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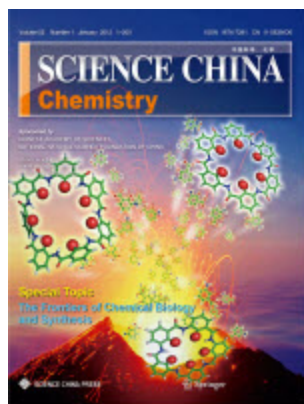
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Trifluoromethyl Radical Triggered Radical Cyclization of N-Benzoyl Ynamides leading to Isoindolinones

Maud Cassé^{1,2}, Christian Nisole², Héloïse Dossmann¹, Yves Gimbert^{1,3}, Jean-Marie Fourquez², Laure Haberkorn², Cyril Ollivier^{1*} & Louis Fensterbank^{1*}

¹Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 75005 Paris, France

²Institut de Recherches Servier, 78290 Croissy-sur-Seine, France

³Département de Chimie Moléculaire, CNRS, Université Grenoble Alpes, 38610 Gières, France

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Under photocatalytic reductive conditions, trifluoromethyl radical addition onto an ynamide followed by cyclization on a benzoyl moiety produces diverse isoindolinone platforms with good yields. The selectivity of the radical cyclization, N-benzoyl vs. N-benzyl as radical acceptor and the E/Z ratio of isomers have been rationalized by modeling.

Ynamides, trifluoromethylation, photocatalysis, cascade reactions, tandem processes, isoindolinones, modeling

1 Introduction

Inter- and intramolecular radical addition – cyclization tandems constitute a powerful method to assemble various scaffolds depending on the used partners [1-9]. For instance, this approach has been applied by using a trifluoromethyl radical as a trigger [10-12] to synthesize valuable fluorine containing substrates [13-16]. Because they have already proved to be versatile acceptors of electrophilic radicals like thiyl radicals (Scheme 1.1) [17-18], ynamides flanked with a

pending aryl group are particularly attractive as partners since they would allow a direct access to isoindolinones bearing a vinyltrifluoromethyl moiety (Scheme 1.3). Benzoyl ynamides have previously been used as radical acceptors in cascades leading to the formation of isoindoles, isoindolinones, and pyridoisoindolones (Scheme 1.2) [19-21]. Very recently, this chemistry has been nicely extended by Evano and coworkers by using copper(I) photoredox catalysis (Scheme 1.2) [22]. These comforting reports set the ground for our project and among the specifications of the aimed synthesis, was the use of photoredox catalysis for the generation of the radical species which

*Corresponding authors: cyril.ollivier@sorbonne-universite.fr
louis.fensterbank@sorbonne-universite.fr

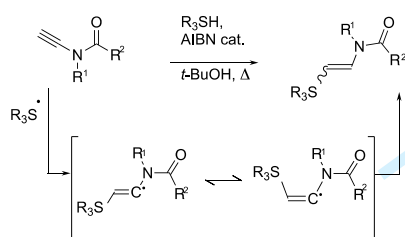
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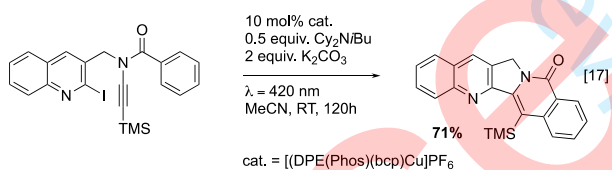
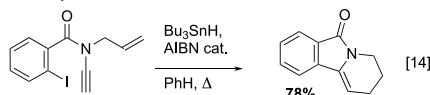
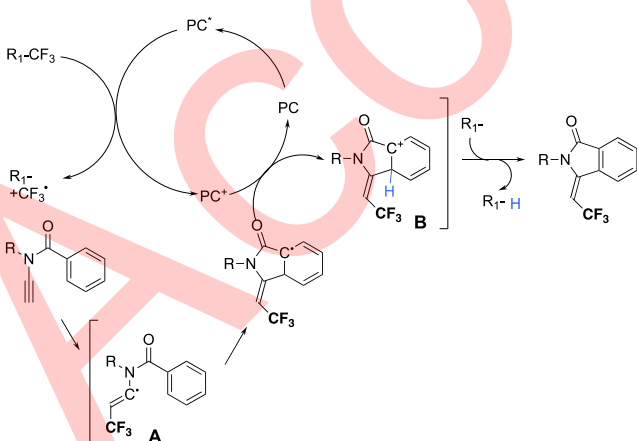
allows for sustainability as well as mild conditions to ensure molecular diversity [23-29]. We focused on generic precursors consisting of N-benzoyl ynamides. After intermolecular addition of the CF₃ radical, the resulting vinyl radical **A** would undergo intramolecular addition on the pendant aromatic ring. Rearomatization involving the photocatalytic cycle would terminate the synthetic sequence and produce the isoindolinone products (Scheme 1.3).

Previous works

1) intermolecular addition of an electrophilic radical onto an ynamide [12]



2) radical - cyclization tandems

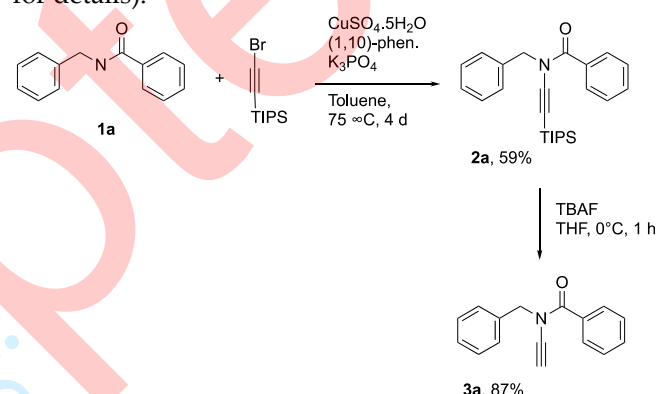
**This work**3) intermolecular addition of CF₃ radical - cyclization tandem in photoredox catalyzed conditions

Scheme 1 Ynamides as radical acceptors: context and objective of the work

2 Results and discussion

To study the scope of this transformation, several terminal ynamides were prepared through Hsung's

approach and conditions [30-32]. Copper-catalyzed alkylation of the corresponding amides **1** using TIPS protected acetylene showed the best versatility with different tested substrates. Thus when using a combination of CuSO₄·5H₂O, 1,10-phenanthroline and a weak base (K₃PO₄), no degradation was observed, despite long reaction times and the expected protected ynamides **2** were isolated in moderate to correct yields. As a representative example shown (Scheme 2), terminal ynamide **3a** was obtained in 51 % yield (2 steps) after deprotection of **2a** with TBAF (Scheme 2). This synthetic pathway was applied for all the ynamide precursors **3a-q** (see Supporting Information for details).



Scheme 2 Synthesis route for the ynamide **3a**

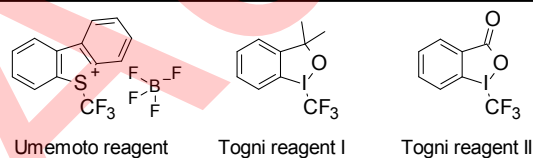
Our preliminary attempts of radical cyclization focused on the simplest term **3a** with no substitution on the aromatic rings. Several parameters were examined such as the solvent, the source of trifluoromethyl radical and the photocatalyst (see Table 1). Acetonitrile, a traditional solvent in photoredox reaction conditions was first used as well as Togni II reagent as a trifluoromethyl radical source [33,34] and we varied the photocatalyst keeping in mind the reduction potential of Togni II reagent (-0,32 V/SCE in MeCN) [35]. While the use of Ru(bpy)₃Cl₂ (E Ru(II)* / Ru(III) = -0.81 V/SCE in MeCN) [36] validated the strategy, a slightly improved yield was obtained with the more reducing Ir(ppy)₂(dtbpy).PF₆ (E Ir(III)* / Ir(IV) = -0.96V/SCE in MeCN). A trend which was confirmed with Ir(ppy)₃ (E Ir(III)* / Ir(IV) = -1.73V/SCE in MeCN) since the best yield of **4a** was obtained (71%). While rarely used in photoreductive processes [37-40], 4CzIPN could provide some interesting reactivity but in a weaker yield (50 % of **4a**).

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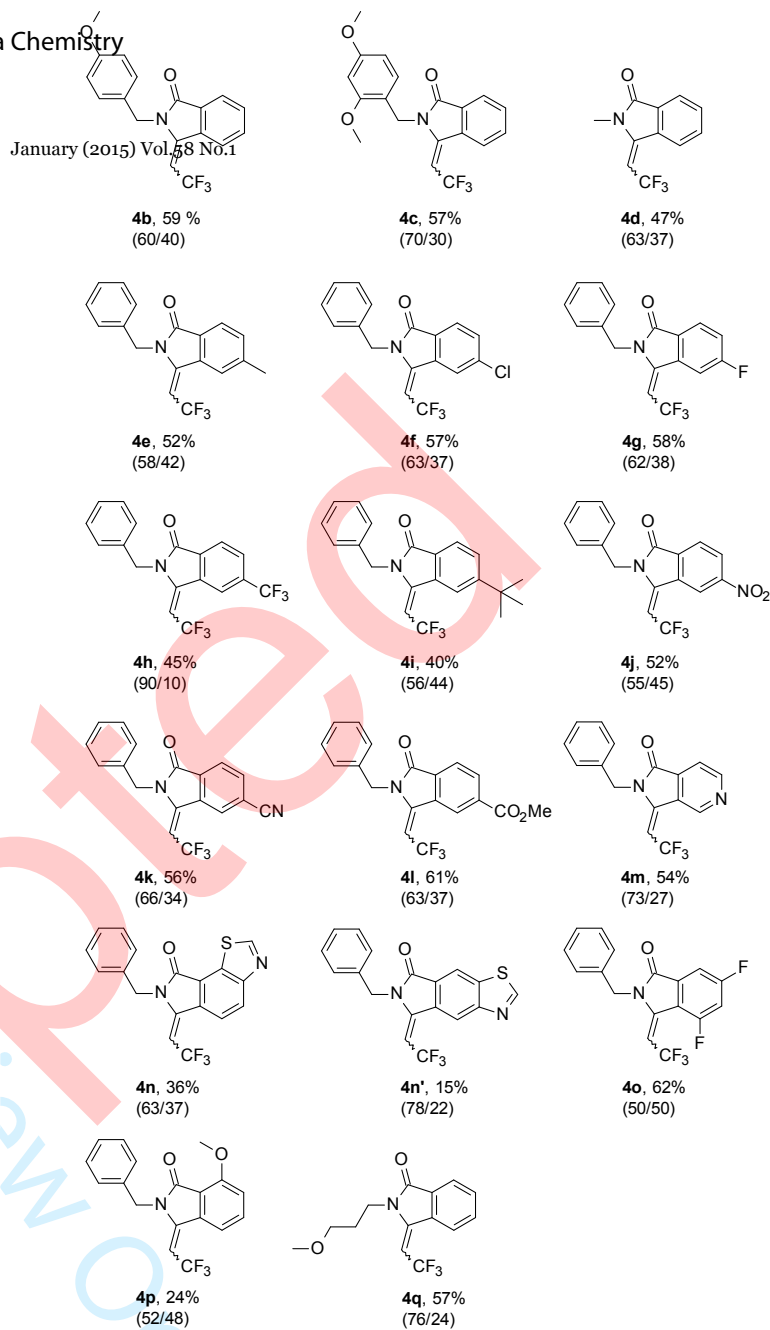
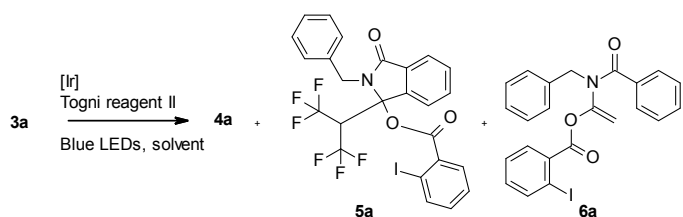
We thus pursued our optimization study with Ir(ppy)₃ and showed that Umemoto reagent was not very competent in this reaction compared to Togni I & II reagents (entry 5 vs. entries 3 & 6). Solvent screening confirmed that acetonitrile was the best (entry 3 vs. entries 7-10). Reactions with Togni II generally showed the presence of minor carboxylate adducts **5a** and **6a** (approximately 5-8% of **5a** and 3% of **6a** detected by HPLC) resulting from the carboxylation of the ynamide moiety and a double addition of the radical CF₃ (Scheme 3) [41,42]. We therefore stuck to the use of Togni I reagent in further studies.

Table 1. Optimization of the reaction conditions

Entry	Catalyst	CF ₃ reagent	Solvent	Time	Yield (%), E : Z
1	Ru(bpy) ₃ Cl ₂	Togni II	MeCN	48 h	36, 97 : 3
2	Ir(ppy) ₂ (dtbpy).PF ₆	Togni II ^{b)}	MeCN	21 h	45, 50 : 50
3	Ir(ppy) ₃	Togni II	MeCN	6 h	71, 86 : 14
4	4CzIPN ^{b)}	Togni II	MeCN	4 h	50, 92 : 8
5	Ir(ppy) ₃ ^{b)}	Umemoto	MeCN	23 h	14 ^{c)} , 100 : 0
6	Ir(ppy) ₃	Togni I	MeCN	5 h	64 ^{d)} , 81 : 19
7	Ir(ppy) ₃	Togni II	Acetone	4 h	54, 85 : 15
8	Ir(ppy) ₃	Togni II	DMF	3 h	51, 62 : 38
9	Ir(ppy) ₃	Togni II	t-BuOH	24 h	55, 75 : 25
10	Ir(ppy) ₃	Togni II	AcOEt	3 h	62, 92 : 8



a) Reaction conditions: N-benzyl-N-ethynyl-benzamide (**3a**, 0.2 mmol, 1 equiv.), CF₃ reagent (1.2 eq), catalyst (2.5 mol% unless otherwise specified), solvent (0.1M, 2 mL), freeze pump, irradiation under blue LEDs for 3-48h. b) Catalyst loading: 5 mol%, c) addition 1.2 equiv. of Li₂CO₃, d) 2 trials on a 1 mmol scale.



Scheme 3 By-products formed from the use of the Togni II reagent

Table 1 also shows that the E/Z ratio of product **4a** is very variable and is notably dependent on the photocatalyst and the reaction time. The stereochemistry of the E/Z isomers was attributed by NOESY and fully confirmed by a X-ray diffraction analysis of both isomers E and Z. Logically, we could show that E/Z isomerization is dependent on the reaction conditions [43]. For instance, starting from a 84:16 E/Z mixture of **4a**, a 55:45 mixture could be obtained after 2 h of LED irradiation with 4CzIPN and after 18 h with Ir(ppy)₃.

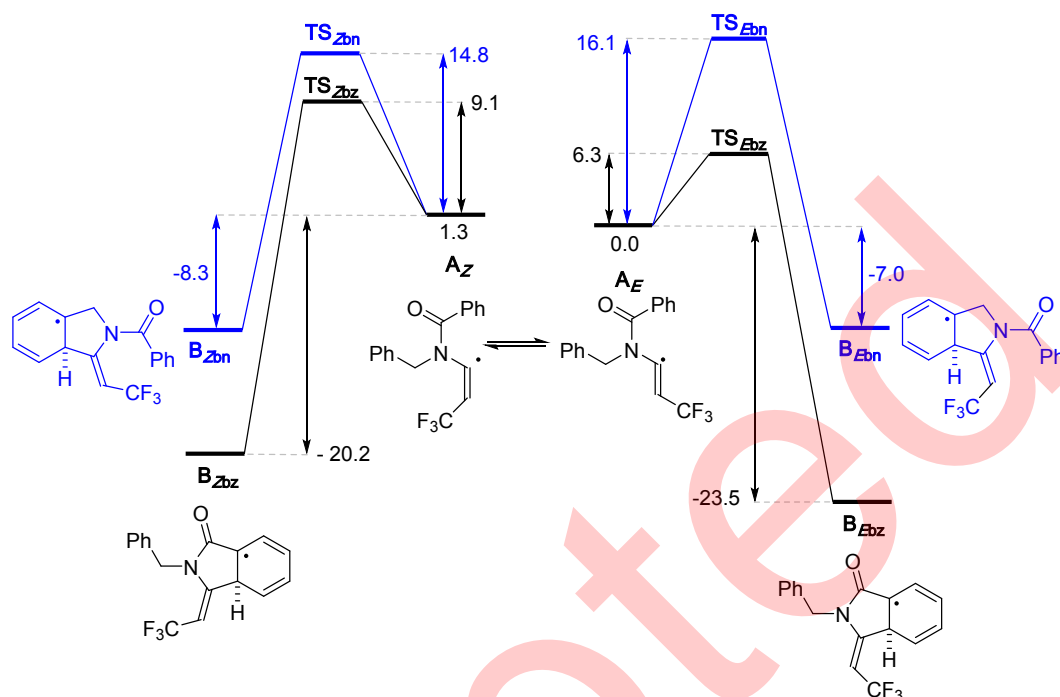
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We nevertheless studied other ynamide precursors **3** and obtained cyclization products **4** (Scheme 4) in moderate to good yields. The N-group was substituted by a p-methoxybenzyl (PMB) and a 2,4-dimethoxybenzyl protecting groups (**4b** and **4c**) without trouble. Finally, the N-methyl substituted isoindolinone **4d** could also be obtained in 47 %. We also varied the aryl group of the benzoyl moiety. The transformation was compatible with a broad range of substituents on para position such as alkyles (**4e**, **4i**), halogens (**4f**, **4g**, **4h**) or other electron-withdrawing groups (nitro **4j**, cyano **4k**, ester **4l**) leading to cascade adducts in moderate to good yields (40 – 61 %). Pleasingly, a pyridyl moiety was amenable to this tandem process giving rise to an original heterocyclic framework (54 % of **4m**). With ortho-substituted benzoyl moieties, the reaction proved to be more sluggish (24% of **4p**) but only one regioisomer was isolated, resulting from the homolytic aromatic substitution at the non-substituted position [44].

It was also observed that the cyclisation process was favored compared to a 1.5-*H* shift on an alkyl chain (57% of **4q**) [45].

Scheme 4 Scope of the process (E/Z ratio precised)



Scheme 5 Energetic profiles for cyclisation of ynamides: energies given are ΔG in kcal/mol.

All these findings confirmed the validity of this approach to synthesize isoindolinones. It was also notable that the cyclization of the intermediate vinyl radical always took place on the N-benzoyl moiety and no product resulting from the cyclization on the benzyl group was isolated. To rationalize this observation, electronic structure calculations were performed, using the PBE0-D3BJ/def2TZVP level (Scheme 5). The addition of the CF_3 radical on the ynamide happens to be a very exothermic barrier-free process ($\Delta G = -33.7$ kcal/mol, see SI). The E or Z configuration of the vinyl radical does not seem to influence the stability of the species, both indeed differ only by 1.3 kcal/mol. From the vinyl radical A_E , the intramolecular cyclization towards the benzoyl moiety proceeds via a barrier of 6.3 kcal/mol whereas the addition of the radical on the benzyl side costs 16.1 kcal/mol (black and blue pathways, Scheme 5). The same observation was made for the vinyl radical of Z configuration although the difference between the barriers of the two paths is smaller (ca. 6 vs 10 kcal/mol for the E variant). Finally, cyclohexadienyl radicals of type **B**, obtained after cyclization, are again much more stable than the cyclohexadienyl radicals resulting from the cyclization onto the benzyl group (by 16.5 kcal/mol for the E isomer and 11.9 kcal/mol for the Z isomer).

Considering more carefully the electronic structure and molecular orbitals (MOs) of the intermediate vinyl radical helps to shed more light on the unexpected regioselectivity of this cyclization process. The DFT-computed electronic structure of radical **A** is displayed on Figure 1 together with the Kohn-Sham orbitals. The SOMO orbital is localized mainly on the vinyl moiety, in accordance with the expected structure of this intermediate. Interestingly, the three first LUMO exhibit an electron density localized on the same region but also on the benzoyl moiety. This observation aligns with the experimental observation that the benzoyl moiety favours cyclisation. Therefore, the weaker LUMO-SOMO gap orients the radical attack on the benzoyl group only.

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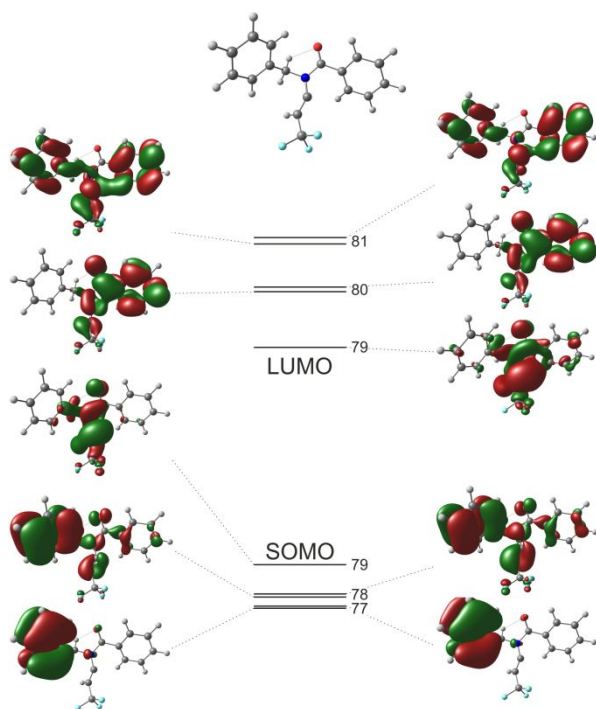
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Figure 1 DFT-computed structure of **4aE** and corresponding Kohn-Sham orbitals.

4 Conclusions

In summary, we reported a new cascade reaction for the synthesis of trifluoromethyl substituted isoindolinones, involving sequential radical trifluoromethylation of ynamides followed by radical cyclization onto benzoyl moieties under photocatalytic conditions. The regioselectivity of the cyclization process (N-benzyl vs. N-benzoyl) is controlled and the *E* isomer is formed as major diastereomer. These findings were supported by DFT calculations.

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Conflict of interest The authors declare that they have no conflict of interest.

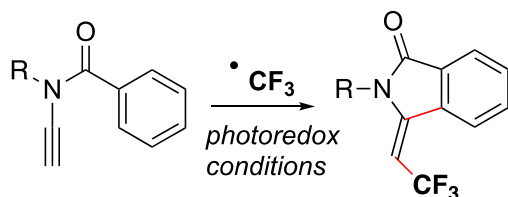
Supporting information The supporting information is available online at <http://chem.scichina.com> and <http://link.springer.com/journal/11426>. The X-Ray crystal structures were deposited at the Cambridge Crystallographic Data Centre with numbers CCDC 1949295 (compound **4aE**) and CCDC 1949296 (compound **4aZ**) and can be obtained free of charge via www.ccdc.cam.ac.uk.

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regio- and stereoselective tandem

SUPPORTING INFORMATION

**Trifluoromethyl Radical Triggered
Radical Cyclization of N-Benzoyl
Ynamides leading to Isoindolinones**

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¹Sorbonne Universit , CNRS, Institut Parisien de Chimie Mol culaire, IPCM, 75005 Paris, France

²Institut de Recherches Servier, 78290 Croissy-sur-Seine, France

³D partement de Chimie Mol culaire, CNRS, Universit  Grenoble Alpes, 38610 Gi res, France

E-mail : cyril.ollivier@sorbonne-universite.fr

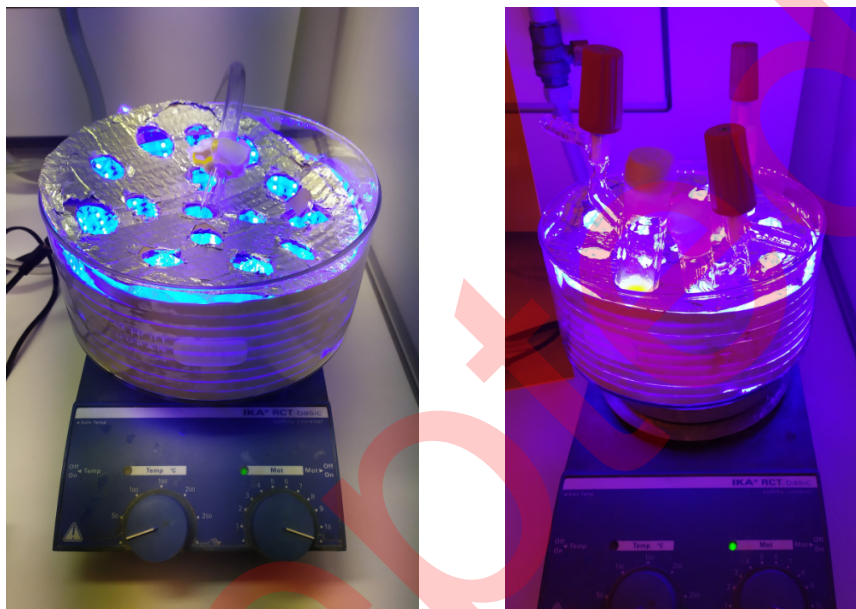
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General informations

Photocatalyzed reactions were irradiated under a blue LED light array homemade apparatus. Reactions were carried out in Schlenk tubes at a distance of approximately 2 cm from the LEDs and an average temperature of 27°C was maintained by an air cooling system.



If there were issues with solubility (syntheses of compounds **4j** and **4k**), reactions were heated at 40°C in an oil bath and irradiation occurred with a 365 nm EvoluChem™ LED.

All reactions were performed under an atmosphere of argon unless otherwise stated, and monitored by thin layer chromatography (T.L.C.) or UPLC-MS. T.L.C. were carried out on ready for use plates of silica gel 60 F254 (Merck) and visualization was performed under an U.V. lamp at 254 nm. Reaction monitoring was conducted with Waters Acquity® instrument, fitted with PDA and SQD2 detectors (ESI source in positive mode). Injection volumes were 0.5 or 1 μL , the column was a Waters Acquity UPLC® BEH C_{18} 1.7 μm and temperature was kept at 40°C. Mobile phase A consisted of $\text{H}_2\text{O}/\text{MeCN}/\text{formic acid}$ (98/2/0.1) and mobile phase B of $\text{MeCN}/\text{H}_2\text{O}/\text{formic acid}$ (98/2/0.1). Gradient ran from 100% A to 100% B in 3 min. Products were purified by flash chromatography using packed silica gel columns. Unless otherwise specified, all commercially available reagents were used as received.

All the analyses were conducted by Servier analysis department. ^1H and ^{13}C NMR spectra were recorded on Brüker 400 or 500 MHz machine operating at ambient temperature probe, in $\text{DMSO}-d_6$ or CDCl_3 . ^1H NMR spectra were recorded at 400 MHz or 500 MHz, ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz and ^{19}F spectra were recorded at 376 MHz on a Brüker 400 MHz machine

Chemical shifts (δ) were quoted in parts per million (ppm). For ^1H NMR spectra, the chemical shifts were attributed relative to residual CHCl_3 (7.26 ppm) or residual DMSO (2.50 ppm). For ^{13}C NMR spectra (JMOD), the attributions were done relative to residual CHCl_3 (77.16 ppm) or residual DMSO (40 ppm). Coupling constants (J) were quoted in Hertz (Hz). The following abbreviations were used to give the multiplicity of the NMR signals: s: singlet, bs: broad singlet, d: doublet, t: triplet, q: quartet, quint: quintet, dd: doublet – doublet... Infrared spectra were recorded with the ATR technic on a

Brüker Tensor 27 spectrometer. Mass spectrometry (HRMS) was performed with a Thermo-Fischer Scientific spectrometer (by ESI+: Orbitrap Velos Pro or by EI: HREIGC, HRMS magnetic Sector Ms DFS). In a few cases, the mass spectrometry was done on an Agilent Technologies (ESI; LC/MSD TOF). Melting points were measured on the Büchi Melting point B-540 apparatus.

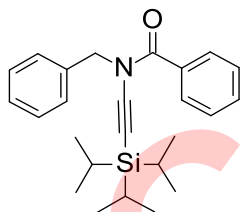
General procedure 1 for the synthesis of protected ynamides 2a-q

Amides **1a-q** were synthesized according to the literature.¹

In a sealed tube (Radley) was loaded the amide **1** (1 equiv.), CuSO₄·5H₂O (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.) and K₃PO₄ (2.2 equiv.) under argon. To this mixture was added the 2-bromoethynyl(triisopropyl)silane^{2,3} (1.1 equiv., 0.1M) in toluene. The reaction mixture was capped and heated at 75°C for a given reaction time. The reaction mixture was cooled down to room temperature, filtrated through Celite (rinced with DCM). The filtrate was concentrated under vacuum. The crude product was purified by silica gel flash column chromatography (liquid deposit in Heptane/ CH₂Cl₂ 50/50; gradient eluent, CH₂Cl₂ in heptane/pentane or diethyl ether in pentane).

General procedure 1': use of CuSO₄·5H₂O (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), K₃PO₄ (2 equiv.) and 2-bromoethynyl(triisopropyl)silane (1.2 equiv., 0.1M).

N-benzyl-N-(2-triisopropylsilylethynyl)benzamide **2a**



Starting from N-benzylbenzamide **1a** (2.83 g, 13.5 mmol), CuSO₄·5H₂O (335 mg, 1.4 mmol), 1,10-phenanthroline (485 mg, 2.7 mmol), K₃PO₄ (5.71 g, 26.9 mmol) and 2-bromoethynyl(triisopropyl)silane (4.21 g, 16.0 mmol) under argon, using **General procedure 1'** and heating at 75°C for 3.5 days. The crude was purified to afford N-benzyl-N-(2-triisopropylsilylethynyl)benzamide **2a** as a yellow oil (3.10 g, 59 % yield). Spectral data are in accordance with those reported in the literature.⁴

IR (neat): 2167, 1676, 881, 745 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.7 (d, *J* = 7.7 Hz, 2 H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.4 (m, 5 H), 4.85 (s, 2 H), 0.8 (s, 21 H)

¹ For the synthesis of the amides, see: Couty S, Liegault B, Meyer C, Cossy J. *Tetrahedron* **2006**, *62*, 3882-3895

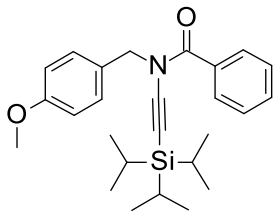
² Nicolai S, Sedigh-Zadeh R, Waser J. *J. Org. Chem.* **2013**, *78*, 3783-3801

³ Rubin Y, Lin SS, Knobler CB, Anthony J, Boldi AM, Diederich F. *J. Am. Chem. Soc.* **1991**, *113*, 6943-6949

⁴ Zhang X, Zhang Y, Huang J, Hsung RP, Tracey MR, Kurtz KCM, Oppenheimer J, Petersen ME, Sagamanova IK, Shen L, Tracey MR. *J. Org. Chem.* **2006**, *71*, 4170-4177

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.6, 136.2, 133.8, 131.7, 128.9 (2C), 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.4, 99.4, 71.5, 52.3, 18.7 (6C), 11 (3C)

N-[(4-methoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2b**



Starting from N-[(4-methoxyphenyl)methyl]benzamide **1b** (6.04 g, 25 mmol), CuSO₄·5H₂O (445 mg, 2.5 mmol), 1,10-phenanthroline (902 mg, 5.0 mmol), K₃PO₄ (6.71 g, 50.1 mmol) and 2-bromoethynyl(triisopropyl)silane (7.85 g, 30.0 mmol) under argon, using **General procedure 1'** and heating at 75°C for 4.5 days. The crude was purified to afford N-[(4-methoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2b** as a yellow oil (1.87 g, 18 % yield).

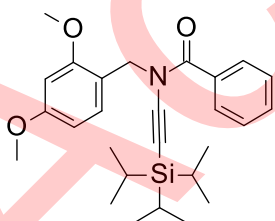
IR (neat): 2171, 1678 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.69 (d, *J* = 7.5 Hz, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 4.75 (s, 2 H), 3.74 (s, 3 H), 0.82 (s, 18 H), 0.82 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.9, 160, 134.2, 132.2, 130.5 (2C), 128.5 (2C), 128.3 (2C), 128.1, 114.3 (2C), 100, 71.6, 55.6, 51.9, 18.8 (6C), 11.1 (3C)

HRMS (ESI): calcd. for C₂₆H₃₆N O₂ Si ([M+H]⁺) 422.2510, found 422.2511

N-[(2,4-dimethoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2c**



Starting from N-[(2,4-dimethoxyphenyl)methyl]benzamide **1c** (940 mg, 3 mmol), CuI (57 mg, 0.3 mmol), 1,10-phenanthroline (108 mg, 0.6 mmol), K₃PO₄ (1.27 g, 6 mmol) and 2-bromoethynyl(triisopropyl)silane (941 mg, 3.6 mmol) under argon, using **General procedure 1'** and heating at 75°C for 4 days. The crude was purified to afford N-[(2,4-dimethoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2c** as a yellow oil (423 mg, 30 % yield).

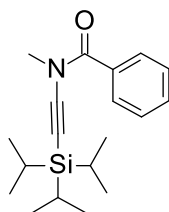
IR (neat): 2170, 1681, 1612, 1591, 1512 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.65 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.5 (tt, *J* = 7.4, 1.3 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.2 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 2.4 Hz, 1 H), 6.49 (dd, *J* = 8.3, 2.4 Hz, 1 H), 4.71 (s, 2 H), 3.77/3.75 (2 s, 6 H), 0.76 (d, 18 H), 0.75 (m, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.7, 161.3, 159, 134.4, 131.8, 131.5, 128.5 (2C), 128.4 (2C), 115.6, 105.01, 99.3, 98.8, 71.3, 56, 55.7, 47.1, 18.7 (6C), 11.02 (3C)

HRMS (ESI): calcd. for C₂₇H₃₇N O₃ Si ([M]⁺) 451.2537, found 451.2518

N-methyl-N-(2-triisopropylsilylethynyl)benzamide **2d**



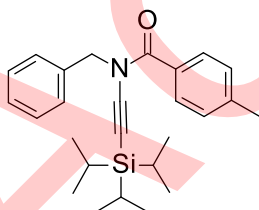
Starting from N-methyl-N-(2-triisopropylsilylethynyl)benzamide **1d** (700 mg, 5.18 mmol), CuSO₄·5H₂O (129 mg, 0.52 mmol), 1,10-phenanthroline (187 mg, 1.0 mmol), K₃PO₄ (2.20 g, 10.4 mmol) and 2-bromoethynyl(triisopropyl)silane (1.49 g, 5.7 mmol, 1.1 equiv.) under argon, using **General procedure 1'** and heating at 75°C for 4 days. The crude was purified to afford N-methyl-N-(2-triisopropylsilylethynyl)benzamide **2d** as a yellow oil (682 mg, 42 % yield). Spectral data are in accordance with those reported in the literature⁴.

IR (neat): 2167, 1680, 1603, 1580 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ ppm 7.81-7.76 (m, 2 H), 7.48-7.41 (m, 1 H), 7.40-7.33 (m, 2 H), 3.35 (s, 3 H), 0.94 (s, 21 H)

¹³C NMR (100 MHz, CDCl₃) δ ppm 171.4, 133.8, 131.7, 128.7 (2C), 127.9 (2C), 100.3, 70.0, 37.9, 18.6 (6C), 11.4 (3C)

N-benzyl-4-methyl-N-(2-triisopropylsilylethynyl)benzamide **2e**



Starting from N-benzyl-4-methyl-benzamide **1e** (406 mg, 1.8 mmol), CuSO₄·5H₂O (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol), K₃PO₄ (1.02 g, 4.8 mmol) and 2-bromoethynyl(triisopropyl)silane (523 mg, 2.0 mmol) under argon, using **General procedure 1** and heating at 75°C for 4.5 days. The crude was purified to afford N-benzyl-4-methyl-N-(2-triisopropylsilylethynyl)benzamide **2e** as a colorless oil (335 mg, 41 % yield).

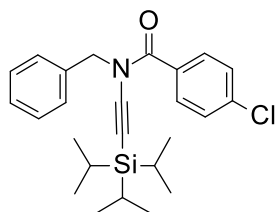
IR (neat): 2166, 1676, 749, 675 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ ppm 7.76 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 7.5 Hz, 2 H), 7.35 (m, 3 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 4.85 (s, 2 H), 2.35 (s, 3 H), 0.88 (s, 18 H), 0.87 (s, 3 H)

¹³C NMR (100 MHz, CDCl₃) δ ppm 170.5, 141.5, 136.2, 130.6, 128.8, 128.4, 128.4, 127.8, 99.4, 72.1, 53.1, 41.6, 21.5, 18.4 (6C), 11.4 (3C)

HRMS (EI): calcd. for C₂₆H₃₅N O Si ([M]⁺) 405.2482, found 405.2479

N-benzyl-4-chloro-N-(2-triisopropylsilylethynyl)benzamide **2f**



Starting from N-benzyl-4-chloro-benzamide **1f** (310 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-4-chloro-N-(2-triisopropylsilylethynyl)benzamide **2f** as a colorless oil (366 mg, 67 % yield).

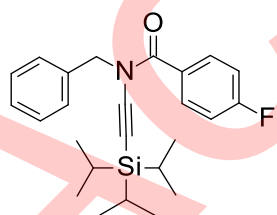
IR (neat): 2168, 1681, 752, 699, 676 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.73 (d, *J* = 8.3 Hz, 2 H), 7.51 (d, *J* = 8.3 Hz, 2 H), 7.35 (m, 5 H), 4.82 (s, 2 H), 0.81 (s, 18 H), 0.81 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.9, 135.4, 135, 131.2, 129.4 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 127.3, 98.6, 71, 51.4, 17.8 (6C), 10.1 (3C)

HRMS (EI): calcd. for C₂₅H₃₂Cl N O Si ([M]⁺) 425.1936, found 425.1939

N-benzyl-4-fluoro-N-(2-triisopropylsilylethynyl)benzamide **2g**



Starting from N-benzyl-4-fluoro-benzamide **1g** (2.1 g, 9.1 mmol), CuSO₄·5H₂O (161 mg, 0.9 mmol), 1,10-phenanthroline (327 mg, 1.8 mmol), K₃PO₄ (2.43 g, 18.2 mmol) and 2-bromoethynyl(triisopropyl)silane (2.61 g, 10.0 mmol, 1.1 equiv.) under argon, using **General procedure 1'** and heating at 75°C for 3.5 days. The crude was purified to afford N-benzyl-4-fluoro-N-(2-triisopropylsilylethynyl)benzamide **2g** as a colorless oil (1.72 g, 46 % yield).

IR (neat): 2166, 1677, 1604 cm⁻¹

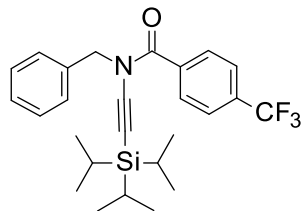
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.8 (m, 2 H), 7.4 (m, 5 H), 7.3 (m, 2 H), 4.8 (s, 2 H), 0.8 (m, 21 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 169.7, 164.1 (d, *J* = 250 Hz), 136.1, 131.4 (d, *J* = 9.0 Hz, 2C), 130.4 (d, *J* = 3.1 Hz), 128.9 (2C), 128.9 (2C), 128.5, 115.6 (d, *J* = 22.3 Hz, 2C), 99.3, 71.7, 52.3, 18.7 (6C), 11 (3C)

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -108.5

HRMS (EI): calcd. for C₂₅ H₃₂ F N O Si ([M]⁺) 409.2232, found 409.2223

N-benzyl-4-(trifluoromethyl)-N-(2-triisopropylsilylethynyl)benzamide **2h**



Starting from N-benzyl-4-(trifluoromethyl)benzamide **1h** (350 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-4-(trifluoromethyl)-N-(2-triisopropylsilylethynyl)benzamide **2h** as a colorless oil (355 mg, 61 % yield).

IR (neat): 2169, 1684, 1170, 1131, 744, 698, 676 cm⁻¹

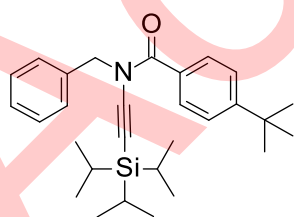
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.87 (d, *J* = 8.3 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H), 7.44-7.31 (m, 5 H), 4.85 (s, 2 H), 0.75 (s, 18 H), 0.75 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 169.8, 138.3, 135.9, 131.4 (q, *J* = 32 Hz), 129.0 (4C), 129.0 (2C), 128.4, 125.7 (q, *J* = 3.8 Hz, 2C), 124.4 (q, *J* = 273 Hz), 98.7, 72.4, 51.8, 18.2 (6C), 10.9 (3C)

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -61.7

HRMS (ESI): calcd. for C₂₆ H₃₃ F₃ N O Si ([M+H]⁺) 460.2278, found 460.228

N-benzyl-4-tert-butyl-N-(2-triisopropylsilylethynyl)benzamide **2i**



Starting from N-benzyl-4-tert-butylbenzamide **1i** (340 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-4-tert-butyl-N-(2-triisopropylsilylethynyl)benzamide **2i** as a colorless oil (215 mg, 38 % yield).

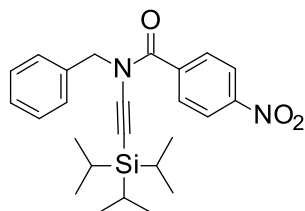
IR (neat): 2167, 1678, 770, 747, 697 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.64 (d, *J* = 8.3 Hz, 2 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 7.41-7.30 (m, 5 H), 4.81 (s, 2 H), 1.28 (s, 9 H), 0.8 (s, 18 H), 0.8 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.7, 154.3, 136.1, 130.5, 128.8 (2C), 128.7 (2C), 128.3 (2C), 128.2, 125.2 (2C), 99, 71.4, 52.2, 34.6, 31.1 (3C), 18.8 (6C), 10.9 (3C)

HRMS (EI): calcd. for C₂₉H₄₁N O Si ([M]⁺) 447.2952, found 447.2942

N-benzyl-4-nitro-N-(2-triisopropylsilylethynyl)benzamide **2j**



Starting from N-benzyl-4-nitro-benzamide **1j** (320 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-4-nitro-N-(2-triisopropylsilylethynyl)benzamide **2j** as a colorless oil (408 mg, 73 % yield).

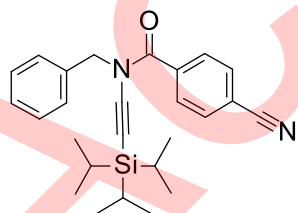
IR (neat): 2169, 1680, 1525, 1346, 851, 719, 698 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.3 (d, *J* = 8.5 Hz, 2 H), 7.95 (d, *J* = 8.5 Hz, 2 H), 7.43-7.37 (m, 4 H), 7.36 (t, *J* = 6.9 Hz, 1 H), 4.85 (s, 2 H), 0.75 (s, 18 H), 0.75 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 168.3, 148, 139.4, 134.7, 128.7 (2C), 127.9 (2C), 127.9 (2C), 127.4, 122.8 (2C), 97.4, 71.7, 50.9, 17.5 (6C), 9.9 (3C)

HRMS (EI): calcd. for C₂₅H₃₂N₂O₃Si ([M]⁺) 436.2177, found 436.2179

N-benzyl-4-cyano-N-(2-triisopropylsilylethynyl)benzamide **2k**



Starting from N-benzyl-4-cyano-N-ethynyl-benzamide **1k** (360 mg, 1.5 mmol), CuSO₄·5H₂O (53 mg, 0.3 mmol), 1,10-phenanthroline (110 mg, 0.6 mmol), K₃PO₄ (0.48 g, 3.6 mmol, 2.4 equiv.) and 2-bromoethynyl(triisopropyl)silane (390 mg, 30.0 mmol, 0.8 equiv.) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-4-cyano-N-(2-triisopropylsilylethynyl)benzamide **2k** as a colorless oil (232 mg, 37 % yield).

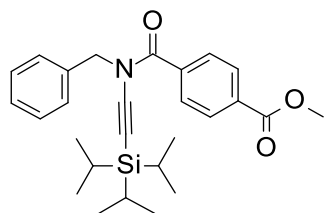
IR (neat): 2231, 2169, 1679, 1609, 1273 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.35 (m, 5 H), 4.82 (s, 2 H), 0.8 (m, 21 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 169.6, 138.7, 135.8, 132.8, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.5, 128.5, 118.5, 113.8, 98.5, 72.6, 52, 18.7 (6C), 11 (3C)

HRMS (EI): calcd. for $C_{26}H_{32}N_2O Si$ ($[M]^+$) 416.2278, found 416.2279

methyl 4-[benzyl(2-triisopropylsilylethynyl)carbamoyl]benzoate **2l**



Starting from methyl 4-(benzylcarbamoyl)benzoate **1l** (340 mg, 1.3 mmol), $CuSO_4 \cdot 5H_2O$ (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K_3PO_4 (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford methyl 4-[benzyl(2-triisopropylsilylethynyl)carbamoyl]benzoate **2l** as a colorless oil (315 mg, 55 % yield).

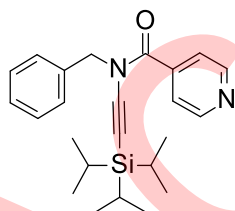
IR (neat): 2168, 1728, 1678, 1271, 1106, 727, 699, 675 cm^{-1}

1H NMR (500 MHz, $DMSO-d_6$) δ ppm 8.00/7.82 (2d, $J = 8.2$ Hz, 4 H), 7.43-7.31 (m, 5 H), 4.84 (s, 2 H), 3.88 (s, 3 H), 0.78 (s, 18 H), 0.78 (s, 3 H)

^{13}C NMR (125 MHz, $DMSO-d_6$) δ ppm 169, 164.9, 137.5, 135, 131.1, 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.6 (2C), 127.4, 97.8, 71.4, 51.9, 51, 17.5 (6C), 10.9 (3C)

HRMS (EI): calcd. for $C_{27}H_{35}N O_3 Si$ ($[M]^+$) 449.2381, found 449.2378

N-benzyl-N-(2-triisopropylsilylethynyl)pyridine-4-carboxamide **2m**



Starting from N-benzylpyridine-4-carboxamide **1m** (382 mg, 1.8 mmol), $CuSO_4 \cdot 5H_2O$ (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol), K_3PO_4 (1.02 g, 4.8 mmol) and 2-bromoethynyl(triisopropyl)silane (523 mg, 2.0 mmol) under argon, using **General procedure 1** and heating at 75°C for 4.5 days. The crude was purified to afford N-benzyl-N-(2-triisopropylsilylethynyl)pyridine-4-carboxamide **2m** as a yellow oil (514 mg, 73 % yield).

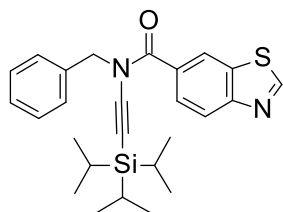
IR (neat): 2170, 1683, 753, 673 cm^{-1}

1H NMR (400 MHz, $CDCl_3$) δ ppm 8.68 (d, $J = 4.9$ Hz, 2 H), 7.6 (d, $J = 4.8$ Hz, 2 H), 7.43 (dd, $J = 7.6, 1.8$ Hz, 2 H), 7.35 (m, 3 H), 4.86 (s, 2 H), 0.89 (s, 18 H), 0.89 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.6, 149.8 (2C), 141.4, 135.2, 129.0 (2C), 128.7 (2C), 128.3, 122.9 (2C), 97.7, 73.9, 52.9, 18.9 (6C), 11.6 (3C)

HRMS (EI): calcd. for $C_{24}H_{32}N_2 O Si$ ($[M]^+$) 392.2278, found 392.228

N-benzyl-N-(2-triisopropylsilylethynyl)-1,3-benzothiazole-6-carboxamide **2n**



Starting from N-benzyl-1,3-benzothiazole-6-carboxamide **1n** (340 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-N-(2-triisopropylsilylethynyl)-1,3-benzothiazole-6-carboxamide **2n** as a colorless oil (401 mg, 70 % yield).

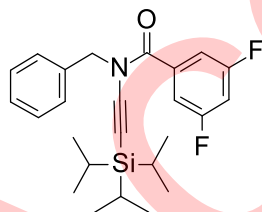
IR (neat): 2167, 1674, 877, 740, 698, 675 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.53 (s, 1 H), 8.6 (d, *J* = 1.4 Hz, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 7.83 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.44 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 4.88 (s, 2 H), 0.74 (s, 18 H), 0.74 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.3, 159.5, 154.9, 136.1, 133.6, 130.9, 129.0 (2C), 128.9 (2C), 128.4, 126.5, 123.5, 123.1, 99.3, 71.8, 52.3, 18.6 (6C), 11 (3C)

HRMS (EI): calcd. for C₂₆H₃₂N₂O S Si ([M]⁺) 448.1999, found 448.1977

N-benzyl-3,5-difluoro-N-(2-triisopropylsilylethynyl)benzamide **2o**



Starting from N-benzyl-3,5-difluoro-benzamide **1o** (310 mg, 1.3 mmol), CuSO₄·5H₂O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K₃PO₄ (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General procedure 1** and heating at 75°C for 3 days. The crude was purified to afford N-benzyl-3,5-difluoro-N-(2-triisopropylsilylethynyl)benzamide **2o** as a colorless oil (333 mg, 61 % yield).

IR (neat): 2169, 1680, 1594, 751, 698, 675 cm⁻¹

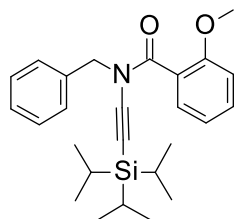
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.46 (m, 2 H), 7.39 (m, 1 H), 7.36 (m, 5 H), 4.82 (s, 2 H), 0.81 (s, 18 H), 0.81 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.5, 162.4 (dd, *J* = 247.9, 12.4 Hz, 2 C), 137.5 (t, *J* = 9.2 Hz), 135.8, 129.2 (4C), 128.5, 112.1 (d, *J* = 27.2 Hz, 2C), 107.0 (t, *J* = 25.9 Hz), 98.6, 72.7, 52.2, 18.8 (6C), 11.1 (3C)

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -108.9 ppm

HRMS (EI): calcd. for C₂₅H₃₁F₂N O Si ([M]⁺) 427.2137, found 427.2135

N-benzyl-2-methoxy-N-(2-triisopropylsilylethynyl)benzamide **2p**



Starting from N-benzyl-2-methoxy-benzamide **1p** (434 mg, 1.8 mmol), CuSO₄·5H₂O (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol), K₃PO₄ (1.02 g, 4.8 mmol) and 2-bromoethynyl(triisopropyl)silane (523 mg, 2.0 mmol) under argon, using **General procedure 1** and heating at 75°C for 9.5 days. The crude was purified to afford N-benzyl-2-methoxy-N-(2-triisopropylsilylethynyl)benzamide **2p** as a colorless oil (447 mg, 59 % yield).

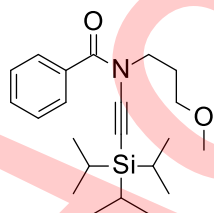
IR (neat): 2172, 1686, 1251, 750, 675 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.38 (m, 5 H), 7.33 (m, 1 H), 7.29 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 6.97 (t, *J* = 7.7 Hz, 1 H), 4.82 (s, 2 H), 3.79 (s, 3 H), 0.73 (s, 18 H), 0.73 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 170.1, 156.1, 136.2, 131.8, 128.8 (2C), 128.4 (2C), 128.1, 127.9, 125.2, 120.7, 111.9, 99.1, 70, 56.1, 51.3, 18.6 (6C), 11 (3C)

HRMS (EI): calcd. for C₂₆H₃₅N O₂ Si ([M]⁺) 421.2432, found 421.2416

N-(3-methoxypropyl)-N-(2-triisopropylsilylethynyl)benzamide **2q**



Starting from N-(3-methoxypropyl)benzamide **1q** (500 mg, 2.6 mmol), CuSO₄·5H₂O (129 mg, 0.5 mmol), 1,10-phenanthroline (187 mg, 1.0 mmol), K₃PO₄ (0.69 g, 5.2 mmol, 2.0 equiv.) and 2-bromoethynyl(triisopropyl)silane (0.74 g, 2.8 mmol) under argon, using **General procedure 1** and heating at 75°C for 5 days. The crude was purified to afford N-(3-methoxypropyl)-N-(2-triisopropylsilylethynyl)benzamide **2q** as a yellow oil (189 mg, 20 % yield).

IR (neat): 2165, 1678, 1278, 1118, 709, 673 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.67 (d, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.4 Hz, 2 H), 3.7 (t, *J* = 6.8 Hz, 2 H), 3.44 (t, *J* = 6.3 Hz, 2 H), 3.24 (s, 3 H), 1.95 (quint, *J* = 6.6 Hz, 2 H), 0.9 (s, 18 H), 0.9 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 170.9, 134.2, 131.6, 128.5 (2C), 128.4 (2C), 99.6, 71.3, 69.5, 58.6, 46.4, 27.7, 18.8 (6C), 11.2 (3C)

HRMS (ESI): calcd. for C₂₂ H₃₆ N O₂ Si ([M+H]⁺) 374.2437, found 374.2512

General procedure 2 for the synthesis of ynamides 3a-q

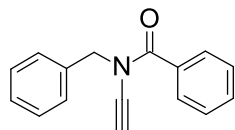
To a solution of the protected ynamide **2** (1 equiv.) in tetrahydrofuran (0.2 M) under argon at 0°C/-5°C was added tetrabutylammonium fluoride (1M in THF, 1.2 equiv.) dropwise.

The reaction mixture was stirred at 0°C for the given amount of time.

After completion of the reaction, a mixture of an aqueous solution of NH₄Cl (10 % w/w) was added, the aqueous phase was extracted three times with diethyl ether. After washing with a saturated solution of NaCl, the organic phases were dried over Na₂SO₄ and concentrated.

The crude was purified either by trituration in pentane at -20°C (if 400 mg of crude obtained, 4 mL of pentane was added) or by silica gel flash column chromatography (gradient eluent, EtOAc in heptane).

N-benzyl-N-ethynyl-benzamide **3a**



Starting from N-benzyl-N-(2-triisopropylsilylethynyl)benzamide **2a** (1.33 g, 3.4 mmol), TBAF 1M/THF (4.1 mL, 4.1 mmol) under argon, using **General procedure 2** and stirring at 0°C for 1 h. The crude was purified by silica gel flash column chromatography to afford N-benzyl-N-ethynyl-benzamide **3a** as a white solid (699 mg, 87 % yield). Spectral data are in accordance with those reported in the literature.⁵

IR (neat): 3242, 2146, 1649 cm⁻¹

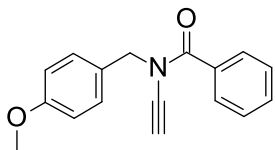
¹H NMR (400MHz, DMSO-*d*₆) δ ppm 7.73 (d, *J* = 7.7 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.4 (m, 4 H), 7.32 (m, 1 H), 4.82 (s, 2 H), 3.82 (s, 1 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 170.6, 136.5, 133.7, 132, 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 78.9, 64.2, 52.3

HRMS (ESI): calcd. for C₁₆ H₁₄ N O ([M+H]⁺) 236.1070, found 236.1071

mp: 45.5-48°C

⁵ B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1998**, *37*, 489

N-ethynyl-N-[(4-methoxyphenyl)methyl]benzamide 3b

Starting from N-[(4-methoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2b** (1.87 g, 4.4 mmol), TBAF 1M/THF (5.3 mL, 5.3 mmol) under argon, using **General procedure 2** and stirring at 0°C for 10 min. The crude was purified by silica gel flash column chromatography to afford N-ethynyl-N-[(4-methoxyphenyl)methyl]benzamide **3b** as a white solid (806 mg, 69 % yield).

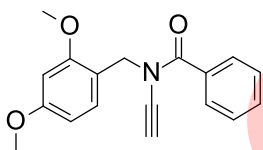
IR (neat): 3242, 2142, 1645 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ ppm 7.8 (d, $J = 7.6$ Hz, 2 H), 7.48 (t, $J = 7.4$ Hz, 1 H), 7.39 (m, 4 H), 6.9 (d, $J = 8.2$ Hz, 2 H), 4.8 (s, 2 H), 3.81 (s, 3 H), 2.75 (s, 1 H)

^{13}C NMR (125 MHz, CDCl_3) δ ppm 170.75, 159.51, 133.41, 131.45, 130.26 (2C), 128.68 (2C), 128.06, 127.8 (2C), 113.9 (2C), 78.62, 61.7, 55.27, 52.25

HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{16}\text{N O}_2$ ($[\text{M}+\text{H}]^+$) 266.1176, found 266.1177

mp: 86.8-88.7°C

N-[(2,4-dimethoxyphenyl)methyl]-N-ethynyl-benzamide 3c

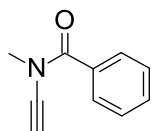
Starting from N-[(2,4-dimethoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2c** (405 mg, 0.90 mmol), TBAF 1M/THF (1.08 mL, 1.08 mmol) under argon, using **General procedure 2** and stirring at 0°C for 30 min. The crude was purified by trituration in pentane to afford N-[(2,4-dimethoxyphenyl)methyl]-N-ethynyl-benzamide **3c** as a beige solid (198 mg, 75 % yield).

IR (neat): 3244, 2131, 1660 cm^{-1}

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 7.67 (d, $J = 7.4$ Hz, 2 H), 7.54 (t, $J = 7.4$ Hz, 1 H), 7.47 (t, $J = 7.4$ Hz, 2 H), 7.18 (d, $J = 8.3$ Hz, 1 H), 6.6 (d, $J = 2.3$ Hz, 1 H), 6.53 (dd, $J = 8.3, 2.3$ Hz, 1 H), 4.7 (s, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.65 (s, 1 H)

^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ ppm 170.6, 161, 158.9, 134, 131.8, 130.9, 128.5 (4C), 116, 105, 99, 78.7, 64, 56, 55.6, 47.3

HRMS (EI): calcd. for $\text{C}_{18}\text{H}_{17}\text{N O}_3$ ($[\text{M}]^+$) 295.1203, found 295.1201

N-ethynyl-N-methyl-benzamide 3d

Starting from N-methyl-N-(2-triisopropylsilylethynyl)benzamide **2d** (500 mg, 1.6 mmol), TBAF 1M/THF (2.10 mL, 2.1 mmol, 1.3 equiv.) under argon, using **General procedure 2** and stirring at 0°C for 60 min. The crude was purified by silica gel flash column chromatography to afford N-ethynyl-N-methyl-benzamide **3d** as a yellow oil (180 mg, 71 % yield).

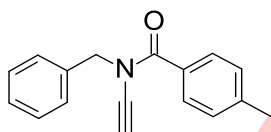
IR (neat): 2138, 1647, 704 cm^{-1}

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ ppm 7.7 (d, $J = 7.6$ Hz, 2 H), 7.56 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 7.6$ Hz, 2 H), 3.85 (s, 1 H), 3.25 (s, 3 H)

^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ ppm 170.9, 134.2, 132, 128.6 (2C), 128.5 (2C), 62.9, 62.9, 37.8

HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_9\text{NO}$ ($[\text{M}+\text{H}]^+$) 160.0757, found 160.0757

mp: 42.1-45.5°C

N-benzyl-N-ethynyl-4-methyl-benzamide 3e

Starting from N-benzyl-4-methyl-N-(2-triisopropylsilylethynyl)benzamide **2e** (335 mg, 0.83 mmol), TBAF 1M/THF (0.99 mL, 1.0 mmol) under argon, using **General procedure 2** and stirring at 0°C for 30 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-N-ethynyl-4-methyl-benzamide **3e** as a white solid (142 mg, 69 % yield).

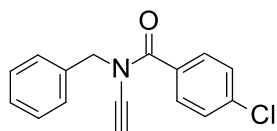
IR (neat): 3246, 2138, 1664 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.65 (d, $J = 8.0$ Hz, 2 H), 7.39 (m, 4 H), 7.34 (m, 1 H), 7.28 (d, $J = 7.9$ Hz, 2 H), 4.82 (s, 2 H), 3.81 (s, 1 H), 2.36 (s, 3 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 170.5, 142.2, 136.7, 130.9, 129.2 (4C), 128.8 (2C), 128.4 (2C), 128.2, 79.3, 63.9, 52.1, 21

HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{16}\text{NO}$ ($[\text{M}+\text{H}]^+$) 250.1226, found 250.1227

mp: 57.7-58.3°C

N-benzyl-4-chloro-N-ethynyl-benzamide 3f

Starting from N-benzyl-4-chloro-N-(2-triisopropylsilylethynyl)benzamide **2f** (366 mg, 0.86 mmol), TBAF 1M/THF (1.0 mL, 1.0 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-4-chloro-N-ethynyl-benzamide **3f** as a white solid (145 mg, 63 % yield).

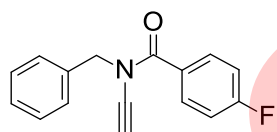
IR (neat): 3242, 2136, 1670 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.77 (d, $J = 8.3$ Hz, 2 H), 7.56 (d, $J = 8.4$ Hz, 2 H), 7.4/7.35 (2m, 5 H), 4.83 (s, 2 H), 3.87 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 169.7, 136.7, 136.3, 132.4, 130.6 (2C), 129.4 (2C), 129.0 (2C), 128.7 (2C), 128.4, 78.6, 64.6, 52.3

HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{12}\text{ClNO}$ ($[\text{M}]^+$) 269.0602, found 269.0602

mp: 64-66°C

N-benzyl-N-ethynyl-4-fluoro-benzamide 3g

Starting from N-benzyl-4-fluoro-N-(2-triisopropylsilylethynyl)benzamide **2g** (1.72 g, 4.20 mmol), TBAF 1M/THF (5.0 mL, 5.0 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by trituration in pentane to afford N-benzyl-N-ethynyl-4-fluoro-benzamide **3g** as a white solid (742 mg, 70 % yield).

IR (neat): 3242, 2147, 1649, 1604 cm^{-1}

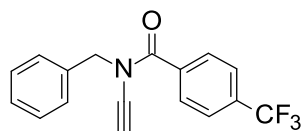
^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.88 (dd, $J = 8.9, 5.6$ Hz, 2 H), 7.35 (m, 5 H), 7.35 (t, $J = 8.8$ Hz, 2 H), 4.86 (s, 2 H), 3.9 (s, 1 H)

^{13}C NMR (100 MHz, $\text{dmsO-}d_6$) δ ppm 169.6, 164.2 (d, $J = 249.5$ Hz), 136.4, 131.6 (d, $J = 9.3$ Hz, 2C), 130.1 (d, $J = 3.0$ Hz), 129.0 (2C), 128.5 (2C), 128.3, 115.6 (d, $J = 22.1$ Hz, 2C), 78.8, 64.4, 52.3

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm -108.0

HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{12}\text{FN O}$ ($[\text{M}]^+$) 253.0897, found 253.0895

mp: 63.7-66.1°C

N-benzyl-N-ethynyl-4-(trifluoromethyl)benzamide 3h

Starting from N-benzyl-4-(trifluoromethyl)-N-(2-triisopropylsilylethynyl)benzamide **2h** (355 mg, 0.77 mmol), TBAF 1M/THF (0.93 mL, 0.9 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-N-ethynyl-4-(trifluoromethyl)benzamide **3h** as a white solid (139 mg, 59 % yield).

IR (neat): 3238, 2135, 1664, 1319, 1136, 1124 cm^{-1}

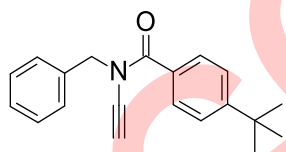
^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.93 (d, $J = 7.9$ Hz, 2 H), 7.87 (d, $J = 7.9$ Hz, 2 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.85 (s, 2 H), 3.88 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 169.6, 137.8, 136.2, 131.6 (q, $J = 32.0$ Hz), 129.4 (2C), 129.1 (2C), 128.5 (2C), 128.4, 125.6 (q, $J = 3.7$ Hz, 2C), 124.0 (q, $J = 271.9$ Hz), 78.3, 64.9, 52.2

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm - 61.4

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N O}$ ($[\text{M}]^+$) 303.0866, found 303.0869

mp: 67-69°C

N-benzyl-4-tert-butyl-N-ethynyl-benzamide 3i

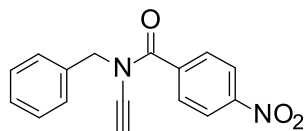
Starting from N-benzyl-4-tert-butyl-N-(2-triisopropylsilylethynyl)benzamide **2i** (215 mg, 0.48 mmol), TBAF 1M/THF (0.58 mL, 0.6 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-4-tert-butyl-N-ethynyl-benzamide **3i** as a colorless oil (82 mg, 59 % yield).

IR (neat): 3230, 2137, 1672 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.71 (d, $J = 8.2$ Hz, 2 H), 7.5 (d, $J = 8.2$ Hz, 2 H), 7.39 (m, 4 H), 7.34 (m, 1 H), 4.82 (s, 2 H), 3.85 (s, 1 H), 1.3 (s, 9 H)

^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ ppm 170.7, 155.1, 136.9, 131.1, 129.0 (2C), 128.8 (2C), 128.4 (2C), 128.2, 125.3 (2C), 79.4, 64, 52.3, 35.3, 31.4 (3C)

HRMS (EI): calcd. for $\text{C}_{20}\text{H}_{21}\text{N O}$ ($[\text{M}]^+$) 291.1618, found 291.1608

N-benzyl-N-ethynyl-4-nitro-benzamide 3j

Starting from N-benzyl-4-nitro-N-(2-triisopropylsilylethynyl)benzamide **2j** (408 mg, 0.93 mmol), TBAF 1M/THF (1.1 mL, 1.1 mmol) under argon, using **General procedure 2** and stirring at 0°C for 25 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-N-ethynyl-4-nitro-benzamide **3j** as a beige solid (170 mg, 65 % yield).

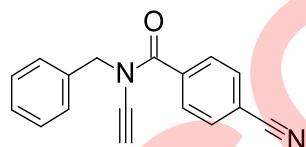
IR (neat): 3236, 2133, 1668, 1602, 1523, 1350 cm^{-1}

$^1\text{H NMR}$ (400MHz, $\text{DMSO-}d_6$) δ ppm 8.32 (d, $J = 8.5$ Hz, 2 H), 7.98 (d, $J = 8.6$ Hz, 2 H), 7.41 (m, 4 H), 7.35 (m, 1 H), 4.86 (s, 2 H), 3.9 (s, 1 H)

$^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ ppm 169.7, 149.3, 139.8, 136.1, 130.0 (2C), 129.1 (2C), 128.6 (2C), 128.4, 123.9 (2C), 78.6, 65.1, 52.3

HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$ ($[\text{M}]^+$) 280.0842, found 280.083

mp: 42.9-44.4°C

N-benzyl-4-cyano-N-ethynyl-benzamide 3k

Starting from N-benzyl-4-cyano-N-(2-triisopropylsilylethynyl)benzamide **2k** (239 mg, 0.57 mmol), TBAF 1M/THF (0.69 mL, 0.7 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by trituration in pentane to afford N-benzyl-4-cyano-N-ethynyl-benzamide **3k** as a white solid (116 mg, 78 % yield).

IR (neat): 3232, 2235, 2137, 1670, 1609 cm^{-1}

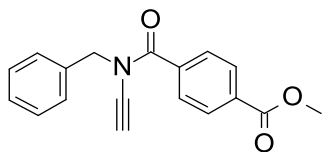
$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.0 (d, $J = 8.2$ Hz, 2 H), 7.9 (d, $J = 8.2$ Hz, 2 H), 7.35 (m, 5 H), 4.86 (s, 2 H), 3.9 (s, 1 H)

$^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ ppm 169.5, 138.1, 135.9, 132.8 (2C), 129.3 (2C), 129.0 (2C), 128.5 (2C), 128.4, 118.6, 114.2, 78.1, 65, 52.2

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}$ ($[\text{M}]^+$) 260.0944, found 260.0929

mp: 114-118°C

methyl 4-[benzyl(ethynyl)carbamoyl]benzoate **3l**



Starting from methyl 4-[benzyl(2-triisopropylsilylethynyl)carbamoyl]benzoate **2l** (315 mg, 0.70 mmol), TBAF 1M/THF (0.8 mL, 0.8 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford methyl 4-[benzyl(ethynyl)carbamoyl]benzoate **3l** as a yellow solid (121 mg, 59 % yield).

IR (neat): 3230, 2137, 1718, 1674 cm^{-1}

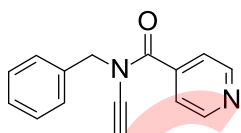
^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.04 (d, $J = 8.2$ Hz, 2 H), 7.84 (d, $J = 8.3$ Hz, 2 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.85 (s, 2 H), 3.89 (s, 3 H), 3.85 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 170.9, 166.6, 138.9, 136.2, 132.3, 129.4 (2C), 129.0 (2C), 128.9 (2C), 128.5 (2C), 128.2, 78.2, 64.7, 52.9, 52.3

HRMS (EI): calcd. for $\text{C}_{18}\text{H}_{15}\text{N O}_3$ ($[\text{M}]^+$) 293.1046, found 293.1034

mp: 93.3-95.3°C

N-benzyl-N-ethynyl-pyridine-4-carboxamide **3m**



Starting from N-benzyl-N-(2-triisopropylsilylethynyl)pyridine-4-carboxamide **2m** (514 mg, 1.31 mmol), TBAF 1M/THF (1.6 mL, 1.6 mmol) under argon, using **General procedure 2** and stirring at 0°C for 30 min. The crude was purified by trituration in pentane to afford N-benzyl-N-ethynyl-pyridine-4-carboxamide **3m** as a white solid (179 mg, 58 % yield).

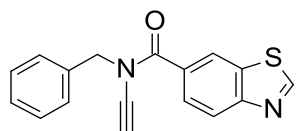
IR (neat): 3233, 2139, 1674, 831, 739, 696 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.74 (d, $J = 4.9$ Hz, 2 H), 7.65 (d, $J = 4.7$ Hz, 2 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.84 (s, 2 H), 3.9 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 169.2, 150.2 (2C), 141.4, 136.2, 129.1 (2C), 128.5 (2C), 128.4, 122.1 (2C), 77.9, 64.8, 51.6

HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}$ ($[\text{M}+\text{H}]^+$) 237.1022, found 237.1022

mp: 62.5-64.5°C

N-benzyl-N-ethynyl-1,3-benzothiazole-6-carboxamide 3n

Starting from N-benzyl-N-(2-triisopropylsilylethynyl)-1,3-benzothiazole-6-carboxamide **2n** (401 mg, 0.89 mmol), TBAF 1M/THF (1.07 mL, 1.07 mmol) under argon, using **General procedure 2** and stirring at 0°C for 25 min. The crude was purified by silica gel flash column chromatography to N-benzyl-N-ethynyl-1,3-benzothiazole-6-carboxamide **3n** as a yellow solid (178 mg, 68 % yield).

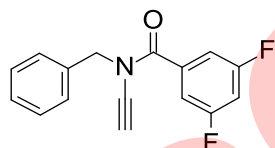
IR (neat): 3234, 2137, 1668 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 9.56 (s, 1 H), 8.62 (d, $J = 1.5$ Hz, 1 H), 8.17 (d, $J = 8.5$ Hz, 1 H), 7.88 (dd, $J = 8.4, 1.7$ Hz, 1 H), 7.42 (m, 4 H), 7.36 (m, 1 H), 4.88 (s, 2 H), 3.84 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 170.3, 160, 155, 136.4, 133.8, 130.7, 129.1 (2C), 128.5 (2C), 128.3, 126.6, 123.7, 122.9, 78.7, 64.3, 52.3

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O S}$ ($[\text{M}]^+$) 292.0665, found 292.0657

mp: 125.7-127.7°C

N-benzyl-N-ethynyl-3,5-difluoro-benzamide 3o

Starting from N-benzyl-3,5-difluoro-N-(2-triisopropylsilylethynyl)benzamide **2o** (333 mg, 0.78 mmol), TBAF 1M/THF (0.93 mL, 0.9 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-N-ethynyl-3,5-difluoro-benzamide **3o** as a white solid (73 mg, 35 % yield).

