

Supporting Information

Copper-catalyzed *ortho*-C(sp²)-H amination of benzamides and picolinamides with alkylamines using oxygen as green oxidant

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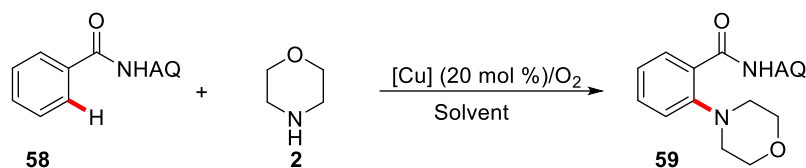
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1. Optimization of Cu-catalyzed C–H amination of N-quinolinybenzocarboxamide with morpholine^a



entry	Cat./O ₂	solvent	T (°C)	yield (%) ^b
1	Cu(OAc) ₂	toluene	110	11
2	Cu(OTf) ₂	toluene	110	trace
3	CuOAc	toluene	110	10
4	CuCl	toluene	110	33
5	CuBr	toluene	110	38
6	CuI	toluene	110	37
7	CuBr	MeCN	110	10
8	CuBr	dioxane	110	65
9	CuBr	THF	110	57
10	CuBr	DMF	110	trace
11	CuBr	xylene	110	18
12 ^c	CuBr	dioxane	110	49
13 ^d	CuBr	dioxane	110	<2

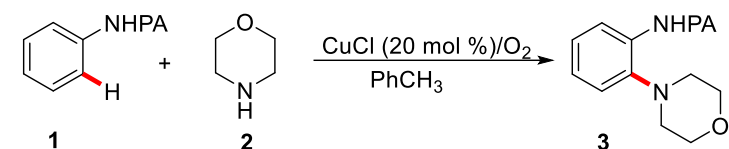
^aReactions conditions: N-quinolinybenzocarboxamide **58** (0.2 mmol, 1.0 equiv), morpholine **2** (0.4 mmol, 2.0 equiv) and copper catalyst (0.04 mmol, 0.2 equiv) in solvent (1 mL) under Oxygen for 12 h in a sealed tube. ^bIsolated yield. ^cAir instead of oxygen. ^dUnder Ar atmosphere.

A mixture of N-quinolinybenzocarboxamide **58** (0.2 mmol, 1.0 equiv), copper catalyst (0.04 mmol, 0.2 equiv) and morpholine **2** (0.4 mmol, 2.0 equiv) in toluene (1.0 mL) in a 10 mL glass vial (purged with O₂, sealed with PTFE cap) was heated at 110 °C for 12 hours. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography (PE/EtOAc) to give the amination product **59**.

2. Preliminary mechanistic experiments

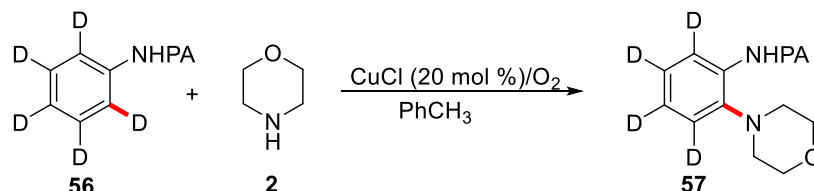
2-1 Parellel kinetic isotope effect of Picolinamide

A mixture of picolinamide **1** (39.6 mg, 0.2 mmol, 1.0 equiv), CuCl (4.0 mg, 0.04 mmol, 0.2 equiv) and morpholine **2** (34.8 μL, 0.4 mmol, 2.0 equiv) in toluene (1.0 mL) in a 10 mL glass vial (purged with O₂, sealed with PTFE cap) was heated at 110 °C. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography (PE/EtOAc 8:1) to give the amination product **3**.

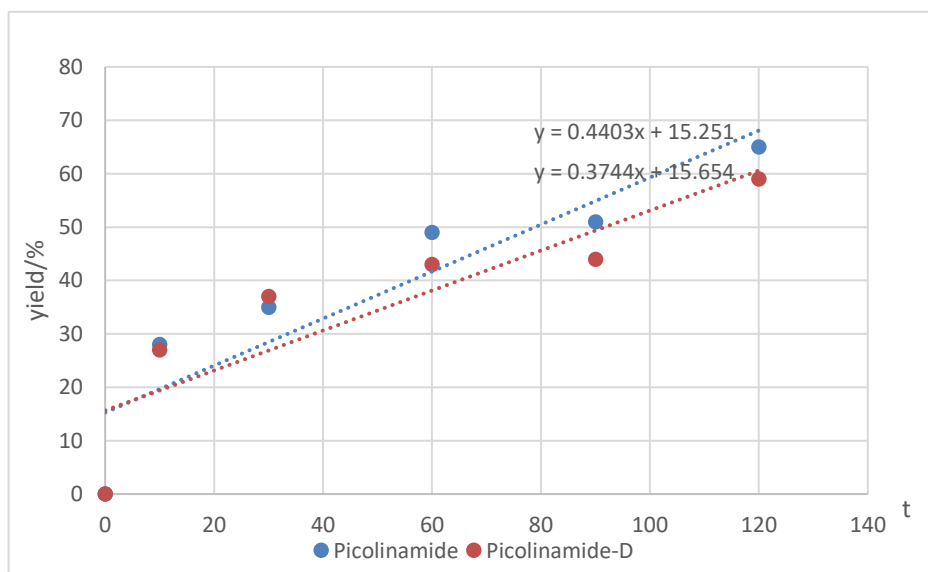


entry	time(min)	yield(%)
1	10	28
2	30	35
3	60	49
4	90	51
5	120	65

Another mixture of N-(phenyl-d₅)picolinamide **56** (40.7 mg, 0.2 mmol, 1.0 equiv), CuCl (4.0 mg, 0.04 mmol, 0.2 equiv) and morpholine **2** (34.8 μ L, 0.4 mmol, 2.0 equiv) in toluene (1.0 mL) in a 10 mL glass vial (purged with O₂, sealed with PTFE cap) was heated at 110 °C. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography (PE/EtOAc 8:1) to give the amination product **57**.



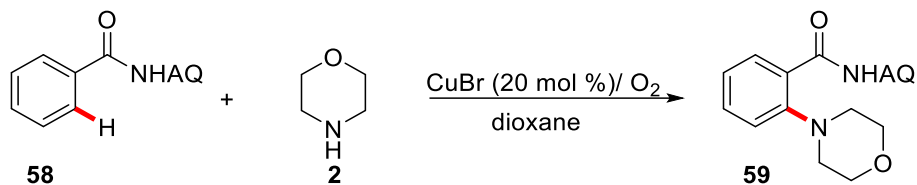
entry	time(min)	yield(%)
1	10	27
2	30	37
3	60	43
4	90	44
5	120	59



KIE: $k_H/k_D = 0.4403/0.3744 = 1.18$

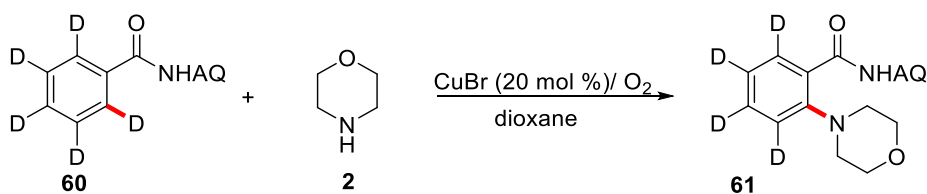
2-2 KIE of N-quinolinybenzocarboxamide

A mixture of N-quinolinybenzocarboxamide **58** (49.7 mg, 0.2 mmol, 1.0 equiv), CuBr (5.7 mg, 0.04 mmol, 0.2 equiv) and morpholine **2** (34.8 μ L, 0.4 mmol, 2.0 equiv) in dioxane (1.0 mL) in a 10 mL glass vial (purged with O₂, sealed with PTFE cap) was heated at 110 °C. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography (PE/EtOAc 10:1) to give the amination product **59**.

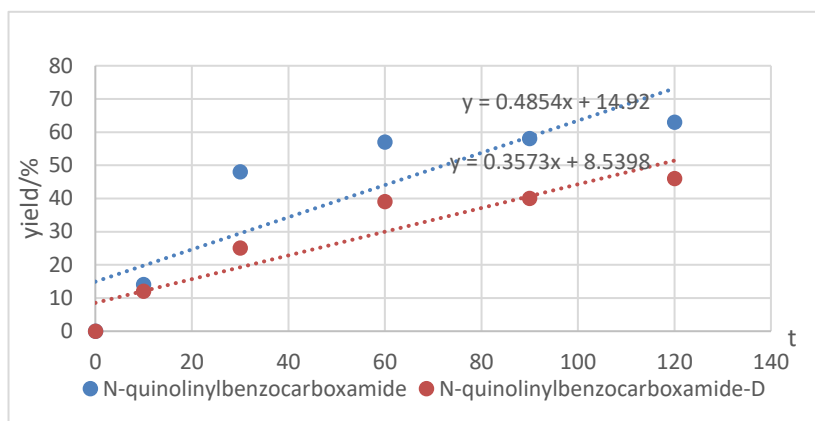


entry	time(min)	yield(%)
1	10	14
2	30	48
3	60	57
4	90	58
5	120	63

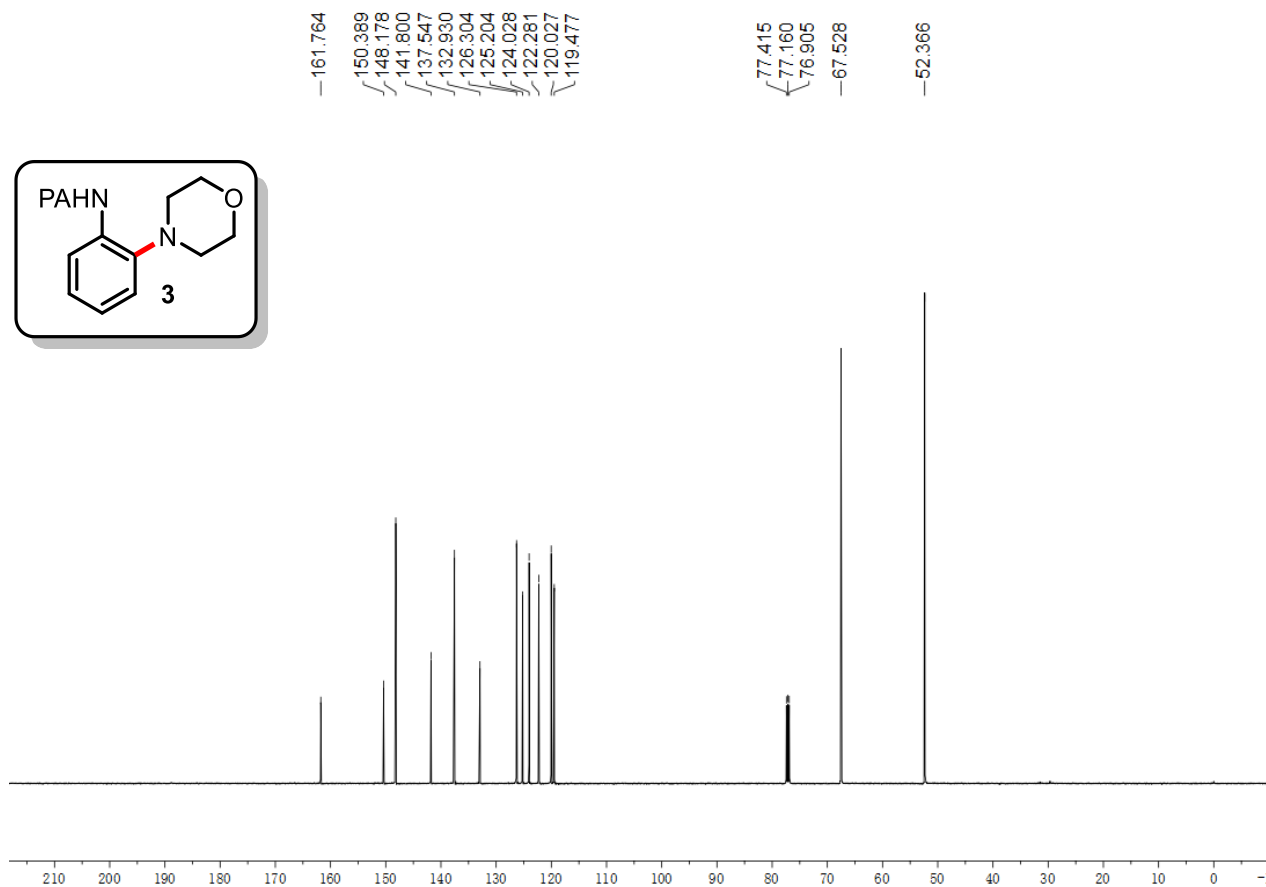
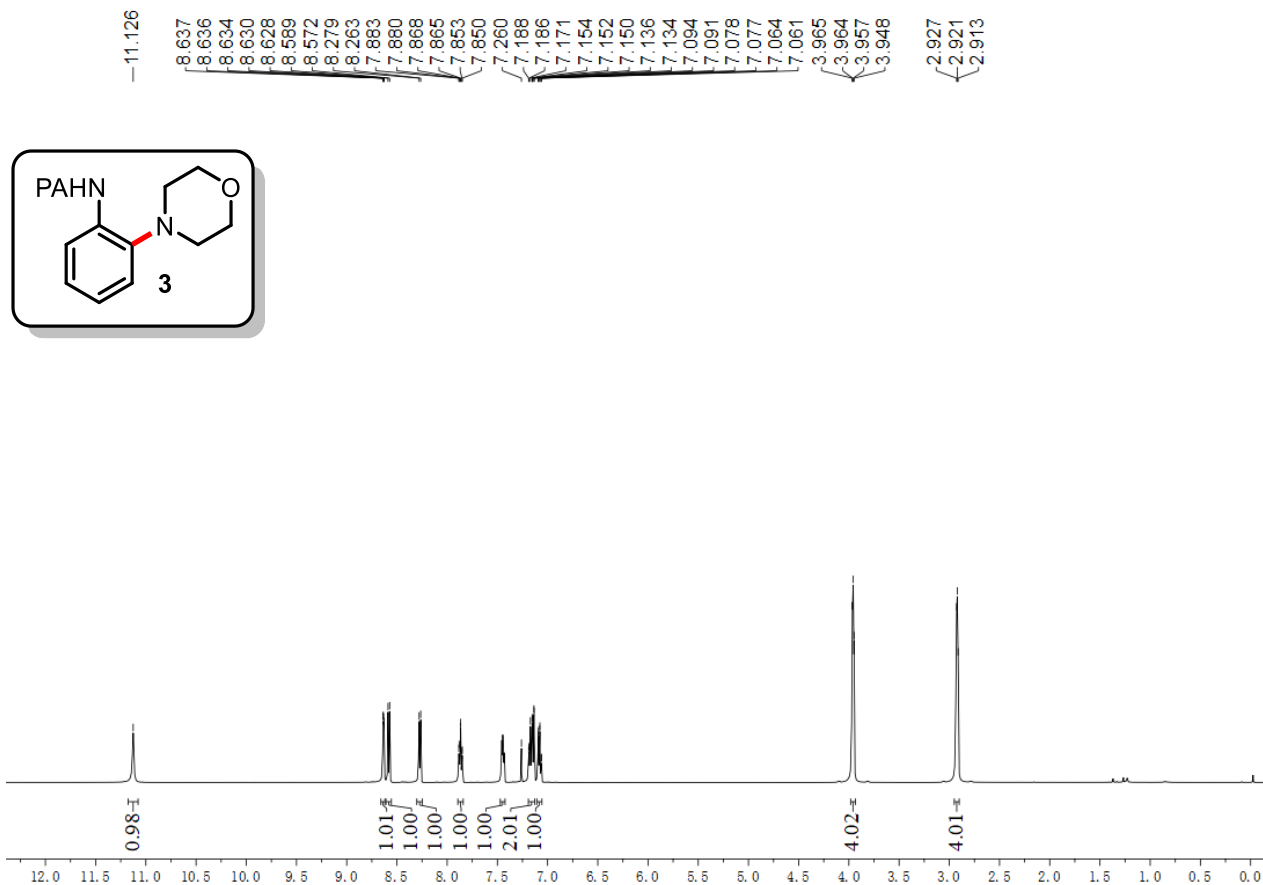
Another mixture of N-(quinolin-8-yl)benzamide-2,3,4,5,6-d₅ **60** (50.7 mg, 0.2 mmol, 1.0 equiv), CuBr (5.7 mg, 0.04 mmol, 0.2 equiv) and morpholine **2** (34.8 μ L, 0.4 mmol, 2.0 equiv) in dioxane (1.0 mL) in a 10 mL glass vial (purged with O₂, sealed with PTFE cap) was heated at 110 °C. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography (PE/EtOAc 10:1) to give the amination product **61**.

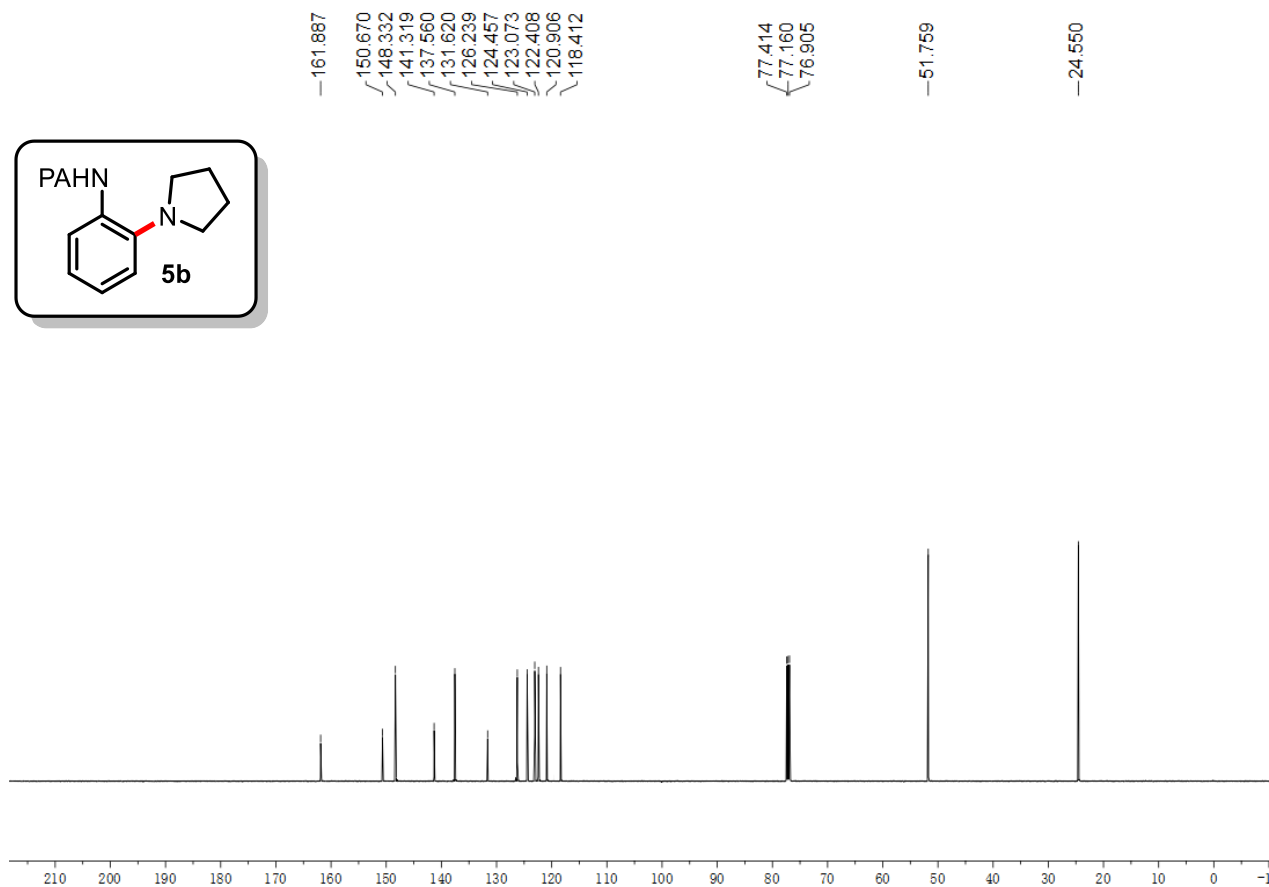
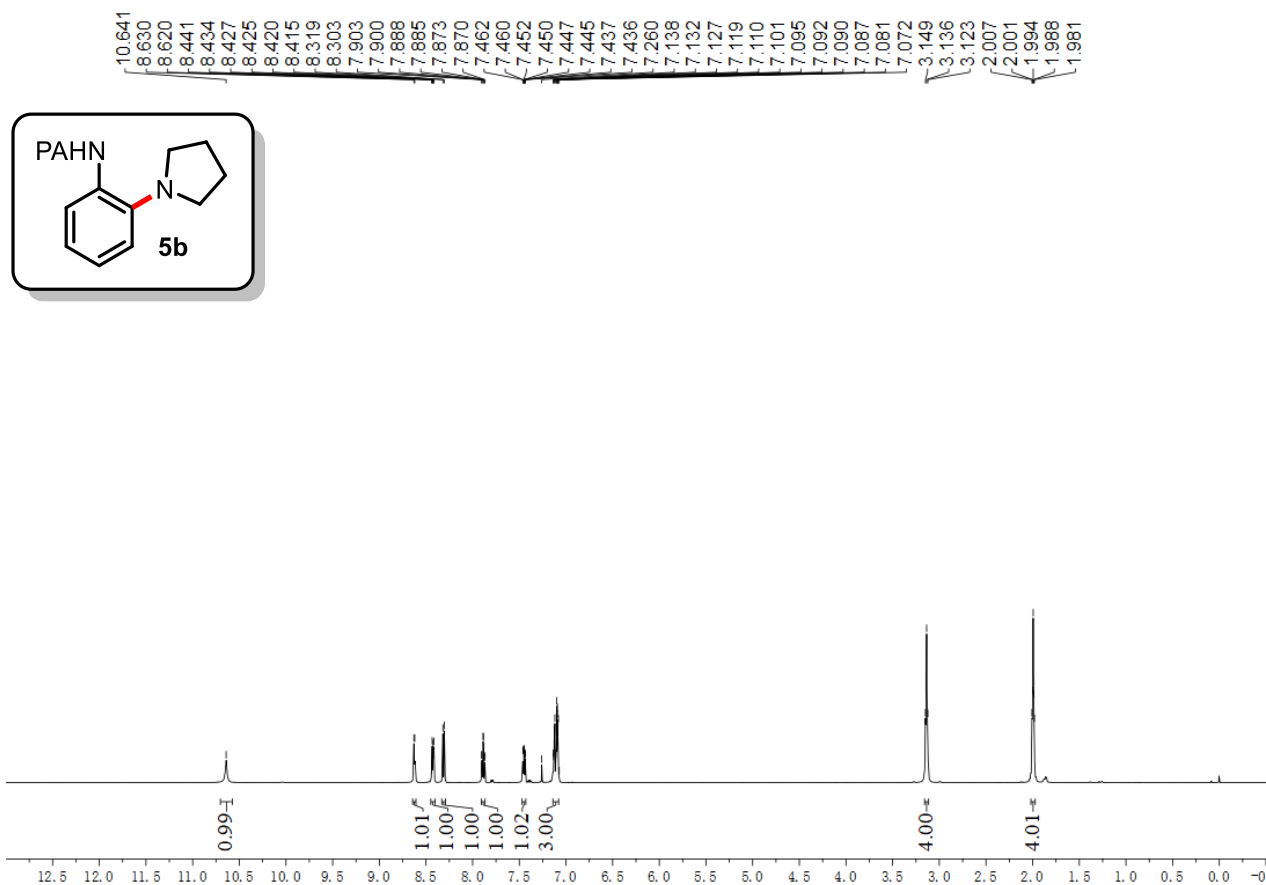


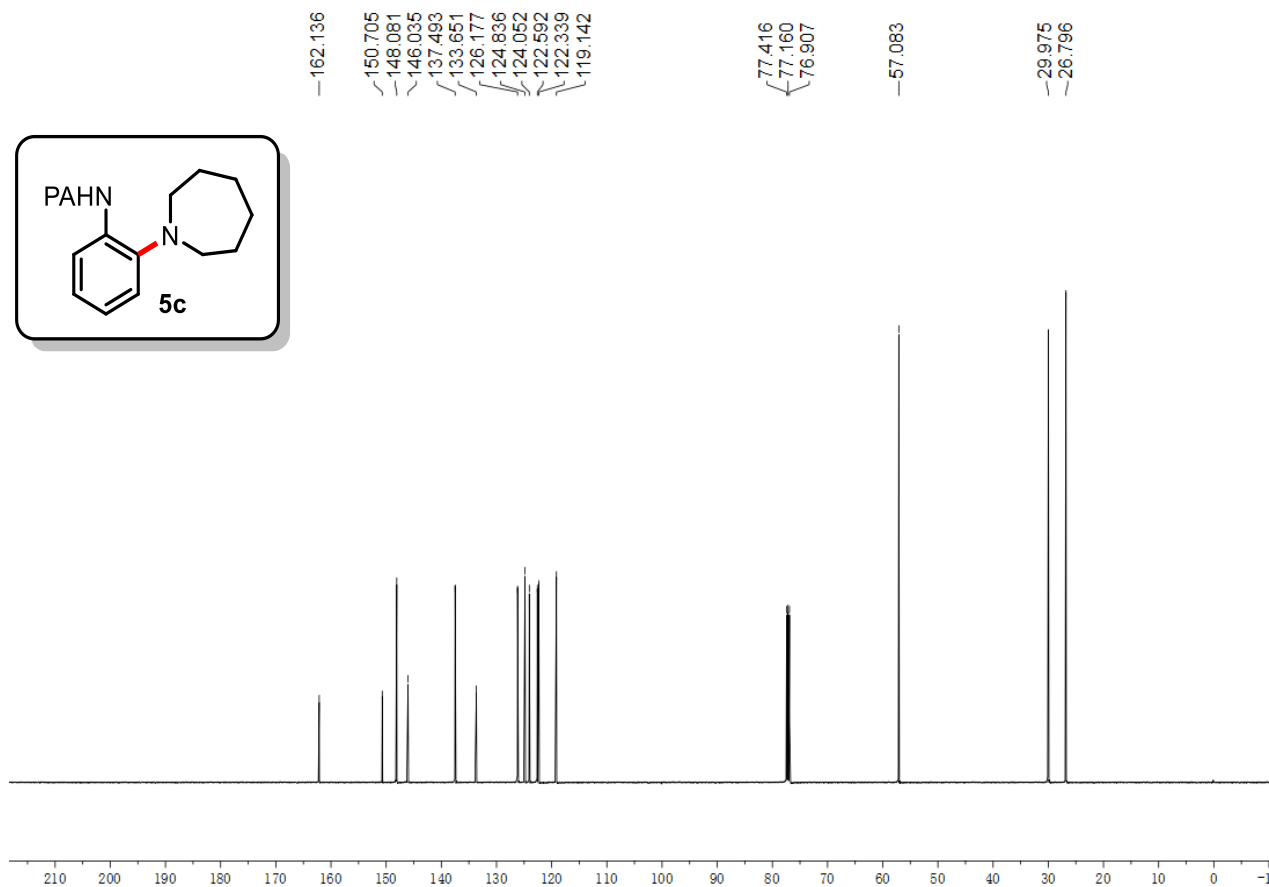
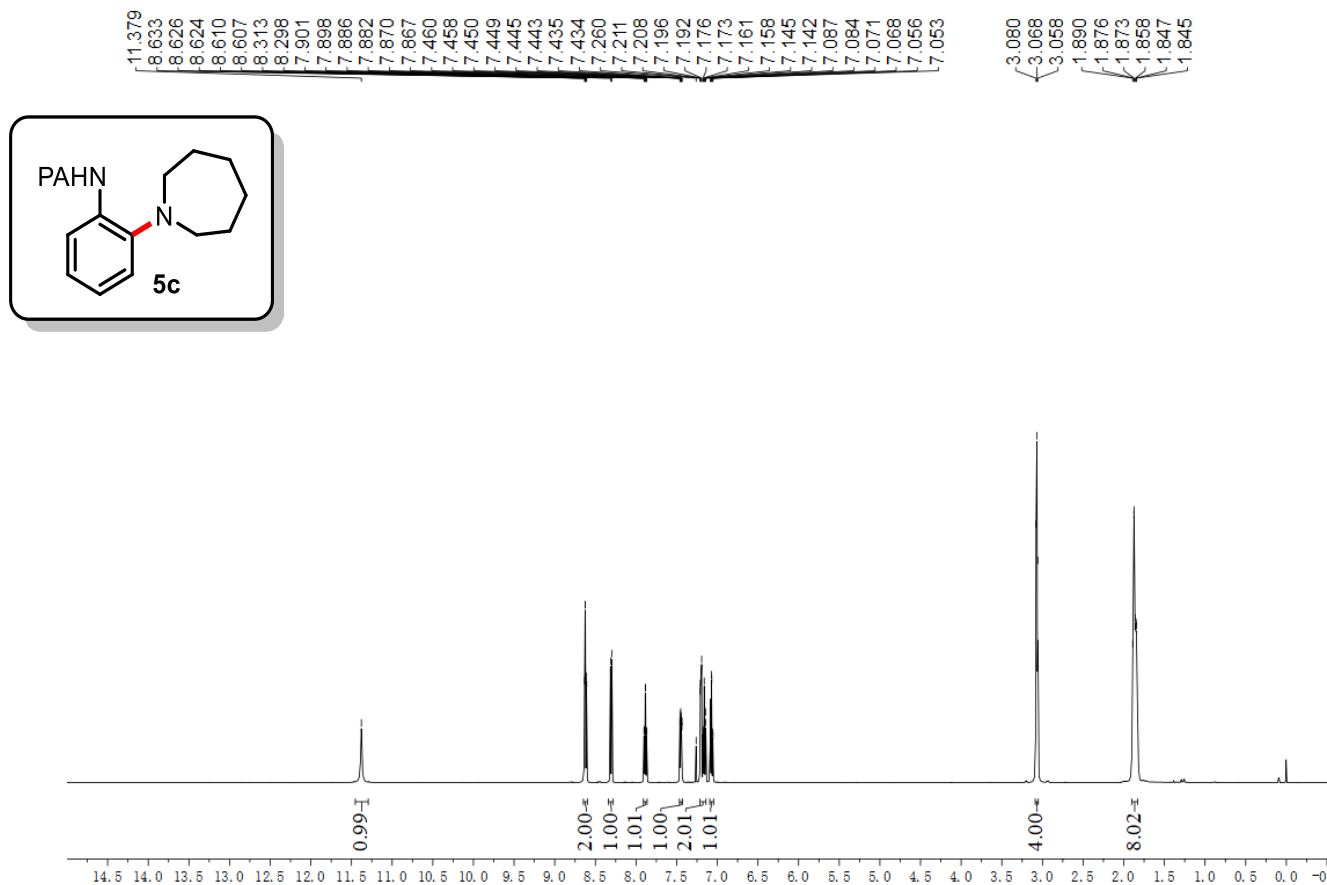
entry	time(min)	yield(%)
1	10	12
2	30	25
3	60	39
4	90	40
5	120	46

