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One-pot synthesis of quinazolin-4(3*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones utilizing *N*-(2-aminobenzoyl)benzotriazoles

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Abstract: A convenient and efficient method has emerged for the one-pot synthesis of substituted quinazolin-4(3*H*)-ones and nonaromatic alkaloids. 2-Substituted quinazolin-4(3H)-ones, 2,3-disubstituted quinazolin-4(3*H*)-ones, and 2,3-dihydroquinazolin-4(1*H*)-ones were obtained at yields of 46% to 95% by a one-pot reaction of *N*-(2-aminobenzoyl) benzotriazoles with amines and orthoesters or aldehydes under catalyst-free conditions.

Key words: Benzotriazole, *N*-(2-aminobenzoyl)benzotriazole, quinazolin-4(3*H*)-one, 2,3-dihydroquinazolin-4(1*H*)-one, 2-substituted quinazolin-4(3*H*)-one

1. Introduction

4(3*H*)-Quinazolinones represent an important set of heterocycles, since they exist in natural products and exhibit a broad range of pharmacological activities, including antibacterial, antimalarial, anticancer, antitumor, antiinflammation, antihypertensive, antidepressant, and anticonvulsant activities [1–6]. Some plants containing quinazolinone have long been used for traditional remedies. For example, a Chinese plant root called chang shan (*Dichroa febrifuga* Lour.) has been used for the treatment of malaria for more than 2000 years because it contains antimalarial active quinazolinone alkaloids, febrifugine and iso-febrifugine (lately, however, it was discontinued due to its toxic effects) [7]. Rutaecarpine, originally extracted from *Evodia rutaecarpa*, is a COX-2 inhibitor and has diverse pharmacological properties, including antithrombotic, anticancer, antiinflammatory and antiobesity activities [8–11]. Vasicinone is another quinazolinone alkaloid that was originally isolated from the leaves of *Adhatoda vasica* and has bronchodilatory activity [12]. Luotonin A is a pyrroloquinazolinoquinoline alkaloid extracted from *Peganum nigellastrum* that has shown cytotoxicity against the murine leukemia P-388 cell line [13]. Aside from natural analogs, synthetic quinazolinone derivatives are also highly active pharmaceutical cores [14,15]. Among them, raltitrexed (Tomudex, ZD 1694) [16] is an antimetabolite drug that inhibits thymidylate synthase and is used in the treatment of colorectal cancer species. Gefinitib (Iressa, ZD1839) [17,18], erlotinib (Tarceva, OSI-774) [19,20], lapatinib (Tyverb, Tykerb) [21,22], and vandetanib (ZD6474, Zactima, Caprelsa) [23,24] are 4-aminoquinazoline drugs derived from 4-quinazolinones that have all shown antineoplastic activity and are still used in cancer chemotherapy.

As a highly active pharmaceutical core, the quinazolinone moiety has drawn much attention in synthetic chemistry and many reaction pathways have been proposed over the years. Recent advancements in the field

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of synthetic methodologies for the quinazolinone scaffold were discussed in detail by Rohokale and Kshirsagar, He et al., and Kshirsagar [1,2,5]. Classical routes in the preparation of quinazolin-4(3*H*)-one have been mostly based on the Niementowski reaction, which utilizes the ring closure of anthranilic acid or its derivatives with an amine and a carbonyl group, whereas nonclassical methods utilize metal-catalyzed coupling reactions by C-C or N-C bond formations [25–28] and the metal-catalyzed reduction of nitroarenes and subsequent cyclizations [29,30]. The classical routes are often boosted by 1-pot multicomponent procedures, by featuring higher yields in a shorter reaction time and fewer side products when compared to divergent pathways. The components of the quinazolinone ring (anthranilic acid-derivative, carbonyl compound or its equivalent, and amine) are reacted together in one pot under neat or solvent conditions. Those multicomponent reactions can be accelerated by microwave heating [31–33], ionic liquids [34], or such catalysts as acids (acetic acid [35], trifluoroacetic acid [36], or *p*-toluenesulfonic acid [37]) and Lewis acids ($KAl(SO_4)_2 \bullet 12H_2O$, $Yb(OTf)_3$ [38], α-MnO_2 [39], $[Cp^*IrCl_2]_2$ [40], ZnI_2 [41], CuI_2 [42], $InCl_3$ [43], $La(NO_3)_3 \bullet 6H_2O$, $AlCl_3/ZnCl_2$-SiO_2 [44], $NaHSO_4$-SiO_2, amberlyst-15 [45], $FeCl_3 \bullet 6H_2O$ [46], $Al(NO_3)_3 \bullet 9H_2O$, [47] I_2/KI [48], $Ga(OTf)_3$ [49], $Sc(OTf)_3$ [50], Fe_3O_4 nanoparticle [51], molecular iodine [52], activated carbon (Darco KB), etc.). Recently, Yoshimura et al. examined the catalytic activity of various heavy metal salts and Ru-complexes in the synthesis of 4(3*H*)-quinazolinone through the condensation of 2-aminobenzamide with formamide [38]. The yields of those reactions in mesitylene at 165 °C for 6 h under an Ar atmosphere ranged from 5% to 99%. The best yields (>99%) were obtained when $AlCl_3$, $FeCl_3$, $NiBr_2 \bullet xH_2O$, and $Yb(OTf)_3$ were used as catalysts. Some of the outlined procedures still have some drawbacks, such as harsh reaction conditions, longer reaction times, and low yields, and many of them suffer from the used catalyst because of their high cost, limited availability, and toxicity. Therefore, exploring simple, green, efficient reaction systems is still highly desirable.

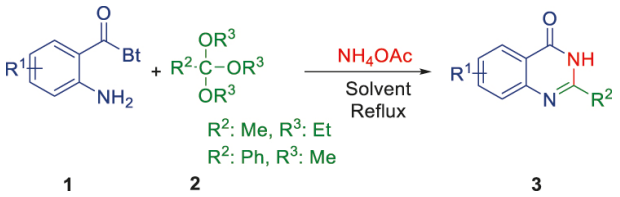
N-(2-Aminobenzoyl)benzotriazoles are versatile reagents that are stable in crystalline form and easy to prepare and handle. These compounds have excelled as ideal synthetic auxiliaries in the synthesis of anthranilic acid amides [53], esters-thioesters [54], and heterocycles [55–57]. Their synthetic utility was recently shown in the preparation of 2-substituted quinolone-3-carboxylates and 4-hydroxyquinoline-2,3-dicarboxylates [56]. As a continuation of our efforts, we herein present a new protocol for the one-pot synthesis of 2,3-disubstituted quinazolin-4(3*H*)-one and its alkaloids under catalyst-free and environmentally friendly conditions starting from *N*-(2-aminobenzoyl)benzotriazoles.

2. Results and discussion

2.1. Preparation of 2-substituted quinazolin-4(3*H*)-one (3a–3j)

N-(2-aminobenzoyl)benzotriazoles **1** were prepared following our previously reported procedure. In the preparation of 2-substituted quinazolin-4(3*H*)-ones **3a**–**3j**, a model reaction between *N*-(2-aminobenzoyl)benzotriazole **1b** or **1g**, triethyl orthoacetate **2b**, and ammonium acetate was initially carried out to optimize the reaction conditions (Scheme 1 and Table 1). The reactions were performed in both polar protic and aprotic solvents, such as ethanol (EtOH), dimethylformamide (THF), and dioxane, and also under neat conditions at the boiling temperature of the mixtures. Upon the better yields of the desired products, **3c** and **3h** were obtained after 6–10 h of reactions in dioxane, and all 2-substituted quinazolin-4(3*H*)-ones (**3a**–**3j**) were prepared in dioxane under reflux conditions (Table 2).

Via a 2D NOESY experiment, the structure of **3e** was investigated because it might have been in the form of 4-quinazolinone or 4-hydroxyquinazoline (Figure 1a). In the 2D NOESY spectra for compound **3e**, the



Scheme 1. Synthesis of 2-substituted quinazolin-4(3*H*)-one (**3a**–**3j**).

Table 1. Model reaction for the preparation of 2-substituted quinazolin-4(3*H*)-one **3c** and **3h**.

Entry	R^1	R^2	Product	Solvent	Yield, %
a	6-Me	Me	**3c**	EtOH	52
b	6-Me	Me	**3c**	THF	28
c	6-Me	Me	**3c**	Dioxane	82
d	6-Me	Me	**3c**	Neat	45
e	7-Cl	Me	**3h**	EtOH	62
f	7-Cl	Me	**3h**	THF	40
g	7-Cl	Me	**3h**	Dioxane	68
h	7-Cl	Me	**3h**	Neat	54

Table 2. Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**3a**–**3j**).

Entry	R^1	R^2	Product	Yield, %
a	H	H	**3a**	85
b	H	Me	**3b**	95
c	6-Me	Me	**3c**	82
d	6-Cl	Me	**3d**	78
e	6-Br	Ph	**3e**	80
f	6-I	Ph	**3f**	92
g	7-F	Me	**3g**	81
h	7-Cl	Me	**3h**	68
i	7-Me	Me	**3i**	95
j	8-Me	Ph	**3j**	68

cross peak between the H2' and H6' protons at 8.14 ppm and the H3 proton at 12.71 ppm indicated that these protons interacted spatially (Figure 1b). The spatial interactions among the other protons were observed as expected in the 2D NOESY spectra. In addition to the 2D NOESY experiment, the observation of sharp peaks between 1707 and 1645 cm^{-1} in the IR spectra showed that the carbonyl group was formed in the structure of 4-quinazolinone. The results obtained from the 2D NOESY experiment and IR spectra showed that the obtained compounds were in the form of 4-quinazolinone.

2.2. Preparation of 2,3-disubstituted quinazolin-4(3*H*)-ones (4a–4d)

2,3-Disubstituted quinazolin-4(3*H*)-ones (**4a-4d**) were prepared by the reaction of *N*-(2-aminobenzoyl) benzotriazoles **1** with primary amines and orthoesters **2** under neat reaction conditions for 8 h (Scheme 2 and Table 3). While the reactions were performed in anhydrous dioxane, the cyclization reactions were completed after 16

h and provided lower yields than neat conditions. The structures of 2,3-disubstituted quinazolin-4(3*H*)-ones (**4a**–**4d**) were characterized by NMR spectroscopy. The hydrogen atoms on C2 of **4a**–**4c** were observed between 8.10 and 8.30 ppm, while the atoms on C4 appeared between 160 and 161 ppm (Supplemental information). Moreover, HRMS and IR spectral data were also in accordance with the proposed structures.

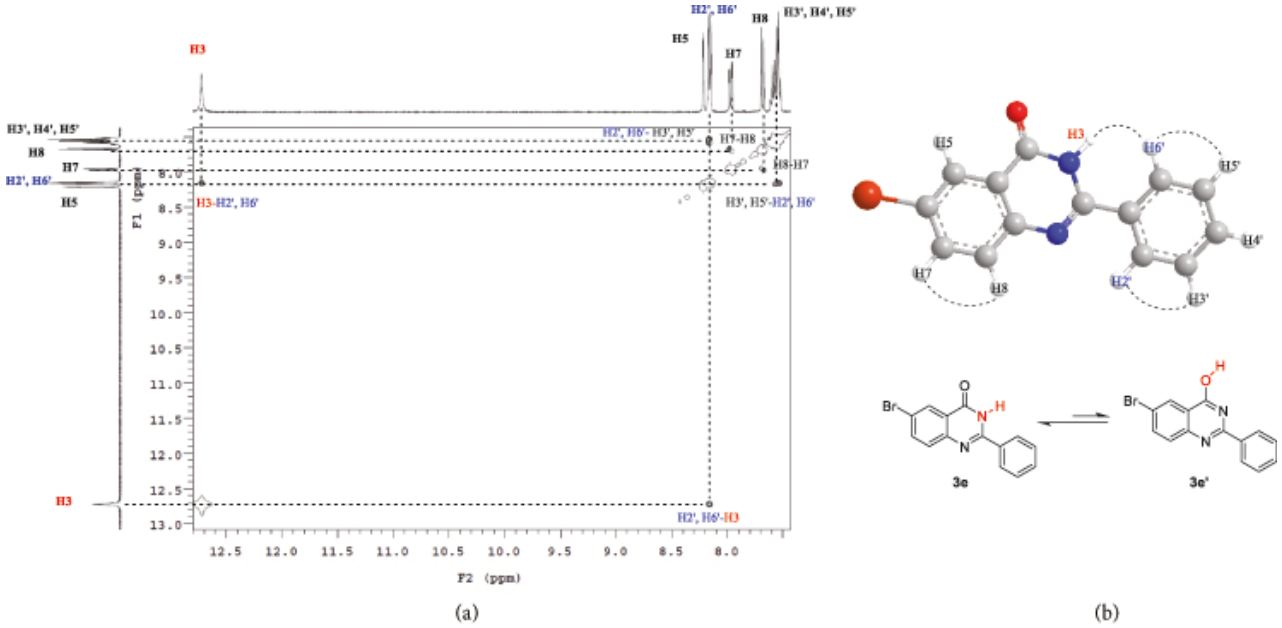
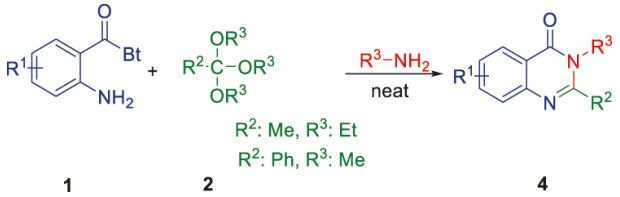


Figure 1. The 2D NOESY spectrum (a) and 3D structure (b) of **3e**.



Scheme 2. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (**4a**–**4d**).

Table 3. 2,3-Disubstituted quinazolin-4(3*H*)-ones (**4a**–**4d**).

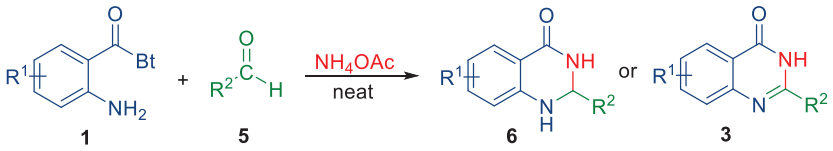
Entry	R^1	R^2	R^3	Product	Yield, %
a	H	H	*i*-Bu	**4a**	79
b	H	H	*c*-Hexyl	**4b**	53
c	H	H	4-MeO-phenyl	**4c**	51
d	H	Me	*i*-Bu	**4d**	81

2.3. Preparation of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones (6a–6g)

2,3-Dihydroquinazolinones are the saturated derivatives of quinazolinones and can be readily oxidized to their quinazolin-4(3*H*)-one analogs. 2,3-Dihydroquinazolinones were previously prepared by the reaction of isatoic

anhydride and aldehydes or ketones in the presence of such catalysts as ZnO [58], Fe_3O_4, TiO_2 [59], nanoparticles, Fe_3O_4@SiO_2-imid-PMA^n nanocatalyst [60], [$Al(H_2PO_4)_3$] [61], and montmorillonite K-10 [62] starting from 2-aminobenzamide using zirconium tetrakis(dodecyl sulfate) [Zr(DS)4] [63]. Herein, a new catalyst and solvent-free methodology is proposed for the selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones starting from *N*-(2-aminobenzoyl)benzotriazoles.

N-(2-aminobenzoyl)benzotriazoles were reacted with aromatic or aliphatic aldehydes **5** in the presence of ammonium acetate under neat conditions to provide 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones (**6a**–**6g**) at yields of 54%–95% (Scheme 3 and Table 4). As seen in Table 4, when **1h** and **1i** were used as starting material, 2-substituted quinazolin-4(3*H*)-ones (**3k** and **3l**), instead of 2,3-dihydroquinazolin-4(1*H*)-ones (**6h** and **6i**), were obtained at yields of 74% and 88%, respectively. It was thought that the oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones (**6h** and **6i**) via atmospheric air could lead to obtaining 2-substituted quinazolin-4(3*H*)-ones (**3k** and **3l**).



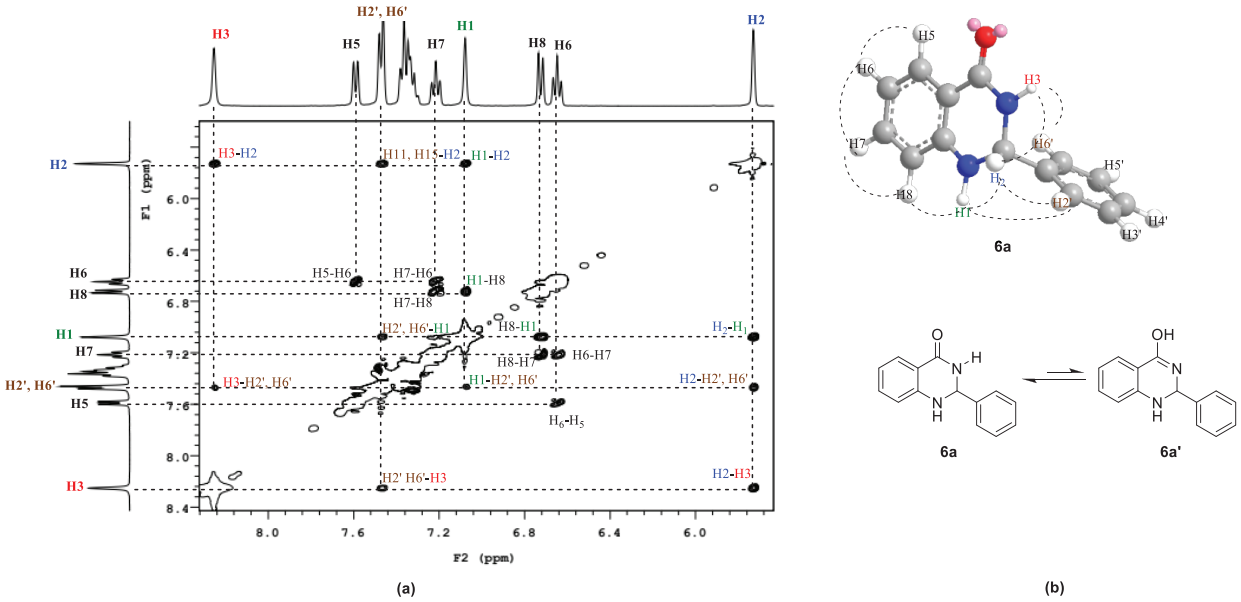
Scheme 3. Synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones (**6a**–**6g**).

Table 4. 2-Substituted 2,3-dihydroquinazolin-4(1*H*)-ones (**6a**–**6g**).

Entry	R^1	R^2	Product	Yield, %
a	H	Ph	**6a**	76
b	7-Cl	Et	**6b**	72
c	7-Me	(2-Furanyl)	**6c**	95
d	6-Br	(2-Thiophenyl)	**6d**	54
e	6-I	Ph-^{4}F	**6e**	84
f	7-F	Ph-^{4}Br	**6f**	84
g	6,8-diCl	Ph	**6g**	62
h	H	4-Py	**3k**	74
i	6,7-diMeO	Ph	**3l**	88

The structures of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones **(6a–6g)** were characterized by NMR spectroscopy. A characteristic singlet observed between 4 and 6 ppm in the ^{1}H NMR spectra was assigned to the hydrogen atom on N1. The hydrogen atom on N3 was observed between 8.63 ppm and 6.57 ppm (Supplemental information). 2,3-Dihydroquinazolin-4(1*H*)-one **6a** could also be formulated in a different tautomeric form, depicted as 1,2-dihydroquinazolin-4-ol **6a**'. To determine which tautomeric form was predominant or formed, a 2D NOESY experiment was performed for compound **6a** in DMSO-*d*6 (Figure 2a). In the 2D NOESY spectra for compound **6a**, the cross peaks among the H2 protons at 5.73 ppm and the H2' and H6' protons at 7.47 ppm with the H3 proton at 8.27 ppm indicated that these protons interacted spatially (Figure 2b). The cross peaks among the H2 proton at 5.73 ppm, H8 proton at 6.72 ppm, and H2' and H6' protons at 7.47 ppm with the H1 proton at 7.09 ppm showed that there were spatial interactions among these protons. Similar cross peaks among the H1 proton at 7.09 ppm, H2' and H6' protons at 7.47 ppm, and H3 proton at 8.27 ppm with

the H2 proton at 5.73 ppm were observed in the 2D NOESY spectra. The spatial interactions among other protons were observed as expected in the 2D NOESY spectra. In addition to the 2D NOESY experiment, the observation of sharp peaks between 1688 and 1645 cm^{-1} in the IR spectra showed that the carbonyl group was formed in the structure of 2,3-dihydroquinazolin-4(1*H*)-one.

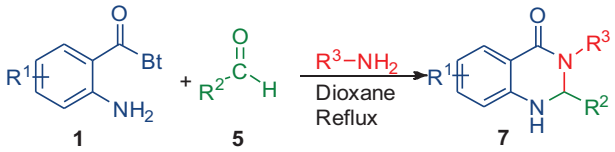


(a) (b)

Figure 2. The 2D NOESY spectrum (a) and 3D structure (b) of **6a**.

2.4. Preparation of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (7a–7b)

2,3-Disubstituted 2,3-dihydroquinazolin-4 (1*H*)-ones (**7a**–**7b**) were prepared from the reaction of *N*-(2-aminobenzoyl) benzotriazoles with aromatic aldehydes **5** and primary amines in yields of 46%–74% (Scheme 4 and Table 5). The reactions were performed in anhydrous dioxane within 4 h, while the cyclization reactions performed under neat conditions provided poor yields. The pyrimidine ring closure of **7a** and **7b** was proven by NMR spectroscopy. The racemic hydrogen atom on C2 of **7a** showed a singlet at 5.69 ppm and the C2 atom provided a peak at 67.6 ppm, while the hydrogen atom on C2 of **7b** provided a singlet at 5.68 ppm and the C2 atom appeared at 72.1 ppm (Supplemental information).



Scheme 4. Synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (**7a**–**7b**).

