Catalytic Friedel-Crafts Reaction of Aminocyclopropanes.

Florian de Nanteuil, Joachim Loup and Jérôme Waser*

Laboratory of Catalysis and Organic Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland.

jerome.waser@epfl.ch

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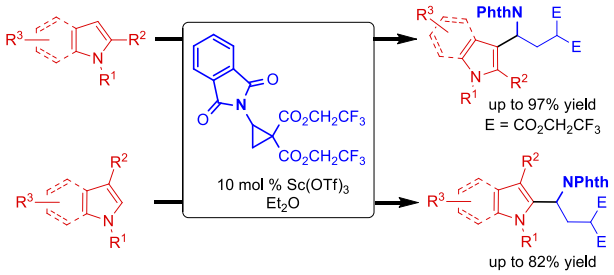
ABSTRACT



A Lewis acid catalyzed Friedel-Crafts reaction between donor-acceptor aminocyclopropanes and indoles and other electron-rich aromatic compounds is reported. Indole alkylation at the C3 position was generally obtained for a broad range of functional groups and substitution patterns. In the case of C3-substituted indoles, C2 alkylation was observed. The reaction gives a rapid access to gamma amino acid derivatives present in numerous bioactive molecules.

Substituted γ-aminobutyric acid (GABA) derivatives are found in numerous natural and synthetic neurotransmitters,[1] in peptidomimetics[2] and in the core of a large number of alkaloid natural products. In particular, electron-rich aromatic substituents are frequently encountered in the γ position of GABA derivatives in important classes of natural products, such as the indole alkaloids vindoline (**1**) and eburnamonine (**2**) or the *Erythrina* alkaloid 3-demethoxyerythratidinone (**3**) (Scheme 1). Consequently, a fast and general approach to these key building blocks would be highly desirable.[3]

In this context, the nucleophilic attack of an electron-rich aromatic or an amine at the γ position of a carbonyl group would give an efficient entry into this important class of GABA derivatives (Scheme 1). In order to achieve this transformation, the *Umpolung* of the normal reactivity at the nucleophilic γ position is required. Activated donor-acceptor (DA) cyclopropanes represent such *Umpolung* synthons and have been used in the past as olefin homologs.[4] In previous studies the nucleophilic attack of an amine onto aromatic DA cyclopropanes has been reported to access GABA analogs (Scheme 1, (1)).[5] If a high diversity in the aromatic substituent is desired, an alternative approach involving attack of a nucleophilic aromatic compound onto a nitrogen-substituted synthon as represented by an aminocyclopropane would be more efficient (Scheme 1, (2)). Nevertheless, such an approach has not yet been exploited.

(1) (a) Johnston, G. A. R. *Pharm.Ther.* **1996**, *69*, 173. (b) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427.

(2) Sudev, P. G.; Chatterjee, S.; Shamala, N.; Balaram, P. *Chem. Rev.* **2011**, *111*, 657.

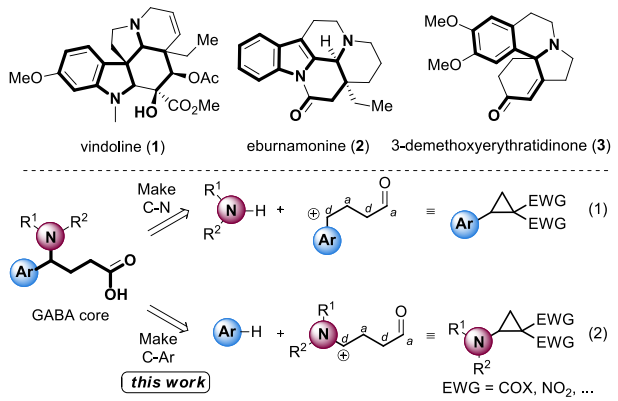
(3) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.

(4) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev* **2007**, *107*, 3117. (d) De Simone, F.; Waser, J. *Synthesis* **2009**, *2009*, 3353. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. Theoretical study: (f) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848.

(5) (a) Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1986**, *51*, 1372-1374. (b) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (c) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972. (d) So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444. (e) Zhou, Y. Y.; Wang, L. J.; Li, J.; Sun, X. L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066. (f) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634.

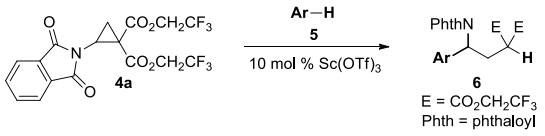
On the other hand, intermolecular Friedel-Crafts reactions between donor-acceptor cyclopropanes and electron-rich aromatic compounds including indoles have been studied in the past, especially by the groups of Kerr, Pagenkopf and Ivanova.[6] In 2013, Johnson developed an enantioselective Friedel-Crafts reaction between aryl cyclopropane and silyl-protected indoles using a chiral Lewis acid catalyst.[7] However, only alkyl, aryl or alkoxy substituents have been used as the donating group on the cyclopropane.[8]

Scheme 1. Natural products containing a GABA-derived core and key disconnections.



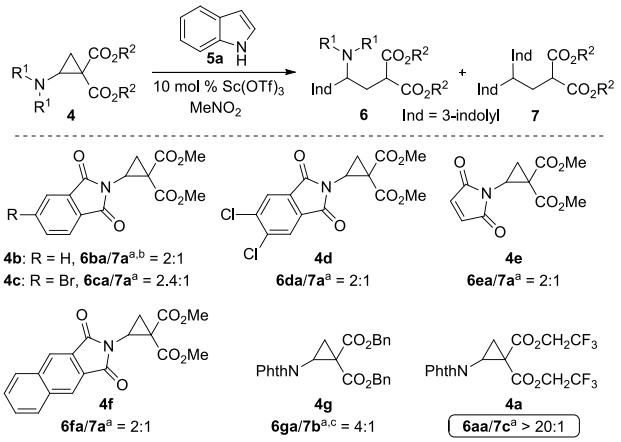
Since 2010, our group has been involved in the study of the reactivity of aminocyclopropanes.[9] The release of ring strain combined with bond polarization allowed the generation of reactive a 1,3 zwitterionic synthon, which could cyclize on indoles or react with enol ethers, aldehydes and ketones to afford cyclopentyl- and tetrahydrofuryl- amines. In this latter work, optimization of the electronic properties of the substituents on the nitrogen resulted in the discovery that phthalimide-substituted cyclopropane diesters afford the right balance between reactivity and stability.[9c-e] Herein, we would like to report the first successful intermolecular Friedel-Crafts reaction of indoles with aminocyclopropanes based on fine-tuning of the electron-withdrawing properties of the diester group and the identification of scandium triflate as the best catalyst (Scheme 2). The reaction worked with unprotected indoles as well as other electron-rich aromatic compounds and tolerated a broad range of functional groups. In the case of C3-substituted indoles, C2-alkylated products could be obtained, probably via a selective 1,2-shift of the amino acid side-chain.

Scheme 2. Friedel-Crafts with diester aminocyclopropane **4a**



Preliminary screening of Lewis acids and solvents allowed us to identify scandium triflate in nitromethane as promising conditions for the alkylation of N-protected indoles with the phthaloyl protected aminocyclopropane diester **4b** at room temperature.[10] However, when switching to unprotected indole (**5a**), double addition product **7a** was observed as major side product in the reaction mixture (Scheme 3). Even after extensive optimization of the reaction conditions, it was not possible to achieve full selectivity toward the desired product **6**.

Scheme 3. Fine-tuning of the aminocyclopropane structure for the Friedel-Crafts alkylation of indole (**5a**).



Reaction conditions: cyclopropane (0.034 mmol), **5a** (0.051 mmol), $Sc(OTf)_3$ (3.4 µmol), nitromethane (0.2 mL), rt, 1 h. [a]Determined by ^1H NMR of the crude reaction mixture. [b]DCM (0.5 mL) was used. [c]The bis-indole adduct **7b** was not isolated. The NMR ratio was determined by analogy with **7a**.

(6) (a) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (b) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671. (c) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992. (d) Grover, H. K.; Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 220. (e) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180. (f) Bajtos, B.; Yu, M.; Zhao, H. D.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (g) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, 5329 (h) Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385.

(7) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558.

(8) There is a single example of aminocyclopropanes opening by trimethoxybenzene: Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem.* **2012**, *10*, 1735. During their recent work on the Friedel-Crafts alkylation of indoles,[7] Johnson and co-workers studied the use of phthalimido-cyclopropanes, but no reactivity was observed under their conditions.

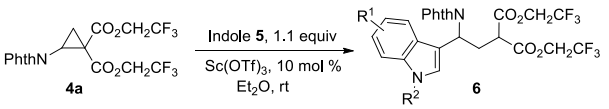
(9) (a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767. (b) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527. (c) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. (d) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. (e) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844.

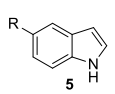
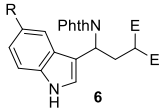
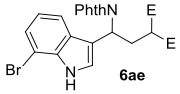
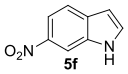
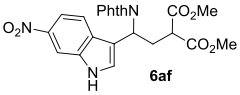
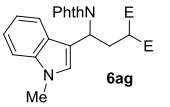
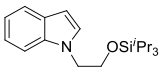
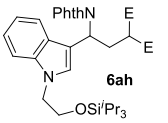
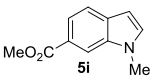
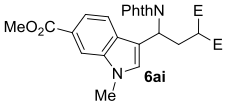
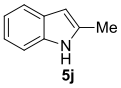
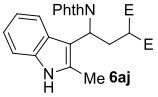
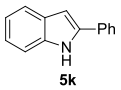
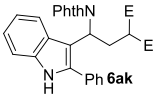
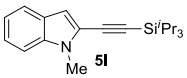
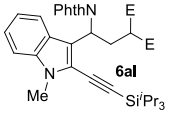
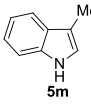
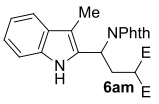
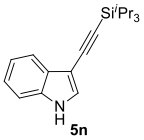
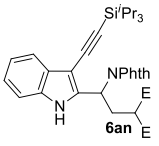
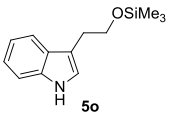
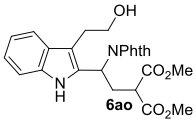
(10) See Supporting Information for a complete list of tested reaction conditions and Lewis acids.

We then turned our attention to the further adjustment of the structure of the aminocyclopropane. A series of aminocyclopropanes **4c-f** with different nitrogen protecting groups were examined in the alkylation reaction. The use of electron-poor bromo and dichloro derivatives **4c** and **4d** of phthalimide as well as a smaller maleimide **4e** or a larger naphthylimide **4f** on the cyclopropane did not have a favorable impact on the selectivity. In contrast, modification of the acceptor diester group (cyclopropanes **4g** and **4a**) had a strong influence on the reaction outcome. The best selectivity was obtained using the more electron-withdrawing trifluoro ethanol derivative **4a**, which afforded only the desired product. Finally, replacing the toxic nitromethane by diethyl ether was possible without loss of selectivity.

With this simple protocol for the addition of indole to aminocyclopropanes in hand, we investigated the scope of the reaction (Table 1). As showed during optimization, unprotected indole (**5a**) was a suitable partner for the reaction and the product **6aa** could be isolated in 85 % yield on a 0.2 mmol scale and in 87 % yield on a 2.8 mmol scale, showing that scaling up was straightforward for this transformation (entry 1). Electron-donating (methoxy) and -withdrawing (chloro, bromo and nitro) substituents on the benzene ring were well tolerated (entries 2-6). The compatibility with halogens or a boronic ester is particularly interesting, as the obtained products are easily further functionalized via cross-coupling reactions. Next, the use of N-alkyl substituted indoles was investigated (entries 7-9). N-methyl indole (**5g**) afforded the alkylation product **6ag** in 94 % yield on a 0.2 mmol scale and in 83 % yield on a 2.4 mmol scale (entry 7). A protected alcohol on the N-alkyl chain (entry 8) as well as an ester group on the benzene ring (entry 9) were well tolerated. Alkylation of indoles substituted at the position C2 by an alkyl, an aryl or a more sensitive alkynyl[11] functionality was also possible in 52-97% yield (entries 10-12). When C3-substituted indoles were examined as substrates, selective C2-alkylation was observed (entries 13-15). This product is probably formed by C3-alkylation, followed by 1,2-alkyl shift.[6c,12] This result is interesting, as in most reactions of C3-substituted indoles with cyclopropanes, a [3+2] annulation occurs preferentially over 1,2-shift.[6b,13] The observed outcome could be due to the ability of the nitrogen substituent to stabilize a partial positive charge during the alkyl shift.

Table 1. Friedel-Crafts reaction with aminocyclopropane **4a**.



entry	indole	product	yield(%)[a]
			
1	R = H (**5a**)	**6aa**	85 (87)[b]
2	R = Cl (**5b**)	**6ab**	82
3	R = OMe (**5c**)	**6ac**	68
4	R = Bpin (**5d**)	**6ad**	63
5			70
6			58[c]
7			94 (83%)[d]
8			80
9			86
10			97
11			93
12			52
13			82[e]
14			49[f]
15			72[c,f]

E = $CO_2CH_2CF_3$. Reaction conditions: **4a** (0.20 mmol), indole (0.22 mmol), $Sc(OTf)_3$ (0.01 mmol), Et_2O (1.2 mL), rt. [a]Isolated yields. [b]On a 1.5 g scale. [c]Isolated after transesterification (see Supporting Information for more details). [d]On a 1.3 g scale. [e]Reaction in Et_2O at 35 °C. [f]Reaction in toluene at 60 °C.

(11) Obtained in one step by the alkynylation of N-methyl indole (**5g**) using a method developed in our group: Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112.

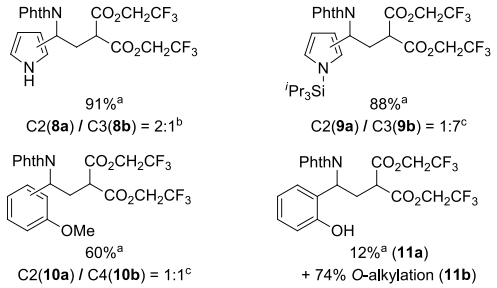
(12) Alternative mechanisms involving direct addition on the C2 position or reversible C3-addition in competition with irreversible C2 addition cannot be completely excluded, but appeared less probable: The former due to the higher electron-density at the C3 position, and the latter as it would require the formation of an highly reactive carbocationic intermediate or a strained cyclopropane.

(13) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851.

The C2 alkylation was not limited to skatole (entry 13), but the reaction was slower for other substrates and heating to 60 °C was required to obtain full conversion in the case of 3-alkynyl indole **5n**[14] (entry 14) and protected tryptophol **5o** (entry 15). For the latter, protection of the oxygen was required to prevent side reactions.

Finally, we wondered if this protocol could be extended to other classes of electron-rich aromatic compounds (Figure 1). Although furans and thiophenes were unreactive under these conditions, pyrrole reacted efficiently to give a 2:1 C2/C3 mixture of regioisomers 8a and 8b in 91% yield.15 Protection of the nitrogen of pyrrole with a triisopropylsilyl group allowed to switch the selectivity and to isolate the C3-alkylated product 9b with good selectivity. Anisole could also be used, leading to a mixture of para/ortho alkylation products 10a and 10b. In the case of phenol, product 11b resulting from O alkylation was the major product. These preliminary results highlight the broad potential of donor-acceptor substituted aminocyclopropanes for the Friedel-Crafts alkylation of electron-rich aromatic compounds.

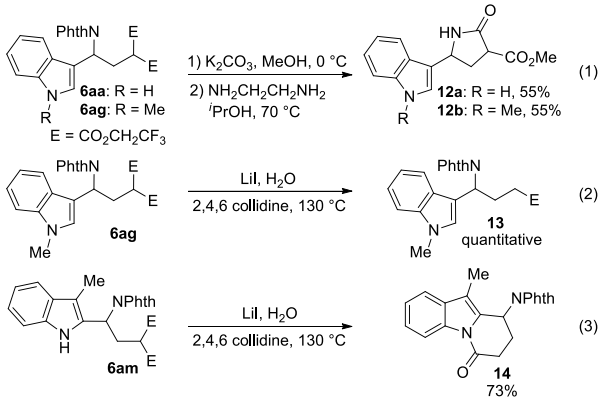
Figure 1. Products of the alkylation of electron-rich aromatic compounds.



[a]Reaction conditions: **4a** (0.20 mmol), aromatic compound (0.22 mmol), $Sc(OTf)_3$ (0.01 mmol), Et_2O (1.2 mL), rt.; Isolated yield. [b]Ratio of isolated material. [c]Determined by ^1H NMR.

In order to show that the products are useful synthetic precursors, deprotection of the phthalimide was conducted using diaminoethane in isopropanol after transesterification of the difluoroethanol malonate (Scheme 4, (1)). During this process, the free amine cyclized on the malonic ester giving lactam **12a** and **12b** as a 1:1 ratio of equilibrating diastereoisomers. An efficient access to substituted γ lactams is interesting, as they represent an important class of bioactive natural products and synthetic drugs. Modified Krapcho conditions[16] allowed us to obtain the mono-ester derivative **13** in quantitative yield (Scheme 4, (2)). When these conditions were applied to C2 adduct **6am**, tricyclic product **14**, which correspond to the core skeleton of natural products such as eburnamonine (**2**), was isolated in 73 % yield (Scheme 4, (3)).

Scheme 4. Synthetic transformations of the alkylation products.



In conclusion, we have shown that phthaloyl protected diester aminocyclopropanes are powerful homo-olefin equivalents in Friedel-Crafts alkylation reactions and readily react with electron-rich aromatic compounds to afford GABA analogues. C2-alkylation was observed for C3-substitued indoles, which is probably the result of C3-alkylation followed by selective shift of the amino-substituted alkyl chain. Finally, the synthetic potential of the products was highlighted by the easy removal of the phthaloyl protecting group, as well as Krapcho decarboxylation. Future works will focus on the development of enantioselective methods, as well as the application of this transformation in the synthesis of bioactive natural products.

Supporting Information. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowlegment. We thank the EPFL and SNF (grant 200021_129874) for funding and F. Hoffmann-La Roche Ltd for an unrestricted research grant. Eloisa Serrano and Nicolas Gaeng (both EPFL) are acknowledged for the synthesis of starting materials.

(14) Obtained in one step by the alkynylation of indole (**5a**) using a method developed in our group: Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346.

(15) These results are in accordance with the lower nucleophilicity of furans and thiophenes as quantified by Mayr's reactivity scale: Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.

(16) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246.

Supporting Information

76 pages

Catalytic Friedel-Crafts Reaction of Aminocyclopropanes.

Florian de Nanteuil, Joachim Loup and Jérôme Waser

Laboratory of Catalysis and Organic Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland.

jerome.waser@epfl.ch

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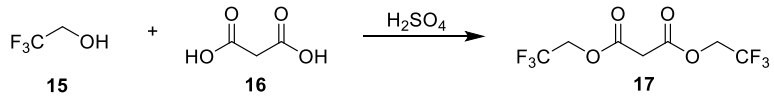
1. General Methods

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography, technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. Tetrahydrofuran, Diethyl ether, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 7 ppm, *Karl-Fischer* titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F_{254} TLC plastic plates and visualized with UV light, CAN stain or *p*-anisaldehyde stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, integration, coupling constant(s) in Hz, interpretation). ^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.16 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prism and are reported as cm-1 (w = weak, m = medium, s = strong). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC, IB or IA column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used. Scandium triflate was stored and weighted in a glovebox. Commercially available N-Vinyl Phthalimide [3485-84-5], p-Acetamidobenzenesulfonyl Azide [2158-14-7] were used

2. **Synthesis of diazo compounds**

Bis(2,2,2-trifluoroethyl) malonate (17)

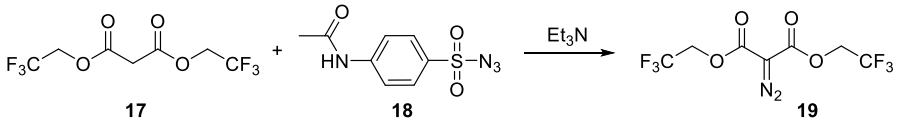


Following a reported procedure,[1] a 250 mL round-bottom flask equipped with a condenser was charged with malonic acid (**16**) (8.00 g, 77.0 mmol, 1 equiv), 2,2,2-trifluoroethanol (**15**) (29.6 mL, 412 mmol, 5.4 equiv), benzene (40.0 mL) and sulfuric acid (1.00 mL, 19.0 mmol, 0.25 equiv). The flask was flushed with nitrogen and the reaction mixture refluxed overnight under nitrogen atmosphere. Afterwards, the reaction mixture was allowed to cool to room temperature, diluted with additional benzene (80 mL), and washed sequentially with 10% sodium carbonate (3 x 80 mL), water (80 mL), and brine (80 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford bis(2,2,2-trifluoroethyl) malonate (**17**) (7.19 g, 26.8 mmol, 35%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (q, 4 H, J = 8.3 Hz, CH_2-CF_3), 3.60 (s, 2 H, CH_2-$(CO)_2$);
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 122.5 (q, $J_{C\text{-}F}$ = 277 Hz), 61.1 (q, $J_{C\text{-}F}$ = 37 Hz), 40.0;
^{19}F NMR (376 MHz, $CDCl_3$) δ -74.11 (t, J = 8.3 Hz);

The characterization data correspond to the reported values.[1]

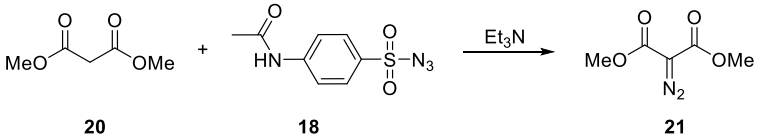
Bis(2,2,2-trifluoroethyl) 2-diazomalonate (19)



Bis(2,2,2-trifluoroethyl) malonate (**17**) (5.00 g, 18.7 mmol, 1 equiv), triethylamine (2.84 mL, 20.5 mmol, 1.1 equiv) and 4-acetamidobenzenesulfonyl azide (**18**) (4.93 g, 20.5 mmol, 1.1 equiv) were dissolved in acetonitrile (180 mL) at room temperature. After stirring the resulting mixture overnight, the suspension was filtered through a plug of cotton wool and the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane (200 mL), filtered through a plug of cotton wool, and partitioned between dichloromethane and water (200 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and dried under vacuum. Filtration through a plug of silica (AcOEt/hexane 1/1 + 1% NEt_3, 500 mL) afforded bis(2,2,2-trifluoroethyl) 2-diazomalonate (**19**) (5.44 g, 18.5 mmol, 99% yield) as a yellow oil which was not further purified.

R_f 0.67 (hexane/ethyl acetate 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (q, 4 H, J = 8.2 Hz, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 60.9 (q, $J_{C\text{-}F}$ = 37 Hz)[2];
IR 2985 (w), 2154 (m), 1777 (s), 1715 (m), 1417 (m), 1357 (m), 1280 (s), 1168 (s), 1102 (s);
HRMS (ESI) calcd for $C_7H_4F_6N_2NaO_4^+$ $[M+Na]^+$ 316.9967; found 316.9972.

Dimethyl 2-diazomalonate (21)



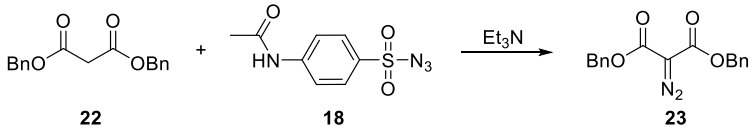
Dimethyl malonate (**20**) (3.20 g, 24.2 mmol, 1 equiv), triethylamine (5.00 mL, 36.1 mmol, 1.5 equiv) and 4-acetamidobenzenesulfonyl azide (**18**) (6.00 g, 25.0 mmol, 1 equiv) were dissolved in acetonitrile (65.0 mL) at

[1] J. M. Takacs, Z. Xu, X.-T. Jiang, A. P. Leonov, G. C. Theriot, *Org. Lett.* **2002**, *4*, 3843.
[2] The diazo carbon could not be detected.

room temperature. After stirring the resulting mixture overnight, the suspension was filtered through a plug of cotton wool and the solvent was removed under reduced pressure. The crude was partitioned between dichloromethane (75 mL) and water (75 mL) and filtered through a plug of cotton wool. The two layers were separated and the aqueous layer was extracted with dichloromethane (75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Filtration over a plug of silica (ethyl acetate/hexane 1/1, 150 mL)) afforded dimethyl 2-diazomalonate (**21**) (3.60 g, 22.8 mmol, 94% yield) as pale yellow crystals.
R_f 0.32 (PET/Diethyl ether 1/1);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 1 H, *OCH_3*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 52.4.[3]

The ^{1}H NMR correspond to the reported values.[4]

Dibenzyl 2-diazomalonate (23)



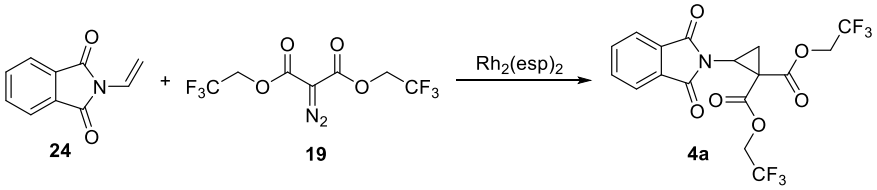
Dibenzyl malonate (**22**) (2.00 g, 7.03 mmol, 1 equiv), triethylamine (1.10 mL, 7.70 mmol, 1.1 equiv) and 4-acetamidobenzenesulfonyl azide (**18**) (1.81 g, 7.53 mmol, 1.1 equiv) were dissolved in acetonitrile (70.0 mL) at room temperature. After stirring the resulting mixture overnight, the suspension was filtered through a plug of cotton wool and the solvent was removed under reduced pressure. The crude was partitioned between dichloromethane (100 mL) and water (100 mL), and filtered through a plug of cotton wool. The two layers were separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and dried under vacuum. Filtration over a plug of silica (Diethyl ether/hexane 1/1, 150 mL) afforded dibenzyl 2-diazomalonate (**23**) (2.03 g, 6.53 mmol, 93% yield) as a yellow solid.

R_f 0.69 (6/4 Hexane/AcOEt);
Mp 48.2 – 51.1 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 10 H, *Ar*), 5.28 (s, 4 H, *CH_2*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 135.4, 128.8, 128.6, 128.4, 67.2, 41.7;
IR 3064 (w), 3035 (w), 2950 (w), 2888 (w), 2140 (s), 1756 (s), 1732 (s), 1692 (m), 1456 (w), 1385 (m), 1315 (s), 1268 (m), 1087 (s).
HRMS (ESI) calcd for $C_{17}H_{15}N_2O_4^+$ $[M+H]^+$ 311.1026; found 311.1016.

[3] The diazo carbon could not be detected.
[4] P. Wyatt, A. Hudson, J. Charmant, A. G. Orpen, H. Phetmung, *Org. Biomol. Chem.* **2006**, *4*, 2218.

3. Synthesis of Aminocyclopropanes

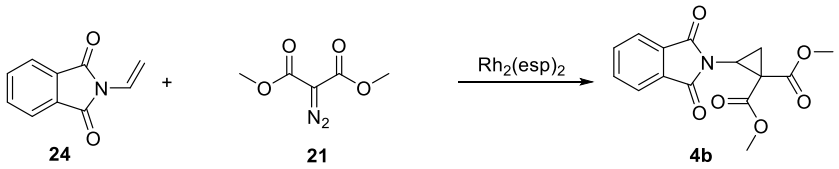
Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4a)



Following a modified procedure,[5] a solution of bis(2,2,2-trifluoroethyl) 2-diazomalonate (**19**) (1.0 g, 3.4 mmol, 1.1 equiv) in dichloromethane (4.0 mL) was added dropwise over 5 minutes to a solution of 2-vinylisoindoline-1,3-dione (**24**) (540 mg, 3.1 mmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (4.7 mg, 6.2 µmol, 0.2 mol %) in dichloromethane (6.0 mL) at 0 °C. After stirring the resulting mixture overnight at room temperature, the solution was concentrated under reduced pressure. Purification by silica gel chromatography (hexane/AcOEt 95/5 to 75/25) afforded bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4a**) (1.3 g, 3.0 mmol, 97% yield) as a colorless solid.

R_f 0.61 (hexane/ethyl acetate 6/4);
Mp 76.3 – 78.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.82 (m, 2 H, *Phth*), 7.77-7.72 (m, 2 H, *Phth*), 4.61 (q, 2 H, *J* = 8.2 Hz, CH_2-CF_3), 4.50-4.30 (m, 2 H, CH_2-CF_3), 3.83 (dd, 1 H, *J* = 8.6, 6.9 Hz, *CH-Phth*), 2.90 (dd, 1 H, *J* = 6.8, 6.8 Hz, CH_2), 2.19 (dd, 1 H, *J* = 8.6, 6.6 Hz, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 166.4, 164.5, 134.7, 131.4, 123.8, 122.7 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 61.7 (q, J_{C-F} = 37 Hz), 61.5 (q, J_{C-F} = 37 Hz), 36.4, 32.7, 21.0;
IR 3495 (w), 3121 (w), 3037 (w), 2981 (w), 1724 (s), 1397 (m), 1277 (s), 1163 (s), 1116 (s), 975 (m);
HRMS (ESI) calcd for $C_{17}F_6H_{12}NO_6^+$ $[M+H]^+$ 440.0563; found 440.0555.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4b) :



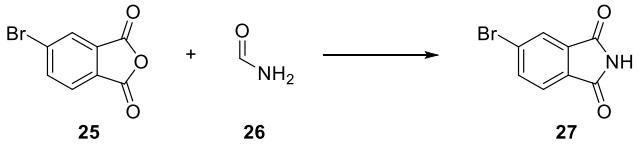
Following a modified procedure,[5] bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (11 mg, 0.014 mmol, 0.1 mol%) is weighted in the glovebox. The flask is closed with a septum and put under N_2 atmosphere. A solution of *N*-vinyl-phthalimide (**24**) (2.5 g, 14 mmol, 1 equiv) in 30 mL of dry dichloromethane is added and the resulting green suspension is cooled down to 0°C with an ice/water bath. A solution of dimethyl-2-diazomalonate (**21**) (2.5 g, 15 mmol, 1.1 equiv) in dichloromethane (20 mL) is added over five minutes. When the addition is complete, the reaction is allowed to warm to room temperature. After 5 h at room temperature, the solvent is removed under reduced pressure and the crude is directly purified by column chromatography (9:1 Hexane/Ethyl Acetate to 7:3 Hexane/Ethyl Acetate) to afford **4b** (3.4 g, 11 mmol, 78% yield) as a colorless solid.

R_f 0.27 (6:4, Hexane/Ethyl acetate);
Mp 124.6-125 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2 H, *Phth*), 7.75 (m, 2 H, *Phth*), 3.85 (s, 3 H, *OMe*), 3.72 (dd, 1 H, *J* = 8.5, 6.6 Hz, *N-CH*), 3.64 (s, 3 H, *OMe*), 2.73 (dd, 1 H, *J* = 6.5, 6.5 Hz, CH_2), 2.06 (dd, 1 H, *J* = 8.5, 6.4 Hz, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 167.8, 166.9, 134.3, 131.4, 123.5, 53.1, 53.0, 34.9, 33.1, 19.6;
IR 2956 (w), 1783 (w), 1727 (s), 1468 (w), 1439 (w), 1399 (m), 1329 (m), 1294 (m), 1222 (m), 1134 (w), 909 (w), 876 (w), 720 (m);
HRMS (ESI) calcd for $C_{15}H_{14}NO_6^+$ $[M+H]^+$ 304.0816; found 304.0804.

[5] F. Gonzalez-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Catal.* **2008**, *350*, 813.

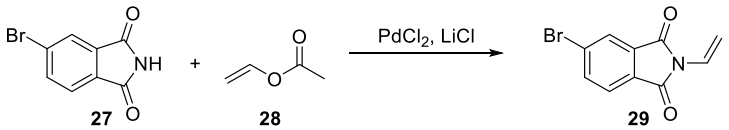
The characterization data correspond to the reported values.[6]

Dimethyl 2-(5-bromo-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4c)



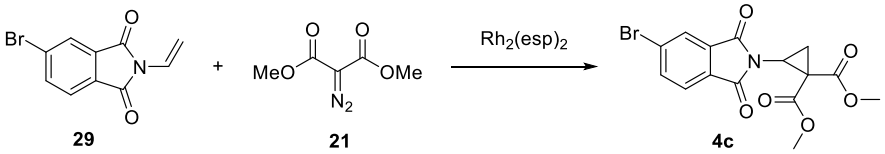
Following a modified procedure[7], 5-bromoisobenzofuran-1,3-dione (**25**) (500 mg, 2.20 mmol, 1 equiv) and formamide (**26**) (8.82 mL, 220 mmol, 100 equiv) were added in a 20 mL microwave vial and sealed with a microwave cap. The mixture was stirred until the product was completely dissolved. The mixture was heated twice at 200 °C for 30 sec with 10 sec pre-stirring, using Biotage Initiator 2.0 microwave reactor. The product crystallized spontaneously as colorless needles in the pale yellow solution. The mixture was cooled to 0 °C and cold water (10 mL) was added into the tube. The solid was filtrated over a filter paper, washed with water (15 mL) and hexane (20 mL) and dried under reduced pressure to afford 5-bromoisoindoline-1,3-dione (**27**) (394 mg, 1.75 mmol, 79% yield) as a colorless solid which was used without further purification.

^{1}H NMR (400 MHz, DMSO) δ 11.4 (s, 1 H, *NH*), 8.04-7.99 (m, 2 H, *Ar*), 7.76 (d, 1 H, *J* = 7.7 Hz, *Ar*).



Following a modified procedure,[8] 5-bromoisoindoline-1,3-dione (**27**) (1.50 g, 6.64 mmol, 1 equiv), palladium(II) chloride (118 mg, 0.664 mmol, 0.1 equiv), lithium chloride (28.0 mg, 0.660 mmol, 0.1 equiv) and vinyl acetate (**28**) (16.5 mL, 178 mmol, 27 equiv) were added in a microwave tube sealed with a microwave cap. The mixture was stirred for 28 hours at 80 °C, and then cooled down to room temperature. The solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate 20/1 to 15/1) afforded 5-bromo-2-vinylisoindoline-1,3-dione (**29**) (1.66 g, 6.59 mmol, 99% yield) as a yellow solid.

R_f 0.47 (hexane/ethyl acetate 9/1);
Mp 74.9-75.6 °C;
^{1}H NMR (400 MHz, DMSO) δ 8.11 (d, 1 H, *J* = 1.4 Hz, *Ar*), 8.07 (dd, 1 H, *J* = 8.0, 1.8 Hz, *Ar*), 7.84 (d, 1 H, *J* = 7.9 Hz, *Ar*), 6.81 (dd, 1 H, *J* = 16.3, 9.8 Hz, *=CH*), 5.93 (d, 1 H, *J* = 16.3 Hz, *=CH*), 5.08 (d, 1 H, *J* = 9.8 Hz, *=CH*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 165.1, 138.6, 133.3, 130.1, 129.5, 127.0, 125.0, 123.7, 105.1;
IR 2927 (w), 2854 (w), 2361 (m), 1728 (s), 1640 (w), 1377 (s), 1303 (w), 1169 (m);
HRMS (ESI) calcd for $C_{10}{}^{79}BrH_7NO_2^+$ $[M+H]^+$ 251.9655; found 251.9656.

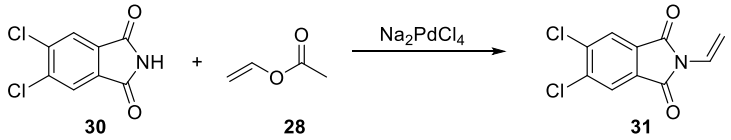


Following a modified procedure,[5] a solution of dimethyl 2-diazomalonate (**21**) (0.05 g, 0.3 mmol, 1.5 equiv) in dichloromethane (0.4 mL) was added dropwise over 5 minutes to a solution of 5-bromo-2-vinylisoindoline-1,3-dione (**29**) (0.05 g, 0.2 mmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (0.3 mg, 0.4 μmol, 0.2 mol %) in dichloromethane (0.6 mL) at 0 °C. After stirring the resulting mixture overnight at room temperature, the solution was concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate 75/25 to 70/30) afforded dimethyl 2-(5-bromo-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4c**) (0.08 g, 0.2 mmol, 100%) as a colorless oil.

[6] F. de Nanteuil, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 12075-12079.
[7] K. Kacprzak, *Synth. Commun.* **2003**, *33*, 1499-1507.
[8] N. Baret, J.-P. Dulcere, J. Rodriguez, J.-M. Pons, R. Faure, *Eur. J. Org. Chem.* **2000**, *2000*, 1507-1516.

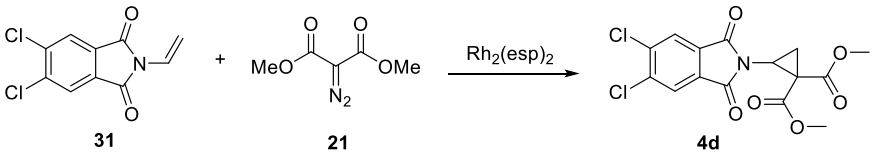
R_f 0.30 (hexane/ethyl acetate 3/1);
Mp 114.8 – 117.5 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.95 (m, 1 H, *Ar*), 7.86 (dd, 1 H, *J* = 7.9, 1.6 Hz, *Ar*), 7.70 (d, 1 H, *J* = 7.9 Hz, *Ar*), 3.82 (s, 3 H, *Me-O*), 3.70-3.64 (m, 1 H, *CH-NPhth*), 3.62 (s, 3 H, *Me-O*), 2.66 (dd, 1 H, *J* = 6.5, 6.5 Hz, *CH_2*), 2.06-2.01 (m, 1 H, *CH_2*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.0, 167.0, 166.5, 137.4, 133.1, 130.0, 129.4, 126.9, 124.9, 53.2, 53.0, 34.9, 33.1, 19.6;
IR 2956 (w), 2855 (w), 2361 (w), 1782 (w), 1730 (s), 1605 (w), 1439 (w), 1397 (m), 1331 (m), 1295 (w), 1223 (m), 1134 (w);
HRMS (ESI) calcd for $C_{15}{}^{79}BrH_{13}NO_6^+$ $[M+H]^+$ 381.9921; found 381.9920.

Dimethyl 2-(5,6-dichloro-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4d)



Following a modified procedure,[8] Na_2PdCl_4 (27.0 mg, 0.0930 mmol, 2 mol%) was added to a stirred solution of 4,5-dichlorophthalimide (**30**) (1.00 g, 4.63 mmol, 1.00 equiv) in vinyl acetate (**28**) (11.5 mL, 124 mmol, 26.8 equiv), and the mixture was heated under reflux for 48 h. After solvent evaporation, the crude was purified by Biotage (SNAP Cartridge KP-Sil 25 g, 8:2 Hexane/AcOEt) to obtain5,6-dichloro-2-vinylisoindoline-1,3-dione (**31**) (1.12 g, 4.63 mmol, 46% yield) as a yellow solid.

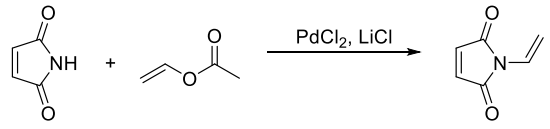
R_f 0.53 (6:4 Hexane/AcoEt).
Mp 164.7 – 166.6 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2 H, *Ar*), 6.84 (dd, 1 H, *J* = 16.4, 9.8 Hz, *=CH*), 6.09 (dd, 1 H, *J* = 16.4, 0.3 Hz, *=CH*), 5.10 (dd, 1 H, *J* = 9.8, 0.3 Hz, *=CH*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 139.7, 130.8, 125.8, 123.7, 105.6.
IR 3065 (w), 3034 (w), 2952 (w), 1726 (s), 1392 (m), 1322 (m), 1288 (m), 1217 (m), 1194 (m), 1131 (m).
HRMS (APPI ionization) calcd for $C_{10}{}^{35}Cl_2H_6NO_2^+$ $[M+H]^+$ 241.9770; found 241.9771.



Following a modified procedure,[5] a solution of dimethyl 2-diazomalonate (**21**) (0.70 g, 4.4 mmol, 1.5 equiv) in dichloromethane (8.0 mL) was added dropwise over 5 minutes to a solution of 5,6-dichloro-2-vinylisoindoline-1,3-dione (**31**) (72 mg, 3.0 mmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (4.5 mg, 5.9 µmol, 0.2 mol %) in dichloromethane (4.0 mL) at 0 °C. After stirring the resulting mixture overnight at room temperature, the solution was concentrated under reduced pressure. Purification by Biotage (SNAP cartridge KP-Sil 25 g, hexane/AcOEt 95/5 to 60/40) afforded dimethyl 2-(5,6-dichloro-1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4d**) (0.81 g, 2.2 mmol, 74% yield) as a colorless solid.

R_f 0.27 (hexane/ethyl acetate 8/2);
Mp 145.9 – 148.1 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2 H, *Ar*), 3.82 (s, 3 H, *Me-O*), 3.66 (dd, 1 H, *J* = 8.5, 6.7 Hz, *CH-Phth*), 3.63 (s, 3 H, *Me-O*), 2.64 (dd, 1 H, *J* = 6.5. 6.5 Hz, *CH_2*), 2.07-2.01 (m, 1 H, *CH_2*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.1, 166.0, 139.5, 130.6, 125.7, 53.3, 53.2, 35.0, 33.1, 19.8;
IR 3096 (w), 3033 (w), 2955 (w), 2851 (w), 1787 (m), 1725 (s), 1438 (m), 1398 (s), 1308 (m), 1222 (m), 1134 (m);
HRMS (ESI) calcd for $C_{15}{}^{35}Cl_2H_{12}NO_6^+$ $[M+H]^+$ 372.0036; found 372.0022.

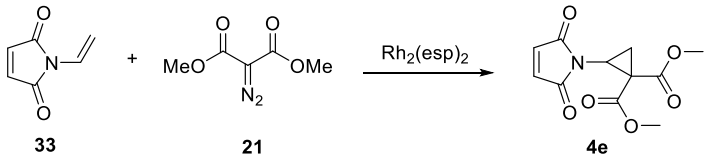
Dimethyl 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)cyclopropane-1,1-dicarboxylate (4e)



32 **28** **33**

Following a modified procedure,[8] maleimide (**32**) (1.30 g, 13.4 mmol, 1 equiv), palladium (II) chloride (0.237 g, 1.34 mmol, 0.1 equiv), lithium chloride (57.0 mg, 1.34 mmol, 0.1 equiv) and vinyl acetate (**28**) (33.2 mL, 359 mmol, 27 equiv) were added in a microwave tube sealed with a microwave cap. After stirring at 80 °C for 23 h, the resulting mixture was cooled down to room temperature. Purification by Biotage (SNAP cartridge KP-Sil 50 g, hexane/AcOEt 93/7 to 40/60) afforded 1-vinyl-1*H*-pyrrole-2,5-dione (**33**) (1.74 g, 14.1 mmol, quantitative) as a bright yellow oil.

R_f 0.54 (hexane/ethyl acetate 7/3);
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 2 H, *CH-C=O*), 6.67 (dd, 1 H, *J* = 16.4, 9.8 Hz, *CH-N*), 5.87 (d, 1 H, *J* = 16.3 Hz, *=CH$_2$*), 4.94 (d, 1 H, *J* = 9.8 Hz, *=CH$_2$*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 134.5, 123.1, 103.4;
IR 3087 (w), 2359 (w), 2113 (w), 1716 (s), 1641 (m), 1384 (s), 1307 (w), 1221 (w), 1130 (w), 896 (w), 845 (m);
HRMS (APPI) calcd for $C_6H_5NO_2$ [M^+] 123.0320; found 123.0323.

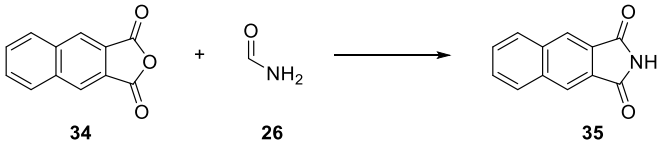


33 **21** **4e**

Following a modified procedure,[5] a solution of dimethyl 2-diazomalonate (**21**) (96 mg, 0.61 mmol, 1.5 equiv) in dichloromethane (1.0 mL) was added dropwise over 5 minutes to a solution of 1-vinyl-1*H*-pyrrole-2,5-dione (**33**) (50. mg, 0.41 mmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (0.7 mg, 0.9 µmol, 0.2 mol %) in dichloromethane (2.0 mL) at 0 °C. The resulting mixture was stirred for 5 hours at room temperature and finally concentrated under reduced pressure. Purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 95/5 to 70/30) afforded dimethyl 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)cyclopropane-1,1-dicarboxylate (**4e**) (66.9 mg, 0.264 mmol, 65% yield) as a colorless oil.

R_f 0.38 (hexane/ethyl acetate 6/4);
Mp 78.4-80.7 °C ;
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 2 H, *CH-C=O*), 3.79 (s, 3 H, *Me-O*), 3.66 (s, 3 H, *Me-O*), 3.56-3.51 (m, 1 H, *CH-N*), 2.56 (dd, 1 H, *J* = 6.4, 6.5 Hz, *CH$_2$*), 1.96-1.91 (m, 1 H, *CH$_2$*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.4, 167.0, 134.1, 53.1, 53.0, 34.3, 32.9, 19.3;
IR 2363 (w), 1727 (s), 1437 (w), 1332 (w), 1296 (w), 1220 (w), 1135 (w);
HRMS (ESI) calcd for $C_{11}H_{11}NNaO_6^+$ [M+Na]$^+$ 276.0479; found 276.0485.

Dimethyl 2-(1,3-dioxo-1*H*-benzo[*f*]isoindol-2(3*H*)-yl)cyclopropane-1,1-dicarboxylate (4f)

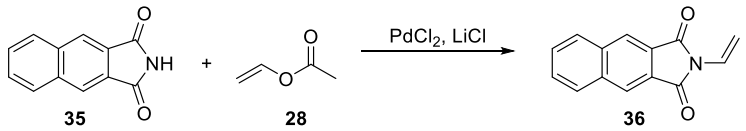


34 **26** **35**

Following a modified procedure,[7] naphtho[2,3-*c*]furan-1,3-dione (**34**) (500 mg, 2.52 mmol, 1 equiv) and formamide (**26**) (10.0 mL, 252 mmol, 100 equiv) were added in a 20 mL microwave vial and sealed with a microwave cap. The mixture was stirred until the product was completely dissolved. The mixture was heated twice at 200 °C for 30 sec with 10 sec pre-stirring, using Biotage Initiator 2.0 microwave reactor. The mixture was cooled to 0 °C and cold water (10 mL) was added into the tube. The solid was filtrated over a filter paper, washed with water (15 mL) and hexane (20 mL) and dried under reduced pressure to afford 1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (**35**) (432 mg, 2.19 mmol, 87% yield) as a beige solid which was used without further purification.

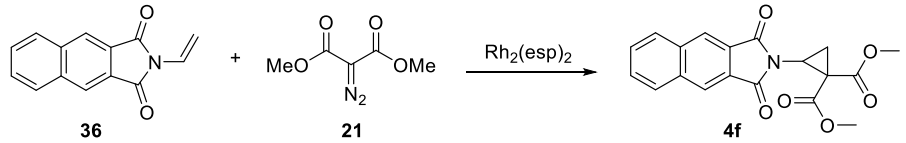
R_f 0.44 (Hexane/AcOEt 6/4);

Mp 267 °C decomp.;
^{1}H NMR (400 MHz, DMSO) δ 11.5 (s, 1 H, *NH*), 8.45 (s, 2 H, *Ar*), 8.26 (dd, 2 H, *J* = 6.1, 3.3 Hz, *Ar*), 7.76 (dd, 2 H, *J* = 6.6, 3.3 Hz, *Ar*);
^{13}C NMR (101 MHz, DMSO) δ 168.9, 135.1, 130.2, 129.1, 128.7, 124.2;
IR 3224 (w), 3071 (w), 2925 (w), 2852 (w), 1707 (s), 1447 (w), 1316 (m), 1113 (m), 1012 (w), 905 (w);
HRMS (ESI) calcd for $C_{12}H_7NNaO_2^+$ $[M+Na]^+$ 220.0369; found 220.0380.



Following a modified procedure,[8] **Error! Bookmark not defined.** 1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (**35**) (1.70 g, 8.62 mmol, 1 equiv), palladium(II) chloride (0.150 g, 0.860 mmol, 0.1 equiv), lithium chloride (0.0370 g, 0.860 mmol, 0.1 equiv) and vinyl acetate (**28**) (21.4 mL, 231 mmol, 27 equiv) were added in a microwave tube sealed with a microwave cap. After stirring for 31 h at 80 °C, the resulting mixture was cooled down to room temperature. Purification by silica gel chromatography (hexane/ethyl acetate 17/1 to 10/1) afforded 2-vinyl-1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (**36**) (1.26 g, 5.66 mmol, 66% yield) as a colorless solid.

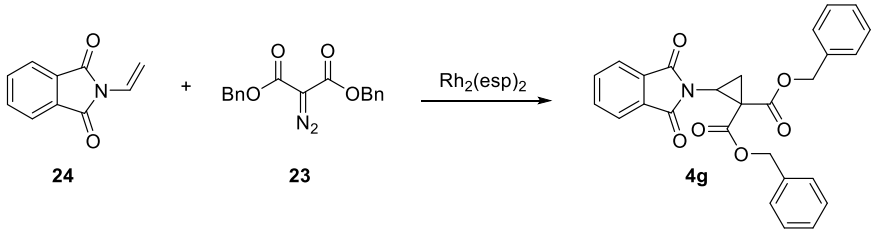
R_f 0.51 (hexane/ethyl acetate 8/2);
Mp 201.9 – 202.8 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2 H, *Ar*), 8.07 (dd, 2 H, *J* = 6.1, 3.4 Hz, *Ar*), 7.72 (dd, 2 H, *J* = 6.3, 3.3 Hz, *Ar*), 6.97 (dd, 1 H, *J* = 16.4, 9.7 Hz, *=CH*), 6.20 (d, 1 H, *J* = 16.4 Hz, *=CH*), 5.12 (d, 1 H, *J* = 9.9 Hz, *=CH*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 135.9, 130.5, 129.6, 127.3, 125.4, 124.3, 105.3;
IR 3029 (w), 2949 (w), 1704 (s), 1379 (w), 1303 (w), 1218 (w), 1139 (m), 1012 (w), 975 (w), 882 (w);
HRMS (ESI) calcd for $C_{14}H_{10}NO_2^+$ $[M+H]^+$ 224.0706; found 224.0710.



Following a modified procedure,[5] a solution of dimethyl 2-diazomalonate (**21**) (0.20 g, 1.3 mmol, 1.5 equiv) in dichloromethane (2.0 mL) was added dropwise over 5 minutes to a solution of 2-vinyl-1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (**36**) (0.19 g, 0.85 mmol, 1 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (1.3 mg, 1.7 µmol, 0.2 mol %) in dichloromethane (3.0 mL) at 0 °C. After stirring the resulting mixture for 26 hours at room temperature the solution was concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate 8/2 to 6/4) afforded dimethyl 2-(1,3-dioxo-1*H*-benzo[*f*]isoindol-2(3*H*)-yl)cyclopropane-1,1-dicarboxylate (**4f**) (0.28 g, 0.80 mmol, 94% yield) as a colorless solid.

R_f 0.39 (hexane/ethyl acetate 6/4);
Mp 165.6 – 167.5 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2 H, *Ar*), 8.06 (dd, 2 H, *J* = 6.0, 3.3 Hz, *Ar*), 7.70 (dd, 2 H, *J* = 6.3, 3.3 Hz, *Ar*), 3.84 (s, 3 H, *Me-O*), 3.77 (dd, 1 H, *J* = 8.5, 6.7 Hz, *CH-N*), 3.60 (s, 3 H, *Me-O*), 2.78 (dd, 1 H, *J* = 6.5, 6.5 Hz, *CH_2*), 2.08 (dd, 1 H, *J* = 8.5, 6.4, *CH_2*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 167.7, 167.0, 135.7, 130.4, 129.4, 127.2, 125.1, 53.2, 53.1, 35.3, 33.3, 19.8;
IR 3034 (w), 2955 (w), 1720 (s), 1439 (m), 1393 (m), 1332 (m), 1292 (m), 1222 (m), 1134 (m), 912 (m);
HRMS (ESI) calcd for $C_{19}H_{16}NO_6^+$ $[M+H]^+$ 354.0972; found 354.0968.

Dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (4g)

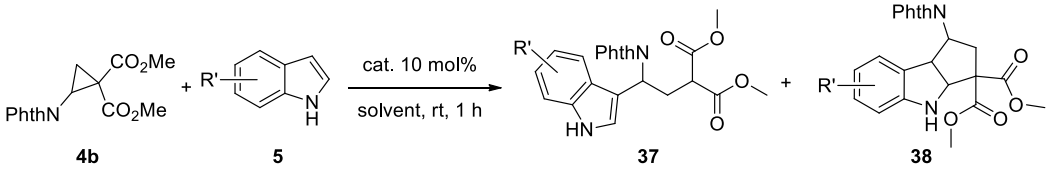


Following a modified procedure,[5] a solution of dibenzyl 2-diazomalonate (**23**) (2.0 g, 6.5 mmol, 1.10 equiv) in dichloromethane (12.0 mL) was added dropwise over 5 minutes to a solution of 2-vinylisoindoline-1,3-dione (**24**) (1.0 g, 5.9 mmol, 1.00 equiv) and bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (9.0 mg, 0.012 mmol, 0.2 mol %) in dichloromethane (10.0 mL) at 0 °C. After stirring the resulting mixture overnight at room temperature, the solution was concentrated under reduced pressure. Purification by Biotage (SNAP cartridge KP-Sil 50 g, hexane/AcOEt 90/10 to 20/80) afforded dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4g**) (0.91 g, 2.0 mmol, 34% yield) as a colorless oil.

R_f 0.60 (hexane/ethyl acetate 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (m, 2 H, *Phth*), 7.72-7.67 (m, 2 H, *Phth*), 7.36-7.28 (m, 5 H, *Ar*), 7.20-7.13 (m, 5 H, *Ar*), 5.29-5.19 (m, 2 H, *CH_2-Ph*), 5.04-4.95 (m, 2 H, *CH_2-Ph*), 3.73 (dd, 1 H, *J* = 8.5, 6.7 Hz, *CH-Phth*), 2.79 (dd, 1 H, *J* = 6.5, 6.5 Hz, *CH_2*), 2.02 (m, 1 H, *CH_2*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.8, 166.2, 135.4, 135.1, 134.3, 131.5, 128.7, 128.4, 128.4, 128.3, 128.1, 123.6, 67.8, 67.7, 35.3, 33.5, 19.8;[9]
IR 3063 (w), 3034 (w), 2954 (w), 1722 (s), 1388 (m), 1319 (m), 1285 (m), 1215 (m), 1128 (m), 980 (w);
HRMS (ESI) calcd for $C_{27}H_{21}NNaO_6^+$ $[M+Na]^+$ 478.1261; found 478.1262.

[9] One of the aromatic carbons is overlapping.

4. 1st screening of catalysts



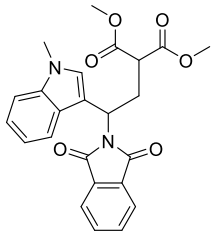
4b **5** **37** **38**

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4b**) (10 mg, 0.034 mmol, 1 equiv) and indole **5** (0.051 mmol, 1.5 equiv) were dissolved in solvent (0.20 mL) and added to the Lewis acid (3.4 µmol, 0.1 equiv) in a sealed tube closed with a septum. The mixture was stirred at room temperature for 1 hour. The mixture was then filtered through a short plug of silica gel (AcOEt/hexane 1/1, deactivated with 2% NEt_3, 1 mL) and concentrated under reduced pressure to remove volatiles. The crude was analyzed by ^{1}H NMR.

