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Graphical Abstract

Synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives promoted by EtOH-AcOH solvent system

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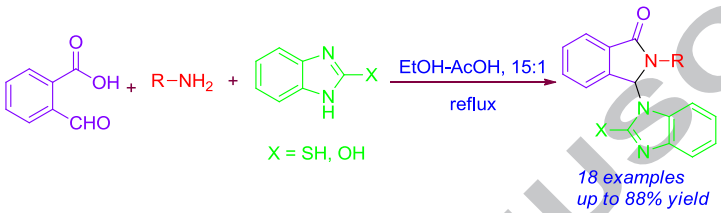

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Synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives promoted by EtOH-AcOH solvent system

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ABSTRACT

A simple and efficient method for the synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives by a one-pot, three-component condensation reaction of phthalaldehydic acid, primary amine, and 2-mercaptobenzimidazole or 2-hydroxybenzimidazole is described. By using EtOH-AcOH (v/v, 15:1) as the solvent system, the reaction proceeds smoothly to give corresponding products in good yields.

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Isoindolin-1-one derivatives have been reported to possess diverse pharmacological properties, such as antihypertensive,[1] antiulcer,[2] anesthetic,[3] antipsychotic,[4] as well as efficacy as vasodilatory agents.[5] In recent year, the alkaloids containing the isoindolin-1-one core unit have been received wide attention as they are found to be potent MDM2-p53 interaction inhibitors,[6] and U-II receptor antagonists.[7] Moreover, isoindolin-1-ones are also used as the important synthons for the synthesis of various drugs[8] and natural products.[9] Therefore, due to the importance of isoindolin-1-one derivatives, it is of great value to develop simple and efficient method for the synthesis of the compounds containing isoindolin-1-one core unit.

One-pot multi-component reactions (MCRs) by virtue of their convergence, productivity, facile execution, and high yield have attracted considerable attention in recent years.[10] MCRs have been also considered as one of the most efficient methods to construct heterocyclic compounds from simple starting materials in a single operation.[11] As part of a continuing effort in our laboratory toward the development of new multi-component condensation reactions, and the development of mild and practical protocols for the synthesis of useful heterocyclic compounds,[12] herein we wish to report that a three-component condensation reaction can be carried out effectively to obtain 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives in satisfactory yields using phthalaldehydic acid, primary amine, and 2-mercaptobenzimidazole or 2-hydroxybenzimidazole as the starting materials. To the best of our knowledge, this is the first report for the synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives (Scheme 1).

Initially, we studied the three-component condensation reaction of phthalaldehydic acid **1** (3 mmol) with benzylamine **2a** (3.6 mmol), and 2-mercaptobenzimidazole **3a** (3 mmol) in 5 mL EtOH at reflux temperature for 12 h to obtain the desired product **4aa** in 45% yield. To further improve the yields of this synthetic approach, various solvents had been applied to promote this transformation and the results are summarized in Table 1.

As shown in Table 1, the usual organic solvents, such as EtOH, MeOH, MeCN, THF, DCM, DMF, DMSO, and H_2O, proved to be ineffective, and low yields (0-45%) of the desired product **4aa** were obtained in these solvents (Table 1, entries 1-8). In our preliminary studies, we have investigated the multi-component reaction of 2-cyanobenzaldehyde, amine, and EtOH, using EtOH-AcOH as the solvent system, to obtain the corresponding 2-substituent-3-alkoxy-isoindolin-1-imine derivatives.[13] Threrfore, we carried out the reaction of phthalaldehydic acid **1**, benzylamine **2a**, and 2-mercaptobenzimidazole **3a** in 5 mL EtOH-AcOH (10:1, v/v) as the solvent at reflux temperature for 4 h. To our surprise, we discovered that the solvent of EtOH-AcOH was also effective to obtain the product **4aa** in 80% yield (Table 1, entry 11). In order to improve the reaction efficiency, we varied the volume ratios of EtOH and AcOH, when a ratio of 15:1 was used, the product **4aa** was isolated in the highest yield (84%).

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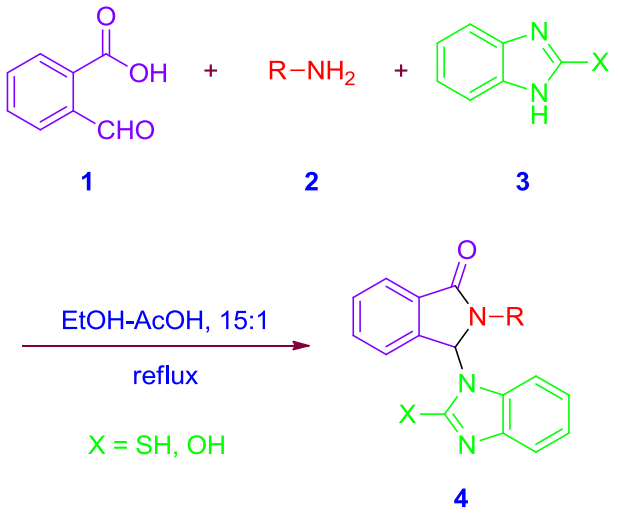
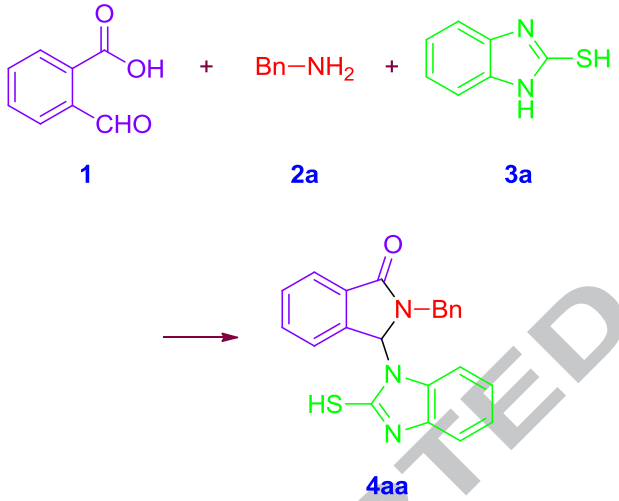


Scheme 1 The condensation of phthalaldehydic acid **1**, primary amine **2**, and 2-mercaptobenzimidazole **3a** or 2-hydroxybenzimidazole **3b**

Table 1. Optimization of the reaction conditions[a]



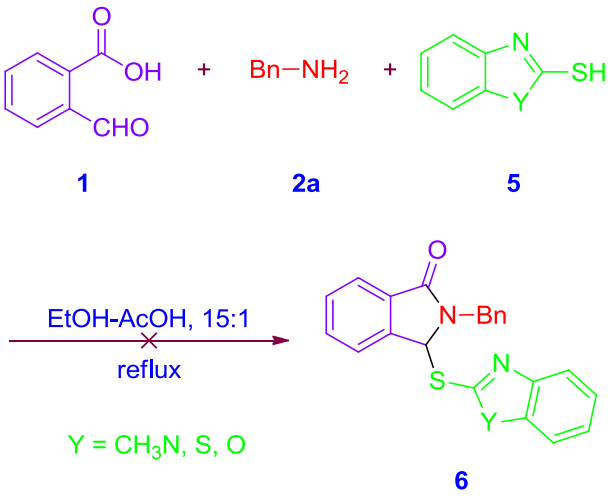
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	EtOH	reflux	12	45
2	MeOH	reflux	12	20
3	MeCN	reflux	12	25
4	THF	reflux	12	30
5	DCM	reflux	12	0
6	DMF	80	12	35
7	DMSO	80	12	35
8	H_2O	80	12	0
9	EtOH-AcOH (3:1, v/v)	reflux	3	70
10	EtOH-AcOH (5:1, v/v)	reflux	3	74
11	EtOH-AcOH (10:1, v/v)	reflux	4	80
12	EtOH-AcOH (15:1, v/v)	reflux	4	84
13	EtOH-AcOH (20:1, v/v)	reflux	6	80
14	EtOH-AcOH (30:1, v/v)	reflux	6	55

[a]Reaction conditions: Phthalaldehydic acid **1** (3 mmol), benzylamine **2a** (3.6 mmol), and 2-mercaptobenzimidazole **3a** (3 mmol), solvent (5 mL).

[b]Isolated yields.

Moreover, we also carried out the reaction in the presence of 20 mol % Brønsted acids or Lewis acids, such as *p*-TsOH, sulfamic acid, $ZnCl_2$ and $Cu(OTf)_2$, as the catalysts in EtOH under reflux for 12 h. However, only moderate yields (50-60%) of the desired product **4aa** were obtained. Therefore, the best reaction conditions were obtained by using EtOH- AcOH (15:1, v/v) as the solvent under reflux temperature.

In order to gauge the scope of these conditions, several amines and benzimidazole analogues were examined under the optimized conditions using EtOH-AcOH (v/v, 15:1) as the solvent system.[14,15] The results have been summarized in Table 2, which clearly indicates the generality and scope of the reaction with respect to various aryl-alkyl, heteroaryl-alkyl, and alkyl amines. In all cases studied, the three-component reaction using aryl-alkyl as starting materials proceeded smoothly to give the corresponding **4** in good yields. Moreover, moderate yields of the corresponding products **4** were obtained when using heteroaryl-alkyl, or alkyl amines as substrates. In order to study the steric effects on this three-component condensation reaction, amines, including *iso*-propylamine **2k**, cyclopentylamine **2l**, and *tert*-butylamine **2n** were investigated (Table 2, entries 17, 18, 20). The results revealed that the reaction could proceed smoothly when using *iso*-propylamine **2k** and cyclopentylamine **2l** as starting materials to obtained desired product **4kb** and **4lb** in 58% and 60% yields, respectively. However, the reaction was sluggish when using *tert*-butylamine **2n** as substrate, and the desired product **4nb** was not determined by LC-MS. Furthermore, we also carried out the reaction with aromatic amine under similar reaction conditions, unfortunately, no products were observed (Table 2, entry 19).



Scheme 2 To exam whether the mercapto could be as the nucleophilic group

In this three-component reaction, 2-mercaptobenzimidazole **3a** or 2-hydroxybenzimidazole **3b** were employed to synthesis 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives **4**. The results indicated that both **3a** and **3b** could react to give corresponding products. The yields of the products were somewhat lower when using 2-hydroxybenzimidazole **3b** (58–80%) as a substrate than using 2-mercaptobenzimidazole **3a** (74–88%). Furthermore, we also carried out the reaction of phthalaldehydic acid **1**, benzylamine **2a**, and benzimidazole by using EtOH- AcOH (15:1, v/v) as the solvent under reflux temperature. The result showed that this three-component reaction could not take place, which demonstrated that the 2-mercapto or 2-hydroxy of benzimidazole were very important for this three-component reaction.

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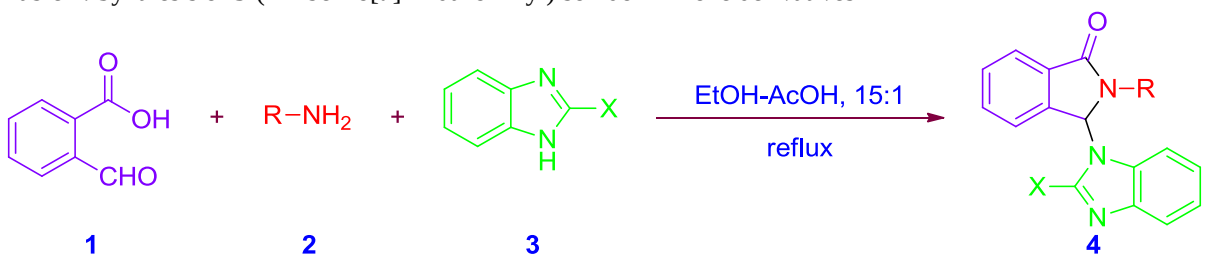
Table 2. Synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives[a]

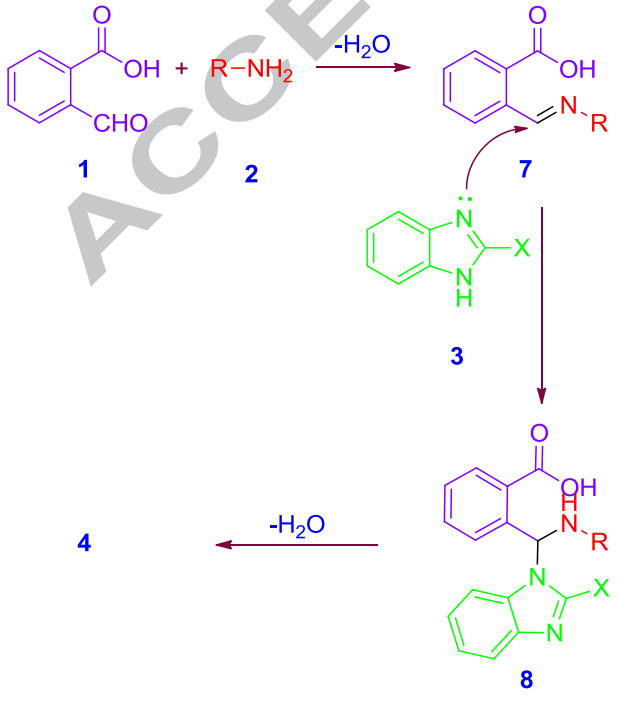


1 2 3 4

Entry	R	X	Time (h)	Product **4**	Yield of **4** (%)[b]
1	$C_6H_5CH_2$ **2a**	SH **3a**	4	**4aa**	84
2	4-$ClC_6H_4CH_2$ **2b**	SH **3a**	4	**4ba**	81
3	4-$FC_6H_4CH_2$ **2c**	SH **3a**	4	**4ca**	86
4	4-$CH_3OC_6H_4CH_2$ **2d**	SH **3a**	4	**4da**	80
5	3,4-$(CH_3O)_2C_6H_3CH_2$ **2e**	SH **3a**	5	**4ea**	82
6	3,4-$(CH_3O)_2C_6H_3CH_2$ CH_2 **2f**	SH **3a**	5	**4fa**	88
7	Pyridin-3-ylmethyl **2g**	SH **3a**	3	**4ga**	78
8	Furan-2-ylmethyl **2h**	SH **3a**	3	**4ha**	78
9	$CH_3CH_2CH_2$ **2i**	SH **3a**	3	**4ia**	74
10	$CH_3CH_2CH_2CH_2$ **2j**	SH **3a**	3	**4ja**	77
11	$C_6H_5CH_2$ **2a**	OH **3b**	5	**4ab**	72
12	4-$ClC_6H_4CH_2$ **2b**	OH **3b**	5	**4bb**	70
13	3,4-$(CH_3O)_2C_6H_3CH_2$ CH_2 **2f**	OH **3b**	5	**4fb**	65
14	Pyridin-3-ylmethyl **2g**	OH **3b**	5	**4gb**	60
15	$CH_3CH_2CH_2$ **2i**	OH **3b**	5	**4ib**	78
16	$CH_3CH_2CH_2CH_2$ **2j**	OH **3b**	5	**4jb**	80
17	$(CH_3)_2CH$ **2k**	OH **3b**	5	**4kb**	58
18	Cyclopentyl **2l**	OH **3b**	5	**4lb**	60
19	C_6H_5 **2m**	OH **3b**	12	**4mb**	0
20	$(CH_3)_3C$ **2n**	OH **3b**	12	**4nb**	0

[a]Reaction conditions: Phthalaldehydic acid **1** (3 mmol), primary amine **2** (3.6 mmol), and 2-mercaptobenzimidazole **3a** or 2-hydroxybenzimidazole **3b** (3 mmol), EtOH-AcOH (15:1, v/v), reflux.

[b]Isolated yields.



Scheme 3 The probable mechanism for the formation of compound **4**

It was well known that mercapto was an important nucleophilic group in organic chemistry. And the compounds containing mercapto were used widely as the nucleophilic reagents in organic synthesis.[16] Hence, 1-methyl-2-mercaptobenzimidazole **5a**, 2-mercaptobenzothiazole **5b**, and 2-mercaptobenzoxazole **5c** were chosen as the starting materials to exam whether the mercapto could be as the reaction group to form corresponding products **6** (Scheme 2). Unfortunately, none of **5a**, **5b** or **5c** could react to give the product **6**.

On the basis of the experimental results, a possible mechanism for the formation of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives **4** is presented in Scheme 3. The initial step in this reaction is the nucleophilic attack of amine **1** to formyl group to afford the imine intermediate **7**, which subsequently reacts with **3** to form another intermediate **8**, and intermediate **8** undergoes an intramolecular cyclization to give the final product **4**.

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives **4** using EtOH-AcOH (v/v, 15:1) as the solvent system. For all the presented reactions, EtOH-AcOH solvent was used, which is relatively environmentally benign and supporting 'green chemistry'. Moreover, the simple experimental procedure combined with the easy workup and good yields of products are salient features of the presented method.

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Acknowledgments

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14. **General procedure for the synthesis of compounds 4aa-4ja**: A mixture of phthalaldehydic acid **1** (3 mmol), amine **2** (3.6 mmol), and 2-mercaptobenzimidazole **3a** (3 mmol) in EtOH-AcOH (5 mL, v/v, 15:1) was refluxed for 3-5 h. After completion of the reaction (TLC), the solid was filtered off, washed with water and further purified by recrystallisation from ethanol (5 mL) to yield pure products **4aa-4ja**.
15. **General procedure for the synthesis of compounds 4ab-4lb**: A mixture of phthalaldehydic acid **1** (3 mmol), amine **2** (3.6 mmol), and hydroxybenzimidazole **3b** (3 mmol) in EtOH-AcOH (5 mL, v/v, 15:1) was refluxed for 5 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford the corresponding products **4ab-4lb**.
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Supporting Information

Synthesis of 3-(1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one derivatives promoted by EtOH-AcOH solvent system

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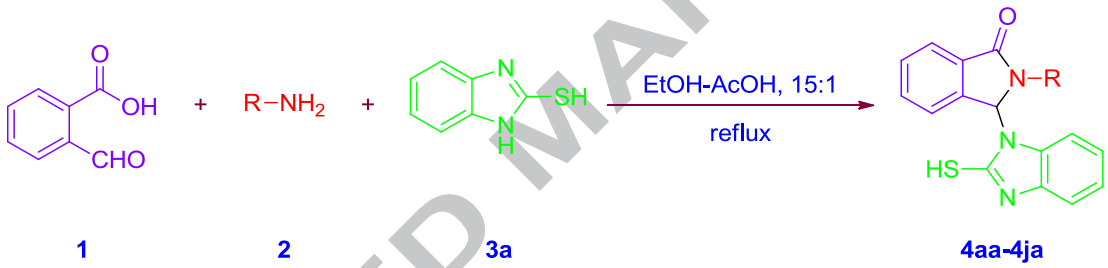
General information

Melting points were measured by a WRS-1B micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 400 instrument or Bruker AMX 500 instrument using solvent peaks as DMSO-d_6 solutions. HRESIMS were determined on a Micromass Q-Tof Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China).

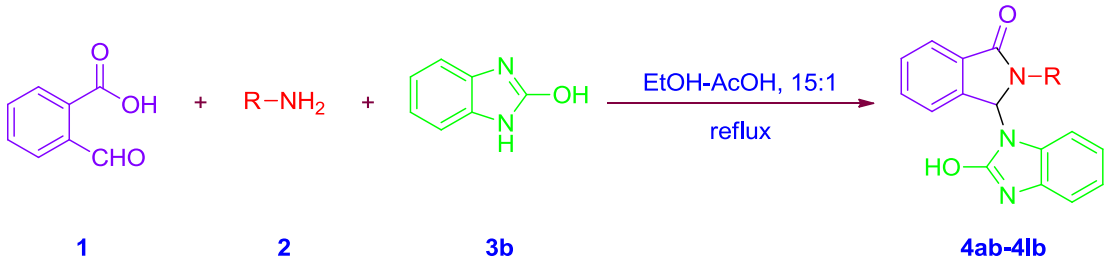
General procedure for the synthesis of compounds 4aa-4ja



1 **2** **3a** **4aa-4ja**

A mixture of phthalaldehydic acid **1** (3 mmol) , amine **2** (3.6 mmol), and 2-mercaptobenzimidazole **3a** (3 mmol) in EtOH-AcOH (5 mL, v/v, 15:1) was refluxed for 3-5 h. After completion of the reaction (TLC), the solid was filtered off, washed with water and further purified by recrystallisation from ethanol (5 mL) to yield pure products **4aa-4ja**.

General procedure for the synthesis of compounds 4ab-4lb



1 **2** **3b** **4ab-4lb**

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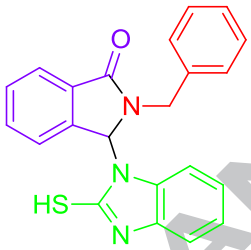
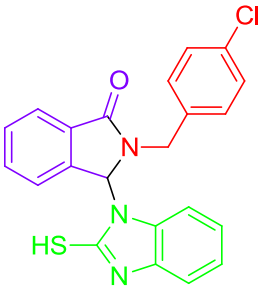
A mixture of phthalaldehydic acid **1** (3 mmol) ,amine **2** (3.6 mmol), and hydroxybenzimidazole **3b** (3 mmol) in EtOH-AcOH (5 mL, v/v, 15:1) was refluxed for 5 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford the corresponding products **4ab-4lb**.

Analytical data for compound 4



2-Benzyl-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4aa**):

White solid; Mp: 282.0–282.7 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.52 (d, *J* = 15.2 Hz, 1 H), 4.61 (d, *J* = 15.2 Hz, 1 H), 5.83 (d, *J* = 8.1 Hz, 1 H), 6.78 (t, *J* = 7.7 Hz, 1 H), 6.98–7.14 (m, 7 H), 7.41 (d, *J* = 7.3 Hz, 1 H), 7.64 (t, *J* = 7.3 Hz, 1 H), 7.70 (t, *J* = 7.3 Hz, 1 H), 7.82 (s, 1 H), 7.97 (d, *J* = 7.3 Hz, 1 H), 13.09 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.6, 69.0, 109.6, 110.6, 122.8, 123.7, 123.8, 124.1, 127.5, 128.0, 128.3, 120.0, 131.0, 131.3, 132.3, 133.6, 136.6, 140.7, 167.3, 170.4; MS (ESI): *m/z* 370 ([M – H]$^{-}$); HRMS (ESI) calcd for $C_{22}H_{17}N_3OS$ [M + H]$^{+}$ 372.1092, found 372.1080.



2-(4-Chlorobenzyl)-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ba**):

White solid; Mp: 243.4–244.5 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.51 (d, *J* = 15.3 Hz, 1 H), 4.62 (d, *J* = 15.3 Hz, 1 H), 5.77 (d, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 6.9 Hz, 1 H), 6.98–7.04 (m, 4 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 7.3 Hz, 1 H), 7.63 (t, *J* = 7.3 Hz, 1 H), 7.70 (t, *J* = 7.3 Hz, 1

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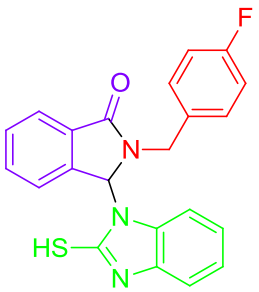
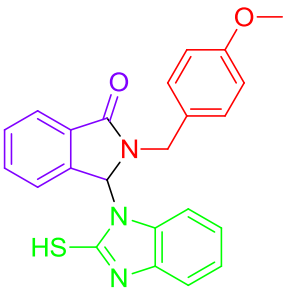
H), 7.83 (s, 1 H), 7.97 (d, *J* = 7.3 Hz, 1 H), 13.07 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.9, 69.0, 109.6, 110.6, 122.8, 123.7, 123.8, 124.2, 128.2, 129.7, 129.9, 131.0, 131.2, 132.1, 132.2, 133.6, 135.6, 140.6, 167.3, 170.4; MS (ESI): *m/z* 404 ([M – H]$^-$); HRMS (ESI) calcd for $C_{22}H_{17}ClN_3OS$ [M + H]$^+$ 406.0775, found 406.0762.



2-(4-Fluorobenzyl)-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ca**):

White solid; Mp: 256.3–256.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.53 (d, *J* = 17.2 Hz, 1 H), 4.62 (d, *J* = 17.2 Hz, 1 H), 5.78 (d, *J* = 8.1 Hz, 1 H), 6.74–6.82 (m, 3 H), 6.97–7.05 (m, 2 H), 7.11–7.15 (m, 2 H), 7.41 (d, *J* = 7.4 Hz, 1 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.69 (t, *J* = 7.4 Hz, 1 H), 7.83 (s, 1 H), 7.97 (d, *J* = 7.4 Hz, 1 H), 13.08 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.9, 69.0, 109.5, 110.5, 114.9 and 115.0 ($^2J_{CF}$ = 17.0 Hz), 122.7, 123.7, 123.8, 124.1, 129.9, 129.9 and 130.0 ($^3J_{CF}$ = 7.0 Hz), 130.9, 131.2, 132.2, 132.8 and 132.8 ($^4J_{CF}$ = 2.0 Hz), 133.6, 140.6, 160.6 and 162.6 ($^1J_{CF}$ = 193.0 Hz), 167.2, 170.4; MS (ESI): *m/z* 388 ([M – H]$^-$); HRMS (ESI) calcd for $C_{22}H_{17}FN_3OS$ [M + H]$^+$ 390.1071, found 390.1083.



