



Departamento de Química Orgánica II
Kimiko Organikoa II Saila

Phosphine oxides as privileged ligands for Palladium-catalyzed α -arylation and heteroannulation reactions in water

MEMORIA PRESENTADA POR

Iratxe Astarloa Maseda

PARA OPTAR AL GRADO DE DOCTOR CON
MENCIÓN "DOCTOR INTERNACIONAL"

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Ama y Aita

Aimar

Amama y Aitite

"I was taught that the way of progress was neither swift nor easy"

Marie Curie (1867-1934)

"A person who never made a mistake never tried anything new."

Albert Einstein (1879-1955)

Quisiera expresar mi más sincero agradecimiento a I@s Drs. Esther Domínguez, Raul SanMartin y Maite Herrero por concederme la oportunidad y la confianza para trabajar en el laboratorio de investigación que dirigen, y de ese modo poder realizar esta Tesis Doctoral bajo su supervisión. Así como agradezco sus consejos, dedicación y ayuda durante este tiempo.

I am really grateful to Dr. Hans Jörg Roth (director of Macrocycles in Novartis Pharma AG in Basel, Switzerland) for giving me the opportunity of joining his research department of Global Discovery Chemistry (Novartis Institute for Biomedical Research, Macrocycles (GDC/NIBR)) and all my partners working there, specially Dr. Marianne Fouche and Angela Vitrey for their help and for being so nice with me.

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A mis compañeros de laboratorio, los que están ahora y todos los que ya no están (doctorandos, masterandos y grados), por el gran ambiente de trabajo creado. Sin olvidarnos de los muchos compañeros del departamento y otros departamentos de esta facultad, como Rebeca y Mainer que han estado desde el primer año de carrera. A todas esas personas que me han acompañado durante este tiempo, ya fuese codo con codo o a distancia, en especial a Aimar Garcia,

Nerea Conde, Eider Aranzamendi, Iker Jauregibeitia y Ania Sevilla por el apoyo ofrecido en buenos y malos momentos. De aquí me llevo grandes amigos.

En especial a mi familia por su cariño y sobre todo por su inquebrantable e inagotable comprensión y apoyo moral. No existen palabras que describan lo agradecida que les estoy por la infinita paciencia que han tenido todo este tiempo. A mis amig@s por su amistad e incondicional apoyo.

Eskerrik asko guztioi

Part of the results of this dissertation have been reported in the following publications and patents:

“Procedimiento para la síntesis de derivados 1,2-di(hetero)ariletanonas y 1,2,2-tri(hetero)ariletanonas en agua”

Astarloa, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E.

Patente Española

Nº de registro: P201630409

Válida en España

“Aqueous α -arylation of mono- and diarylethanone nulates at low catalyst loading”

Astarloa, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E.

Adv. Synth. Catal. 2018 (accepted)

DOI: 10.1002/adsc.201701596

Moreover, the following contributions have been presented to conferences and symposia:

“A straightforward access to pyrazolo(benzo)thienoquinolines”

Hernández, S.; Perea, M.; Churruca, F.; SanMartin, R.; Conde, N.; Herrero, M.T.;
García, A.; Astarloa, I.; Domínguez, E.
European Symposium on Organic Chemistry (ESOC 2013)
Marsella (France), 7-12 July 2013 (Poster Commun.)

“Catalytic activity of palladium CNC pincers in Mizorocki-Heck and Sonogashira reactions”

Inés, B.; Moure, M.J.; SanMartín, R.; Herrero, M.T.; Astarloa, I.; Domínguez, E.
XXXIV Reunión Bienal de la Real Sociedad Española de Química
Santander (Spain), 15-18 September 2013 (Poster Commun.)

“Síntesis, caracterización y propiedades catalíticas de un nuevo complejo pincer de paladio”

Lacret, R.; SanMartin, R.; Churruca, F.; Herrero, M. T.; Astarloa, I.; Domínguez E.
XXXIV Reunión Bienal de la Real Sociedad Española de Química
Santander (Spain), 15-18 September 2013 (Poster Commun.)

“Un nuevo acceso al núcleo indolo[1,2-c]quinazolinico de la Hinckdentina A”

Diaz de Sarralde, R. J.; Herrero, M. T.; SanMartin, R.; García, A.; Astarloa, I.;
Domínguez, E.
XXXIV Reunión Bienal de la Real Sociedad Española de Química
Santander (Spain), 15-18 September 2013 (Poster Commun.)

“New synthetic methodologies based on sustainable procedures”

Domínguez, E.; SanMartín, R.; Tellitu, I.; Herrero, M. T.; Moreno, I.; Moure, M. J.;
Diad de Sarralde, J.; Urgoitia, G.; Conde, N.; Astarloa, I.; Rincon, J. A.; Davila, I.
IV Jornadas de Investigación de la Facultad de Ciencia y Tecnología
Leioa (Spain), 12-13 February 2014 (Poster Commun.)

“Catalytic Activity of a New PCN Palladium Complex”

García, A.; Astarloa, I.; SanMartín, R.; Herrero, M. T.; García, A.; Domínguez, E.
XXV Reunión Bienal de Química Orgánica. Meeting on Organic Chemistry
Alacant (Spain), 4-6 June 2014 (Oral Commun.)

*“Suzuki Biaryl Coupling in the presence of a New Non-Symmetric Palladium
Pincer complex”*

García, A.; I. Astarloa, I.; SanMartín, R.; Herrero, M. T.; Domínguez, E.
I International Symposium on Synthesis and Catalysis (ISySyCat I)
Évora (Portugal), 2-4 September 2015 (Poster Commun.)

“An efficient catalyst for the oxygen-mediated cleavage of arylacetylenes”

Urgoitia, G.; SanMartín, R.; Herrero, M. T.; Astarloa, I.; Domínguez, E.
I International Symposium on Synthesis and Catalysis (ISySyCat I)
Évora (Portugal), 2-4 September 2015 (Poster Commun.)

*“A highly active catalyst for the aerobic oxidations of alcohols and methylene
compounds”*

SanMartín R.; Conde N.; Herrero MT.; Urgoitia G.; Astarloa I.; García A.; Dominguez
E.
11th Spanish–Italian Symposium on Organic Chemistry (SISOC XI)
Donostia - San Sebastián (Spain), 13-15 July 2016 (Poster Commun.)

“A very efficient catalyst for the cycloisomerization of alkynoic acids”

Urgoitia, G.; Maiztegi, A.; SanMartin, R.; Herrero, M. T.; Dominguez, E.; Astarloa, I.; Garcia, A.

Third Iberoamerican Symposium on Organic Chemistry (SIBEAQO-III)
Oporto (Portugal), 23-26 September 2016 (Poster Commun.)

“A more efficient catalyst for the cycloisomerization of alkynoic acids”

Llorente, G.; García, A.; Domínguez, E.; Urgoitia, G.; Astarloa, I.; Herrero, M. T.; Conde, N.; SanMartin, R.

MOL2NET 2017, International Conference on Multidisciplinary Sciences, 3rd edition

“Enaminoketone derivatives as key intermediates for the synthesis of 4-quinolones”

Alvaro, A.; García, A.; Domínguez, E.; Llorente, G.; Urgoitia, G.; Astarloa, I.; Herrero, M. T.; SanMartin, R.

MOL2NET 2017, International Conference on Multidisciplinary Sciences, 3rd edition
Leioa (Spain), 2018 (On-line Commun.)

“Aryl halides as convenient arylating agents for the “on water” efficient functionalization of deoxybenzoin”

Astarloa, I.; SnMartin, R.; Garcia, A.; Urgoitia, G.; Llorente, G.; Herrero, M. T.; Domínguez, E.

VI Jornadas de Investigación de la Facultad de Ciencia y Tecnología
Leioa (Spain), 14-15 March 2018 (Oral Commun.)

Internship during the PhD formation:

Internship as a Medicinal Chemistry trainee (2016) at Novartis Pharma AG. (Lichtstrasse 35, 4056, Basel, Switzerland) in the Global Discovery Chemistry department, Novartis Institute for Biomedical Research, Macrocycles (GDC/NIBR) in order to develop Chemistry Synthesis skills during a 3-months period (May 1-July 31) under the supervision of Dr. Hans-Jörg Roth, Director of Macrocycles.

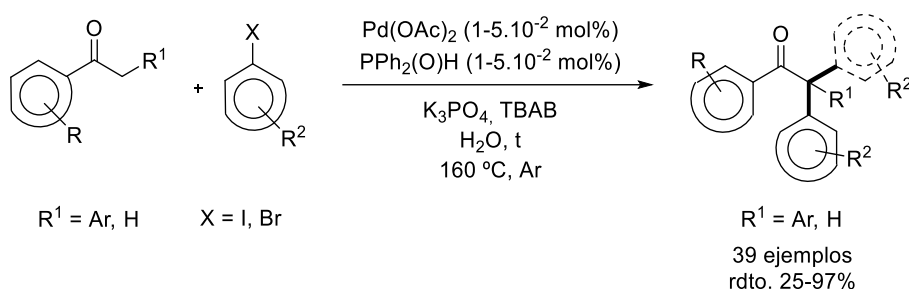
The contents of this internship work cannot be disclosed (Confidential Information)

El trabajo de investigación que se recoge en la presente memoria se ha centrado en el estudio del potencial catalítico de los óxidos de fosfinas secundarias combinado con fuentes de paladio comerciales para llevar a cabo diferentes transformaciones sintéticas en medio acuoso.

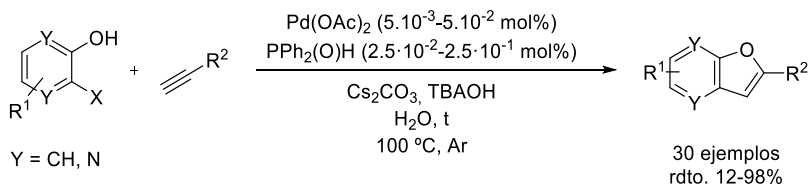
De esta manera, en el primer capítulo, se han sintetizado 1,2-diaril- y 1,2,2-triariletanonas *via* α -arilación de cetonas aromáticas. Primero se realizaron varios ensayos para optimizar las condiciones de reacción, tras lo que se aplicaron una serie de acetofenonas y desoxibenzoínas y bromuros y yoduros de arilo, consiguiendo los productos de monoarilación y diarilación correspondientes. Los resultados obtenidos fueron excelentes, no sólo con respecto a los rendimientos obtenidos, sino también desde un punto de vista de la eficiencia catalítica, habiendo conseguido la carga catalítica más baja hasta la fecha, tanto en

Resumen

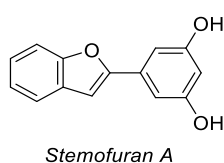
disolventes orgánicos como en medio acuoso. Así mismo, el análisis mediante ICP-MS del producto de etanona final reveló unos niveles de paladio inferiores al límite de detección del aparato, por lo que los productos sintetizados mediante esta metodología son compatibles con la administración oral como intravenosa de dichos compuestos finales en cuanto al contenido en paladio.



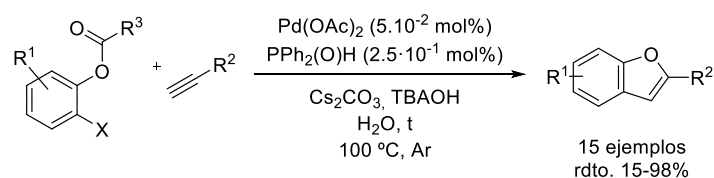
El segundo capítulo está centrado en una transformación sintética diferente, basada en el sistema catalítico optimizado en el capítulo anterior. En este caso, se analizó una reacción *one-pot* de alquilación-hidrofenoilación, en la que se empleó *o*-yodohidroxiarenos y acetilenos terminales para la formación de benzo[*b*]furanos 2-substituidos. En este capítulo se recogen los ensayos realizados con menor carga catalítica publicados hasta el momento, con resultados excelentes y completa regioselectividad, empleando de nuevo agua como único disolvente de reacción. Yendo un paso más lejos, acetilenos alquílicos y alquenílicos fueron usados con éxito, aunque rendimientos moderados.



De nuevo el análisis del contenido de paladio en los benzofuranos obtenidos y el escalado de la reacción demostraron la aplicación industrial del método puesto a punto. Como prueba adicional del potencial sintético de este sistema catalítico, se ha propuesto una nueva aproximación a un producto natural empleando este procedimiento, el *Stemofuran A*.

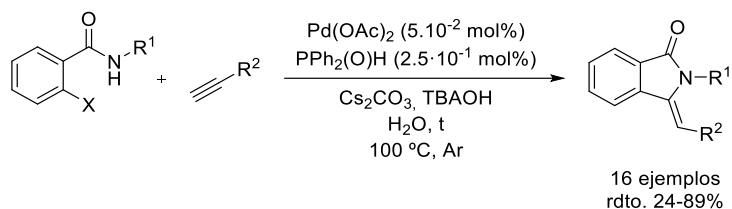


Dado que en muchos casos el acceso a benzofuranos de interés a través de metodologías que impliquen heteroanulación requiere de una protección del grupo hidroxilo de precursores fenólicos, y a la vista del trabajo, tiempo y pasos extra que esto conlleva, se ha puesto a punto un procedimiento que permite la heteroanulación intermolecular entre *o*-iodoaril ésteres y alquinos terminales para proporcionar benzo[*b*]furanos en agua, de tal modo que en un proceso en cascada se produce dicha heteroanulación acompañada de la hidrólisis.



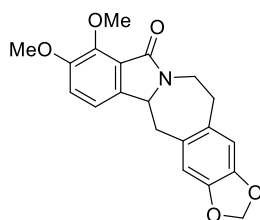
Finalmente, en el último apartado de este segundo Capítulo, el protocolo empleado para la formación de benzofuranos, se aplicó a una colección de 2-yodobenzamidas y acetilenos, generando así 3-alquenilisoindolonas.

Resumen



Esta reacción transcurre empleando el mismo sistema catalítico y en medio acuoso consiguiendo (*Z*)-isoindolonas de manera regio- y diastereoselectiva. Esta diastereoselectividad fue confirmada mediante experimentos RMN y difracción de rayos X.

Esta última estrategia se aplicó en la síntesis de un intermedio clave para la obtención de un producto natural con estructura benzoazepinoisindolónica, la *Lennoxamina*, mediante una síntesis convergente. De este modo se obtuvo el intermedio deseado con muy buen rendimiento, empleando una cantidad exigua de catalizador y reemplazando los disolventes orgánicos por agua en la etapa de heteroanulación intermolecular.

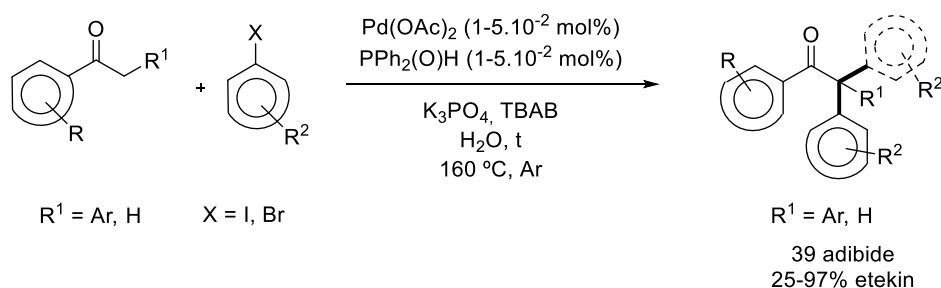


Lennoxamina

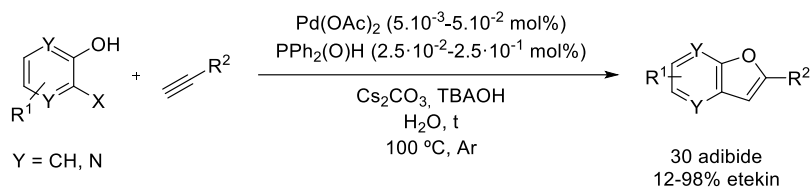
Memoria honetan bildutako ikerketa lanaren laburpena fosfina oxido komertzialen eta paladiozko iturri baten aplikazioanoinarrিতa dago; SPO (bigarren mailako fosfina oxidoa) hauen aktibitate katalitiko potentzialaren araketan transformazio sintetiko desberdinetan, alegia. Halaber, hausnarketa zentratu egin zen SPO konposatu hauen erabilera uretan garatutako erreakzioetan.

Modu honetan, lehenengo Kapituluak 1,2-diaril- eta 1,2,2-triariletanonon sintesira bideratuta dago konposatu karboniliko α -arilazio erreakzioan oinarrituta. Baldintzen optimizazio erreakzio saiakeren ondoren, zenbait azetofenona deribatu eta deoxibenzoina frogatu ziren bromo eta iodoarenodesberdinekin, diarilazio eta monoarilazio produktuak eskuratuz optimizatutako baldintzetan aldaketa txikiak eginez. Lortutako emaitzak onak izan ziren, ez bakarrik etekinaren ikuspuntutik (zeinetan etekinak emaitza moderatuetatik oso onetara mugitzen diren, erabilitako

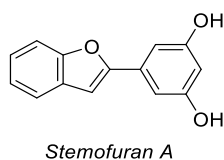
hasierako errektiboen arabera), baita katalizatzailearen kantitatearen ikuspuntutik, erabilitako kantitaterik txikiena dena momentu honetara arte, bai disolbatzaile organikoetan zein urtsuan. Honetaz gain, arilatutakoetanona konposatu finalen paladio edukinaren balioa ICP-MS detekzio-mugaren azpitik zegoen. Honekin, administrazio orala eta parenterala ahalbidetuta egongo litzateke, legediak onartzen duen paladio kantitatearen azpitik baitago.



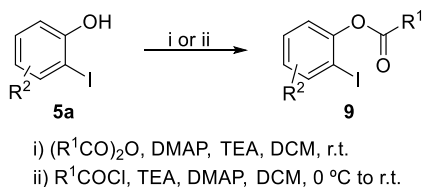
Bigarren kapitulari dagokionez, bestelako transformazio sintetiko bat arakatu da, aurreko kapitulan erabilitako sistema katalitikoan oinarrituta. Kasu honetan, one-pot erreakzioa, Sonogashira-hydrofenozilazio sintesia aztertu da, 2-iodohidroxiarenoak eta azetilenok erabili dira 2 posizioan ordezkaturako bentzo[b]furano produktuak lortzeko. Kapitulu honek argitaratutako katalizatzailearen karga katalitiko kantitaterik txikiena biltzen du, emaitza oso onekin eta erregioselektiboki, ura erabiliz erreakzioko disolbatzaile bakar moduan. Are gehiago, lan honen eraginkortasuna luzatzeko asmoz, alkil- eta alkenilazetilenok erabili ziren, nahiz eta prozesukonplexua izan, etekin moderatuak lortuz.



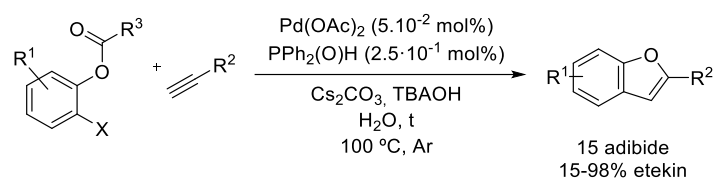
Aipatutakoaz gain, 2-arilbentzofurano produktu baten paladioaren edukina neurtu da, balio oso txikia lortuz, aurreko kapituluan gertatu den moduan, estrategia hau jarraituz, produktu natural baten sintesia proposatu da, *Stemofuran A* hain zuzen ere.



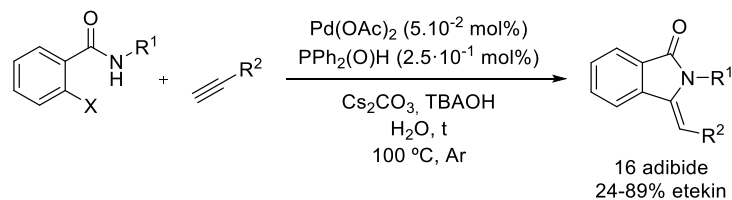
Hau guztia gutxi balitz, aurreko metodologia gehiago arakatu da, momentura arte ikasitakoa aplikatuz *one-pot* transformazioari, literaturako adibide askotan hidroxi taldearen babespena (azetitazioa) beharrezkoa baita, prozesua luzatuz gainerako erreakzio pausuengatik. Aurretiaz prestatutako 2-iodoaril ester desberdinak zenbait arilazetilenoeekin erreakzionarazi ziren *one-pot* erreakzioko sistema katalitikoaz, goiko prozeduran lortutako 2-aril bentzo[*b*]furan produktu berdinak eskuratuz.



Saiatutako *one-pot* erreakzio berri honetan Sonogashira-hidrolisi-heteroanulazio erreakzio bat ematen dela proposatu da, goian adierazitako heterozikloak eratzuz. 2-Iodohidroxiarenoen kasuan bezala, etekin oso onak lortu ziren katalizatzailearen kantitate txikiak erabiliz.

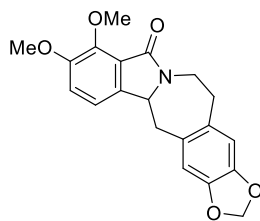


Azkenik, bigarren kapitulu honen bukaeran, prozedura berdina aplikatu da aurretiaz prestatutako *o*-iodobenzamida desberdinei, azetileno desberdinak gehituta, heteroziklo desberdin bat eratzeko ideiarekin, alkilidenisoidolonak, alegia.



Zorionez, proposatutako *one-pot* erreakzio hau eraginkorra izan zen sistema katalitiko beraren kantitate txikia erabiltzean ingurune urtsuan, (*Z*)-isoidolonak lortuz regio- eta diastereoselektiboki. Selektibitate hau konfirmatzeko, EMNzko datu bibliografikoak erabili ziren, ahal izan zen kasuetan. Bestelako konposatuekin EMNzkoesperimentobidimentzionalak behar izan ziren. Azkenik, hainbat kasutan monokristal egokiak eskuratu ziren eta euren X-izpien difraktometriaren bidez egituren konfigurazio absolutua berretsi zen.

Horrenbestez, prozeduraha produktu natural baten (*Lennoxamine*) sintesiarenoinarrizkobitartekari baten sintesianerabili zen, bidesintetikokobergentearen bitartez. Bitartekarihausintetizatzea posible izan zen, sistema katalitiko eta baldintzak mantenduz, etekin altuarekin, kargakatalitikobaxuarekin, eta are gehiago, disolbatzaile organikoak, urarekin ordezkatu.



Lennoxamina

Note:

The bibliographic references of this Doctoral Thesis are collected at the end of each page, and they are chapter-independent. In several cases, the references have been repeated for the convenience of the reader.

CONCLUSIONS

CONCLUSIONS

- ❖ 1,2,2-Triarylethanones, 1,2-diarylethanones and related heterocyclic derivatives can be successfully obtained by an “on water” α -arylation reaction in the presence of small amounts (0.01-0.05 mol%) of a common palladium source, palladium acetate.
- ❖ 2-Aryl-, 2-alkenyl or 2-alkyl[b]furans, 3-alkylideneisoindolones and related heterocyclic derivatives can be successfully obtained by an aqueous intermolecular heteroannulation reaction process between *o*-iodoarene derivatives (phenols, esters and amides) and alkynes in the presence of small amounts (0.005-0.05 mol%) of a palladium acetate.
- ❖ When combined to such a relatively mild base as potassium phosphate, the catalyst system composed of commercially available palladium(II) acetate and diphenylphosphine oxide show a high catalytic activity for both, the α -arylation of ketone enolates and the cascade intermolecular heteroannulation reaction (and hydrolysis) in water.
- ❖ The combination of a very low catalyst loading and water as solvent allows for isolation of products with minimal traces of residual palladium, thus avoiding the use of scavenger resins or further purification steps in order to suppress metal contamination in the products.
- ❖ The optimized conditions are suitable for the synthesis of two natural products, *Stemofuran A* and *Lennoxamine* by competitive routes in comparison with those reported in the literature, as lower catalytic loadings and in an environmentally more sustainable media are used.
- ❖ Although several common features were found for both reactions in the conversion rate vs time kinetic curves and poisoning assays performed to shed light on the reaction mechanism, slight differences also appeared in transmission electron microscopy images. The participation of both

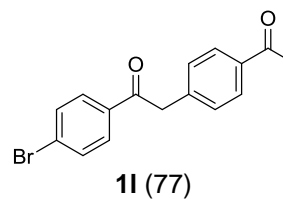
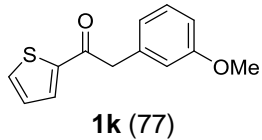
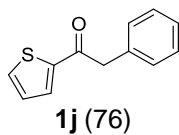
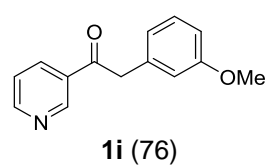
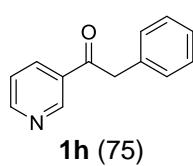
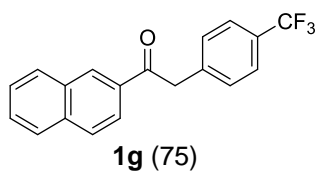
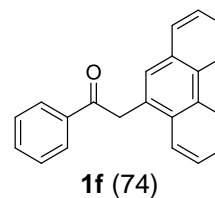
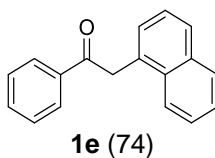
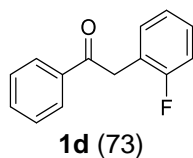
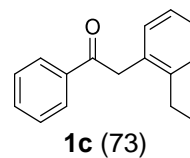
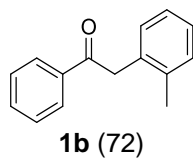
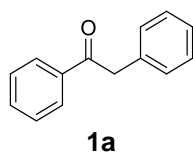
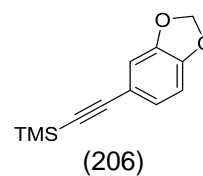
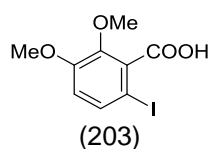
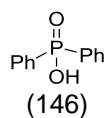
Conclusions

catalytically active homogeneous and heterogeneous species can be suggested from the above experiments, leading to suggest a tentative mechanism based on the active role of palladium phosphinous acid complexes.

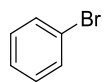
SUMMARY OF COMPOUNDS

SUMMARY OF COMPOUNDS

In this summary all synthesized compounds collected in this PhD thesis are showed, with their corresponding code (number and letter). The number between parentheses refers to the corresponding page of the experimental part where those compounds are described



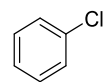
Summary of compounds



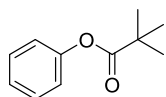
2a



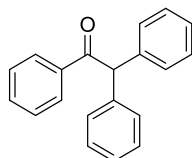
2b



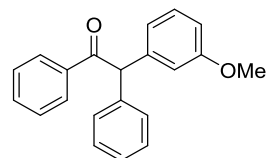
2c



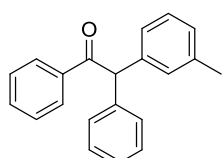
2d (54)



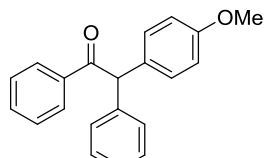
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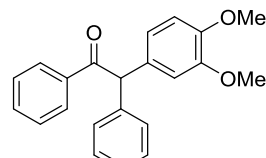
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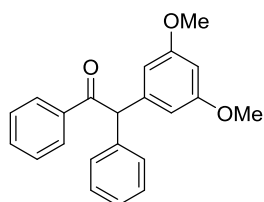
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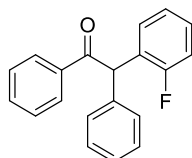
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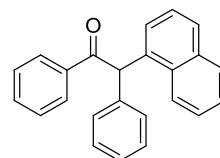
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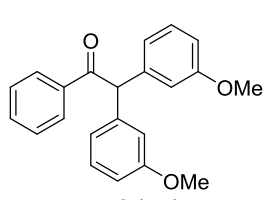
3af (58)



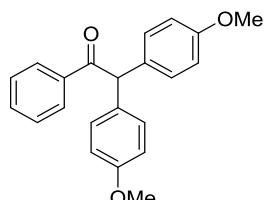
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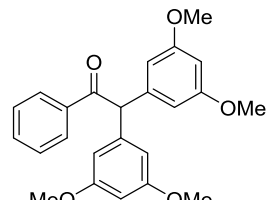
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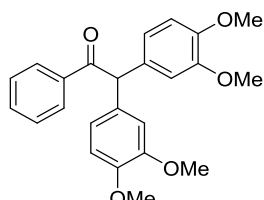
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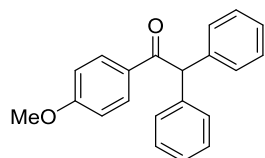
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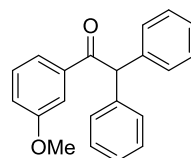
3ak (62)



3al (62)

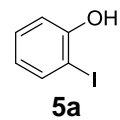
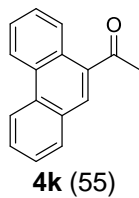
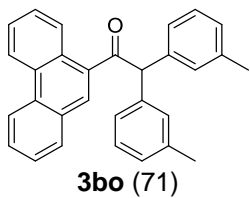
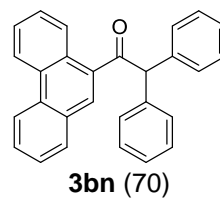
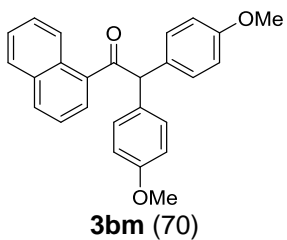
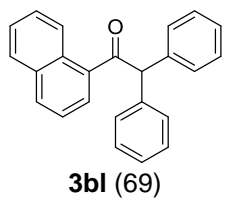
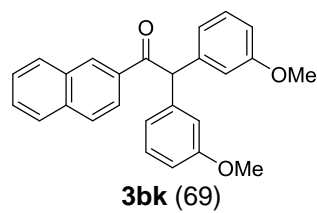
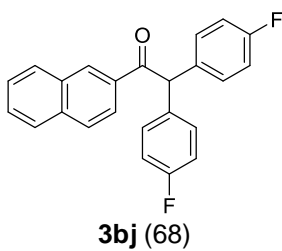
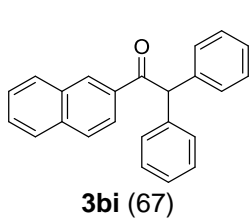
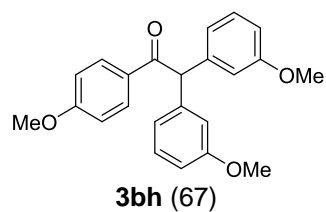
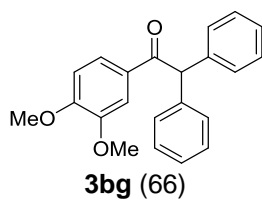
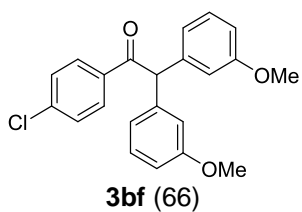
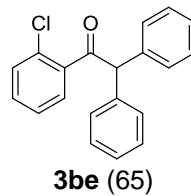
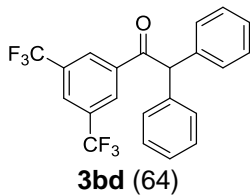
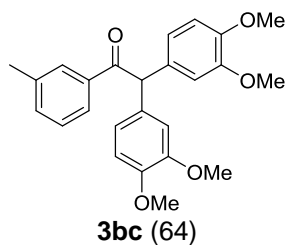


3ba (63)

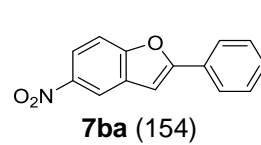
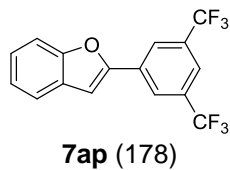
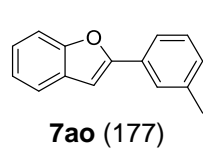
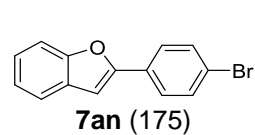
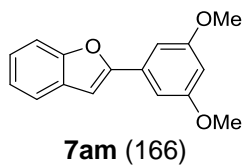
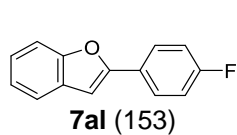
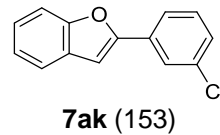
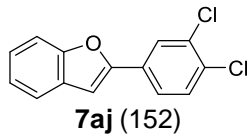
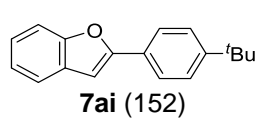
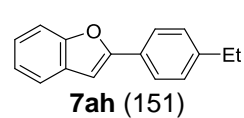
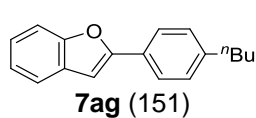
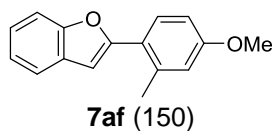
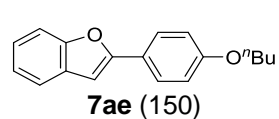
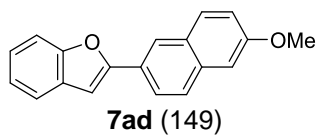
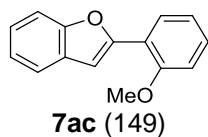
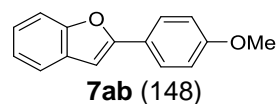
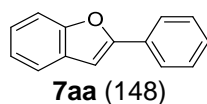
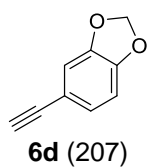
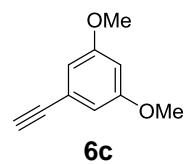
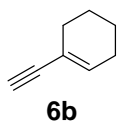
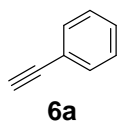


3bb (63)

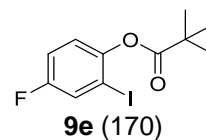
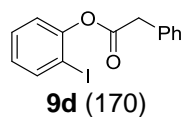
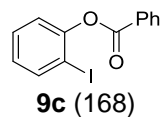
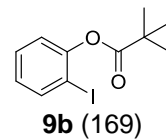
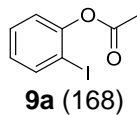
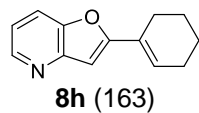
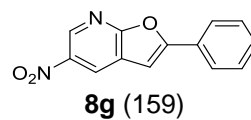
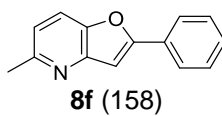
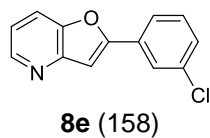
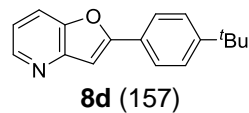
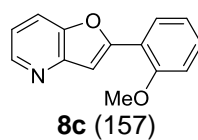
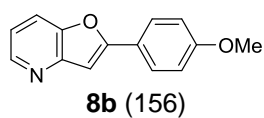
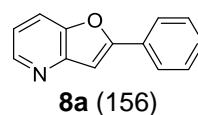
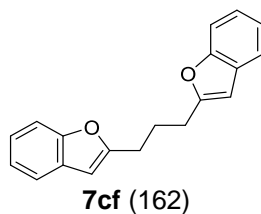
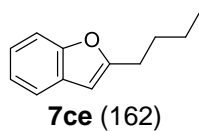
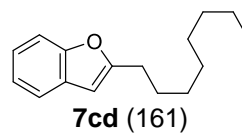
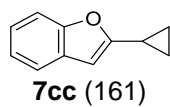
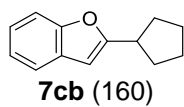
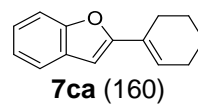
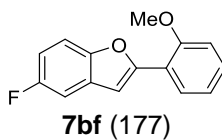
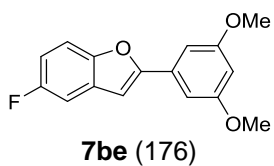
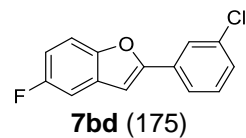
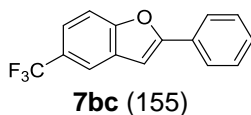
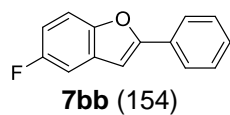
Summary of compounds



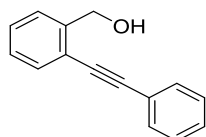
Summary of compounds



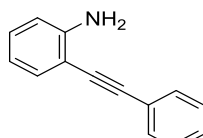
Summary of compounds



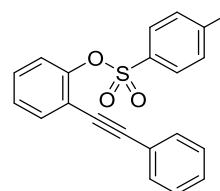
Summary of compounds



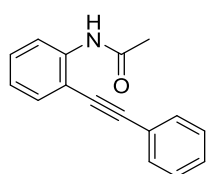
10a (163)



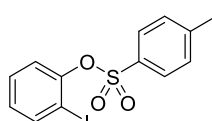
10b (164)



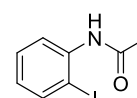
10c (179)



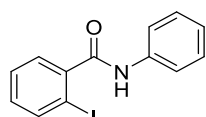
10d (179)



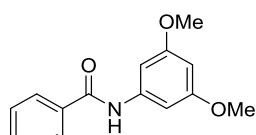
11a (171)



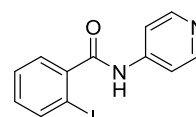
11b (172)



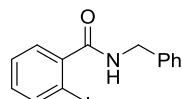
12a (180)



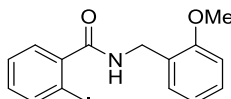
12b (181)



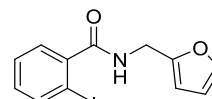
12c (182)



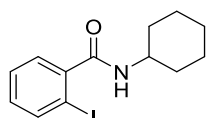
12d (182)



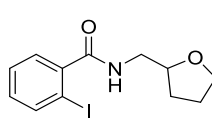
12e (183)



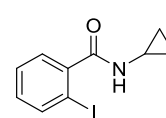
12f (183)



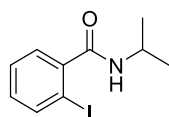
12g (184)



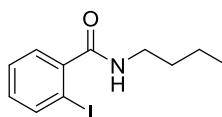
12h (184)



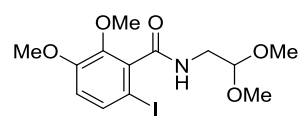
12i (185)



12j (185)

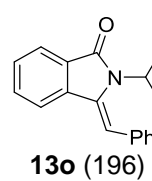
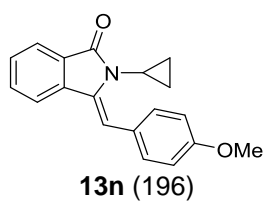
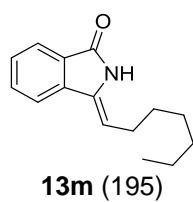
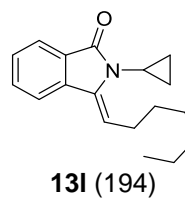
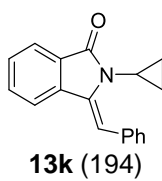
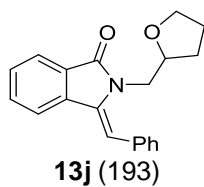
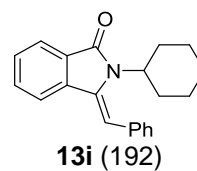
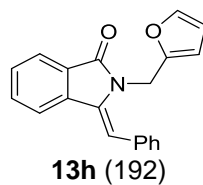
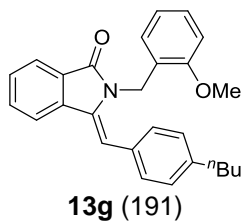
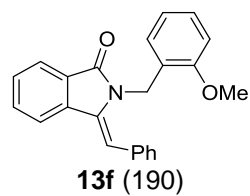
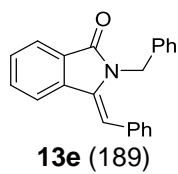
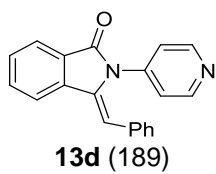
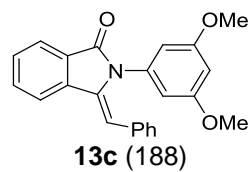
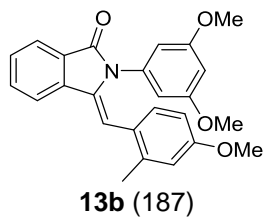
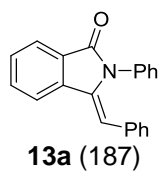


