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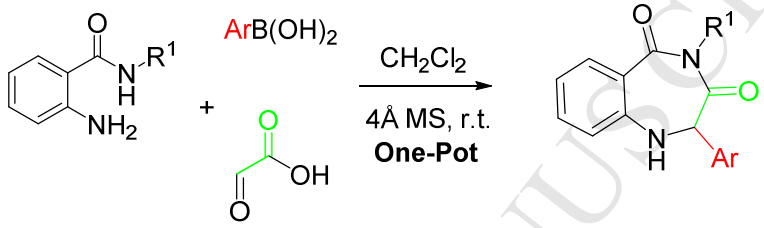

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ABSTRACT

A new design for the synthesis of 1,2-dihydro-4*H*-benzo[*e*][1,4]diazepine-3,5-diones based on Petasis reaction followed by intramolecular amidation in one-pot manner is reported. By employing different primary aromatic and aliphatic amines along with boronic acid derivatives, the desired products have been obtained at ambient temperature in moderate to good yields.

1. Introduction

After the first report on multi-component reaction (MCR) by Strecker,[1] many efforts have been devoted to investigate new types of this strategic pathway due to their importance in the synthesis of complex molecules.[2] A quick literature survey enabled us to claim that the vast majority of MCRs were founded by the reaction between amines and carbonyls. The enhanced tendency of the third component to the resultant adducts (like imines) compared to the parent carbonyl despite inherent electrophilic character kept chemists enthusiasm fresh to create effective compounds. Accordingly in 1993, the first application of boronic acids with the key pair of amine and carbonyl in multi-component reactions was reported by Petasis.[3] The boronic acid building block is mild, air-stable and non-toxic with reluctant character towards the carbonyl moiety providing the above mentioned factor.[4] Therefore, Petasis reaction known as the type II MCR according to Dömling and Ugi's classification,[5] has emerged as a promising strategy for the construction of structurally diverse molecules[6-8] with biological activities.[9]

Seven-membered heterocyclic rings are amongst the most appealing fragments owing to their prevalence in molecules with biological activities. Benzodiazepines, a prominent substructure in medicinal chemistry since the discovery of chlordiazepoxide and diazepam in the late 1950s,[10] represent a wide range of bioactivities.[11] Various derivatives of benzodiazepines have been reported to date regarding this point that every new inserted structural unit to benzodiazepine core donates new bioactivities to the molecule.

For instance, 1,4-benzodiazepine-2,5-diones showed herbicidal[12] properties whereas in the case of pyrrolo-[2,1-*c*][1,4] benzodiazepine-5,11-diones additional antitumor, analgesic and antiphage activities have been reported accompanied by the primary herbicidal activity.[13] Given the high level of activities, 1,4-benzodiazepine-3,5-dione analogues have received less attention. To date, reported routes have been limited to the intramolecular amide bond formation employing DCC (dicyclohexylcarbodiimide) as a coupling reagent[14] and Et_3N/ethyl chloroformate[15] to promote the cyclization. Recently, our group revealed an intermolecular cyclization of 2-aminobenzamides by means of dichloro epoxide under the Bargellini-type condition.[16] Therefore, considering the possible effects of structural variations on biological responses, we decided to serve 1,4-benzodiazepine-3,5-diones as an interesting goal to establish innovative synthetic pathway.

2. Results and discussion

In light of our interest in the synthesis of nitrogen-containing seven-membered rings[17] and 2-amino benzamide chemistry,[18] herein, we disclose the first multi-component synthesis of 1,2-

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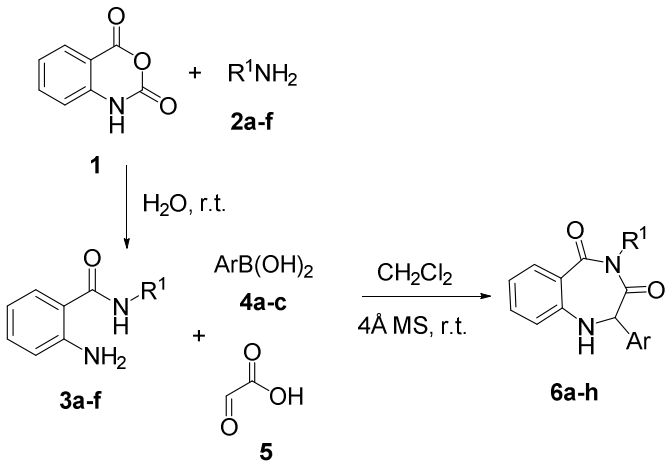
dihydro-4*H*-benzo[*e*][1,4]diazepine-3,5-diones starting from boronic acid derivatives **4a-c**, glyoxalic acid **5** and 2-amino-*N*-substituted benzamide derivatives **3a-f** in the presence of molecular sieves at ambient temperature (Scheme 1). Different benzamide derivatives were prepared via the simple reaction between isatoic anhydride **1** and various amines **2a-f** in water at room temperature.[16]



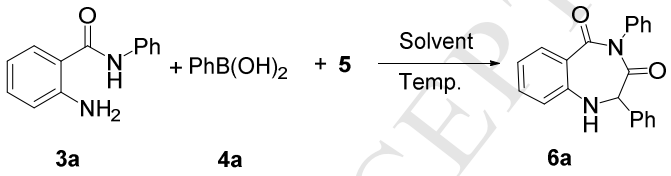
2a R^1 = Ph
2b R^1 = 4-Me-Bn
2c R^1 = 4-Cl-Bn
2d R^1 = 4-F-Bn
2e R^1 = 3,4-$(OMe)_2C_6H_3CH_2CH_2$
2f R^1 = *n*-Bu

4a Ar = Ph
4b Ar = 4-$OMeC_6H_4$
4c Ar = 4-FC_6H_4

Scheme 1. Synthesis of benzodiazepine-3,5-diones **6a-h**.

