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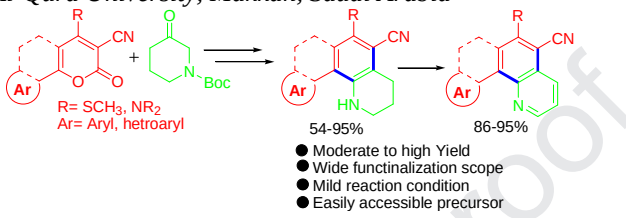
[a]*Department of Chemistry, University of Delhi, North campus, Delhi, India-110007*
[b]*Department of Chemistry, Umm Al-Qura University, Makkah, Saudi Arabia*



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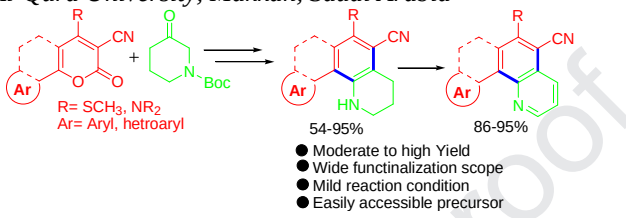

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ABSTRACT

An efficient synthesis of 1,2,3,4-tetrahydroquinolines with donor and acceptor group has been delineated by base mediated ring transformation of 6-aryl-4-substituted-2*H*-pyran-2-one-3-carbonitriles by N-boc-3-piperidone followed by consecutive deprotection of Boc group under acidic conditions. This reaction involves 2 new bond formations namely C4a-C5 and C8a-C8 in order to create the nucleus. Various donor and acceptor functional groups like aryl, heteroaryl, nitrile, methylsulfanyl and secondary amine were installed in 1,2,3,4-tetrahydroquinolines. We extended our approach to synthesize the fused 1,2,3,4-tetrahydroquinolines by using 2-oxobenzo[*h*]chromenes as precursor. Further, we synthesized fused and isolated quinolines through aromatization of 1,2,3,4-tetrahydroquinolines by DDQ in excellent yields. Single-crystal X-ray analysis of the Boc protected tetrahydroisoquinoline **6t** showed the steric hinderance between N-Boc and aryl group.

1. Introduction

1,2,3,4-Tetrahydroquinolines are extremely important motif and present as main skelton or substructure of various natural products and pharmaceutical agents.[1] Tetrahydroquinoline based molecules exhibit diverse biological activities, such as antiHIV,[2] antifungal,[3] antimalarial,[4] antibacterial,[5] antidiabetic,[5] antialzheimer,[6] antipsychotic,[6] antidepressants,[6] antitumor,[6] and vasodillator[6] activities. They are also reported for control gene expression in ecdysone responsive system.[7] The compounds with these skeleton are also used in preparation of molecular glasses, pesticides, antioxidants, fluorescent dyes and dye-sensitized solar cells.[8] Additionally, tetrahydroquinoline based scaffolds are also used as chiral ligands in asymmetric synthesis.[9] Due to remarkable significance of tetrahydroquinolines, various research groups are interested in the development of new synthetic approach. The development of such fluorescence molecules with large stokes shift and photo-stability is much important in biological applications.[10] The organic dyes with high photo-stability are beneficial for long term cellular imaging, which is of great importance for biological processes, pathological pathways, and therapeutic effects.[11] The molecules with large stokes shift (typically, $\Delta\lambda > 80$) can minimize the signal to noise ratio between excitation source and emission for cellular imaging.[12]

In general, tetrahydroquinolines can be achieved by Povarov reaction[13] and reductions of quinolines[14] by using various reducing agents. These methods have limited substrate scope and required very harsh reaction condition. To overcome this problem, various research groups have reported the synthesis of 1,2,3,4-tetrahydroquinolines by inter- and intramolecular cyclizations reaction in presence of palladium, iridium, gold, rhodium and cobalt based catalytic system.[15] Apart from transition metal catalyzed synthesis, acid catalyzed cyclization approach is also used.[16] 1,2,3,4-Tetrahydroquinolines are achieved by $BF_3.OEt_2$ mediated reaction of N-arylimines and arylvinylidenecyclopropanes.[17] In another method, reaction of 2-aminoarylaldehydes and alkenyltrifluoroborates provides tetrahydroquinolines in the presence of TMSCl and Et_3N followed by hydrogenation.[18] Since, presence of functional groups limits the scope of synthesis of tetrahydroquinoline nucleus, further modification could be required and multiple steps needed. Konishi *et.al.* reported a site-selective C-H borylation of tetrahydroquinoline at C-8 position through iridium catalyzed reaction,[19a] which may be use as precursor for the synthesis of 8-aryl-1,2,3,4-tetrahydroquinolines. The functionalized quinolines were also afforded by benzanulaion reactions.[19b,c]

* Corresponding author. Tel/Fax: +91 27666646; Email address: ramendrapratap@gmail.com (Ramendra Pratap)

The earlier reported approach for the synthesis of 1,2,3,4-tetrahydroquinoline ring includes one or more bond formation as shown in retrosynthetic approach and possible bonds are N-C2, C2-C3, C3-C4, C4-C4a, and C8a-N.[13] Herein, we have developed a new approach, which involved 2 bond formation namely C4a-C5 and C8a-C8 in the same pot to create the tetrahydroqinolines (Figure 1).

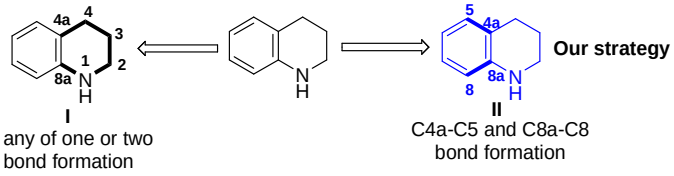
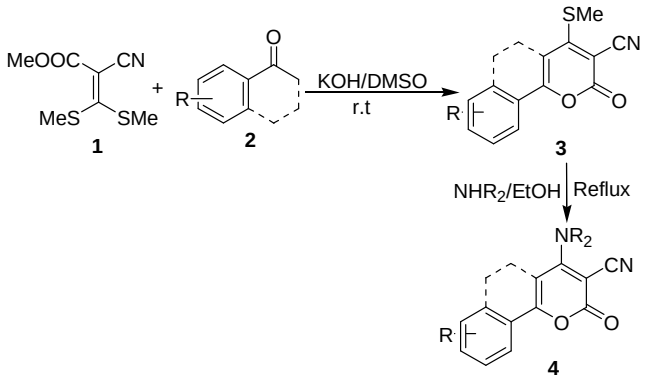


Figure 1. Synthesis of 1,2,3,4-tetrahydroquinolines through disconnection approach (Earlier versus our approach)

2. Result and discussion

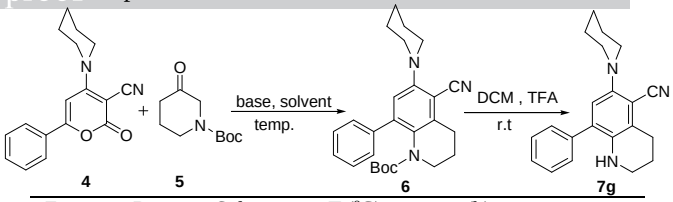
To perform our synthetic approach 6-aryl-2-oxo-4-(*sec*.amino)-2*H*-pyran-3-carbonitriles[20] and 2-oxo-4-(*sec*.amino)-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** were used as precursor and synthesized in two steps from 2-cyano-3,3-bis(methylthio)acrylate **1**. The first step provides **3** by reaction of **1** and aryl methyl ketones and 2-tetralones **2** respectively. The aminated pyrans **4** can be achieved by amination of synthesized compounds with various secondary amine under reflux conditions (Scheme 1).[21]

Once, we had precursor in our hand, we started the optimization of reaction conditions for the synthesis of tetrahydroquinolines. During the optimization of reaction conditions, we performed the ring transformation reaction followed by deprotection of Boc group of crude under acidic condition. To study, we have selected 2-oxo-6-phenyl-4-piperidin-1-yl-2*H*-pyran-3-carbonitrile **4** and 3-oxo-piperidine-1-carboxylic acid tert-butyl ester **5** as model substrates. Deprotection of Boc group was performed by literature procedure using TFA in dichloromethane at room temperature.[22] We started the assessment by using triethyl amine as a base in DMSO and DMF at r.t. and 60 ^{o}C, but no reaction was observed (Table 1, entries 1, 2 and 3). Then, we used cesium carbonate in DMSO and DMF at room temperature as well as at 90 ^{o}C and yield of desired product up to 45% was obtained (Table 1, entries 4-6). Use of lithium hydroxide in DMSO followed by deprotection of Boc group provides 45% tetrahydroquinolines (Table 1, entry 7). Then, we moved to potassium hydroxide in DMF and DMSO and 58-60 %



Scheme 1: Synthesis of 6-aryl-2-oxo-4-(*sec*.amino)-2*H*-pyran-3-carbonitriles and 2-oxo-4-(*sec*.amino)-5,6-tetrahydro-2*H*-benzo[*h*]chromene-3-carbonitriles

Table 1: Optimization of reaction conditions[a]

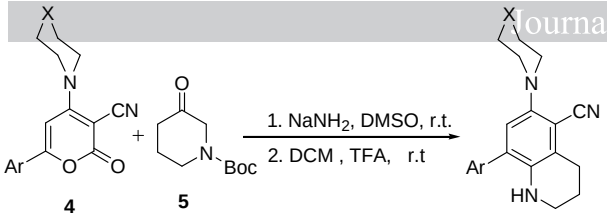


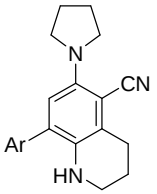
Entry	Base	Solvent	T (^{o}C)	t (h)	Yield (%) 3
1	Et_3N	DMSO	r.t.[b]	12	-[d]
2	Et_3N	DMF	r.t.[b]	12	-[d]
3	Et_3N	DMSO	60	12	-[d]
4	Cs_2CO_3	DMSO	r.t.[b]	12	45
5	Cs_2CO_3	DMF	r.t.[b]	12	45
6	Cs_2CO_3	DMSO	90	12	42
7	LiOH	DMSO	r.t.[b]	8	45
8	KOH	DMSO	r.t.[b]	6	60
9	KOH	DMF	r.t.[b]	6	60
10	KOH	DMSO	90	5	58
11	NaH	DMSO	r.t.[b]	4	55
12	NaH	DMSO	90	4	57
13	KO^{t}Bu	DMSO	r.t.[b]	12	61
14	**$NaNH_2$**	**DMSO**	**r.t.[b]**	**3**	**95**
15	$NaNH_2$	DMF	r.t.[b]	6	90
16	$NaNH_2$	DMSO	90	8	70
17	$NaNH_2$	THF	Reflux	12	70

a) All reactions were performed by stirring 2-oxo-6-phenyl-4-piperidin-1-yl-2*H*-pyran-3-carbonitrile **4** (0.5 mmol), **5** (0.6 mmol) and base (1.0 mmol) in solvent (5.0 mL) at different temperature and crude obtained was treated with TFA in dichloromethane at room temperature; (b) Room temperature was ranging between 25-35 ^{o}C, (c) Isolated yield was reported, (d) 2-pyranone left unconsumed

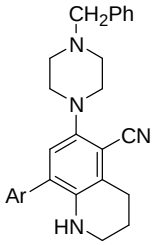
yield of desired product was isolated (Table 1, entries 8-10). However, used of sodium hydride in DMSO at room temperature and 90 ^{o}C provides 55 and 57% yield respectively (Table 1, entries 11-12). Then potassium tertiary butoxide was used as base in DMSO and 61 % of tetrahydroquinoline was obtained (Table 1, entry 13), while sodamide in DMSO at room temperature provides 95 % of desired product in a shorter reaction time (Table 1, entry 14). Then, we tested sodamide in DMF at room temperature and afforded 90% of desired product (Table 1, entries 15). On the other hand conducting the reaction at higher temperature in DMSO provided 70 % of the compound (Table 1, entry 16). Then, we switched the solvent DMSO to THF at reflux temperature to afford **7g** in a good yield (Table 1 entry 17). The optimization of reaction condition shows that reaction of 2-pyranone **4** and **5** in DMSO in presence of sodamide at room temperature act as best reaction condition. The crude thus obtained was treated with TFA in DCM to afford **7** in excellent yield.

We tried to isolate the Boc protected tetrahydroisoquinolines but proton NMR shows presence of some aliphatic impurity which was difficult to remove, so we crystallized one compound and the structure of the Boc protected product was confirmed by X-ray crystallographic analysis (Figure 2; Table 1 in SI). Using the optimized reaction conditions, the scope and general applicability of this methodology was investigated and a series of highly functionalized tetrahydroquinolines was synthesized in 65-95 % yield. Further, we observed that various electron donating and withdrawing aryl group in pyran ring didn't affect the yield significantly. The bulky aryl group like naphthyl and 2-substituted aryl group in pyran ring significantly reduce the yield due to steric hindrance. Interestingly, 8-heteroatyl-1,2,3,4-tetrahydroquinolines was achieved in good yield.





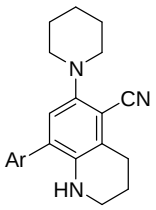
7a-d



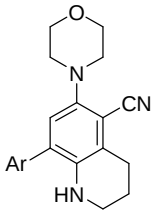
7e-f

7a) Ar = 4-Br.C_6H_4; 89%
7b) Ar = 2.4.$(Cl)_2C_6H_3$; 70%
7c) Ar = 2-napthyl; 65%
7d) Ar = Thienyl; 91%

7e) Ar = 4-OMe.C_6H_4; 80%
7f) Ar = 4-Br.C_6H_4; 81%



7g-n



7o-t

7g) Ar = C_6H_5; 95%
7h) Ar = 4-CH_3.C_6H_4; 95%
7i) Ar = 4-OMe.C_6H_4; 80%
7j) Ar = 3.4.$(OMe)_2C_6H_3$; 80%
7k) Ar = 4-F.C_6H_4; 89%
7l) Ar = 4-Cl.C_6H_4; 84%
7m) Ar = 2-Thienyl; 90%
7n) Ar = 2-Furyl; 88%

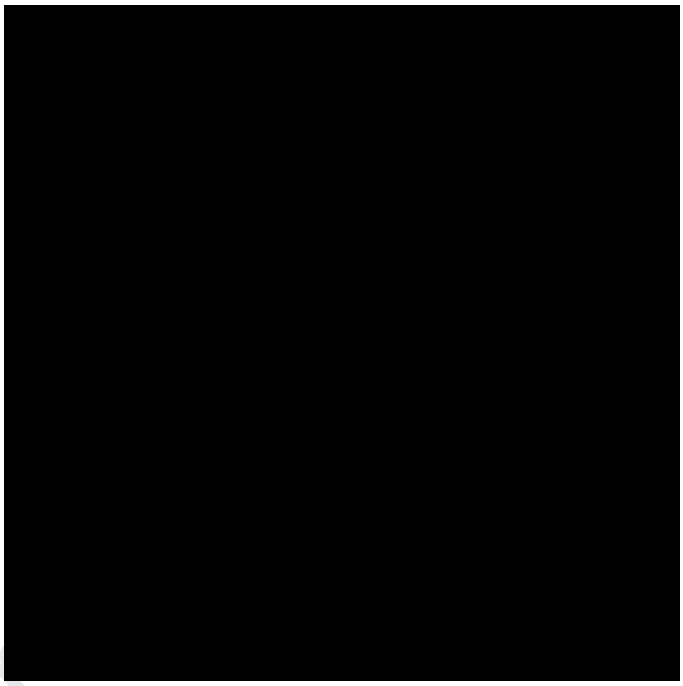
7o) Ar = C_6H_5; 95%
7p) Ar = 4-CH_3.C_6H_4; 95%
7q) Ar = 4-F.C_6H_4; 84%
7r) Ar = 4-Cl.C_6H_4; 85%
7s) Ar = 4-Br.C_6H_4; 81%
7t) Ar = 4-OMe.C_6H_4; 88%

Scheme 2. Synthesis of various functionalized 1,2,3,4-tetrahydro-quinolines[a,b] [a) All reactions were performed by stirring **4** (0.5 mmol), **5** (0.6 mmol) and sodamide (1.0 mmol) in DMSO (5.0 mL) at room temperature and crude obtained was treated with TFA in dichloromethane at room temperature (25-35 °C), (b) Isolated yield was reported.]

We further investigated the scope of reaction for the synthesis of naphtho-fused quinolines; hexahydro-1-aza-benzo[*c*]phenanthrenes **8**. The ring transformation of 2-oxobenzo[*h*]chromenes **4** with **5** under similar reaction conditions afforded fused tetrahydroquinolines and interestingly, good yield of product was observed (Scheme 3).

To further investigate the scope of reaction, we have used compound **3** as a precursor to check the tolerance of reaction on functional group. Previously, we have observed that presence of methylthio group provides some side reaction and afford complex mixture or low yield of product.[23] Interestingly, reaction of **3** with **5** in presence of $NaNH_2$ in DMSO afforded the desired product **9** in the moderate yield 52-64% (Scheme 4).

A plausible mechanism for the formation of **7** is shown in scheme 5. The structural investigation of 2-pyranone shows that C2, C4 and C6 position is highly reactive towards nucleophilic attack and position C6 is more reactive due to extended conjugation with electron withdrawing groups. The compound **5** can generate two different nucleophiles at position 2 and 4 and their involvement in the reaction can provides quinoline or isoquinoline skeleton. Mechanistically, if reaction follows path A, carbanion generated at position 2 of N-Boc-3-piperidone attacks at C-6 of pyran via Michael addition followed by ring opening and provides intermediate **A**. The intermediate **A** undergoes decarboxylation and protonation and provides intermediate **B**. In the presence of excess of base intermediate **B**



Scheme 3. Scope of 2-oxobenzo[*h*]chromenes for the synthesis of fused quinolines[a,b] [All reactions were performed by stirring **4** (0.5 mmol), **5** (0.6 mmol) and sodamide (1.0 mmol) in DMSO (5.0 mL) at room temperature and crude obtained was treated with TFA in dichloromethane at room temperature (25-35 °C), (b) Isolated yield is reported.]

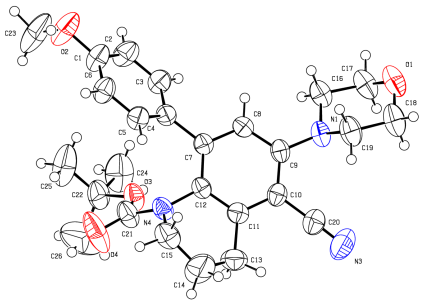
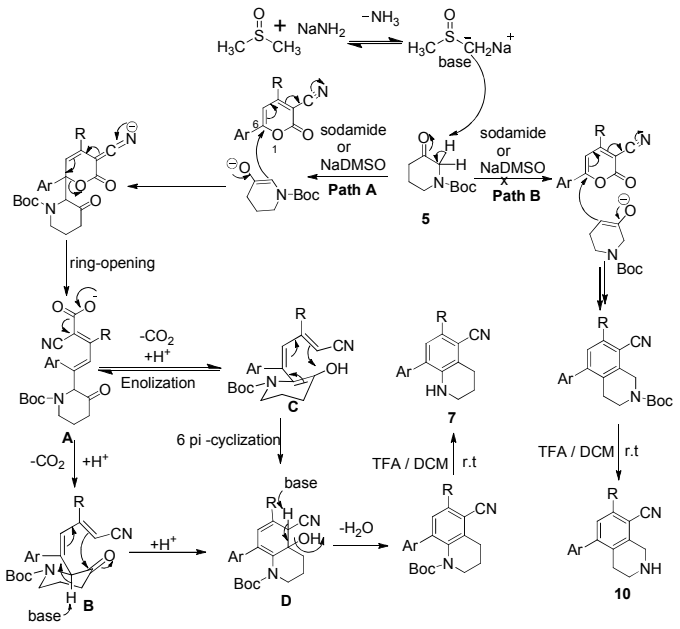
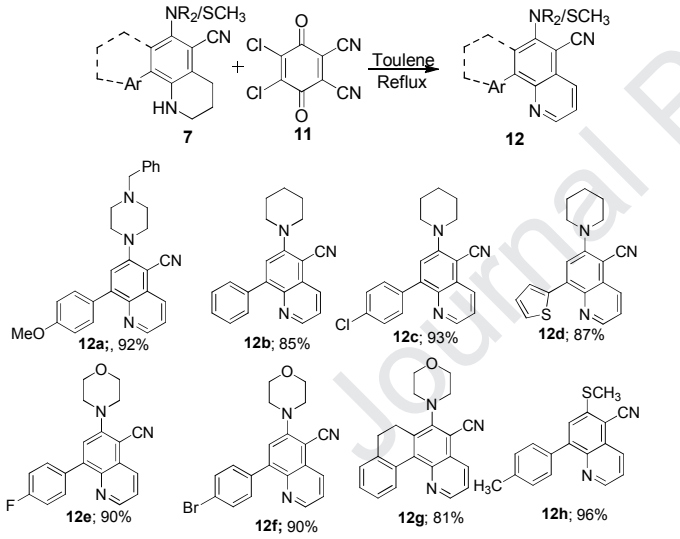


Figure 2. ORTEP diagram of tert-butyl 5-cyano-8-(4-methoxyphenyl)-6-morpholino-3,4-dihydroquinoline-1(2*H*)-carboxylate **6t**

Scheme 4: Synthesis of methylthio group containing 1,2,3,4-tetrhydroquinolines **9a,b**.[a)All reactions were performed by stirring 3 (0.5 mmol), 5 (0.6 mmol) and sodamide (1.0 mmol) in DMSO (5.0 mL) at room temperature and crude obtained was treated with TFA in dichloromethane at room temperature (25-35 °C), (b) Isolated yield was reported.



Scheme 5. Plausible mechanism for the synthesis of 8-aryl-6-substituted-1,2,3,4-tetrahydroquinoline-5-carbonitriles



Scheme 6. Synthesis of functionalized quinolines[a] [Reaction was carried out by refluxing tetrahydroquinolines (0.2 mmol), DDQ (0.4 mmol) in toulene (3.0 mL) at 120 °C and isolated yield is reported.]

provides carbanion, which undergoes intramolecular cyclization by involving carbonyl carbon to afford intermediate **D**. In addition, intermediate **A** can also provides intermediate **C** by decarboxylation, protonation and enolization. Intermediat **C** can undergo 6π-electrocyclization to afford intermediate **D**, which undergoes aromatization by loss of water to give the N-Boc-1,2,3,4-tetrahydroquinolines. At last, we performed the deprotection of Boc group under acidic condition to afford the functionalized 1,2,3,4-tetrahydroquinolines. If the reaction follows another path B, reaction involves the carbanion generated from position 4 of N-Boc-3-piperidone and tetrahydroisoquinoline can be achieved following the same mechanistic pathways as reported for path A. The reaction provides exclusively 1,2,3,4-tetrahydroquinolines, which support the formation of carbanion at position 2 of 3-piperidone. Most likely, presence of Boc group supports the formation of carbanion at C2 due to additional negative Inductive effect. Further, we have aromatized the tetrahydroquinolines by using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in toluene to afford the quinoline in excellent yield (Scheme 6).[24] This reaction works smoothly and provides the functionalized quinolines in excellent yield.

Alternatively, compound **7** can also aromatized to produce 8-aryl-6-(*sec.amino*)-quinoline-5-carbonitriles in moderate yield in presence PIDA using toluene as solvent. We tried the different ratio of 1,2,3,4-tetrahydroquinoline and DDQ and 1:2 ratio works perfectly for aromatization reaction. We have selected both isolated and fused quinolines as substrate for aromatization and isolated the product in excellent yield. Interestingly, in case of fused tetrahydroquinolines the bridge ethylene group was not oxidized even in presence excess of DDQ.

3. Conclusions

In summary, we have developed an efficient transition metal free approach for the synthesis of highly functionalized 1,2,3,4-tetrahydroquinoline, which can easily provides quinoline simply by oxidation in presence of DDQ. The amusing qualities of the synthetic chemistry include high regioselectivity, easily available starting material and wide functional group tolerance. This method provides new class of functionalized fused and isolated 1,2,3,4-tetrahydroquinolines and quinolines. This method open a new avenue for the construction of highly functionalized 1,2,3,4-tetrahydroquinolines and quinolines from easily accessible precursor under basic condition through C4a-C5 and C8a-C8 bond formation reactions.

4. Experimental

4.1. General

All the required reagents and solvents were purchased from Sigma Aldrich, Spectrochem and Alfa Aesar. These compounds were directly used without further purification. The required precursors; 2*H*-pyran-2-one has been synthesized earlier by various research groups[20,22,23] and extensively used for ring transformation reactions. Herein, we have synthesized some newly functionalized 2-pyranones along with reported compounds and characterization data for new compounds has been provided in experimental section. IR spectrophotometer was used to study the stretching frequencies and data were reported in wave number (cm^{-1}). The proton NMR (400 MHz) and carbon NMR (100 MHz) spectra were recorded in $CDCl_3$ solution (residual peaks of chloroform at 7.26 ppm for ^1H and 77.0 ppm for ^{13}C were used as reference) or in DMSO-d_6 solution (residual peaks of DMSO at 2.50 ppm for ^1H and 39.5 ppm for ^{13}C were used as reference). The coupling constant *J* are reported in Hz and signal patterns for proton NMR is reported as s, singlet; d, doublet; br, broad signal; t, triplet; q, quartet; m, multiplet; dd, double doublet etc. High-resolution mass spectra were recorded on a quadrupole-time-of-flight mass spectrometer.

4.2. General Procedure for the synthesis of 8-aryl/heteroaryl-1,2,3,4-tetrahydroquinolines 7: To a vacuum dried RB flask a mixture of the appropriate 6-aryl-2-oxo-4-(*sec*.amino)-2*H*-pyran-3-carbonitrile **4** (0.5 mmol), N-boc-3-piperidone **5** (0.6 mmol), $NaNH_2$ (1.0 mmol) in DMSO (5.0 ml) was stirred at r.t. for 3 h. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured slowly onto ice–water with constant stirring. The mixture was quenched with 10% aqueous HCl. The resulting precipitate was collected by filtration, washed with H_2O, and dried. Crude product was treated with TFA (10 mmol) in DCM

(3.0 mL) at room temperature for 30-35 minutes and then poured the reaction mixture onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and than evaporated in vacuo. Crude products **7** were purified by silica gel column chromatography using 10% ethyl acetate in hexane.

Tert-butyl 5-cyano-8-(4-methoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate 6i

A mixture of 6-(4-methoxyphenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.155 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. After completion, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The crude products thus obtained was purified by column chromatography on neutral alumina using 5% ethyl acetate in hexane as an eluent to afford **6i** as yellow solid; yield: 192 mg (86%); mp = 85–87 °C; IR (KBr): 3055, 2931, 2212, 1448-1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.974 (s, 9H), 1.78-1.88 (m, 6H), 3.00-3.14 (m, 8H), 3.82-3.85 (m, 5H), 6.81 (s, 1H, ArH), 6.95 (brm, 2H, ArH), 7.26-7.34 (brm, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 24.0, 26.0, 27.3, 28.2, 42.7, 53.3, 55.2, 80.2, 103.7, 114.0, 117.0, 118.0, 128.8, 129.7, 130.7, 131.8, 140.1, 142.1, 154.8, 159.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{34}N_3O_3$: 448.2595; found: 448.2609.

Tert-butyl 5-cyano-8-(4-methoxyphenyl)-6-morpholino-3,4-dihydroquinoline-1(2H)-carboxylate 6t

A mixture of 6-(4-methoxyphenyl)-4-morpholino-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.156 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. After completion, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The crude products thus obtained was purified by column chromatography on neutral alumina using 5% ethyl acetate in hexane as an eluent to afford **6t** as Yellow solid; yield: 200 mg (89%); mp = 76–78 °C; IR (KBr): 3053, 2959, 2217, 1450-1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.979 (s, 9H), 1.87 (s, 1H), 2.26 (s, 1H), 3.09-3.21 (m, 6H), 3.82 (s, 3H, -OMe), 3.86-3.91 (m, 6H), 6.82 (s, 1H, ArH), 6.94-6.96 (m, 2H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.4, 25.7, 28.1, 42.6, 51.8, 55.4, 66.4, 79.7, 103.0, 114.0, 116.6, 118.0, 118.5, 129.1, 130.3, 131.3, 146.7, 153.0, 154.0, 159.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{32}N_3O_4$: 450.2387; found: 450.2374.

8-(4-Bromophenyl)-6-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7a

A mixture of 6-(4-bromophenyl)-2-oxo-4-(*sec*.amino)-2*H*-pyran-3-carbonitrile **4** (0.5 mmol, 0.172 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7a** yellow solid; yield: 170 mg (89%); mp = 145–147 °C; IR (KBr): 3401, 2926, 2206, 1441-1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.94-2.00 (m, 6H), 2.95 (t, J = 6.8 Hz, 2H), 3.15 (t, J = 5.6 Hz, 2H), 3.46 (t, J = 6.8 Hz, 4H), 6.39 (s, 1H, ArH), 7.28 (d, J = 8 Hz, 2H, ArH), 7.56 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 25.5, 26.4, 41.7, 50.5, 98.0, 114.5, 114.5 119.1, 122.0, 126.0, 130.6, 131.2, 131.8, 132.0, 137.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}BrN_3$: 382.0913; found: 382.0907.

8-(2,4-Dichlorophenyl)-6-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile7b

A mixture of 6-(2,4-dichlorophenyl)-2-oxo-4-(pyrrolidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.167 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3.5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7b** yellow solid; yield: 130 mg (70%); mp = 83–85 °C; IR (KBr): 3396, 2924, 2216, 1439-1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.85-1.91 (m, 6H), 2.88 (t, J = 6.4 Hz, 2H), 3.08-3.12 (m, 2H), 3.37-3.40 (m, 4H), 6.24 (s, 1H, ArH), 7.15 (d, J = 8.2 Hz, 1H, ArH), 7.26 (dd, J = 2.0 Hz, 8.0 Hz, 1H, ArH), 7.43 (d, J = 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 25.5, 26.4, 41.7, 50.5, 114.5, 119.1, 126.0, 127.5, 127.7, 129.5, 129.8, 132.2, 132.3, 134.0, 134.2, 134.6, 135.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}Cl_2N_3$: 372.1029; found: 372.1014.

8-(Naphthalen-2-yl)-6-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7c

A mixture of 6-(naphthalen-2-yl)-2-oxo-4-(pyrrolidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.158 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3.5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained 0 crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was

neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7c** yellow solid; yield: 115 mg (65%); mp = 86–88 °C; IR (KBr): 3410, 2931, 2215, 1445-1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.95-2.05 (m, 6H), 2.99 (t, J = 6.6 Hz, 2H), 3.15 (t, J = 5.2 Hz, 2H), 3.47-3.51 (m, 4H), 6.53 (s, 1H, ArH), 7.50-7.54 (m, 3H, ArH), 7.85-7.92 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 25.5, 26.4, 41.5, 50.5, 97.7, 115.4, 119.4, 125.2, 125.6, 125.7, 126.1, 126.5, 127.1, 128.3, 131.1, 131.6, 133.6, 134.8, 136.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}N_3$: 354.1965; found: 354.1974.

6-(Pyrrolidin-1-yl)-8-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7d

A mixture 2-oxo-4-(pyrrolidin-1-yl)-6-(thiophen-2-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.136 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7d** yellow solid; yield: 141 mg (91%); mp = 130–132 °C; IR (KBr): 3397, 2923, 2201, 1439-1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.96-2.03 (m, 6H), 2.96 (t, J = 6.4 Hz, 2H), 3.22 (brm, 2H), 3.48 (brm, 4H), 6.59 (s, 1H, ArH), 7.12 (dd, J = 4.0 Hz, 5.2 Hz, 1H, ArH), 7.23 (d, J = 3.2 Hz, 1H, ArH) 7.38 (d, J = 4.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.4, 25.0, 26.0, 41.4, 50.2, 115.0, 118.5, 120.6, 121.3, 123.6, 130.6, 131.0, 131.1, 131.6, 132.6, 146.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}N_3S$: 310.1372; found: 310.1375.

6-(4-Benzylpiperazin-1-yl)-8-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7e

A mixture of 4-(4-benzylpiperazin-1-yl)-6-(4-methoxyphenyl)-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.200 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7e** yellow solid; yield: 176 mg (80%); mp = 136–138 °C; IR (KBr): 3407, 2924, 2215, 1447-1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (quint, J = 8 Hz, 2H), 2.59-2.64 (m, 4H), 2.89 (t, J = 6 Hz, 2H), 3.00-3.01 (brm, 4H), 3.12-3.15 (brm, 2H), 3.53 (s, 2H, -CH_2), 3.77 (s, 3H, -OMe), 3.90 (br, 1H, NH), 6.59 (s, 1H, ArH), 6.91 (d, J = 14.4 Hz, 2H, ArH), 7.18-7.21 (m, 2H, ArH), 7.23-7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 26.3, 41.4, 52.1, 53.2, 55.3, 62.7, 107.3, 114.4, 117.2, 119.2, 125.3, 127.3, 128.3, 129.2, 129.5, 130.0, 130.2 131.1, 138.2, 146.4, 159.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{31}N_4O$: 439.2492; found: 439.2479.

6-*(*4-Benzylpiperazin-1-yl)-8-(4-bromophenyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7f

A mixture of 4-(4-benzylpiperazin-1-yl)-6-(4-bromophenyl)-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.224 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7f** yellow solid; yield: 198 mg (81%); mp = 143–145 °C; IR (KBr): 34113, 3028, 2217, 1446-1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.86 (quint, J = 7.6 Hz, 2H), 2.59 (brm, 4H), 2.90 (t, J = 6.92 Hz, 2H), 2.99 (brm, 2H), 3.12-3.16 (m, 2H), 3.49-3.54 (m, 2H), 3.79 (s, 2H, -CH_2), 6.55 (s, 1H, ArH), 7.17-7.20 (m, 4H, ArH), 7.23-7.28 (m, 3H, ArH), 7.50 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 26.3, 41.3, 51.8, 53.1, 62.6, 108.0, 117.0, 119.0, 122.1, 125.8, 127.6, 128.3, 129.6, 129.8, 130.5, 132.1, 136.8, 138.0, 146.2; HRMS (ESI): *m/z* $[M + 2H]^+$ calcd for $C_{27}H_{29}BrN_4$: 489.1472; found: 489.1475.