12k (186)

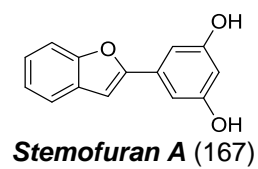
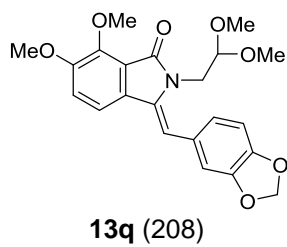
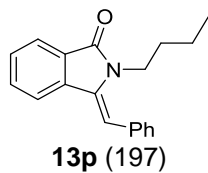


12l (204)

Summary of compounds



Summary of compounds



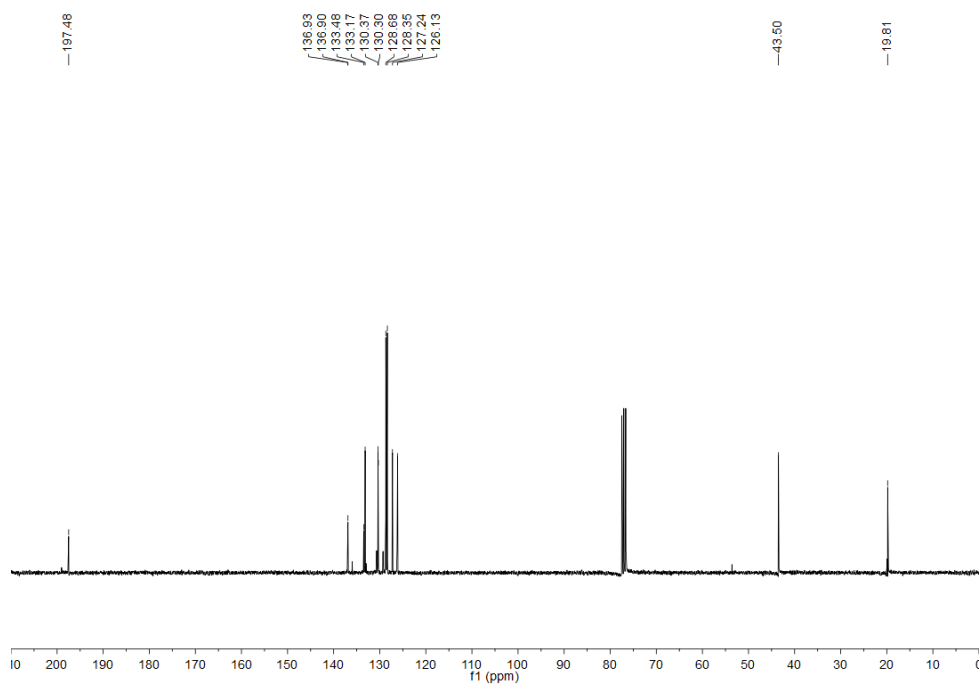
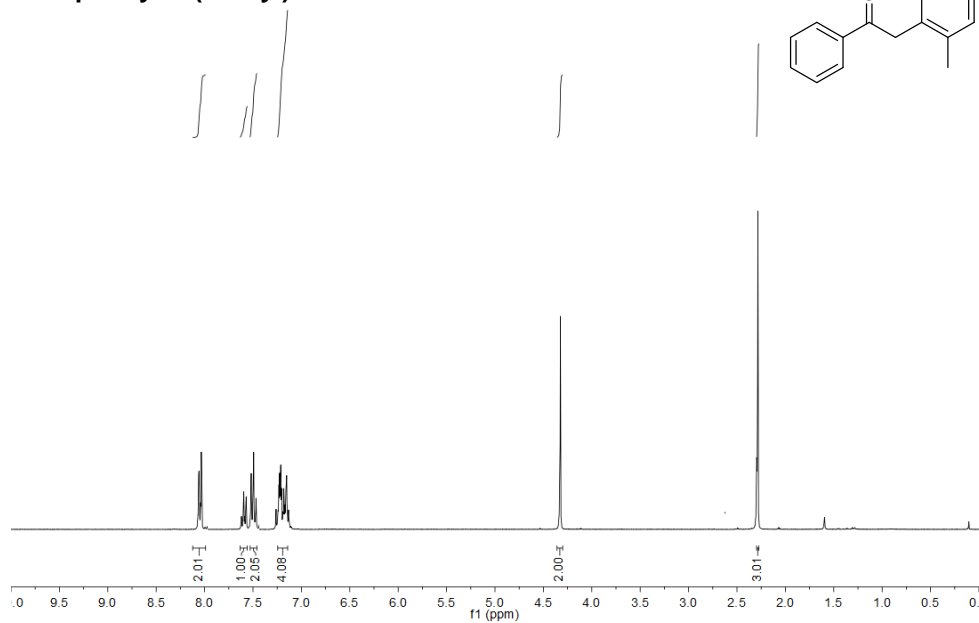
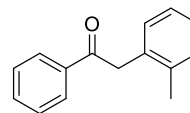
Appendix

Selection of Representative Spectra

1b: 1-phenyl-2-(o-tolyl)ethan-1-one
1c: 2-(2-ethylphenyl)-1-phenylethan-1-one
1f: 2-(phenanthren-9-yl)-1-phenylethan-1-one
1g: 1-(naphthalen-2-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one
1h: 2-phenyl-1-(pyridin-3-yl)ethan-1-one
1i: 2-(3-methoxyphenyl)-1-(pyridin-3-yl)ethan-1-one
1j: 2-phenyl-1-(thiophen-2-yl)ethan-1-one
1k: 2-(3-methoxyphenyl)-1-(thiophen-2-yl)ethan-1-one
1l: 2-(4-acetylphenyl)-1-(4-bromophenyl)ethan-1-one
3ab: 2-(3-methoxyphenyl)-1,2-diphenylethanone
3ae: 2-(3,4-dimethoxyphenyl)-1,2-diphenylethanone
3af: 2-(3,5-dimethoxyphenyl)-1,2-diphenylethanone
3ah: 2-(naphthalen-1-yl)-1,2-diphenylethanone
3ai: 2,2-bis(3-methoxyphenyl)-1-phenylethanone
3aj: 2,2-bis(4-methoxyphenyl)-1-phenylethanone
3ak: 2,2-bis(3,5-dimethoxyphenyl)-1-phenylethanone
3ba: 1-(4-methoxyphenyl)-2,2-diphenylethanone
3bb: 1-(3-methoxyphenyl)-2,2-diphenylethan-1-one
3bc: 2,2-bis(3,4-dimethoxyphenyl)-1-(m-tolyl)ethanone
3bf: 1-(4-chlorophenyl)-2,2-bis(3-methoxyphenyl)ethanone
3bg: 1-(3,4-dimethoxyphenyl)-2,2-diphenylethanone
3bh: 2,2-bis(3-methoxyphenyl)-1-(4-methoxyphenyl)ethanone
3bj: 2,2-bis(4-fluorophenyl)-1-(naphthalen-2-yl)ethanone
3bk: 2,2-bis(3-methoxyphenyl)-1-(naphthalen-2-yl)ethanone
3bm: 2,2-bis(4-methoxyphenyl)-1-(naphthalen-1-yl)ethanone
3bn: 1-(phenanthren-9-yl)-2,2-diphenylethanone
3bo: 1-(phenanthren-9-yl)-2,2-di-m-tolylethan-1-one
6-Iodo-2,3-dimethoxybenzoic acid
7ab: 2-(4-Methoxyphenyl)benzofuran
7ac: 2-(2-Methoxyphenyl)benzofuran
7ad: 2-(6-Methoxynaphthalen-2-yl)benzofuran
7ae: 2-(4-Butoxyphenyl)benzofuran
7af: 2-(4-Butoxyphenyl)benzofuran
7ag: 2-(4-Butylphenyl)benzofuran
7ai: 2-(4-(tert-Butyl)phenyl)benzofuran
7ak: 2-(3-Chlorophenyl)benzofuran

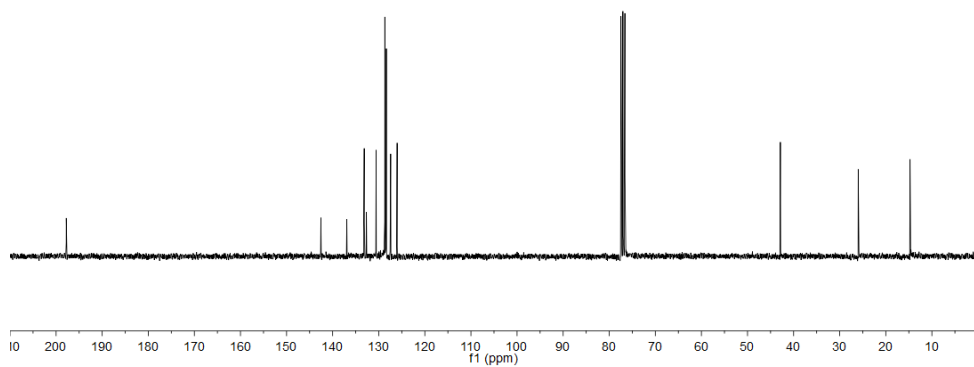
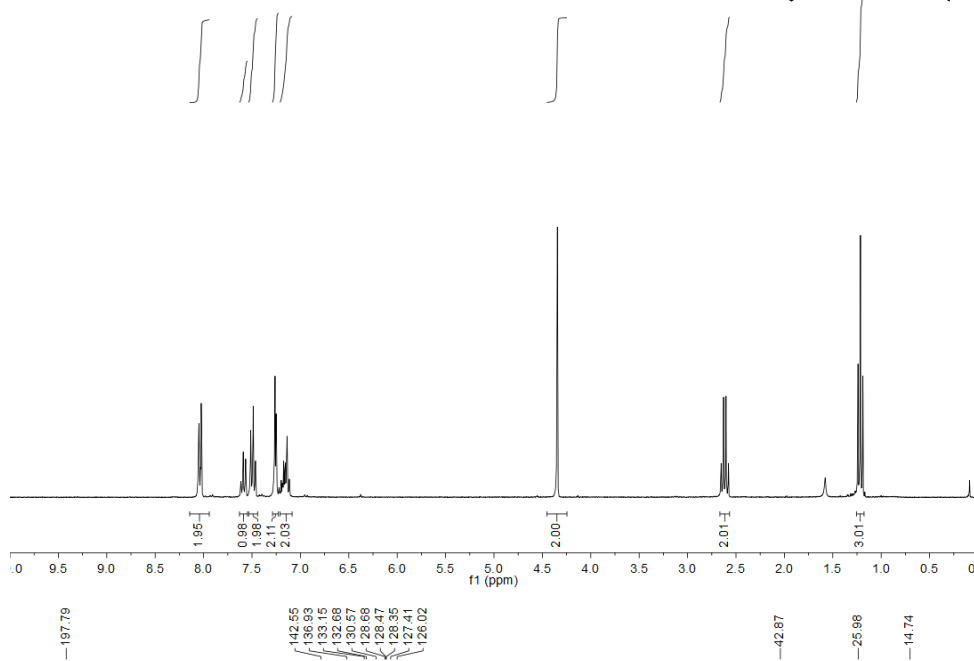
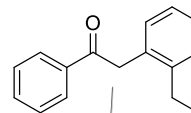
- 7am:** 2-(3,5-Dimethoxyphenyl)benzofuran
7an: 2-(4-Bromophenyl)benzofuran
7ao: 2-(m-Tolyl)benzofuran
7bd: 2-(3-Chlorophenyl)-5-fluorobenzofuran
7be: 2-(3,5-Dimethoxyphenyl)-5-fluorobenzofuran
7bf: 5-Fluoro-2-(2-methoxyphenyl)benzofuran
7cc: 2-Cyclopropylbenzofuran
8b: 2-(4-Methoxyphenyl)furo[3,2-b]pyridine
8f: 5-Methyl-2-phenylfuro[3,2-b]pyridine
8g: 5-Nitro-2-phenylfuro[2,3-b]pyridine
Stemofuran A: 5-(Benzofuran-2-yl)benzene-1,3-diol
9b: 2-iodophenyl pivalate
9e: 4-Fluoro-2-iodophenyl pivalate
10a: (2-(Phenylethynyl)phenyl)methanol
10c: 2-(Phenylethynyl)phenyl 4-methylbenzenesulfonate
12c: 2-Iodo-N-(pyridin-4-yl)benzamide
12f: N-(Furan-2-ylmethyl)-2-iodobenzamide
12h: 2-Iodo-N-((tetrahydrofuran-2-yl)methyl)benzamide
12i: N-Cyclopropyl-2-iodobenzamide
12k: N-Butyl-2-iodobenzamide
12l: N-(2,2-Dimethoxyethyl)-6-iodo-2,3-dimethoxybenzamide
13b: (Z)-2-(3,5-Dimethoxyphenyl)-3-(4-methoxy-2-methylbenzylidene)isoindolin-1-one
13c: (Z)-3-Benzylidene-2-(3,5-dimethoxyphenyl)isoindolin-1-one
13d: (Z)-3-Benzylidene-2-(pyridin-4-yl)isoindolin-1-one
13f: (Z)-3-Benzylidene-2-(2-methoxybenzyl)isoindolin-1-one
13g: (Z)-3-(4-Butylbenzylidene)-2-(2-methoxybenzyl)isoindolin-1-one
13h: (Z)-3-Benzylidene-2-(furan-2-ylmethyl)isoindolin-1-one
13j: (Z)-3-Benzylidene-2-cyclohexylisoindolin-1-one
13k: (Z)-3-Benzylidene-2-cyclopropylisoindolin-1-one
13l: (Z)-2-Cyclopropyl-3-heptylideneisoindolin-1-one
13m: (Z)-3-Heptylideneisoindolin-1-one
13o: (Z)-3-Benzylidene-2-isopropylisoindolin-1-one, 10o

1b:1-phenyl-2-(o-tolyl)ethan-1-one

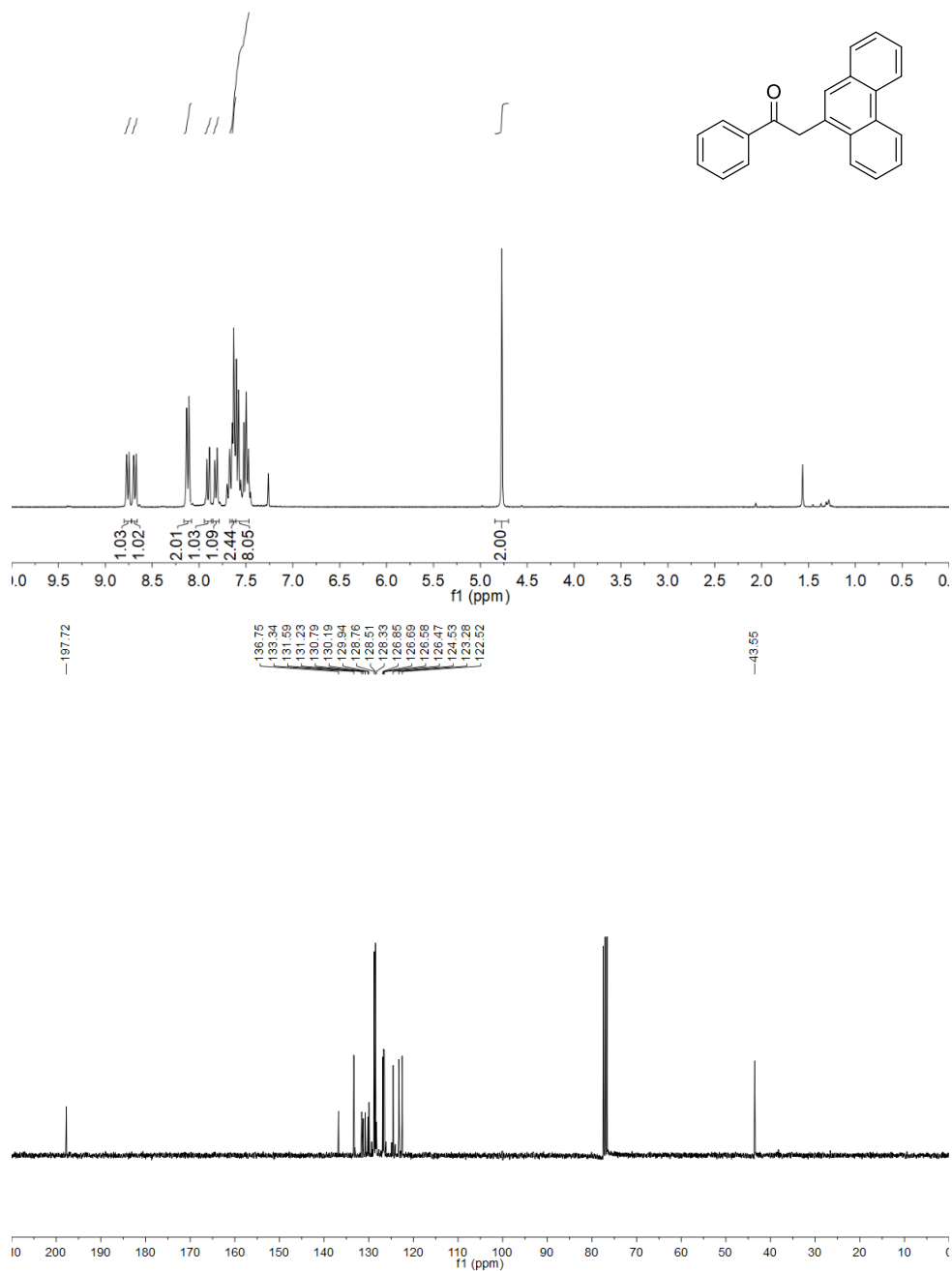


Appendix of spectra

1c: 2-(2-ethylphenyl)-1-phenylethan-1-one

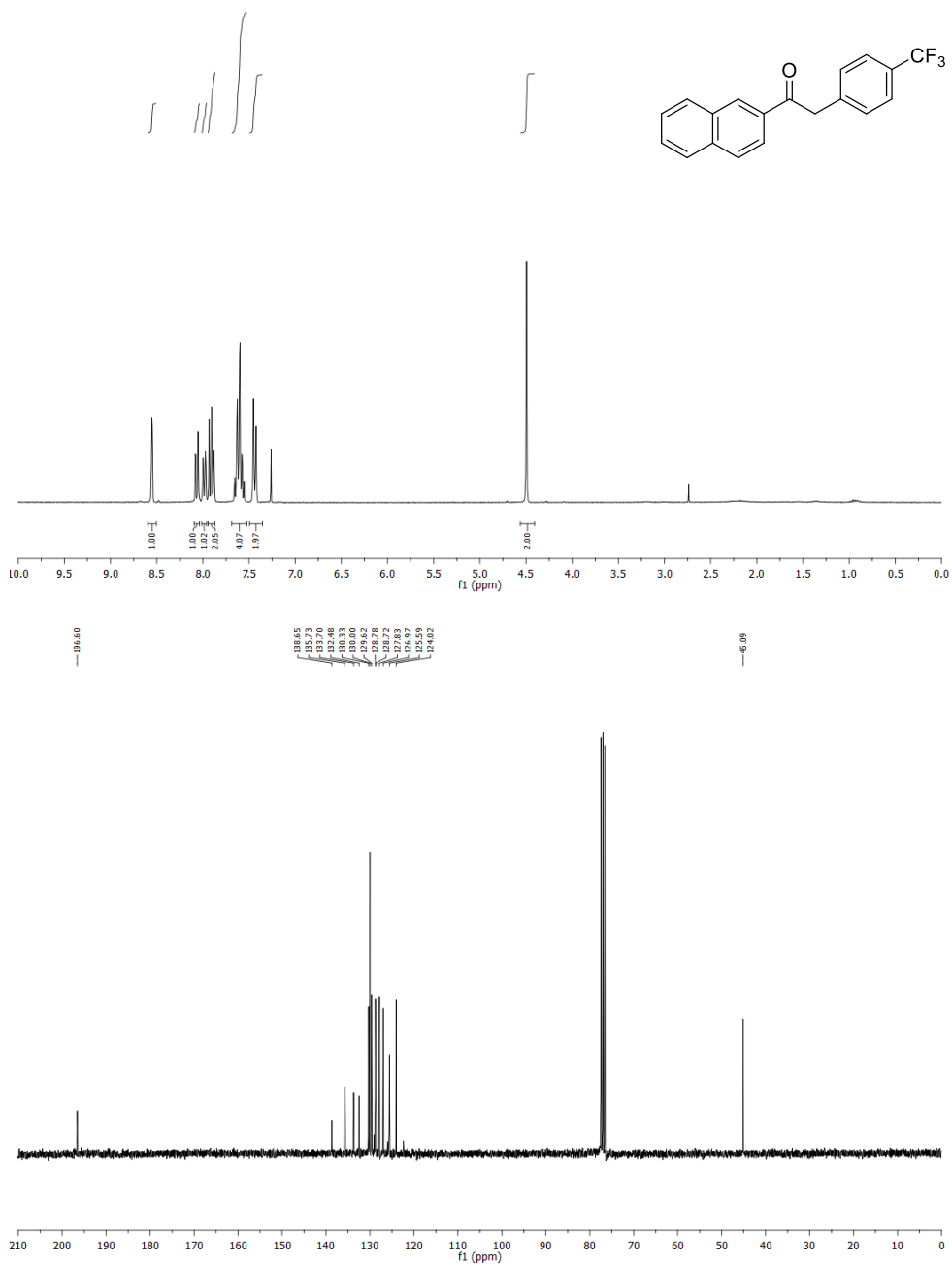


1f: 2-(phenanthren-9-yl)-1-phenylethan-1-one

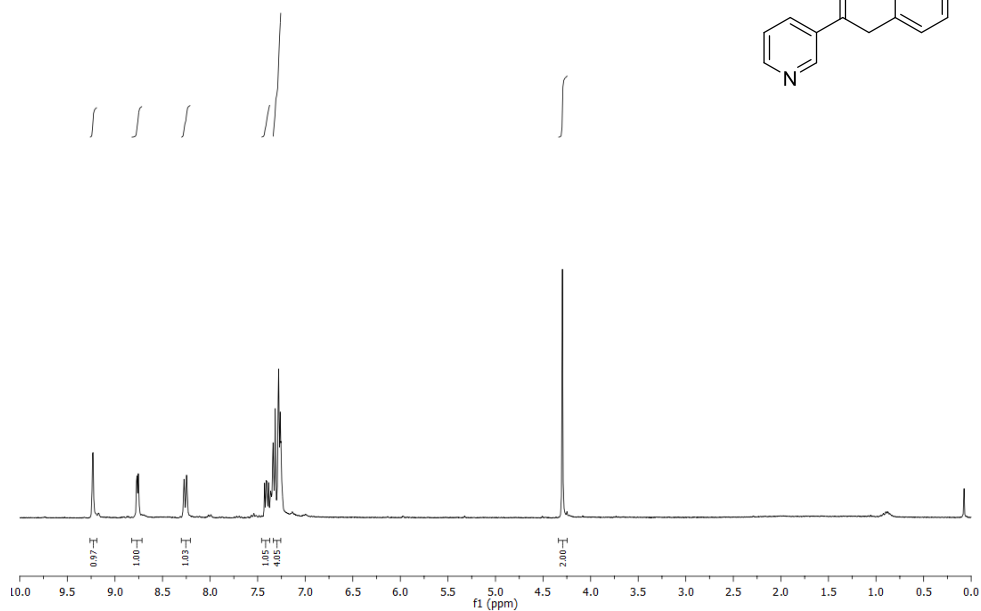
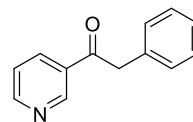


Appendix of spectra

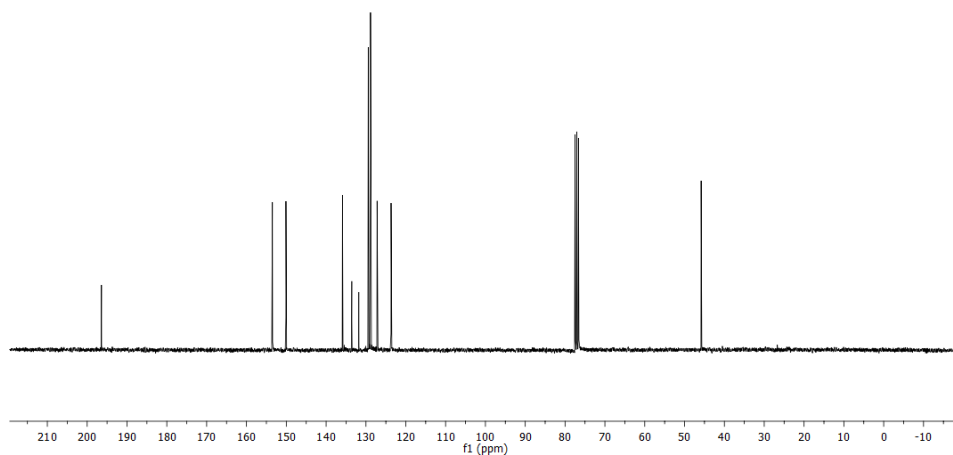
1g: 1-(naphthalen-2-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one



1h: 2-phenyl-1-(pyridin-3-yl)ethan-1-one

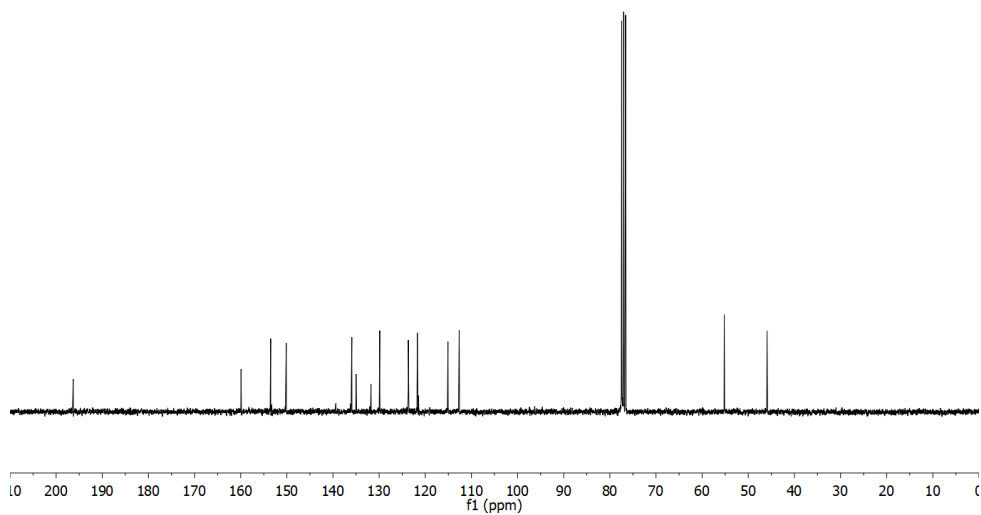
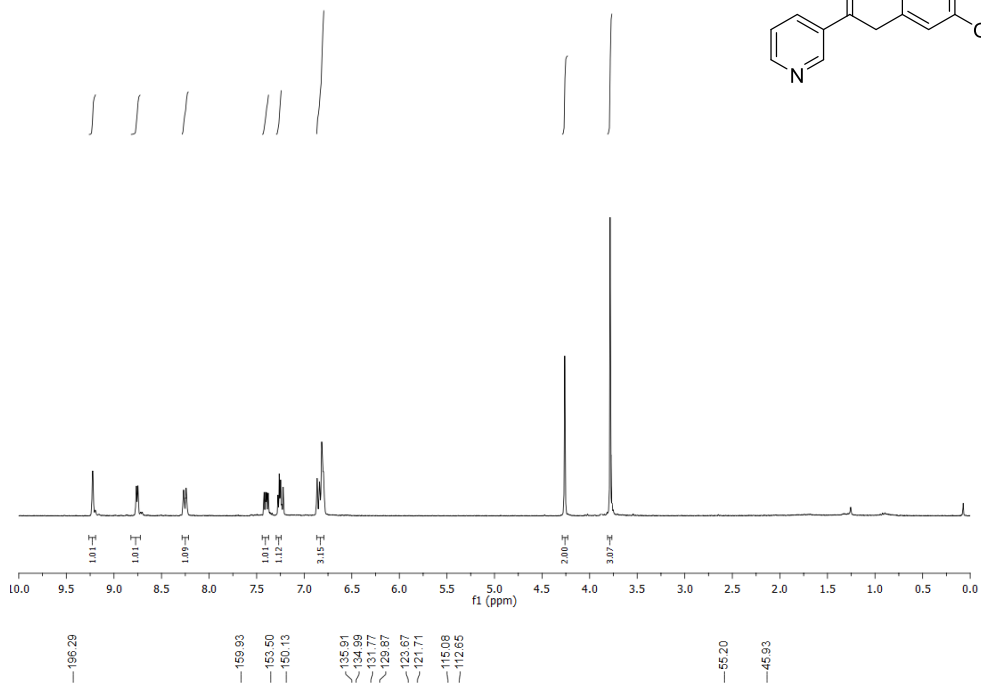
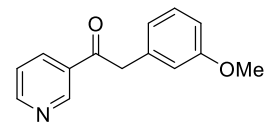


196.41, 153.49, 150.08, 138.85, 133.85, 131.79, 129.62, 127.20, 123.69, 46.04

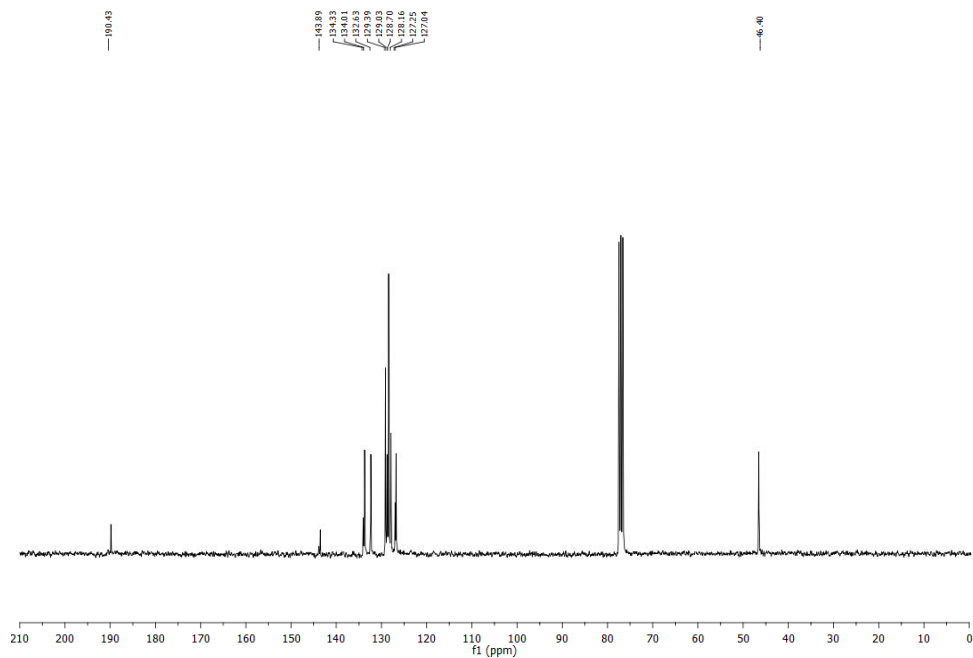
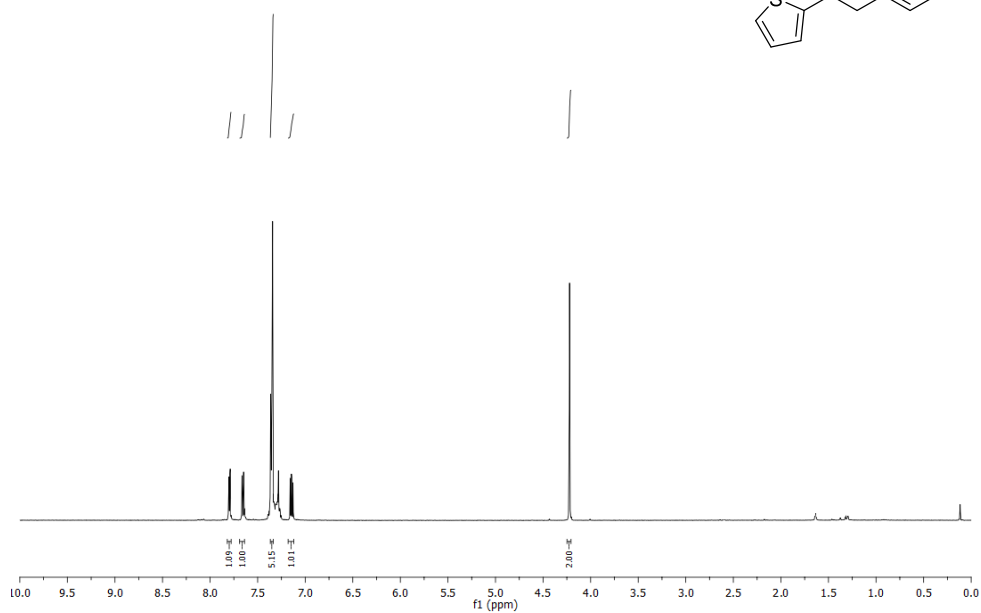
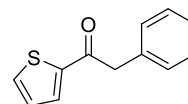


Appendix of spectra

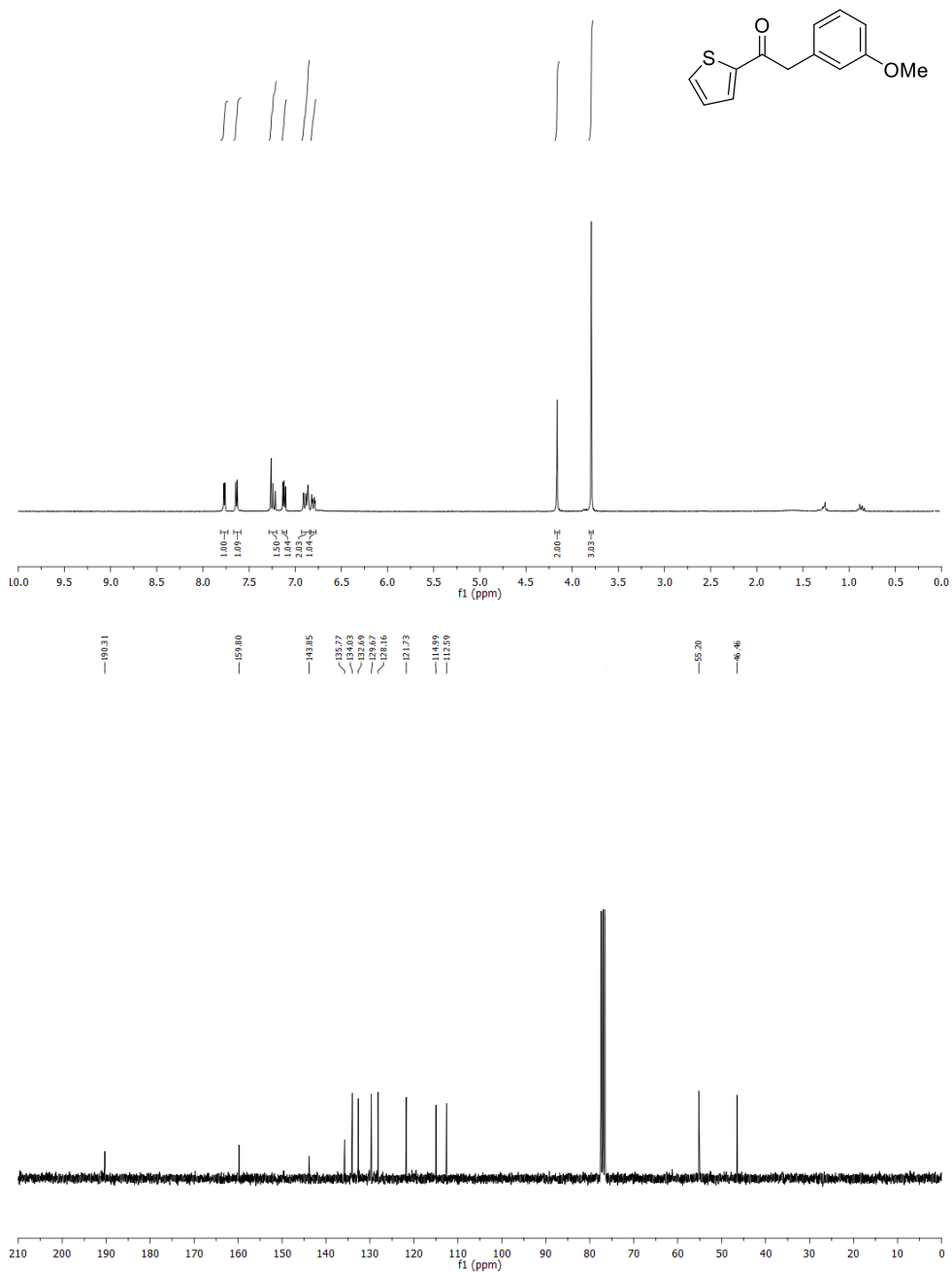
1i: 2-(3-methoxyphenyl)-1-(pyridin-3-yl)ethan-1-one



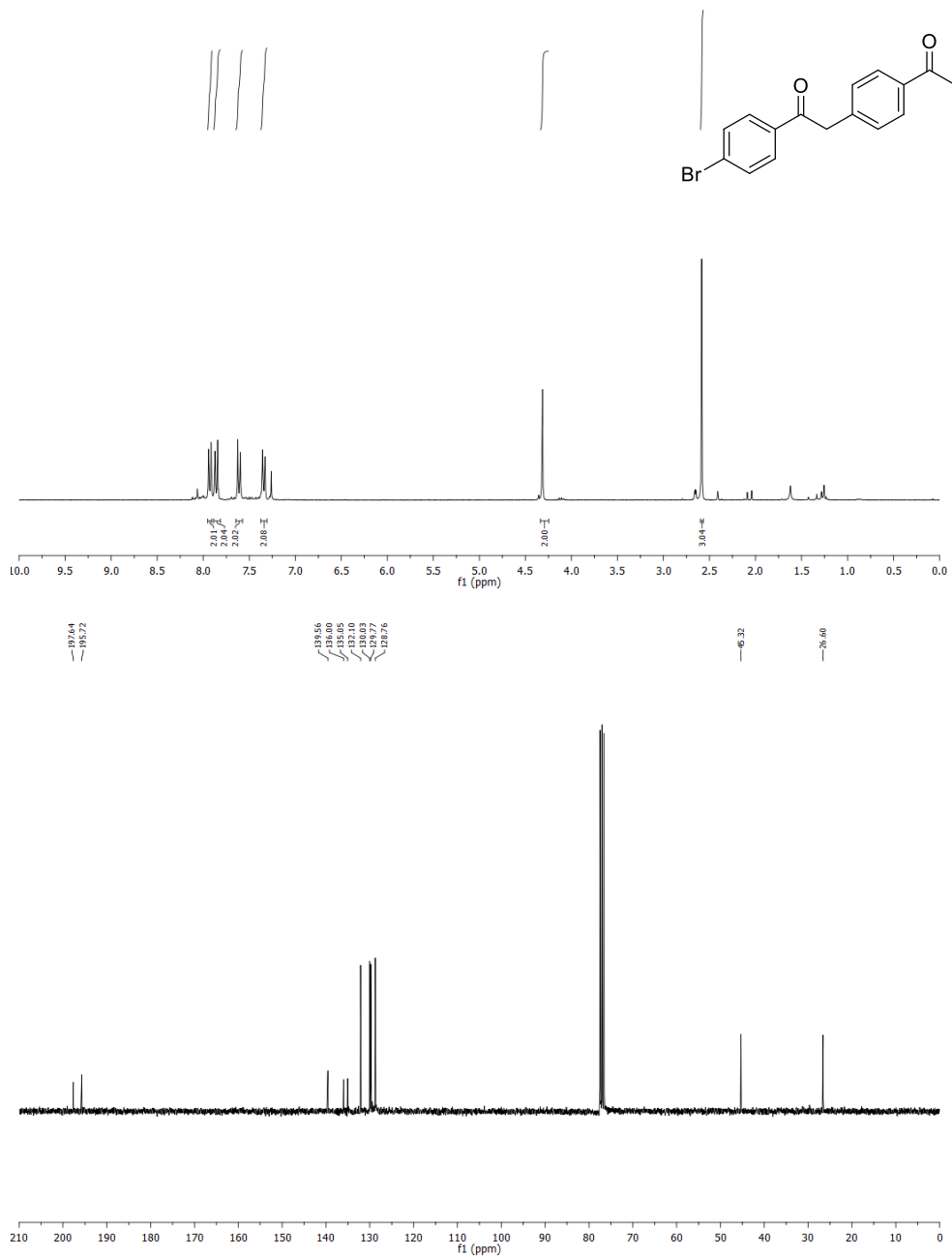
1j: 2-phenyl-1-(thiophen-2-yl)ethan-1-one



