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Diversity-oriented approach to spirocycles with indole moiety via Fischer indole cyclization, olefin metathesis and Suzuki–Miyaura cross-coupling reactions

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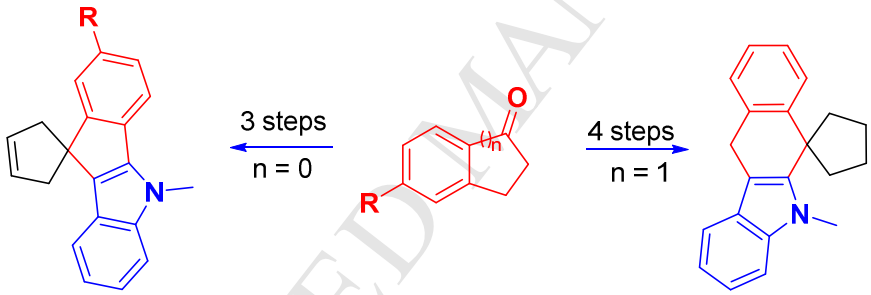
ABSTRACT

A range of aryl substituted spirocycles containing the indole moiety have been assembled through Claisen rearrangement, Fischer indole cyclization, ring-closing metathesis and the Suzuki–Miyaura cross-coupling reactions. Some of these molecules contain either a spirocyclic system or an indeno[1,2-*b*]indole framework which is present in diverse bioactive targets. Here, we have used simple and readily available starting materials to generate a library of spirocycles with an indole unit in their structures.

Graphical abstract



Keywords

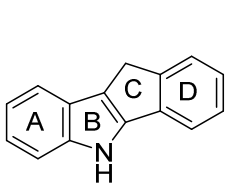
Spirocycles, Claisen rearrangement, Fischer indole cyclization, Ring-closing metathesis, Suzuki–Miyaura cross-coupling

1. Introduction

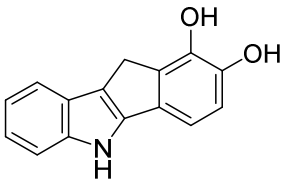
Indole is a unique heterocycle and functionalized indoles have been referred as privileged structures because they are a feature in a large number of bioactive molecules.[1] The construction and derivatization of compounds containing an indole moiety has drawn a considerable amount of attention of synthetic organic chemists. Over the last decade, several efforts have been directed to develop simple and efficient methodologies[2] for the synthesis of indole-based compounds. More specifically, the indeno[1,2-*b*]indole framework **1** (Fig. 1) has gained importance in the realm of biological as well as pharmacologically active substances.[3] The structures of some important bioactive molecules containing the indole moiety are shown in Fig. 1.[4]

Spirocycles have drawn a considerable amount of attention of the synthetic as well as material chemists due to the challenges involved in the creation of a quaternary centre.[5] A variety of complex molecules such as fredericamycin, fenestrindane alicyclic [5.5.5.5]fenestrane contain a spiro linkage as a structural unit.[6] Even though numerous methods[7] are available in the literature to construct spirocycles, most of them have limitations due to functional-group tolerence[5k] and group diversity.

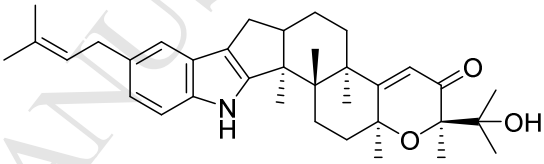
In view of the importance of spirocycles as well as indoles, we envisioned a novel synthetic approach to spirocycles with an indole moiety through Claisen rearrangement (CR), Fischer indole cyclization (FIC), ring-closing metathesis (RCM)[8-9] and Suzuki–Miyaura (SM) cross-coupling reactions. Furthermore, incorporation of the SM cross-coupling reaction during the construction of spirocyclic systems is rather scarce.[10]



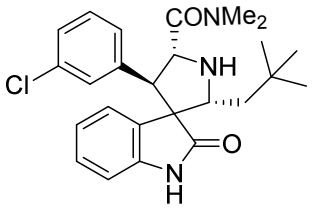
1
indeno[1,2-*b*]indole



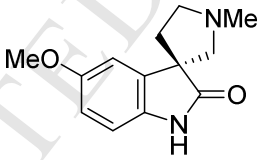
2
antioxidant activity



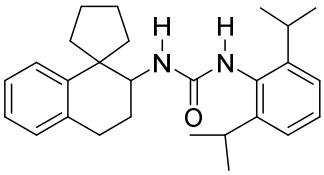
3
(–)-21-isopentenylpaxilline (antiinsectant)



4
MDM2-p53 inhibitor

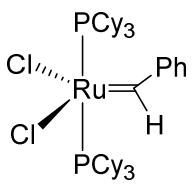


5
(–)-horsfiline (analgesic)

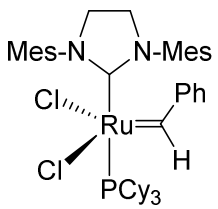


6
ACAT inhibitor

Fig 1. Some biologically important compounds



G-I (I)



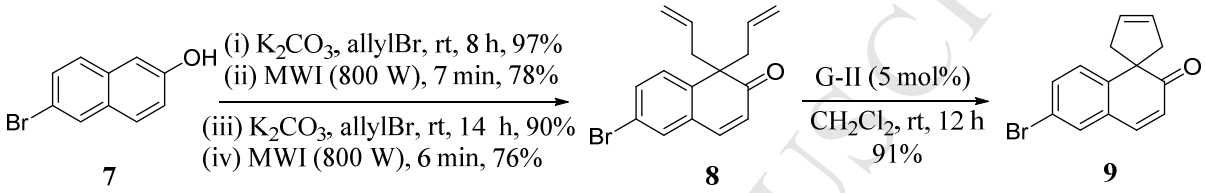
G-II (II)

Fig. **2**. Ru-catalysts [G-(I-II)] used in our study

Our interest in spirocycles containing an indole moiety encompasses to prepare a range of intricate spirocycles with an indole unit and further enhance the indole library via the SM cross-coupling reaction.[11]

2. Results and discussion

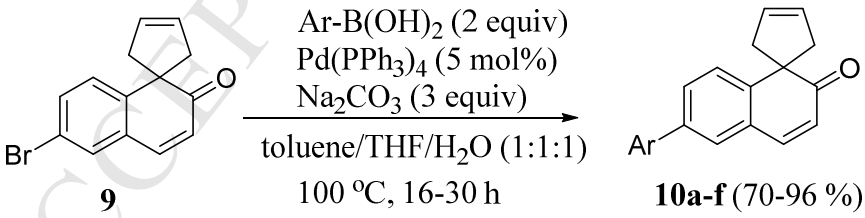
To begin with, we generated the di-allyl derivative **8** by treating 6-bromo-2-naphthol **7** with allyl bromide followed by a microwave irradiated (MWI) CR. The di-allylated compound **8** was then subjected to the RCM sequence in the presence of Grubbs' second generation catalyst (Fig. 2) to deliver the known spiro compound **9** (Scheme 1).[12]



7 **8** **9**

Scheme 1. Design and synthesis of building block **9**

Next, the tricyclic spiro derivative **9** was subjected to SM cross-coupling with phenylboronic acid to furnish the desired cross-coupling product **10a** in 96% yield (Scheme 2, Fig. 3). The scope of the cross-coupling reaction was further extended by using other arylboronic acids to deliver the desired products **10b-f** in good to excellent yields (Fig. 3). The new compounds were fully characterized by ^{1}H, ^{13}C NMR spectroscopy and further supported by high-resolution mass spectrometric (HRMS) data.



9 **10a-f** (70-96 %)

Scheme 2. The SM cross-coupling of compound **9**

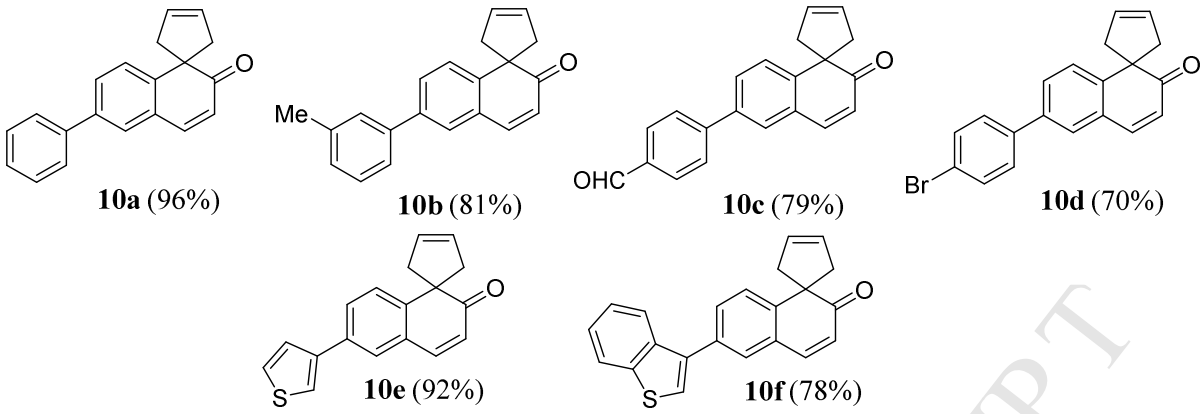
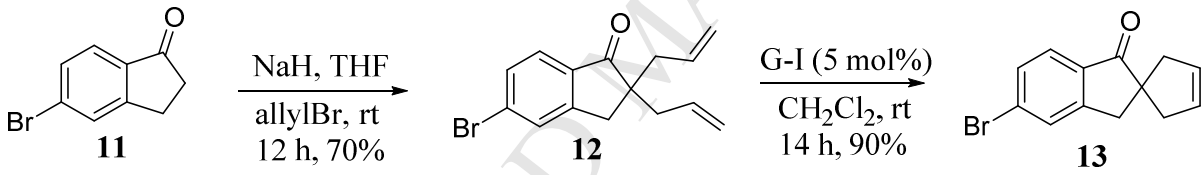


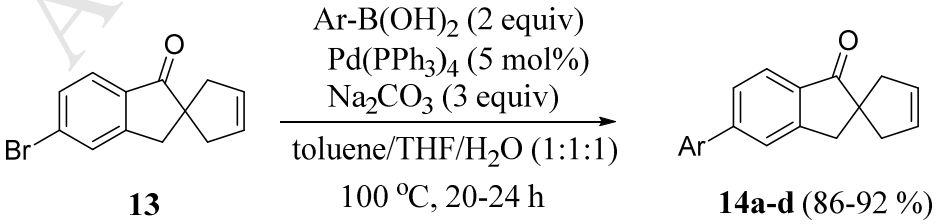
Fig. 3. List of the SM cross-coupling products of **9**

To further expand the substrate scope to spirocycles, we have also selected 5-bromo-1-indanone **11** as a starting material. The allylation of the indanone **11** under NaH/allyl bromide conditions furnished the di-allyl ketone **12** in 70% yield. This compound was then subjected to the RCM sequence with the aid of Grubbs' first generation catalyst (Fig. 2) to generate the required spirocyclic framework **13** in excellent yield (Scheme 3).[12]



Scheme 3. Synthesis of 1-indanone-based spirocyclic analogue **13**

Having the bromo derivative **13** in hand, the SM cross-coupling reaction with phenylboronic acid using $Pd(PPh_3)_4$, Na_2CO_3 in a THF/toluene/water solvent mixture gave the coupling product **14a** in 92% yield (Scheme 4, Fig. 4). Additionally, other SM coupling products **14b-d** were also generated by treating the compound **13** with other functionalized arylboronic acids (Scheme 4, Fig. 4).



Scheme 4. Synthesis of 1-indanone-based spirocycles **14a-d**

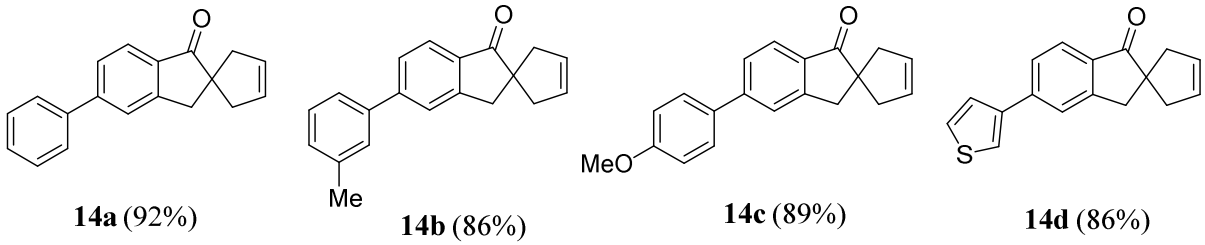
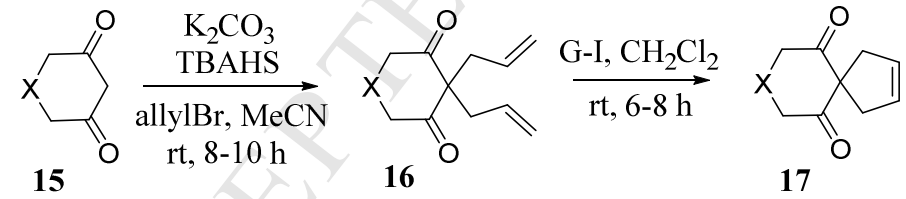


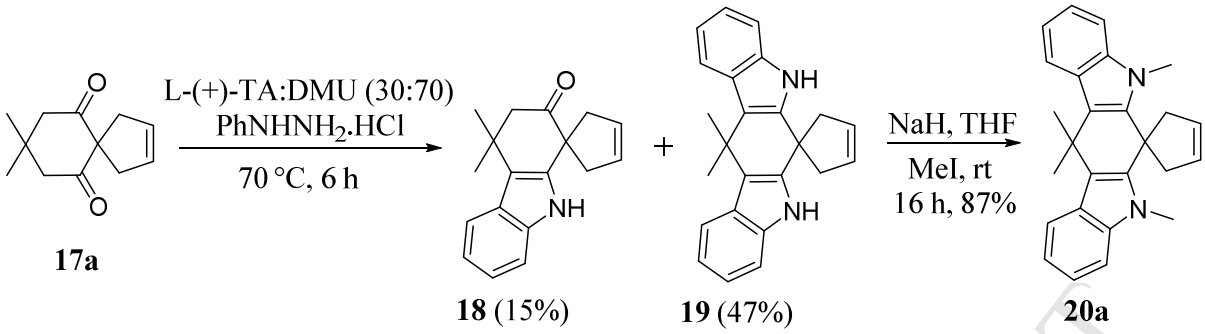
Fig. 4. List of SM cross-coupling products obtained from **13**

Spirocycles as well as indole motif containing compounds are useful candidates from a biological point of view.[13] Therefore, the molecular skeleton which integrates spirocyclic as well as indole moieties might possess properties of both and provide new chemical probes in drug design and development. For this, we are interested in applying the RCM sequence to assemble a library of hybrid molecules containing both of these units in their structures. To achieve this goal, the known compounds **17a-c**, **24** and **27** were prepared from the readily available starting materials **15a-c** (Scheme 5) and **22** (Scheme 8), respectively. Compound **17a** was then subjected to FIC with phenylhydrazine hydrochloride using a low melting mixture of L-(+)-tartaric acid:*N*,*N*-dimethylurea [L-(+)-TA:DMU] (30:70) to afford the desired di-indole derivative **19** along with mono-indole derivative **18** (Scheme 6). The di-indole derivative **19** on treatment with NaH/MeI in THF afforded the *N*,*N*-dimethylated di-indole derivative **20a** in 87% yield.



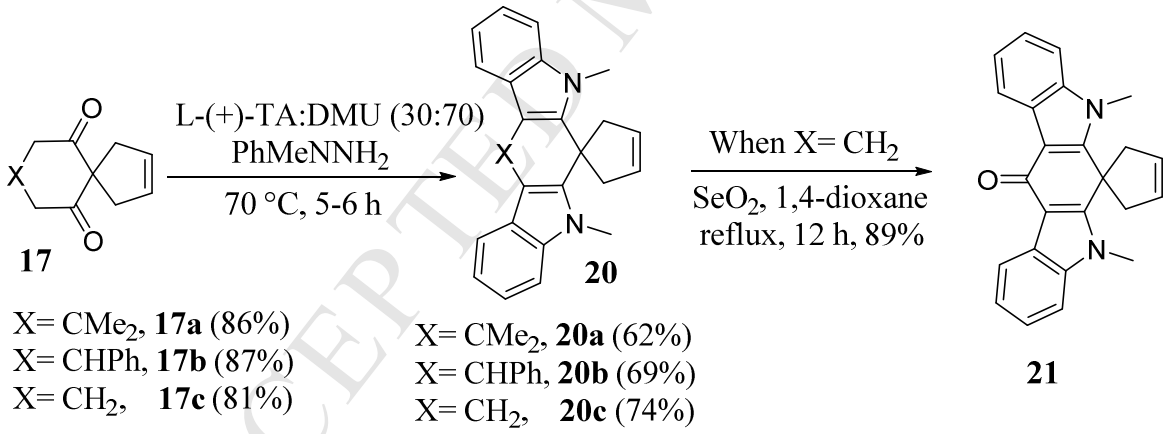
X= CMe_2, **15a**	X= CMe_2, **16a** (67%)	X= CMe_2, **17a** (86%)
X= CHPh, **15b**	X= CHPh, **16b** (70%)	X= CHPh, **17b** (87%)
X= CH_2, **15c**	X= CH_2, **16c** (62%)	X= CH_2, **17c** (81%)

Scheme 5. Preparation of **17a-c** (TBAHS = Tetrabutylammonium hydrogen sulphate)

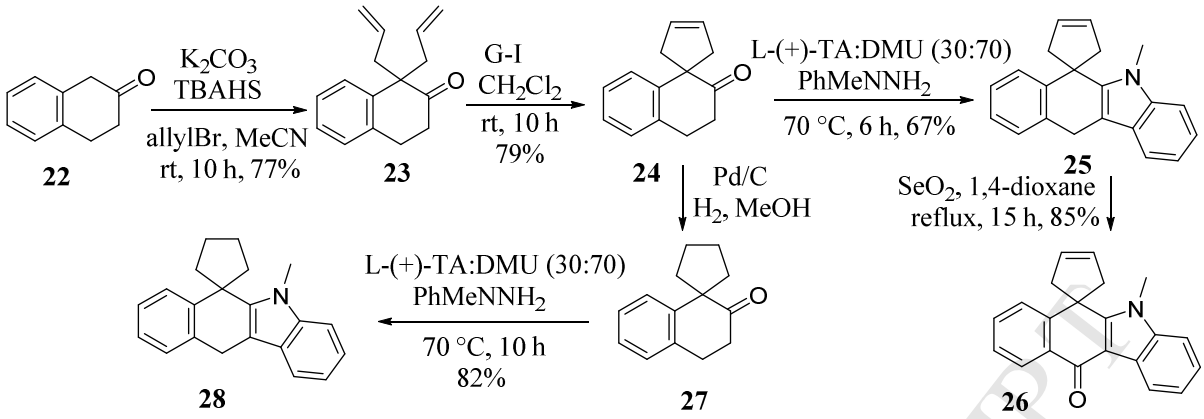


Scheme 6. Synthesis of spirocycles containing the indole moiety

We found that the non-*N*-methylated indole derivatives were unstable and difficult to handle, therefore, we synthesized the *N*-methylated indole derivatives **20a-c** (Scheme 7), **25** and **28**, (Scheme 8) directly by treating their corresponding keto precursors **17a-c** (Scheme 7), **24** and **27** (Scheme 8) with 1-methyl-1-phenylhydrazine by using a low melting mixture of L-(+)-TA:DMU (30:70). Several natural products[14] contain the quinone subunit in their structure. In this context, we have also synthesized quinone-based spiroindole derivatives **21** and **26**, starting with the corresponding indoles **20c** and **25** under selenium dioxide[15] (SeO_2) conditions in 89% and 85% yields, respectively (Schemes 7 and 8).

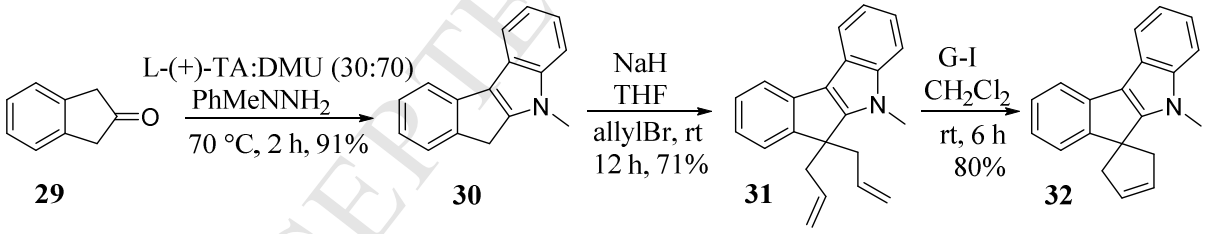


Scheme 7. Synthesis of quinone-based spiroindole derivative **21**



Scheme 8. Synthesis of spirocycles containing an indole unit

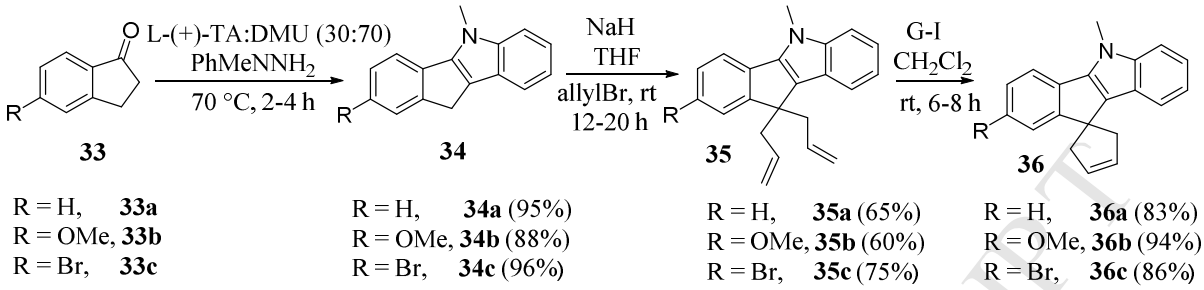
To further expand the utility of spiroindole derivatives, we used a different sequence i.e. Fischer indole cyclization, allylation followed by the RCM reaction. Here, the indeno[1,2-*b*]indole frameworks are used as the active methylene moiety which were obtained from the FIC of 1-indanone derivatives. To this end, we performed the FIC of 2-indanone **29** using a low melting mixture of L-(+)-TA:DMU (30:70) to furnish the indeno[1,2-*b*]indole derivative **30** in 91% yield (Scheme 9). Compound **30** was then subjected to di-allylation by using NaH/allyl bromide in THF to afford the compound **31** in 71% yield. Next, compound **31** was exposed to the RCM sequence with the aid of the G-I catalyst to deliver compound **32** in 80% yield (Scheme 9).



Scheme 9. Synthesis of spirocycles containing an indole moiety starting with 2-indanone **29**

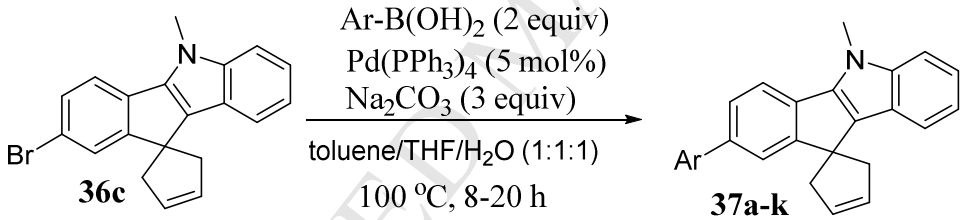
To explore the scope of this methodology in terms of substituent effect at the 5-position of the 1-indanone derivatives, the compounds **33a-c** were subjected to FIC using a low melting mixture of L-(+)-TA:DMU (30:70) to deliver the spiroindole derivatives **34a-c** in good to excellent yields (Scheme 10). The indeno[1,2-*b*]indole derivatives **34a-c** were then treated with NaH/allyl bromide to furnish the di-allylated systems **35a-c** in good yields, which on a subsequent RCM sequence with the aid of G-I catalyst afforded the spirocyclic systems with an indole unit in their structures (Scheme 10). Here, we observed that electron

withdrawing group at 5-position of 1-indanone is useful to provide better yields during the course of allylation sequence (Scheme 10).



Scheme 10. Synthesis of spirocycles containing the indeno[1,2-*b*]indole framework

Compounds **36a-c** contain the indeno[1,2-*b*]indole framework which is present in many biologically relevant molecules (e.g. **2**, Fig. 1). Therefore, it was worthy to derivatize compound **36c** through the SM cross-coupling reaction by varying the boronic acid to generate a library of spirocycles containing the indeno[1,2-*b*]indole framework. These reactions proceeded in good to excelent yields (Scheme 11, Fig. 5).



Scheme 11. The SM cross-coupling reaction of **36c**

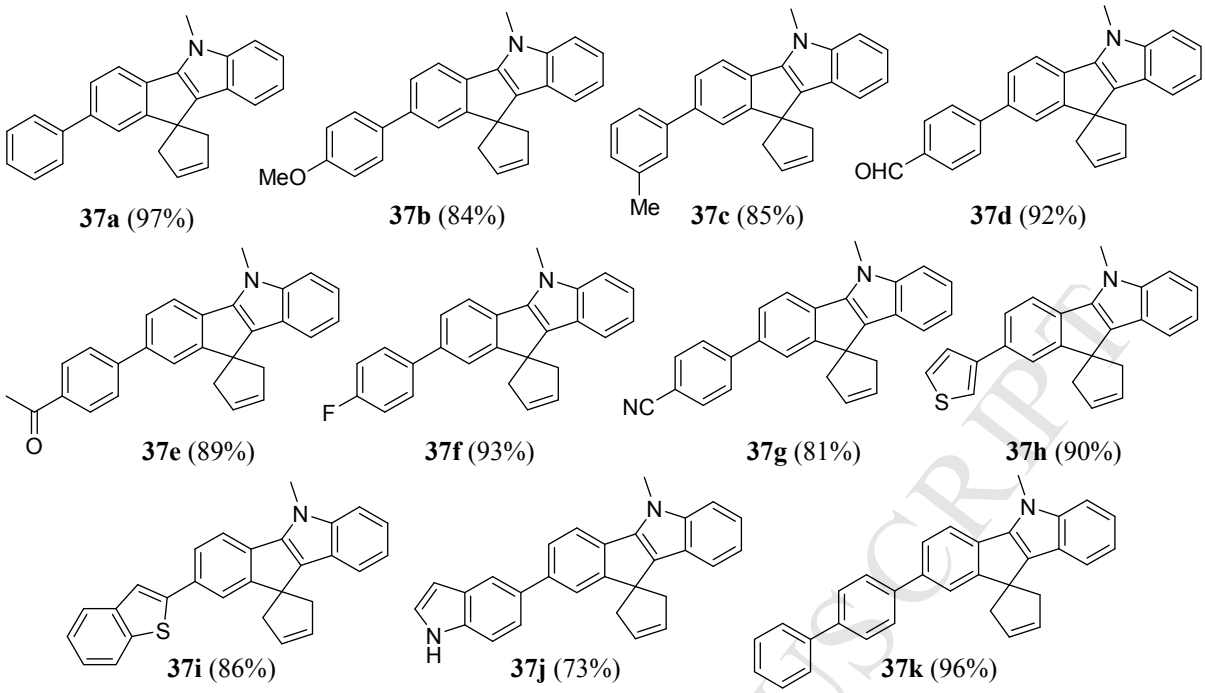


Fig. 5. Substrate scope of spirocycles containing the indeno[1,2-*b*]indole framework

3. Conclusions

We have demonstrated a simple strategy to assemble densely functionalized spirocycles containing the indole moiety in their structure. Here, we have used CR, FIC, RCM and SM cross-coupling reactions. There are several diversity points embedded in our strategy for example, by utilizing commercially available boronic acids, one can generate a library of compounds in a diversity oriented manner. We have demonstrated this idea with substrates **9**, **13** and **36c** by using a variety of boronic acids to assemble a range of spirocycles. In addition, our theme has diversity points in terms of strategies as well as starting ketone components used. Here, we have prepared around 46 new compounds with several option for divercification.[16]

4. Experimental section

All commercially accessible reagents were used without further purification and reactions involving air sensitive catalysts or reagents were performed in degassed solvents. Moisture sensitive materials were transferred using syringe-septum techniques and the reactions were maintained under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on (7.5×2.5 cm) glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder) by using a suitable mixture of EtOAc and petroleum ether for development. Column chromatography was performed by using Acme's silica gel (100-

200 mesh) with an appropriate mixture of EtOAc and petroleum ether. The coupling constants (*J*) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from internal standard, tetramethylsilane (TMS). The abbreviations, s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublets, and triplet of doublets respectively. Grubbs' catalysts were purchased from Sigma Aldrich. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer in $CHCl_3$. Proton nuclear magnetic resonance (^{1}H NMR, 300 MHz, 400 MHz and 500 MHz) spectra and carbon nuclear magnetic resonance (^{13}C NMR, 75 MHz, 100 MHz and 125 MHz) spectra were recorded on a Bruker spectrometer. The high-resolution mass measurements were carried out by using electrospray ionization (ESI, Q-ToF) spectrometer. Melting points were recorded on a Veego melting point apparatus.

Preparation of the known compounds 9 and 13, 17a and 17c, 17b, 24 and 27, 30, 34a:

All these compounds were prepared using literature reported procedures, the ^{1}H and ^{13}C NMR spectra of these compounds matched with the literature reported spectroscopic data, respectively.[12, 17-21]

General procedure for the Fischer indole cyclization: To a clear melted mixture (1.5 g) of L-(+)-TA-DMU (30:70) at 70 ^{o}C, was added 1-methyl-phenyl hydrazine (1.5-3 equiv) and the ketone components (1 equiv). The reaction mixture was stirred at at 70 ^{o}C for 2-10 h. At the conclusion of the reaction (TLC monitoring), the warm reaction mixture was diluted with water. The reaction mixture was cooled to room temperature, filtered through sintered glass funnel and the solid material was washed with water (4 x 20 mL). The crude products were purified by silica gel column chromatography using appropriate mixture of ethyl acetate /petroleum ether to afford the desired products.

General procedure for the allylation of 30 and 34a-c: To a suspension of sodium hydride (3 equiv) in dry THF (20 mL), was added the compound **30** or **34a-c** and the reaction mixture was stirred for 15 min at room temperature. Allyl bromide (3 equiv) was then added and stirring was continued for 10-30 h at the same temperature. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with EtOAc and the solvent was removed under reduced pressure. Compounds were then extracted with CH_2Cl_2 and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the desired di-allylated compound **31** or **35a-c**.

General procedure for RCM sequence of 31 and 35a-c: The solution of compound **31** or **35a-c** in CH_2Cl_2 (20 mL) was degassed with nitrogen for 15-20 min. Then, G-I (5 mol%) catalyst was added and the reaction mixture was stirred at room temperature for 10-12 h. At

the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the RCM product **32** or **36a-c**.

General procedure for the Suzuki–Miyaura cross-coupling reaction: To a solution of bromo derivatives **9**, **13** or **36c** in THF/toluene/water (1:1:1, each 10 mL) were added Na_2CO_3 (3.0 equiv) and arylboronic acid (2.0 equiv). The reaction mixture was degassed with nitrogen for 20 min. $Pd(PPh_3)_4$ (5 mol%) was then added and the reaction mixture was heated at 100 ^oC. At the conclusion of the reaction (8-30 h, TLC monitoring), the reaction mixture was diluted with water and the organic layer was extracted with CH_2Cl_2. The organic layer was washed with water as well as brine and dried (Na_2SO_4). The solvent was removed on rotavapour and the crude products were purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the desired Suzuki coupling products.

Synthesis of compound 10a: This compound was prepared according to the general procedure by using bromo derivative **9** (40 mg, 0.15 mmol) and phenylboronic acid (35.5 mg, 0.30 mmol), Na_2CO_3 (62 mg, 0.58 mmol) and the catalyst $Pd(PPh_3)_4$ (16.8 mg, 0.014 mmol) for 12 h. The crude material was purified by silica gel column chromatography (2% EtOAc-petroleum ether) to yield the desired product **10a** (38 mg, 96%) as a colorless solid; R_f = 0.45 (silica gel, 5% EtOAc-petroleum ether); mp 122-126 °C; R_f = 0.45 (silica gel, 5% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.60 (m, 9H), 6.26 (d, J = 9.8 Hz, 1H), 5.82 (s, 2H), 3.20 (d, J = 13.8 Hz, 2H), 2.66 (d, J = 13.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 148.5, 145.5, 140.2, 140.0, 129.3, 129.1, 128.8, 128.5, 127.8, 127.7, 127.1, 126.4, 125.5, 55.9, 49.5; IR (KBr): υ_{max} 3054, 2986, 2305, 1429, 1265 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{20}H_{17}O$ $[M+H]^+$ 273.1279; found: 273.1288.

Synthesis of compound 10b: Colourless solid; yield = 81% (42 mg, starting from 50 mg of **9**); reaction time = 18 h; mp 146-148 °C; R_f = 0.17 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.59 (m, 7H), 7.19 (d, J = 6.7 Hz, 1H), 6.26 (d, J = 9.7 Hz, 1H), 5.82 (s, 2H), 3.21 (d, J = 13.9 Hz, 2H), 2.68 (d, J = 13.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 148.3, 145.4, 140.1, 138.6, 129.2, 128.9, 128.7, 128.5, 128.4, 127.8, 127.7, 126.2, 125.4, 124.2, 55.9, 49.4, 21.6; IR (KBr): υ_{max} 3055, 2922, 2849, 2304, 1661 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{21}H_{19}O$ $[M+H]^+$ 287.1436; found: 287.1436.

Synthesis of compound 10c: Colourless solid; yield = 79% (43 mg, starting from 50 mg of **9**); reaction time = 30 h; mp 134-136 °C; R_f = 0.40 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.76-7.82 (m, 4H), 7.64 (dd, J_1 = 8.1 Hz, J_2 = 2.0 Hz, 1H), 7.51-7.59 (m, 3H), 6.29 (d, J = 9.9 Hz, 1H), 5.83 (s, 2H), 3.21 (d, J = 13.8 Hz, 2H), 2.66 (d, J = 13.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 191.9, 149.6, 146.0, 145.7, 144.9, 138.4, 136.1, 135.6, 130.54, 130.52, 129.4, 128.8, 128.2, 127.9, 127.6, 126.6, 125.8, 55.9, 49.4; IR (KBr): υ_{max} 3053, 2985, 2304, 1700, 1604 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{21}H_{17}O_2$ $[M+H]^+$ 301.1229; found: 301.1218.

Synthesis of compound 10d: Colourless solid; yield = 70% (45 mg, starting from 50 mg of **9**); reaction time = 16 h; mp 118-122 °C; R_f = 0.18 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.60 (m, 8H), 6.27 (d, J = 9.9 Hz, 1H), 5.82 (s, 2H), 3.21 (d, J = 13.8 Hz, 2H), 2.67 (d, J = 13.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 148.9, 145.2, 139.1, 138.8, 132.2, 132.1, 129.0, 128.8, 128.7, 128.6, 127.6, 127.5, 126.5, 125.7, 122.1, 55.9, 53.6, 49.4; IR (KBr): υ_{max} 3054, 2987, 2305, 1655 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{20}H_{16}O^{79}Br$ $[M+H]^+$ 351.0385; found: 351.0375.

Synthesis of compound 10e: Colourless solid; yield = 92% (46 mg, starting from 50 mg of **9**); reaction time = 20 h; mp 156-158 °C; R_f = 0.17 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.59 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.46-7.51 (m, 3H), 7.38-7.42 (m, 3H), 6.26 (d, J = 9.8 Hz, 1H), 5.81 (s, 2H), 3.19 (d, J = 13.7 Hz, 2H), 2.66 (d, J = 13.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 148.3, 145.3, 141.3, 134.7, 128.8, 128.6, 128.5, 126.9, 126.7, 126.4, 126.3, 125.5, 120.7, 55.9, 49.4; IR (KBr): υ_{max} 3101, 3055, 2920, 2849, 1660, 1562 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{18}H_{15}OS$ $[M+H]^+$ 279.0844; found: 279.0835.

Synthesis of compound 10f: Colourless solid; yield = 78% (37 mg, starting from 40 mg of **9**); reaction time = 21 h; mp 161-163 °C; R_f = 0.52 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.86 (m, 2H), 7.71 (dd, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.57 (s, 1H), 7.53 (d, J = 6.9 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.32-7.39 (m, 2H), 6.29 (d, J = 9.8 Hz, 1H), 5.83 (s, 2H), 3.20 (d, J = 13.8 Hz, 2H), 2.66 (d, J = 13.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 149.2, 144.8, 142.9. 140.6, 139.5, 133.1, 128.7, 128.4, 126.8, 126.4, 125.8, 124.8, 124.7, 123.7, 122.4, 119.8, 55.9, 49.3; IR (KBr): υ_{max} 3052, 2986, 1224, 1268 cm^{-1}; HRMS (Q-Tof): *m/z* calcd. for $C_{22}H_{17}OS$ $[M+H]^+$ 329.1000; found: 329.0995.

Synthesis of compound 14a: This compound was prepared according to the general procedure by using bromo derivative **13** (50 mg, 0.19 mmol), phenylboronic acid (35 mg, 2.9 mmol), $Pd(PPh_3)_4$ (11.0 mg, 5 mol%) and Na_2CO_3 (81 mg, 0.76 mmol) in THF/toluene/water (10 mL) for 18 h. Analytically pure product **14a** was isolated by silica gel column chromatography (1% EtOAc-petroleum ether). (50 mg, 92%) as a thick colorless liquid; R_f = 0.60 (silica gel, 1% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.8 Hz, 1H), 7.61-7.64 (m, 4H), 7.41-7.50 (m, 3H), 5.75 (s, 2H), 3.23 (s, 2H), 2.93 (d, J = 14.7 Hz, 2H), 2.38 (d, J = 14.7 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 153.7, 148.0, 140.4, 135.3, 129.1, 128.9, 128.5, 127.6, 127.1, 125.1, 124.7, 55.9, 45.7, 45.6; IR (neat): υ_{max} 3058, 2919, 2841, 1706, 1607, 1283 cm^{-1}; HRMS (Q-Tof): calcd. for $C_{19}H_{17}O$ $[M+H]^+$ 261.1279; found 261.1263.