IR (neat): 3247, 2137, 1674, 1622, 1591 cm^{-1}

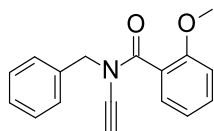
^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.45 (m, 3 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.83 (s, 2 H), 3.92 (s, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 168.3, 162.3 (dd, $J = 248.2, 12.7$ Hz, 2C), 137.3 (t, $J = 9.2$ Hz), 136.1, 129.0 (2C), 128.5 (2C), 128.2, 112.2 (d, $J = 27.3$ Hz, 2C), 107.2 (t, $J = 25.6$ Hz), 78.1, 65.1, 52.5

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm -108.8

HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_2\text{N O}$ ($[\text{M}]^+$) 271.0803, found 271.0775

mp: 87.7-91.4°C

N-benzyl-N-ethynyl-2-methoxy-benzamide 3p

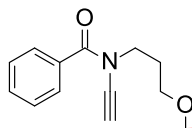
Starting from N-benzyl-2-methoxy-N-(2-triisopropylsilylethynyl)benzamide **2p** (447 mg, 1.06 mmol), TBAF 1M/THF (1.27 mL, 1.3 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by trituration in pentane to afford N-benzyl-N-ethynyl-2-methoxybenzamide **3p** as a white solid (200 mg, 71 % yield).

IR (neat): 3245, 2146, 1672, 751, 703 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.45 (ddd, $J = 8.0, 7.7, 1.7$ Hz, 1 H), 7.38 (m, 5 H), 7.31 (dd, $J = 7.8, 1.6$ Hz, 1 H), 7.12 (d, $J = 8.2$ Hz, 1 H), 7.01 (t, $J = 7.5$ Hz, 1 H), 4.82 (s, 2 H), 3.82 (s, 3 H), 3.55 (bs, 1 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 170.1, 156.4, 136.5, 132, 128.8 (2C), 127.9 (2C), 128.3, 127.9, 124.8, 120.8, 112.1, 78.2, 62.8, 56.3, 51

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{15}\text{N O}_2$ ($[\text{M}]^+$) 265.1097, found 265.1096

N-ethynyl-N-(3-methoxypropyl)benzamide 3q

Starting from N-(3-methoxypropyl)-N-(2-triisopropylsilylethynyl)benzamide **2q** (189 mg, 0.51 mmol), TBAF 1M/THF (0.61 mL, 0.6 mmol) under argon, using **General procedure 2** and stirring at 0°C for 1h30. The crude was purified by silica gel flash column chromatography to afford N-ethynyl-N-(3-methoxypropyl)benzamide **3q** as a yellow oil (86 mg, 78 % yield).

IR (neat): 2136, 1671, 1601 cm^{-1}

^1H NMR (500 MHz, $\text{dmsO-}d_6$) δ ppm 7.68 (d, $J = 7.5$ Hz, 2 H), 7.54 (t, $J = 7.3$ Hz, 1 H), 7.47 (t, $J = 7.5$ Hz, 2 H), 3.85 (s, 1 H), 3.69 (t, $J = 6.9$ Hz, 2 H), 3.42 (t, $J = 6.2$ Hz, 2 H), 3.24 (s, 3 H), 1.81 (quint, $J = 6.6$ Hz, 2 H)

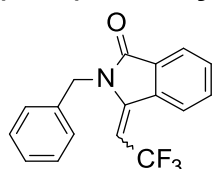
^{13}C NMR (100 MHz, $\text{dmsO-}d_6$) δ ppm 170.5, 134.2, 131.7 (2C), 128.3 (2C), 128.2, 78.7, 69.5, 63.7, 58.5, 46.5, 27.7

HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{15}\text{N O}_2$ ($[\text{M}+\text{H}]^+$) 218.1181, found 218.1176

General procedure 3 for the cascade processes: Synthesis of isoindolinones 4a-q

In a 10 mL Schlenk tube (preably dried under vacuum) under argon, were loaded the ynamide **3** (1 equiv.), Togni I reagent (3,3-dimethyl-1-(trifluoromethyl)-1λ³,2-benziodoxole) (1.2 equiv.) and Ir(ppy)₃ (0.025 equiv.). The tube was degassed with 3 vacuum/argon cycles. Anhydrous acetonitrile on molecular sieves (0.1M) followed by dichloromethane (5% v/v) were added under argon. The reaction mixture was freeze pumped once to deoxygenate the solvent. The reaction mixture was irradiated under blue LED at 27°C approximately for the given amount of time. After completion of the reaction, the reaction mixture was concentrated under vacuum. The crude was purified by silica gel flash column chromatography (solid deposit on Celite, gradient eluent using a mixture of EtOAc 2% /CH₂Cl₂ 1% in heptane). The separation was tricky, the by-product of Togni I was eluted close to the expected product.

(3E/Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4a**



In a 25 mL Schlenk tube, starting from N-benzyl-N-ethynyl-benzamide **3a** (250 mg, 1.06 mmol), Togni I reagent (421 mg, 1.3 mmol) and Ir(ppy)₃ (17.5 mg, 0.03 mmol), using **General procedure 3** and stirring at 27°C for 5 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4a** as a pale yellow oil (213 mg, 64 % yield) (E/Z mixture 81/19).

(3E)-2-benzyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4aE**

IR (neat): 1732, 1656, 1319, 1109 cm⁻¹ (mixture 81/19 E/Z)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.96/7.94 (2d, *J* = 8.2 Hz, 2 H), 7.85/7.77 (2t, *J* = 7.6 Hz, 2 H), 7.35 (m, 3 H), 7.27 (m, 2 H), 5.93 (q, *J* = 9.5 Hz, 1 H), 5.05 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 166.4, 144.5 (q, *J* = 6.3 Hz), 136, 134.1, 132.4, 131.9 (2C), 129.2 (2C), 127.5, 127.4 (2C), 125.5, 124.8 (q, *J* = 268.6 Hz), 124.1, 95.9 (q, *J* = 38.0 Hz), 42.6

167.7, 141.4, 136.9, 136.5, 132.2, 129/128.4, 125.7, 123.9, 122.2, 92.2, 44.7

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.87

HRMS (ESI): calcd. for C₁₇H₁₂F₃N O ([M+H]⁺) 304.0944, found 304.0942

mp: 94.6-101.9°C

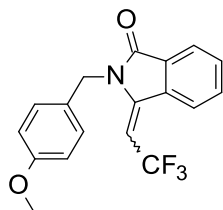
(3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4aZ**

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.23 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.73 (t, *J* = 7.5 Hz, 2 H), 7.31 (m, 3 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 6.37 (q, *J* = 10.1 Hz, 1 H), 5.12 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 167.7, 141.4 (q, *J* = 6.6 Hz), 136.9 (2C), 136.5, 132.2 (2C), 129 (2C), 128.4, 125.7 (2C), 123.9, 122.9 (q, *J* = 268.6 Hz), 122.2, 92.2 (q, *J* = 38.0 Hz), 44.7

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -48.85

(3E/Z)-2-[(4-methoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4b



Starting from N-[(2,4-dimethoxyphenyl)methyl]-N-ethynyl-benzamide **3b** (106 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 5.5 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-[(4-methoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4b** as a pale yellow oil (78 mg, 59 % yield) (E/Z mixture 60/40).

(3E)-2-[(4-methoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4bE

IR (neat): 1728, 1655, 1244, 1086 cm⁻¹ (mixture 60/40 E/Z)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.95 (d, *J* = 8.1 Hz, 1 H), 7.93 (d, *J* = 8.1 Hz, 1 H), 7.84 (t, *J* = 7.7 Hz, 1 H), 7.76 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 6.91 (d, *J* = 8.5 Hz, 2 H), 5.95 (q, *J* = 9.4 Hz, 1 H), 4.97 (s, 2 H), 3.73 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 166.5, 159.1, 144.4 (q, *J* = 6.3 Hz), 134, 132.1, 132.1, 130.1, 128.7 (2C), 128.3, 123.7/125.8 (q, *J* = 267.9 Hz), 124.3, 124, 114.3 (2C), 95.9 (q, *J* = 37.9 Hz), 55.4, 42.1

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.8

HRMS (ESI): calcd. for C₁₈H₁₅F₃N O₂ ([M+H]⁺) 334.1049, found 334.105

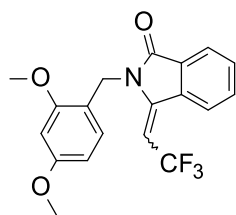
mp: 76.5-84.2°C (mixture 60/40 E/Z)

(3Z)-2-[(4-methoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4bZ

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.22 (d, *J* = 7.8 Hz, 1 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 7.81 (t, *J* = 7.9 Hz, 1 H), 7.73 (t, *J* = 7.5 Hz, 1 H), 7 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.35 (q, *J* = 10.04 Hz, 1 H), 5.04 (s, 2 H), 3.71 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.4, 158.5, 142 (q, *J* = 6.5 Hz), 137.3, 134.2, 132, 128.8, 127.1, 127 (2C), 123.8 (q, *J* = 266.9 Hz), 123.8, 122, 114.4 (2C), 91.9 (q, *J* = 37.9 Hz), 55.5, 44.2

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -48.8

(3E/Z)-2-[(2,4-dimethoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4c

Starting from N-[(2,4-dimethoxyphenyl)methyl]-N-ethynyl-benzamide **3c** (82 mg, 0.28 mmol), Togni I reagent (110 mg, 0.33 mmol) and Ir(ppy)₃ (4.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 3 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-[(2,4-dimethoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4cE** as a white solid (39 mg) and (3Z)-2-[(2,4-dimethoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4cZ** as a white solid (18 mg) (E/Z ratio 70/30, 57 % overall yield).

(3E)-2-[(2,4-dimethoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4cE

IR (neat): 1723, 1659, 1614, 1258, 1093 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.97/7.93 (2d, *J* = 7.6 Hz, 2 H), 7.86/7.79 (2t, *J* = 7.6 Hz, 2 H), 6.9 (d, *J* = 8.5 Hz, 1 H), 6.63 (d, *J* = 2.4 Hz, 1 H), 6.5 (dd, *J* = 8.4 Hz, 1 H), 5.85 (q, *J* = 9.5 Hz, 1 H), 4.9 (s, 2 H), 3.85/3.75 (s, 6 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 166.4, 160.6, 157.9, 145 (q, *J* = 6.8 Hz), 134, 132.3, 132.1, 129.9, 129, 125 (q, *J* = 267.6 Hz), 124.6, 124, 116, 105.6, 98.9, 95 (q, *J* = 37.8 Hz), 56, 55.7, 37.6

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.8

HRMS (ESI): calcd. for C₁₉H₁₇F₃N O₃ ([M+H]⁺) 364.1155, found 364.1157

mp: 132.0-134.8°C

(3Z)-2-[(2,4-dimethoxyphenyl)methyl]-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4cZ

IR (neat): 1719, 1660, 1610, 1134, 1095 cm⁻¹

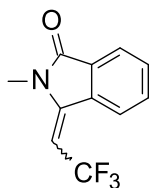
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.22 (d, *J* = 7.7 Hz, 1 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 7.81 (tt, *J* = 7.7, 1.1 Hz, 1 H), 7.73 (t, *J* = 7.5 Hz, 1 H), 6.59 (df, *J* = 2.3 Hz, 1 H), 6.49 (d, *J* = 8.3 Hz, 1 H), 6.37 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.33 (q, *J* = 10.0 Hz, 1 H), 4.97 (sl, 2 H), 3.83 (s, 3 H), 3.71 (s, 3 H)

¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm 168.1, 159.6, 157.1, 141.9 (q, *J* = 6.4 Hz), 137.3, 134, 132, 127, 125.4, 123.7 (q, *J* = 267.8 Hz), 123.7, 121.9, 116.5, 104.6, 98.5, 91.8 (q, *J* = 37.6 Hz), 56, 55.6, 40.3

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -49.3

HRMS (ESI): calcd. for C₁₉H₁₇F₃N O₃ ([M+H]⁺) 364.1155, found 364.1157

mp: 137.0-139.5°C

(3E/Z)-2-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4d

Starting from N-ethynyl-N-methyl-benzamide **3d** (64 mg, 0.4 mmol), Togni I reagent (139 mg, 0.42 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 4 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **3dE** as a white solid (27 mg) and (3Z)-2-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **3dZ** as a white solid (16 mg) (E/Z ratio 63/37, 47 % overall yield).

(3E)-2-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4dE

IR (neat): 1716, 1654, 1336, 1124 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.95 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H), 7.8 (td, *J* = 7.5, 0.7 Hz, 1 H), 7.72 (td, *J* = 7.5, 0.7 Hz, 1 H), 5.99 (q, *J* = 9.4 Hz, 1 H), 3.21 (s, 3 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 165.5, 145.1 (q, *J* = 6.5 Hz), 133.2, 131.6, 131.5, 129.7, 124.3 (q, *J* = 268.4 Hz), 123.9, 123.2, 94.6 (q, *J* = 37.6 Hz), 26

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.8

HRMS (ESI): calcd. for C₁₁H₉F₃N O ([M+H]⁺) 228.0631, found 228.0632

mp: 100.5-105.3°C

(3Z)-2-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4dZ

IR (neat): 1721, 1655, 1121, 1090 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.14 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.4 Hz, 1 H), 7.76 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.68 (td, *J* = 7.5, 0.6 Hz, 1 H), 6.32 (q, *J* = 7.7 Hz, 1 H), 3.32 (q⁶, *J* = 2.3 Hz, 3 H)

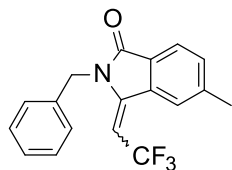
¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 167.9, 143.3 (q, *J* = 6.3 Hz), 136.9, 133.8, 131.5, 127.4, 123.9 (q, *J* = 268.0 Hz), 123.2, 121.6, 91.4 (q, *J* = 37.3 Hz), 28.1

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -47.1

HRMS (ESI): calcd. for C₁₁H₉F₃N O ([M+H]⁺) 228.0631, found 228.0632

mp: 105.5-107.0°C

⁶ Through space coupling

(3E/Z)-2-benzyl-5-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4e

Starting from N-benzyl-N-ethynyl-4-methyl-benzamide **3e** (100 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 5.3 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-benzyl-5-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4e** as a white solid (66 mg, 52 % yield) (E/Z mixture 58/42).

(3E)-2-benzyl-5-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4eE

IR (neat): 1718, 1654, 1317, 1257, 1157, 1134 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.82 (d, *J* = 7.7 Hz, 1 H), 7.73 (s, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 7.38-7.22 (m, 5 H), 5.88 (q, *J* = 9.5 Hz, 1 H), 5.03 (s, 2 H), 2.5 (s, 3 H, under the DMSO peak)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 166.5, 144.6 (q, *J* = 6.4 Hz), 137.7, 136.5, 133, 132.5, 129.3 (4C), 125.9, 127.4, 126.8 (q, *J* = 268.8 Hz), 124.6, 123.9, 95.7 (q, *J* = 37.8 Hz), 42.4, 22.6

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.7

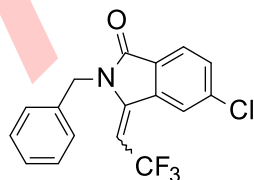
HRMS (ESI): calcd. for C₁₈ H₁₅ F₃ N O ([M+H]⁺) 318.1111, found 318.1098

(3Z)-2-benzyl-5-methyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4eZ

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.06 (s, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 7.36-7.21 (m, 3 H), 7.06 (d, *J* = 7.5 Hz, 2 H), 6.29 (q, *J* = 9.9 Hz, 1 H), 5.09 (s, 2 H), 2.5 (s, 3 H, under the DMSO peak)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.4, 142.1 (q, *J* = 6.5 Hz), 137.6, 137.2, 137.1, 132.5, 129.0 (2C), 126.5, 125.2, 124.8 (q, *J* = 267.9 Hz), 124.7, 123.6, 122.2, 91.4 (q, *J* = 37.6 Hz), 44.8, 22.5

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -48.8

(3E/Z)-2-benzyl-5-chloro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4f

Starting from N-benzyl-4-chloro-N-ethynyl-benzamide **3f** (108 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 4.7 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-5-chloro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4fE** as a white solid (50 mg) and (3Z)-2-benzyl-5-

chloro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4fz** as a white solid (27 mg) (E/Z ratio 63/37, 57% overall yield).

(3E)-2-benzyl-5-chloro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4fE

IR (neat): 1309, 1654, 1309, 1269, 1249, 1128 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 (d, *J* = 8.1 Hz, 1 H), 7.86 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.83 (bs, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.31-7.25 (m, 3 H), 6.03 (q, *J* = 9.4 Hz, 1 H), 5.05 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 165.4, 143.3 (q, *J* = 6.4 Hz), 138.8, 136.1, 133.7, 132.6, 129.2 (2C), 128.8, 128.4, 127.7 (2C), 126, 124.6 (q, *J* = 269.1 Hz), 124.3, 96.9 (q, *J* = 37.5 Hz), 42.7

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.8

HRMS (ESI): calcd. for C₁₇H₁₂ClF₃N O ([M+H]⁺) 338.0554, found 338.0556

mp: 102.6-110.3°C

(3Z)-2-benzyl-5-chloro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4fZ

IR (neat): 1722, 1660, 1301, 1274, 1255, 1134 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.45 (df, *J* = 1.5 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.78 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.3 (t, *J* = 7.4 Hz, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 2 H), 6.48 (q, *J* = 9.9 Hz, 1 H), 5.1 (s, 2 H)

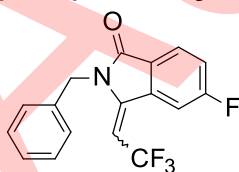
¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.2, 141.3 (q, *J* = 6.4 Hz), 139.8, 139.3, 137.6, 132.2, 128.9 (2C), 127.4, 126.1, 125.8 (2C), 125.5, 123.6 (q, *J* = 268.8 Hz), 122.4, 93.4 (q, *J* = 37.5 Hz), 44.9

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -49.1

HRMS (ESI): calcd. for C₁₇H₁₂ClF₃N O ([M+H]⁺) 338.0554, found 338.0556

mp: 138.2-146.4°C

(3E/Z)-2-benzyl-5-fluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4g



Starting from N-benzyl-N-ethynyl-4-fluoro-benzamide **3g** (101 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** (in CH₂Cl₂) and stirring at 27°C for 6.5 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-benzyl-5-fluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4g** as a yellow oil (74 mg, 58 % yield) (E/Z mixture 62/38).

(3E)-2-benzyl-5-fluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4gE

IR (neat): 1730, 1658, 1109 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.01 (dd, *J* = 8.4, 5.2 Hz, 1 H), 7.65 (td, *J* = 8.6 Hz, 1 H), 7.6 (d, *J* = 8.7 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.28 (m, 3 H), 6.02 (q, *J* = 9.4 Hz, 1 H), 5.05 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 165.5, 165.5 (d, *J* = 250.1 Hz), 143.4 (q, *J* = 6.3 Hz), 136.5, 134.3 (2C), 129.1 (2C), 127.7 (2C), 126.4, 126.2, 124.4 (q, *J* = 268.0 Hz), 119.9 (d, *J* = 23.5 Hz, 2C), 112.1, 96.5 (q, *J* = 37.7 Hz), 42.7

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.9, -105

HRMS (EI): calcd. for C₁₇H₁₁F₄N O ([M]⁺) 321.0777, found 321.0772

(3Z)-2-benzyl-5-fluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4gZ

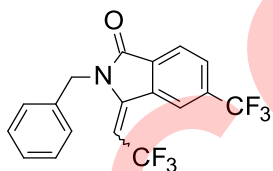
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.2 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.94 (dd, *J* = 8.5 Hz, 1 H), 7.57 (td, *J* = 8.6, 2.3 Hz, 1 H), 7.3 (t, *J* = 7.6 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 6.42 (q, *J* = 10.0 Hz, 1 H), 5.1 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 166.8, 165.5 (d, *J* = 249.9 Hz), 140.7 (q, *J* = 6.4 Hz), 139.9 (d, *J* = 11.1 Hz), 136.4, 128.7 (2C), 127.1, 126.5 (d, *J* = 10.1 Hz), 123.8 (2C), 123.8 (d, , 123.6 (q, *J* = 268.3 Hz), 119.6 (d, *J* = 24.1 Hz), 109.5 (d, *J* = 26.3 Hz), 93.1 (q, *J* = 37.8 Hz), 44.9

¹⁹F NMR (376 MHz, dmsO-d6) δ ppm -49.1, -105

HRMS (ESI): calcd. for C₁₇H₁₂F₄N O ([M+H]⁺) 322.0850, found 322.0852

(3E/Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)-5-(trifluoromethyl)isoindolin-1-one 4h



Starting from N-benzyl-N-ethynyl-4-(trifluoromethyl)benzamide **3h** (121 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 4.7 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-3-(2,2,2-trifluoroethylidene)-5-(trifluoromethyl)isoindolin-1-one **4hE** as a colorless oil (65 mg) and (3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)-5-(trifluoromethyl)isoindolin-1-one **4hZ** as a yellow oil (8 mg) (E/Z mixture 90/10, 45% overall yield).

(3E)-2-benzyl-3-(2,2,2-trifluoroethylidene)-5-(trifluoromethyl)isoindolin-1-one 4hE

IR (neat): 1733, 1313, 1120, 1103 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.17 (s, 2 H), 8.11 (sl, 1 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.3 (m, 3 H), 6.13 (q, *J* = 9.3 Hz, 1 H), 5.1 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 165.5, 143.3 (q, *J* = 6.2 Hz), 136.2, 133.7, 133.5, 132.6, 129.7 (bq, *J* = 3.3 Hz), 129 (2C), 127.6 (2C), 127.6, 125, 124.5 (q, *J* = 268.6 Hz), 124 (q, *J* = 272.7 Hz), 120.7 (bq, *J* = 5.0 Hz), 97.4 (q, *J* = 37.6 Hz), 42.9

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.9, -61.6

HRMS (EI) : calcd. for C₁₈ H₁₁ F₆ N O ([M]⁺) 371.0739, found 371.0730

(3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)-5-(trifluoromethyl)isoindolin-1-one **4hZ**

IR (neat): 1724, 1660, 1323, 1130, 1110, 1097 cm⁻¹

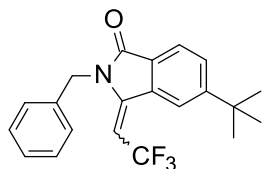
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.78 (s, 1 H), 8.08 (bs, 2 H), 7.3 (t, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.1 (d, *J* = 7.65 Hz, 2 H), 6.69 (q, *J* = 10.09 Hz, 1 H), 5.14 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 167.1, 141 (q, *J* = 6.1 Hz), 138, 136.7, 133.9 (q, *J* = 32.0 Hz), 130.8, 128.8 (bq, *J* = 3.7 Hz), 128.6 (2C), 127, 126 (2C), 124.5, 124.2 (q, *J* = 272.8 Hz), 123.6 (q, *J* = 268.5 Hz), 119.4 (bq, *J* = 3.8 Hz), 93.8 (q, *J* = 37.6 Hz), 45

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -49.2, -61

HRMS (EI): calcd. for C₁₈ H₁₁ F₆ N O ([M]⁺) 371.0739, found 371.0737

(3E/Z)-2-benzyl-5-tert-butyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4i**



Starting from N-benzyl-4-tert-butyl-N-ethynyl-benzamide **3i** (77 mg, 0.26 mmol), Togni I reagent (105 mg, 0.32 mmol) and Ir(ppy)₃ (4.3 mg, 0.007 mmol), using **General procedure 3** and stirring at 27°C for 3.8 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-5-tert-butyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4iE** as a pale yellow oil (25 mg) and (3Z)-2-benzyl-5-tert-butyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4iZ** as a pale yellow oil (18 mg) (E/Z mixture 56/44, 40 % overall yield).

(3E)-2-benzyl-5-tert-butyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4iE**

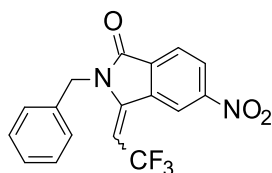
IR (neat): 1726, 1654, 1313, 1253, 1126 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8 (sb, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0, 1.5 Hz, 1 H), 7.4-7.2 (m, 5 H), 5.9 (q, *J* = 9.6 Hz, 1 H), 5.03 (s, 2 H), 1.32 (s, 9 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 166.5, 157.2, 144.7 (q, *J* = 6.1 Hz), 136.6, 132.4, 129.8, 129.2 (2C), 127.9, 127.4, 127.3 (2C), 123.9 (q, *J* = 268.3 Hz), 123.5, 121.3, 95.4 (q, *J* = 37.8 Hz), 42.5, 35.7, 31.2 (3C)

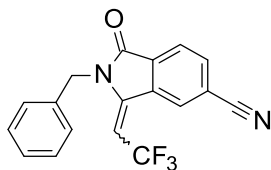
¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.9

HRMS (ESI): calcd. for C₂₁ H₂₂ F₃ N O ([M+H]⁺) 360.1570, found 360.157

(3Z)-2-benzyl-5-tert-butyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4iZ**IR** (neat): 1728, 1660, 1267, 1251, 1197, 1128 cm⁻¹**¹H NMR** (400 MHz, DMSO-*d*₆) δ ppm 8.3 (sb, 1 H), 7.8 (db, *J* = 7.9 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.3 (t, *J* = 7.7 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 6.5 (q, *J* = 10.1 Hz, 1 H), 5.1 (s, 2 H), 1.4 (s, 9 H)**¹³C NMR** (100 MHz, DMSO-*d*₆) δ ppm 169, 158, 142.2 (q, *J* = 6.5 Hz), 137.5, 137.2, 129, 128.9 (2C), 127.3, 125.8 (2C), 124.8, 124.0 (q, *J* = 268.3 Hz), 123.6, 119.3, 91.5 (q, *J* = 37.4 Hz), 44.5, 35.9, 31.5 (3C)**¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ ppm -48.7**HRMS (ESI)**: calcd. for C₂₁H₂₁F₃N O ([M+H]⁺) 360.1570, found 360.157**(3E/Z)-2-benzyl-5-nitro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4j**

Starting from N-benzyl-N-ethynyl-4-nitro-benzamide **3j** (112 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 22 h and then at 40°C for 5.5 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-benzyl-5-nitro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4j** as a white solid (80 mg, 52 % yield) (E/Z mixture 55/45).

(3E)-2-benzyl-5-nitro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4jE**IR** (neat): 1730, 1656, 1533, 1340, 1116, 779, 738 cm⁻¹ (mixture 70/30 E/Z)**¹H NMR** (400 MHz, DMSO-*d*₆) δ ppm 8.63 (df, *J* = 1.5 Hz, 1 H), 8.59 (dd, *J* = 8.3, 1.8 Hz, 1 H), 8.19 (d, *J* = 8.3 Hz, 1 H), 7.39-7.3 (m, 5 H), 6.18 (q, *J* = 9.3 Hz, 1 H), 5.1 (s, 2 H)**¹³C NMR** (100 MHz, DMSO-*d*₆) δ ppm 164.5, 151.1, 143 (q, *J* = 6.0 Hz), 134.6, 132.8, 128.9, 128.7 (2C), 127.6 (2C), 127.6, 125.9, 125.9, 124.4 (q, *J* = 268.9 Hz), 119.9, 97.6 (q, *J* = 37.8 Hz), 43.5**¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ ppm -51.6**HRMS (ESI)**: calcd. for C₁₇H₁₁F₃N₂O ([M+H]⁺) 349.0795, found 349.0796**(3Z)-2-benzyl-5-nitro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4jZ****¹H NMR** (400 MHz, DMSO-*d*₆) δ ppm 9.21 (df, *J* = 1.8 Hz, 1 H), 8.52 (dd, *J* = 8.26, 1.9 Hz, 1 H), 8.13 (d, *J* = 8.3 Hz, 1 H), 7.31 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.11 (d, *J* = 7.4 Hz, 2 H), 6.81 (q, *J* = 10.0 Hz, 1 H), 5.14 (s, 2 H)**¹³C NMR** (100 MHz, DMSO-*d*₆) δ ppm 167.1, 151.6, 140.6 (q, *J* = 6.5 Hz), 138.5, 135.9, 132.2, 128.0 (2C), 127.6, 127.2, 125.9 (2C), 125.3, 124.4 (q, *J* = 267.2 Hz), 117, 95 (q, *J* = 37.6 Hz), 45.6**¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ ppm -49.3**HRMS (ESI)**: calcd. for C₁₇H₁₁F₃N₂O ([M+H]⁺) 349.0795, found 349.0796

(3E/Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carbonitrile 4k

Starting from N-benzyl-4-cyano-N-ethynyl-benzamide **3k** (104 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 6 h and at 40°C for 15 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carbonitrile **4k** as a white solid (64 mg) (E/Z mixture 66/34, 56 % overall yield).

(3E)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carbonitrile 4kE

IR (neat): 2233, 1735, 1654, 1107, 704, 661 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.27 (d, *J* = 7.8 Hz, 1 H), 8.16 (bs, 1 H), 8.13 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.28 (m, 3 H), 6.13 (q, *J* = 9.3 Hz, 1 H), 5.09 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 165.1, 142.9 (q, *J* = 6.2 Hz), 136.4, 136.1, 133.9, 132.6, 129.1 (2C), 128.1, 127.4 (2C), 125.4, 125.3, 124.4 (q, *J* = 269.7 Hz), 118.5, 116.3, 97.6 (q, *J* = 37.7 Hz), 43

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.8

HRMS (EI): calcd. for C₁₈ H₁₁ F₃ N₂ O ([M]⁺) 328.0823, found 328.0818

mp: 122.6-132.0°C (mixture 65/35 E/Z)

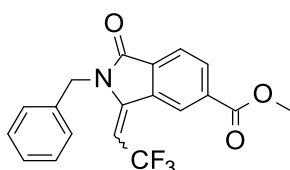
(3Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carbonitrile 4kZ

IR (neat): 2231, 1727, 1662, 1094 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.84 (bs, 1 H), 8.18 (dd, *J* = 7.9, 1.2 Hz, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.1 (d, *J* = 7.5 Hz, 2 H), 6.53 (q, *J* = 9.9 Hz, 1 H), 5.12 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 167, 140.8 (q, *J* = 6.5 Hz), 137.6, 136.6, 135.5, 130.6, 128.7 (2C), 127.3, 126.5, 125.9 (2C), 124.9, 123.5 (q, *J* = 268.9 Hz), 118.3, 116.2, 94.1 (q, *J* = 37.6 Hz), 43.8

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -49.2

methyl (3E/Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carboxylate 4l

Starting from methyl 4-[benzyl(ethynyl)carbamoyl]benzoate **3l** (107 mg, 0.36 mmol), Togni I reagent (145 mg, 0.44 mmol) and Ir(ppy)₃ (6 mg, 0.09 mmol), using **General procedure 3** and stirring at 27°C

for 22 h. The crude was purified by silica gel flash column chromatography to afford a mixture of methyl (3E/Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carboxylate **4I** as a yellow solid (81 mg, 61 % yield) (E/Z mixture 63/37).

methyl (3E)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carboxylate 4IE

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.52 (s, 1 H), 8.31 (dd, *J* = 7.9, 1.2 Hz, 1 H), 8.07 (d, *J* = 7.9 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.3 (m, 3 H), 6.08 (q, *J* = 9.4 Hz, 1 H), 5.08 (s, 2 H), 3.94 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 165.6, 165.6, 143.8 (q, *J* = 6.2 Hz), 136.3, 134.2, 133.5, 132.8, 132.2, 129.2 (2C), 128 (2C), 128, 125.1, 124.9 (q, *J* = 268.0 Hz), 124.9, 96.6 (q, *J* = 37.4 Hz), 52.8, 42.6

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.7

HRMS (ESI): calcd. for C₁₉H₁₅F₃N O₃ ([M+H]⁺) 362.0999, found 362.1001

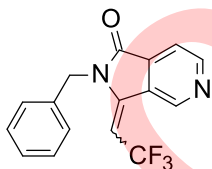
methyl (3Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carboxylate 4IZ

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.82 (s, 1 H), 8.26 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8 (d, *J* = 7.9 Hz, 1 H), 7.3 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.1 (d, *J* = 7.6 Hz, 2 H), 6.67 (q, *J* = 10.01 Hz, 1 H), 5.13 (s, 2 H), 3.95 (s, 3 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 167.6, 166, 141.1 (q, *J* = 6.4 Hz), 137.6, 136.8, 134.7, 132.5, 130.7, 129.1 (2C), 127.2, 125.5 (2C), 124.8, 124.0 (q, *J* = 268.3 Hz), 122.9, 94 (q, *J* = 37.4 Hz), 53.8, 44.7

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -49.1 ppm

(3E/Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)pyrrolo[3,4-c]pyridin-1-one 4m



Starting from N-benzyl-N-ethynyl-pyridine-4-carboxamide **3m** (95 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 20 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-3-(2,2,2-trifluoroethylidene)pyrrolo[3,4-c]pyridin-1-one **4mE** as a yellow solid (40 mg) and (3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)pyrrolo[3,4-c]pyridin-1-one **4mZ** as a yellow oil (28 mg) (E/Z mixture 73/27, 54 % overall yield).

(3E)-2-benzyl-3-(2,2,2-trifluoroethylidene)pyrrolo[3,4-c]pyridin-1-one 4mE

IR (neat): 1728, 1660, 1334, 1105 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.15 (bs, 1 H), 9 (d, *J* = 4.8 Hz, 1 H), 7.97 (dd, *J* = 4.9, 1.2 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.3 (m, 3 H), 6.14 (q, *J* = 9.2 Hz, 1 H), 5.1 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 165.1, 152.9, 145.4, 142.7 (q, *J* = 6.3 Hz), 137.1, 136, 129.2 (2C), 128.0, 127.4 (2C), 127.3, 124.4 (q, *J* = 268.3 Hz), 117.7, 97.2 (q, *J* = 37.6 Hz), 42.8

¹⁹F NMR (376 MHz, dms_o-d₆) δ ppm -52.5

HRMS (ESI): calcd. for C₁₆H₁₂F₃N₂O ([M+H]⁺) 305.0896, found 305.0894

(3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)pyrrolo[3,4-c]pyridin-1-one 4mZ

IR (neat): 1728, 1662, 1126-1100cm⁻¹

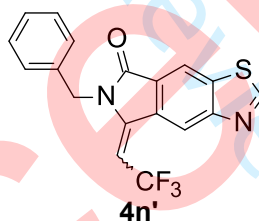
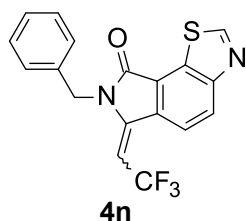
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.55 (s, 1 H), 9 (d, *J* = 4.9 Hz, 1 H), 7.9 (dd, *J* = 4.9, 1.1 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.11 (d, *J* = 7.4 Hz, 2 H), 6.5 (q, *J* = 10.0 Hz, 1 H), 5.17 (s, 2 H)

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 167.4, 152.5, 144, 140.5 (q, *J* = 6.6 Hz), 136.5, 134.3, 131.9, 129 (2C), 127.5, 126 (2C), 123 (q, *J* = 268.9 Hz), 117.5, 94 (q, *J* = 37.6 Hz), 45

¹⁹F NMR (376 MHz, dms_o-d₆) δ ppm -49.2

HRMS (ESI): calcd. for C₁₆H₁₂F₃N₂O ([M+H]⁺) 305.0896, found 305.0896

(6E/Z)-7-benzyl-6-(2,2,2-trifluoroethylidene)pyrrolo[3,4-g][1,3]benzothiazol-8-one 4n and (5E/Z)-6-benzyl-5-(2,2,2-trifluoroethylidene)pyrrolo[3,4-f][1,3]benzothiazol-7-one 4n'



Starting from *N*-benzyl-*N*-ethynyl-1,3-benzothiazole-6-carboxamide **3n** (117 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and Ir(ppy)₃ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 22 h. The crude was purified by silica gel flash column chromatography to afford (6E)-7-benzyl-6-(2,2,2-trifluoroethylidene)pyrrolo[3,4-g][1,3]benzothiazol-8-one **4nE** as a white solid (33 mg), (6Z)-7-benzyl-6-(2,2,2-trifluoroethylidene)pyrrolo[3,4-g][1,3]benzothiazol-8-one **4nZ** as a white solid (19 mg) (E/Z mixture 63/37, 36 % overall yield) and a mixture of (5E/Z)-6-benzyl-5-(2,2,2-trifluoroethylidene)pyrrolo[3,4-f][1,3]benzothiazol-7-one **4n'** as a white solid (22 mg, 15 % yield) (E/Z mixture 78/22).

(6E)-7-benzyl-6-(2,2,2-trifluoroethylidene)pyrrolo[3,4-g][1,3]benzothiazol-8-one 4nE

IR (neat): 3070, 1724, 1652, 1099, 717, 692, 675 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.79 (s, 1 H), 8.47 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.14 (d, *J* = 7.5 Hz, 2 H), 5.79 (q, *J* = 9.6 Hz, 1 H), 5.17 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 168, 160.2, 158.8, 142.5 (q, *J* = 6.3 Hz), 136.8, 132, 128.9 (2C), 127.4, 127.1, 126.8, 126.3 (q, *J* = 268.7 Hz), 125.8 (2C), 125.5, 121.7, 94.5 (q, *J* = 38.4 Hz), 45.2

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -48.9

HRMS (ESI): calcd. for C₁₈H₁₁F₃O S ([M+H]⁺) 361.0617, found 361.0619

mp: 171.7-174.9°C

(6Z)-7-benzyl-6-(2,2,2-trifluoroethylidene)pyrrolo[3,4-g][1,3]benzothiazol-8-one 4nZ

IR (neat): 3060, 1714, 1649, 1110, 777, 713, 678 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.7 (s, 1 H), 8.52 (d, *J* = 8.2 Hz, 1 H), 8.1 (d, *J* = 8.2 Hz, 1 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.3 (m, 3 H), 6.09 (q, *J* = 9.9 Hz, 1 H), 5.16 (s, 2 H)

¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm 166, 159.8, 158.6, 143.1 (q, *J* = 6.2 Hz), 136.4, 130.2, 129.3 (2C), 129, 128.3 (2C), 128.1, 127.6, 127.5, 124.1 (q, *J* = 267.3 Hz), 121.8, 98.7 (q, *J* = 38.0 Hz), 43

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -46.8

HRMS (ESI): calcd. for C₁₈H₁₁F₃O S ([M+H]⁺) 361.0617, found 361.0618

mp: 181.5-185.7°C

(5E)-6-benzyl-5-(2,2,2-trifluoroethylidene)pyrrolo[3,4-f][1,3]benzothiazol-7-one 4n'E

IR (neat): 3076, 1724, 1651, 1132, 1099, 839, 732, 692 cm⁻¹ (mixture 78/22 E/Z)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.7 (s, 1 H), 8.86 (s, 1 H), 8.51 (s, 1 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.3 (m, 3 H), 5.97 (q, *J* = 9.5 Hz, 1 H), 5.11 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 165.9, 161.9, 156.5, 144.1 (q, *J* = 6.2 Hz), 137.8, 136.7, 129.5 (2C), 129.5, 127.9 (2C), 127.7, 126.7, 125.1 (q, *J* = 268.9 Hz), 119.8, 119.3, 95.6 (q, *J* = 37.7 Hz), 43.1

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -52.1

HRMS (ESI): calcd. for C₁₈H₁₁F₃O S ([M+H]⁺) 361.0617, found 361.0619

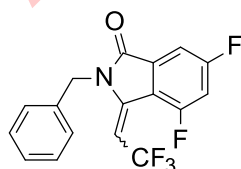
(5Z)-6-benzyl-5-(2,2,2-trifluoroethylidene)pyrrolo[3,4-f][1,3]benzothiazol-7-one 4n'Z

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.69 (s, 1 H), 9 (s, 1 H), 8.8 (s, 1 H), 7.32 (m, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.1 (d, *J* = 7.5 Hz, 2 H), 6.58 (q, *J* = 10.1 Hz, 1 H), 5.16 (s, 2 H)

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm 168.1, 161.9, 156.9, 142 (q, *J* = 6.4 Hz), 137.6, 137, 135.1, 127.4 (2C), 127.4, 124.8 (2C), 124.5, 124 (q, *J* = 268.2 Hz), 119.6, 116.7, 91.4 (q, *J* = 37.7 Hz), 45.2

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -48.5

(3E/Z)-2-benzyl-4,6-difluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4o



Starting from N-benzyl-N-ethynyl-3,5-difluoro-benzamide **3o** (54 mg, 0.2 mmol), Togni I reagent (79 mg, 0.24 mmol) and Ir(ppy)₃ (3.3 mg, 0.005 mmol), using **General procedure 3** and stirring at 27°C for 12 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-4,6-difluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4oE** as a colorless oil (22 mg) and (3Z)-2-benzyl-

4,6-difluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4oZ** as a colorless oil (22 mg) (E/Z mixture 50/50, 62 % overall yield).

(3E)-2-benzyl-4,6-difluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4oE**

IR (neat): 1720, 1658, 1336, 1112 cm^{-1}

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.78 (td, $J = 10.2, 2.3$ Hz, 1 H), 7.73 (dd, $J = 6.6, 2.3$ Hz, 1 H), 7.36 (t, $J = 7.4$ Hz, 2 H), 7.28 (m, 3 H), 6 (q, $J = 9.1$ Hz, 1 H), 5.08 (s, 2 H)

$^{13}\text{C NMR}$ (75 MHz, $\text{DMSO-}d_6$) δ ppm 165.1 (dd, $J = 255.5, 10.9$ Hz), 164.8, 157.5 (dd, $J = 262.3, 13.0$ Hz), 139.7 (bq, $J = 5.7$ Hz), 136.3, 134.7, 129.2 (2C), 127.9, 126.9 (2C), 123.7 (q, $J = 267.7$ Hz), 115.1, 110.1 (t, $J = 27.6$ Hz), 108.3 (dd, $J = 24.1, 3.2$ Hz), 99.4 (q, $J = 38.9$ Hz), 42.6

$^{19}\text{F NMR}$ (376 MHz, $\text{DMSO-}d_6$) δ ppm -50.8, -100.4, -102.2

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_5\text{N O}$ ($[\text{M}]^+$) 339.0677, found 339.067

(3Z)-2-benzyl-4,6-difluoro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4oZ**

IR (neat): 3091, 3068, 3033, 1739, 1656, 1097, 761, 729, 692 cm^{-1}

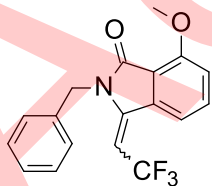
$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.84 (td, $J = 10.1, 2.1$ Hz, 1 H), 7.73 (dd, $J = 9.9, 2.1$ Hz, 1 H), 7.31 (t, $J = 7.4$ Hz, 2 H), 7.24 (t, $J = 7.2$ Hz, 1 H), 7.11 (d, $J = 7.5$ Hz, 2 H), 6.02 (qd⁷, $J = 9.9, 4.2$ Hz, 1 H), 5.11 (s, 2 H)

$^{13}\text{C NMR}$ (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.5, 164.9 (dd, $J = 254.1, 11.0$ Hz), 157.9 (dd, $J = 258.5, 13.0$ Hz), 138.8 (bq, $J = 6.4$ Hz), 136.3, 131.8, 128.6 (2C), 127.3, 125.5 (2C), 123.2 (q, $J = 268.7$ Hz), 119.2, 109.9 (t, $J = 26.4$ Hz), 108.1 (dd, $J = 24.6, 4.2$ Hz), 95.4 (bq, $J = 37.8$ Hz), 45.1

$^{19}\text{F NMR}$ (376 MHz, $\text{DMSO-}d_6$) δ ppm -49.5, -103.2, -111.7

HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_5\text{N O}$ ($[\text{M}+\text{H}]^+$) 339.0677, found 339.0675

(3E/Z)-2-benzyl-7-methoxy-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4p**



Starting from N-benzyl-N-ethynyl-2-methoxy-benzamide **3p** (106 mg, 0.4 mmol), Togni I reagent (158 mg, 0.48 mmol) and $\text{Ir}(\text{ppy})_3$ (6.6 mg, 0.01 mmol), using **General procedure 3** and stirring at 27°C for 20 h. The crude was purified by silica gel flash column chromatography to afford (3E)-2-benzyl-7-methoxy-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4pE** as a white solid (13 mg) and (3Z)-2-benzyl-7-methoxy-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4pZ** as a white solid (10 mg) (E/Z mixture 52/48, 24 % overall yield).

(3E)-2-benzyl-7-methoxy-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4pE**

⁷ Through space coupling

IR (neat): 1724, 1643, 1292/1249, 1105, 758, 700 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.75 (t, $J = 7.9$ Hz, 1 H), 7.49 (d, $J = 7.3$ Hz, 1 H), 7.45 (d, $J = 8.4$ Hz, 1 H), 7.35 (t, $J = 7.4$ Hz, 2 H), 7.30-7.21 (m, 3 H), 5.68 (q, $J = 9.6$ Hz, 1 H), 5.05 (s, 2 H), 3.91 (s, 3 H)

^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.4, 156, 141.7 (q, $J = 6.6$ Hz), 136.9, 134.8, 131.9, 129.0 (2C), 127.7, 127.2 (2C), 121.2 (q, $J = 268.0$ Hz), 119.4, 117.6, 115.8, 98.1 (q, $J = 39.3$ Hz), 55.9, 42.5

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm -48.7

HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N O}_2$ ($[\text{M}+\text{H}]^+$) 334.1049, found 334.105

mp: 124.0-127.1 $^\circ\text{C}$

(3Z)-2-benzyl-7-methoxy-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4pZ

IR (neat): 1726, 1651, 1247, 1080, 748, 731, 694 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.71 (t, $J = 7.8$ Hz, 1 H), 7.50 (m, 2 H), 7.3 (t, $J = 7.5$ Hz, 2 H), 7.22 (t, $J = 7.4$ Hz, 1 H), 7.06 (d, $J = 7.7$ Hz, 2 H), 6.5 (q, $J = 10.5$ Hz, 1 H), 6.1 (s, 2 H), 4.04 (s, 3 H)

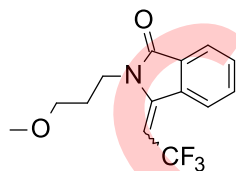
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 168.1, 156, 141.5 (q, $J = 6.8$ Hz), 136.8, 133.6, 132.7 (q, $J = 267.2$ Hz), 129.2, 127.8 (2C), 127.5, 126.4 (2C), 122, 117.4, 116, 94.6 (q, $J = 37.6$ Hz), 56.8, 44.7

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm -48.6

HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N O}_2$ ($[\text{M}+\text{H}]^+$) 334.1049, found 334.1049

mp: 135.4-136.8 $^\circ\text{C}$

(3E/Z)-2-(3-methoxypropyl)-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4q



Starting from N-ethynyl-N-(3-methoxypropyl)benzamide **3q** (80 mg, 0.37 mmol), Togni I reagent (146 mg, 0.44 mmol) and $\text{Ir}(\text{ppy})_3$ (6.1 mg, 0.009 mmol), using **General procedure 3** and stirring at 27°C for 2.7 h. The crude was purified by silica gel flash column chromatography to afford a mixture of (3E/Z)-2-(3-methoxypropyl)-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4q** as a beige solid (60 mg, 57 % yield) (E/Z mixture 76/24).

(3E)-2-(3-methoxypropyl)-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4qE

IR (neat): 1728, 1655 cm^{-1} (mixture 78/22 E/Z)

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ ppm 7.96 (d, $J = 7.8$ Hz, 1 H), 7.86 (d, $J = 7.4$ Hz, 1 H), 7.81 (m, 1 H), 7.73 (t, $J = 7.5$ Hz, 1 H), 6.04 (q, $J = 9.5$ Hz, 1 H), 3.82 (t, $J = 7$ Hz, 2 H), 3.35 (m, 2 H), 3.22 (s, 3 H), 1.81 (m, 2 H)

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 166.3, 144.4 (q, $J = 6.2$ Hz), 133.7, 132, 131.9, 130.1, 125.2 (q, $J = 267.9$ Hz), 124.5, 123.5, 94.8 (q, $J = 37.6$ Hz), 69.6, 58.3, 36.8, 28.1

1
2
3 ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -51.6
4

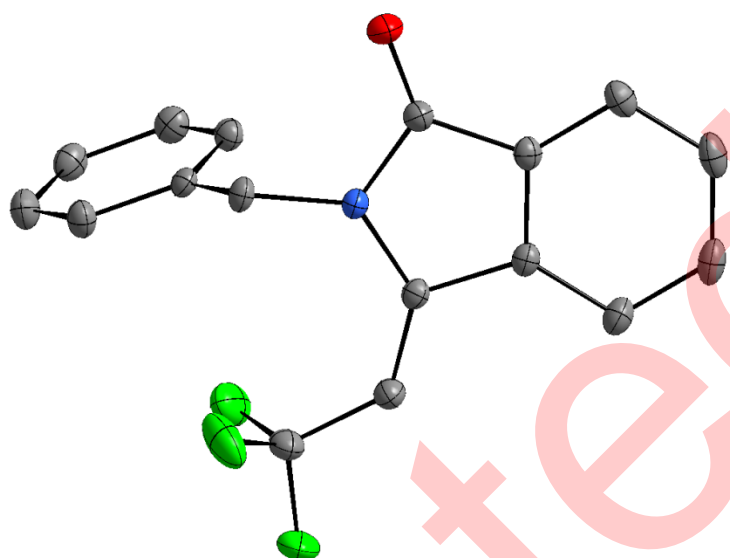
5 HRMS (ESI): calcd. for C₁₄H₁₅F₃N O₂ ([M+H]⁺) 286.1049, found 286.1051
6
7

8 *(3Z)*-2-(3-methoxypropyl)-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4qZ
9

10 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.15 (d, *J* = 7.6 Hz, 1 H), 7.81 (m, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H),
11 7.68 (t, *J* = 7.4 Hz, 1 H), 6.29 (q, *J* = 10.2 Hz, 1 H), 3.88 (t, *J* = 7.6 Hz, 2 H), 3.35 (m, 2 H), 3.21 (s, 3 H),
12 1.8 (m, 2 H)
13

14 ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 168.4, 142.1 (q, *J* = 6.5 Hz), 137, 133.3, 132, 127.4, 124.2 (q, *J* =
15 267.9 Hz), 123, 121.7, 91.1 (q, *J* = 37.6 Hz), 69.7, 58.3, 39.5, 28.1
16

17 ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -49
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X-Ray crystal structure of compound **4aZ** (Z isomer)

Crystal data and structure refinement for 4aE

CCDC number	1949295
Empirical formula ^a	C ₁₇ H ₁₂ F ₃ NO
Moiety Formula	C ₁₇ H ₁₂ F ₃ NO
Formula weight (g/mol)	303.28
Temperature (K)	200
Crystal system	Monoclinic
Space group	C2/c
a (Å)	22.9645(6)
b (Å)	8.0352(2)
c (Å)	15.3941(4)
α (°)	90
β (°)	104.553(2)
γ (°)	90
Volume (Å ³)	2749.45(12)
Z	8
ρ _{calc} (g/cm ³)	1.465
Absorption coefficient μ (mm ⁻¹)	0.119 (MoKα)
F(000)	1248
Crystal size (mm ²)	0.39 x 0.28 x 0.20
Wavelength λ (Å)	0.71073
2θ range (°)	5.39 – 61.16
Miller indexes ranges	-32 ≤ h ≤ 32, -11 ≤ k ≤ 11, -22 ≤ l ≤ 22
Measured reflections	21356
Unique reflections	4223
R _{int} / R _{sigma}	0.0223 / 0.0192
Completeness	0.999
Reflections [I ≥ 2σ(I)]	3239
Restraints	0
Parameters	199
Goodness-of-fit F ²	1.021
Final R indexes ^{b,c} [all data]	R1 = 0.0611, wR2 = 0.1201
Final R indexes ^{b,c} [I ≥ 2σ(I)]	R1 = 0.0438 wR2 = 0.1080
Largest diff. peak/hole (e/Å ³)	0.30/-0.25

^a Including solvent molecules (if presence)

$${}^b R1 = \sum ||F_o| - |F_c|| / \sum |F_o| \quad {}^c wR2 = \sqrt{\sum (w(F_o^2 - F_c^2)) / \sum (w(F_o^2)^2)}$$

Crystal data and structure refinement for 4aZ

CCDC number	1949296
Empirical formula ^a	C ₁₇ H ₁₂ F ₃ NO
Moiety Formula	C ₁₇ H ₁₂ F ₃ NO
Formula weight (g/mol)	303.28
Temperature (K)	200
Crystal system	Monoclinic
Space group	P2 ₁ /c
a (Å)	8.6387(3)
b (Å)	12.9185(4)
c (Å)	12.5678(4)
α (°)	90
β (°)	92.705(2)
γ (°)	90
Volume (Å ³)	1400.99(8)
Z	4
ρ _{calc} (g/cm ³)	1.438
Absorption coefficient μ (mm ⁻¹)	0.117 (MoKα)
F(000)	624
Crystal size (mm ²)	0.34 x 0.32 x 0.26
Wavelength λ (Å)	0.71073
2θ range (°)	4.524 – 61.314
Miller indexes ranges	-12 ≤ h ≤ 12, -18 ≤ k ≤ 18, -17 ≤ l ≤ 17
Measured reflections	38461
Unique reflections	4319
R _{int} / R _{sigma}	0.0464 / 0.0214
Completeness	1.000
Reflections [I ≥ 2σ(I)]	3394
Restraints	0
Parameters	199
Goodness-of-fit F ²	1.052
Final R indexes ^{b,c} [all data]	R1 = 0.0622, wR2 = 0.1329
Final R indexes ^{b,c} [I ≥ 2σ(I)]	R1 = 0.0459 wR2 = 0.1175
Largest diff. peak/hole (e/Å ³)	0.39/-0.30

^a Including solvent molecules (if presence)

$${}^b R1 = \sum ||F_o| - |F_c|| / \sum |F_o| \quad {}^c wR2 = \sqrt{\sum (w(F_o^2 - F_c^2)) / \sum (w(F_o^2)^2)}$$

DFT calculation method, energetics data and cartesian coordinates

All calculations were performed using the Gaussian 09 software package⁸. Optimization of geometries, frequency and single point energy calculations were done using the PBE0 functional including the D3BJ dispersion term^{9,10} with the def2-TZVP basis set¹¹. The effect of solvation (in MeCN) was modeled using the 'SMD' model¹². The nature of all stationary points was confirmed by analyzing the harmonic vibrational frequencies.

Table 1. Energetics data (kcal/mol) relative to Scheme 5 obtained at the PBE0-D3BJ/def2-TZVP level of theory.

PBE0-D3BJ/ Def2-TZVP	ΔE	$\Delta E+ZPE$	ΔG	ΔG_{MeCN}
A_E	0.0	0.0	0.0	0.0
A_Z^a	0.4	0.8	1.3	2.1
TS_{Ebz}^a	5.5	4.9	6.3	5.7
B_{Ebz}^a	-26.1	-25.4	-23.5	-26.1
TS_{Eb}^a	12.3	10.9	13.5	12.8
B_{Eb}^a	-12.5	-12.2	-9.8	-12.4
TS_{Zbz}^b	9.4	8.4	9.1	6.9
B_{Zbz}^b	-21.8	-21.6	-20.2	-24.9
TS_{Zb}^b	13.7	12.7	14.8	12.0
B_{Zb}^b	-10.6	-10.7	-8.3	-13.1

^a energies relative to **A_E**; ^b energies relative to **A_Z**

⁸ Gaussian 09, Revision **D.01**, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA, Jr. Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ. Gaussian, Inc., Wallingford CT, **2009**

⁹ Perdew JP, Burke K, Ernzerhof M. *Phys. Rev. Lett.* **1996**, *77*, 3865-3868

¹⁰ Adamo C, Barone V. *J. Chem. Phys.* **1999**, *110*, 6158

¹¹ Weigend F, Ahlrichs R, *Chem. Phys.*, **2005**, *7*, 3297

¹² Marenich AV, Cramer CJ, Truhlar DG. *J. Phys. Chem.* **2009**, *113*, 6378

Cartesian coordinates of all compounds
involved in this work

A_E

6	-3.365420	0.074014	0.406803
6	-2.455636	-0.957565	0.604963
6	-2.555934	-2.110505	-0.170126
6	-3.546940	-2.221952	-1.130720
6	-4.449927	-1.185406	-1.325824
6	-4.359371	-0.037839	-0.554360
1	-3.295008	0.974473	1.007441
1	-1.848302	-2.916816	-0.013204
1	-3.618446	-3.123429	-1.728301
1	-5.225425	-1.274422	-2.077780
1	-5.061276	0.774679	-0.701394
6	-1.360961	-0.828872	1.621984
1	-1.580888	-0.031411	2.332684
1	-1.224597	-1.760742	2.168840
7	-0.050643	-0.529786	1.009825
6	0.169828	0.691613	0.506142
6	-0.257366	1.913163	0.740477
6	0.828429	-1.596575	0.791873
8	0.490128	-2.729347	1.049702
6	2.162520	-1.276729	0.225915
6	2.714723	-2.207448	-0.649995
6	3.960479	-1.982842	-1.207420
6	4.674316	-0.840097	-0.872422
6	4.141367	0.074551	0.023115
6	2.885559	-0.137468	0.569004
1	2.150014	-3.101036	-0.885663
1	4.378588	-2.701452	-1.902291
1	5.652279	-0.665448	-1.305886
1	4.704145	0.958020	0.299608
1	2.484796	0.575486	1.278429
6	0.060554	3.052343	-0.158723
9	0.760811	4.005257	0.486489
9	0.773290	2.690448	-1.225342
9	-1.058262	3.651754	-0.603870
1	-0.842269	2.173924	1.621526

A_Z

6	-3.212168	-0.331151	-0.230761
6	-2.205029	-1.001811	0.453430
6	-2.128439	-2.389522	0.362491
6	-3.041424	-3.090516	-0.407707
6	-4.042230	-2.414169	-1.092315
6	-4.127798	-1.033950	-1.000594
1	-3.279531	0.748707	-0.159572
1	-1.346360	-2.913046	0.900794
1	-2.975719	-4.170705	-0.470455
1	-4.757423	-2.964619	-1.692660
1	-4.909688	-0.500441	-1.528674
6	-1.200005	-0.238123	1.264952
1	-1.562634	0.761448	1.495160
1	-0.977075	-0.756765	2.195818
7	0.098434	-0.096148	0.569331
6	0.176228	0.672676	-0.528341
6	-0.216484	1.860261	-0.936660
1	-0.159138	2.119073	-1.988139
6	1.103924	-1.016962	0.892741
8	0.890806	-1.909593	1.681104

6	2.421950	-0.840678	0.234932
6	3.121130	-1.994297	-0.108972
6	4.369331	-1.899711	-0.697597
6	4.939089	-0.653010	-0.919133
6	4.258681	0.497550	-0.550049
6	2.998804	0.407741	0.019852
1	2.670098	-2.958282	0.092023
1	4.903437	-2.799567	-0.978826
1	5.920501	-0.578911	-1.373252
1	4.710691	1.470332	-0.702955
1	2.479370	1.308777	0.319569
6	-0.706135	2.962914	-0.056699
9	-2.051832	3.049196	-0.032969
9	-0.310723	2.824736	1.216832
9	-0.258398	4.148325	-0.488353

TS_{Ebz} Frequencies -- -367.5841

6	3.560159	0.378455	-0.638144
6	2.573951	-0.589361	-0.499780
6	2.578946	-1.405438	0.627073
6	3.552536	-1.249382	1.599208
6	4.535507	-0.279434	1.454690
6	4.539602	0.533104	0.332415
1	3.560422	1.020520	-1.513559
1	1.817907	-2.170308	0.737178
1	3.546581	-1.889314	2.474002
1	5.295665	-0.157921	2.217480
1	5.302309	1.293860	0.213252
6	1.526337	-0.763507	-1.563875
1	1.609161	0.030838	-2.310010
1	1.643674	-1.727767	-2.062991
7	0.164645	-0.755043	-1.045042
6	-0.421359	0.378294	-0.589935
6	0.062502	1.586402	-0.361963
6	-0.548869	-1.951425	-0.949279
8	-0.073948	-3.025425	-1.228997
6	-1.882117	-1.683028	-0.379976
6	-2.387751	-2.493409	0.614783
6	-3.461786	-2.055086	1.382012
6	-4.004450	-0.791921	1.156591
6	-3.528009	0.015517	0.141570
6	-2.448968	-0.413323	-0.651293
1	-1.903064	-3.442065	0.814197
1	-3.858257	-2.684222	2.169465
1	-4.833521	-0.449440	1.765261
1	-3.997468	0.967912	-0.066266
1	-2.326984	0.039743	-1.630738
6	-0.776232	2.745259	0.032719
9	-2.042400	2.657232	-0.403349
9	-0.843049	2.913368	1.365928
9	-0.266665	3.884967	-0.464251
1	1.131674	1.786473	-0.385847

B_{Ebz}

6	3.565688	0.115946	-0.658995
6	2.476641	-0.713236	-0.425428
6	2.374448	-1.368403	0.796495
6	3.345850	-1.193337	1.768215
6	4.432641	-0.363865	1.528304
6	4.542162	0.289416	0.311023
1	3.649737	0.635124	-1.608863
1	1.529977	-2.022131	0.985814

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1	3.255322	-1.708016	2.717793
1	5.190548	-0.225743	2.290474
1	5.385297	0.942249	0.116988
6	1.438439	-0.919460	-1.497065
1	1.553435	-0.164873	-2.281267
1	1.556684	-1.905552	-1.953876
7	0.082747	-0.884990	-1.010329
6	-0.563827	0.255399	-0.579439
6	0.033598	1.450597	-0.513473
6	-0.698111	-2.043534	-0.950438
8	-0.312850	-3.141675	-1.280425
6	-1.967226	-1.622861	-0.376305
6	-2.903485	-2.411189	0.224769
6	-3.837535	-1.818018	1.081603
6	-3.690050	-0.455280	1.448685
6	-2.771836	0.359627	0.870616
6	-2.006029	-0.135780	-0.310998
1	-2.851416	-3.488144	0.108618
1	-4.594362	-2.423403	1.564008
1	-4.313014	-0.062971	2.244738
1	-2.669751	1.388463	1.184379
1	-2.560260	0.229105	-1.201192
6	-0.634559	2.724499	-0.168317
9	0.055170	3.759804	-0.666293
9	-1.888298	2.818154	-0.653410
9	-0.735874	2.942547	1.160330
1	1.091543	1.546553	-0.713080

TS_{Eb} Frequencies -- -405.3270

6	2.493770	-0.380783	-0.682944
6	2.188027	-1.707646	-0.291212
6	2.780906	-2.256753	0.822448
6	3.721632	-1.526135	1.548422
6	4.031559	-0.221877	1.173599
6	3.444176	0.346982	0.061178
1	2.296817	-0.066298	-1.704176
1	2.491255	-3.249119	1.151148
1	4.195084	-1.968376	2.416801
1	4.757028	0.344207	1.746243
1	3.715257	1.346682	-0.252121
6	0.960471	-2.255378	-0.926277
1	1.051838	-2.363318	-2.012053
1	0.646940	-3.213769	-0.517958
7	-0.075191	-1.246676	-0.611810
6	0.376183	0.031602	-0.516024
6	-0.159348	1.238362	-0.569884
6	-1.400344	-1.678166	-0.664384
8	-1.665512	-2.735881	-1.189110
6	-2.436649	-0.843508	-0.006617
6	-2.223648	-0.268813	1.242517
6	-3.244806	0.429164	1.863453
6	-4.473042	0.572590	1.232380
6	-4.688090	-0.003144	-0.011743
6	-3.676622	-0.724228	-0.624042
1	-1.259574	-0.369414	1.726331
1	-3.081094	0.866748	2.841055
1	-5.266774	1.130886	1.715138
1	-5.648716	0.102835	-0.501697
1	-3.834690	-1.204101	-1.582393
6	0.652760	2.474532	-0.415196
9	-0.121607	3.558095	-0.564930
9	1.246512	2.582679	0.786833
9	1.644728	2.579911	-1.324805

1 -1.221238 1.409852 -0.718683

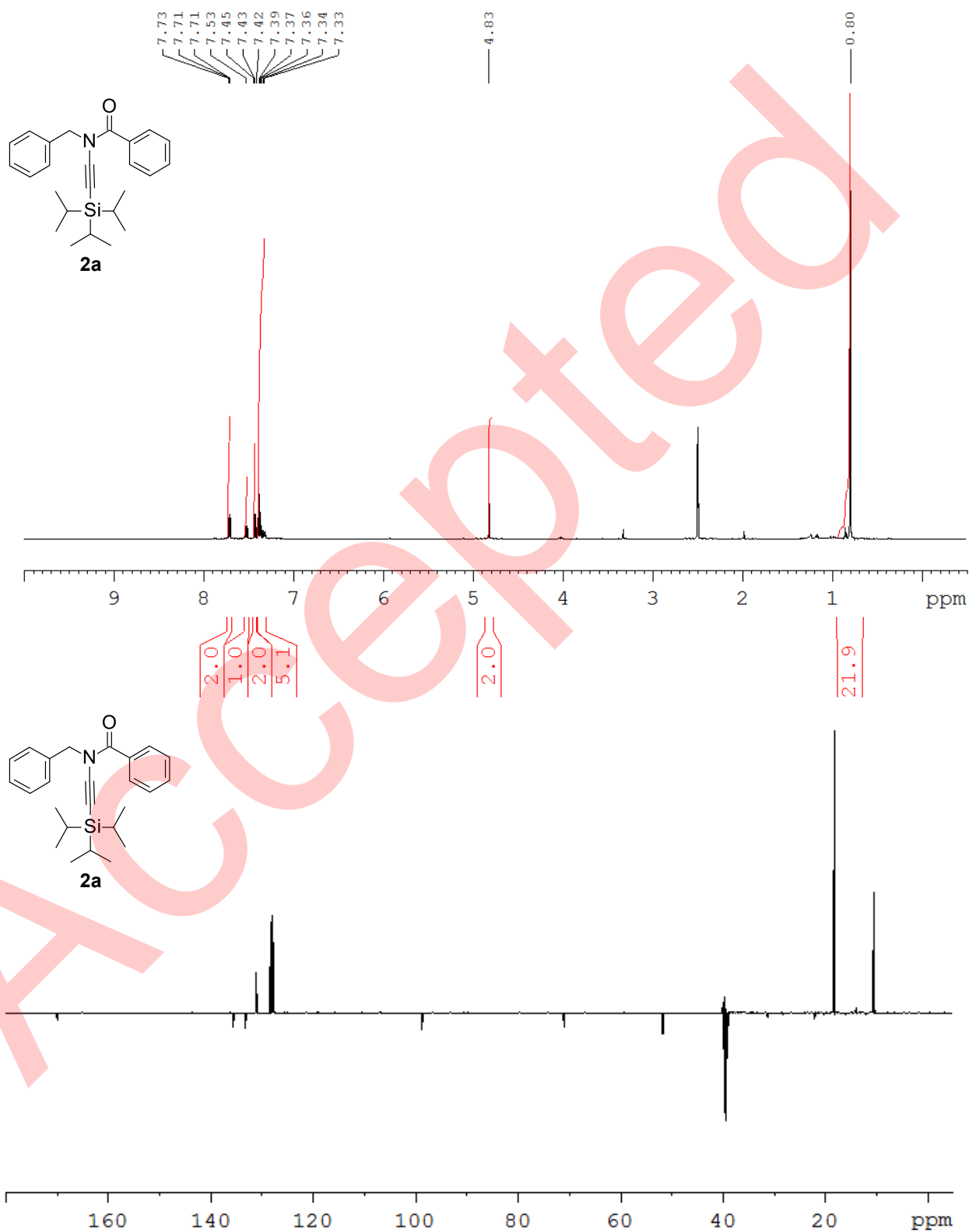
B_{Eb}

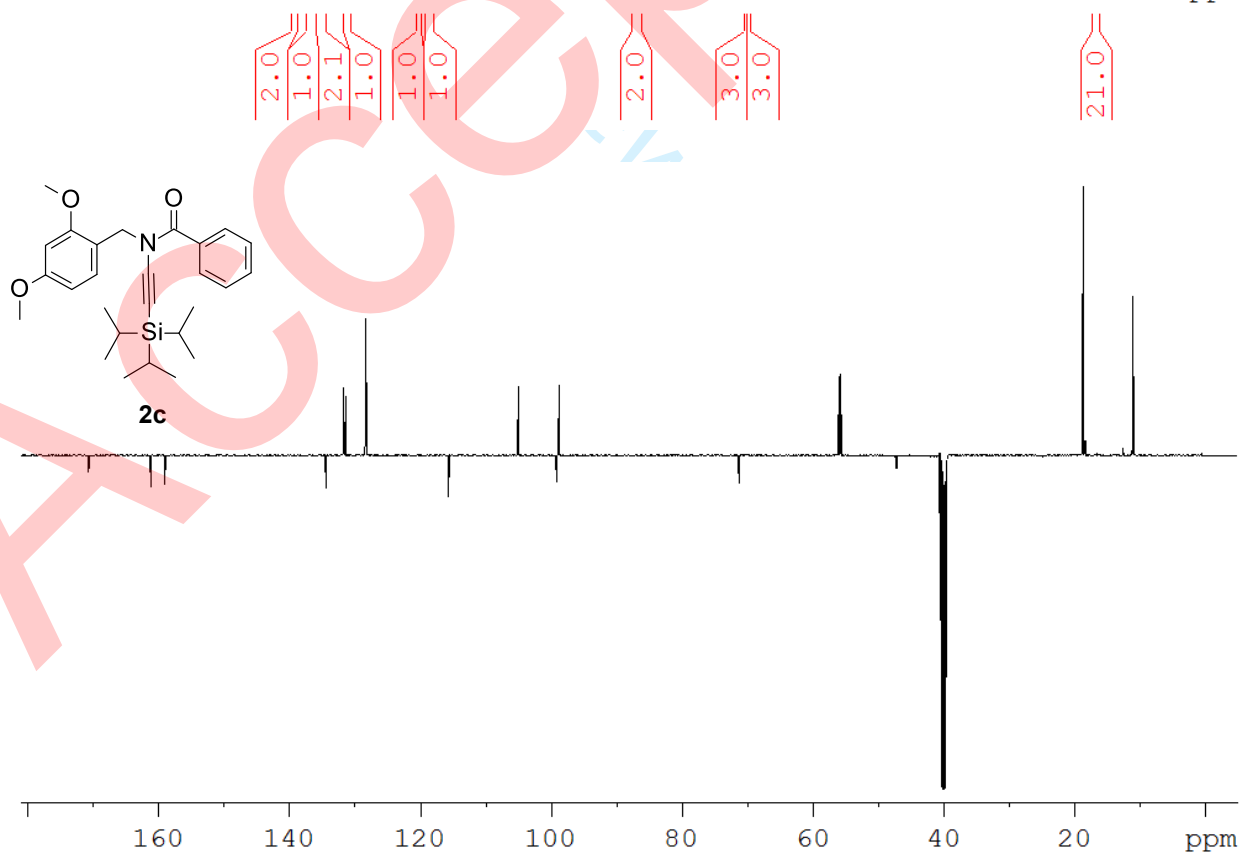
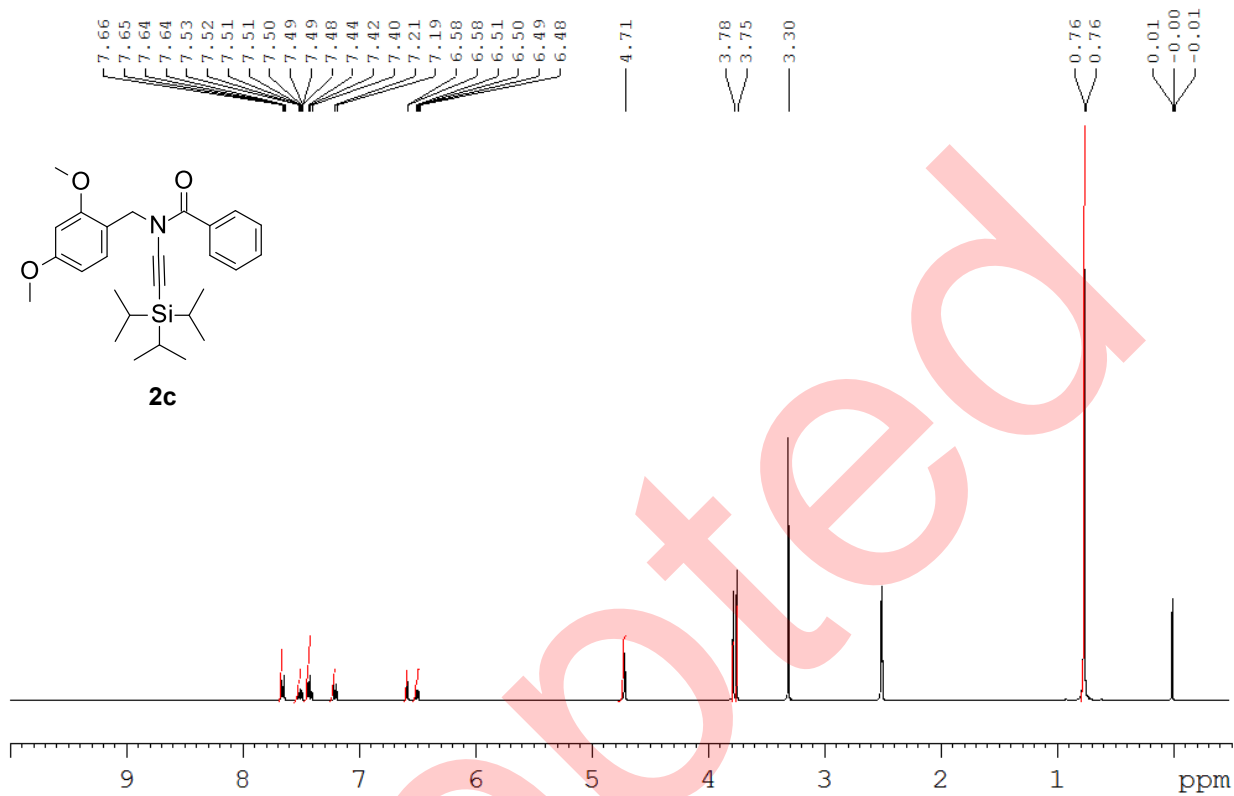
6	1.921892	-0.217183	-0.643206
6	2.366934	-1.581360	-0.209283
6	3.665304	-1.886927	0.025627
6	4.657631	-0.891989	-0.069570
6	4.277304	0.448688	-0.290186
6	2.987194	0.815015	-0.507050
1	1.651556	-0.274370	-1.721788
1	3.936034	-2.890104	0.339702
1	5.696351	-1.141138	0.103326
1	5.041081	1.218320	-0.269600
1	2.741898	1.850911	-0.684779
6	1.165707	-2.419833	0.045734
1	0.943246	-3.135797	-0.753656
1	1.231495	-2.987777	0.977015
7	0.093501	-1.426200	0.116675
6	0.576005	-0.114080	0.057477
6	-0.069863	0.930882	0.578334
1	-0.992999	0.778509	1.118568
6	-1.191409	1.895536	0.304756
8	-1.360285	-3.045646	0.652910
6	-2.346135	-1.011994	-0.013247
6	-3.453249	-1.048642	0.825605
6	-4.572140	-0.286194	0.531169
6	-4.600248	0.488883	-0.618779
6	-3.507703	0.500929	-1.475486
6	-2.379727	-0.239841	-1.170120
1	-3.425126	-1.680893	1.704964
1	-5.427327	-0.303675	1.196396
1	-5.477420	1.080977	-0.852452
1	-3.534001	1.093747	-2.382097
1	-1.522754	-0.220371	-1.832901
6	0.290182	2.362351	0.428352
9	0.613039	2.700364	-0.837353
9	-0.753261	3.128768	0.775516
9	1.322406	2.753227	1.197008

