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Maud Cassé, Christian Nisole, Héloïse Dossmann, Yves Gimbert, Jean-Marie Fourquez, et al.. Trifluoromethyl Radical Triggered Radical Cyclization of N-Benzoyl Ynamides leading to Isoindolinones. Science China Chemistry, 2019, 62, pp.1542-1546. 10.1007/s11426-019-9627-x . hal-02616094

**HAL Id: hal-02616094**

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Submitted on 24 May 2020

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Citation: [SCIENCE CHINA Chemistry](#); doi: 10.1007/s11426-019-9627-x

View online: <http://engine.scichina.com/doi/10.1007/s11426-019-9627-x>

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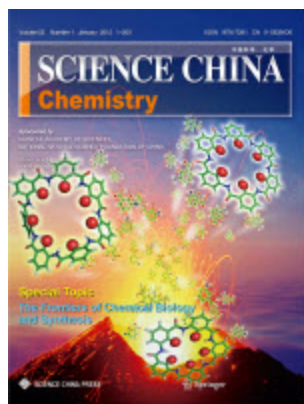
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|                               |   |
|-------------------------------|---|
| Journal:                      | <i>SCIENCE CHINA Chemistry</i>  |
| Manuscript ID                 | SCC-2019-0633.R1  |
| Manuscript Type:              | Communication   |
| Date Submitted by the Author: | 24-Sep-2019   |
| Complete List of Authors:     | Fensterbank, Louis<br>Casse, Maud<br>Christian, Nisole<br>Dossmann, Heloise; Sorbonne Université<br>Gimbert, Yves ; Université Joseph Fourier<br>Fourquez, Jean-Marie<br>Haberhorn, Laure<br>Ollivier, Cyril; Sorbonne Université |
| Keywords:                     | radical, photoredox chemistry, ynamide  |
| Speciality:                   | Organic Chemistry   |
|                               |   |

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

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Received .....; accepted .....; published online .....

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

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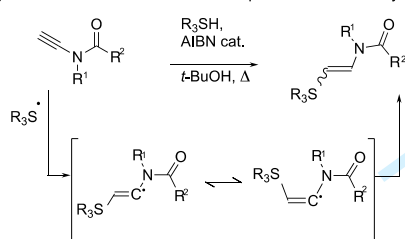
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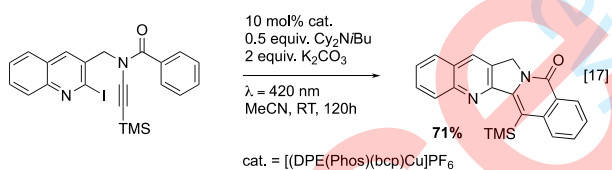
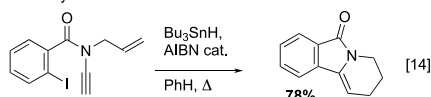
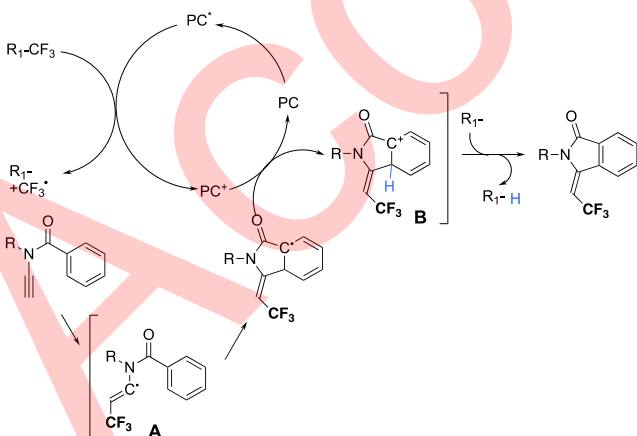
allows for sustainability as well as mild conditions to ensure molecular diversity [23-29]. We focused on generic precursors consisting of N-benzoyl ynamides. After intermolecular addition of the CF<sub>3</sub> radical, the resulting vinyl radical **A** would undergo intramolecular addition on the pendant 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

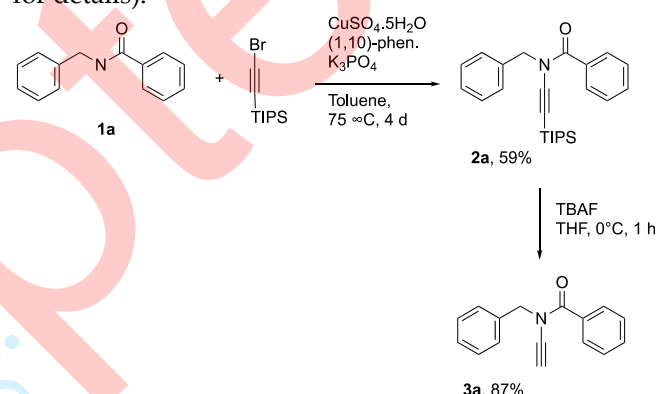
**This work**3) intermolecular addition of CF<sub>3</sub> radical - cyclization tandem in photoredox catalyzed conditions

**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 CuSO<sub>4</sub>·5H<sub>2</sub>O, 1,10-phenanthroline and a weak base (K<sub>3</sub>PO<sub>4</sub>), 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**

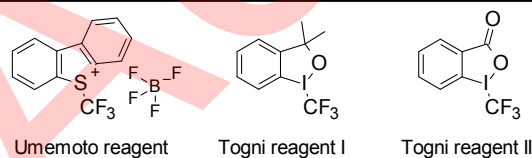
Our preliminary attempts of radical cyclization focused on the simplest term **3a** with no substitution on the aromatic rings. Several parameters were examined such as the solvent, the source of trifluoromethyl radical and the photocatalyst (see Table 1). Acetonitrile, a traditional solvent in photoredox 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)<sub>3</sub>Cl<sub>2</sub> (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)<sub>2</sub>(dtbpy).PF<sub>6</sub> (E Ir(III)\* / Ir(IV) = -0.96V/SCE in MeCN). A trend which was confirmed with Ir(ppy)<sub>3</sub> (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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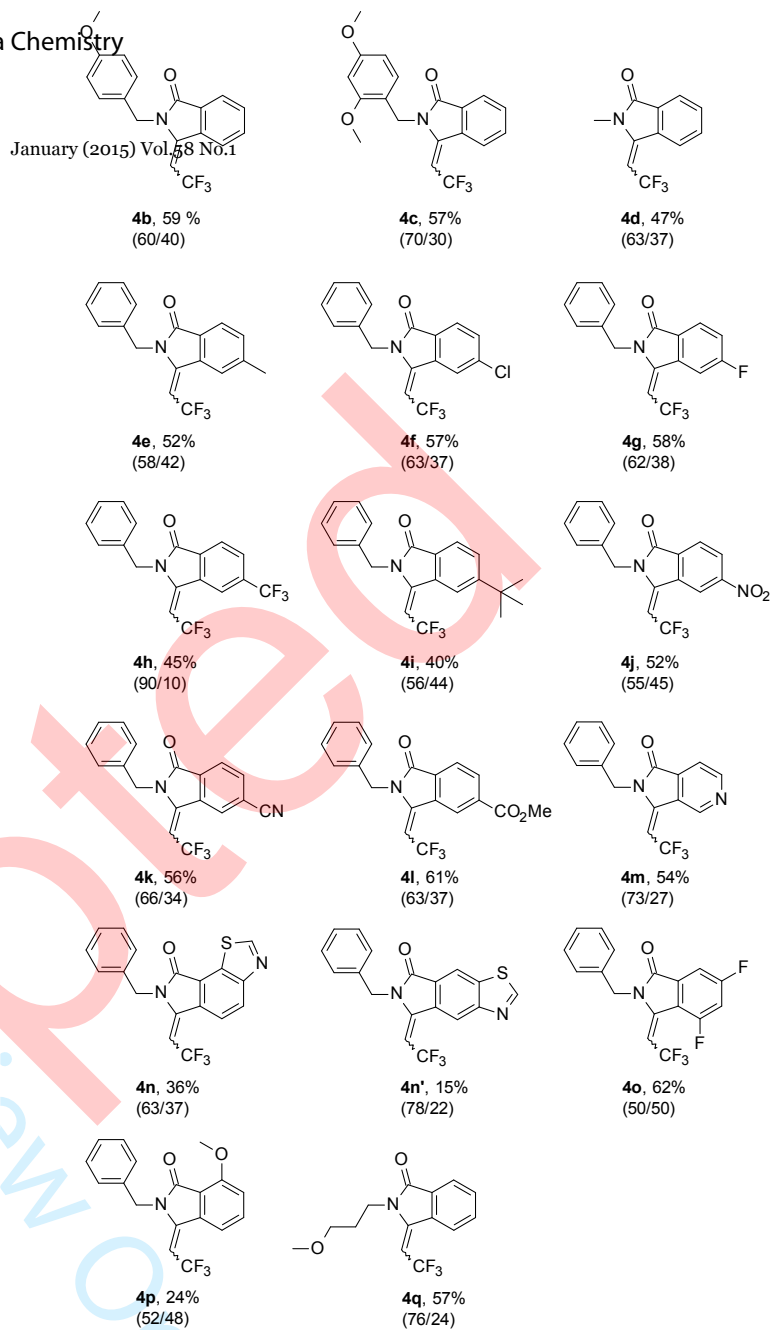
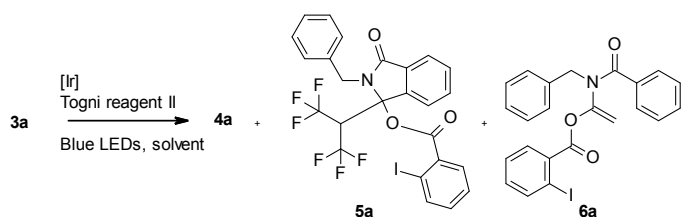
We thus pursued our optimization study with Ir(ppy)<sub>3</sub> and showed that Umemoto reagent was not very competent in this reaction compared to Togni I & II reagents (entry 5 vs. entries 3 & 6). Solvent screening confirmed that acetonitrile was the best (entry 3 vs. entries 7-10). Reactions with 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 CF<sub>3</sub> (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 <sub>3</sub> reagent | Solvent | Time | Yield (%), E : Z           |
|-------|--|-------------------------|---------|------|----------------------------|
| 1     | Ru(bpy) <sub>3</sub> Cl <sub>2</sub>         | Togni II                | MeCN    | 48 h | 36, 97 : 3                 |
| 2     | Ir(ppy) <sub>2</sub> (dtbpy).PF <sub>6</sub> | Togni II <sup>b)</sup>  | MeCN    | 21 h | 45, 50 : 50                |
| 3     | Ir(ppy) <sub>3</sub>                         | Togni II                | MeCN    | 6 h  | 71, 86 : 14                |
| 4     | 4CzIPN <sup>b)</sup>                         | Togni II                | MeCN    | 4 h  | 50, 92 : 8                 |
| 5     | Ir(ppy) <sub>3</sub> <sup>b)</sup>           | Umemoto                 | MeCN    | 23 h | 14 <sup>c)</sup> , 100 : 0 |
| 6     | Ir(ppy) <sub>3</sub>                         | Togni I                 | MeCN    | 5 h  | 64 <sup>d)</sup> , 81 : 19 |
| 7     | Ir(ppy) <sub>3</sub>                         | Togni II                | Acetone | 4 h  | 54, 85 : 15                |
| 8     | Ir(ppy) <sub>3</sub>                         | Togni II                | DMF     | 3 h  | 51, 62 : 38                |
| 9     | Ir(ppy) <sub>3</sub>                         | Togni II                | t-BuOH  | 24 h | 55, 75 : 25                |
| 10    | Ir(ppy) <sub>3</sub>                         | Togni II                | AcOEt   | 3 h  | 62, 92 : 8                 |



a) Reaction conditions: N-benzyl-N-ethynyl-benzamide (**3a**, 0.2 mmol, 1 equiv.), CF<sub>3</sub> 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 Li<sub>2</sub>CO<sub>3</sub>, 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)<sub>3</sub>.

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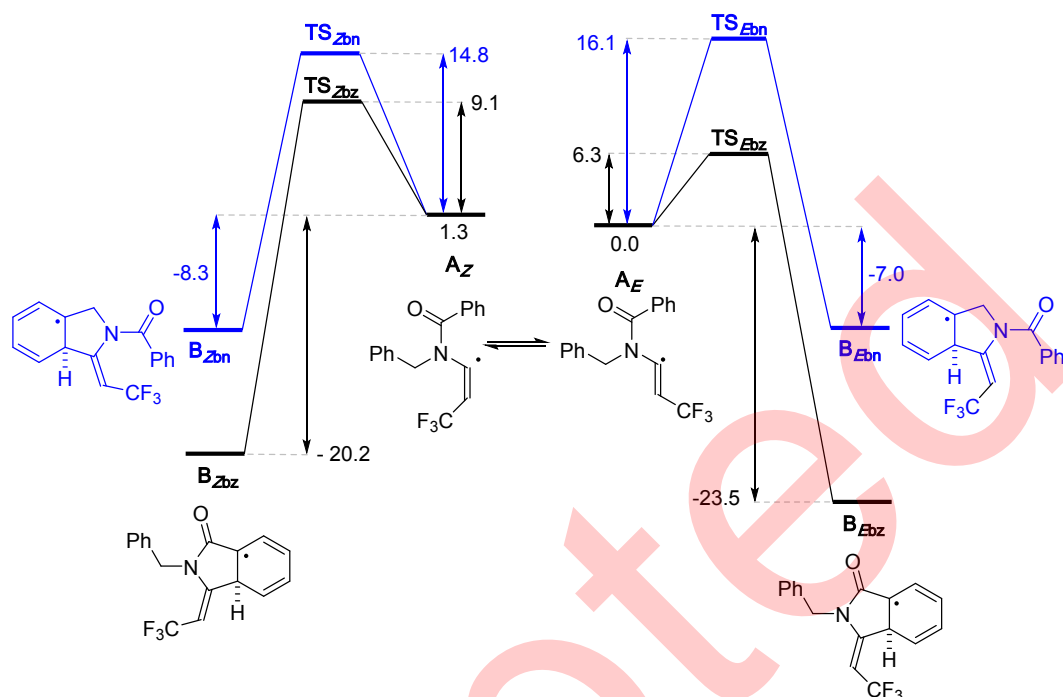
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We nevertheless studied other ynamide precursors **3** and obtained cyclization products **4** (Scheme 4) in moderate to good yields. The N-group was substituted by a p-methoxybenzyl (PMB) and a 2,4-dimethoxybenzyl protecting groups (**4b** and **4c**) 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)





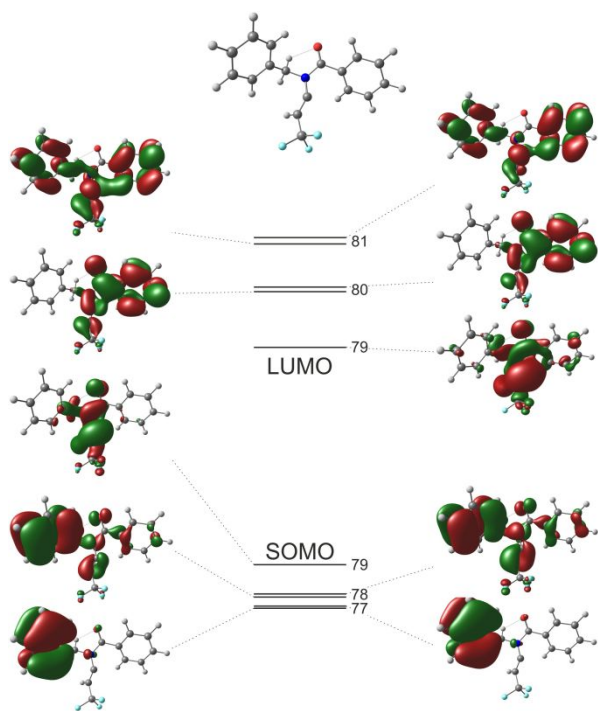
**Scheme 5** Energetic profiles for cyclisation of ynamides: energies given are  $\Delta G$  in kcal/mol.

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  $\text{CF}_3$  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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**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.

**Acknowledgments** We thank Sorbonne Université, CNRS and Servier for funding. The authors wish to acknowledge the analytical department of IDRS - Servier for the compounds analyses (IR, NMR, HR-MS) and the SRIMC department for the syntheses on big scale. This work was granted access to the high performance computing (HPC) resources of the HPCaVe Centre at Sorbonne Université and to the HPC resources of IDRIS under the allocation 2018-A0050810312 made by GENCI. The authors wish to acknowledge support from the ICMG Chemistry Nanobio Platform-PCECIC, Grenoble, for calculations facilities. Jérémy Forté is acknowledged for the X-ray diffraction analyses as well as Conor Dent Cullen for proofreading the manuscript.

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

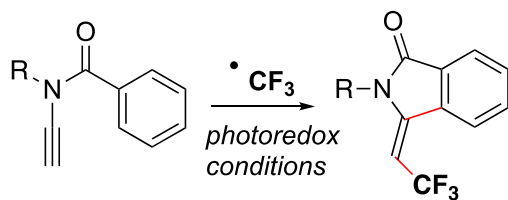
**Supporting information** The supporting information is available online at <http://chem.scichina.com> and <http://link.springer.com/journal/11426>. The X-Ray crystal structures were deposited at the Cambridge Crystallographic Data Centre with numbers CCDC 1949295 (compound **4aE**) and CCDC 1949296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

- Albert M, Fensterbank L, Lacôte E, Malacria M. *Topics Current Chemistry*, **2006**, *264*, 1–62
- Baralle A, Baroudi A, Daniel M, Fensterbank L, Goddard JP, Lacôte E, Larrauffie MH, Maestri G, Malacria M, Ollivier C. Radical Cascade Reactions. In: Chatgililoglu C, Studer A, Eds. *Encyclopedia of Radicals in Chemistry, Biology and Materials*. John Wiley & Sons: Chichester, U. K., **2012**, 729–766
- Godineau E, Landais Y. *Chem Eur J*, **2009**, *15* (13), 3044–3055
- Liautard V, Landais Y, in: Zhu J, Wang Q, Wang MX, Eds. *Multicomponent Reactions*. Wiley, 2nd Edition. **2014**, 401–438
- Chen JR, Yu XY, Xiao WJ, *Synthesis*, **2015**, *47*, 604–629
- Zhang Y, Sun K, Lv Q, Chen X, Qu L, Yu B, *Chin Chem Lett*, **2019**, *30*, 1361–1368
- Xuan J, Studer A, *Chem Soc Rev*, **2017**, *46*, 4329–4346
- Huang HM, Garduno-Castro MH, Morrill C, Procter DJ, *Chem Soc Rev*, **2019**, *48*, 4626–4638
- Dutta S, Mallick RK, Prasad R, Gandon V, Sahoo KA, *Angew Chem Int Ed*, **2019**, *58*, 2289–2294
- Wang J, Sánchez-Roselló M, Acena JL, del Pozo C, Sorochinsky A E, Fustero S, Soloshonok VA, Liu H. *Chem. Rev.* **2014**, *114*, 2432–2506
- Dagoussset G, Carboni A, Masson G, Magnier E. Visible light-induced (per)fluoroalkylation by photoredox catalysis. In *Modern Synthesis Process and Reactivity of Fluorinated Compounds: Progress in Fluorine Science*; Elsevier, **2017**, 389–426
- Oh EH, Kim HJ, Han SB. *Synthesis*, **2018**, *50*, 3346–3358
- Fuentes N, Kong W, Fernandez-Sanchez L, Merino E, Nevado C. *J Am Chem Soc*, **2015**, *137*, 964–973
- Zheng J, Deng Z, Zhang Y, Cui S. *Adv Synth Cat*, **2016**, *358*, 746–751
- Li Y, Lu Y, Qiu G, Ding Q. *Org Lett*, **2014**, *16*, 4240–4243
- Noto N, Miyazawa K, Koike T, Akita M. *Org Lett*, **2015**, *17*, 3710–3713
- Baneerjee B, Litvinov DN, Kang J, Bettale JD, Castle SL. *Org Lett*, **2010**, *12*, 2650–2652
- Sato A, Yorimitsu H, Oshima K. *Synlett*, **2009**, 28–31
- Marion F, Courillon C, Malacria M. *Org Lett*, **2003**, *5*, 5095–5097
- Marion F, Coulomb J, Servais A, Courillon C, Fensterbank L, Malacria M. *Tetrahedron*, **2006**, *63*, 3856–3871
- Balieu S, Toutah K, Carro L, Chamoreau LM, Rousselière H, Courillon C. *Tetrahedron Lett*, **2011**, 2876–2880
- Baguia H, Deldaele C, Romero E, Michelet B, Evano G. *Synthesis*, **2018**, *50*, 3022–3030
- Wang CS, Dixneuf PH, Soulé JF. *Chem Rev*, **2018**, *118*, 7532–7585
- Staveness D, Bosque I, Stephenson CRJ. *Acc Chem Res*, **2016**, *49*,

- 2295–2306
- 25 Shaw MH, Twilton J, MacMillan DWC. *J Org Chem*, **2016**, *81*, 6898–6926
- 26 Pawlowski R, Stanek F, Stodulski M, *Molecules*, **2019**, *24*, 1533-1566
- 27 Festa AA, Voskressensky LG, Van der Eycken EV, *Chem Soc Rev*, **2019**, *48*, 4401-4423
- 28 Chen JR, Hu XQ, Lu LQ, Xiao WJ, *Acc Chem Res*, **2016**, *49*, 1911-1923
- 29 Tanoury GJ, *Synthesis*, **2016**, *48*, 2009-2025
- 30 Cook AM, Wolf C. *Tetrahedron Lett*, **2015**, *56*, 2377-2392
- 31 Evano G, Coste A, Jouvin K. *Angew Chem Int Ed*, **2010**, *49*, 2840-2859
- 32 Zhang Y, Hsung RP, Tracey MR, Kurtz KCM, Vera EL. *Org Lett*, **2004**, *6*, 1151-1154
- 33 Charpentier J, Früh N, Togni A. *Chem Rev*, **2015**, *115*, 650-682
- 34 Eisenberger P, Gischig S, Togni A. *Chem Eur J*, **2006**, *12*, 2579-2586
- 35 For trifluoromethyl-containing compounds redox potentials: Jiang Y, Yu H, Fu Y, Liu L. *Sci China Chem*, **2015**, *58*, 673-683
- 36 For photocatalysts redox potentials: Prier CK, Rankic DA, MacMillan DWC. *Chem Rev*, **2013**, *113*, 5322-5363
- 37 For first uses in photoredox catalysis, see: Luo J, Zhang J. *ACS Catal*, **2016**, *6*, 873-877
- 38 For first uses in photoredox catalysis, see: Lévêque C, Chenneberg L, Corcé V, Ollivier C, Fensterbank L. *Chem Comm*, **2016**, *52*, 9877-9880
- 39 For a review, see: Shang TY, Lu LH, Cao Z, Liu Y, He WM, Yu B. *Chem Commun*, **2019**, *55*, 5408-5419
- 40 For a revision of the redox potentials, see: Vaillant FL, Garreau M, Nicolai S, Gryn'ova G, Corminboeuf C, Waser J. *Chem Sci*, **2018**, *9*, 5883-5889
- 41 Jacquet J, Blanchard S, Derat E, Desage El-Murr M, Fensterbank L. *Chem Sci*, **2016**, *7*, 2030-2036
- 42 Singh K, Staig SJ, Weaver JD. *J Am Chem Soc*, **2014**, *136*, 5275–5278
- 43 Lin QY, Xu XH, Qing FL. *J Org Chem*, **2014**, *79*, 10434-10446
- 44 Larraufie MH, Courillon C, Ollivier C, Lacôte E, Malacria M, Fensterbank L. *J Am Chem Soc*, **2010**, *132*, 4381-4387
- 45 Bogen S, Gulea M, Fensterbank L, Malacria M. *J Org Chem*, **1999**, *64*, 4920-4925

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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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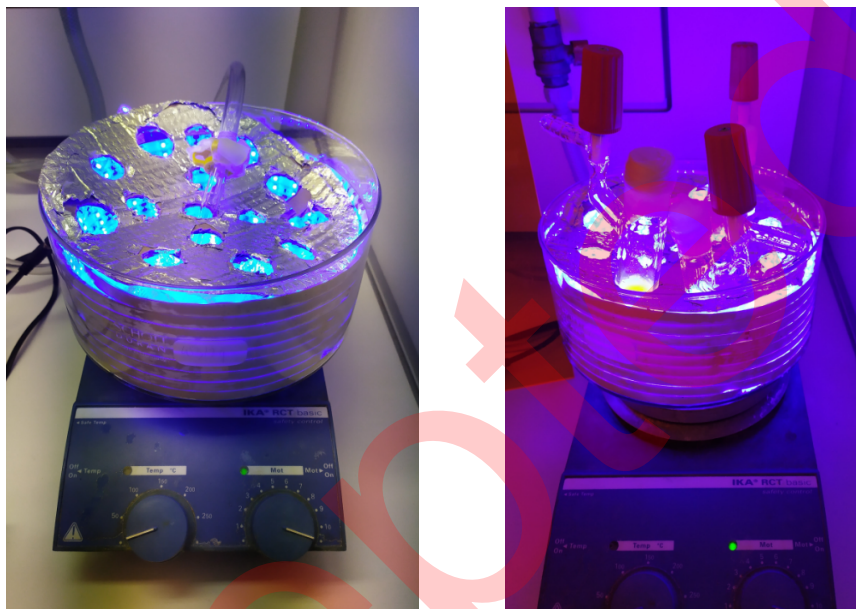
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## General informations

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  $\mu$ L, the column was a Waters Acquity UPLC® BEH C<sub>18</sub> 1.7  $\mu$ m and temperature was kept at 40°C. Mobile phase A consisted of H<sub>2</sub>O/MeCN/formic acid (98/2/0.1) and mobile phase B of MeCN/ H<sub>2</sub>O /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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Brüker 400 or 500 MHz machine operating at ambient temperature probe, in DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub>. <sup>1</sup>H NMR spectra were recorded at 400 MHz or 500 MHz, <sup>13</sup>C NMR spectra were recorded at 75 MHz or 100 MHz and <sup>19</sup>F spectra were recorded at 376 MHz on a Brüker 400 M Hz machine

Chemical shifts ( $\delta$ ) were quoted in parts per million (ppm). For <sup>1</sup>H NMR spectra, the chemical shifts were attributed relative to residual CHCl<sub>3</sub> (7.26 ppm) or residual DMSO (2.50 ppm). For <sup>13</sup>C NMR spectra (JMOD), the attributions were done relative to residual CHCl<sub>3</sub> (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.

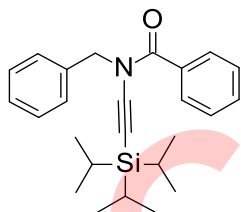
## General procedure 1 for the synthesis of protected ynamides 2a-q

Amides **1a-q** were synthesized according to the literature.<sup>1</sup>

In a sealed tube (Radley) was loaded the amide **1** (1 equiv.), CuSO<sub>4</sub>·5H<sub>2</sub>O (0.2 equiv.), 1,10-phenanthroline (0.4 equiv.) and K<sub>3</sub>PO<sub>4</sub> (2.2 equiv.) under argon. To this mixture was added the 2-bromoethynyl(triisopropyl)silane<sup>2,3</sup> (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/ CH<sub>2</sub>Cl<sub>2</sub> 50/50; gradient eluent, CH<sub>2</sub>Cl<sub>2</sub> in heptane/pentane or diethyl ether in pentane).

**General procedure 1'**: use of CuSO<sub>4</sub>·5H<sub>2</sub>O (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), K<sub>3</sub>PO<sub>4</sub> (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), CuSO<sub>4</sub>·5H<sub>2</sub>O (335 mg, 1.4 mmol), 1,10-phenanthroline (485 mg, 2.7 mmol), K<sub>3</sub>PO<sub>4</sub> (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.<sup>4</sup>

IR (neat): 2167, 1676, 881, 745 cm<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

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

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

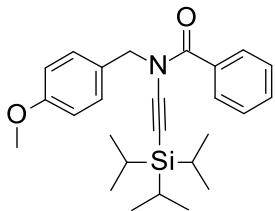
<sup>3</sup> Rubin Y, Lin SS, Knobler CB, Anthony J, Boldi AM, Diederich F. *J. Am. Chem. Soc.* **1991**, *113*, 6943-6949

<sup>4</sup> 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



<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (445 mg, 2.5 mmol), 1,10-phenanthroline (902 mg, 5.0 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

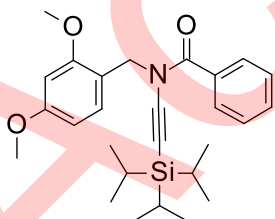
IR (neat): 2171, 1678 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>26</sub>H<sub>36</sub>N O<sub>2</sub> Si ([M+H]<sup>+</sup>) 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), K<sub>3</sub>PO<sub>4</sub> (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).

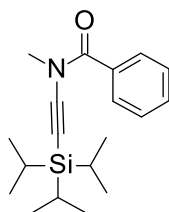
IR (neat): 2170, 1681, 1612, 1591, 1512 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{C}_{27}\text{H}_{37}\text{N O}_3\text{Si}$  ( $[\text{M}]^+$ ) 451.2537, found 451.2518

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



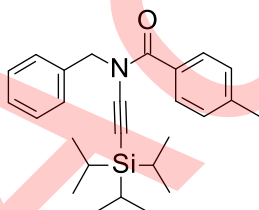
Starting from N-methyl-N-(2-triisopropylsilylethynyl)benzamide **1d** (700 mg, 5.18 mmol),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (129 mg, 0.52 mmol), 1,10-phenanthroline (187 mg, 1.0 mmol),  $\text{K}_3\text{PO}_4$  (2.20 g, 10.4 mmol) and 2-bromoethynyl(triisopropyl)silane (1.49 g, 5.7 mmol, 1.1 equiv.) under argon, using **General procedure 1'** and heating at  $75^\circ\text{C}$  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 literature<sup>4</sup>.

**IR** (neat): 2167, 1680, 1603,  $1580\text{ cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol),  $\text{K}_3\text{PO}_4$  (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  $75^\circ\text{C}$  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,  $675\text{ cm}^{-1}$

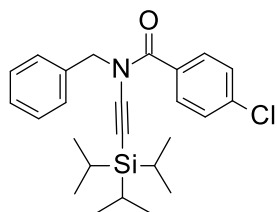
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.76 (d,  $J = 8.1\text{ Hz}$ , 2 H), 7.44 (d,  $J = 7.5\text{ Hz}$ , 2 H), 7.35 (m, 3 H), 7.15 (d,  $J = 7.9\text{ Hz}$ , 2 H), 4.85 (s, 2 H), 2.35 (s, 3 H), 0.88 (s, 18 H), 0.87 (s, 3 H)



**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) 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 C<sub>26</sub>H<sub>35</sub>N O Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

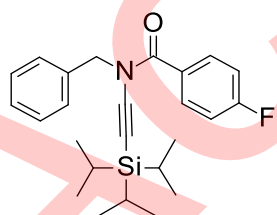
**IR** (neat): 2168, 1681, 752, 699, 676 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>25</sub>H<sub>32</sub>Cl N O Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (161 mg, 0.9 mmol), 1,10-phenanthroline (327 mg, 1.8 mmol), K<sub>3</sub>PO<sub>4</sub> (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<sup>-1</sup>

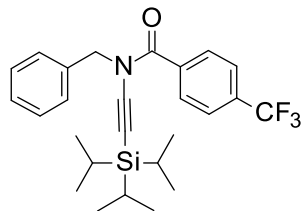
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.8 (m, 2 H), 7.4 (m, 5 H), 7.3 (m, 2 H), 4.8 (s, 2 H), 0.8 (m, 21 H)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -108.5

HRMS (EI): calcd. for C<sub>25</sub> H<sub>32</sub> F N O Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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<sup>-1</sup>

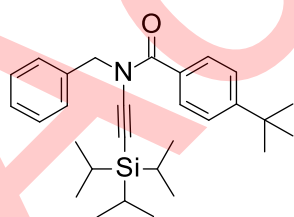
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.87 (d, *J* = 8.3 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H), 7.44-7.31 (m, 5 H), 4.85 (s, 2 H), 0.75 (s, 18 H), 0.75 (s, 3 H)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -61.7

HRMS (ESI): calcd. for C<sub>26</sub> H<sub>33</sub> F<sub>3</sub> N O Si ([M+H]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

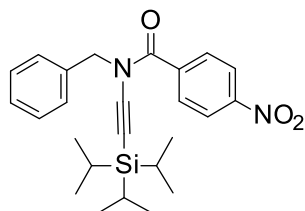
IR (neat): 2167, 1678, 770, 747, 697 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>29</sub>H<sub>41</sub>N O Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

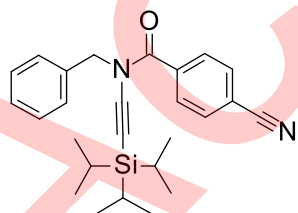
**IR** (neat): 2169, 1680, 1525, 1346, 851, 719, 698 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (53 mg, 0.3 mmol), 1,10-phenanthroline (110 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

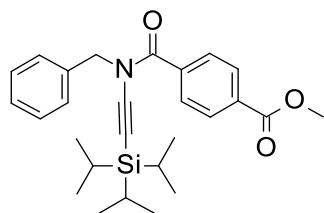
**IR** (neat): 2231, 2169, 1679, 1609, 1273 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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).

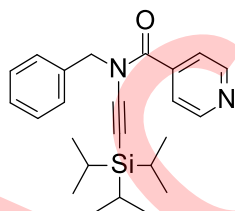
**IR** (neat): 2168, 1728, 1678, 1271, 1106, 727, 699, 675  $cm^{-1}$

**$^1H$  NMR** (500 MHz,  $DMSO-d_6$ )  $\delta$  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,  $DMSO-d_6$ )  $\delta$  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**



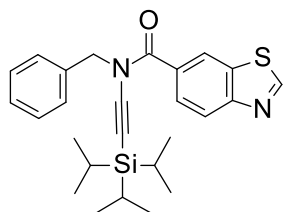
Starting from N-benzylpyridine-4-carboxamide **1m** (382 mg, 1.8 mmol),  $CuSO_4 \cdot 5H_2O$  (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol),  $K_3PO_4$  (1.02 g, 4.8 mmol) and 2-bromoethynyl(triisopropyl)silane (523 mg, 2.0 mmol) under argon, using **General procedure 1** and 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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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**

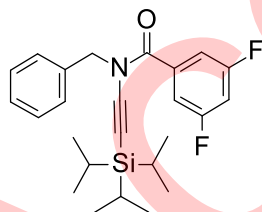
Starting from N-benzyl-1,3-benzothiazole-6-carboxamide **1n** (340 mg, 1.3 mmol), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (0.71 g, 3.0 mmol) and 2-bromoethynyl(triisopropyl)silane (370 mg, 1.4 mmol) under argon, using **General 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<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O S Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (70 mg, 0.3 mmol), 1,10-phenanthroline (100 mg, 0.6 mmol), K<sub>3</sub>PO<sub>4</sub> (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<sup>-1</sup>

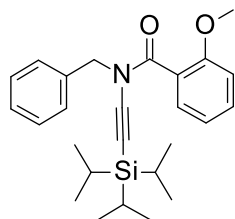
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.46 (m, 2 H), 7.39 (m, 1 H), 7.36 (m, 5 H), 4.82 (s, 2 H), 0.81 (s, 18 H), 0.81 (s, 3 H)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ -108.9 ppm

HRMS (EI): calcd. for C<sub>25</sub>H<sub>31</sub>F<sub>2</sub>N O Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (71 mg, 0.3 mmol, 0.15 equiv.), 1,10-phenanthroline (144 mg, 0.8 mmol), K<sub>3</sub>PO<sub>4</sub> (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).

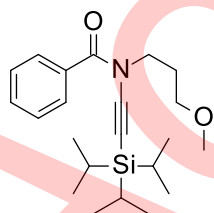
IR (neat): 2172, 1686, 1251, 750, 675 cm<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>26</sub>H<sub>35</sub>N O<sub>2</sub> Si ([M]<sup>+</sup>) 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), CuSO<sub>4</sub>·5H<sub>2</sub>O (129 mg, 0.5 mmol), 1,10-phenanthroline (187 mg, 1.0 mmol), K<sub>3</sub>PO<sub>4</sub> (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<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>22</sub> H<sub>36</sub> N O<sub>2</sub> Si ([M+H]<sup>+</sup>) 374.2437, found 374.2512

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

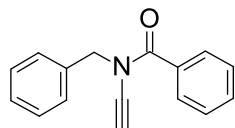
To a solution of the protected ynamide **2** (1 equiv.) in tetrahydrofuran (0.2 M) under argon at 0°C/-5°C was added tetrabutylammonium fluoride (1M in THF, 1.2 equiv.) dropwise.

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 NH<sub>4</sub>Cl (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 Na<sub>2</sub>SO<sub>4</sub> 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.<sup>5</sup>

IR (neat): 3242, 2146, 1649 cm<sup>-1</sup>

<sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) 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)

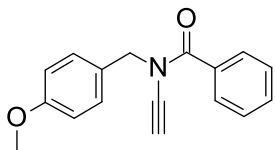
<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ ppm 170.6, 136.5, 133.7, 132, 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 78.9, 64.2, 52.3

HRMS (ESI): calcd. for C<sub>16</sub> H<sub>14</sub> N O ([M+H]<sup>+</sup>) 236.1070, found 236.1071

mp: 45.5-48°C

<sup>5</sup> 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).

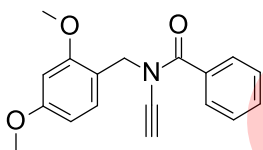
**IR** (neat): 3242, 2142, 1645  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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**

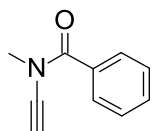
Starting from N-[(2,4-dimethoxyphenyl)methyl]-N-(2-triisopropylsilylethynyl)benzamide **2c** (405 mg, 0.90 mmol), TBAF 1M/THF (1.08 mL, 1.08 mmol) under argon, using **General procedure 2** and stirring at 0°C for 30 min. The crude was purified by trituration in pentane to afford N-[(2,4-dimethoxyphenyl)methyl]-N-ethynyl-benzamide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

**IR** (neat): 3244, 2131, 1660  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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).

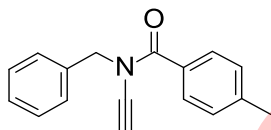
**IR** (neat): 2138, 1647, 704  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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).

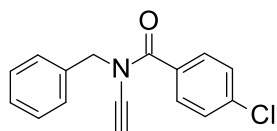
**IR** (neat): 3246, 2138, 1664  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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).

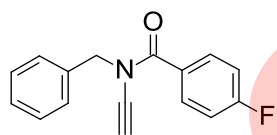
**IR** (neat): 3242, 2136, 1670  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz, DMSO- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$

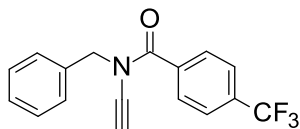
**$^1\text{H}$  NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 7.88 (dd,  $J$  = 8.9, 5.6 Hz, 2 H), 7.35 (m, 5 H), 7.35 (t,  $J$  = 8.8 Hz, 2 H), 4.86 (s, 2 H), 3.9 (s, 1 H)

**$^{13}\text{C}$  NMR** (100 MHz, dmsO- $d_6$ )  $\delta$  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

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

**HRMS (EI)**: calcd. for  $\text{C}_{16}\text{H}_{12}\text{FNO}$  ( $[\text{M}]^+$ ) 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<sup>-1</sup>

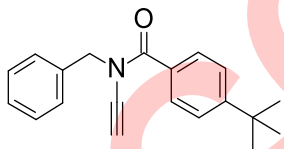
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.93 (d, *J* = 7.9 Hz, 2 H), 7.87 (d, *J* = 7.9 Hz, 2 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.85 (s, 2 H), 3.88 (s, 1 H)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm - 61.4

**HRMS (EI)**: calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N O ([M]<sup>+</sup>) 303.0866, found 303.0869

**mp**: 67-69°C

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

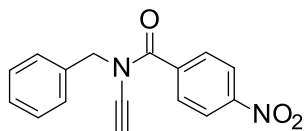
Starting from N-benzyl-4-tert-butyl-N-(2-triisopropylsilylethynyl)benzamide **2i** (215 mg, 0.48 mmol), TBAF 1M/THF (0.58 mL, 0.6 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by silica gel flash column chromatography to afford N-benzyl-4-tert-butyl-N-ethynyl-benzamide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

**IR** (neat): 3230, 2137, 1672 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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 C<sub>20</sub>H<sub>21</sub>N O ([M]<sup>+</sup>) 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).

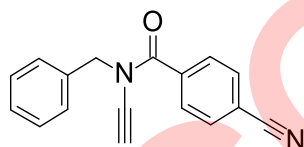
**IR** (neat): 3236, 2133, 1668, 1602, 1523, 1350  $\text{cm}^{-1}$

**$^1\text{H NMR}$**  (400MHz,  $\text{DMSO-}d_6$ )  $\delta$  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,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{cm}^{-1}$

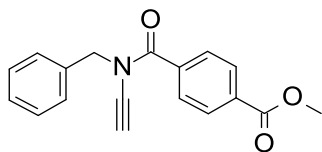
**$^1\text{H NMR}$**  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  ppm 8.0 (d,  $J = 8.2$  Hz, 2 H), 7.9 (d,  $J = 8.2$  Hz, 2 H), 7.35 (m, 5 H), 4.86 (s, 2 H), 3.9 (s, 1 H)

**$^{13}\text{C NMR}$**  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{cm}^{-1}$

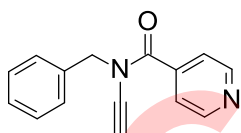
**$^1\text{H NMR}$**  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  ppm 8.04 (d,  $J = 8.2$  Hz, 2 H), 7.84 (d,  $J = 8.3$  Hz, 2 H), 7.4 (m, 4 H), 7.35 (m, 1 H), 4.85 (s, 2 H), 3.89 (s, 3 H), 3.85 (s, 1 H)

**$^{13}\text{C NMR}$**  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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).

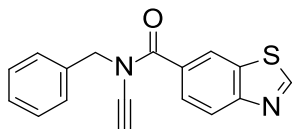
**IR** (neat): 3233, 2139, 1674, 831, 739, 696  $\text{cm}^{-1}$

**$^1\text{H NMR}$**  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

**$^{13}\text{C NMR}$**  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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).

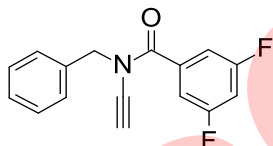
**IR** (neat): 3234, 2137, 1668  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

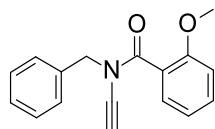
**$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  ppm 168.3, 162.3 (dd,  $J = 248.2, 12.7$  Hz, 2C), 137.3 (t,  $J = 9.2$  Hz), 136.1, 129.0 (2C), 128.5 (2C), 128.2, 112.2 (d,  $J = 27.3$  Hz, 2C), 107.2 (t,  $J = 25.6$  Hz), 78.1, 65.1, 52.5

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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**

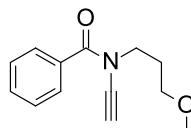
Starting from N-benzyl-2-methoxy-N-(2-triisopropylsilylethynyl)benzamide **2p** (447 mg, 1.06 mmol), TBAF 1M/THF (1.27 mL, 1.3 mmol) under argon, using **General procedure 2** and stirring at 0°C for 40 min. The crude was purified by trituration in pentane to afford N-benzyl-N-ethynyl-2-methoxybenzamide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

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

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{dmsO-}d_6$ )  $\delta$  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)

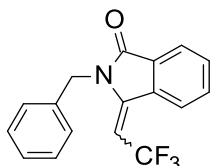
**$^{13}\text{C}$  NMR** (100 MHz,  $\text{dmsO-}d_6$ )  $\delta$  ppm 170.5, 134.2, 131.7 (2C), 128.3 (2C), 128.2, 78.7, 69.5, 63.7, 58.5, 46.5, 27.7

**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)-1λ<sup>3</sup>,2-benziodoxole) (1.2 equiv.) and Ir(ppy)<sub>3</sub> (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% /CH<sub>2</sub>Cl<sub>2</sub> 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)<sub>3</sub> (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<sup>-1</sup> (mixture 81/19 E/Z)

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.87

HRMS (ESI): calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 304.0944, found 304.0942

mp: 94.6-101.9°C

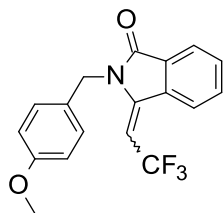
#### (3Z)-2-benzyl-3-(2,2,2-trifluoroethylidene)isoindolin-1-one **4aZ**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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<sup>-1</sup> (mixture 60/40 E/Z)

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.8

HRMS (ESI): calcd. for C<sub>18</sub>H<sub>15</sub>F<sub>3</sub>N O<sub>2</sub> ([M+H]<sup>+</sup>) 334.1049, found 334.105

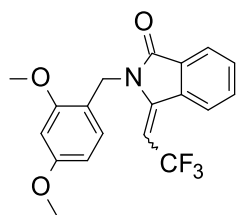
mp: 76.5-84.2°C (mixture 60/40 E/Z)

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

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.8

**HRMS (ESI)**: calcd. for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N O<sub>3</sub> ([M+H]<sup>+</sup>) 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<sup>-1</sup>

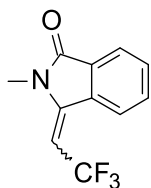
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.22 (d, *J* = 7.7 Hz, 1 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 7.81 (tt, *J* = 7.7, 1.1 Hz, 1 H), 7.73 (t, *J* = 7.5 Hz, 1 H), 6.59 (df, *J* = 2.3 Hz, 1 H), 6.49 (d, *J* = 8.3 Hz, 1 H), 6.37 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.33 (q, *J* = 10.0 Hz, 1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

**<sup>13</sup>C NMR** (75 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -49.3

**HRMS (ESI)**: calcd. for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N O<sub>3</sub> ([M+H]<sup>+</sup>) 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)<sub>3</sub> (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<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.8

HRMS (ESI): calcd. for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 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<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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 (q<sup>6</sup>, *J* = 2.3 Hz, 3 H)

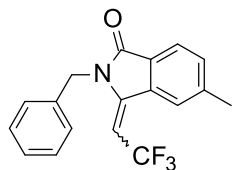
<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ ppm 167.9, 143.3 (q, *J* = 6.3 Hz), 136.9, 133.8, 131.5, 127.4, 123.9 (q, *J* = 268.0 Hz), 123.2, 121.6, 91.4 (q, *J* = 37.3 Hz), 28.1

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -47.1

HRMS (ESI): calcd. for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 228.0631, found 228.0632

mp: 105.5-107.0°C

<sup>6</sup> 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)<sub>3</sub> (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<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.7

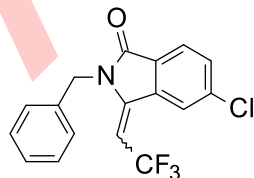
**HRMS (ESI)**: calcd. for C<sub>18</sub>H<sub>15</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 318.1111, found 318.1098

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

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.8

HRMS (ESI): calcd. for C<sub>17</sub>H<sub>12</sub>ClF<sub>3</sub>NO ([M+H]<sup>+</sup>) 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<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

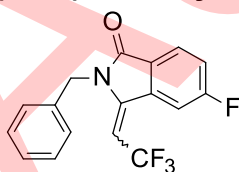
<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ ppm 168.2, 141.3 (q, *J* = 6.4 Hz), 139.8, 139.3, 137.6, 132.2, 128.9 (2C), 127.4, 126.1, 125.8 (2C), 125.5, 123.6 (q, *J* = 268.8 Hz), 122.4, 93.4 (q, *J* = 37.5 Hz), 44.9

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -49.1

HRMS (ESI): calcd. for C<sub>17</sub>H<sub>12</sub>ClF<sub>3</sub>NO ([M+H]<sup>+</sup>) 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)<sub>3</sub> (6.6 mg, 0.01 mmol), using **General procedure 3** (in CH<sub>2</sub>Cl<sub>2</sub>) 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<sup>-1</sup>



**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.9, -105

**HRMS (EI)** : calcd. for C<sub>17</sub> H<sub>11</sub> F<sub>4</sub> N O ([M]<sup>+</sup>) 321.0777, found 321.0772

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

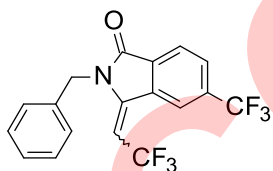
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.2 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.94 (dd, *J* = 8.5 Hz, 1 H), 7.57 (td, *J* = 8.6, 2.3 Hz, 1 H), 7.3 (t, *J* = 7.6 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 6.42 (q, *J* = 10.0 Hz, 1 H), 5.1 (s, 2 H)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, dmsO-d6) δ ppm -49.1, -105

**HRMS (ESI)**: calcd. for C<sub>17</sub> H<sub>12</sub> F<sub>4</sub> N O ([M+H]<sup>+</sup>) 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)<sub>3</sub> (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<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.9, -61.6

**HRMS (EI)**: calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>6</sub>N O ([M]<sup>+</sup>) 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<sup>-1</sup>

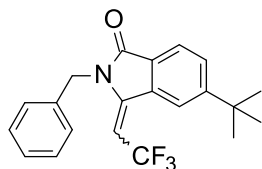
**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.78 (s, 1 H), 8.08 (bs, 2 H), 7.3 (t, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.1 (d, *J* = 7.65 Hz, 2 H), 6.69 (q, *J* = 10.09 Hz, 1 H), 5.14 (s, 2 H)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -49.2, -61

**HRMS (EI)**: calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>6</sub>N O ([M]<sup>+</sup>) 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)<sub>3</sub> (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**

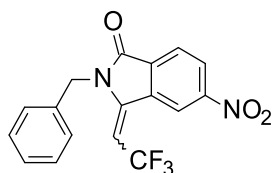
**IR** (neat): 1726, 1654, 1313, 1253, 1126 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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)

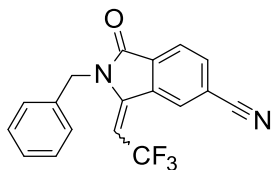
**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.9

**HRMS (ESI)**: calcd. for C<sub>21</sub>H<sub>22</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 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<sup>-1</sup>**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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)**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -48.7**HRMS (ESI)**: calcd. for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N O ([M+H]<sup>+</sup>) 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)<sub>3</sub> (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<sup>-1</sup> (mixture 70/30 E/Z)**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.6**HRMS (ESI)**: calcd. for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O ([M+H]<sup>+</sup>) 349.0795, found 349.0796**(3Z)-2-benzyl-5-nitro-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4jZ****<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)**<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) 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**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -49.3**HRMS (ESI)**: calcd. for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O ([M+H]<sup>+</sup>) 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)<sub>3</sub> (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<sup>-1</sup>

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.8

**HRMS (EI)**: calcd. for C<sub>18</sub> H<sub>11</sub> F<sub>3</sub> N<sub>2</sub> O ([M]<sup>+</sup>) 328.0823, found 328.0818

**mp**: 122.6-132.0°C (mixture 65/35 E/Z)

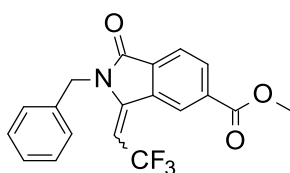
*(3Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carbonitrile 4kZ*

**IR** (neat): 2231, 1727, 1662, 1094 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) 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)

**<sup>13</sup>C NMR** (125 MHz, DMSO-*d*<sub>6</sub>) 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

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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*

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.7

HRMS (ESI): calcd. for C<sub>19</sub>H<sub>15</sub>F<sub>3</sub>N O<sub>3</sub> ([M+H]<sup>+</sup>) 362.0999, found 362.1001

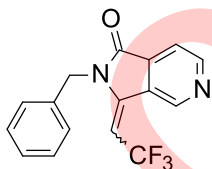
*methyl (3Z)-2-benzyl-1-oxo-3-(2,2,2-trifluoroethylidene)isoindoline-5-carboxylate 4IZ*

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm -52.5

HRMS (ESI): calcd. for C<sub>16</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O ([M+H]<sup>+</sup>) 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<sup>-1</sup>

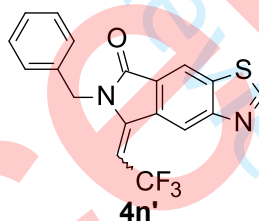
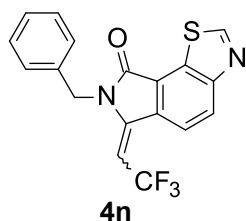
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 9.55 (s, 1 H), 9 (d, *J* = 4.9 Hz, 1 H), 7.9 (dd, *J* = 4.9, 1.1 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.11 (d, *J* = 7.4 Hz, 2 H), 6.5 (q, *J* = 10.0 Hz, 1 H), 5.17 (s, 2 H)

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, dms<sub>o</sub>-d<sub>6</sub>) δ ppm -49.2

HRMS (ESI): calcd. for C<sub>16</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O ([M+H]<sup>+</sup>) 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)<sub>3</sub> (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<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -48.9

HRMS (ESI): calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>3</sub>O S ([M+H]<sup>+</sup>) 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<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -46.8

HRMS (ESI): calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>3</sub>O S ([M+H]<sup>+</sup>) 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<sup>-1</sup> (mixture 78/22 E/Z)

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -52.1

HRMS (ESI): calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>3</sub>O S ([M+H]<sup>+</sup>) 361.0617, found 361.0619

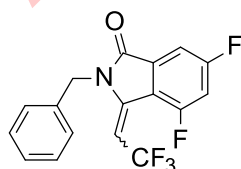
(5Z)-6-benzyl-5-(2,2,2-trifluoroethylidene)pyrrolo[3,4-f][1,3]benzothiazol-7-one 4n'Z

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 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)

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) 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

<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) 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)<sub>3</sub> (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  $\text{cm}^{-1}$

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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,  $\text{DMSO-}d_6$ )  $\delta$  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,  $\text{DMSO-}d_6$ )  $\delta$  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  $\text{cm}^{-1}$

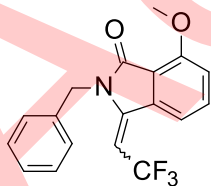
$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  ppm 7.84 (td,  $J = 10.1, 2.1$  Hz, 1 H), 7.73 (dd,  $J = 9.9, 2.1$  Hz, 1 H), 7.31 (t,  $J = 7.4$  Hz, 2 H), 7.24 (t,  $J = 7.2$  Hz, 1 H), 7.11 (d,  $J = 7.5$  Hz, 2 H), 6.02 (qd<sup>7</sup>,  $J = 9.9, 4.2$  Hz, 1 H), 5.11 (s, 2 H)

$^{13}\text{C NMR}$  (75 MHz,  $\text{DMSO-}d_6$ )  $\delta$  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,  $\text{DMSO-}d_6$ )  $\delta$  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**

<sup>7</sup> Through space coupling

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

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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)

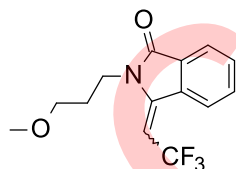
**$^{13}\text{C}$  NMR** (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 168.1, 156, 141.5 (q,  $J = 6.8$  Hz), 136.8, 133.6, 132.7 (q,  $J = 267.2$  Hz), 129.2, 127.8 (2C), 127.5, 126.4 (2C), 122, 117.4, 116, 94.6 (q,  $J = 37.6$  Hz), 56.8, 44.7

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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  $27^{\circ}\text{C}$  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  $\text{cm}^{-1}$  (mixture 78/22 E/Z)

**$^1\text{H}$  NMR** (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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)

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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

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3 <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -51.6  
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5 HRMS (ESI): calcd. for C<sub>14</sub>H<sub>15</sub>F<sub>3</sub>N O<sub>2</sub> ([M+H]<sup>+</sup>) 286.1049, found 286.1051  
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7

8 *(3Z)*-2-(3-methoxypropyl)-3-(2,2,2-trifluoroethylidene)isoindolin-1-one 4qZ  
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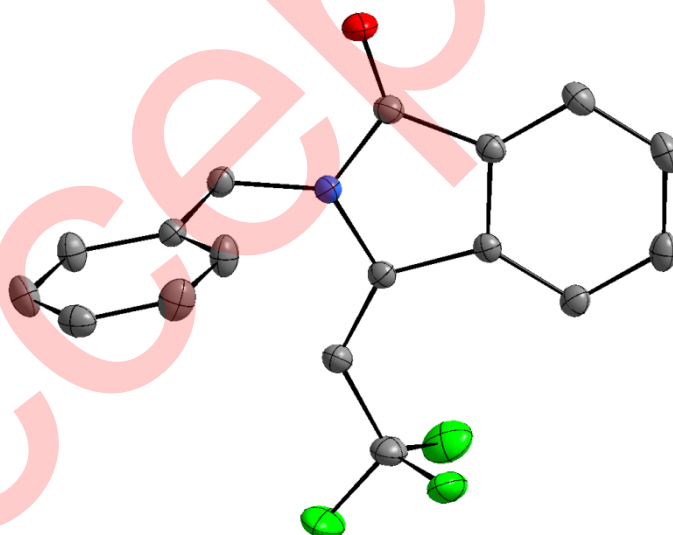
10 <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.15 (d, *J* = 7.6 Hz, 1 H), 7.81 (m, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H),  
11 7.68 (t, *J* = 7.4 Hz, 1 H), 6.29 (q, *J* = 10.2 Hz, 1 H), 3.88 (t, *J* = 7.6 Hz, 2 H), 3.35 (m, 2 H), 3.21 (s, 3 H),  
12 1.8 (m, 2 H)  
13

14 <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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

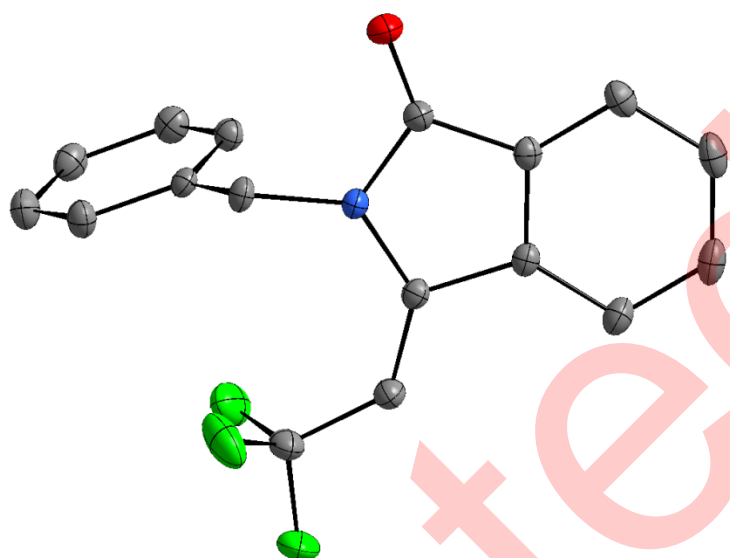
17 <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>) δ ppm -49  
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## X-Ray crystal structure determination of compounds **4aE** and **4aZ**

A single crystal of each compound (**4aE** and **4aZ**) was selected, mounted onto a cryoloop and transferred into a cold nitrogen gas stream. Intensity data were collected with a Bruker Kappa-APEXII diffractometer using graphite-monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Data collection was performed with the Bruker APEXII suite. Unit-cell parameters determination, integration and data reduction were carried out with SAINT program. SADABS was used for scaling and absorption corrections. The structures were solved with SHELXS-2014<sup>1</sup> for **4aZ** or SHELXT-2014<sup>2</sup> for **4aE**, and refined by full-matrix least-squares methods with SHELXL-2014<sup>3</sup> using the Olex2 software package<sup>4</sup>. All non-hydrogen atoms were refined anisotropically. The structures were deposited at the Cambridge Crystallographic Data Centre with numbers CCDC 1949295 to 1949296 and can be obtained free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).