8-Phenyl-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7g

A mixture of 2-oxo-6-phenyl-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.140 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography

using 10% ethyl acetate in hexae as an eluent to afford **7g** yellow solid; yield: 150 mg (95%); mp = 113-115 °C; IR (KBr): 3421, 2926, 2216, 1419-1489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.43-1.44 (m, 2H), 1.58-1.59 (m, 4H), 1.77-1.79 (m, 2H), 2.78-2.84 (m, 6H), 3.06 (brm, 2H), 4.80 (br, 1H, NH), 6.59 (s, 1H, ArH), 7.34-7.44 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.0, 26.3, 29.6, 41.4, 54.2, 107.7, 117.2, 119.0, 125.4, 127.8, 128.8, 129.0, 131.2, 137.5, 138.3, 148.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}N_3$: 318.1965; found: 318.1961.

6-(Piperidin-1-yl)-8-(p-tolyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7h

A mixture of 2-oxo-4-(piperidin-1-yl)-6-(p-tolyl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.147 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7h** yellow solid; yield: 157 mg (95%); mp = 140–142 °C; IR (KBr): 3417, 2924, 2218, 1490-1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (quint, J = 6 Hz, 2H), 1.72-1.77 (m, 4H), 1.98 (quint, J = 8 Hz, 2H), 2.39 (s, 3H), 2.96-2.99 (m, 6H), 3.18 (t, J = 5.3 Hz, 2H), 6.66 (s, 1H, ArH), 7.24-7.28 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.4, 24.0, 26.3, 29.6, 41.4, 54.1, 107.4, 117.2, 119.0, 119.1, 125.2, 128.6, 129.6, 131.2, 135.2, 137.6, 148.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_3$: 332.2121; found: 332.2123.

8-(4-Methoxyphenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7i

A mixture of 6-(4-methoxyphenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.155 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7i** yellow solid; yield: 139 mg (80%); mp = 80–82 °C; IR (KBr): 3412, 2926, 2216, 1444-1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.49-1.53 (m, 2H), 1.70-1.75 (m, 4H), 1.92 (quint, J = 6 Hz, 2H), 2.94-2.97 (m, 6H), 3.17 (t, J = 5.6 Hz, 2H), 3.83 (s, 3H, -OMe), 6.63 (s, 1H, ArH), 6.93-6.98 (m, 2H, ArH), 7.27-7.31 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.0, 24.0, 26.3, 41.4, 54.2, 55.3, 107.4, 114.3, 117.2, 119.1, 125.3, 125.4, 130.0, 130.4, 131.0, 148.3, 159.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_3O$: 348.2070; found: 348.2081.

8-(3,4-Dimethoxyphenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7j

A mixture of 6-(3,4-dimethoxyphenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.170 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexae as an eluent to afford **7j** yellow solid; yield: 152 mg (80%); mp = 103–105 °C; IR (KBr): 3403, 2926, 2214, 1459-1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.44-1.48 (m, 2H), 1.65-1.73 (m, 4H), 1.93 (quint, J = 7.2 Hz, 2H), 2.90 (t, J = 6.4 Hz, 6H), 3.13 (t, J = 5.4 Hz, 2H), 3.82 (s, 3H, -OMe), 3.85 (s, 3H, -OMe), 6.59 (s, 1H, ArH), 6.81-6.82 (m, 1H, ArH), 6.85-6.86 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.0, 26.3, 29.6, 41.4, 54.1, 55.9, 55.9, 107.4, 111.4, 112.0, 117.2, 119.0, 121.1, 125.3, 130.7, 131.1, 137.6, 148.1, 148.6, 149.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}N_3O_2$: 378.2176; found: 378.2163.

8-(4-Fluorophenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7k

A mixture of 6-(4-fluorophenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.149 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 4 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7k** yellow solid; yield: 149 mg (89%); mp = 125–127 °C; IR (KBr): 3417, 2933, 2217, 1491-1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.42-1.48 (m, 2H), 1.66-1.69 (m, 4H), 1.91 (quint, J = 6.4 Hz, 2H), 2.88-2.91 (m, 6H), 3.12 (t, J = 5.6 Hz, 2H), 3.75 (br, 1H, NH), 6.55 (s, 1H, ArH), 7.03-7.08 (m, 2H, ArH), 7.25-7.29 (m, 2H,

ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 24.0, 26.3, 29.6, 41.5, 54.3, 108.0, 116.0 (d, J_{C-F} = 20 Hz), 117.1, 119.1, 125.6, 130.2, 130.6 (d, J_{C-F} = 10 Hz), 134.2, 137.6, 148.2, 162.3 (d, J_{C-F} = 240 Hz); **HRMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}FN_3$: 336.1871; found: 336.1870.

8-(4-Chlorophenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7l

A mixture of 6-(4-chlorophenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.157 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7l** yellow solid; yield: 148 mg (84%); mp = 105-107 °C; IR (KBr): 3413, 2930, 2216, 1488-1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49-1.55 (m, 2H), 1.74 (brm, 4H), 1.93 (quint, *J* = 6.4 Hz, 2H), 2.95-2.98 (m, 6H), 3.19 (t, *J* = 5.4 Hz, 2H), 3.79 (br, 1H, NH), 6.61 (s, 1H, ArH), 7.30-7.33 (m, 2H, ArH), 7.39-7.42 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.1, 26.3, 29.6, 41.5, 54.2, 115.8, 116.0, 119.0, 119.1, 129.1, 130.2, 130.3, 130.6, 130.7, 136.7, 148.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}ClN_3$: 352.1575; found: 352.1579.

6-(Piperidin-1-yl)-8-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7m

A mixture of 2-oxo-4-(piperidin-1-yl)-6-(thiophen-2-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.143 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 4 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7m** yellow solid; yield: 145 mg (90%); mp = 130–132 °C; IR (KBr): 3408, 2925, 2215, 1435-1568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49-1.55 (m, 2H), 1.73–1.75 (m, 4H), 1.99 (quint, *J* = 6.8 Hz, 2H), 2.95-2.98 (m, 6H), 3.24 (t, *J* = 5.4 Hz, 2H), 4.37 (br, 1H, NH), 6.79 (s, 1H, ArH), 7.11 (dd, *J* = 3.6 Hz, *J* = 5.2 Hz, 1H, ArH), 7.19 (dd, *J* = 1.2 Hz, *J* = 3.6 Hz, 1H, ArH), 7.37 (dd, *J* = 1.2 Hz, *J* = 5.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 24.1, 26.4, 26.5, 41.6, 54.3, 108.4, 117.2, 119.7, 123.4, 126.0, 126.2, 126.7, 127.8, 138.1, 139.7, 148.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}N_3S$: 324.1529; found: 324.1520.

8-(Furan-2-yl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7n

A mixture of 6-(furan-2-yl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.135 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7n** yellow solid; yield: 136 mg (88%); mp = 103–105 °C; IR (KBr): 3451, 2928, 2215, 1450-1676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.60 (m, 2H), 1.70-1.84 (m, 4H), 2.01 (quint, *J* = 6 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 6H), 3.34 (t, *J* = 6.6 Hz, 2H), 6.52-6.53 (m, 1H, ArH), 6.63-6.68 (m, 1H, ArH), 7.03 (s, 1H, ArH), 7.50-7.52 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 24.0, 26.4, 29.0, 41.4, 54.0, 108.3, 111.0, 113.0, 116.8, 119.6, 126.1, 126.3, 127.7, 138.7, 139.3, 149.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}N_3O$: 308.1757; found: 308.1744.

6-Morpholino-8-phenyl-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7o

A mixture of 4-morpholino-2-oxo-6-phenyl-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.141 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7o** yellow solid; yield: 152 mg (95%); mp = 130–132 °C; IR (KBr): 3417, 2922, 2217, 1420- 1576 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (quint, *J* = 6.8 Hz, 2H), 2.97 (t, *J* = 6.6 Hz, 2H), 3.02 (t, *J* = 4.2 Hz, 4H), 3.19 (t, *J* = 5.6 Hz, 2H), 3.86 (t, *J* = 4.6 Hz, 4H), 6.67 (s, 1H, ArH), 7.35-7.39 (m, 3H, ArH), 7.43-7.46 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.4, 26.1, 41.0, 52.3, 66.4, 106.6, 116.7, 119.2, 125.3, 127.7, 128.7, 128.8, 130.6, 131.0, 138.0, 145.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{22}N_3O$: 320.1757; found: 320.1745.

6-Morpholino-8-(p-tolyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7p

A mixture of 4-morpholino-2-oxo-6-(p-tolyl)-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.148 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7o** yellow solid; yield: 159 mg (95%); mp = 130–132 °C; IR (KBr): 3415, 2926, 2217, 1445-1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (quint, J = 8 Hz, 2H), 2.38 (s, 3H, $-CH_3$), 2.96 (t, J = 8 Hz, 2H), 3.01-3.03 (m, 4H), 3.18 (t, J = 12 Hz, 2H), 3.85-3.87 (m, 4H), 6.67 (s, 1H, ArH), 7.21-7.25 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 21.2, 26.2, 41.5, 52.7, 67.0, 107.2, 117.0, 119.1, 126.3, 128.7, 129.0, 129.7, 130.2, 132.0, 134.7, 138.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}N_3O$: 334.1914; found: 334.1918.

8-(4-Fluorophenyl)-6-morpholino-1,2,3,4-tetrahydroquinoline-5-carbonitrile7q

A mixture of 6-(4-fluorophenyl)-4-morpholino-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.150 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7q** yellow solid; yield: 142 mg (84%); mp = 130–132 °C; IR (KBr): 3400, 2922, 2216, 1441-1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.01-2.05 (m, 2H), 3.01 (quint, J = 6.4 Hz, 2H), 3.12-3.14 (m, 4H), 3.19-3.23 (m, 2H), 3.91-3.93 (m, 4H), 6.79 (s, 1H, ArH), 7.13-7.18 (m, 2H, ArH), 7.37-7.40 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 26.3, 41.6, 52.7, 67.0, 107.7, 116.0 (d, J_{C-F} = 20 Hz), 116.7, 119.2, 126.4, 130.7 (d, J_{C-F} = 10 Hz), 131.0, 133.6, 137.3, 146.4, 162.4 (d, J_{C-F} = 250 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}FN_3O$: 338.1663; found: 338.1656.

8-(4-Chlorophenyl)-6-morpholino-1,2,3,4-tetrahydroquinline -5-carbonitrile 7r

A mixture of 6-(4-chlorophenyl)-4-morpholino-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.158 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 4 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7r** yellow solid; yield: 151 mg (85%); mp = 130–132 °C; IR (KBr): 3395, 2926, 2217, 1452-1570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.98 (quint, J = 6.8 Hz, 2H), 2.96 (t, J = 6 Hz, 2H), 3.01-3.03 (m, 4H), 3.19 (t, J = 4.8 Hz, 2H), 3.86 (t, J = 4.2 Hz, 4H), 6.63 (s, 1H, ArH), 7.29-7.32 (m, 2H, ArH), 7.40-7.42 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 26.3, 41.5, 52.7, 67.0, 108.0, 116.7, 116.8, 119.0, 126.4, 128.4, 129.2, 130.3, 131.6, 134.1, 136.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}ClN_3O$: 354.1368; found: 354.1344.

8-(4-Bromophenyl)-6-morpholino-1,2,3,4-tetrahydroquinolin e -5-carbonitrile 7s

A mixture of 6-(4-bromophenyl)-4-morpholino-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.249 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **7s** yellow solid; yield: 162 mg (81%); mp = 145–147 °C; IR (KBr): 3395, 2953, 2217, 1443-1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.99 (quint, J = 6.4 Hz, 2H), 2.96-2.98 (m, 2H), 3.00-3.03 (m, 4H), 3.22 (t, J = 5.6 Hz, 2H), 3.86 (t, J = 4.4 Hz, 4H), 6.63 (s, 1H, ArH), 7.25-7.28 (m, 2H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 26.3, 41.4, 52.8, 67.1, 108.1, 116.8, 118.7, 122.1, 126.0, 130.0, 130.6, 132.2, 137.0, 138.0, 146.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}BrN_3O$: 398.0863; found: 398.0864.

8-(4-Methoxyphenyl)-6-morpholino-1,2,3,4-tetrahydroquinoline-5-carbonitrile 7t

A mixture of 6-(4-methoxyphenyl)-4-morpholino-2-oxo-2*H*-pyran-3-carbonitrile 4 (0.5 mmol, 0.156 g), N-boc-3-piperidone 5 (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 4 hours. When the compound 4 was

completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford 7t Yellow solid; yield: 154 mg (88%); mp = 123–125 °C; IR (KBr): 3408, 2924, 2215, 1444-1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.97 (quint, J = 6.8 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.99-3.01 (m, 4H), 3.19 (t, J = 5.2 Hz, 2H), 3.83 (s, 3H, -OMe,), 3.84-3.86 (m, 4H), 6.63 (s, 1H, ArH), 6.96 (d, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 26.3, 41.4, 52.8, 55.3, 67.1, 107.3, 114.4, 117.0, 119.0, 125.6, 130.0, 130.1, 131.2, 138.2, 146.2, 159.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_2$: 350.1863; found: 350.1857.

4.3. General Procedure for 6-*sec*.amino-1,2,3,4,7,8-hexahydro-1-aza-benzo[*c*]phenanthrene-5-carbonitriles 8: 2-Oxobenzo[*h*]chromenes **4** (0.5 mmol), N-boc-3-piperidone **5** (0.6 mmol), $NaNH_2$ (1.0 mmol) and DMSO (5.0 ml) was added to RB flask. The resulting solution was stirred at r.t. for 3 h until the 2-oxobenzo[*h*]chromenes **4** was completely consumed (monitored by TLC). After completion of the reaction, the reaction mixture was poured onto crushed ice. The mixture was neutralized with 10% aq. HCl and resulting precipitate was collected by filtration and dried. Crude product treated with TFA (10 mmol) in DCM (3mL) at room temperature for 30-35 min. After completion, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with $NaHCO_3$ and extracted with dichlromethane (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and than solvent was removed under vacuum. The crude was purified by silica gel column chromatography using mixture of hexane/ethyl acetate (85:15) to obtain a pure 6-*sec*.amino-1,2,3,4,7,8-hexahydro-1-aza-benzo[*c*]phenanthrene-5-carbonitriles **8**.

6-(Pyrrolidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile 8a

A mixture of 6-(4-bromophenyl)-4-morpholino-2-oxo-2H-pyran-3-carbonitrile **4** (0.5 mmol, 0.146 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 15% ethyl acetate in hexane as an eluent to afford **8a** yellow solid; yield: 124 mg (75%); mp = 130–132 °C; IR (KBr): 3398, 2933, 2216, 1431-1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (quint, J = 6 Hz, 6H), 2.59 (brm, 4H), 2.91 (t, J = 6.4 Hz, 2H), 3.16-3.22 (m, 6H), 4.68 (br, 1H, NH), 7.13-7.24 (m, 3H, ArH), 7.97 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6, 24.3, 25.7, 26.0, 28.7, 41.1, 51.3, 110.1, 117.2, 123.7, 125.4, 125.6, 126.1, 126.4, 127.1, 127.4, 127.8, 132.3, 137.5, 139.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}N_3$: 330.1965; found: 330.1955.

6-(4-Methylpiperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-*h*]quinoline-5-carbonitrile 8b

A mixture of 4-(4-methylpiperazin-1-yl)-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile **4** (0.5 mmol, 0.160 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 13% ethyl acetate in hexane as an eluent to afford **8b** yellow solid; yield: 143 mg (80%); mp = 98–100 °C; IR (KBr): 3395, 2951, 2214, 11422-1579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (quint, J = 7.6 Hz, 2H), 2.63-2.66 (m, 2H), 2.73-2.76 (m, 2H), 2.97 (t, J = 5.6 Hz, 4H), 3.25 (t, J = 5.2 Hz, 2H), 3.38 (brm, 2H), 3.79-3.89 (m, 7H), 6.81 (dd, J = 1.2 Hz, J = 8.4 Hz, 2H, ArH), 6.86 (s, 1H, ArH), 7.99 (d, J = 9.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 23.8, 26.0, 30.5, 41.5, 46.4, 51.3, 57.5, 107.8, 118.2, 123.8, 125.4, 126.1, 127.4, 128.0, 132.5, 132.7, 136.8, 139.1, 140.4, 143.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{27}N_4$: 359.2230; found: 359.2234.

6-(Piperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-*h*]quinoline-5-carbonitrile 8c

A mixture 2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile **4** (0.5 mmol, 0.153s g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 15% ethyl acetate in hexane as an eluent to afford **8c** yellow solid; yield: 138 mg (80%); mp = 143-145 °C; IR (KBr): 2924, 2225, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41-1.62 (m, 6H), 1.96 (quint, J = 6 Hz, 2H), 2.55-2.58 (m, 2H), 2.65-2.69 (m, 2H), 2.89 (t, J = 6.8 Hz, 4H), 3.14-3.21 (m, 4H), 4.63 (br,

1H, NH), 7.14-7.23 (m, 3H, ArH), 7.96 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.1, 24.6, 26.1, 26.8, 29.4, 41.6, 52.2, 118.0, 121.2, 124.3, 125.5, 126.0, 126.2, 127.2, 127.5, 128.0, 131.3, 132.6, 136.7, 140.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{26}N_3$: 344.2121; found: 344.2141.

10-Methoxy-6-(piperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile 8d

A mixture 8-methoxy-2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile **4** (0.5 mmol, 0.168 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 5 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 12% ethyl acetate in hexane as an eluent to afford **8d** yellow solid; yield: 146 mg (78%); mp = 130–132 °C; IR (KBr): 3391, 2930, 2215, 1450-1650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.64 (m, 6H), 1.99 (quint, *J* = 5.2 Hz, 2H), 2.54-2.57 (m, 2H), 2.66-2.69 (m, 2H), 2.88 (t, *J* = 6.4 Hz, 4H), 3.16 (t, *J* = 5.2 Hz, 4H), 3.77 (s, 3H, -OMe), 6.71-6.74 (m, 1H, ArH), 6.77-6.78 (m, 1H, ArH), 7.92 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 22.6, 24.0, 24.7, 26.0, 29.6, 42.0, 52.4, 55.3, 111.3, 113.6, 113.7, 114.0, 118.0, 124.9, 124.9, 127.2, 135.8, 138.1, 139.2, 142.2, 159.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{28}N_3O$: 374.2227; found: 374.2228.

6-Morpholino-1,2,3,4,7,8-hexahydronaphtho[2,1-*h*]quinoline-5-carbonitrile 8e

A mixture of 4-morpholino-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile **4** (0.5 mmol, 0.154 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **4** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 15% ethyl acetate in hexane as an eluent to afford **8e** yellow solid; yield: 140 mg (81%); **mp** = 150–152 °C; **IR** (KBr): 3397, 2951, 2215, 1422-1558 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.97 (quint, *J* = 6.4 Hz, 2H), 2.56-2.59 (m, 2H), 2.65-2.68 (m, 2H), 2.89 (t, *J* = 6.8 Hz, 4H), 3.16-3.29 (m, 4H), 3.73-3.84 (m, 4H), 7.13-7.24 (m, 3H, ArH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 24.7, 26.2, 29.3, 41.5, 51.0, 67.8, 110.2, 117.7, 124.1, 125.0, 125.3, 126.2, 127.5, 128.0, 132.5, 137.0, 139.9, 140.0, 141.2; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}N_3O$: 346.1914; found: 346.1915.

4.4. General Procedure for 6-(methylthio)-8-aryl-1,2,3,4-tetrahydroquinoline-5-carbonitrile 9: A mixture of 4-(methylthio)-2-oxo-6-aryl-2*H*-pyran-3-carbonitriles **3** (0.5 mmol), N-boc-3-piperidone **5** (0.6 mmol), $NaNH_2$ (1.0 mmol) in DMSO was stirred at room temp for 1 h. Then reaction mixture was poured in to crushed ice with vigorous stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration and dried. Crude product treated with TFA (10 mmol) in DCM (3.0 mL) at room temperature for 20-25 minutes. Then mixture was poured onto crushed ice and neutralized with saturated $NaHCO_3$ solution followed by extraction with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated the solvent under reduced pressure. The crude was purified by silica gel column chromatography using hexane/ethyl acetate mixture (90:10) as an eluent to obtain 6-(methylthio)-8-aryl-1,2,3,4-tetrahydroquinoline-5-carbonitriles **9**.

6-(Methylthio)-8-phenyl-1,2,3,4-tetrahydroquinoline-5-carbonitrile 9a

A mixture of 4-(methylthio)-2-oxo-6-phenyl-2H-pyran-3-carbonitrile **3** (0.5 mmol, 0.121 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **3** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **9a** yellow solid; yield: 88 mg (62%); mp = 78–80 °C; IR (KBr): 3425, 2923, 2219, 1487-1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (quint, *J* = 7.2 Hz, 2H), 2.45 (s, 3H, -SMe), 2.98 (t, *J* = 6.6 Hz, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 7.05 (s, 1H, ArH), 7.34-7.39 (m, 3H, ArH), 7.43-7.46 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 20.8, 26.4, 41.2, 115.1, 116.5, 125.5, 126.5, 128.1, 128.8, 129.1, 130.5, 131.2, 137.4, 141.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2S$: 281.1107; found: 281.1092.

6-(Methylthio)-8-(p-tolyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 9b

A mixture of 4-(methylthio)-2-oxo-6-(p-tolyl)-2H-pyran-3-carbonitrile **3** (0.5 mmol, 0.128 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **3** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM

(3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **9b** yellow solid; yield: 95 mg (64%); mp = 80–82 °C; IR (KBr): 3414, 2924, 2218, 1438- 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (quint, J = 6.8 Hz, 2H), 2.32 (s, 3H, -SMe), 2.38 (s, 3H, -CH_3), 2.92 (t, J = 6.4 Hz, 2H), 3.16 (t, J = 5.6 Hz, 2H), 4.19 (br, 1H, NH), 6.98 (s, 1H, ArH), 7.16-7.18 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.8, 21.1, 26.4, 41.1, 115.0, 116.6, 125.3, 126.4, 128.6, 129.8, 130.6, 131.2, 134.3, 138.0, 141.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2S$: 295.1263; found: 295.1269.

8-(4-Methoxyphenyl)-6-(methylthio)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 9c

A mixture of 6-(4-methoxyphenyl)-4-(methylthio)-2-oxo-2H-pyran-3-carbonitrile **3** (0.5 mmol, 0.136 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 3 hours. When the compound **3** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (4.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **9c** yellow solid; yield: 88 mg (56%); mp = 83–85°C; IR (KBr): 3416, 2925, 2218, 1434-1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.92 (quint, J = 8 Hz, 2H), 2.38 (s, 3H, -SMe), 2.91 (t, J = 6.6 Hz, 2 H), 3.16 (t, J = 5.6 Hz, 2H), 3.77 (s, 3H, -OMe), 6.91 (d, J = 7.6 Hz, 2H, ArH), 6.97 (s, 1H, ArH), 7.22 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.8, 26.3, 41.2, 55.3, 114.5, 114.8, 116.6, 125.3, 126.4, 129.4, 130.0, 130.4, 131.3, 141.5, 159.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2OS$: 311.1213; found: 311.1219.

8-(Furan-2-yl)-6-(methylthio)-1,2,3,4-tetrahydroquinoline-5-carbonitrile 9d

A mixture of 6-(furan-2-yl)-4-(methylthio)-2-oxo-2H-pyran-3-carbonitril **3** (0.5 mmol, 0.136 g), N-boc-3-piperidone **5** (0.6 mmol, 0.119 g), sodamide (1.0 mmol, 0.039 g) in DMSO (5.0 mL) was stirred at r.t. for 2 hours. When the compound **3** was completely consumed in the reaction as indicated by TLC, the crude mixture was poured drop-wise onto ice–water with constant stirring and neutralized with 10% aq. HCl. The resulting precipitate was collected by filtration, washed with water and dried. The obtained crude product was treated with TFA (10.0 mmol, 0.76 ml) in DCM (3.0 mL) at room temperature for 30-35 minutes. Then reaction mixture was poured onto crushed ice. Reaction mixture was neutralized with $NaHCO_3$ and extracted with DCM (25.0 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and excess of solvent was removed under vacuum. The crude products thus obtained was purified by silica gel column chromatography using 10% ethyl acetate in hexane as an eluent to afford **9d** yellow solid; yield: 71 mg (52%); mp = 90–92°C; IR (KBr): 3418, 2926, 2216, 1450-1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (quint, J = 6.8 Hz, 2H), 2.48 (s, 3H, -SMe), 3.01 (t, J = 6.4 Hz, 2H), 3.39 (t, J = 5.4 Hz, 2H), 6.54 (dd, J = 1.6 Hz, J = 3.2 Hz, 1H, ArH), 6.67 (d, J = 2.8 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.53 (d, J = 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 20.5, 26.6, 41.2, 108.6, 111.6, 115.3, 116.5, 118.3, 126.0, 126.8, 129.0, 140.8, 142.2, 151.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2OS$: 271.0900; found: 271.0903.

4.5. General Procedure for the synthesis of fused and isolated quinolines 12: Compound **12** were synthesized by reaction of tetrahydroquinolines (**7**, **8** and **9**) and (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol), in toluene (3.0 mL) at 120 ^oC. The mixture was reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines. The excess of solvent was removed under reduced pressure and crude product was purified by column chromatography using 8% ethylacetate in hexane.

6-(4-Benzylpiperazin-1-yl)-8-(4-methoxyphenyl)quinoline-5-carbonitrile 12a

A mixture of 6-(4-benzylpiperazin-1-yl)-8-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7e** (0.2 mmol, 0.087 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7e**. The excess of solvent was removed under reduced pressure and crude product was purified bsilica gel column chromatography using 10% ethylacetate in hexane as an eluent to afford **12a** yellow solid; yield: 72 mg (92%); mp = 138–140 °C; IR (KBr): 2925, 2217, 1450-1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.71 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.61 (s, 2H, -CH_2), 3.88 (s, 3H, -OMe), 7.04 (d, J = 8.4 Hz, 2H, ArH), 7.27-7.38 (m, 6H, ArH), 7.47 (dd, J = 3.6 Hz, J = 8.4 Hz, 1H, ArH), 7.61 (d, J = 9.2 Hz, 2H, ArH), 8.42 (d, J = 8.4 Hz, 1H, ArH), 8.81 (d, J = 3.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.1, 53.0, 55.3, 62.8, 95.4, 113.6, 117.2, 122.1 123.0, 127.2, 128.3, 129.2, 130.5, 131.5, 131.6, 132.2, 137.4, 141.4, 146.5, 148.5, 155.0, 159.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O$: 435.2179; found: 435.2175.

8-Phenyl-6-(piperidin-1-yl)quinoline-5-carbonitrile 12b

A mixture of 8-phenyl-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7g** (0.2 mmol, 0.063 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7g**. The excess of solvent was removed under reduced pressure and crude product was purified bsilica gel column chromatography using 6% ethylacetate in hexane as an eluent to afford **12b** yellow solid; yield: 53 mg (85%); mp = 128-130 °C; IR (KBr): 2922, 2225, 1445-1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.67-171 (m, 2H), 1.80-1.85 (m, 4H), 3.49-3.53 (m, 4H), 7.39-7.40 (m, 1H, ArH), 7.43-7.55 (m, 4H, ArH), 7.64 (d, J = 12 Hz, 2H, ArH), 8.42-8.44 (m, 1H, ArH), 8.78-8.79 (m, 1H, ArH); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 24.0, 26.2, 52.6, 94.7, 117.4, 123.0, 128.0, 128.2, 128.8, 130.2, 130.3, 130.5, 132.1, 138.4, 141.1, 148.2, 155.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3$: 314.1652; found: 314.1670.

8-(4-Chlorophenyl)-6-(piperidin-1-yl)quinoline-5-carbonitrile 12c

A mixture of 8-(4-chlorophenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7l** (0.2 mmol, 0.070 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7l**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 10% ethylacetate in hexane as an eluent to afford **12c** yellow solid; yield: 65 mg (93%); mp = 143–145 °C; IR (KBr): 2927, 2225, 1441-1606 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.64 (m, 2H), 1.71-1.77 (m, 4H), 3.43 (t, *J* = 5.4 Hz, 4H), 7.28 (s, 1H, ArH), 7.36-7.40 (m, 3H, ArH), 7.48-7.51 (m, 2H, ArH), 8.33 (dd, *J* = 1.2 Hz, *J* = 4 Hz, 1H), 8.68 (dd, *J* = 1.2 Hz, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 26.1, 52.6, 95.0, 117.2, 122.8, 123.0 128.3, 130.6, 131.6, 132.1, 134.4, 136.7, 141.0, 145.2, 148.2, 155.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}ClN_3$: 348.1262; found: 348.1280.

6-(Piperidin-1-yl)-8-(thiophen-2-yl)quinoline-5-carbonitrile 12d

A mixture of 6-(piperidin-1-yl)-8-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7m** (0.2 mmol, 0.064 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7m**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 8% ethylacetate in hexane as an eluent to afford **12d** yellow solid; yield: 55 mg (87%); mp = 146–148 °C; IR (KBr): 2924, 2215, 1445-1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.65-170 (m, 2H), 1.79-1.82 (m, 4H), 3.44-3.51 (m, 4H), 7.37-7.38 (m, 1H, ArH), 7.42-7.50 (m, 3H, ArH), 7.62 (d, *J* = 6.8 Hz, 1H, ArH), 8.40-8.42 (m, 1H, ArH), 8.76-8.77 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 26.2, 52.6, 94.7, 122.8, 128.0, 128.2, 128.8, 130.2, 130.3, 130.5, 132.0, 135.5, 138.1, 138.4, 146.6, 155.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}N_3S$: 320.1216; found: 320.1223.

8-(4-Fluorophenyl)-6-morpholinoquinoline-5-carbonitrile 12e

A mixture of 8-(4-fluorophenyl)-6-morpholino-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7q** (0.2 mmol, 0.067 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7q**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 8% ethylacetate in hexane as an eluent to afford **12e** yellow solid; yield: 60 mg (90%); mp = 140–142 °C; IR (KBr): 2928, 2218, 1434-1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.44 (t, *J* = 5.4 Hz, 4H), 3.87 (t, *J* = 4.6 Hz, 4H), 7.09-7.14 (m, 2H, ArH), 7.30 (s, 1H, ArH), 7.43 (dd, *J* = 4 Hz, *J* = 8.8 Hz, 1H, ArH), 7.53-7.58 (m, 2H, ArH), 8.37-8.39 (m, 1H, ArH), 8.76 (dd, *J* = 0.8 Hz, *J* = 3.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.4, 66.8, 96.6, 115.1 (d, J_{C-F} = 30 Hz), 116.8, 122.0, 123.2, 130.3, 132.0 (d, J_{C-F} = 10 Hz), 132.3, 134.0, 141.4, 146.0, 149.0, 154.7, 162.8 (d, J_{C-F} = 280 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}FN_3O$: 334.1350; found: 334.1352.

8-(4-Bromophenyl)-6-morpholinoquinoline-5-carbonitrile 12f

A mixture of 8-(4-bromophenyl)-6-morpholino-1,2,3,4-tetrahydroquinoline-5-carbonitrile **7s** (0.2 mmol, 0.079 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **7s**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 8% ethylacetate in hexane as an eluent to afford **12f** yellow solid; yield: 71 mg (90%); mp = 145–147 °C; IR (KBr): 2923, 2208, 1450-1584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (t, *J* = 4.6 Hz, 4H), 3.95 (t, *J* = 4.6 Hz, 4H), 7.38 (s, 1H, ArH), 7.51-7.54 (m, 3H, ArH), 7.64 (d, *J* = 7.6 Hz, 2H, ArH), 8.46 (d, *J* = 7.6 Hz, 1H), 8.83-8.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.4, 67.0, 96.8, 116.7, 122.0, 123.0, 123.3, 130.4, 131.3, 132.0, 132.4, 137.0, 141.2, 145.8, 149.1, 154.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}BrN_3O$: 394.0550; found: 394.0542.

6-Morpholino-7,8-dihydronaphtho[2,1-h]quinoline-5-carbonitrile 12g

A mixture of 6-morpholino-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile **8e** (0.2 mmol, 0.069 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **8e**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 12% ethylacetate in hexane as an eluent to afford **12f** yellow solid; yield: 55 mg (81%); mp = 163–165 °C; IR (KBr): 2924, 2211, 1443-1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.81-2.84 (m, 2H), 2.97-3.01 (m, 2H), 3.47-3.52 (m, 4H), 3.92-3.96 (m, 4H), 7.33-7.35 (m, 2H, ArH), 7.37-7.42 (m, 1H, ArH), 7.53 (dd, *J* = 4 Hz, *J* = 8 Hz, 1H, ArH), 8.50-8.54 (m, 2H, ArH), 8.95 (dd, *J* = 1.6 Hz, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 29.5, 51.5, 67.3, 100.5, 117.0, 122.2, 126.0, 126.8, 128.6, 128.7, 131.7, 132.1, 132.8, 138.9, 139.0, 139.2, 142.0, 149.2, 153.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}N_3O$: 342.1601; found: 342.1605 .

6-(Methylthio)-8-(p-tolyl)quinoline-5-carbonitrile 12h

A mixture of 6-(methylthio)-8-(p-tolyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile **9b** (0.2 mmol, 0.059 g), (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) DDQ **11** (0.4 mmol, 0.090 g), in toluene (3.0 mL) was stirred at reflux for 1 hours until TLC show complete consumption of tetrahydroquinolines **9b**. The excess of solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using 10% ethylacetate in hexane as an eluent to afford **12h** white solid; yield: 56 mg (96%); mp = 138–140 °C; IR (KBr): 2921, 2213, 1436-1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, -SMe), 2. 69 (m, 3H, $-CH_3$), 7.33 (d, *J* = 8.0 Hz, 2H, ArH), 7.53-7.55 (m, 2H, ArH), 7.56 (d, *J* = 4.0 Hz, 1H, ArH), 7.62 (s, 1H, ArH), 8.46

(dd, J = 1.6 Hz, J = 8.4 Hz, 1H, ArH), 8.93 (dd, J = 1.6 Hz, J = 4.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 21.4, 105.8, 115.4, 123.4, 127.0, 129.1, 129.6, 130.5, 132.7, 135.0, 138.8, 143.6, 145.2, 146.2, 150.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2S$: 295.1263; found: 295.1261.

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5. References and notes

Electronic Supporting Information: ^{1}H and ^{13}C spectra of the entire synthesized compound are provided in ESI.