Entry[a]	R'	LA	solvent	37/38[b]	dr[b]
1	1-Me	$Cu(OTf)_2$	DCM	1:19	1.2:1
2	1-Me	$FeCl_3/Al_2O_3$	DCM	2:1	3.5:1
3	1-Me	$Sn(OTf)_2$	DCM	1:1.4	6:1
4	1-Me	$SnCl_4/SiO_2$	DCM	2:1	>20:1
5	1-Me	$In(OTf)_3$	DCM	1:1.3	3.5:1
6	1-Me	$Sc(OTf)_3$	DCM	>20:1	nd
7	H	$Sc(OTf)_3$	DCM	>20:1	nd
8	5-Cl	$Sc(OTf)_3$	DCM	complex mixture	nd
9	5-Cl	$Sc(OTf)_3$	$MeNO_2$	1:0.6[c]	nd

[a]Reaction conditions (unless specified otherwise): **4b** (0.034 mmol), indole (0.051 mmol), cat. (3.4 µmol), solvent (0.2 mL), rt, 1 h. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]The cyclized product was not isolated. The NMR ratio was determined by analogy with the cyclized product **38**.

Dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1H-indol-3-yl)ethyl)malonate (37)

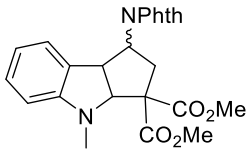


37

R_f 0.40 (Hexane/AcOEt 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2 H, Phth), 7.75-7.71 (m, 1 H, ArH), 7.71-7.65 (m, 2 H, Phth), 7.41 (s, 1 H, ArH), 7.32-7.27 (m, 1 H, ArH), 7.26-7.19 (m, 1 H, ArH), 7.16-7.09 (m, 1 H, ArH), 5.79 (dd, 1 H, *J* = 9.7, 6.5 Hz, N-C-H), 3.80 (s, 3 H, Me), 3.76 (s, 3 H, Me), 3.68 (s, 3 H, Me), 3.53-3.47 (m, 1 H, CH), 3.30-3.20 (m, 1 H, CH_2), 3.09-3.00 (m, 1 H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 169.2, 168.1, 136.5, 133.9, 131.9, 128.7, 126.9, 123.2, 121.9, 119.6, 119.0, 111.6, 109.3, 52.8, 52.7, 49.6, 44.5, 33.0, 30.9.

IR 2953 (w), 2365 (w), 1753 (m), 1736 (s), 1711 (s), 1614 (w), 1543 (w), 1469 (w), 1436 (w), 1383 (m), 1355 (w), 1329 (m), 1275 (w), 1158 (w), 913 (w), 739 (m), 728 (s);
HRMS (ESI) calcd for $C_{24}H_{23}N_2O_6^+$ $[M+H]^+$ 435.1551; found 435.1548.

Dimethyl-1-(1,3-dioxoisoindolin-2-yl)-4-methyl-1,3a,4,8b-tetrahydrocyclopenta[b]indole-3,3(2H)-dicarboxylate (38)



38

Diastereomer 1:

R*f* 0.50 (Hexane/AcOEt 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2 H, *Phth*), 7.78-7.72 (m, 2 H, *Phth*), 7.10-7.04 (m, 1 H, Ar*H*), 6.87-6.83 (m, 1 H, Ar*H*), 6.59 (td, 1 H, *J* = 7.4, 0.9 Hz, Ar*H*), 6.41 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 5.26 (dt, 1 H, *J* = 11.3, 7.4 Hz, C*H*), 4.96 (d, 1 H, *J* = 11.2 Hz, C*H*), 4.44 (dd, 1 H, *J* = 11.0, 8.1 Hz, C*H*), 3.80 (s, 3 H, CH_3), 3.58 (s, 3 H, CH_3), 2.92 (s, 3 H, CH_3), 2.79 (dd, 1 H, *J* = 12.9, 11.3 Hz, CH_2), 2.57 (dd, 1 H, *J* = 12.9, 7.0 Hz, CH_2);
^{13}C NMR (101 MHz, CDCl3) δ 171.5, 170.1, 168.2, 152.0, 134.3, 131.9, 129.9, 128.5, 123.5, 123.3, 118.3, 107.5, 74.8, 65.4, 56.9, 53.0, 52.5, 49.1, 36.2, 35.9;
IR 2954 (w), 2257 (w), 1731 (s), 1710 (s), 1378 (m), 1256 (m), 719 (s);
HRMS (ESI) calcd for $C_{24}H_{23}N_2O_6^+$ $[M+H]^+$ 435.1551; found 435.1567.

Diastereomer 2:

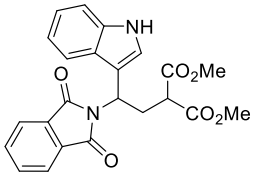
R*f* 0.50 (Hexane/AcOEt 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.56 (m, 4 H, *Phth*), 7.08-7.01 (m, 1 H, Ar*H*), 6.52 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 6.45-6.41 (m, 1 H, Ar*H*), 6.32 (td, 1 H, *J* = 7.4, 0.7 Hz, Ar*H*), 4.76-4.66 (m, 1 H, C*H*), 4.64 (dd, 1 H, *J* = 8.1, 0.8 Hz, C*H*), 4.27 (t, 1 H, *J* = 8.9 Hz, C*H*), 3.98 (t, 1 H, *J* = 13.4 Hz, CH_2), 3.84 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3), 2.34 (dd, 1 H, *J* = 13.0, 6.4 Hz, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 168.8, 155.4, 134.3 (br), 128.9, 127.5, 124.2, 123.3, 118.6, 109.4, 76.1, 64.0, 53.7, 53.3, 52.7, 48.5, 38.8, 30.8;[10]
IR 2955 (w), 2924 (w), 1732 (s), 1714 (s), 1375 (m), 1268 (w), 1130 (w), 719 (s);
HRMS (ESI) calcd for $C_{24}H_{23}N_2O_6^+$ $[M+H]^+$ 435.1551; found 435.1533.

[10] Some phthalimide peaks could not be resolved.

5. Tuning of the aminocyclopropane structure (Scheme 3).

Cyclopropane, (0.034 mmol, 1 equiv) and indole (**5a**) (6.0 mg, 0.051 mmol, 1.5 equiv) were dissolved in nitromethane (0.20 mL) and added to the catalyst (3.4 µmol, 0.100 equiv) in a tube sealed with a septum. The mixture was stirred at room temperature for 1 hour. The mixture was then filtered through a short plug of silica gel (AcOEt/hexane 1/1, deactivated with 2% NEt_3, 1 mL) and concentrated under reduced pressure to remove volatiles and the crude was analyzed by ^{1}H NMR.

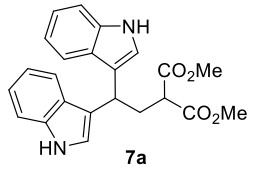
Dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (6ba)



6ba

R$_f$ 0.19 (hexane/AcOEt 6/4);
Mp 78.2 – 82.9 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H, N*H*), 7.80-7.73 (m, 2 H, *Phth*), 7.71 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 7.68-7.62 (m, 2 H, *Phth*), 7.50 (d, 1 H, *J* = 1.9 Hz, Ar*H*), 7.34 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.19-7.14 (m, 1 H, Ar*H*), 7.13-7.08 (m, 1 H, Ar*H*), 5.79 (dd, 1 H, *J* = 9.8, 6.4 Hz, PhthN-C*H*), 3.74 (s, 3 H, CH_3), 3.65 (s, 3 H, CH_3), 3.50 (t, 1 H, *J* = 7.4 Hz, C*H*-$(CO)_2$), 3.26 (ddd, 1 H, *J* = 14.2, 9.9, 6.9 Hz, CH_2), 3.09-3.00 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 169.3, 168.2, 135.8, 134.1, 131.8, 126.4, 124.3, 123.3, 122.5, 120.1, 118.9, 113.2, 111.3, 53.0, 52.9, 49.7, 44.6, 30.8;
IR 3403 (w), 2954 (w), 2865 (w), 2363 (w), 2093 (w), 1753 (m), 1733 (s), 1710 (s), 1358 (m); **HRMS** (ESI) calcd for $C_{23}H_{20}N_2NaO_6^+$ $[M+Na]^+$ 443.1214; found 443.1216.

Dimethyl 2-(2,2-di(1H-indol-3-yl)ethyl)malonate (7a)



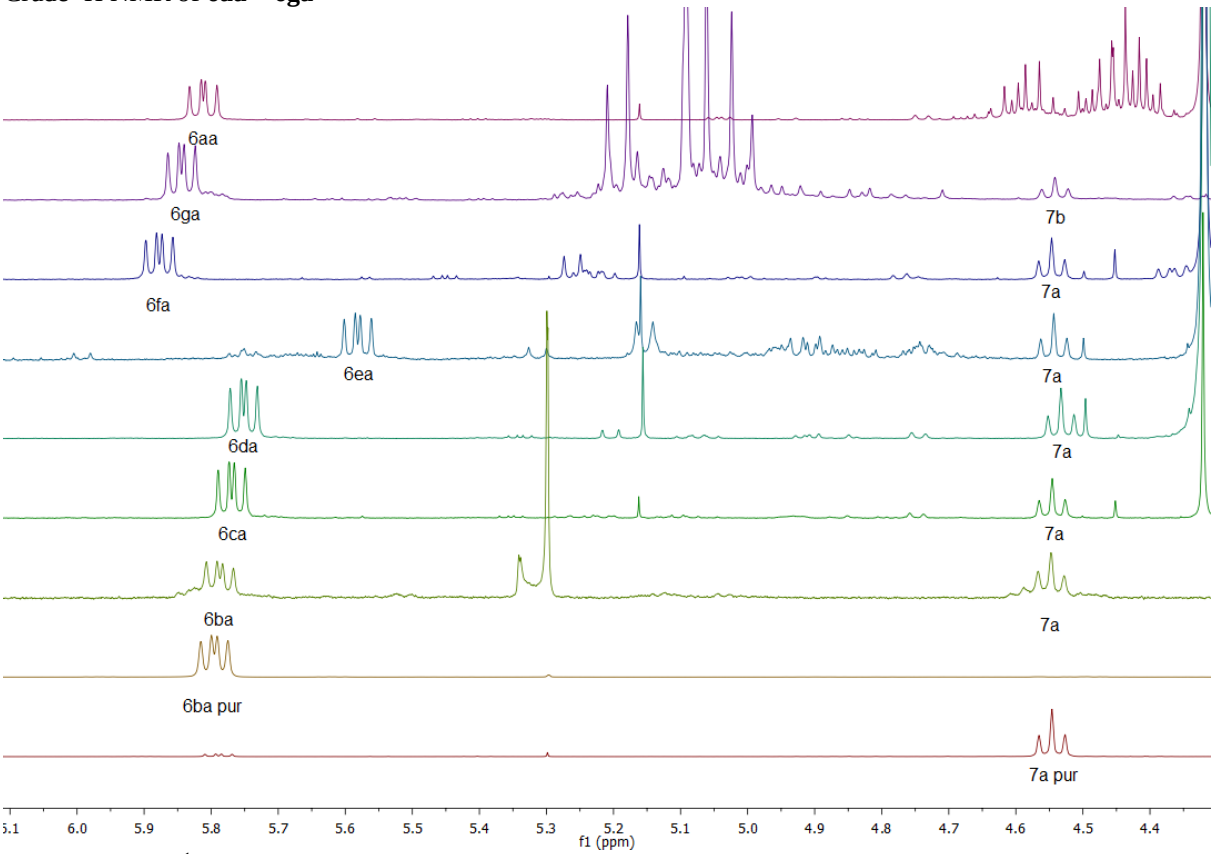
7a

R$_f$ 0.54 (hexane/AcOEt 1/1);
^{1}H NMR (400 MHz, $CDCl_3$)[11] δ 7.97 (s, 2 H, N*H*), 7.63 (d, 2 H, *J* = 7.9 Hz, Ar*H*), 7.36-7.32 (m, 2 H, Ar*H*), 7.19-7.14 (m, 2 H, Ar*H*), 7.07-7.03 (m, 2 H, Ar*H*), 7.02 (d, 2 H, *J* = 1.7 Hz, Ar*H*), 4.55 (t, 1 H, *J* = 7.8 Hz, C*H*), 3.67 (s, 6 H, CH_3), 3.53 (t, 1 H, *J* = 7.4 Hz, C*H*), 2.85 (t, 2 H, *J* = 7.5 Hz, CH_2);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 136.7, 126.9, 122.0, 121.8, 119.7, 119.3, 118.5, 111.1, 52.5, 50.4, 34.5, 32.3;
IR 3414 (m), 3056 (w), 2952 (w), 2865 (w), 2360 (w), 1731 (s), 1458 (m), 1437 (m), 1342 (m), 1269 (m), 1229 (m), 1159 (m);
HRMS (ESI) calcd for $C_{23}H_{22}N_2NaO_4^+$ $[M+Na]^+$ 413.1472; found 413.1468.

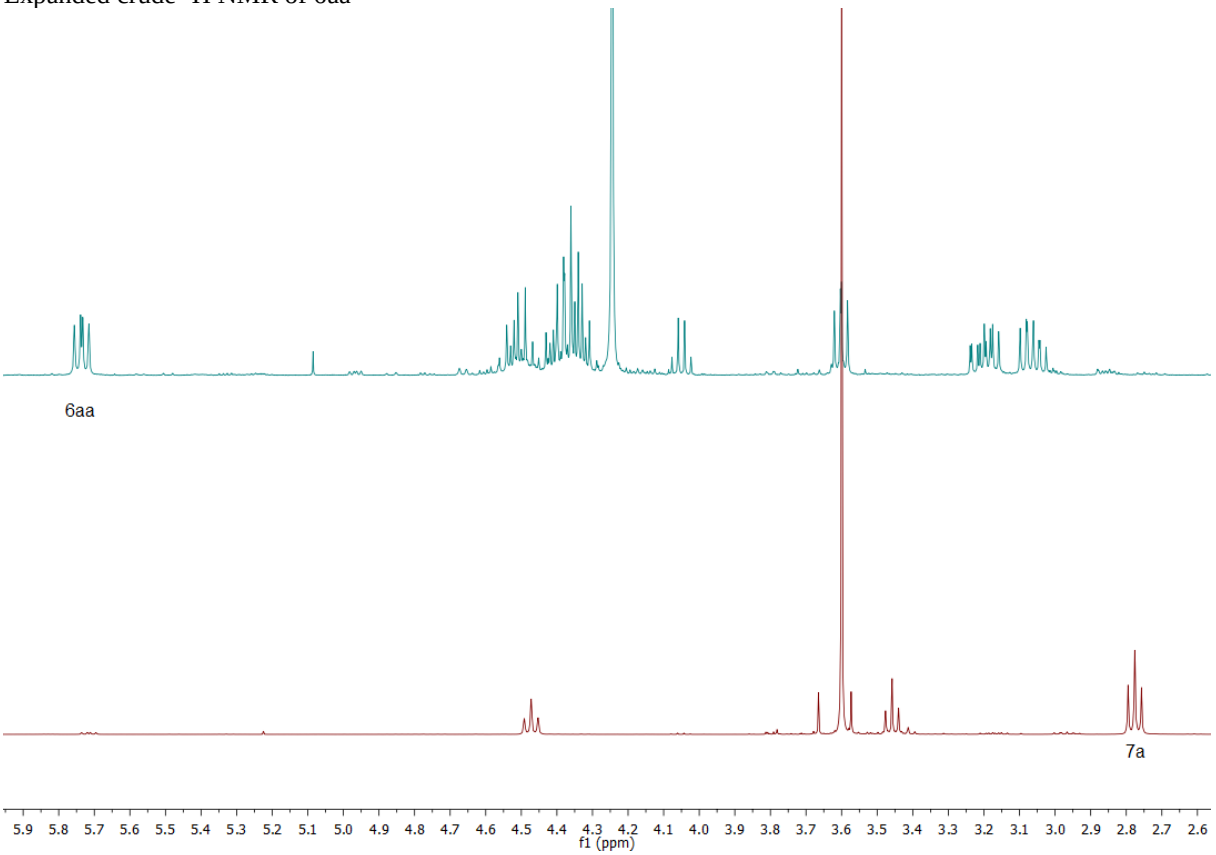
[11] Measured at 268 K.
[12] An impurity is present in approx. 5% in ^{1}H NMR spectrum.

Ratios of Friedel-Crafts products **6** and side product **7a** were obtained by integrating the doublet of doublet at 5.7-5.9 ppm for **6** and the triplet at 4.55 ppm for **7a**.
For **6aa**, absence of **7a** was confirmed by checking the crude at 2.75 ppm.

Crude ^{1}H NMR of **6aa** – **6ga**

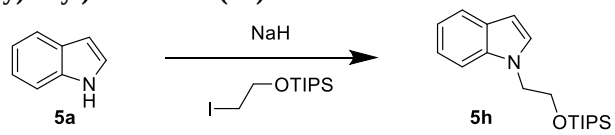


Expanded crude ^{1}H NMR of 6aa



6. Synthesis of indoles

1-(2-((Tri*iso*propylsilyl)oxy)ethyl)-1*H*-indole (5h)

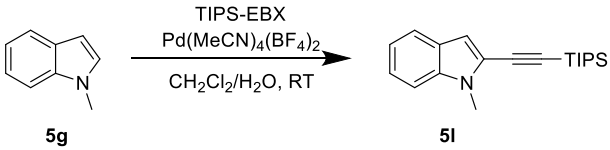


1*H*-indole (**5a**) (0.843 g, 7.20 mmol, 1.2 equiv) was dissolved in N,N-dimethylformamide (6 mL) and NaH (60% in mineral oil, 0.360 g, 9.00 mmol, 1.33 equiv, 1.25 equiv compared to indole) was added at rt under strong stirring and the reaction mixture was stirred for one hour. N,N-Dimethylformamide (18 mL) was added to dissolve the white precipitate and to give a greenish solution. The reaction was cooled to 0 °C and (2-iodoethoxy)triisopropylsilane (1.97 g, 6.00 mmol, 1 equiv) was added dropwise. The reaction was stirred overnight and let to slowly warm up to rt. The reaction was then quenched with water (20 mL) and the reaction mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (10 mL), brine (3x10 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude product was dried under vacuum with stirring. The crude NMR did not show the presence of the alkylating agent. TLC (10:1 hexanes: EtOAc, Rf prod.: 0.7). Purification by flash chromatography (SiO_2, 1% to 10% EtOAc in hexane) gave 1-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indole (**5h**) (1.56 g, 4.91 mmol, 82% yield) as a colorless oil.

R_f: 0.65 (hexanes:EtOAc 10:1);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1 H, ArH), 7.38 (dd, 1 H, *J* = 8.2, 0.8 Hz, ArH), 7.25-7.19 (m, 2H, ArH) 7.13 (m, 1 H, ArH), 6.52 (dd, 1 H, *J* = 3.1, 0.8 Hz, ArH), 4.30 (t, 2 H, *J* = 6.0 Hz, CH_2), 4.04 (t, 2 H, *J* = 5.8 Hz, CH_2), 1.17-0.85 (m, 21 H, TIPS);
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 128.7, 128.6, 121.3, 120.9, 119.2, 109.3, 101.0, 62.8, 48.8, 17.9, 11.9;
IR 3056 (w), 2942 (m), 2891 (m), 2865 (s), 1514 (w), 1464 (s), 1439 (w), 1400 (w), 1387 (w), 1360 (w), 1334 (w), 1317 (m), 1250 (w), 1200 (w), 1115 (s), 1077 (m), 1013 (m), 997 (w), 923 (m), 883 (s), 819 (w);
HRMS (ESI) calcd for $C_{19}H_{32}NOSi^+$ $[M+H]^+$ 318.2248; found 318.2236.

The characterization data correspond to the reported values.[13]

1-Methyl-2-((triisopropylsilyl)ethynyl)-1*H*-indole (5l)



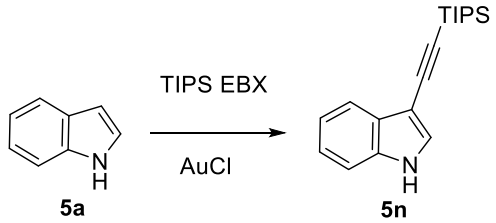
In a 10 mL round bottom-flask, 1-methyl-1*H*-indole (**5g**) (64 µl, 66 mg, 0.50 mmol, 1 equiv) and 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (0.64 g, 1.5 mmol, 3 equiv) were dissolved in DCM (5 mL) under air, then water was added (0.10 mL). Lastly $Pd(MeCN)_4(BF_4)_2$ (4.4 mg, 10 µmol, 2%) was added with strong stirring. The flask was closed and the reaction mixture was stirred overnight, when it became brownish. The solvent was evaporated under reduced pressure. EtOAc (25 mL) was added to the crude product, and the solution was washed with $NaOH_{aq}$ (0.1 M, 25 mL), conc. $NaHCO_3$ (2 x 25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO_2, hexane to hexane/DCM 90/10) gave 1-methyl-2-((triisopropylsilyl)ethynyl)-1*H*-indole (**5l**) (102 mg, 0.33 mmol, 66%) as a pale yellow oil.

R_f: 0.75 (hexanes:EtOAc 10:1);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dt, 1 H, *J* = 8.0, 0.9 Hz, ArH), 7.33-7.28 (m, 2 H, ArH), 7.16 (q, 1 H, *J* = 4 Hz, ArH), 6.86 (s, 1 H, ArH), 3.78 (s, 3 H, Me), 1.30-1.09 (m, 21 H, TIPS);
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1, 127.1, 123.1, 122.3, 121.1, 120.1, 109.4, 107.7, 98.2, 97.8, 30.6, 18.8, 11.4;
IR 3058 (w), 2942 (s), 2891 (m), 2864 (s), 2150 (s), 1463 (s), 1429 (w), 1383 (m), 1364 (m), 1339 (s), 1317 (m), 1238 (m), 1170 (w), 1152 (w), 1073 (w), 1012 (m), 997 (m), 920 (m), 883 (s), 854 (m);
HRMS (ESI) calcd. for $C_{20}H_{30}NSi^+$ $[M+H]^+$ 312.2142; found 312.2147.

[13] G. L. Tolnai, S. Ganss, J. P. Brand, J. Waser, *Org. Lett.* **2013**, *15*, 112.

The characterization data correspond to the reported values.[13]

3-((Tri*iso*-propylsilyl)ethynyl)-*1H*-indole (5n)



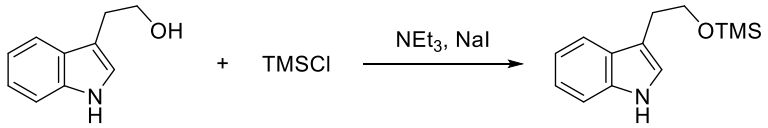
5a **5n**

1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (206 mg, 0.480 mmol, 1.2 equiv) was added to a stirring solution of AuCl (4.6 mg, 0.020 mmol, 0.05 equiv) and *N*-H indole (**5a**) (0.400 mmol, 1.0 equiv) in Et_2O (8 mL) under air. The reaction was sealed and stirred at room temperature for 12 h. Et_2O (10 mL) was added, the organic layer was washed twice with 0.1 M NaOH (15 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (PET/Et_2O 8/2) afforded (**5n**) (102 mg, 0.342 mmol, 86%) as brown solid.

R*f* 0.4 (PET/Et_2O 7/3, UV/Anisaldehyde);
Mp 55-58°C;
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.11 (br s, 1 H; NH), 7.79 (m, 1 H; ArH), 7.40 (d, *J(H,H)*= 2.7 Hz, 1 H; ArH), 7.36 (m, 1 H), 7.26 (m, 2 H; ArH), 1.22 (m, 21 H; TIPS);
^{13}C NMR ($CDCl_3$, 100MHz) δ 135.1, 128.9, 128.3, 123.1, 120.8, 120.1, 111.4, 100.4, 99.3, 92.19, 18.8, 11.5;
IR ν 3407 (m), 3062 (w), 2942 (s), 2891 (m), 2864 (s), 2152 (s), 1620 (w), 1532 (w), 1457 (s), 1416 (m), 1383 (w), 1341 (w), 1325 (m), 1239 (s), 1128 (m), 1071 (m), 996 (m), 910 (m), 883 (s), 774 (s), 742 (s), 676 (s), 658 (s), 628 (s);
HRMS(ESI) calcd for $C_{19}H_{28}NSi^+$ $[M+H]^+$ 298.1991, found 298.2001.

The characterization data correspond to the reported values.[14]

3-(2-((Trimethylsilyl)oxy)ethyl)-1*H*-indole (5o)



39 **40** **5o**

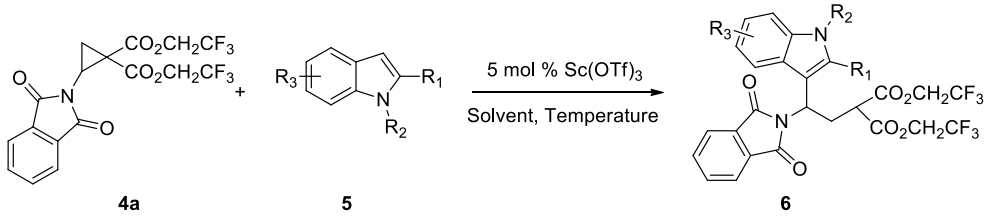
Sodium iodide (581 mg, 3.88 mmol, 1.25 equiv), 2-(1*H*-indol-3-yl)ethanol (**39**) (500 mg, 3.10 mmol, 1 equiv), acetonitrile (5.00 mL) and hexane (5.00 mL) were mixed in a 25 mL flask. Triethylamine (0.537 mL, 3.88 mmol, 1.25 equiv) followed by chlorotrimethylsilane (0.496 mL, 3.88 mmol, 1.25 equiv) were added in one portion with efficient stirring of the bi-phasic mixture. The mixture was then stirred for 1 hour at room temperature. The two immiscible layers were separated with a separatory funnel. The organic layer was filtered through a plug of silica gel (hexane/AcOEt 8/2, deactivated with 2% NEt_3, 30 mL) and concentrated under reduced pressure to afford 3-(2-((trimethylsilyl)oxy)ethyl)-1*H*-indole (**5o**) (131 mg, 0.560 mmol, 18% yield) as a colorless solid. The product was used without further purification.

R_f 0.49 (hexane/ethyl acetate 8/2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1 H, N*H*), 7.63 (dd, 1 H, *J* = 7.9, 0.6 Hz, Ar*H*), 7.38-7.34 (m, 1 H, Ar*H*), 7.23-7.18 (m, 1 H, Ar*H*), 7.16-7.11 (m, 1 H, Ar*H*), 7.05-7.02 (m, 1 H, Ar*H*), 3.87 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.03 (td, 2 H, *J* = 7.7, 0.6 Hz, CH_2), 0.12 (s, 9 H, *TMS*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 127.8, 122.1, 122.0, 119.4, 119.0, 113.1, 111.2, 63.4, 29.1, -0.3;
HRMS (APPI) calcd for $C_{13}H_{20}NOSi^+$ $[M+H]^+$ 234.1309; found 234.1300.

[14] J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem., Int. Ed*. **2009**, *48*, 9346.

7. Scope of the reaction

7.1. General procedures for the synthesis of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1H-indol-3-yl)ethyl)malonates



7.1.1.1. Method **A**

Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate **4a** (0.088 g, 0.20 mmol, 1 equiv) and the corresponding indole (0.22 mmol, 1.1 equiv) were dissolved in diethyl ether (1.2 mL) and added to $Sc(OTf)_3$ (4.9 mg, 10 µmol, 5.0%) in a tube sealed with a septum. The mixture was stirred at room temperature until full conversion was observed by TLC (6:4 Hexane/EtOAc, Anisaldehyde). The mixture was then filtered over a short plug of silica gel (AcOEt/hexane 1/1, 5 mL). The crude was concentrated under reduced pressure to remove volatiles. Purification by Biotage (SNAP cartridge KP-Sil 10 g) afforded the desired product.

7.1.1.2. Method **B**

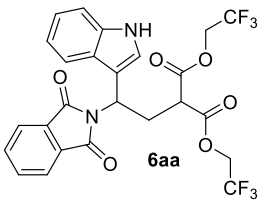
Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate **4a** (0.088 g, 0.20 mmol, 1 equiv) and the corresponding indole (0.22 mmol, 1.1 equiv) were dissolved in diethyl ether (1.2 mL) and added to $Sc(OTf)_3$ (4.9 mg, 10 µmol, 5.0%) in a tube sealed with a septum. The mixture was stirred at 35 °C until full conversion was observed by TLC (6:4 Hexane/EtOAc, Anisaldehyde). The mixture was then filtered over a short plug of silica gel (AcOEt/hexane 1/1, 5 mL). The crude was concentrated under reduced pressure to remove volatiles. Purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt) afforded the desired product.

7.1.1.3. Method **C**

Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate **4a** (0.088 g, 0.20 mmol, 1 equiv) and the corresponding indole (0.22 mmol, 1.1 equiv) were dissolved in toluene (1.2 mL) and added to $Sc(OTf)_3$ (4.9 mg, 10 µmol, 5.0%) in a tube sealed with a septum. The mixture was stirred at 60 °C until full conversion was observed by TLC (6:4 Hexane/EtOAc, Anisaldehyde). The mixture was then filtered over a short plug of silica gel (AcOEt/hexane 1/1, 5 mL). The crude was concentrated under reduced pressure to remove volatiles. Purification by Biotage (SNAP cartridge KP-Sil) afforded the desired product.

7.2. Friedel Crafts products : Indoles

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (6aa)



Following method **A** and starting from 1*H*-indole (**5a**) (26 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**6aa**) (95 mg, 0.17 mmol, 85% yield) was obtained as a colorless solid after a reaction time of 1 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 98/2 to 75/25 + 1% AcOH).

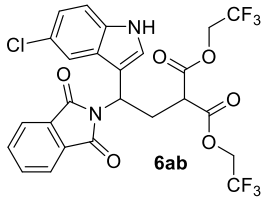
Larger scale procedure:

Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4a**) (1.40 g, 3.19 mmol, 1 equiv) and indole (**5a**) (411 mg, 3.51 mmol, 1.1 equiv) were dissolved in diethyl ether (19 mL) and added to

$Sc(OTf)_3$ (78.0 mg, 159 µmol, 5.0 mol%) in a one neck flask sealed with a septum under nitrogen atmosphere. The mixture was stirred at room temperature for 50 minutes, when full conversion was observed by TLC (6:4 Hexane/EtOAc, Anisaldehyde). The mixture was then filtered over a short plug of silica gel (AcOEt/hexane 1/1, 5 mL). The crude was concentrated under reduced pressure to remove volatiles. Purification by column chromatography (silica gel, hexane:AcOEt 95:5 to 70:30) afforded bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**6aa**) (1.54 g, 2.77 mmol, 87% yield).

R_f 0.49 (hexane/ethyl acetate 1/1);
Mp 69.3 – 72.6 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H, N*H*), 7.81-7.75 (m, 2 H, *Phth*), 7.72 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.70-7.65 (m, 2 H, *Phth*), 7.52 (d, 1 H, *J* = 2.5 Hz, Ar*H*), 7.37-7.33 (m, 1 H, Ar*H*), 7.21-7.16 (m, 1 H, Ar*H*), 7.15-7.10 (m, 1 H, Ar*H*), 5.81 (dd, 1 H, *J* = 9.4, 6.9 Hz, PhthN-C*H*), 4.65-4.36 (m, 4 H, CF_3-CH_2), 3.71-3.66 (m, 1 H, C*H*-$(CO)_2$), 3.32-3.23 (m, 1 H, CH_2), 3.18-3.10 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 166.7, 166.6, 135.8, 134.2, 131.8, 126.3, 124.3, 123.4, 122.7, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 120.4, 118.9, 112.8, 111.4, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 49.0, 44.3, 30.7;
IR 3412 (w), 3061 (w), 2979 (w), 1757 (m), 1708 (s), 1381 (m), 1357 (m), 1330 (m), 1283 (s), 1166 (s), 975 (m);
HRMS (ESI) calcd for $C_{25}H_{18}F_6N_2NaO_6^+$ $[M+Na]^+$ 579.0961; found 579.0964.

Bis(2,2,2-trifluoroethyl) 2-(2-(5-chloro-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (6ab)

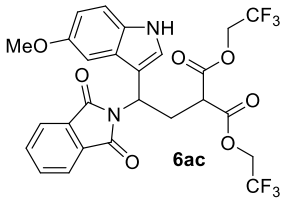


6ab

Following method **A** and starting from 5-chloro-1*H*-indole (**5b**) (33 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(5-chloro-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (**6ab**) (97 mg, 0.16 mmol, 82% yield) was obtained as a colorless solid after a reaction time of 1.5 hours and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 98/2 to 75/25 + 1% AcOH).

R_f 0.40 (hexane/ethyl acetate 6/4);
Mp 98.7 – 102.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H, N*H*), 7.83-7.78 (m, 2 H, *Phth*), 7.72-7.67 (m, 2 H, *Phth*), 7.67 (d, 1 H, *J* = 2.0 Hz, Ar*H*), 7.55 (d, 1 H, *J* = 2.6 Hz, Ar*H*), 7.26 (dd, 1 H, *J* = 8.7, 0.4 Hz, Ar*H*), 7.14 (dd, 1 H, *J* = 8.5, 1.9 Hz, Ar*H*), 5.72 (dd, 1 H, *J* = 9.6, 6.7 Hz, PhthN-C*H*), 4.66-4.37 (m, 4 H, CF_3-CH_2), 3.67-3.62 (m, 1 H, C*H*-$(CO)_2$), 3.30-3.21 (m, 1 H, CH_2), 3.12-3.03 (m, 1 H, CH_2);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.6, 166.5, 134.4, 134.1, 131.8, 127.4, 126.3, 125.7, 123.6, 123.2, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 118.4, 112.7, 112.4, 61.6 (q, *J* = 37 Hz), 61.4 (q, *J* = 37 Hz), 48.9, 44.0, 30.7;
IR 3419 (w), 1757 (m), 1709 (s), 1464 (w), 1384 (m), 1286 (s), 1170 (s), 973 (w), 724 (m);
HRMS (ESI) calcd for $C_{25}{}^{35}ClF_6H_{18}N_2O_6^+$ $[M+H]^+$ 591.0752; found 591.0761.

Bis(2,2,2-trifluoroethyl) 2-(2-(5-methoxy-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (6ac)

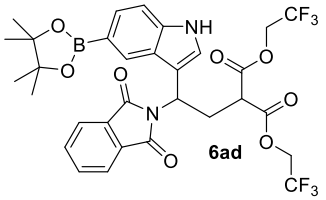


6ac

Following method **A** and starting from 5-methoxy-1*H*-indole (**5c**) (32 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(5-methoxy-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (**6ac**) (79 mg, 0.14 mmol, 68% yield) was obtained as a colorless solid after a reaction time of 0.5 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 97/3 to 75/25 + 1% AcOH).

R_f 0.41 (hexane/ethyl acetate 6/4);
Mp 92.6 – 96.8 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1 H, N*H*), 7.81-7.76 (m, 2 H, *Phth*), 7.70-7.65 (m, 2 H, *Phth*), 7.48 (d, 1 H, *J* = 2.6 Hz, Ar*H*), 7.23 (d, 1 H, *J* = 8.8 Hz, Ar*H*), 7.18 (d, 1 H, *J* = 2.4 Hz, Ar*H*), 6.84 (dd, 1 H, *J* = 8.8, 2.4 Hz, Ar*H*), 5.76 (dd, 1 H, *J* = 9.4, 6.9 Hz, PhthN-C*H*), 4.65-4.38 (m, 4 H, CF_3-CH_2), 3.84 (s, 3 H, O*Me*), 3.71-3.66 (m, 1 H, C*H*-$(CO)_2$), 3.31-3.23 (m, 1 H, CH_2), 3.17-3.09 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 166.7, 166.6, 154.6, 134.3, 131.8, 130.8, 126.8, 124.9, 123.4, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 113.2, 112.6, 112.1, 100.4, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 55.9, 49.0, 44.4, 30.6;
IR 3414 (w), 2949 (w), 2840 (w), 1758 (m), 1708 (s), 1490 (w), 1284 (s), 1170 (s), 975 (m), 721 (m);
HRMS (ESI) calcd for $C_{26}F_6H_{21}N_2O_7^+$ $[M+H]^+$ 587.1247; found 587.1252.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)malonate (6ad)

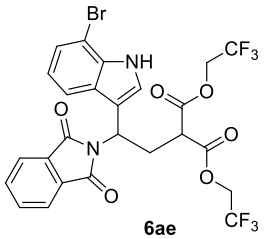


6ad

Following method **A** and starting from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**5d**) (54 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)malonate (**6ad**) (86 mg, 0.13 mmol, 63% yield) was obtained as an colorless solid after a reaction time of 1 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 97/3 to 75/25).

R_f 0.47 (hexane/ethyl acetate 6/4);
Mp 83.6 – 87.2 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H, N*H*), 8.16 (s, 1 H, Ar*H*), 7.82-7.77 (m, 2 H, *Phth*), 7.70-7.65 (m, 2 H, *Phth*), 7.63 (d, 1 H, *J* = 8.2 Hz, Ar*H*), 7.57 (d, 1 H, *J* = 2.5 Hz, Ar*H*), 7.34 (d, 1 H, *J* = 8.2 Hz, Ar*H*), 5.89-5.84 (m, 1 H, PhthN-C*H*), 4.65-4.36 (m, 4 H, CF_3-CH_2), 3.63 (t, 1 H, *J* = 7.4 Hz, C*H*-$(CO)_2$), 3.24-3.06 (m, 2 H, CH_2), 1.35 (s, 6 H, CH_3), 1.35 (s, 6 H, CH_3);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.7, 166.6, 137.6, 134.2, 131.9, 128.9, 126.1, 124.6, 123.5, 122.6 (q, J_{C-F} = 277 Hz), 122.6 (q, J_{C-F} = 277 Hz), 120.3 (br), 113.4, 110.8, 83.7, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 49.0, 44.2, 31.6, 25.1, 24.9;
IR 3405 (w), 2982 (w), 2934 (w), 1759 (m), 1712 (s), 1357 (s), 1286 (s), 1170 (s), 969 (w), 723 (m);
HRMS (ESI) calcd for $C_{31}H_{29}{}^{11}BF_6N_2NaO_8^+$ $[M+Na]^+$ 705.1813; found 705.1801.

Bis(2,2,2-trifluoroethyl) 2-(2-(7-bromo-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (6ae)



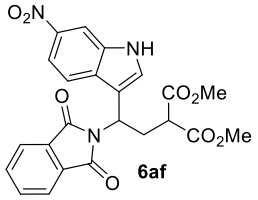
6ae

Following method **A** and starting from 7-bromo-1*H*-indole (**5e**) (43 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(7-bromo-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (**6ae**) (89 mg, 0.14 mmol, 70% yield) was obtained as a pale yellow solid after a reaction time of 50 minutes and purification by Biotage (SNAP cartridge KP-Sil 25 g, hexane/AcOEt 90/10 to 45/55).

R_f 0.52 (hexane/ethyl acetate 6/4);
Mp 182.9 – 184.2 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H, N*H*), 7.75-7.67 (m, 2 H, *Phth*), 7.65-7.60 (m, 2 H, *Phth*), 7.58 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.52 (d, 1 H, *J* = 2.4 Hz, Ar*H*), 7.34 (d, 1 H, *J* = 7.6 Hz, Ar*H*), 7.01 (t, 1 H, *J* = 7.8 Hz, Ar*H*), 5.69 (dd, 1 H, *J* = 9.5, 6.8 Hz, PhthN-C*H*), 4.61-4.48 (m, 1 H, CF_3-CH_2), 4.47-4.28 (m, 3 H, CF_3-CH_2), 3.62-3.55 (m, 1 H, C*H*-$(CO)_2$), 3.26-3.15 (m, 1 H, CH_2), 3.09-2.99 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.63, 166.61, 134.5, 134.4, 131.8, 127.4, 125.1, 124.8, 123.5, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 121.6, 118.2, 114.2, 105.0, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 48.9, 44.3, 30.6;[12]
IR 3387 (w), 1774 (m), 1759 (m), 1712 (s), 1386 (w), 1333 (m), 1286 (m), 1173 (s);
HRMS (ESI) calcd for $C_{25}{}^{79}BrF_6H_{18}N_2O_6^+$ $[M+H]^+$ 635.0247; found 635.0240.

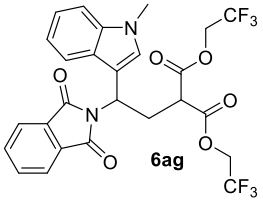
Dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(6-nitro-1*H*-indol-3-yl)ethyl)malonate (6af)



Method **A** was followed using 6-nitro-1*H*-indole (**5f**) (36 mg, 0.22 mmol, 1.1 equiv). The mixture was stirred at room temperature for 30 min and then filtered over a short plug of silica gel (AcOEt/hexane 1/1). The crude was concentrated under reduced pressure to remove volatiles. Potassium carbonate (2.77 mg, 0.0200 mmol, 0.100 equiv) was added to a solution of the crude in MeOH (2.00 mL) at 0 °C. The resulting suspension was stirred for 40 min. The mixture was then partitioned between dichloromethane (5 mL) and saturated aqueous ammonium chloride-brine (1:2) (5 mL). The aqueous layer was extracted two times with dichloromethane (5 mL) and the combined organic layers were washed with brine (5 mL) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure. The crude was then purified by Biotage (SNAP cartridge KP-Sil 10 g, pentane/AcOEt 87/13 to 1/99) to afford dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-(2-hydroxyethyl)-1*H*-indol-2-yl)ethyl)malonate (**6af**) (53.7 mg, 0.115 mmol, 58% yield) as a yellow solid.

R_f 0.21 (hexane/ethyl acetate 6/4);
Mp 171.3 – 174.2 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H, N*H*), 8.32 (d, 1 H, *J* = 1.9 Hz, Ar*H*), 8.00 (dd, 1 H, *J* = 8.9, 2.0 Hz, Ar*H*), 7.84-7.78 (m, 3 H, *Phth* + Ar*H*), 7.75 (d, 1 H, *J* = 8.9 Hz, Ar*H*), 7.73-7.67 (m, 2 H, *Phth*), 5.78 (dd, 1 H, *J* = 10.1, 6.0 Hz, PhthN-C*H*), 3.75 (s, 3 H, O*Me*), 3.65 (s, 3 H, O*Me*), 3.49-3.44 (m, 1 H, C*H*-$(CO)_2$), 3.31-3.22 (m, 1 H, CH_2), 3.04-2.96 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 169.1, 168.1, 143.8, 134.4, 134.2, 131.7, 131.0, 129.9, 123.6, 119.1, 115.8, 114.6, 108.3, 53.1, 53.0, 49.5, 44.1, 30.7;
IR 3367 (w), 2359 (w), 1734 (s), 1712 (s), 1513 (m), 1338 (s);
HRMS (ESI) calcd for $C_{23}H_{19}N_3NaO_8^+$ $[M+Na]^+$ 488.1064; found 488.1059.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (6ag)



Following method **A** and starting from 1-methyl-1*H*-indole (**5g**) (29 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (**6ag**) (108 mg, 0.188 mmol, 94% yield) was obtained as a colorless solid after a reaction time of 0.5 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 97/3 to 85/15 + 1% AcOH).

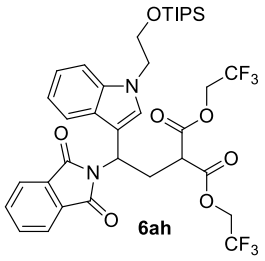
Larger scale procedure:

Bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (**4a**) (1.25 g, 2.85 mmol, 1 equiv) and 1-methyl-1*H*-indole (**5g**) (411 mg, 3.13 mmol, 1.1 equiv) were dissolved in diethyl ether (17 mL) and

added to $Sc(OTf)_3$ (70.0 mg, 142 µmol, 5.0 mol%) in a one neck flask sealed with a septum under nitrogen atmosphere. The mixture was stirred at room temperature for 50 minutes, when full conversion was observed by TLC (6:4 Hexane/EtOAc, Anisaldehyde). The mixture was then filtered over a short plug of silica gel (AcOEt/hexane 1/1, 5 mL). The crude was concentrated under reduced pressure to remove volatiles. Purification by column chromatography (silica gel, hexane:AcOEt 95:5 to 70:30) afforded bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**6ag**) (1.34 g, 2.35 mmol, 83% yield).

R_f 0.49 (hexane/ethyl acetate 6/4);
Mp 47.8 – 49.5 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.01 (m, 1 H, Ar*H*), 7.94-7.89 (m, 1 H, Ar*H*), 7.81-7.74 (m, 2 H, *Phth*), 7.69-7.63 (m, 2 H, *Phth*), 7.26-7.22 (m, 1 H, Ar*H*), 7.16-7.09 (m, 2 H, Ar*H*), 5.80 (dd, 1 H, *J* = 9.3, 7.1 Hz, PhthN-C*H*), 4.65-4.37 (m, 4 H, CF_3-CH_2), 3.78 (s, 3 H, CH_3), 3.70-3.65 (m, 1 H, C*H*-$(CO)_2$), 3.30-3.21 (m, 1 H, CH_2), 3.18-3.09 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.7, 166.6, 136.6, 134.2, 131.9, 128.9, 126.9, 123.4, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 122.2, 119.9, 119.0, 111.1, 109.5, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 49.0, 44.3, 33.1, 30.9;
IR 3059 (w), 2921 (w), 1758 (m), 1712 (s), 1382 (m), 1327 (m), 1284 (s), 1169 (s), 977 (m), 724 (m);
HRMS (ESI) calcd for $C_{26}H_{20}F_6N_2NaO_6^+$ $[M+Na]^+$ 593.1118; found 593.1136.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indol-3-yl)ethyl)malonate (6ah)

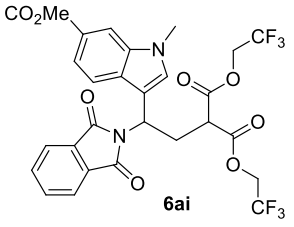


6ah

Following method **A** and starting from 1-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indole (**5h**) (64 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indol-3-yl)ethyl)malonate (**6ah**) (0.12 g, 0.16 mmol, 80% yield) was obtained as an colorless solid after a reaction time of 45 minutes and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 95/5 to 78/22).

R_f 0.68 (hexane/ethyl acetate 6/4);
Mp 68.8 – 72.3 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 2 H, *Phth*), 7.71 (d, 1 H, *J* = 8.1 Hz, Ar*H*), 7.69-7.65 (m, 2 H, *Phth*), 7.48 (s, 1 H, Ar*H*), 7.32-7.29 (m, 1 H, Ar*H*), 7.18 (t, 1 H, *J* = 7.2 Hz, Ar*H*), 7.10 (t, 1 H, *J* = 7.4 Hz, Ar*H*), 5.78 (dd, 1 H, *J* = 9.8, 6.7 Hz, PhthN-C*H*), 4.67-4.55 (m, 1 H, CF_3-CH_2), 4.54-4.36 (m, 3 H, CF_3-CH_2), 4.30-4.18 (m, 2 H, CH_2), 3.99 (t, 2 H, *J* = 5.6 Hz, CH_2), 3.68-3.63 (m, 1 H, C*H*-$(CO)_2$), 3.34-24 (m, 1 H, CH_2), 3.12-3.03 (m, 1 H, CH_2), 1.06-0.85 (m, 21 H, *TIPS*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.7, 166.6, 136.1, 134.2, 131.9, 128.6, 127.0, 123.4, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 122.0, 119.8, 119.0, 111.4, 109.7, 62.7, 61.5 (q, J_{C-F} = 37 Hz), 61.3 (q, J_{C-F} = 37 Hz), 49.1, 49.0, 44.4, 30.9, 17.9, 17.9, 11.9;
IR 2946 (w), 2868 (w), 1775 (m), 1760 (m), 1714 (s), 1469 (w), 1286 (m), 1173 (s);
HRMS (ESI) calcd for $C_{36}H_{42}F_6N_2NaO_7Si^+$ $[M+Na]^+$ 779.2563; found 779.2548.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(6-(methoxycarbonyl)-1-methyl-1*H*-indol-3-yl)ethyl)malonate (6ai)

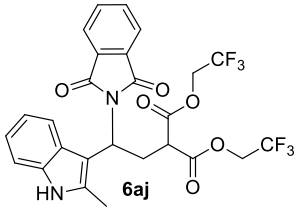


6ai

Following method **A** and starting from methyl 1-methyl-1*H*-indole-6-carboxylate (**5i**) (38 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(6-(methoxycarbonyl)-1-methyl-1*H*-indol-3-yl)ethyl)malonate (**6ai**) (0.11 g, 0.17 mmol, 86% yield) was obtained as a colorless solid after a reaction time of 1.5 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 94/6 to 68/32).

R_f 0.26 (hexane/ethyl acetate 6/4);
Mp 69.2 – 73.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 1 H, *J* = 0.6 Hz, Ar*H*), 7.81-7.76 (m, 3 H, *Phth* + Ar*H*), 7.72-7.65 (m, 3 H, *Phth* + Ar*H*), 7.55 (s, 1 H, Ar*H*), 5.79 (dd, *J* = 9.5, 6.9 Hz, PhthN-C*H*), 4.66-4.36 (m, 4 H, CF_3-CH_2), 3.92 (s, 3 H, CH_3), 3.84 (s, 3 H, CH_3), 3.68-3.62 (m, 1 H, C*H*-$(CO)_2$), 3.31-3.21 (m, 1 H, CH_2), 3.14-3.04 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 168.0, 166.6, 166.5, 136.0, 134.3, 132.1, 131.7, 130.3, 123.9, 123.5, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 121.0, 118.6, 112.0, 111.7, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 52.1, 48.9, 44.0, 33.3, 30.8;
IR 3406 (w), 2954 (w), 2867 (w), 2094 (w), 1774 (m), 1713 (s), 1474 (w), 1439 (w), 1385 (m), 1278 (s), 1174 (s);
HRMS (ESI) calcd for $C_{28}F_6H_{23}N_2O_8^+$ $[M+H]^+$ 629.1353; found 629.1347.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-methyl-1*H*-indol-3-yl)ethyl)malonate (6aj)

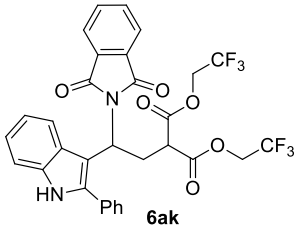


6aj

Following method **A** and starting from 2-methyl-1*H*-indole (**5j**) (29 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-methyl-1H-indol-3-yl)ethyl)malonate (**6aj**) (0.11 g, 0.19 mmol, 97% yield) was obtained as an colorless solid after a reaction time of 0.5 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 97/3 to 85/15 + 1% AcOH).

R_f 0.52 (hexane/ethyl acetate 6/4);
Mp 49.4 – 52.3 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2 H, *Phth*), 7.72 (dt, *J* = 8.0, 1.0 Hz, 1 H, *ArH*), 7.69 – 7.64 (m, 2H, *Phth*), 7.40 (s, 1 H, *NH*), 7.28 (dt, *J* = 8.3, 1.0 Hz, 1 H, *ArH*), 7.22 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H, *ArH*), 7.12 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1 H, *ArH*), 5.80 (dd, *J* = 9.3, 7.1 Hz, 1 H, *NCH*), 4.67 – 4.53 (m, 1 H, *CH_2CF_3*), 4.53 – 4.36 (m, 3 H, *CH_2CF_3*), 3.78 (s, 3 H, *Me*), 3.68 (dd, *J* = 7.9, 6.9 Hz, 1 H, *CH*), 3.26 (ddd, *J* = 14.0, 9.3, 6.9 Hz, 1 H, *CH_2*), 3.13 (ddd, *J* = 14.1, 8.0, 7.1 Hz, 1 H, *CH_2*) ;
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 166.5, 166.5, 136.5, 134.1, 131.8, 128.8, 126.7, 123.3, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 122.1, 119.8, 118.9, 111.0, 109.4, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 37 Hz), 48.9, 44.2, 33.0, 30.7.
IR 3396 (w), 3060 (w), 2974 (w), 2949 (w), 2872 (w), 1759 (m), 1711 (s), 1463 (w), 1356 (m), 1287 (m), 1174 (s);
HRMS (ESI) calcd for $C_{26}F_6H_{21}N_2O_6^+$ $[M+H]^+$ 571.1298; found 571.1303.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-phenyl-1*H*-indol-3-yl)ethyl)malonate (6ak)

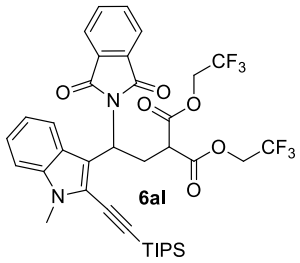


6ak

Following method **A** and starting from 2-methyl-1*H*-indole (**5k**) (42 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-methyl-1*H*-indol-3-yl)ethyl)malonate (**6ak**) (118 mg, 0.187 mmol, 93% yield) was obtained as a colorless solid after a reaction time of 45 minutes and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 98/2 to 70/30).

R_f 0.56 (hexane/ethyl acetate 6/4);
Mp 81.6 – 84.9 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H, N*H*), 8.14-8.10 (m, 1 H, Ar*H*), 7.79-7.74 (m, 2 H, *Phth*), 7.69-7.62 (m, 4 H, *Phth* + Ar*H*), 7.52-7.43 (m, 3 H, Ar*H*), 7.37-7.33 (m, 1 H, Ar*H*), 7.25-7.16 (m, 2 H, Ar*H*), 5.80-5.73 (m, 1 H, PhthN-C*H*), 4.48-4.36 (m, 1 H, CF_3-CH_2), 4.35-4.19 (m, 3 H, CF_3-CH_2), 3.58-3.53 (m, 1 H, C*H*-$(CO)_2$), 3.40-3.31 (m, 1 H, CH_2), 3.27-3.17 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.6, 166.5, 138.0, 135.8, 134.2, 132.4, 131.9, 129.8, 128.9, 128.8, 126.6, 123.4, 122.7, 122.5 (q, J_{C-F} = 277 Hz), 121.2, 120.6, 111.0, 109.6, 61.2 (q, J_{C-F} = 37 Hz), 61.2 (q, J_{C-F} = 37 Hz), 49.0, 47.1, 30.7;
IR 3395 (w), 3063 (w), 2977 (w), 1757 (m), 1709 (s), 1454 (w), 1356 (m), 1284 (s), 1168 (s), 977 (m), 720 (m);
HRMS (ESI) calcd for $C_{31}F_6H_{23}N_2O_6^+$ $[M+H]^+$ 633.1455; found 633.1476.

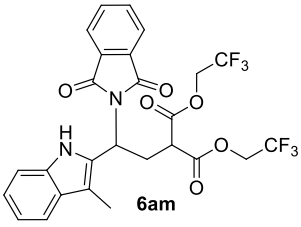
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-2-((triisopropylsilyl)ethynyl)-1*H*-indol-3-yl)ethyl)malonate (6al)



Following method **A** and starting from 1-methyl-2-((triisopropylsilyl)ethynyl)-1*H*-indole (**5l**) (62 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-2-((triisopropylsilyl)ethynyl)-1*H*-indol-3-yl)ethyl)malonate (**6al**) (78 mg, 0.10 mmol, 52% yield) was obtained as a colorless solid after a reaction time of 1 hour and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 95/5 to 75/25).