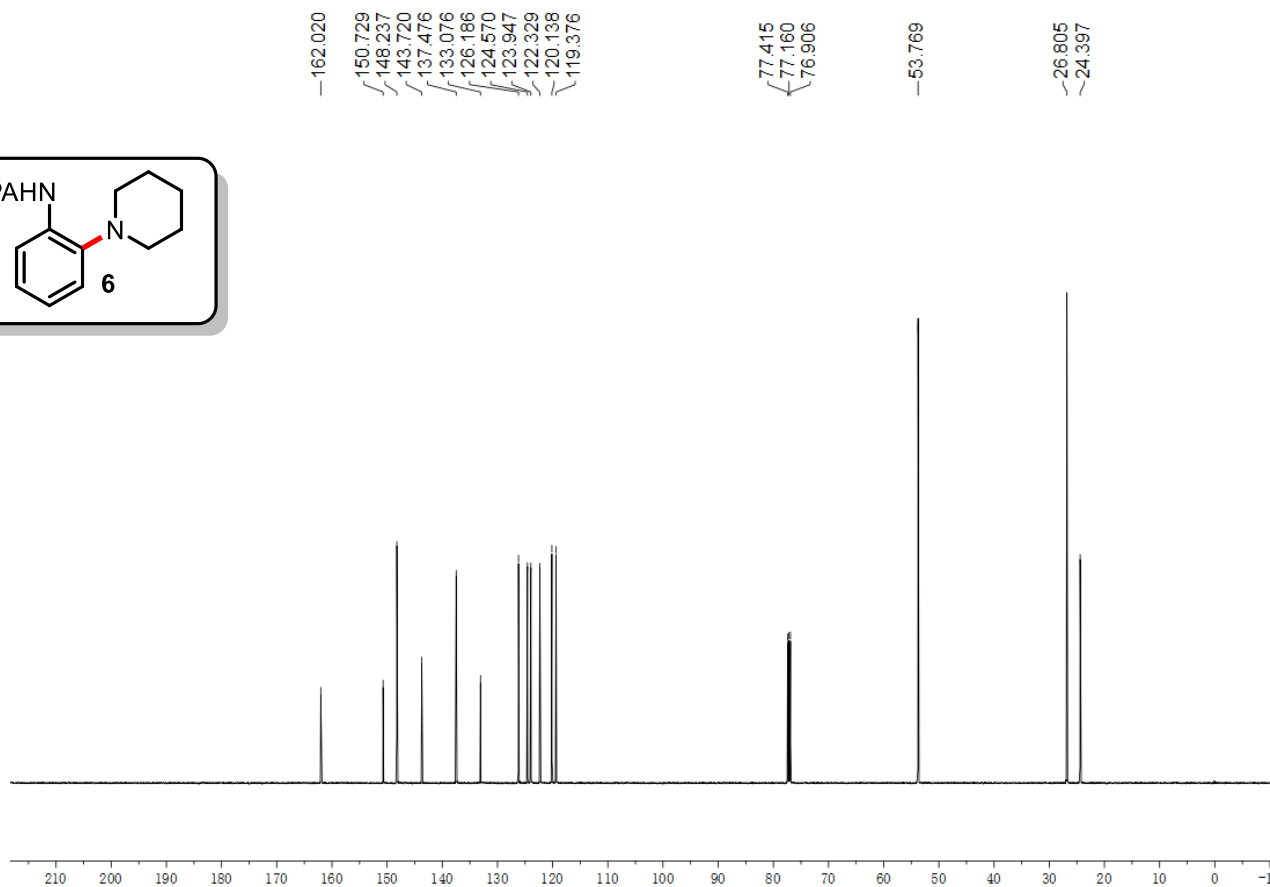
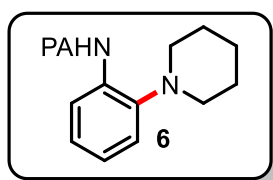
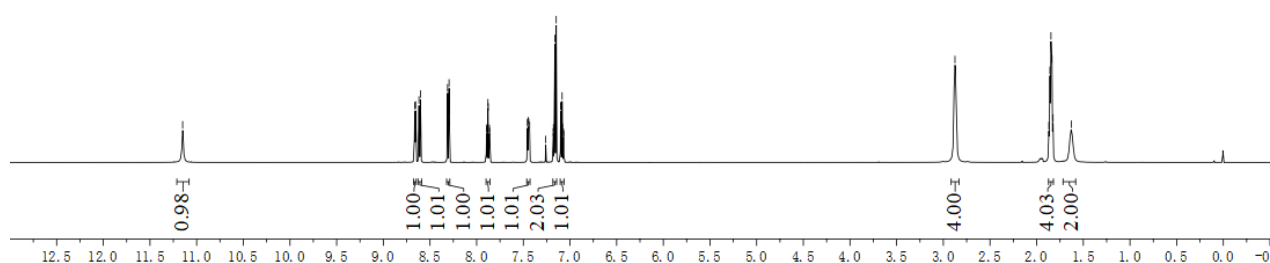
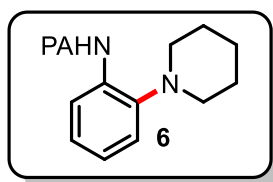


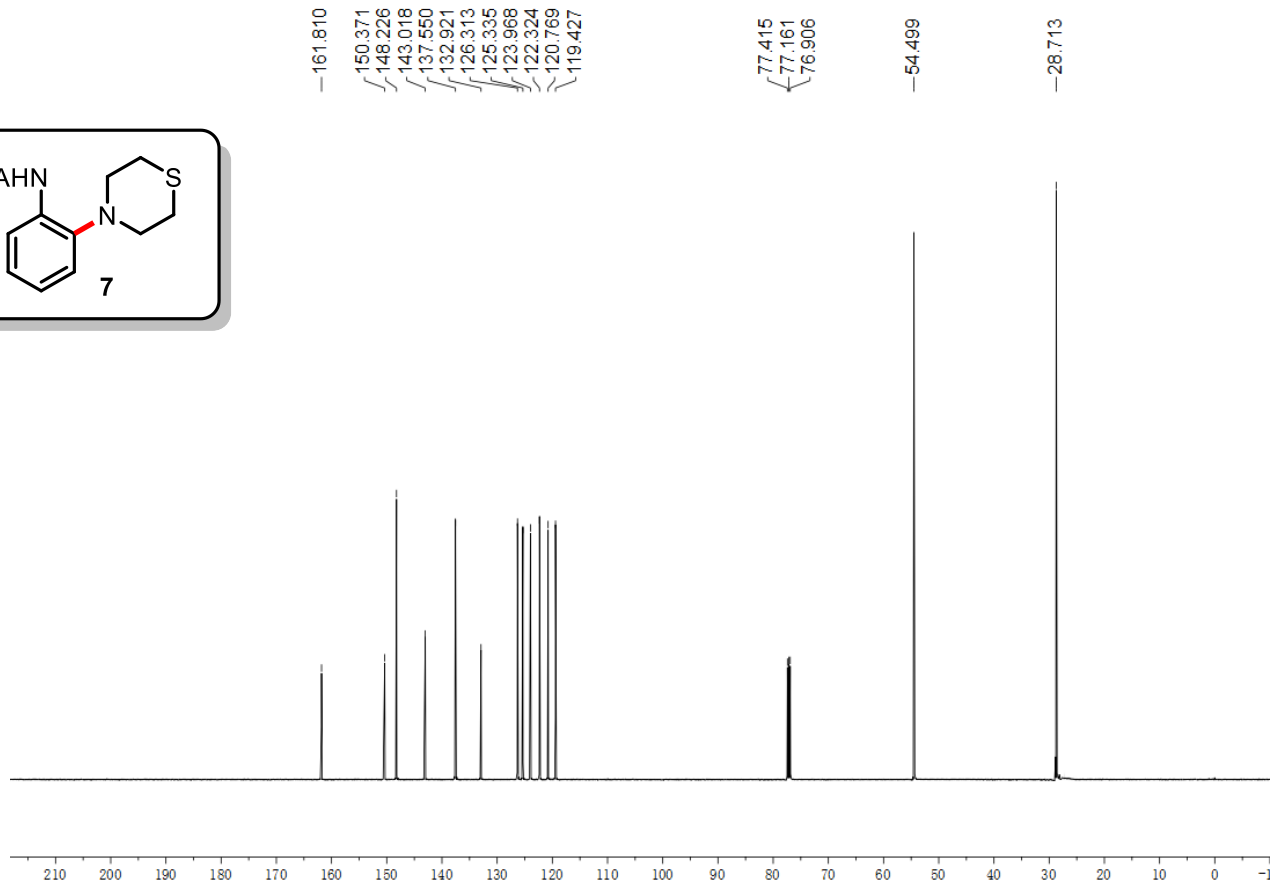
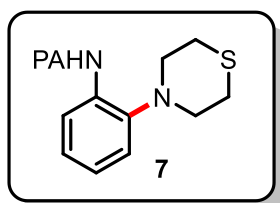
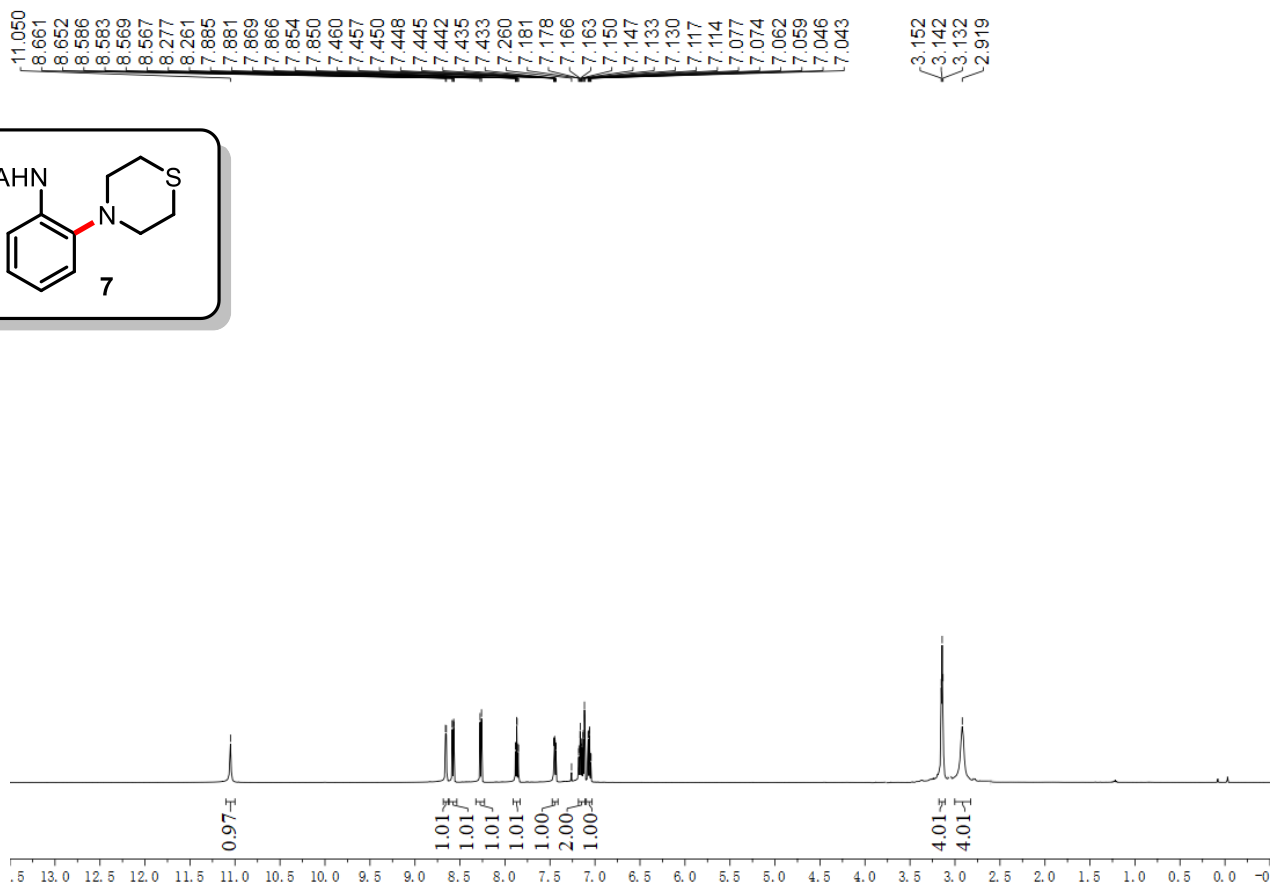
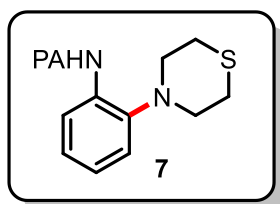
KIE: $k_H/k_D = 0.4854/0.3573 = 1.36$

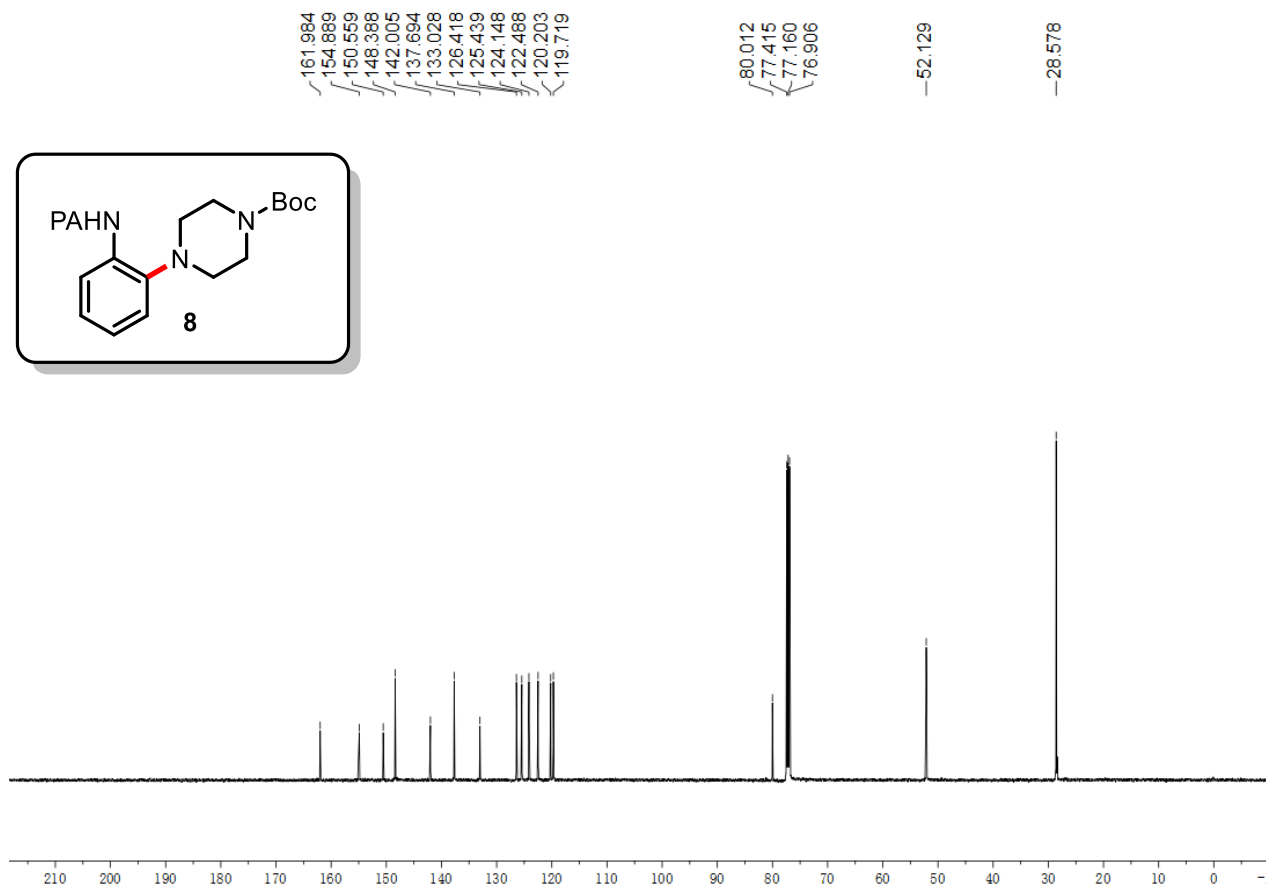
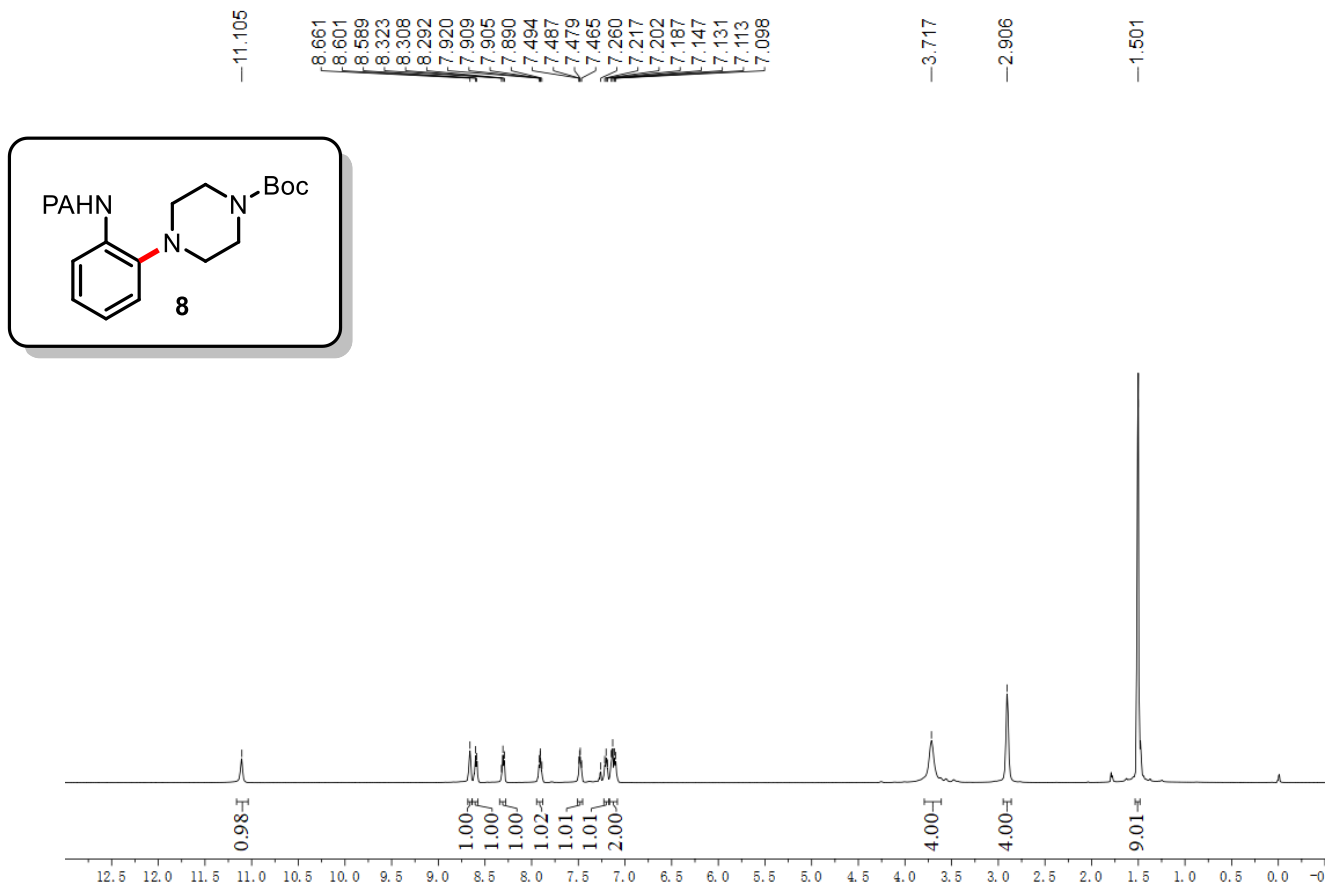


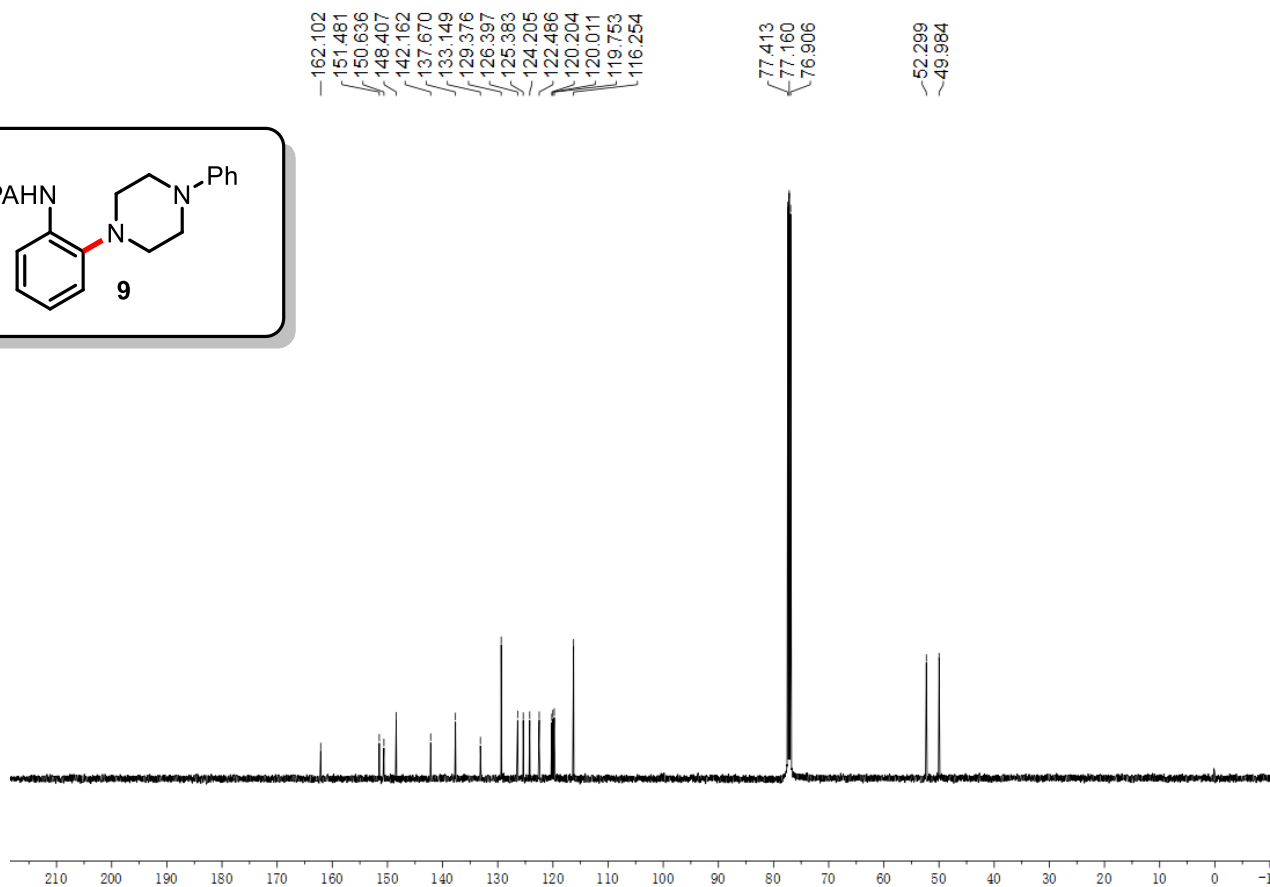
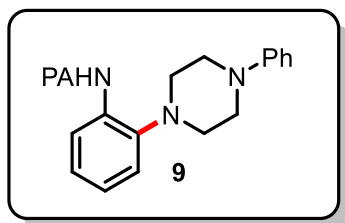
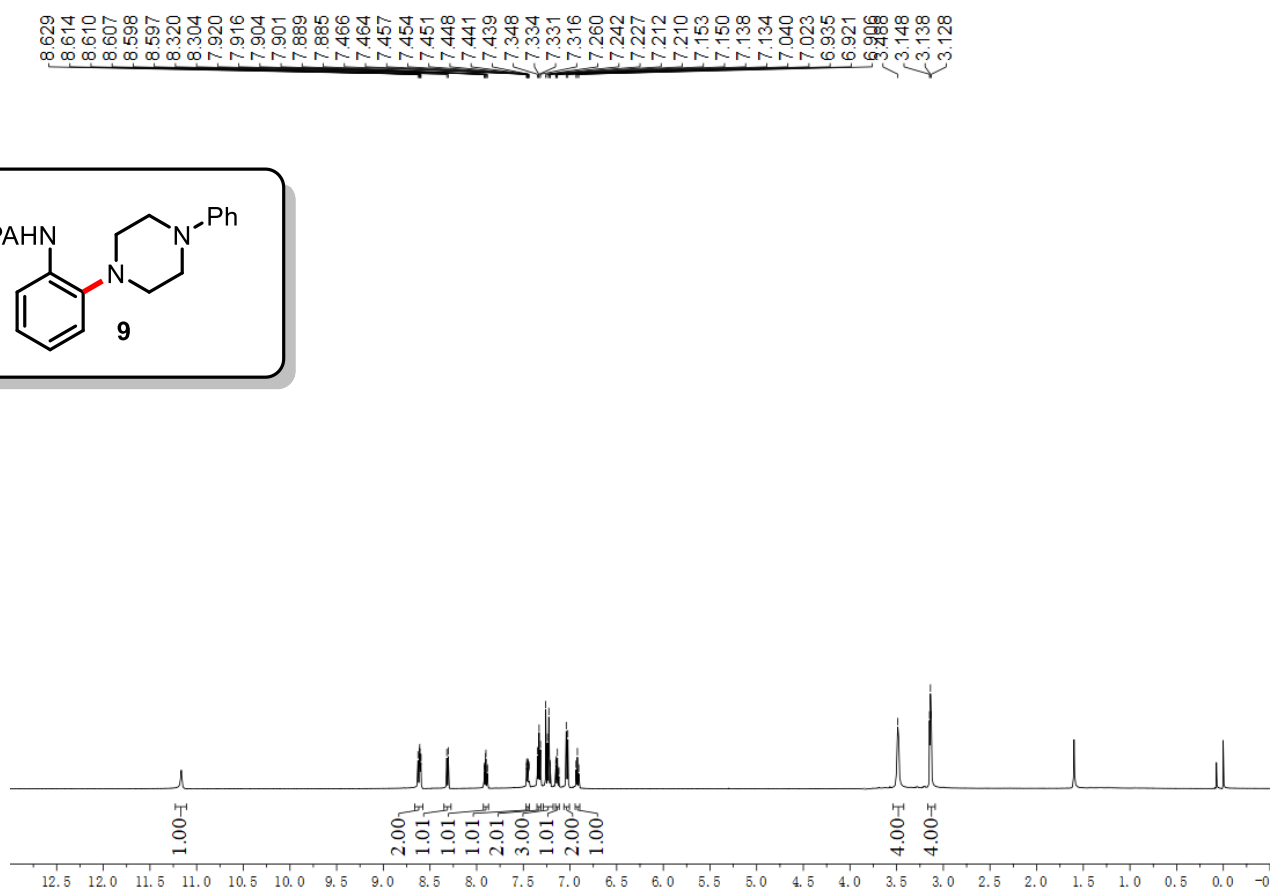
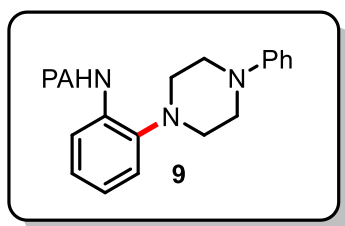


