Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of amides directly from carboxylic acids and hydrazines

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Section S1. Observations from investigation on Beddomeilactone (BML).

Beddomeilactone (BML) is a triterpenoid, scaled-up (5gm) from barks of *Dysoxylum malabaricum,* during our efforts on medicinal chemistry of BML to synthesize its derivatives, present synthetic method was discovered. One of the targeted modifications was the conversion of ketone group into indole by Fisher indole synthesis using different phenylhydrazines, for which we used phenylhydrazine in presence of $ZnCl_2$ with acetic acid. Reaction produced a complex mixture as observed on TLC. When we analyzed this crude by LCMS (direct infusion) we didn't notice the peak of desired indole derivative. Three major peaks m/z: 136 (100%), 485 (100%), and 560 (10%) noticed in ESI-positive. Furthermore, the purification of the reaction mixture; recovered unreacted BML and unexpectedly N-phenylacetamide obtained as major product. Here, we assumed that m/z 135 and 560 belongs to the amides of acetic acid and BML. This unexpected result was then implemented to establish a facile methodology for synthesis amides, directly from carboxylic acid and hydrazine as amine partners in presence of Zinc chloride.

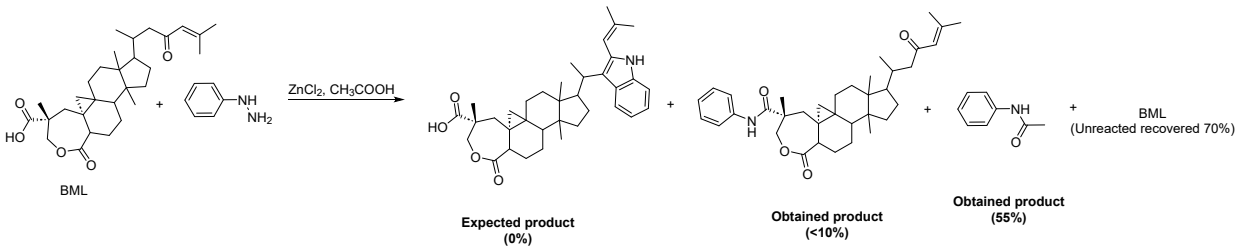
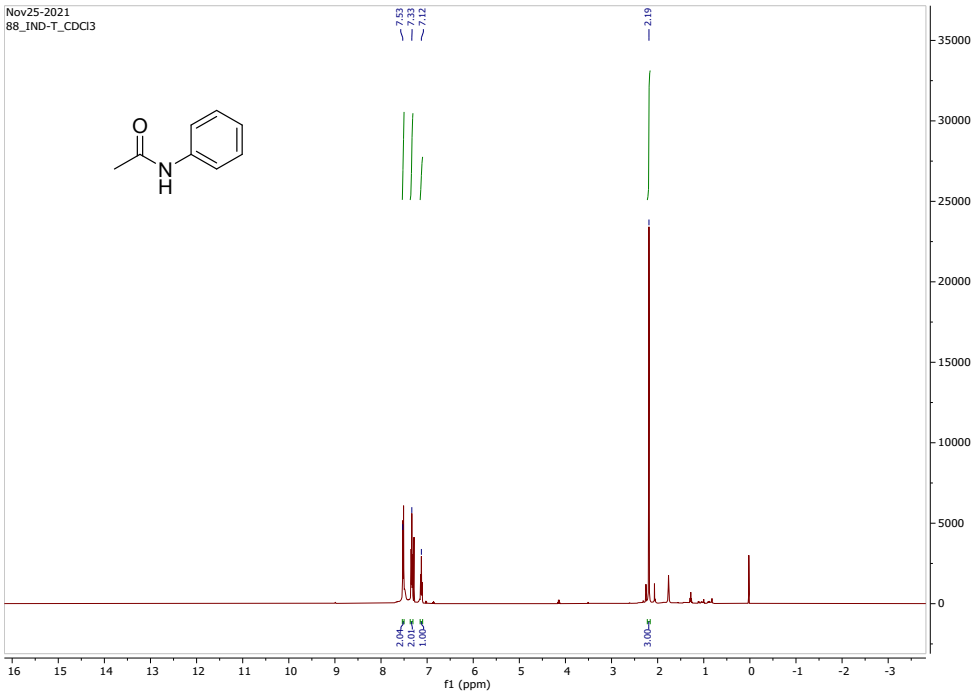


Figure S1. Observation from the BML derivatization.

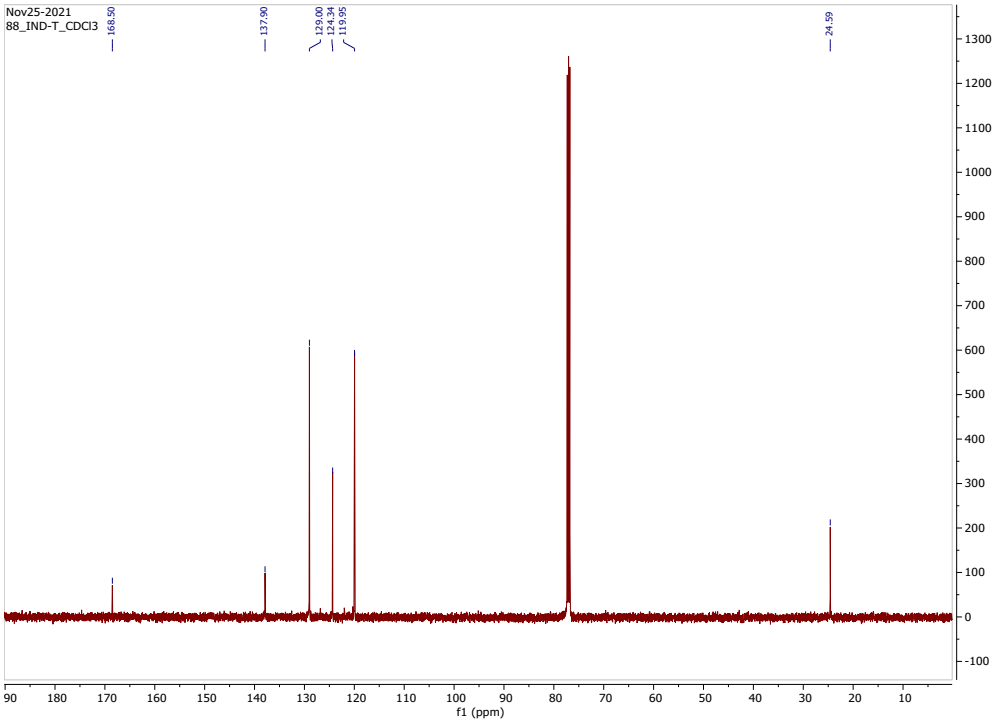
Section 2: Experimental section and spectroscopic data of synthesized compounds

NMR and mass data of compounds 1c to 30c

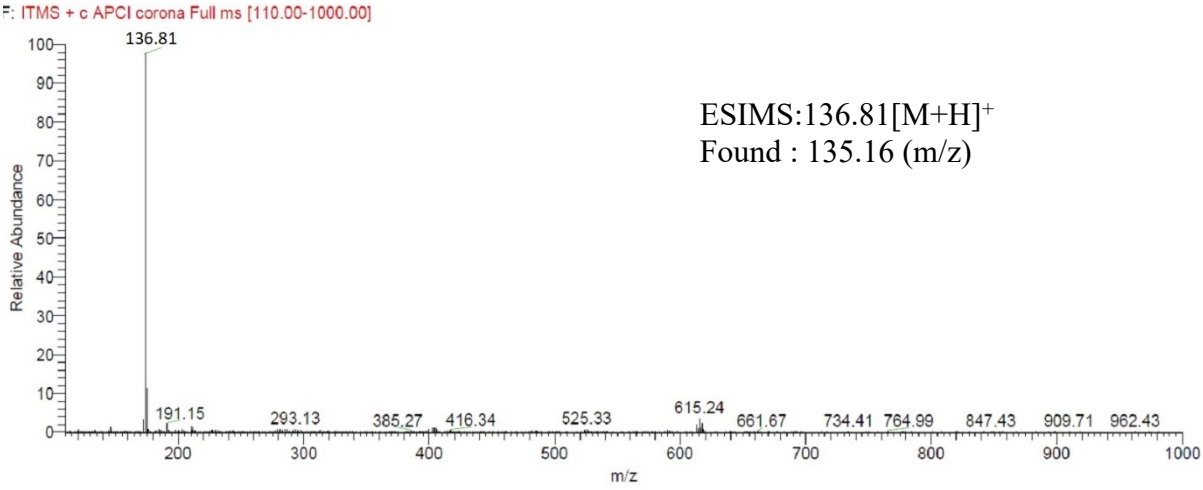
^{1}H-NMR spectrum of N-phenylacetamide (1c):



^{13}C-NMR spectrum of N-phenylacetamide (1c)

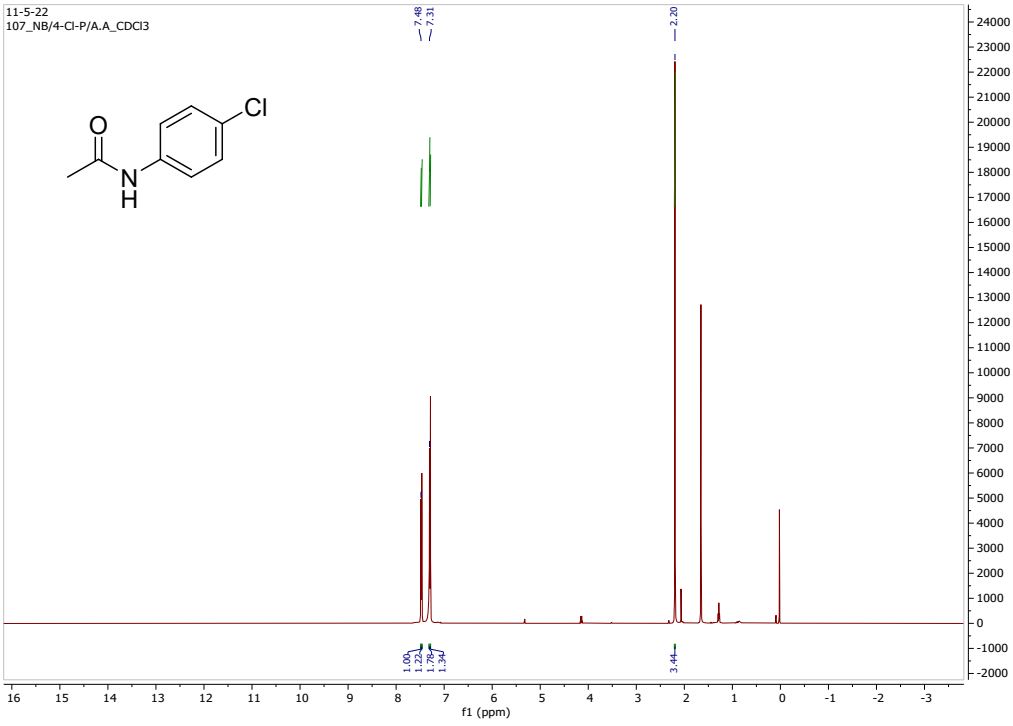


Mass of N-phenylacetamide (1c)

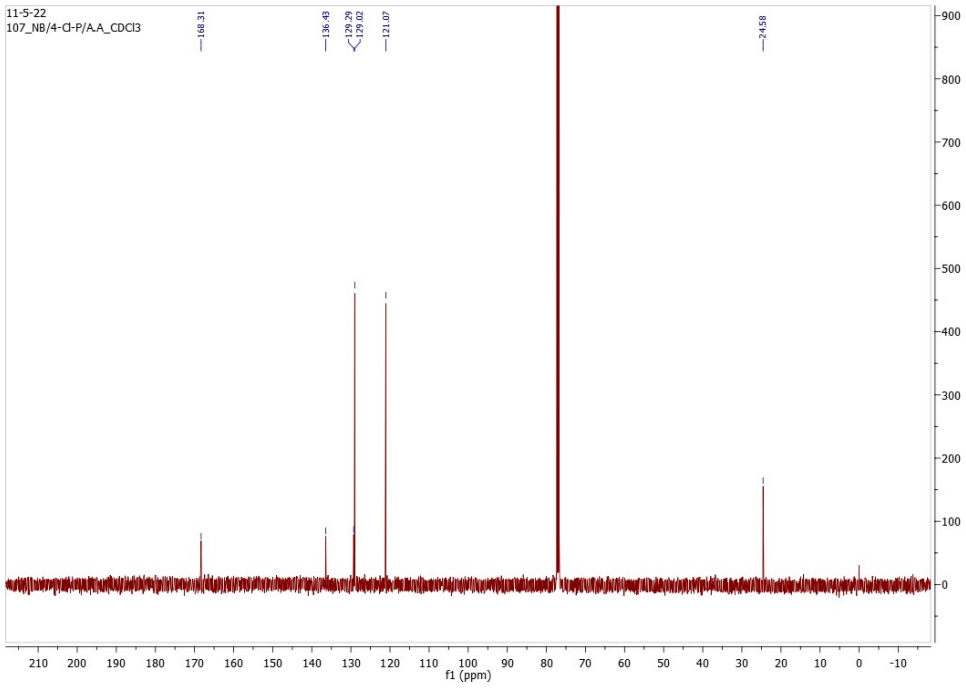


ESIMS:136.81$[M+H]^+$
Found : 135.16 (m/z)

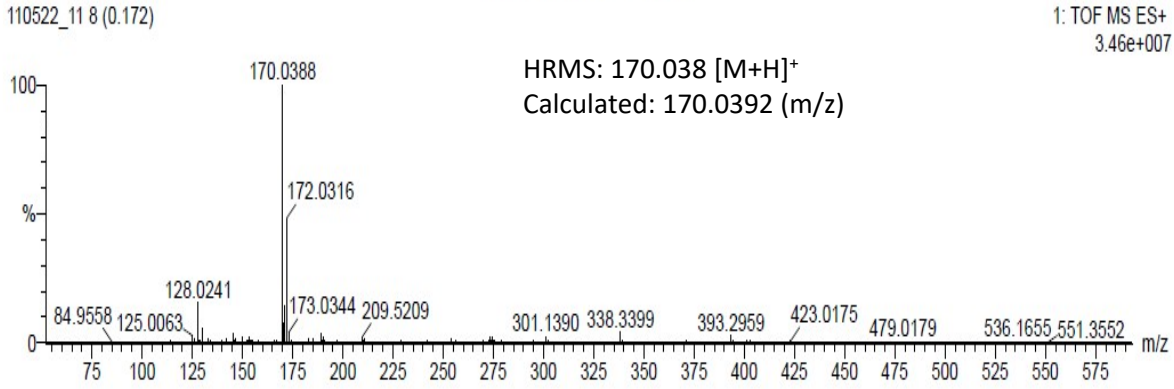
^{1}H-NMR spectrum of N-(4-chlorophenyl)acetamide (2c)



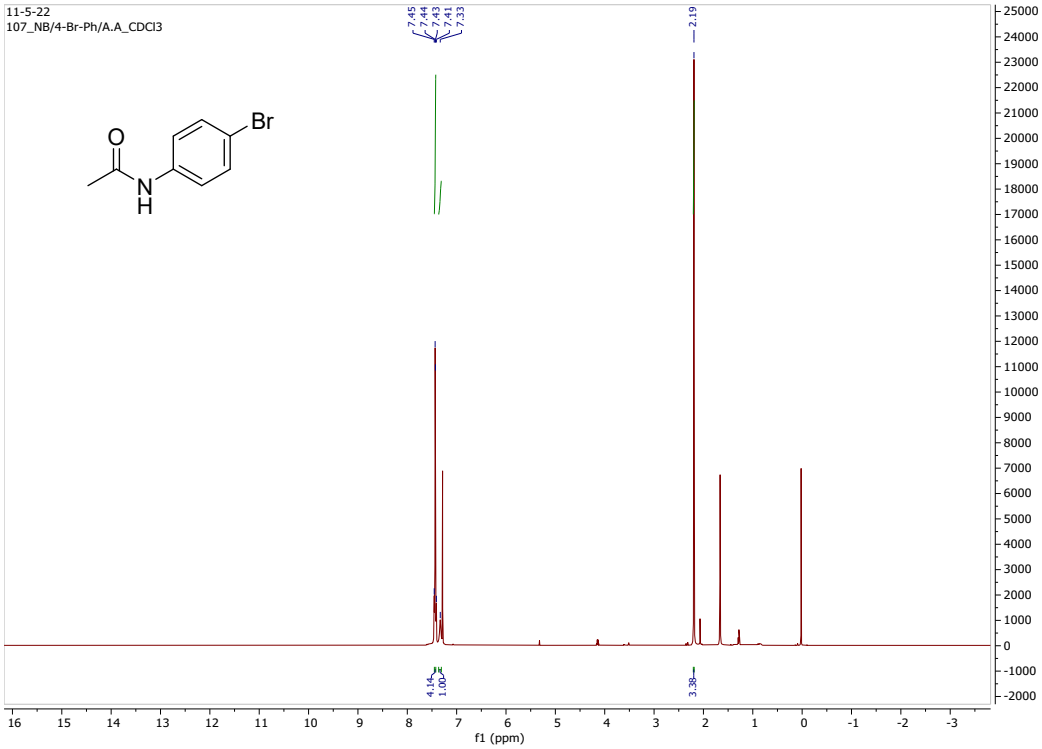
^{13}C NMR spectrum of N-(4-chlorophenyl) acetamide(2c)



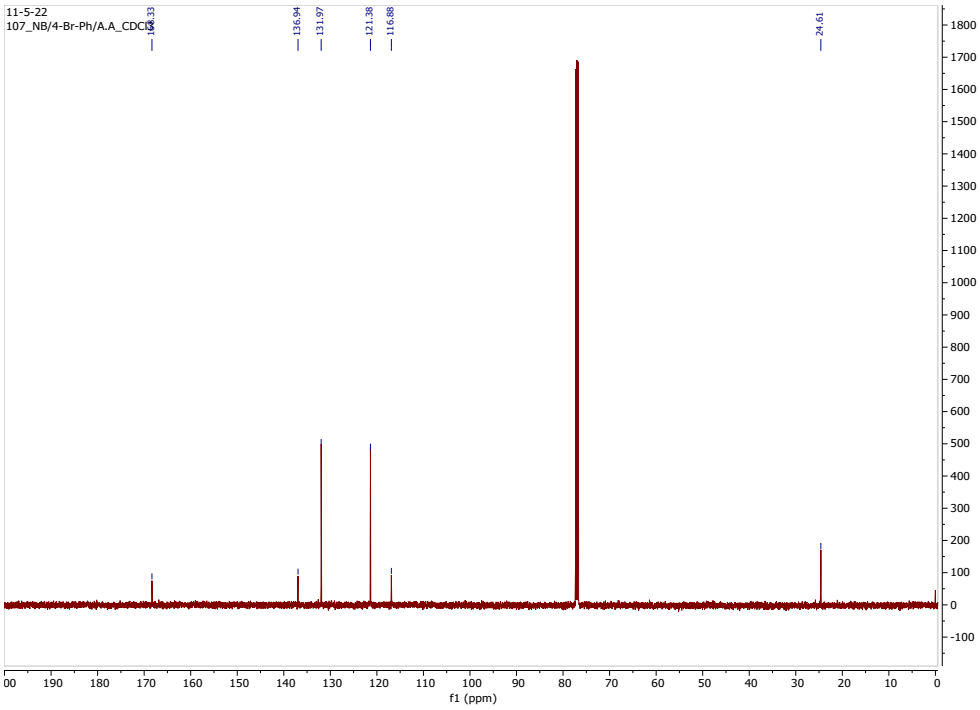
HRMS spectrum of N-(4-chlorophenyl)acetamide (2c)



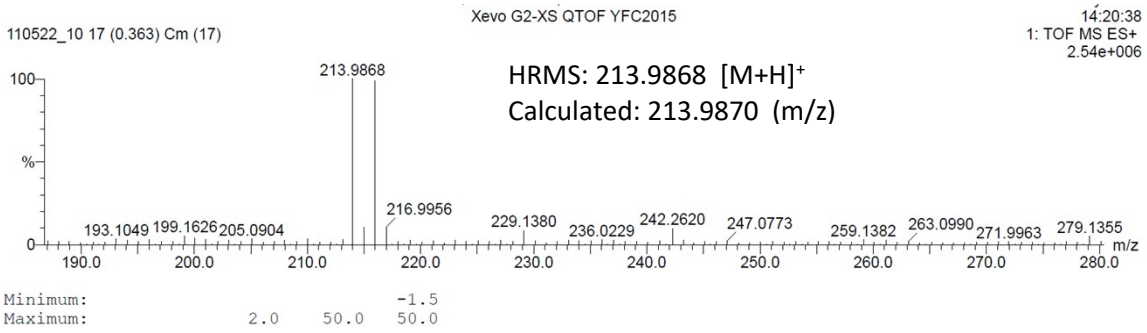
[1] H NMR spectrum of N-(4-bromophenyl)acetamide (3c)



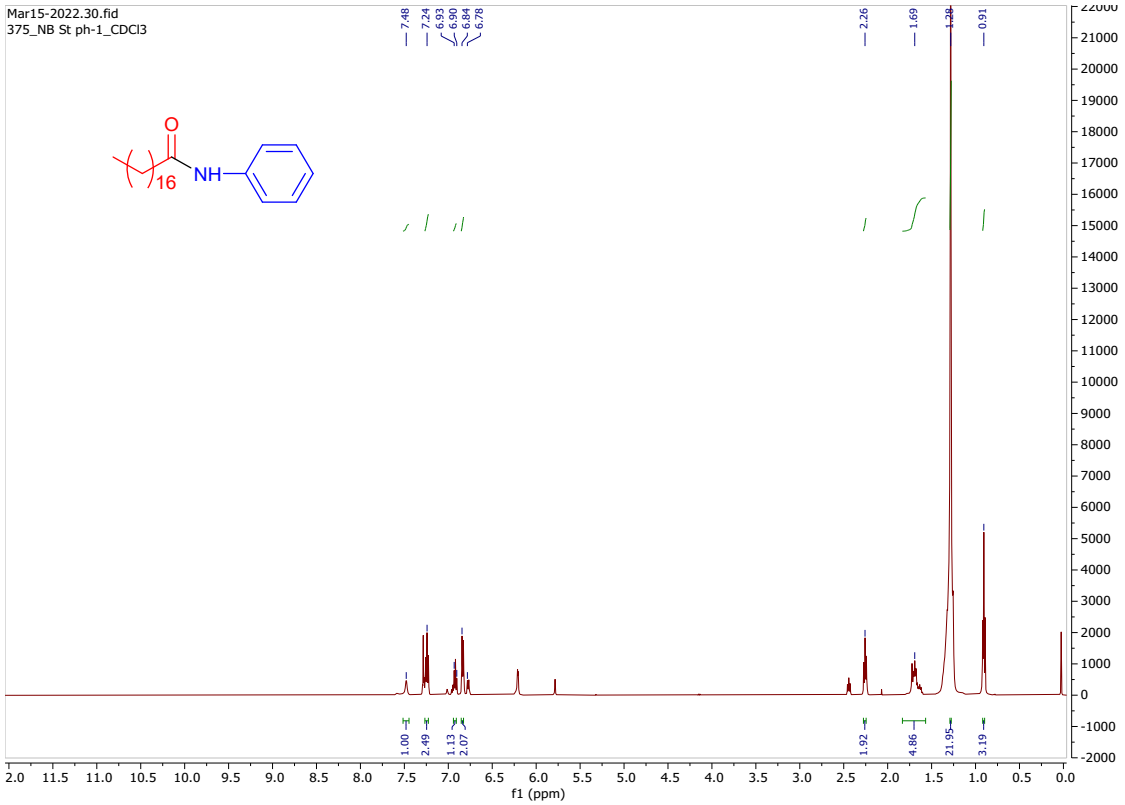
[13]C-NMR spectrum of N-(4-bromophenyl)acetamide (3c)



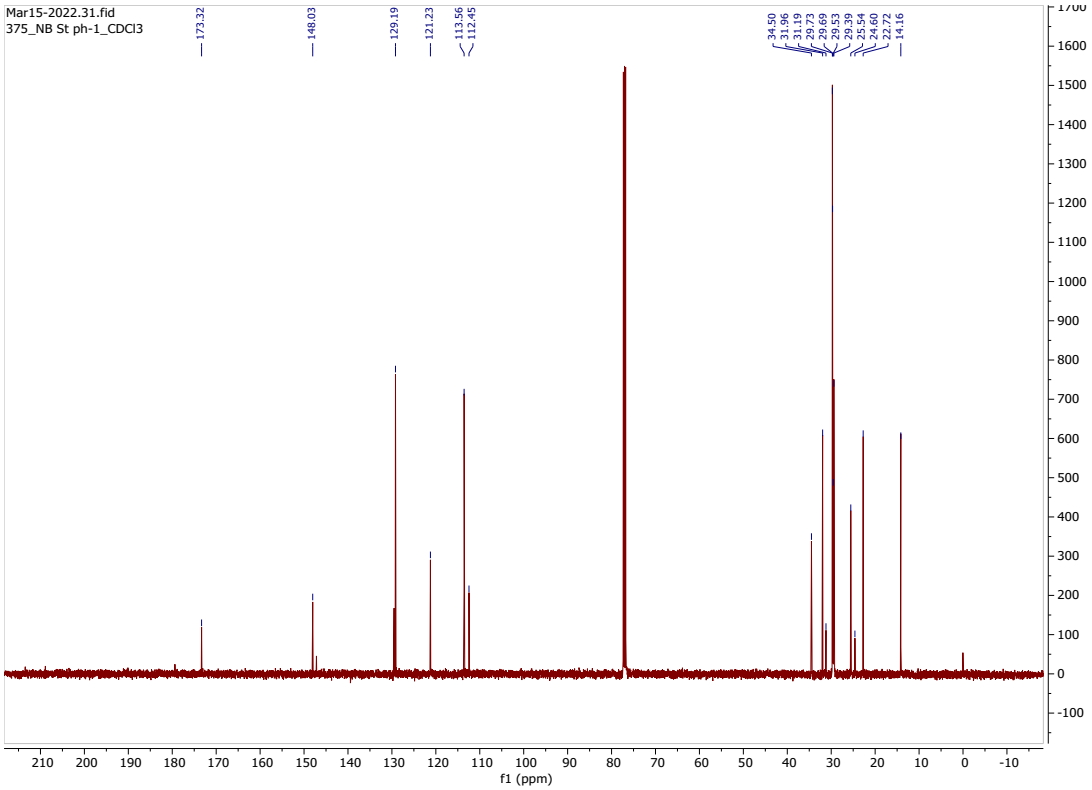
HRMS spectrum of N-(4-bromophenyl)acetamide (3c)