X-Ray crystal structure of compound **4aE** (E isomer)



X-Ray crystal structure of compound **4aZ** (Z isomer)

## Crystal data and structure refinement for 4aE

|  |   |
|--|---|
| CCDC number                                  | 1949295   |
| Empirical formula <sup>a</sup>               | C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> NO |
| Moiety Formula                               | C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> 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 <sup>3</sup> )                     | 2749.45(12)                                       |
| Z  | 8   |
| ρ <sub>calc</sub> (g/cm <sup>3</sup> )       | 1.465   |
| Absorption coefficient μ (mm <sup>-1</sup> ) | 0.119 (MoKα)                                      |
| F(000)                                       | 1248  |
| Crystal size (mm <sup>2</sup> )              | 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,<br>-11 ≤ k ≤ 11,<br>-22 ≤ l ≤ 22    |
| Measured reflections                         | 21356   |
| Unique reflections                           | 4223  |
| R <sub>int</sub> / R <sub>sigma</sub>        | 0.0223 / 0.0192                                   |
| Completeness                                 | 0.999   |
| Reflections [I ≥ 2σ(I)]                      | 3239  |
| Restraints                                   | 0   |
| Parameters                                   | 199   |
| Goodness-of-fit F <sup>2</sup>               | 1.021   |
| Final R indexes <sup>b,c</sup> [all data]    | R1 = 0.0611,<br>wR2 = 0.1201                      |
| Final R indexes <sup>b,c</sup> [I ≥ 2σ(I)]   | R1 = 0.0438<br>wR2 = 0.1080                       |
| Largest diff. peak/hole (e/Å <sup>3</sup> )  | 0.30/-0.25  |

<sup>a</sup> 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 <sup>a</sup>               | C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> NO |
| Moiety Formula                               | C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> NO |
| Formula weight (g/mol)                       | 303.28  |
| Temperature (K)                              | 200   |
| Crystal system                               | Monoclinic  |
| Space group                                  | P2 <sub>1</sub> /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 <sup>3</sup> )                     | 1400.99(8)  |
| Z  | 4   |
| ρ <sub>calc</sub> (g/cm <sup>3</sup> )       | 1.438   |
| Absorption coefficient μ (mm <sup>-1</sup> ) | 0.117 (MoKα)                                      |
| F(000)                                       | 624   |
| Crystal size (mm <sup>2</sup> )              | 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,<br>-18 ≤ k ≤ 18,<br>-17 ≤ l ≤ 17    |
| Measured reflections                         | 38461   |
| Unique reflections                           | 4319  |
| R <sub>int</sub> / R <sub>sigma</sub>        | 0.0464 / 0.0214                                   |
| Completeness                                 | 1.000   |
| Reflections [I ≥ 2σ(I)]                      | 3394  |
| Restraints                                   | 0   |
| Parameters                                   | 199   |
| Goodness-of-fit F <sup>2</sup>               | 1.052   |
| Final R indexes <sup>b,c</sup> [all data]    | R1 = 0.0622,<br>wR2 = 0.1329                      |
| Final R indexes <sup>b,c</sup> [I ≥ 2σ(I)]   | R1 = 0.0459<br>wR2 = 0.1175                       |
| Largest diff. peak/hole (e/Å <sup>3</sup> )  | 0.39/-0.30  |

<sup>a</sup> 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 package<sup>8</sup>. Optimization of geometries, frequency and single point energy calculations were done using the PBE0 functional including the D3BJ dispersion term<sup>9,10</sup> with the def2-TZVP basis set<sup>11</sup>. The effect of solvation (in MeCN) was modeled using the 'SMD' model<sup>12</sup>. 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/<br>Def2-TZVP             | $\Delta E$ | $\Delta E+ZPE$ | $\Delta G$ | $\Delta G_{MeCN}$ |
|-------------------------------------|------------|----------------|------------|-------------------|
| <b>A<sub>E</sub></b>                | 0.0        | 0.0            | 0.0        | 0.0               |
| <b>A<sub>Z</sub><sup>a</sup></b>    | 0.4        | 0.8            | 1.3        | 2.1               |
| <b>TS<sub>Ebz</sub><sup>a</sup></b> | 5.5        | 4.9            | 6.3        | 5.7               |
| <b>B<sub>Ebz</sub><sup>a</sup></b>  | -26.1      | -25.4          | -23.5      | -26.1             |
| <b>TS<sub>Eb</sub><sup>a</sup></b>  | 12.3       | 10.9           | 13.5       | 12.8              |
| <b>B<sub>Eb</sub><sup>a</sup></b>   | -12.5      | -12.2          | -9.8       | -12.4             |
| <b>TS<sub>Zbz</sub><sup>b</sup></b> | 9.4        | 8.4            | 9.1        | 6.9               |
| <b>B<sub>Zbz</sub><sup>b</sup></b>  | -21.8      | -21.6          | -20.2      | -24.9             |
| <b>TS<sub>Zb</sub><sup>b</sup></b>  | 13.7       | 12.7           | 14.8       | 12.0              |
| <b>B<sub>Zb</sub><sup>b</sup></b>   | -10.6      | -10.7          | -8.3       | -13.1             |

<sup>a</sup> energies relative to **A<sub>E</sub>**; <sup>b</sup> energies relative to **A<sub>Z</sub>**

<sup>8</sup> 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**

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

<sup>10</sup> Adamo C, Barone V. *J. Chem. Phys.* **1999**, *110*, 6158

<sup>11</sup> Weigend F, Ahlrichs R, *Chem. Phys.*, **2005**, *7*, 3297

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

Cartesian coordinates of all compounds  
involved in this work

**A<sub>E</sub>**

|   |           |           |           |
|---|-----------|-----------|-----------|
| 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<sub>Z</sub>**

|   |           |           |           |
|---|-----------|-----------|-----------|
| 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<sub>Ebz</sub> 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<sub>Ebz</sub>**

|   |          |           |           |
|---|----------|-----------|-----------|
| 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<sub>Eb</sub> 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

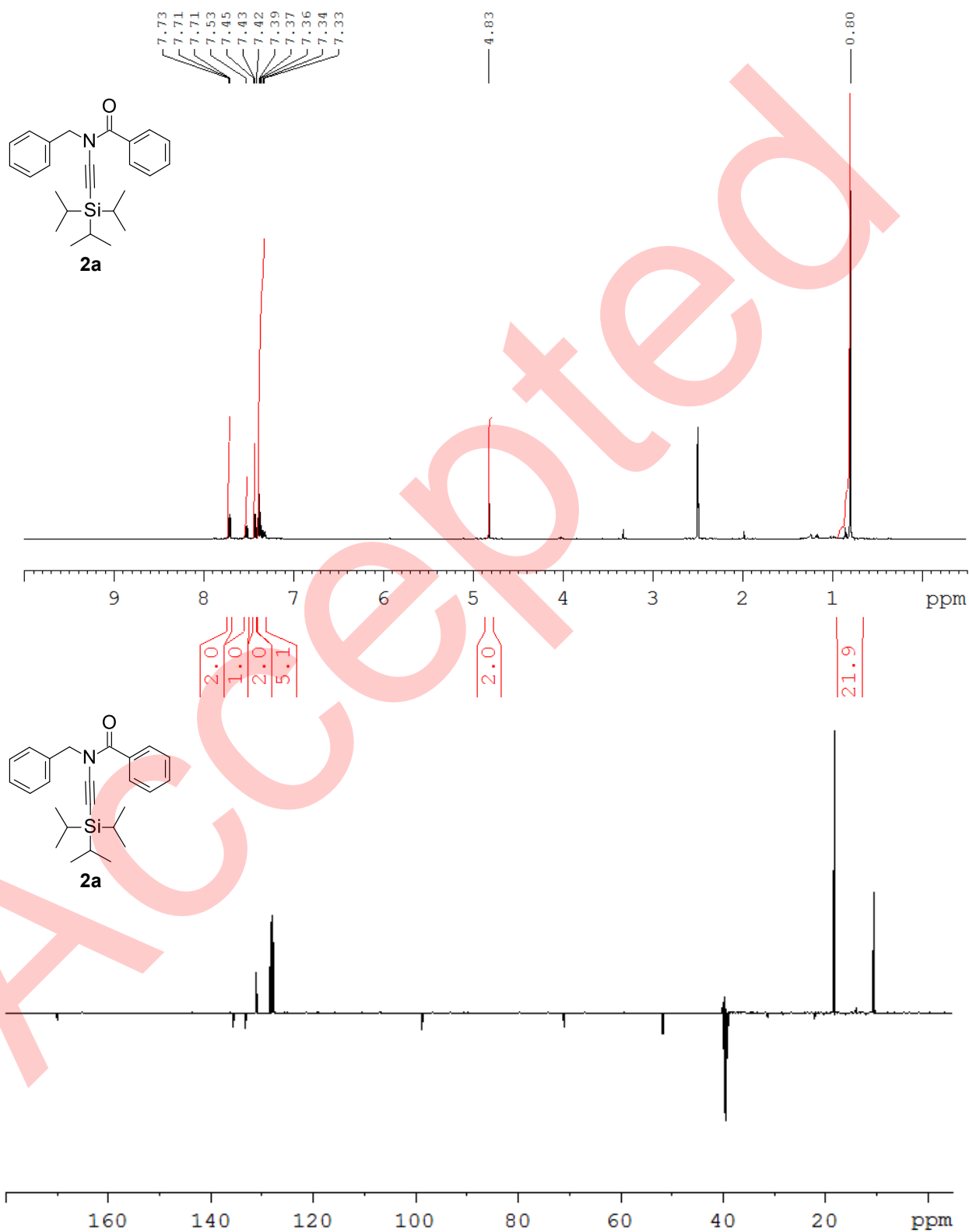
**B<sub>Eb</sub>**

|   |           |           |           |
|---|-----------|-----------|-----------|
| 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  |

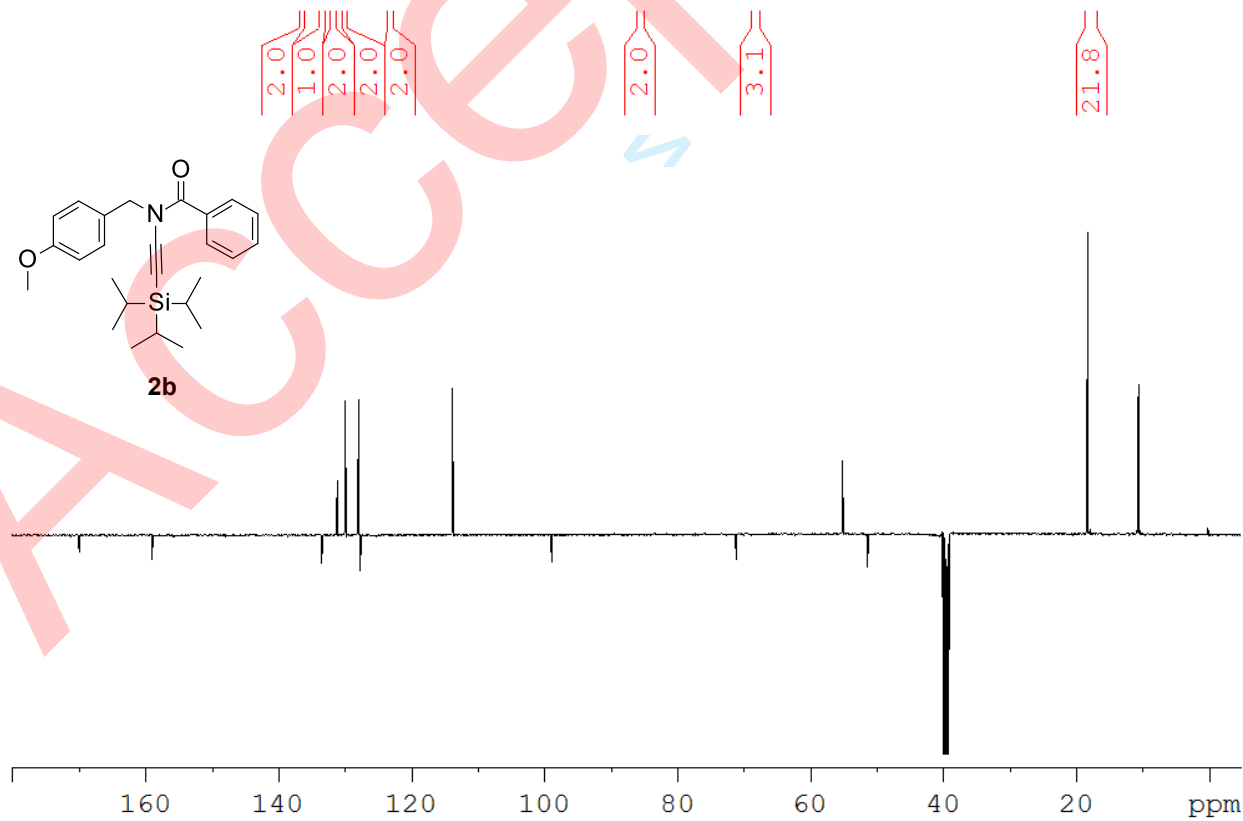
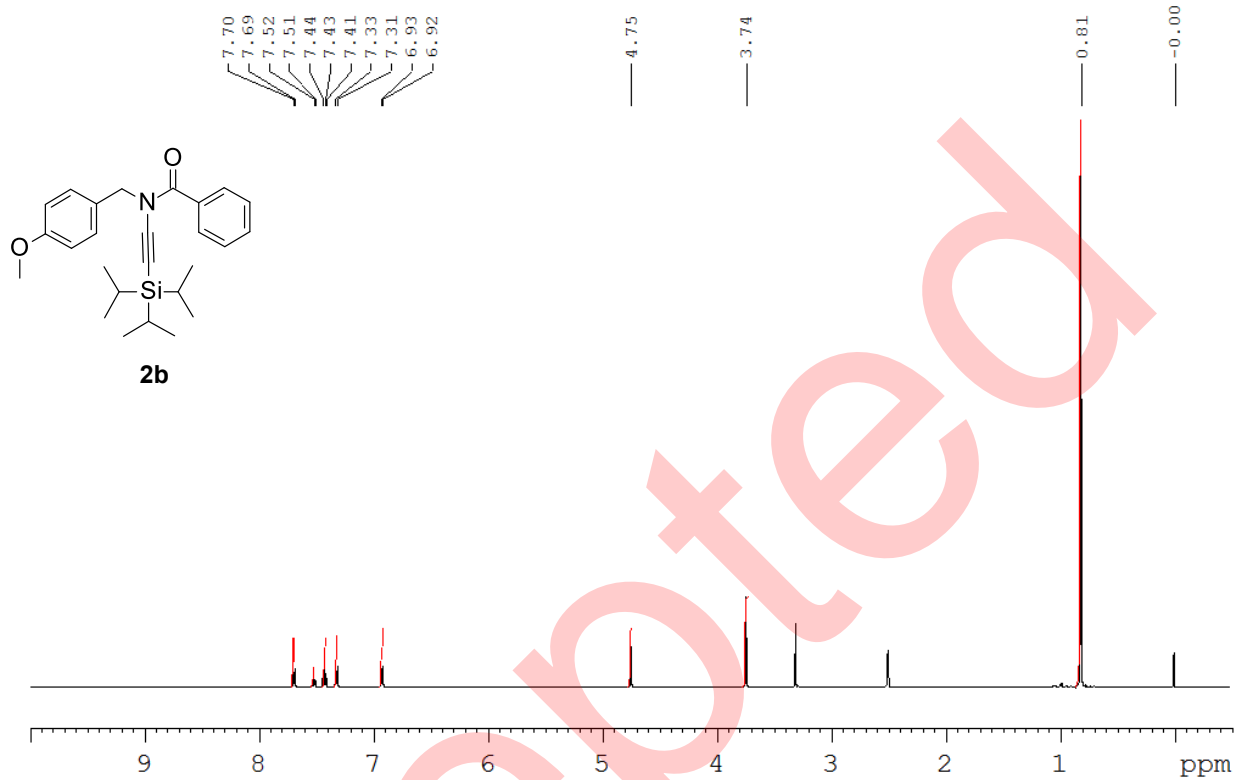
**TS<sub>Zbz</sub> Frequencies -- -338.5570**

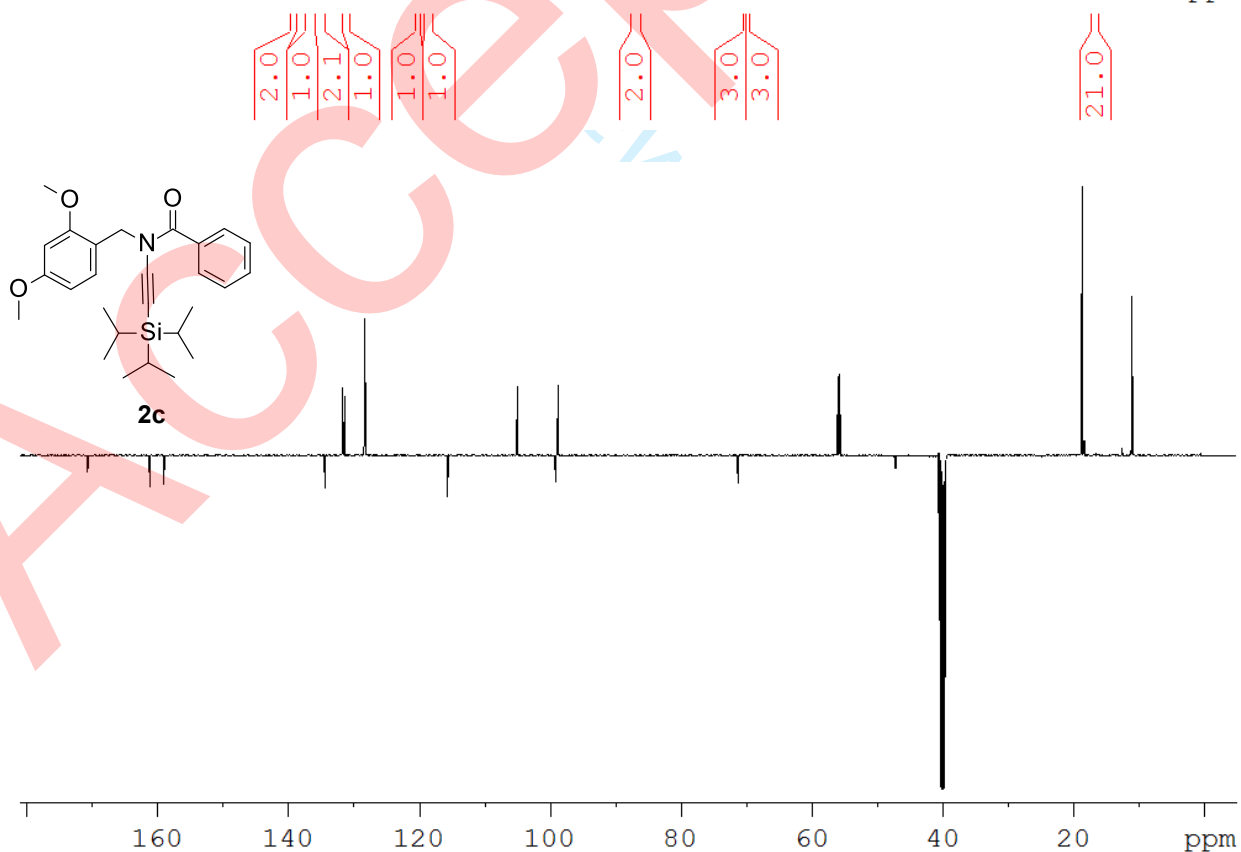
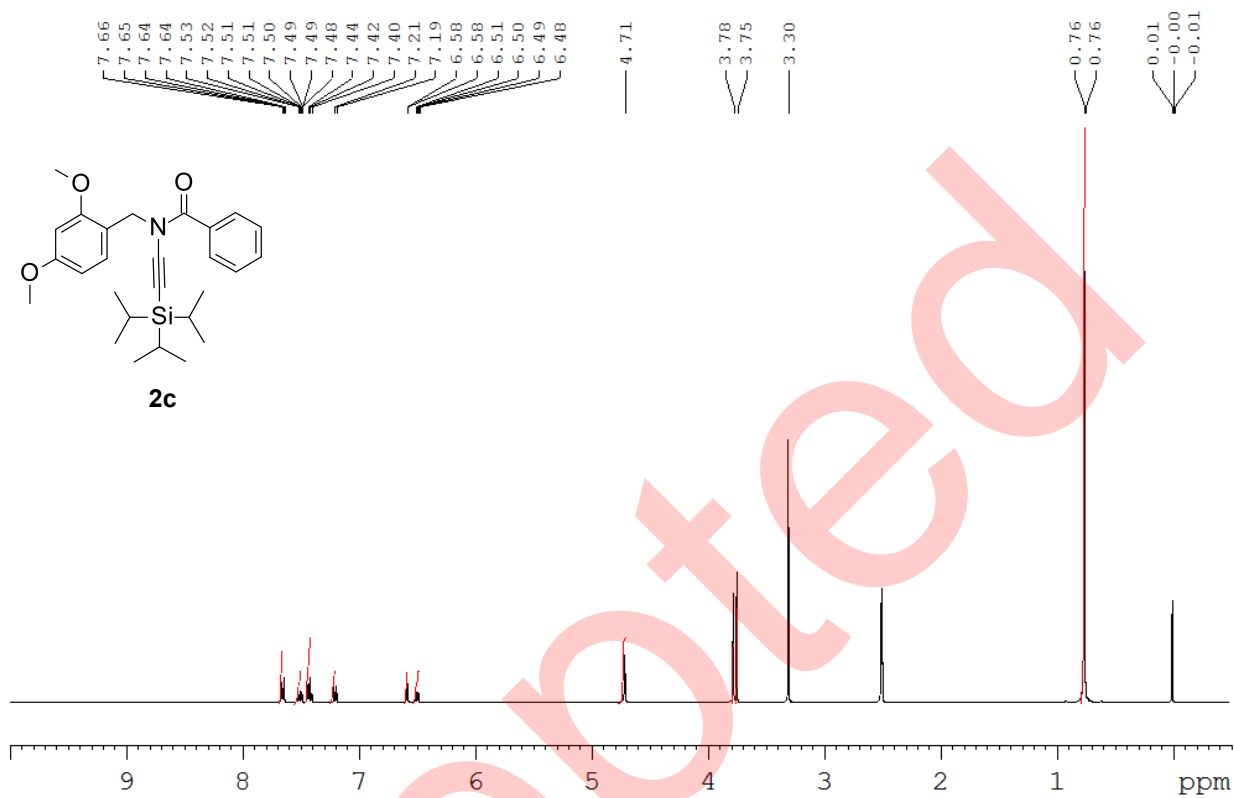
|   |           |           |           |
|---|-----------|-----------|-----------|
| 6 | 1.597330  | -1.261953 | 0.859718  |
| 6 | 2.005406  | -0.910154 | -0.417484 |
| 6 | 3.315683  | -1.172296 | -0.802731 |
| 6 | 4.202328  | -1.773923 | 0.073767  |
| 6 | 3.788161  | -2.124051 | 1.351285  |
| 6 | 2.483909  | -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  |

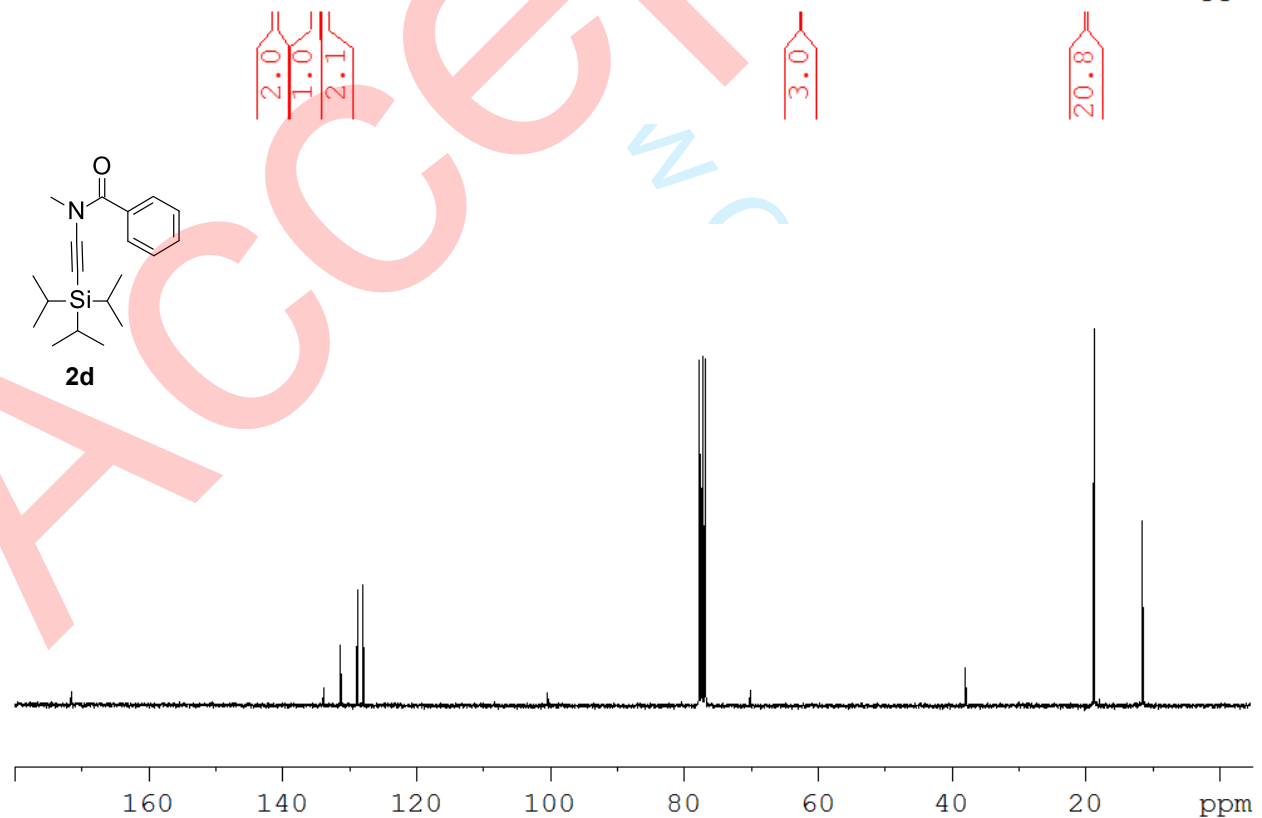
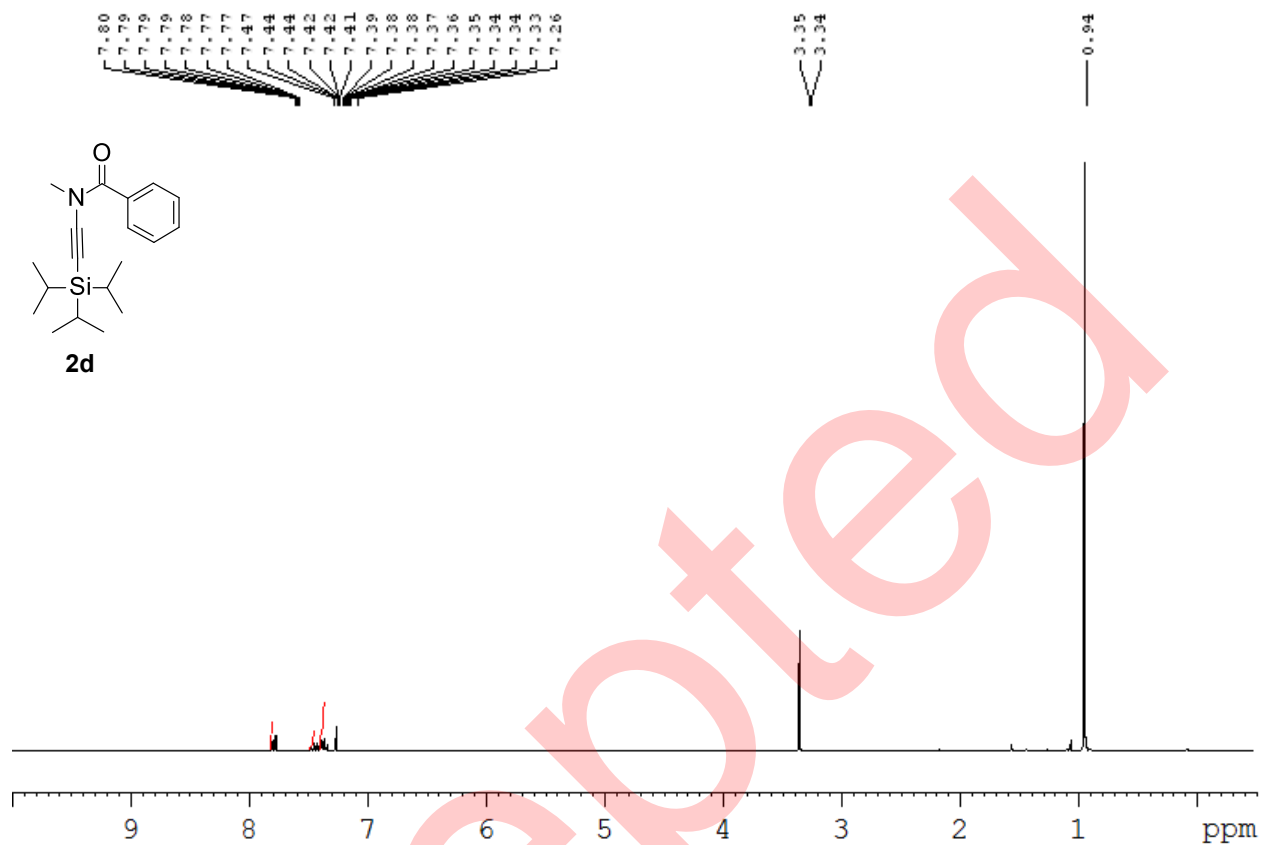
|    |                        |           |           |           |                                       |                  |           |           |
|----|------------------------|-----------|-----------|-----------|---------------------------------------|------------------|-----------|-----------|
| 1  |                        |           |           |           |                                       |                  |           |           |
| 2  |                        |           |           |           |                                       |                  |           |           |
| 3  | 6                      | -3.958601 | 0.672262  | 0.270536  | 7                                     | -0.363739        | -0.197864 | -1.002545 |
| 4  | 6                      | -2.903943 | 0.308612  | -0.580208 | 6                                     | -0.931803        | 0.859193  | -0.326176 |
| 5  | 1                      | -2.615080 | -2.967755 | 0.304274  | 6                                     | -0.428145        | 2.012063  | 0.132676  |
| 6  | 1                      | -4.525658 | -2.315930 | 1.772357  | 1                                     | -1.124943        | 2.686946  | 0.610082  |
| 7  | 1                      | -5.321364 | 0.021384  | 1.783788  | 6                                     | -1.252453        | -1.269106 | -1.216149 |
| 8  | 1                      | -4.358844 | 1.678270  | 0.232621  | 8                                     | -0.950412        | -2.287938 | -1.788696 |
| 9  | 1                      | -2.701601 | 0.933700  | -1.445055 | 6                                     | -2.499523        | -0.886190 | -0.572193 |
| 10 | 6                      | 0.826250  | 2.746090  | 0.195463  | 6                                     | -3.510776        | -1.694242 | -0.144061 |
| 11 | 9                      | 1.800350  | 1.994912  | 0.727826  | 6                                     | -4.420425        | -1.193618 | 0.795823  |
| 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>B<sub>Zbz</sub></b> |           |           |           | 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  | <b>TS<sub>Zb</sub> Frequencies --</b> | <b>-412.0166</b> |           |           |
| 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>B<sub>Zb</sub></b>                 |                  |           |           |
| 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 |
| 33 | 6                      | -4.199258 | -1.259882 | -1.013444 | 6                                     | 3.908373         | -1.134812 | -0.354237 |
| 34 | 6                      | -4.167593 | -0.032280 | -1.670237 | 6                                     | 4.525885         | -0.870864 | 0.887453  |
| 35 | 6                      | -3.519638 | 1.048871  | -1.105630 | 6                                     | 3.938197         | 0.050462  | 1.783160  |
| 36 | 1                      | -2.647216 | 1.796207  | 0.708645  | 6                                     | 2.865281         | 0.808419  | 1.434819  |
| 37 | 1                      | -3.497305 | -2.393982 | 0.678751  | 1                                     | 2.729726         | 1.705929  | -0.464447 |
| 38 | 1                      | -4.723005 | -2.098594 | -1.455973 | 1                                     | 4.240432         | -1.978031 | -0.951106 |
| 39 | 1                      | -4.680658 | 0.082556  | -2.618200 | 1                                     | 5.383693         | -1.452452 | 1.199376  |
| 40 | 1                      | -3.545219 | 2.016762  | -1.592491 | 1                                     | 4.341767         | 0.132705  | 2.786427  |
| 41 | 6                      | -1.834164 | -0.496154 | 1.831979  | 1                                     | 2.416064         | 1.498461  | 2.139352  |
| 42 | 1                      | -1.951517 | 0.221825  | 2.649786  | 6                                     | 1.841887         | -0.656355 | -1.812673 |
| 43 | 1                      | -1.754770 | -1.493953 | 2.256245  | 1                                     | 1.991767         | -0.045173 | -2.712305 |
| 44 | 7                      | -0.586311 | -0.204012 | 1.089042  | 1                                     | 1.768469         | -1.697526 | -2.120701 |
| 45 | 6                      | -0.714139 | 0.773435  | 0.165574  | 7                                     | 0.608279         | -0.254050 | -1.120704 |
| 46 | 6                      | 0.016154  | 1.721953  | -0.390120 | 6                                     | 0.858711         | 0.770945  | -0.221108 |
| 47 | 1                      | -0.417828 | 2.319475  | -1.185210 | 6                                     | 0.054962         | 1.717307  | 0.272176  |
| 48 | 6                      | 0.525161  | -1.016549 | 1.344143  | 1                                     | 0.489811         | 2.416720  | 0.975197  |
| 49 | 8                      | 0.601773  | -1.607432 | 2.395590  | 6                                     | -0.540960        | -0.999179 | -1.353286 |
| 50 | 6                      | 1.520265  | -1.195891 | 0.259137  | 8                                     | -0.668843        | -1.589070 | -2.402696 |
| 51 | 6                      | 1.136168  | -1.325435 | -1.071170 | 6                                     | -1.508992        | -1.165144 | -0.239312 |
| 52 | 6                      | 2.086962  | -1.594302 | -2.041141 | 6                                     | -1.089180        | -1.292778 | 1.080086  |
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| 56 | 1                      | 0.093009  | -1.229539 | -1.347371 | 6                                     | -2.854925        | -1.315286 | -0.555274 |
| 57 | 1                      | 1.784205  | -1.706107 | -3.075505 | 1                                     | -0.038236        | -1.202947 | 1.327458  |
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| 59 | 1                      | 4.849915  | -1.692333 | -0.084652 | 1                                     | -4.082778        | -1.862428 | 2.547708  |
| 60 | 1                      | 3.133818  | -1.268521 | 1.657438  | 1                                     | -4.829440        | -1.650803 | 0.199085  |
|    | 6                      | 1.393411  | 2.141237  | -0.005657 | 1                                     | -3.160289        | -1.236746 | -1.591319 |
|    | 9                      | 1.469513  | 3.483341  | 0.035502  | 6                                     | -1.338977        | 2.067030  | -0.091939 |
|    | 9                      | 1.758502  | 1.690355  | 1.201636  | 9                                     | -1.450319        | 3.407427  | -0.166330 |
|    | 9                      | 2.332111  | 1.741243  | -0.878949 | 9                                     | -1.718285        | 1.582647  | -1.282689 |
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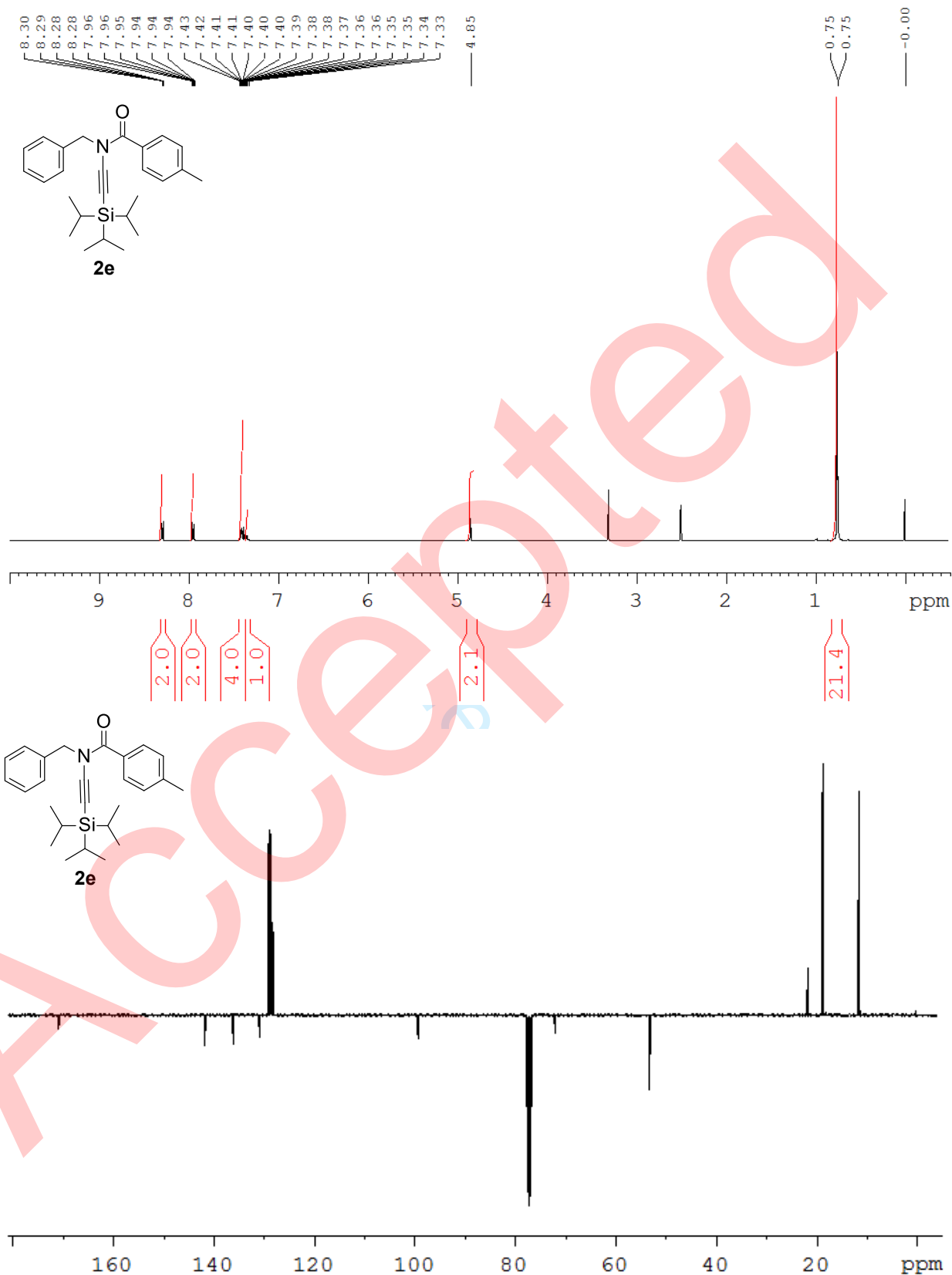
$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra

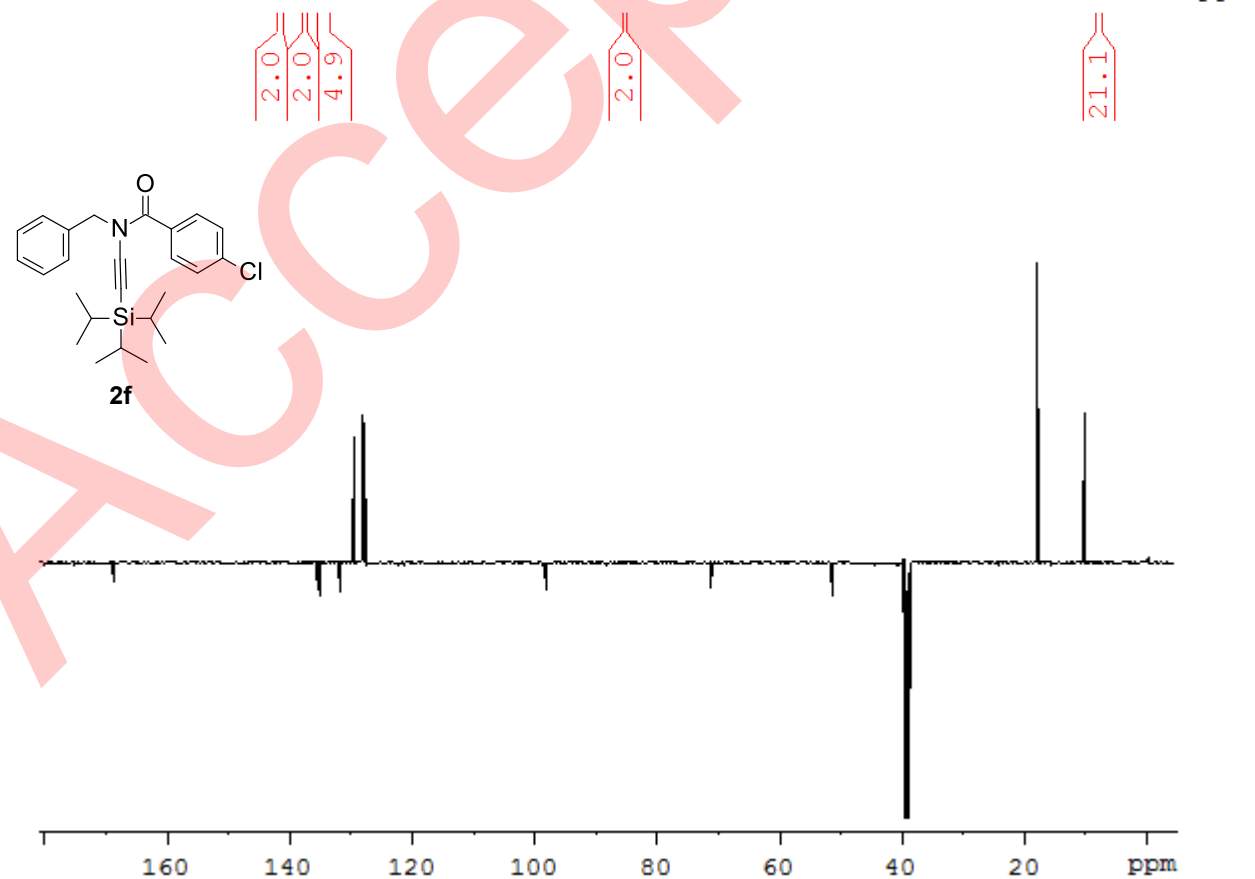
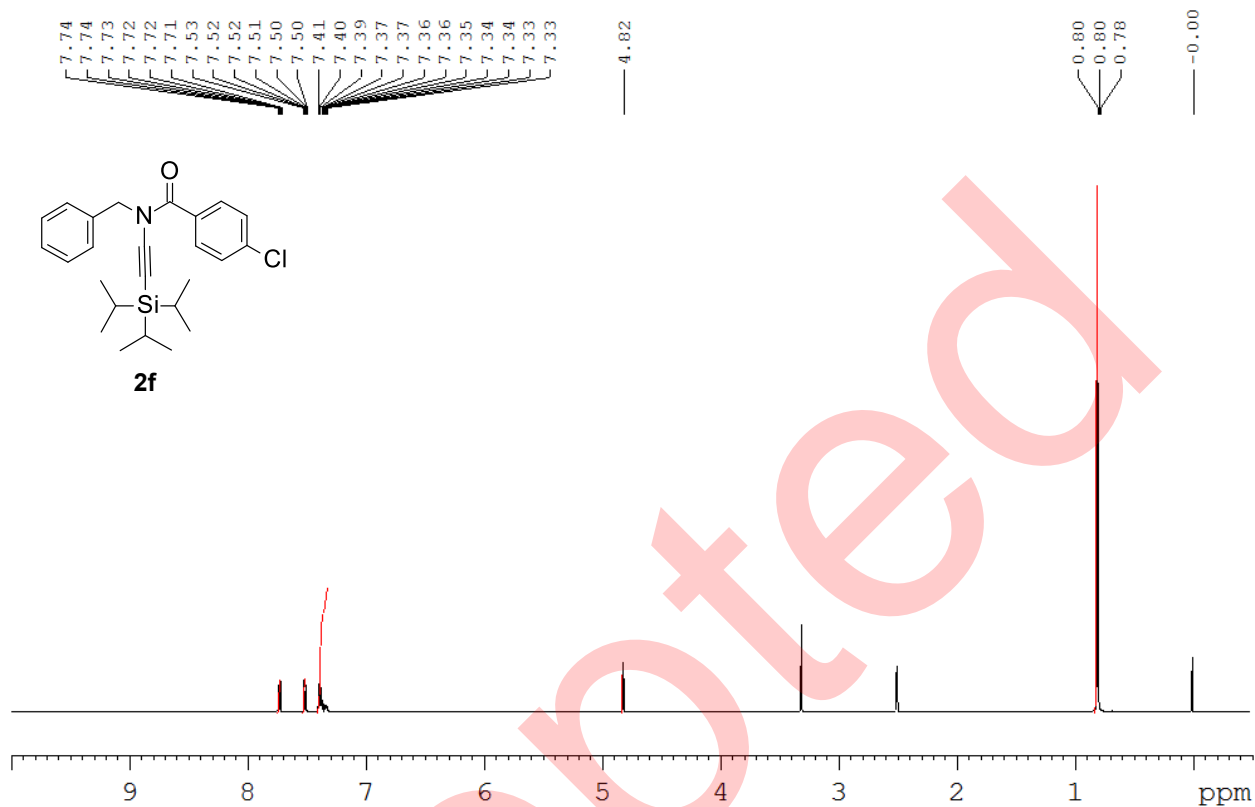


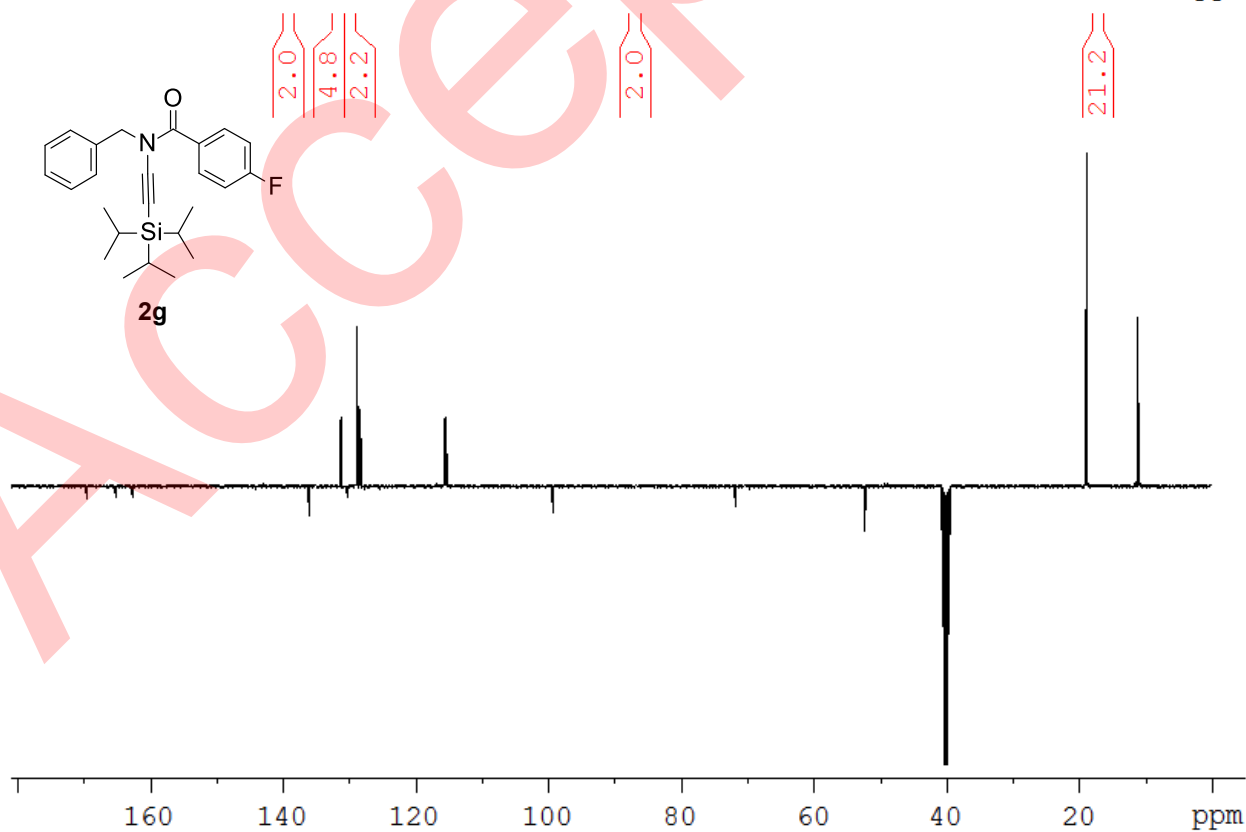
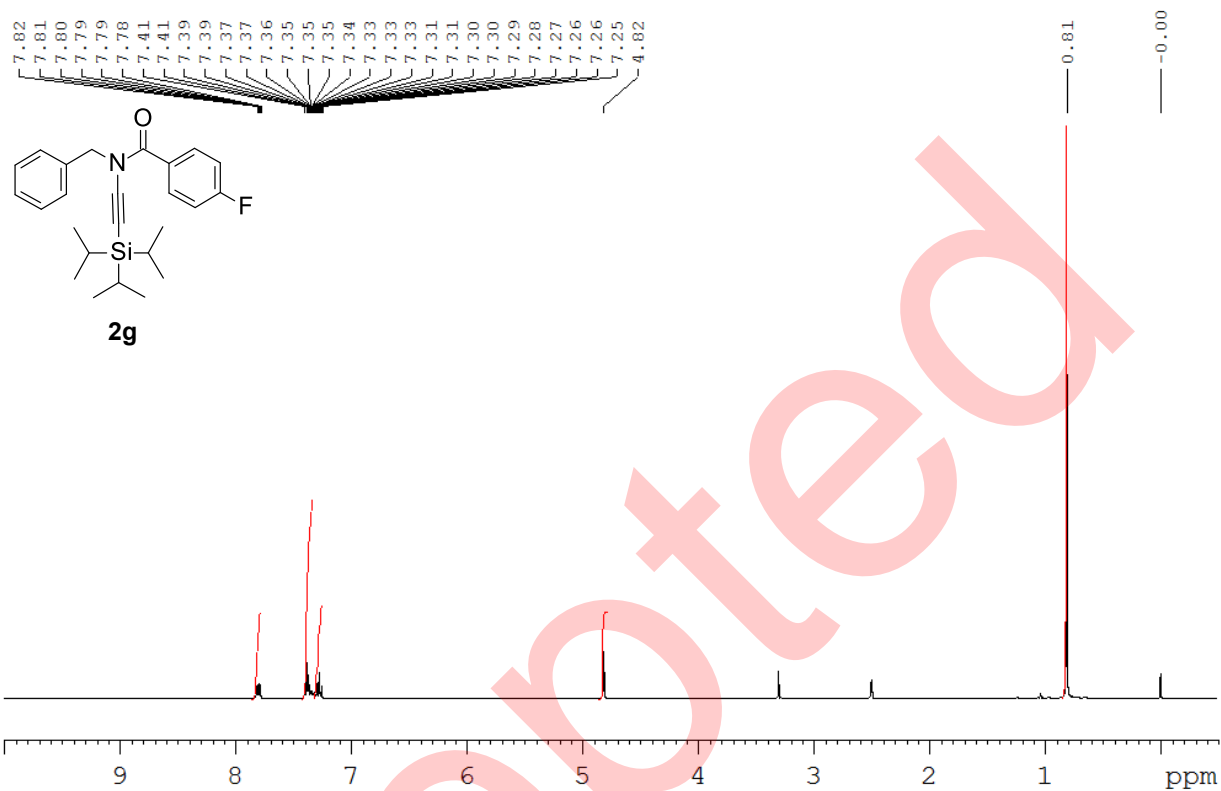




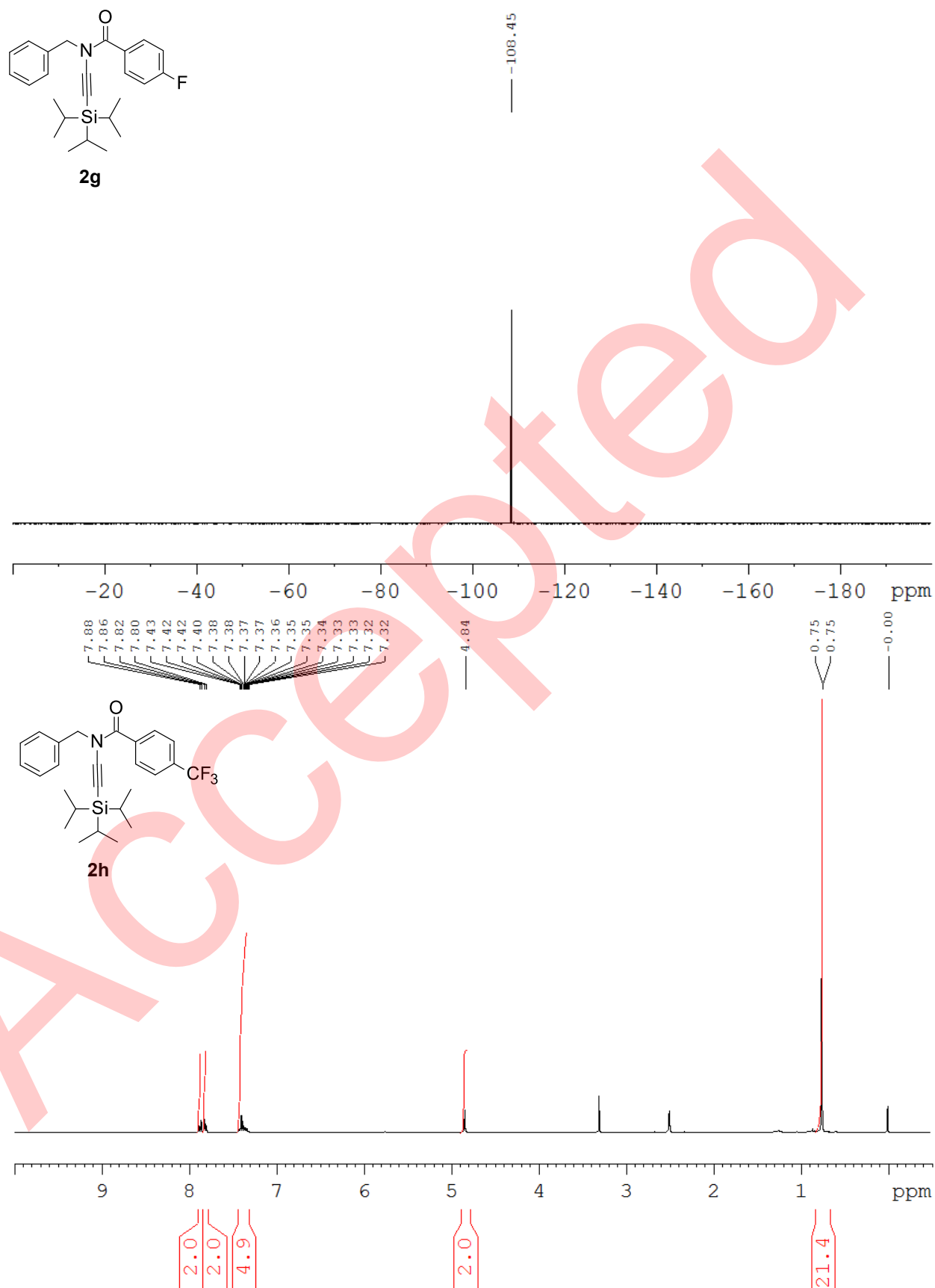


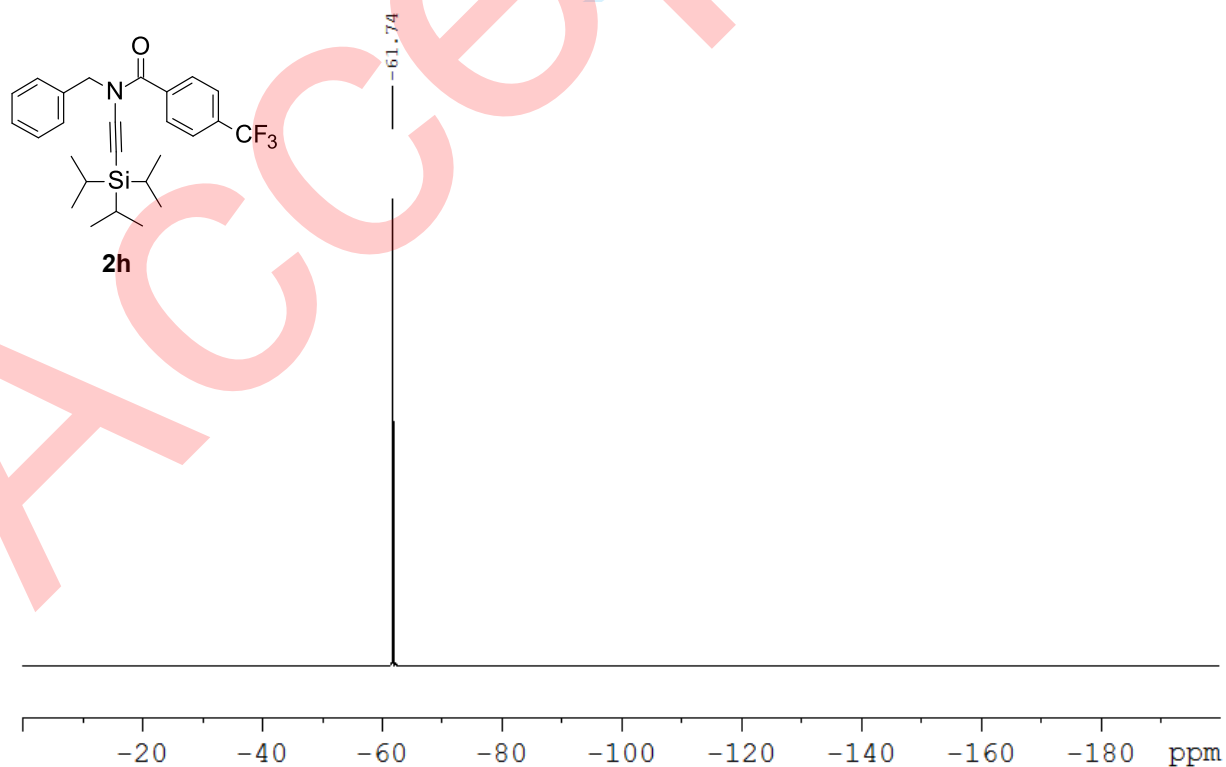
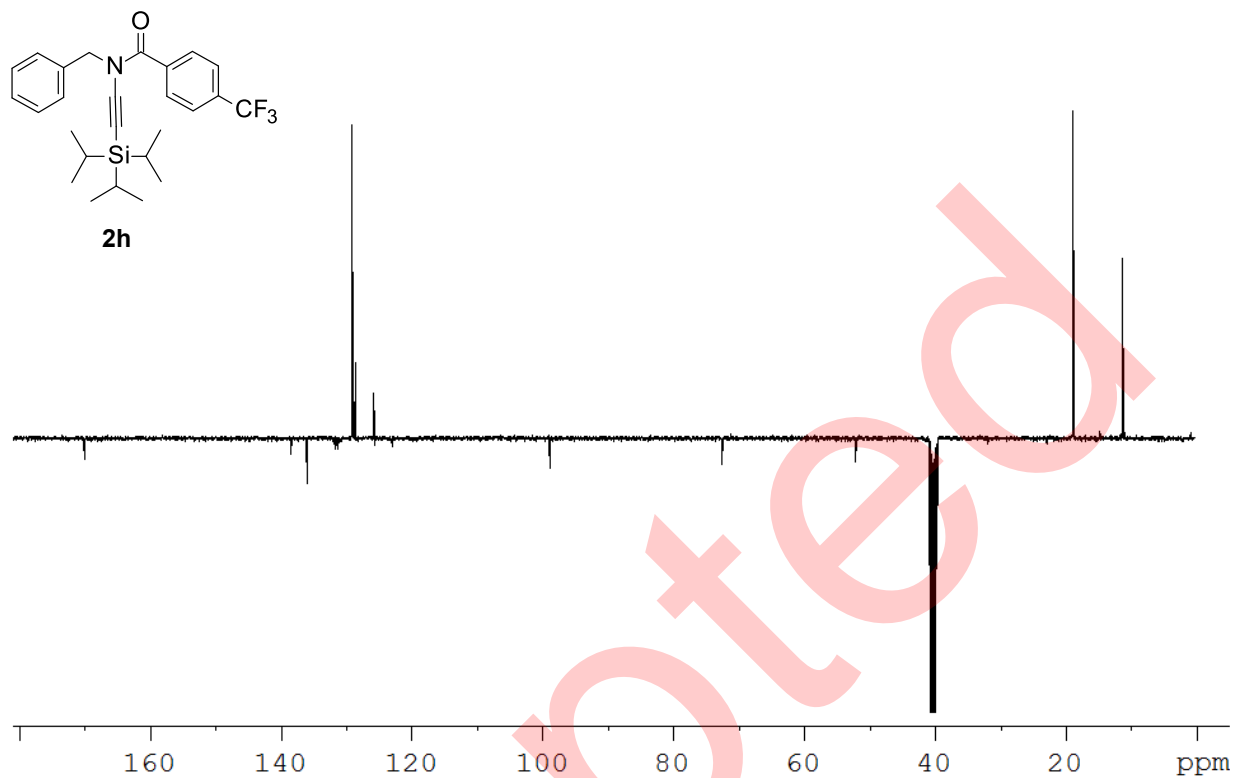


