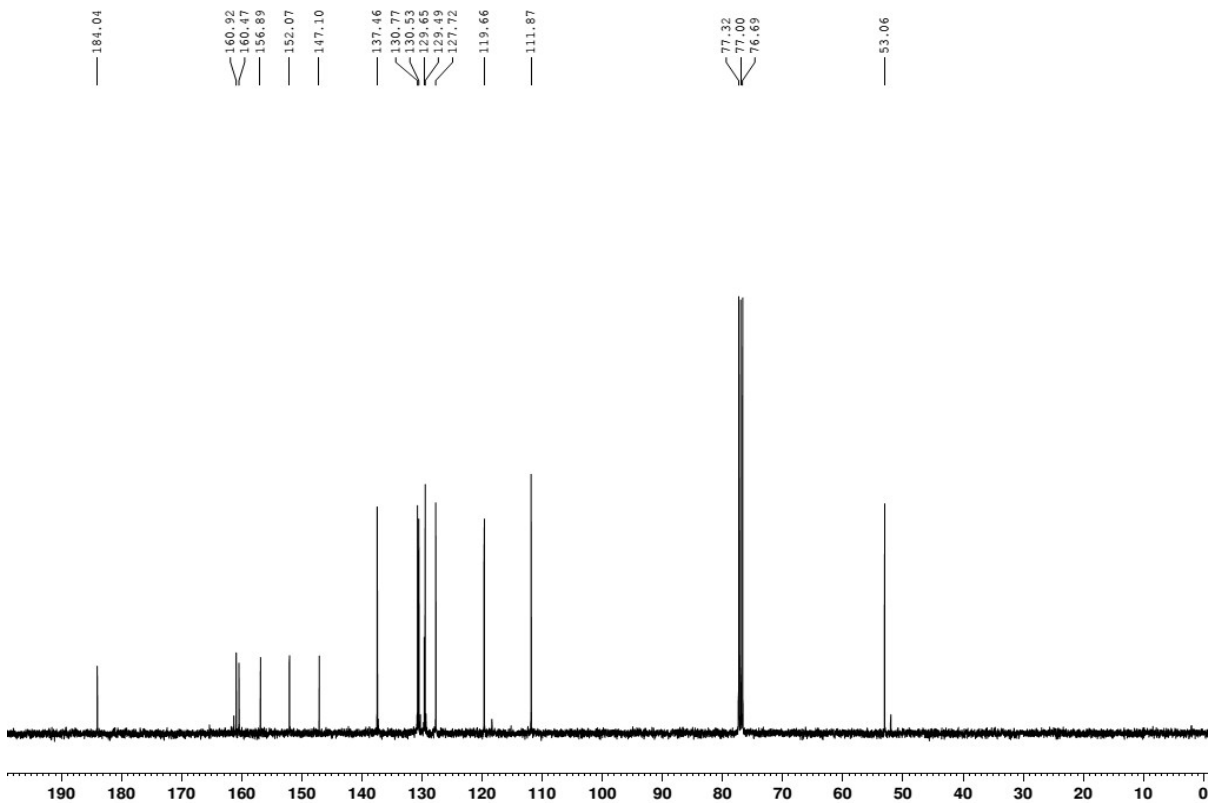