First, solvent screening (Table 1) for a simple model reaction between phenylboronic acid, 2-amino-*N*-phenylbenzamide and glyoxalic acid revealed dichloromethane as the solvent of choice and provided the product in 72% at room temperature (entry 6). It is noteworthy that increasing the temperature to reflux temperature resulted in reduced yield (entry 7).

Table 1. The optimization of the model reaction[a]



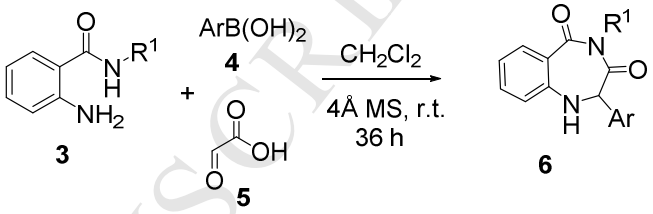
Entry	Solvent	Temperature	Time (h)	Yield[b] (%)
1	CH_3CN	r.t.	36	43
2	DMF	r.t.	36	39
3	THF	r.t.	36	26
4	EtOH	r.t.	36	41
5	MeOH	r.t.	36	14
6	CH_2Cl_2	r.t.	36	72
7	CH_2Cl_2	reflux	48	29
8[c]	CH_2Cl_2	r.t.	48	35

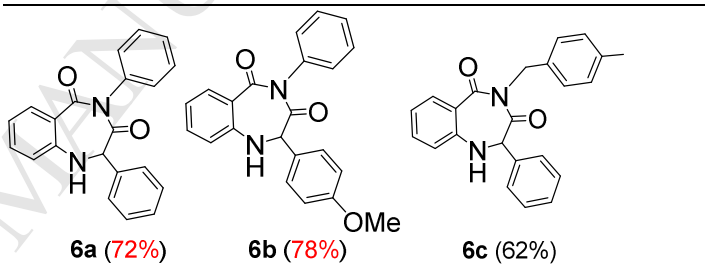
[a] **3a** (1.2 mmol), **4a** (1 mmol) and **5** (1 mmol) and molecular sieves (200 mg) in solvent (4 mL). [b] Isolated yield. [c] Without molecular sieves.

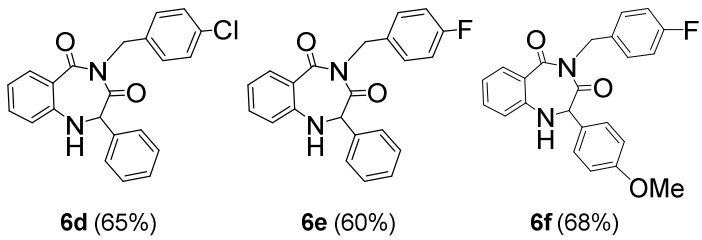
The role of activated molecular sieves in speeding up the reaction was clearly observed by performing the reaction in the absence of the drying agent (entry 8). The increased rate would be attributed to the facile formation of imine upon removal of water from the reaction medium which shifts the equilibrium to the desired product.

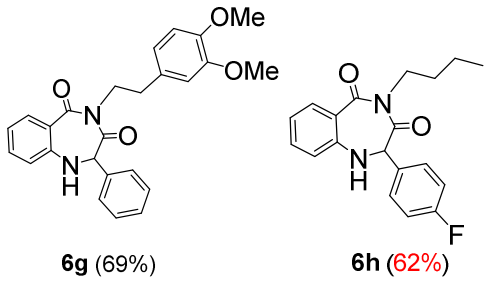
With these results in hand, the scope of the reaction has been explored for 2-amino-*N*-substituted benzamide derivatives synthesized via different primary amines and phenylboronic acids bearing electron-withdrawing or electron-donating substituents. The reaction smoothly furnished **6a-h** in 60-78% yields by combining these reagents in three-component fashion. However, utilizing electron-rich boronic acid led to the better results compared to unsubstituted derivatives.

Table 2. Investigation of substrate scope[a,b]





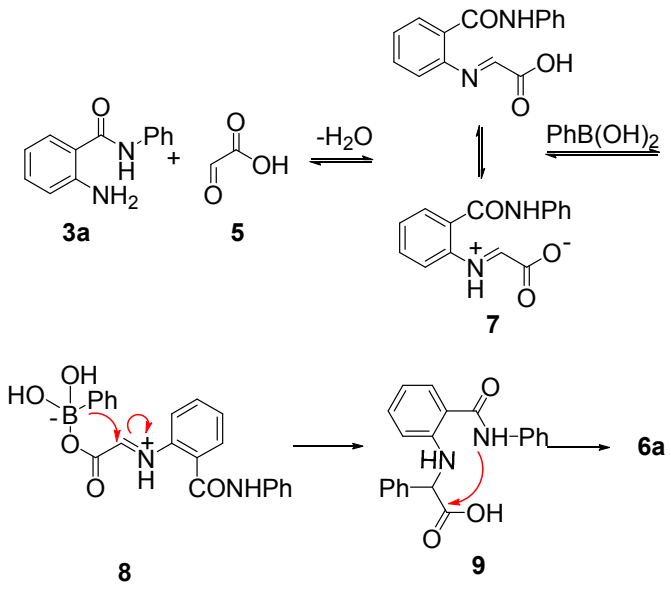




[a] Reaction condition **3** (1 mmol), **4** (1.2 mmol), **5** (1 mmol) and molecular sieves 4Å (200 mg) in 4 mL CH_2Cl_2. [b] Isolated yields.

A mechanistic rationalization according to the previous studies is depicted in Scheme 2.[19,20] 2-Aminobenzamide derivatives formed in situ from isatoic anhydride and amine derivatives undergo condensation with aldehyde component of glyoxalic acid to generate imine intermediate **7**. The reaction of boronic acid with **7** leads to the formation of ate complex **8**. Based on DFT

calculation, the irreversible and rate-limiting transfer of boron substituent occurs through five-membered transition state. Then, intramolecular amidation affords **6a** in 72% yield.