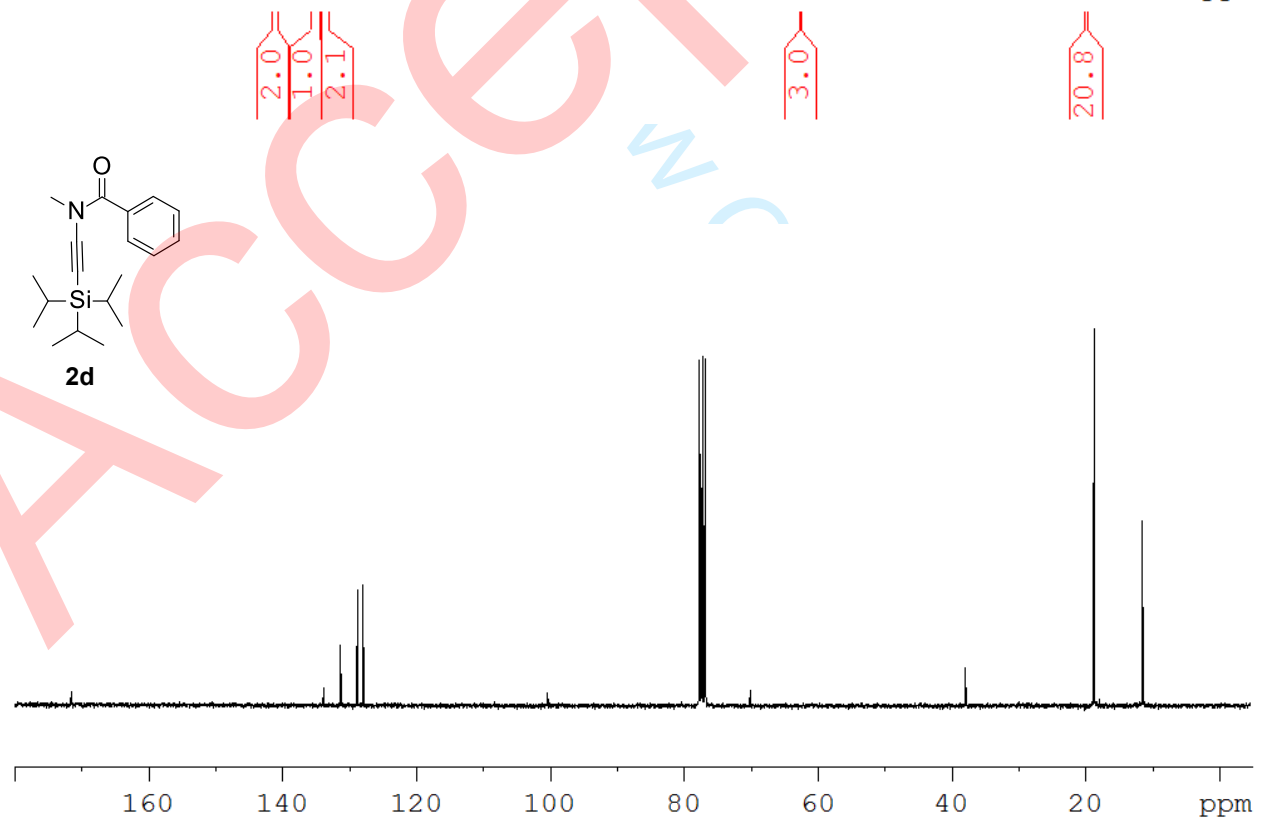
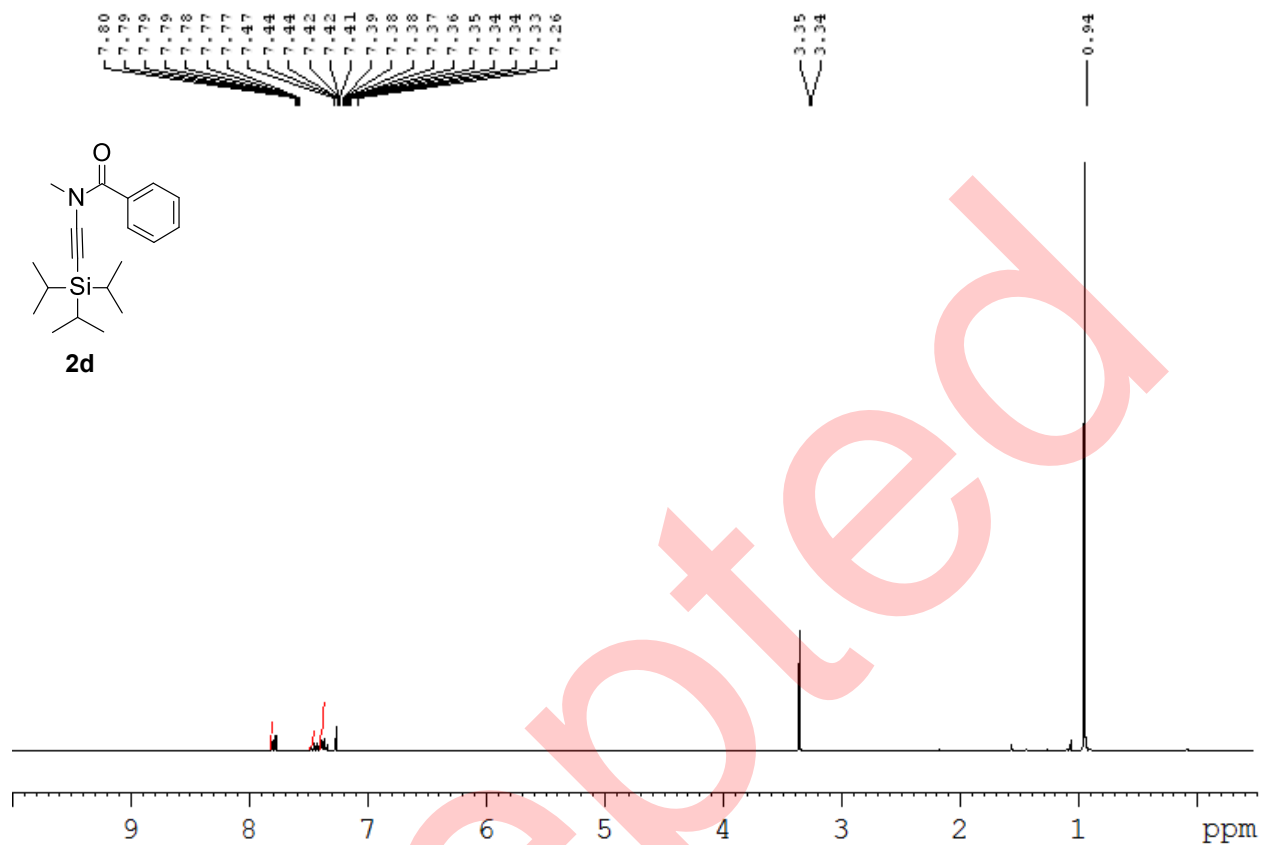
TS_{Zbz} Frequencies -- -338.5570

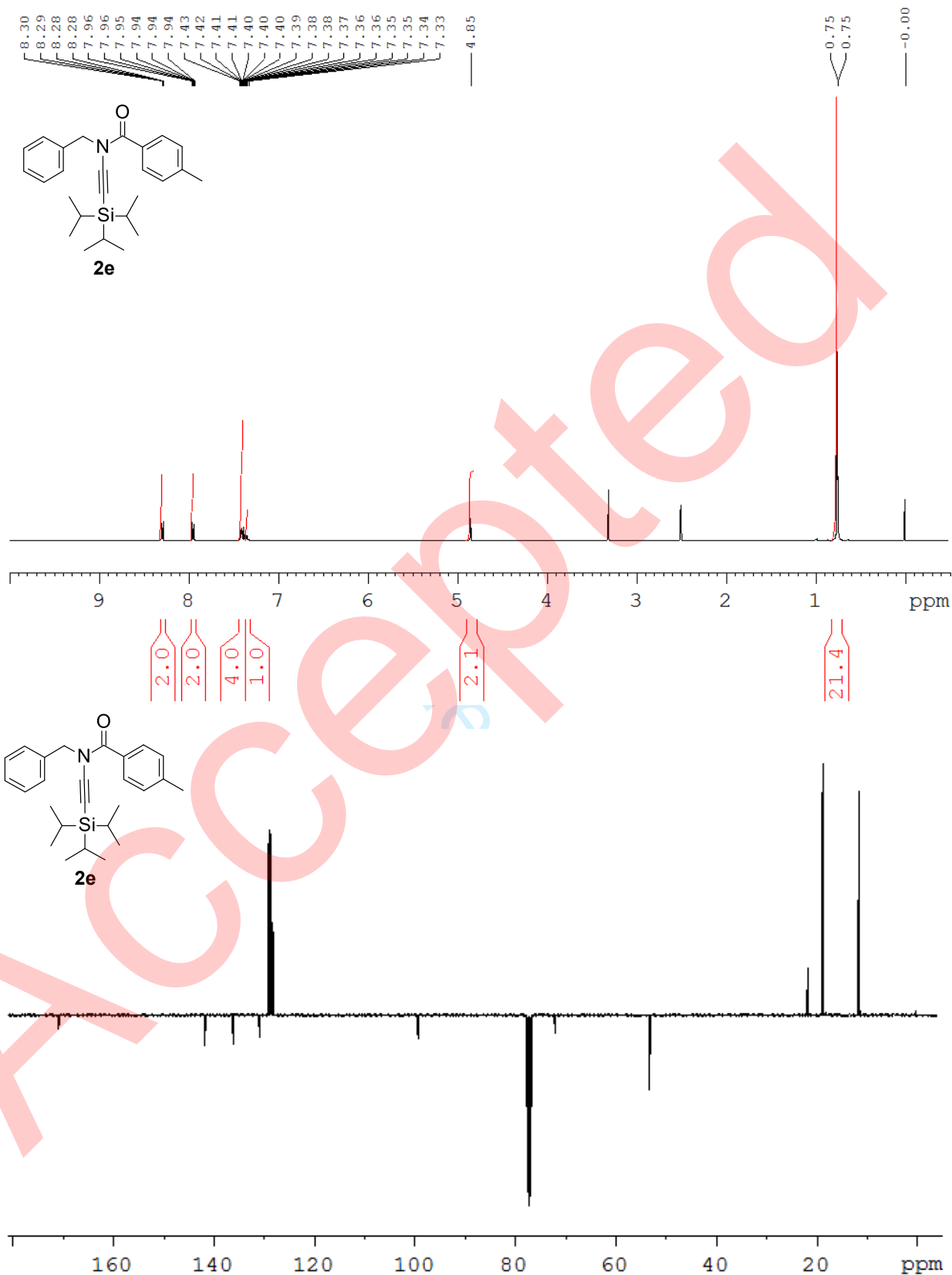
6	1.597330	-1.261953	0.859718
6	2.005406	-0.910154	-0.417484
6	3.315683	-1.172296	-0.802731
6	4.202328	-1.773923	0.073767
6	3.788161	-2.124051	1.351285
6	2.483909	-1.866111	1.739590
1	0.582590	-1.059909	1.182294
1	3.644995	-0.903478	-1.801680
1	5.220075	-1.972223	-0.242138
1	4.479935	-2.596028	2.039031
1	2.150054	-2.134323	2.735337
6	1.088154	-0.246321	-1.412518
1	1.441057	0.757310	-1.651580
1	1.077742	-0.829395	-2.335763
7	-0.296806	-0.147718	-0.974016
6	-0.821298	0.898009	-0.305811
6	-0.509291	2.080926	0.190860
1	-1.298232	2.672440	0.642581
6	-1.119735	-1.273661	-1.158123
8	-0.726815	-2.283002	-1.682050
6	-2.440968	-1.026424	-0.549648
6	-3.021396	-1.963278	0.279384
6	-4.069904	-1.586854	1.113647
6	-4.511615	-0.266752	1.123174

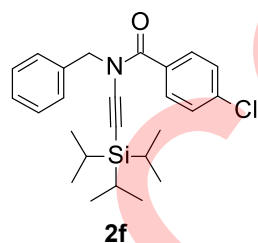
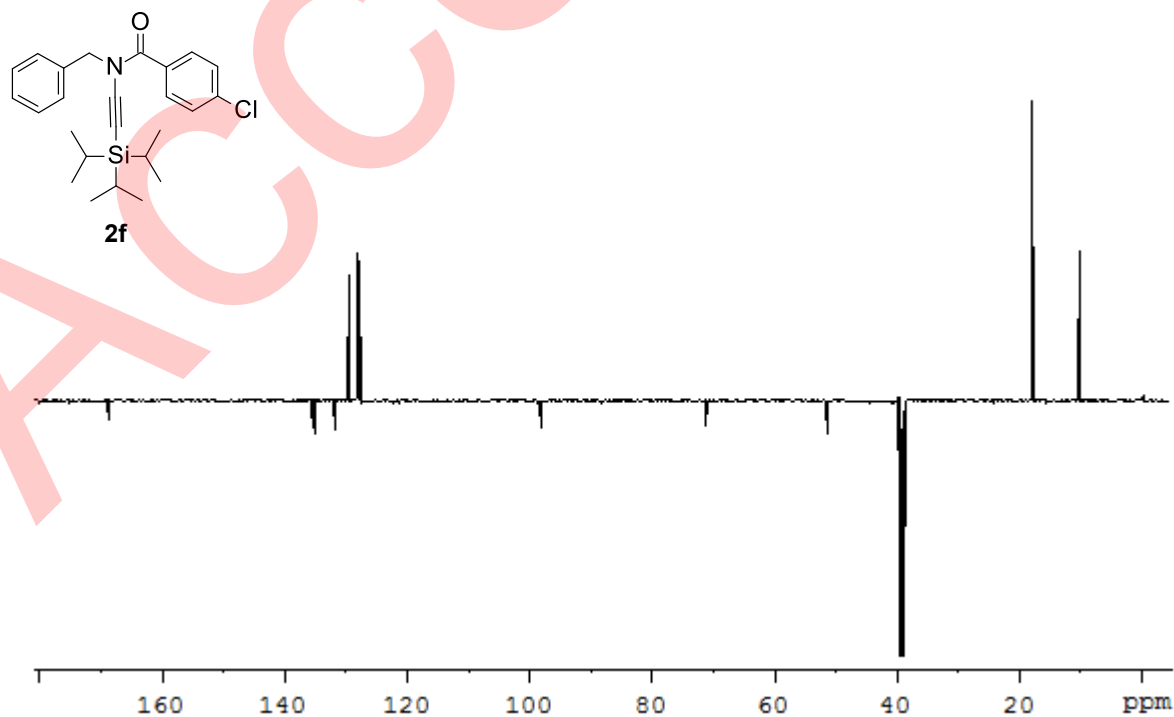
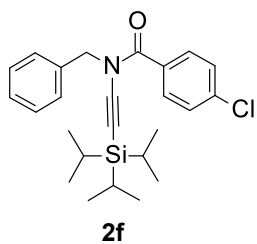
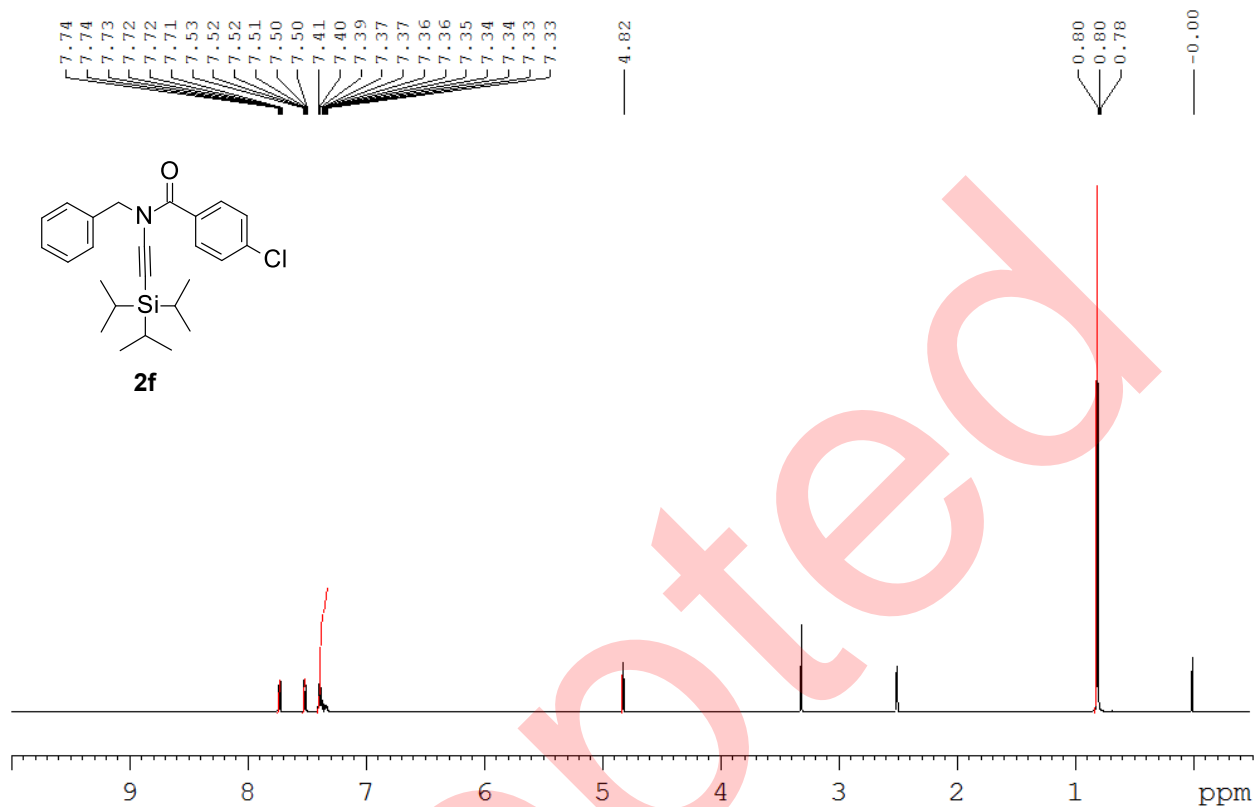
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12	9	1.250270	3.077647	-1.044933	6	-4.195018	0.070954	1.401208
13	9	0.773121	3.884024	0.898556	6	-3.200496	0.900195	0.995332
14					6	-2.416736	0.550289	-0.218665
15	B_{Zbz}				1	-3.544952	-2.730274	-0.462237
16	6	1.419090	-1.624781	0.745710	1	-5.232566	-1.816019	1.149340
17	6	1.911294	-0.985704	-0.381705	1	-4.821930	0.364068	2.235899
18	6	3.285638	-0.947528	-0.589234	1	-3.037236	1.853702	1.482671
19	6	4.152568	-1.539385	0.313226	1	-2.869992	1.122966	-1.056313
20	6	3.654233	-2.177079	1.440728	6	0.945533	2.568228	0.062186
21	6	2.286091	-2.216088	1.653579	9	1.883751	1.794276	0.623309
22	1	0.351527	-1.664482	0.926900	9	1.362934	2.805199	-1.203247
23	1	3.680919	-0.439823	-1.463544	9	0.982813	3.749120	0.696730
24	1	5.221692	-1.497365	0.139562				
25	1	4.330874	-2.637916	2.150800	TS_{Zb} Frequencies --	-412.0166		
26	1	1.886448	-2.710454	2.531565				
27	6	1.010880	-0.356869	-1.415855				
28	1	1.406471	0.606140	-1.733538				
29	1	0.977965	-1.008281	-2.293508				
30	6	-2.841231	0.901798	0.122722	B_{Zb}			
31	6	-2.881807	-0.354954	0.781322	6	2.364082	0.783511	0.032339
32	6	-3.533409	-1.419406	0.203390	6	2.848393	-0.390532	-0.749780
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38	1	-4.723005	-2.098594	-1.455973	1	4.240432	-1.978031	-0.951106
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54	6	3.806890	-1.592776	-0.360685	6	-3.358952	-1.671563	1.763728
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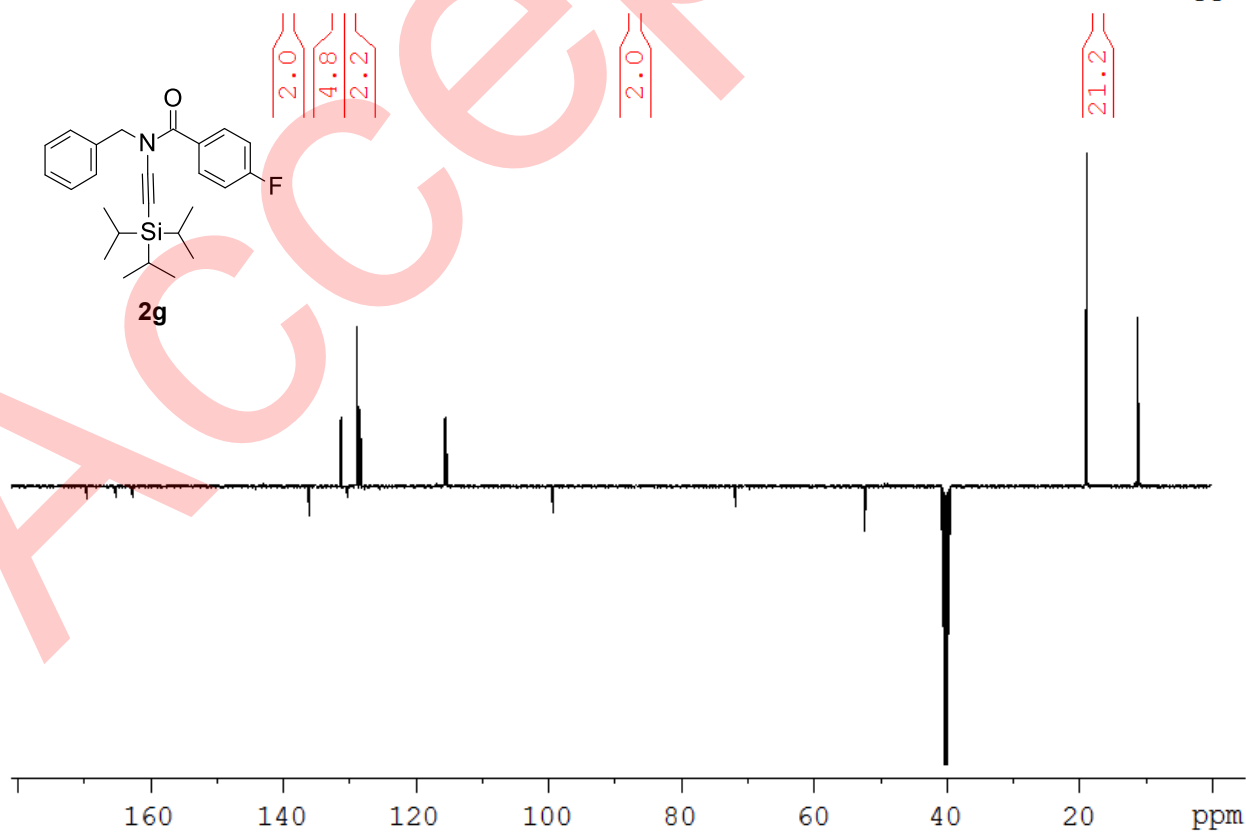
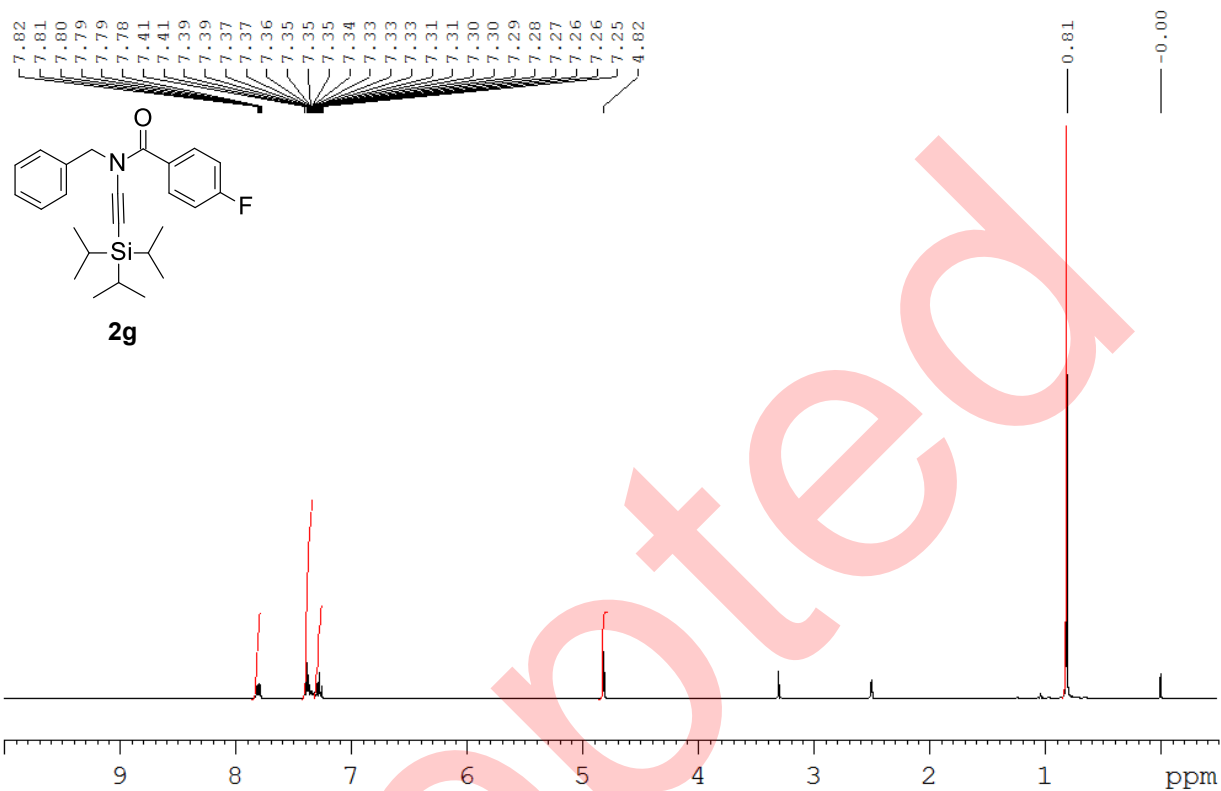
^1H , ^{13}C and ^{19}F NMR spectra

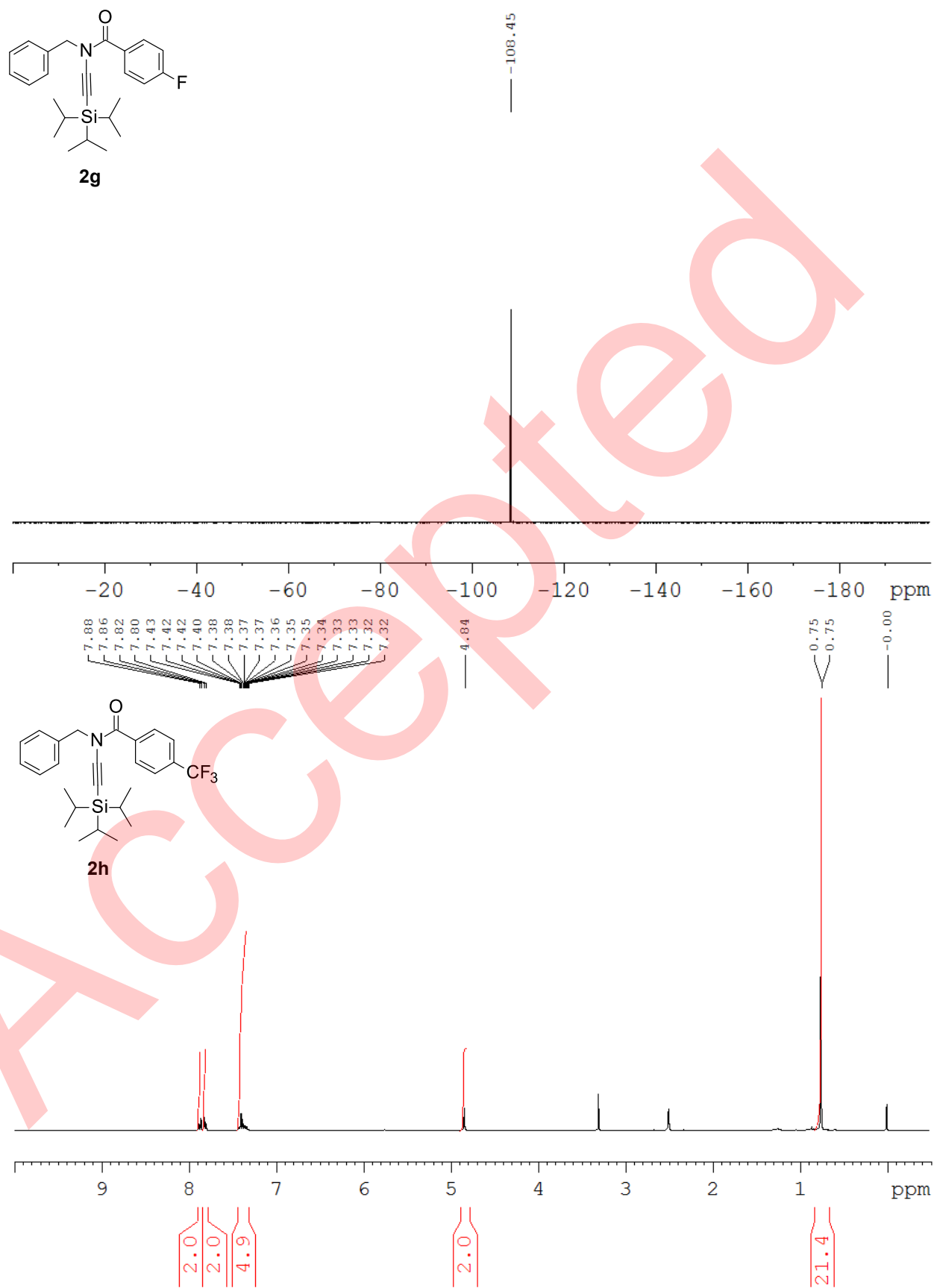


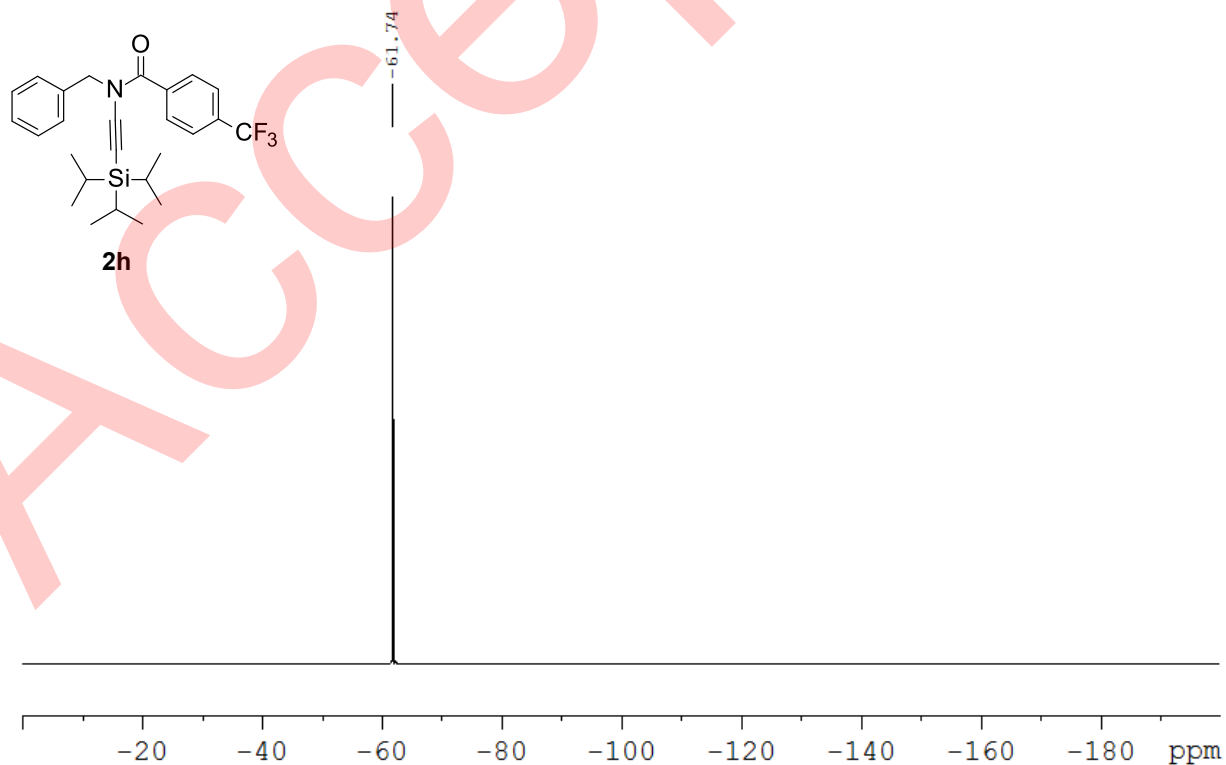
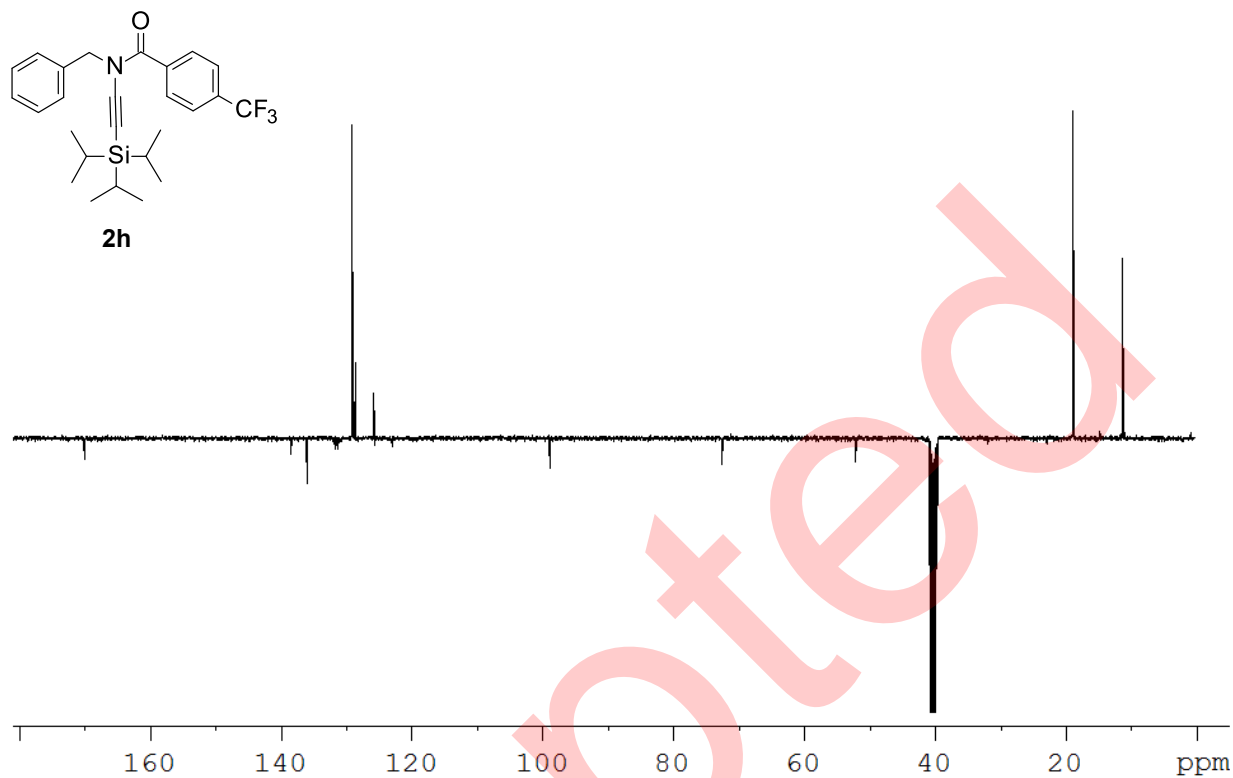


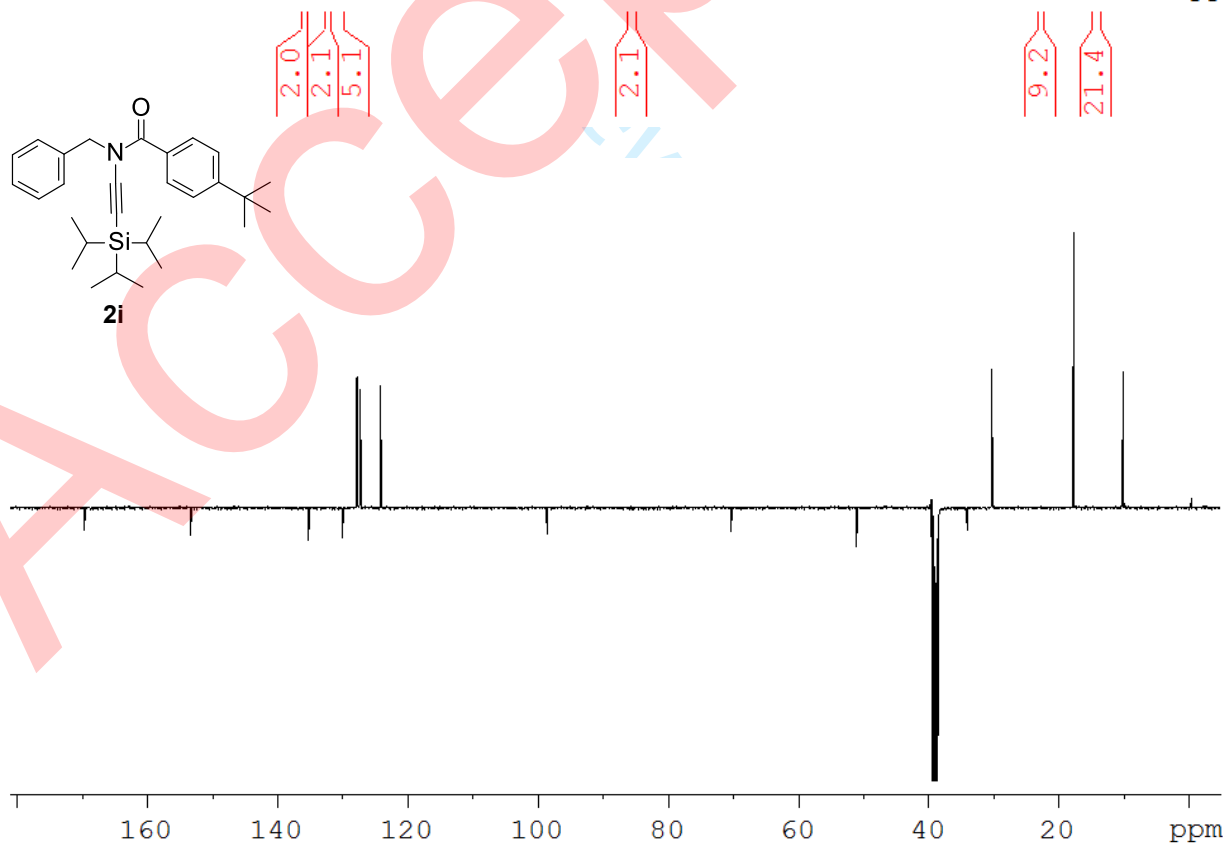
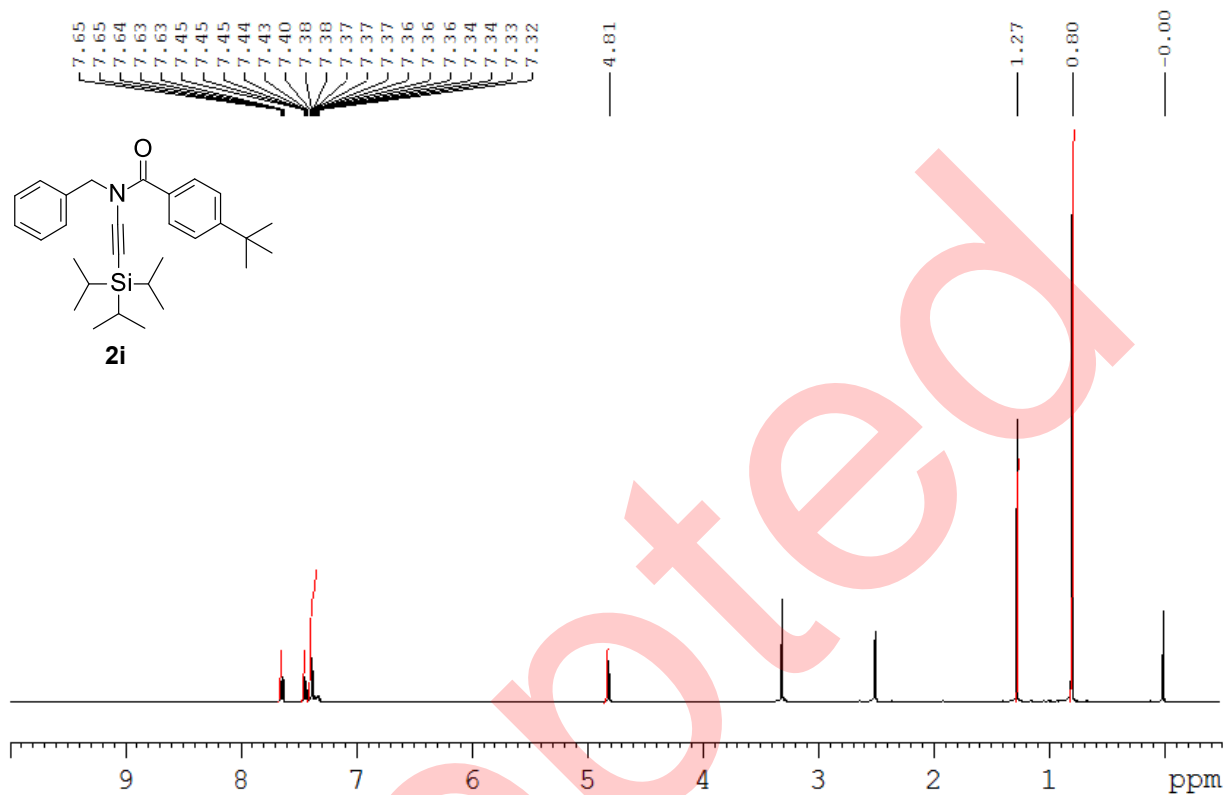


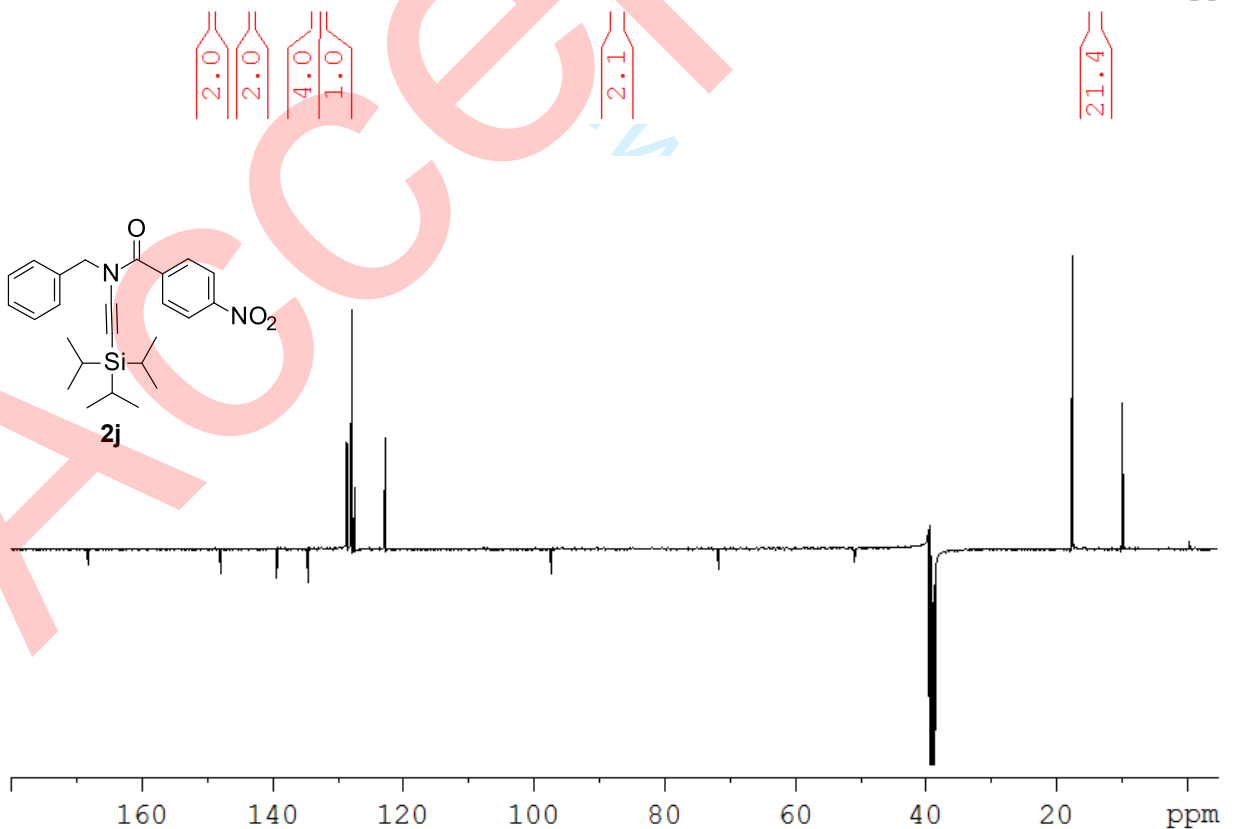
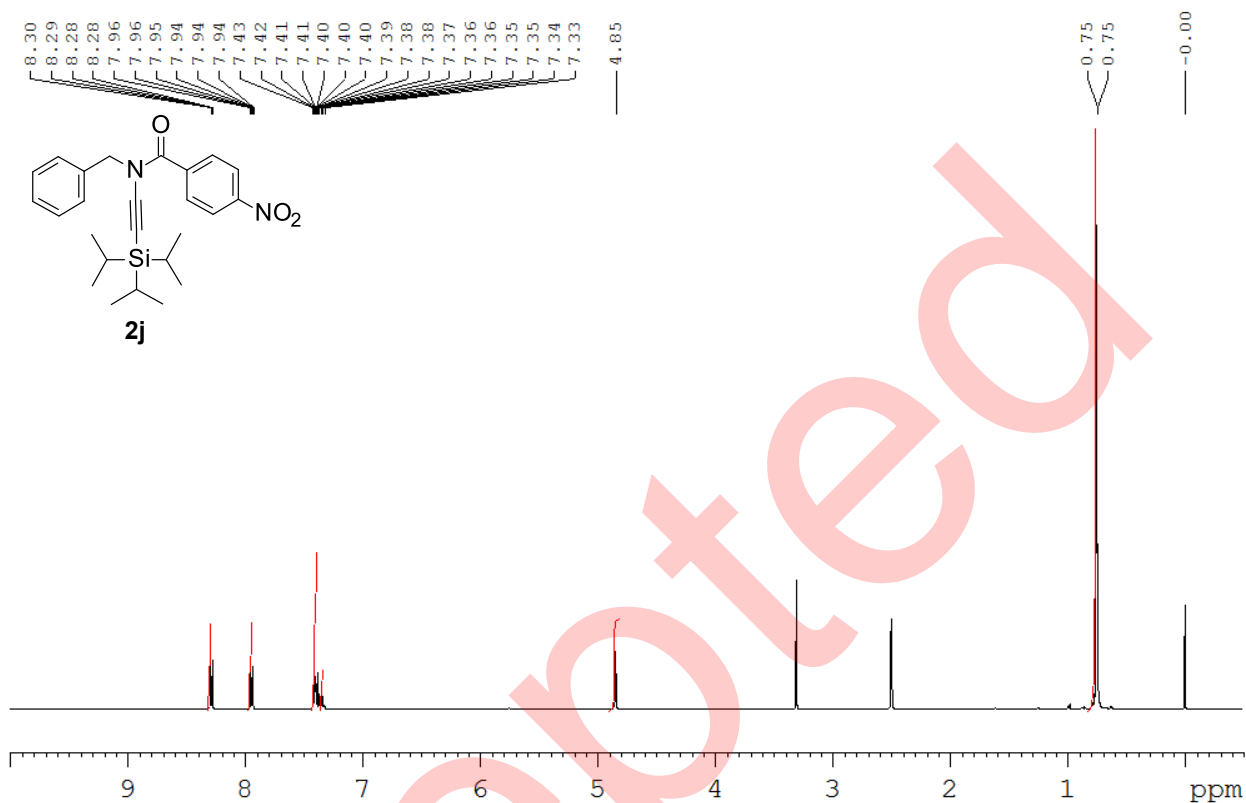


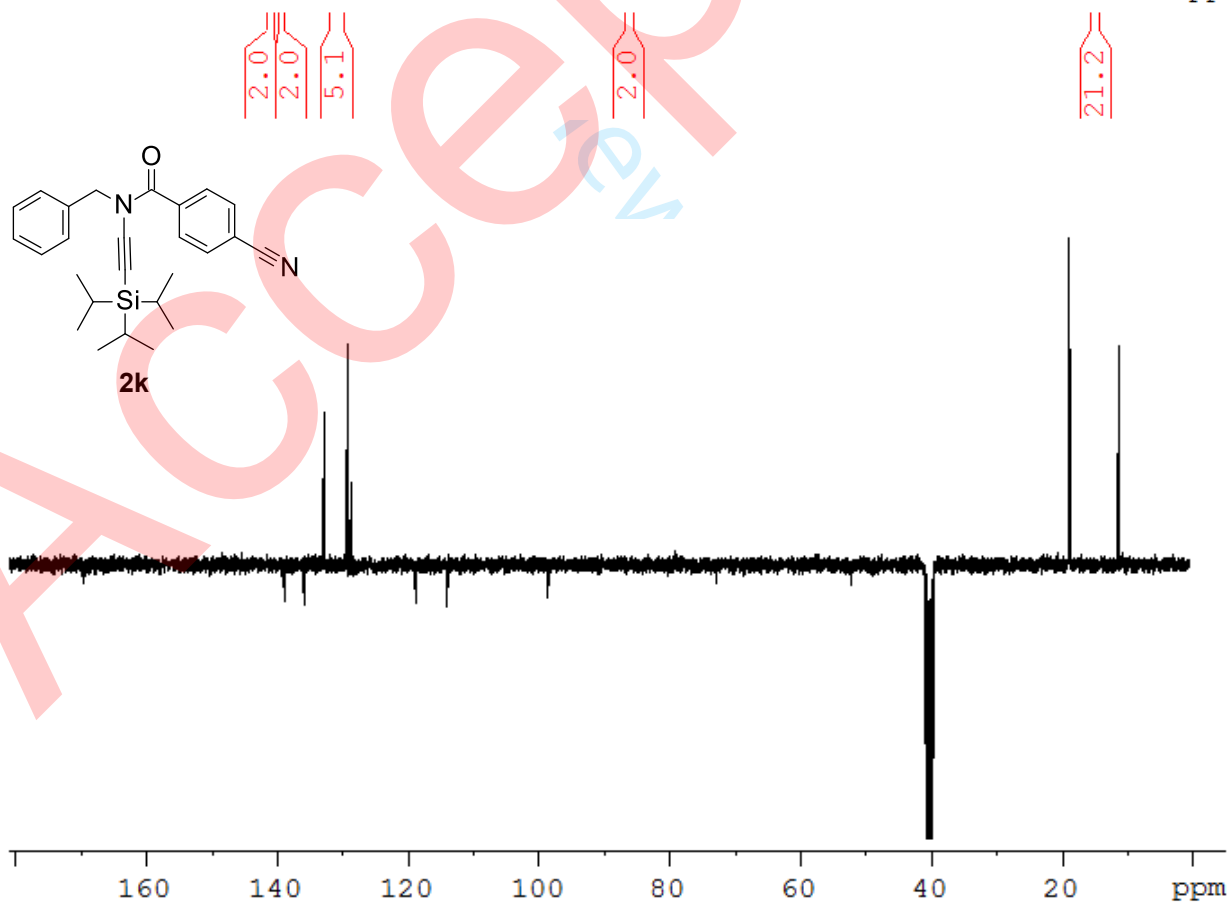
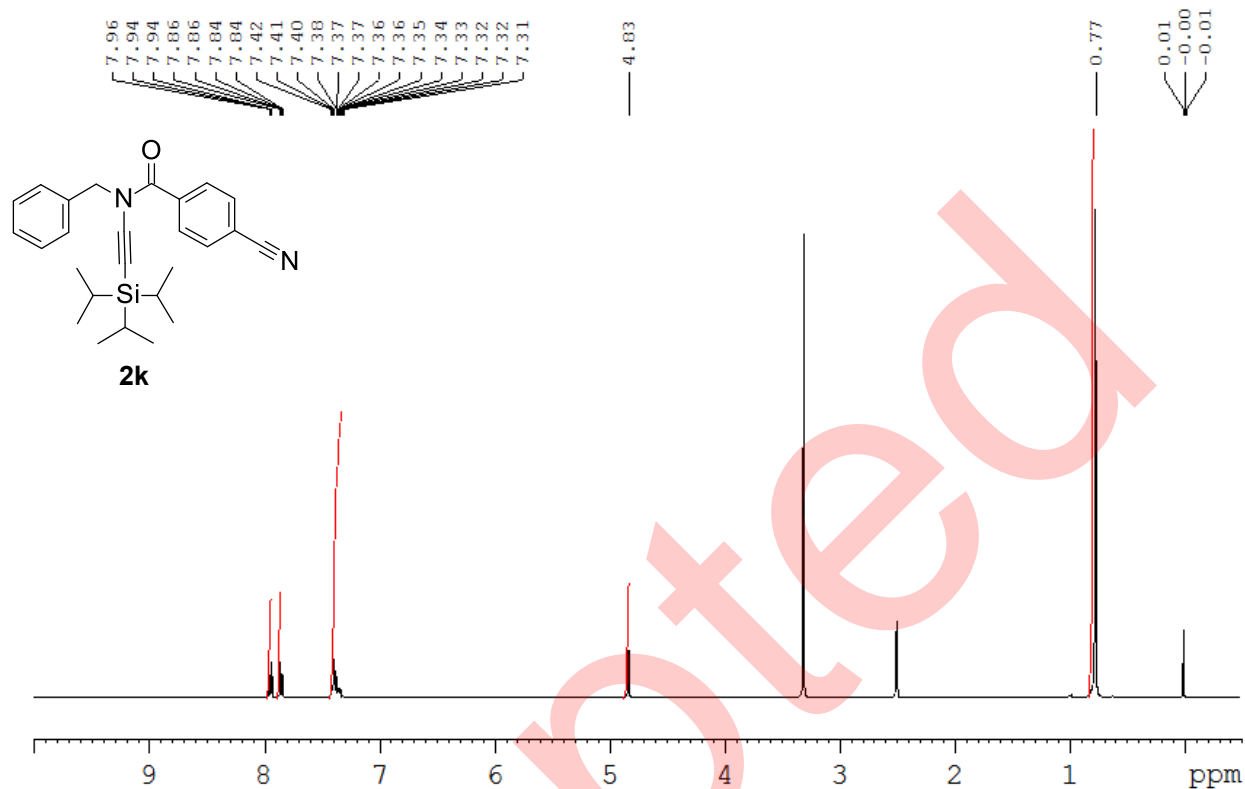


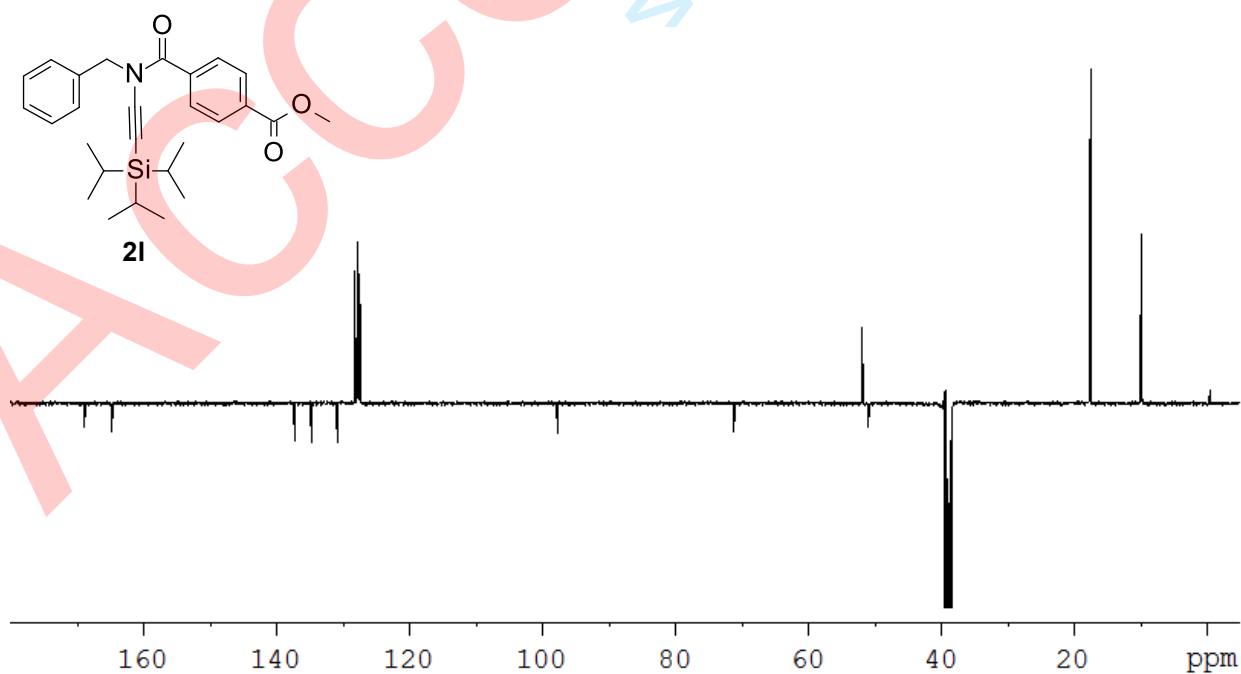
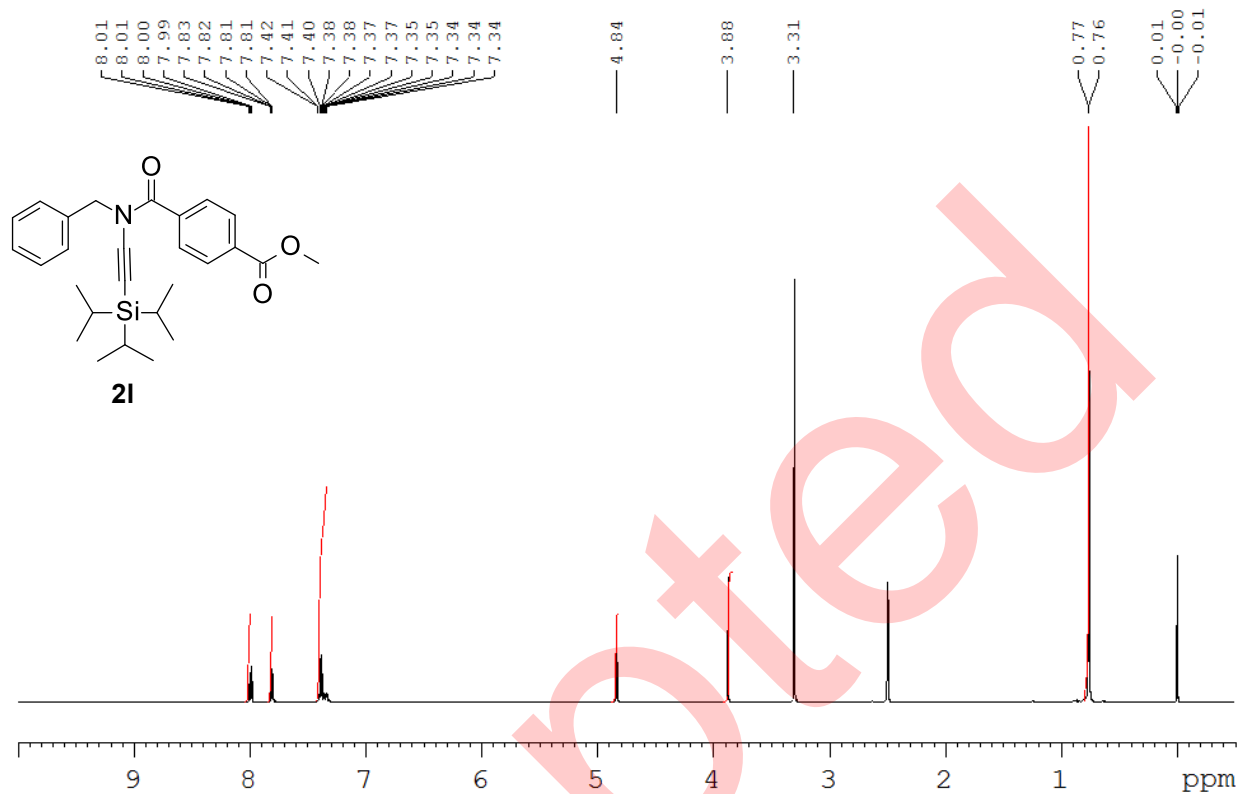


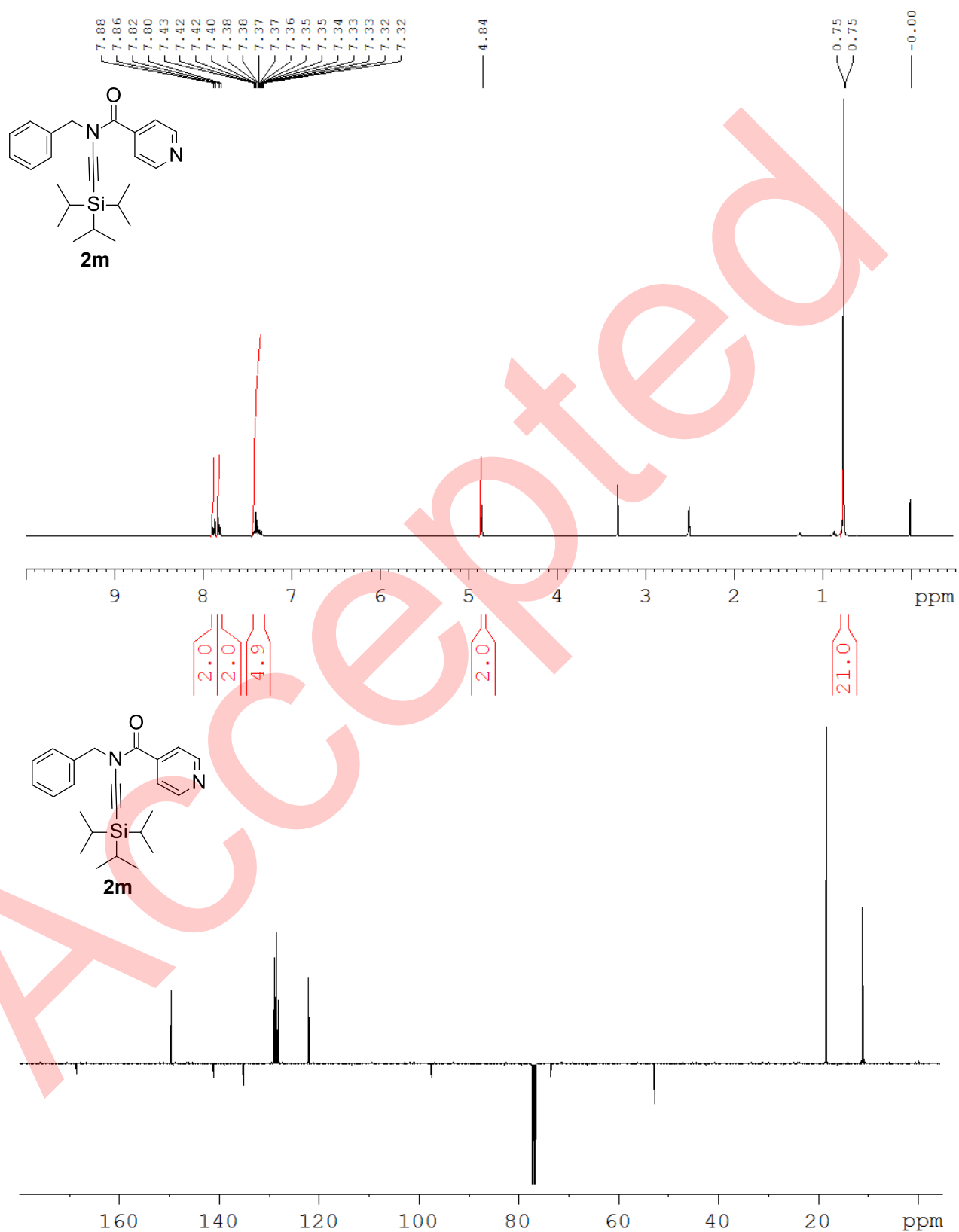


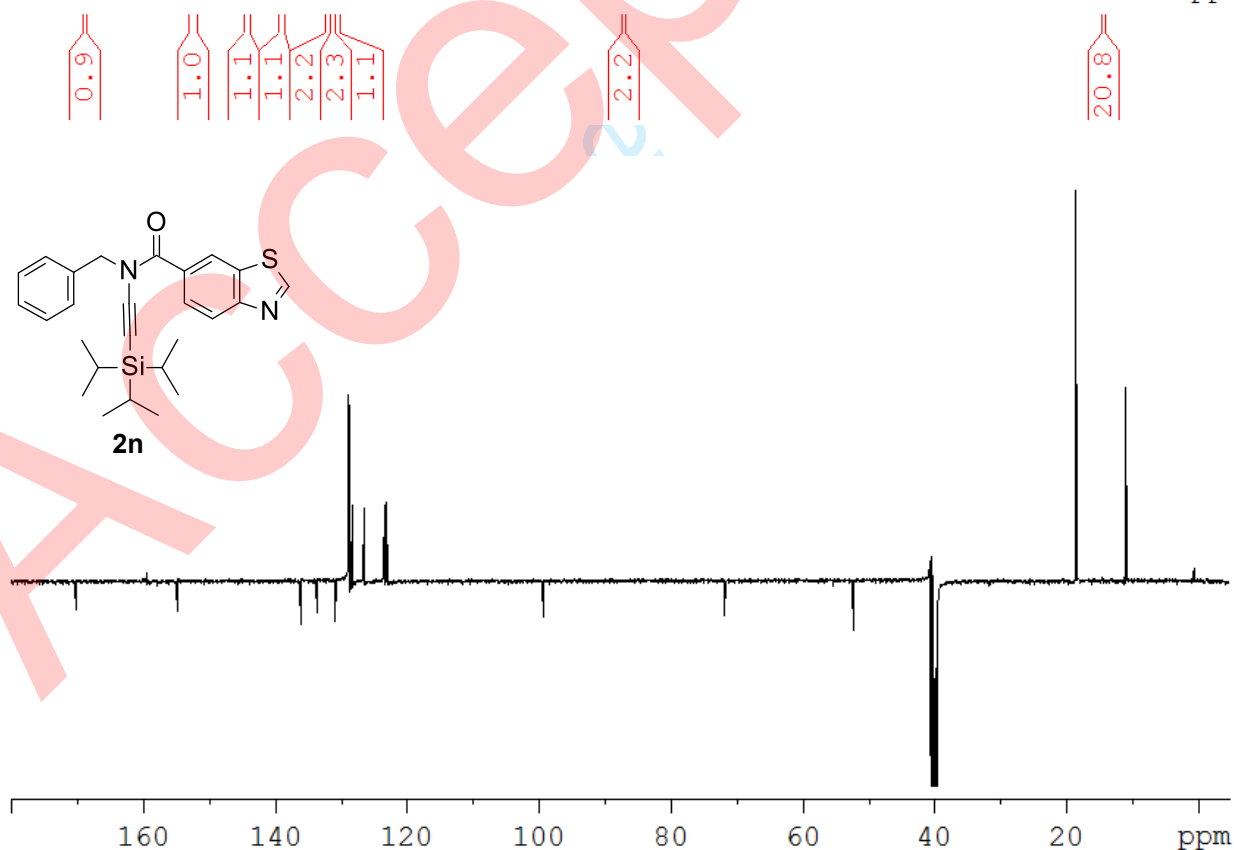
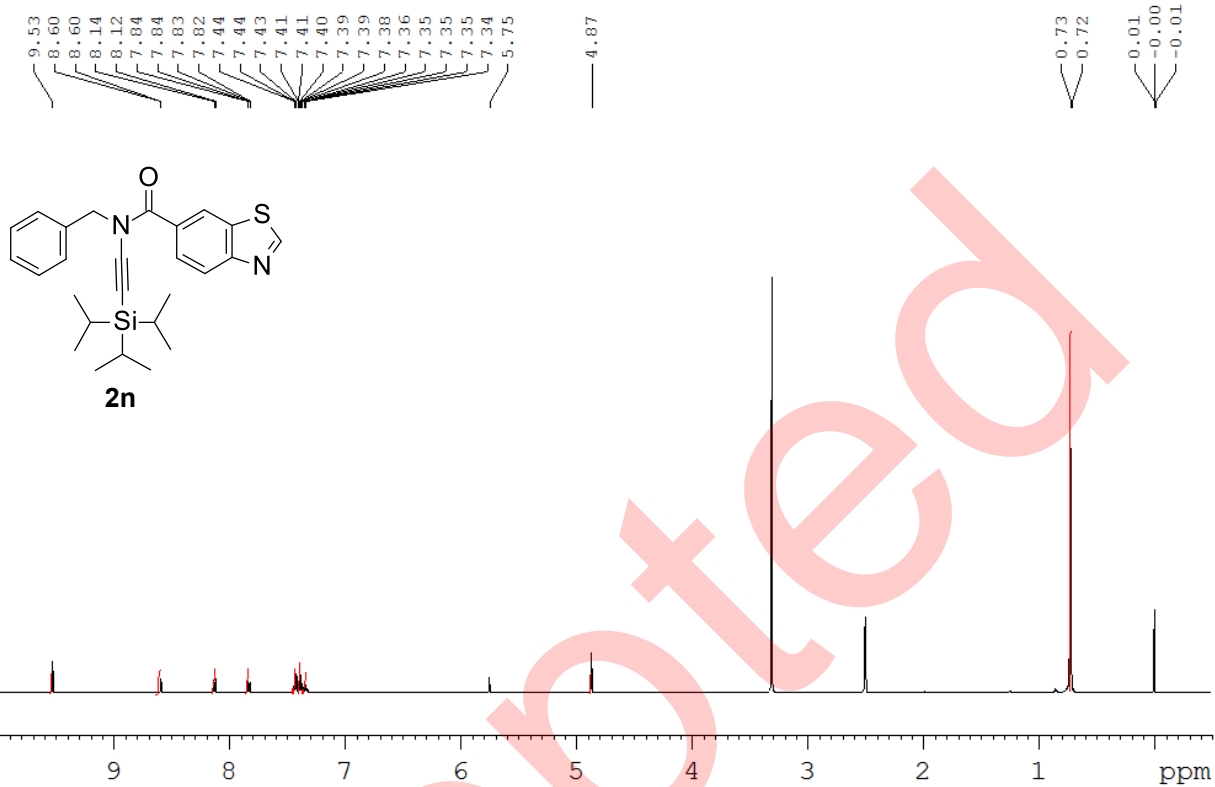