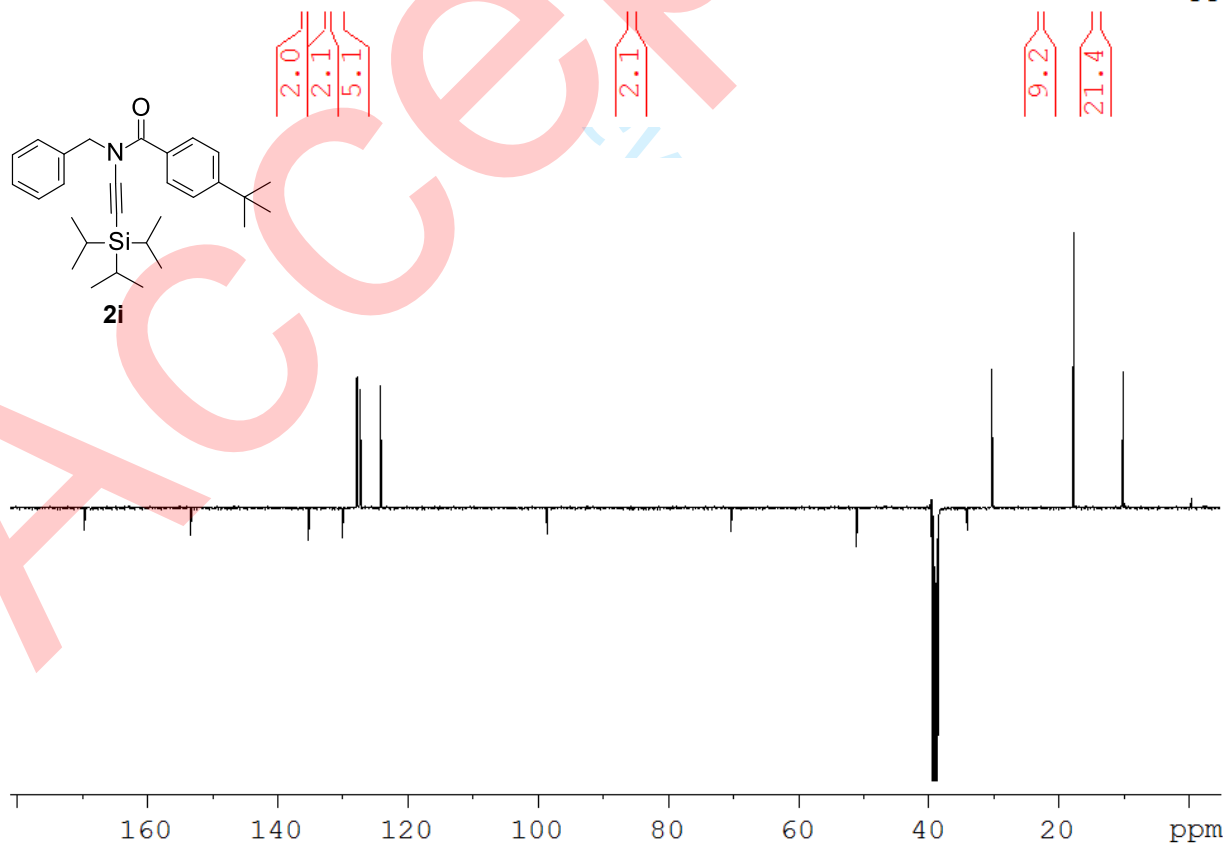
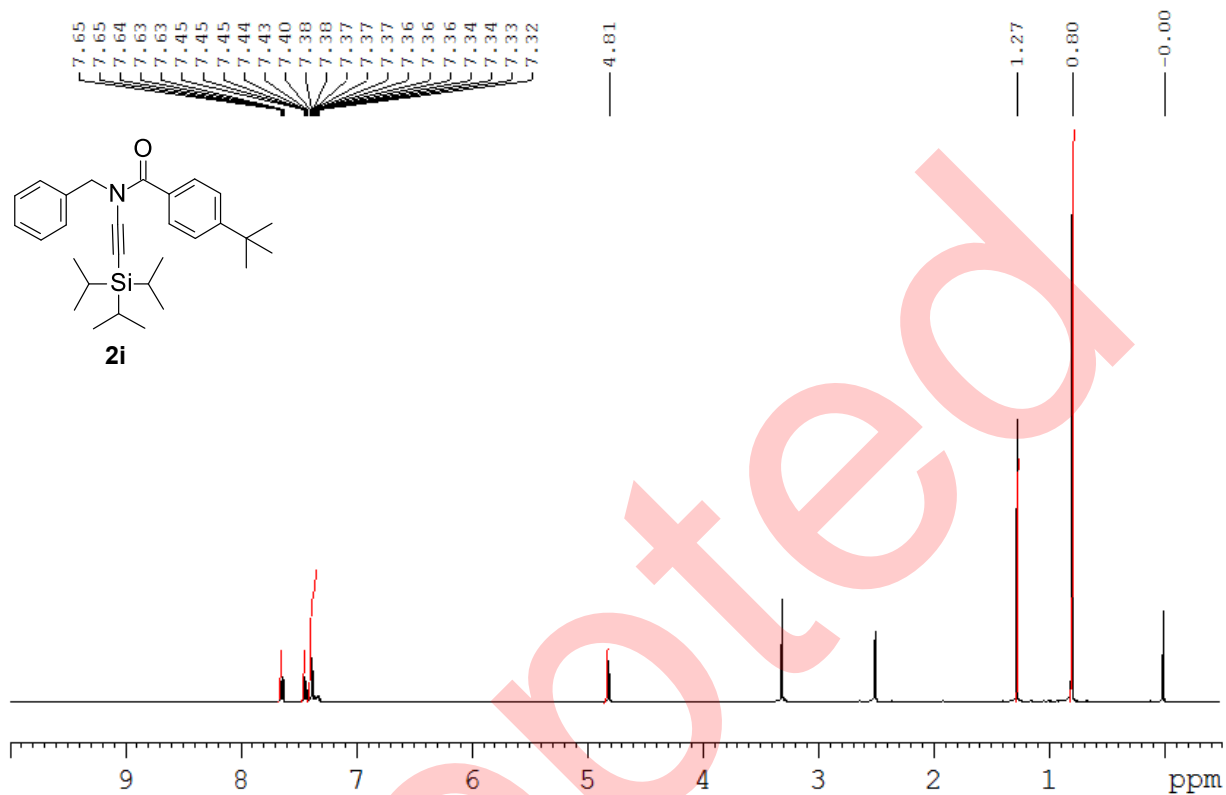


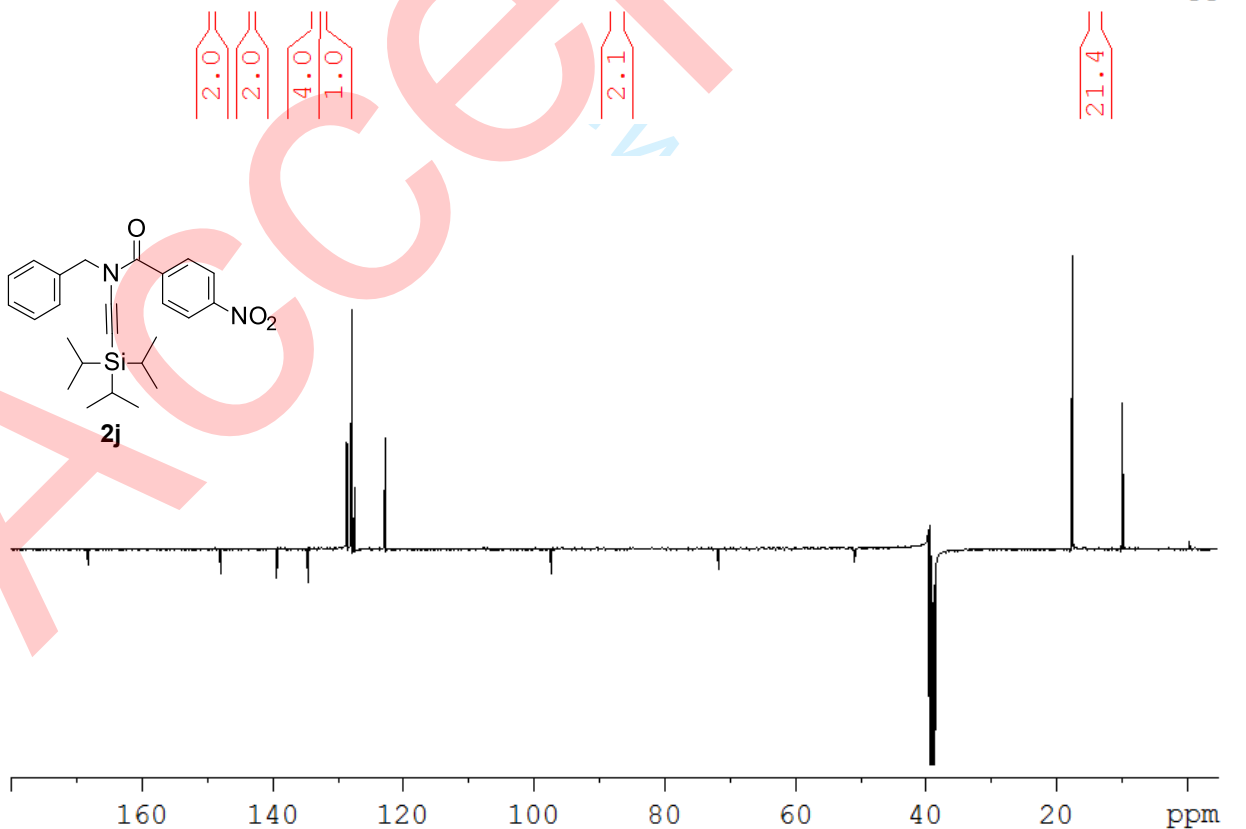
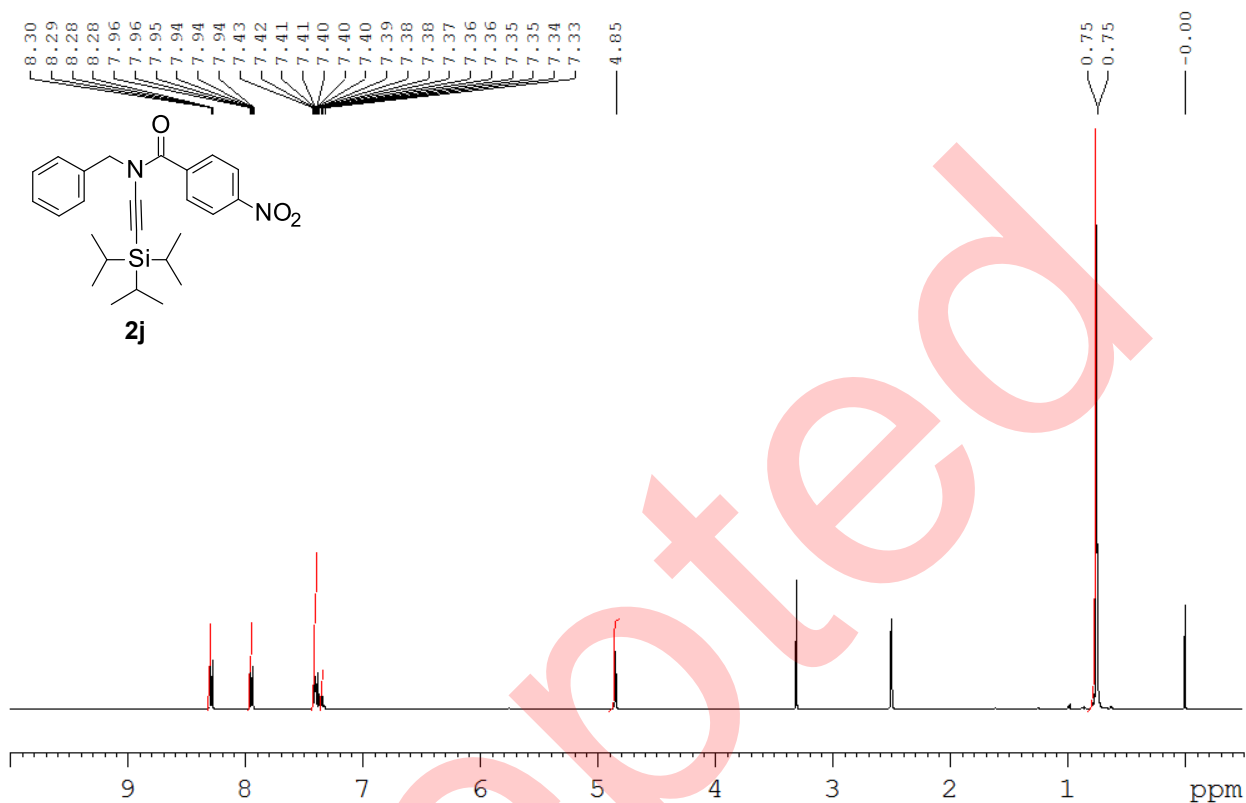


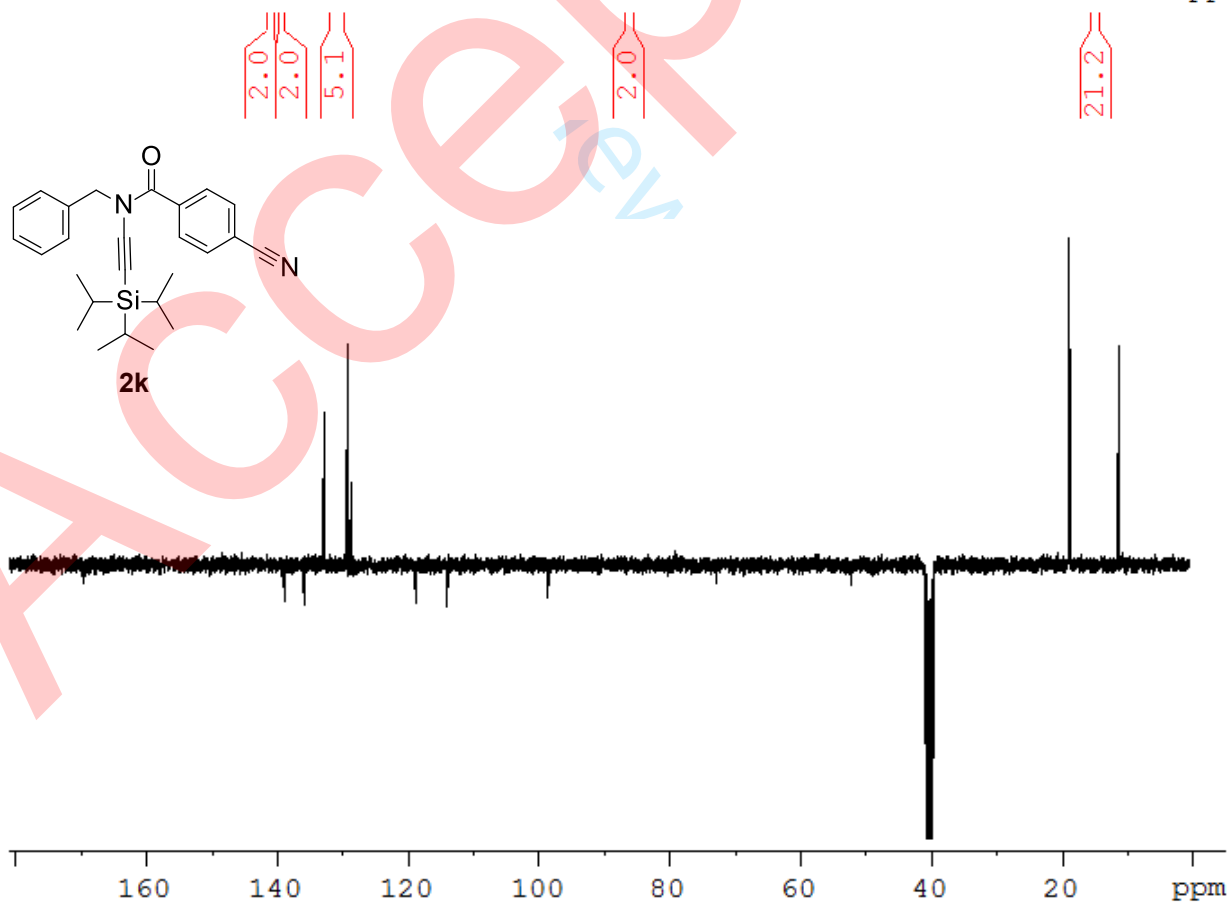
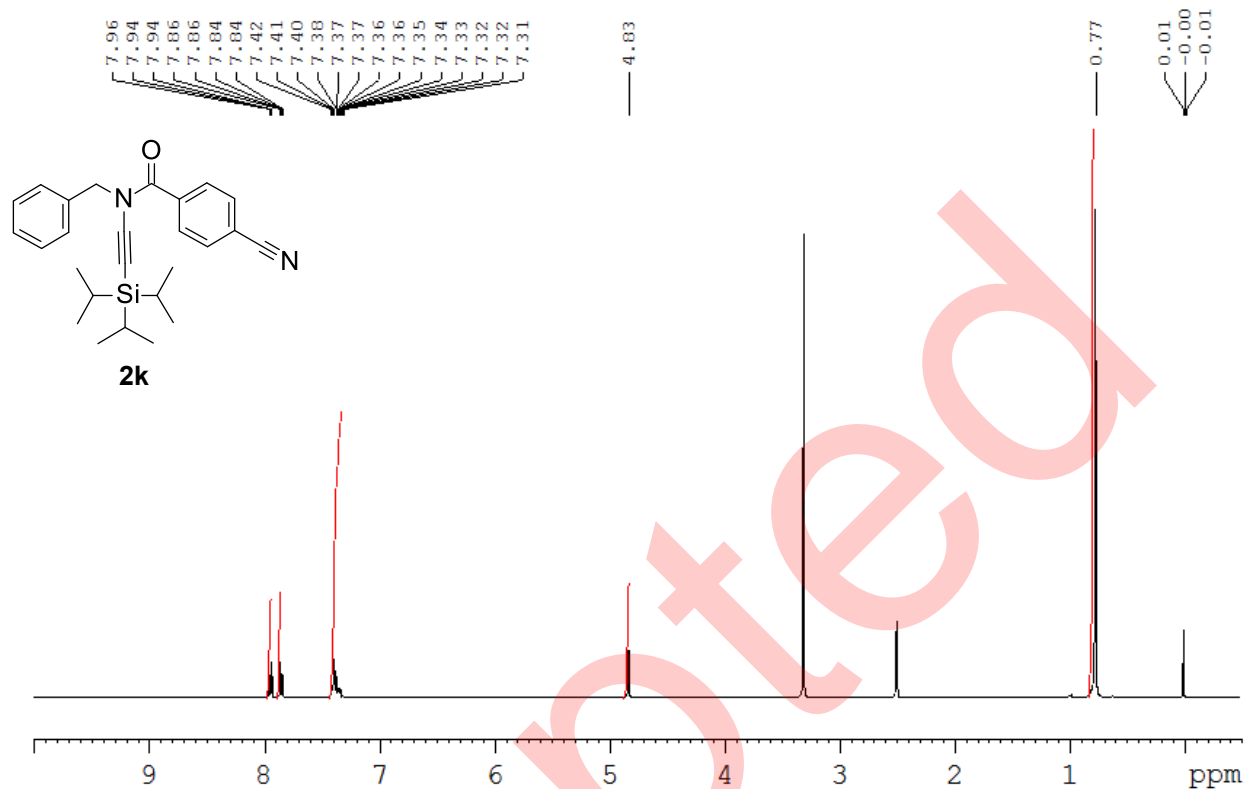


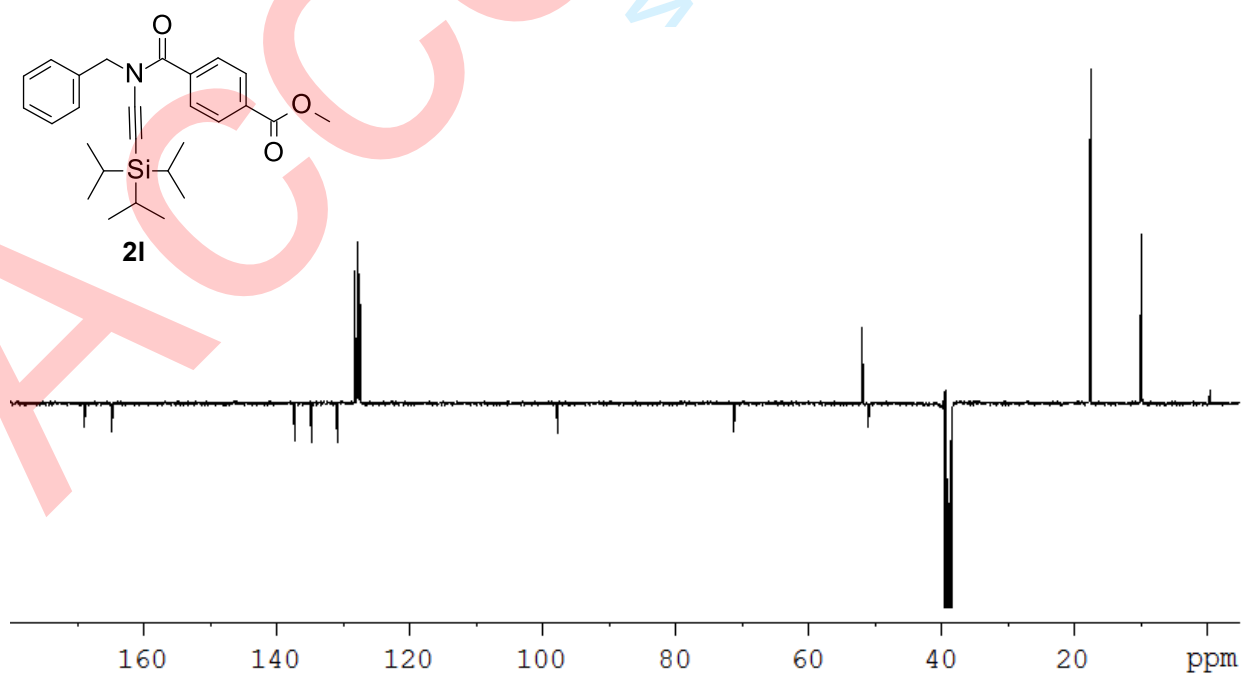
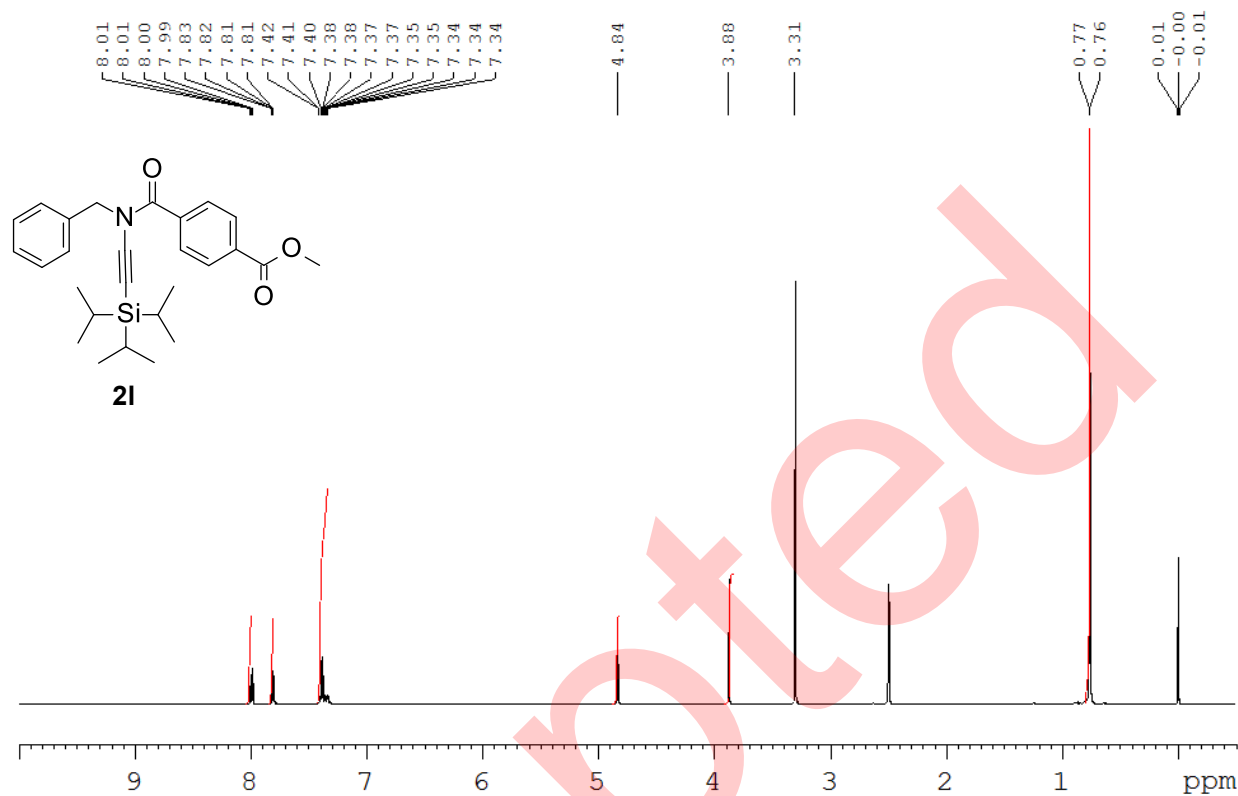


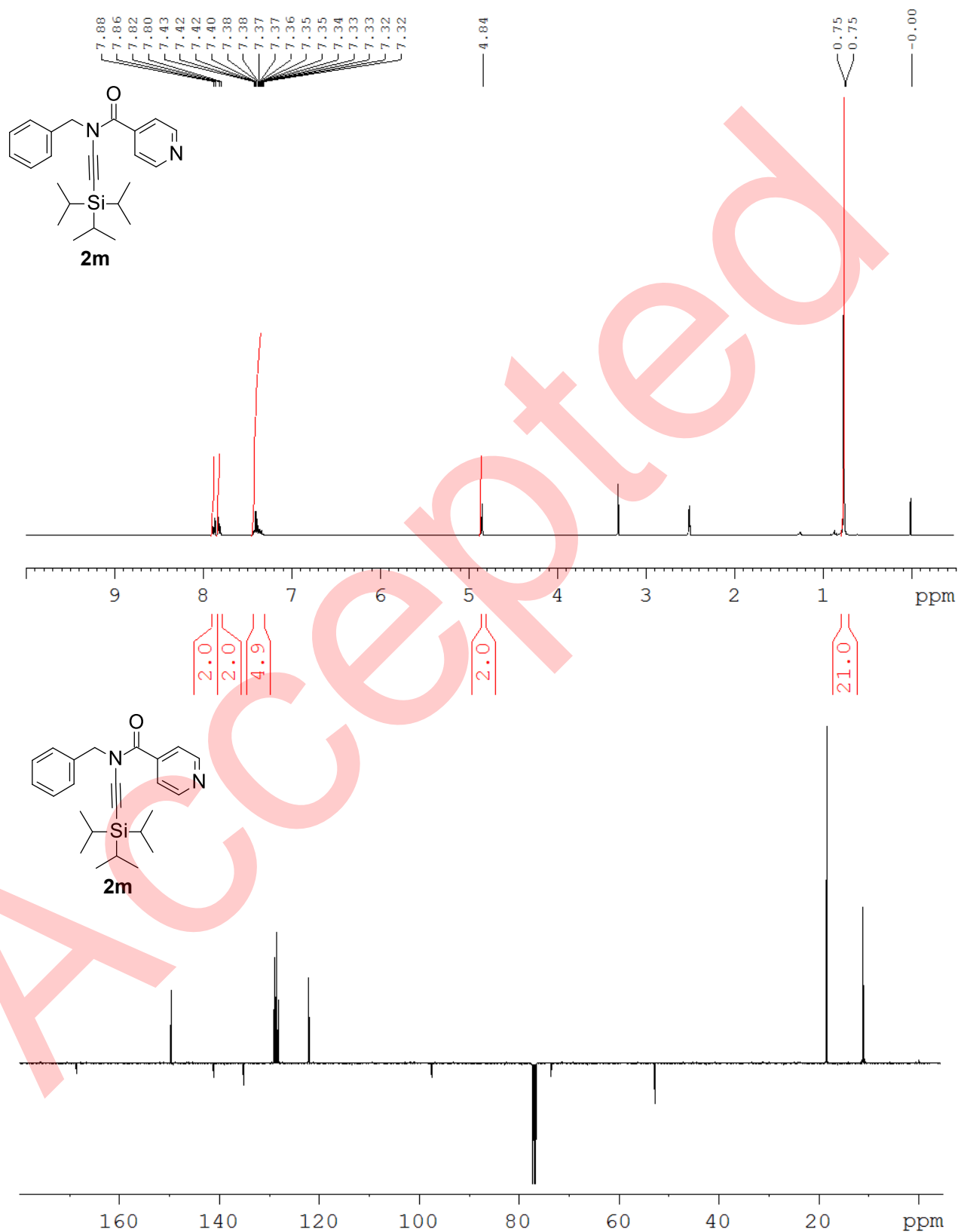




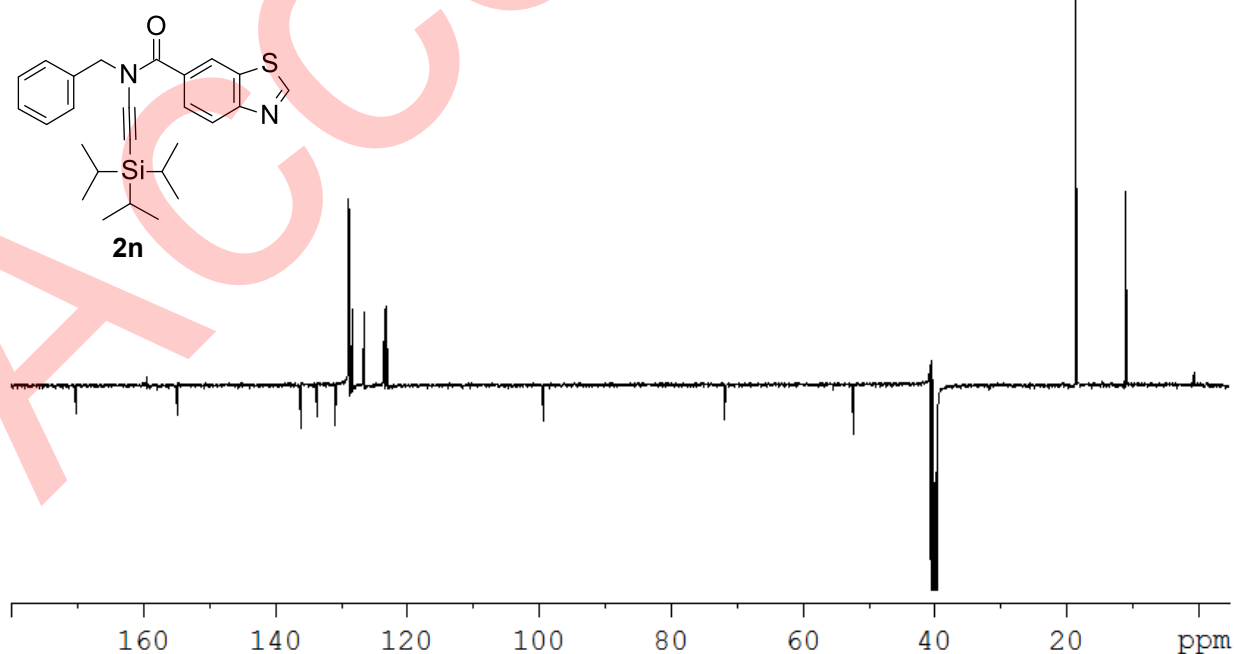
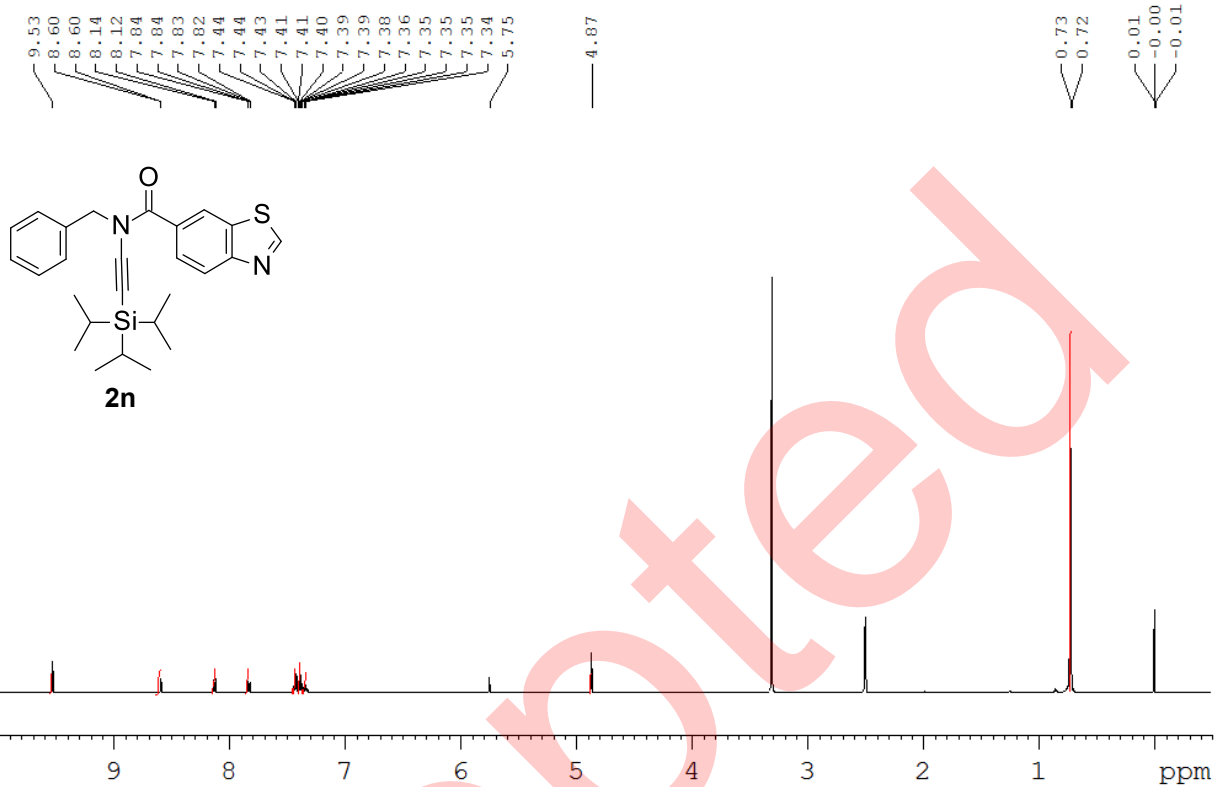


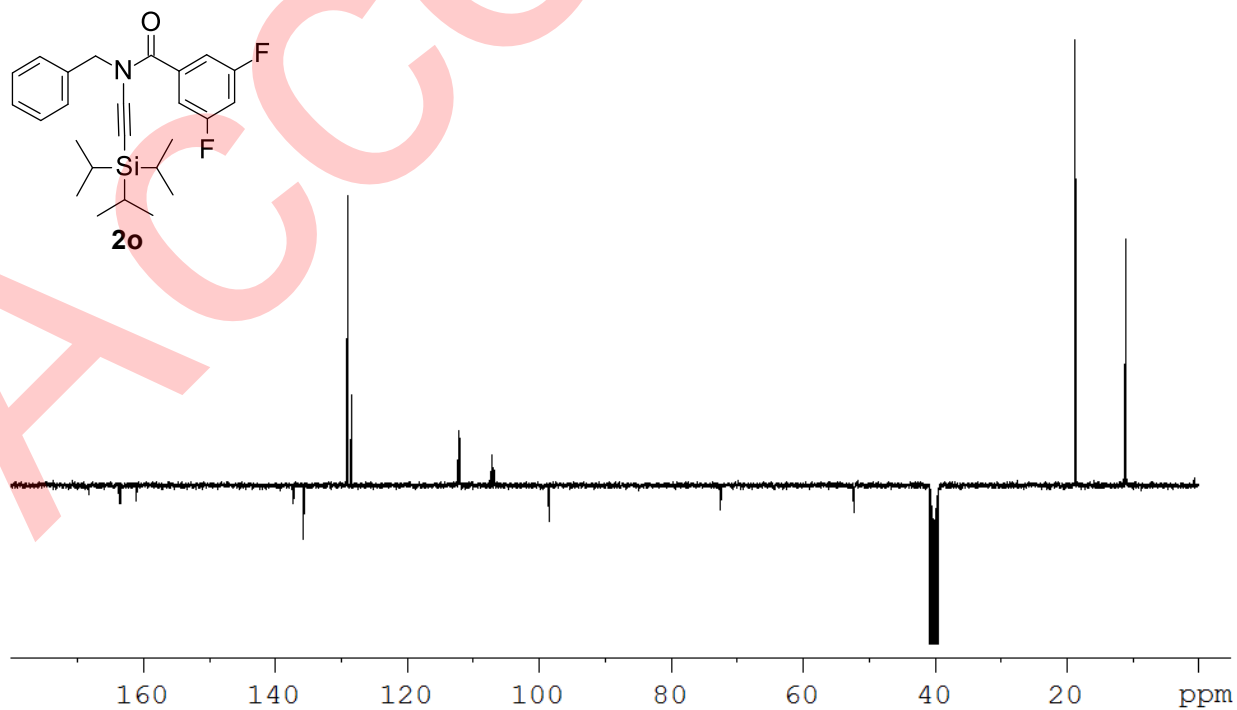
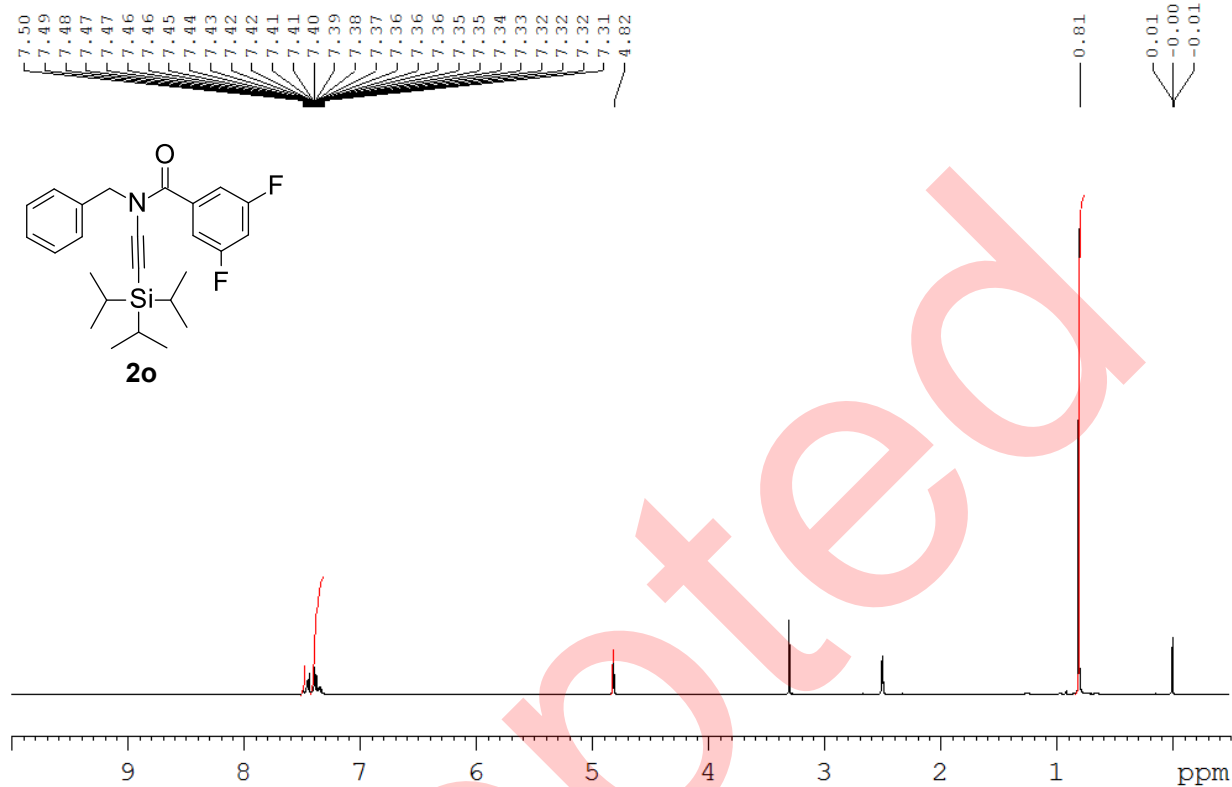


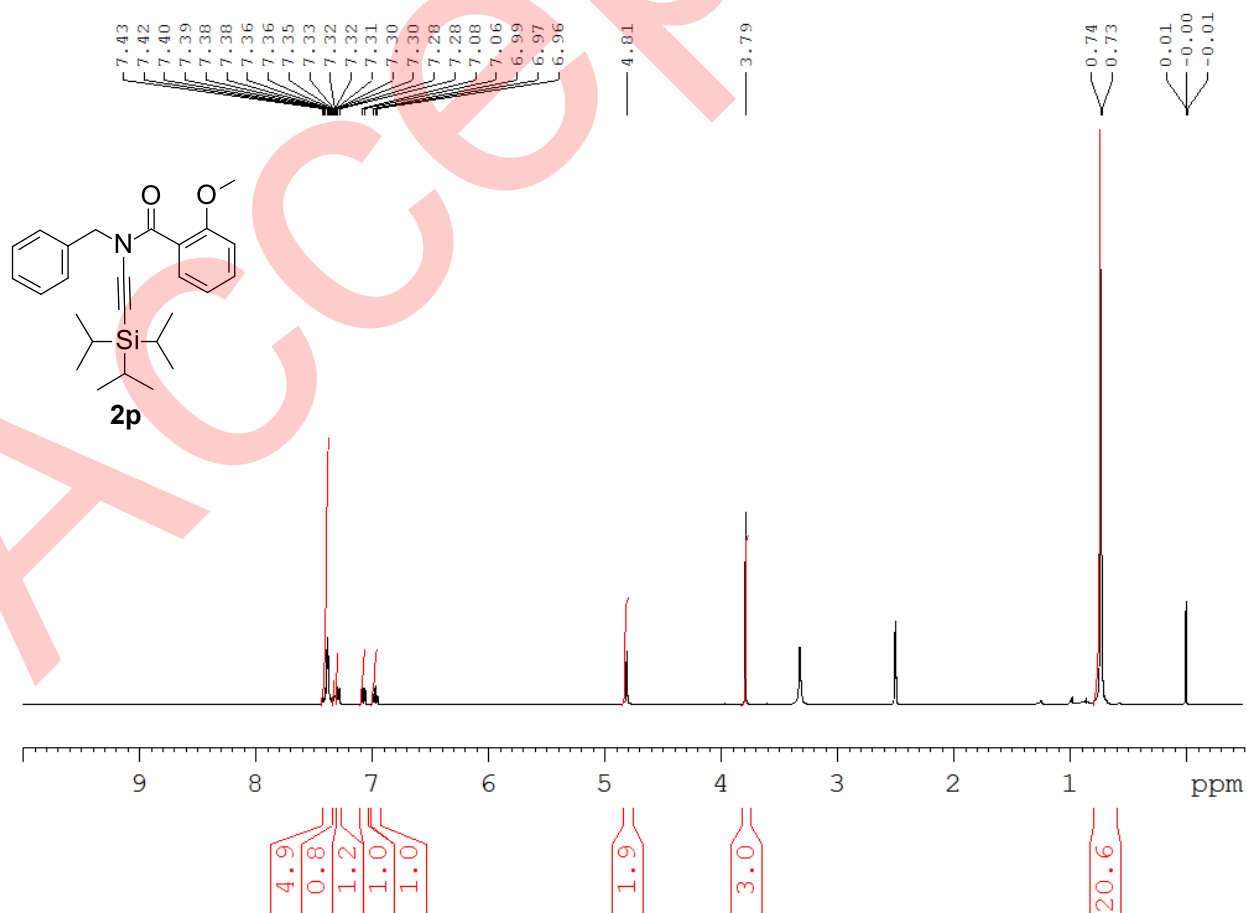
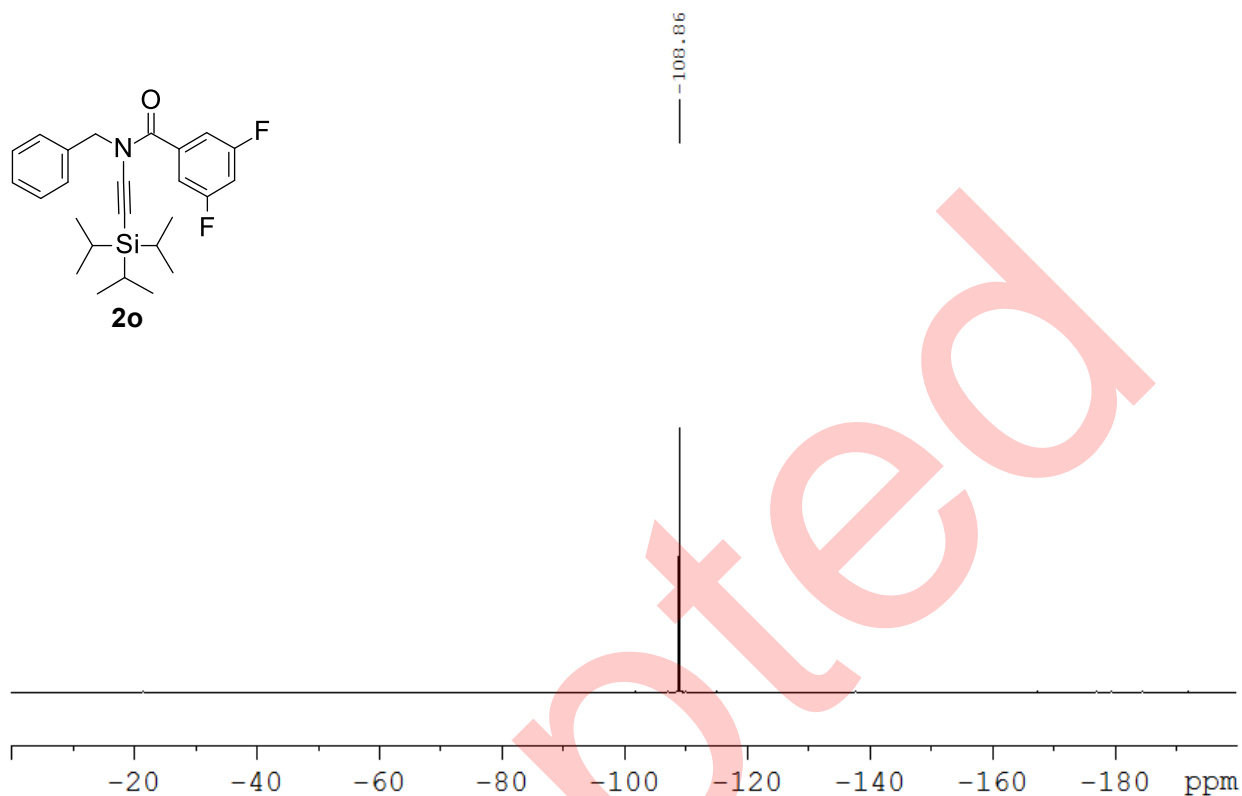


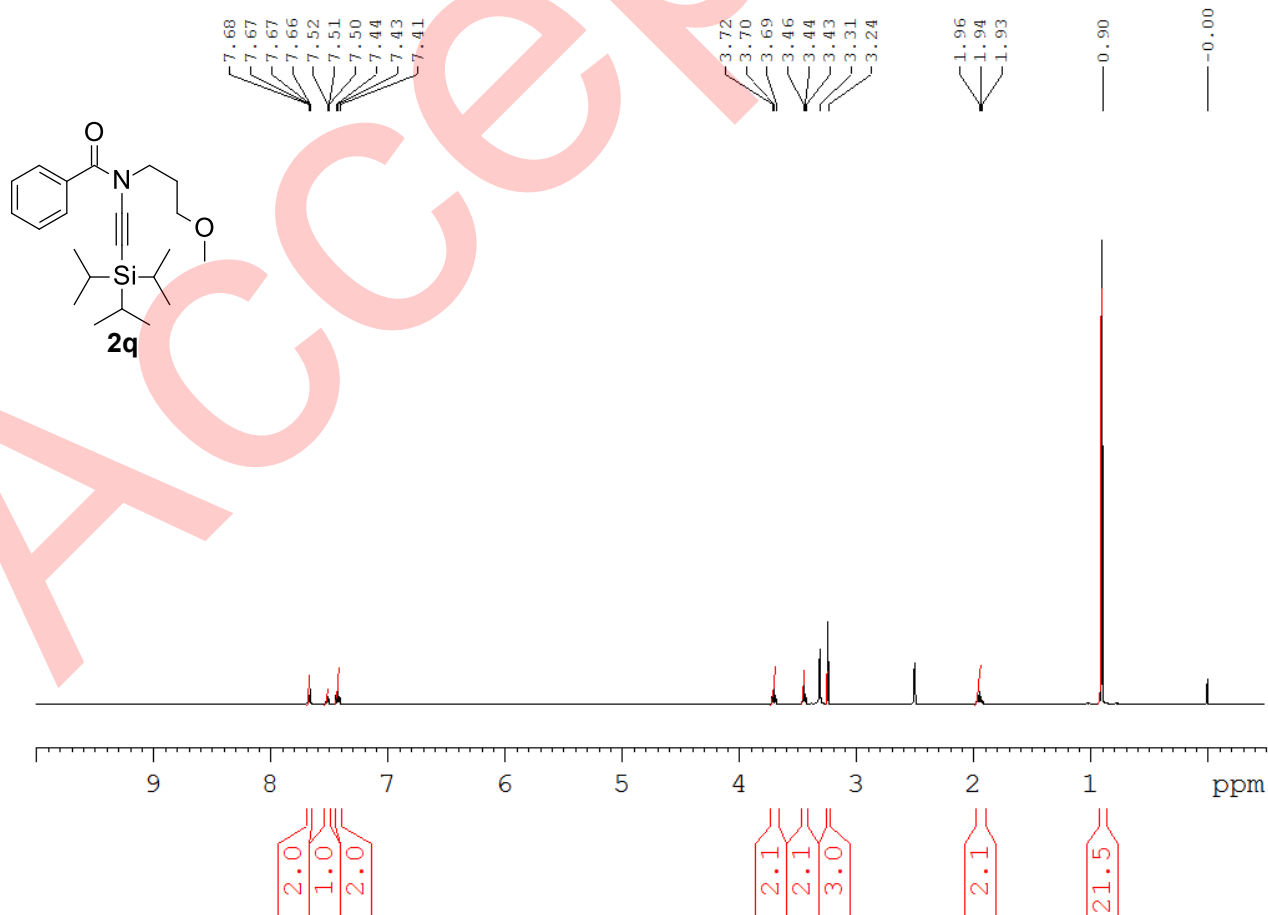
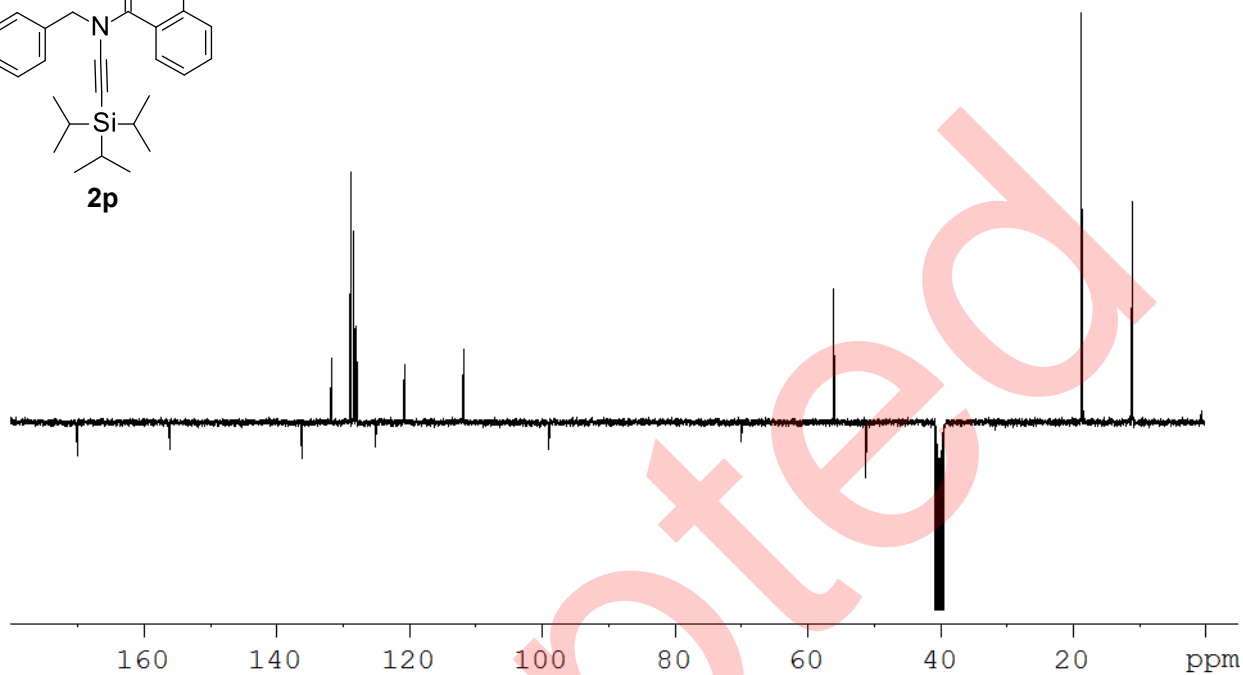
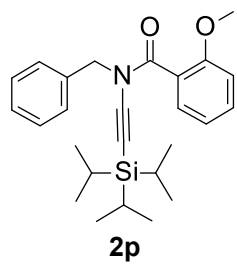


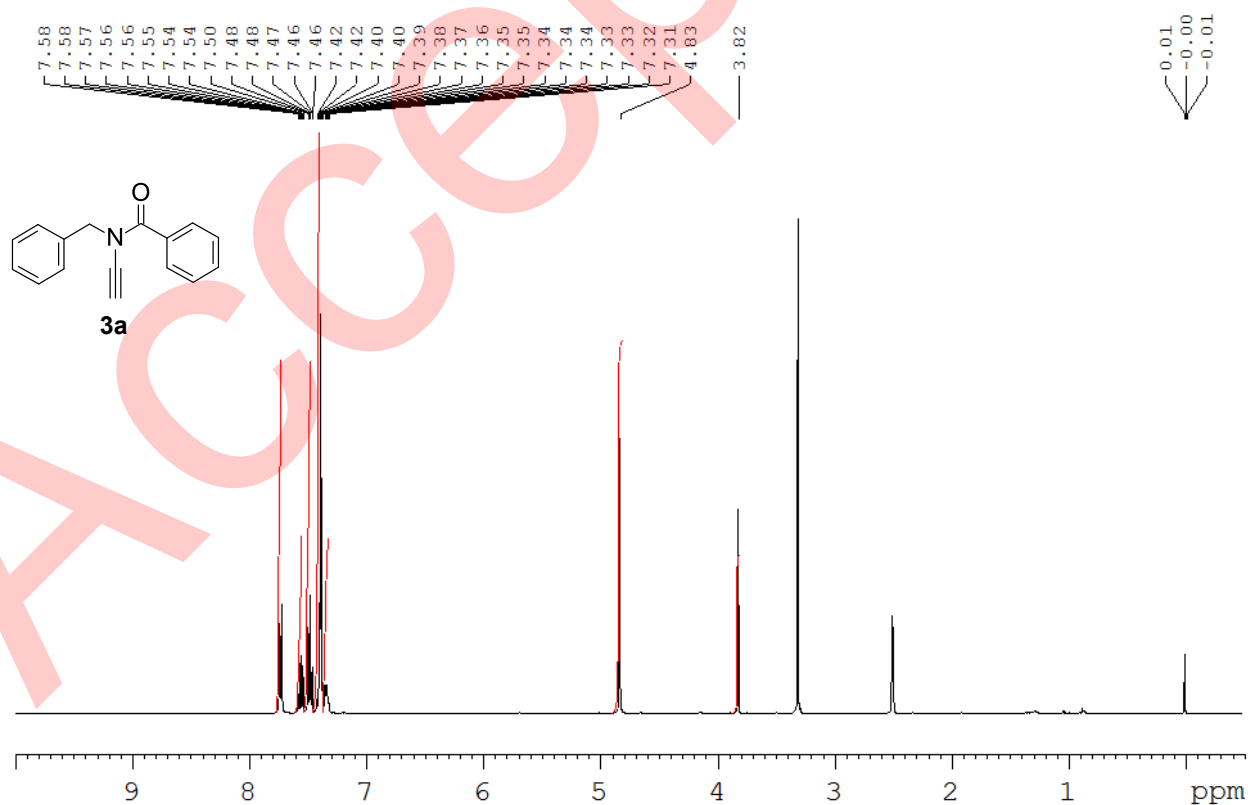
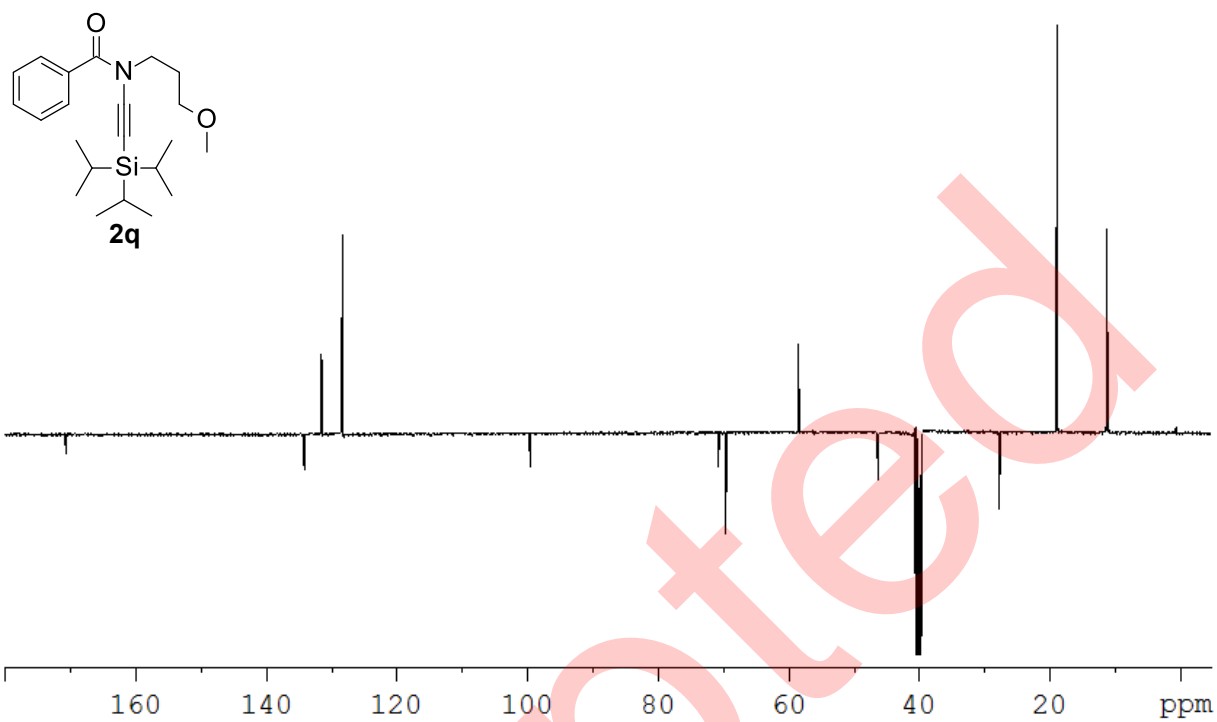


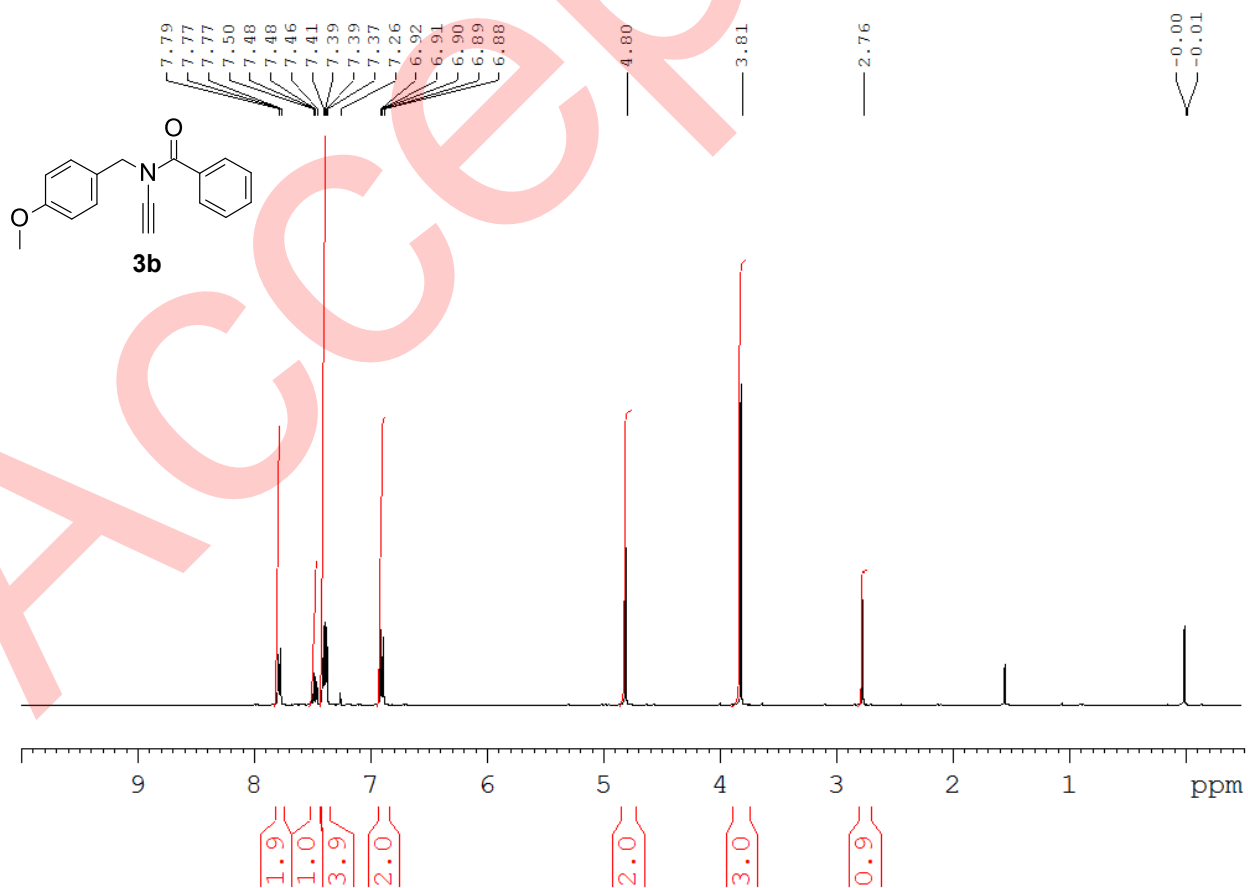
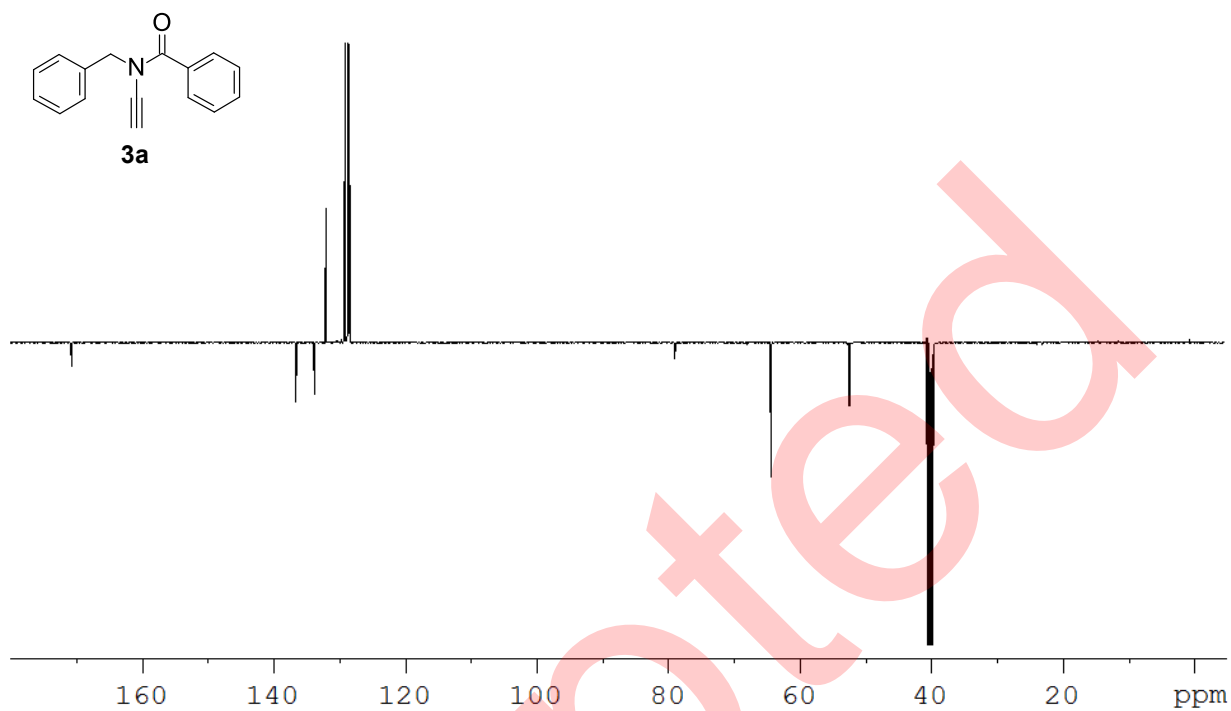