R_f 0.56 (hexane/ethyl acetate 7/3);
Mp 71.6 – 74.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1 H, *J* = 8.1 Hz, Ar*H*), 7.80-7.75 (m, 2 H, *Phth*), 7.68-7.63 (m, 2 H, *Phth*), 7.28-7.21 (m, 2 H, Ar*H*), 7.17-7.12 (m, 1 H, Ar*H*), 5.97-5.92 (m, 1 H, PhthN-C*H*), 4.54-4.31 (m, 4 H, CF_3-CH_2), 3.79 (s, 3 H, CH_3), 3.70-3.64 (m, 1 H, C*H*-$(CO)_2$), 3.54-3.45 (m, 1 H, CH_2), 3.40-3.31 (m, 1 H, CH_2), 1.32-1.13 (m, 21 H, *TIPS*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 166.6, 166.5, 137.0, 134.0, 132.0, 125.6, 123.6, 123.4, 122.7, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 120.9, 120.6, 115.5, 109.6, 103.3, 96.6, 61.3 (q, J_{C-F} = 37 Hz), 61.3 (q, J_{C-F} = 37 Hz), 49.2, 46.2, 30.8, 30.1, 18.8, 11.5;
IR 2944 (w), 2867 (w), 2153 (w), 1776 (m), 1761 (m), 1718 (s), 1286 (m), 1173 (s);
HRMS (ESI) calcd for $C_{37}F_6H_{41}N_2O_6Si^+$ $[M+H]^+$ 751.2633; found 751.2633.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-methyl-1*H*-indol-2-yl)ethyl)malonate (6am)

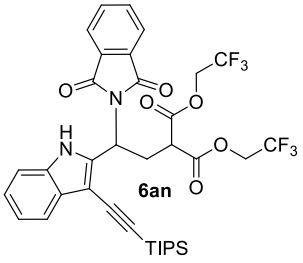


Following method **B** and starting from 3-methyl-1*H*-indole (**5m**) (29 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-methyl-1*H*-indol-2-yl)ethyl)malonate (**6am**) (94 mg, 0.16 mmol, 82% yield) was obtained as a colorless solid after a reaction time of 1.5 hours and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/ dichloromethane 80/20 to 2/98).

R_f 0.50 (hexane/ethyl acetate 7/3);
Mp 59.9 – 64.0 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1 H, N*H*), 7.88-7.83 (m, 2 H, *Phth*), 7.77-7.71 (m, 2 H, *Phth*), 7.52 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 7.36 (d, 1 H, *J* = 8.2 Hz, Ar*H*), 7.21 (td, 1 H, *J* = 7.1, 0.8 Hz, Ar*H*), 7.13-7.08 (m, 1 H, Ar*H*), 5.85 (dd, 1 H, *J* = 9.5, 6.5 Hz, PhthN-C*H*), 4.57-4.36 (m, 3 H, CF_3-CH_2), 4.25-4.15 (m, 1 H, CF_3-CH_2), 3.49 (t, 1 H, *J* = 7.3 Hz, C*H*-$(CO)_2$), 3.26-3.17 (m, 1 H, CH_2), 2.92-2.83 (m, 1 H, CH_2), 2.34 (s, 3 H, CH_3);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.4, 166.2, 136.1, 134.6, 131.6, 129.5, 127.9, 123.8, 123.2, 122.5 (q, J_{C-F} = 277 Hz), 119.7, 119.3, 111.4, 61.5 (q, J_{C-F} = 37 Hz), 48.6, 44.0, 31.2, 8.4;[15]
IR 1773 (m), 1713 (s), 1288 (m), 1176 (s), 978 (w);
HRMS (ESI) calcd for $C_{26}F_6H_{21}N_2O_6^+$ $[M+H]^+$ 571.1298; found 571.1307.

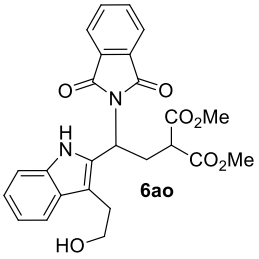
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-((triisopropylsilyl)ethynyl)-1*H*-indol-2-yl)ethyl)malonate (6an)



Following method **C** and starting from 3-((triisopropylsilyl)ethynyl)-1*H*-indole (**5n**) (66 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-((triisopropylsilyl)ethynyl)-1*H*-indol-2-yl)ethyl)malonate (**6an**) (71 mg, 0.097 mmol, 49% yield) was obtained as a colorless solid, after a reaction time of 6 hours and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/toluene 6/4 to 9/1).

R_f 0.60 (hexane/ethyl acetate 6/4);
Mp 49.2 – 51.8 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1 H, N*H*), 7.91-7.86 (m, 2 H, *Phth*), 7.78-7.73 (m, 2 H, *Phth*), 7.64 (d, 1 H, *J* = 7.8 Hz, Ar*H*), 7.40-7.36 (m, 1 H, Ar*H*), 7.27-7.22 (m, 1 H, Ar*H*), 7.19-7.14 (m, 1 H, Ar*H*), 6.13-6.08 (m, 1 H, PhthN-C*H*), 4.53-4.28 (m, 3 H, CF_3-CH_2), 3.97-3.87 (m, 1 H, CF_3-CH_2), 3.63 (dd, 1 H, *J* = 8.2, 2.3 Hz, C*H*-$(CO)_2$), 3.14 (dt, 1 H, *J* = 14.1, 8.8 Hz, CH_2), 2.87 (ddd, 1 H, J = 13.9, 7.8, 5.9 Hz, CH_2), 1.22 (s, 21 H, *TIPS*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 166.2, 165.8, 137.1, 135.5, 134.7, 131.6, 128.1, 124.1, 123.9, 122.5 (q, J_{C-F} = 275 Hz), 121.1, 120.4, 111.8, 100.1, 98.3, 96.0, 61.5 (q, J_{C-F} = 37 Hz), 61.3 (q, J_{C-F} = 37 Hz), 48.5, 45.3, 31.5, 18.9, 11.5;
IR 3394 (w), 2151 (w), 1776 (m), 1716 (m), 1277 (s), 1173 (s);
HRMS (ESI) calcd for $C_{36}F_6H_{39}N_2O_6Si^+$ $[M+H]^+$ 737.2476; found 737.2480.

Dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-(2-hydroxyethyl)-1*H*-indol-2-yl)ethyl)malonate (6ao)



Method **C** was followed using 3-(2-((trimethylsilyl)oxy)ethyl)-1*H*-indole (**5o**) (51 mg, 0.22 mmol, 1.1 equiv). The mixture was stirred at 60 °C for 25 min and then filtered over a short plug of silica gel (AcOEt/hexane 1/1). The crude was concentrated under reduced pressure to remove volatiles. Potassium carbonate (2.77 mg, 0.0200 mmol, 0.100 equiv) was added to a solution of the crude in MeOH (2.00 mL) at 0 °C. The resulting suspension was stirred for 30 min. The mixture was then partitioned between dichloromethane (5 mL) and saturated aqueous ammonium chloride-brine (1:2) (5 mL). The aqueous layer was extracted two times with dichloromethane (5 mL) and the combined organic layers were washed with brine (5 mL) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure. The crude was then purified by Biotage (SNAP

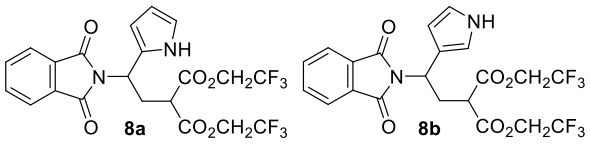
[15] Only one CF_3 peak could be detected.

cartridge KP-Sil 10 g, pentane/AcOEt 85/15 to 50/50) to afford dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-(2-hydroxyethyl)-1*H*-indol-2-yl)ethyl)malonate (**6ao**) (67 mg, 0.14 mmol, 72% yield) as a pale yellow oil.

R_f 0.13 (hexane/ethyl acetate 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1 H, N*H*), 7.88-7.81 (m, 2 H, *Phth*), 7.77-7.70 (m, 2 H, *Phth*), 7.56 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.36 (d, 1 H, *J* = 8.1 Hz, Ar*H*), 7.22-7.17 (m, 1 H, Ar*H*), 7.11-7.06 (m, 1 H, Ar*H*), 5.85 (t, 1 H, *J* = 8.2 Hz, PhthN-C*H*), 3.90-3.85 (m, 2 H, CH_2), 3.69 (s, 3 H, O*Me*), 3.63 (s, 3 H, O*Me*), 3.37 (t, 1 H, *J* = 7.3 Hz, C*H*-$(CO)_2$), 3.18-2.90 (m, 4 H, CH_2);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 168.6, 136.0, 134.5, 131.7, 131.6, 127.3, 123.7, 123.0, 119.7, 119.2, 111.6, 111.4, 62.9, 52.9, 49.1, 44.3, 31.3, 27.9;
IR 3550 (w), 3406 (w), 3058 (w), 2954 (w), 2884 (w), 1735 (s), 1708 (s), 1440 (m), 1385 (m), 1333 (m), 1165 (m);
HRMS (ESI) calcd for $C_{25}H_{25}N_2O_7^+$ $[M+H]^+$ 465.1656; found 465.1661.

7.3. Friedel Crafts products: Electron rich Aromatics

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-2-yl)ethyl)malonate (8a)
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-3-yl)ethyl)malonate (8b)



Following method **A** and using 1*H*-pyrrole (0.015 mL, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-2-yl)ethyl)malonate (**8a**) (62 mg, 0.12 mmol, 61% yield) and bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-3-yl)ethyl)malonate (**8b**) (31 mg, 0.059 mmol, 30% yield) were obtained as colorless solids, after a reaction time of 1.5 hours and purification by Biotage (SNAP cartridge KP-Sil 10 g, Hex/AcOEt 96/4 to 75/25). The structures were assigned by 2D NMR experiments.

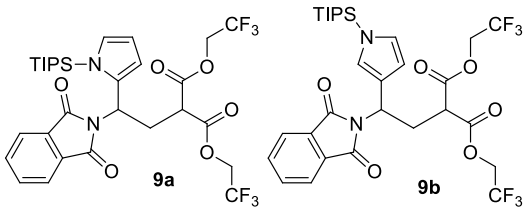
Regioisomer 1: **bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-2-yl)ethyl)malonate (8a)**

R*f* 0.55 (hexane/ethyl acetate 6/4);
Mp 122.2 – 123.8 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1 H, N*H*), 7.86-7.80 (m, 2 H, *Phth*), 7.75-7.70 (m, 2 H, *Phth*), 6.80-6.77 (m, 1 H, Ar*H*), 6.21-6.17 (m, 1 H, Ar*H*), 6.10-6.07 (m, 1 H, Ar*H*), 5.49 (dd, 1 H, *J* = 9.2, 7.7 Hz, PhthN-C*H*), 4.56-4.45 (m, 3 H, CF_3-CH_2), 4.42-4.31 (m, 1 H, CF_3-CH_2), 3.47 (t, 1 H, *J* = 7.3 Hz, C*H*-$(CO)_2$), 3.04 (ddd, 1 H, *J* = 14.0, 9.2, 7.4 Hz, CH_2), 2.82-2.74 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 166.4, 166.3, 134.6, 131.7, 127.0, 123.7, 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 122.5 (q, $J_{C\text{-}F}$ = 277 Hz), 119.7, 109.6, 108.0, 61.5 (q, $J_{C\text{-}F}$ = 37 Hz), 61.4 (q, $J_{C\text{-}F}$ = 37 Hz), 48.8, 46.4, 31.7;
IR 3418 (w), 1760 (m), 1708 (s), 1386 (m), 1359 (m), 1283 (s), 1165 (s), 974 (m), 724 (m);
HRMS (ESI) calcd for $C_{21}F_6H_{17}N_2O_6^+$ $[M+H]^+$ 507.0985; found 507.0986.

Regioisomer 2: **bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-pyrrol-3-yl)ethyl)malonate (8b)**

R*f* 0.48 (hexane/ethyl acetate 6/4);
Mp 81.7 – 84.0 **°C**;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H, N*H*), 7.83-7.78 (m, 2 H, *Phth*), 7.72-7.67 (m, 2 H, *Phth*), 6.92-6.89 (m, 1 H, Ar*H*), 6.73-6.69 (q, 1 H, *J* = 2.6 Hz, Ar*H*), 6.38-6.34 (m, 1 H, Ar*H*), 5.38 (t, 1 H, *J* = 8.2 Hz, PhthN-C*H*), 4.62-4.38 (m, 4 H, CF_3-CH_2), 3.58 (t, 1 H, *J* = 7.6 Hz, C*H*-$(CO)_2$), 3.04 (t, 2 H, *J* = 8.1 Hz, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.7, 134.2, 132.0, 123.4, 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 120.8, 118.4, 117.3, 108.5, 61.4 (q, $J_{C\text{-}F}$ = 37 Hz), 61.3 (q, $J_{C\text{-}F}$ = 37 Hz), 49.0, 46.3, 31.4; [16]
IR 3405 (w), 2359 (w), 2335 (w), 1774 (w), 1758 (w), 1712 (m), 1384 (w), 1278 (m), 1176 (m), 751 (s);
HRMS (ESI) calcd for $C_{21}F_6H_{17}N_2O_6^+$ $[M+H]^+$ 507.0985; found 507.0980.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-(triisopropylsilyl)-1*H*-pyrrol-2-yl)ethyl) malonate (9a)
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)ethyl) malonate (9b)



Following method **A** and starting from 1-(triisopropylsilyl)-1*H*-pyrrole (49 mg, 0.22 mmol, 1.1 equiv), a 7:1 mixture of two regioisomers was obtained as a colorless oil (0.12 g, 0.18 mmol, 88% yield) after a reaction time

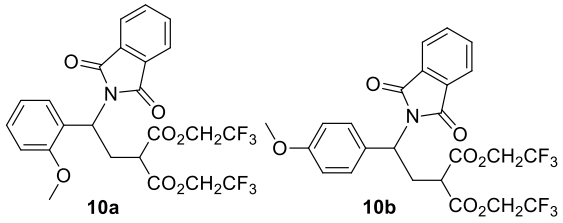
[16] Two carbonyls peaks are not overlapping.

of 25 minutes and purification by Biotage (SNAP cartridge KP-Sil 10 g, hexane/AcOEt 93/7 to 55/45). Peaks at 5.47 and 5.36 ppm in the ^{1}H NMR spectrum were integrated to determine the ratio of regioisomer. The structure of the regioisomers was assigned through 2D NMR experiments. The major isomer was isolated in pure form after a second purification by column chromatography for characterization.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)ethyl) malonate (9b)

R$_f$ 0.38 (hexane/ethyl acetate 8/2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 2 H, *Phth*), 7.73-7.66 (m, 2 H, *Phth*), 6.83 (t, 1 H, *J* = 1.7 Hz, Ar*H*), 6.67 (t, 1 H, *J* = 2.5 Hz, Ar*H*), 6.42 (dd, 1 H, *J* = 2.7, 1.4 Hz, Ar*H*), 5.36 (t, 1 H, *J* = 8.3 Hz, PhthN-C*H*), 4.62-4.39 (m, 4 H, CF_3-CH_2), 3.53 (t, 1 H, *J* = 7.7 Hz, C*H*-$(CO)_2$), 3.08-2.95 (m, 2 H, CH_2), 1.41 (hept, 3 H, *J* = 7.5 Hz, Si-C*H*), 1.07 (d, 9 H, *J* = 2.8 Hz, CH_3), 1.05 (d, 9 H, *J* = 2.8 Hz, CH_3);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.7, 134.1, 132.0, 124.8, 123.6, 123.4, 122.9 (q, $J_{C\text{-}F}$ = 277 Hz), 122.9 (q, $J_{C\text{-}F}$ = 277 Hz), 122.4, 110.4, 61.4 (q, $J_{C\text{-}F}$ = 37 Hz), 61.3 (q, $J_{C\text{-}F}$ = 37 Hz), 49.0, 46.4, 31.5, 17.9, 11.7;[16]
IR 2951 (w), 2869 (w), 1775 (m), 1760 (m), 1715 (s), 1287 (m), 1173 (s);
HRMS (ESI) calcd for $C_{30}F_6H_{37}N_2O_6Si^+$ $[M+H]^+$ 663.2320; found 663.2317.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-methoxyphenyl)ethyl)malonate (10a)
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(4-methoxyphenyl)ethyl)malonate (10b)

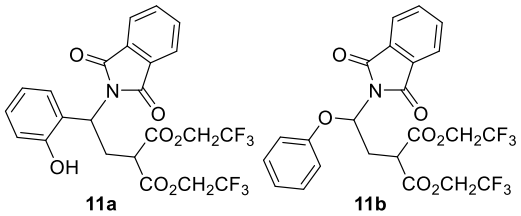


Following method **A** and starting from anisole (0.024 mL, 0.22 mmol, 1.1 equiv), an inseparable mixture of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-methoxyphenyl)ethyl)malonate (**10a**) and bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(4-methoxyphenyl)ethyl)malonate (**10b**) (66 mg, 0.12 mmol, 60% yield) was obtained as a colorless solid after a reaction time of 45 minutes and purification by Biotage (SNAP cartridge KP-Sil 10 g, Hex/AcOEt 93/7 to 70/30). The integration of the peaks at 5.81 and 5.33 ppm in the ^{1}H NMR spectrum were used to determine the ratio of regioisomers.

R$_f$ 0.60 (hexane/ethyl acetate 6/4);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 4 H, *Phth*, *Isomer 1 & 2*), 7.73-7.68 (m, 4 H, *Phth*, *Isomer 1 & 2*), 7.62 (dd, 1 H, *J* = 7.7, 1.3 Hz, Ar*H*, *Isomer 1*), 7.47 (d, 2 H, *J* = 8.7 Hz, Ar*H*, *Isomer 2*), 7.30-7.25 (m, 1 H, Ar*H*, *Isomer 1*), 6.97 (dt, 1 H, *J* = 7.5, 0.9 Hz, Ar*H*, *Isomer 1*), 6.88-6.82 (m, 3 H, Ar*H*, *Isomer 1 & 2*), 5.81 (dd, 1 H, *J* = 10.1, 5.9 Hz, PhthN-C*H*, *Isomer 1*), 5.33 (dd, 1 H, *J* = 9.7, 7.0 Hz, PhthN-C*H*, *Isomer 2*), 4.66-4.54 (m, 2 H, CF_3-CH_2, *Isomer 1 & 2*), 4.53-4.35 (m, 6 H, CF_3-CH_2, *Isomer 1 & 2*), 3.78 (s, 3 H, O*Me*), 3.77 (s, 3 H, O*Me*), 3.63 (dd, 1 H, *J* = 8.5, 6.3 Hz, C*H*-$(CO)_2$, *Isomer 1*), 3.55 (dd, 1 H, *J* = 8.5, 6.8 Hz, C*H*-$(CO)_2$, *Isomer 2*), 3.26-3.13 (m, 2 H, CH_2, *Isomer 1 & 2*), 3.07-2.98 (m, 1 H, CH_2, *Isomer 2*), 2.97-2.89 (m, 1 H, CH_2, *Isomer 1*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 168.2, 166.7, 166.6, 166.5, 159.7, 156.9, 134.3, 134.2, 131.8, 131.8, 130.0, 129.6, 128.6, 126.0, 123.6, 123.5, 122.7 (q, $J_{C\text{-}F}$ = 277 Hz), 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 122.6 (q, $J_{C\text{-}F}$ = 277 Hz), 120.6, 114.3, 110.8, 61.5 (q, $J_{C\text{-}F}$ = 37 Hz), 61.4 (q, $J_{C\text{-}F}$ = 37 Hz), 55.7, 55.4, 52.0, 48.9, 46.3, 30.3, 30.1;[17]
IR 2937 (w), 2846 (w), 1761 (m), 1715 (s), 1361 (m), 1286 (s), 1172 (s);
HRMS (ESI) calcd for $C_{24}F_6H_{20}NO_7^+$ $[M+H]^+$ 548.1138; found 548.1119.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-hydroxyphenyl)ethyl)malonate (11a)
Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-phenoxyethyl)malonate (11b)

[17] Not all carbons could be resolved.



Following method **A** and starting from phenol (21 mg, 0.22 mmol, 1.1 equiv), bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-hydroxyphenyl)ethyl)malonate (**11a**) (13mg, 0.024 mmol, 12% yield) and bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-phenoxyethyl)malonate (**11b**) (79 mg, 0.15 mmol, 74% yield) were obtained as colorless solids after a reaction time of 40 minutes and purification by Biotage (SNAP cartridge KP-Sil 10 g, Hex/AcOEt 95/5 to 70/30).

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(2-hydroxyphenyl)ethyl)malonate (11a)

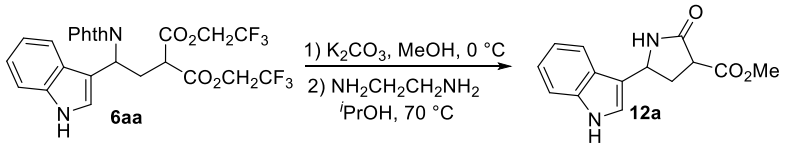
R_f 0.46 (hexane/ethyl acetate 6/4);
Mp 103.5 – 106.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.81 (m, 2 H, *Phth*), 7.76-7.70 (m, 2 H, *Phth*), 7.52 (d, 1 H, *J* = 7.7 Hz, Ar*H*), 7.22 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 6.94 (t, 1 H, *J* = 7.5 Hz. Ar*H*), 6.89 (d, 1 H, *J* = 8.1 Hz, Ar*H*), 6.76 (s, 1 H, O*H*), 5.62 (t, 1 H, *J* = 8.1 Hz, PhthN-C*H*), 4.62-4.38 (m, 4 H, CF_3-CH_2), 3.58 (t, 1 H, *J* = 7.4 Hz, C*H*-$(CO)_2$), 3.26-3.09 (m, 2 H, CH_2);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 166.2, 154.0, 134.5, 131.3, 130.2, 129.5, 123.6, 123.3, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz),121.1, 117.9, 61.5 (q, J_{C-F} = 37 Hz), 61.4 (q, J_{C-F} = 38 Hz), 48.6, 47.4, 29.0.
IR 3452 (w), 3062 (w), 2932 (w), 1766 (m), 1715 (s), 1378 (m), 1287 (s), 1172 (s);
HRMS (ESI) calcd for $C_{23}F_6H_{18}NO_7^+$ $[M+H]^+$ 534.0982; found 534.0989.

Bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-phenoxyethyl)malonate (11b)

R_f 0.63 (hexane/ethyl acetate 6/4);
Mp 110.2 – 111.9 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H, *Phth*), 7.76-7.70 (m, 2 H, *Phth*), 7.26-7.20 (m, 2 H, Ar*H*), 7.02-6.95 (m, 3 H, Ar*H*), 6.32 (dd, 1 H, *J* = 8.6, 5.1 Hz, PhthN-C*H*), 4.65-4.43 (m, 4 H, CF_3-CH_2), 3.99-3.94 (m, 1 H, C*H*-$(CO)_2$), 3.43-3.33 (m, 1 H, CH_2), 2.80-2.71 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 166.4, 155.5, 134.7, 131.4, 129.9, 124.0, 123.2, 122.6 (q, J_{C-F} = 277 Hz), 122.5 (q, J_{C-F} = 277 Hz), 116.8, 76.6, 61.5 (q, J_{C-F} = 37 Hz), 61.5 (q, J_{C-F} = 37 Hz), 47.7, 31.6;[16]
IR 3068 (w), 2940 (w), 1765 (m), 1723 (s), 1361 (m), 1289 (s), 1174 (s);
HRMS (ESI) calcd for $C_{23}H_{17}F_6NNaO_7^+$ $[M+Na]^+$ 556.0801; found 556.0804.

8. Product modifications.

Methyl 5-(1*H*-indol-3-yl)-2-oxopyrrolidine-3-carboxylate (12 a)



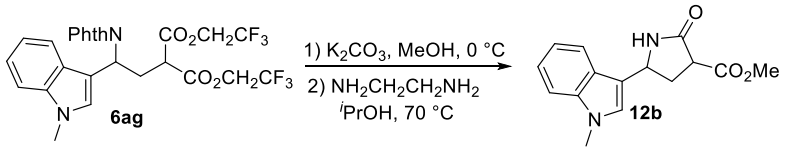
To a solution of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**6aa**) (556 mg, 1.00 mmol, 1 equiv) in MeOH (10.0 mL) was added potassium carbonate (13.8 mg, 0.100 mmol, 0.1 equiv) at 0 °C. The resulting suspension was stirred for 30 minutes and was partitioned between dichloromethane (20 mL) and saturated aqueous ammonium chloride-brine (1:2) (20 mL). The aqueous layer was extracted with dichloromethane (20 mL) twice and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford the crude as a yellow solid, which was purified by Biotage (SNAP cartridge KP-Sil 25 g, pentane/AcOEt 85/15 to 60/40) to afford dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**41**) (302 mg, 0.717 mmol, 72% yield) as an colorless solid.

R*f* 0.19 (hexane/AcOEt 6/4);
Mp 78.2 – 82.9 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H, N*H*), 7.80-7.73 (m, 2 H, *Phth*), 7.71 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 7.68-7.62 (m, 2 H, *Phth*), 7.50 (d, 1 H, *J* = 1.9 Hz, Ar*H*), 7.34 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.19-7.14 (m, 1 H, Ar*H*), 7.13-7.08 (m, 1 H, Ar*H*), 5.79 (dd, 1 H, *J* = 9.8, 6.4 Hz, PhthN-C*H*), 3.74 (s, 3 H, CH_3), 3.65 (s, 3 H, CH_3), 3.50 (t, 1 H, *J* = 7.4 Hz, C*H*-$(CO)_2$), 3.26 (ddd, 1 H, *J* = 14.2, 9.9, 6.9 Hz, CH_2), 3.09-3.00 (m, 1 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 169.3, 168.2, 135.8, 134.1, 131.8, 126.4, 124.3, 123.3, 122.5, 120.1, 118.9, 113.2, 111.3, 53.0, 52.9, 49.7, 44.6, 30.8;
IR 3403 (w), 2954 (w), 2865 (w), 2363 (w), 2093 (w), 1753 (m), 1733 (s), 1710 (s), 1358 (m);
HRMS (ESI) calcd for $C_{23}H_{20}N_2NaO_6^+$ $[M+Na]^+$ 443.1214; found 443.1216.

Following a modified procedure,[18] dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1*H*-indol-3-yl)ethyl)malonate (**41**) (84.0 mg, 0.200 mmol, 1 equiv) was added in a tube sealed with a septum with ethane-1,2-diamine (0.0410 mL, 1.00 mmol, 5 equiv). Isopropanol (1.30 mL) was added and the resulting mixture was stirred at 70 °C for 30 minutes. The solution was concentrated under reduced pressure and the crude was purified by Biotage (SNAP cartridge KP-Sil 25 g, pentane/AcOEt 75/25 to 0/100) to afford methyl 5-(1H-indol-3-yl)-2-oxopyrrolidine-3-carboxylate (**12a**) (39.1 mg, 0.151 mmol, 76% yield) as an inseparable 1:1 mixture of diastereomers as a colorless solid.

R*f* 0.40/0.32 (ethyl acetate);
Mp 51.2 – 53.6 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.11 (m, 2 H, N*H*, *Isomer 1 & 2*), 7.74 (d, 1 H, *J* = 7.9 Hz, Ar*H*, *Isomer 2*), 7.61 (d, 1 H, *J* = 7.9 Hz, Ar*H*, *Isomer 1*), 7.42 (s, 1 H, Ar*H*), 7.40 (s, 1 H, Ar*H*), 7.28-7.22 (m, 3 H, Ar*H*), 7.20-7.13 (m, 3 H, Ar*H*), 5.97 (s, 1 H, N*H*, *Isomer 1*), 5.90 (s, 1 H, N*H*, *Isomer 2*), 5.26 (t, 1 H, *J* = 6.9 Hz, C*H*-NH, *Isomer 1*), 5.05 (t, 1 H, *J* = 8.0 Hz, C*H*-NH, *Isomer 2*), 3.83 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 3.69-3.60 (m, 2 H, C*H*-$(CO)_2$, *Isomer 1 & 2*), 2.98-2.90 (m, 1 H, CH_2, *Isomer 1*), 2.89-2.73 (m, 2 H, CH_2, *Isomer 2*), 2.57-2.47 (m, 1 H, CH_2, *Isomer 1*);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 172.6, 170.6, 137.0, 136.9, 125.2, 125.0, 122.7, 122.6, 122.3, 121.6, 120.0, 119.9, 119.1, 118.8, 116.2, 115.3, 111.9, 111.8, 52.9, 52.8, 50.5, 50.1, 48.9, 48.1, 33.5, 33.5;[17]
IR 3274 (w), 2955 (w), 2361 (w), 1738 (s), 1696 (s), 1438 (w), 1268 (w);
HRMS (ESI) calcd for $C_{14}H_{15}N_2O_3^+$ $[M+H]^+$ 259.1077; found 259.1086.

Methyl 5-(1-methyl-1*H*-indol-3-yl)-2-oxopyrrolidine-3-carboxylate (12b)



[18] O. Kanie, S. C. Crawley, M. M. Palcic, O. Hindsgaul, *Carbohydr. Res.* **1993**, *243*, 139-164.

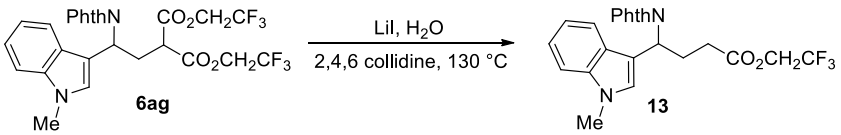
To a solution of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (**6ag**) (570 mg, 1.00 mmol, 1 equiv) in MeOH (10.0 mL) was added potassium carbonate (13.8 mg, 0.100 mmol, 0.1 equiv) at 0 °C. The resulting suspension was stirred for 30 minutes. Then, the mixture was partitioned between dichloromethane (20 mL) and saturated aqueous ammonium chloride-brine (1:2) (20 mL). The aqueous layer was extracted with dichloromethane (20 mL) twice and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford the crude as a yellow solid, which was purified by Biotage (SNAP cartridge KP-Sil 25 g, pentane/AcOEt 85/15 to 60/40) to afford dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (**37**) (299 mg, 0.688 mmol, 69% yield) as an colorless solid.

See screening in section 4 for characterization of **37.**

Following a modified procedure,[18] dimethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (**37**) (87.0 mg, 0.200 mmol, 1 equiv) was added into a tube sealed with a septum with ethane-1,2-diamine (0.0410 mL, 1.00 mmol, 5 equiv). Isopropanol (1.30 mL) was added and the resulting mixture was stirred at 70 °C for 30 minutes. The solution was concentrated under reduced pressure and the crude was purified by Biotage (SNAP cartridge KP-Sil 25 g, pentane/AcOEt 75/25 to 0/100) to afford Methyl 5-(1-methyl-1H-indol-3-yl)-2-oxopyrrolidine-3-carboxylate (**12b**) (43.7 mg, 0.160 mmol, 80% yield) as an inseparable 1:1 mixture of diastereomers as a colorless solid.

R*f* 0.42/0.28 (ethyl acetate);
Mp 189.8 – 191.2 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 1 H, *J* = 8.0 Hz, Ar*H*, *Isomer 2*), 7.59 (d, 1 H, *J* = 7.9 Hz, Ar*H*, *Isomer 1*), 7.36-7.31 (m, 2 H, Ar*H*), 7.30-7.27 (m, 2 H, Ar*H*), 7.19-7.12 (m, 2 H, Ar*H*), 7.09 (s, 1 H, Ar*H*, *Isomer 2*), 7.00 (s, 1 H, Ar*H*, *Isomer 1*), 6.00 (br s, 1 H, N*H*, *Isomer 1*), 5.92 (br s, 1 H, N*H*, *Isomer 2*), 5.24 (t, 1 H, *J* = 6.9 Hz, C*H*-NH, *Isomer 1*), 5.03 (t, 1 H, *J* = 7.9 Hz, C*H*-NH, *Isomer 2*), 3.83 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 3.68-3.59 (m, 2 H, C*H*-$(CO)_2$, *Isomer 1 & 2*), 2.96-2.88 (m, 1 H, CH_2, *Isomer 1*), 2.87-2.70 (m, 2 H, CH_2, *Isomer 2*), 2.55-2.46 (m, 1 H, CH_2, *Isomer 1*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 172.1, 170.6, 170.5, 137.7, 137.6, 126.9, 126.2, 125.7, 125.5, 122.5, 122.5, 119.8, 119.7, 119.3, 119.0, 114.8, 113.8, 109.9, 109.8, 53.0, 52.9, 50.4, 49.8, 48.8, 48.1, 33.9, 33.7, 33.0;[17]
IR 3235 (w), 2953 (w), 1741 (s), 1703 (s), 1475 (w), 1334 (w), 1264 (w), 1168 (w);
HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 295.1053; found 295.1059.

2,2,2-Trifluoroethyl 4-(1,3-dioxoisoindolin-2-yl)-4-(1-methyl-1*H*-indol-3-yl)butanoate (13)



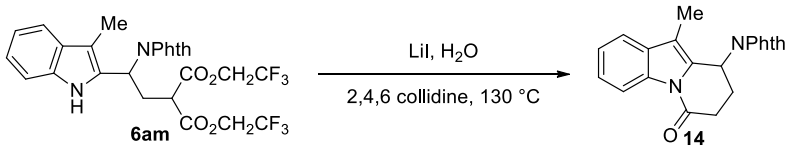
Following a modified procedure,[19] a mixture of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethyl)malonate **6ag** (114 mg, 0.200 mmol, 1 equiv), lithium iodide (40.2 mg, 0.300 mmol, 1.5 equiv) and water (7.20 µl, 0.400 mmol, 2 equiv) in 2,4,6-collidine (2.00 mL) in a microwave vial sealed with a microwave cap was heated at 130 °C for 3 hours. After cooling down to room temperature, the mixture was diluted with AcOEt (5 mL), washed with 1 M HCl (5 mL) four times and sat. $NaHCO_3$-brine (1:3) (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the product (**13**) as a pale yellow solid (90.3 mg, 0.200 mmol, 100% yield).

R*f* 0.58 (hexane/AcOEt 6/4);
Mp 54.6 – 57.0 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.76 (m, 2 H, *Phth*), 7.74 (d, 1 H, *J* = 8.1 Hz, Ar*H*), 7.69-7.63 (m, 2 H, *Phth*), 7.39 (s, 1 H, Ar*H*), 7.31-7.26 (m, 1 H, Ar*H*), 7.22 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.15-7.09 (m, 1 H, Ar*H*), 5.77 (dd, 1 H, *J* = 9.1, 7.1 Hz, PhthN-C*H*), 4.52-4.38 (m, 2 H, CF_3-CH_2), 3.79 (s, 3 H, CH_3), 2.98-2.76 (m, 2 H, CH_2), 2.63-2.49 (m, 2 H, CH_2);
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 168.3, 136.6, 134.0, 132.0, 128.8, 127.0, 123.3, 123.0 (q, J_{C-F} = 277 Hz), 122.0, 119.7, 119.1, 111.9, 109.4, 60.5 (q, J_{C-F} = 37 Hz), 45.9, 33.1, 31.4, 26.9;

[19] Y. Kaburagi, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2004**, *126*, 10246-10247.

IR 3061 (w), 2941 (w), 1761 (m), 1711 (s), 1473 (w), 1384 (m), 1330 (m), 1285 (m), 1171 (s);
HRMS (ESI) calcd for $C_{23}F_3H_{20}N_2O_4^+$ $[M+H]^+$ 445.1370; found 445.1356.

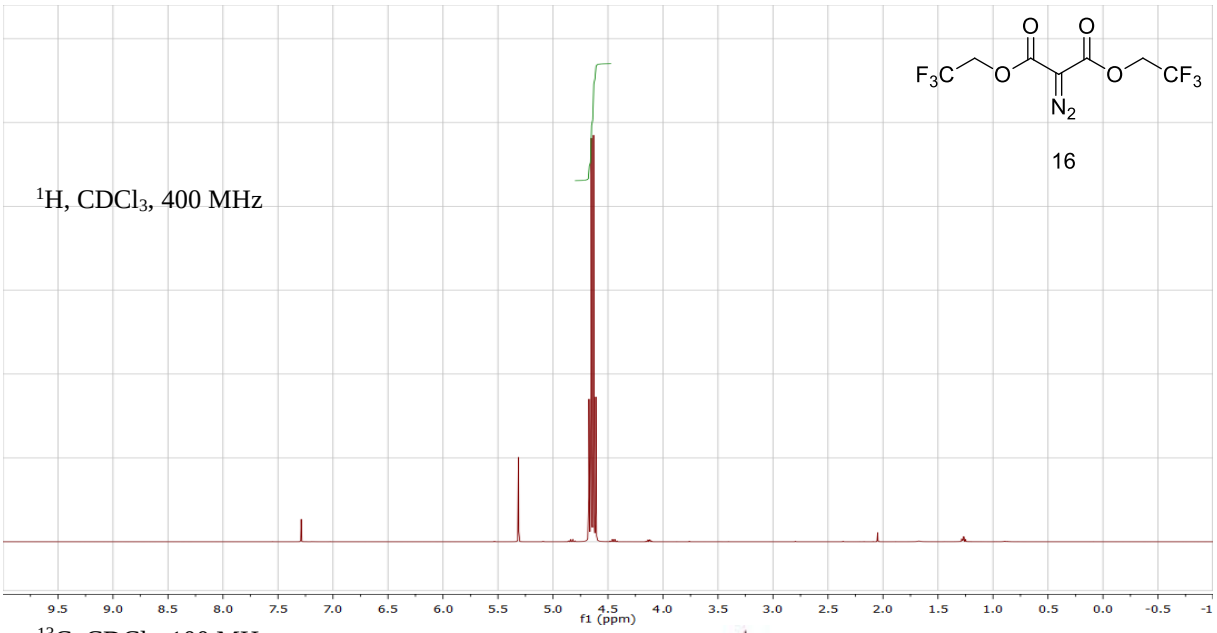
2-(10-Methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-9-yl)isoindoline-1,3-dione (14)

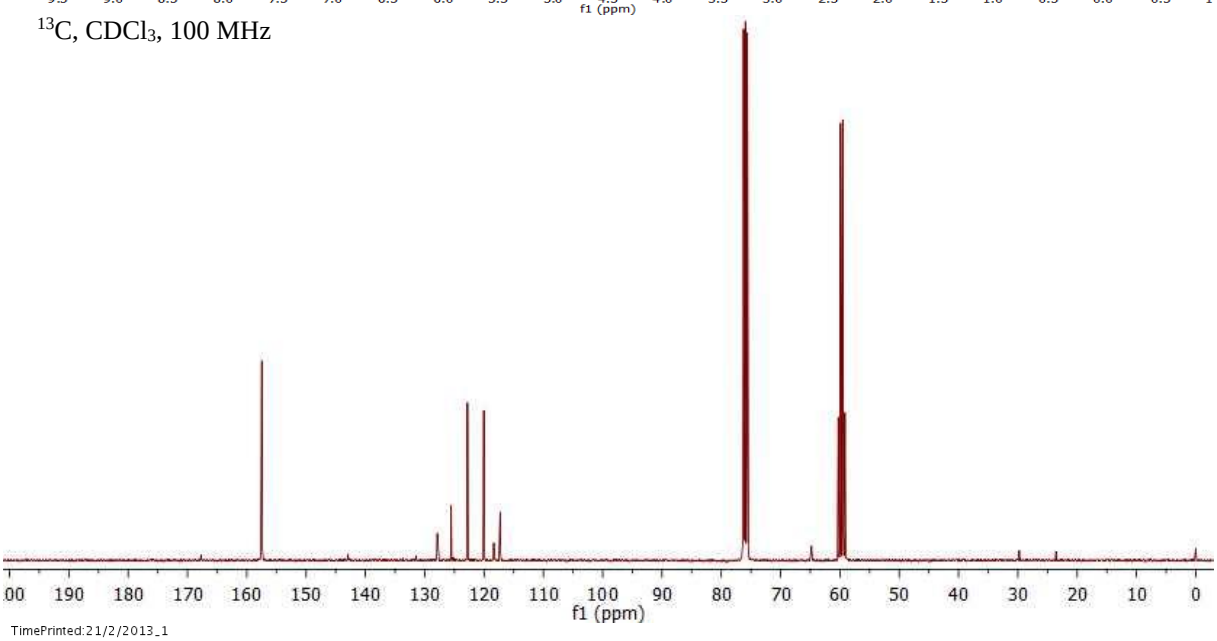


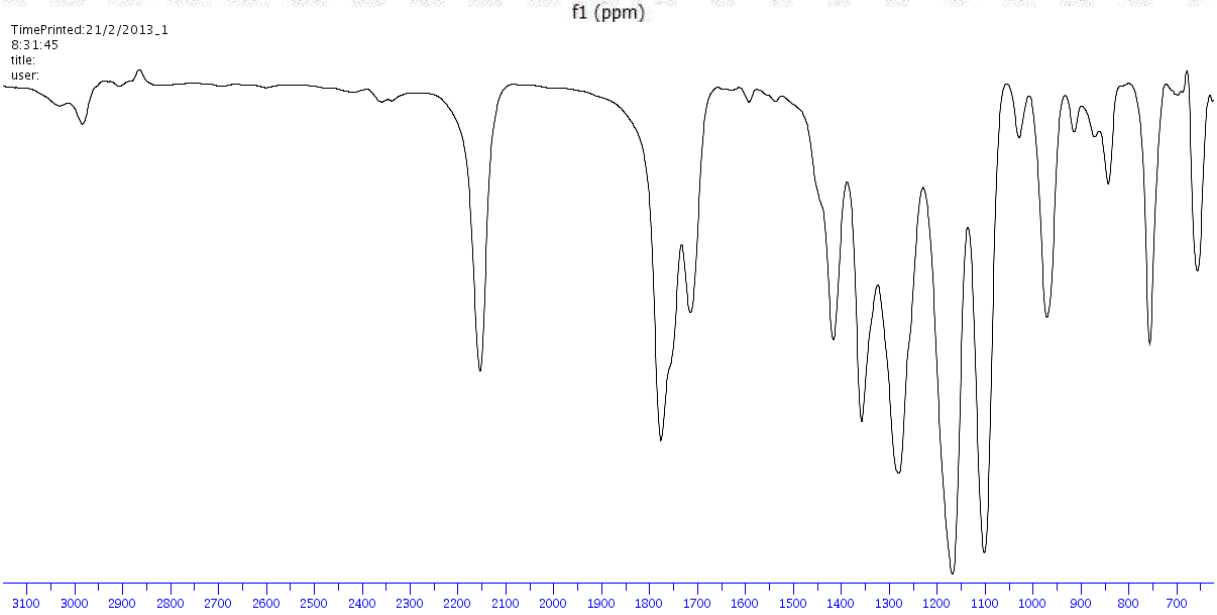
A suspension of bis(2,2,2-trifluoroethyl) 2-(2-(1,3-dioxoisoindolin-2-yl)-2-(3-methyl-1*H*-indol-2-yl)ethyl)malonate **6am** (122 mg, 0.214 mmol, 1equiv), lithium iodide (42.9 mg, 0.321 mmol, 1.5 equiv) and water (7.71 µl, 0.428 mmol, 2 equiv) in 2,4,6-collidine (2.10 mL) in a microwave vial sealed with a microwave cap was heated at 130 °C for 18.5 hours and then at 140 °C for 5.5 hours. After cooling down to room temperature, the mixture was diluted with AcOEt (5 mL), washed with 1 M HCl (5 mL) four times and sat. $NaHCO_3$-brine (1:3) (5 mL) twice, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude as a light brown solid. The crude was purified by Biotage (SNAP cartridge KP-Sil 25 g, pentane/AcOEt 90/10 to 61/39) to afford 2-(10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-9-yl)isoindoline-1,3-dione **14** (53.4 mg, 0.155 mmol, 73% yield) as an colorless solid.

R_f 0.40 (hexane/AcOEt 6/4);
Mp 177.5 – 180.8 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, 1 H, *J* = 8.2 Hz, Ar*H*), 7.87-7.81 (m, 2 H, *Phth*), 7.78-7.71 (m, 2 H, *Phth*), 7.43 (d, 1 H, *J* = 7.7 Hz, Ar*H*), 7.40-7.34 (m, 1 H, Ar*H*), 7.31-7.27 (m, 1 H, Ar*H*), 5.85 (t, 1 H, *J* = 4.9 Hz, PhthN-C*H*), 3.12-3.01 (m, 1 H, CH_2), 2.83 (dt, 1 H, *J* = 17.4, 5.1 Hz, CH_2), 2.54-2.37 (m, 2 H, CH_2),2.09 (s, 3 H);[12]
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 167.8, 134.9, 134.5, 131.6, 130.4, 129.2, 125.6, 123.9, 123.7, 118.5, 116.8, 115.4, 42.0, 31.6, 27.3, 8.5;
IR 3068 (w), 1773 (w), 1713 (s), 1458 (m), 1388 (m), 1366 (m), 1326 (m);
HRMS (ESI) calcd for $C_{21}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 367.1053; found 367.1037.

9. Spectra of new compounds.


^{1}H, CDCl$_3$, 400 MHz
F3C
O
O
O
O
CF3
N2
16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


^{13}C, CDCl$_3$, 100 MHz
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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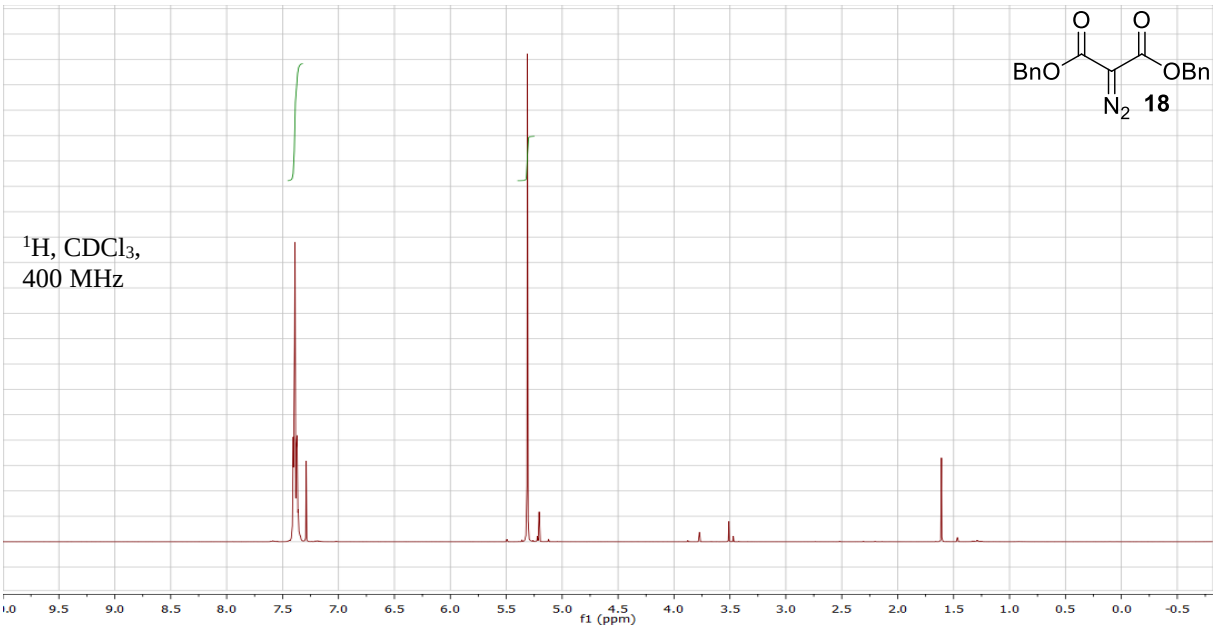
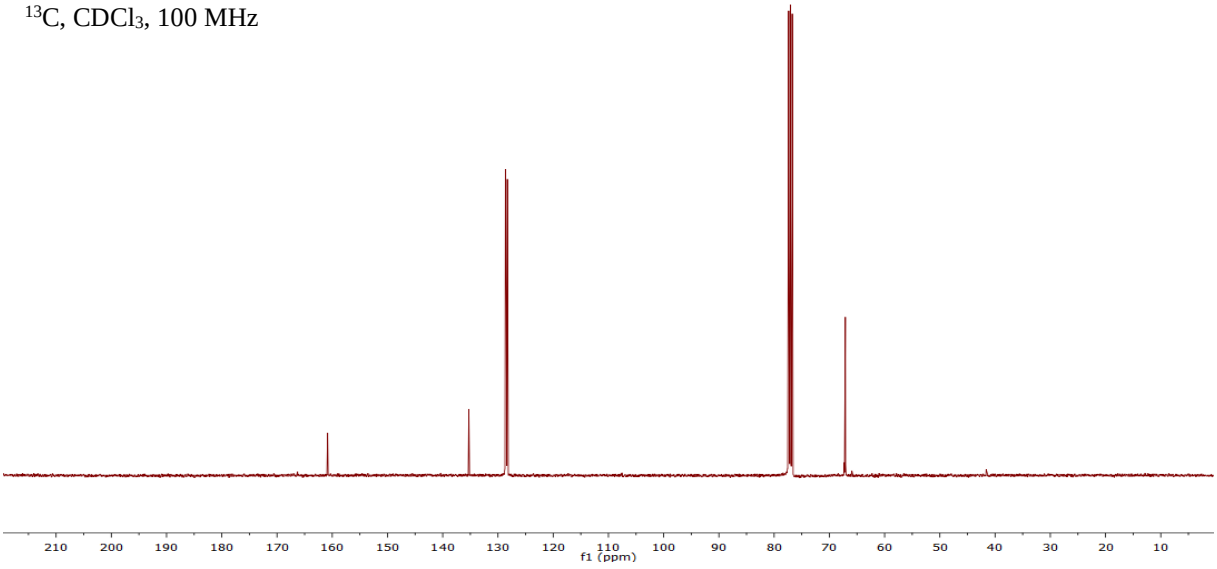
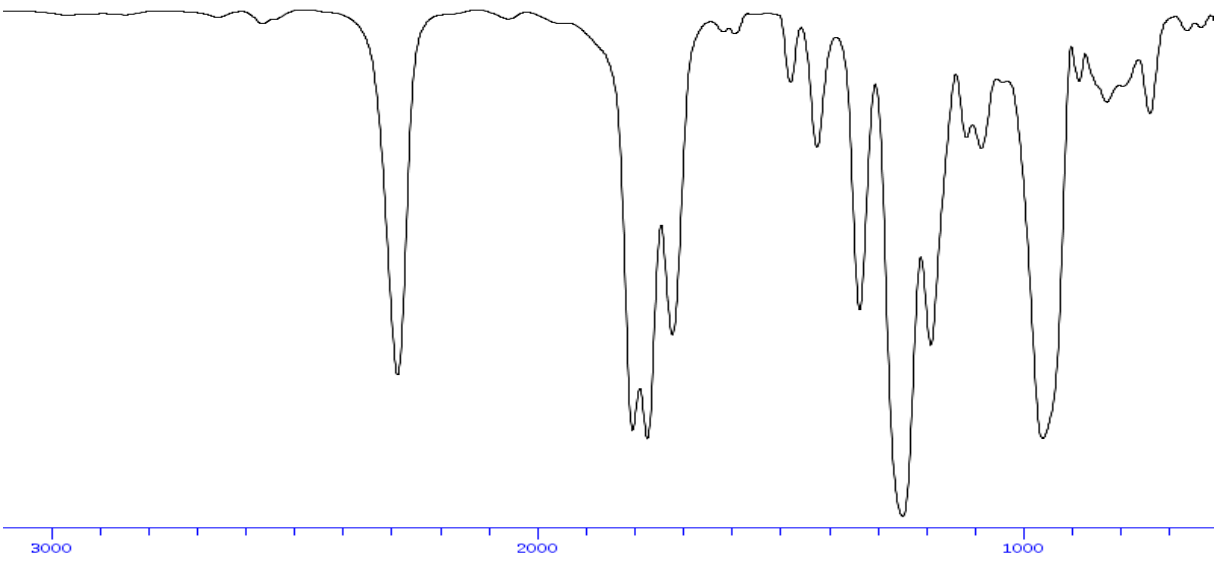
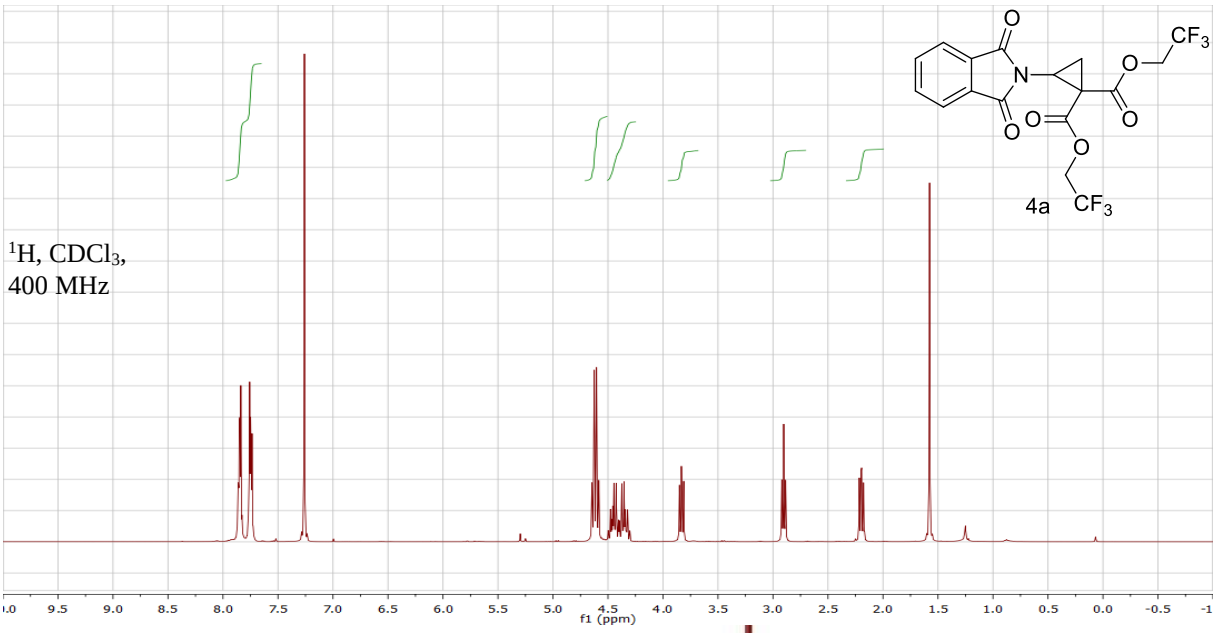
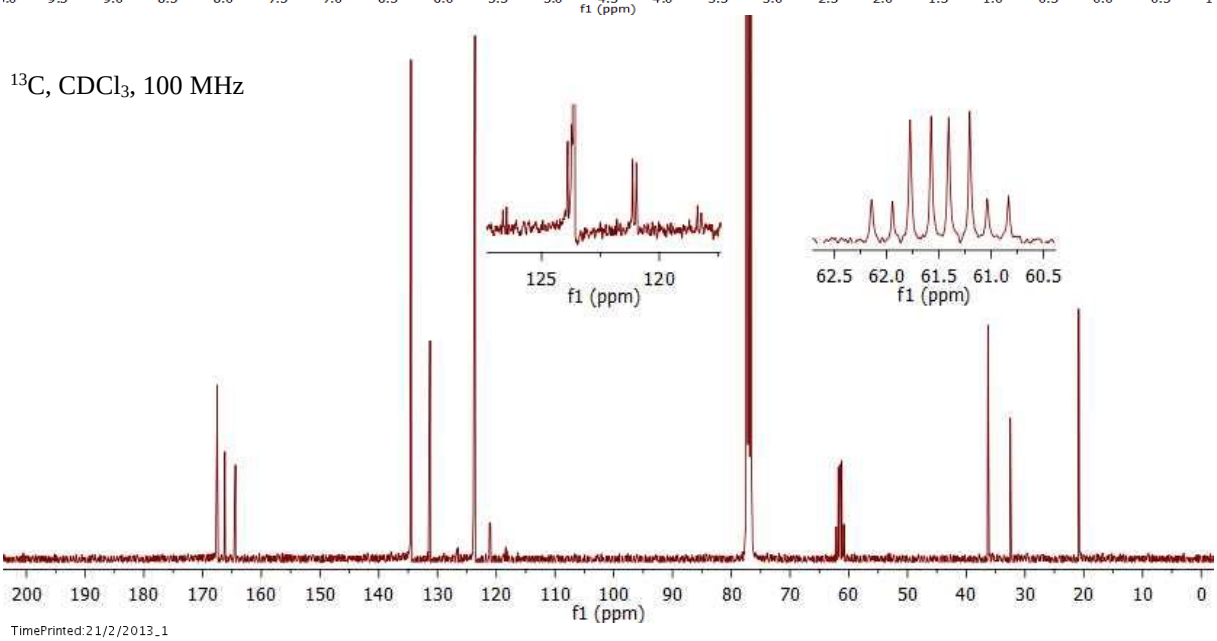
8:31:45
title:
user:
3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700

