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Synthesis and evaluation of new benzimidazole-based COX inhibitors: a naproxen-like interaction detected by STD-NMR

Supporting Information

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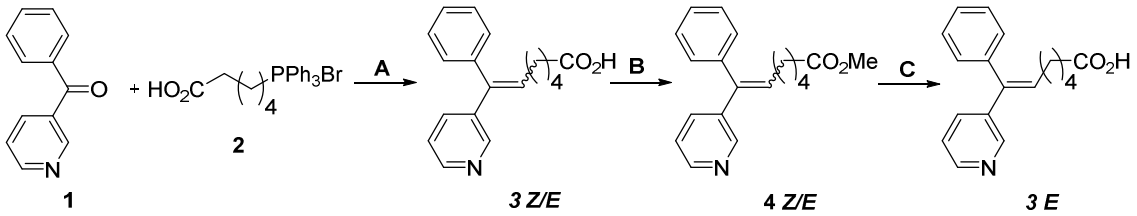
1. Synthesis of (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acid

The synthesis of (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acid **3*E*** was carried according to the procedure described by Terao and coworkers.[1] Thus, the first attempt to prepare (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acid **3*E*** was based on this procedure that considers the condensation of phenyl(pyridin-3-yl)methanone **1** with phosphonium bromide **2** in the presence of sodium hydride in dimethyl sulfoxide, although no product was obtained. Changing the solvent to THF, increasing the amount of sodium hydride, phosphonium bromide **2** or temperature did not improve the reaction and no product was isolated. When potassium *tert*-butoxide (4 equiv) was used as base in dry THF to generate *in situ* the (5-carboxypentyl)triphenylphosphorane from (5-carboxypentyl)triphenylphosphonium bromide **2** an isomeric mixture of (*Z*)- and (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acids **3*Z/E*** was obtained in 28% yield, (*Z*/*E*-isomeric ratio: 66/34). The use of lithium bases such as *n*-butyllithium (2.5 equiv, 1.6 M in hexane) or lithium *tert*-butoxide (2.86 equiv, 1.0 M in THF) slightly improved (*E*)-selectivity. Although in both cases the (*Z*)-product was the major compound and the diastereomeric mixture **3*Z/E*** was obtained in low yields (22% and 18%, respectively).

In an effort to improve the (*E*)-selectivity and the reaction yield we attempted the Schlosser modification[2] of the Wittig reaction. Performing the Schlosser-Wittig reaction of (5-carboxypentyl)triphenylphosphonium bromide **2** with phenyl(pyridin-3-yl)methanone **1** in the presence of phenyllithium (2.24 equiv plus 1.12 equiv, 2.0 M in Bu_2O) and lithium chloride (2.24 equiv) in dry THF a (50/50) diastereomeric mixture of (*Z*)- and (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acids **3*Z/E*** was obtained in 26% yield. Since the isomers could not be isolated in a pure acid form, the obtained isomeric mixture **3*Z/E*** was esterified to the corresponding methyl esters with methanol in the presence of sulfuric acid at 60 ºC to simplify the separation. The methyl ester **4*E*** was purified by thin layer chromatography (dichloromethane:acetone, 8:2). Hydrolysis of methyl (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoate **4*E*** in the presence of sodium hydroxide yielded the corresponding (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acid **3*E*** in good yield (72%). The ^{1}H NMR spectra of (*E*)-7-phenyl-7-(pyridin-3-yl)hept-6-enoic acid **3 *E*** was in agreement with the literature.[1]



Scheme 1: *Reaction Conditions:*
A: 1) 1.09 mmol of **1**, 1 equiv of **2**, 2.24 equiv + 1.12 equiv PhLi (2.0 M in Bu_2O), LiCl (2.24 equiv), THF, -78 ºC → rt; 2) HCl (1.12 equiv), Et_2O, -78 ºC; 3) ^{t}BuOK (1.2 equiv), rt, **3*Z/E*** (26%);
B: 0.19 mmol of **3*Z/E***, H_2SO_4 (0.05 mL), MeOH (1 mL), 60 ºC, 3h. Isolated by pTLC **4*E*** (39%);
C: 0.57 mmol of **3*E***, 10 equiv NaOH (aq., 1 M), EtOH (1.5 mL), rt, 3 h. **3*E*** (72%).

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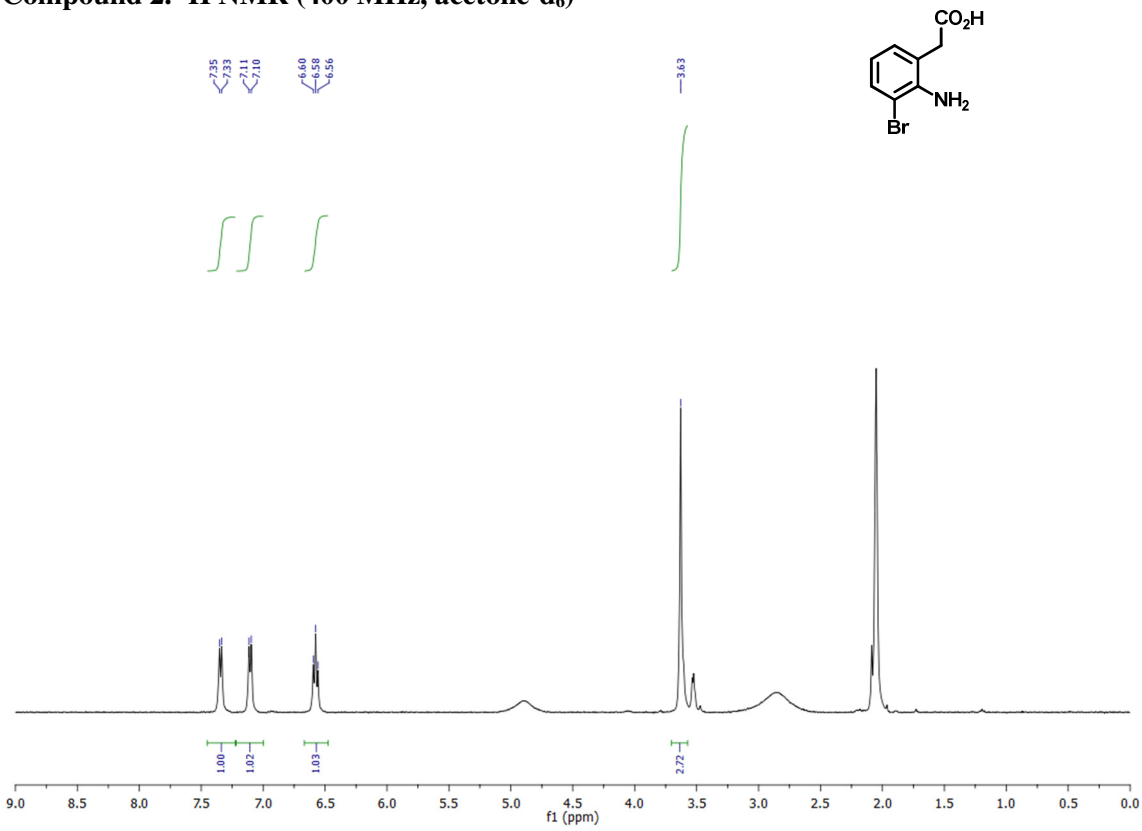
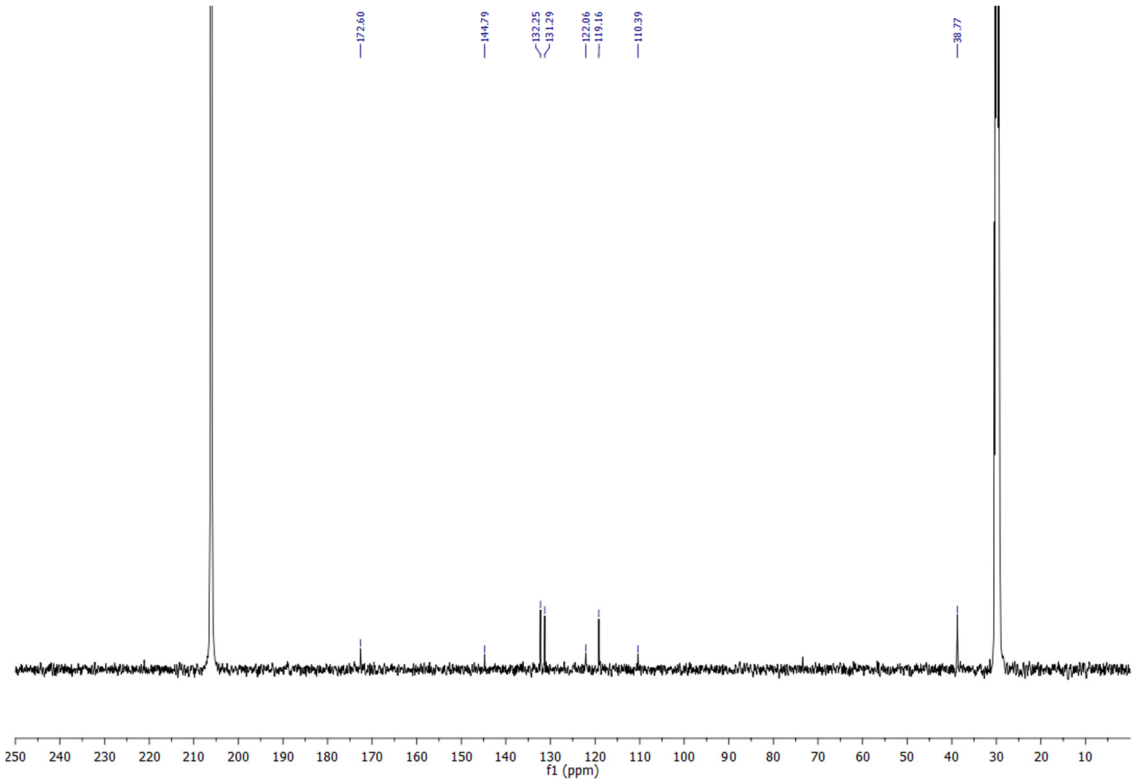
[1] K. Kato, S. Ohkawa, S. Terao, Z.-I. Terashita, K. Nishikawa, *J. Med. Chem.* **1985**, *28*, 287–294
[2] Q. Wang, D. Deredas, C. Huynh, M. Schlosser, *Chem. Eur. J.* **2003**, *9*, 570–574

2. ^{1}H and ^{13}C NMR spectra of the described products

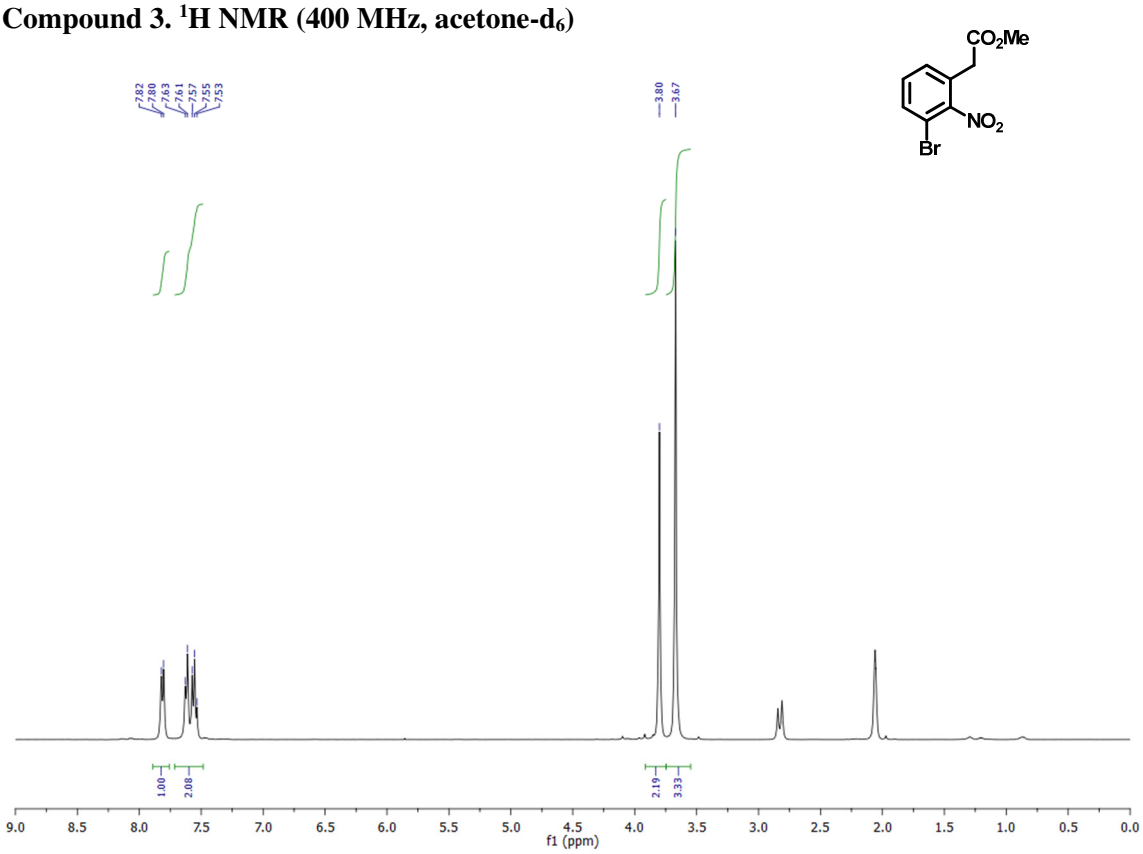
Compound 2. ^{1}H NMR (400 MHz, acetone-d_6)



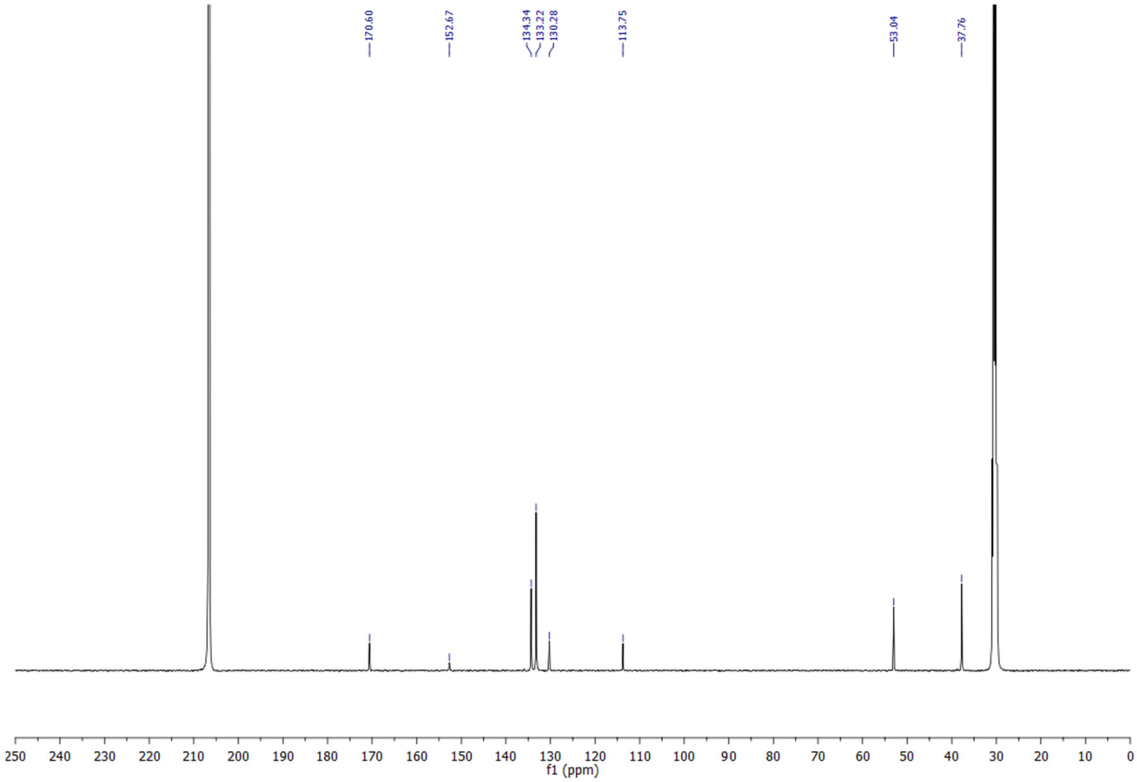
Compound 2. ^{13}C NMR (100 MHz, acetone-d_6)