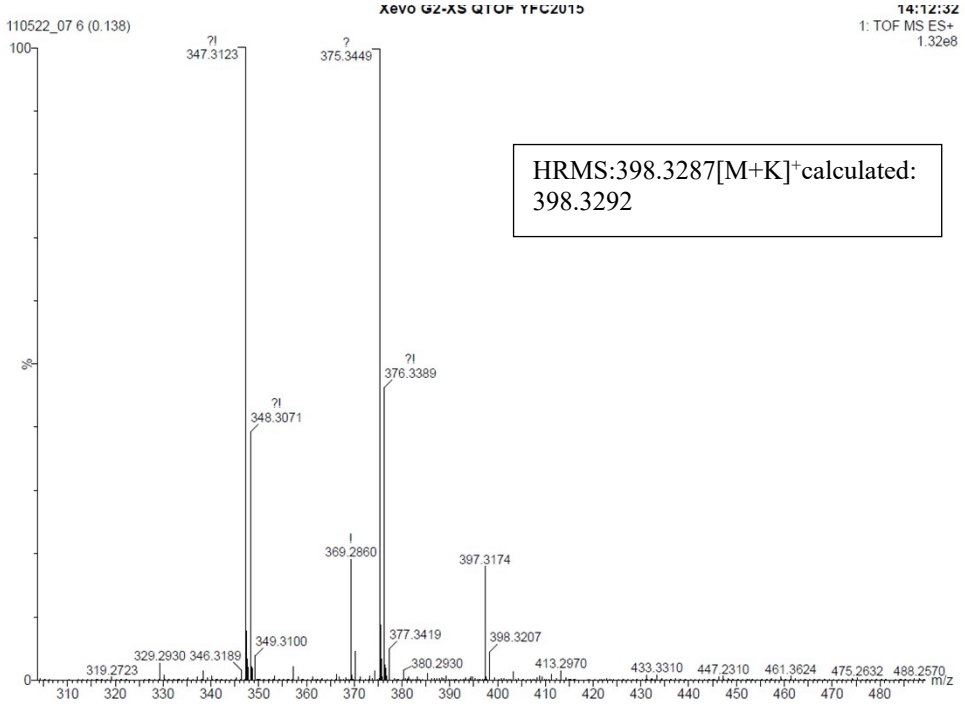
^{1}H-NMR spectrum of (N-phenylstearamide) (4c)



^{13}C-NMR spectrum of (N-phenylstearamide) (4c)

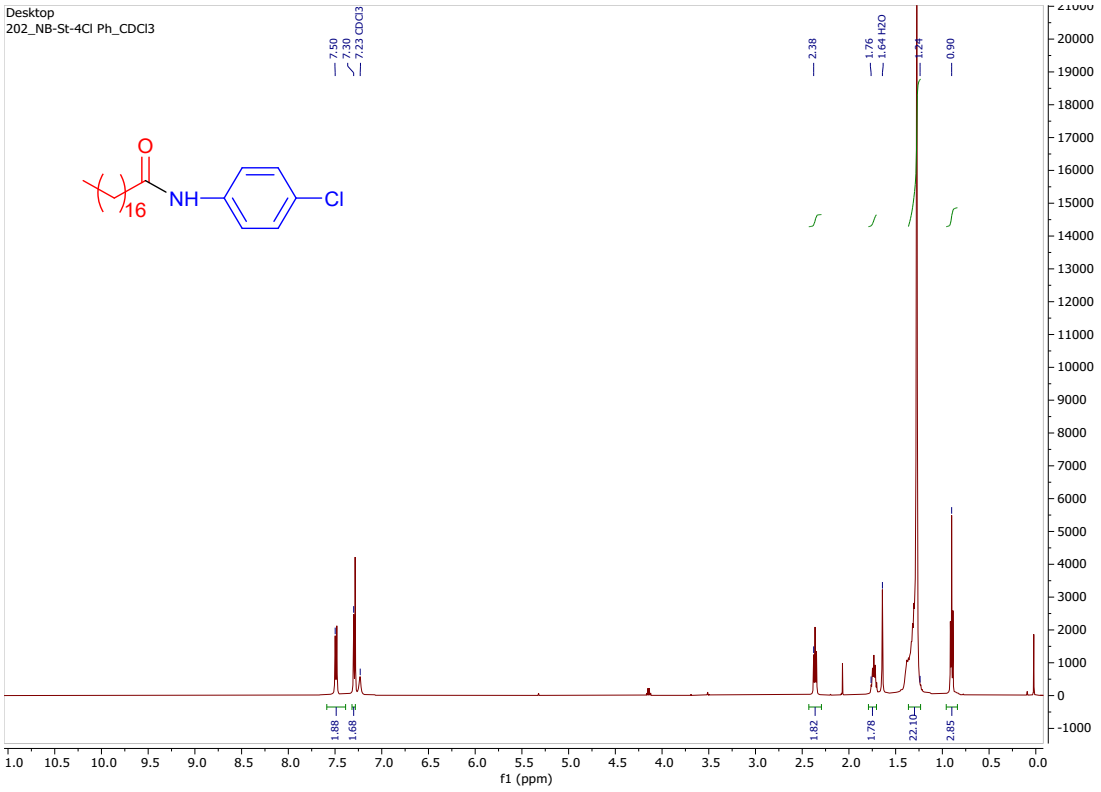


HRMS spectrum of (N-phenylstearamide) (4c)

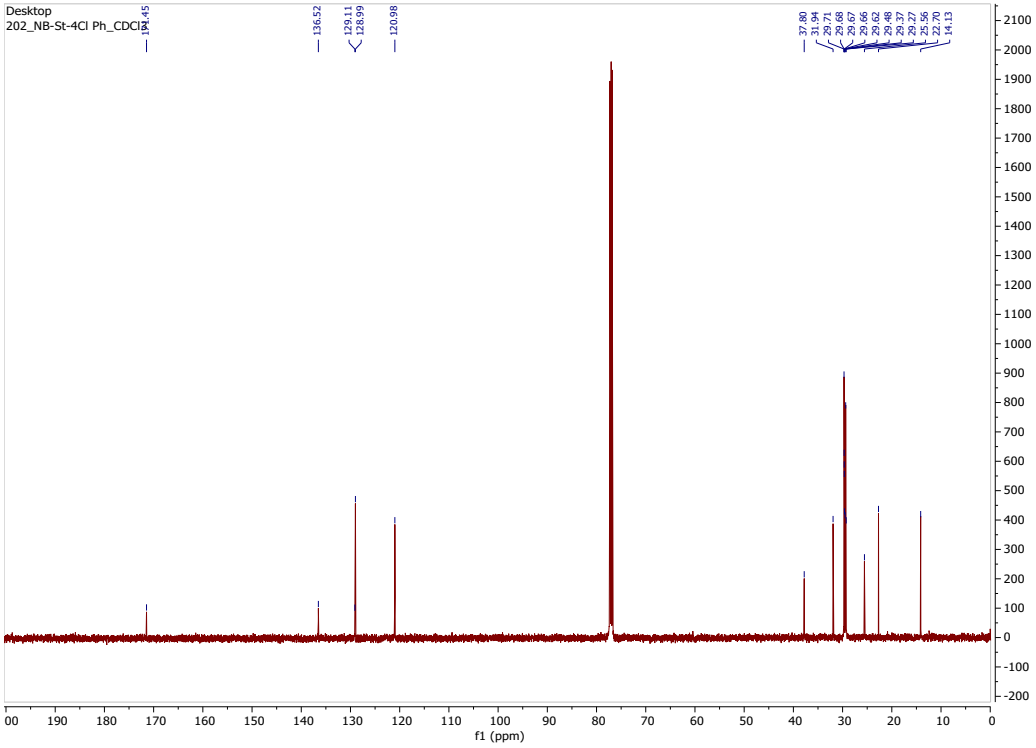


HRMS:398.3287[M+K]$^{+}$calculated: 398.3292

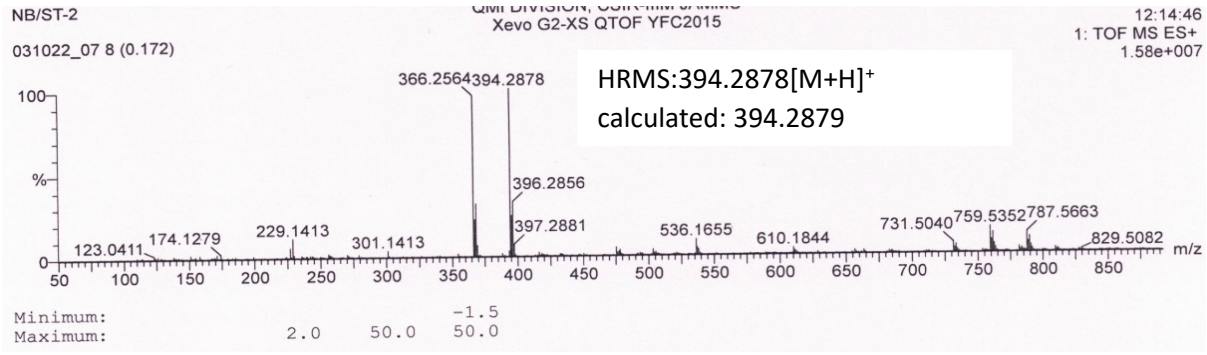
^{1}H-NMR spectrum of N-(4-chlorophenyl)stearamide (5c)



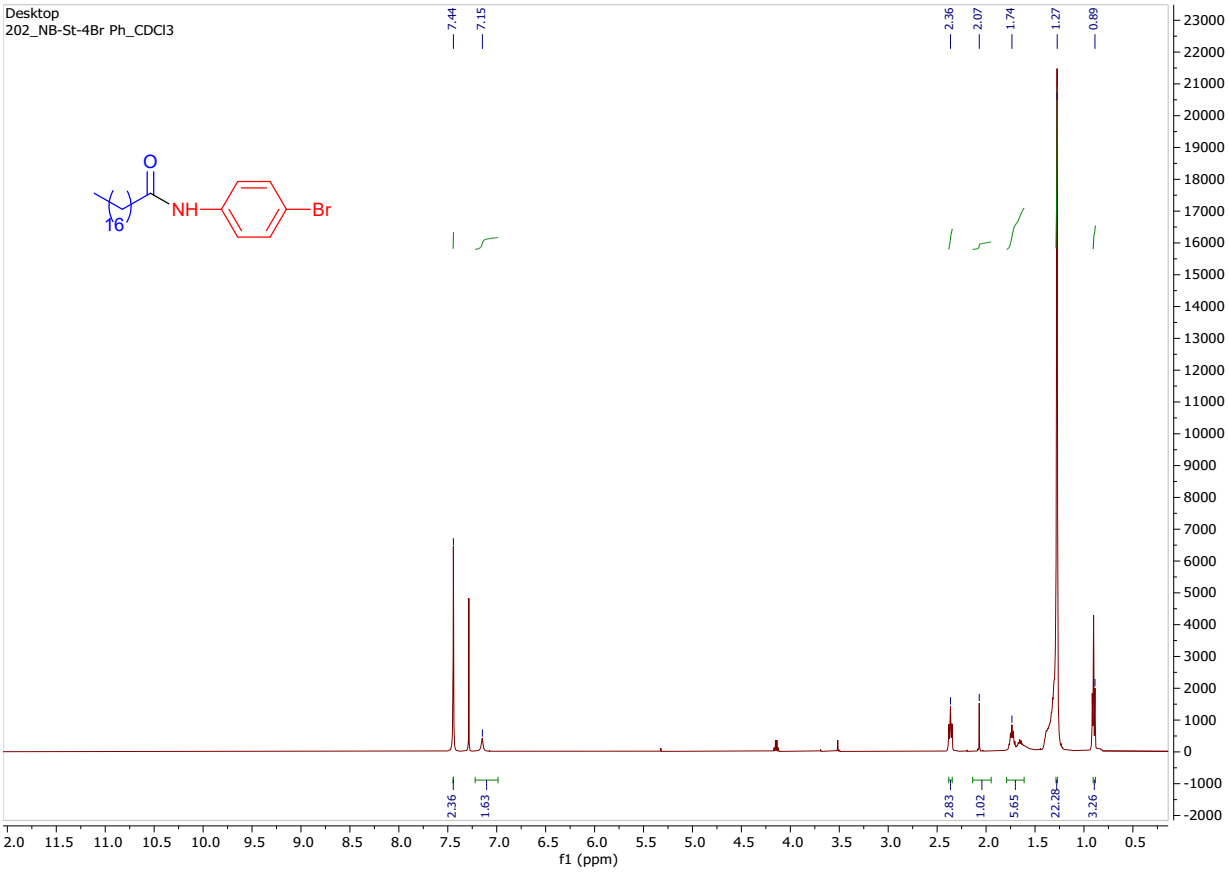
^{13}C-NMR spectrum of N-(4-chlorophenyl)stearamide (5c)



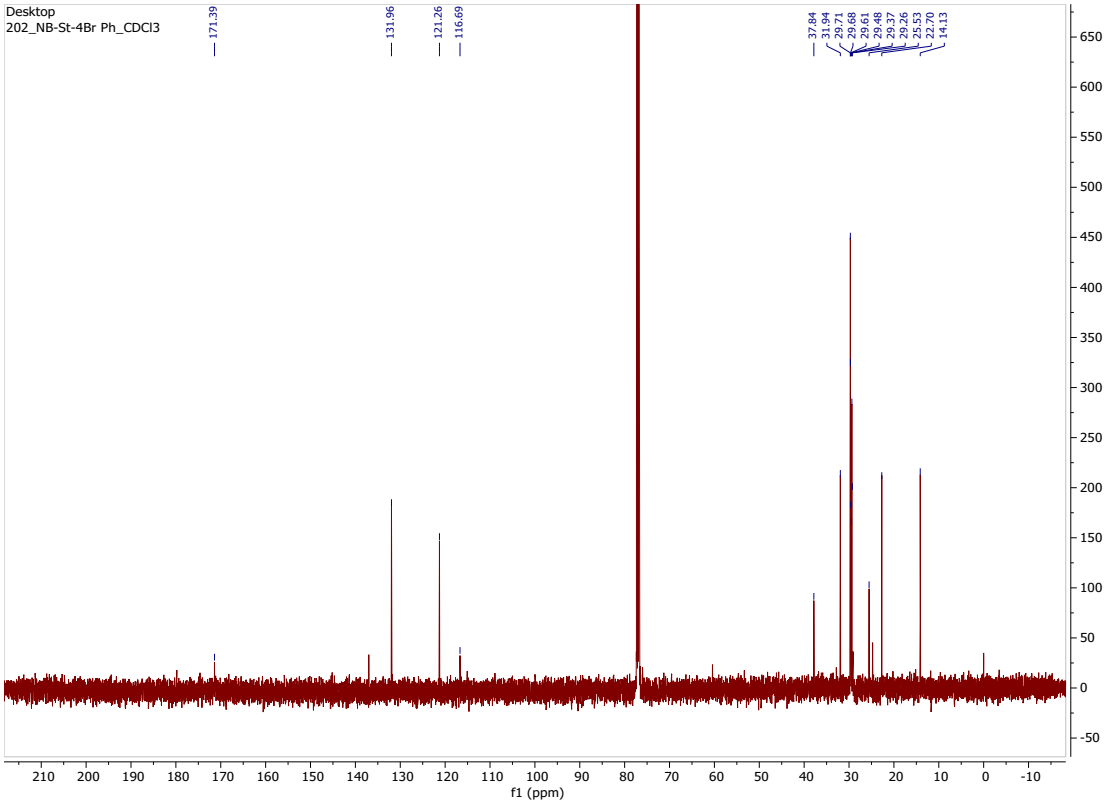
HRMS spectrum of compound (N-(4-chlorophenyl)stearamide) (5c)



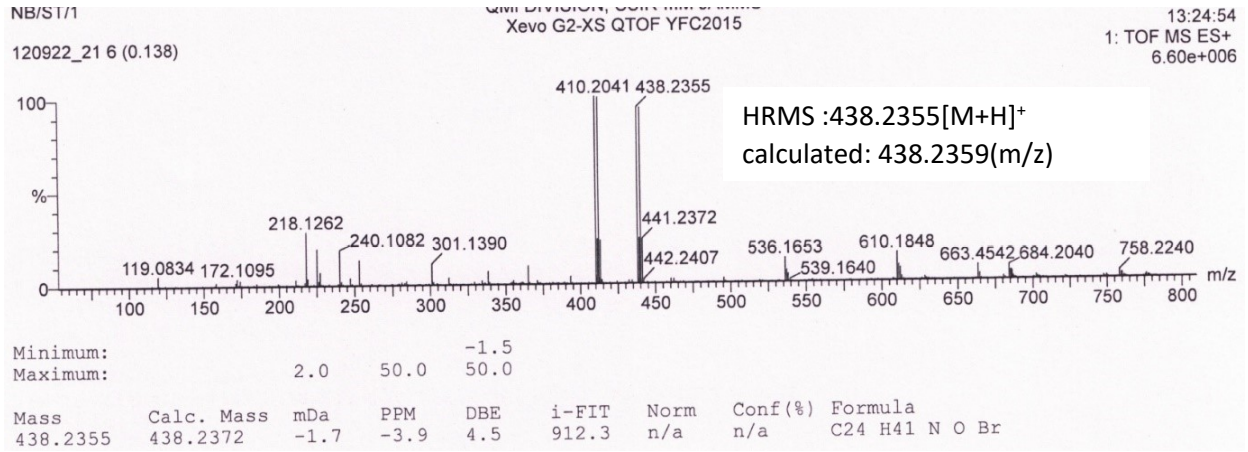
^{1}H-NMR spectrum of N-(4-bromophenyl)stearamide (6c)



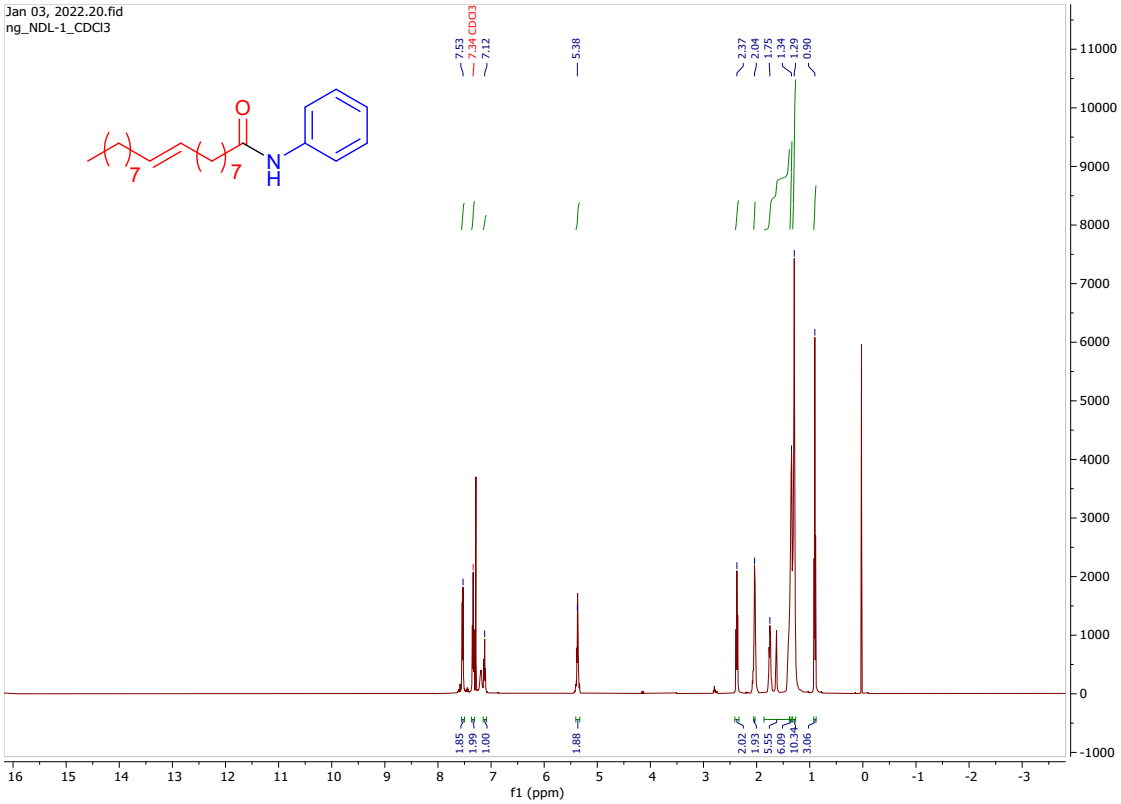
^{13}C-NMR spectrum of N-(4-bromophenyl)stearamide (6c)



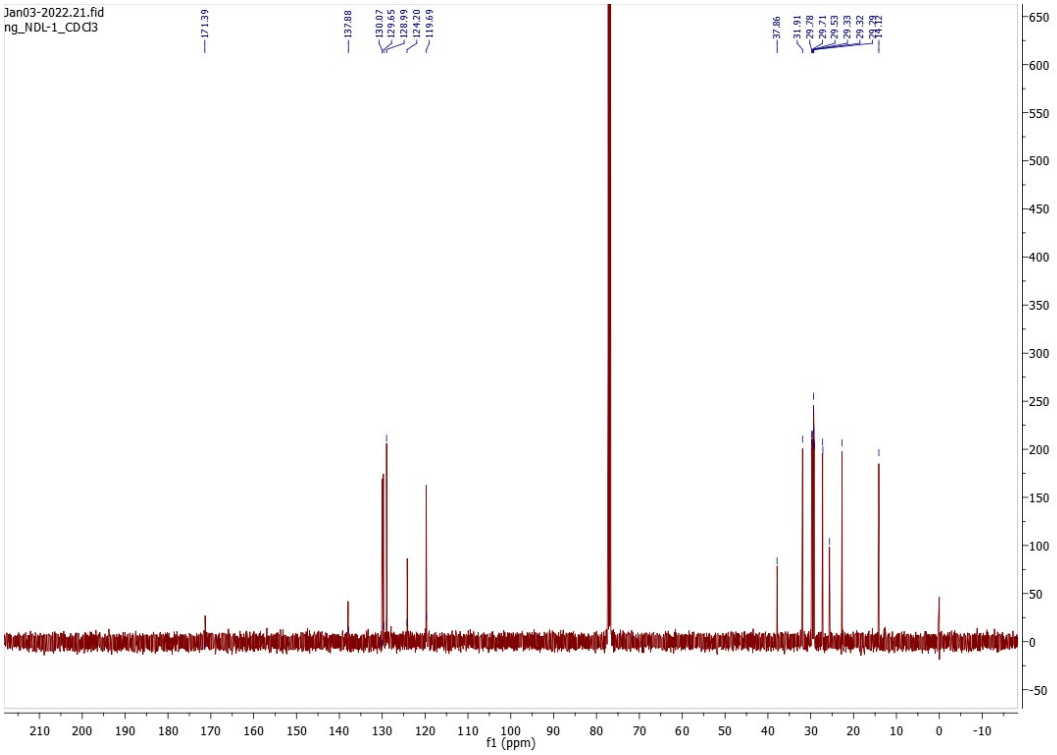
HRMS spectrum of N-(4-bromophenyl)stearamide(6c)



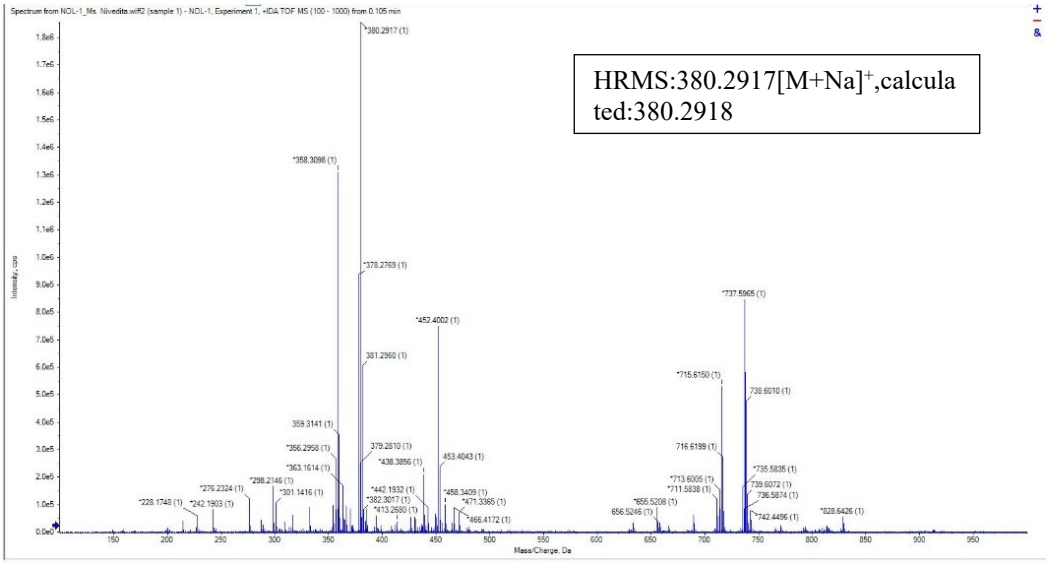
[1] H-NMR spectrum of N-phenyloleamide (7c)



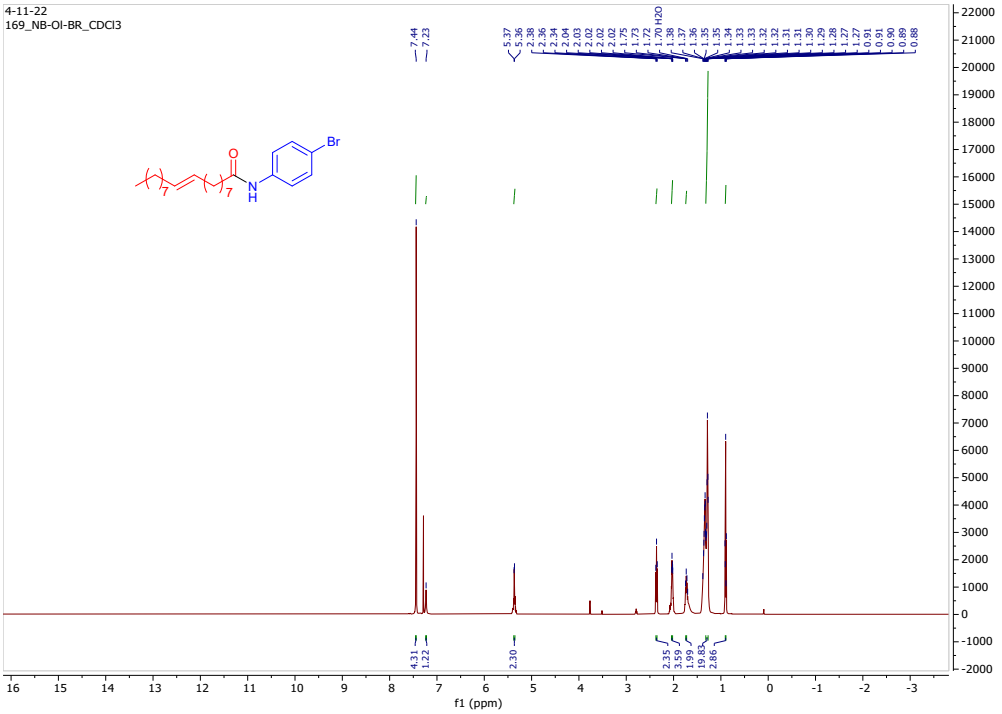
[13]C-NMR spectrum of N-phenyloleamide (7c)