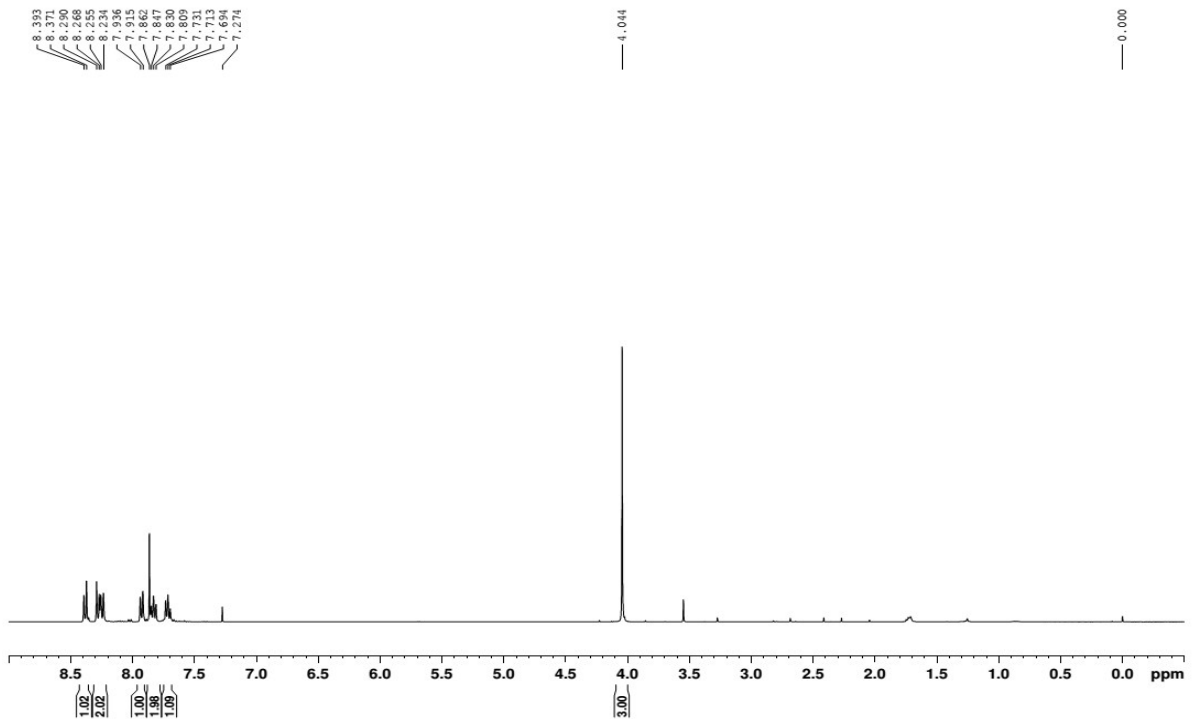