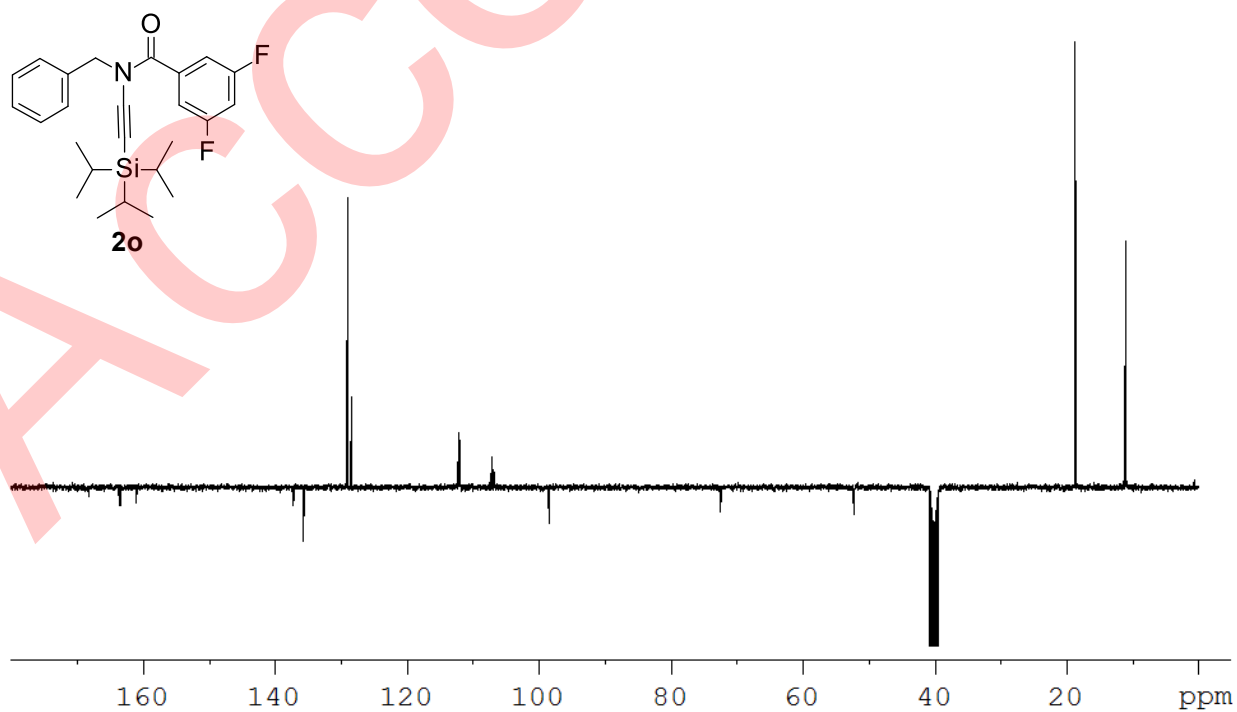
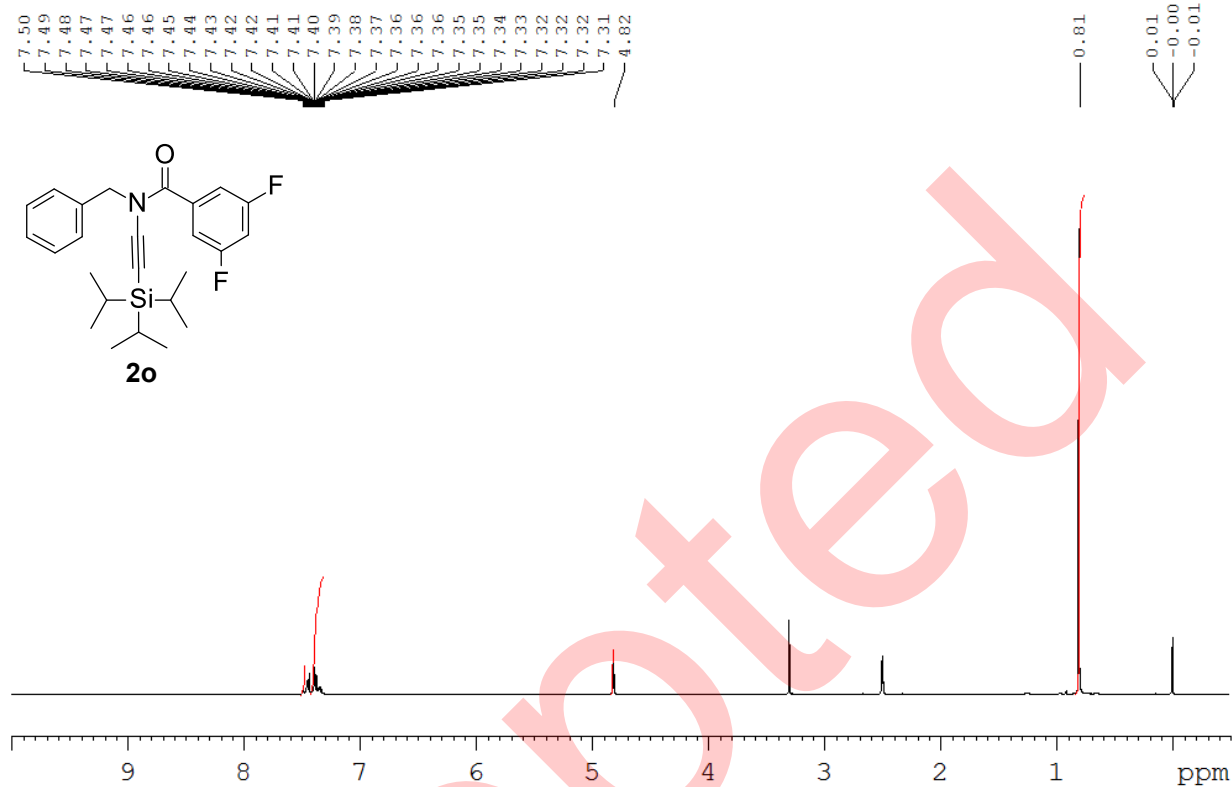


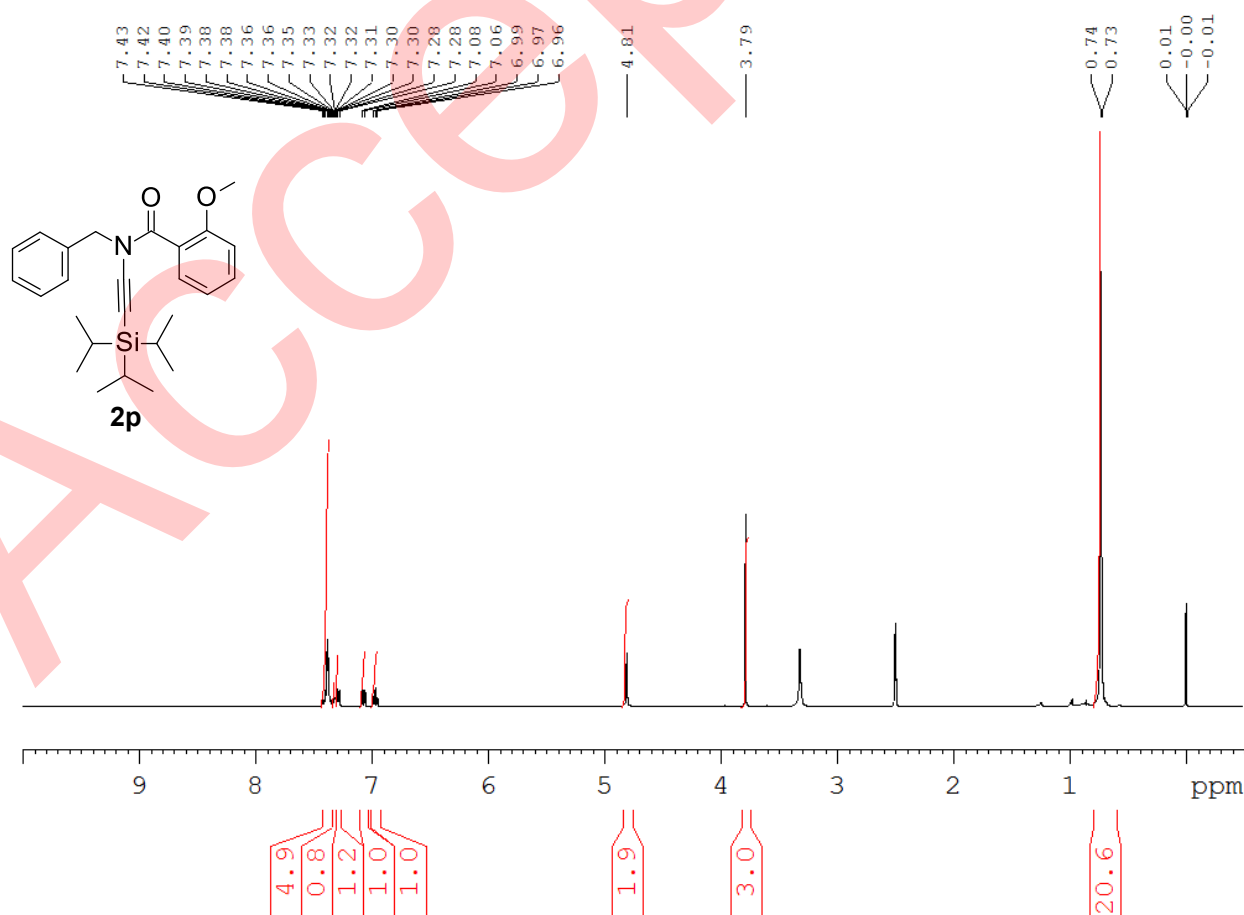
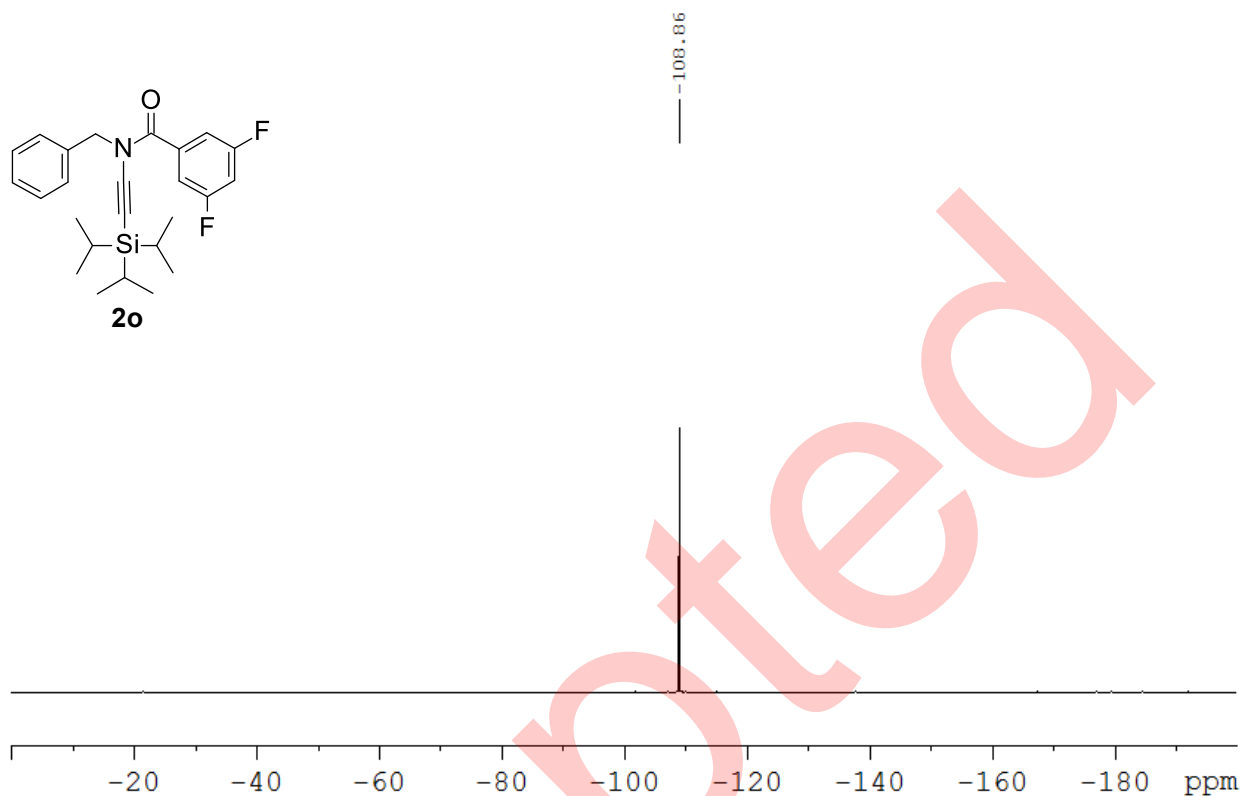


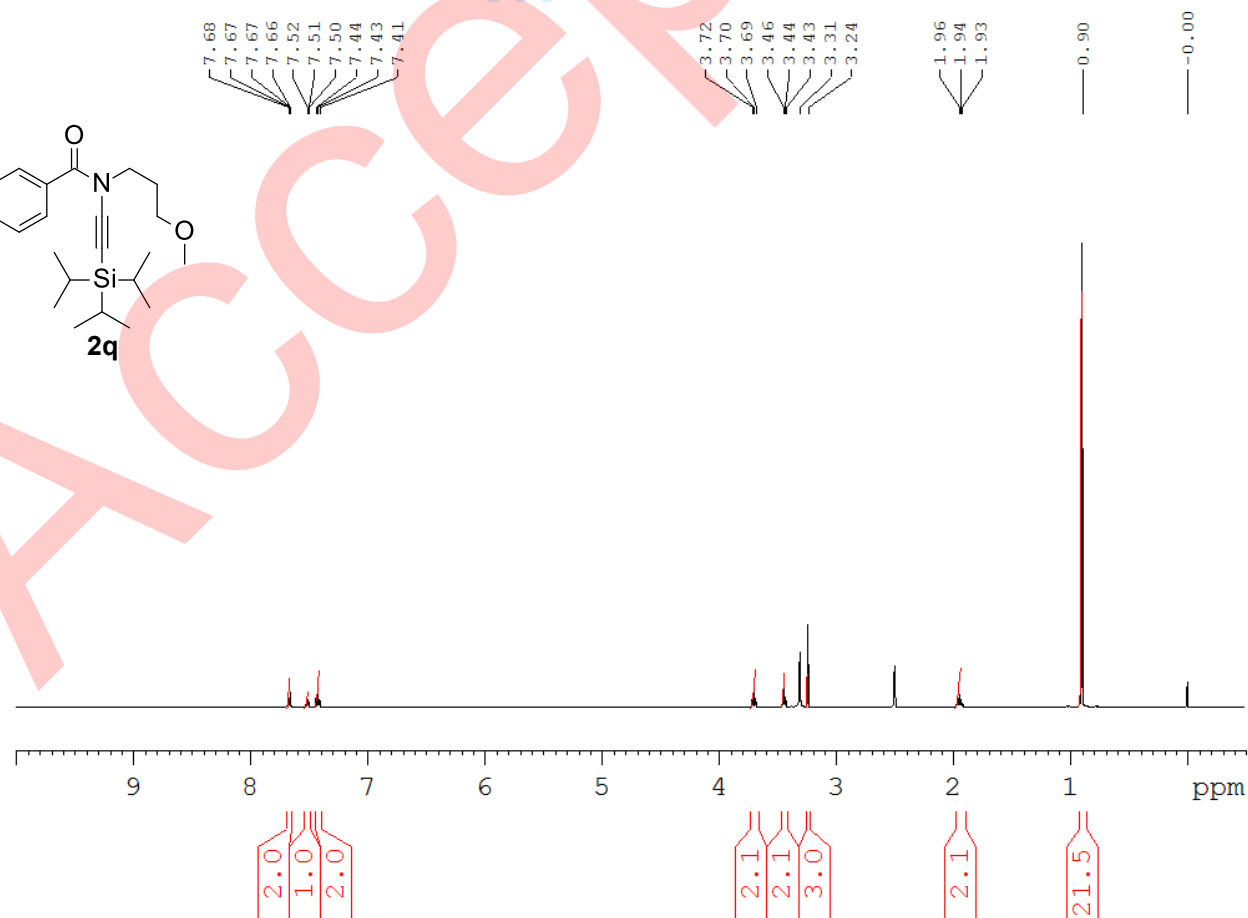
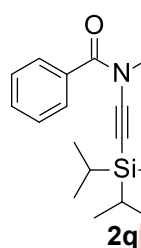
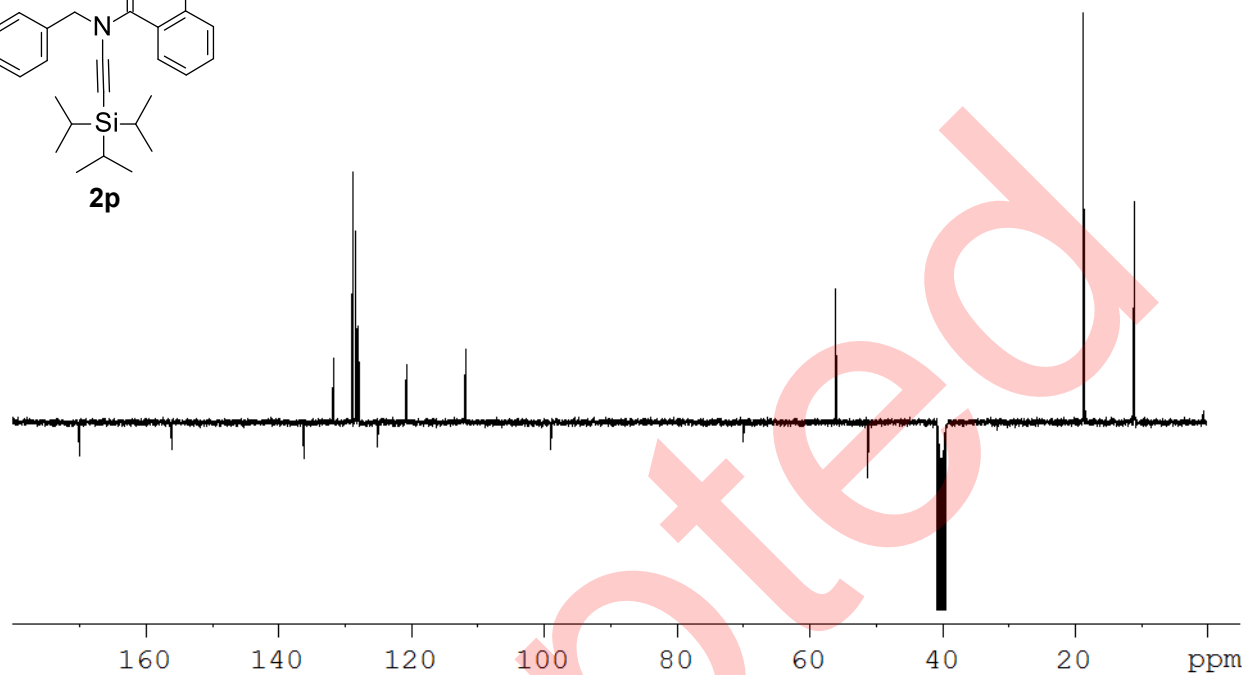
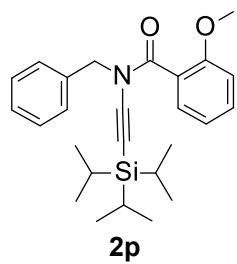


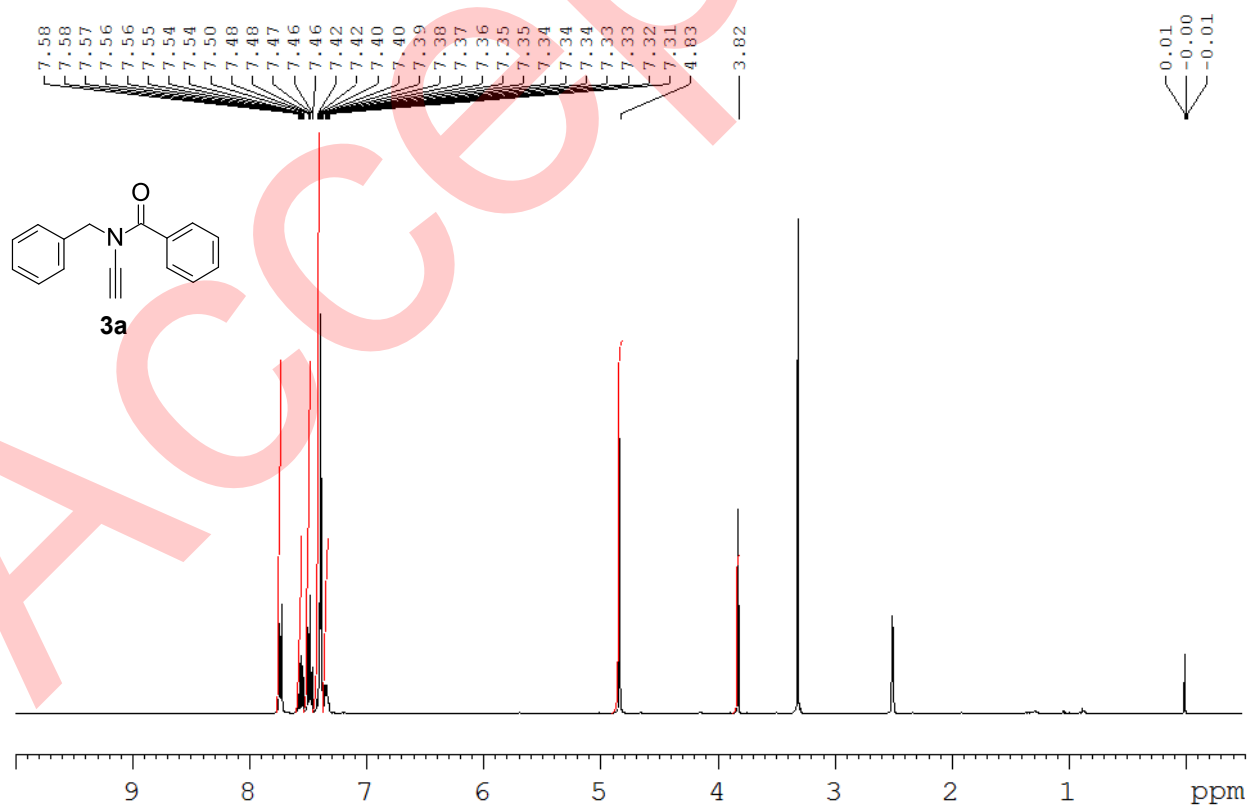
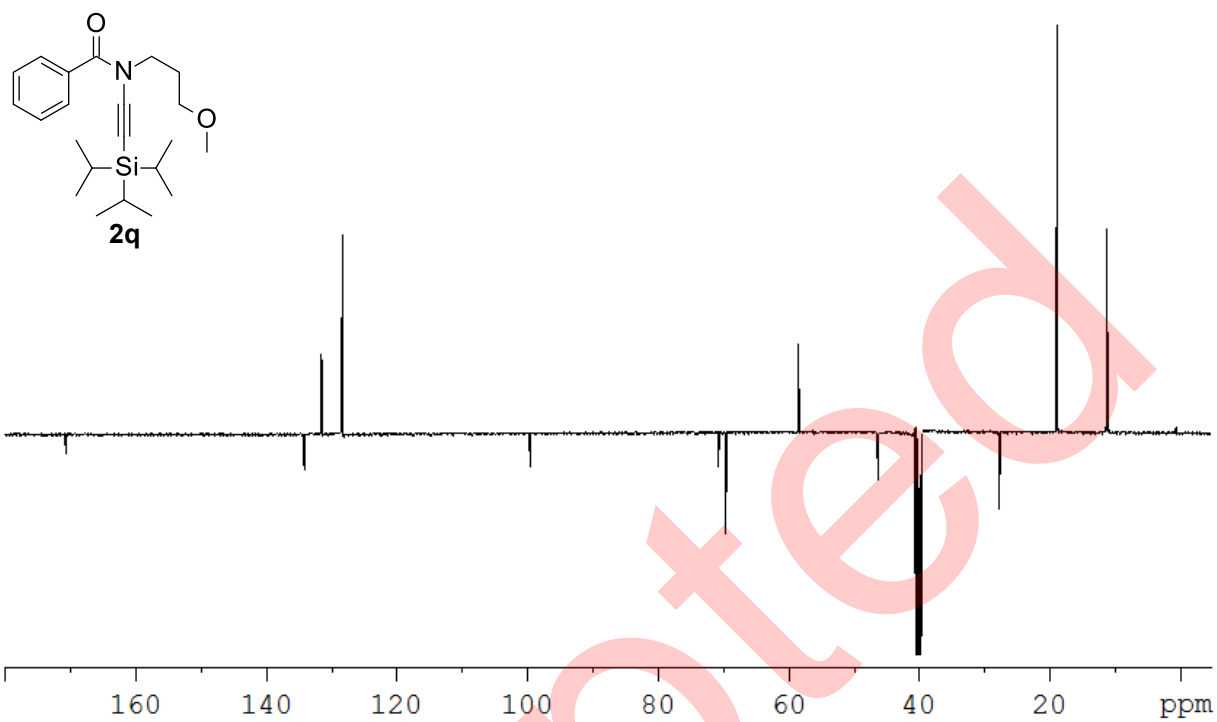


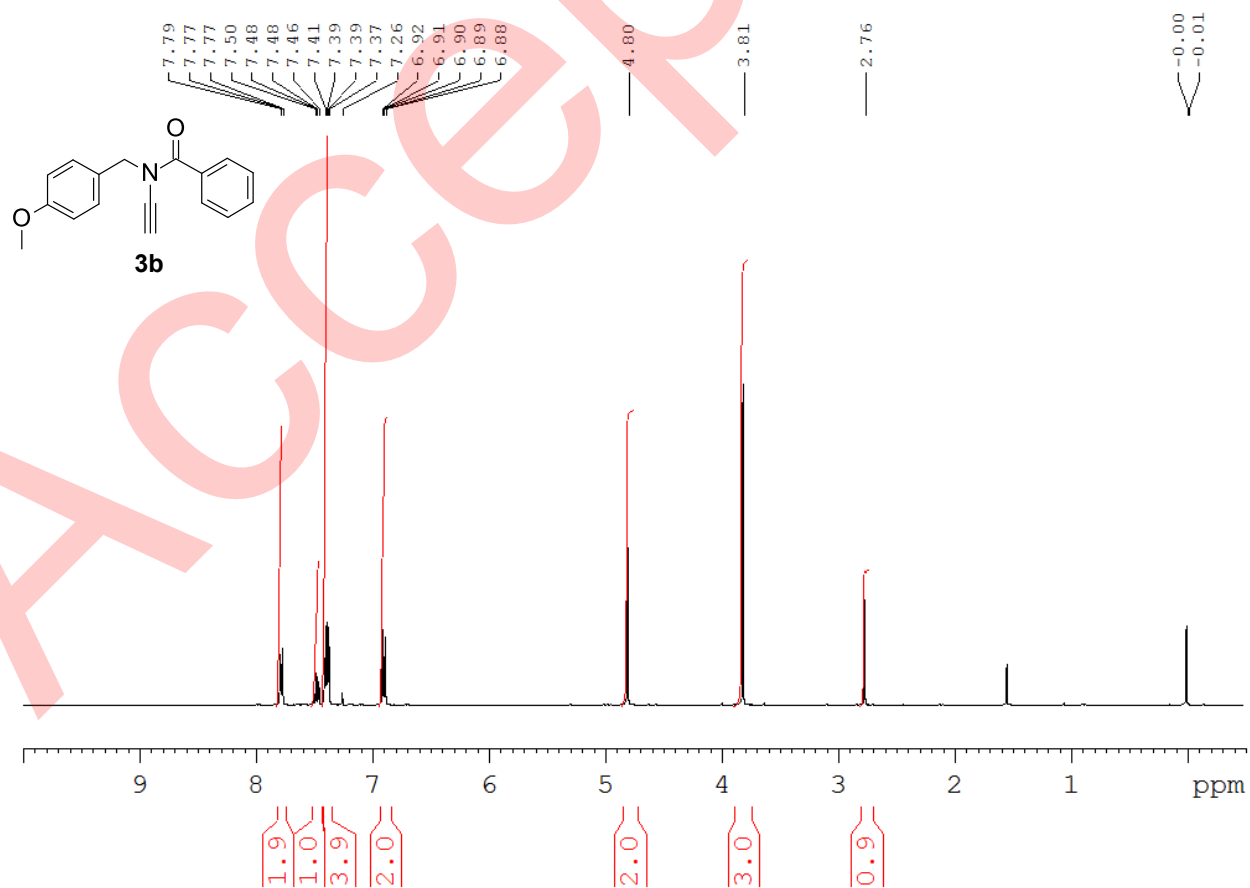
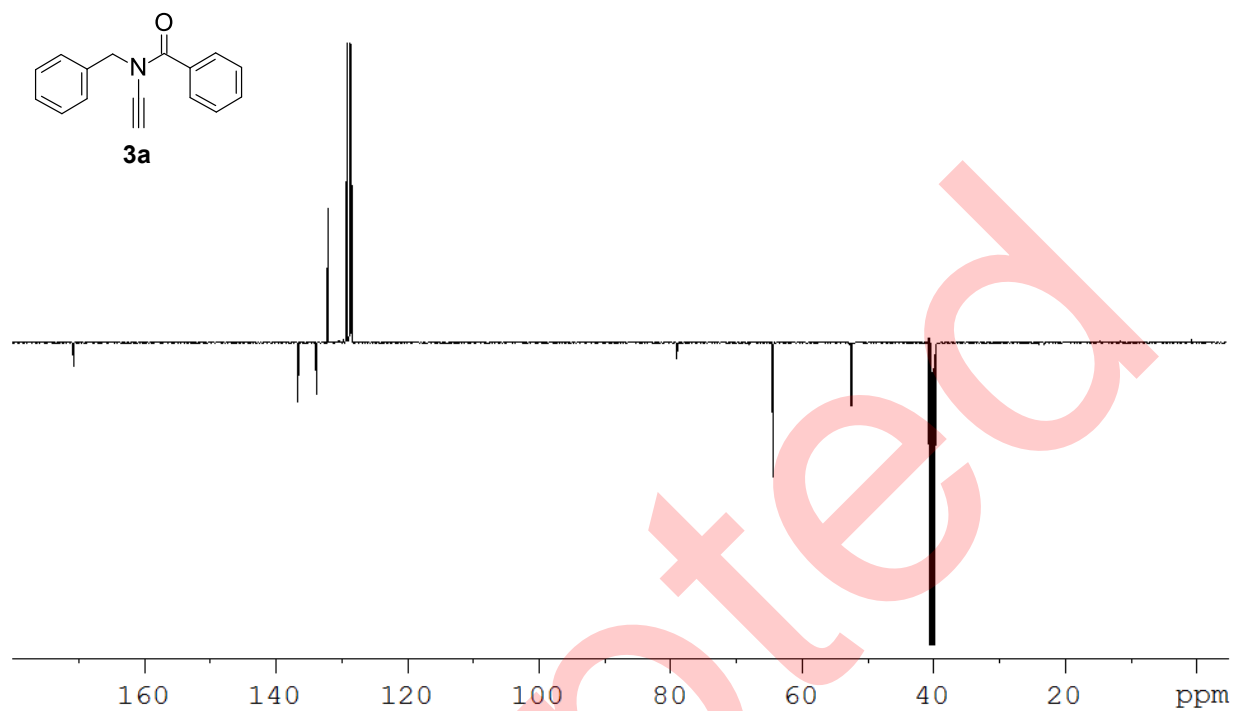


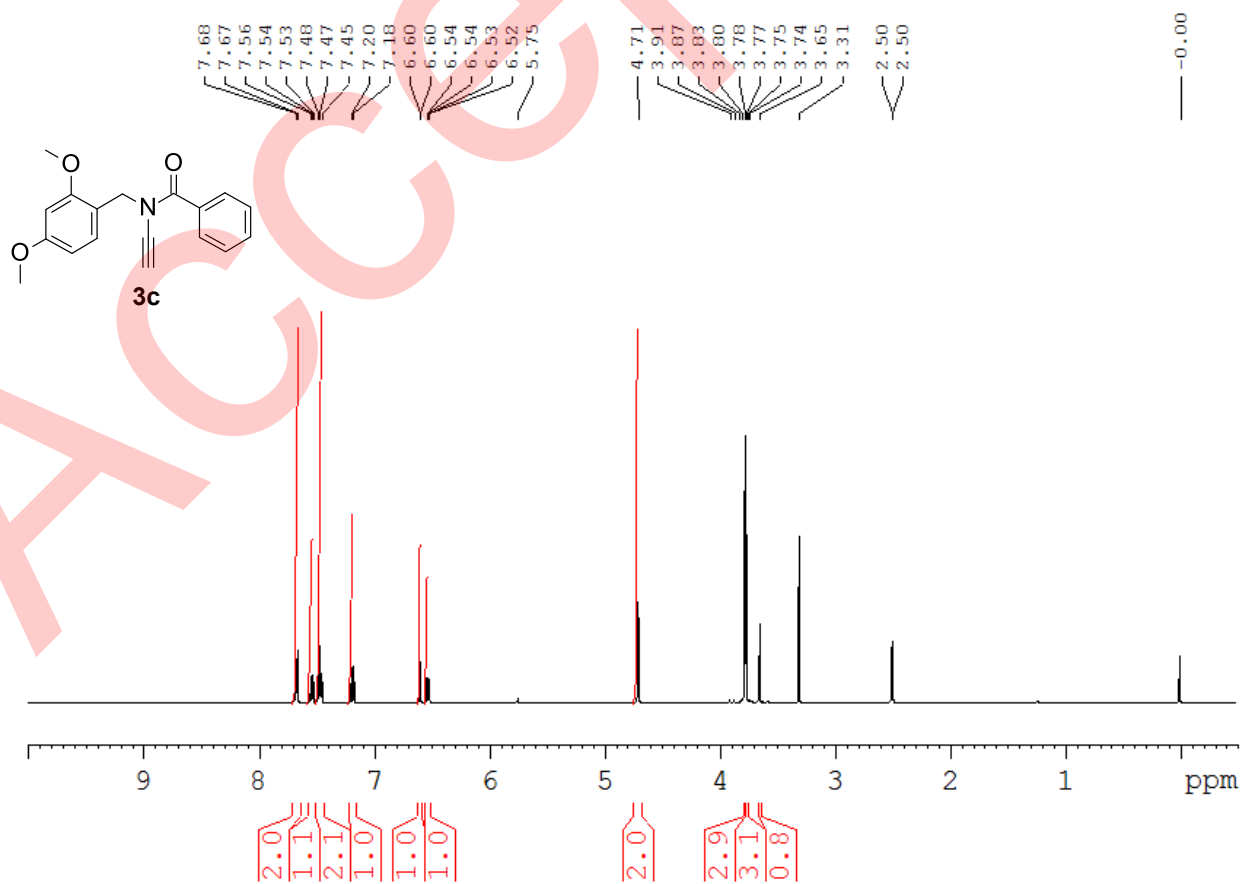
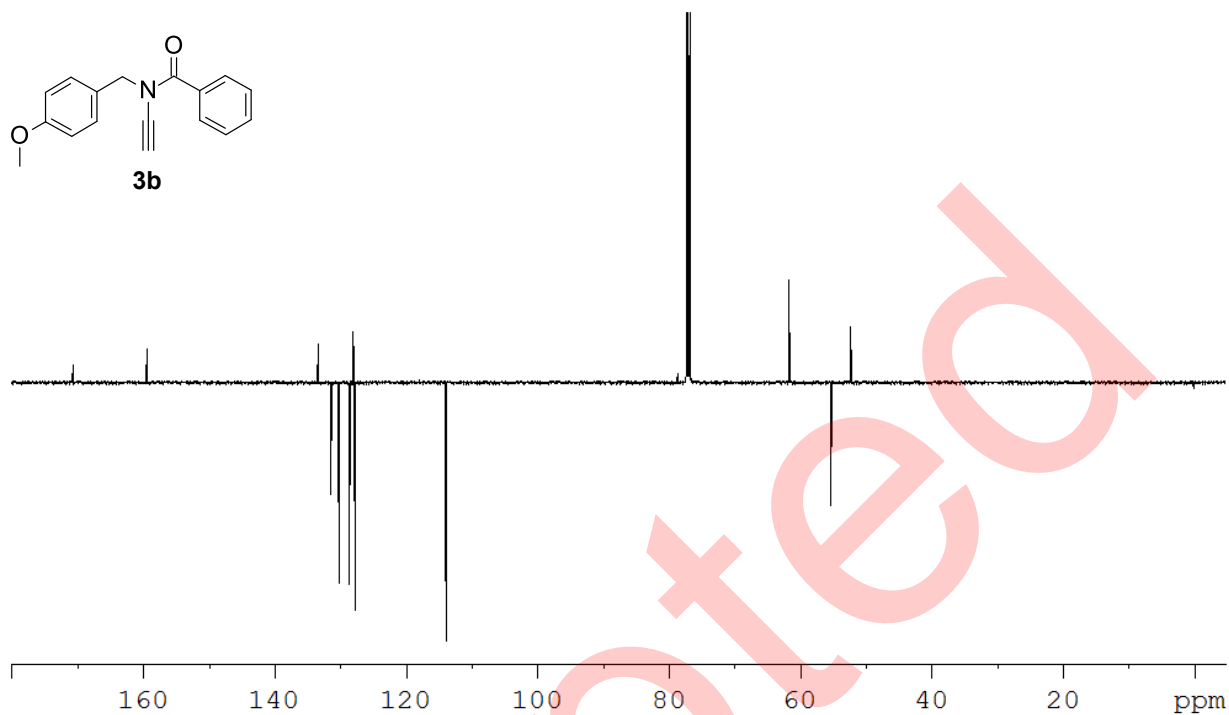


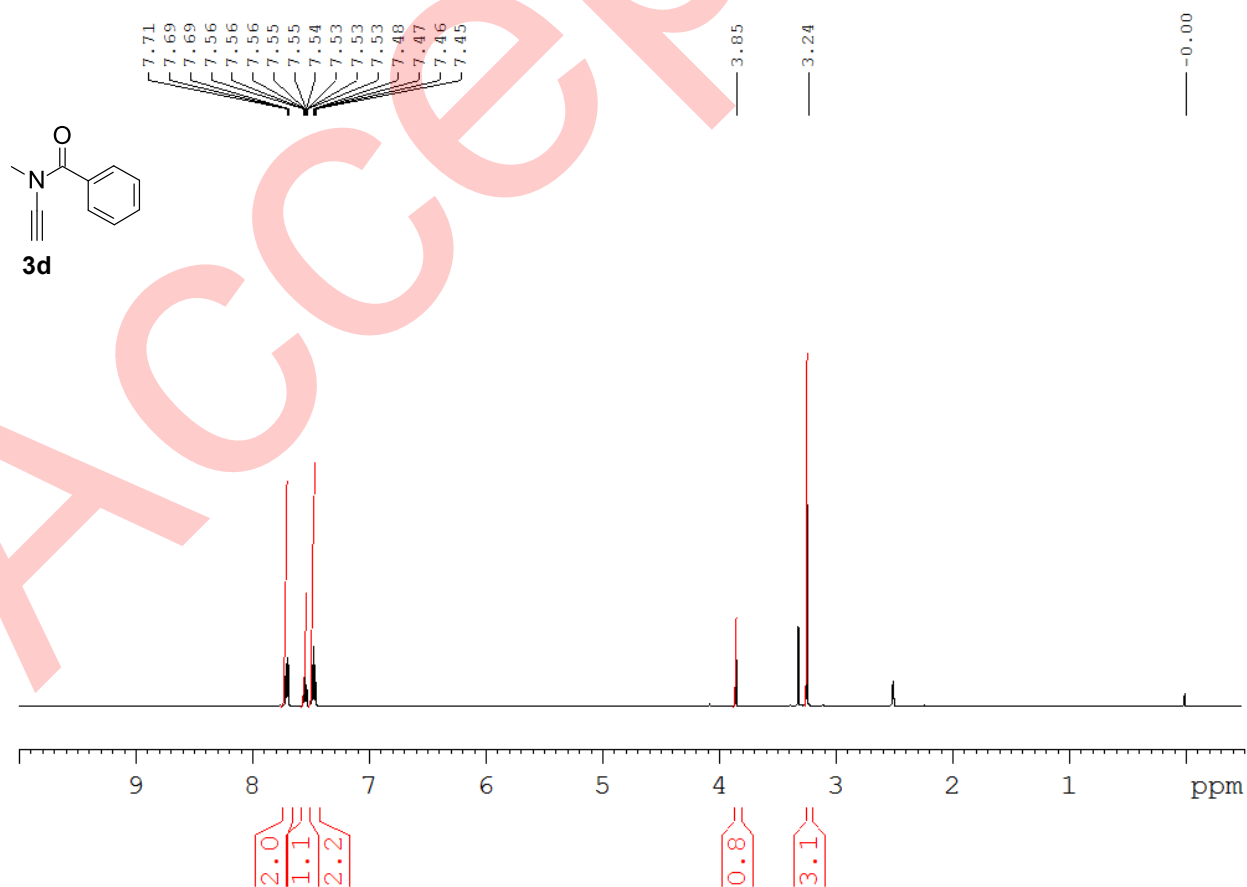
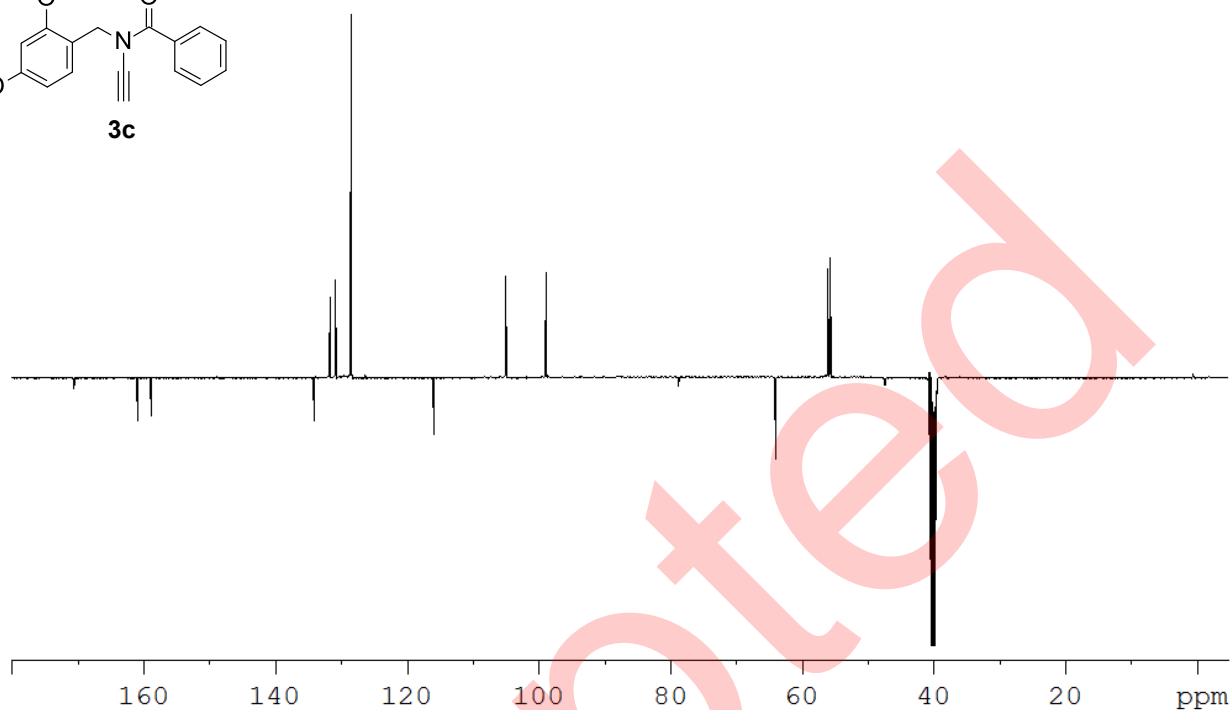
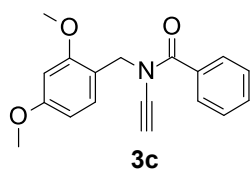


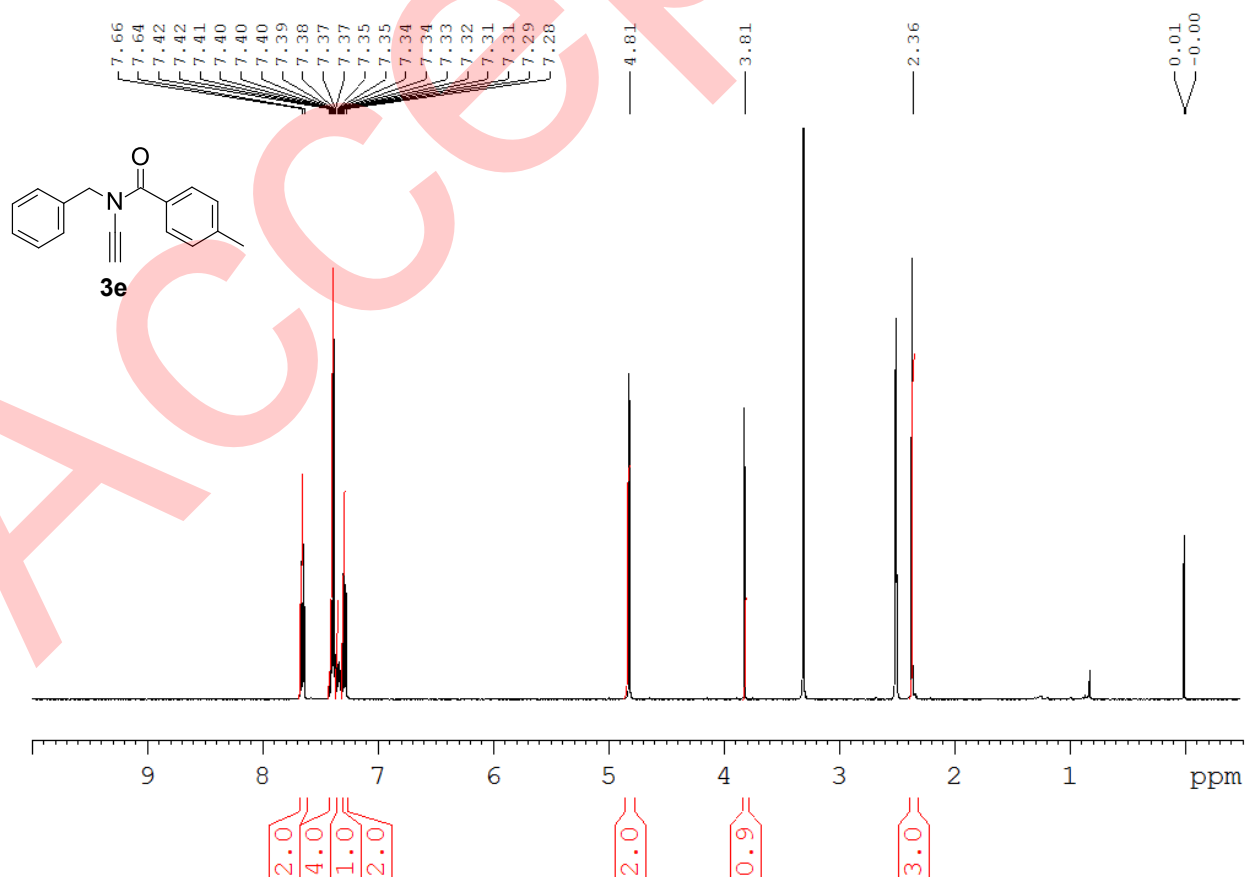
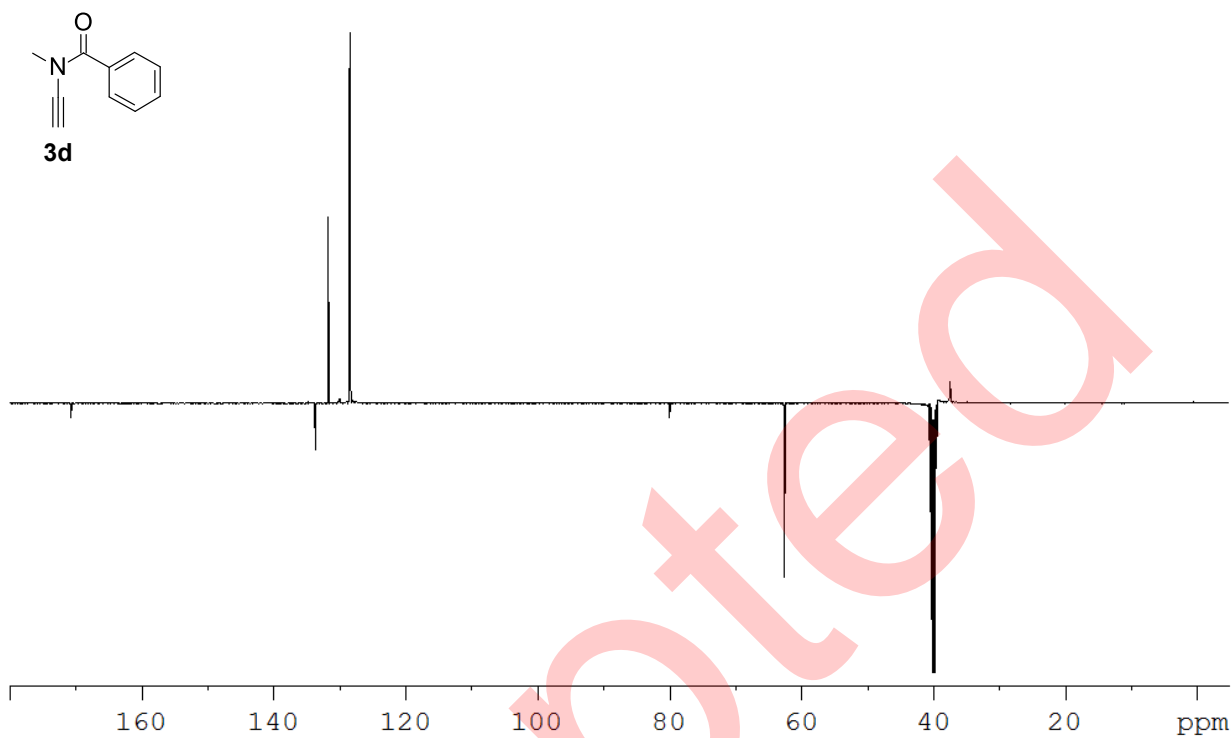


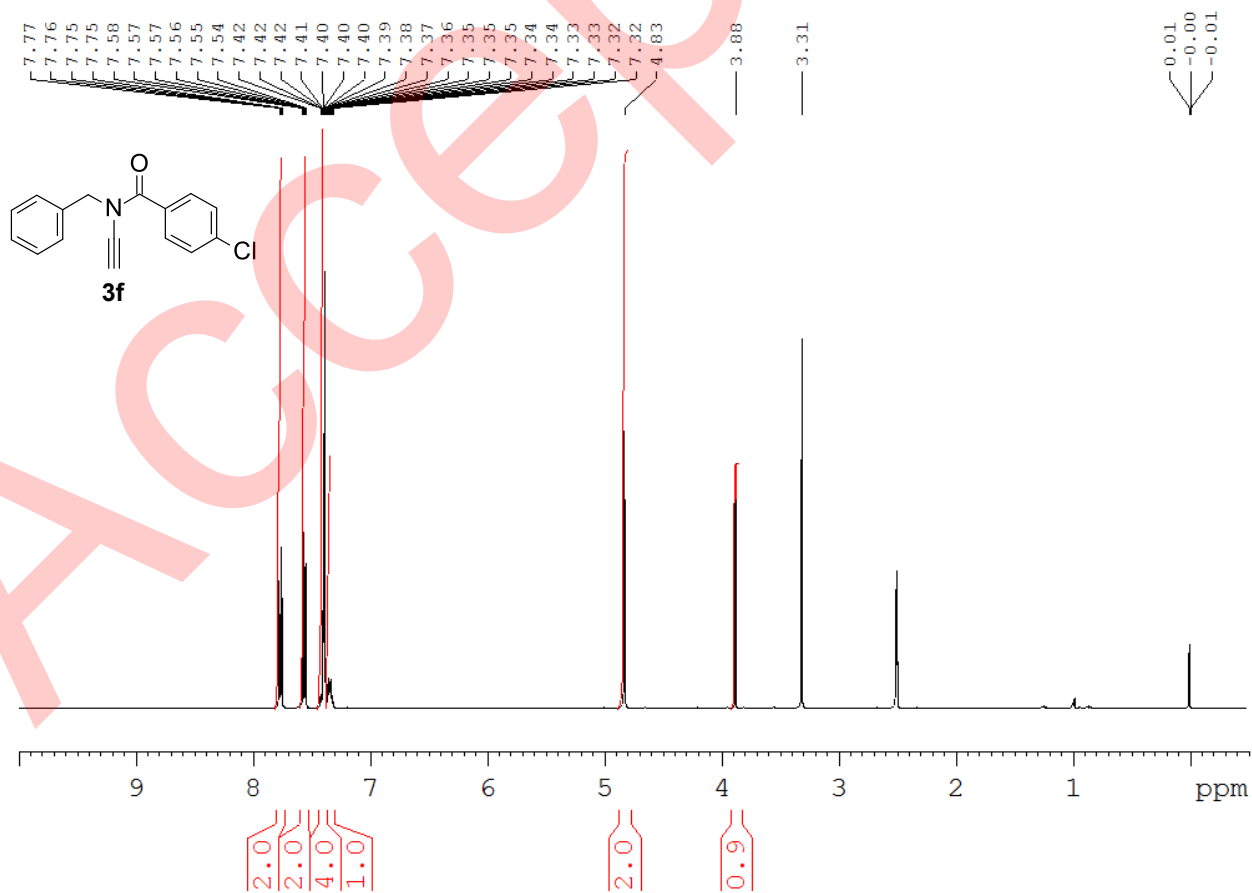
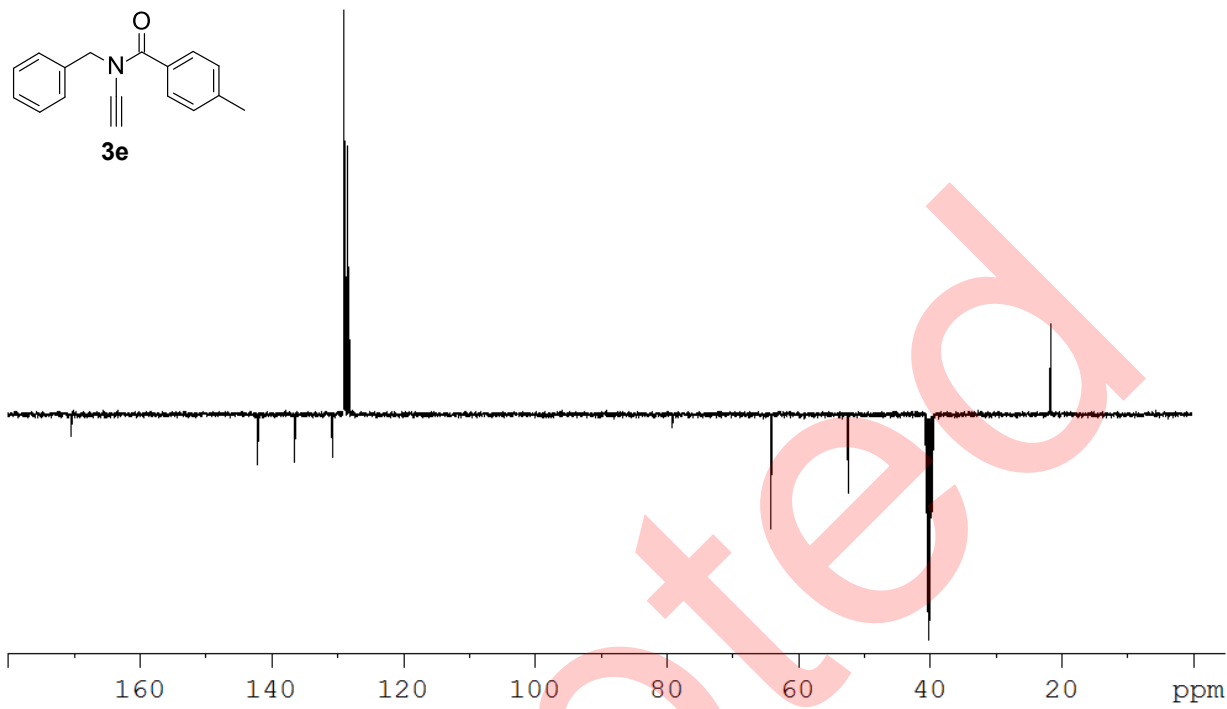


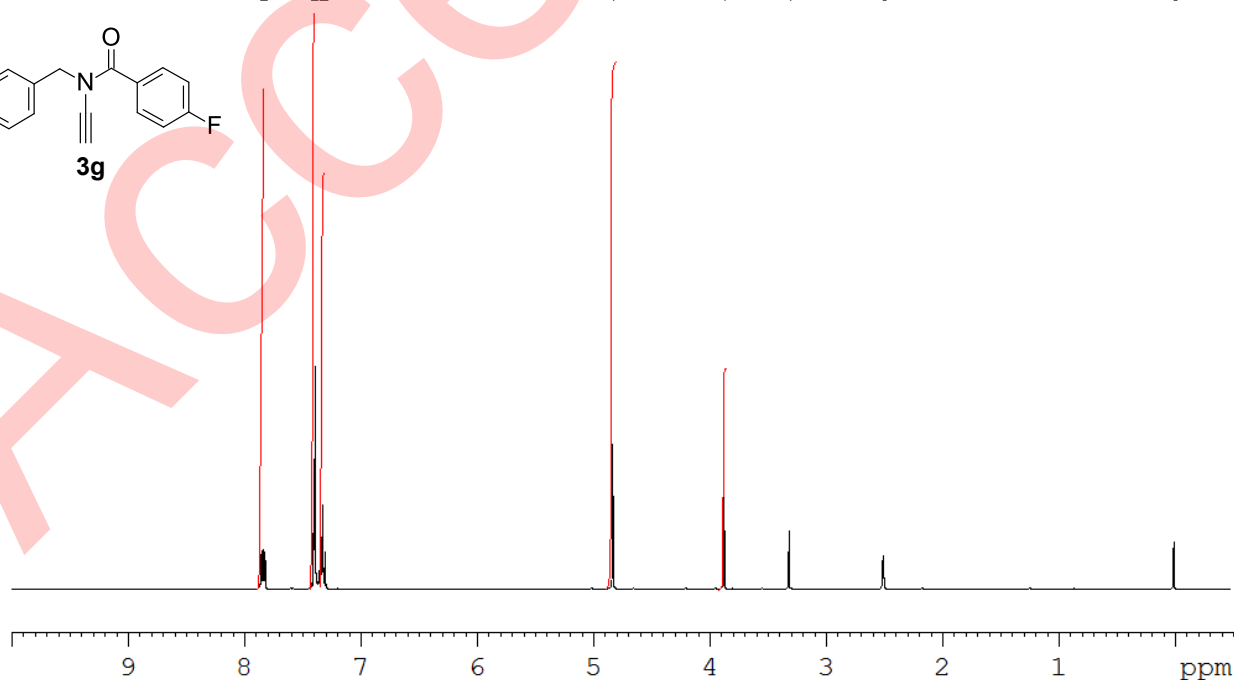
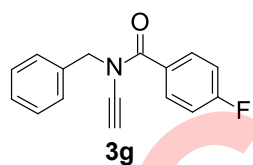
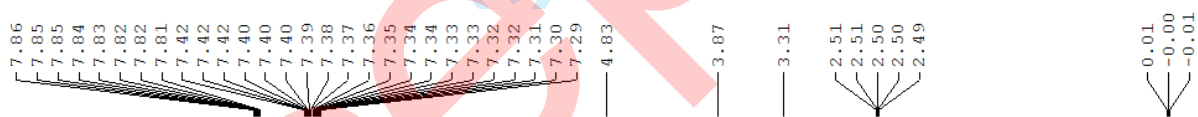
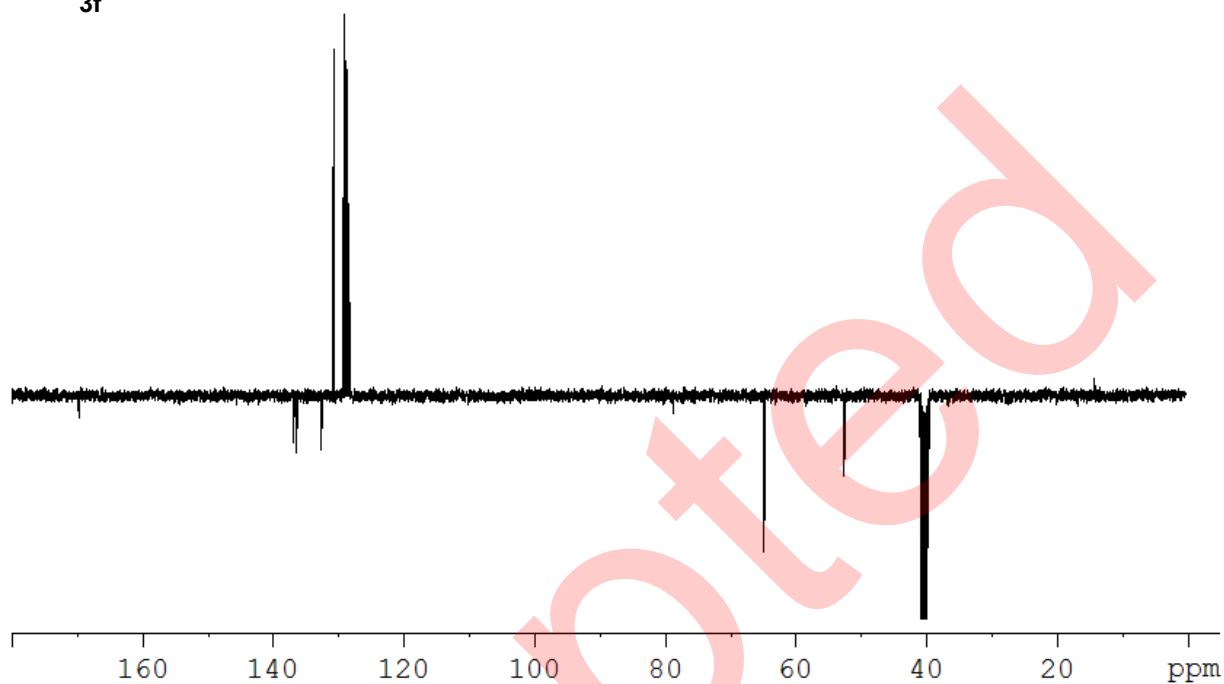
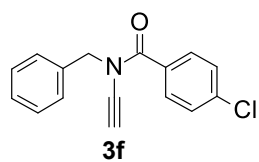


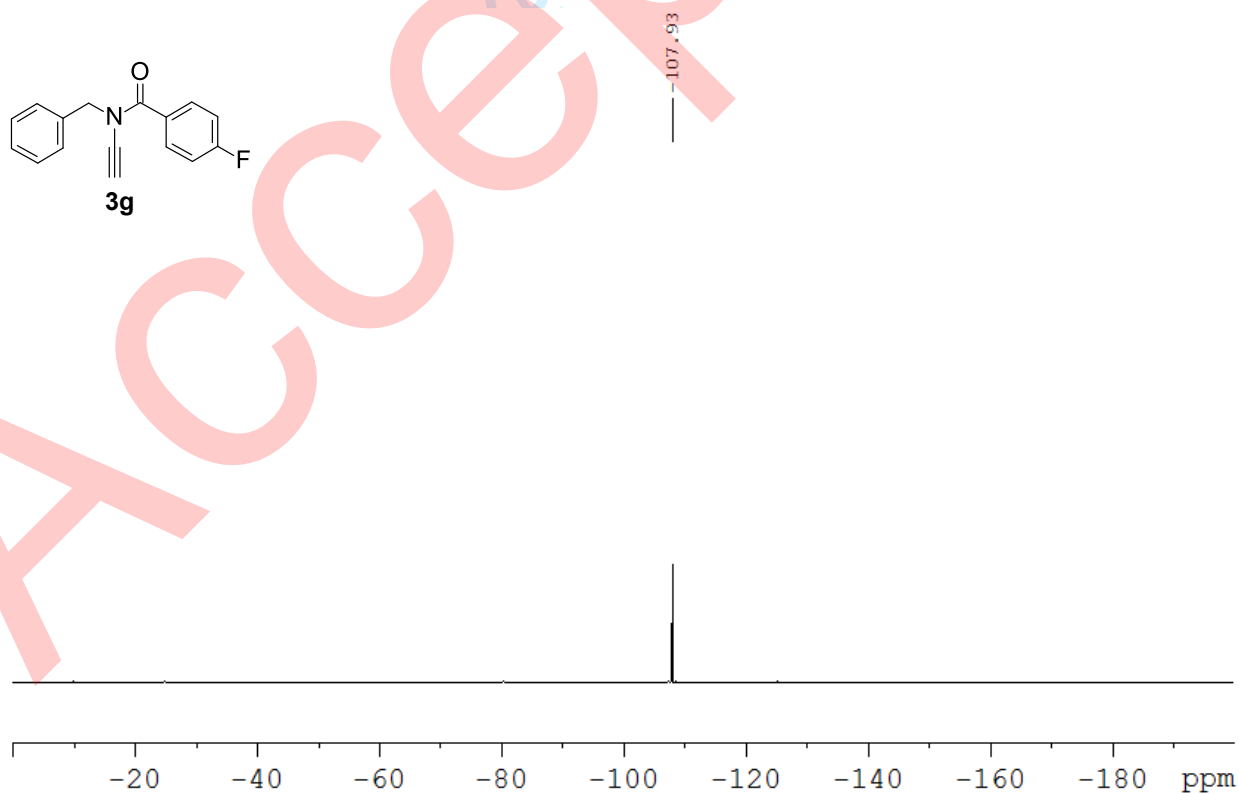
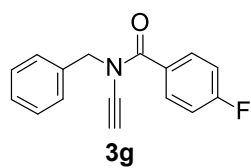
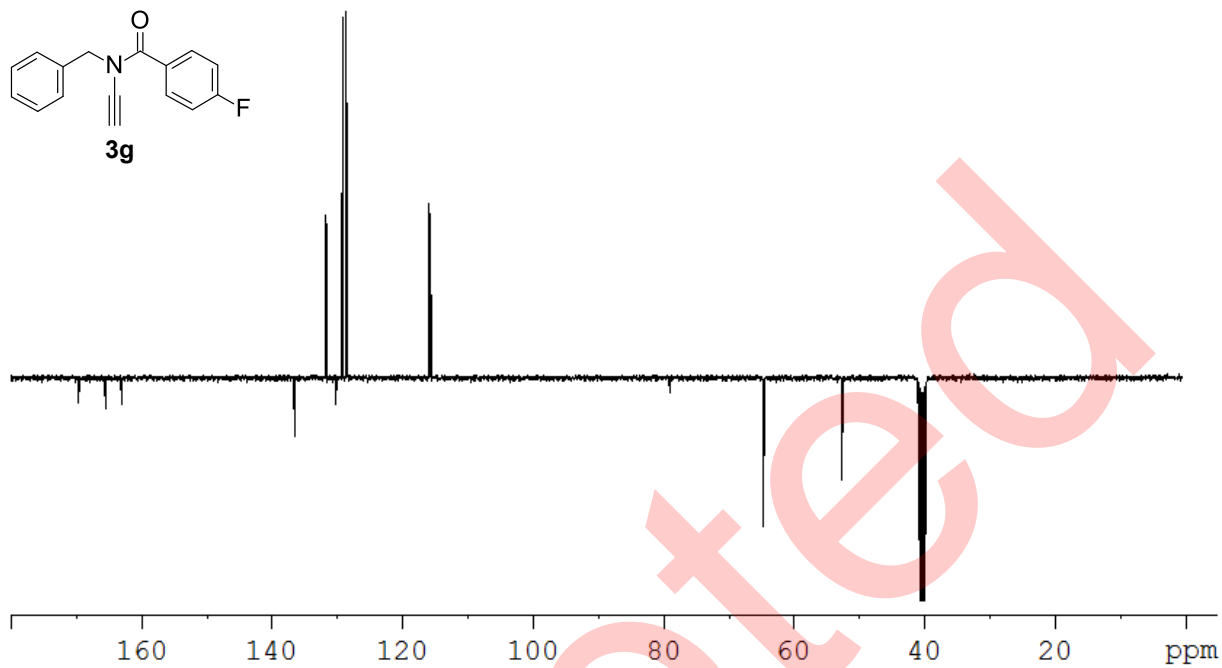
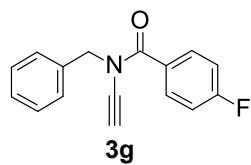