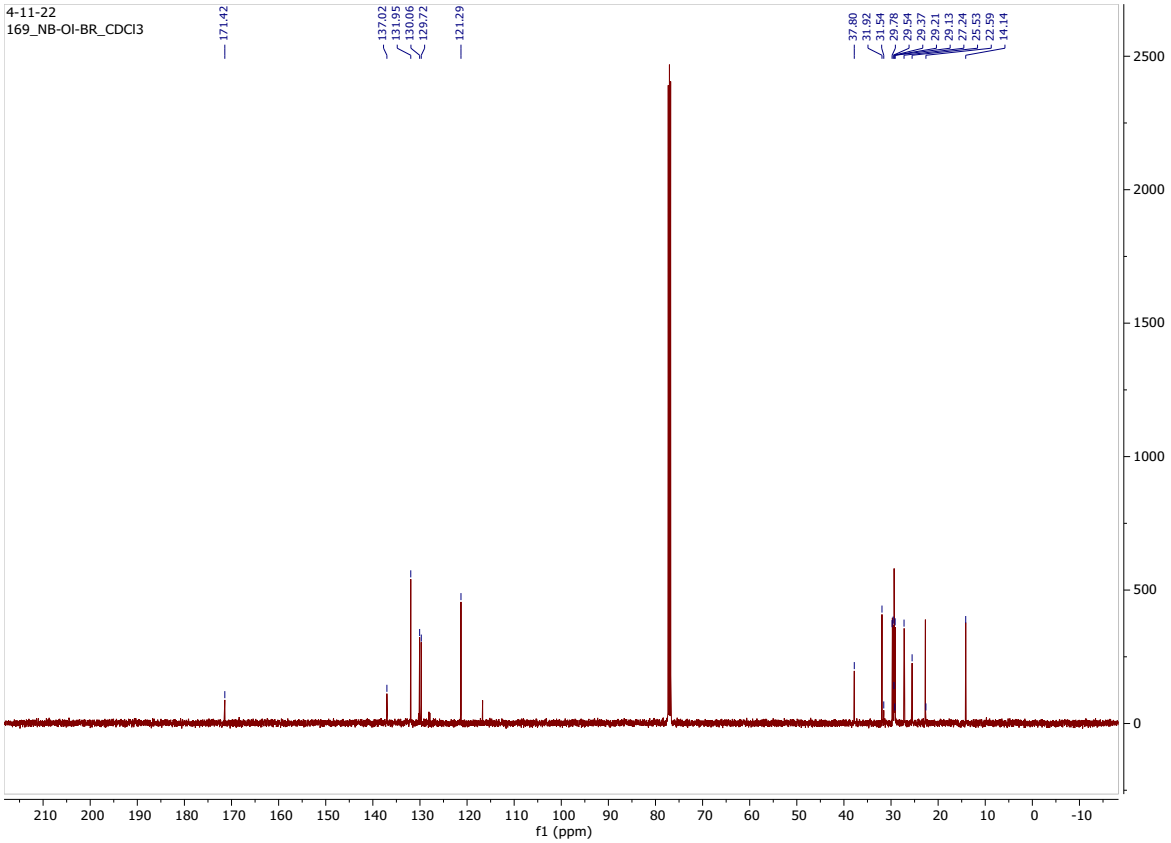
HRMS spectrum of N-phenyloleamide (7c)



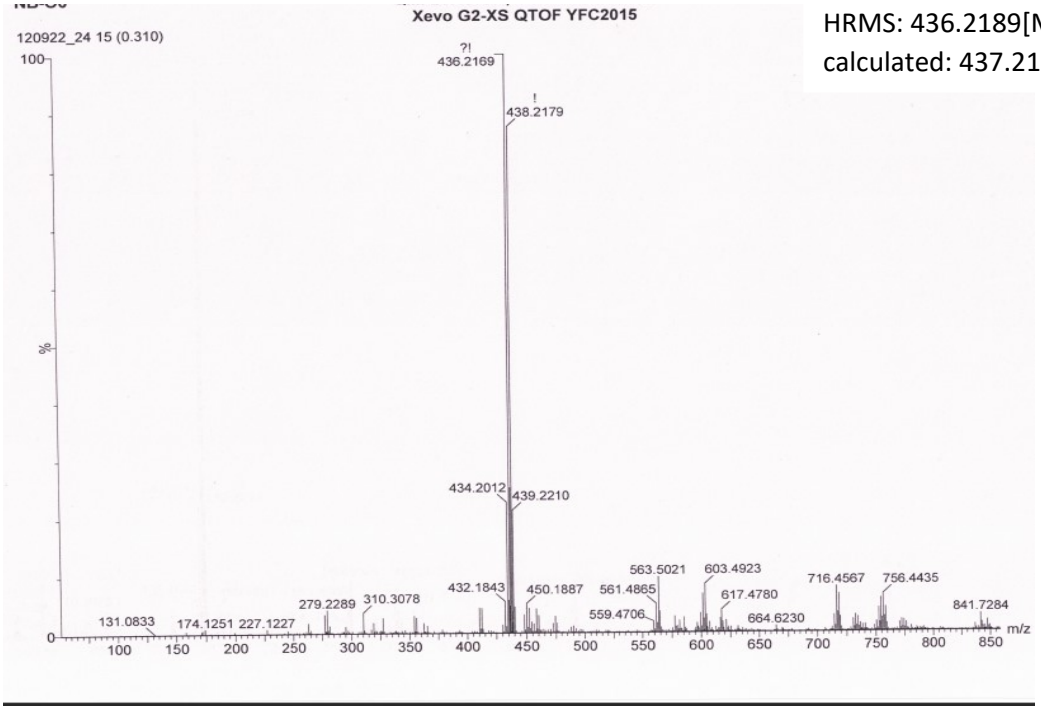
^{1}H-NMR spectrum of N-(4-bromophenyl)oleamide (8c)



^{13}C-NMR spectrum of N-(4-bromophenyl)oleamide (8c)

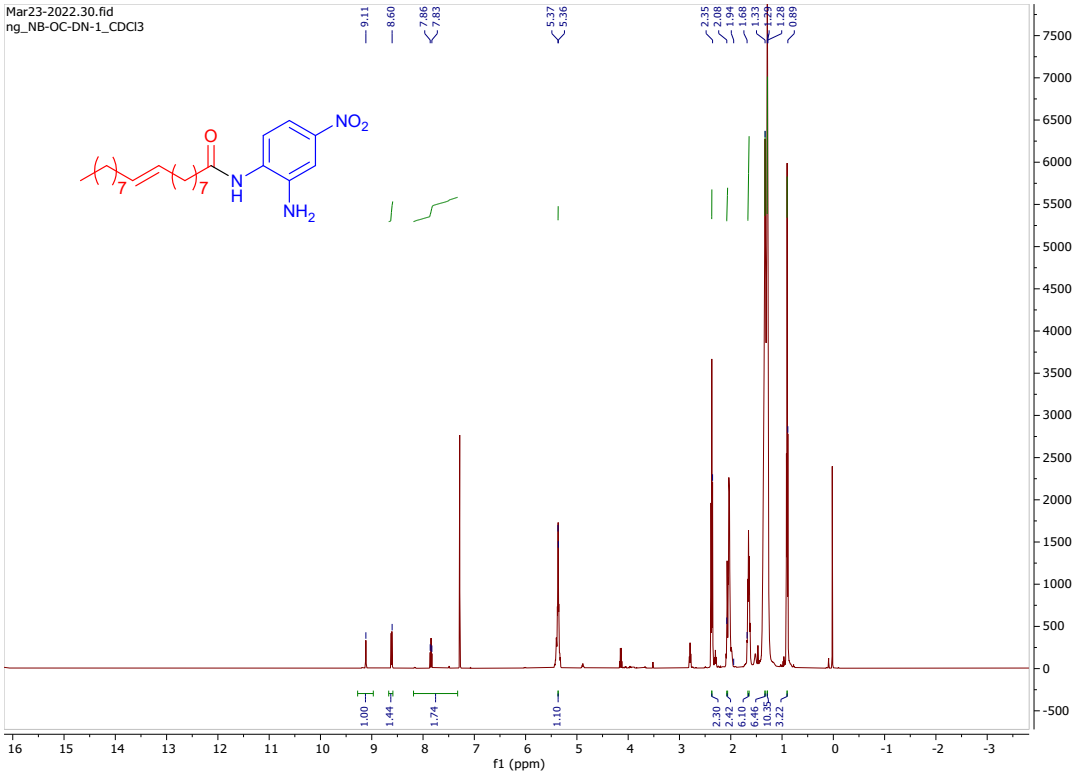


HRMS spectrum of N-(4-bromophenyl)oleamide (8c)

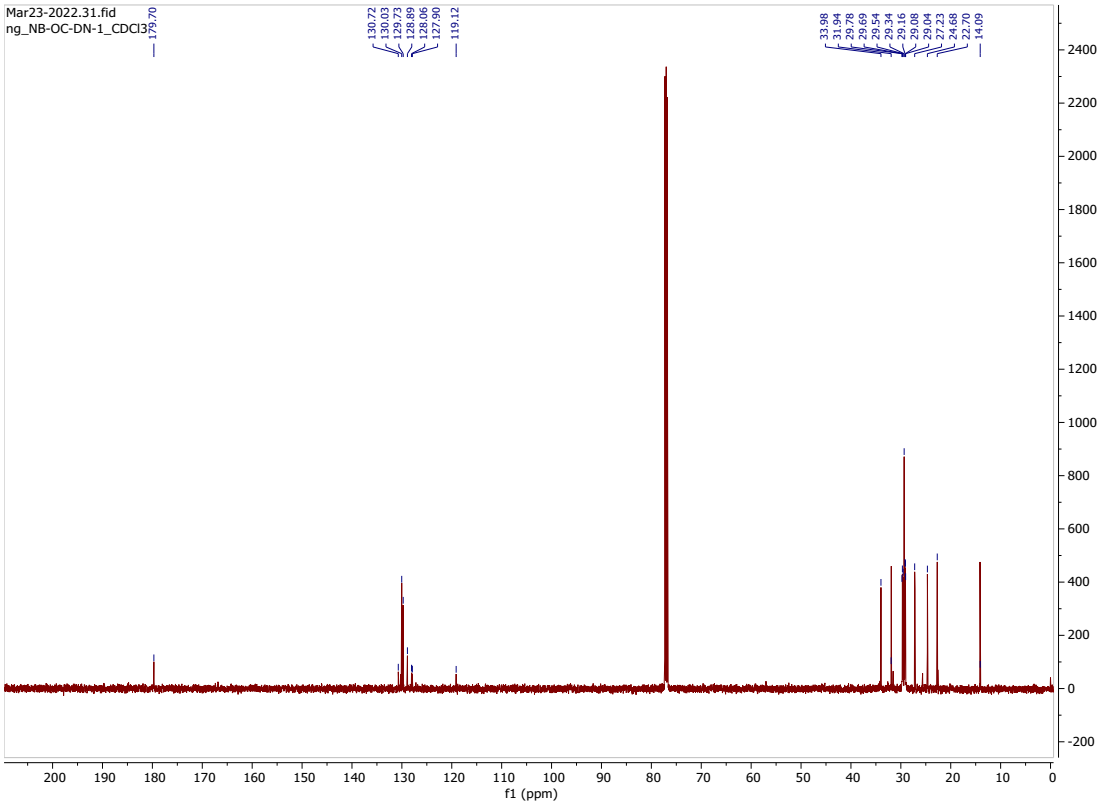


HRMS: 436.2189[M+H]$^{+}$
calculated: 437.2192

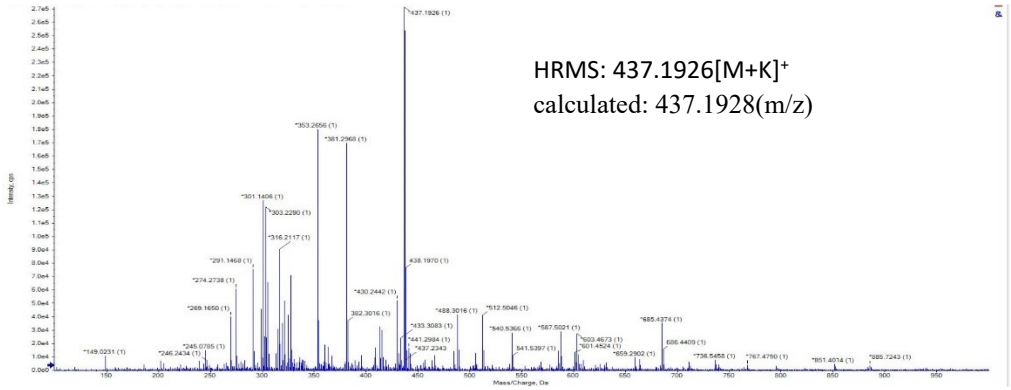
^{1}H-NMR spectrum of N-(2-amino-4-nitrophenyl)oleomide (9c)



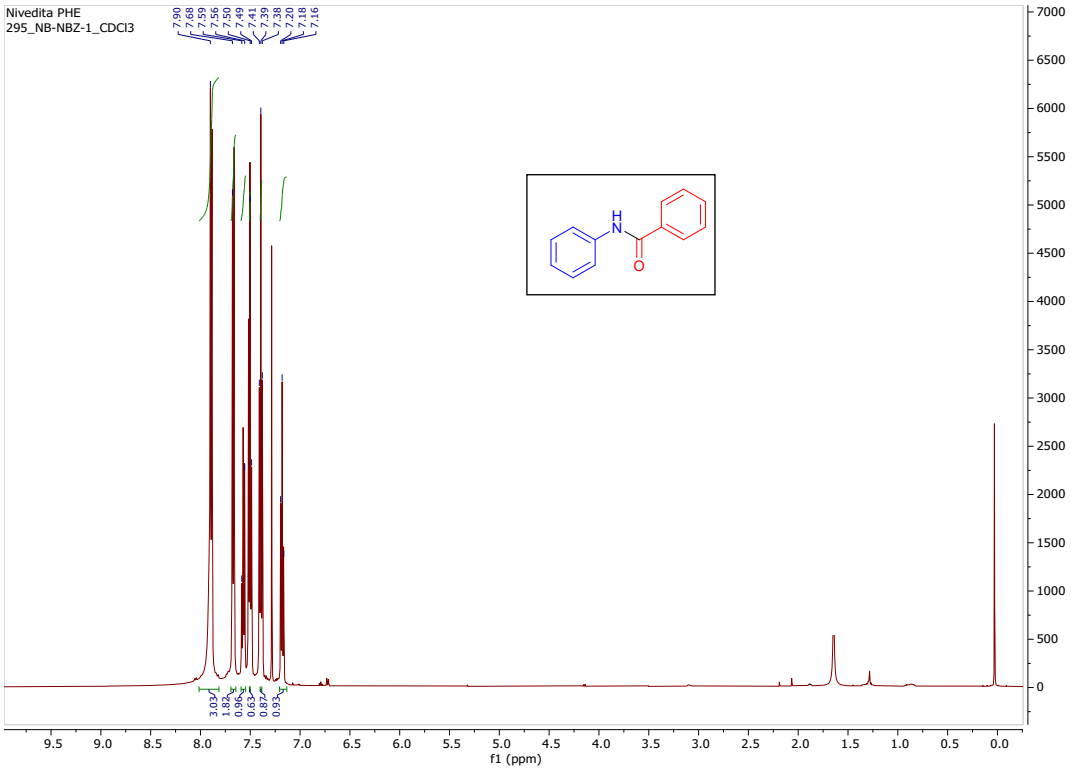
^{13}CNMR spectrum of N-(2-amino-4-nitrophenyl)oleomide (9c)



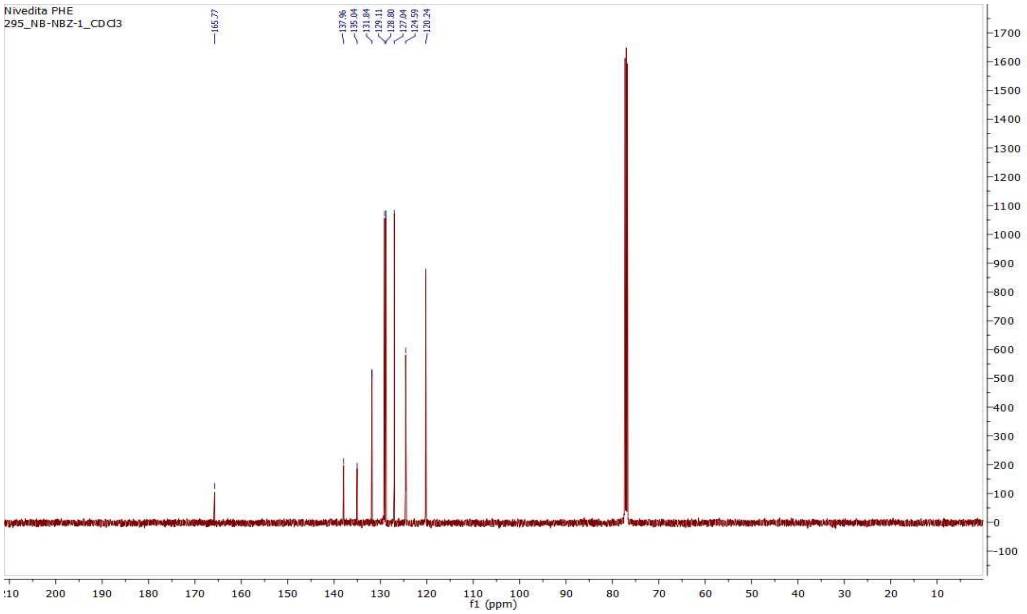
HRMS spectrum of N-(2-amino-4-nitrophenyl)oleomide (9c)



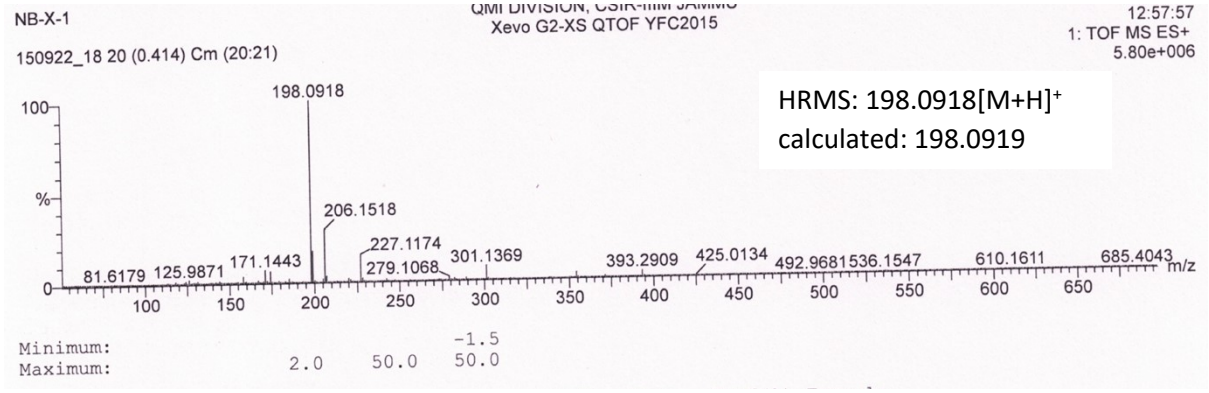
^{1}H-NMR spectrum of N-phenylbenzamide (10c)



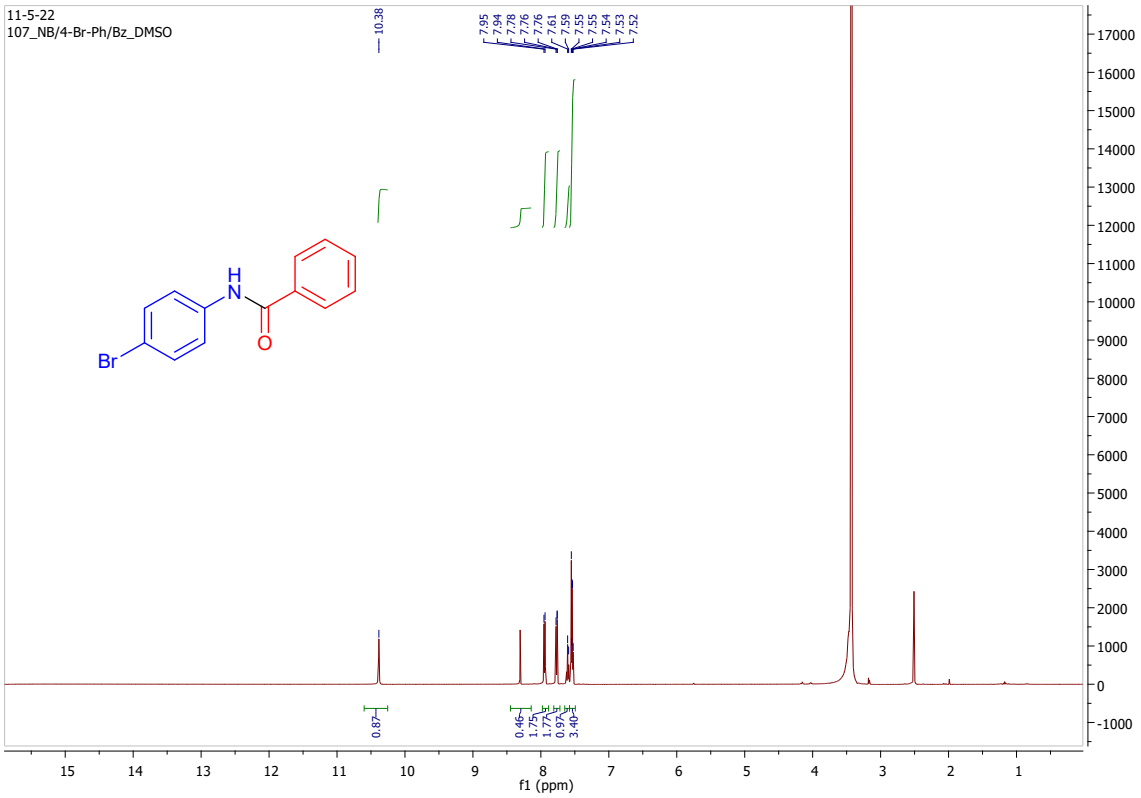
^{13}C-NMR spectrum of N-phenylbenzamide (10c)



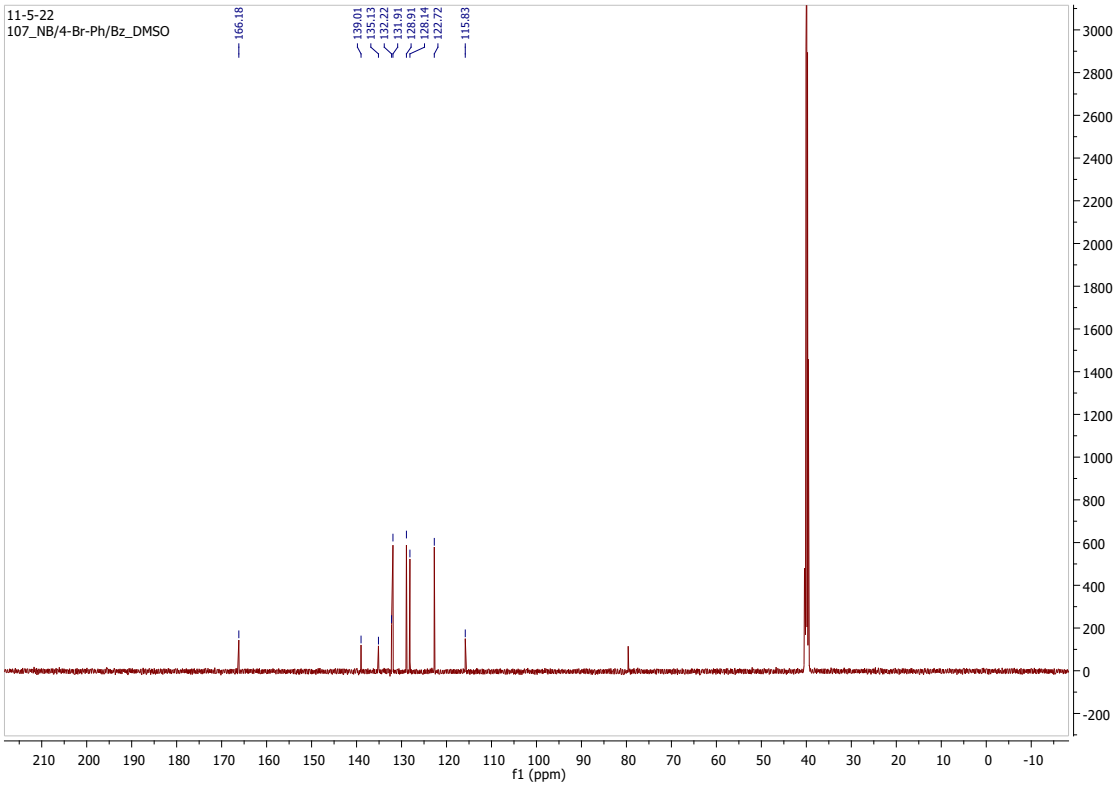
HRMS spectrum of N-phenylbenzamide (10c)



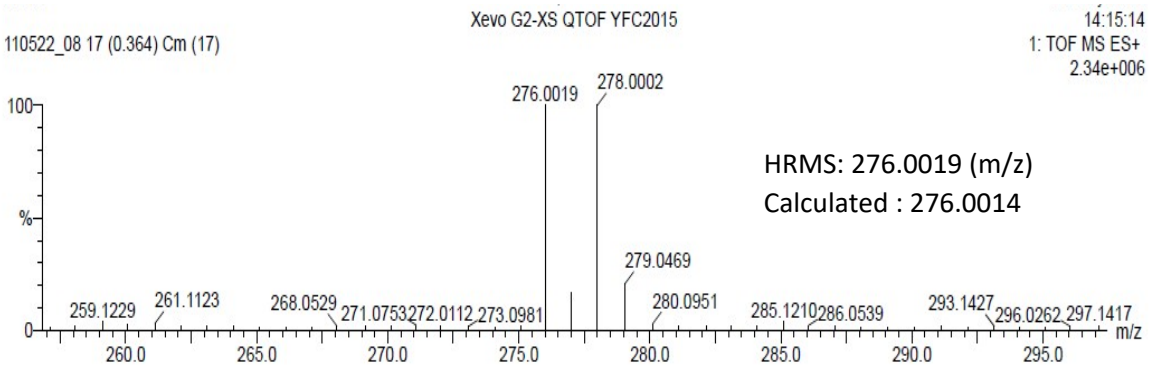
^{1}H-NMR spectrum of compound N-(4-Bromophenyl)-benzamide (11c)