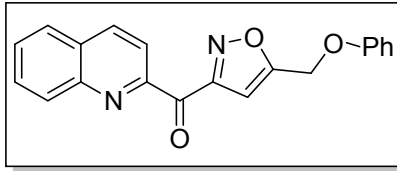
3r



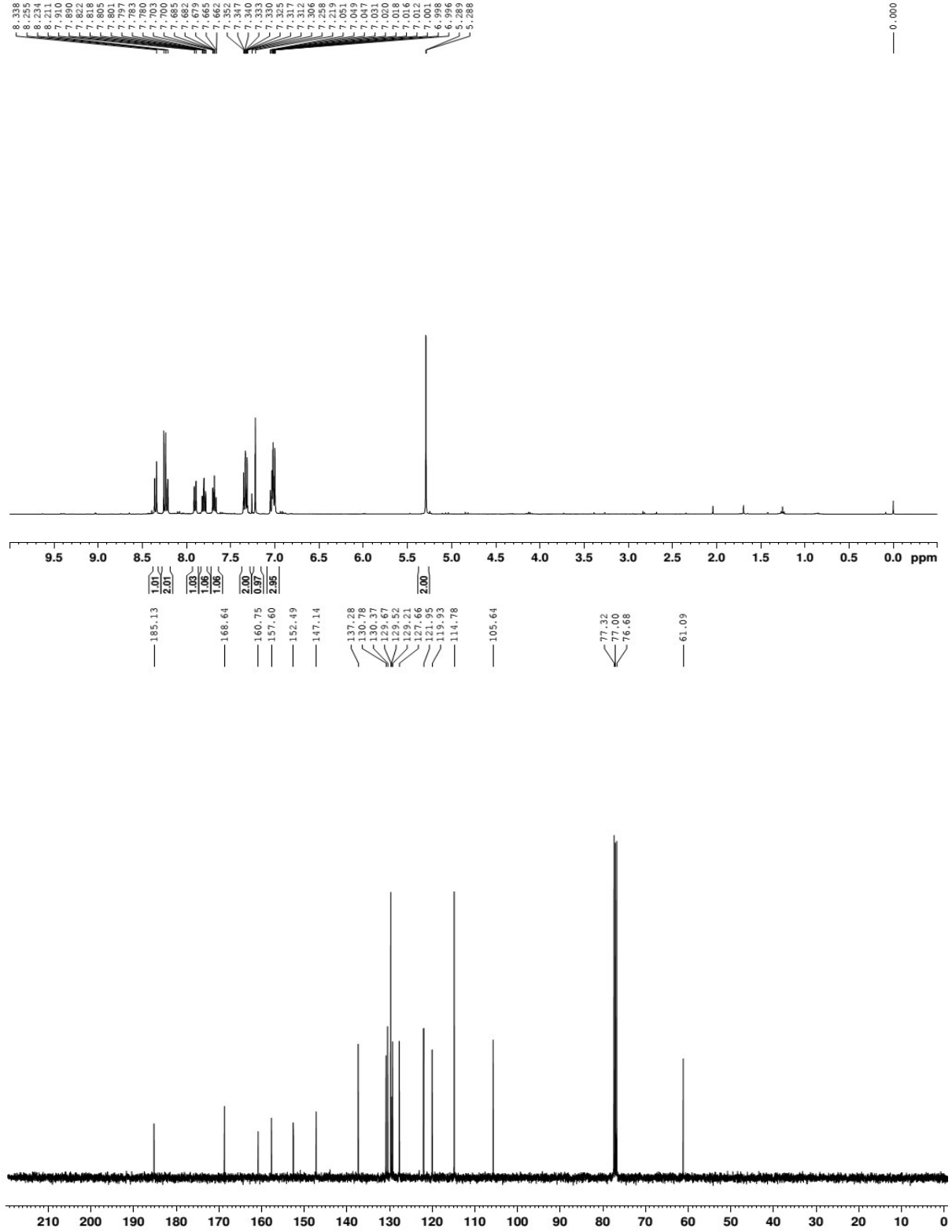


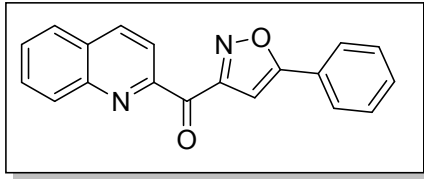