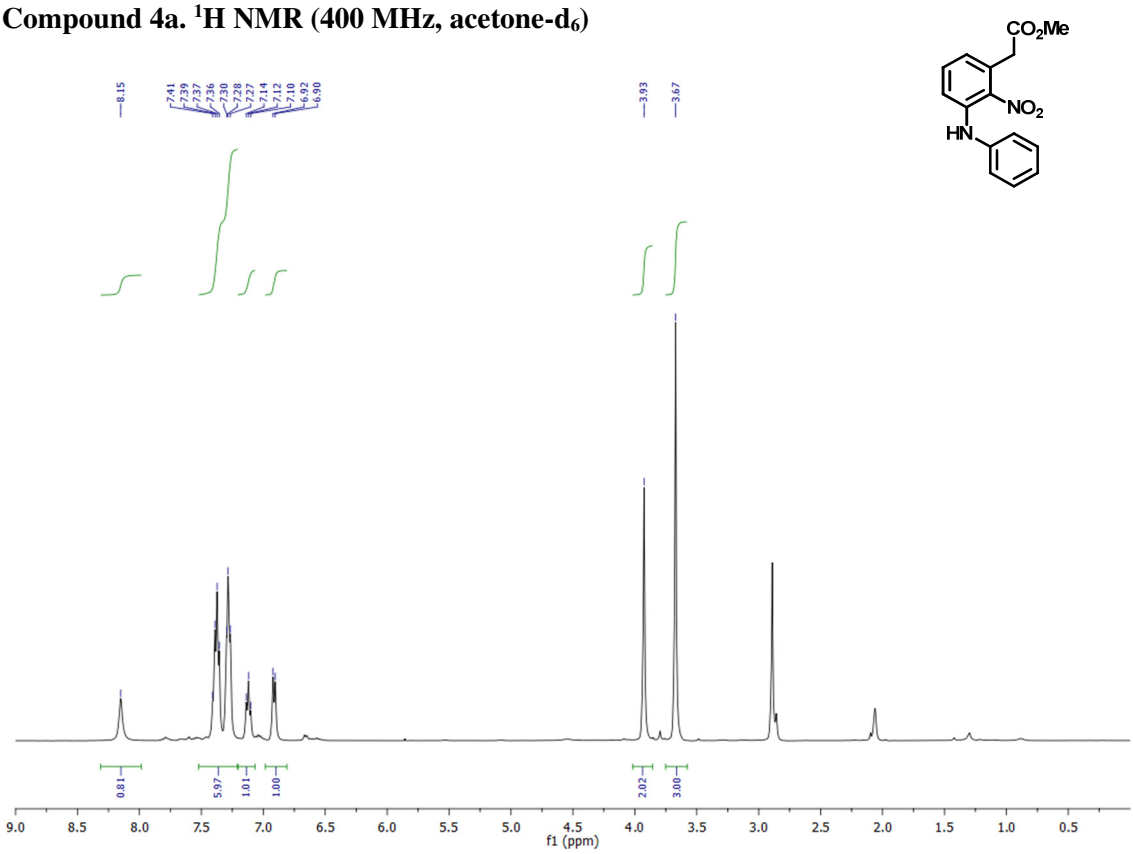
Compound 3. ^{1}H NMR (400 MHz, acetone-d_6)



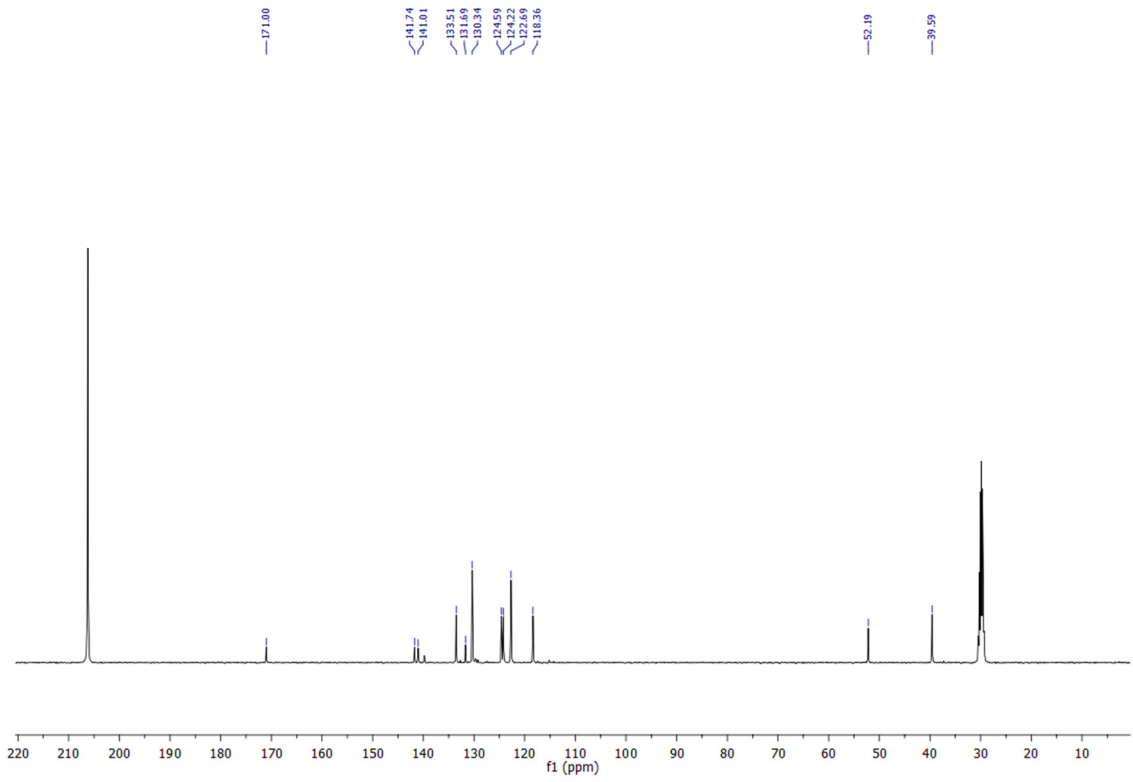
Compound 3. ^{13}C NMR (100 MHz, acetone-d_6)



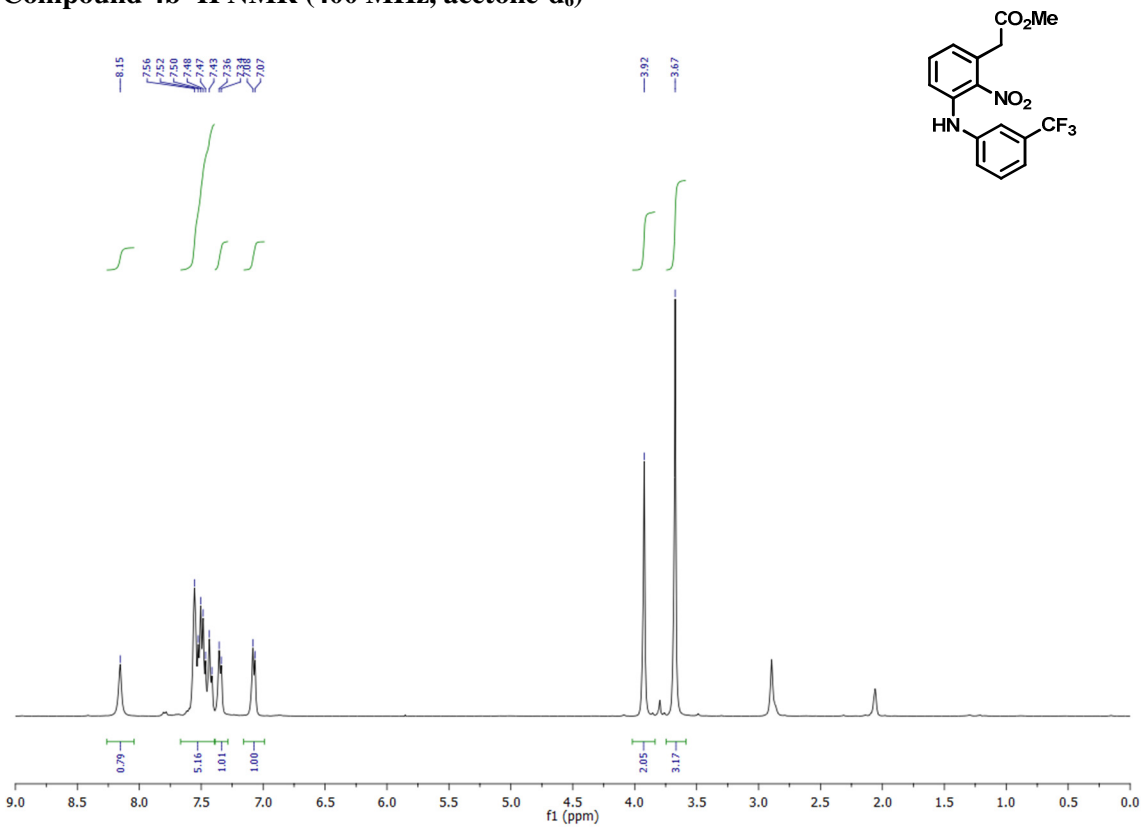
Compound 4a. ^{1}H NMR (400 MHz, acetone-d$_6$)



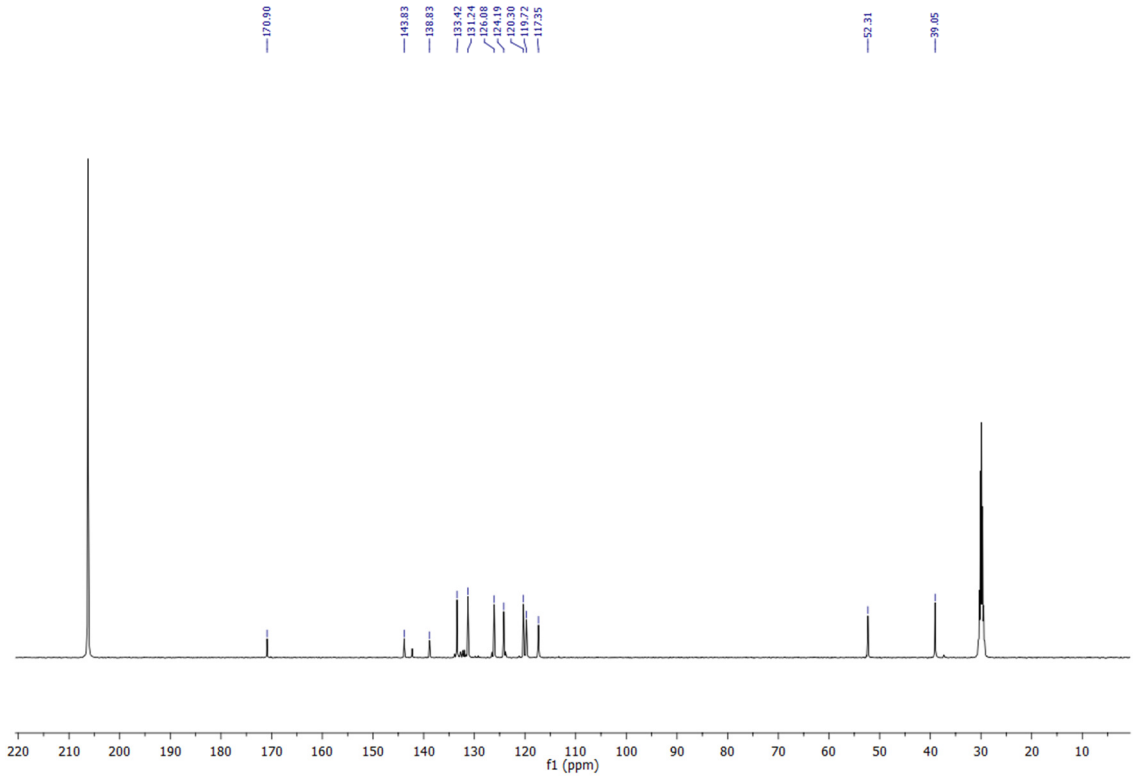
Compound 4a. ^{13}C NMR (100 MHz, acetone-d$_6$)



Compound 4b ^{1}H NMR (400 MHz, acetone-d$_6$)



Compound 4b ^{13}C NMR (100 MHz, acetone-d$_6$)



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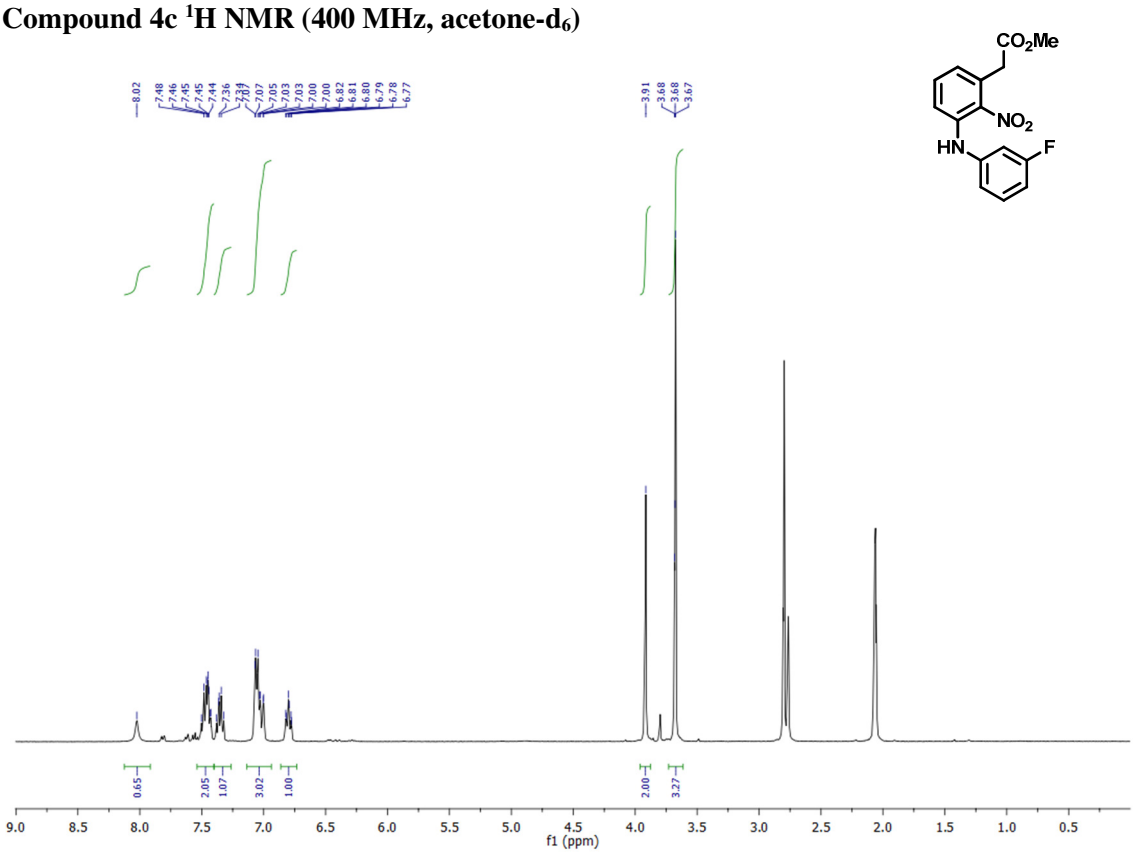
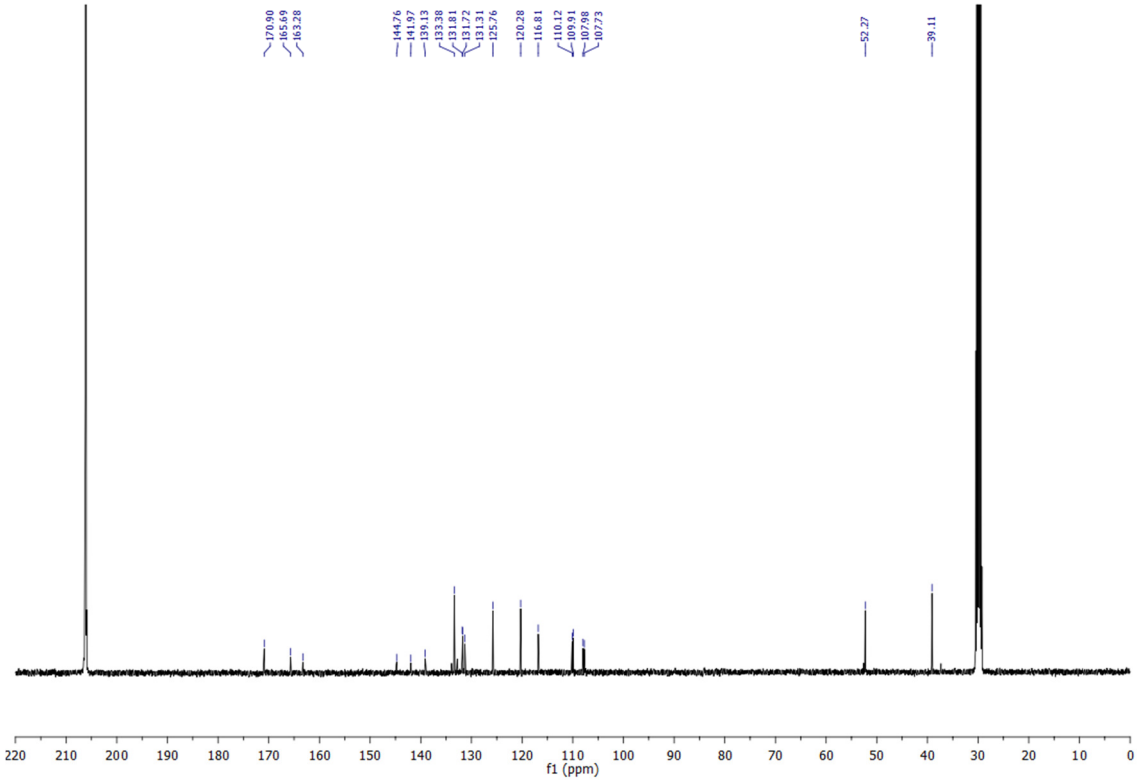