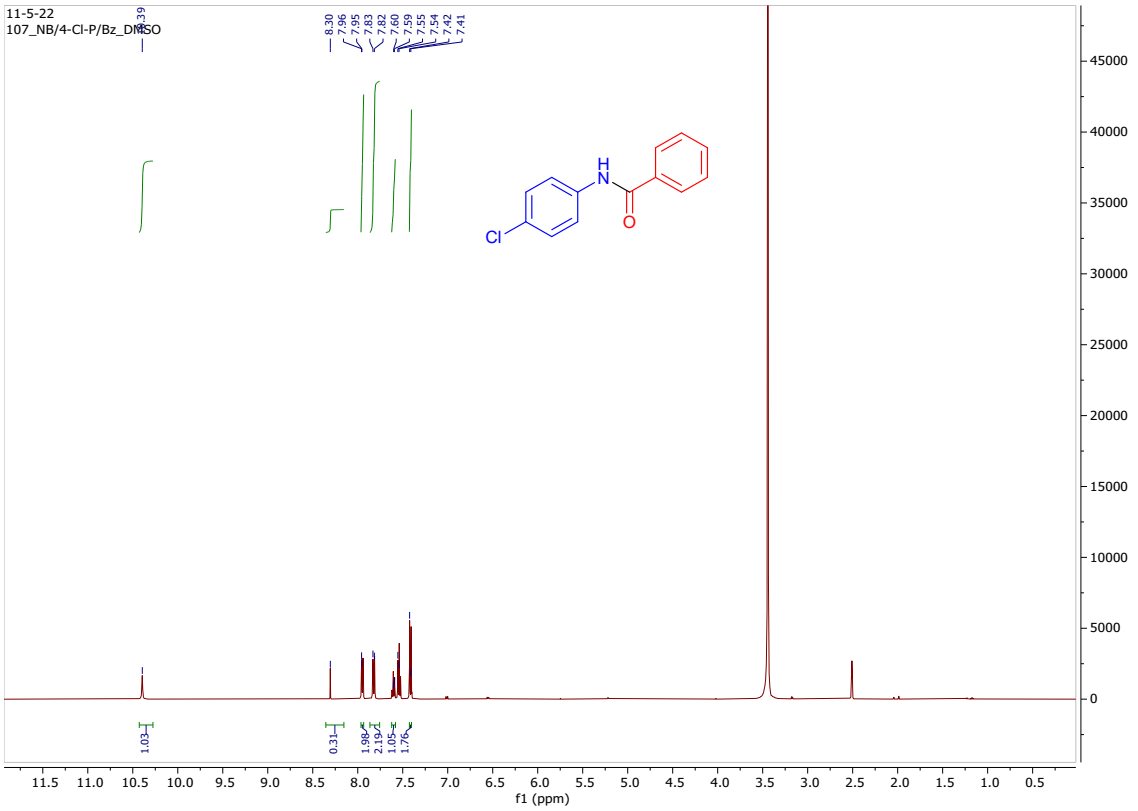
^{13}C-NMR spectrum of N-(4-Bromophenyl)-benzamide (11c)



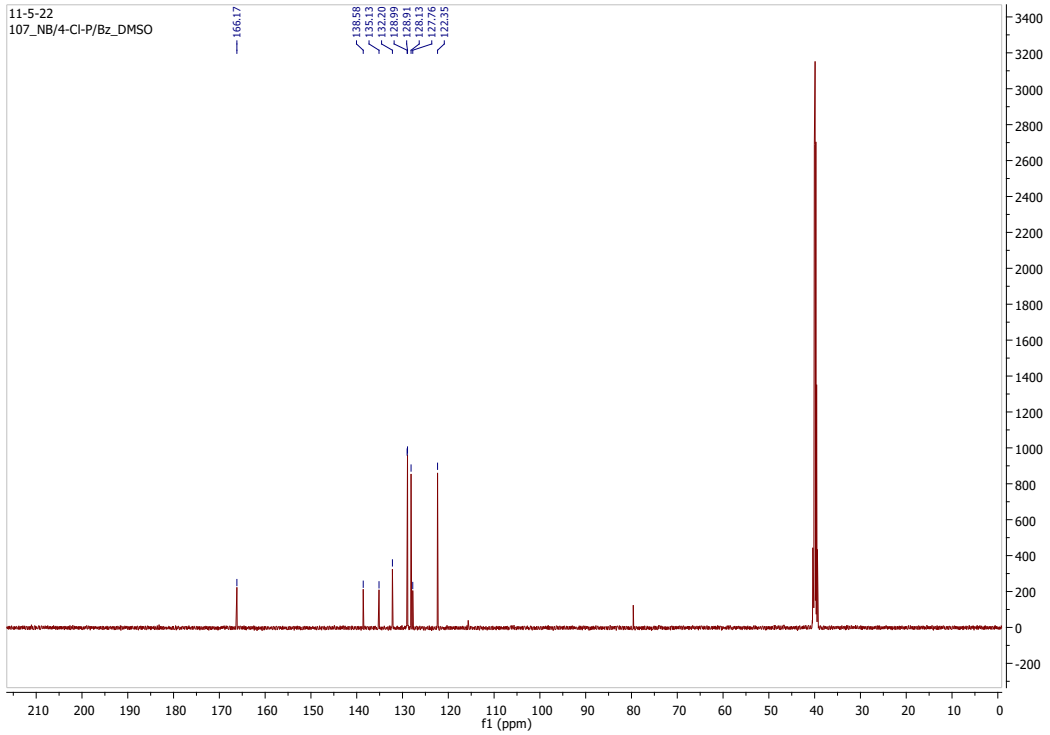
HRMS spectrum of N-(4-Bromophenyl)-benzamide (11c)



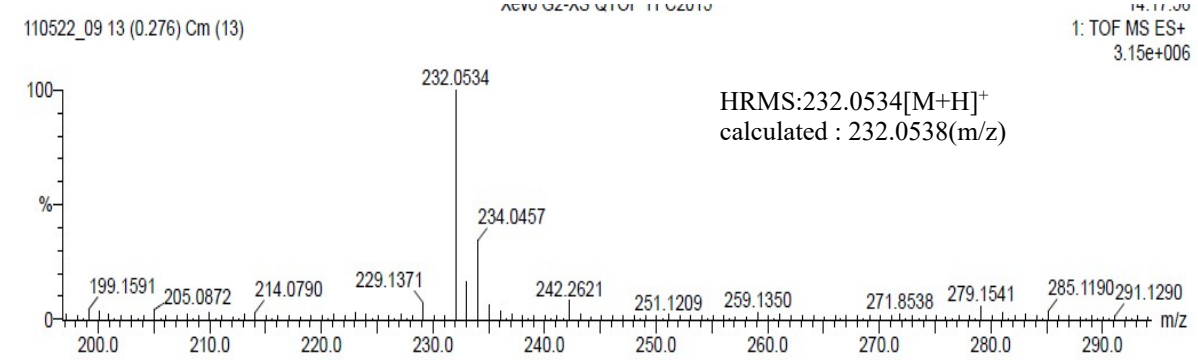
[1]H-NMR spectrum of N-(4-Chlorophenyl-benzamide (12c)



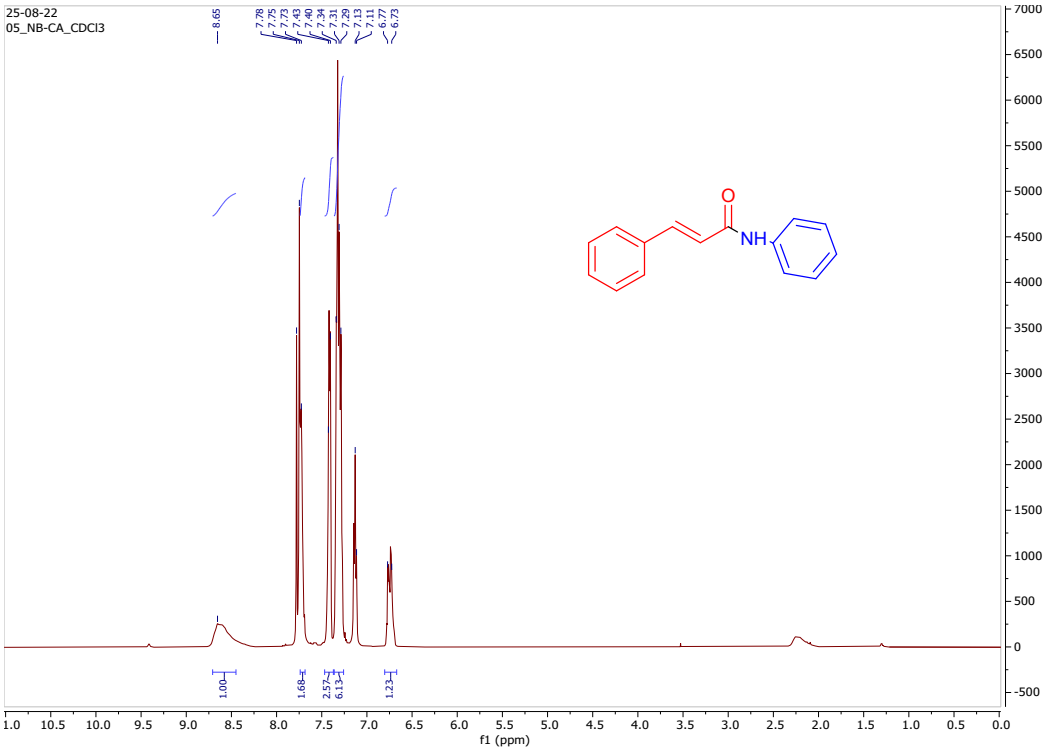
[13]C-NMR spectrum of N-(4-Chlorophenyl-benzamide (12c)



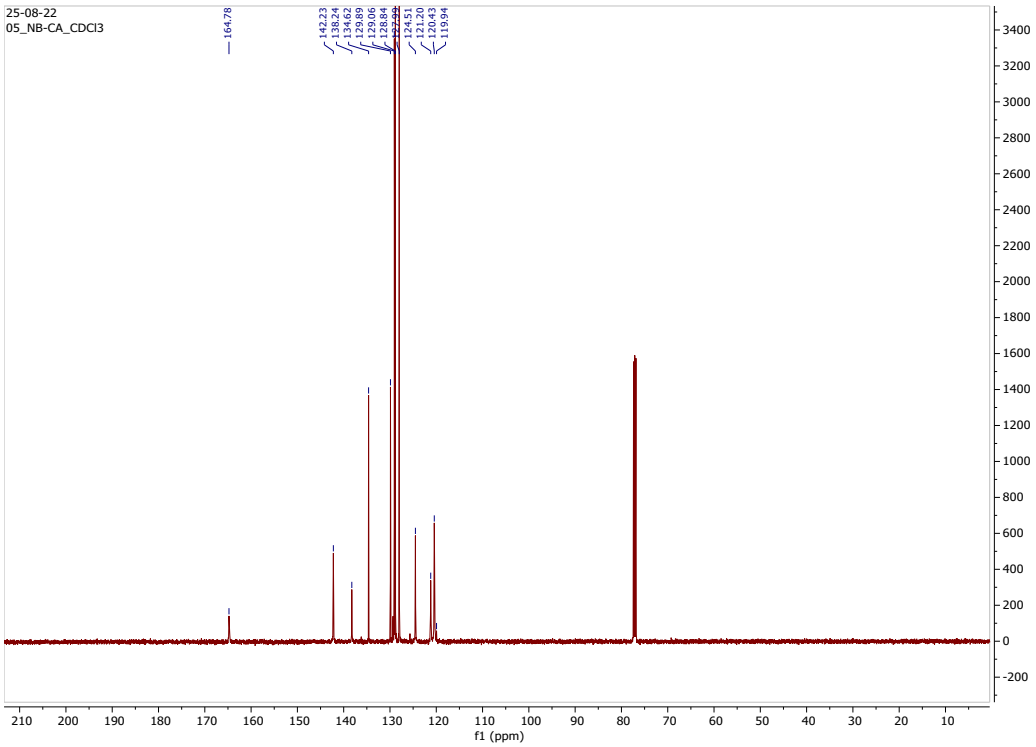
HRMS spectrum of N-(4-Chlorophenyl-benzamide (12c)



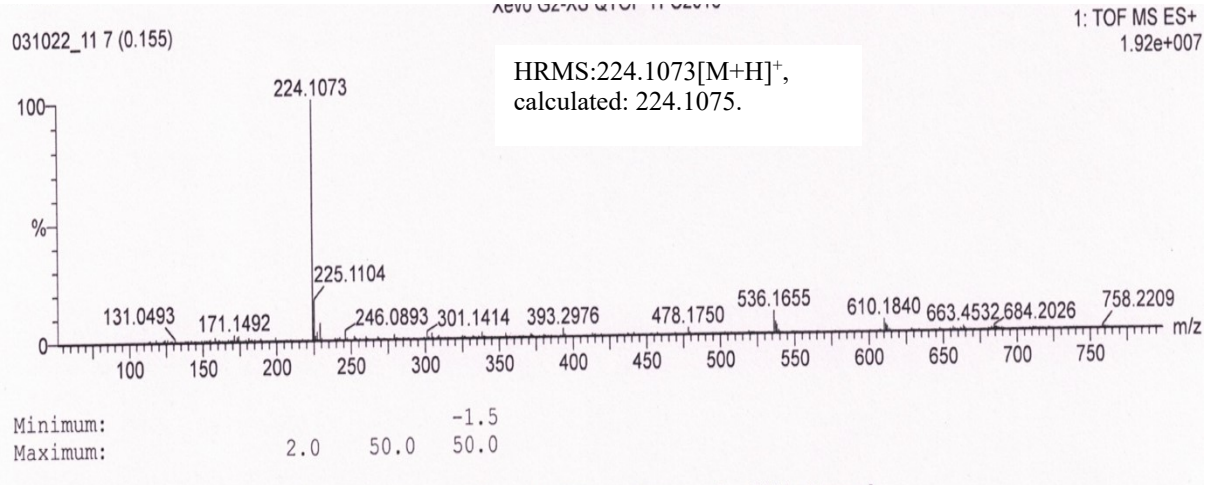
[1]H-NMR spectrum of N-phenylcinnamamide (13c)



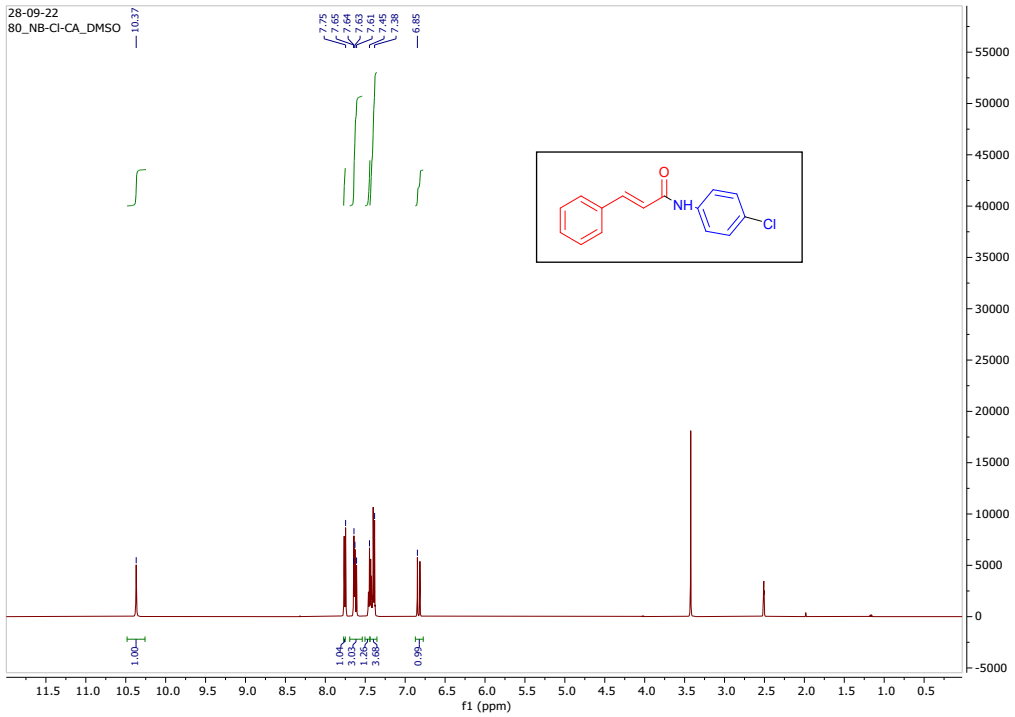
^{13}C-NMR spectrum of N-phenylcinnamamide (13c)



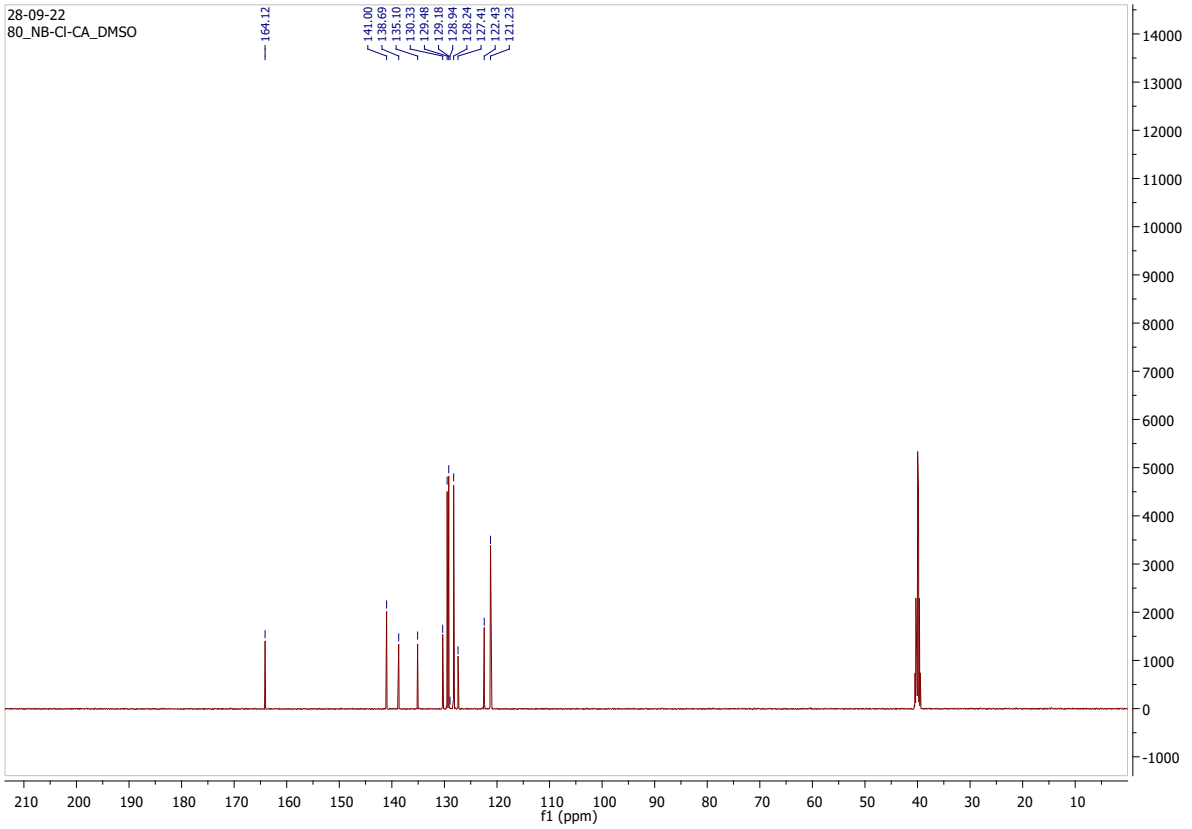
HRMS spectrum of N-phenylcinnamamide (13c)



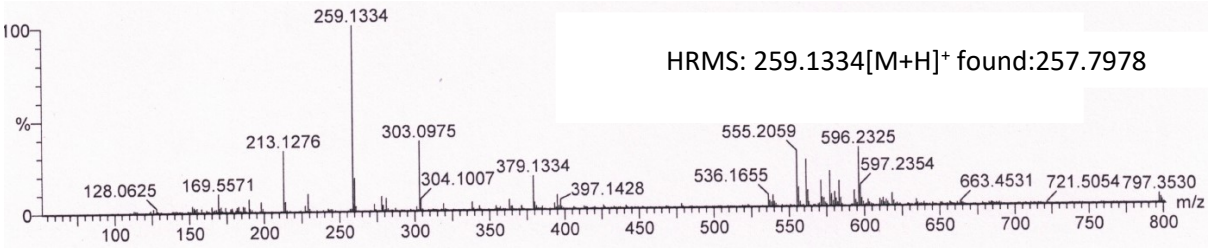
^{1}H-NMR spectrum of *N*-4-(chlorophenyl)cinnamide (14c)



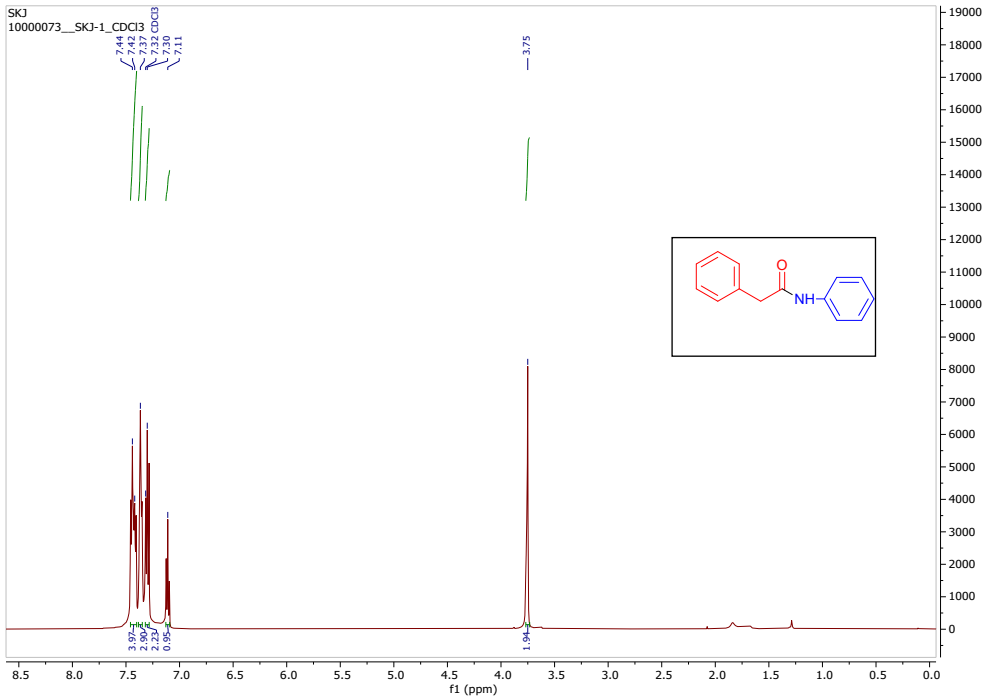
^{13}C-NMR spectrum of N-4-(chlorophenyl)cinnamide (14c)



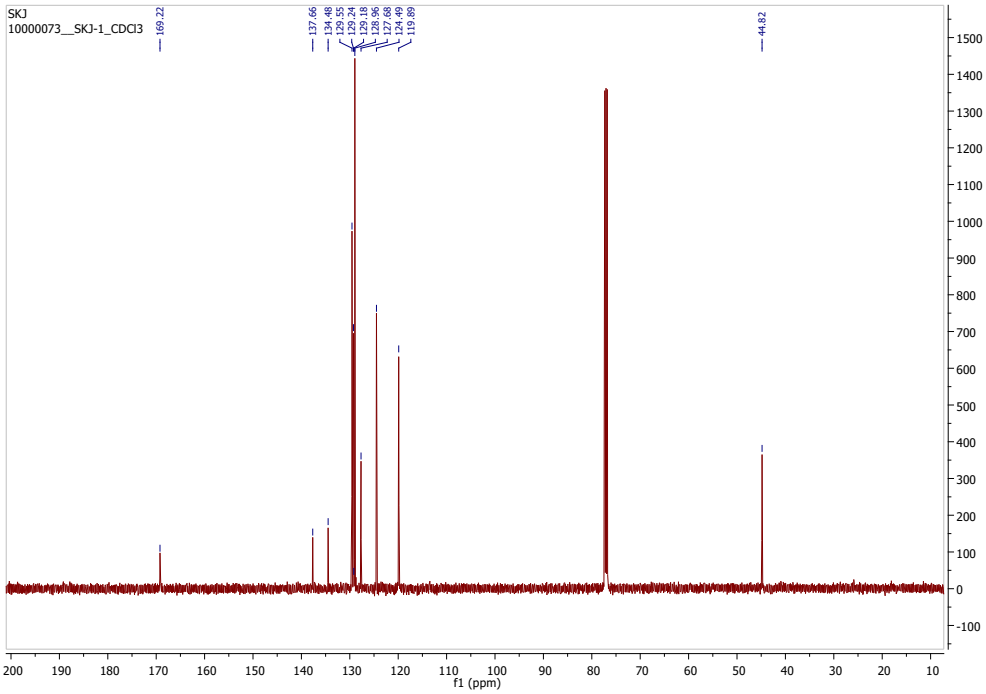
HRMS spectrum of N-4-(chlorophenyl)cinnamide (14c)



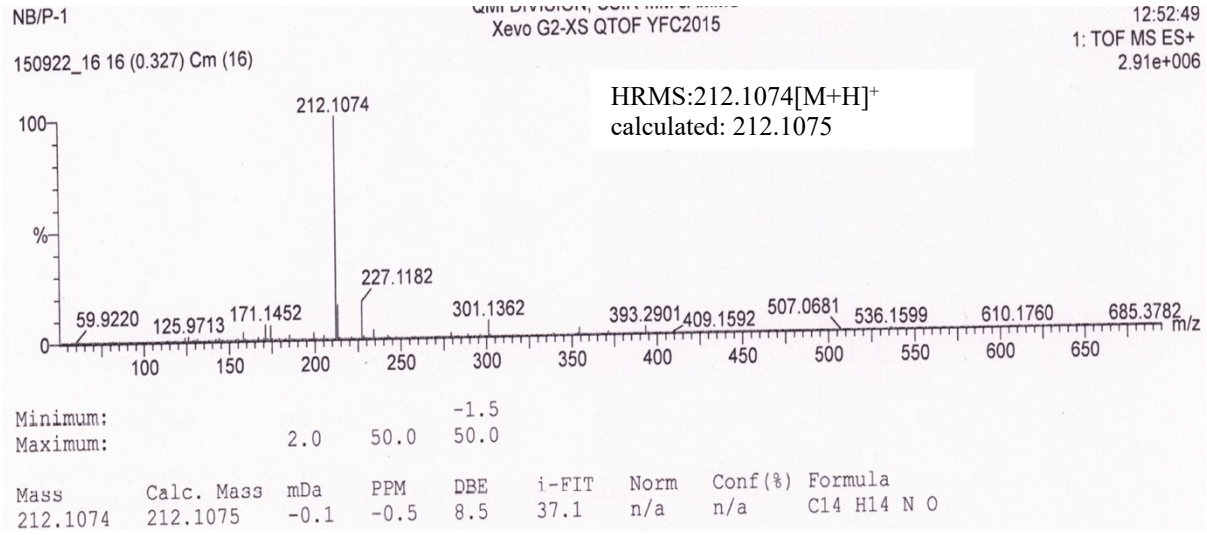
^{1}H-NMR spectrum of compound N, 2-diphenylacetamide (15c)