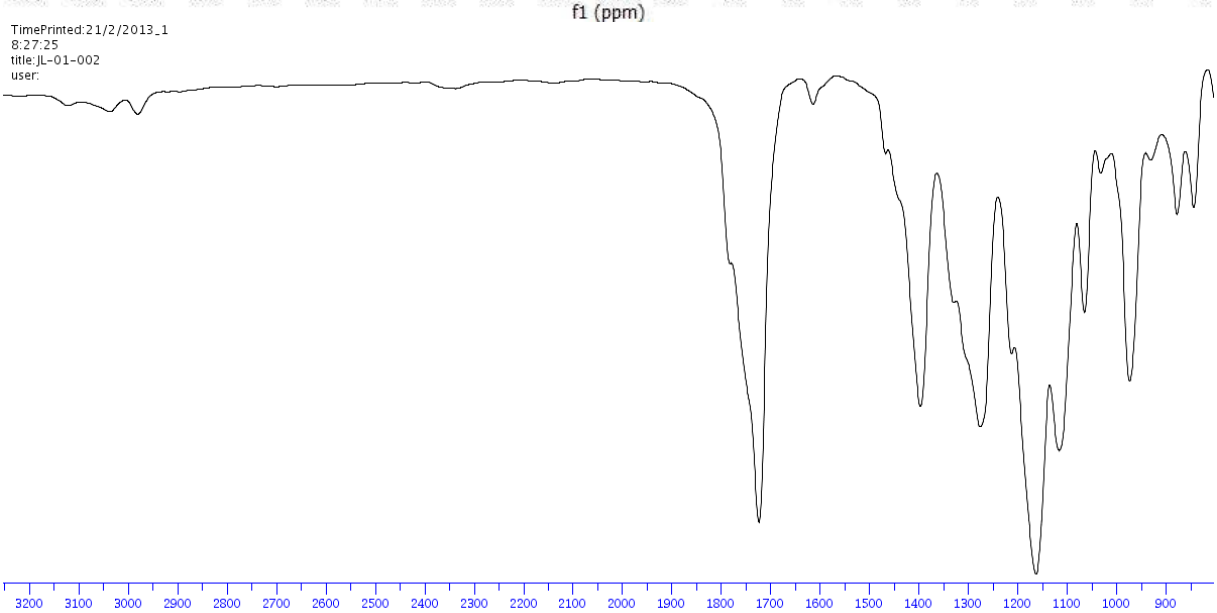

O
O
BnO
OBn
N2
18
1H, CDCl3,
400 MHz
f1 (ppm)


13C, CDCl3, 100 MHz
f1 (ppm)


3000
2000
1000


^{1}H, CDCl$_3$,
400 MHz
4a
CF$_3$
f1 (ppm)


^{13}C, CDCl$_3$, 100 MHz
125
120
62.5 62.0 61.5 61.0 60.5
f1 (ppm)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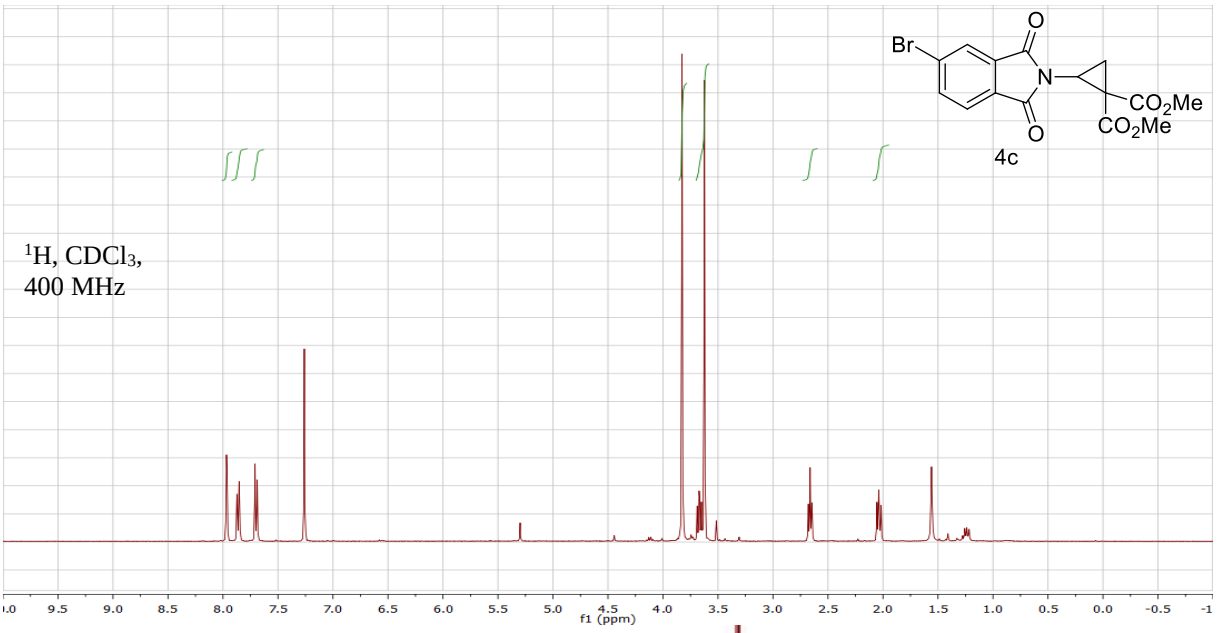
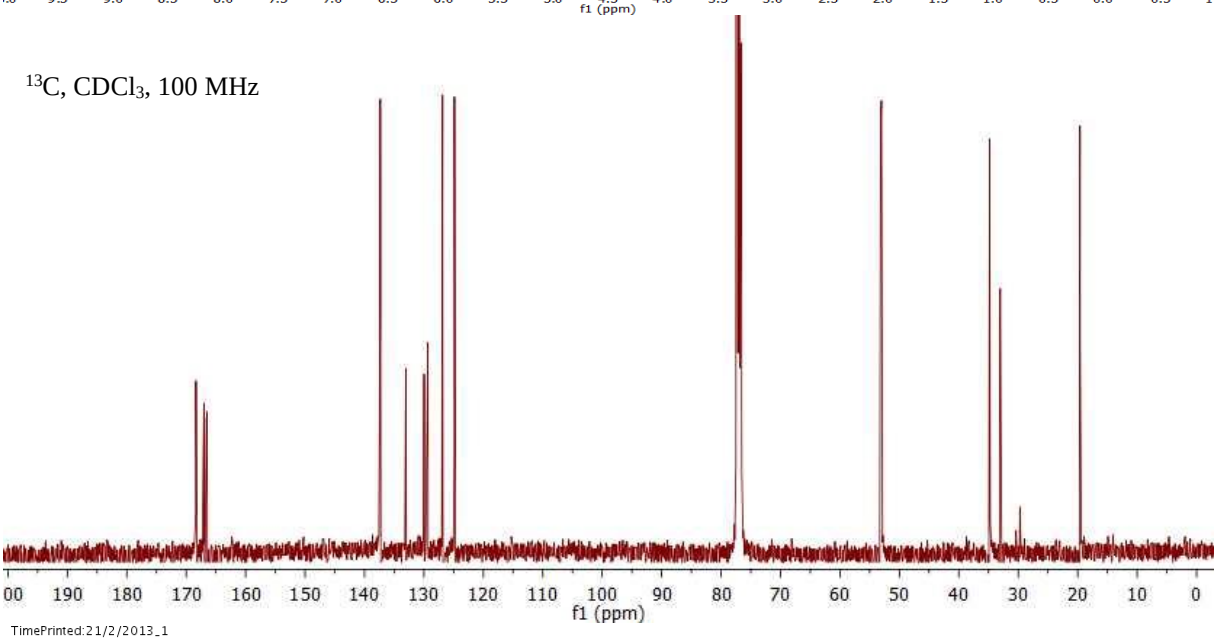
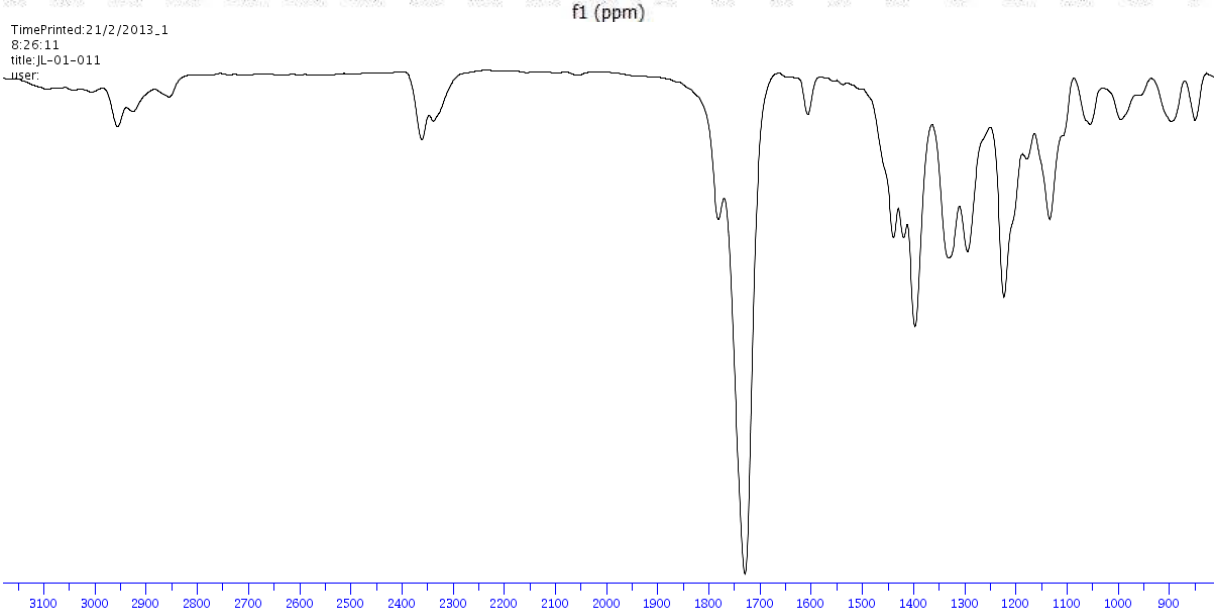
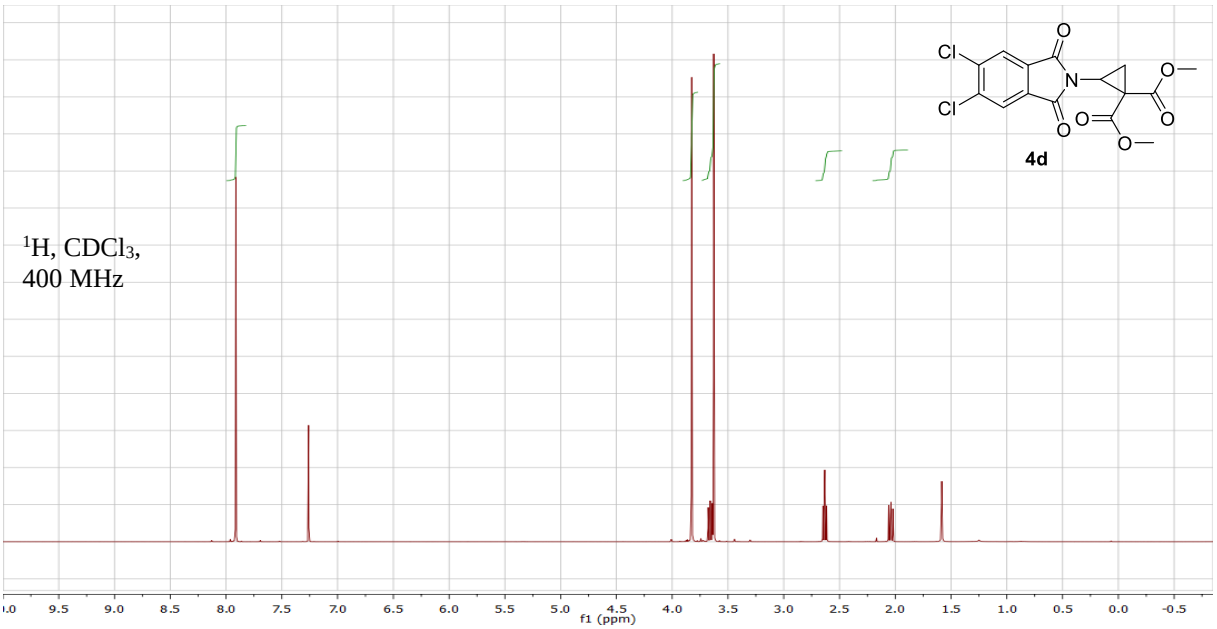
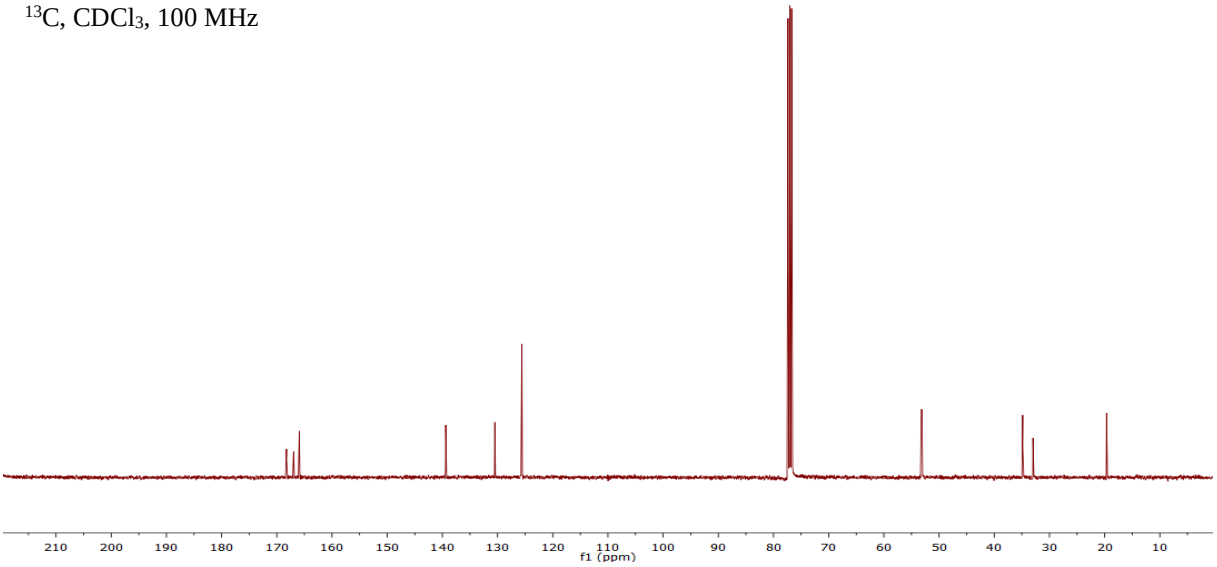
8:27:25
title:JL-01-002
user:

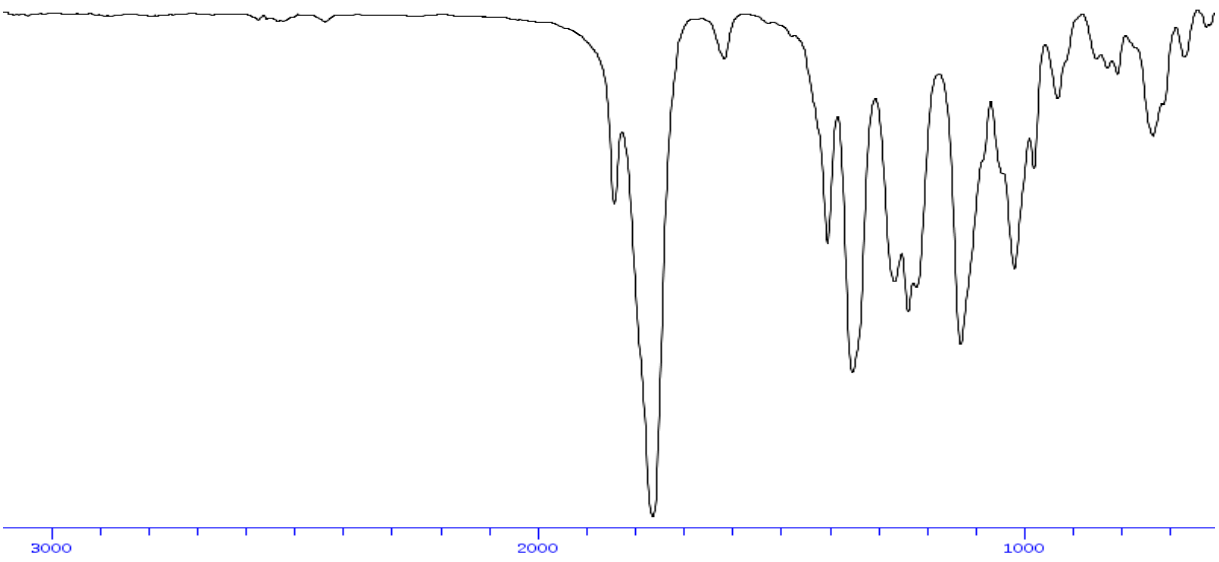

Br
O
N
O
CO2Me
CO2Me
4c
1H, CDCl3,
400 MHz
f1 (ppm)

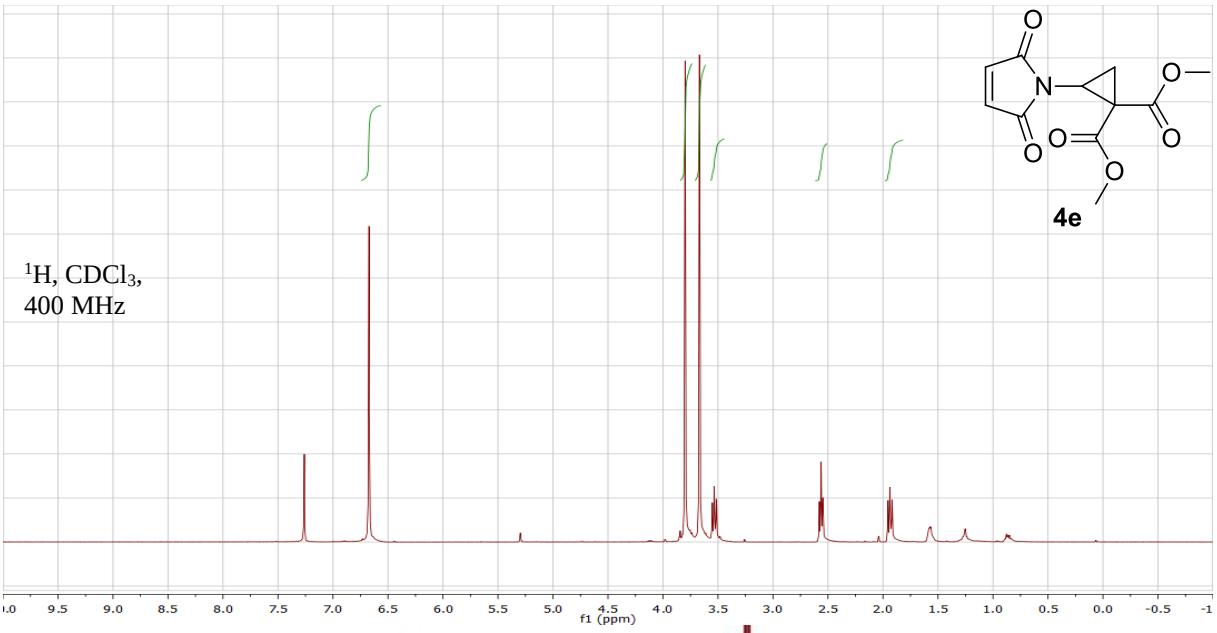

13C, CDCl3, 100 MHz
f1 (ppm)

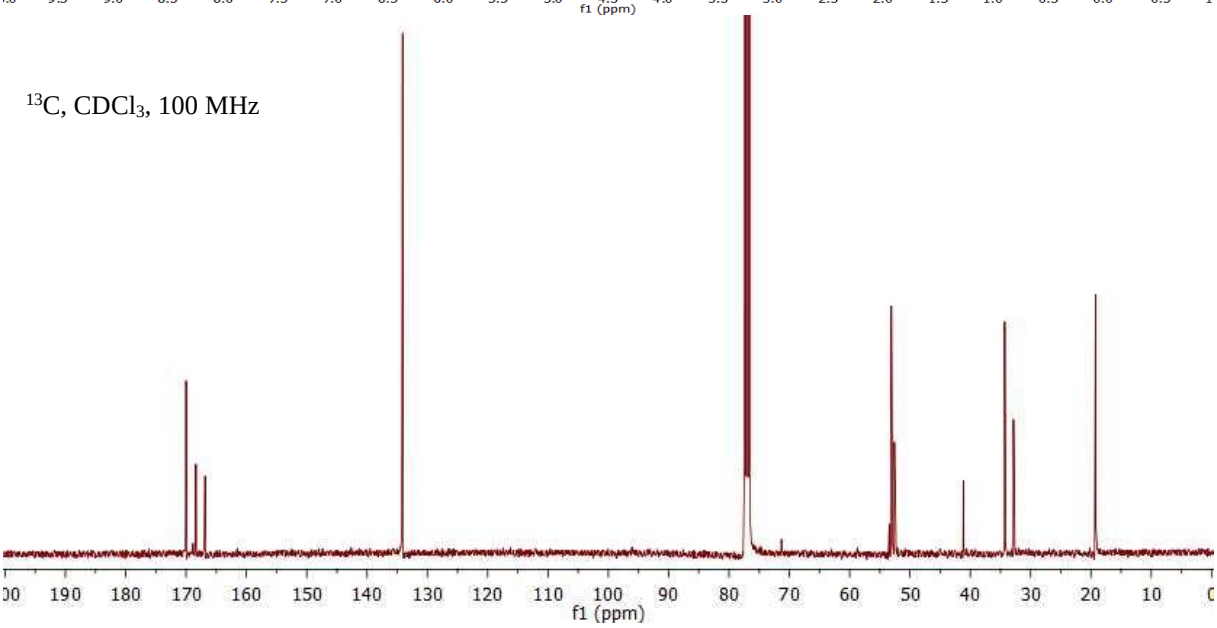

TimePrinted:21/2/2013_1
8:26:11
title:JL-01-011
user:

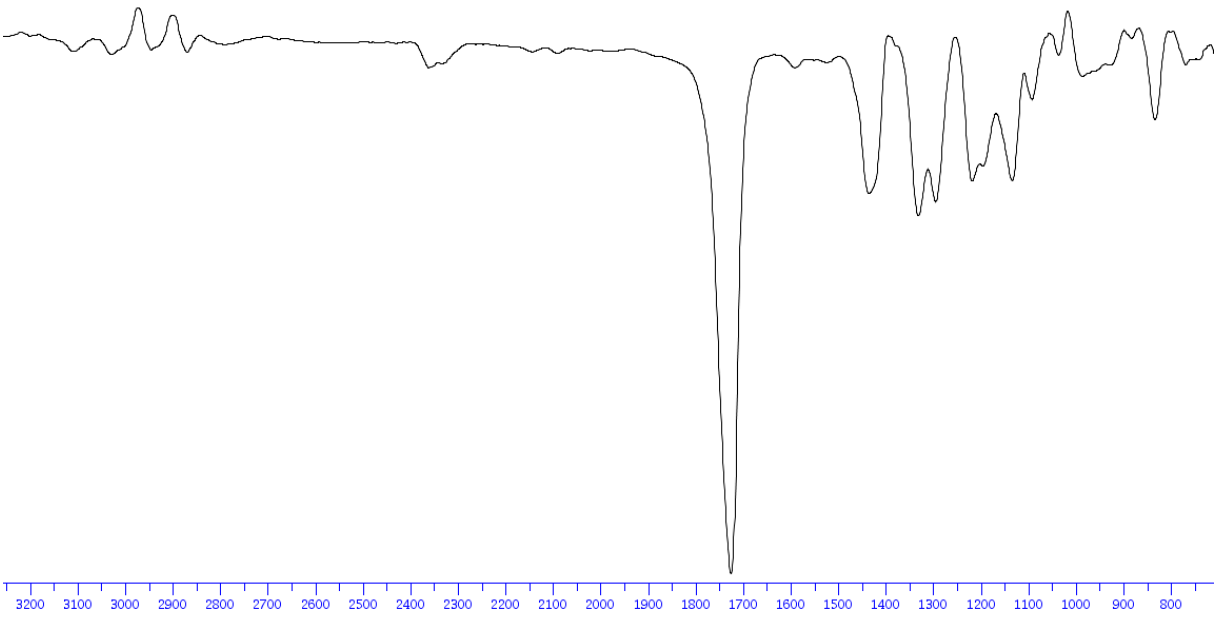

Cl
Cl
O
N
O
O
O
O
O
4d
^{1}H, $CDCl_3$,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

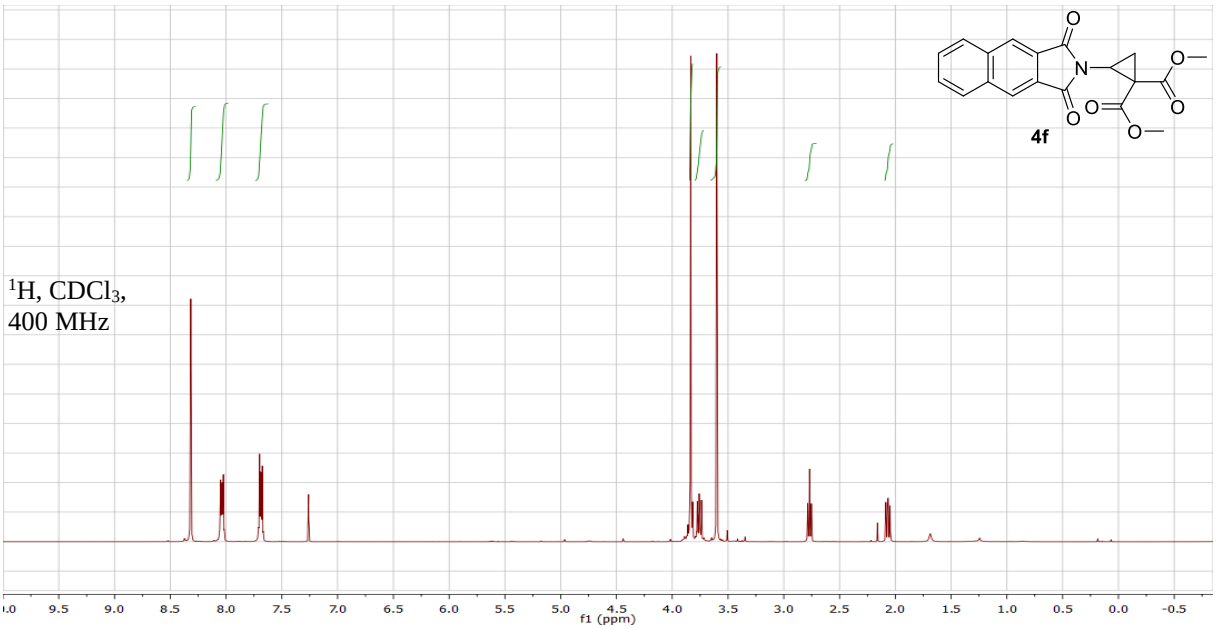

^{13}C, $CDCl_3$, 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

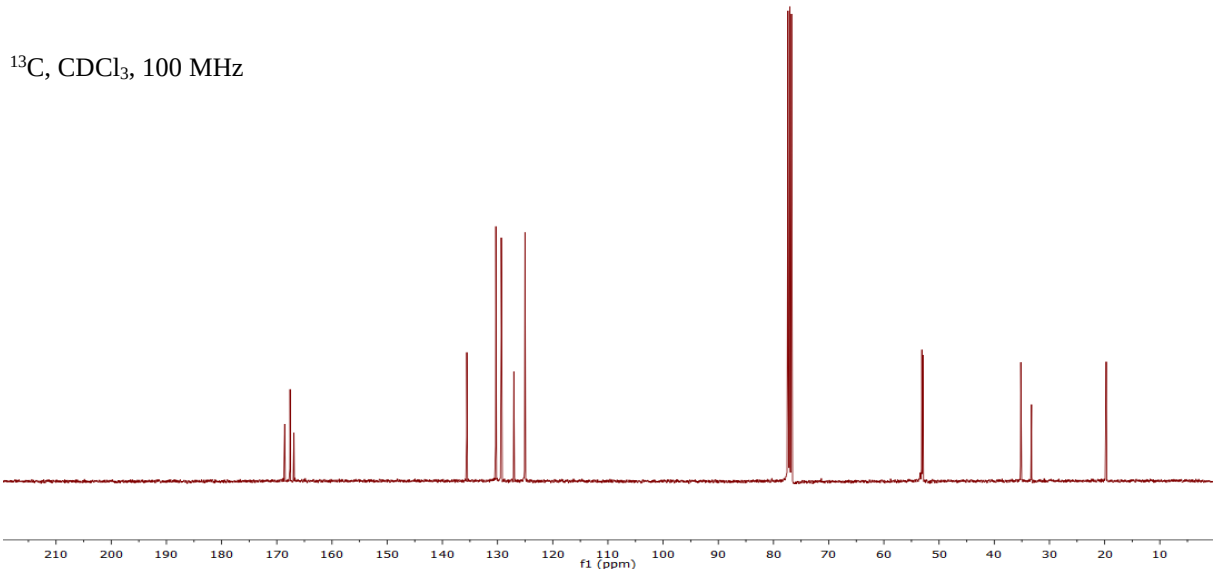

3000
2000
1000

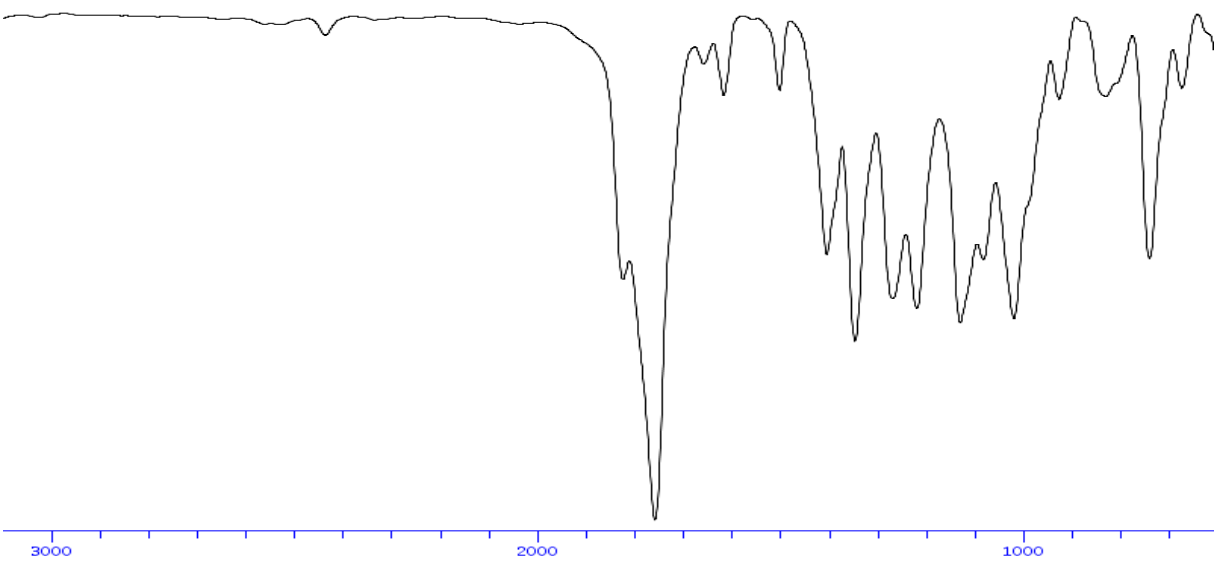

^{1}H, $CDCl_3$,
400 MHz
4e
f1 (ppm)

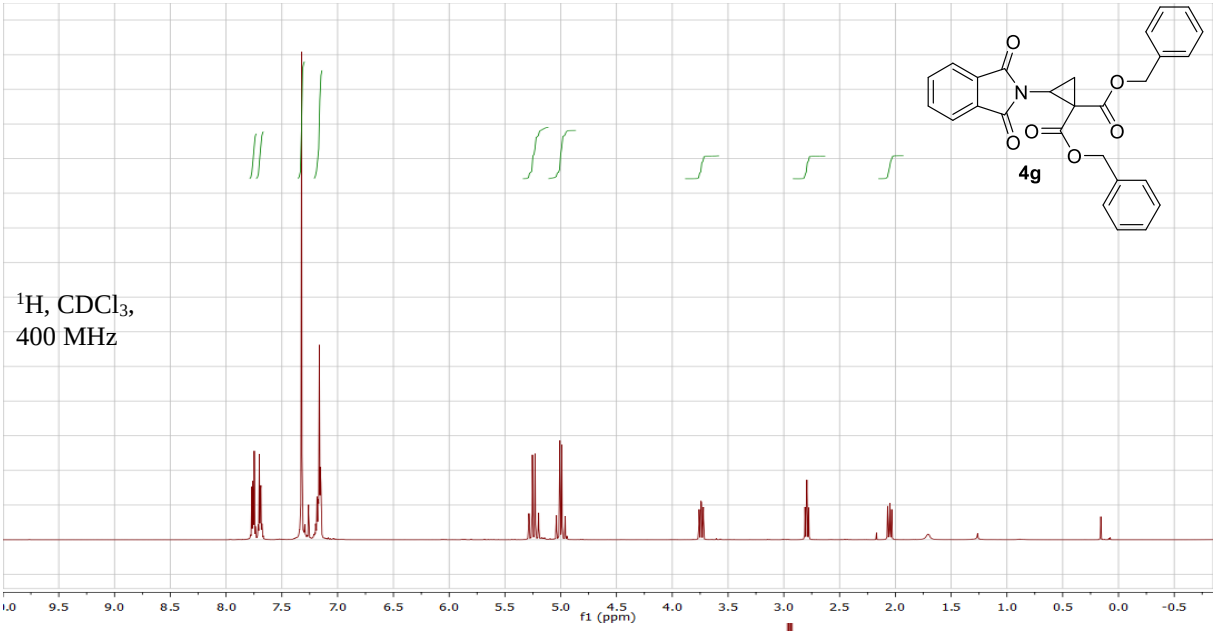

^{13}C, $CDCl_3$, 100 MHz
f1 (ppm)

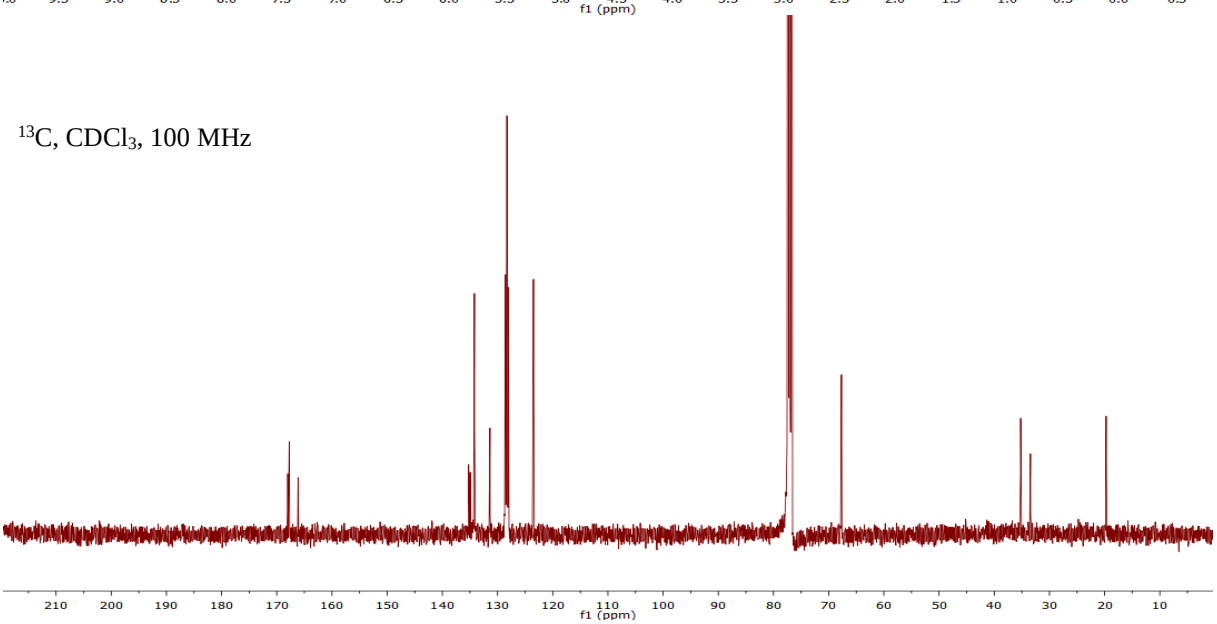


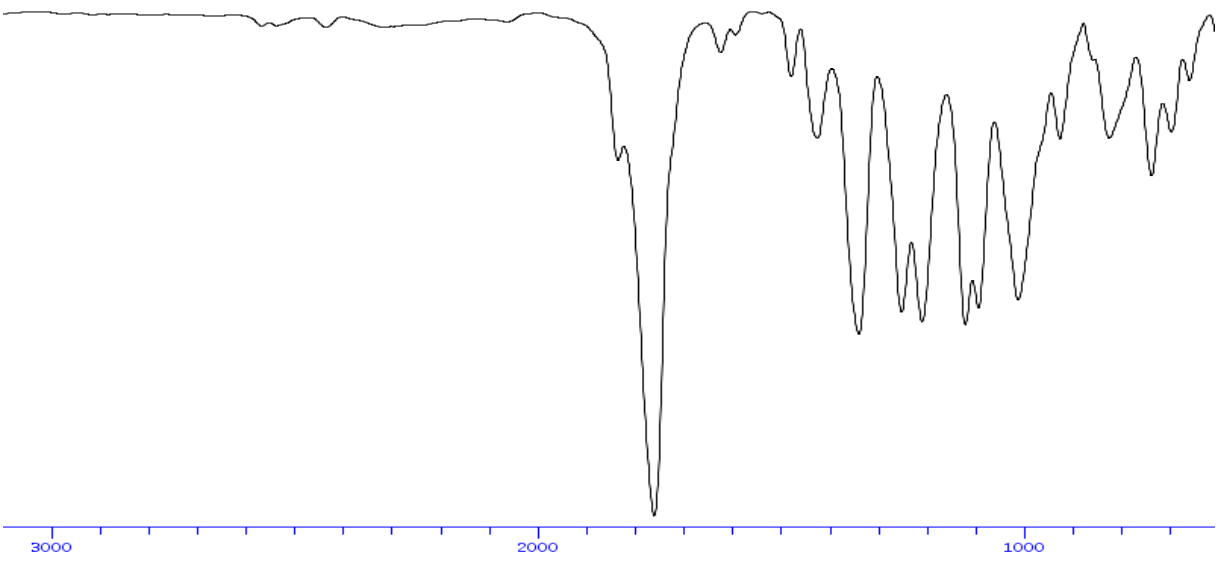

4f
^{1}H, $CDCl_3$,
400 MHz
f1 (ppm)

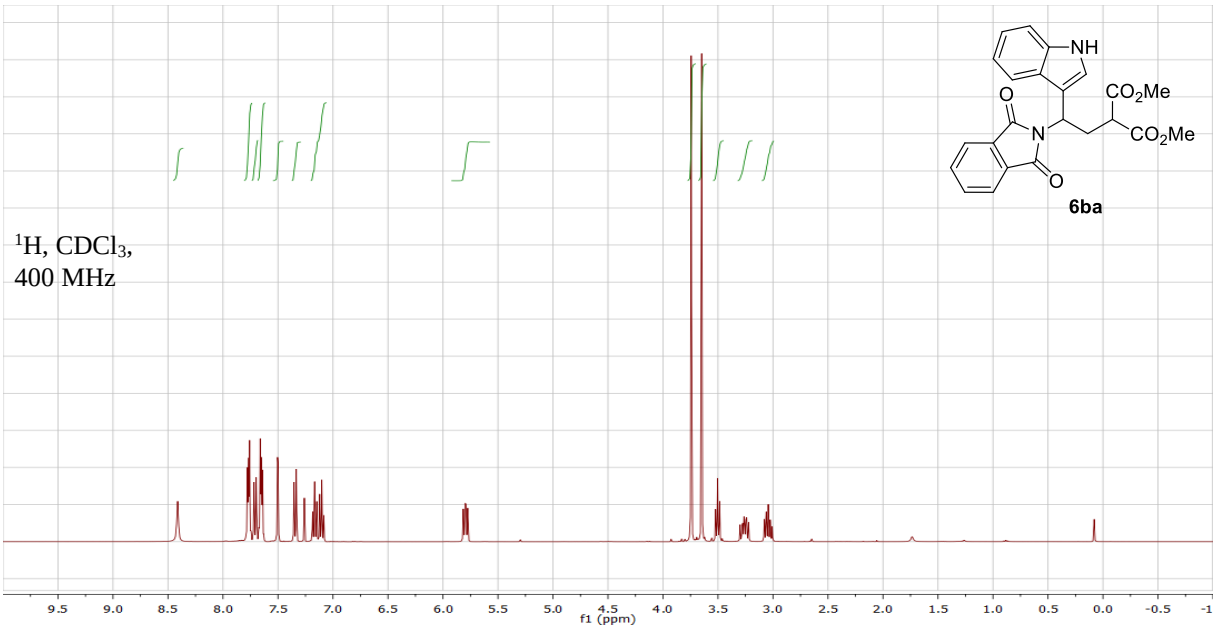

^{13}C, $CDCl_3$, 100 MHz
f1 (ppm)

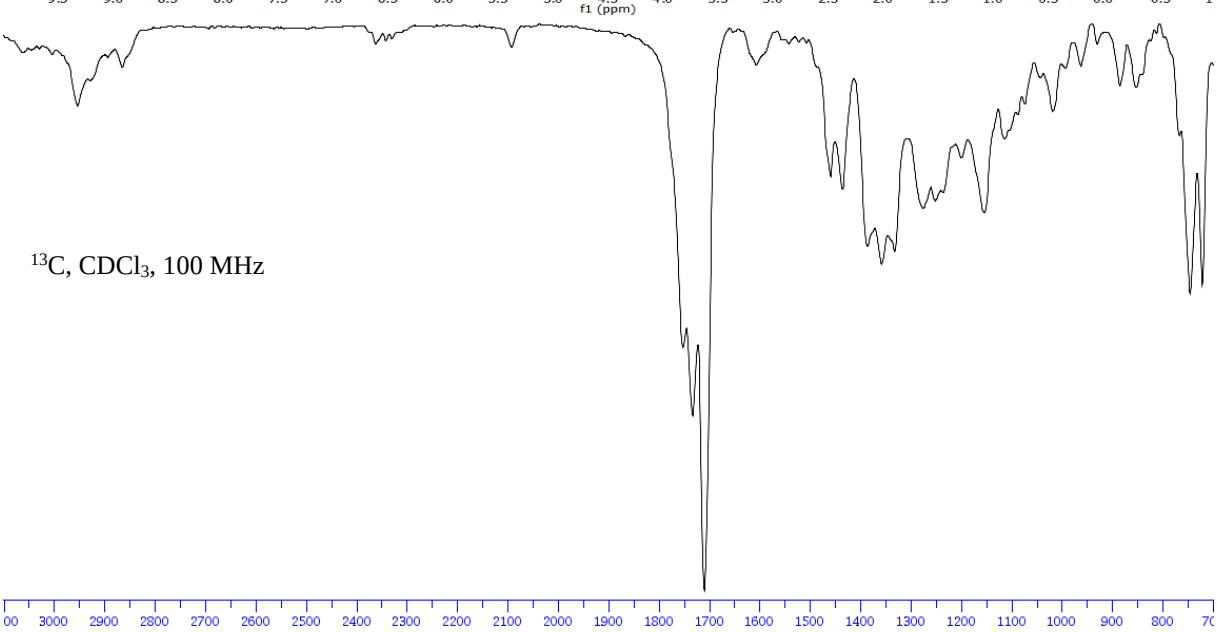

3000
2000
1000

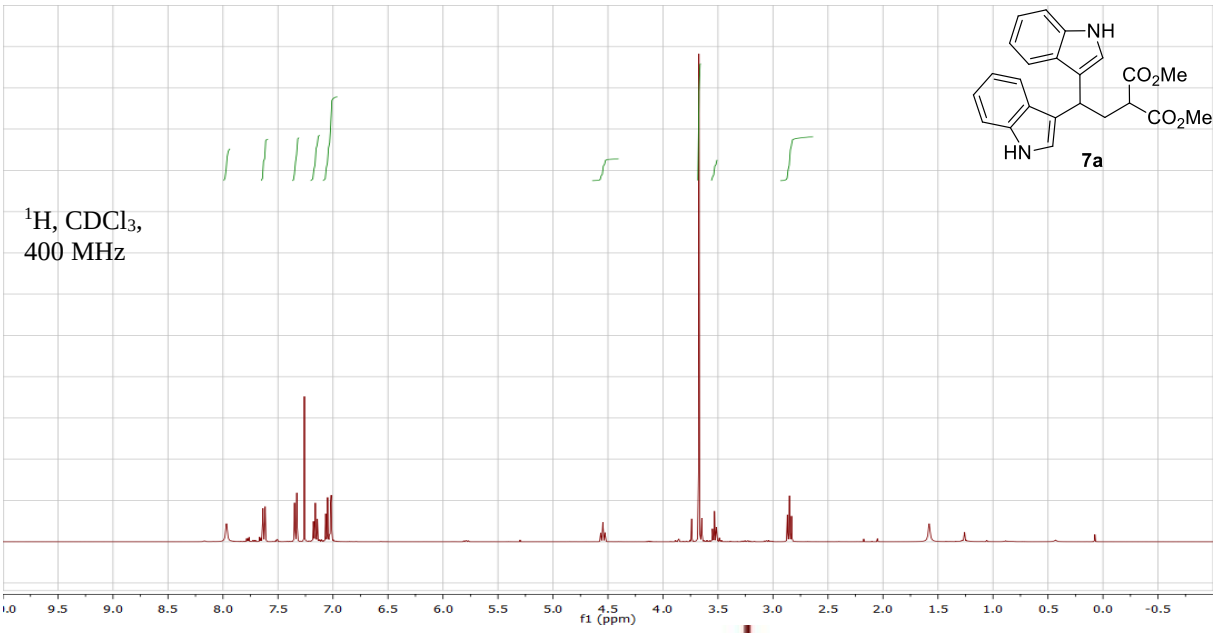

4g
^{1}H, $CDCl_3$,
400 MHz
f1 (ppm)

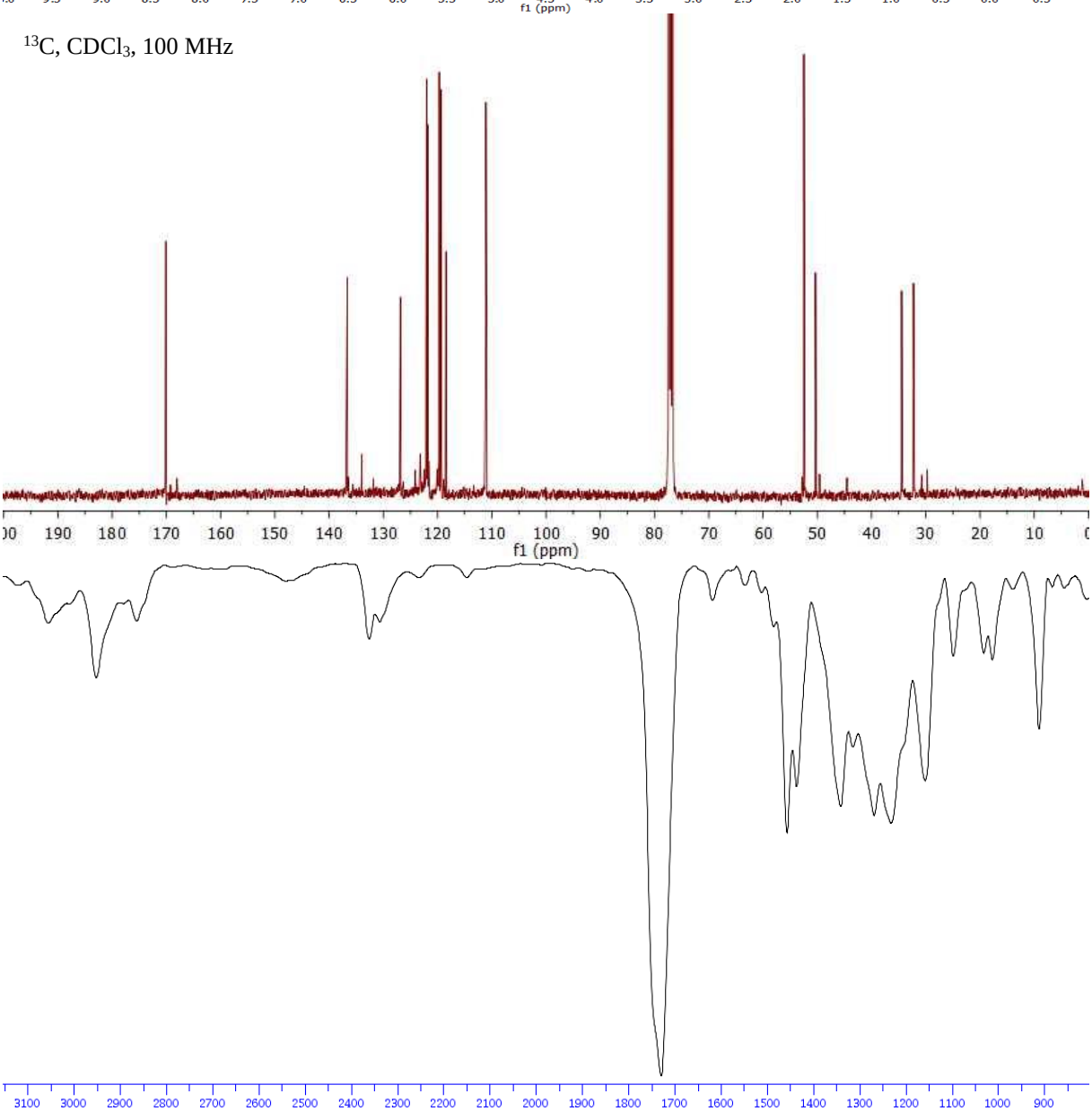

^{13}C, $CDCl_3$, 100 MHz
f1 (ppm)

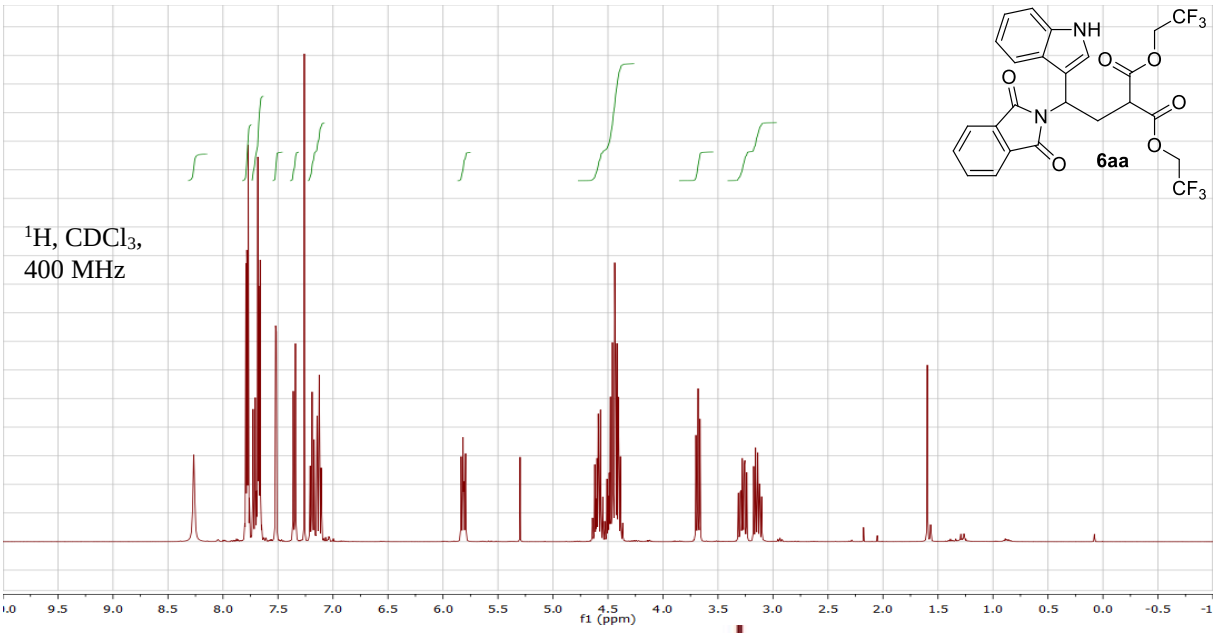

3000
2000
1000

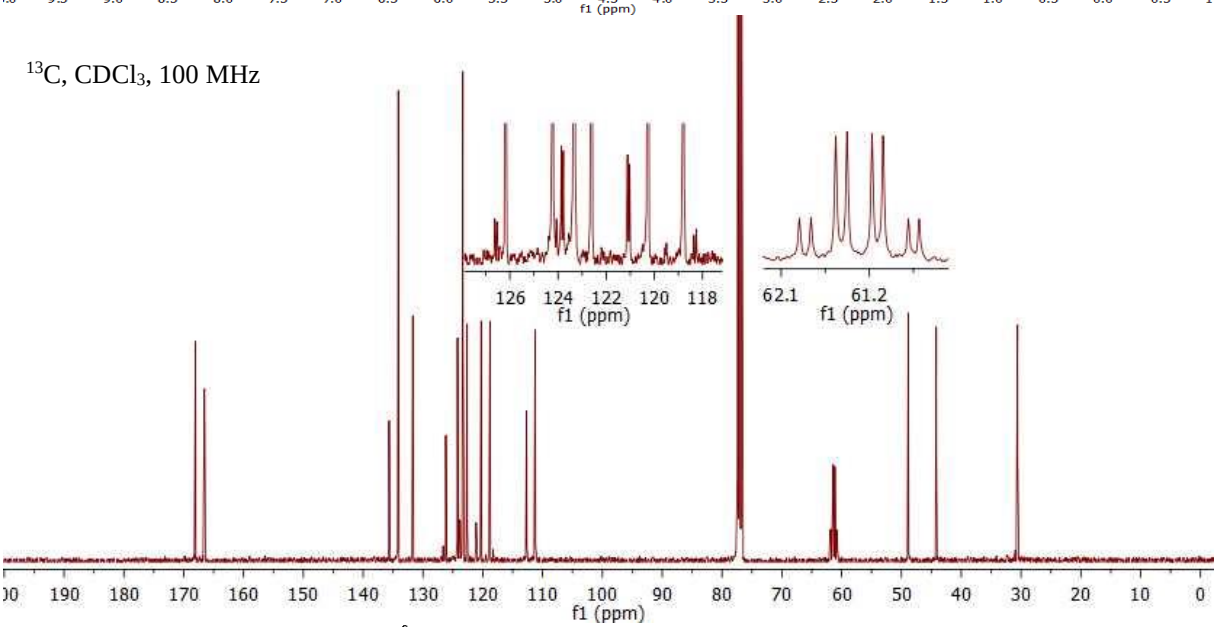

NH
O
N
O
CO2Me
CO2Me
O
6ba
1H, CDCl3,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