Compound 4c ^{13}C NMR (100 MHz, acetone-d$_6$)



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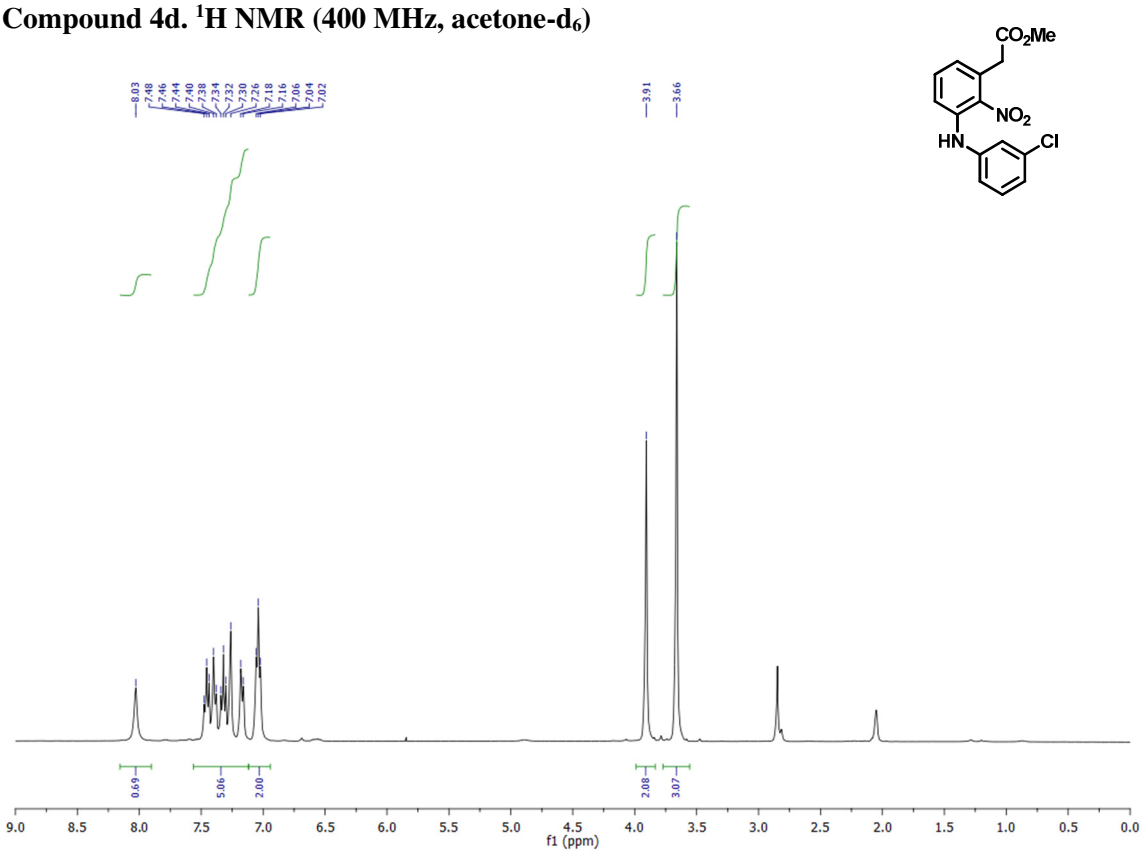
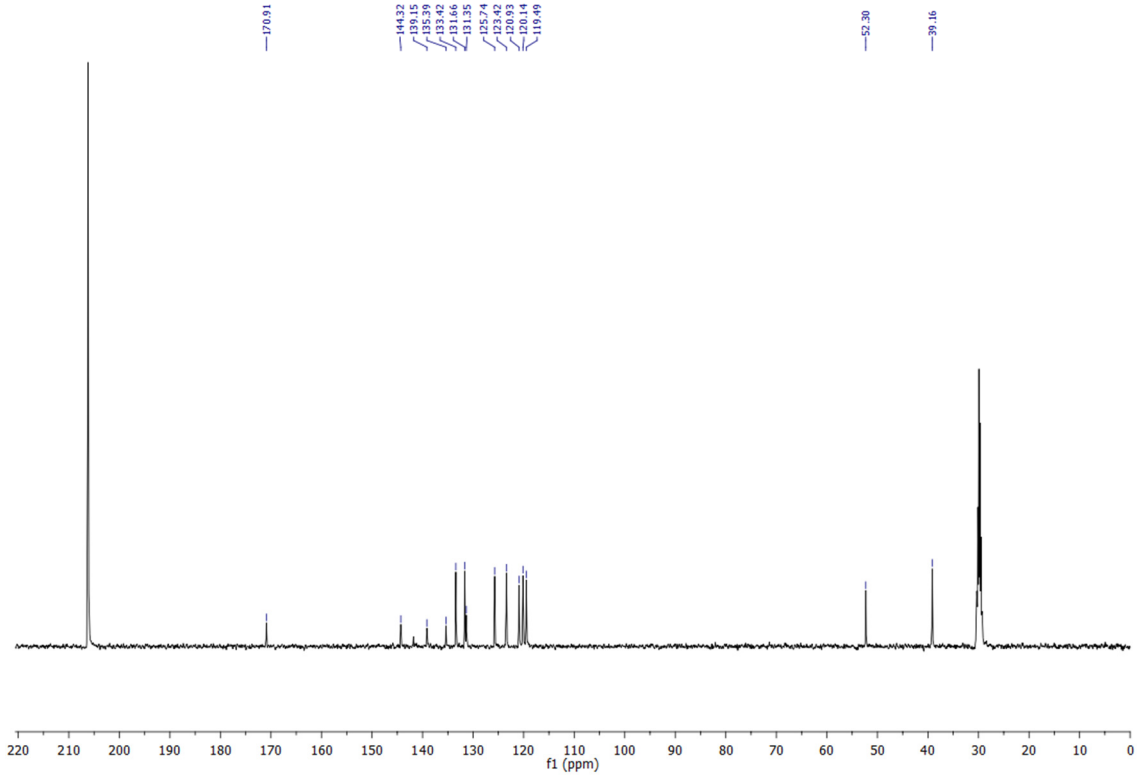
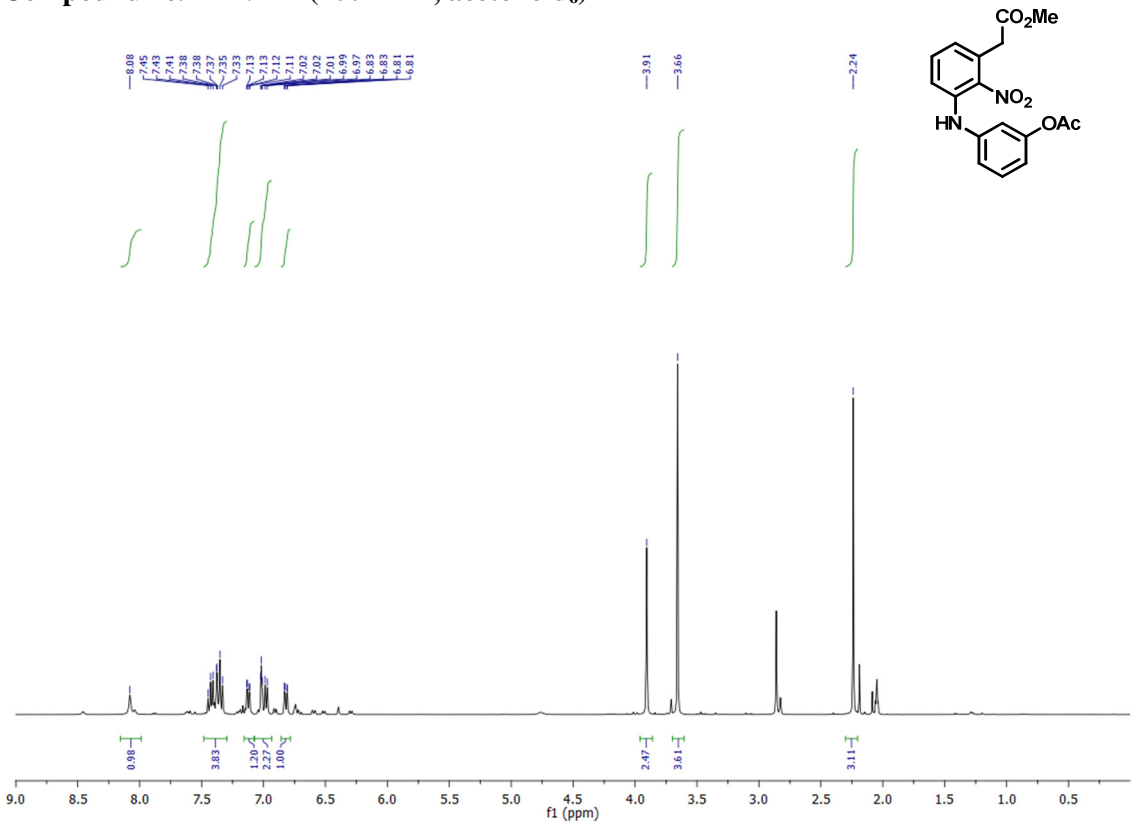


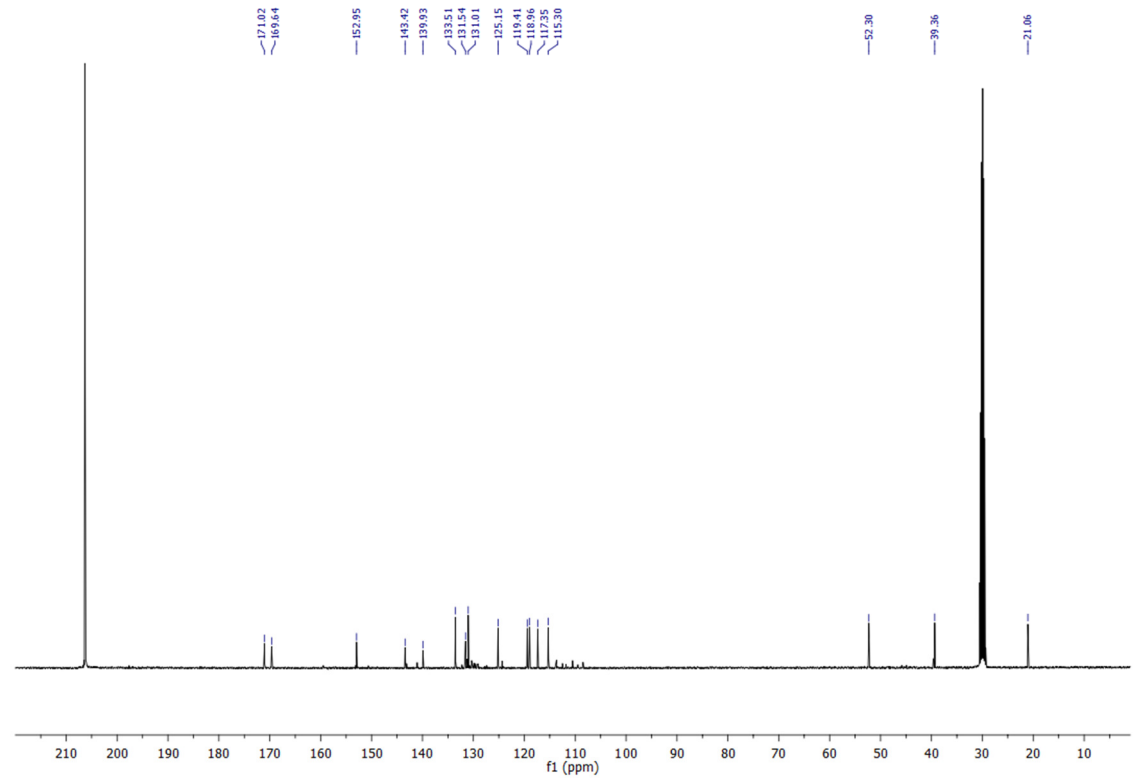
Compound 4d. ^{13}C NMR (100 MHz, acetone -d_6)



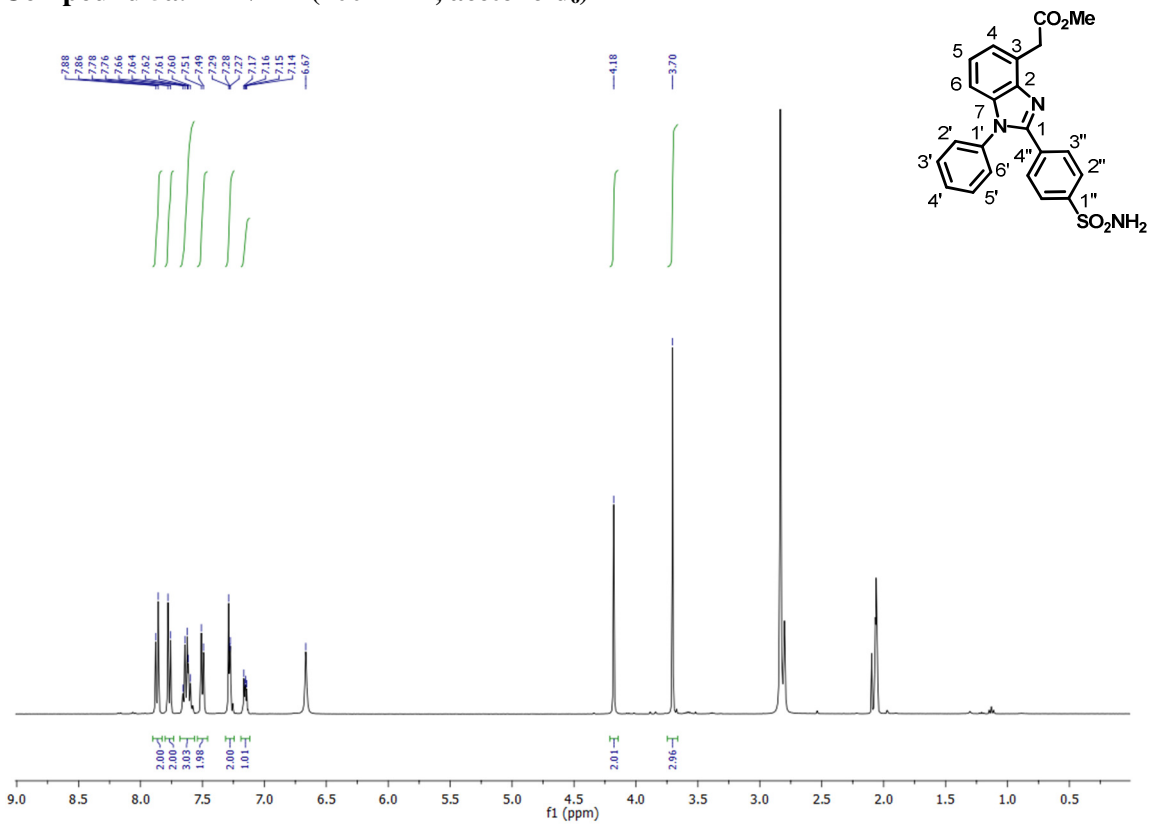
Compound 4e. ^{1}H NMR (400 MHz, acetone-d$_6$)