3. Conclusions

A new method for the synthesis of substituted quinazolin-4(3*H*)-ones and their alkaloids has been developed. Benzotriazole-assisted synthesis of 2- and 2,3-disubstituted quinazolin-4(3*H*)-ones (**3a**–**3l**, **4a**–**4d**) and 2- and 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (**6a**–**6g**, **7a**, and **7b**) was achieved at high yields by one-pot

Table 5. 2,3-Disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (**7a** and **7b**).

Entry	R^1	R^2	R^3	Product	Yield, %
a	H	Ph(3,4-diMeO)	*c*-Hexyl	**7a**	46
b	6-Cl	Ph	*i*-Bu	**7b**	74

reactions of *N*−(2-aminobenzoyl)benzotriazoles with amines and orthoesters. In comparison with other studies, the reactions were performed within a shorter time using stable and easily handled reagents under catalyst-free conditions.

4. Experimental section

4.1. General information

Melting points were determined with a Mettler Toledo MP90 apparatus (Mettler Toledo International Inc., Columbus, OH, USA) and were uncorrected. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on an Agilent DD2 400 MHz spectrometer (Agilent Technologies, Santa Clara, CA, USA) in DMSO-*d*6 with tetramethylsilane as an internal standard. HRMS analyses were measured on a Shimadzu LCMS-IT-TOF system (Shimadzu Corporation, Kyoto, Japan). A PerkinElmer 100 FTIR spectrometer (PerkinElmer Inc., Waltham, MA, USA) was used for the IR analyses. DMF was dried and distilled over CaH_2. THF was dried and distilled over metallic Na in the presence of benzophenone. Aliphatic-aromatic aldehydes **5** and primary amines were purchased from commercial sources and used without further purification.

4.2. General method for synthesis of 2-substituted quinazolin-4(3*H*)-one (3a–3j)

N-(2-aminobenzoyl)benzotriazoles (0.25 mmol) **1** previously synthesized by our group were reacted with orthoester (0.50 mmol) **2** and ammonium acetate (1.0 mmol) in dioxane for 6–10 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The reaction mixture was purified by column chromatography over silica gel with a EtOAc/*n*-hexane mixture (from 1:2 or 1:1) to obtain white crystals (62%–95%).

Quinazolin-4(3*H*)-one (3a)

White solid (31 mg, 85%, lit. [64] 91%); mp: 217–218 °C (lit. [64] 217 °C). FTIR υ_{max} (KBr): 3424, 1707, 1667, 1612 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 12.24 (s, 1H) δ 8.12 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 8.09 (s, 1H), 7.84–7.79 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.54–7.50 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.2, 149.2, 145.9, 134.8, 127.6, 127.2, 126.3, 123.1. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_8H_7N_2O$: 147.0514; found: m/z 147.0482.

2-Methylquinazolin-4(3*H*)-one (3b)

White solid (38 mg, 95%, lit. [65] 81%); mp: 238–240 °C (lit. [65] 235–239 °C). FTIR υ_{max} (KBr): 3415, 1671, 1610, 1468 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (br s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 154.7, 149.4, 134.7, 127.0, 126.3, 126.1, 121.0, 21.9. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_9N_2O$: 161.0709; found: m/z 161.0701.

2,6-Dimethylquinazolin-4(3*H*)-one (3c)

White solid (36 mg, 82%, lit. [65] 82%); mp: 245–246 °C (lit. [65] 246–248 °C). FTIR υ_{max} (KBr): 3440, 1679, 1629, 1489 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (br s, 1H), 7.83–7.82 (m, 1H), 7.55 (dd, A part of AB system, J = 8.0 Hz, 2.8 Hz, 1H), 7.43 (d, B part of system, J = 8.4 Hz, 1H), 2.38 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 153.7, 147.4, 136.0, 135.8, 126.9, 125.5, 120.8, 21.8, 21.2. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O$: 175.0886; found: m/z 175.0870.

6-Chloro-2-methylquinazolin-4(3*H*)-one (3d)

White solid (38 mg, 78%, lit. [65] 84%), mp: 310 °C decomp. (lit. [65] 292–294 °C). FTIR υ_{max} (KBr): 3453, 1678, 1620, 1454, 830 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.79 (dd, A part of AB system, J = 8.8, 2.4 Hz, 1H), 7.59 (d, B part of AB system, J = 8.4 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 156.0, 147.1, 135.0, 130.8, 128.6, 125.2, 122.2, 21.6. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_8N_2O_{35}Cl$: 195.0320; found: m/z 195.0322.

6-Bromo-2-phenylquinazolin-4(3*H*)-one (3e)

White solid (60 mg, 80%, lit. [66] 84%); mp: 303–305 °C (lit. [66] 284–286 °C). FTIR υ_{max} (KBr): 3418, 1675, 1589, 1477, 689 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.71 (s, 1H), 8.19 (s, 1H), 8.14 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.58–7.50 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 153.4, 148.2, 137.9, 132.9, 132.1, 130.3, 129.1, 128.3, 128.3, 123.0, 119.4. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{10}N_2O_{79}Br$: 300.9971; found: m/z 300.9970.

6-Iodo-2-phenylquinazolin-4(3*H*)-one (3f)

White solid (80 mg, 92%, lit. [67] 76%), mp: 303–305 °C (lit. [67] >300 °C). FTIR υ_{max} (KBr): 3440, 1673, 1597, 1478, 699 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.67 (s, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.15–8.12 (m, 2H), 8.09 (dd, J = 8.4, J = 2.0 Hz, 1H), 7.57–7.49 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.4, 153.4, 148.5, 143.4, 134.6, 132.9, 132.1, 130.1, 129.1, 128.3, 123.3, 92.0. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{10}N_2OI$: 348.9832; found: m/z 348.9832.

7-Fluoro-2-methylquinazolin-4(3*H*)-one (3g)

White solid (36 mg, 81%, lit. [68] 91%); mp: 296–298 °C (lit. [68] 255 °C decomp.). FTIR υ_{max} (KBr): 3437, 1678, 1620, 1454, 795 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.09 (dd, J = 8.8, 6.4 Hz, 1H), 7.33–7.25 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 166.1, 161.4, 156.4, 151.6, 129.2, 118.1, 114.9, 112.1, 21.9. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_8N_2OF$: 179.0615; found: m/z179.0622.

7-Chloro-2-methylquinazolin-4(3*H*)-one (3h)

White solid (30 mg, 68%, lit. [65] 83%); mp: 266–267 °C (lit. [65] 291–293 °C). FTIR υ_{max} (KBr): 3431, 1682, 1627, 1440, 778 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 156.6, 150.5, 139.2, 128.2, 126.5, 126.1, 120.0, 22.0. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O_{35}Cl$: 195.0320; found m/z 195.0316.

2,7-Dimethylquinazolin-4(3*H*)-one (3i)

White solid (41 mg, 95%, lit [69] 49%); mp: 255–256 °C. (lit. [69] 263–264 °C). FTIR υ_{max} (KBr): 3431, 1682, 1616, 1456 cm^{-1}. ^{1}H NMR (400 NMR, DMSO-d_6): δ 12.06 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 162.0, 154.7, 149.5, 141.1, 127.7, 126.7, 126.0, 118.7, 21.9, 21.8. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O$: 175.0866; found: m/z 175.0862.

8-Methyl-2-phenylquinazolin-4(3*H*)-one (3j)

White solid (40 mg, 68%, lit. [65] 83%); mp: 260–261 °C. (lit. [65] 237–239 °C). FTIR υ_{max} (KBr): 3427, 1676, 1605, 1508 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.53 (s, 1H), 8.20 (d, J = 6.8 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.57–7.52 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0, 151.5, 147.6, 136.1, 135.4, 133.4, 131.8, 129.1, 128.2, 126.5, 123.9, 121.3, 17.6. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{13}N_2O$: 237.1022; found: m/z 237.1029.

4.3. General method for synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (4a–4d)

N-(2-Aminobenzoyl)benzotriazole (0.25 mmol) **1** was reacted with orthoester (1 mL) **2** and primary amines (1.0 mmol) at the boiling point of this mixture for 7–10 h in the absence of a solvent. The reaction was monitored with thin-layer chromatography (TLC) using an eluent system of EtOAc-*n*-hexane (1:1 or 1:3). After completion of the reaction, the mixture was diluted with ethyl acetate, washed with saturated sodium carbonate and brine solution, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified over silica gel using EtOAc/*n*-hexane as an eluent system (from 1:4 to 1:1) to obtain the desired product (51%–81%).

3-(2-Methylpropyl)quinazolin-4(3*H*)-one (4a)

Light yellow solid (40 mg, 79%); mp: 62–64 °C. FTIR υ_{max} (KBr): 2965, 2873, 1679, 1611, 1461 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 8.14 (d,J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.53 (t,J = 7.6 Hz, 1H), 3.80 (d, J = 7.2, 2H), 2.09 (t,J = 6.8 Hz, 1H), 0.87 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.1, 148.1, 146.9, 134.1, 127.4, 127.2, 126.8, 54.1, 28.1, 19.9. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{12}H_{15}N_2O$: 203.1179; found: m/z 203.1171.

3-Cyclohexylquinazolin-4(3*H*)-one (4b)

White solid (30 mg, 53%, lit. [70] 10%); mp: 112–113 °C (lit. [70] 116–118 °C). FTIR υ_{max} (KBr): 2927, 2857, 1667, 1598, 1478 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$-d_1): δ 8.31 (d, J = 7.6 Hz, 1H), 8.18 (s, 1H), 7.78–7.73 (m, 2H), 7.53–7.5 (m, 1H), 4.86–4.78 (m, 1H), 2.02–1.93 (m, 4H), 1.79 (d, J = 13.2 Hz, 2H), 1.69–1.46 (m, 2H), 1.32–1.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$-d_1): δ 160.3, 144.2, 134.4, 127.5, 127.1, 126.5, 121.6, 53.7, 32.6, 26.2, 25.8, 25.2. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{17}N_2O$: 229.1335; found: m/z 229.1326.

3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (4c)

White solid (32 mg, 51%); mp: 195–196 °C (lit. [71] 194–195 °C). FTIR υ_{max} (KBr): 2995, 1682, 1516, 1471 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$-d_1): δ 8.36 (d, J = 7.6 Hz, 1H), 8.13 (s, 1H), 7.82–7.76 (m, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 7.8 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$-d_1): δ 160.6, 159.7, 148.2, 148.0, 135.0, 130.7, 129.1, 127.8, 127.7, 126.8, 122.4, 114.8, 55.9. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{13}N_2O_2$: 253.0972; found: m/z 253.0981.

2-Methyl-3(2-methylpropyl)quinazolin-4(3*H*)-one (4d)

Orange solid (44 mg, 81%); mp: 71–73 °C. FTIR υ_{max} (KBr): 2963, 2870, 1669, 1594, 1473 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.07 (dd, J = 7.8 Hz, 2 Hz, 1H), 7.79–7.74 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.48–7.44 (m, 1H), 3.91 (d, J = 7.2 Hz, 2H), 2.58 (s, 3H), 2.10 (t, J = 6.8 Hz, 1H), 0.88 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 154.6, 147.0, 134.2, 126.9, 126.4, 126.3, 120.4, 51.1, 28.1, 23.5, 20.1. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{17}N_2O$: 217.1335; found: m/z 217.1334.

4.4. General method for synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones (6a–6g)

N-(2-Aminobenzoyl)benzotriazoles (0.2 mmol) **1** were reacted with aldehydes (0.3 mmol) **5** and ammonium acetate (0.3 mmol) under solvent-free conditions. After completion of the reaction, the mixture was washed with water. The desired product was recrystallized from ethyl alcohol. (54%–95%).

2-Phenyl-2,3-dihydro quinazolin-4(1*H*)-one (6a)

White solid (34 mg, 76%, lit. [72] 95%); mp: 235–236 °C (lit. [72] 225–227 °C). FTIR υ_{max} (KBr): 3309, 1655, 1512 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.58 (d, J = 8 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.38–7.32 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 6.72 (d, J = 8 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 5.73 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0, 148.3, 142.0, 133.7, 128.9, 128.8, 127.8, 127.3, 117.5, 115.4, 114.8, 67.0. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{13}N_2O$: 225.1022; found: m/z 225.1020.

7-Chloro-2-ethyl-2,3-dihydroquinazolin-4(1*H*)-one (6b)

White solid (32 mg, 72%, lit. [73] 30%); mp: 133–134 °C (lit. [73] 130–132 °C). FTIR υ_{max} (KBr): 3363, 3218, 2968, 1645, 1476, 779 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.65 (s, 1H), 6.57 (br s, 1H), 4.83 (t, J = 5.6 Hz, 1H), 4.34 (br s, 1H), 1.82–1.72 (m, 2H), 1.02 (t, J = 3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 148.1, 139.7, 130.0, 119.5, 114.3, 114.1, 66.4, 28.6, 8.2. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{12}N_2O_{35}Cl$: 211.0633; found: m/z 211.0636.

2-(2-Furanyl)-7-methyl-2,3-dihydroquinazolin-4(1*H*)-one (6c)

Pale yellow solid (43 mg, 95%); mp: 187–188 °C. FTIR υ_{max} (KBr): 3300, 3185, 1647, 1489, 1014 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 6.68 (d, J = 8 Hz, 1H), 6.48 (s, 1H), 6.40 (d, J = 3.2 Hz, 1H), 6.35 (s, 1H), 6.32 (s, 1H), 5.87 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 152.2, 146.1, 145.0, 143.1, 128.5, 121.2, 115.2, 113.3, 110.5, 108.2, 62.0, 21.8. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{13}N_2O_2$: 229.0972, found: m/z 229.0964.

6-Bromo-(2-thiophenyl)-2,3-dihydro quinazolin-4(1*H*)-one (6d)

White solid (33 mg, 54%), mp: 229–230 °C. FTIR υ_{max} (KBr): 3305, 1654, 1482, 819 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H), 7.63 (d, J = 2 Hz, 1H), 7.50 (s, 1H), 7.44 (d, J = 5.2 Hz, 1H), 7.38 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 7.09 (d, J = 3.6 Hz, 1H), 6.96–6.94 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.02 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 146.7, 146.4, 136.3, 129.7, 127.0, 126.6, 126.3, 117.5, 117.1, 108.8, 62.7. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{12}H_{10}N_2OS_{79}Br$: 308.9692; found: m/z 308.9692.

2-(4-Fluorophenyl)-6-iodo-2,3-dihydroquinazolin-4(1*H*)-one (6e)

White solid (62 mg, 84%); mp: 222 °C decomp. (lit. [74] 294–295 °C). FTIR υ_{max} (KBr): 3299, 1651, 1503, 816 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.49–7.46 (m, 3H), 7.31 (s, 1H), 7.20 (t, J = 8.8 Hz, 2H), 6.56 (d, J = 8.4 Hz, 1H), 5.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6, 162.5, 147.6, 141.7, 137.9, 135.8, 129.4, 117.5, 115.7, 115.6, 78.6, 66.1. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{11}N_2OFI$: 368.9895; found: m/z 368.9897.

2-(4-Bromophenyl)-7-fluoro-2,3-dihydroquinazolin-4(1*H*)-one (6f)

White solid (54 mg, 84%); mp: 232–233 °C. FTIR υ_{max} (KBr): 3300, 1688, 1487 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.63–7.56 (m, 3H), 7.41–7.38 (m, 3H), 6.47–6.42 (m, 2H), 5.76 (t, J = 4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 163.9, 149.9, 141.3, 131.7, 130.7, 129.4, 122.1, 112.0, 105.1, 100.5, 66.2. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{11}N_2OFBr$: 321.0033; found: m/z 321.0046.

6,8-Dichloro-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (6g)

White solid (36 mg, 62%); mp: 172–173 °C. FTIR υ_{max} (KBr): 3324, 3186, 1663, 1497, 768 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 7.56 (s, 1H), 7.50 (s, 1H), 7.37–7.27 (m, 6H), 5.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5, 143.3, 133.6, 129.6, 129.4, 127.1, 126.9, 121.5, 119.8, 118.4, 65.7. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{11}N_2O^{35}Cl_2$: 293.0243; found: m/z 293.0249.

2-(4-Pyridinyl)quinazolin-4(3*H*)-on (3k)

White solid (30 mg, 74%, lit. [66] 82%); mp: 278–279 °C (lit. [66] 281–283 °C). FTIR υ_{max} (KBr): 3032, 1681, 1552, 1469 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.75 (s, 1H), 8.76 (d, J = 6.4 Hz, 2H), 8.15 (dd, J = 7.6, 1.6 Hz, 1H), 8.08 (dd, J = 4.4, 1.6 Hz, 2H), 7.87–7.83 (m, 1H), 7.76 (dd, J = 8.6, 2.0 Hz, 1H), 7.857–7.53 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5, 151.0, 150.7, 148.7, 140.4, 135.2, 128.2, 127.9, 126.4, 122.0, 121.9. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{10}N_3O$; 224.0818; found: m/z 224.0810.

2-Phenyl-6,7-dimethoxyquinazolin-4(3*H*)-on (3l)

White solid (125 mg, 88%, lit. [66] 88%); mp: 288–289 °C (lit. [66] 307–309 °C. FTIR υ_{max} (KBr): 3068, 1667, 1495, 1459, 1101 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (s, 1H), 8.13 (dd, J = 7 Hz, 2.6 Hz, 2H), 7.534–7.474 (m, 3H), 7.45 (s, 1H), 7.18 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0, 155.2, 151.2, 149.0, 145.2, 133.2, 131.5, 129.0, 127.9, 114.4, 108.7, 105.3, 56.4, 56.1. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{16}H_{15}N_2O_3$; 283.1077; found: m/z 283.1073.

4.5. General method for synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones (7a and 7b)

N-(2-Aminobenzoyl)benzotriazoles (0.25 mmol) **1** were reacted with aldehydes (0.5 mmol) **5** and primary amines (1 mmol) under solvent-free conditions. The reactions were monitored using TLC chromatography [EtOAc:*n*-hexane (1:1)]. After completion of the reaction, the crude product was dissolved in EtOAc (10 mL) and washed with saturated sodium carbonate, 3 N HCl, and brine solutions, respectively. The solution was dried over sodium carbonate and the solvent was evaporated. The residue was purified over silica gel using EtOAc/*n*-hexane as an eluent system (from 1:3 to 1:1) to obtain the desired product (46%–74%).

3-Cyclohexyl-2-(3,4-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (7a)

Orange oil (42 mg, 46%); FTIR υ_{max} (KBr): 3286, 2932, 1627, 1515, 1140 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$-d_1): δ 7.94 (dd, J = 7.9 Hz, 1.5 Hz, 1H), 7.22–7.13 (m, 1H), 6.86–6.77 (m, 2H), 6.77 (d, J = 2.1 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 5.69 (s, 1H), 3.97–3.84 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 1.69 (dd, J = 12.6 Hz, 3.5 Hz, 1H), 1.65–1.53 (m, 6H), 1.41 (t, J = 12.9 Hz, 1H), 1.32–1.22 (m, 1H), 1.12–0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$-d_1): δ 162.5, 149.1, 149.0, 144.1, 134.8, 133.1, 128.2, 119.5, 118.0, 117.8, 114.8, 110.8, 108.6, 108.5, 67.6, 55.8, 53.7, 31.0, 25.9, 25.5. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{27}N_2O_3$: 367.2016; found: m/z 367.2011.

6-Chloro-3-isobutyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (7b)

Orange solid (58 mg, 74%); mp: 160–162 °C. FTIR υ_{max} (KBr): 3302, 2965, 1629, 1465, 822 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$-d_1): δ 10.02 (s, 1H), 8.04–7.76 (m, 1H), 7.43–7.22 (m, 5H), 7.15 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 6.46 (d, J = 8.5 Hz, 1H), 5.68 (s, 1H), 3.99 (dd, J = 16 Hz, 8 Hz, 1H), 2.44 (dd, J = 14 Hz, 6 Hz, 1H), 2.11–1.89 (m, 1H), 0.93 (t, J = 9.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$-d_1): δ 162.2, 143.1, 139.5, 133.2, 129.2, 129.1, 128.1, 126.1, 124.4, 117.6, 115.9, 72.1, 52.2, 27.1, 20.2. HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{18}H_{20}N_2O^{35}Cl$: 315.1259; found: m/z 315.1248.