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Supporting Information

Base-promoted regioselective synthesis of 1,2,3,4-terahydroquinolines and quinolines from N-Boc-3-piperidone

Shally, Ismail Althagafi, Divya Singhal, Rahul Panwar, Ranjay Shaw, Amr Elagamy and

*Ramendra Pratap**

Department of Chemistry, University of Delhi, North Campus, Delhi, India, Pin-110007

Table of Contents:

X-ray Crystallographic Data for compound 6t

Crystal data for $C_{26}H_{31}N_3O_4$ (CCDC No 1918629): A yellow crystal (0.220 x 0.200 x 0.180 mm^3) was mounted on a capillary tube for indexing and intensity data collection at 298K on an Oxford Xcalibur Sapphire3 CCD single-crystal diffractometer (MoKα radiation, λ = 0.71073 Å).[1] Routine Lorentz and polarization corrections were applied, and an absorption correction was performed using the ABSCALE 3 program [CrysAlis Pro software system, Version 171.34; Oxford Diffraction Ltd., Oxford, U.K., 2011]. Data reduction was performed with the CrysAllis-PRO.[1] The structure was solved by direct methods using SIR-92 program[2] and refined on F2 using all data by full matrix least-squares procedures with SHELXL-2016/6 incorporated in WINGX 1.8.05 crystallographic collective package.[3] The hydrogen atoms were placed at the calculated positions and included in the last cycles of the refinement. All calculations were done using the WinGX software package.[4-5] Crystallographic data collection and structure solution parameters are summarized in Table S1. This data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.uk/data_request/cif.

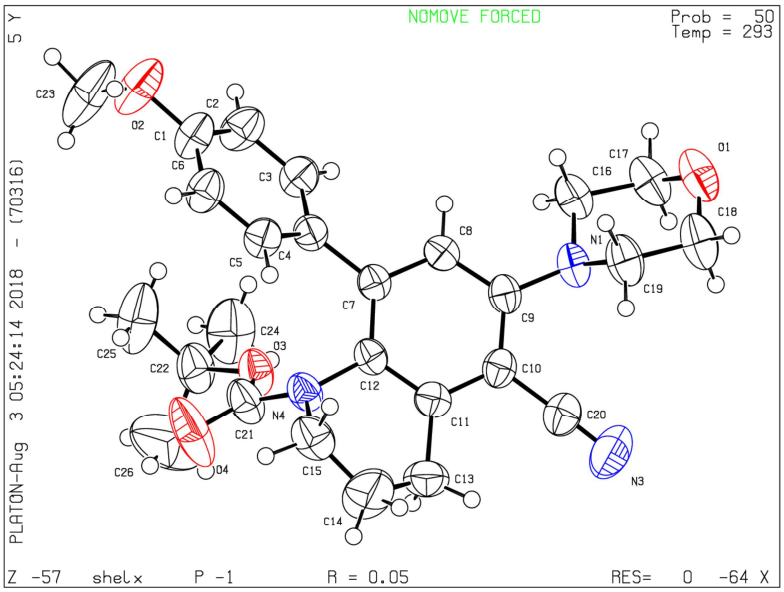

Figure 1. ORTEP diagram of **6t**; thermal ellipsoids are drown at the 50% probability level

Table 1. Crystal data and structure refinement for **6t**

CCDC No.	1918629
Empirical formula	C_{26} H_{31} N_3 O_4
Formula weight	449.54
Temperature/k	293
Crystal system	triclinic
Space group	P -1
a/Å	9.4402(4)
b/Å	12.1551(7)
c/Å	12.3895(7)
α/°	98.825(5)
β/°	111.143(5)
γ/°	104.139(4)
Volume/$Å^3$	1239.09(13)
Z	2
$\rho_{calc}g/cm^3$	1.205
μ/mm^{-1}	0.082
F(000)	480.0
2Θ range for data collection/°	2.854 to 25.000
Index ranges	-11<=h<=11, -14<=k<=14, -20<=l<=20
Reflections collected	14950
Independent reflections	4350 [R_{int} = 0.0281, R_{sigma} = 0.0323]
Data/restraints/parameters	4350/304/354

Goodness-of-fit on F^2	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0539, wR_2 = 0.1298
Final R indexes [all data]	R_1 = 0.0753, wR_2 = 0.1409
Largest diff. peak/hole / e $Å^{-3}$	0.21/-0.23

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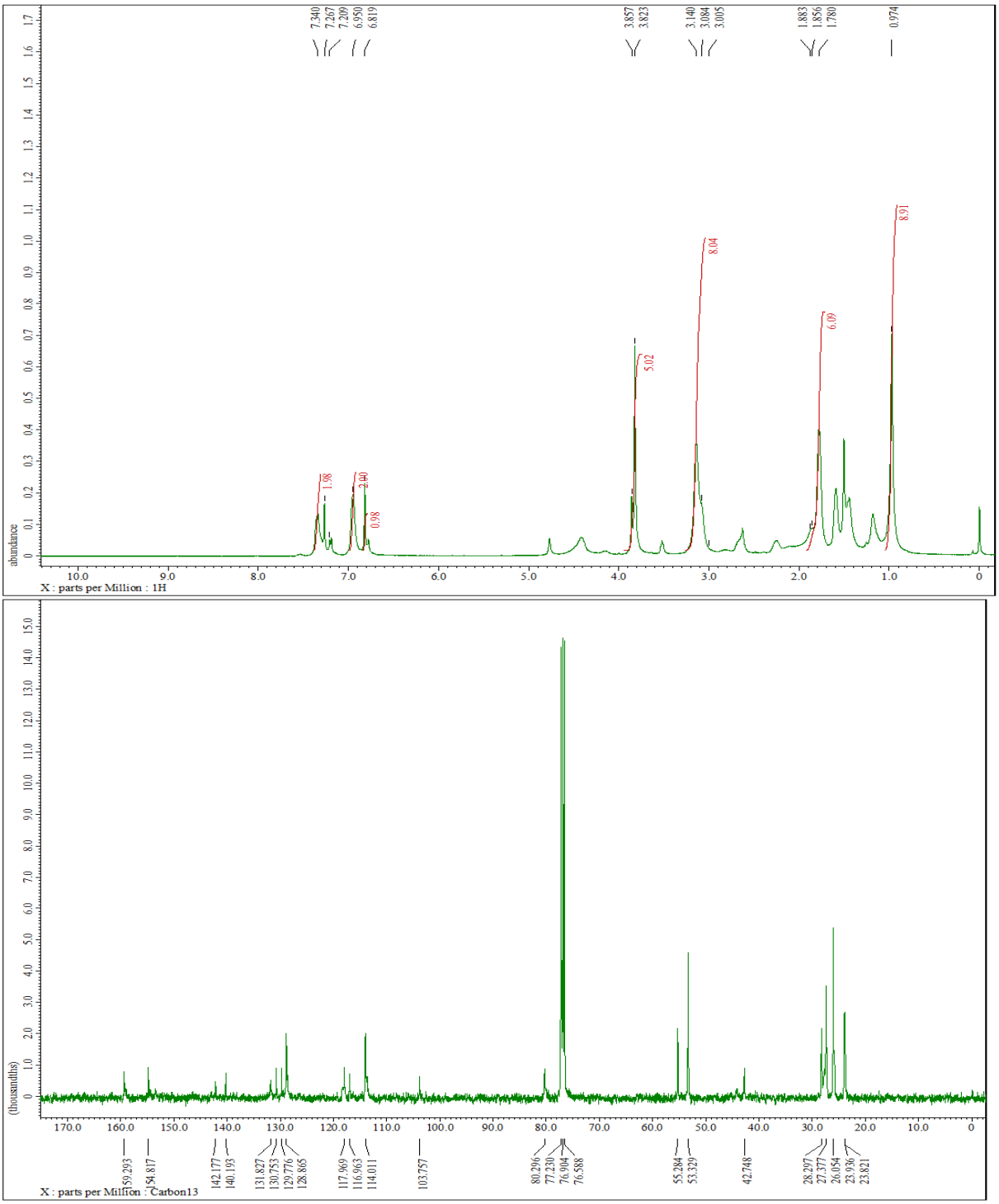
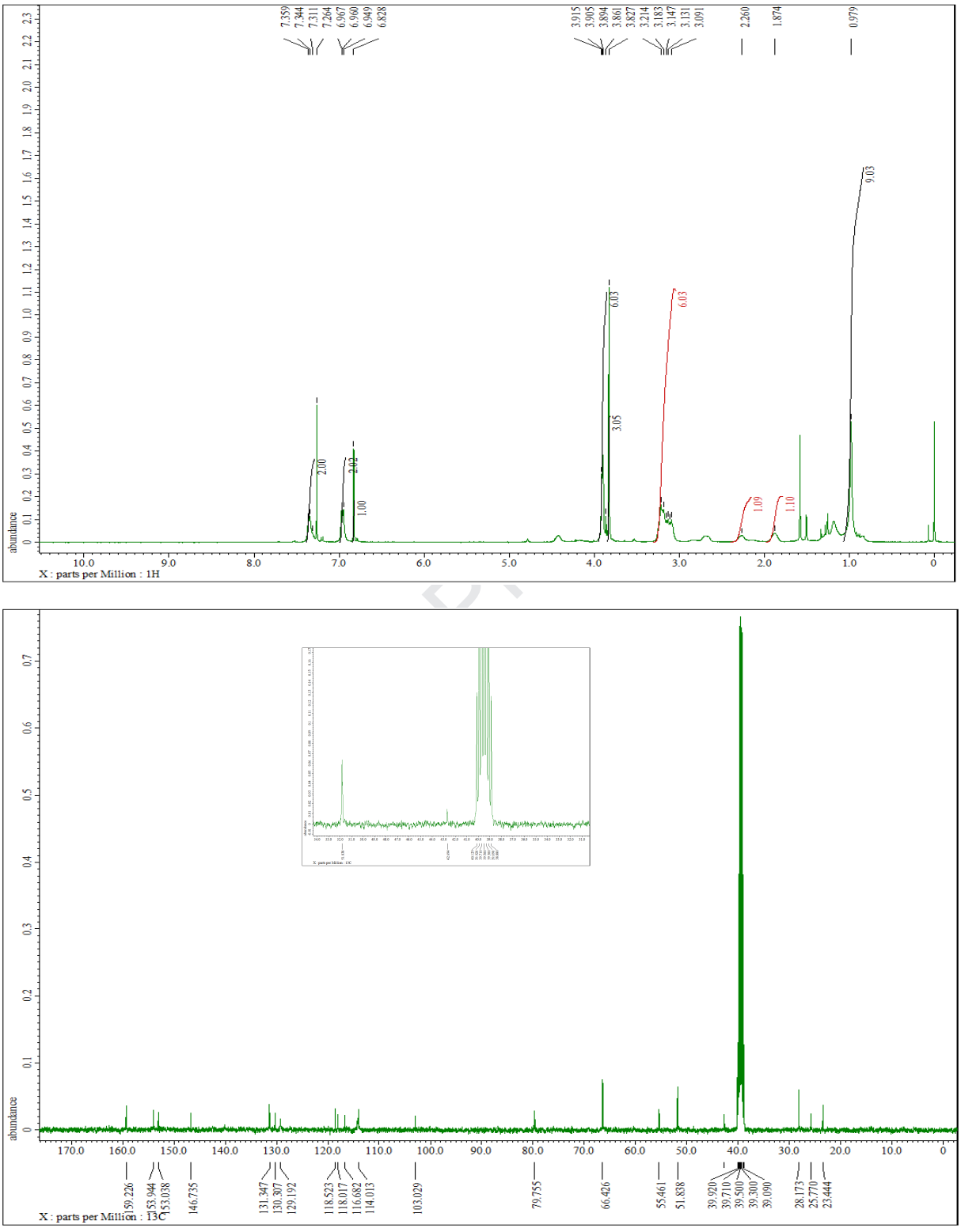
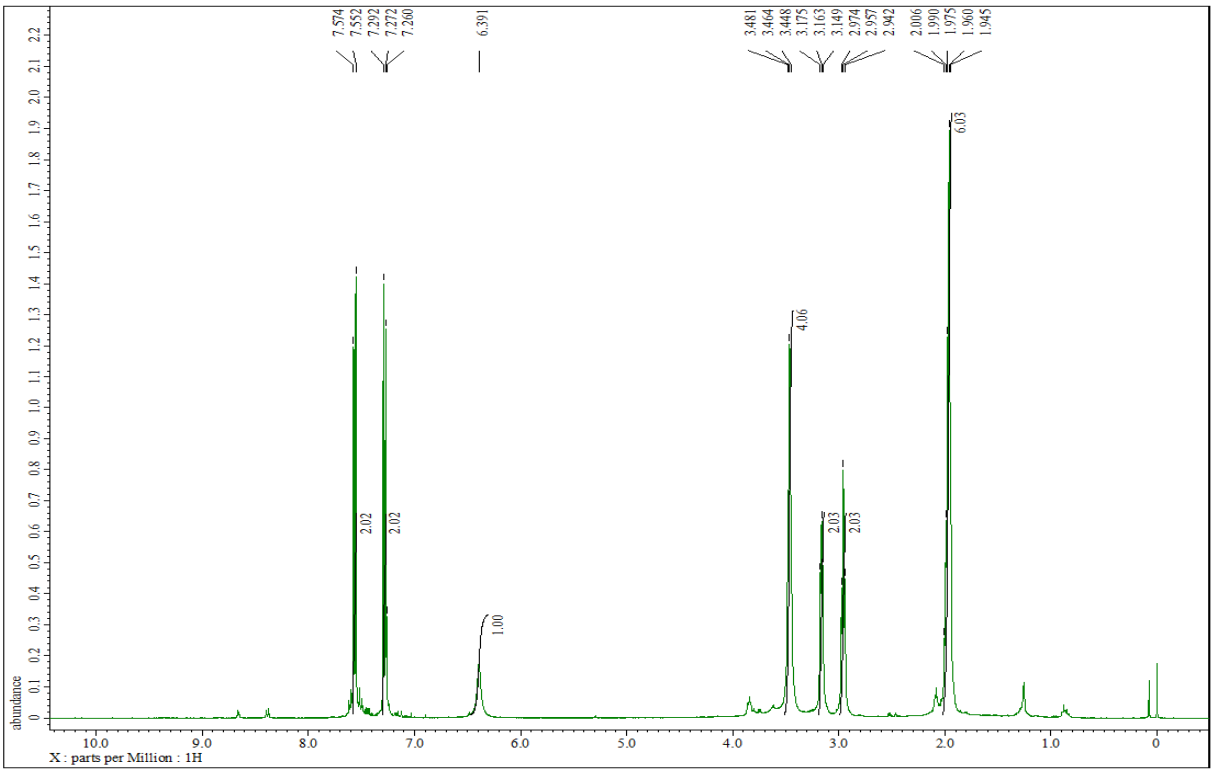
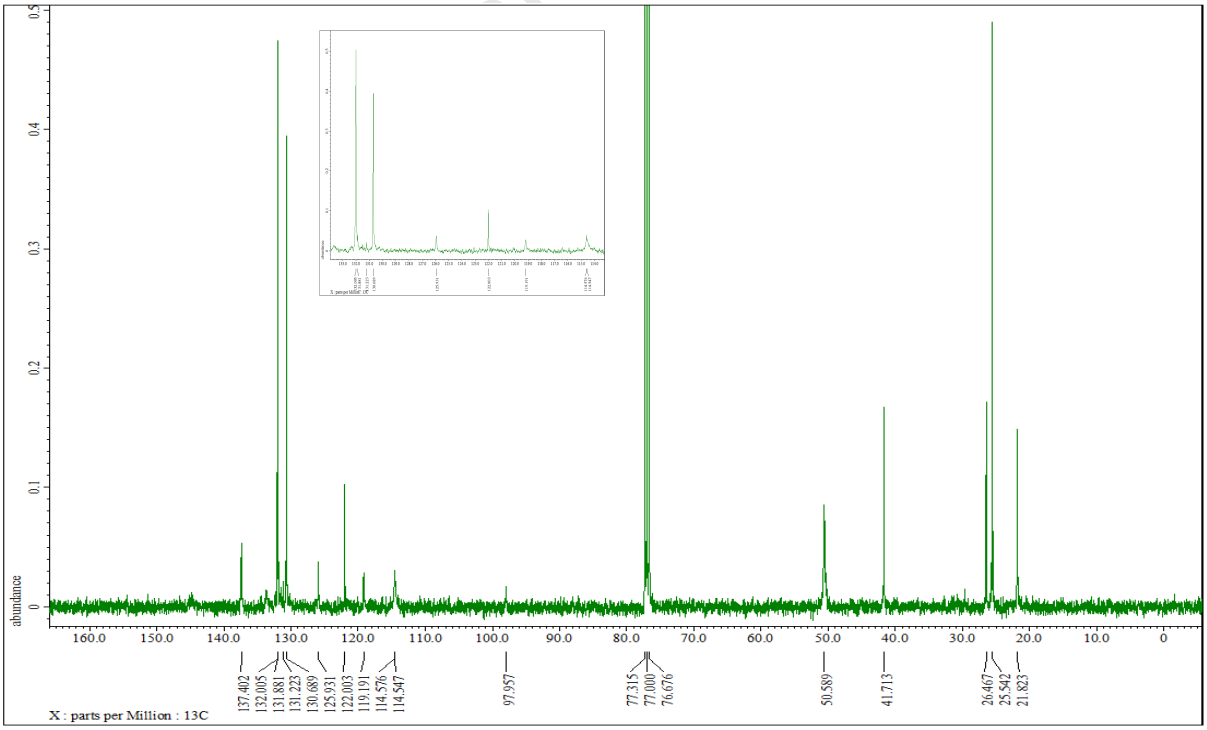


[1]HNMR and [13]C NMR spectrum of tert-butyl 5-cyano-8-(4-methoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate

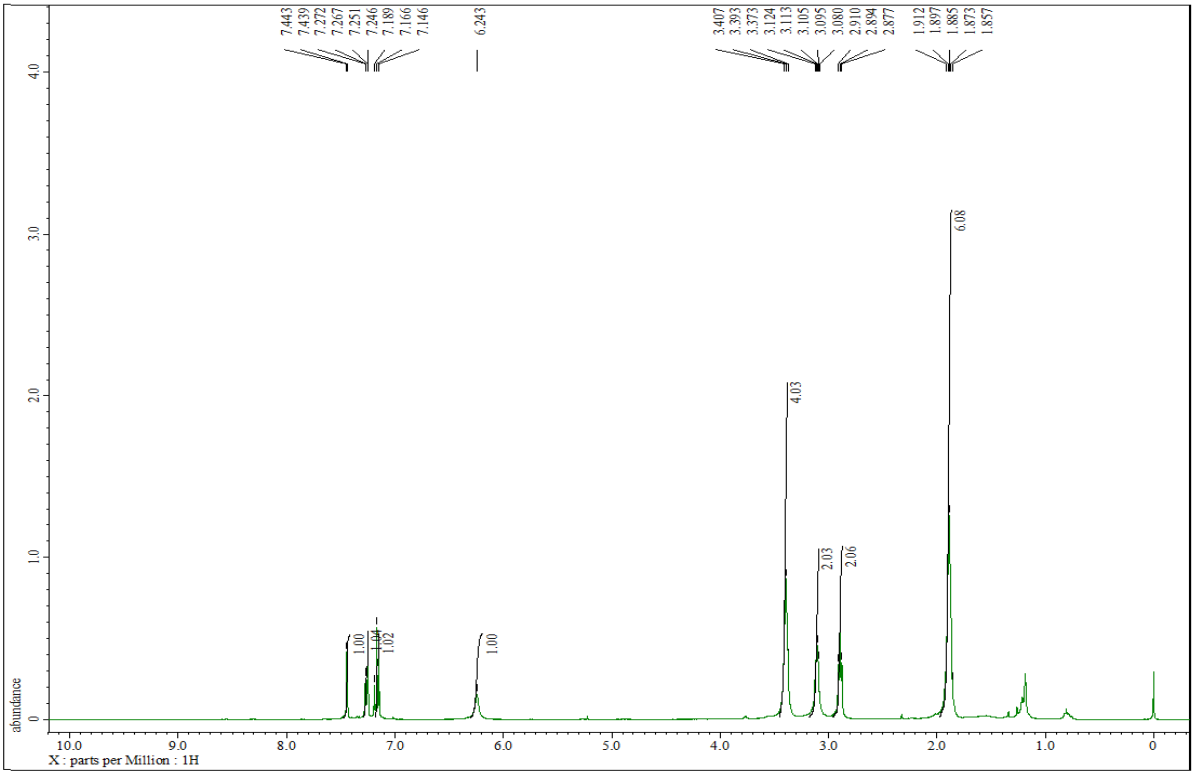


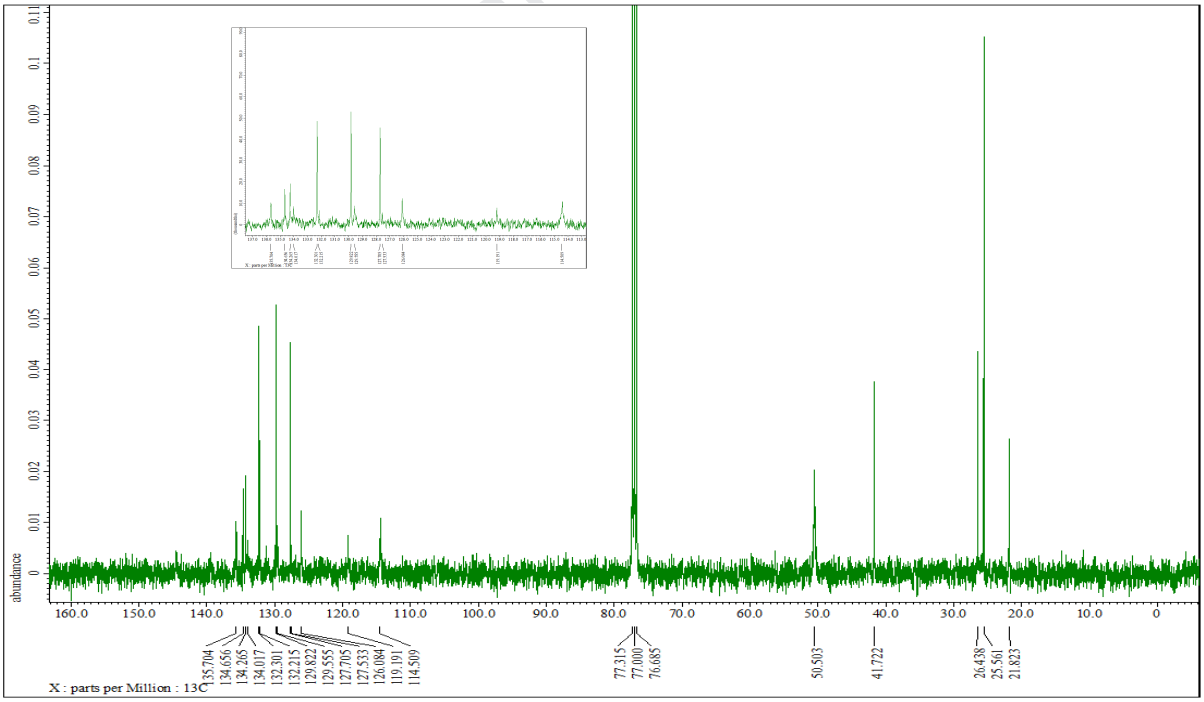
^{1}HNMR and ^{13}C NMR spectrum of tert-butyl 5-cyano-8-(4-methoxyphenyl)-6-morpholino-3,4-dihydroquinoline-1(2*H*)-carboxylate





[1]HNMR and [13]C NMR spectrum of 8-(4-bromophenyl)-6-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile





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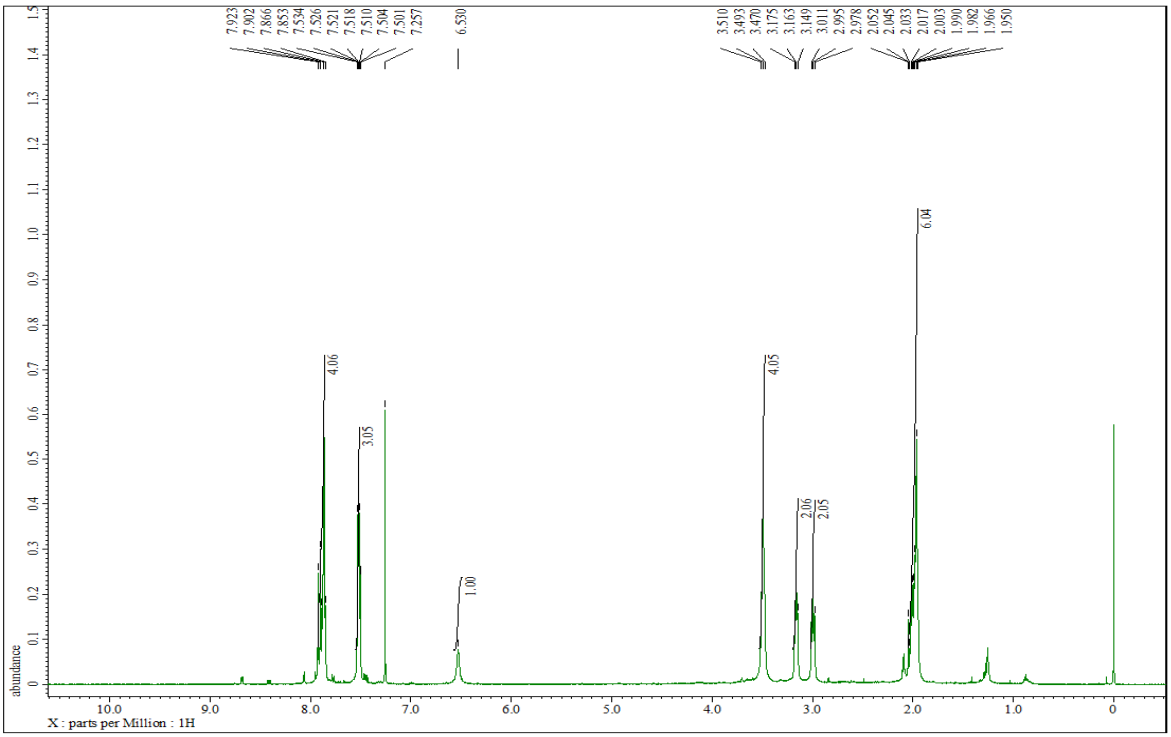

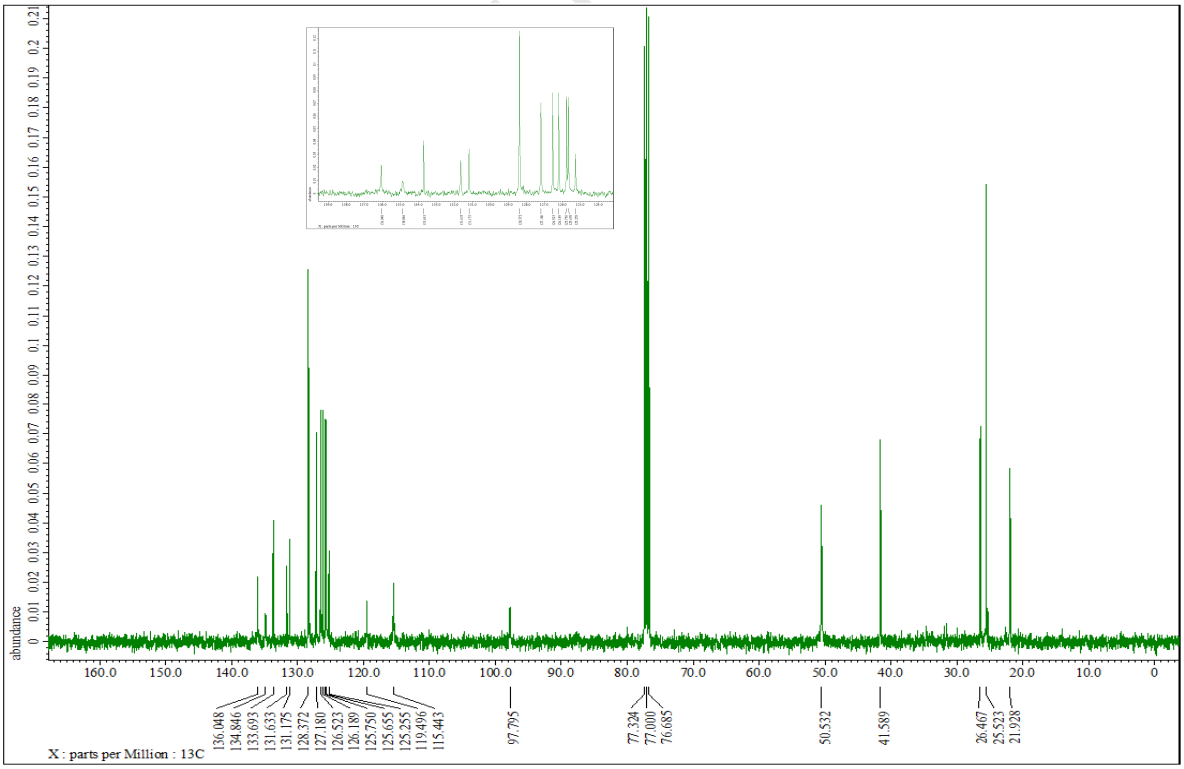

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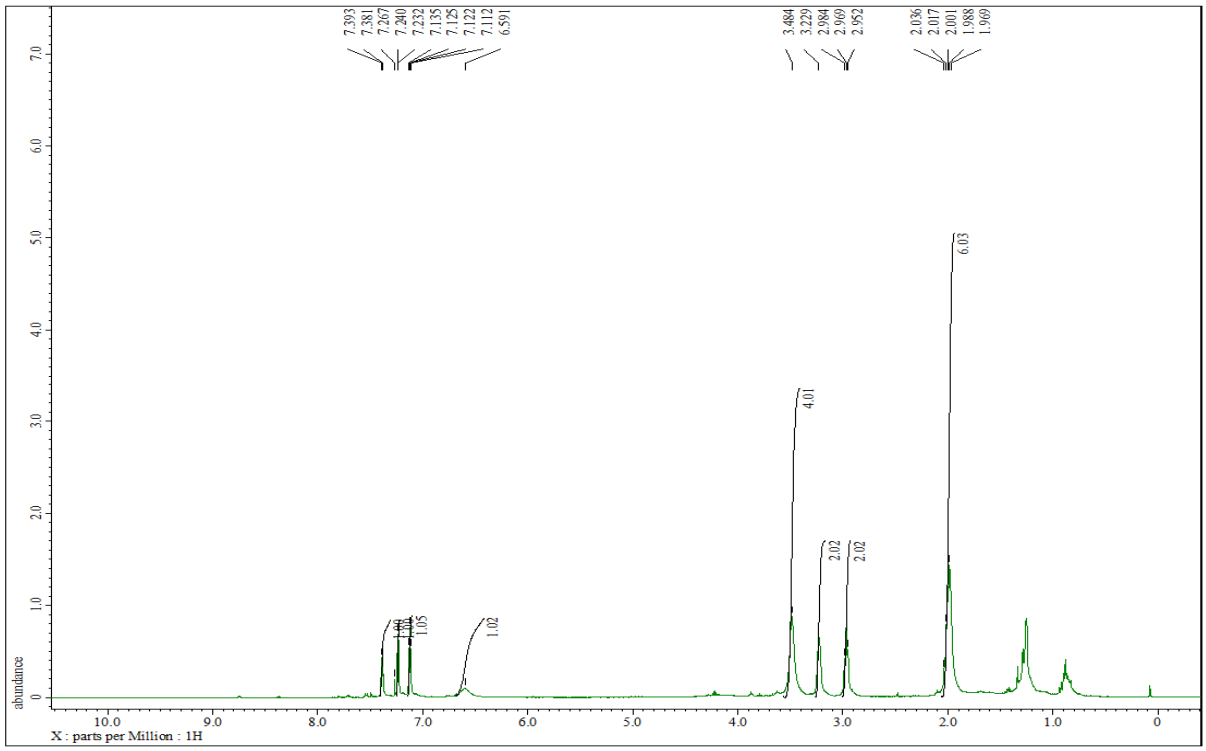