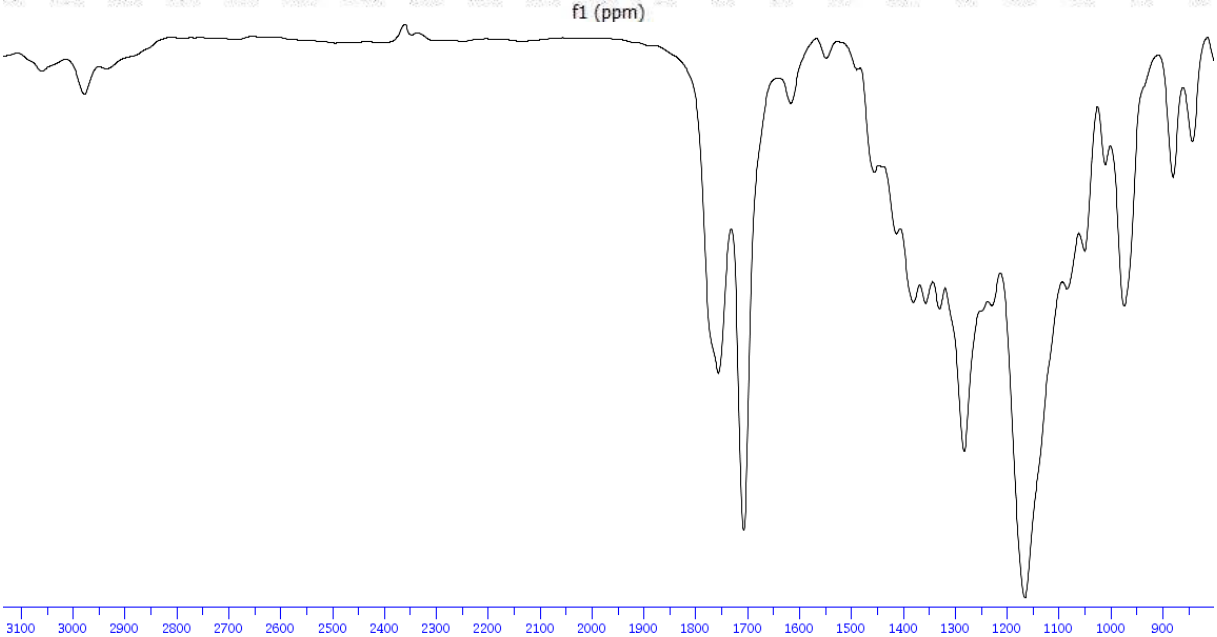

13C, CDCl3, 100 MHz
00 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 70
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

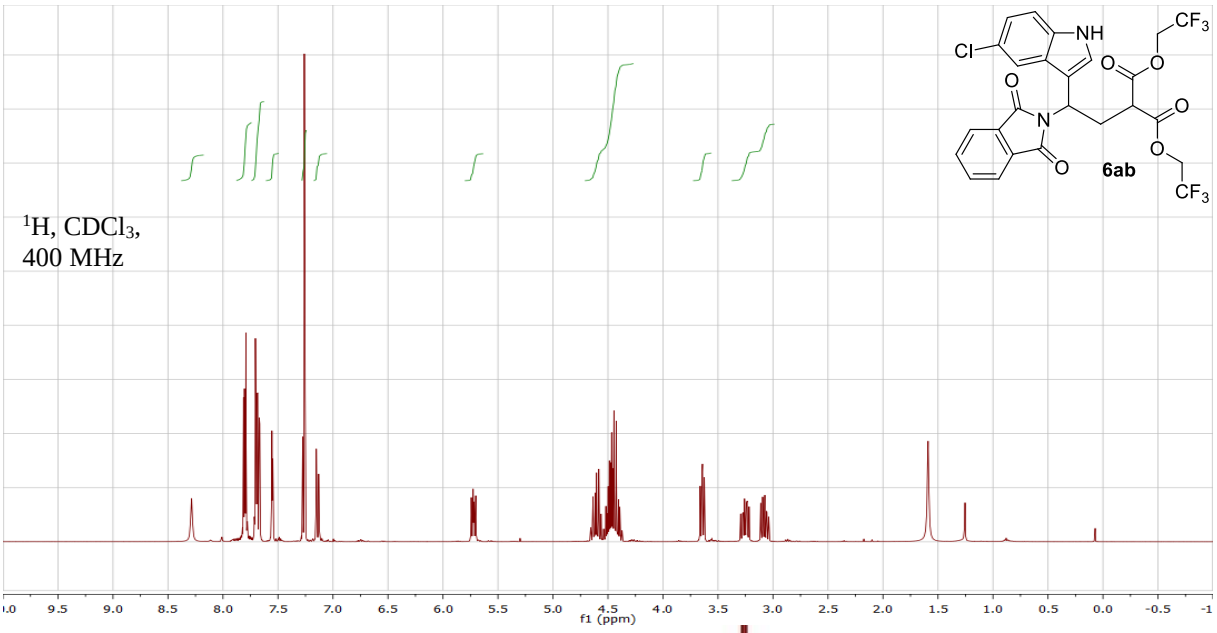

NH
CO2Me
CO2Me
HN
7a
1H, CDCl3,
400 MHz
f1 (ppm)

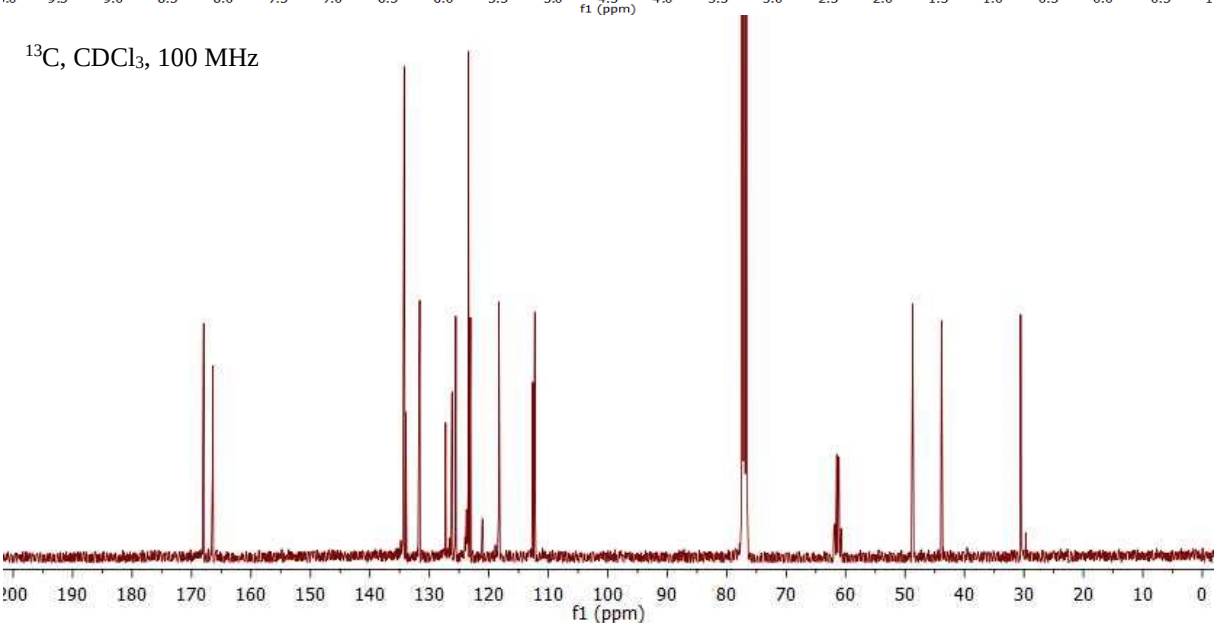

13C, CDCl3, 100 MHz
f1 (ppm)

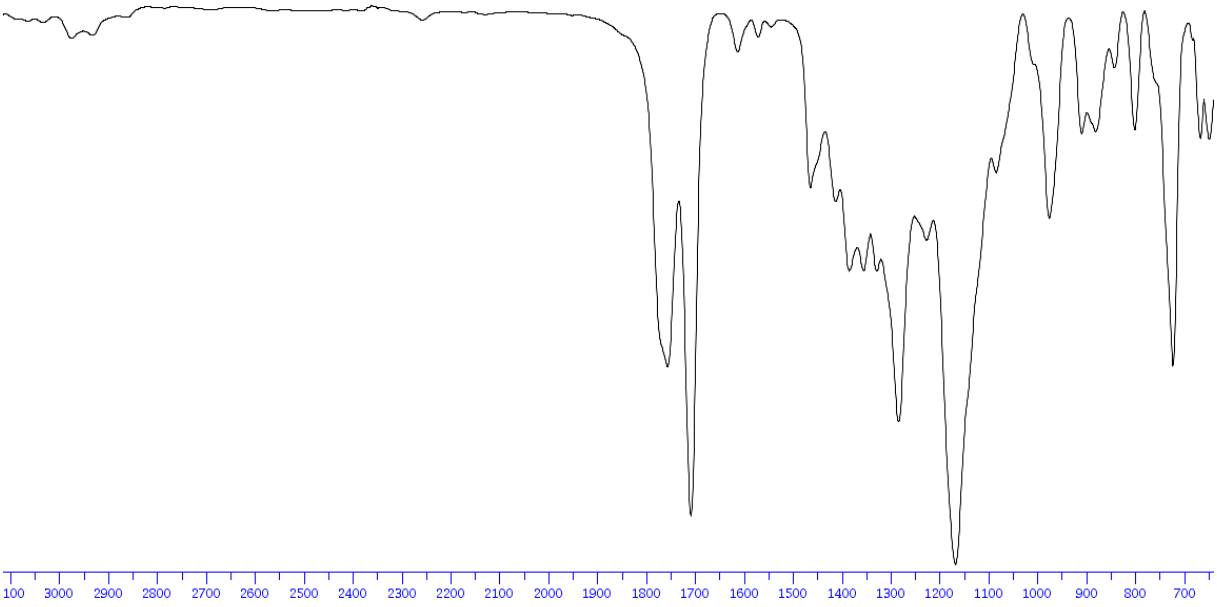

^{1}H, CDCl$_3$,
400 MHz
NH
O
O
O
N
O
O
O
O
CF$_3$
CF$_3$
6aa
f1 (ppm)

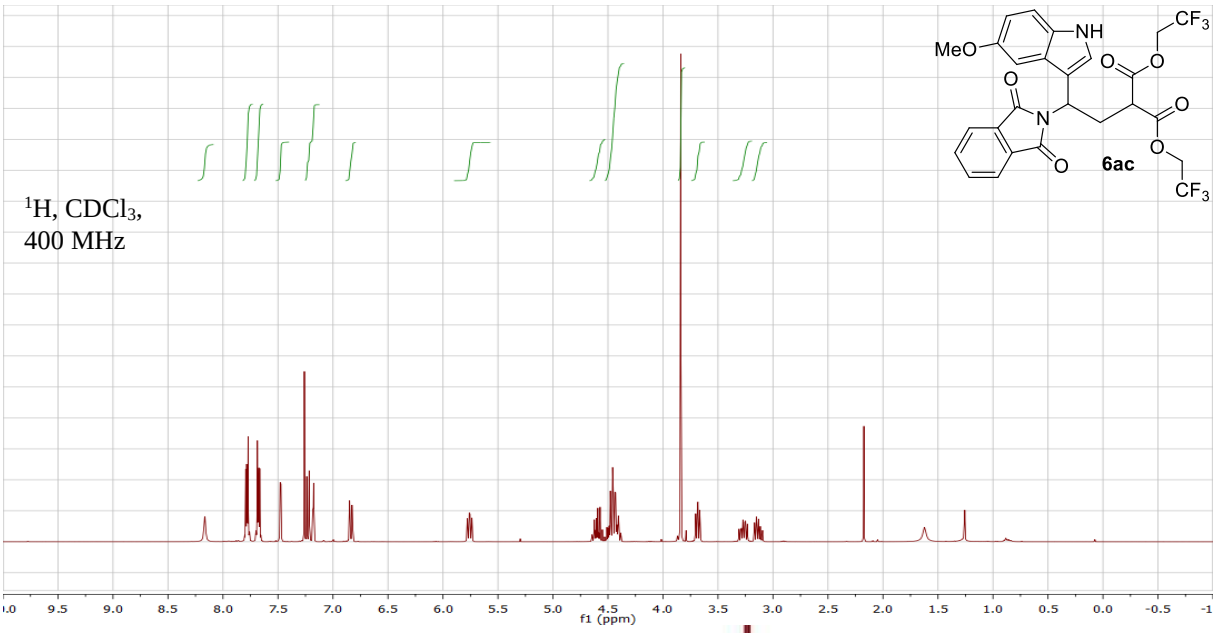

^{13}C, CDCl$_3$, 100 MHz
126 124 122 120 118
f1 (ppm)
62.1 61.2
f1 (ppm)
f1 (ppm)



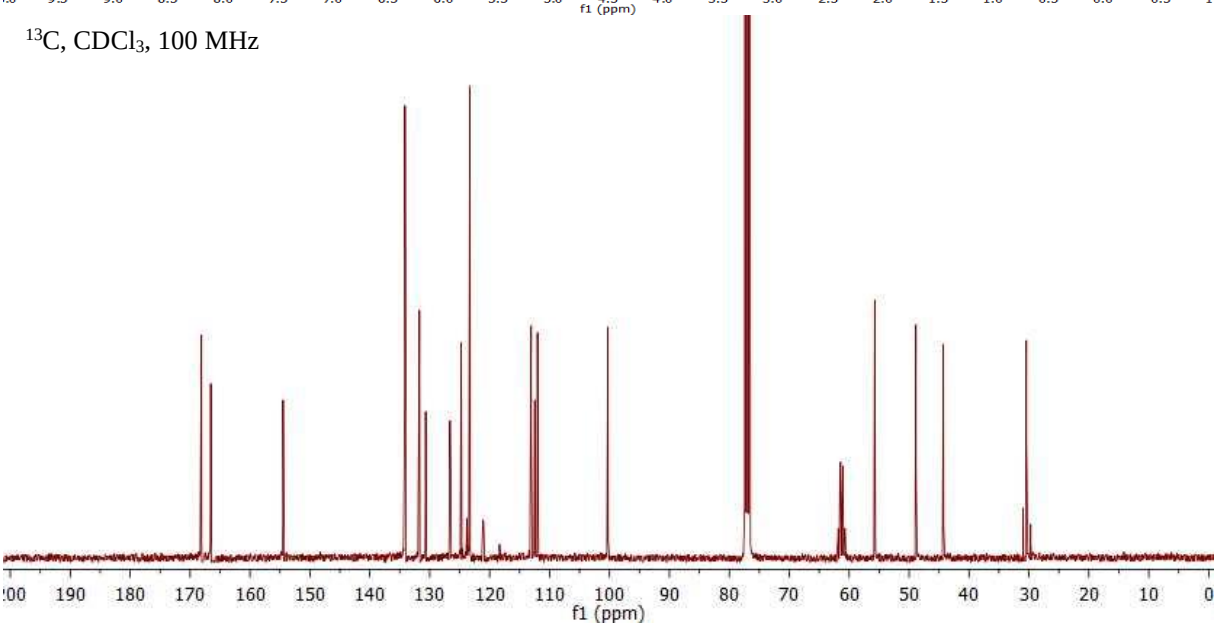

^{1}H, $CDCl_3$,
400 MHz
Cl
NH
O
O
O
N
O
O
O
O
CF_3
CF_3
6ab
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


^{13}C, $CDCl_3$, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

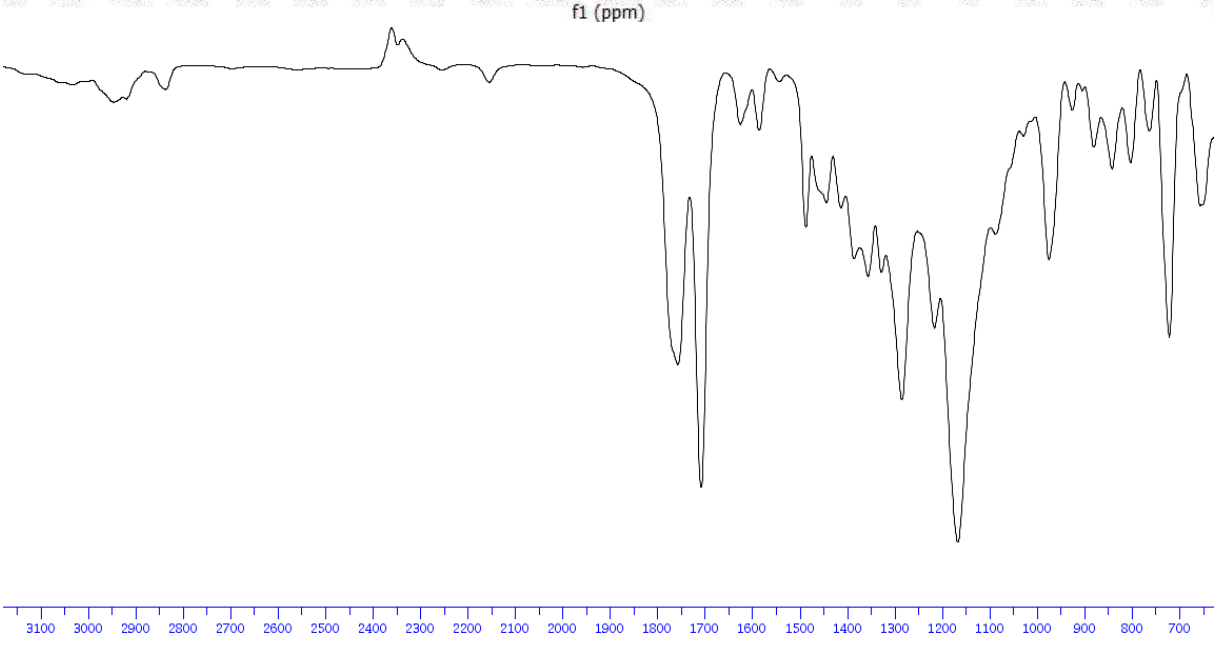

3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700

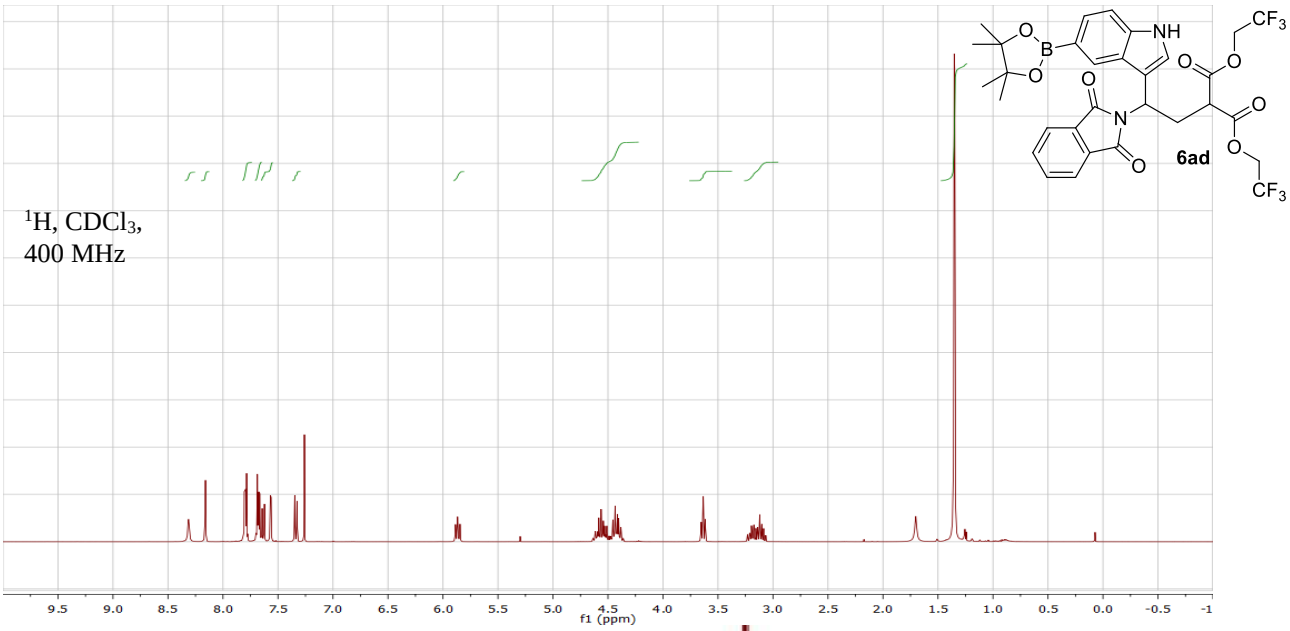


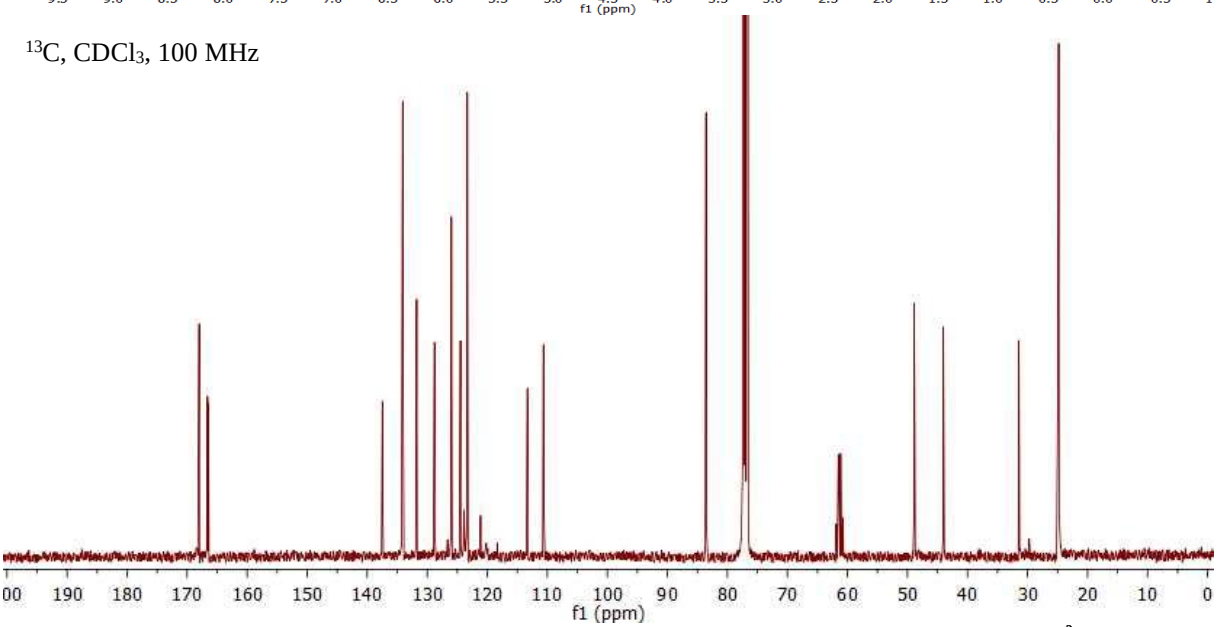
^{1}H, $CDCl_3$, 400 MHz

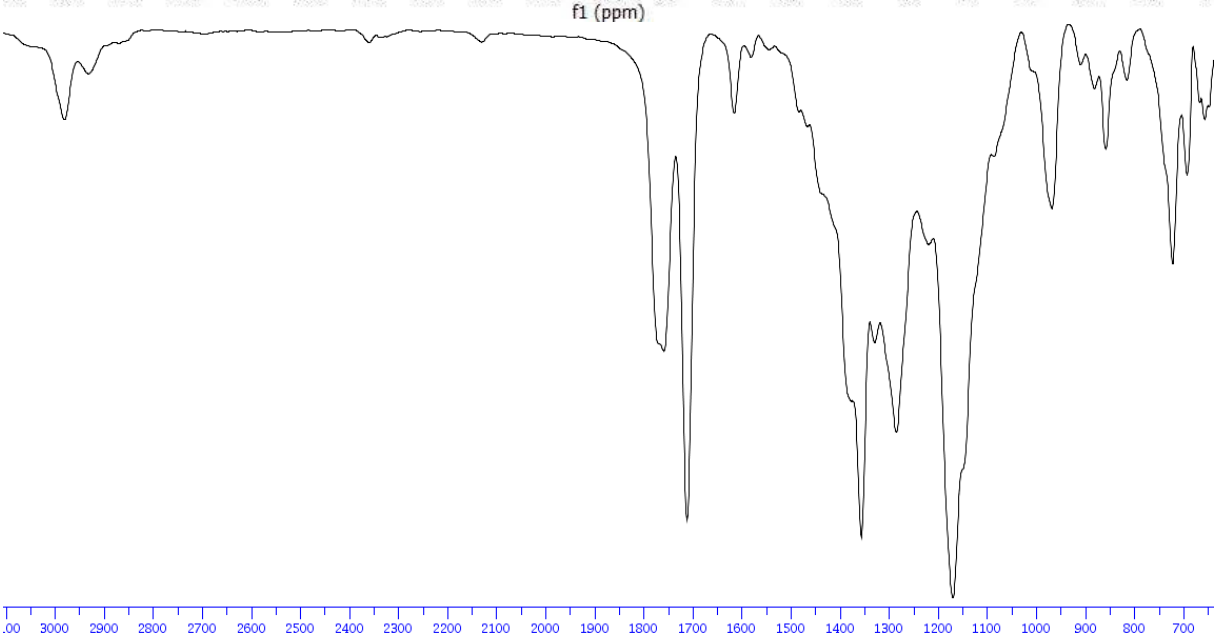


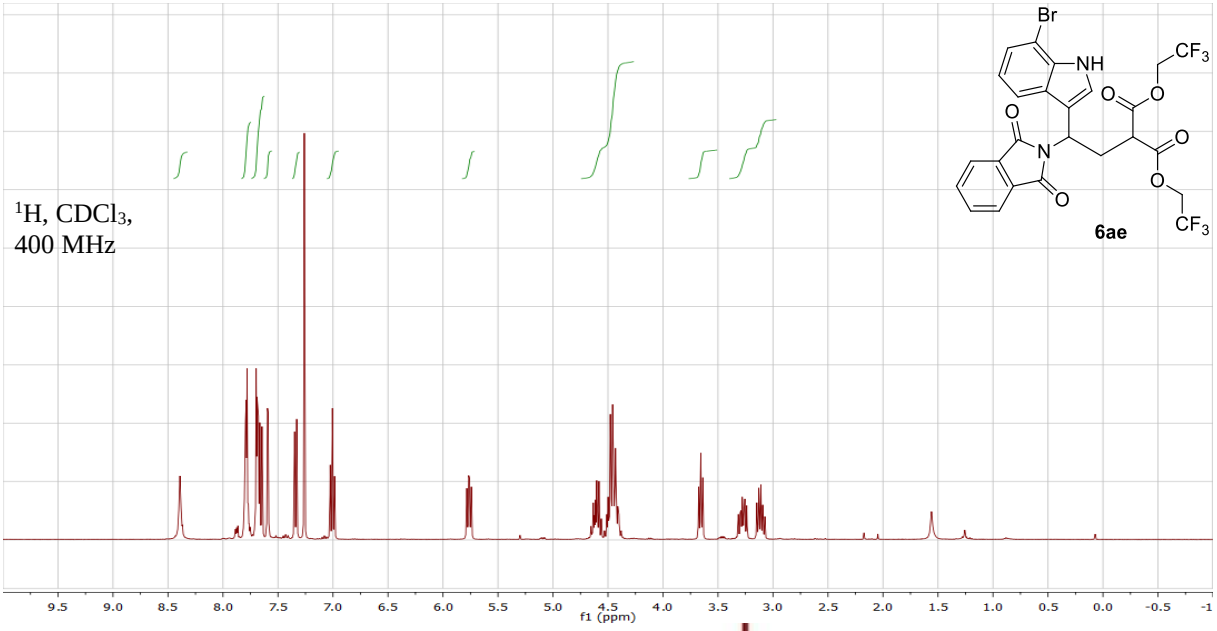
^{13}C, $CDCl_3$, 100 MHz

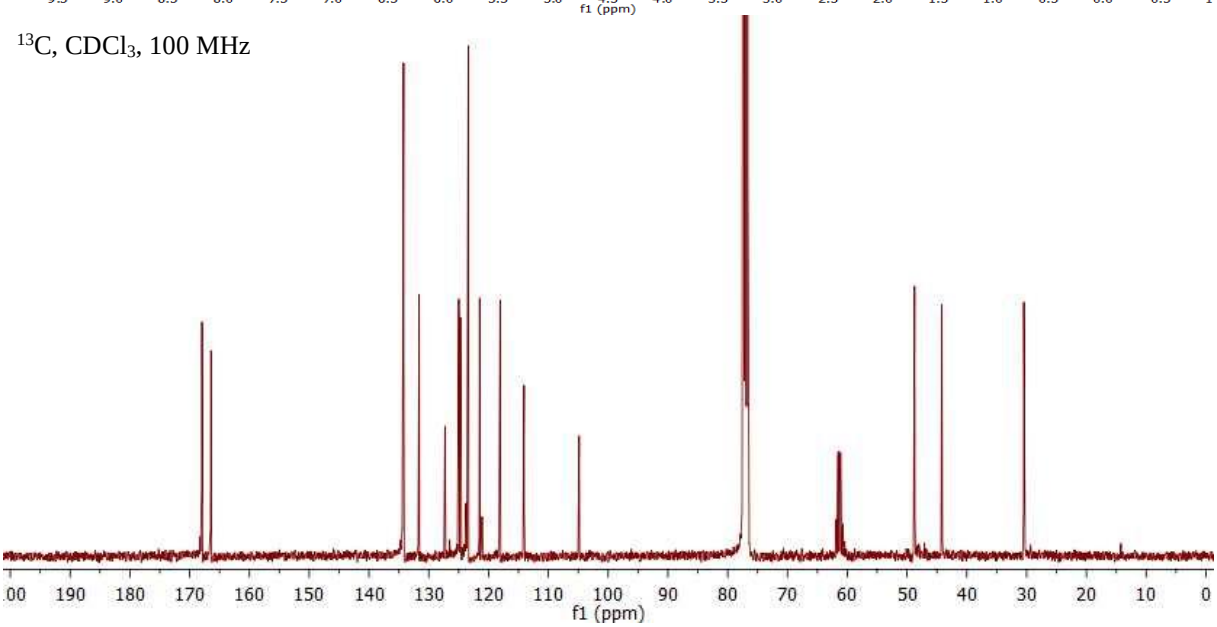


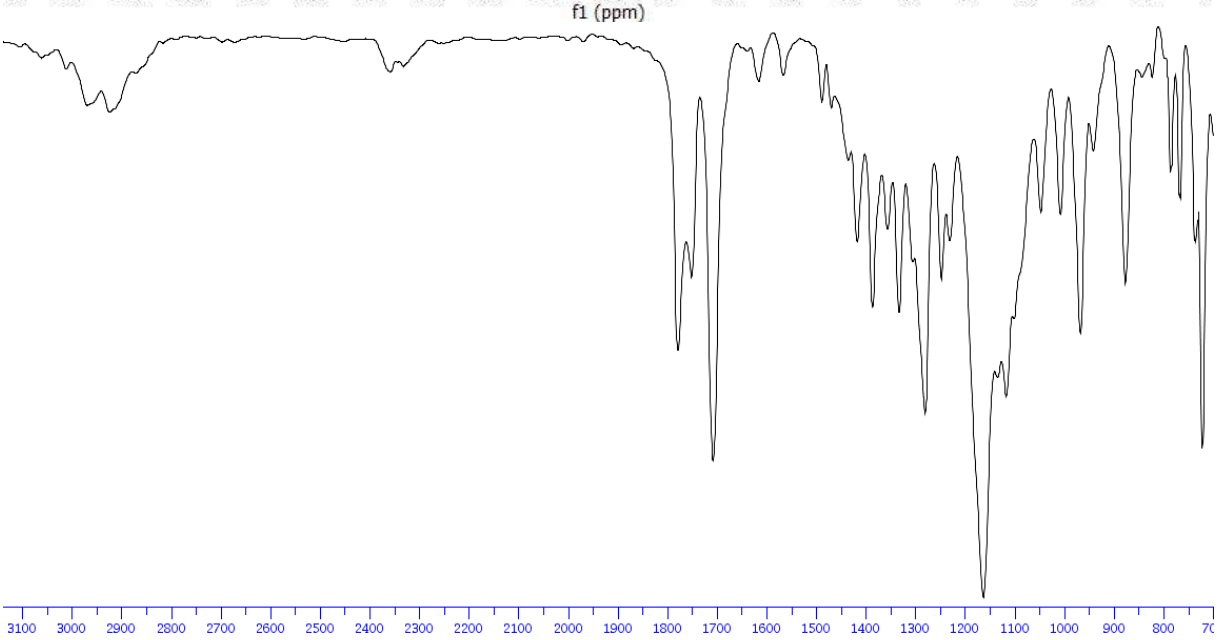

^{1}H, CDCl$_3$,
400 MHz
6ad
f1 (ppm)

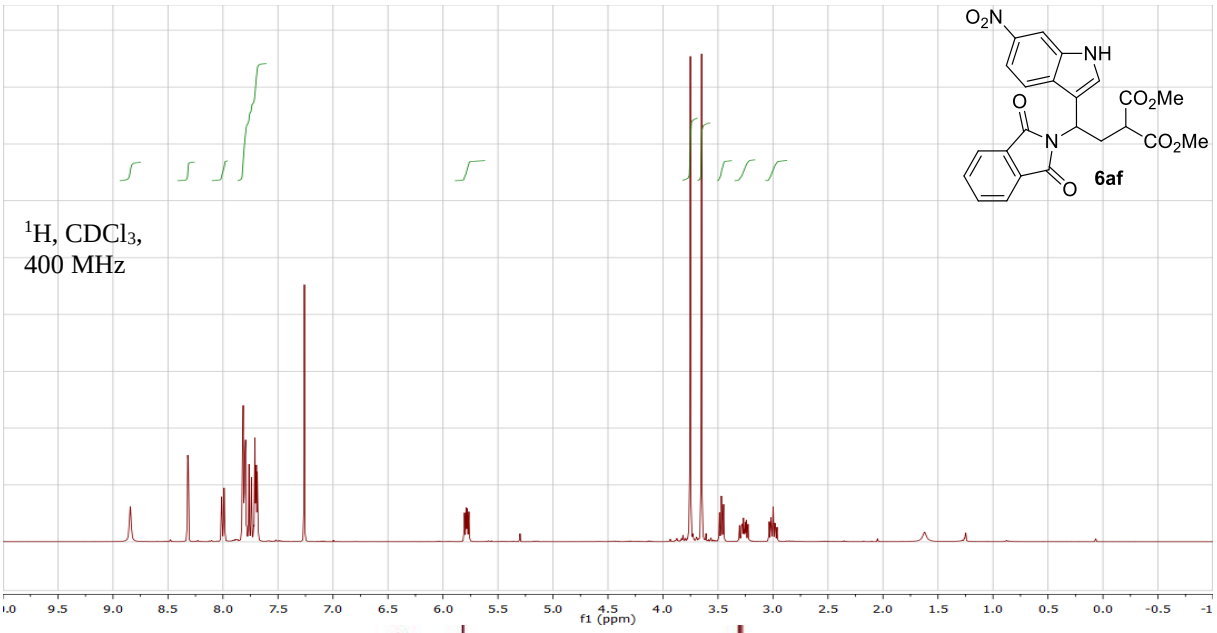

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)

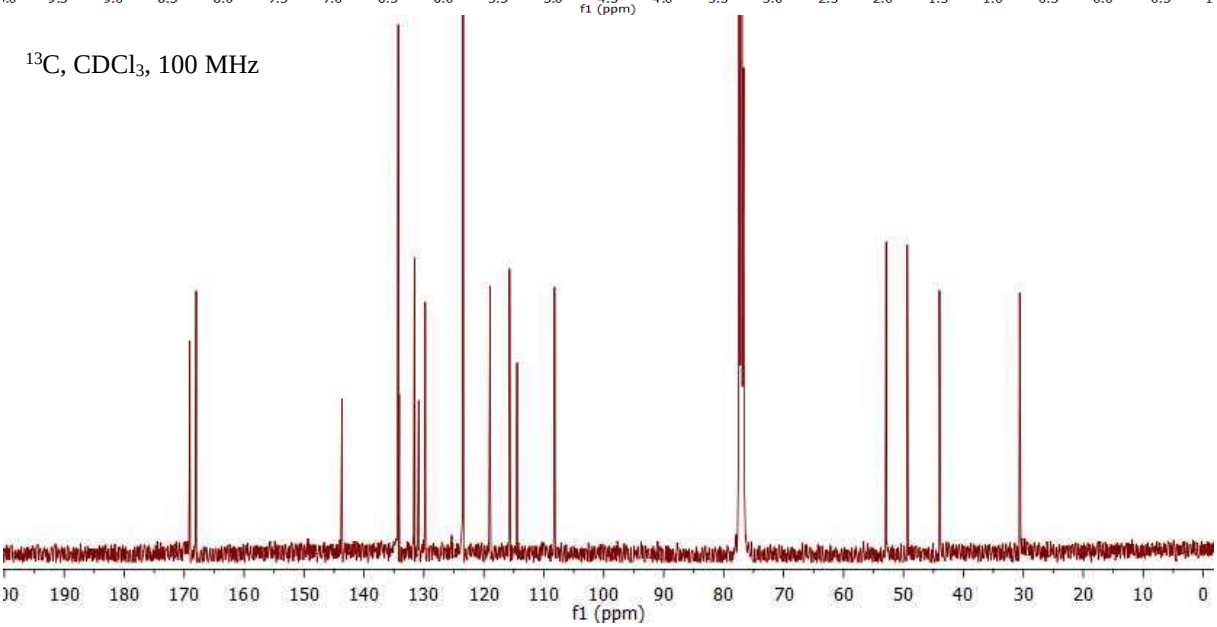


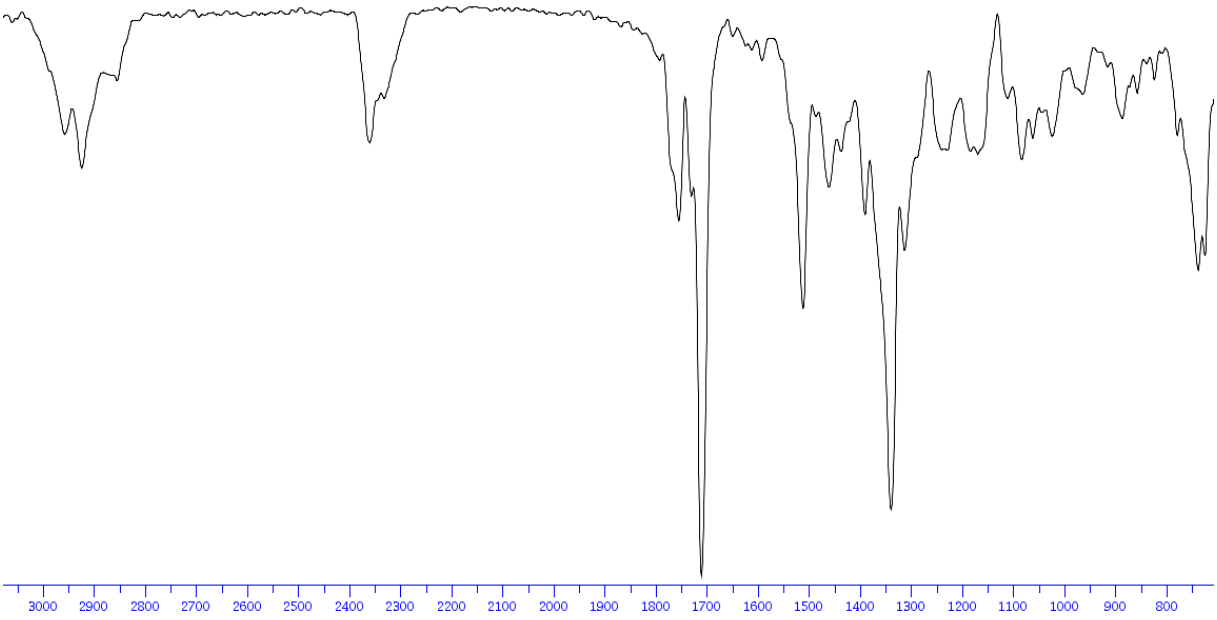

Br
NH
CF3
O
O
O
O
N
O
O
O
CF3
6ae
1H, CDCl3,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

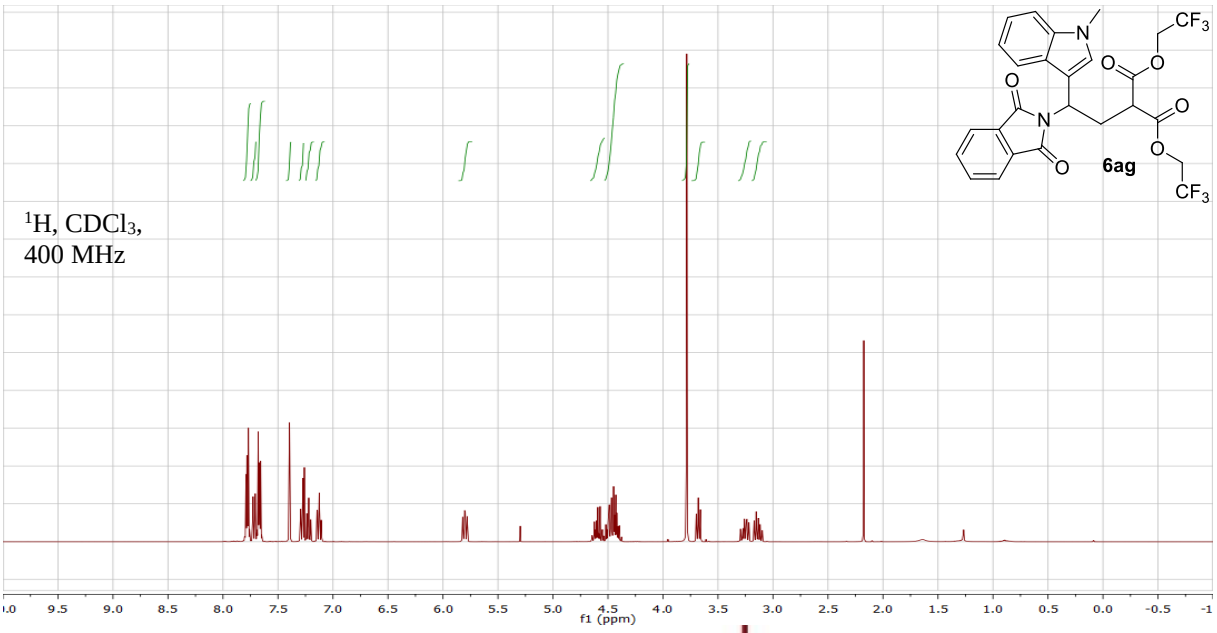

13C, CDCl3, 100 MHz
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

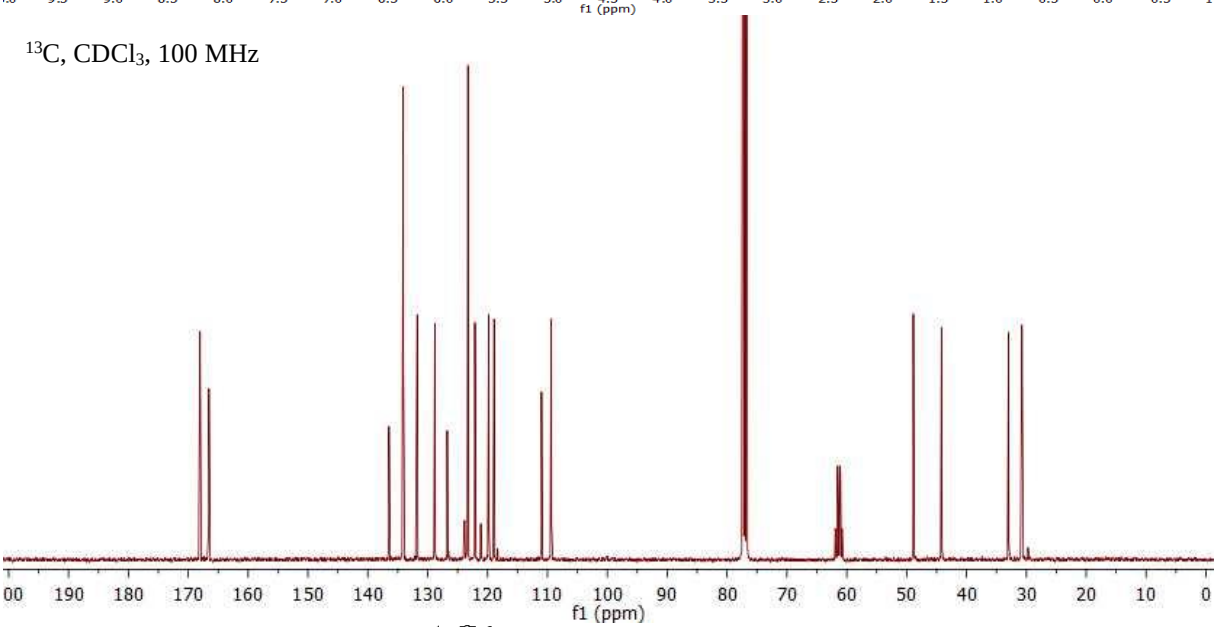

3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800

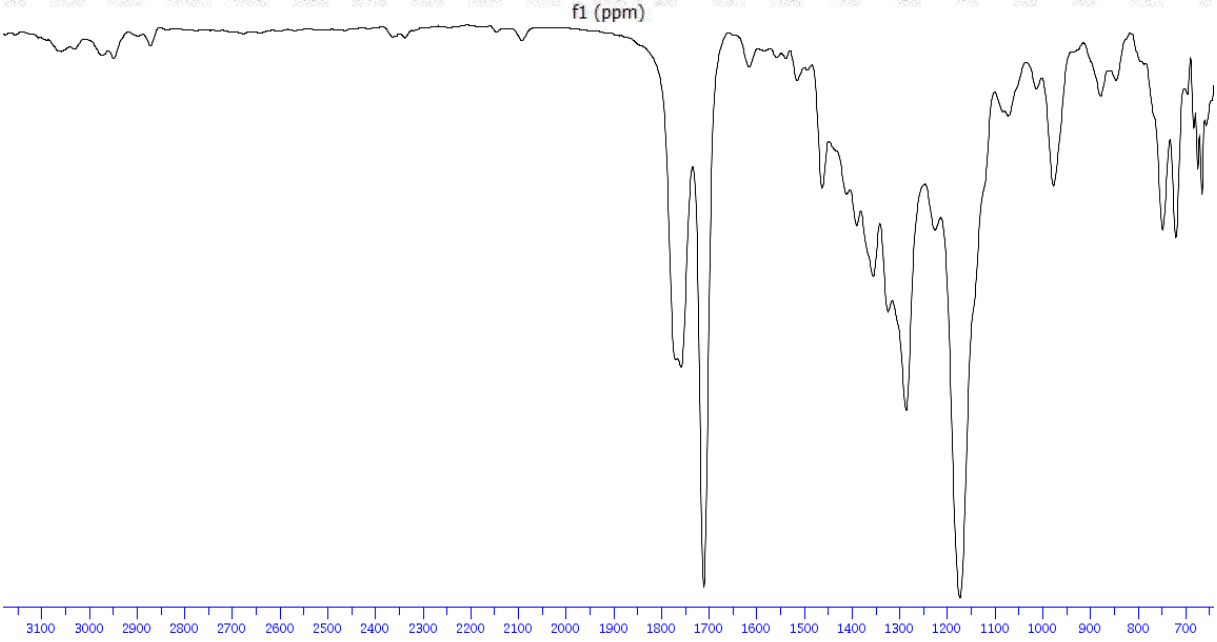

^{1}H, CDCl$_3$,
400 MHz
O$_2$N
NH
CO$_2$Me
CO$_2$Me
O
N
O
O
6af
f1 (ppm)

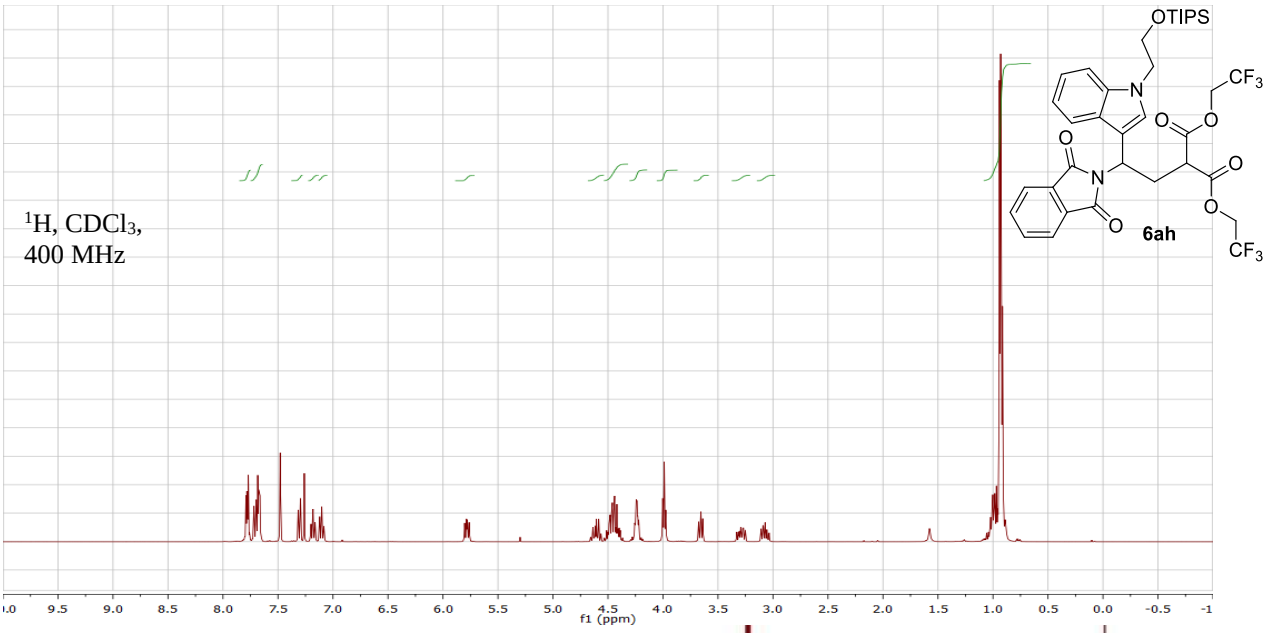

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)

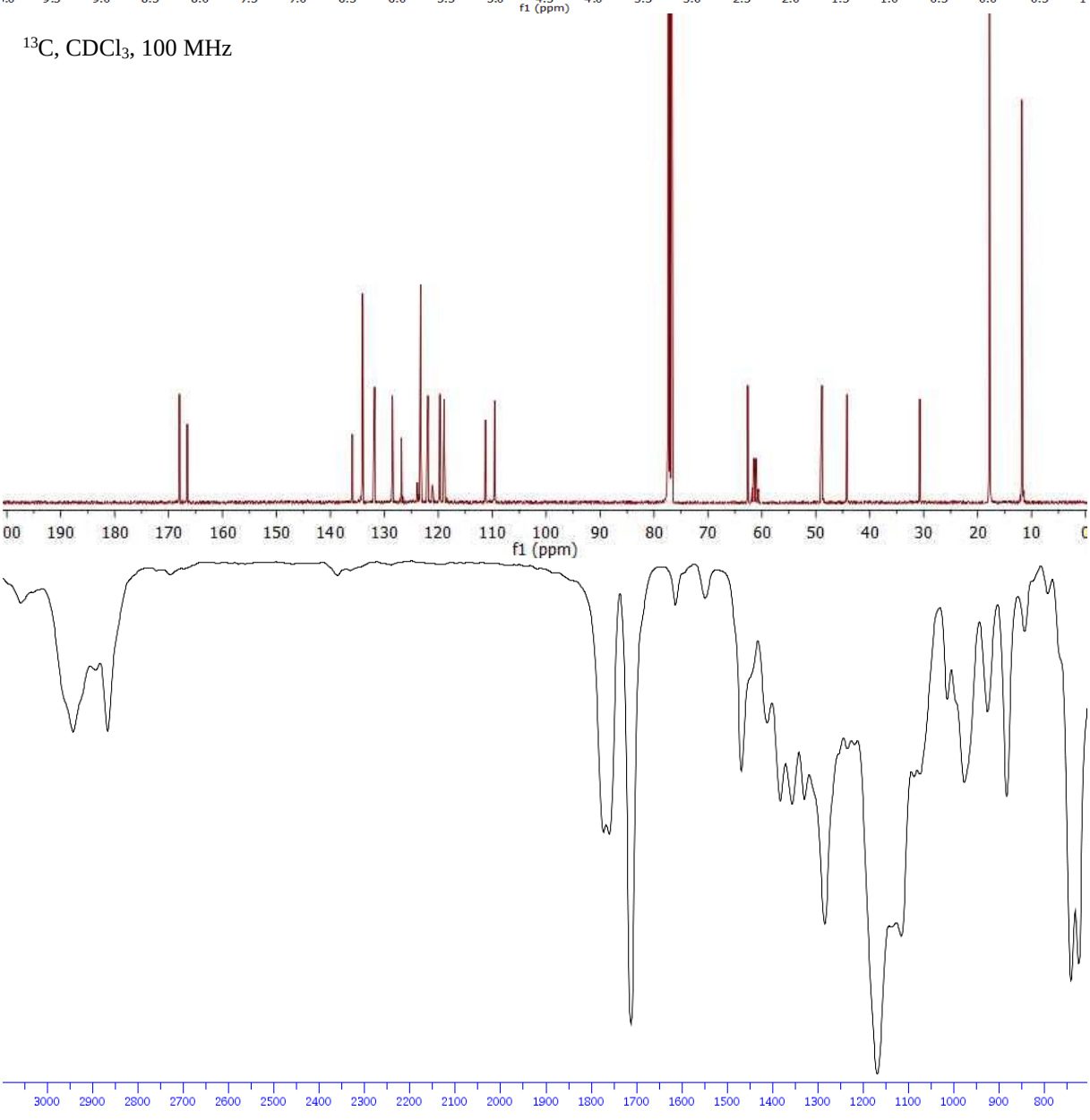


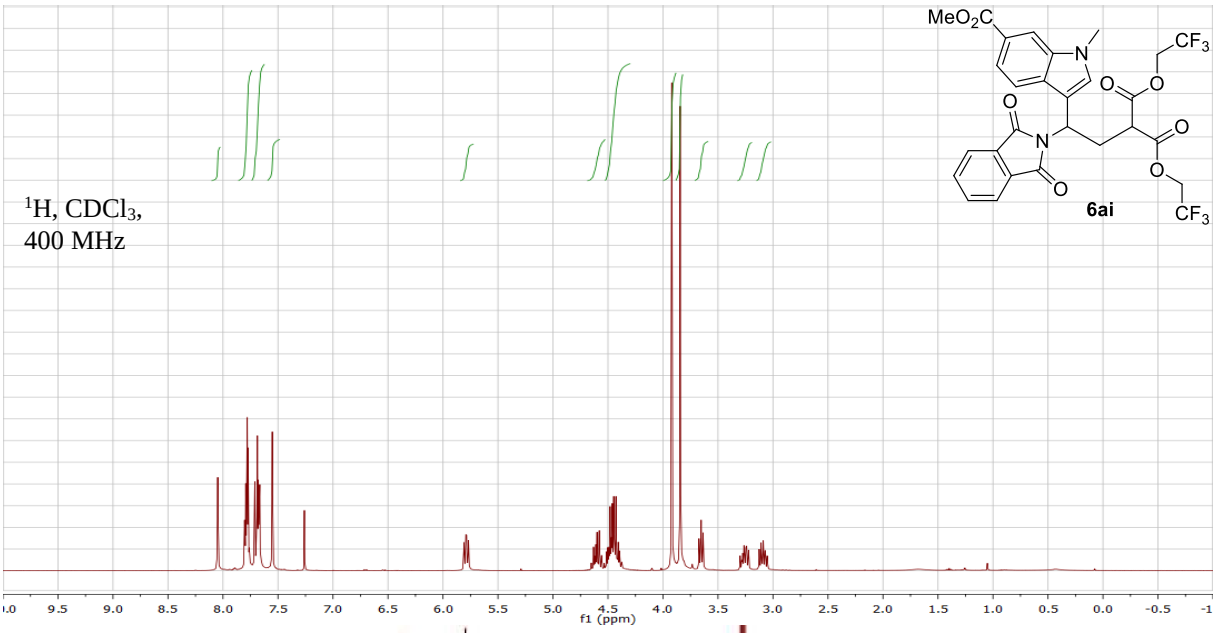

^{1}H, $CDCl_3$,
400 MHz
6ag
f1 (ppm)