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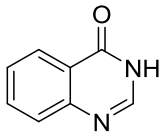
Supplemental information

^{1}H and ^{13}C NMR spectra of **3a**



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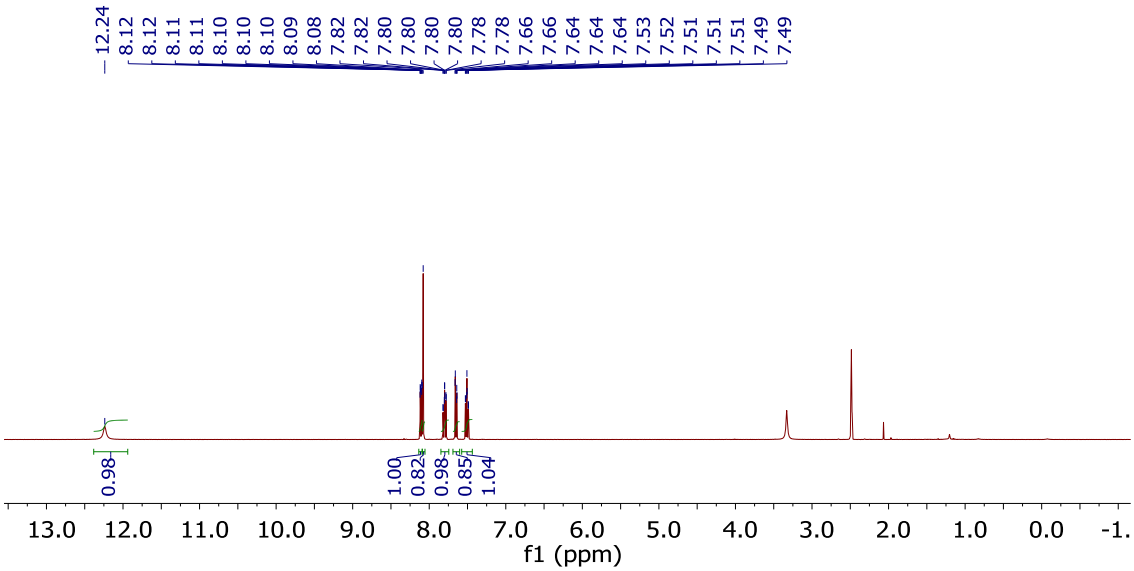

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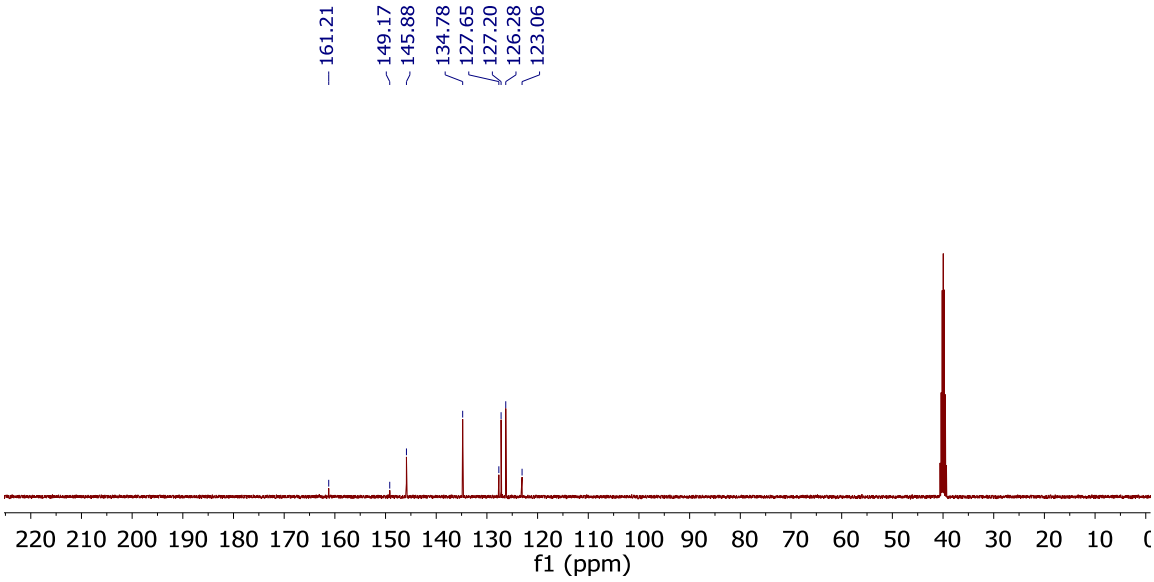

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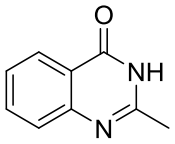

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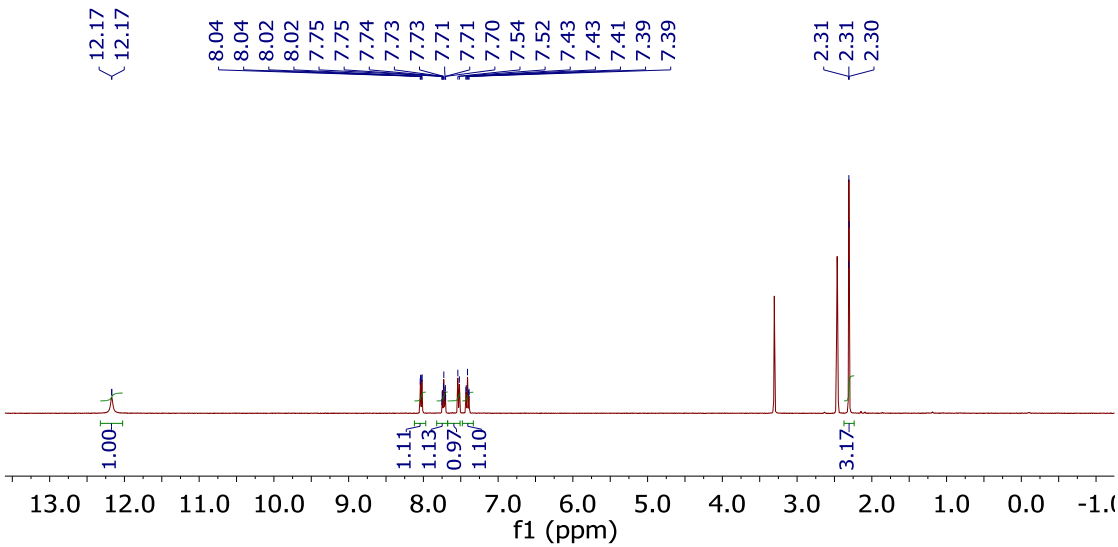

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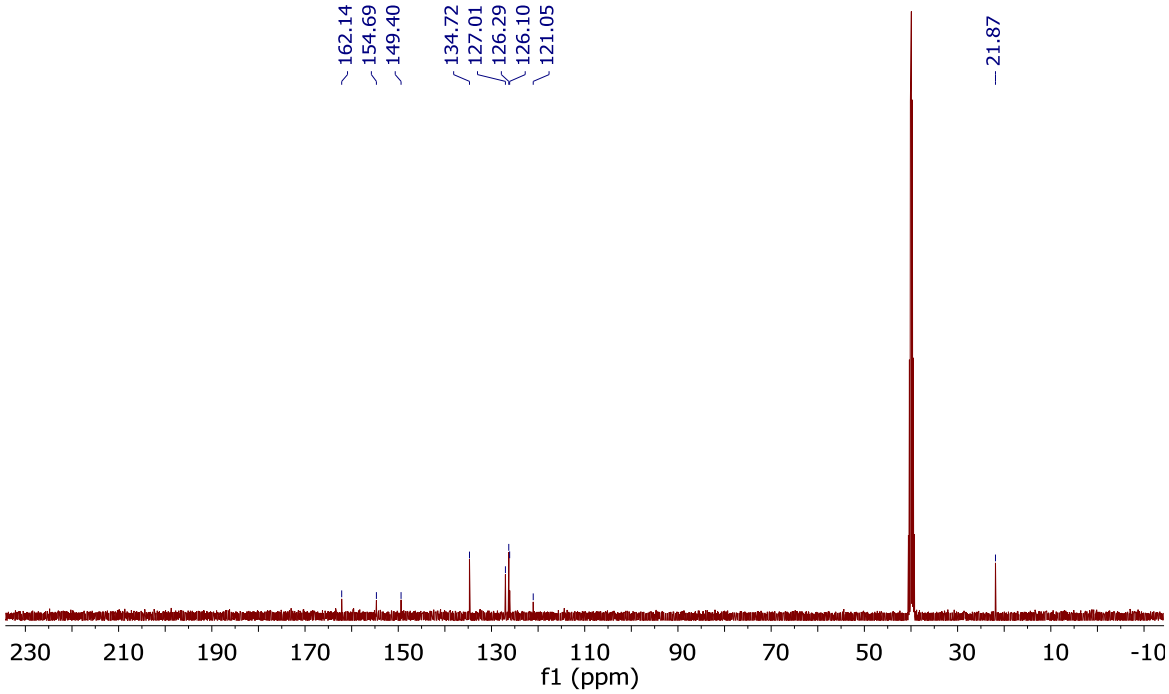

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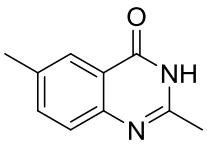

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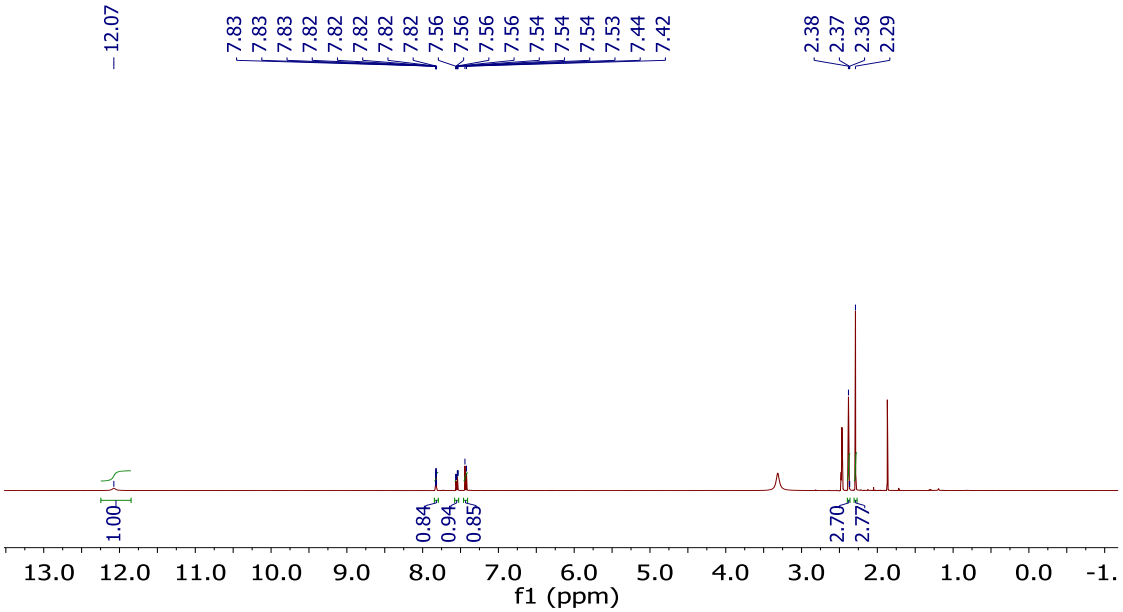

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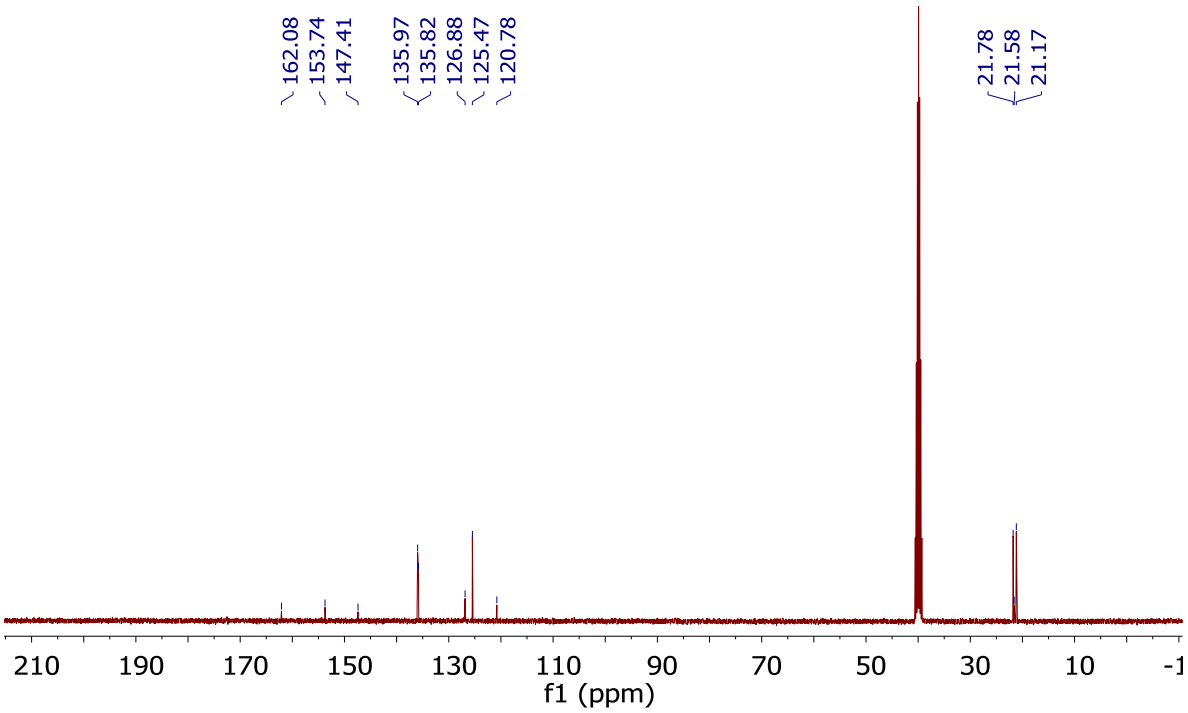

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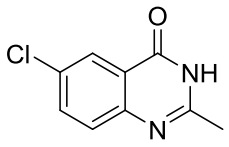

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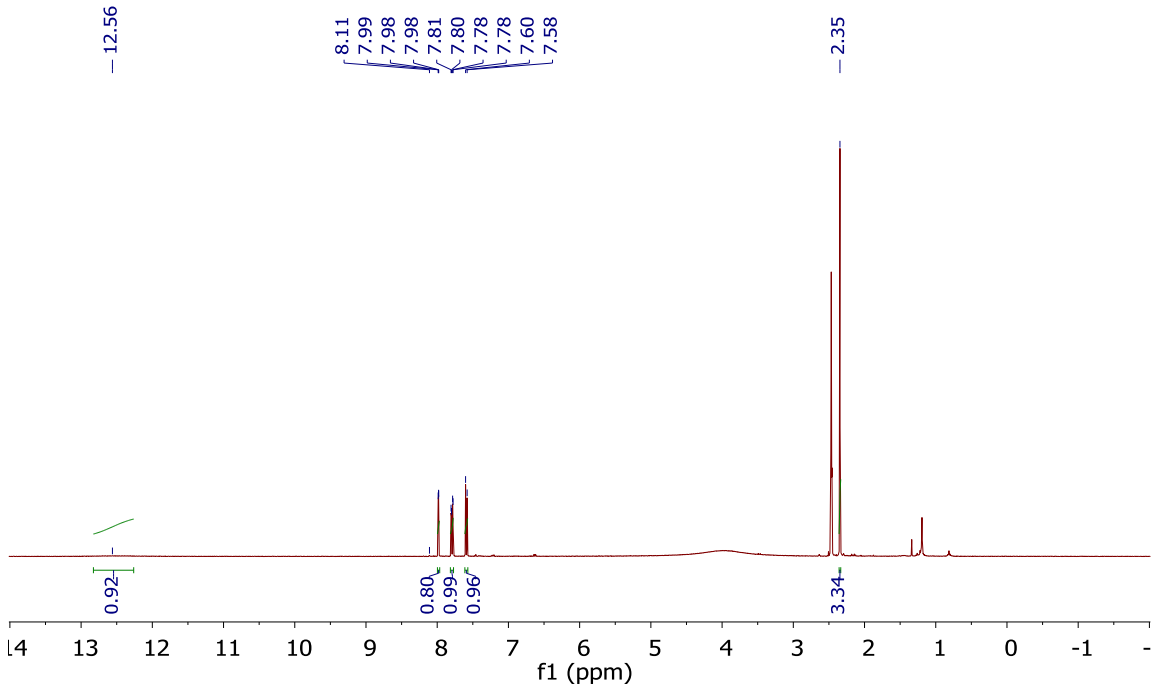

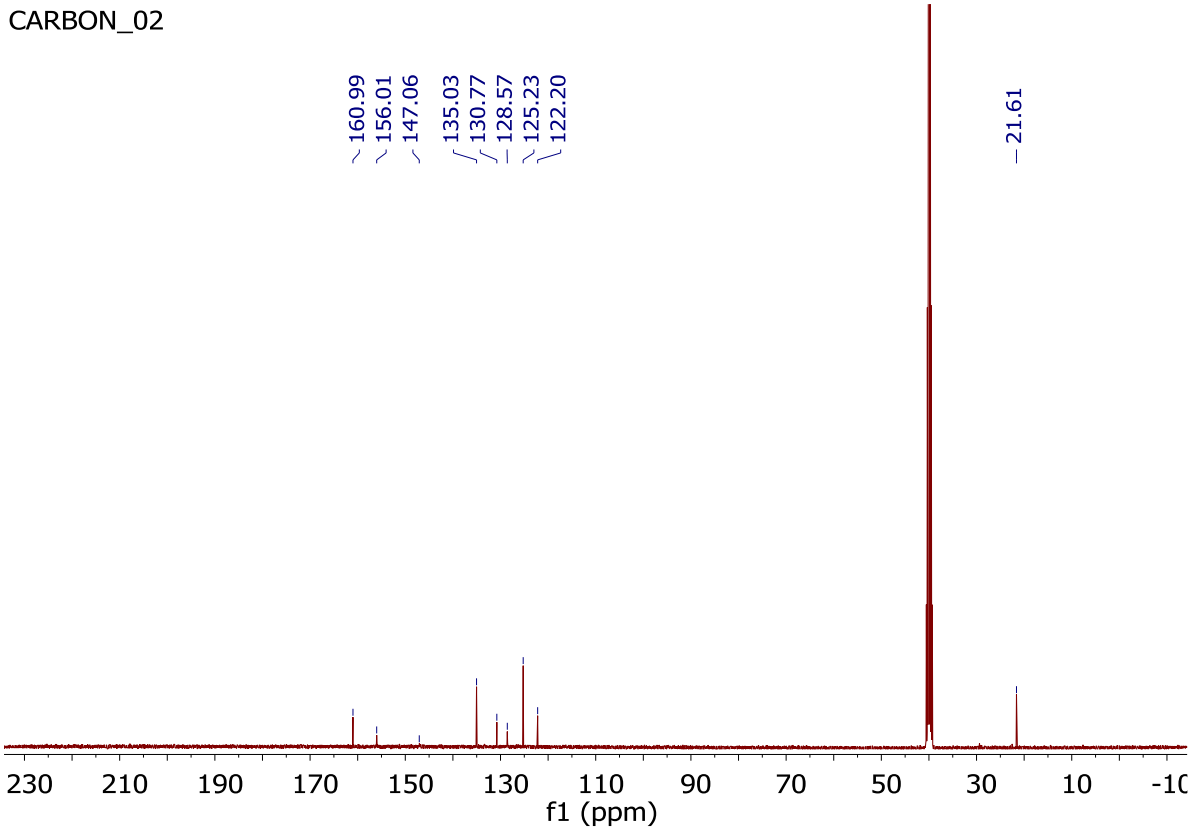

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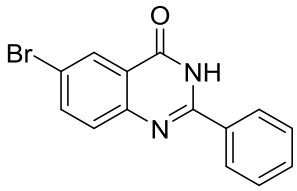

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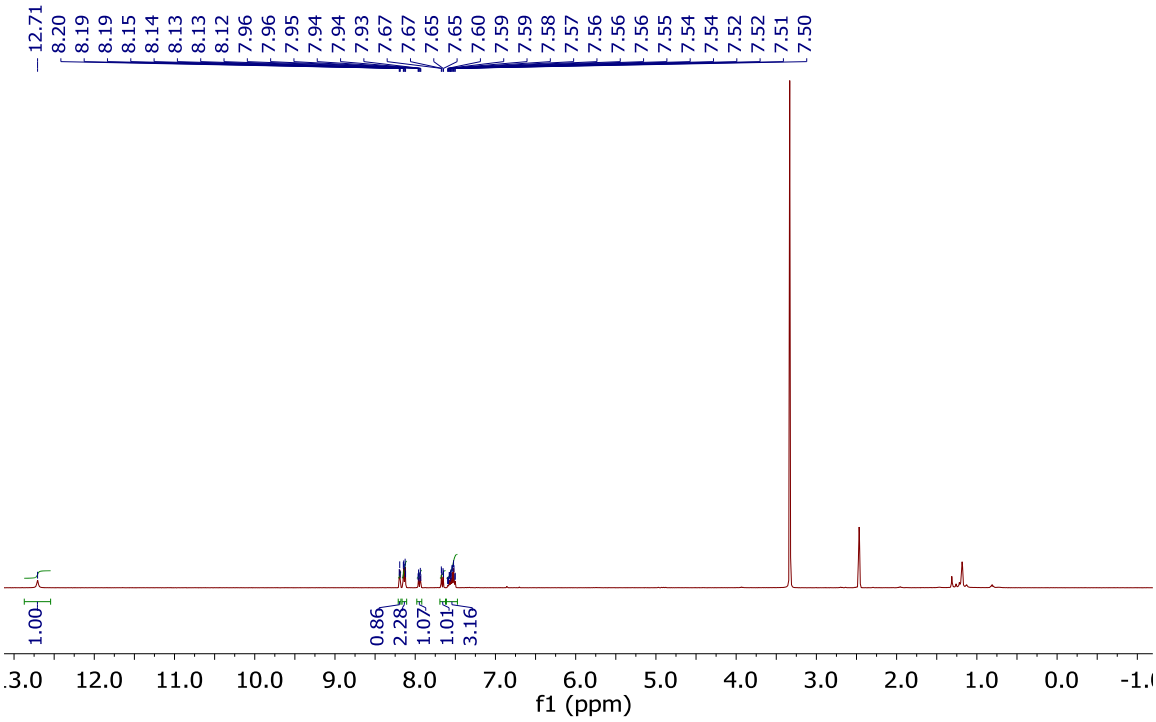

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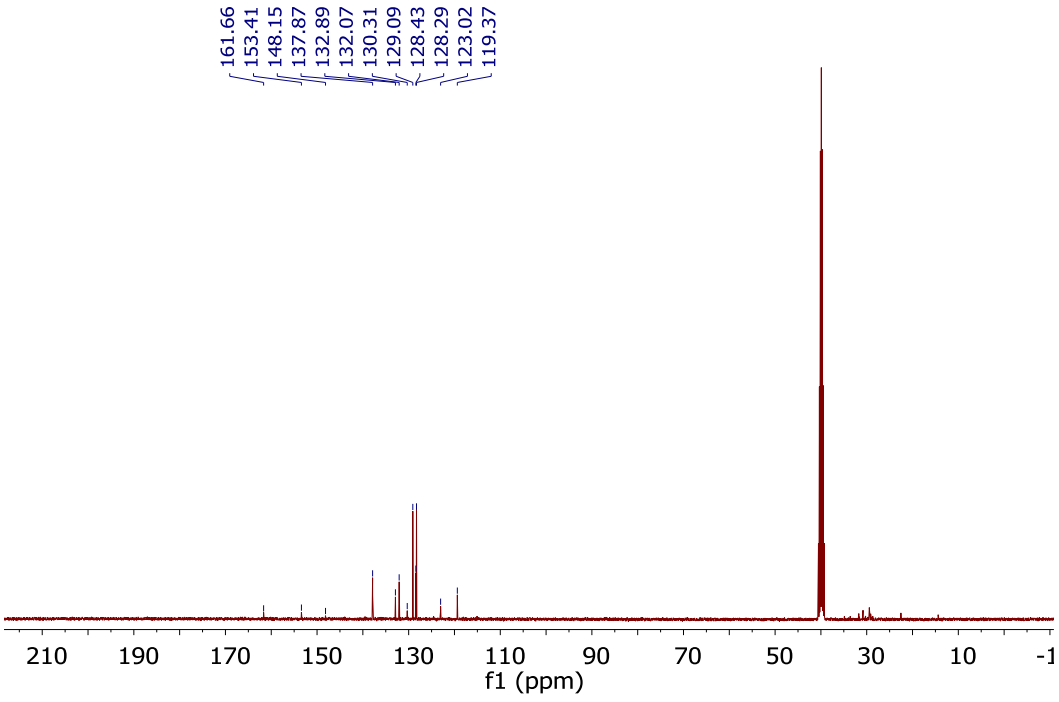