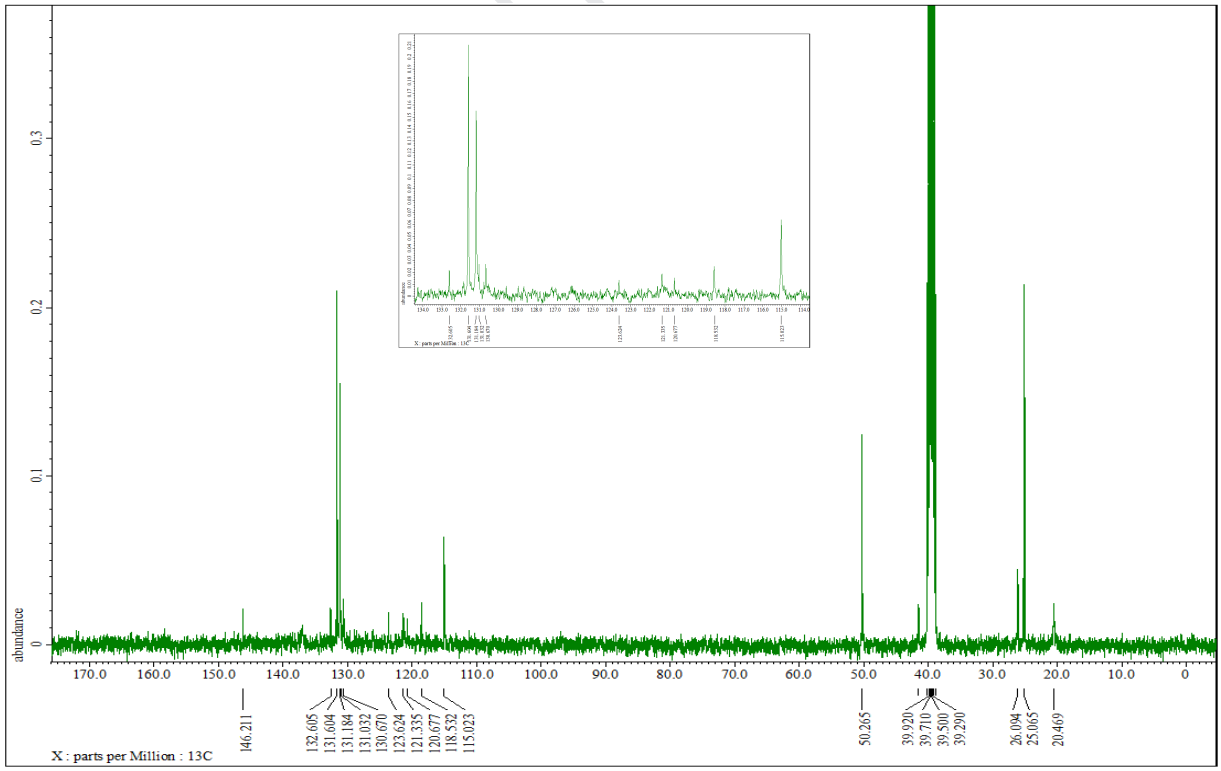

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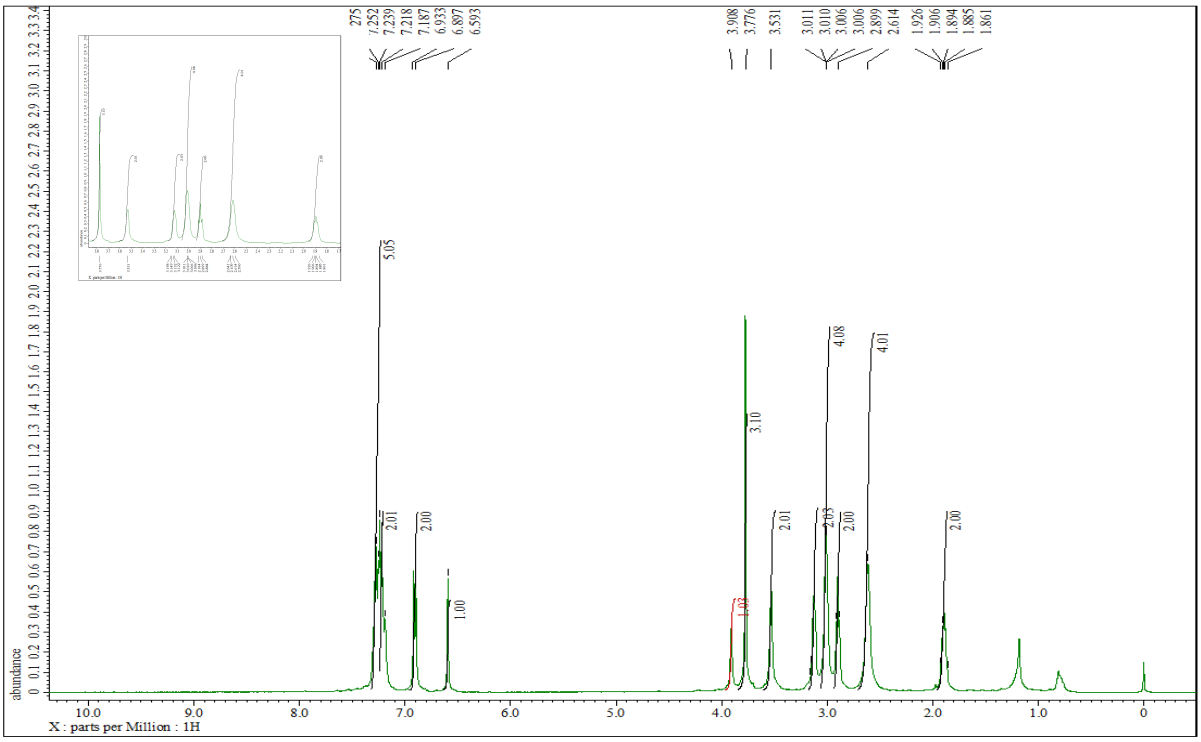
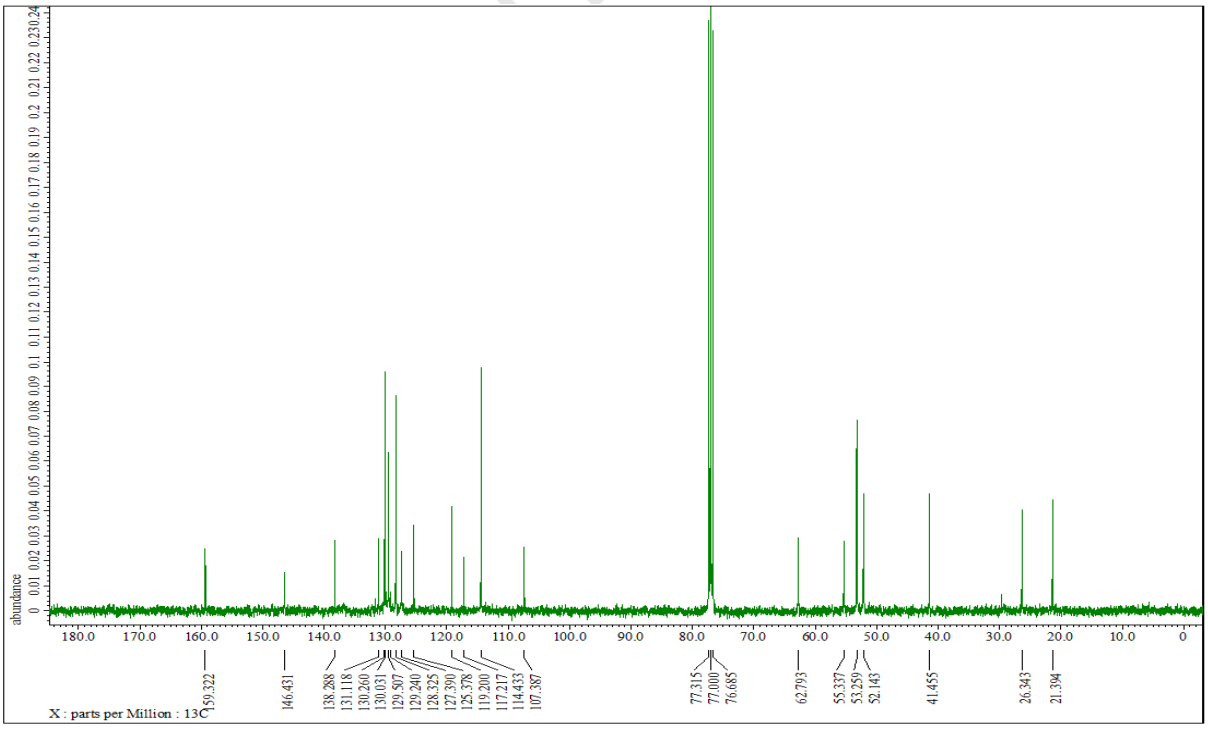
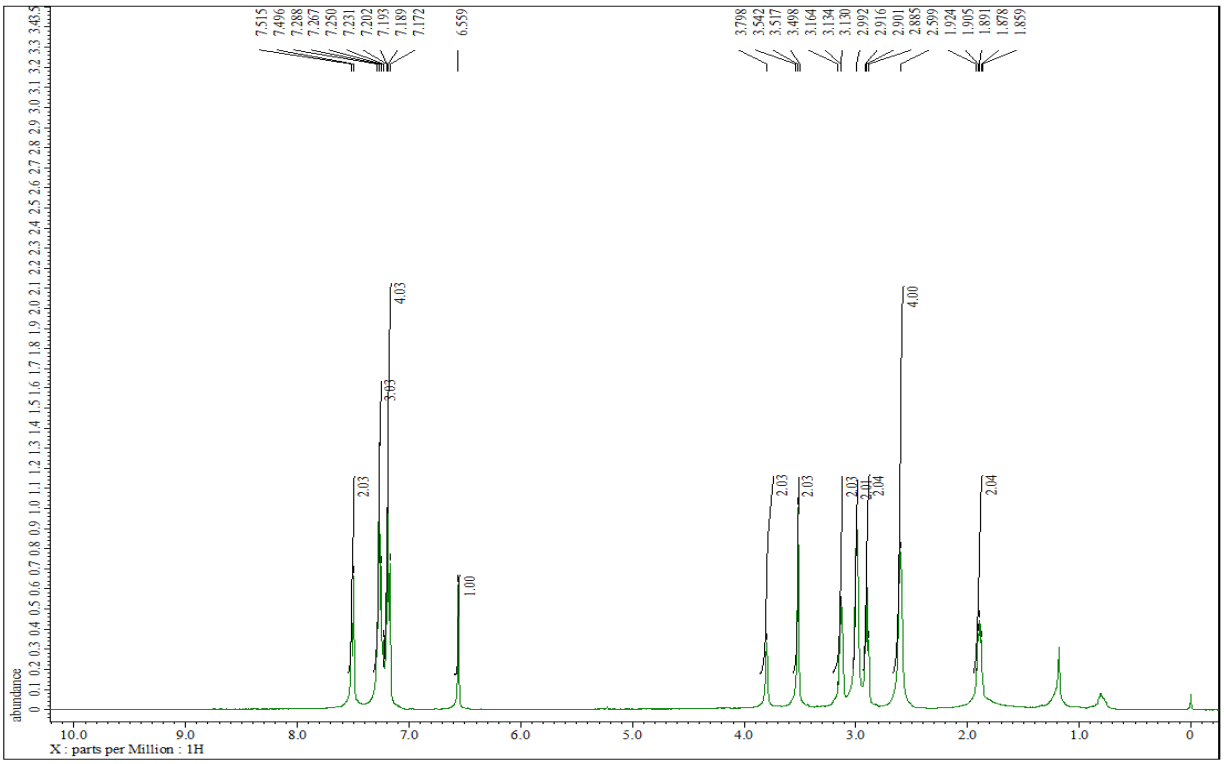
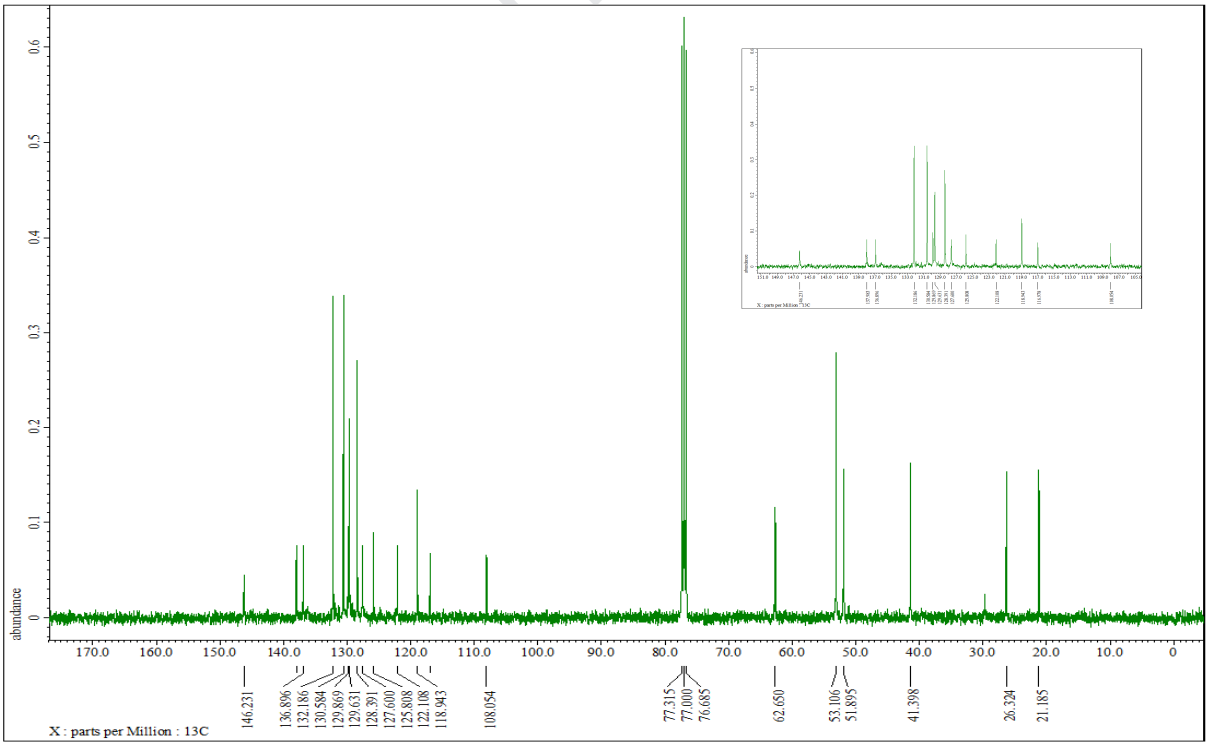




^{1}HNMR and ^{13}C NMR spectrum of 6-(4-benzylpiperazin-1-yl)-8-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile





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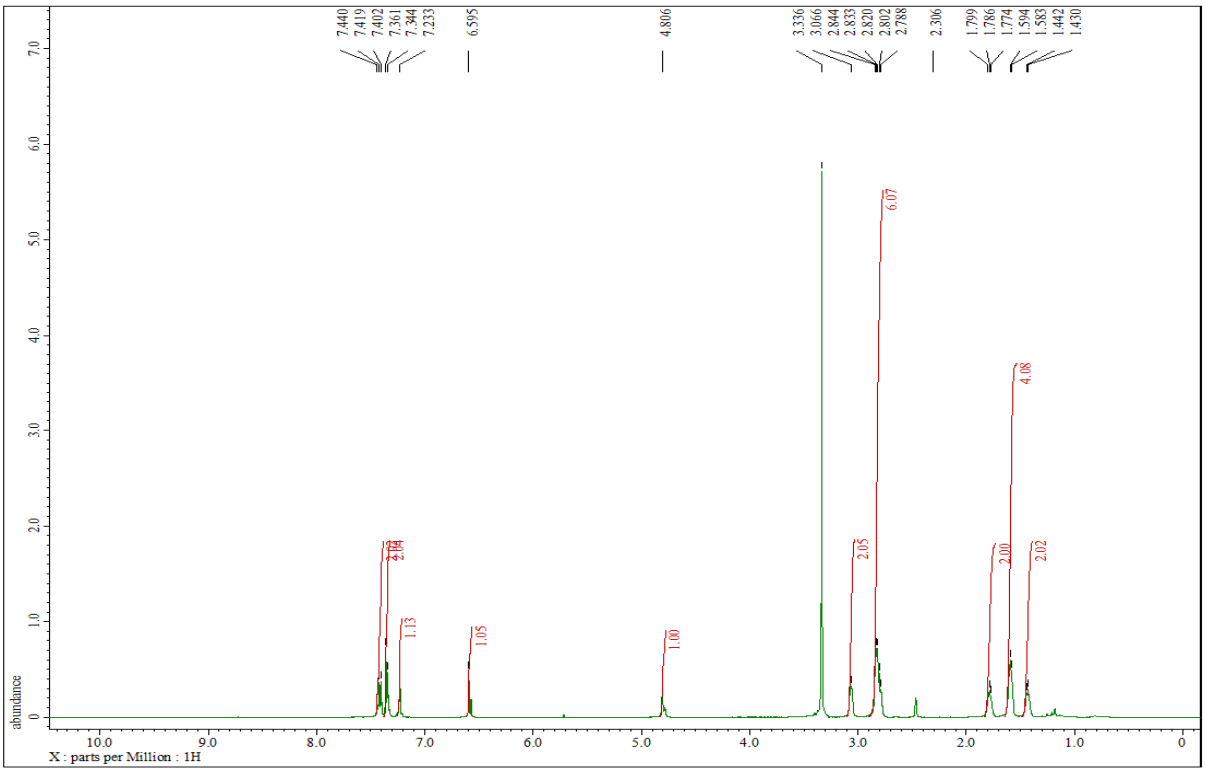

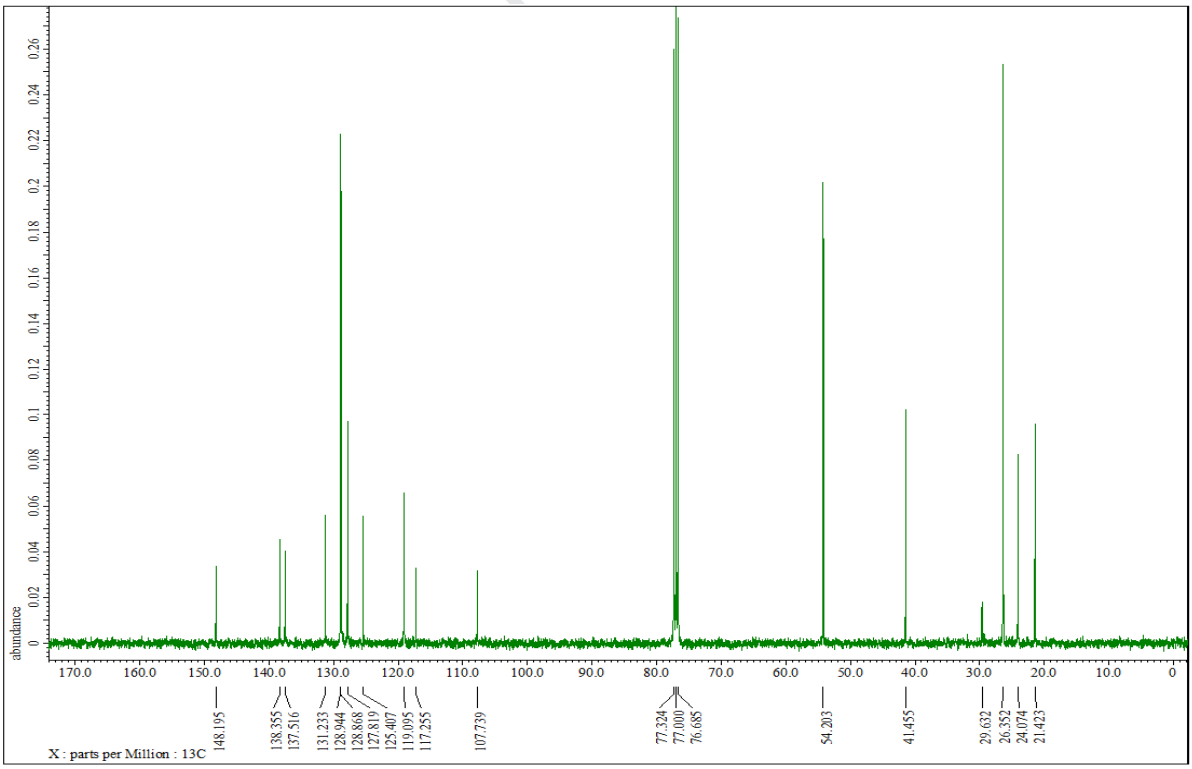

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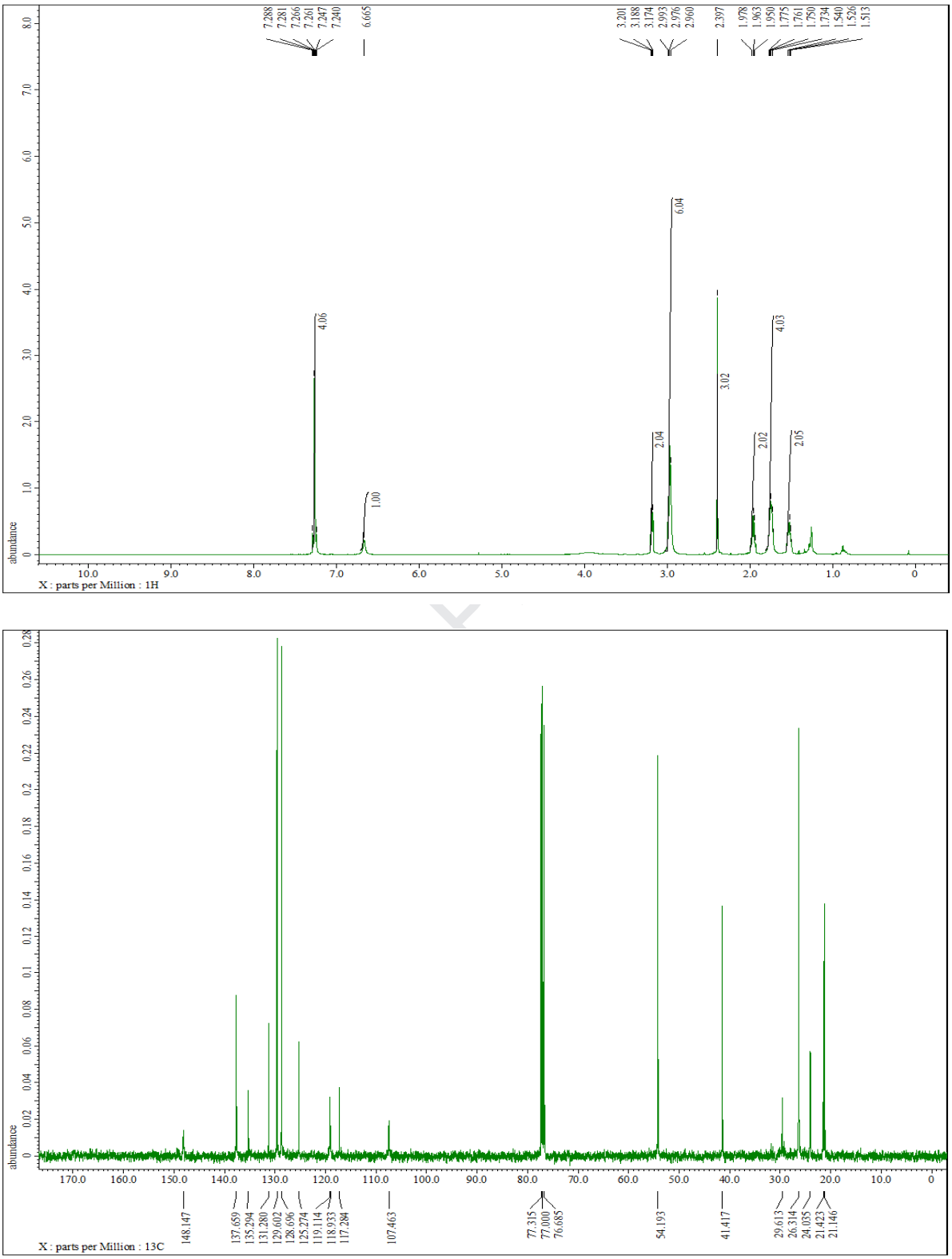
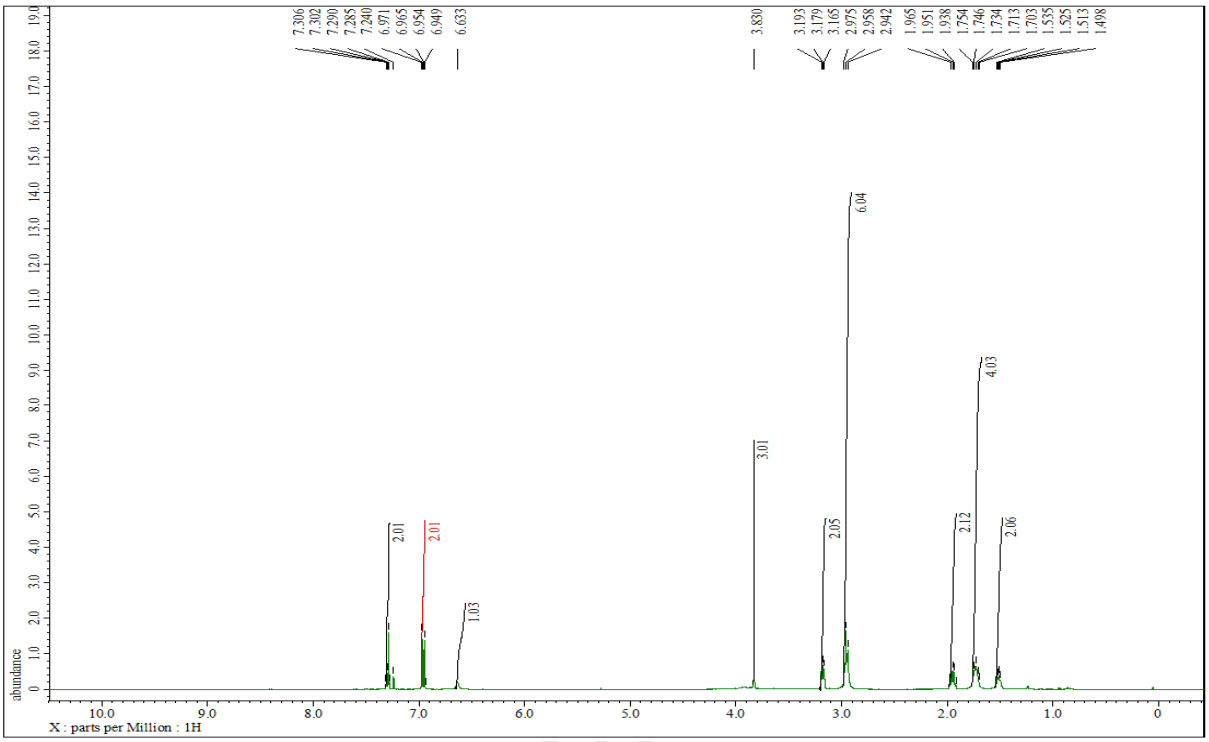
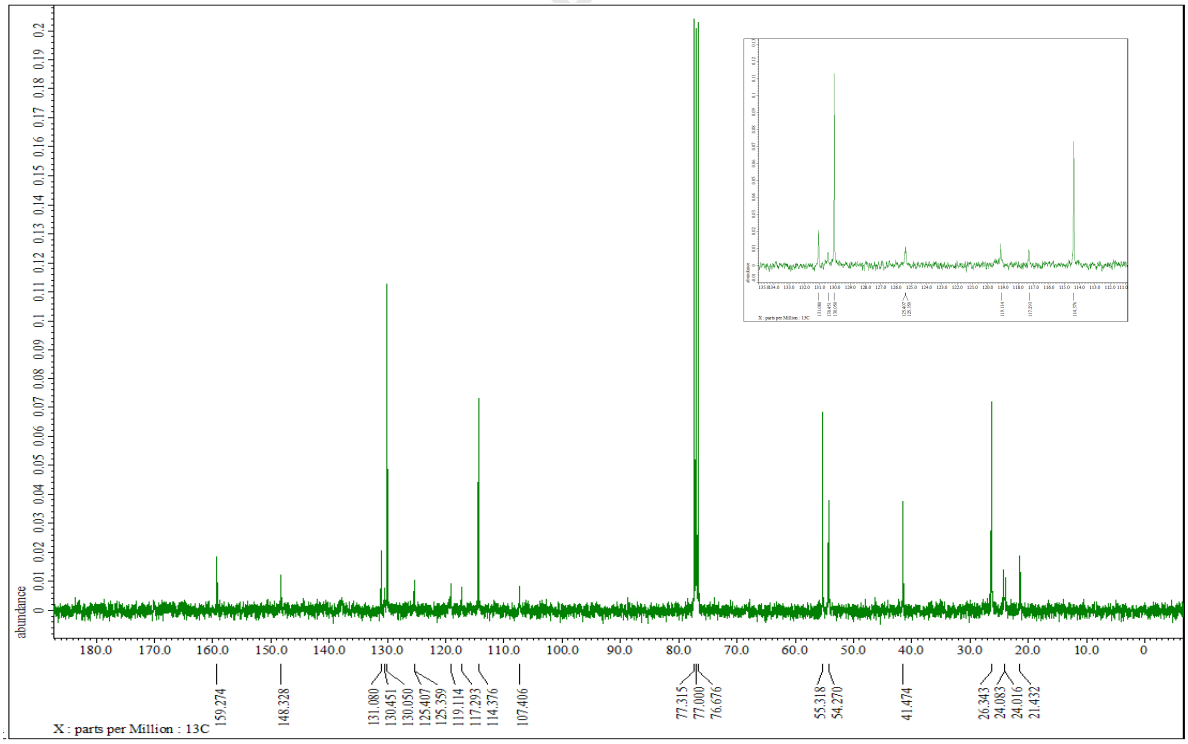


[1]HNMR and [13]C NMR spectrum of 6-(piperidin-1-yl)-8-(p-tolyl)-1, 2,3,4-tetrahydroquinoline-5-carbonitrile





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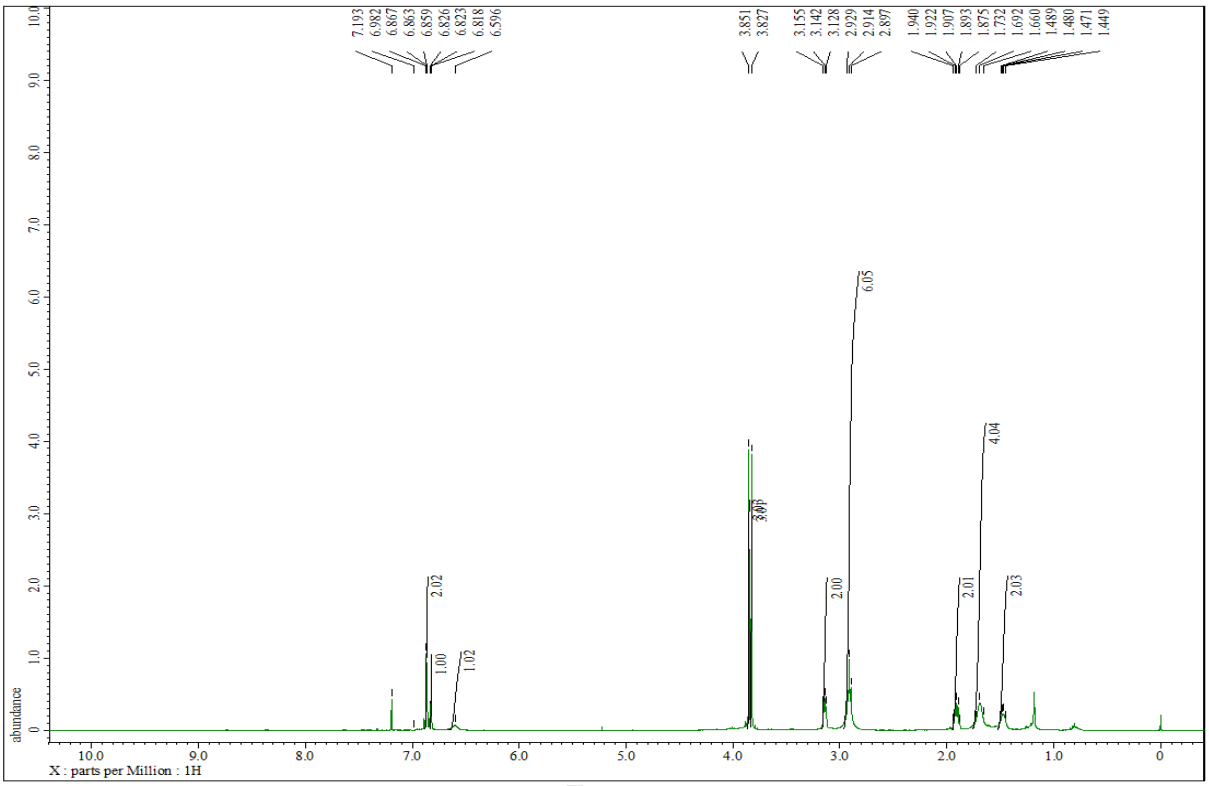

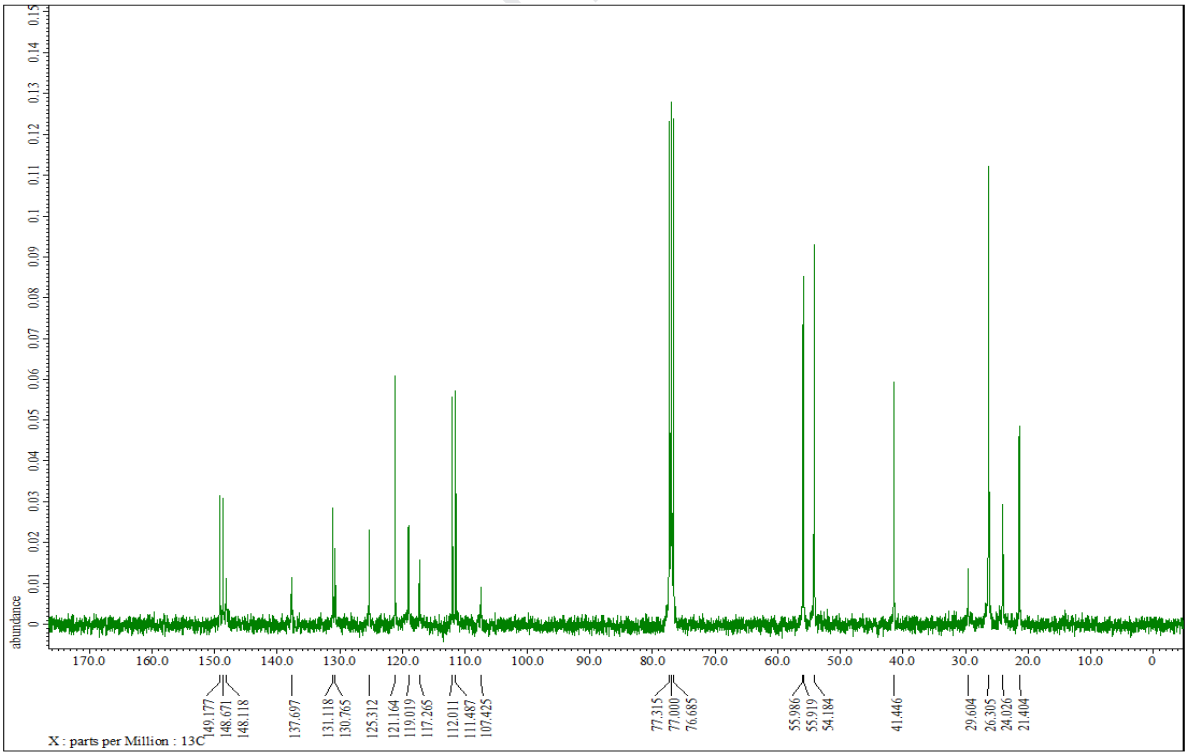

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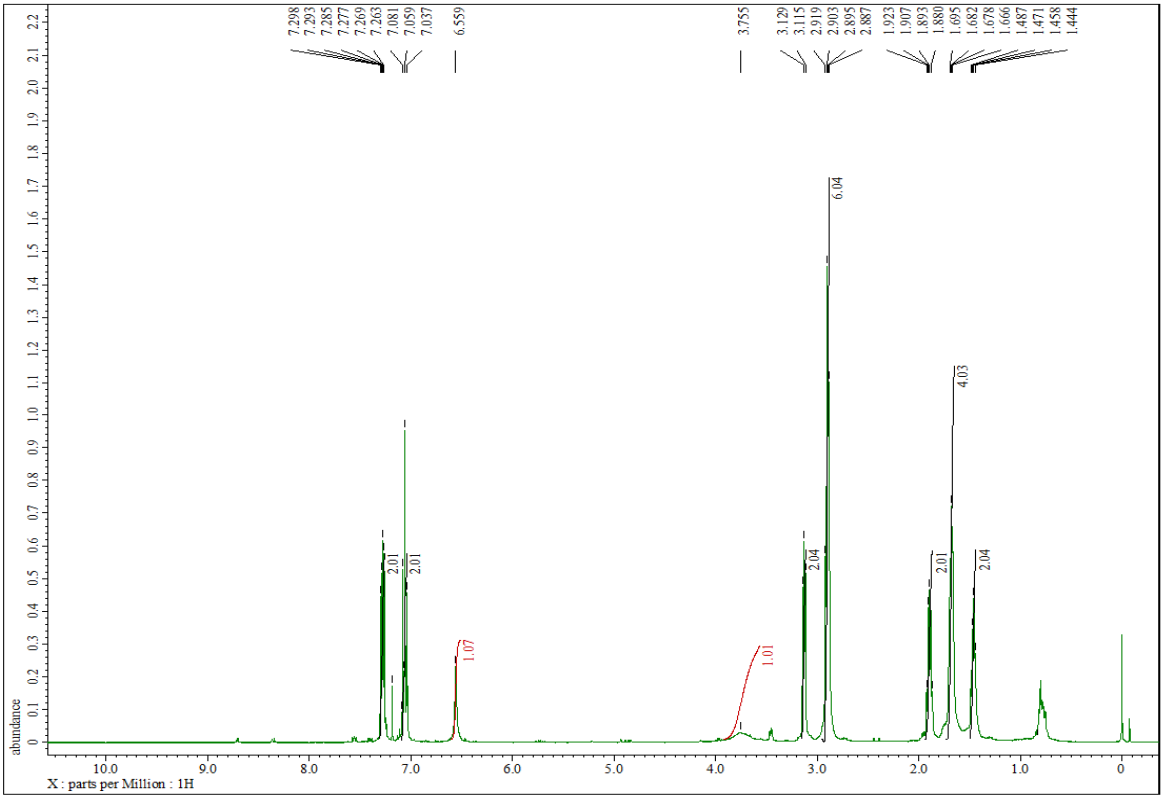