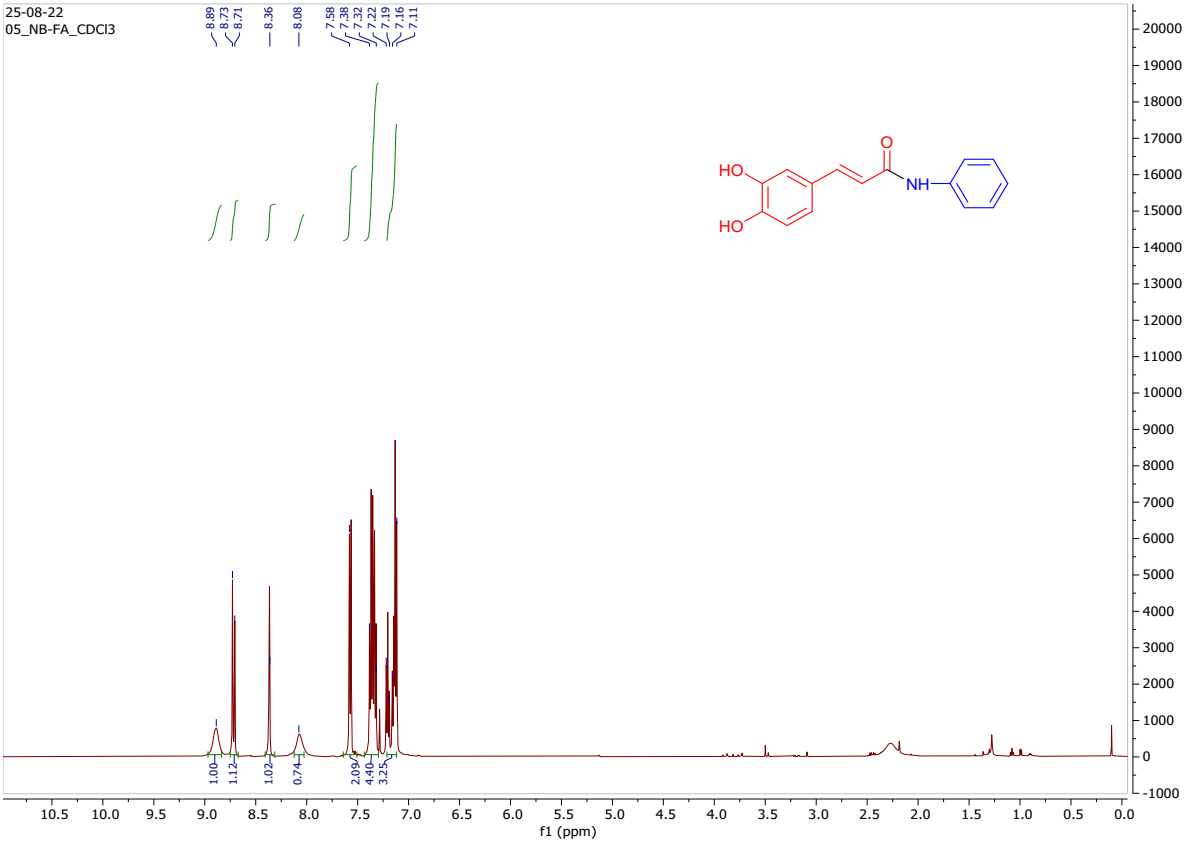
^{13}C-NMR spectrum of N, 2-diphenylacetamide (15c)



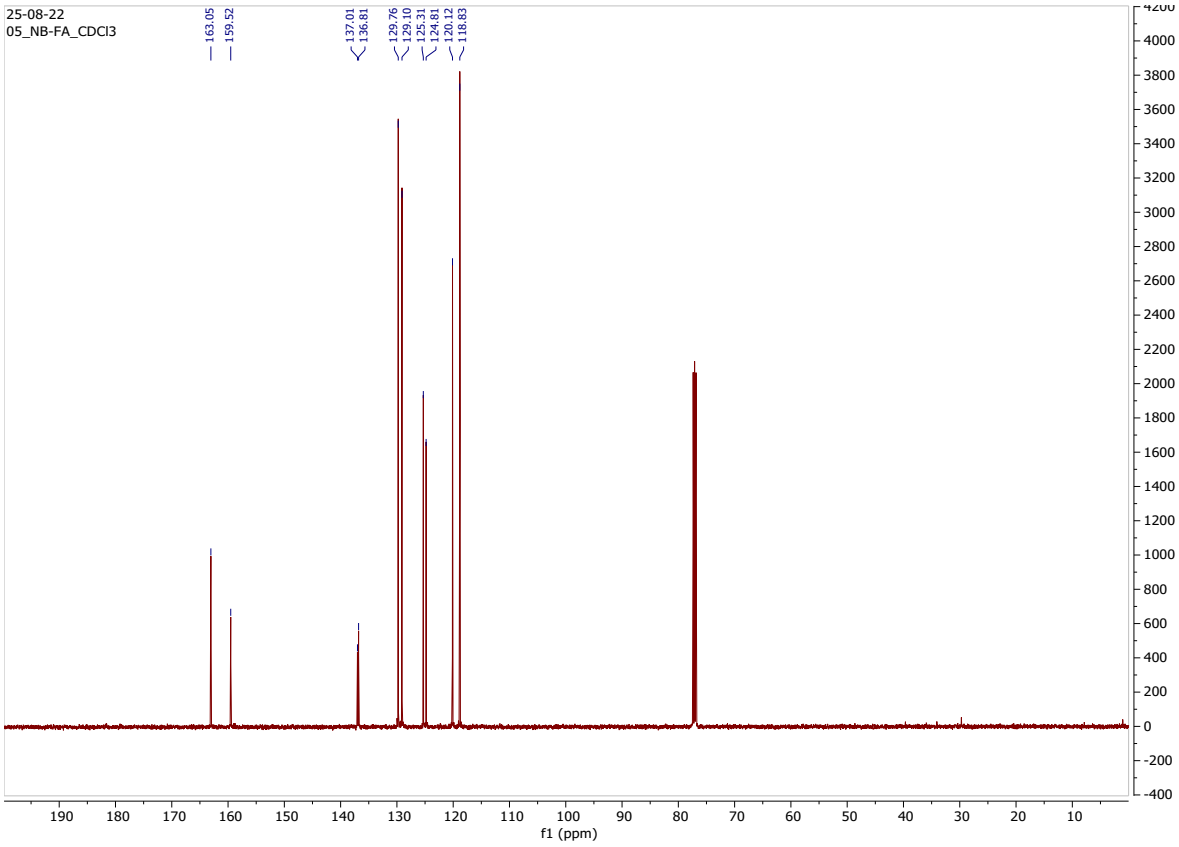
HRMS of N, 2-diphenylacetamide (15c)



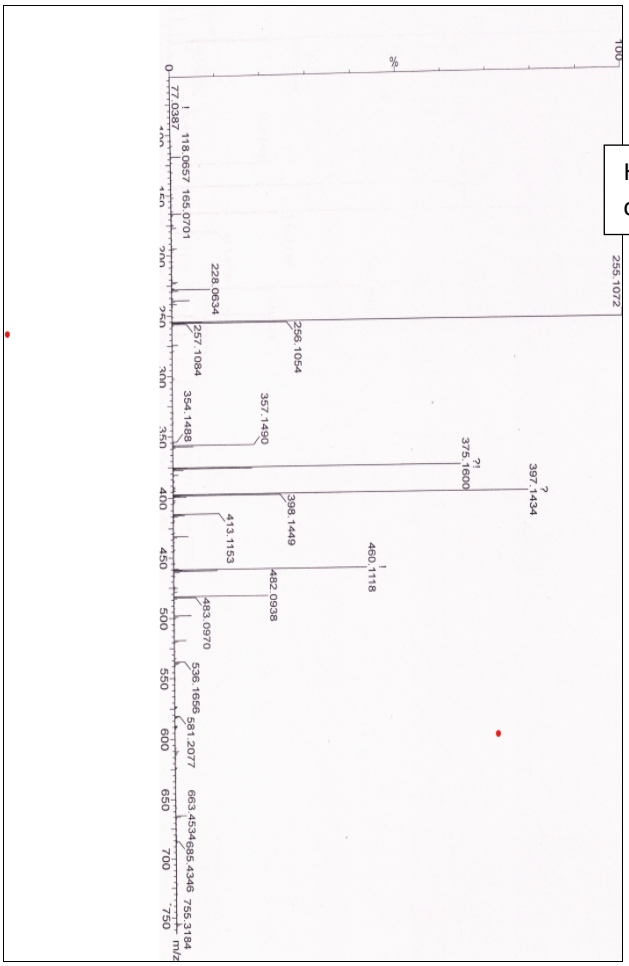
^{1}H-NMR spectrum of 3-(3,4-dihydroxyphenyl)-N-phenylacrylamide (16c)



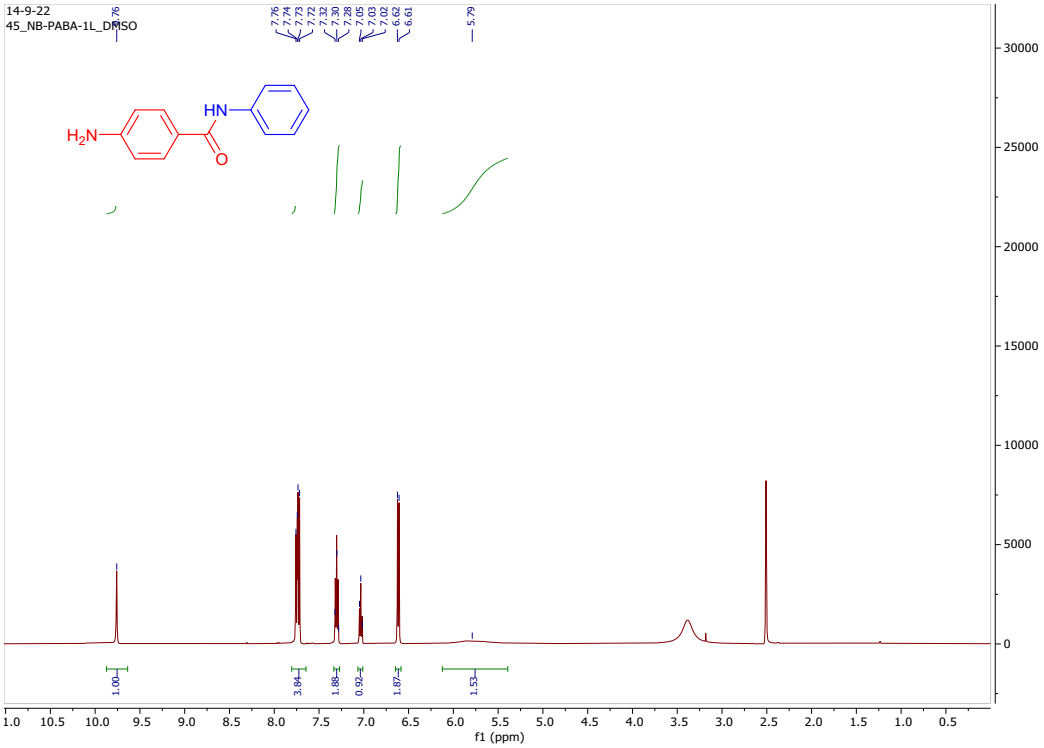
^{13}C-NMR spectrum of 3-(3,4-dihydroxyphenyl)-N-phenylacrylamide (16c)



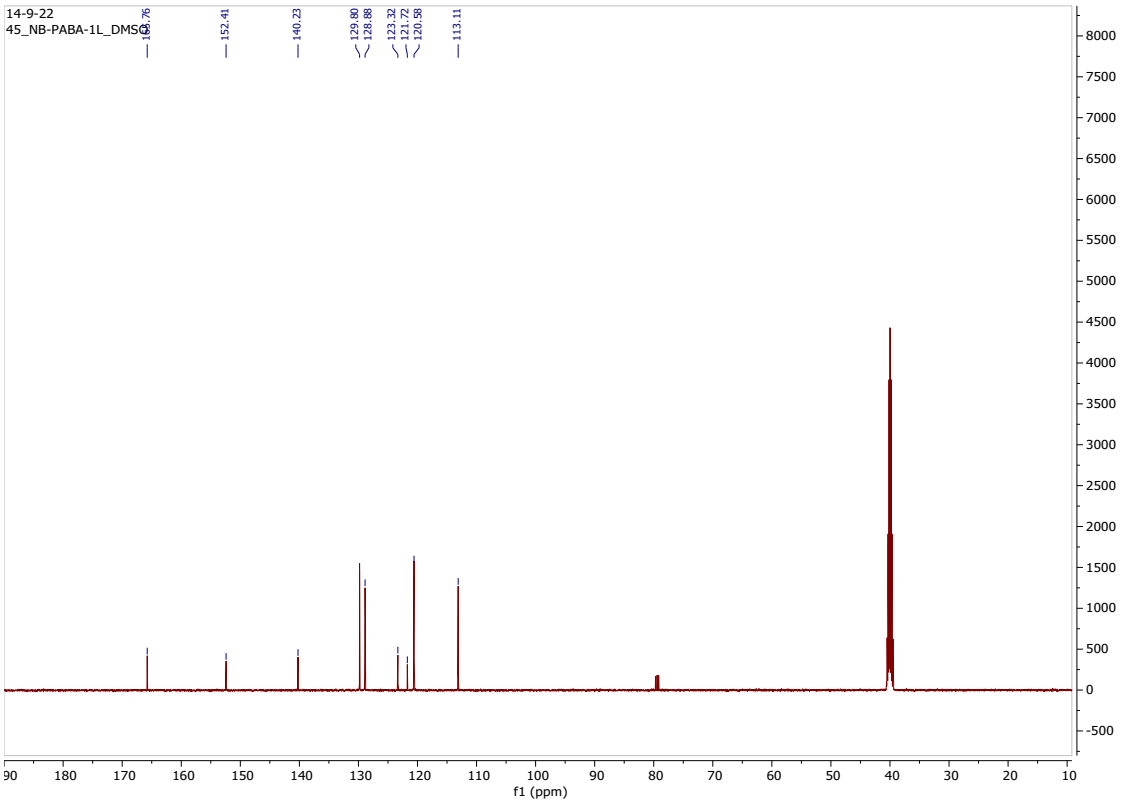
HRMS spectrum of compound 3-(3,4-dihydroxyphenyl)-N-phenylacrylamide (16c)



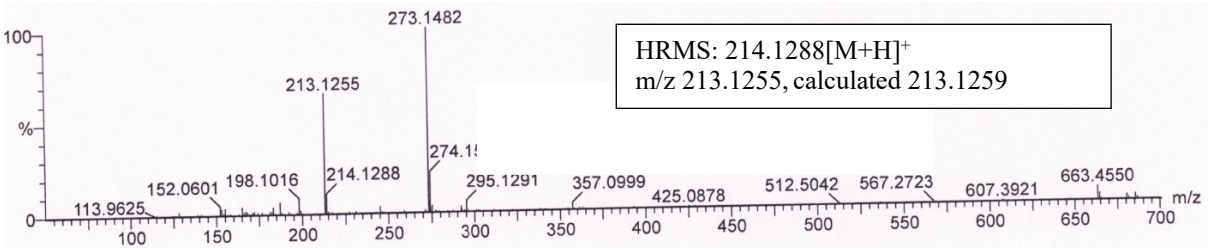
[1]H-NMR spectrum of compound 4-amino-N-phenylbenzamide (17c)



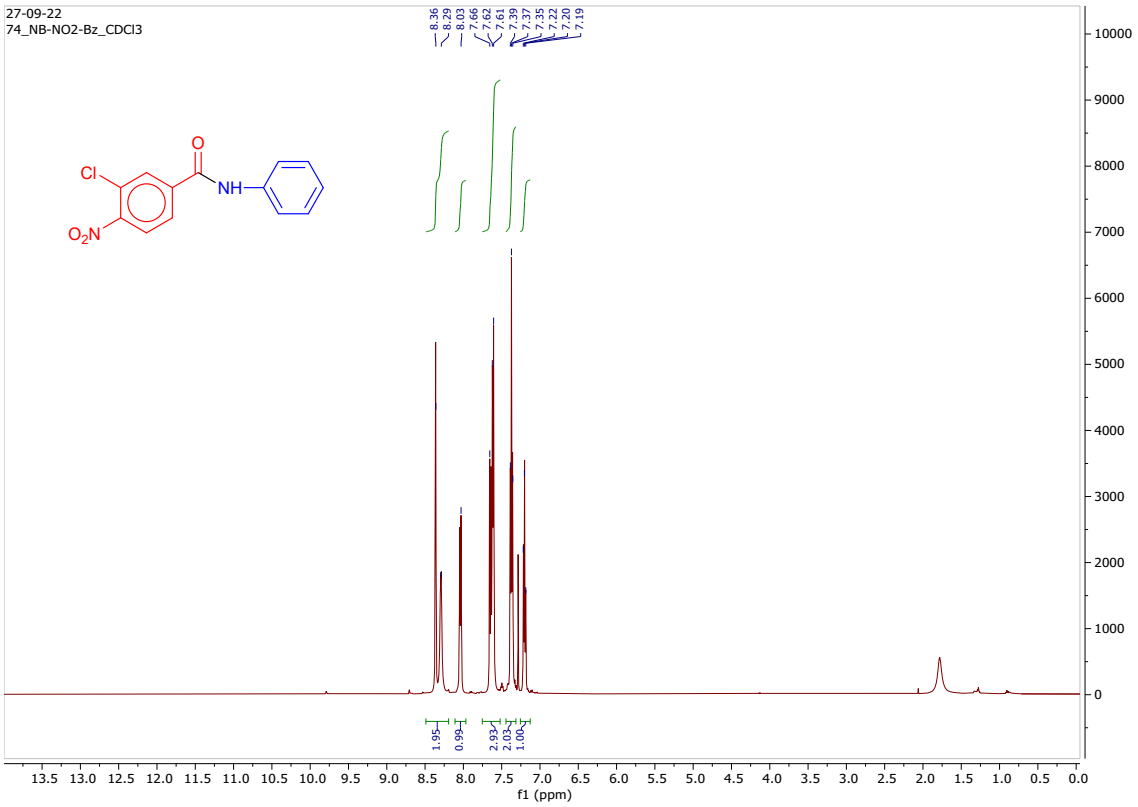
^{13}C-NMR spectrum of compound 4-amino-N-phenylbenzamide (17c)



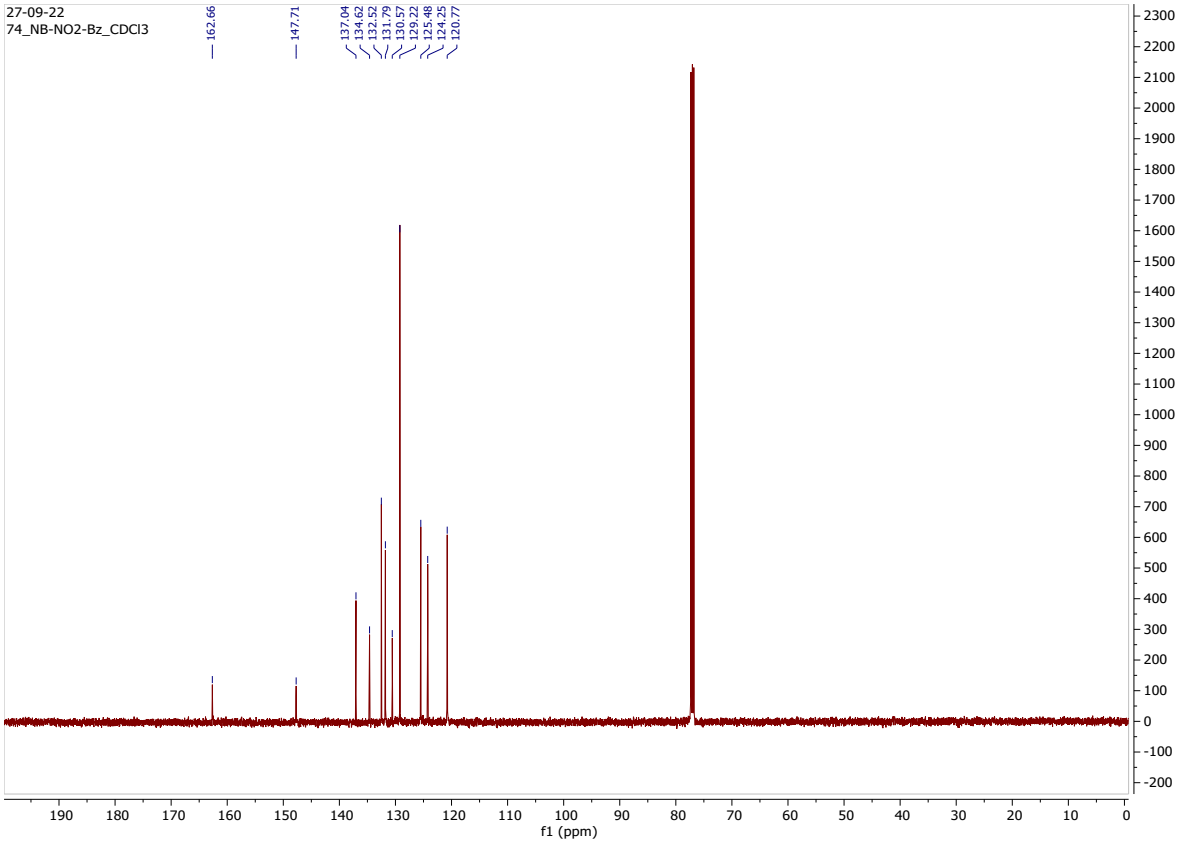
HRMS spectrum of 4-amino-N-phenylbenzamide(17c)



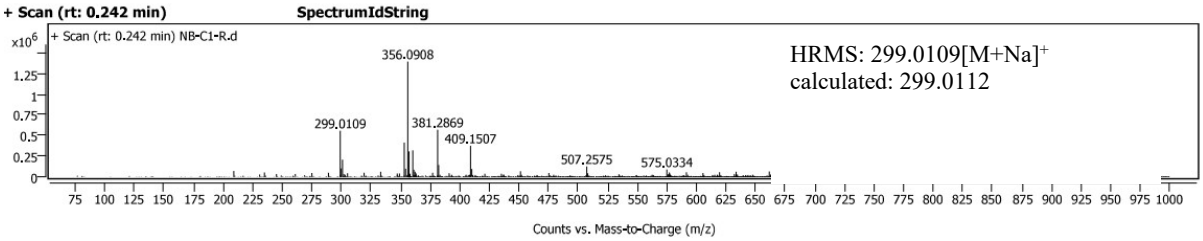
^{1}H-NMR spectrum of 3-chloro-4-nitro-N-phenylbenzamide (18c)



^{13}C-NMR spectrum of 3-chloro-4-nitro-N-phenylbenzamide (18c)

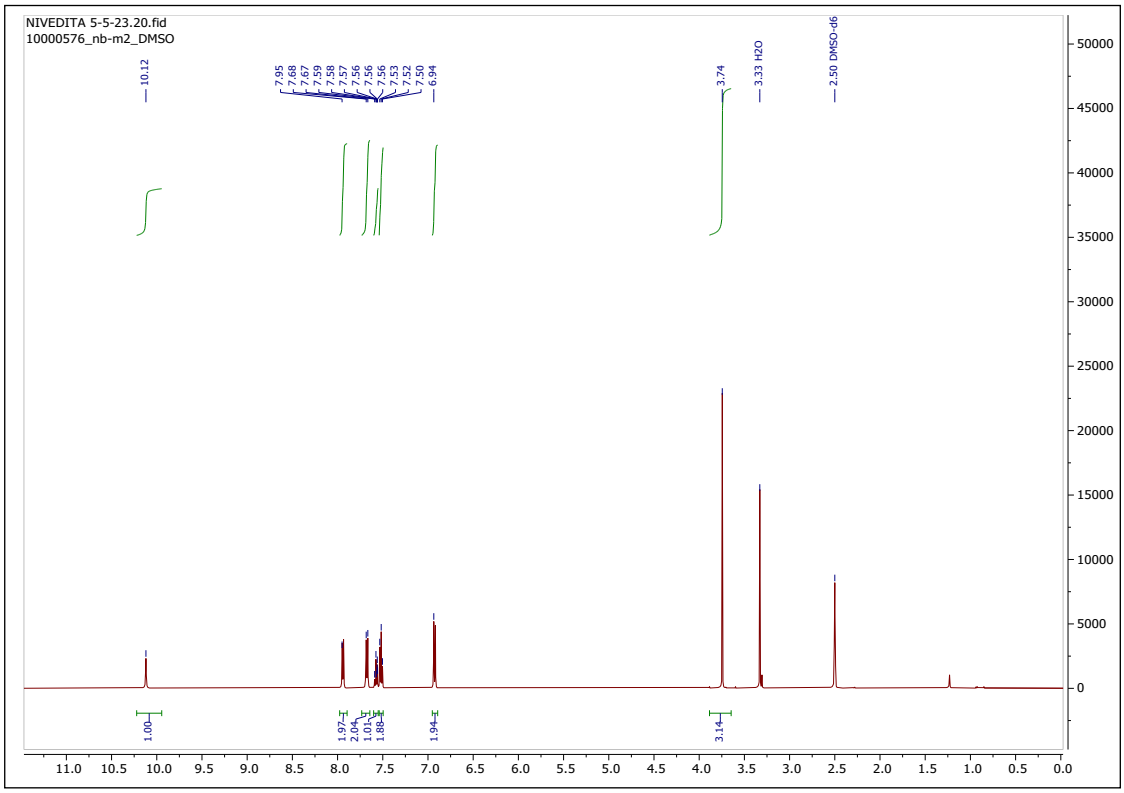


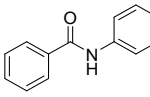
HRMS spectrum of 3-chloro-4-nitro-N-phenylbenzamide (18c)



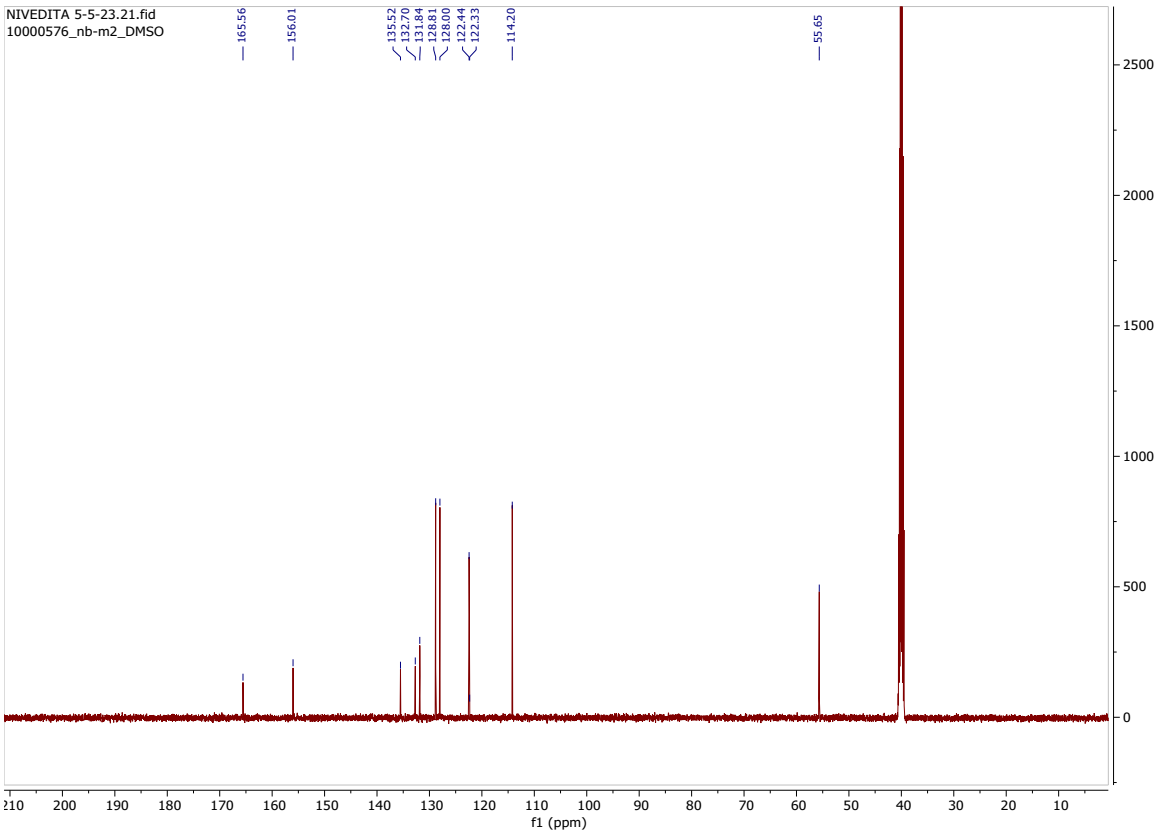
HRMS: 299.0109[M+Na]$^+$
calculated: 299.0112