3-(2-Mercapto-1*H*-benzo[*d*]imidazol-1-yl)-2-(4-methoxybenzyl)isoindolin-1-one (**4da**):

White solid; Mp: 222.7–226.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 4.63 (d, *J* = 14.8 Hz, 1 H), 4.71 (d, *J* = 14.8 Hz, 1 H), 6.08 (d, *J* = 8.2 Hz, 1 H), 6.54 (t, *J* = 8.6 Hz, 2 H), 6.81 (t, *J* = 7.8 Hz, 1 H), 7.06 (t, *J* = 8.8 Hz, 1 H), 7.14 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 8.6 Hz, 2 H), 7.43 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.56 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.64 (t, *J* = 8.6 Hz, 1 H), 7.89 (s, 1 H),

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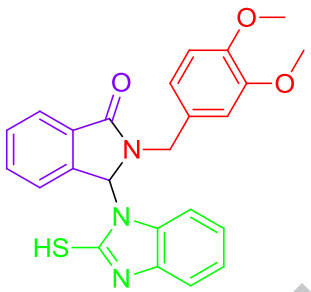
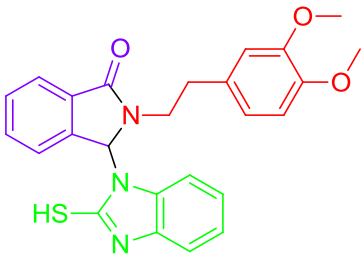
8.09 (d, *J* = 7.6 Hz, 1 H), 13.33 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3, 55.2, 69.3, 110.0, 110.5, 113.4, 123.1, 123.5, 123.7, 124.3, 127.9, 129.7, 130.0, 130.3, 130.4, 132.3, 132.9, 140.1, 158.8, 167.7, 170.0; MS (ESI): *m/z* 400 ([M – H]$^-$); HRMS (ESI) calcd for $C_{23}H_{20}N_3O_2S$ [M + H]$^+$ 402.1271, found 402.1260.



2-(3,4-Dimethoxybenzyl)-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ea**): White solid; Mp: 221.5–222.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 3.79 (s, 3 H), 4.65 (d, *J* = 14.8 Hz, 1 H), 4.70 (d, *J* = 14.8 Hz, 1 H), 6.09 (d, *J* = 8.2 Hz, 1 H), 6.51 (d, *J* = 8.2 Hz, 1 H), 6.81 (td, *J* = 8.4, 1.2 Hz, 1 H), 6.87–90 (m, 2 H), 7.06 (t, *J* = 7.9 Hz, 1 H), 7.14 (d, *J* = 7.9 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 7.56 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.92 (s, 1 H), 8.10 (d, *J* = 7.5 Hz, 1 H), 11.29 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3, 55.3, 55.4, 68.9, 109.4, 109.7, 110.1, 111.2, 120.5, 122.5, 122.9, 123.3, 123.8, 127.8, 129.4, 129.8, 129.9, 131.7, 132.4, 139.6, 147.6, 147.8, 167.3, 169.6; MS (ESI): *m/z* 430 ([M – H]$^-$); HRMS (ESI) calcd for $C_{24}H_{22}N_3O_3S$ [M + H]$^+$ 432.1376, found 432.1366.



2-(3,4-Dimethoxyphenethyl)-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4fa**): White solid; Mp: 231.3–232.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.65–2.73 (m, 1 H), 2.84–2.93 (m, 1 H), 3.09–3.17 (m, 1 H), 3.65 (s, 3 H), 3.69 (s, 3 H), 3.87–3.95 (m, 1 H), 5.84 (d, *J* = 8.1 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 8.1 Hz, 1 H), 6.76 (s, 1 H), 6.83 (t, *J* = 7.7 Hz, 1 H), 7.08 (t, *J* = 7.7 Hz, 1 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.60 (t, *J* =

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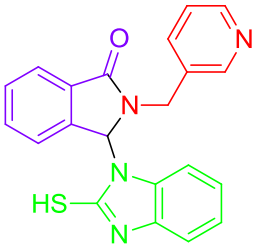
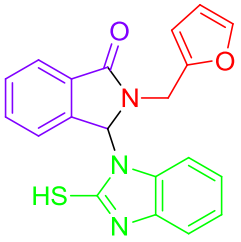
7.3 Hz, 1 H), 7.66 (t, *J* = 7.0 Hz, 1 H), 7.80 (s, 1 H), 7.90 (d, *J* = 7.3 Hz, 1 H), 13.32 (brs, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.4, 41.9, 55.7, 55.7, 68.4, 109.5, 110.9, 112.0, 112.5, 120.7, 123.0, 123.8, 123.9, 123.9, 129.9, 130.8, 130.9, 131.5, 132.5, 133.3, 140.4, 147.6, 148.9, 167.1, 170.6; MS (ESI): *m/z* 444 ([M – H]$^-$); HRMS (ESI) calcd for $C_{25}H_{24}N_3O_3S$ [M + H]$^+$ 446.1533, found 446.1541.



3-(2-Mercapto-1*H*-benzo[*d*]imidazol-1-yl)-2-(pyridin-3-ylmethyl)isoindolin-1-one (**4ga**):

White solid; Mp: 291.3–291.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.56 (d, *J* = 15.4 Hz, 1 H), 4.69 (d, *J* = 15.4 Hz, 1 H), 5.77 (d, *J* = 8.1 Hz, 1 H), 6.76 (t, *J* = 7.0 Hz, 1 H), 6.93–7.04 (m, 3 H), 7.40–7.46 (m, 2 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.70 (t, *J* = 7.4 Hz, 1 H), 7.86 (s, 1 H), 7.98 (d, *J* = 7.4 Hz, 1 H), 8.18 (d, *J* = 3.5 Hz, 1 H), 8.32 (brs, 1 H), 13.11 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.3, 69.1, 109.5, 110.6, 122.8, 123.2, 123.8, 123.9, 124.2, 129.8, 131.0, 131.2, 132.1, 132.2, 133.6, 135.6, 140.6, 148.7, 149.1, 167.4, 170.4; MS (ESI): *m/z* 371 ([M – H]$^-$); 373 ([M + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{17}N_4OS$ [M + H]$^+$ 373.1118, found 373.1129.



2-(Furan-2-ylmethyl)-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ha**):

White solid; Mp: 291.6–293.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.58 (d, *J* = 16.6 Hz, 1 H), 4.63 (d, *J* = 16.6 Hz, 1 H), 5.86 (d, *J* = 8.2 Hz, 1 H), 6.06 (s, 1 H), 6.10 (s, 1 H), 6.78 (t, *J* = 7.8 Hz, 1 H), 7.03 (t, *J* = 7.8 Hz, 1 H), 7.08–7.15 (m, 2 H), 7.40 (d, *J* = 7.4 Hz, 1 H), 7.60–7.69 (m, 2 H), 7.83 (s, 1 H), 7.94 (d, *J* = 7.4 Hz, 1 H), 13.16 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.7, 69.0, 108.2, 109.4, 110.4, 110.5, 122.7, 123.7, 123.8, 124.1, 129.9, 130.9, 131.4, 132.0, 133.6,

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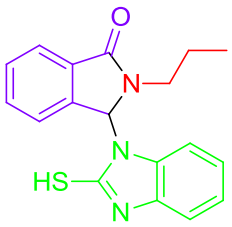
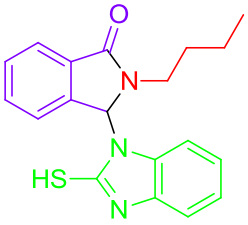
140.7, 142.7, 149.7, 167.0, 170.5; MS (ESI): *m/z* 360 ([M – H]$^-$); HRMS (ESI) calcd for $C_{20}H_{16}N_3O_2S$ [M + H]$^+$ 362.0958, found 362.0950.



3-(2-Mercapto-1*H*-benzo[*d*]imidazol-1-yl)-2-propylisoindolin-1-one (**4ia**):

White solid; Mp: 284.7–287.6 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.73 (t, *J* = 7.4 Hz, 3 H), 1.42–1.53 (m, 2 H), 2.86–2.94 (m, 1 H), 3.54–3.63 (m, 1 H), 5.93 (d, *J* = 8.1 Hz, 1 H), 6.88 (t, *J* = 7.8 Hz, 1 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.67 (t, *J* = 7.3 Hz, 1 H), 7.78 (s, 1 H), 7.92 (d, *J* = 7.4 Hz, 1 H), 13.28 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.6, 21.4, 41.9, 68.5, 109.5, 110.9, 123.1, 123.8, 123.9, 124.0, 123.0, 130.8, 131.5, 132.5, 133.3, 140.6, 167.2, 170.6; MS (ESI): *m/z* 322 ([M – H]$^-$); HRMS (ESI) calcd for $C_{18}H_{18}N_3OS$ [M + H]$^+$ 324.1165, found 324.1177.



2-Butyl-3-(2-mercapto-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ja**):

White solid; Mp: 242.7–243.4 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.72 (t, *J* = 7.3 Hz, 3 H), 1.05–1.21 (m, 2 H), 1.38–1.47 (m, 2 H), 2.90–2.99 (m, 1 H), 3.58–3.66 (m, 1 H), 5.93 (d, *J* = 8.1 Hz, 1 H), 6.88 (t, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.67 (t, *J* = 7.3 Hz, 1 H), 7.78 (s, 1 H), 7.91 (d, *J* = 7.3 Hz, 1 H), 13.29 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 19.8, 30.0, 39.9, 68.5, 109.5, 110.9, 123.1, 123.7, 123.9, 124.0, 130.0, 130.8, 131.5, 132.5, 133.3, 140.6, 167.2, 170.6; MS (ESI): *m/z* 336 ([M – H]$^-$); HRMS (ESI) calcd for $C_{19}H_{20}N_3OS$ [M + H]$^+$ 338.1322, found 338.1318.

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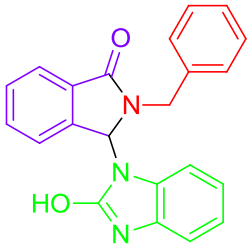
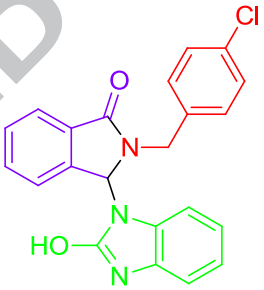


2-Benzyl-3-(2-hydroxy-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4ab**):

White solid; Mp: 216.0–216.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (d, *J* = 15.4 Hz, 1 H), 4.89 (d, *J* = 15.4 Hz, 1 H), 5.89 (d, *J* = 8.0 Hz, 1 H), 6.71–6.75 (m, 1 H), 6.96–7.03 (m, 3 H), 7.12–7.15 (m, 3 H), 7.29–7.33 (m, 2 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.59 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 8.09 (d, *J* = 7.5 Hz, 1 H), 10.17 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.4, 65.9, 109.8, 109.9, 121.7, 122.4, 123.5, 124.2, 127.0, 127.5, 127.9, 128.3, 128.4, 130.3, 132.4, 132.8, 135.9, 140.2, 155.8, 167.6; MS (ESI): *m/z* 354 ([M – H]$^-$); HRMS (ESI) calcd for $C_{22}H_{18}N_3O_2$ [M + H]$^+$ 356.1394, found 356.1381.



2-(4-Chlorobenzyl)-3-(2-hydroxy-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4bb**):

White solid; Mp: 202.3–203.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (d, *J* = 15.1 Hz, 1 H), 4.73 (d, *J* = 15.1 Hz, 1 H), 5.79 (d, *J* = 8.0 Hz, 1 H), 6.70–6.74 (m, 1 H), 6.97–7.00 (m, 3 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 7.5 Hz, 1 H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 8.08 (d, *J* = 7.5 Hz, 1 H), 9.67 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.9, 66.0, 109.7, 109.9, 121.8, 122.5, 123.5, 124.3, 126.9, 127.6, 128.3, 129.6, 130.4, 132.2, 132.9, 133.4, 134.4, 140.0, 155.6, 167.5; MS (ESI): *m/z* 388 ([M – H]$^-$); HRMS (ESI) calcd for $C_{22}H_{17}ClN_3O_2$ [M + H]$^+$ 390.1004, found 389.9892.

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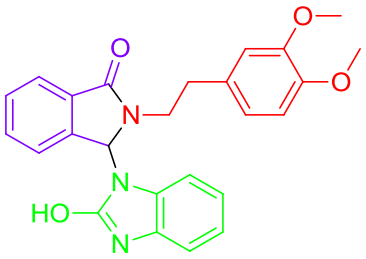
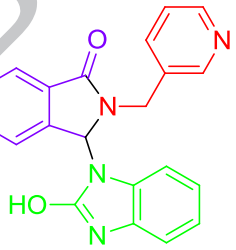


2-(3,4-Dimethoxyphenethyl)-3-(2-hydroxy-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4fb**): White solid; Mp: 212.3–212.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83–2.91 (m, 1 H), 2.99–3.06 (m, 1 H), 3.30–3.37 (m, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.04–4.12 (m, 1 H), 5.82 (d, *J* = 8.0 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 6.70–6.76 (m, 3 H), 6.95 (s, 1 H), 7.01 (td, *J* = 7.7, 1.0 Hz, 1 H), 7.12 (d, *J* = 7.7 Hz, 1 H), 7.41 (d, *J* = 7.5 Hz, 1 H), 7.57 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 1 H), 10.11 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.7, 41.9, 55.7, 55.7, 66.0, 109.9, 109.9, 111.0, 111.6, 120.7, 121.9, 122.5, 123.4, 124.0, 127.0, 127.8, 130.3, 130.7, 132.6, 132.7, 139.9, 147.4, 148.7, 155.8, 167.6; MS (ESI): *m/z* 428 ([M – H]$^-$); HRMS (ESI) calcd for $C_{25}H_{24}N_3O_4$ [M + H]$^+$ 430.1761, found 430.1755.



3-(2-Hydroxy-1*H*-benzo[*d*]imidazol-1-yl)-2-(pyridin-2-ylmethyl)isoindolin-1-one (**4gb**): White solid; Mp: 254.5–255.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 15.6 Hz, 1 H), 4.94 (d, *J* = 15.6 Hz, 1 H), 5.82 (d, *J* = 8.0 Hz, 1 H), 6.65–6.70 (m, 1 H), 6.90–7.00 (m, 3 H), 7.13 (s, 1 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 7.41 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 1 H), 7.60 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 8.08 (d, *J* = 7.4 Hz, 1 H), 8.33 (d, *J* = 4.9 Hz, 1 H), 9.78 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.1, 66.5, 109.6, 109.8, 121.5, 122.2, 122.2, 122.2, 123.5, 124.3, 127.0, 127.8, 130.2, 132.3, 132.8, 136.3, 140.4, 149.1, 155.6, 155.8, 167.7; MS (ESI): *m/z* 355 ([M – H]$^-$); HRMS (ESI) calcd for $C_{21}H_{16}N_4O_2$ [M + H]$^+$ 356.1273, found 356.1279.

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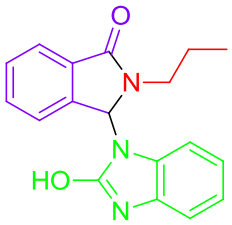
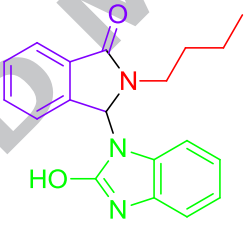


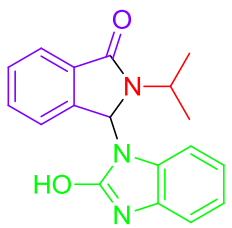
3-(2-Hydroxy-1*H*-benzo[*d*]imidazol-1-yl)-2-propylisoindolin-1-one (**4ib**):

White solid; Mp: 273.1–273.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.59–1.73 (m, 2 H), 2.98–3.05 (m, 1 H), 3.76–3.84 (m, 1 H), 5.93 (d, *J* = 7.9 Hz, 1 H), 6.76 (td, *J* = 7.9, 1.1 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.13 (d, *J* = 7.5 Hz, 1 H), 7.45 (d, *J* = 7.4 Hz, 1 H), 7.58 (td, *J* = 7.4, 1.3 Hz, 1 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 8.04 (d, *J* = 7.4 Hz, 1 H), 9.73 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 21.3, 41.6, 65.6, 109.9, 109.9, 122.0, 122.5, 123.3, 124.0, 127.0, 127.8, 130.2, 132.5, 132.7, 140.0, 155.7, 167.6; MS (ESI): *m/z* 306 ($[M - H]^-$); HRMS (ESI) calcd for $C_{18}H_{18}N_3O_2$ $[M + H]^+$ 308.1394, found 308.1387.



2-Butyl-3-(2-hydroxy-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4jb**):

White solid; Mp: 243.8–244.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3 H), 1.29–1.39 (m, 2 H), 1.58–1.66 (m, 2 H), 3.00–3.07 (m, 1 H), 3.82–3.89 (m, 1 H), 5.93 (d, *J* = 8.0 Hz, 1 H), 6.76 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.15 (d, *J* = 7.7 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.58 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 8.04 (d, *J* = 7.4 Hz, 1 H), 10.12 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 20.1, 30.0, 39.7, 65.6, 109.9, 109.9, 121.9, 122.5, 123.3, 124.0, 127.0, 127.8, 130.2, 132.5, 132.7, 140.1, 155.8, 167.6; MS (ESI): *m/z* 320 ($[M - H]^-$); HRMS (ESI) calcd for $C_{19}H_{20}N_3O_2$ $[M + H]^+$ 322.1550, found 322.1558.



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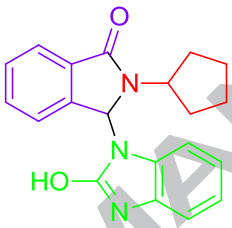
3-(2-Hydroxy-1*H*-benzo[*d*]imidazol-1-yl)-2-isopropylisoindolin-1-one (**4kb**):

White solid; Mp: 261.1–261.9 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.0 Hz, 3 H), 1.45 (d, *J* = 7.0 Hz, 3 H), 4.48–4.55 (m, 1 H), 6.04 (d, *J* = 8.0 Hz, 1 H), 6.78 (t, *J* = 7.9 Hz, 1 H), 7.02 (t, *J* = 7.7 Hz, 1 H), 7.10 (s, 1 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 7.4 Hz, 1 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 8.01 (d, *J* = 7.4 Hz, 1 H), 10. 16 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 19.8, 43.6, 64.1, 109.4, 109.6, 121.4, 121.9, 122.6, 123.3, 126.6, 127.3, 129.7, 132.1, 132.2, 140.0, 154.9, 167.2; MS (ESI): *m/z* 306 ([M – H]$^-$); HRMS (ESI) calcd for $C_{18}H_{18}N_3O_2$ [M + H]$^+$ 308.1394, found 308.1390.



2-Cyclopentyl-3-(2-hydroxy-1*H*-benzo[*d*]imidazol-1-yl)isoindolin-1-one (**4lb**):

White solid; Mp: 228.1–228.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.58 (m, 3 H), 1.62–1.66 (m, 1 H), 1.74–1.84 (m, 3 H), 2.03–2.08 (m, 1 H), 4.32–4.40 (m, 1 H), 6.09 (d, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 8.0 Hz, 1 H), 7.03 (t, *J* = 7.7 Hz, 1 H), 7.10 (s, 1 H), 7.15 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 7.3 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 8.00 (d, *J* = 7.4 Hz, 1 H), 10. 16 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 23.9, 29.0, 29.1, 54.1, 65.7, 109.9, 110.1, 122.0, 122.4, 123.0, 123.7, 127.1, 127.8, 130.2, 132.6, 132.9, 140.4, 155.4, 168.0; MS (ESI): *m/z* 332 ([M – H]$^-$); HRMS (ESI) calcd for $C_{18}H_{18}N_3O_3$ [M + H]$^+$ 334.1550, found 334.1540.

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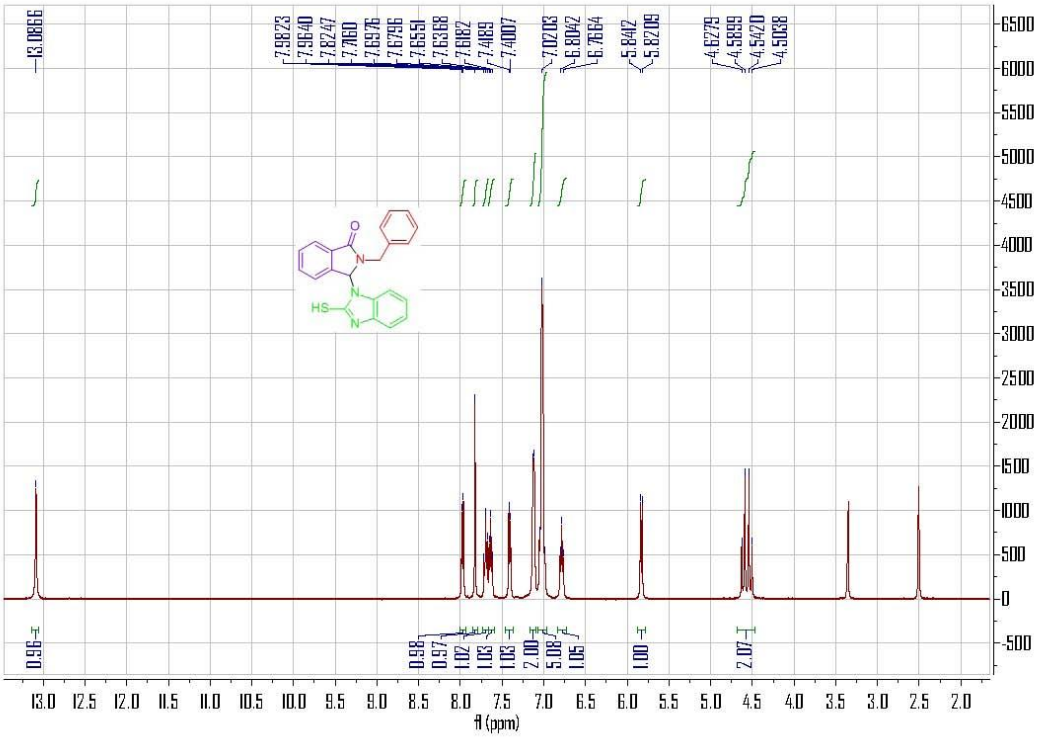
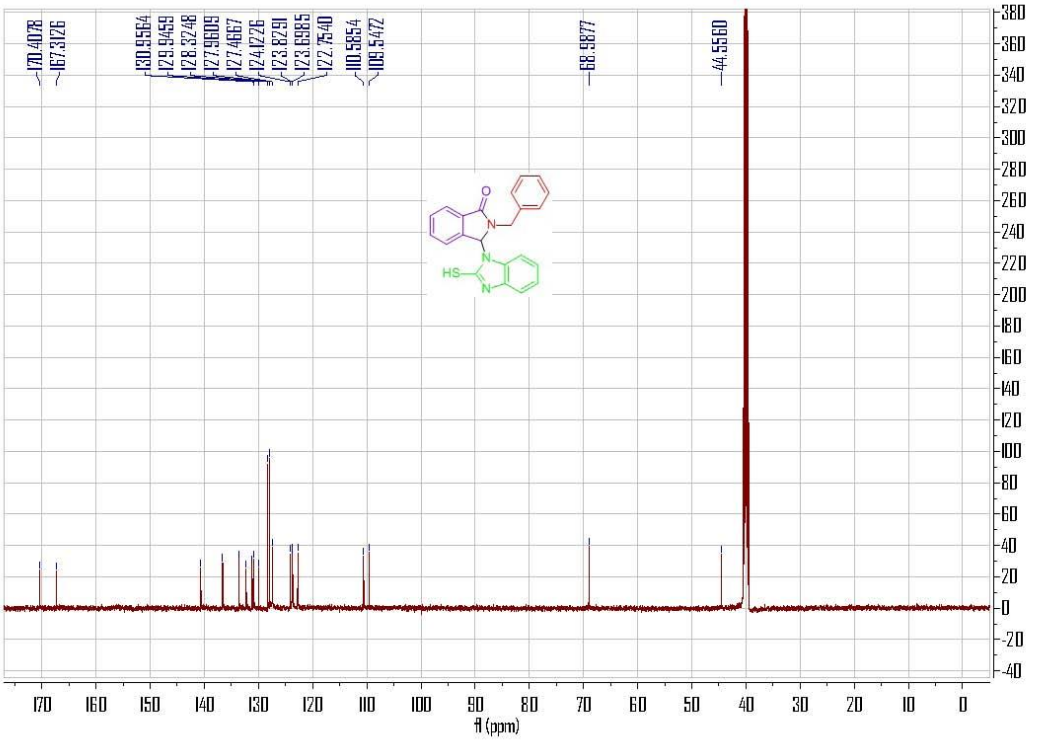
^{1}H, ^{13}C NMR, and LC-MS of compound 4aa