3u



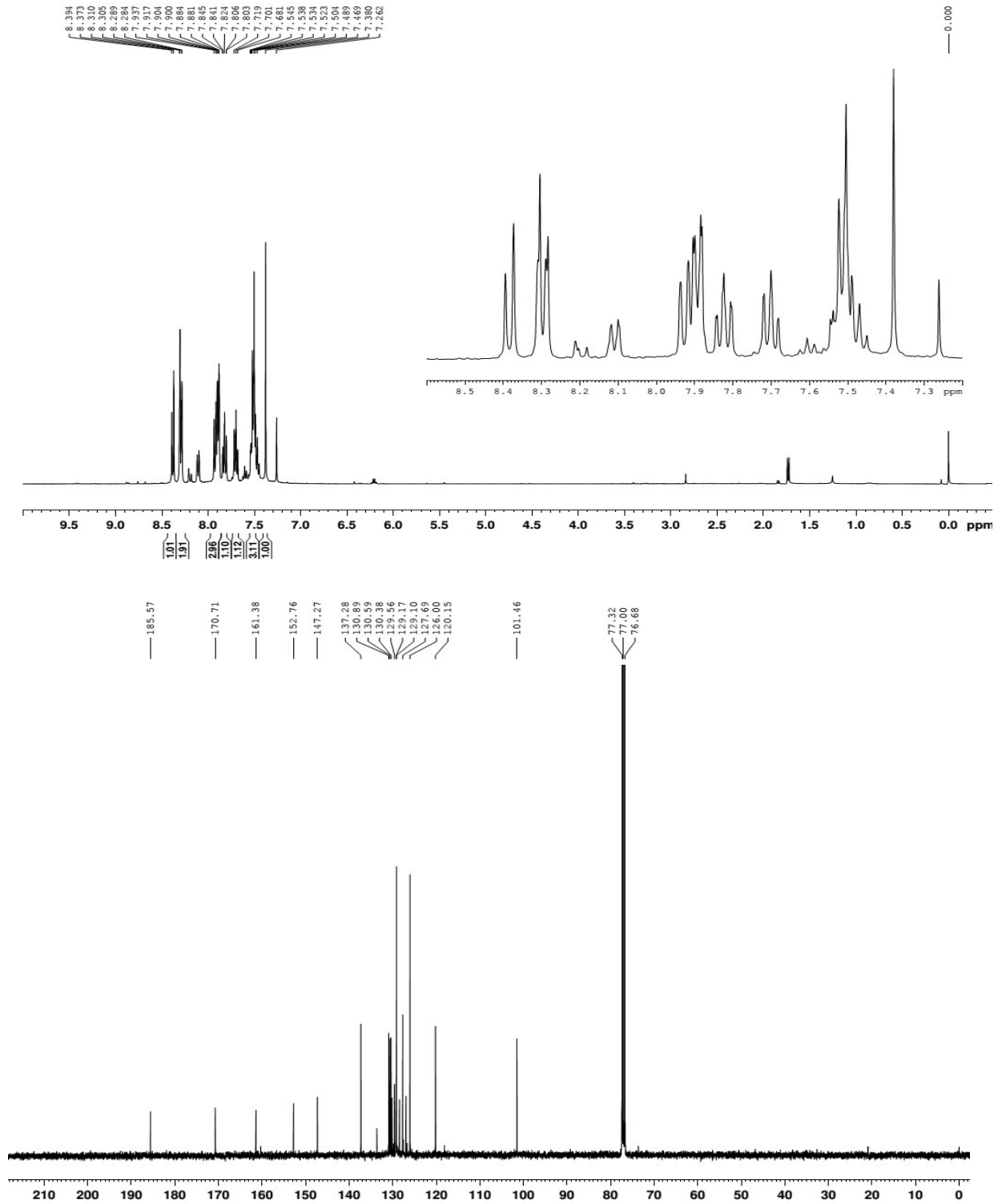


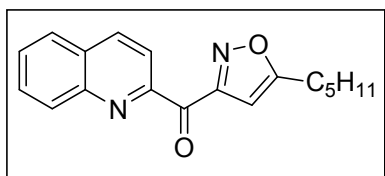
3v