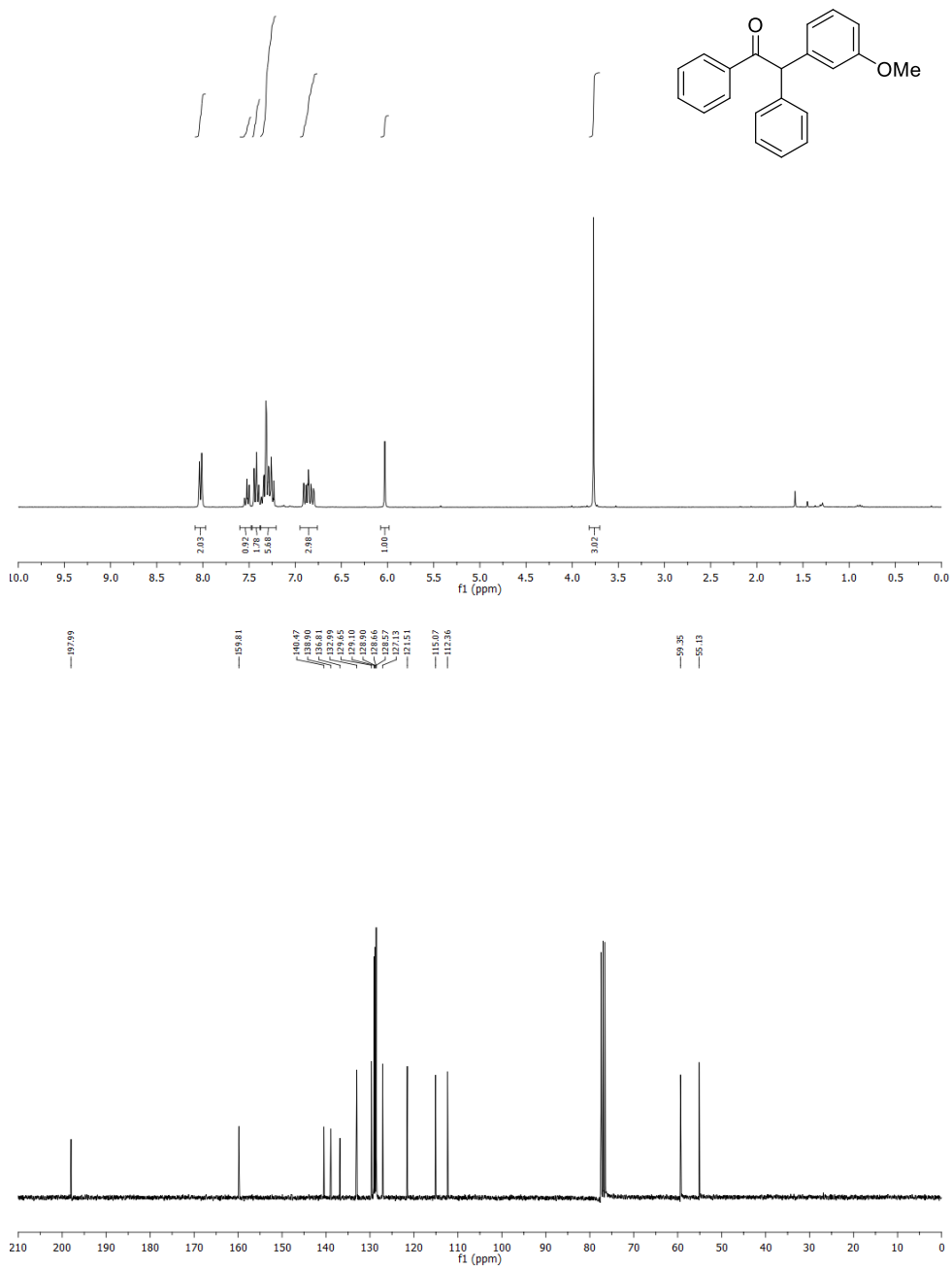
1k: 2-(3-methoxyphenyl)-1-(thiophen-2-yl)ethan-1-one

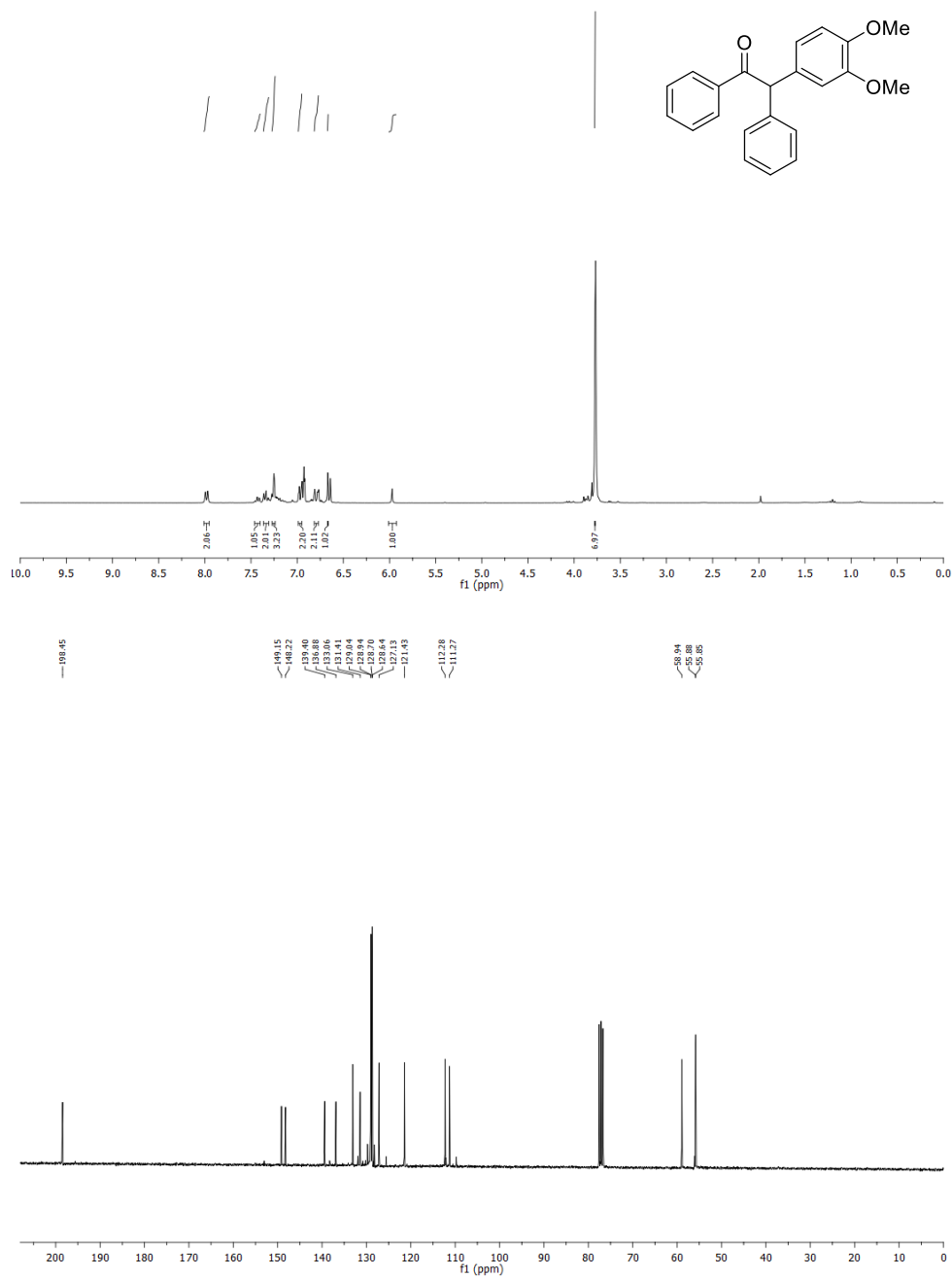


11: 2-(4-acetylphenyl)-1-(4-bromophenyl)ethan-1-one

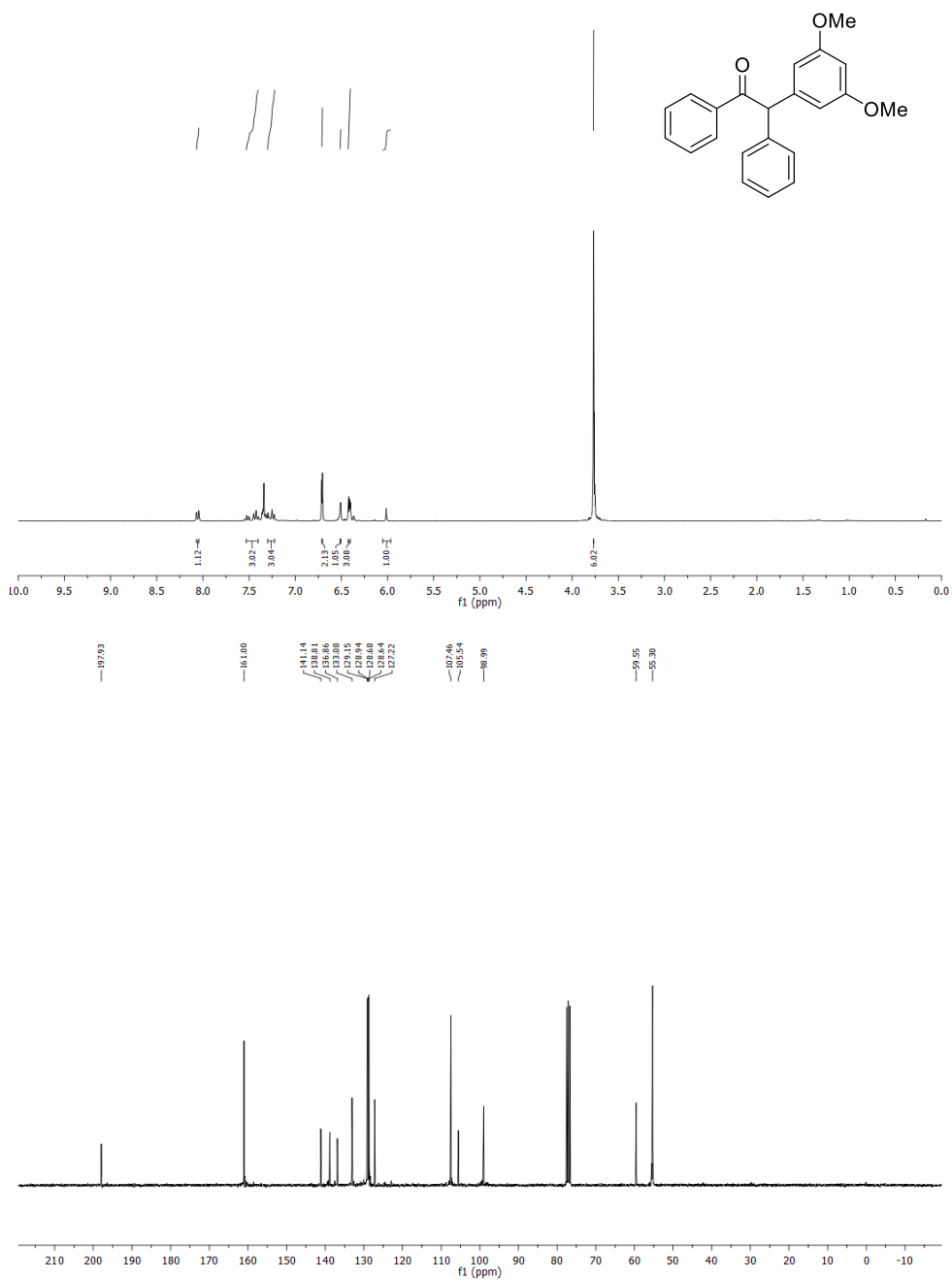


3ab: 2-(3-methoxyphenyl)-1,2-diphenylethanone

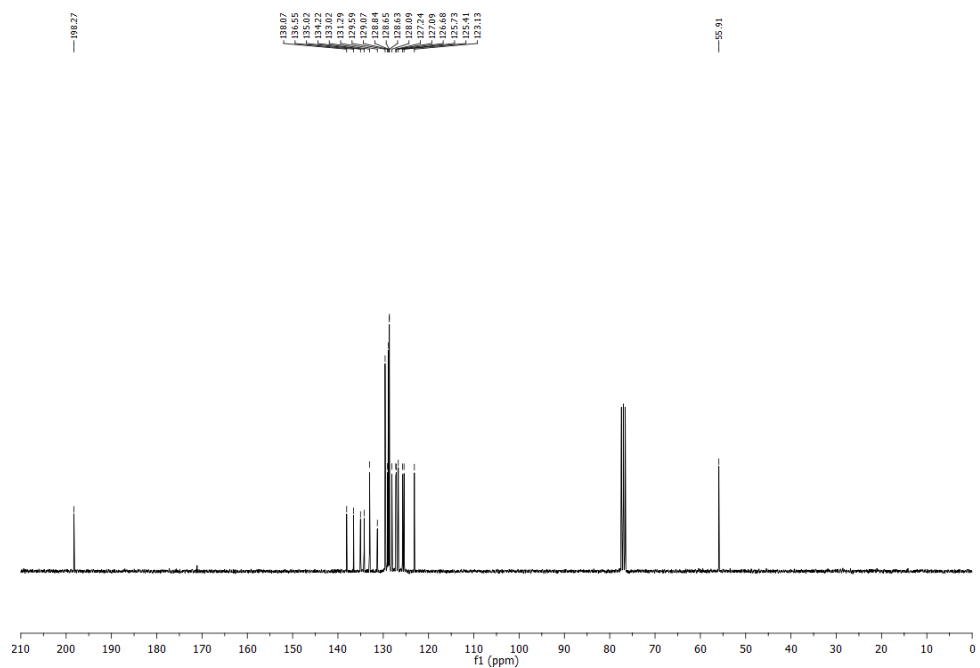
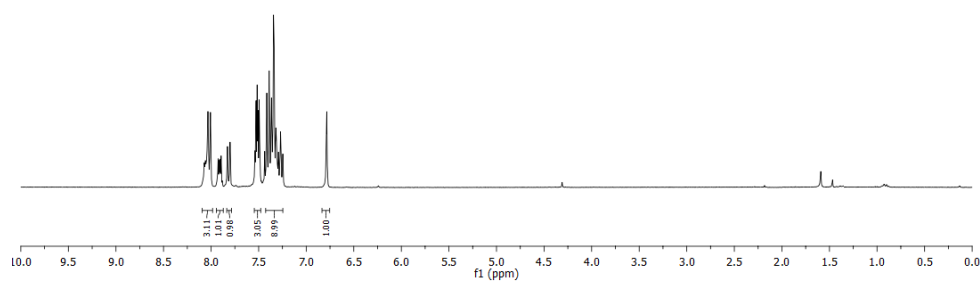
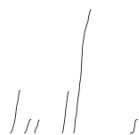
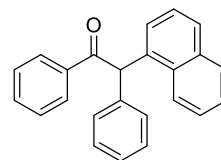


3ae: 2-(3,4-dimethoxyphenyl)-1,2-diphenylethanone

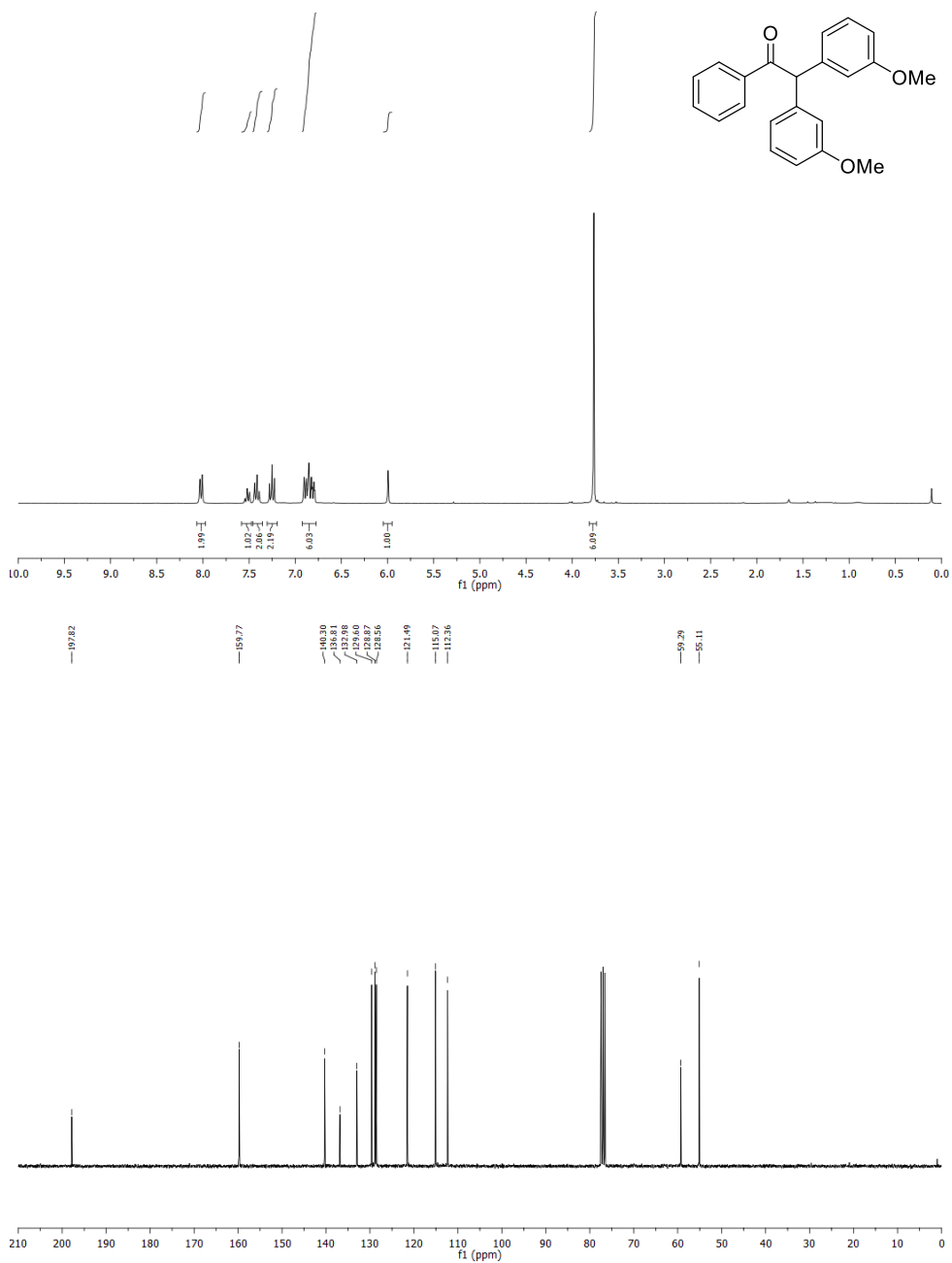
3af: 2-(3,5-dimethoxyphenyl)-1,2-diphenylethanone



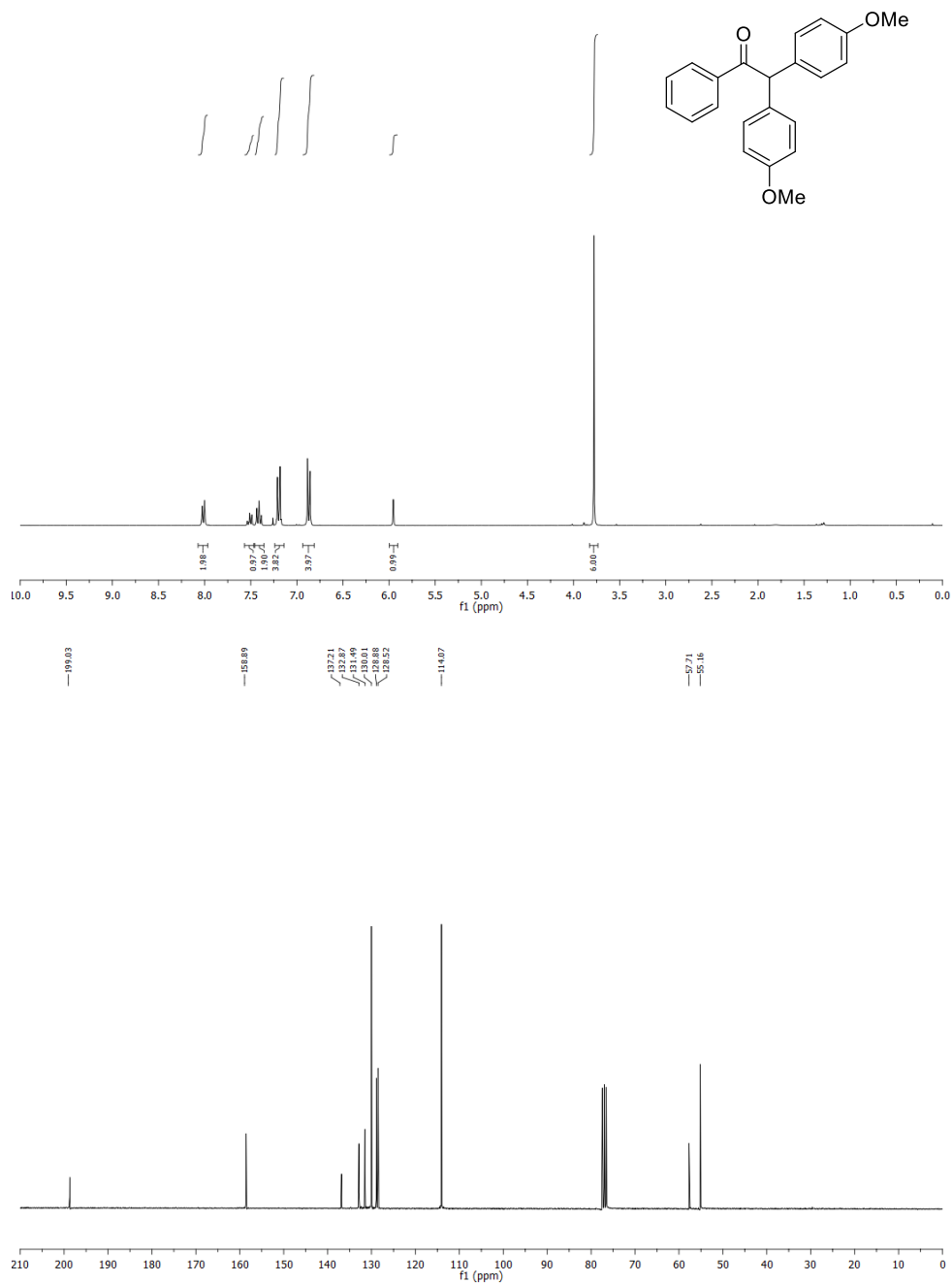
3ah: 2-(naphthalen-1-yl)-1,2-diphenylethanone



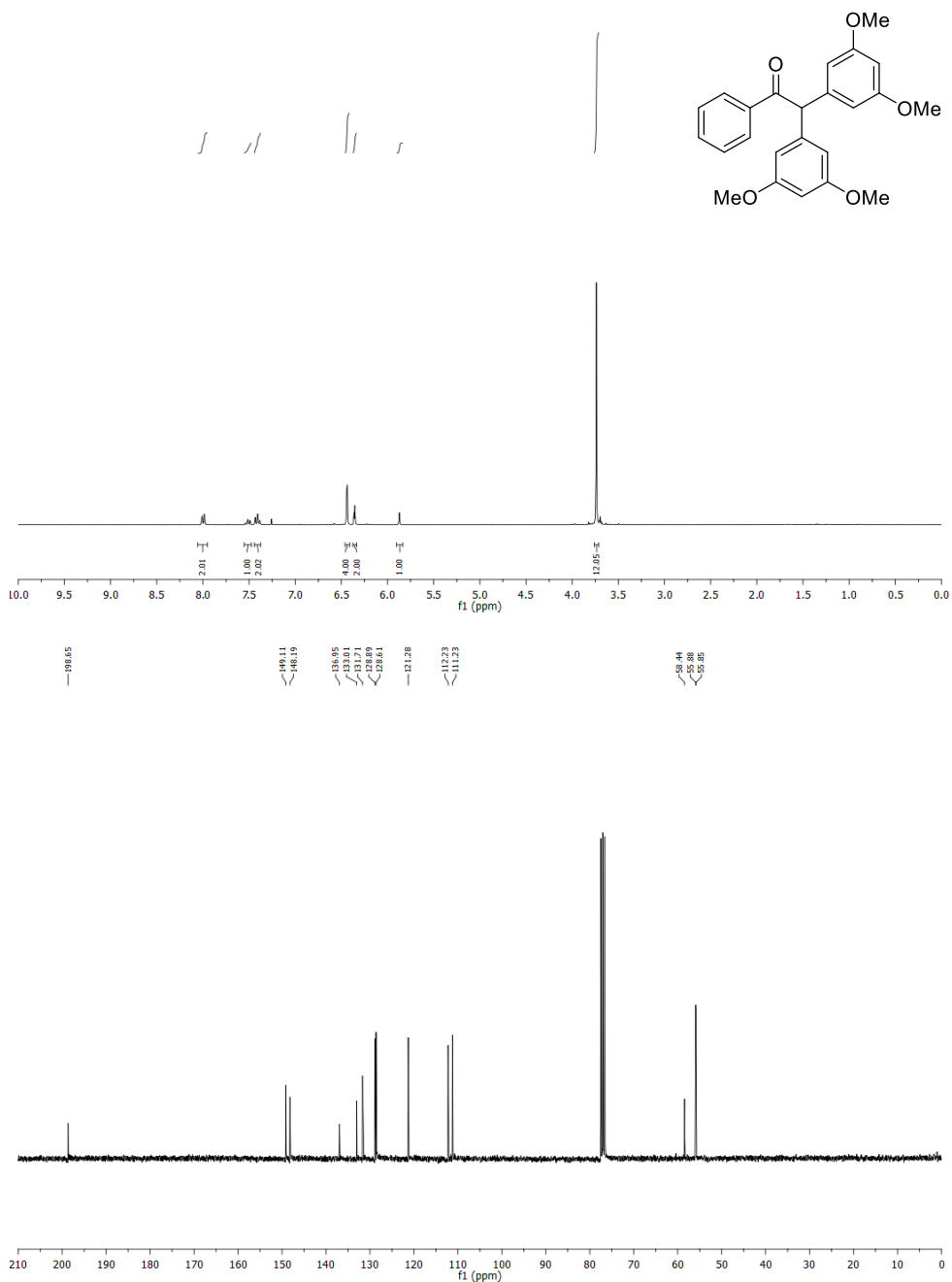
3ai: 2,2-bis(3-methoxyphenyl)-1-phenylethanone



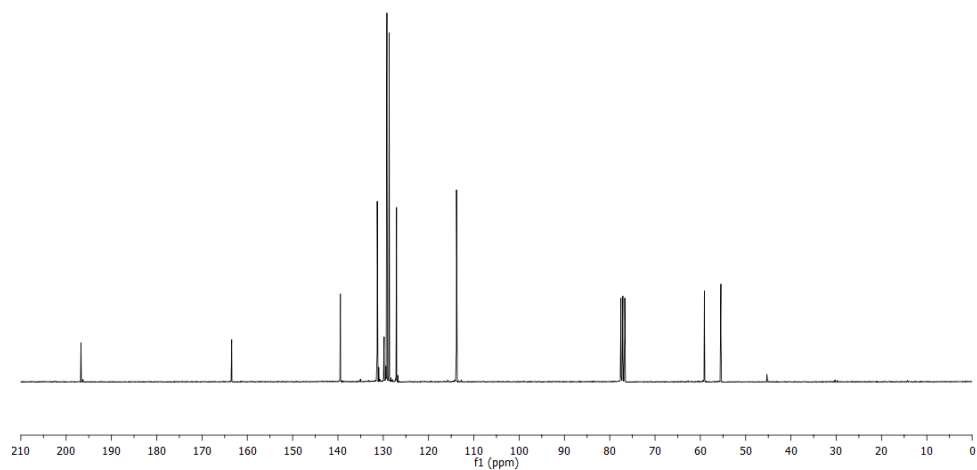
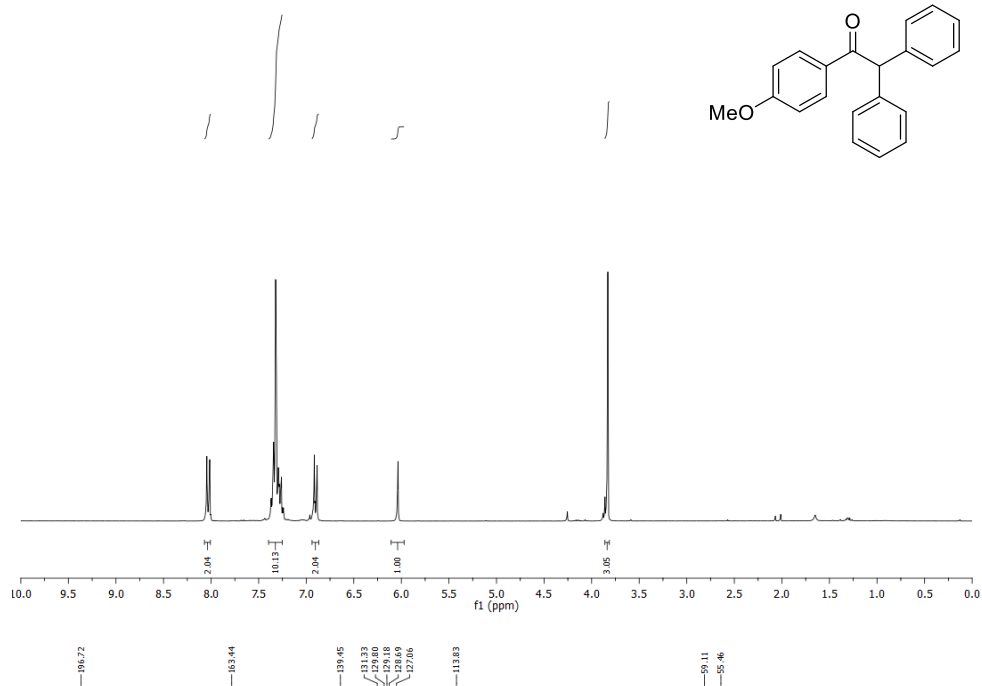
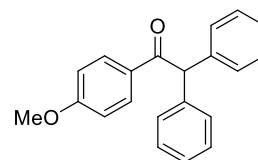
3aj: 2,2-bis(4-methoxyphenyl)-1-phenylethanone



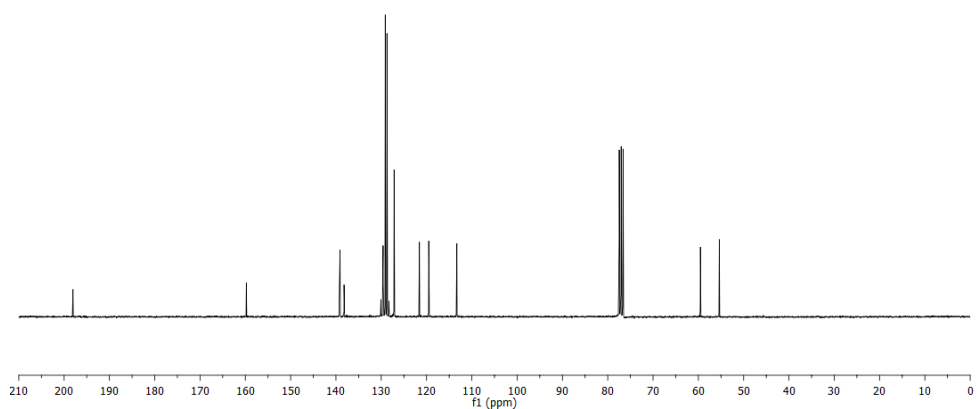
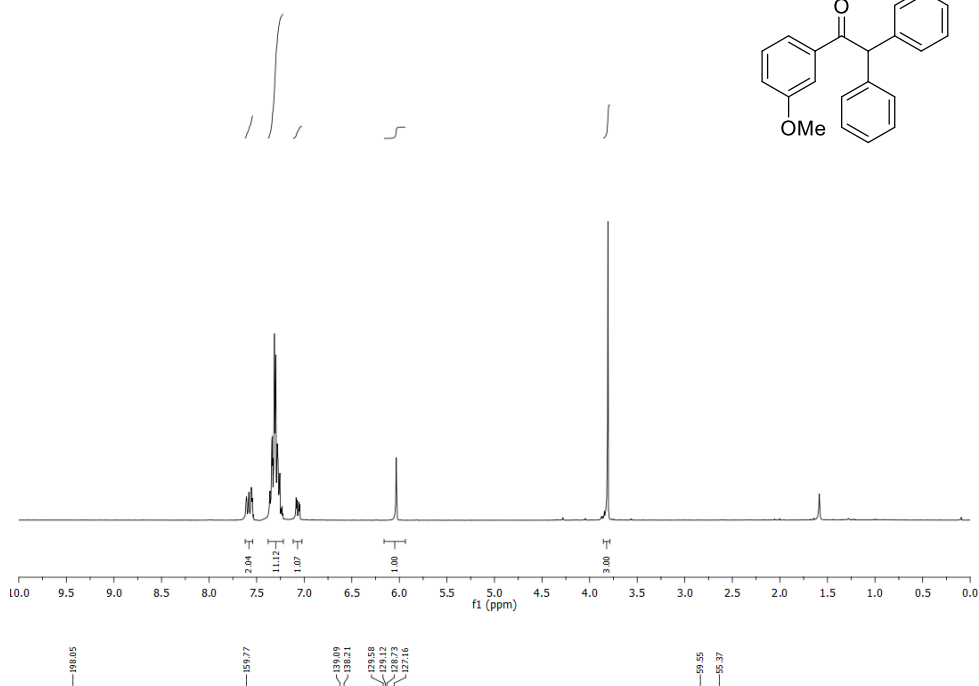
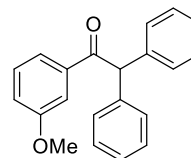
3ak: 2,2-bis(3,5-dimethoxyphenyl)-1-phenylethanone



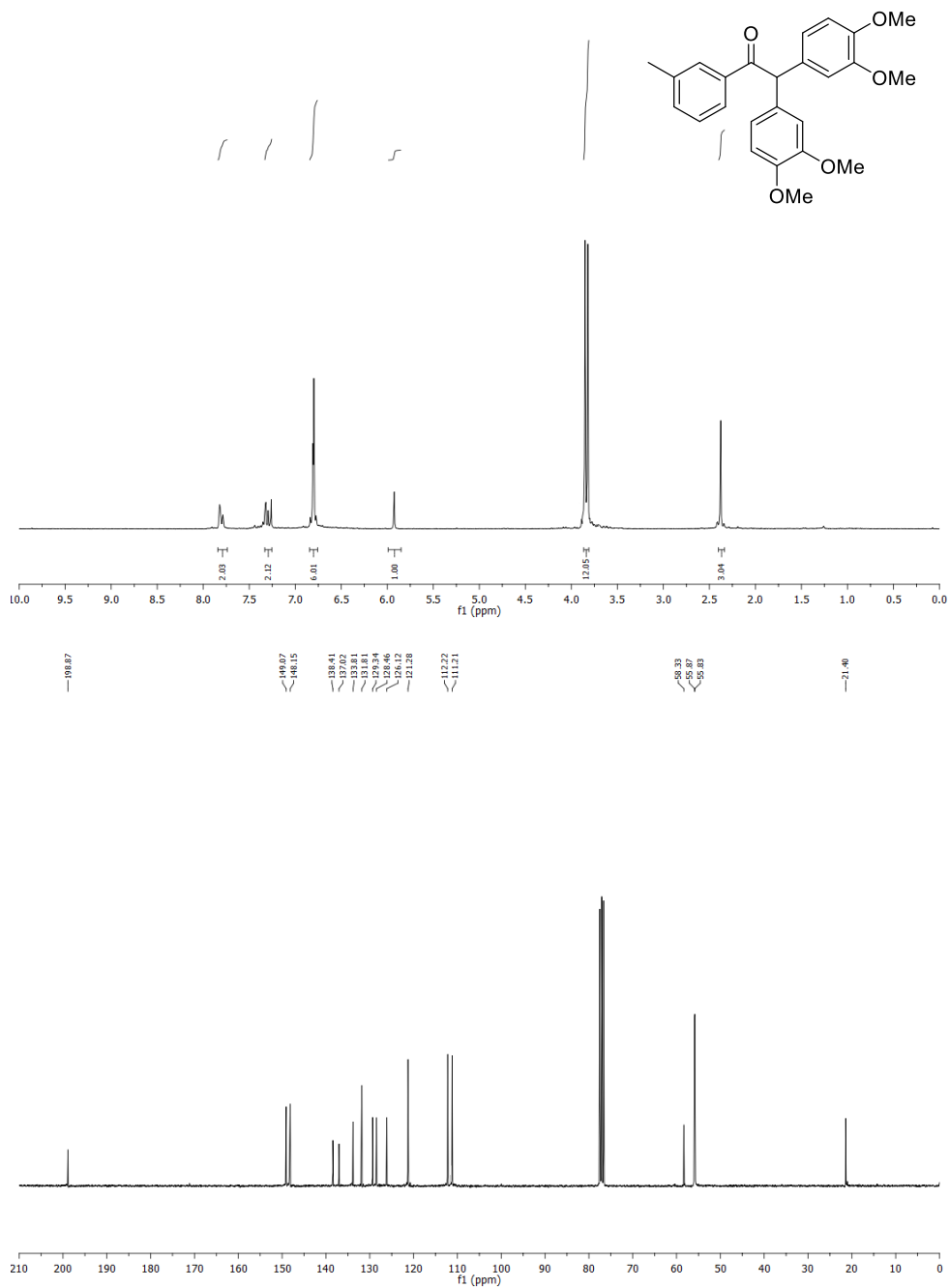
3ba: 1-(4-methoxyphenyl)-2,2-diphenylethanone



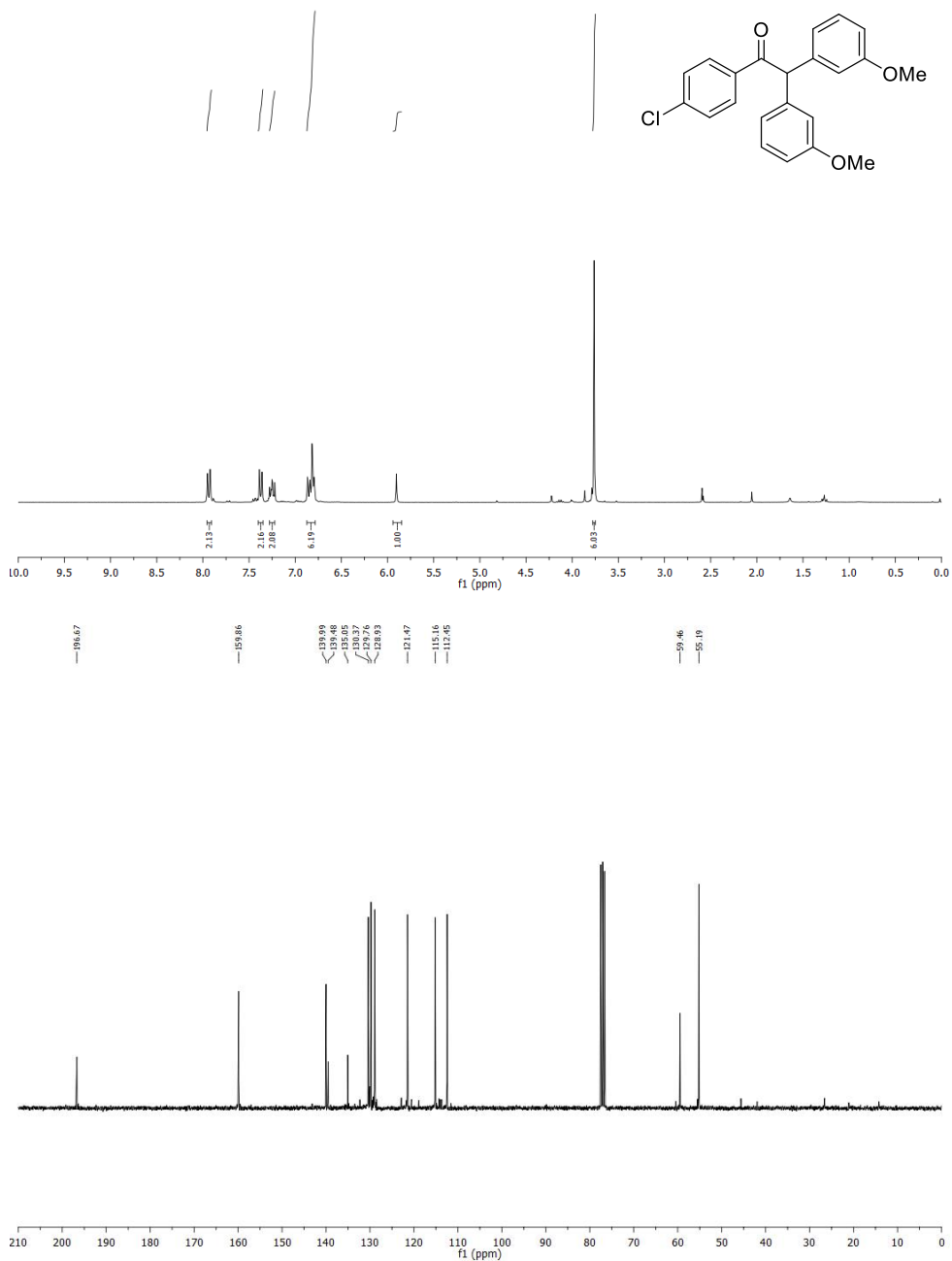
3bb: 1-(3-methoxyphenyl)-2,2-diphenylethan-1-one