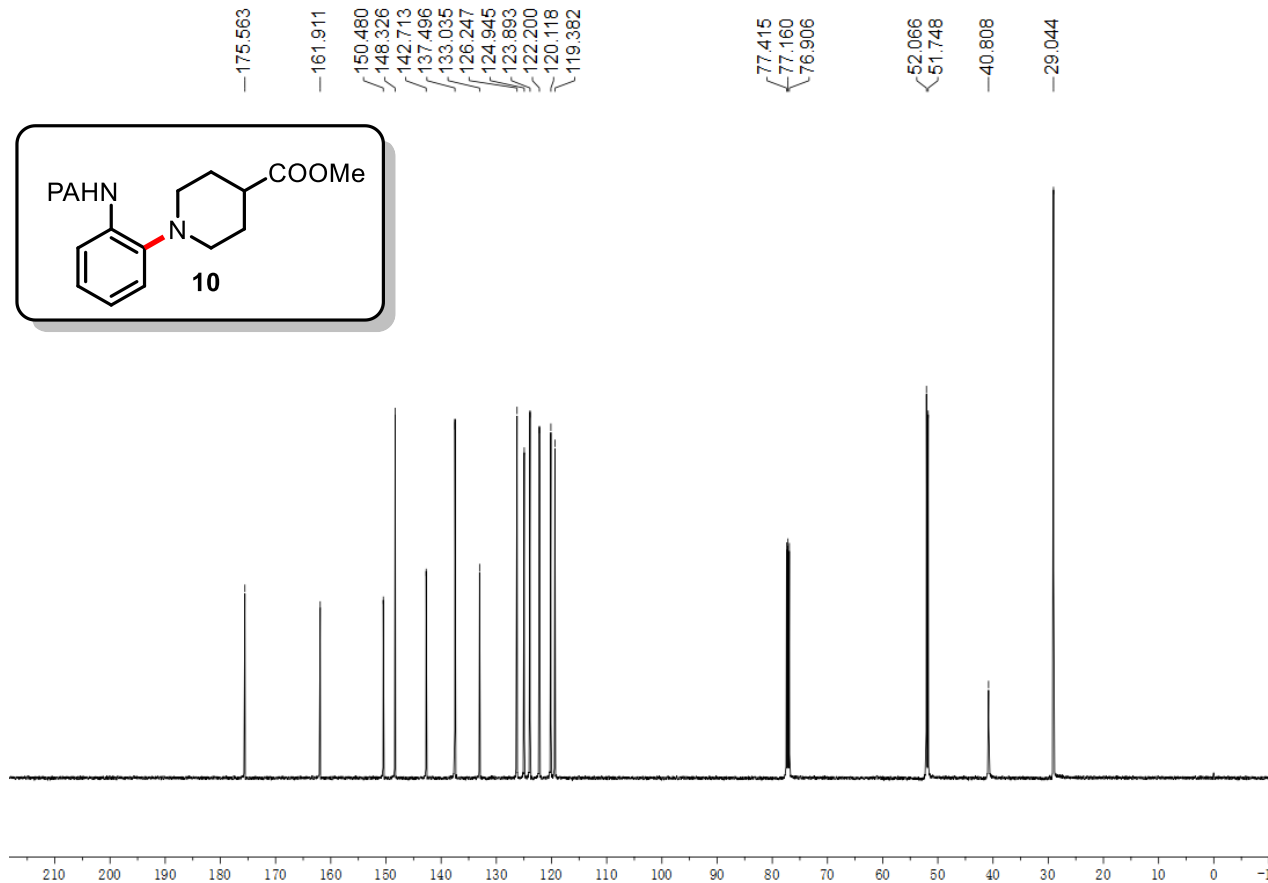
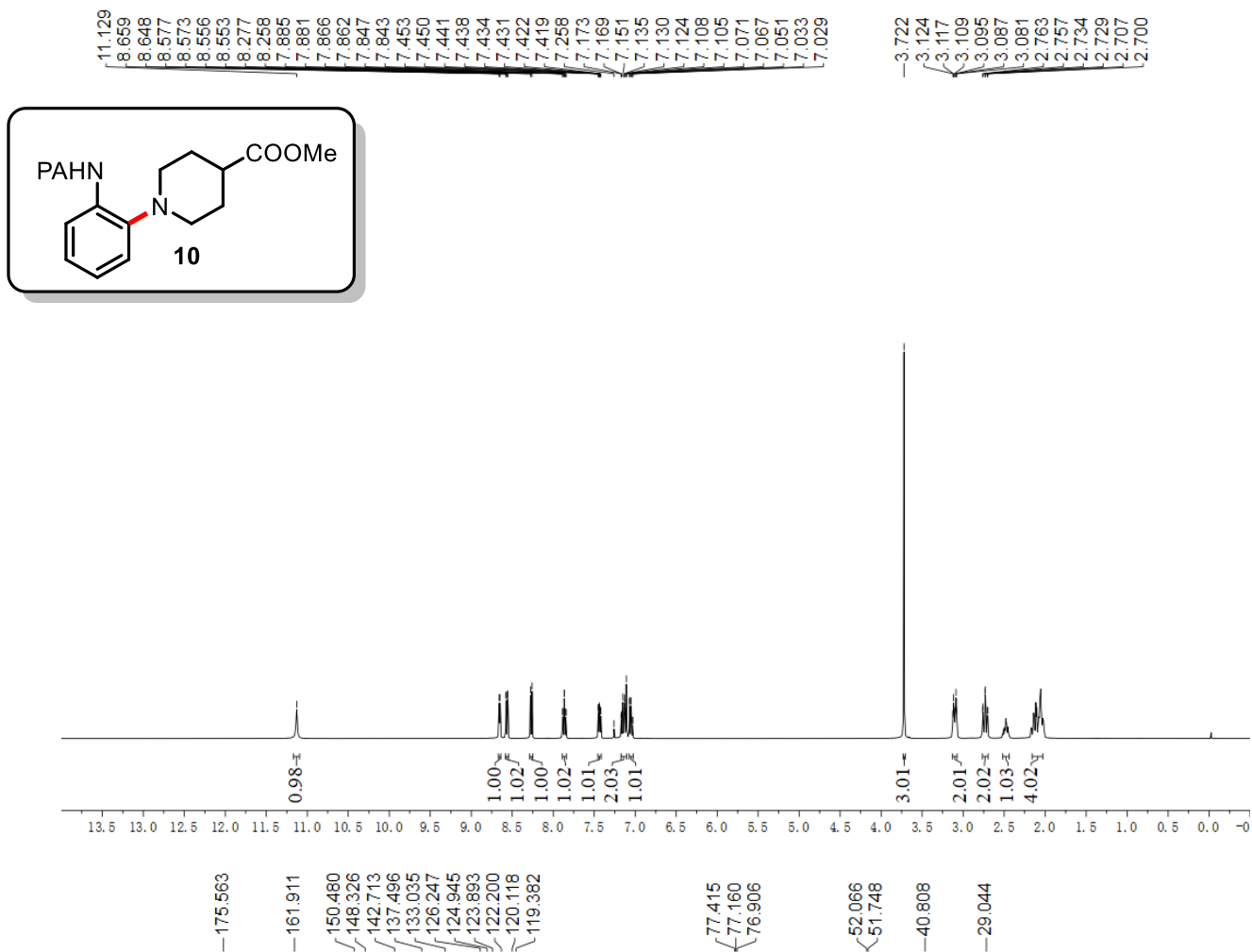


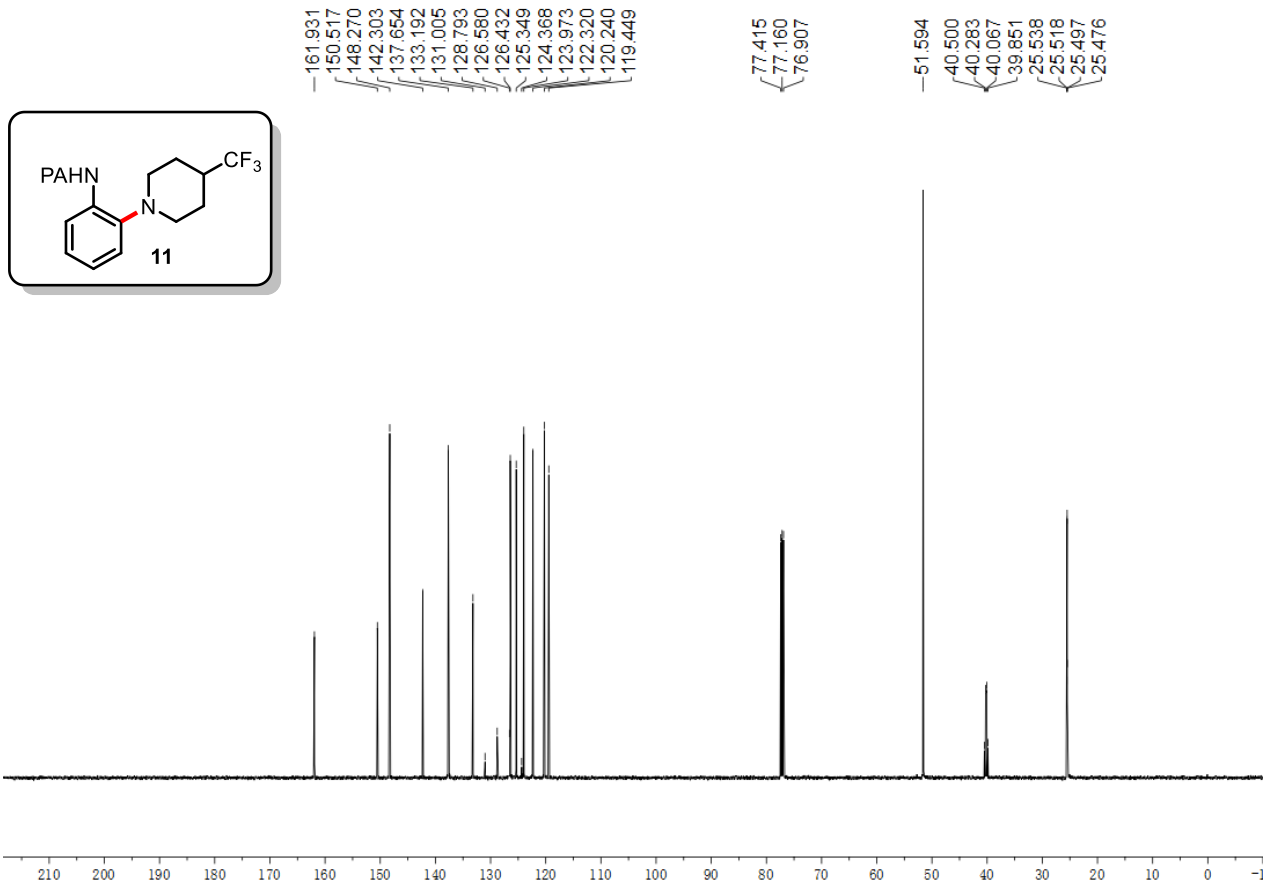
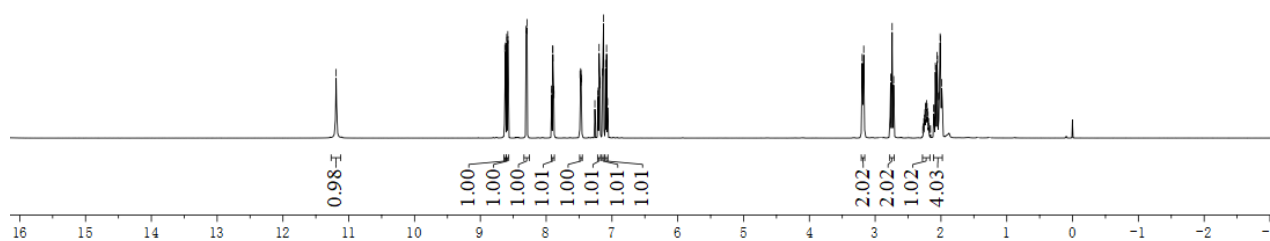
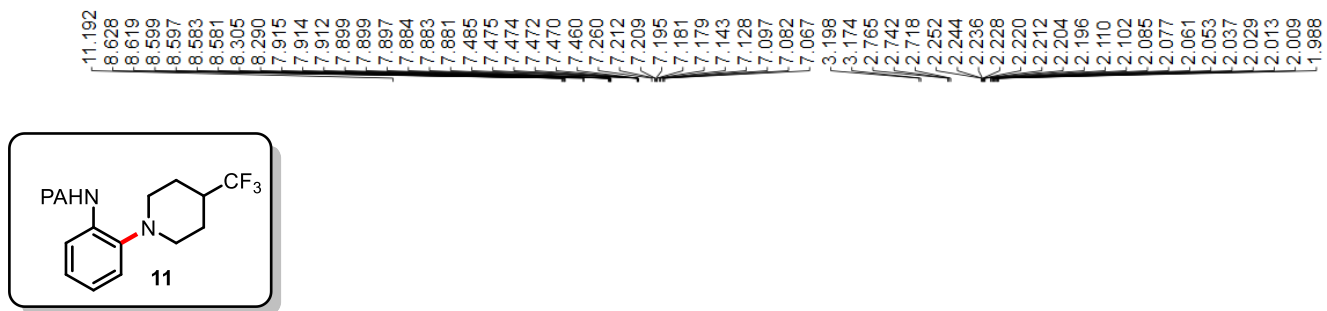


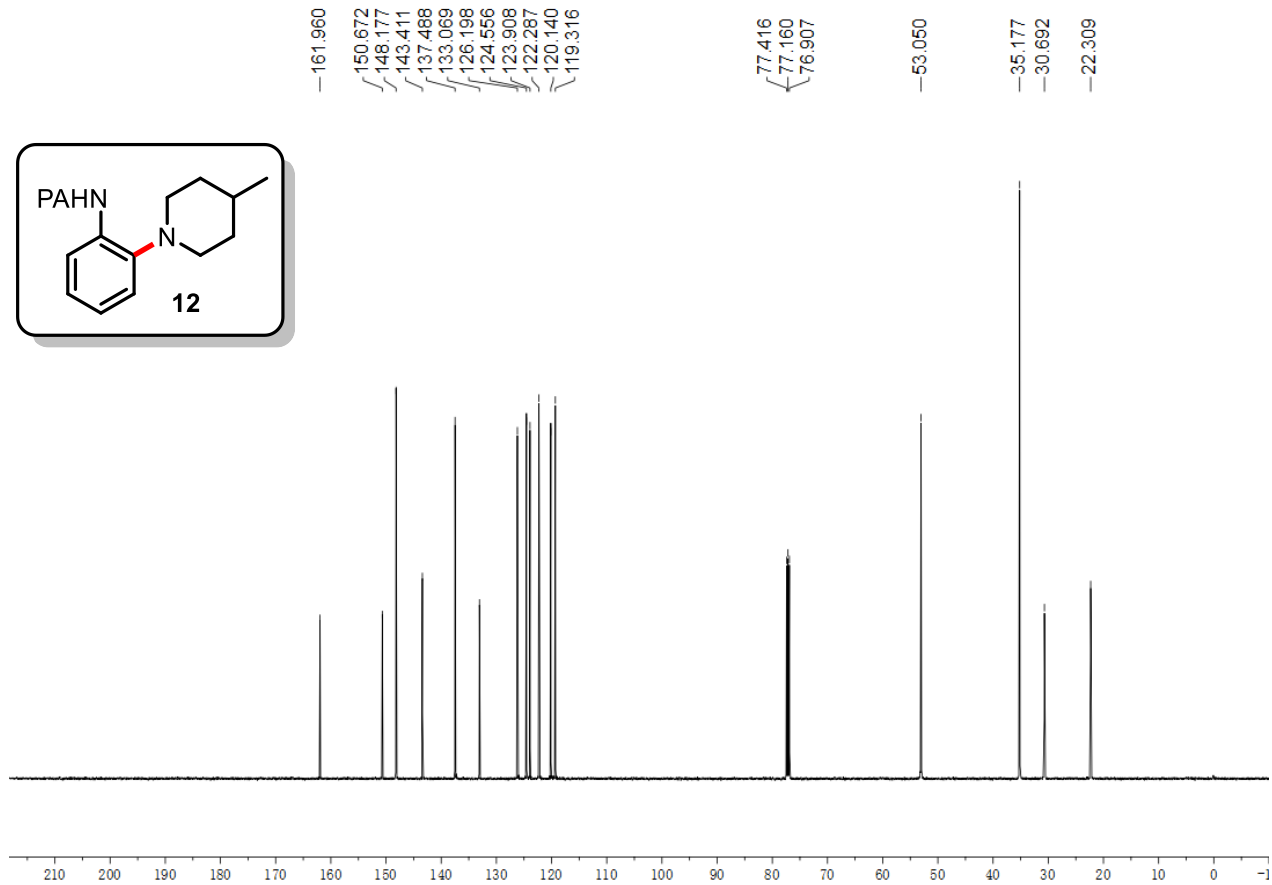
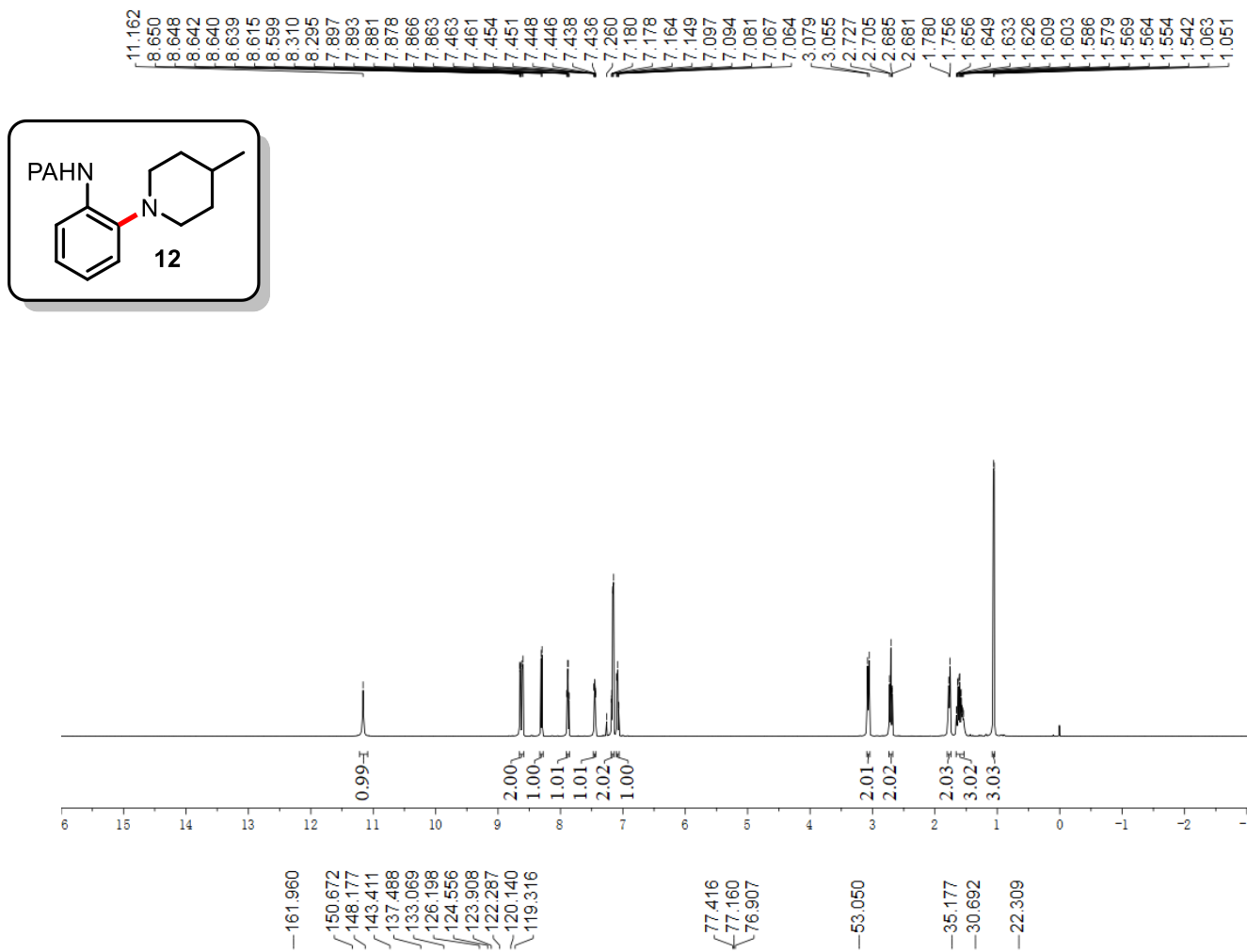


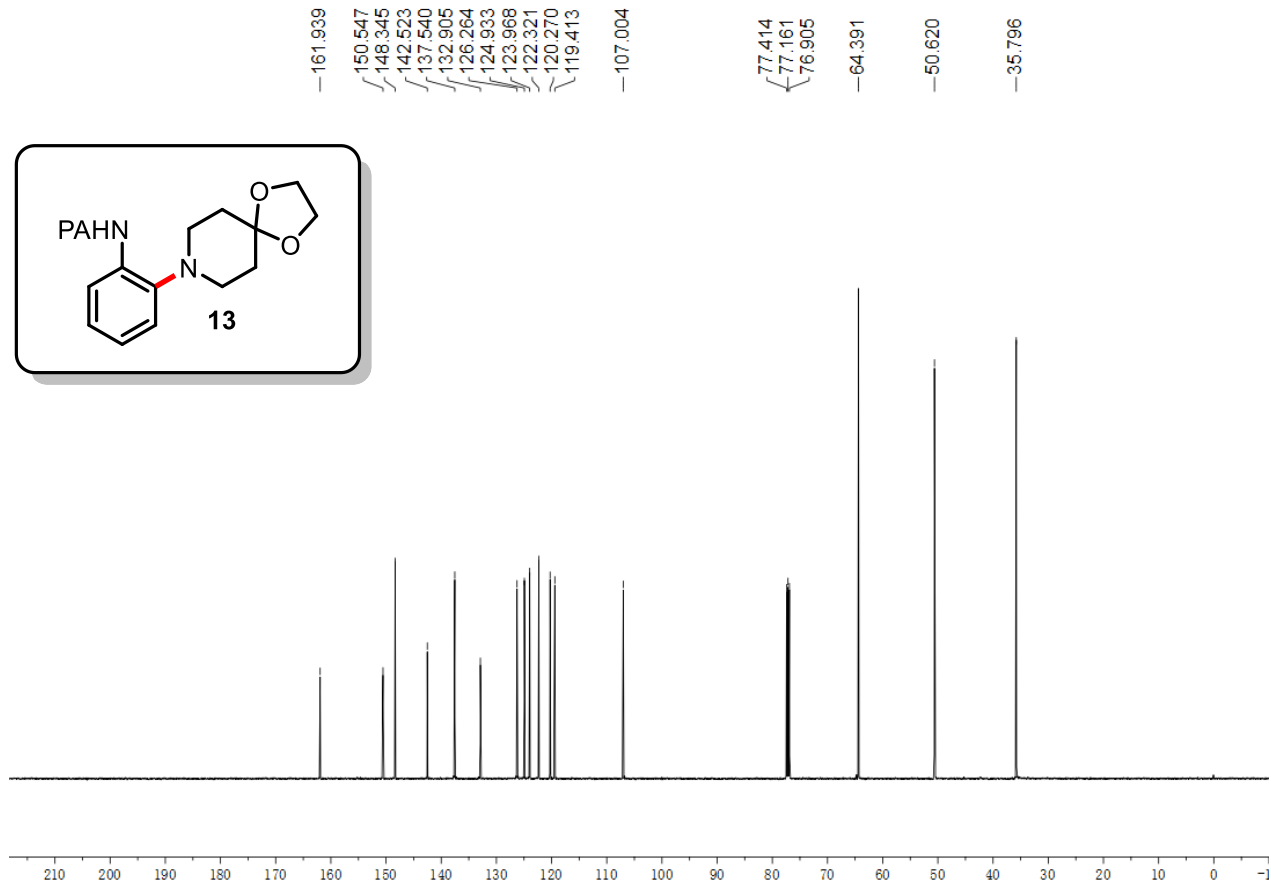
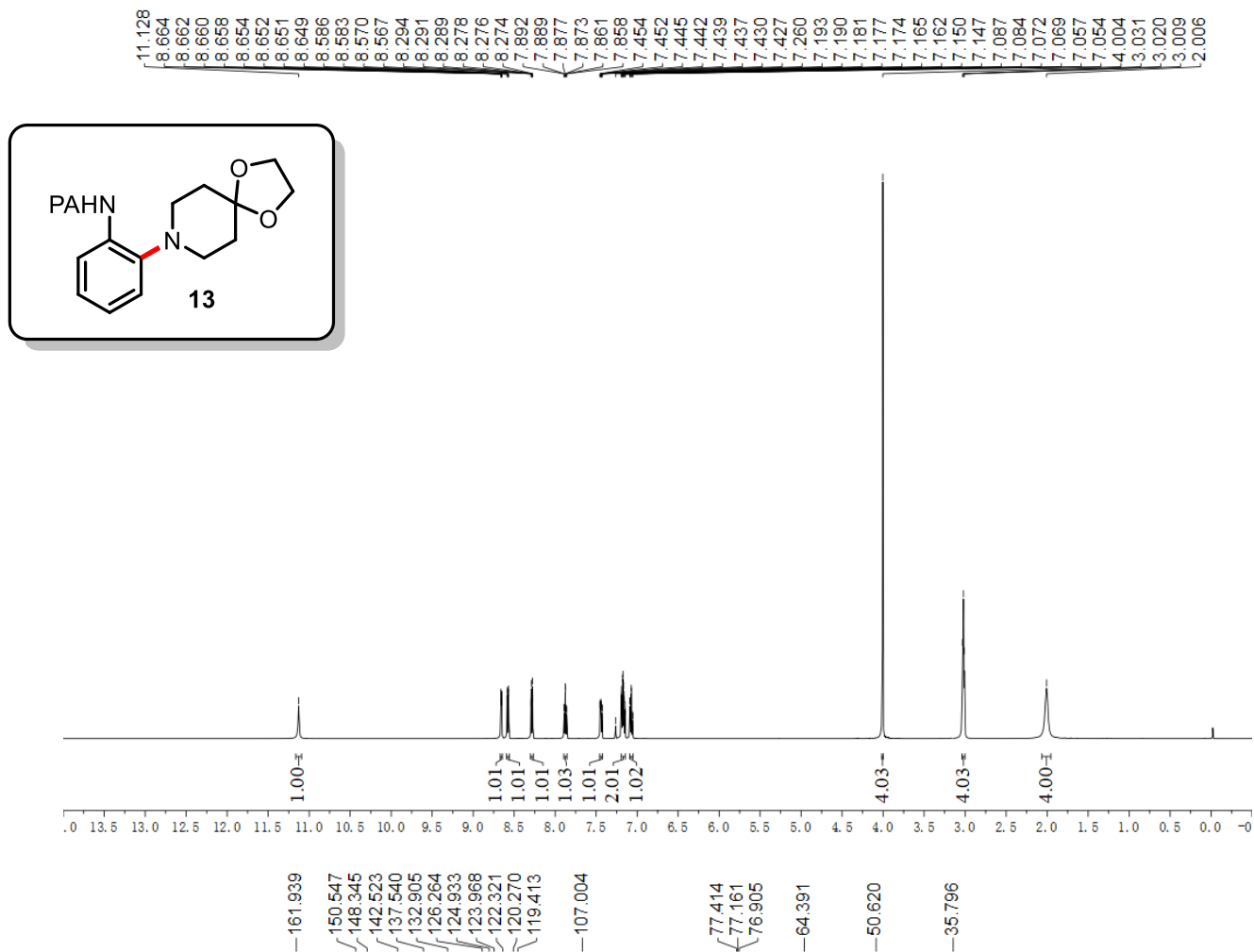