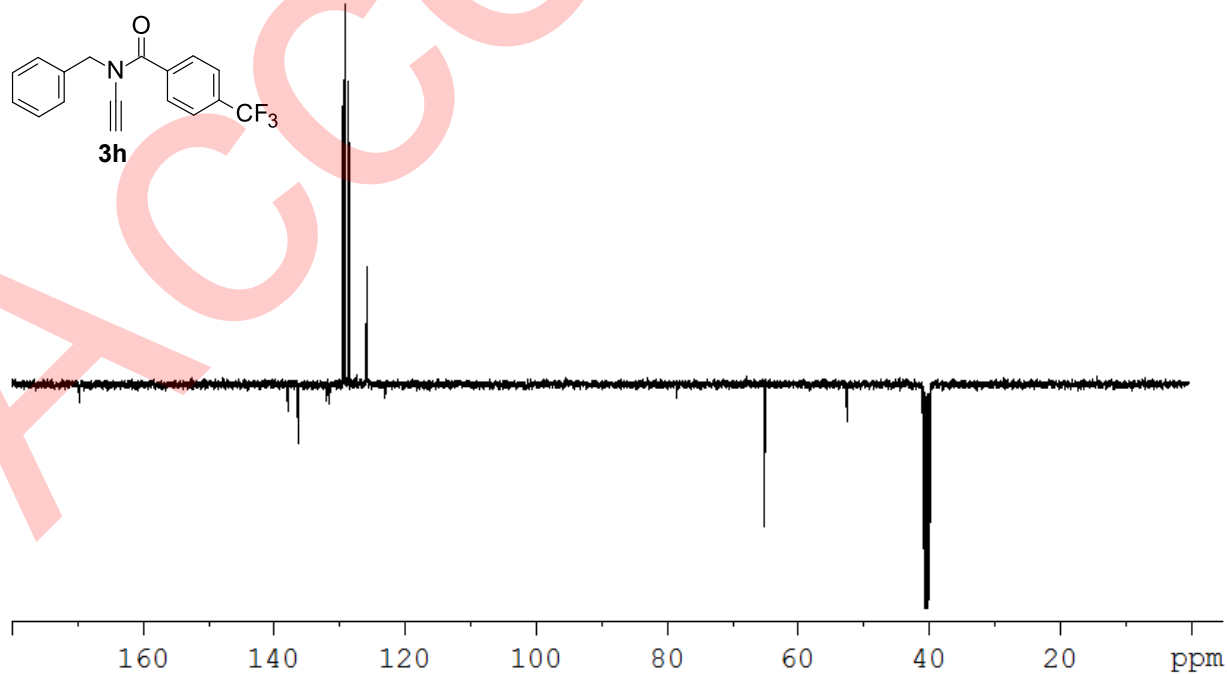
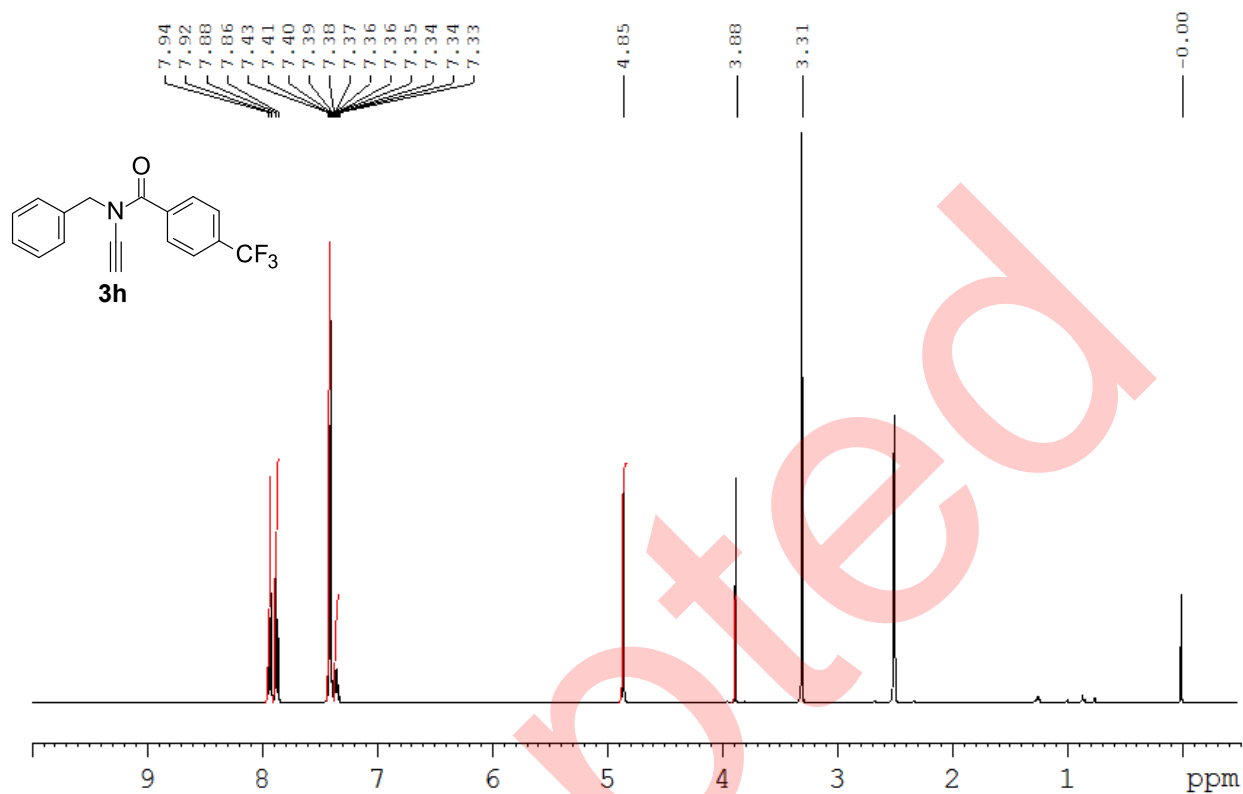


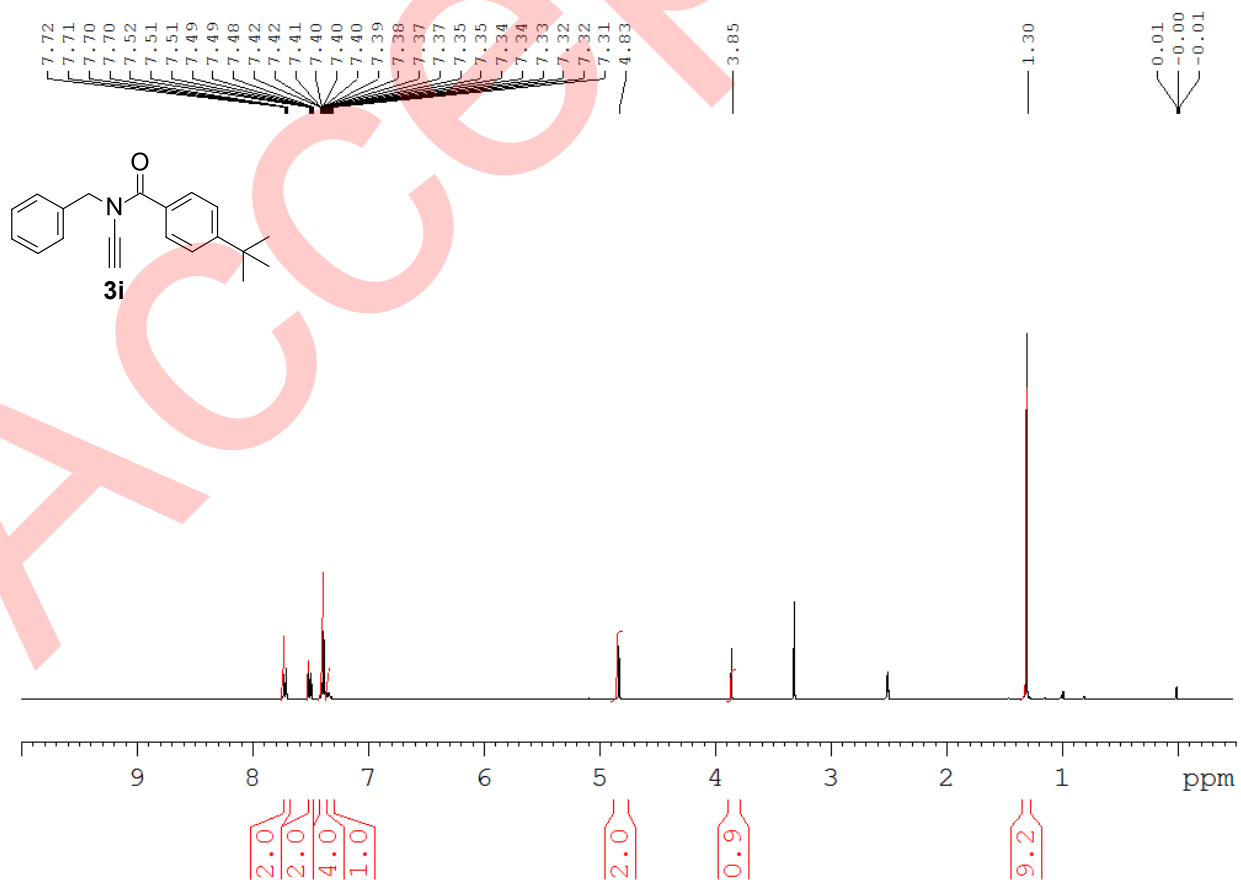
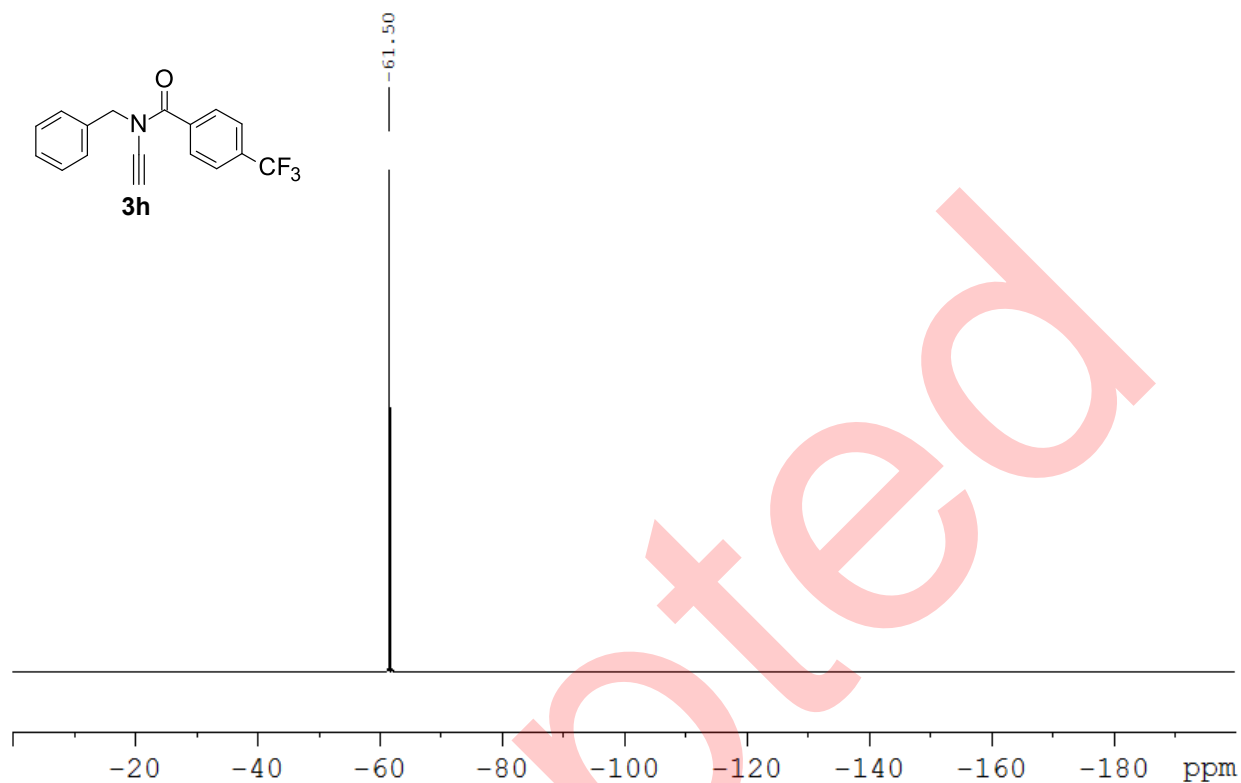


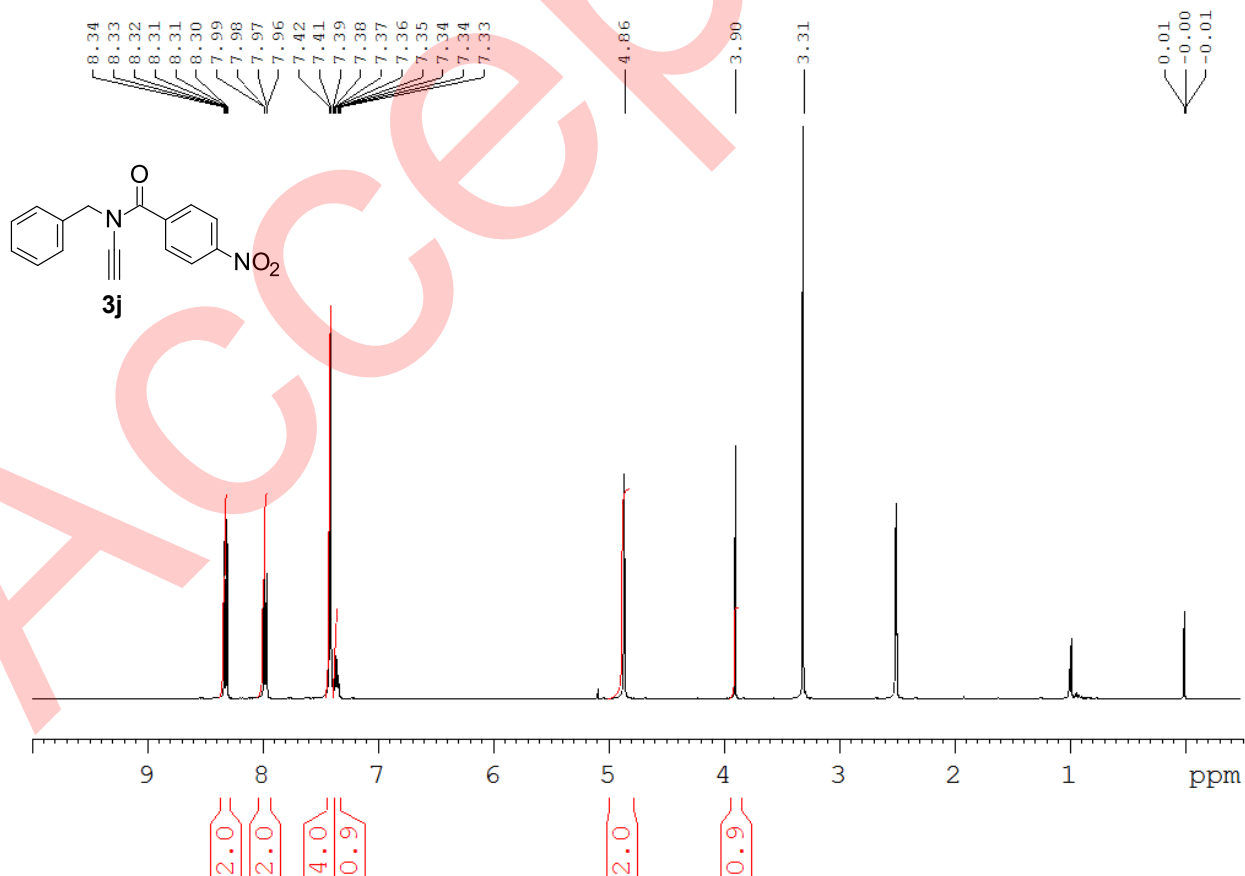
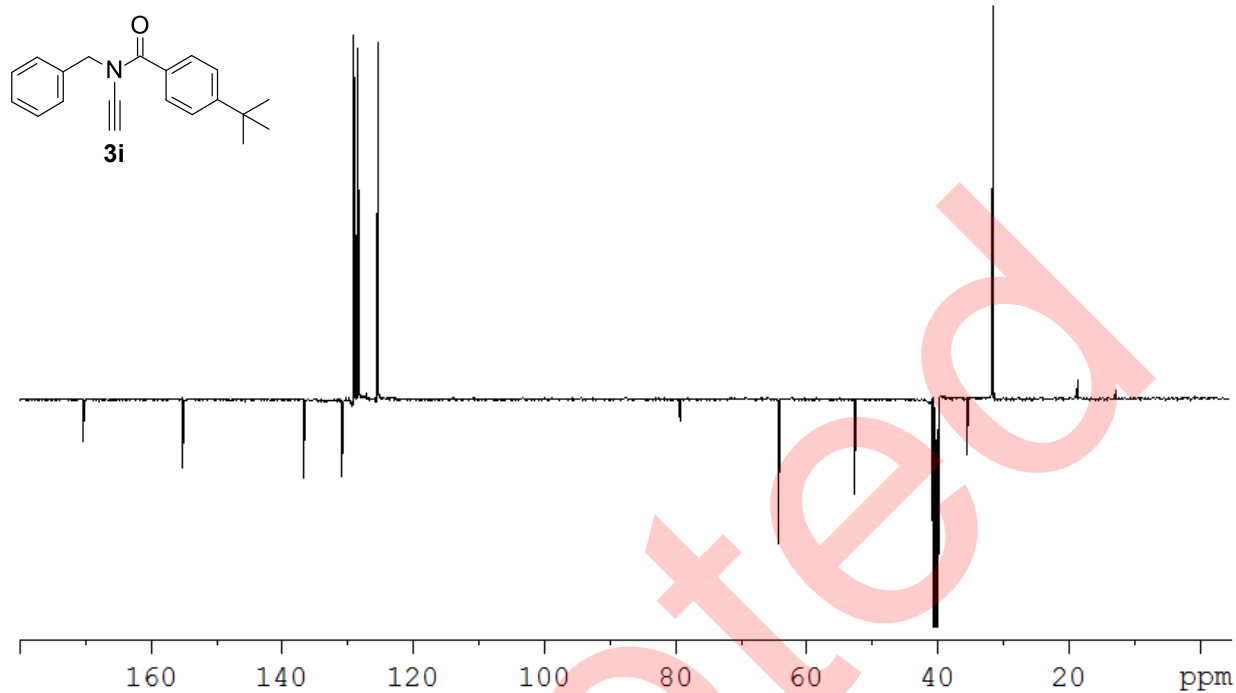


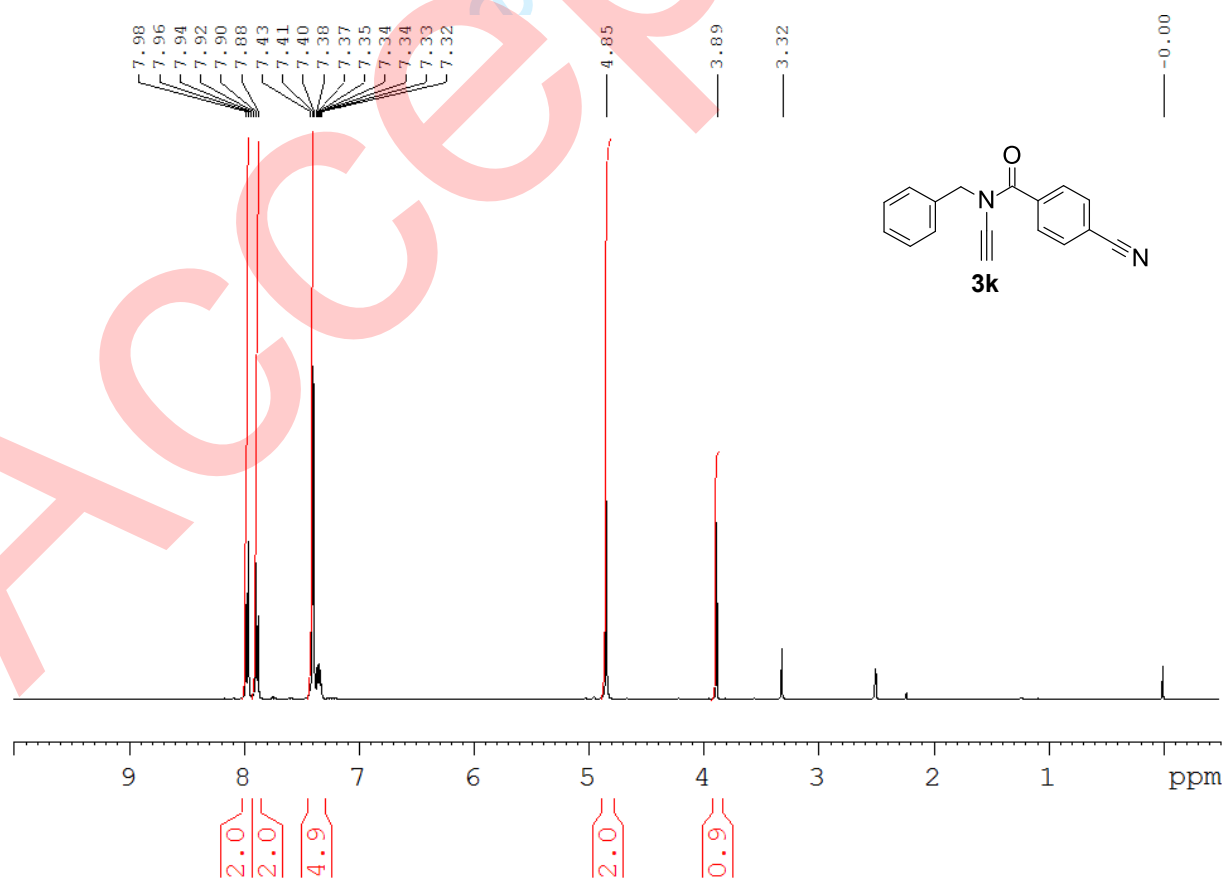
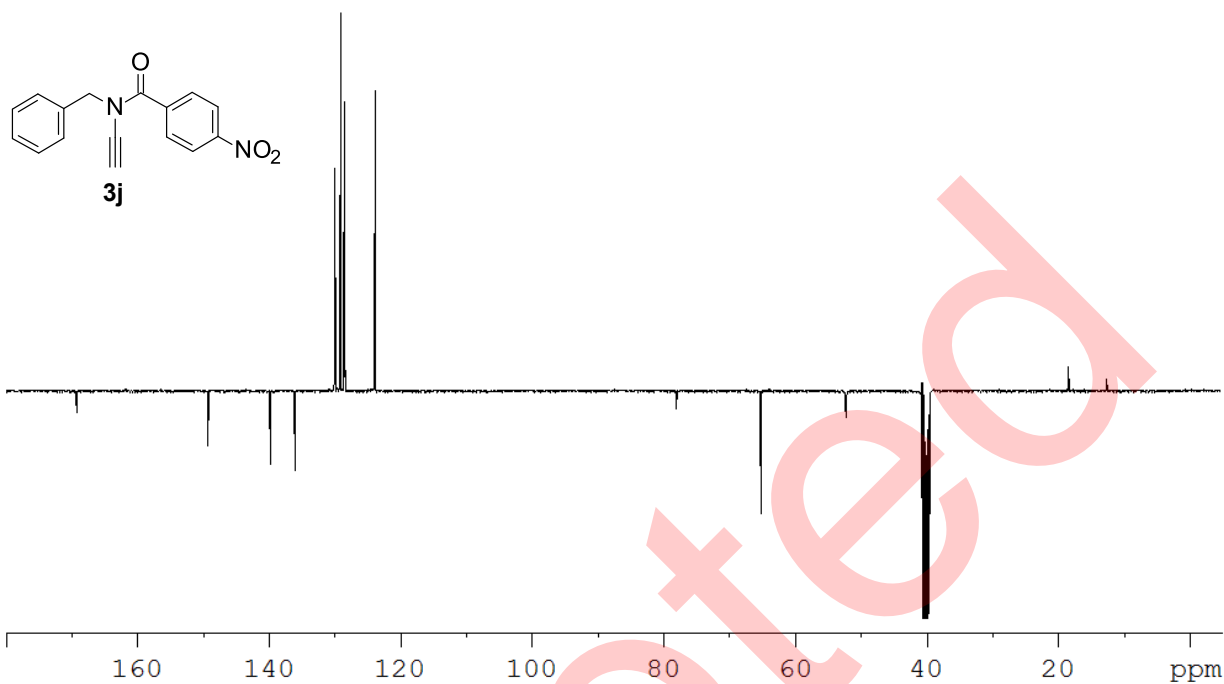


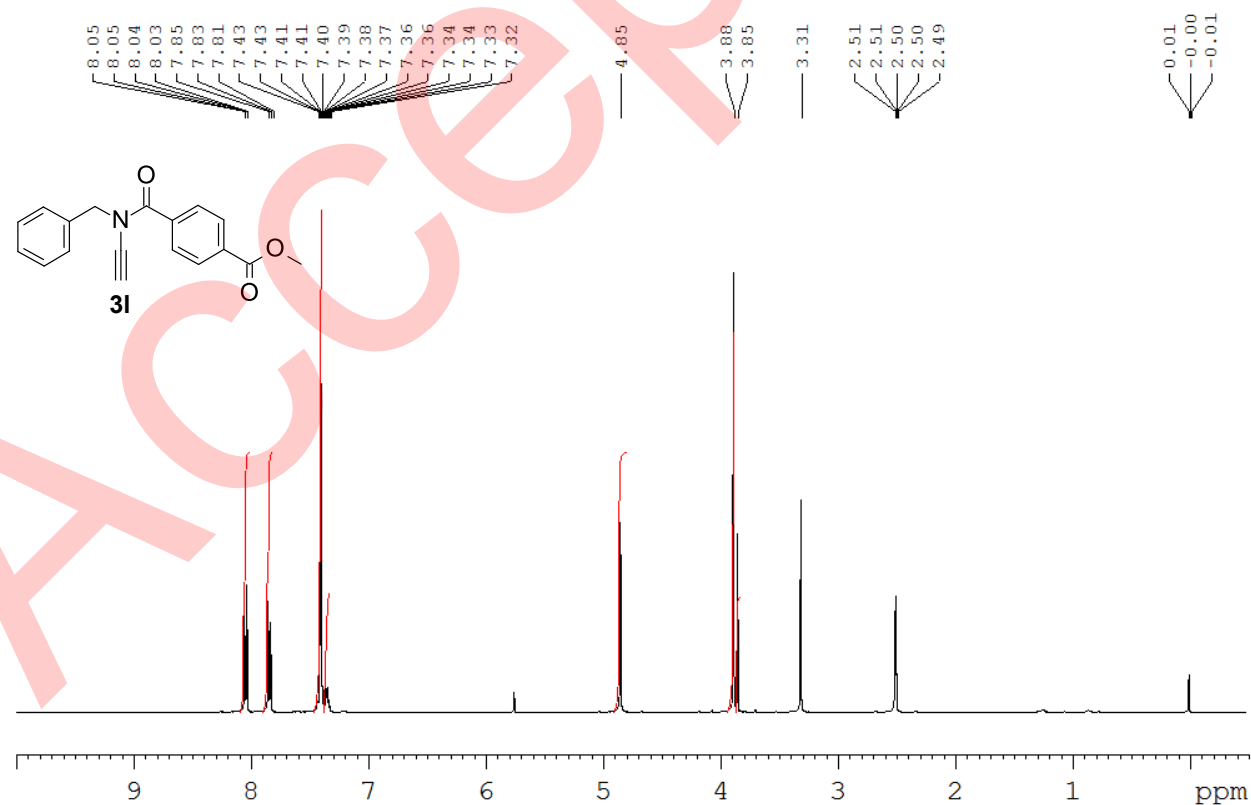
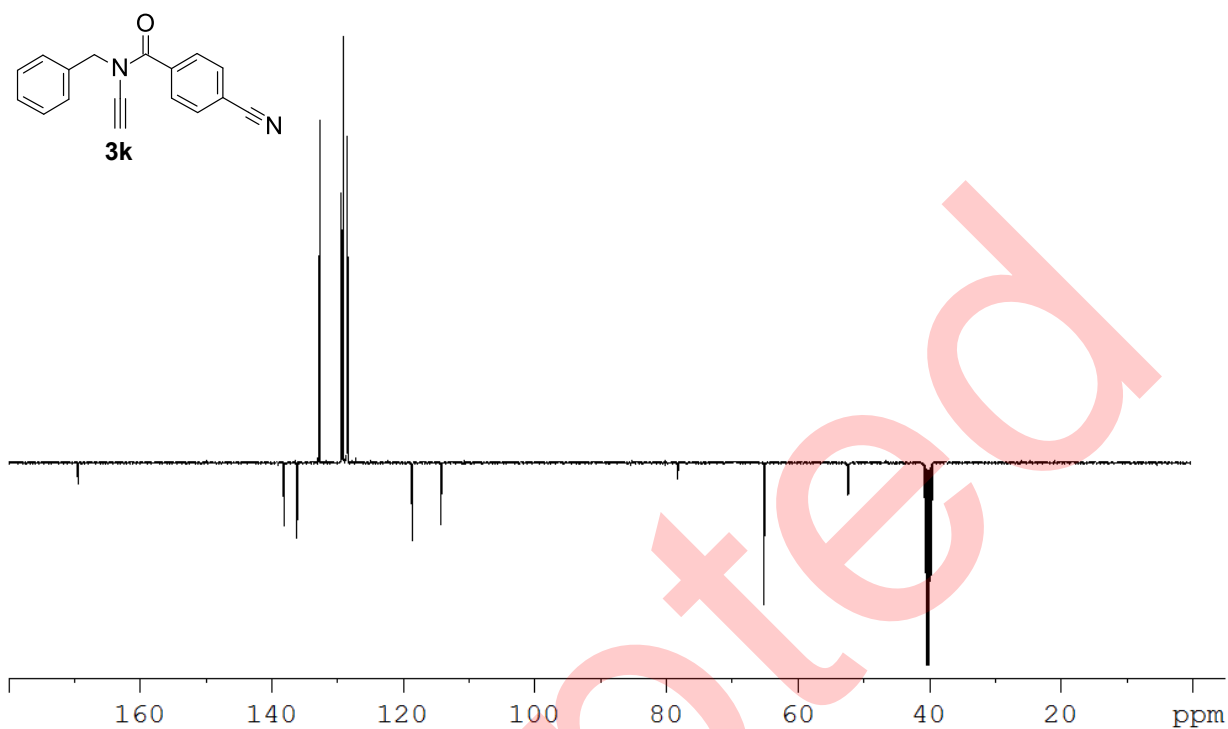


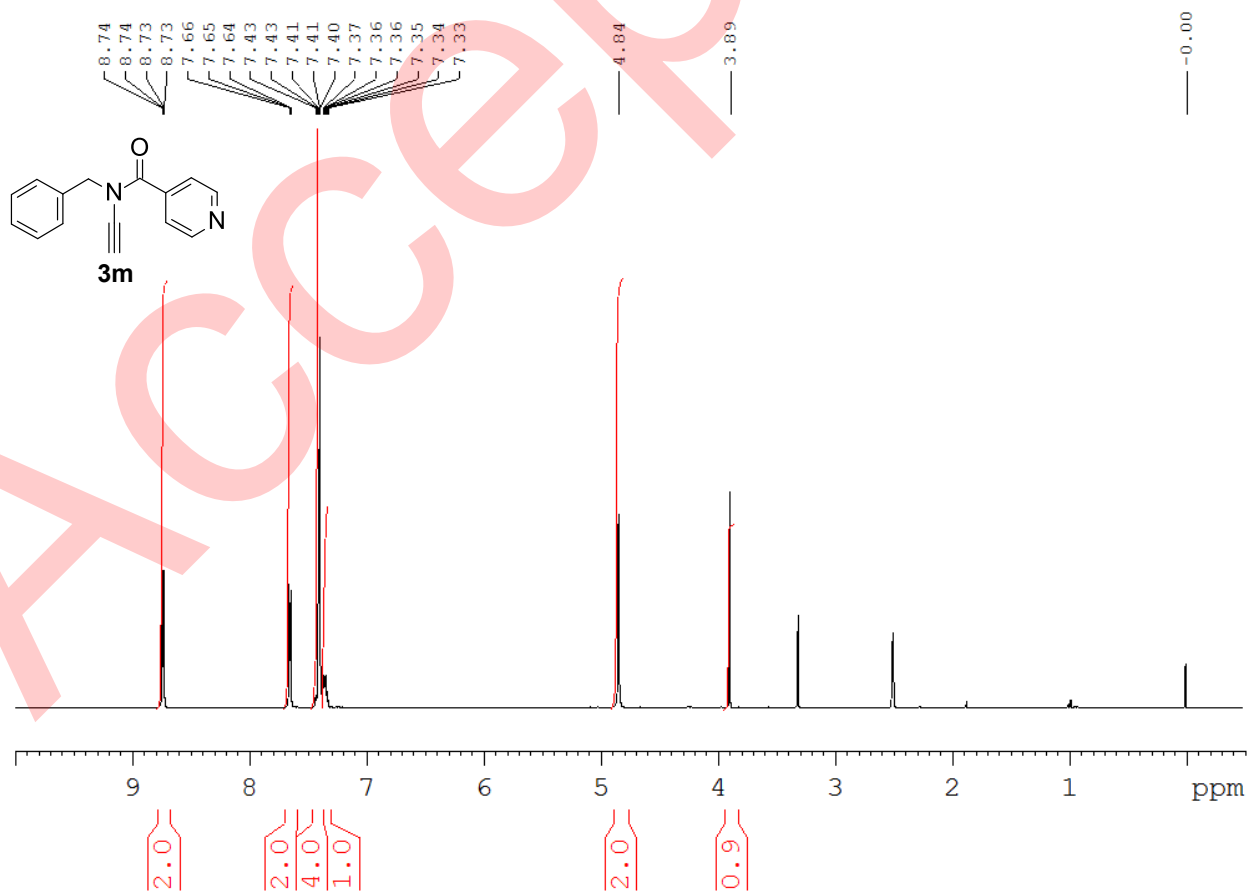
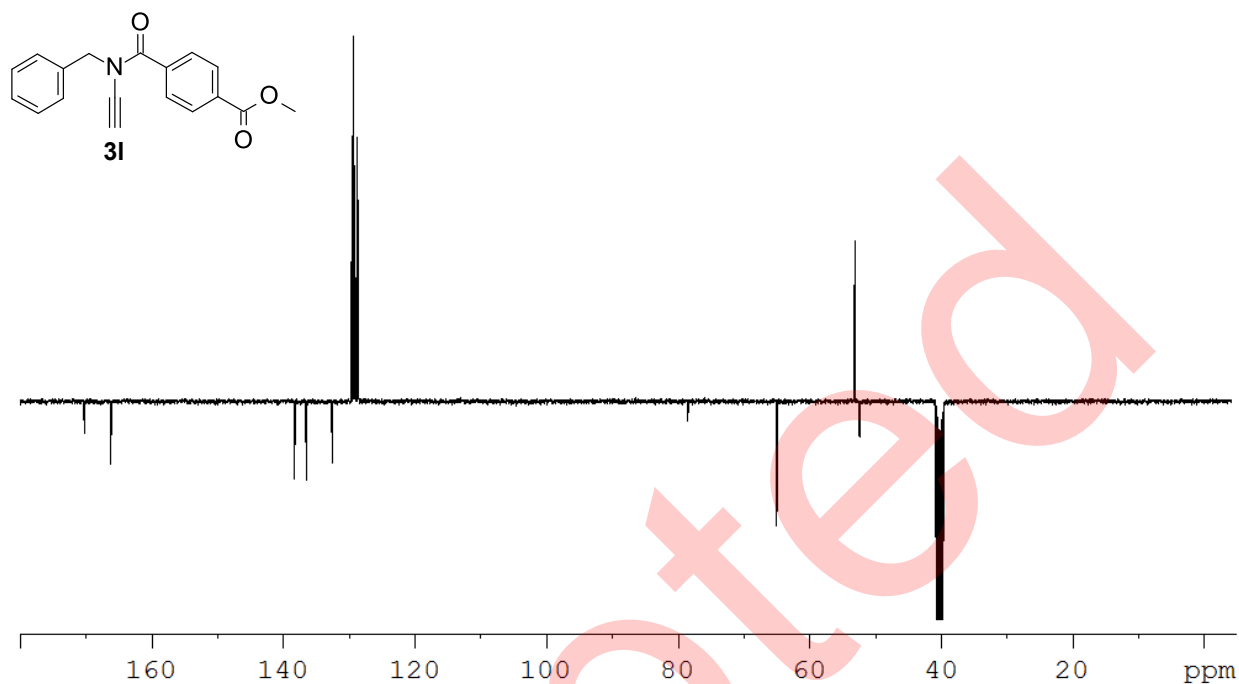


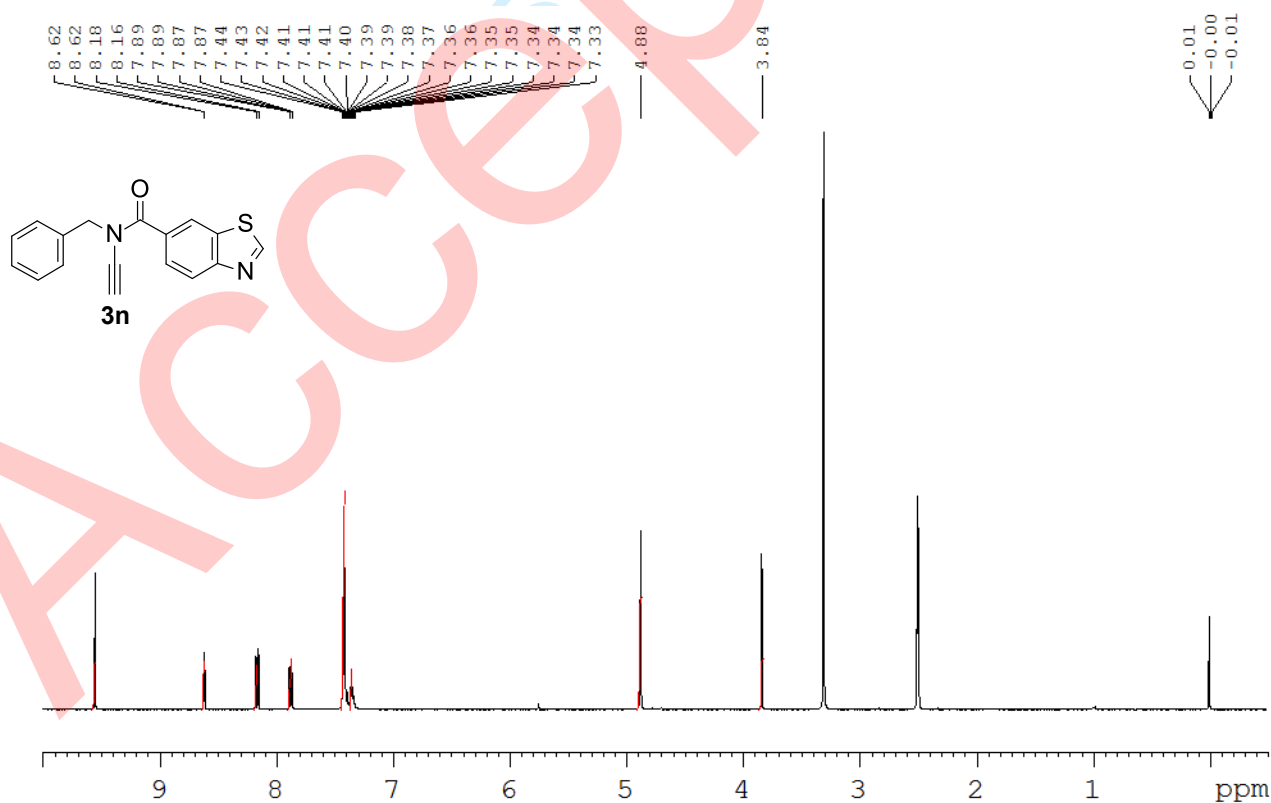
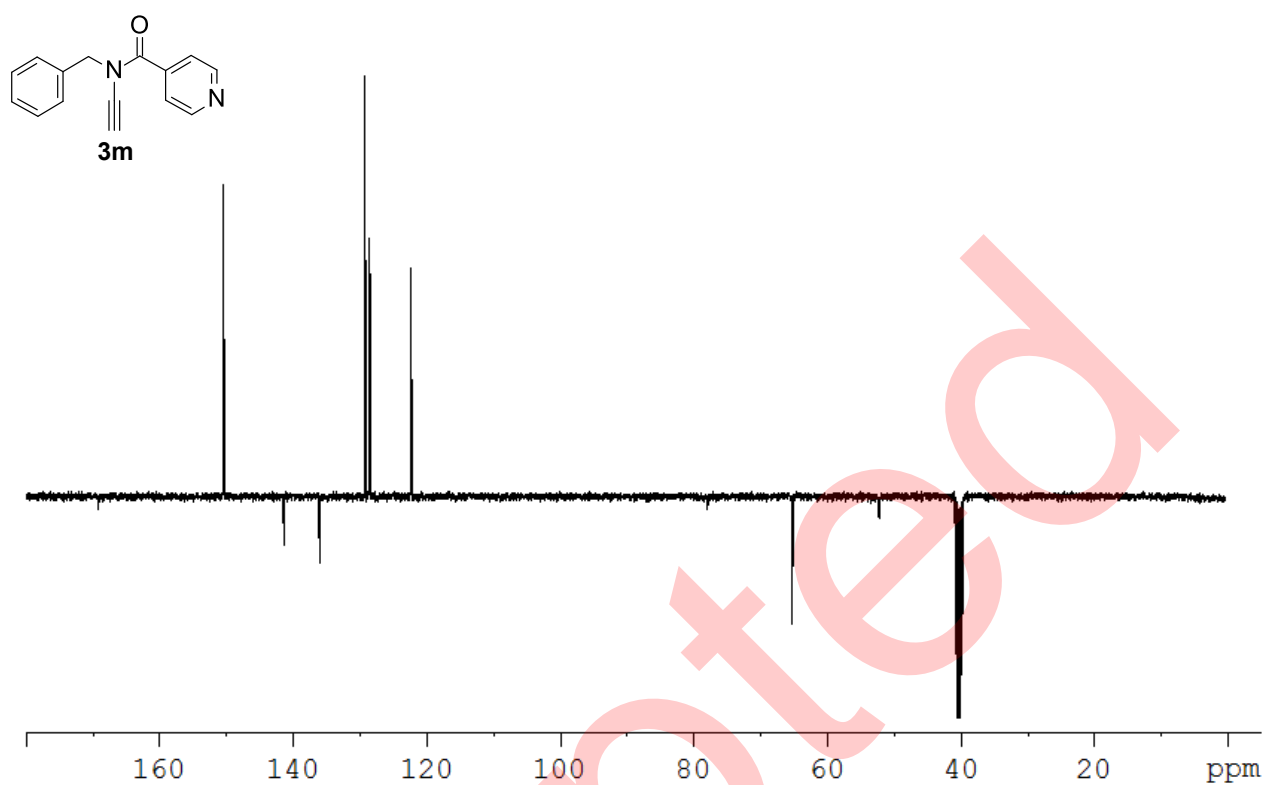


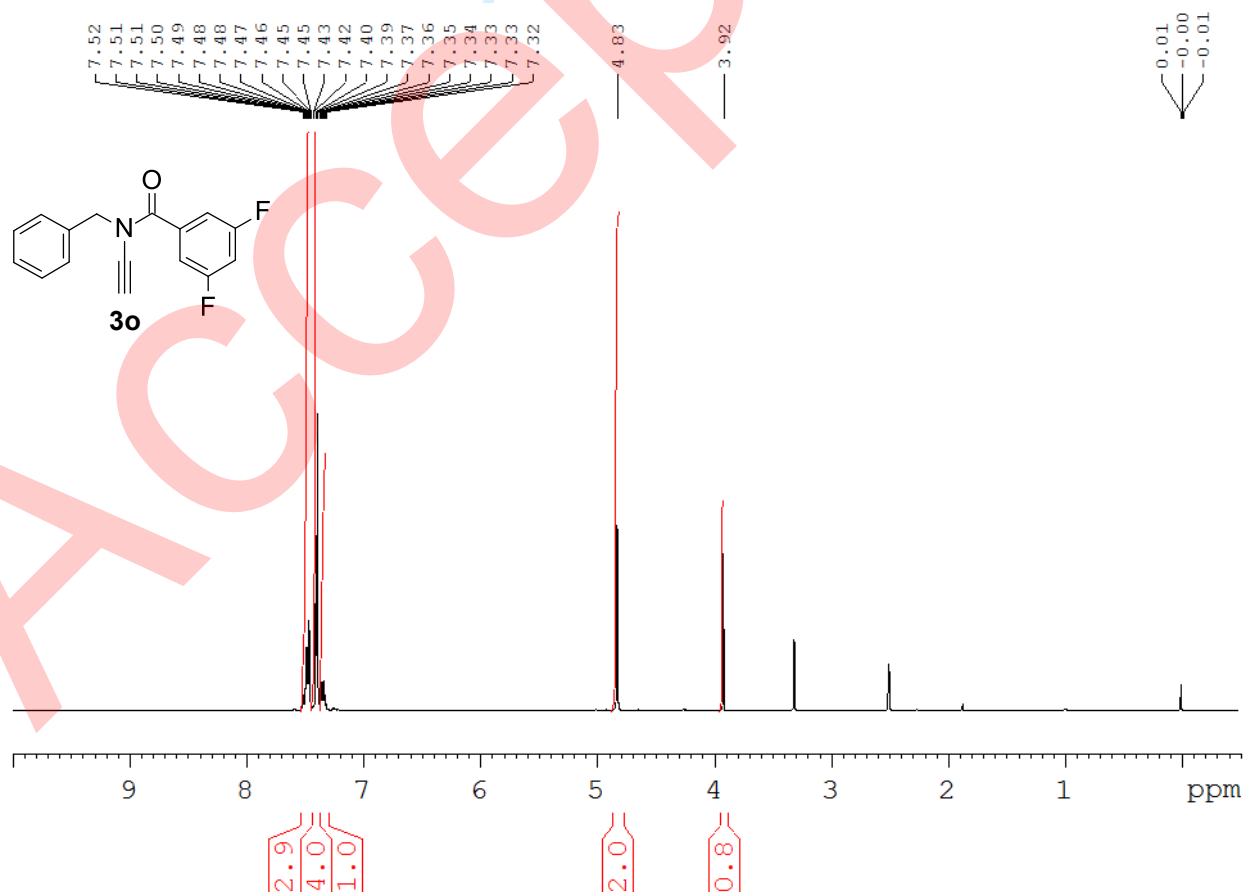
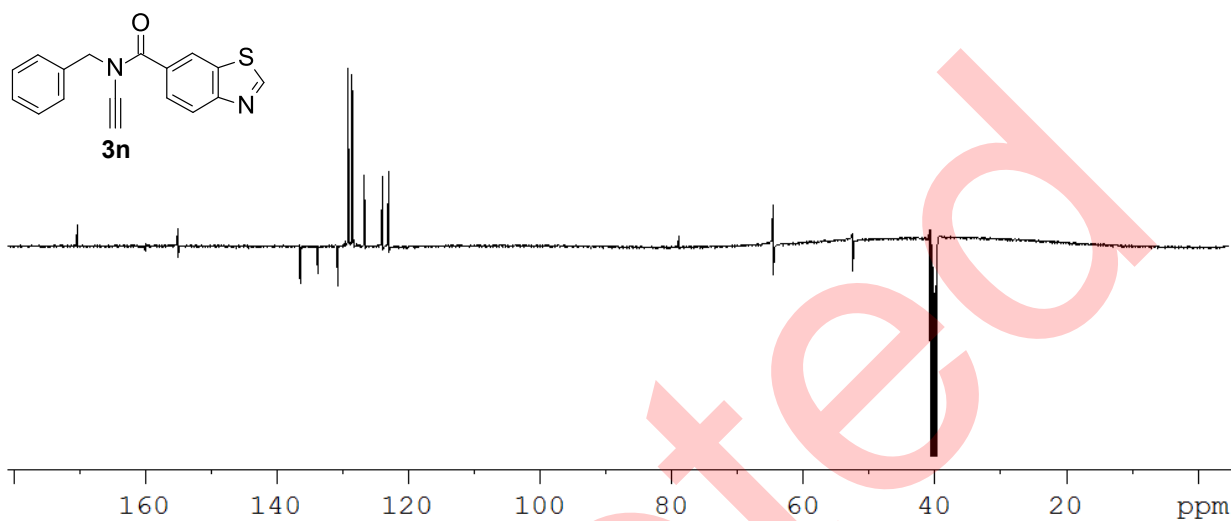


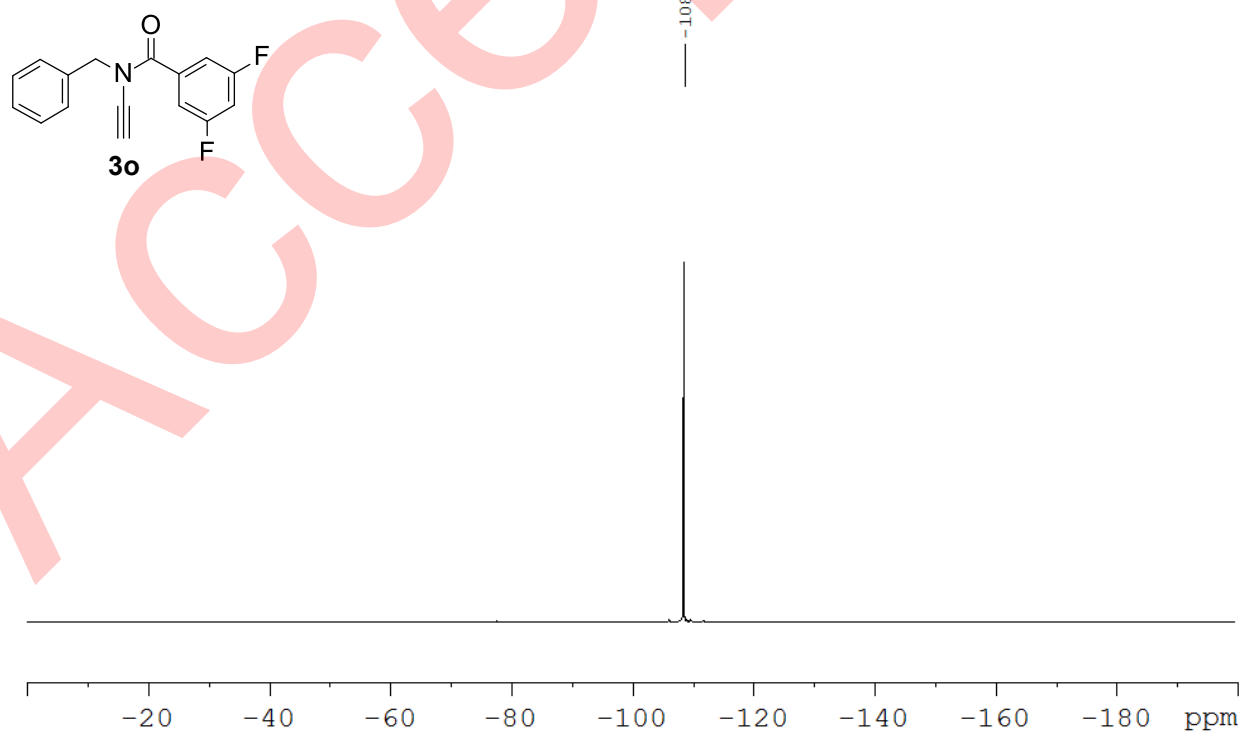
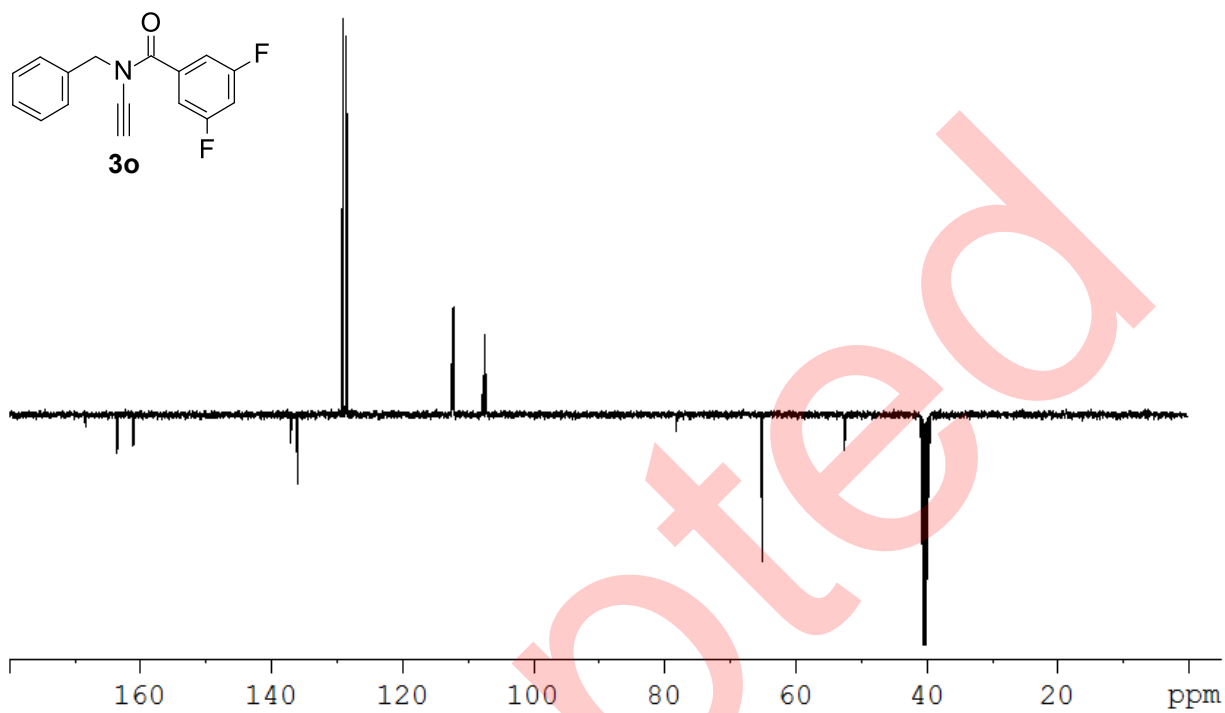


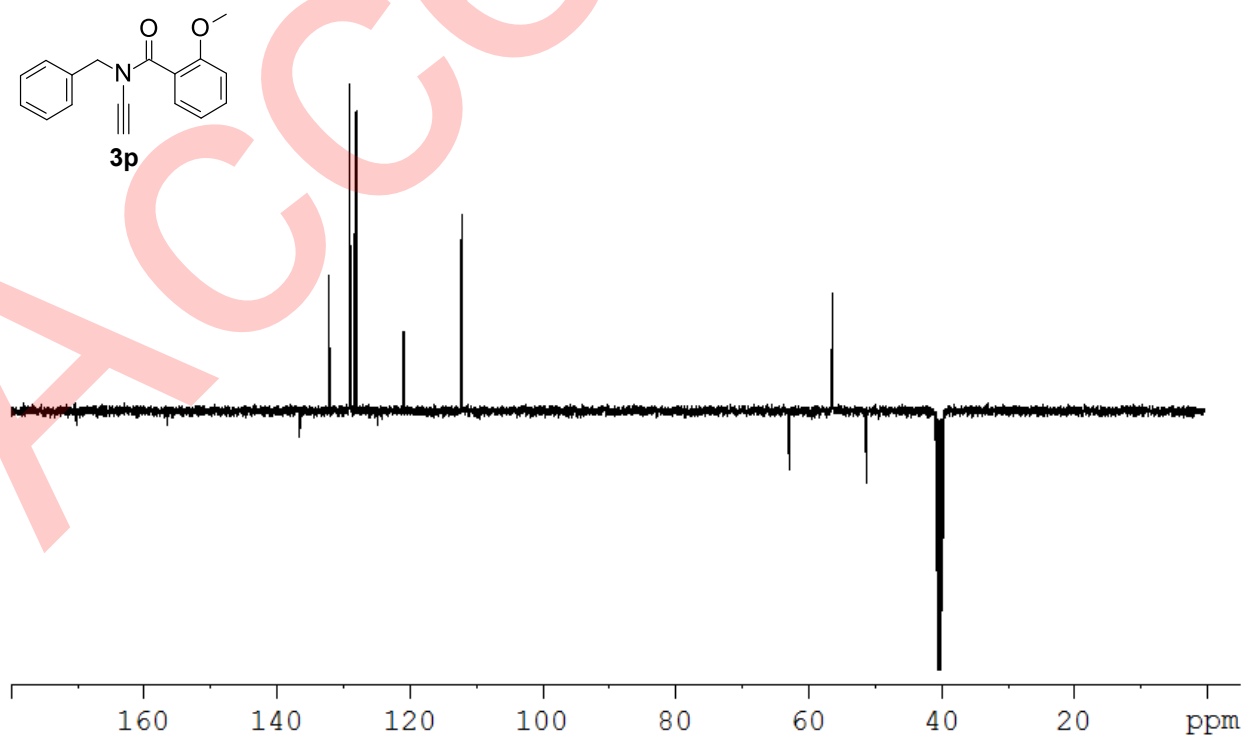
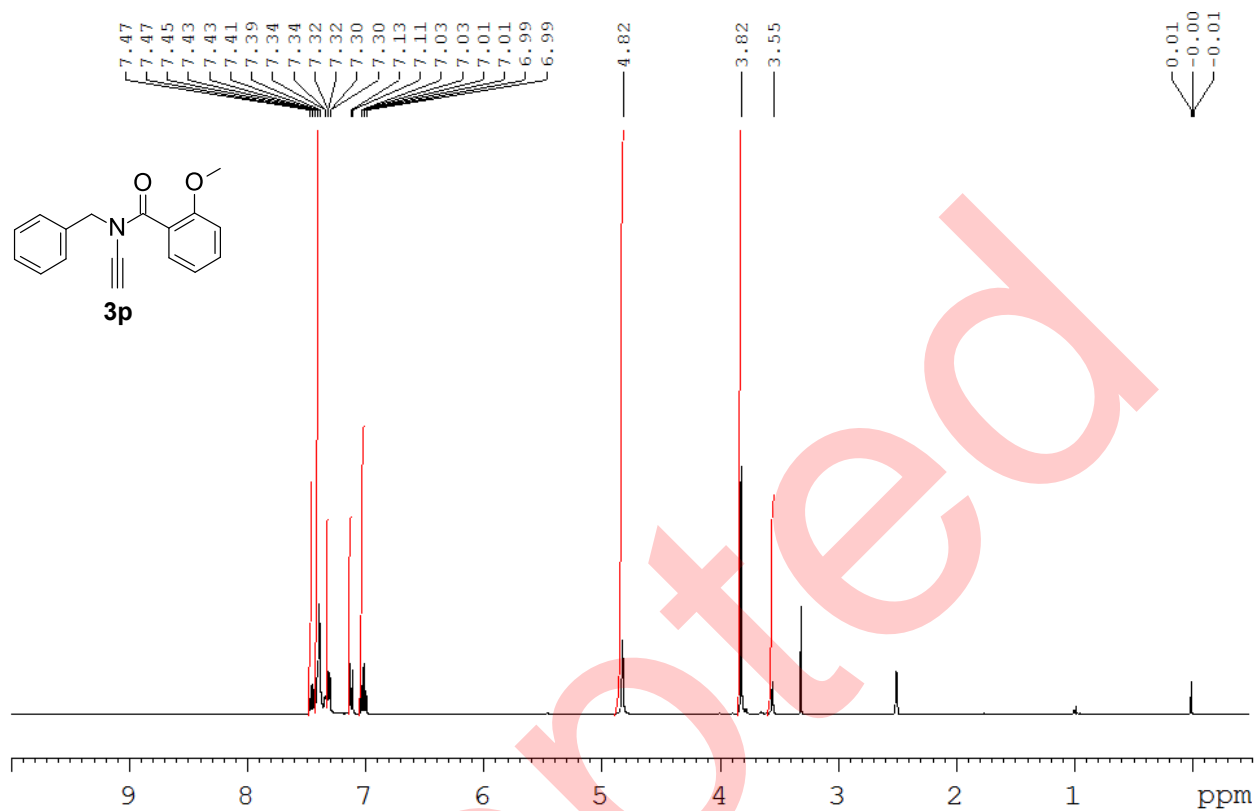


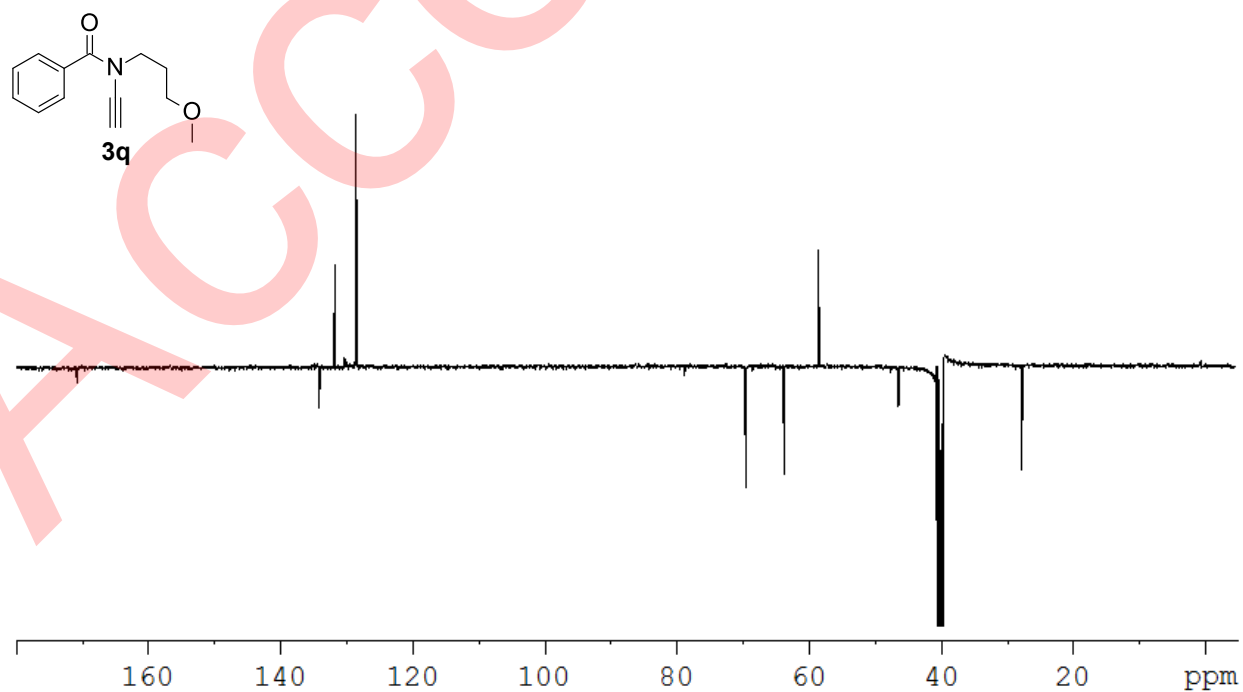
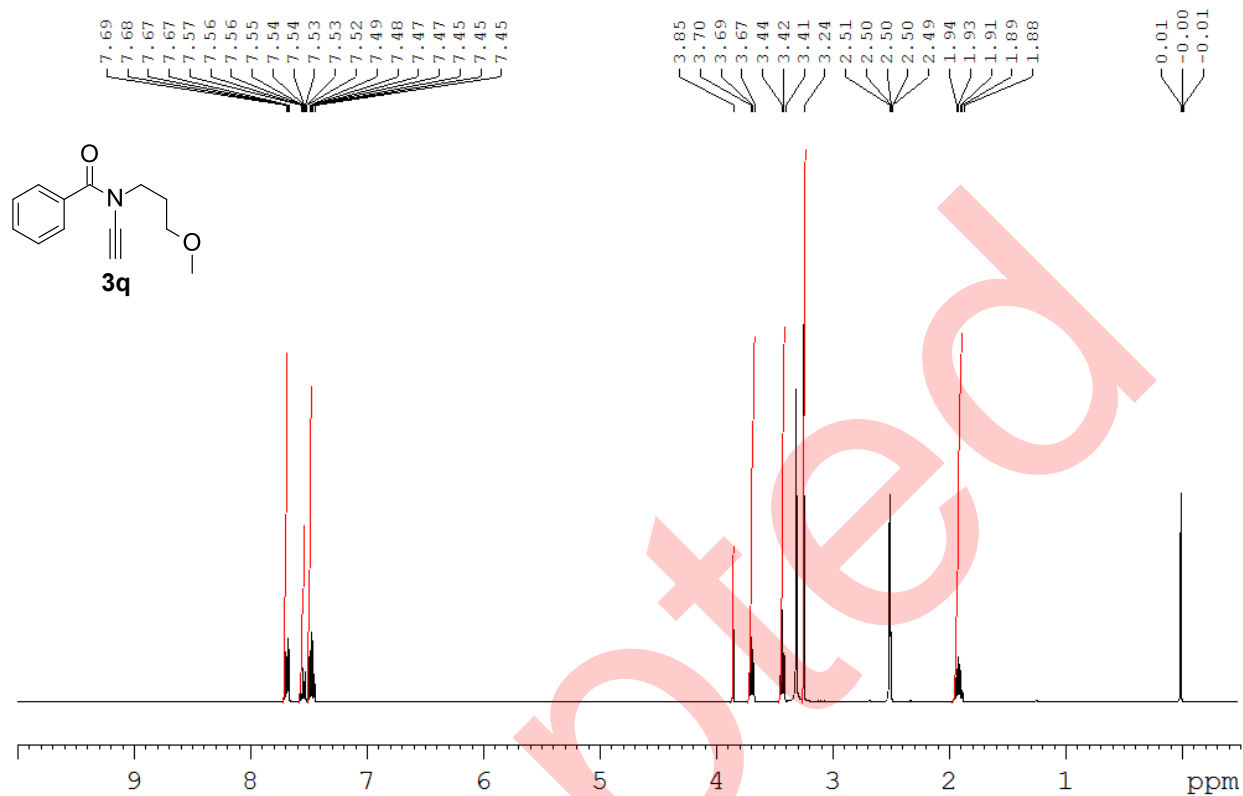


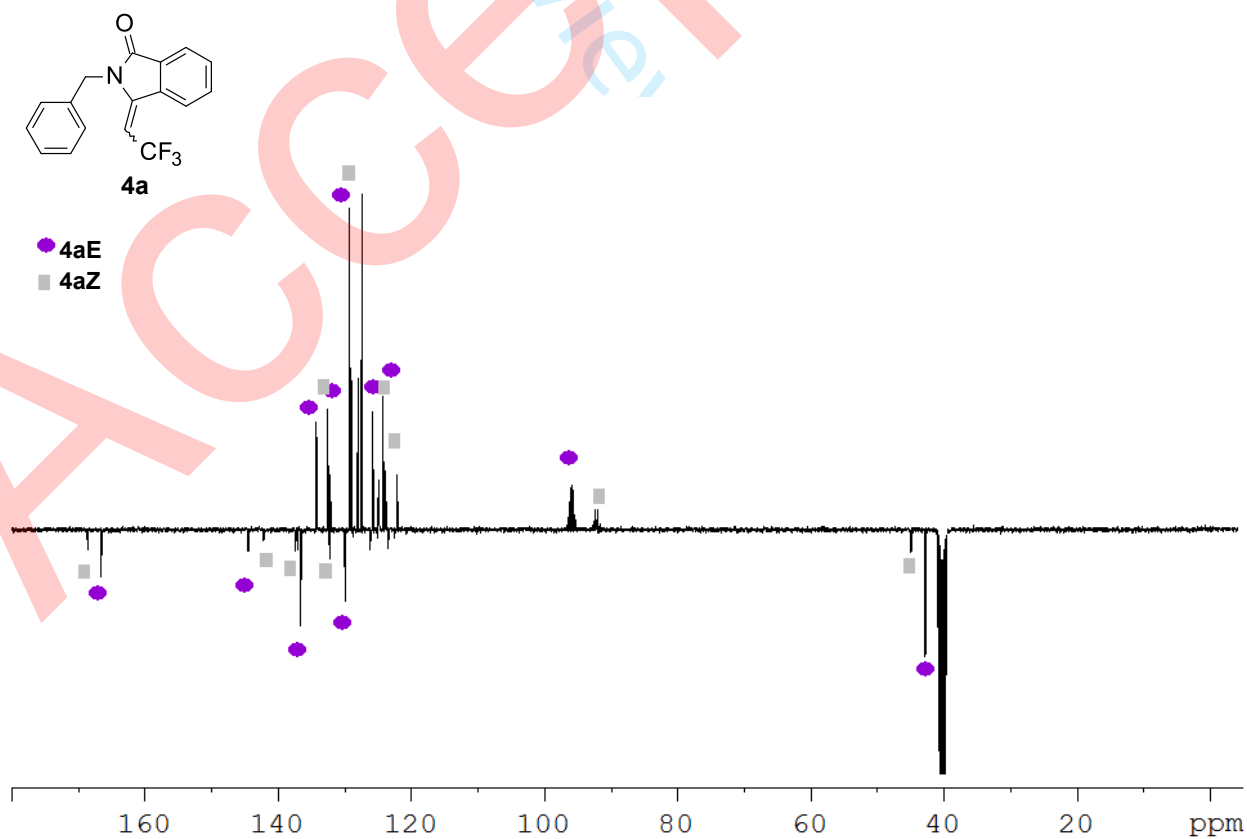
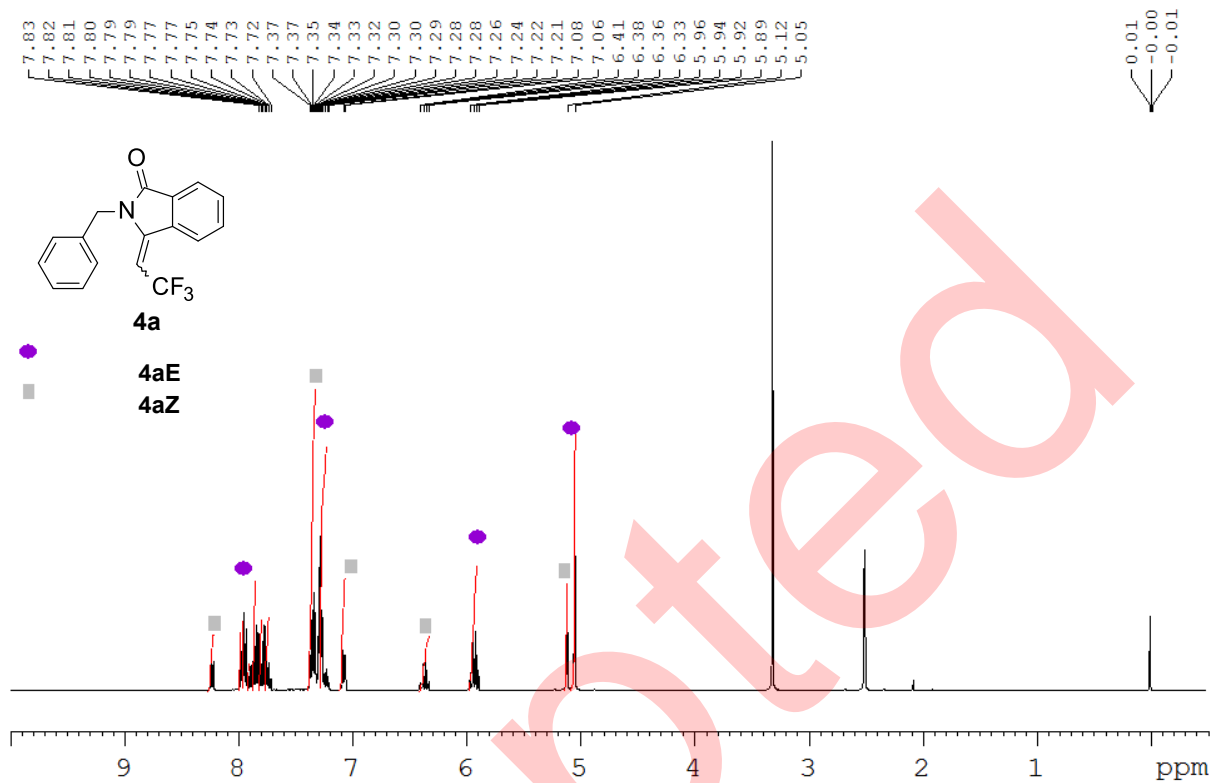