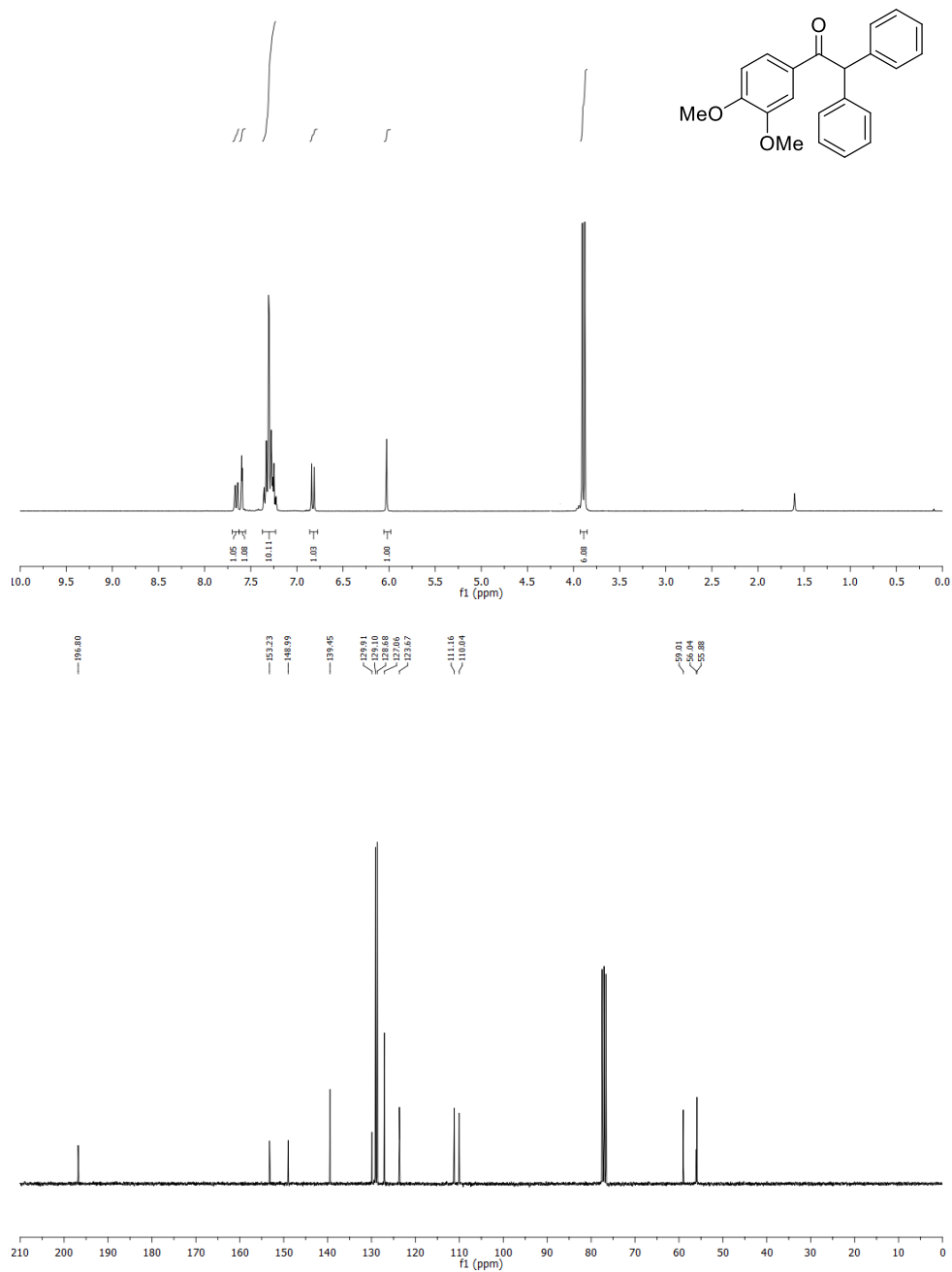
3bc: 2,2-bis(3,4-dimethoxyphenyl)-1-(m-tolyl)ethanone



3bf: 1-(4-chlorophenyl)-2,2-bis(3-methoxyphenyl)ethanone

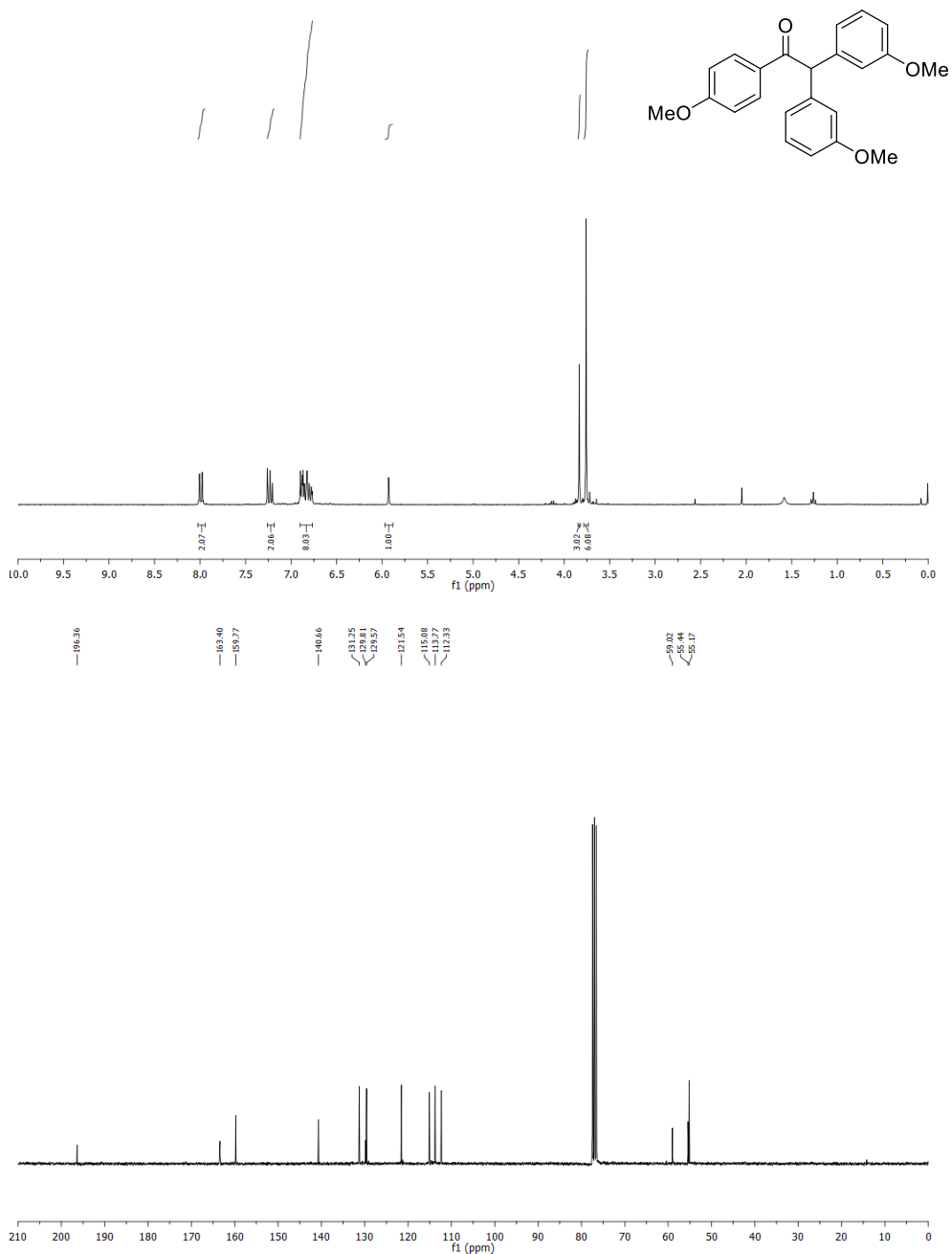


3bg: 1-(3,4-dimethoxyphenyl)-2,2-diphenylethanone

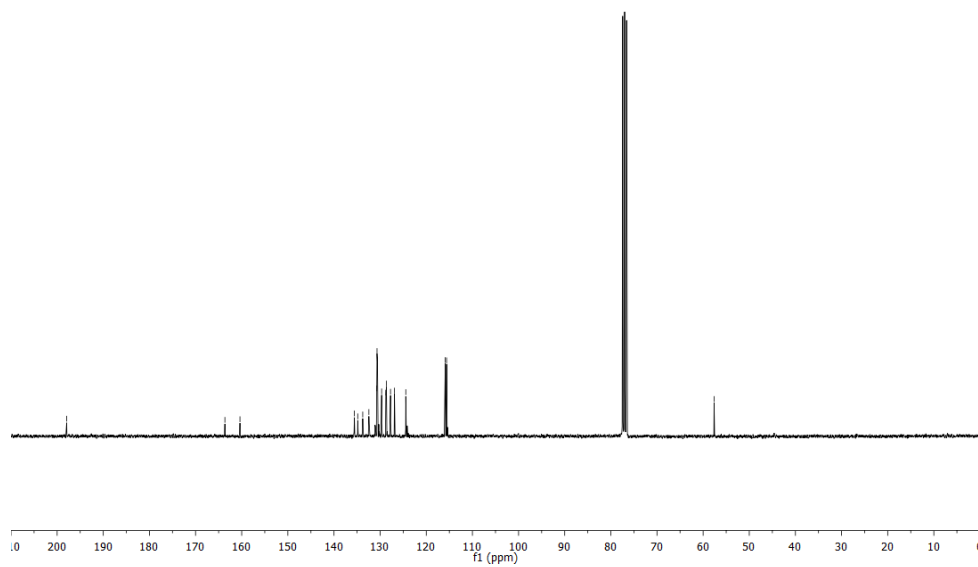
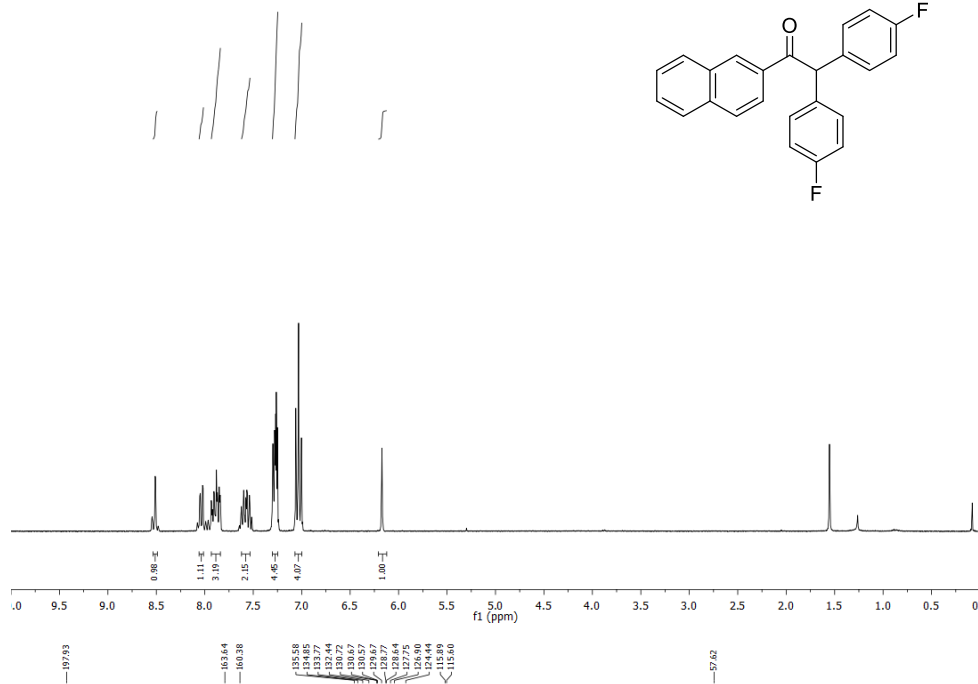
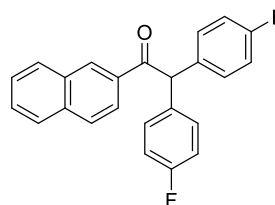


Appendix of spectra

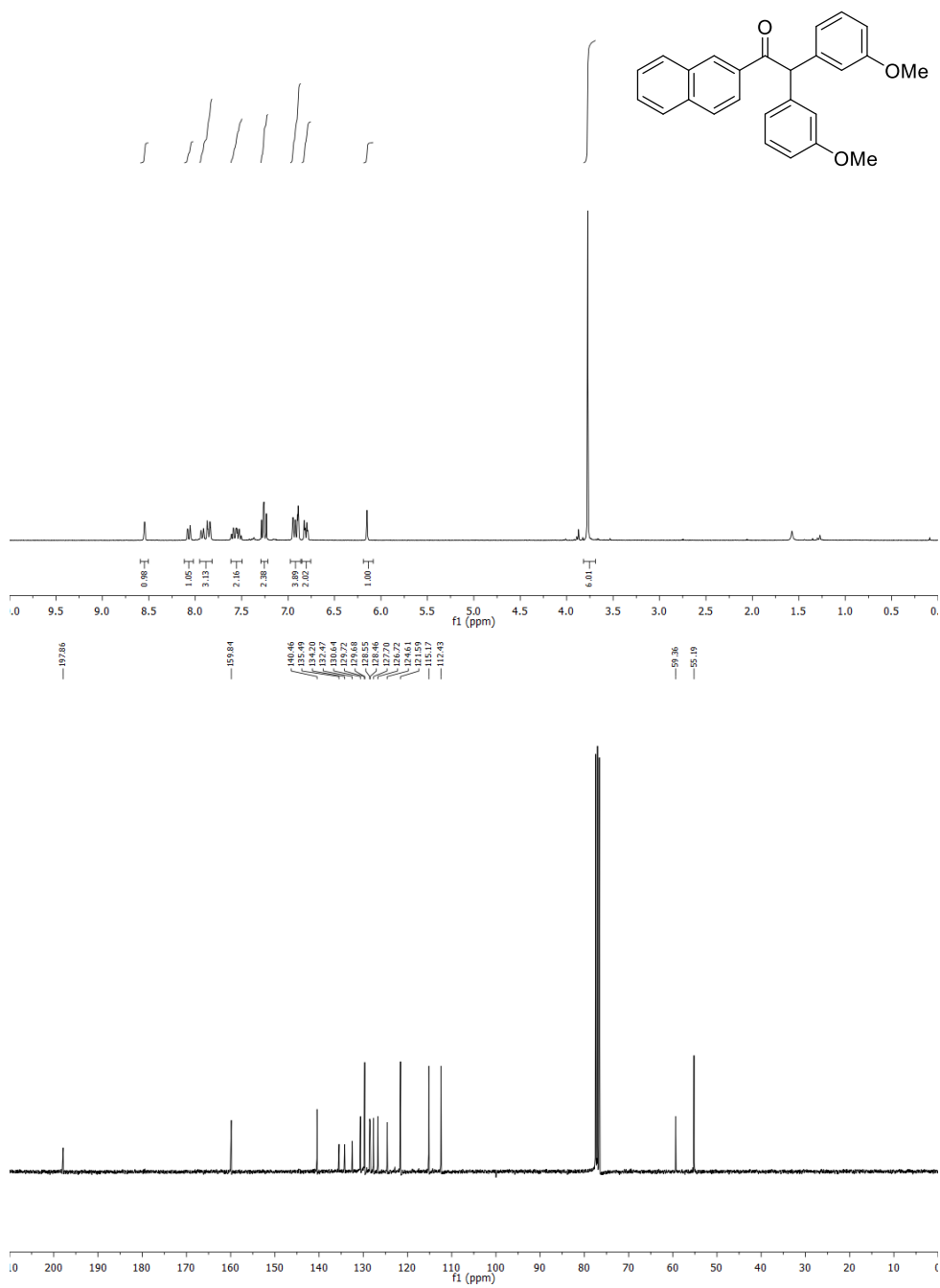
3bh: 2,2-bis(3-methoxyphenyl)-1-(4-methoxyphenyl)ethanone



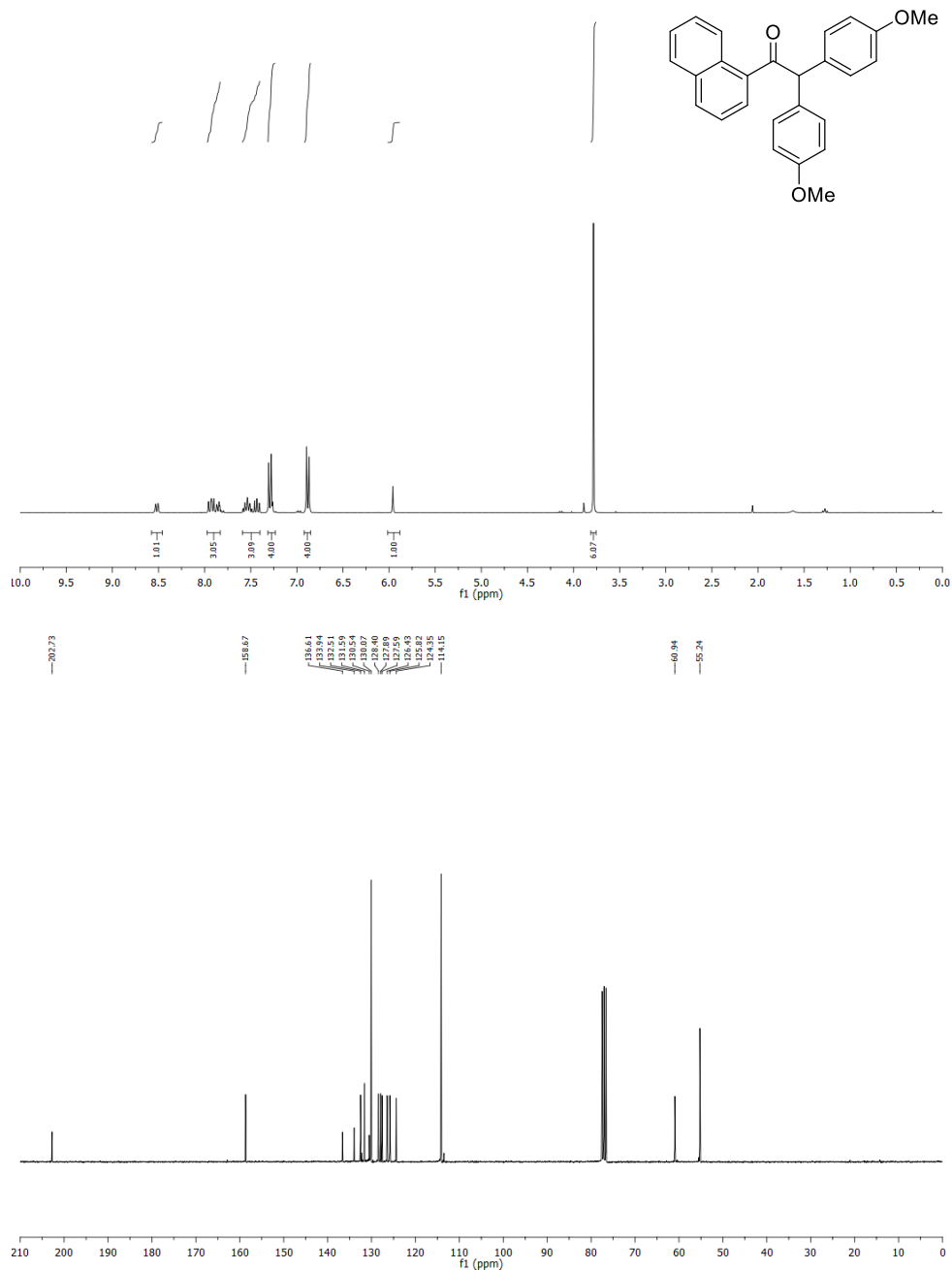
3bj: 2,2-bis(4-fluorophenyl)-1-(naphthalen-2-yl)ethanone



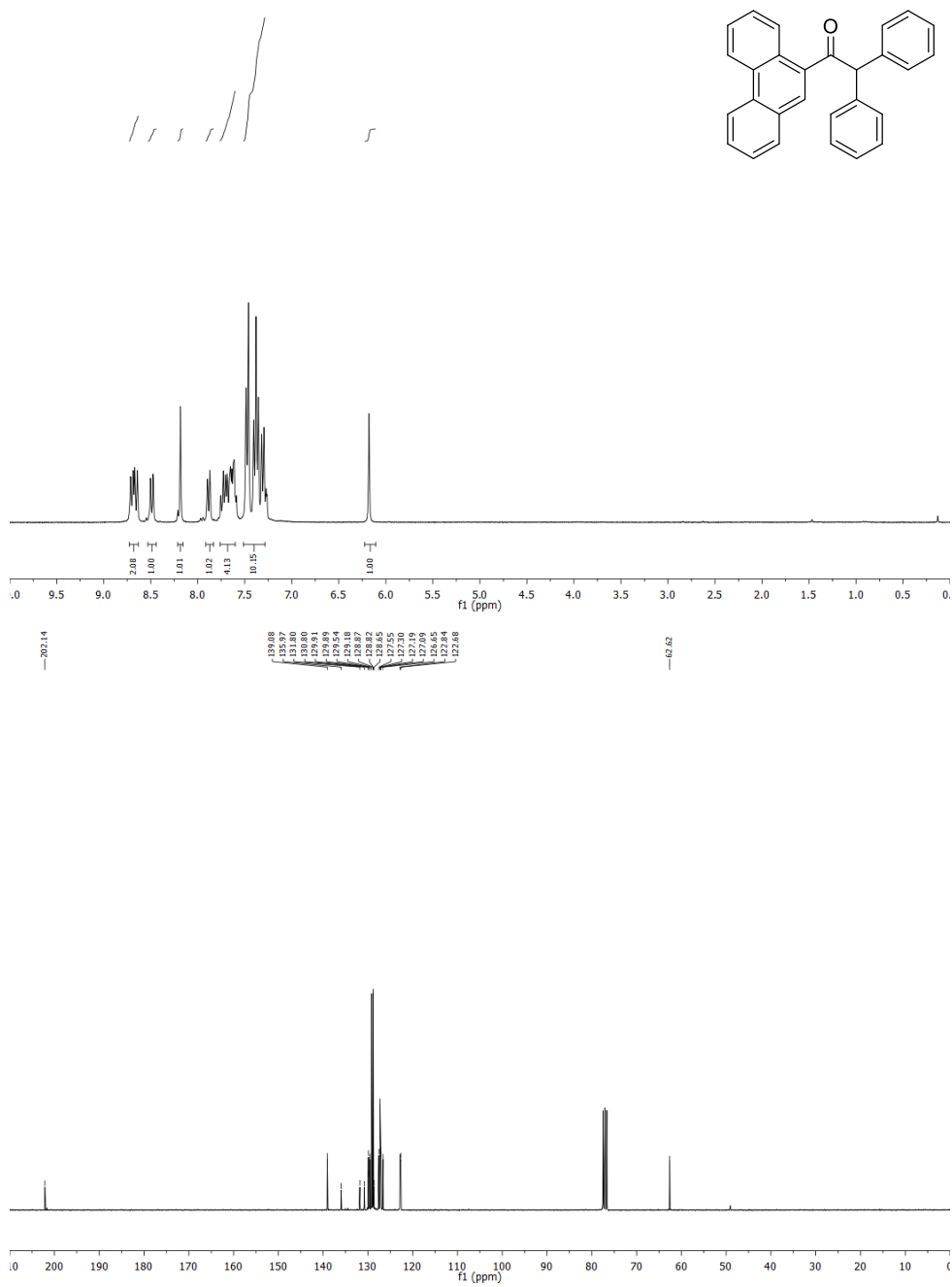
3bk: 2,2-bis(3-methoxyphenyl)-1-(naphthalen-2-yl)ethanone



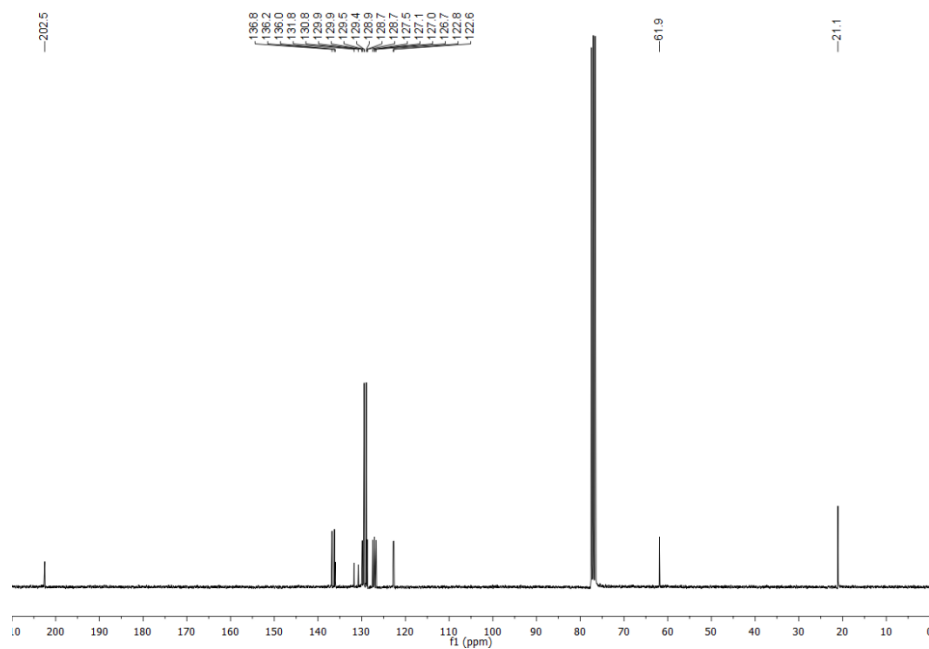
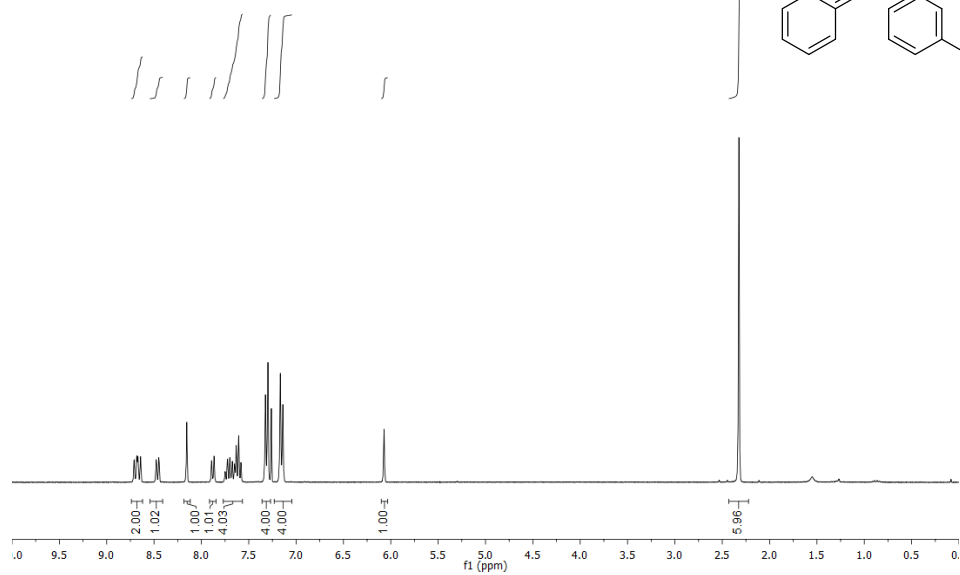
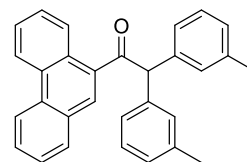
3bm: 2,2-bis(4-methoxyphenyl)-1-(naphthalen-1-yl)ethanone



3bn: 1-(phenanthren-9-yl)-2,2-diphenylethanone

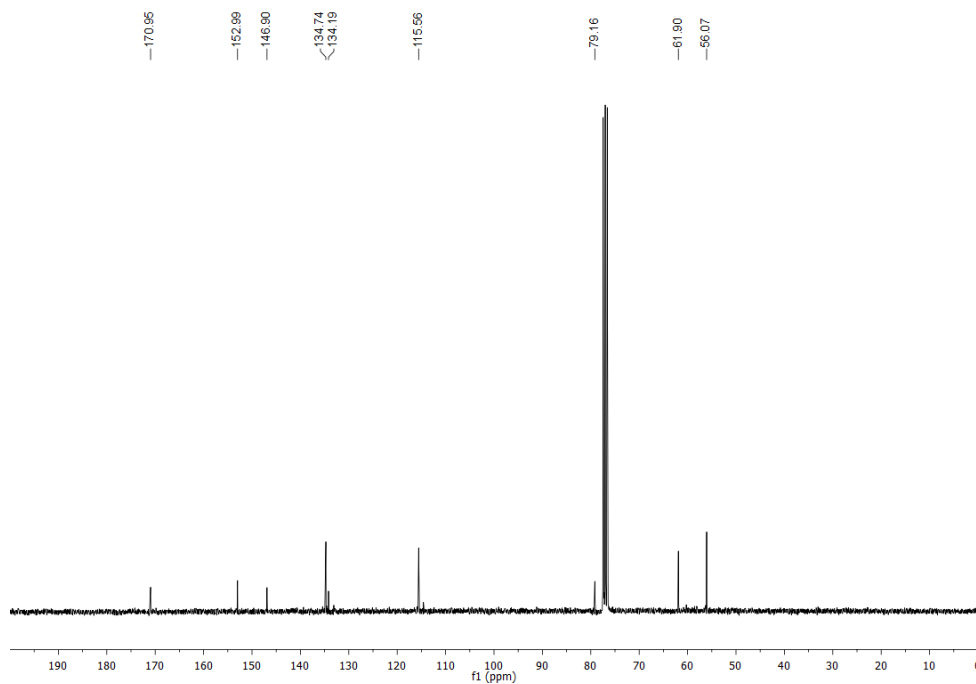
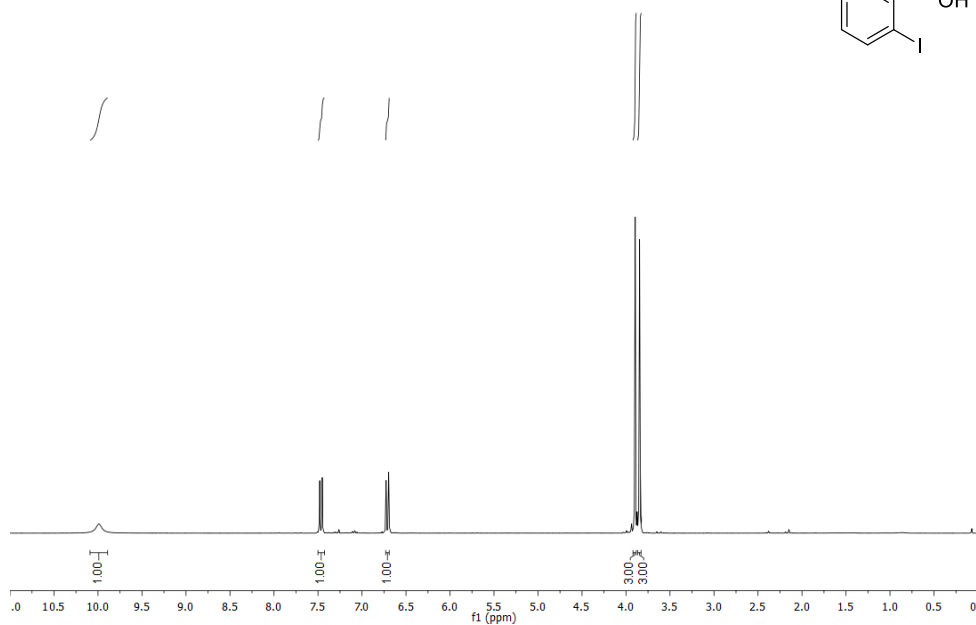
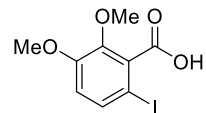


3bo: 1-(phenanthren-9-yl)-2,2-di-m-tolyethan-1-one

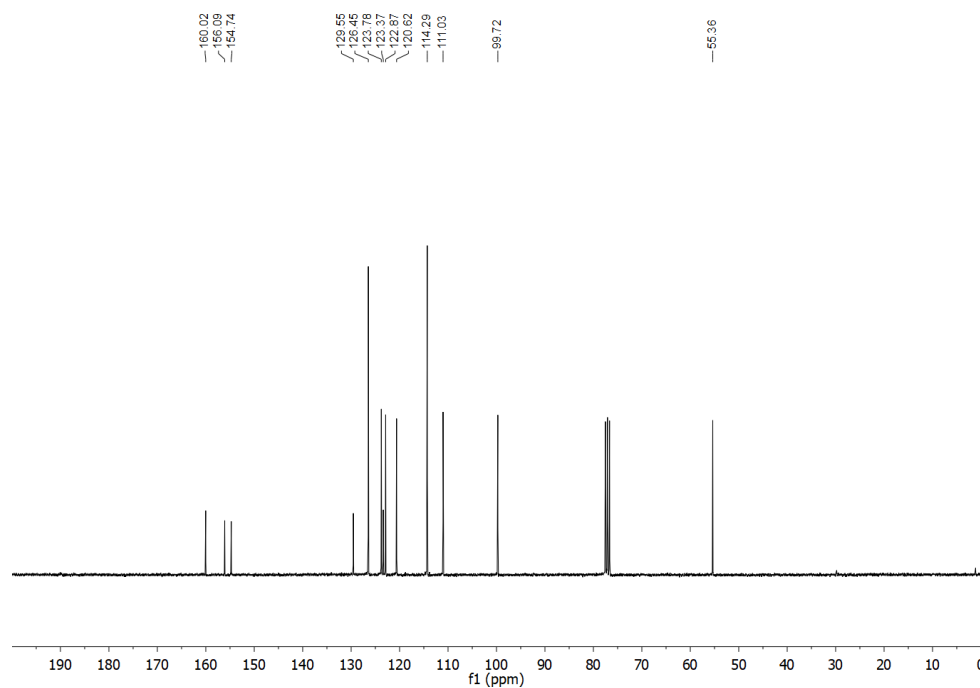
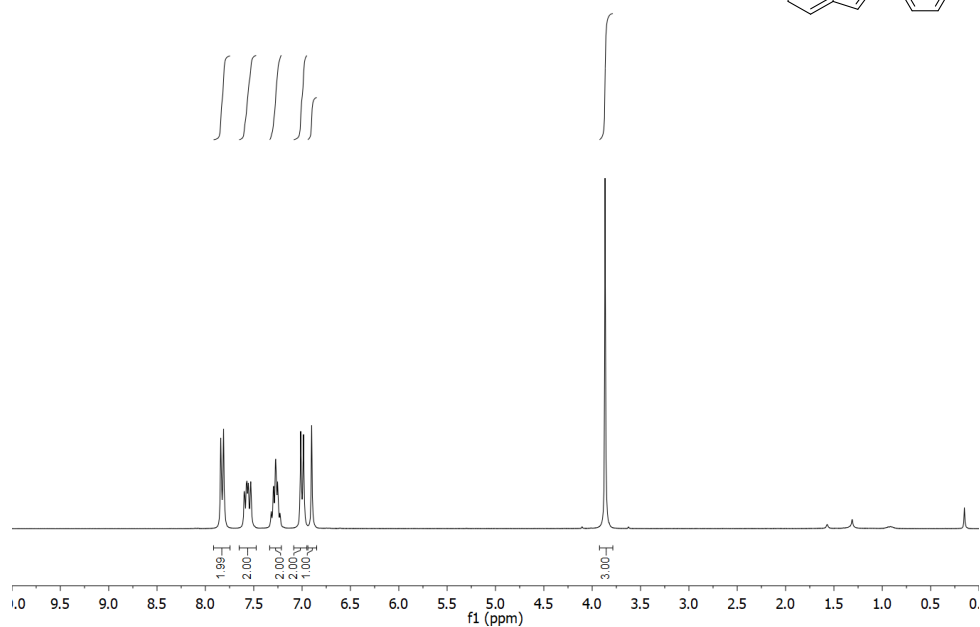
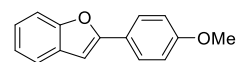


Appendix of spectra

6-Iodo-2,3-dimethoxybenzoic acid

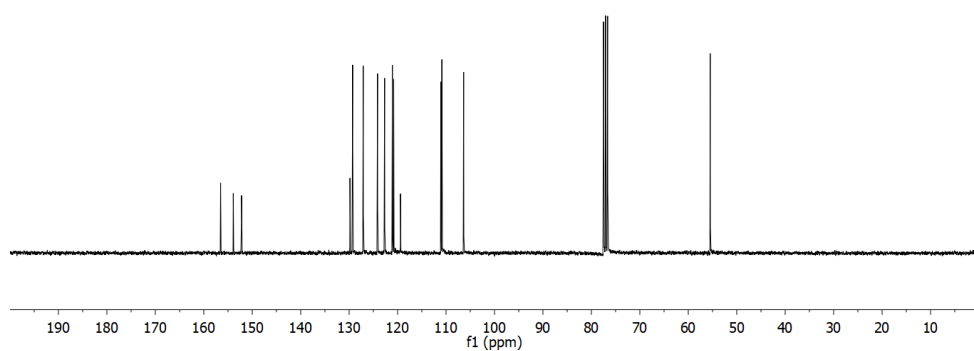
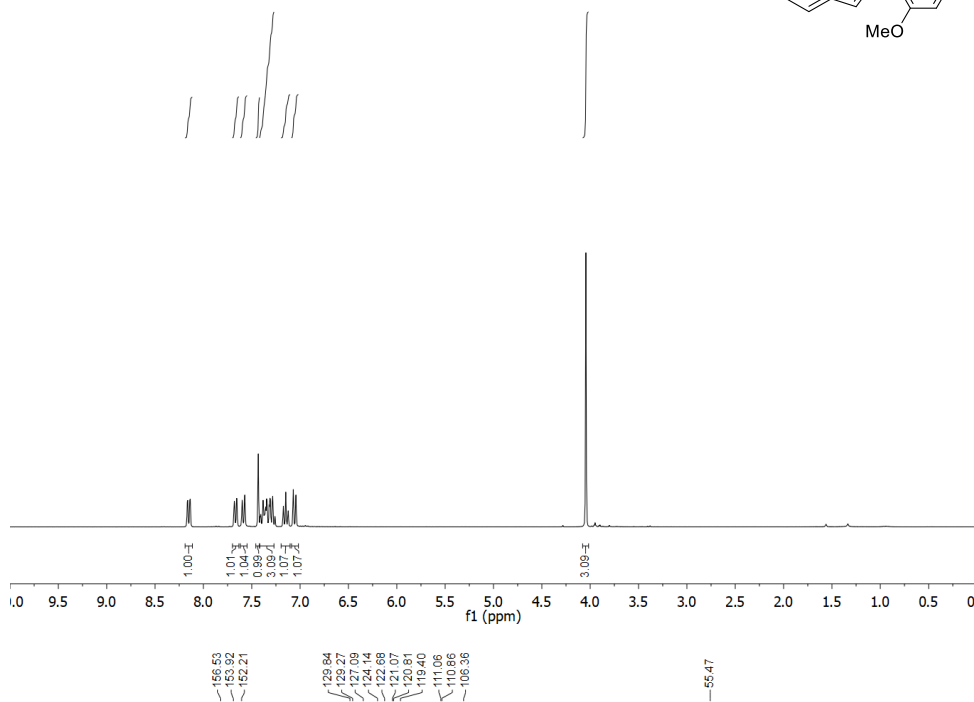
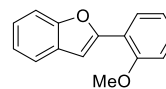