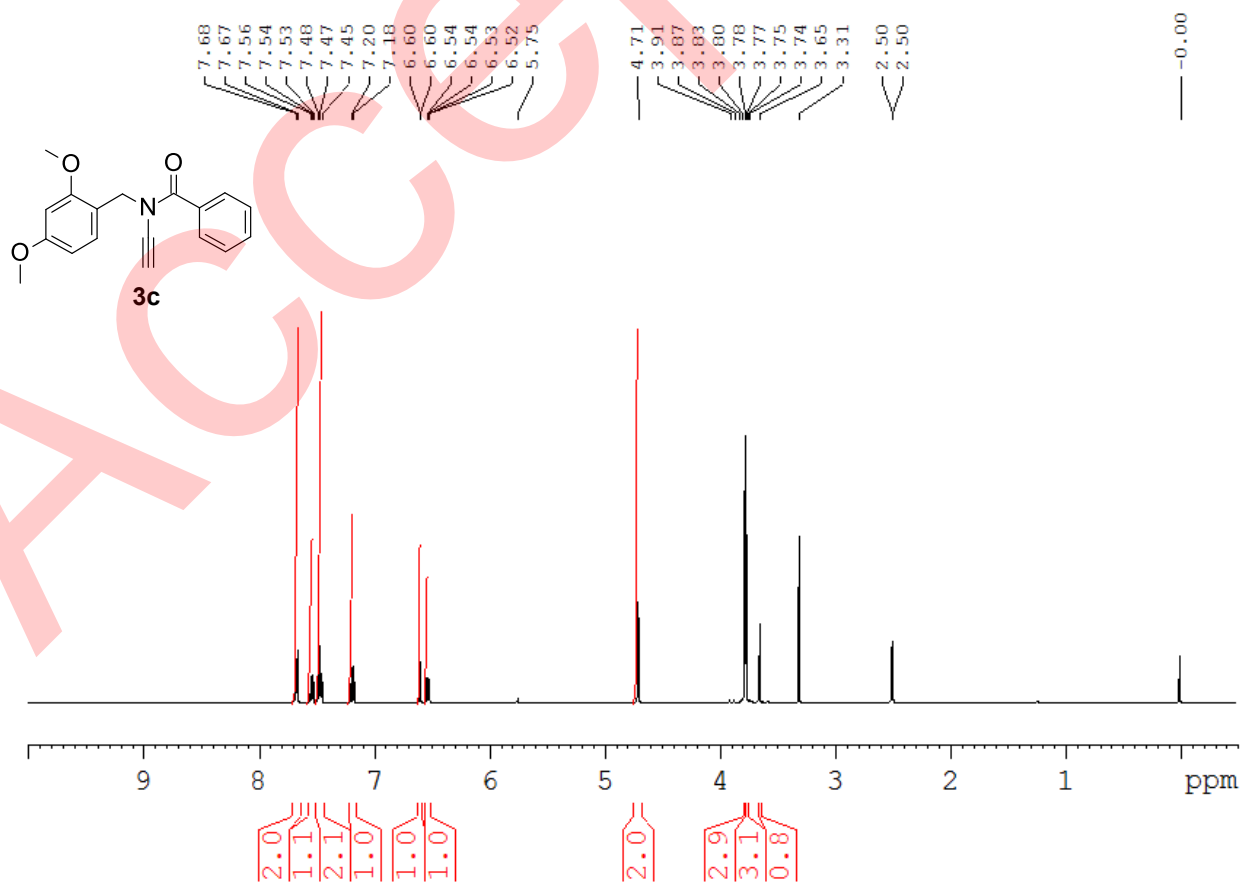
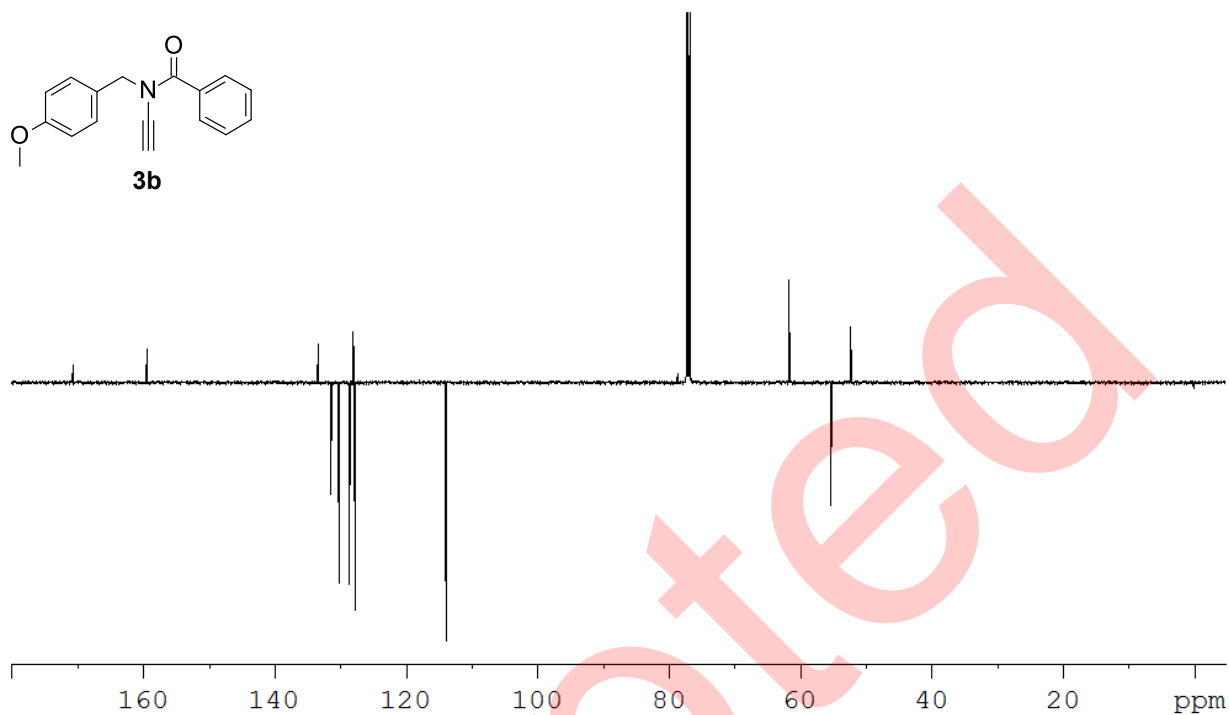




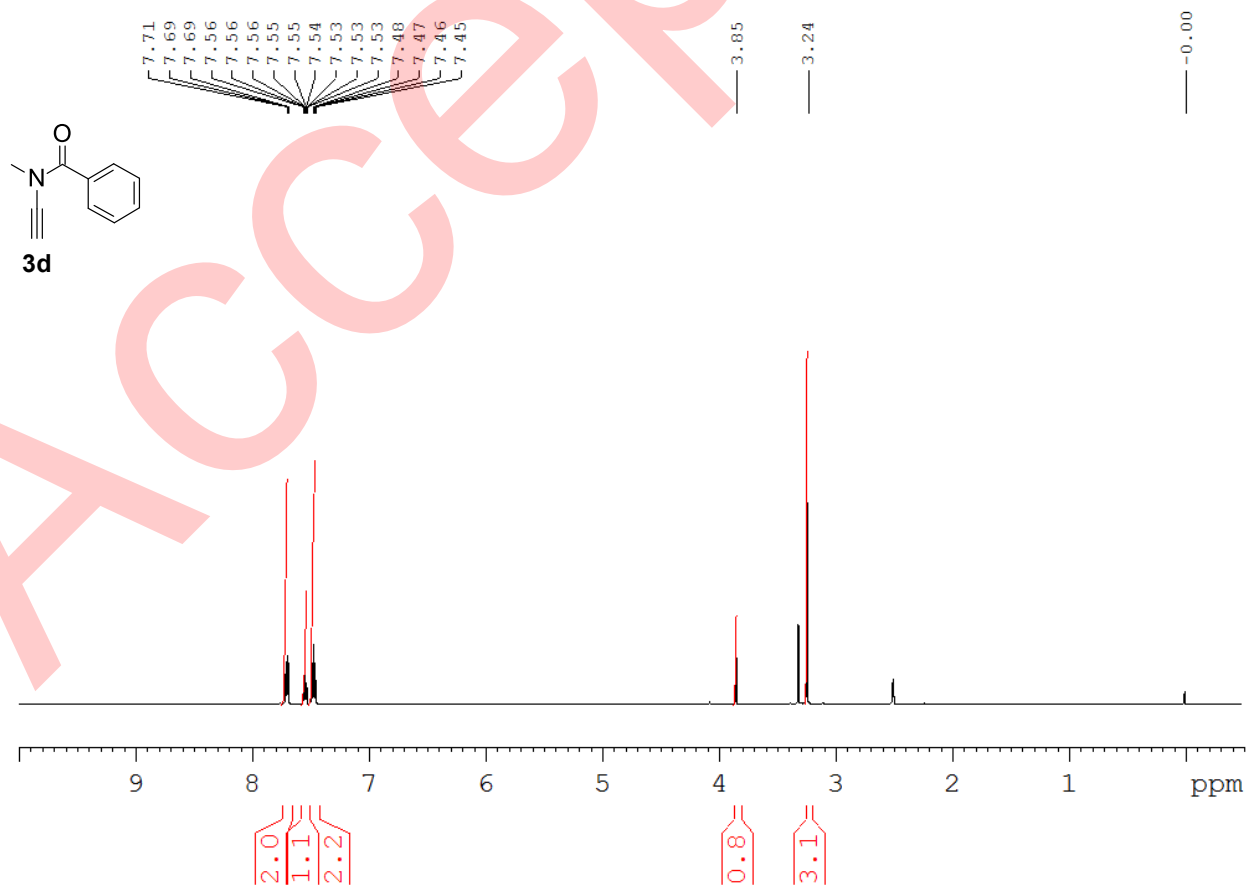
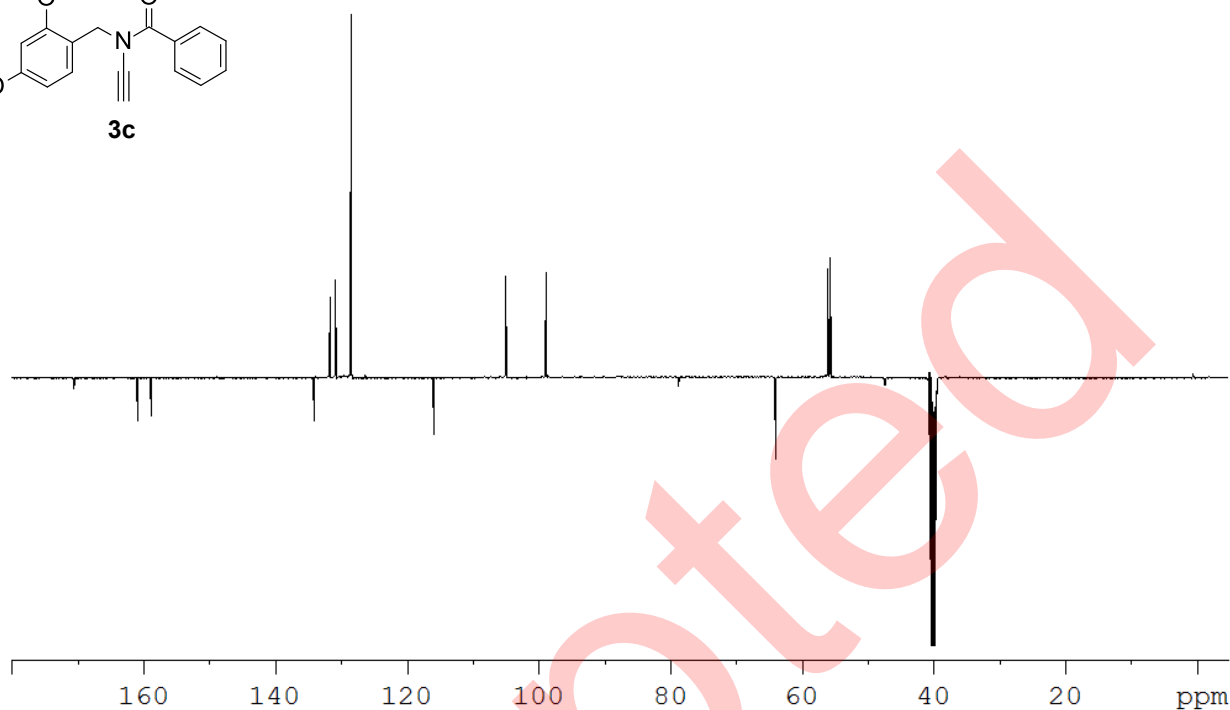
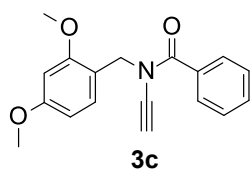


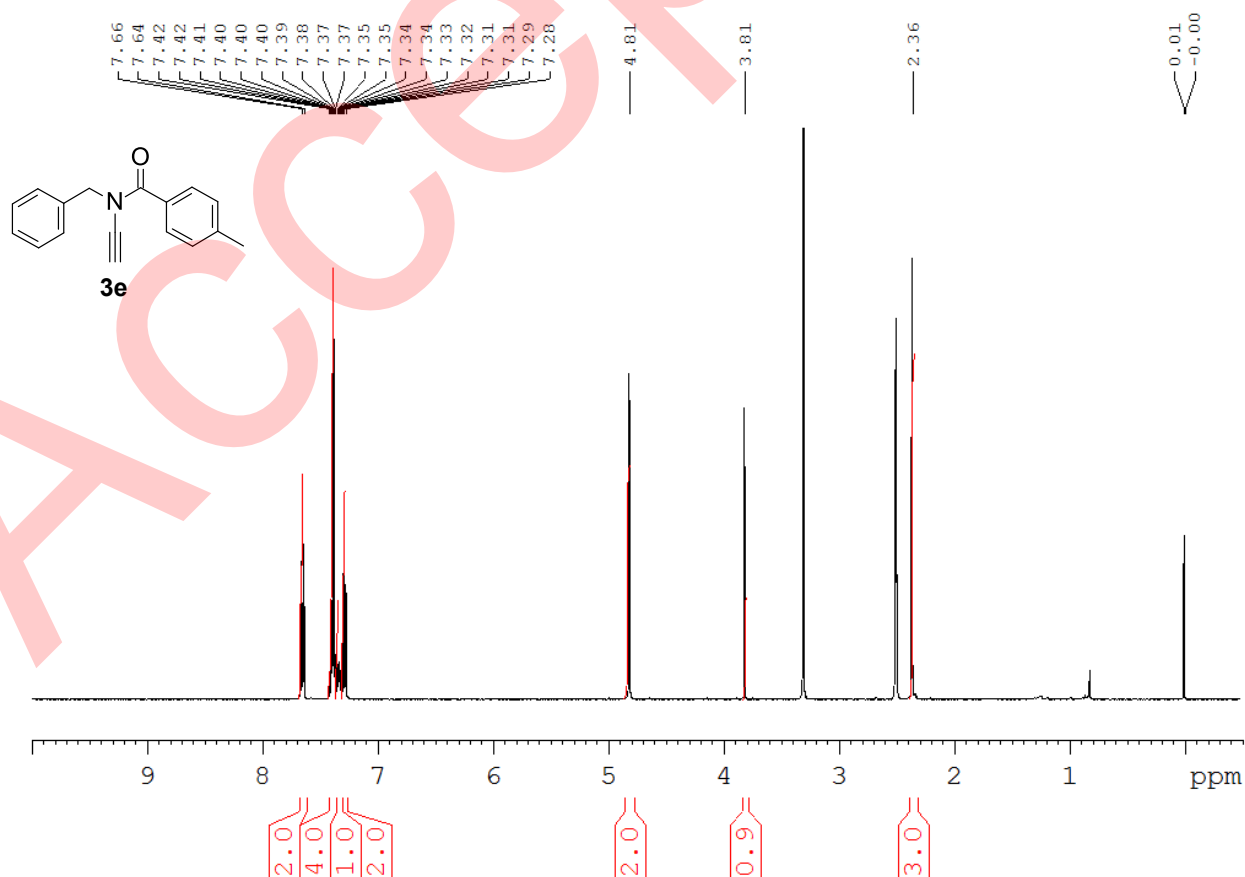
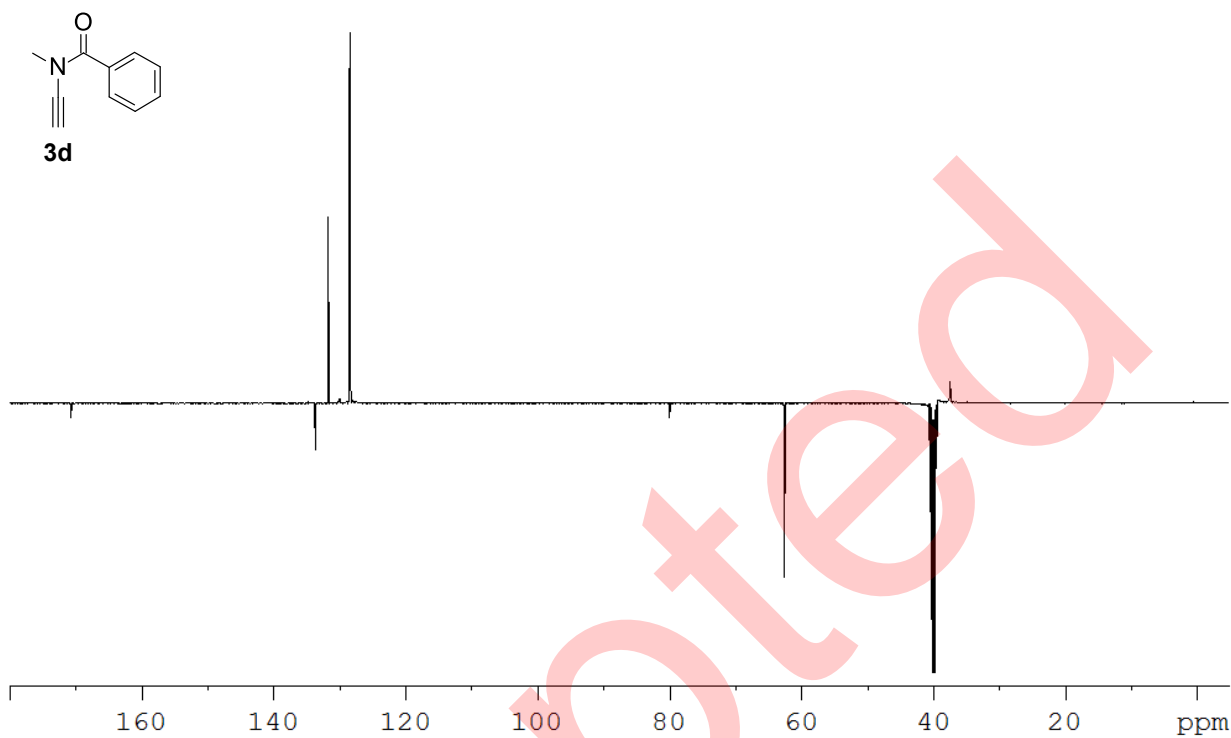


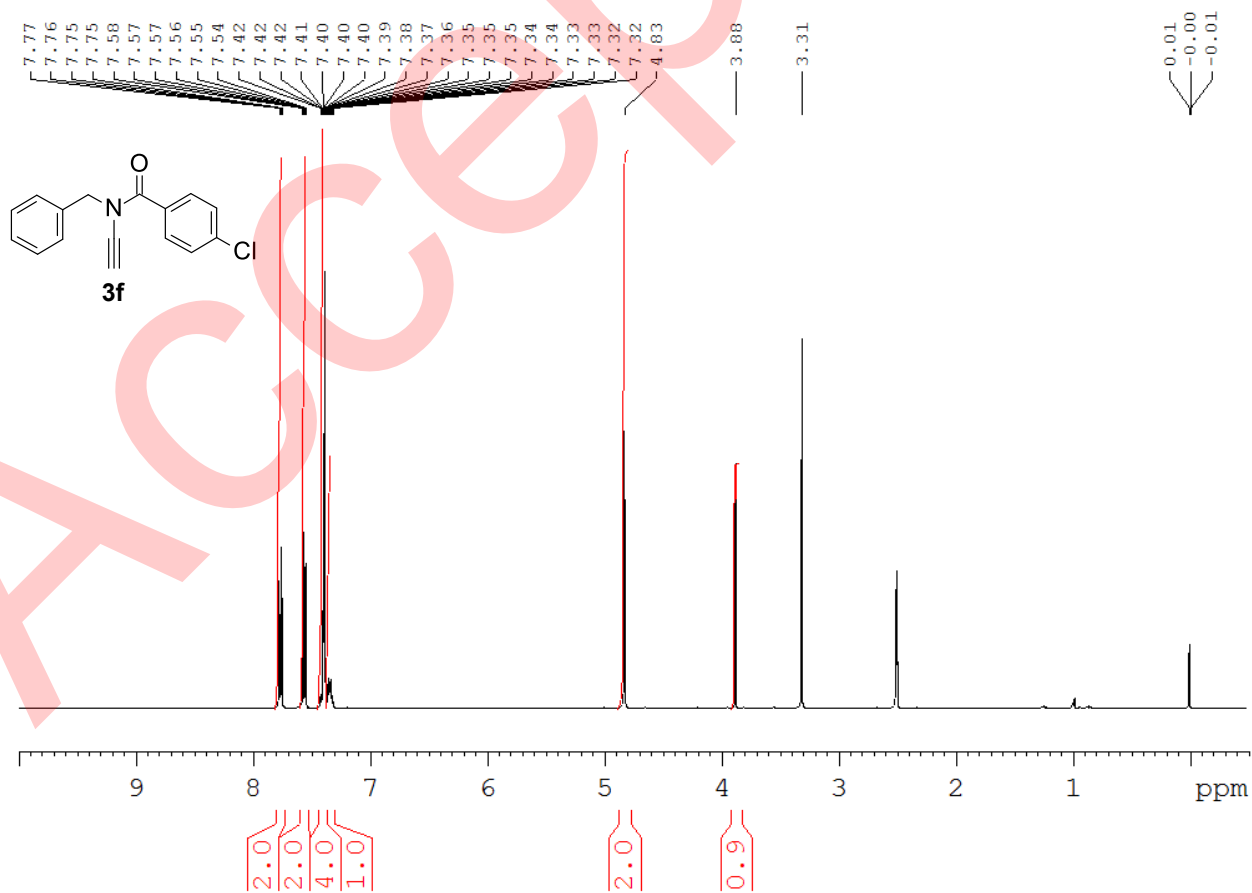
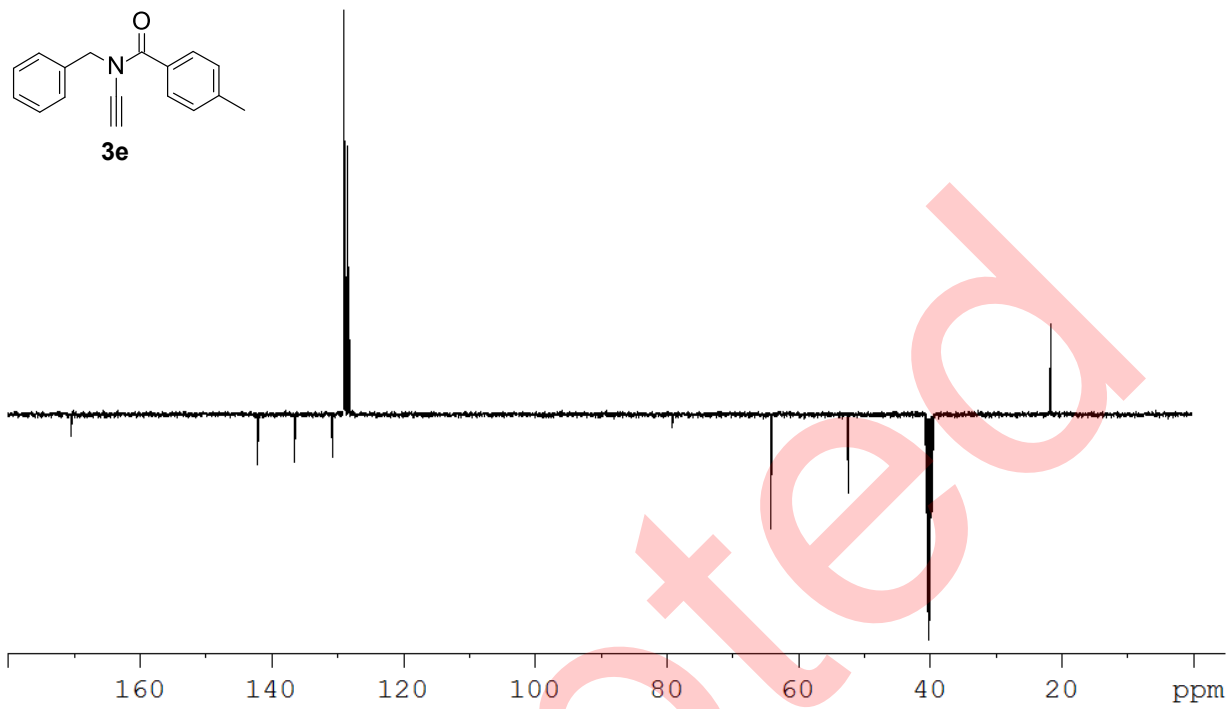


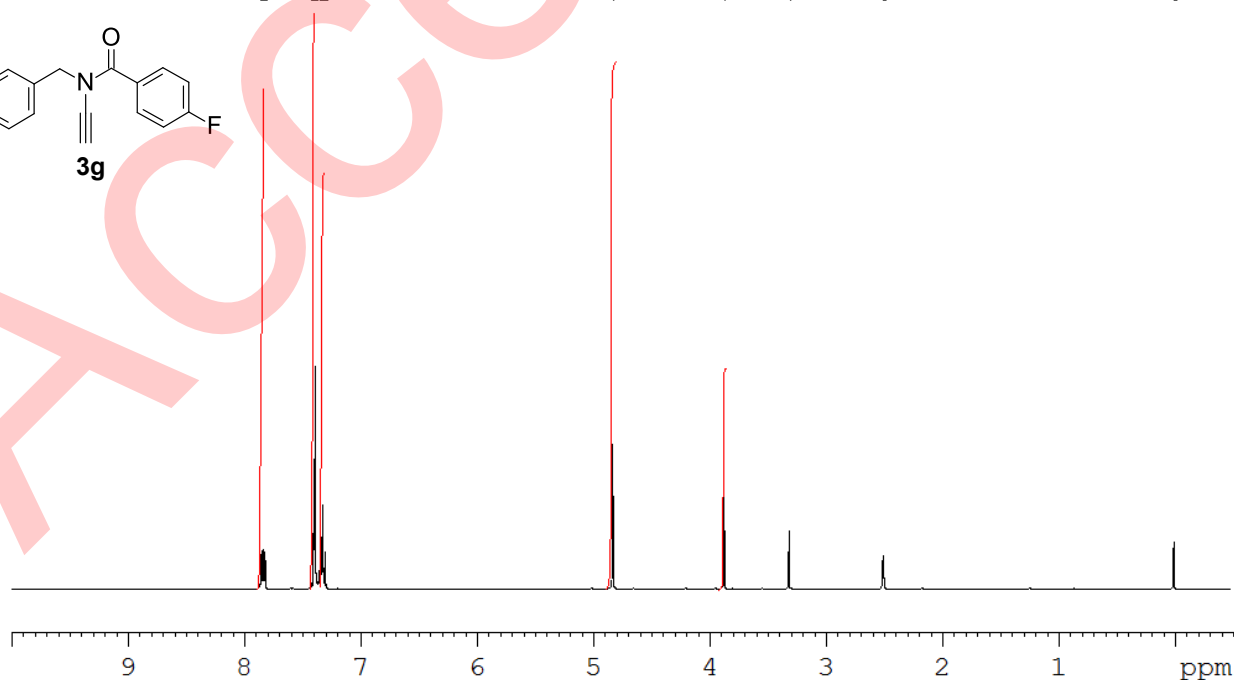
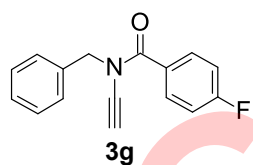
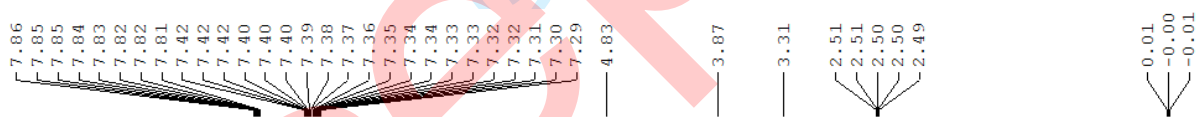
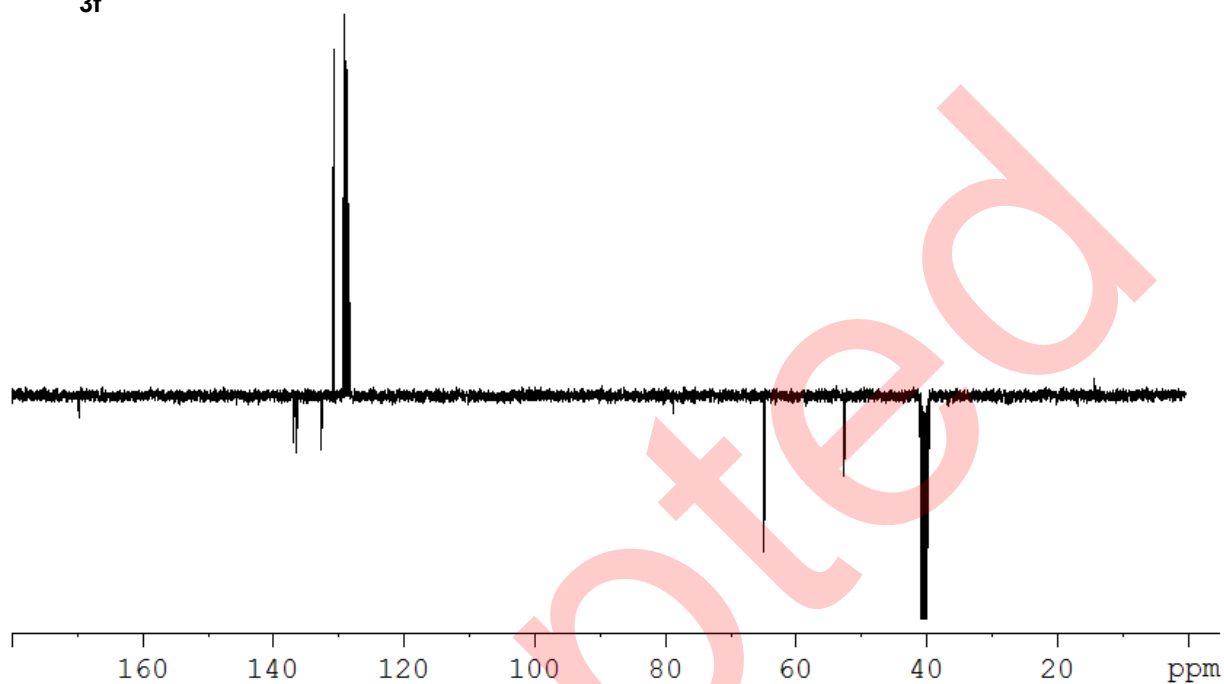
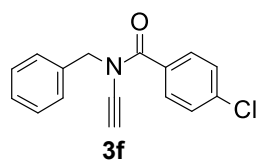








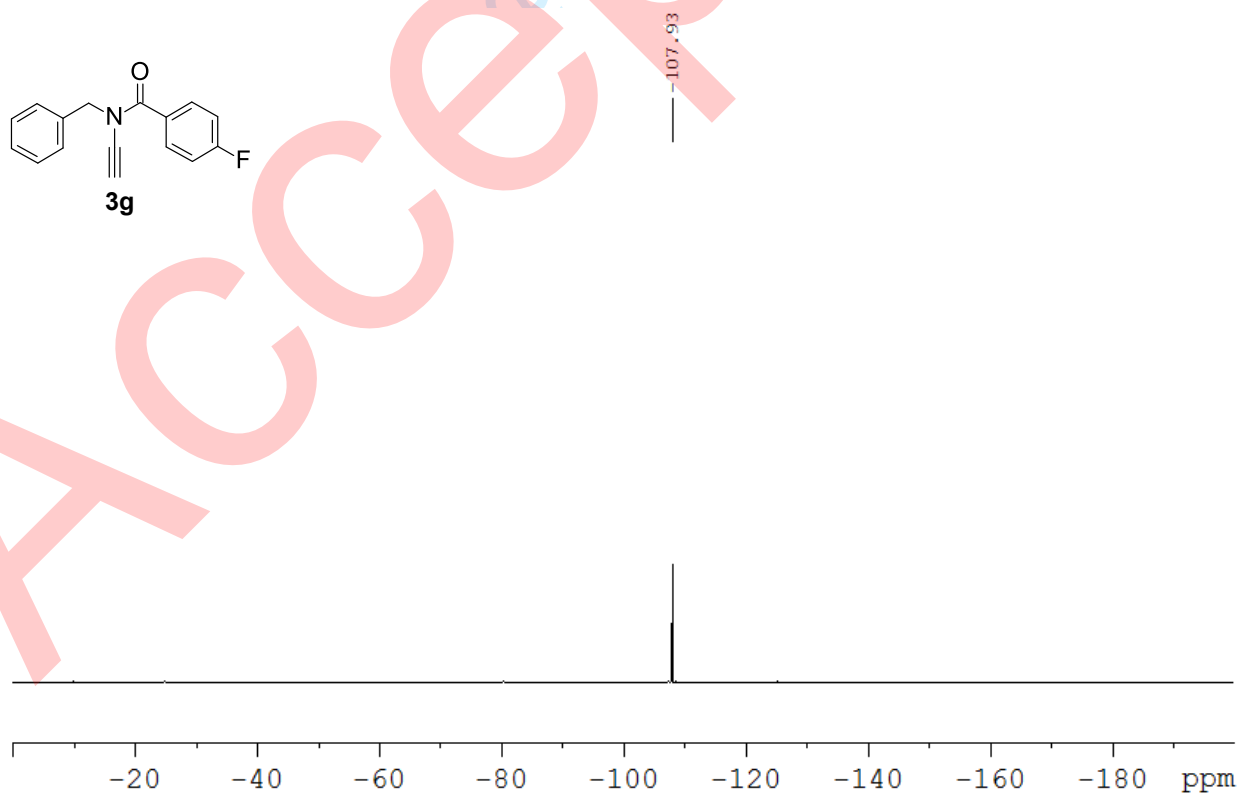
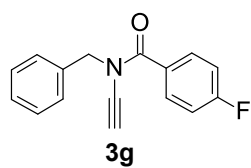
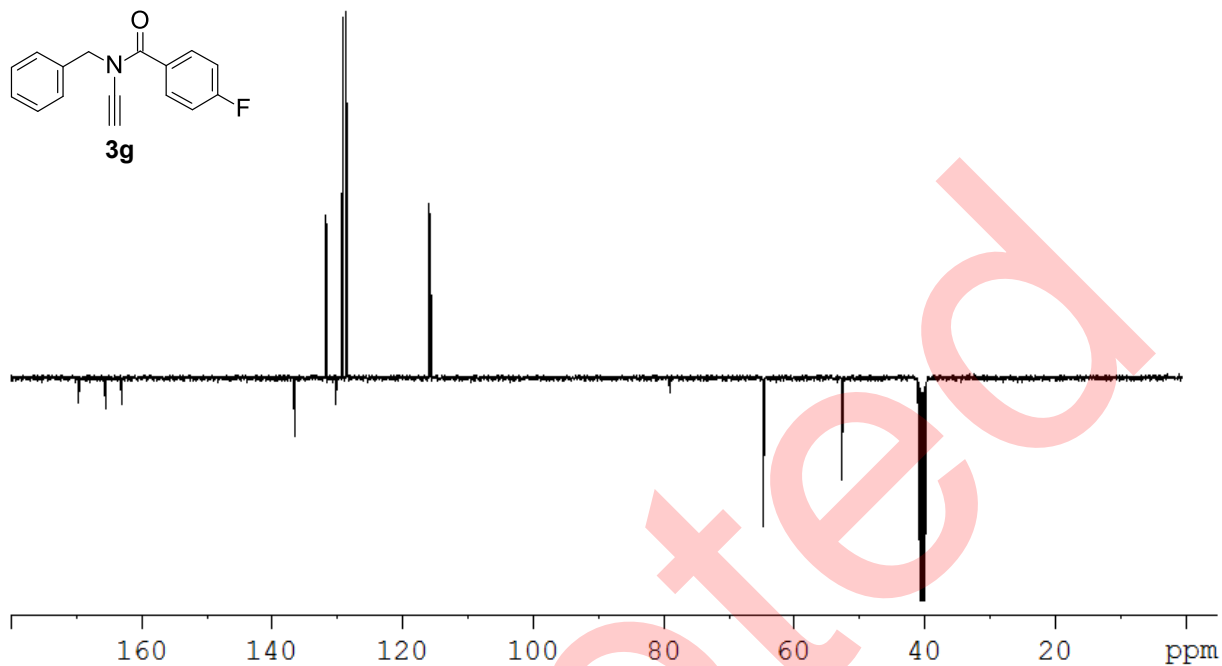
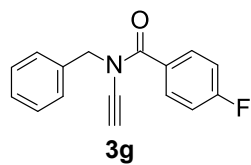


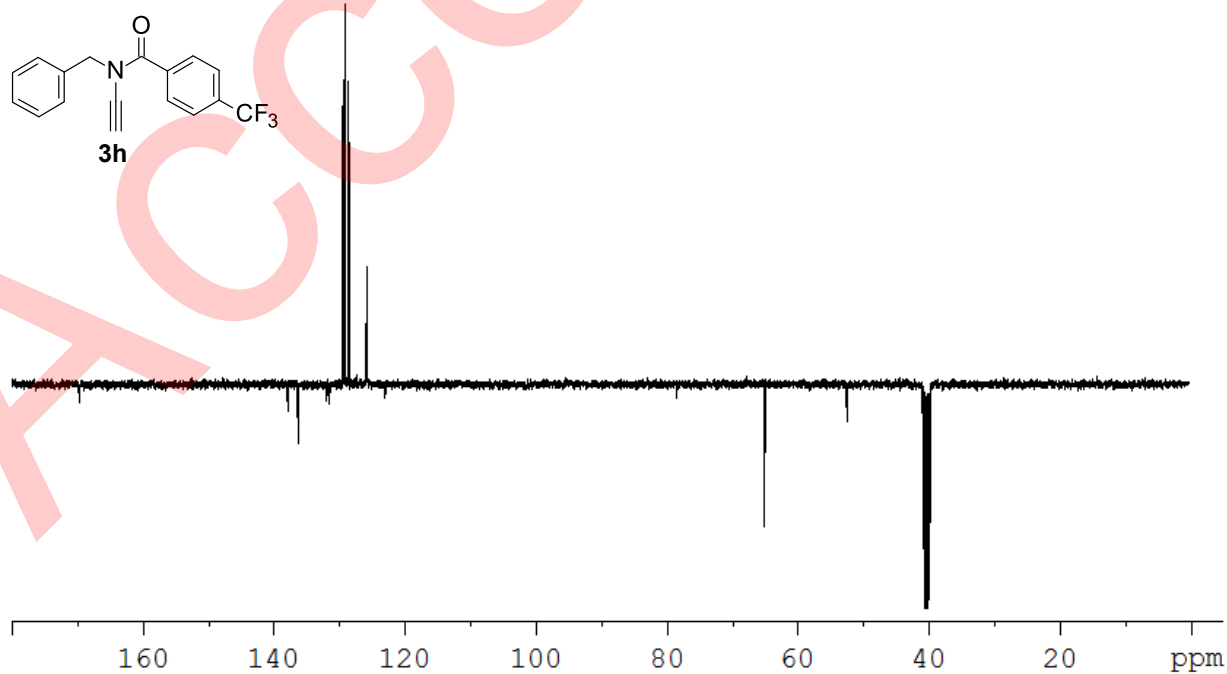
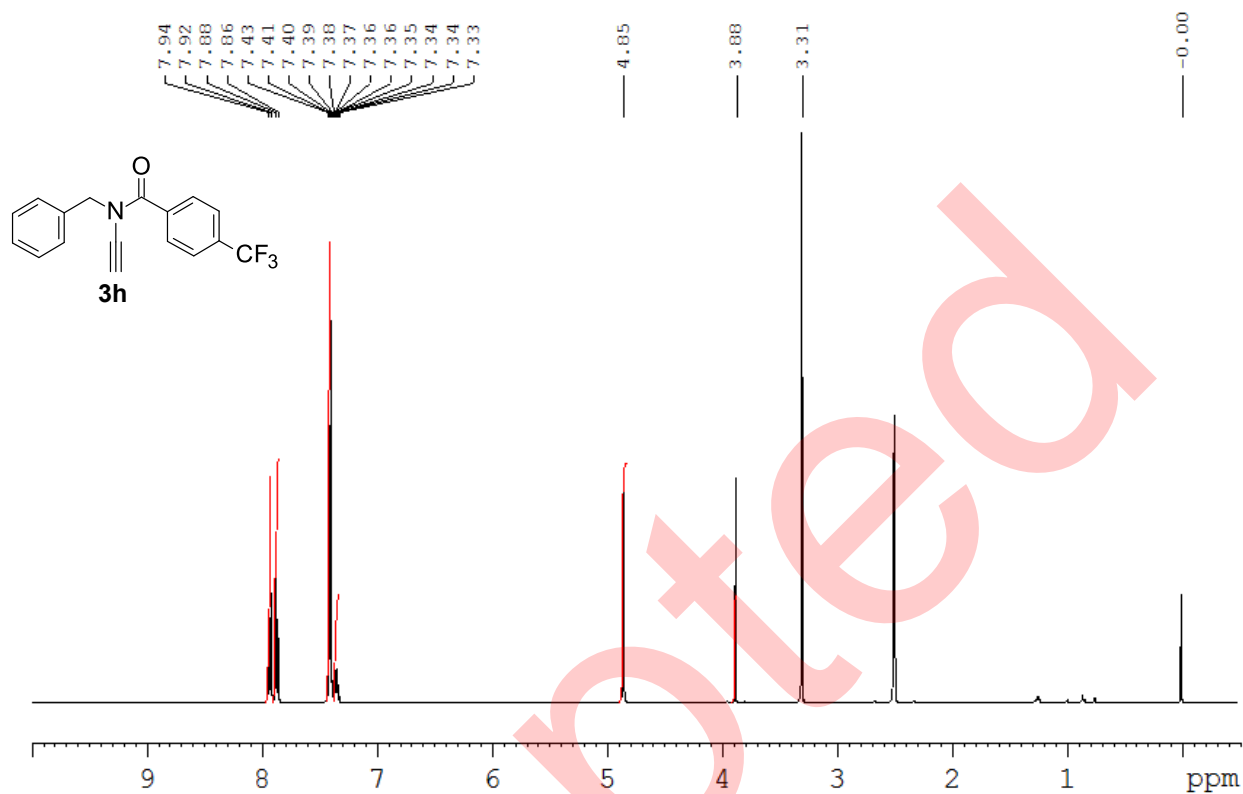


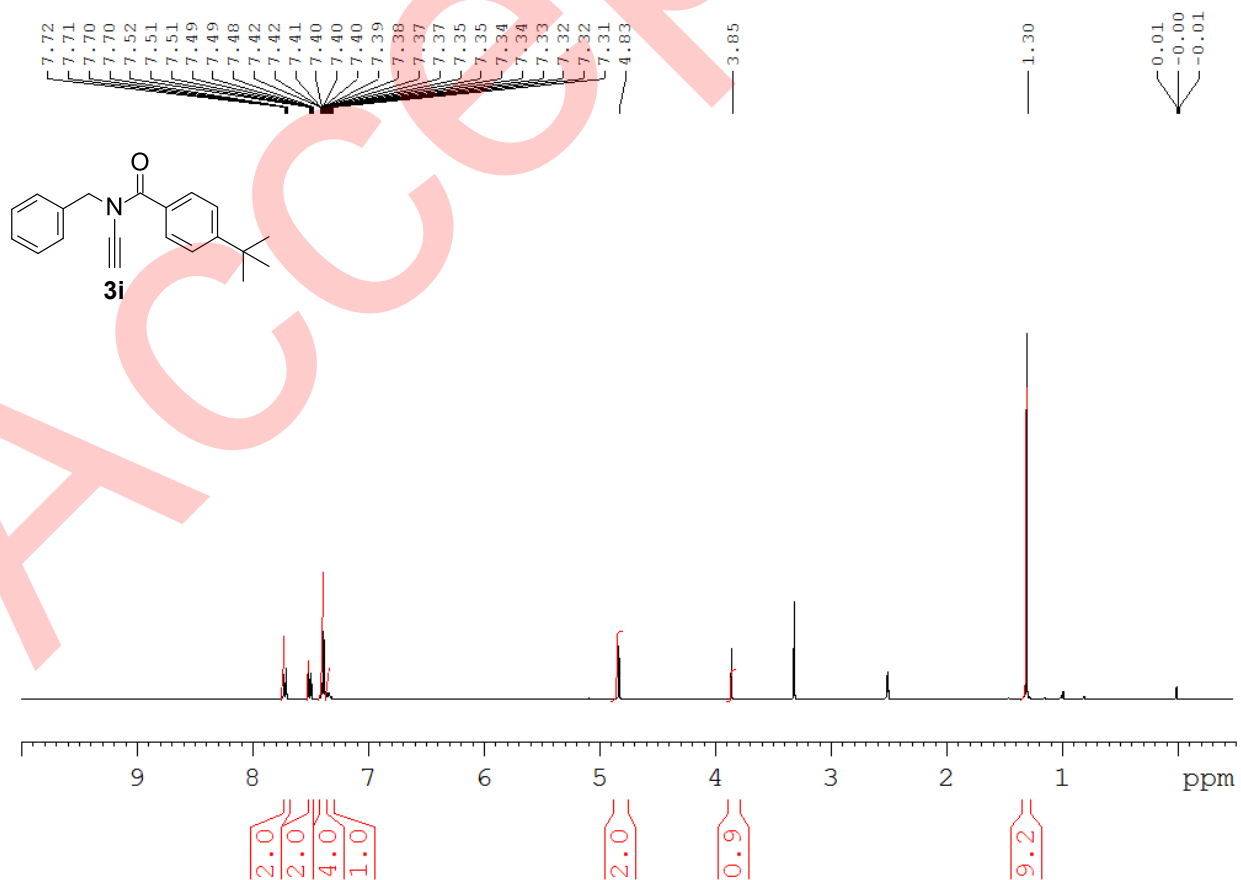
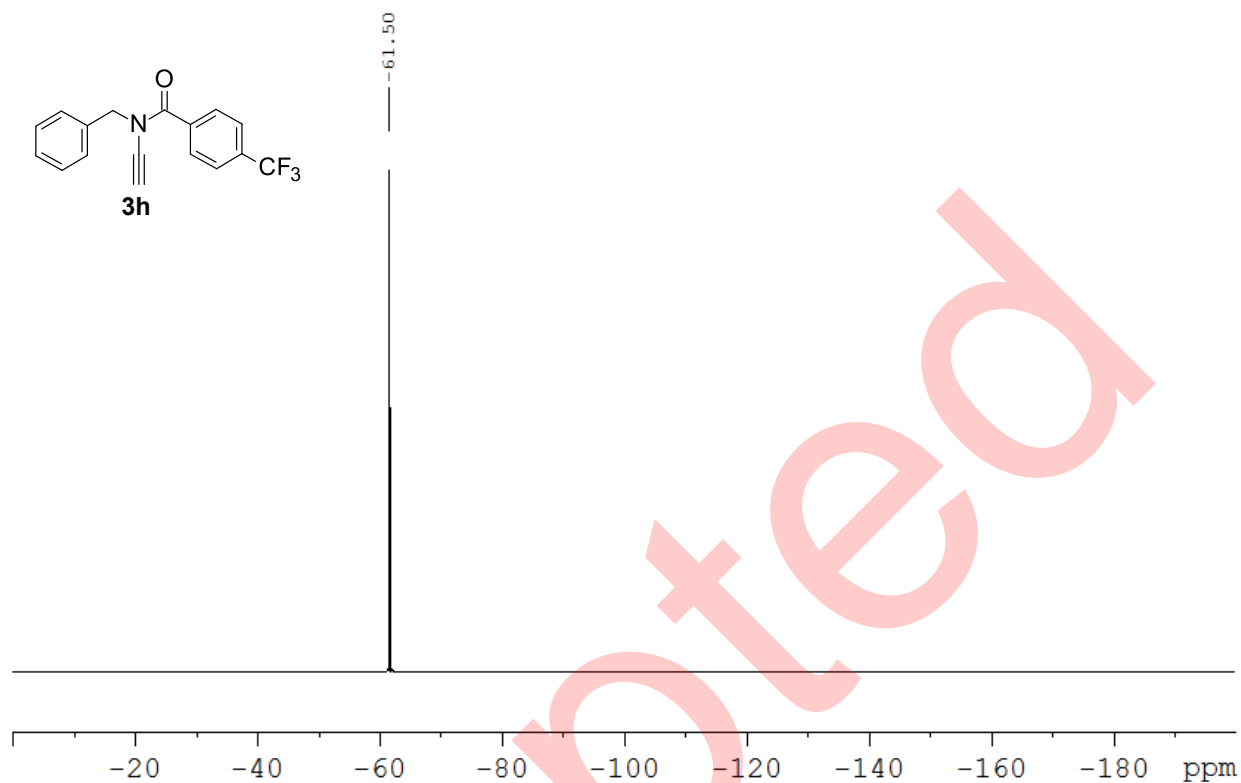
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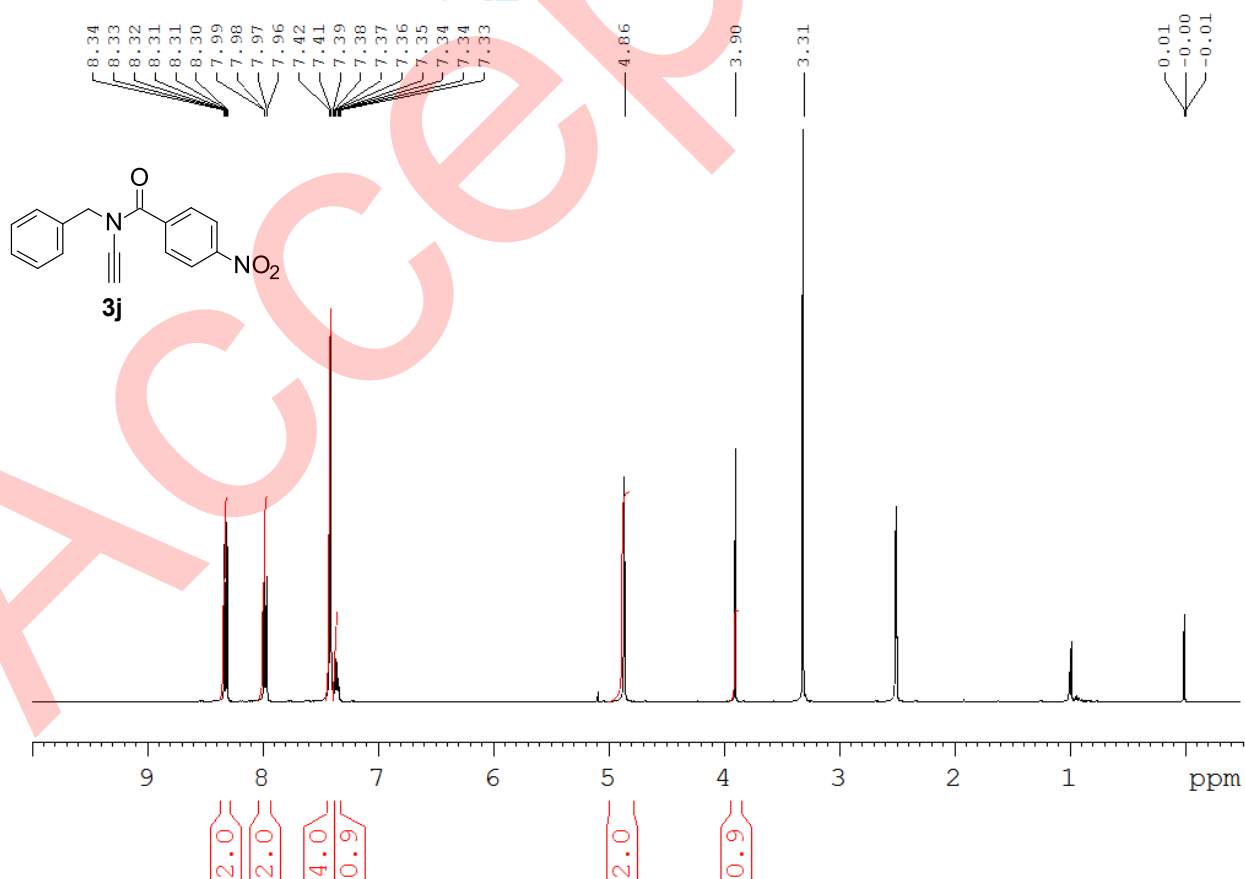
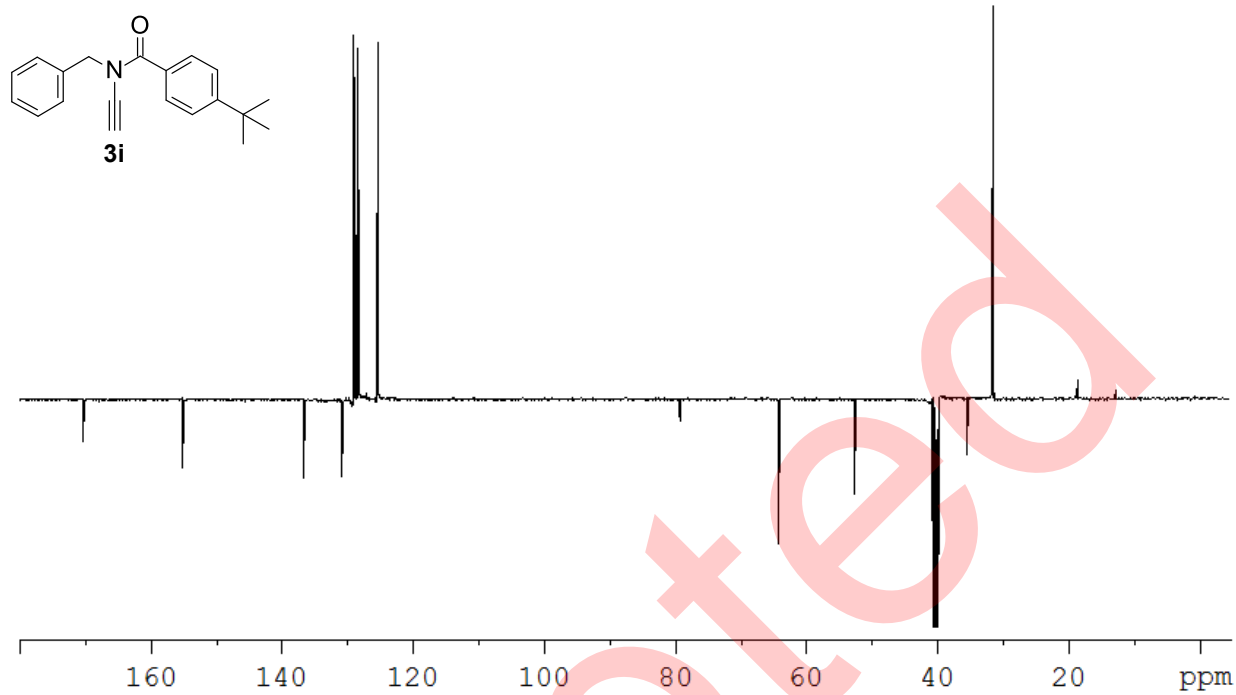
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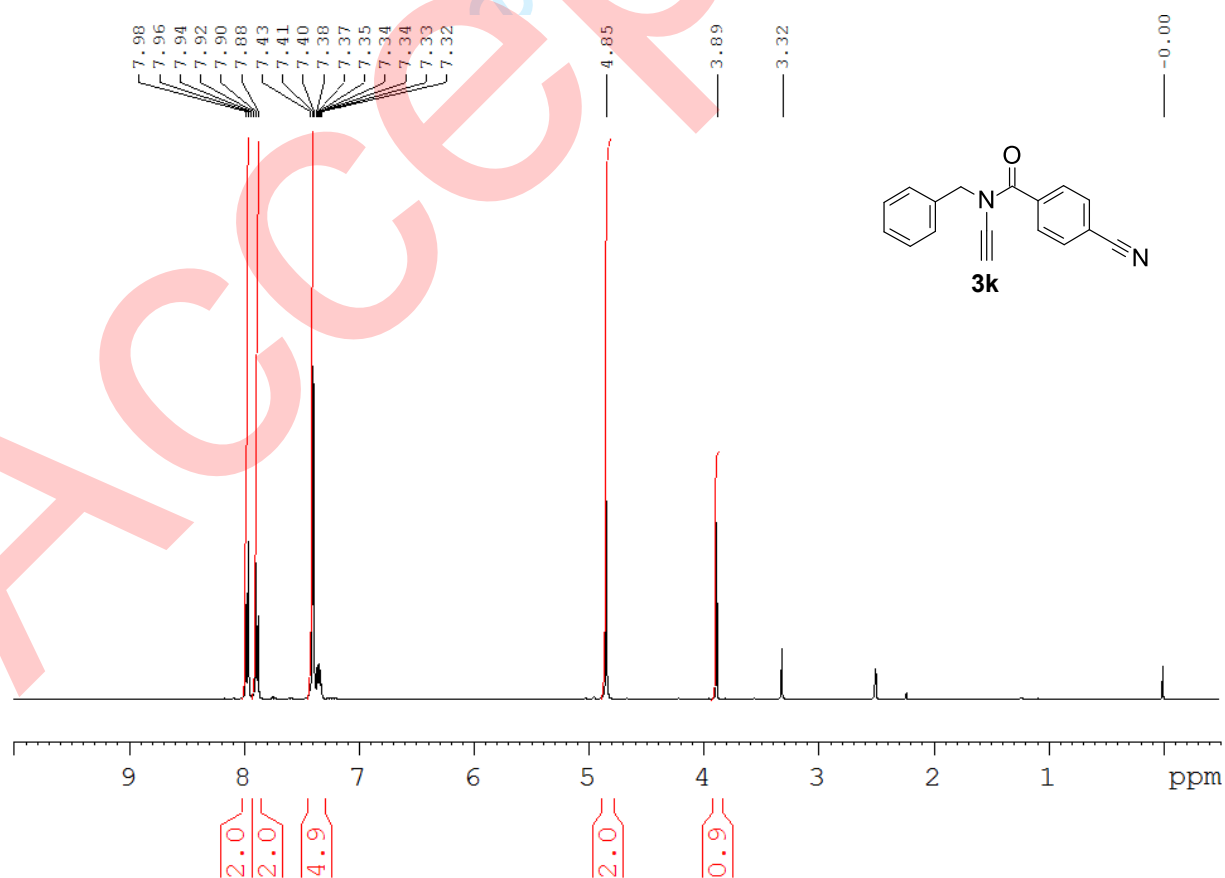
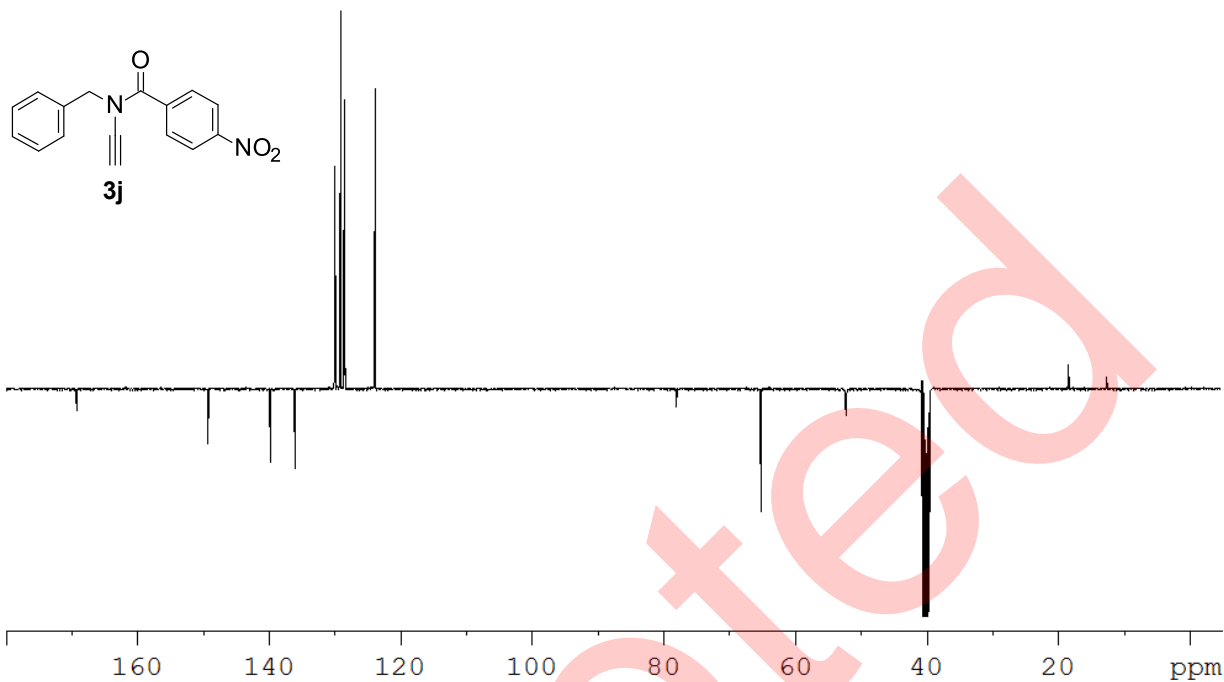