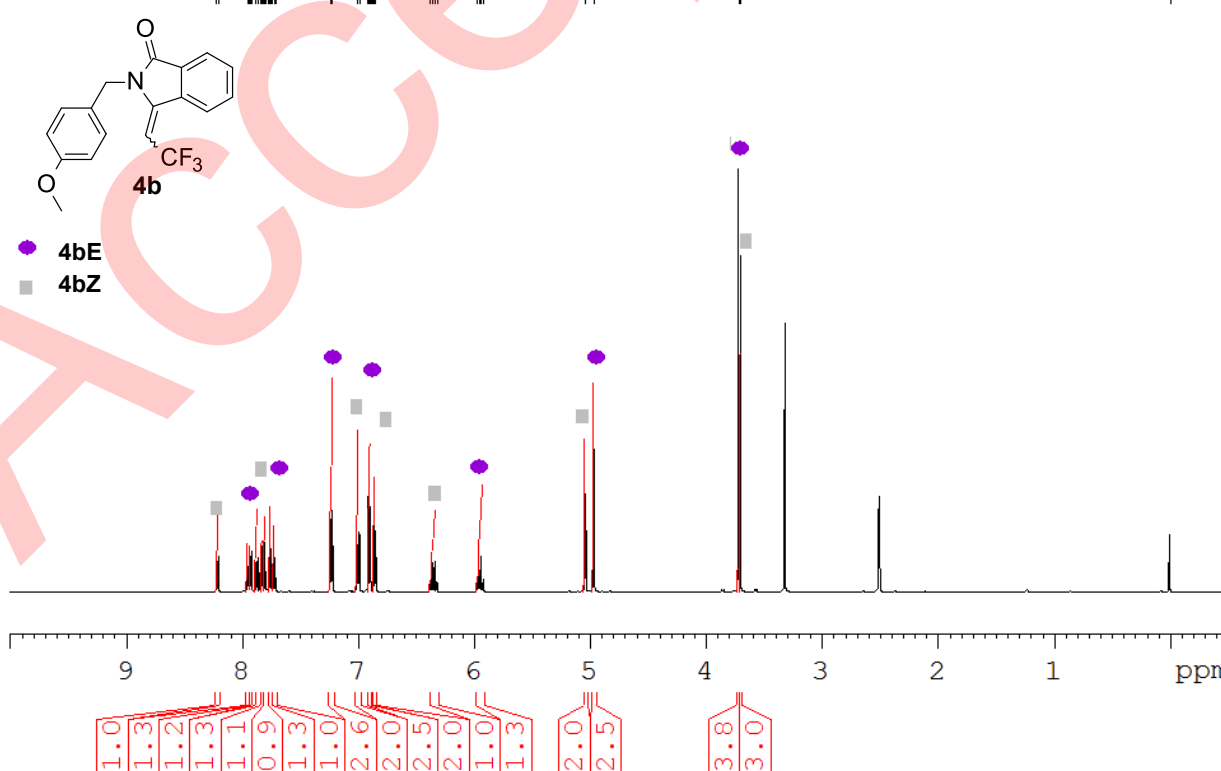
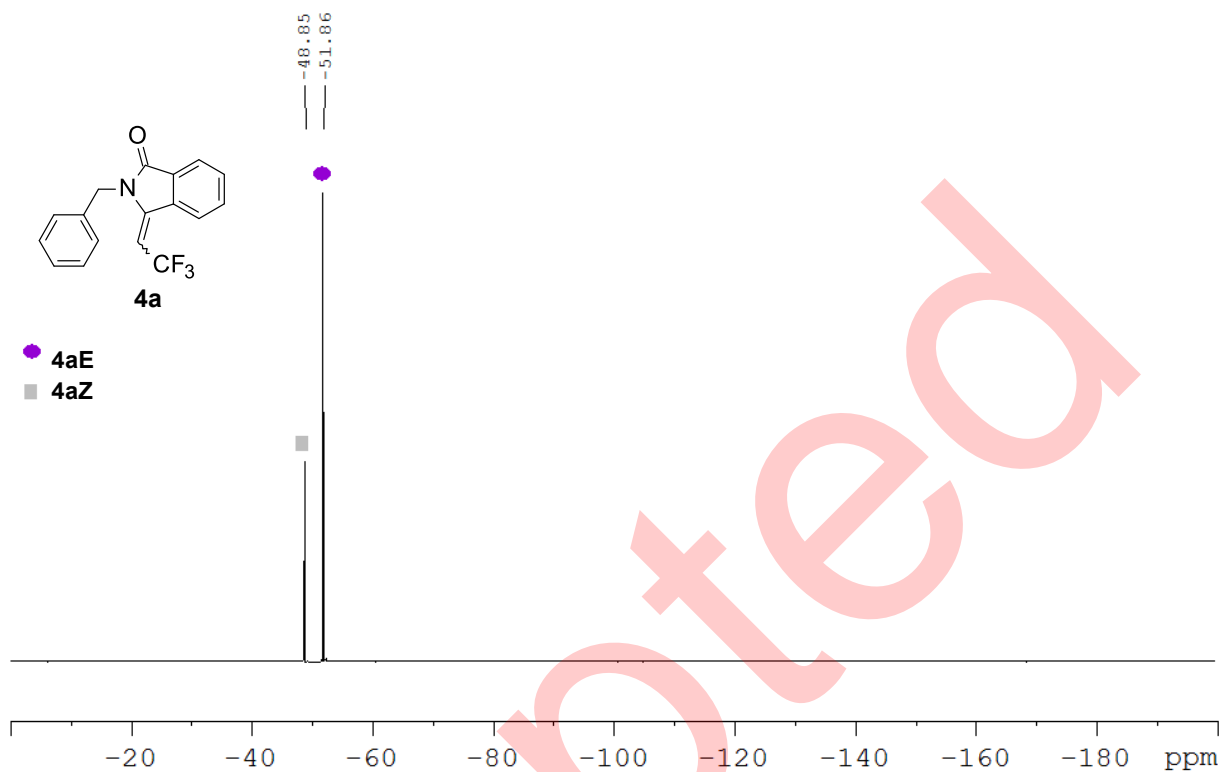


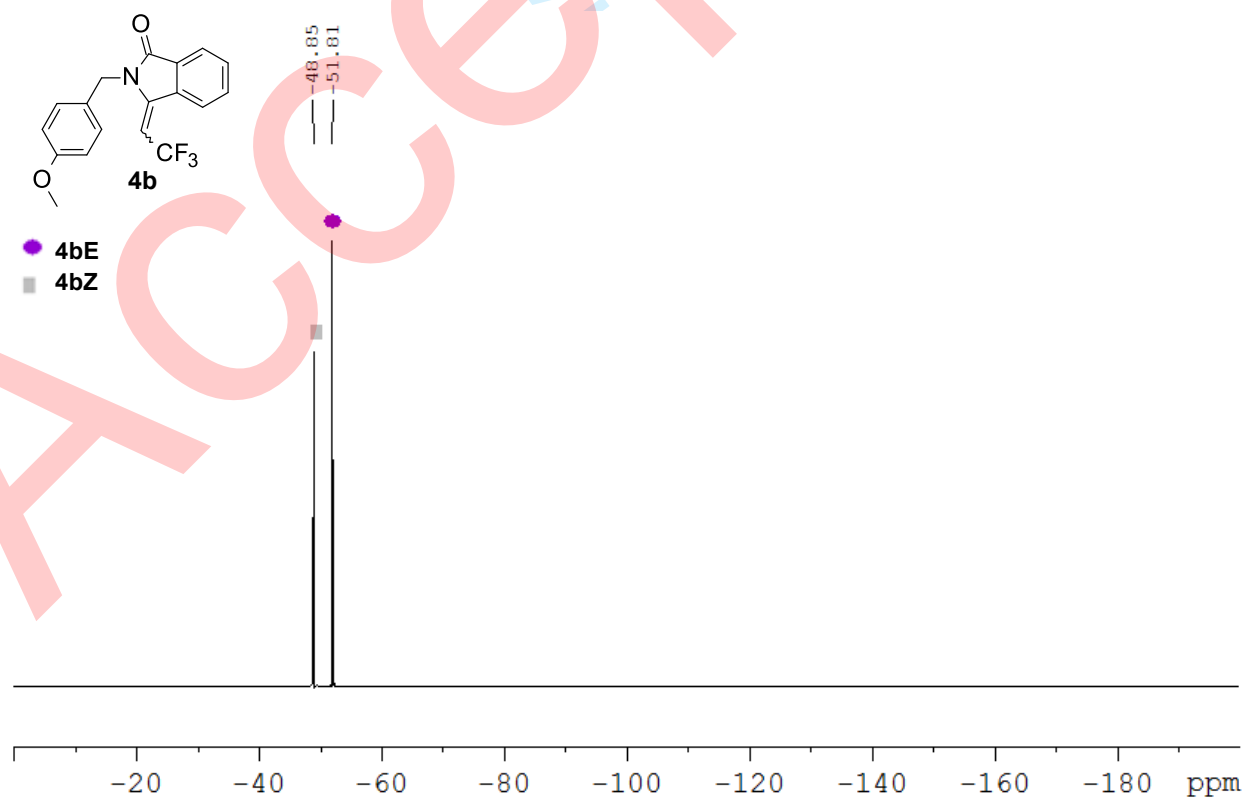
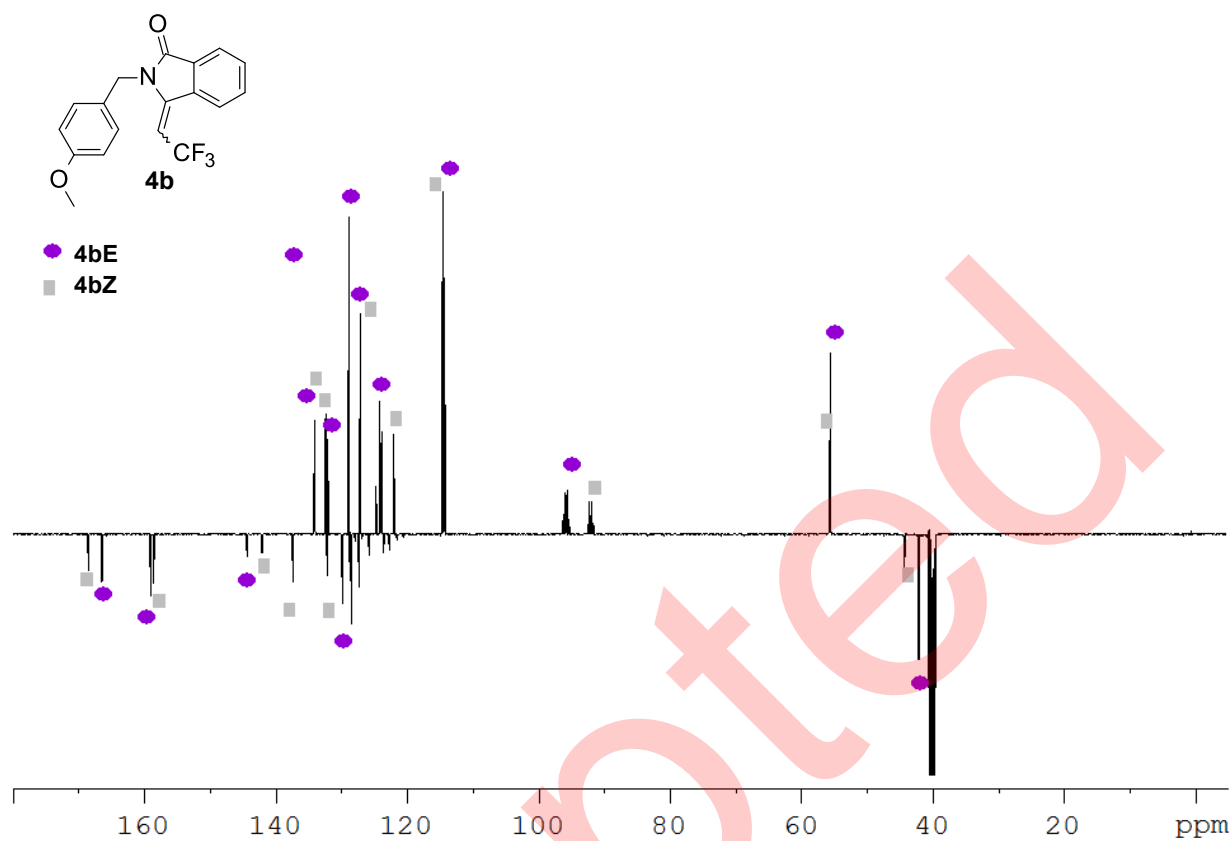


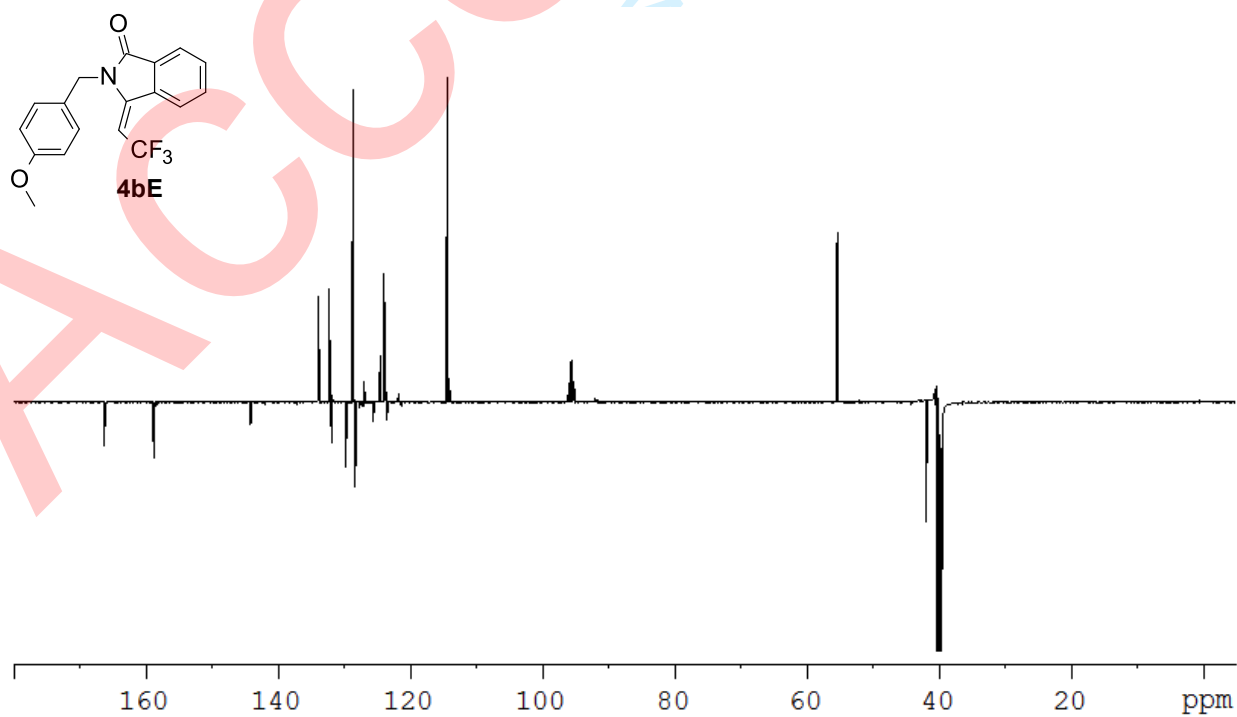
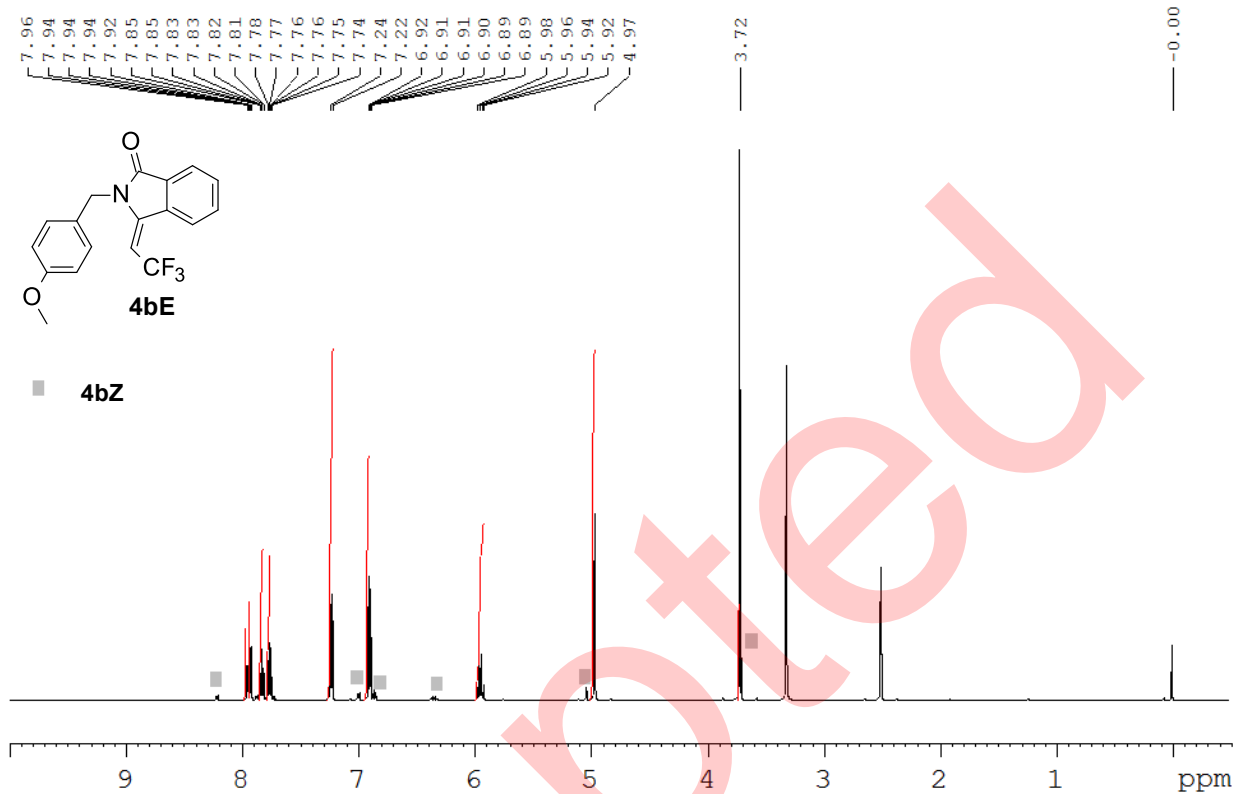


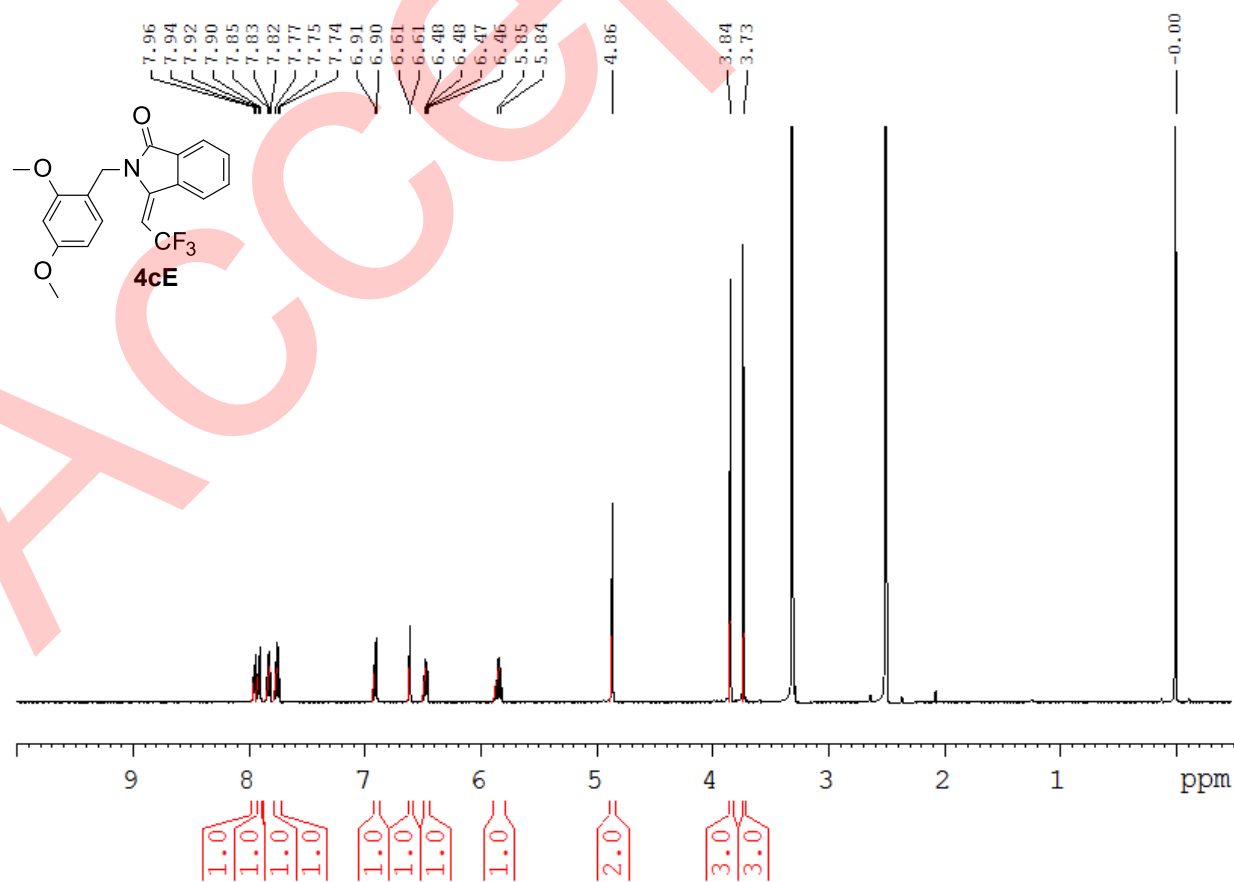
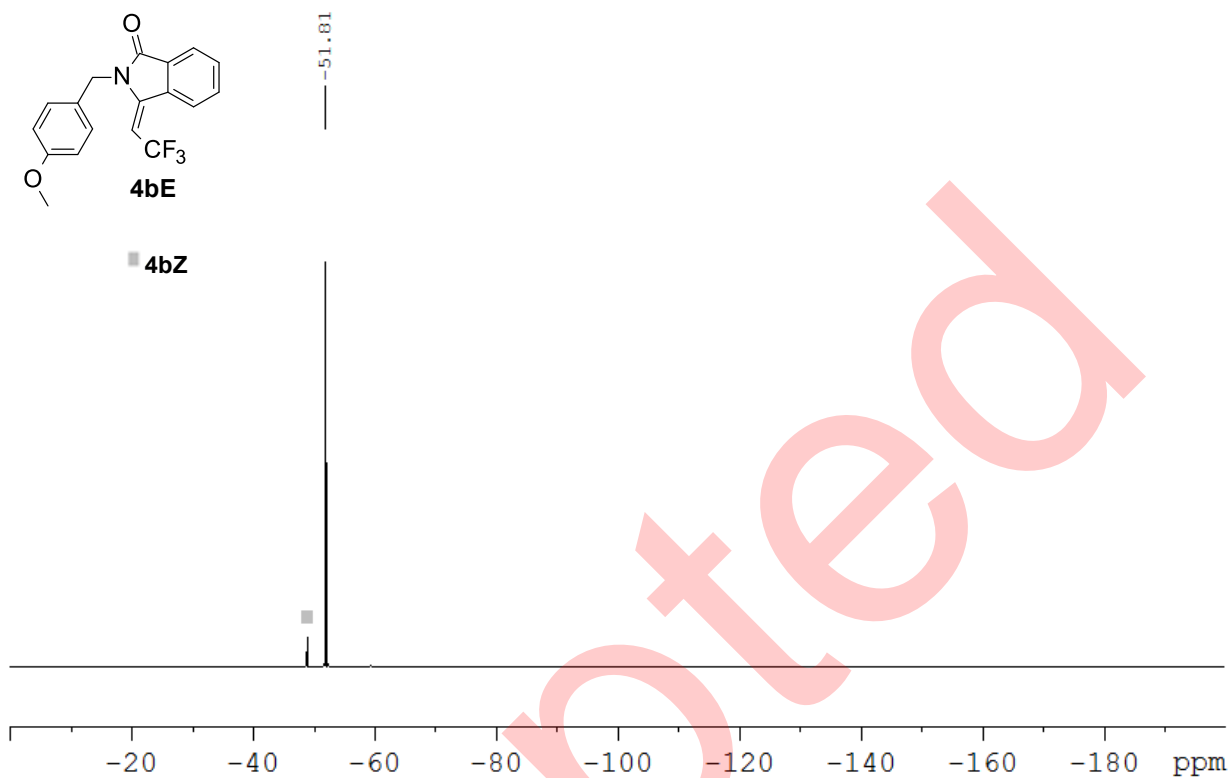


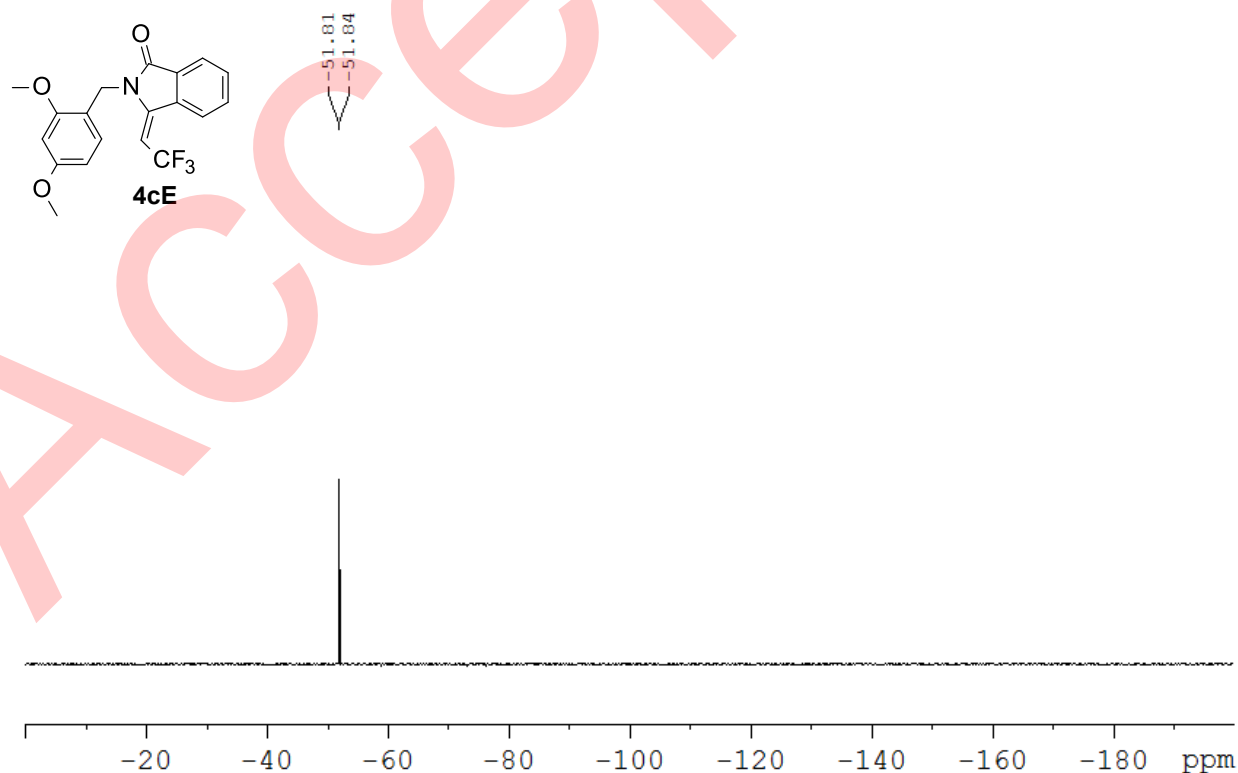
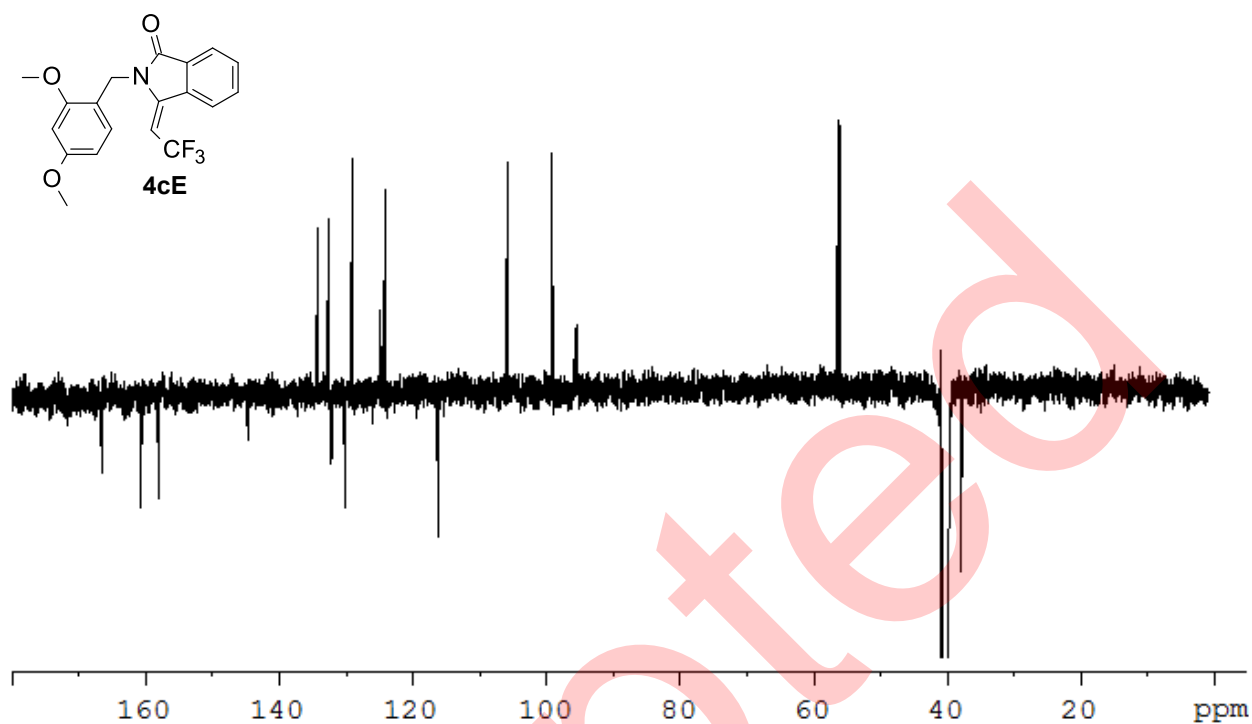


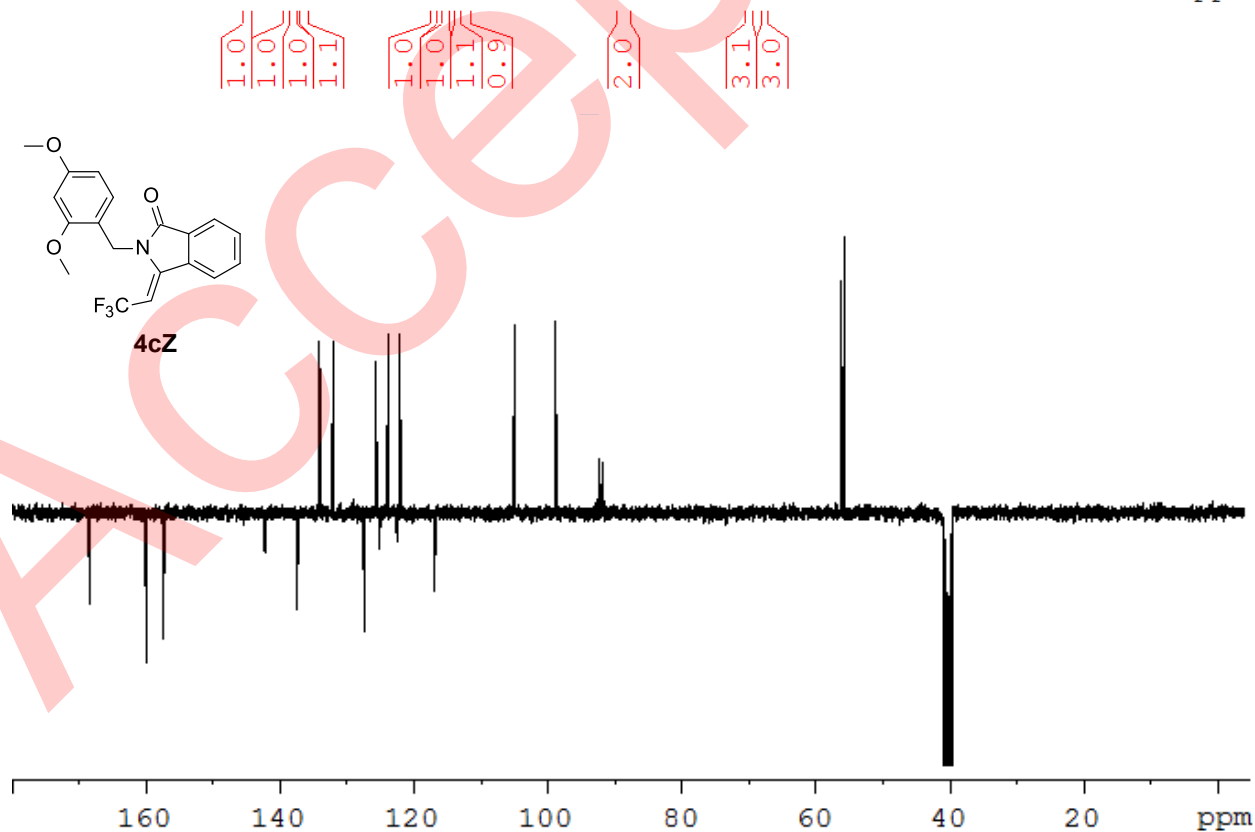


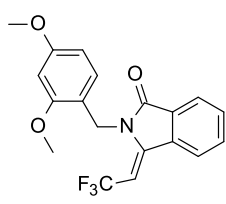






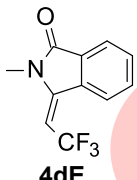
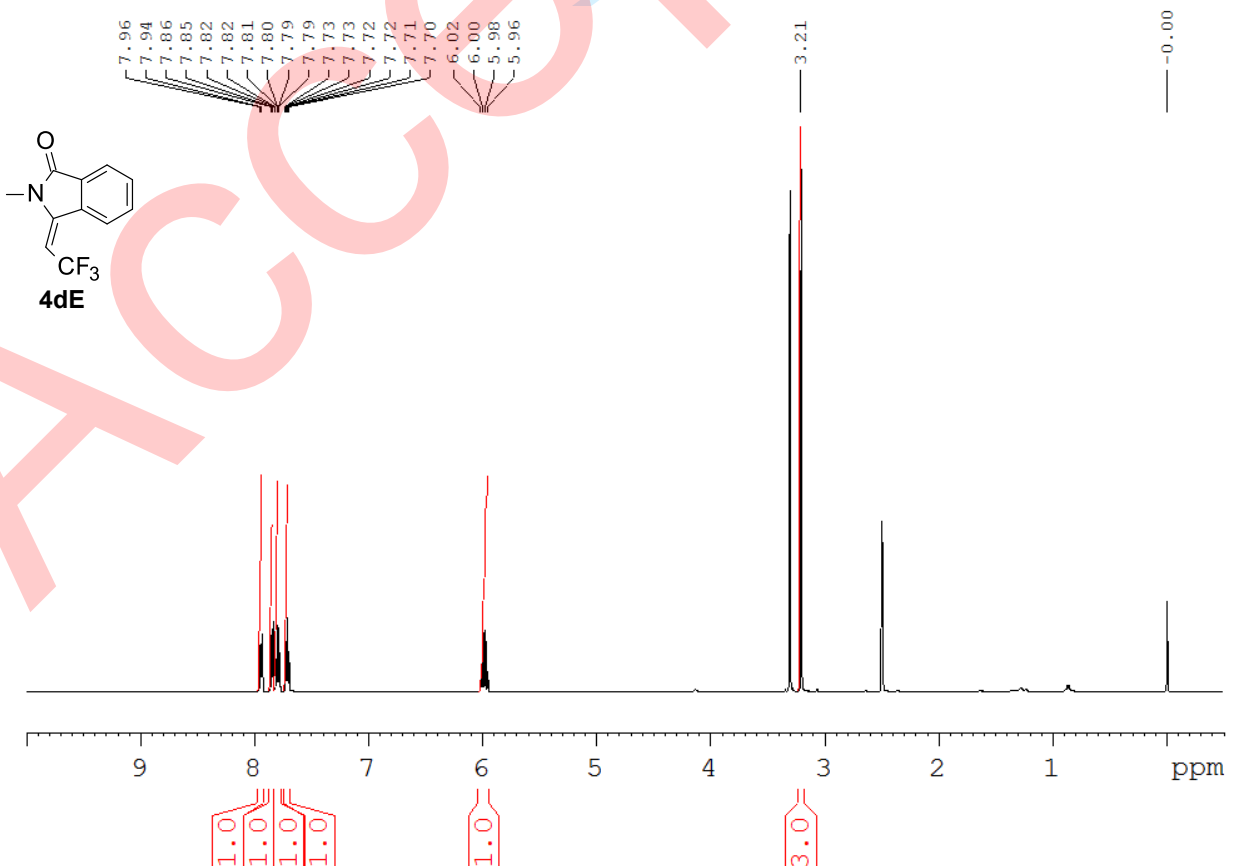
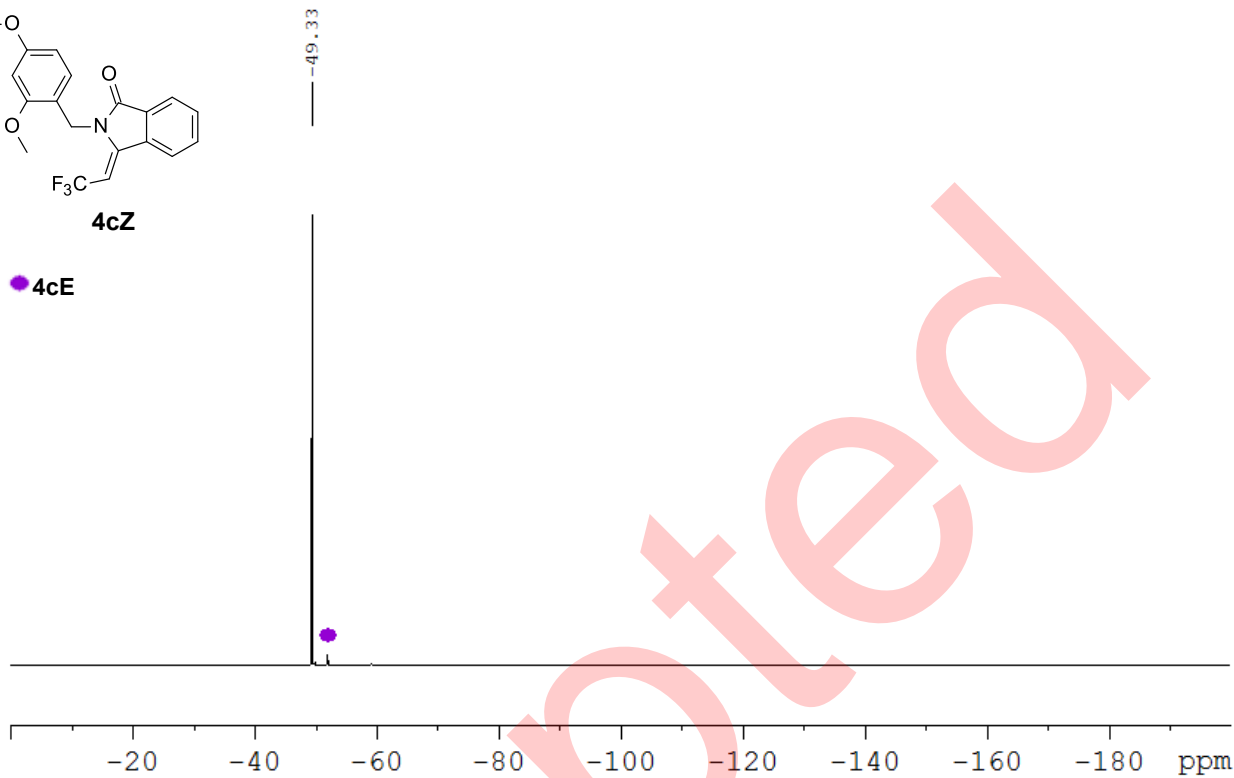




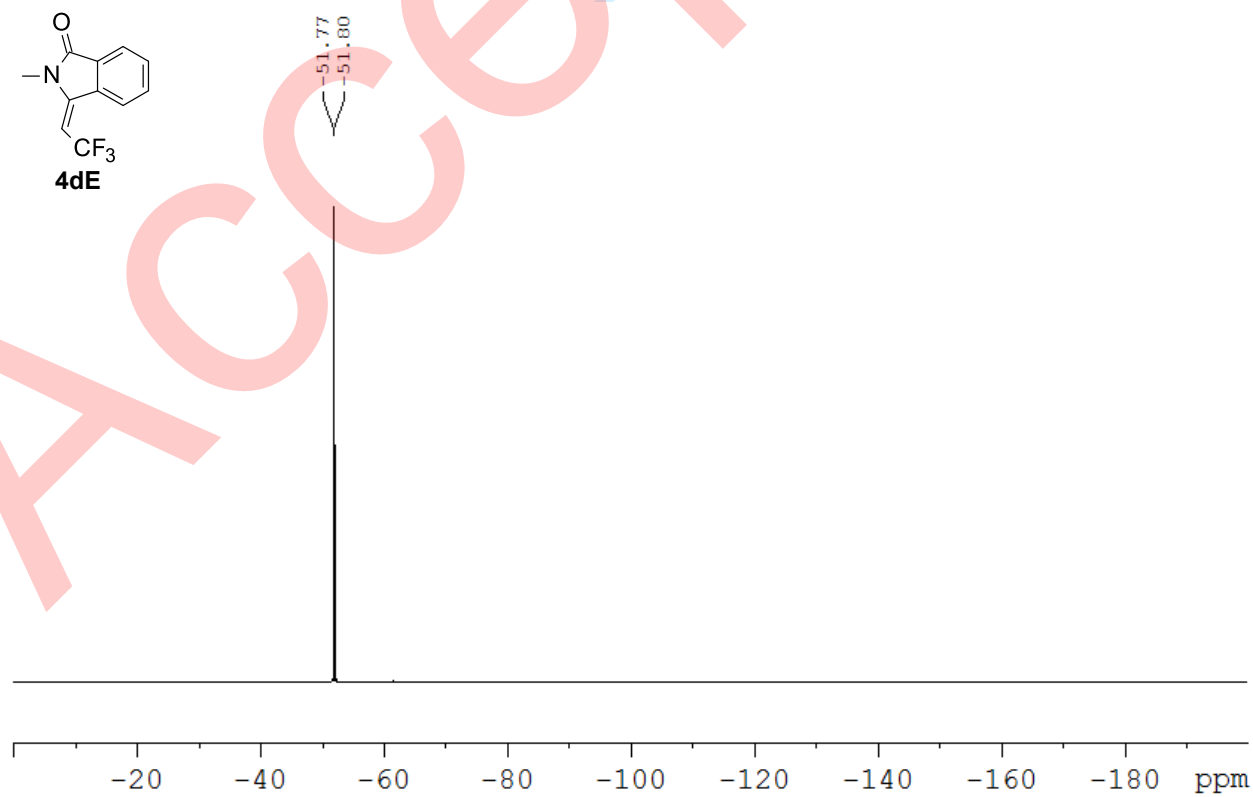
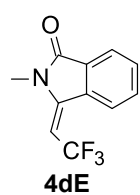
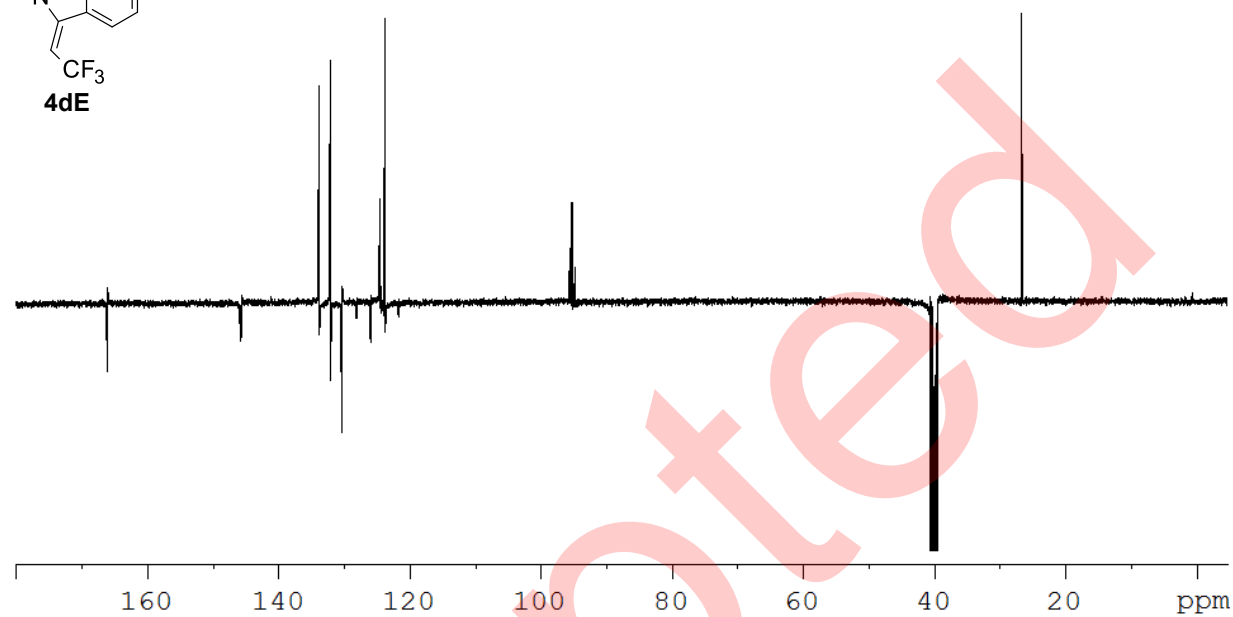
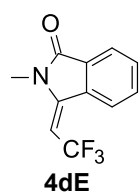


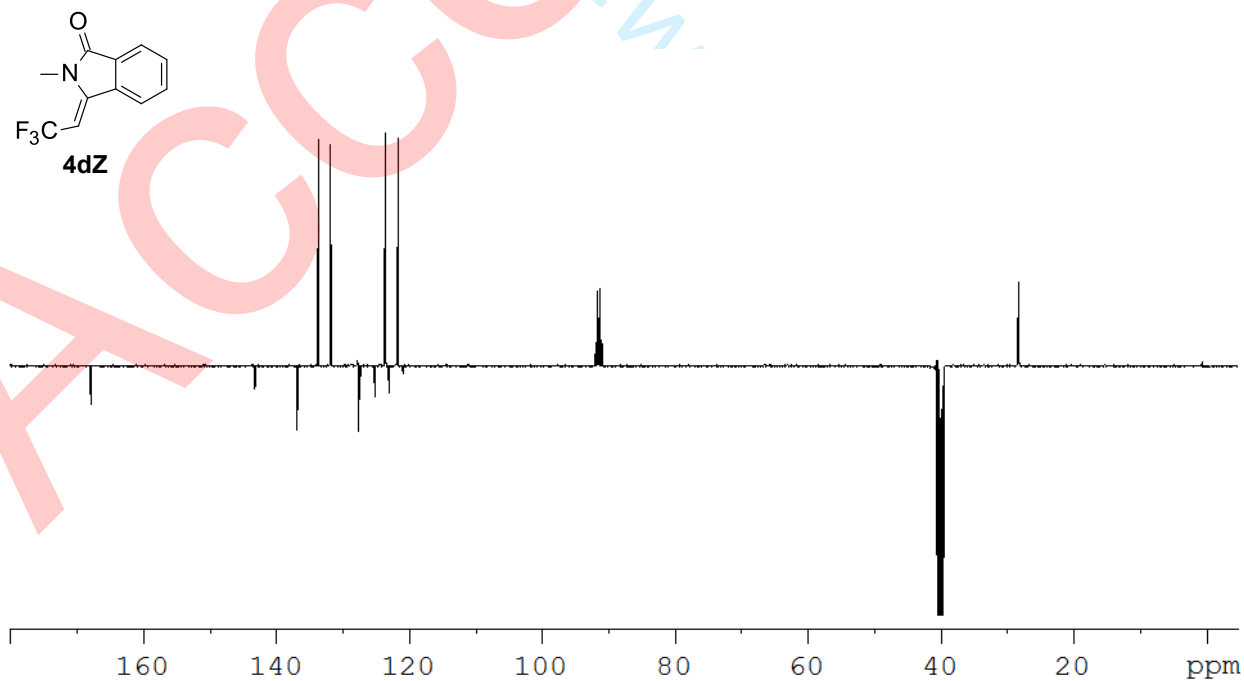
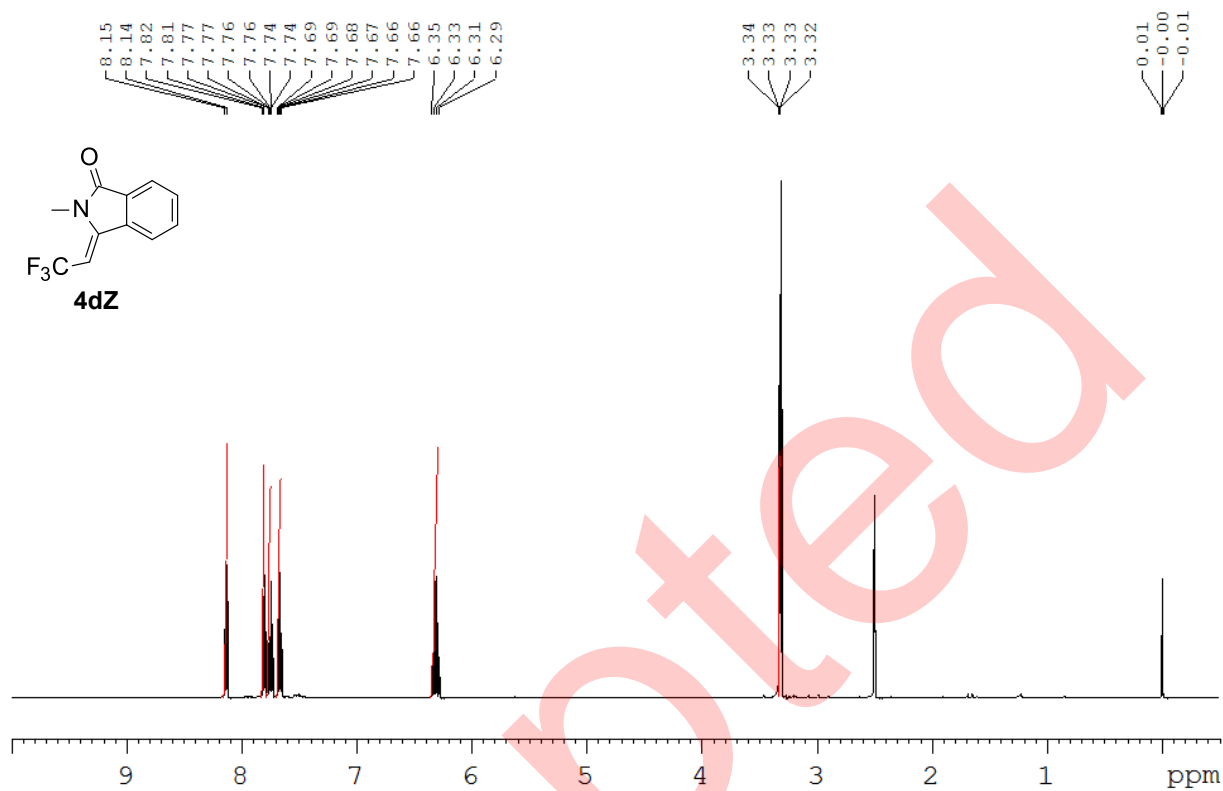
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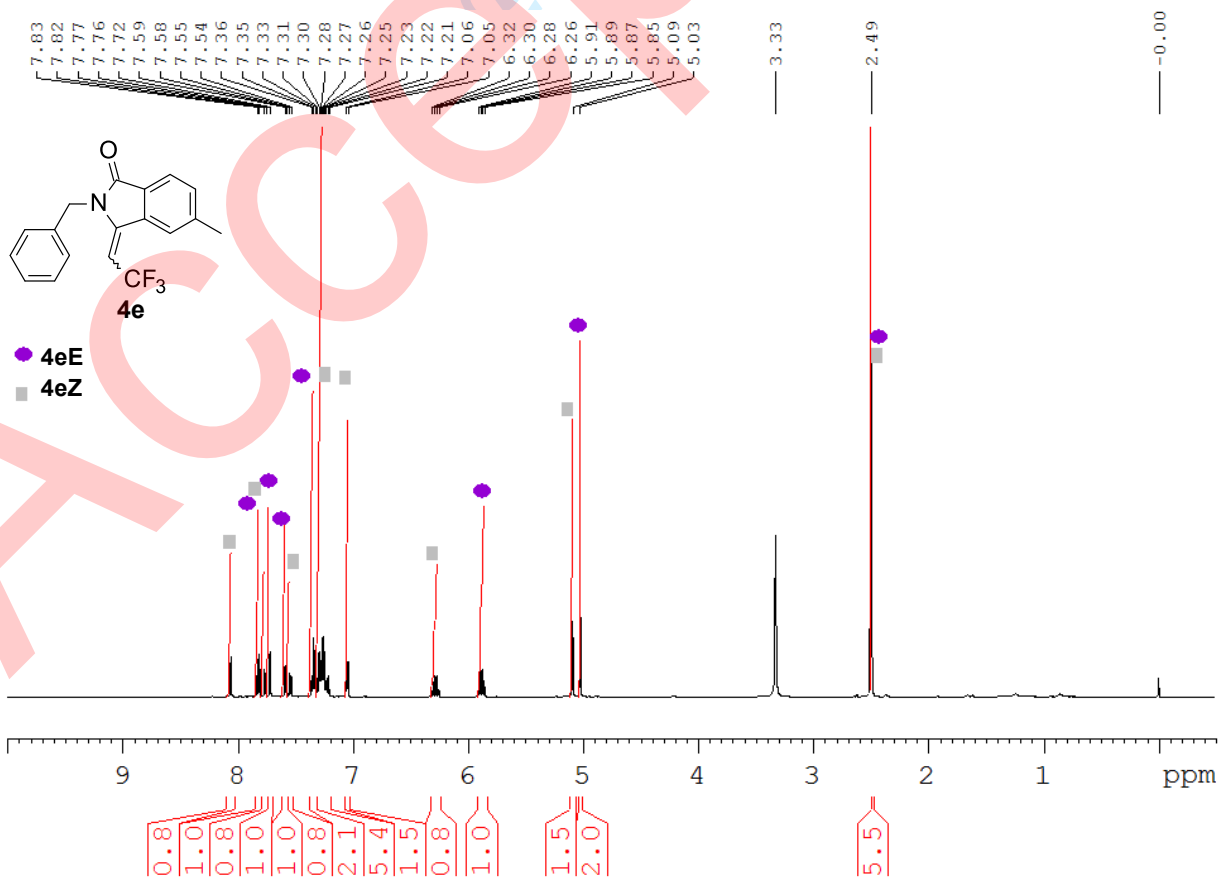
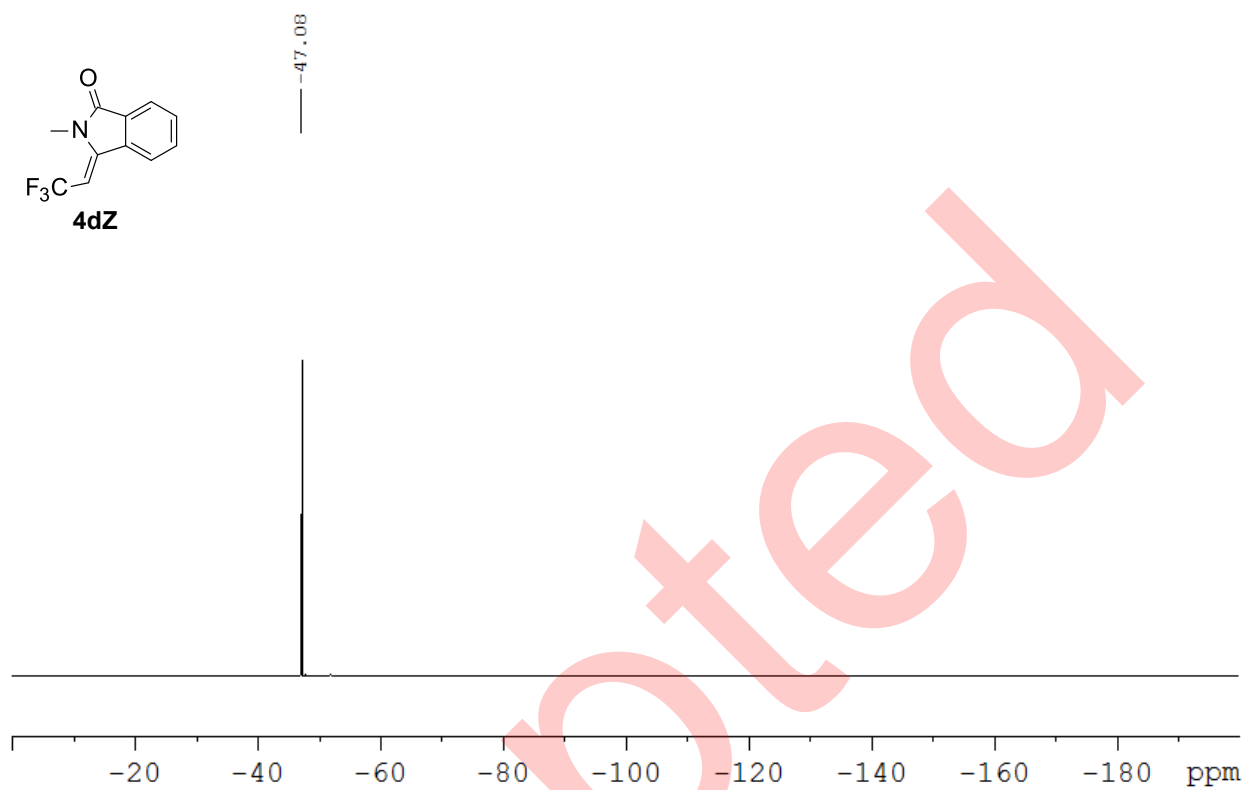
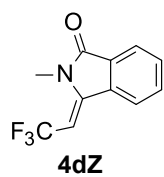
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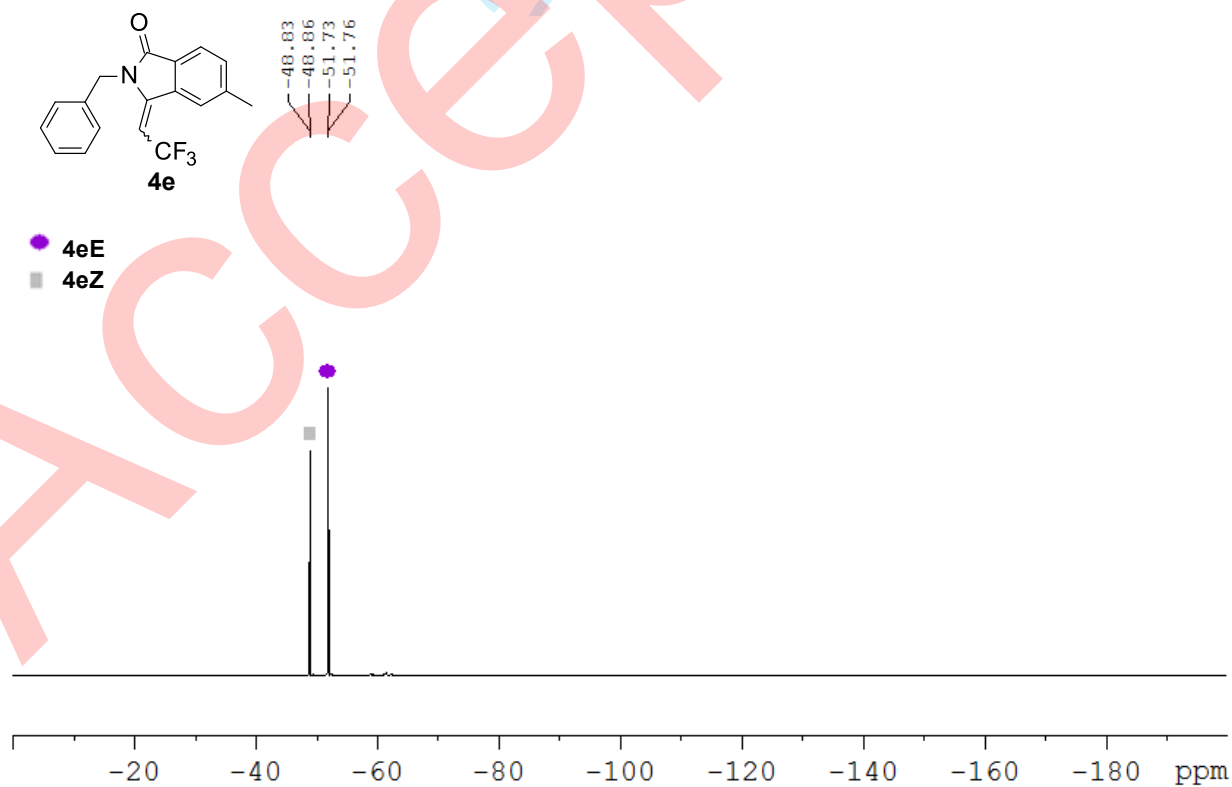
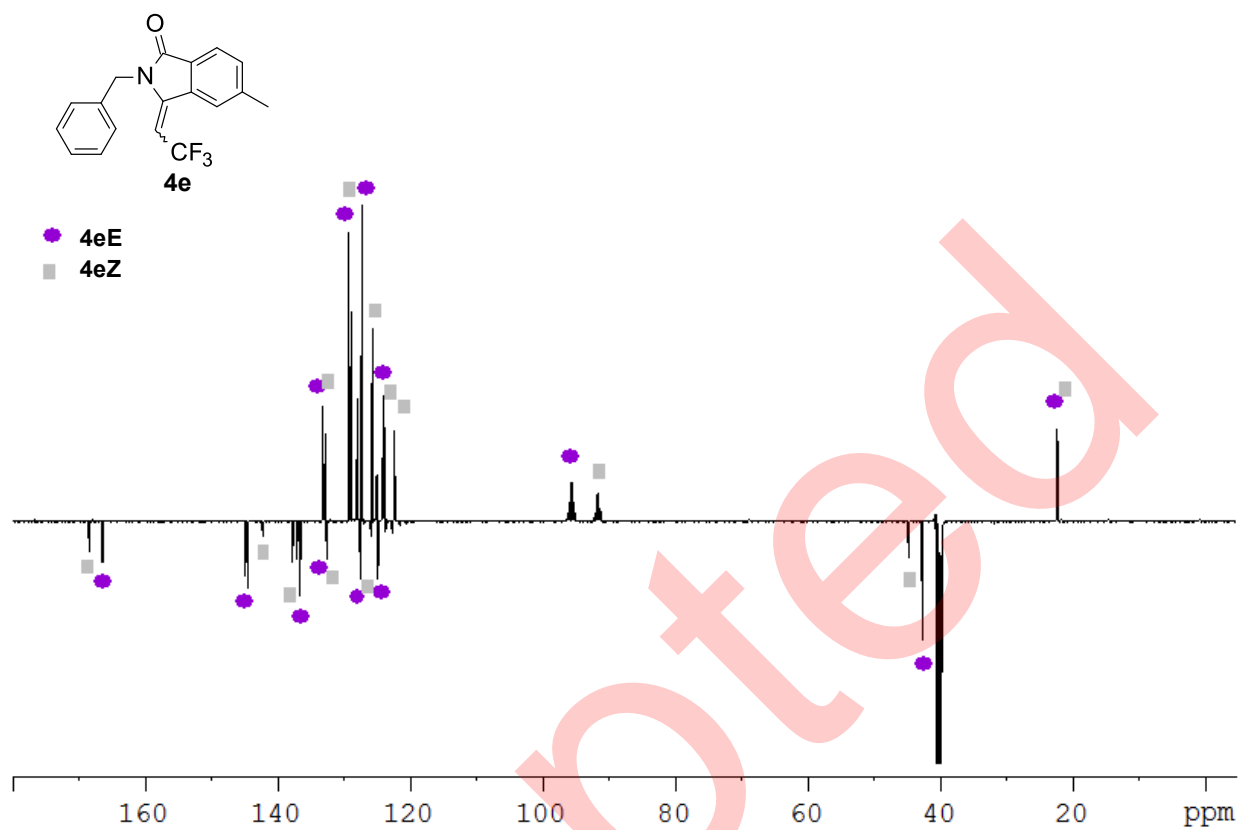


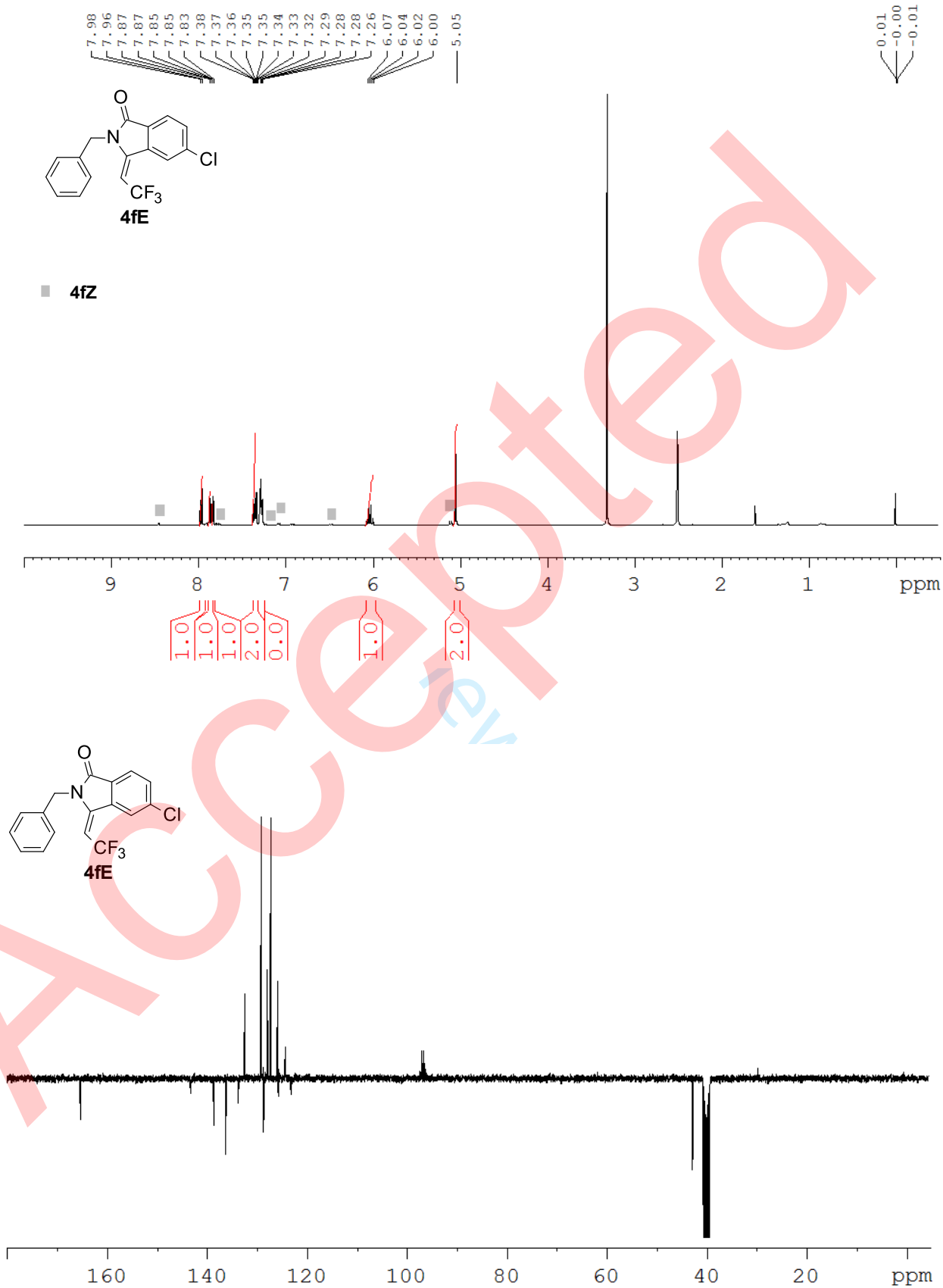
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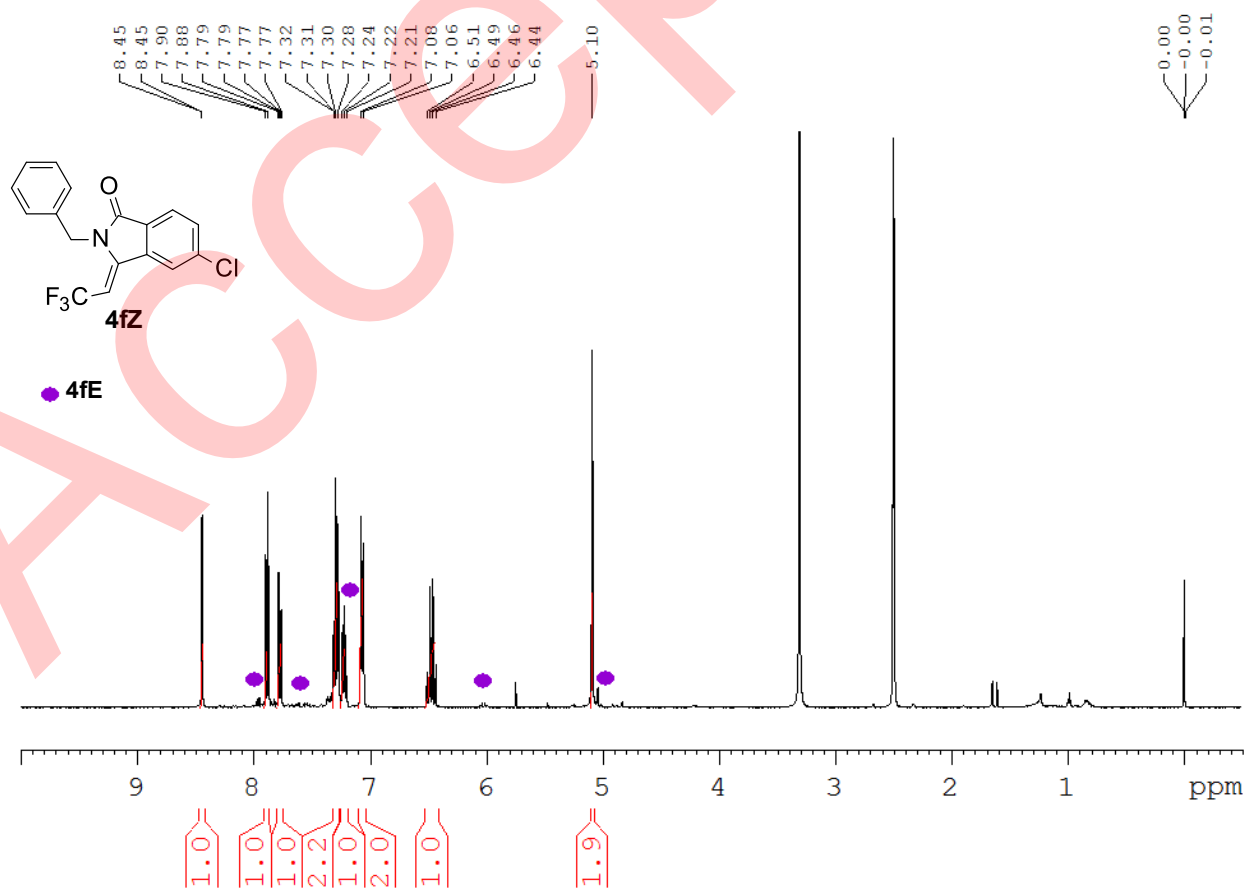
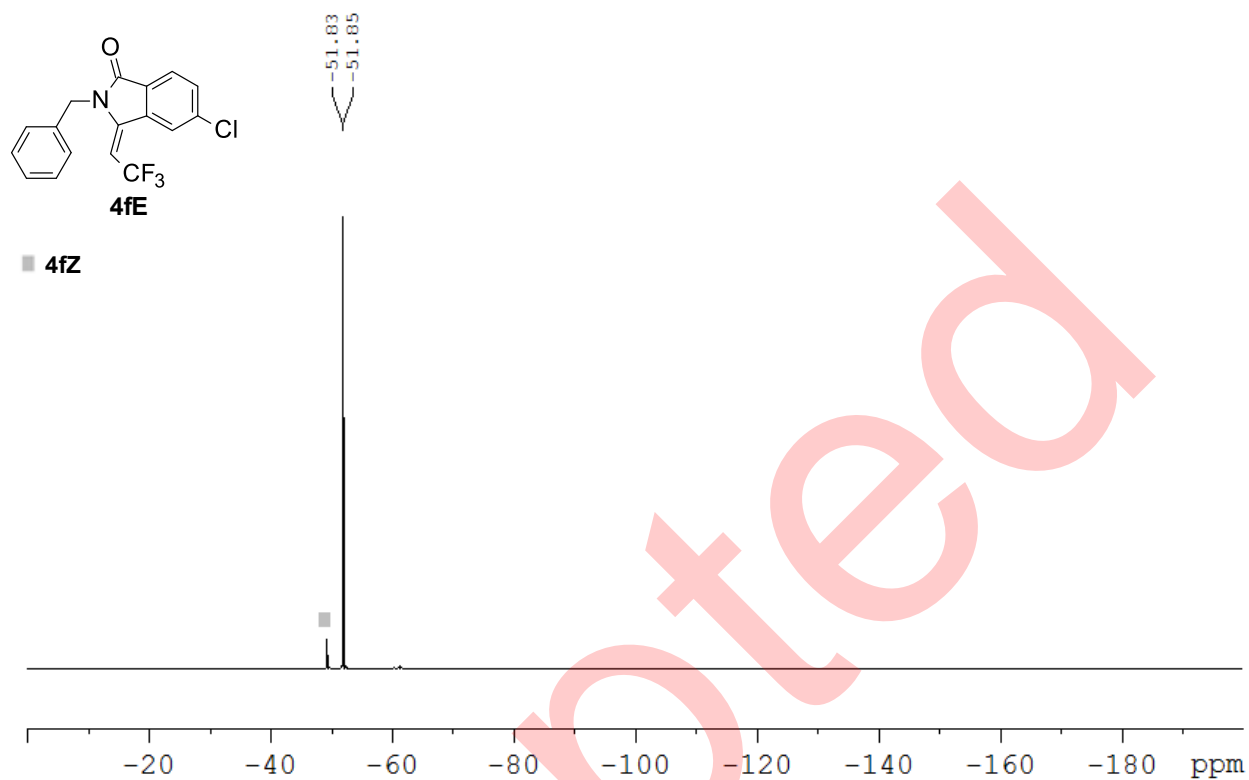