Scheme 2. Plausible pathway for the reaction.

3. Conclusion

In summary, our interest in the synthesis of medium-sized heterocycles led us to discover an unprecedented approach to 1,4-benzodiazepine-3,5-diones through Petasis reaction followed by lactamization. Mild condition, simplicity, available reactants and high yields are considered as the advantageous features of this novel multi-component reaction. We are completely assured that this work will inspire researchers seeking for new ways to unique synthetic fragments.

4. Experimental section

4.1. General

Commercially available reagents were used without further purification. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker FT-400, 500, using TMS as an internal standard. IR spectra were obtained with a Shimadzu 470 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysen system GmbH Vario ELCHNS mode.

4.2. General procedure for the synthesis of 6a

To a magnetically stirred solution of 2-amino-*N*-phenyl benzamide (1 mmol), glyoxalic acid (50%, 1 mmol) and 4Å molecular sieves (200 mg) in CH_2Cl_2 (4 mL) was added phenylboronic acid (1.2 mmol). The mixture was stirred at room temperature for 36 h, then the solvent was removed under reduced pressure and the residue was purified by silica column chromatography with gradient solvent system starting from ethyl acetate to ethyl acetate/ethanol (5:1). The product was recrystallized from petroleum ether/ethyl acetate (1:1) to afford **6a** as a white powder.

4.2.1. 2,4-diphenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6a**). (236 mg, 72%); white powder; mp: 117-119 °C; IR (KBr): 3309 (NH), 1685, 1635, 1246, 741, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (s, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.23-7.25 (m, 1H), 7.32-7.40 (m, 4H), 7.52-7.56 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 2H), 8.27 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.57 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.8, 113.0, 116.4, 120.7, 124.6, 127.3, 127.5, 128.0, 129.0, 132.7, 133.2, 133.3, 133.4, 133.5, 135.6, 167.8, 175.2; MS: m/z (%) = 328 (M$^+$, 23), 251 (100), 174 (45), 146 (33), 104 (51), 77 (84); Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.85; H, 4.88; N, 8.54.

4.2.2. 2-(4-methoxyphenyl)-4-phenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6b**). Yield (279 mg, 78%); white powder; mp: 110-112 °C; IR (KBr): 3322 (NH), 1698, 1645, 856, 745, 687 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.70 (s, 3H), 5.04 (s, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.33-7.37 (m, 4H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 8.62 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.1, 59.2, 112.4, 113.9, 114.7, 116.5, 120.6, 123.5, 128.2, 128.6, 129.1, 131.3, 132.4, 139.2, 147.1, 158.6, 168.0, 173.2; Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.73; H, 5.12; N, 7.81.

4.2.3. 4-(4-methylbenzyl)-2-phenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6c**). Yield (221 mg, 62%); white powder; mp: 176-178 °C; IR (KBr): 3213 (NH), 1686, 1654 1306, 862, 764, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 4.60 (d, *J* = 4.0 Hz, 2H), 5.16 (s, 1H), 6.34 (t, *J* = 5.2 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.61 (t, *J* = 7.2 Hz, 1H), 7.17-7.21 (m, 3H), 7.25-7.27 (m, 2H), 7.33-7.40 (m, 3H), 7.56 (d, *J* = 7.4 Hz, 2H), 8.78 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 43.7, 60.6, 112.8, 116.0, 116.2, 127.3, 127.4, 128.0, 128.5, 129.0, 129.5, 132.9, 134.9, 136.9, 137.4, 147.4, 169.3, 175.0; Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.45; H, 5.69; N, 7.84.

4.2.4. 4-(4-chlorobenzyl)-2-phenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6d**). Yield (244 mg, 65%); white powder; mp: 190–191 °C; IR (KBr): 3319 (NH), 1687, 1631, 1391, 1235, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 5.6 Hz, 2H), 5.15 (s, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.58 (t, *J* = 5.4 Hz, 1H), 6.64 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.24-7.28 (m, 2H), 7.32-7.34 (m, 2H), 7.37-7.42 (m, 2H), 7.46-7.49 (m, 1H), 7.54 (d, *J* = 6.8 Hz, 2H), 8.70 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$):δ = 41.8, 60.6, 112.9, 116.3, 127.2, 127.3, 127.4, 128.5, 129.0, 129.1, 129.6, 130.4, 133.0, 133.8, 135.5, 147.5, 167.5, 173.9; Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.13; H, 4.69; N, 7.34.

4.2.5. 4-(4-fluorobenzyl)-2-phenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6e**). Yield (216 mg, 60%); white powder; mp: 123-125 °C; IR (KBr): 3299 (NH), 1698, 1645, 1286, 1145, 764, 855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 (s, 2H), 5.12 (s, 1H), 6.39 (m, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.62 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.30-7.36 (m, 5H), 7.54 (d, *J* = 7.2 Hz, 2H), 8.73 (brs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.1, 60.8, 112.9, 115.5, 121.9, 124.2, 125.2, 126.0, 127.3, 128.4, 128.9, 129.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 131.1, 133.0, 147.7, 159.4 (d, $J_{C\text{-}F}$ = 202.2 Hz), 169.8, 171.3; Anal. Calcd for $C_{22}H_{17}FN_2O_2$: C, 73.32; H, 4.75; N, 7.77. Found: C, 73.28; H, 4.83; N, 7.76.