7ab: 2-(4-Methoxyphenyl)benzofuran

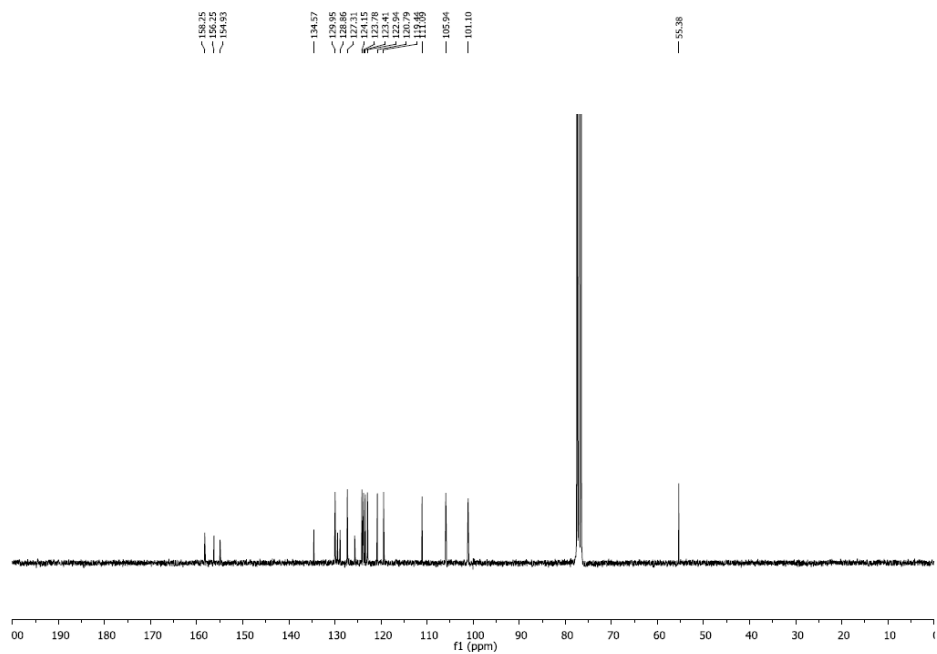
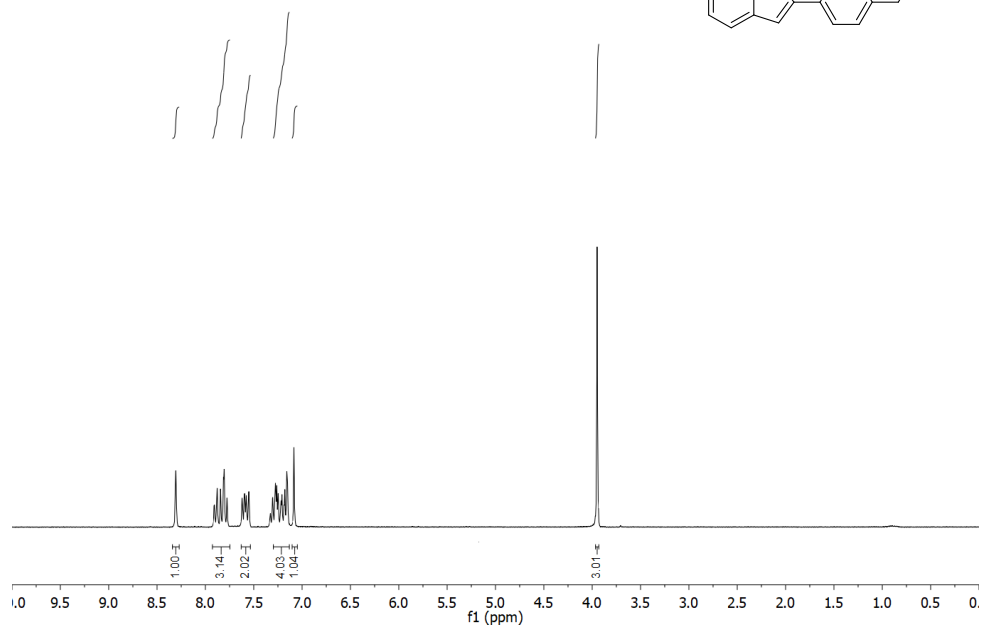
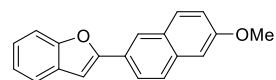


Appendix of spectra

7ac: 2-(2-Methoxyphenyl)benzofuran

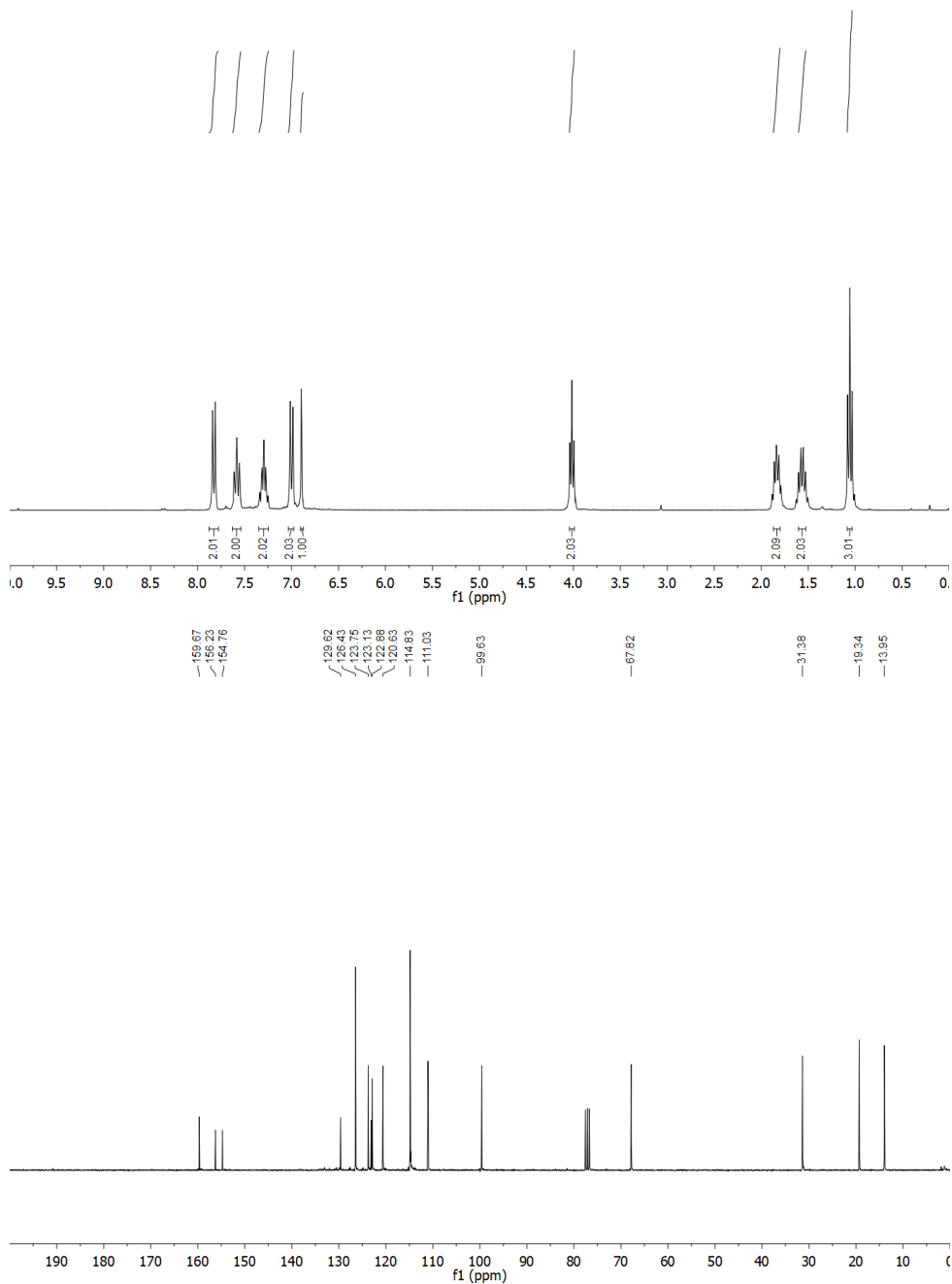
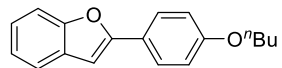


7ad: 2-(6-Methoxynaphthalen-2-yl)benzofuran

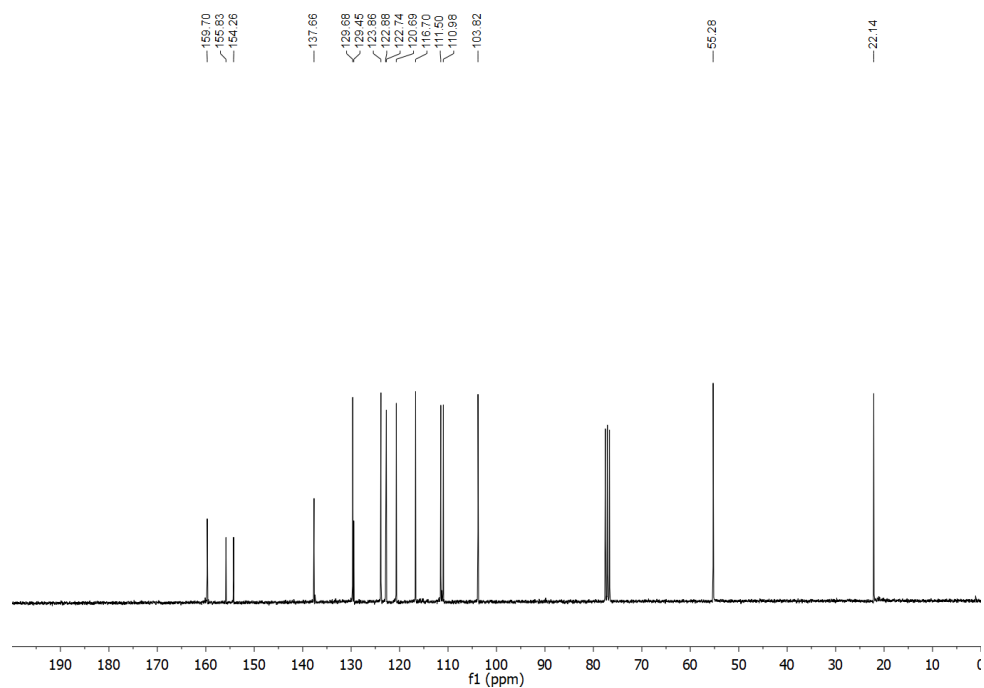
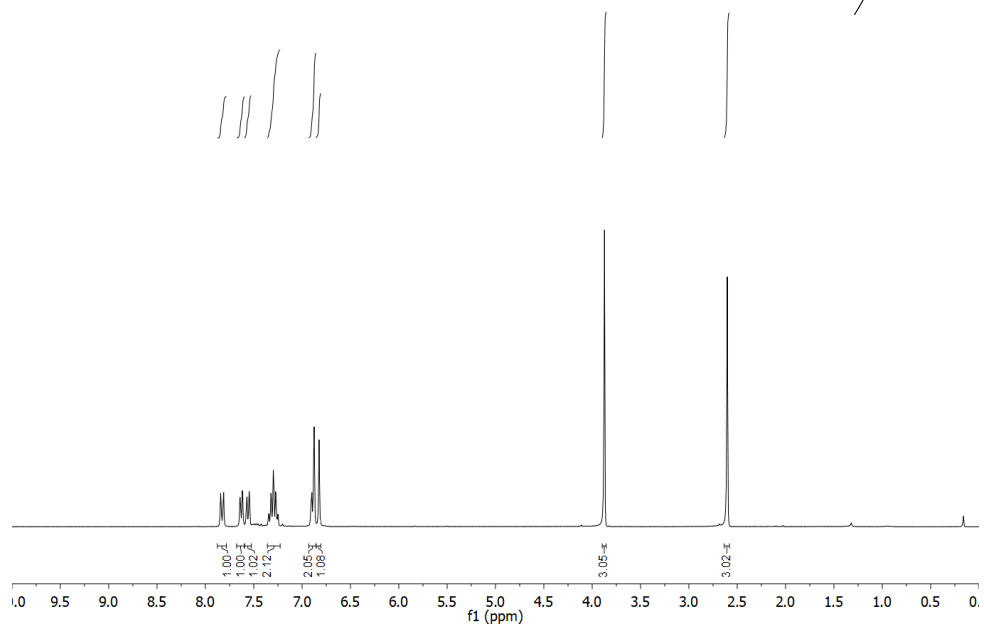
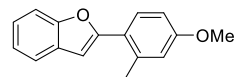


Appendix of spectra

7ae: 2-(4-Butoxyphenyl)benzofuran

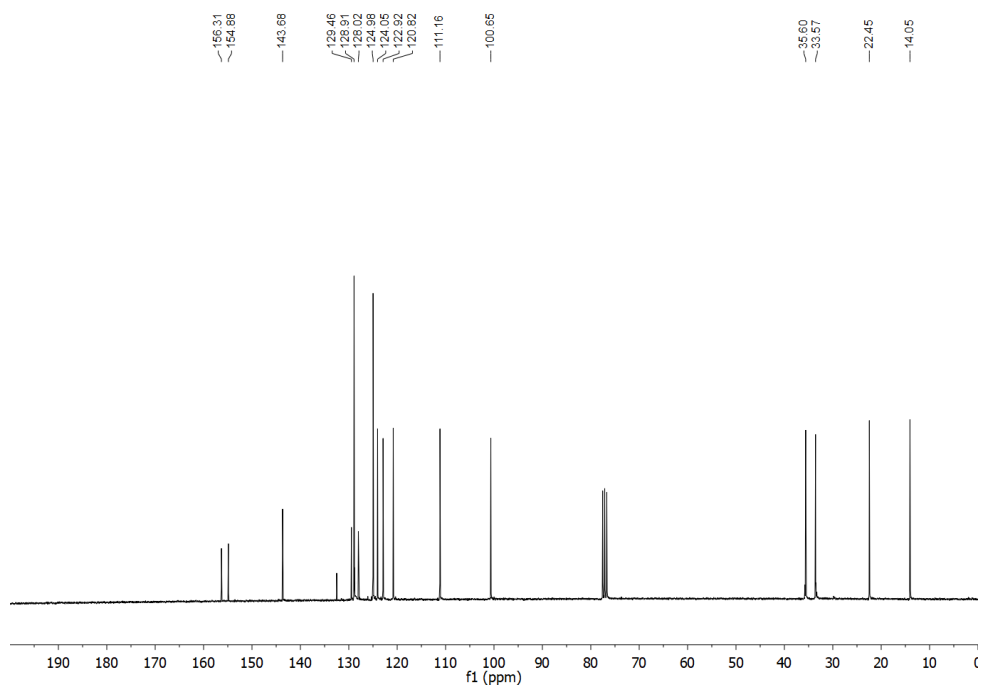
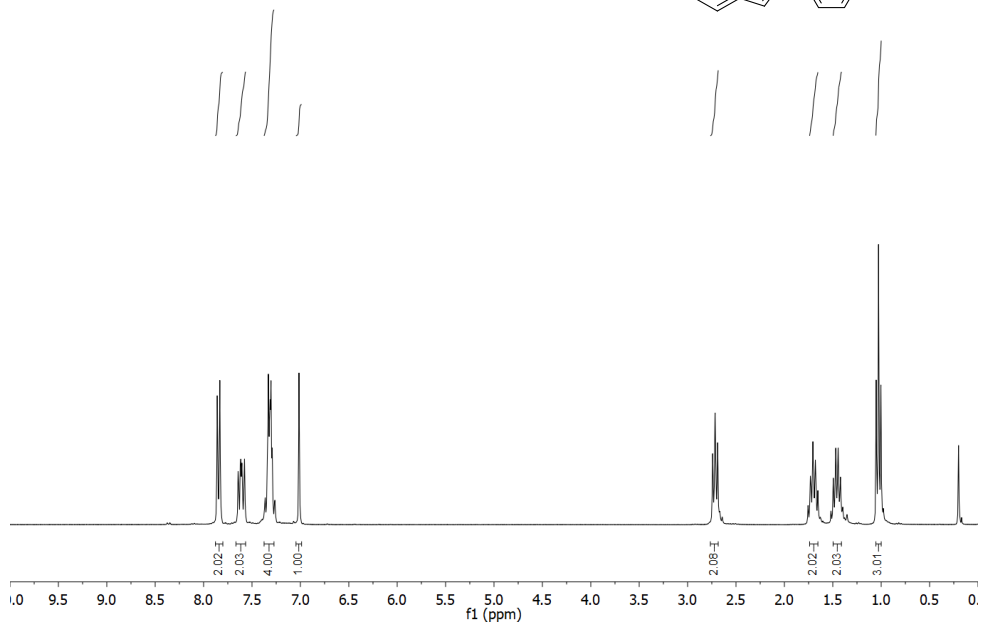
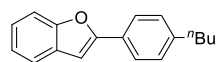


7af: 2-(4-Butoxyphenyl)benzofuran

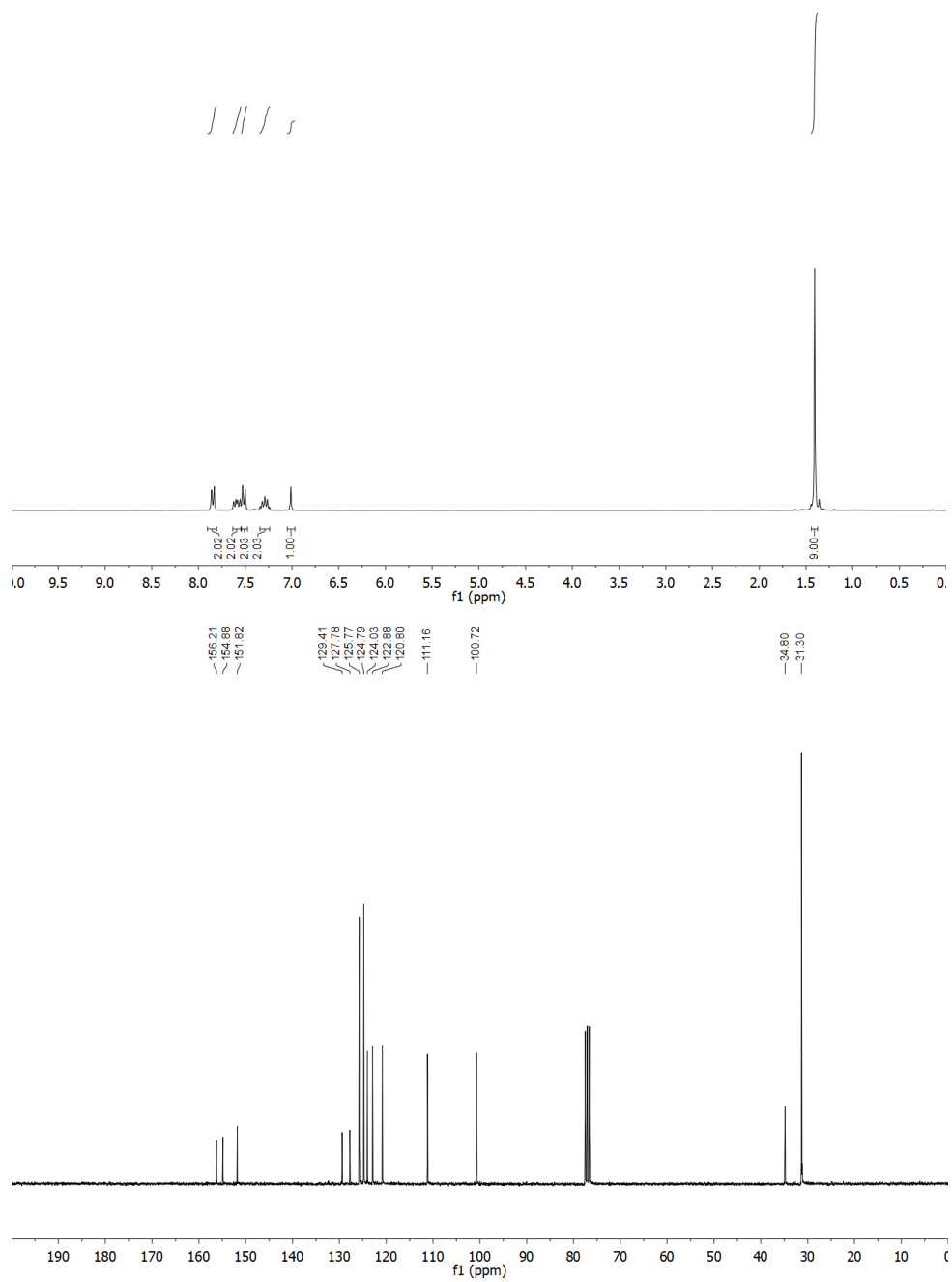
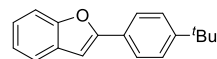


Appendix of spectra

7ag: 2-(4-Butylphenyl)benzofuran

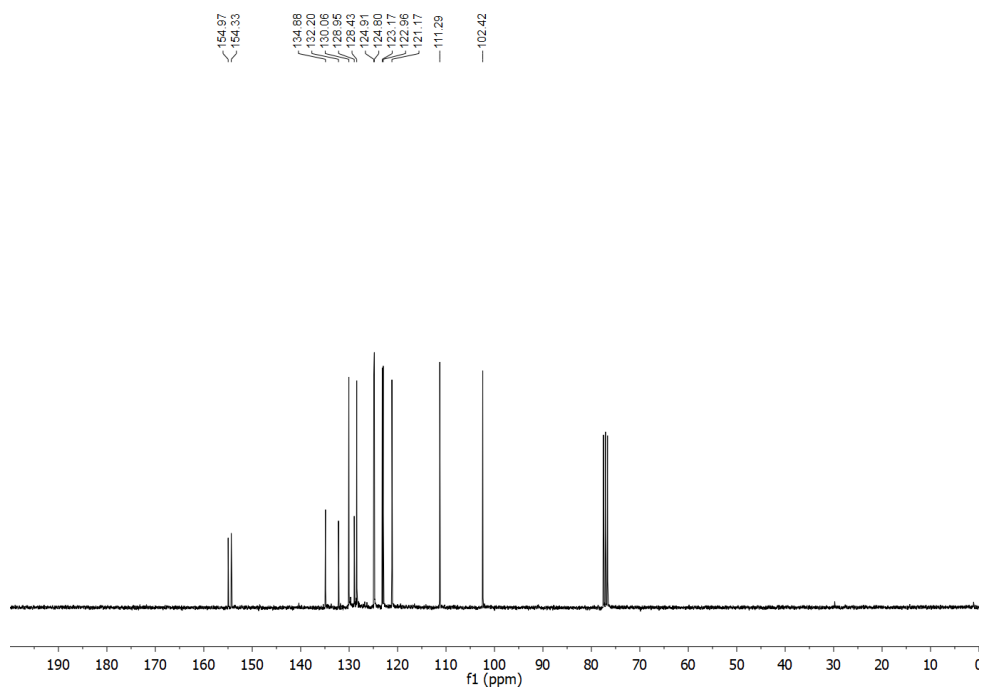
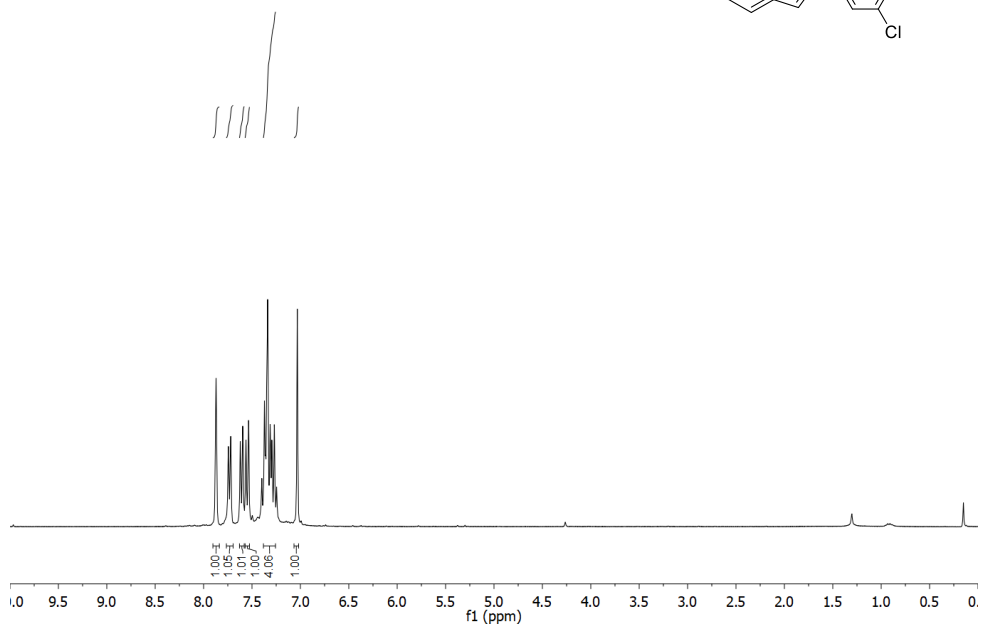
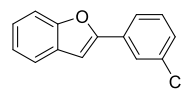


7ai: 2-(4-(tert-Butyl)phenyl)benzofuran

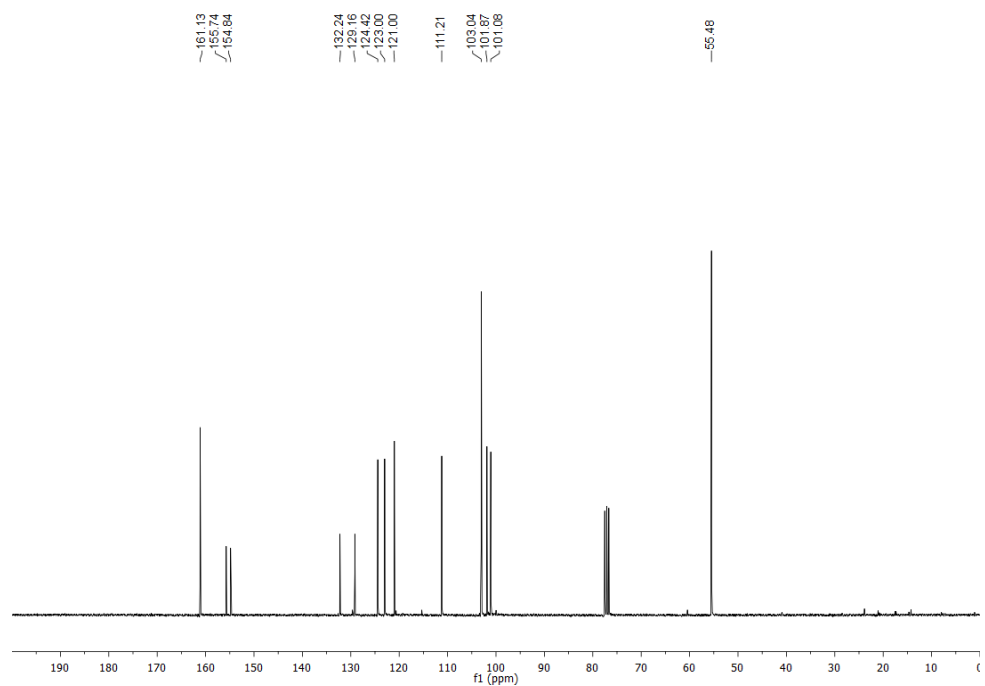
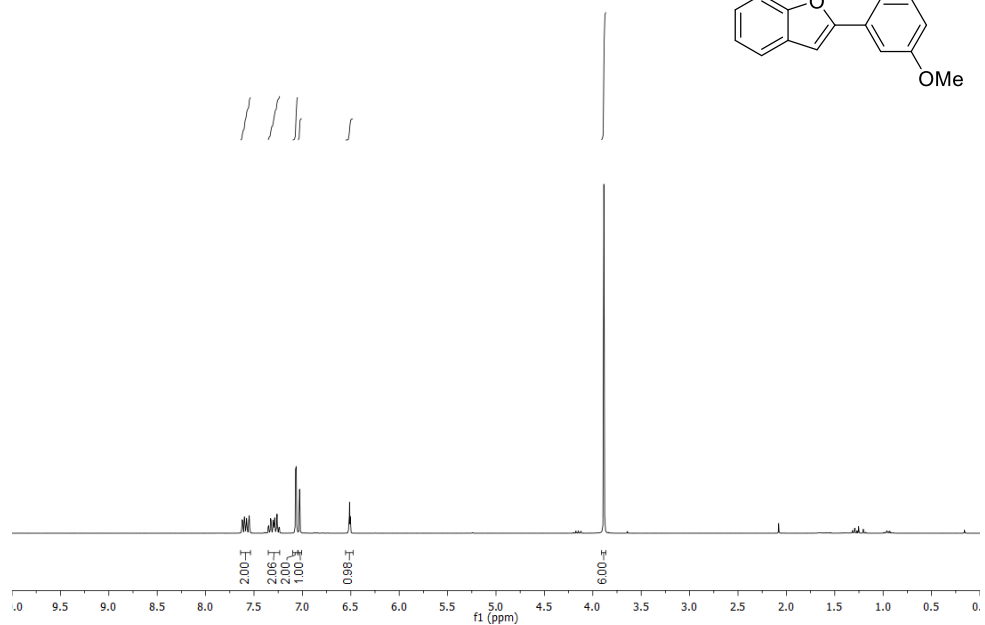
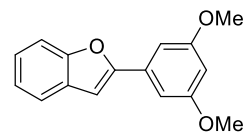


Appendix of spectra

7ak: 2-(3-Chlorophenyl)benzofuran

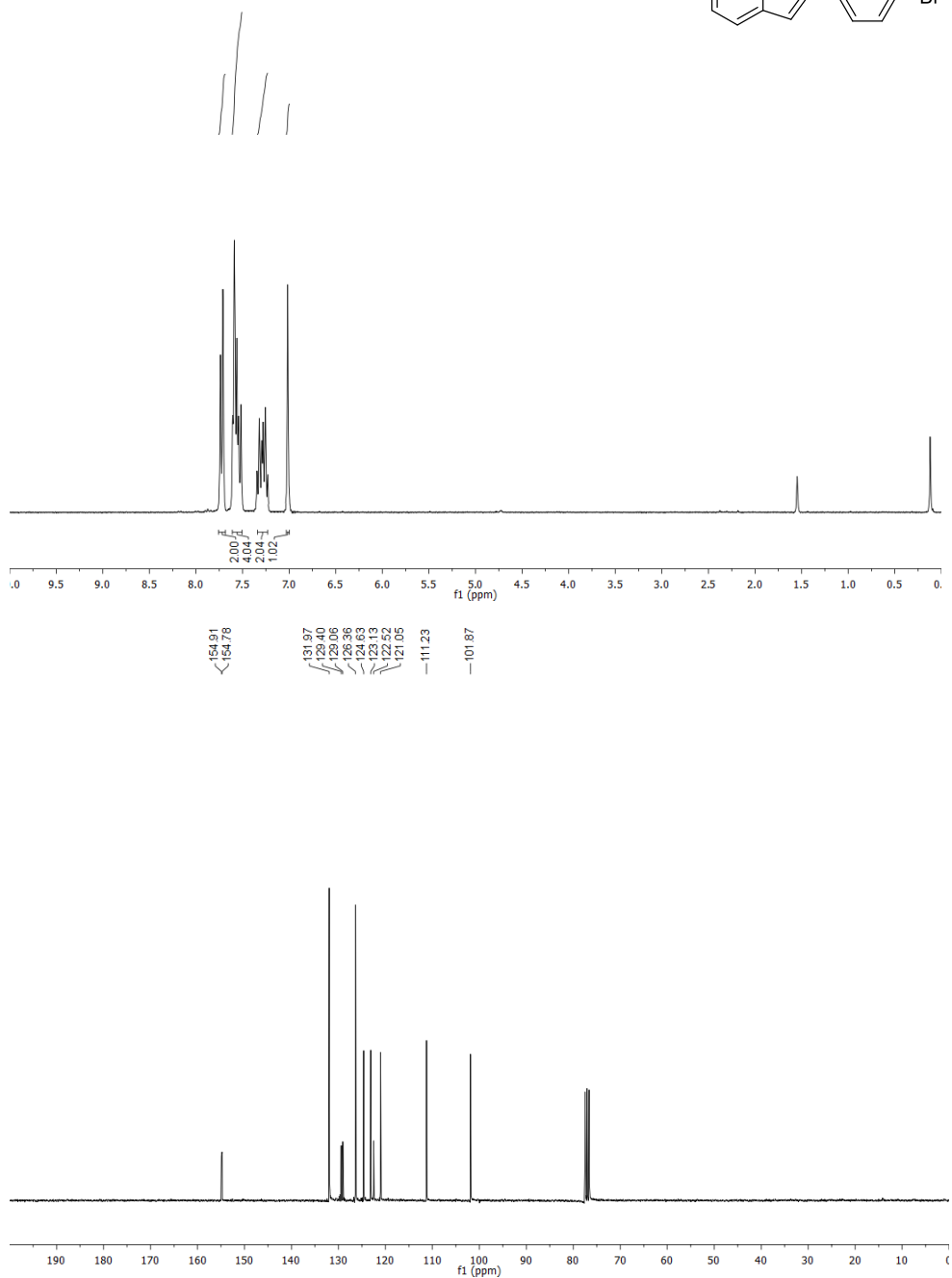
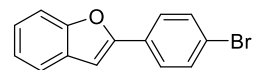


7am: 2-(3,5-Dimethoxyphenyl)benzofuran

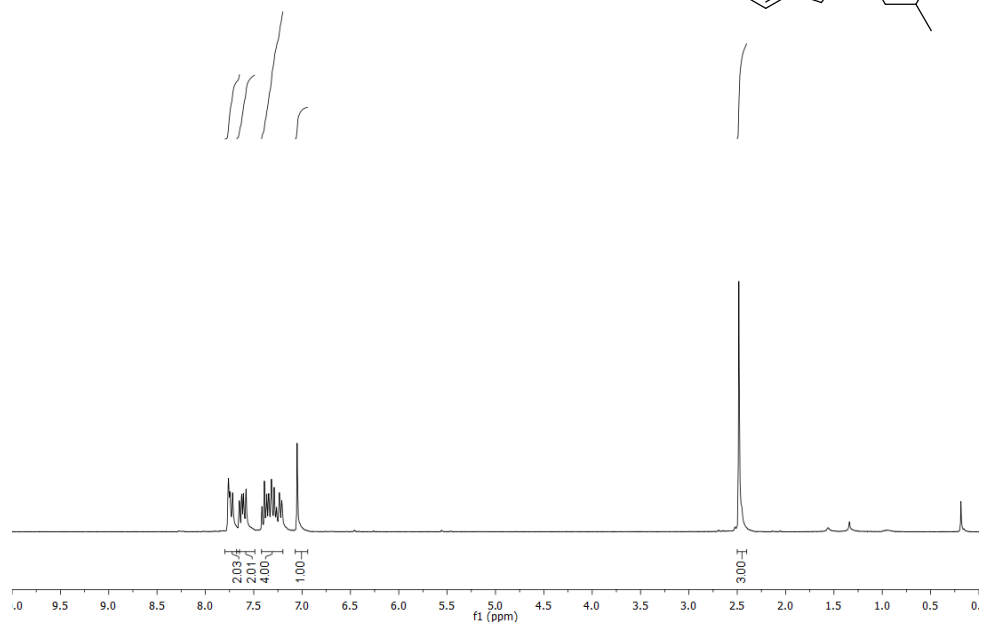
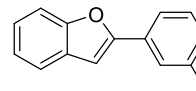


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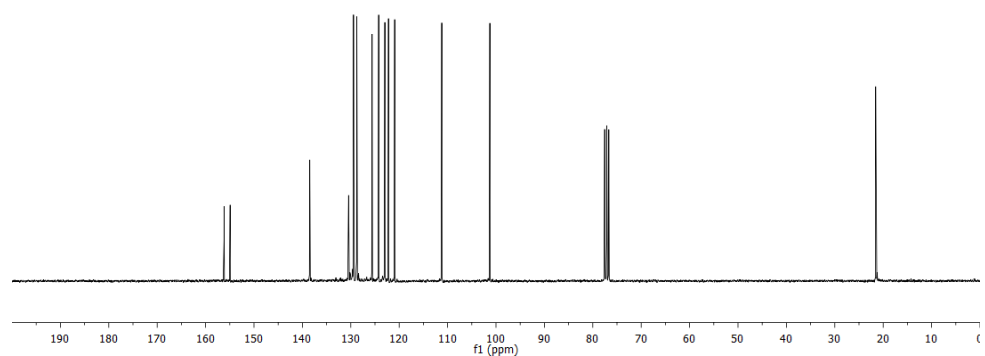
7an: 2-(4-Bromophenyl)benzofuran



7ao: 2-(*m*-Tolyl)benzofuran

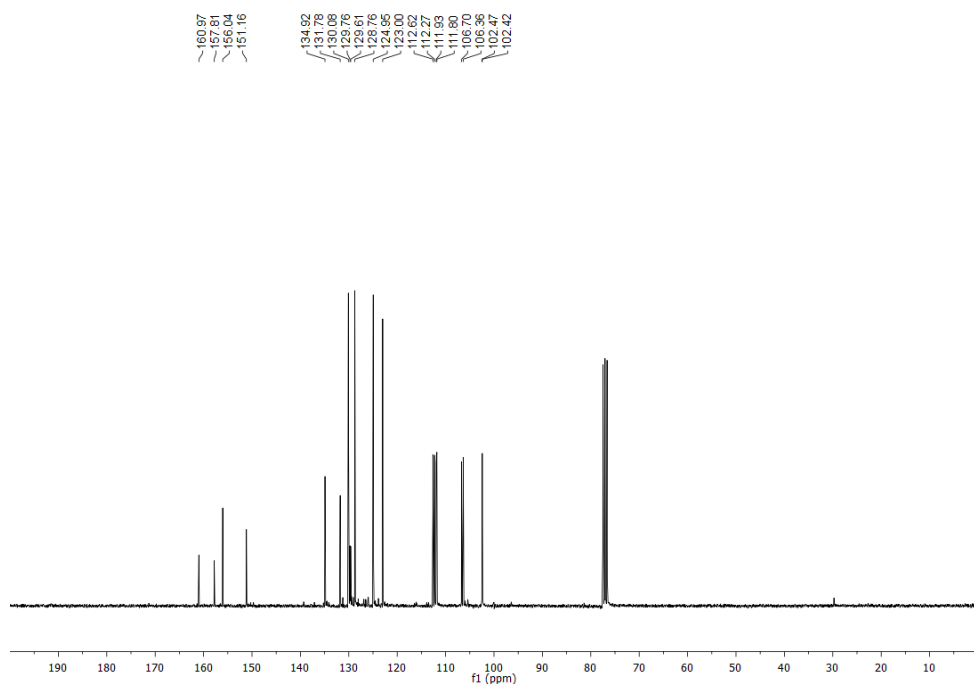
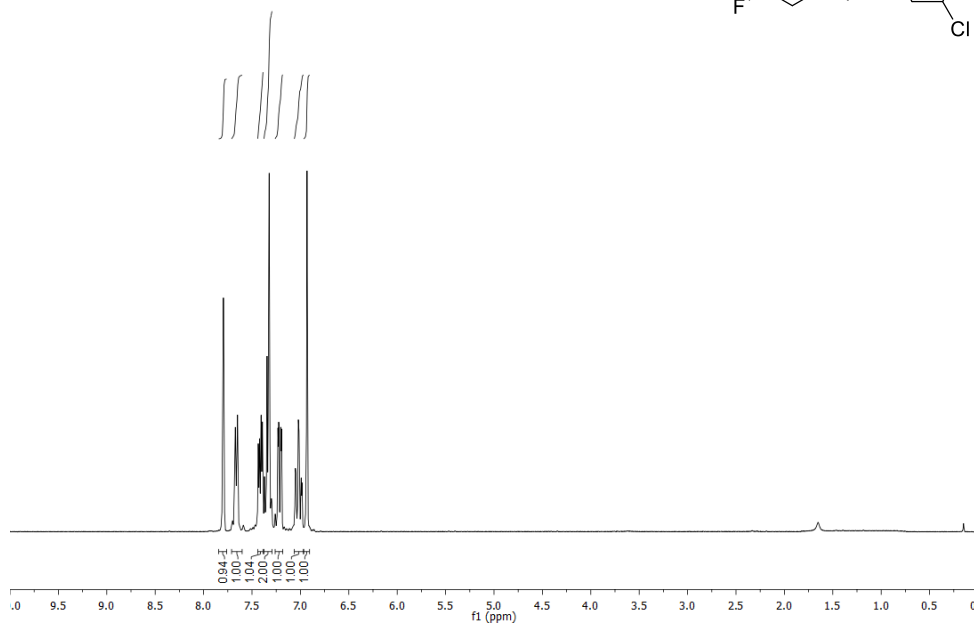
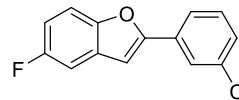