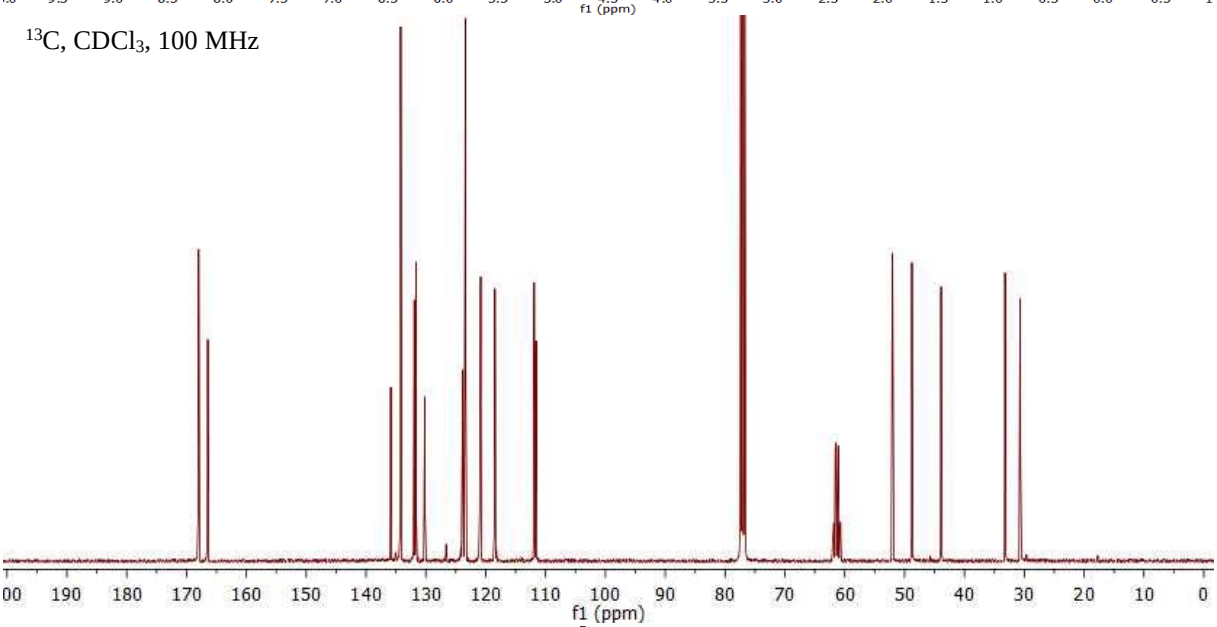

^{13}C, $CDCl_3$, 100 MHz
f1 (ppm)

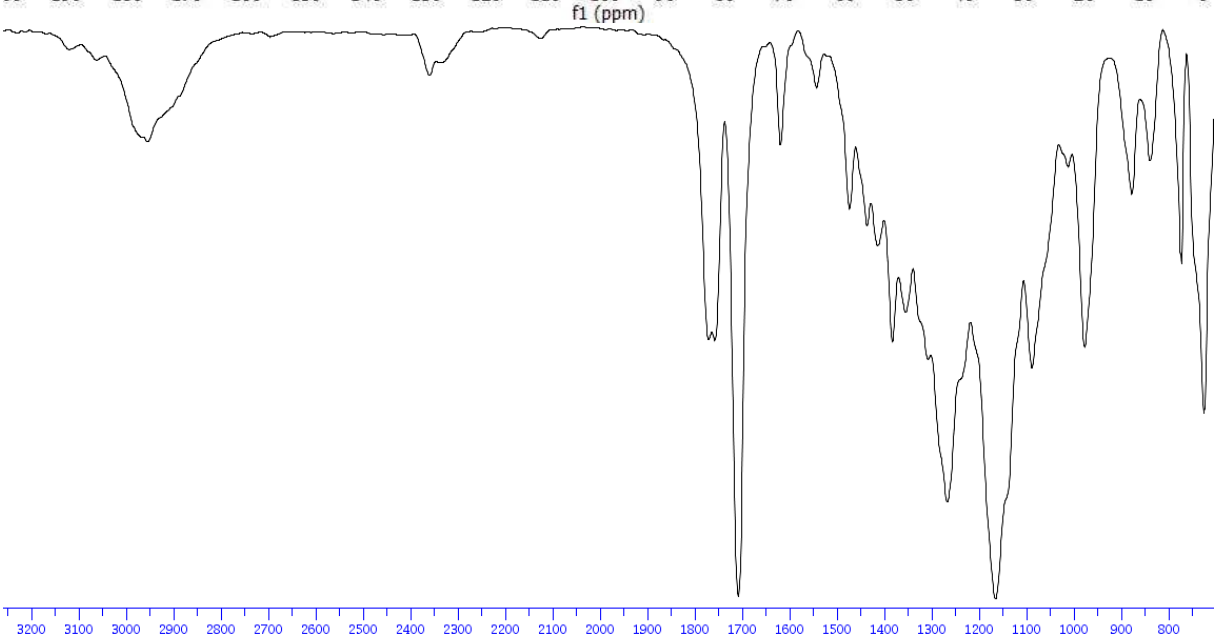


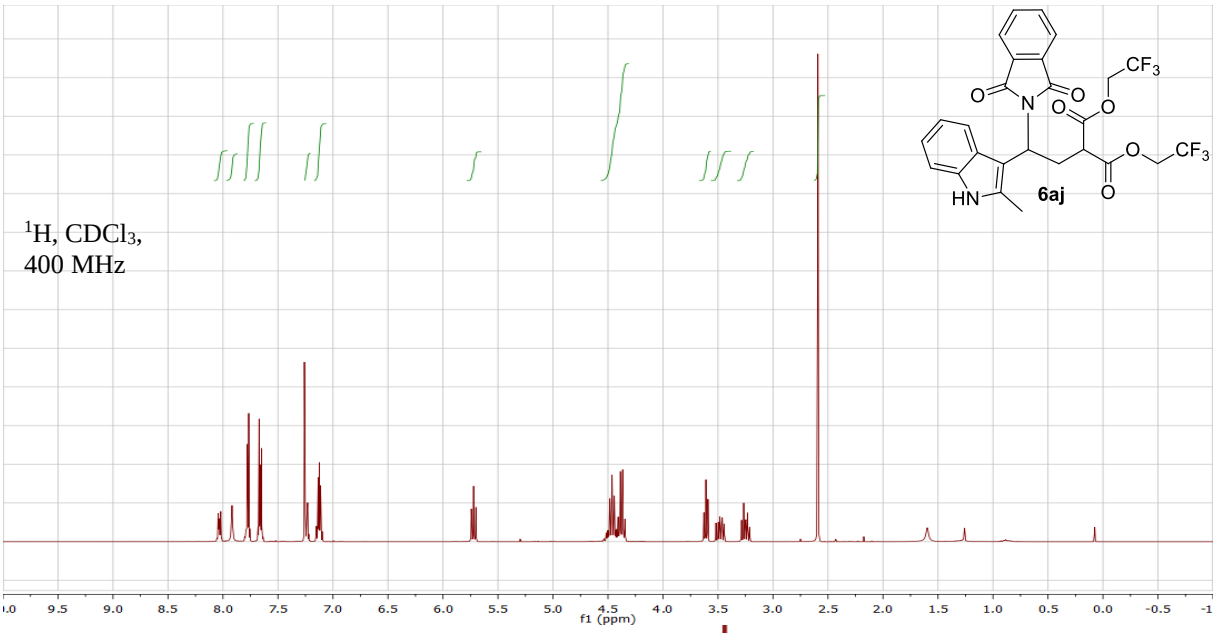

OTIPS
CF3
CF3
6ah
1H, CDCl3,
400 MHz
f1 (ppm)

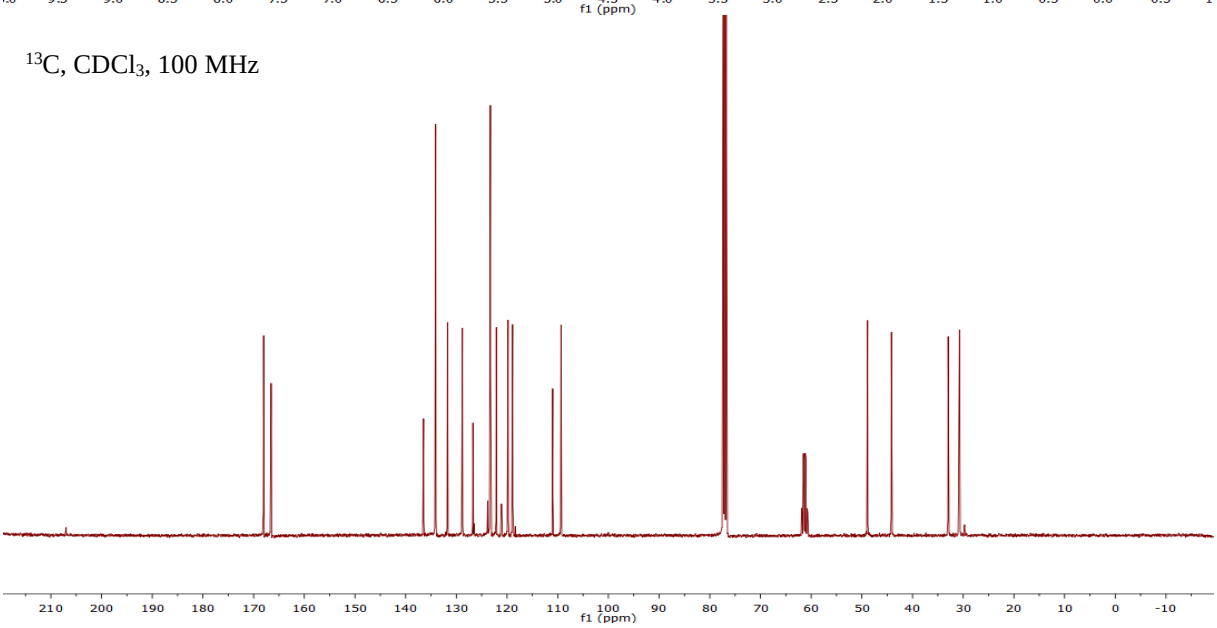

13C, CDCl3, 100 MHz
f1 (ppm)

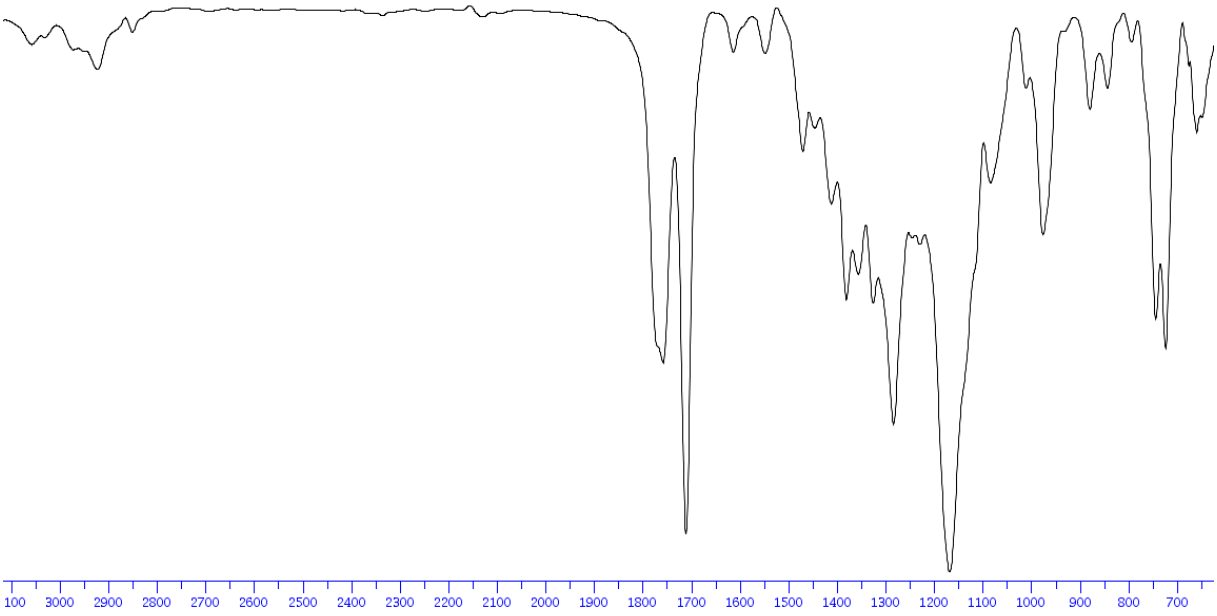

^{1}H, CDCl$_3$,
400 MHz
MeO$_2$C
CF$_3$
N
O
O
O
N
O
O
O
CF$_3$
6ai
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

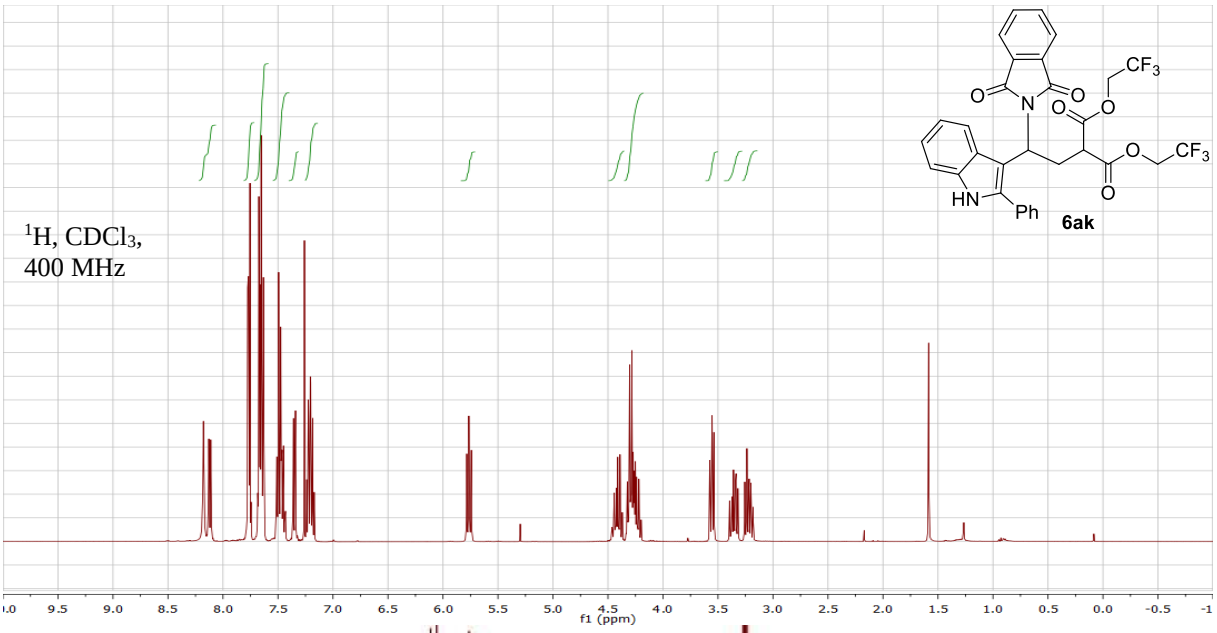

^{13}C, CDCl$_3$, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


3200 3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800


^{1}H, CDCl$_3$,
400 MHz
6aj
f1 (ppm)

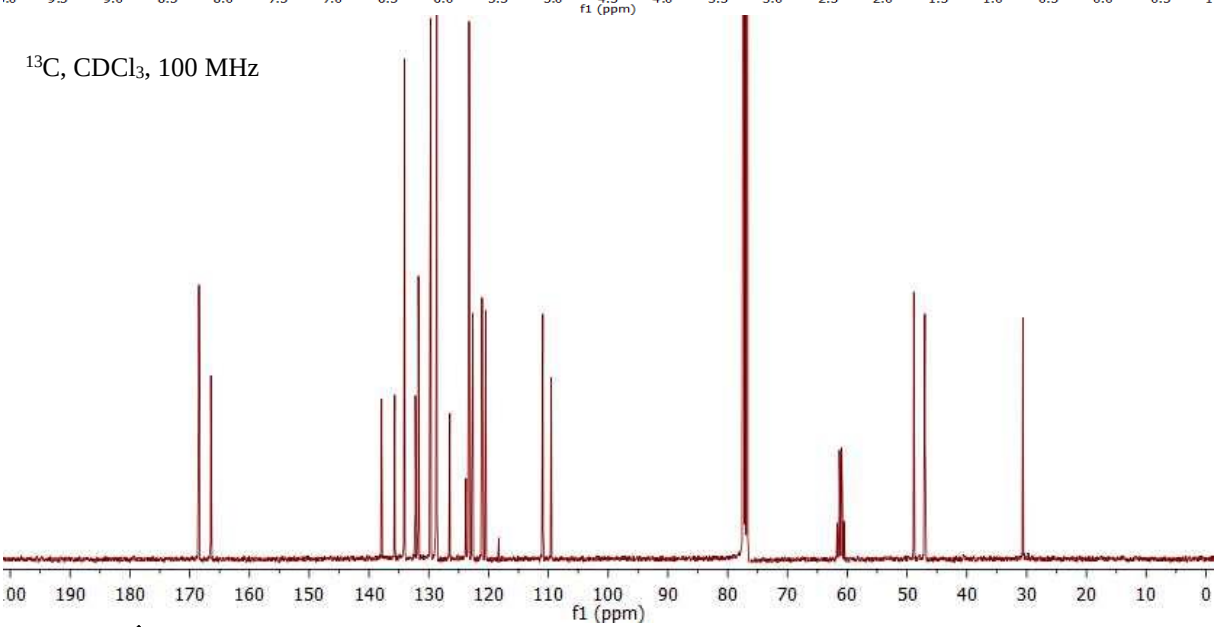

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)

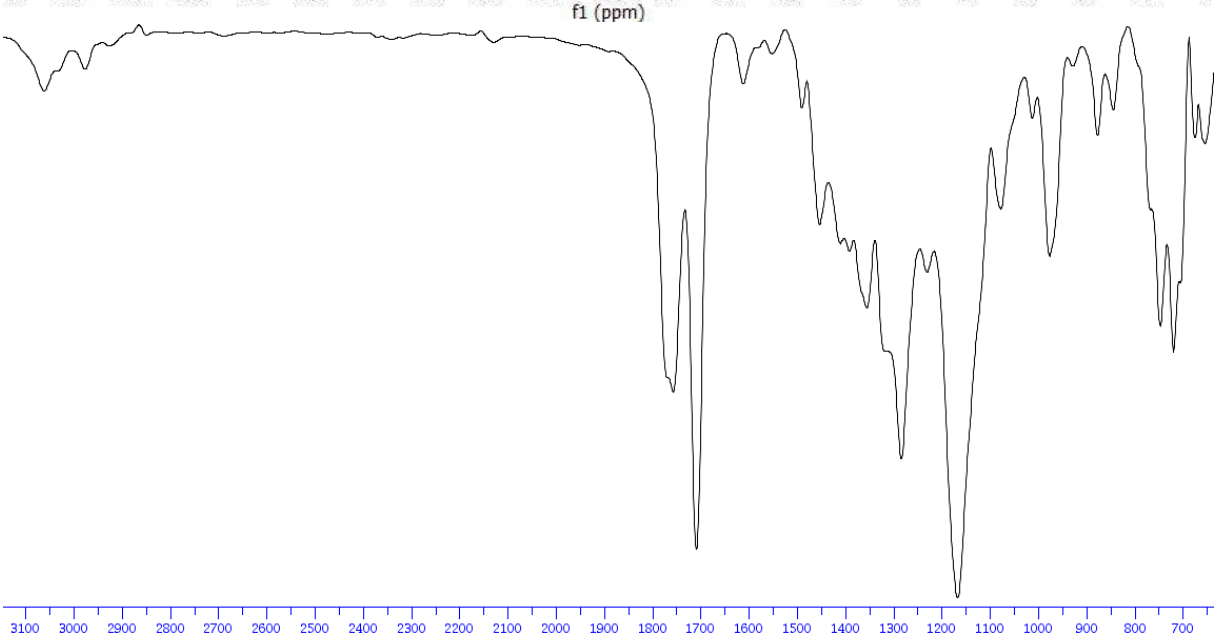


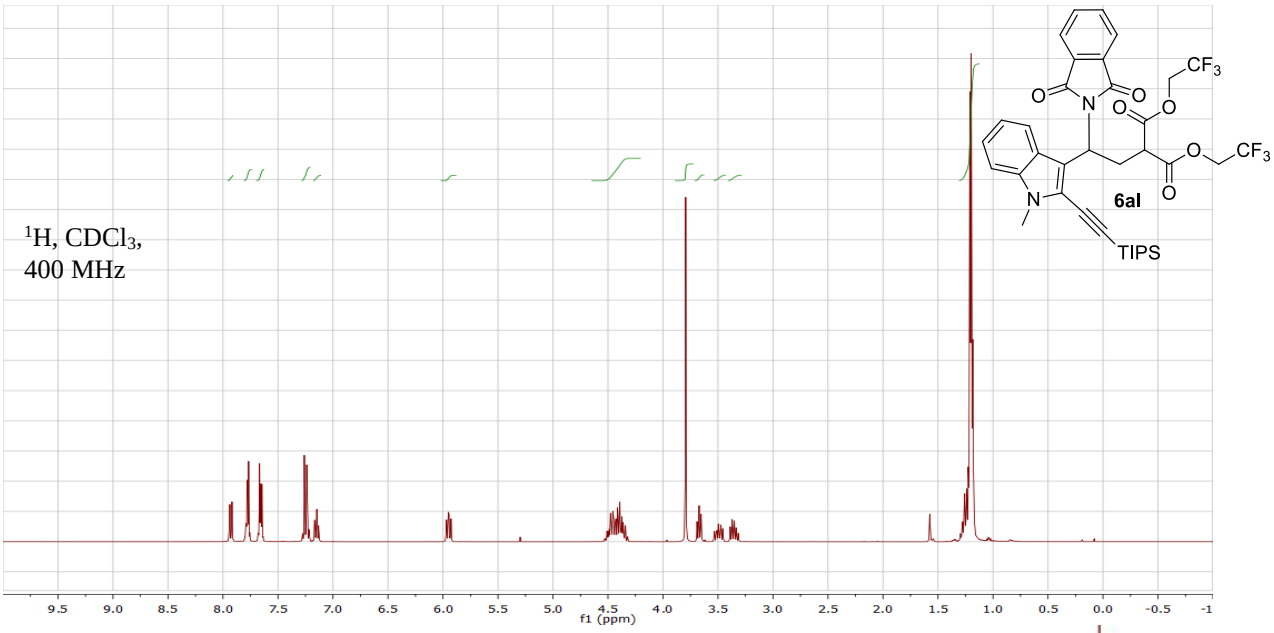

^{1}H, CDCl$_3$,
400 MHz
f1 (ppm)

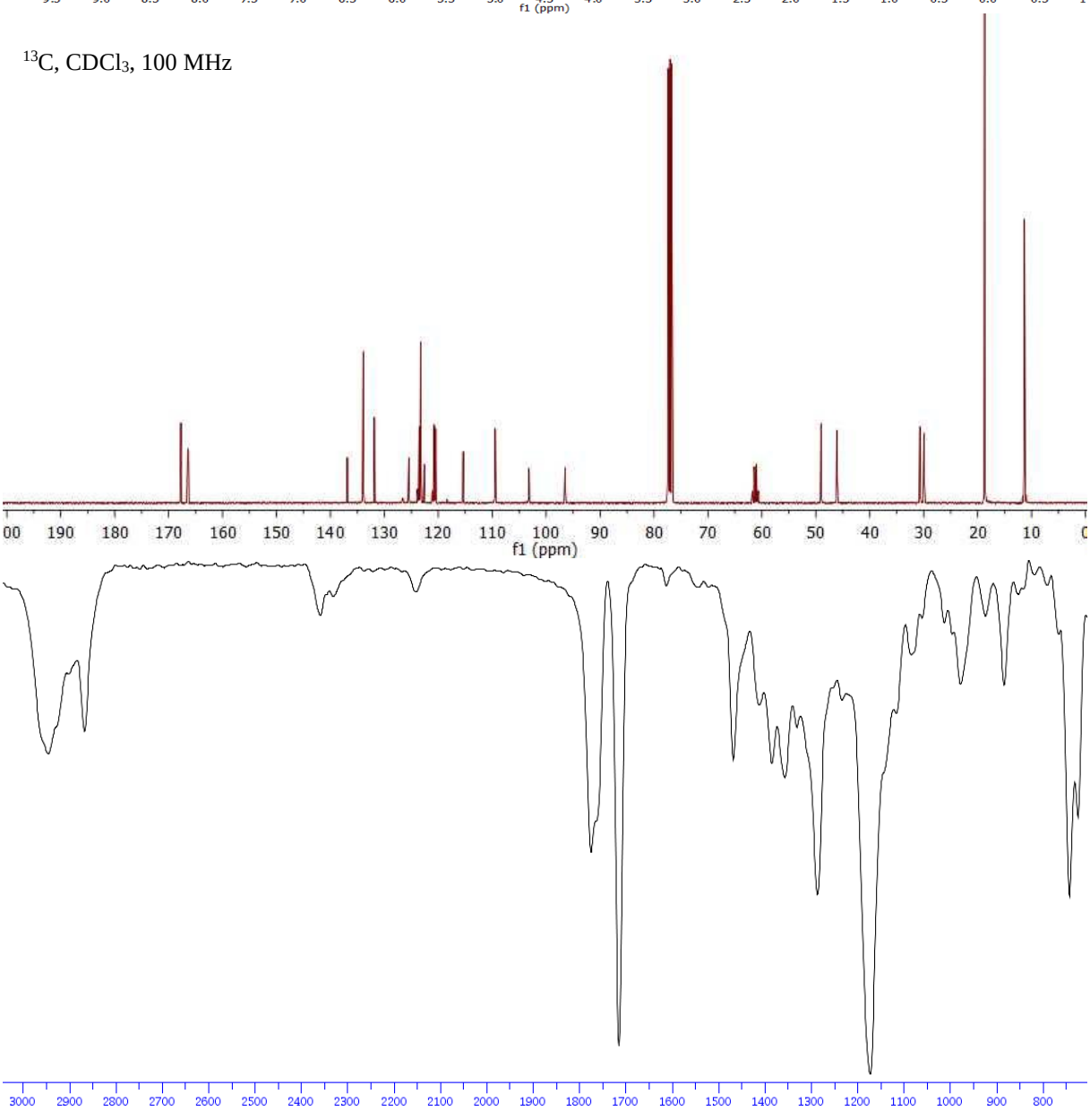
CF3
O
N
O
O
O
O
CF3
HN
Ph

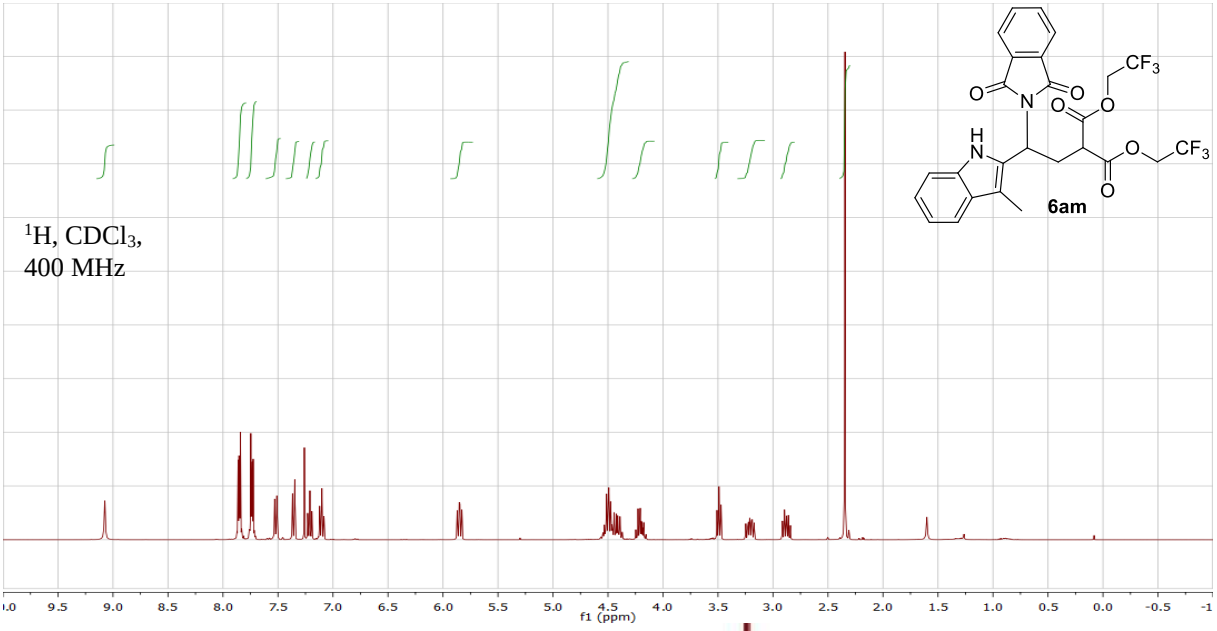
6ak

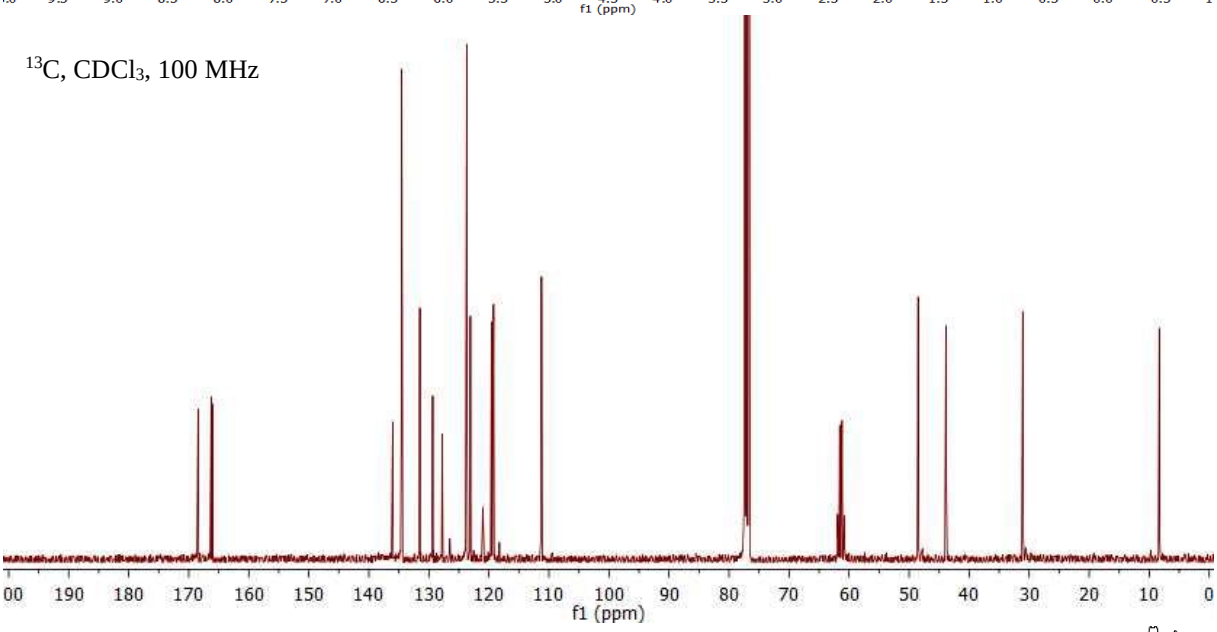

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)

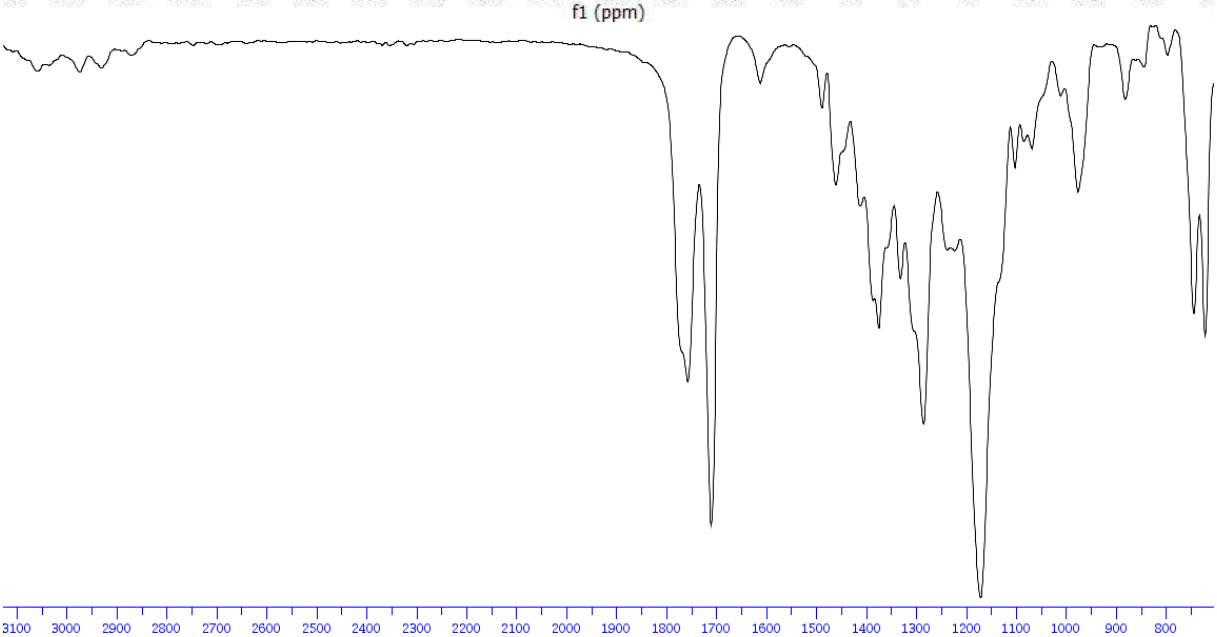



^{1}H, CDCl$_3$,
400 MHz
6al
TIPS
f1 (ppm)

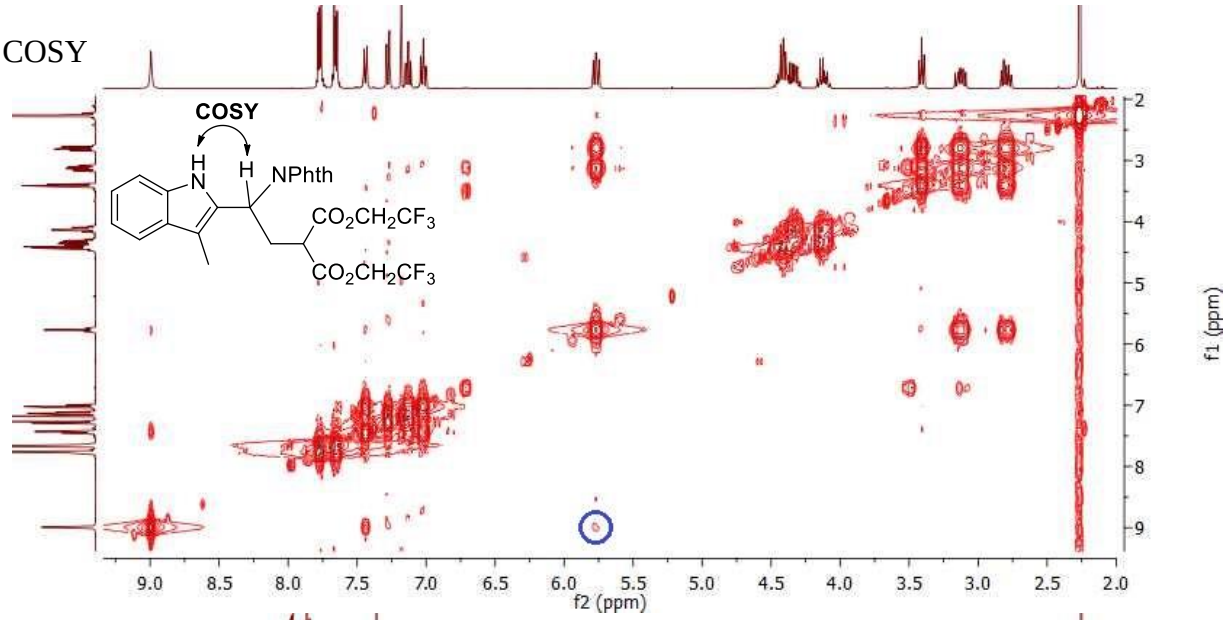

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)


^{1}H, CDCl$_3$,
400 MHz
6am
f1 (ppm)

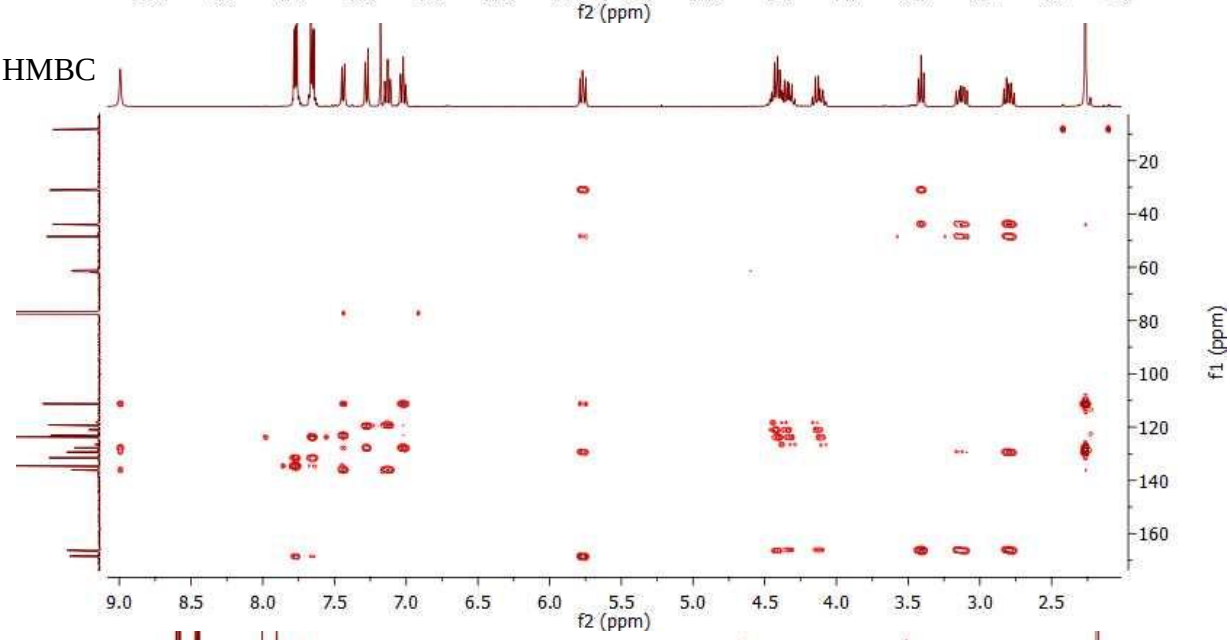

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)



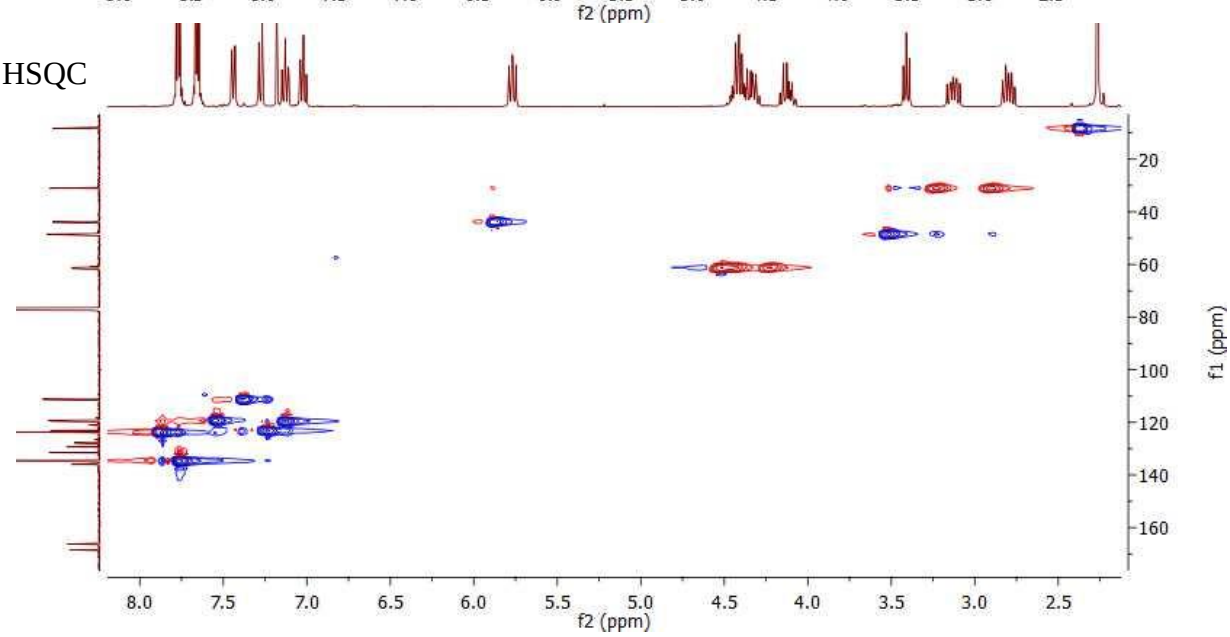
COSY

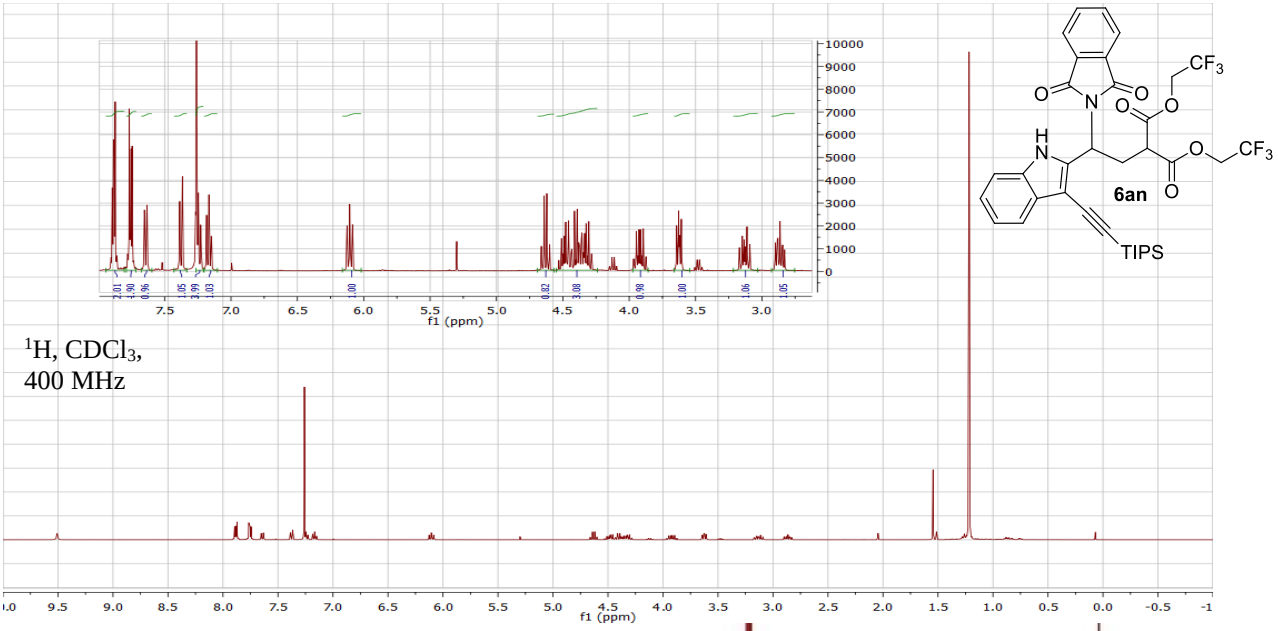


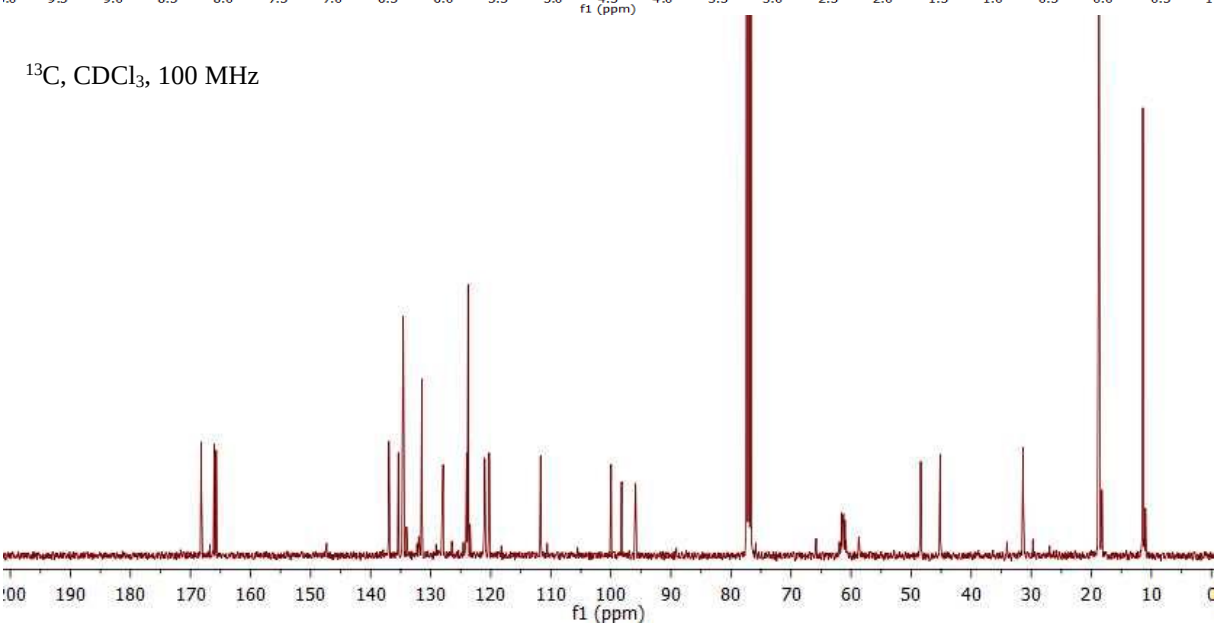
HMBC

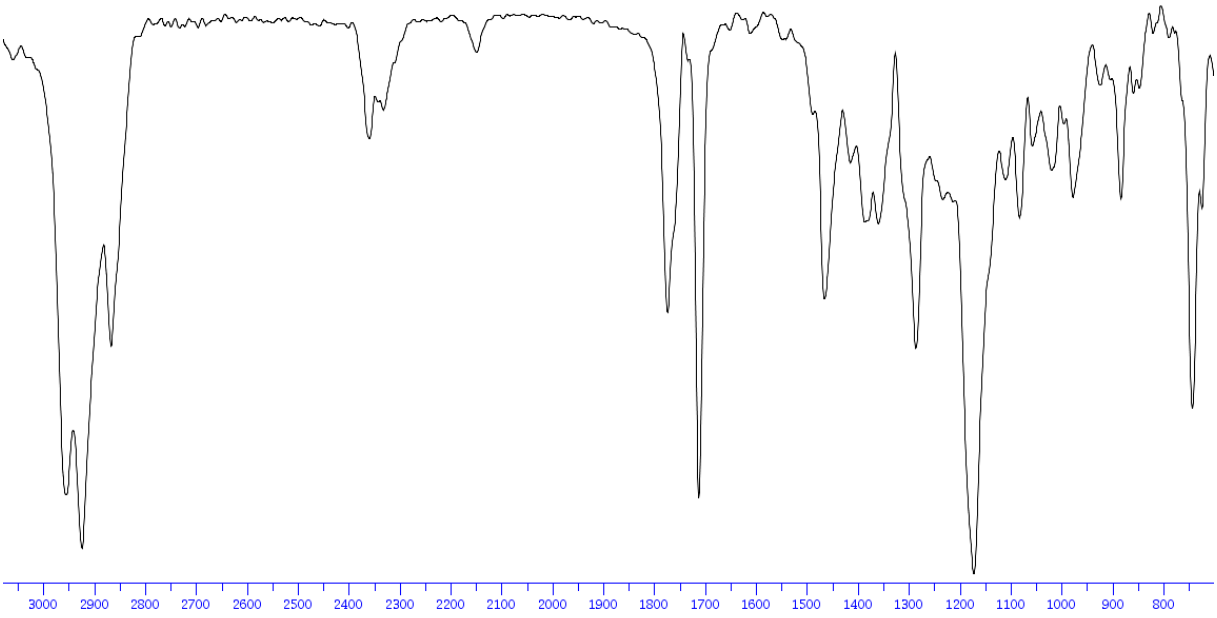


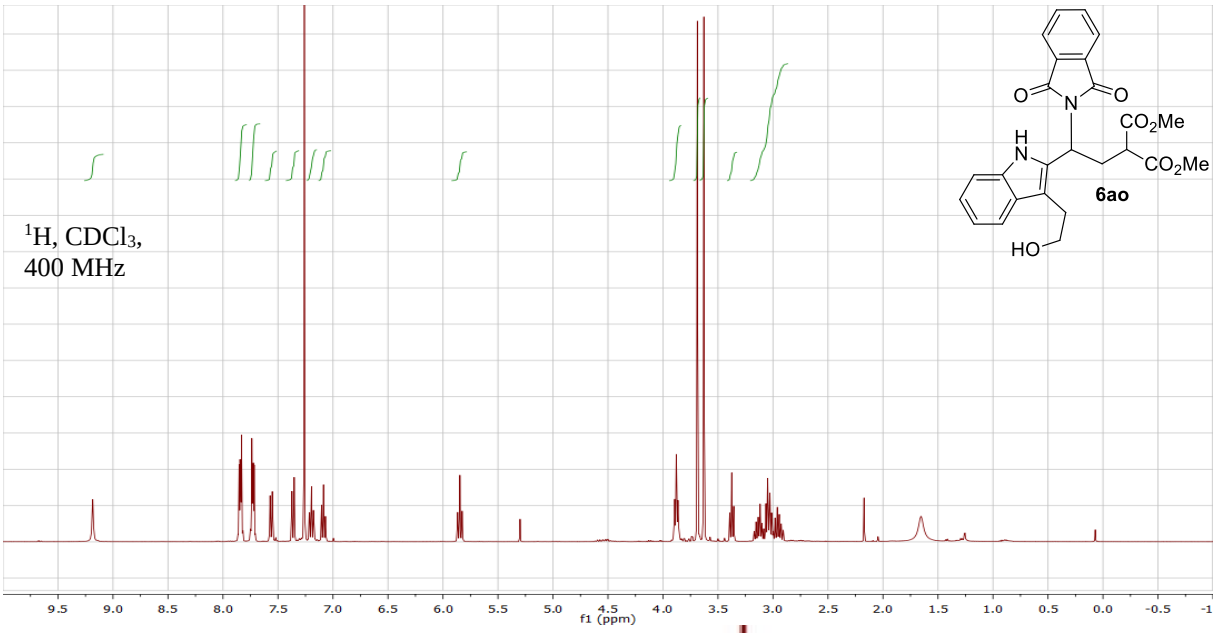
HSQC

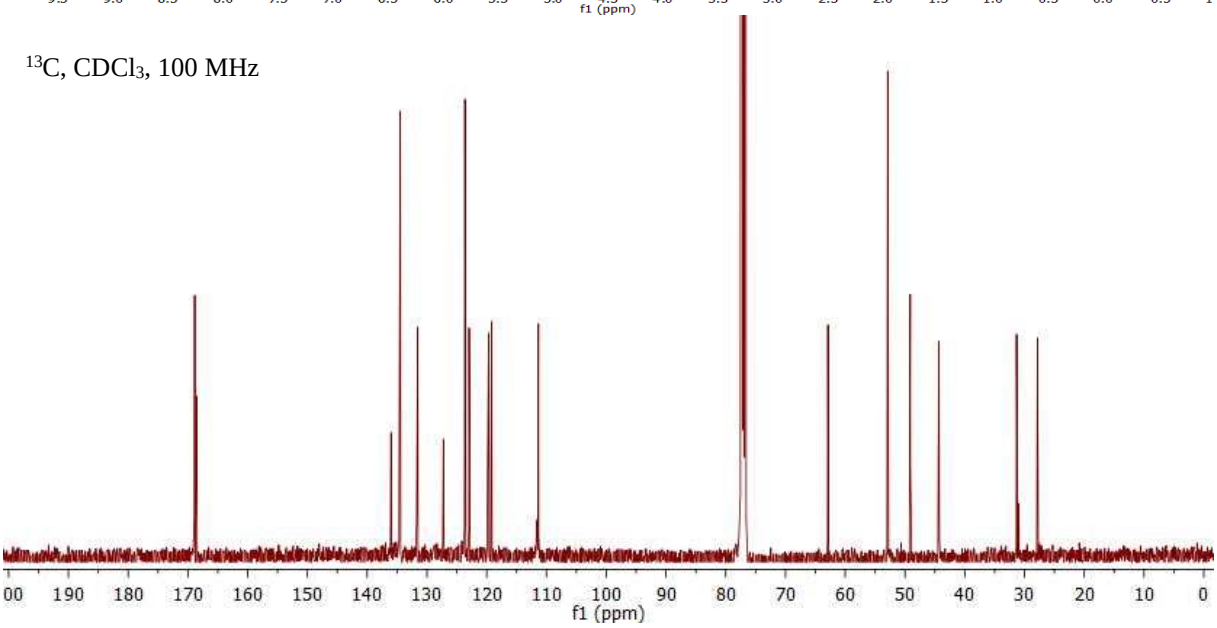


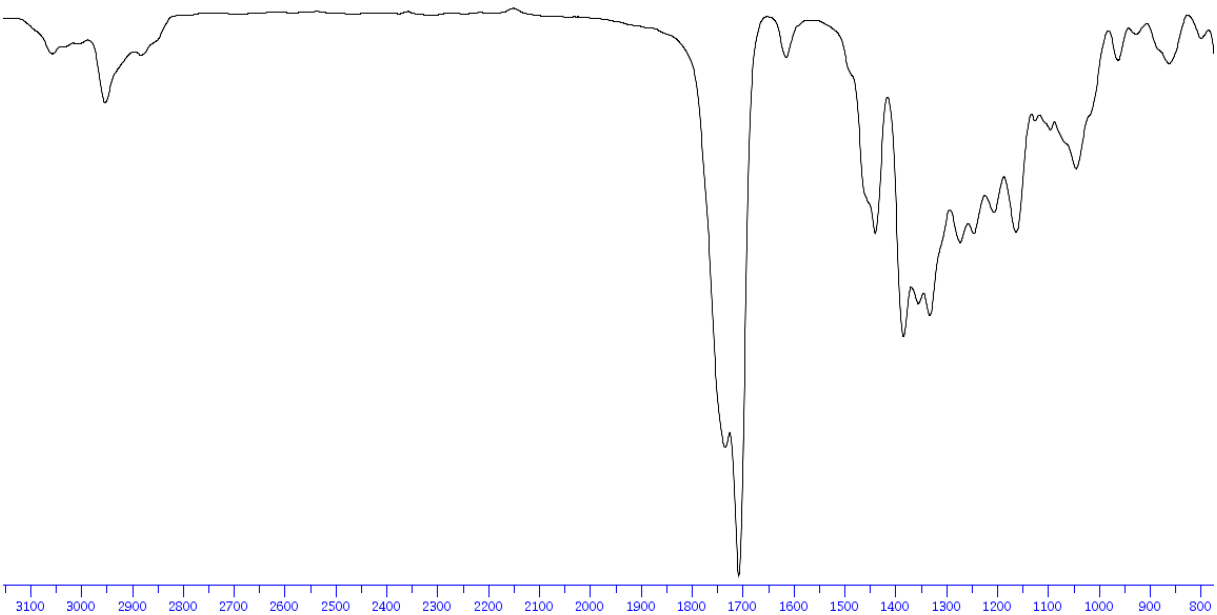

^{1}H, CDCl$_3$,
400 MHz
f1 (ppm)
6an
TIPS
CF$_3$
CF$_3$

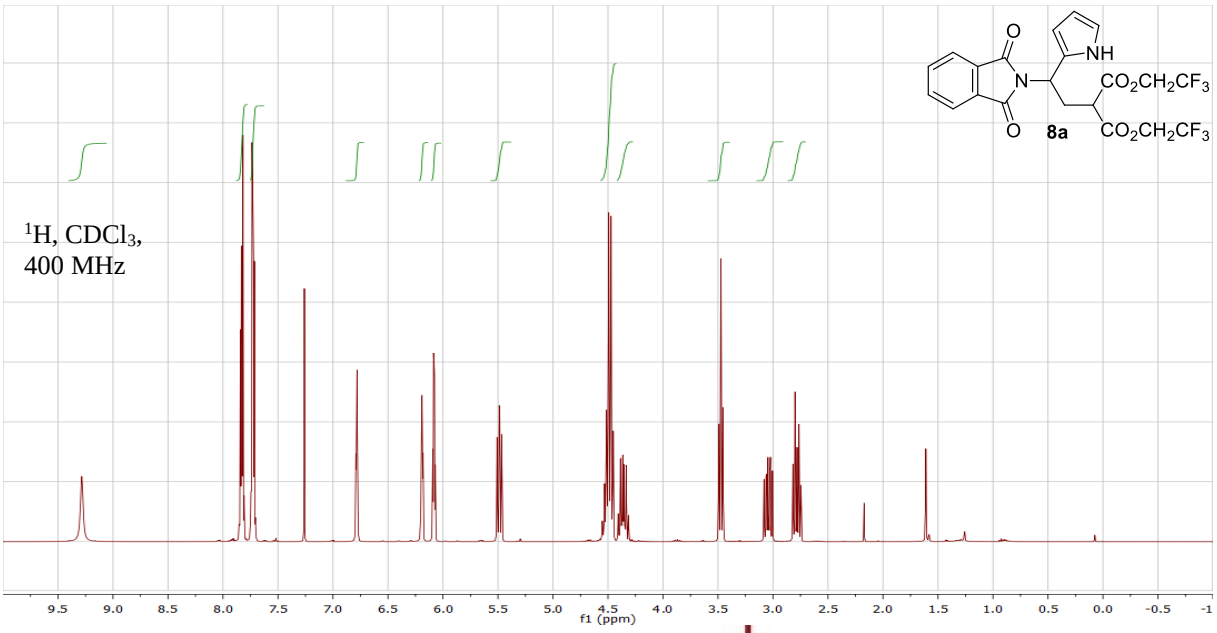

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)