4.2.6. 4-(4-fluorobenzyl)-2-(4-methoxyphenyl)-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6f**). Yield (265 mg, 68%); white powder; mp: 103-105 °C; IR (KBr): 3359 (NH), 1678, 1665, 1281, 1009, 859 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 3.67 (s, 3H), 4.44 (s, 2H), 5.09 (s, 1H), 6.33-6.45 (m, 2H), 6.80 (m, 2H), 7.05-7.15 (m, 3H), 7.33-7.37 (m, 2H), 7.56 (s, 1H), 8.27-8.33 (m, 2H), 8.47 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 41.6, 55.0, 60.5, 112.4, 113.4, 113.8, 114.9, 115.1, 115.3, 128.1 (d, J_{C-F} = 25.3 Hz), 129.1 (d, J_{C-F} = 7.2 Hz), 132.0, 132.8, 136.3, 147.6, 158.2 (d, J_{C-F} = 246.9 Hz), 162.1, 168.9, 174.5; Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18. Found: C, 70.73; H, 4.87; N, 7.20.

4.2.7. 4-(3,4-dimethoxyphenethyl)-2-phenyl-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6g**). Yield (287 mg, 69%); white powder; mp: 144–146 °C; IR (KBr): 3389 (NH), 1672 1632, 1278, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.88 (t, *J* = 6.8 Hz, 2H), 3.71 (dd, *J* = 12.8, 6.4 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 5.15 (s, 1H), 6.16 (t, *J* = 5.4 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.58 (t, *J* = 7.2 Hz, 1H), 6.77-6.85 (m, 2H), 7.15-7.21 (m, 2H), 7.32-7.39 (m, 3H), 7.55 (d, *J* = 6.8 Hz, 2H), 8.73 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.1, 41.0, 55.8, 55.9, 60.6, 111.4, 111.9, 112.8, 115.9, 116.1, 120.7, 127.2, 127.3, 128.4, 129.0, 131.4, 132.8, 137.0, 147.3, 147.7, 149.1, 169.6, 174.6; Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.13; H, 5.82; N, 6.87.

4.2.8. 4-butyl-2-(4-fluorophenyl)-1,2-dihydro-3H-benzo[e][1,4]diazepine-3,5(4H)-dione (**6h**). (202 mg, 62%); white powder; mp: 151–152 °C; IR (KBr): 3201 (NH), 1671, 1634, 1140, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H), 1.42 (m, 2H), 1.59 (quint, *J* = 7.4 Hz, 2H), 3.45 (dd, *J* = 12.8, 6.8 Hz, 2H), 5.10 (s, 1H), 6.19 (m, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 8.6 Hz, 2H), 7.17 (dt, *J* = 7.8, 0.4 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 8.4, 5.2 Hz, 1H), 8.82 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 31.6, 39.7, 60.0, 112.8, 115.7, 115.9, 116.2, 116.4, 127.3, 128.9 (d, J_{C-F} = 8.1 Hz), 132.7 (d, J_{C-F} = 22.1 Hz), 147.1, 161.4 (d, J_{C-F} = 245.5 Hz), 169.7, 174.5; Anal. Calcd for $C_{19}H_{19}FN_2O_2$: C, 69.92; H, 5.87; N, 8.58. Found: C, 69.96; H, 5.87; N, 8.65.

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Supporting information

^1H and ^{13}C NMR spectra were provided as Supplementary data.

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Supporting Information

Efficient multi-component synthesis of 1,4-benzodiazepine-3,5-diones: a Petasis-based approach