^{1}H-NMR spectrum of 4-methoxy-N-phenylbenzamide (20c)

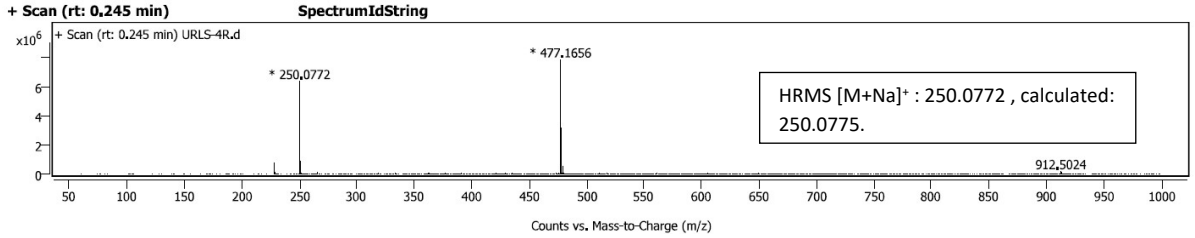




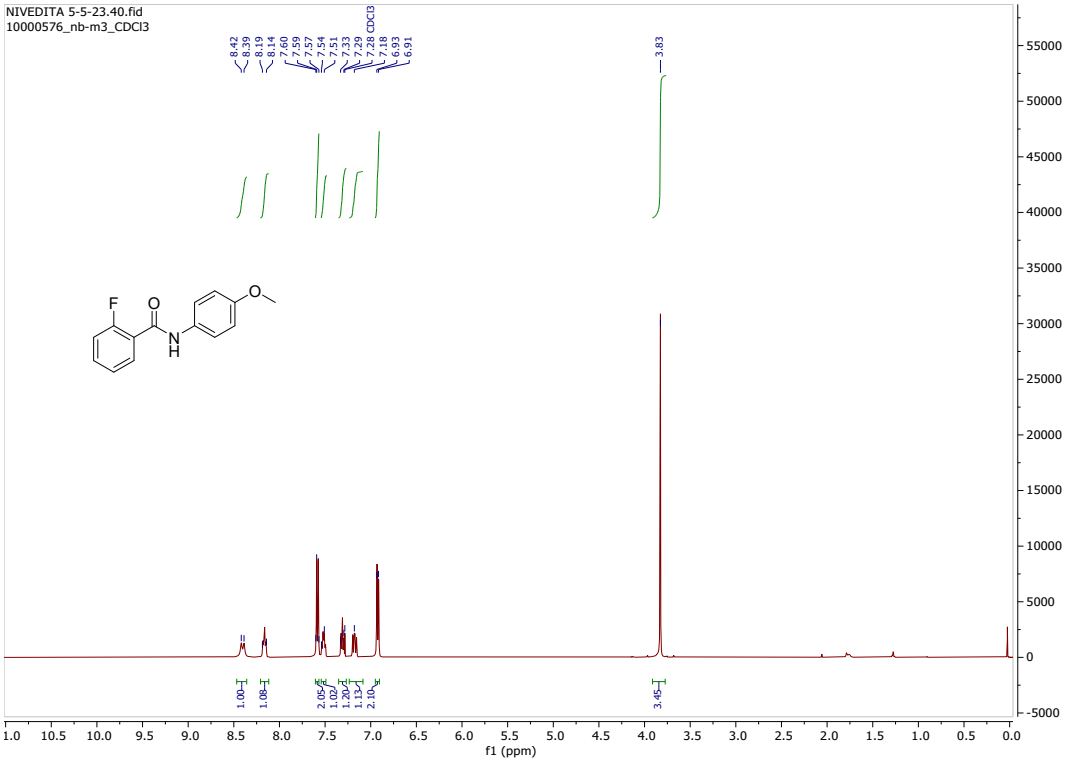
^{13}C-NMR of 4-methoxy-N-phenylbenzamide (20c)



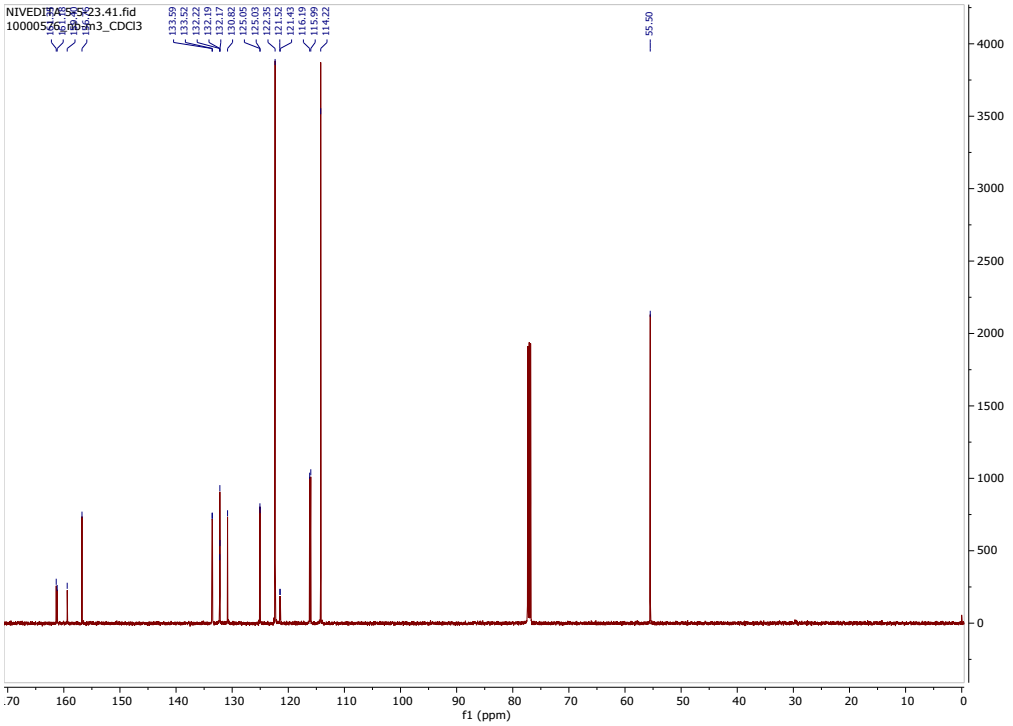
HRMS spectrum of 4-methoxy-N-phenylbenzamide (20c)



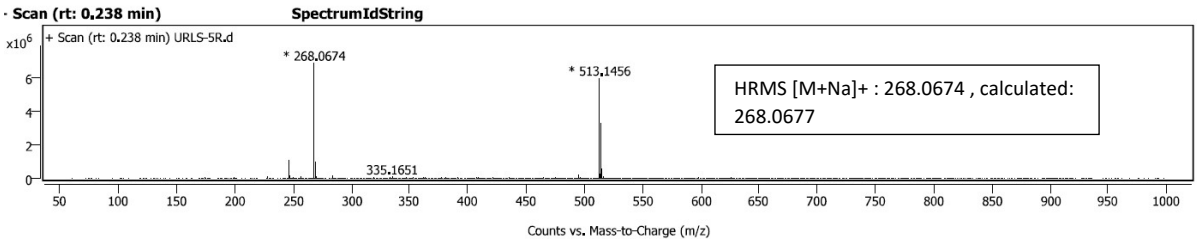
^{1}H-NMR spectrum of 2-fluoro-N-(4-methoxyphenyl)benzamide (21c)



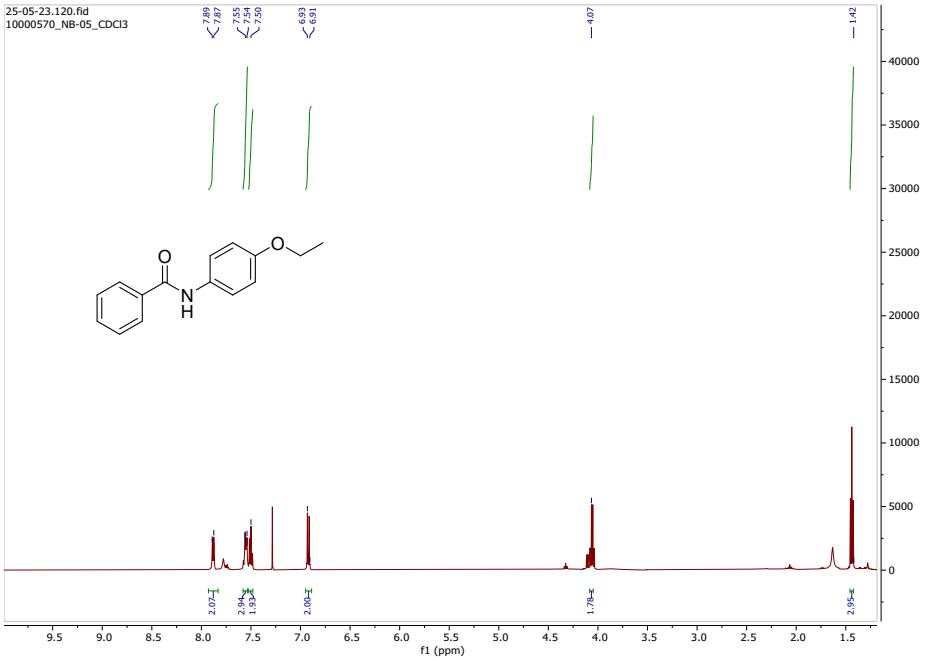
^{13}C-NMR of 2-fluoro-N-(4-methoxyphenyl)benzamide (21c)



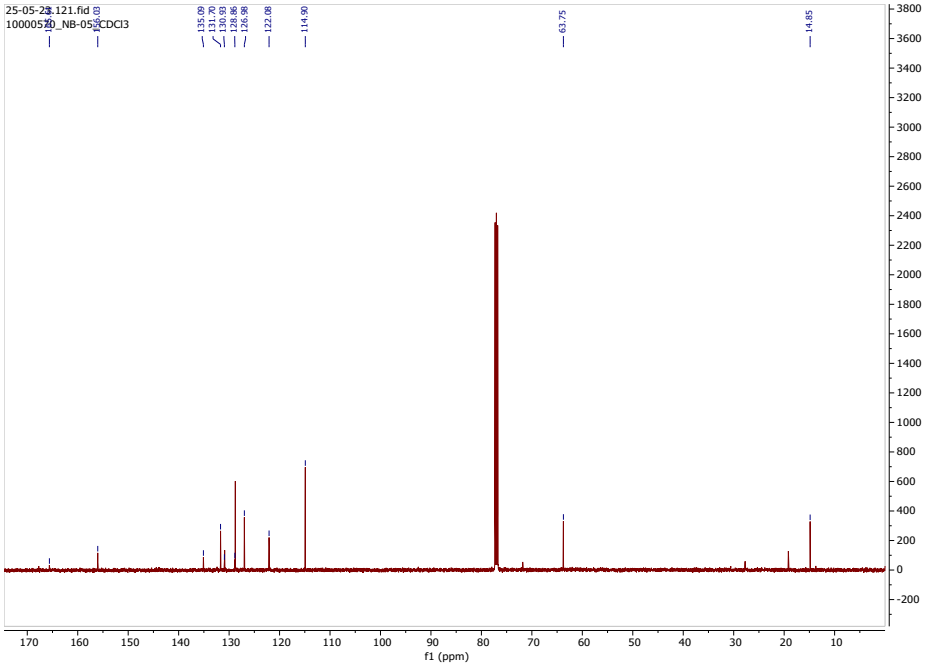
HRMS spectrum of 2-fluoro-N-(4-methoxyphenyl)benzamide (21c)



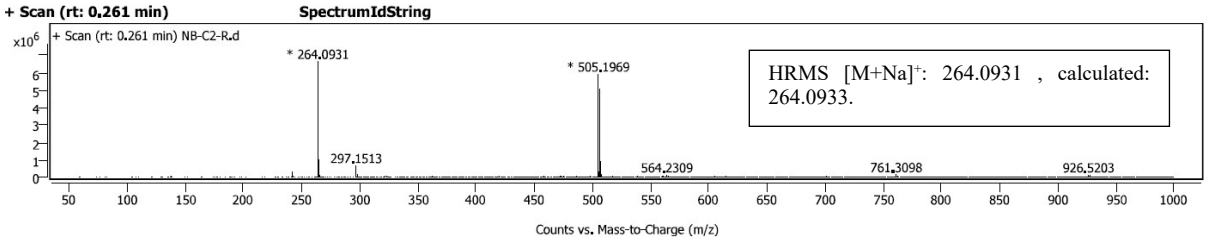
^{1}H-NMR spectrum of N-(4-ethoxyphenyl)benzamide (22c)



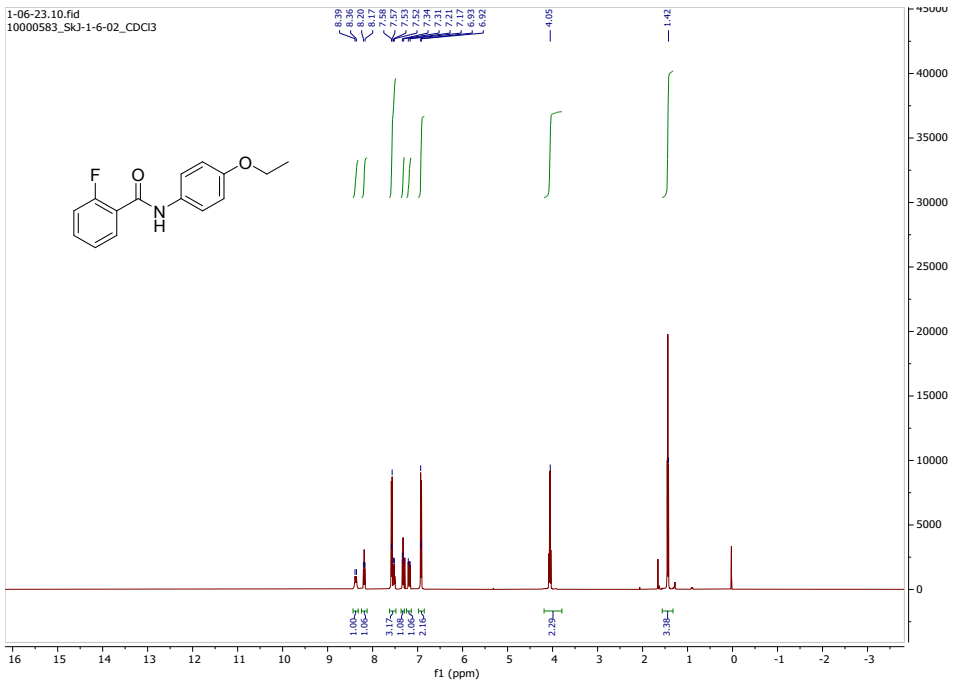
^{13}C-NMR of N-(4-ethoxyphenyl)benzamide (22c)



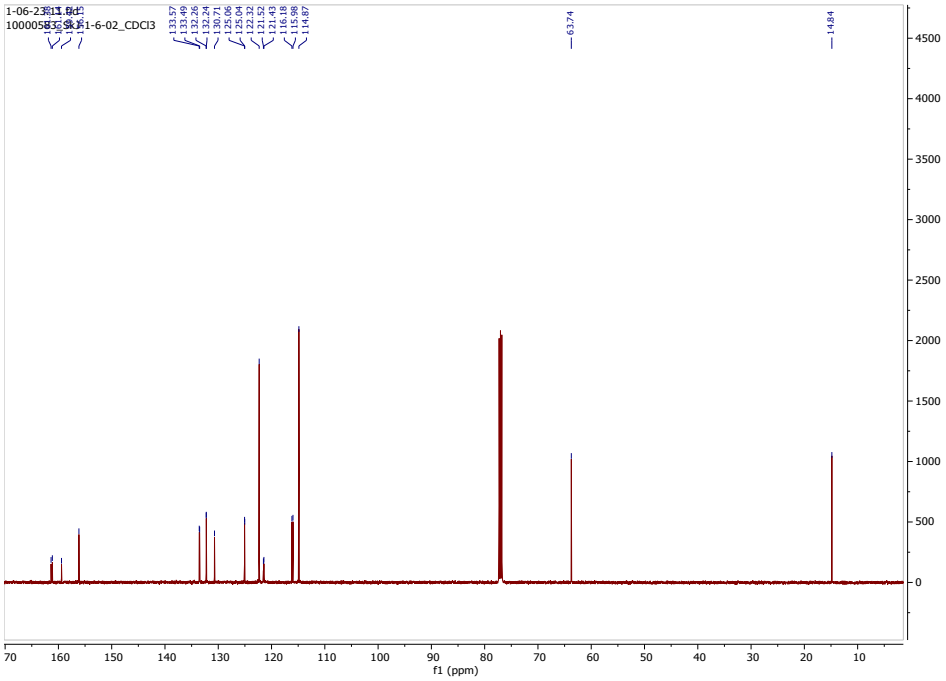
HRMS spectrum of N-(4-ethoxyphenyl)benzamide (22c)



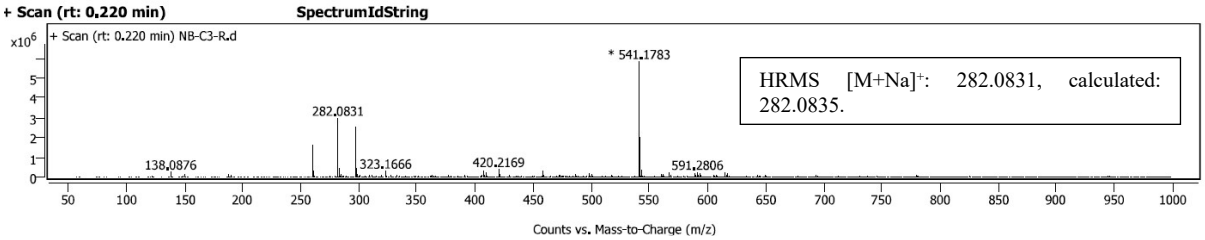
^{1}H-NMR spectrum of N-(4-ethoxyphenyl)-2-fluorobenzamide (23c)



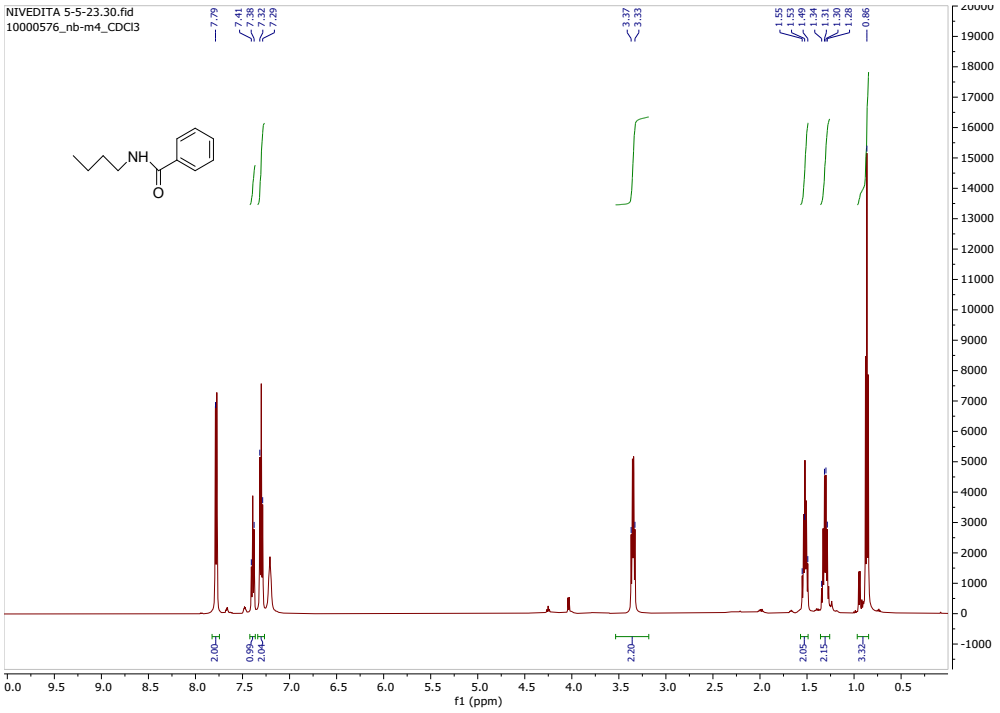
^{13}C-NMR spectrum of N-(4-ethoxyphenyl)-2-fluorobenzamide (23c)



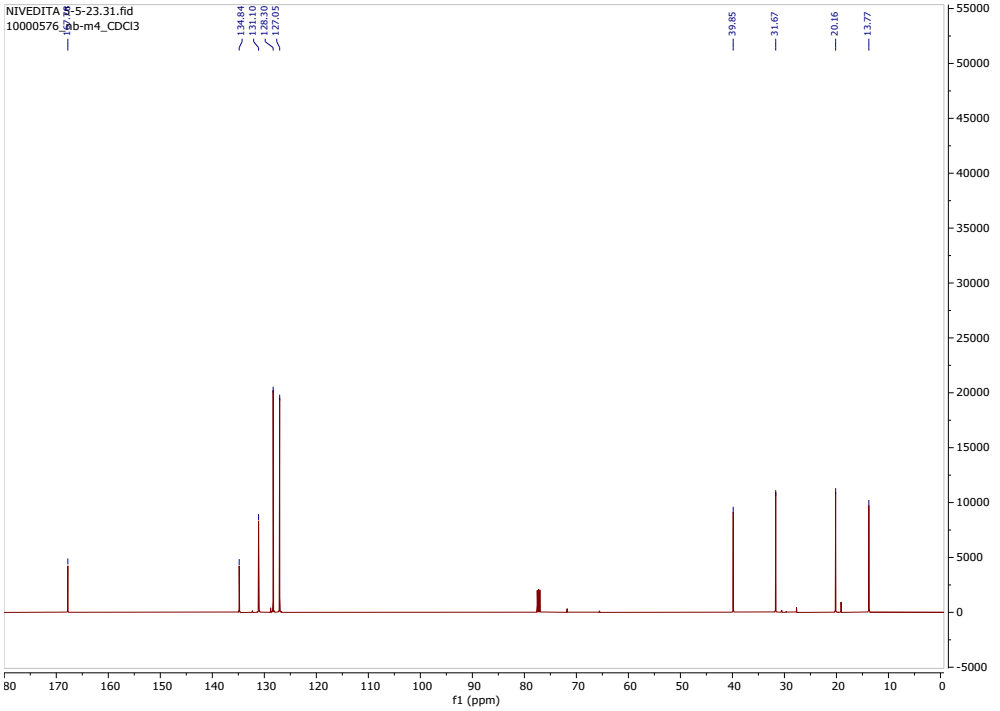
HRMS spectrum of N-(4-ethoxyphenyl)-2-fluorobenzamide (23c)



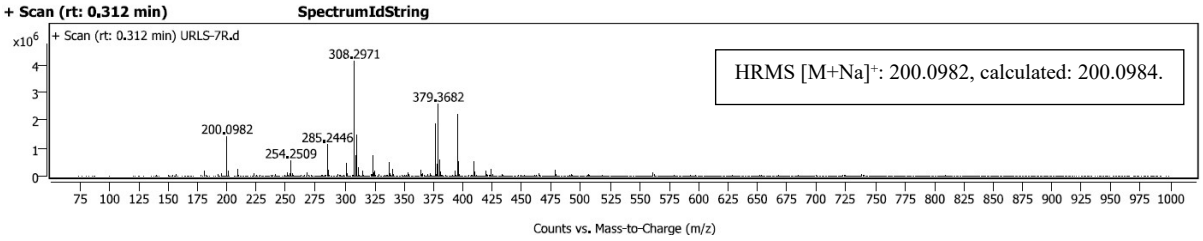
^{1}H-NMR spectrum of N-butylbenzamide (24c)



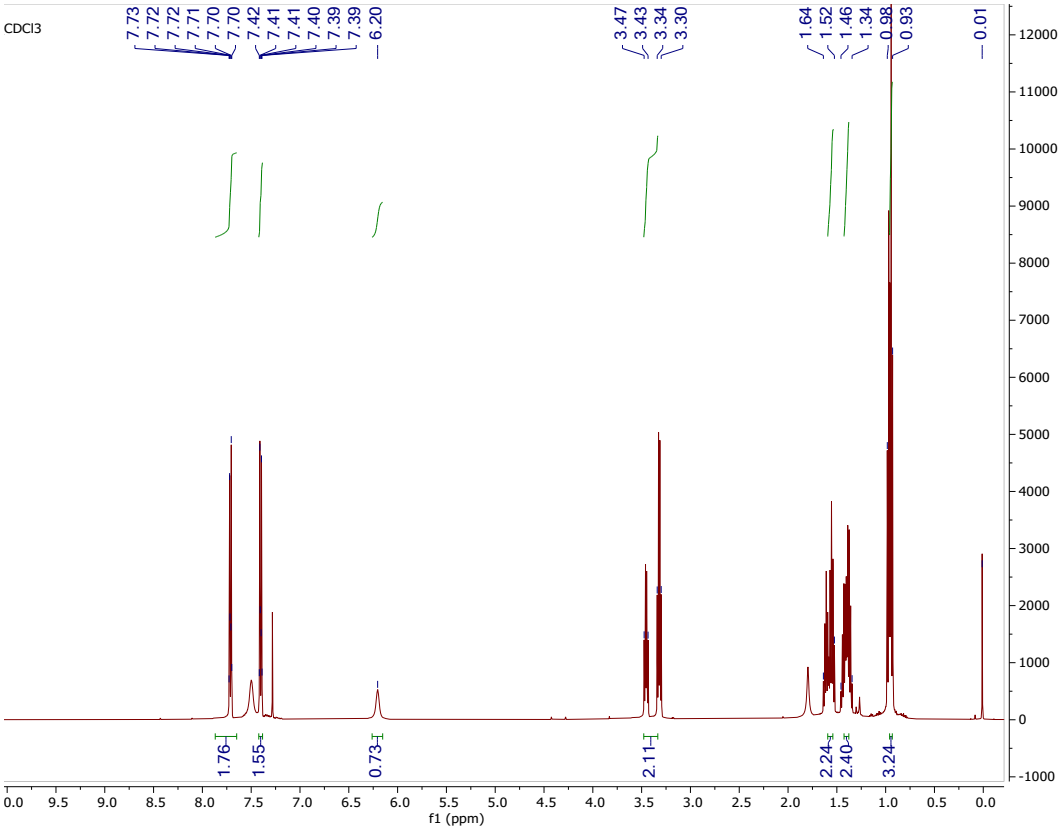
^{13}C-NMR spectrum of N-butylbenzamide (24c)