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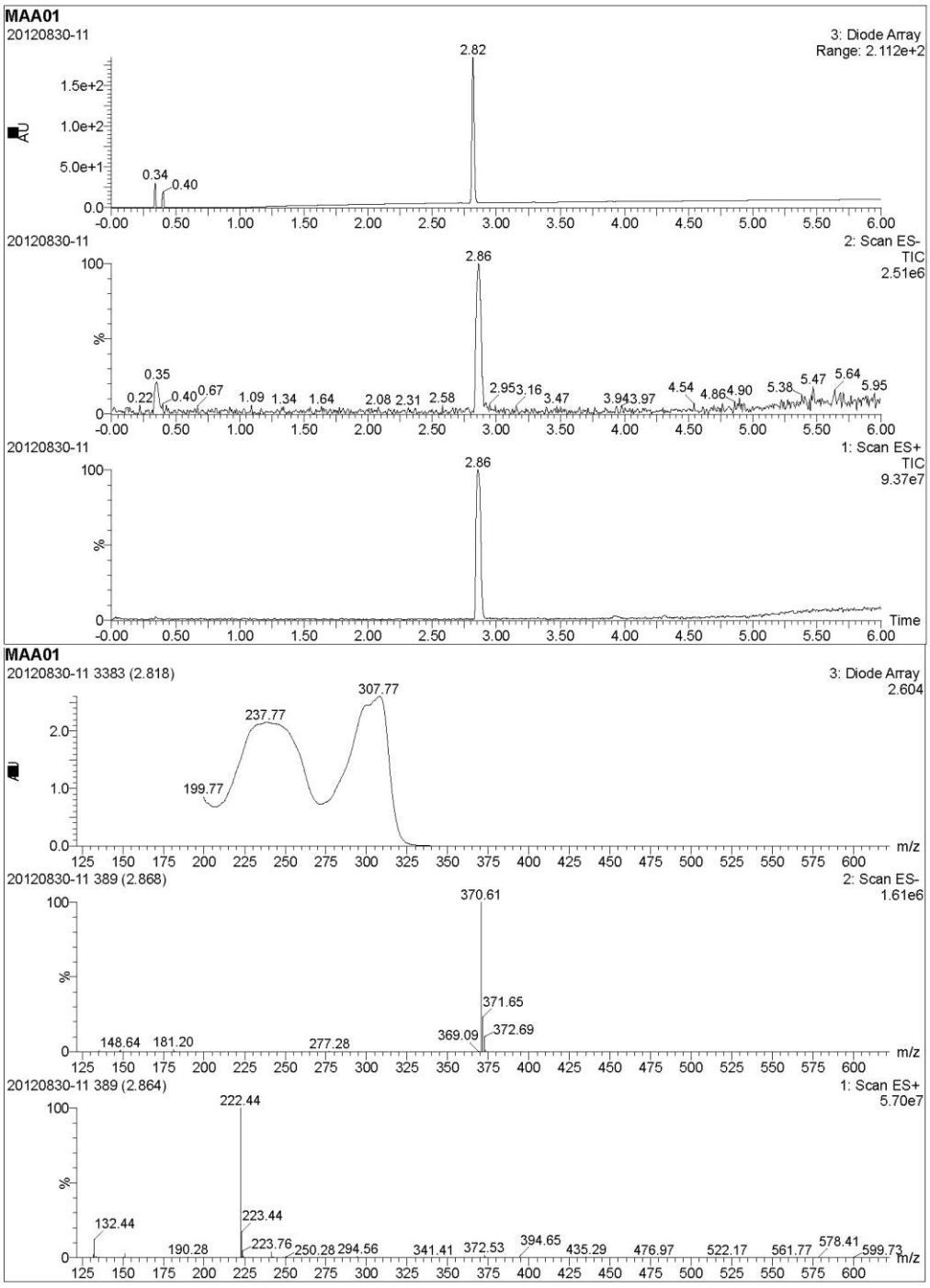

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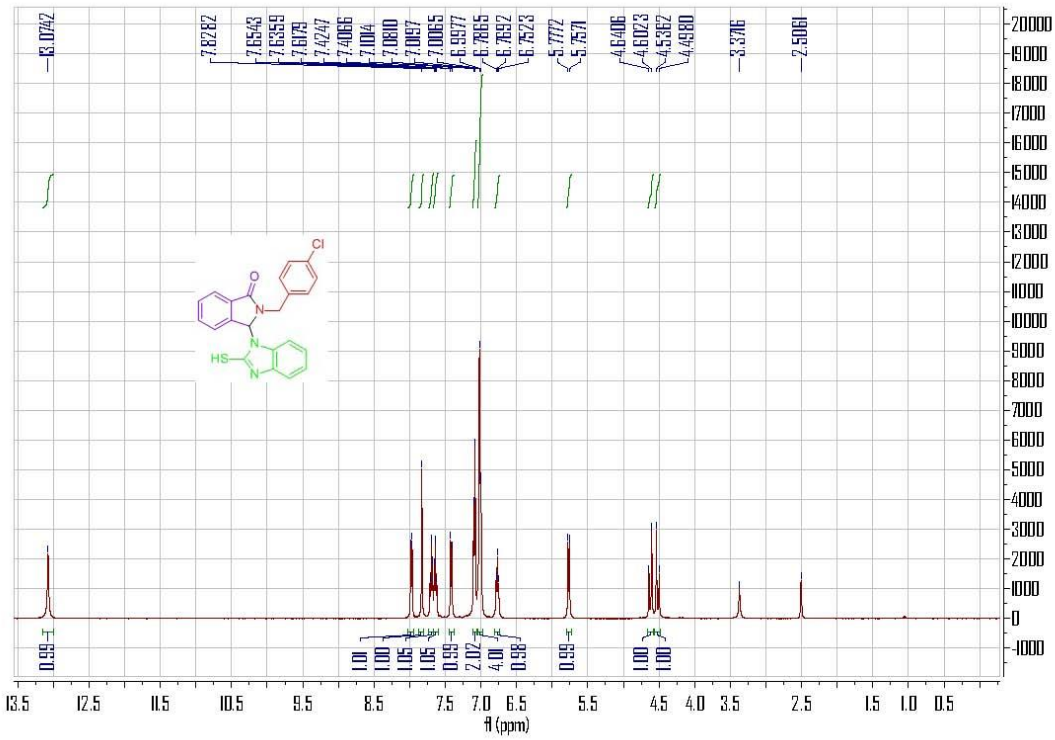
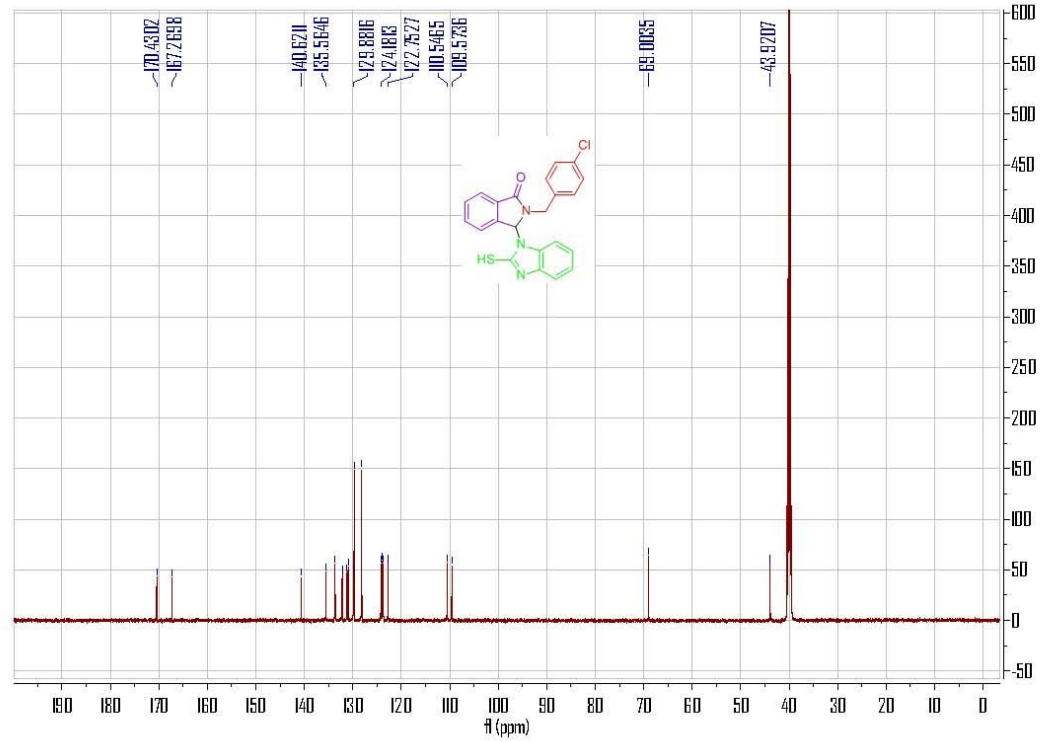
^{1}H, ^{13}C NMR, and LC-MS of compound 4ba





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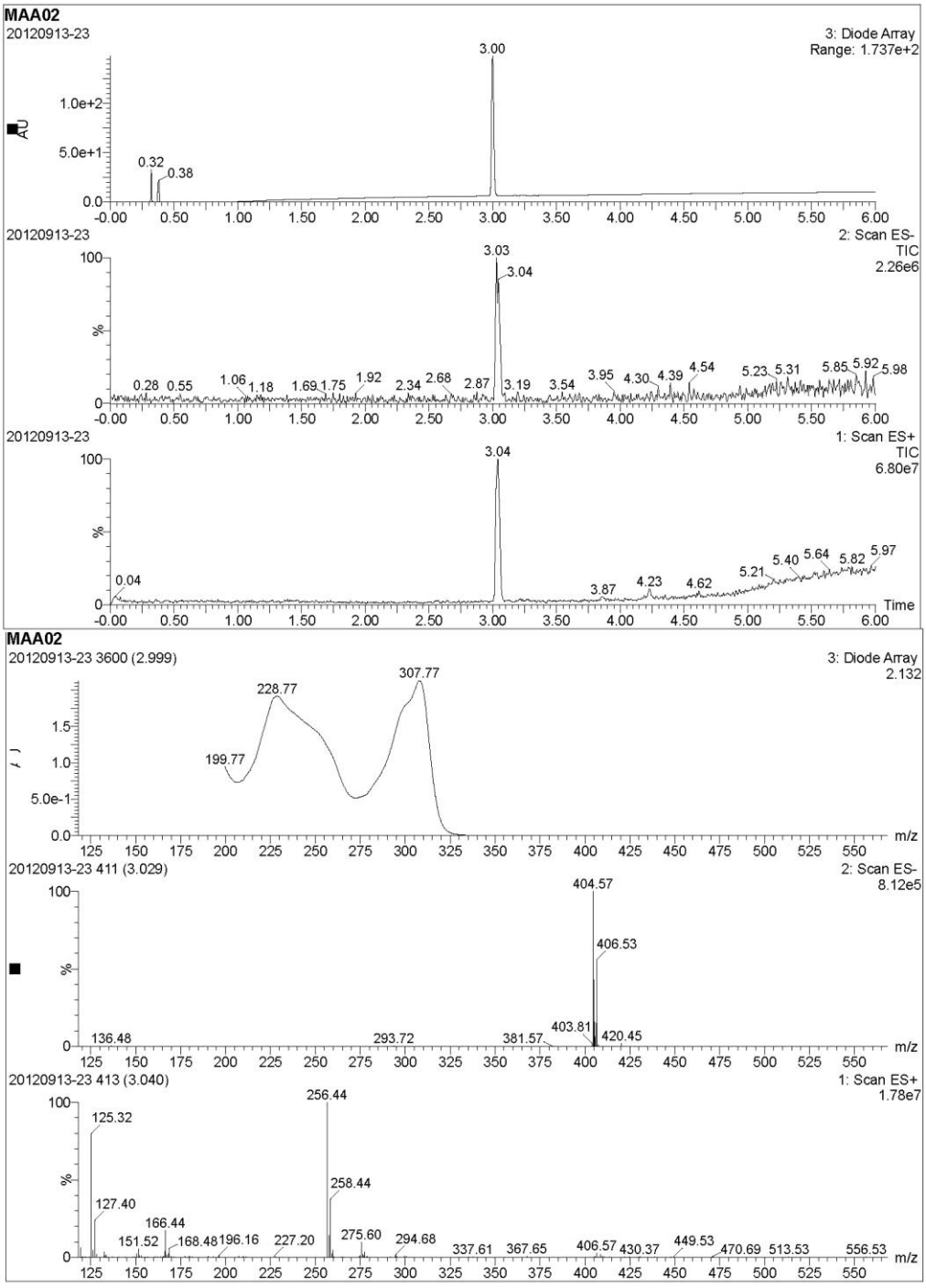

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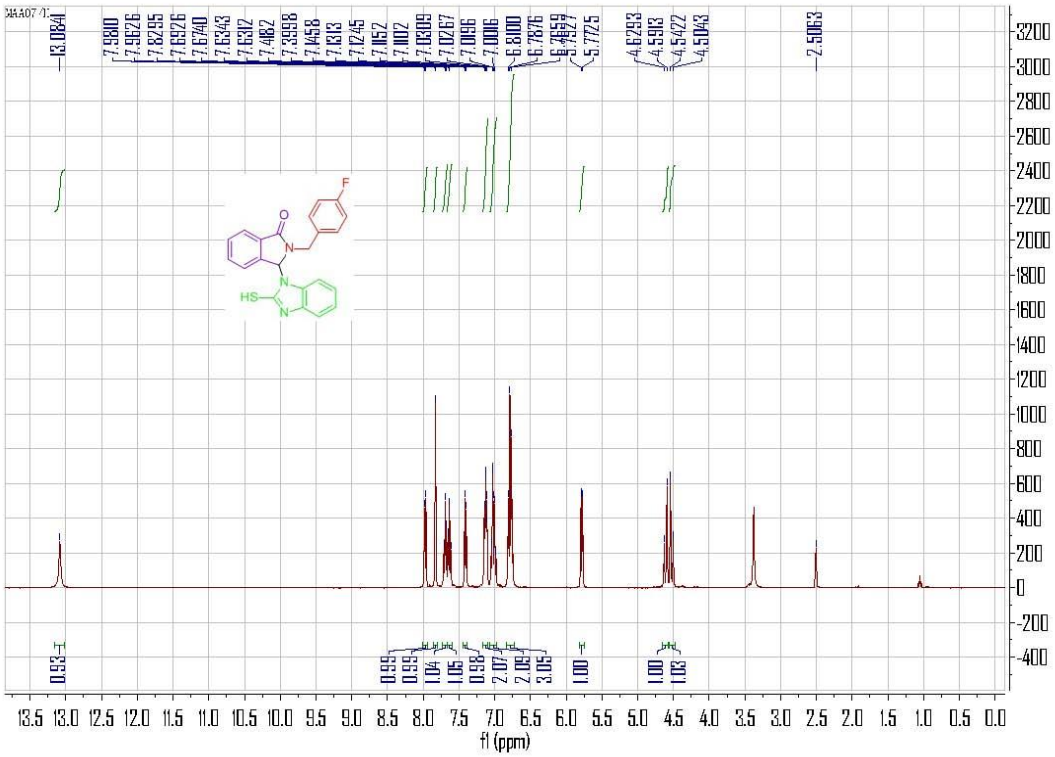
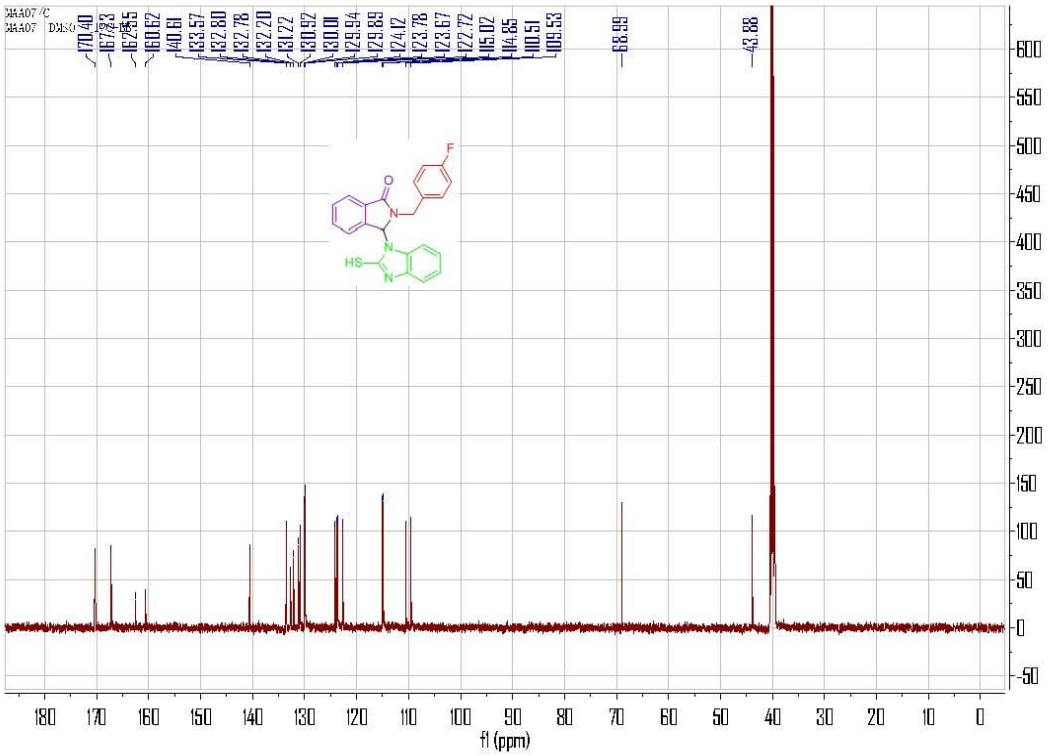
^{1}H, ^{13}C NMR, and LC-MS of compound 4ca





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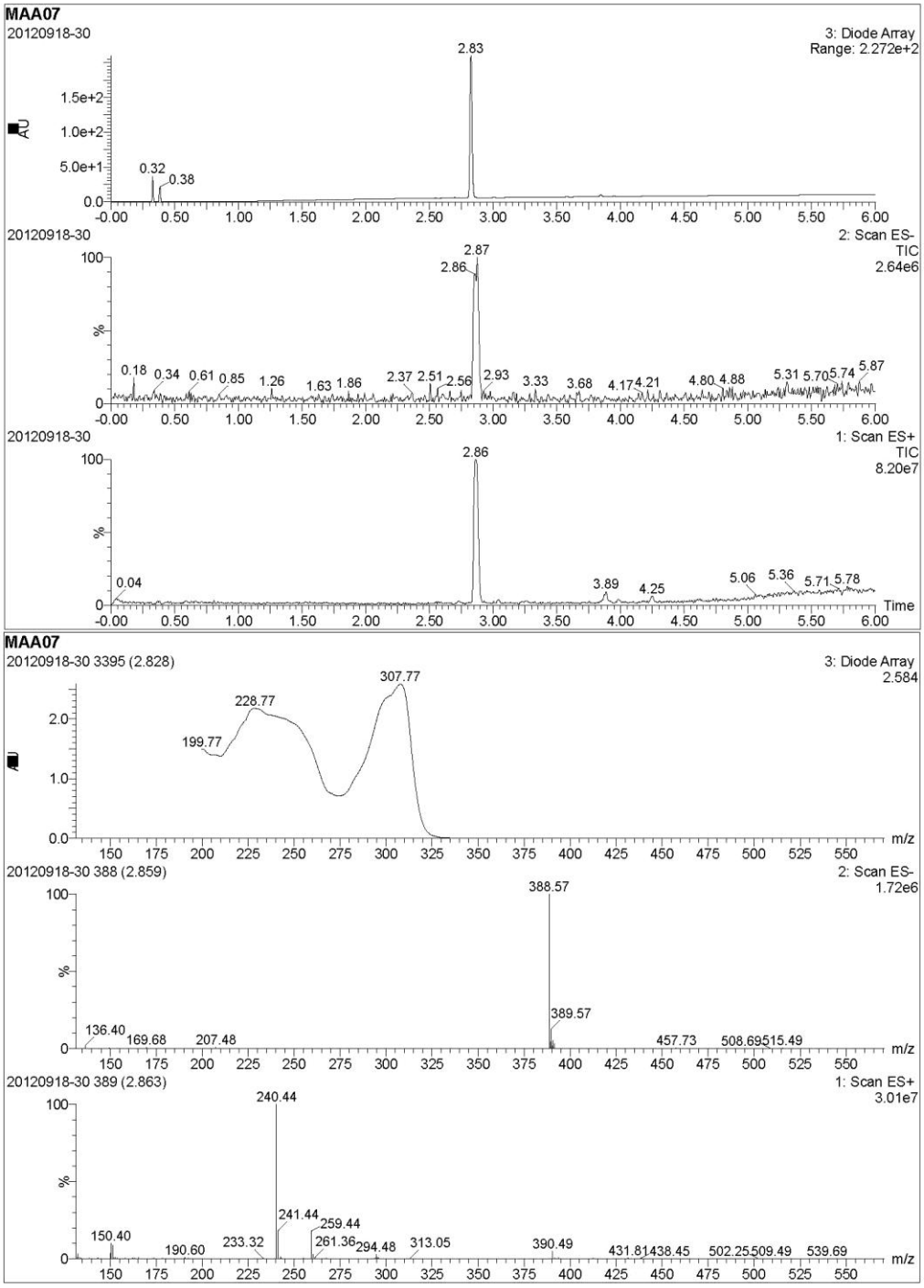

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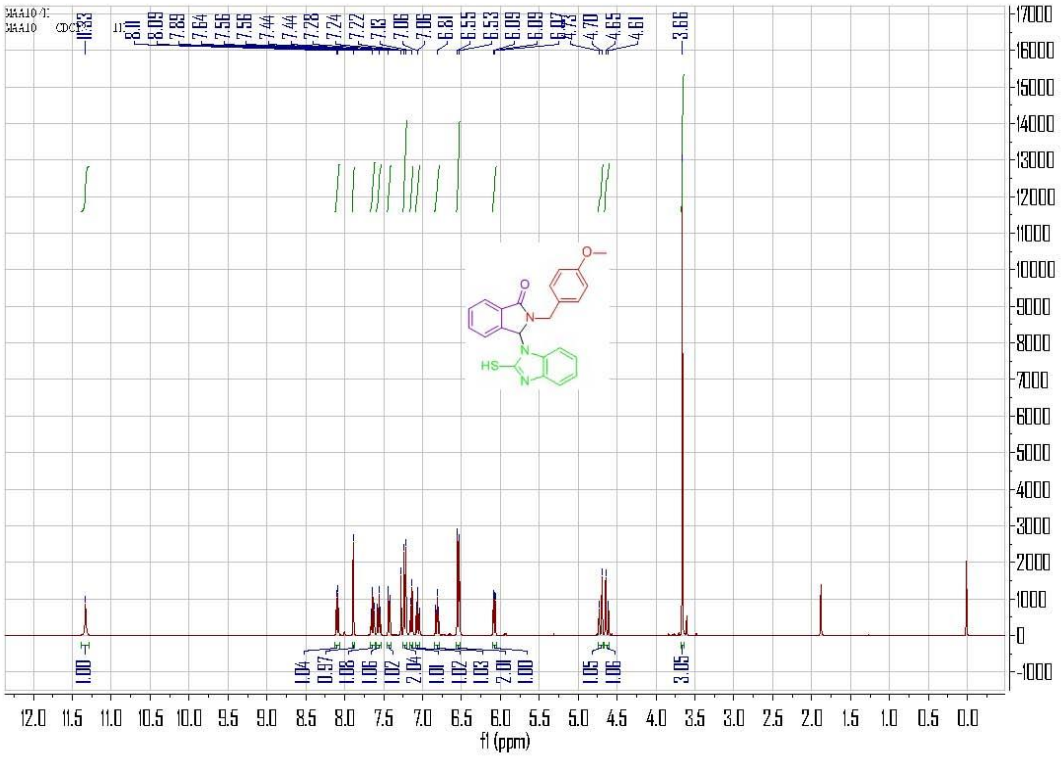
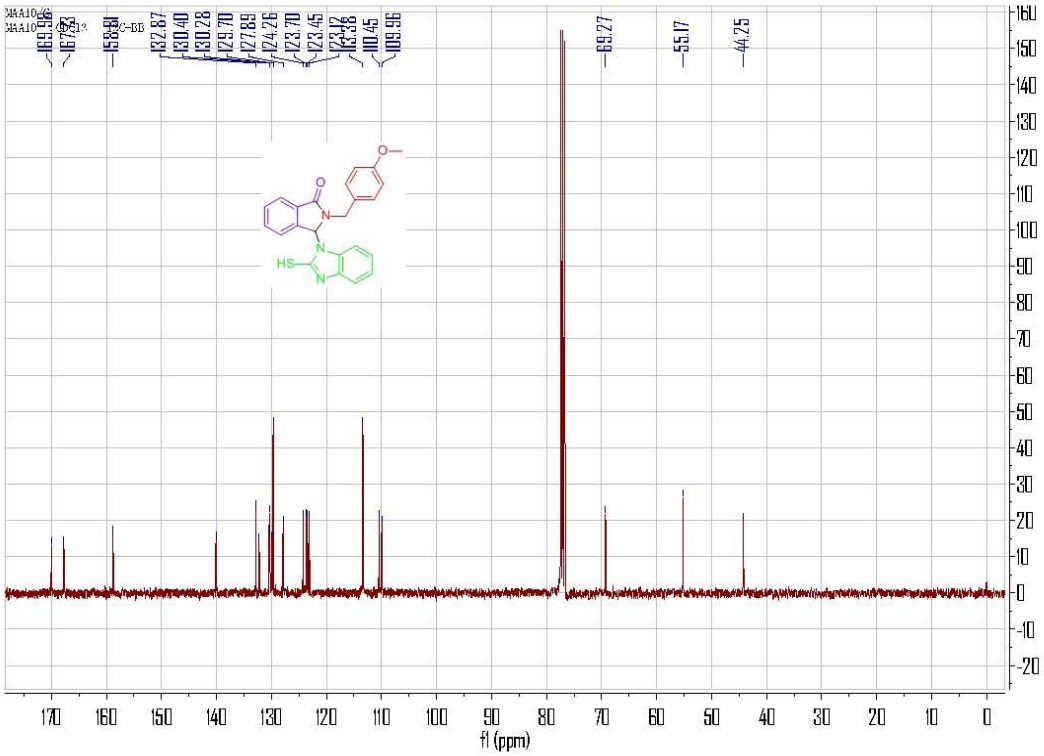
^{1}H, ^{13}C NMR, and LC-MS of compound 4da