Synthesis of compound 14b: Colourless liquid; yield = 86% (53 mg, starting from 50 mg of **13**); reaction time = 24 h; R_f = 0.50 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.8 Hz, 1H), 7.59-7.62 (m, 2H), 7.43 (d, J = 9.2 Hz, 2H), 7.34-7.38 (m, 1H), 7.21-7.25 (m, 1H), 5.74 (s, 2H), 3.22 (s, 2H), 2.92 (d, J = 14.7 Hz, 2H), 2.44 (s, 3H), 2.38 (d, J = 14.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 153.7, 148.2, 140.4, 138.8, 135.2, 129.3, 129.0, 128.9, 128.4, 127.1, 125.1, 124.8, 124.7, 55.9, 45.8, 45.7; IR (neat): υ_{max} 3056, 2923, 2844, 1707, 1607, 1265 cm^{-1}; HRMS (Q-Tof): calcd. for $C_{20}H_{19}O$ $[M+H]^+$ 275.1436; found 275.1425.

Synthesis of compound 14c: Colourless solid; yield = 89% (49 mg, starting from 50 mg of **13**); reaction time = 18 h; mp 160-162 °C; R_f = 0.30 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.83 (m, 1H), 7.57-7.60 (m, 4H), 7.00-7.02 (m, 2H), 5.74 (s, 2H), 3.87 (s, 3H), 3.21 (s, 2H), 2.92 (d, J = 14.7 Hz, 2H), 2.38 (d, J = 14.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 160.2, 153.8, 147.6, 134.8, 132.8, 128.9, 128.8, 126.6, 124.8, 124.4, 114.6, 55.9, 55.6, 45.8, 45.7; IR (neat): υ_{max} 3055, 2909, 2838, 1707, 1604, 1251 cm^{-1}; HRMS (Q-Tof): calcd. for $C_{20}H_{19}O_2$ $[M+H]^+$ 291.1385; found 291.1396.

Synthesis of compound 14d: Colourless solid; yield = 86% (51 mg, starting from 50 mg of **13**); reaction time = 23 h; mp 126-128 °C; R_f = 0.40 (silica gel, 2% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.75 (m, 1H), 7.59-7.60 (m, 2H), 7.40-7.41 (m, 1H), 7.33-7.35 (m, 1H), 7.07-7.09 (m, 1H), 5.69 (s, 2H), 3.14 (s, 2H), 2.86 (d, J = 14.7 Hz, 2H), 2.32 (d, J = 14.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9, 153.9, 143.4, 140.7, 135.3, 128.9, 128.6, 126.9, 125.6, 125.1, 125.0, 123.3, 55.9, 45.8, 45.6; IR (neat): υ_{max} 3048, 2986,

1724, 1684, 1254 cm^{-1}; HRMS (Q-Tof): calcd. for $C_{17}H_{15}OS$ $[M+H]^+$ 267.0844; found 267.0836.

Synthesis of compound 19: To a clear melted mixture (1.5 g) of L-(+)-TA-DMU (30:70) at 70 ^oC, was added phenyl hydrazine hydrochloride (900 mg, 6.25 mmol) and ketone **17a** (400 mg, 2.08 mmol). The reaction mixture was stirred at at 70 ^oC for 6 h. At the conclusion of the reaction (TLC monitoring), the warm reaction mixture was diluted with water. The reaction mixture was cooled to room temperature, filtered through sintered glass funnel and the solid material was washed with water (4 x 20 mL). The crude product was purified by silica gel column chromatography using (5% EtOAc-petroleum ether) to deliver the compound **19** (335 mg, 47%) along with compound **18** (84 mg, 15%) as white solids.

Compound 18: mp 98-99 °C; R_f = 0.53 (silica gel, 10% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (brs, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.05-7.09 (m, 1H), 6.99-7.03 (m, 1H), 5.73 (s, 2H), 3.07 (d, J = 14.7 Hz, 2H), 2.63 (s, 2H), 2.57 (d, J = 14.7 Hz, 2H), 1.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.8, 138.3, 136.9, 128.9, 125.0, 121.9, 120.3, 119.6, 116.8, 111.3, 54.5, 53.9, 44.6, 35.4, 30.1; IR (neat): υ_{max} 3049, 2927, 2851, 1711, 1596, 1470 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{18}H_{19}NKO$ $[M+K]^+$ 304.1098, found: 304.1098.

Compound 19: mp 260-262 °C; R_f = 0.38 (silica gel, 10% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (brs, 2H), 7.86 (d, J = 7.3 Hz, 2H), 7.34 (dd, J_1 = 1.1 Hz, J_2 = 6.8 Hz, 2H), 6.13-6.24 (m, 4H), 6.06 (s, 2H), 3.04 (s, 4H), 1.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 130.5, 125.3, 121.5, 120.6, 119.3, 118.8, 111.2, 48.3, 42.0, 34.3, 29.4; IR (neat): υ_{max} 3417, 3010, 2923, 2840, 1443 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{24}H_{22}N_2K$ $[M+K]^+$ 377.1415, found: 377.1412.

Synthesis of compound 20a: To a suspension of NaH (57 mg, 2.37 mmol) in THF (20 mL), was added compound **19** (200 mg, 0.59 mmol) followed by MeI (0.12 mL, 1.78) and the reaction mixture was stirred at rt for 16 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with EtOAc and the solvent was removed on rotavapour. The compound was extracted with CH_2Cl_2 and the crude product was purified by silica gel column chromatography using (4% EtOAc-petroleum ether) to deliver compound **20a** (189 mg, 87%) as a white solid.

Direct synthesis of compound 20a, 20b, 20c: These compounds were prepared according to the procedure given for compound **19** using 1-methyl-phenyl hydrazine instead of phenyl hydrazine hydrochloride.

Compound 20a White solid; yield = 62% (118 mg, starting from 100 mg of **17a**) reaction time = 5 h; mp 280-283 °C; R_f = 0.58 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.9 Hz, 2H); 7.33 (d, J = 8.1 Hz, 2H), 7.22-7.25 (m, 2H), 7.13-7.20 (m, 2H), 6.14 (s, 2H), 3.74 (s, 6H), 3.14 (s, 4H), 1.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.9, 132.1, 124.3, 121.3, 120.9, 118.9, 118.2, 109.3, 48.9, 40.9, 33.9, 30.9, 29.8; IR (neat): υ_{max} 2950, 2925, 2851, 1654, 1583, 1520, 1456, 1262, 740 cm$^{-1;}$ HRMS (Q-Tof) calcd. for $C_{26}H_{27}N_2$ $[M+H]^+$ 367.2169, found: 367.2166.

Compound 20b: White solid; yield = 69% (59 mg, starting from 50 mg of **17b**); reaction time = 5 h; mp 265-267 °C; R_f = 0.60 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 7.3 Hz, 3H), 7.17 (t, J = 8.2 Hz, 3H), 7.11 (t, J = 7.5 Hz, 2H), 7.06 (t, J = 7.1 Hz, 2H), 6.98-7.04 (m, 1H), 6.87 (t, J = 7.3 Hz, 2H), 6.12 (s, 2H), 5.46 (s, 1H), 3.70 (s, 6H), 3.25 (s, 2H), 3.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 140.5, 138.9, 132.3, 131.9, 128.8, 128.4, 126.1, 125.7, 121.5, 119.7, 119.3, 112.0, 108.9, 48.9, 48.3, 41.1, 39.5, 31.1; IR (neat): υ_{max} 3049, 2927, 2851, 1596, 1470, 1448 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{30}H_{25}N_2$ $[M–H]^+$ 413.2012, found: 413.2012.

Compound 20c: White solid; yield = 74% (123 mg, starting from 80 mg of **17c**); reaction time = 6 h; mp 290-292 °C; R_f = 0.53 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.22-7.25 (m, 2H), 7.15-7.20 (m, 2H), 6.12 (s, 2H), 4.09 (s, 2H), 3.73 (s, 6H), 3.11 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 138.7, 131.9, 126.2, 121.7, 119.3, 118.6, 109.0, 107.3, 48.3, 41.2, 31.0, 19.3; IR (neat): υ_{max} 3043, 2923, 2846, 1475 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{24}H_{22}KN_2$ $[M+K]^+$ 377.1415, found: 377.1417.

Synthesis of compound 21: The solution of compound **20c** (100 mg, 0.30 mmol) and SeO_2 (66 mg, 0.60 mmol) in 1,4-dioxane (20 mL) was heated at reflux temperature for 12 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was filtered through a sintered glass funnel and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using (5% EtOAc-petroleum ether) to deliver the compound **21** (93 mg, 89%) as a white solid.

mp 185-186 °C; R_f = 0.54 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 6.7 Hz, 2H), 7.25-7.34 (m, 6H), 6.19 (s, 2H), 3.75 (s, 6H), 3.15 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 152.0, 138.7, 131.9, 124.1, 123.1, 122.3, 111.9, 109.3, 45.8, 42.1, 31.2; IR (neat): υ_{max} 3043, 2923, 2846, 1475 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{24}H_{21}N_2O$ $[M+H]^+$ 353.1648, found: 353.1637.

Synthesis of compound 25: White solid; yield = 67% (96 mg, starting from 100 mg of **24**); reaction time = 6 h; mp 130-133 °C; R_f = 0.59 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.19-7.33 (m, 5H), 7.12-7.16 (m, 1H), 6.06 (s, 2H), 4.16 (s, 2H), 3.69 (s, 3H), 3.06, 3.13 (ABq, J = 1.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 139.5, 138.3, 131.3, 131.1, 128.6, 127.6, 126.2, 126.0, 125.5, 121.6, 119.2, 118.4, 108.9, 105.8, 53.1, 42.7, 30.5, 26.8; IR (neat): υ_{max} 3049, 2928, 2895, 1522, 1492, 1462 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{21}H_{20}N$ $[M+H]^+$ 286.1596, found: 286.1596.

Synthesis of compound 26: Following the same procedure as for the compound **21**.

White solid; yield = 75% (39 mg, starting from 50 mg of **25**); reaction time = 15 h; mp 125-127 °C; R_f = 0.56 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52-8.54 (m, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 3.8 Hz, 2H), 7.42-7.48 (m, 1H), 7.35-7.39 (m, 3H), 6.17 (s, 2H), 3.79 (s, 3H), 3.14, 3.26 (ABq, J = 17.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 154.9, 151.9, 138.7, 133.1, 131.3, 130.4, 127.1, 125.6, 124.7, 124.4, 123.8, 122.5, 111.3, 109.4, 50.8, 43.2, 31.0; IR (neat): υ_{max} 3007, 2924, 2859, 1631, 1524, 1468 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{21}H_{17}NNa$ $[M+Na]^+$ 322.1202, found: 322.1199.

Synthesis of compound 28: White solid; yield = 82% (59 mg, starting from 50 mg of **27**); reaction time = 10 h; mp 150-152 °C; R_f = 0.61 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J_1 = 2.9 Hz, J_2 = 7.1 Hz, 1H), 7.49 (dd, J_1 = 2.3 Hz, J_2 = 8.0 Hz, 1H), 7.27-7.38 (m, 5H), 7.18-7.20 (m, 1H), 4.22 (s, 2H), 3.89 (s, 3H), 2.49-2.52 (m, 2H), 2.27-2.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 139.9, 138.4, 132.3, 128.9, 127.0, 126.6, 126.2, 125.6, 121.5, 119.1, 118.2, 108.8, 106.8, 47.7, 43.6, 31.8, 27.7, 27.2; IR (neat): υ_{max} 3010, 2945, 2855, 1540 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{21}H_{22}N$ $[M+H]^+$ 288.1752, found: 288.1752.

Synthesis of compound 31: Brown solid; yield = 71% (145 mg, starting from 150 mg of **30**); reaction time = 12 h; mp 105-107 °C; R_f = 0.73 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J_1 = 0.6 Hz, J_2 = 1.5 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.19-7.35 (m, 5H), 7.06-7.09 (m, 1H), 5.15-5.24 (m, 2H), 4.86-4.92 (m, 2H), 4.70-4.73 (m, 2H), 3.89 (s, 3H), 2.86-2.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 149.3, 141.9, 139.6, 133.6, 127.5, 122.7, 122.5, 121.9, 121.0, 120.2, 119.6, 118.3, 117.5, 109.9, 52.1, 41.9, 31.4; IR (neat): υ_{max} 3049, 2929, 2840, 1596, 1525, 1495, 1432 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{22}H_{21}NK$ $[M+K]^+$ 338.1306, found: 338.1309.

Synthesis of compound 32: Brown solid; yield = 80% (73 mg, starting from 100 mg of 3**1**); reaction time = 6 h; mp 160-161 °C; R_f = 0.71 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.82 (m, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.20-7.35 (m 5H), 7.06 (dt, J_1 = 1.1 Hz, J_2 = 7.5 Hz, 1H), 6.05 (s, 2H), 3.79 (s, 3H), 2.98-3.07 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 155.9, 141.8, 138.2, 130.6, 127.2, 123.3, 121.9, 121.6, 121.1, 120.3, 119.5, 118.1, 110.0, 50.3, 43.2, 31.1; IR (neat): υ_{max} 3016, 2928, 2846, 1602, 1522, 1491, 1467 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{20}H_{18}N$ $[M+H]^+$ 272.1434, found: 272.1432.

Synthesis of compound 35a: Brown solid; yield = 65% (89 mg, starting from 100 mg of **34a**); reaction time = 12 h; mp 99-103 °C; R_f = 0.67 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.20 (dt, J_1 = 1.1 Hz, J_2 = 7.5 Hz, 1H), 7.10-7.14 (m, 2H), 7.05 (t, J = 7.0 Hz, 1H), 5.34-5.40 (m, 2H), 4.78-4.82 (m, 4H), 3.92 (s, 3H), 2.79 (dd, J_1 = 7.5 Hz, J_2 = 13.7 Hz, 2H), 2.56 (dd, J_1 = 7.1 Hz, J_2 = 13.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 143.2, 142.2, 135.0, 134.9, 126.9, 126.3, 125.1, 124.1, 123.9, 121.2, 119.7, 119.6, 117.9, 117.4, 109.9, 51.2, 42.6, 31.3; IR (neat): υ_{max} 3069, 2925, 2851, 1637, 1604, 1522, 1492 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{22}H_{21}NNa$ $[M+Na]^+$ 322.1566, found: 322.1566.

Synthesis of compound 36a: Brown solid; yield = 83% (38 mg, starting from 50 mg of **35a**); reaction time= 6 h; mp 190-191 °C; R_f = 0.66 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.48 (m, 3H), 7.27 (d, J = 8.2 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.09-7.13 (m, 2H), 7.02 (t, J = 7.2 Hz, 1H), 6.02 (s, 2H), 3.93 (s, 3H), 2.80 (t, J = 3.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 142.3, 134.3, 130.9, 130.4, 126.8, 125.7, 123.0, 122.7, 121.3, 119.6, 119.4, 117.7, 109.9, 51.6, 43.6, 32.2; IR (neat): υ_{max} 3054, 2924, 2847, 1604, 1523, 1467 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{20}H_{18}N$ $[M+H]^+$ 272.1434, found: 272.1433.

Synthesis of compound 34b: Brown solid; yield = 88% (135 mg, starting from 100 mg of **33b**); reaction time = 4 h; mp 166-168 °C; R_f = 0.69 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.13-7.21 (m, 3H), 6.89 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 1H), 4.02 (s, 3H), 3.88 (s, 3H), 3.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 150.6, 144.9, 141.7, 128.9, 124.5, 120.7, 119.7, 118.7, 118.6, 118.0, 112.8, 111.7, 109.8, 55.8, 31.2, 30.5; IR (neat): υ_{max} 3032, 2974, 1603, 1519, 1463 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1226, found: 250.1229.

Synthesis of compound 35b: Brown solid; yield = 60% (79 mg, starting from 100 mg of **34b**); reaction time = 20 h; mp 115-116 °C; R_f = 0.72 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.10-7.19 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.82 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 1H), 5.43-5.51 (m, 2H), 4.88 (dd, J_1 = 1.2 Hz, J_2 = 7.9 Hz, 2H), 4.80 (dd, J_1 = 1.1 Hz, J_2 = 8.1 Hz, 2H), 4.01 (s, 3H), 3.87 (s, 3H), 2.83 (dd, J_1 = 6.2 Hz, J_2 = 13.7 Hz, 2H), 2.64 (dd, J_1 = 6.9 Hz, J_2 = 13.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 157.6, 143.2, 141.7, 134.9, 128.1, 124.6, 124.3, 120.5, 119.6, 119.1, 118.2, 117.4, 111.4, 111.2, 109.8, 55.7, 51.2, 42.8, 31.2; IR (neat): υ_{max} 3043, 2923, 2840, 1599, 1451 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{23}H_{24}NO$ $[M+H]^+$ 330.1852, found: 330.1859.

Synthesis of compound 36b: Brown solid; yield = 94% (43 mg, starting from 50 mg of **35b**); reaction time = 8 h; mp 147-150 °C; R_f = 0.68 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.12-7.22 (m, 3H), 6.83-6.86 (m, 1H), 6.14 (s, 2H), 4.01 (s, 3H), 3.88 (s, 3H), 2.91 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 158.6, 142.1, 141.8, 130.8, 128.7, 127.3, 122.9, 120.6, 119.5, 118.9, 118.1, 111.2, 110.3, 109.9, 55.7, 51.6, 43.9, 31.1; IR (neat): υ_{max} 3049, 3010, 2929, 2840, 1596, 1525, 1495, 1432 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1539, found: 302.1539.

Synthesis of compound 34c: Brown solid; yield = 96% (270 mg, starting from 200 mg of **33c**); reaction time = 2 h; mp 147-148 °C; R_f = 0.75 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.1 Hz, 2H), 7.39-7.43 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.20-7.23 (m, 1H), 7.14 (t, J = 7.1 Hz, 1H), 3.92 (s, 3H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 143.8, 142.1, 134.5, 129.6, 128.9, 123.9, 121.8, 120.6, 119.9, 119.3, 118.6, 118.4, 109.9, 31.2, 30.2; IR (neat): υ_{max} 3051, 2922, 1596, 1522, 1492, 1462 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{16}H_{12}{}^{79}BrNK$ $[M+K]^+$ 335.9785, found: 335.9786.

Synthesis of compound 35c: Brown solid; yield = 75% (142 mg, starting from 150 mg of **34c**); reaction time = 12 h; mp 142-143 °C; R_f = 0.76 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 7.9 Hz, 1H), 7.53 (t, J = 1.0 Hz, 1H), 7.41 (d, J = 0.9 Hz, 2H), 7.34 (d, J = 8.3 Hz, 1H), 7.20-7.24 (m, 1H), 7.13 (t, J = 7.1 Hz, 1H), 5.38-5.46 (m, 2H), 4.79-4.92 (m, 4H), 3.99 (s, 3H), 2.85 (dd, J_1 = 7.5 Hz, J_2 = 13.7 Hz, 2H), 2.65 (dd, J_1 = 7.0 Hz, J_2 = 13.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 142.3, 142.1, 134.3, 133.9, 129.9, 127.3, 126.5, 123.9, 121.7, 119.9, 119.7, 118.9, 117.9, 110.1, 51.5, 42.4,

31.3; IR (neat): υ_{max} 3071, 3005, 2920, 2857, 1597, 1496, 1434 cm^{-1}; HRMS (Q-Tof) calculated for $C_{22}H_{21}{}^{79}BrN$ $[M+H]^+$ 378.0852, found: 378.0832.

Synthesis of compound 36c: Brown solid; yield = 86% (79 mg, starting from 100 mg of **35c**); reaction time = 6 h; mp 170-172 °C; R_f = 0.73 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J_1 = 0.8 Hz, J_2 = 1.4 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 1.6 Hz, 2H), 7.35 (d, J = 8.3 Hz, 1H), 7.20-7.25 (m, 1H), 7.12 (t, J = 7.0 Hz, 1H), 6.09 (s, 2H), 4.00 (s, 3H), 2.86 (t, J = 1.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 142.4, 141.1, 133.1, 130.9, 130.3, 129.8, 126.4, 122.5, 121.7, 119.8, 119.5, 119.3, 118.7, 110.1, 51.7, 43.3, 31.2; IR (neat): υ_{max} 3054, 2928, 2839, 1610, 1596, 1528, 1495, 1432 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{20}H_{17}{}^{79}BrN$ $[M+H]^+$ 350.0539, found: 350.0532.

Synthesis of compound 37a: Brown solid; yield = 97% (29 mg, starting from 30 mg of **36c**); reaction time = 8 h; mp 165-167 °C; R_f = 0.66 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.61-7.65 (m, 3H), 7.54 (t, J = 6.6 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.24-7.38 (m, 2H), 7.22 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.13 (s, 2H), 4.05 (s, 3H), 2.90, 2.97 (ABq, J = 15.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 142.4, 141.8, 141.6, 138.7, 133.4, 130.9, 128.9, 127.2, 125.9, 122.7, 121.9, 121.4, 119.6, 119.5, 117.9, 110.0, 51.7, 43.7, 31.3; IR (neat): υ_{max} 3053, 2929, 2840, 1598, 1525, 1492, 1444 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{26}H_{22}N$ $[M+H]^+$ 348.1747, found: 348.1744.

Synthesis of compound 37b: Brown solid; yield = 84% (27 mg, starting from 30 mg of **36c**); reaction time = 8 h; mp 188-189 °C; R_f = 0.65 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 1.4 Hz, 1H), 7.53-7.60 (m, 4H), 7.47 (dd, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.12 (s, 2H), 4.04 (s, 3H), 3.85 (s, 3H), 2.89, 2.96 (ABq, J = 15.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 159.2, 142.3, 141.9, 138.4, 134.2, 132.8, 130.9, 130.7, 128.3, 128.2, 125.4, 122.8, 121.5, 121.3, 119.6, 119.4, 117.9, 114.4, 109.9, 55.6, 51.7, 43.8, 31.3; IR (neat): υ_{max} 3057, 2928, 2835, 1610, 1528, 1497, 1432 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{27}H_{24}NO$ $[M+H]^+$ 378.1852, found: 378.1853.

Synthesis of compound 37c: Brown solid; yield = 85% (44 mg, starting from 50 mg of **36c**); reaction time = 10 h; mp 180-183 °C; R_f = 0.66 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.49-7.58 (m, 3H), 7.42 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.08-7.21 (m, 3H), 6.12 (s, 2H), 4.00 (s, 3H), 2.87, 2.96 (ABq, J = 15.3 Hz, 4H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 142.4, 141.8, 141.6, 138.9, 138.5, 133.3, 130.9, 128.9, 127.9, 125.9, 124.4, 122.8, 121.9, 121.3, 119.6, 119.4, 117.8, 109.9,

51.8, 43.7, 31.2, 21.8; IR (neat): υ_{max} 3049, 3016, 2923, 2840, 1606, 1525, 1499, 1448 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{27}H_{24}N$ $[M+H]^+$ 362.1903, found: 362.1903.

Synthesis of compound 37d: Brown solid; yield = 92% (35 mg, starting from 50 mg of **36c**); reaction time = 16 h; mp 193-194 °C; R_f = 0.60 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.78 (t, J = 8.2 Hz, 3H), 7.55, 7.57 (ABq, J = 15.2 Hz, 3H), 7.36 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.14 (s, 2H), 4.02 (s, 3H), 2.90, 2.97 (ABq, J = 15.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 160.3, 147.5, 142.5, 141.4, 136.9, 135.0, 134.6, 131.6, 130.9, 130.5, 127.6, 126.4, 122.6, 121.8, 119.8, 119.6, 118.0, 110.1, 51.7, 43.6, 31.3; IR (neat): υ_{max} 3019, 2923, 2846, 1695, 1600, 1216 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{27}H_{21}NONa$ $[M+Na]^+$ 398.1515, found: 398.1514.

Synthesis of compound 37e: Brown solid; yield = 89% (60 mg, starting from 60 mg of **36c**); reaction time = 20 h; mp 155-158 °C; R_f = 0.63 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 8.3 Hz, 2H), 7.79 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.55, 7.60 (ABq, J = 15.8 Hz, 3H), 7.36 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.14 (s, 2H), 4.02 (s, 3H), 2.88, 2.97 (ABq, J = 15.6 Hz, 4H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 160.2, 146.1, 142.5, 141.5, 137.1, 135.7, 134.3, 131.4, 130.9, 129.1, 127.1, 126.2, 122.7, 121.73, 121.71, 119.8, 119.6, 117.9, 110.1, 51.8, 43.6, 31.3, 26.8; IR (neat): υ_{max} 3019, 2928, 1676, 1599, 1216 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{28}H_{24}NO$ $[M+H]^+$ 390.1852, found: 390.1854.

Synthesis of compound 37f: Brown solid; yield = 93% (39 mg, starting from 40 mg of **36c**); reaction time = 12 h; mp 184-185 °C; R_f = 0.65 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 1.5 Hz, 1H), 7.53-7.59 (m, 4H), 7.46 (dd, J_1 = 1.7 Hz, J_2 = 7.8 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.19-7.23 (m, 1H), 7.10-7.14 (m, 3H), 6.12 (s, 2H), 4.03 (s, 3H), 2.89, 2.92 (ABq, J = 15.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.49 and 161.53 (J = 245.0, ^{13}C-^{19}F coupling), 160.2, 142.4, 141.7, 137.7, 133.4, 130.9, 128.8, 128.7, 125.8, 122.7, 121.7, 121.5, 119.7, 119.5, 117.9, 115.9, 115.7, 110.0, 51.7, 43.7, 31.3; IR (neat): υ_{max} 3019, 2928, 2851, 1590, 1215 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{26}H_{21}NF$ $[M+H]^+$ 366.1653, found: 366.1653.

Synthesis of compound 37g: Brown solid; yield = 81% (43 mg, starting from 50 mg of **36c**); reaction time = 8 h; mp 243-244 °C; R_f = 0.65 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.71 (d, J = 1.3 Hz, 4H), 7.62 (d, J = 7.9 Hz, 1H), 7.51-7.56 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 6.9 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H),

6.13 (s, 2H), 4.04 (s, 3H), 2.89-2.97 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 145.9, 142.6, 141.3, 136.3, 134.74, 132.72, 131.6, 130.9, 127.6, 126.2, 122.6, 121.9, 121.6, 119.8, 119.6, 119.3, 118.0, 110.1, 51.7, 43.6, 31.3; IR (neat): υ_{max} 3049, 2927, 2840, 2223, 1598, 1495, 1444 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{27}H_{21}N_2$ $[M+H]^+$ 373.1699, found: 373.1703.

Synthesis of compound 37h: Brown solid; yield = 90% (46 mg, starting from 50 mg of **36c**); reaction time = 15 h; mp 180-181 °C; R_f = 0.53 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 1.1 Hz, 1H), 7.52-7.58 (m, 3H), 7.36-7.47 (m, 4H), 7.21 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.13 (s, 2H), 4.04 (s, 3H), 2.88, 2.96 (ABq, J = 15.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 142.8, 142.3, 141.8, 133.4, 133.2, 130.9, 130.8, 126.6, 126.4, 125.2, 122.7, 121.4, 121.2, 119.9, 119.6, 119.4, 117.9, 110.0, 51.7, 43.7, 31.3; IR (neat): υ_{max} 3098, 3038, 2928, 2840, 1607, 1519, 1489 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{24}H_{20}NS$ $[M+H]^+$ 354.1311, found: 354.1314.

Synthesis of compound 37i: Brown solid; yield = 86% (25 mg, starting from 25 mg of **36c**); reaction time = 10 h; mp 178-199 °C; R_f = 0.55 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.63 (dd, J_1 = 1.6 Hz, J_2 = 7.9 Hz, 1H), 7.55 (t, J = 5.3 Hz, 3H), 7.29-7.49 (m, 3H), 7.22 (t, J = 6.9 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.15 (s, 2H), 4.01 (s, 3H), 2.89, 2.98 (ABq, J = 15.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 144.9, 142.5, 141.6, 141.0, 139.5, 134.3, 131.6, 131.4, 130.9, 125.5, 124.9, 124.7, 124.3, 123.6, 122.7, 122.4, 121.7, 120.9, 119.7, 119.6, 119.0, 117.9, 110.1, 51.7, 43.6, 31.3; IR (neat): υ_{max} 3021, 2928, 2851, 1618, 1563, 1472 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{28}H_{22}NS$ $[M+H]^+$ 404.1467, found: 404.1468.

Synthesis of compound 37j: Brown solid; yield = 73% (24 mg, starting from 30 mg of **36c**); reaction time = 12 h; mp 188-190 °C; R_f = 0.36 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (brs, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.45-7.63 (m, 4H), 7.37 (d, J = 7.9 Hz, 1H), 7.19-7.24 (m, 3H), 7.10 (t, J = 7.3 Hz, 1H), 6.62 (s, 1H), 6.14 (s, 2H), 4.06 (s, 3H), 2.90, 3.01 (ABq, J = 15.8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 142.3, 142.1, 140.2, 135.4, 133.8, 132.5, 130.9, 130.6, 128.6, 126.0, 125.0, 122.8, 122.2, 122.1, 121.1, 119.6, 119.4, 119.3, 117.8, 111.4, 109.9, 103.2, 51.8, 43.8, 31.3; IR (neat): υ_{max} 3412, 3049, 2923, 2840, 1607, 1443 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{28}H_{23}N_2$ $[M+H]^+$ 387.1856, found: 387.1851.

Synthesis of compound 37k: Brown solid; yield = 96% (46 mg, starting from 40 mg of **36c**); reaction time = 16 h; mp 205-206 °C; R_f = 0.68 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 1.5 Hz, 1H), 7.64-7.73 (m, 7H), 7.59 (dd, J_1 = 1.6

Hz, J_2 = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.44-7.48 (m, 2H), 7.24-7.39 (m, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 6.14 (s, 2H), 4.07 (s, 3H), 2.91, 2.99 (ABq, J = 15.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 142.4, 140.9, 140.5, 140.1, 138.2, 133.5, 131.0, 130.9, 129.0, 127.7, 127.6, 127.5, 127.2, 125.8, 122.8, 121.7, 121.4, 119.7, 119.5, 117.9, 110.0, 51.8, 43.7, 31.3; IR (neat): υ_{max} 3016, 2934, 1643, 1481 cm^{-1}; HRMS (Q-Tof) calcd. for $C_{32}H_{25}NK$ $[M+K]^+$ 462.1619, found: 462.1622.

Acknowledgements

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Supporting Information

Diversity-oriented approach to spirocycles with indole moiety via Fischer indole cyclization, olefin metathesis and Suzuki–Miyaura cross-coupling reactions

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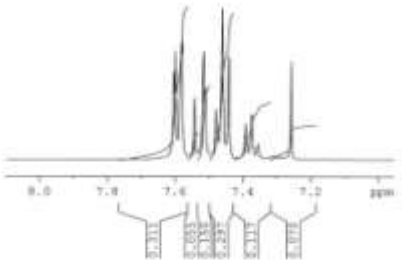
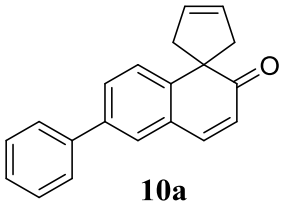
Table of components





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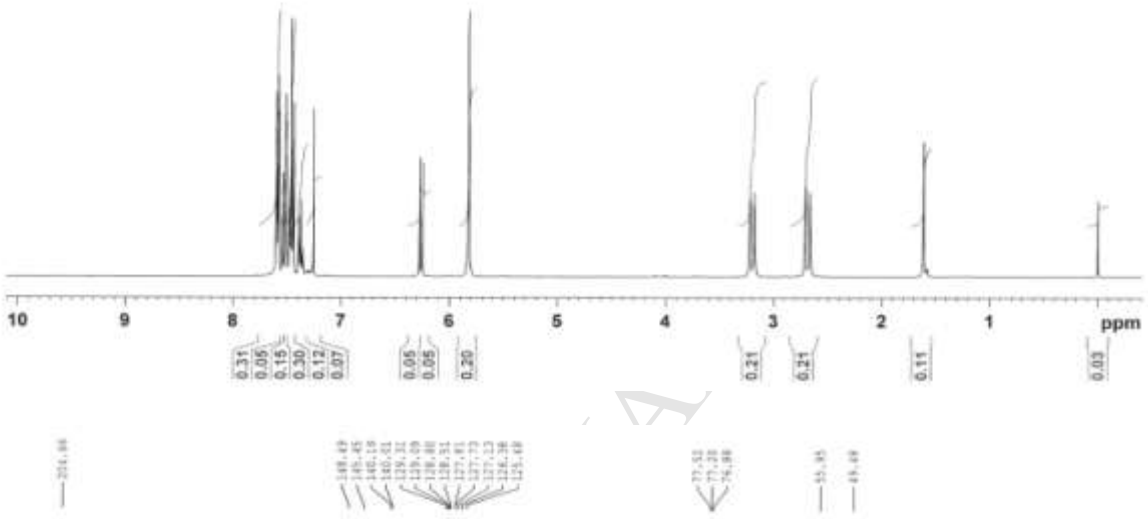

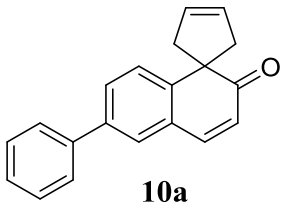

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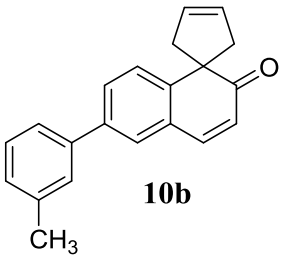
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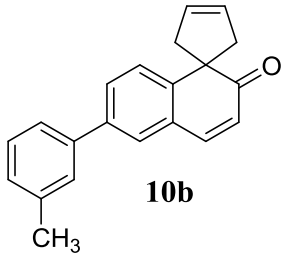
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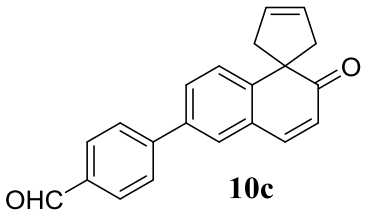
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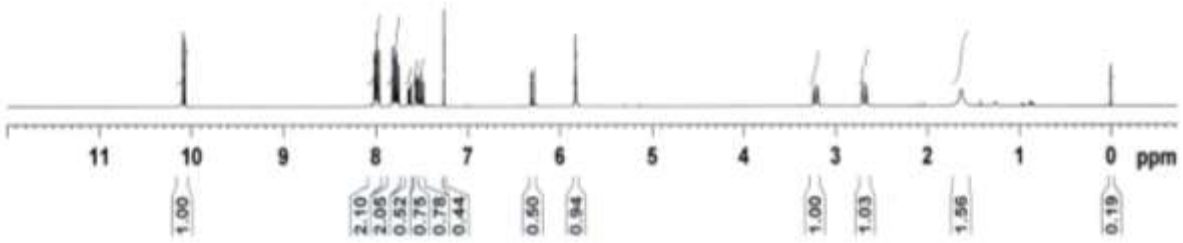
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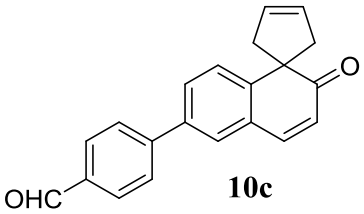
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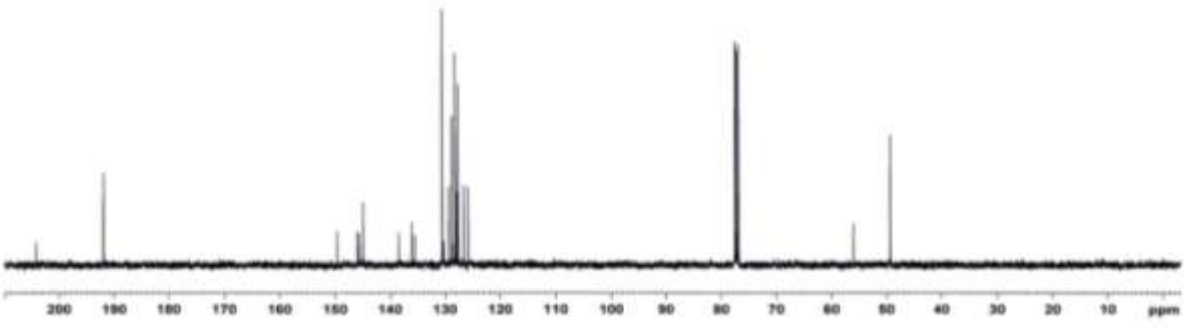
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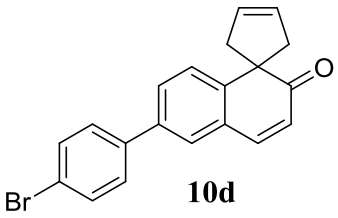

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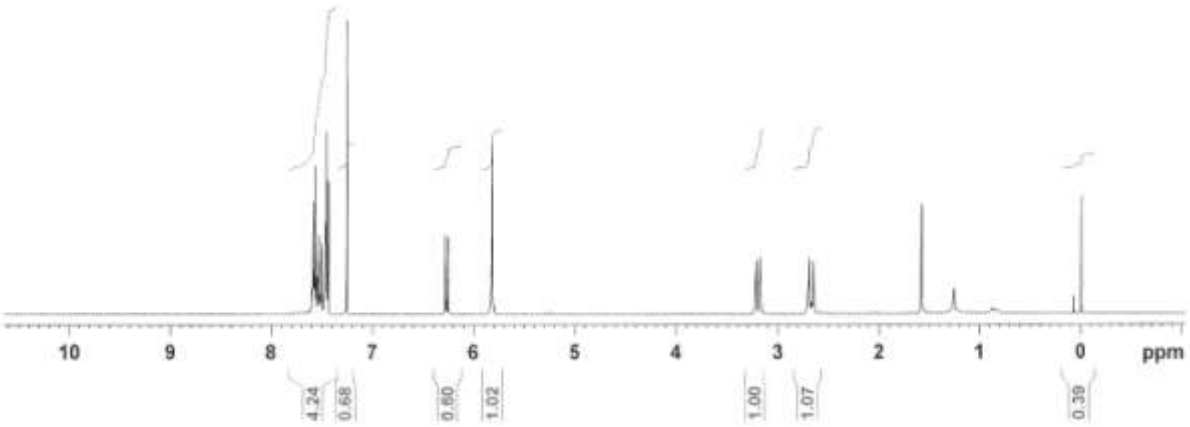