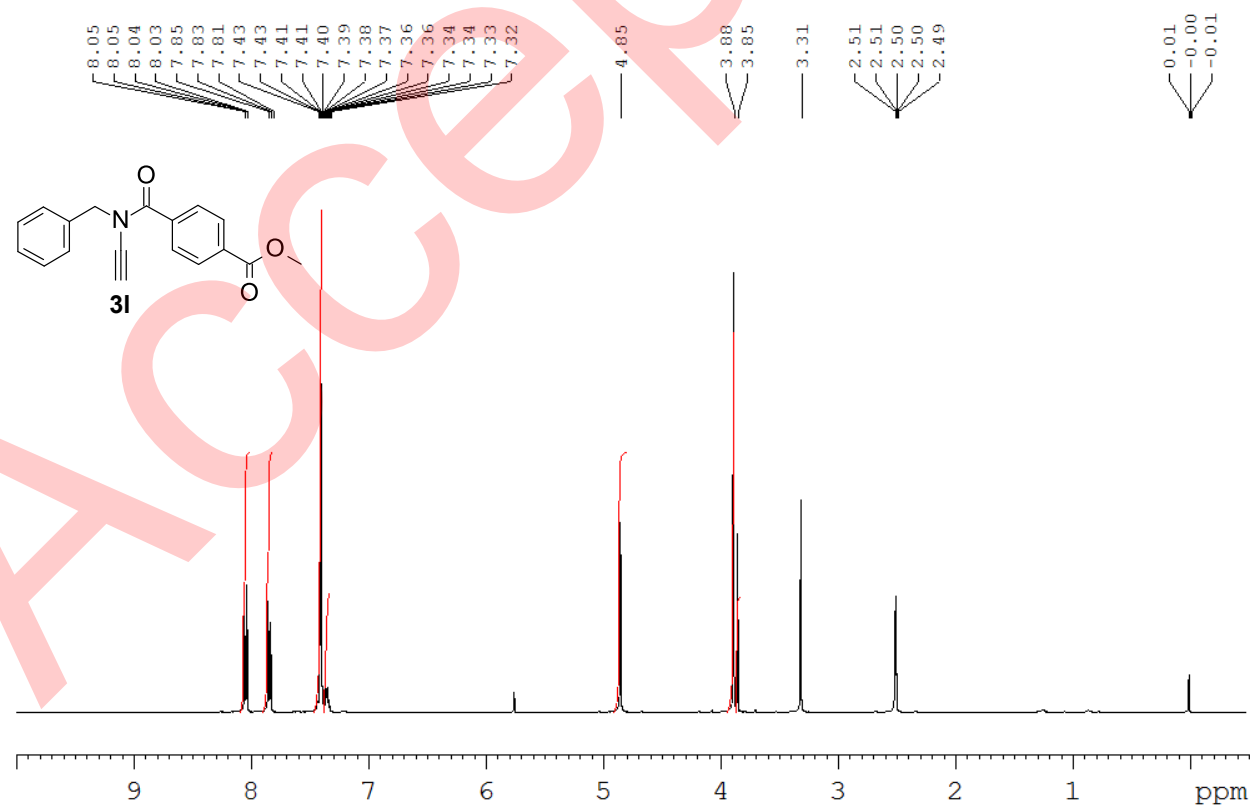
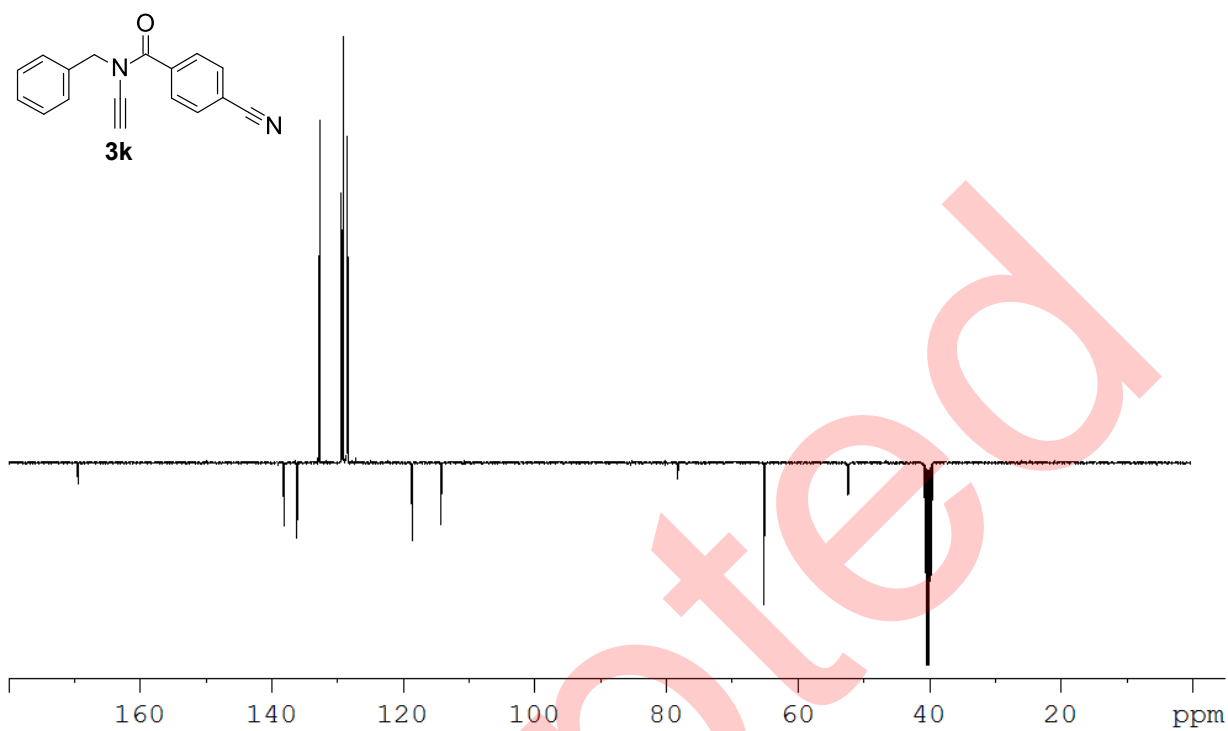


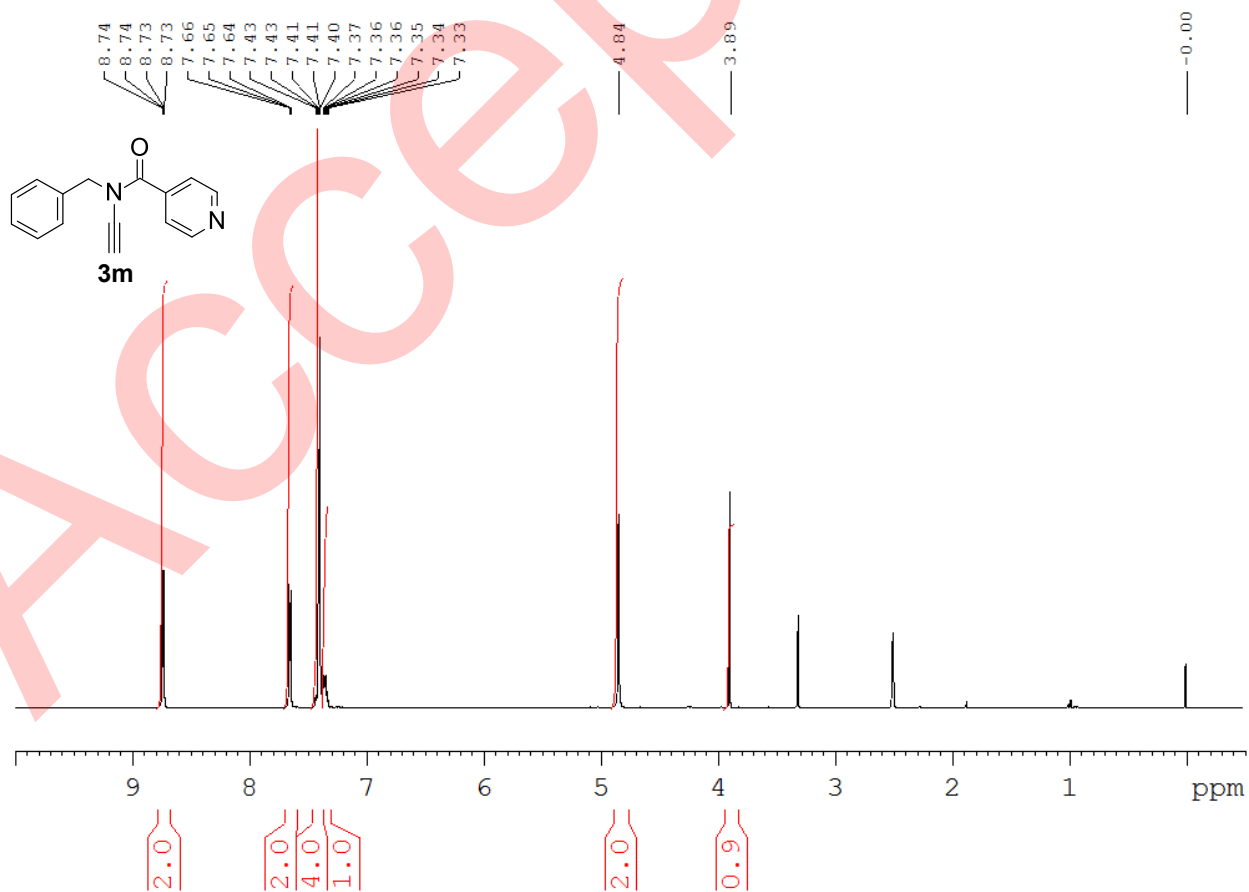
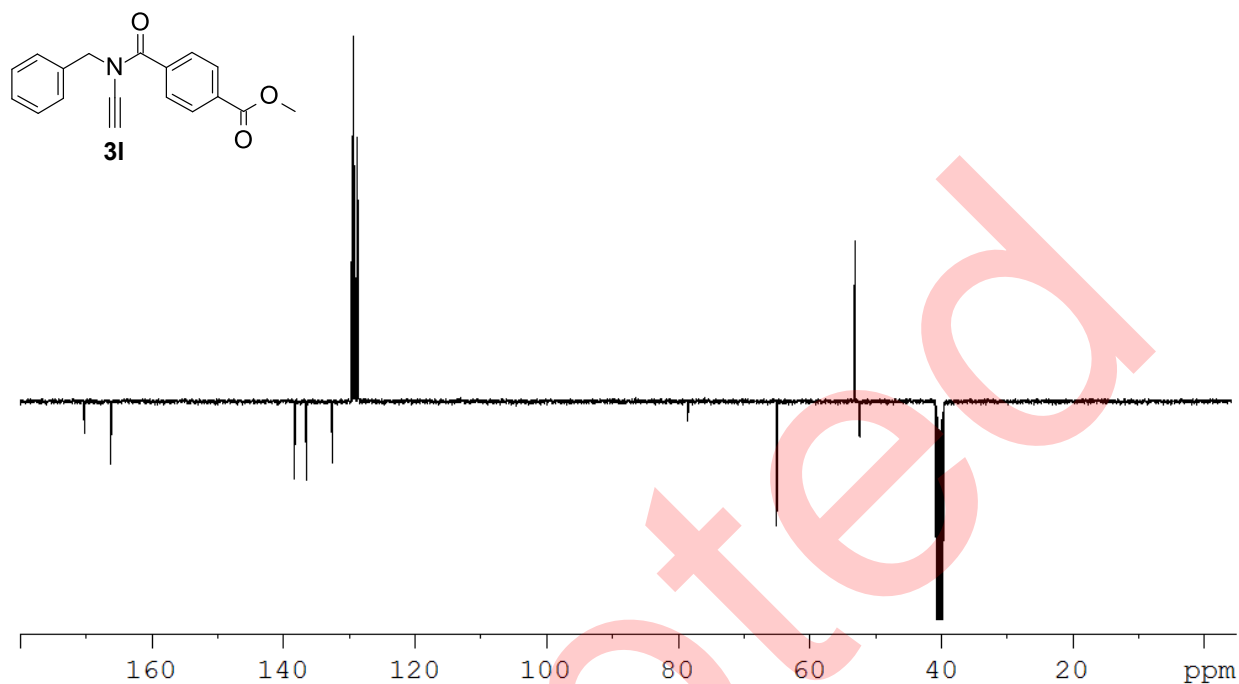


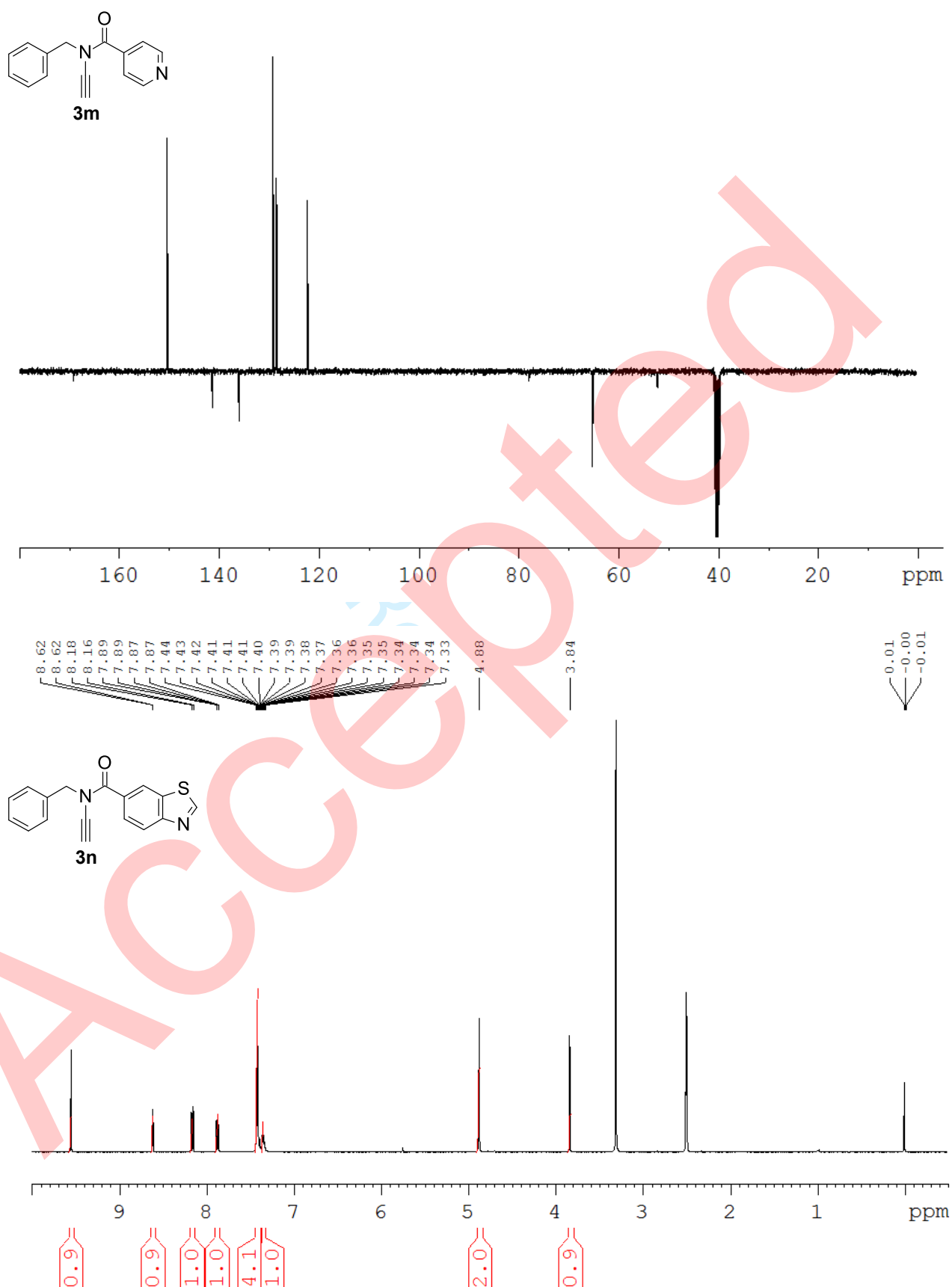


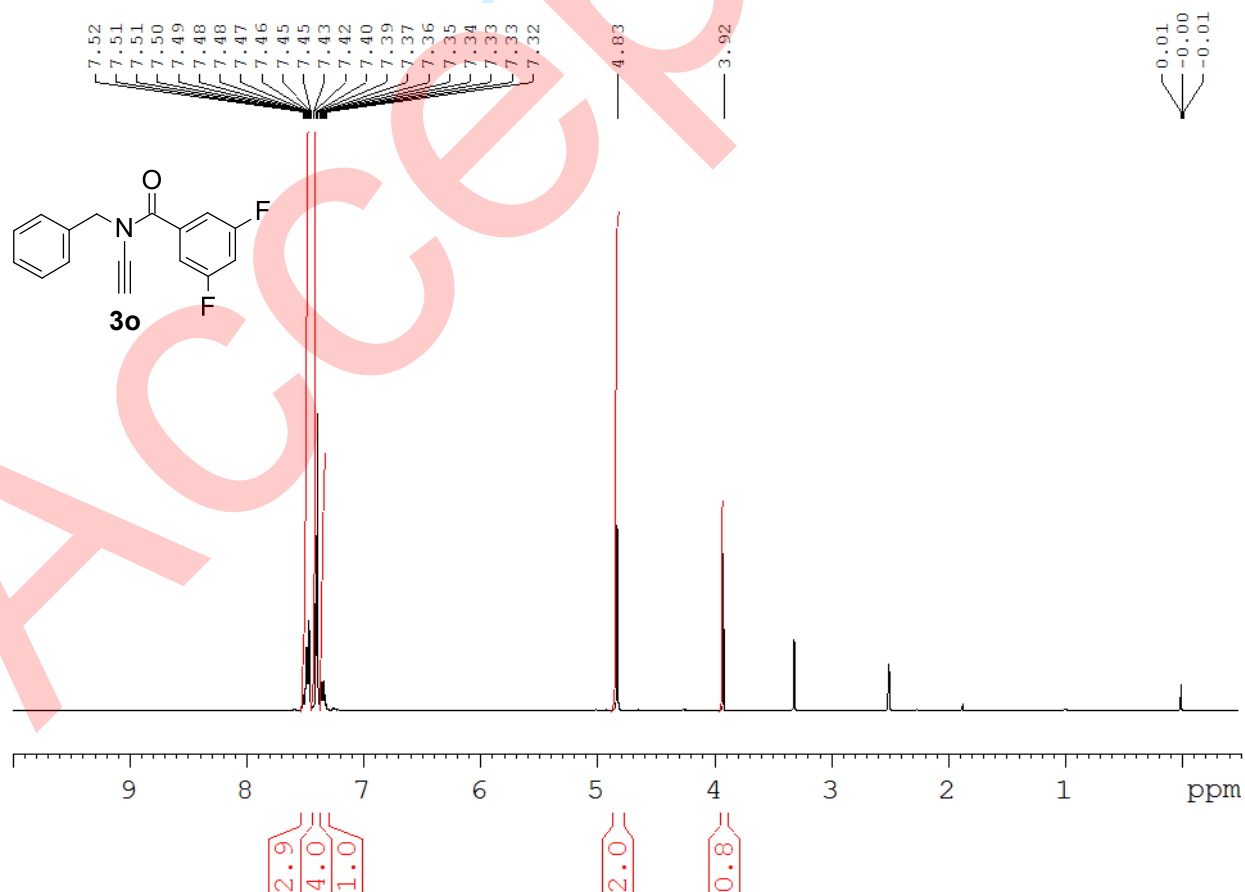
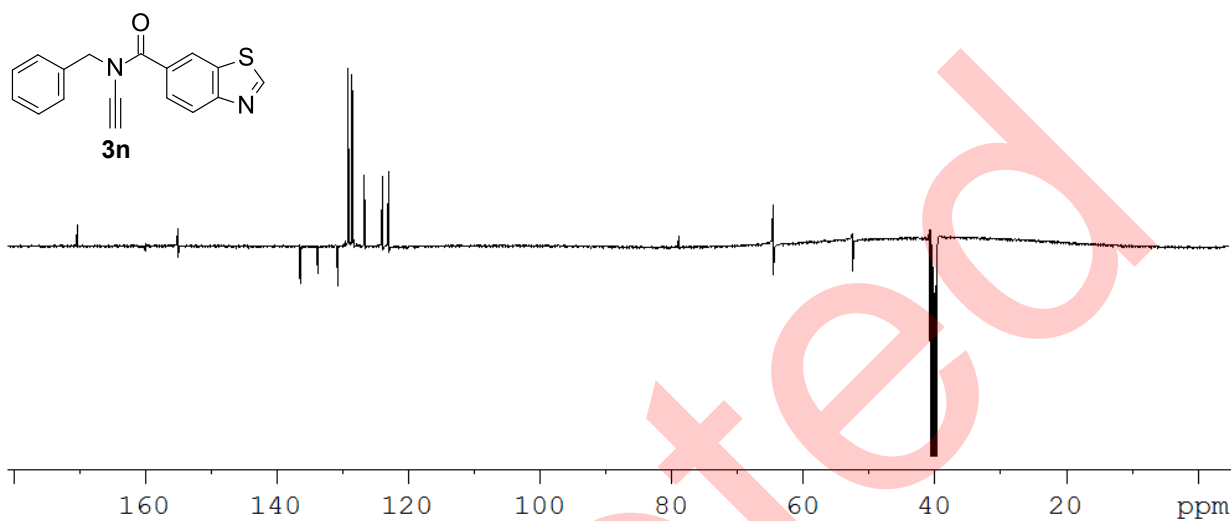


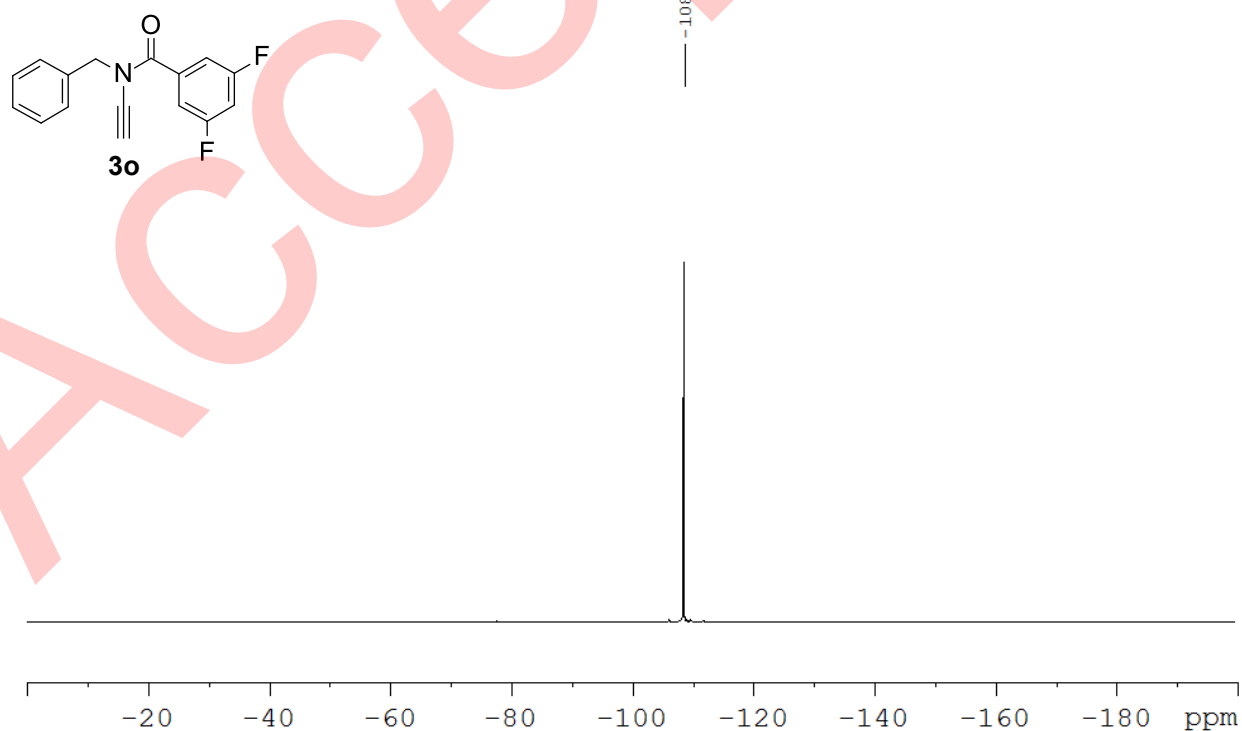
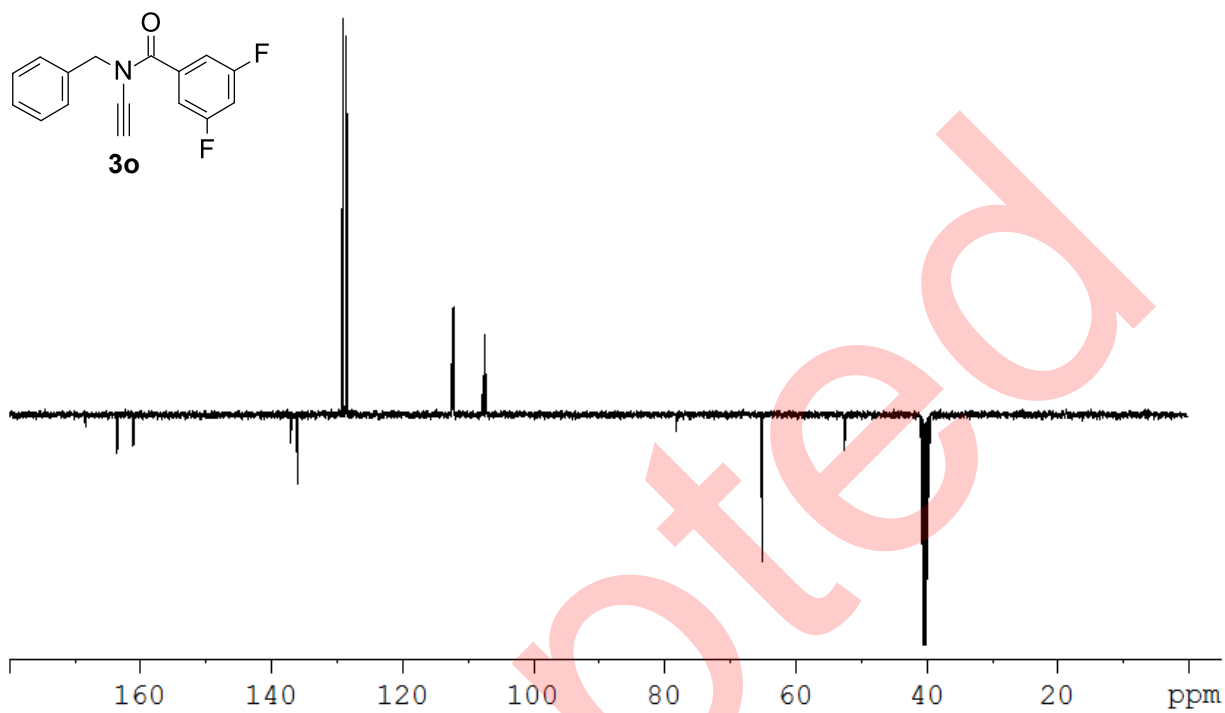




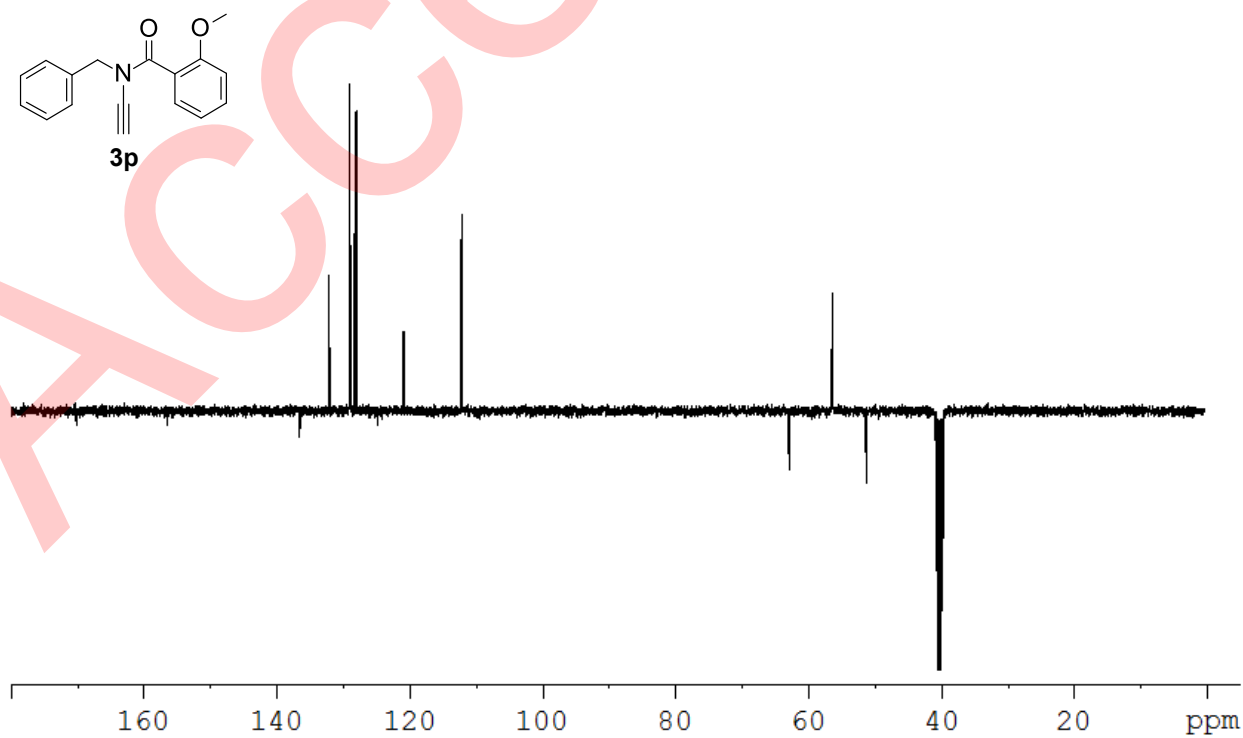
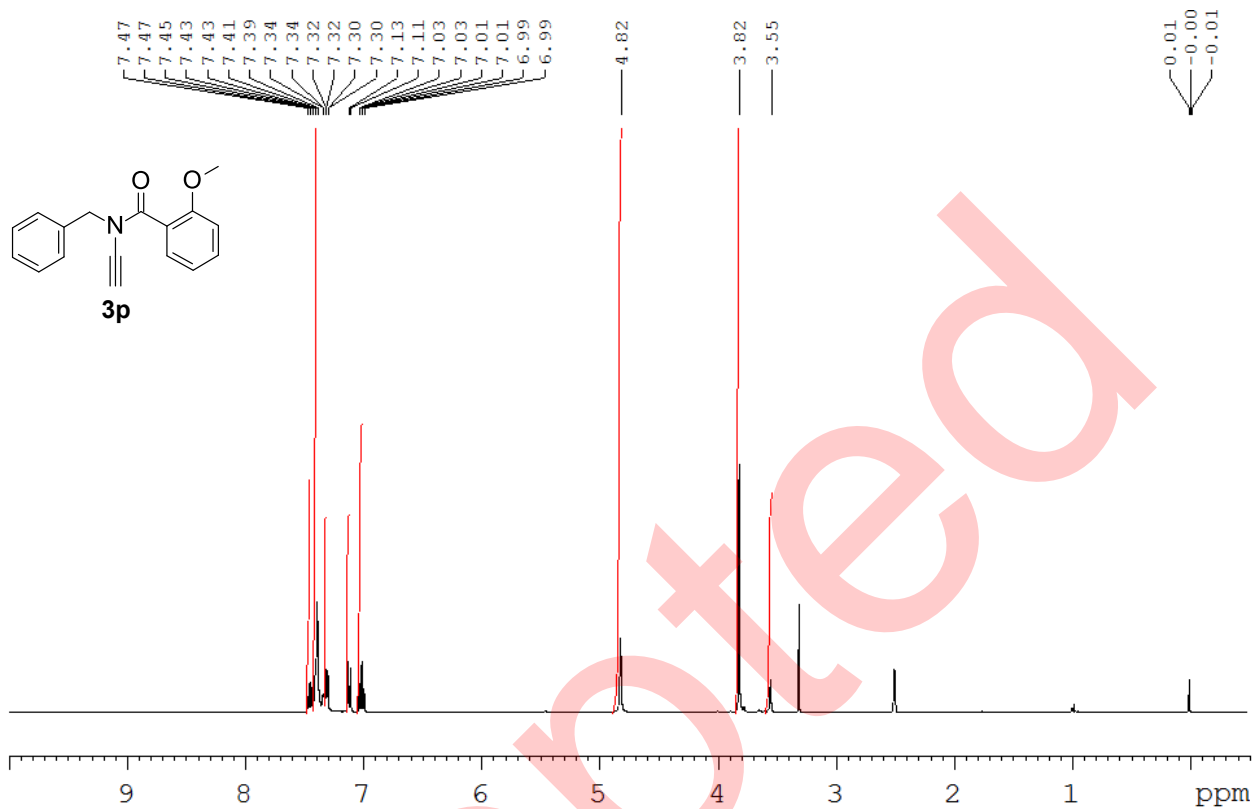


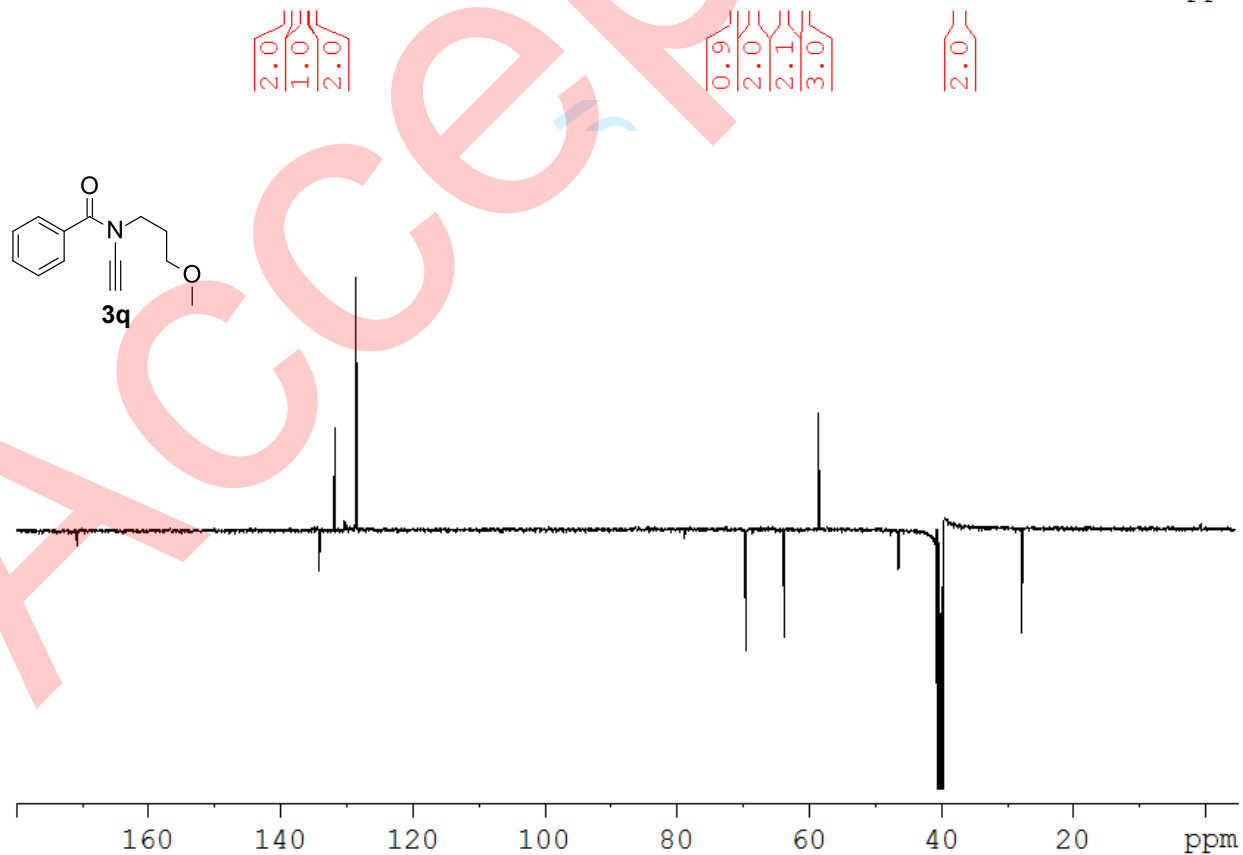
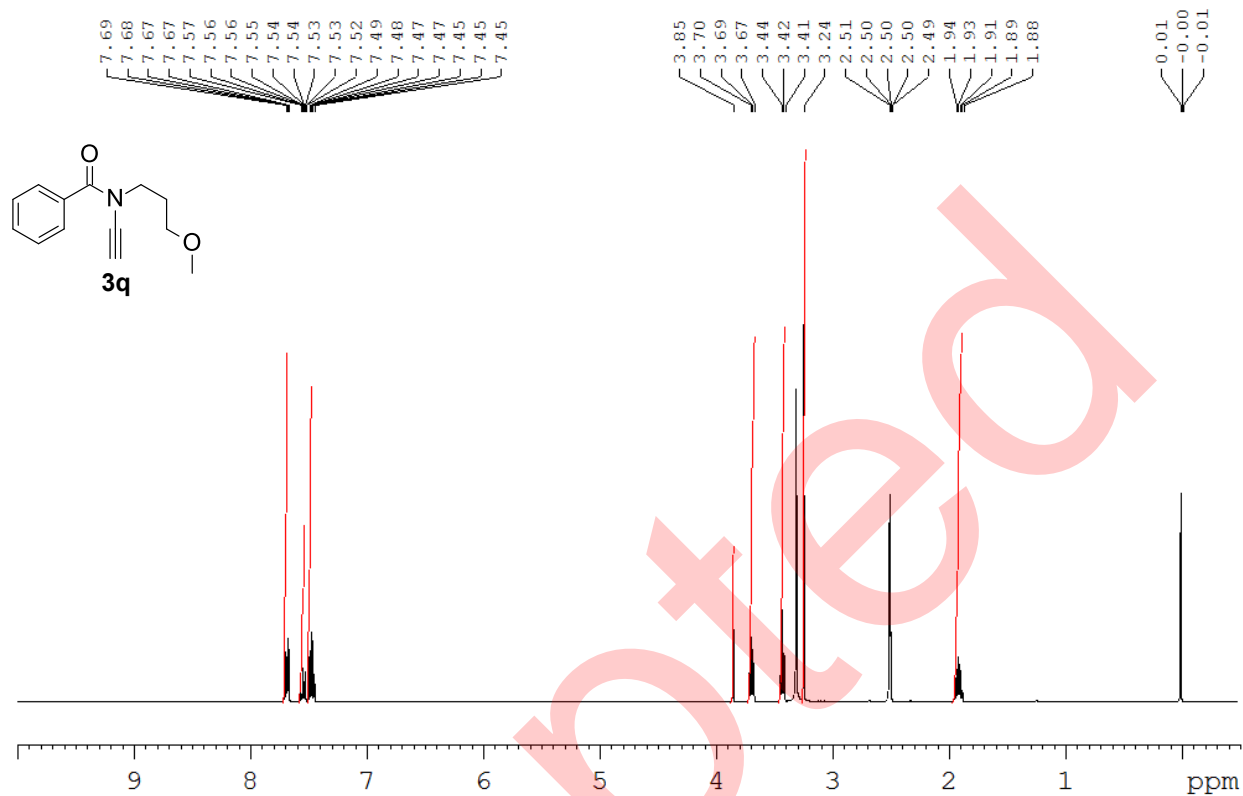


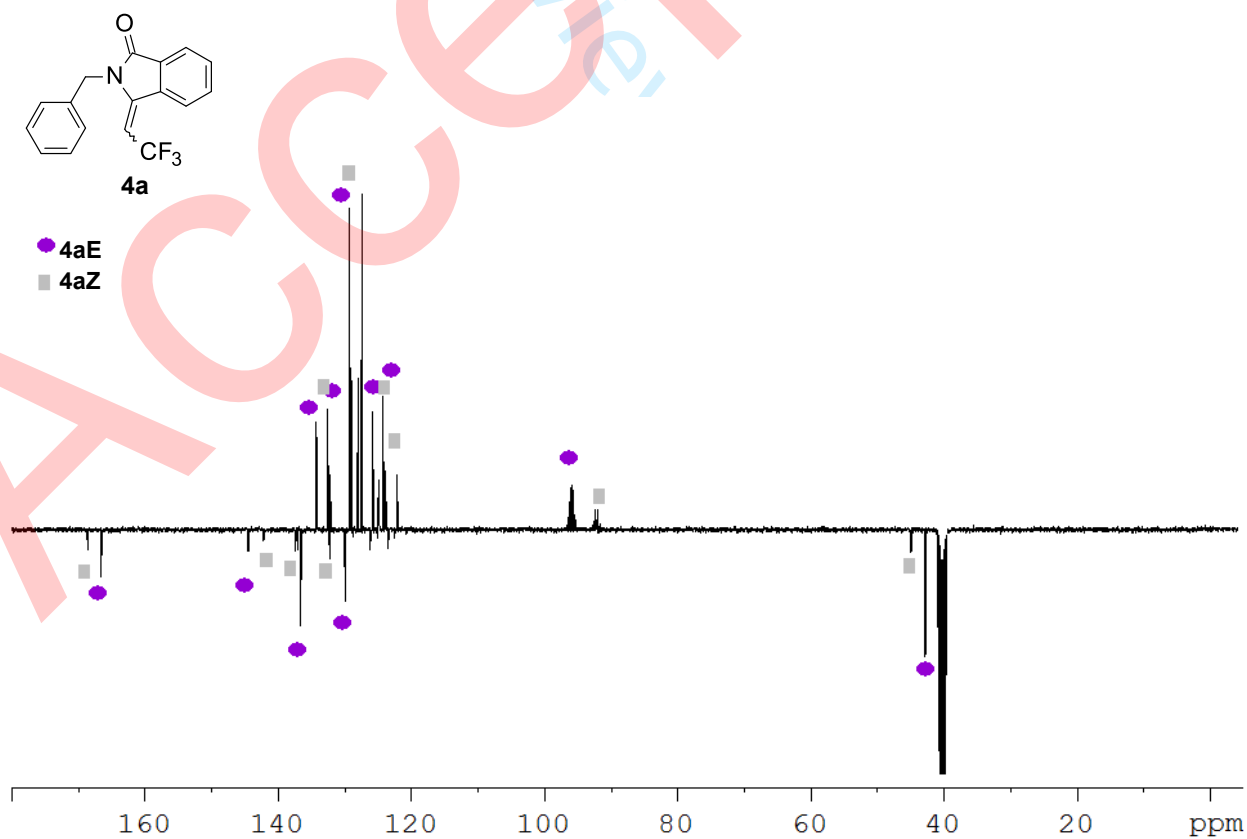
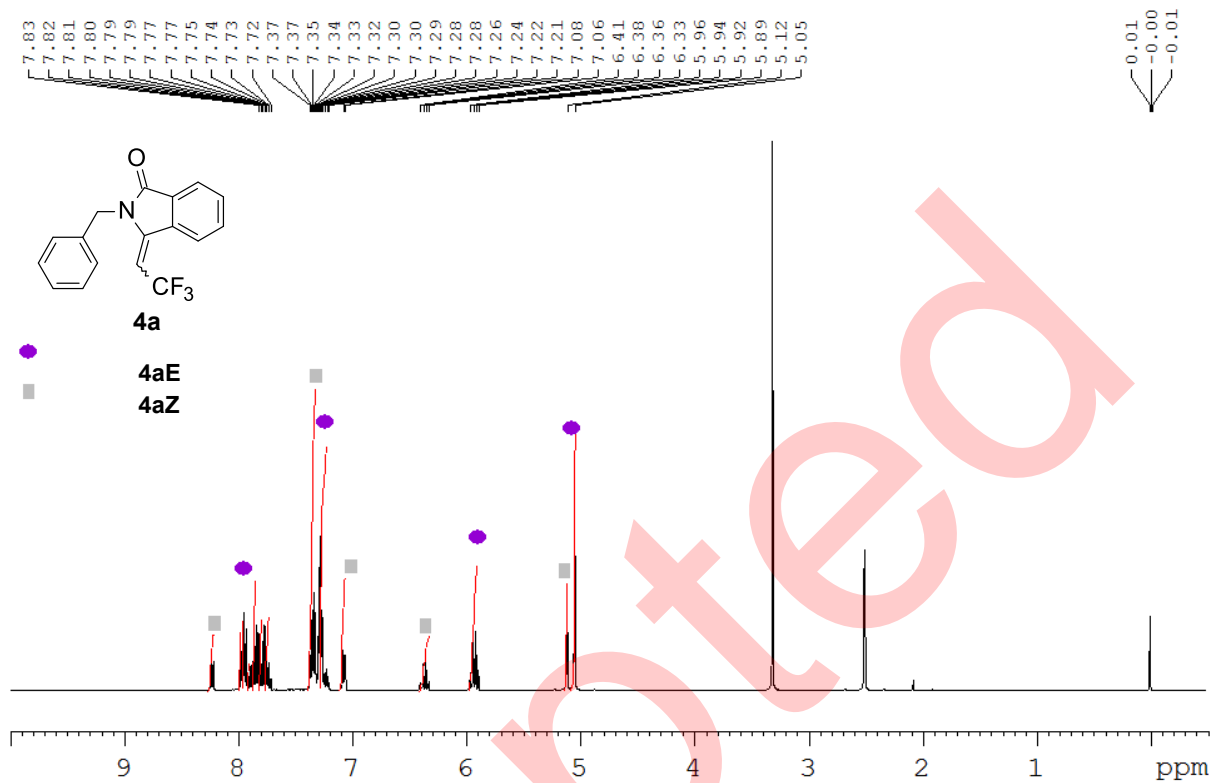


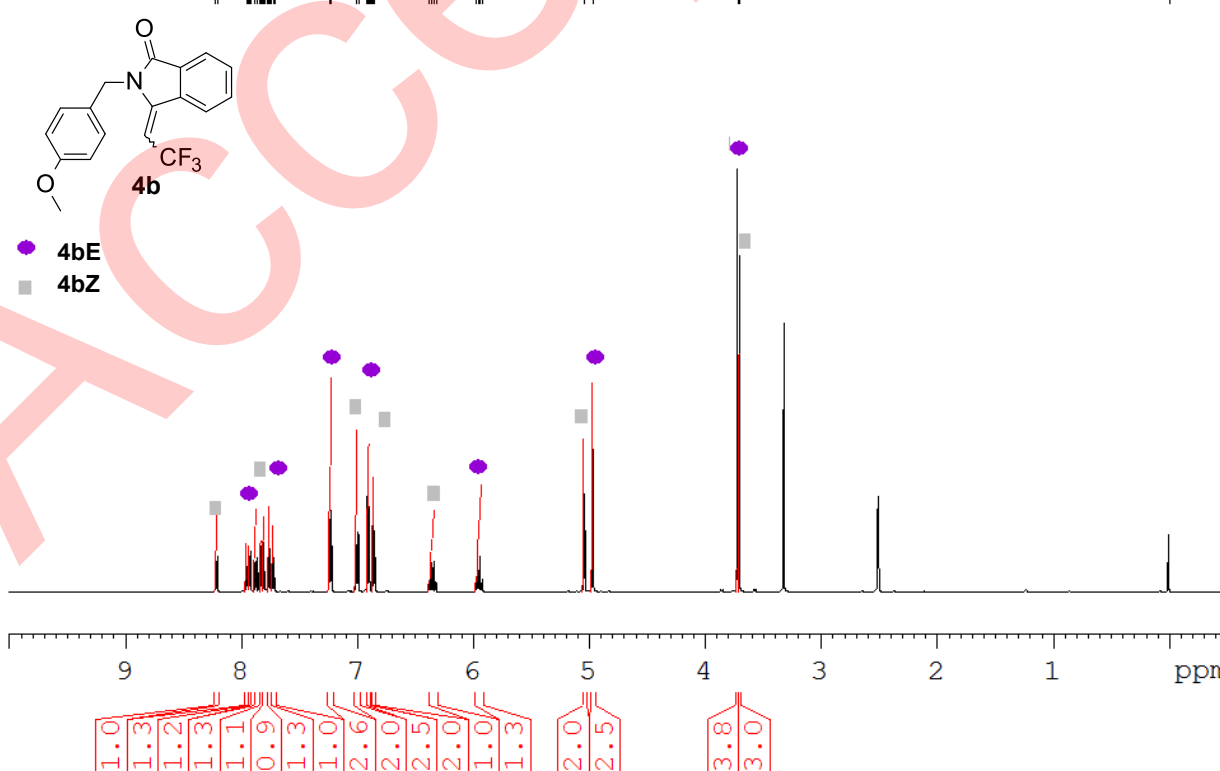
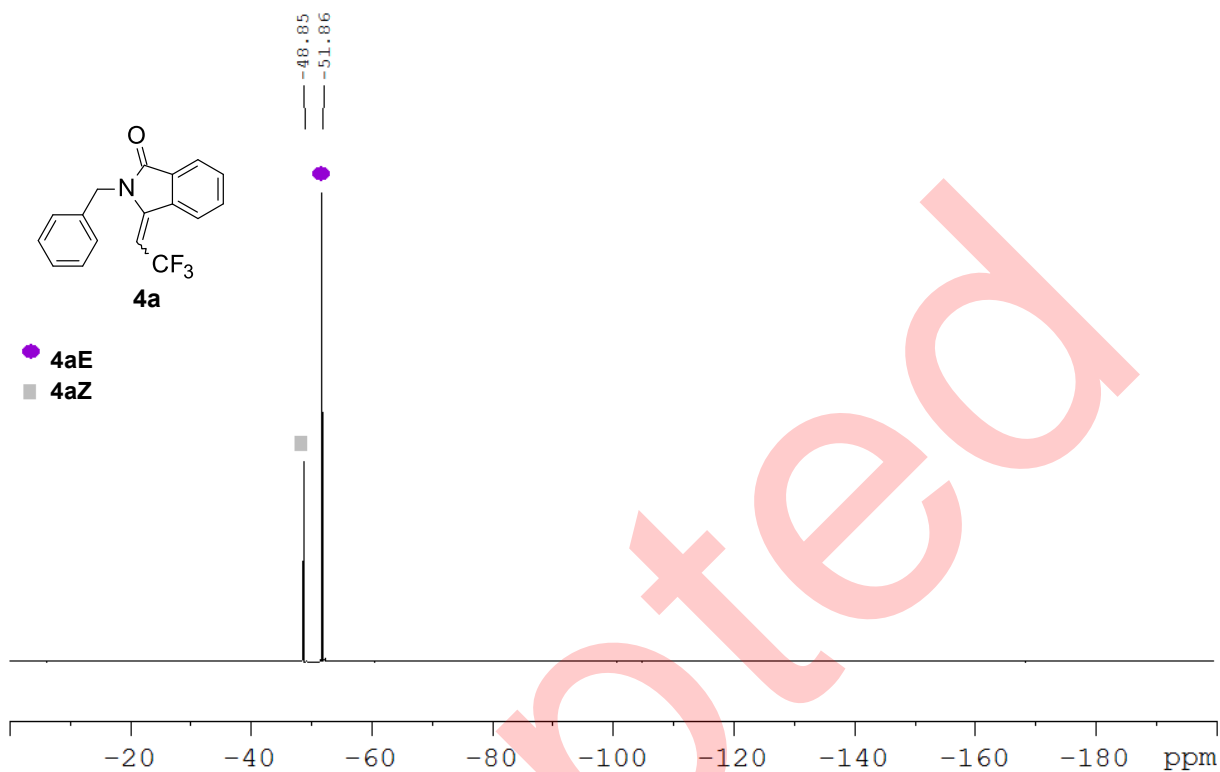


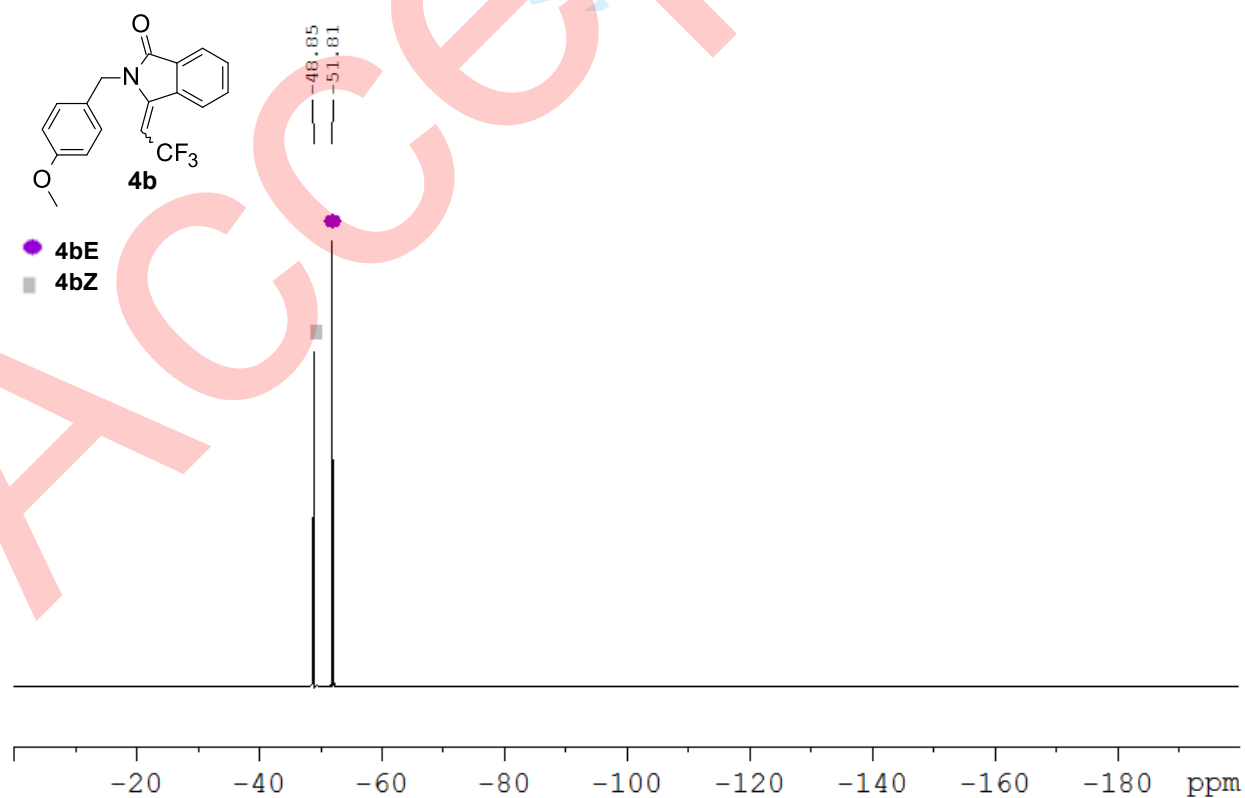
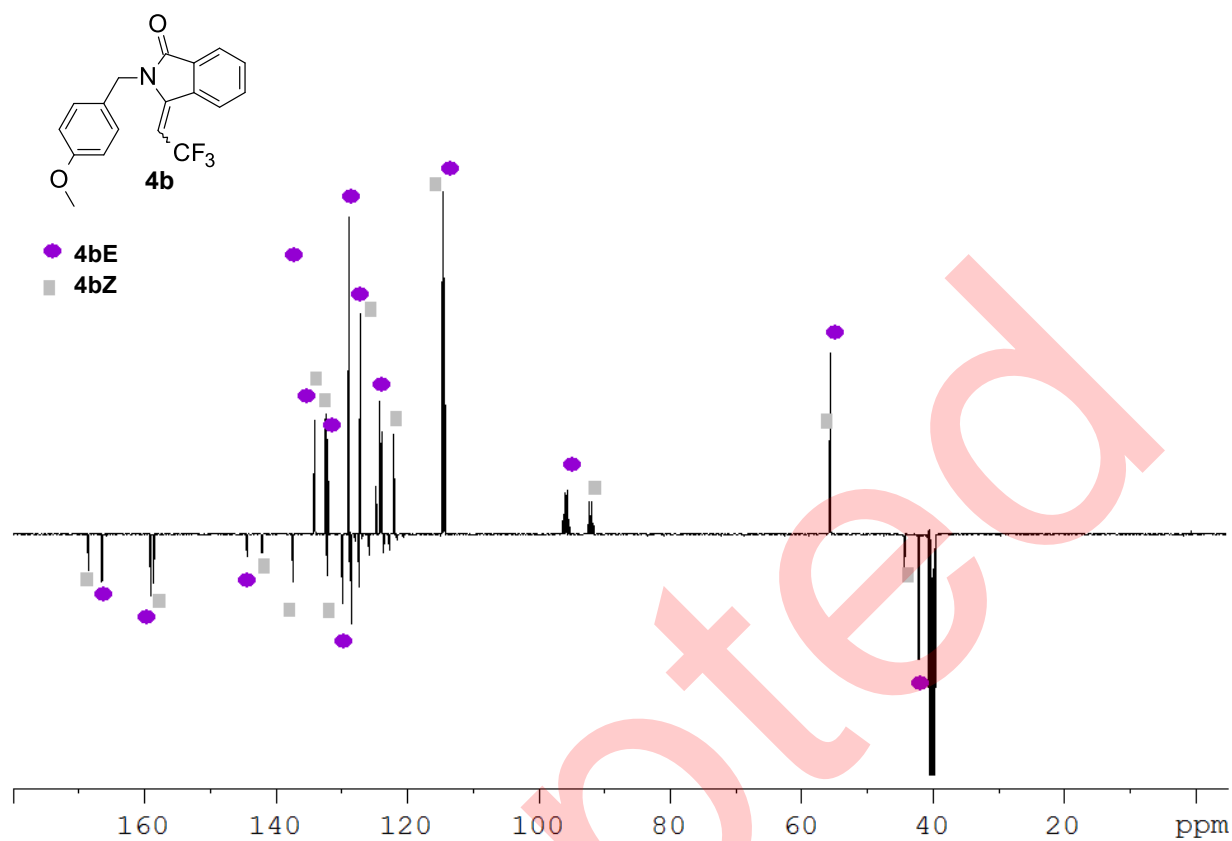


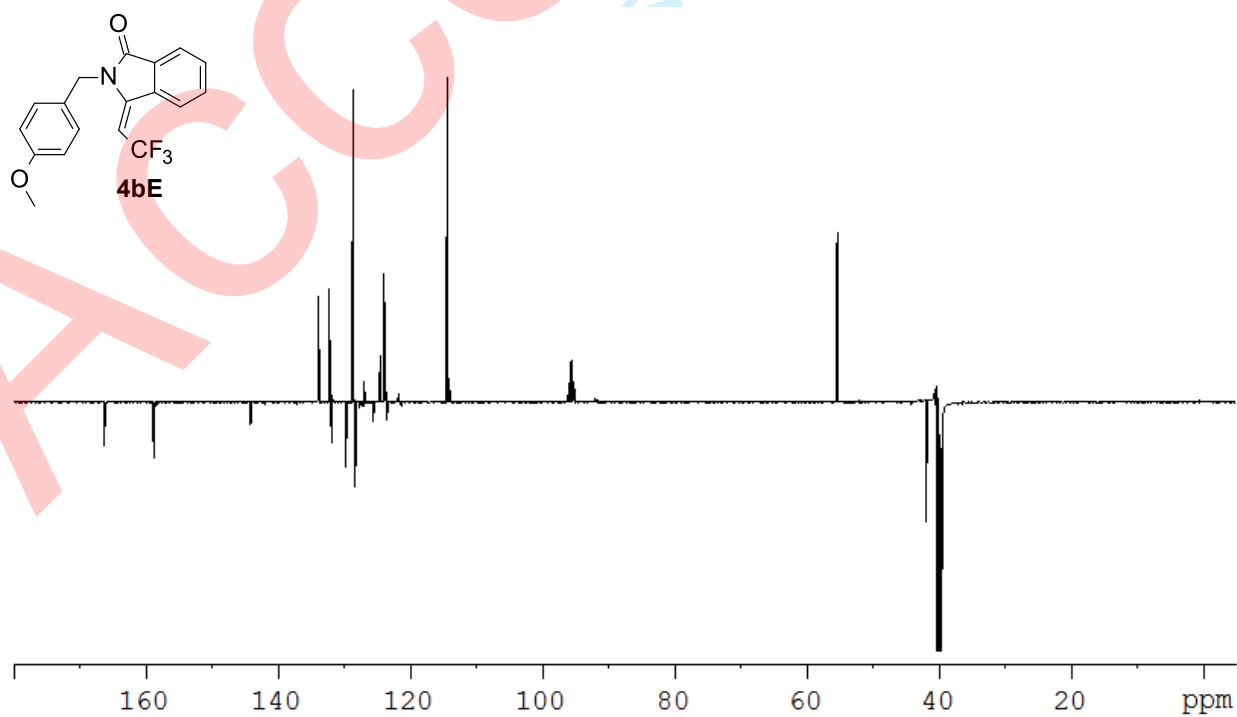
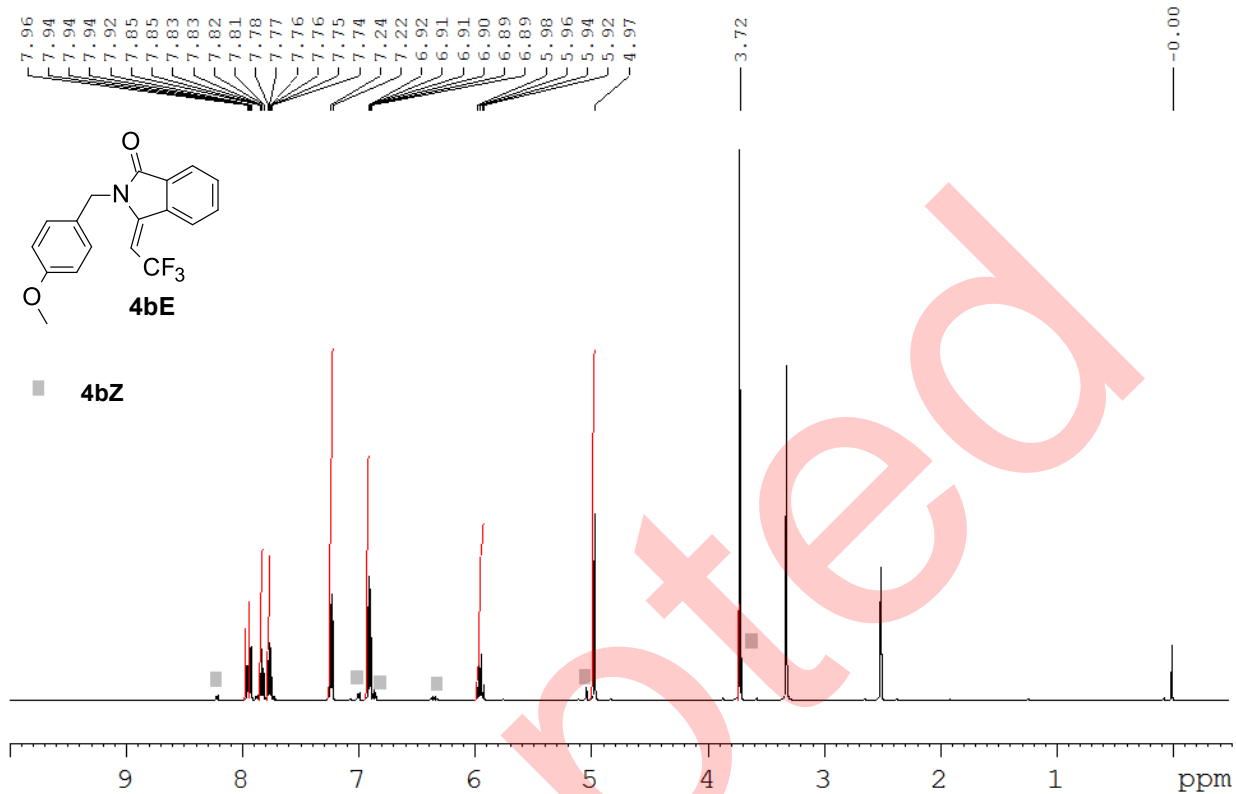