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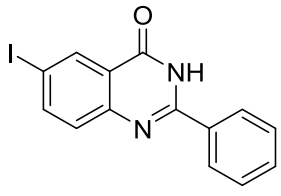
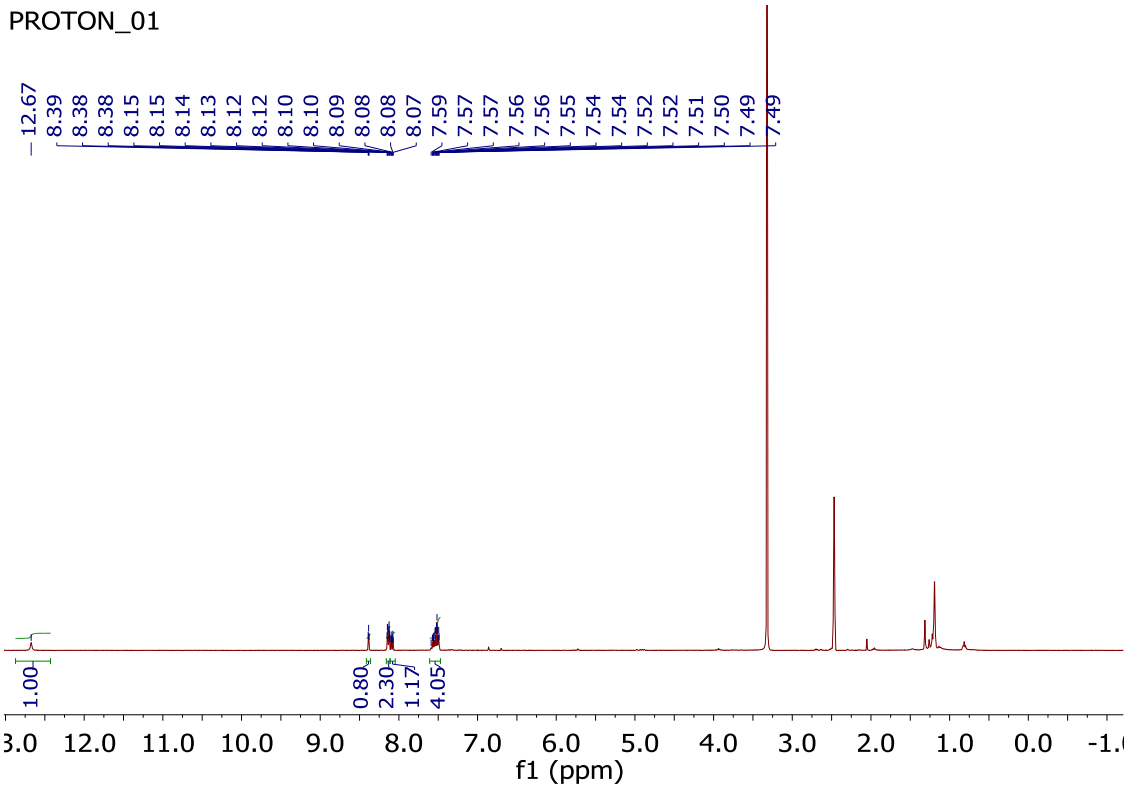
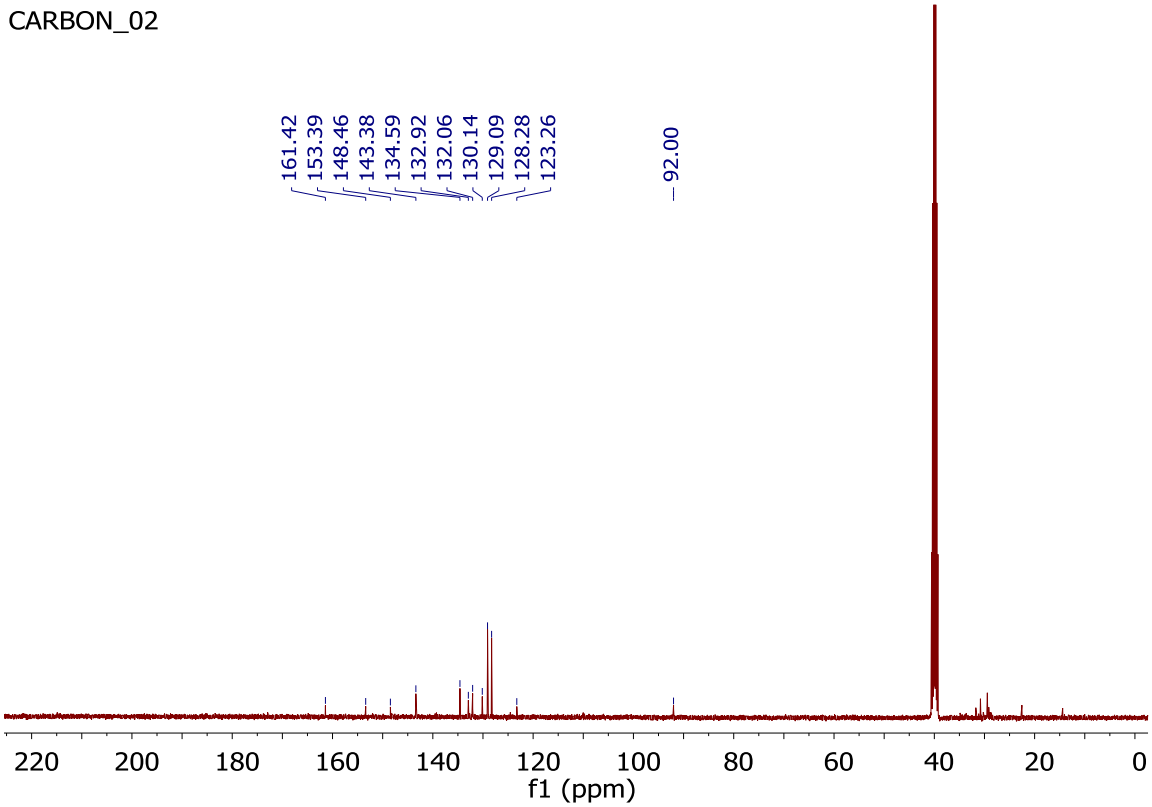
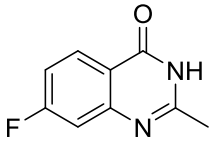






^{1}H and ^{13}C NMR spectra of **3g**



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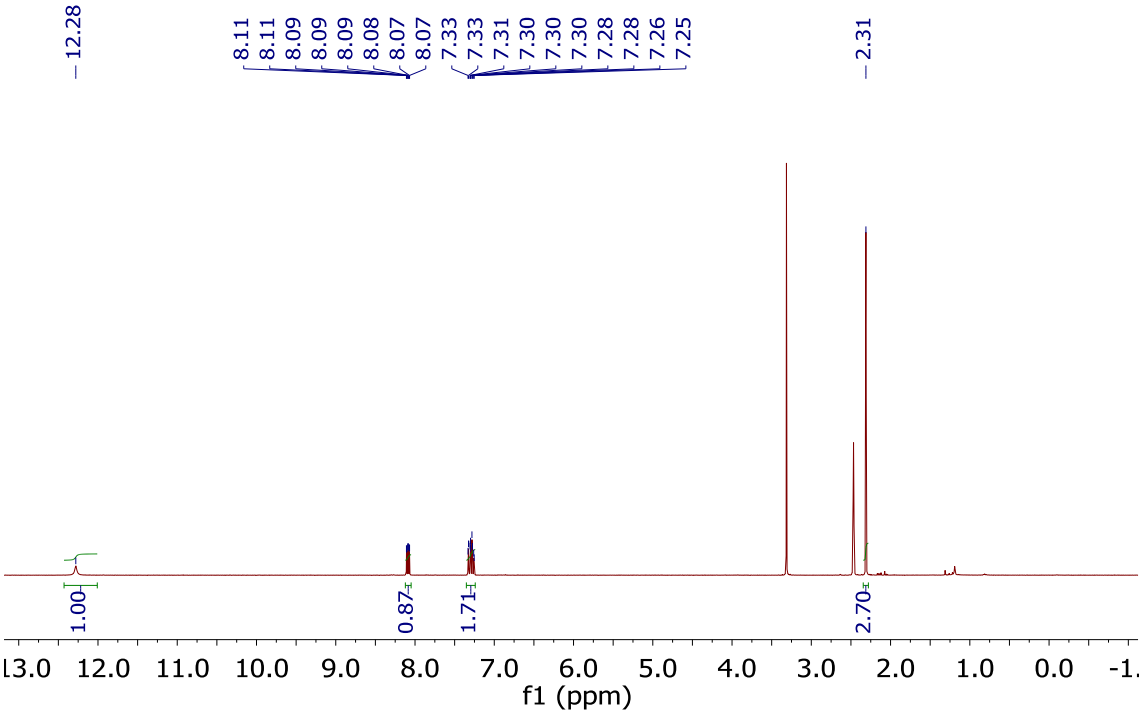

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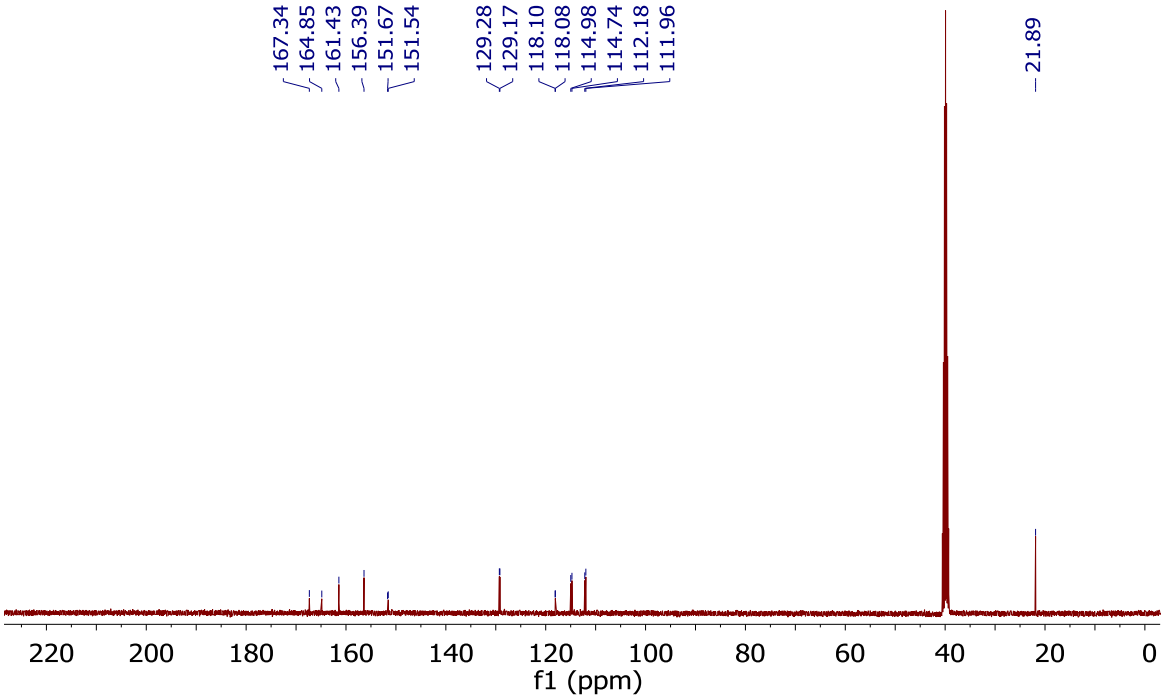
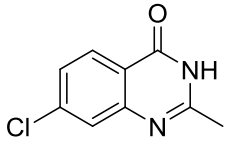


^{1}H and ^{13}C NMR spectra of **3h**



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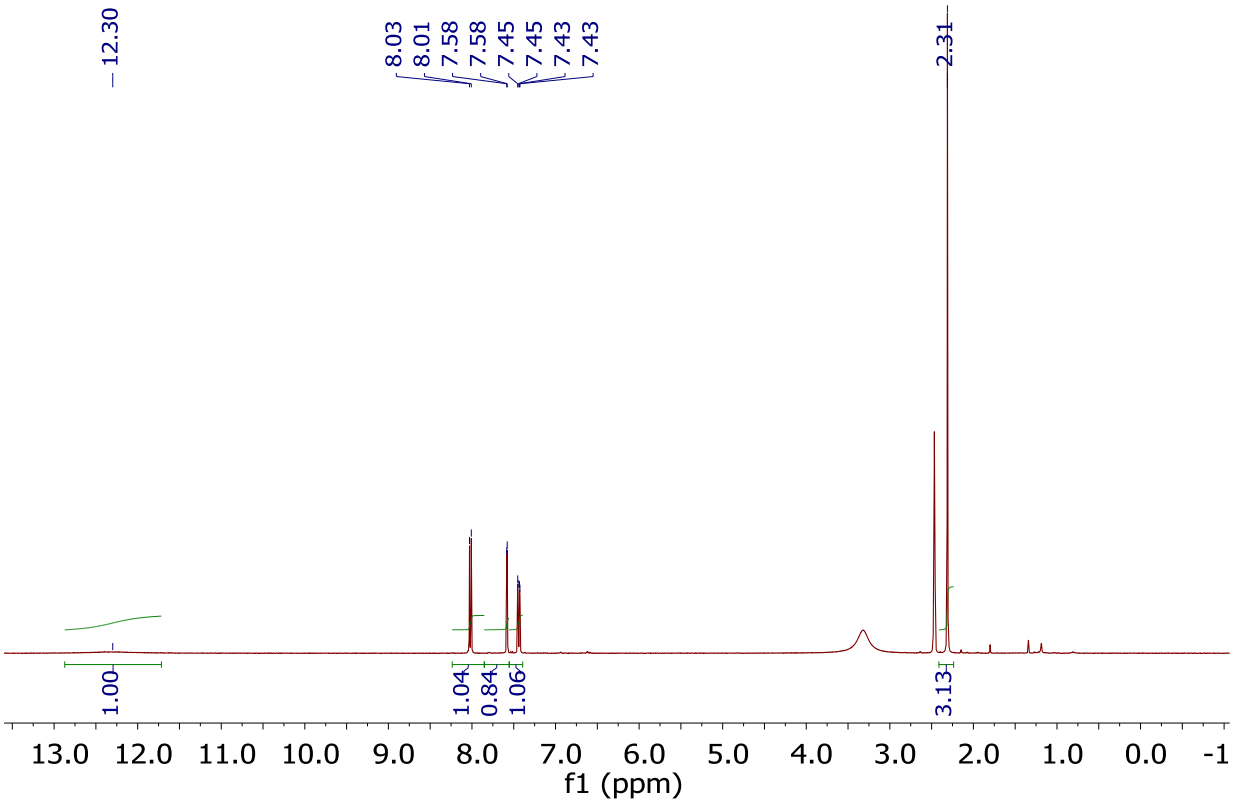

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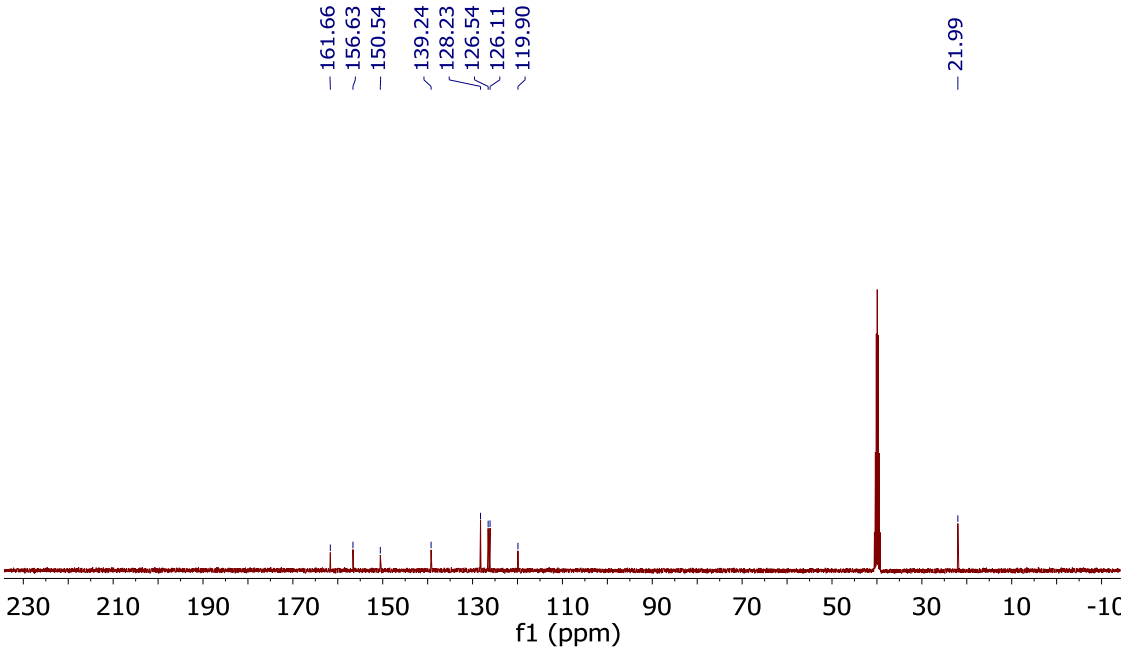
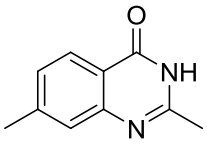


^{1}H and ^{13}C NMR spectra of **3i**



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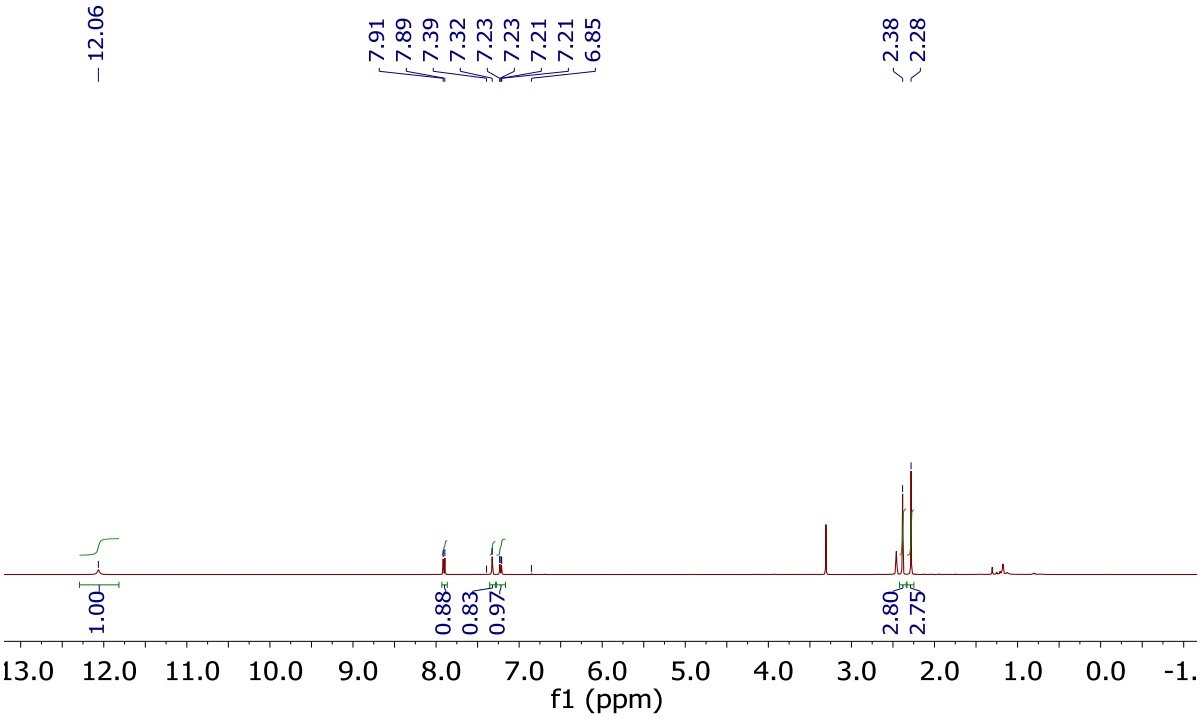