Compound 4e. ^{13}C NMR (100 MHz, acetone-d$_6$)



Compound 5a. ^{1}H NMR (400 MHz, acetone-d$_6$)



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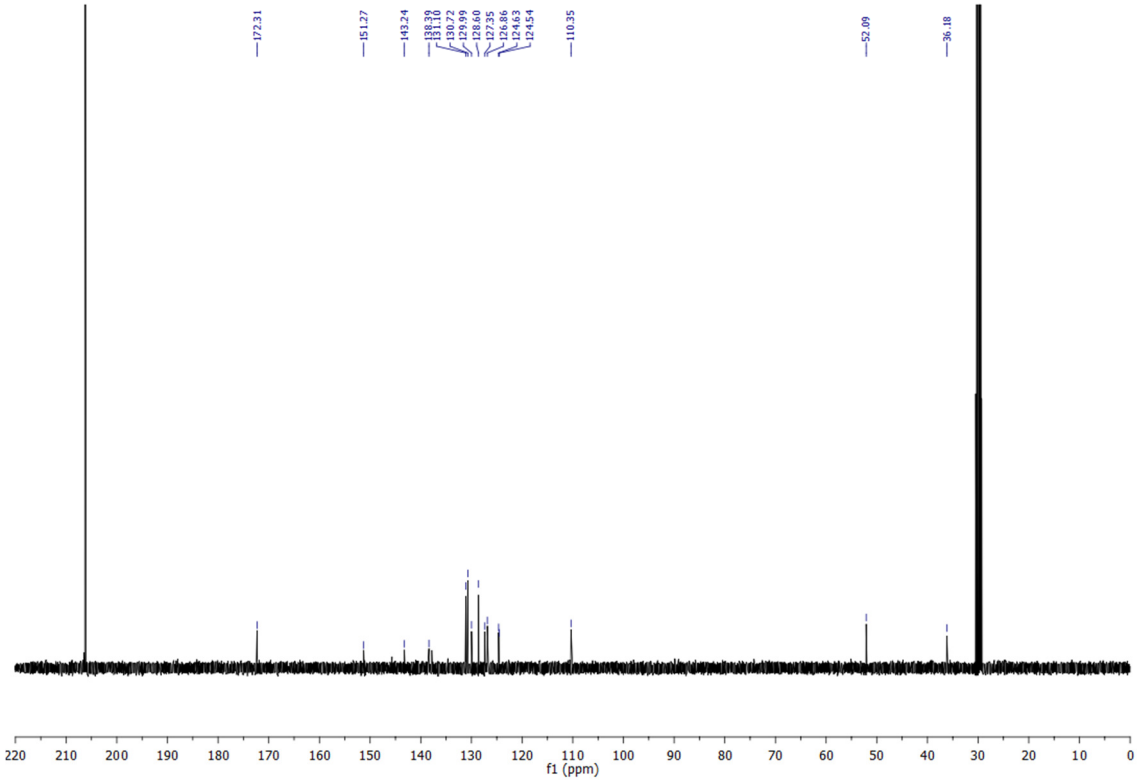
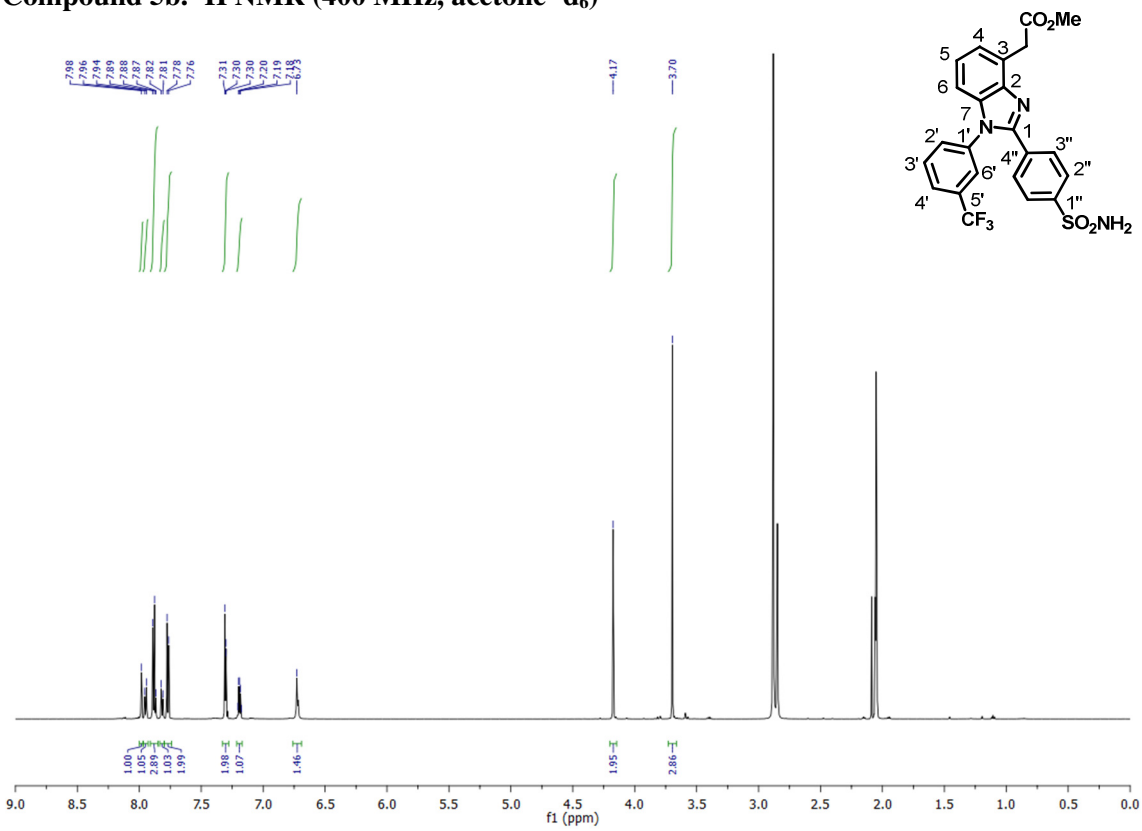


Compound 5b. ^{1}H NMR (400 MHz, acetone -d_6)



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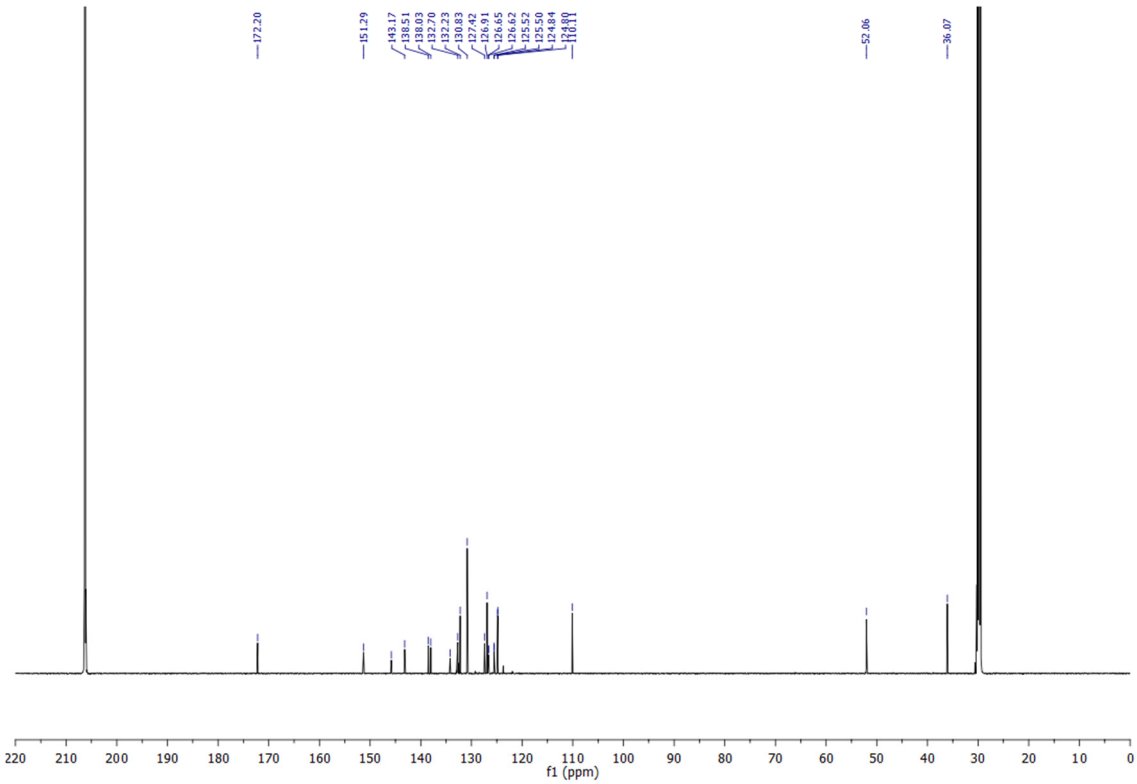

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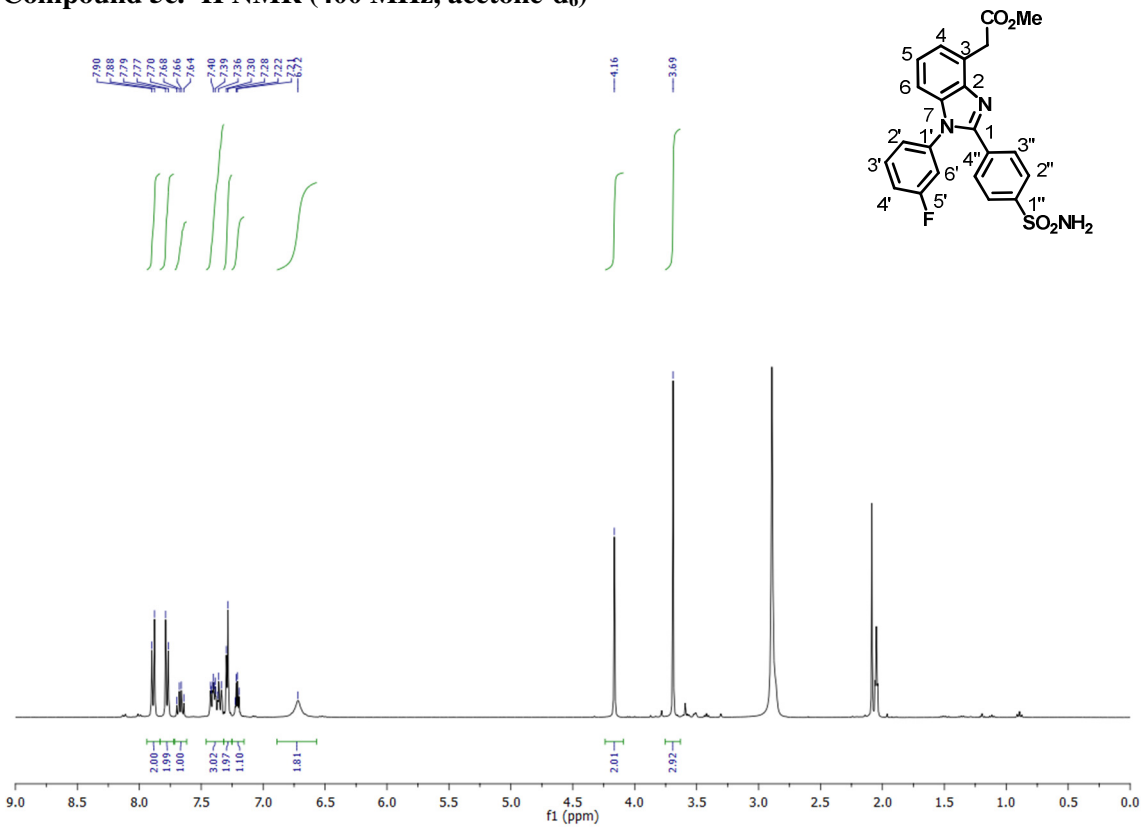

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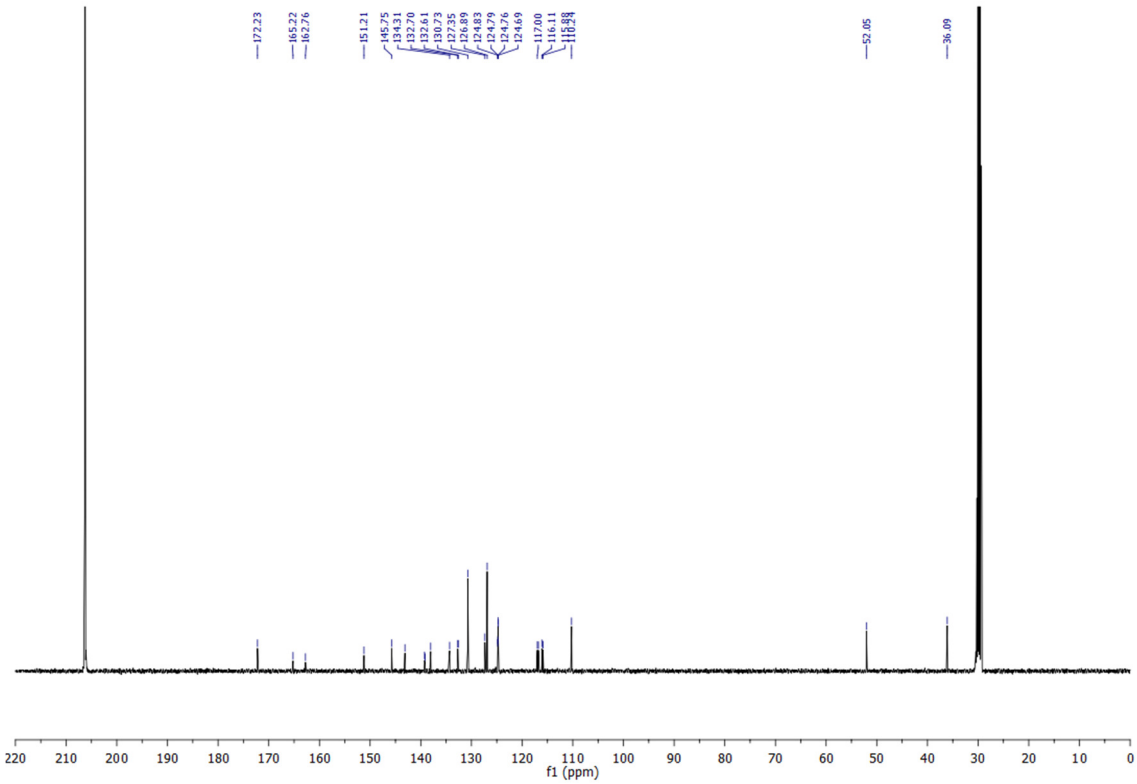

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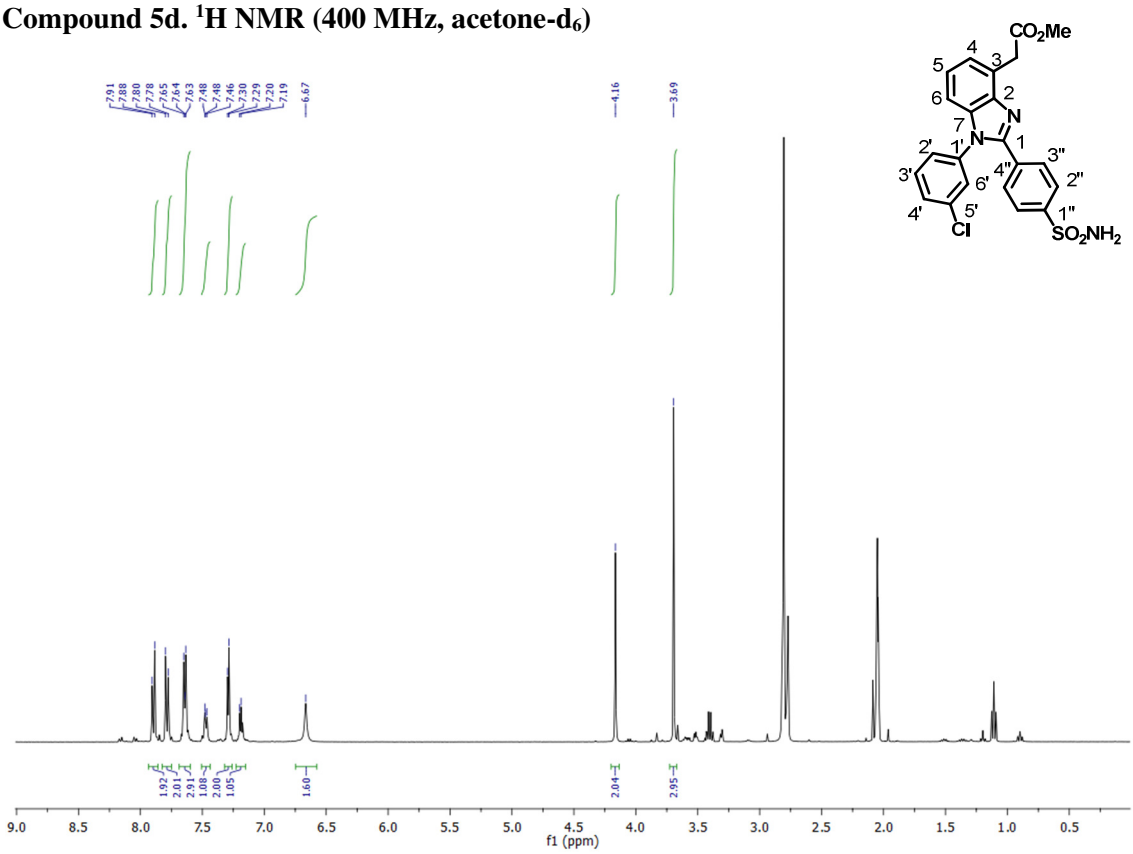