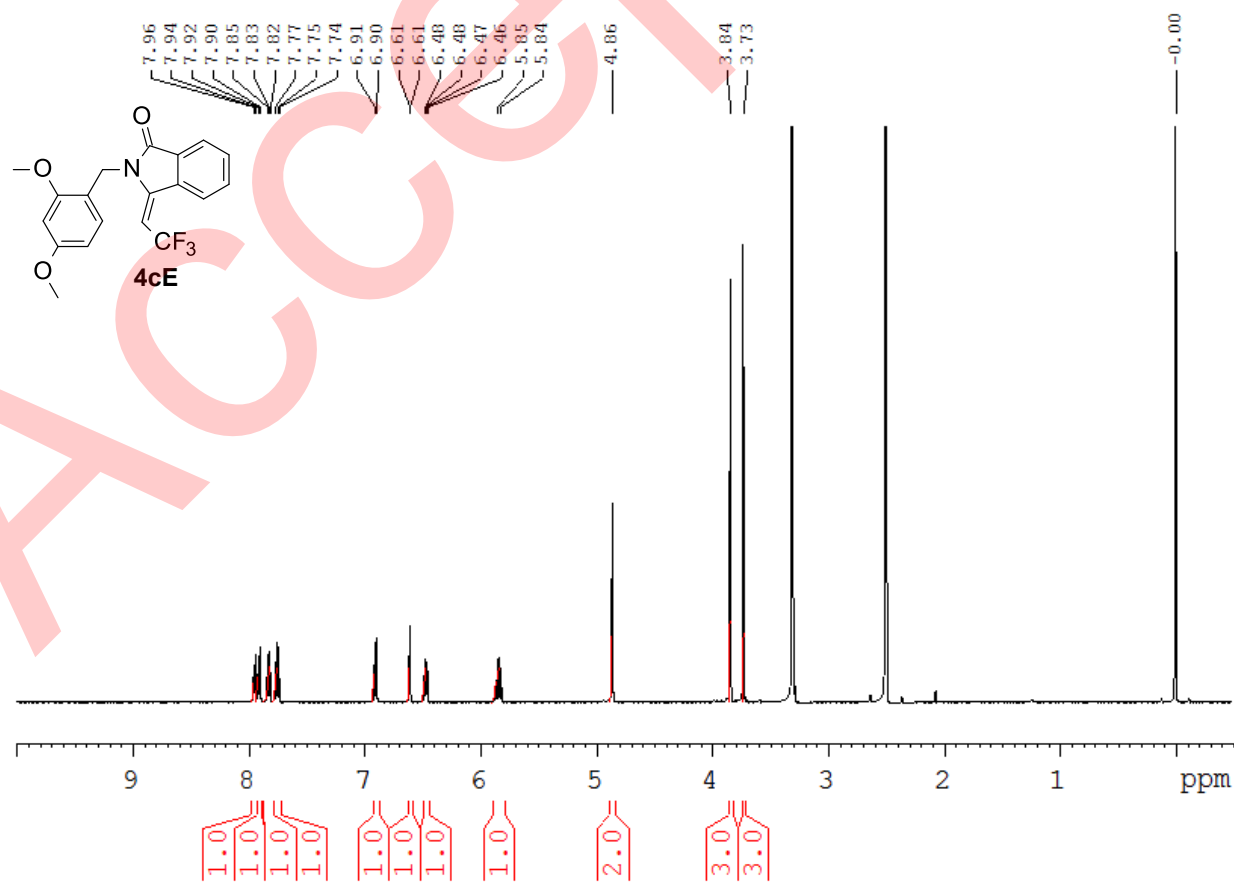
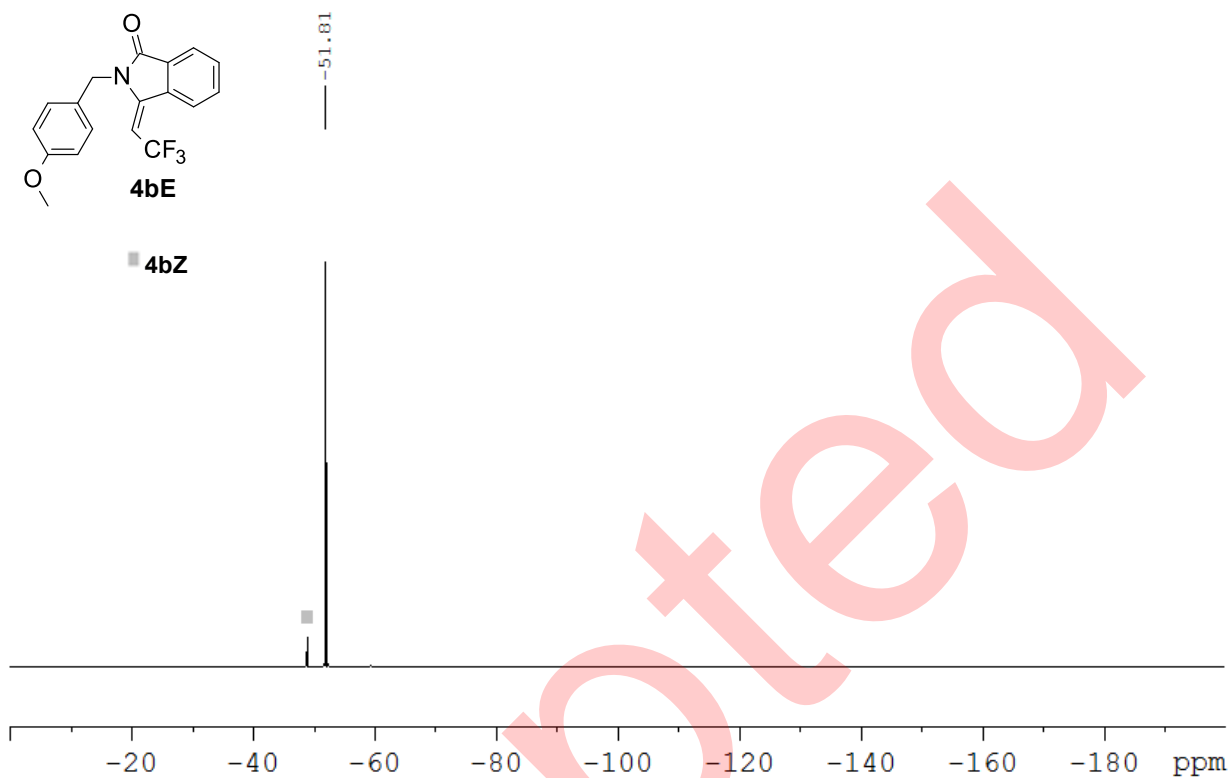




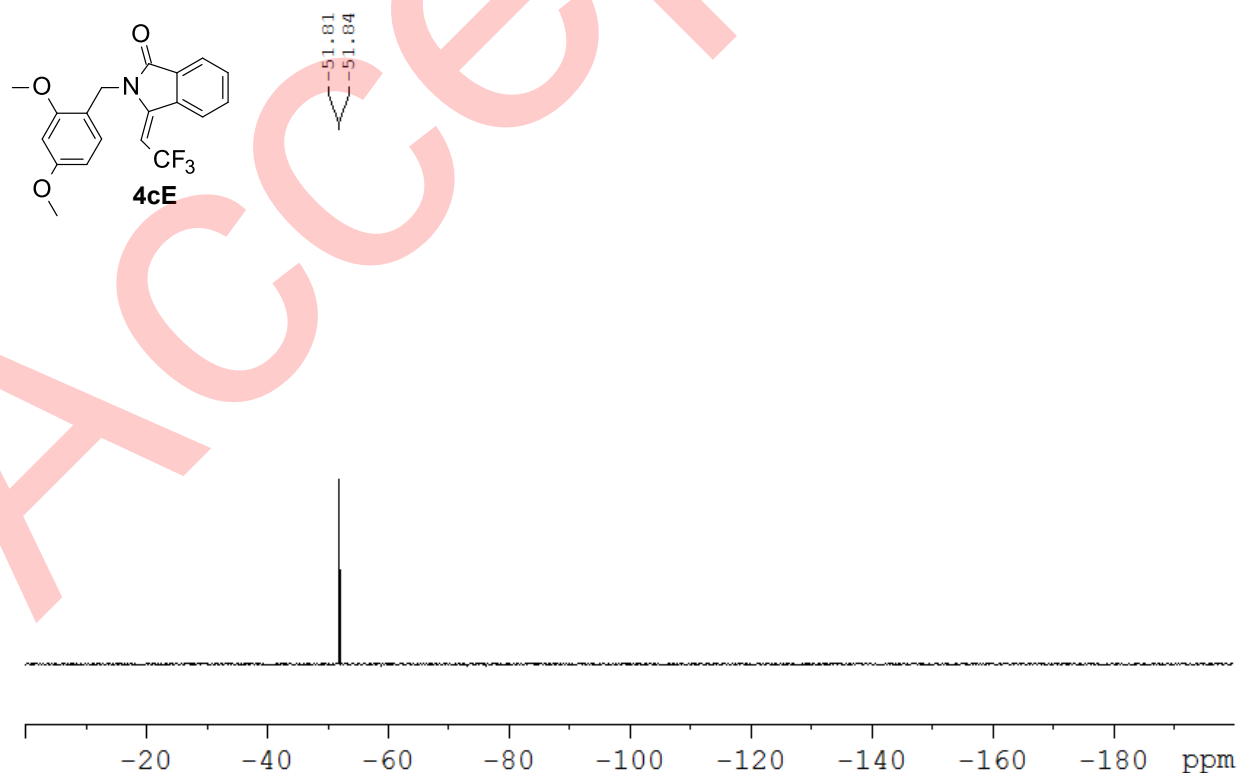
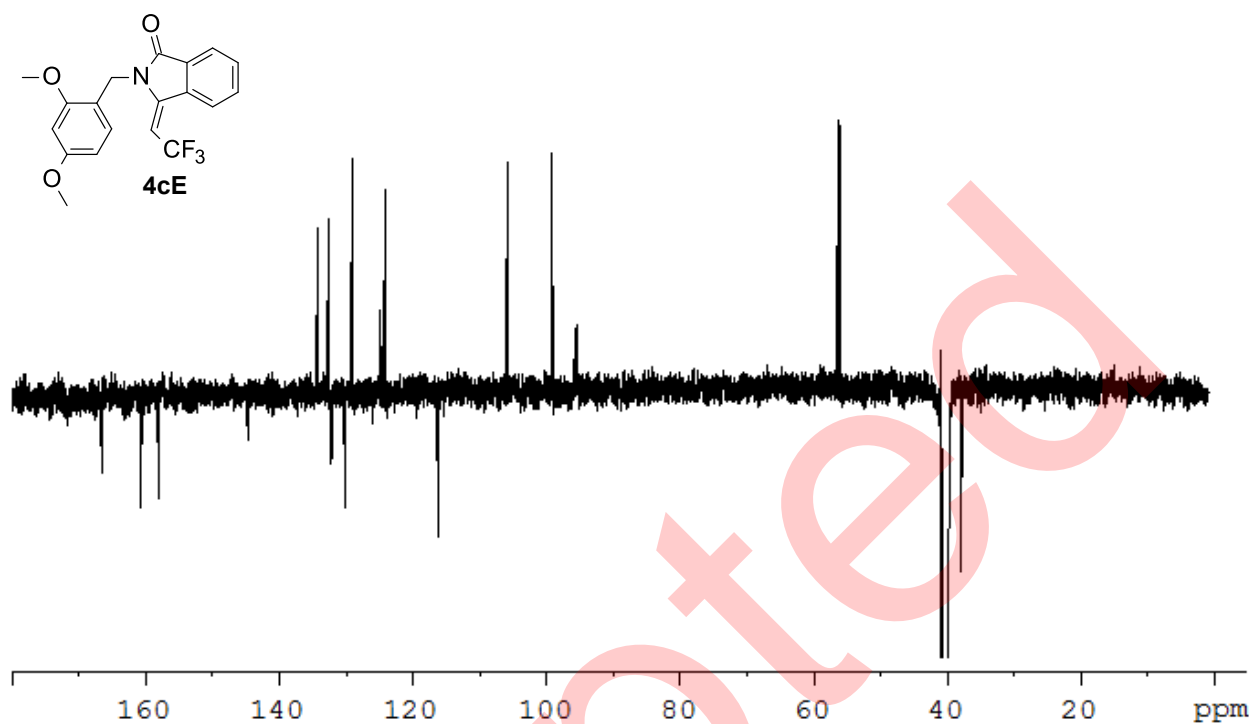


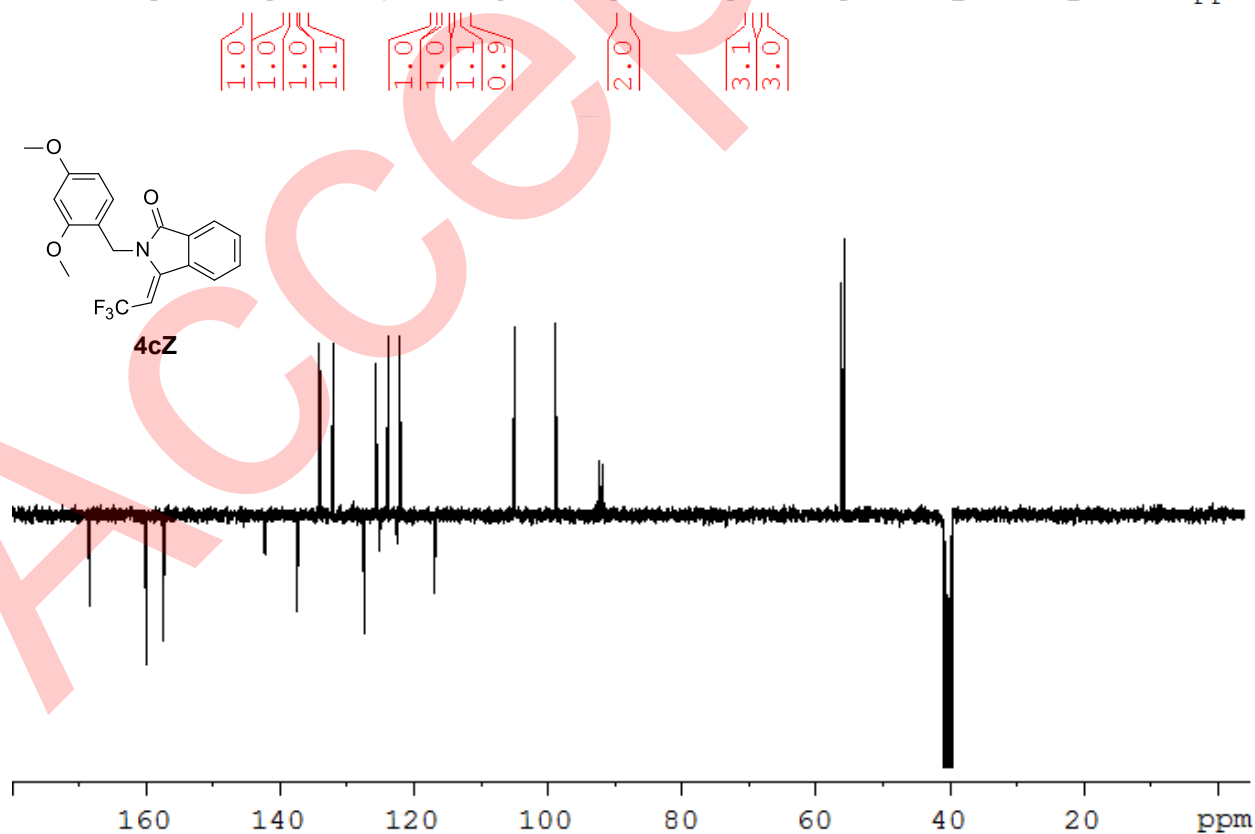
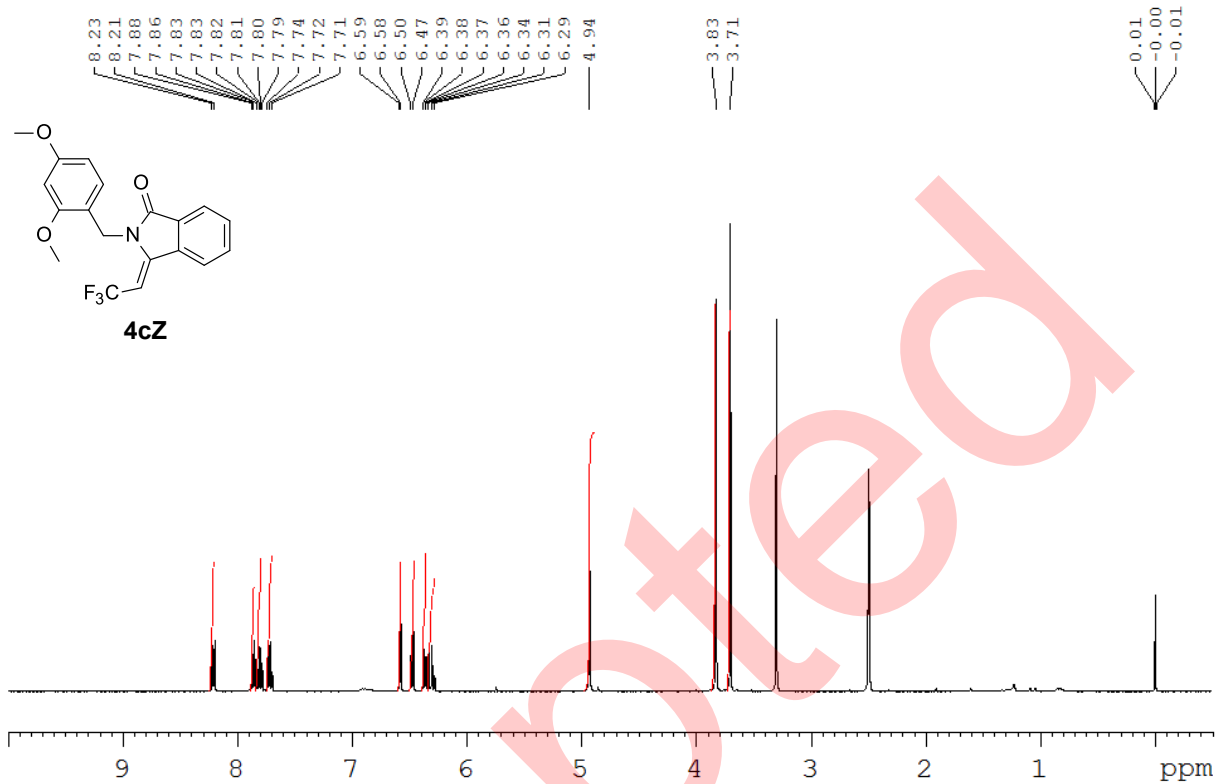


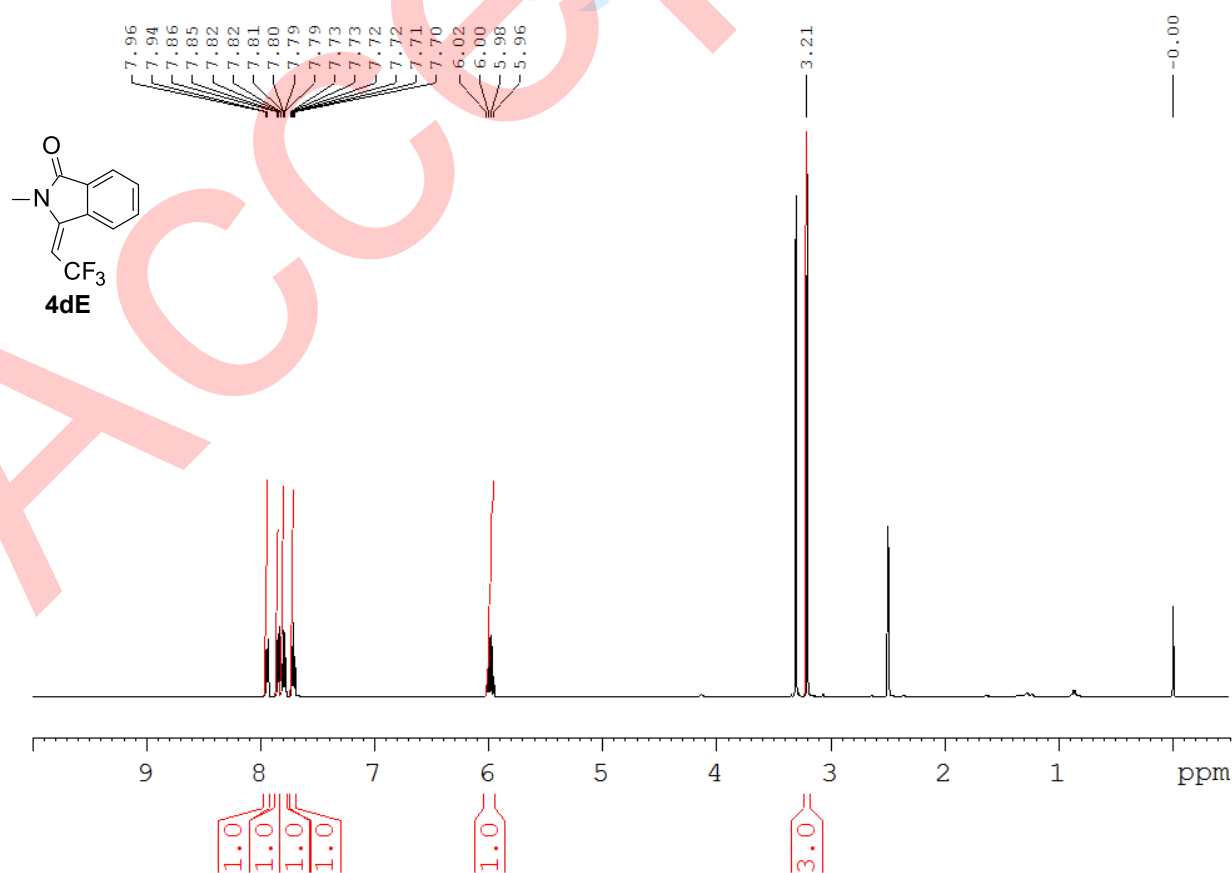
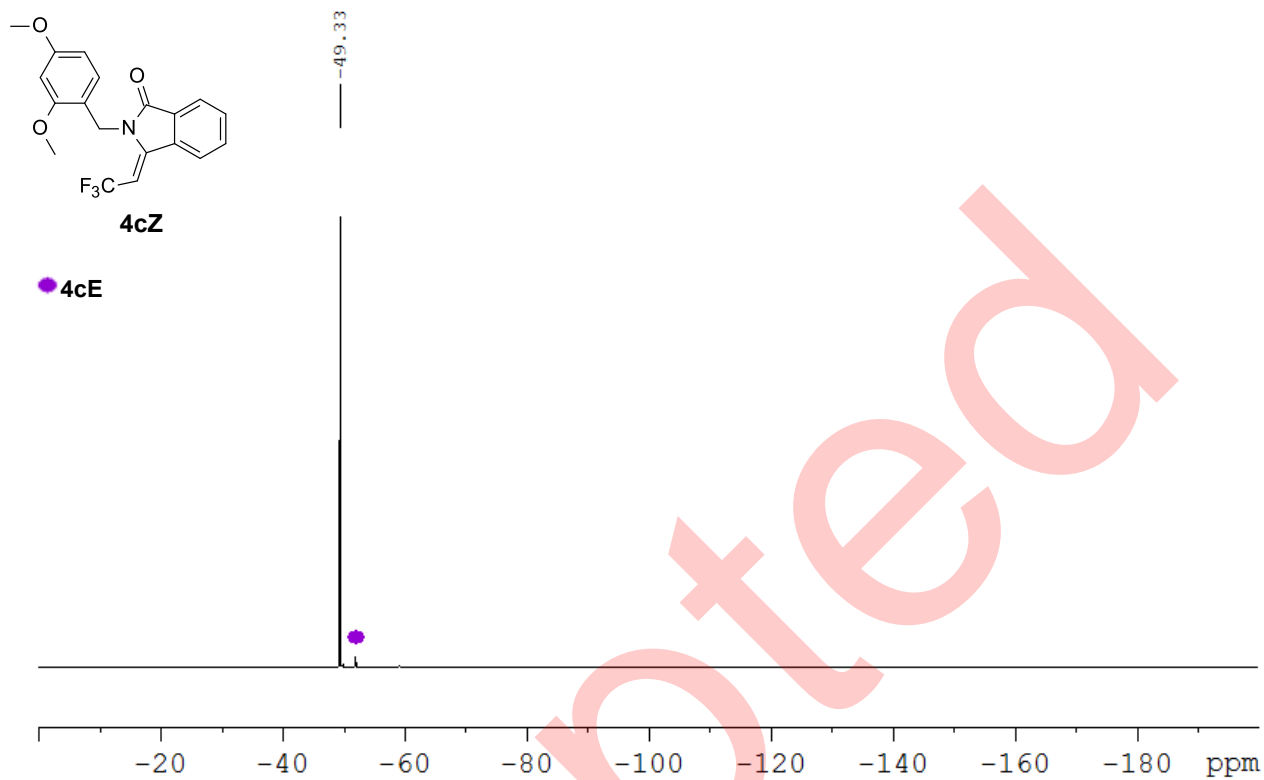


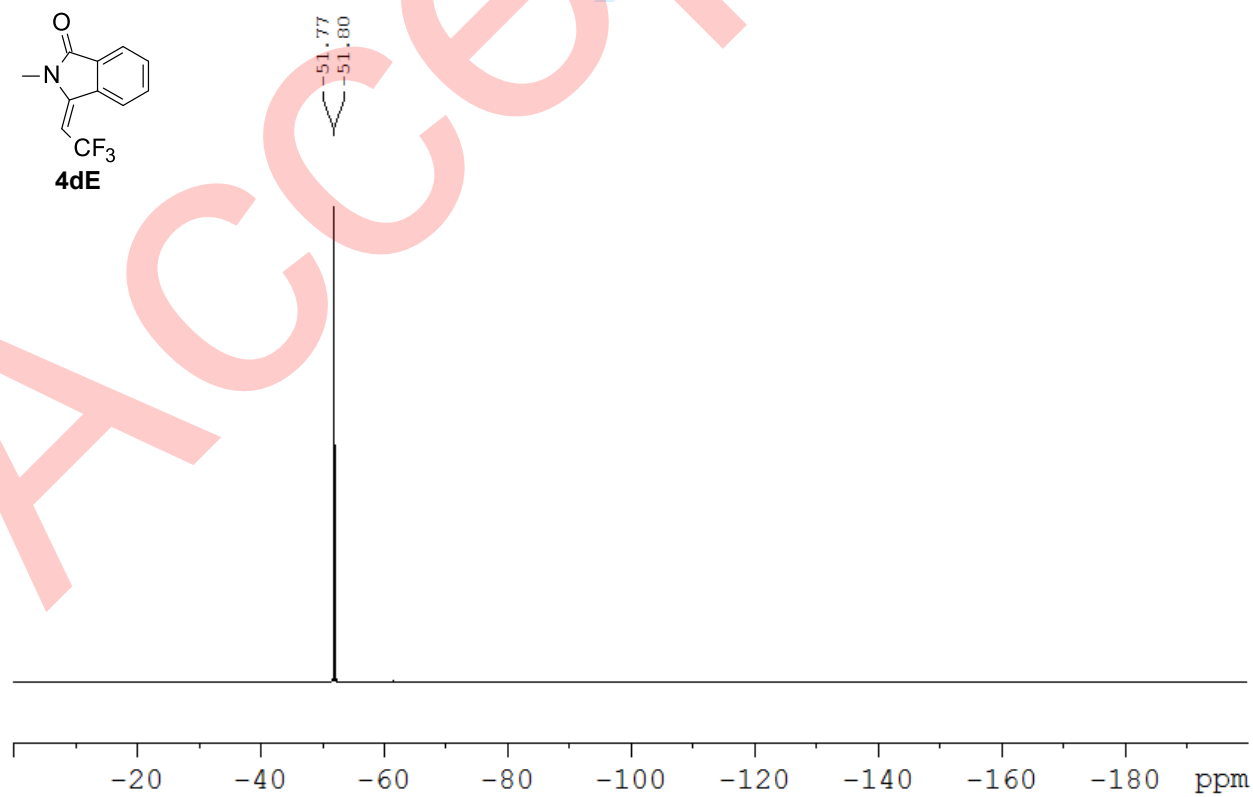
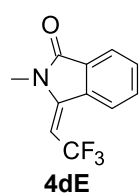
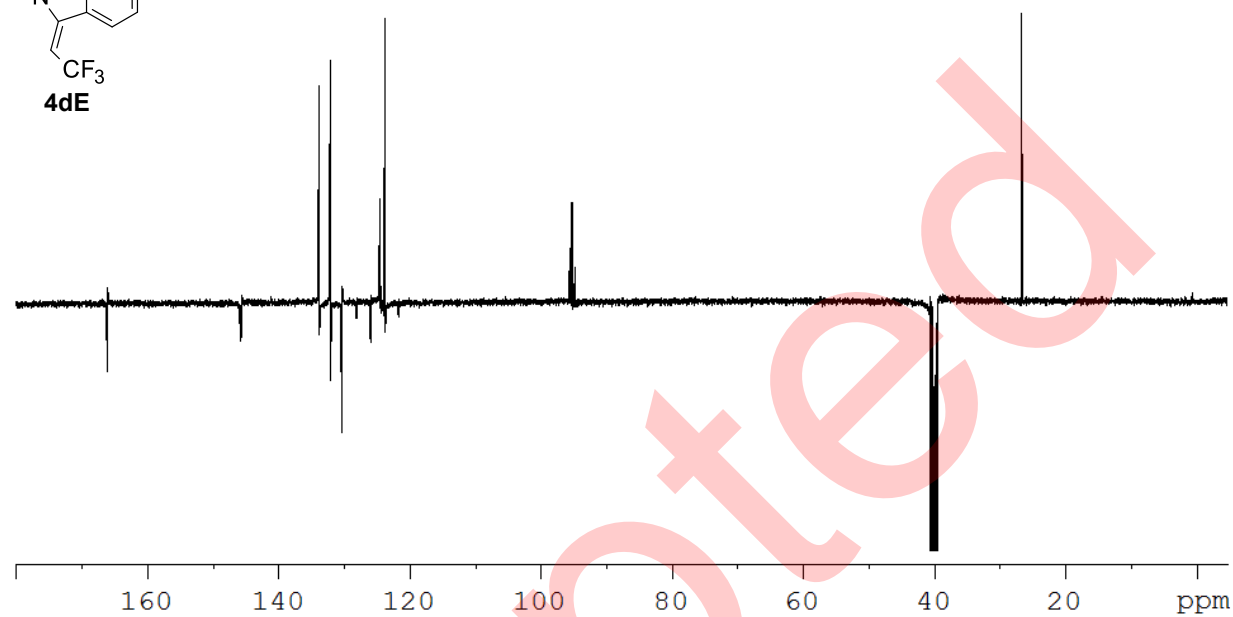
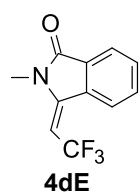


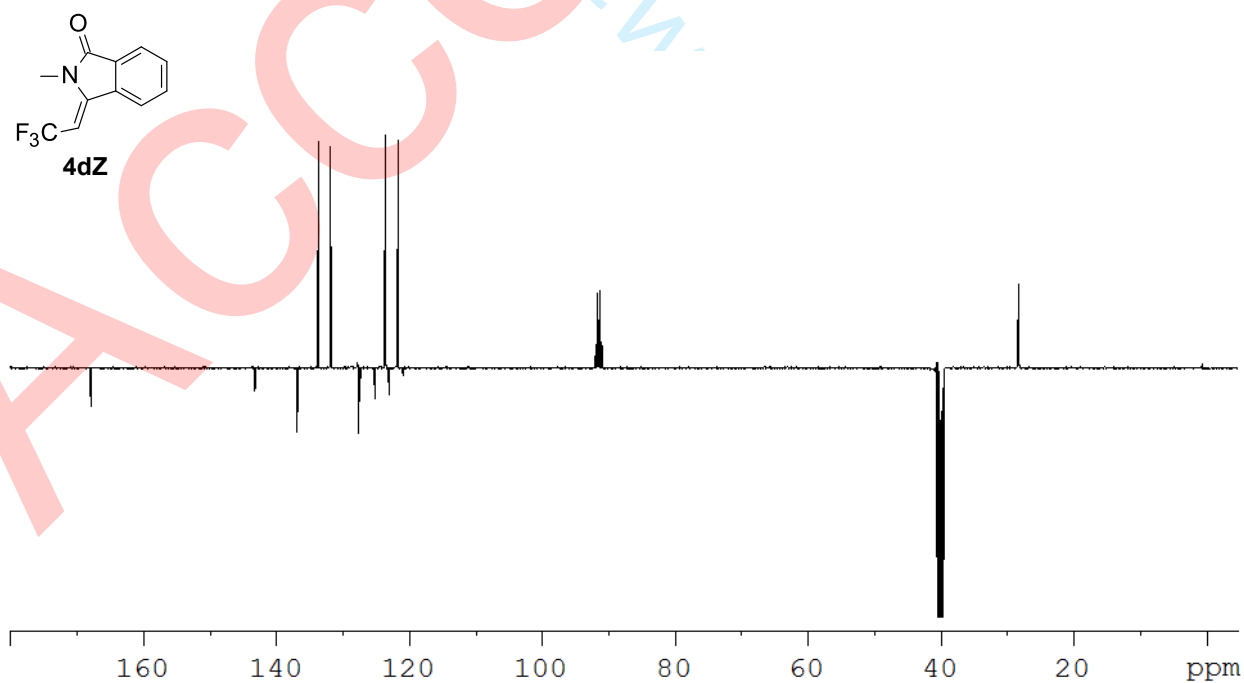
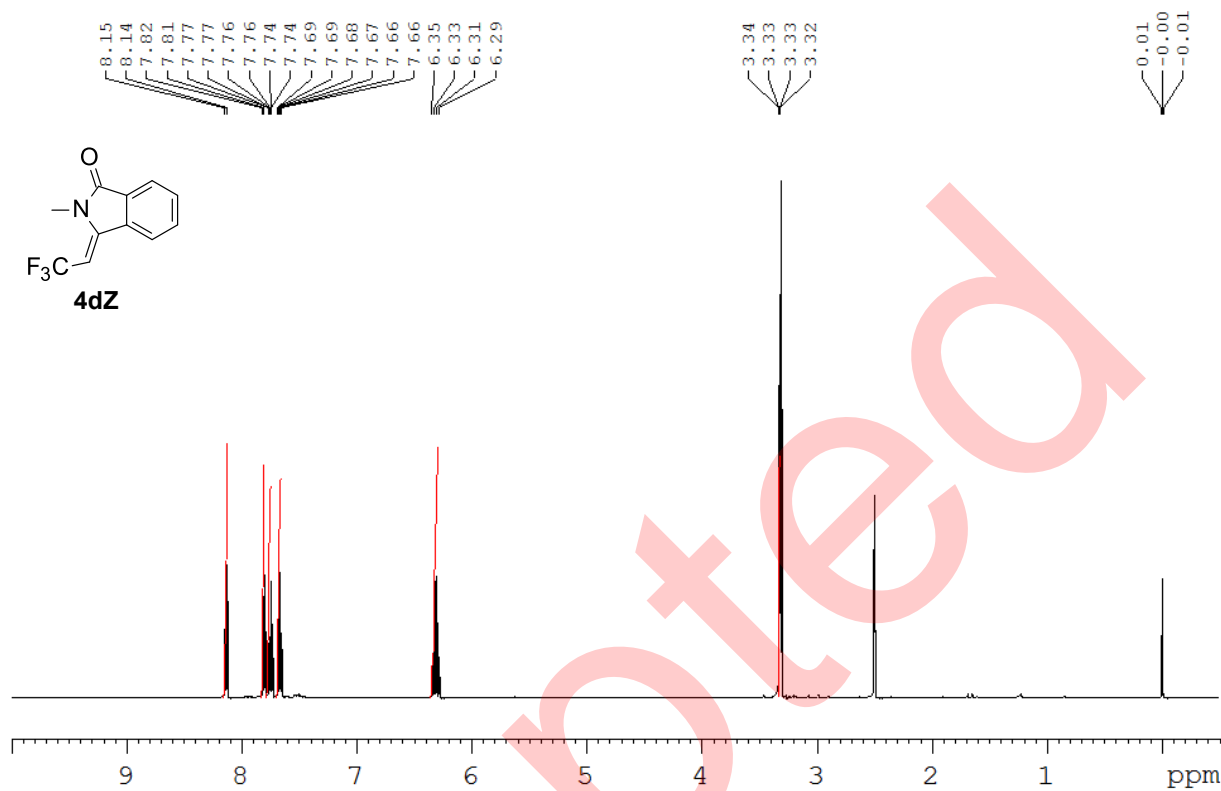


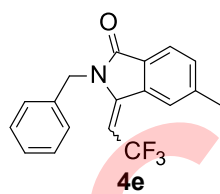
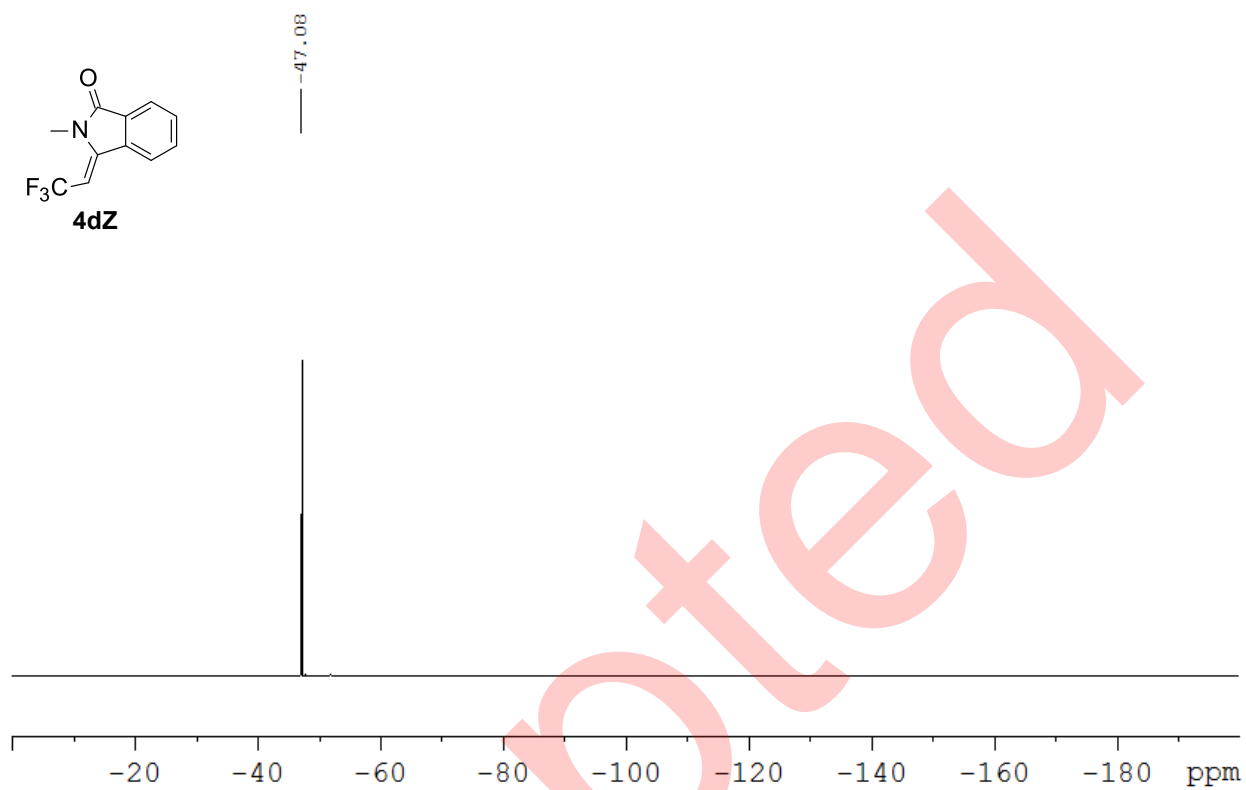
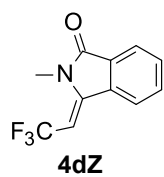




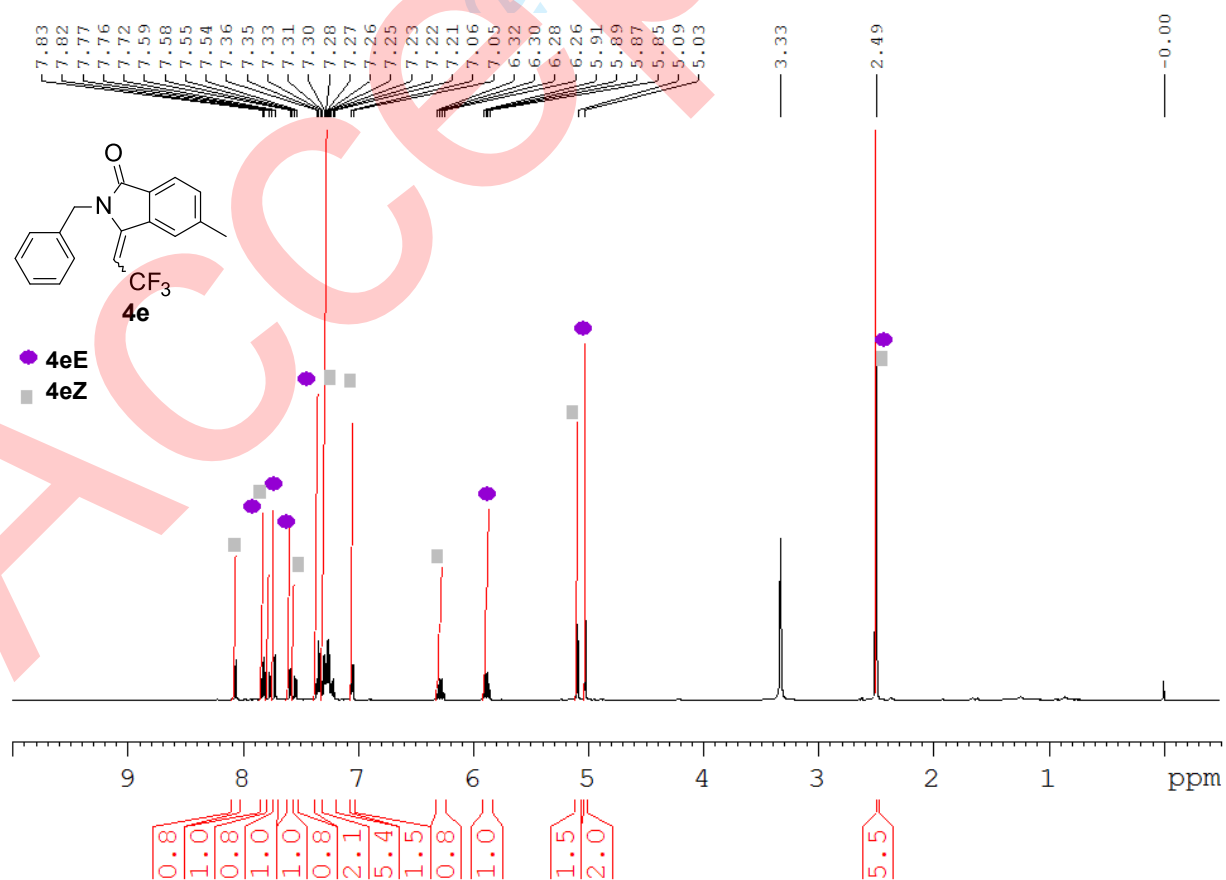


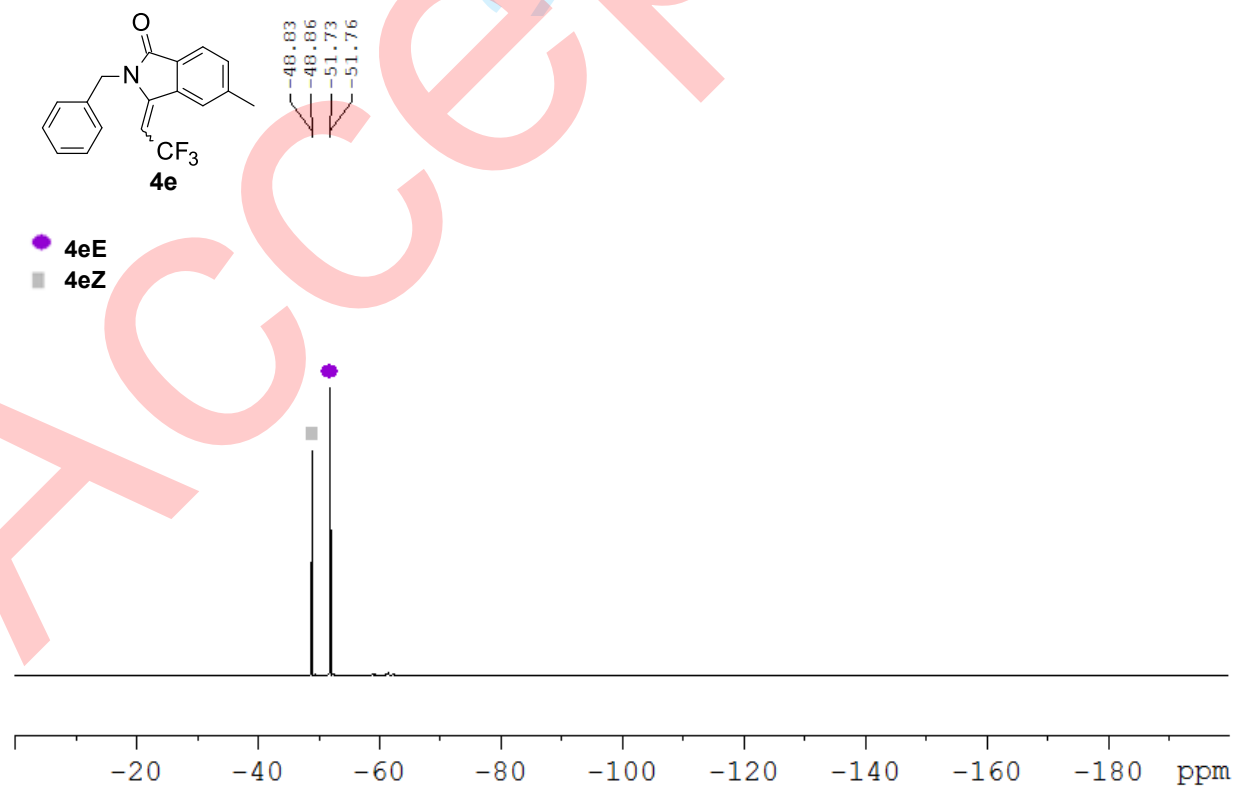
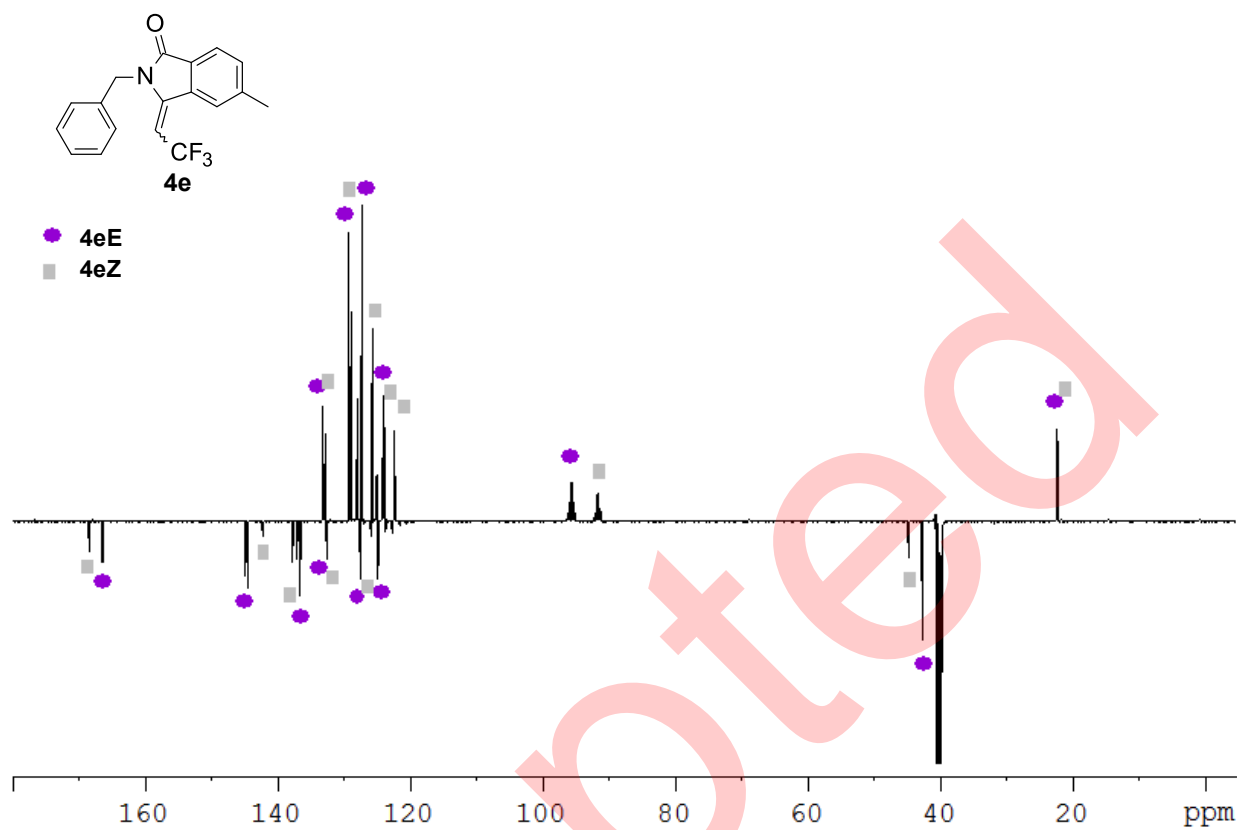


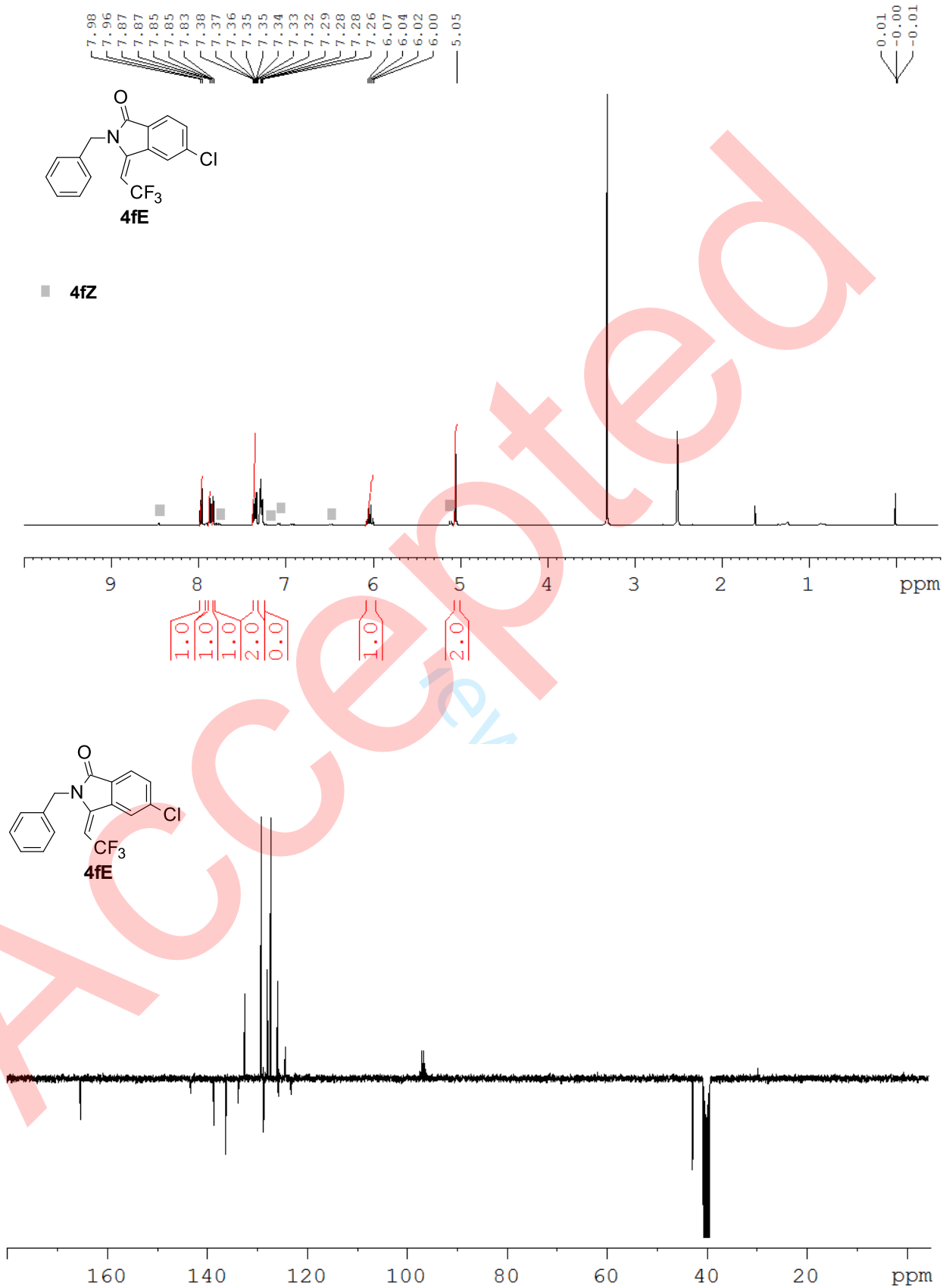




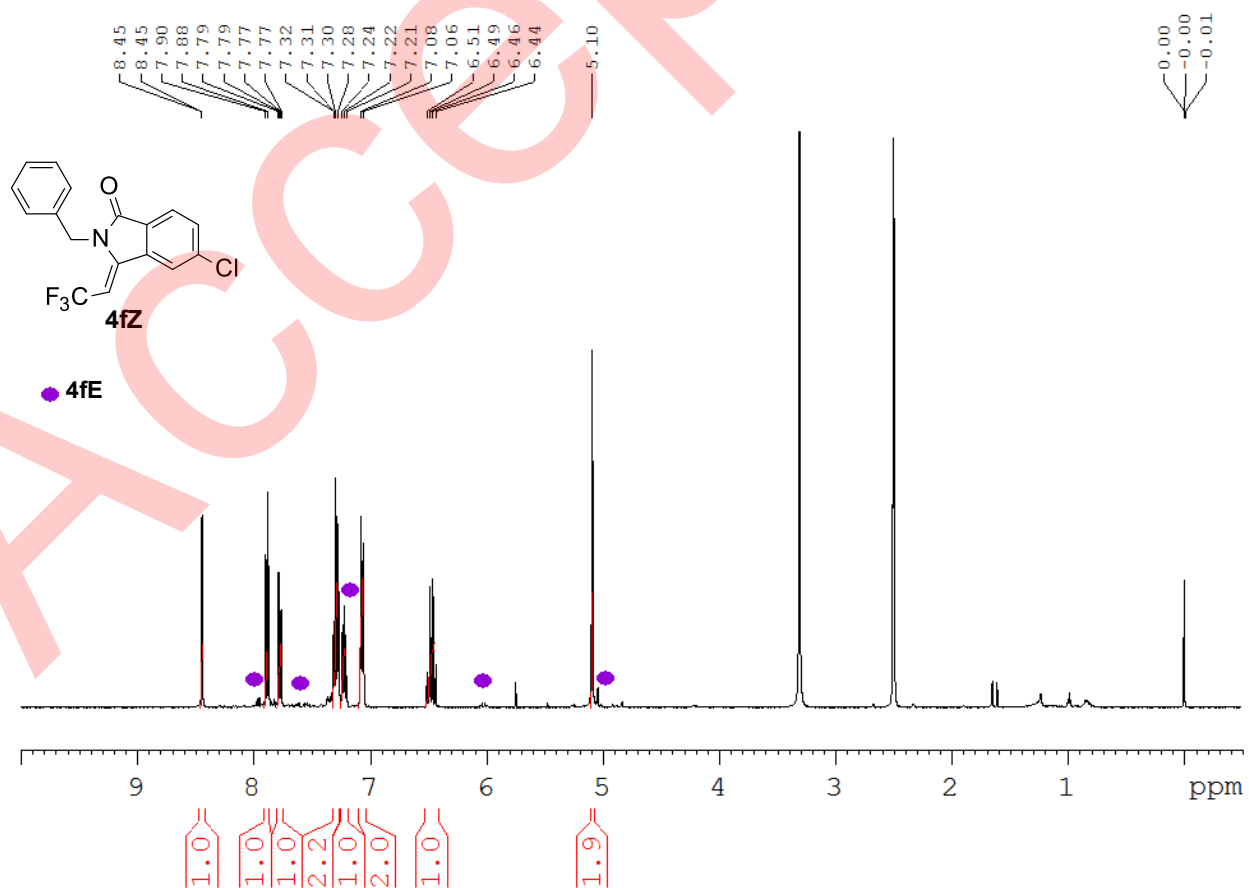
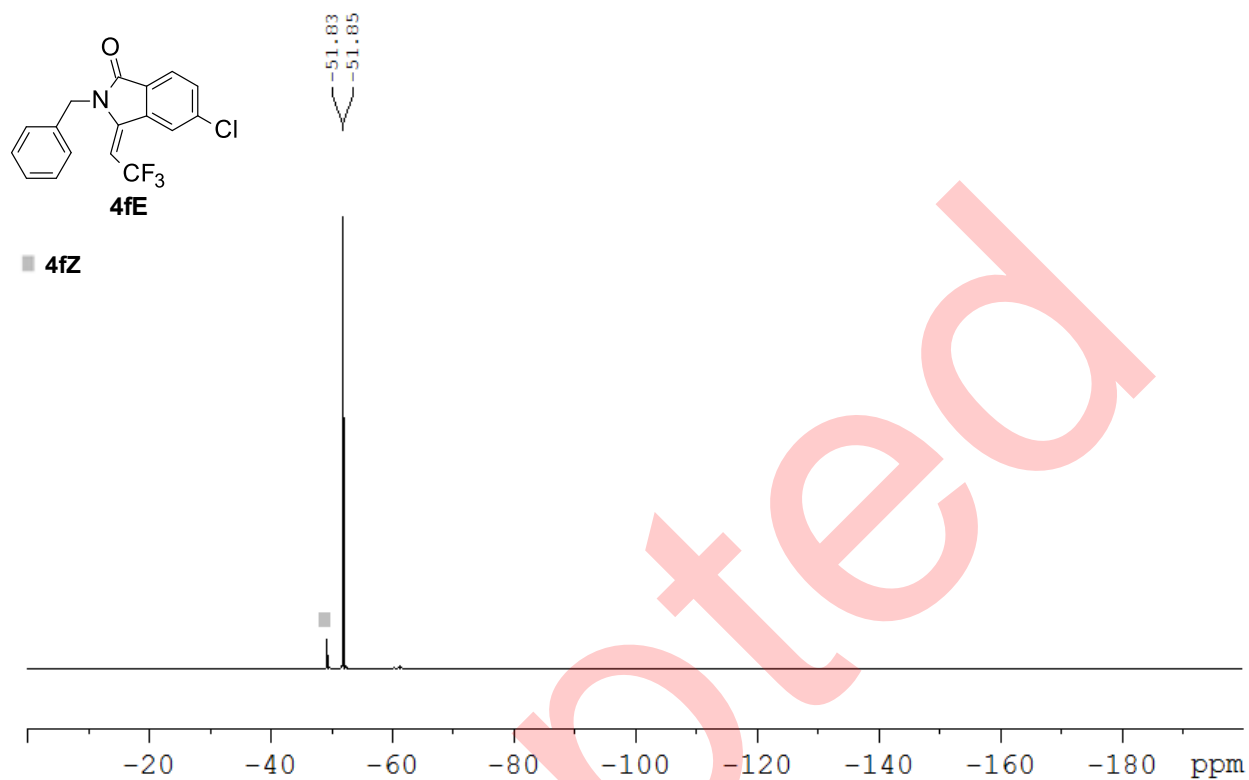
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■ **4eZ**