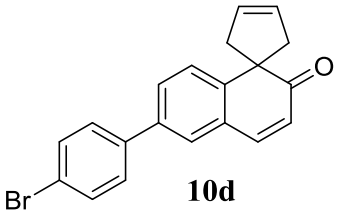

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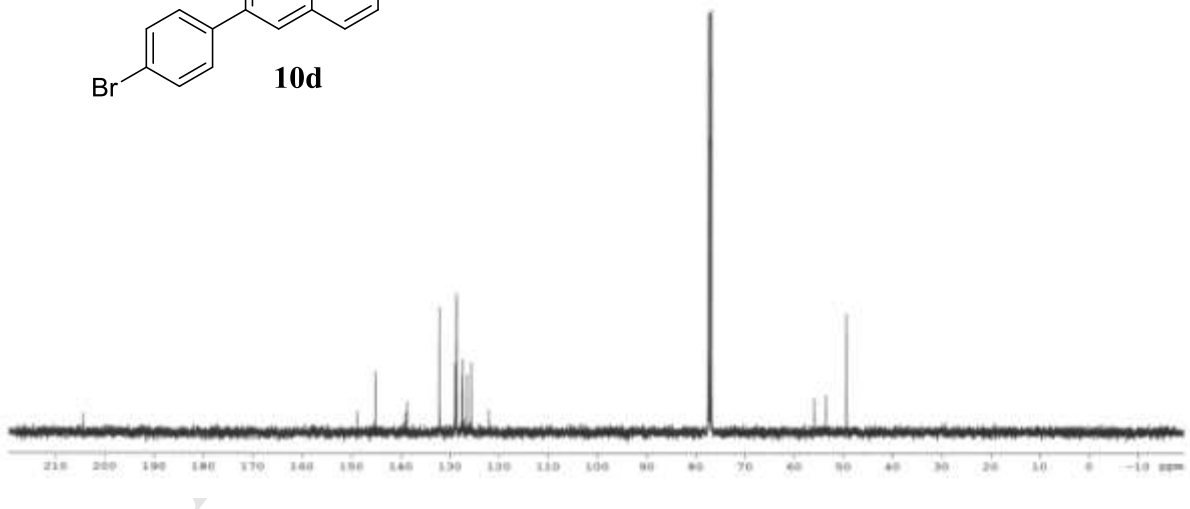

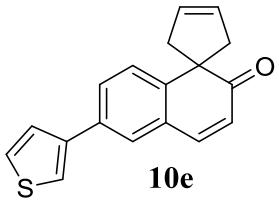
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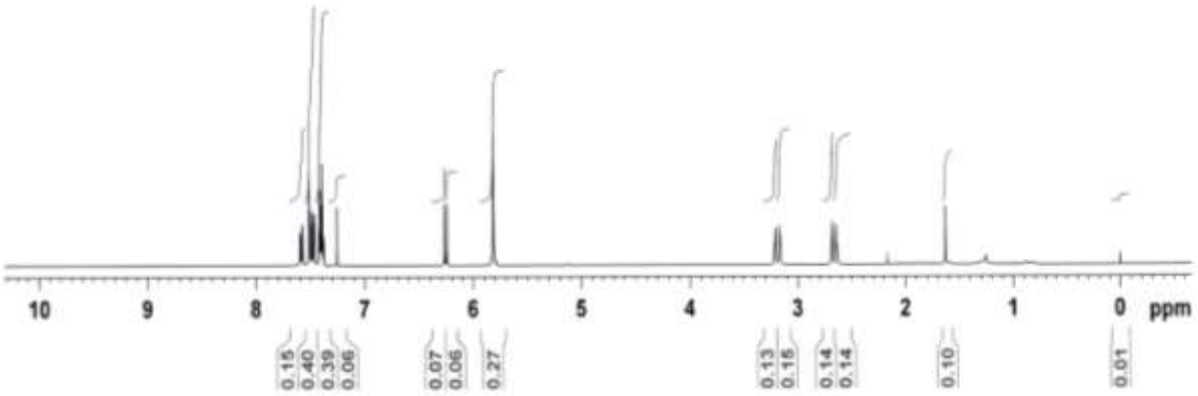
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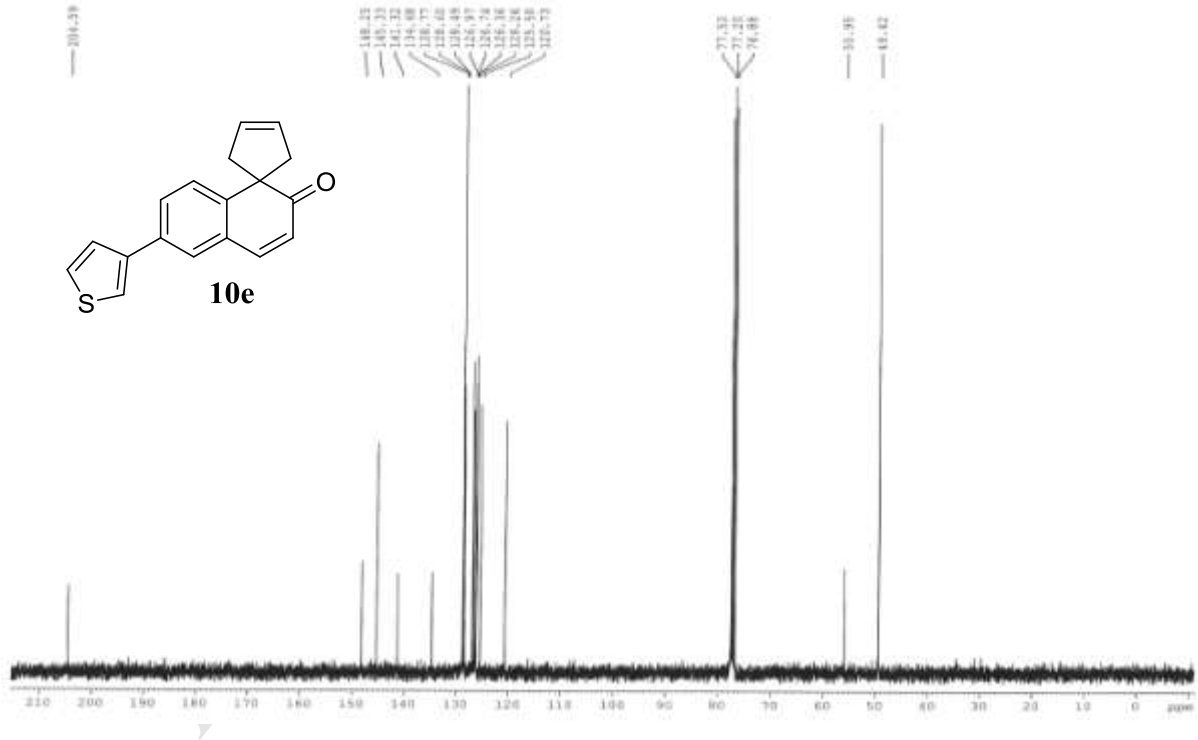
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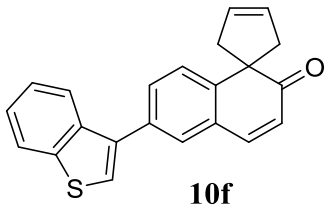
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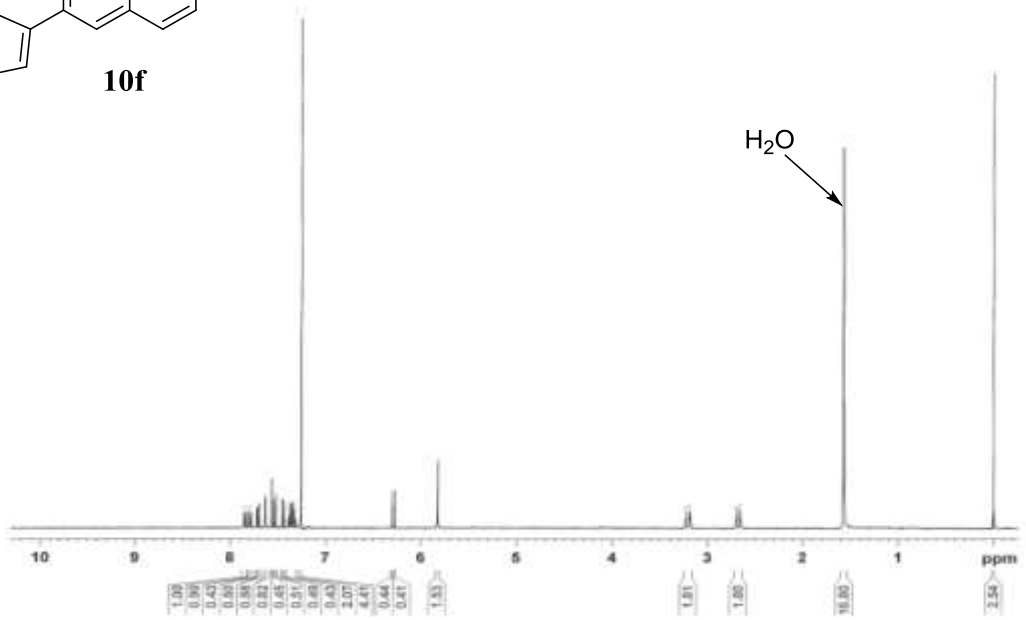
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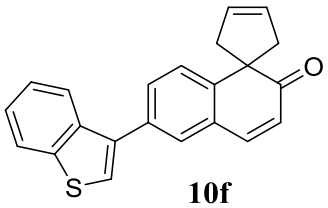
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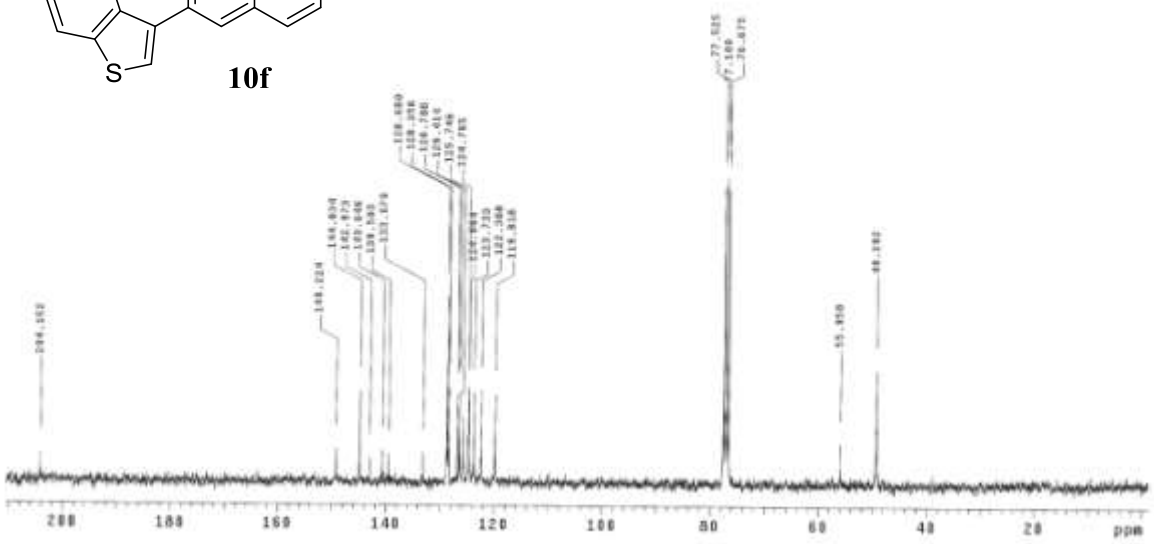
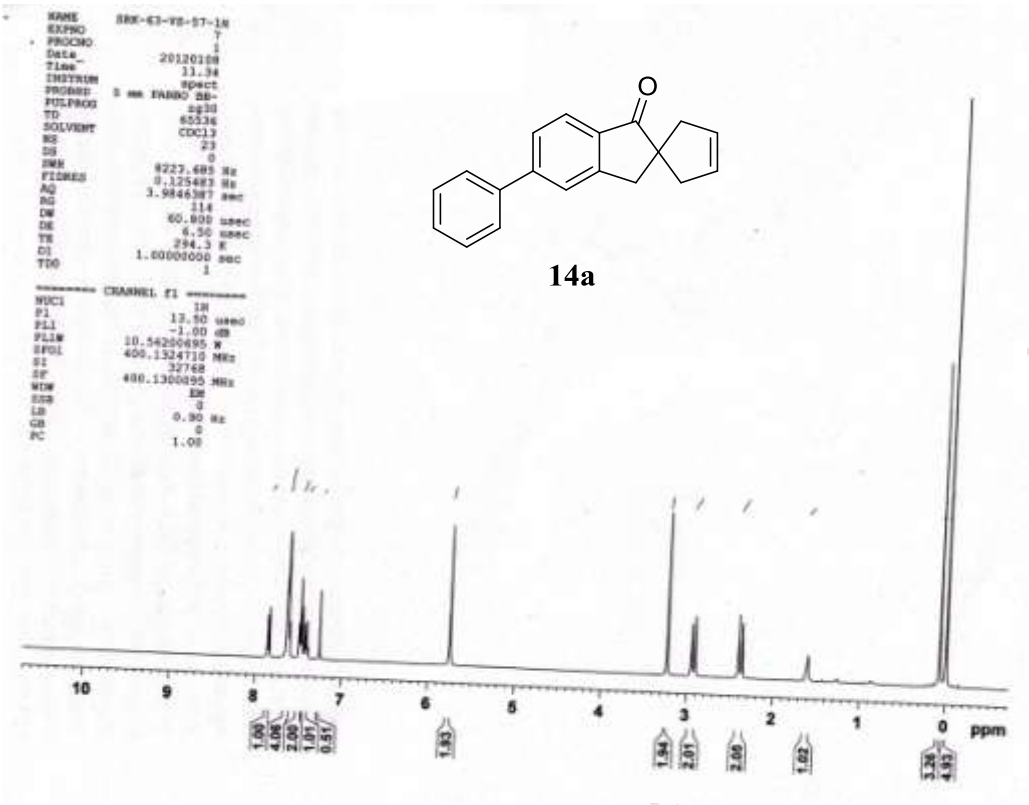
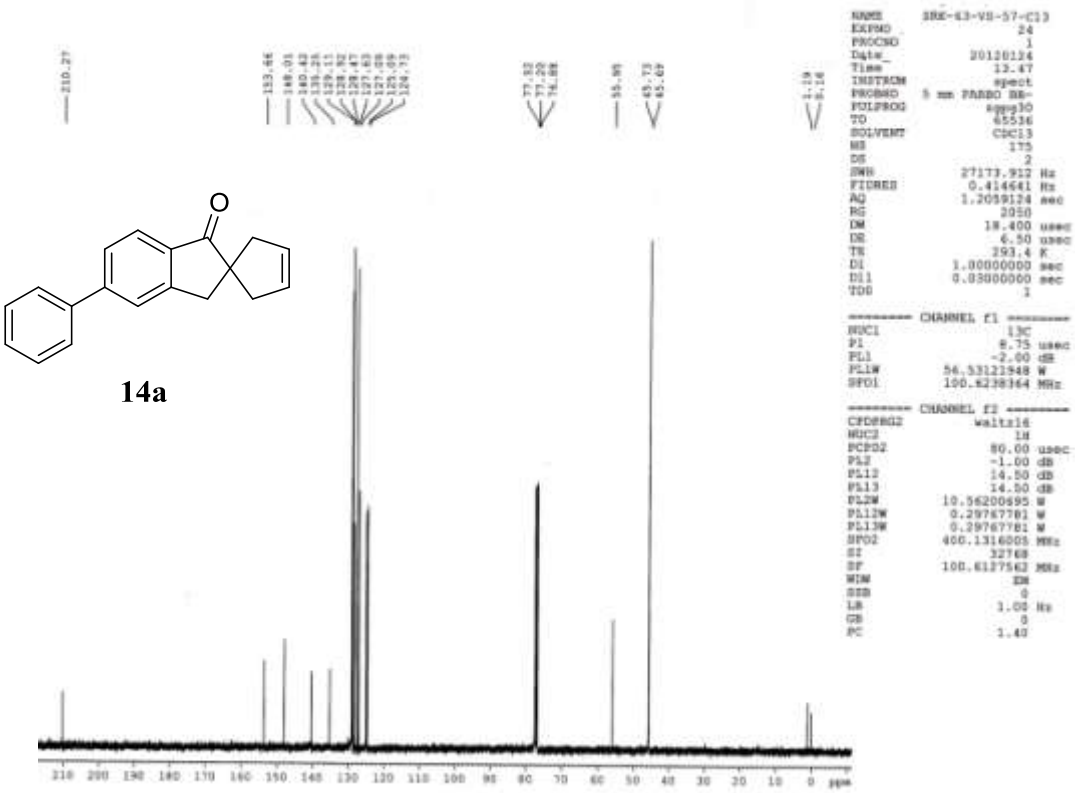
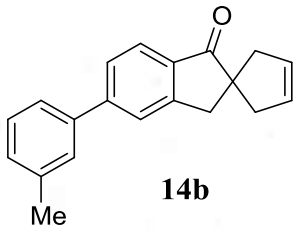

200
180
160
140
120
100
80
60
40
20
ppm

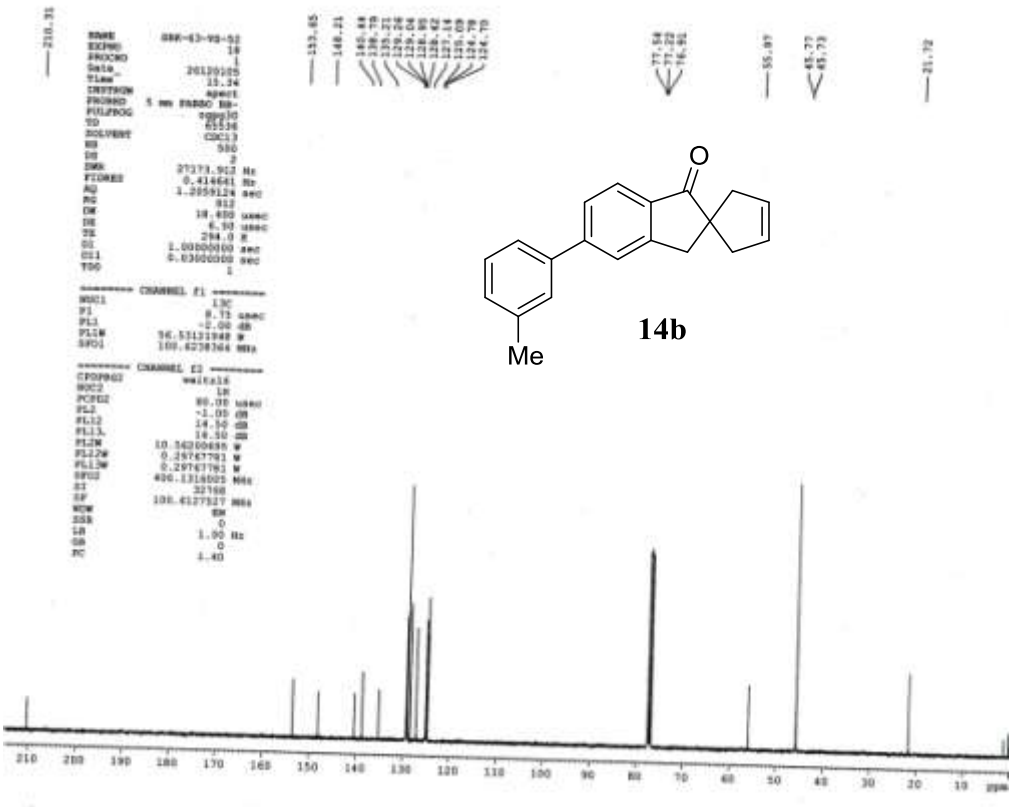

14a
ppm


14a


O
Me

14b

10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.05
2.03
1.04
1.37
1.98
2.01
2.04
2.09
2.07
0.56
0.87


O
Me
210
200
190
180
170
160
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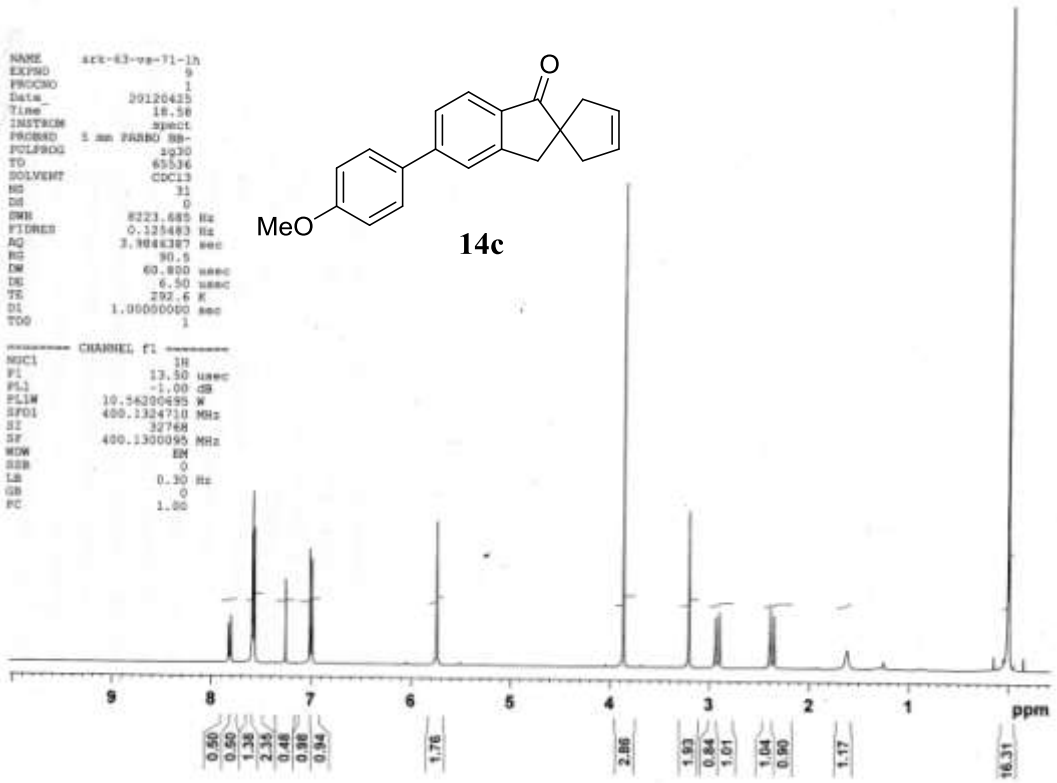
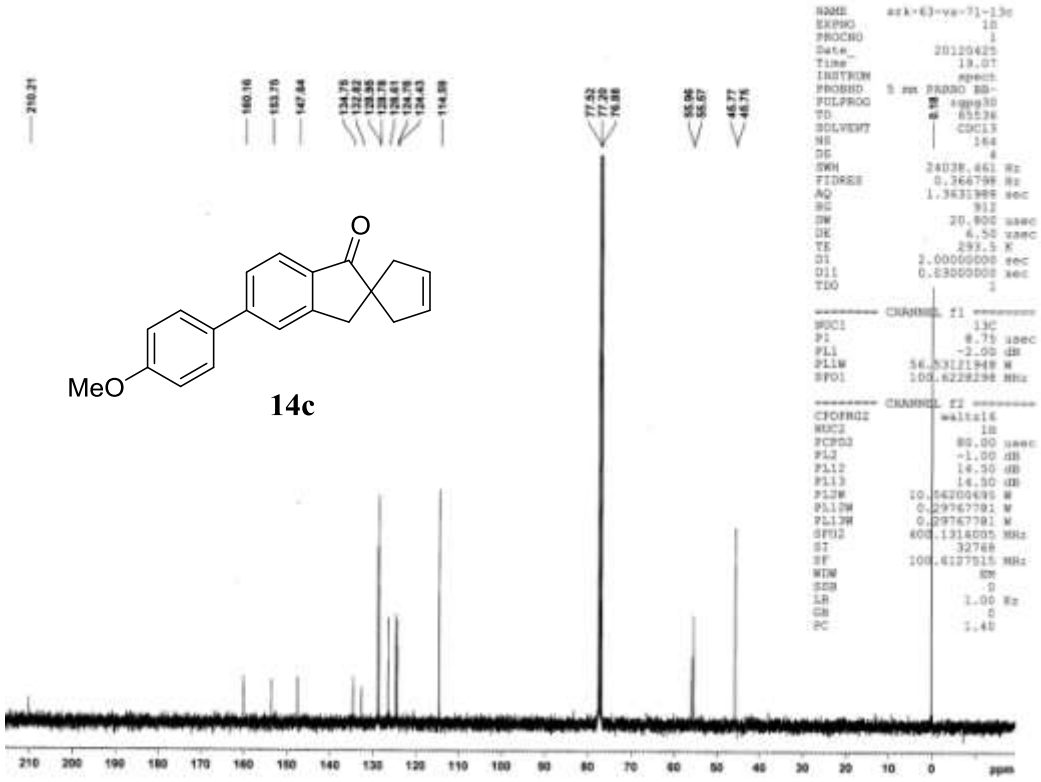
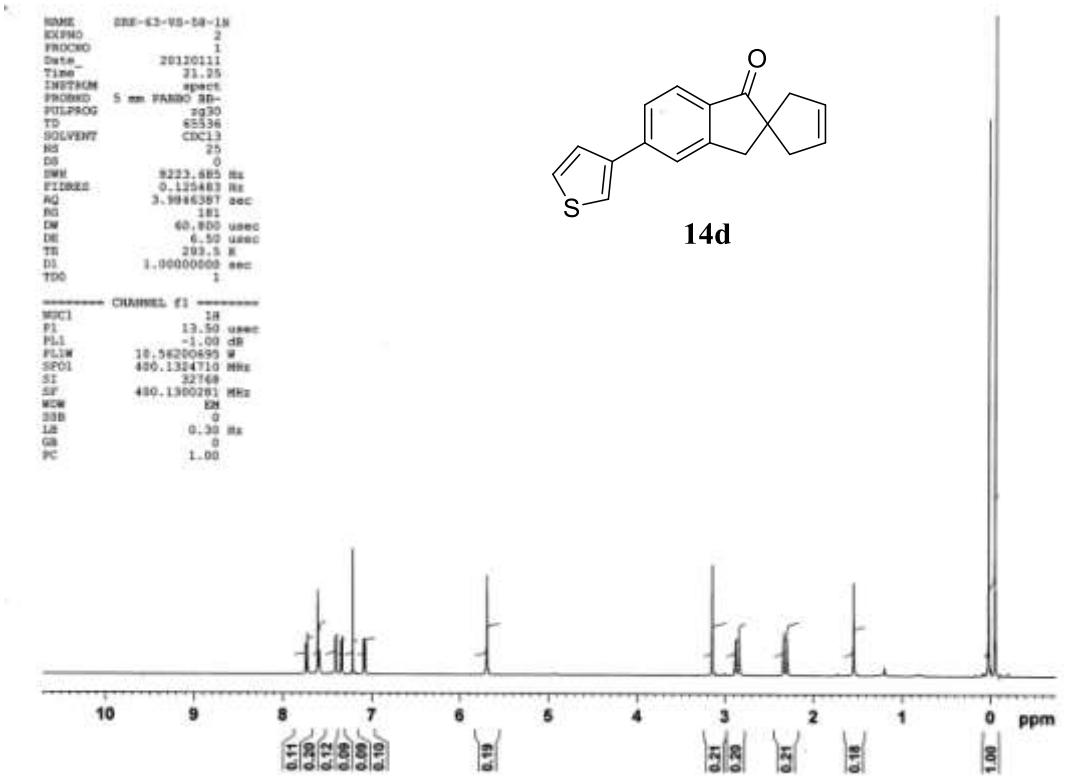
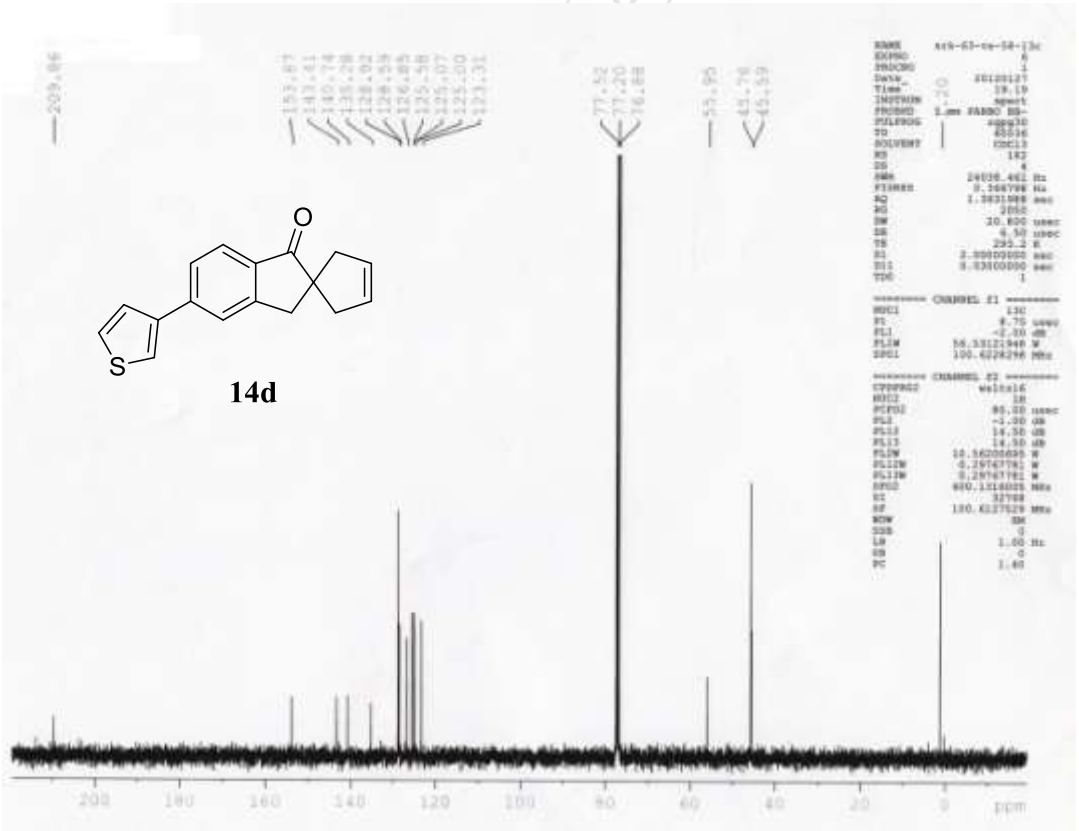
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