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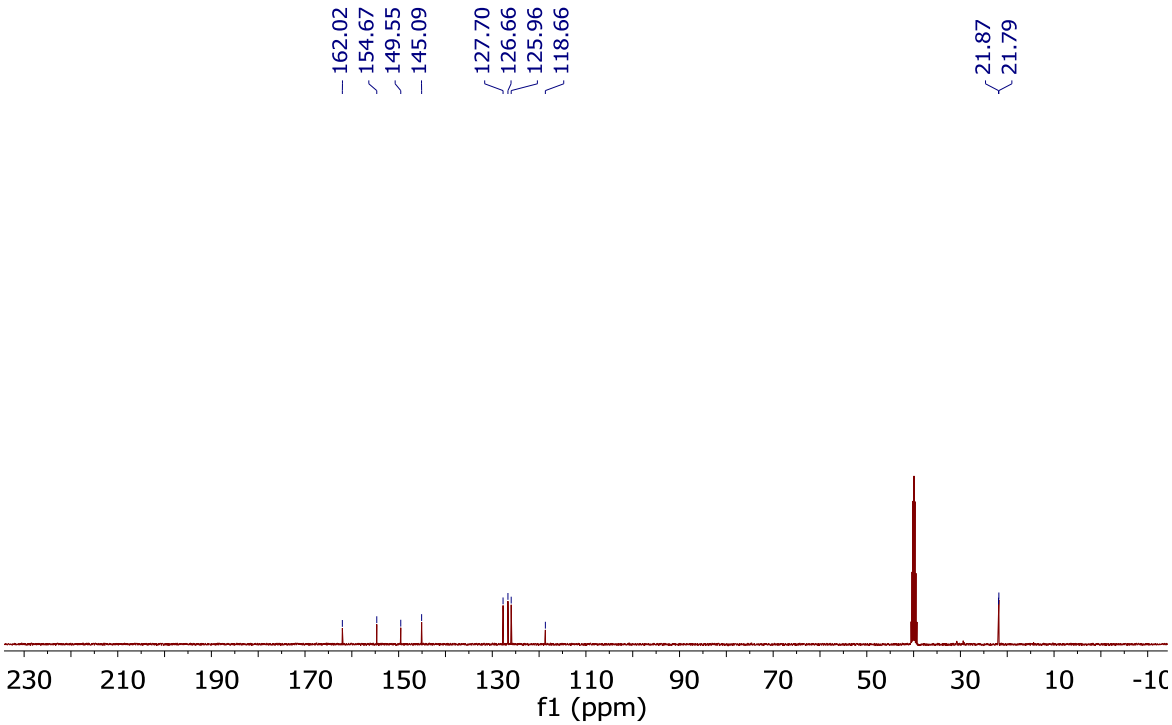
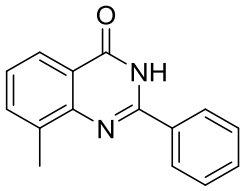


^{1}H and ^{13}C NMR spectra of **3j**



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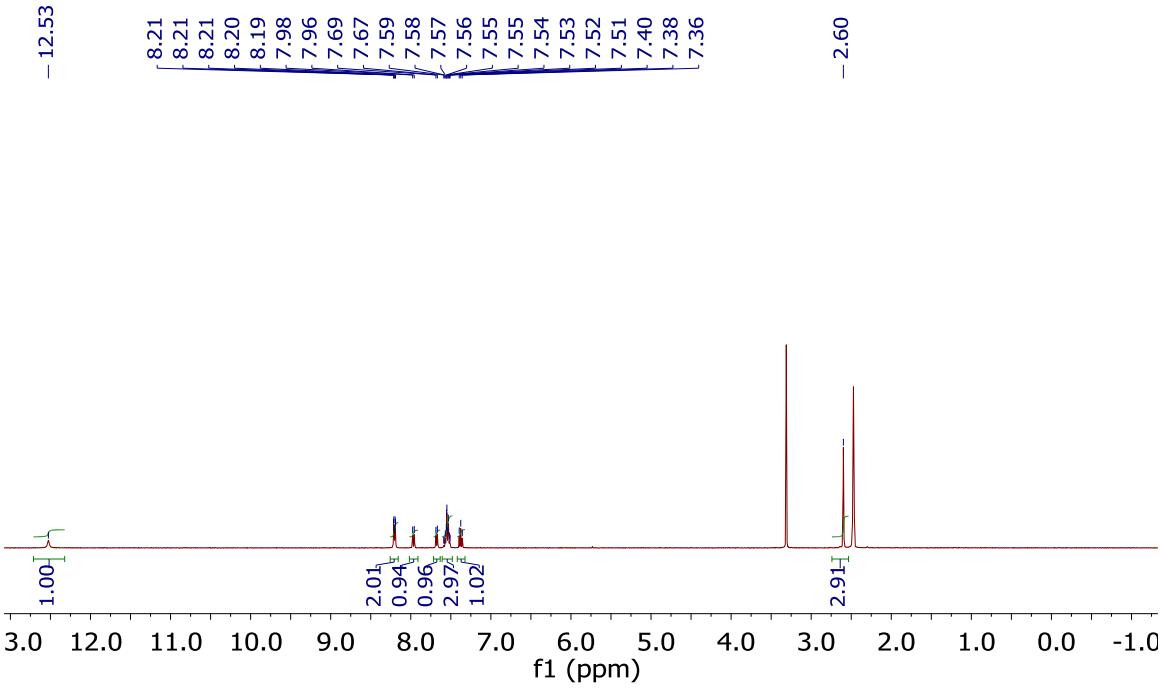

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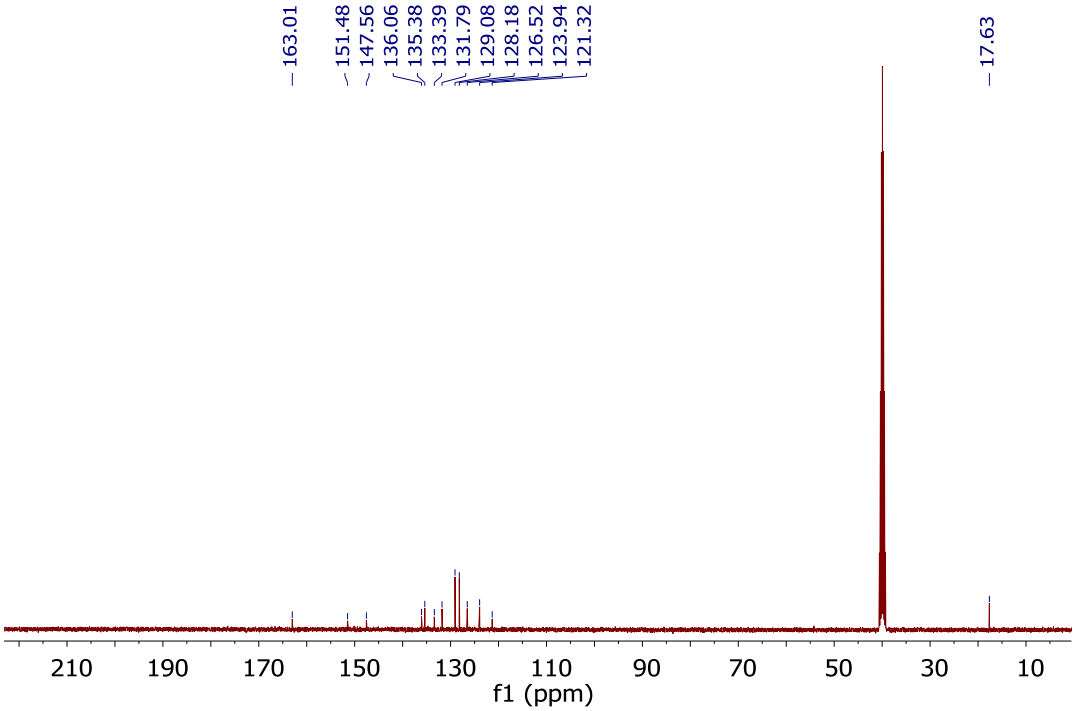
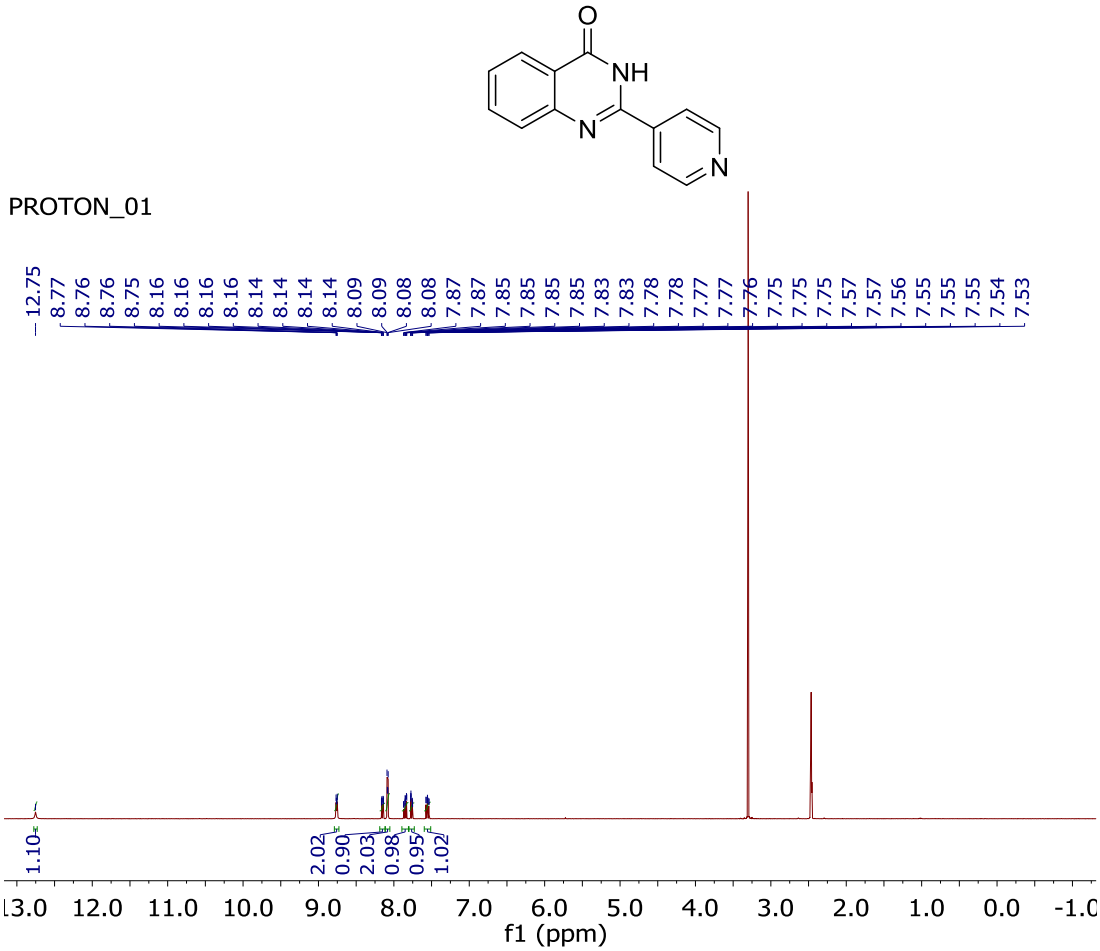
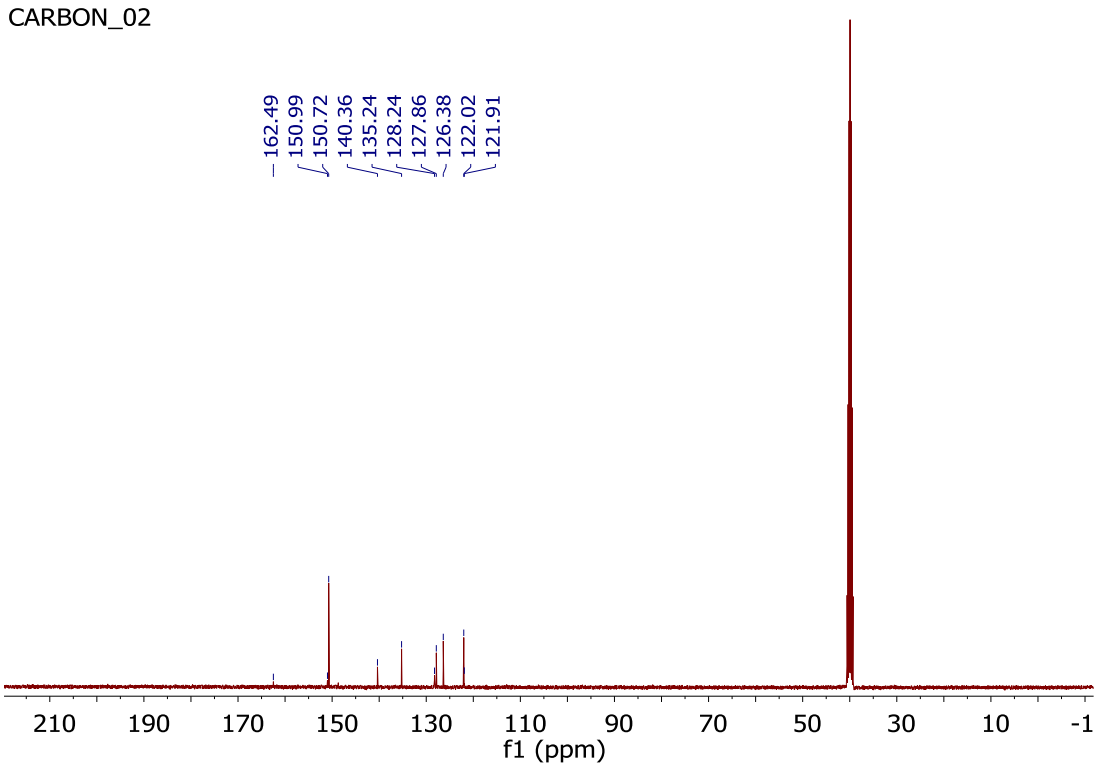
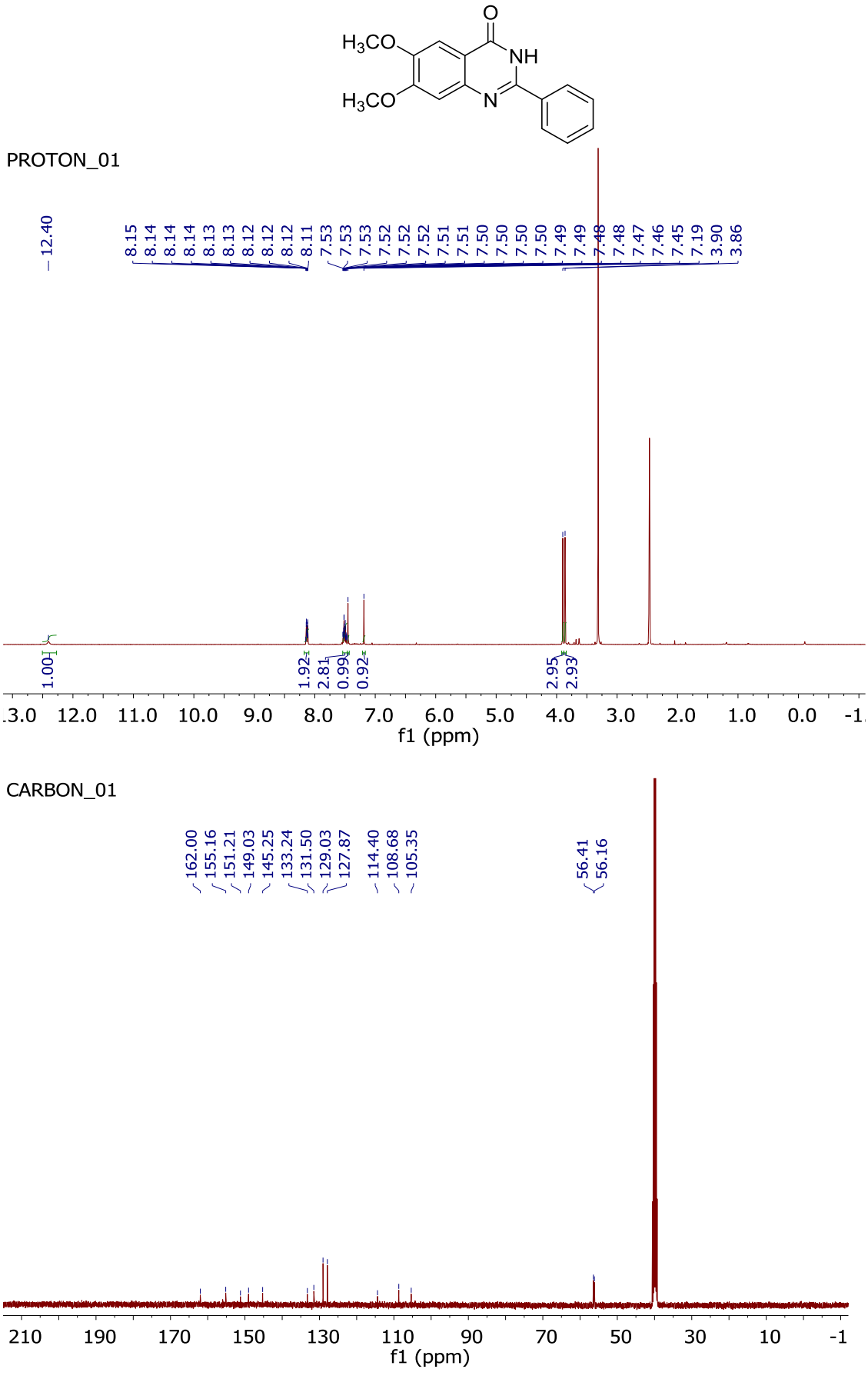


^{1}H and ^{13}C NMR spectra of **3k**

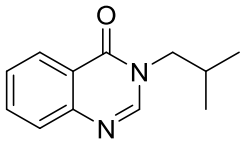




^{1}H and ^{13}C NMR spectra of **3l**



^{1}H and ^{13}C NMR spectra of **4a**



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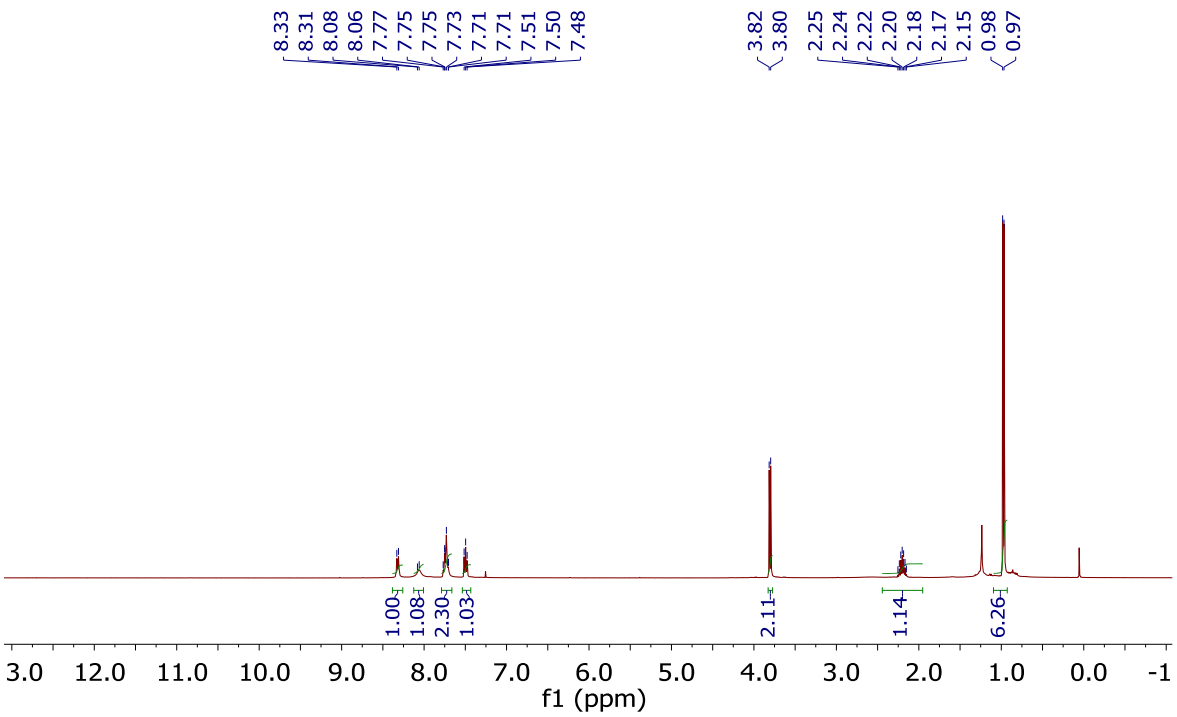

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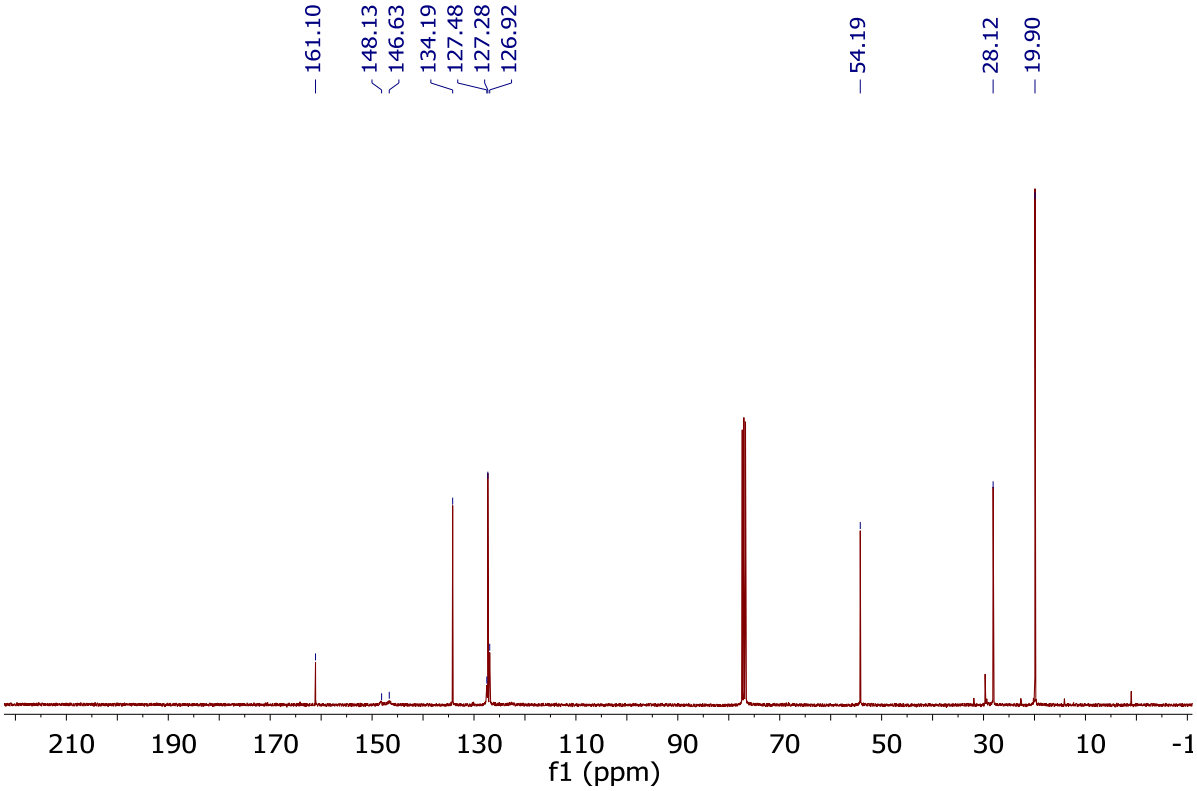
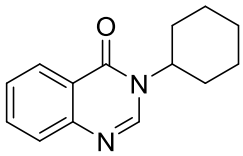