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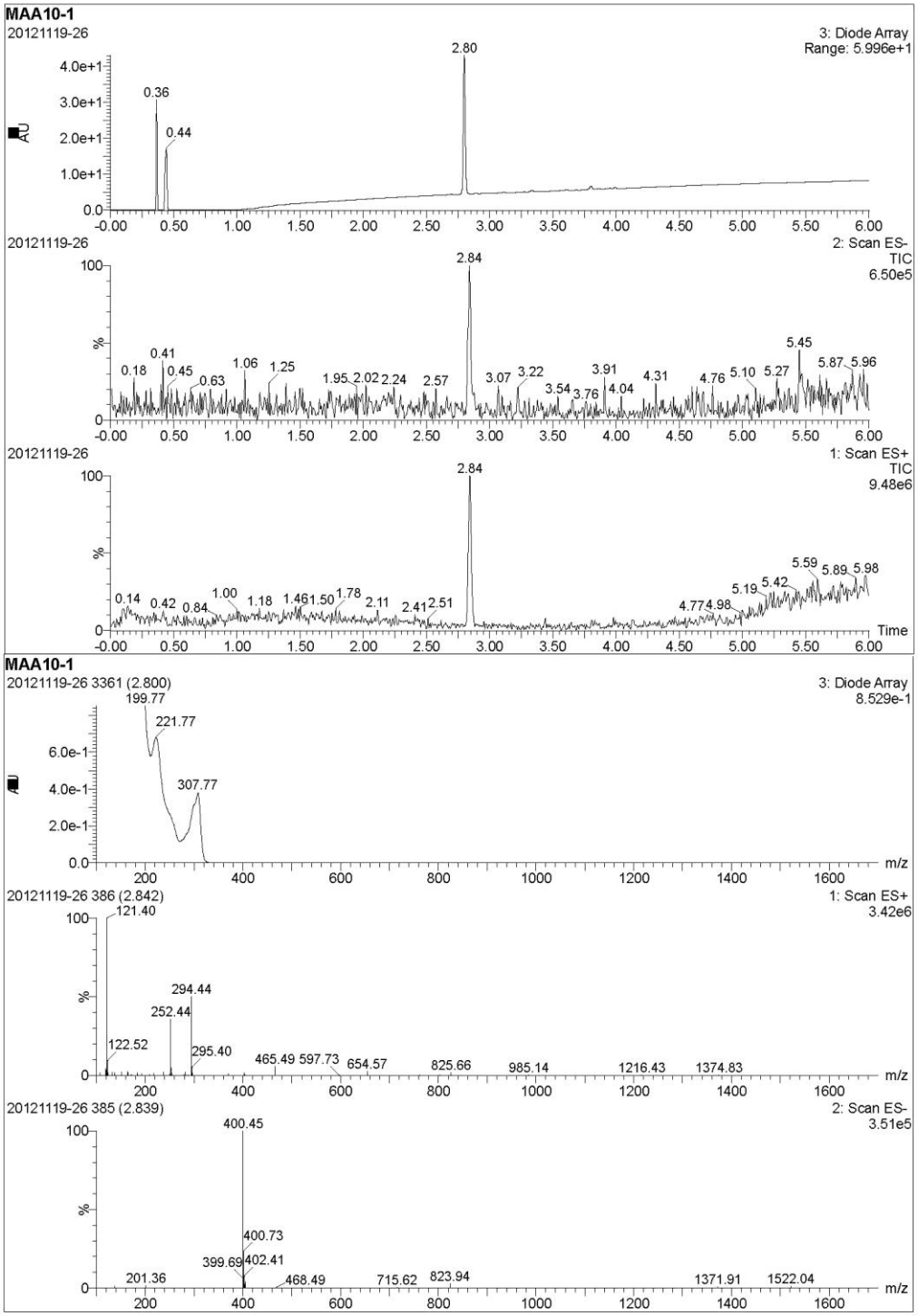

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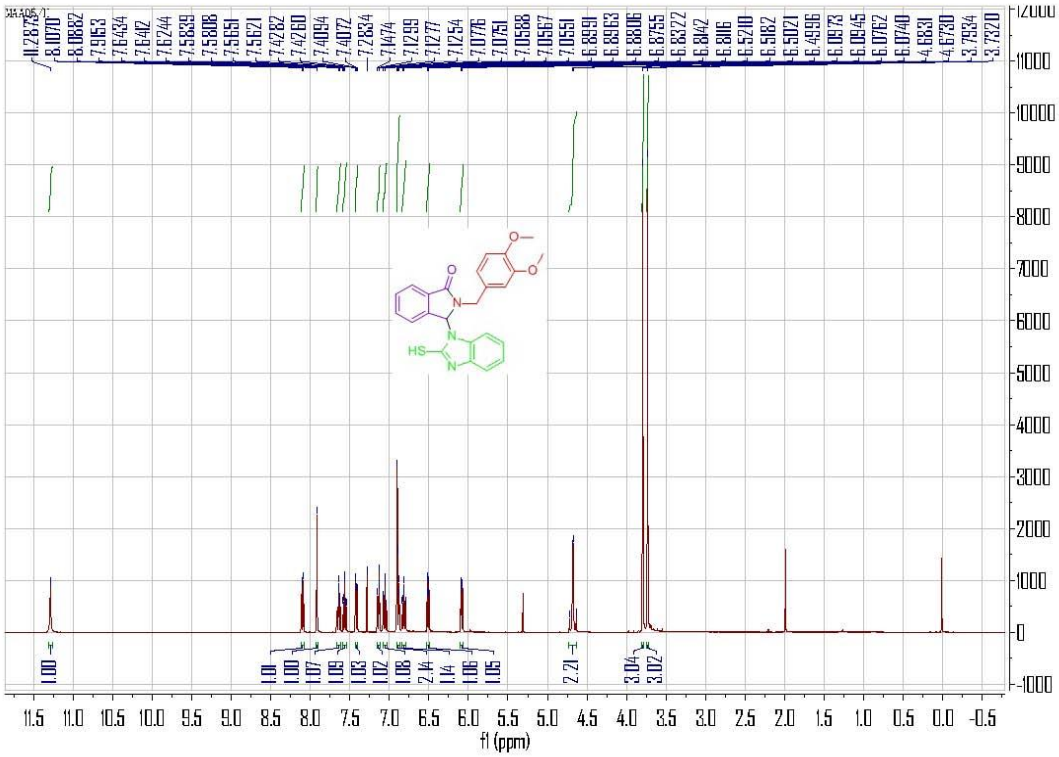
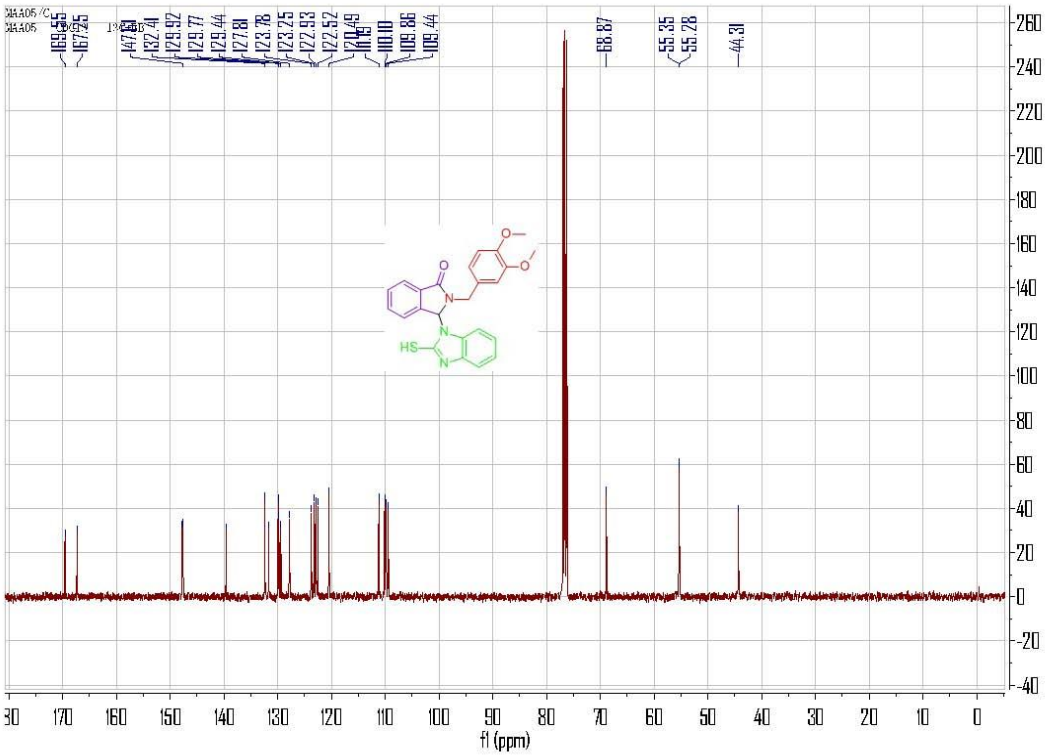
^{1}H, ^{13}C NMR, and LC-MS of compound 4ea





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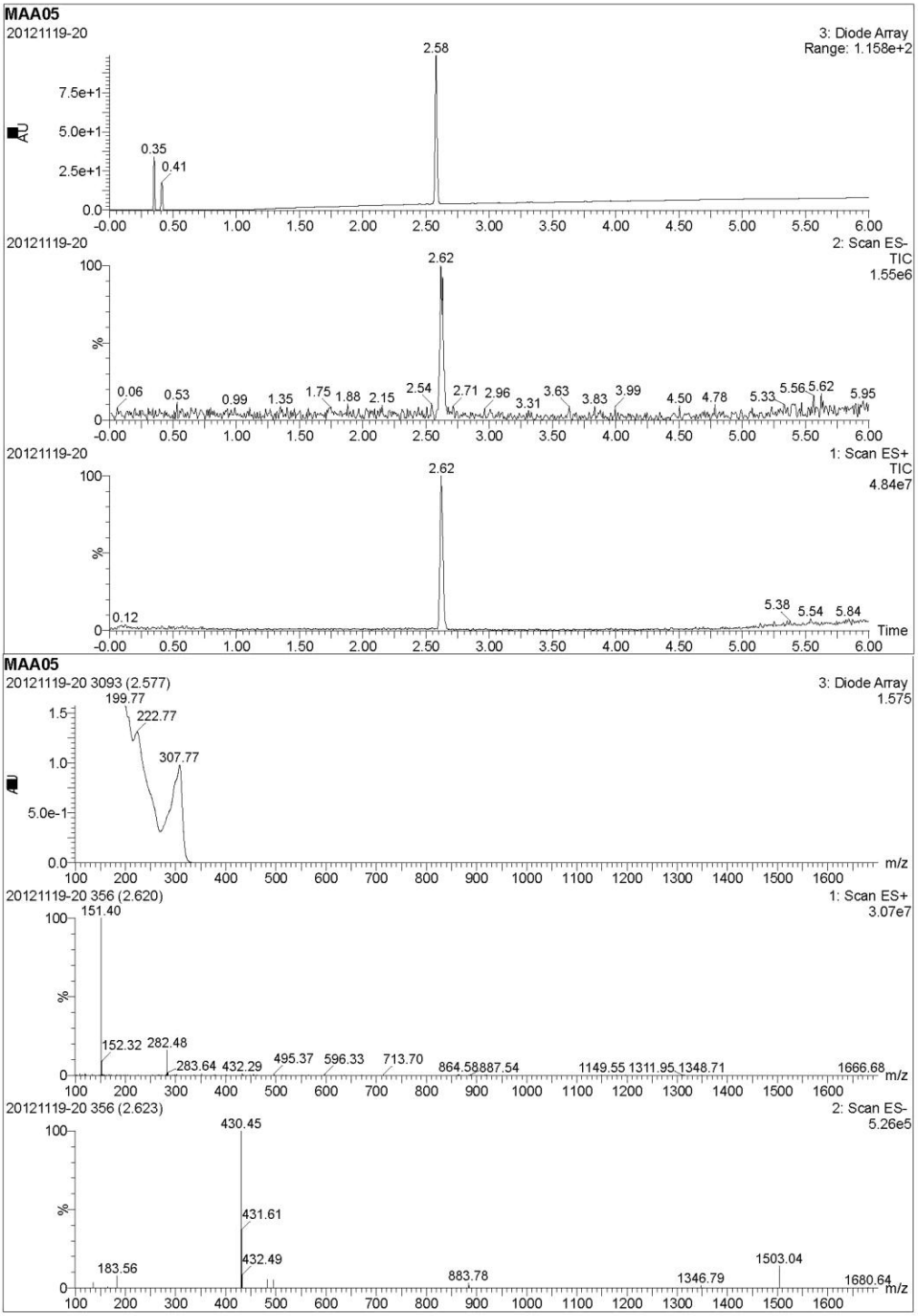

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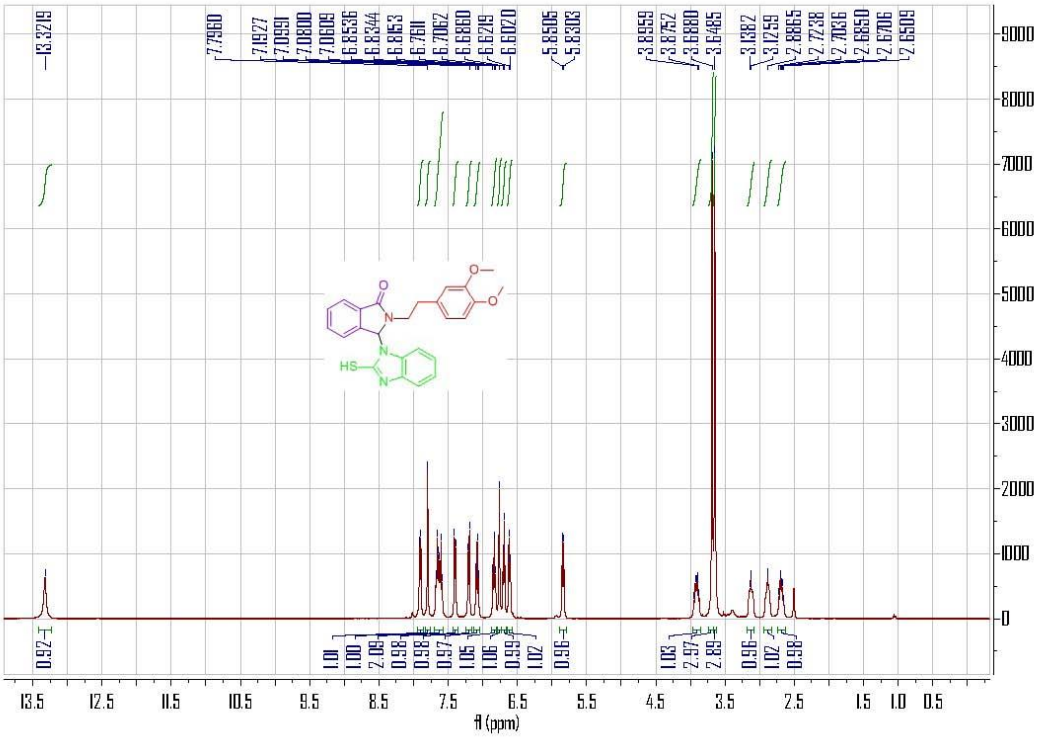
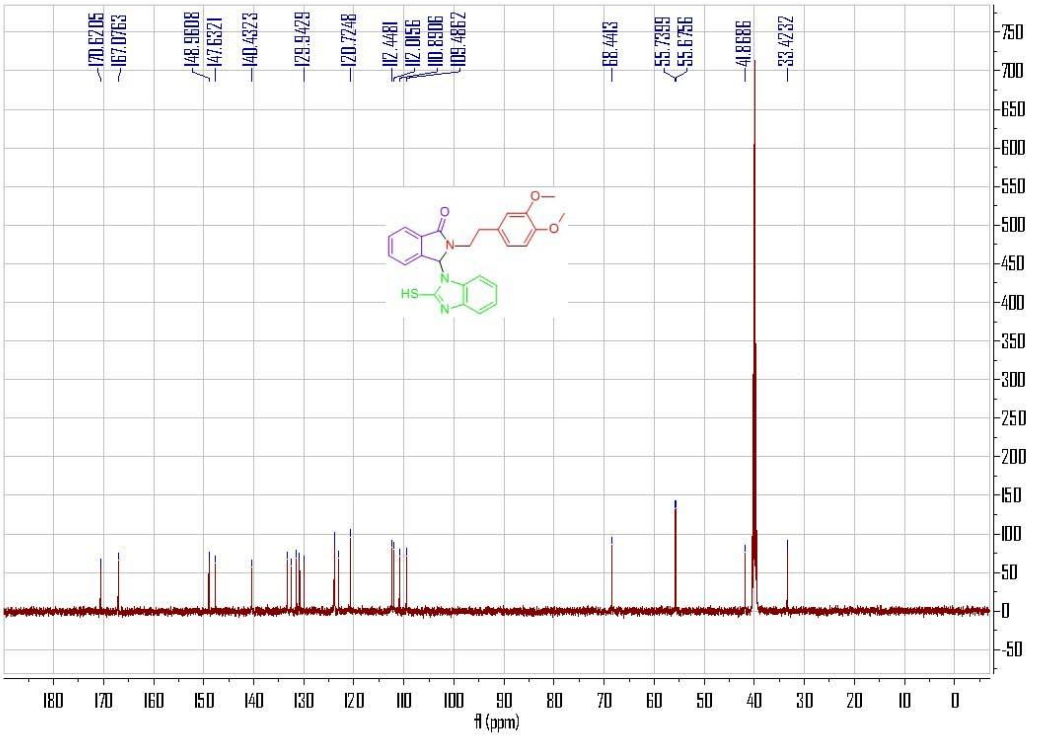
^{1}H, ^{13}C NMR, and LC-MS of compound 4fa





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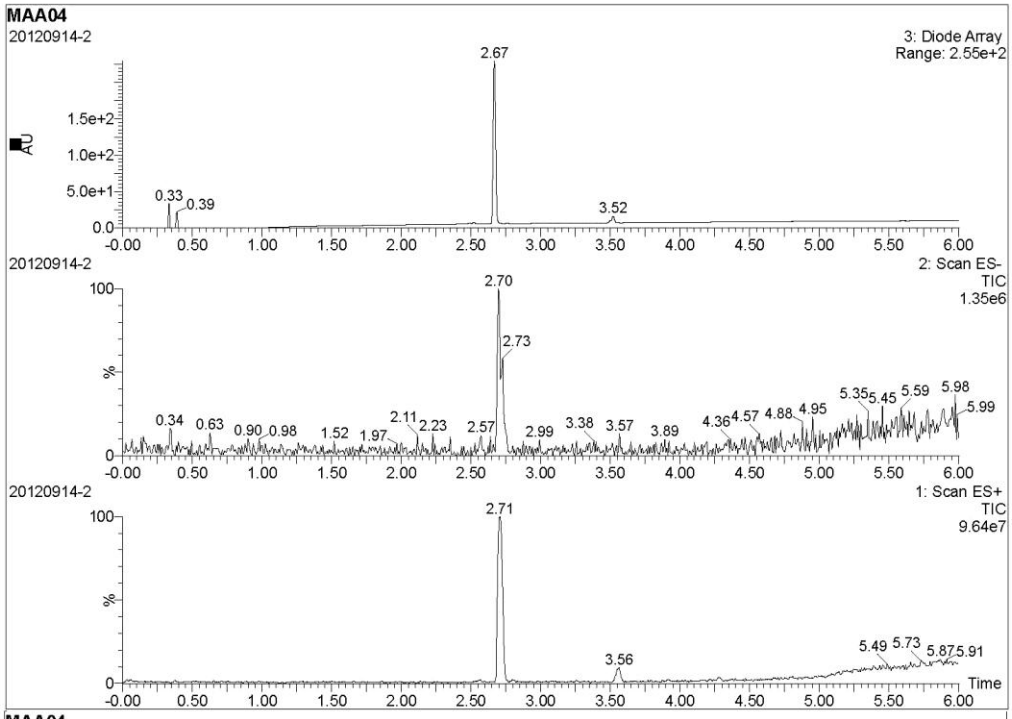

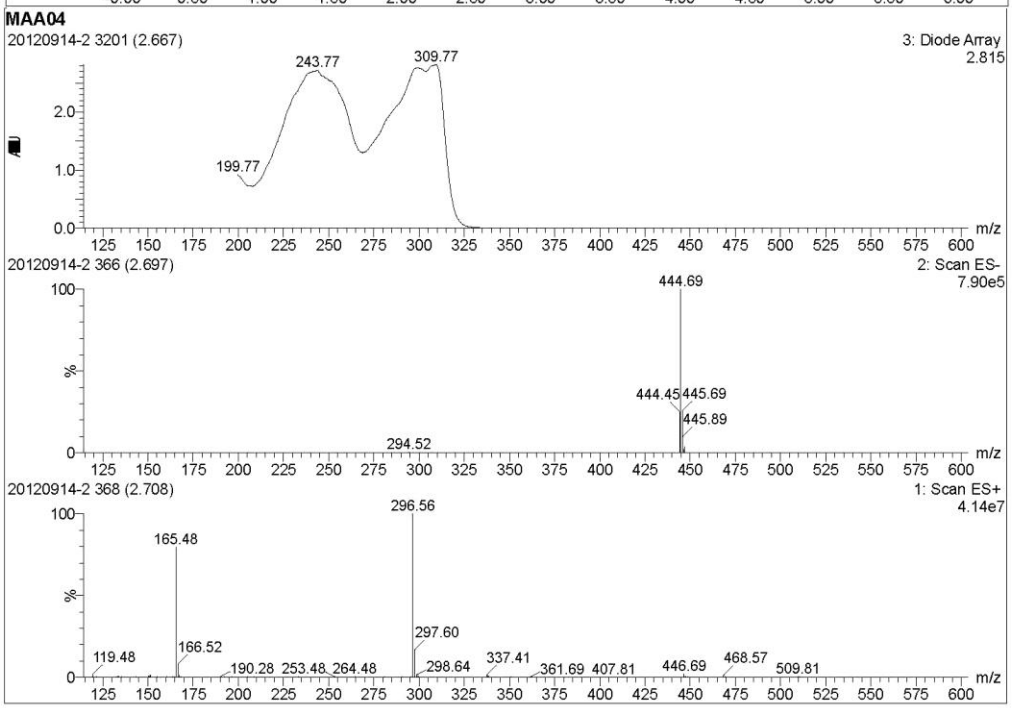

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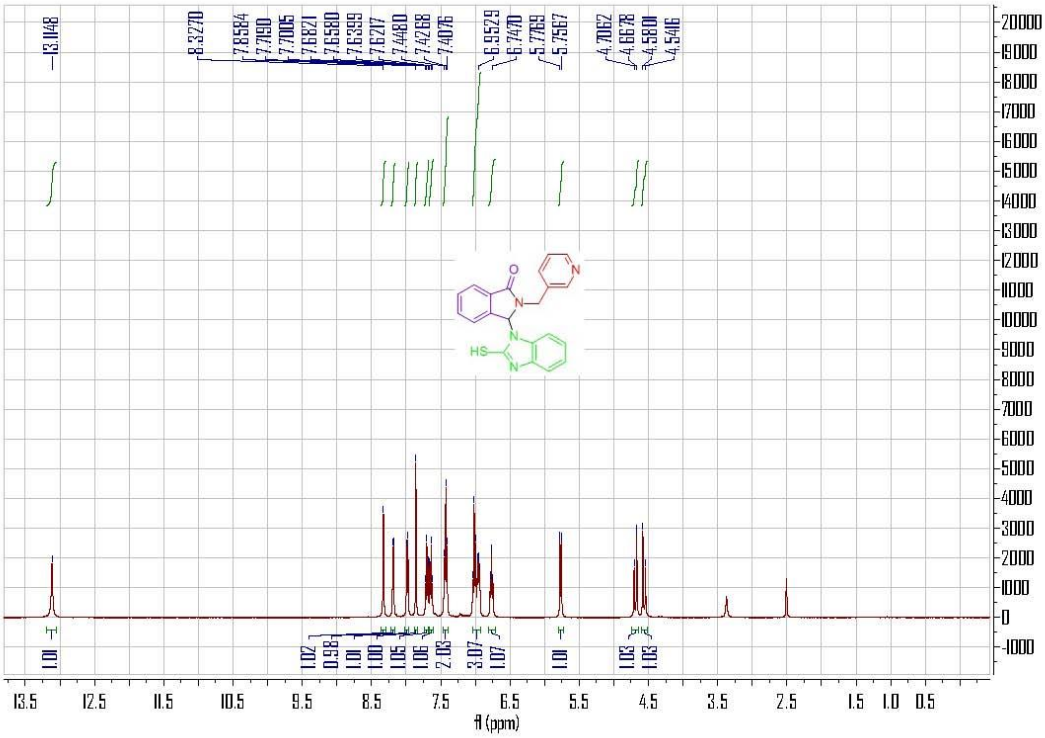
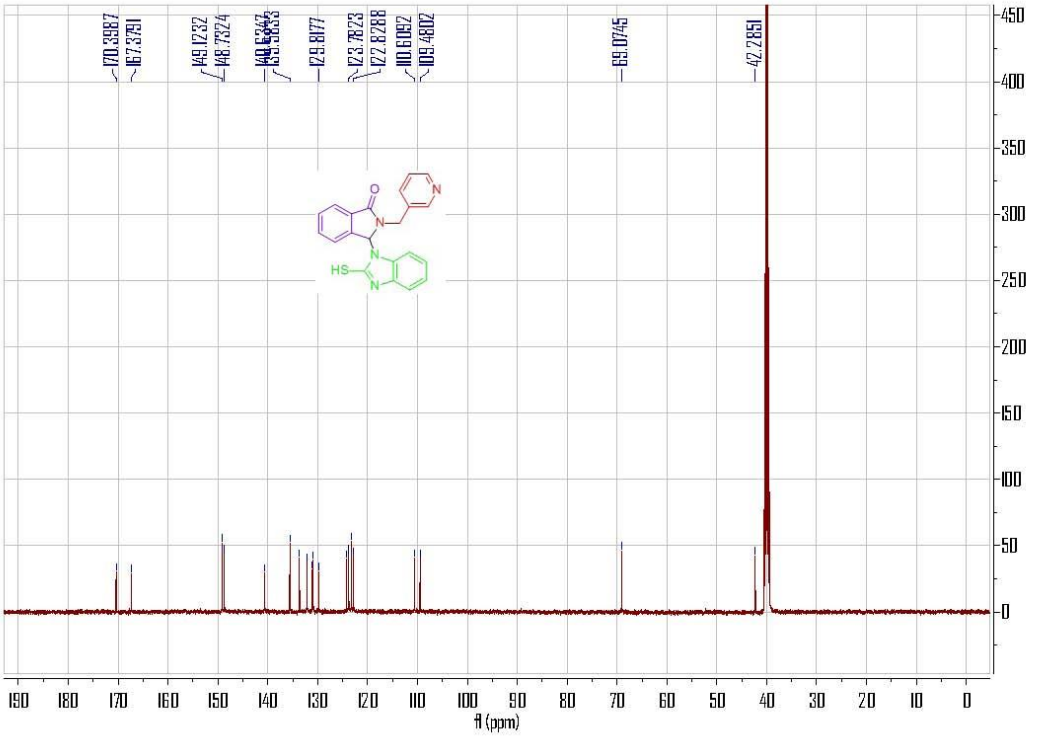
^{1}H, ^{13}C NMR, and LC-MS of compound 4ga