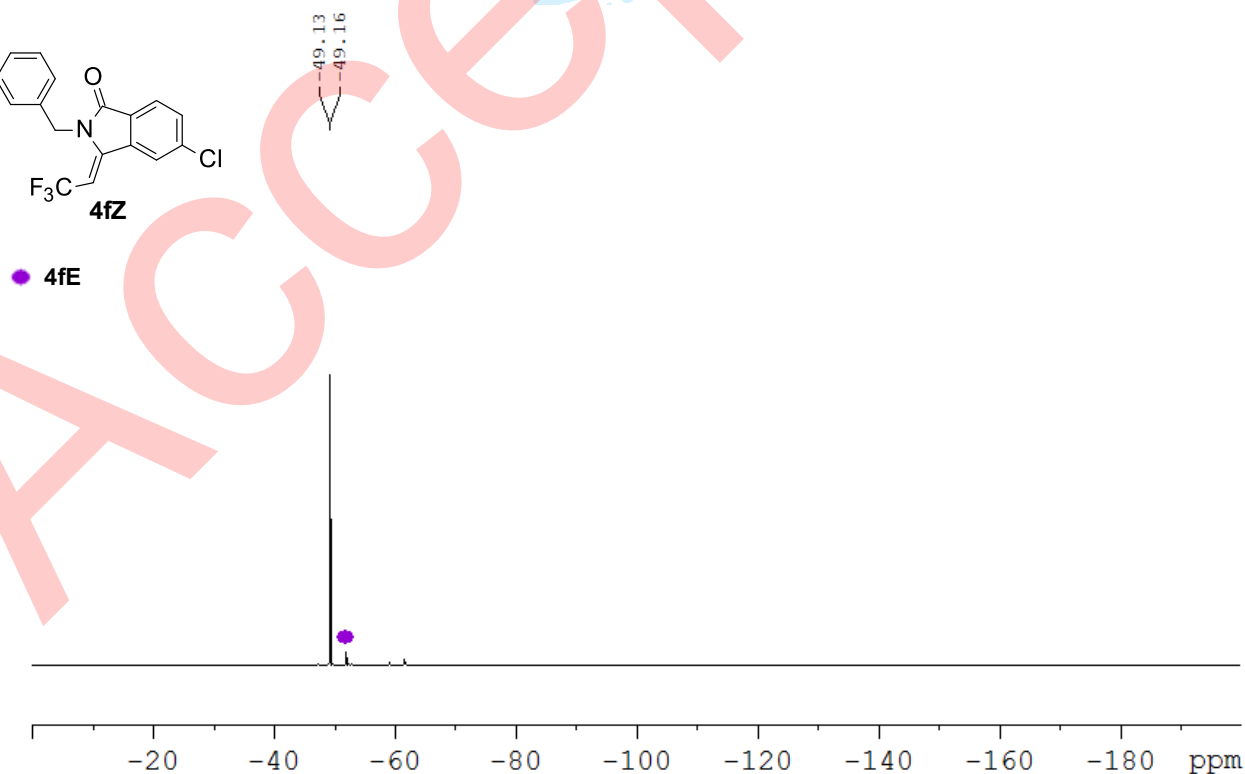
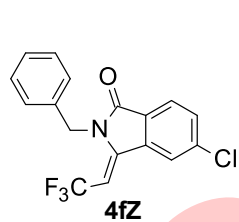
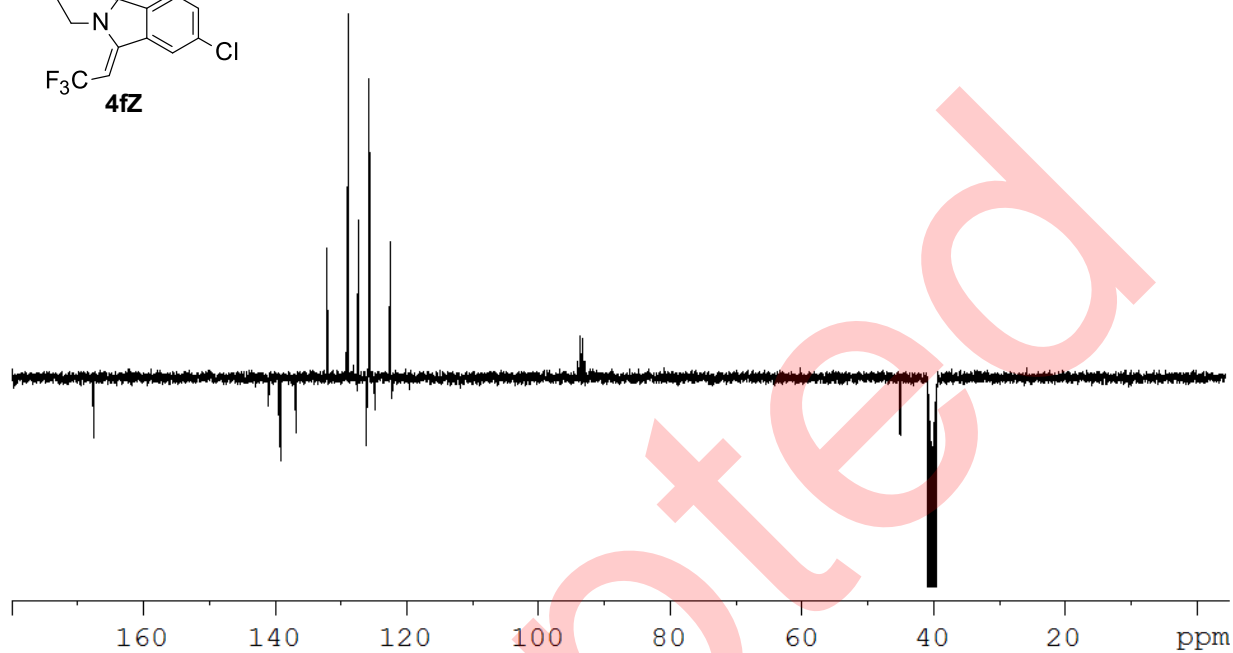
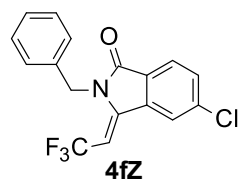


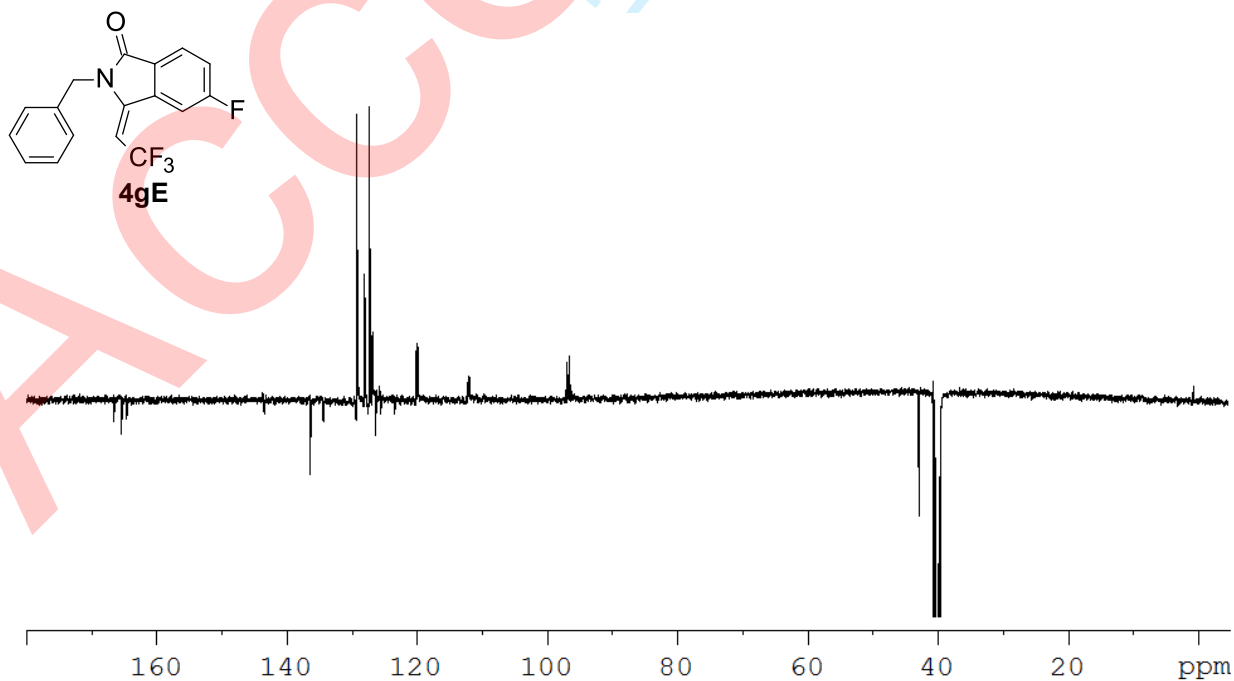
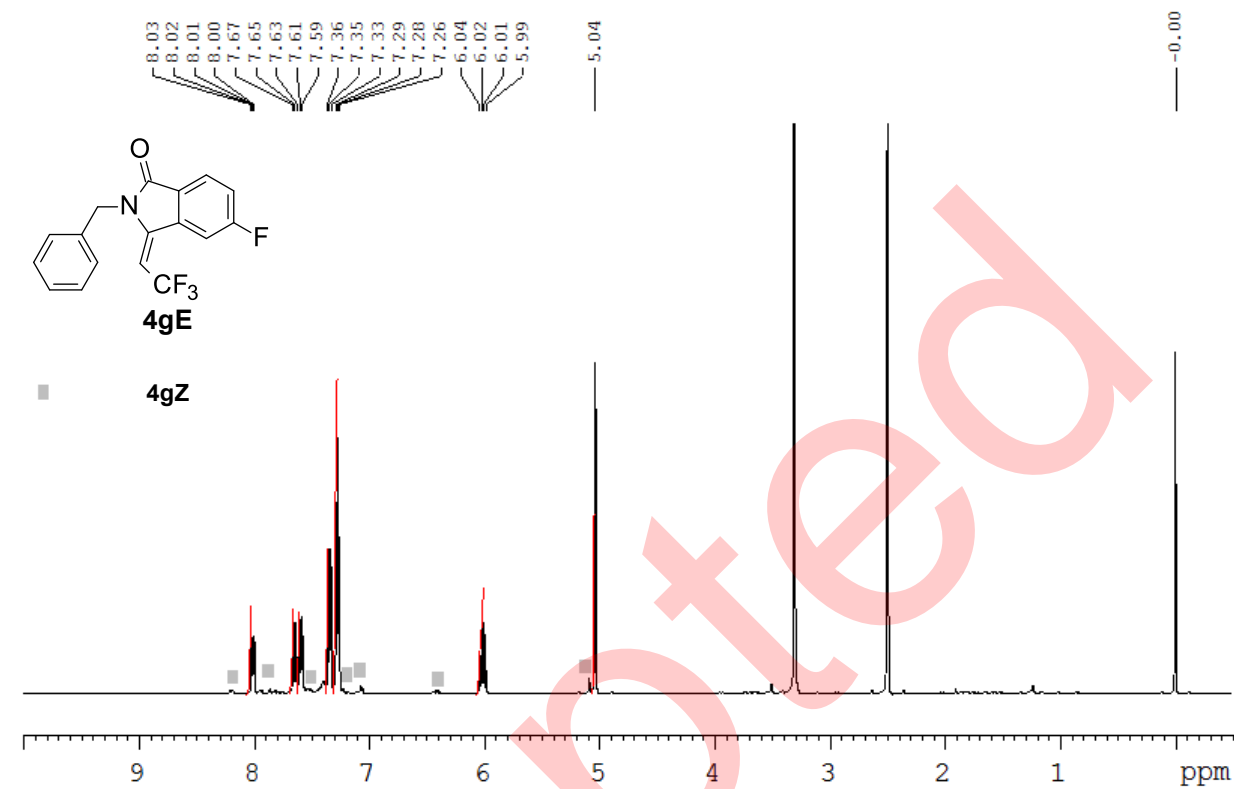


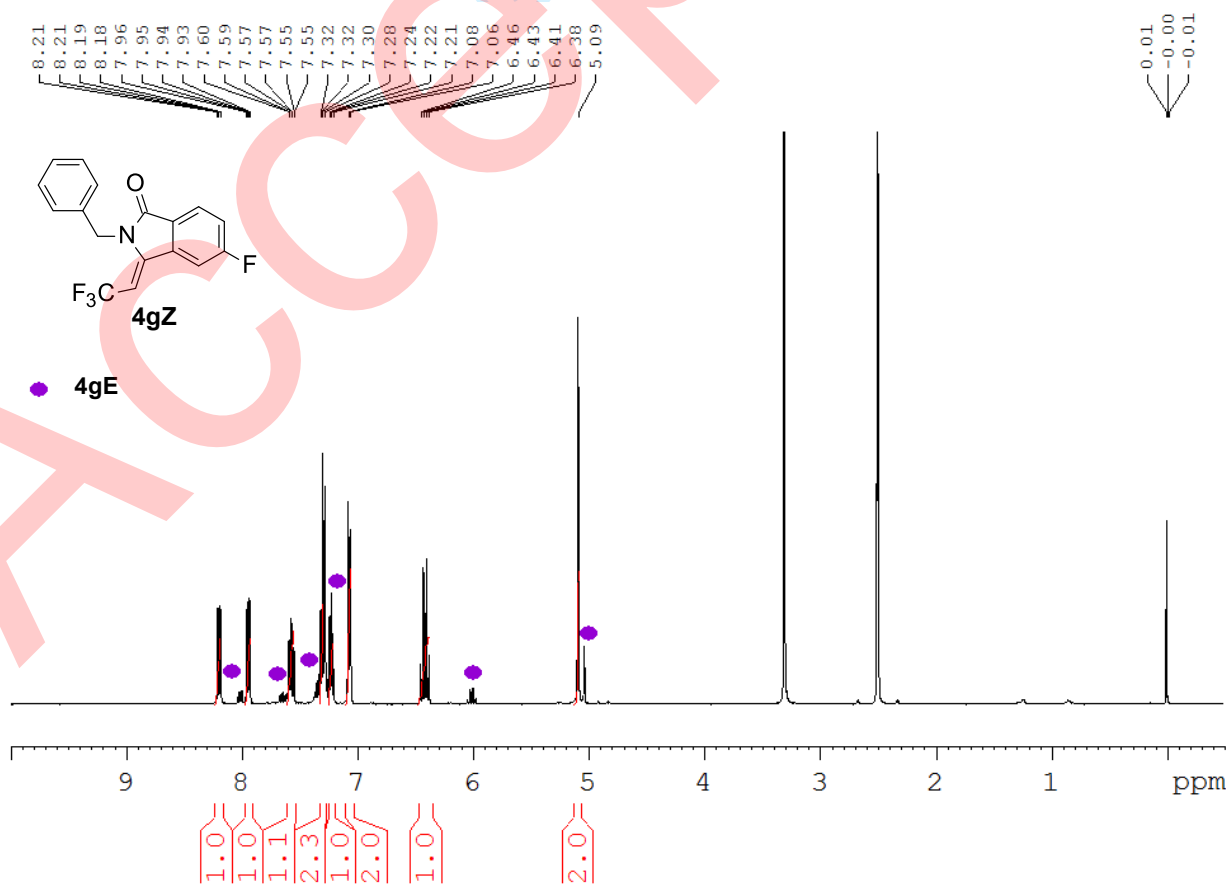
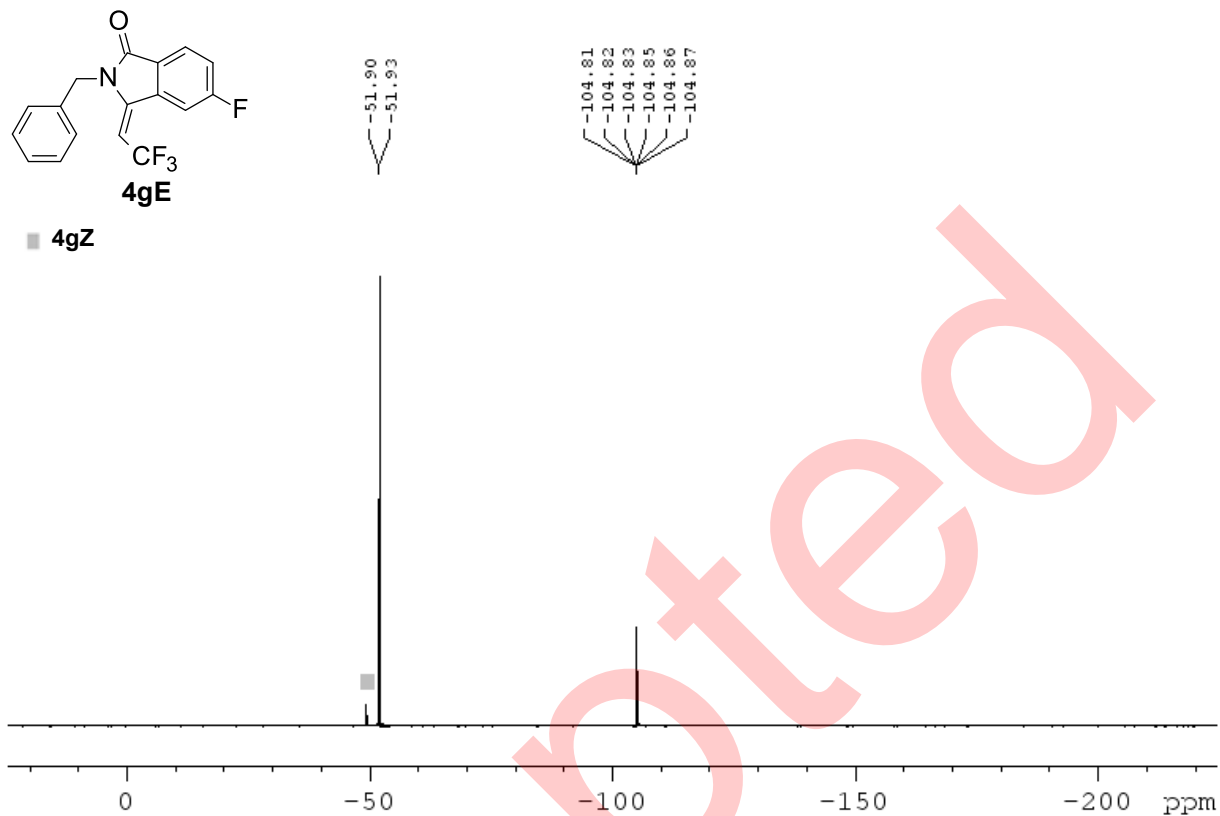


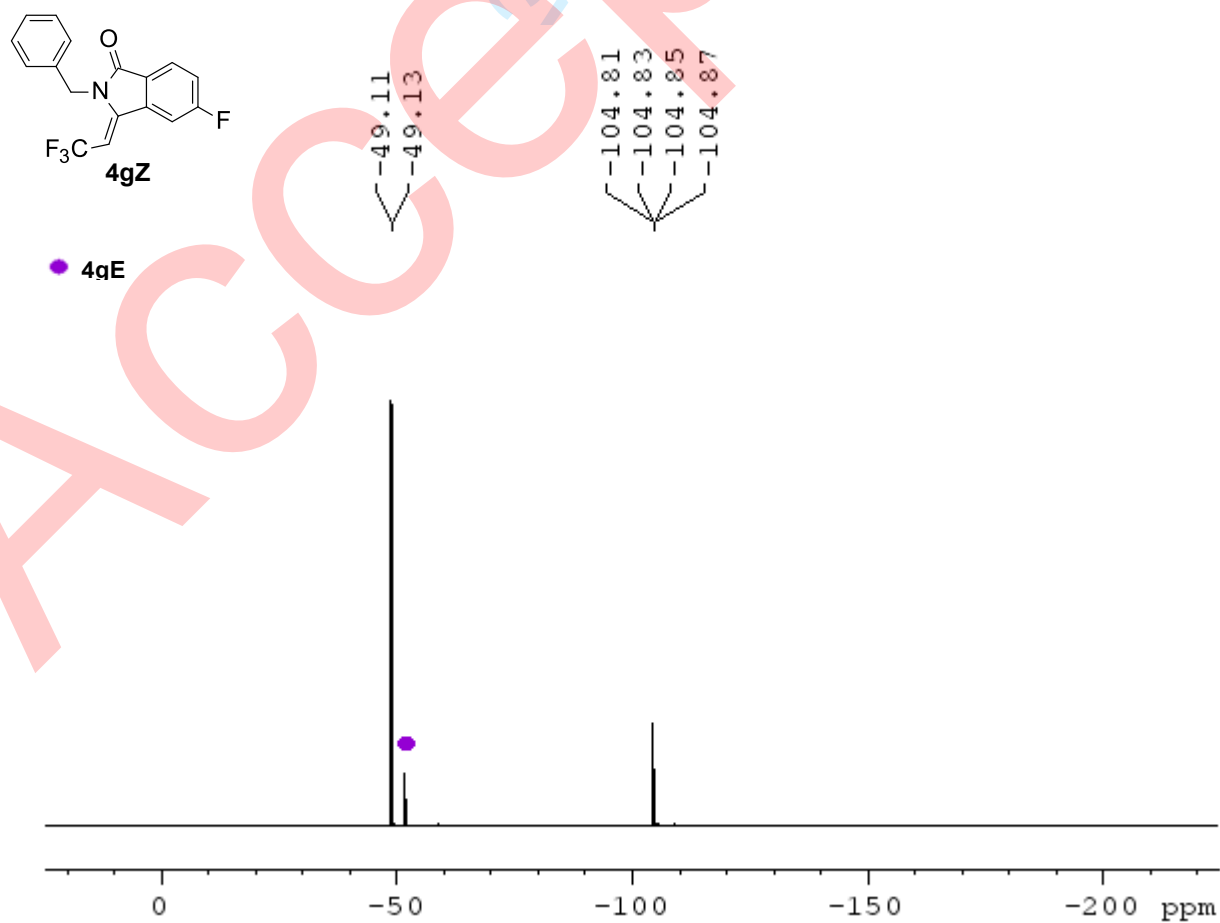
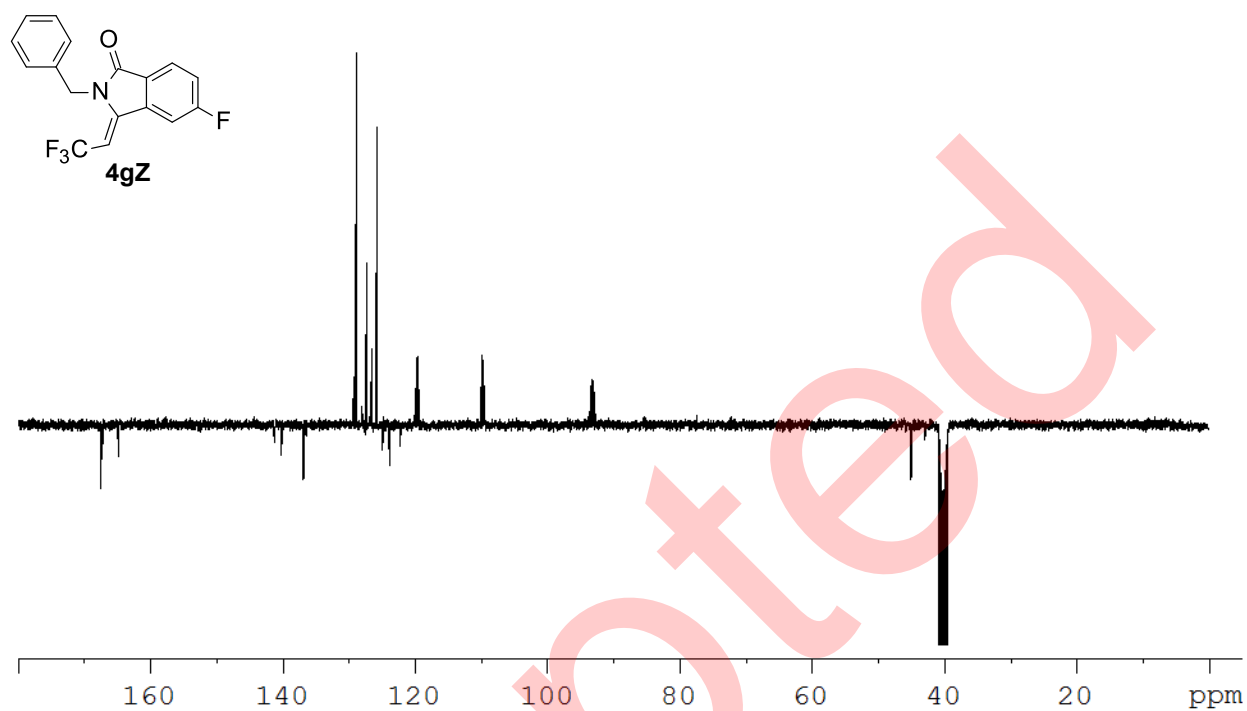


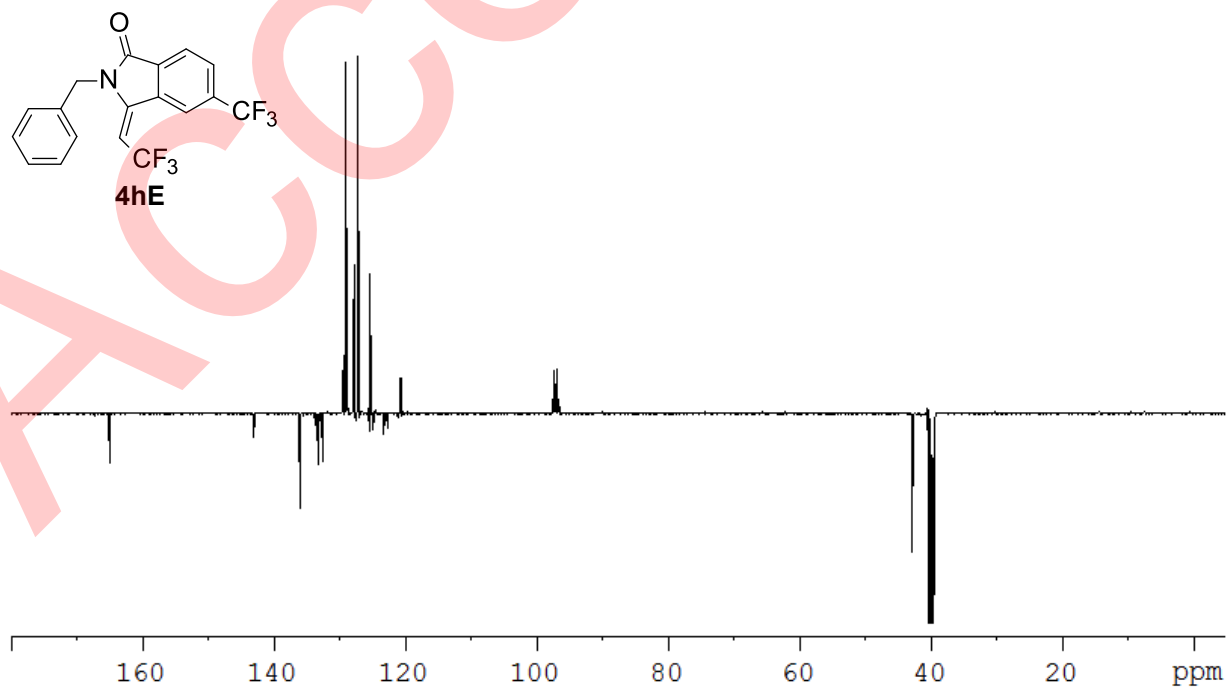
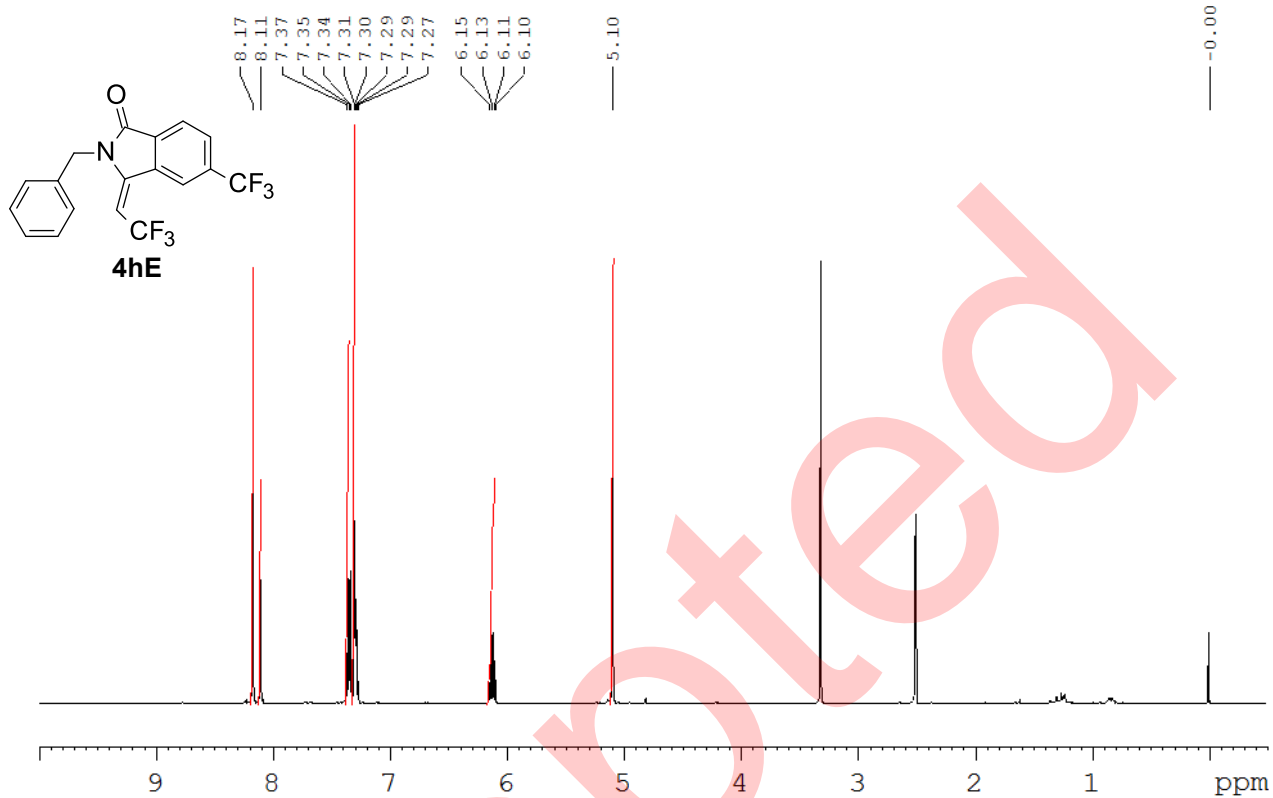


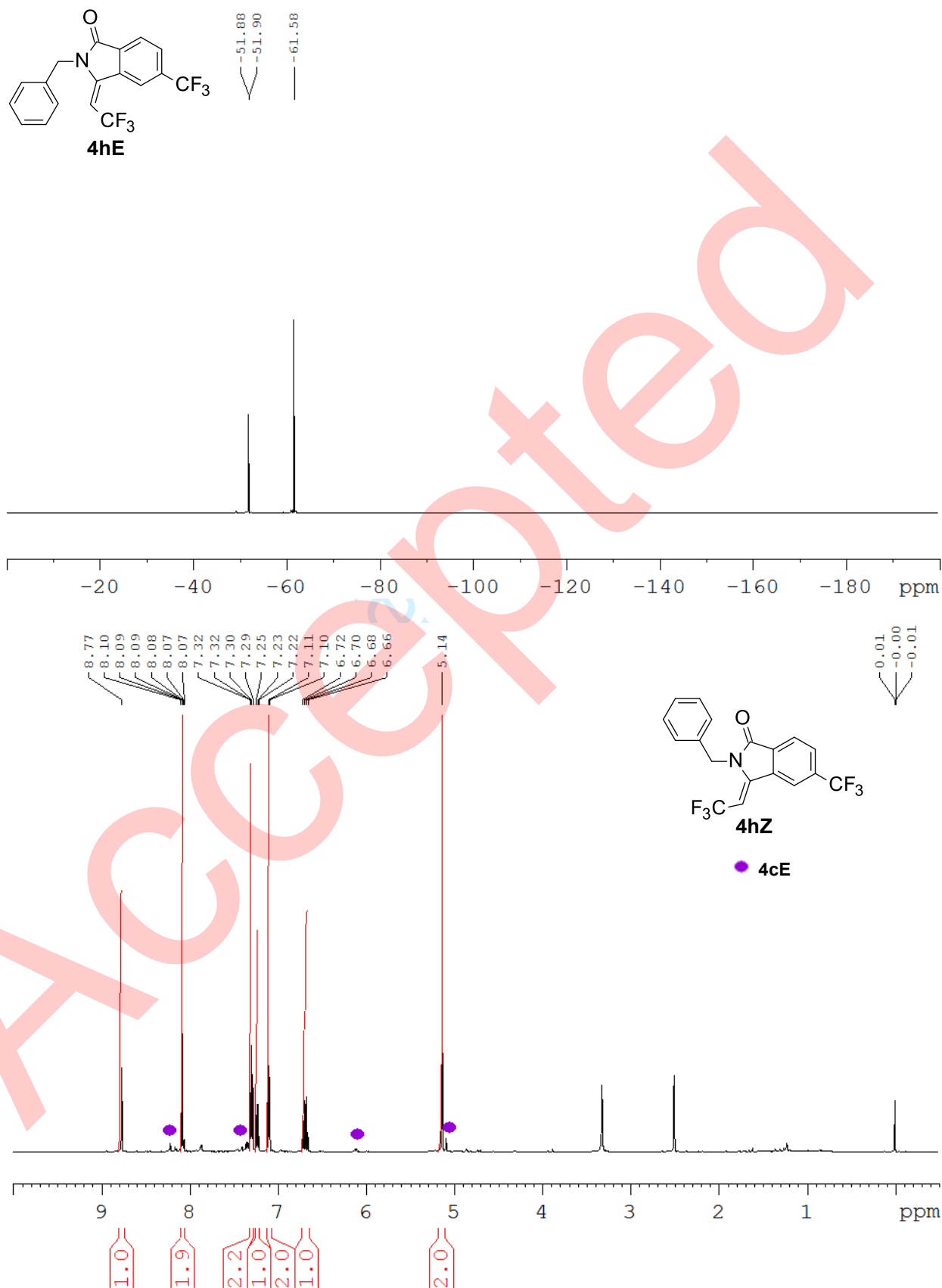


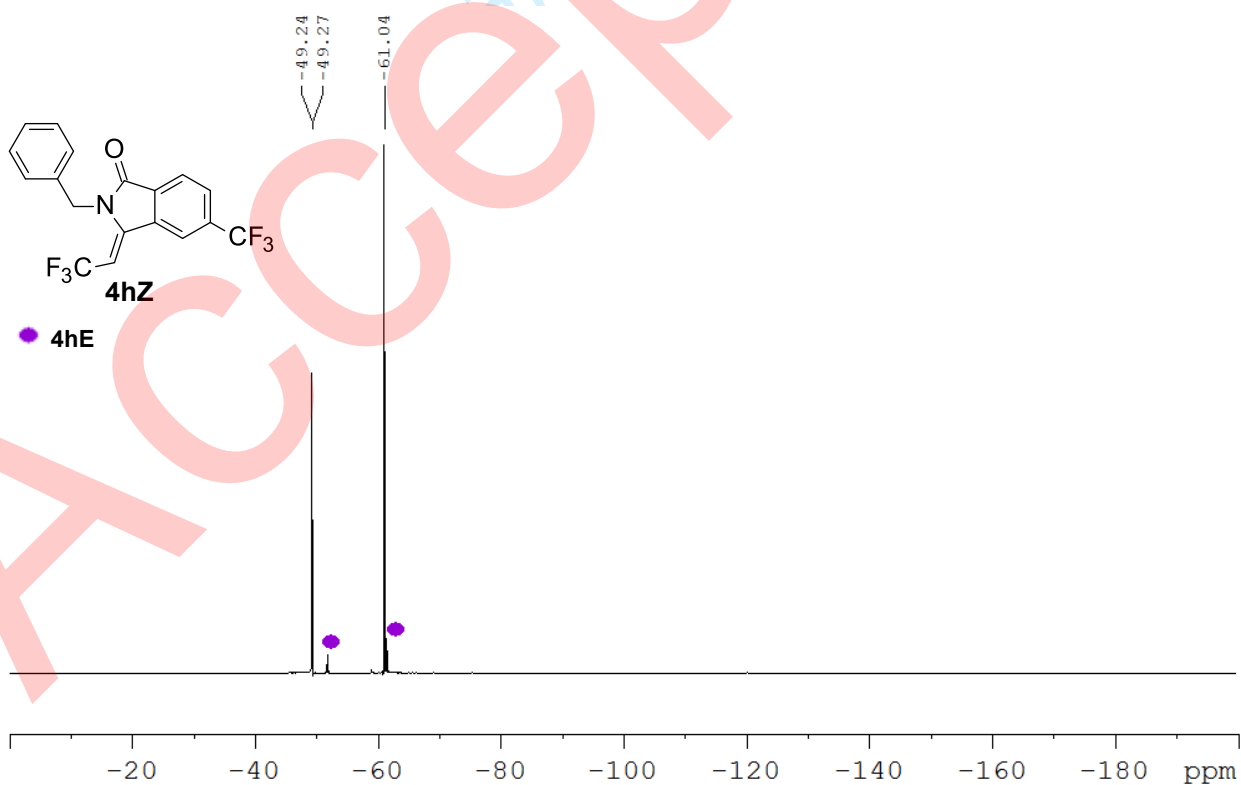
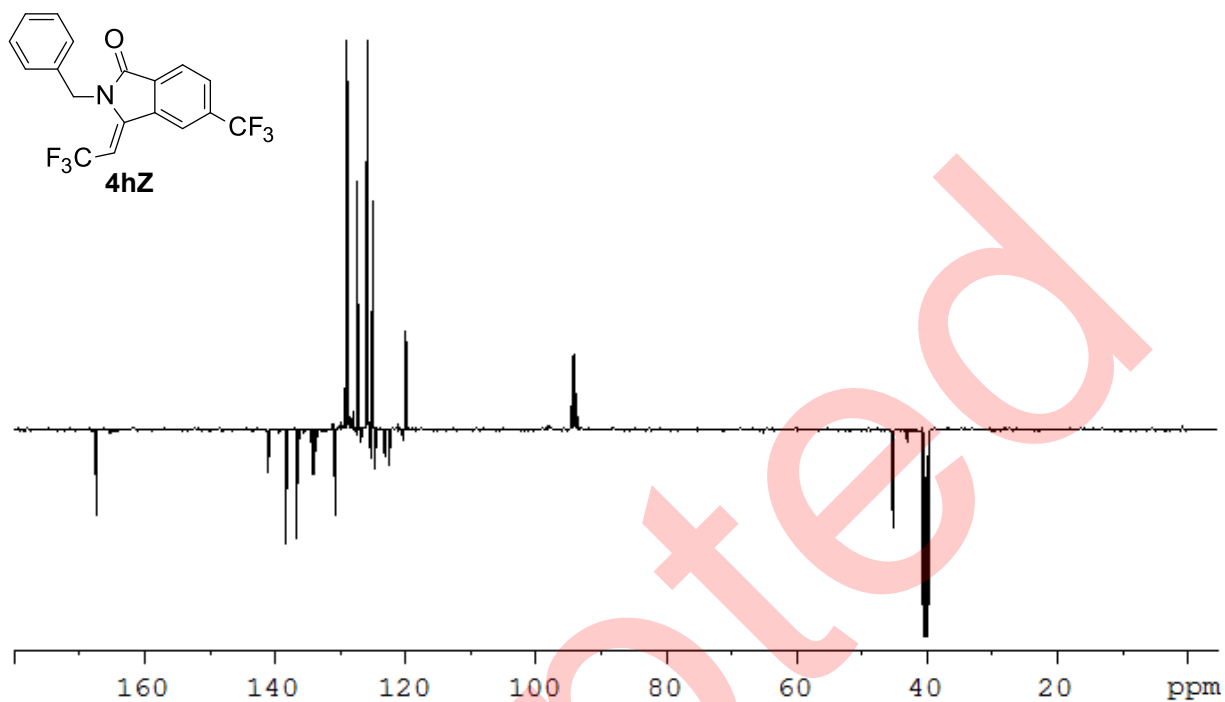


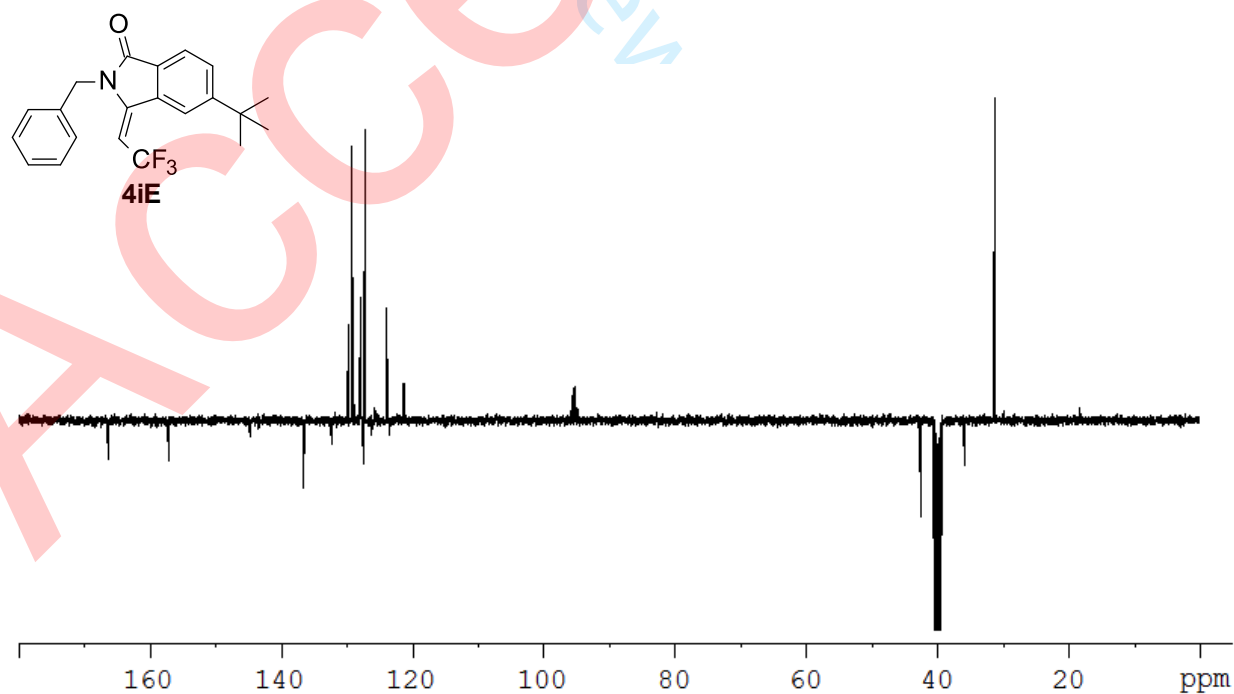
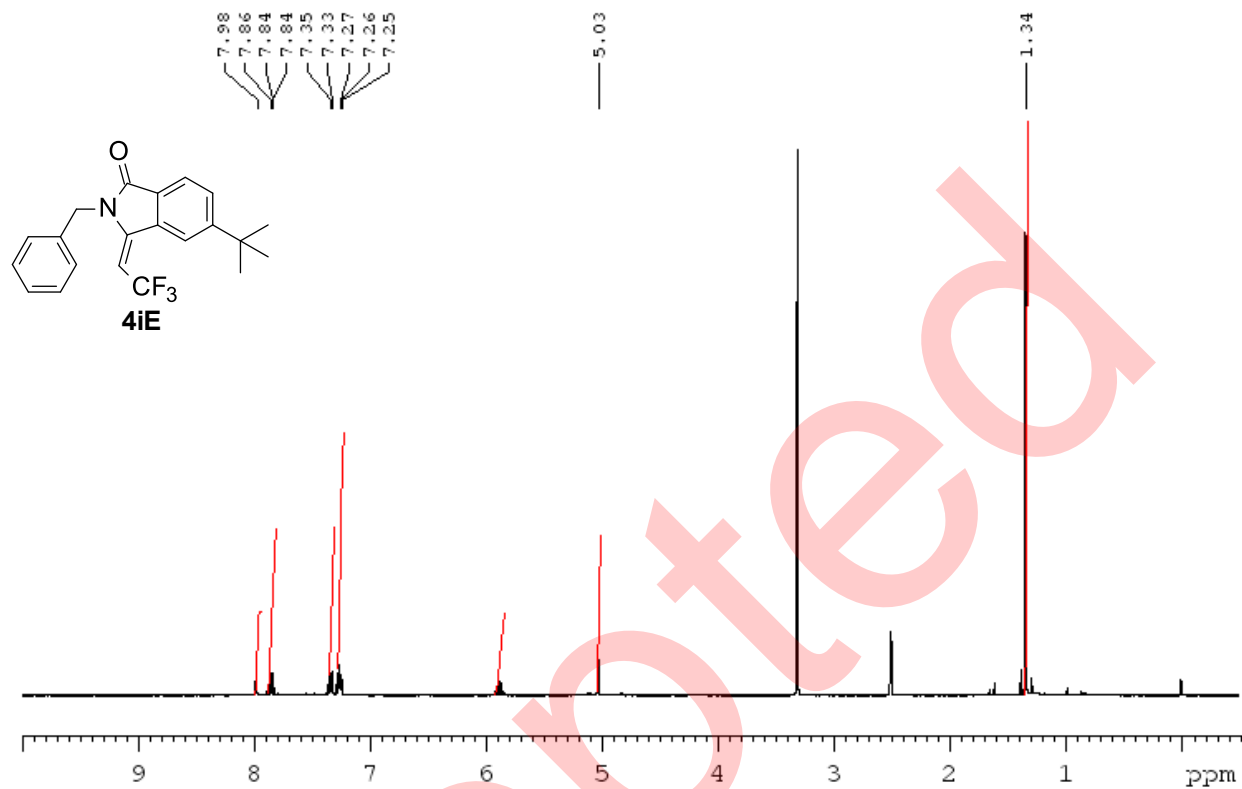


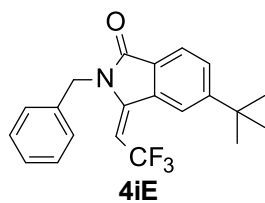








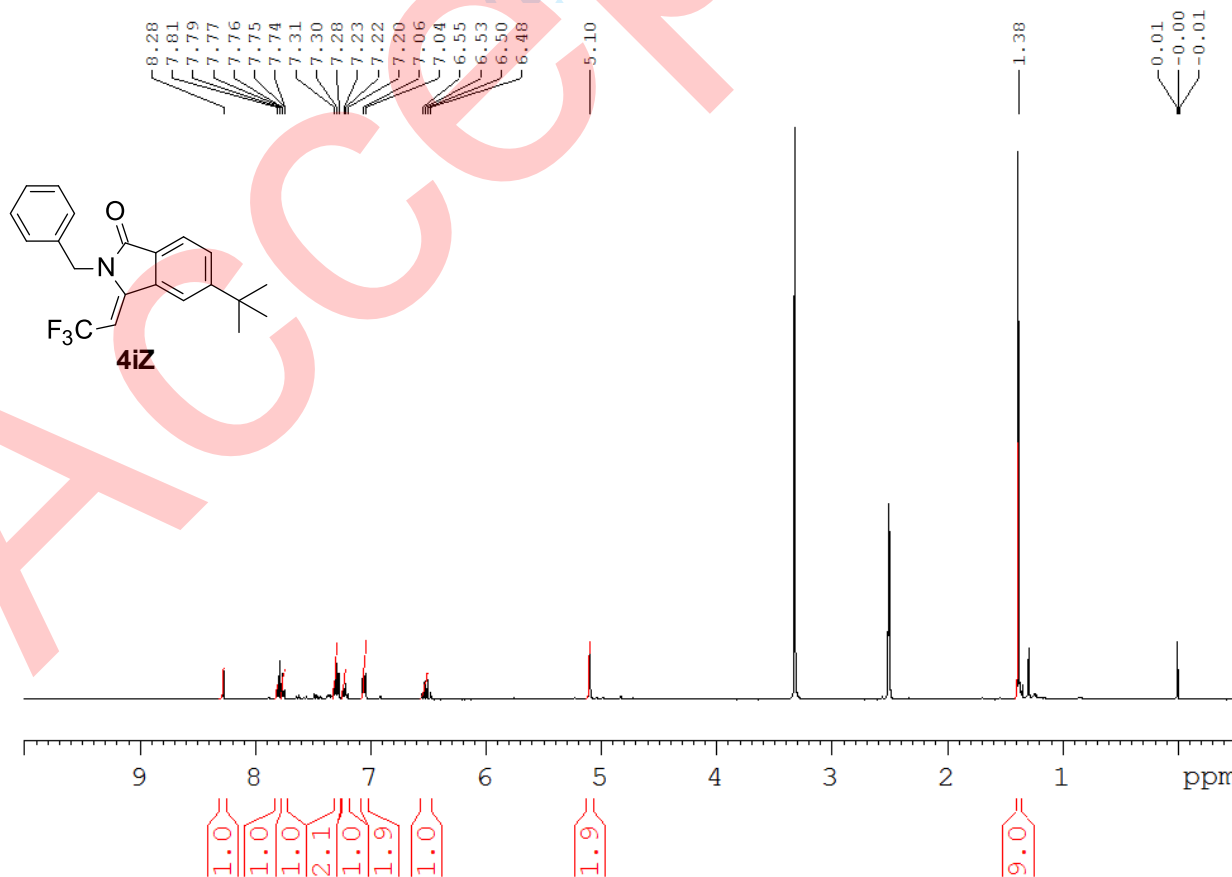
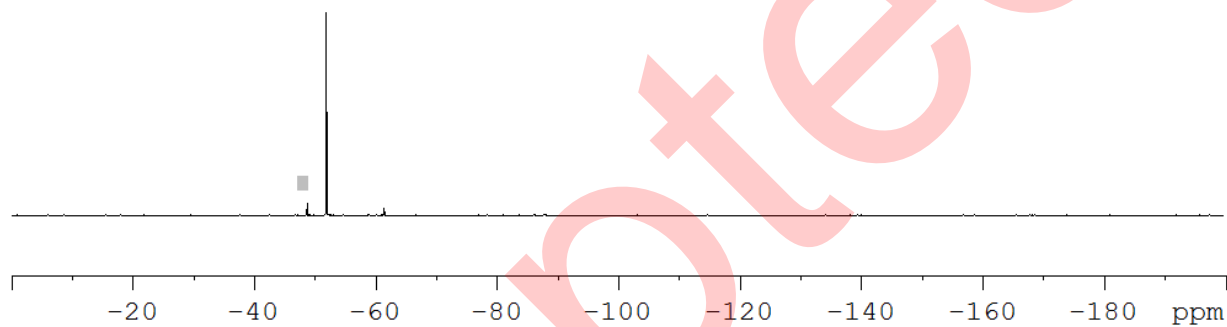


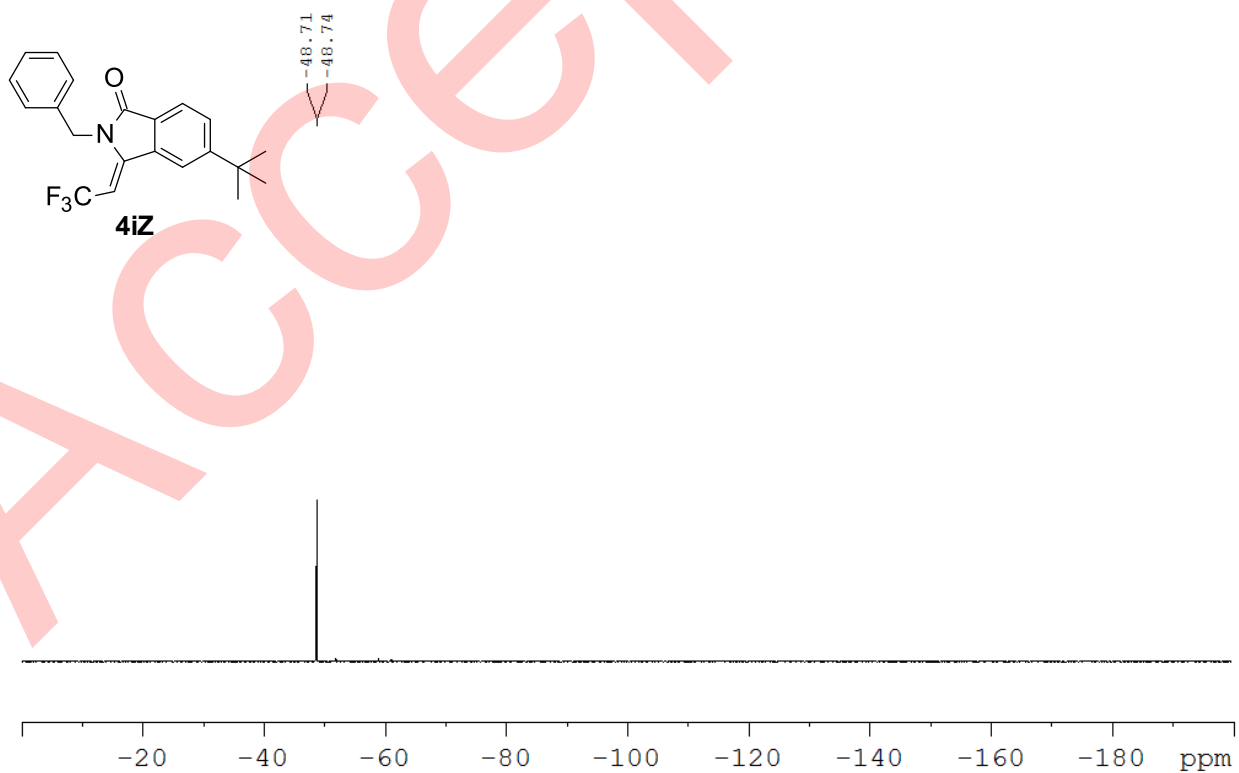
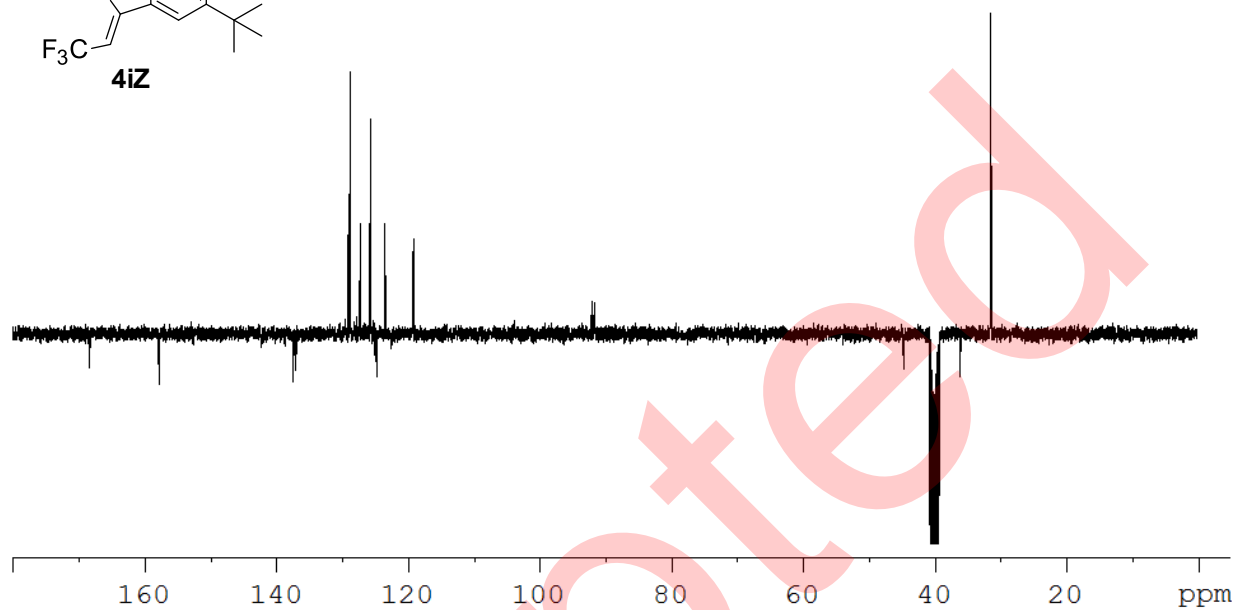
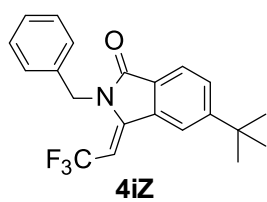