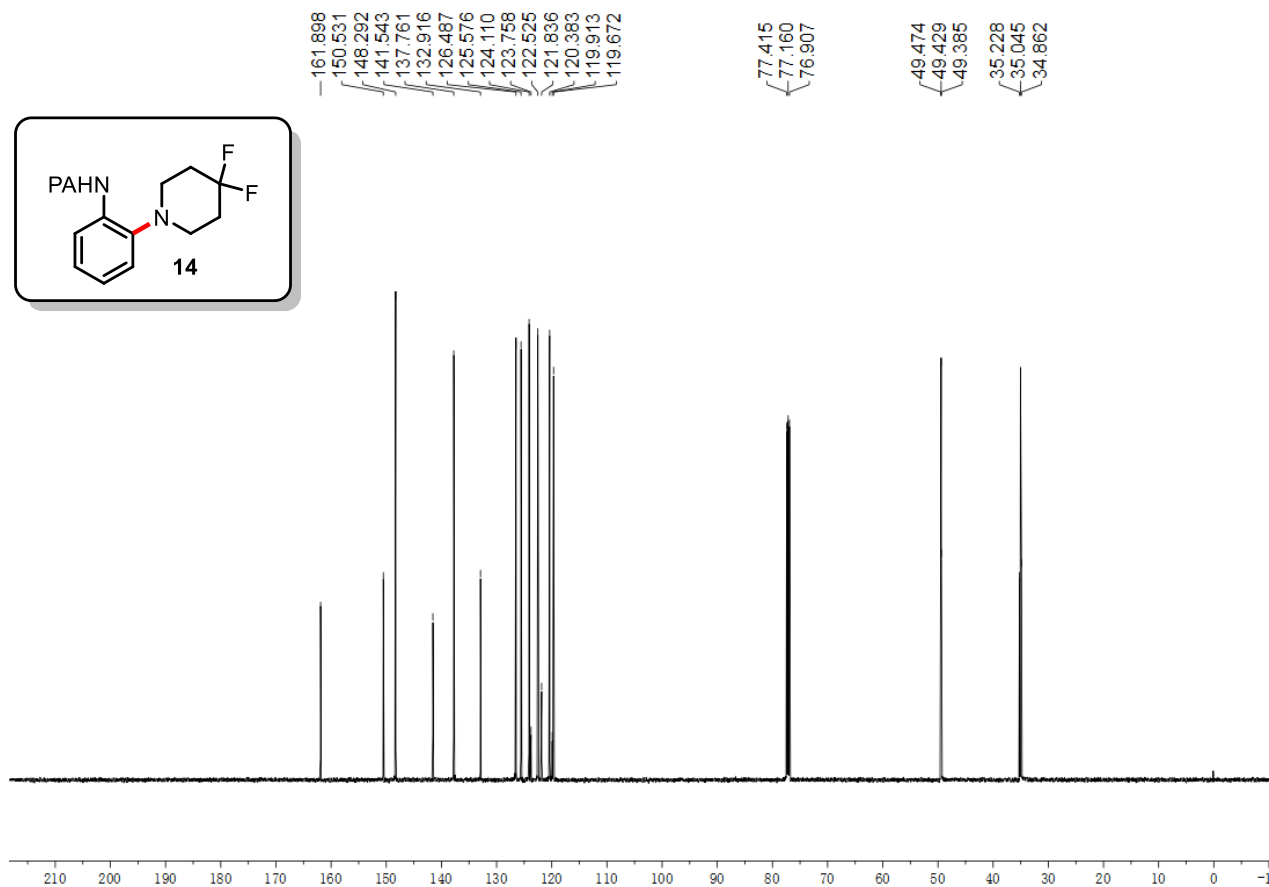
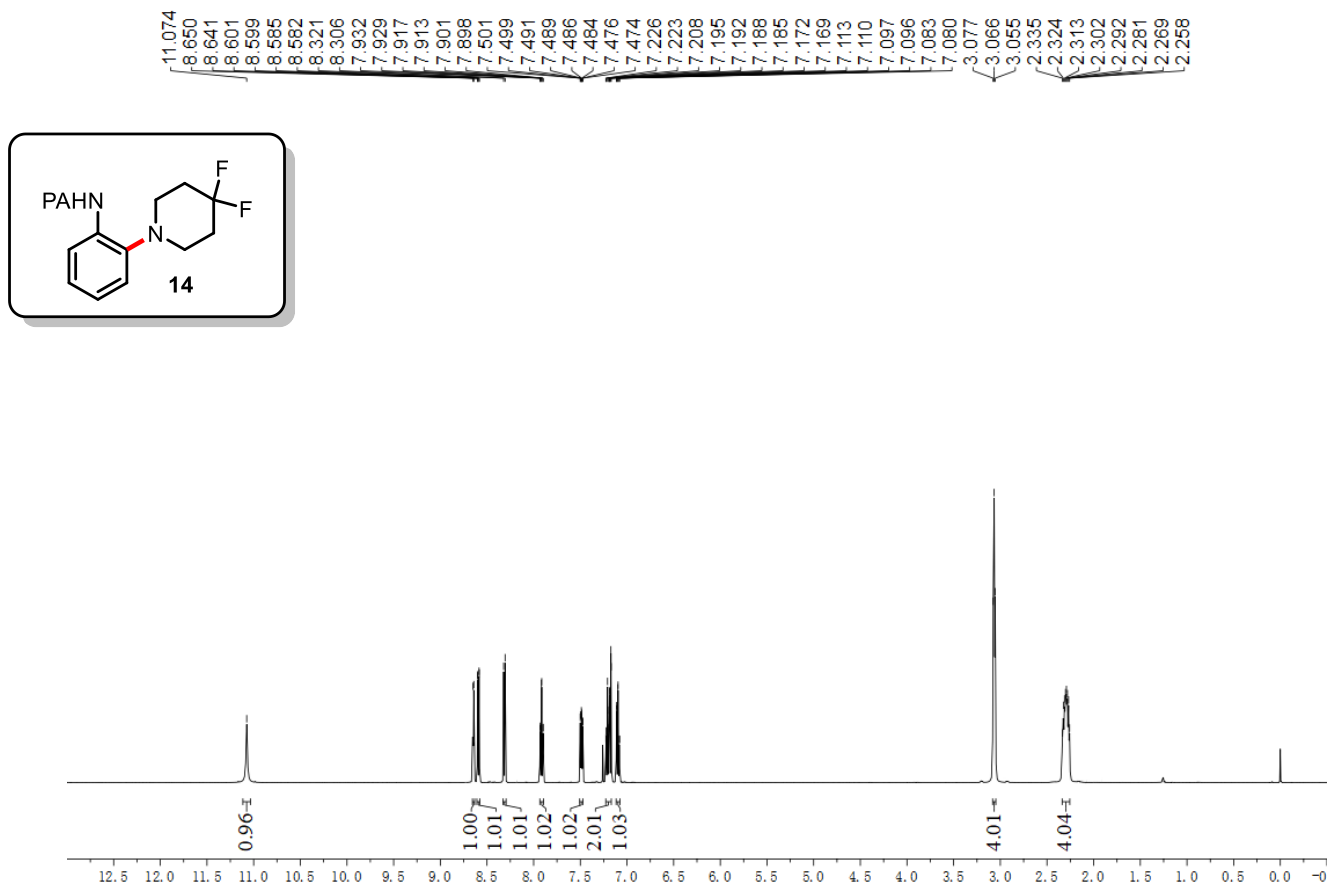


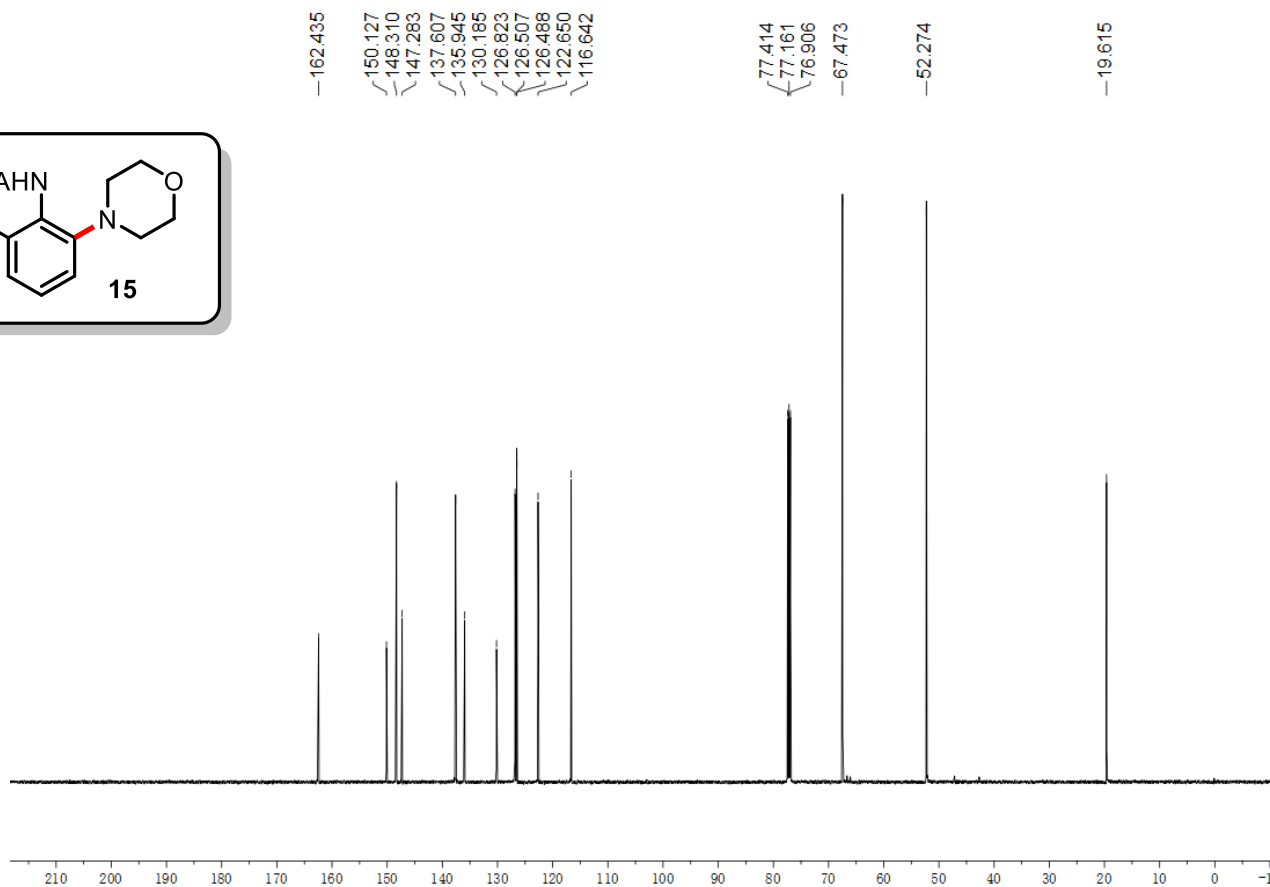
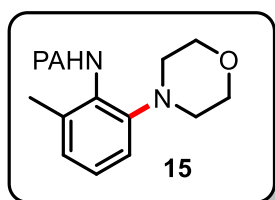
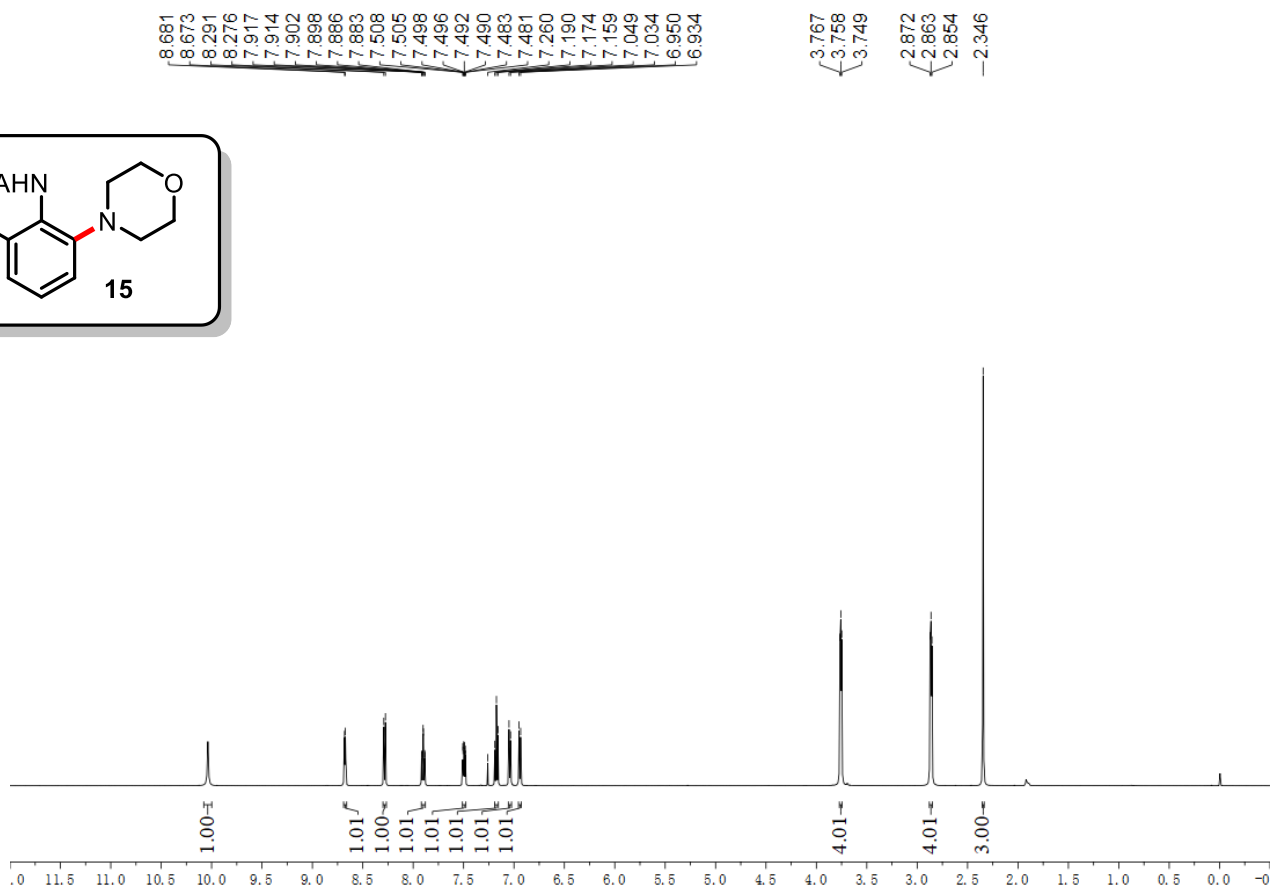
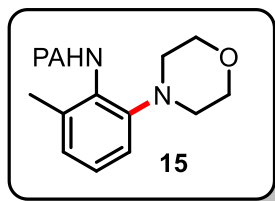


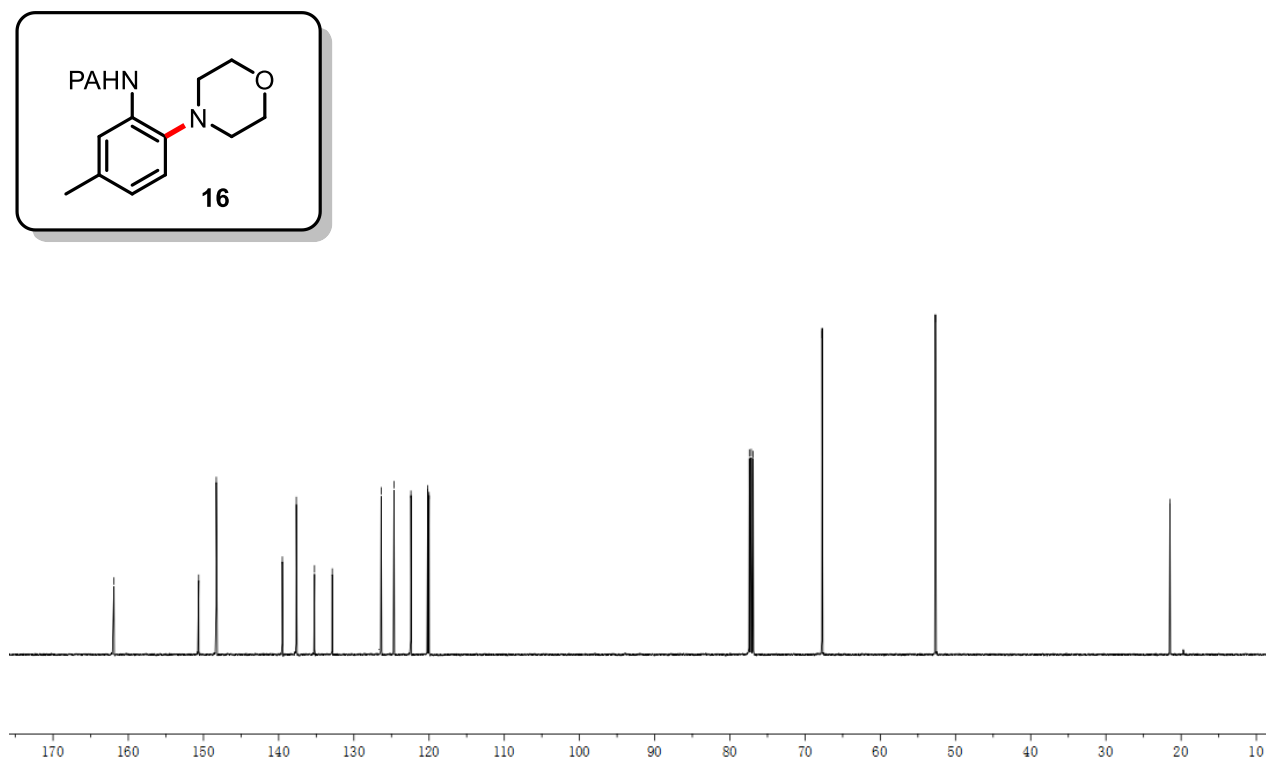
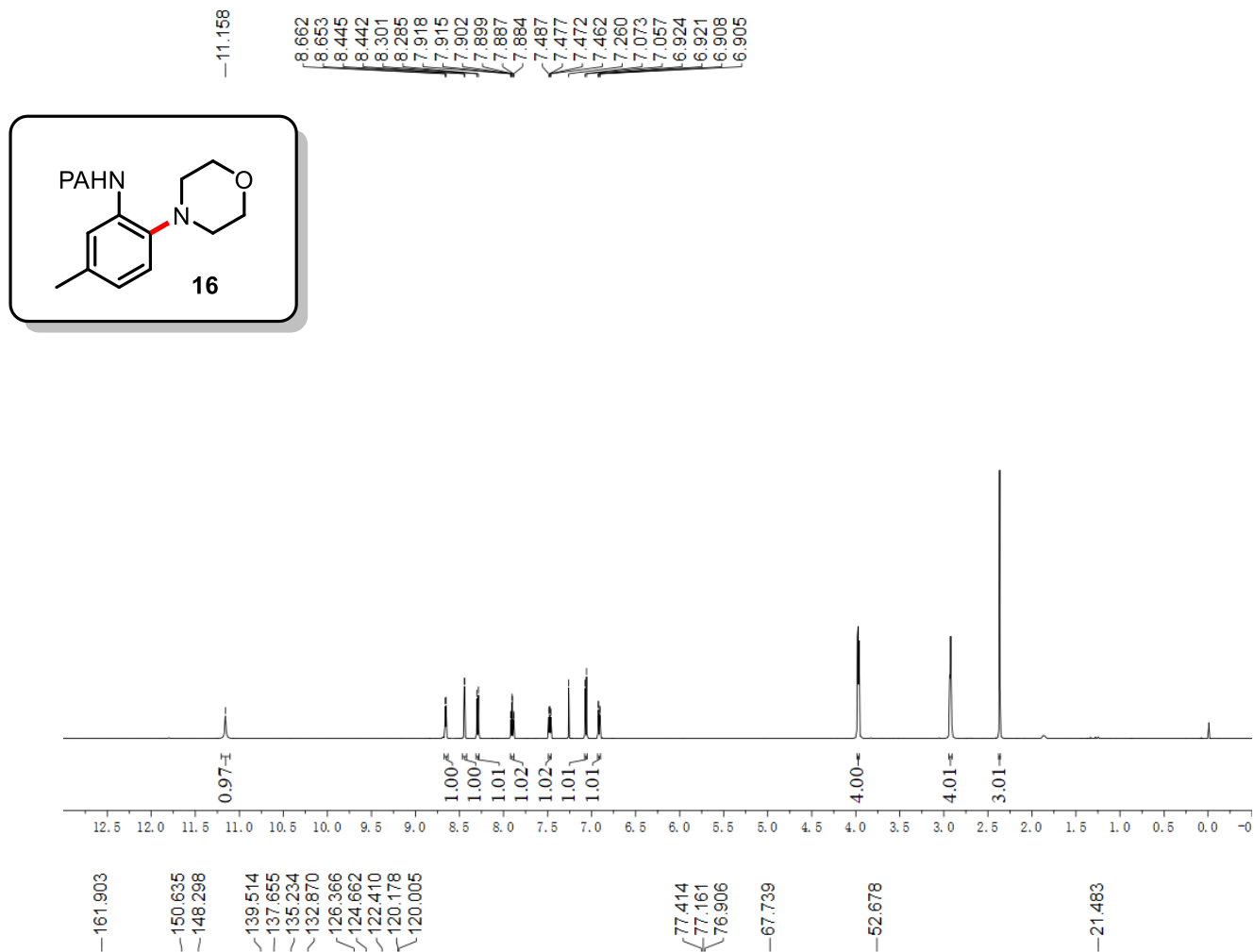