156.18
154.93
138.48
130.45
129.44
129.36
128.76
125.60
124.24
122.96
122.21
120.93
111.20
101.27
21.56

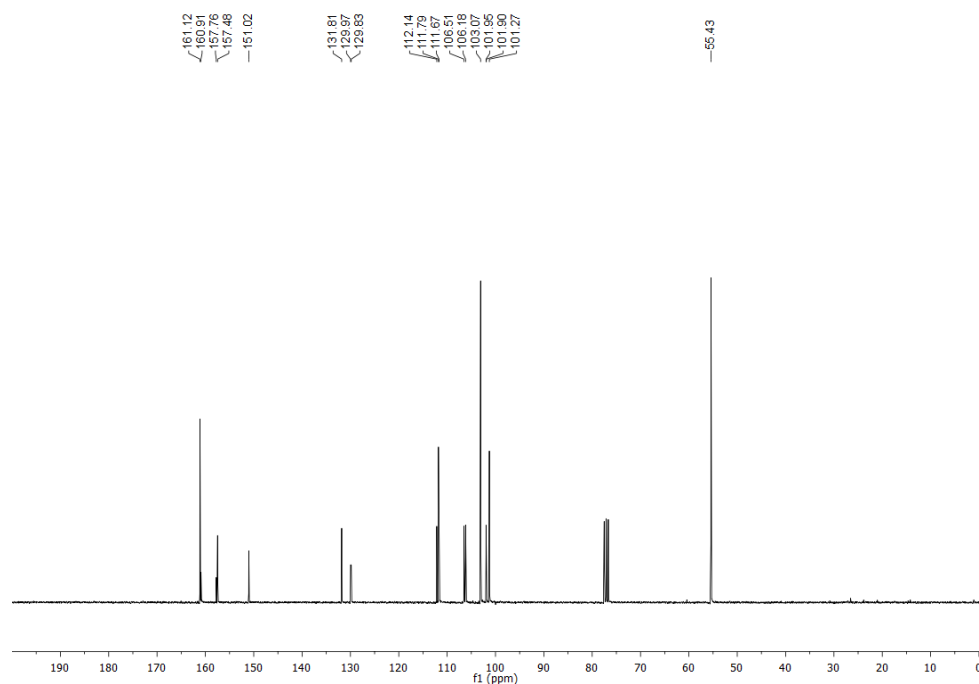
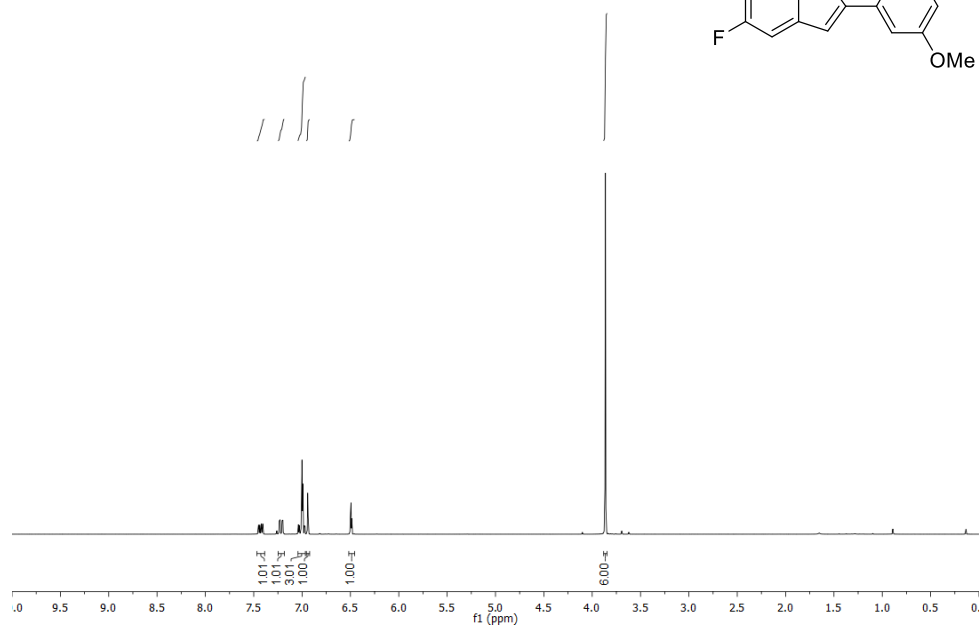
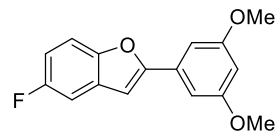


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7bd: 2-(3-Chlorophenyl)-5-fluorobenzofuran

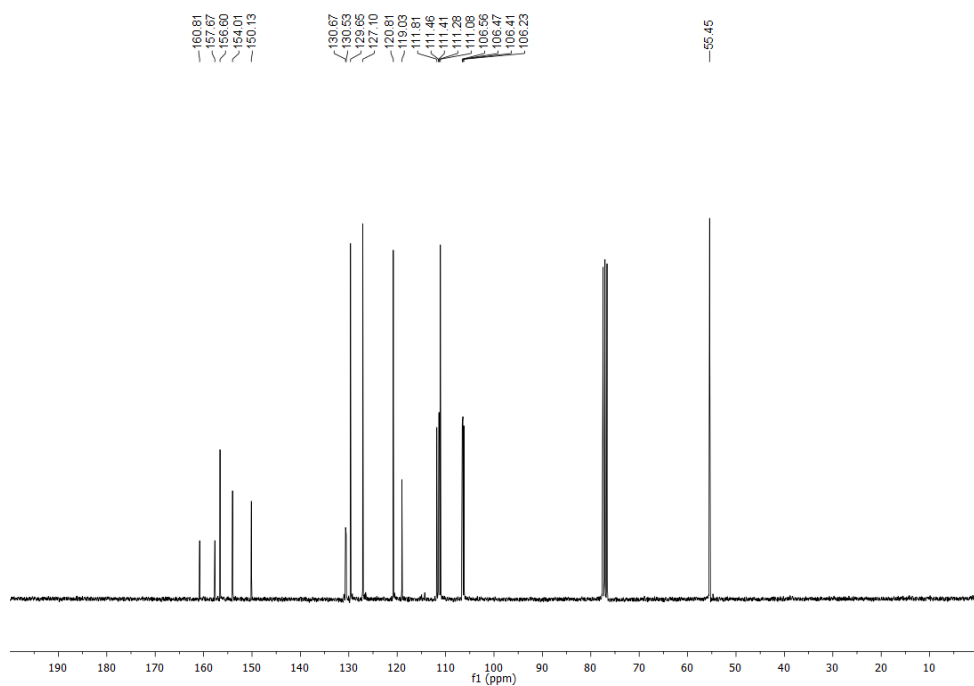
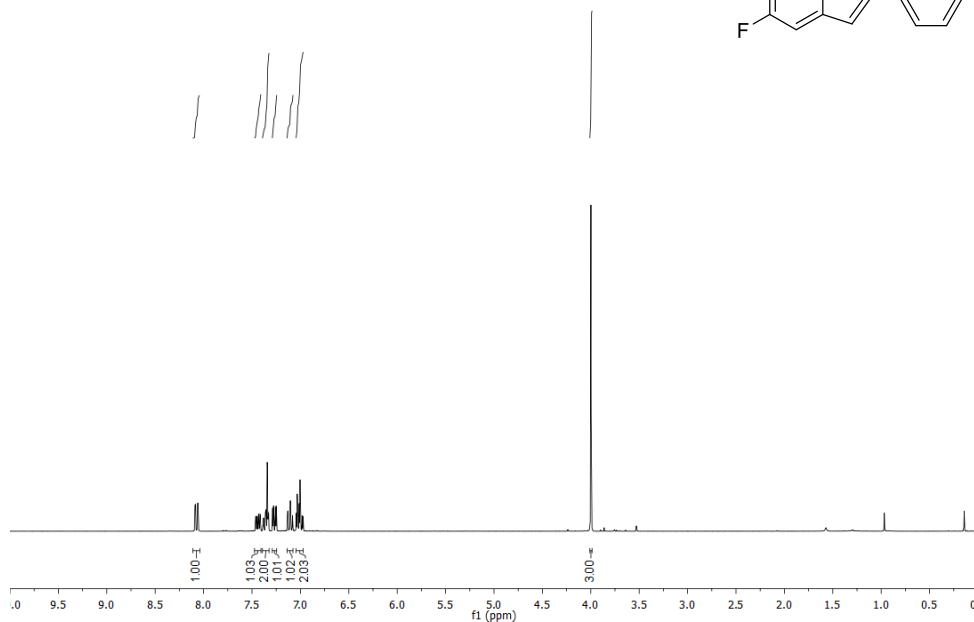
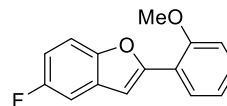


7be: 2-(3,5-Dimethoxyphenyl)-5-fluorobenzofuran

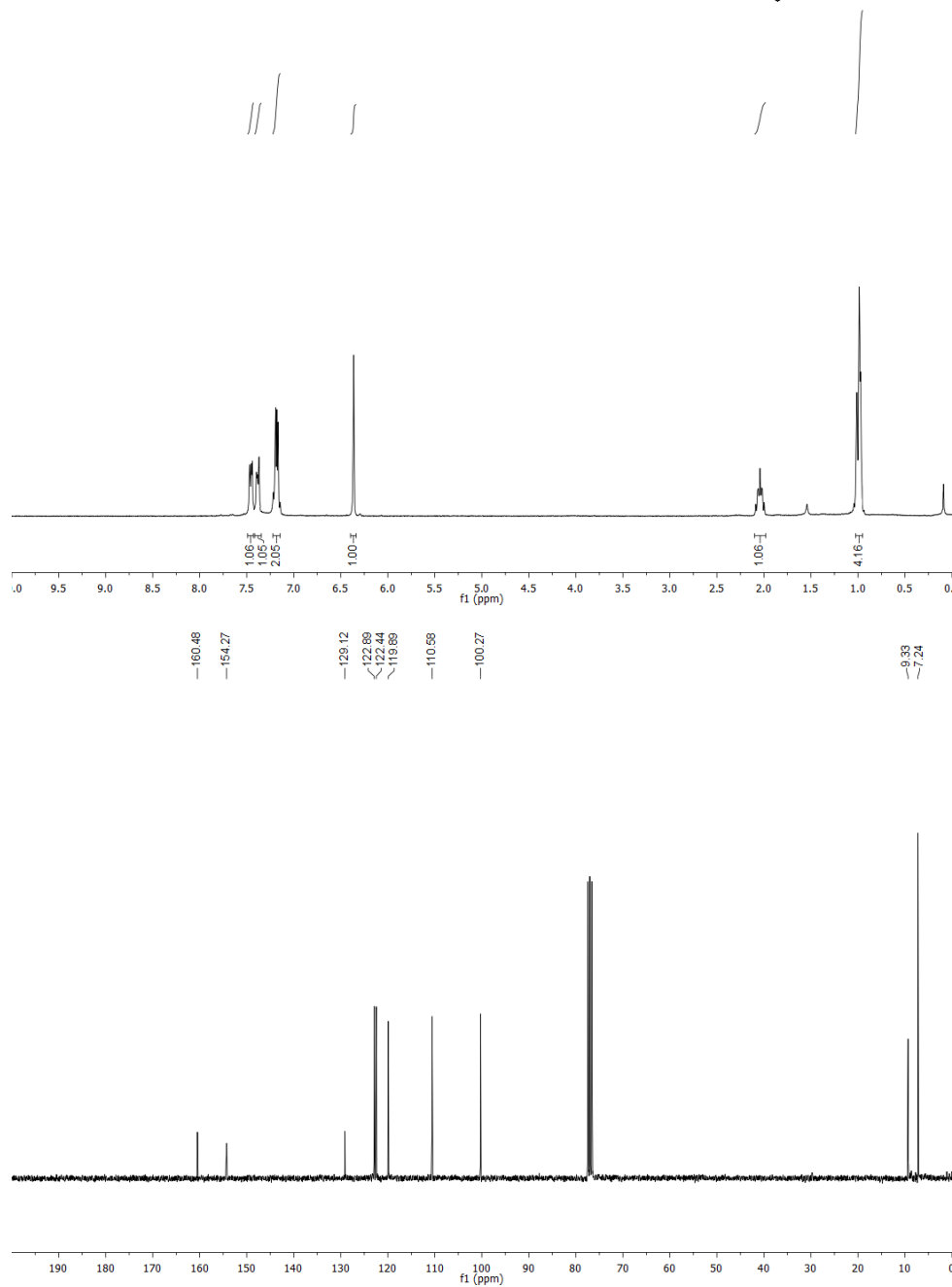
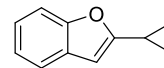


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7bf: 5-Fluoro-2-(2-methoxyphenyl)benzofuran

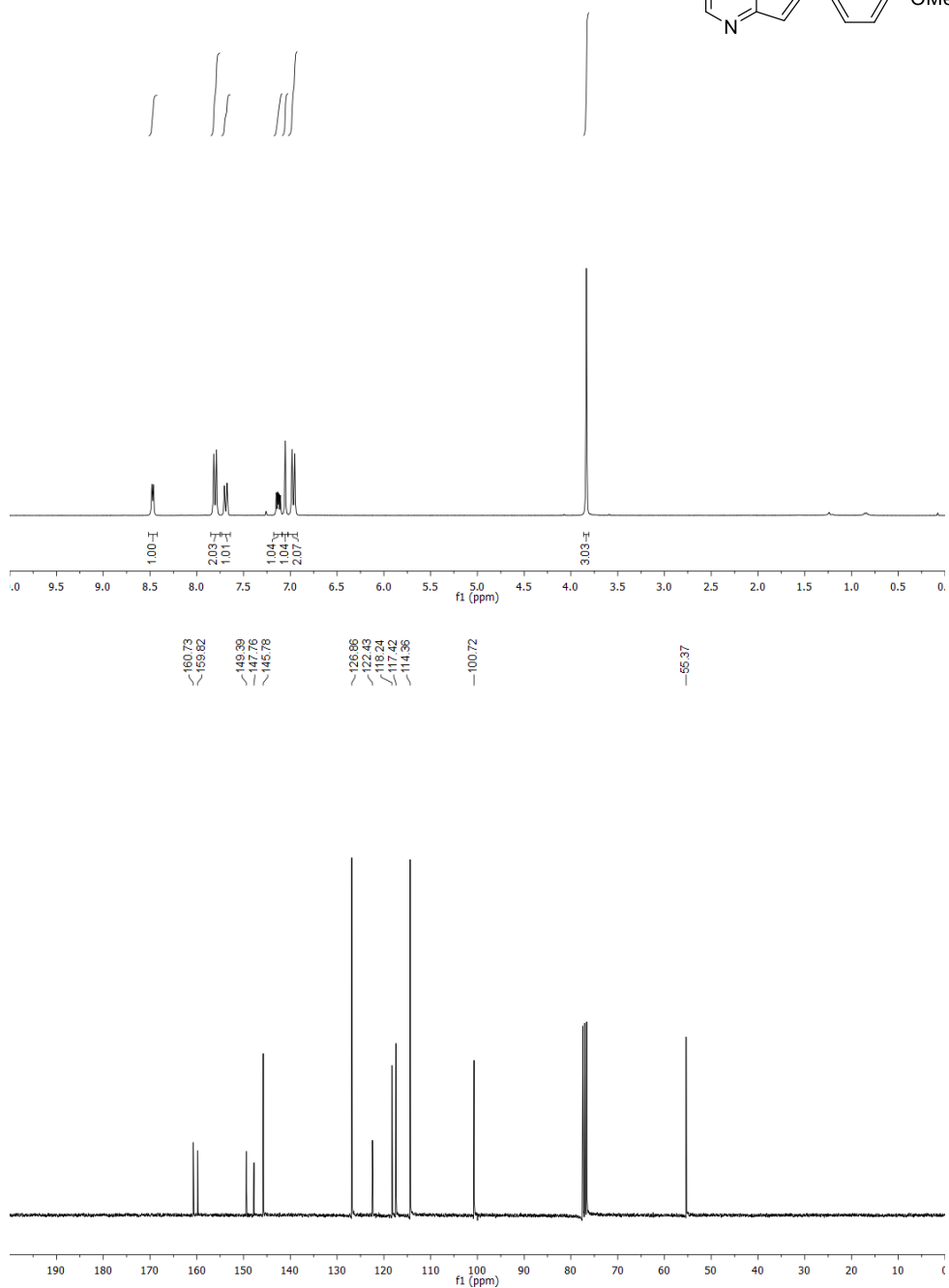
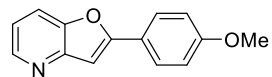


7cc: 2-Cyclopropylbenzofuran

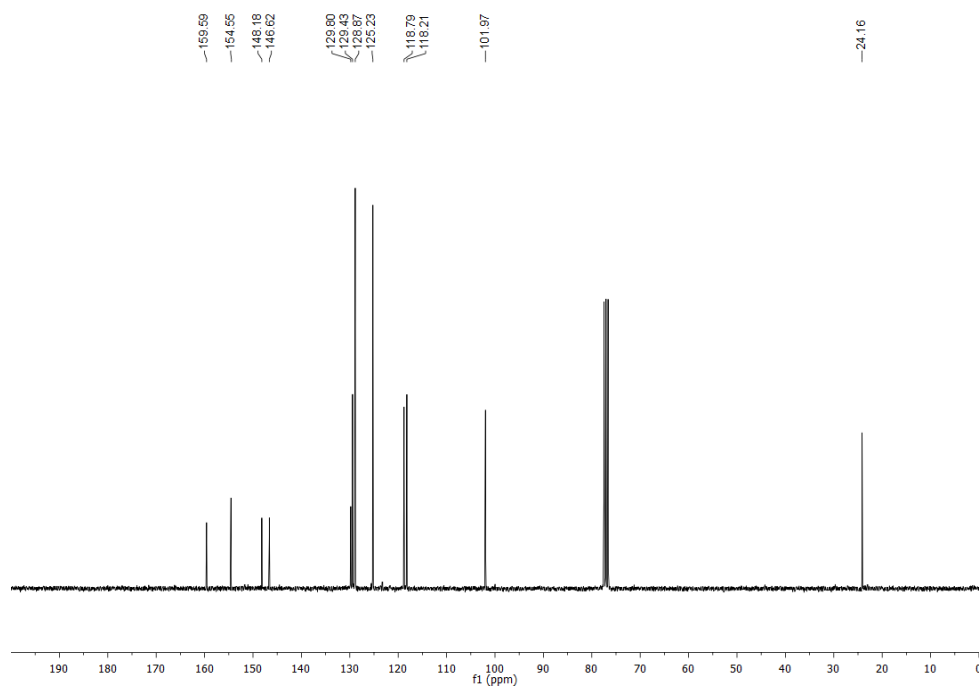
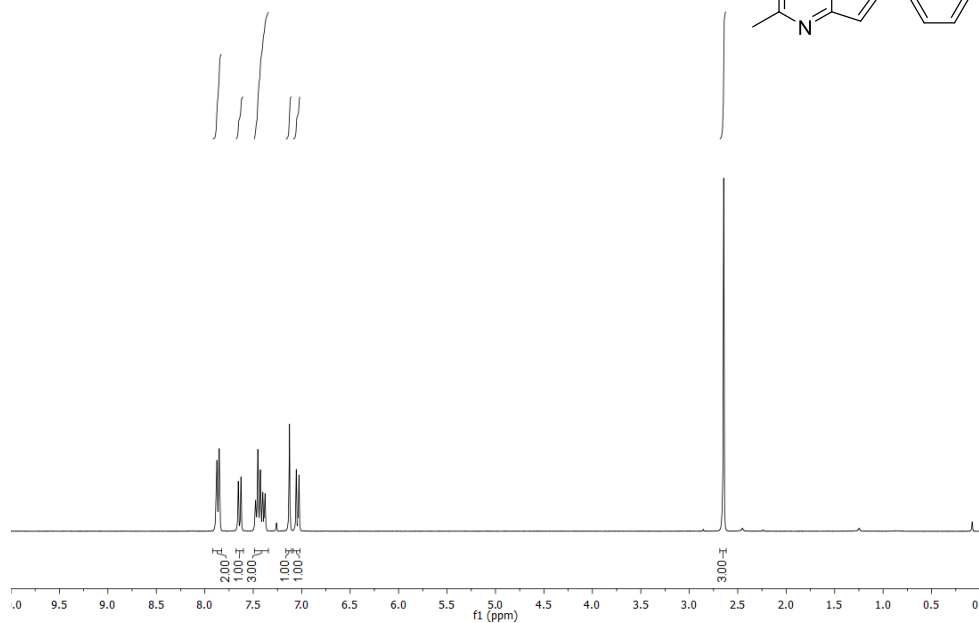
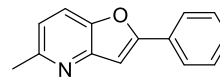


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8b: 2-(4-Methoxyphenyl)furo[3,2-b]pyridine

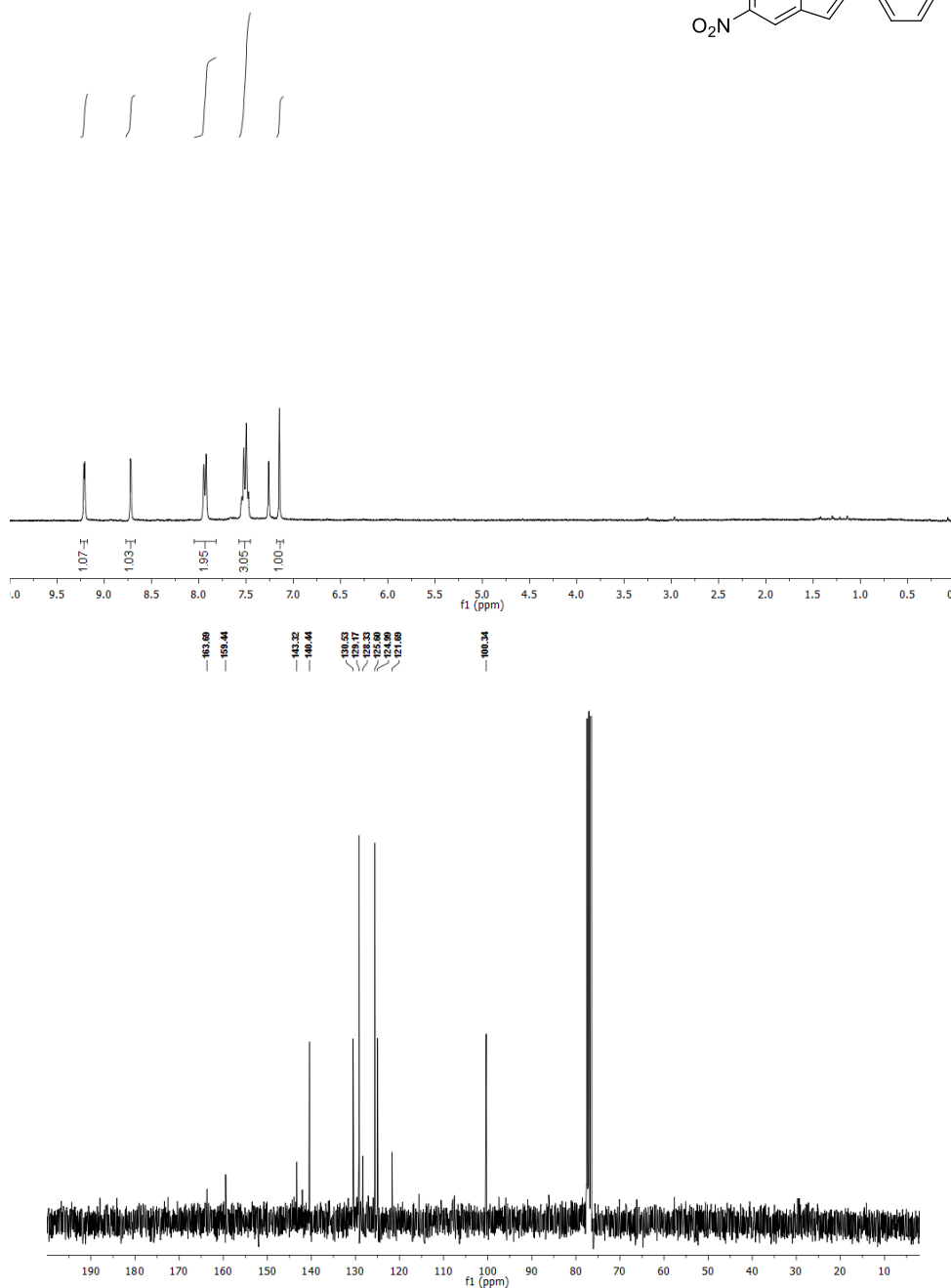
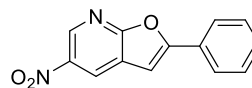


8f: 5-Methyl-2-phenylfuro[3,2-b]pyridine

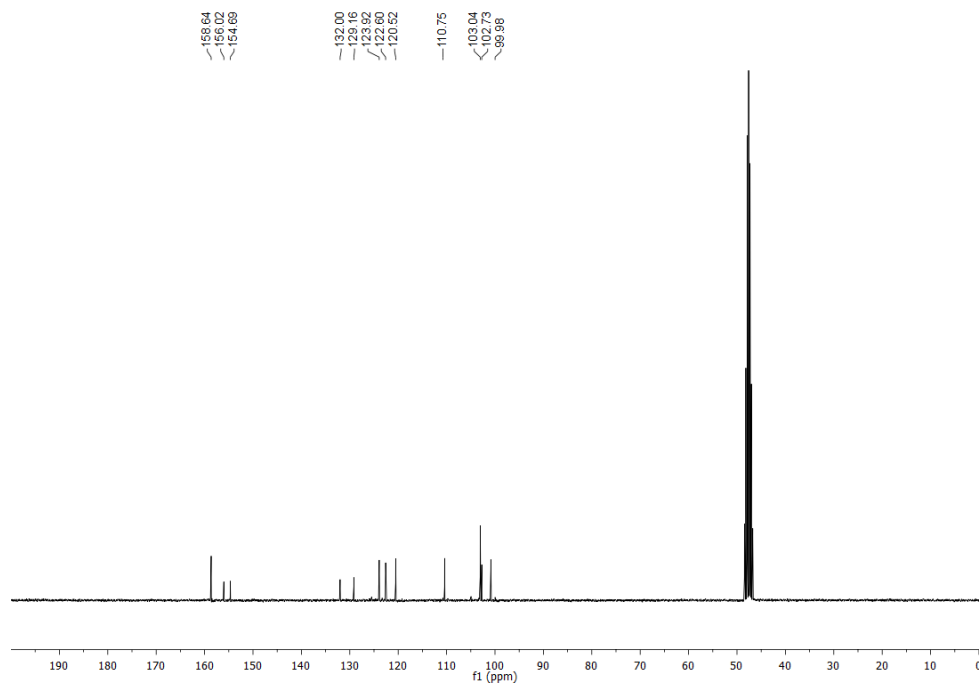
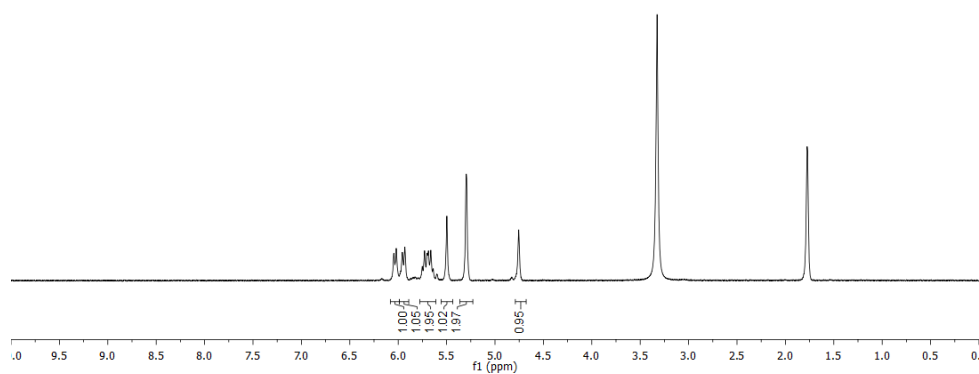
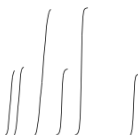
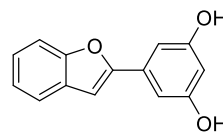


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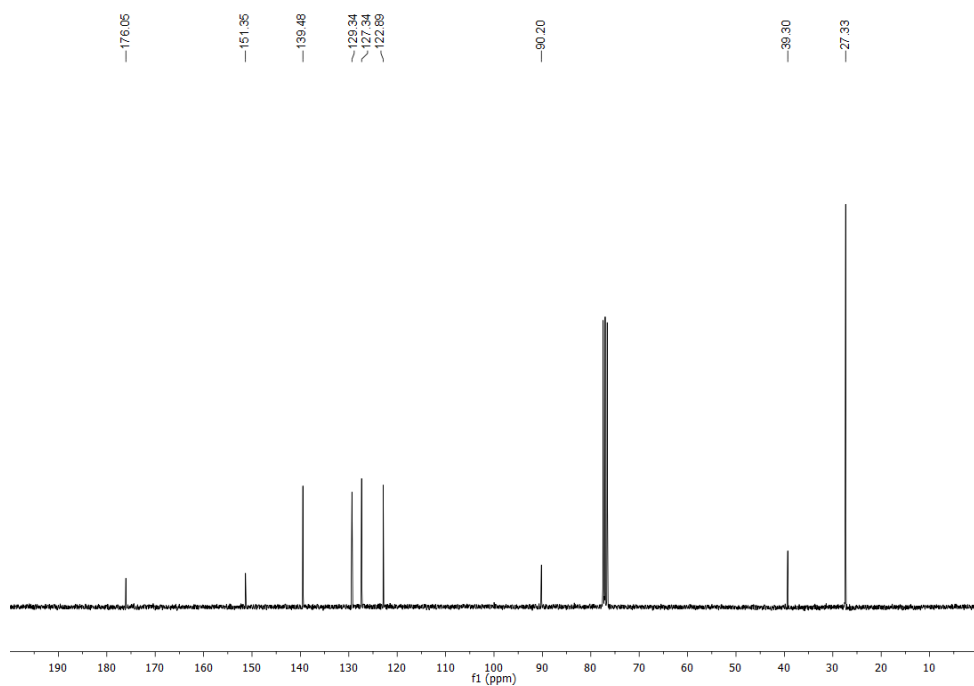
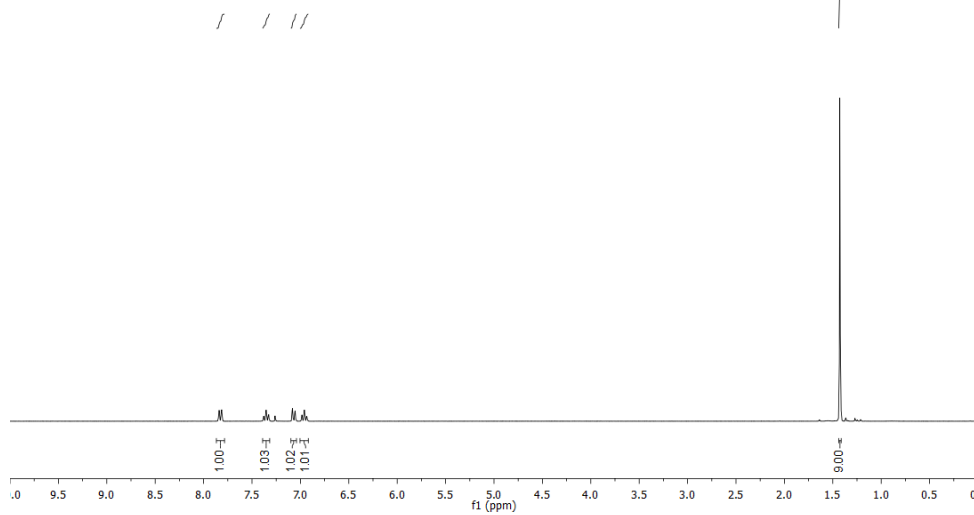
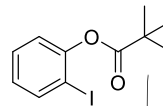
8g: 5-Nitro-2-phenylfuro[2,3-b]pyridine



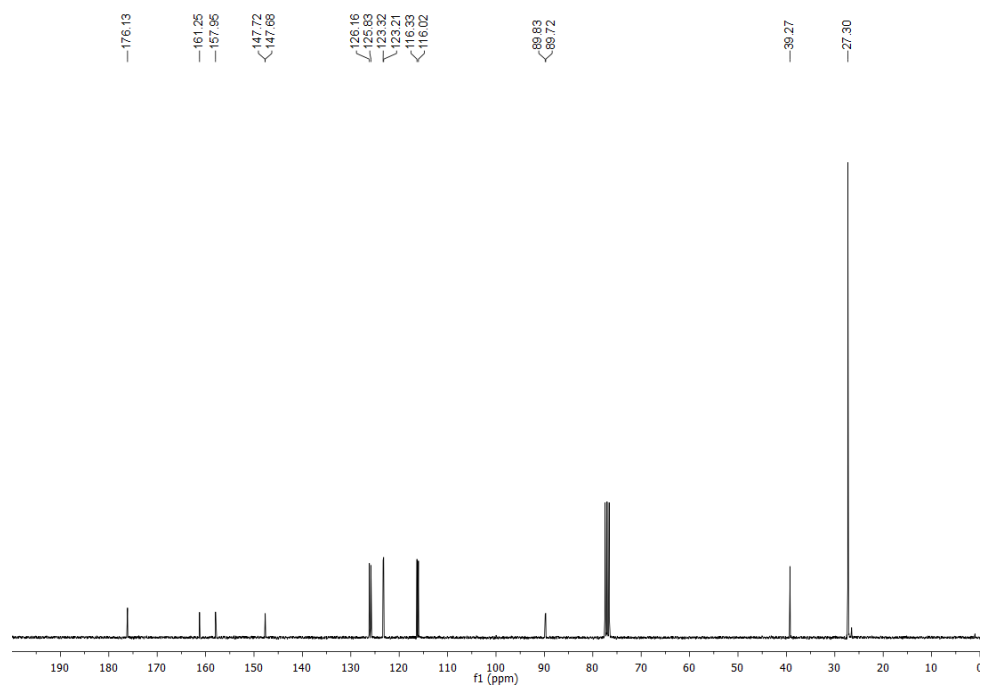
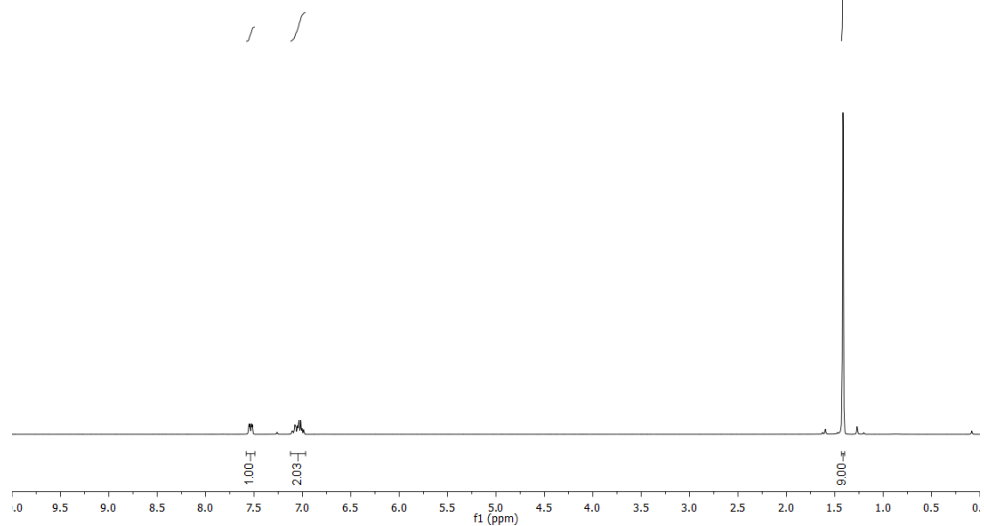
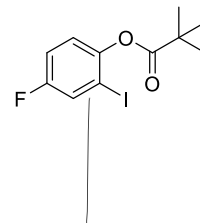
stemofuran A: 5-(Benzofuran-2-yl)benzene-1,3-diol



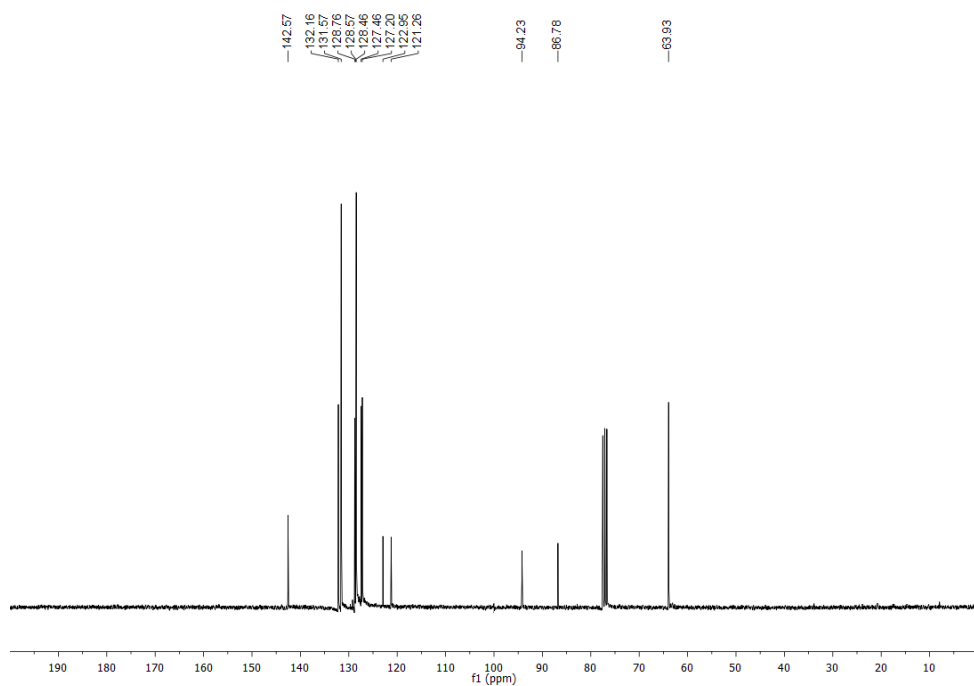
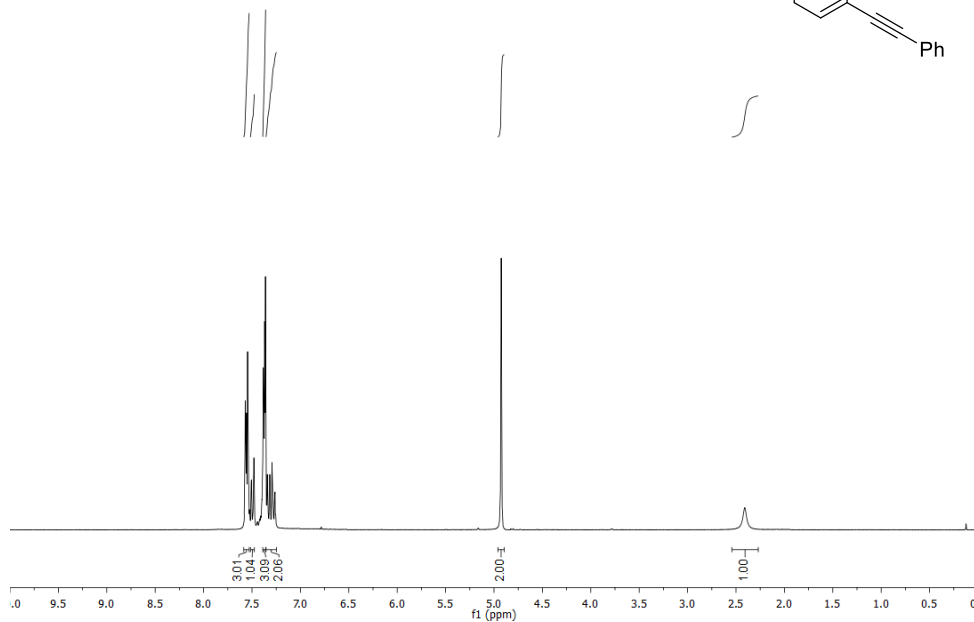
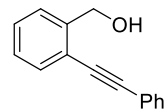
9b: 2-iodophenyl pivalate