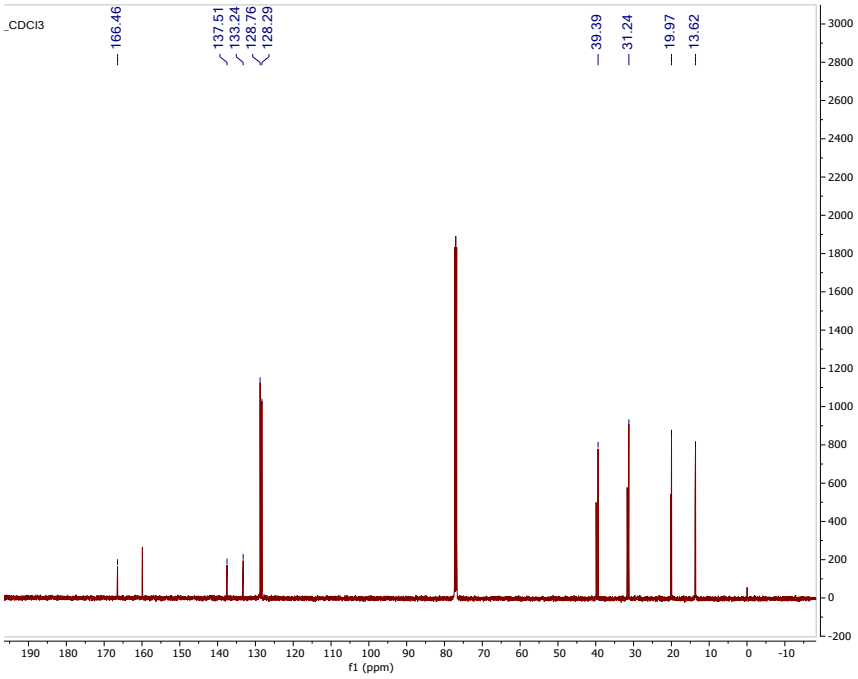
HRMS spectrum of N-butylbenzamide (24c)



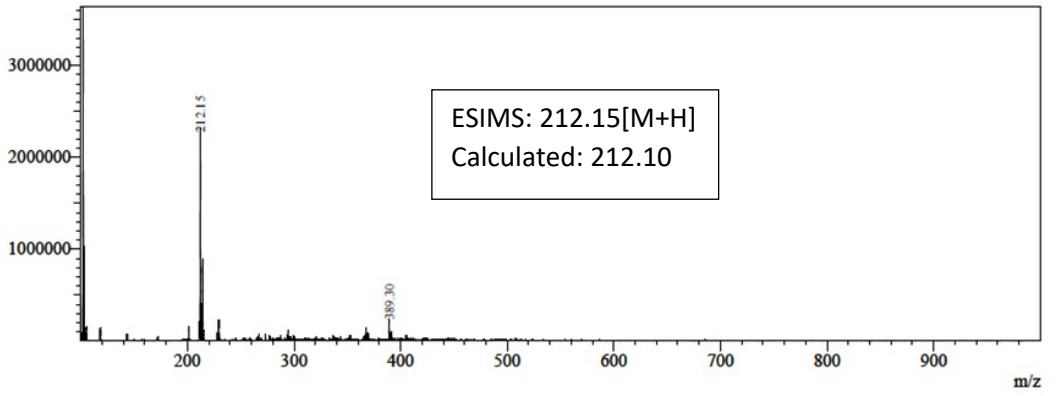
^{1}H-NMR spectrum of N-butyl-4-chlorobenzamide (25c)

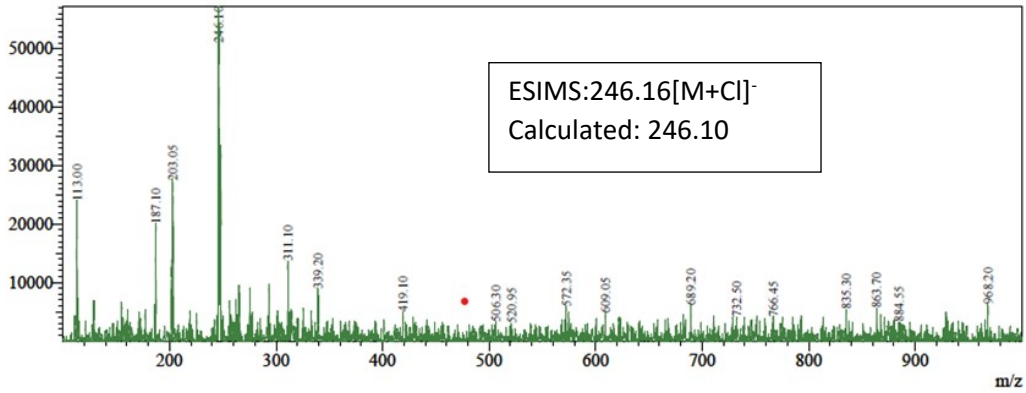


^{13}C-NMR spectrum of N-butyl-4-chlorobenzamide (25c)

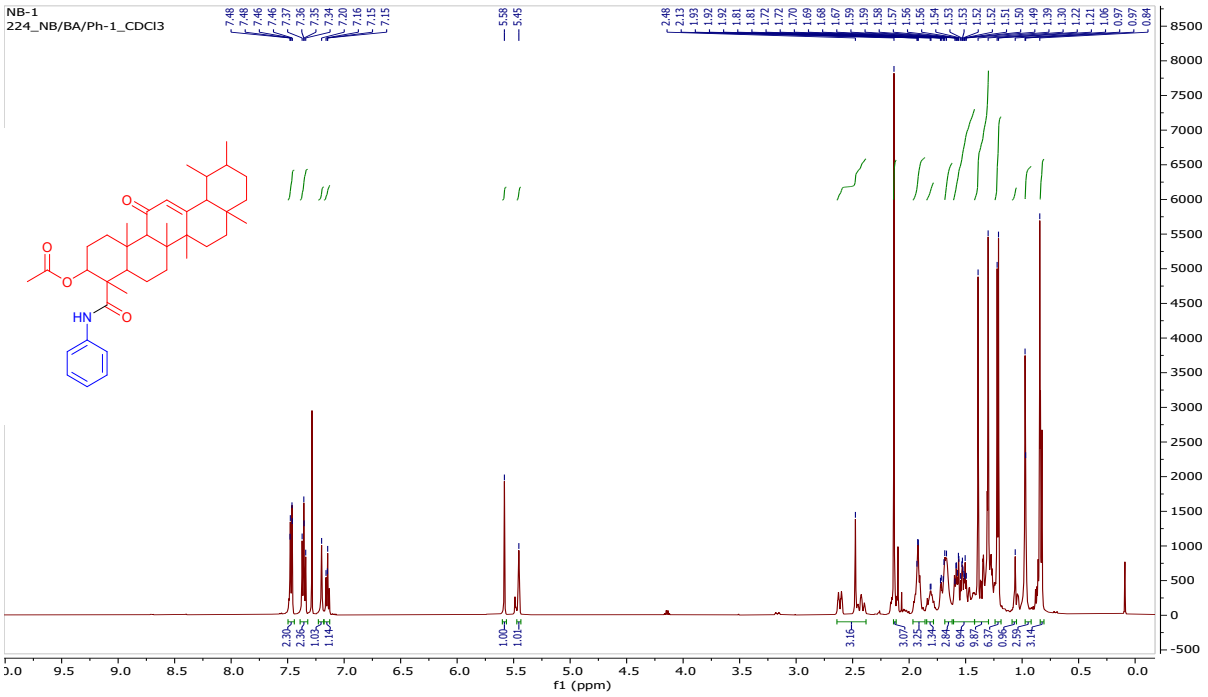


Mass spectrum of N-butyl-4-chlorobenzamide (25c)

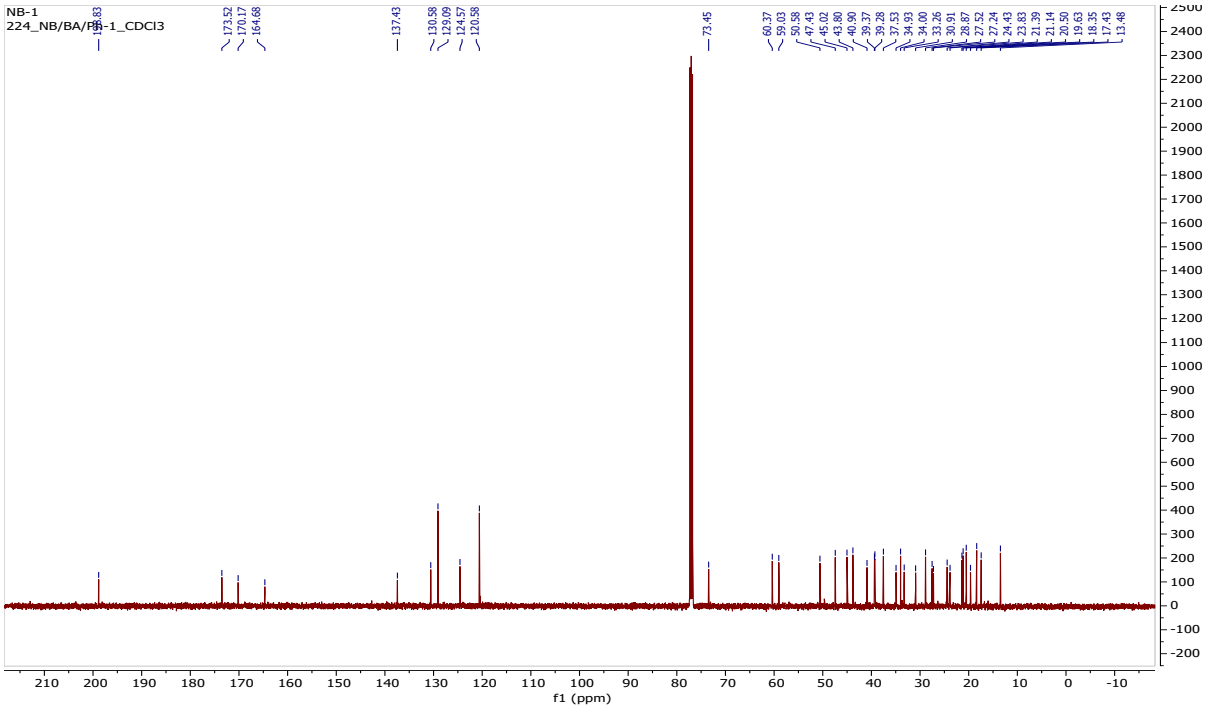




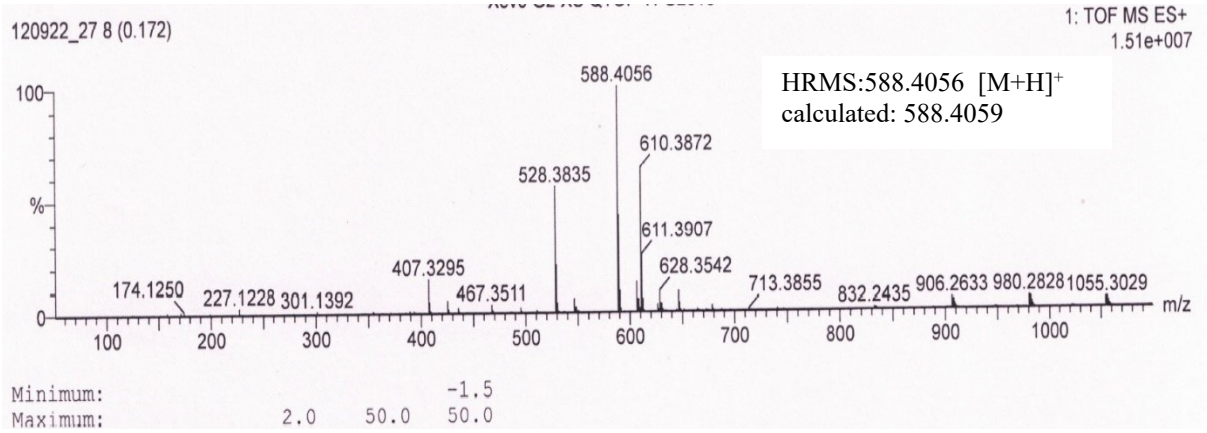
[1]H-NMR spectrum of 4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-4-(phenylcarbamoyl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl acetate (26c)



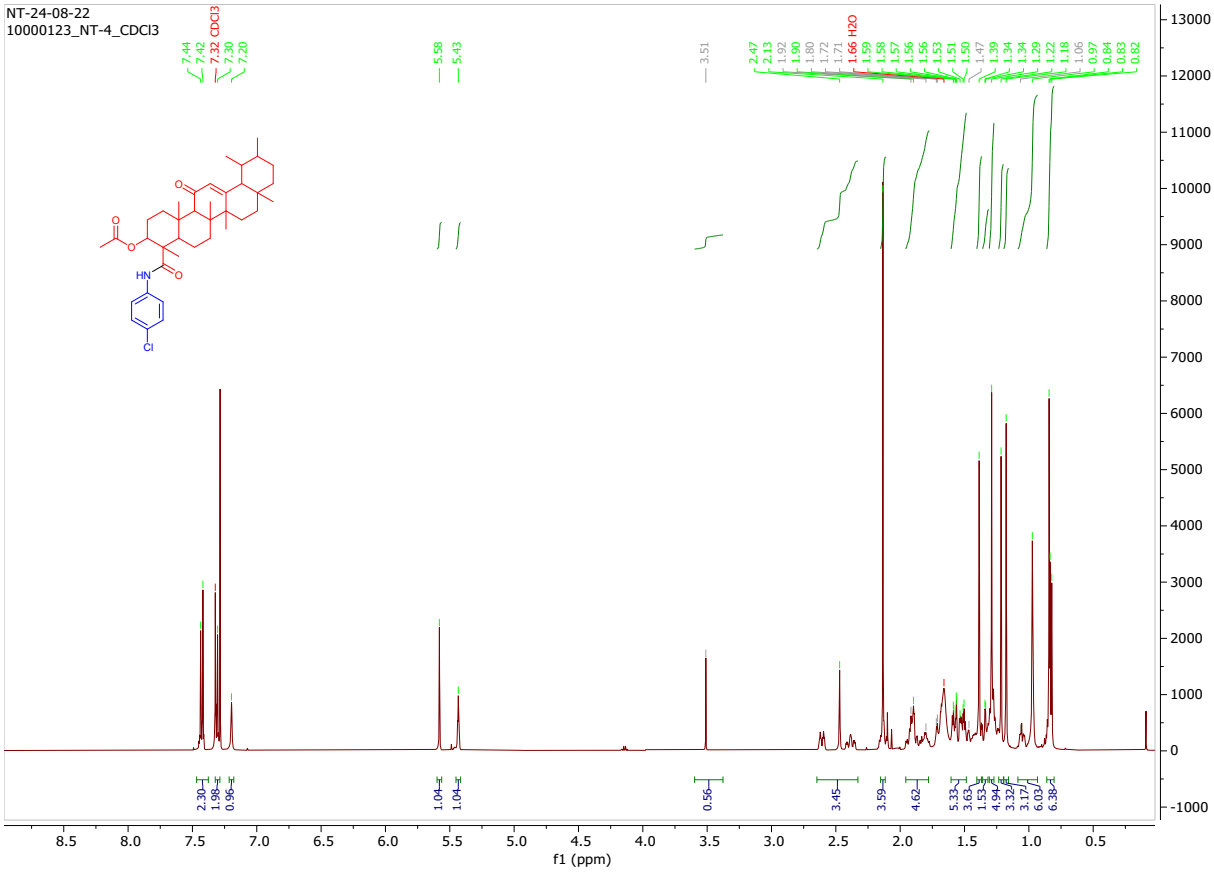
[13]C-NMR spectrum of 4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-4-(phenylcarbamoyl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl acetate (26c)



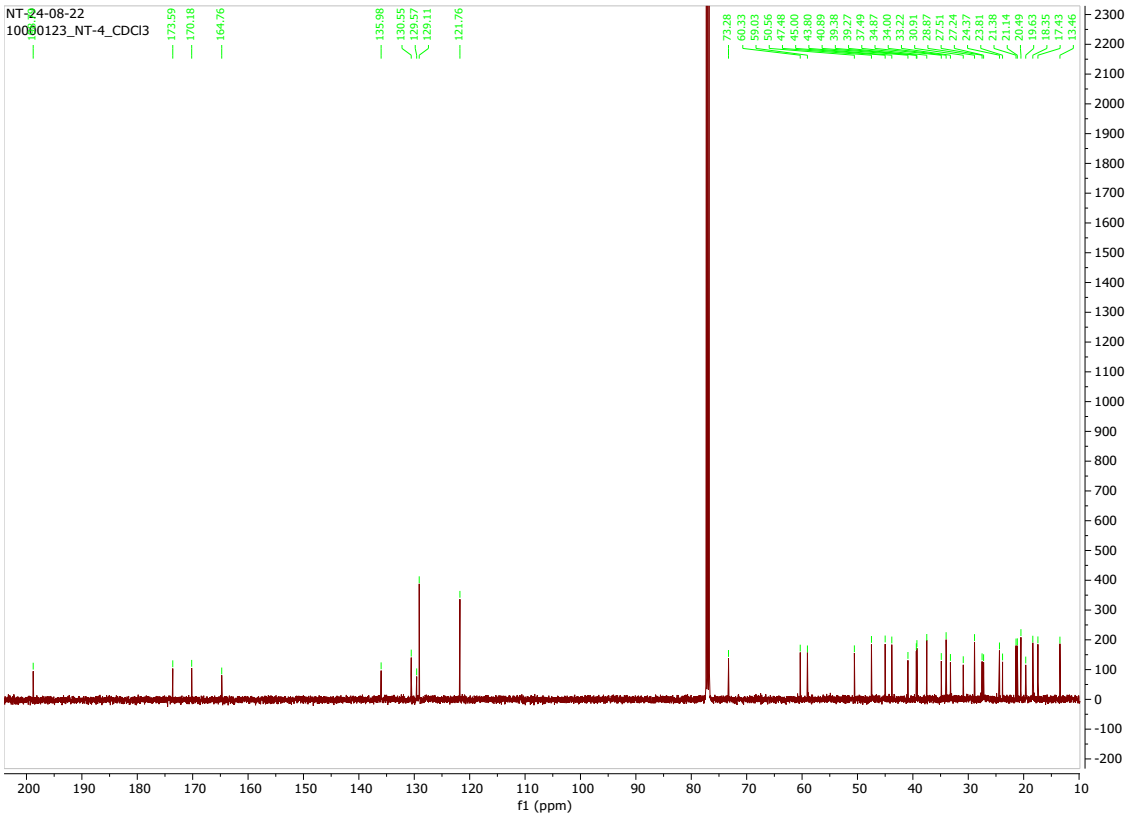
HRMS spectrum of 4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-4-(phenylcarbamoyl)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl acetate (26c)



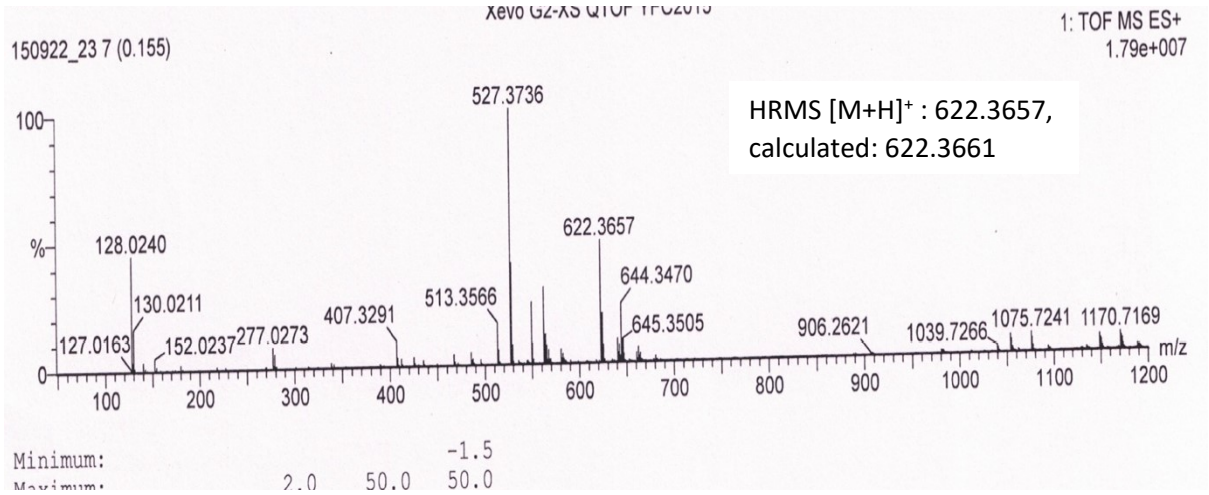
^{1}H- NMR spectrum of 4-((4-chlorophenyl)carbamoyl)-4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-ylacetate (27c)



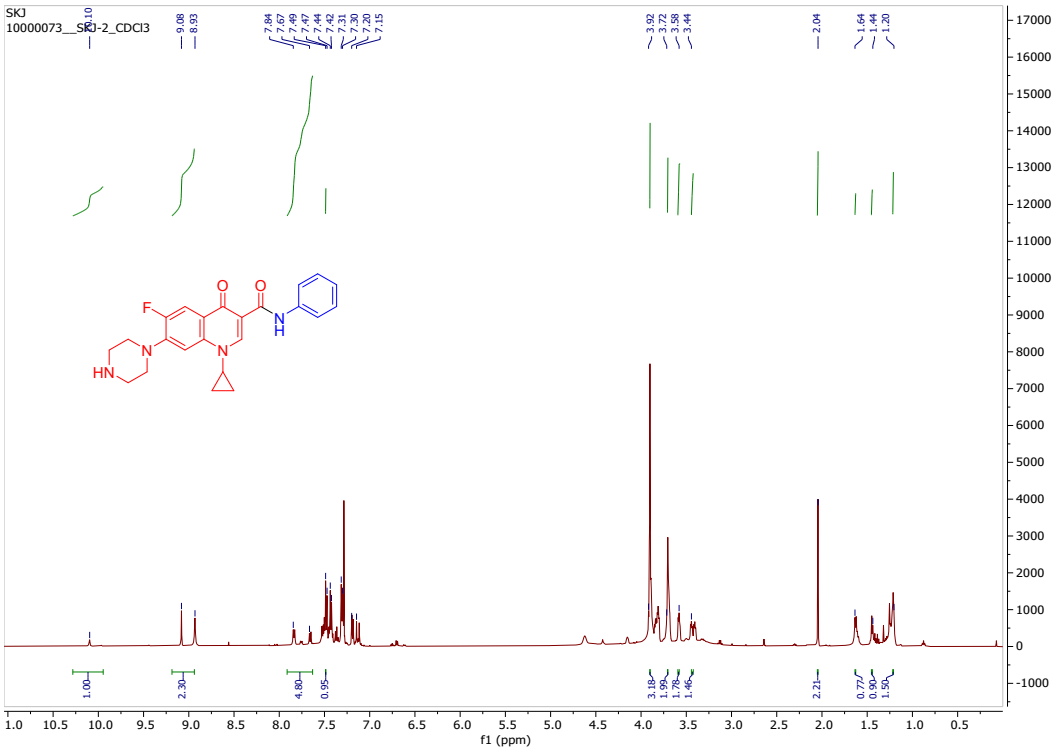
^{13}C-NMR spectrum of 4-((4-chlorophenyl)carbamoyl)-4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-ylacetate(27c)



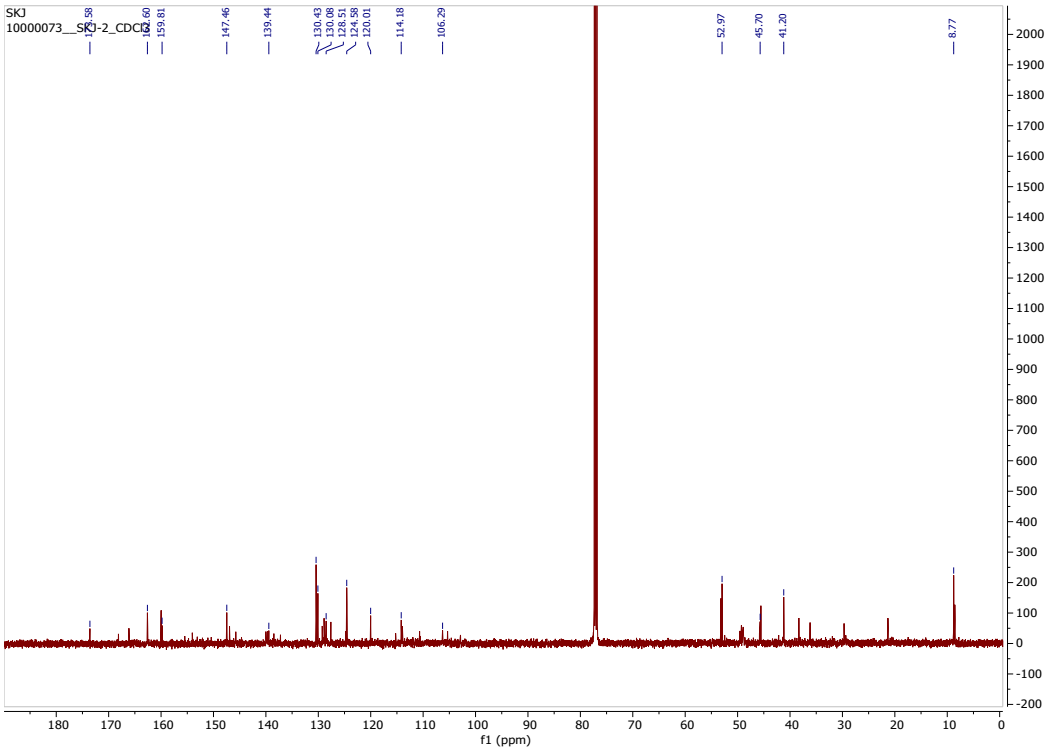
HRMS spectrum of 4-((4-chlorophenyl)carbamoyl)-4,6a,6b,8a,11,12,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-ylacetate (27c)