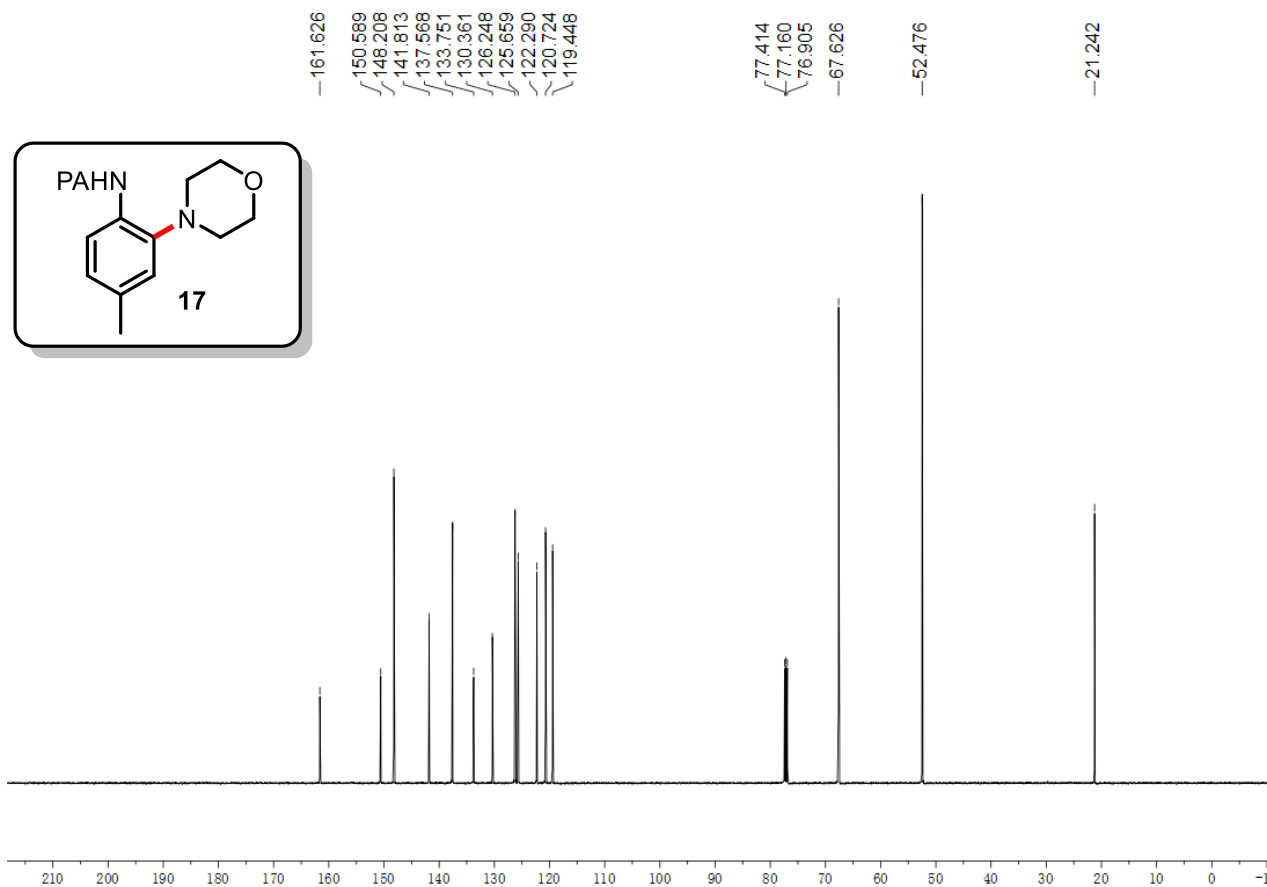
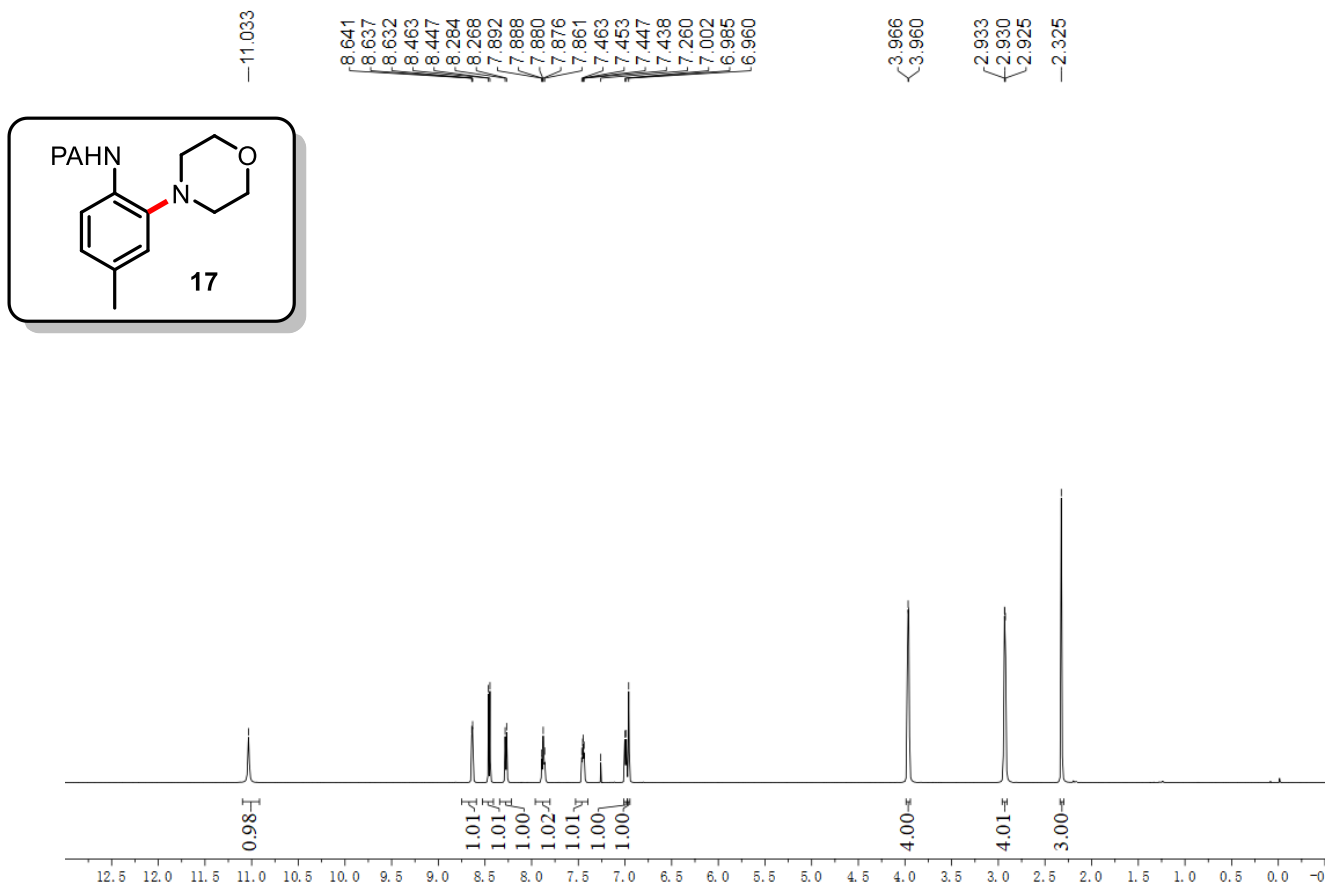


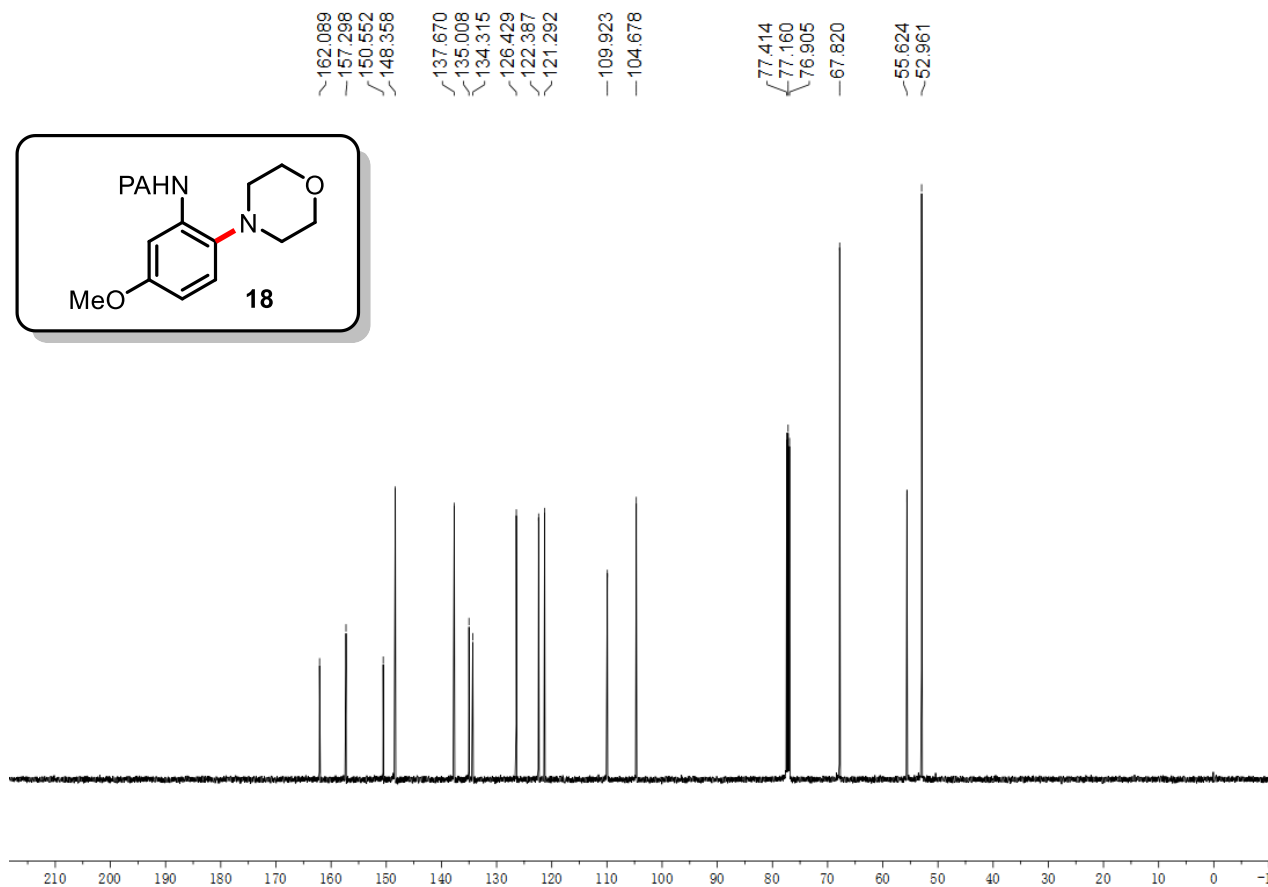
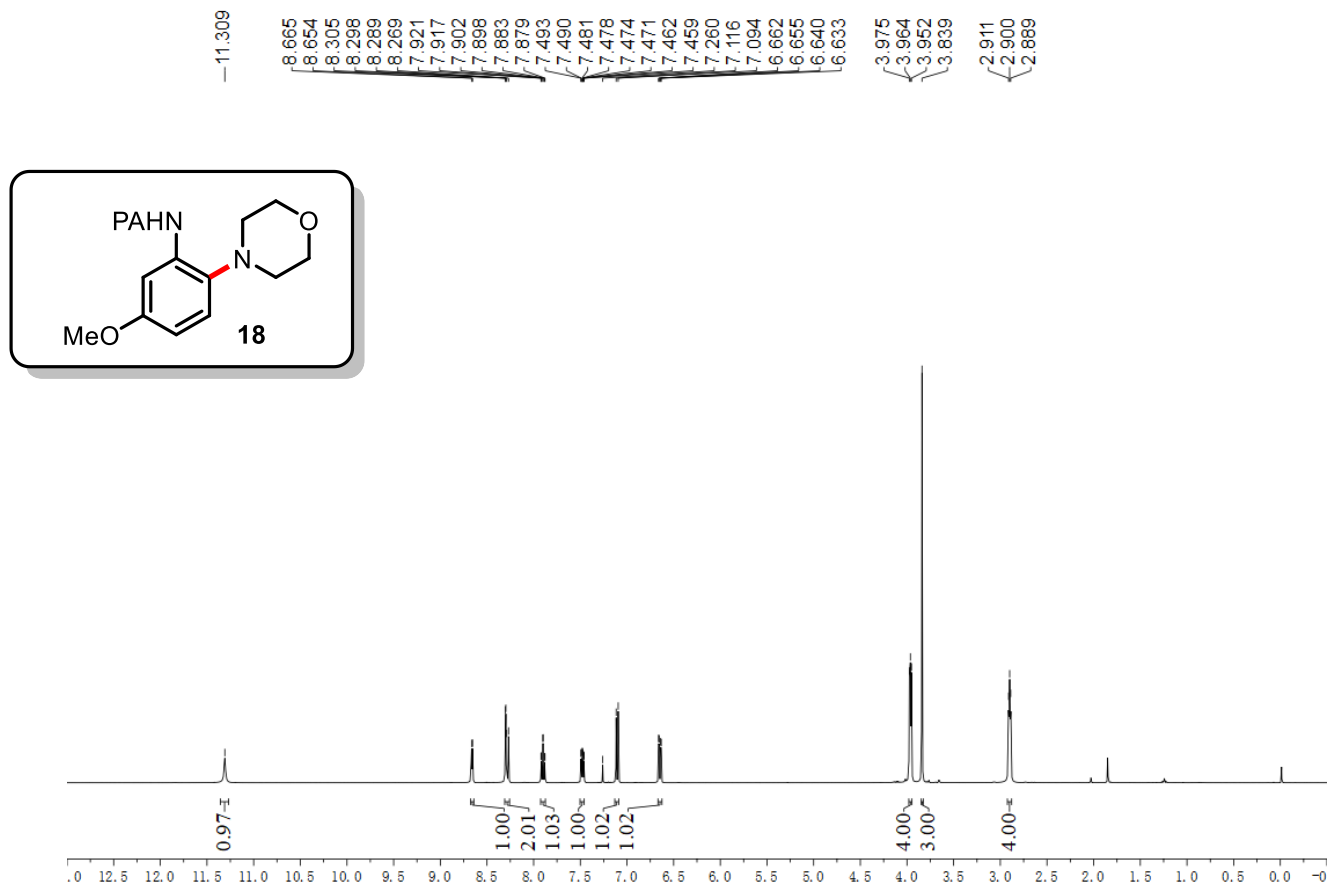


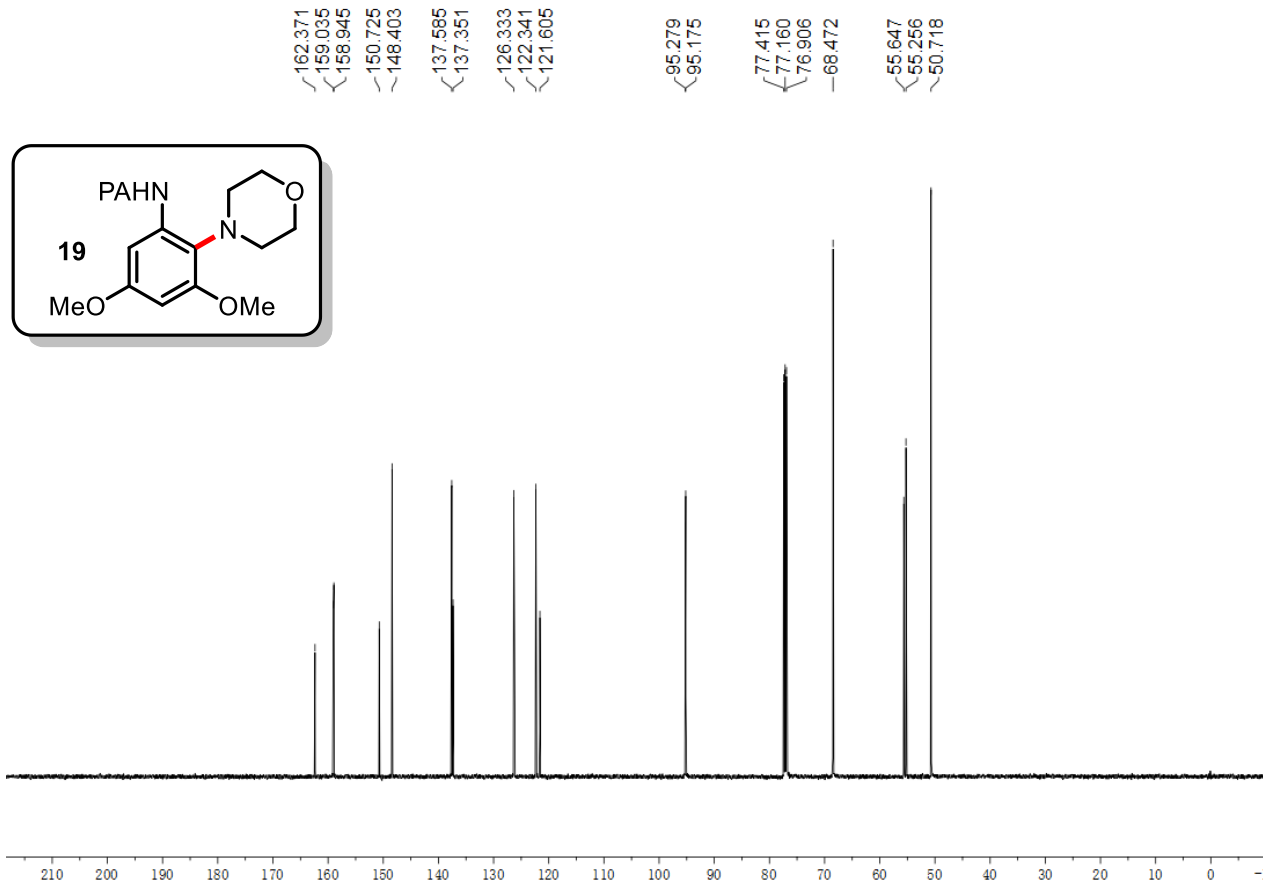
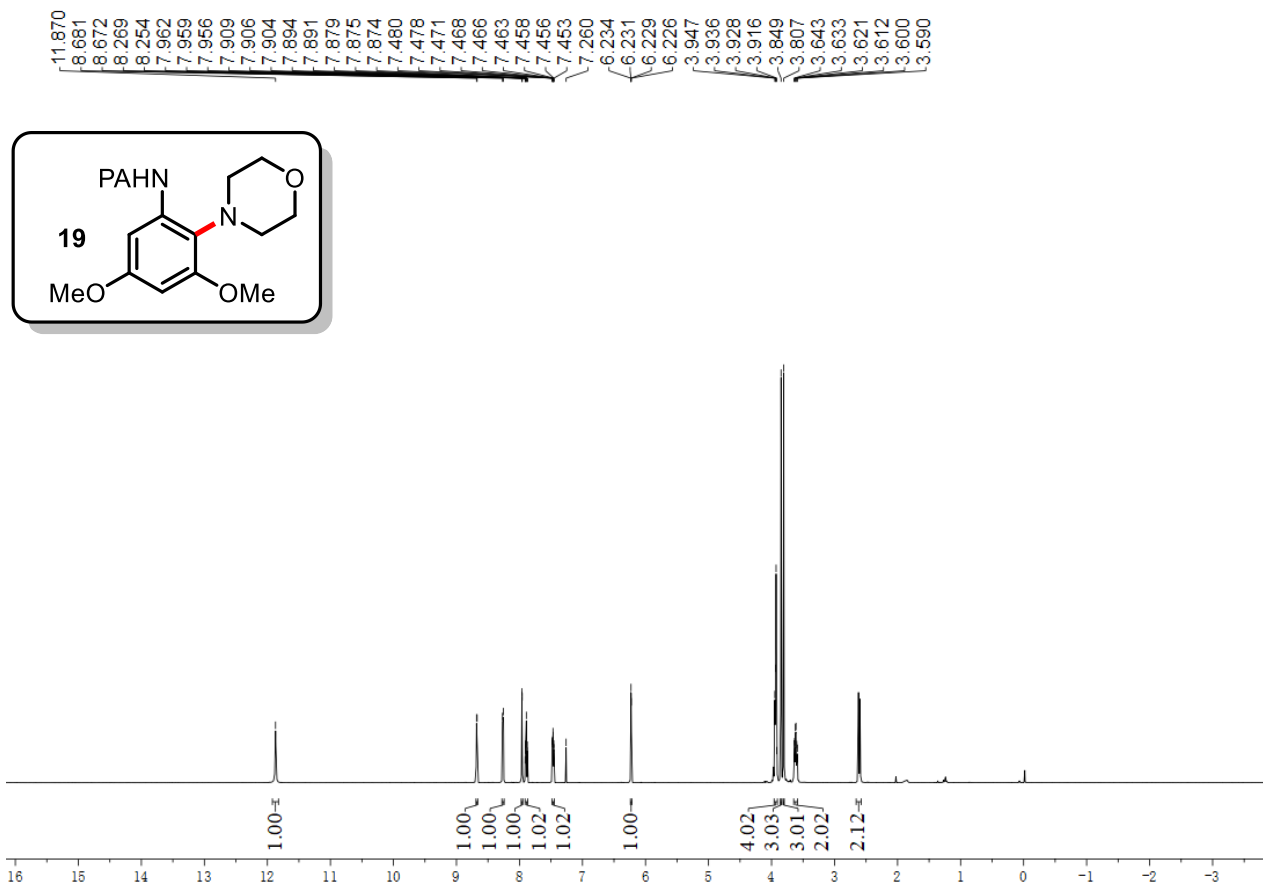


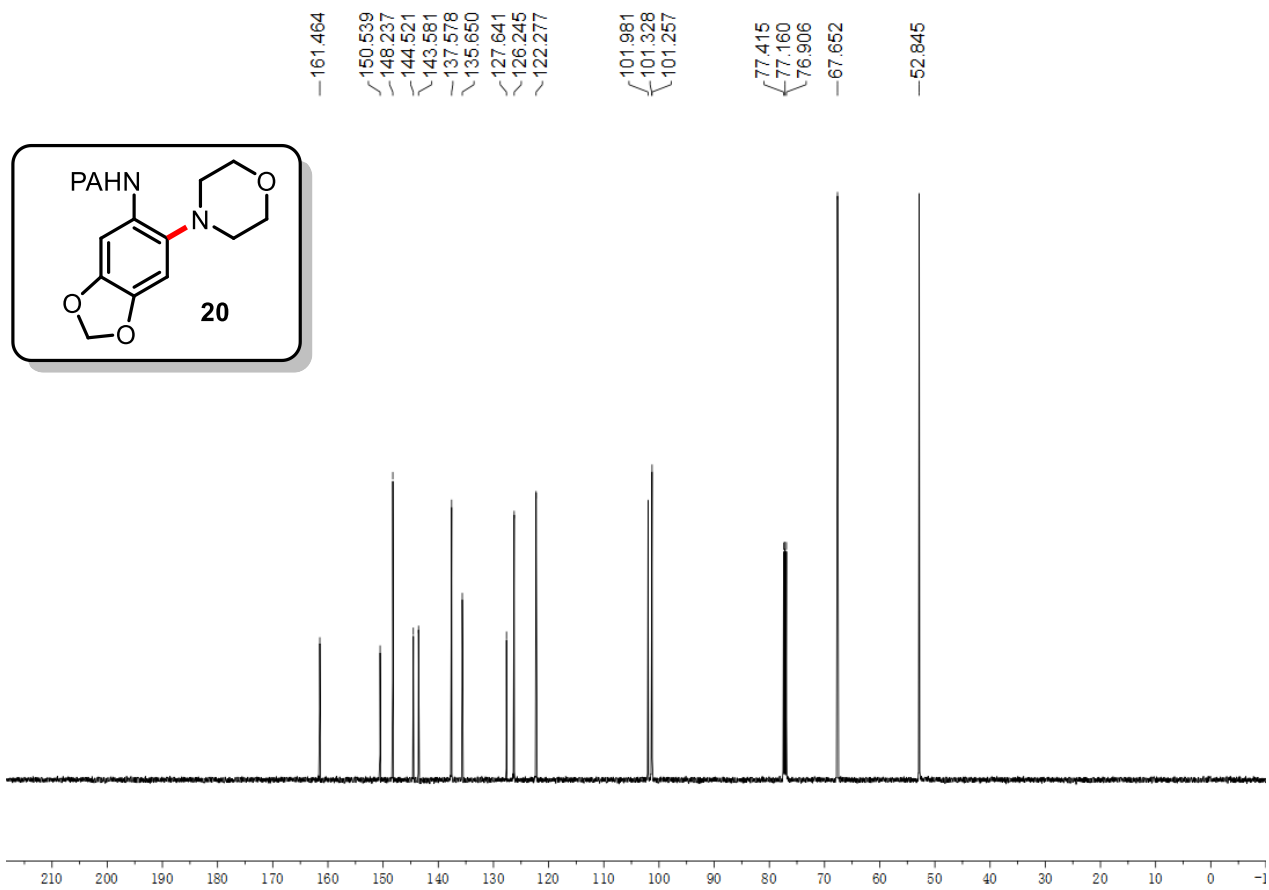
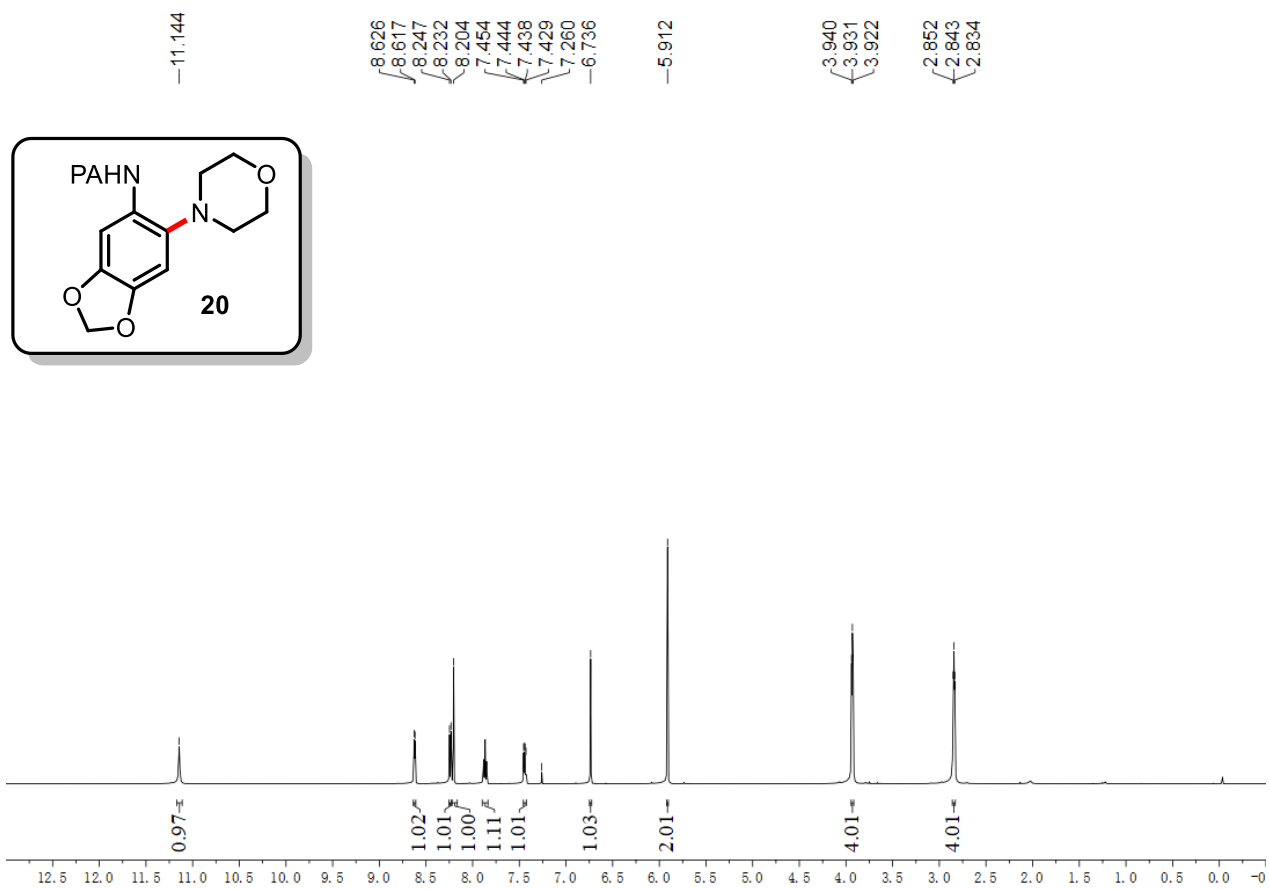






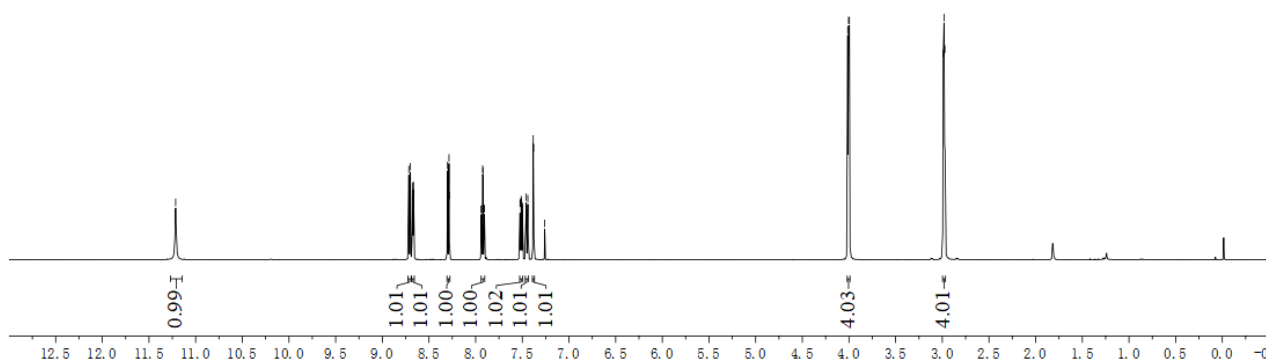
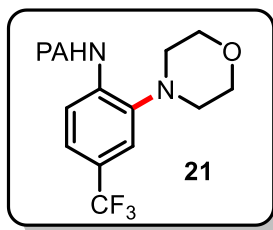