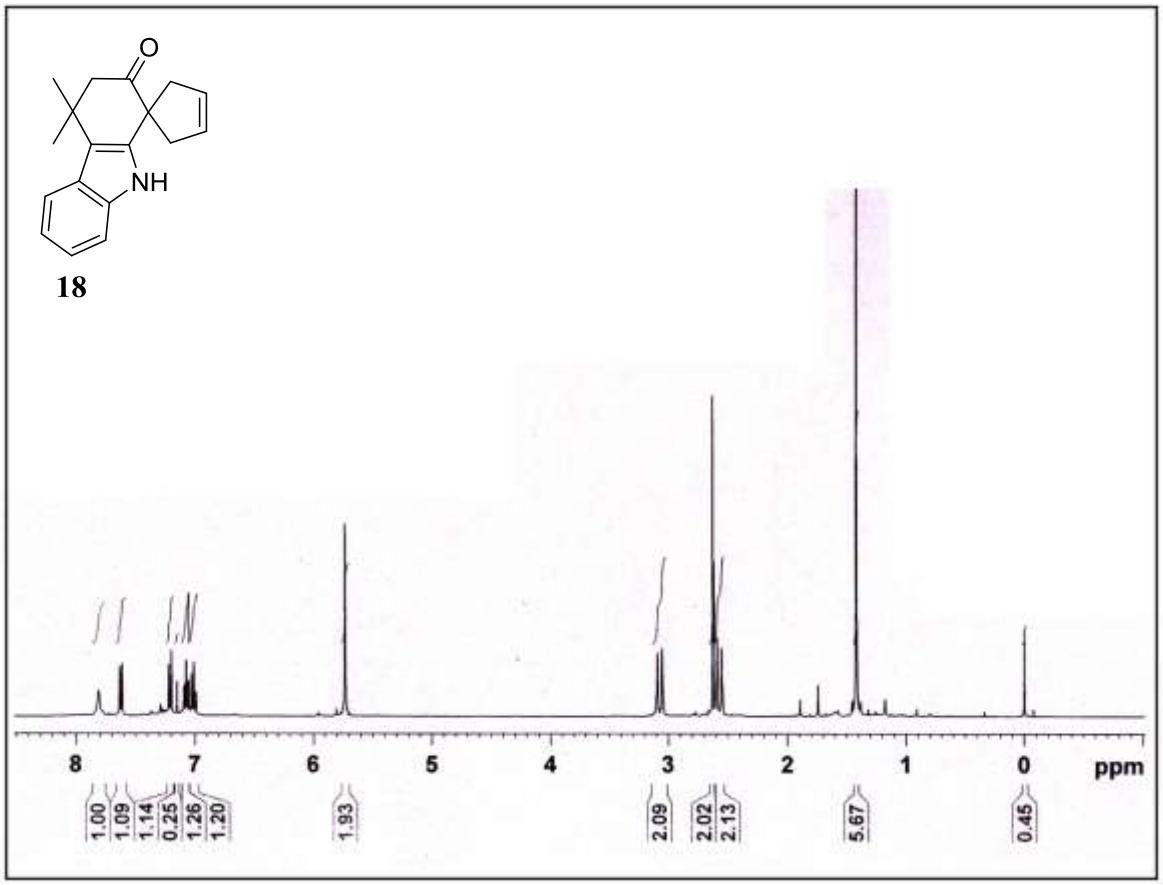
14b

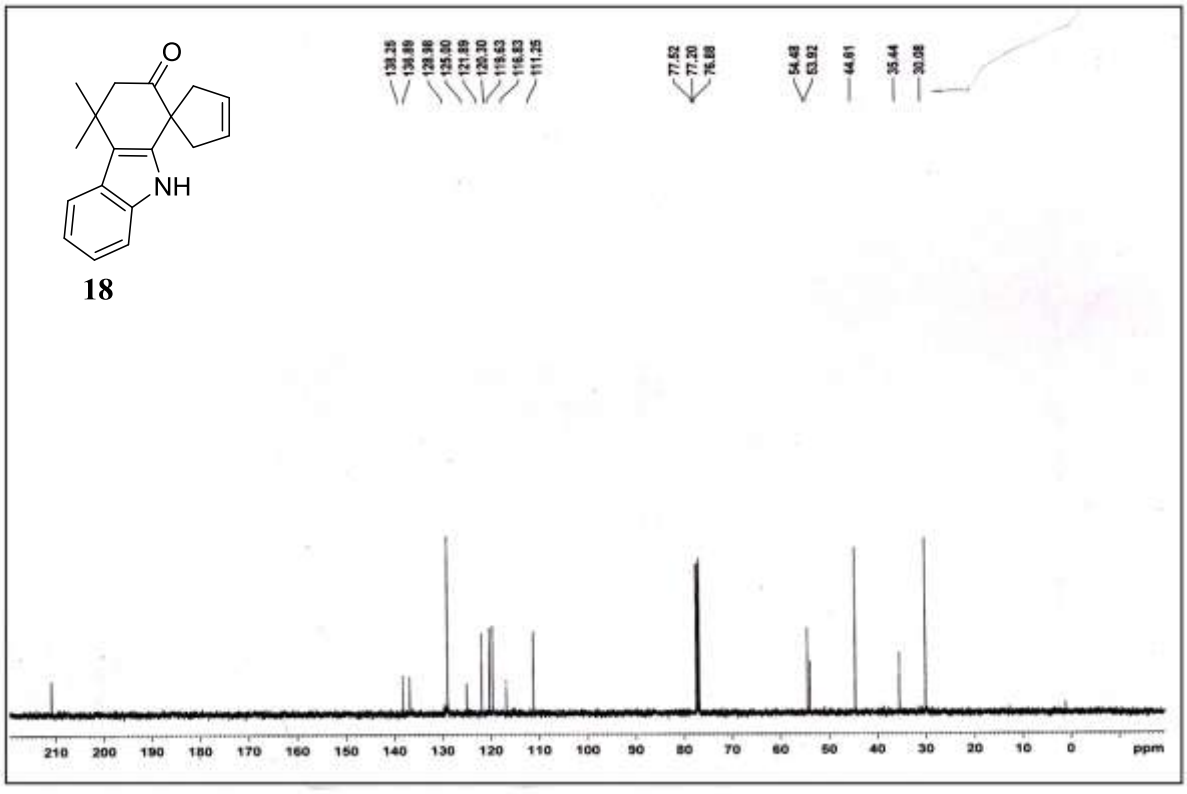

MeO
14c
ppm

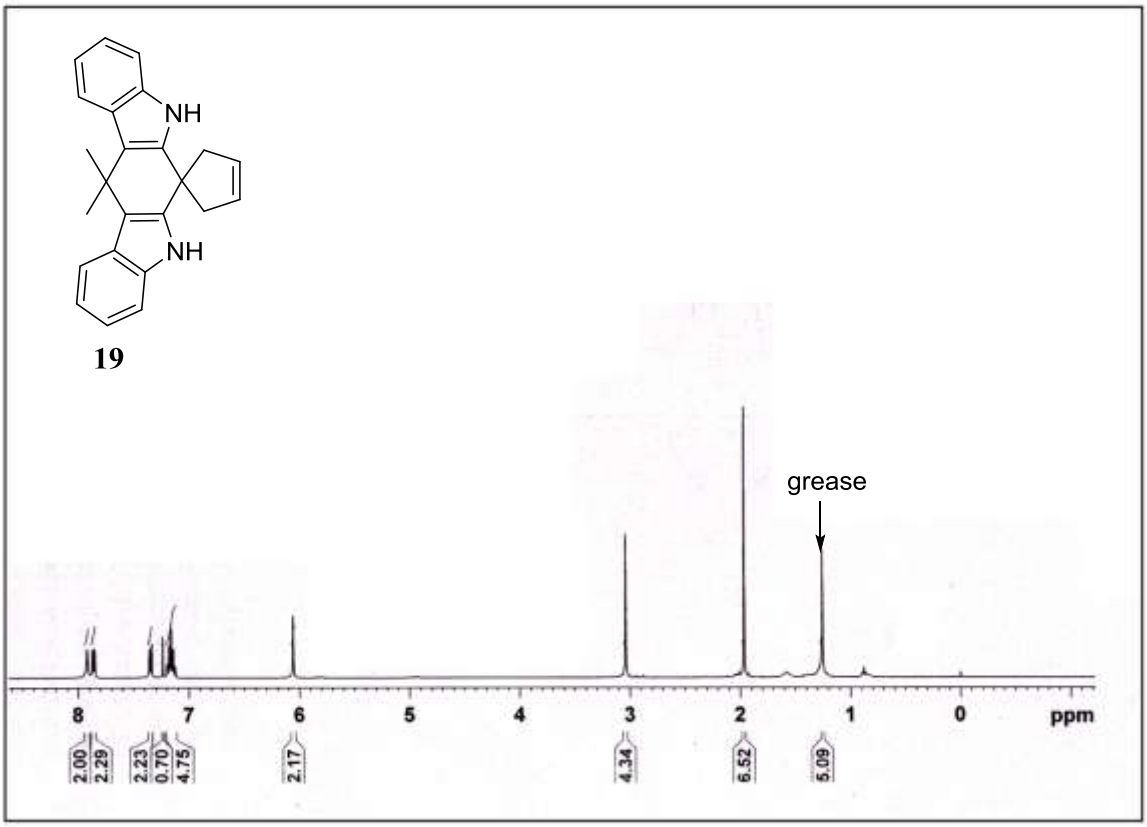

MeO
14c
ppm

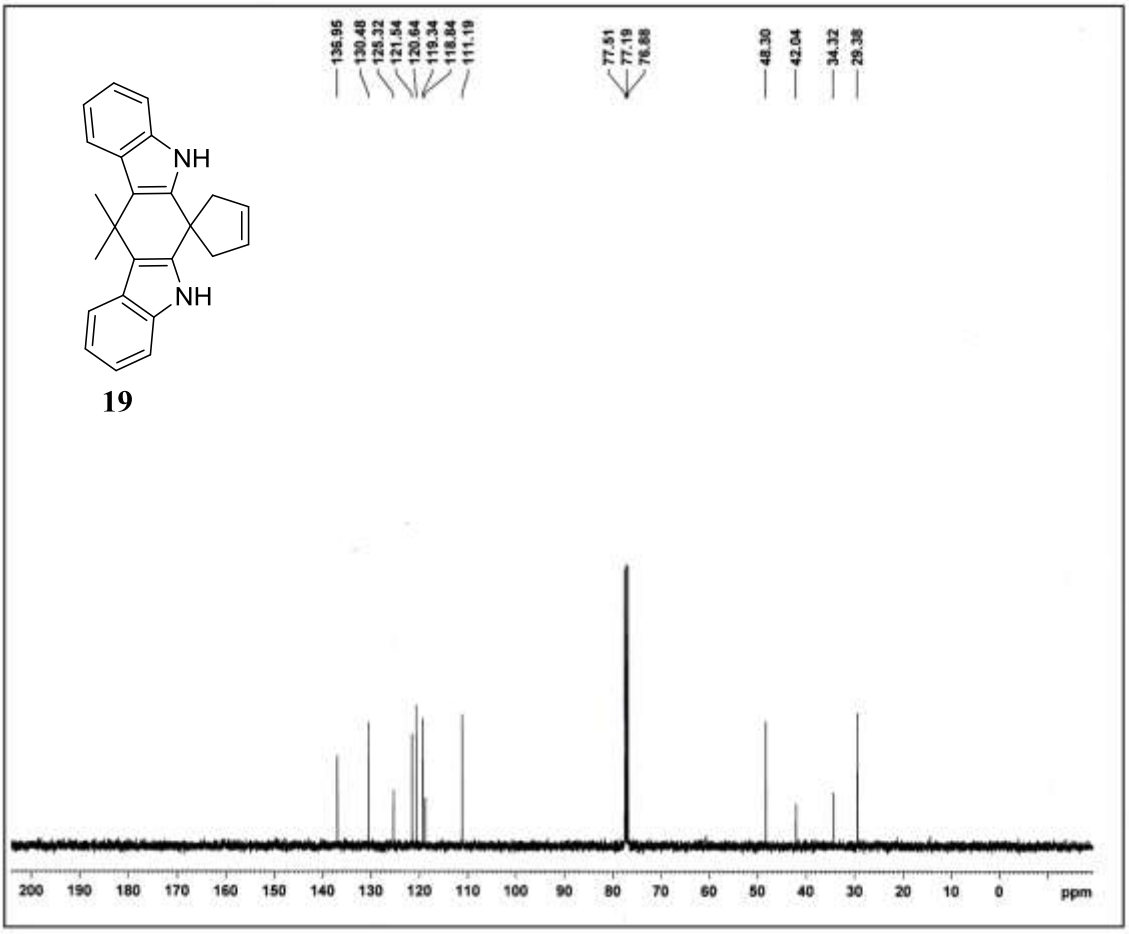

14d
10
9
8
7
6
5
4
3
2
1
0
ppm

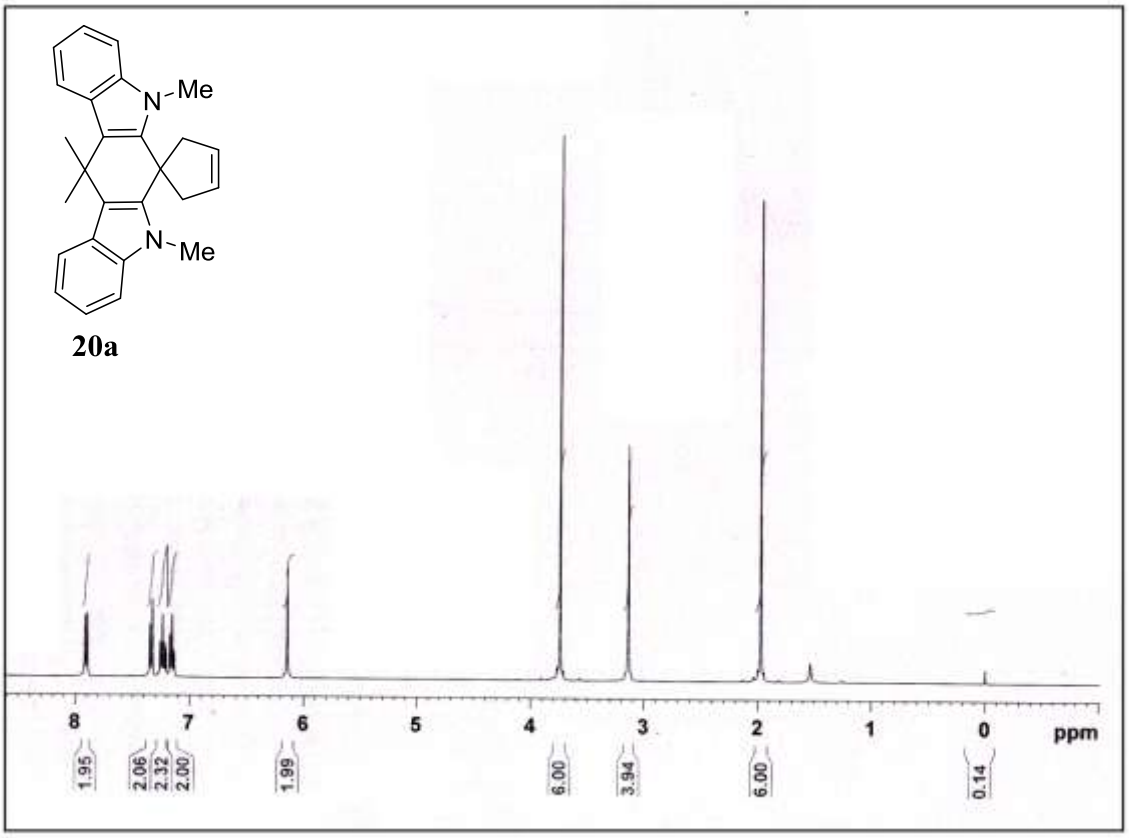

14d
200
180
160
140
120
100
80
60
40
20
0
ppm

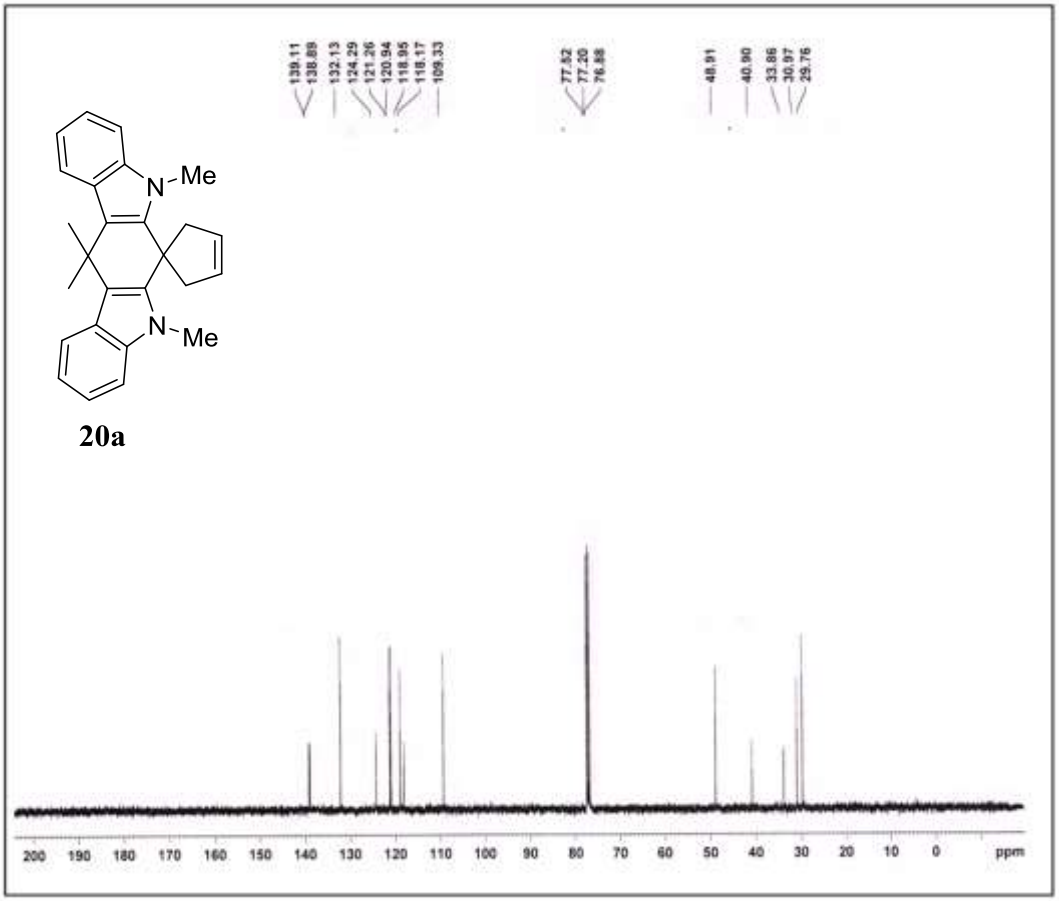

O
NH
18
8
7
6
5
4
3
2
1
0
ppm
1.00
1.09
1.14
0.25
1.26
1.20
1.93
2.09
2.02
2.13
5.67
0.45

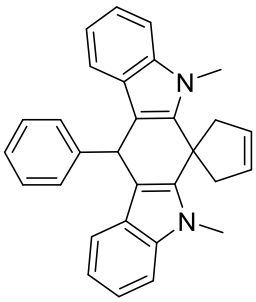

O
NH
18
138.25
136.89
128.96
125.00
121.89
120.30
119.53
116.53
111.25
77.52
77.20
76.88
54.48
53.92
44.61
35.44
30.08
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


NH
NH
19
grease
8
7
6
5
4
3
2
1
0
ppm
2.00
2.29
2.23
0.70
4.75
2.17
4.34
6.52
5.09

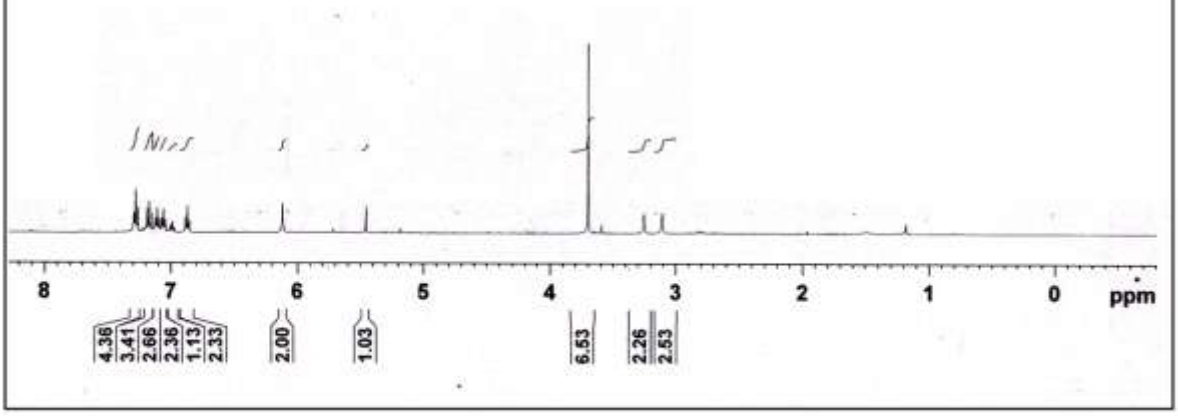

136.95
130.48
128.32
121.54
120.64
119.34
118.84
111.19
77.51
77.19
76.88
48.30
42.04
34.32
29.38
NH
NH
19
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

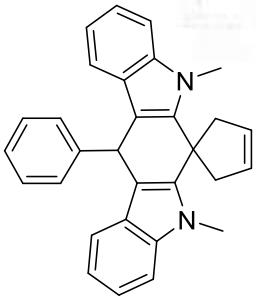

N-Me
N-Me
20a
8
7
6
5
4
3
2
1
0
ppm
1.95
2.06
2.32
2.00
1.99
6.00
3.94
6.00
0.14


139.11
138.89
132.13
124.29
121.26
120.94
118.95
118.17
109.33
77.52
77.20
76.88
48.91
40.90
33.86
30.97
29.76
N-Me
N-Me
20a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



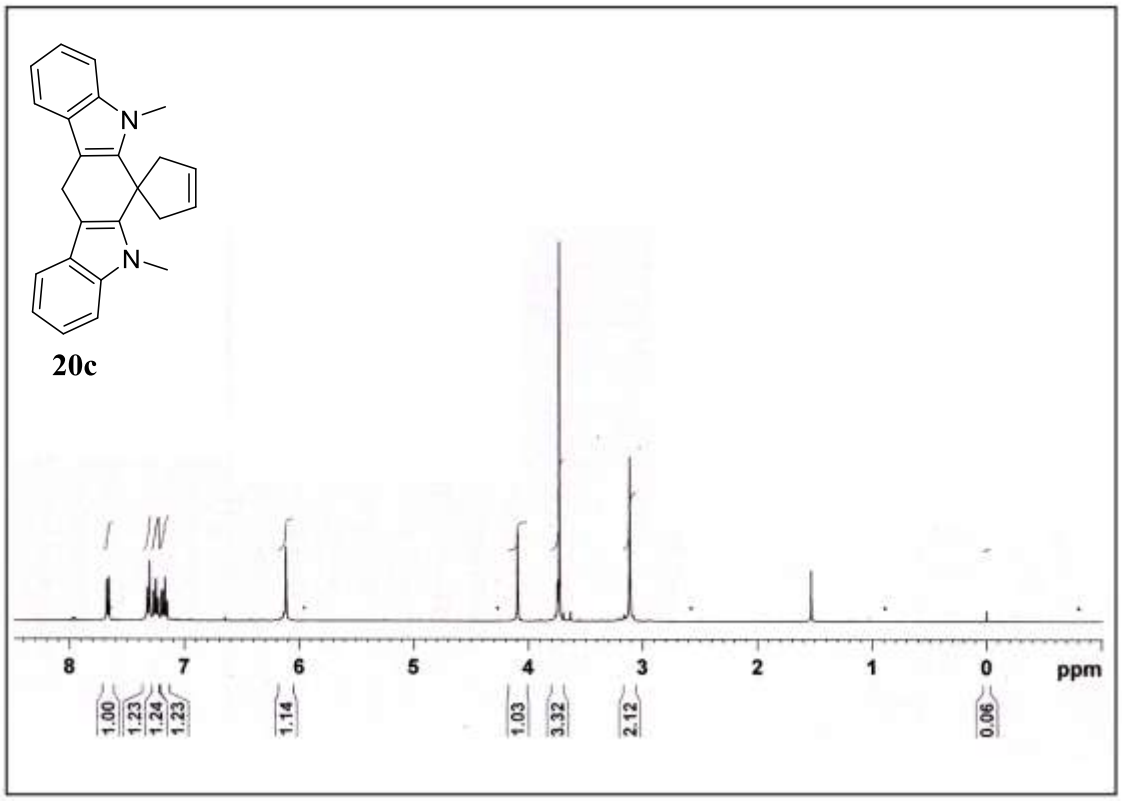
20b

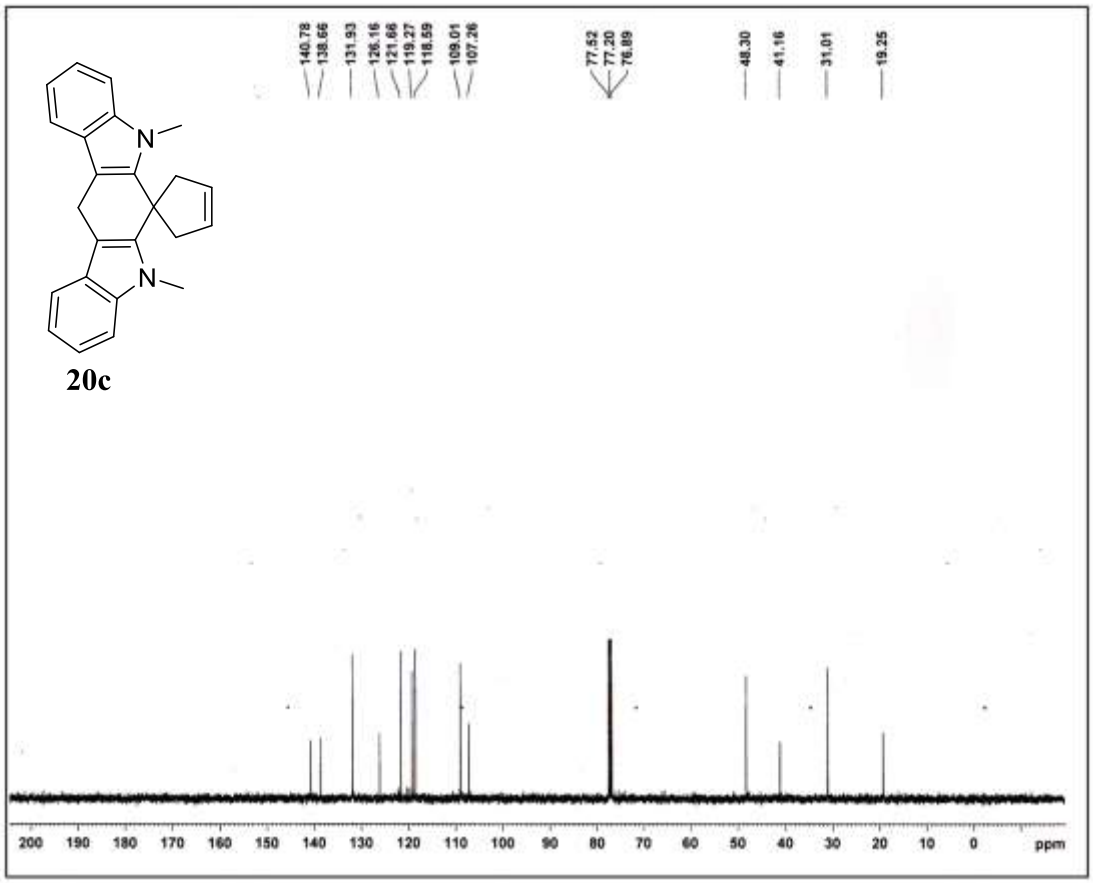

8
7
6
5
4
3
2
1
0
ppm
4.36
3.41
2.66
2.36
1.13
2.33
2.00
1.03
6.53
2.26
2.53

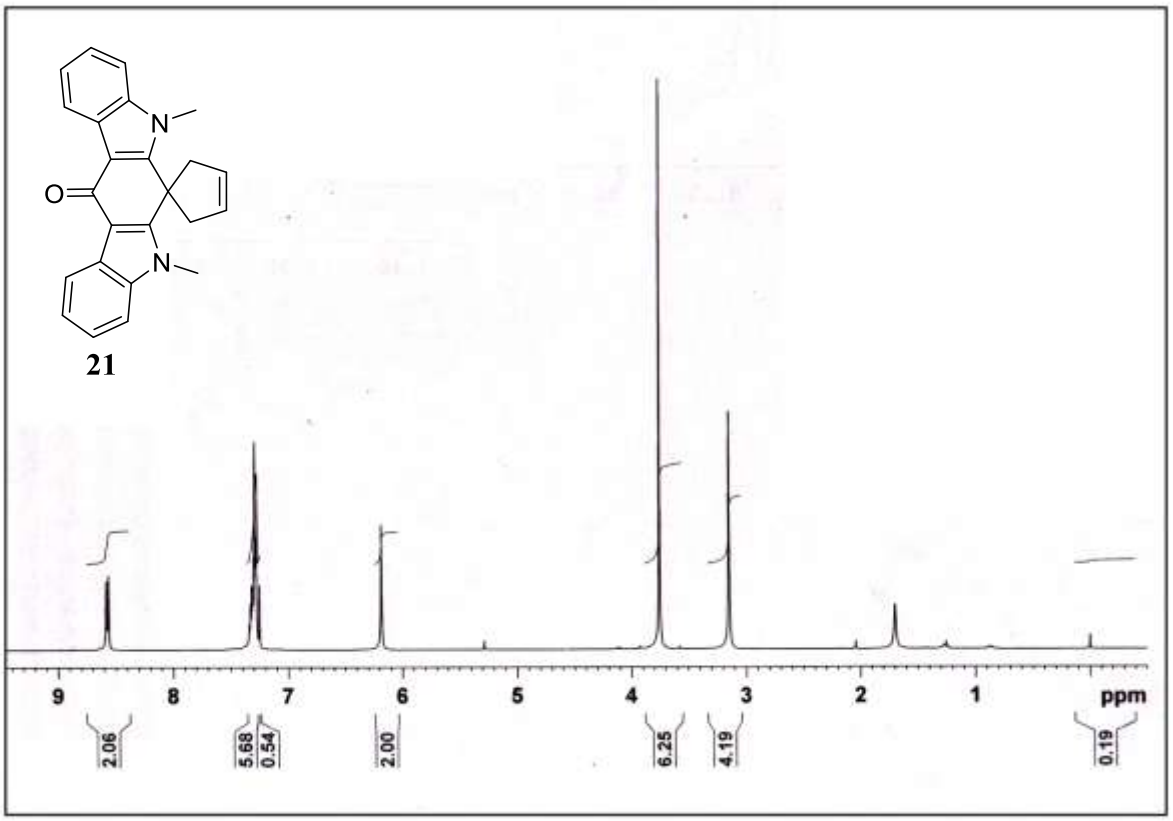


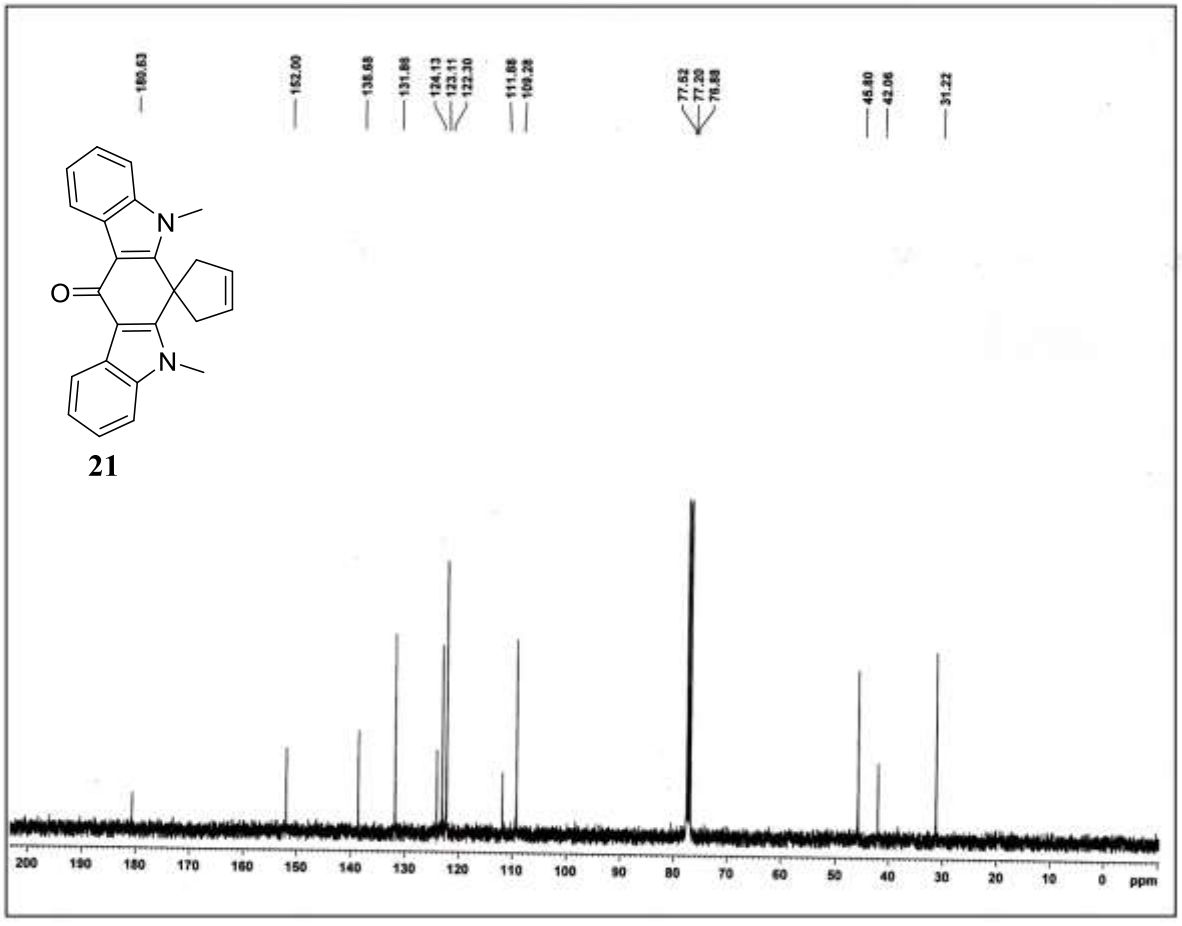
20b

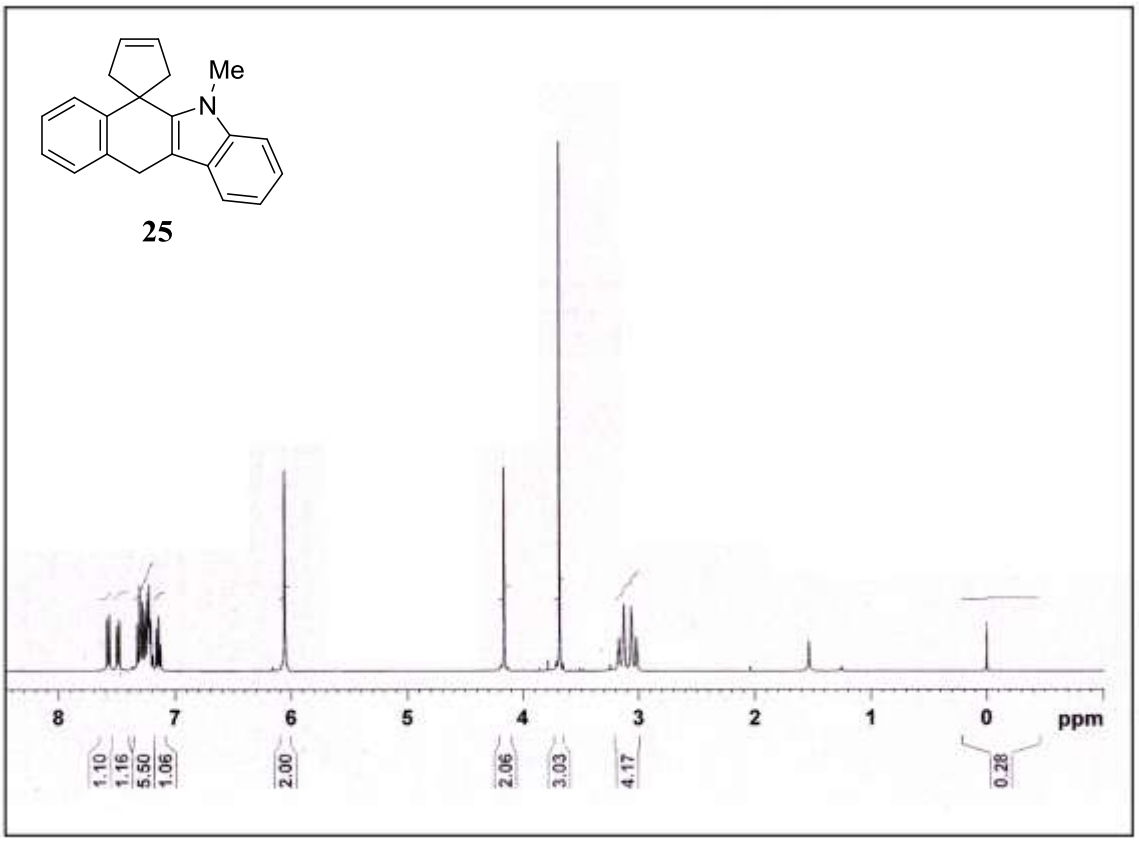
145.90
140.45
138.89
132.28
131.91
128.81
128.40
126.07
125.65
121.82
119.65
119.26
112.02
108.67
77.46
77.20
76.95
48.91
48.31
41.08
39.46
31.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

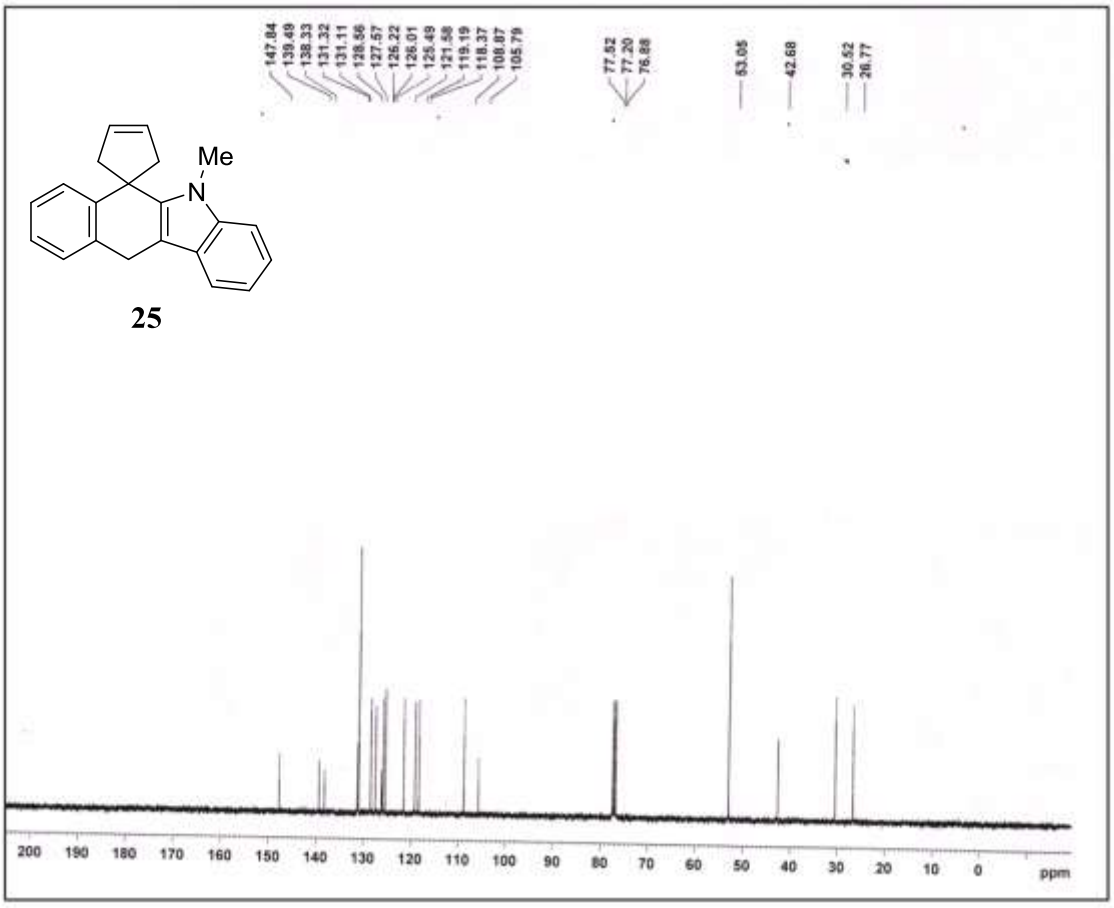

20c
8
7
6
5
4
3
2
1
0
ppm
1.00
1.23
1.24
1.23
1.14
1.03
3.32
2.12
0.06

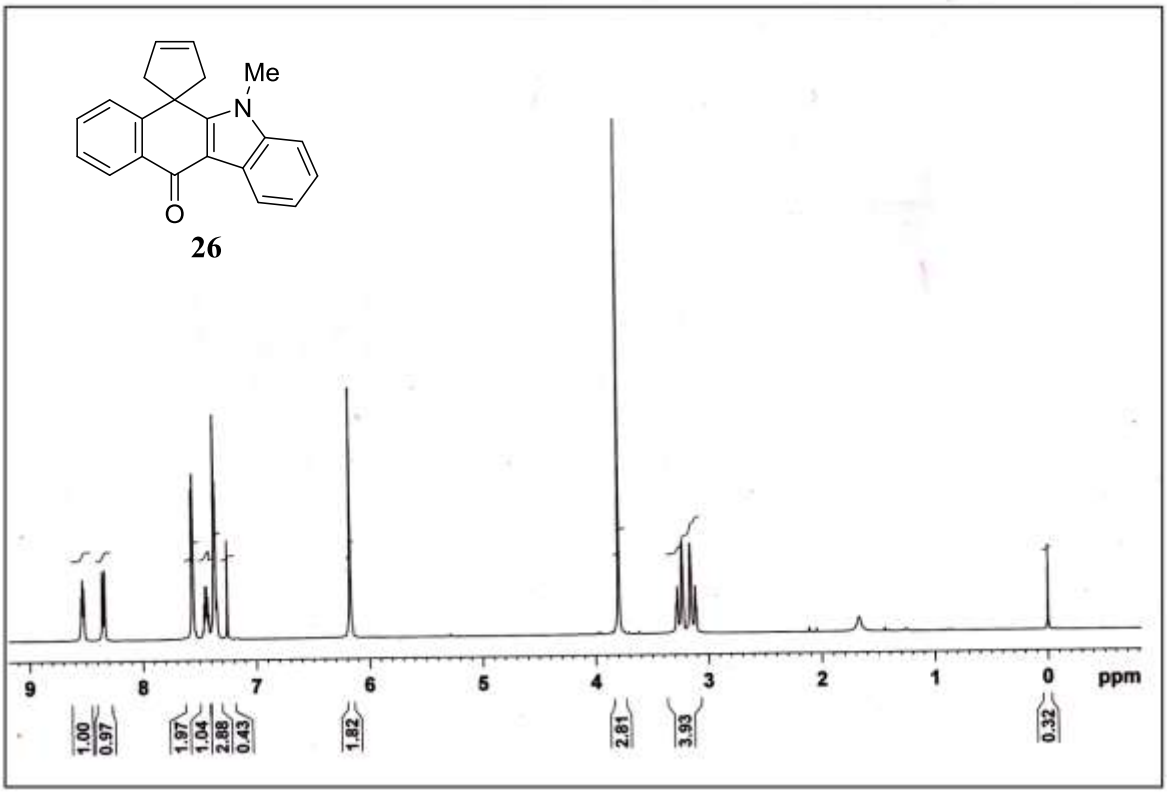

20c
140.78
138.66
131.93
126.16
121.66
119.27
118.59
109.01
107.26
77.52
77.20
76.89
48.30
41.16
31.01
19.25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

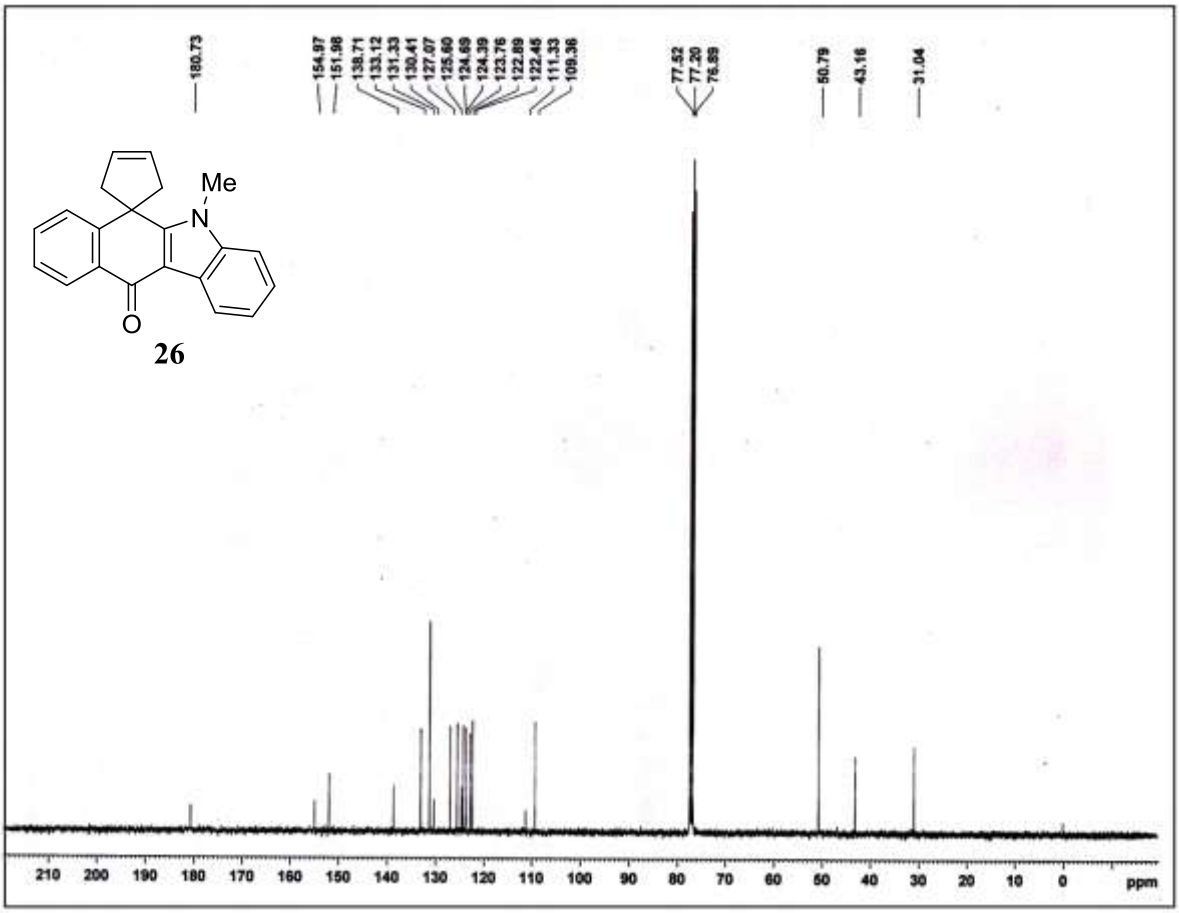

21
9
8
7
6
5
4
3
2
1
ppm
2.06
5.68
0.54
2.00
6.25
4.19
0.19

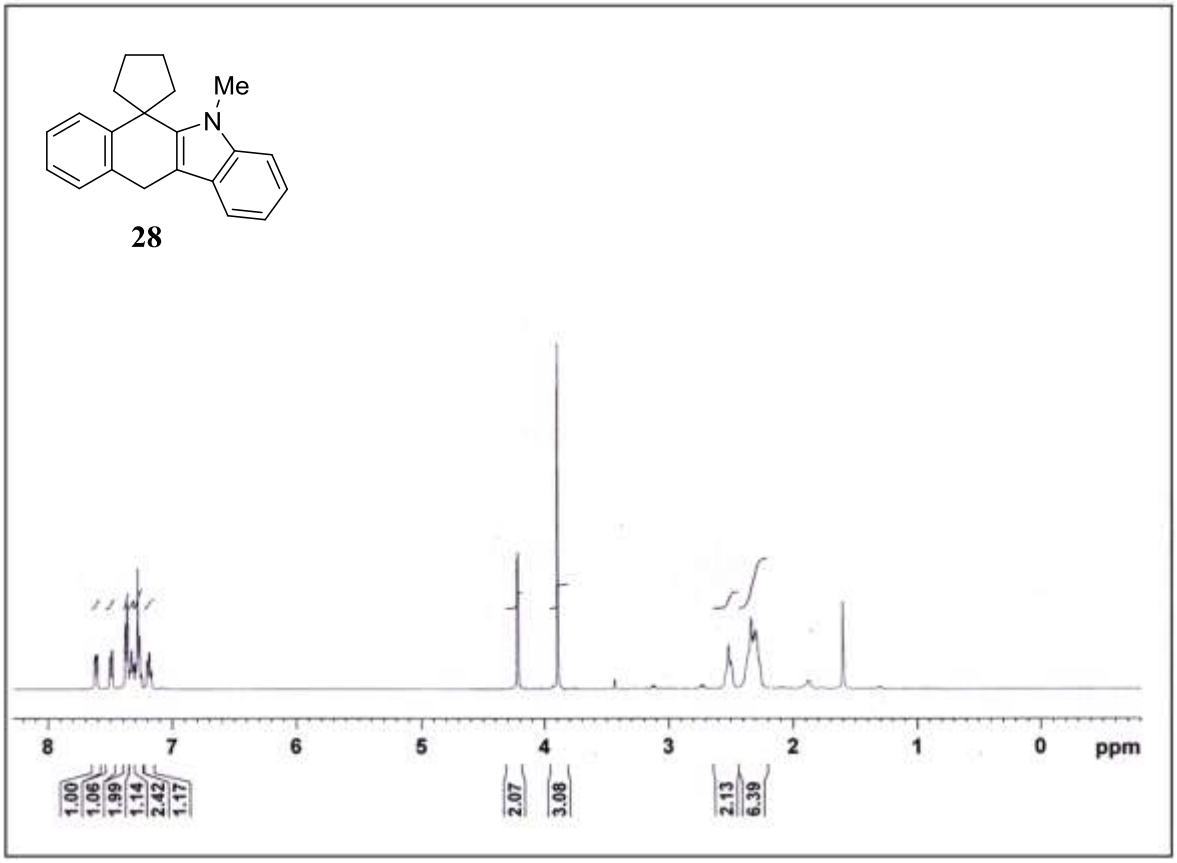

180.63
152.00
138.68
131.86
124.13
123.11
122.30
111.68
109.28
77.52
77.20
76.88
45.80
42.06
31.22
21
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