^{1}H and ^{13}C NMR spectra of **4b**



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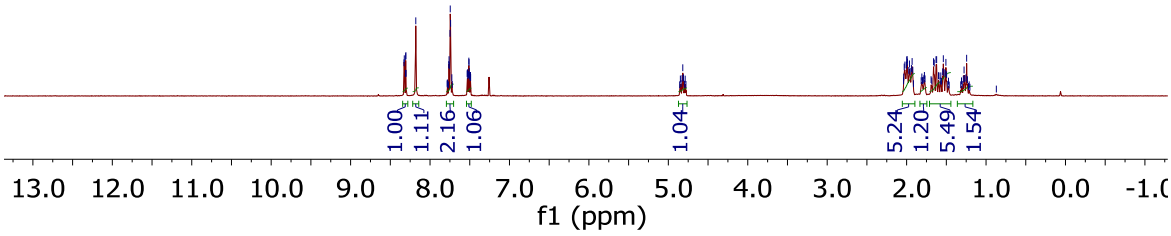

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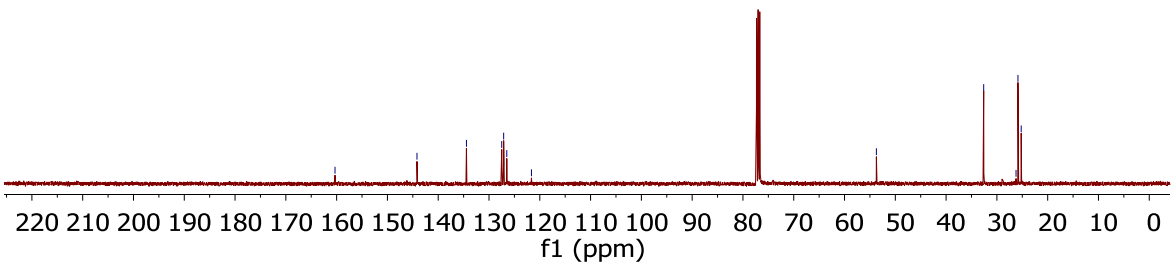
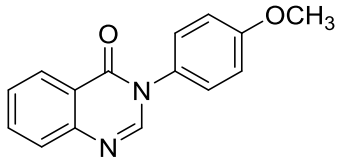


^{1}H and ^{13}C NMR spectra of **4c**



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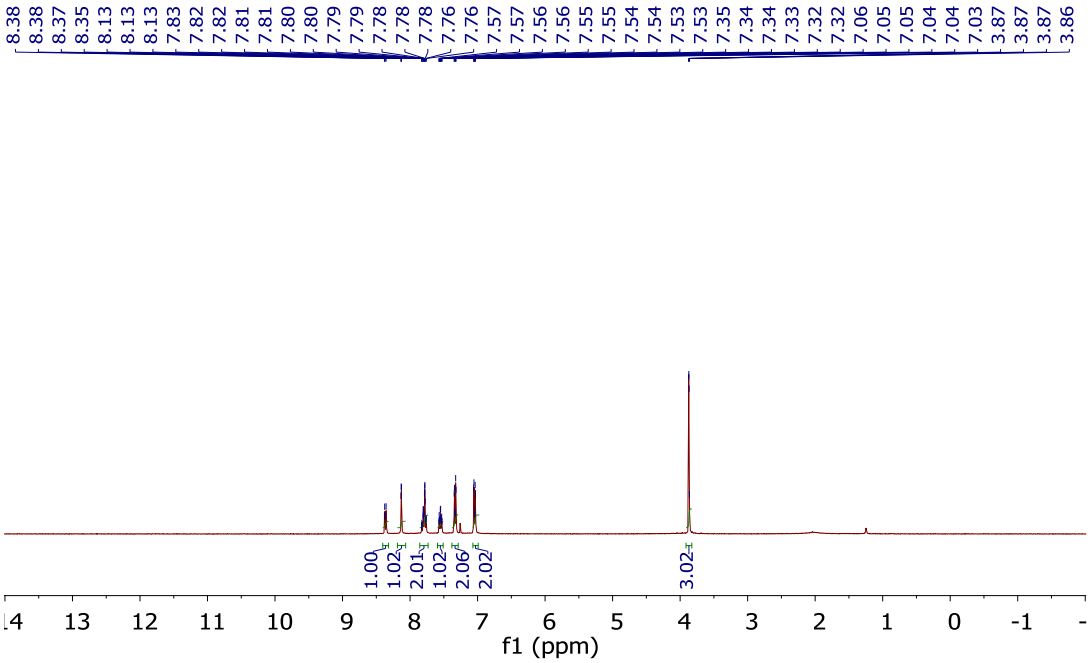

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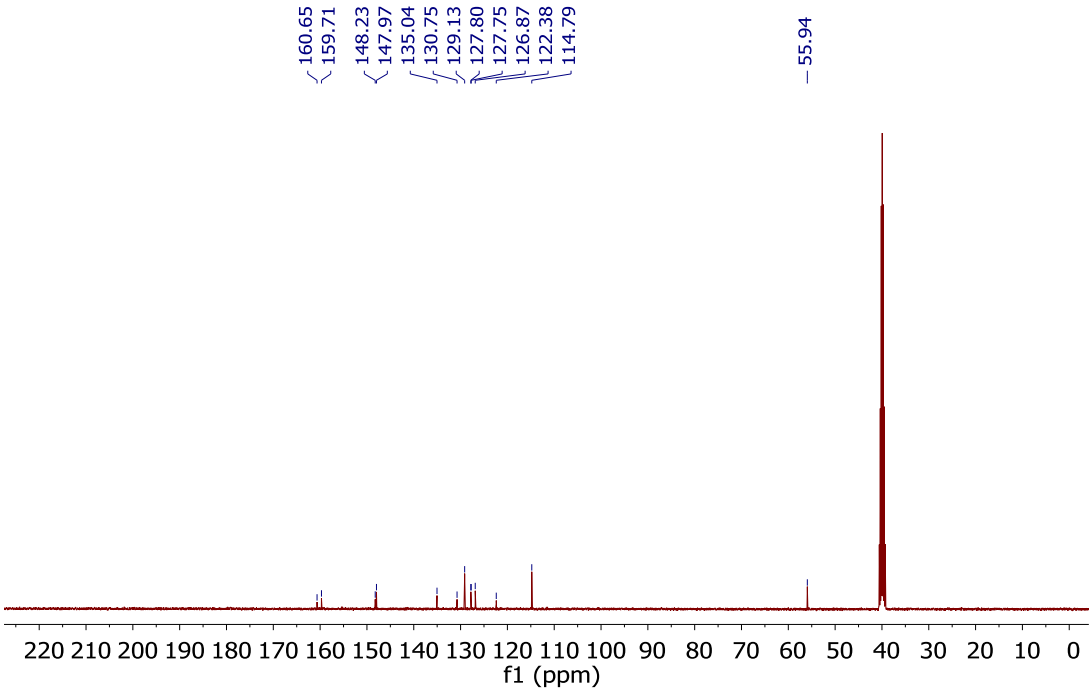
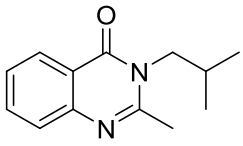


^{1}H and ^{13}C NMR spectra of **4d**



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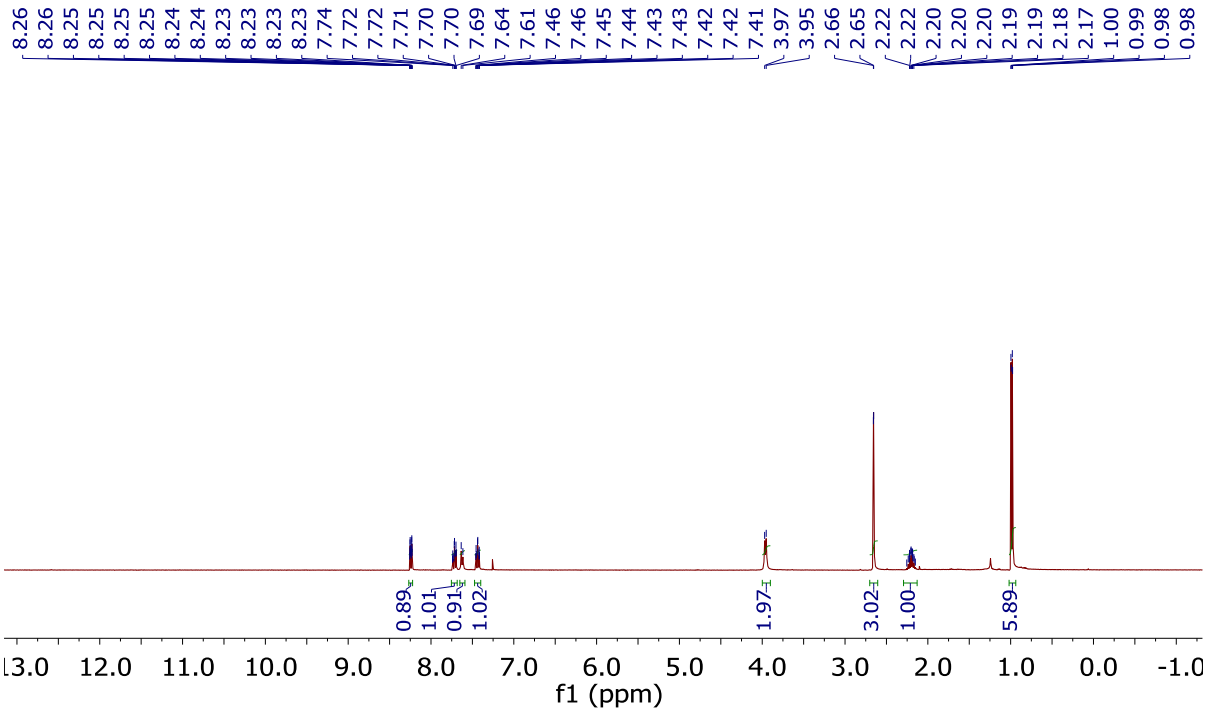

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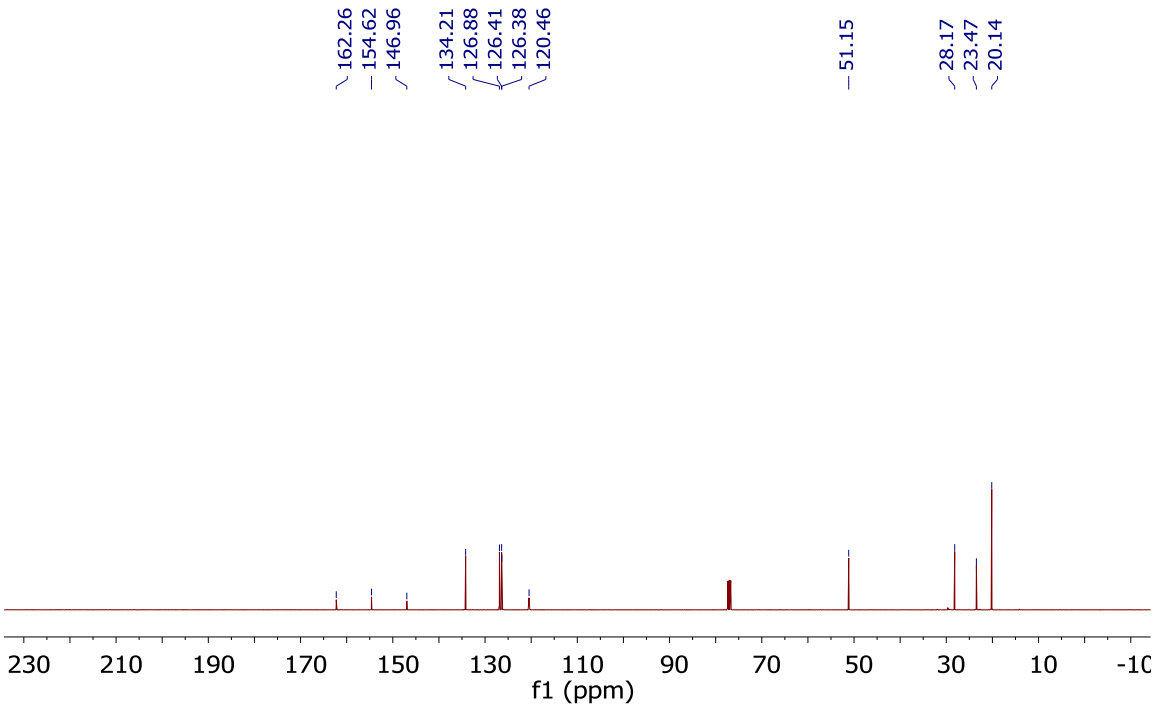
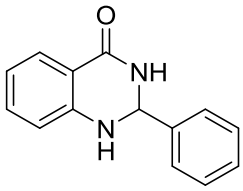


^{1}H and ^{13}C NMR spectra of **6a**



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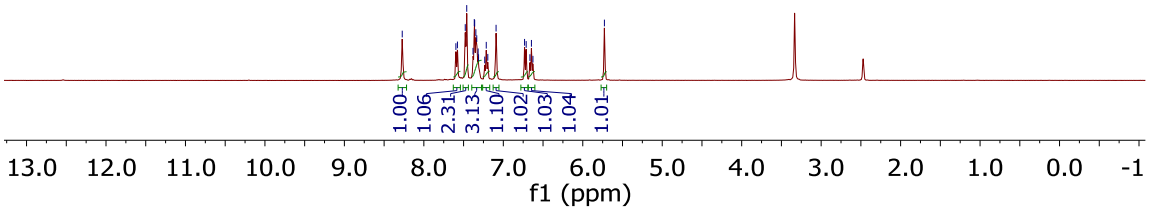

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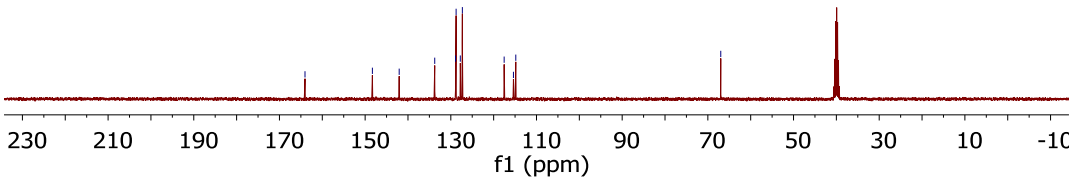
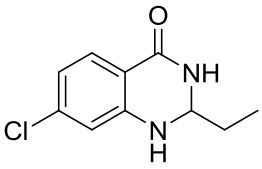


^{1}H and ^{13}C NMR spectra of **6b**



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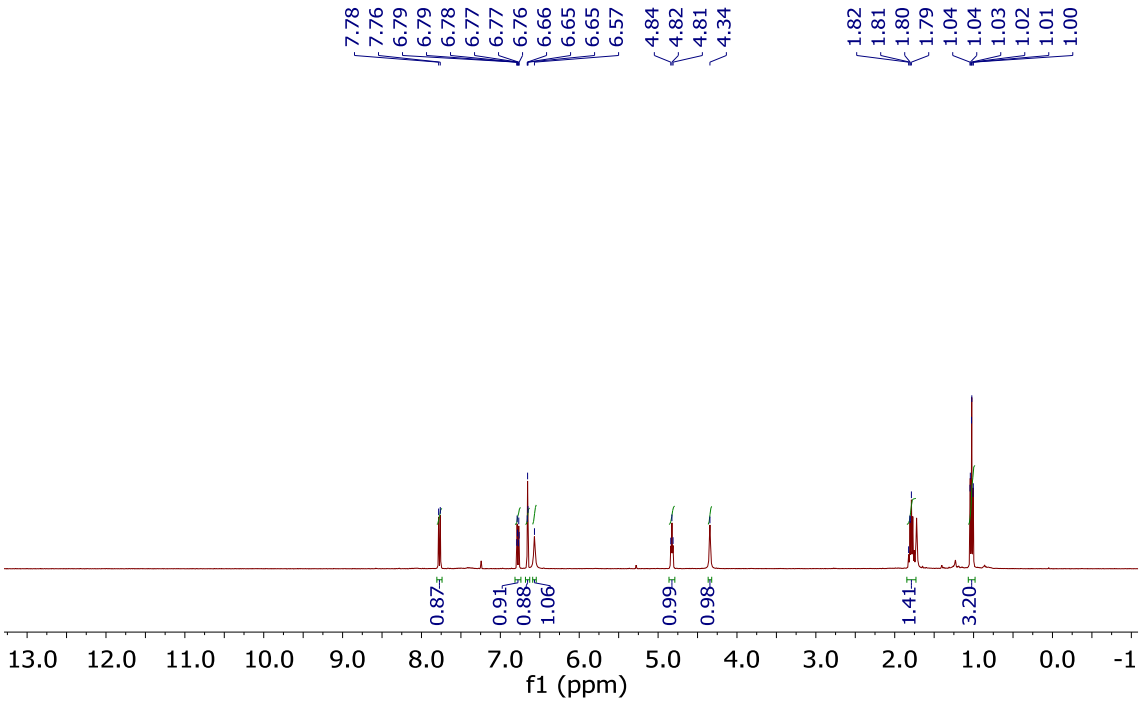

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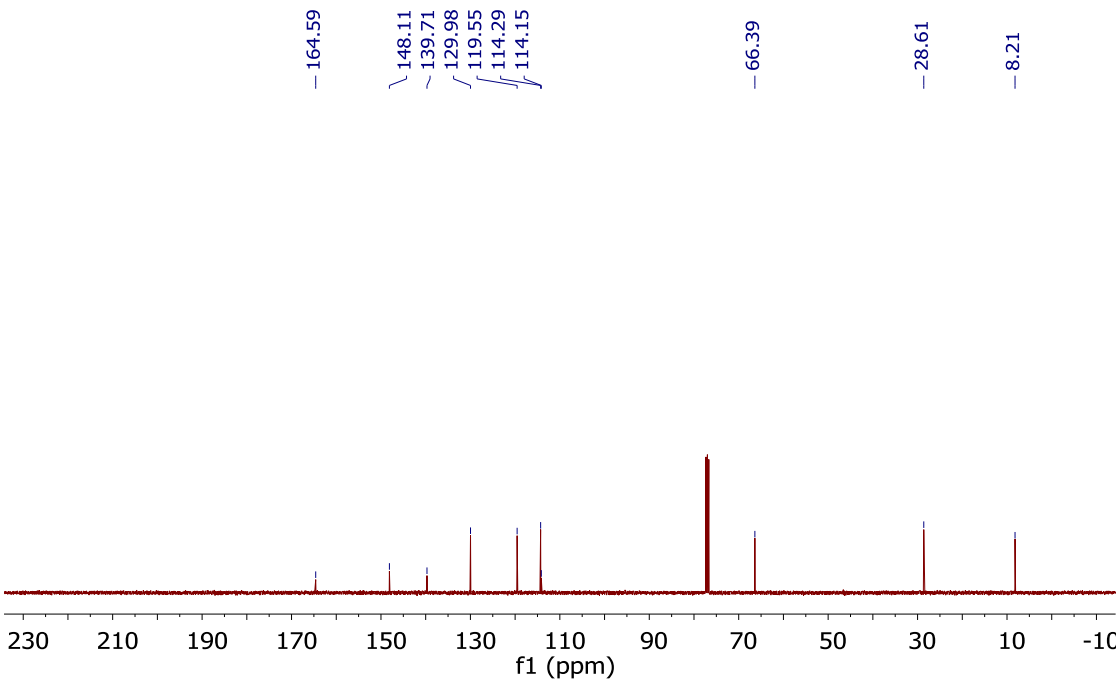
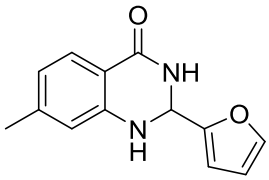


^{1}H and ^{13}C NMR spectra of **6c**



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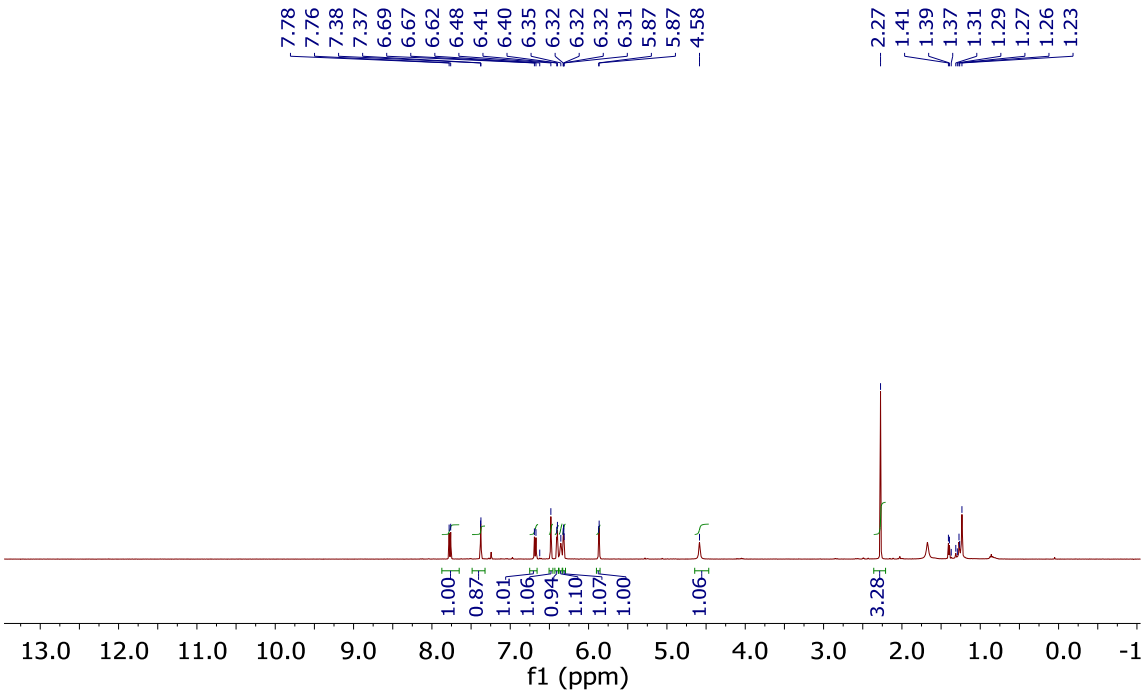