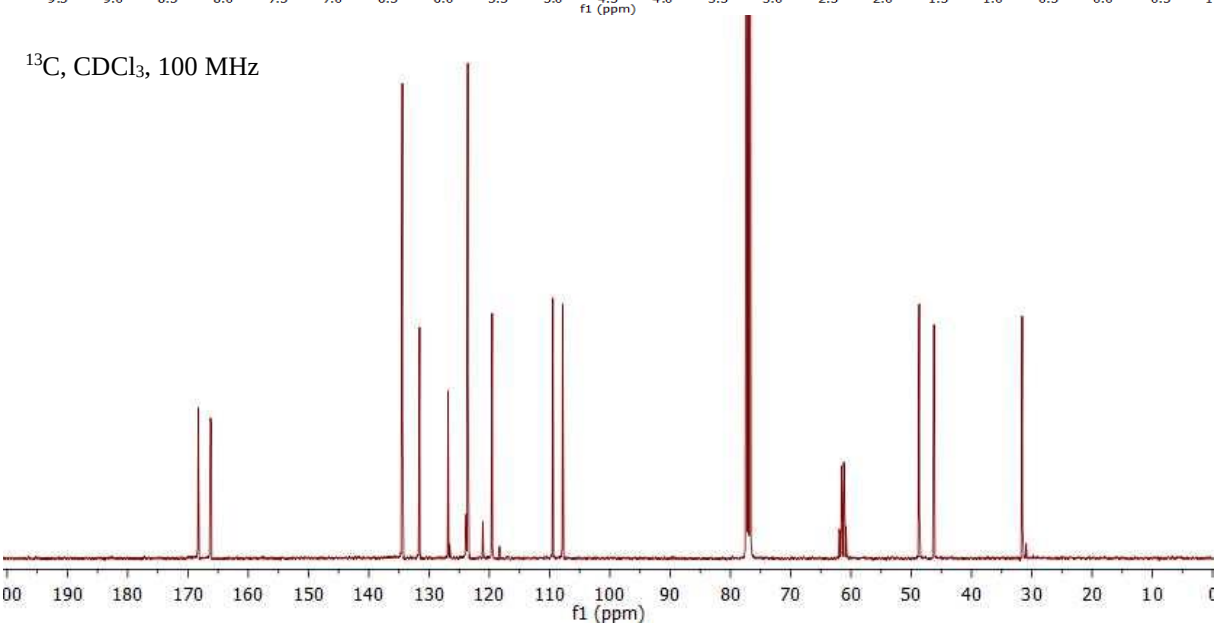


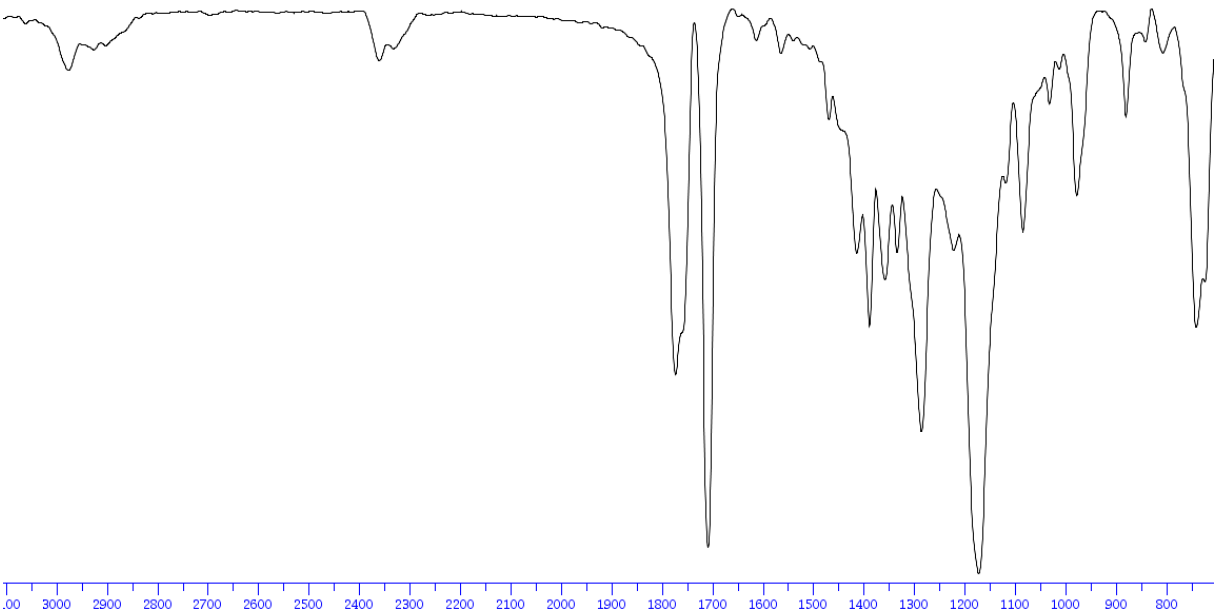

^{1}H, CDCl$_3$,
400 MHz
O
O
N
H
N
CO$_2$Me
CO$_2$Me
6ao
HO
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


^{13}C, CDCl$_3$, 100 MHz
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

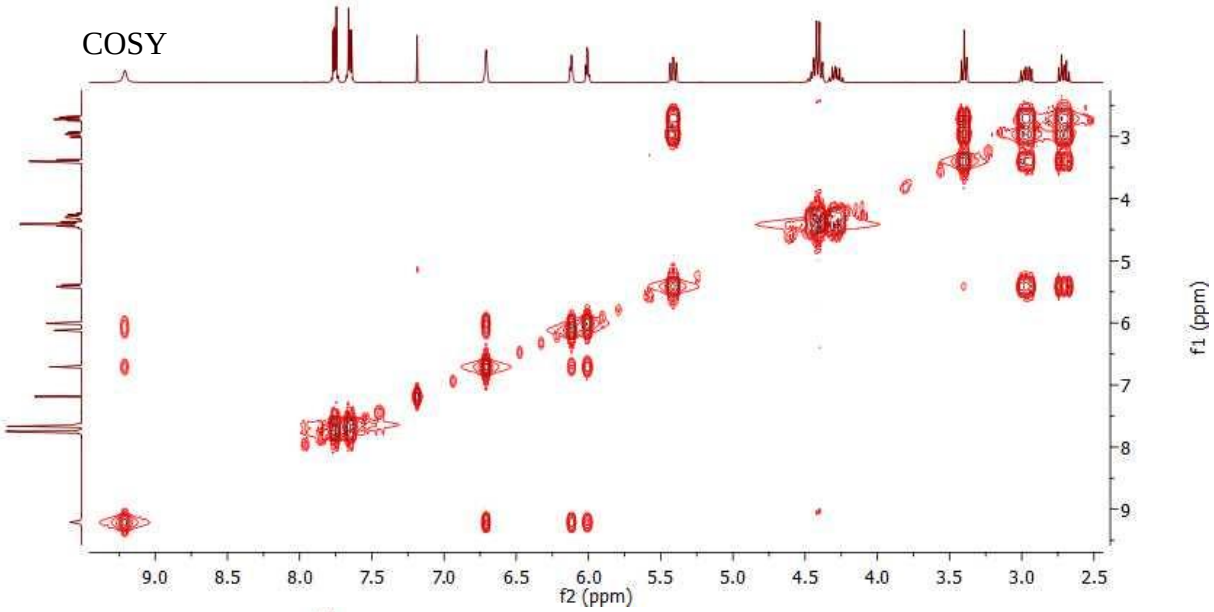

3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800


O
NH
N
CO2CH2CF3
O
8a
CO2CH2CF3
1H, CDCl3,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

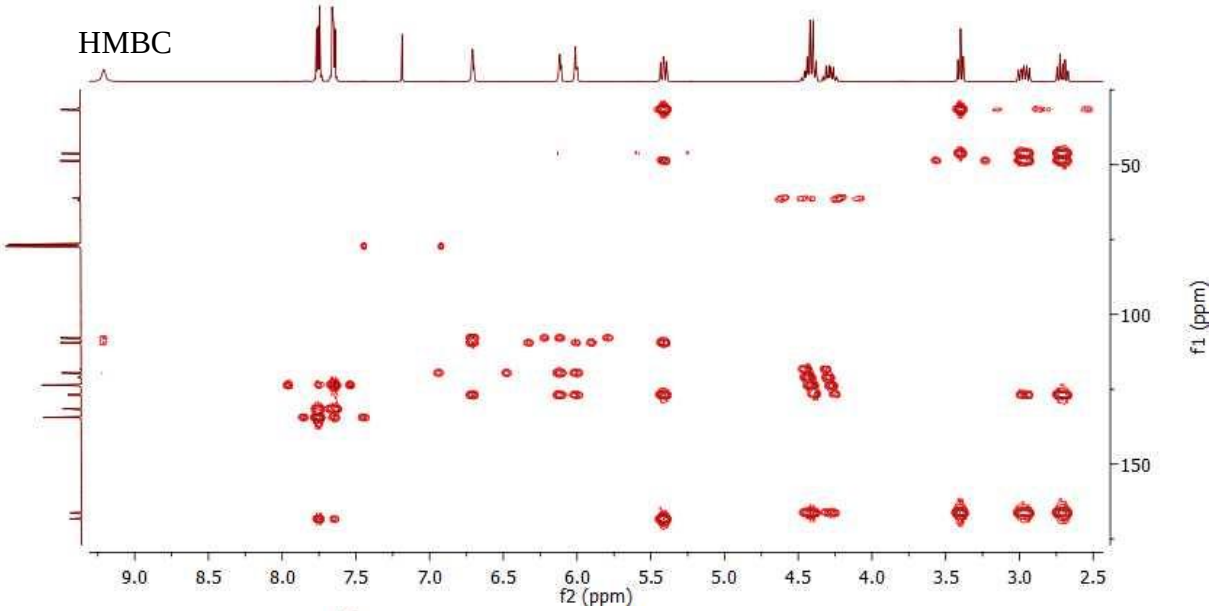

13C, CDCl3, 100 MHz
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


.00 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800

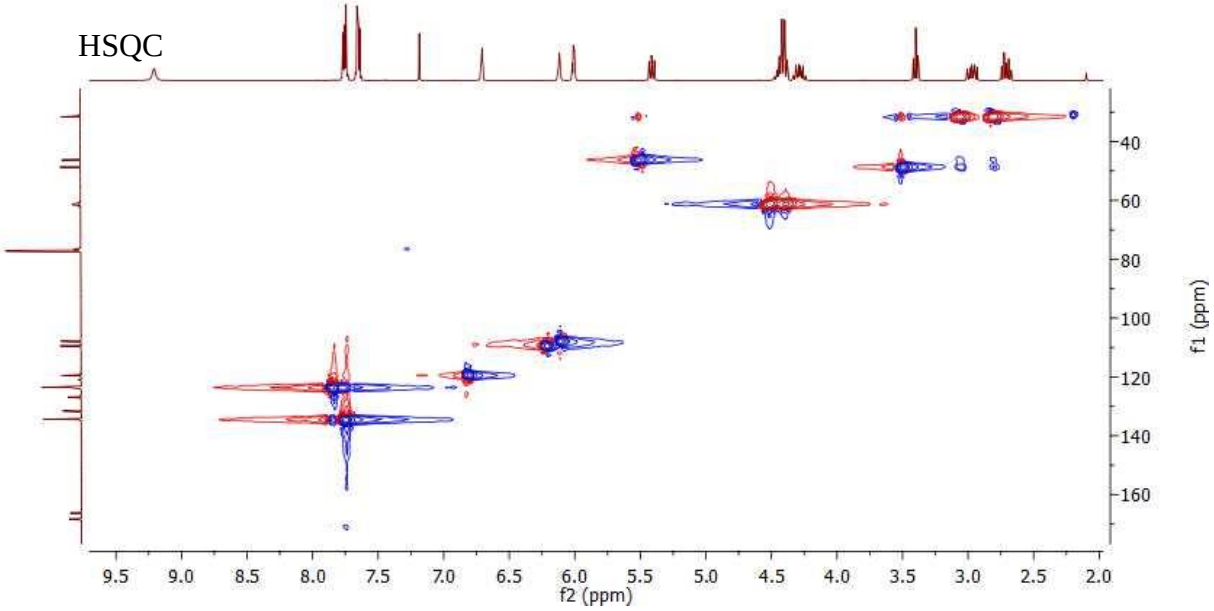
COSY

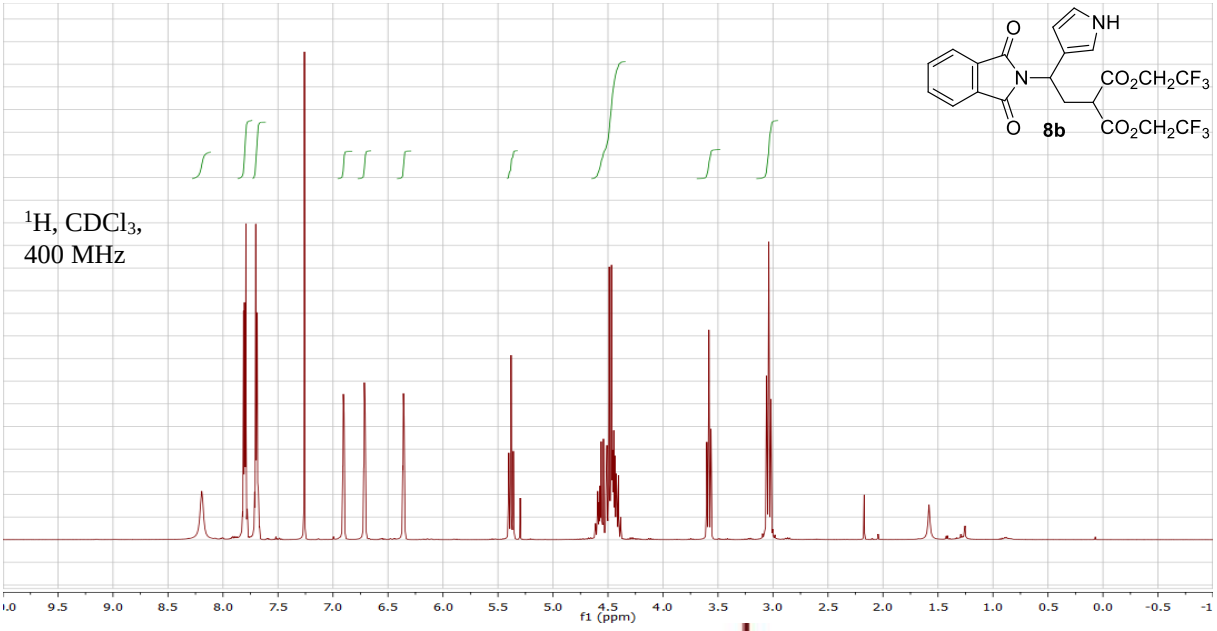


HMBC

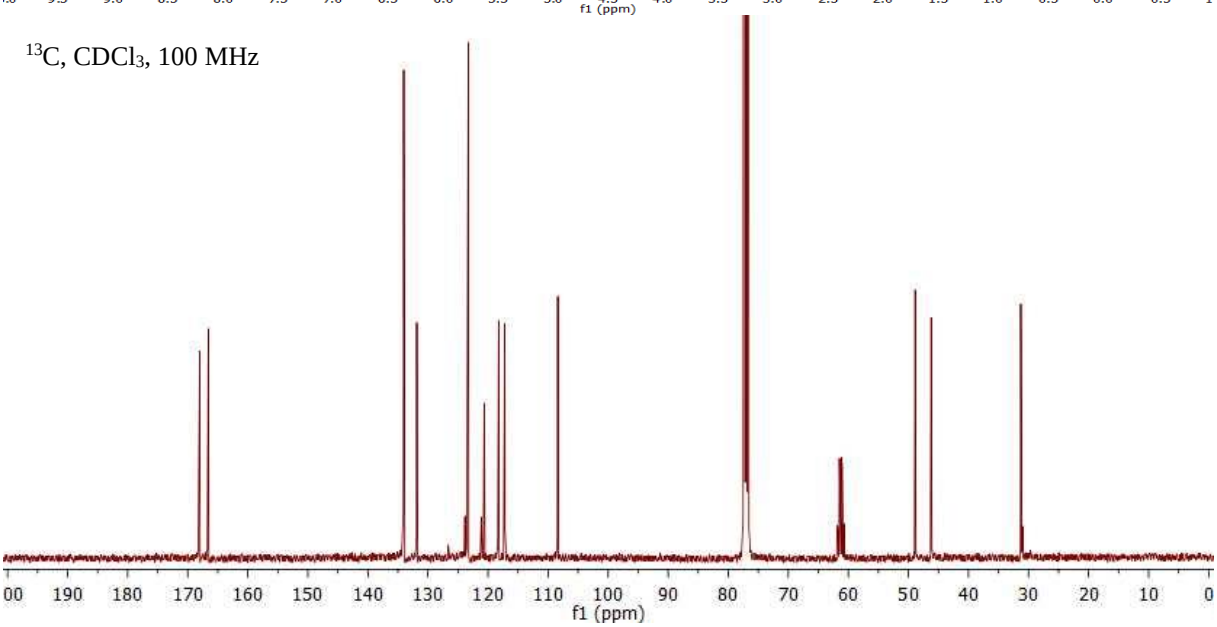


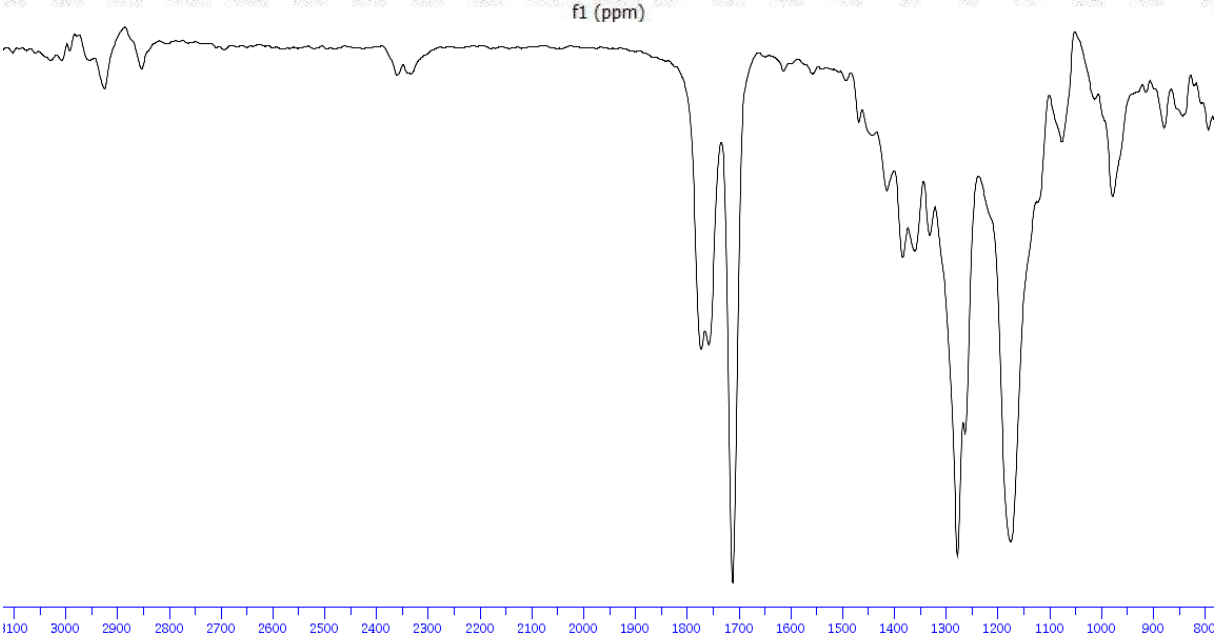
HSQC

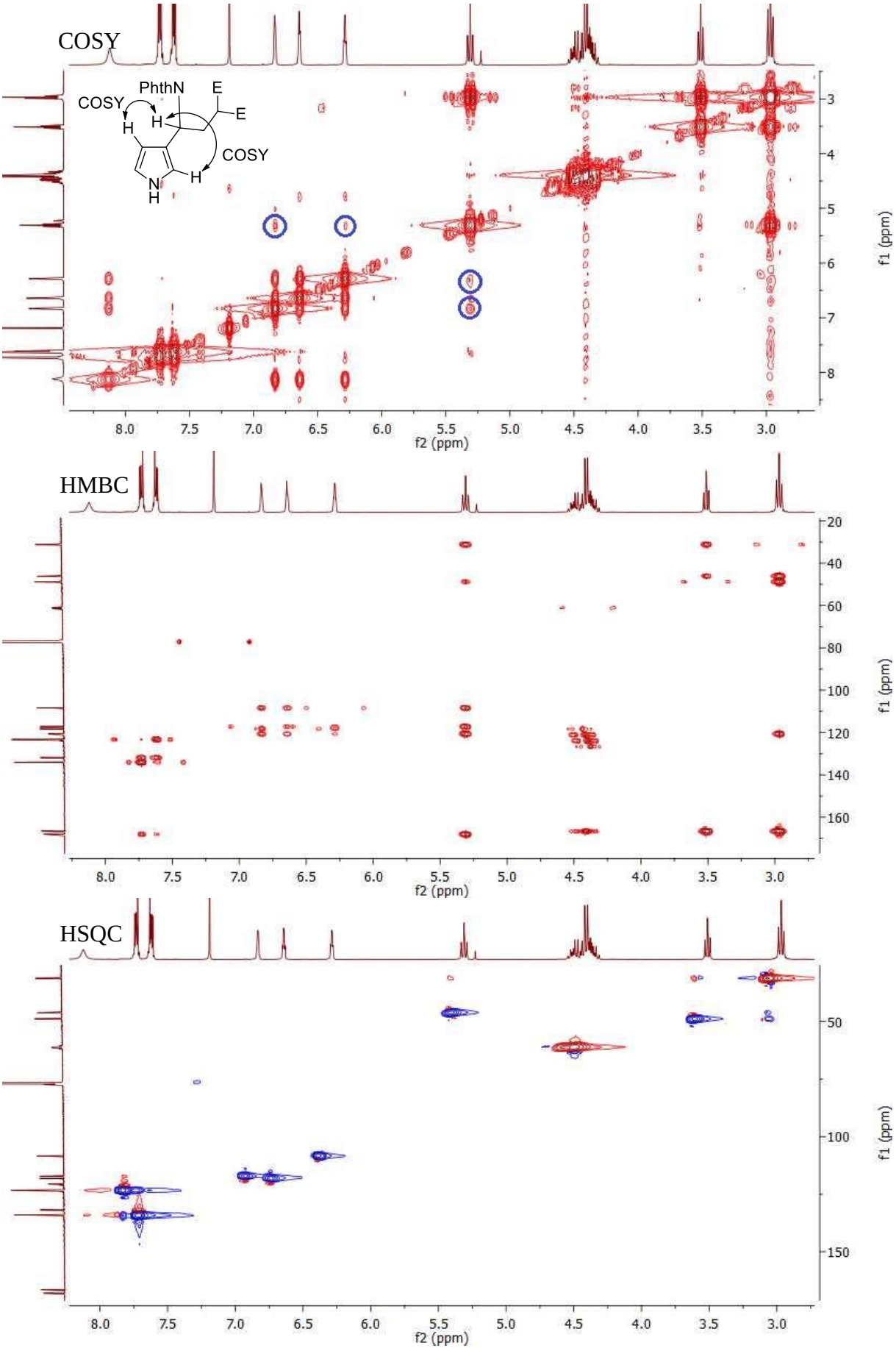


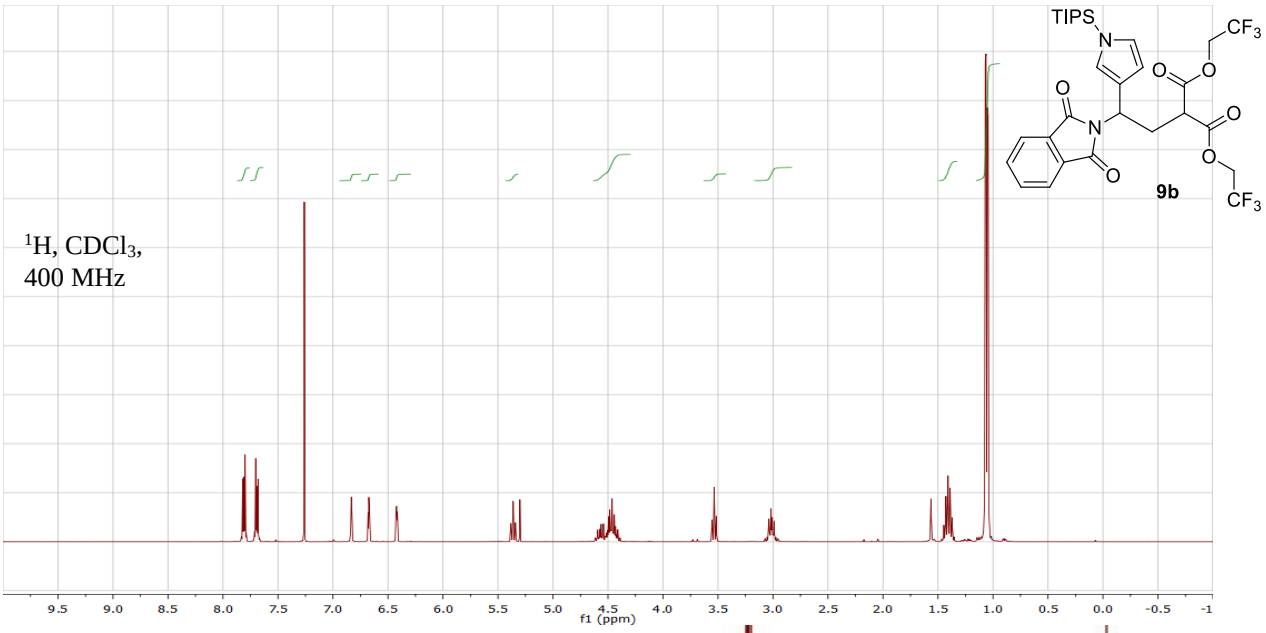

^{1}H, CDCl$_3$,
400 MHz
f1 (ppm)

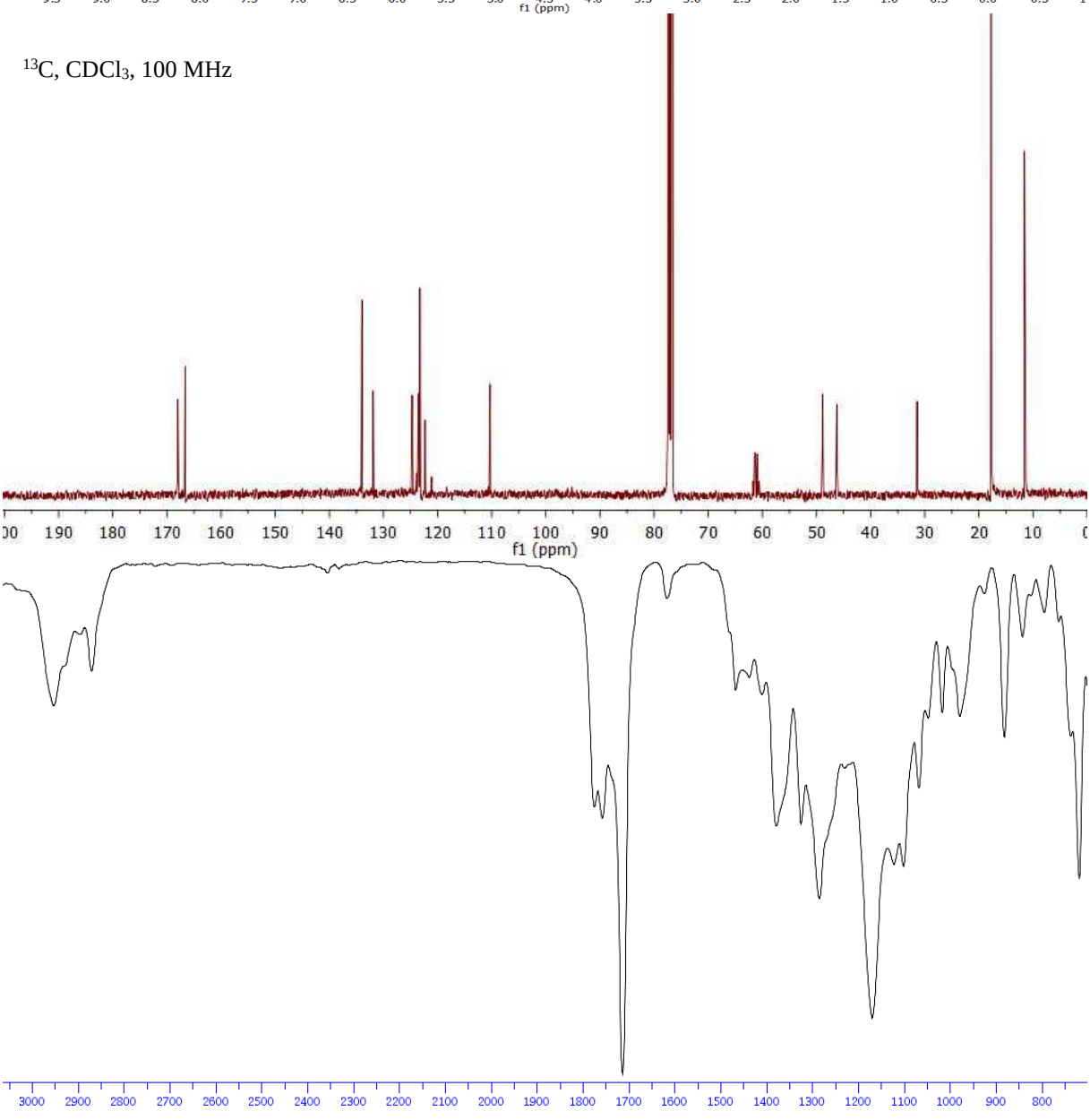
O
NH
N
O
O
$CO_2CH_2CF_3$
$CO_2CH_2CF_3$
8b

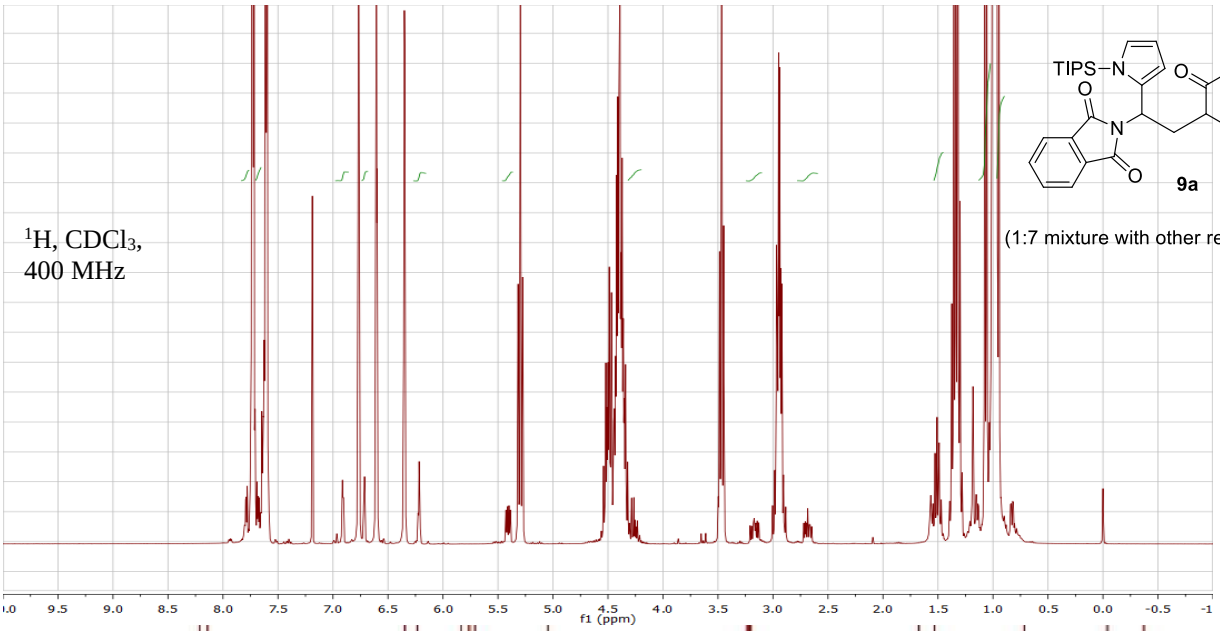

^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)




COSY
PhthN
E
E
COSY
H
H
COSY
H
N
H
f1 (ppm)
f2 (ppm)
HMBC
f1 (ppm)
f2 (ppm)
HSQC
f1 (ppm)
f2 (ppm)

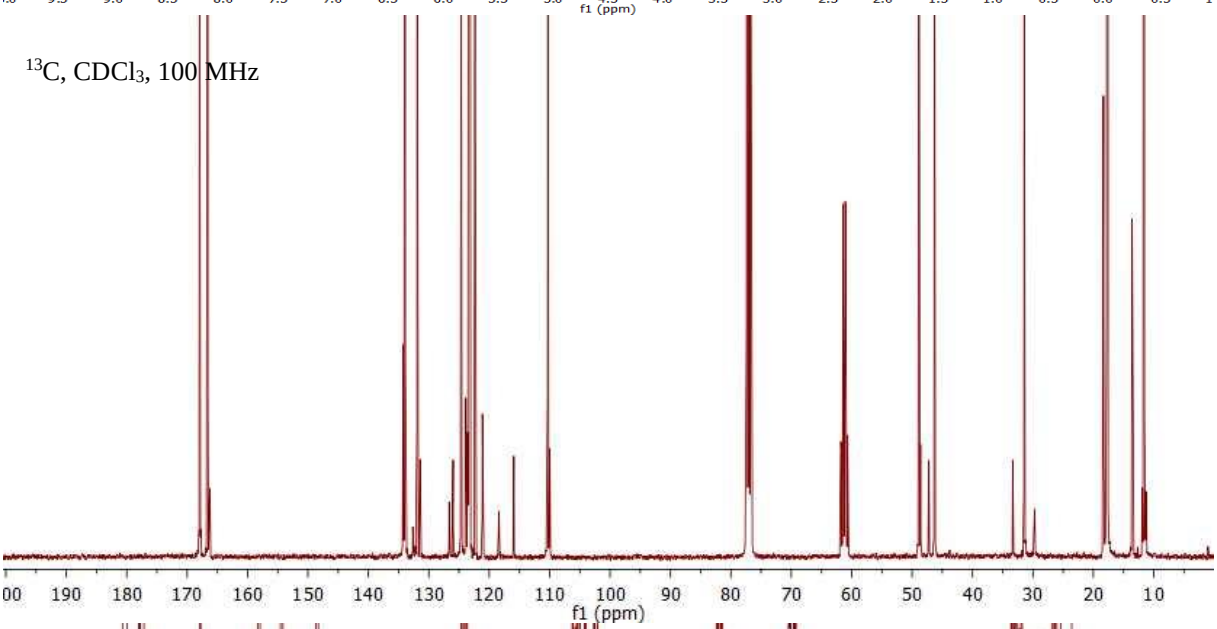

TIPS
N
CF3
O
O
O
N
O
O
O
O
CF3
9b
1H, CDCl3,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


13C, CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)
3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800



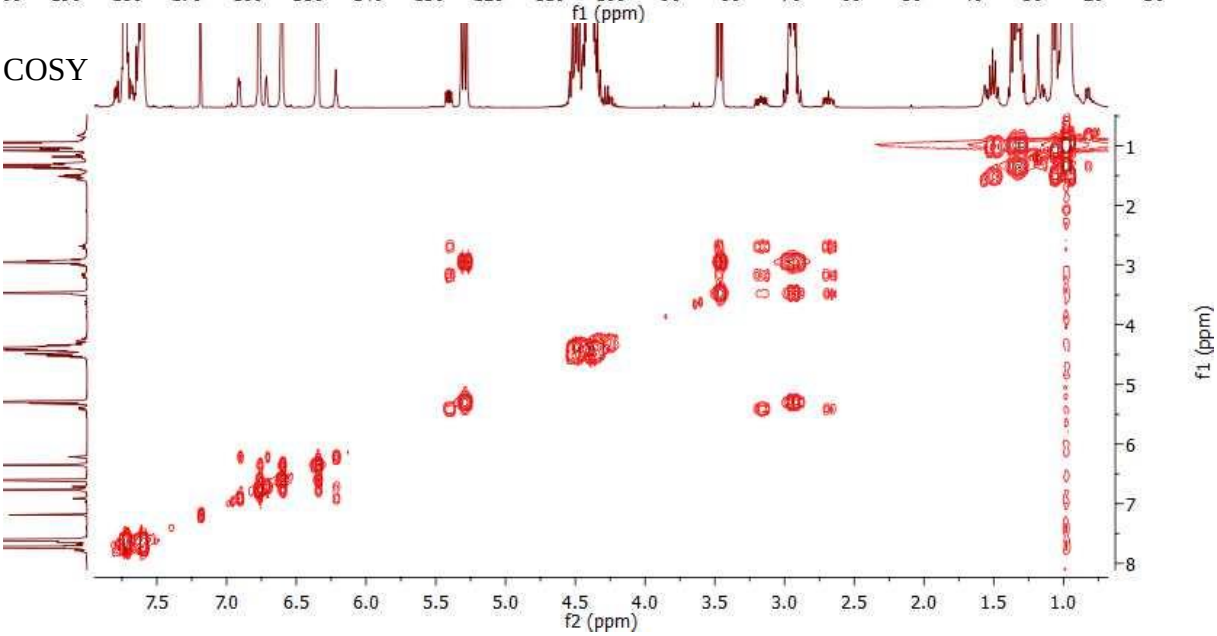
^{1}H, $CDCl_3$, 400 MHz

(1:7 mixture with other regioisomer)

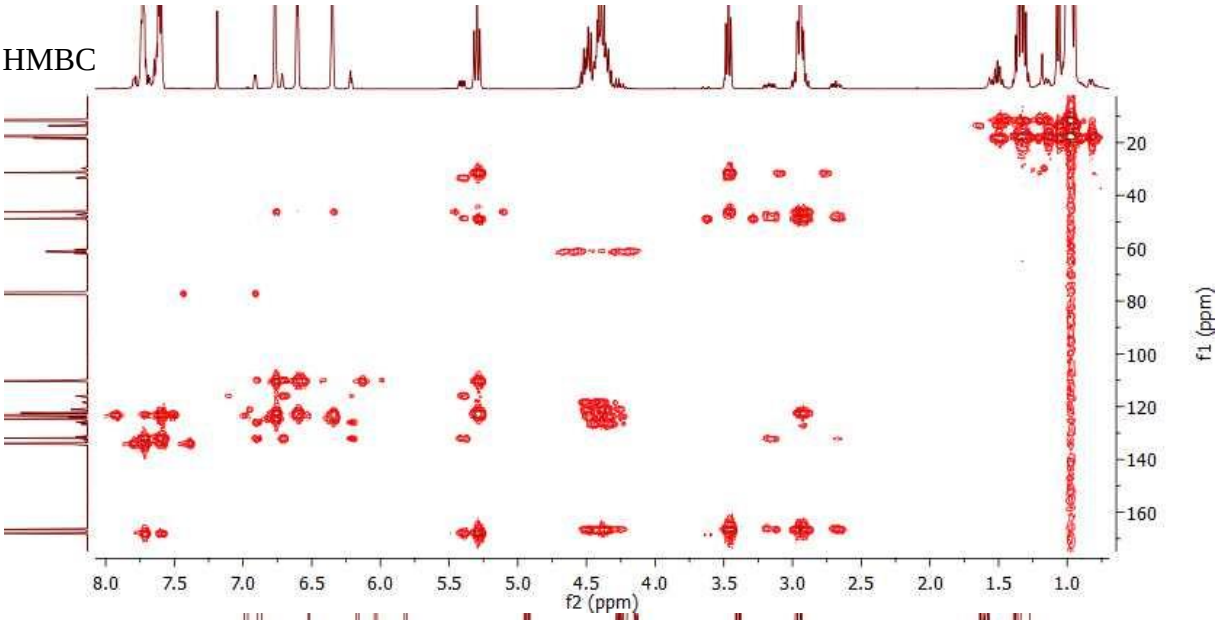


^{13}C, $CDCl_3$, 100 MHz

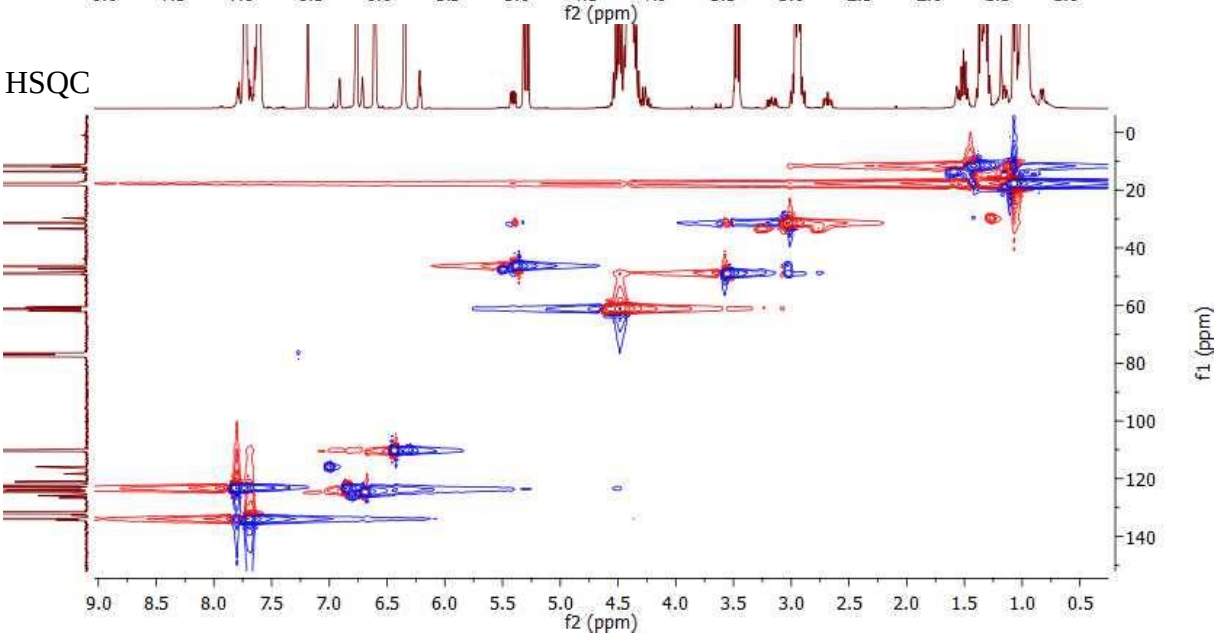
COSY

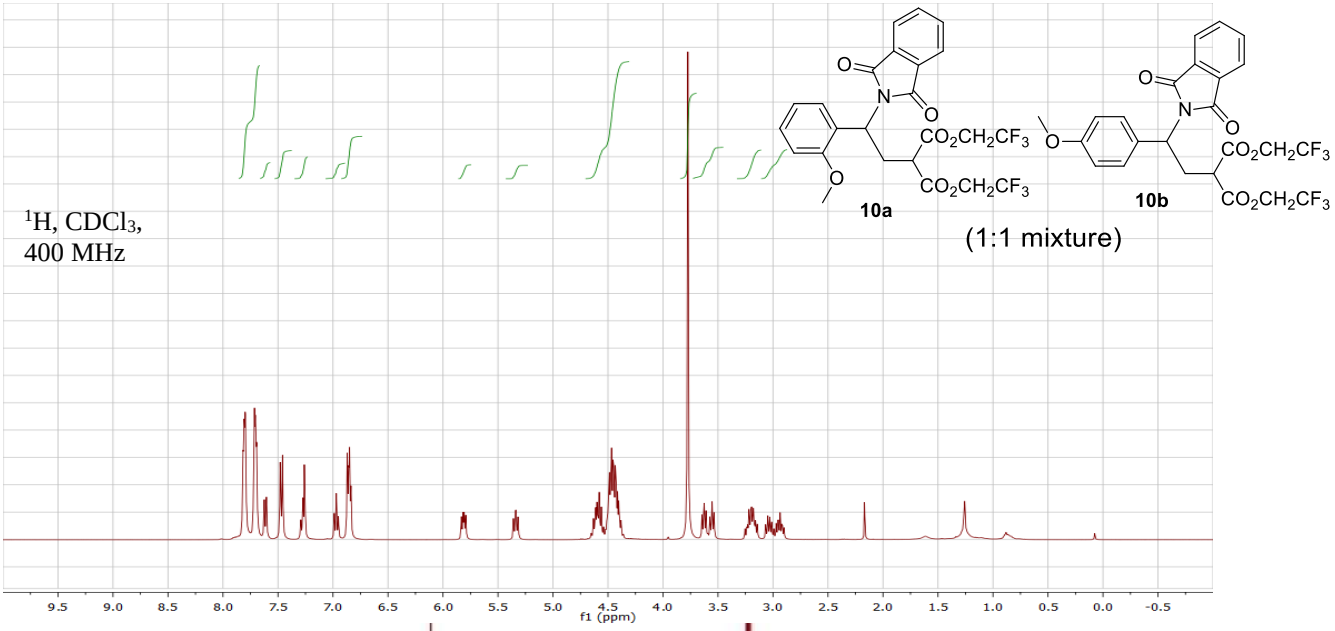


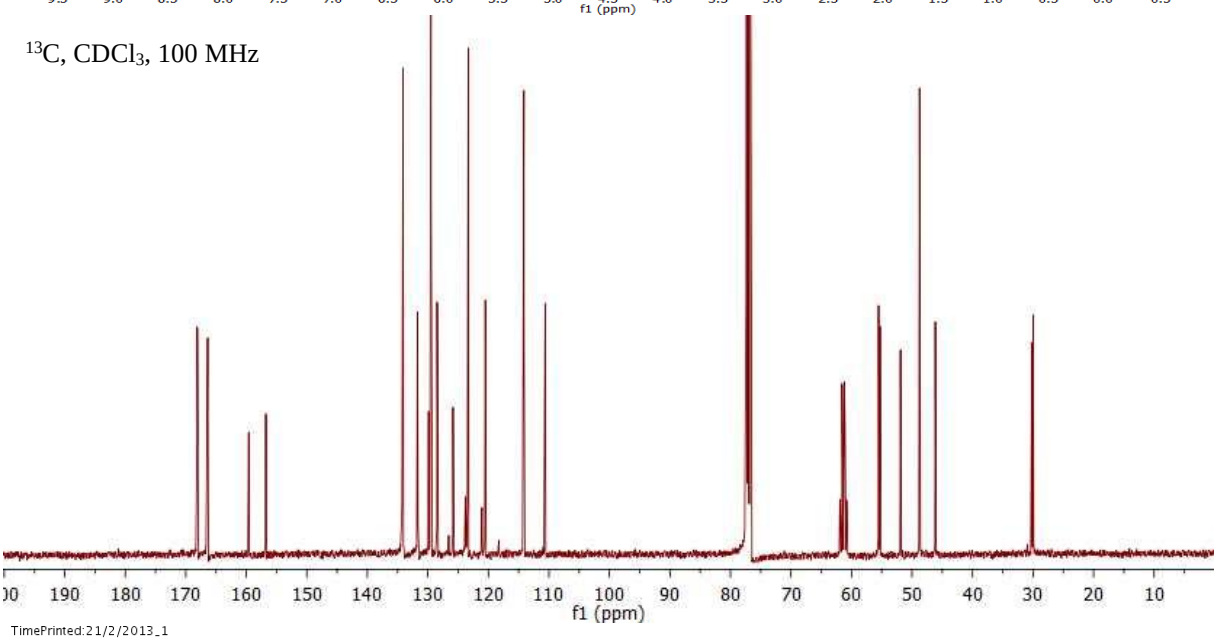
HMBC



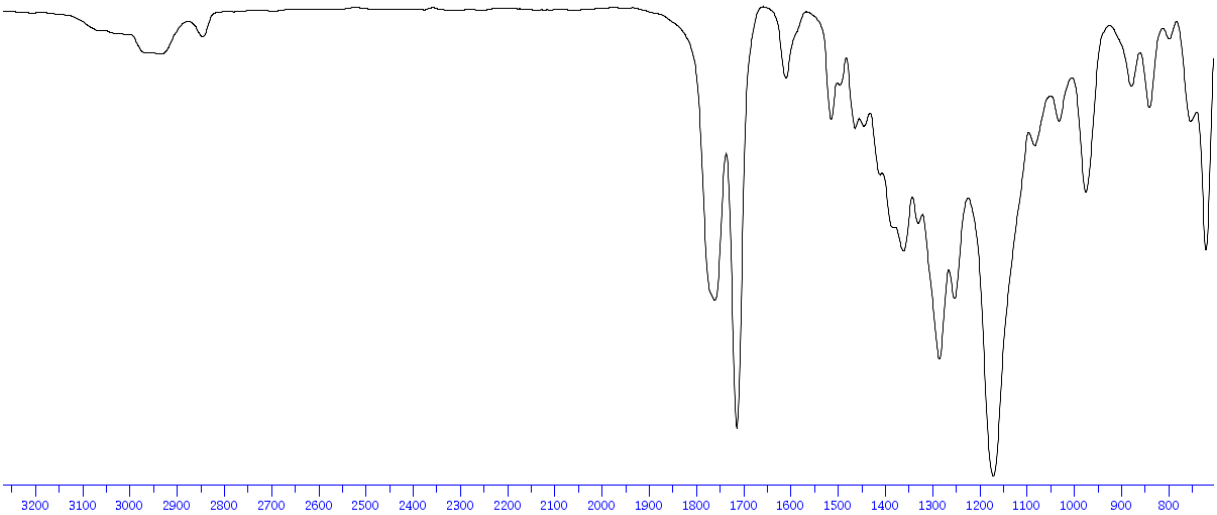
HSQC



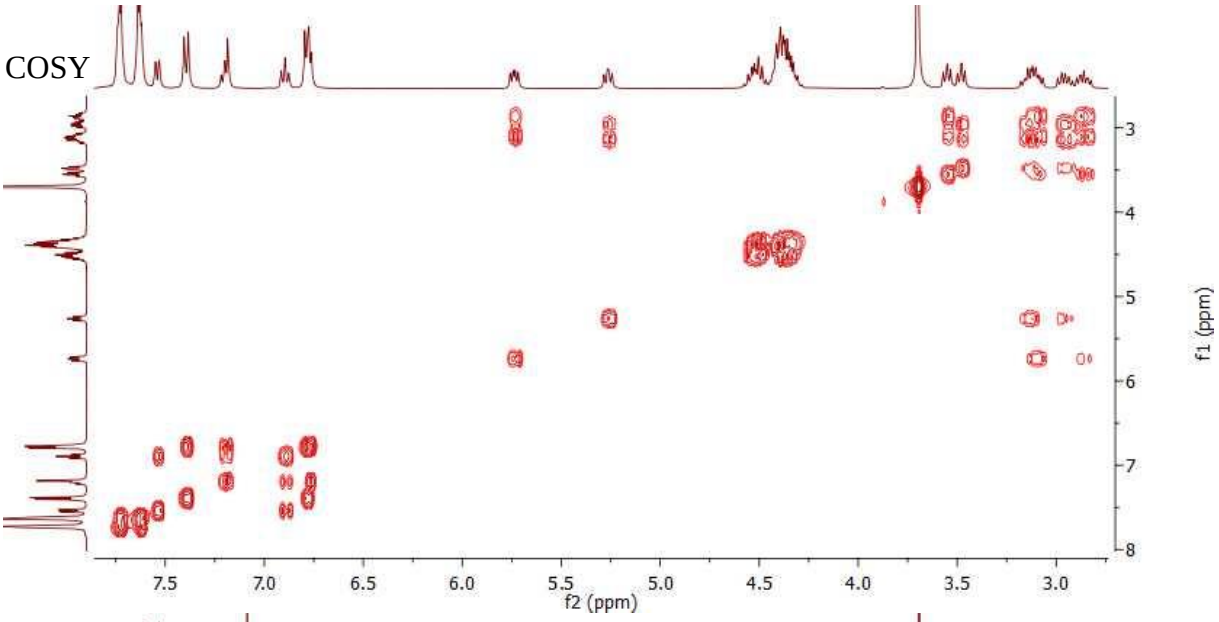




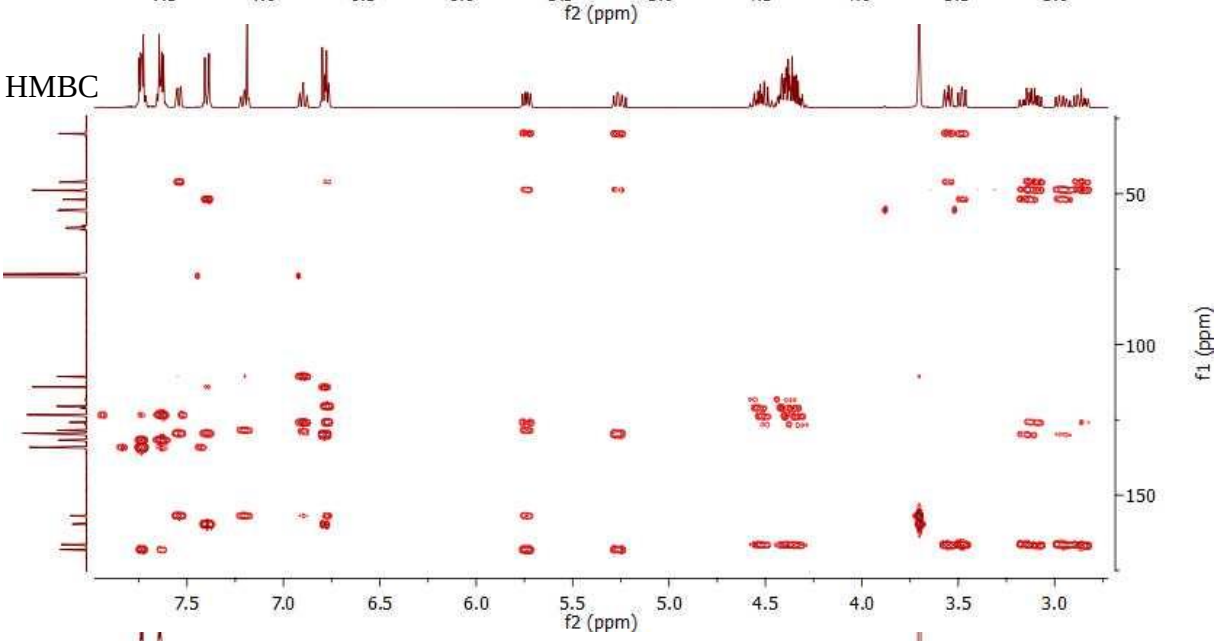
TimePrinted:21/2/2013_17:59:42
title:
user:



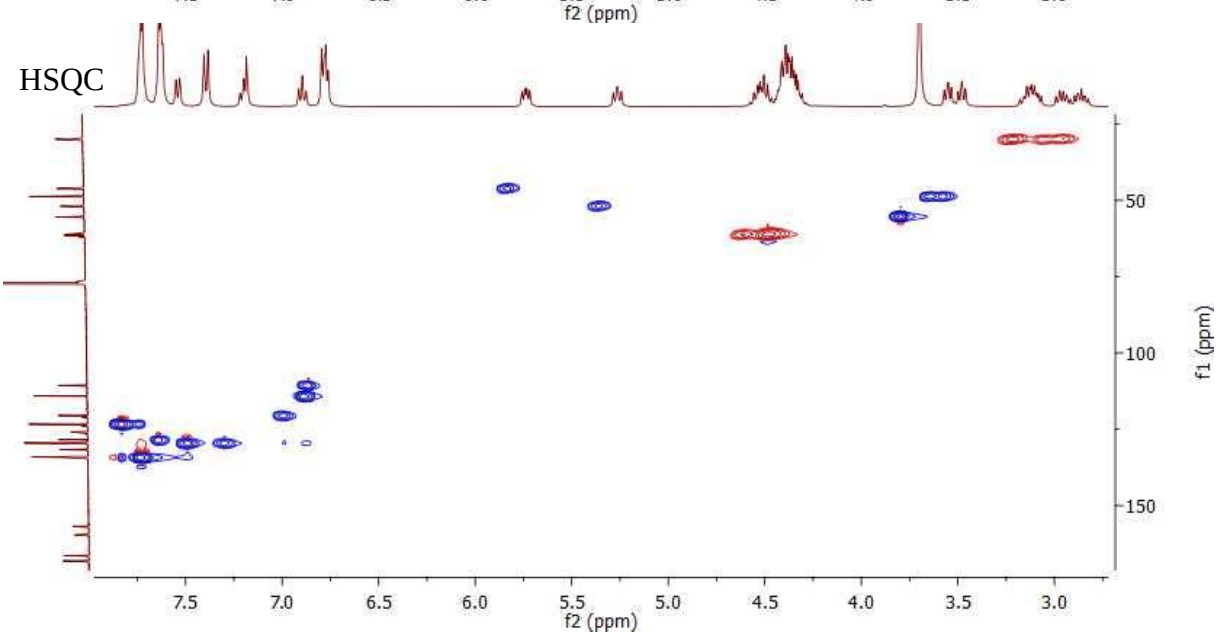
COSY



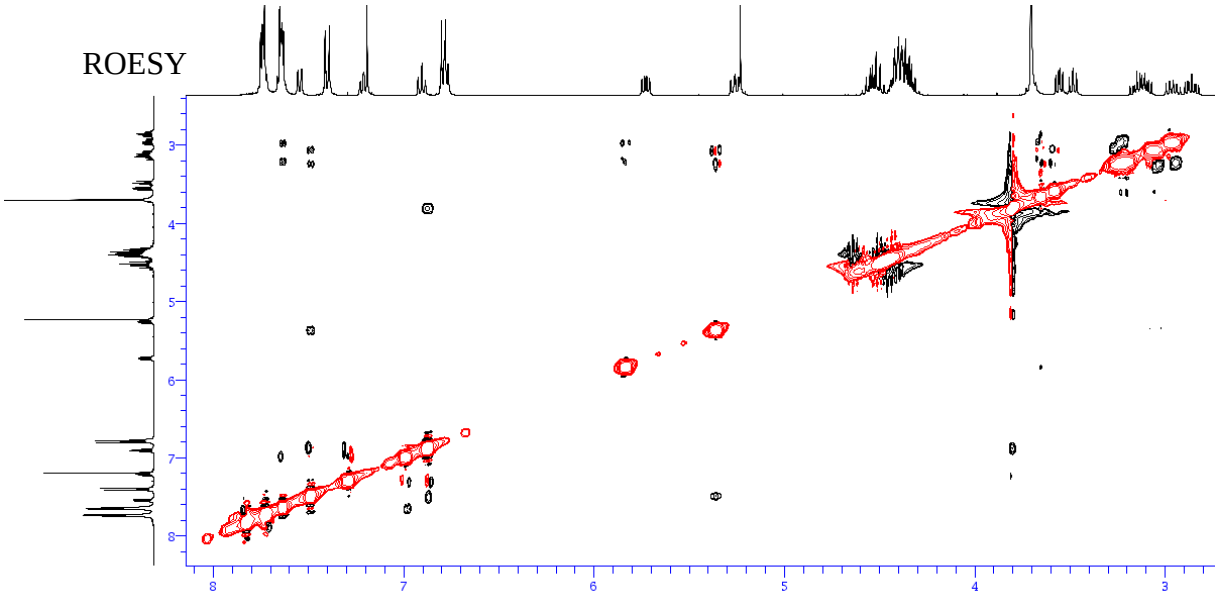
HMBC

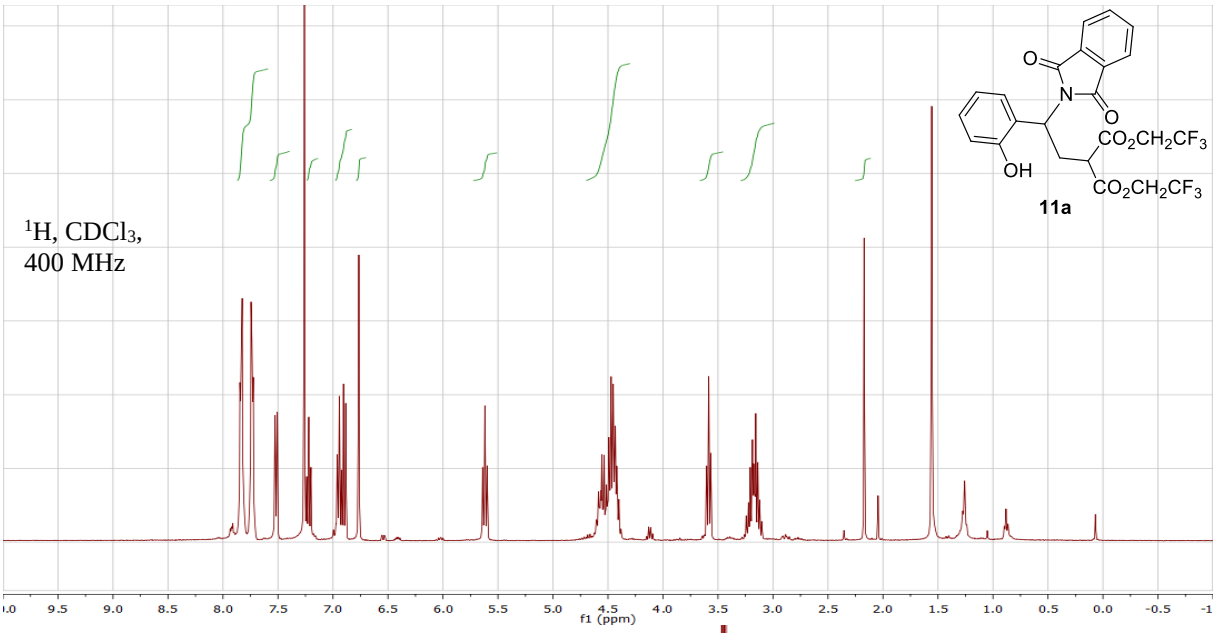


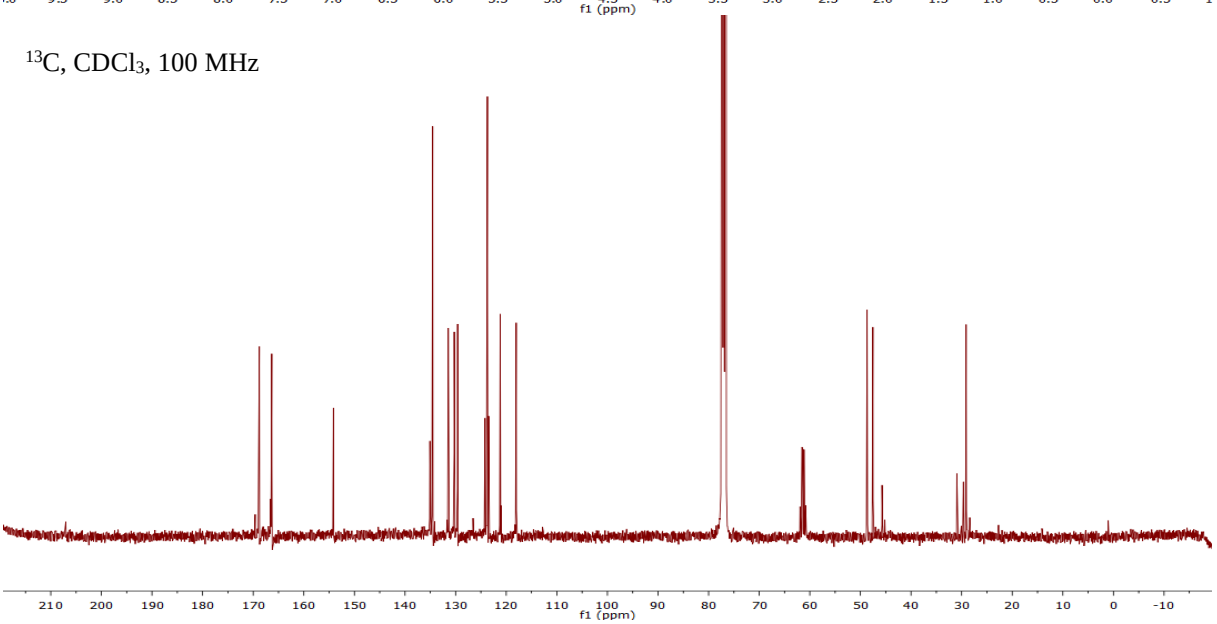
HSQC

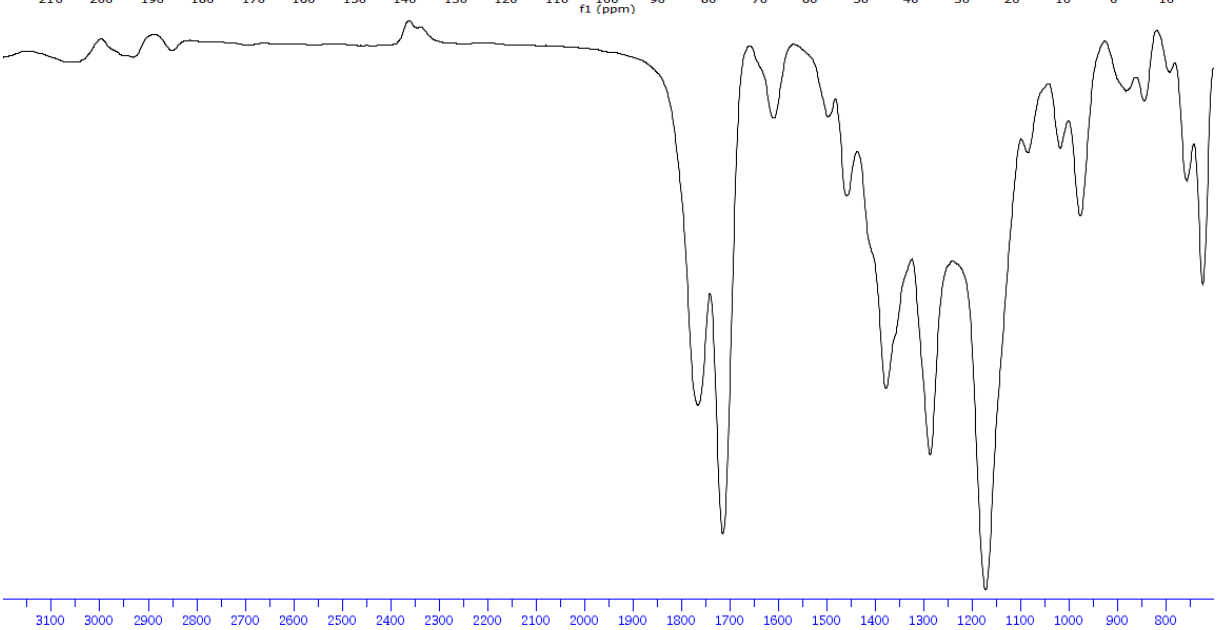


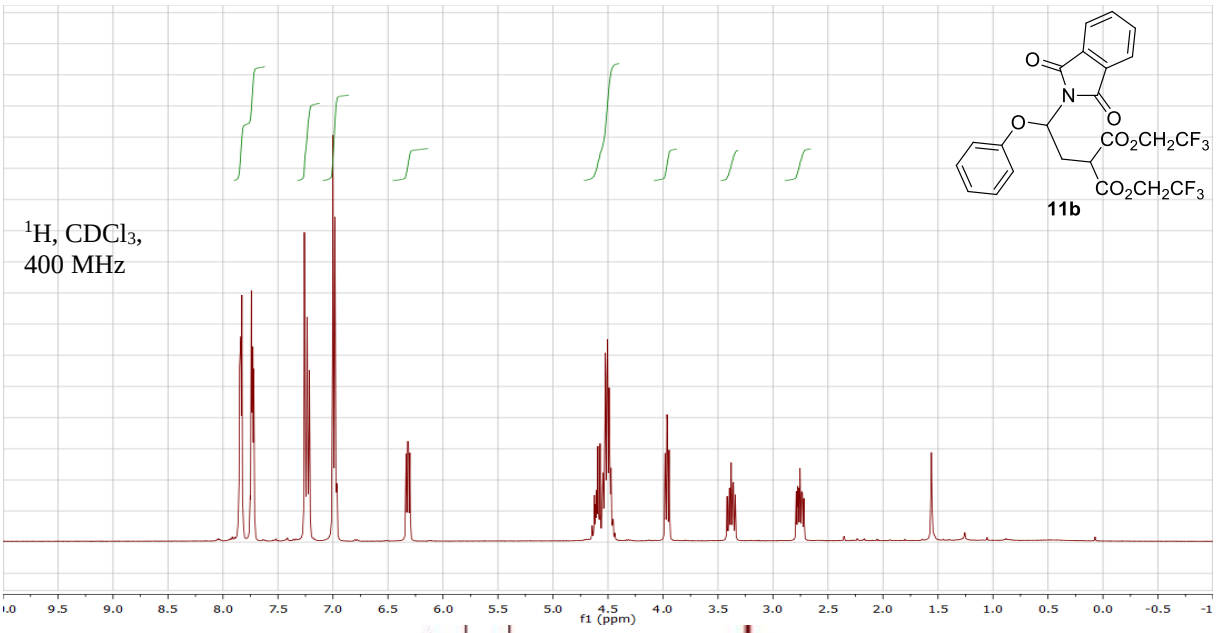
ROESY

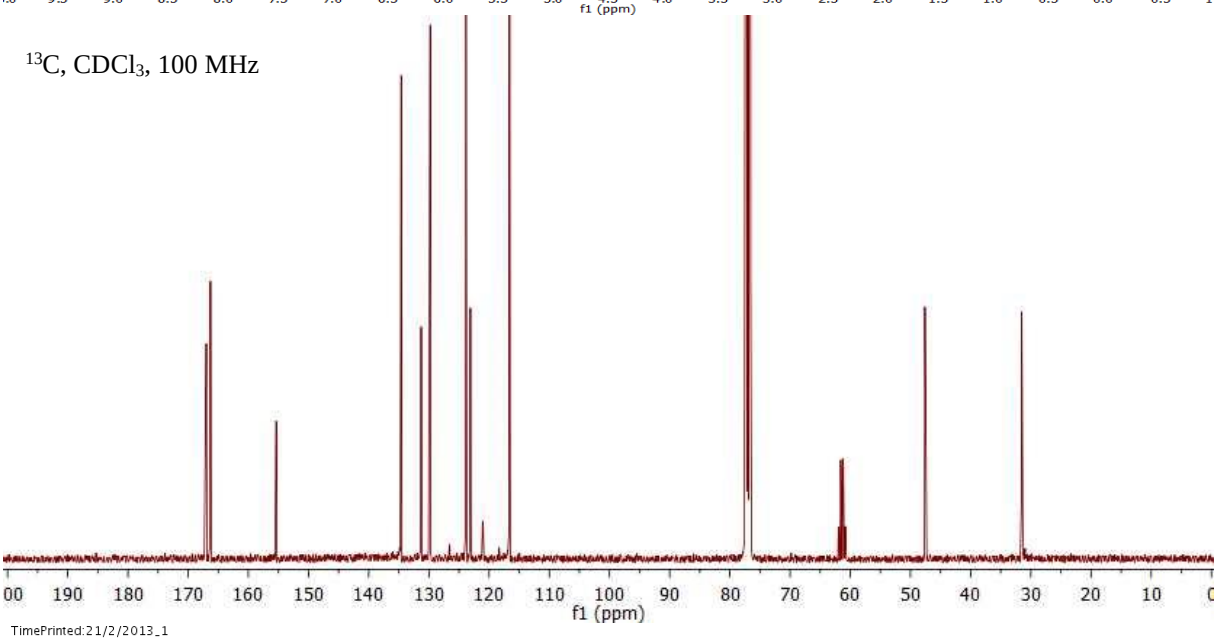


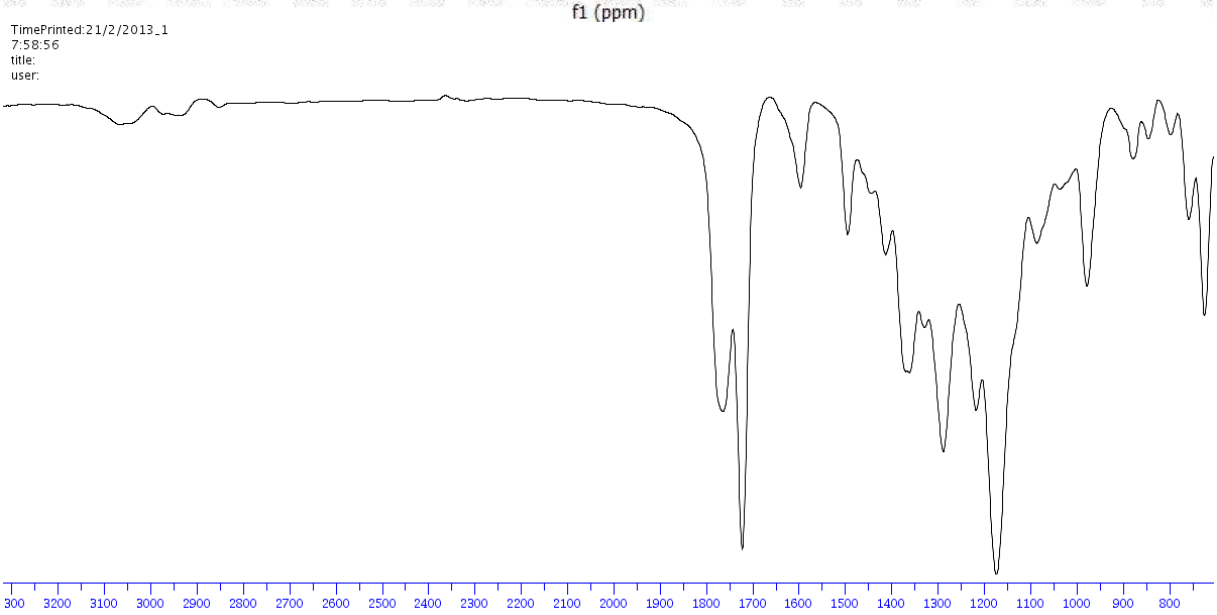

^{1}H, CDCl$_3$,
400 MHz
O
N
O
OH
CO$_2$CH$_2$CF$_3$
CO$_2$CH$_2$CF$_3$
11a
f1 (ppm)


^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)




^{1}H, CDCl$_3$,
400 MHz
O
N
O
O
O
CO$_2$CH$_2$CF$_3$
CO$_2$CH$_2$CF$_3$
11b
f1 (ppm)


^{13}C, CDCl$_3$, 100 MHz
f1 (ppm)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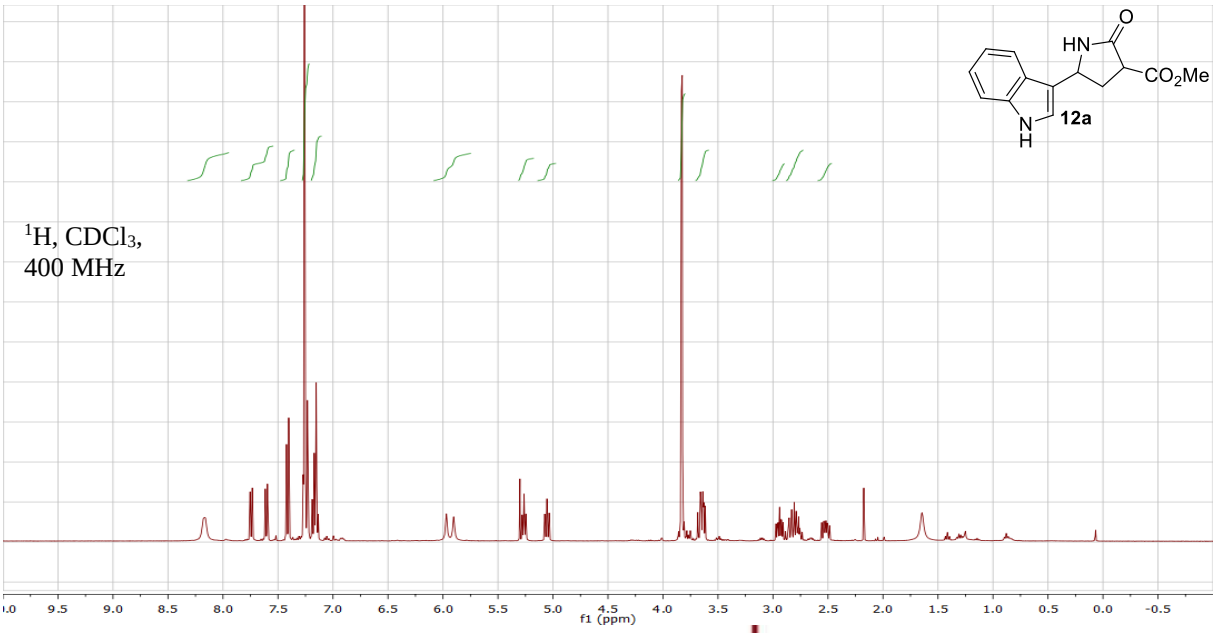
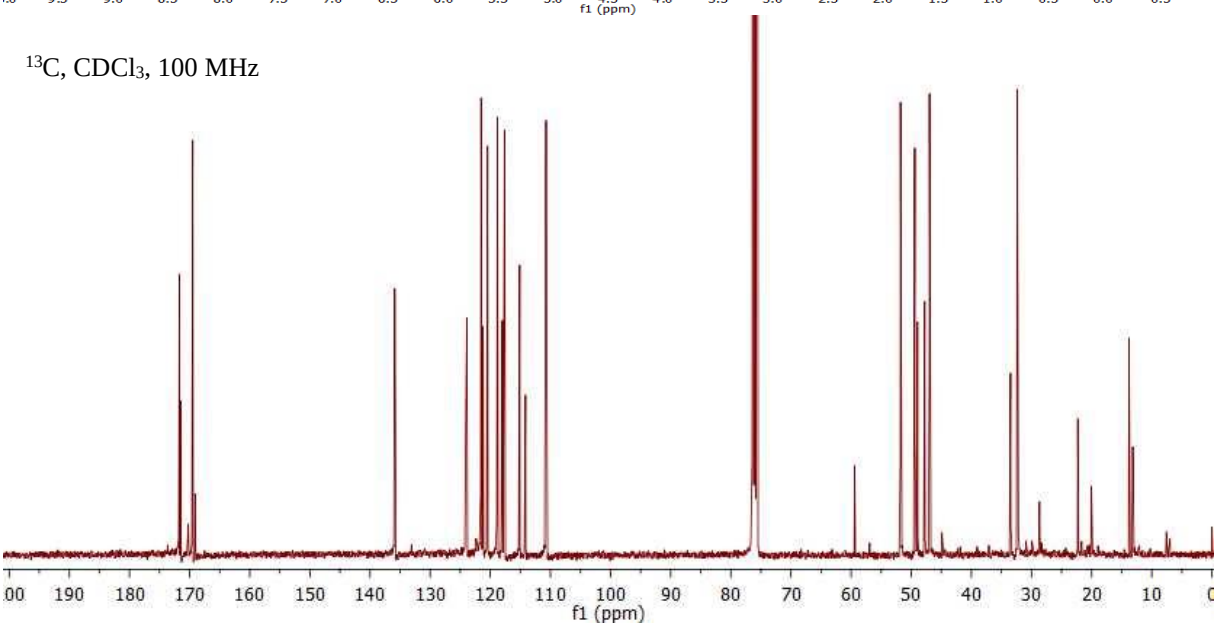
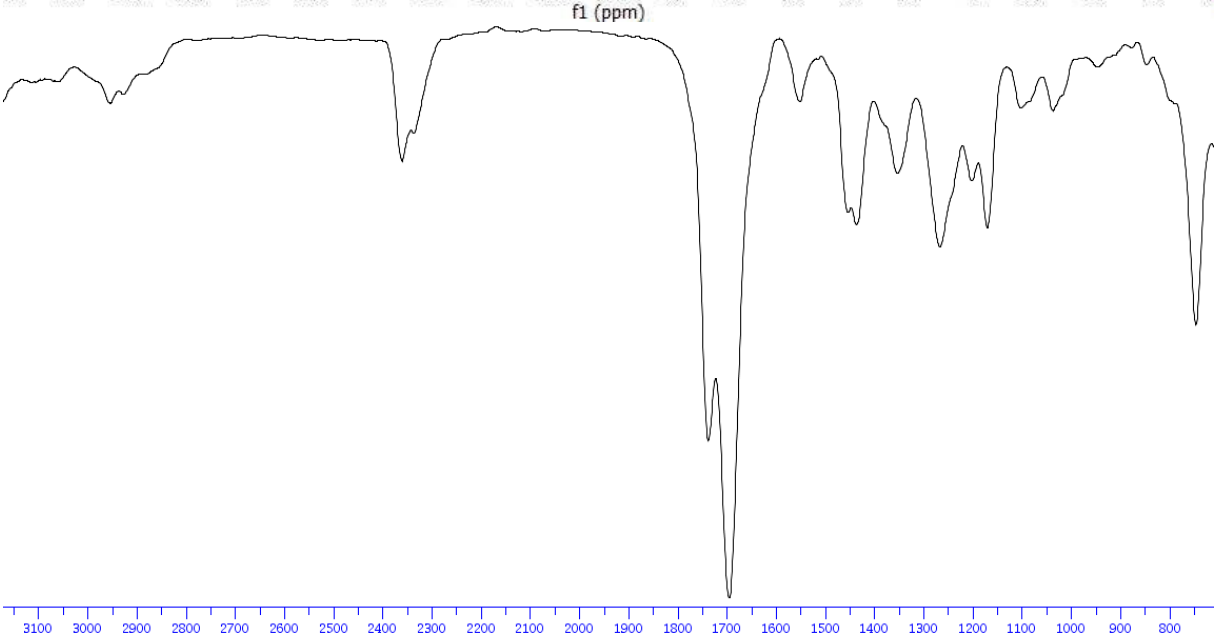
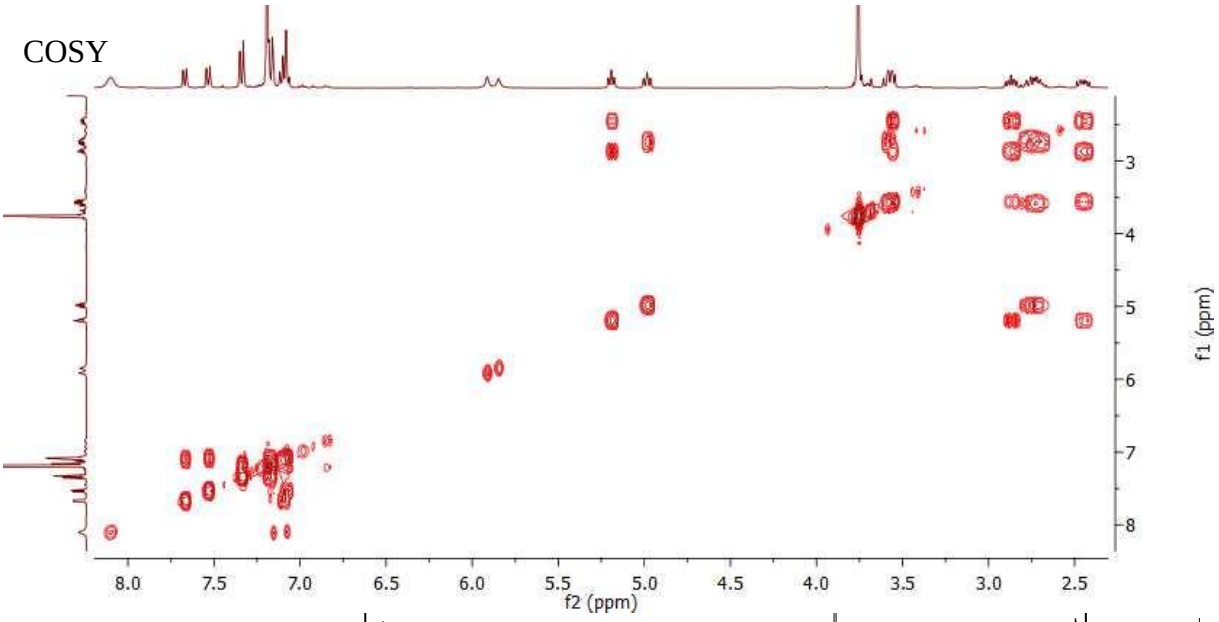

HN
O
CO2Me
N
H
12a
1H, CDCl3,
400 MHz
f1 (ppm)

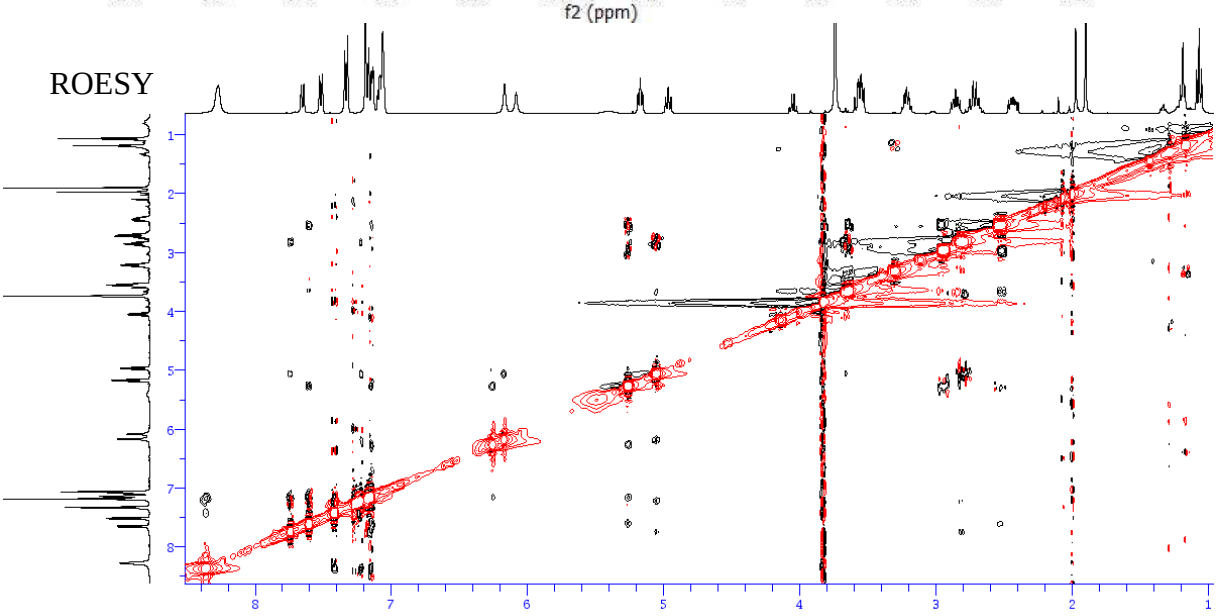

13C, CDCl3, 100 MHz
f1 (ppm)

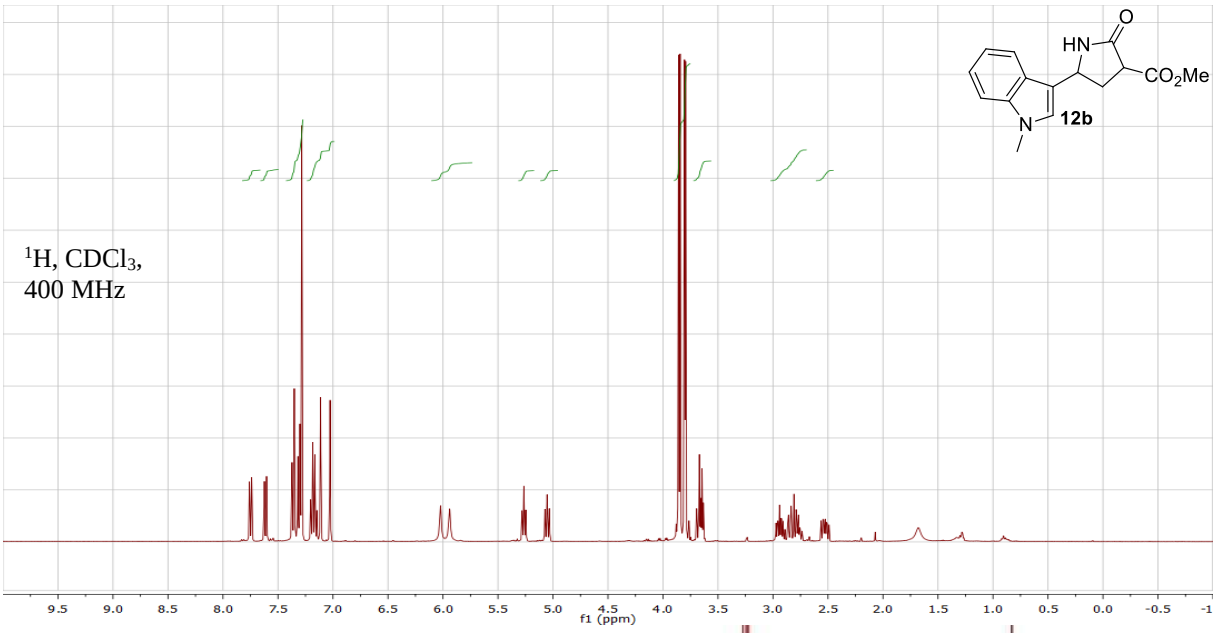


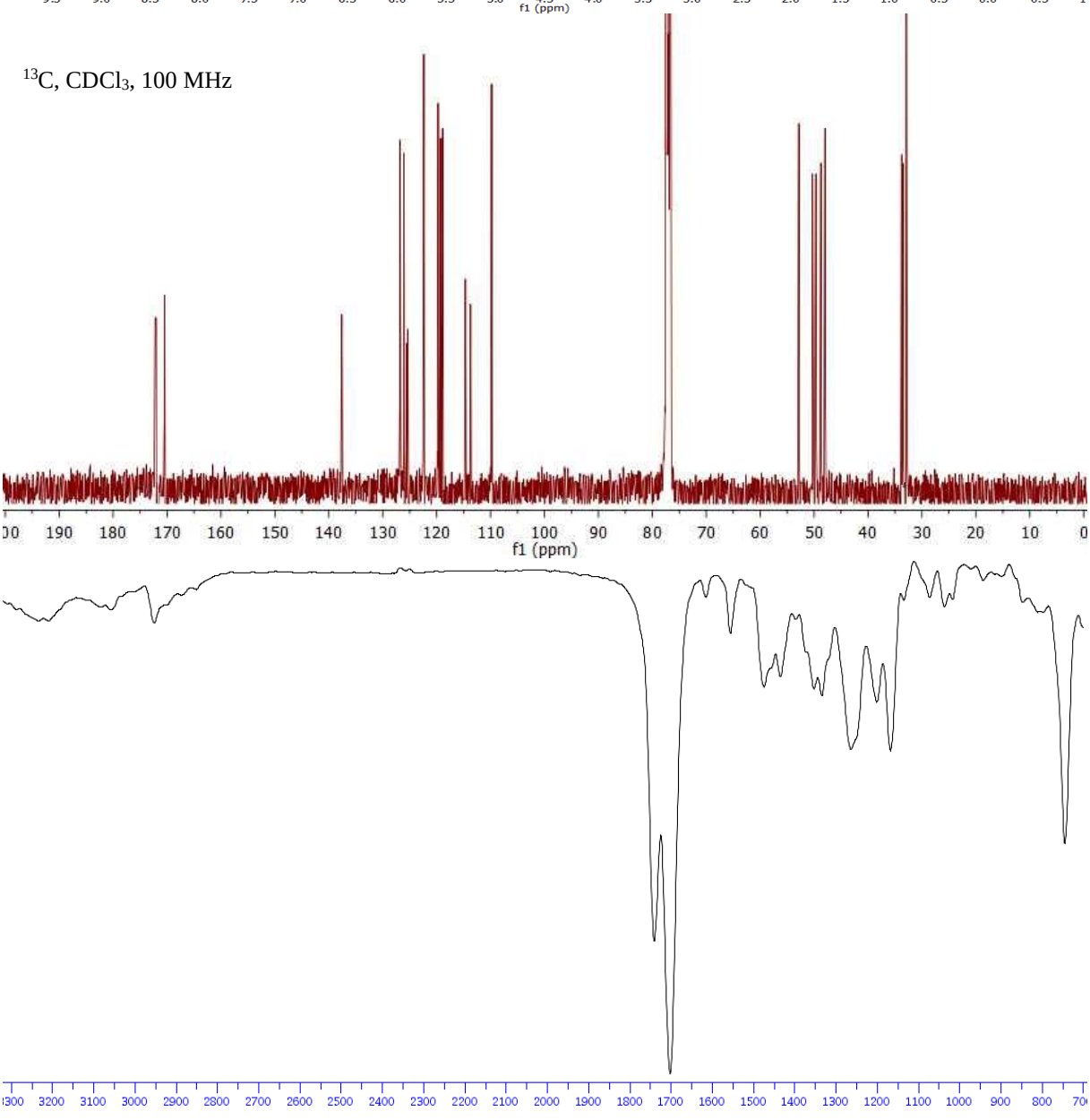
COSY



ROESY

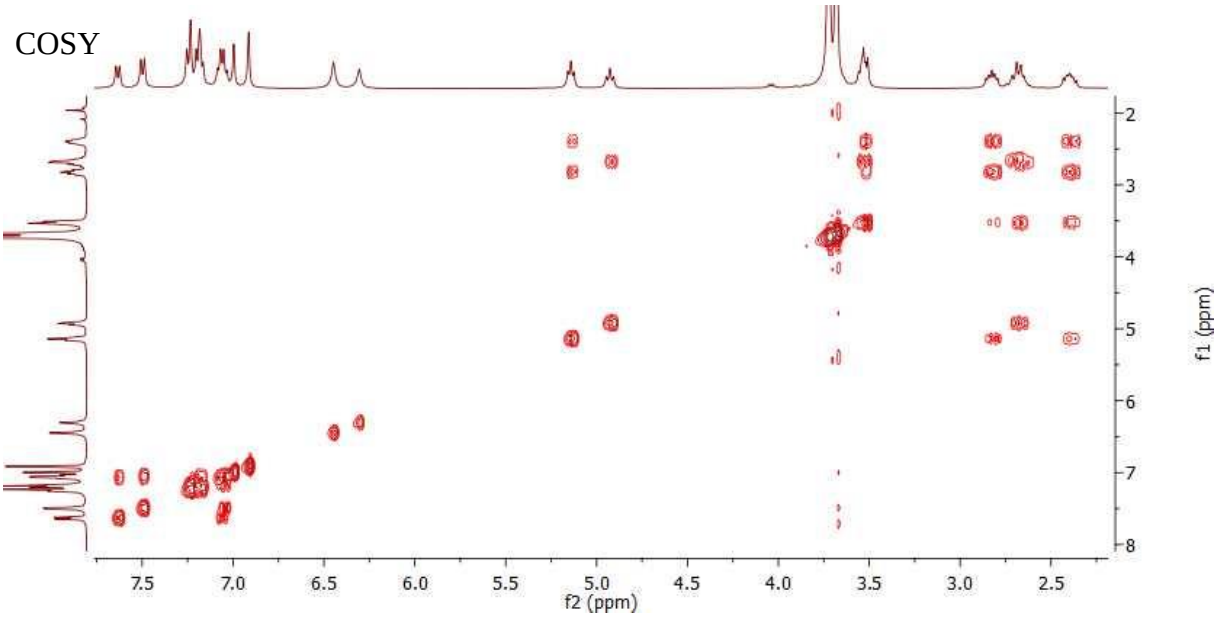


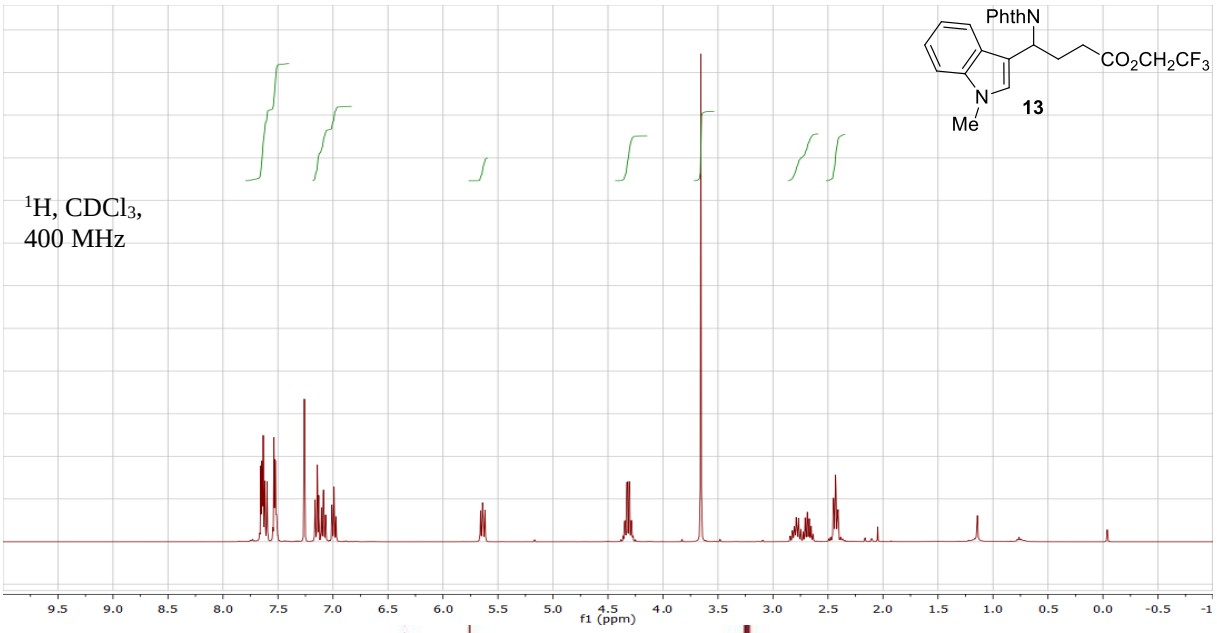

HN
O
CO2Me
N
12b
1H, CDCl3,
400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

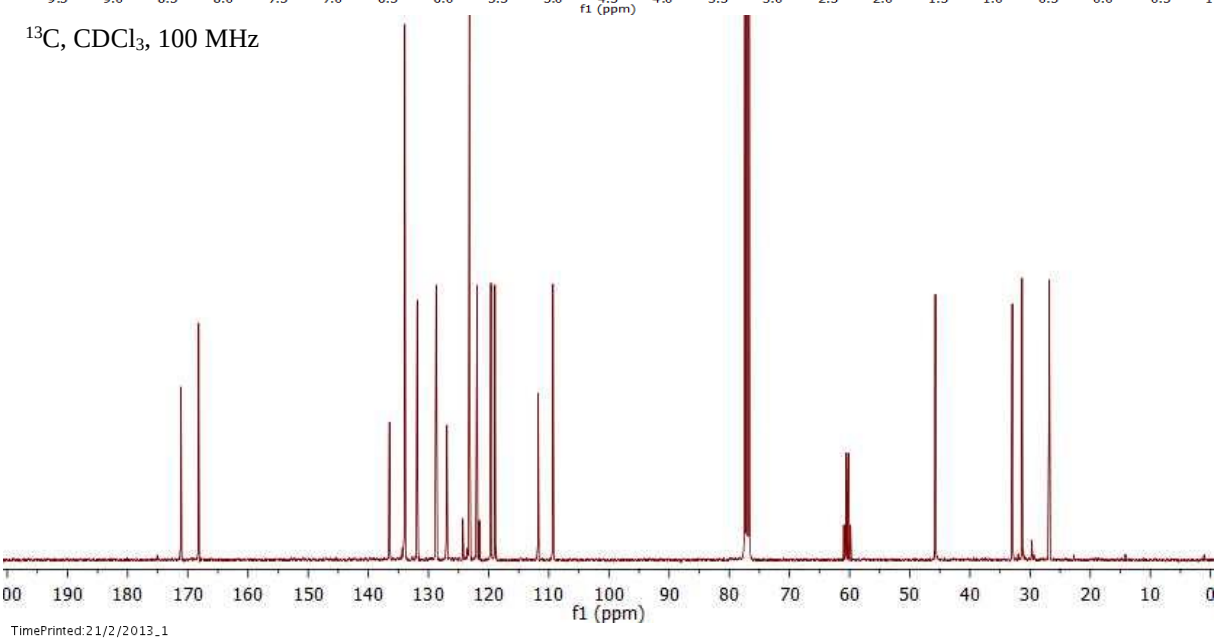

13C, CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3300 3200 3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800

COSY







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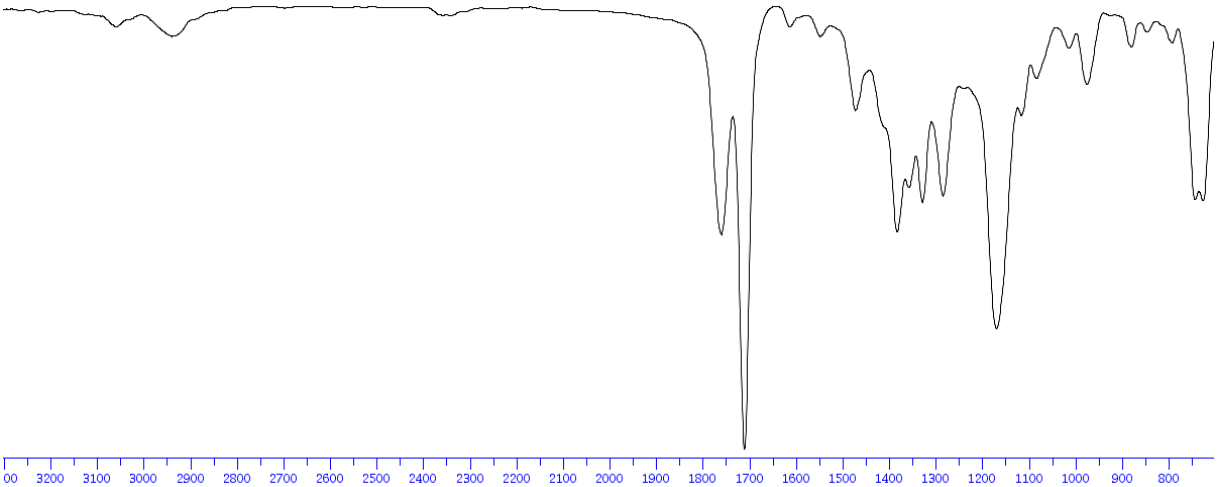

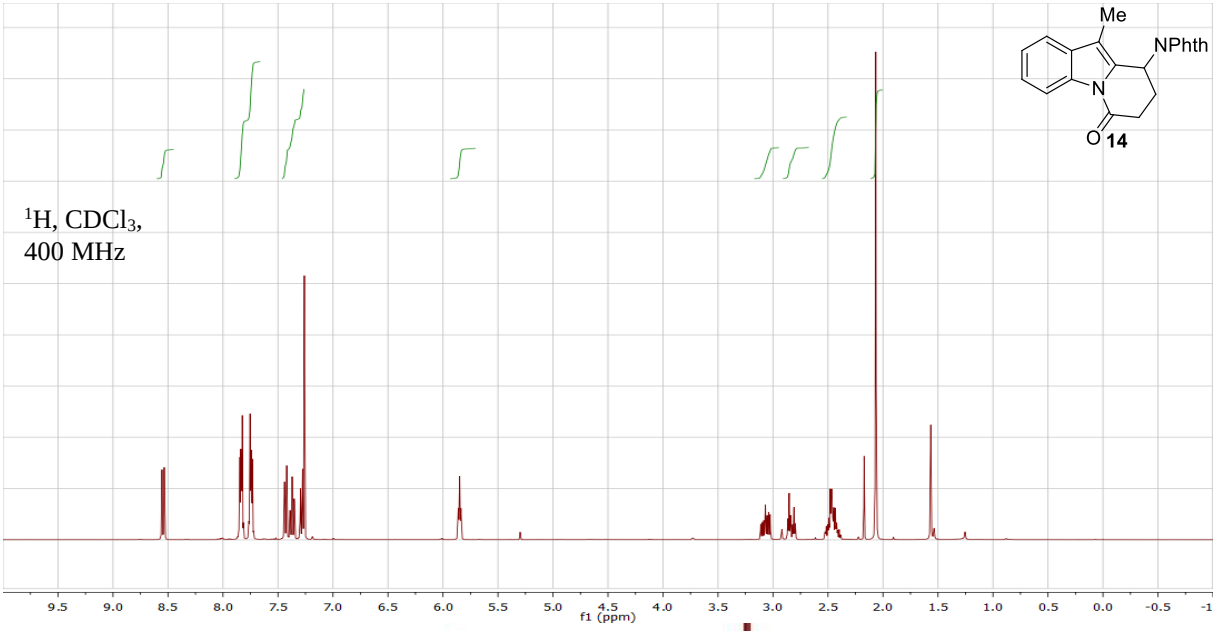

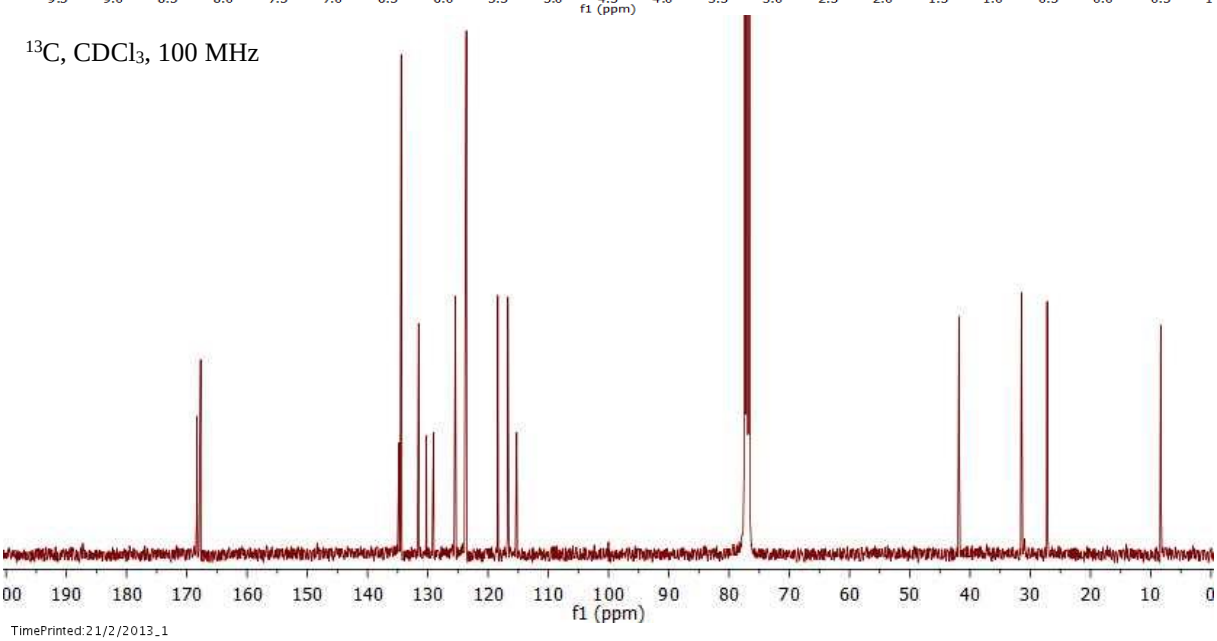

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