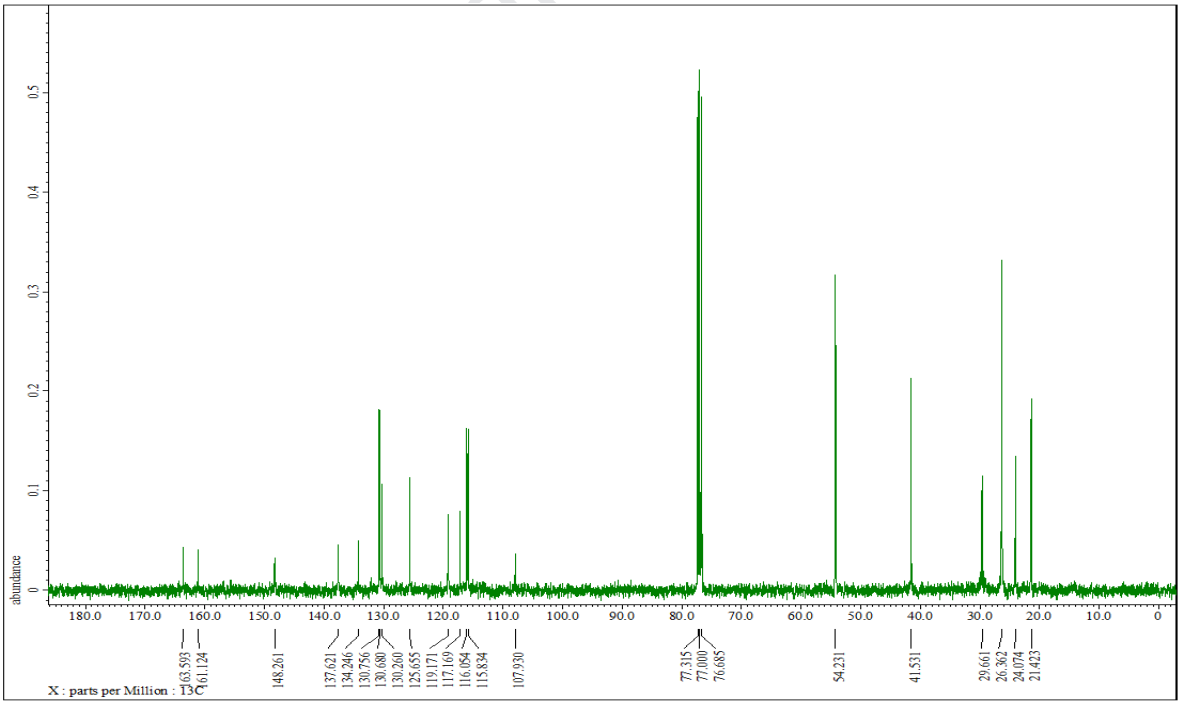

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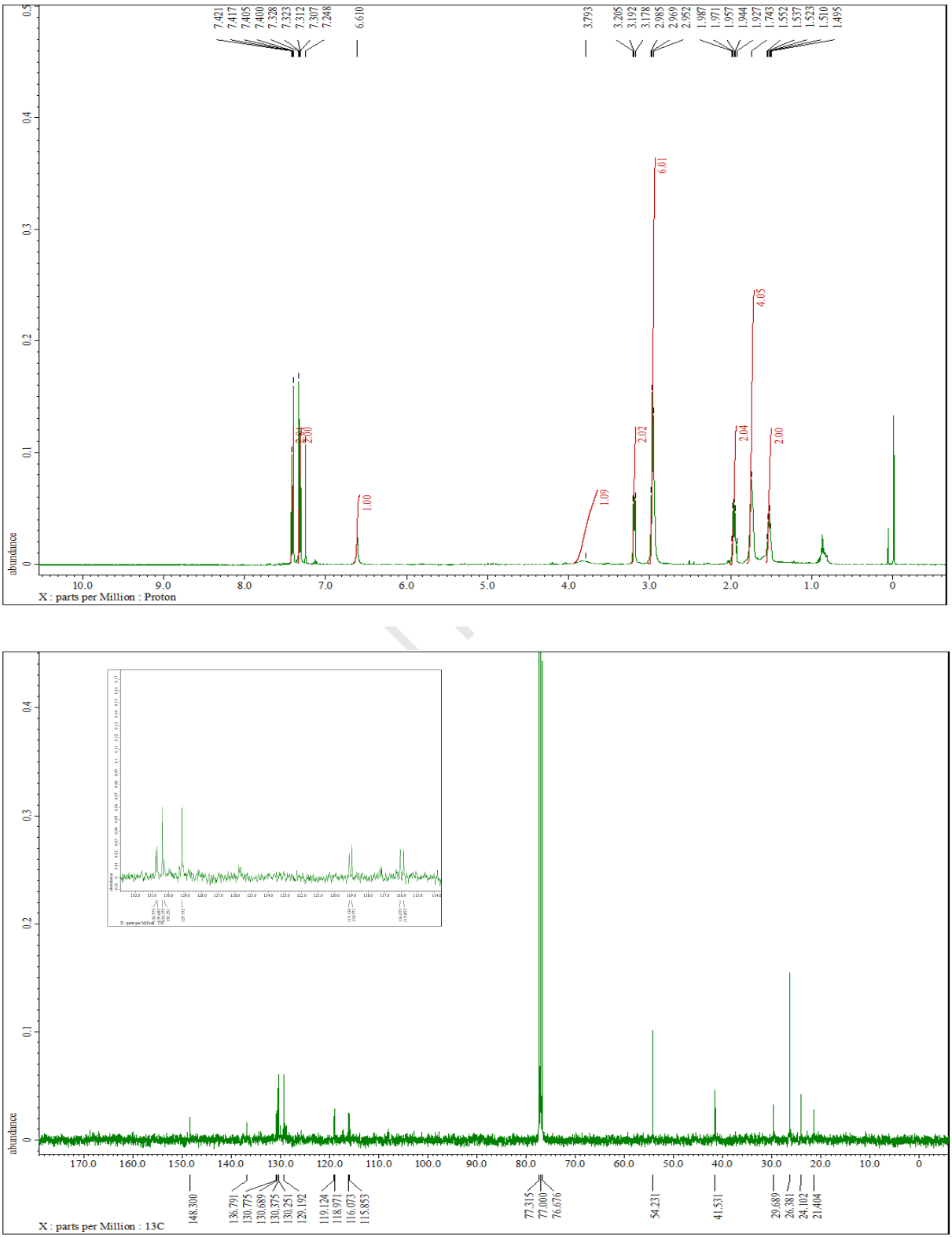

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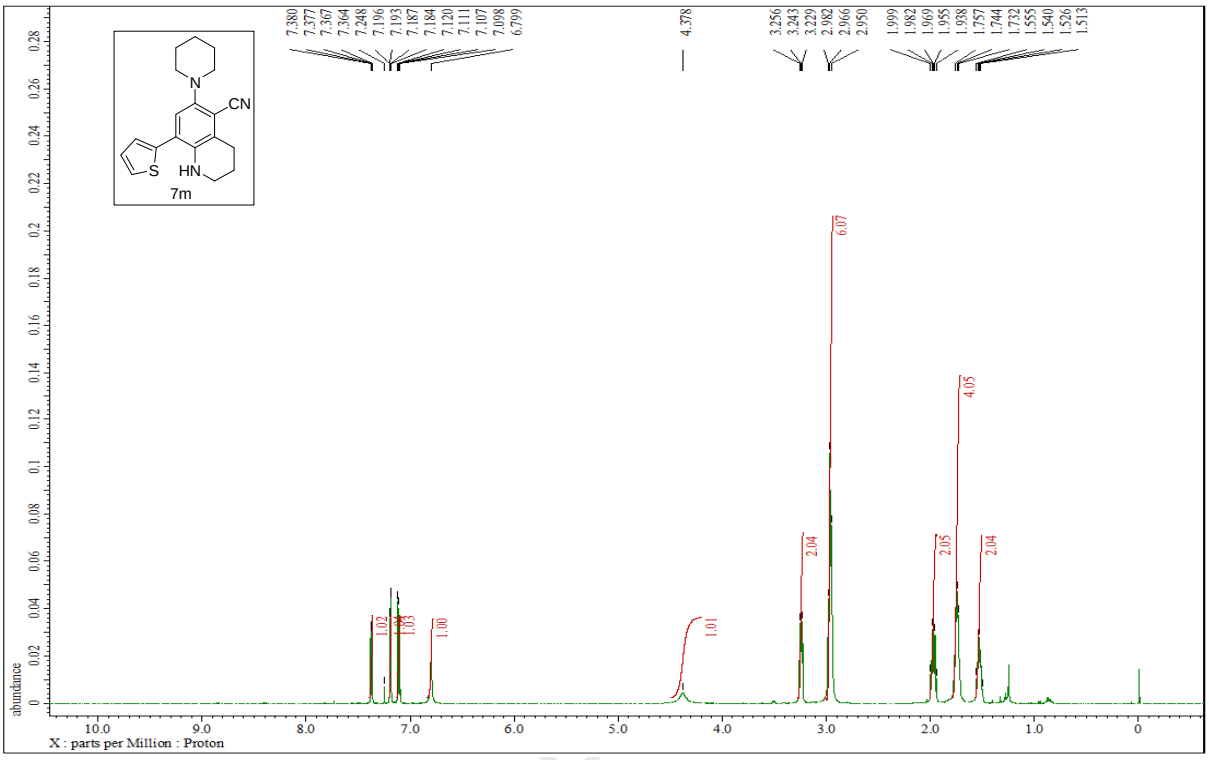

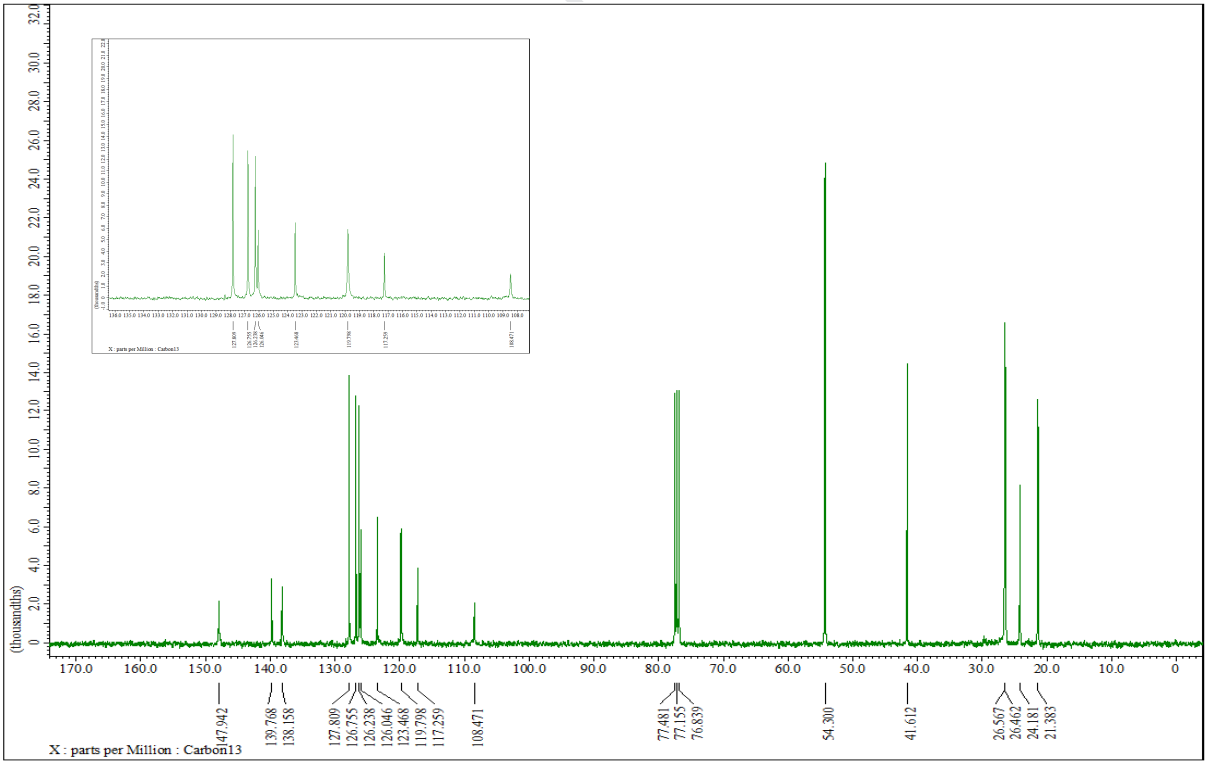

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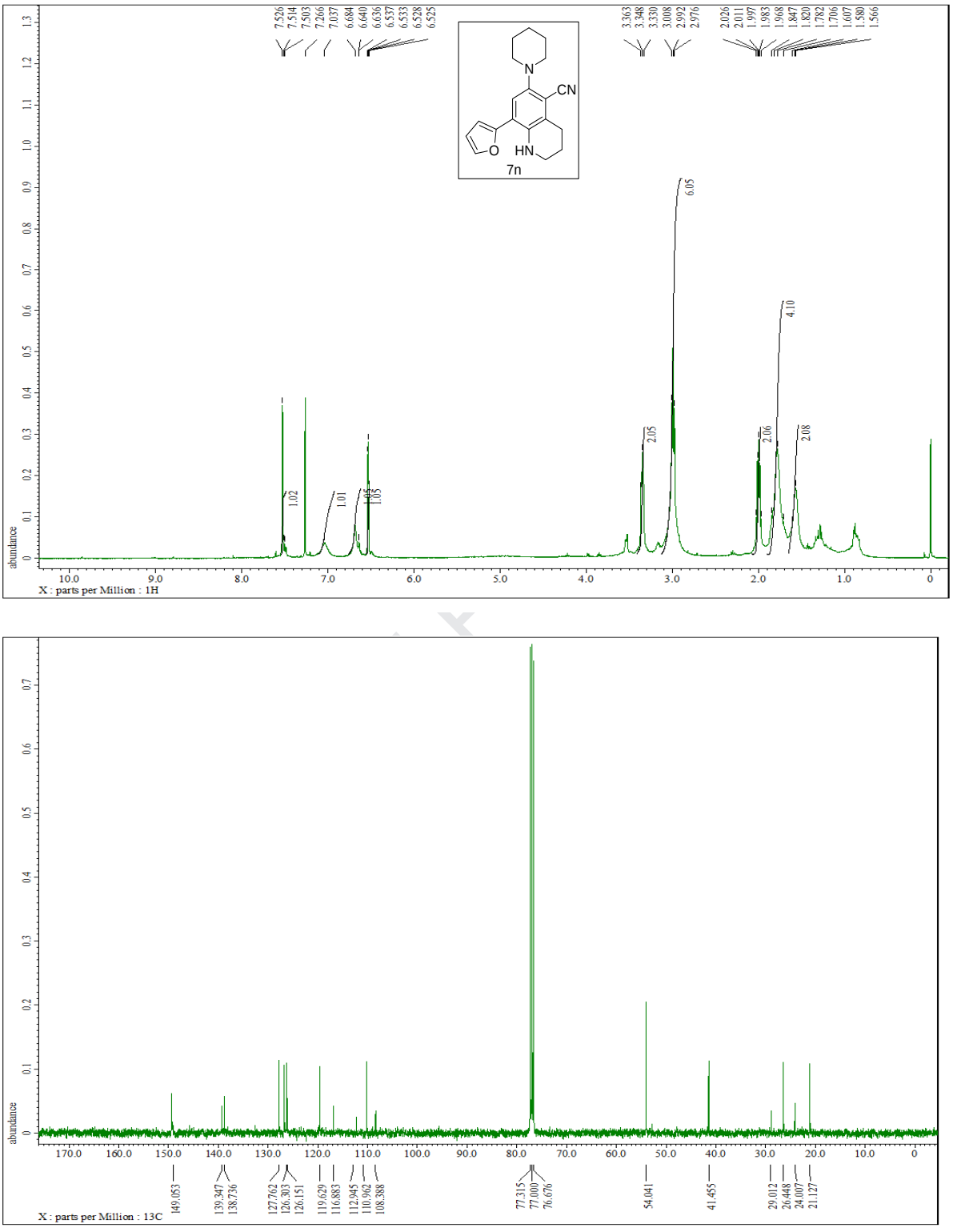

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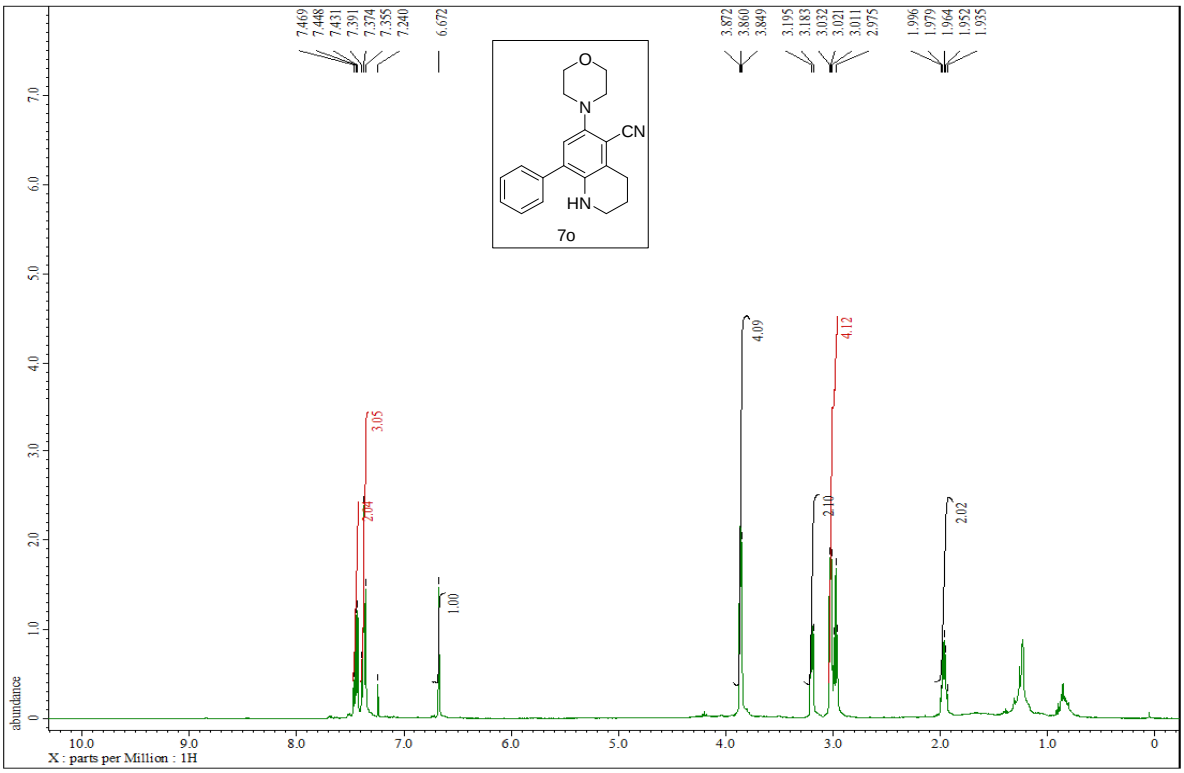
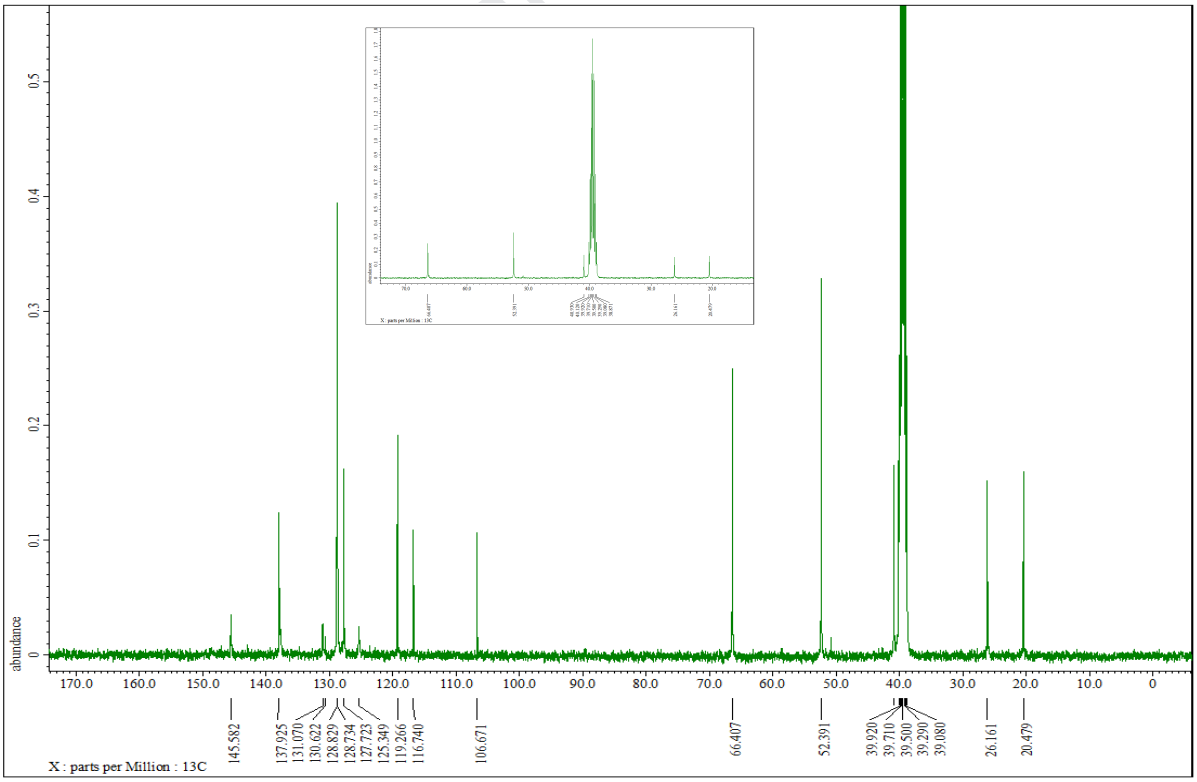
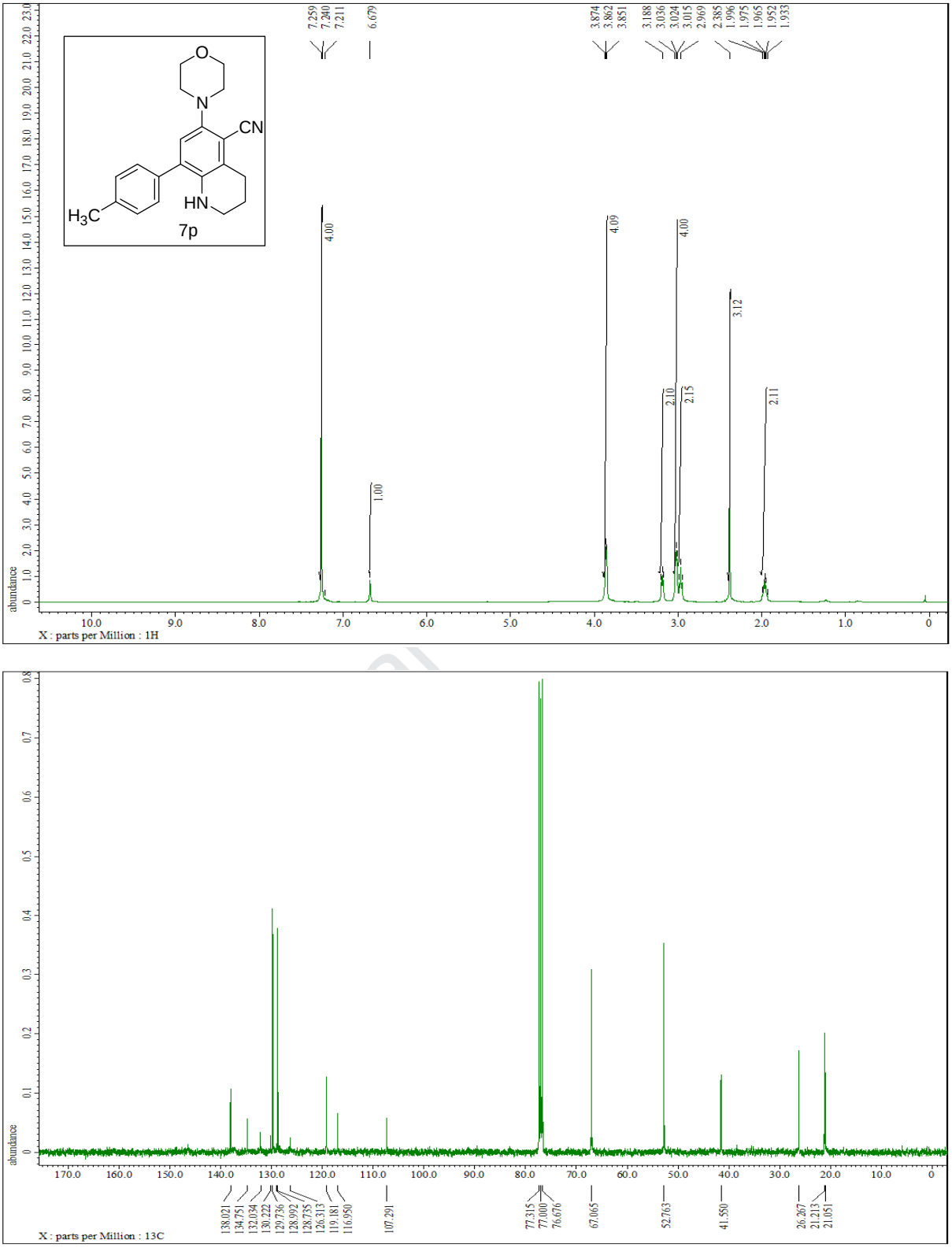




^{1}H NMR and ^{13}C NMR spectrum of 6-morpholino-8-phenyl-1,2,3,4-tetrahydroquinoline-5-carbonitrile



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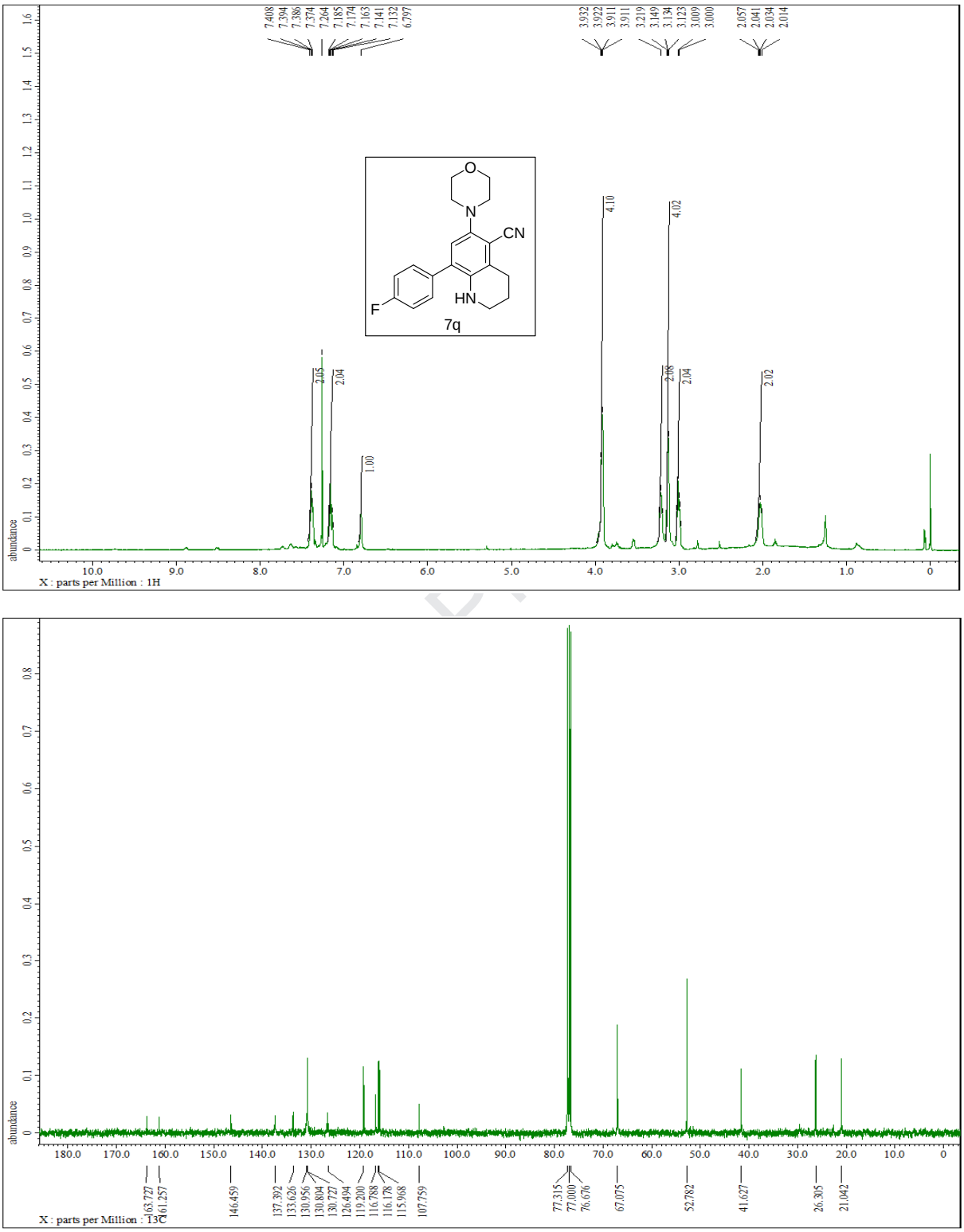

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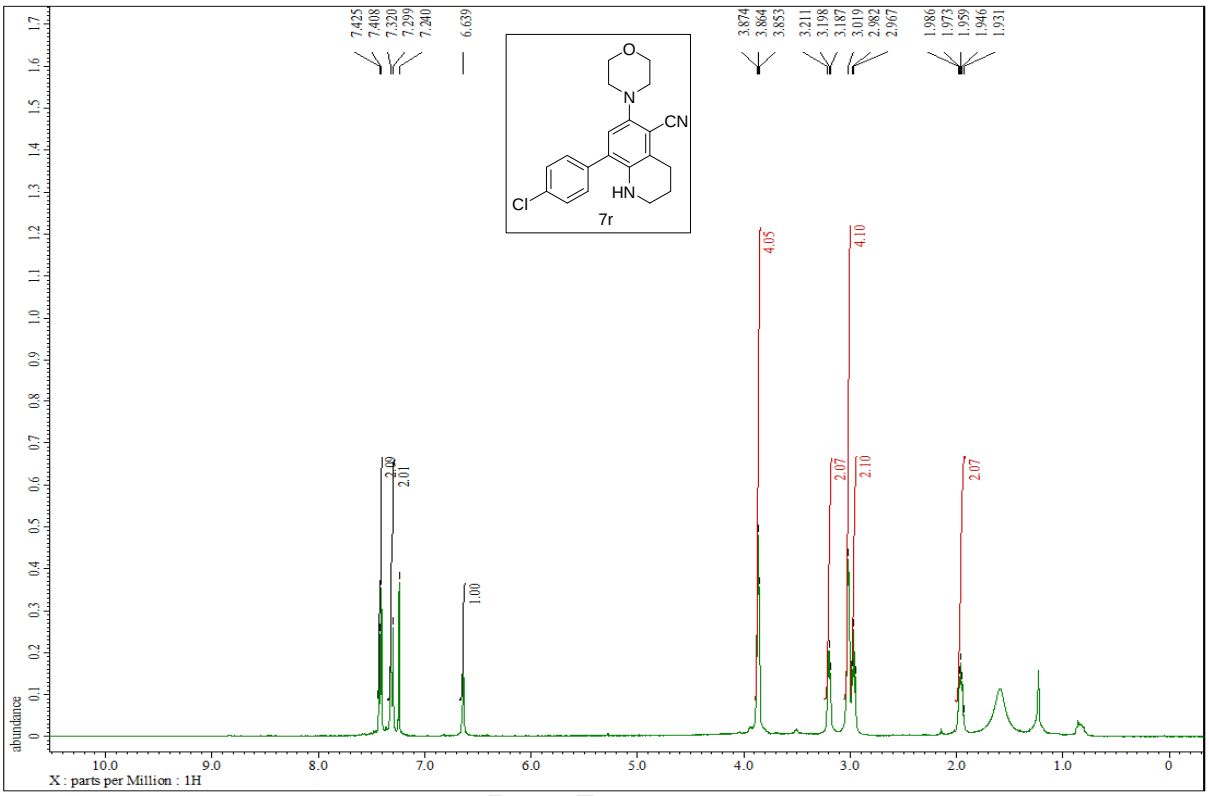