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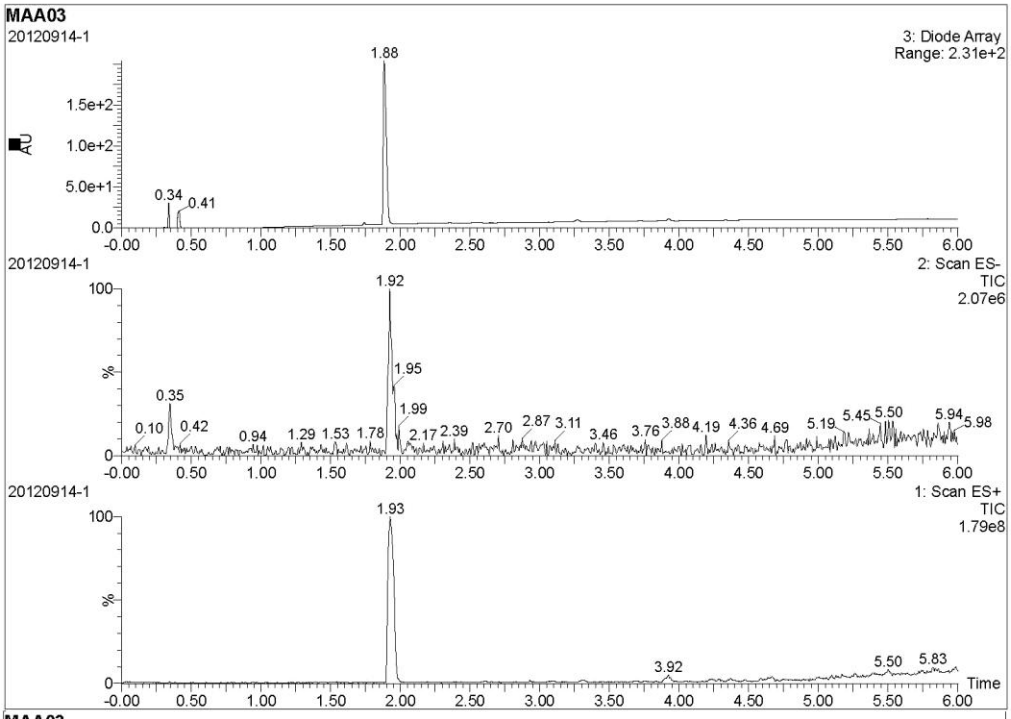

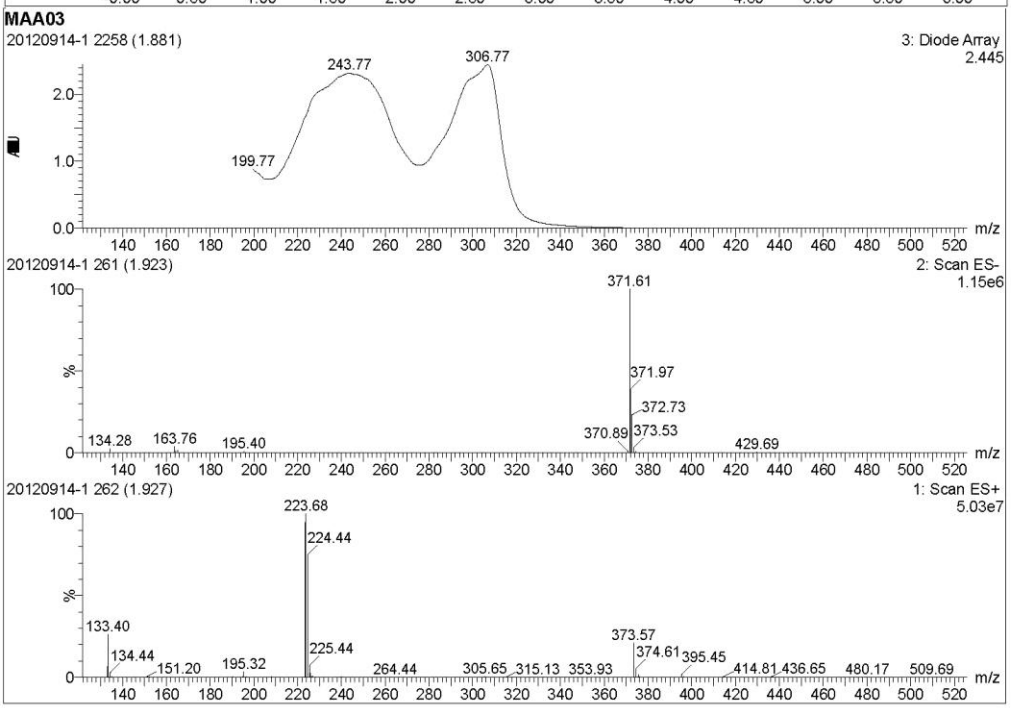

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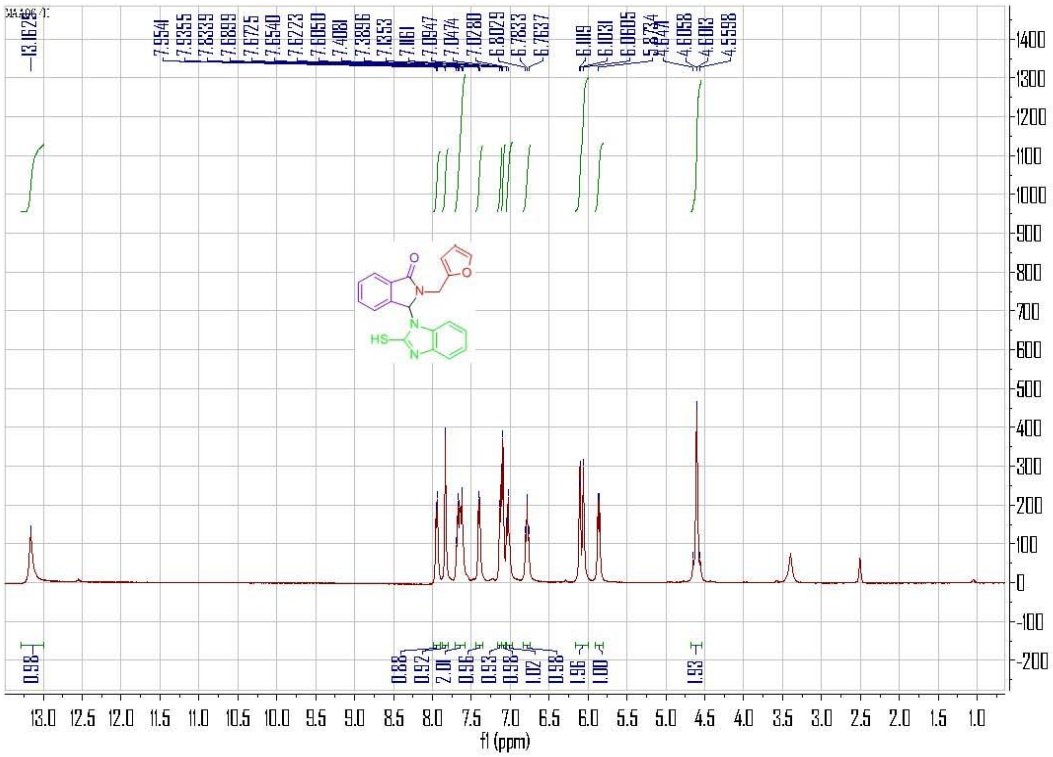
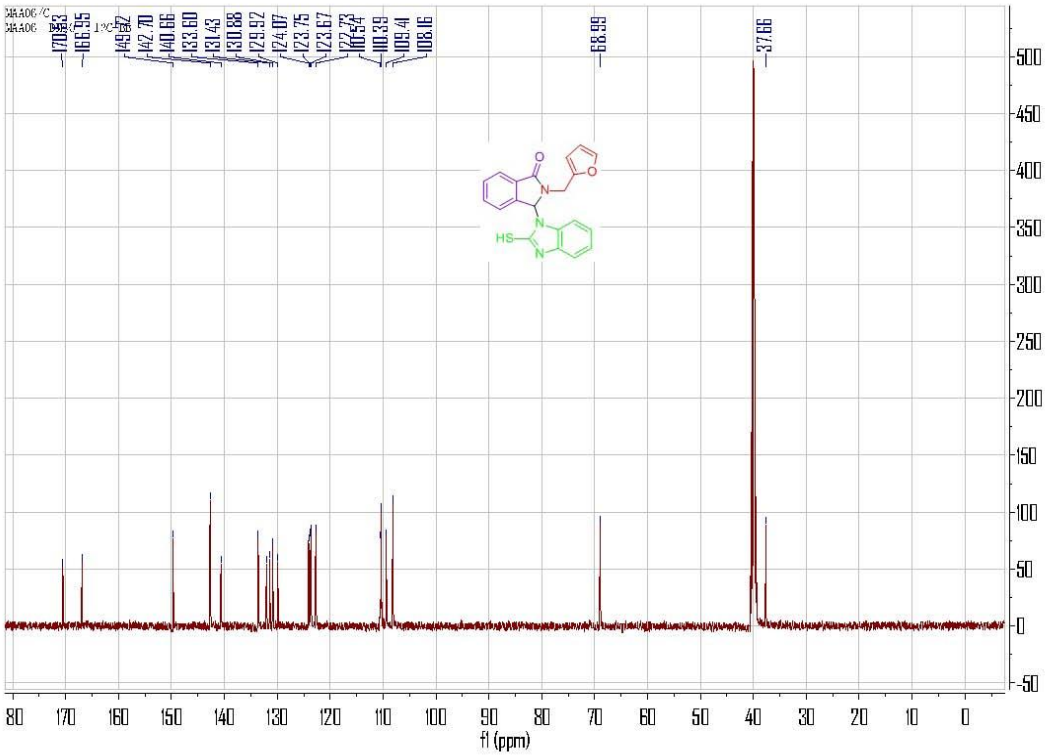
^{1}H, ^{13}C NMR, and LC-MS of compound 4ha





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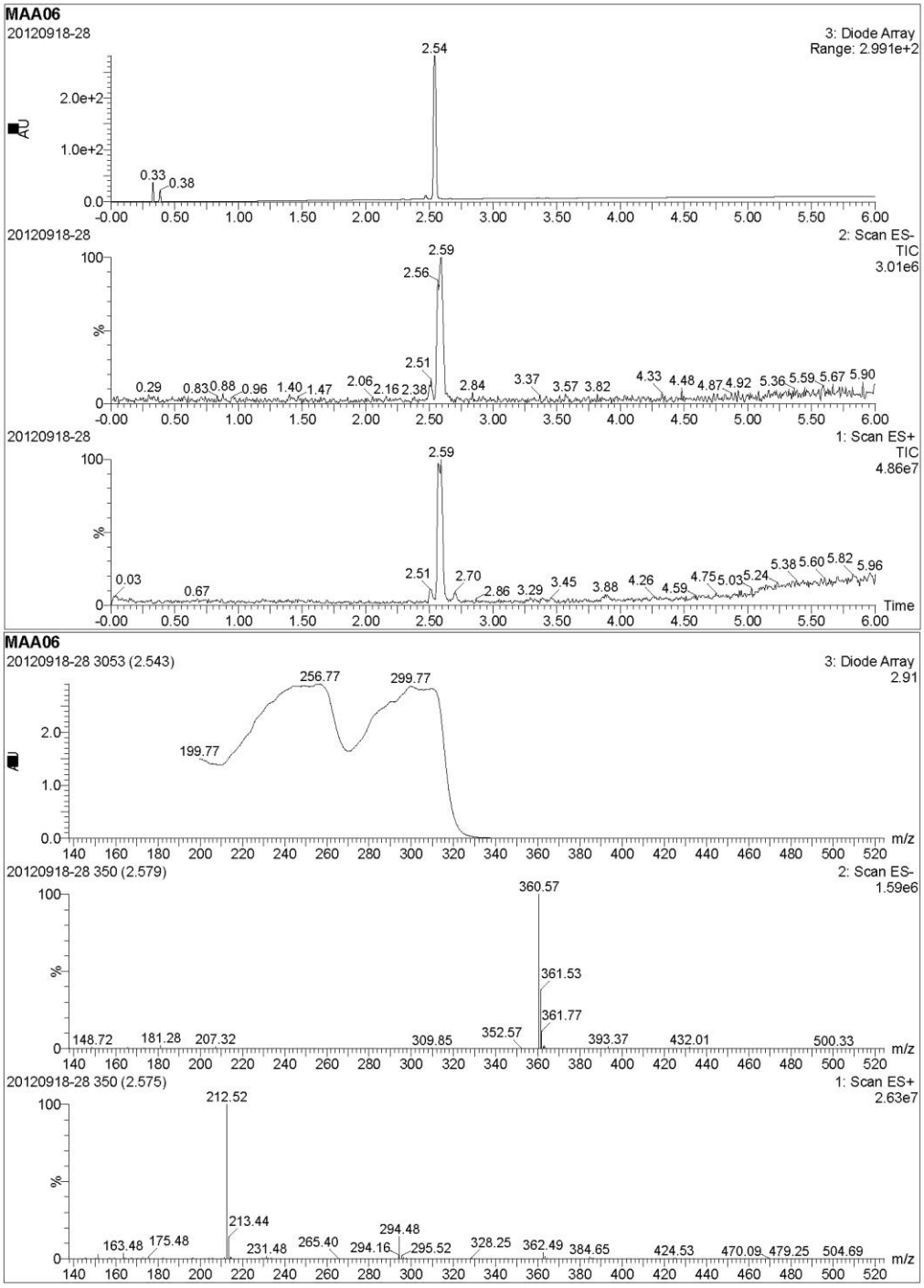

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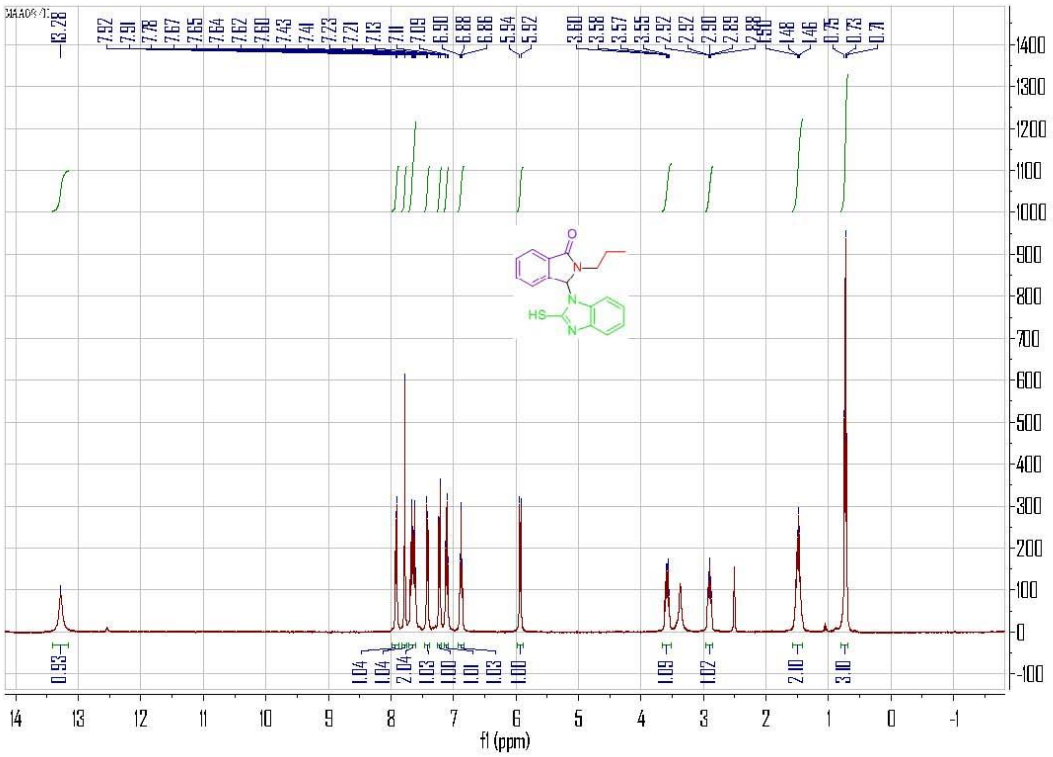
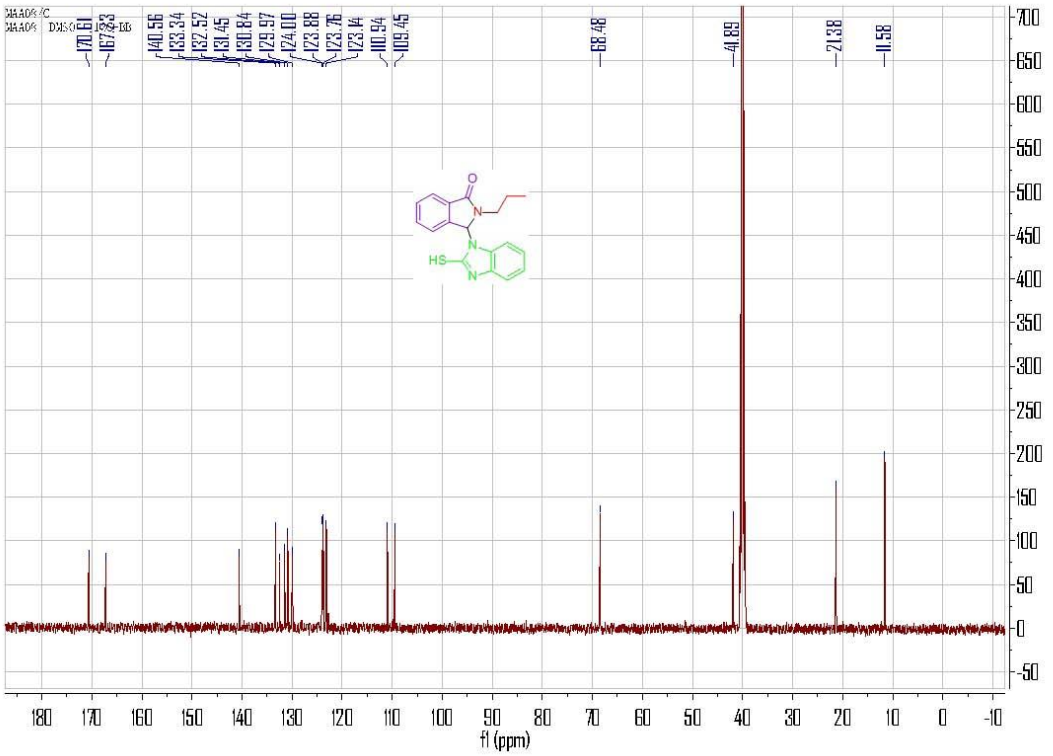
^{1}H, ^{13}C NMR, and LC-MS of compound 4ia





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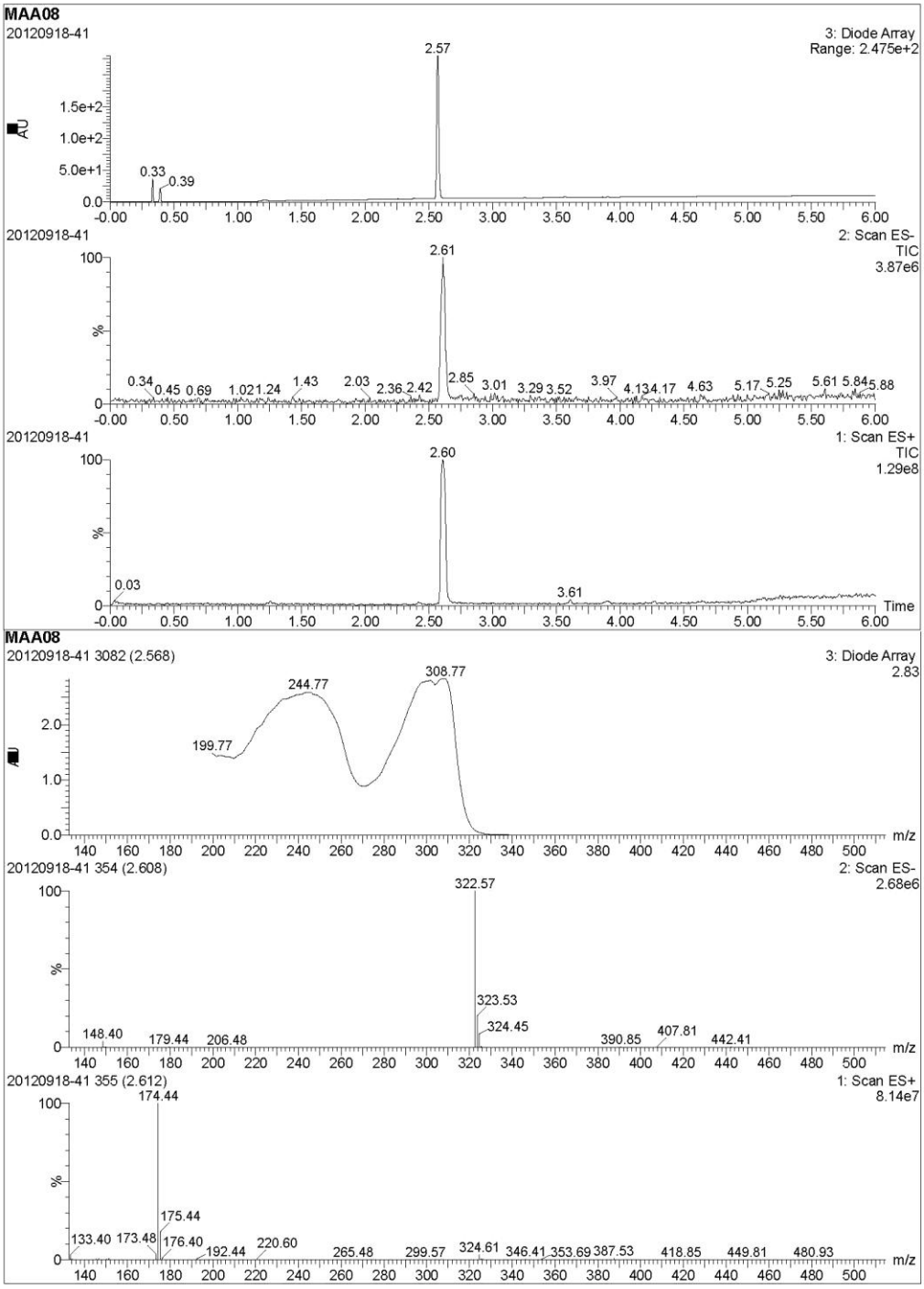