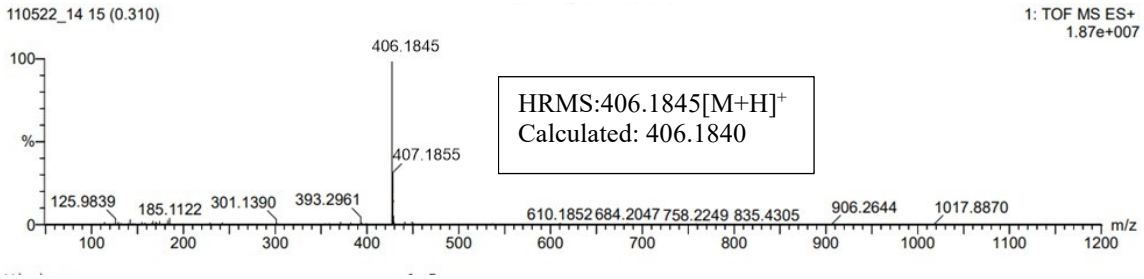
[1]H-NMR spectrum of 1-cyclopropyl-6-fluoro-4-oxo-N-phenyl-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (28c)



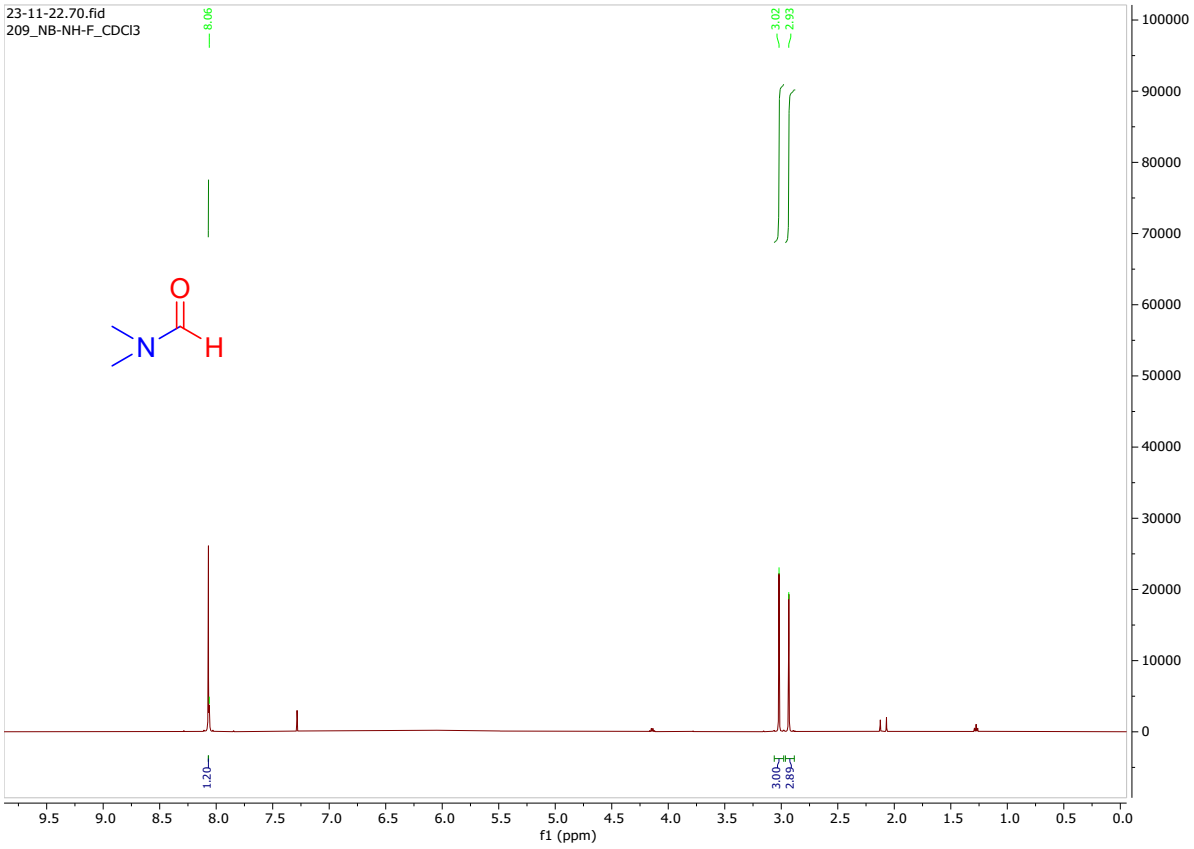
[13]C-NMR spectrum of 1-cyclopropyl-6-fluoro-4-oxo-N-phenyl-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide(28c)



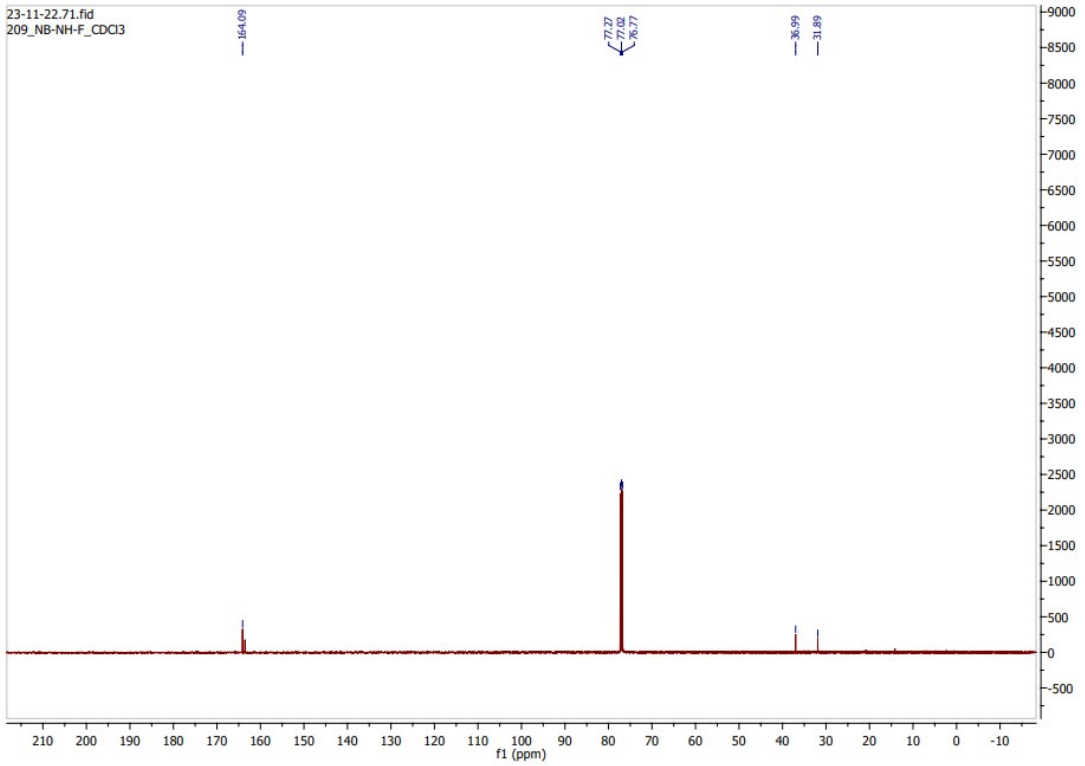
HRMS spectrum of 1-cyclopropyl-6-fluoro-4-oxo-N-phenyl-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide(28c)



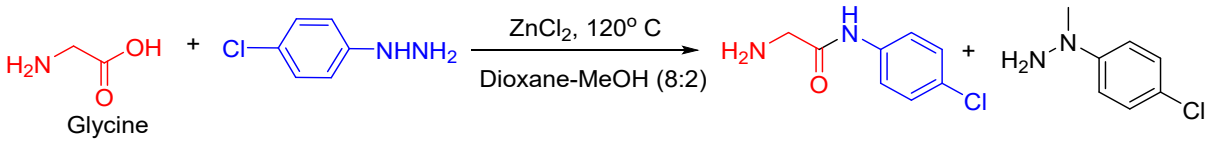
^{1}H-NMR of DMF (**29c**)



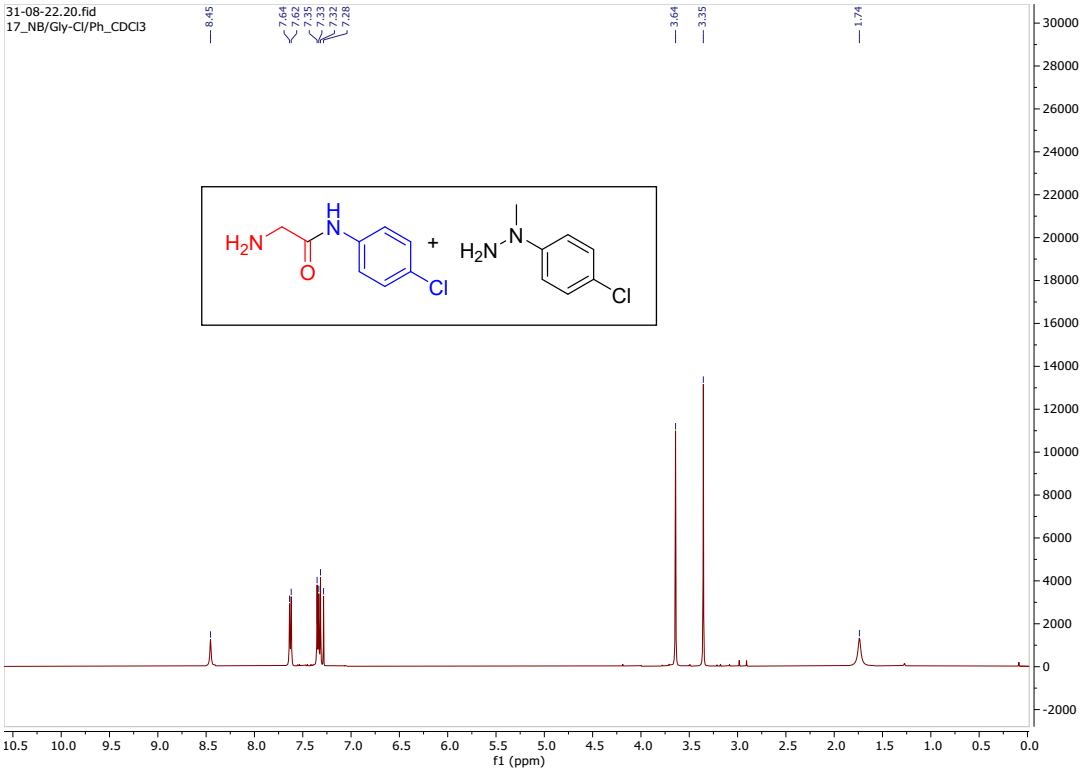
^{13}C-NMR of DMF (**29c**)



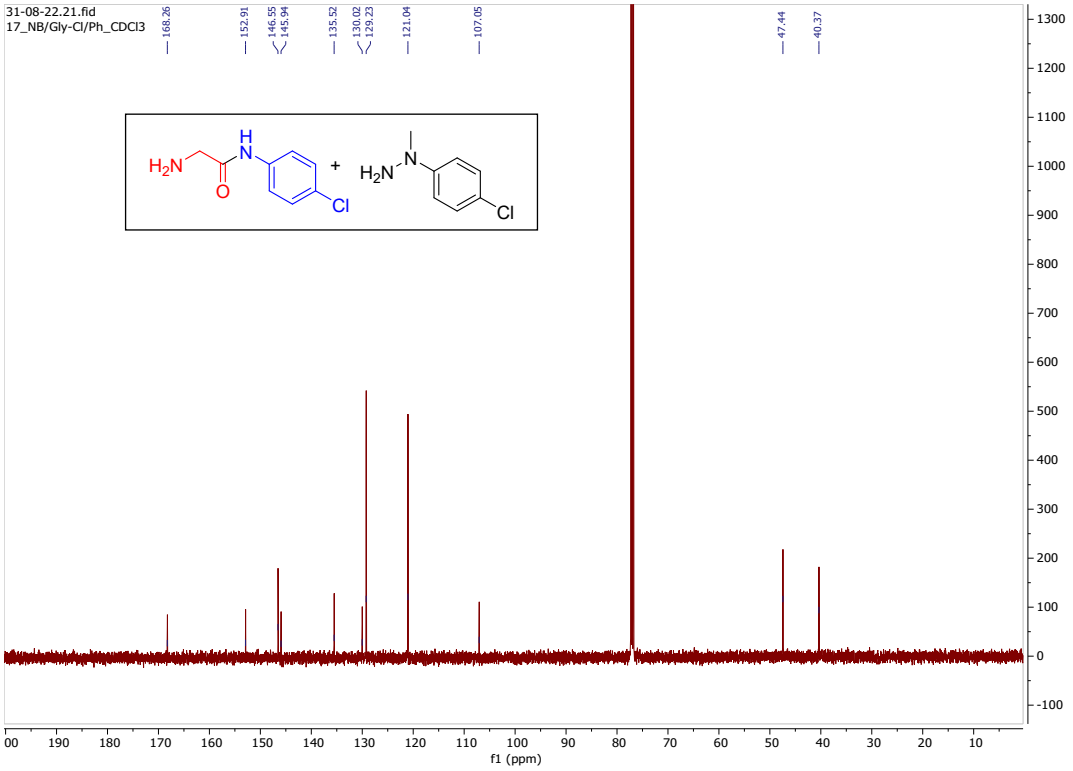
Section S3: Reaction of glycine with 4-chlorophenylhydrazine



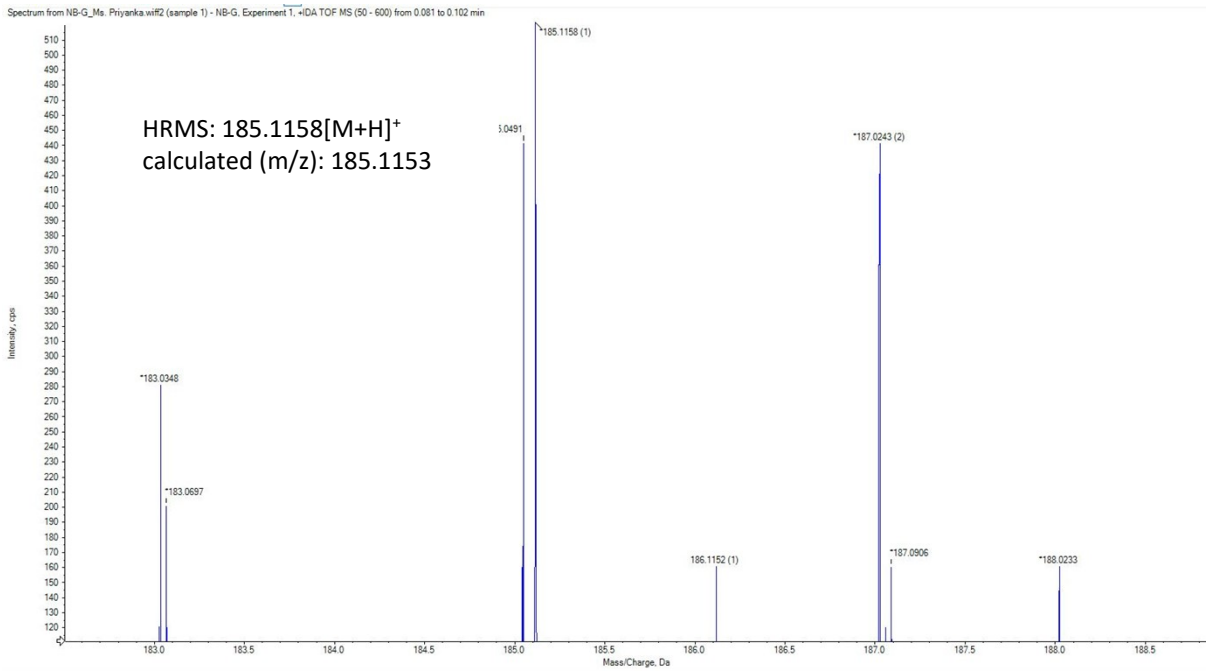
^{1}H NMR spectrum of 2-amino-N-(4-chlorophenyl)acetamide (19c):



^{13}C NMR spectrum of 2-amino-N-(4-chlorophenyl)acetamide (19c):

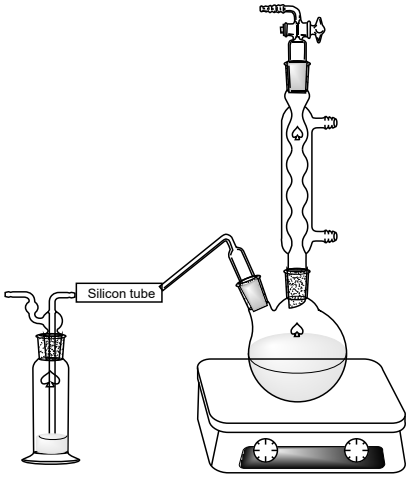


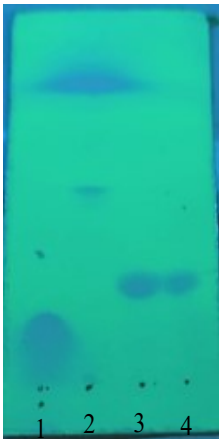
Mass spectrum of 2-amino-N-(4-chlorophenyl)acetamide (19c):



Section S4: Ammonia trapping experiment

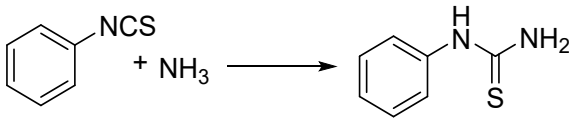
The objective of the experiment was to identify the plausible mechanism of amide formation where a trap system was attached with the reaction mixture of benzoic acid phenylhydrazine and zinc chloride in order to find out the reaction intermediate. Primary amine and ammonia usually convert to urea or thiourea easily when react to phenylisocyanate and phenylisothiocyanate (PITC) respectively. Release ammonia can be fixed in form of thiourea. Ammonia was trapped in the trap solution containing mixture of phenylthioisocynate, and pyridine in methanol. It was observed that the trapped ammonia results in formation of 1-phenylthiourea by reacting with phenylthioisocynate. This is confirmed by co-TLC with standard and NMR.





1. Pyridine
2. PITC
3. Reaction
4. Standard:
   1-phenylthiourea

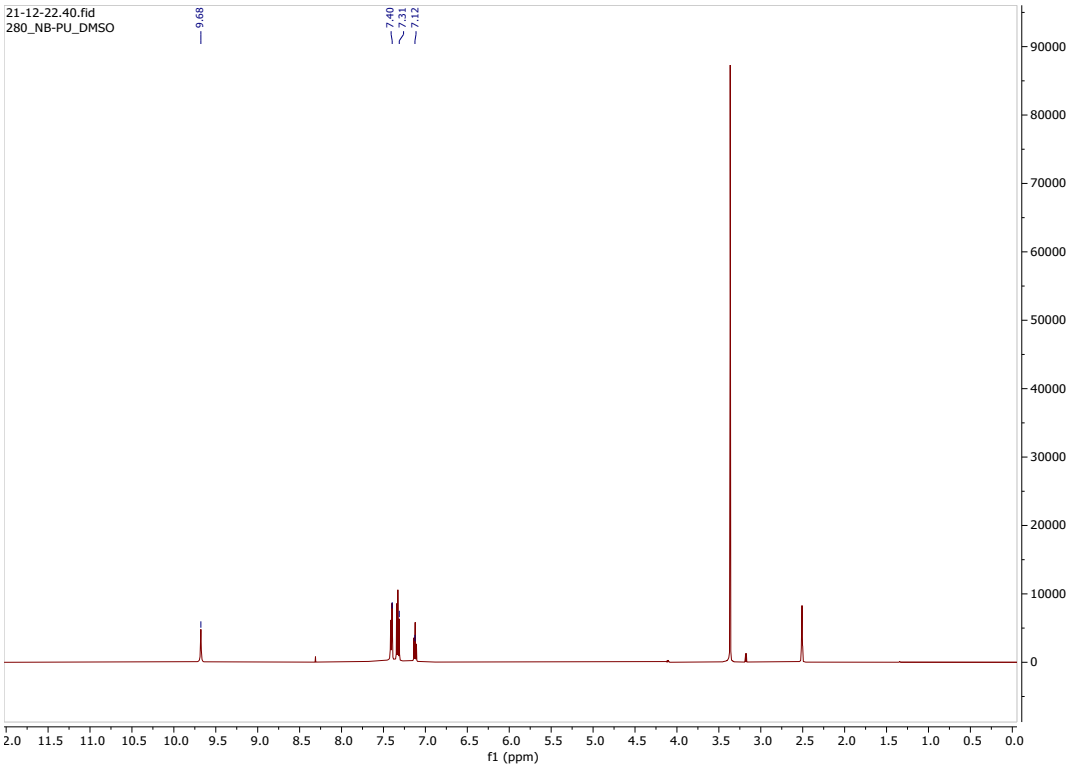
Mobile Phase
4:6:0.1 = Ethylacetate:
Hexane: Acetic acid



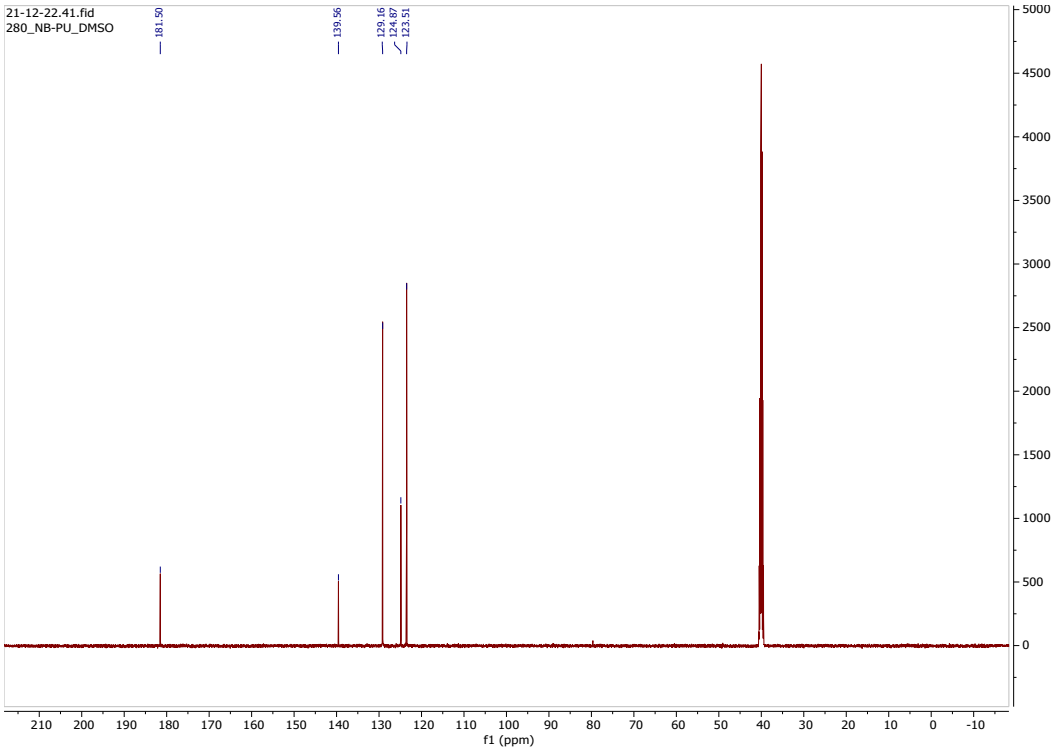
1-phenylthiourea

1-phenylthiourea (30): ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.40(d, *J*= 8.5, 2H), 7.31(m,2H) 7.12(m, 1H), ^{13}C NMR (500 MHz, DMSO-d_6) δ 181.5, 139.6, 129.2, 124.8, 123.5.

^{1}H-NMR spectrum of 1-phenylthiourea (**30**)

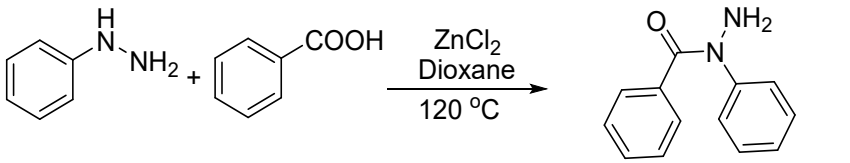


^{13}C-NMR spectrum of 1-phenylthiourea (**30**)



Section S5: Study of reaction intermediate after 5 h

A reaction of phenylhydrazine with benzoic acid was carried out under the optimized reaction condition. After 5.5 h of the reaction, an aliquot was pooled and loaded to preparative TLC to isolate the possible intermediates. We noticed the formation of N-phenylbenzohydrazide. The same intermediate didn't notice at the end of the reaction. It was confirmed by NMR.

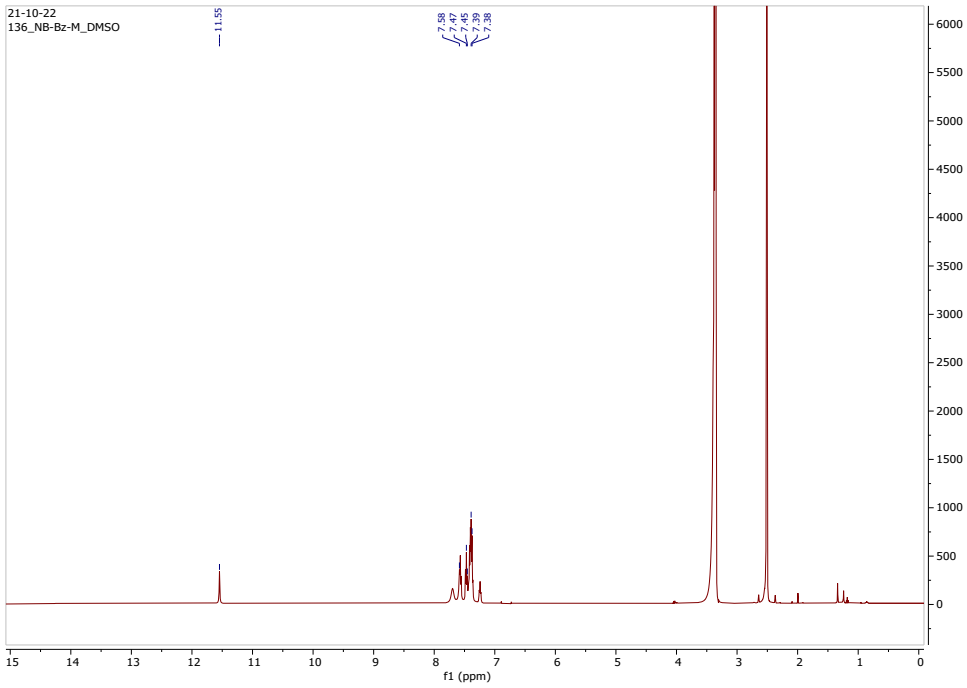


N-phenylbenzohydrazide

N-phenylbenzohydrazide (31):

^{1}H NMR (500 MHz, d_6-DMSO) δ: 11.57(s 2H), 7.58-7.56 (m,2H), 7.48-7.37(m,8H), 7.25-7.22 (m, 1H) ^{13}C NMR (500 MHz, d_6-DMSO) δ 165.8, 132.7, 130.8, 129.2, 129.0, 128.3, 127.7

^{1}H-NMR spectrum of N-phenylbenzohydrazide (31)



^{13} C-NMR spectrum of N-phenylbenzohydrazide (31)