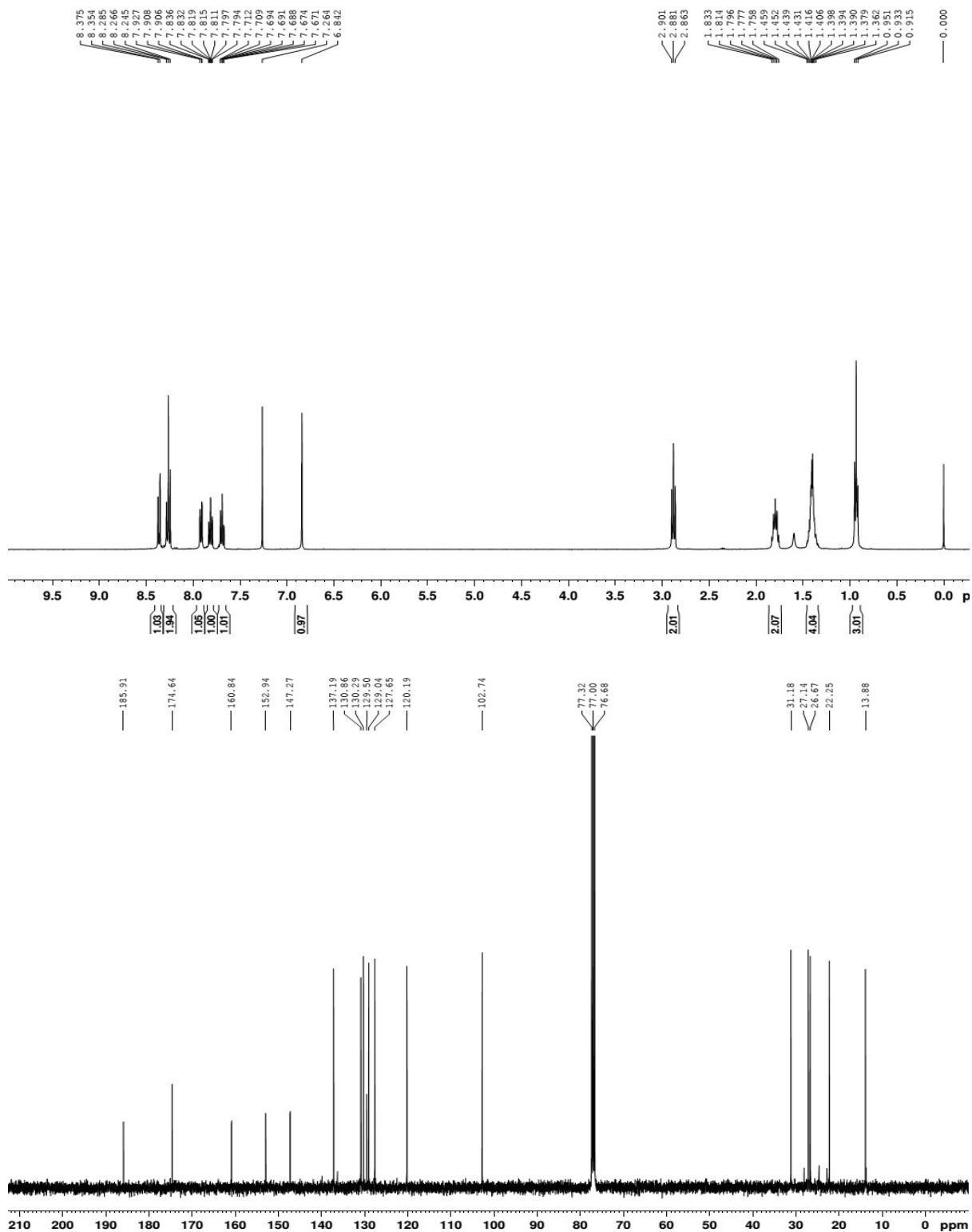


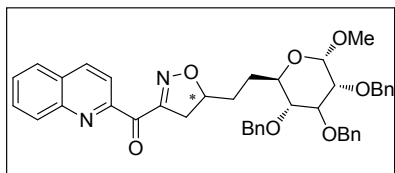
3w mixed with a small amount of impurities.