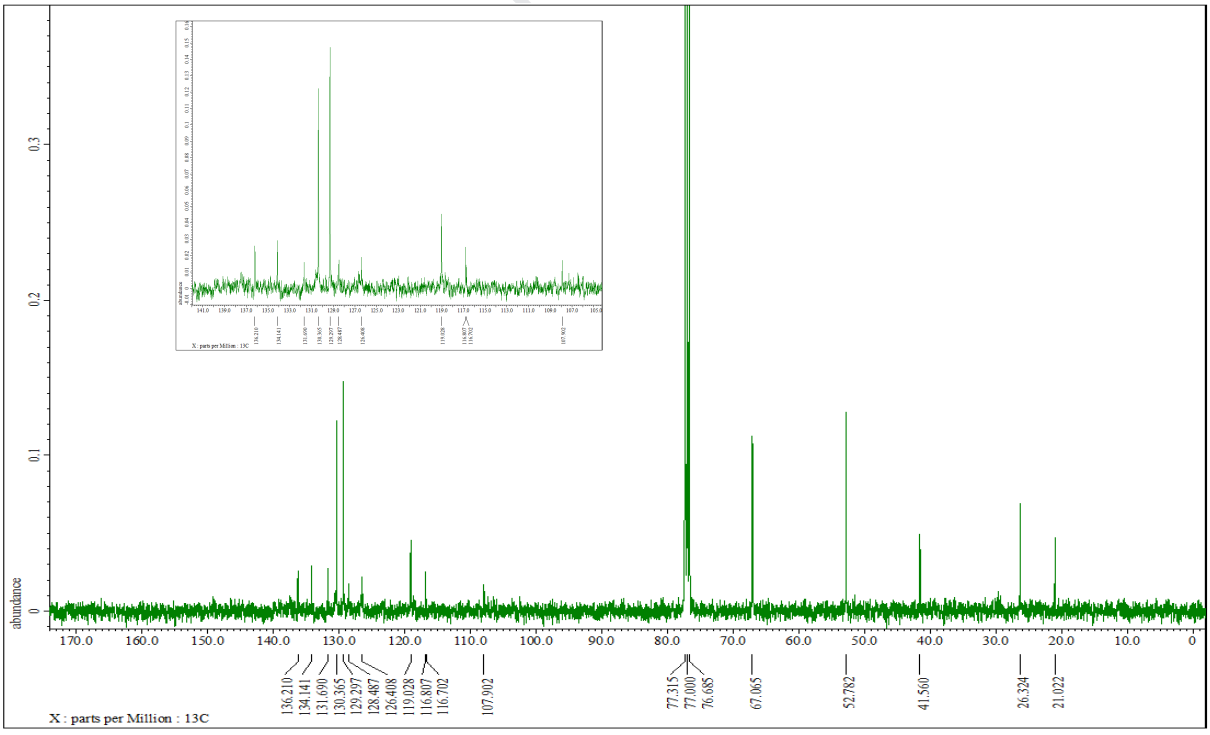

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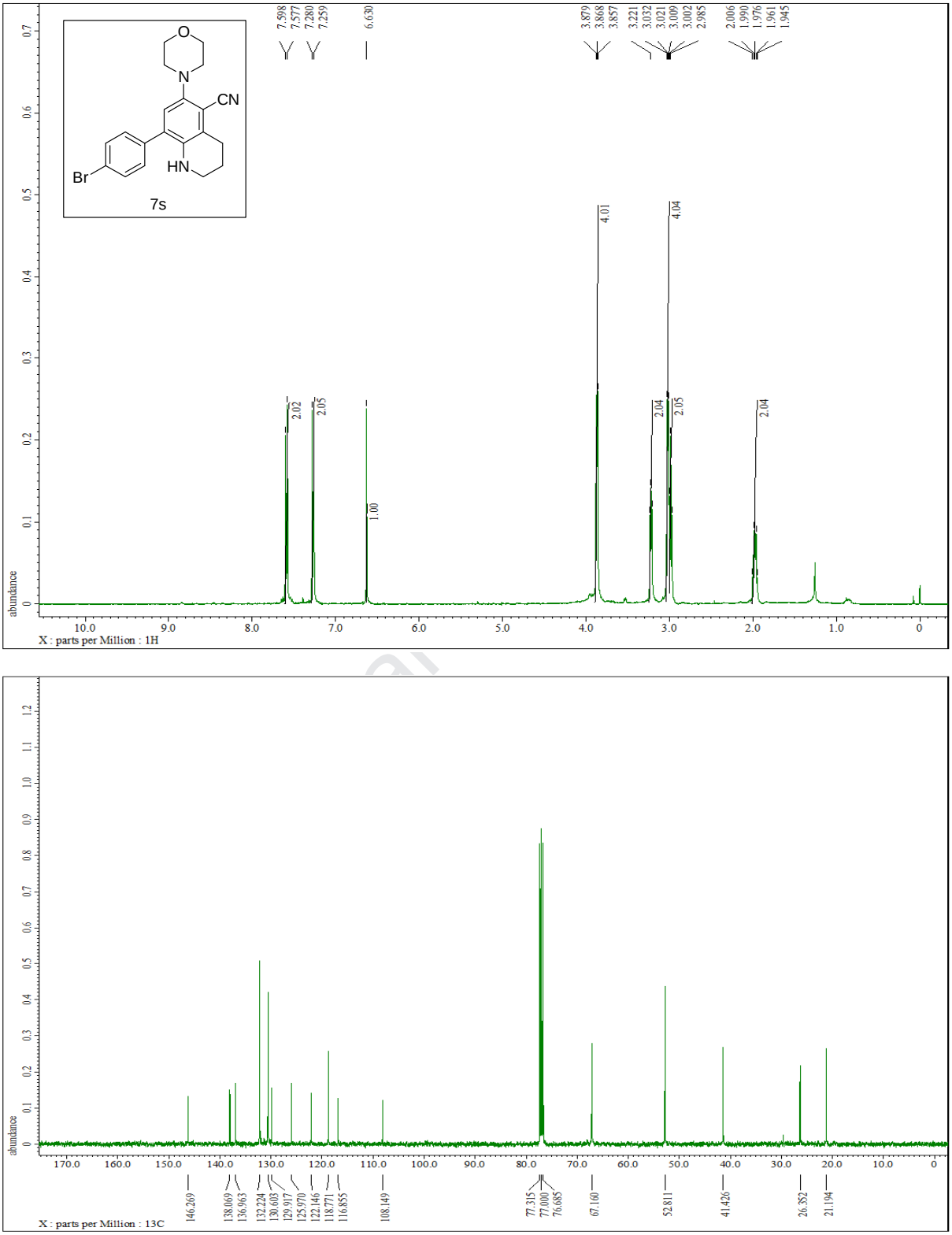

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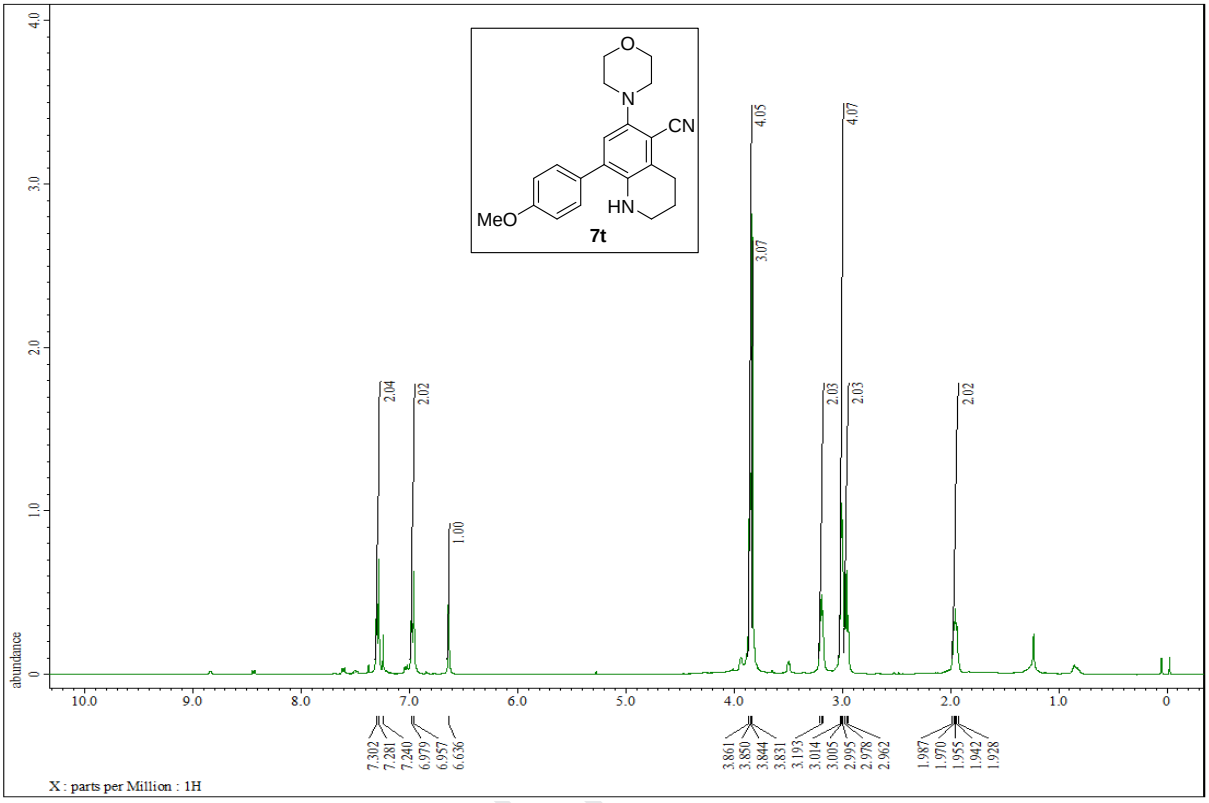
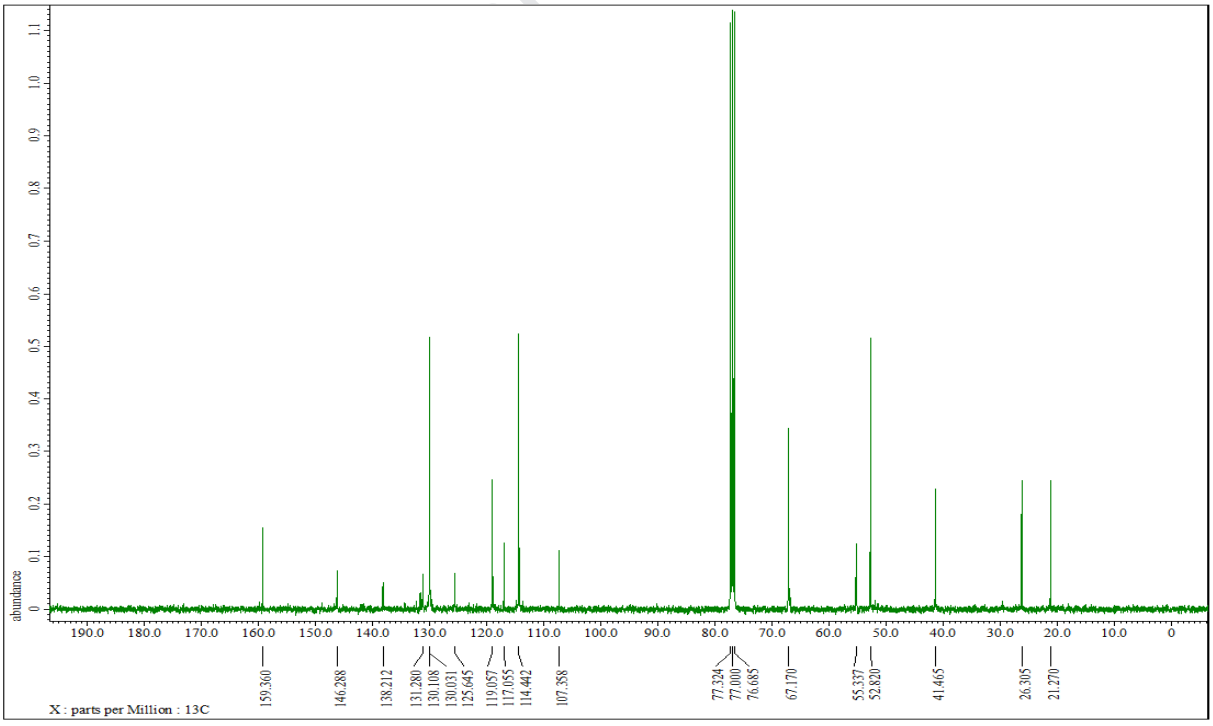
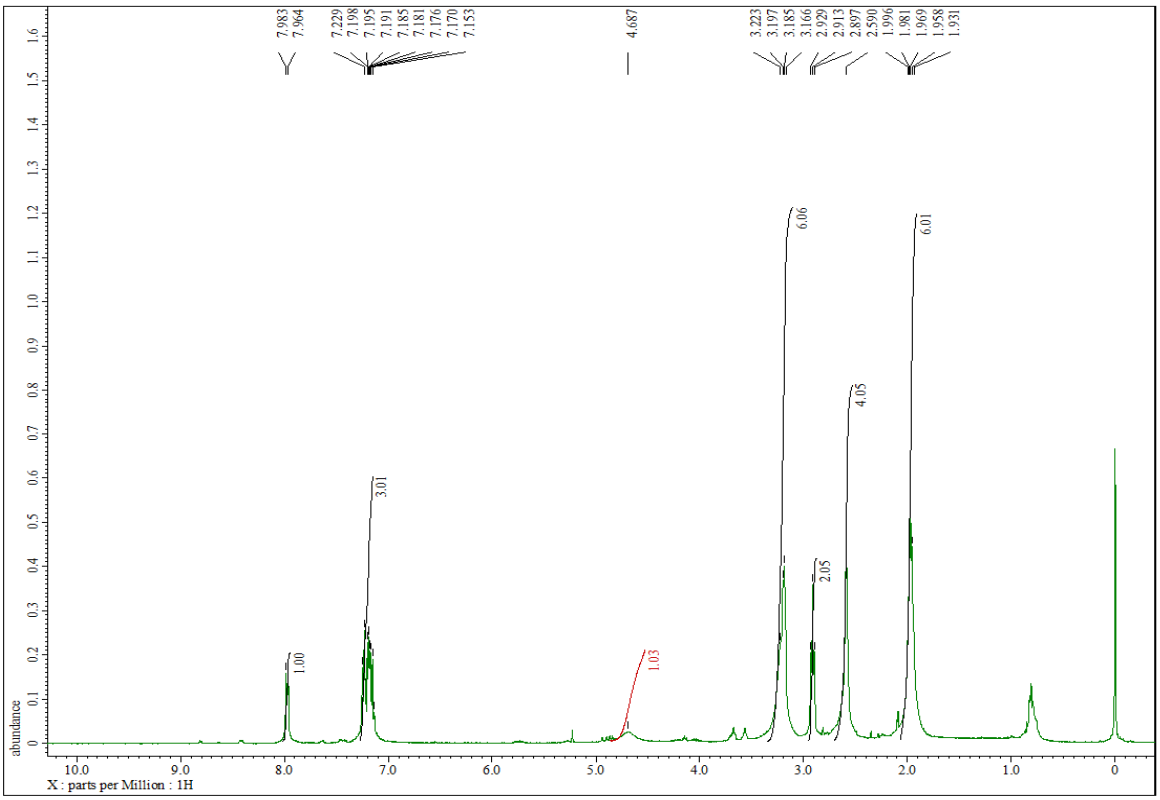
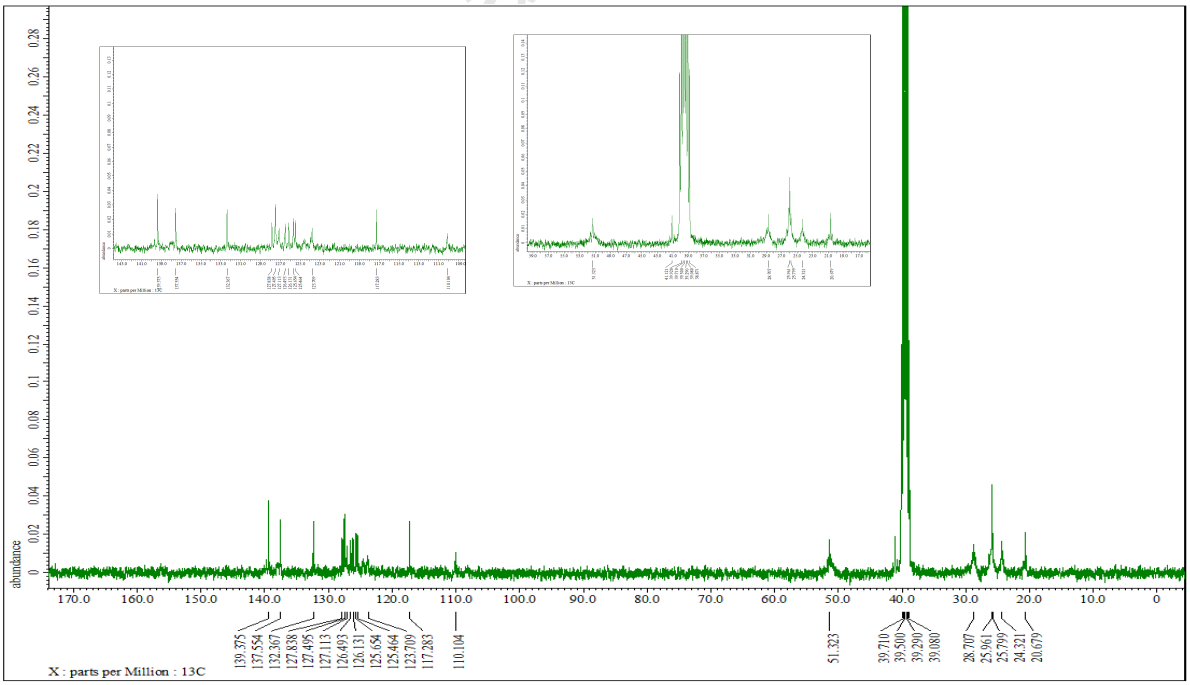


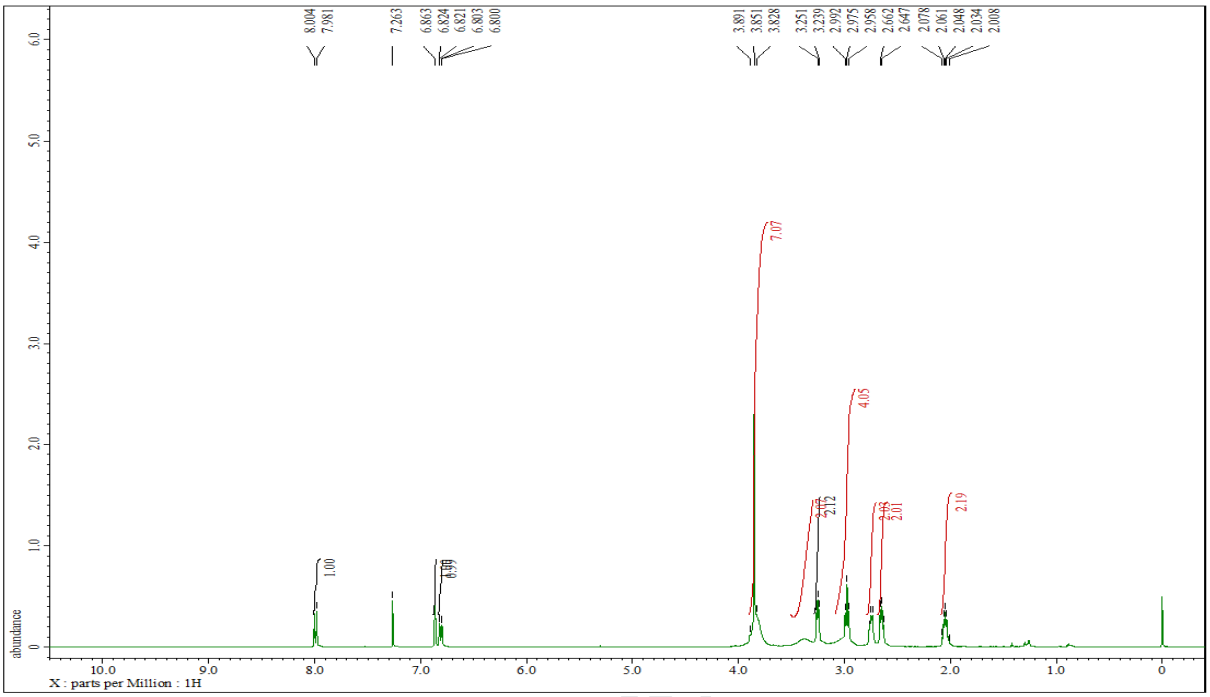


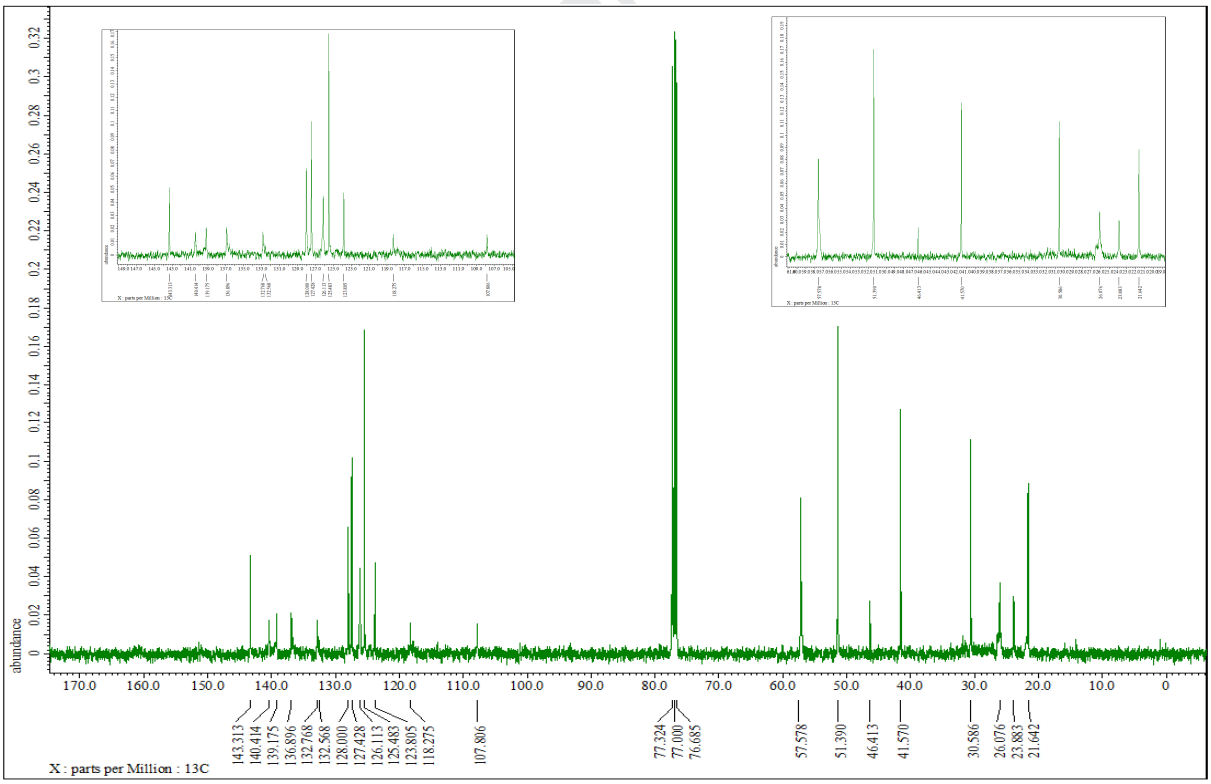
[1]HNMR and [13]C NMR spectrum of 8-(4-methoxyphenyl)-6-morpholino-1,2,3,4-tetrahydroquinoline-5-carbonitrile



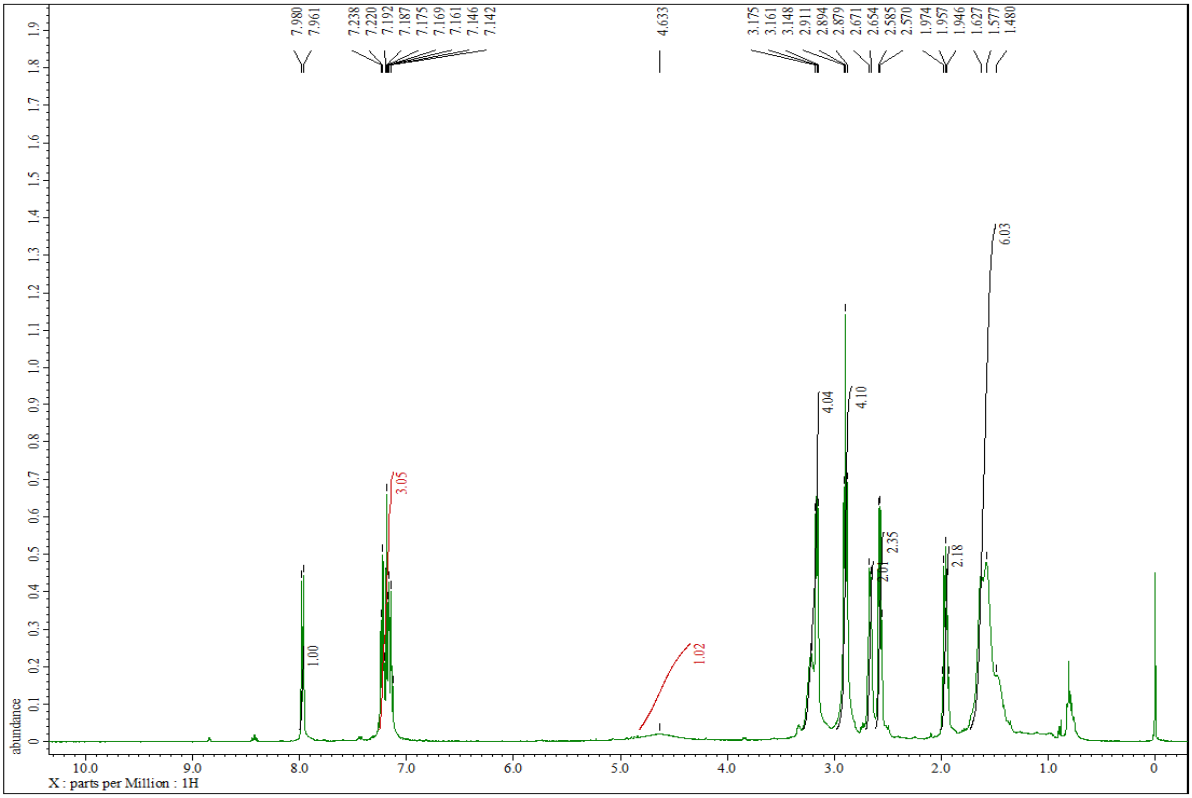


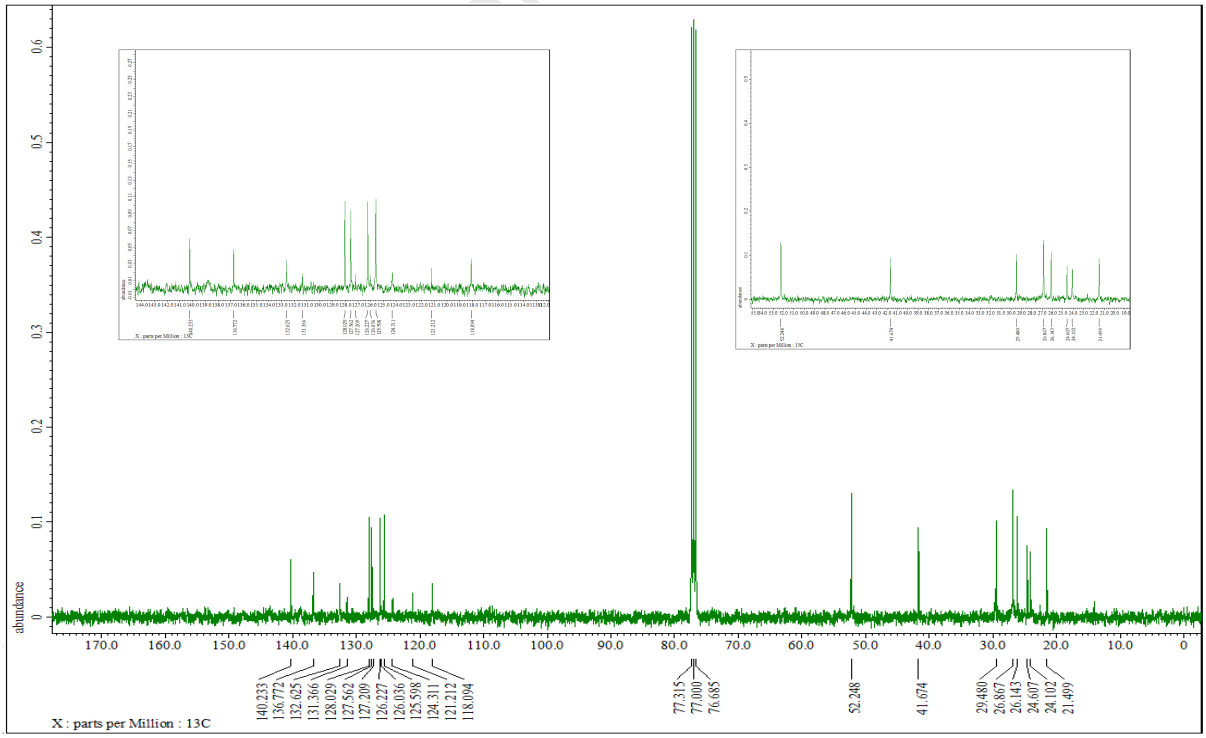
[1]HNMR and [13]C NMR spectrum of 6-(pyrrolidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile



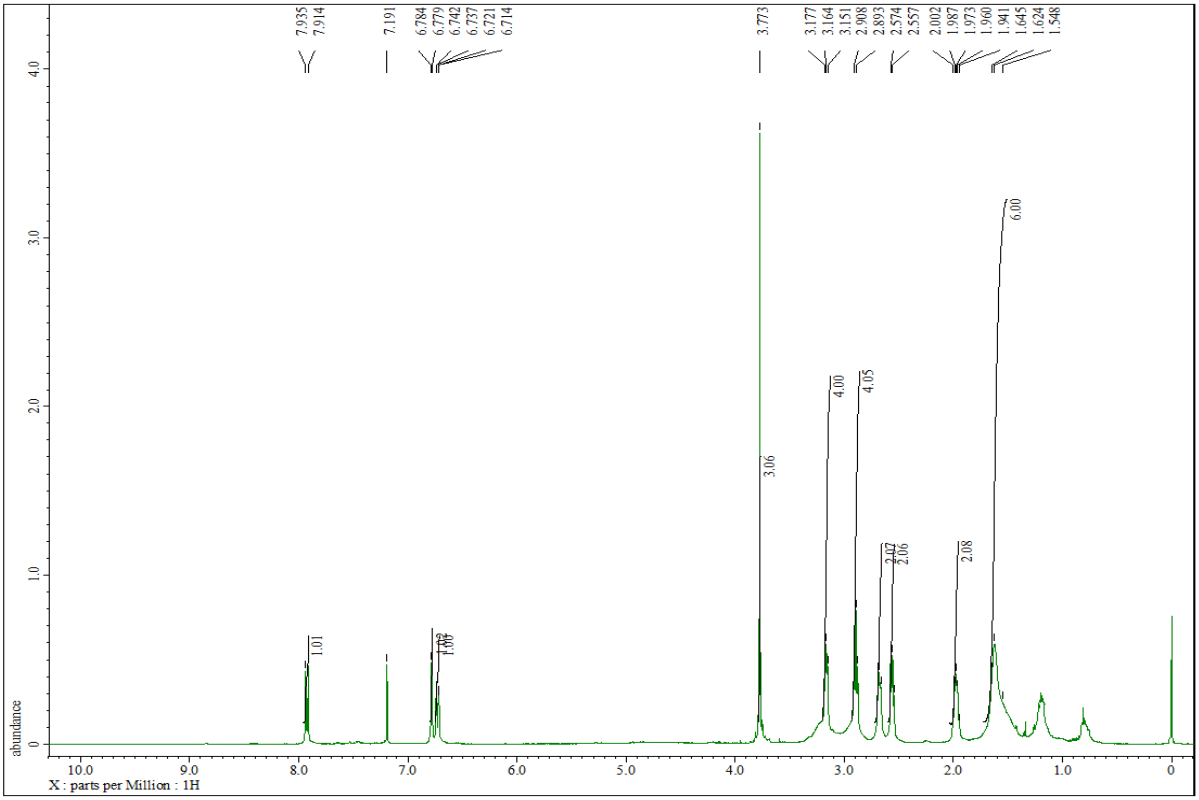


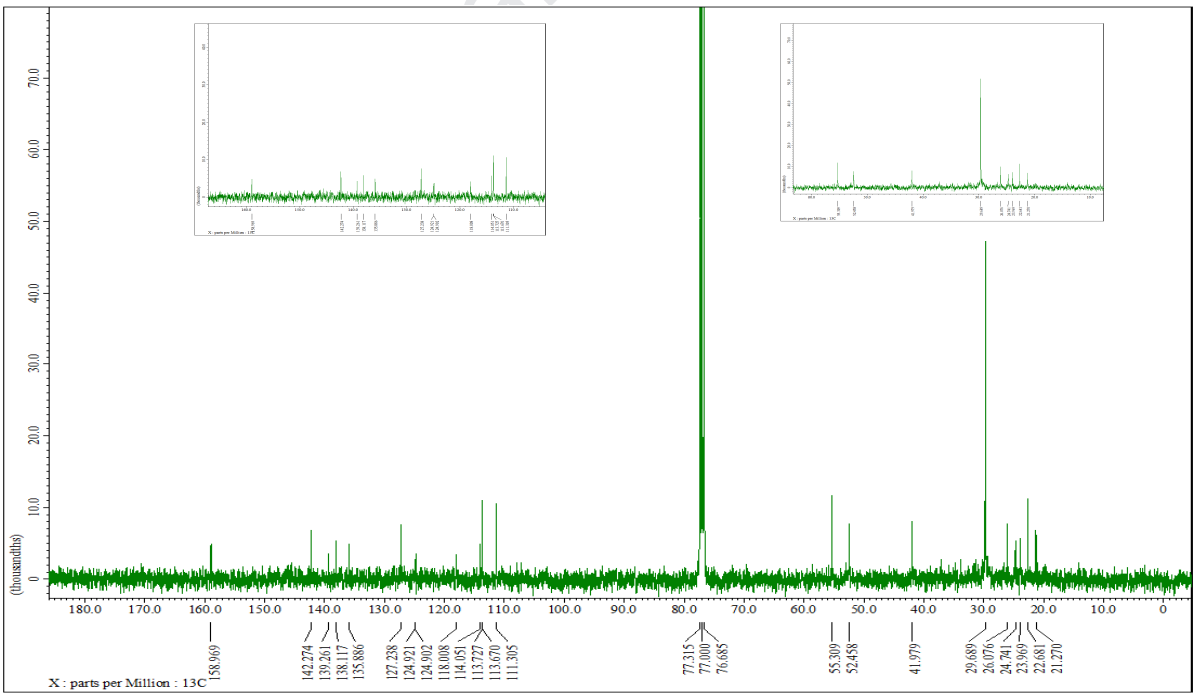
[1]HNMR and [13]C NMR spectrum of 6-(4-methylpiperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile