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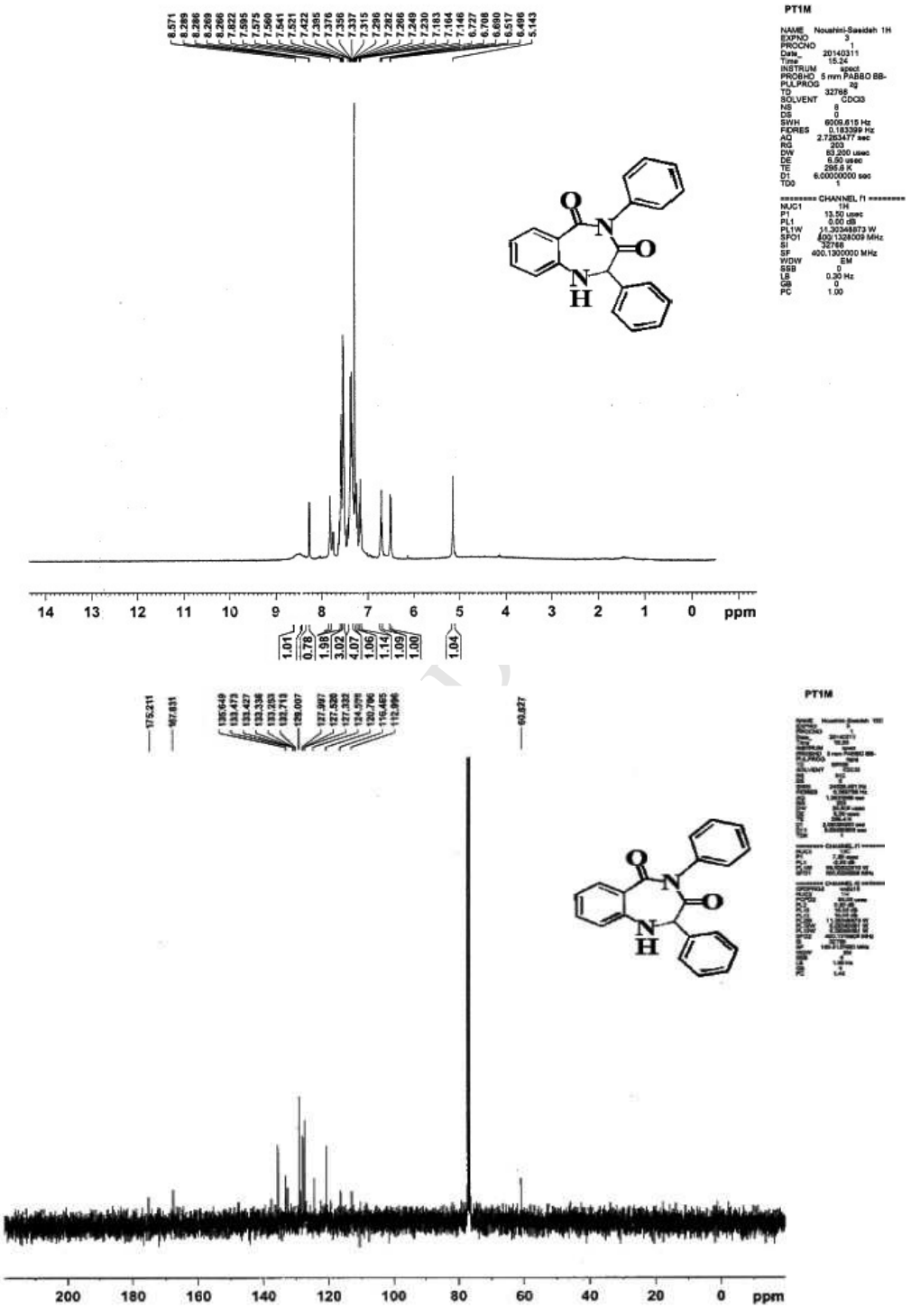
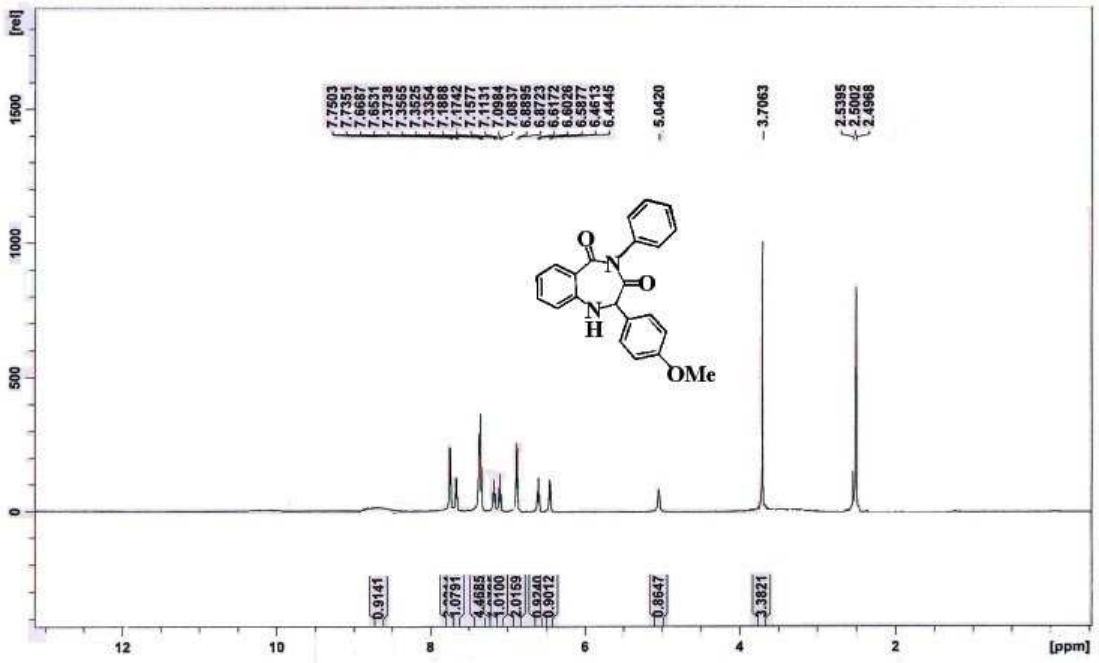
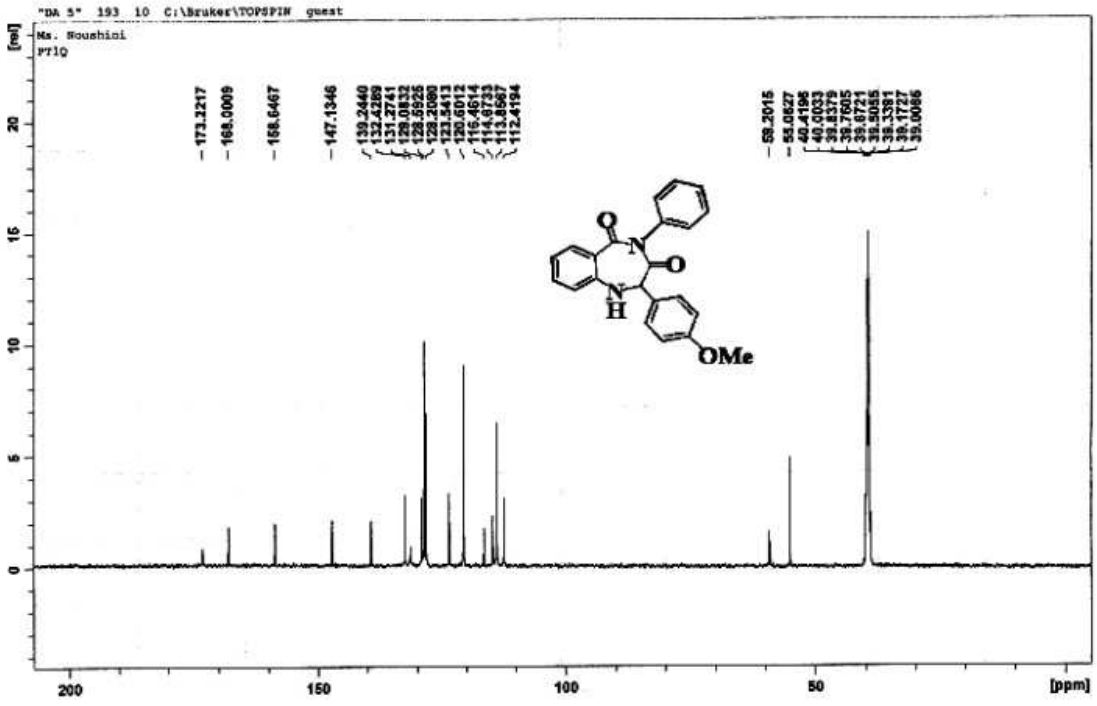
Copies of ^{1}H-NMR and ^{13}C-NMR