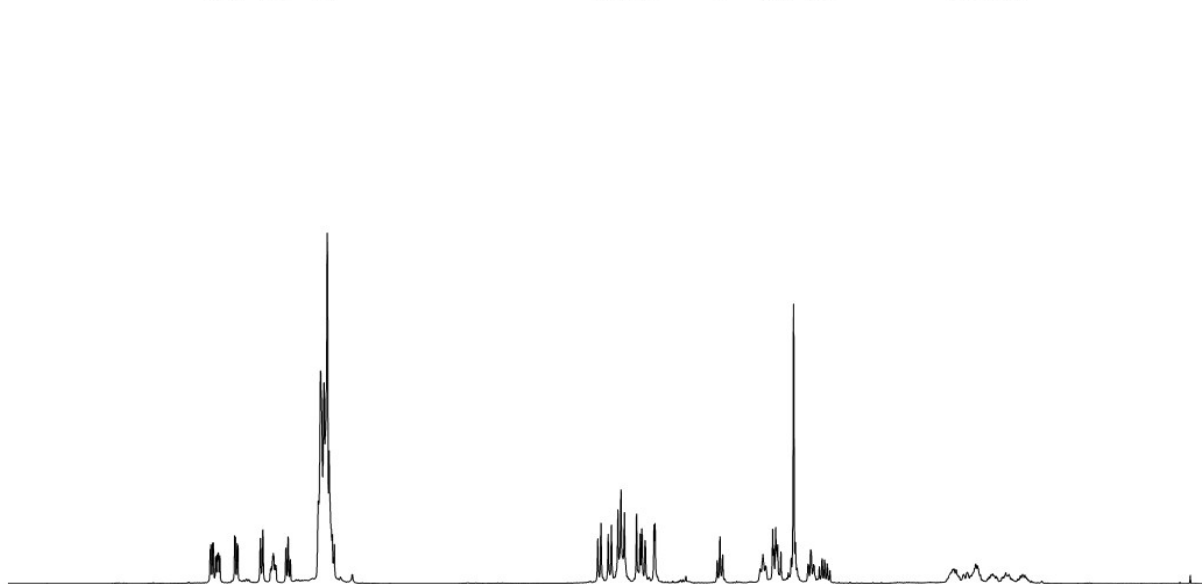


3x

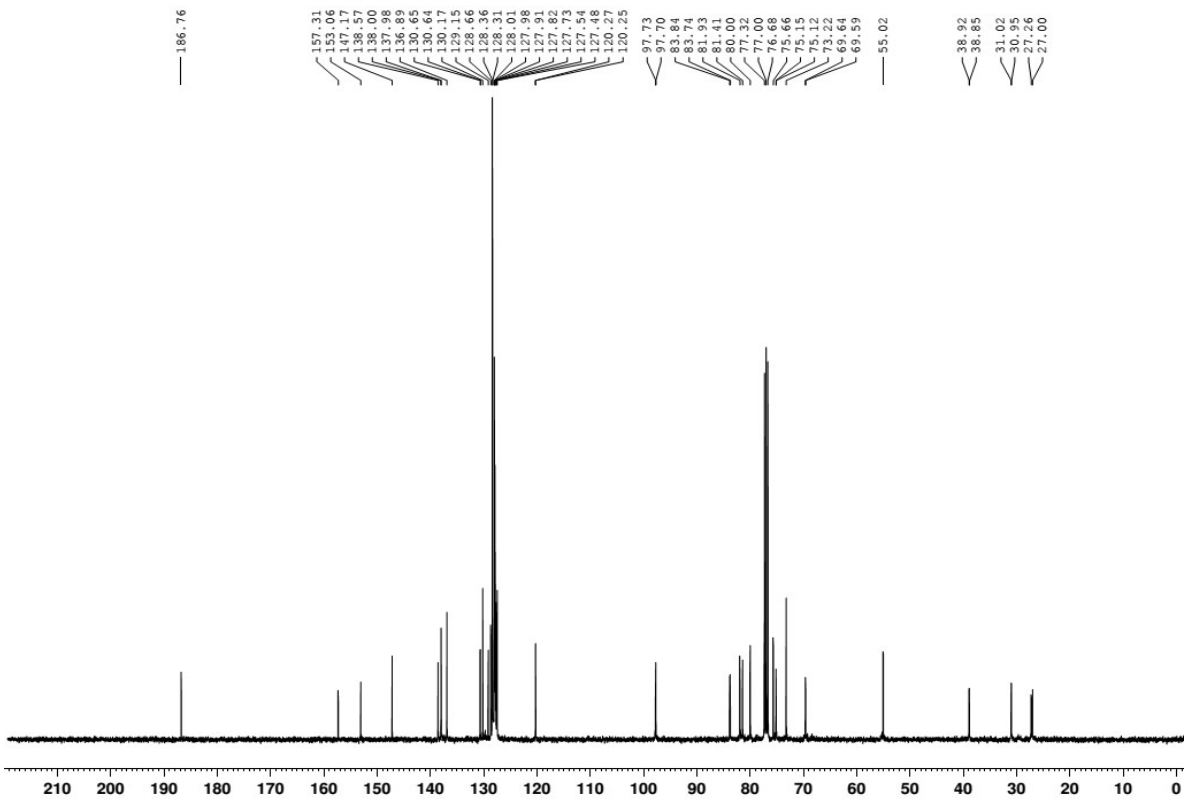




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27.00