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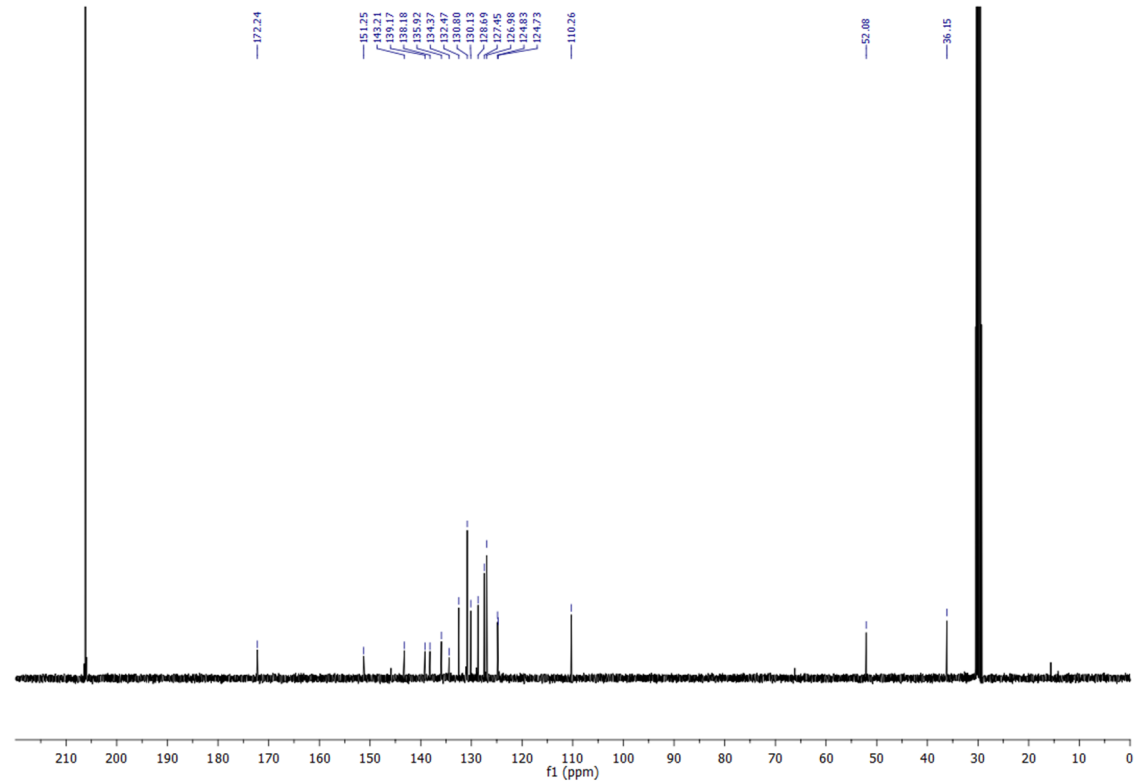

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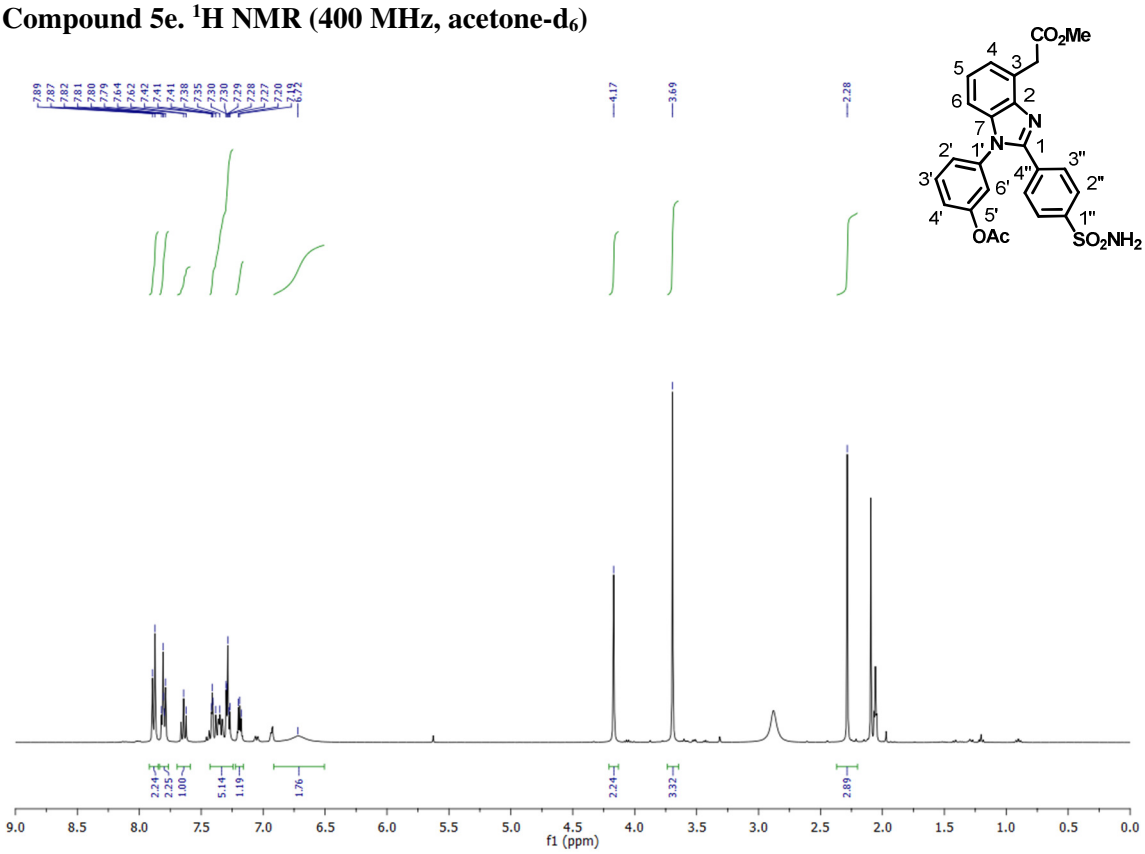
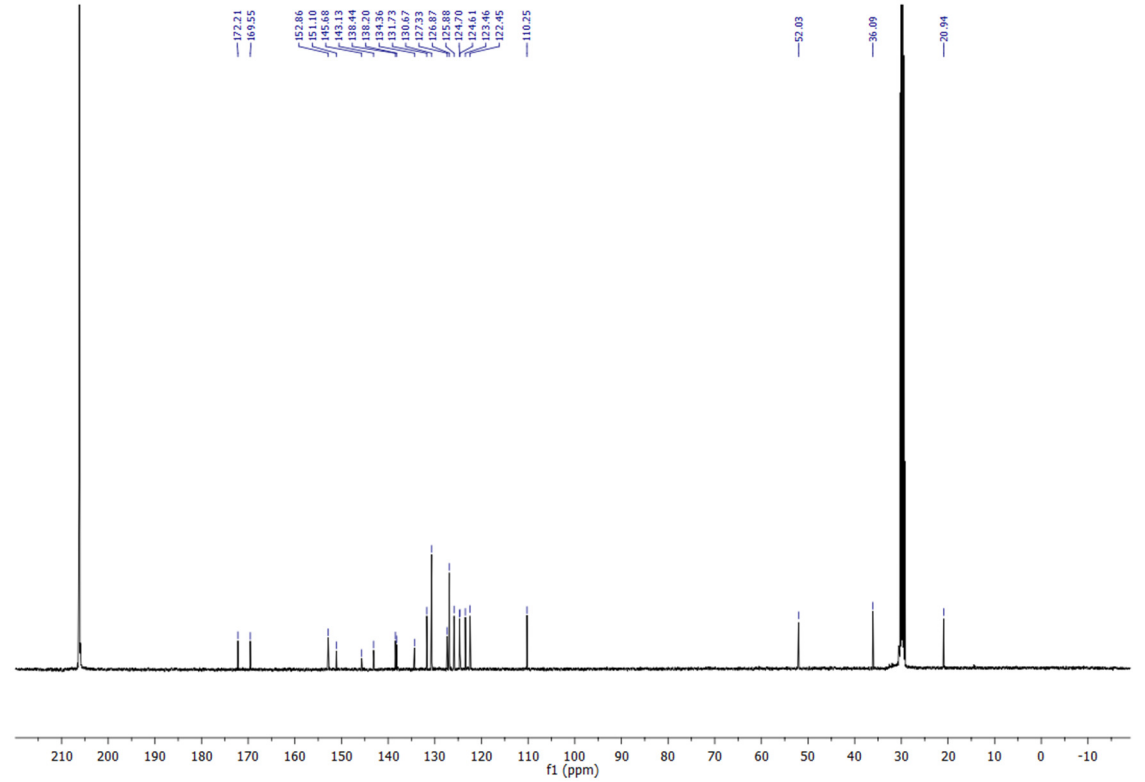
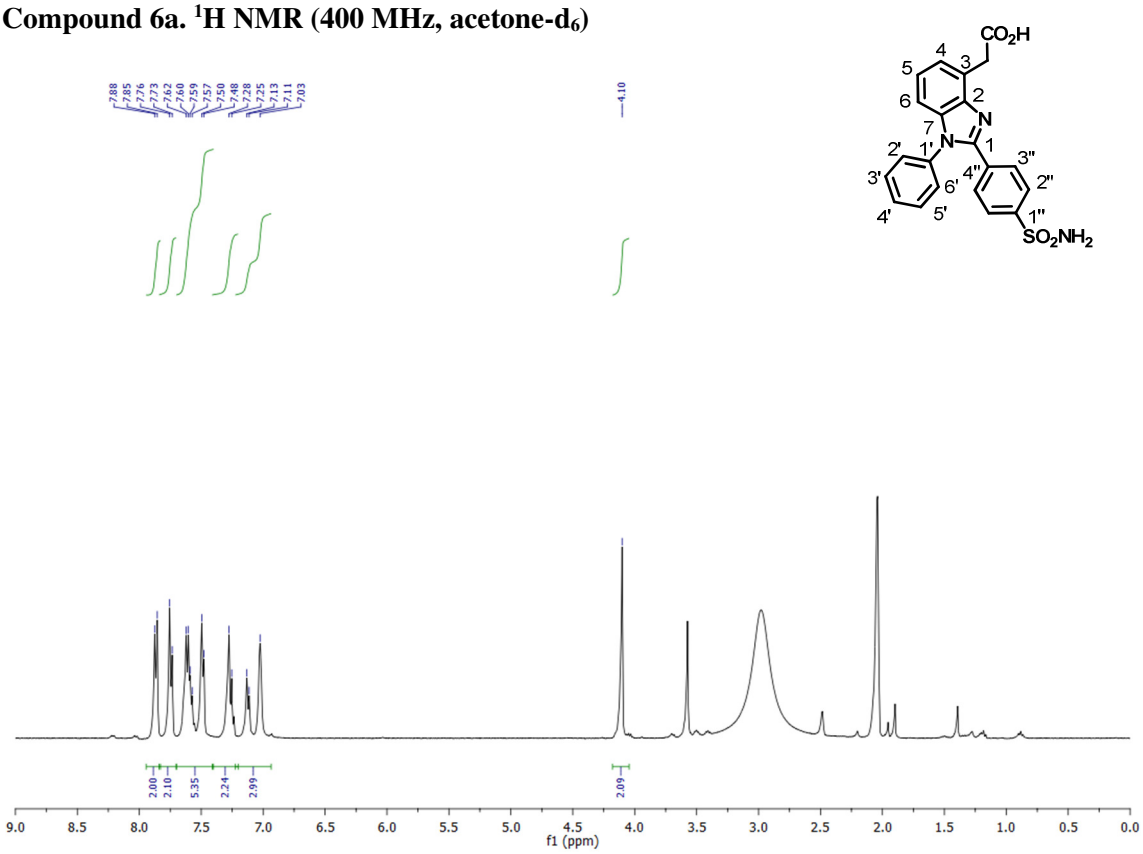


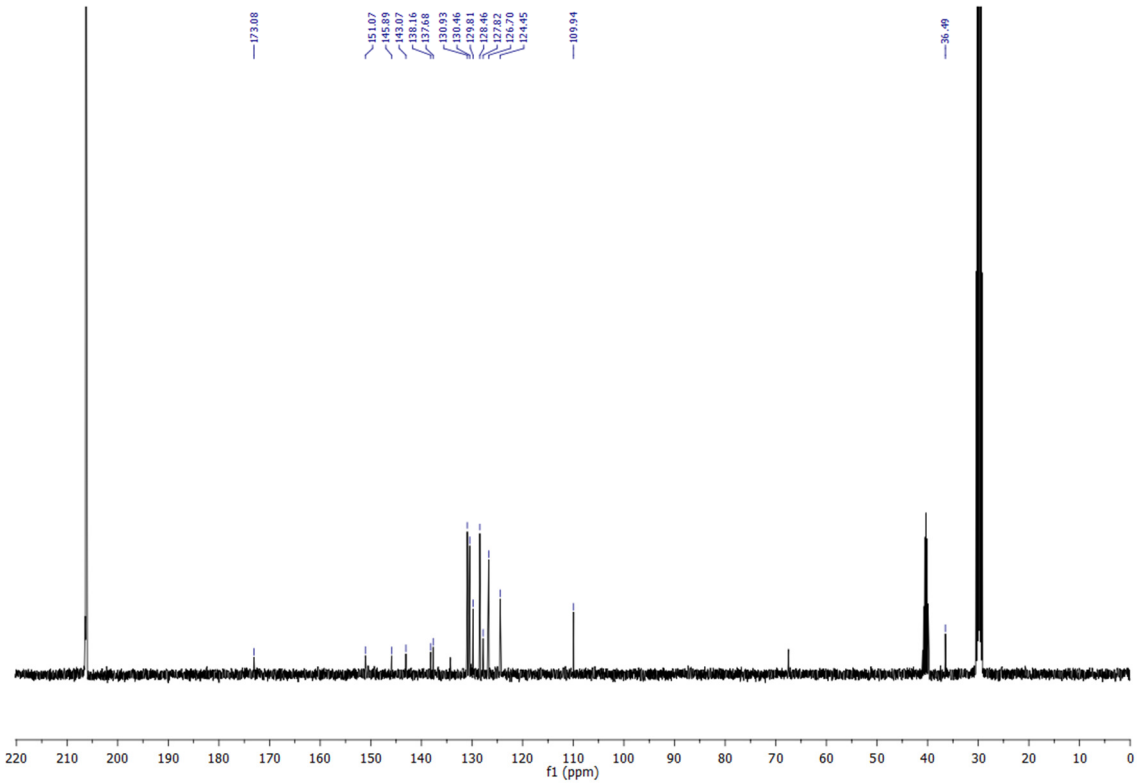
Compound 5e. ^{1}H NMR (100 MHz, acetone-d_6)