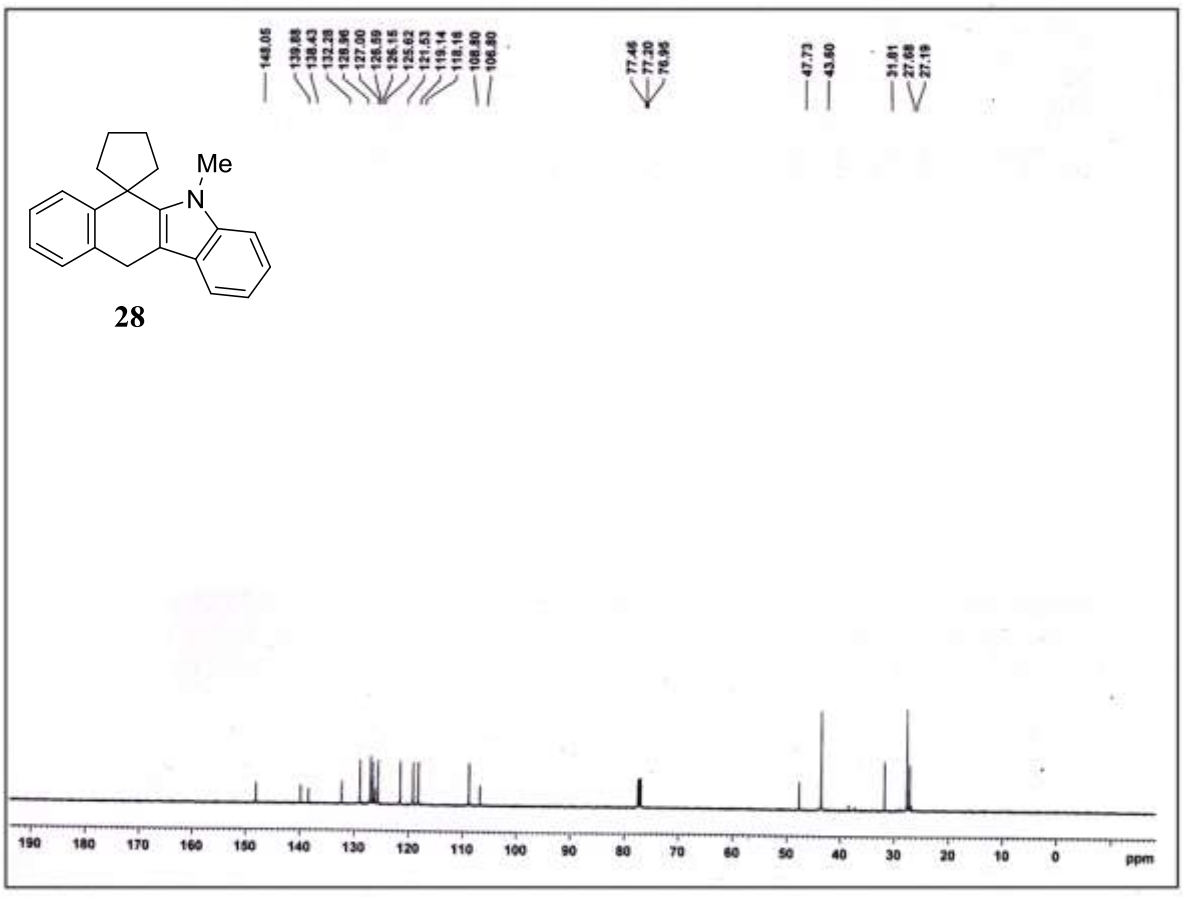

Me
N
25
8
7
6
5
4
3
2
1
0
ppm
1.10
1.16
5.50
1.06
2.00
2.06
3.03
4.17
0.28

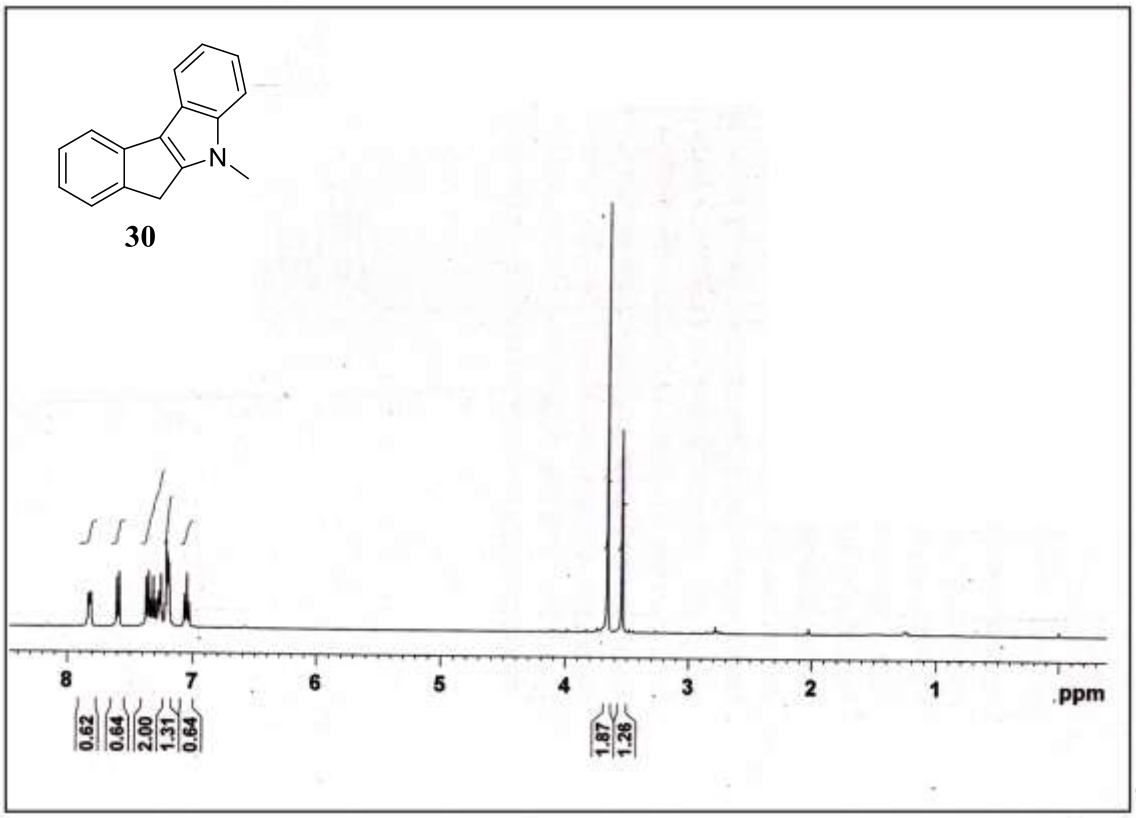

147.84
139.49
138.33
131.32
131.11
128.56
127.57
126.22
126.01
125.49
121.58
119.19
118.37
108.87
105.79
77.52
77.20
76.88
53.05
42.68
30.52
26.77
Me
N
25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

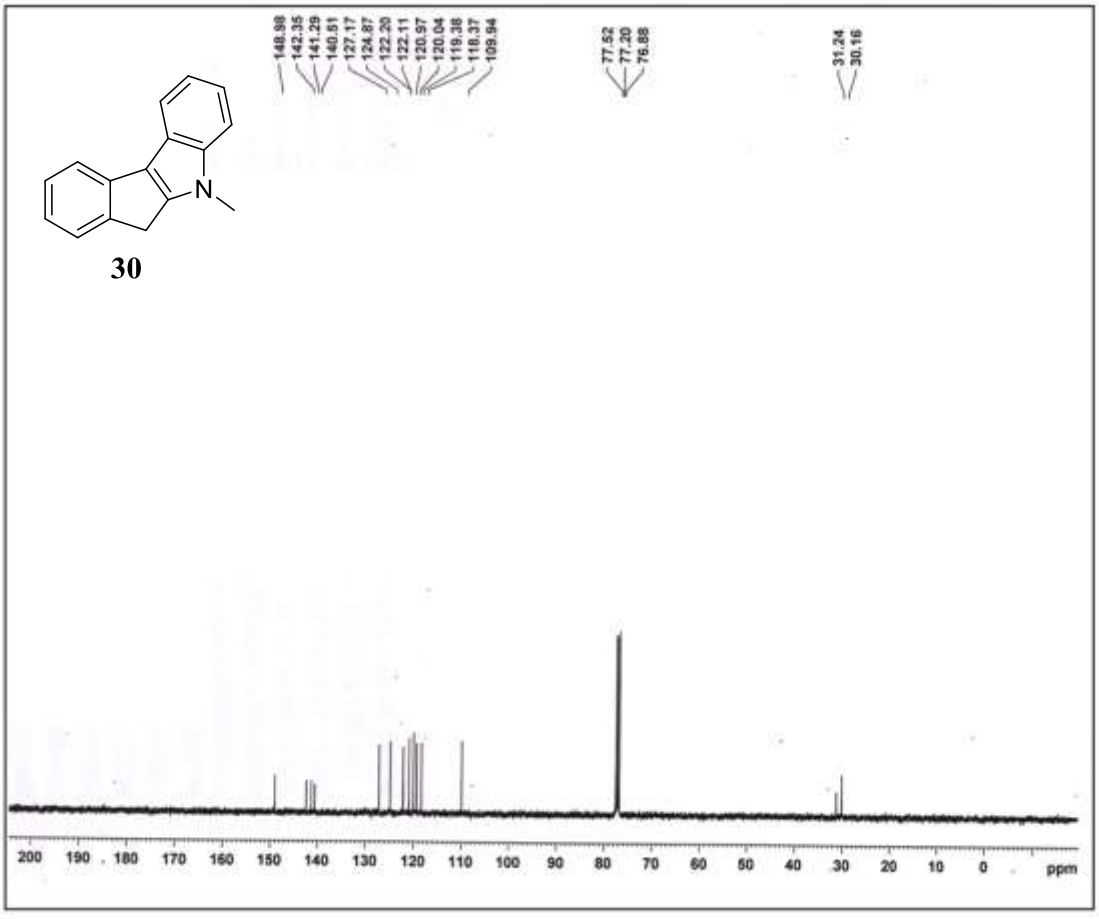

Me
N
O
26
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.97
1.97
1.04
2.88
0.43
1.82
2.81
3.93
0.32

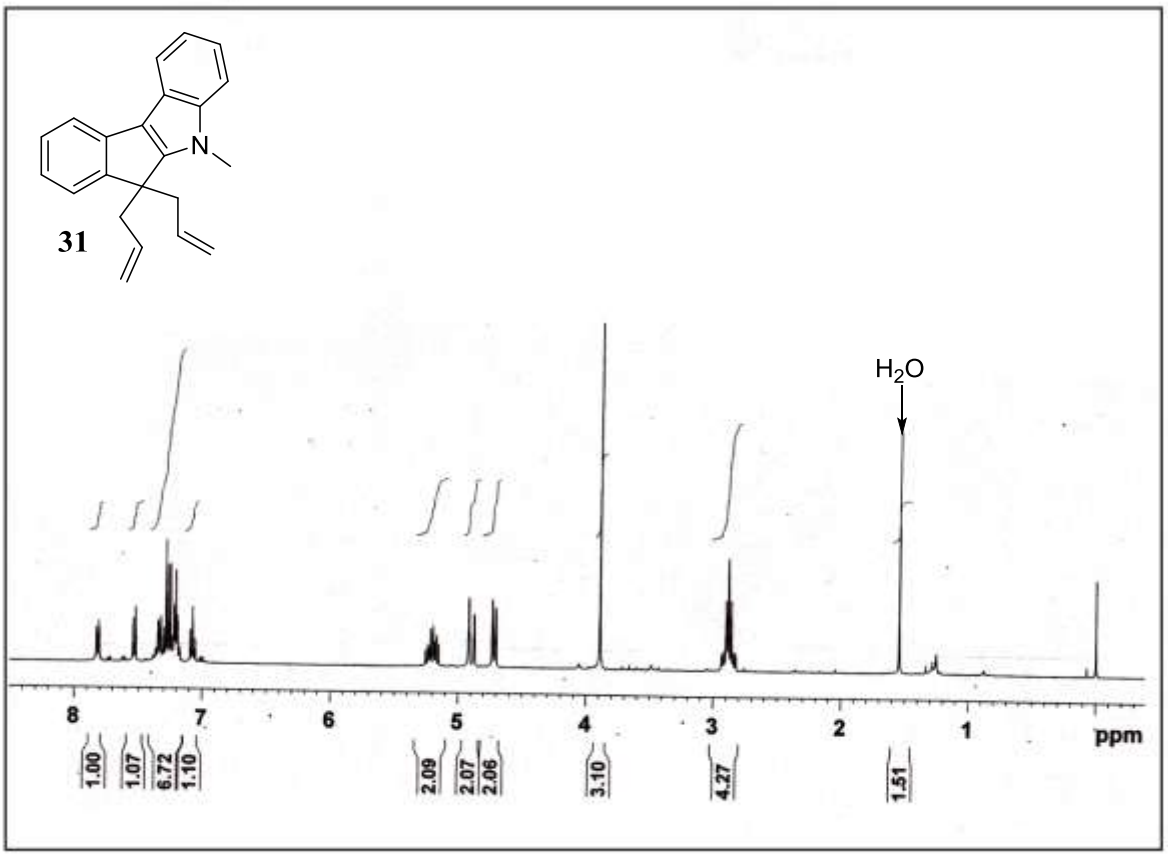

180.73
154.97
151.98
138.71
133.12
131.33
130.41
127.07
125.60
124.69
124.39
123.76
122.89
122.45
111.33
109.36
77.52
77.20
76.89
50.79
43.16
31.04
Me
N
O
26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

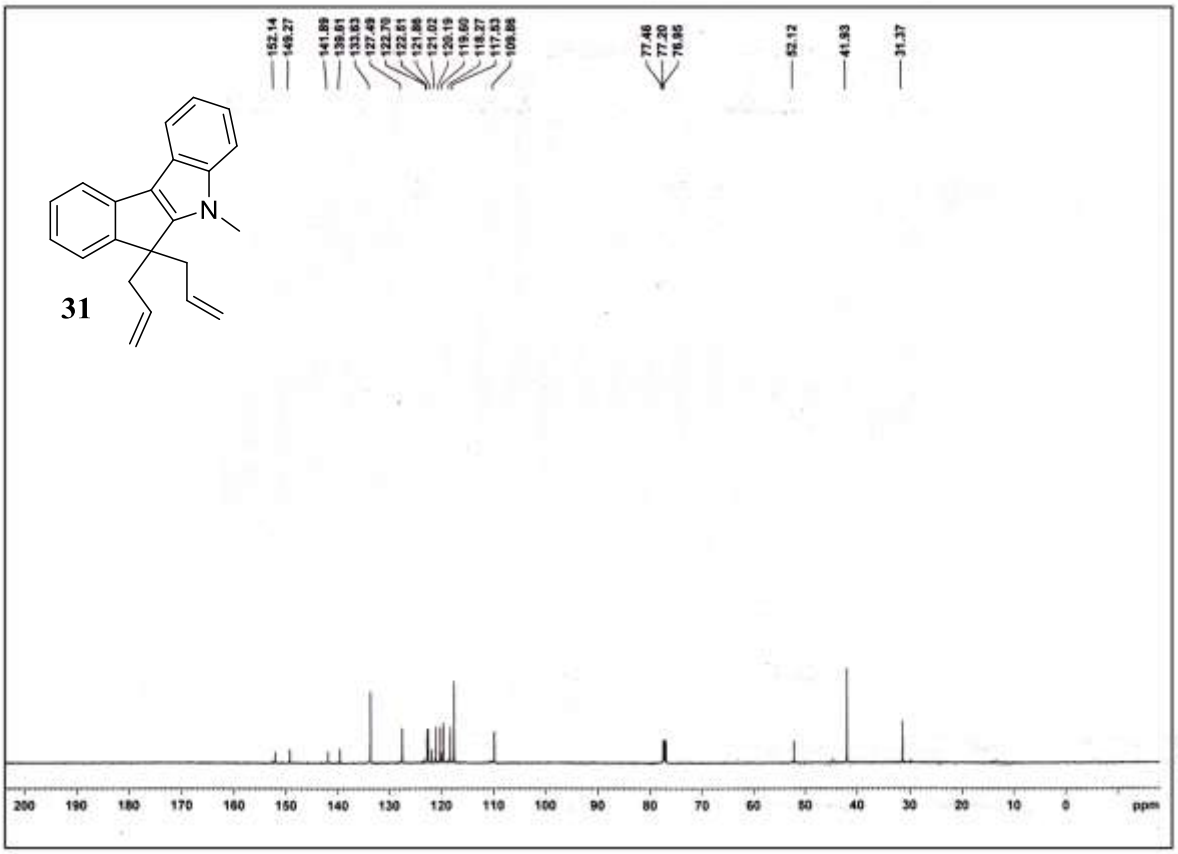

Me
N
28
8
7
6
5
4
3
2
1
0
ppm
1.00
1.06
1.99
1.14
2.42
1.17
2.07
3.08
2.13
6.39

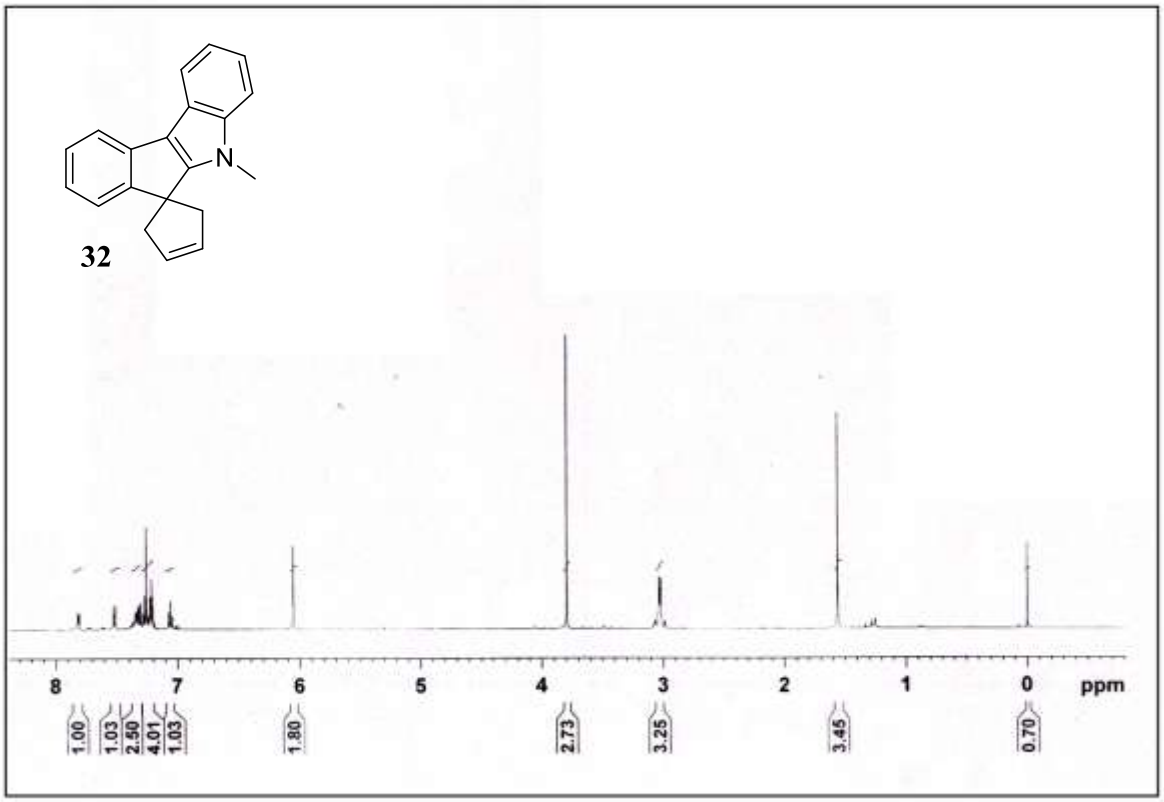

148.05
139.88
138.43
132.28
128.96
127.00
126.59
126.15
125.62
121.53
119.14
118.16
108.80
106.80
77.46
77.20
76.95
47.73
43.80
31.61
27.68
27.19
Me
N
28
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

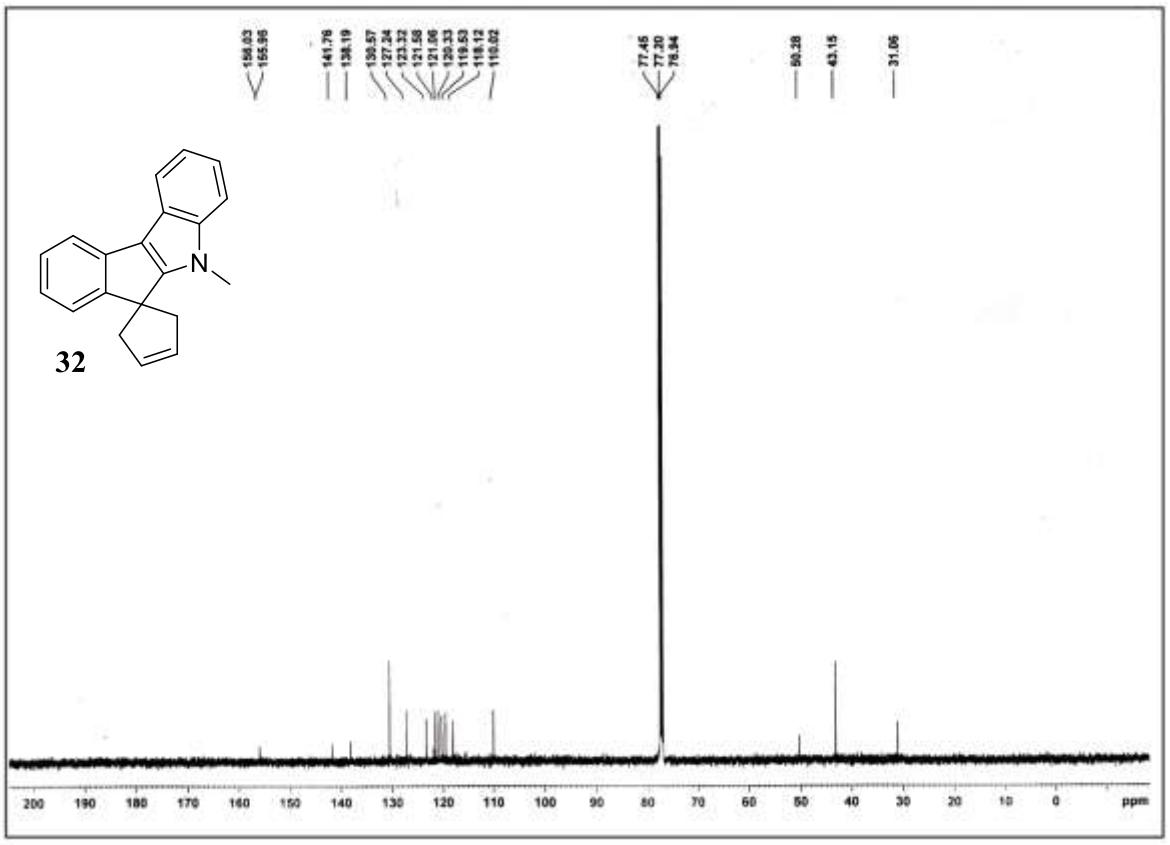

30
8
7
6
5
4
3
2
1
ppm
0.62
0.64
2.00
1.31
0.64
1.87
1.26

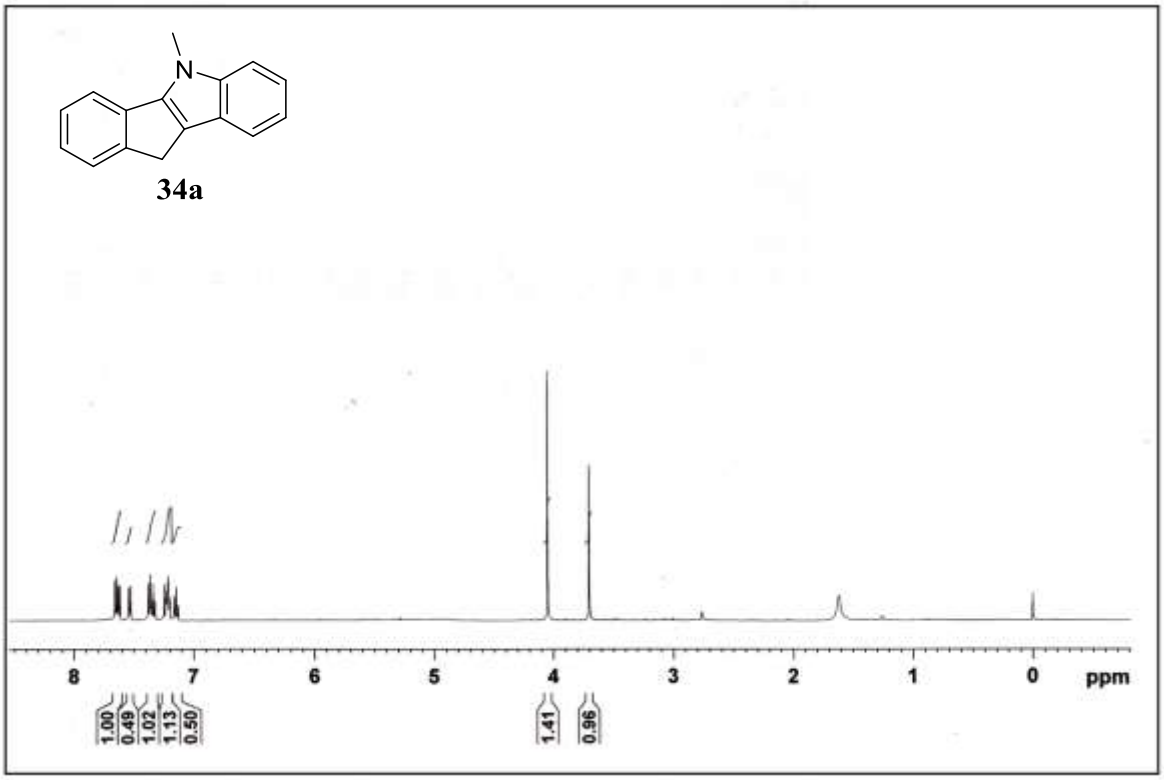

30
148.98
142.35
141.29
140.61
127.17
124.87
122.20
122.11
120.97
120.04
119.38
118.37
109.94
77.52
77.20
76.88
31.24
30.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

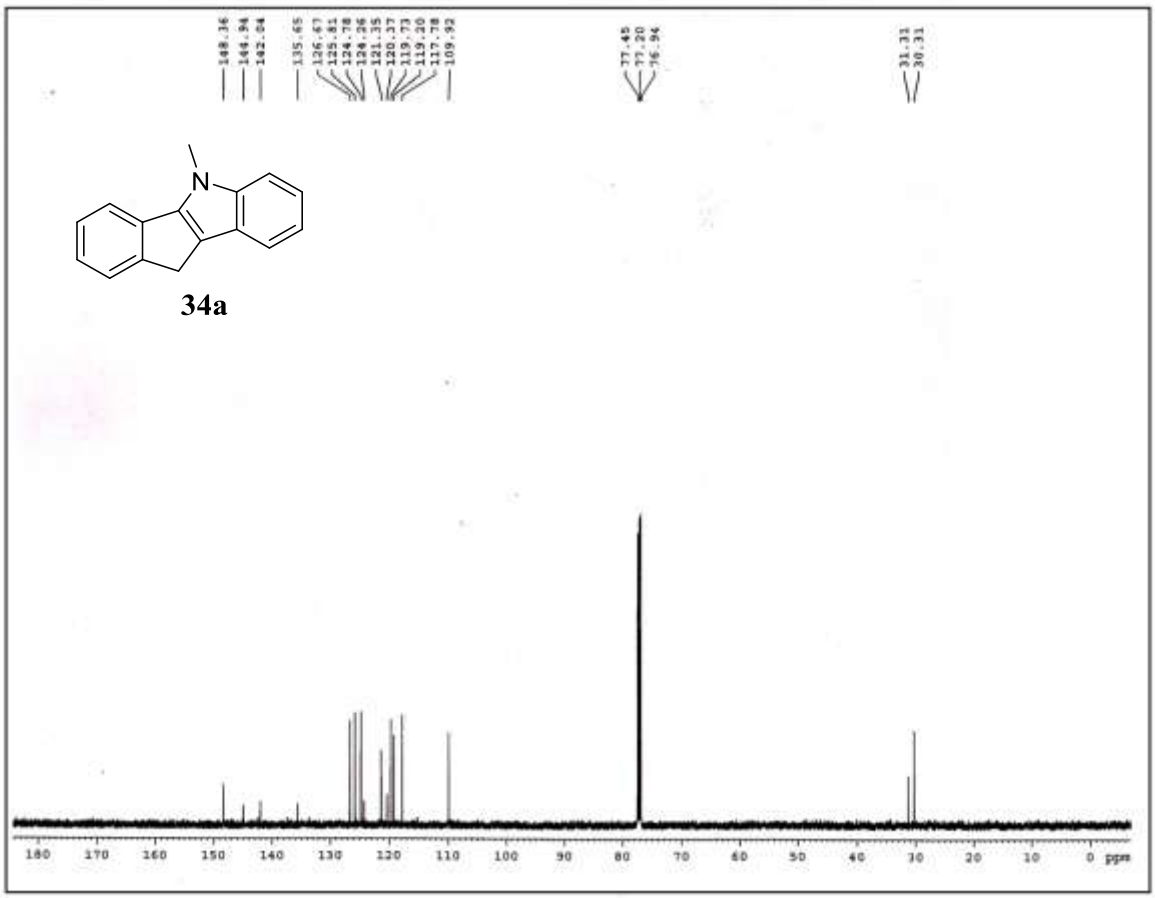

31
H2O
8
7
6
5
4
3
2
1
ppm
1.00
1.07
6.72
1.10
2.09
2.07
2.06
3.10
4.27
1.51


31
152.14
149.27
141.89
139.61
133.63
127.49
122.70
122.51
121.86
121.02
120.19
119.50
118.27
117.53
109.86
77.46
77.20
76.95
52.12
41.53
31.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


32
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
2.50
4.01
1.03
1.80
2.73
3.25
3.45
0.70


32
158.03
155.96
141.76
138.19
130.57
127.24
123.32
121.58
121.06
120.33
119.53
118.12
110.02
77.45
77.20
76.94
50.28
43.15
31.06
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


34a
8
7
6
5
4
3
2
1
0
ppm
1.00
0.49
1.02
1.13
0.50
1.41
0.96


148.36
144.94
142.04
135.65
126.67
125.81
124.78
124.26
121.35
120.37
119.73
119.20
117.78
109.92
77.45
77.20
76.94
31.31
30.31
34a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


35a
8
7
6
5
4
3
2
1
0
ppm
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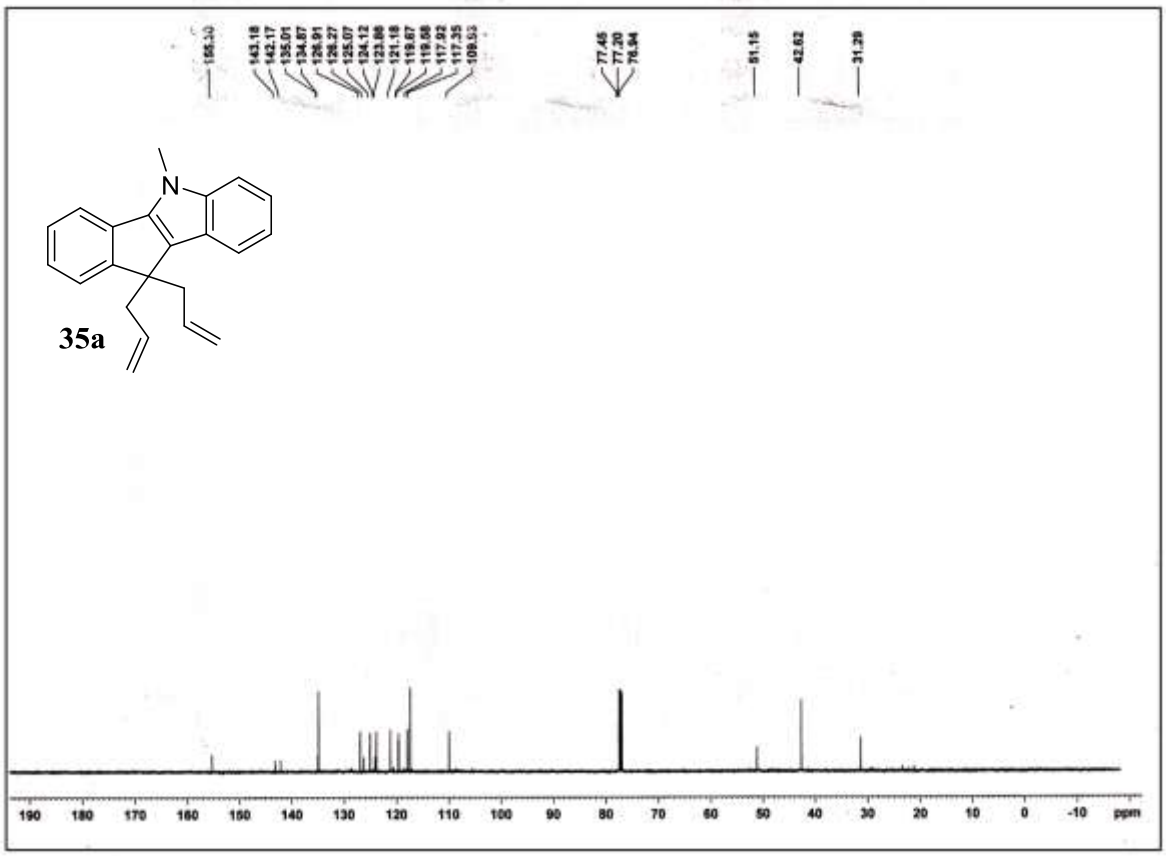
1.02
1.08
1.08
1.08
2.53
1.19
1.94
3.83
3.00
2.07
2.40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142.17
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126.91
126.27
125.07
124.12
123.86
121.18
119.87
119.68
117.92
117.35
109.53
77.45
77.20
76.94
51.15
42.62
31.29
35a
190
180
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130
120
110
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90
80
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50
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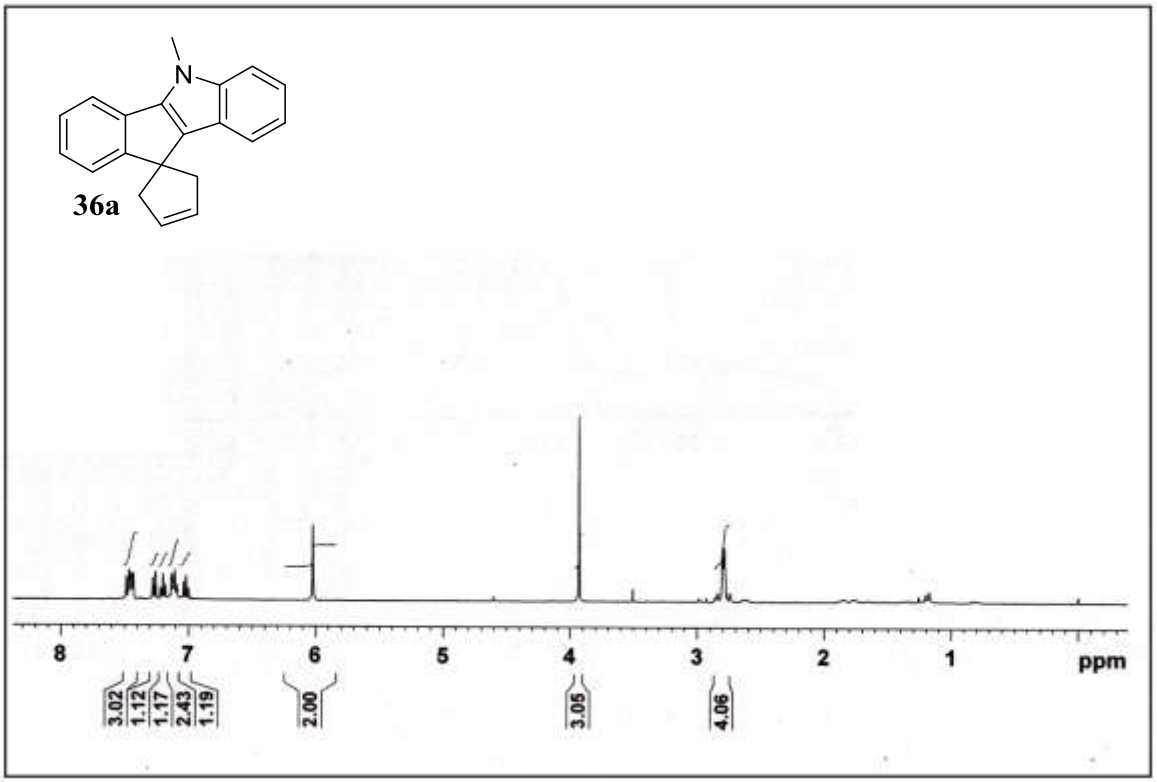
0
-10
ppm