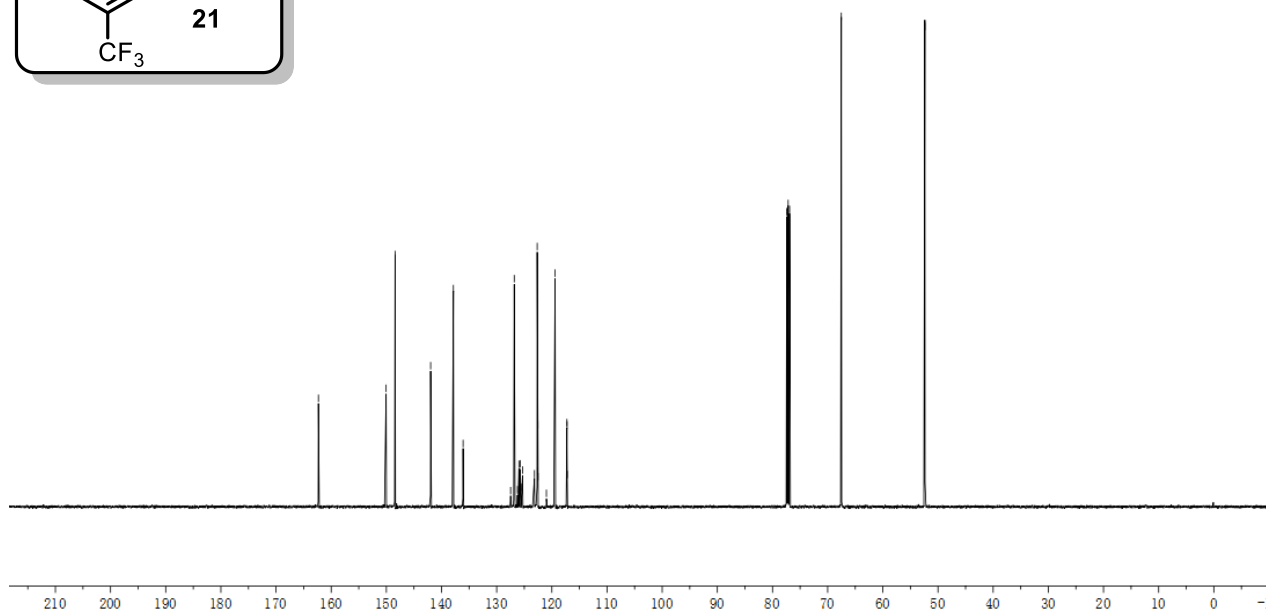
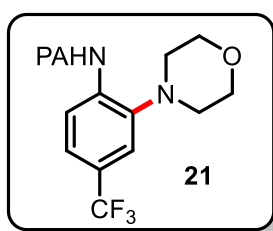


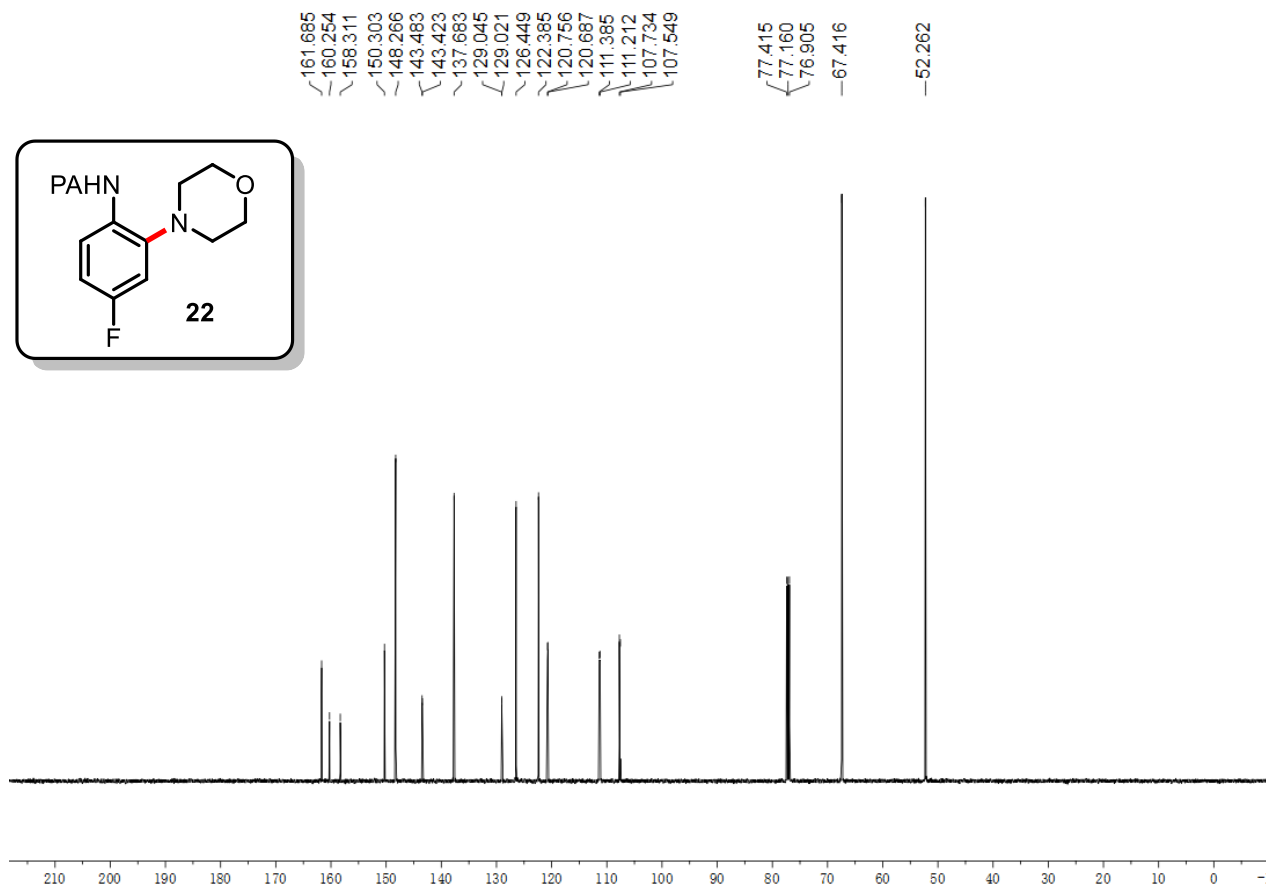
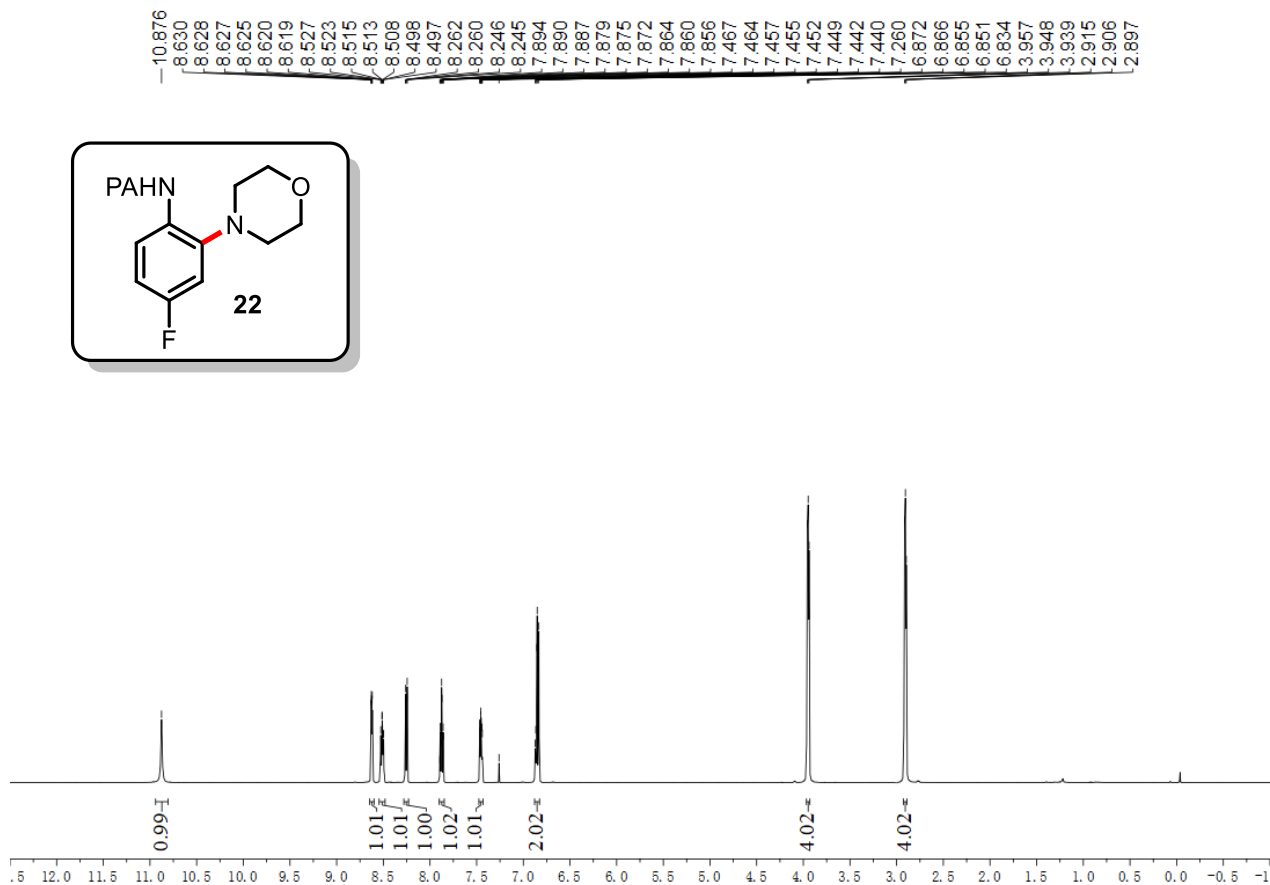
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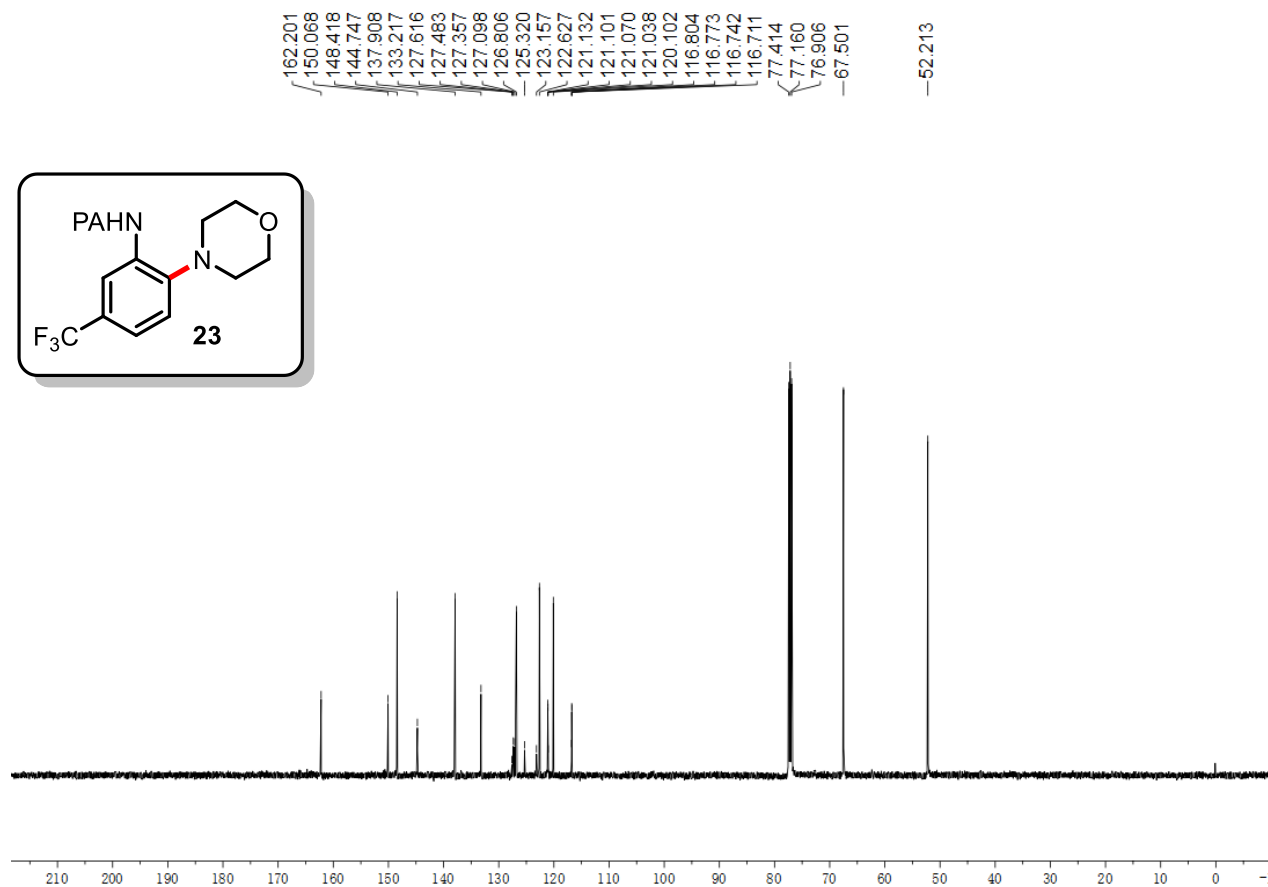
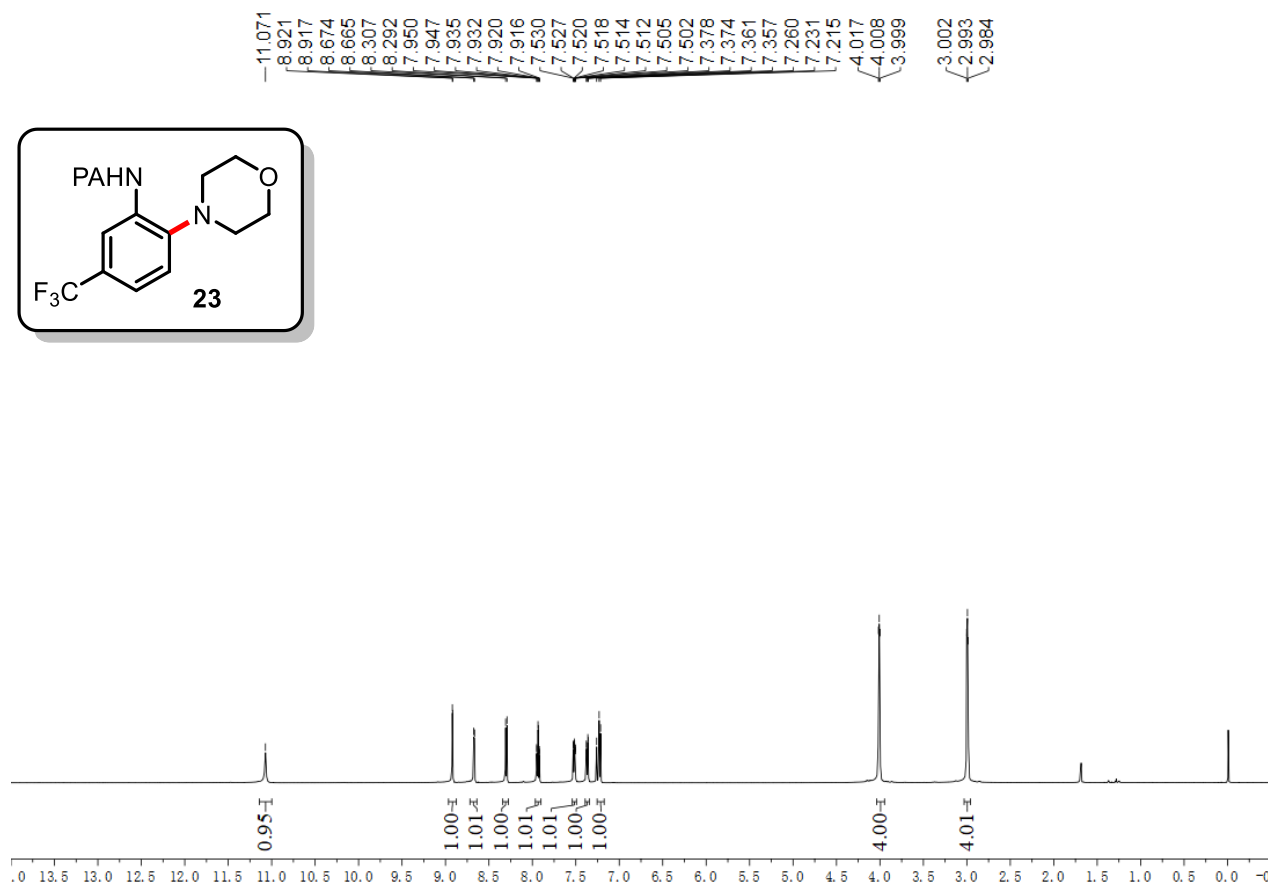
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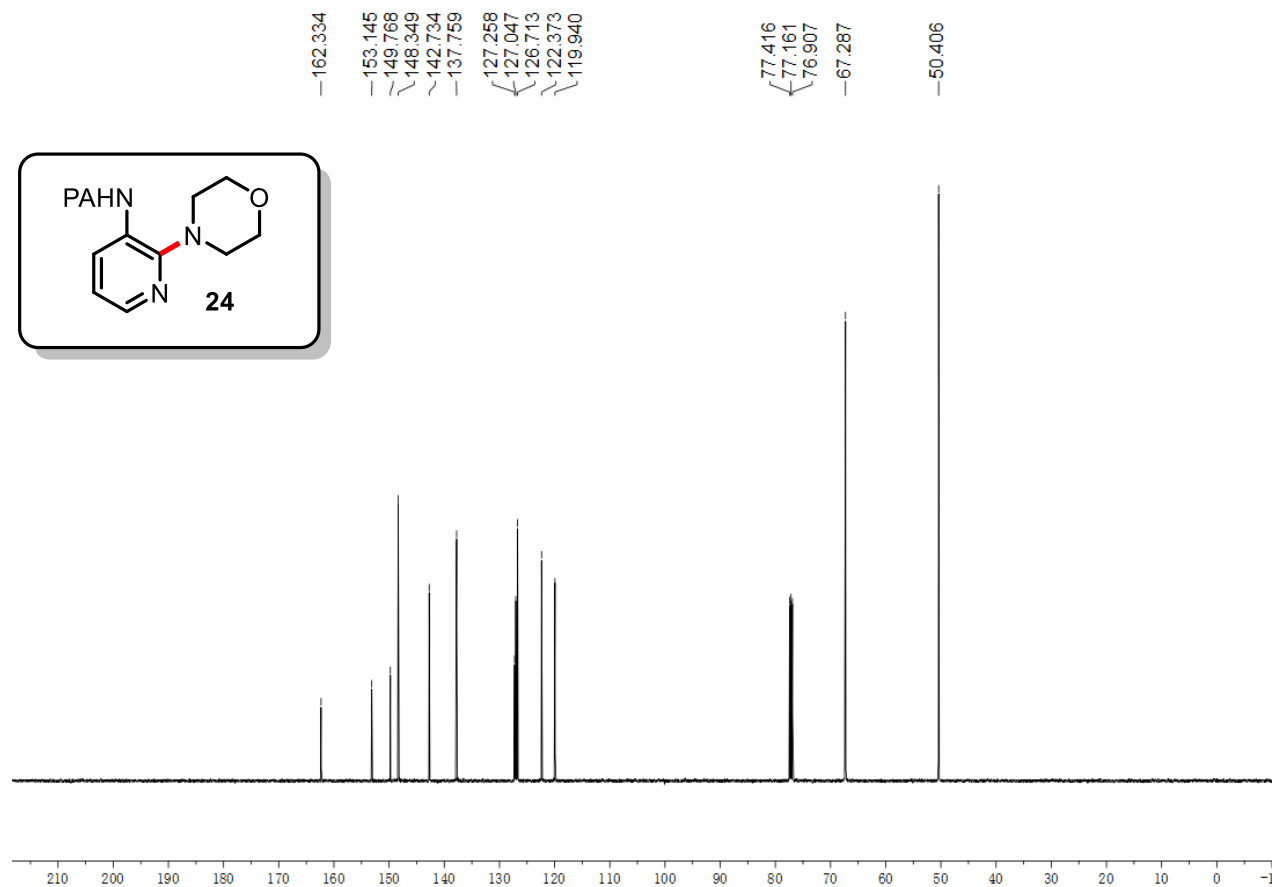
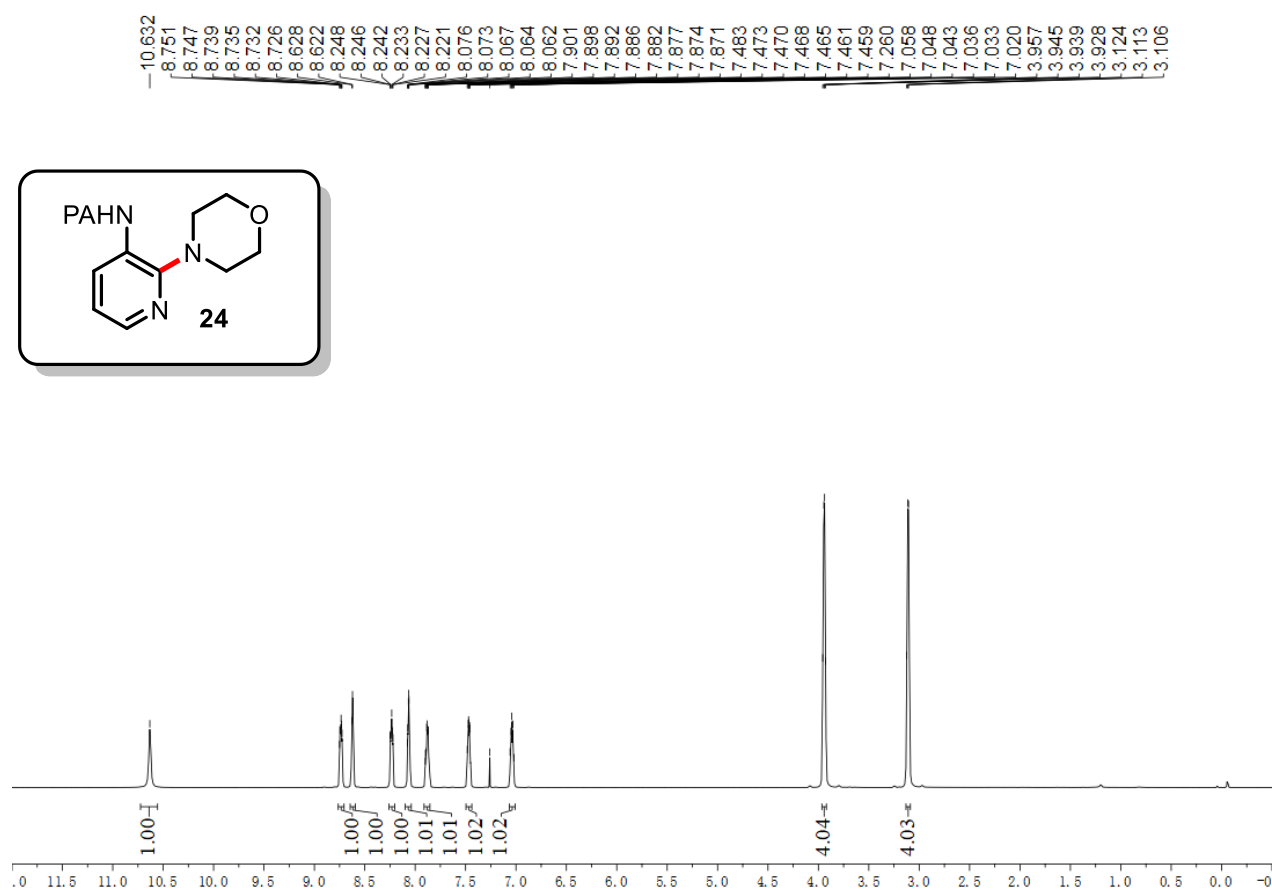