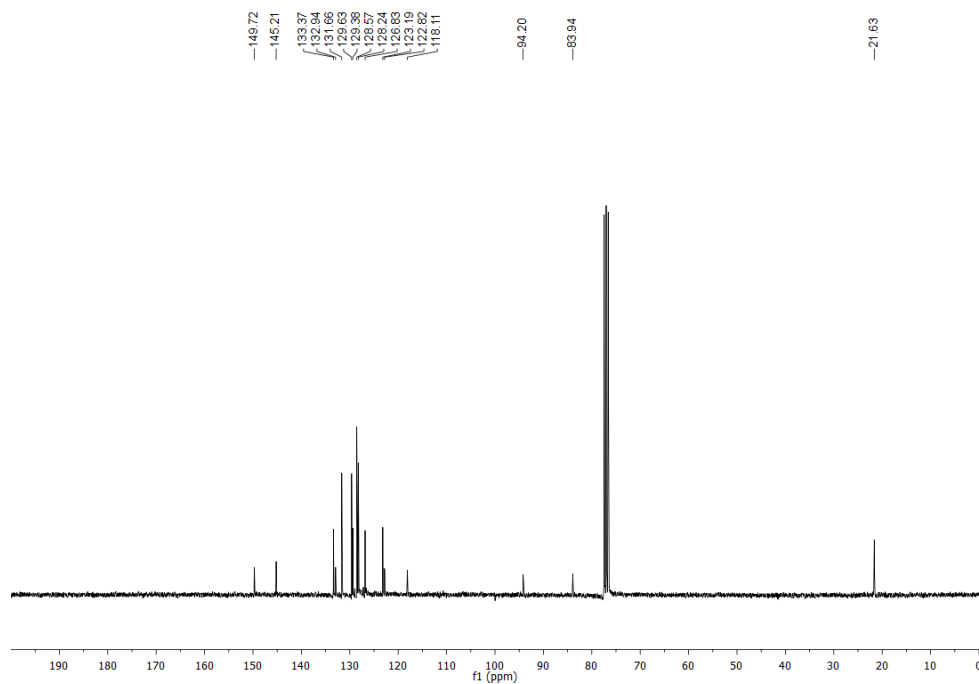
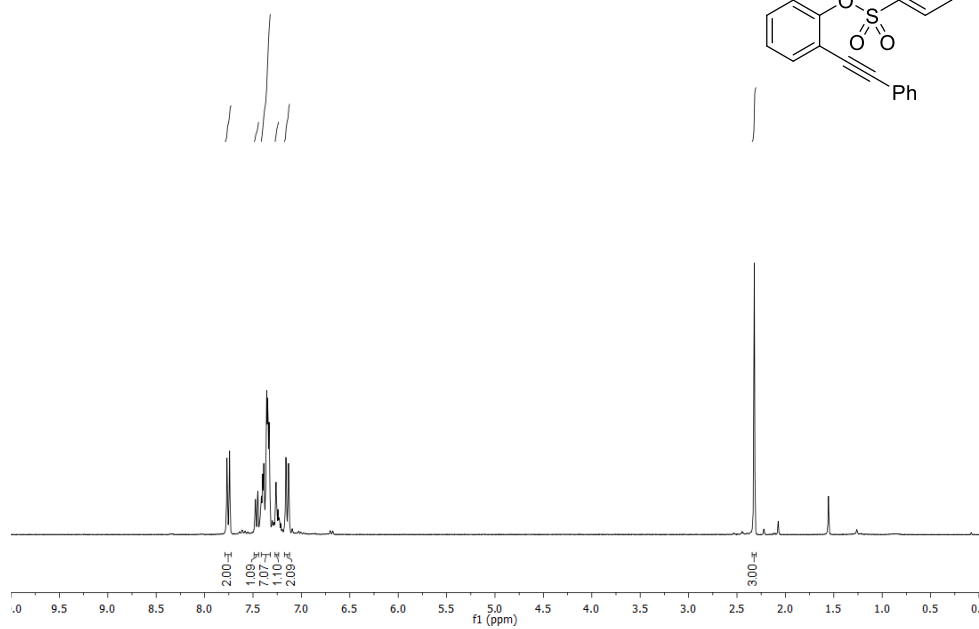
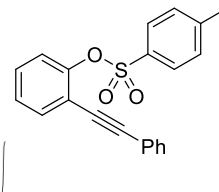
9e: 4-Fluoro-2-iodophenyl pivalate



10a: (2-(Phenylethynyl)phenyl)methanol

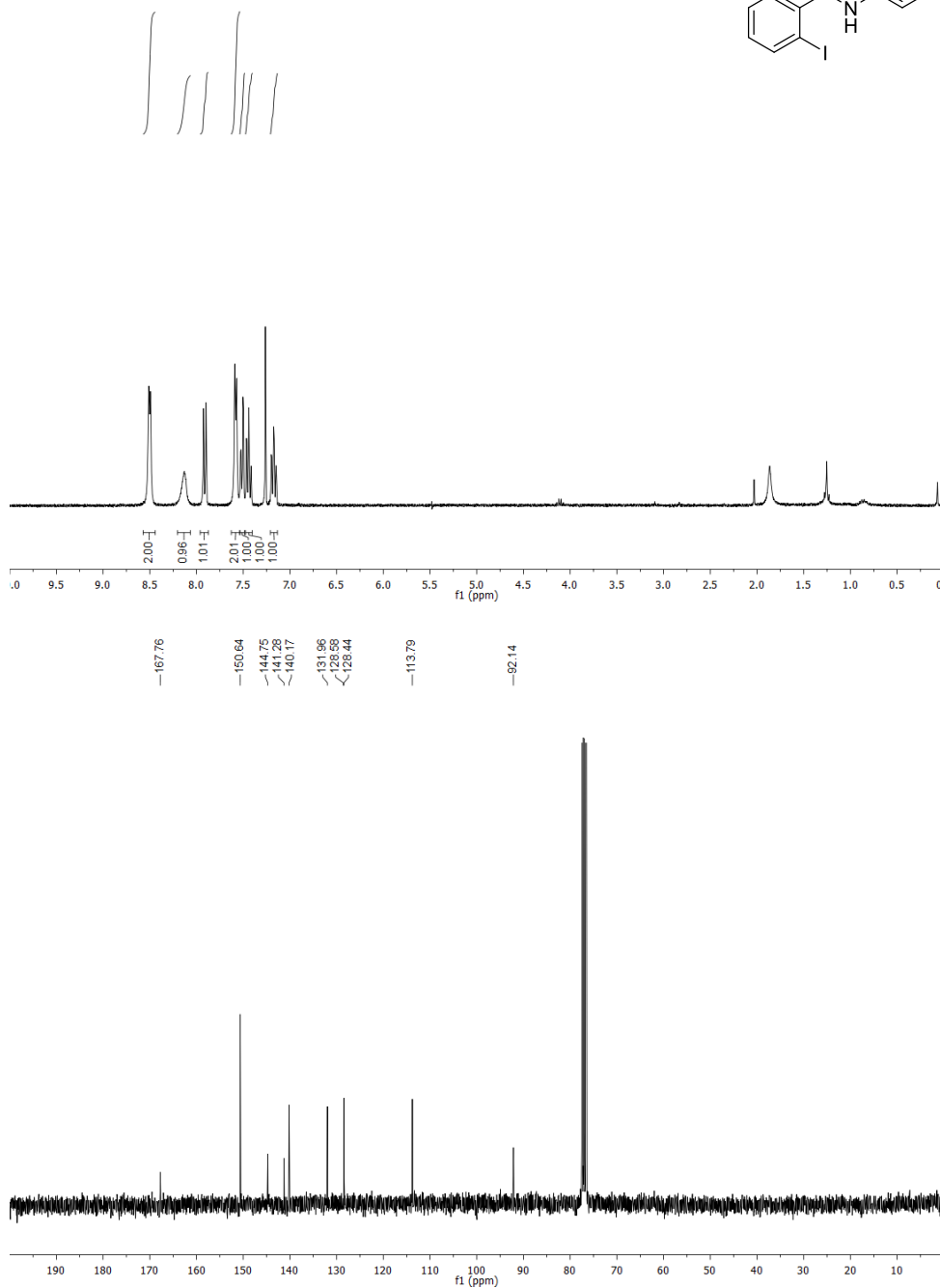
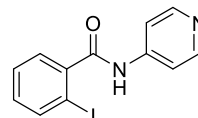


10c: 2-(Phenylethynyl)phenyl 4-methylbenzenesulfonate

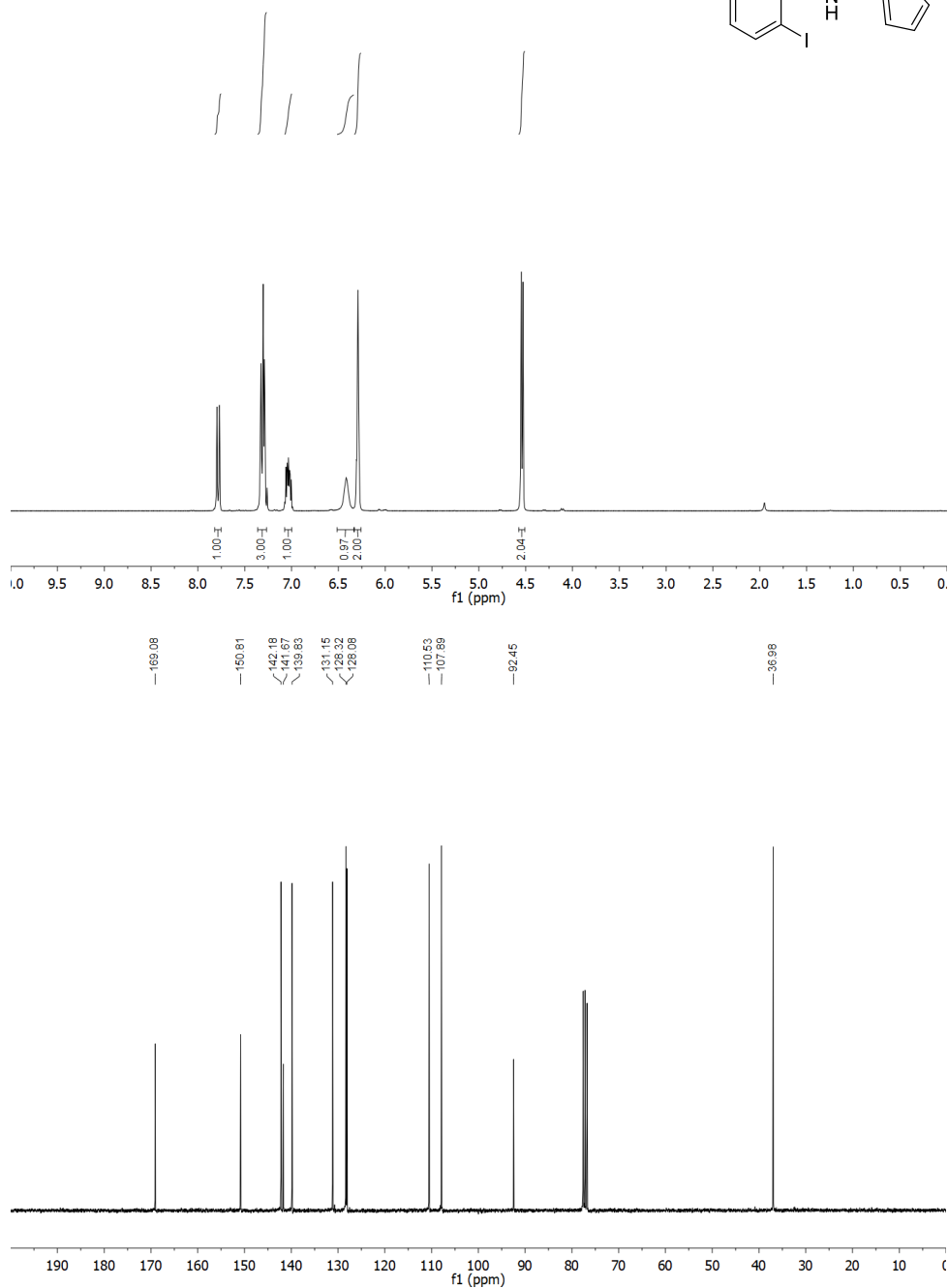
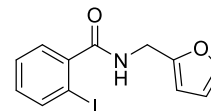


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12c: 2-Iodo-N-(pyridin-4-yl)benzamide

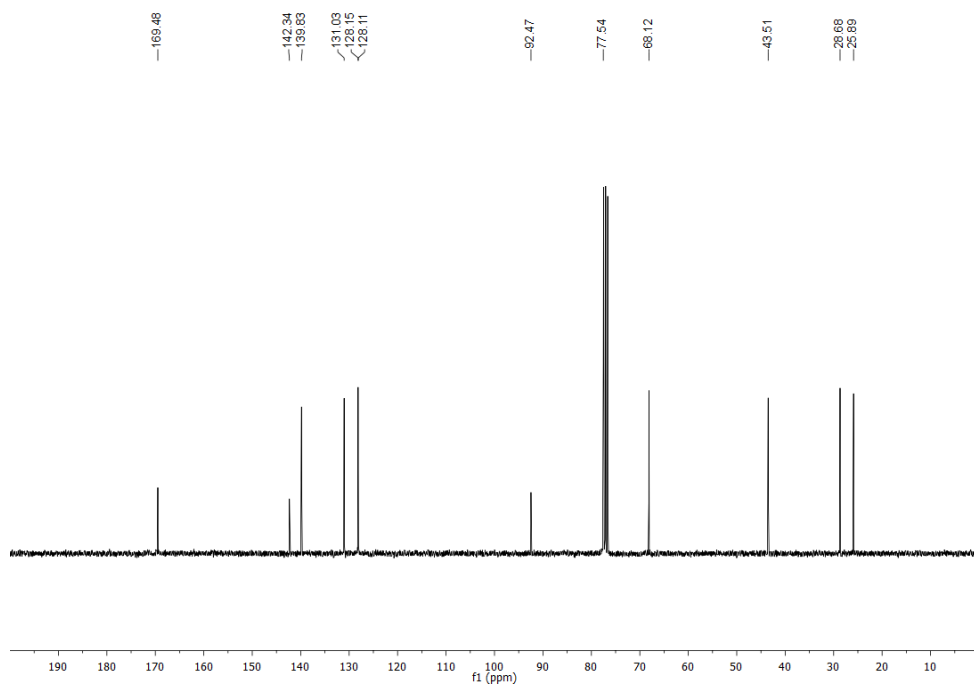
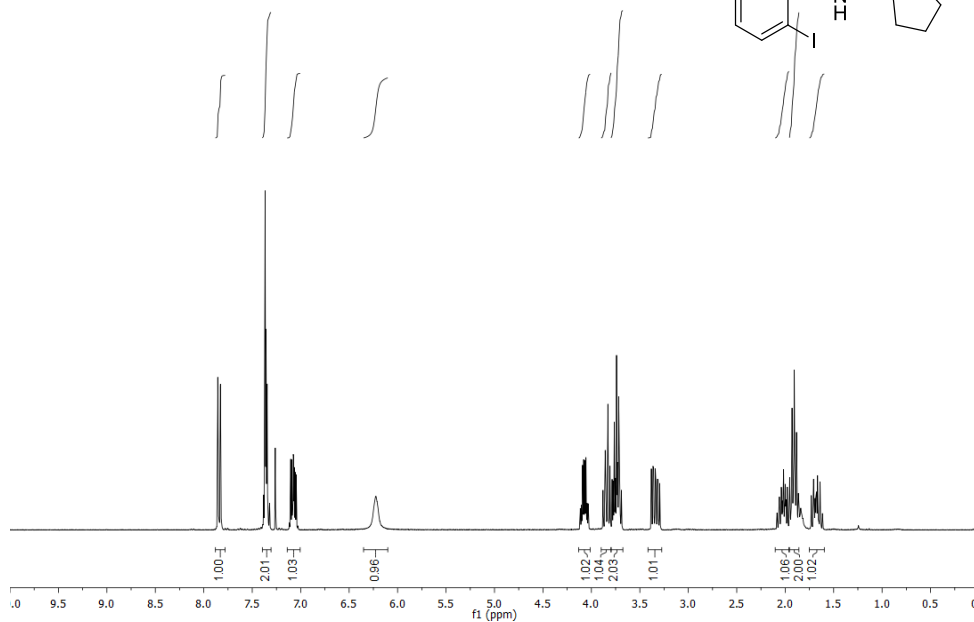
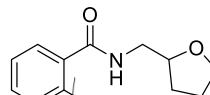


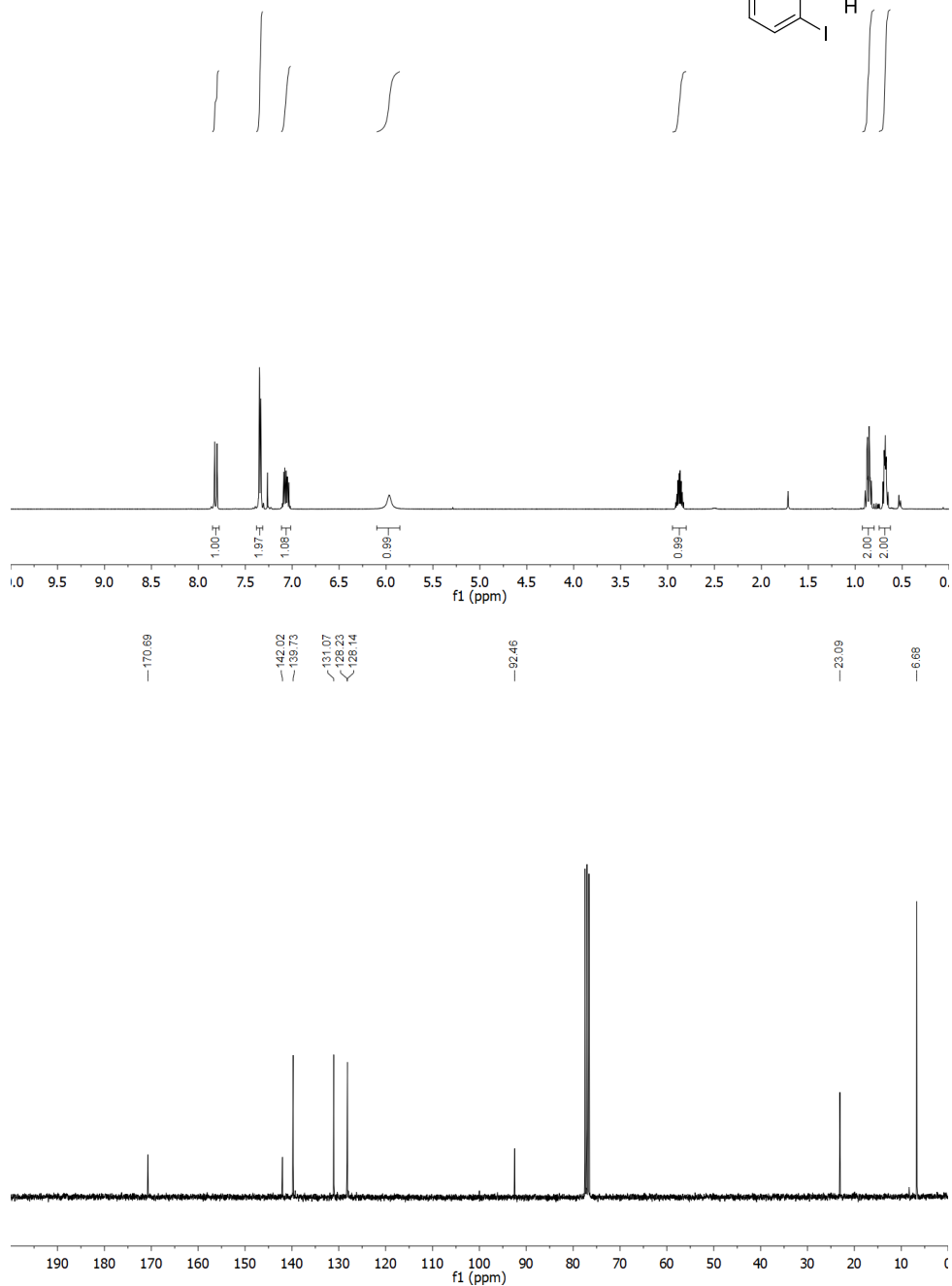
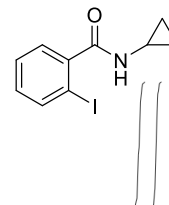
12f: *N*-(Furan-2-ylmethyl)-2-iodobenzamide



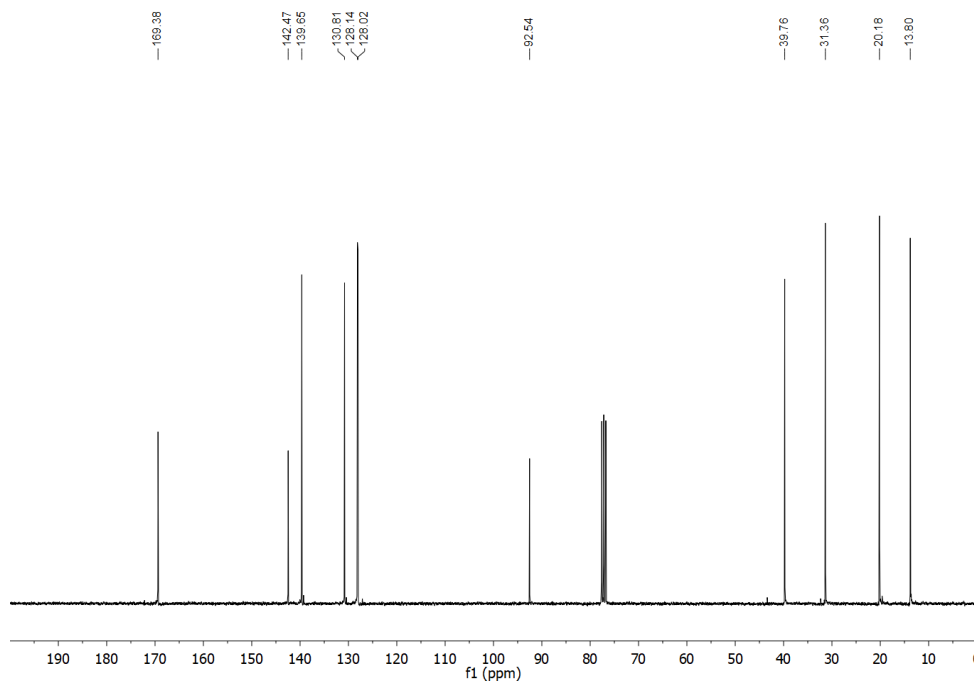
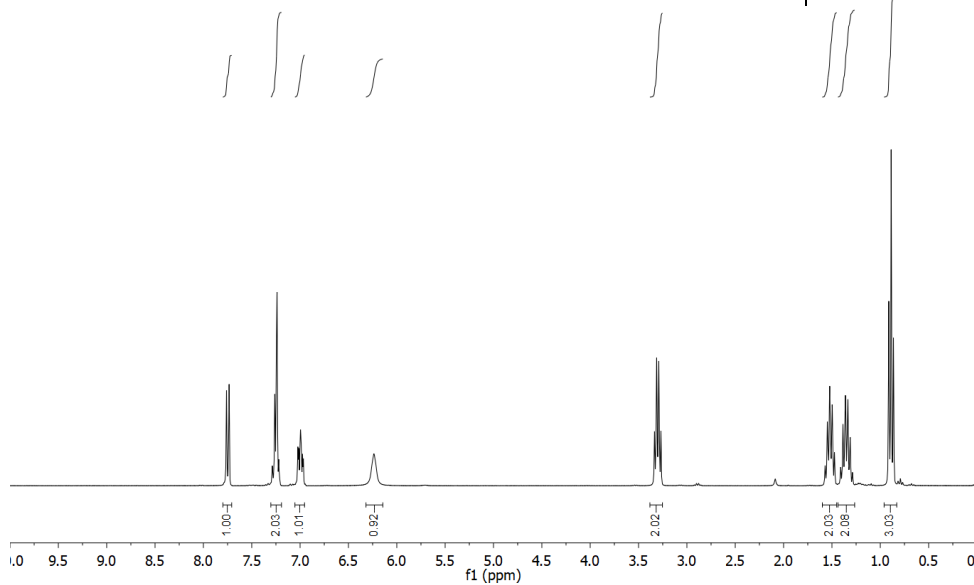
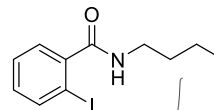
Appendix of spectra

12h: 2-Iodo-N-((tetrahydrofuran-2-yl)methyl)benzamide

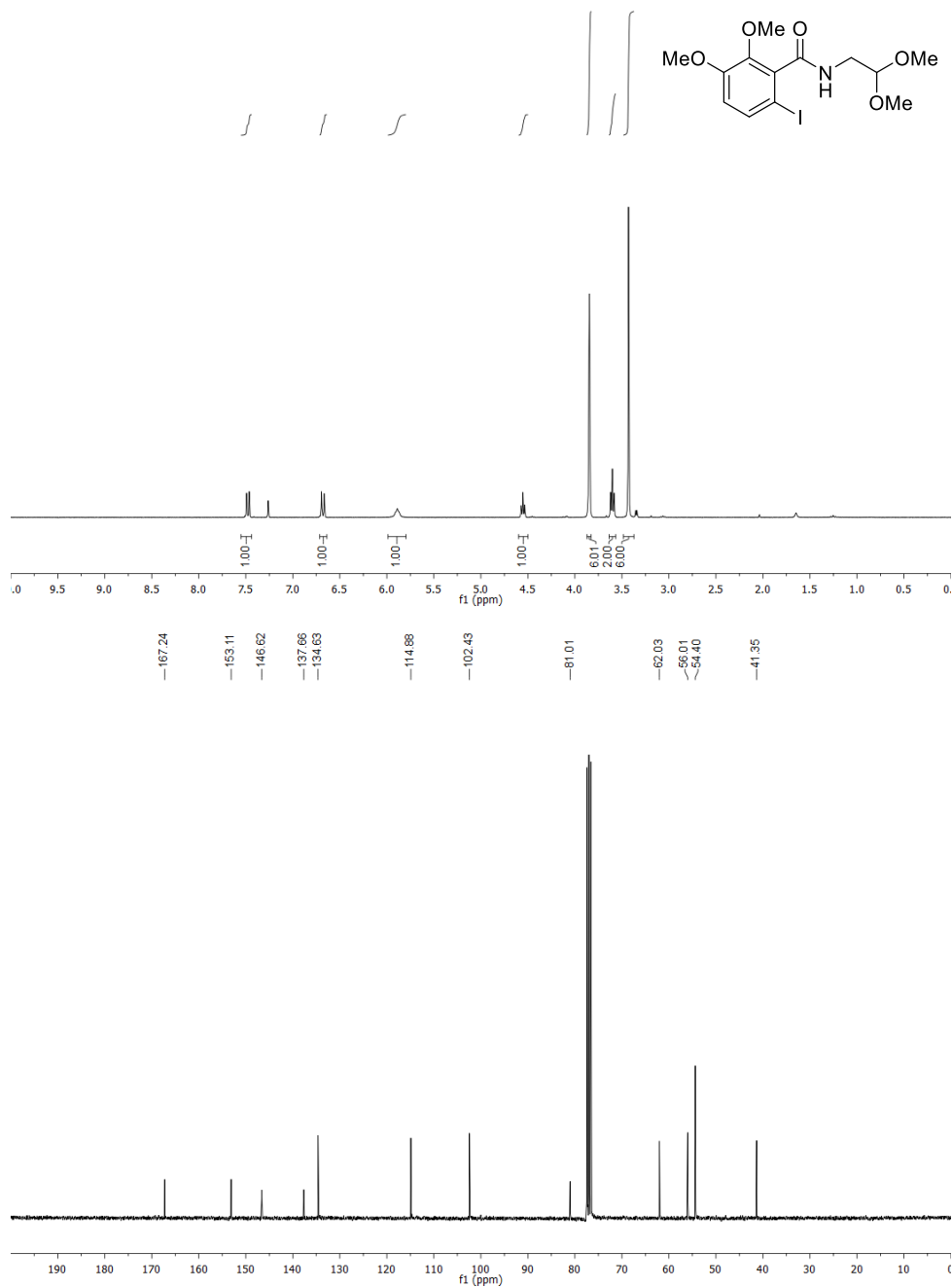


12i: *N*-Cyclopropyl-2-iodobenzamide

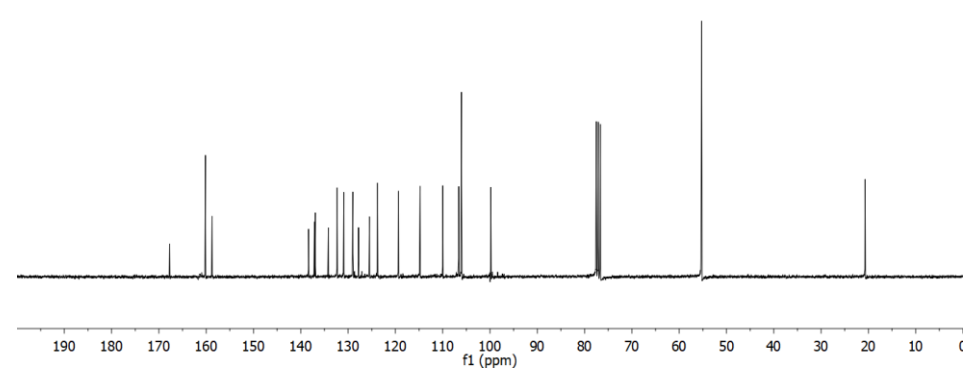
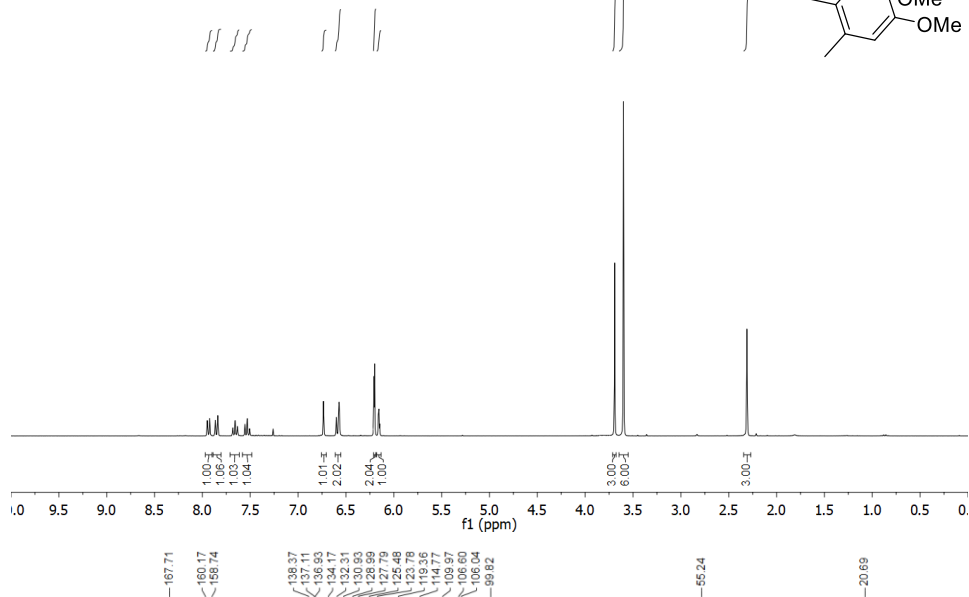
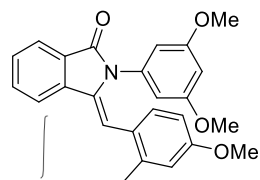
12k: *N*-Butyl-2-iodobenzamide



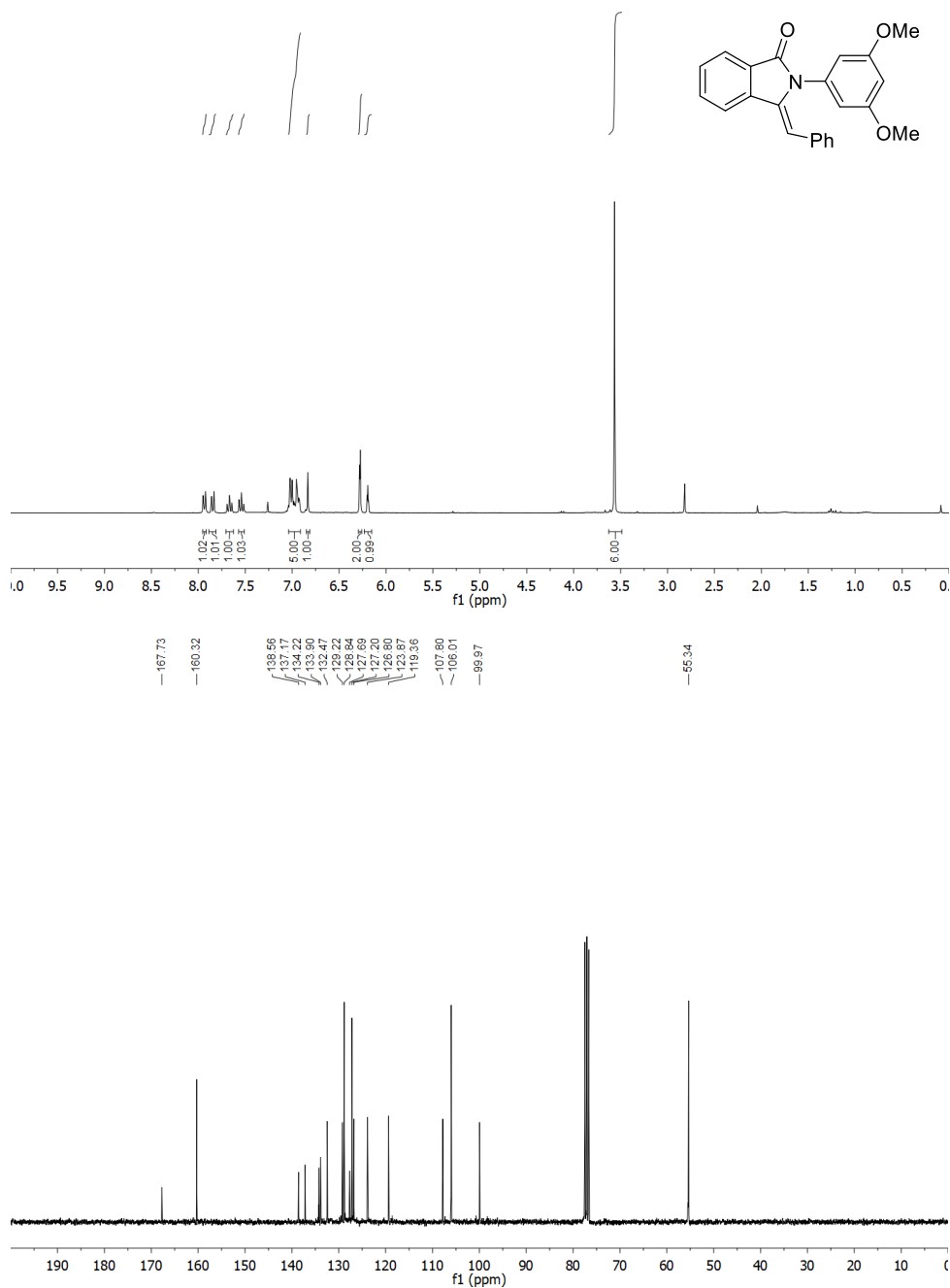
12I: *N*-(2,2-Dimethoxyethyl)-6-iodo-2,3-dimethoxybenzamide



13b: (Z)-2-(3,5-Dimethoxyphenyl)-3-(4-methoxy-2-methylbenzylidene)isoindolin-1-one

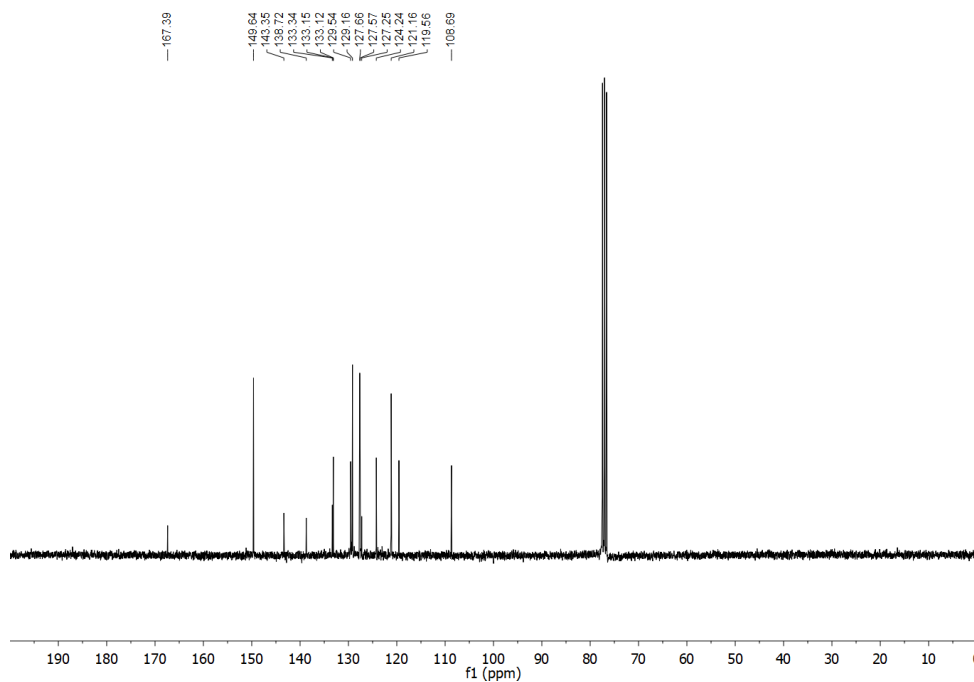
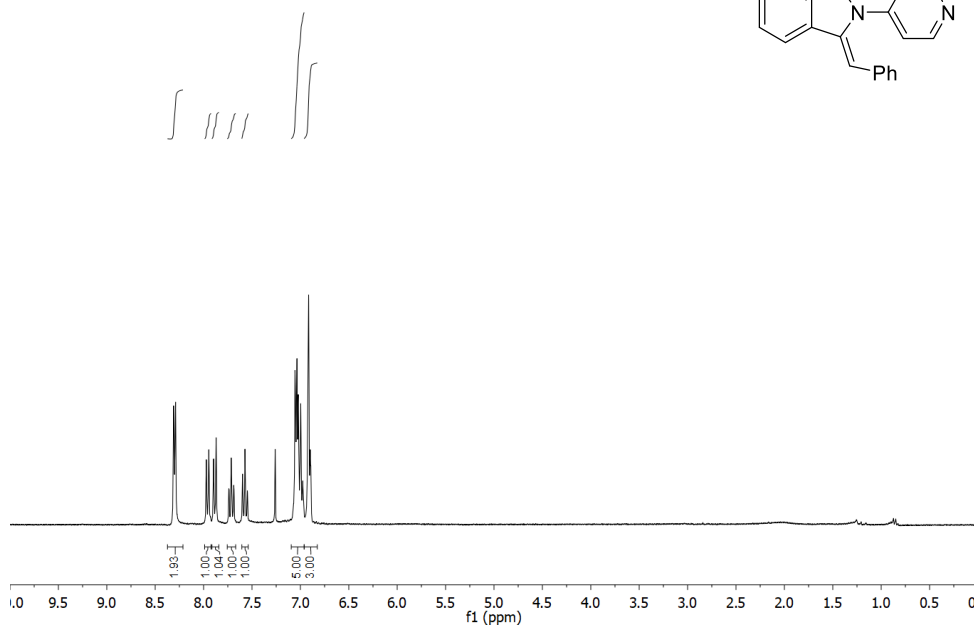
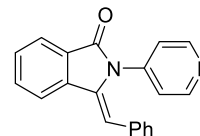