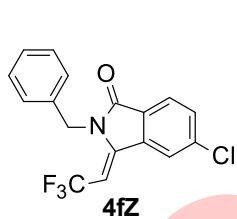
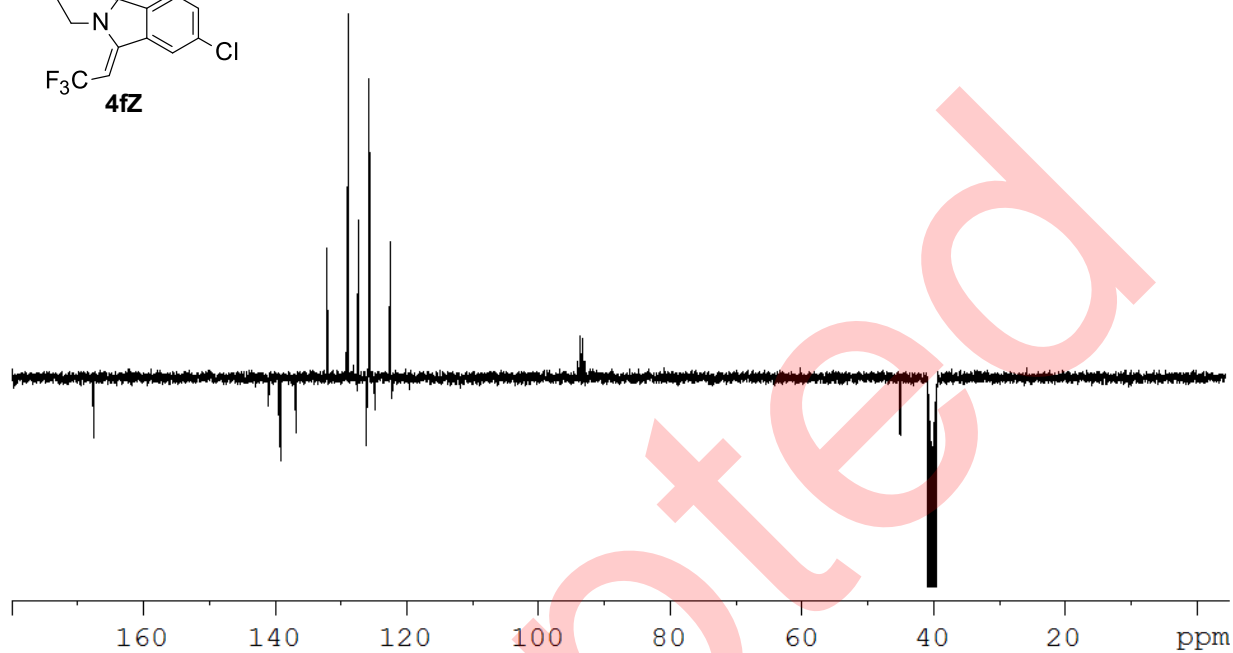
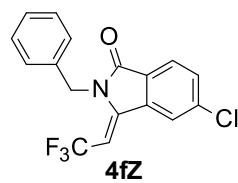




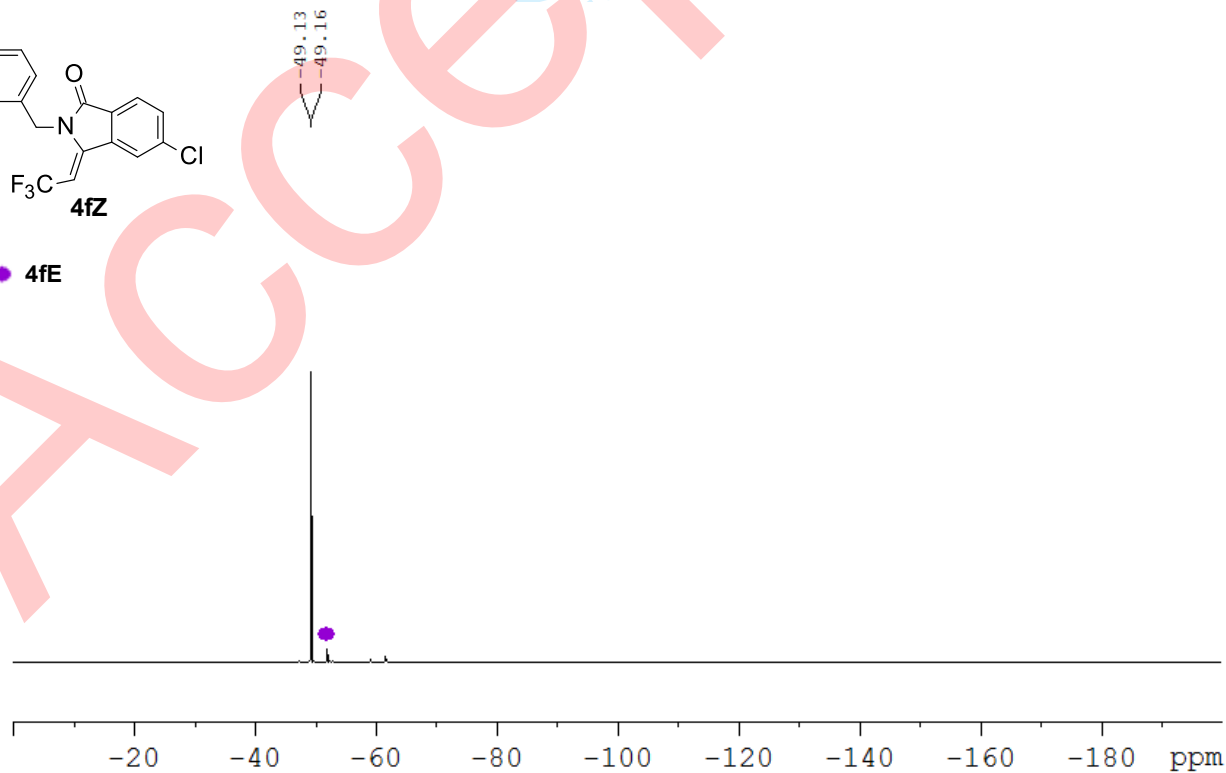


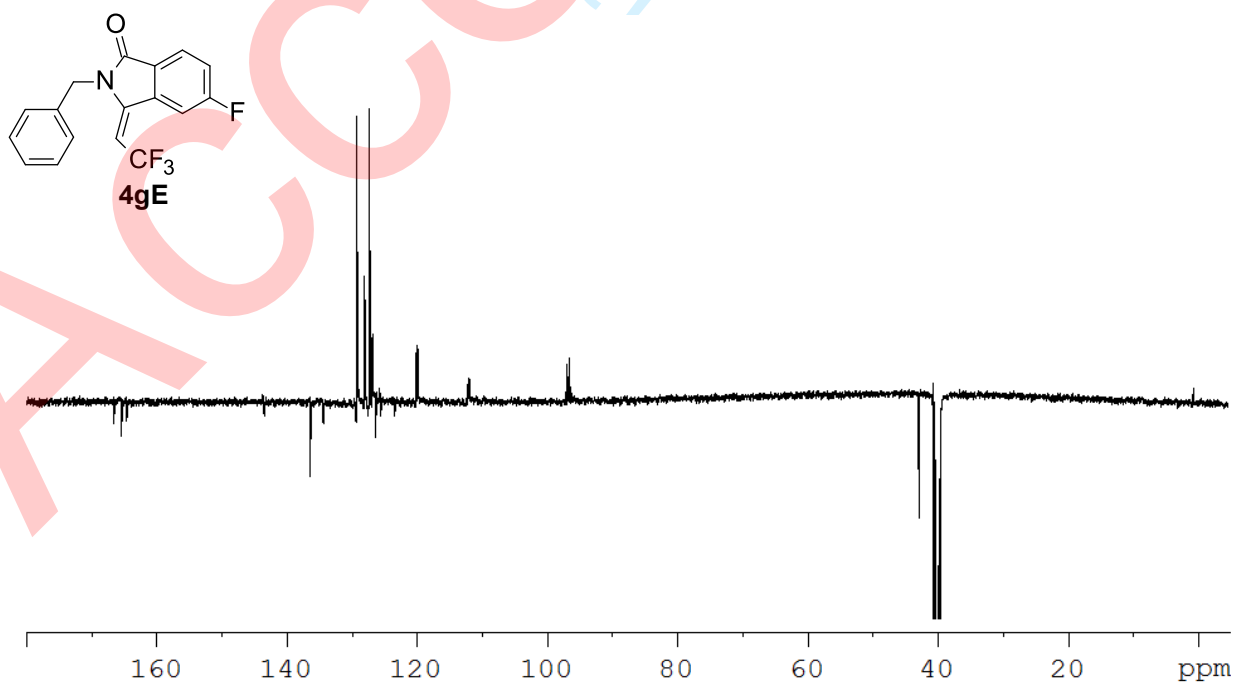
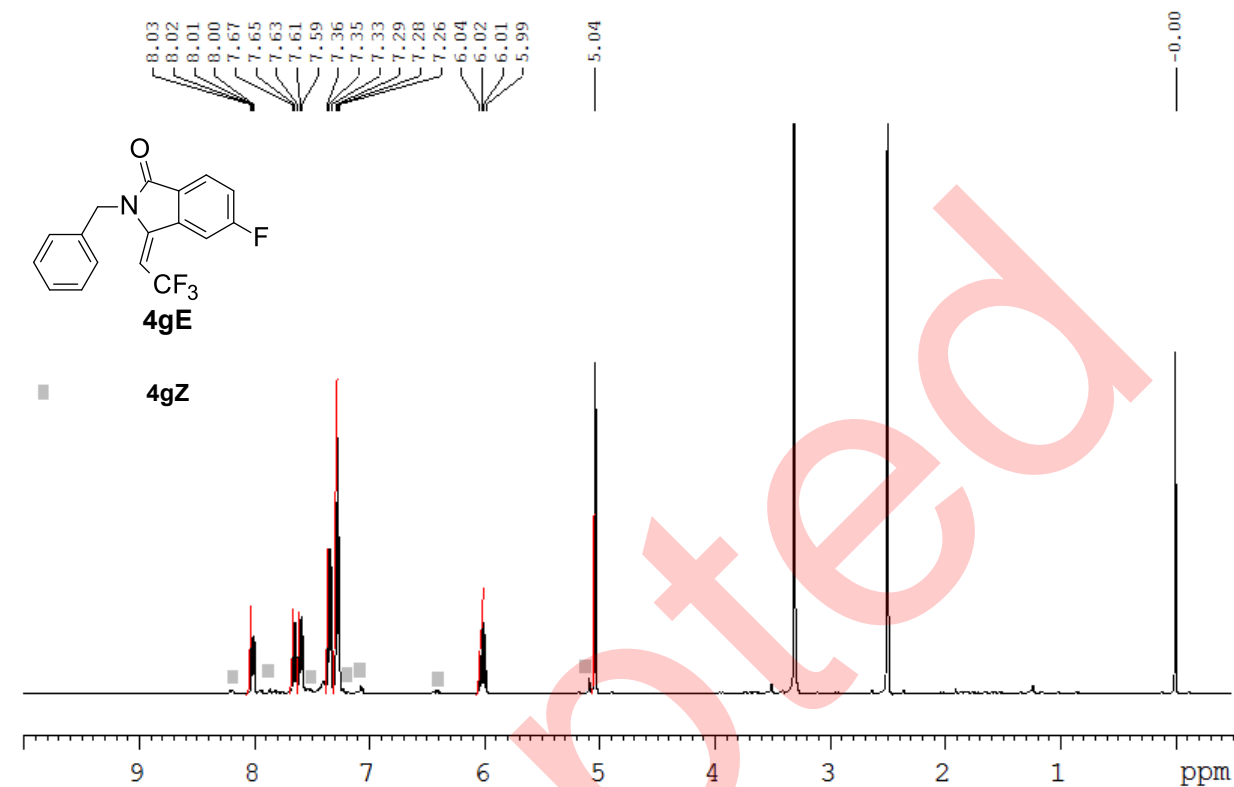


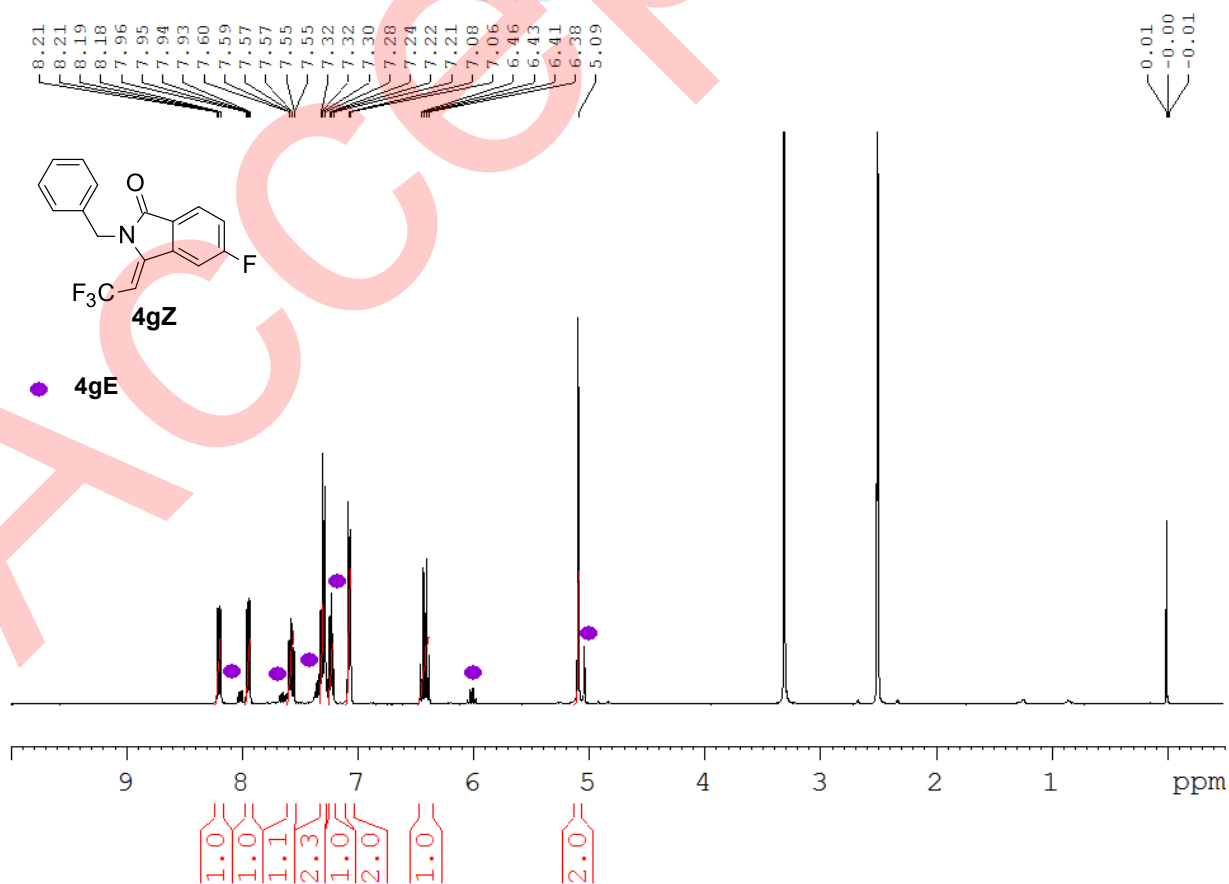
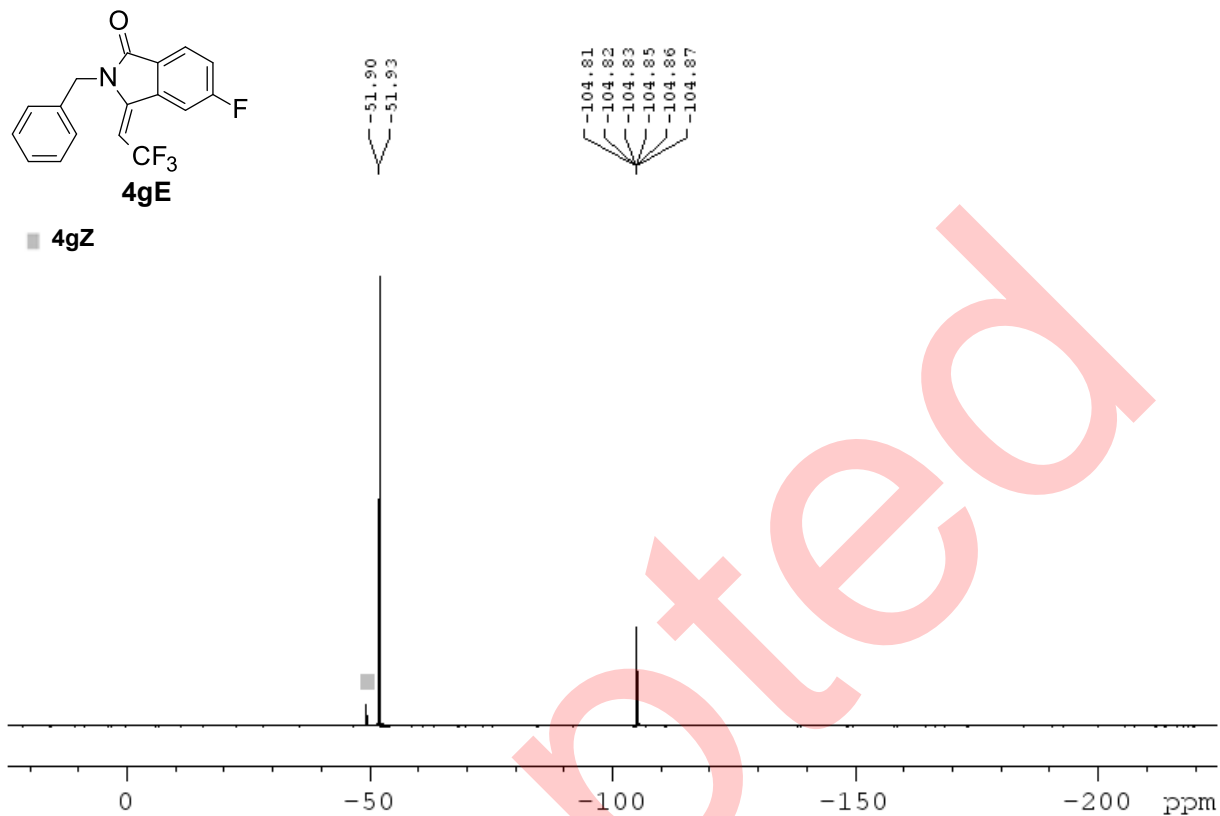


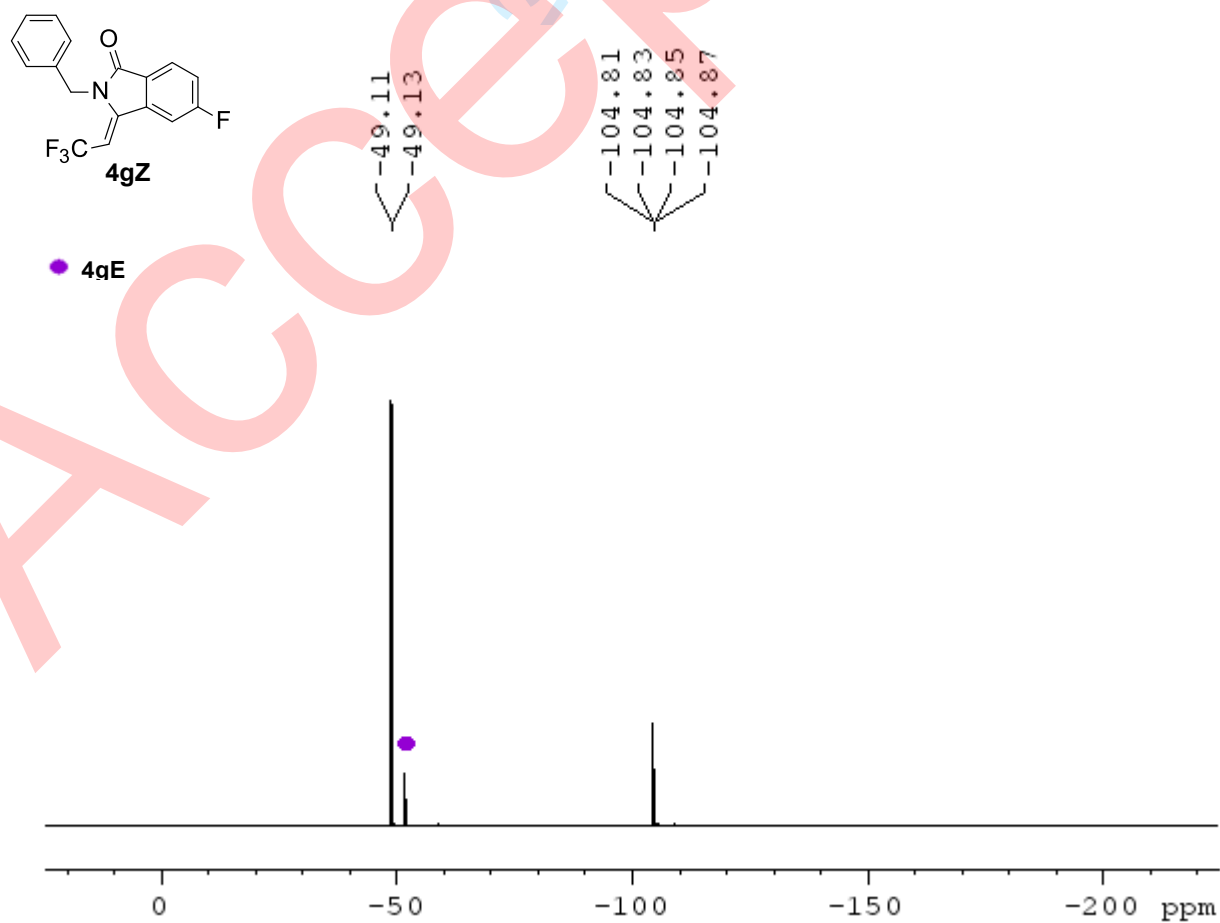
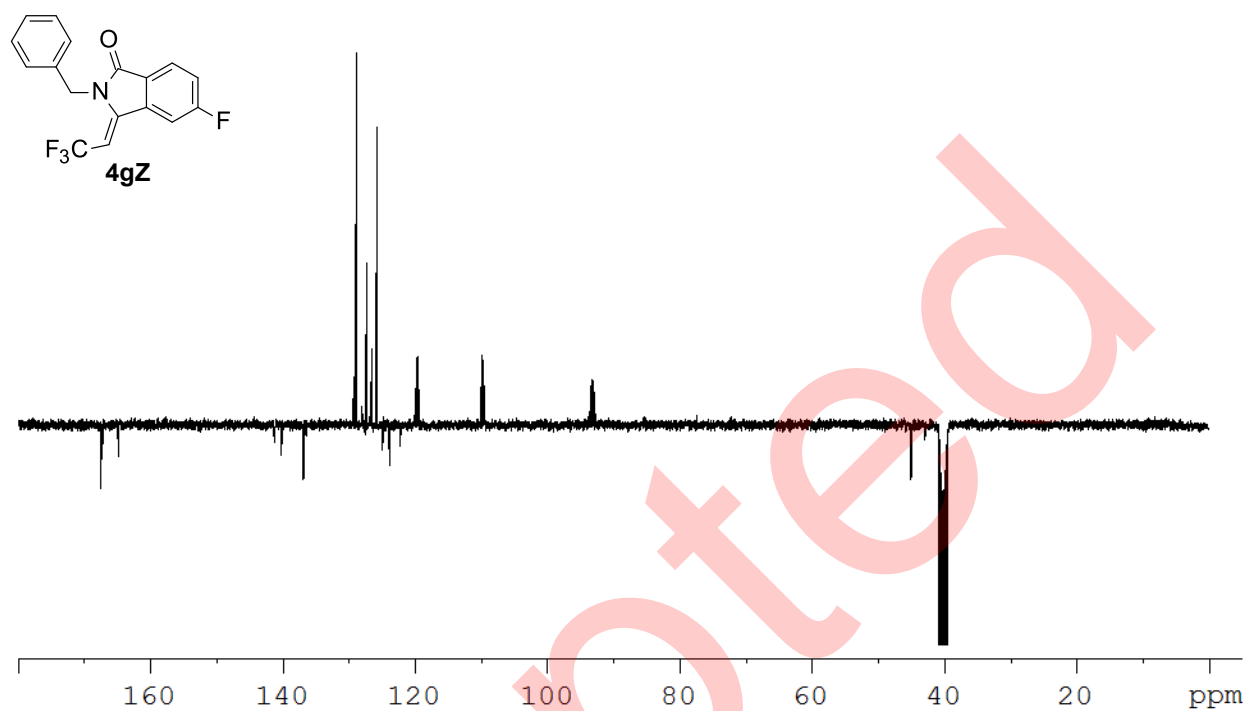


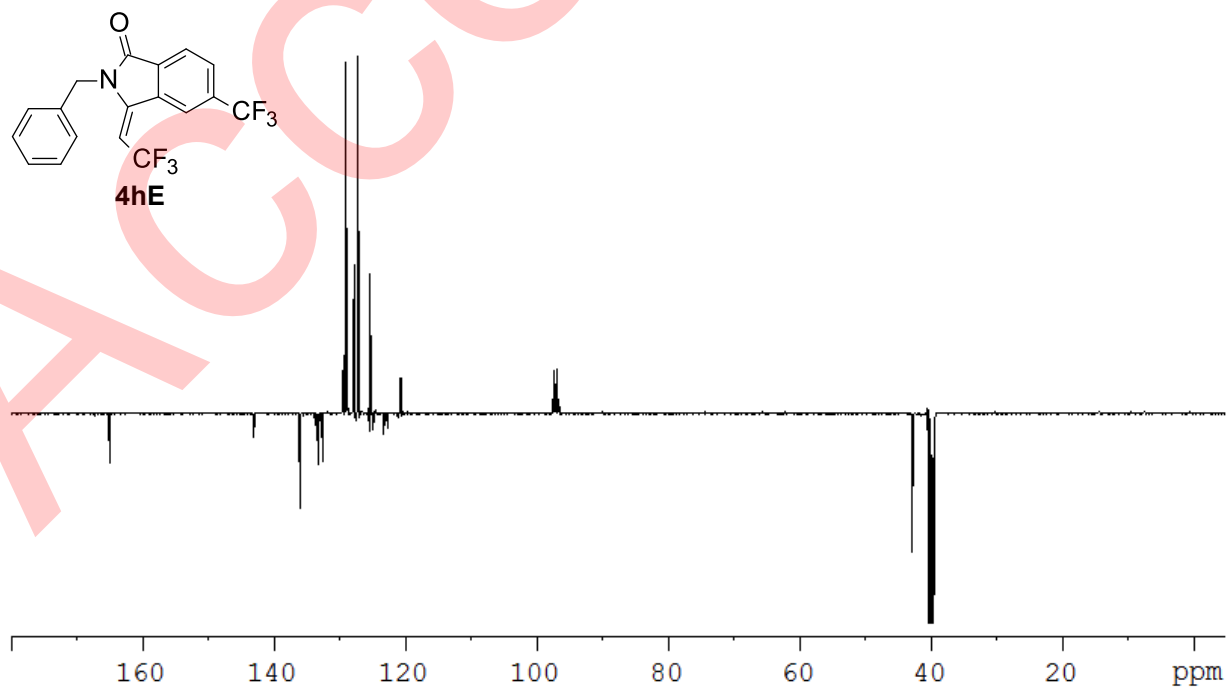
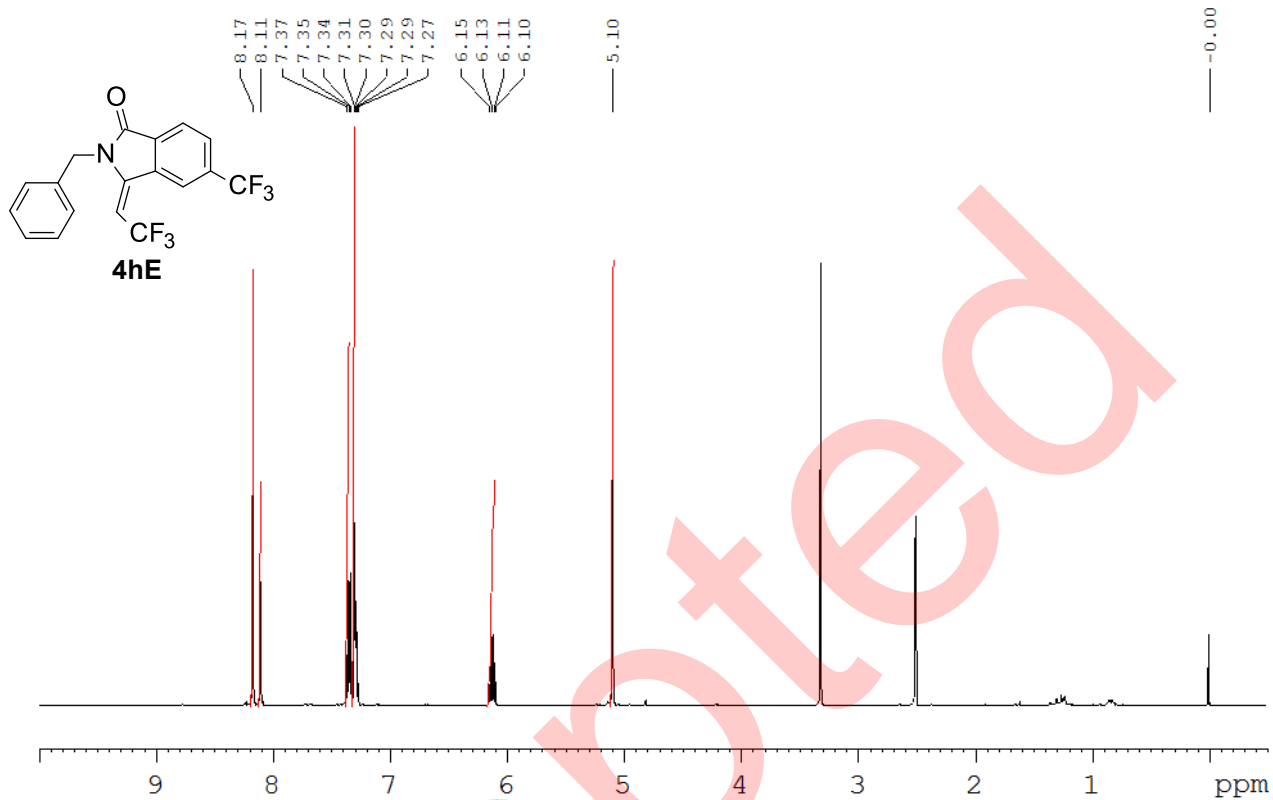
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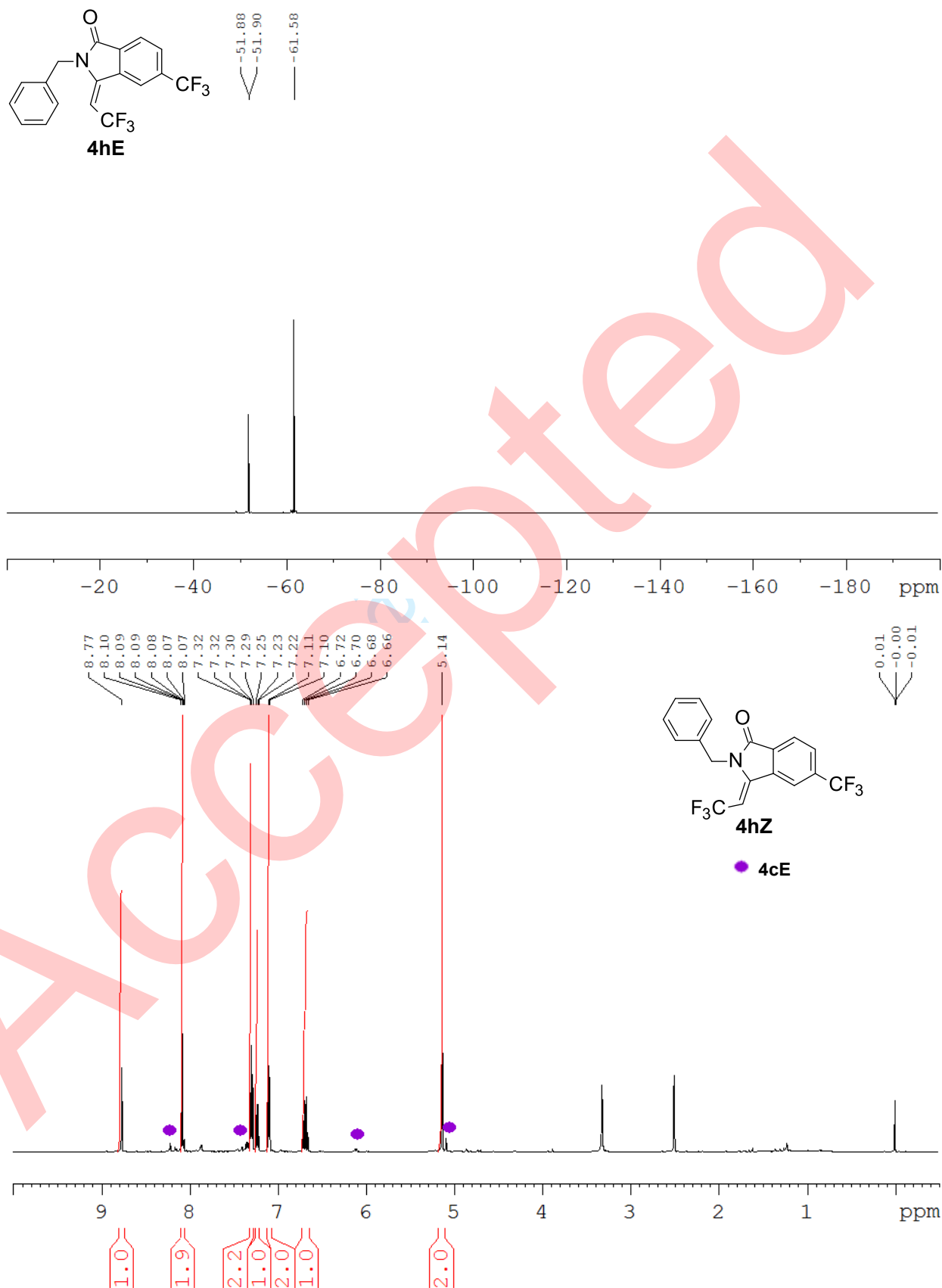


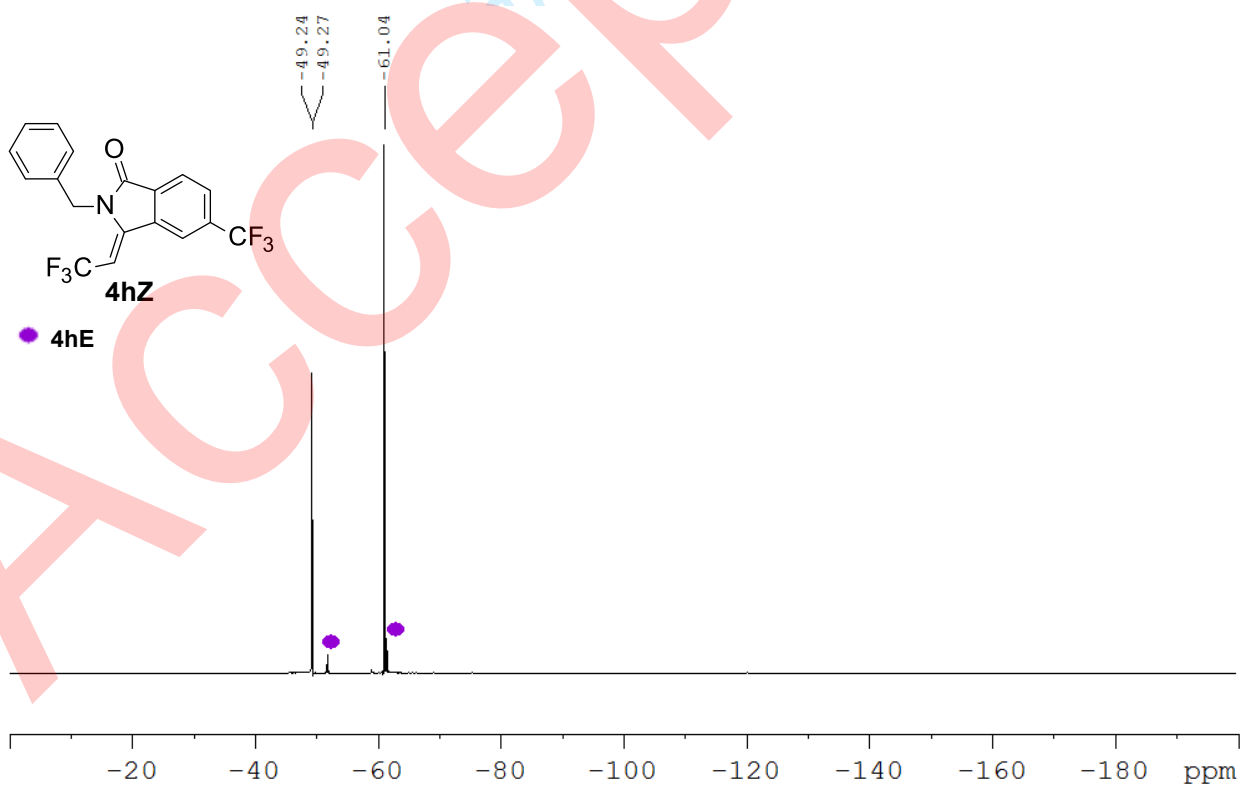
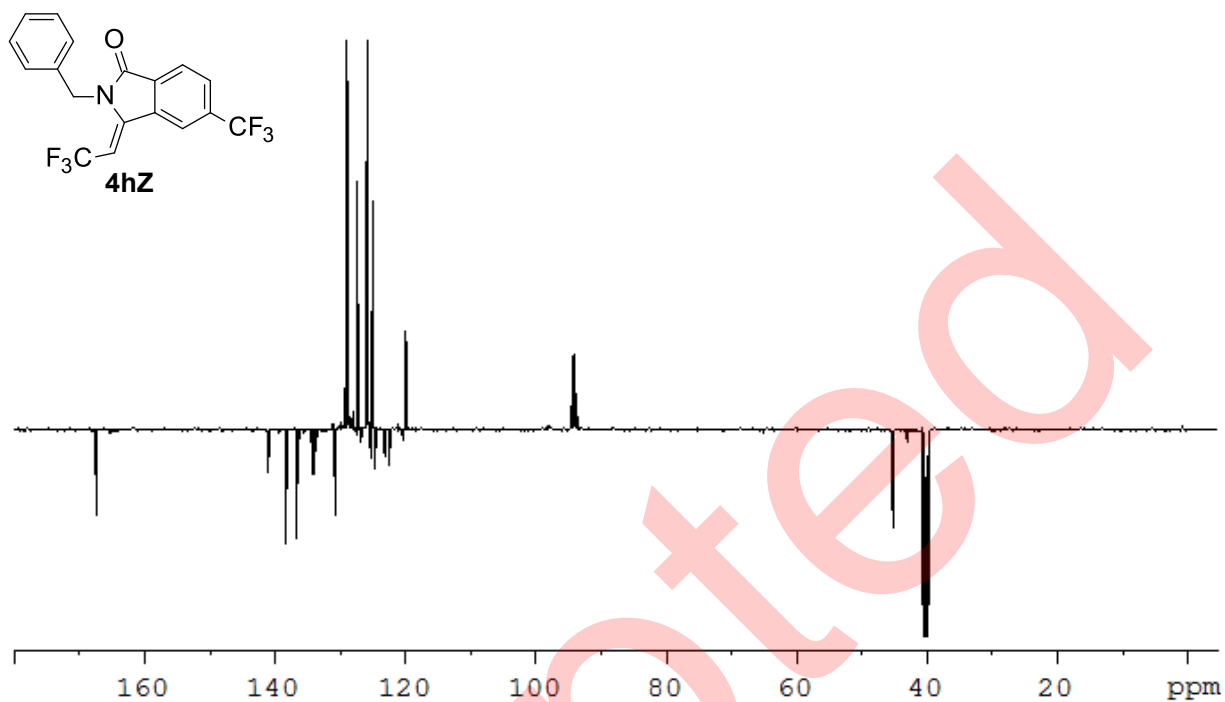




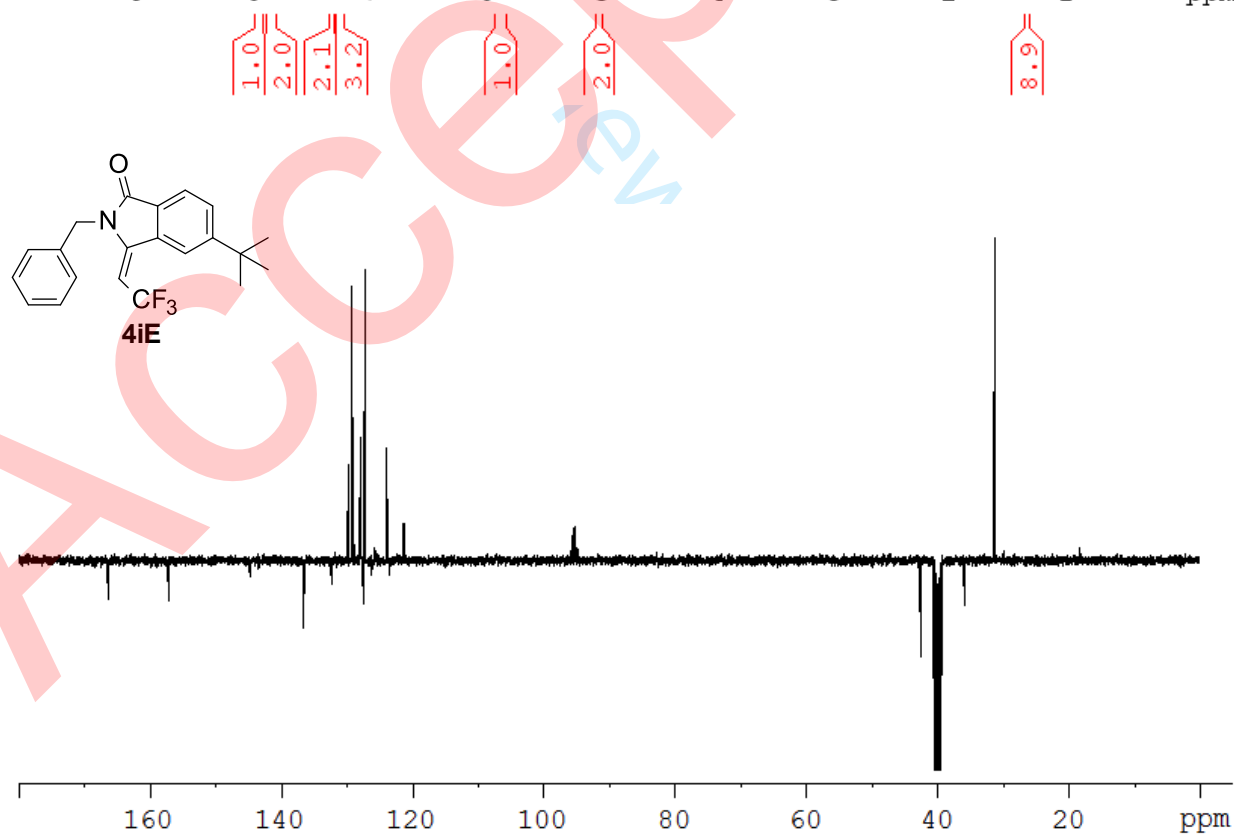
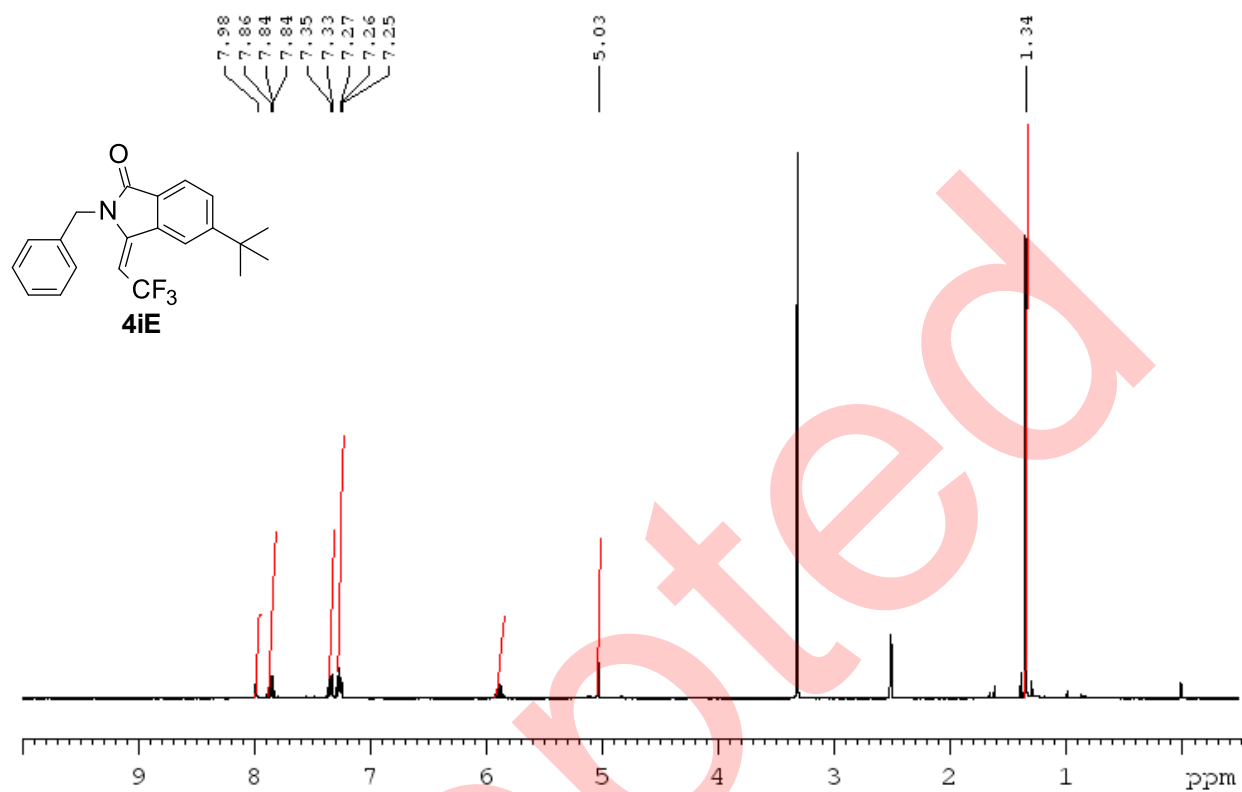


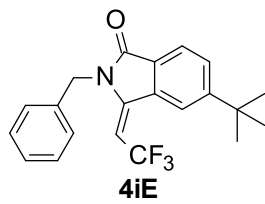








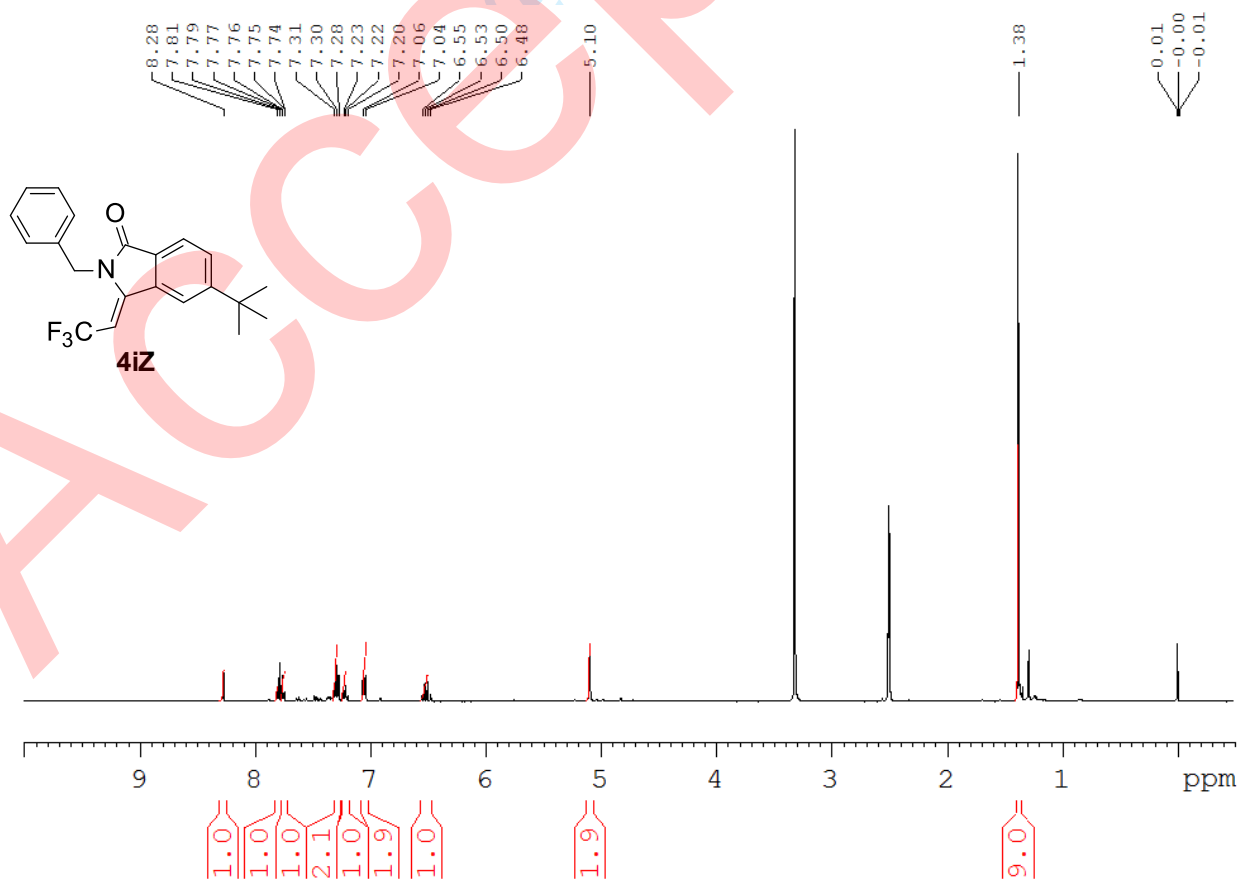
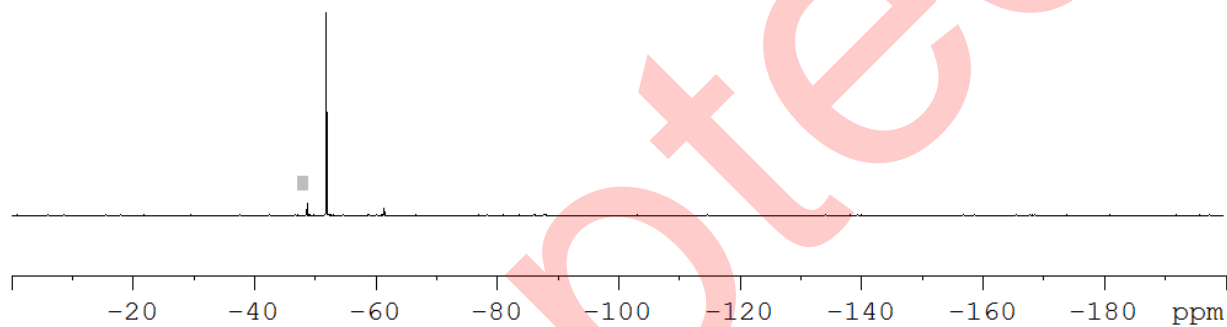


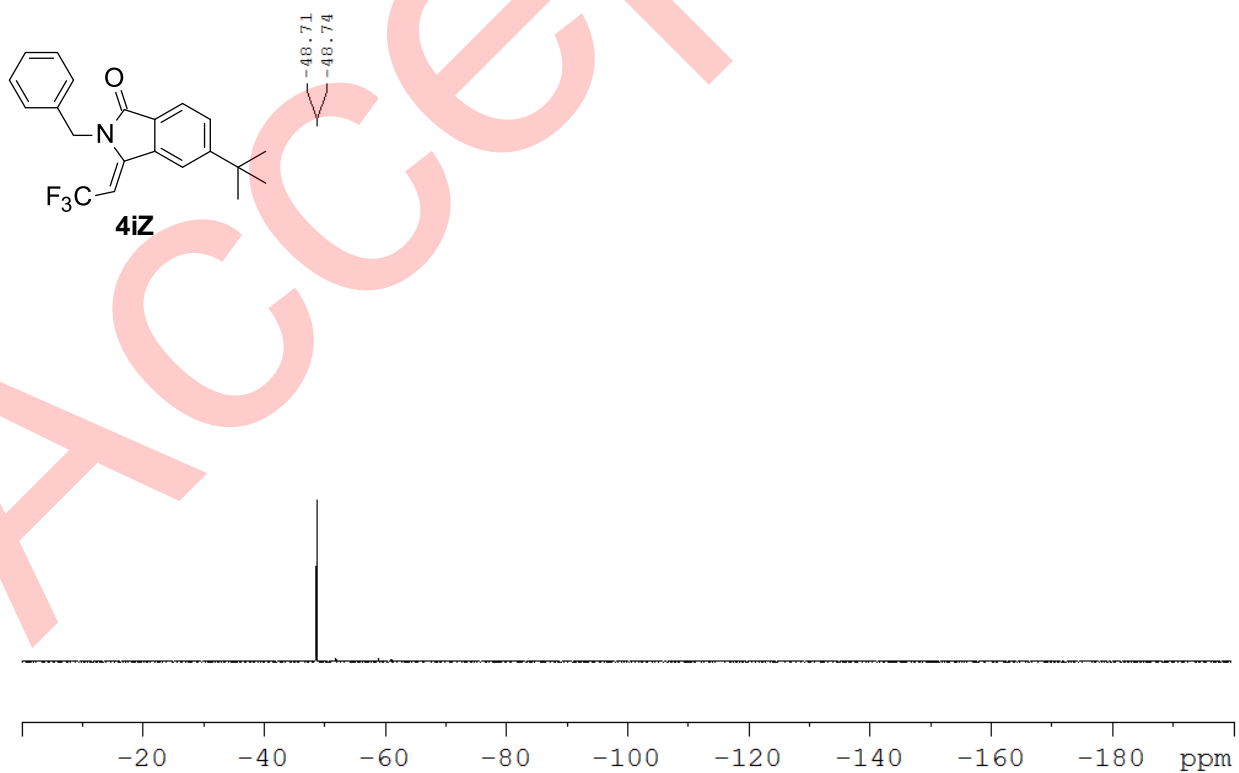
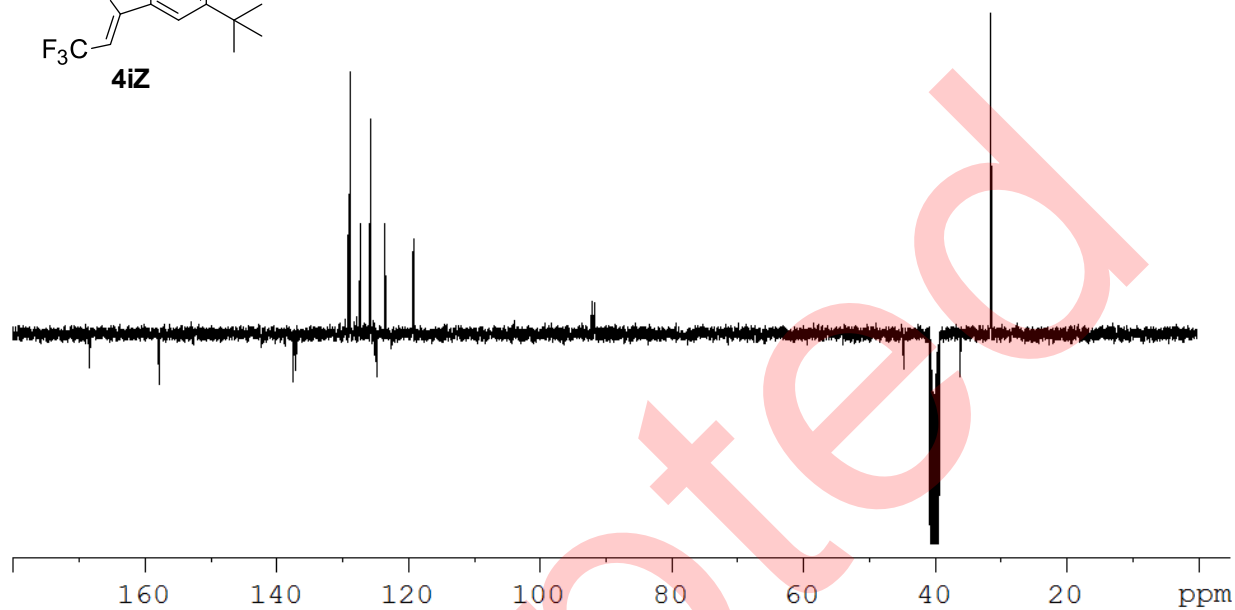
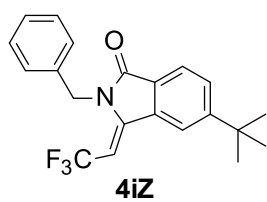