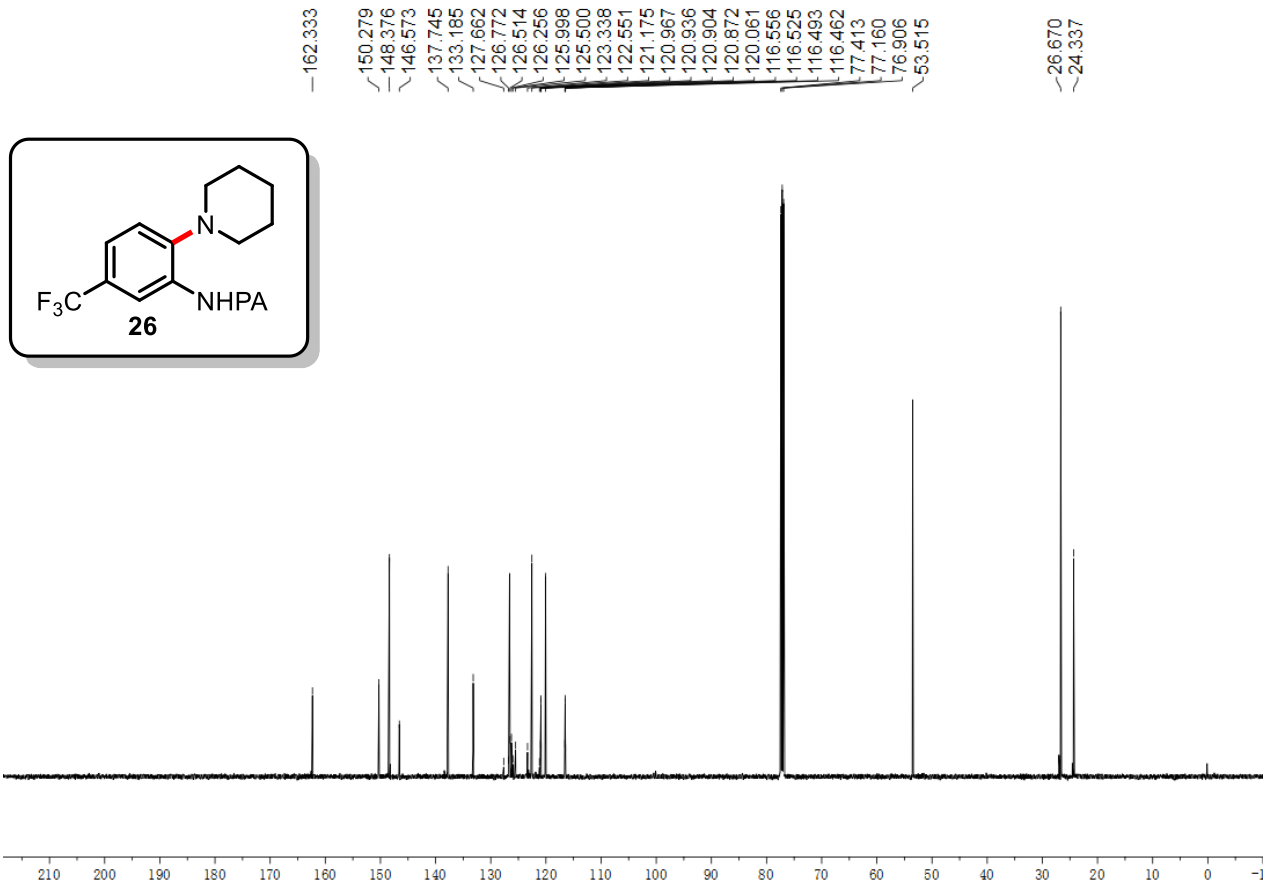
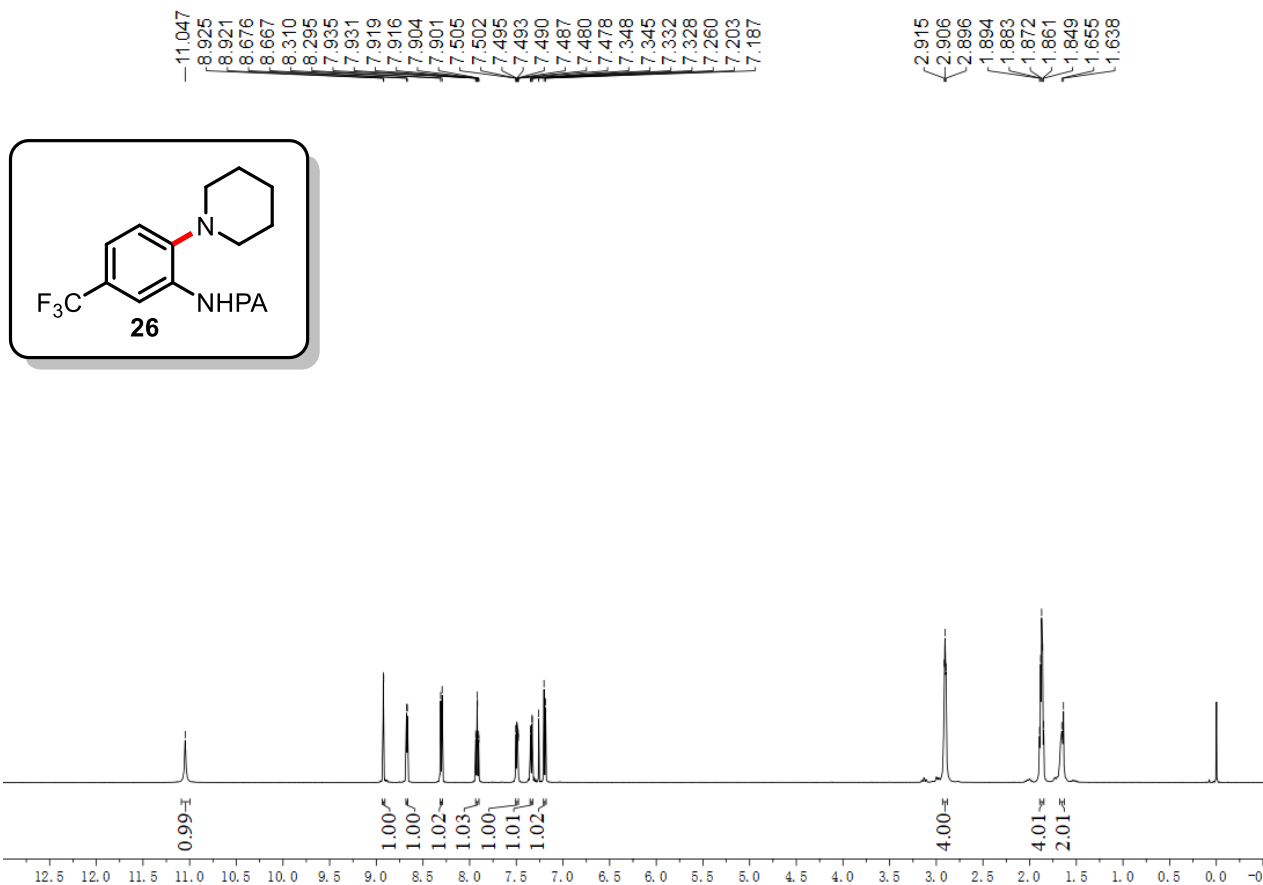
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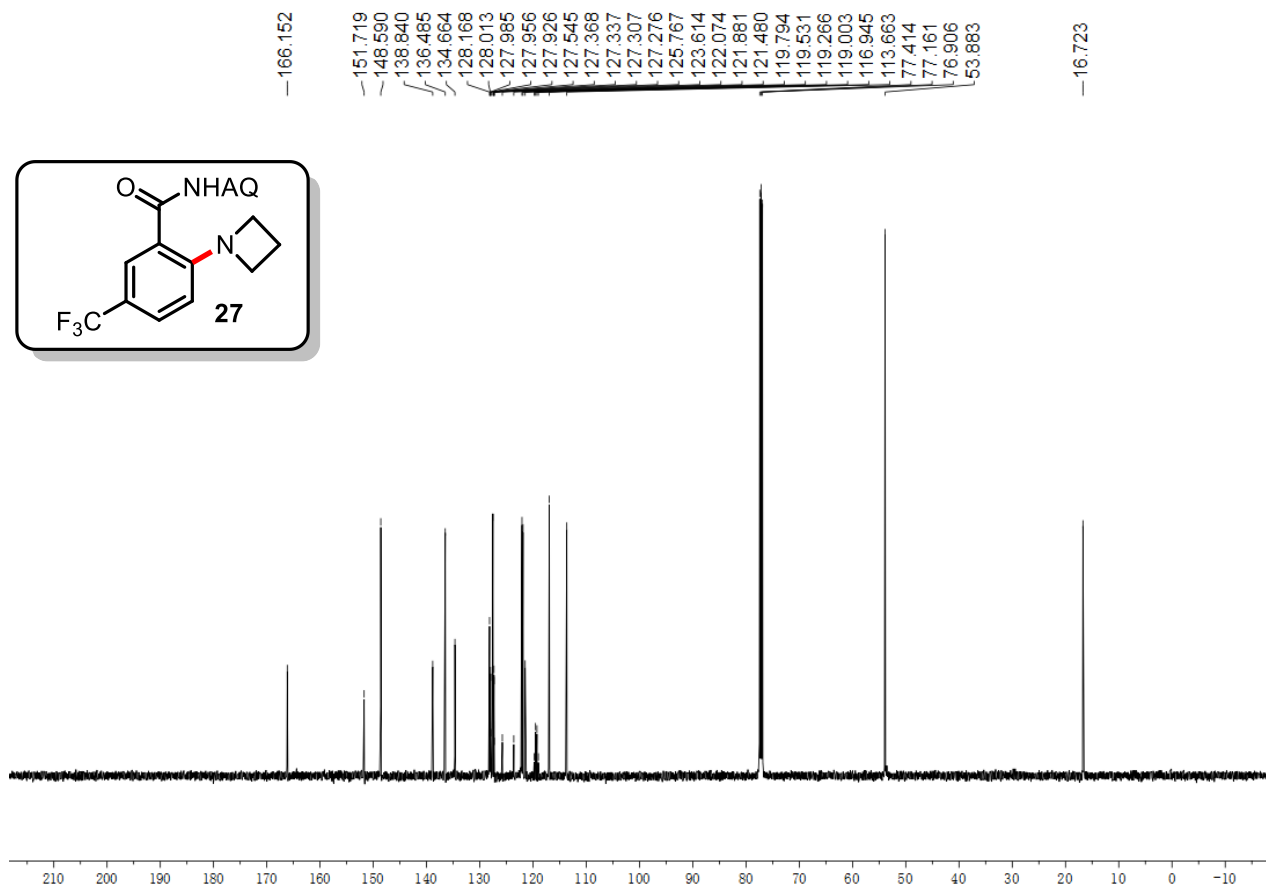
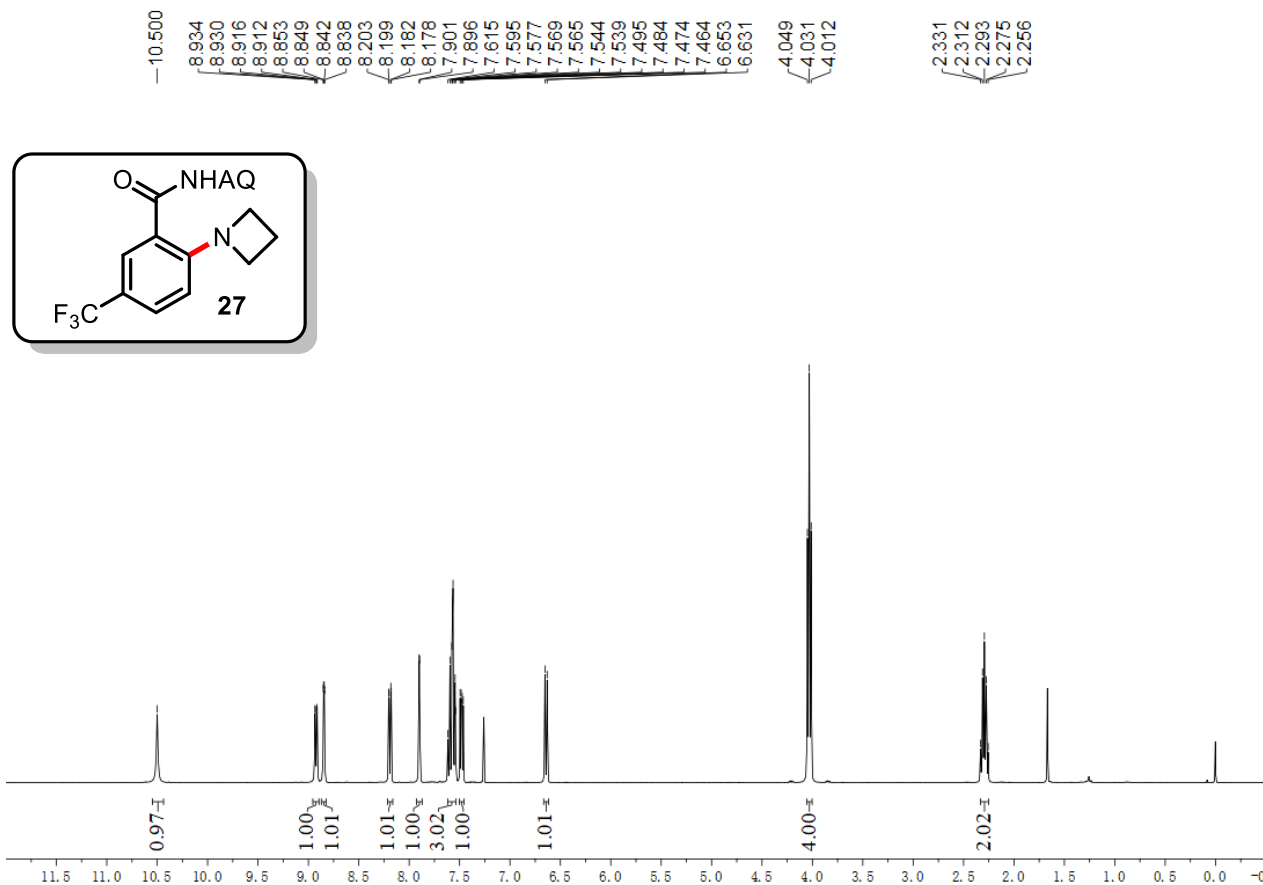


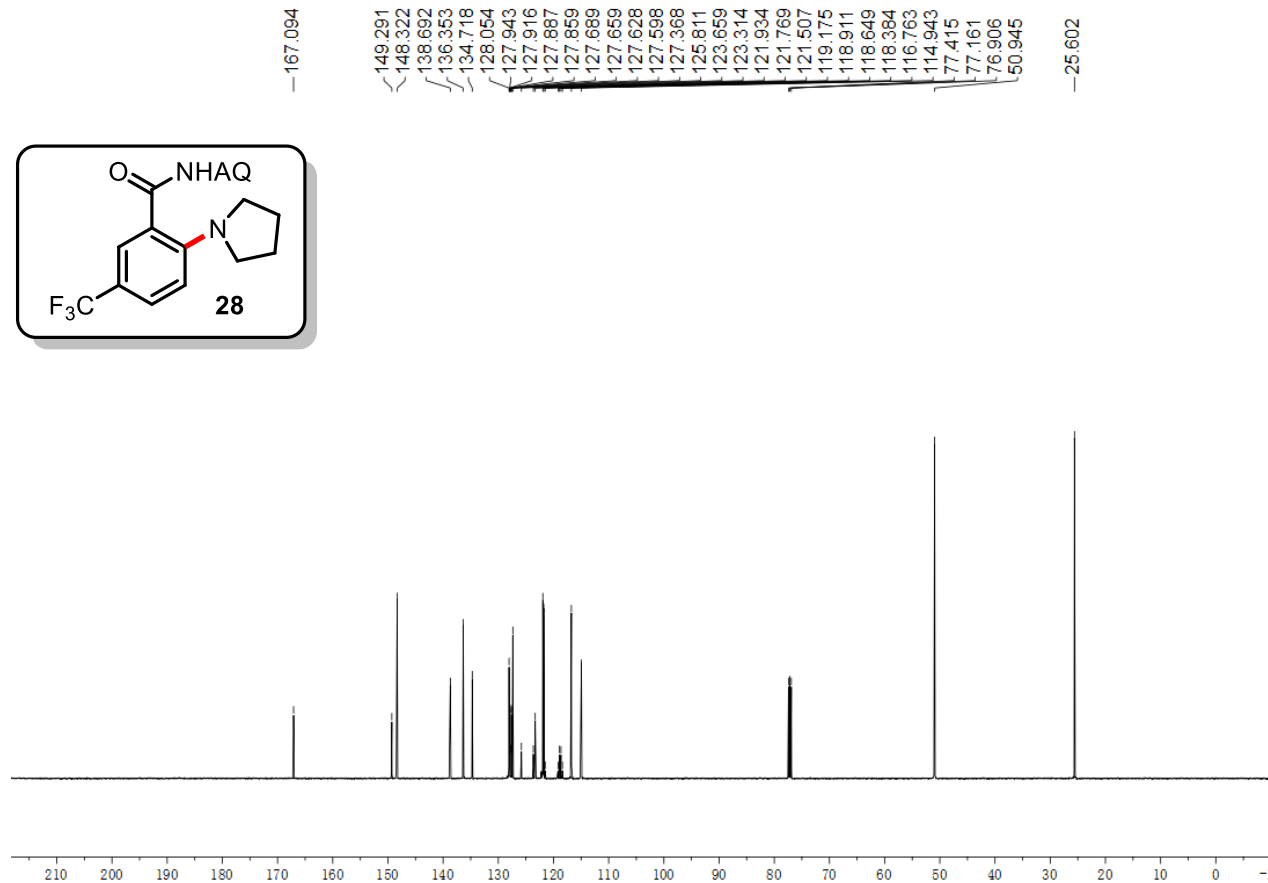
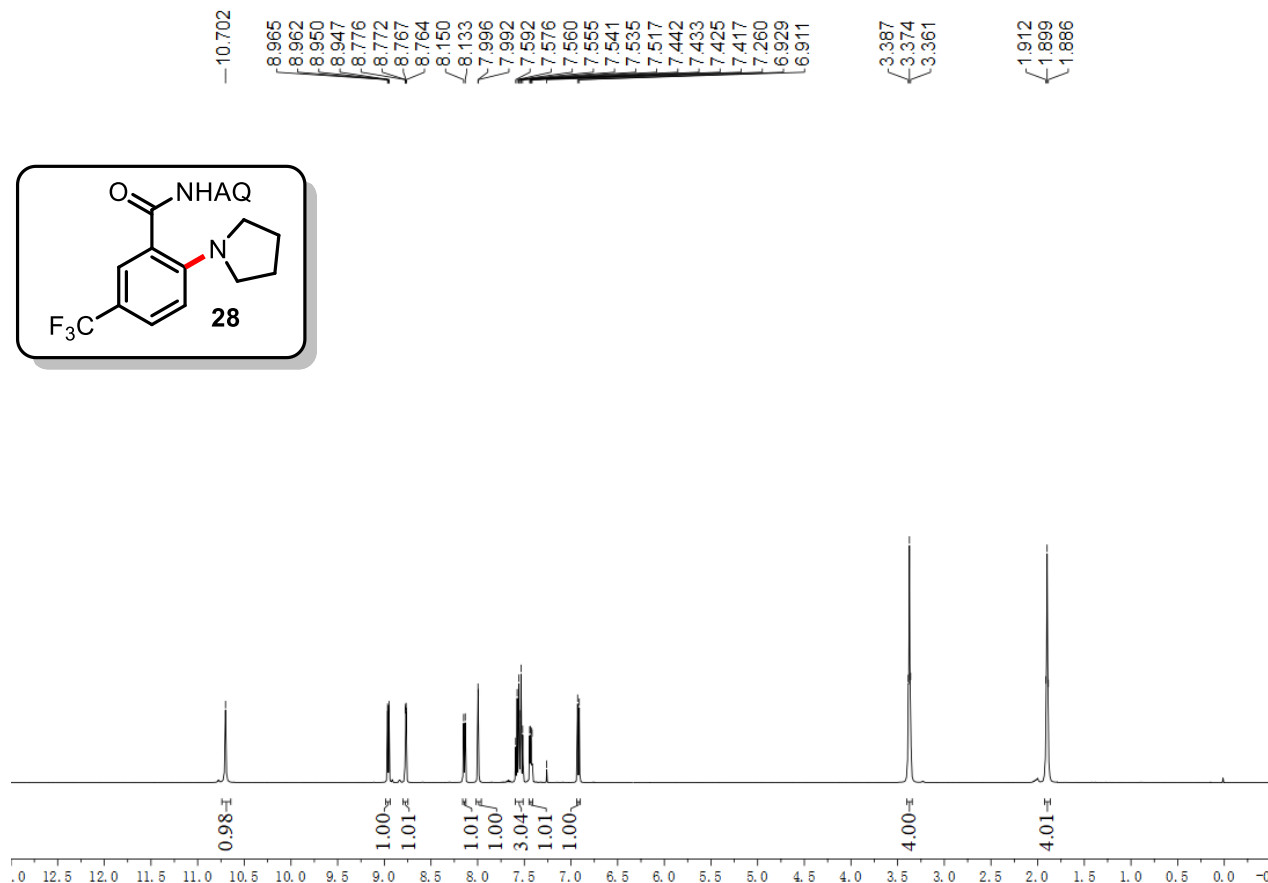


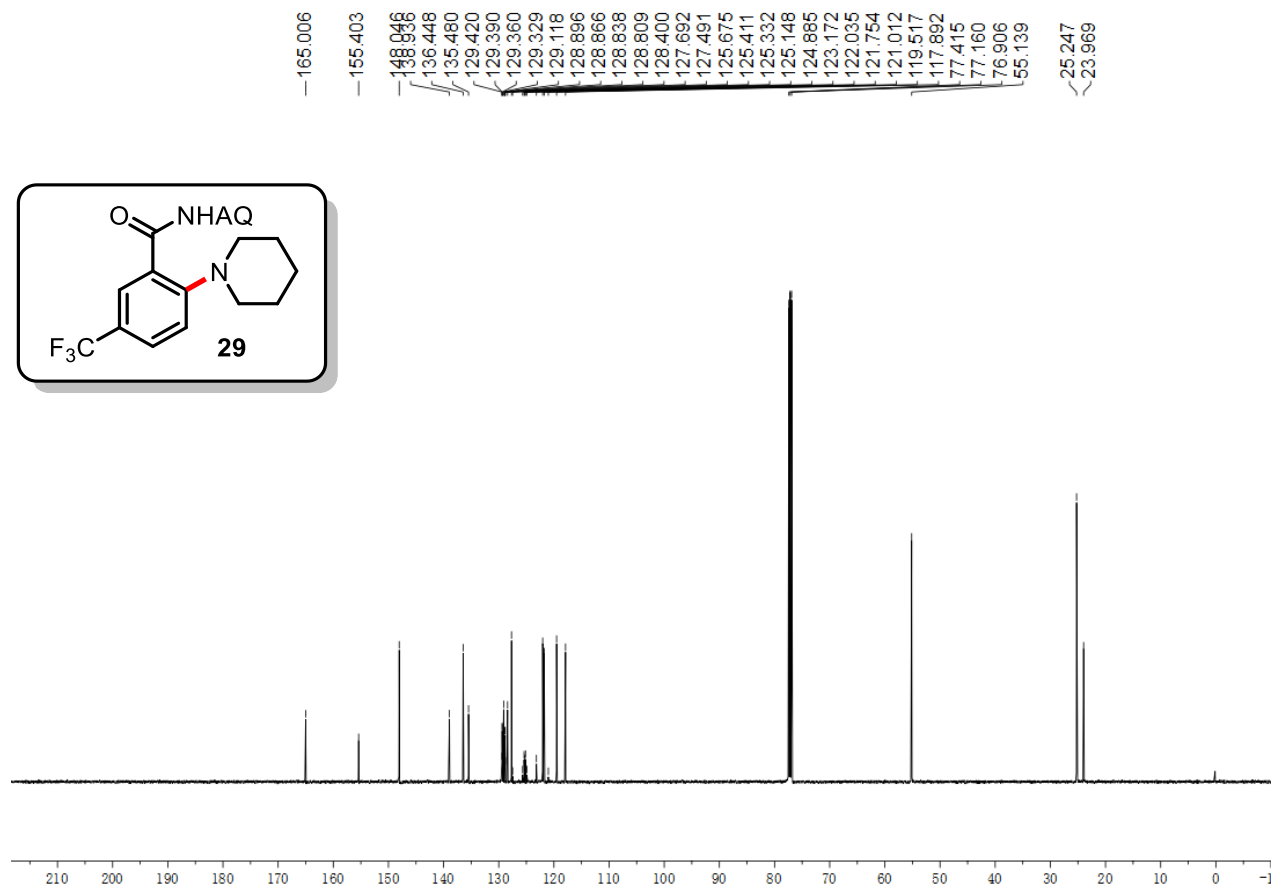
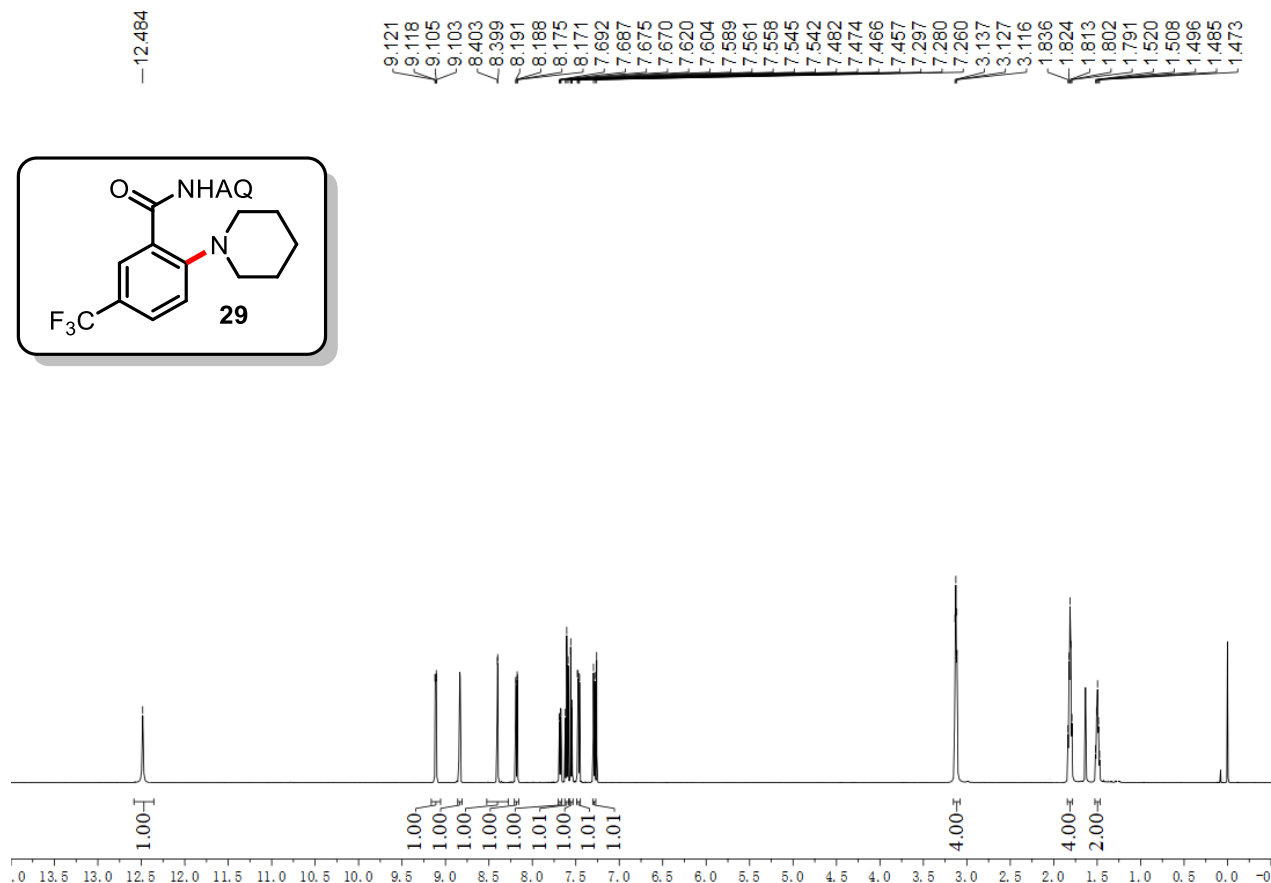