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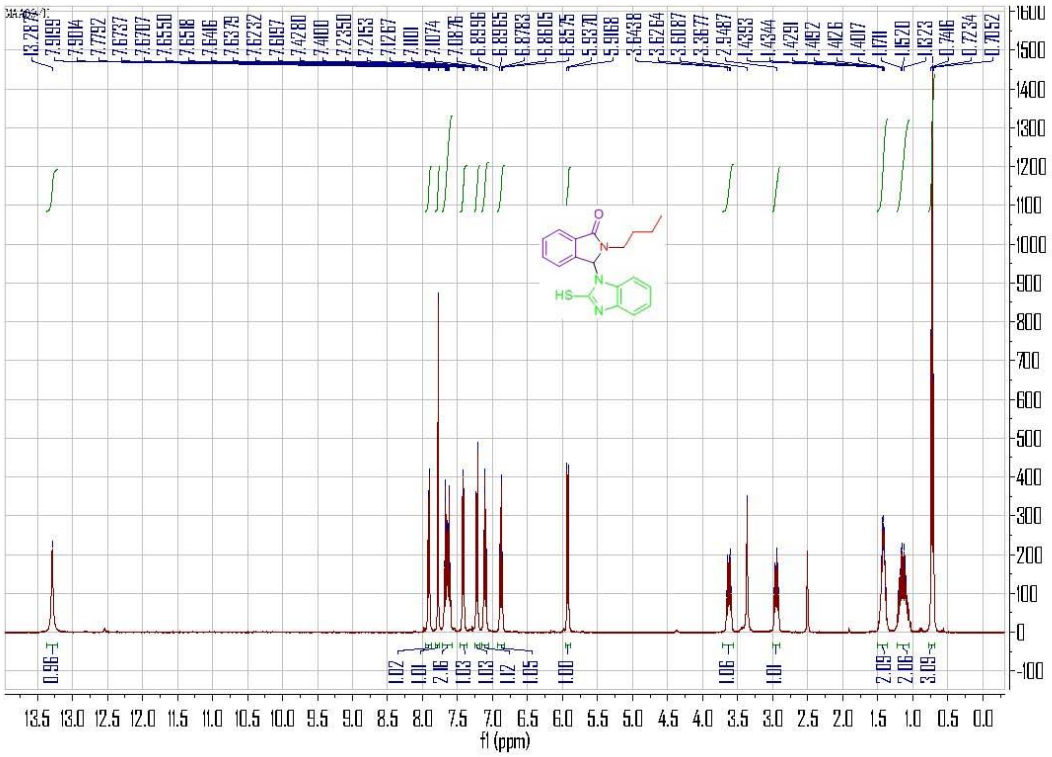
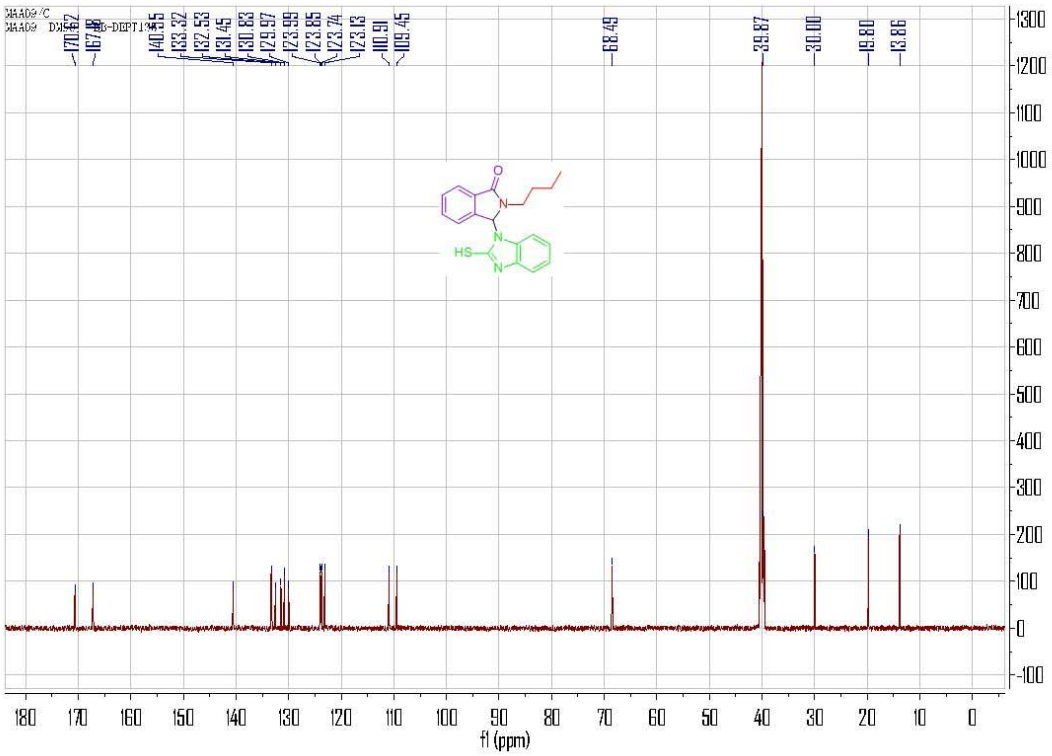
^{1}H, ^{13}C NMR, and LC-MS of compound 4ja





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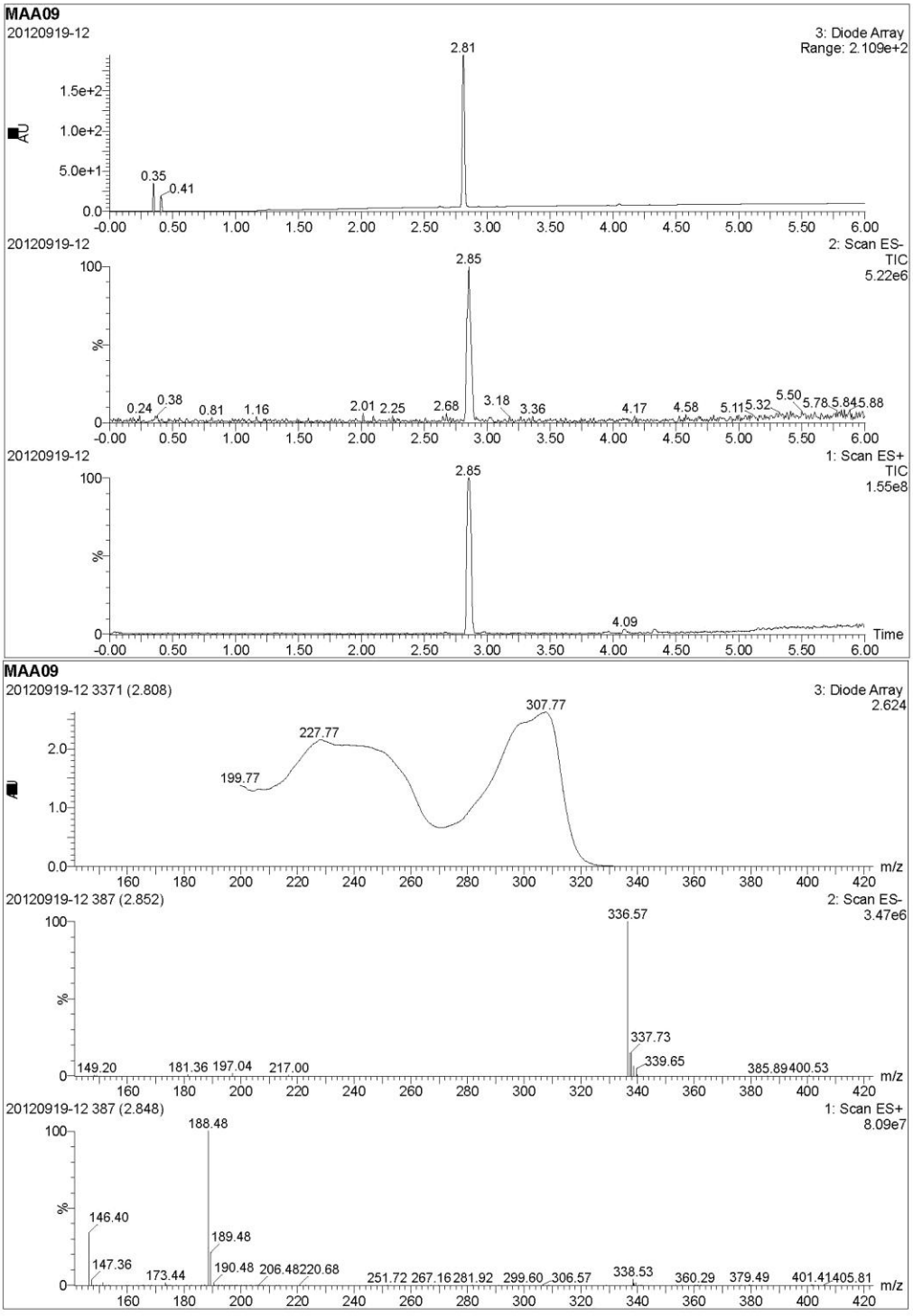
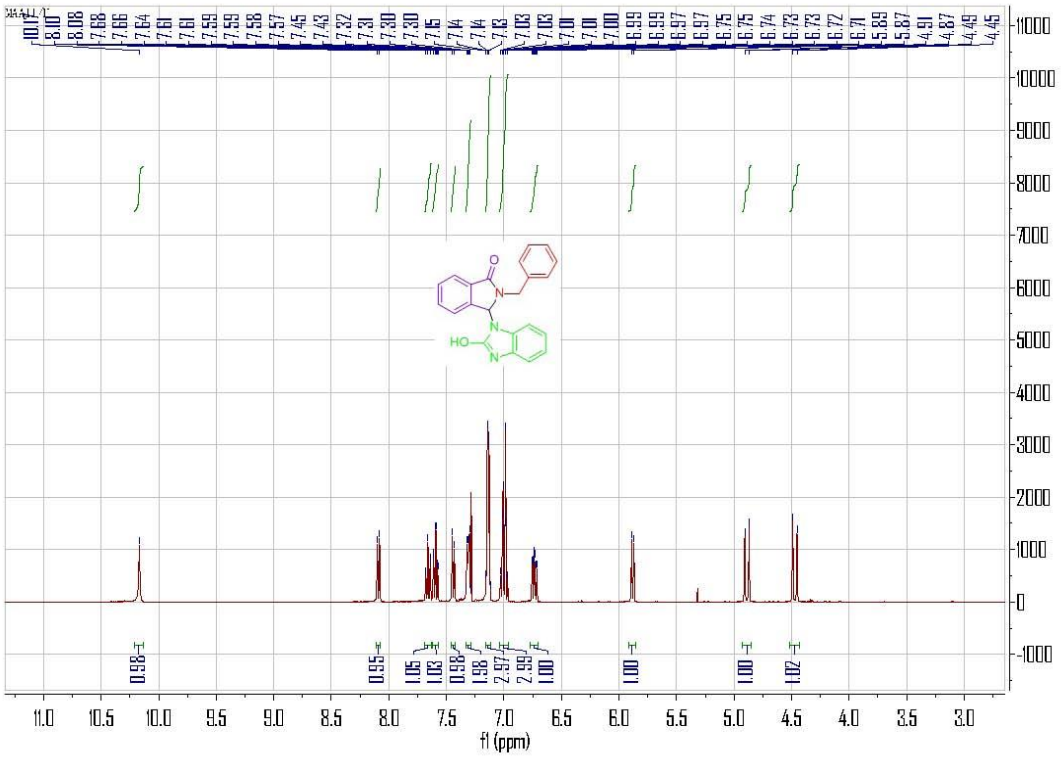
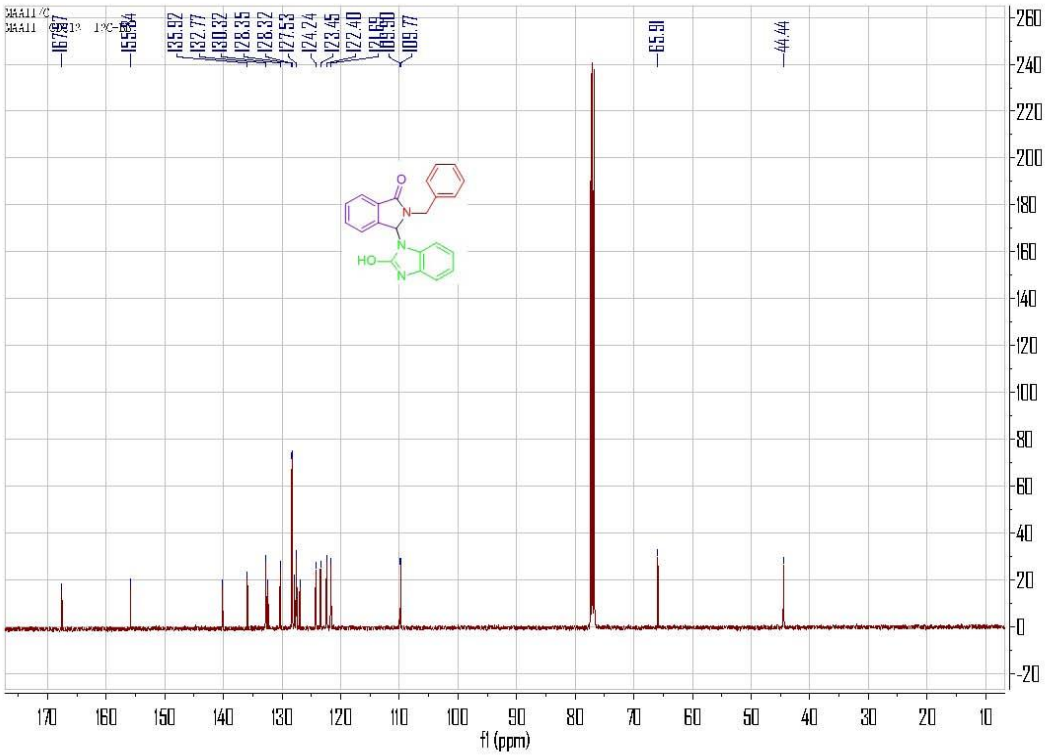


ACCEPTED MANUSCRIPT

^{1}H, ^{13}C NMR, and LC-MS of compound 4ab





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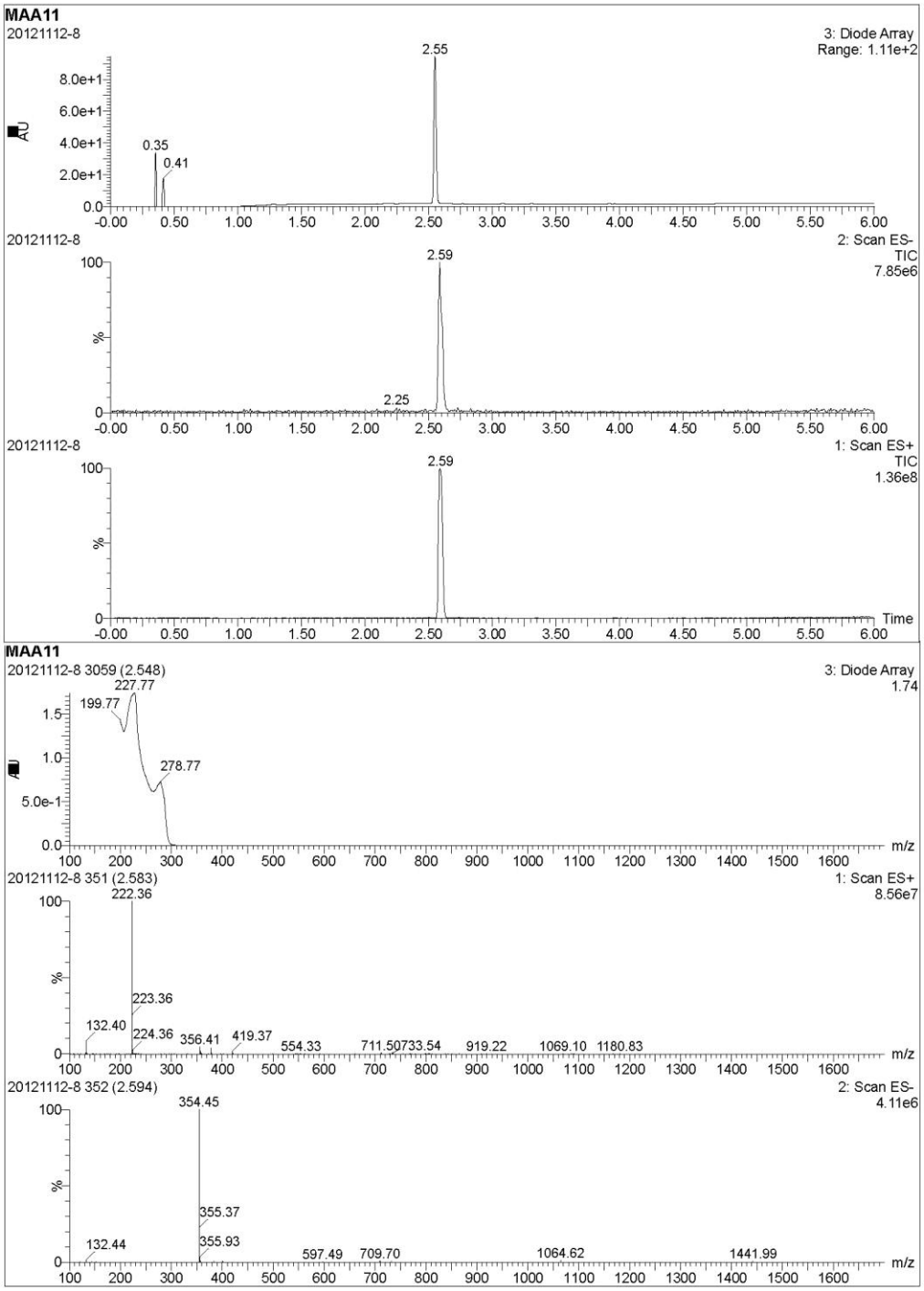
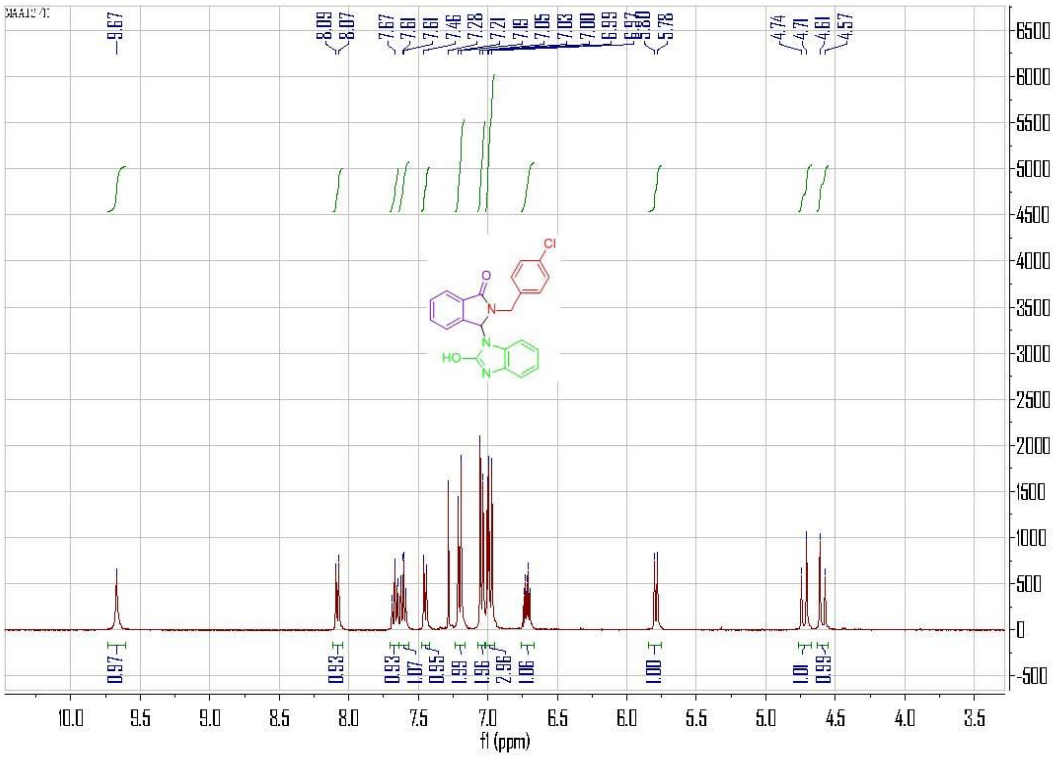
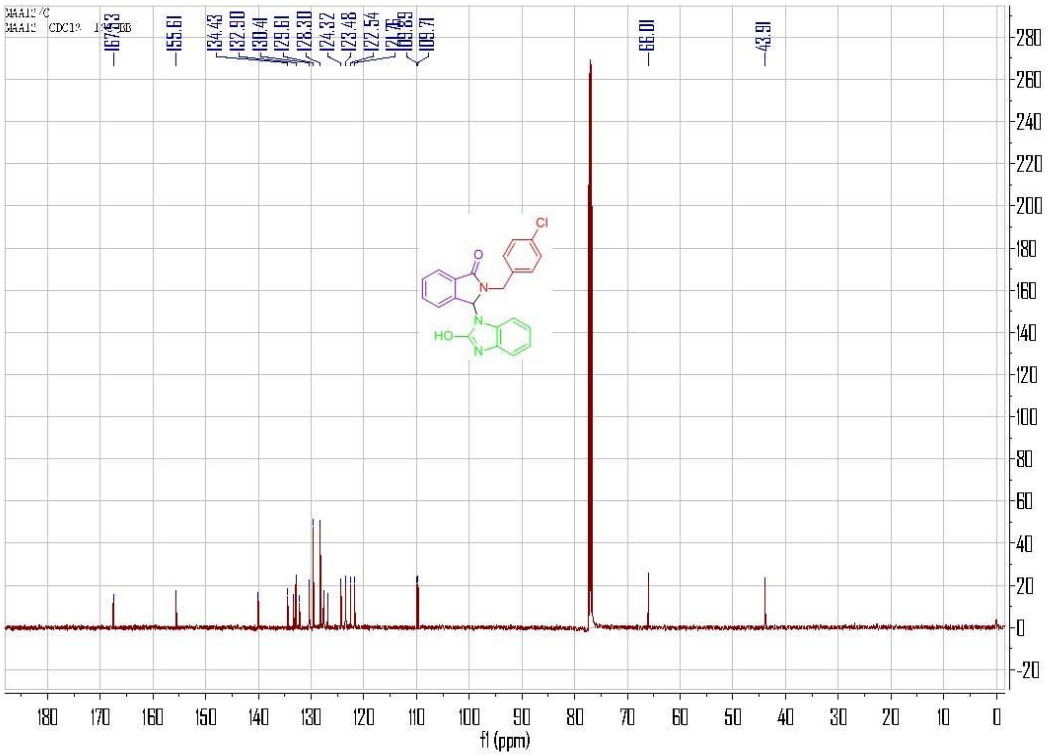