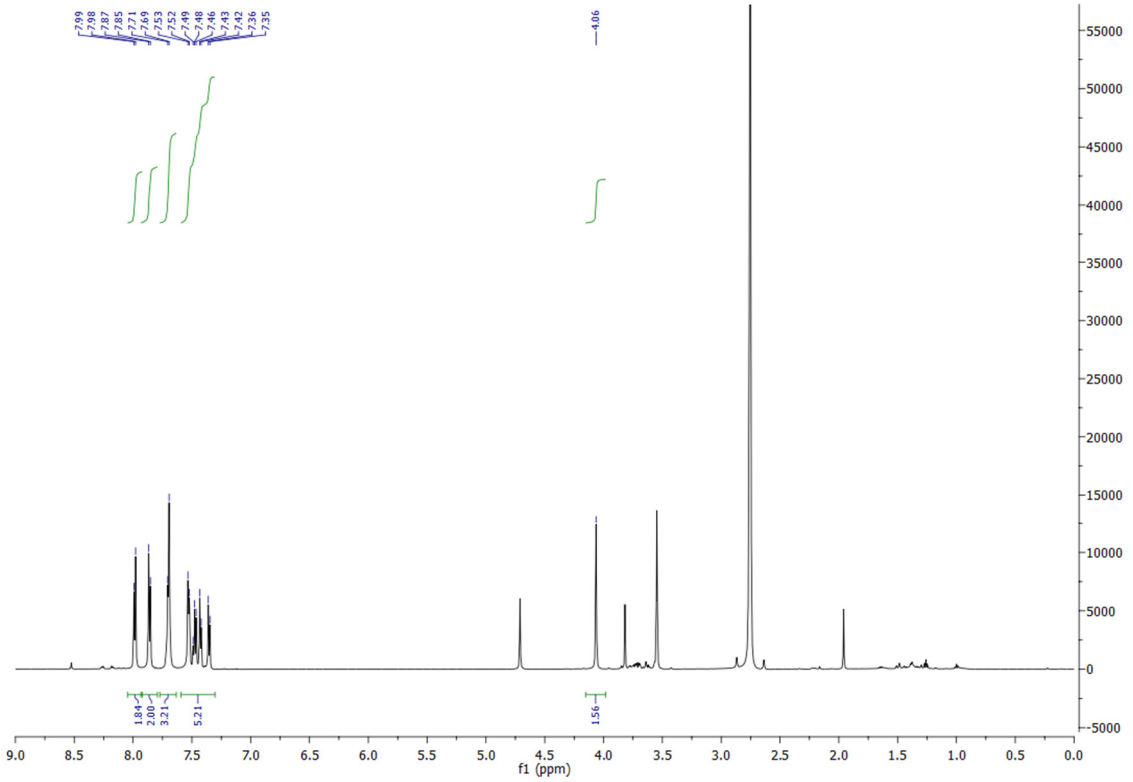
Compound 6a. ^{1}H NMR (400 MHz, acetone-d$_6$)



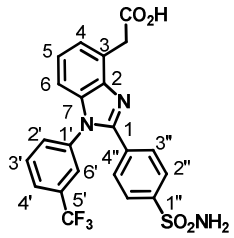
Compound 6a. ^{13}C NMR (100 MHz, acetone-d$_6$)



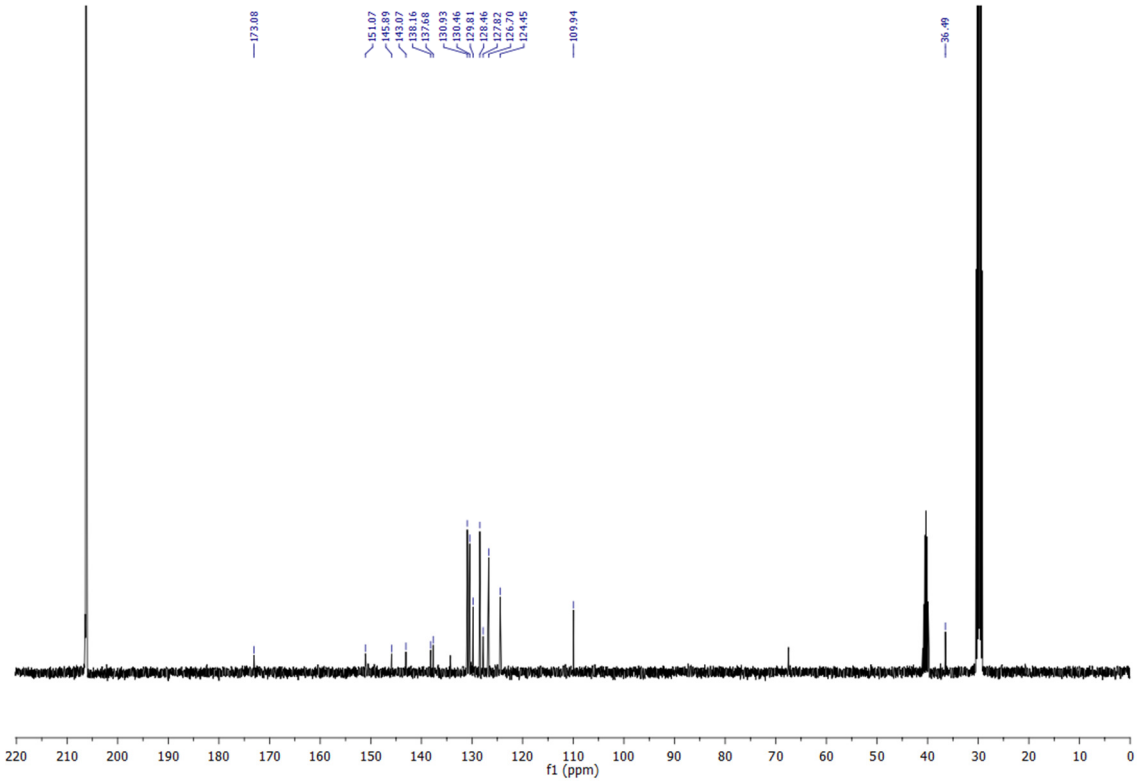
Compound 6a. ^{1}H NMR (600 MHz, D_2O)



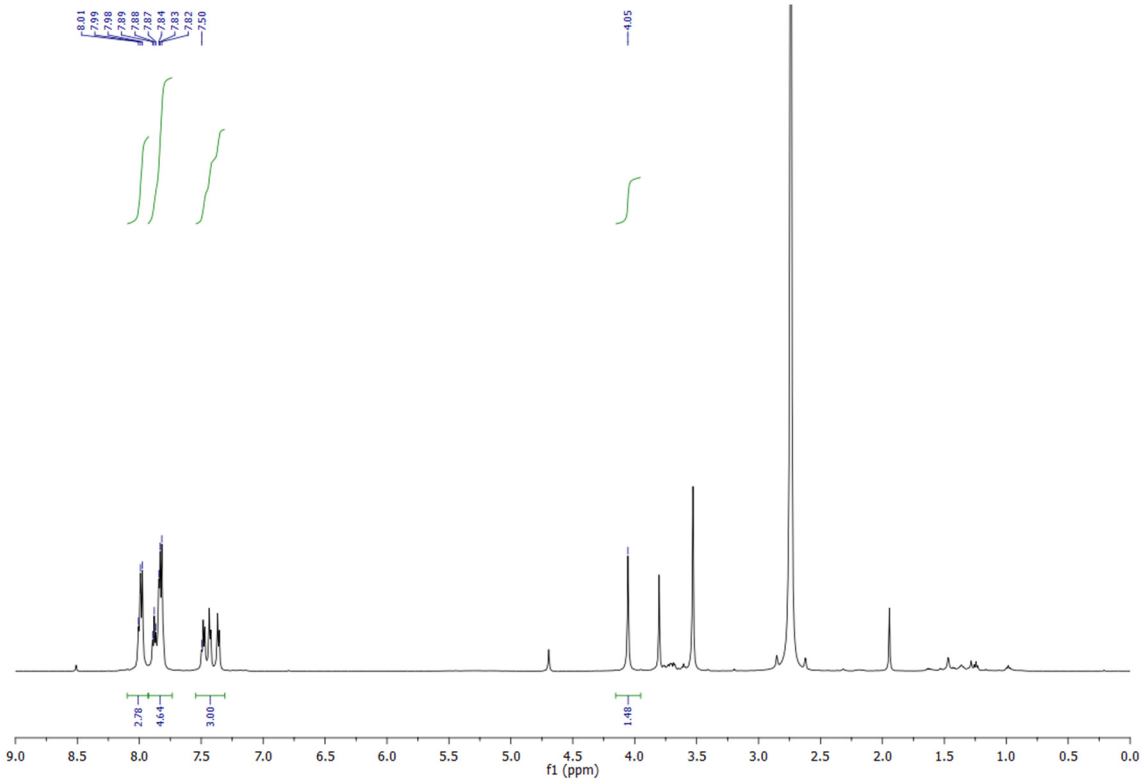
Compound 6b. ^{1}H NMR (400 MHz, acetone-d_6)



Compound 6b ^{13}C NMR (100 MHz, acetone-d_6)



Compound 6b. ^{1}H NMR (600 MHz, D_2O)



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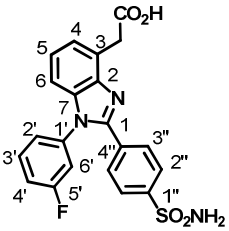
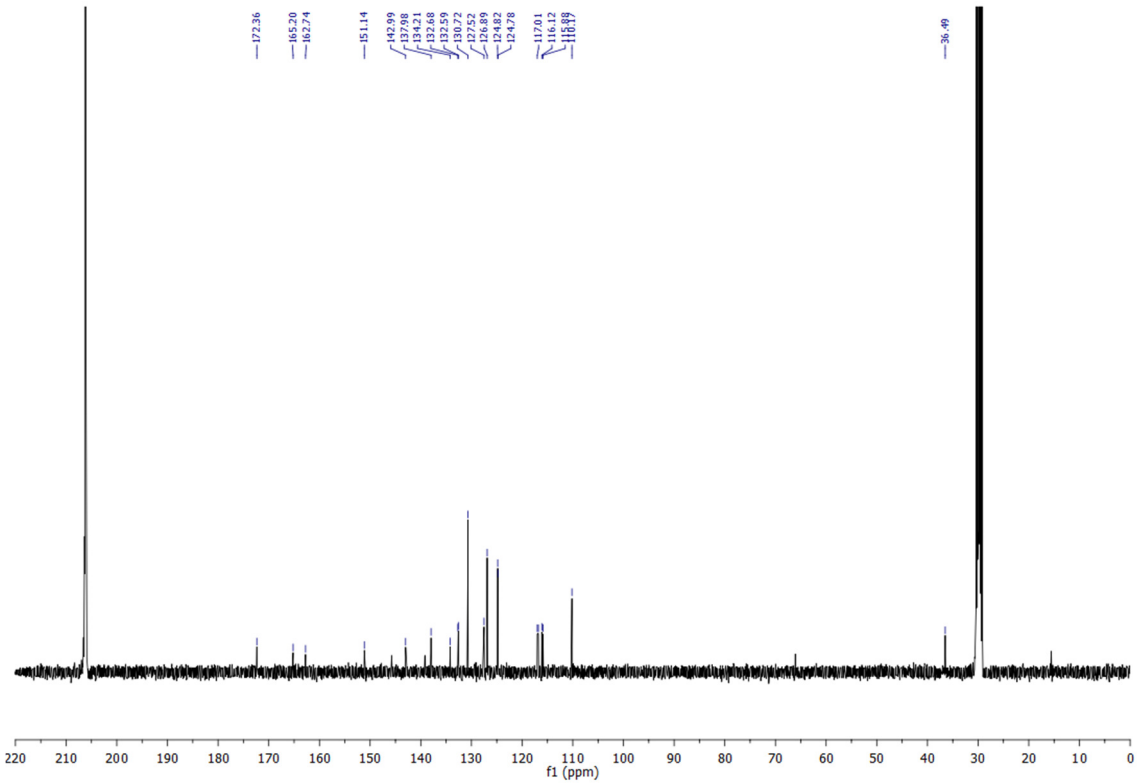
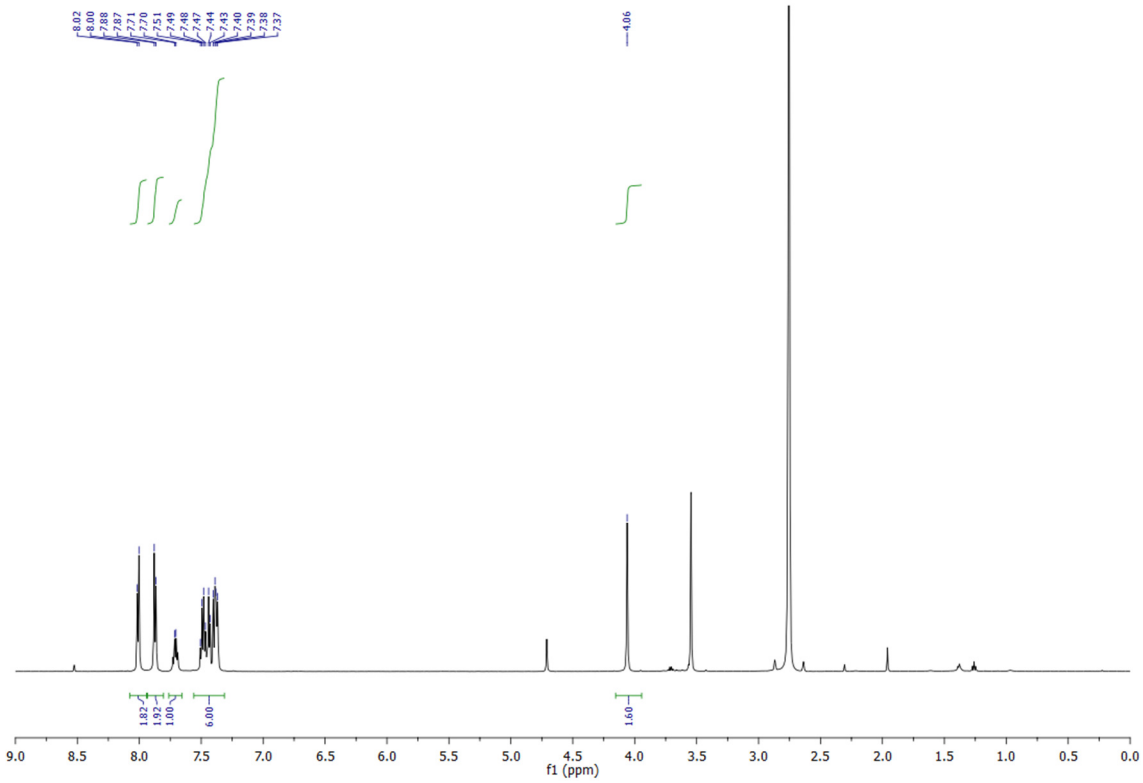


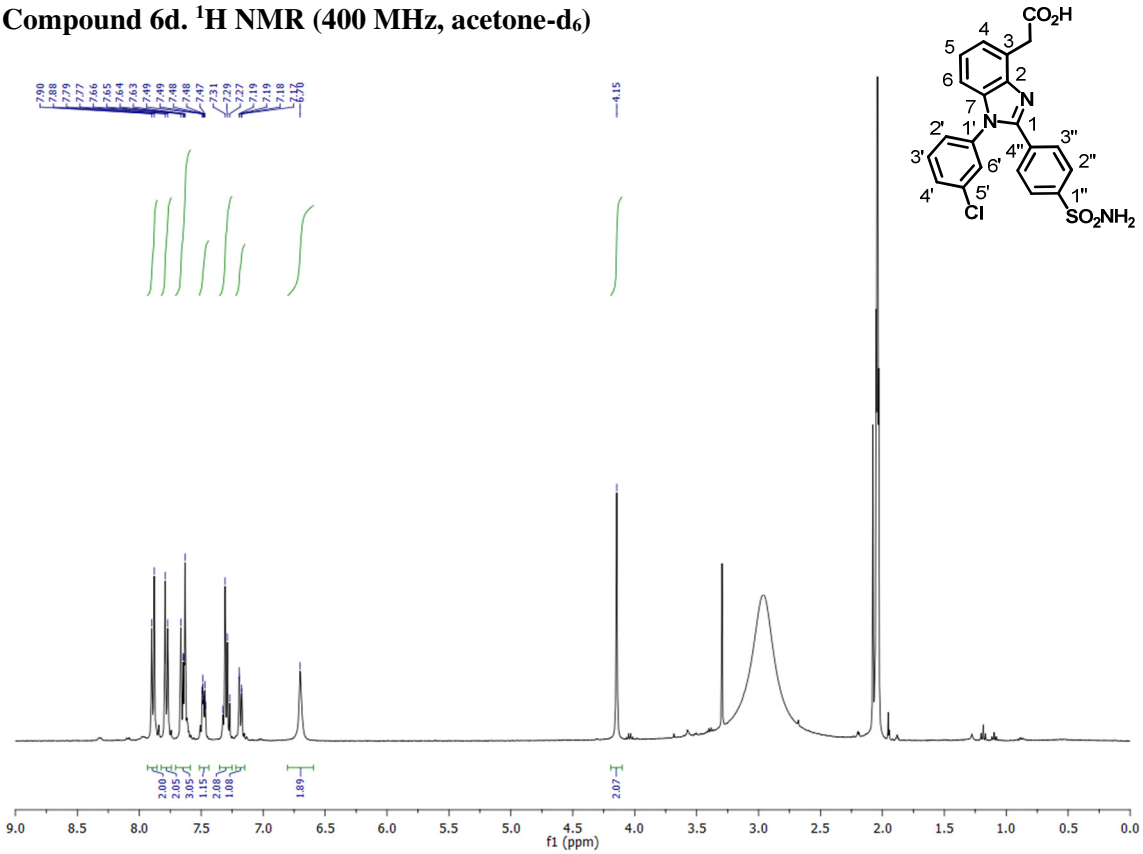
Compound 6c. ^{13}C NMR (100 MHz, acetone-d$_6$)