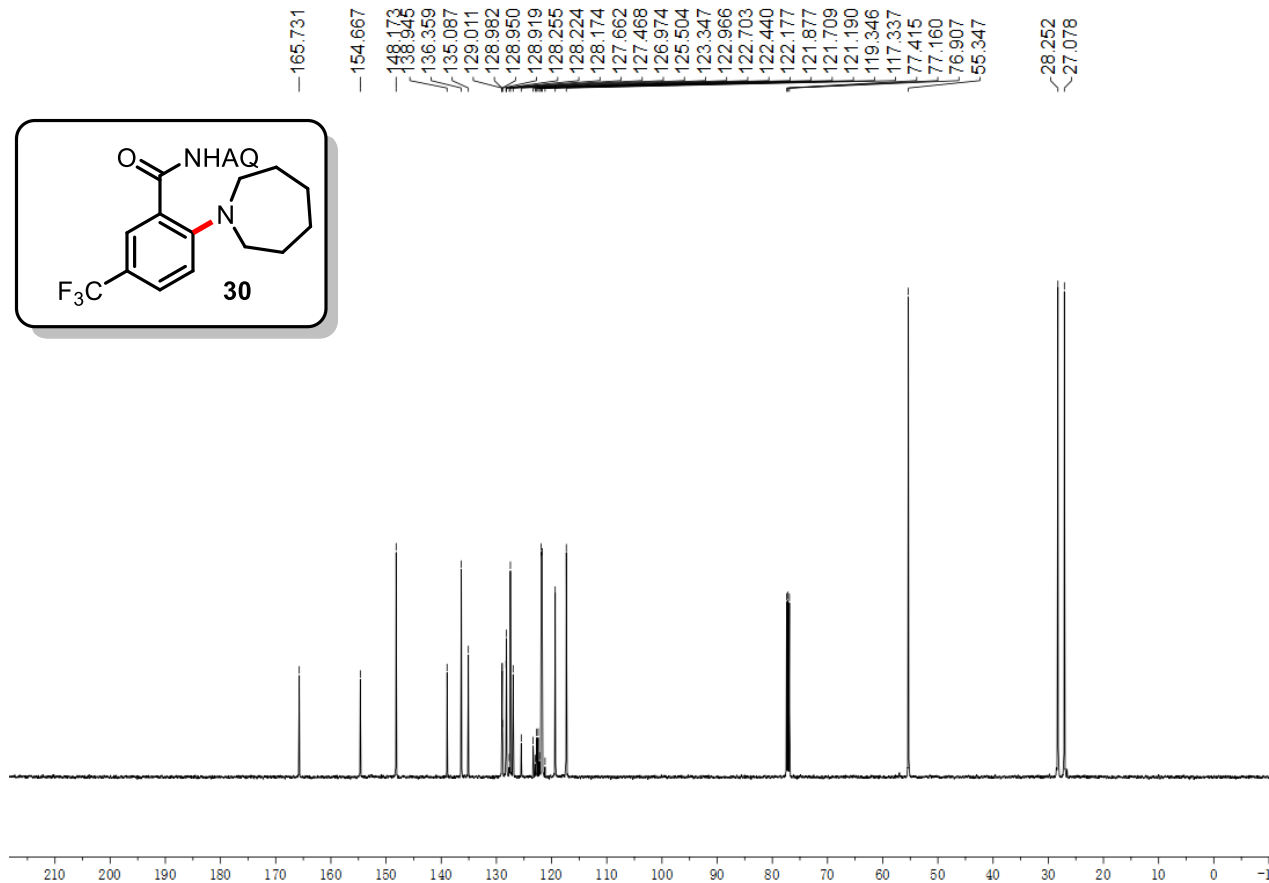
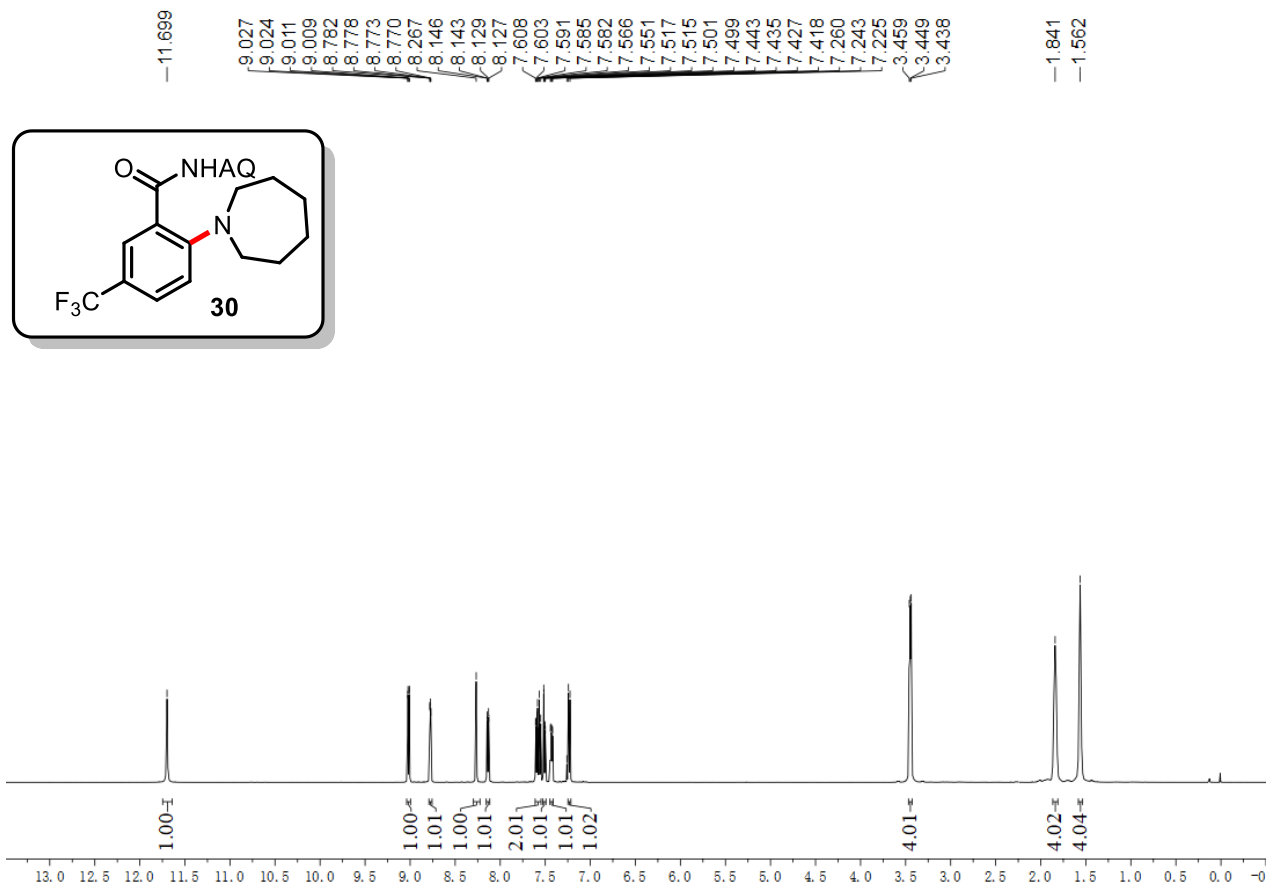


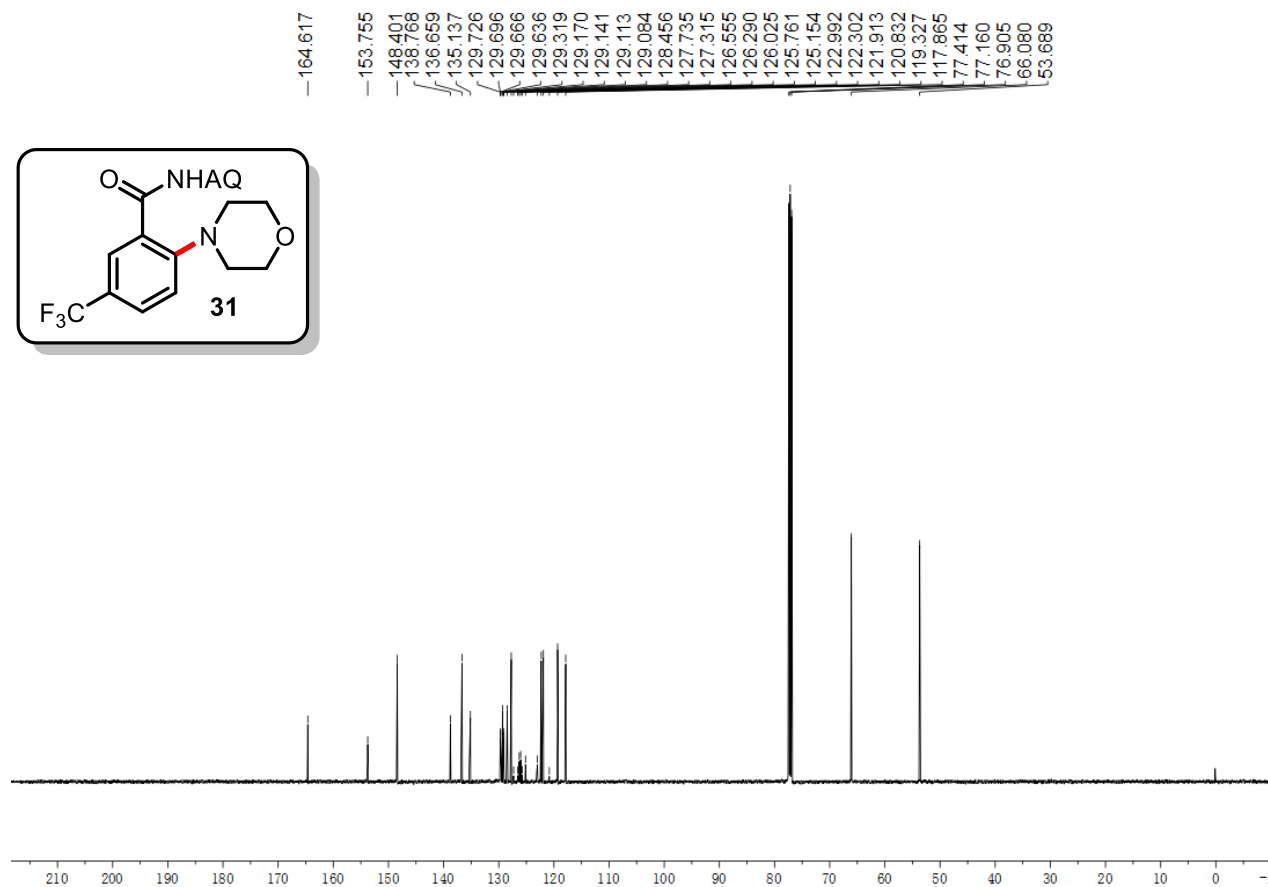
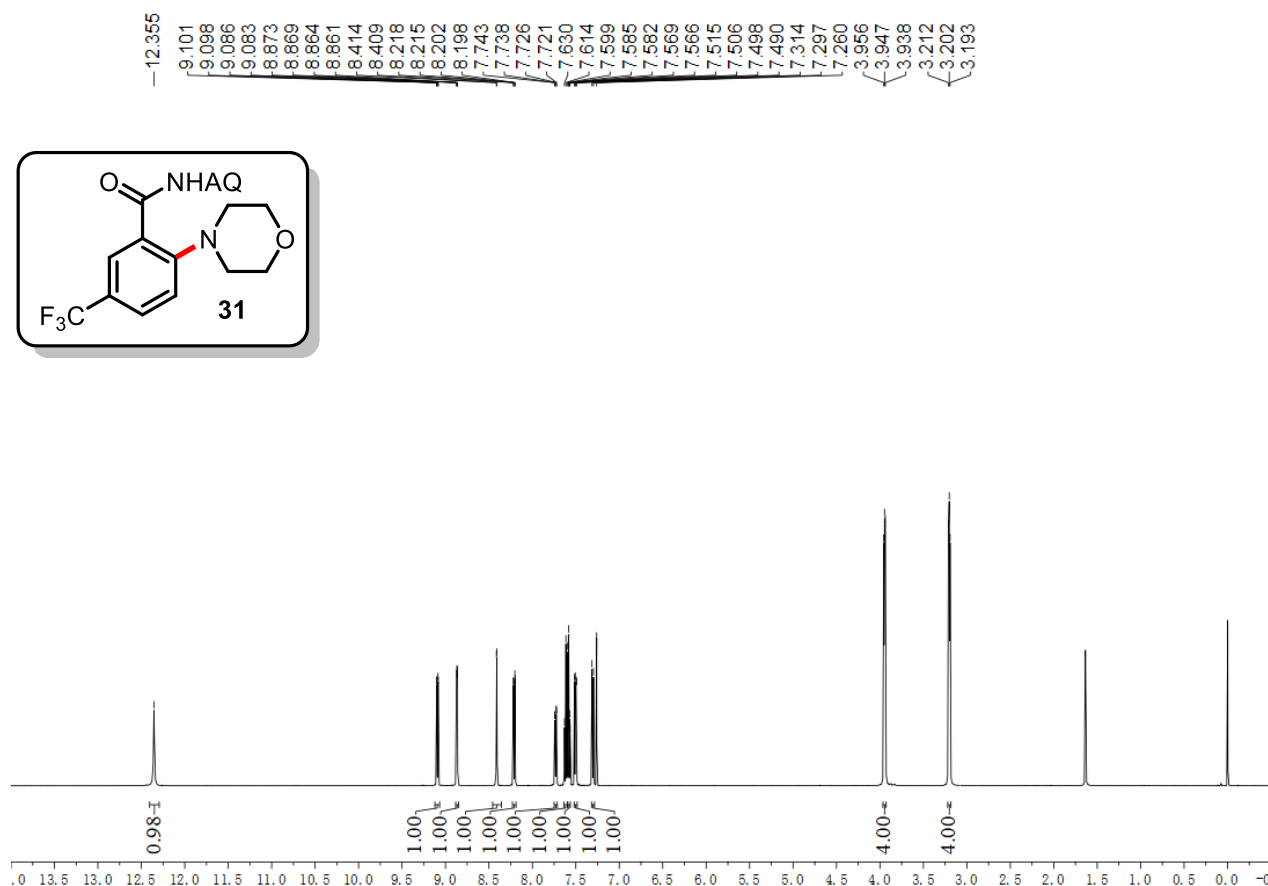


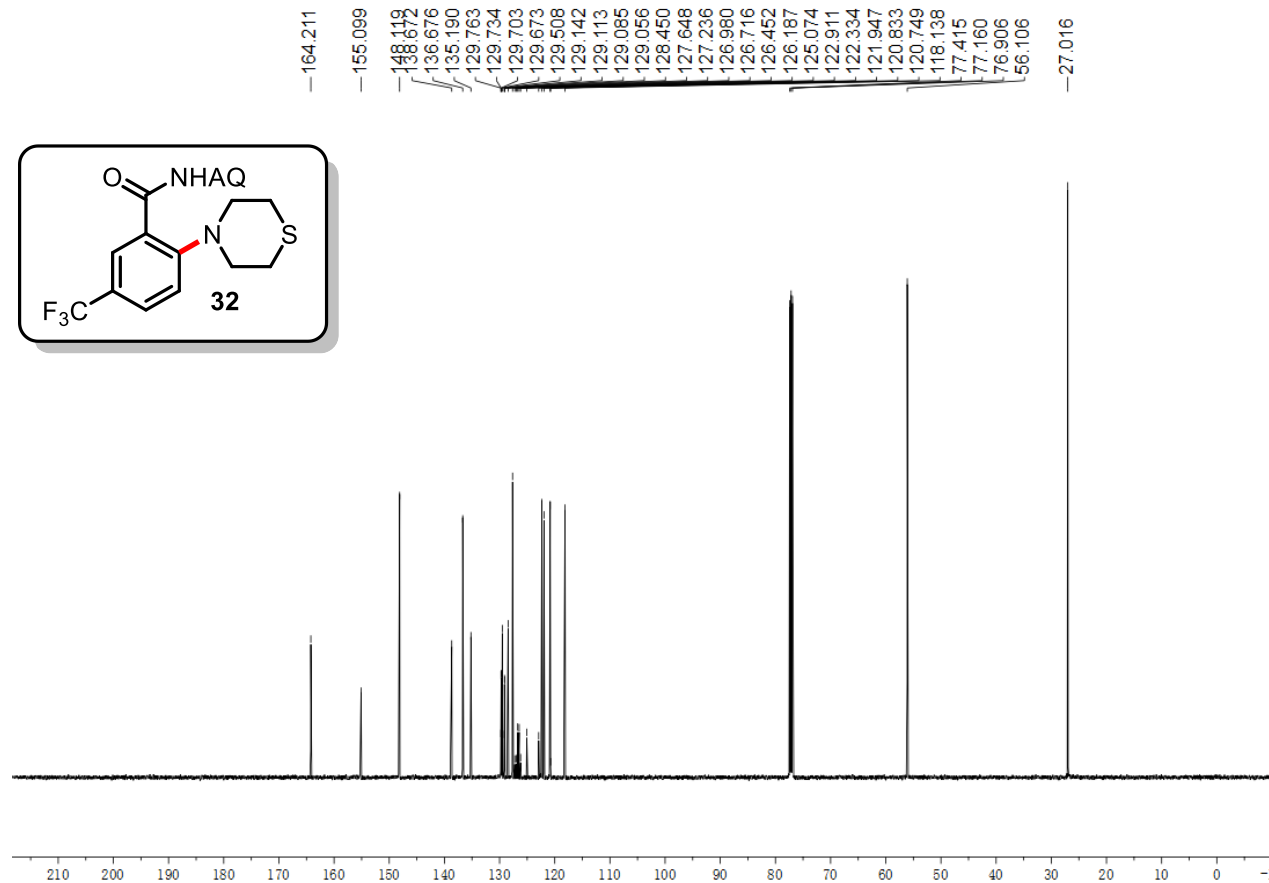
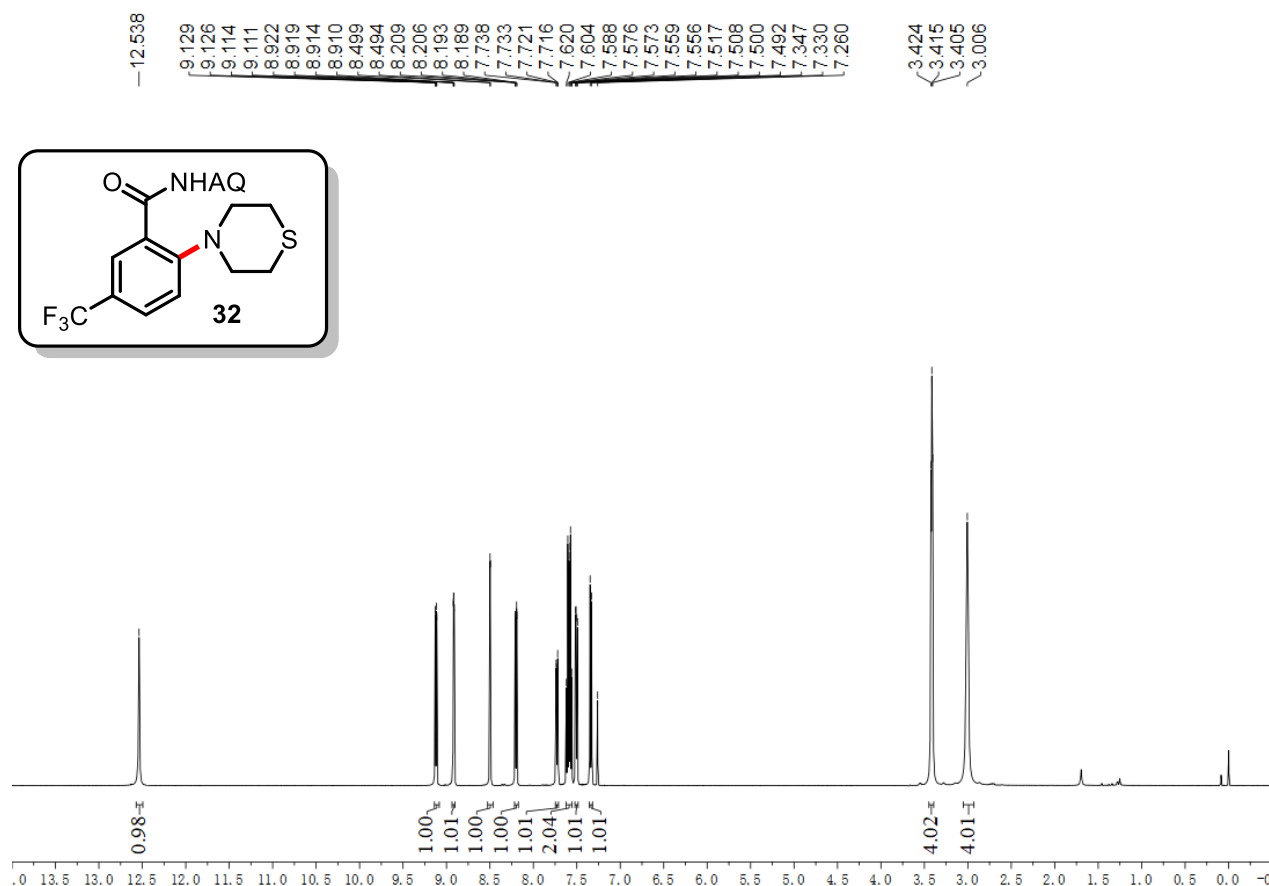


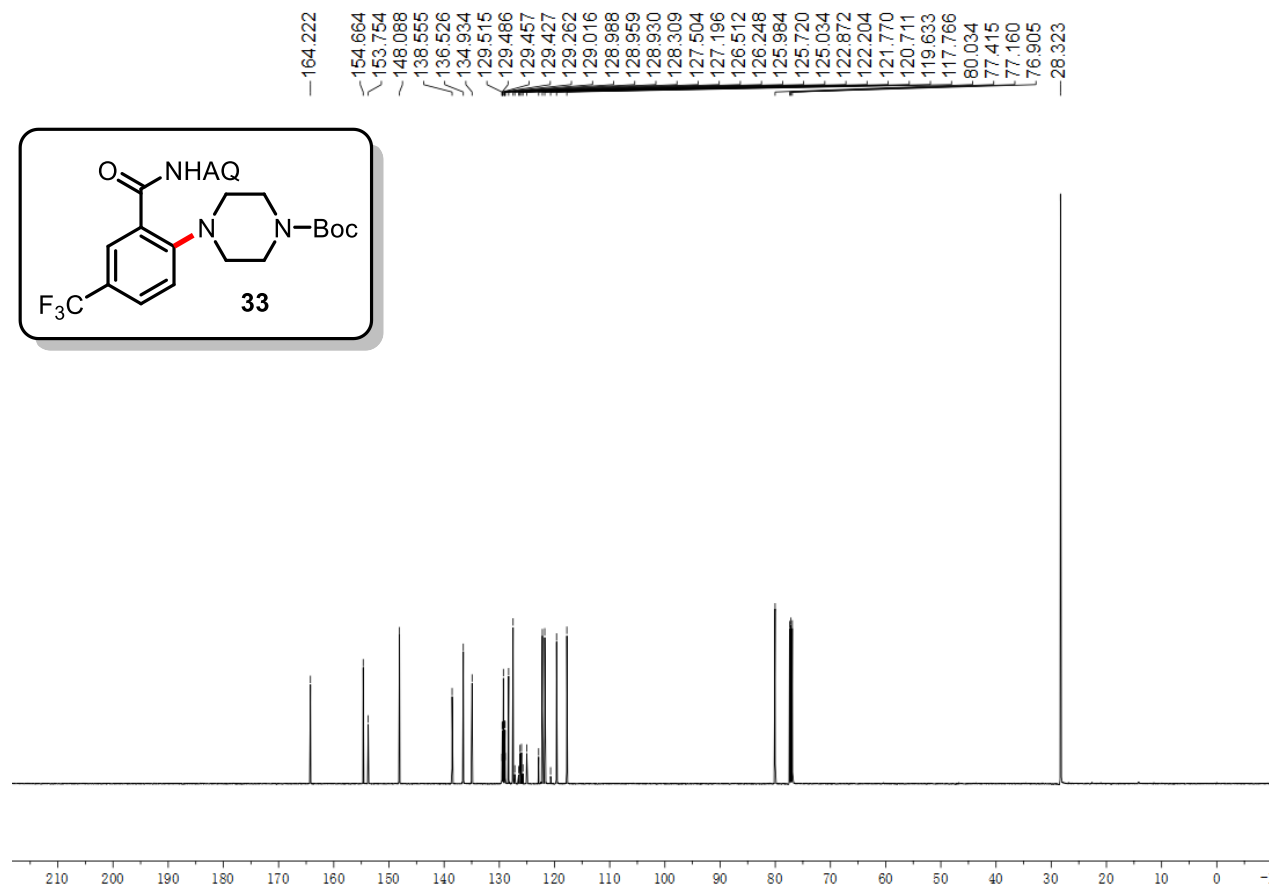
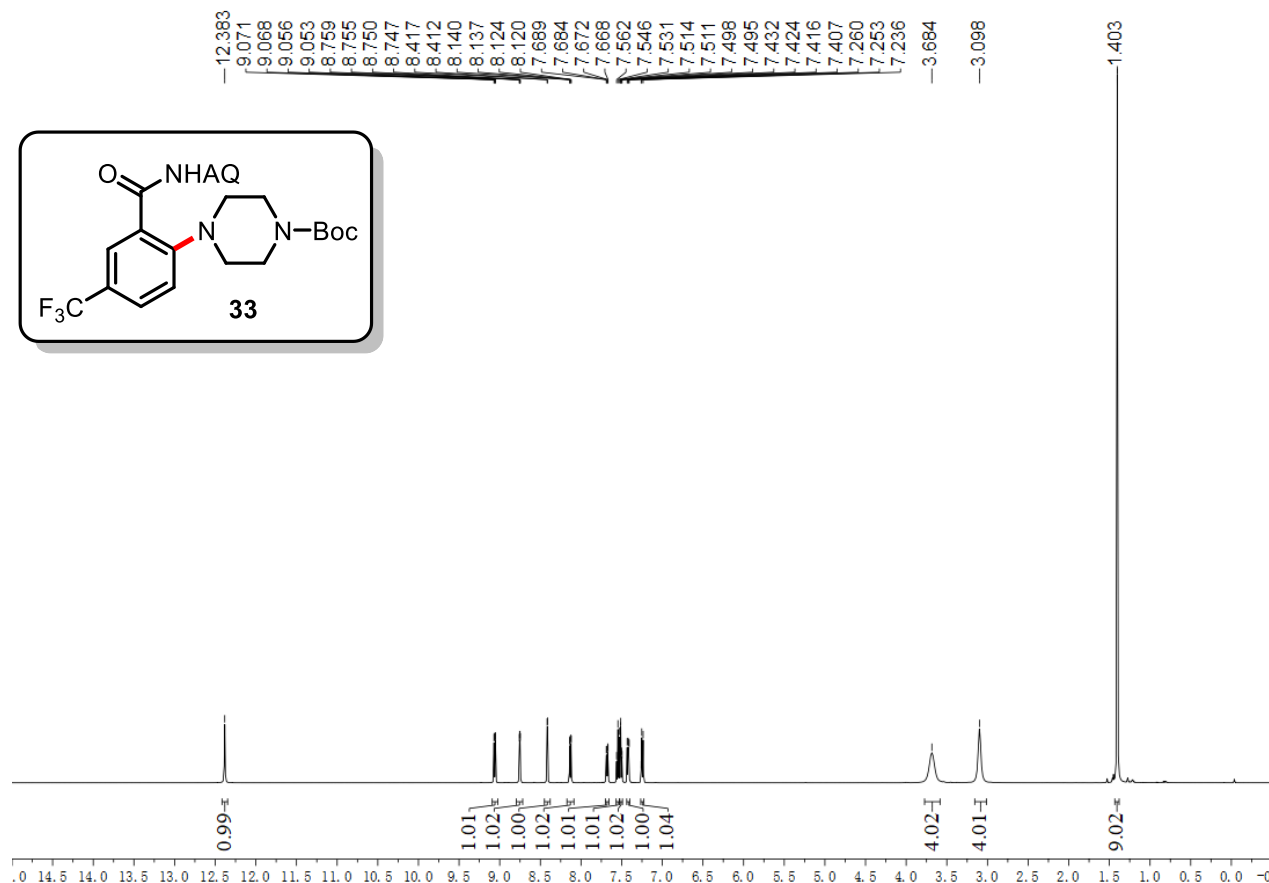




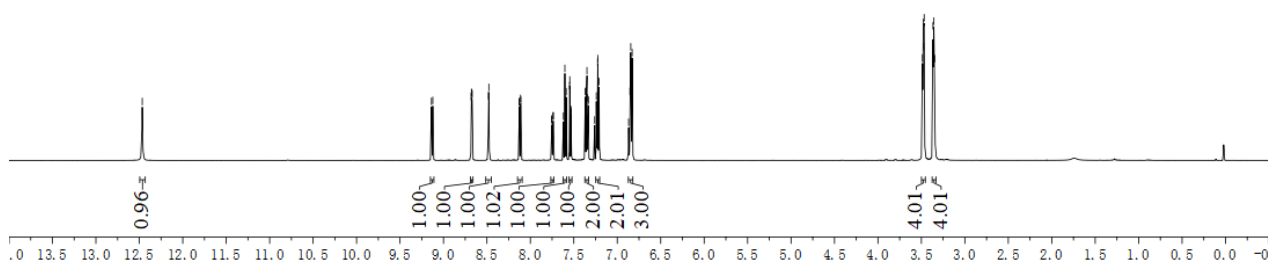
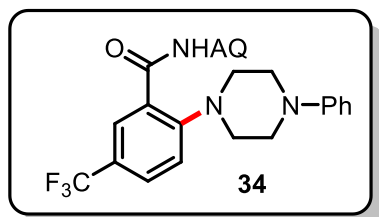








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