13c: (Z)-3-Benzylidene-2-(3,5-dimethoxyphenyl)isoindolin-1-one

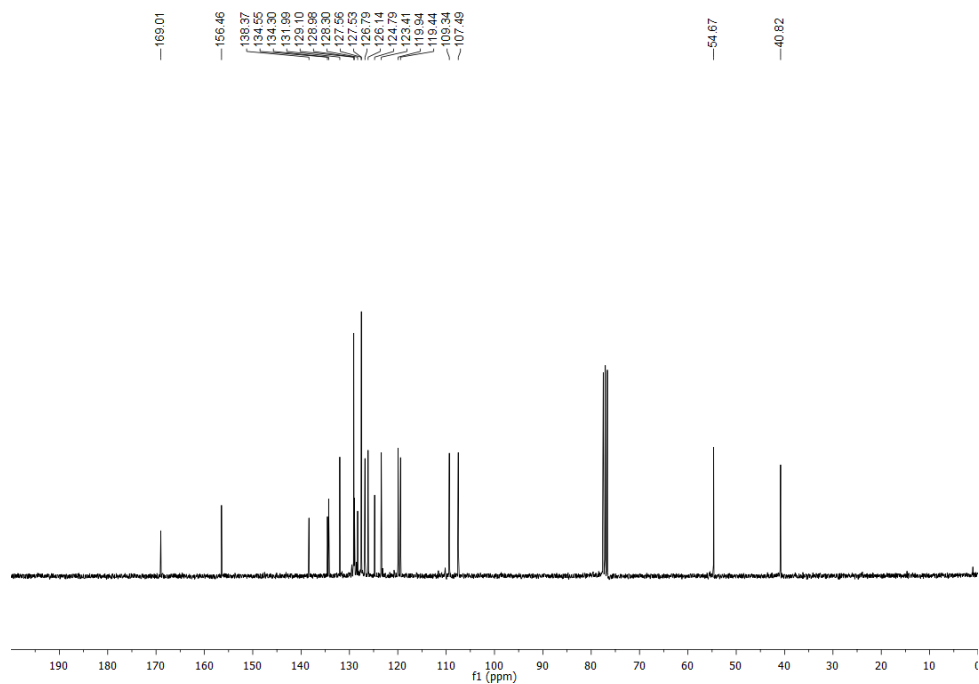
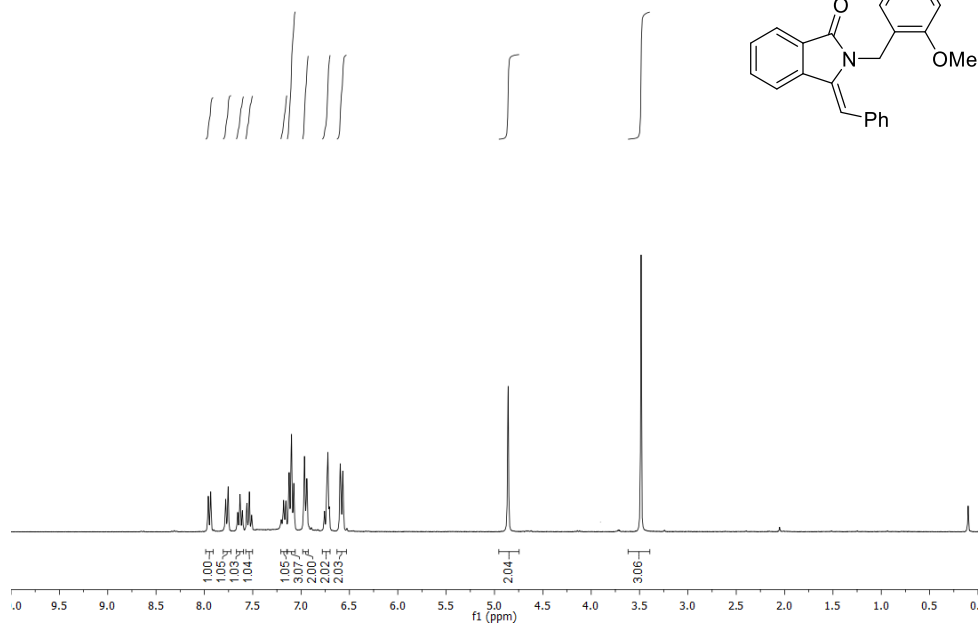
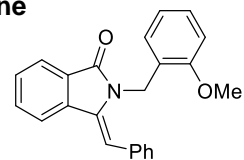


Appendix of spectra

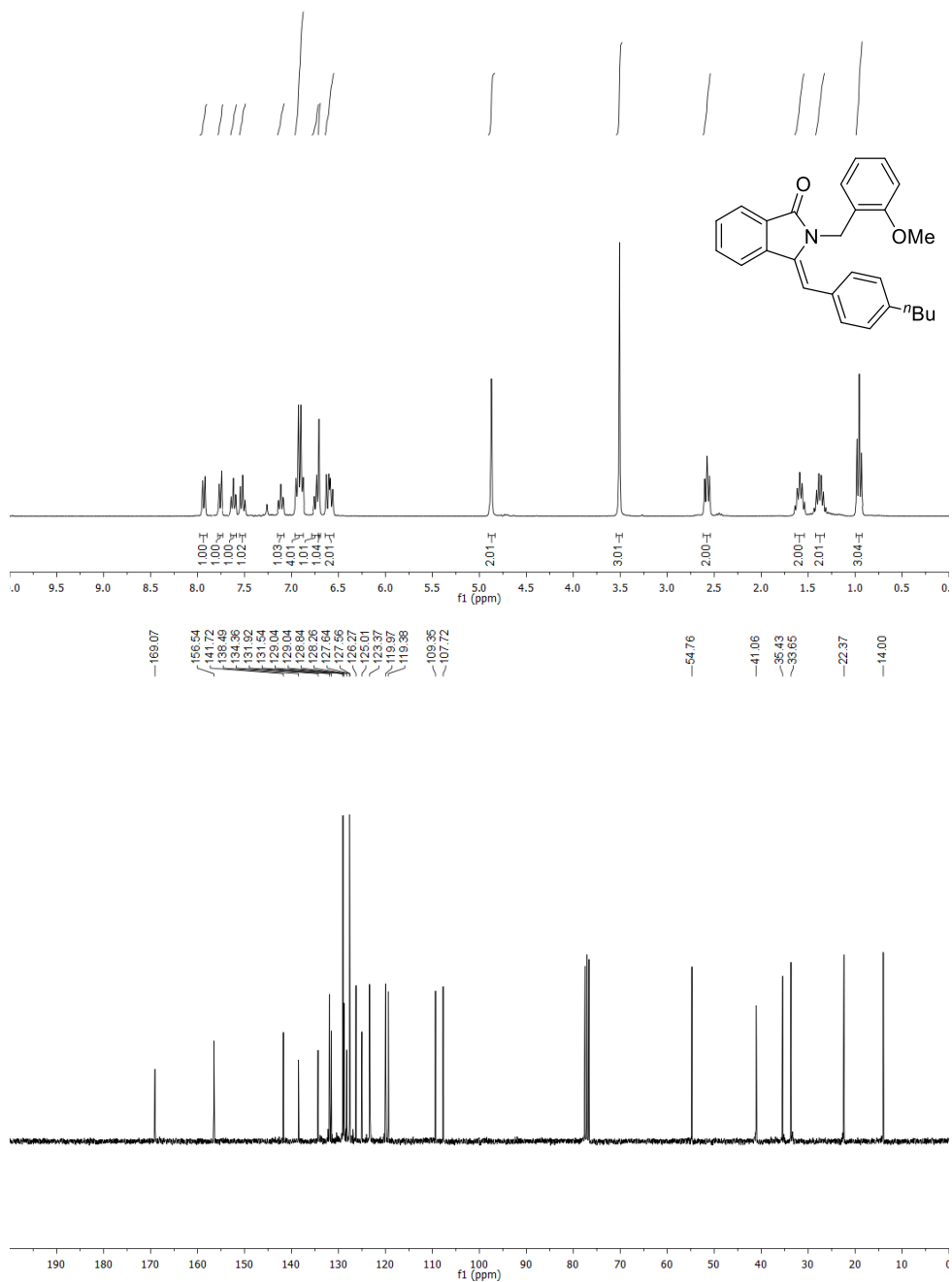
13d: (Z)-3-Benzylidene-2-(pyridin-4-yl)isoindolin-1-one



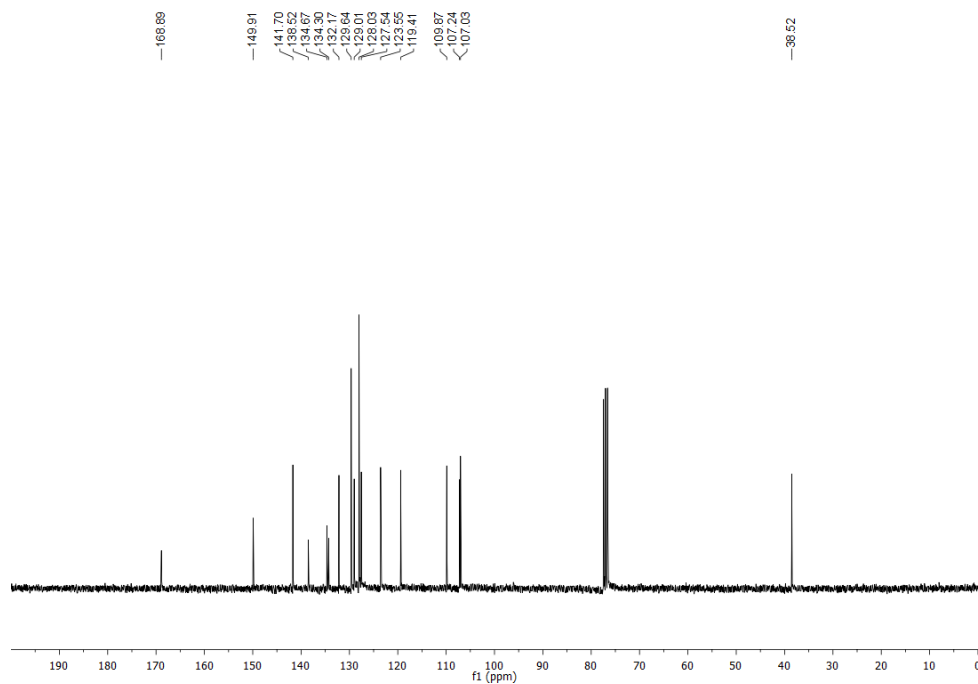
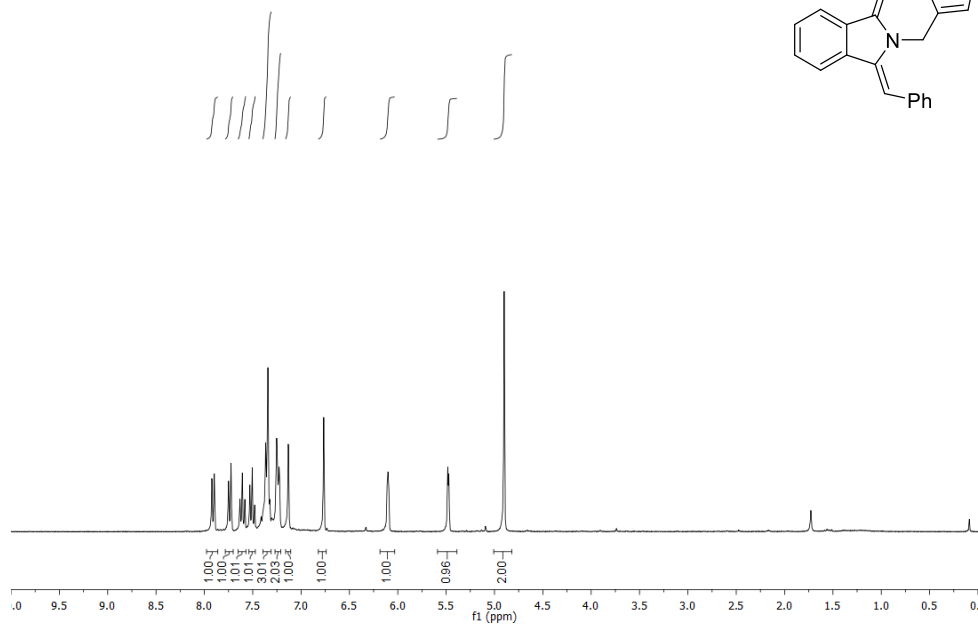
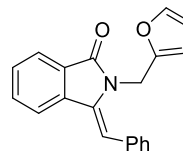
13f: (Z)-3-Benzylidene-2-(2-methoxybenzyl)isoindolin-1-one



13g: (Z)-3-(4-Butylbenzylidene)-2-(2-methoxybenzyl)isoindolin-1-one

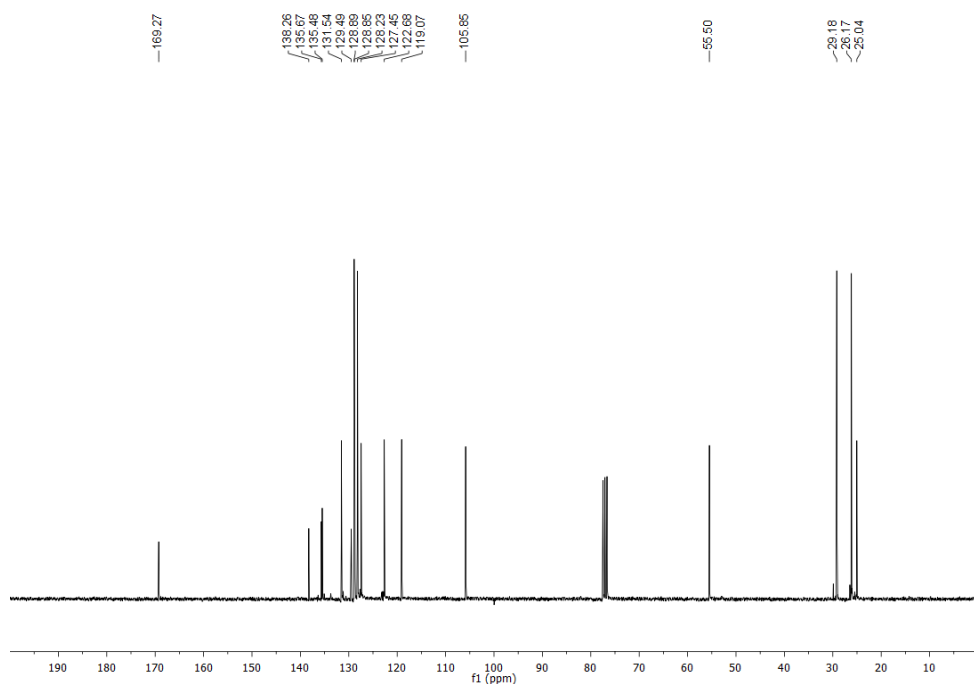
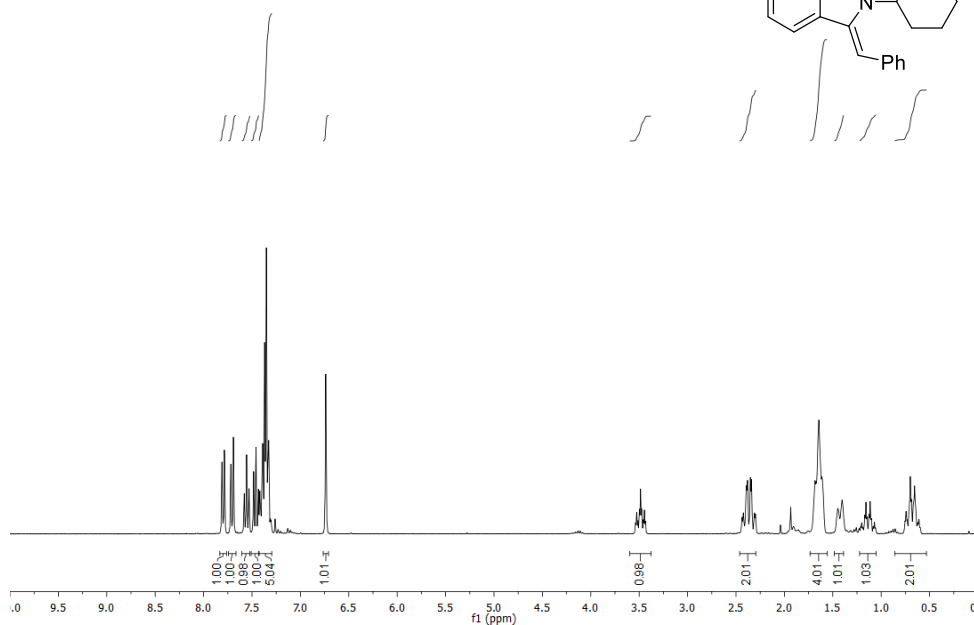
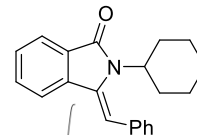


13h: (Z)-3-Benzylidene-2-(furan-2-ylmethyl)isoindolin-1-one

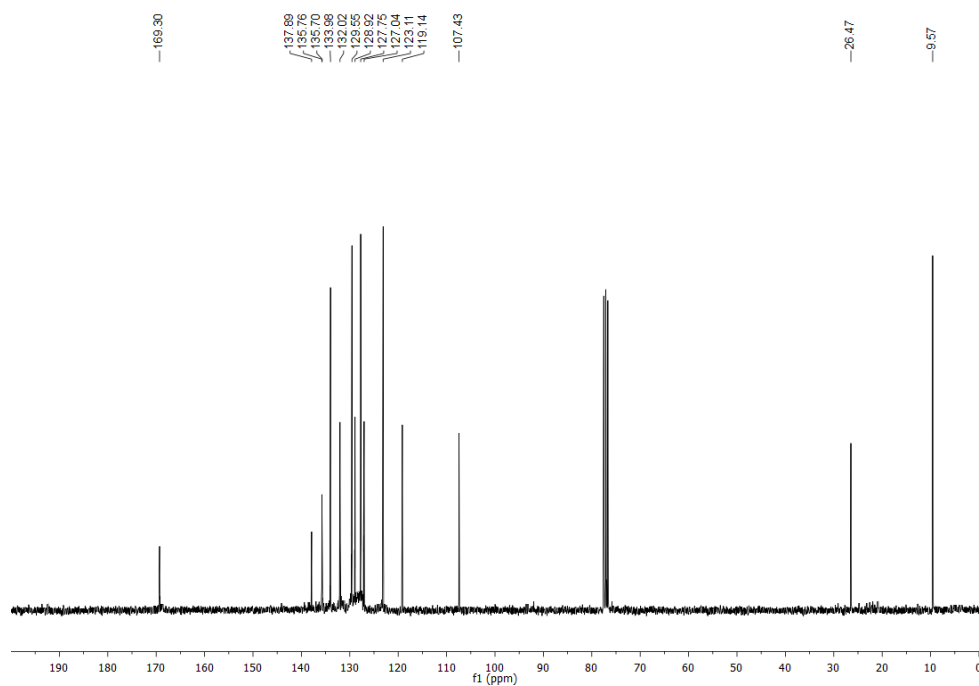
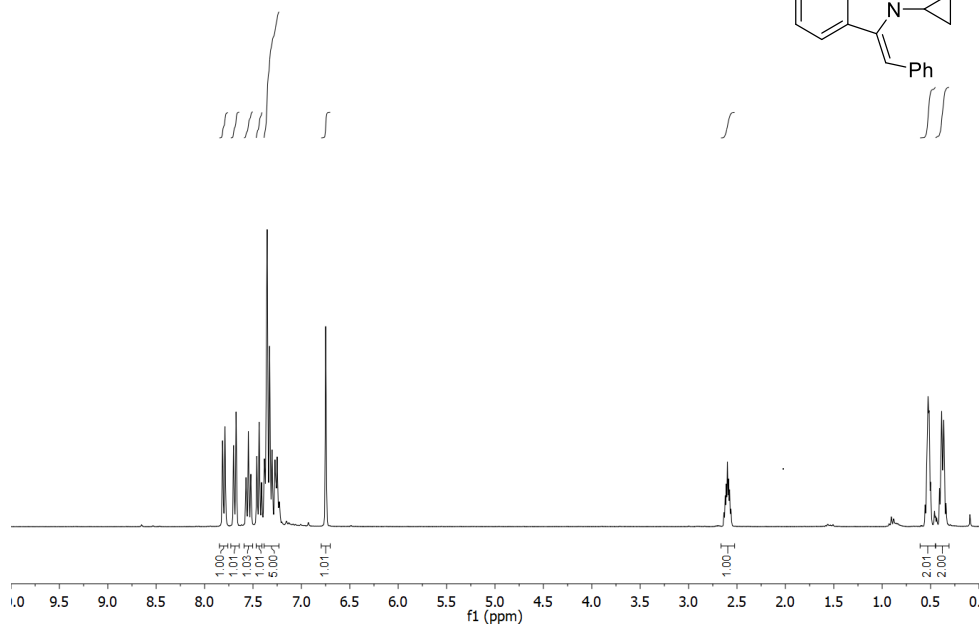
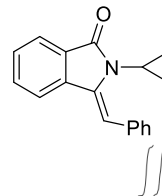


Appendix of spectra

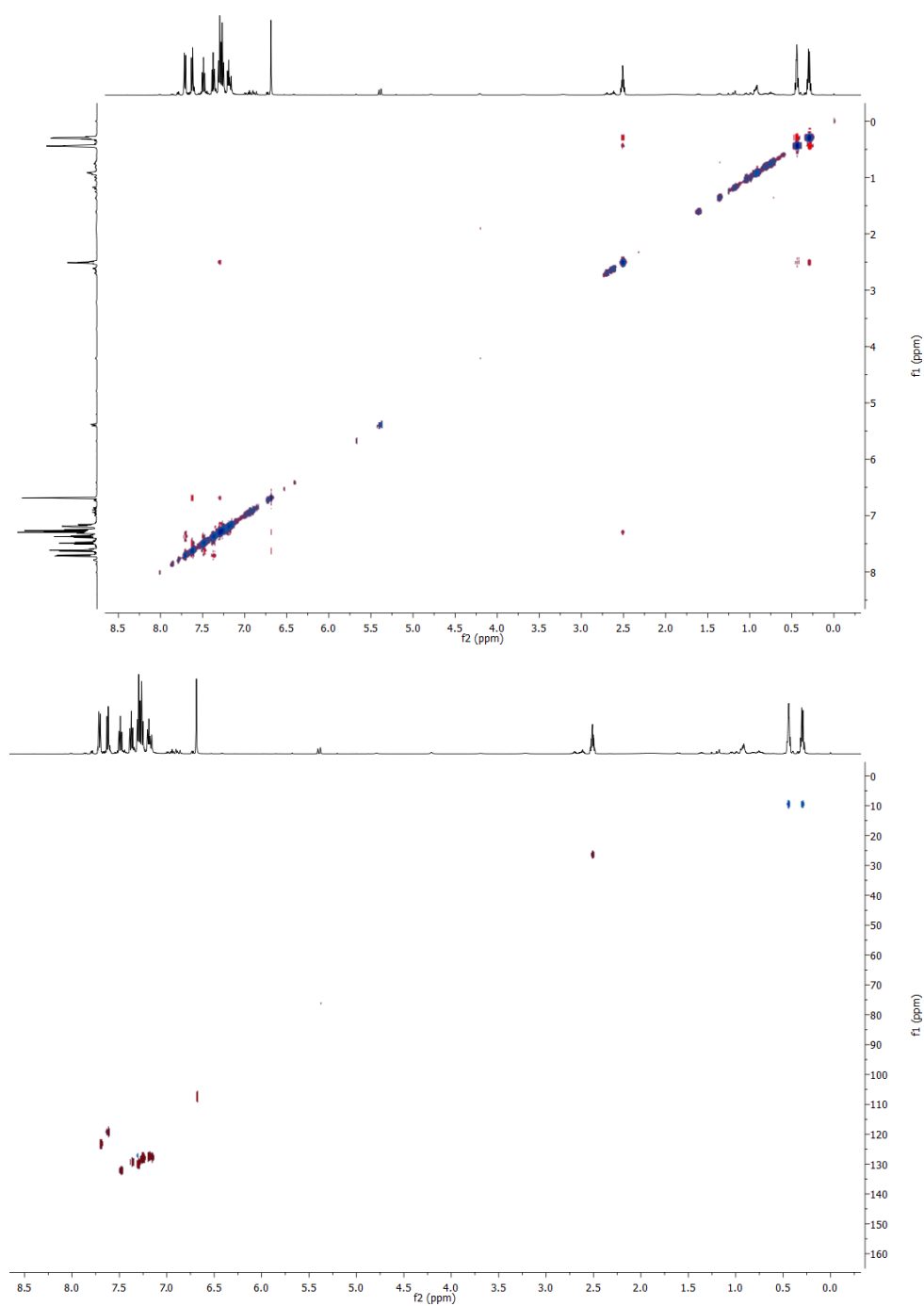
13j: (Z)-3-Benzylidene-2-cyclohexylisoindolin-1-one



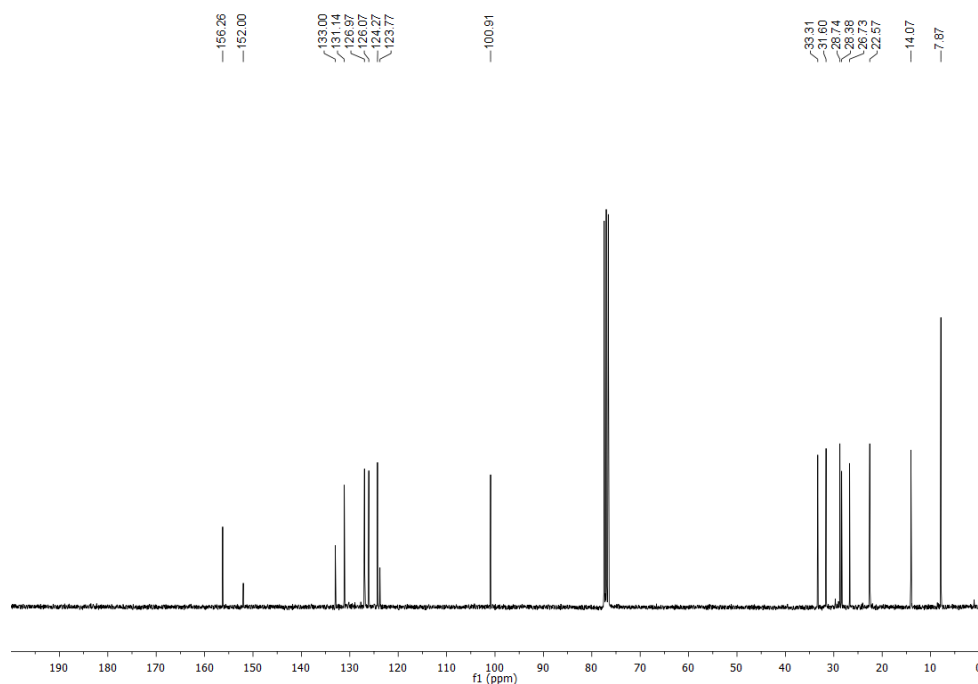
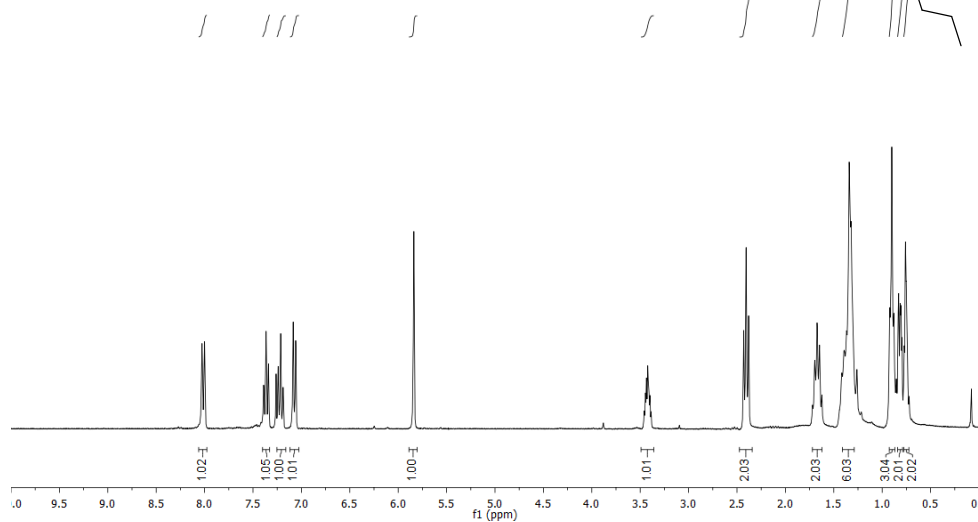
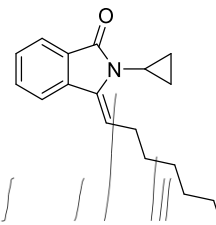
13k: (Z)-3-Benzylidene-2-cyclopropylisoindolin-1-one



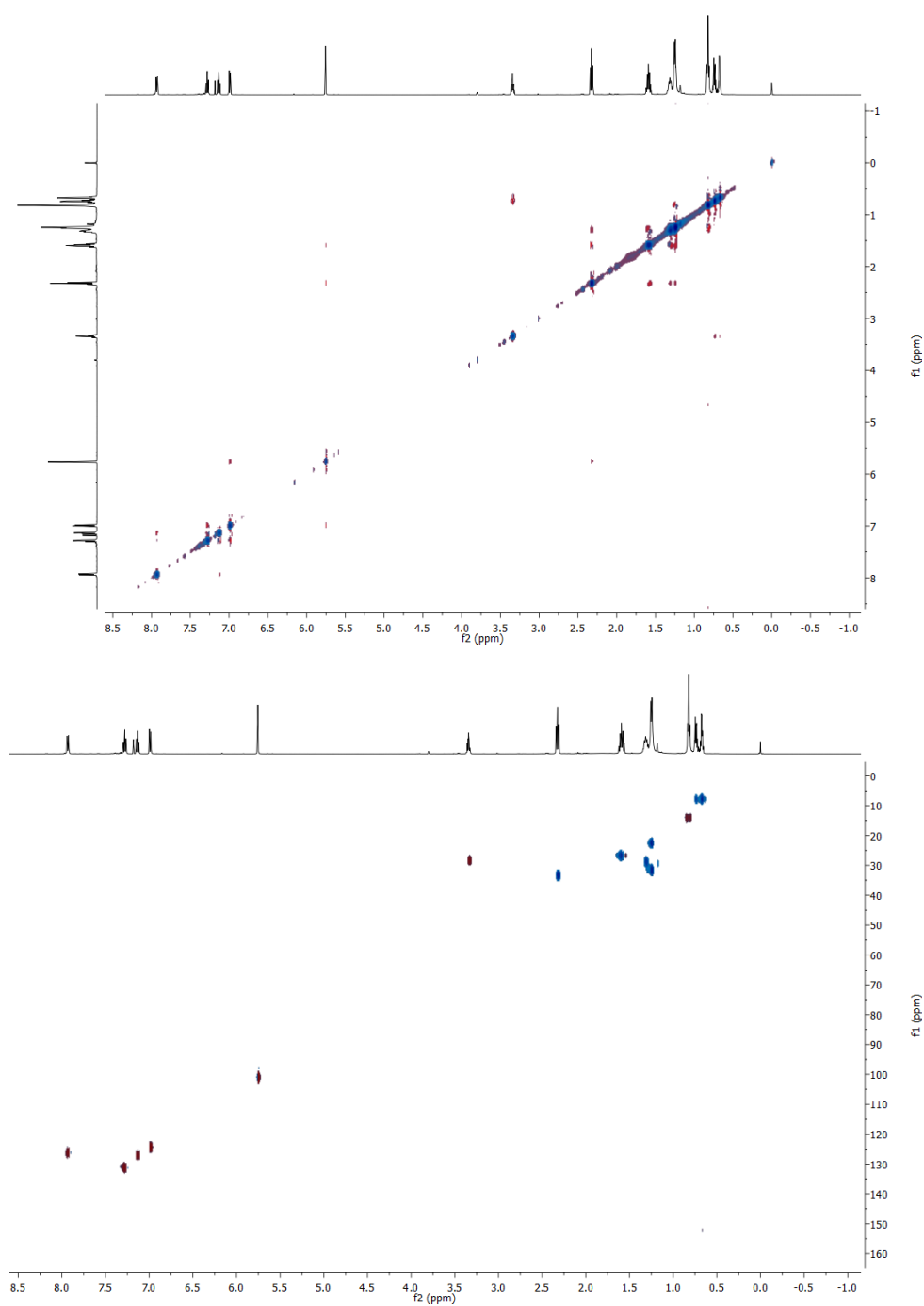
Appendix of spectra



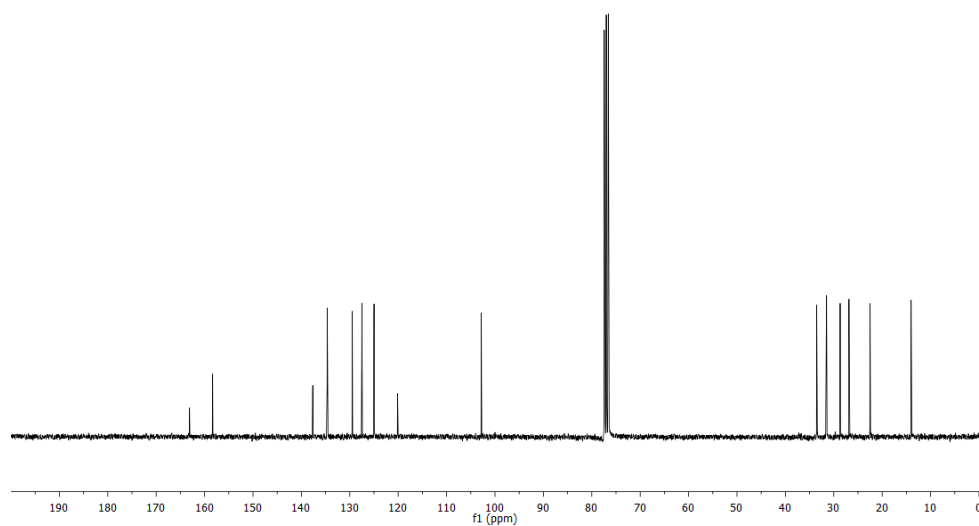
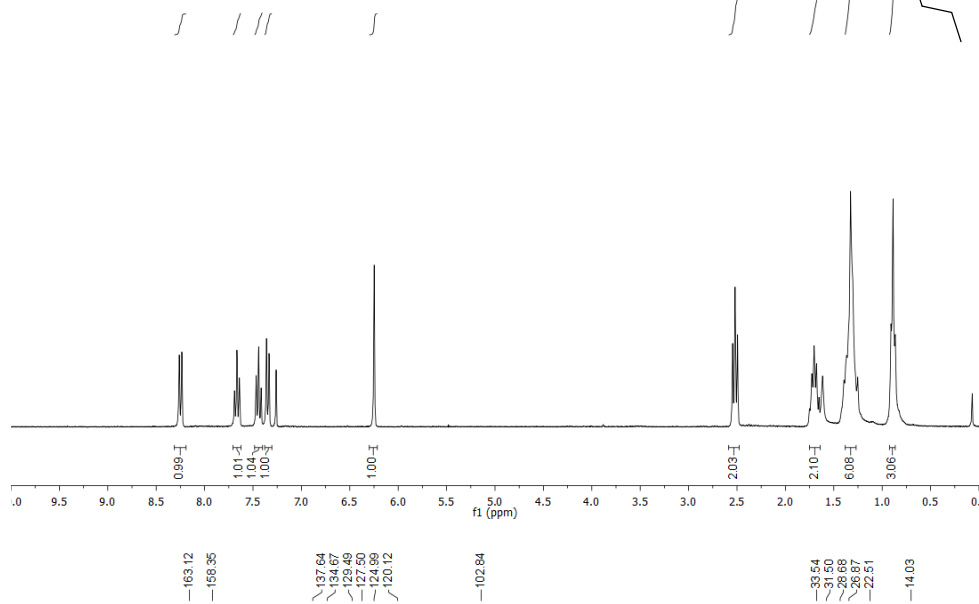
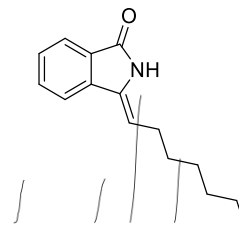
13l: (Z)-2-Cyclopropyl-3-heptylideneisoindolin-1-one



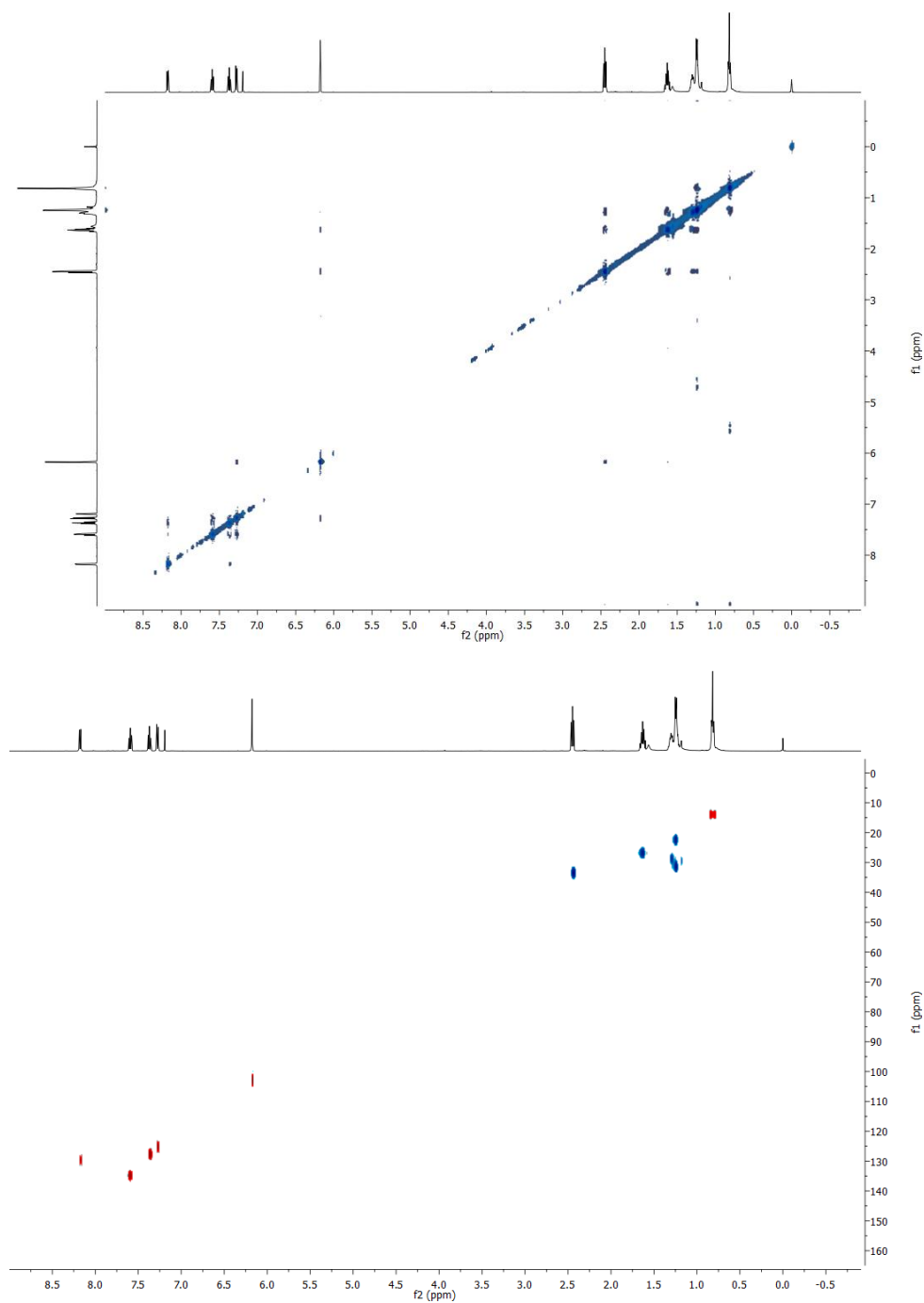
Appendix of spectra



13m: (Z)-3-Heptylideneisoindolin-1-one



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13o: (Z)-3-Benzylidene-2-isopropylisoindolin-1-one, 10o