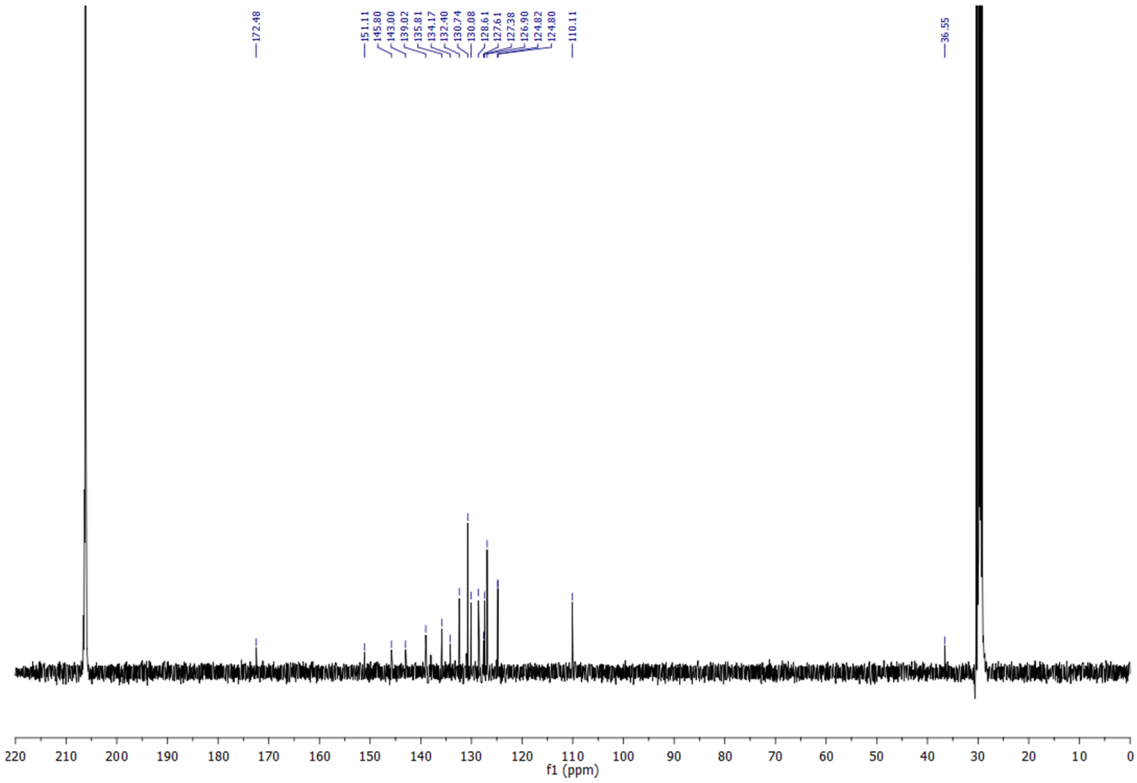
Compound 6c. ^{1}H NMR (600 MHz, D_2O)



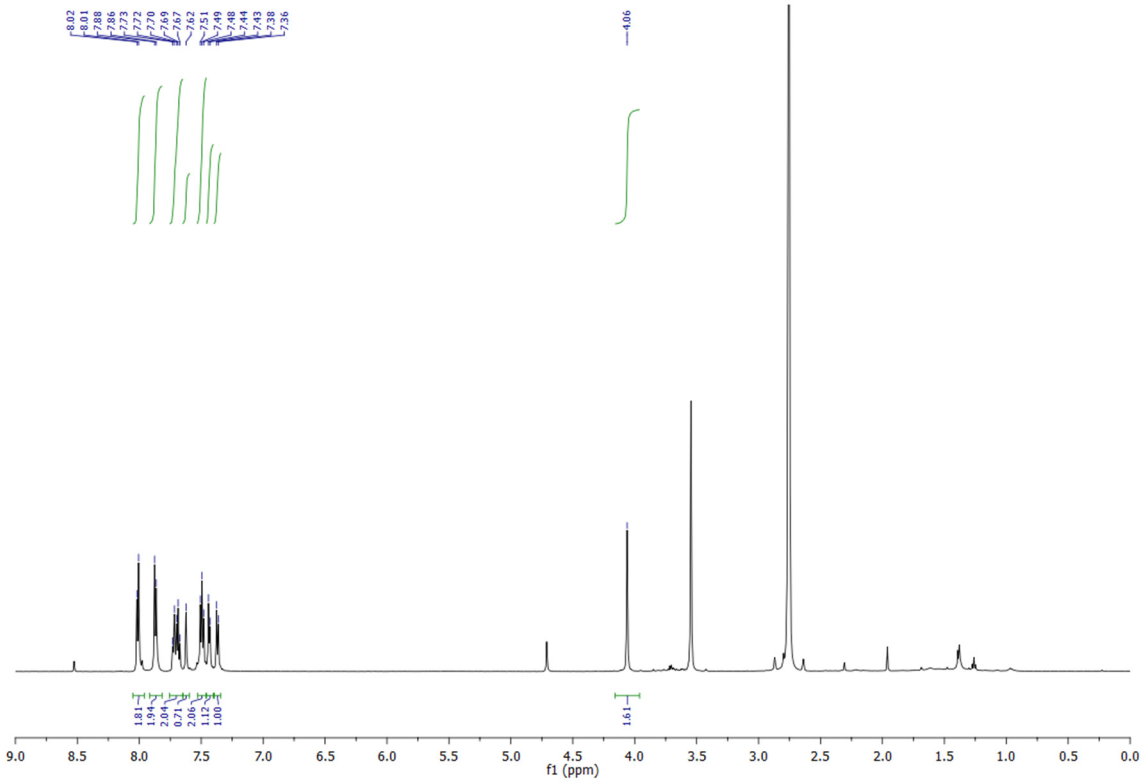
Compound 6d. ^{1}H NMR (400 MHz, acetone-d_6)



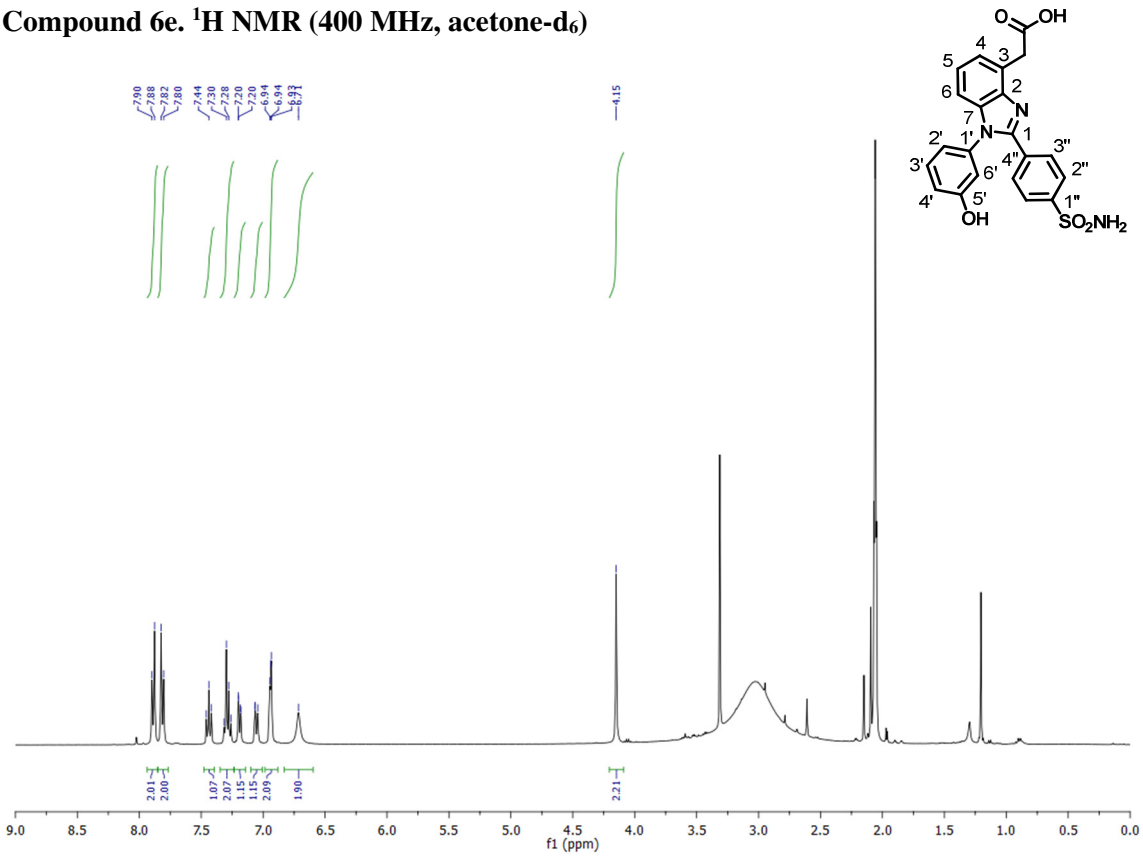
Compound 6d. ^{13}C NMR (100 MHz, acetone-d_6)



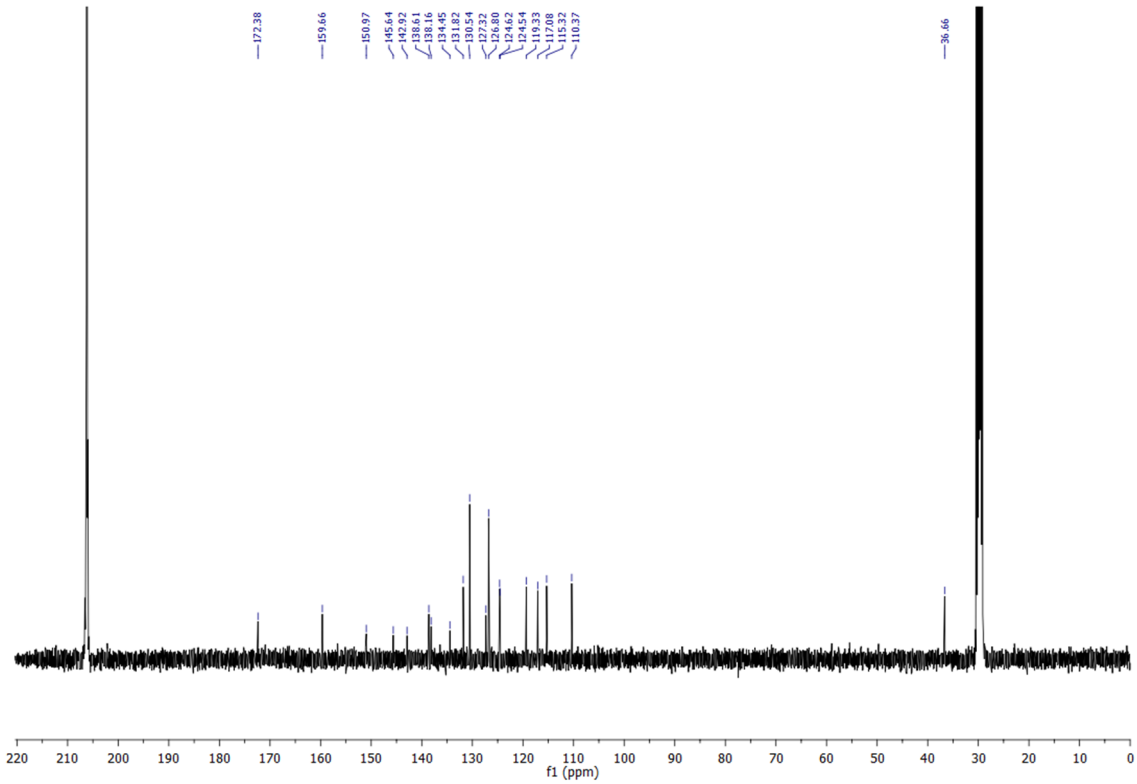
Compound 6d. ^{1}H NMR (600 MHz, D_2O)



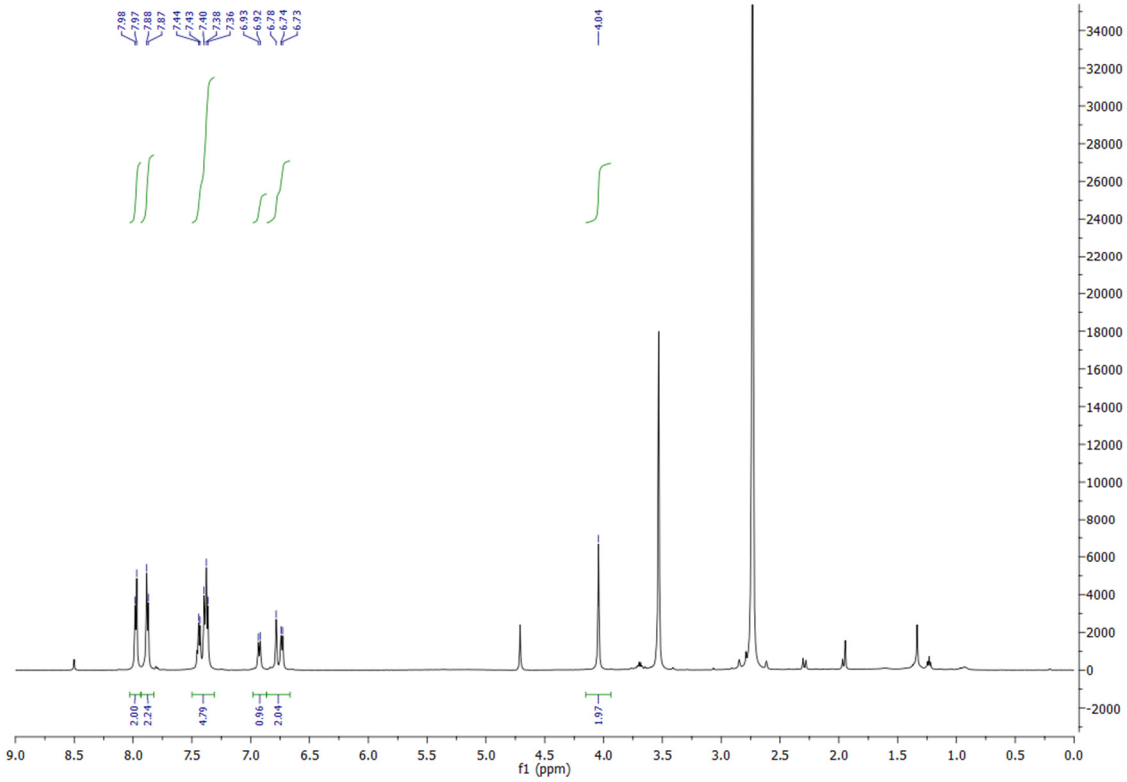
Compound 6e. ^{1}H NMR (400 MHz, acetone-d$_6$)



Compound 6e. ^{13}C NMR (400 MHz, acetone-d$_6$)