ACCEPTED MANUSCRIPT

^{1}H, ^{13}C NMR, and LC-MS of compound 4bb





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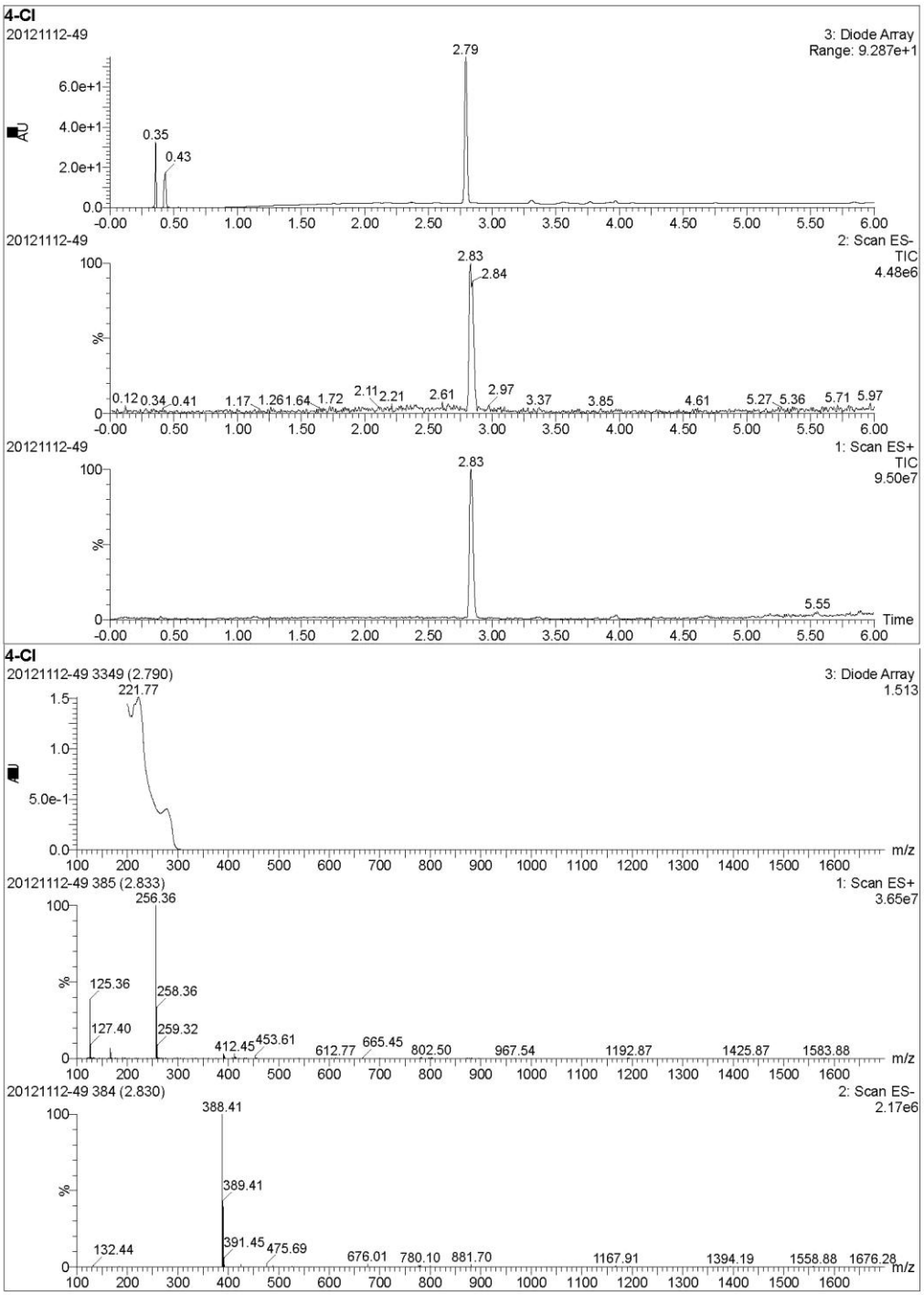
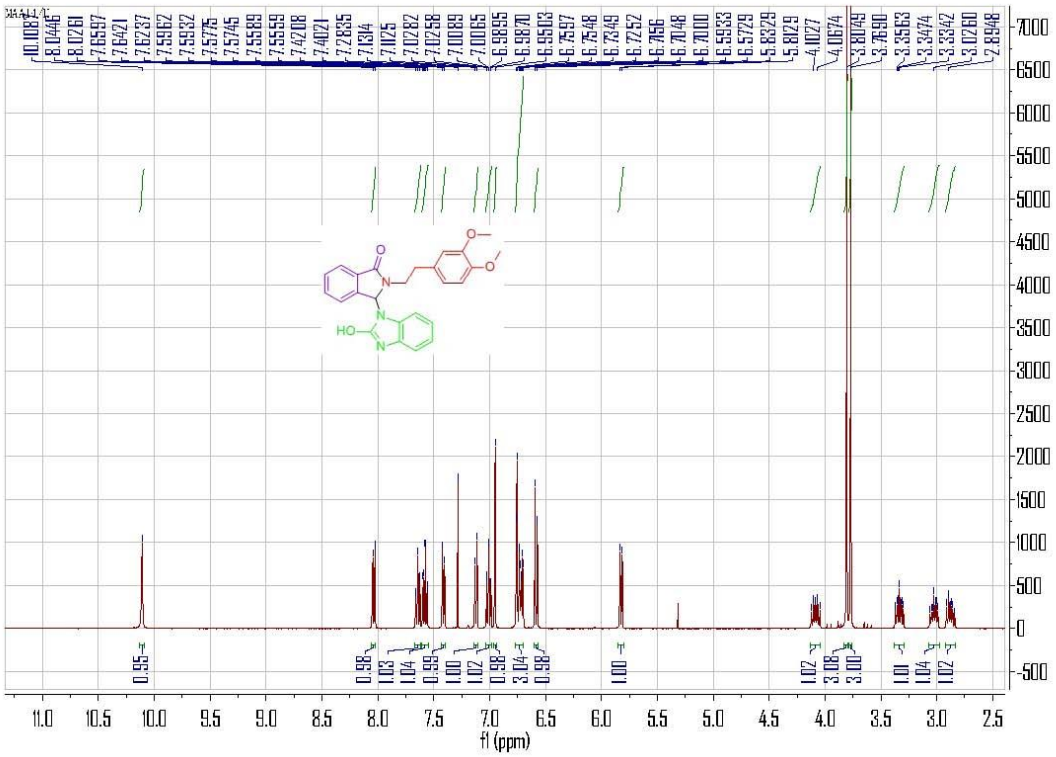
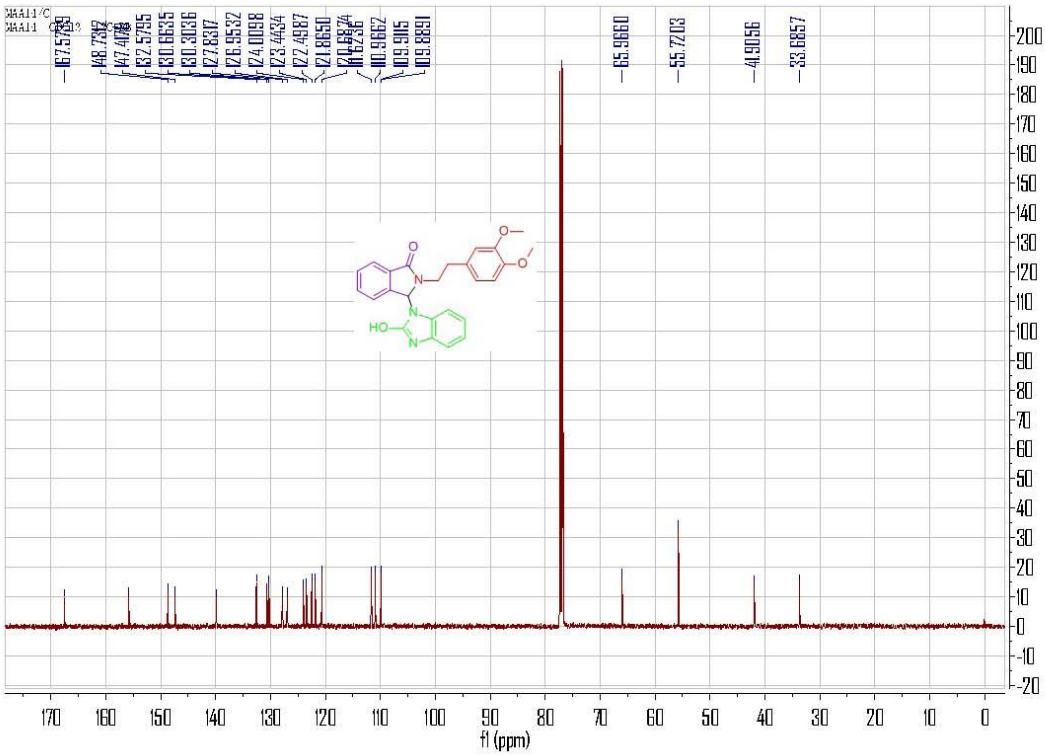


ACCEPTED MANUSCRIPT

^{1}H, ^{13}C NMR, and LC-MS of compound 4fb





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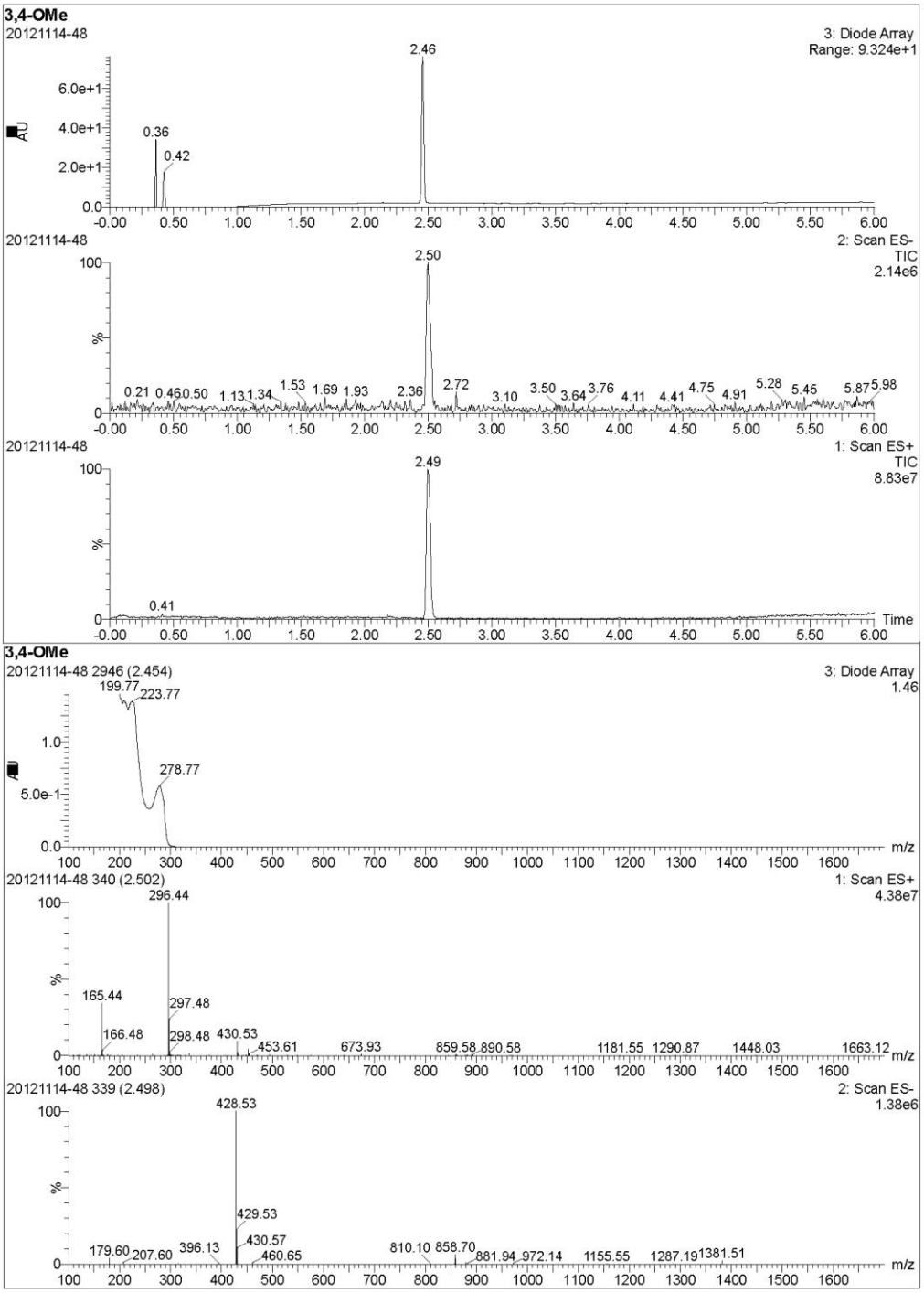

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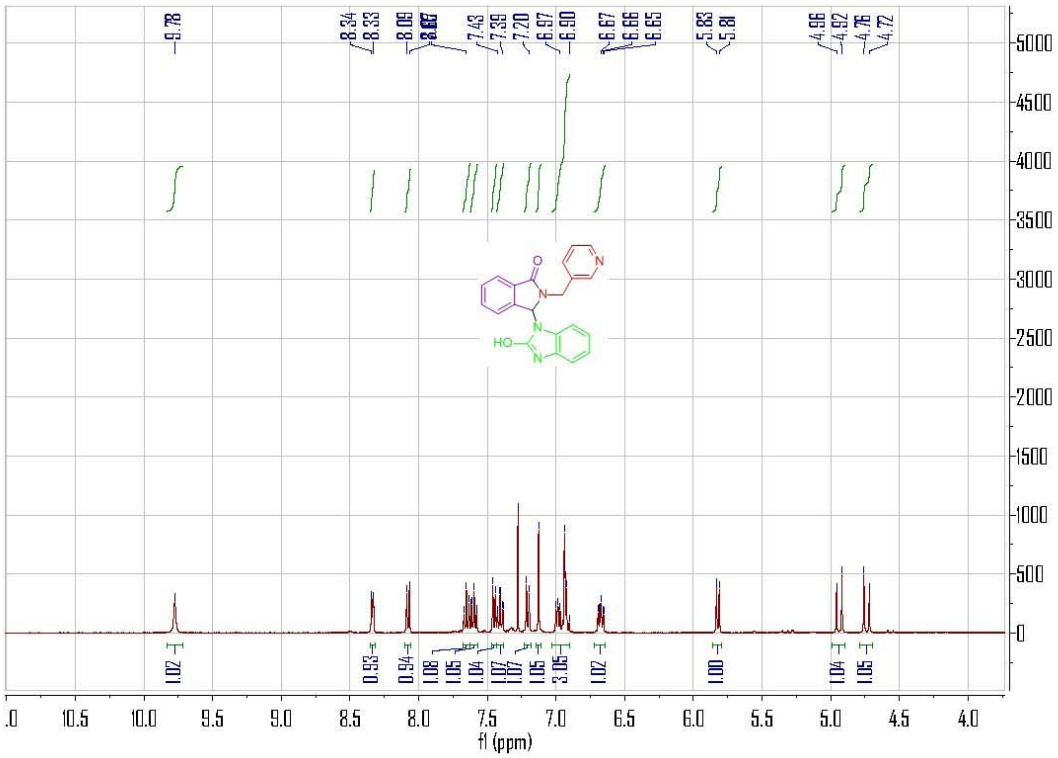
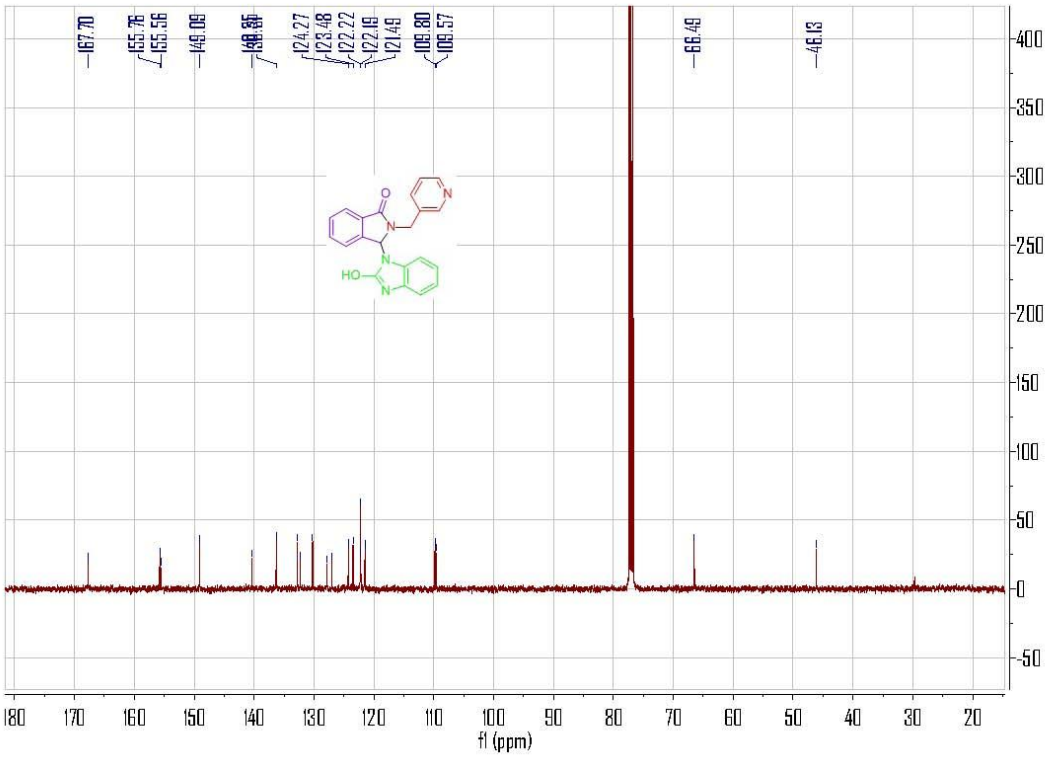
^{1}H, ^{13}C NMR, and LC-MS of compound 4gb





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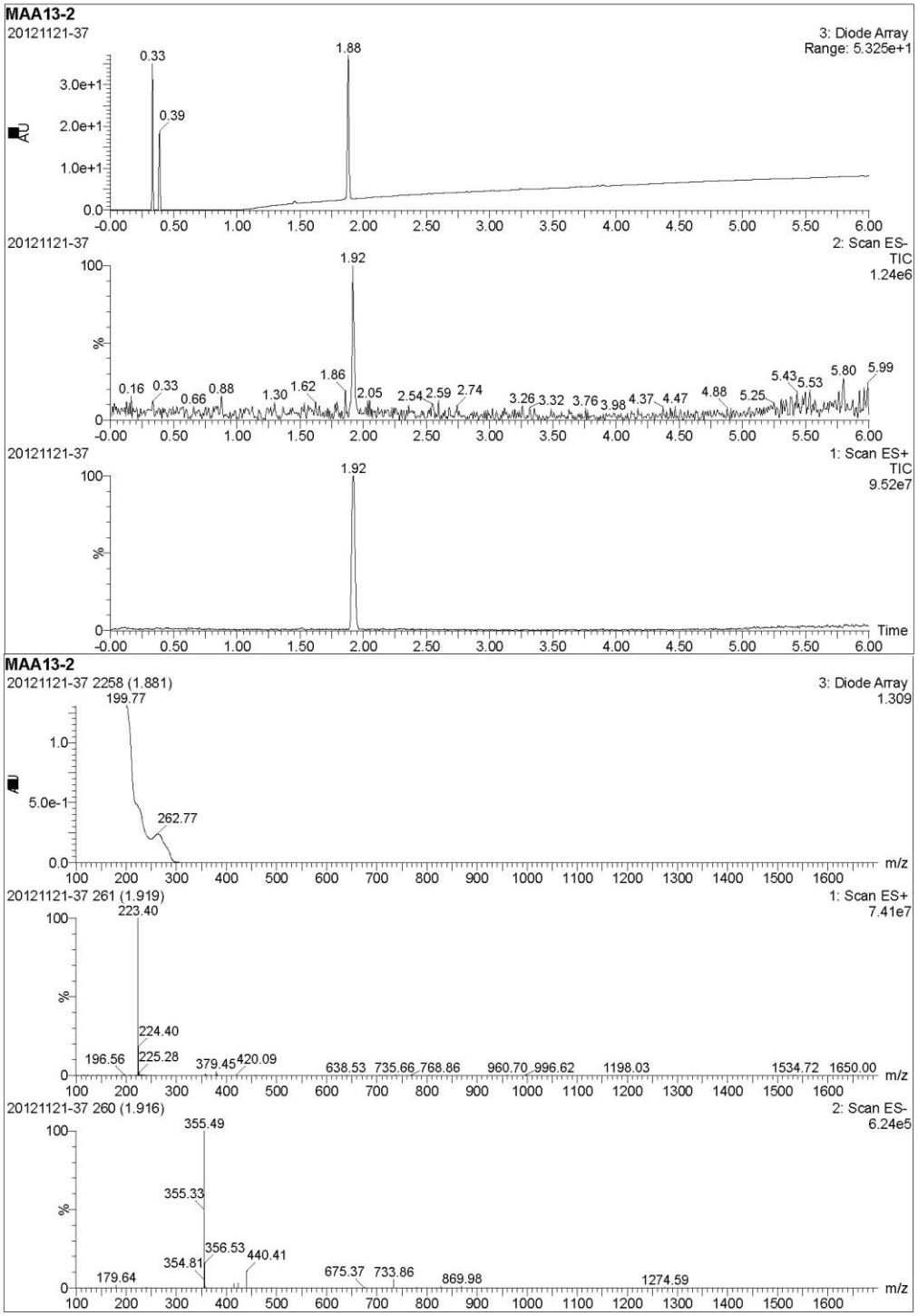

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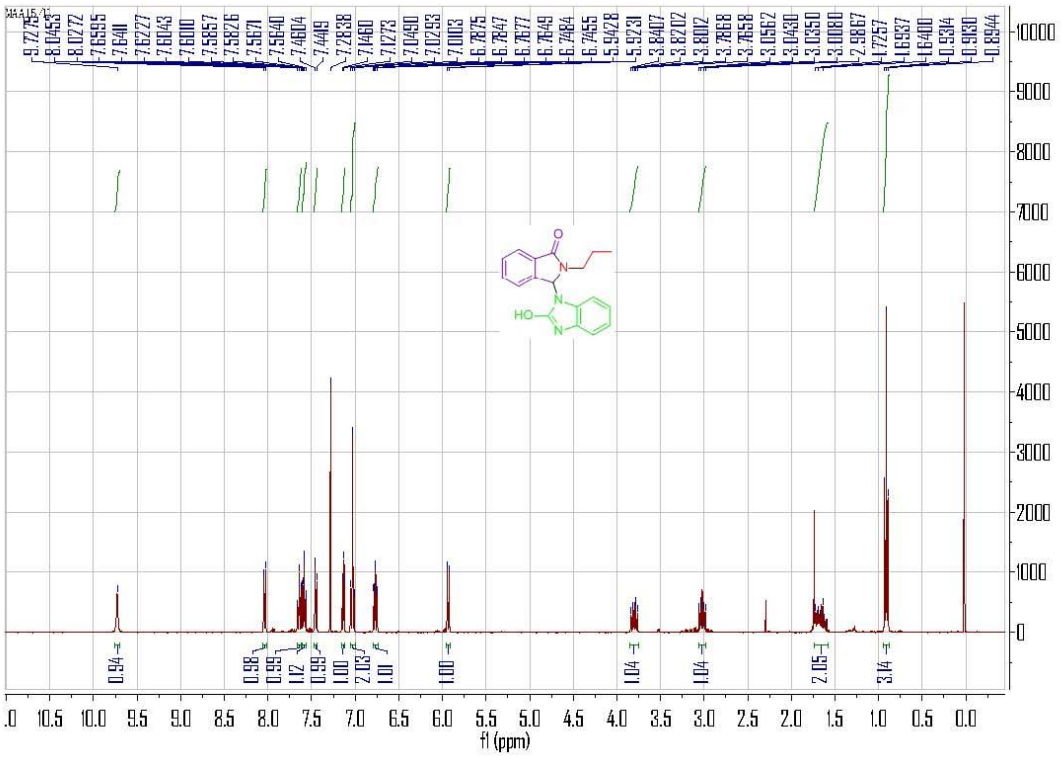
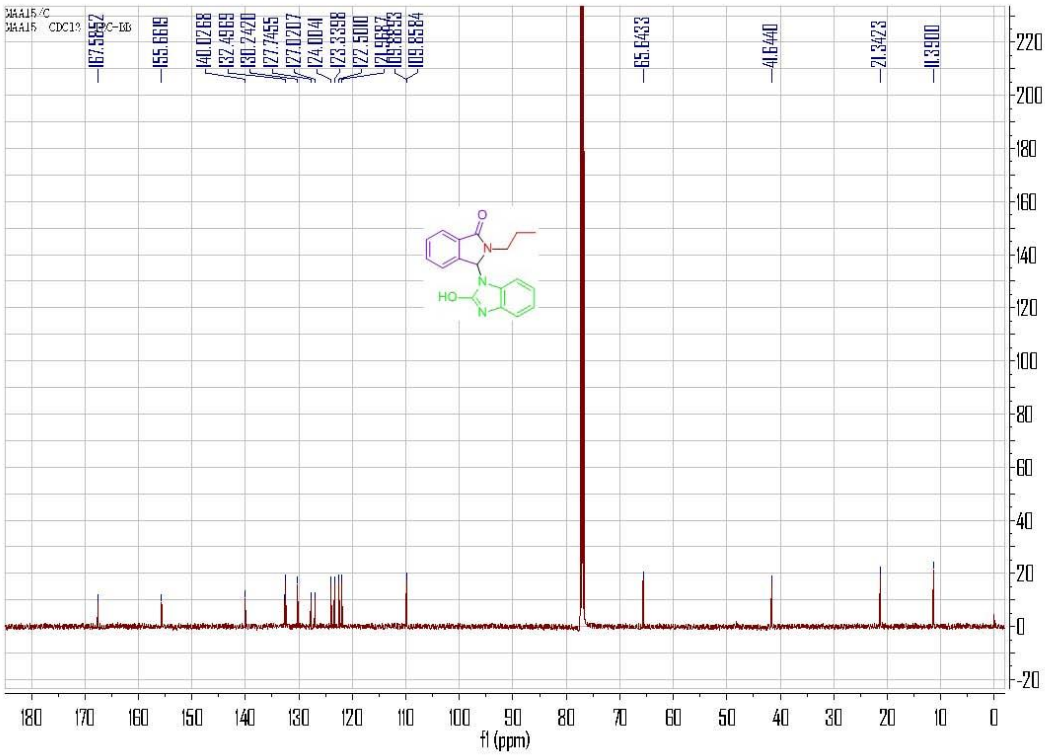
^{1}H, ^{13}C NMR, and LC-MS of compound 4ib