^{1}H and ^{13}C-NMR Spectra of compound 6a ($CDCl_3$, 400 MHz)

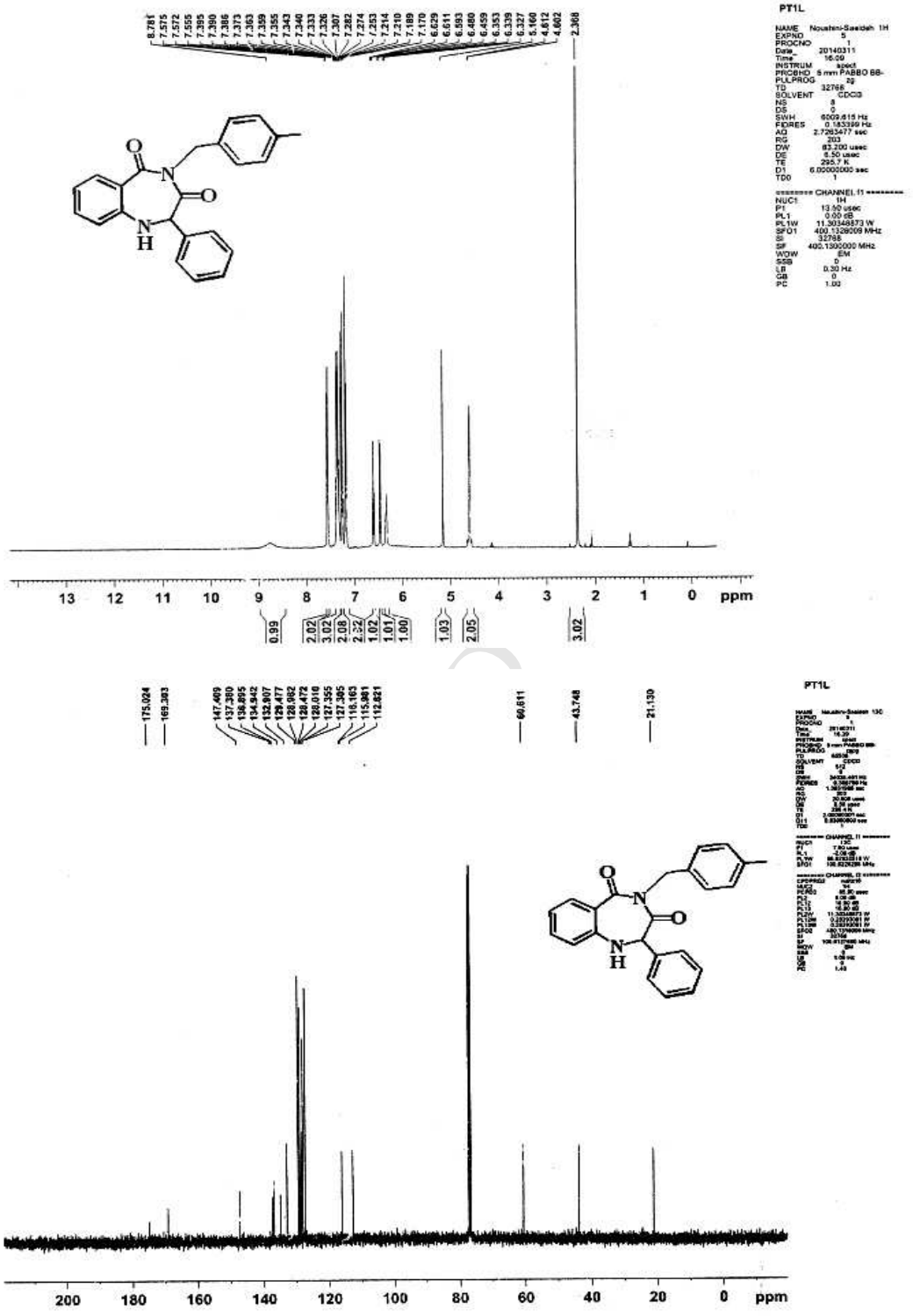


^{1}H and ^{13}C-NMR Spectra of compound 6b (DMSO, 500 MHz)





^{1}H and ^{13}C-NMR Spectra of compound 6c ($CDCl_3$, 400 MHz)