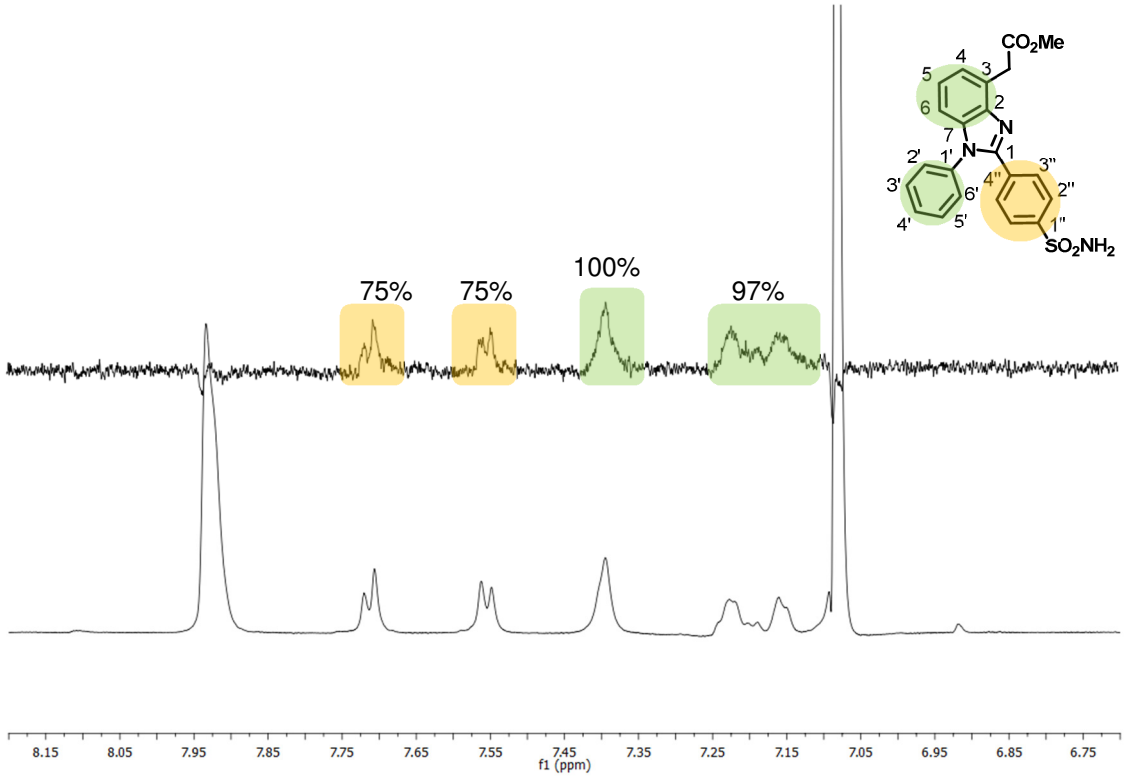


Compound 6e. ^{1}H NMR (600 MHz, D_2O)

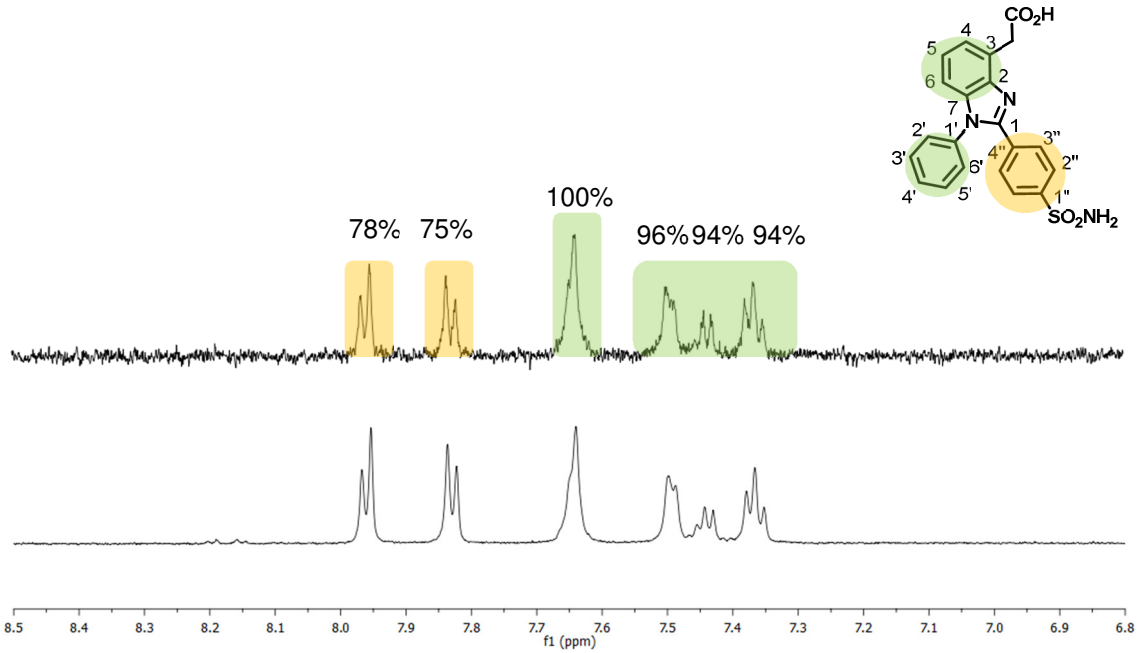


3. STD NMR spectra of compounds 5a and 6a-e

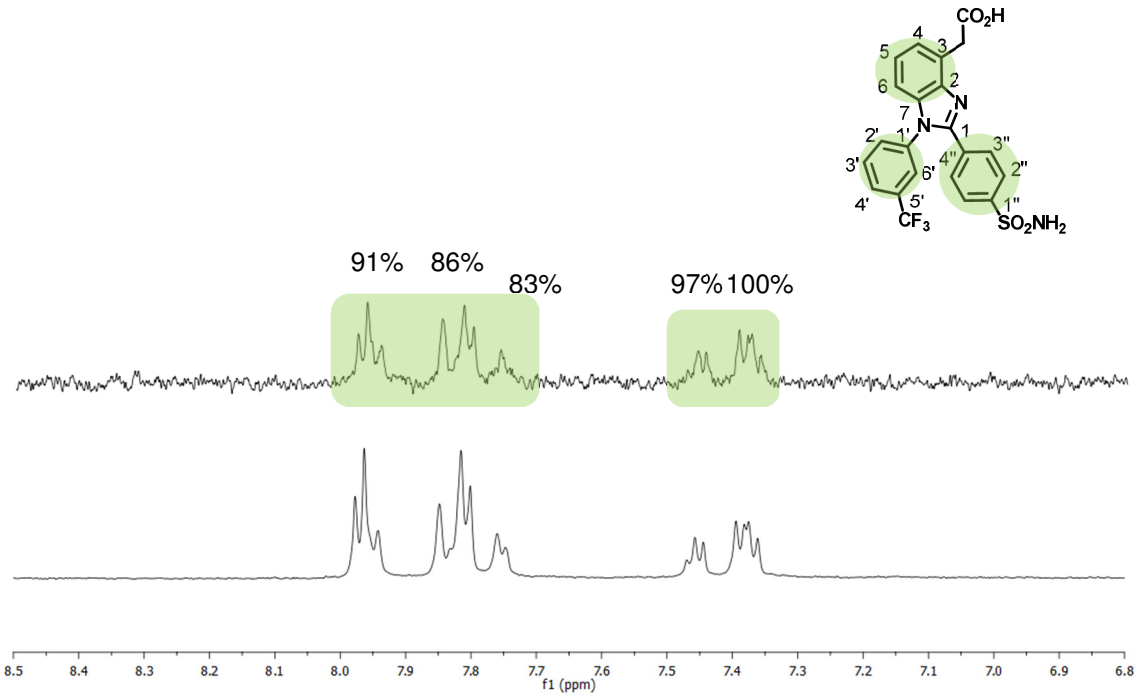
Compound 5a. STD NMR (600 MHz, D_2O), performed with hCOX-2 (1.15 mM)



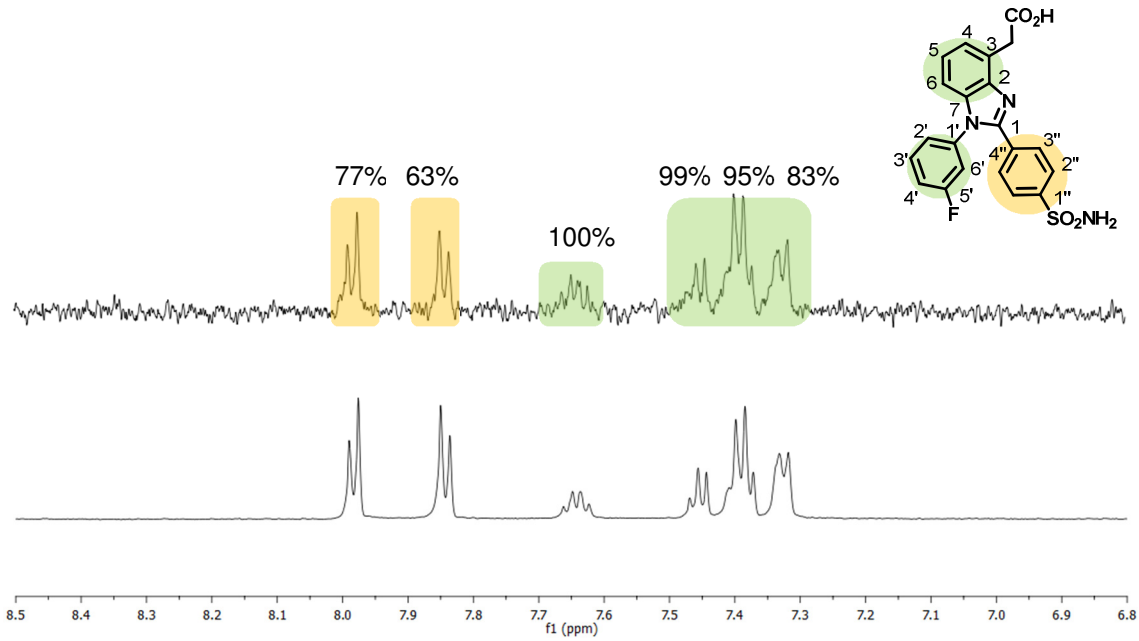
Compound 6a. STD NMR (600 MHz, D_2O), performed with oCOX-2 (3 mM)



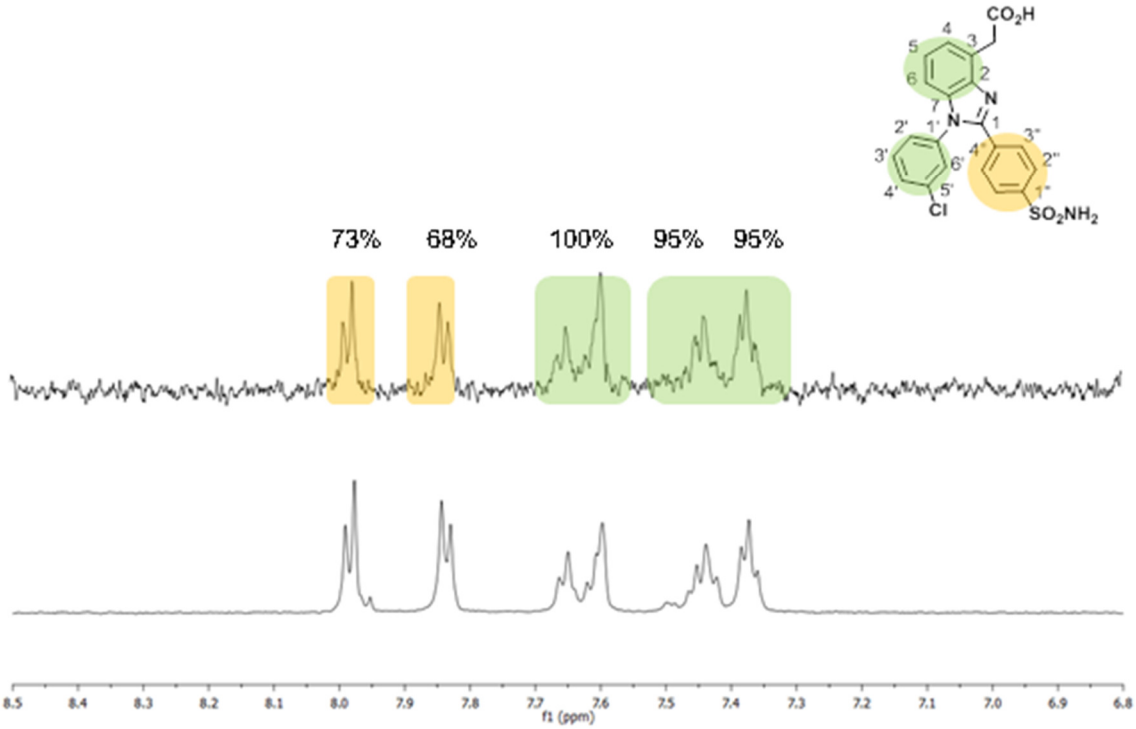
Compound 6b. STD NMR (600 MHz, D_2O), performed with oCOX-2 (3 mM)



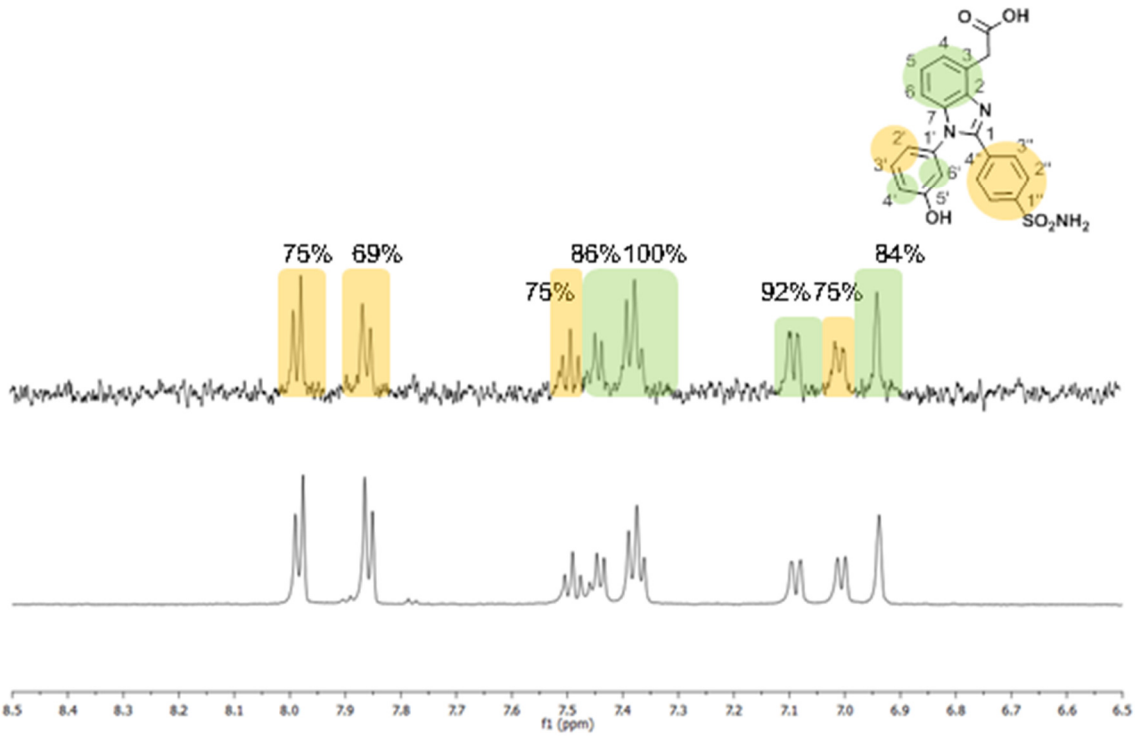
Compound 6c. STD NMR (600 MHz, D_2O), performed with oCOX-2 (3 mM)



Compound 6d. STD NMR (600 MHz, D_2O), performed with oCOX-2 (3 mM)



Compound 6e. STD NMR (600 MHz, D_2O), performed with oCOX-2 (3 mM)



Best docked conformers, energies in kcal/mol.

Compound	COX-1 2AYL	COX-2 3PGH
5a	-11.50	-12.27
5b	-11.86	-12.55
5c	-11.33	-11.96
5d	-12.13	-12.48
5e	-12.29	-12.48
6a	-11.73	-12.65
6b	-11.92	-12.68
6c	-11.52	-12.50
6d	-12.29	-12.87
6e	-11.75	-12.87
Celecoxib	-8.07	-10.41
Indomethacin	-9.33	-10.73
parent-comp*	-10.72	-10.76

*parent compound has a hydrogen on C4 of the the benzimidazole.