36a
8
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6
5
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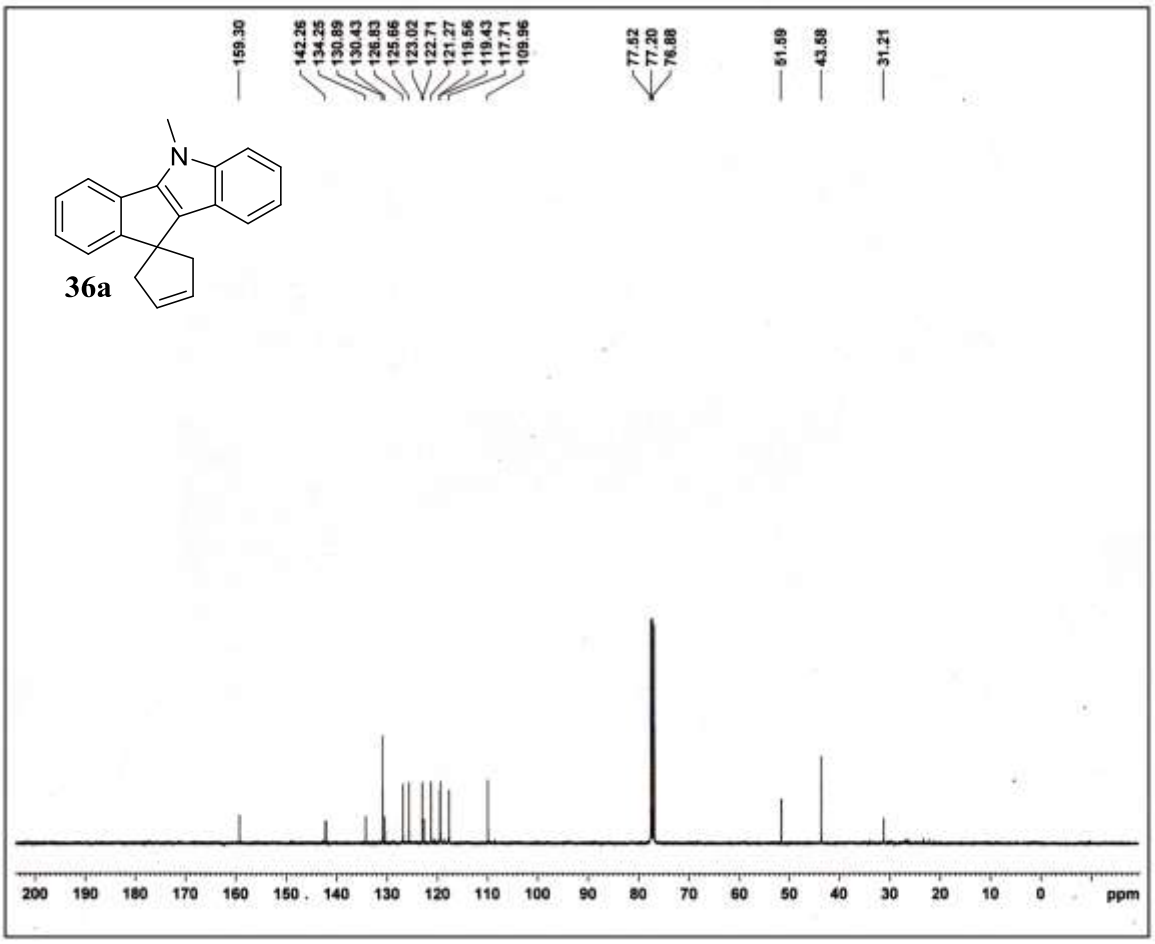
3
2
1
ppm
3.02
1.12
1.17
2.43
1.19
2.00
3.05
4.06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134.25
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130.43
126.83
125.66
123.02
122.71
121.27
119.56
119.43
117.71
109.96
77.52
77.20
76.88
51.59
43.58
31.21
36a
200
190
180
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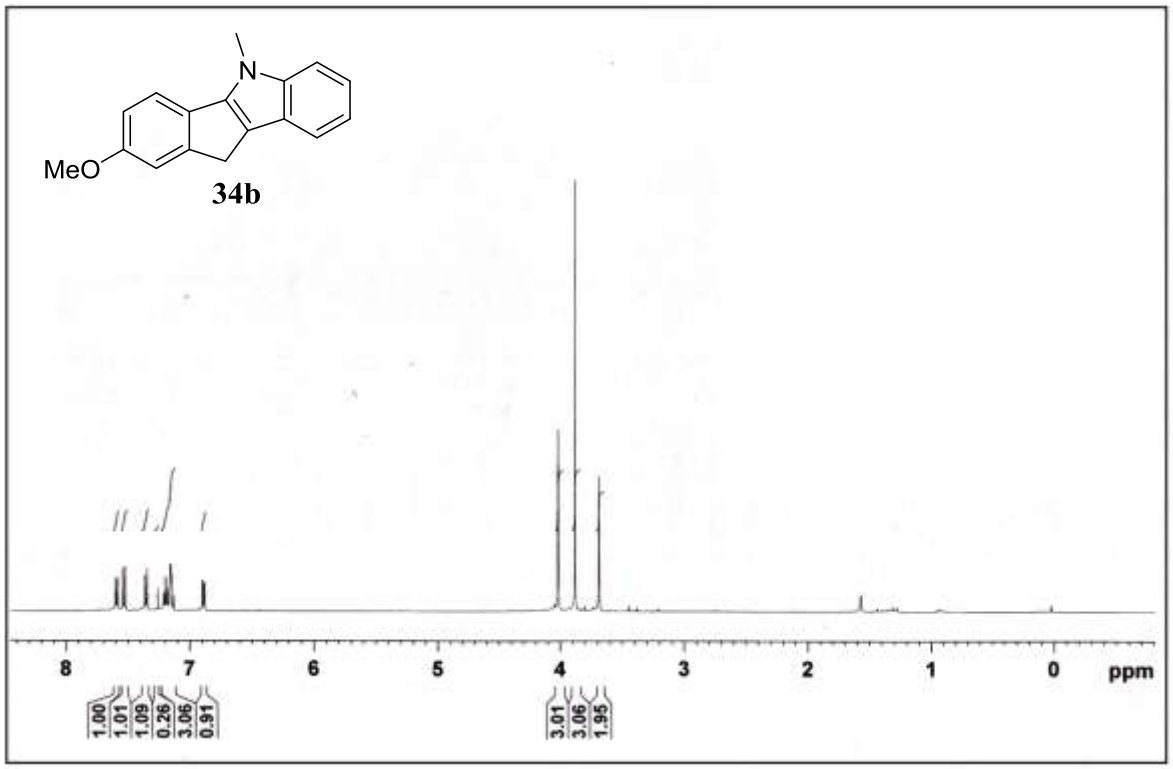
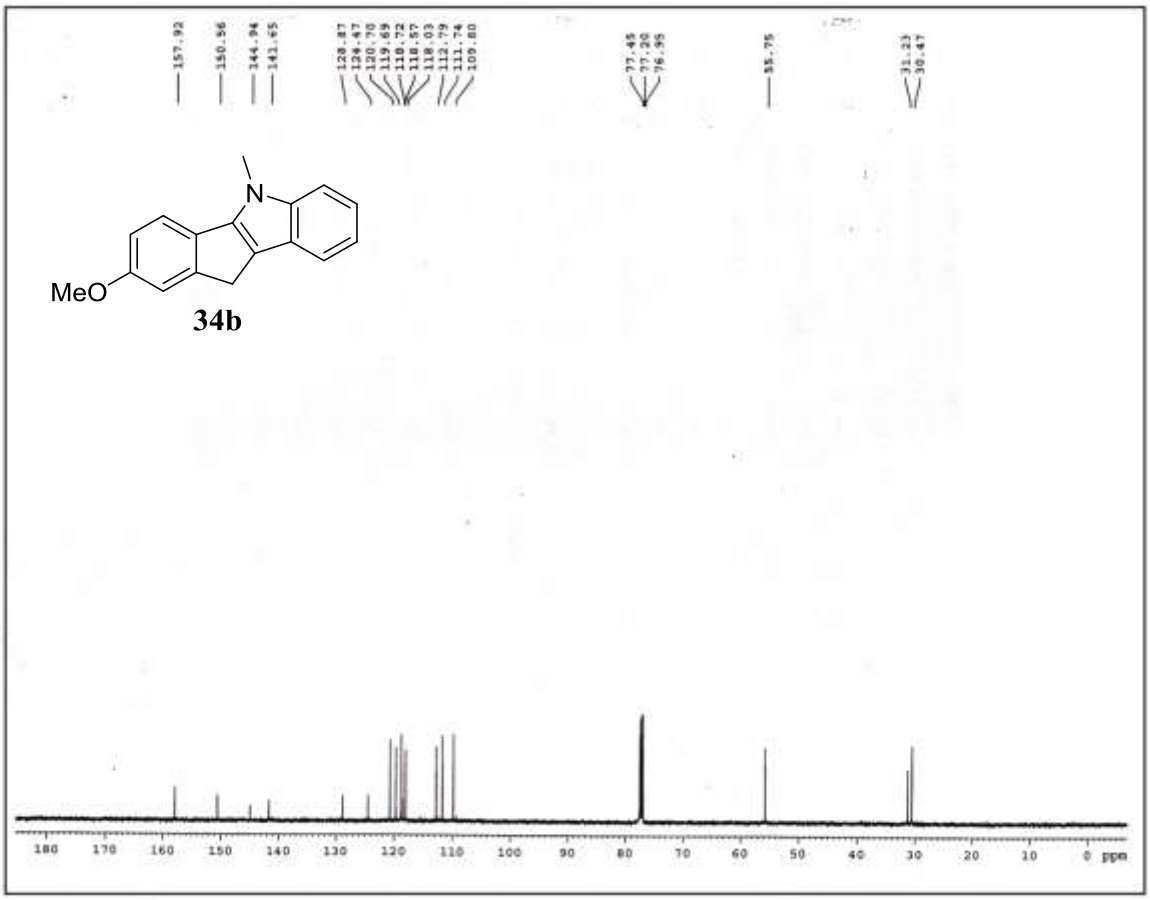
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


MeO
34b
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.09
0.26
3.06
0.91
3.01
3.06
1.95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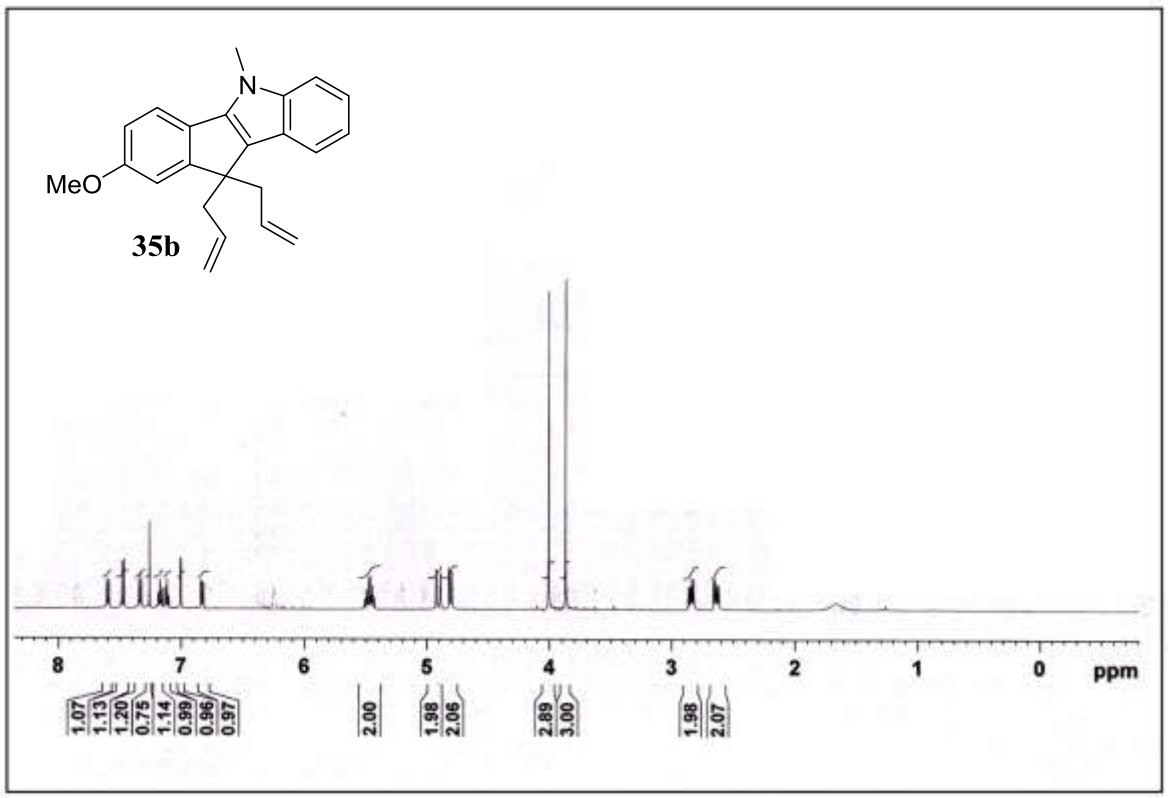
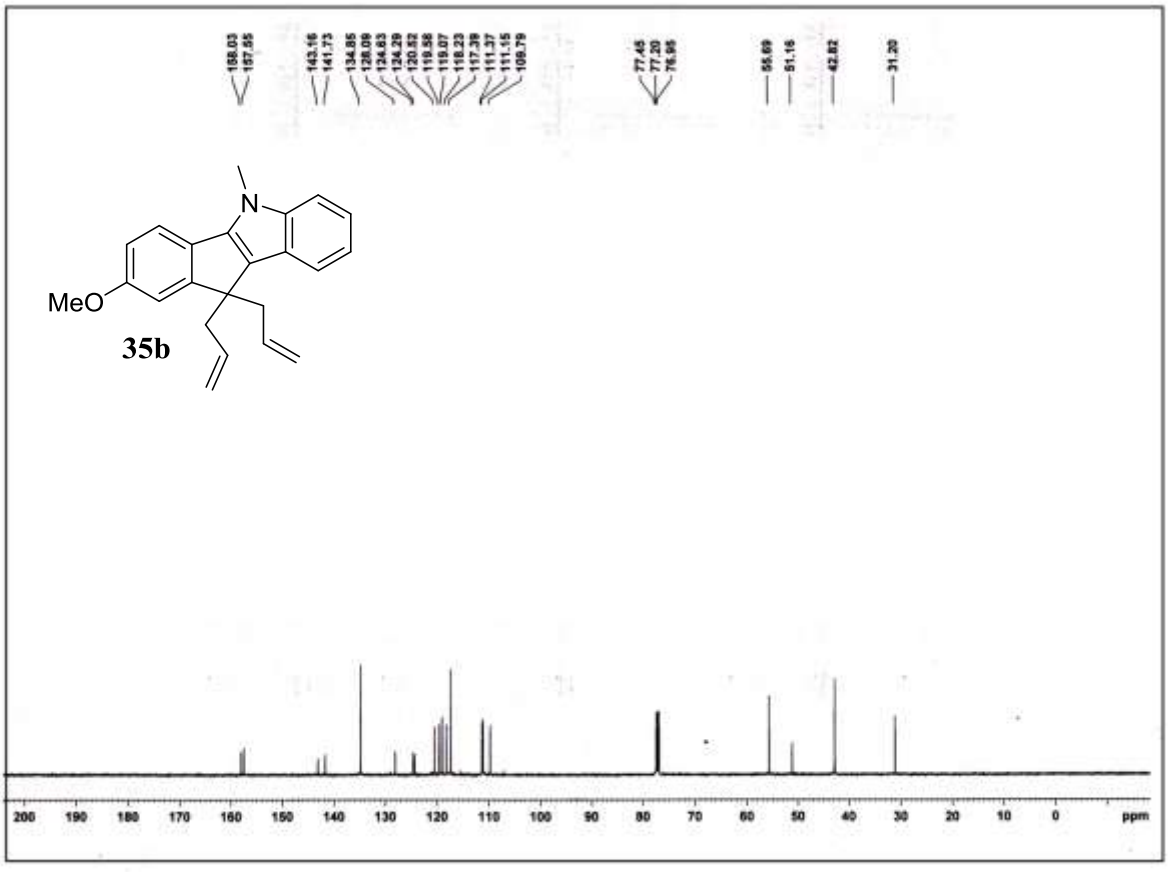
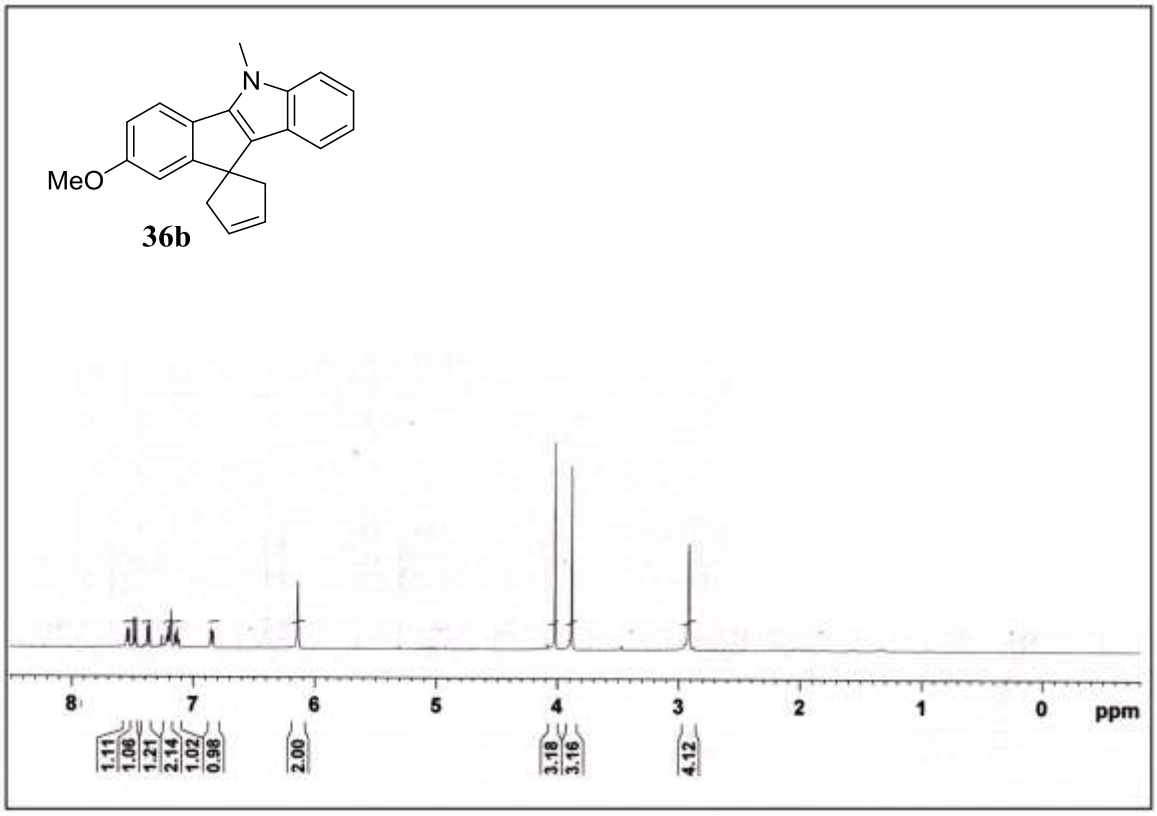
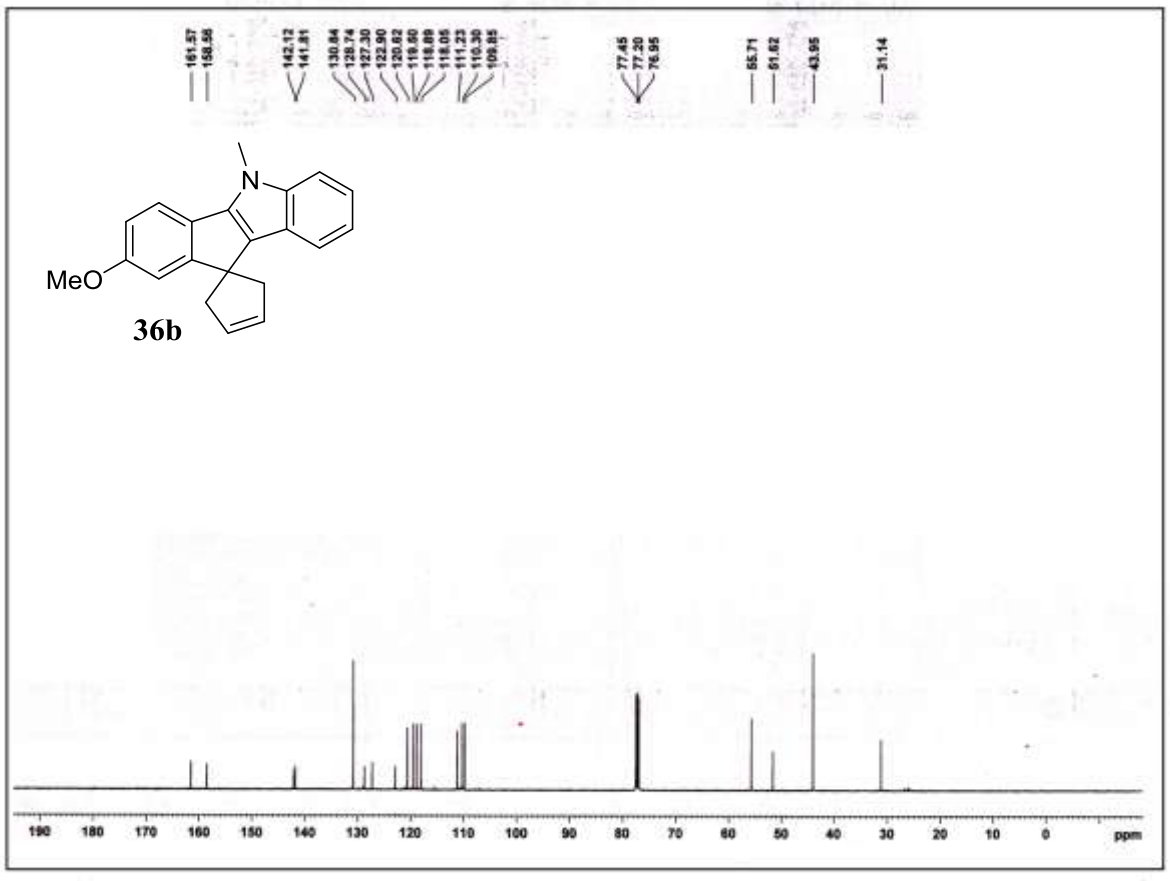
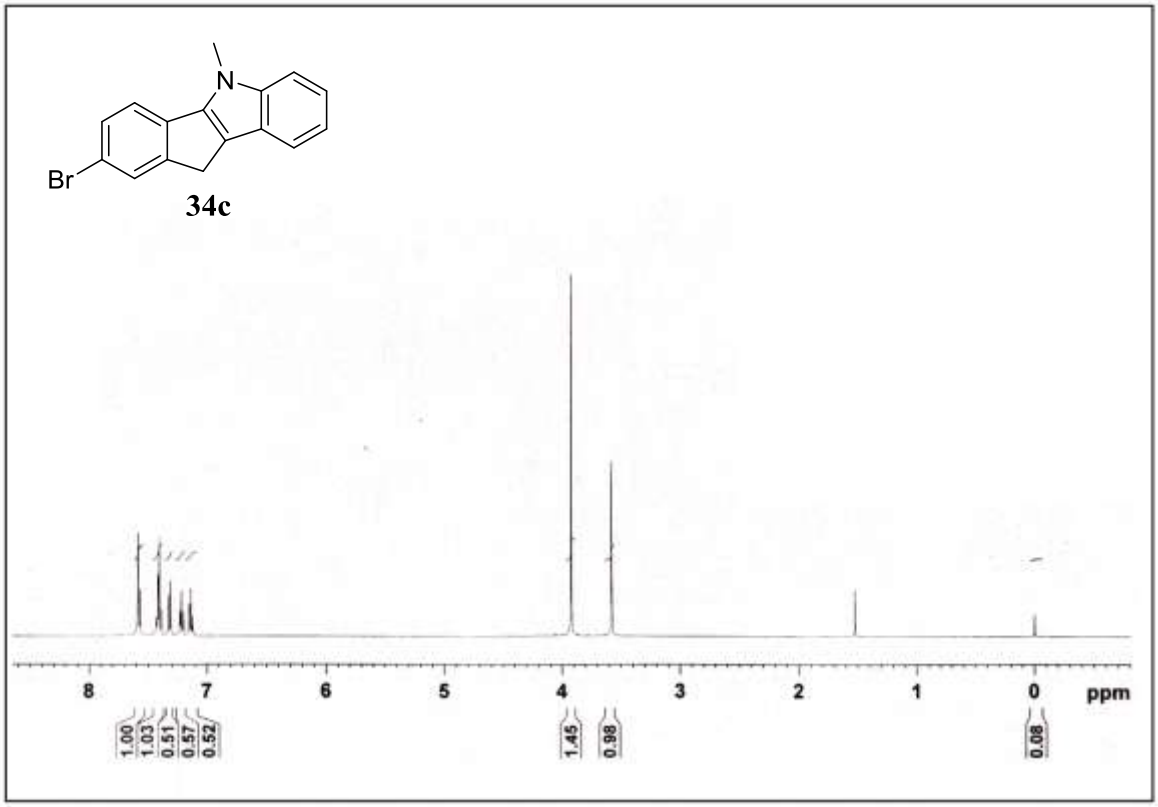
144.94
143.65
128.87
124.47
120.70
119.69
118.72
118.57
118.03
112.79
111.74
109.80
77.45
77.20
76.95
55.75
31.23
30.47
MeO
34b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

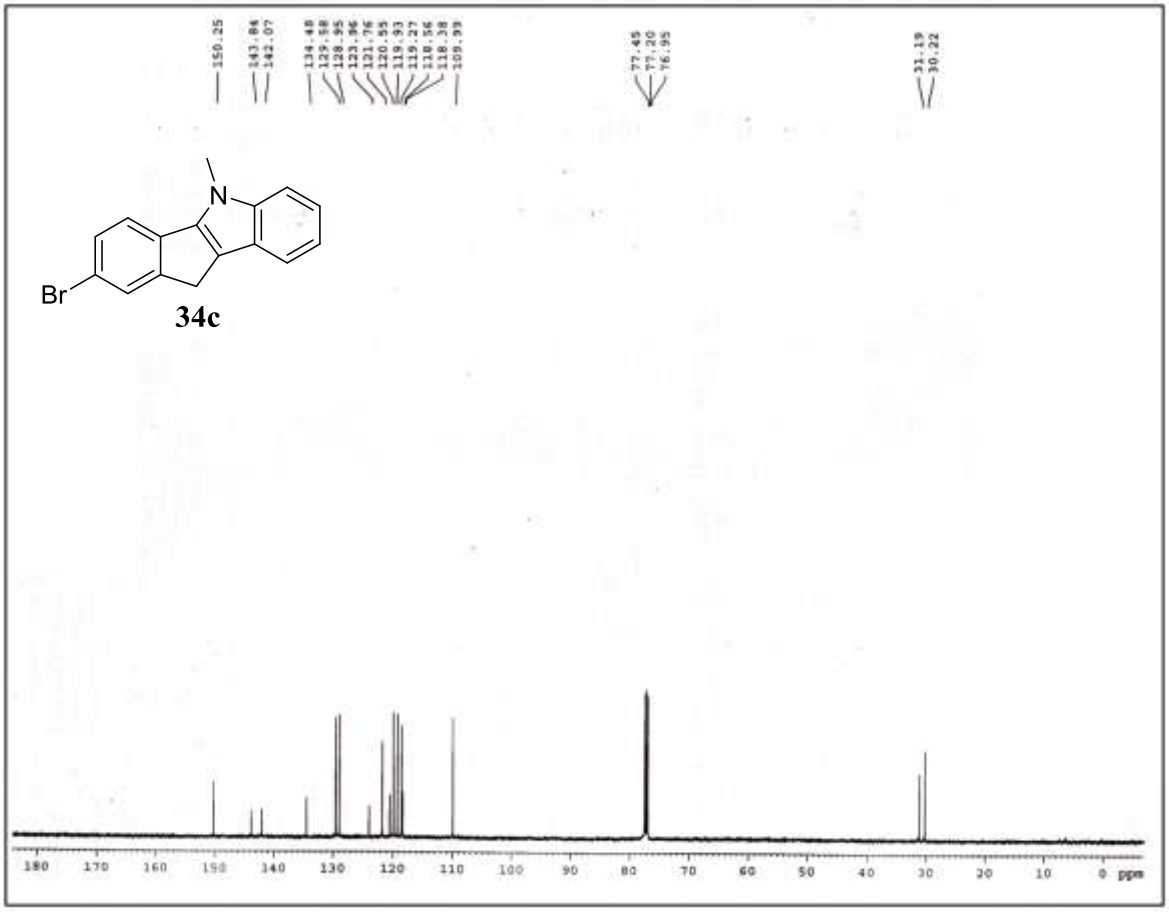

MeO
35b
8
7
6
5
4
3
2
1
0
ppm
1.07
1.13
1.20
0.75
1.14
0.99
0.96
0.97
2.00
1.98
2.06
2.89
3.00
1.98
2.07

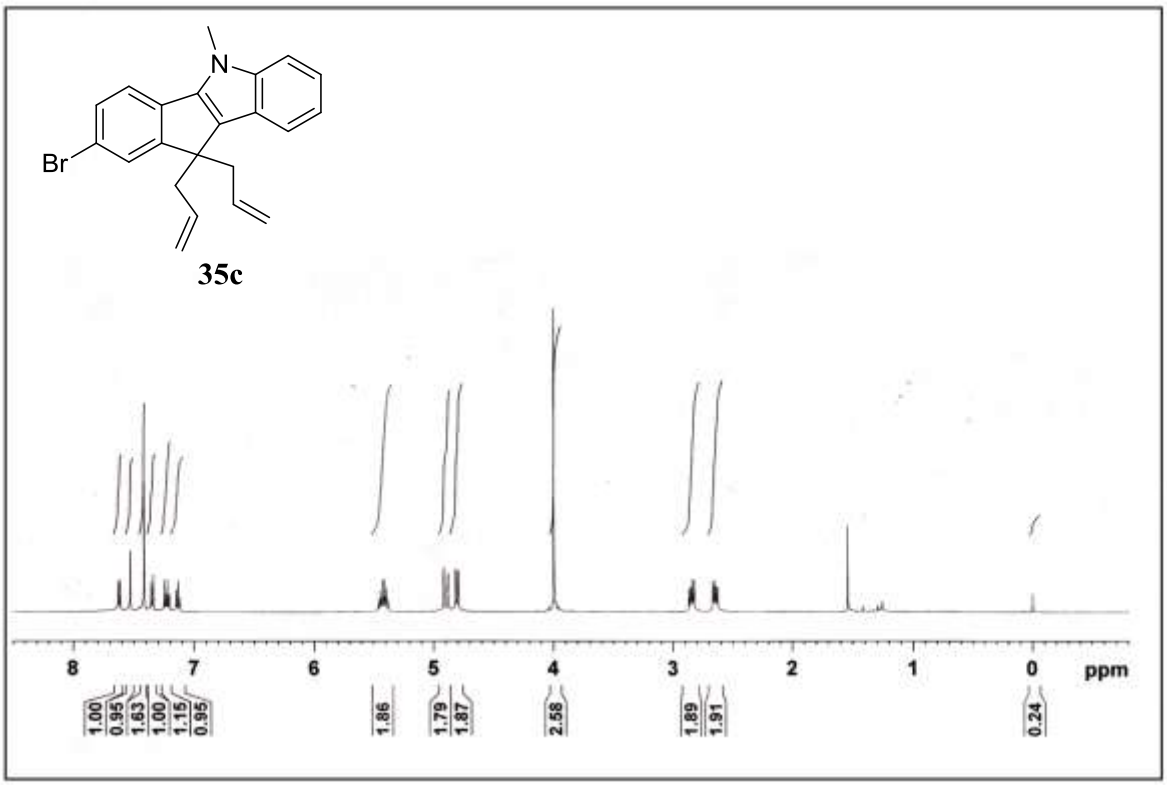

MeO
35b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

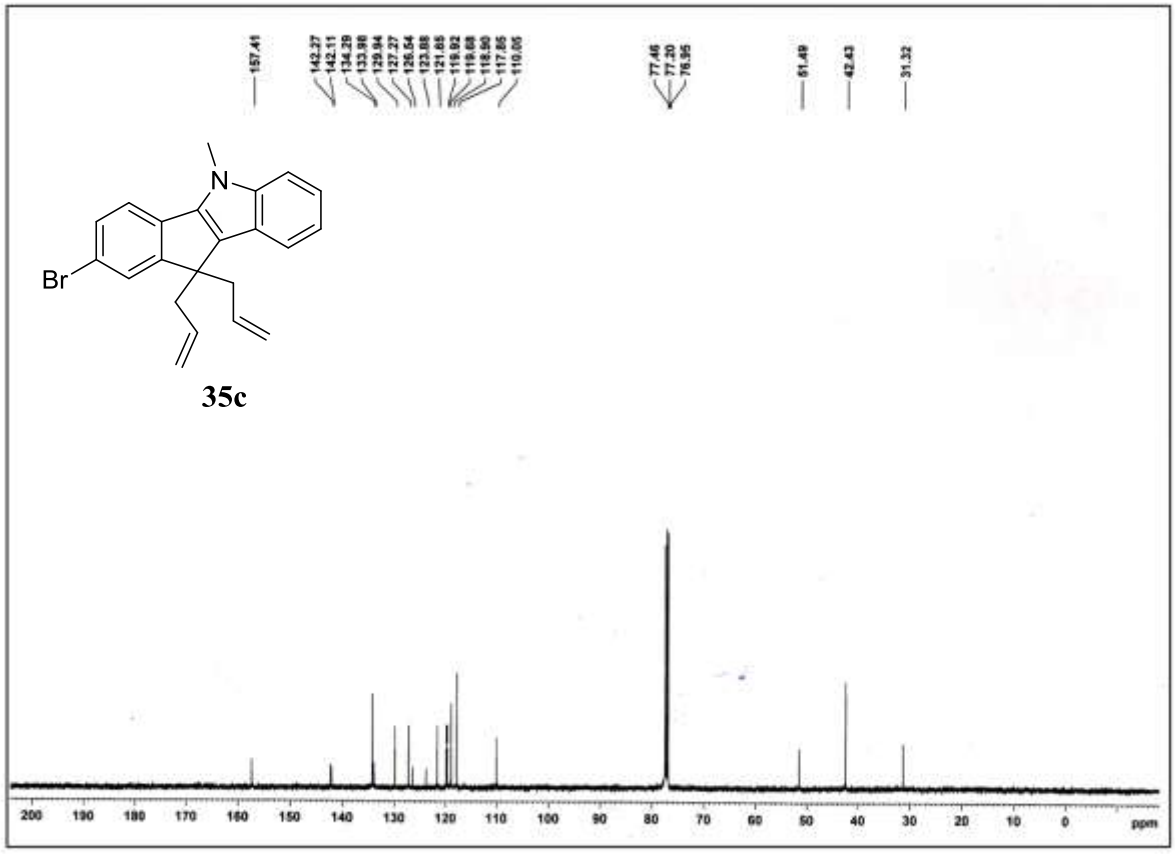

N
MeO
36b
8
7
6
5
4
3
2
1
0
ppm
1.11
1.06
1.21
2.14
1.02
0.98
2.00
3.18
3.16
4.12

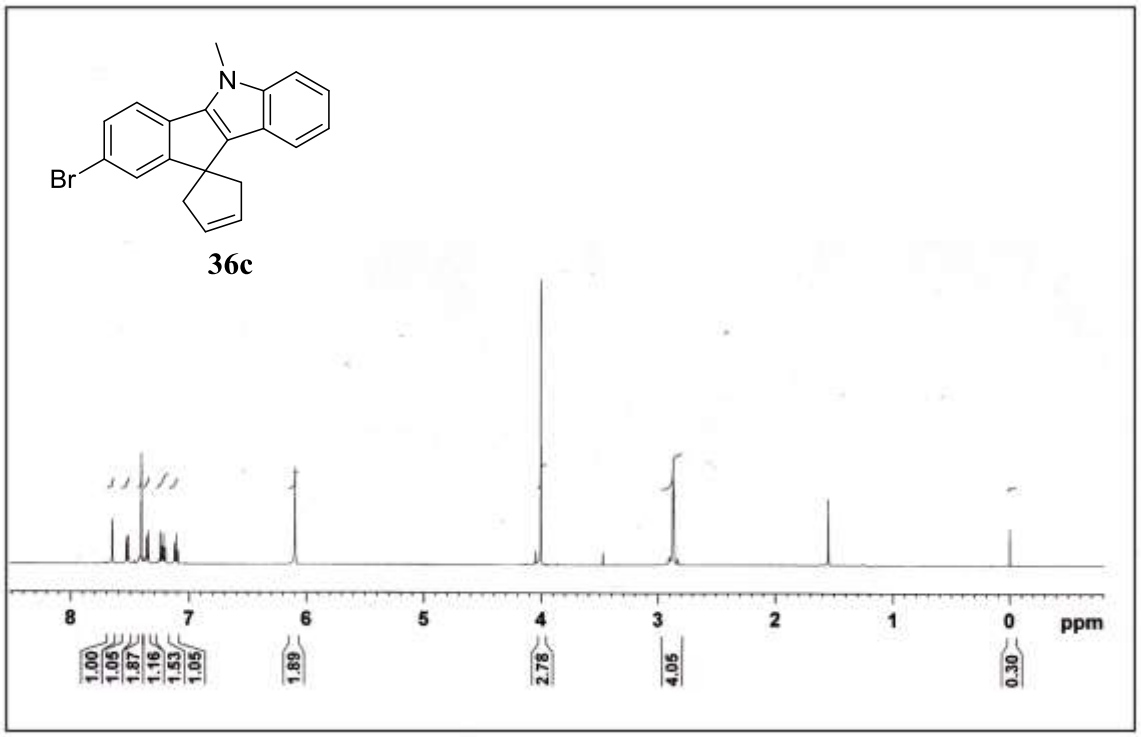

161.57
158.56
142.12
141.81
130.84
128.74
127.30
122.90
120.62
119.60
118.89
118.06
111.23
110.30
109.85
77.45
77.20
76.95
55.71
51.62
43.95
31.14
N
MeO
36b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