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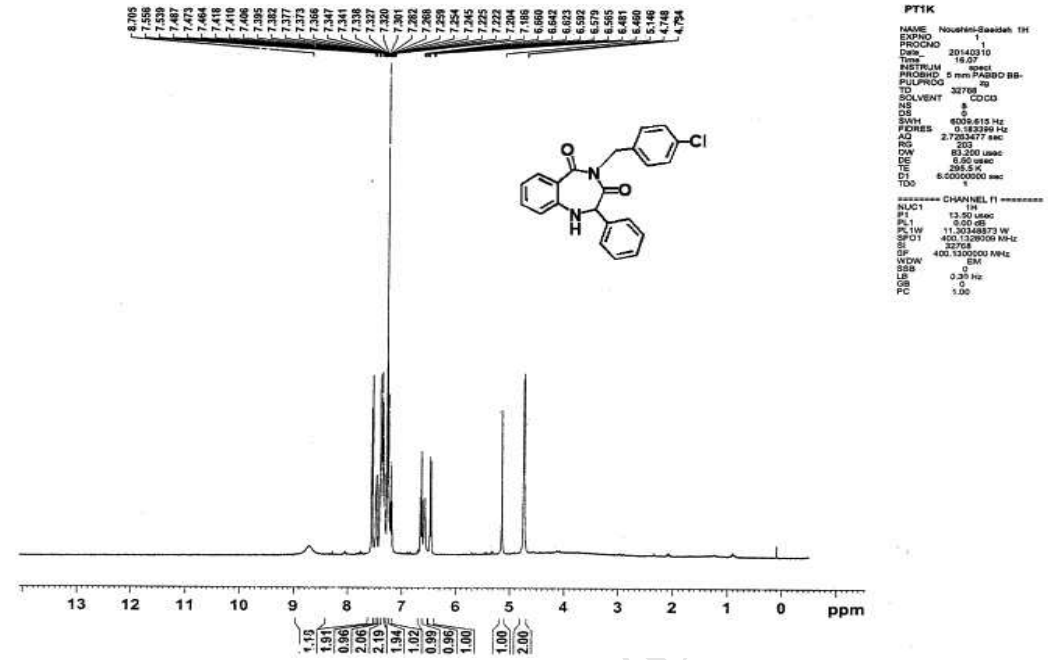
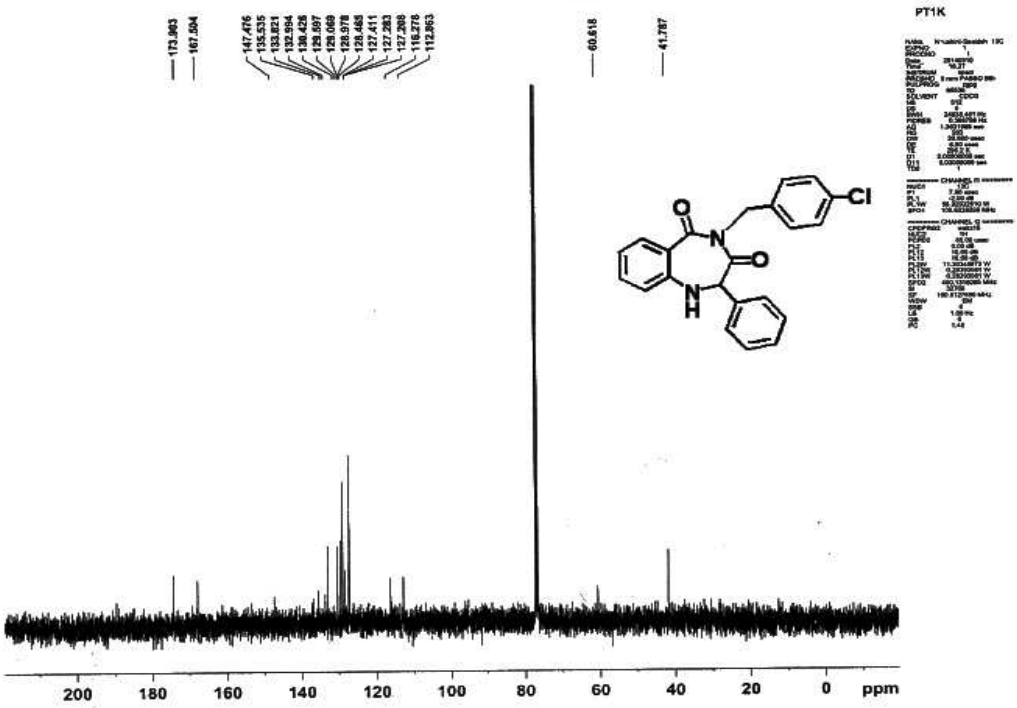
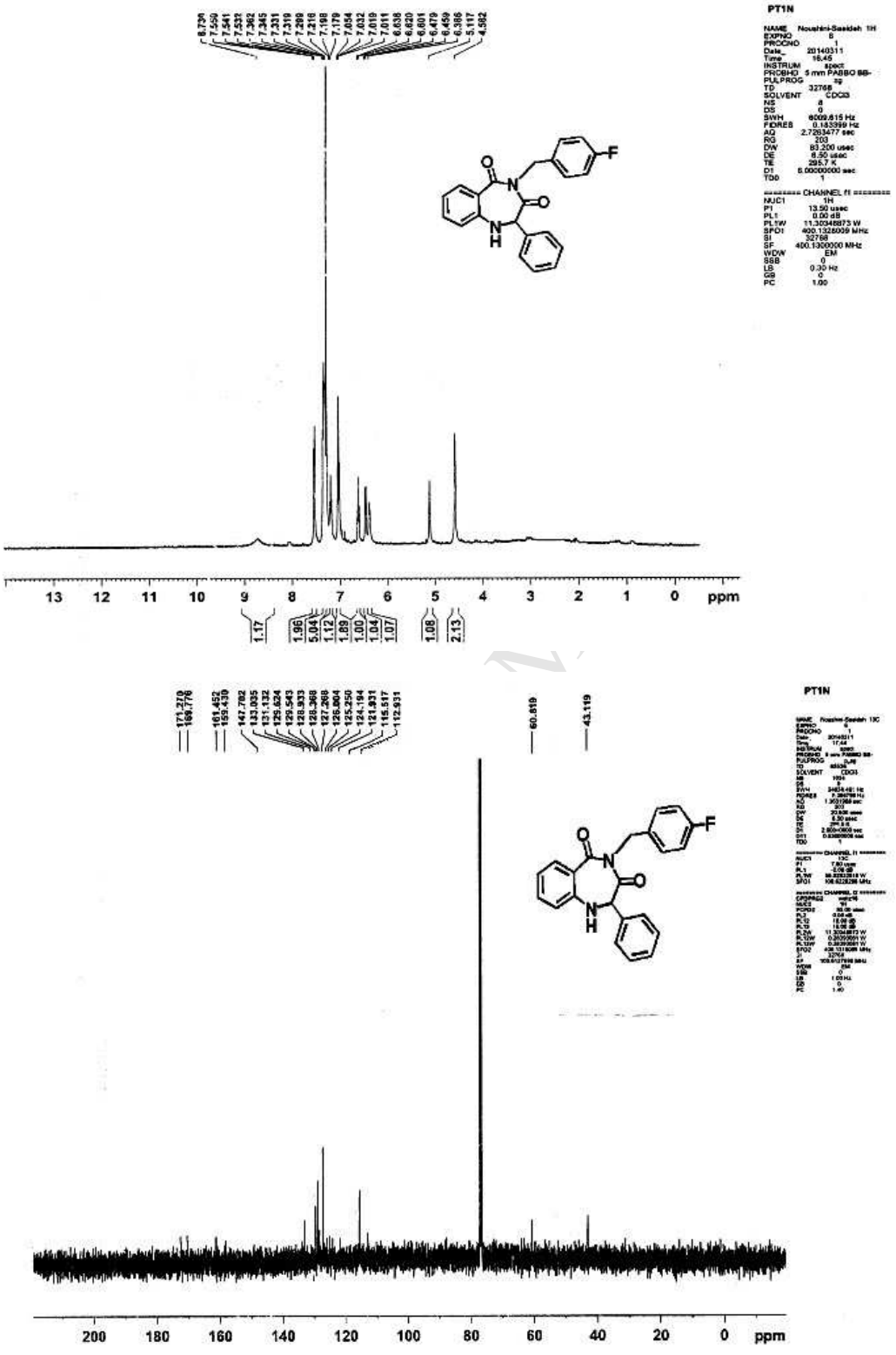