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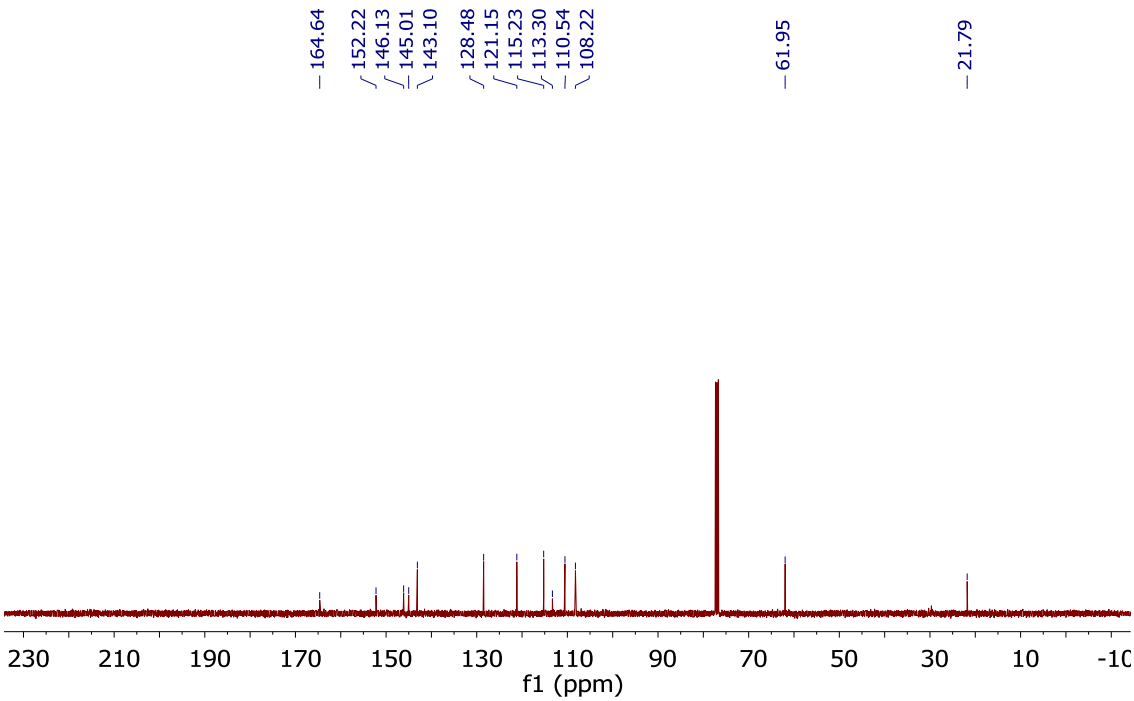
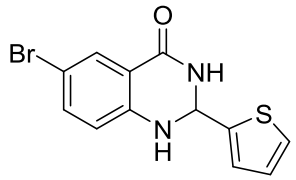


^{1}H and ^{13}C NMR spectra of **6d**



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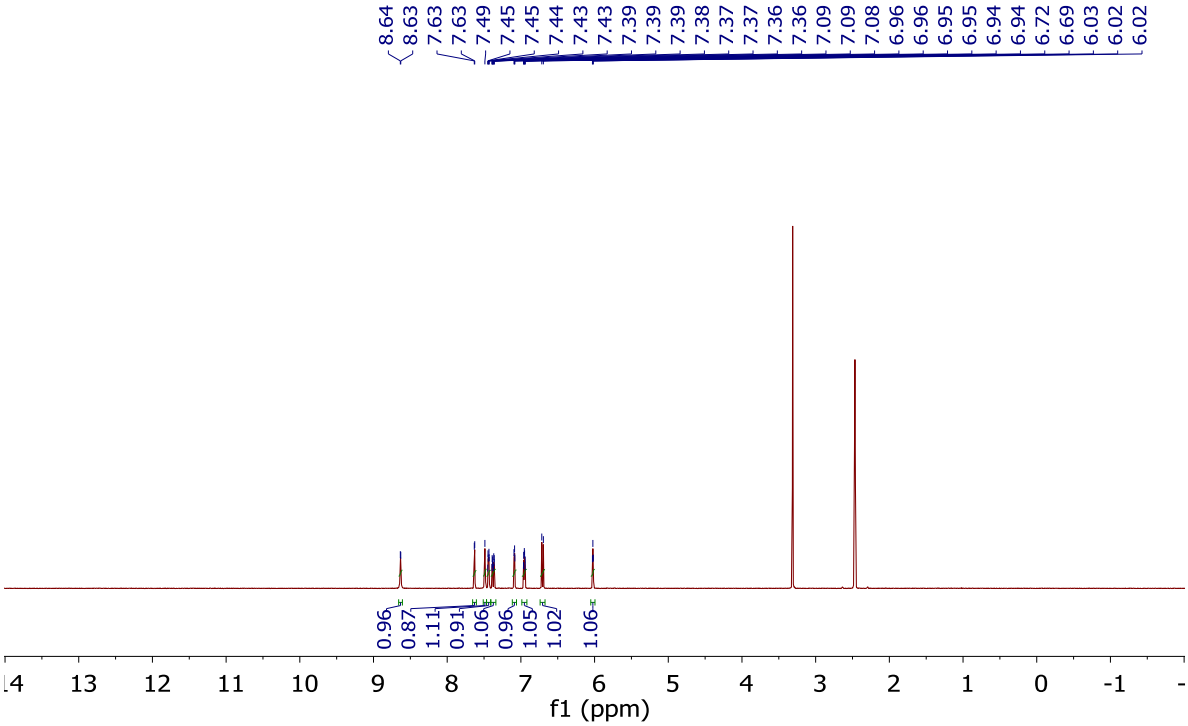

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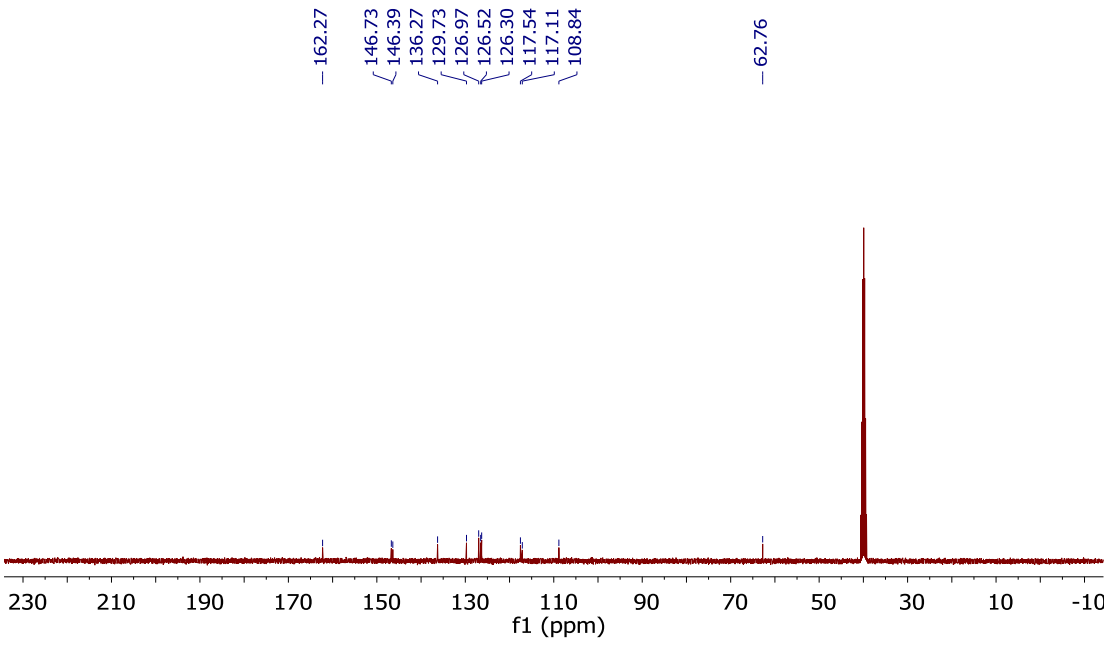
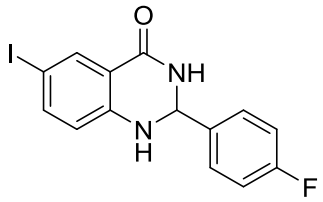
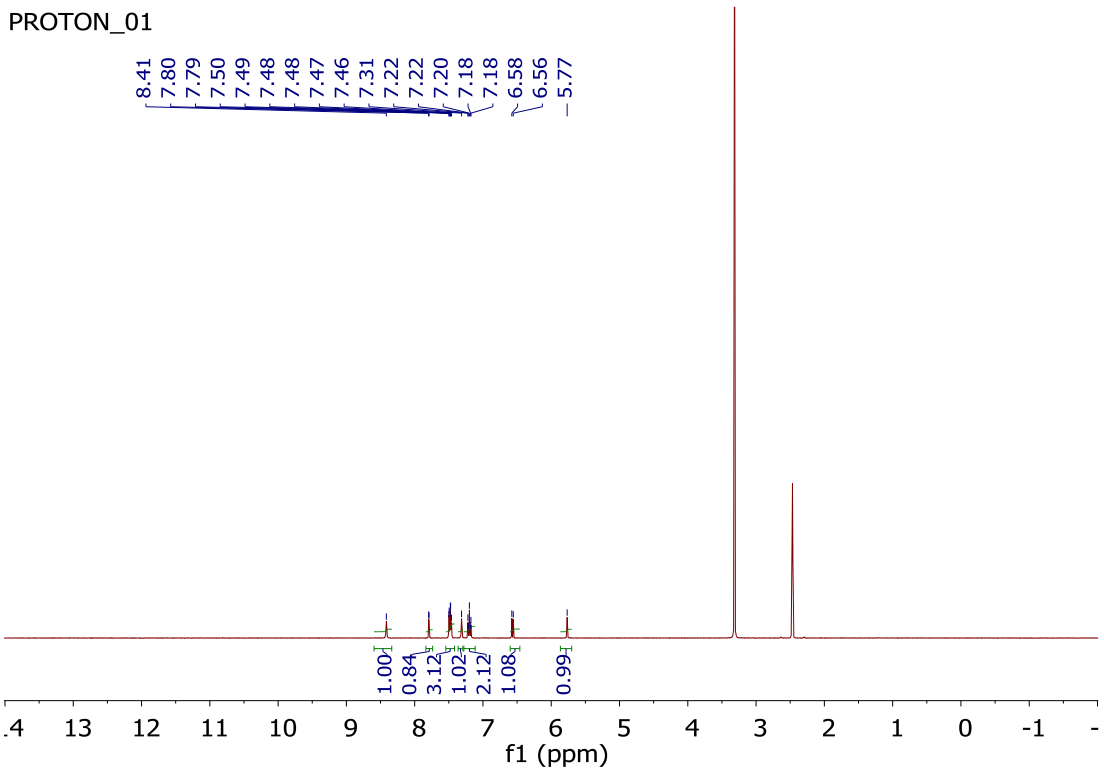
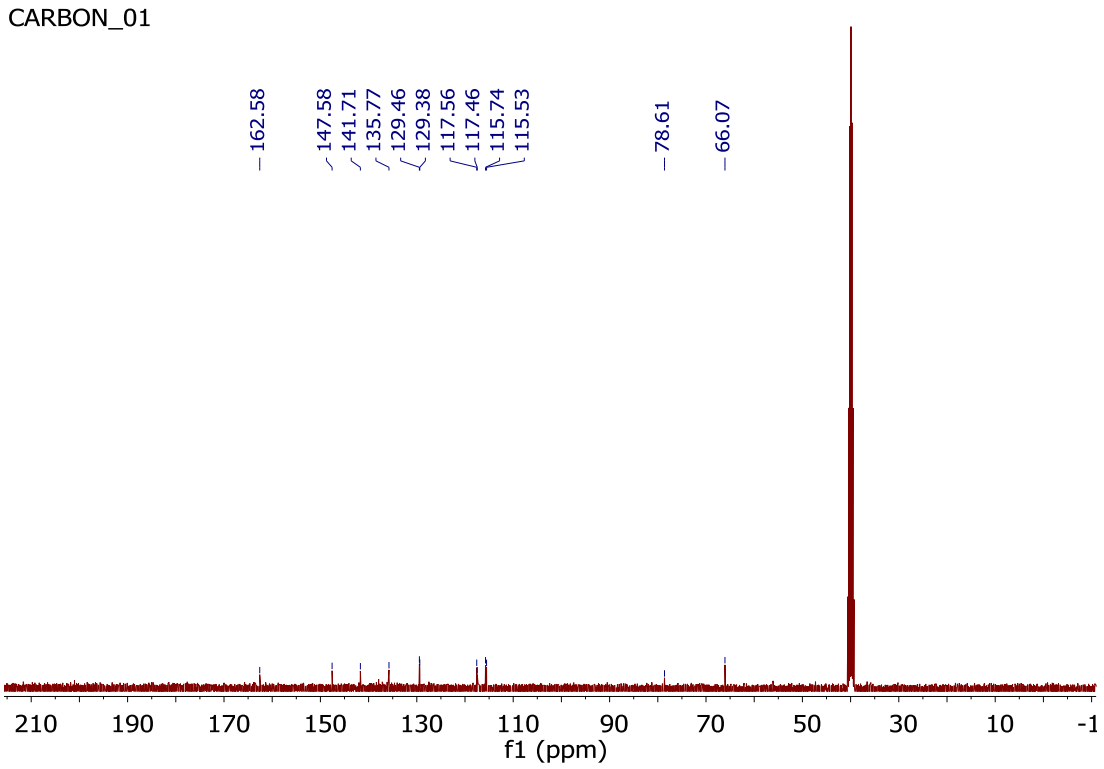


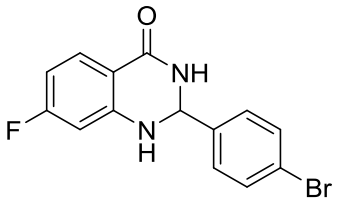
^{1}H and ^{13}C NMR spectra of **6e**







^{1}H and ^{13}C NMR spectra of **6f**



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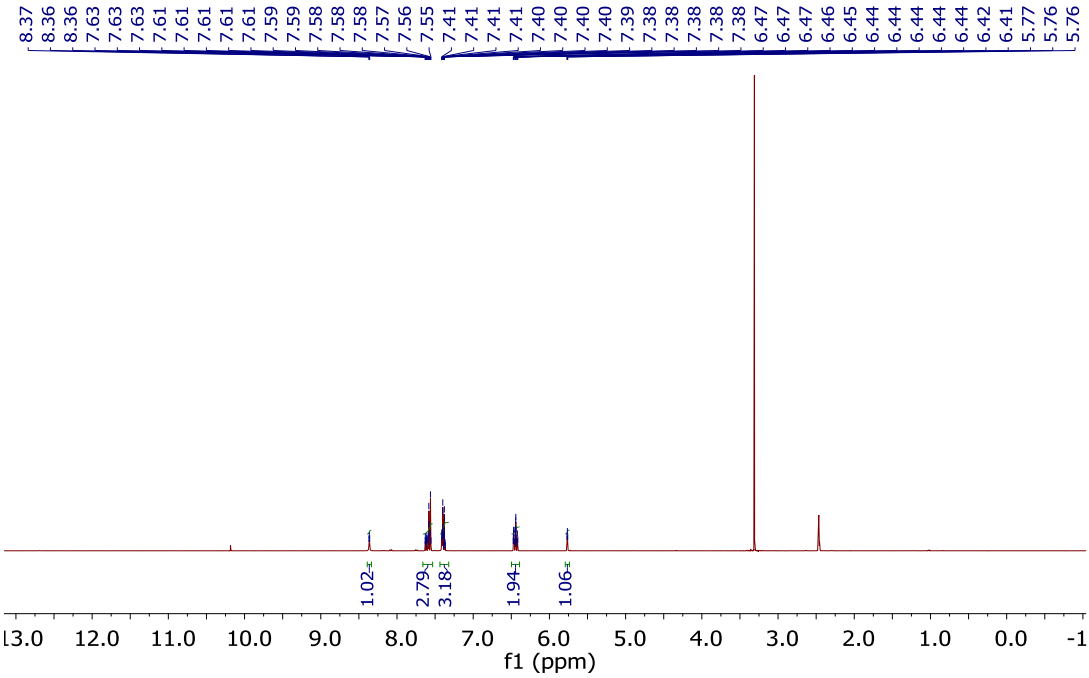

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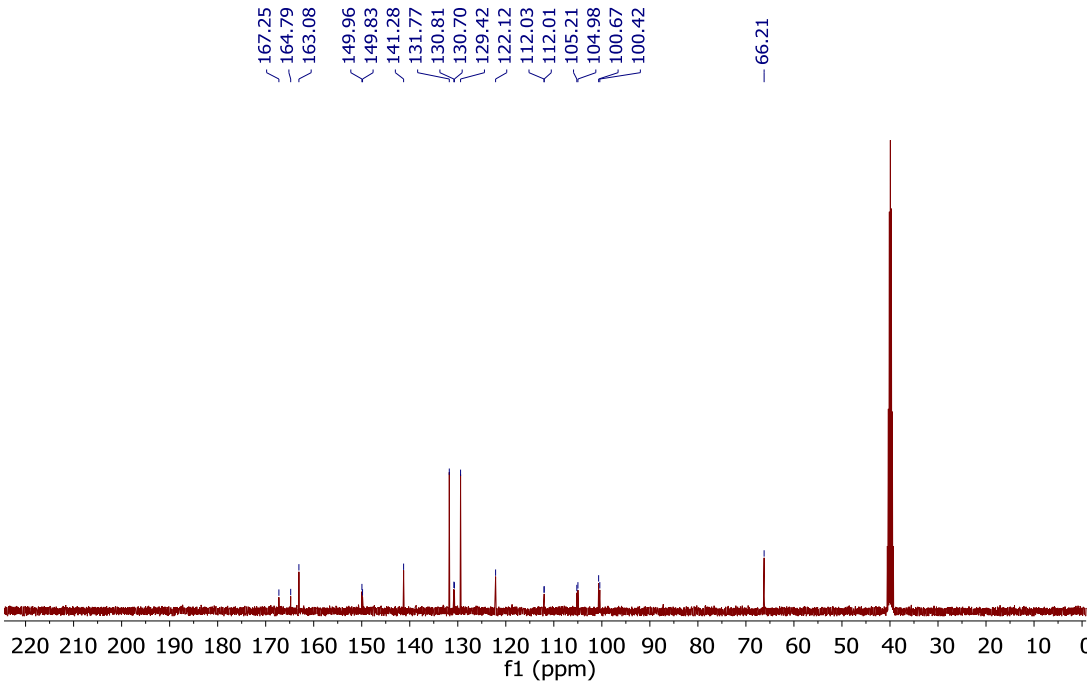
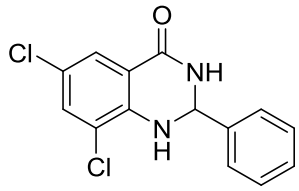


^{1}H and ^{13}C NMR spectra of **6g**



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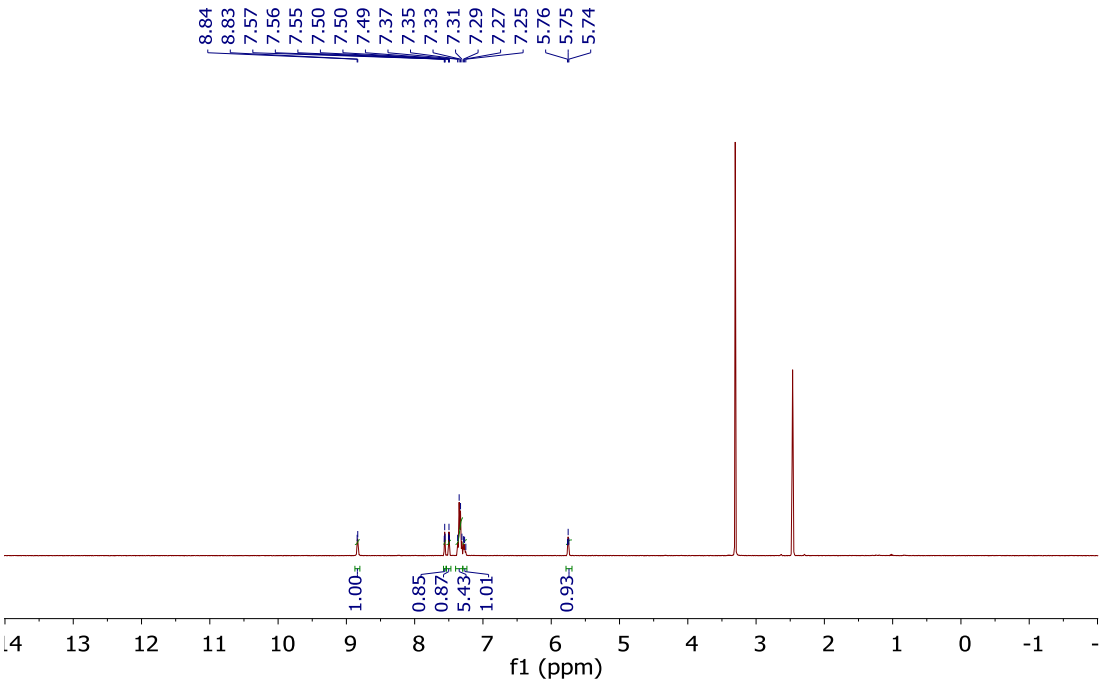