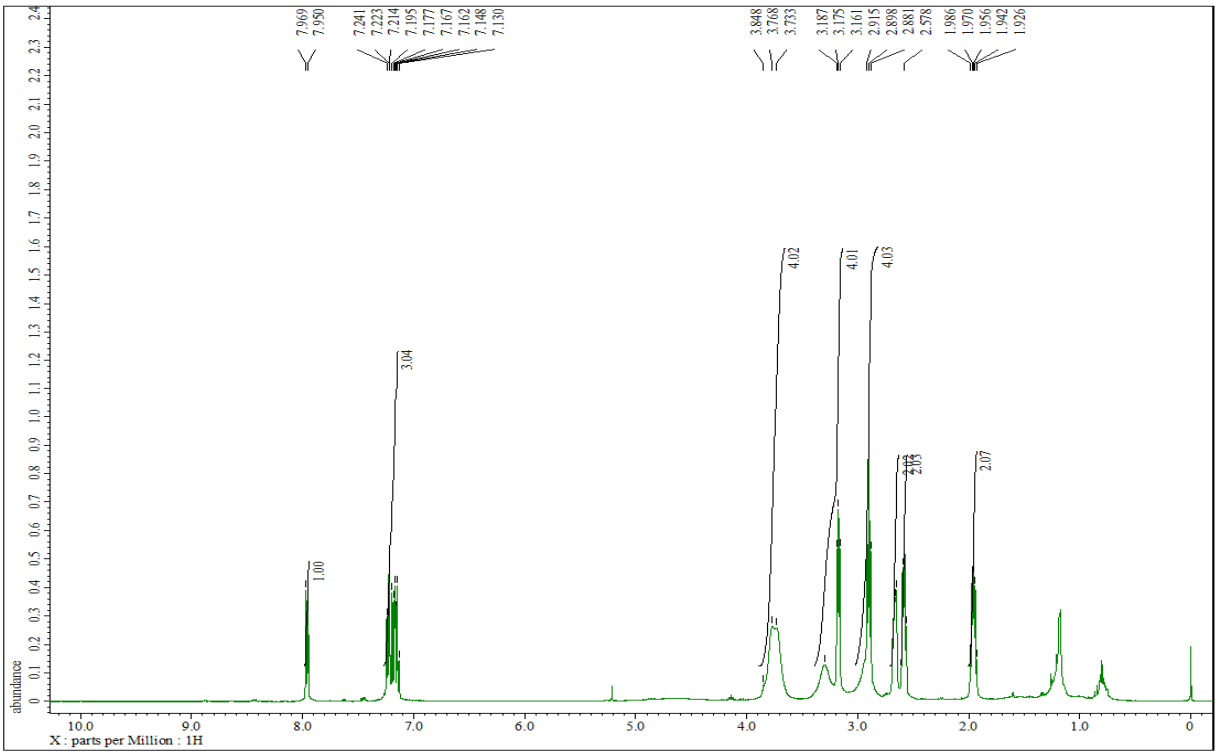


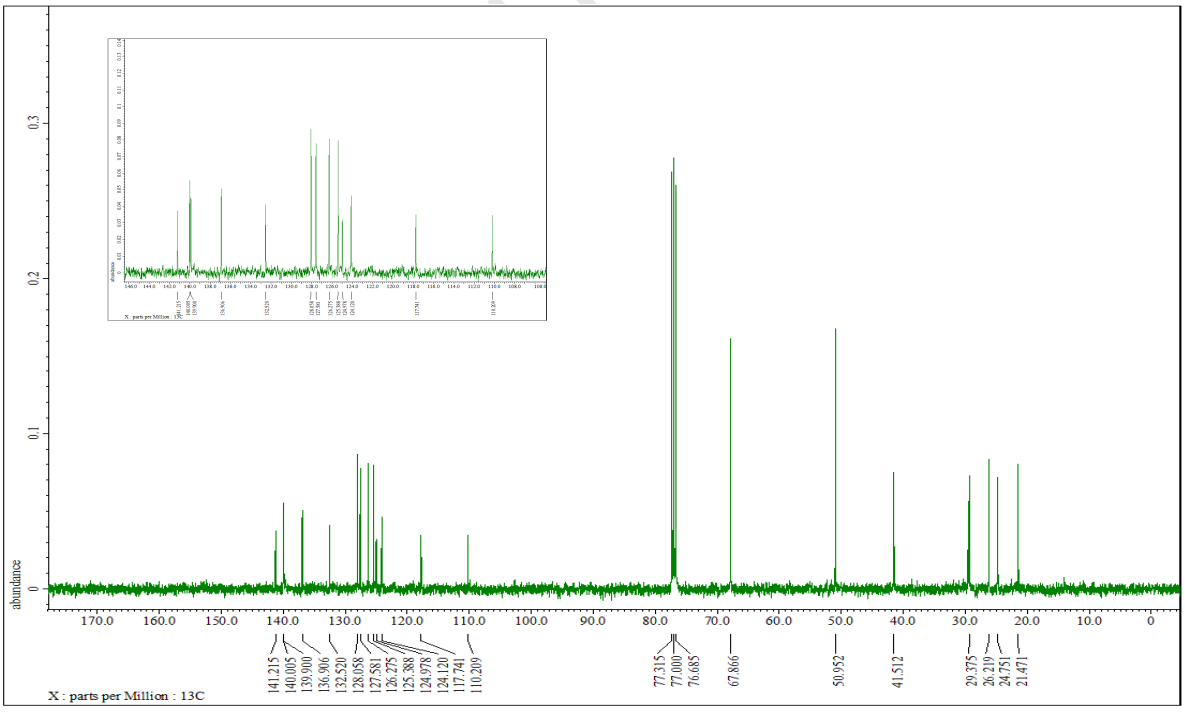
[1]HNMR and [13]C NMR spectrum of 6-(piperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile



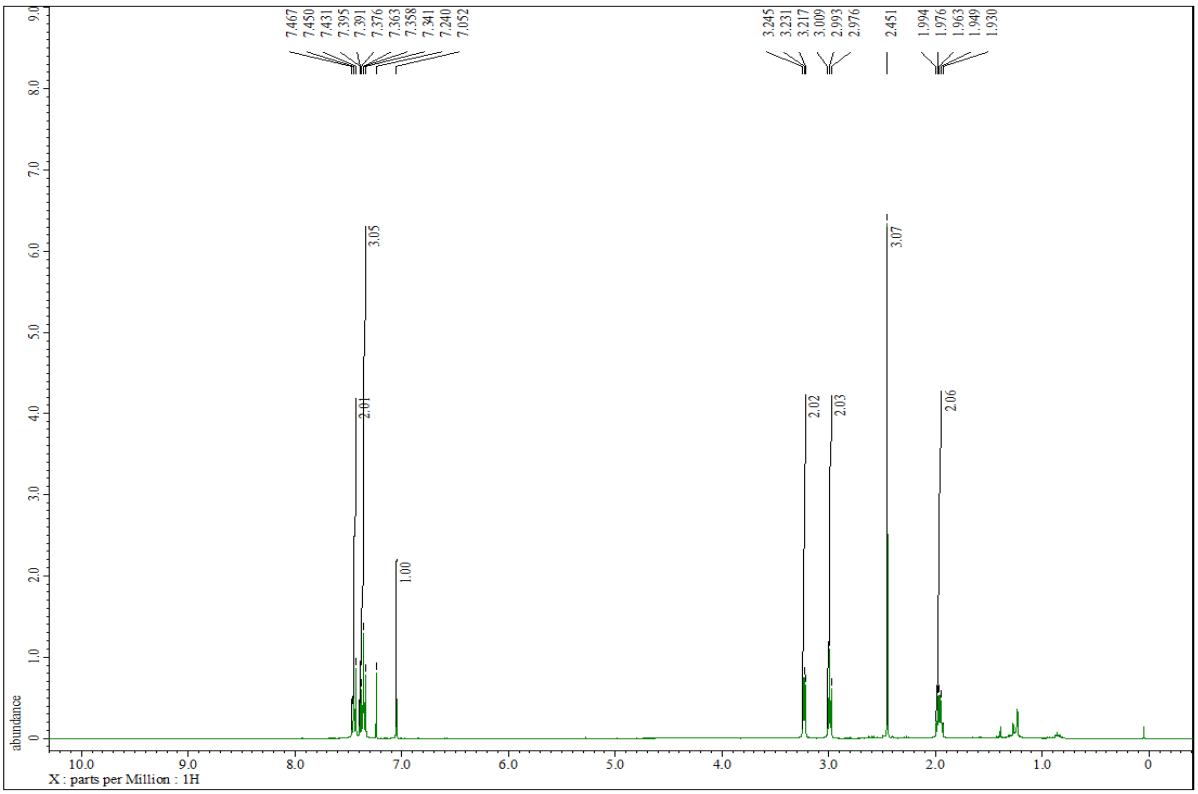


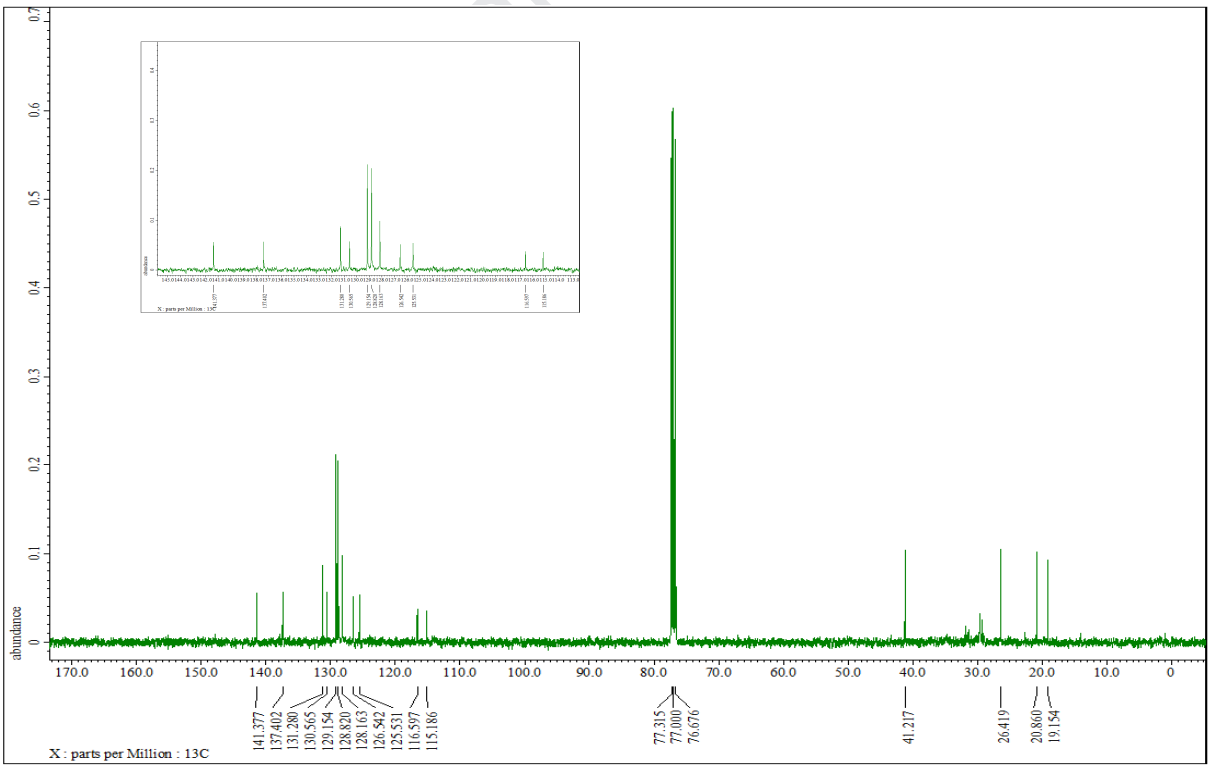
^{1}HNMR and ^{13}C NMR spectrum of 10-methoxy-6-(piperidin-1-yl)-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile



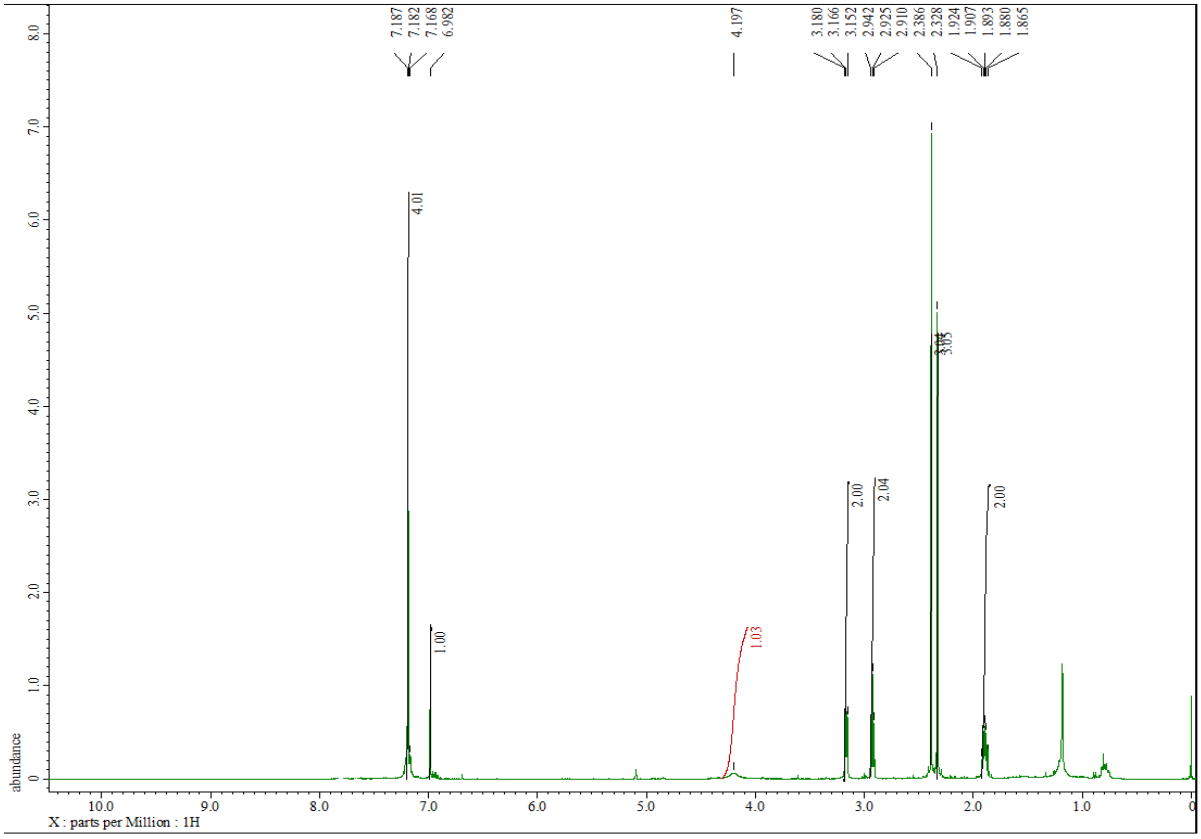


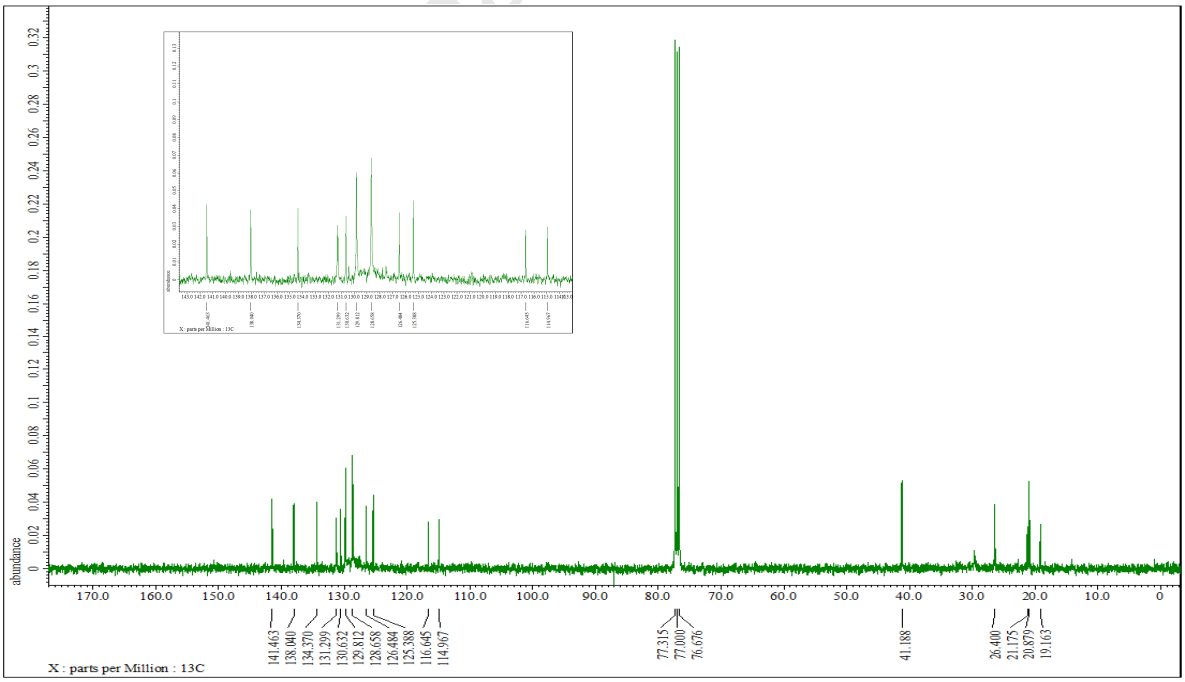
[1]HNMR and [13]C NMR spectrum of 6-morpholino-1,2,3,4,7,8-hexahydronaphtho[2,1-h]quinoline-5-carbonitrile



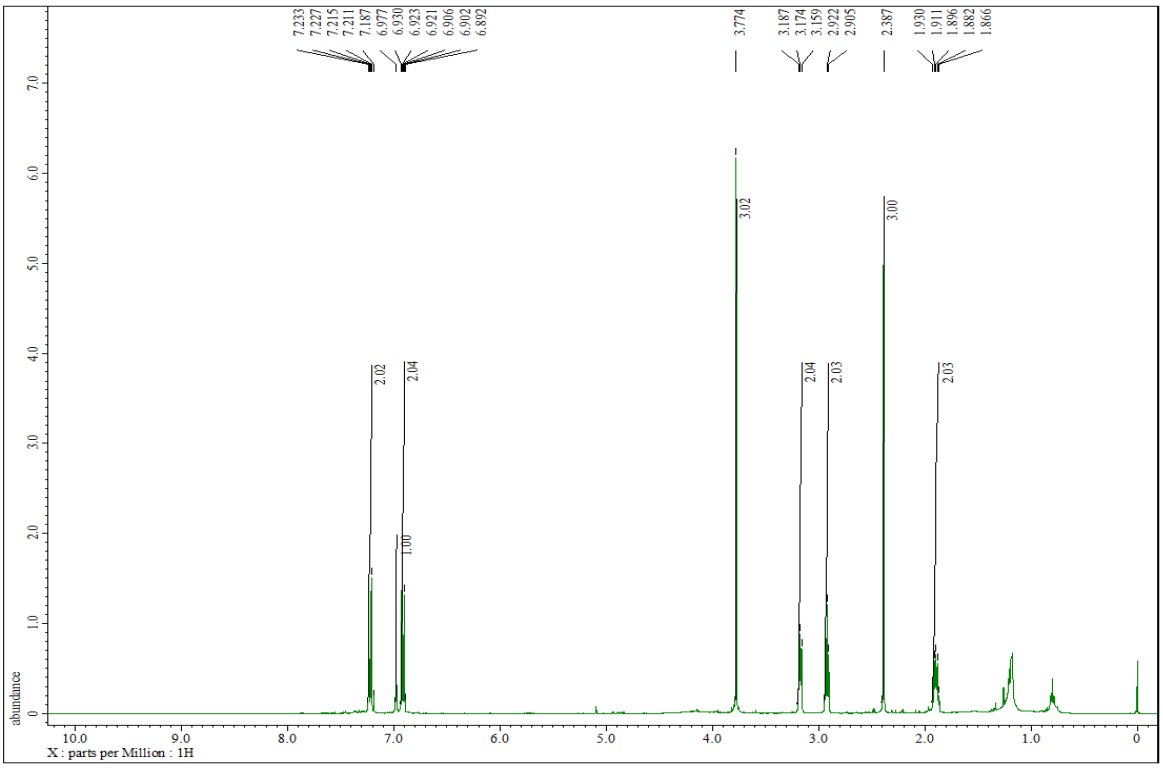


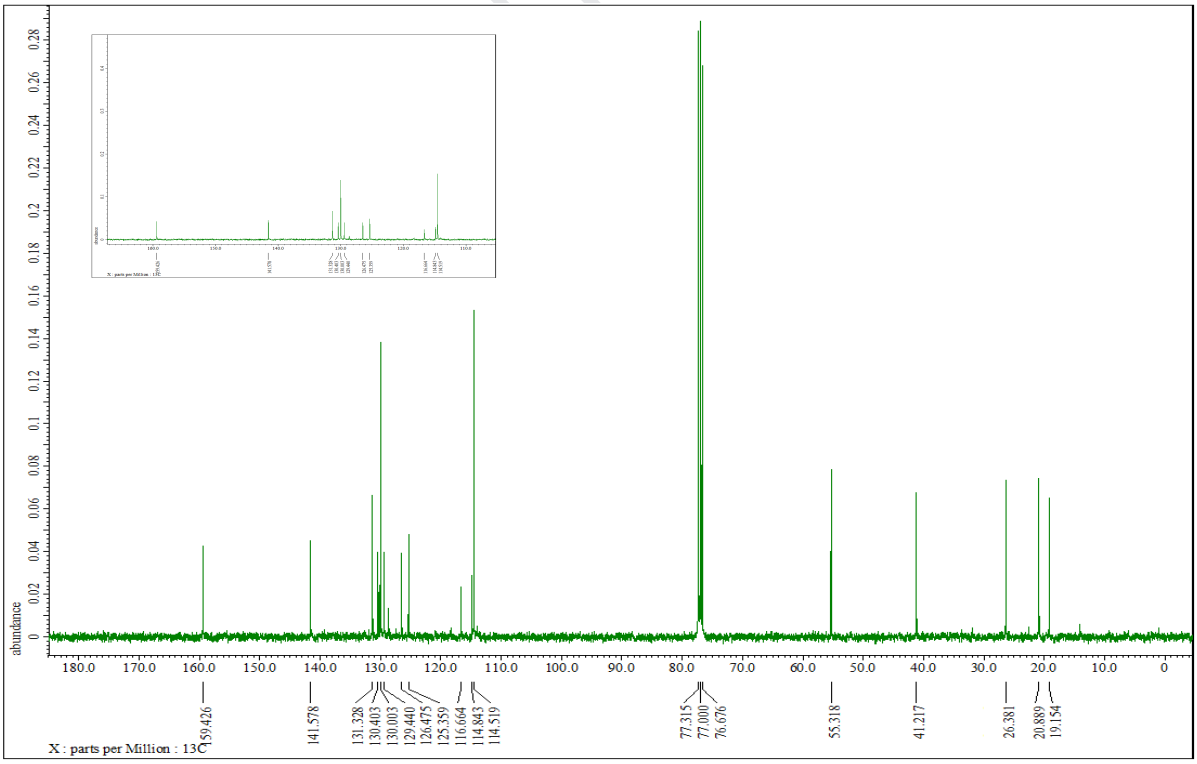
[1]HNMR and [13]C NMR spectrum of 6-(methylthio)-8-phenyl-1,2,3,4-tetrahydroquinoline-5-carbonitrile



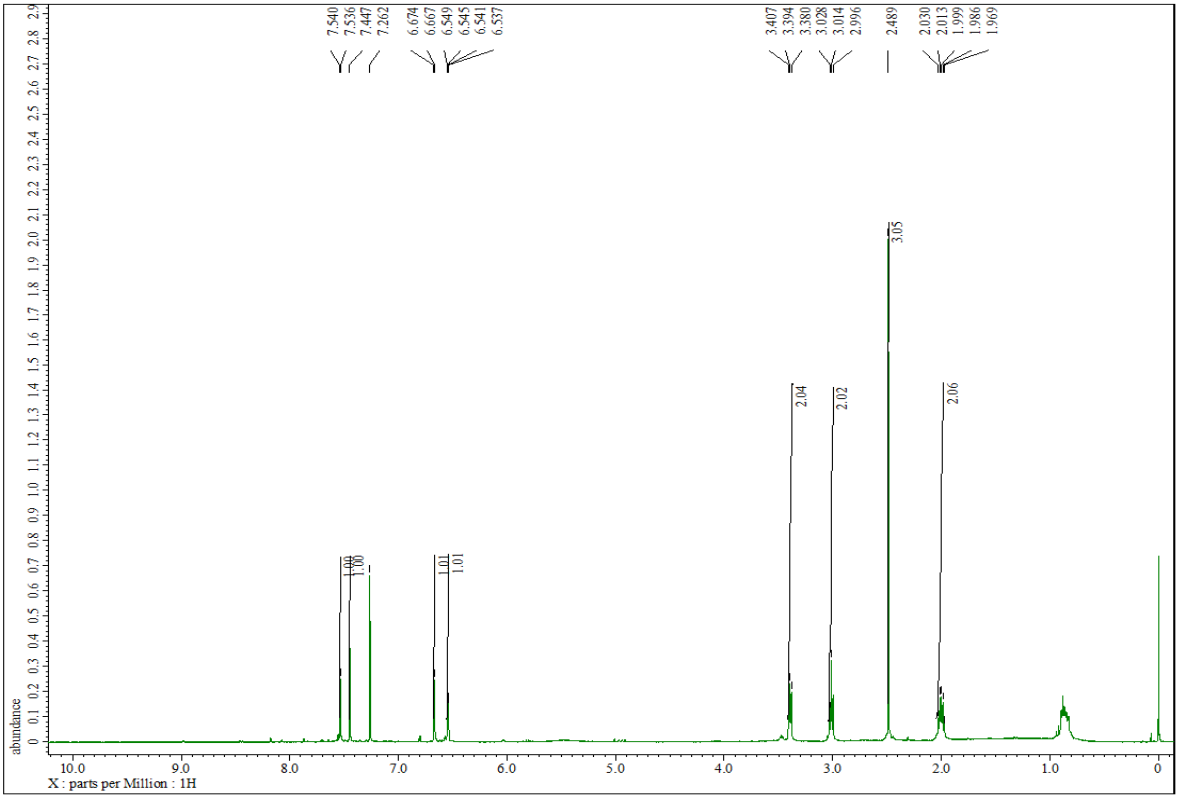


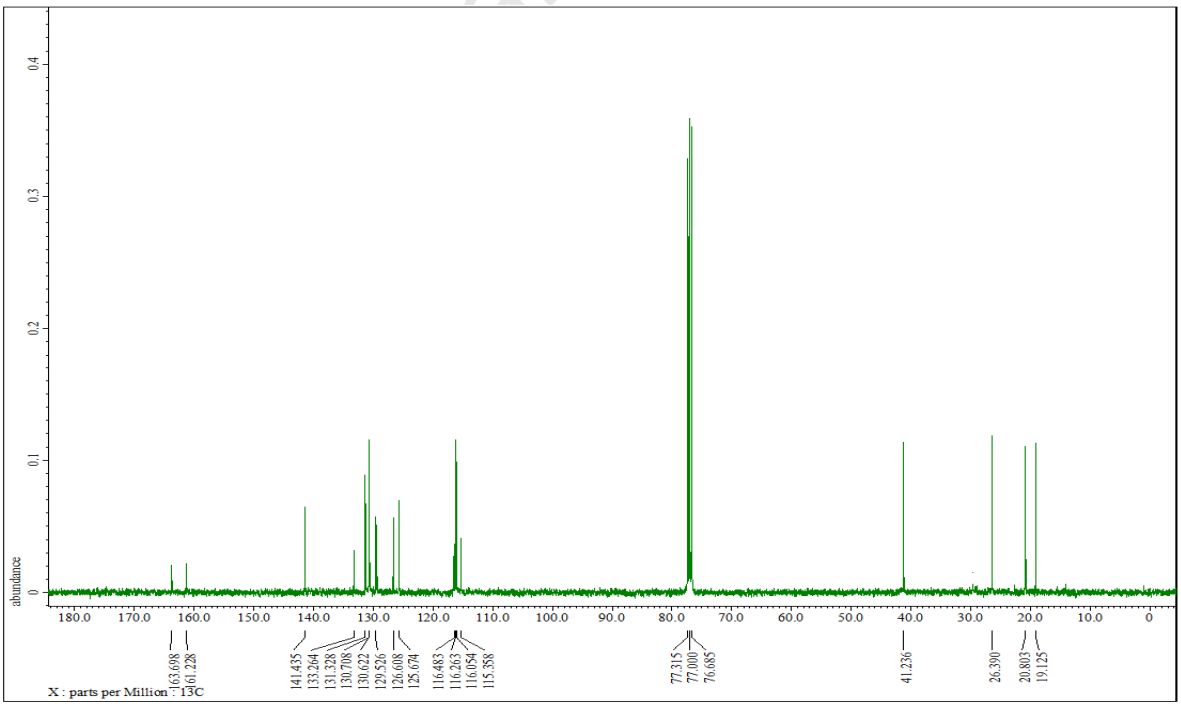
[1]HNMR and [13]C NMR spectrum of `6-(methylthio)-8-(p-tolyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile



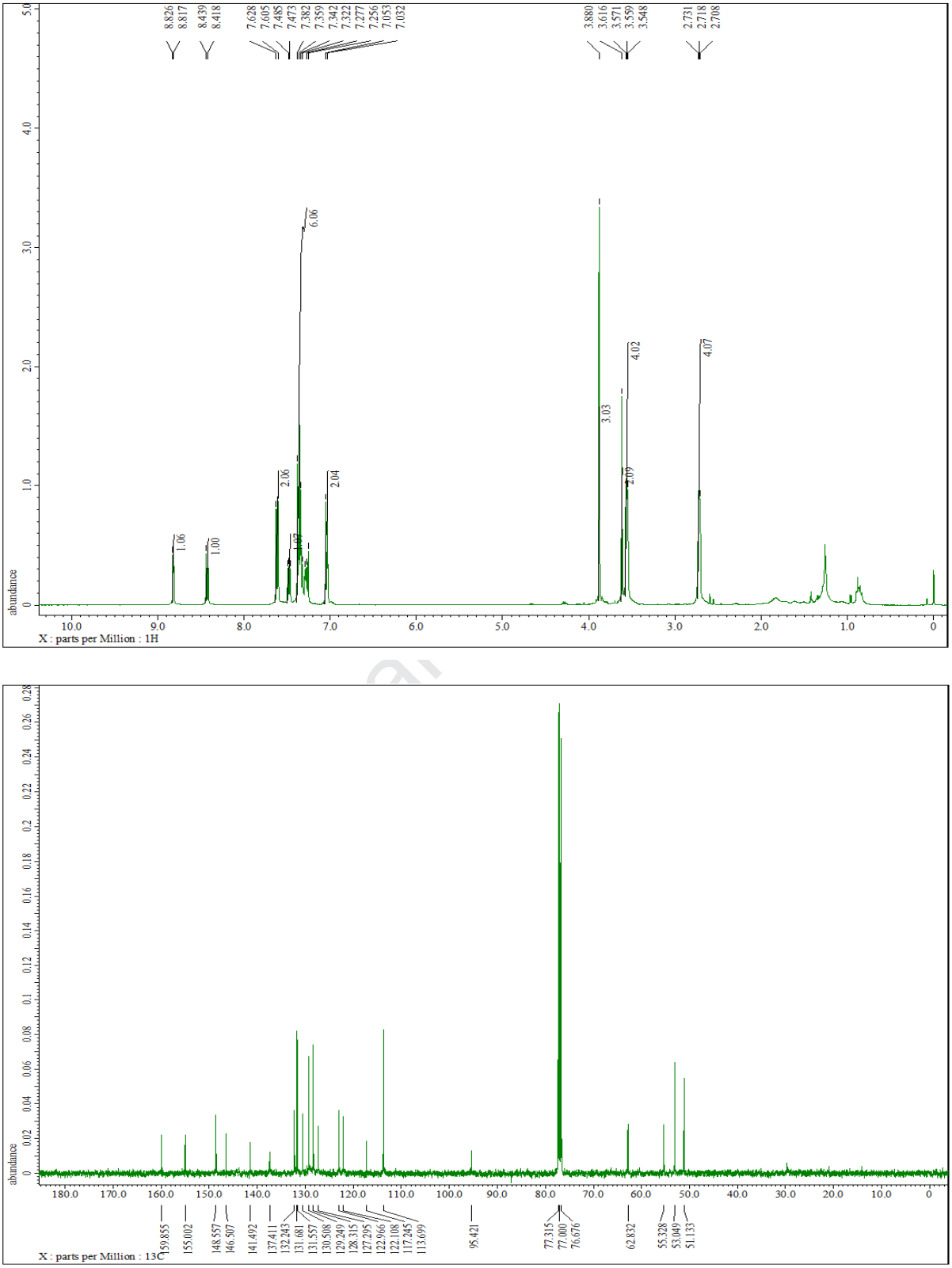


^{1}HNMR and ^{13}C NMR spectrum of 8-(4-methoxyphenyl)-6-(methylthio)-1,2,3,4-tetrahydroquinoline-5-carbonitrile