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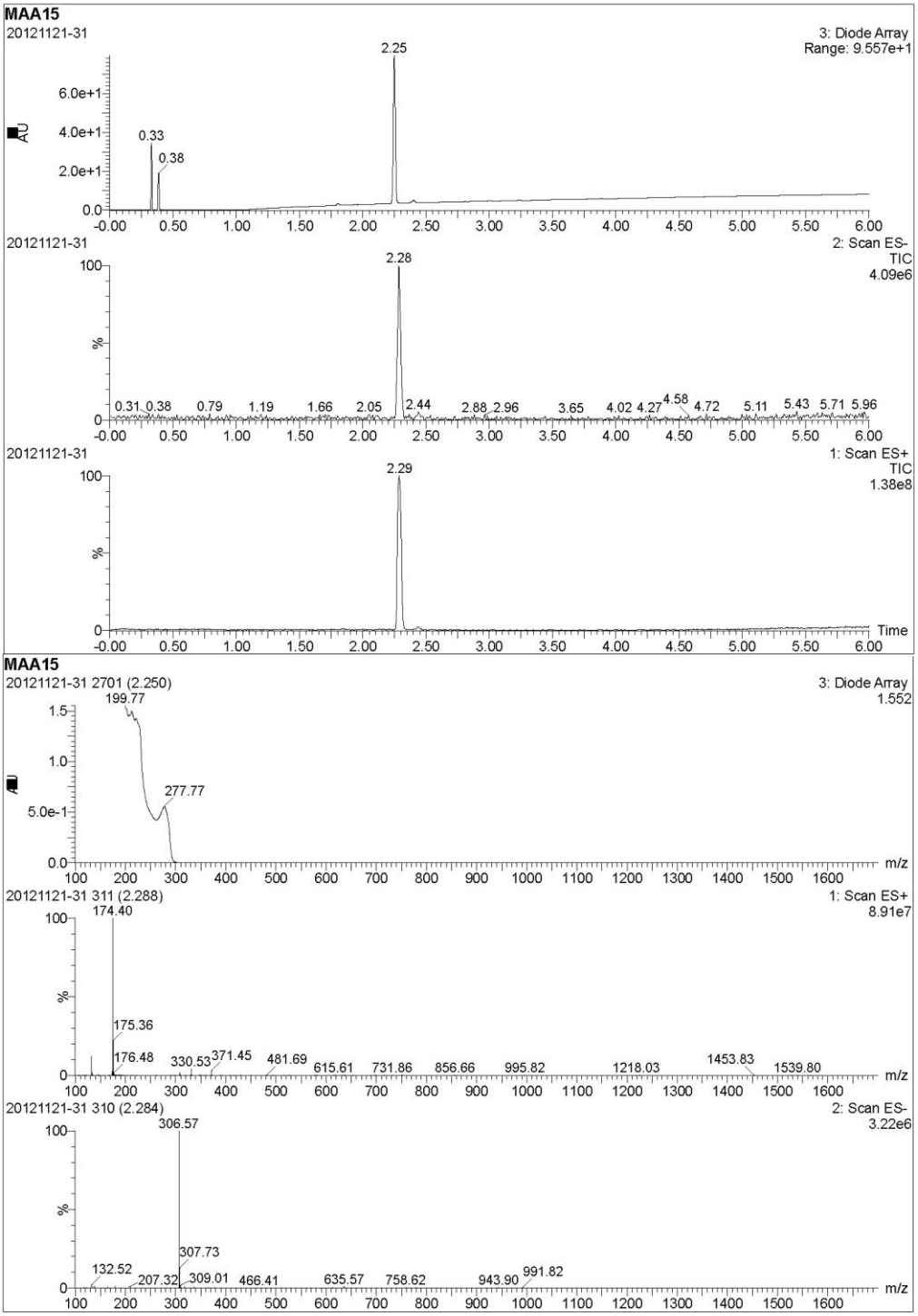
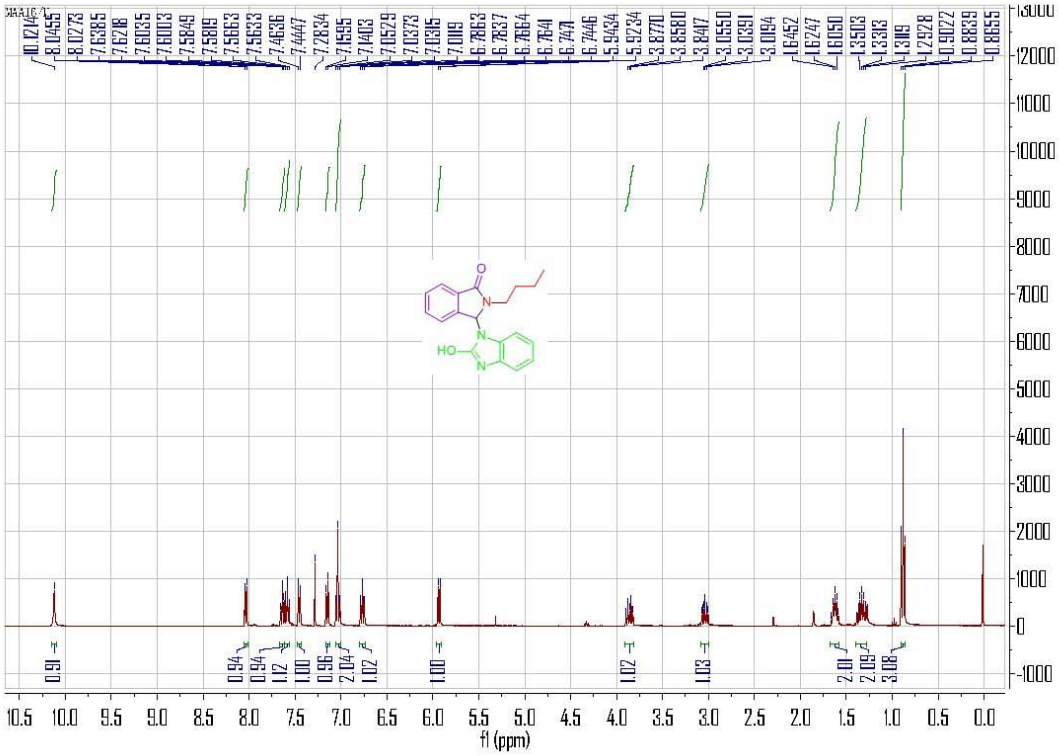
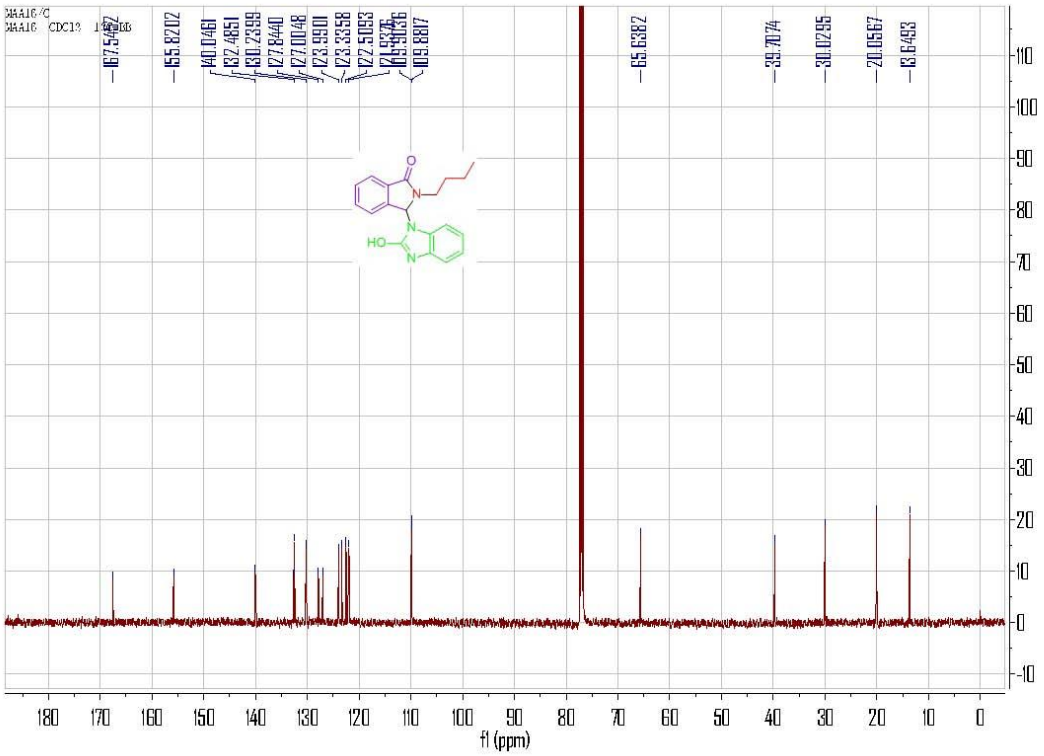


ACCEPTED MANUSCRIPT

^{1}H, ^{13}C NMR, and LC-MS of compound 4jb





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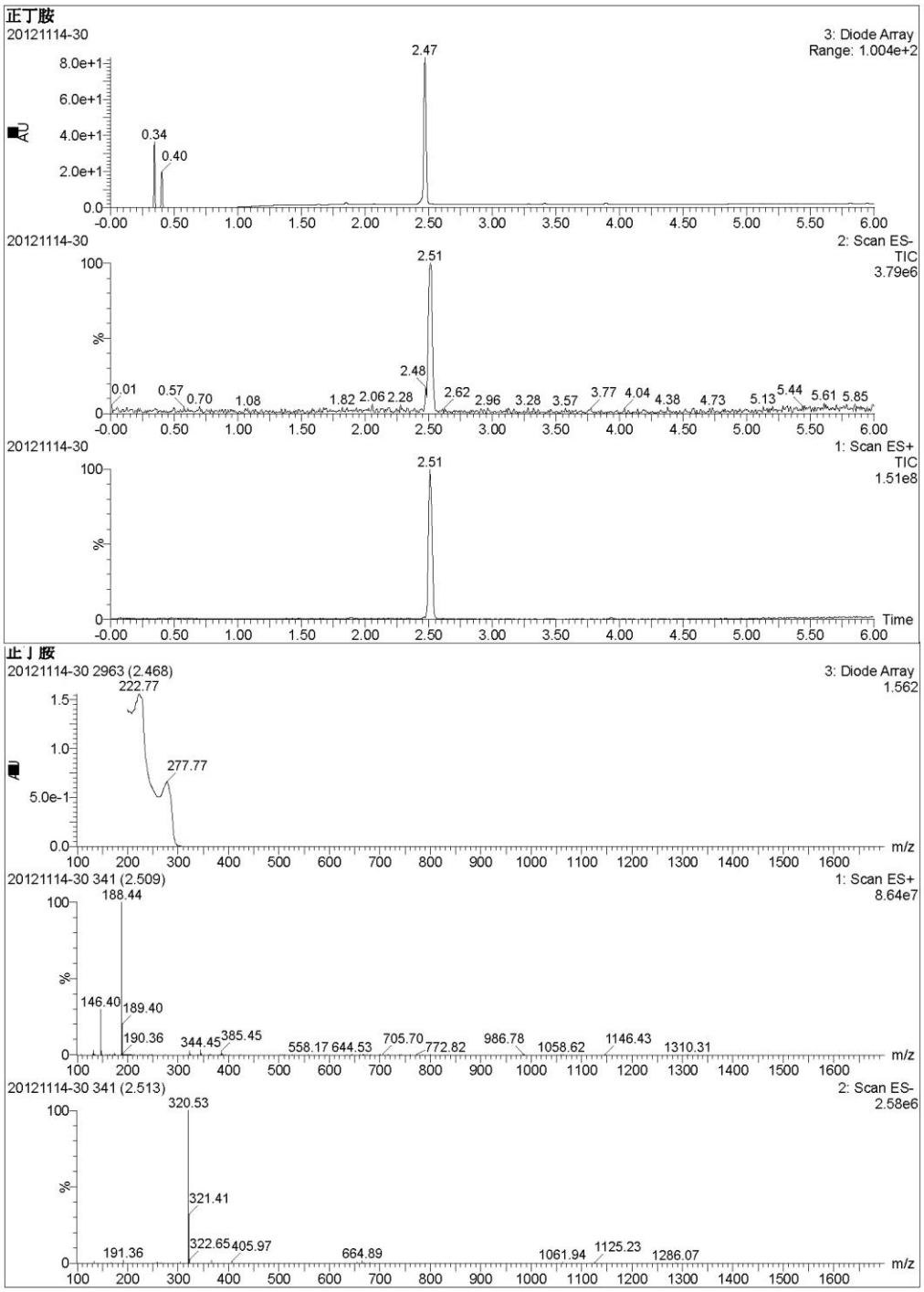
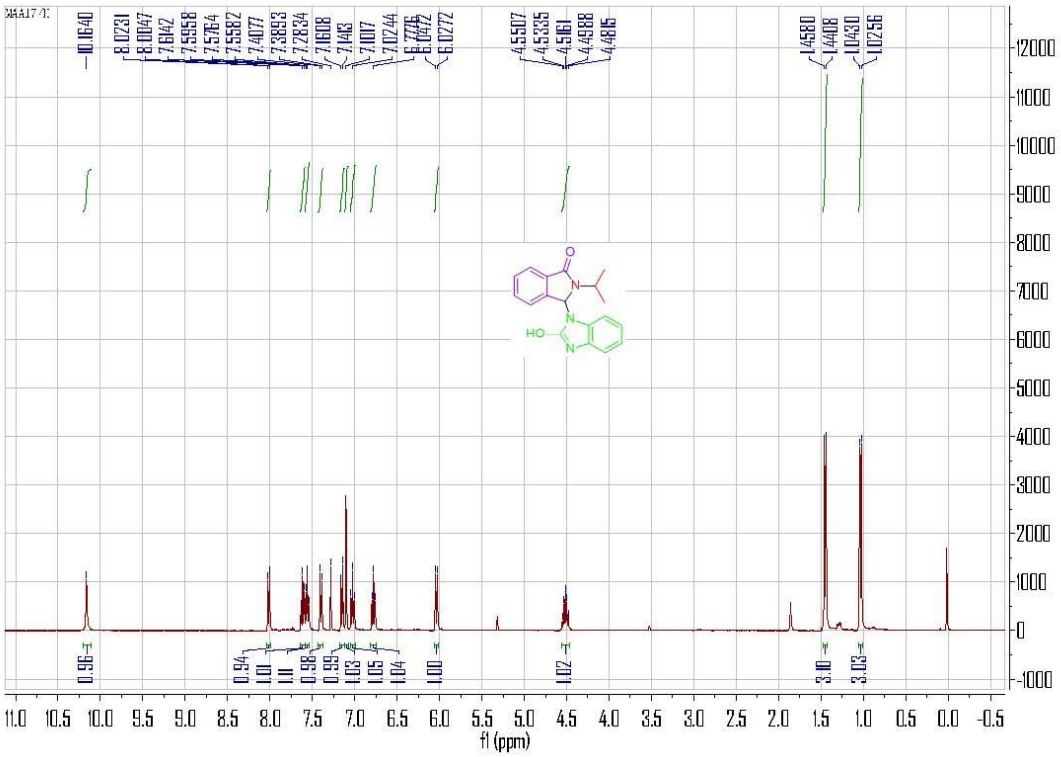
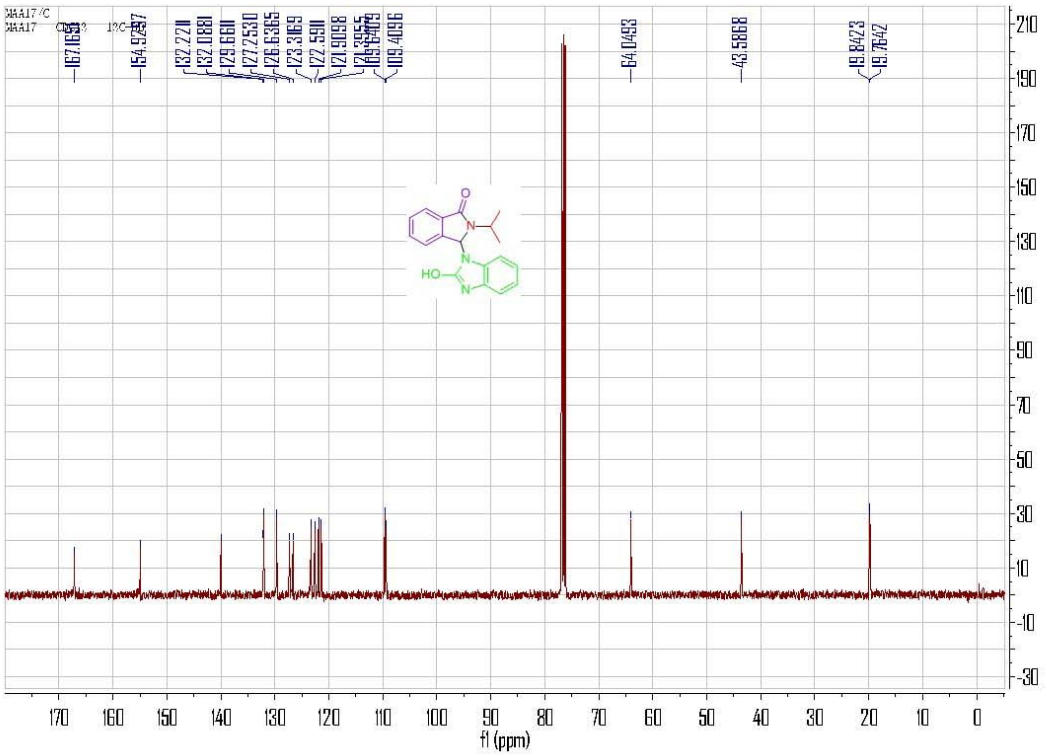


ACCEPTED MANUSCRIPT

^{1}H, ^{13}C NMR, and LC-MS of compound 4kb





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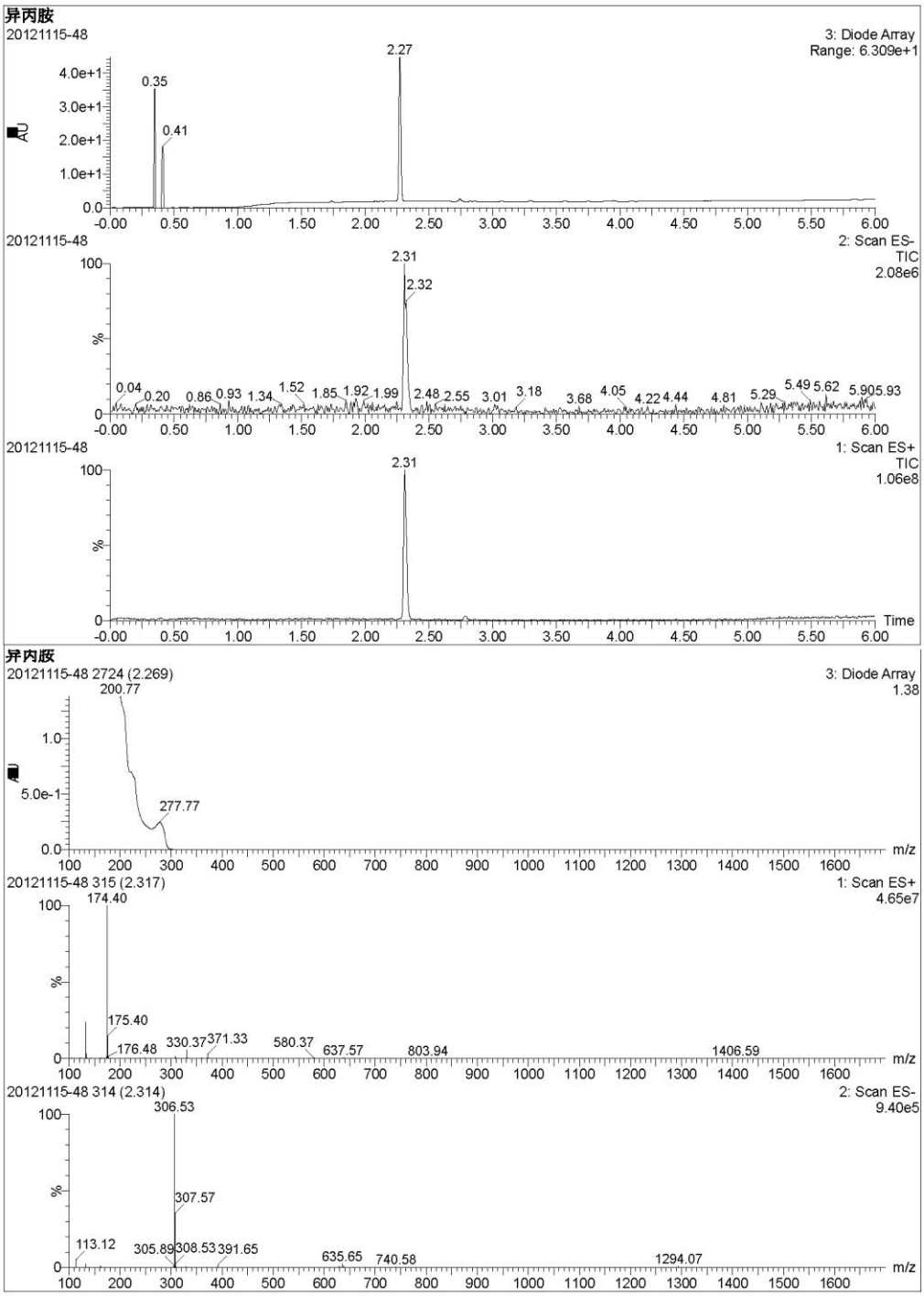

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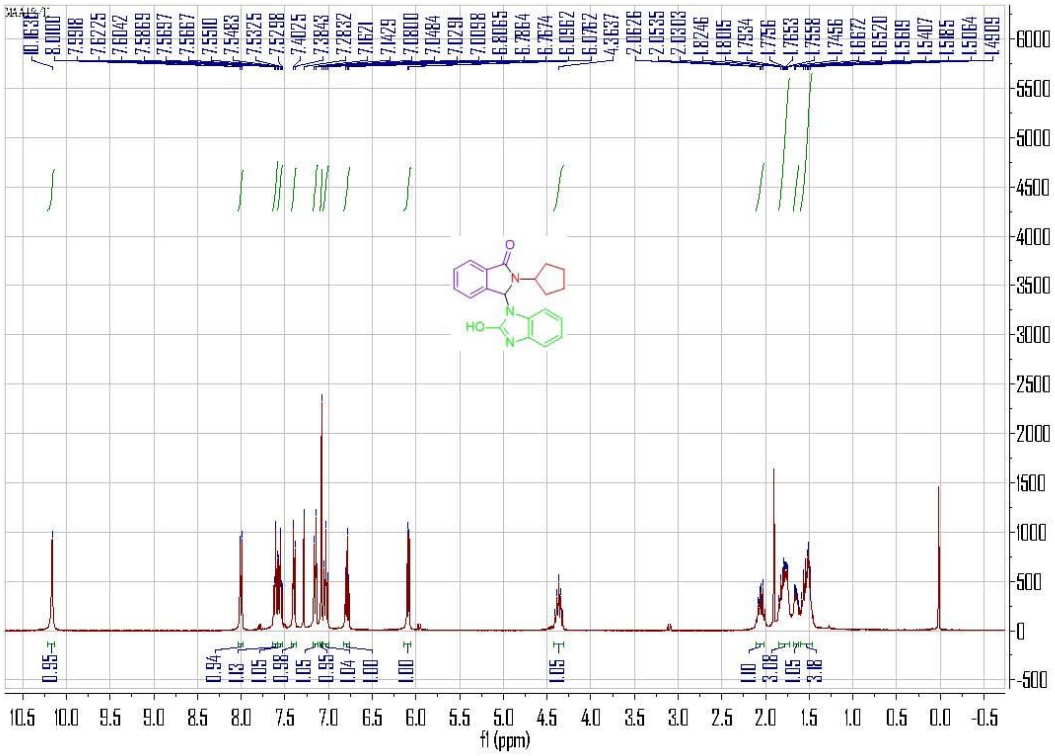
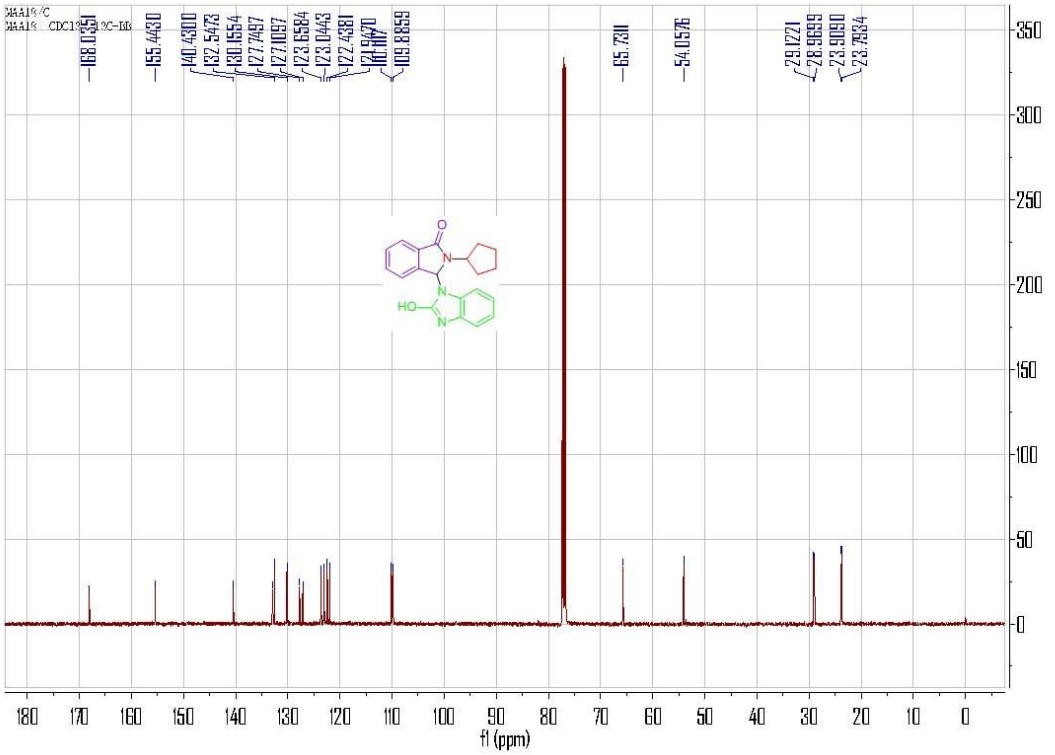
^{1}H, ^{13}C NMR, and LC-MS of compound 4lb





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