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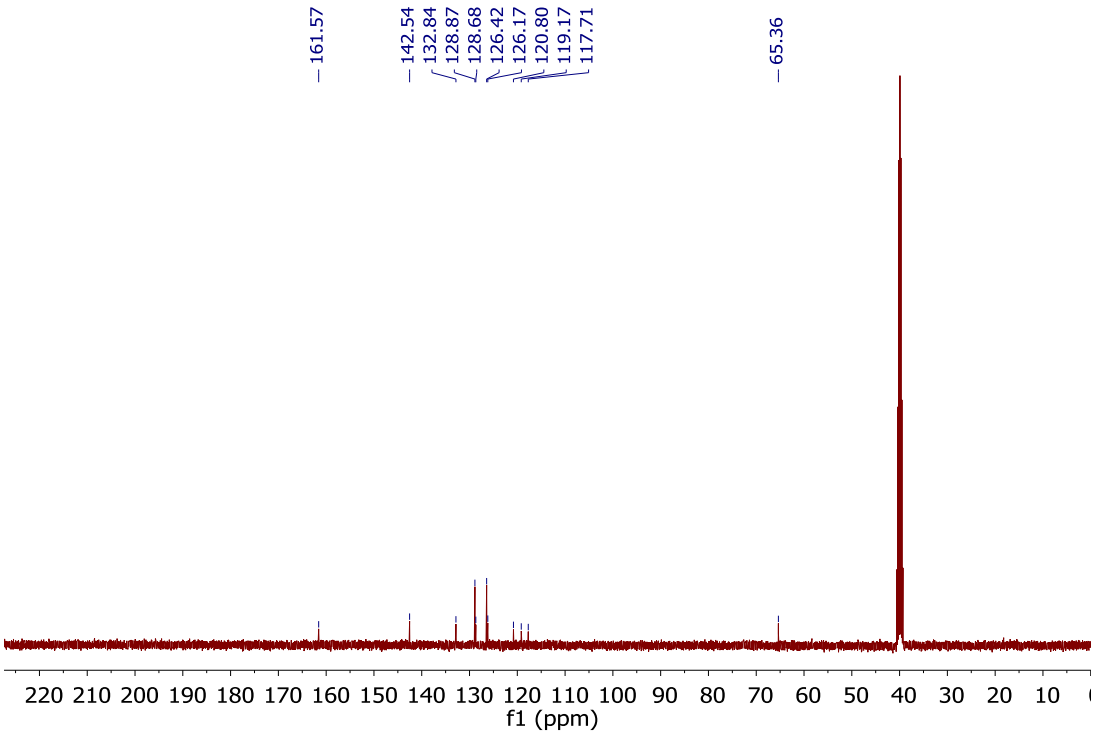
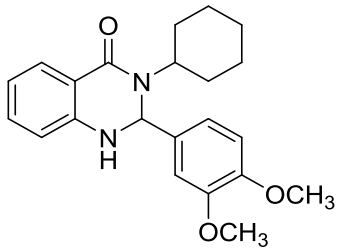


^{1}H and ^{13}C NMR spectra of **7a**



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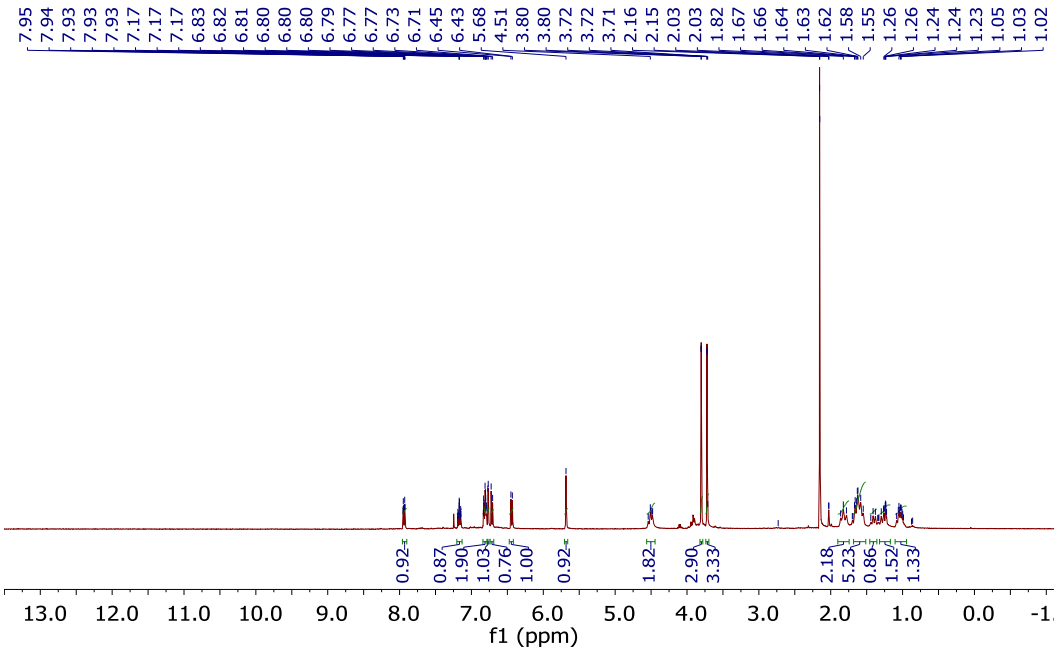

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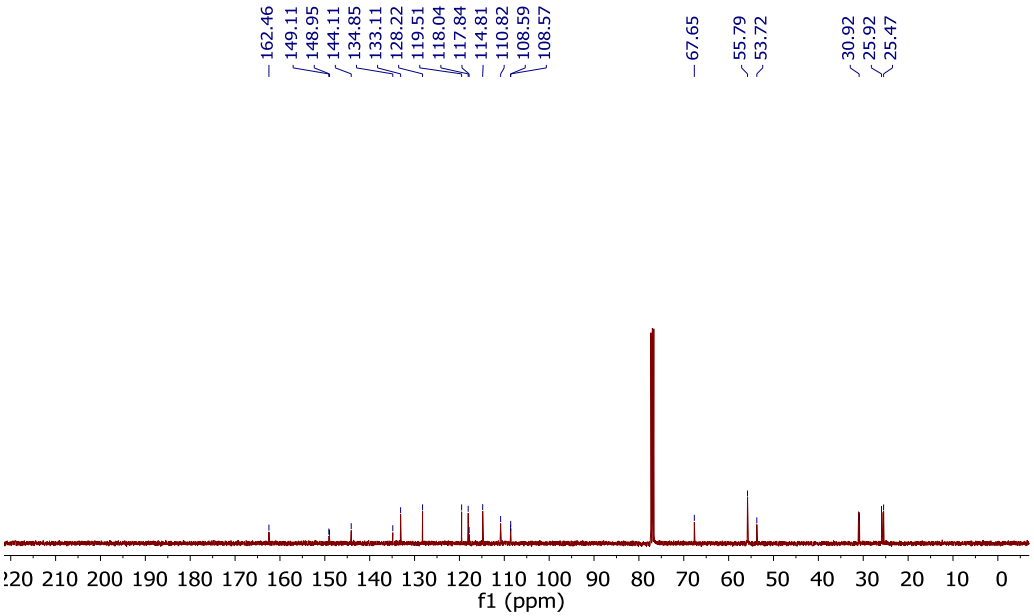
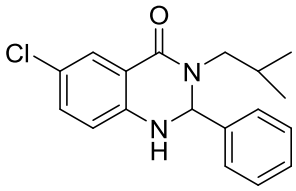
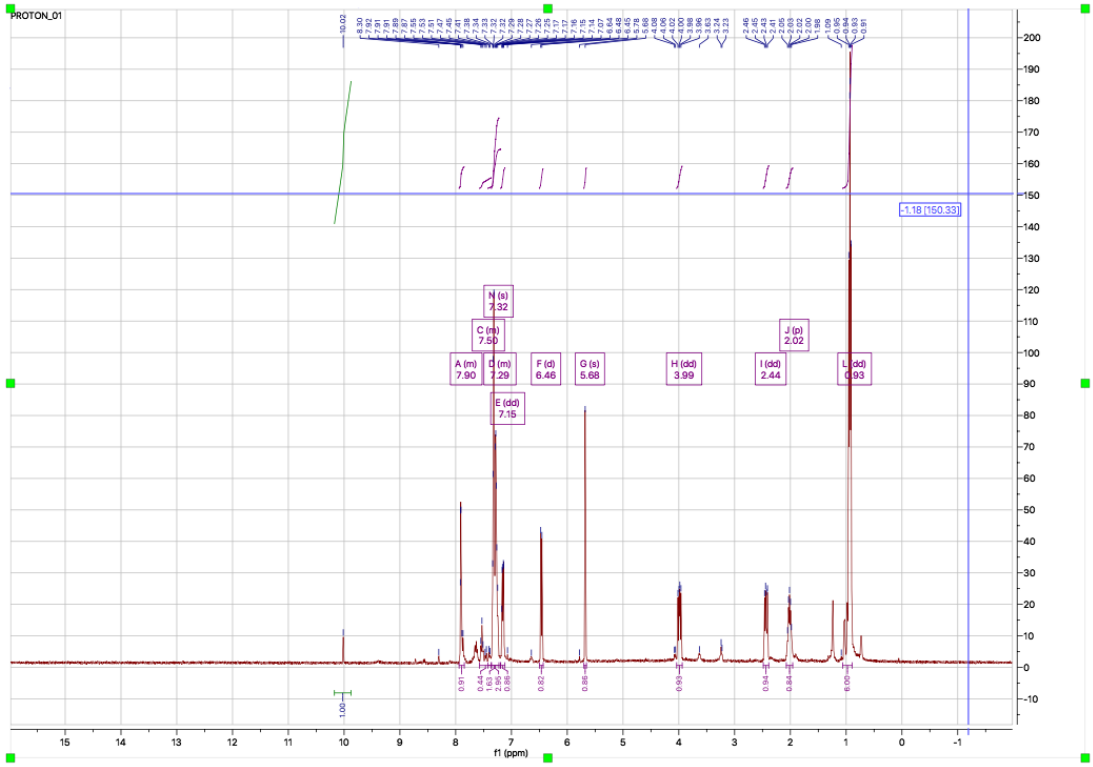
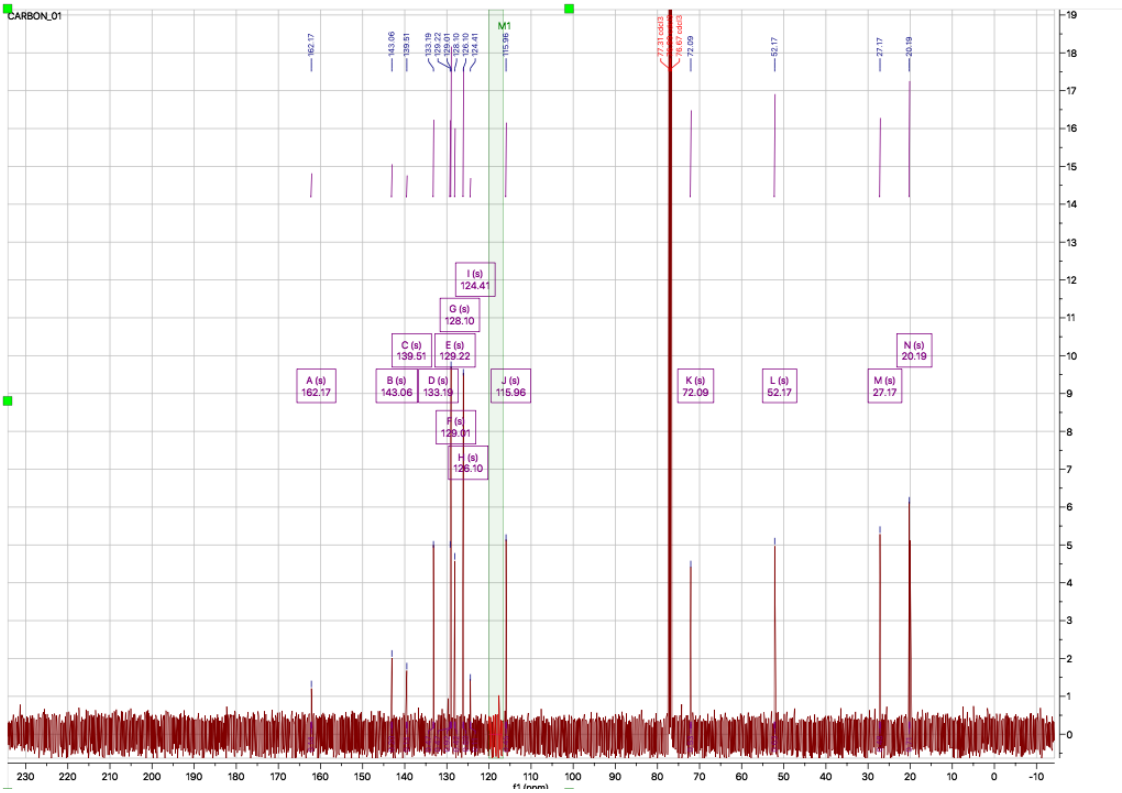


^{1}H and ^{13}C NMR spectra of **7b**







Computational studies of **3e**

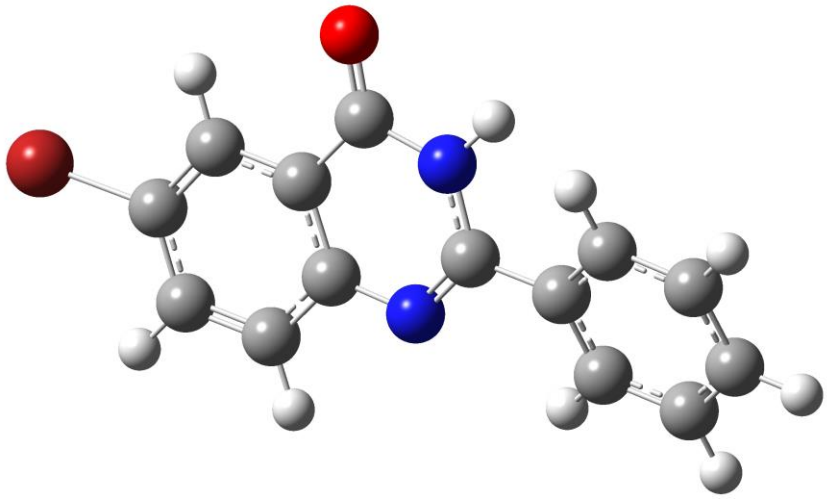


Figure S1. 3D structure of **3e** compound calculated at DFT/uB3LYP/6-31+G(d,p).

Computational data

Symbolic Z-matrix:
Charge = 0 Multiplicity = 1

C	–2.12396	0.7564	–0.02104
C	–2.95048	–0.34739	0.01483
C	–2.40766	–1.63895	0.05203
C	–1.03524	–1.82242	0.05389
C	–0.16897	–0.71246	0.0186
C	–0.7373	0.57829	–0.01901
C	0.13003	1.75768	–0.06804
N	1.20866	–0.9118	0.02548
C	1.99452	0.13257	–0.00807
N	1.49988	1.42442	–0.06314
O	–0.24416	2.93655	–0.11778
C	3.46353	–0.06606	0.00529
Br	–4.86553	–0.1271	0.01407
C	3.94809	–1.37629	–0.14037
C	4.37726	0.98585	0.16888
C	5.74921	0.73288	0.17119
C	6.22287	–0.57077	0.0131
C	5.31638	–1.62497	–0.13956
H	–2.51863	1.76296	–0.05209
H	–3.07443	–2.49027	0.07978
H	–0.59837	–2.81161	0.08381
H	2.13023	2.21826	–0.13607
H	3.2241	–2.17229	–0.24991
H	4.04069	2.00532	0.31963
H	6.44556	1.55251	0.30198
H	7.289	–0.76437	0.01353
H	5.67915	–2.63913	–0.25741

Overview Tab Data Section:
File Type = .log
Calculation Type = FREQ
Calculation Method = UB3LYP
Basis Set = 6-31+G(d,p)
Charge = 0
Spin = Singlet
Solvation = None
E(UB3LYP) = -3295.4519 Hartree
RMS Gradient Norm = 8.612e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 4.7534136 Debye
Polarizability (?) = 222.39667 a.u.
Point Group = C1
Job cpu time: 0 days 1 hours 41 minutes 54.0 seconds

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = –3295.4519 Hartree
Zero-point Energy Correction = 0.200116 Hartree
Thermal Correction to Energy = 0.213807 Hartree
Thermal Correction to Enthalpy = 0.214752 Hartree
Thermal Correction to Free Energy = 0.157549 Hartree
EE + Zero-point Energy = –3295.2518 Hartree
EE + Thermal Energy Correction = –3295.2381 Hartree
EE + Thermal Enthalpy Correction = –3295.2372 Hartree
EE + Thermal Free Energy Correction = –3295.2944 Hartree
E (Thermal) = 134.166 kcal/mol
Heat Capacity (Cv) = 53.868 cal/mol-kelvin
Entropy (S) = 120.394 cal/mol-kelvin

Opt Tab Data Section:
Step number = 1
Maximum force = 1.5e-05 Converged
RMS force = 4e-06 Converged
Maximum displacement = 0.001236 Converged
RMS displacement = 0.000295 Converged
Predicted energy change = –8.372796e-09 Hartree

Computational studies of **6a**

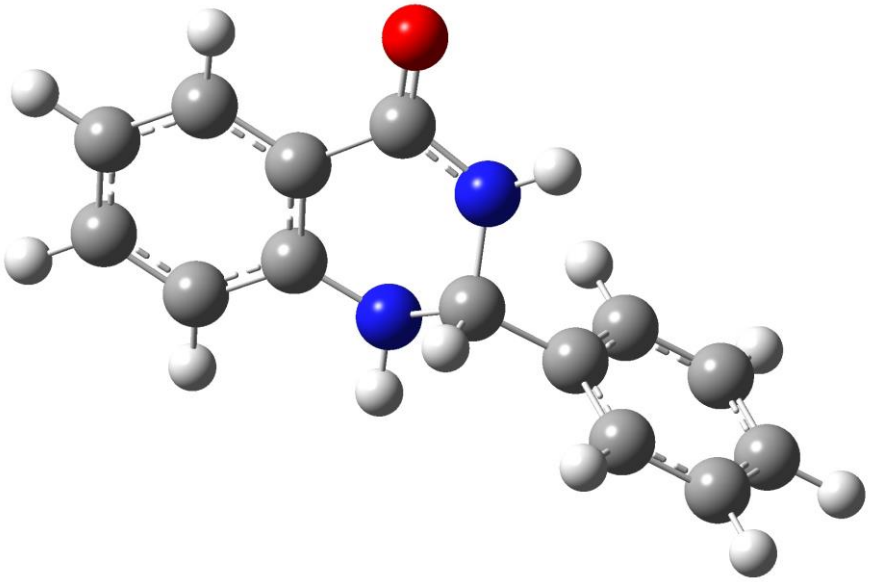


Figure 2. 3D structure of **6a** compound calculated at DFT/uB3LYP/6-31+G(d,p).

Computational data

Symbolic Z-matrix:
Charge = 0 Multiplicity = 1

C	4.40712	–0.47614	–0.01171
C	3.8464	–1.76025	0.04717
C	2.46547	–1.938	0.07244
C	1.61293	–0.82136	0.03672
C	2.1749	0.47375	–0.0127
C	3.56608	0.63255	–0.03578
N	0.22601	–0.95326	0.10371
C	–0.56311	0.10347	–0.52636
N	–0.06135	1.37464	–0.00489
C	1.28763	1.66627	0.03351
O	1.69521	2.82005	0.1495
H	–0.66891	2.18138	–0.07982
H	–0.1263	–1.88327	–0.08688
C	–2.04098	–0.06323	–0.22867
C	–2.49879	–0.10972	1.0963
C	–3.86032	–0.25632	1.36283
C	–4.77686	–0.35718	0.30969
C	–4.3264	–0.3116	–1.01095
C	–2.9611	–0.16538	–1.27756
H	5.4846	–0.34911	–0.03175
H	4.49299	–2.63312	0.06911
H	2.04124	–2.93785	0.11898
H	3.95927	1.64369	–0.06245
H	–0.42498	0.07546	–1.62459

H	–1.78249	–0.03045	1.90805
H	–4.20809	–0.29075	2.39121
H	–5.8365	–0.46999	0.51976
H	–5.03248	–0.38867	–1.83249
H	–2.6105	–0.1285	–2.30623

Overview Tab Data Section:
File Type = .log
Calculation Type = FREQ
Calculation Method = UB3LYP
Basis Set = 6-31+G(d,p)
Charge = 0
Spin = Singlet
Solvation = None
E(UB3LYP) = –725.51646 Hartree
RMS Gradient Norm = 1.8552e-05 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 5.2901742 Debye
Polarizability (?) = 183.637 a.u.
Point Group = C1
Job cpu time: 0 days 5 hours 7 minutes 58.0 seconds

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = –725.51646 Hartree
Zero-point Energy Correction = 0.232935 Hartree
Thermal Correction to Energy = 0.245886 Hartree
Thermal Correction to Enthalpy = 0.24683 Hartree
Thermal Correction to Free Energy = 0.192427 Hartree
EE + Zero-point Energy = –725.28353 Hartree
EE + Thermal Energy Correction = –725.27058 Hartree
EE + Thermal Enthalpy Correction = –725.26963 Hartree
EE + Thermal Free Energy Correction = –725.32404 Hartree
E (Thermal) = 154.296 kcal/mol
Heat Capacity (Cv) = 52.586 cal/mol-kelvin
Entropy (S) = 114.502 cal/mol-kelvin

Opt Tab Data Section:
Step number = 1
Maximum force = 8.2e-05 Converged
RMS force = 1.9e-05 Converged
Maximum displacement = 0.004332 Not converged
RMS displacement = 0.001188 Converged
Predicted energy change = –7.844738e-08 Hartree