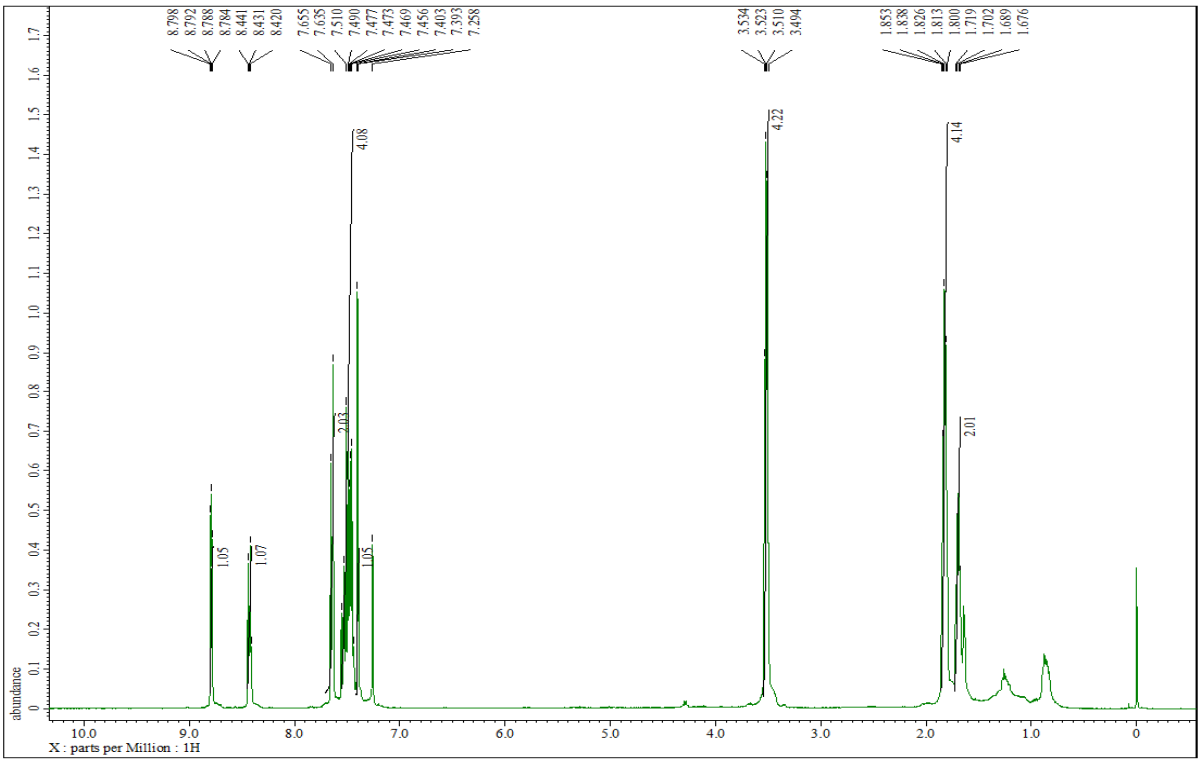


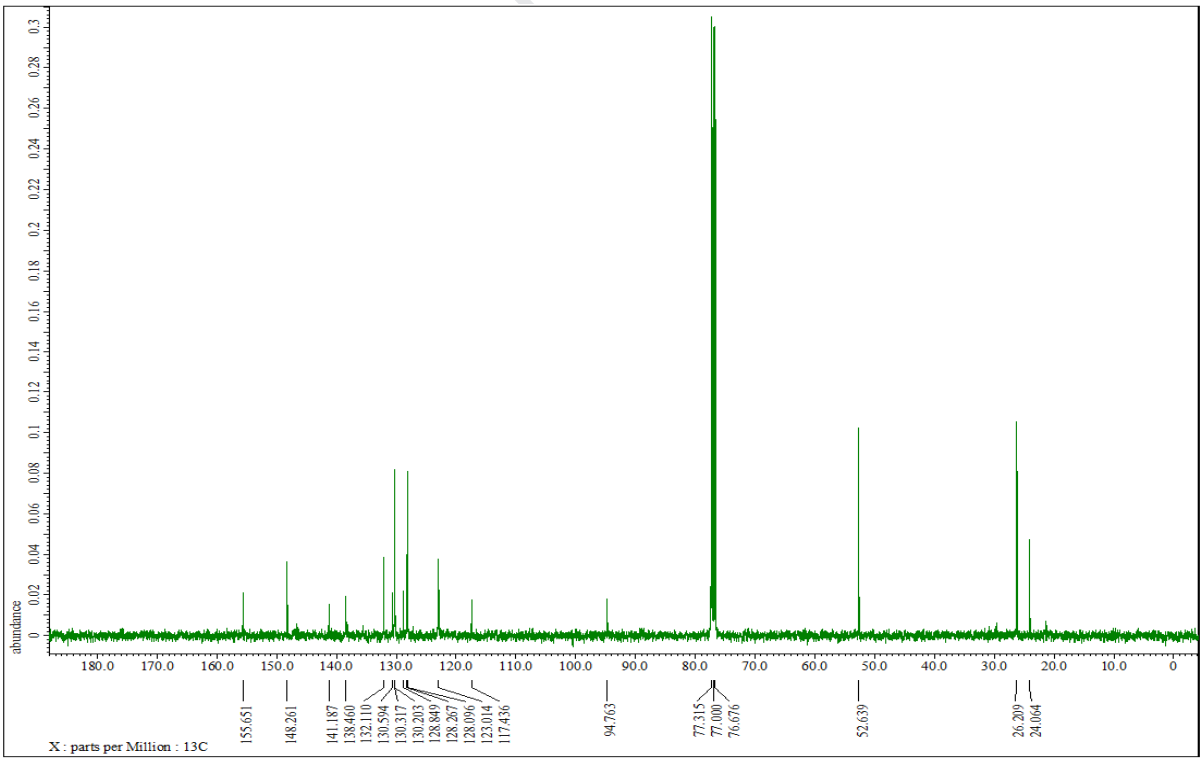


[1]HNMR and [13]C NMR spectrum of 8-(furan-2-yl)-6-(methylthio)-1,2,3,4-tetrahydroquinoline-5-carbonitrile

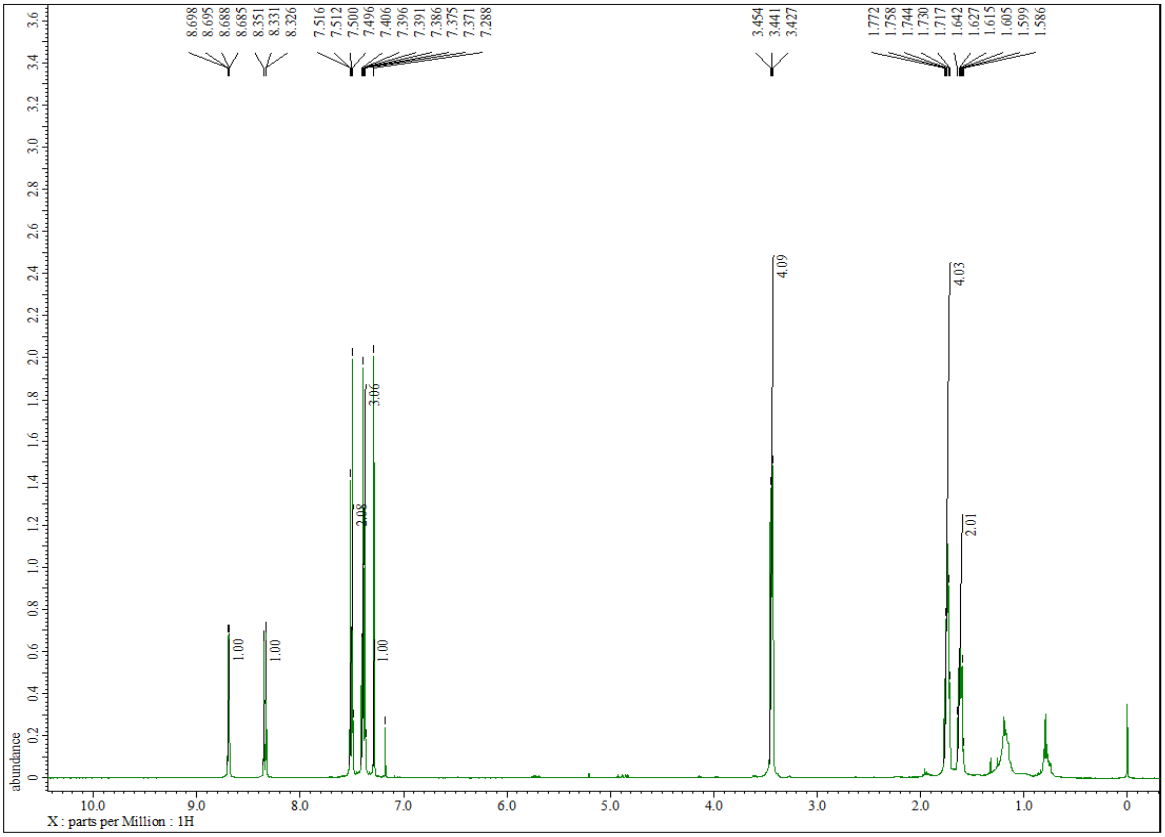


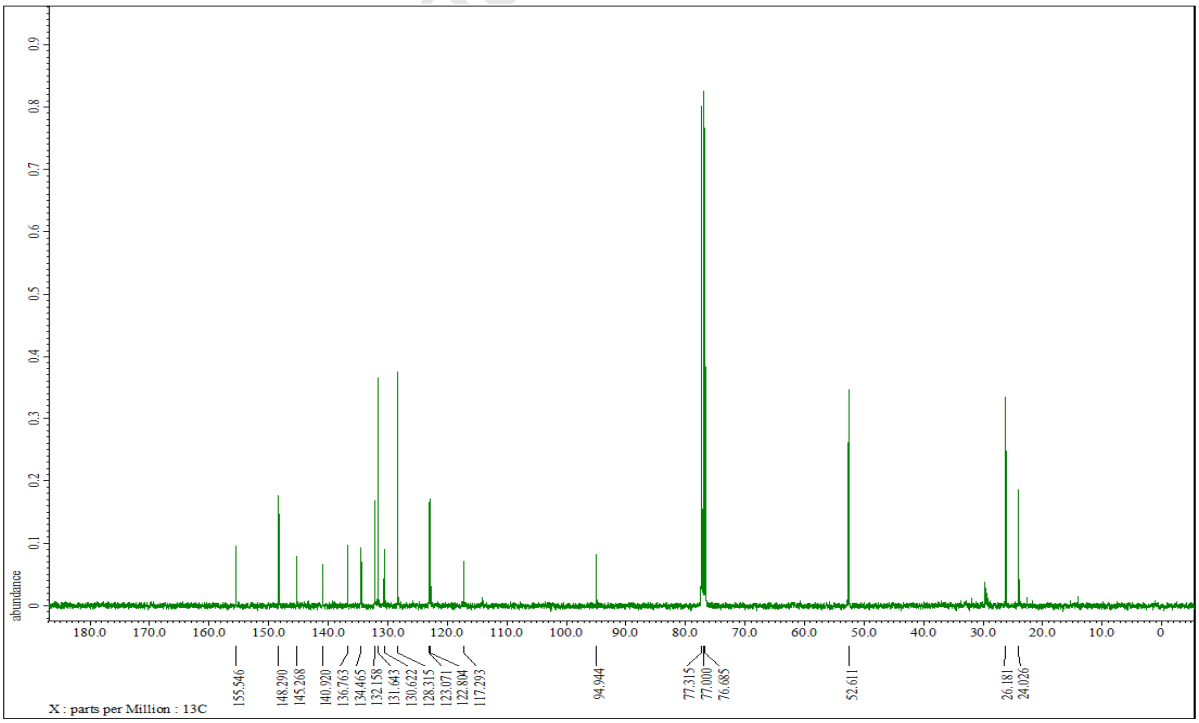
[1]HNMR and [13]C NMR spectrum of 6-(4-benzylpiperazin-1-yl)-8-(4-methoxyphenyl)quinoline-5-carbonitrile



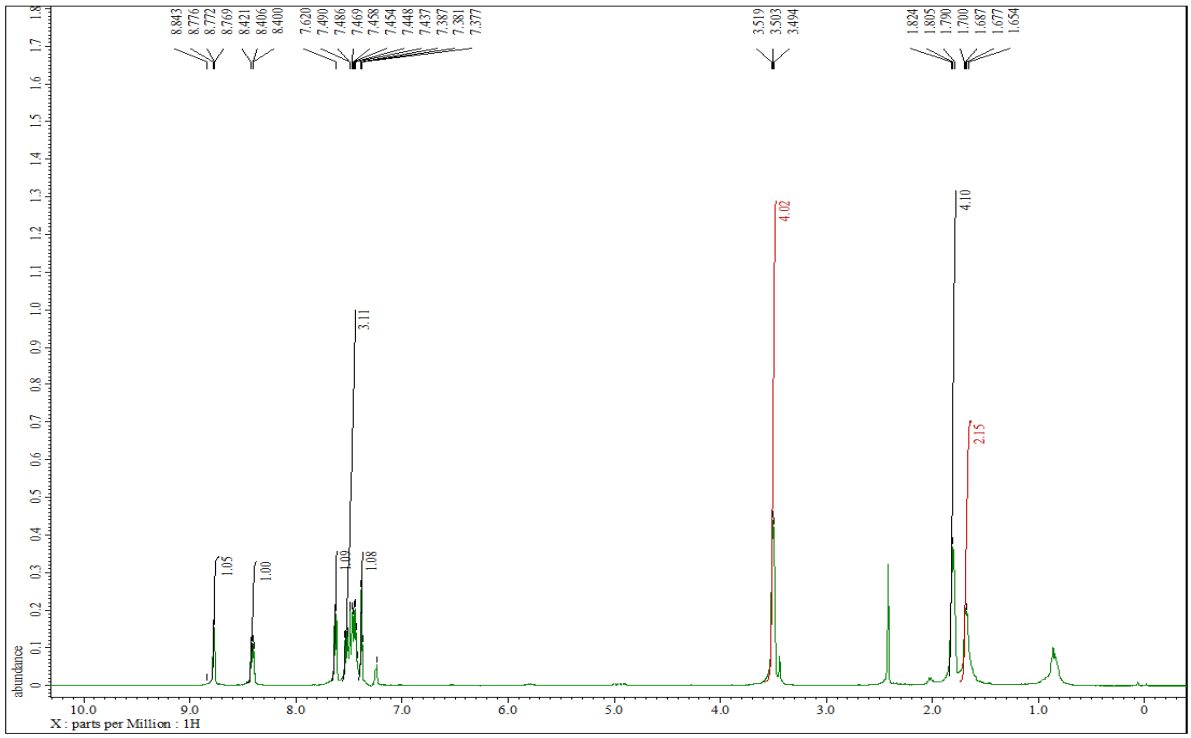


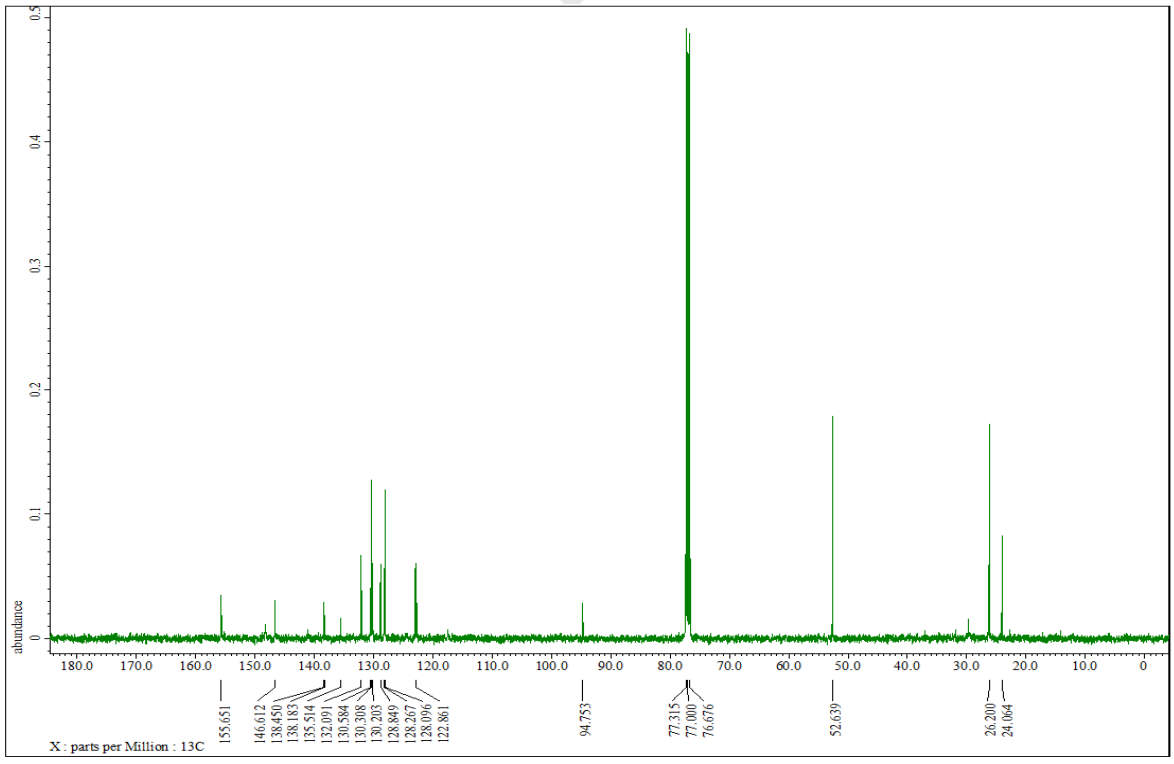
[1]HNMR and [13]C NMR spectrum of 8-phenyl-6-(piperidin-1-yl)quinoline-5-carbonitrile



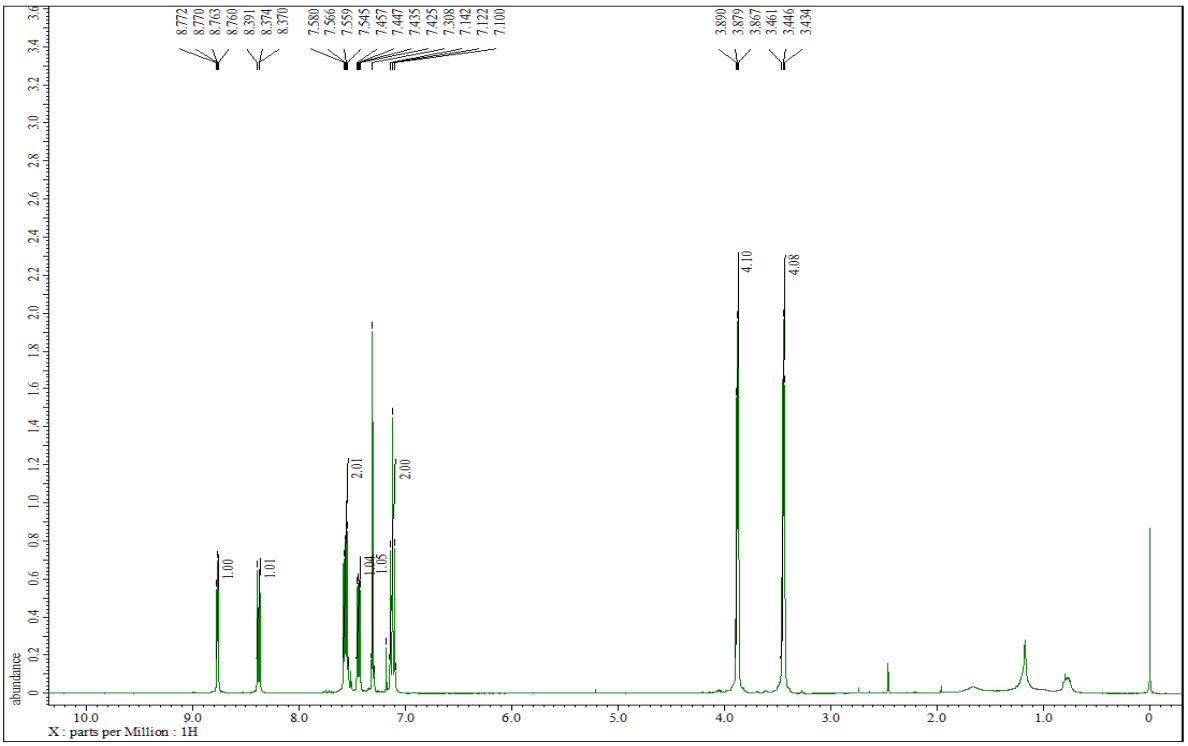


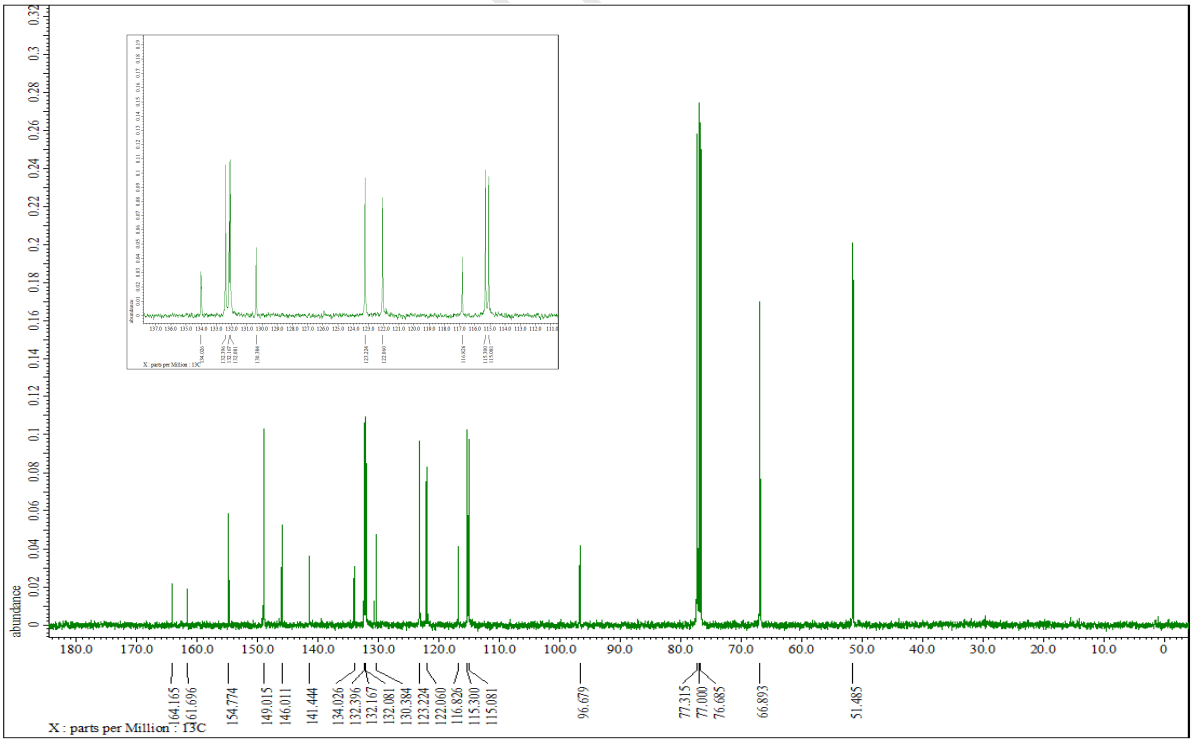
[1]HNMR and [13]C NMR spectrum of 8-(4-chlorophenyl)-6-(piperidin-1-yl) quinoline-5-carbonitrile



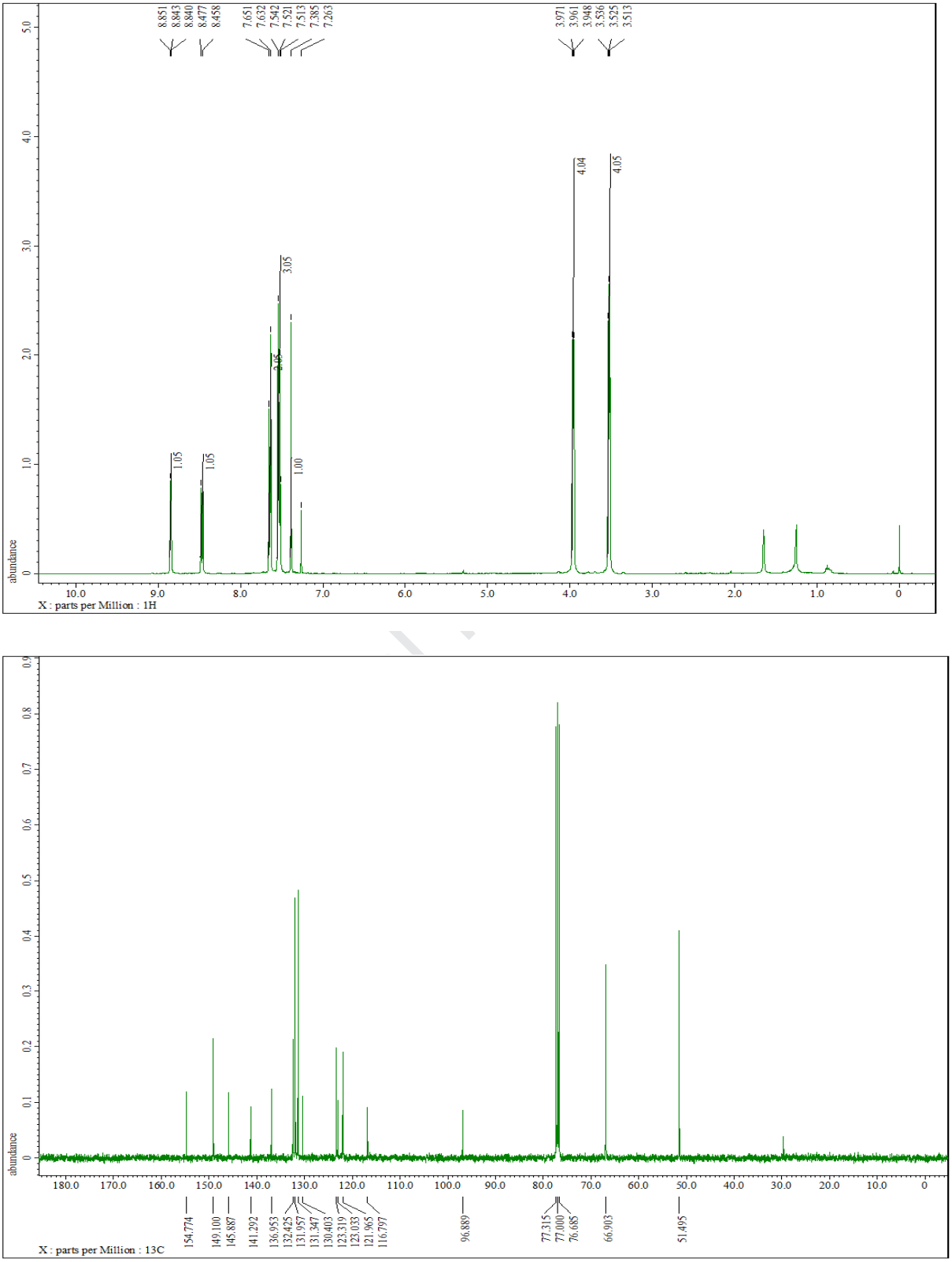


[1]HNMR and [13]C NMR spectrum of 6-(piperidin-1-yl)-8-(thiophen-2-yl) quinoline-5-carbonitrile

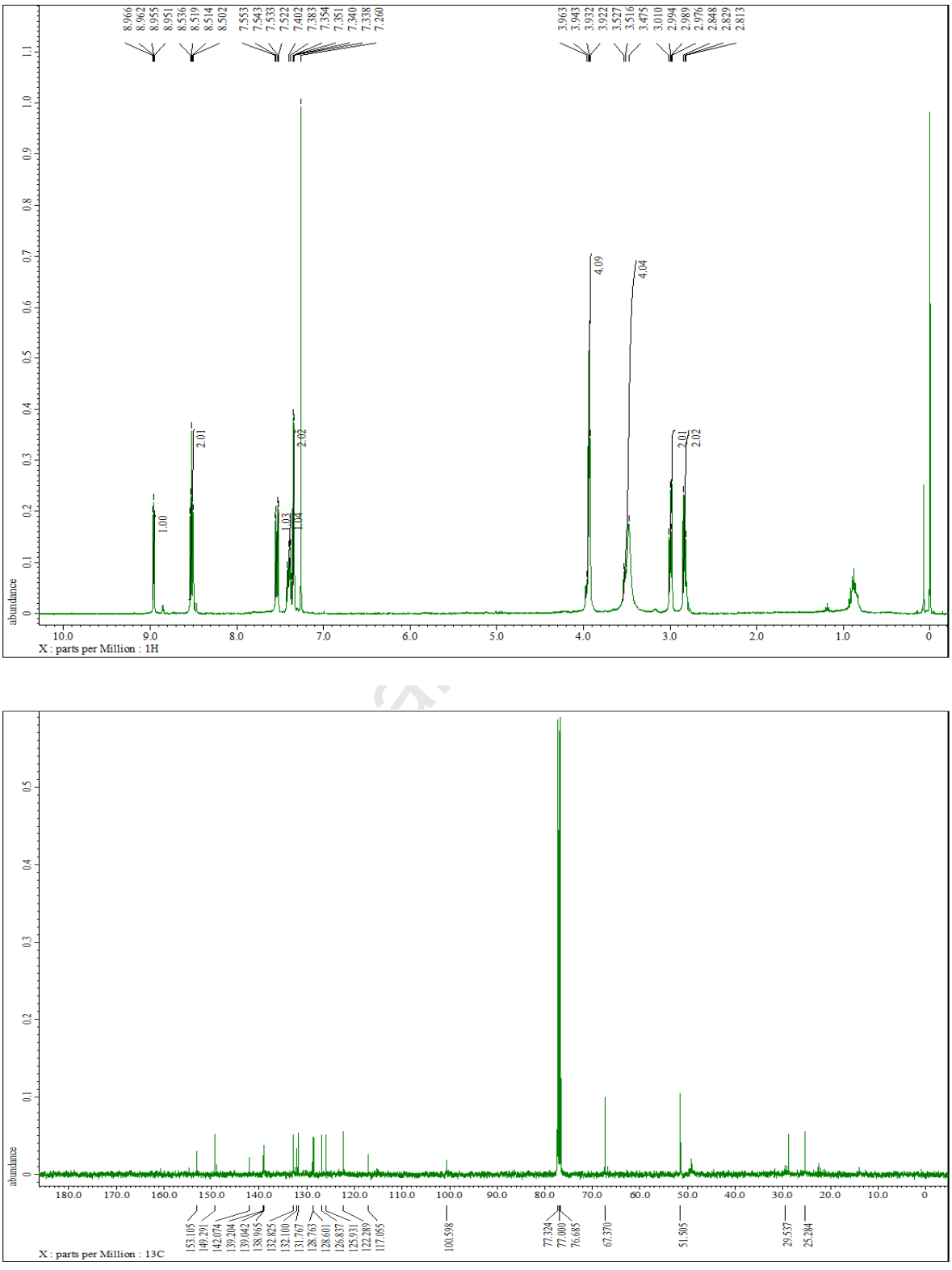




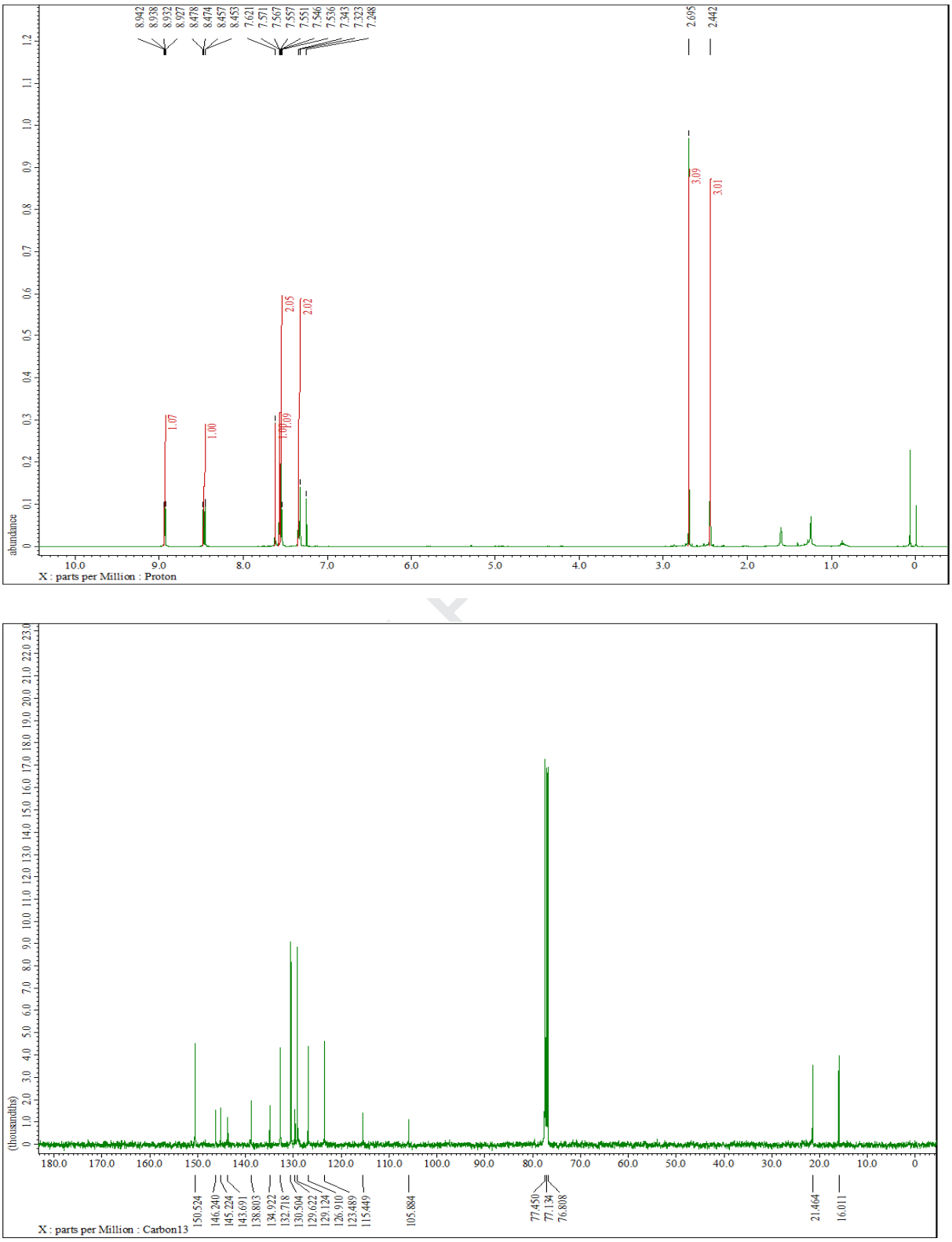
[1]HNMR and [13]C NMR spectrum of 8-(4-fluorophenyl)-6-morpholinoquinoline-5-carbonitrile



[1]HNMR and [13]C NMR spectrum of 8-(4-bromophenyl)-6-morpholinoquinoline-5-carbonitrile



[1]HNMR and [13]C NMR spectrum of 6-(4-benzylpiperazin-1-yl)-8-(4-methoxyphenyl) quinoline-5-carbonitrile



[1]HNMR and [13]C NMR spectrum of 6-(methylthio)-8-(p-tolyl)quinoline-5-carbonitrile