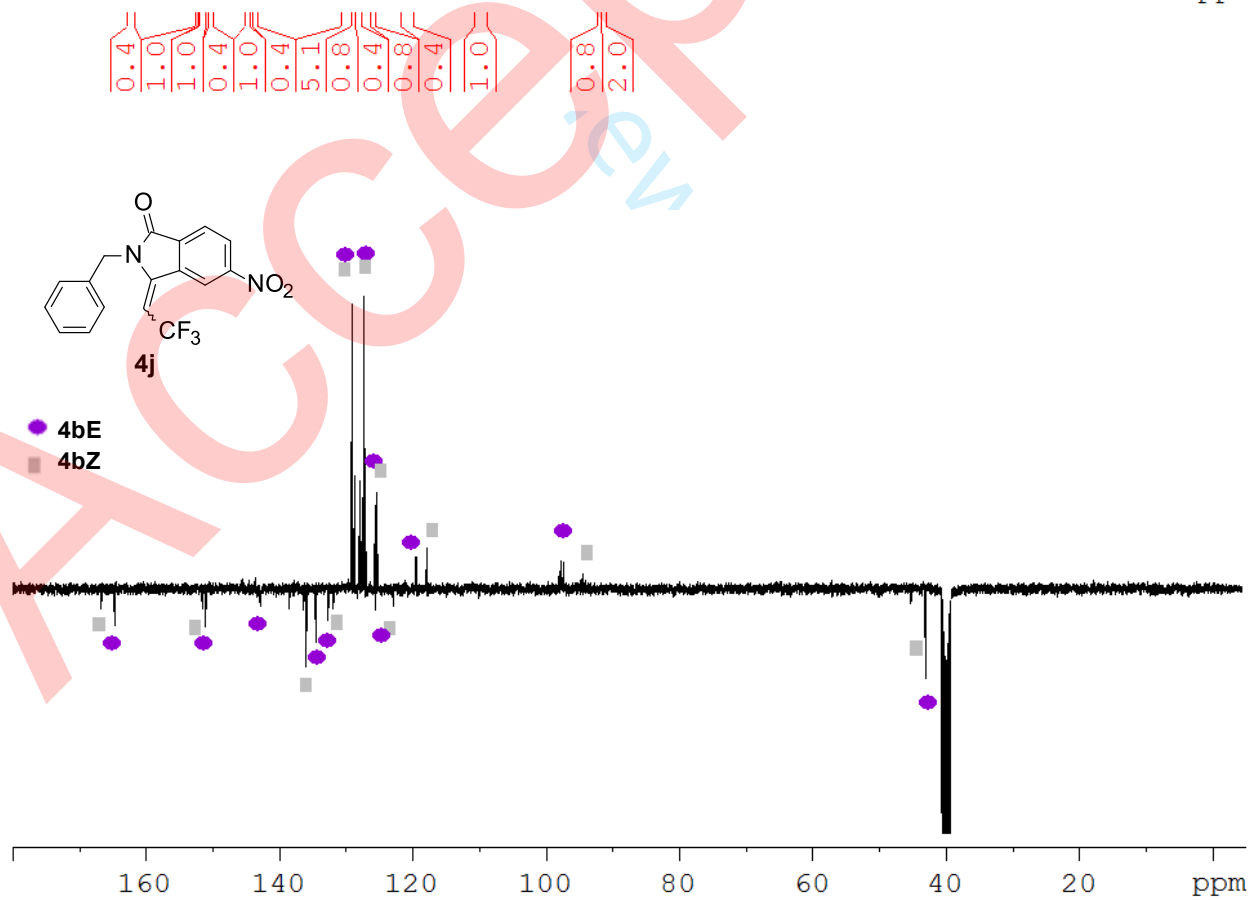
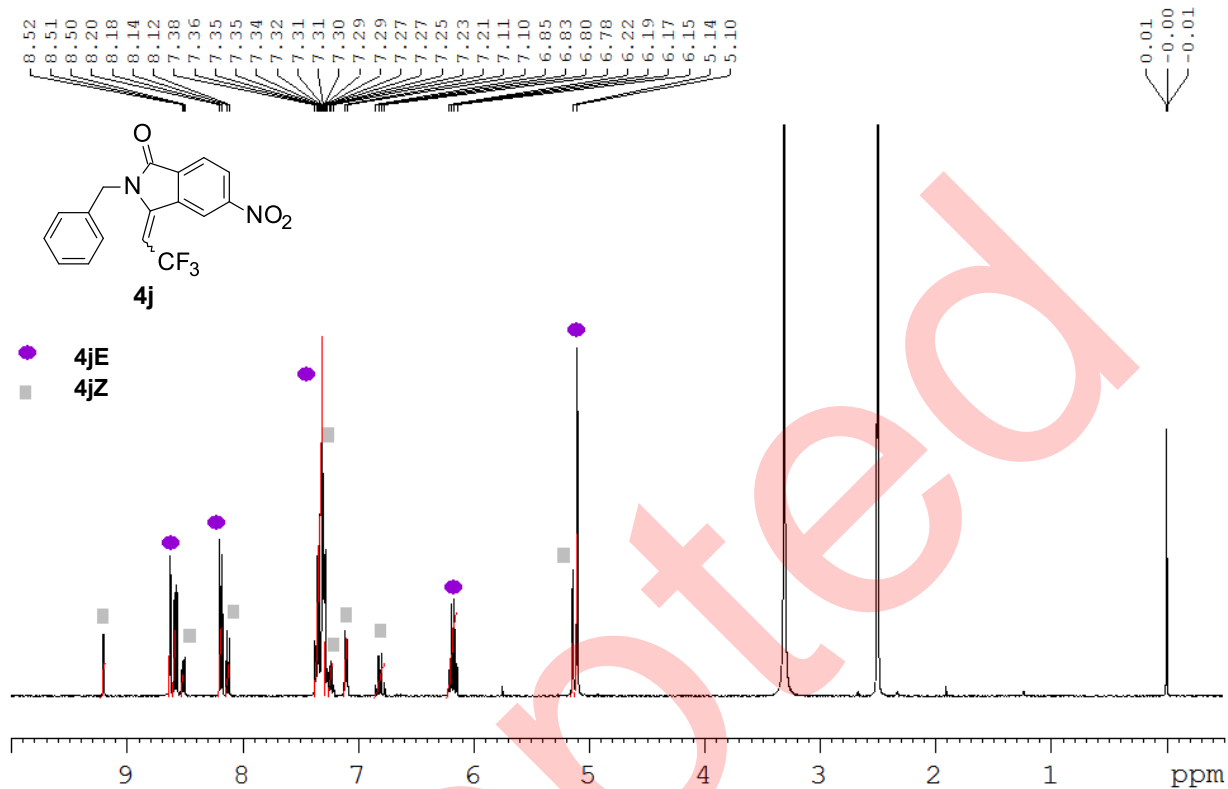
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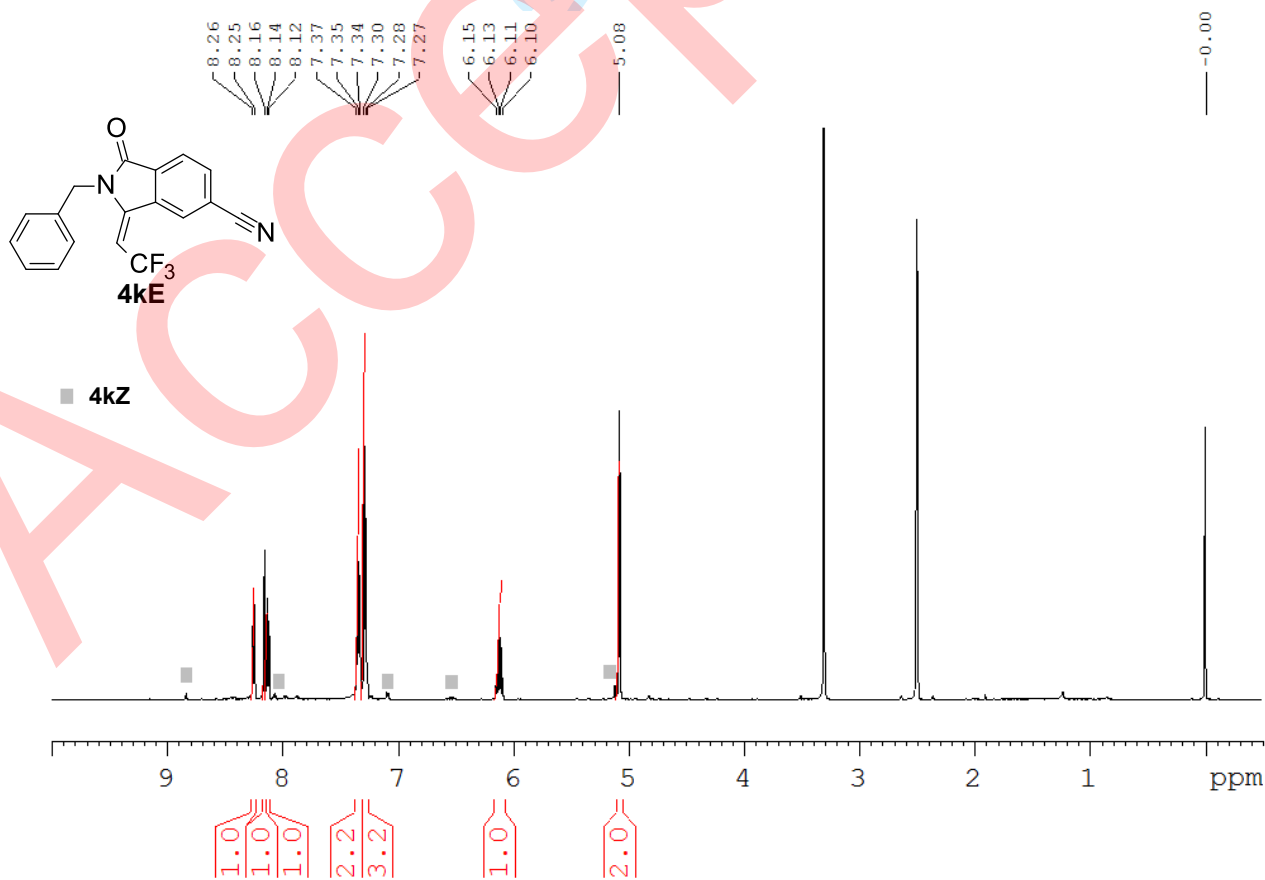
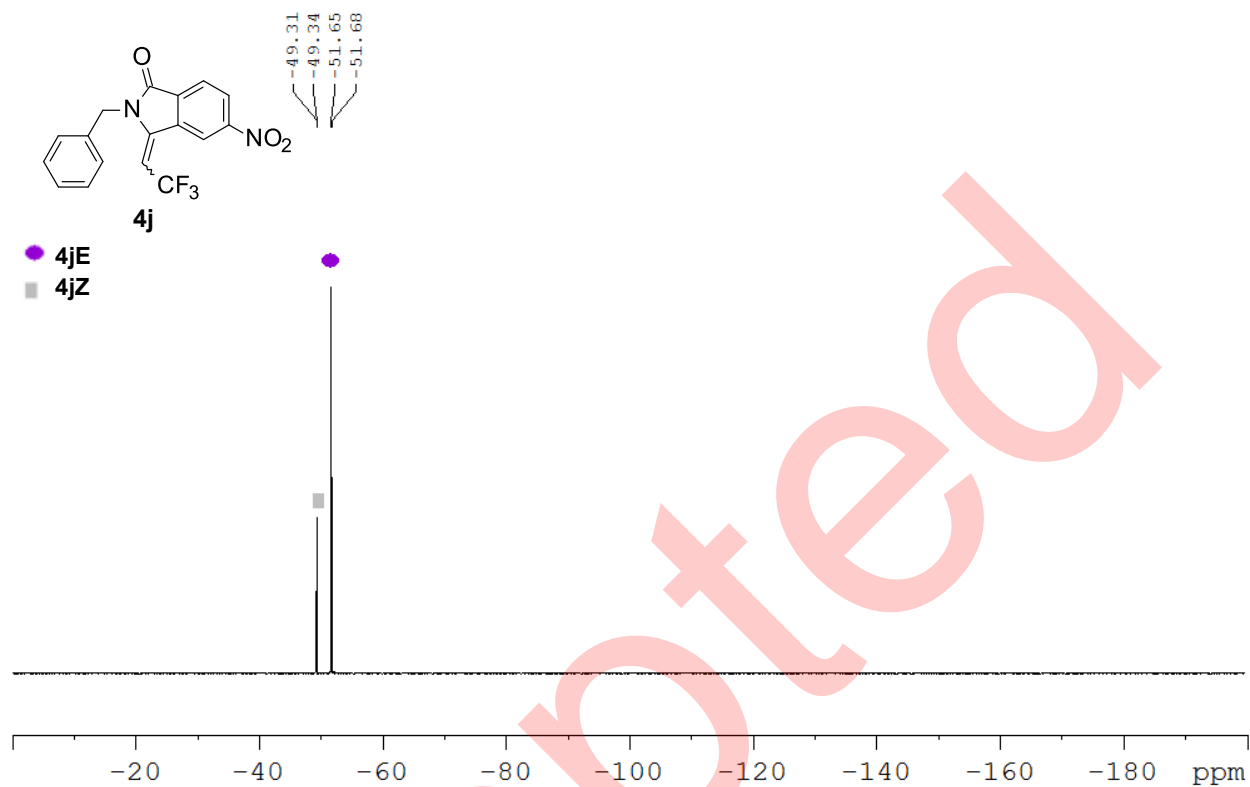
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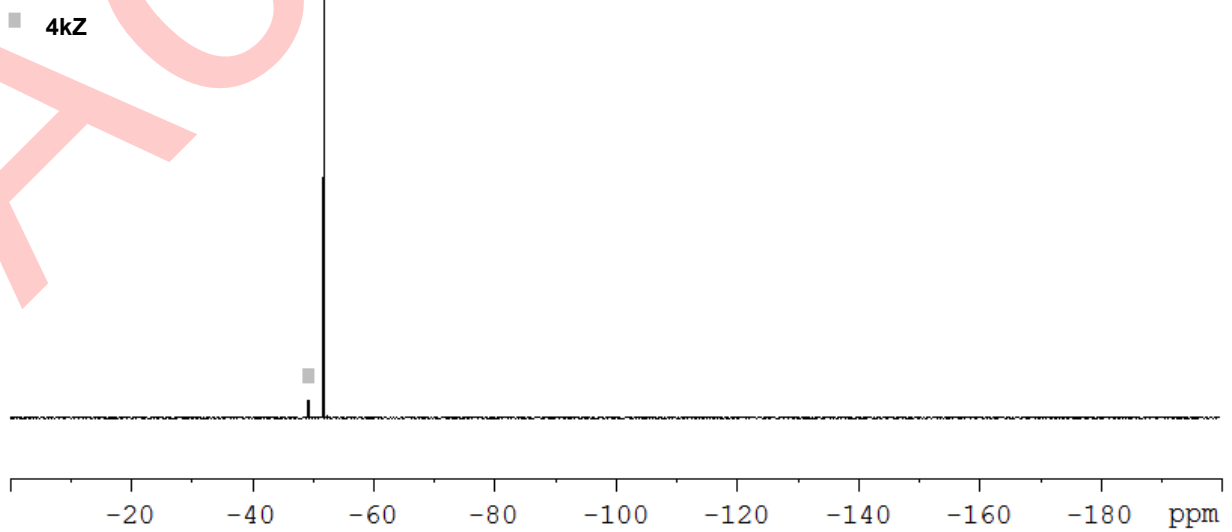
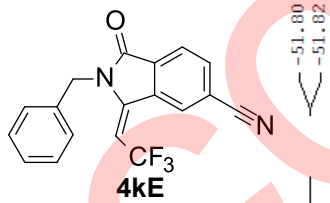
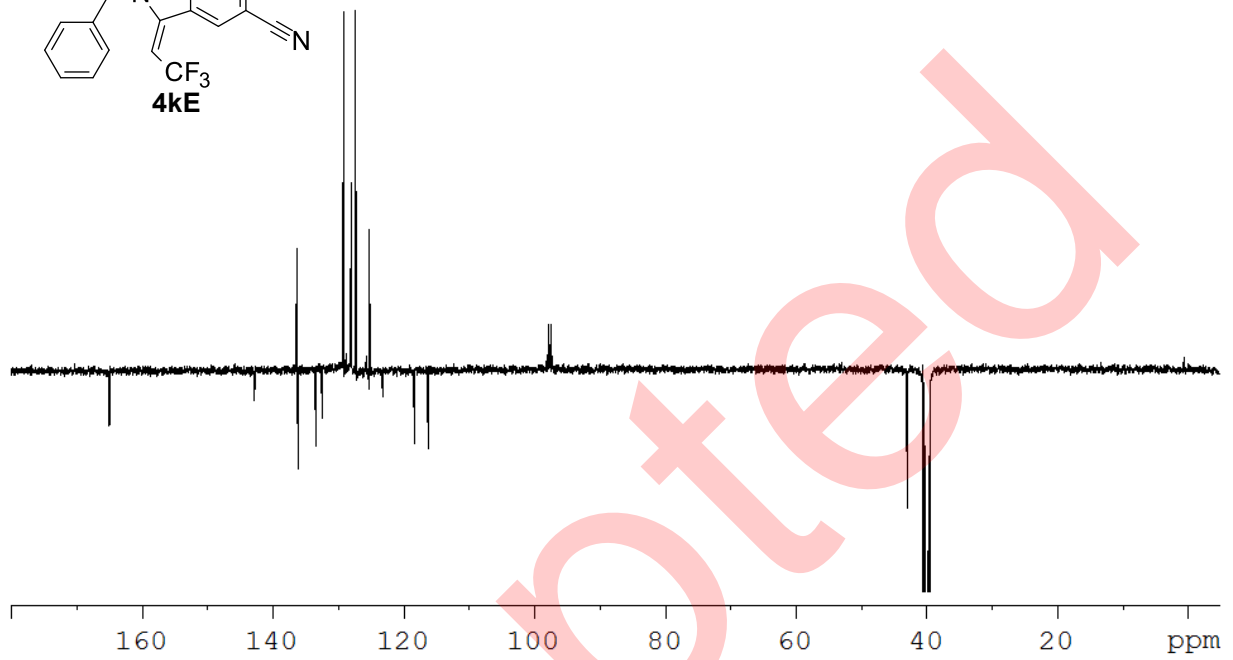
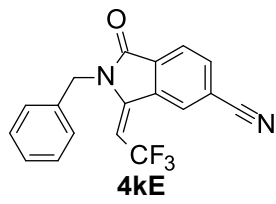
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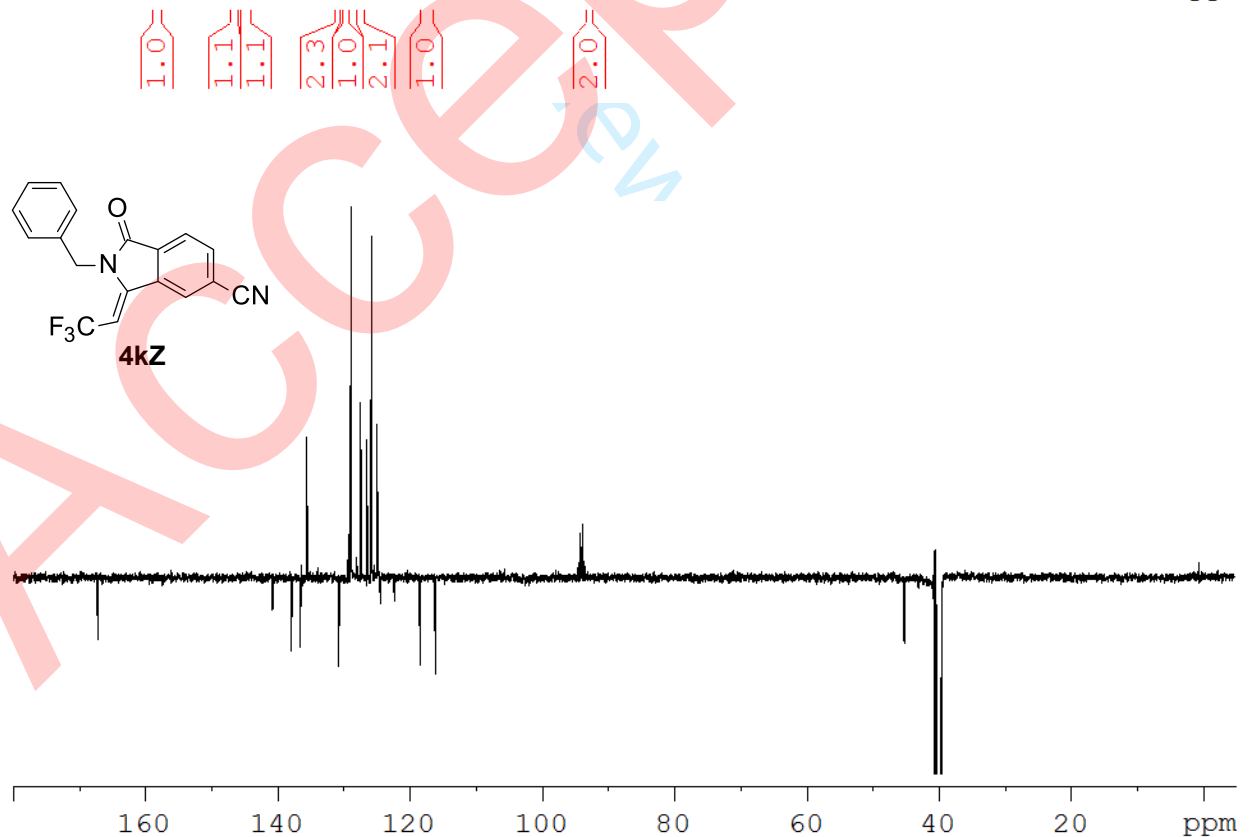
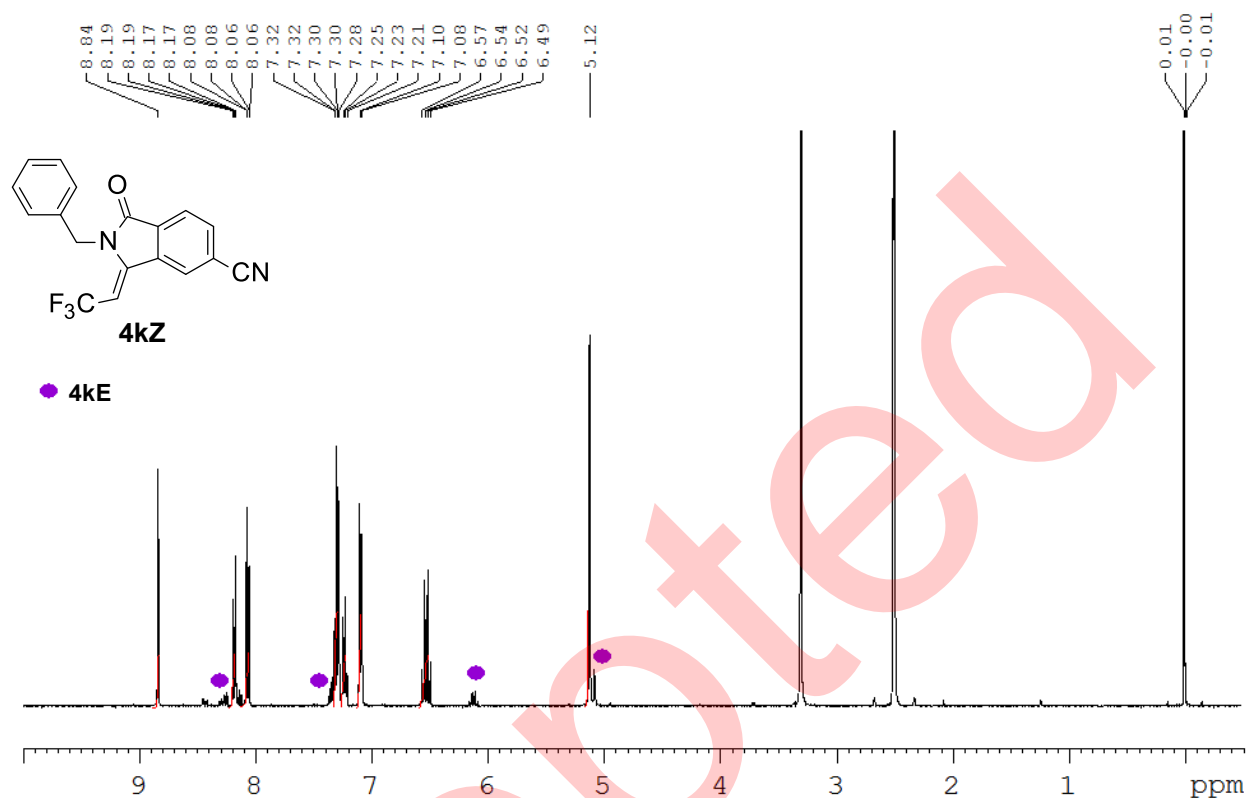


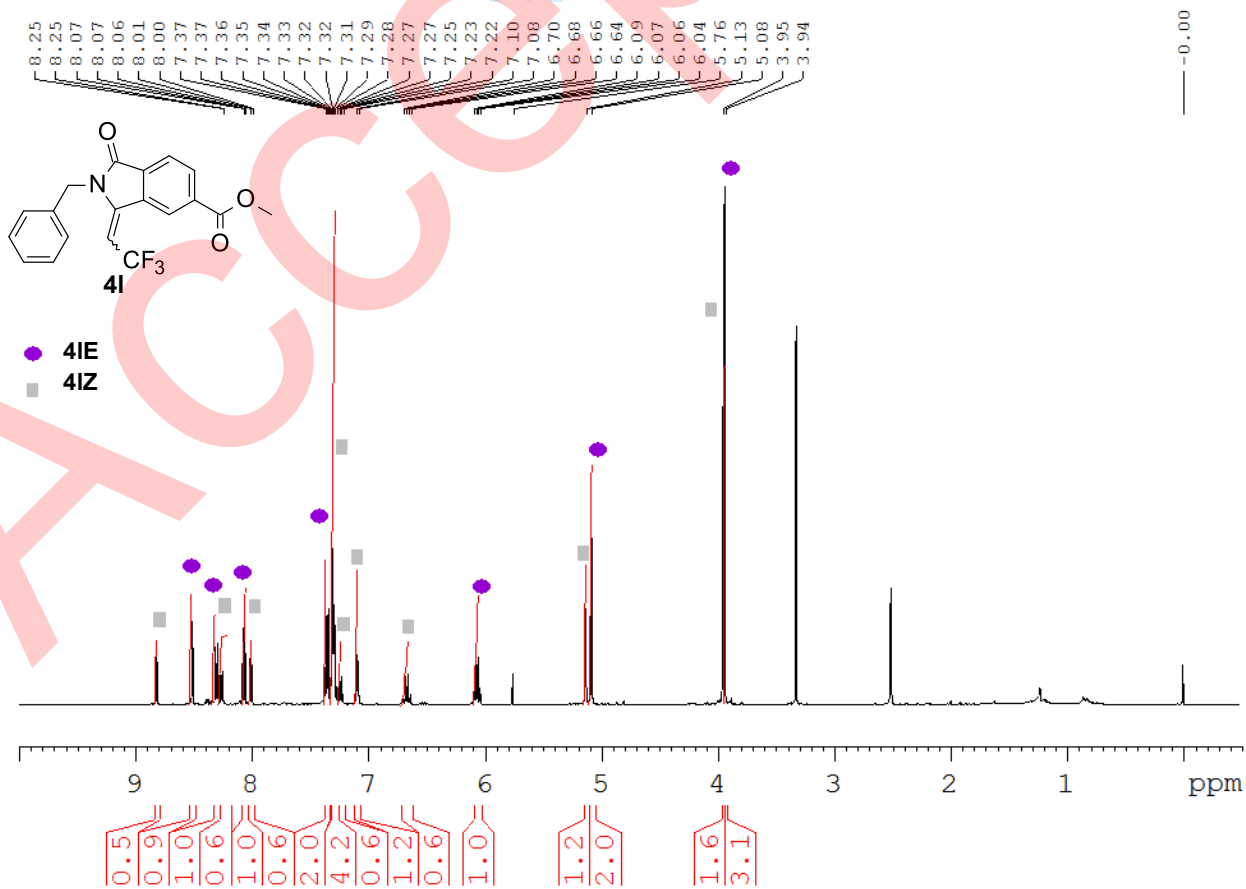
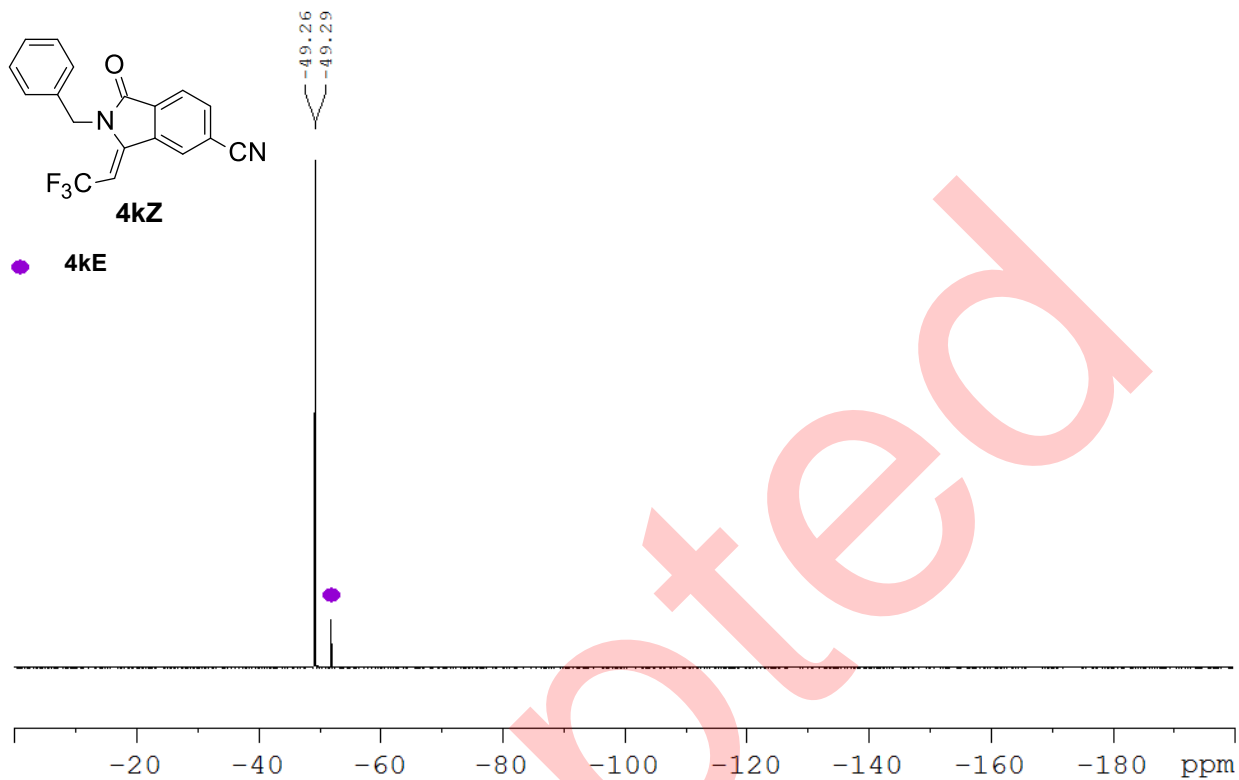




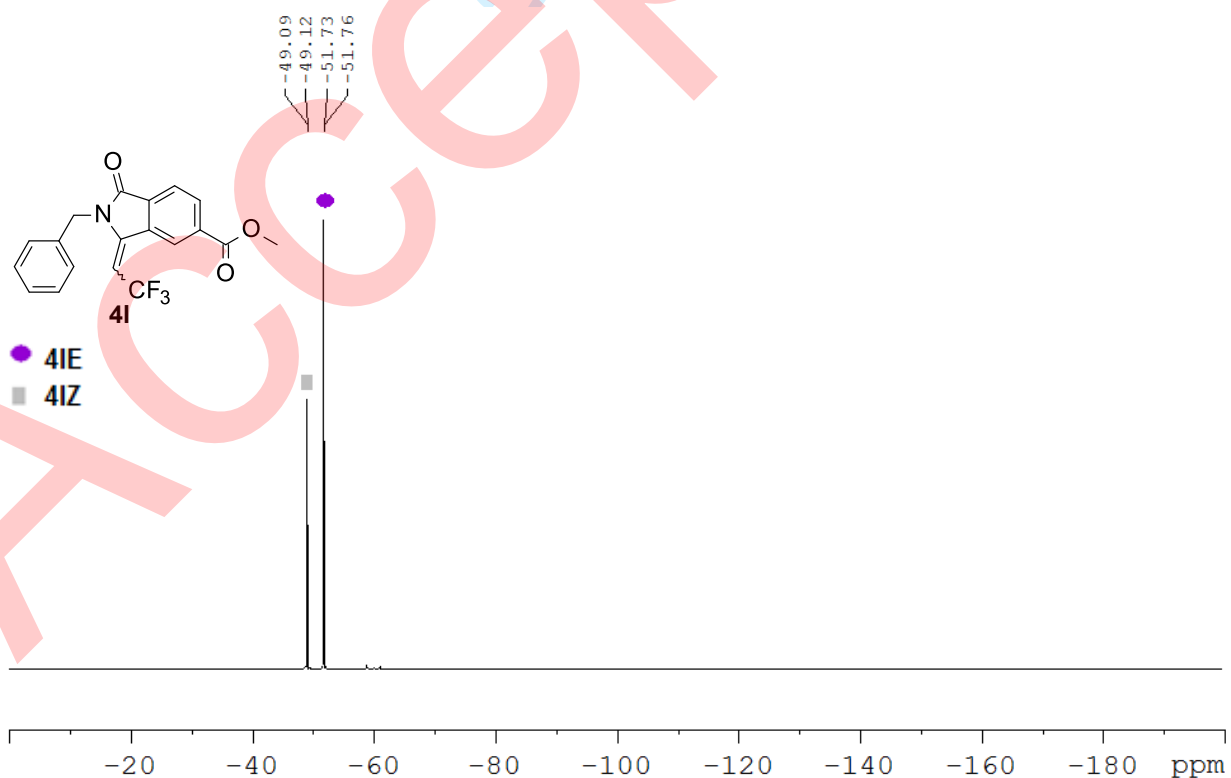
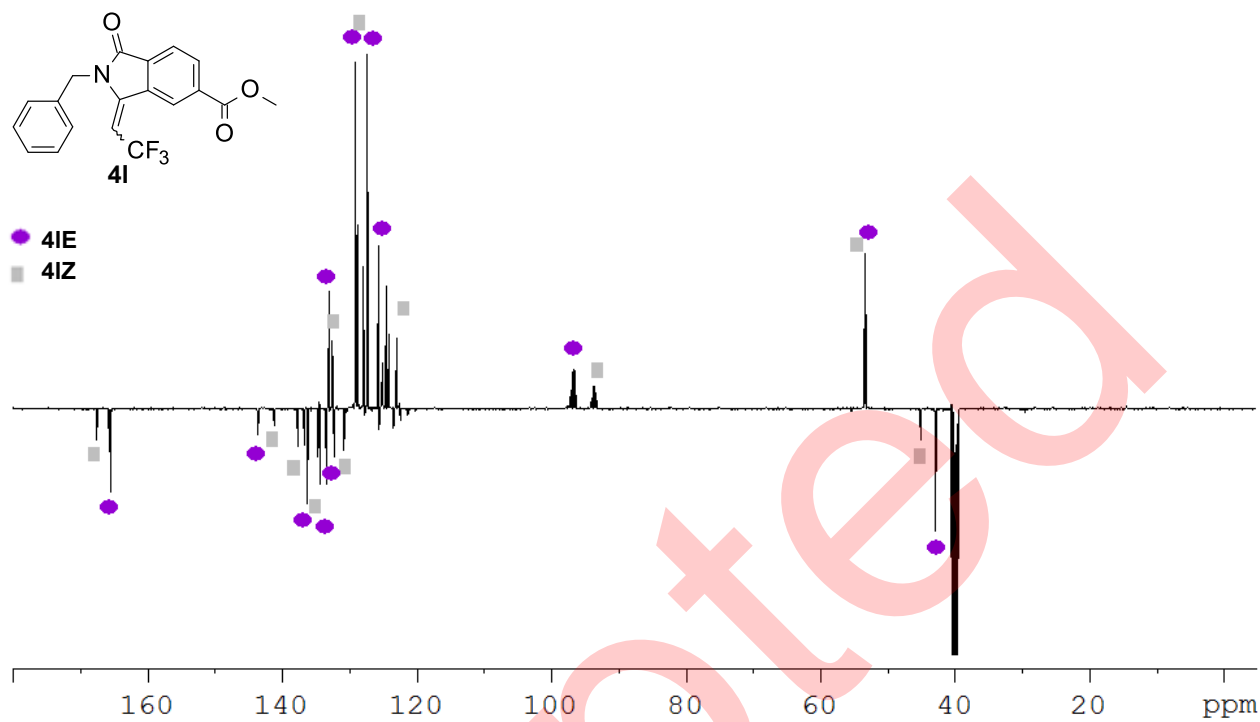


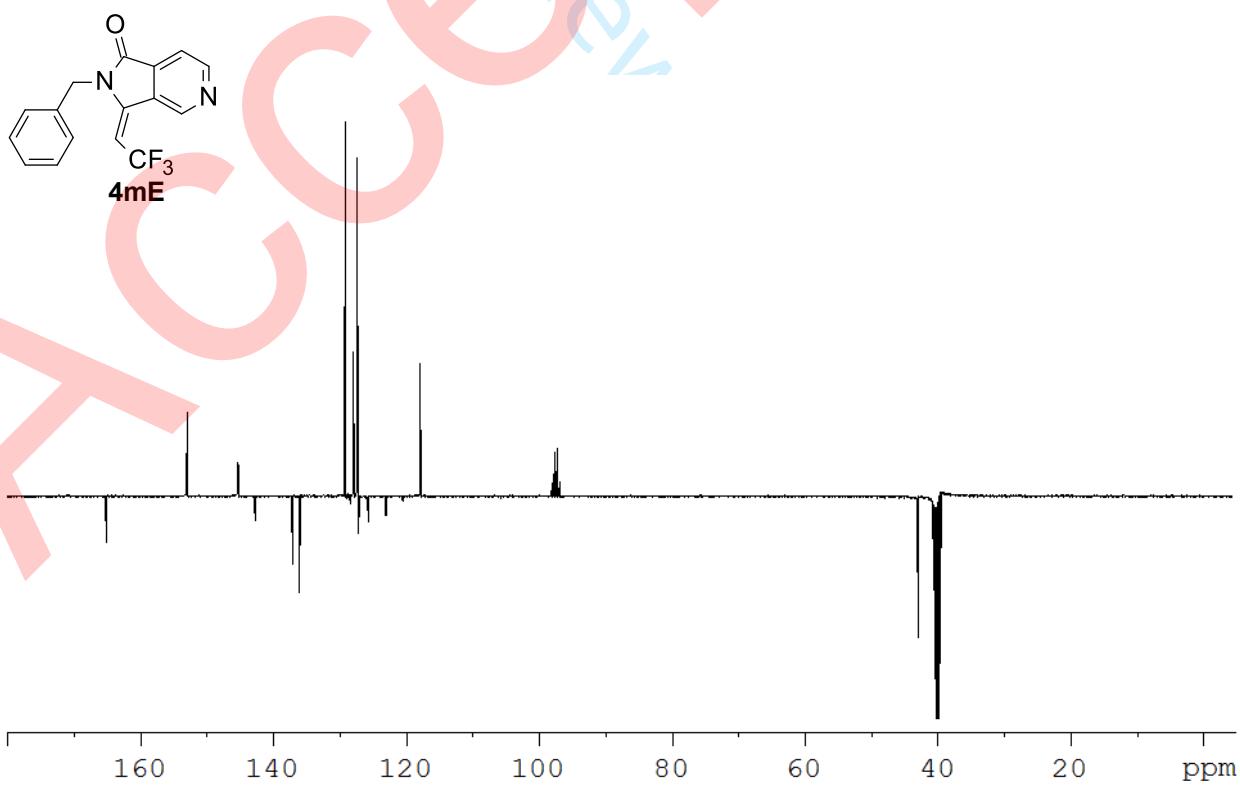
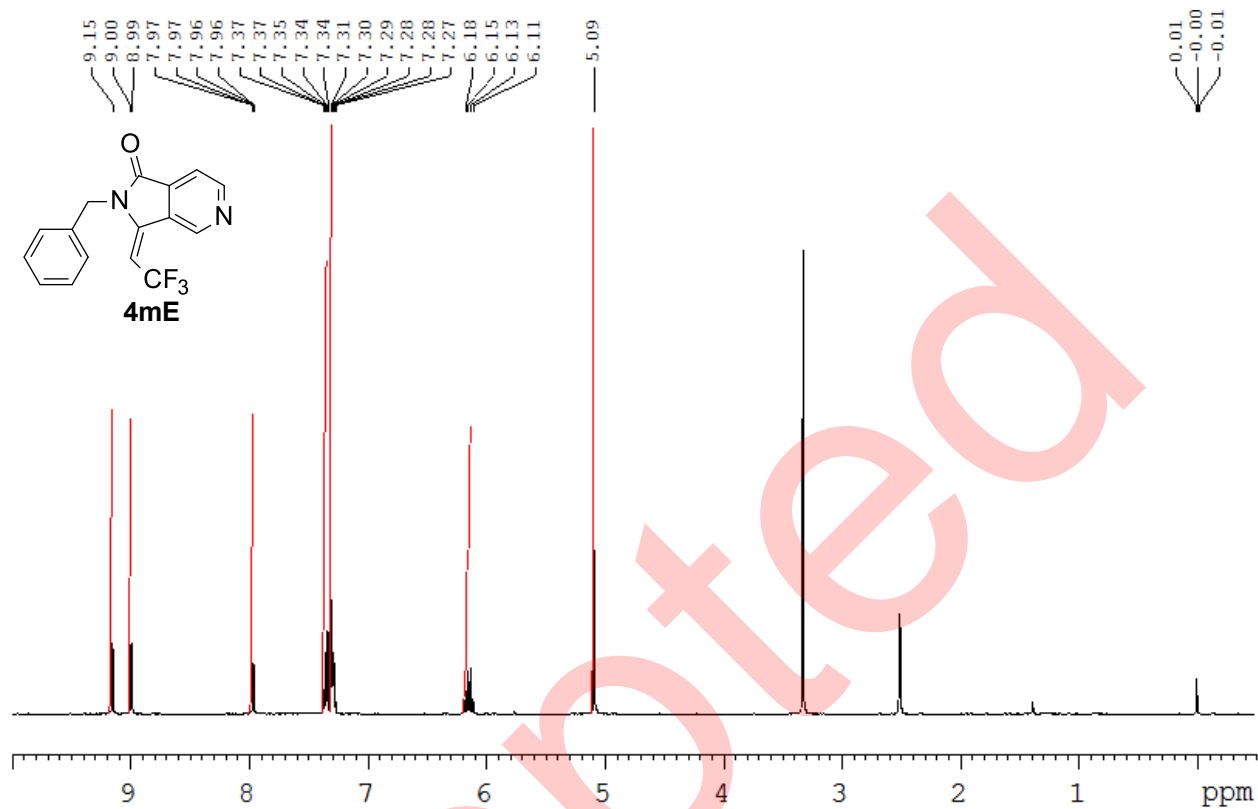


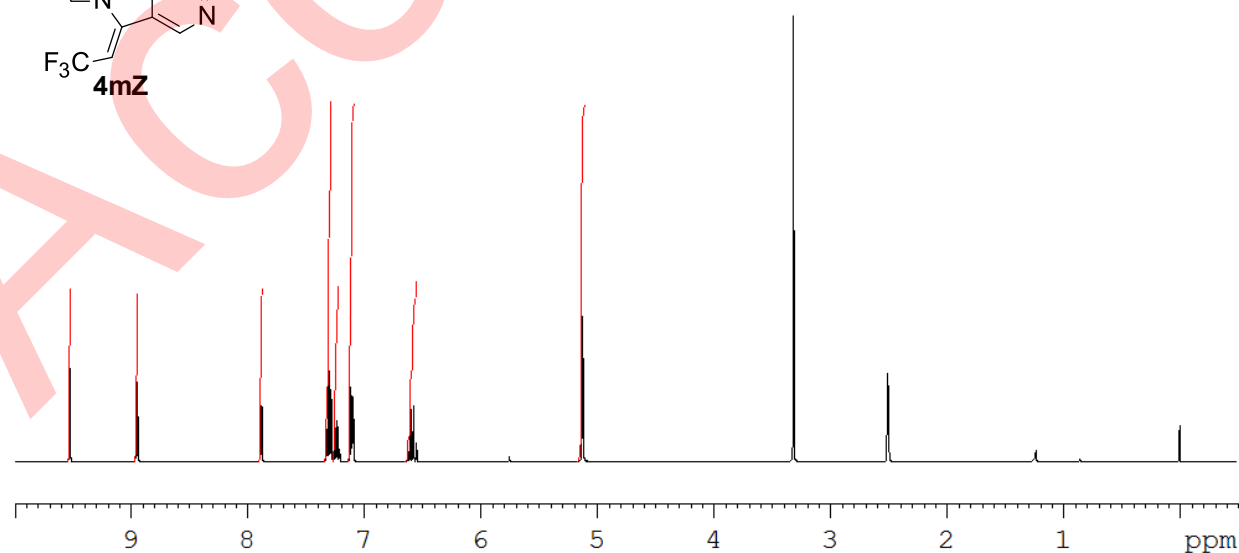
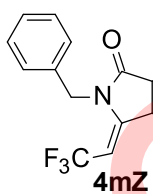
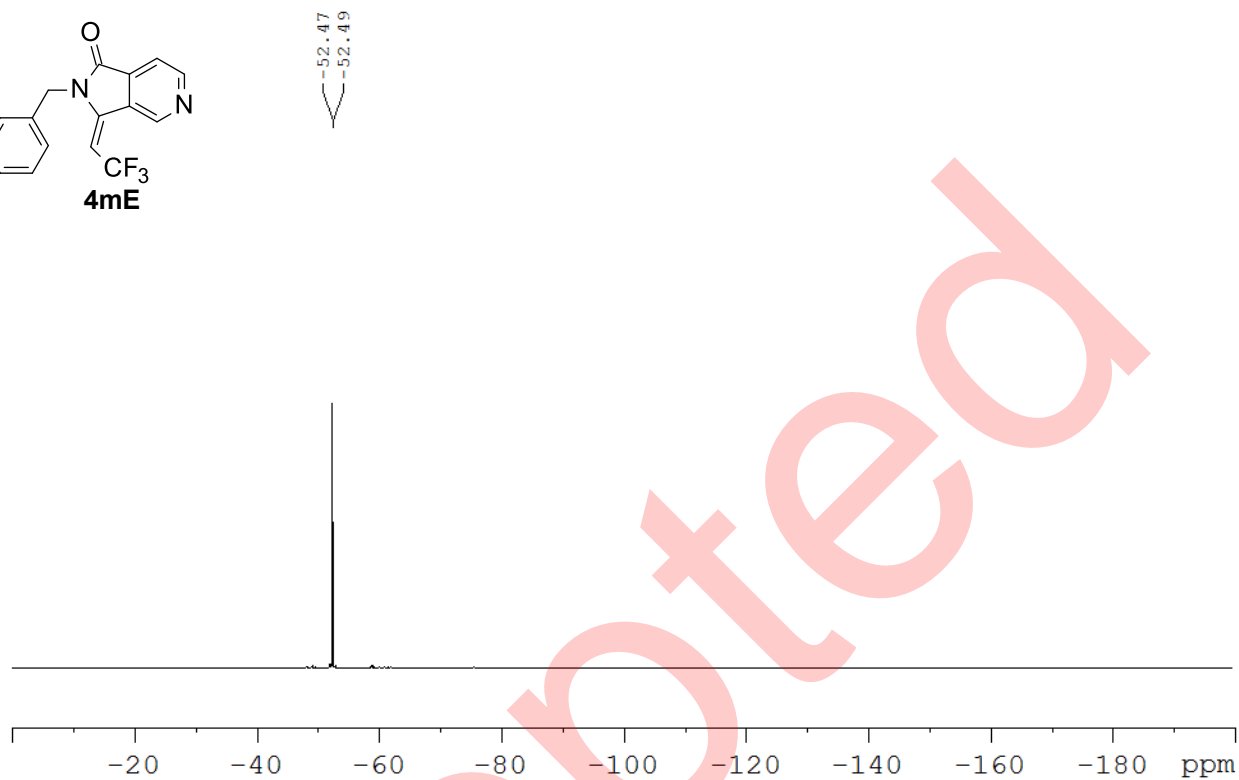
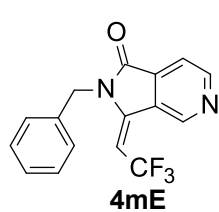


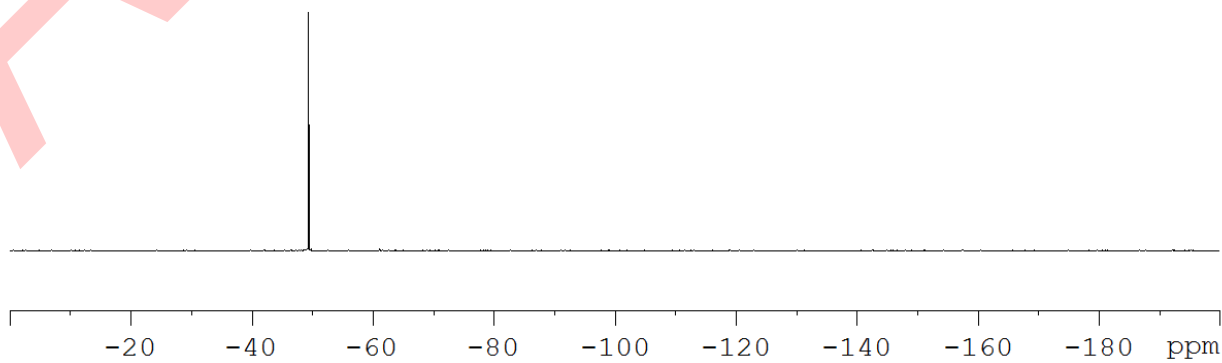
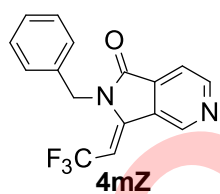
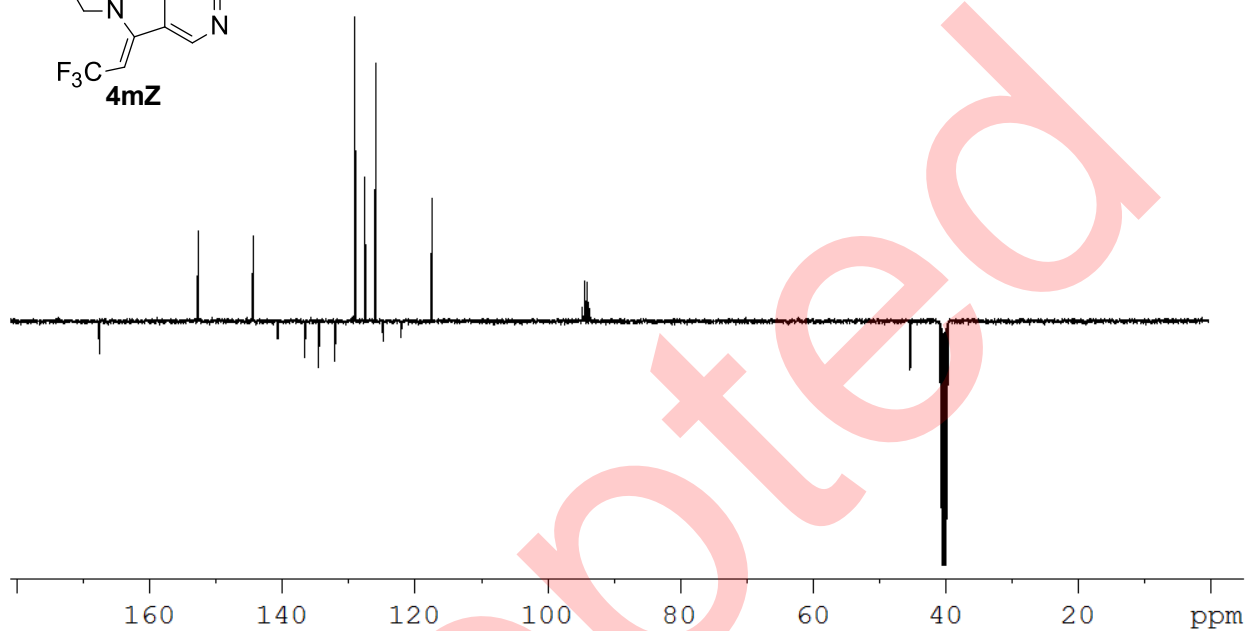
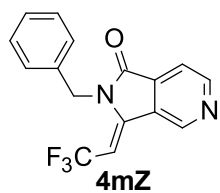


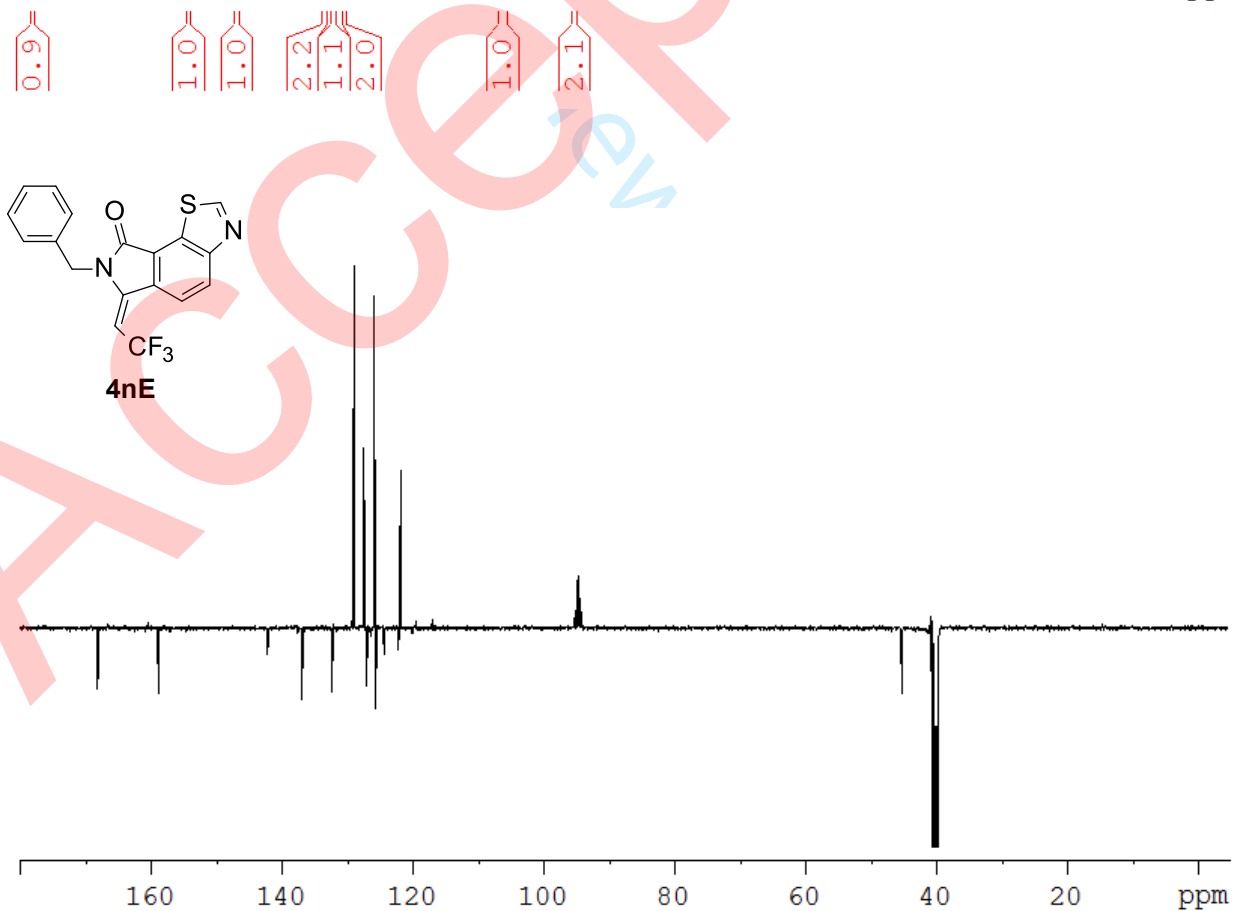
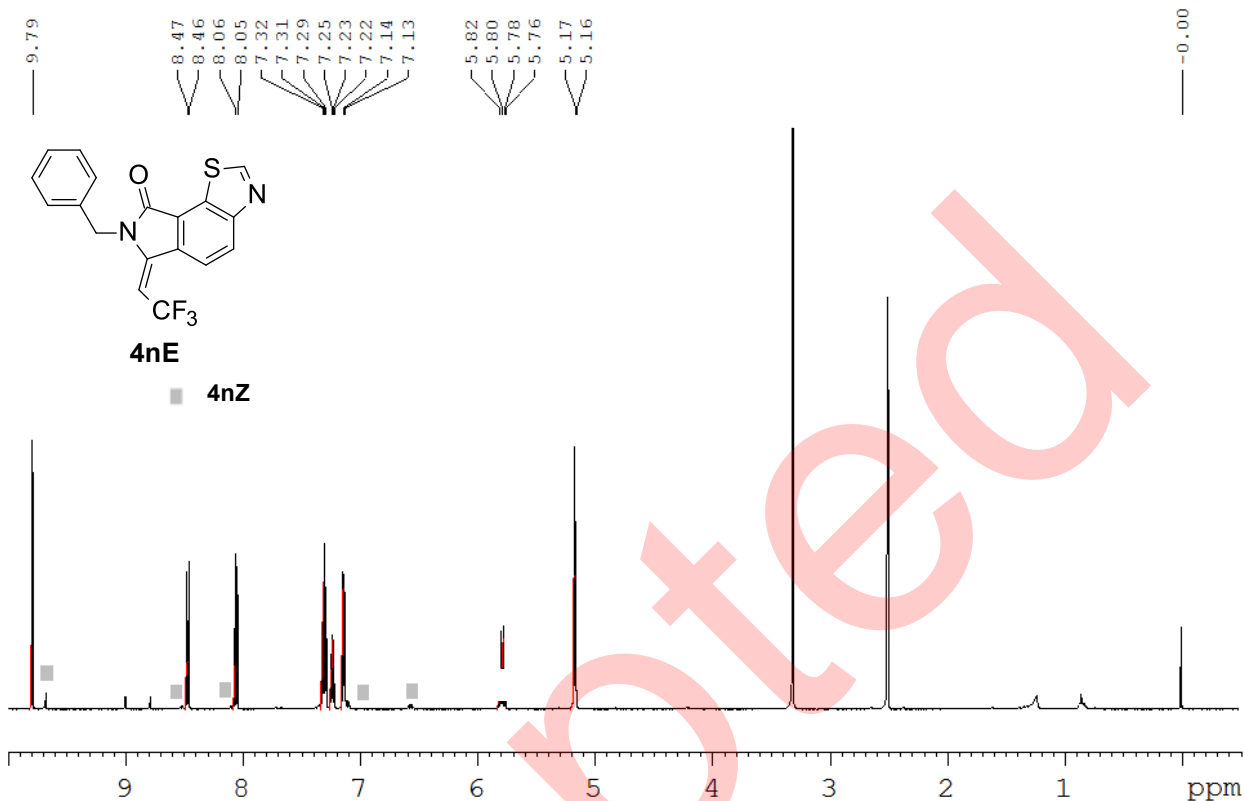


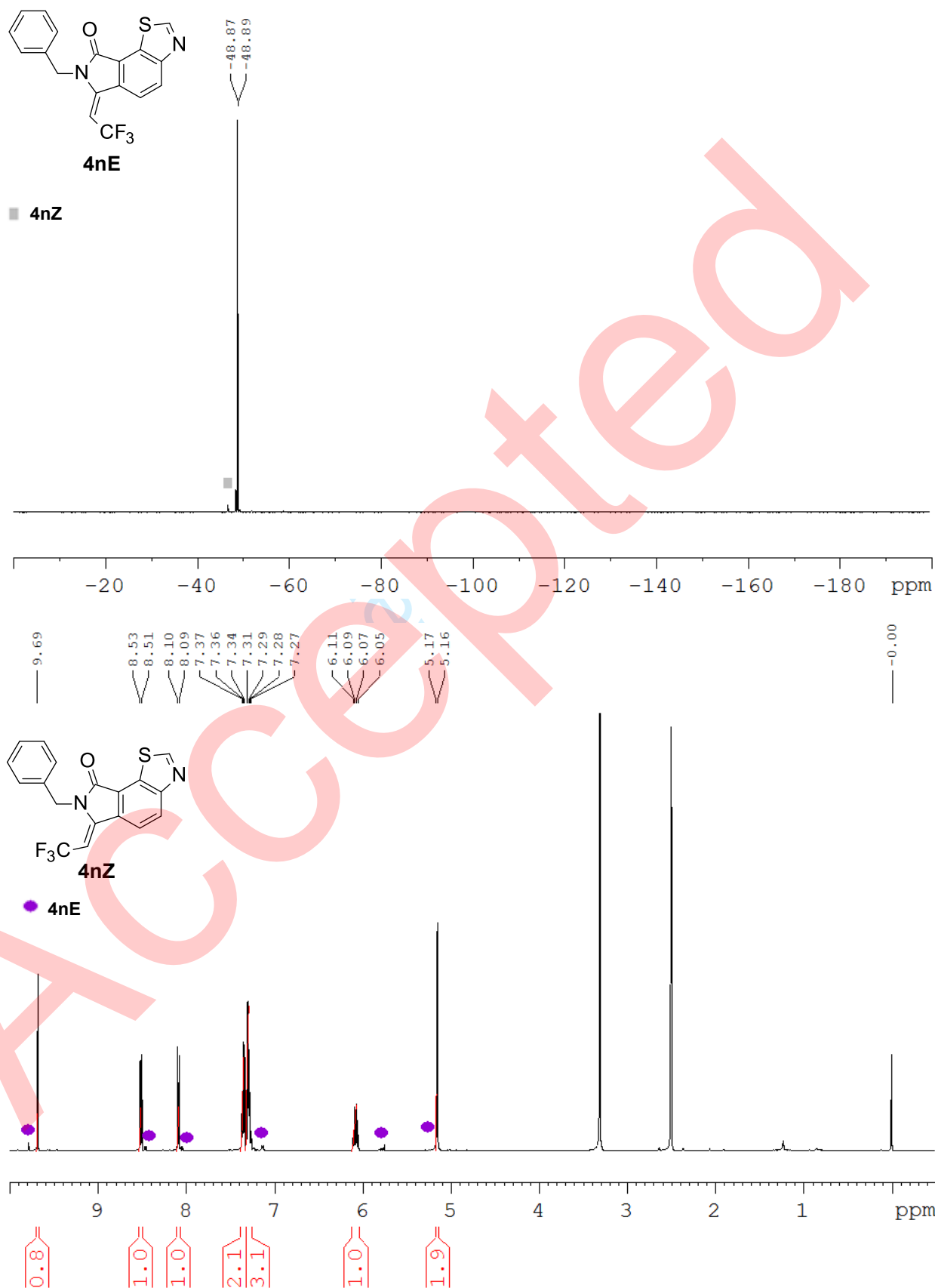


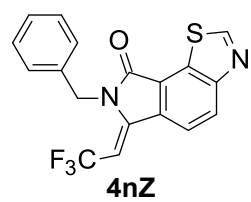
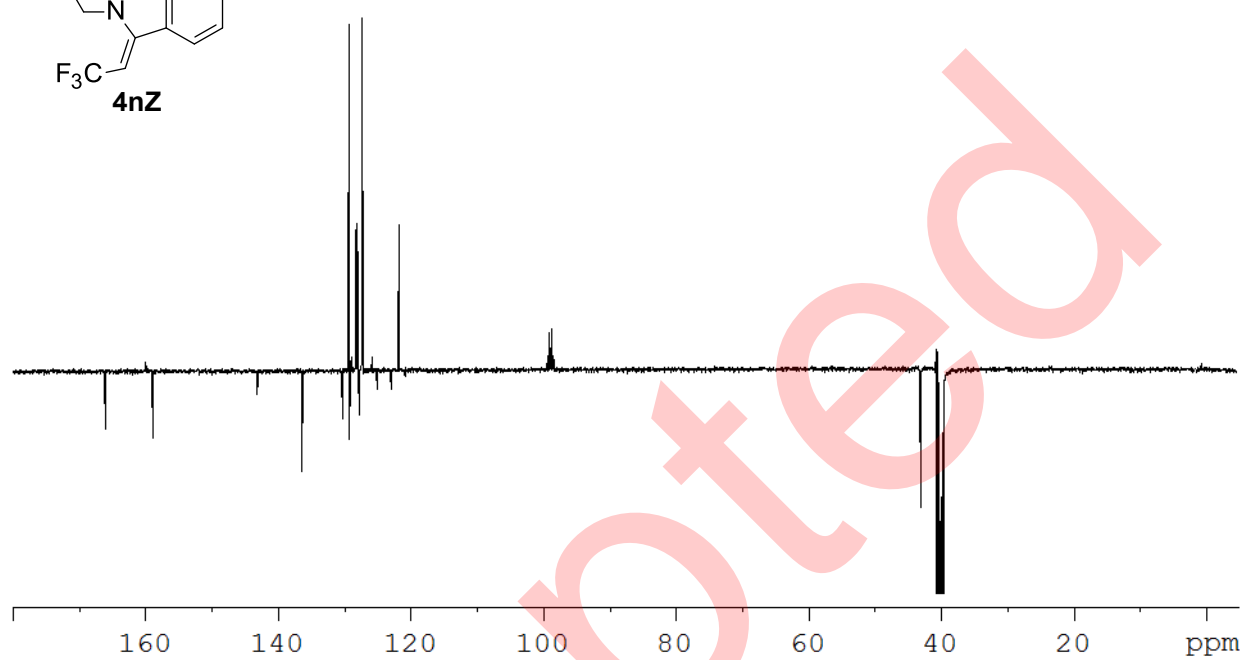
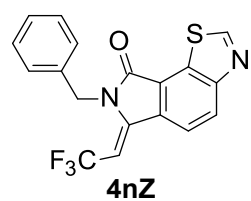












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