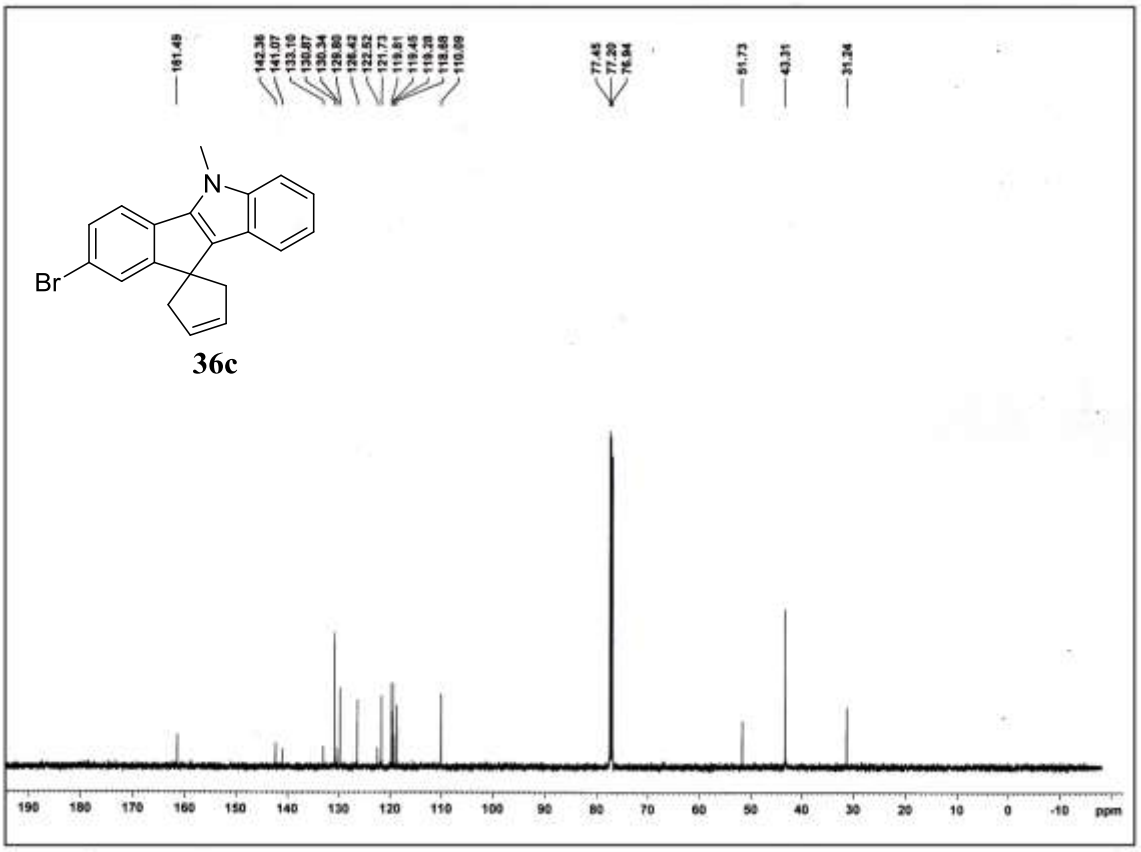

N
Br
34c
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
0.51
0.57
0.52
1.45
0.98
0.08


150.25
143.84
142.07
134.48
129.58
128.95
123.96
121.76
120.55
119.93
119.27
110.56
110.38
109.99
77.45
77.20
76.95
31.19
30.22
N
Br
34c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


N
Br
35c
8
7
6
5
4
3
2
1
0
ppm
1.00
0.95
1.63
1.00
1.15
0.95
1.86
1.79
1.87
2.58
1.89
1.91
0.24


157.41
142.27
142.11
134.29
133.98
129.94
127.27
126.64
123.88
121.65
119.92
119.68
118.50
117.85
110.06
77.46
77.20
76.95
51.49
42.43
31.32
N
Br
35c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


N
Br
36c
8
7
6
5
4
3
2
1
0
ppm
1.00
1.05
1.87
1.16
1.53
1.05
1.89
2.78
4.05
0.30


161.49
142.36
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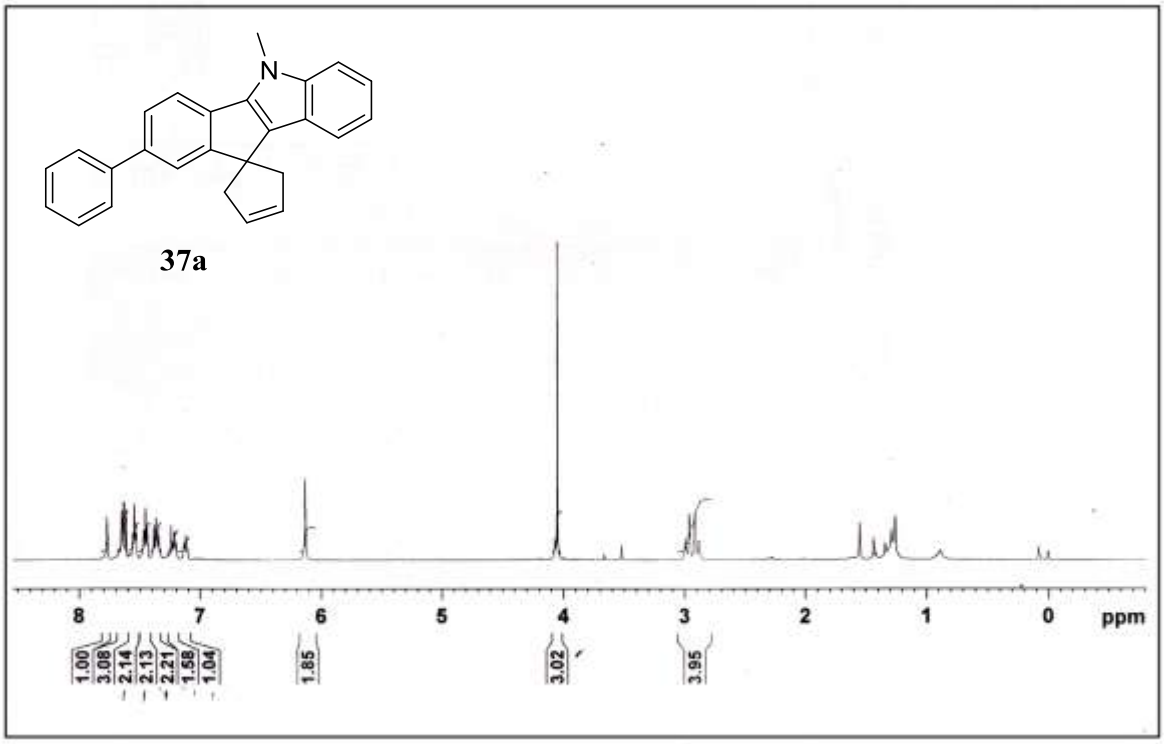
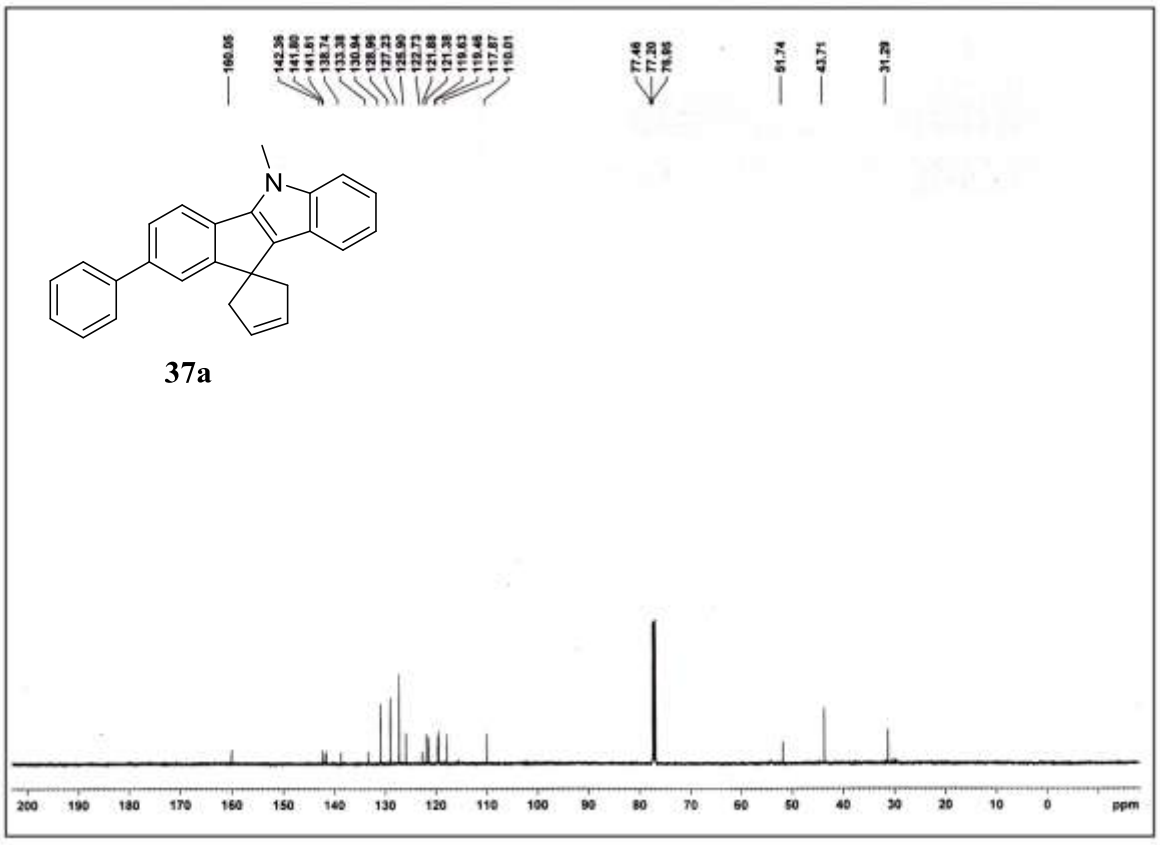
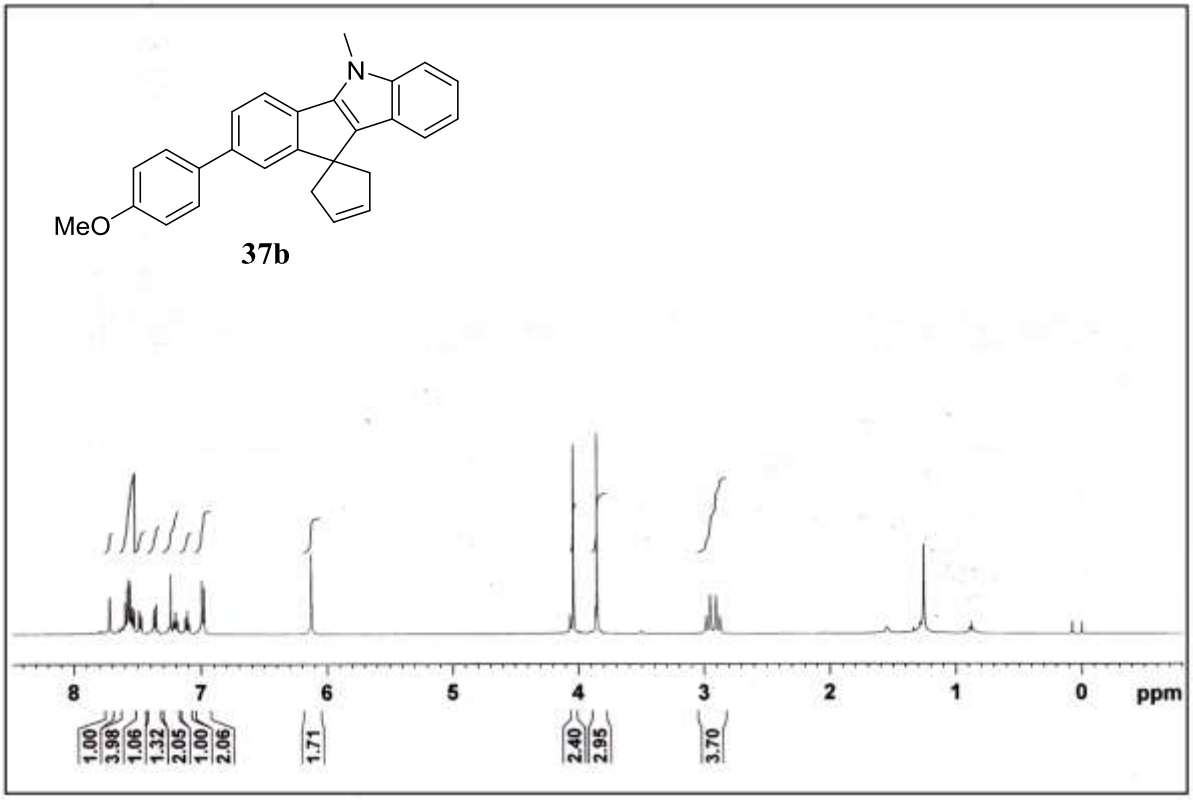
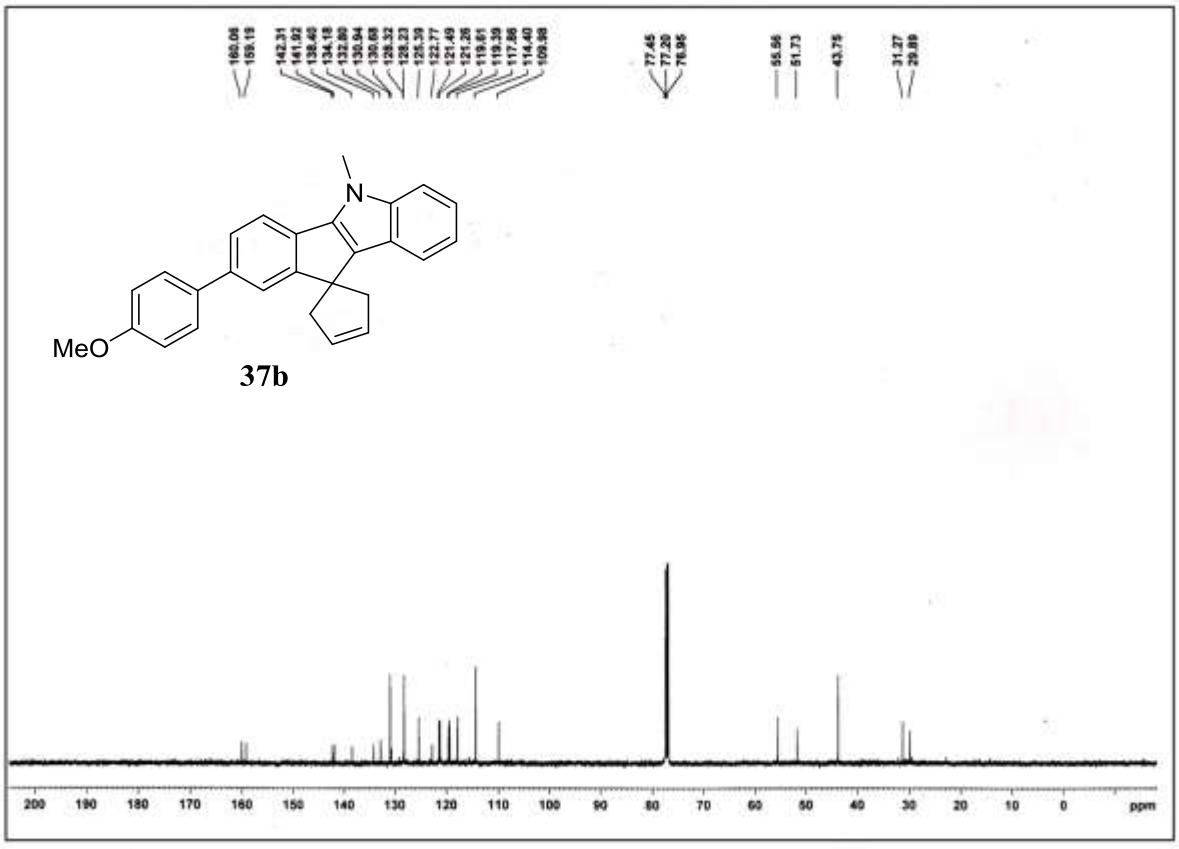
133.10
130.87
130.34
129.80
128.42
122.52
121.73
119.81
119.45
119.20
118.88
110.89
77.45
77.20
76.84
51.73
43.31
31.24
N
Br
36c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


37a
8
7
6
5
4
3
2
1
0
ppm
1.00
3.08
2.14
2.13
2.21
1.58
1.04
1.85
3.02
3.95

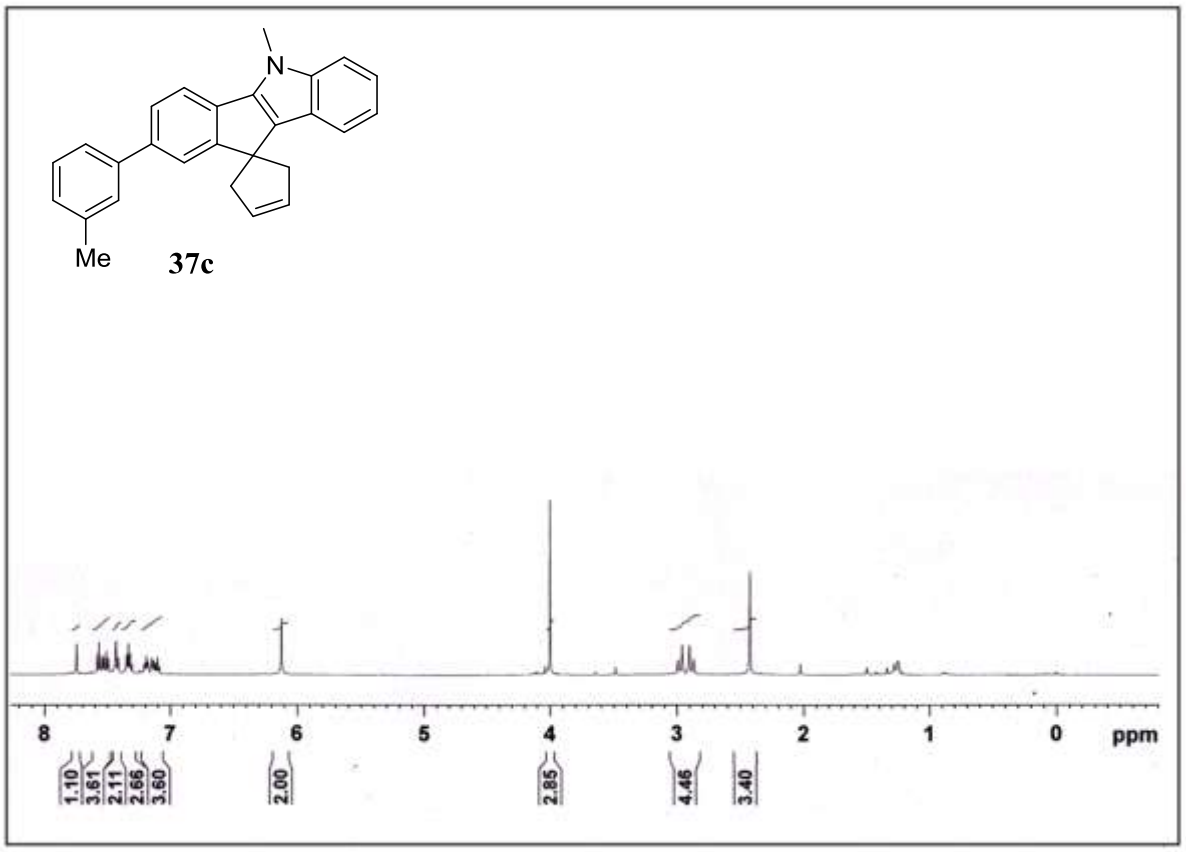

160.06
142.56
141.80
141.61
138.74
133.38
130.94
128.96
127.23
125.99
122.73
121.88
121.38
119.63
119.46
117.87
110.01
77.46
77.20
76.86
51.74
43.71
31.29
37a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

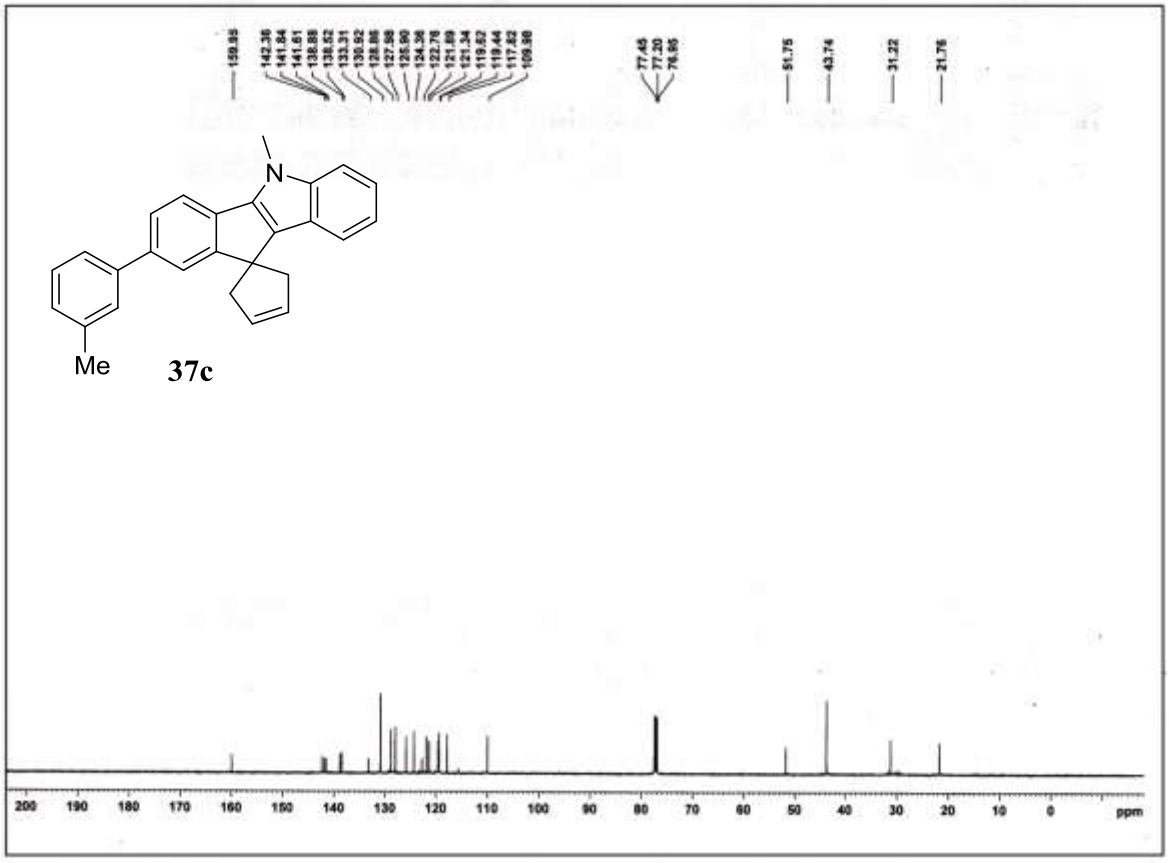

N
MeO
8
7
6
5
4
3
2
1
0
ppm
1.00
3.98
1.06
1.32
2.05
1.00
2.06
1.71
2.40
2.95
3.70

37b


160.06
155.18
142.31
141.02
138.40
134.18
132.80
130.94
130.68
128.32
128.23
125.59
122.77
121.49
121.26
119.61
119.39
117.88
114.40
109.98
77.45
77.20
76.95
55.56
51.73
43.75
31.27
29.89
N
MeO
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

37b


N
Me
37c
8
7
6
5
4
3
2
1
0
ppm
1.10
3.61
2.11
2.66
3.60
2.00
2.85
4.46
3.40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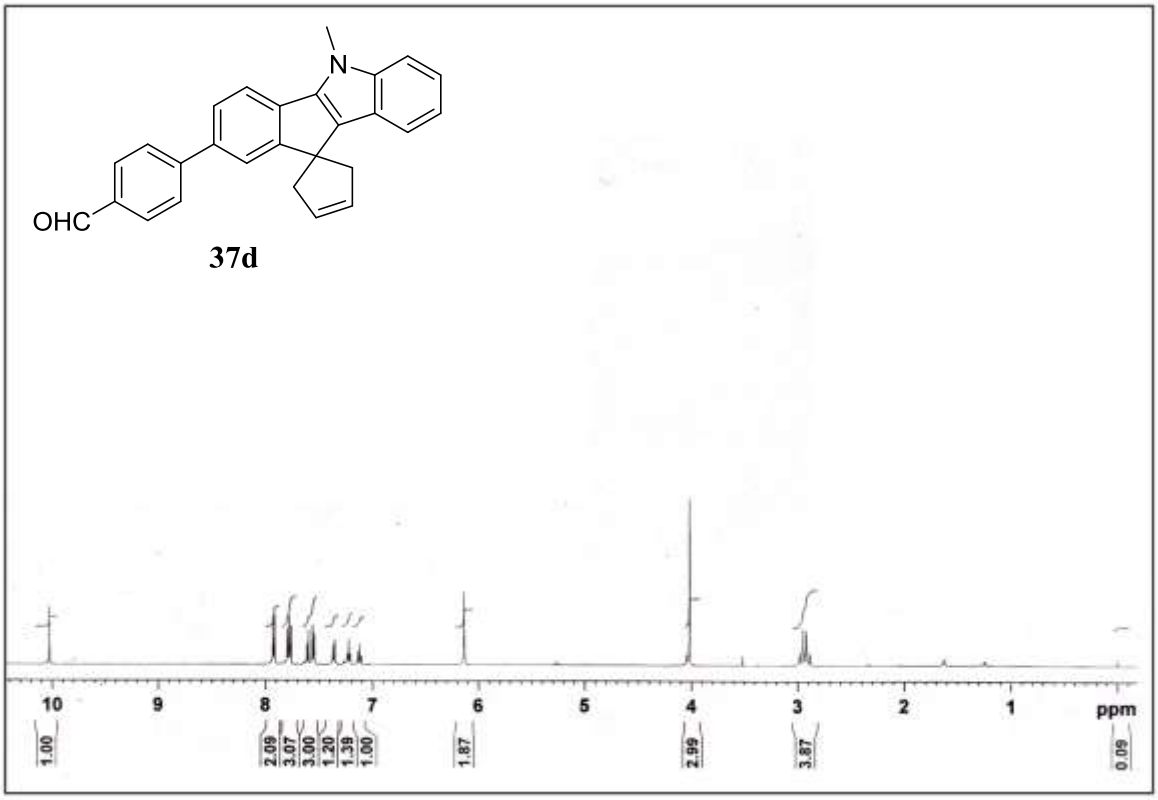
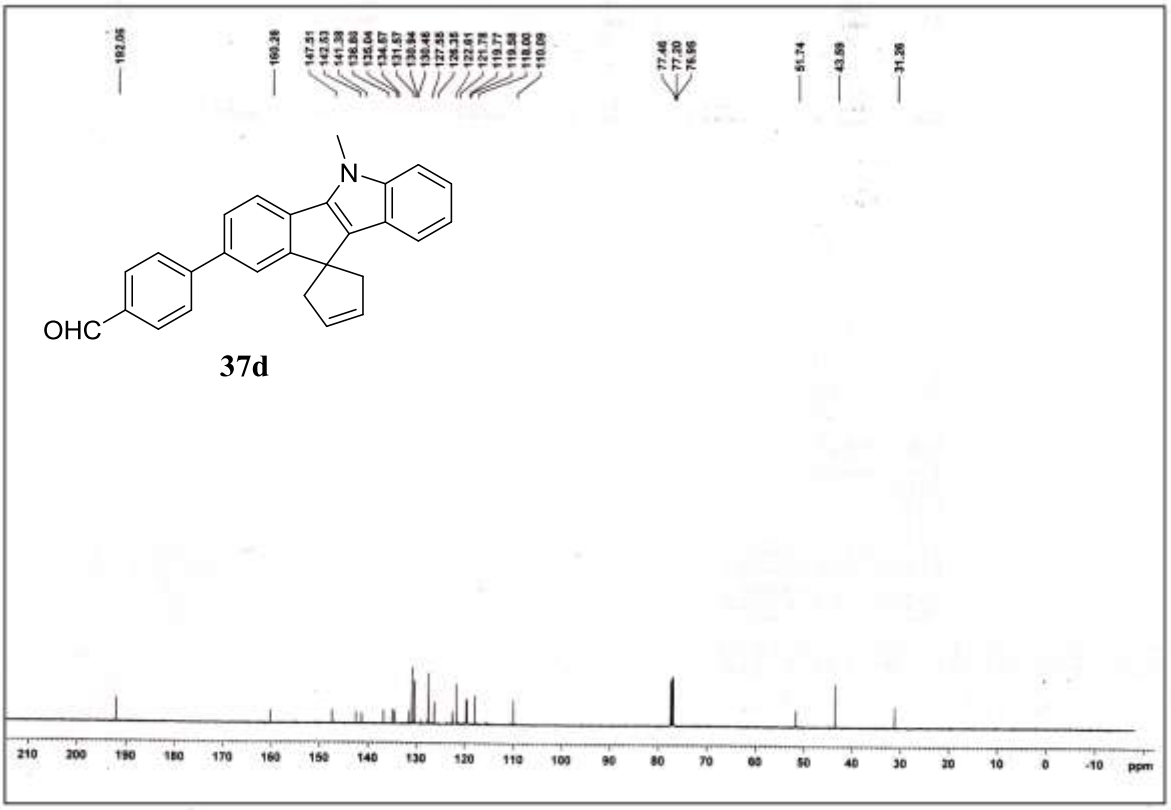
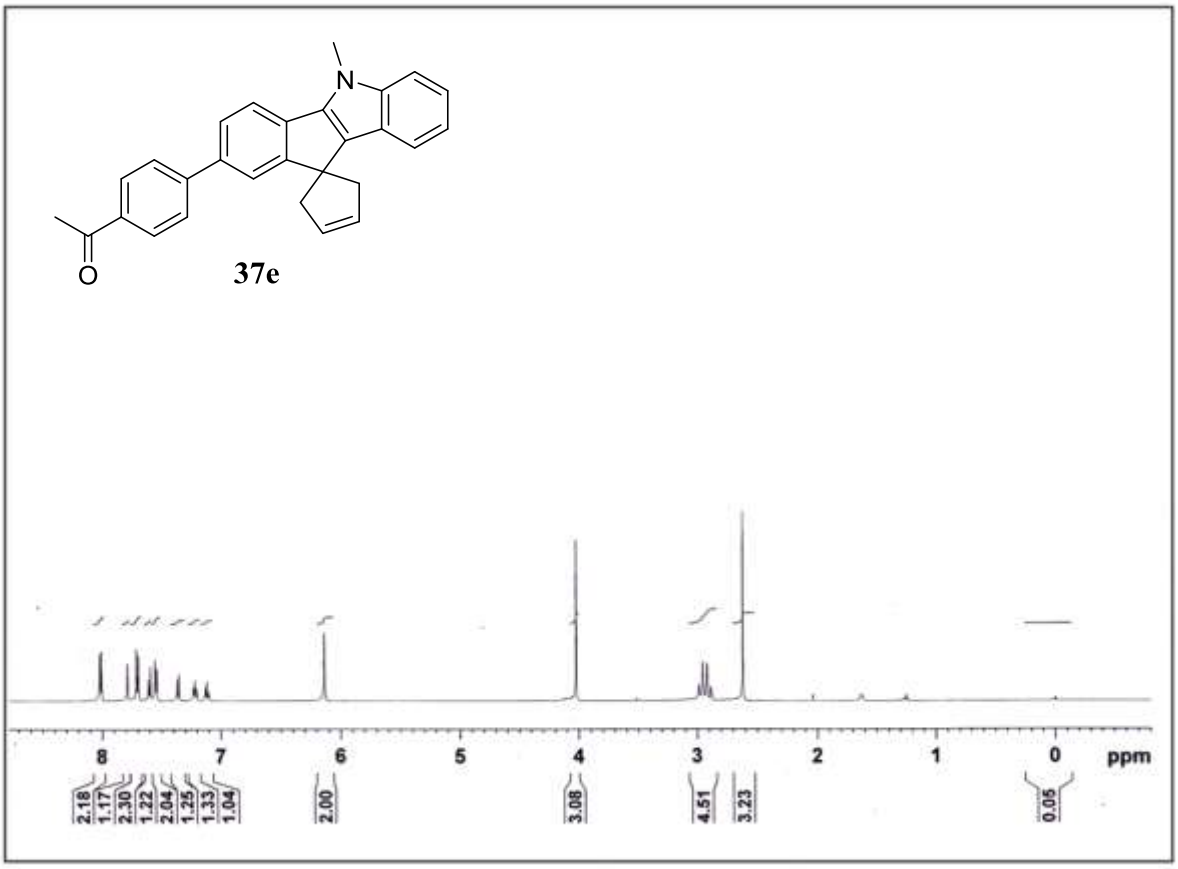
138.88
138.52
133.31
130.62
128.88
127.58
126.90
124.36
122.76
121.89
121.34
119.62
119.44
117.82
109.98
77.45
77.20
76.86
51.75
43.74
31.22
21.76
N
Me
37c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

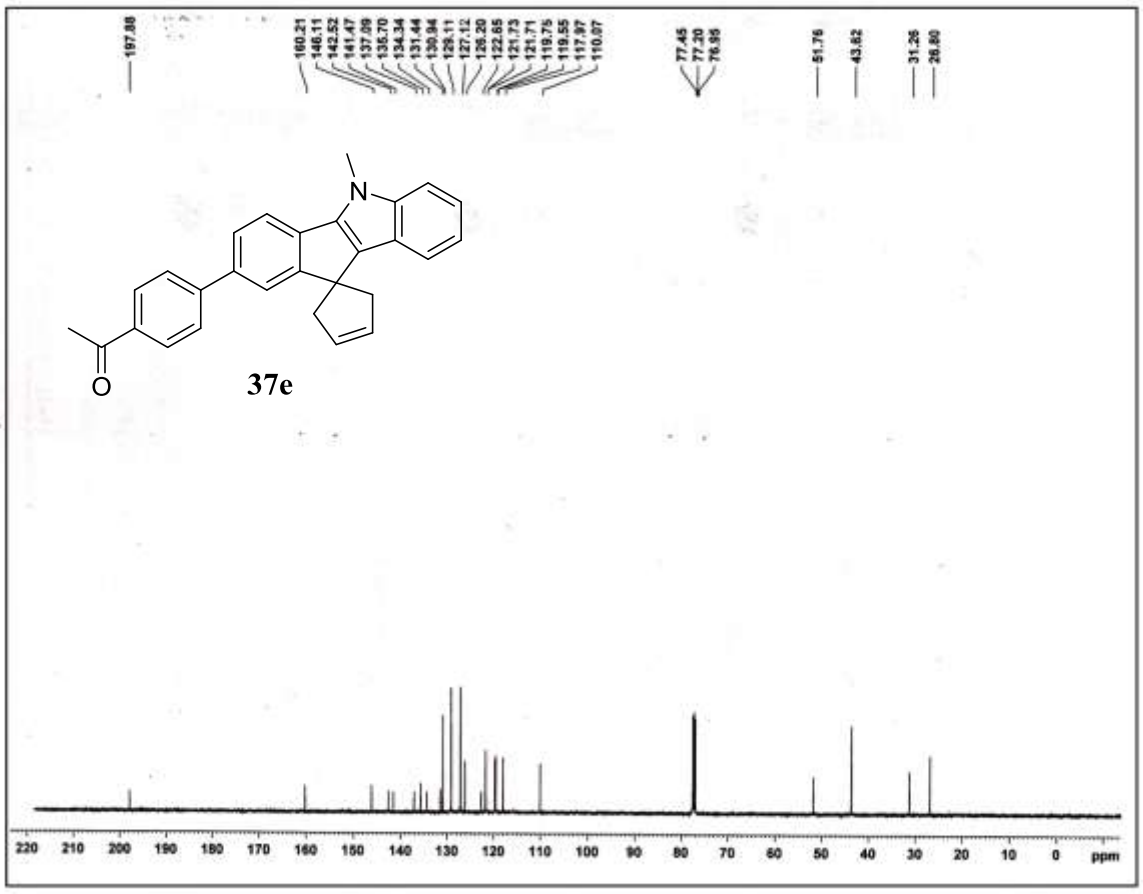

N
OHC
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.09
3.07
3.00
1.20
1.39
1.00
1.87
2.99
3.87
0.09