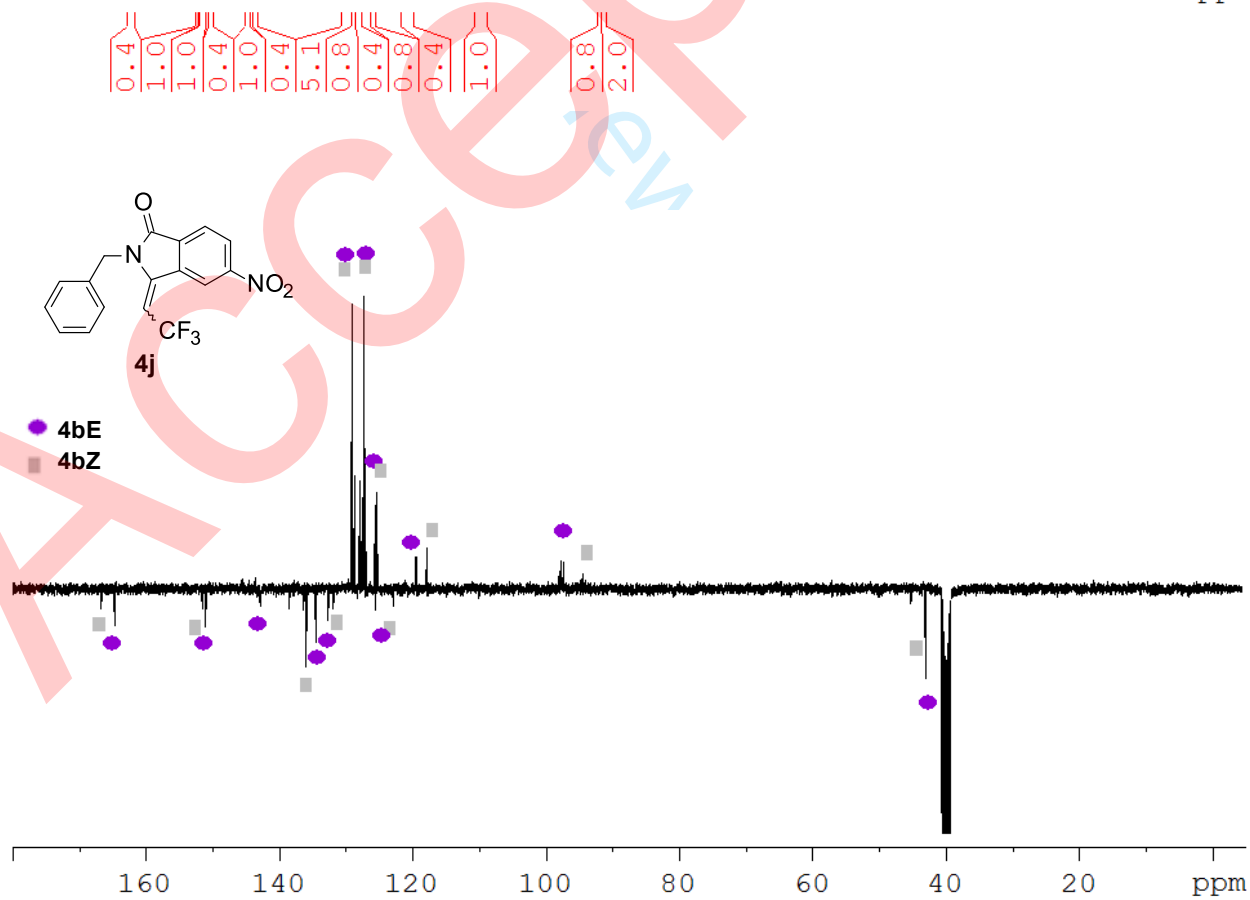
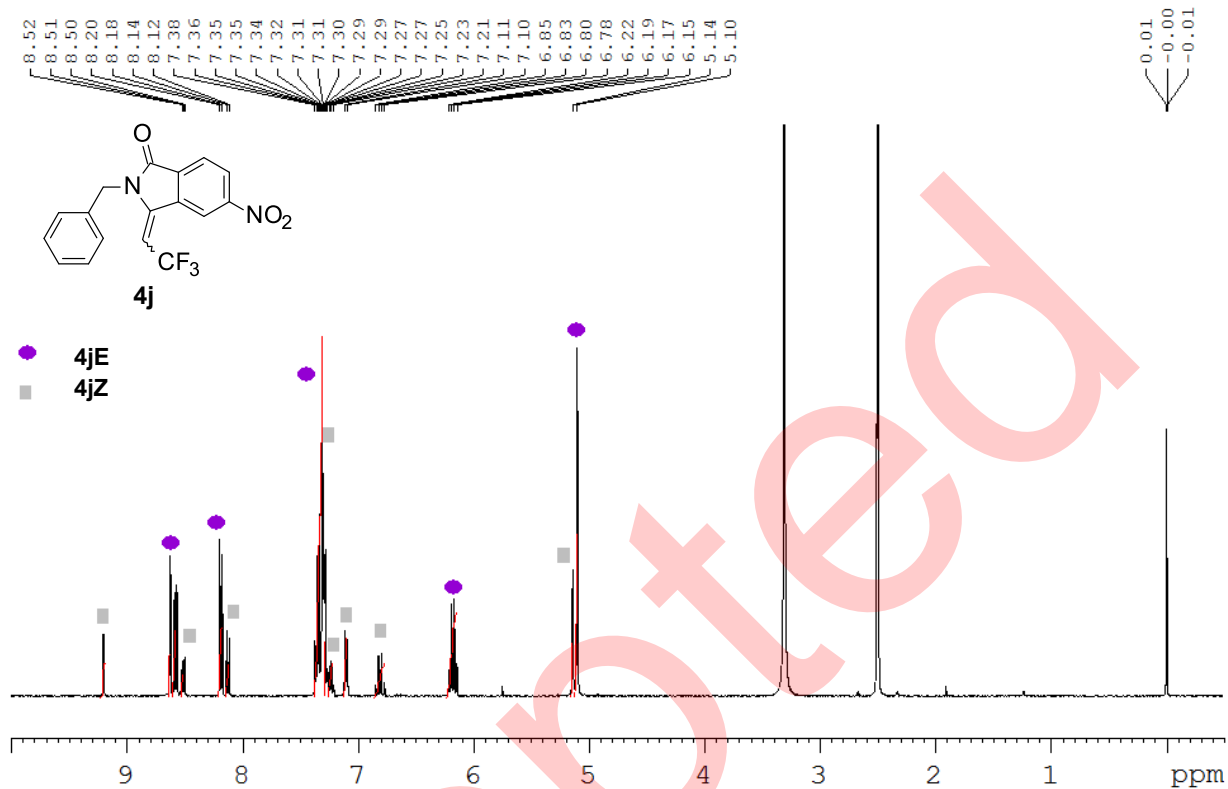
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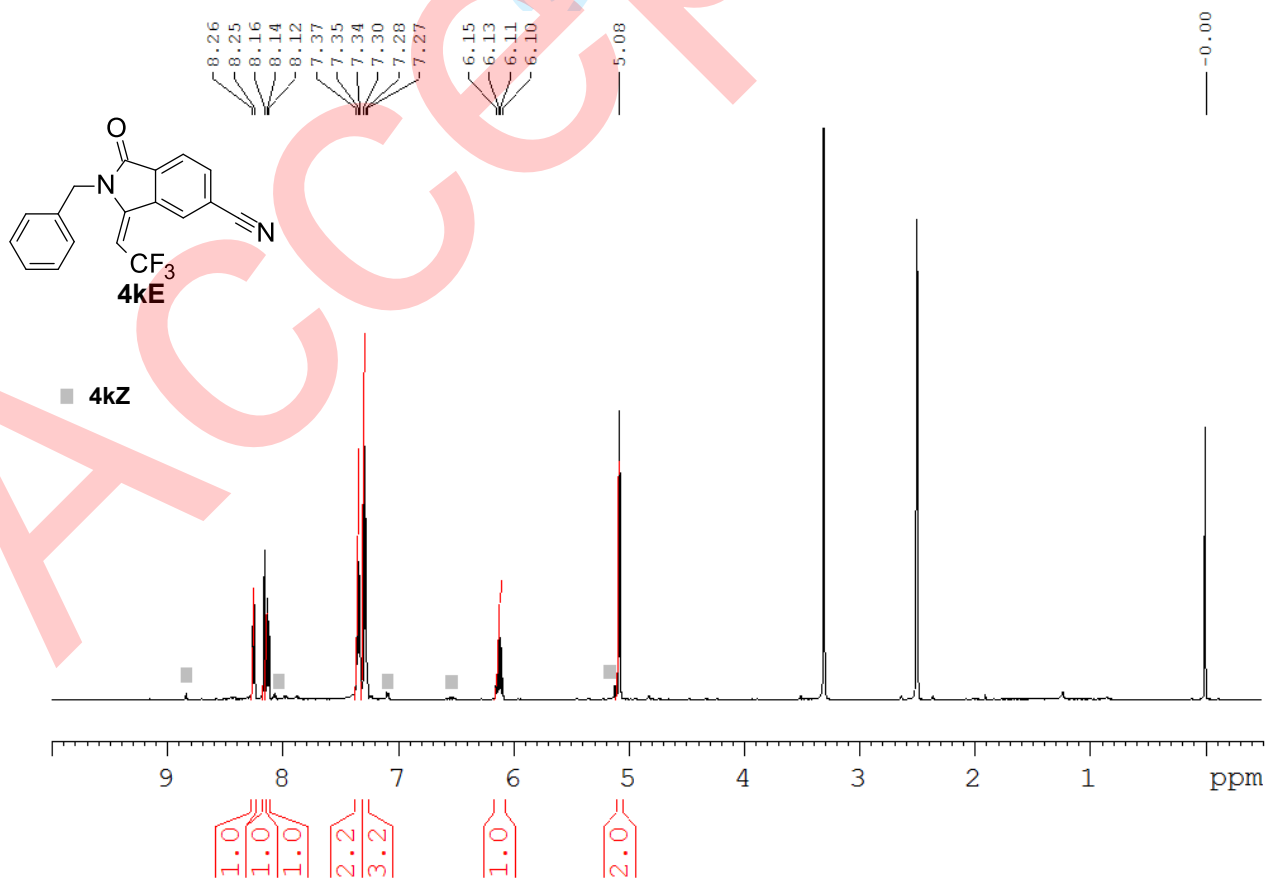
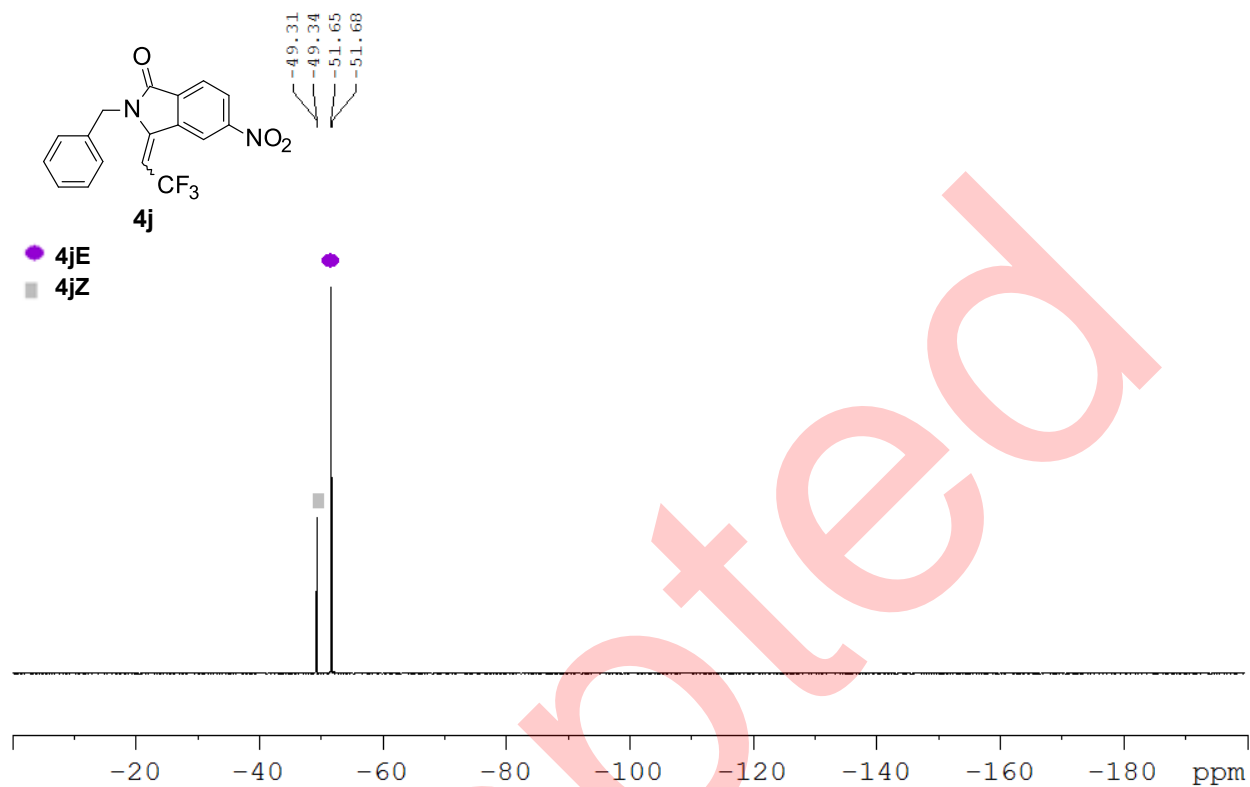
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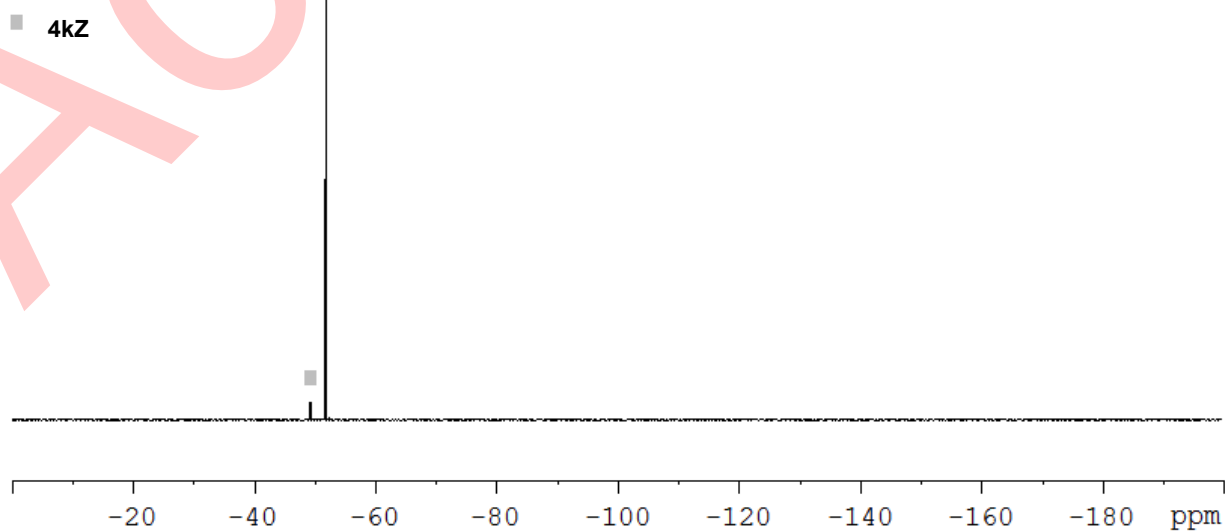
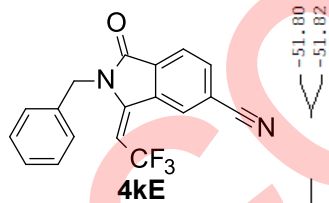
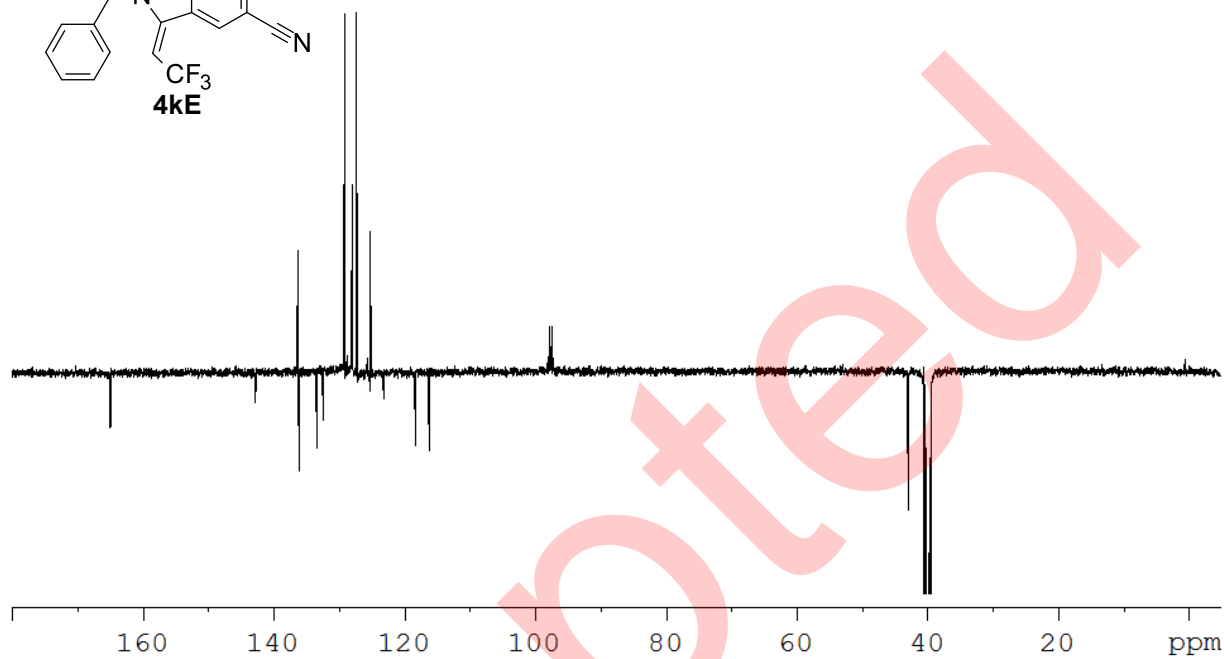
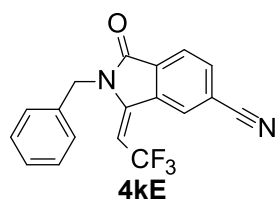
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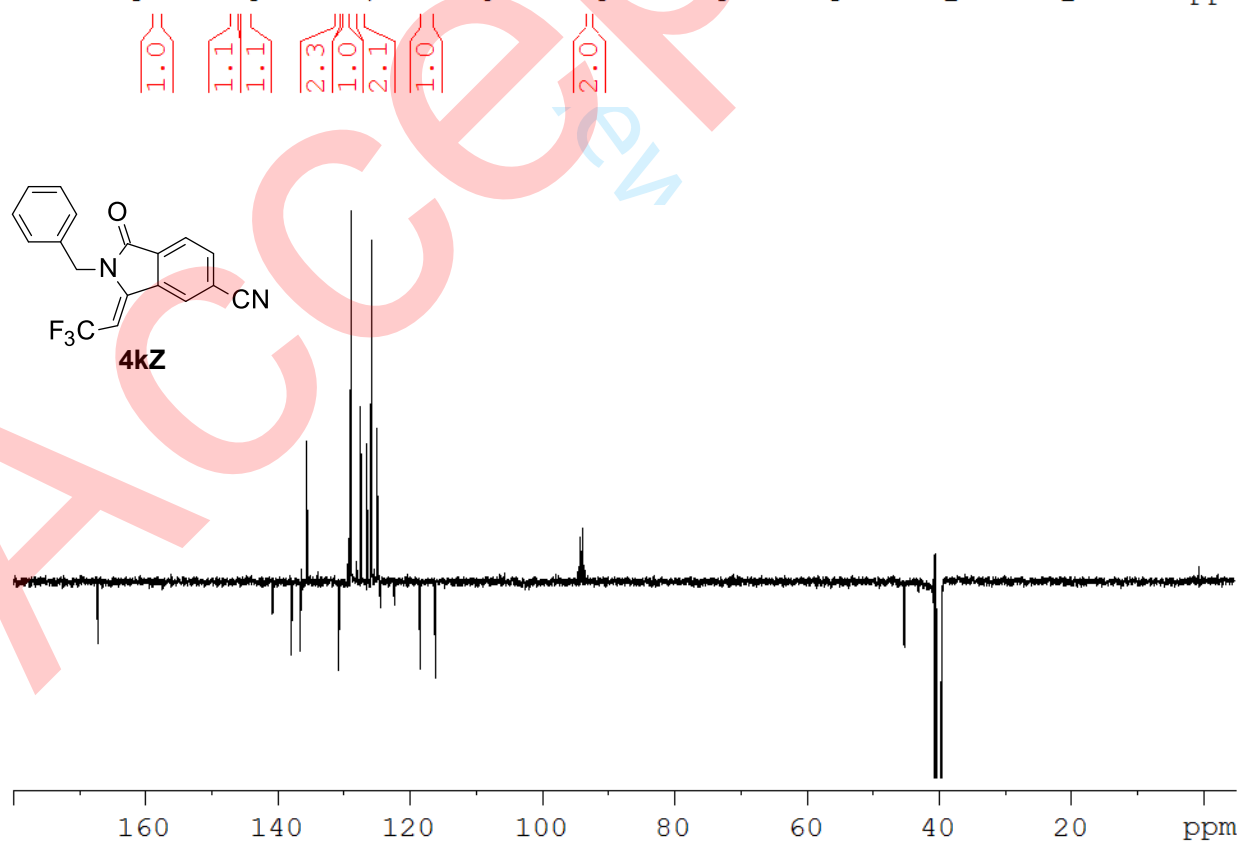
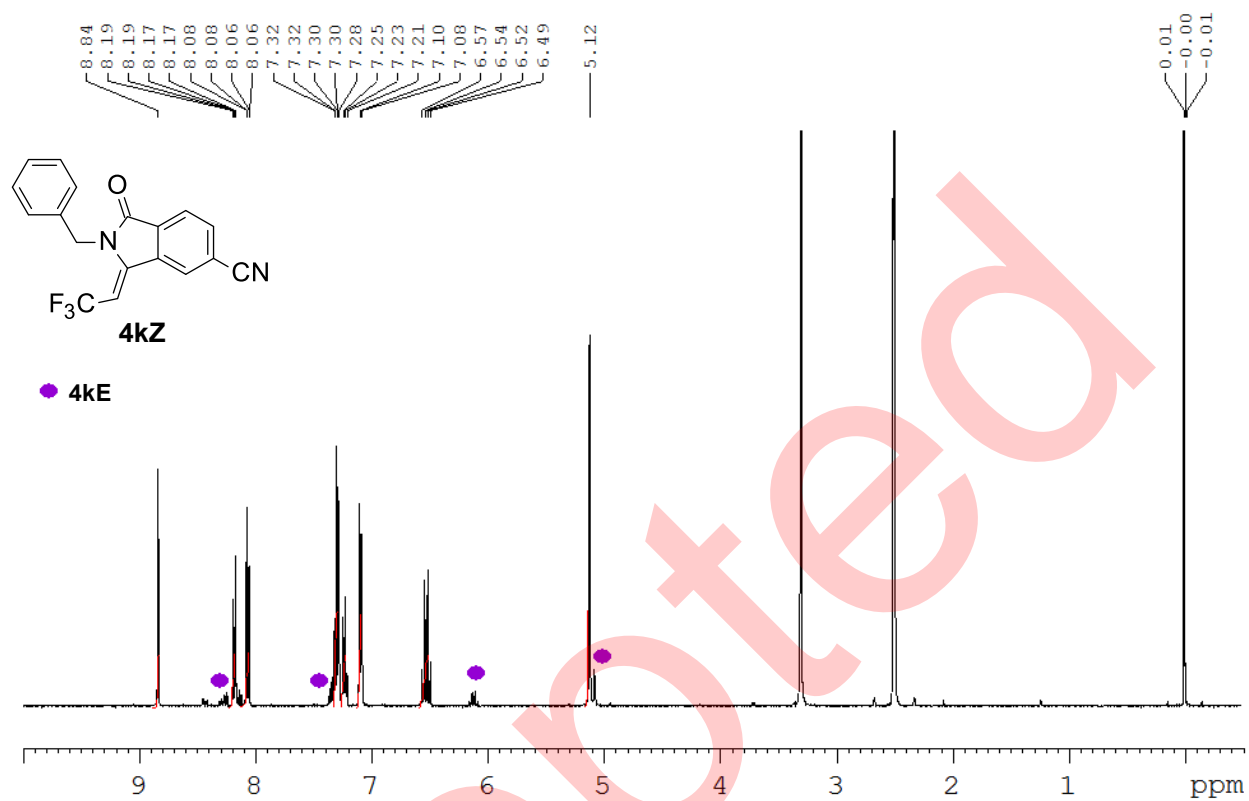


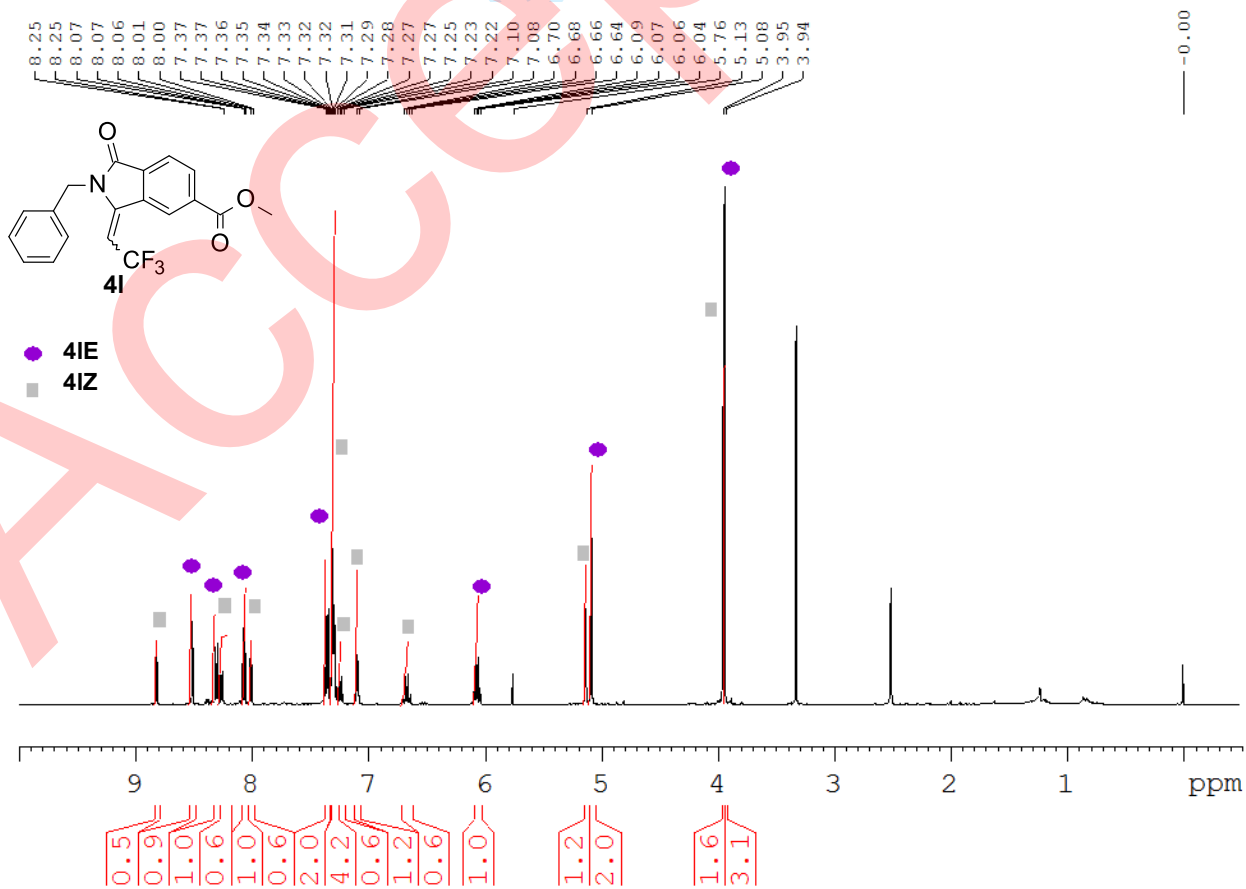
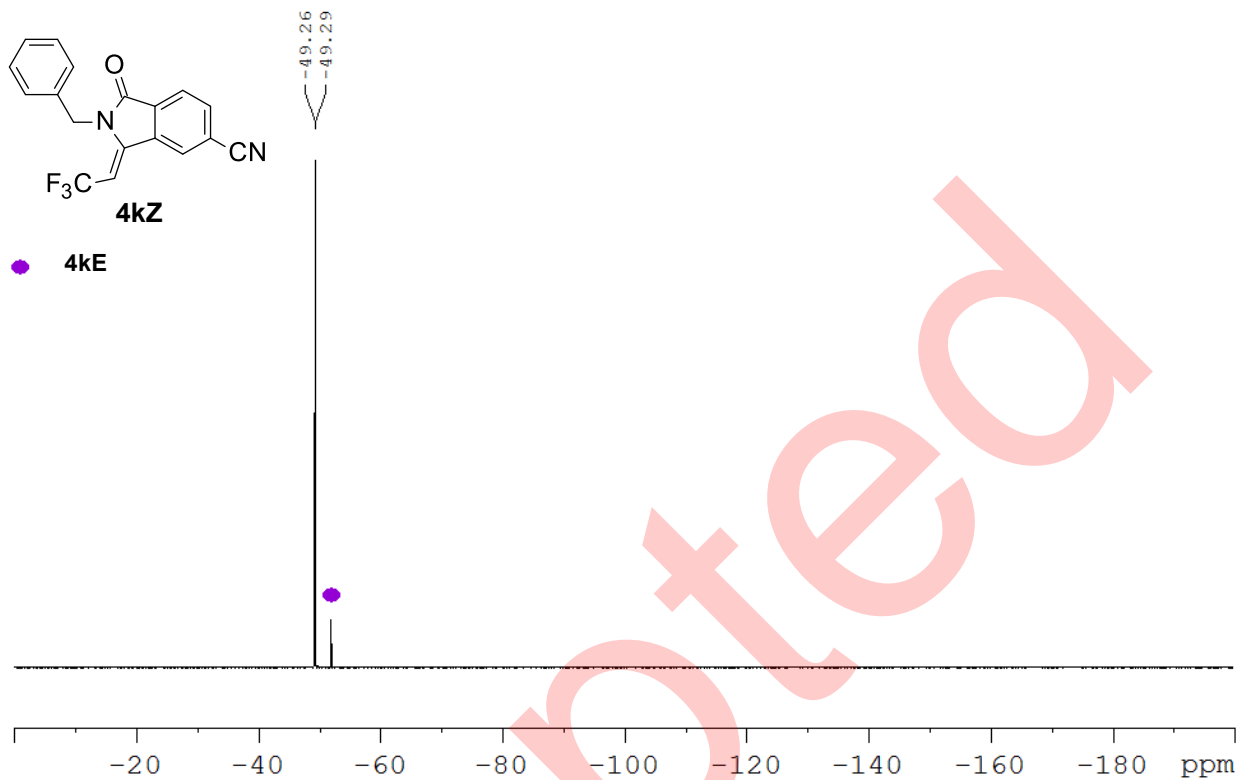


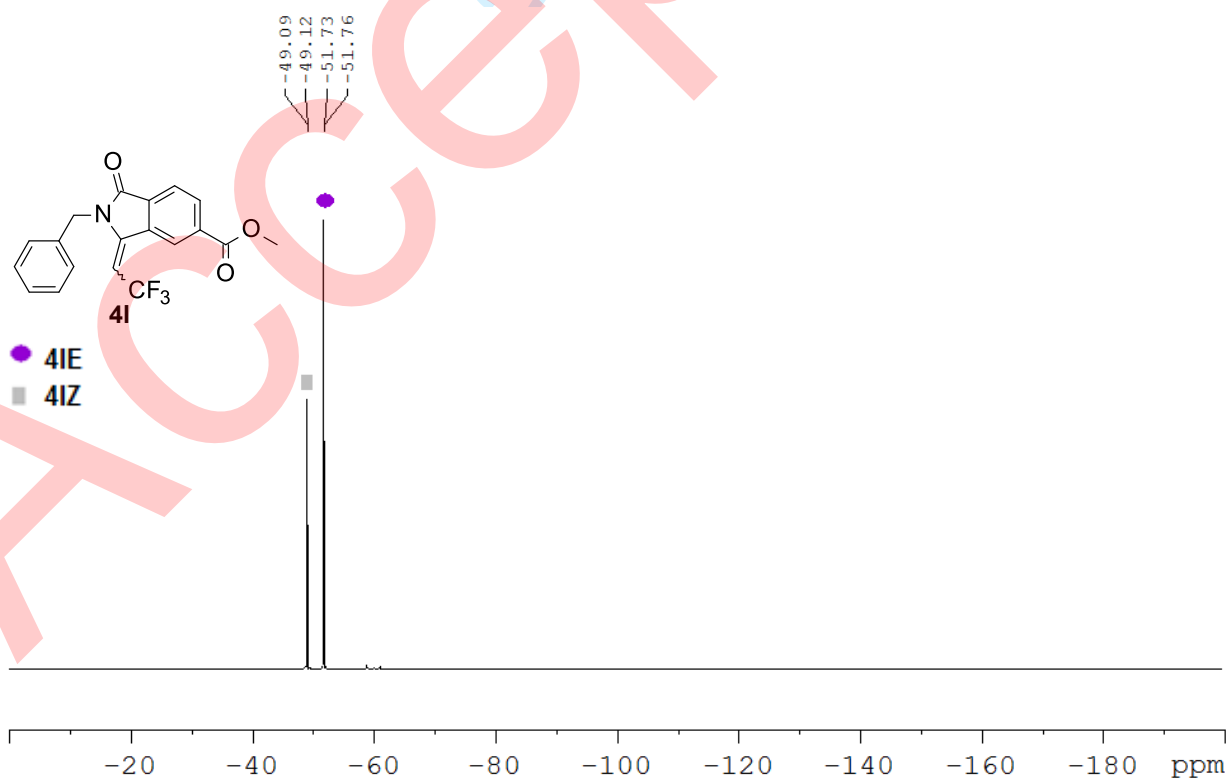
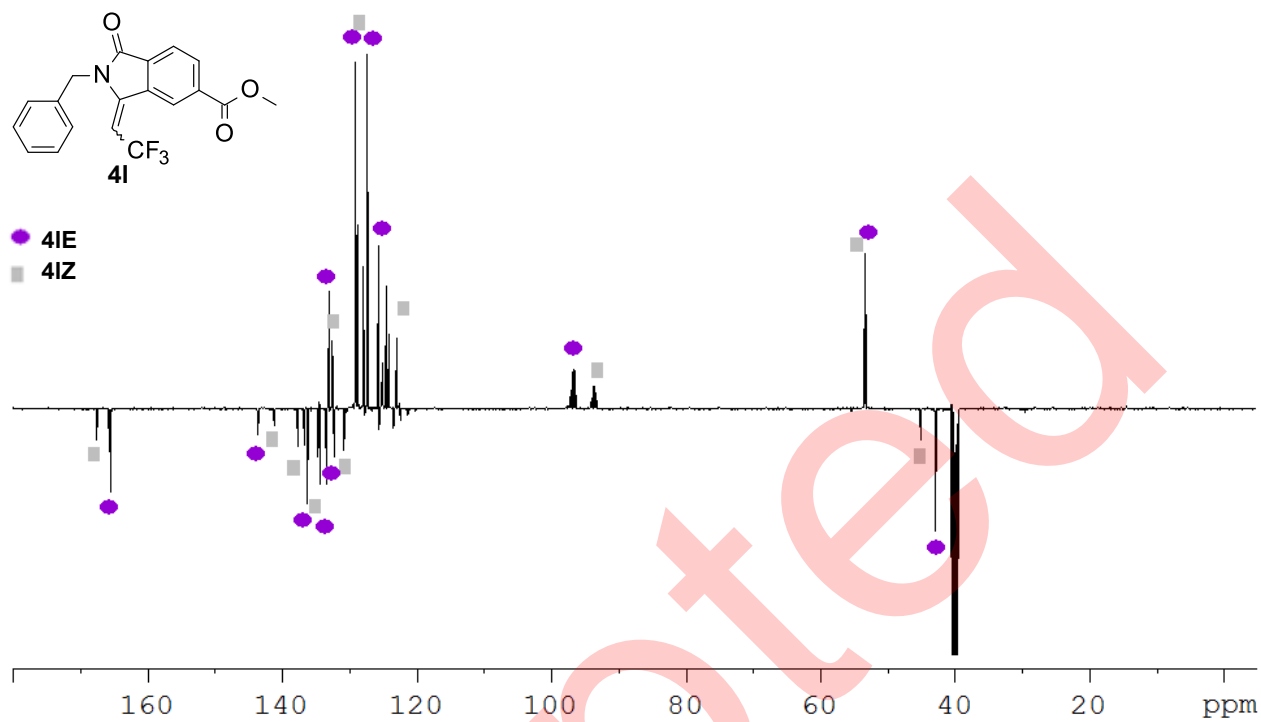


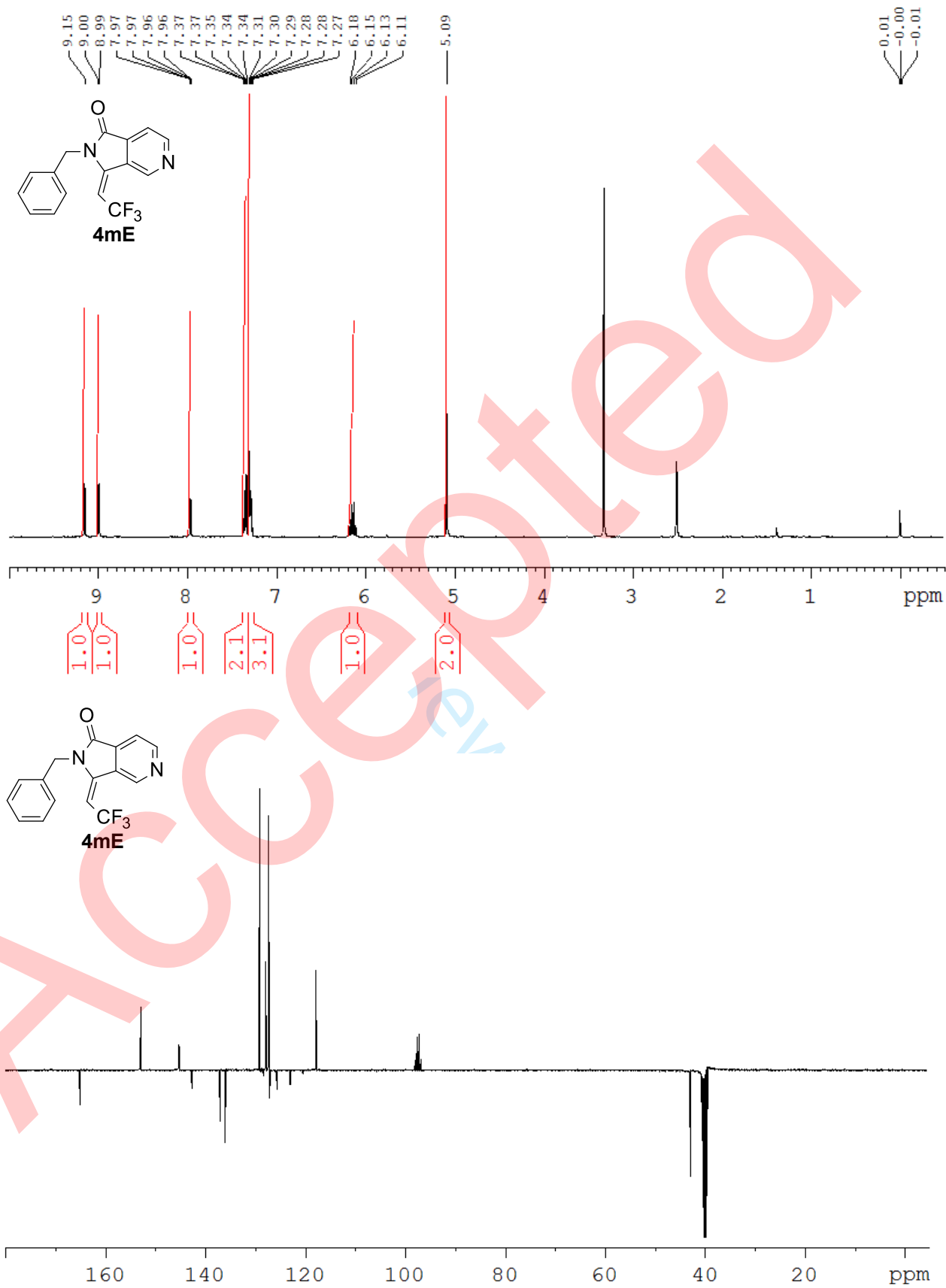


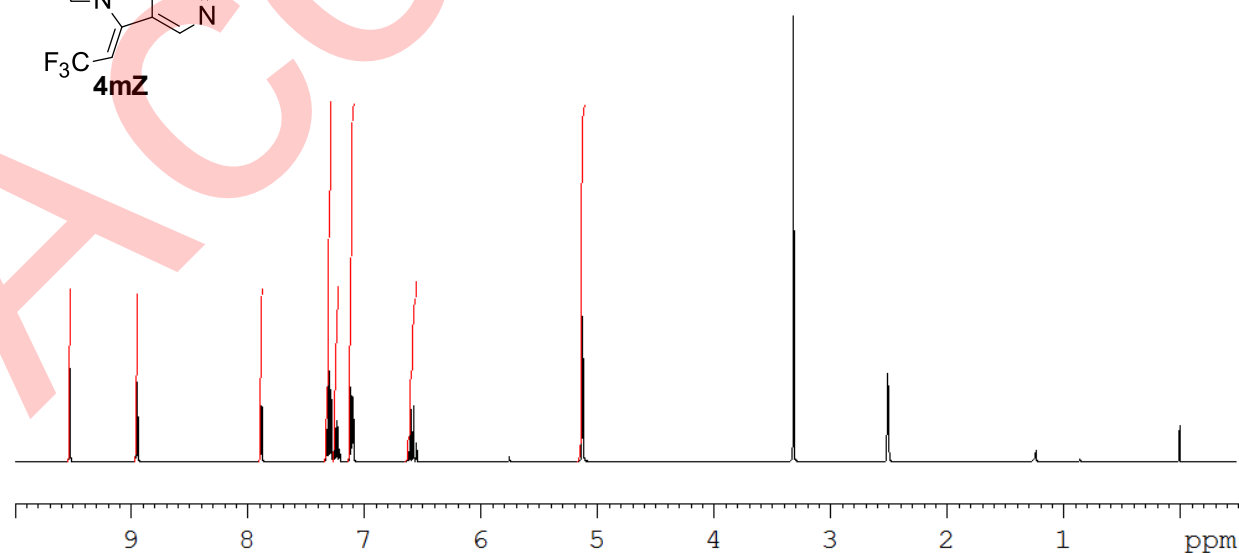
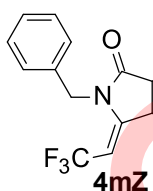
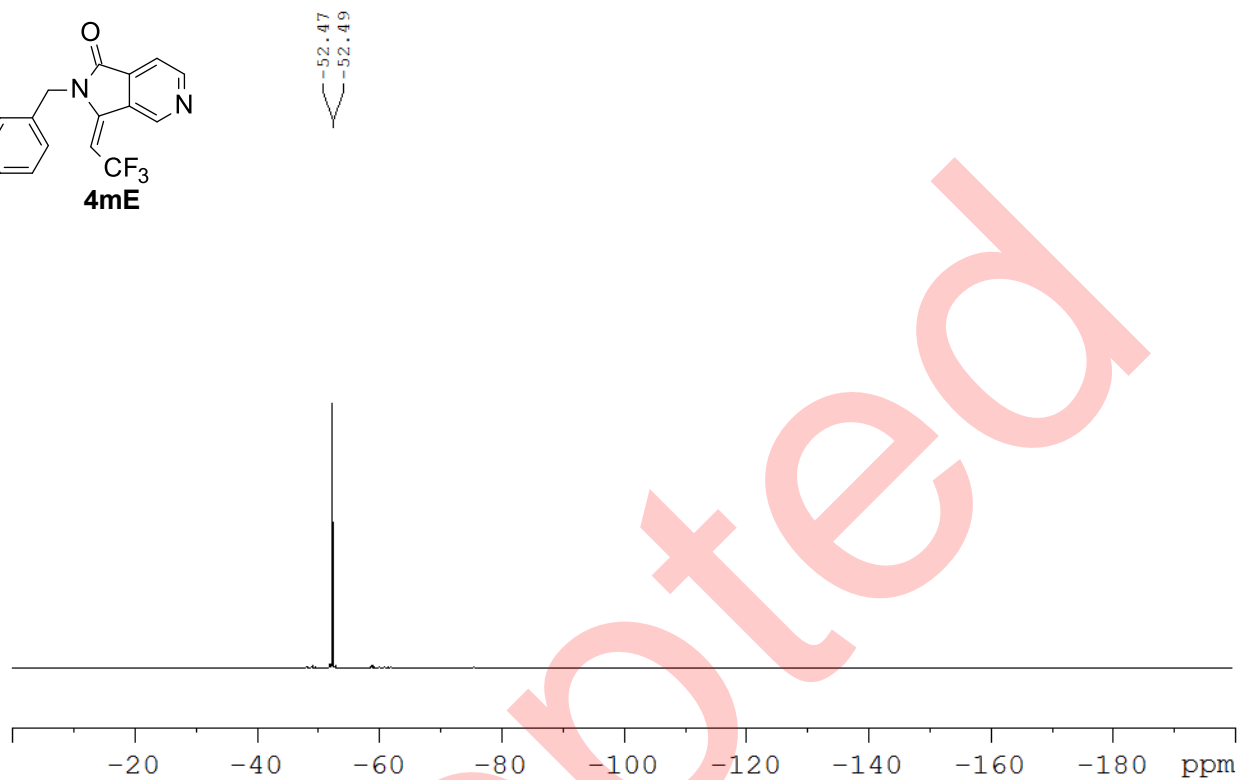
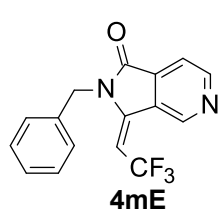


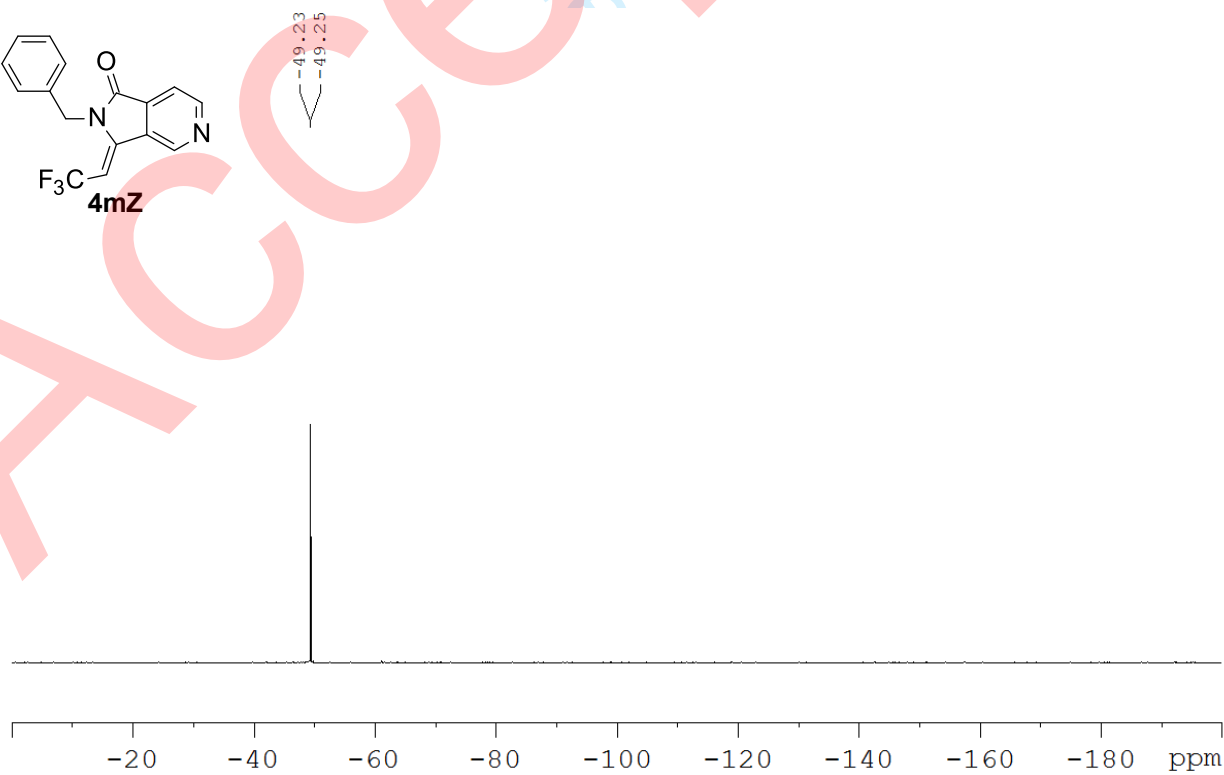
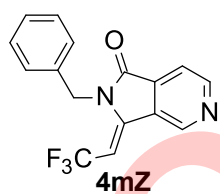
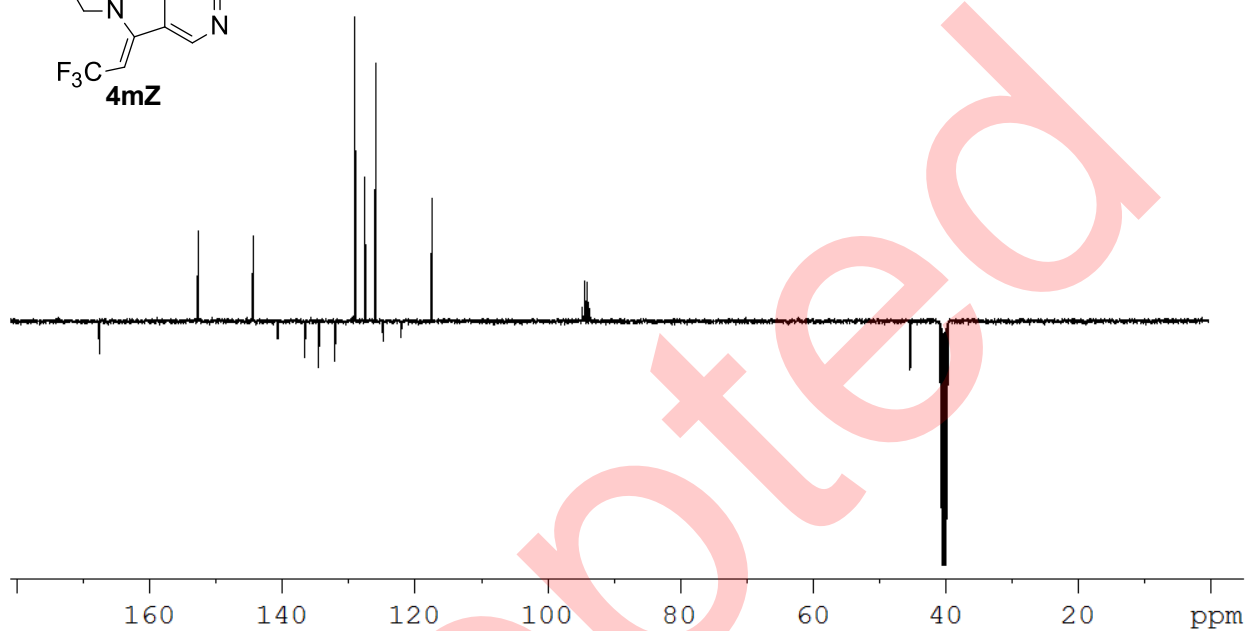
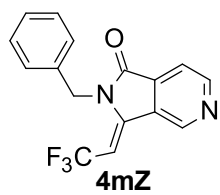


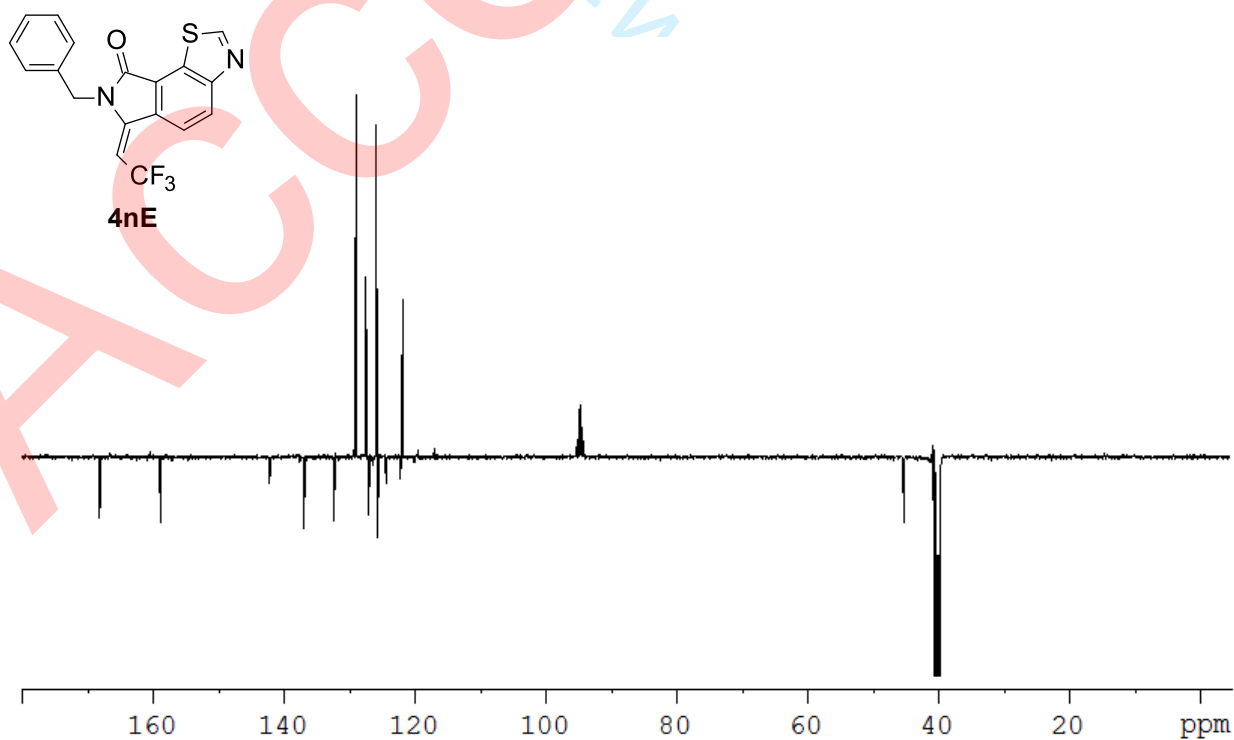
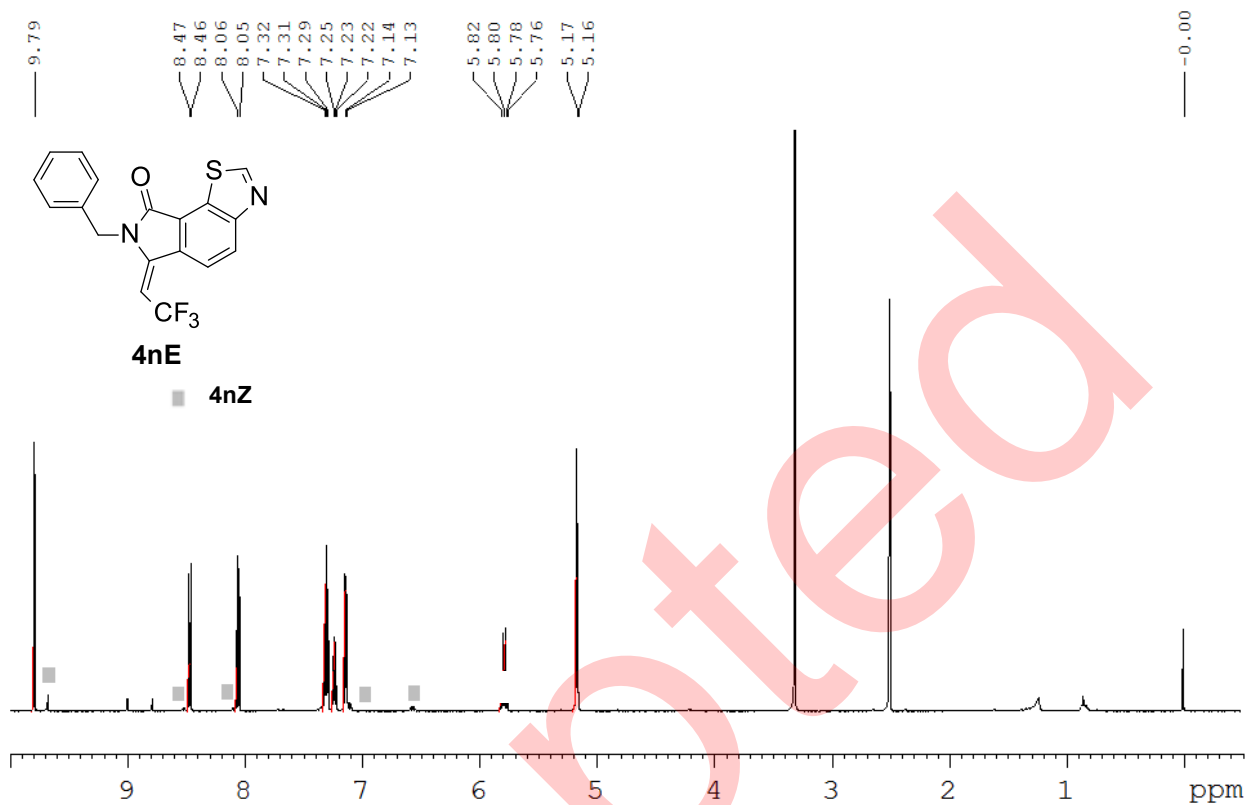


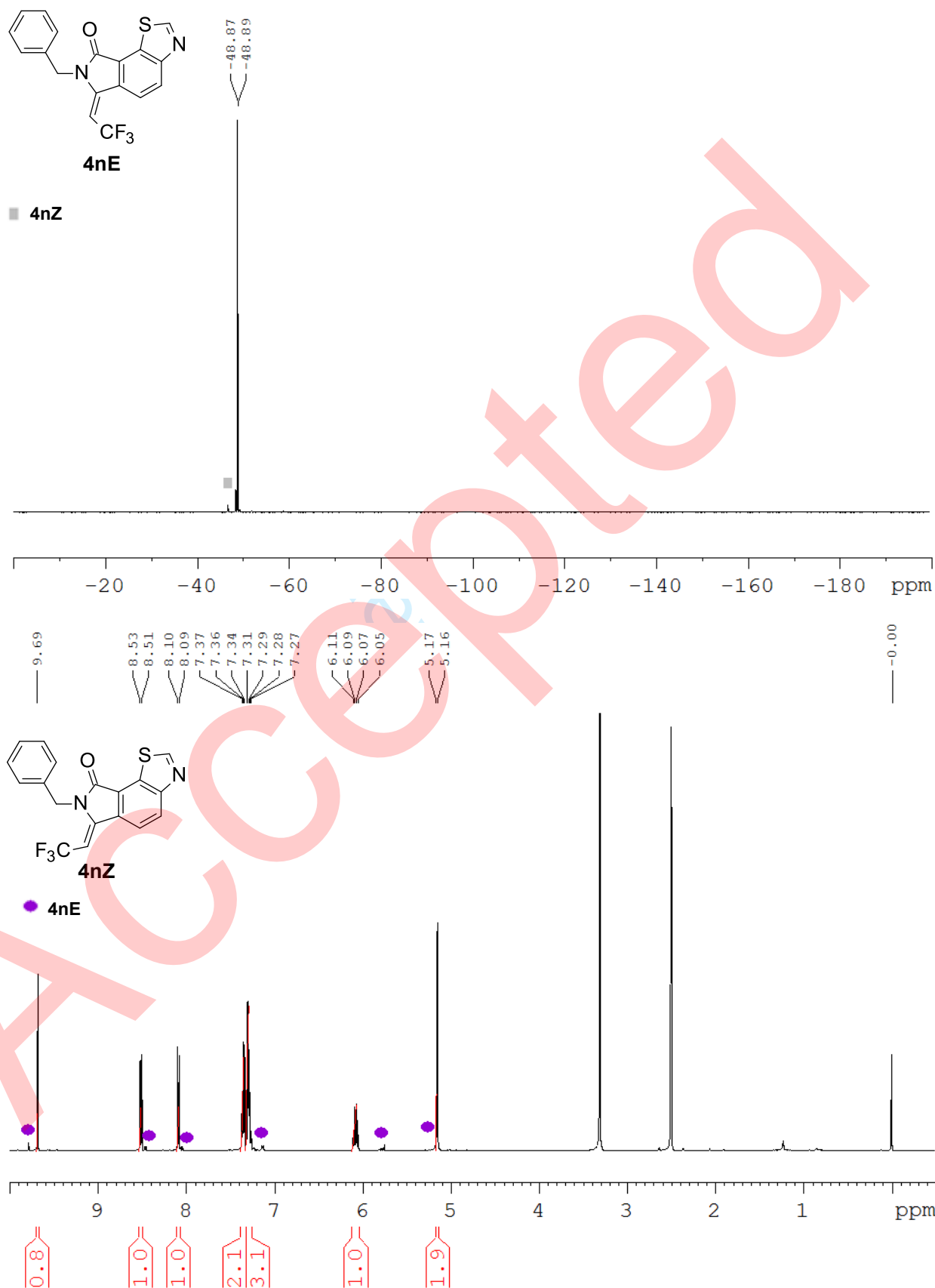


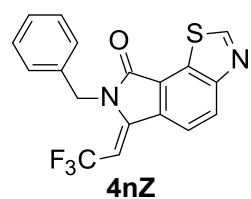
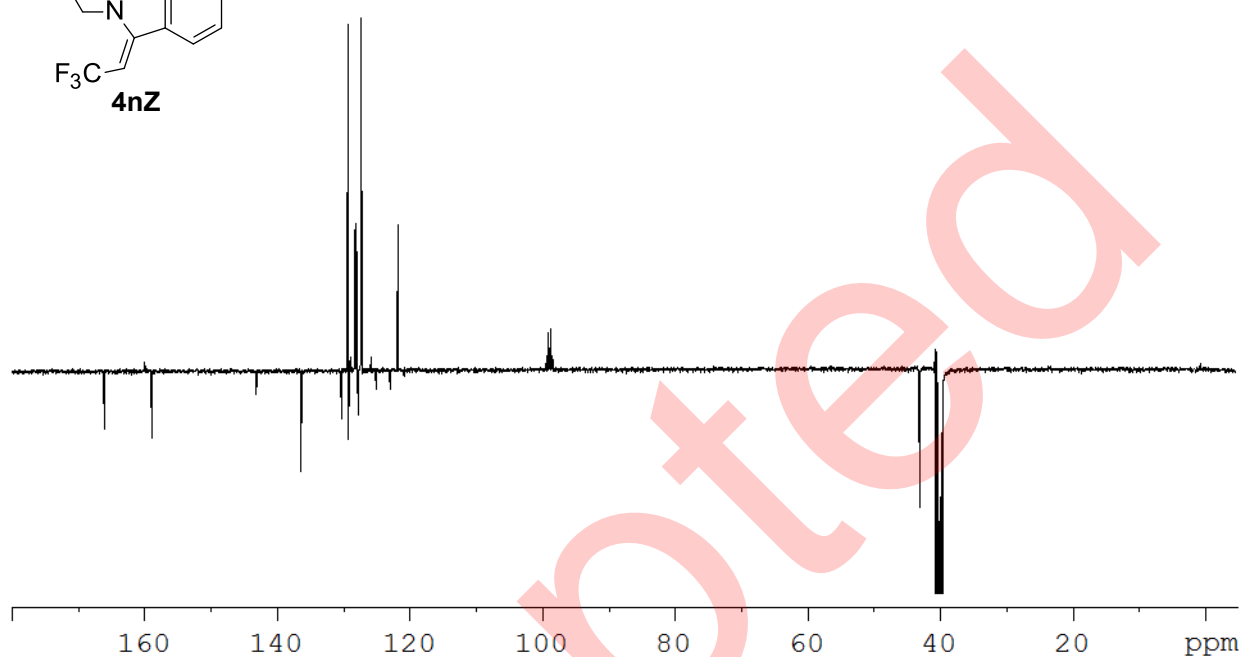
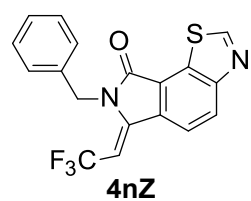




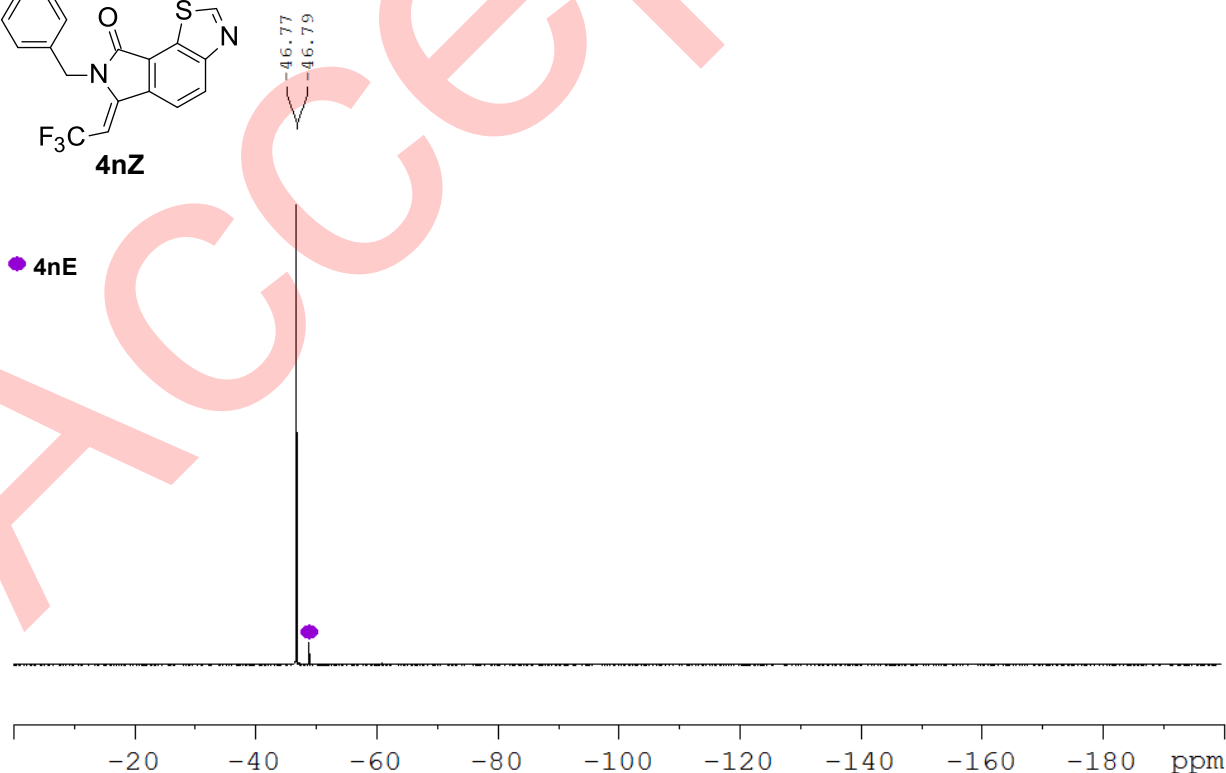


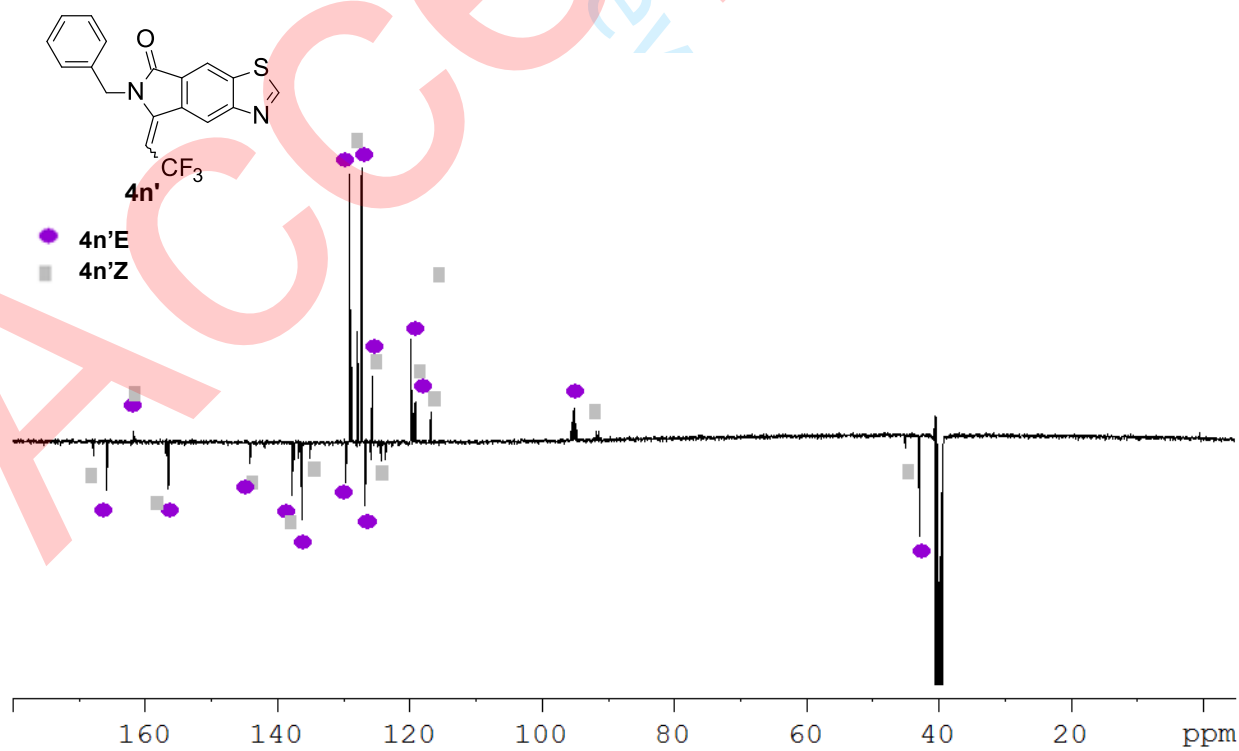
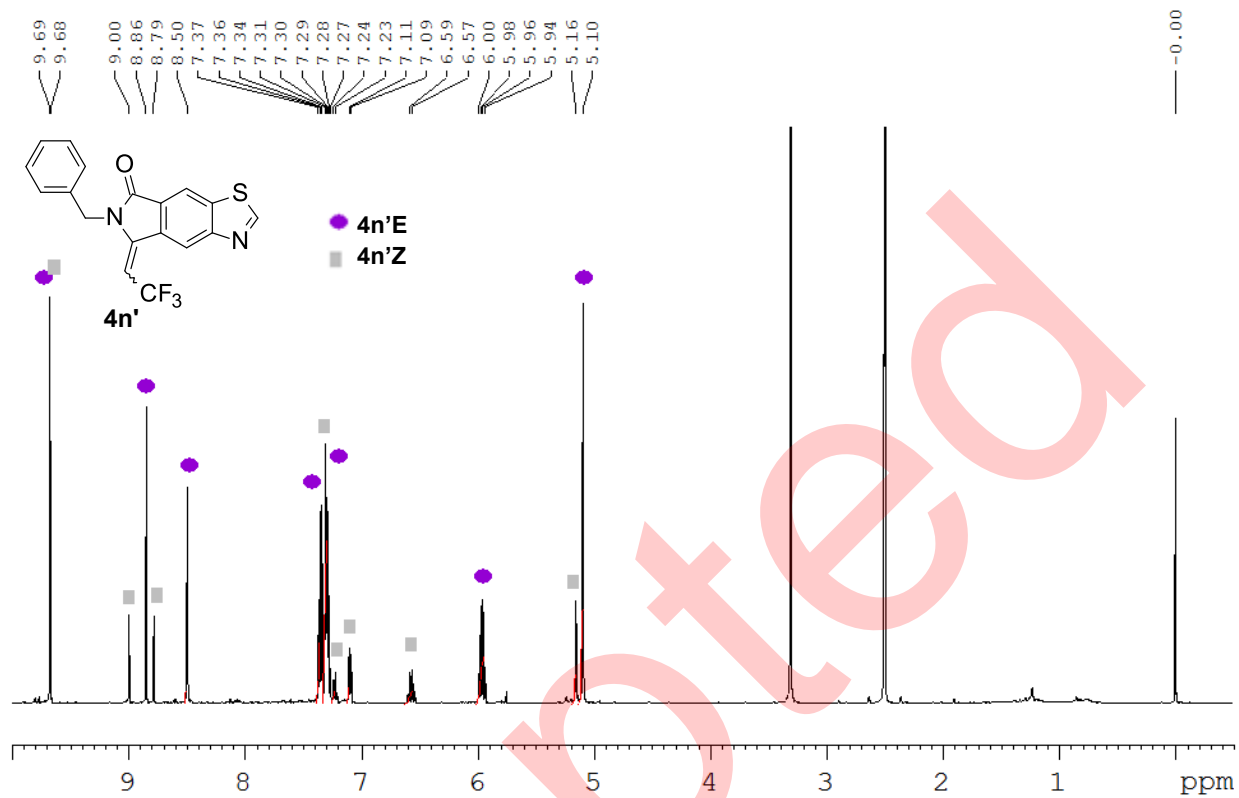


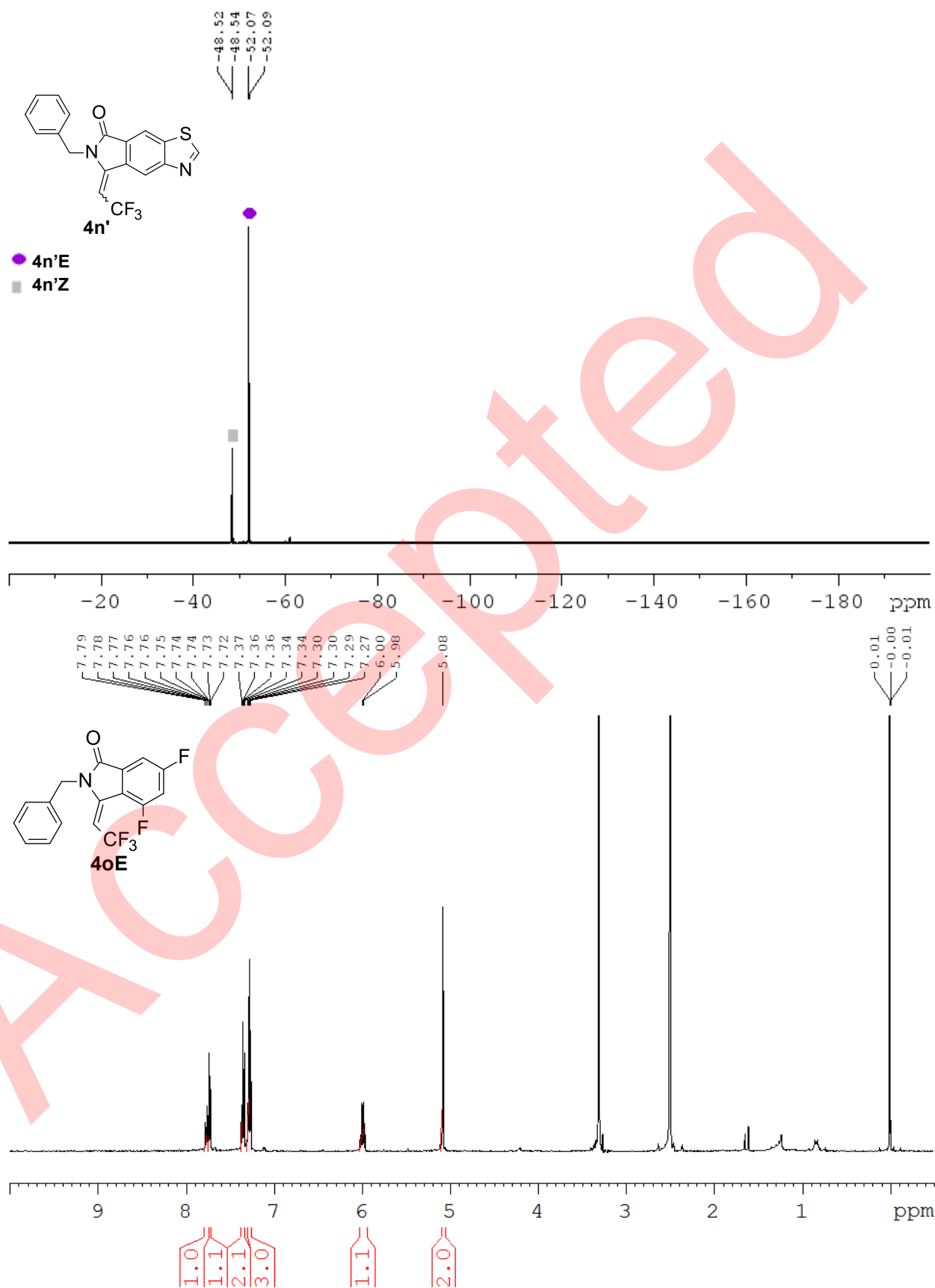


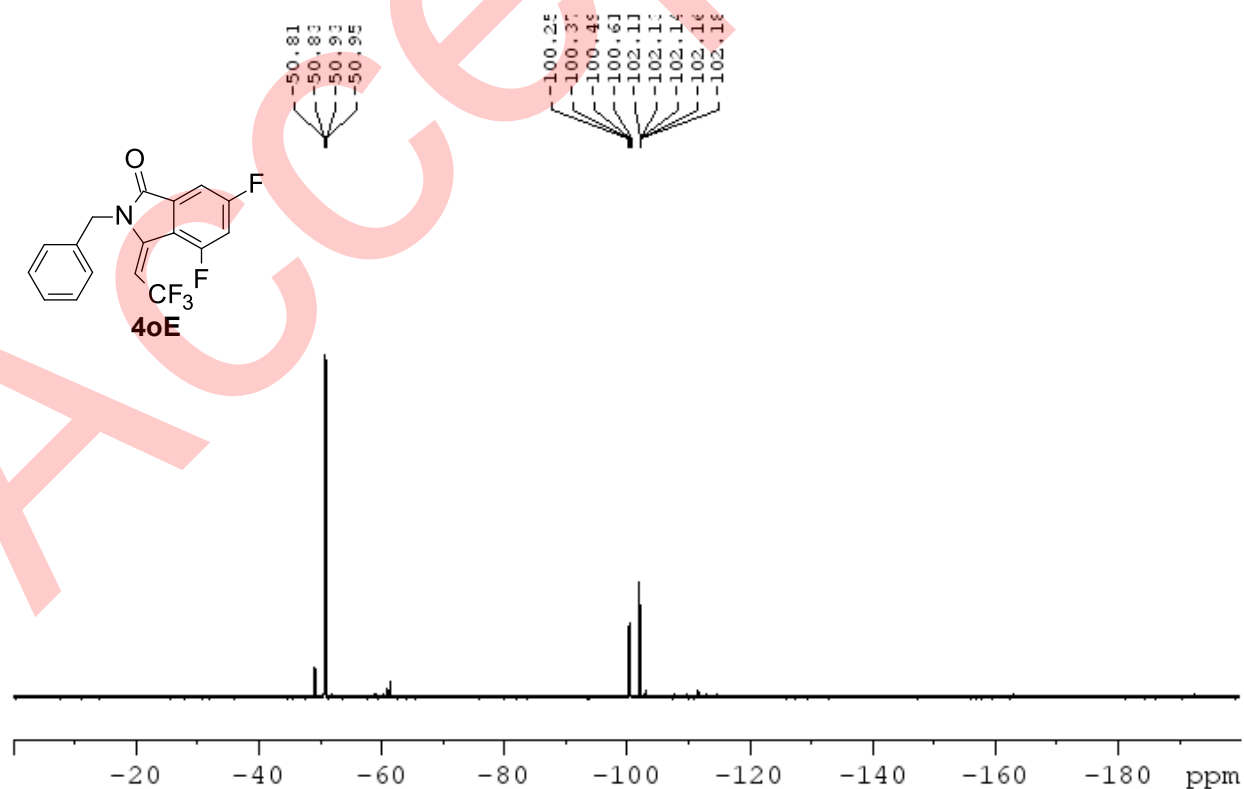
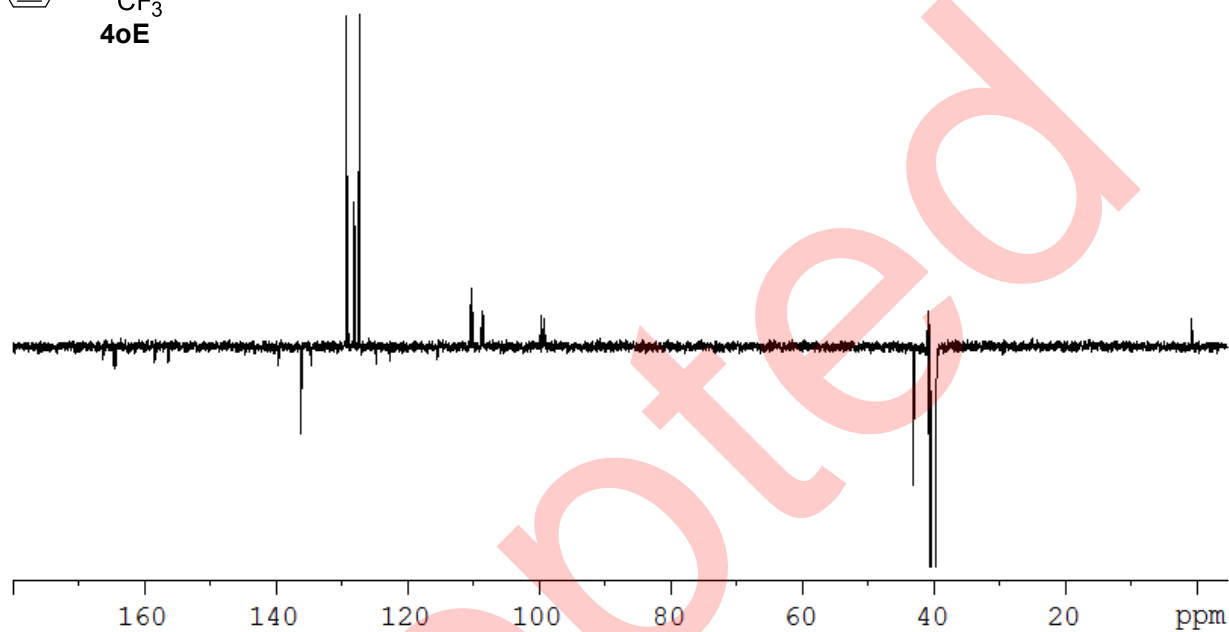
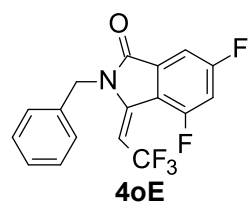


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