^{1}H and ^{13}C-NMR Spectra of compound 6e ($CDCl_3$, 400 MHz)



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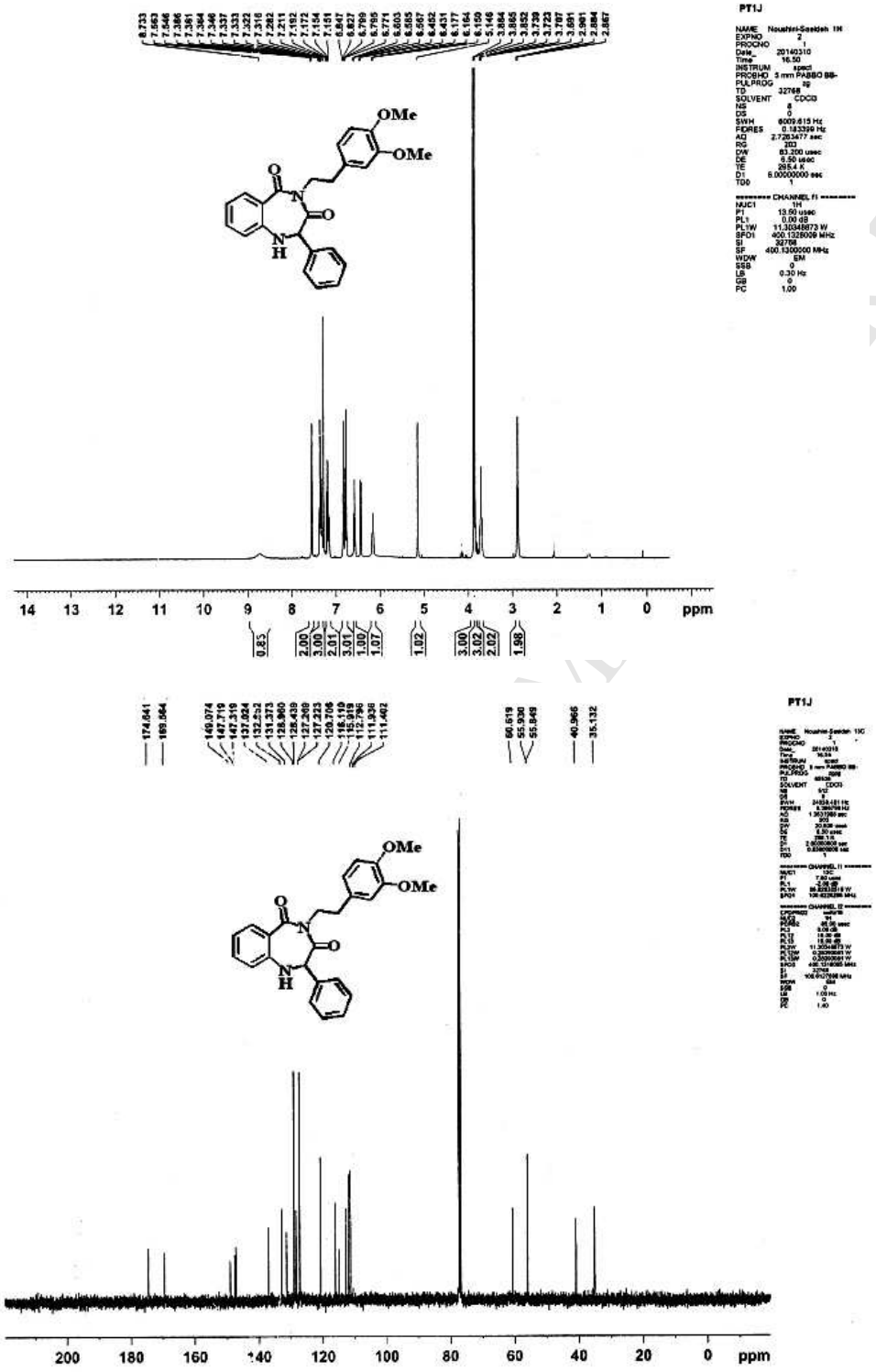

^{1}H and ^{13}C-NMR Spectra of compound 6h ($CDCl_3$, 400 MHz)