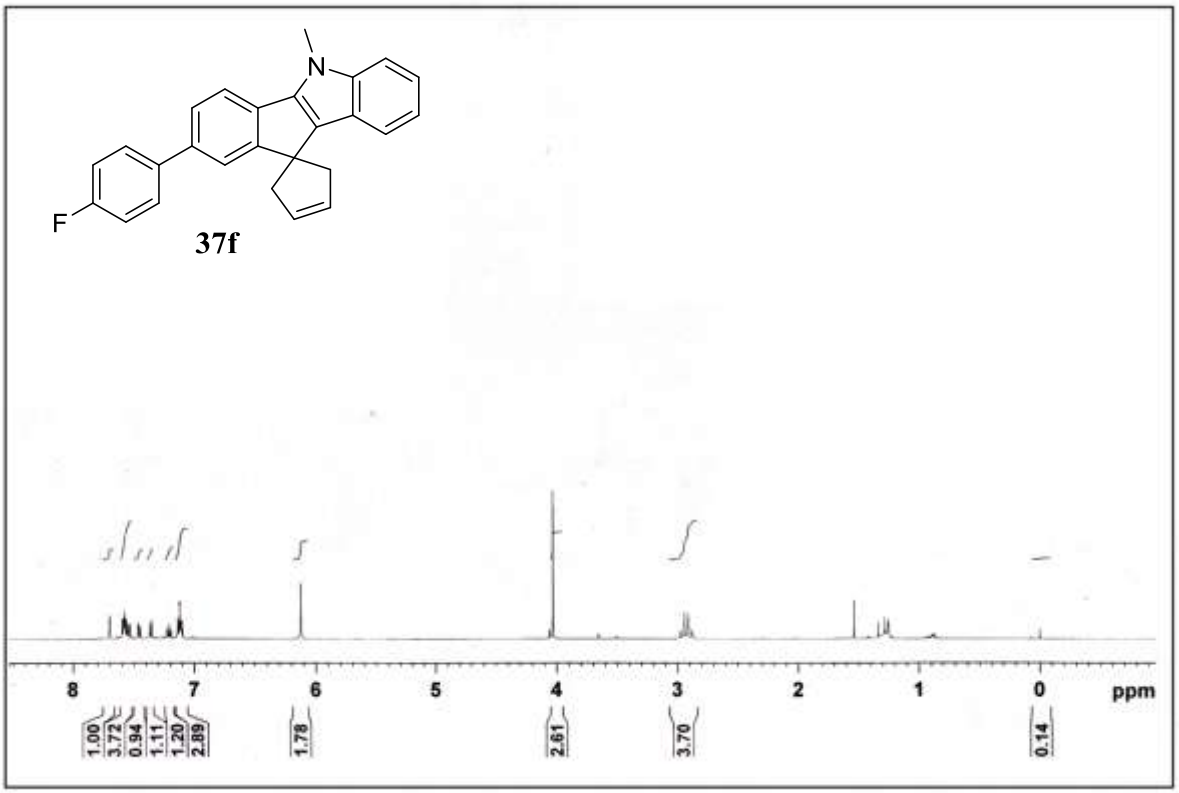
37d

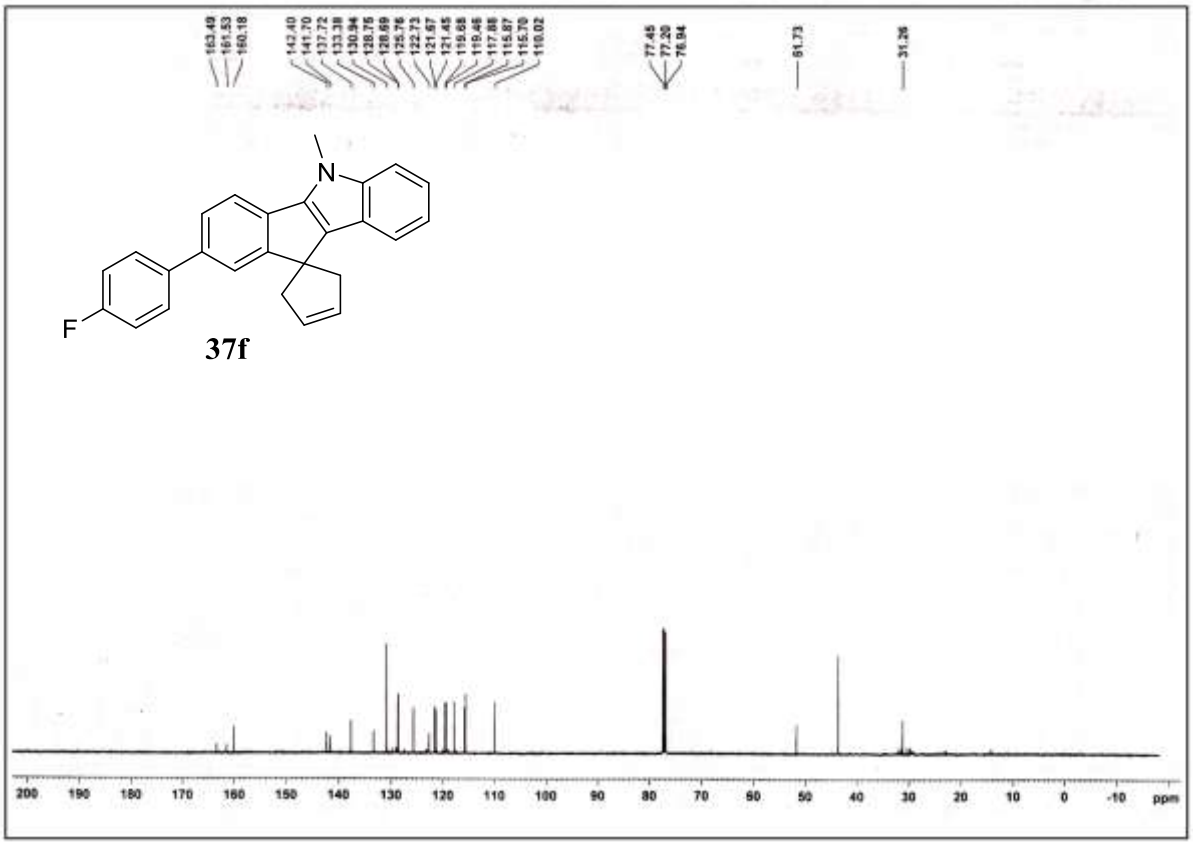

192.05
160.26
147.51
142.53
141.39
136.86
135.04
134.67
131.67
130.94
130.46
127.58
126.35
122.61
121.78
119.77
119.58
118.00
110.09
77.46
77.20
76.95
51.74
43.89
31.26
N
OHC
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

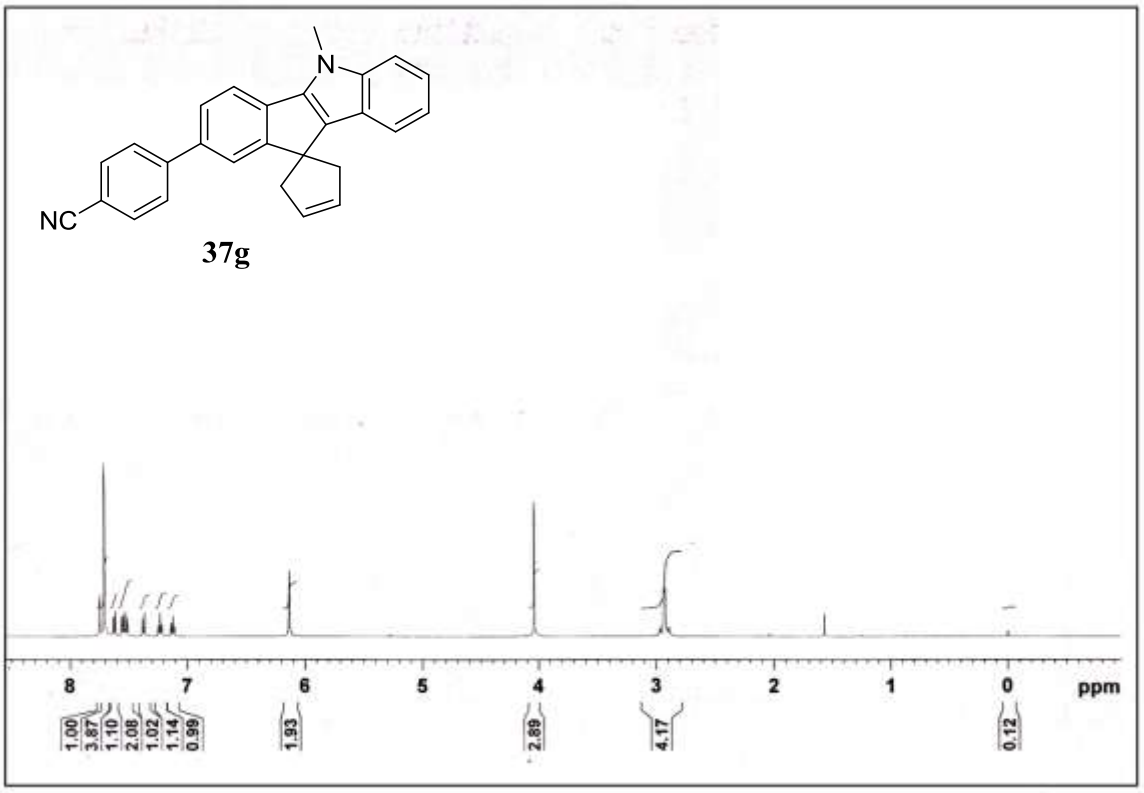
37d

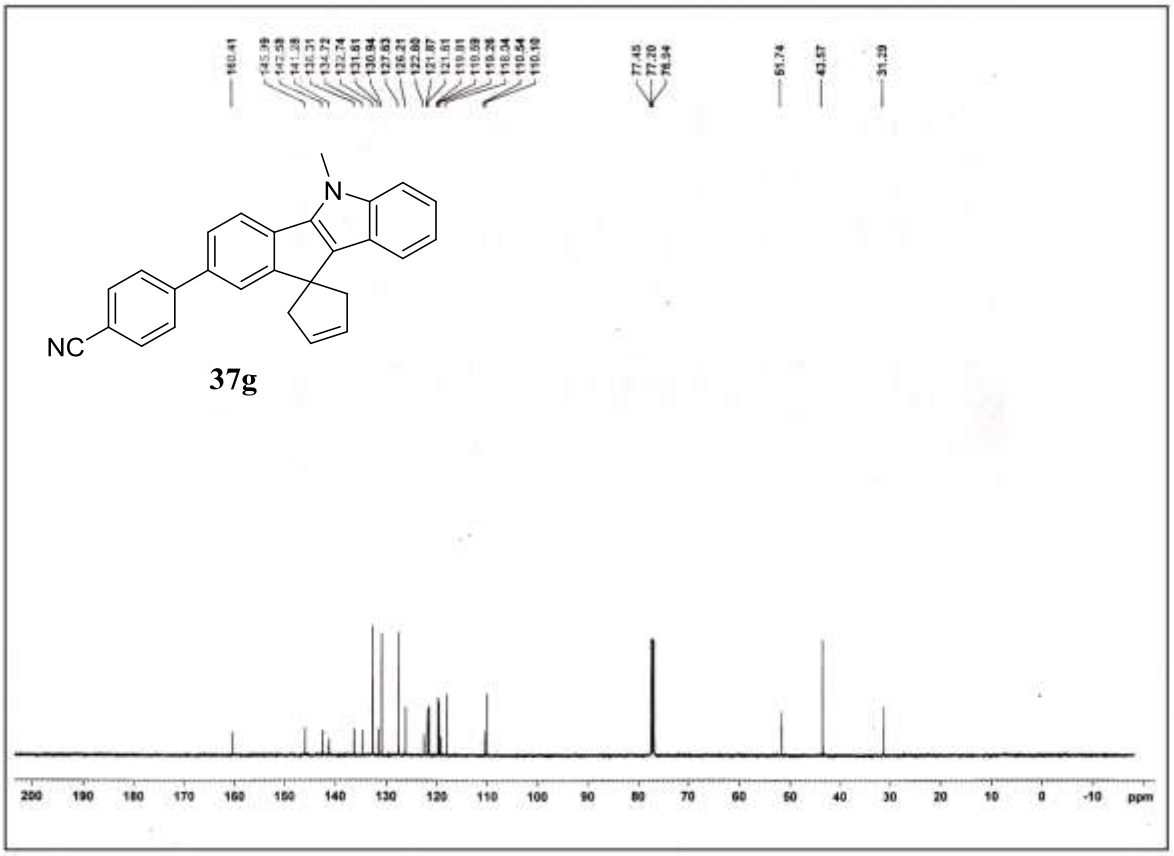

N
O
37e
8
7
6
5
4
3
2
1
0
ppm
2.18
1.17
2.30
1.22
2.04
1.25
1.33
1.04
2.00
3.08
4.51
3.23
0.05

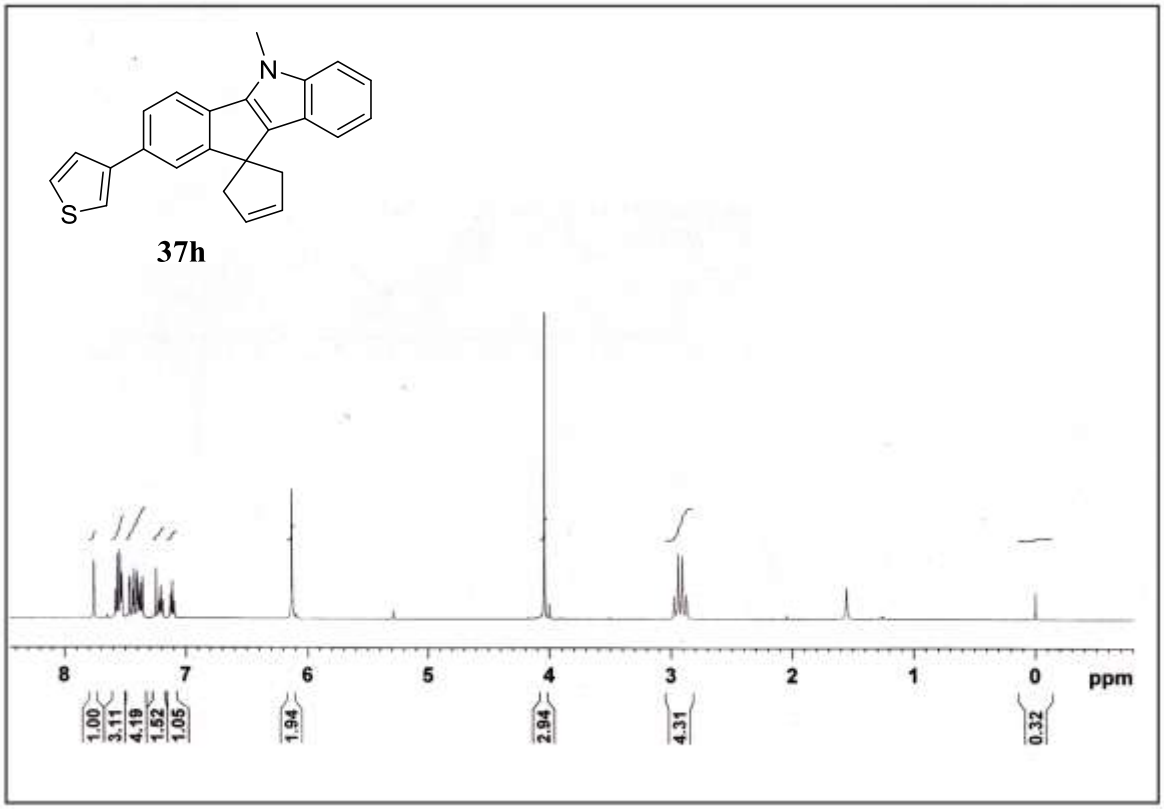

197.88
160.21
146.11
142.52
141.47
137.69
135.70
134.34
131.44
130.94
128.11
127.12
126.20
122.65
121.73
121.71
119.75
119.55
117.97
110.07
77.45
77.20
76.95
51.76
43.62
31.26
26.80
N
O
37e
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

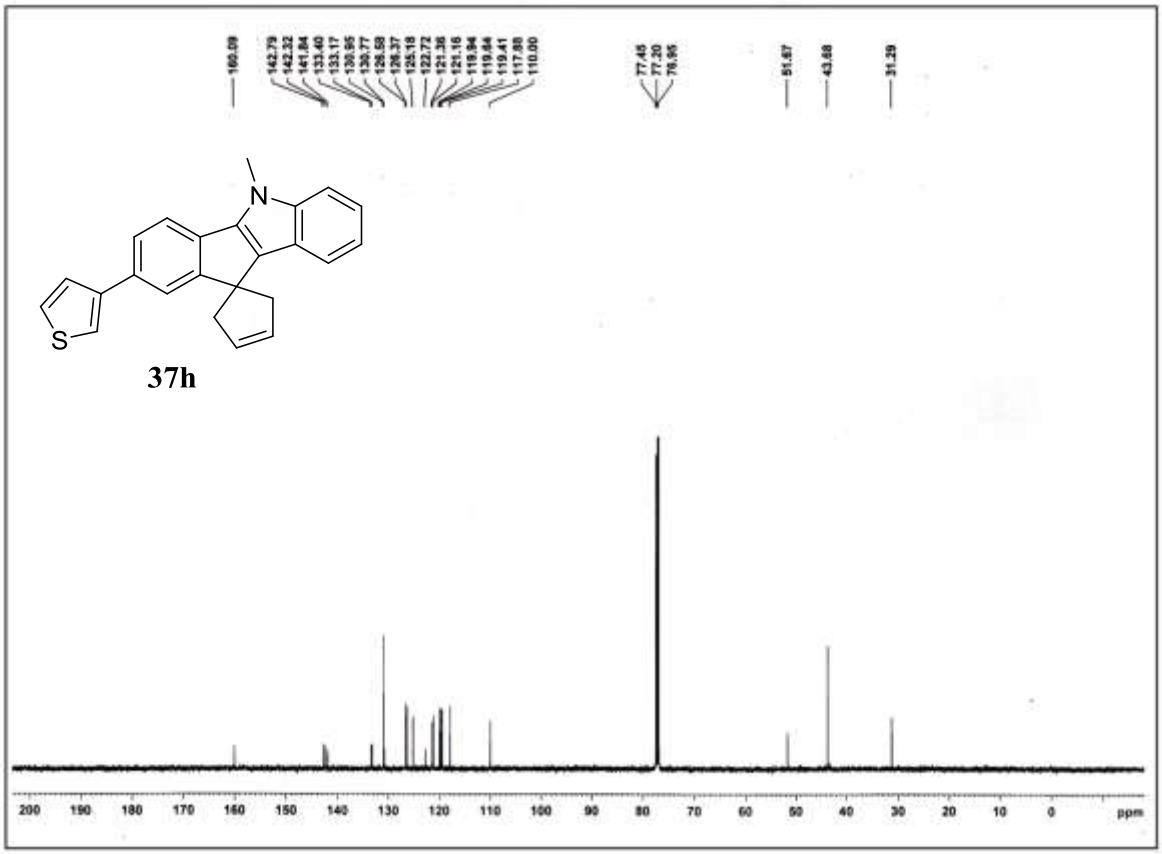

N
F
37f
8
7
6
5
4
3
2
1
0
ppm
1.00
3.72
0.94
1.11
1.20
2.89
1.78
2.61
3.70
0.14

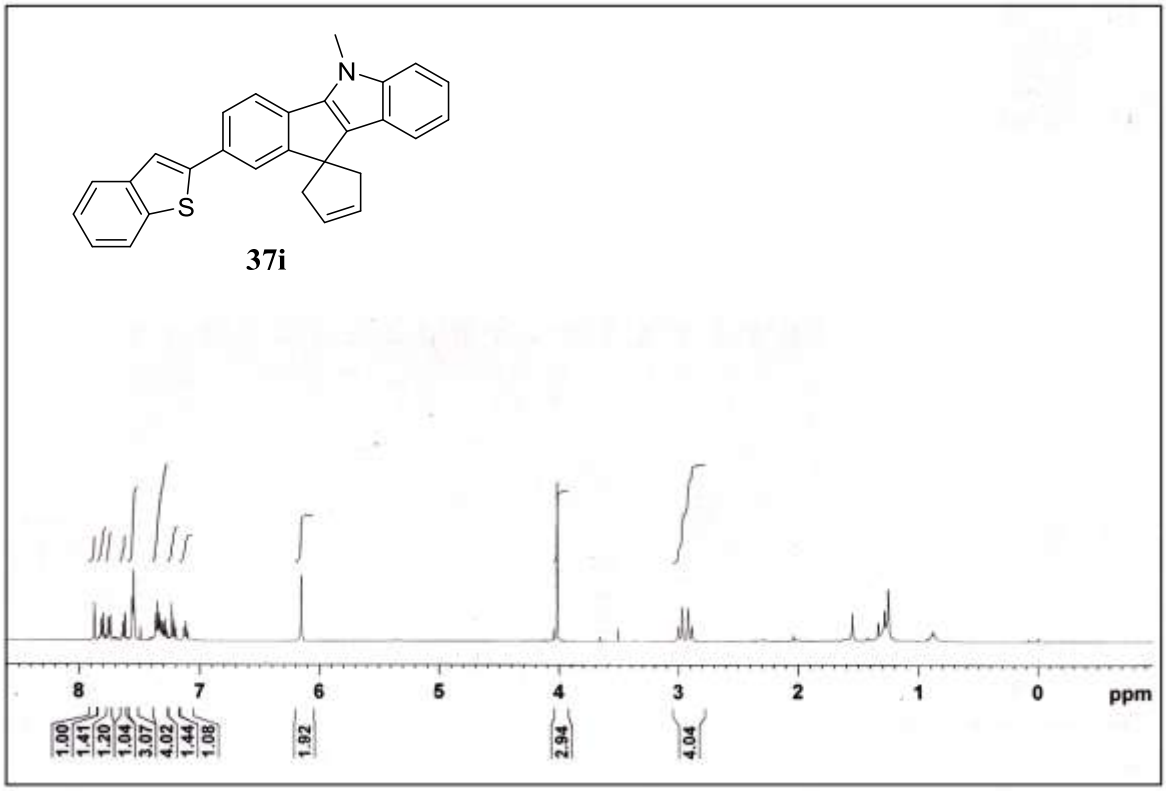

163.49
161.53
160.18
142.40
141.70
137.72
133.38
130.94
128.75
128.69
125.76
122.73
121.67
121.45
119.68
119.46
117.88
115.87
115.70
110.02
77.45
77.20
76.94
51.73
31.26
N
F
37f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

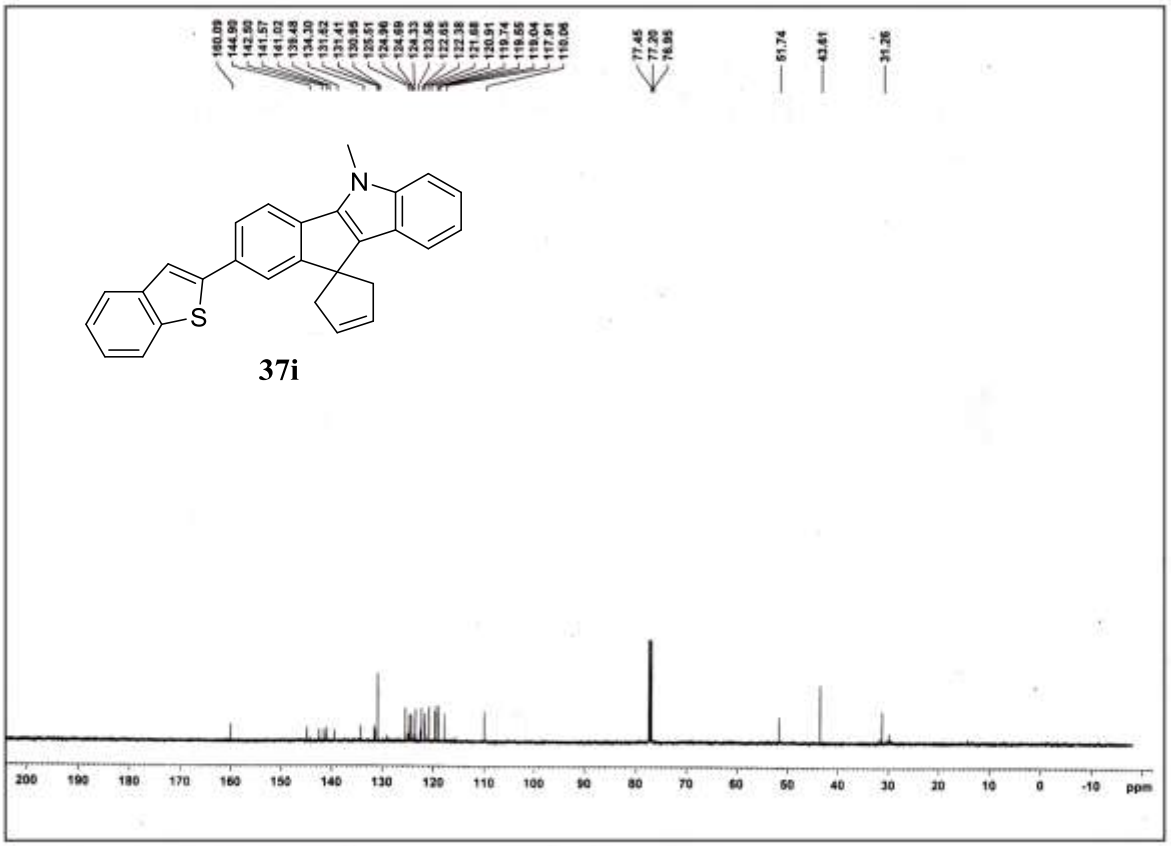

N
NC
37g
8
7
6
5
4
3
2
1
0
ppm
1.00
3.87
1.10
2.08
1.02
1.14
0.99
1.93
2.89
4.17
0.12

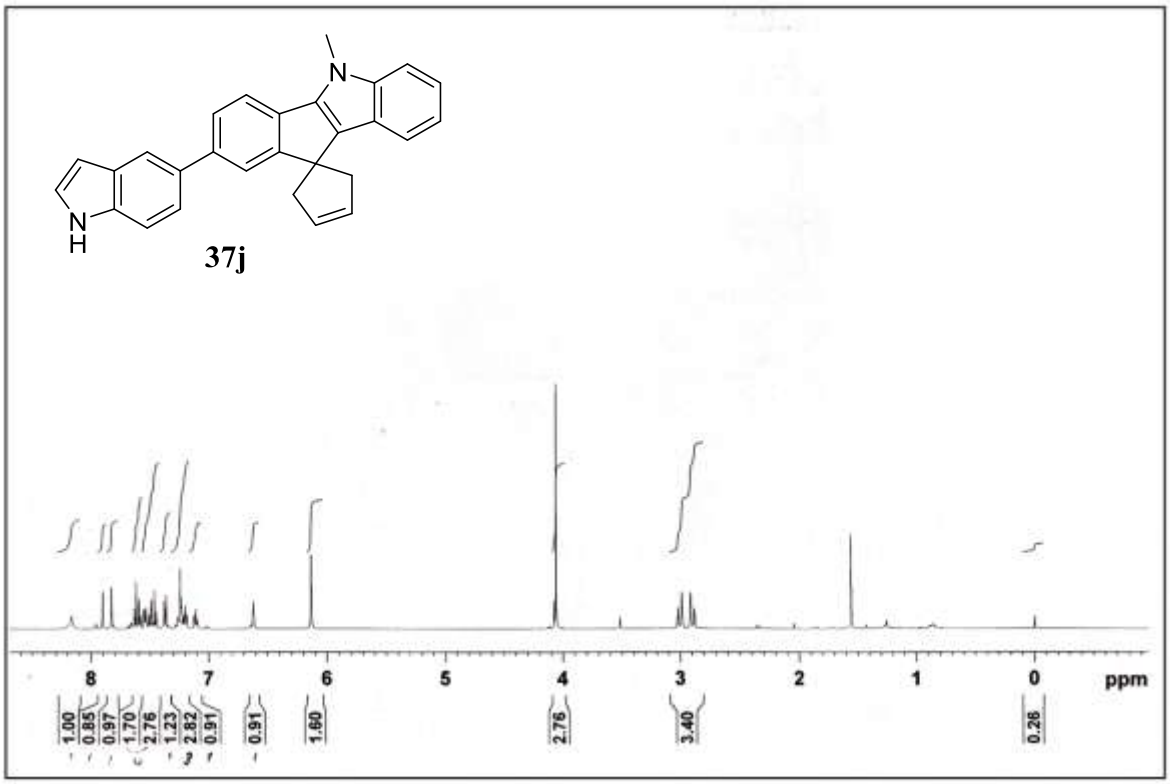

160.41
145.39
142.58
141.28
135.31
134.72
132.74
131.61
130.84
127.63
126.21
122.60
121.87
121.61
119.91
119.59
119.28
118.34
110.54
110.10
77.45
77.20
76.94
51.74
43.57
31.29
N
NC
37g
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

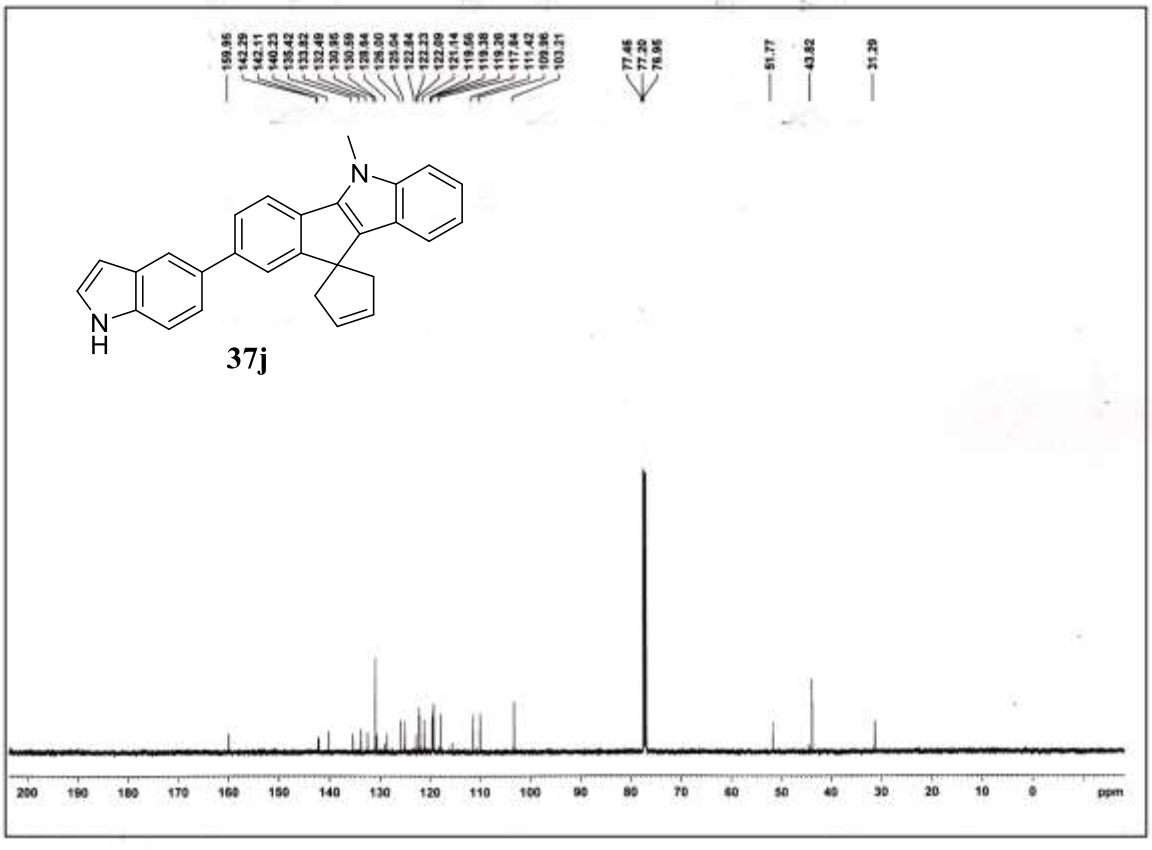

N
S
37h
8
7
6
5
4
3
2
1
0
ppm
1.00
3.11
4.19
1.52
1.05
1.94
2.94
4.31
0.32

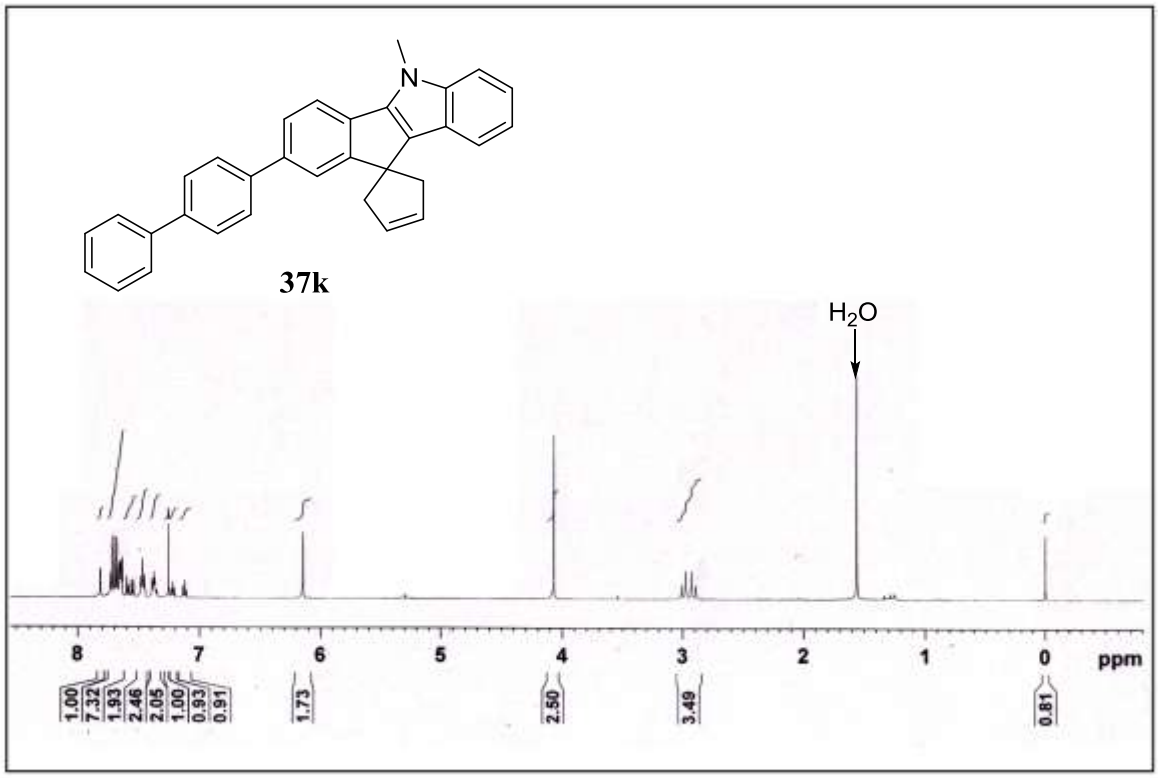

160.09
142.79
142.32
141.84
133.40
133.17
130.95
130.77
128.59
128.37
125.18
122.72
121.36
121.16
119.94
119.84
119.41
117.88
110.00
77.45
77.20
76.95
51.87
43.88
31.29
N
S
37h
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

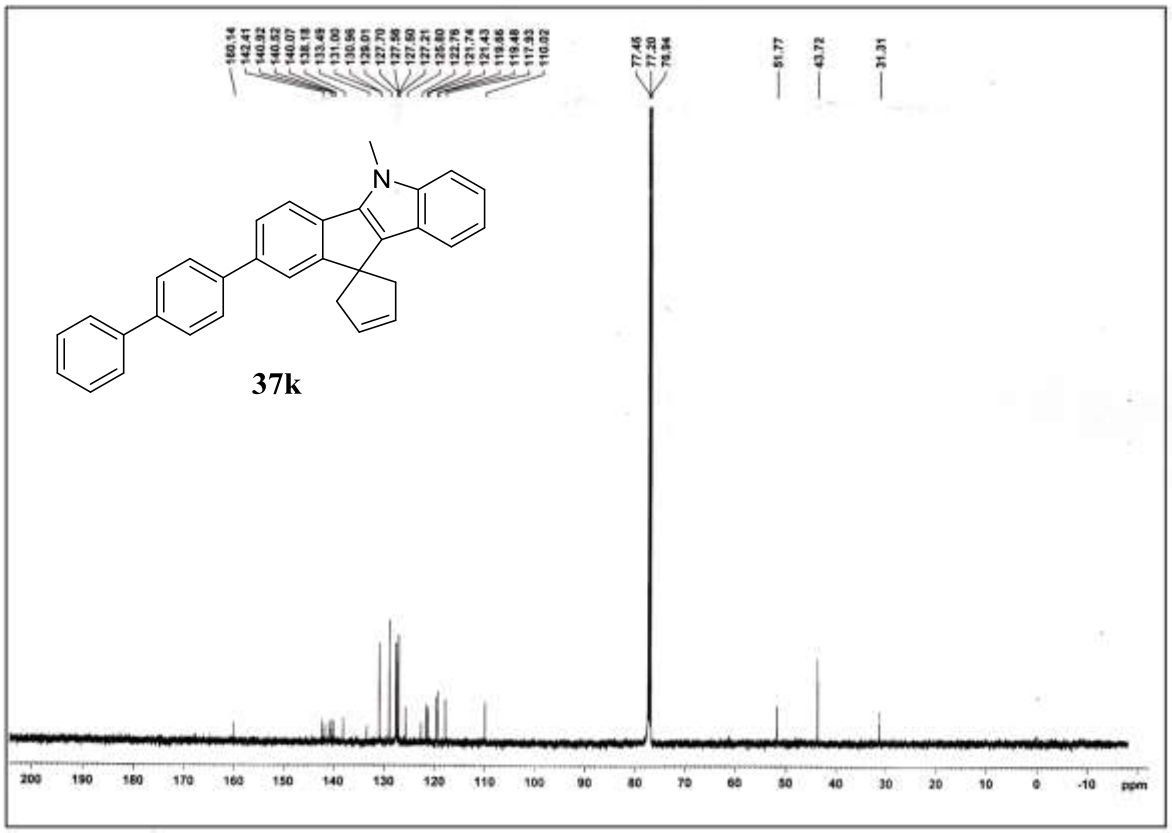

N
S
37i
8
7
6
5
4
3
2
1
0
ppm
1.00
1.41
1.20
1.04
3.07
4.02
1.44
1.08
1.82
2.94
4.04


160.09
144.90
142.50
141.57
141.02
139.48
134.30
131.62
131.41
130.95
125.51
124.96
124.69
124.33
123.56
122.65
122.38
121.68
120.91
119.74
119.55
119.04
117.91
110.06
77.45
77.20
76.95
51.74
43.61
31.26
N
S
37i
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


N
N
H
37j
8
7
6
5
4
3
2
1
0
ppm
1.00
0.85
0.97
1.70
2.76
1.23
2.82
0.91
0.91
1.60
2.76
3.40
0.26


159.95
142.39
142.11
140.23
138.42
133.82
132.49
130.95
130.59
128.84
128.60
125.64
122.84
122.33
122.09
121.14
119.56
119.38
119.26
117.84
111.42
109.96
103.21
77.46
77.20
76.95
51.77
43.82
31.29
N
N
H
37j
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


N
37k
H2O
8
7
6
5
4
3
2
1
0
ppm
1.00
7.32
1.93
2.46
2.05
1.00
0.93
0.91
1.73
2.50
3.49
0.81


160.14
143.41
140.92
140.52
140.07
138.18
133.49
131.00
130.94
128.01
127.70
127.58
127.50
127.21
125.60
122.76
121.74
121.43
119.86
119.48
117.93
110.02
77.46
77.20
76.94
51.77
43.72
31.31
N
37k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm