How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202306128
doi.org/10.1002/anie.202306128

Hypervalent Iodine Reagents

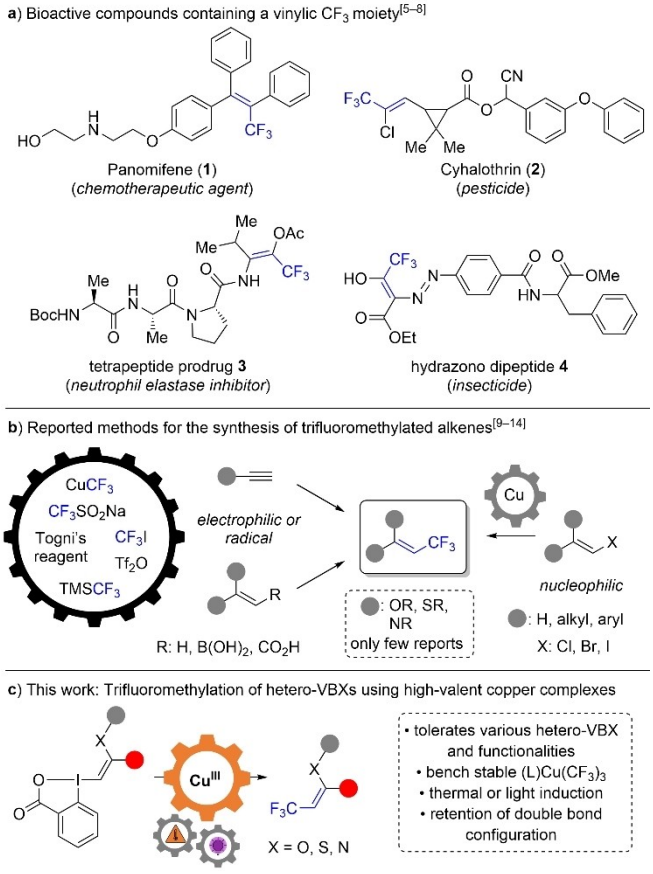
Synthesis of Trifluoromethylated Alkenes: Hypervalent Iodine Meets High-Valent Copper

*Tobias Michael Milzarek and Jerome Waser**

Abstract: The first trifluoromethylation of vinylbenziodoxolones (VBX) is reported herein. The synthetic method is based on the use of bench-stable, high-valent copper(III) species, and the reaction can be initiated under thermal conditions and/or irradiation (365 nm) giving access to trifluoromethylated alkenes in a stereoselective fashion. Various VBX reagents derived from tyrosine, cysteine, small peptides, thiols and amides can be used as precursors. The obtained alkenes could be further functionalized by reduction or epoxidation of the trifluoromethylated double bond. Furthermore, the method could be applied in a large-scale batch/flow synthesis and could be conducted under visible light irradiation.

Introduction

Fluorine and fluorine-containing groups play a key role in the development of new pharmaceuticals and agrochemicals.[1] Accordingly, the amount of fluoro-pharmaceuticals in commercialized drugs has increased to about 20 % in recent years.[2] The basis for this success can be found in the strong electronegativity of fluorine and its resulting influence on the physicochemical properties.[3] Most fluorine-bearing drugs consist of either alkyl or aryl groups containing a single fluorine atom, or a di/trifluoromethyl group.[4] Trifluoromethylated alkenes are an emerging class of fluorinated compounds (Scheme 1a). For example, panomifene (**1**), a chemotherapeutic agent from the tamoxifen class, is used for treating breast cancer.[5] This functionality can also be found in crop protection agents, such as cyhalothrin (**2**),[6] and peptides **3** and **4**, used for the cure of inflammatory diseases[7] and as insecticide, respectively.[8]



Scheme 1. Bioactive compounds with a trifluoromethylated alkene motif (**a**), previous synthesis of C_{vinyl}–CF_3 derivatives (**b**), and this work: synthesis from hypervalent iodine reagents (**c**).

With this rising interest, several methods have been recently developed for the synthesis of trifluoromethylated alkenes (Scheme 1b). The transformations differ in the source of the CF_3 group and the related reactivity of the trifluoromethylation reagents (electrophilic, radical or nucleophilic), using most often either copper-based or light mediated activation. Electrophilic/radical-based copper(I)-catalyzed methods enable the direct trifluoromethylation of terminal alkenes and alkynes[9a] using CF_3I,[9b] sodium trifluoroacetate,[9c] Umemoto's reagent[9d] or Togni's reagent.[9e–j] On the photocatalytic side, α,β-unsaturated carboxylic acids can be trifluoromethylated upon decarboxylation.[10] Unactivated alkenes can also be converted to the corresponding trifluoromethylated products using photoredox catalysis.[11] However, these approaches

[*] Dr. T. M. Milzarek, Prof. Dr. J. Waser
Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL, SB ISIC LCSO, BCH 4306
1015 Lausanne (Switzerland)
E-mail: jerome.waser@epfl.ch
Homepage: http://lcso.epfl.ch/

suffer from the use of highly reactive reagents or the inherent limitations of the use of the CF_3 radical.

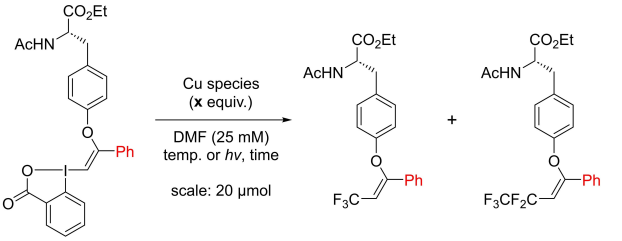
As an alternative approach, the utilization of $Cu^{I}CF_3$ complexes enables the nucleophilic trifluoromethylation of alkene halides.[12] However, careful fine-tuning of the reaction conditions is needed to prevent the formation of CF_2CF_3 side products, due to the in situ formation of a CF_2 carbene.[12a,b,13] Furthermore, a stereoselective access to the halide precursor is required for this approach. Although stereoselective synthesis of simple halogenated alkenes are well established, more substituted derivatives, especially bearing heteroatom substituents, are more difficult to access with high geometrical purity. The Ruppert-Prakash reagent can also be used for the copper-catalyzed formation of (*Z*)-trifluoromethyl enol esters starting from carboxylic acids, but this reaction remains limited to a narrow scope of substrates.[14] A more general access to heteroatom substituted trifluoromethylated alkenes would be of high interest, especially for the pharmaceutical and agrochemical industries.

In the present work, we combine the reactivity of hypervalent hetero-VBXs[15] with the one of trifluoromethylated high-valent copper(III) complexes[16] (Scheme 1c). Hetero-substituted VBX can be accessed in high *Z* or *E* geometrical purity using the method developed by our group[17] and Yoshikai and co-workers,[18] respectively. Furthermore, the use of the high valent Cu^{III} complexes completely suppressed the formation of CF_2 carbenes, leading to high purity trifluoromethylated compounds under simple reaction conditions. The method is applicable to a broad range of different hetero-vinylbenziodoxolones, including amino acid and peptide based ones, as well as vinyl (thio) ethers, enamides, natural products and drugs. In addition, the synthetic method can be performed under thermal conditions or light irradiation. The alkenes can be easily converted to the corresponding trifluoromethylated epoxides or reduced alkanes.

Results and Discussion

We started our investigations of the trifluoromethylation using the UV-active protected L-tyrosine derivative **5a** as model substrate (Table 1). The previously reported $CuCF_3$[19] (3.0 equiv.), reacted directly with VBX **5a** (120 °C, 1 h) to give the desired product **8a** in 51 % yield (entry 1). However, the pentafluoroethylated by-product **8aa** was also formed in 33 % yield. Changing from trifluoromethyl triethylsilane to the Ruppert-Prakash reagent ($TMSCF_3$) in the in situ synthesis of $CuCF_3$ resulted in a diminished formation of the by-product (9 %, entry 2). Reducing the number of $CuCF_3$ equivalents and temperature in order to further decrease the formation of **8aa** led to a lower yield of product **8a** (61 %, entry 3). Overall, the utilization $CuCF_3$ has two disadvantages: On one hand, the generation of the by-product **8aa** cannot be completely suppressed. On the other hand, the reagent must be prepared freshly before the transformation since it is not stable. We therefore turned to more stable Grushin type Cu^{III} trifluoromethyl complexes.[20]

Table 1: Optimization of the trifluoromethylation using L-tyrosine based VBX **5a**.



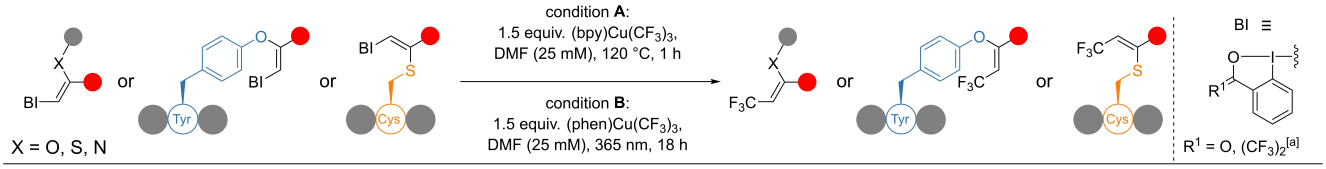
5a **8a** **8aa**

entry	Cu species	x	temp. or *hν*	time	yield[a] [%] **8a**	**8aa**
1	$CuCF_3$[b]	3.0	120 °C	1 h	51 ± 2	33 ± 6
2	$CuCF_3$[c]	3.0	120 °C	1 h	69 ± 5	9 ± 3
3	$CuCF_3$[c]	2.0	90 °C	3 h	61 ± 3	5 ± 2
4	(bpy)$Cu(CF_3)_3$	1.5	60 °C	1 h	1 ± 2	/
5	(bpy)$Cu(CF_3)_3$	1.5	90 °C	1 h	78 ± 3	/
6	(bpy)$Cu(CF_3)_3$	1.5	120 °C	1 h	84 ± 3	/
7	(phen)$Cu(CF_3)_3$	1.5	120 °C	1 h	82 ± 2	/
8	(bpy)$Cu(CF_3)_3$	1.5	365 nm	18 h	66 ± 4	/
9	(phen)$Cu(CF_3)_3$	1.5	365 nm	18 h	75 ± 2	/

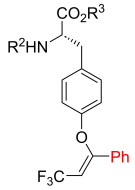
[a] NMR yield determined by addition of 1,3-dinitrobenzene (^1H) and trifluorotoluene (^{19}F) as internal standards after the reaction (mean value given out of three reactions). [b] Copper species synthesized starting from $TESCF_3$. [c] Copper species synthesized starting from $TMSCF_3$.

These $Cu(CF_3)_3$ complexes have been often activated for CF_3 transfer by thermal induction.[19] Accordingly, we screened for the optimal temperature to facilitate the activation of (bpy)$Cu(CF_3)_3$ (entries 4–6). A reaction temperature of 120 °C, together with 1.5 equiv. of copper species gave the best yield after 1 h (entry 6, 84 %). Nearly complete conversion was already observed at 90 °C (entry 5). Furthermore, the formation of the pentafluoroethylated by-product **8aa** could be fully prevented. The use of another complex bearing 1,10-phenanthroline as ligand did not provide higher yields (entry 7). The group of Cook recently described that (bpy)$Cu(CF_3)_3$ can also be activated with UV light (365 nm).[21] In fact, **8a** was obtained in 66–75 % yield when the reaction was performed in a UV reactor, with slight variations depending on the used ligand (bpy: 66 %, phen: 75 %, entries 8 and 9). Further screening (see Supporting Information, Table S1), including solvent, concentration, temperature, and reaction time, confirmed that the reaction conditions of entry 6 (thermal, condition **A**) and 9 (UV irradiation, condition **B**) gave the best yields. To our delight, the use of dimethyl acetamide, *N*-methyl-2-pyrrolidone, and acetonitrile as solvents was also tolerated under condition **A** with yields above 70 % (see Supporting Information).

With two sets of optimized conditions in hands, we studied the scope of different hetero-VBXs ranging from amino acid (**5a–m**) and peptide based ones (**5n–s**), over vinyl (thio) ethers (**6a–k**) and enamides (**6o–q**), to natural products (**7a–f**) and drugs (**7g–h**) (Scheme 2).[17,22] We first investigated L-tyrosine and L-cysteine based hetero-VBX reagents (Scheme 2a). On 80 µmol scale, using thermal conditions **A**, the different *N*-terminal protected (**8a**: Ac,



a) Scope of protected tyrosine and cysteine with different VBX side groups (scale: 80 µmol)

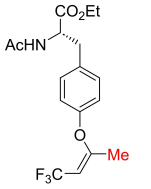


R^2 = Boc, R^3 = Me: **8b**
A: 64% (84%)
B: 80% (90%)

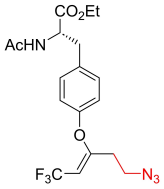
R^2 = Cbz, R^3 = Me: **8c**
A: 40% (46%)
B: 55% (58%)

R^2 = Ac, R^3 = Et: **8a**
A: 80% (86%)
B: 72% (83%)

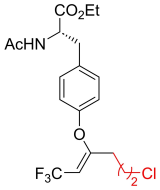
R^2 = Fmoc, R^3 = Me: **8d**
A: 57% (63%)
B: 71% (73%)



8e
A: 57% (62%), (42%)[a]
B: 36% (41%), (30%)[a]



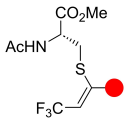
8f
A: 67% (70%)
B: 34% (44%)



8g
A: 65% (77%)
B: 69% (74%)

R = Ph: **8h**
A: 36% (47%)
B: 50% (58%)

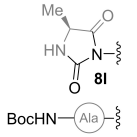
R = Me: **8i**
A: 46% (59%), (57%)[a]
B: 54% (60%), (45%)[a]



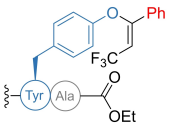
R = $(CH_2)_2N_3$: **8j**
A: 60% (63%)
B: 71% (73%)

R = $(CH_2)_3Cl$: **8k**
A: 43% (59%)
B: 56% (70%)

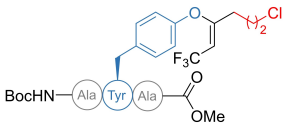
b) Scope of simple peptides with different degree of protection (scale: 80 µmol)



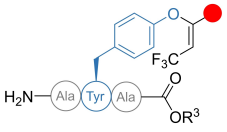
8l



8m
A: 44% (48%), **8l**
B: 63% (66%), **8m**

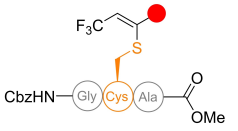


8n
A: 56% (63%)
B: 38% (53%)



R = Ph, R^3 = Et: **8o**
A: nd (20%)
B: nd (13%)

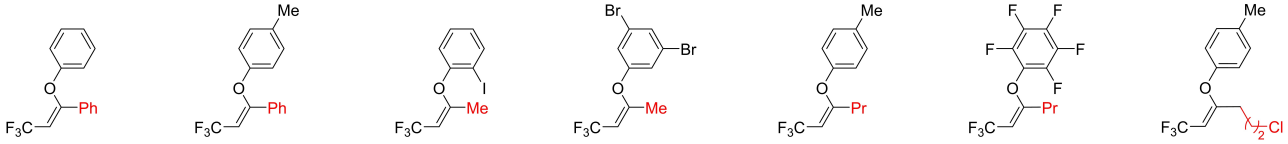
R = $(CH_2)_3Cl$, R^3 = Me: **8p**
A: nd (5%)
B: nd (2%)



R = Ph: **8q**
A: nd (22%)
B: 44% (54%)

R = $(CH_2)_3Cl$: **8r**
A: 62% (65%)
B: 40% (64%)

c) Scope of vinyl (thio) ethers, enamides and nonsubstituted VBX (scale: 100 µmol)



9a
A: 81%[b] (88%)[b]
B: 61% (75%)

9b
A: 68%[b] (75%)[b]
B: 63% (72%)

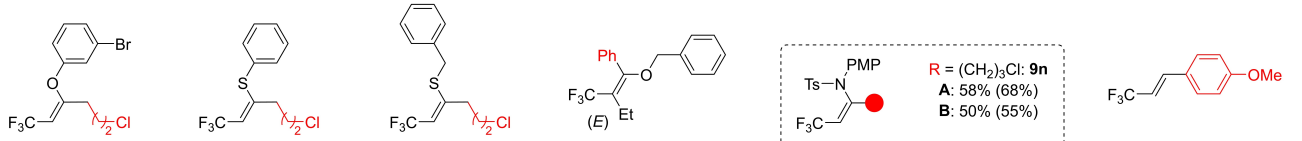
9c
A: 65%[b] (72%)[b]
B: 31% (37%)

9d
A: 73%[b] (74%)[b]
B: 35% (41%)

9e
A: 79%[b] (80%)[b]
B: 32% (38%)

9f
A: 69%[b] (79%)[b]
B: nd (22%)

9g
A: 79%[b] (85%)[b]
B: 37% (42%)



9h
A: 70%[b] (86%)[b]
B: 30% (35%)

9i
A: 74%[b] (81%)[b]
B: 40% (49%)

9j
A: 40%[b] (50%)[b]
B: 45% (61%)

9k
A: 82%[a,b] (92%)[a,b]

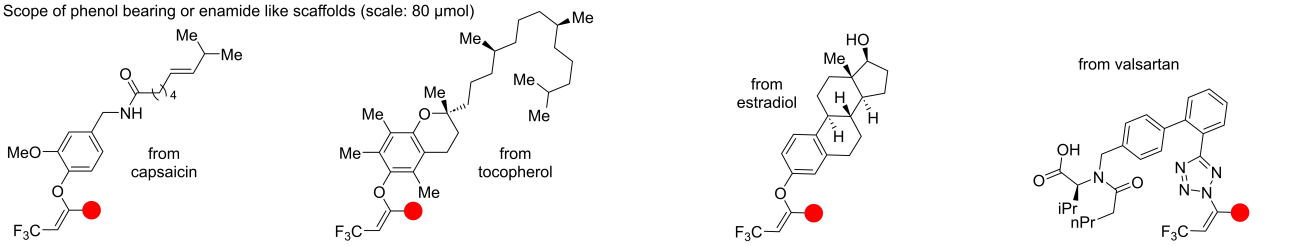
R = $(CH_2)_3Cl$: **9n**
A: 58% (68%)
B: 50% (55%)

R = Me: **9l**
A: 54% (63%)
B: 49% (57%)

R = $CH(CH_2)_2$: **9m**
A: 73% (84%)
B: 44% (54%)

9o
A: 55%[b] (66%)[b]
B: 50%[b] (58%)[b]

d) Scope of phenol bearing or enamide like scaffolds (scale: 80 µmol)



R = Ph, **10a**
A: 69%[b] (75%)[b]

R = $(CH_2)_3Cl$, **10b**
A: 67%[b] (70%)[b]

R = Ph, **10c**
A: 71%[b] (80%)[b]
B: 46% (51%)

R = $(CH_2)_3Cl$, **10d**
A: 83%[b] (91%)[b]
B: nd (6%)

R = Me, **10e**
A: 42%[b] (44%)[b]
B: nd (11%)

R = $(CH_2)_3Cl$, **10f**
A: 32%[b] (38%)[b]
B: 28% (39%)

R = Me, **10g**
A: nd (9%)[b]
B: 37% (47%)

R = $(CH_2)_3Cl$, **10h**
A: nd (7%)[b]
B: 45% (58%)

Scheme 2. Scope of the reaction under thermal (**A**) and UV conditions (**B**) (scale: 80–100 µmol). For **a**), **b**), **c**), **d**) Isolated yield is given first and NMR yield is given in parenthesis. NMR yield determined by the addition of trifluorotoluene (^{19}F) as internal standard after the reaction. [a] Bis(trifluoromethyl)vinyl-dihydrobenzoiodoxoles ($R^1 = (CF_3)_2$) were used instead of vinylbenziodoxolones ($R^1 = O$). [b] 1.5 equiv. of Hünig's base as reductant were added. PMP: *para*-methoxyphenyl, nd: not determined.

8b: Boc, **8c**, Cbz, **8d**: Fmoc) L-tyrosine derivatives **8a–d** with phenyl substitution were obtained in 40–80 % yield. Under UV conditions (**B**), the yields were slightly increased to 55–80 %. Based on the *N*-acetyl protected L-tyrosine,

methyl- (**5e**), azidoethyl- (**5f**), and chloropropyl-substituted (**5g**) VBX derivatives were also tolerated and the corresponding products **8e–g** were obtained in 57–67 % yield for conditions **A** and 34–69 % yield for conditions **B**. In the case of **8e**, the use of the bis(trifluoromethylated) VBX reagent **5f** led to decreased product formation (NMR yields—**A**: 42 %, **B**: 30 %) compared to VBX **5e** (NMR yields—**A**: 62 %, **B**: 41 %). Trifluoromethylation of L-cysteine based *S*-VBX derivatives (**5i–m**) gave access to the products **8h–k** in yields of 36–60 % (condition **A**). This time, the yields upon UV irradiation (condition **B**) were substantially higher (50–71 %). This observation could be rationalized by the fact that substituted cysteine derivatives are prone to elimination at high temperatures.[23]

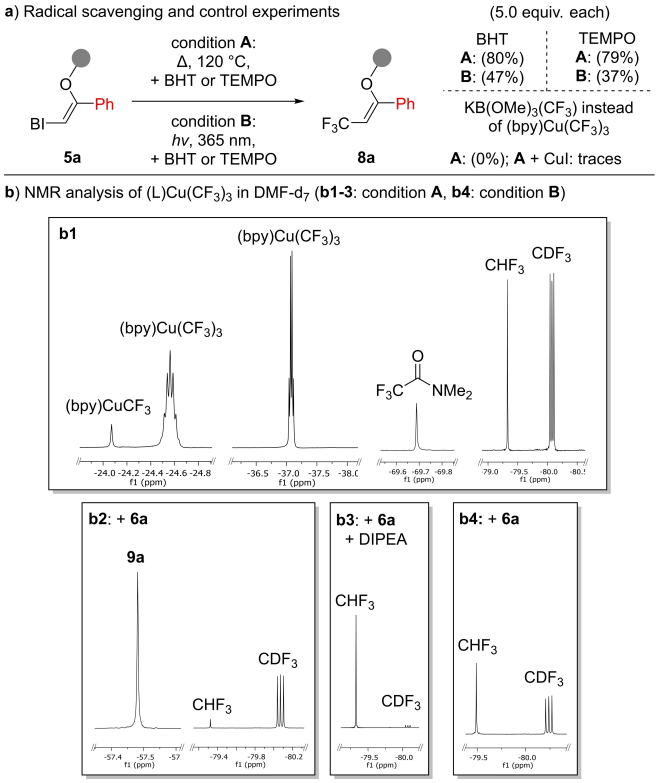
Next, simple tripeptides (**5n–s**) bearing a different degree of protection were examined (Scheme 2b). The phenyl-substituted Boc-Ala-Tyr-Ala-OEt VBX species (**5n**) was converted into the corresponding trifluoromethylated product **8m** (63 % yield) using protocol **B**. Under thermal conditions (**A**), partial reaction of the Boc protecting group to the give imidazolidinedione **8l** (44 % yield) was observed. Chloride-substituted compound **8n** could be synthesized under both conditions (**A**: 56 %, **B**: 38 %). A free N-terminus is not tolerated regardless of the side substitution (**8o**: R = Ph, **8p**: R = $(CH_2)_3Cl$) and thermal or light activation. Apart from tyrosine containing peptides, the synthesis of two cysteine containing, Cbz-protected trifluoromethylated peptides **8q** (R = Ph, **B**: 44 %) and **8r** (R = $(CH_2)_3Cl$, **A**: 62 %, **B**: 40 %) could be achieved. A free C-terminus prevented the formation of the VBX species in organic solvents.[24]

The methodology was further extended to small molecule VBXs (Scheme 2c), like arylic vinyl (thio) ethers (**6a–k**) and *para*-methoxyphenyl-substituted enamides (**6o–q**). The application of thermal conditions (**A**) led to lower yields compared to amino acid and peptide substrates (**9a**: 68 %, **9b**: 47 %), we therefore proceeded to a fast re-optimization (see Supporting Information, Table S2). Based on our speculative reaction mechanism (see below) we screened different reductants and found that the addition of 1.5 equiv. of Hünig's base (DIPEA) is increasing the yield (**9a**: 81 %, **9b**: 68 %). Under UV conditions (**B**) the most basic, phenyl-substituted products derived from phenol (**9a**) and *p*-cresol (**9b**) can be obtained in around 60 %. In this case, adding DIPEA was detrimental (**9b**: 43 %). Numerous other *O*-VBXs (**6c–h**) bearing different aromatic substitution patterns (*ortho*-iodo, *meta*-bromo, *para*-methyl, pentafluoro) and side substituents (alkyl, chloroalkyl) could be converted into the corresponding trifluoromethylated products **9c–h** in yields of 65–79 % for condition **A** (with DIPEA) and 30–40 % for condition **B**. Trifluoromethylated vinyl thioethers are also accessible, starting from the analogous *S*-VBX derivatives **6i–j**. The thiophenol and benzylthiol based products **9i** and **9j** can be obtained in 74 % and 40 % yield (**A**), respectively 40 % and 45 % yield (**B**). Since all tested substrates displayed perfect retention of the (*Z*)-configuration during the trifluoromethylation, we were curious to see if Yoshikai type (*E*)-VBX reagents[17] could be converted selectively to the *E* products. (*E*)-*O*-VBX **6k** could be indeed successfully transformed into the corresponding (*E*)-configured tetrasubstituted olefin **9k** (**A**: 82 %). In addition to vinyl (thio)ethers, trifluoromethylated PMP-substituted enamides (**9l–n**) with different side substitution (**9l**: methyl, **9m**: chloroalkyl, **9n**: cyclopropyl) could also be accessed in 54 %/73 %/58 % yield (**A**) and 49 %/44 %/50 % yield (**B**). Furthermore, non-heteroatom-substituted VBX **6r** could be converted into the corresponding trifluoromethylated species **9o** in 55 % (**A**) and 50 % yield (**B**).

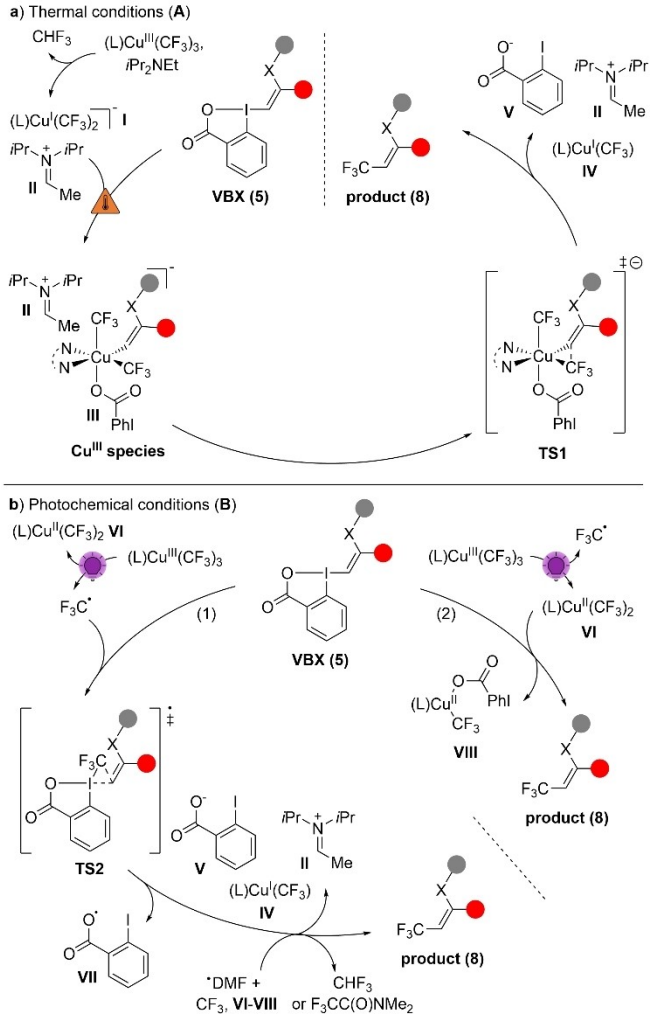
Since the introduction of CF_3 groups into bioactive natural products or pharmaceuticals can significantly improve their properties, we analyzed the trifluoromethylation of several natural products and drugs based VBX derivatives **7a–h**. The synthesis of the capsaicin (active component of pepper and neurotoxin) derived products **10a** (R = Ph) and **10b** (R = $(CH_2)_3Cl$) was possible in around 70 % yield (**A**). Two α-tocopherols (vitamin E) derivatives **10c** and **10d** were synthesized in 71 % and 83 % yield (**A** with DIPEA), respectively 46 % for **10c** and 6 % (NMR yield) for **10d** under condition **B**. Furthermore, the formation of estradiol derived methyl- and chloropropyl-substituted products **10e** and **10f** was achieved in yields around 40 %, except for **10e** under UV irradiation (**B**, 11 % NMR yield). Finally, the valsartan (angiotensin II receptor blocker) based *N*-VBXs **7g** (R = Me) and **7h** (R = $(CH_2)_3Cl$) were trifluoromethylated into the corresponding species **10g** and **10h** in an average yield of slightly over 40 % under UV irradiation (**B**). Following our high temperature protocol (**A**), only low NMR yields (< 10 %) could be observed, which could be attributed to a possible decarboxylation of the carboxylic acid. Overall, almost 40 VBX compounds with different backbones, heteroatom- and side-substitution could be converted into the corresponding trifluoromethylated alkenes.

Preliminary mechanistic studies (see Supporting Information, Chapter 3.4) were performed on the base of radical trapping, control and NMR experiments (Scheme 3). In presence of a radical inhibitor, TEMPO or butylated hydroxytoluene (BHT), the conversions of the thermal approach (**A**) were not affected at all, whereas the ones under UV irradiation (**B**) were reduced by half (Scheme 3a). These results indicated that radical intermediates may be involved under UV conditions (**B**). A control experiment with $KB(OMe)_3(CF_3)$ (Scheme 3a) as CF_3 source, rather than using (bpy)$Cu(CF_3)_3$, showed no product formation (**A**). Repeating the same experiment with additional copper-(I) iodide (1.5 equiv.) enabled the formation of the product in traces. Together with the fact that the transformation also works with $CuCF_3$ (Table 1, entries 1–3), the conclusion can be drawn that copper is essential for the success of the transformation.

When a solution of Grushin's reagent was heated in deuterated DMF-d_7 at 120 °C for 1 h, NMR analysis showed the formation of 2,2,2-trifluoro-*N*,*N*-dimethylacetamide, deuterated and normal fluoroform, as well as (bpy)$CuCF_3$[25] (Scheme 3b1). After addition of VBX **6a**, the ^{19}F NMR signal of product **9a** was observed, together with an increase of deuterated fluoroform compared to fluoroform (Scheme 3b2). This formation of CDF_3 is completely prevented by



Scheme 3. Radical trapping, control and NMR experiments.



Scheme 4. Proposed speculative mechanism.

the addition of Hünig's base. Instead, only the signal of non-deuterated fluoroform is visible, whereby the trifluoromethylated DMF is not obtained anymore (Scheme 3b3). These observations led to the conclusion that Hünig's base instead of DMF delivered a hydrogen (deuterium for DMF-d_7) and is thus oxidized. Furthermore, no CF_3 group is incorporated in the oxidized Hünig's base side product(s). Under UV conditions (**B**), the spectra are similar (Scheme 3b4).

Building on the insights above, we propose two different speculative mechanisms depending on reaction conditions (**A**, **B**) (Scheme 4). The thermal reaction (**A**) would be initiated by a redox process, in which the copper(III) species is reduced to copper(I) complex **I** and Hünig's base gets oxidized under release of a proton to give iminium **II** (Scheme 4a).[26] In absence of Hünig's base, DMF is oxidized leading to the formation of trifluoromethylated DMF. This proton is trapped by a CF_3^- group forming fluoroform. The so generated copper(I) species undergoes oxidative addition on the VBX reagent **5** to give a copper(III) species **III**. The CF_3^- group is then transferred via a reductive elimination step (**TS1**, inner sphere mechanism).[27,28] After reductive elimination, the trifluoromethylated alkene **8** is formed with copper(I) complex **IV** and 2-iodo benzoate (**V**) as by-products. During aqueous work-up, the iminium DIPEA benzoate is probably hydrolyzed into (di*iso*propyl)amine, acetaldehyde and 2-iodobenzoic acid. The obtained $Cu(CF_3)$ species **IV**[25] could in principle perform another trifluoromethylation of the VBX reagent following a similar mechanism, leading to the same product **8** (as supported by the significant amount of product observed when starting from a Cu^I complex, see Table 1, entries 1–3). It should be mentioned that the mechanism could also occur via an outer sphere transfer without a copper carbon bond formation.

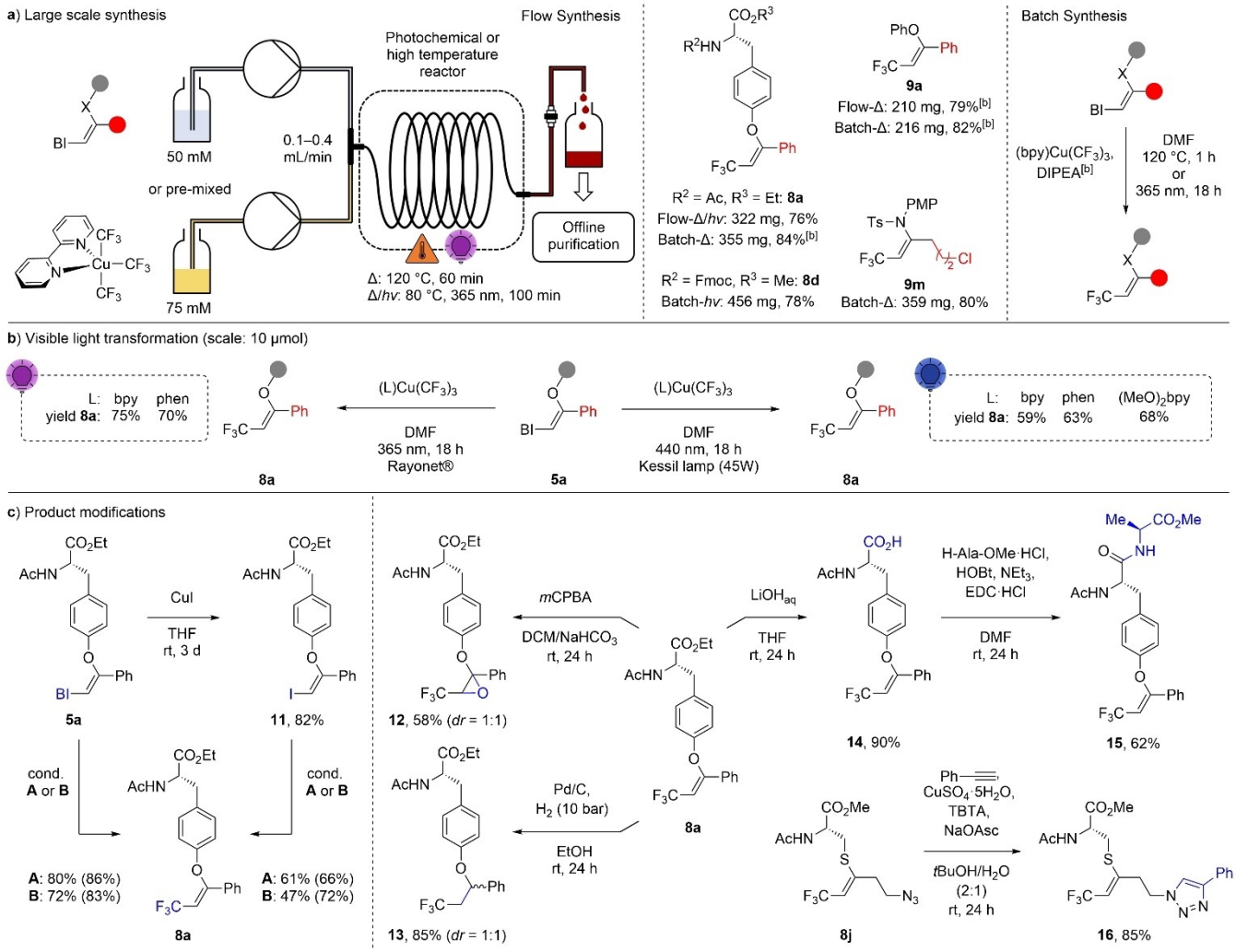
More alternatives are possible for the UV-mediated reaction (**B**) (Scheme 4b). Path (1) would be initiated by homolysis of the $Cu(CF_3)_3$ complex, generating a CF_3 radical and copper(II) complex **VI**.[20,29] The subsequent radical reaction (**TS2**) can be conducted analogously to the reported addition of other radicals to iodine(III) reagents, with generation of carboxy radical **VII**.[30] The high *E*/*Z* selectivity can be tentatively attributed to a concerted radical addition pathway (**TS2**), which has been also proposed for the photo-catalyzed C–C cross-coupling between 4-alkyl-dihydropyridines and VBX reagents.[31] Alternatively, as the polarity of the trifluoromethyl radical is not ideal to react with the electron-poor VBX reagent, complex **VI** could act as a trifluoromethylating reagent for VBX **5** (path (2)). The excess of trifluoromethyl radical and oxidizing intermediates **VI–VIII** could then be reduced by DMF to form the observed fluoroform and/or trifluoromethylated DMF. In addition, the resulting $Cu(CF_3)$ specie similar to **IV** could be used for another trifluoromethylation. With the data avail-

able, it is difficult to assess which of these multiple possible pathways contributes most to the trifluoromethylation reaction.

The trifluoromethylated alkenes synthesized by the present method serve as versatile starting materials for further modifications. To demonstrate the synthetic potential of our methodology, we carried out upscaling experiments (1.0 mmol scale) following the best reaction conditions from the scope (Scheme 5a). Our aim was to illustrate the feasibility of thermal and light activation under both batch and flow conditions, as well as the combination of both approaches using a flow photoreactor. Thus, the use of a combined thermal/UV approach (Δ/*hv*) in a photochemical flow reactor (80 °C, 365 nm) allowed the synthesis of the L-tyrosine derivative **8a** in 76 % yield at a reduced reaction temperature. The large-scale batch reaction with additional DIPEA (**A**) reached a nearly identical yield of 84 %. The Fmoc protected derivative **8d** could be synthesized in 78 % yield by using a pure UV-batch approach. For direct comparison, *O*-VBX **6a** was used as starting material in batch and flow under the same thermal conditions (**A**). This led to the formation of the trifluoromethylated product **9a** in 79 % (flow), or respectively 82 % yield (batch). The generation of the enamide **9m** was achieved in 80 % yield using a thermal batch approach without Hünig's base (**A**).

Due to the higher convenience of organic transformations carried out under irradiation with visible light, we investigated diverse $Cu(CF_3)_3$ complexes under irradiation with light of three different wavelengths (365 nm, 440 nm, 525 nm, Scheme 5b) (see Supporting Information, Chapter 3.6). The bipyridine and phenanthroline based complexes could also be used under visible light, but with a loss of 10–15 % in yield. The 4,4′-dimethoxy analogue of bipyridine displayed the highest product yield of 68 % under irradiation with blue light. Due to significantly higher purchase price of $(MeO)_2$bpy compared to unsubstituted 2,2′-bipyridines,[32] the scope of this work was performed with (phen)$Cu(CF_3)_3$ with UV light.

We then examined further modifications of the obtained trifluoromethylated alkenes (Scheme 5c). In addition to the



Scheme 5. Reaction and product modifications. Experimental details can be found in the Supporting Information. [b] Additional 1.5 equiv. of Hünig's base as reductant was added.

hypervalent iodine species **5a**, the trifluoromethylation can also be accomplished using reduced iodo alkene **11**. However, the yields are lower (**A**: 61 %, **B**: 47 %), and these kinds of derivatives are more difficult to synthesize. Indeed, the most convenient way to access **11** was by reduction of hypervalent iodine **5a**. Concerning product modification, L-tyrosine based product **8a** could be epoxidized to give **12** in 58 % yield. Palladium-catalyzed hydrogenation led to alkane **13** in 85 % yield. Furthermore, the trifluoromethylated building block **8a** can be incorporated into peptide synthesis via saponification to carboxylic acid **14** (90 %). The subsequent peptide coupling enabled the formation of dipeptide **15** in 62 % yield. In addition, 1,3-dipolar Huisgen cycloaddition using azide **8j** and phenylacetylene led to triazole **16** in 85 % yield.

Conclusion

In conclusion, we have developed a methodology to selectively synthesize trifluoromethylated, heteroatom-substituted alkenes starting from a broad range of different hetero- vinylbenziodoxol(on)es. The reaction takes place with perfect retention of the double bond configuration. The use of high valent trifluoromethylated copper complexes was successful under two types of initiation: thermal and UV light irradiation. We speculate that the reaction mechanism potentially involves an oxidative transfer via a Cu^{III} intermediate for the thermal conditions (**A**) or a radical pathway under irradiation (**B**). Our method could be scaled up to 1.0 mmol scale using batch and flow chemistry. The synthesized copper(III) complexes also permitted the use of visible light in our photochemical protocol. Multiple product modifications, such as reduction or epoxidation of the trifluoromethylated double bond and Huisgen cycloaddition of azide groups on the substituents, demonstrated the synthetic versatility of the synthesized compounds. Overall, this work gives a facilitated access to polysubstituted trifluoromethylated compounds and paves the way for the development of further copper-based VBX transformations.

Supporting Information

Experimental procedures, supplementary Figures, and NMR spectra of new compounds. The authors have cited additional references within the Supporting Information.[33–50] Raw data for NMR, IR and MS are freely available on the platform zenodo: https://doi.org/10.5281/zenodo.8021086.

Acknowledgements

This work is supported by the European Research Council (Consolidator Grant SeleCHEM 771170) and EPFL. We thank Dr. S. Nicolai (LCSO, EPFL) for proofreading the manuscript and the Supporting Information and Dr. X. Li (LCSO, EPFL) for providing the precursor for the (*E*)-VBX. We are grateful to M. Sc. A. Despois (LCSA, EPFL) for helping with the high-pressure hydrogenations. The authors are indebted to the team of the research support service of ISIC at EPFL, particularly to the NMR, and the High Resolution Mass Spectrometry Units. Open Access funding provided by École Polytechnique Fédérale de Lausanne.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Flow Chemistry · High-Valent Copper · Hypervalent Iodine Reagents · Trifluoromethylation · Vinylbenziodoxolones

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Manuscript received: May 2, 2023
Accepted manuscript online: June 13, 2023
Version of record online: July 10, 2023

Synthesis of Trifluoromethylated Alkenes: Hypervalent Iodine meets High-Valent Copper

Tobias M. Milzarek,[a] and Jerome Waser[a*]

[a] 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.

Supporting Information

Contents

1 General Methods

Reagents: Solvents for HPLC and MS analysis such as acetonitrile and methanol were purchased from Sigma Aldrich in a purity of over 99% (HPLC-grade). Water was purified and deionized using a Milli-Q® water treatment system. Dry solvents, such as acetonitrile, dichloromethane, diethyl ether, tetrahydrofuran, and toluene were obtained from a dry solvent system using activated alumina columns under nitrogen atmosphere. Commercial materials and other solvents were purchased at the highest commercial quality from the providers Acros Organics, Alfa Aesar, Apollo Scientific, Carl Roth, Fluorochem, Merck, Sigma Aldrich, VWR, TCI Chemicals and Thermo Fisher Scientific. Air- and moisture-sensitive reactions were performed under nitrogen atmosphere using a Schlenk line. Before application, the flasks were repeatedly evacuated (external heating) and refilled with nitrogen.

NMR: ^{1}H and ^{19}F Nuclear Magnetic Resonance Spectra (NMR) was recorded on a Bruker DPX-400 MHz spectrometer at 298 K. ^{13}C and two-dimensional (2D) NMR measurements were performed on a Bruker Ascend 400 spectrometer at the same temperature. The chemical shifts are given in δ-values (ppm) and are calibrated on the residual peak of the deuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; CD_2Cl_2: δ_H = 5.32 ppm, δ_C = 53.5 ppm; DMSO-d_6: δ_H = 2.49 ppm, δ_C = 39.7 ppm; CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32 ppm; MeOD-d_4: δ_H = 3.31 ppm, δ_C = 49.0 ppm). The coupling constants *J* are given in Hertz [Hz]. Following abbreviations were used for the allocation of signal multiplicities: bs – broad signal, s – singlet, d – doublet, dd – doublet of doublets, dt – doublet of triplets, t – triplet, td – triplet of doublets, tq – triplet of quartets, q – quartet, qd – quartet of doublets, qq – quartet of quartets, p – pentet, h – heptet, m – multiplet. Quantitative NMR (qNMR) was performed by addition of internal standards (1,3-dinitrobenzene: δ_H = 9.08 (s), 8.62 (m), 7.87 (m) ppm, trifluorotoluene: δ_F = -62.6 ppm).

MS: Mass spectra were recorded on a LTQ Orbitrap ELITE ETD (Thermo Fisher) equipped with different types of electrospray ionization (ESI, nanoESI, nanochip-ESI) combined with a nanoUPLC 3000 system, or a Xevo® G2-S QTOF system including multi-ionization ESI-APCI and APPI sources.

IR: Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad).

Chromatography: Thin-layer chromatography (TLC) was performed on precoated plates of silica gel F254 (Merck) with UV detection at 254 and 365 nm. Column chromatography was performed on silica gel SiliaFlash® P60 (40–63 µm, 230–400 mesh). For medium pressure liquid chromatography (MPLC) the BÜCHI Pure C-810 Flash system was used together with Reverleris® Reverse Phase (RP) C18 columns (Grace) using UV-detection at 220 nm, 254 nm, and 280 nm. The eluent system consisted of A = H_2O + 0.05% TFA, B = MeCN + 0.05% TFA. The purification method used the following elution gradient: 0–28 min 5% to 95% B, 28–30 min with a flow rate of 20 or 36 mL/min. Deviations from the gradient are shown in the corresponding procedures. Chiral HPLC was performed on an Agilent 1260 Infinity system including a HiP degasser, binary pump, ALS column oven, and 1290 MCT detector. A Daicel CHIRALPAK IB column was used with the following solvent mixture: *n*-hexane/*i*PrOH = 80:20 over 30 min.

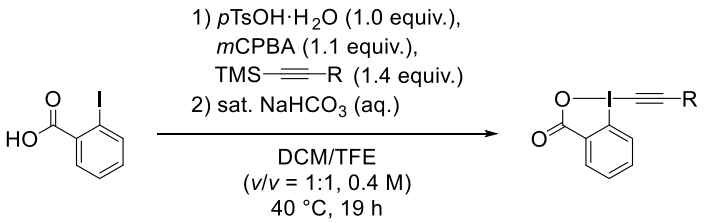
Melting point: Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected.

Optical rotation: The specific rotation was measured with a Jasco P-2000 polarimeter at 20 °C. The given specific rotation is the mean value from 10 measurements. The concentration for the specific rotation measurements is given in 10 mg/mL.

2 Formation of Starting Material

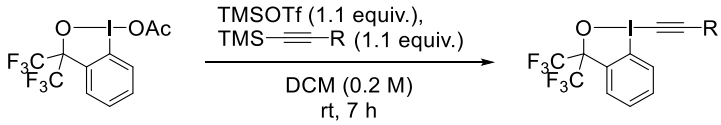
2.1 Synthesis of Ethynylbenziodoxolones (EBX)

General procedure for the synthesis of EBX reagents from TMS species (GP I)



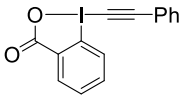
Following a reported procedure[1], 2-iodobenzoic acid (1.0 equiv.), *para*-toluene sulfonic acid monohydrate (1.0 equiv.) and *m*CPBA (77%, 1.1 equiv.) were dissolved in a mixture of dichloroethane and 2,2,2-trifluoroethanol (0.4 M, *v*/*v* = 1:1). After 1 hour stirring at 40 °C, the corresponding alkynyl trimethyl silane species (1.40 equiv.) was added in one portion. The reaction mixture was stirred for additional 18 hours at the same temperature, then the resulting suspension was filtered and the volatiles were removed under reduced pressure. The resultant residue was dissolved in dichloromethane and treated with a solution of saturated aqueous sodium bicarbonate. The mixture was vigorously stirred for 1 hour, before the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3x). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was performed by column chromatography, or recrystallization in MeCN.

General procedure for the synthesis of bis(CF_3)-EBX reagents from TMS species (GP II)



The formation of the bis(CF_3)-EBX reagents was based on 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate as starting material, which was synthesized as described previously.[2,3] To a solution of 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (1.0 equiv.) in dry DCM (0.2 M) was added trimethylsilyl trifluoromethane-sulfonate (1.1 equiv.) dropwise at room temperature, and the reaction mixture was stirred for 1 h. After this time, the alkynyl trimethyl silane species (1.1 equiv.) was added, and the mixture was stirred for 6 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3x). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by column chromatography.

1-[Phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (17a)



Following **GP I** on 20.1 mmol scale and using trimethyl(2-phenyl-ethynyl)silane (5.55 mL, 4.92 g, 28.2 mmol), the EBX compound (**17a**, 3.91 g, 11.2 mmol, 56%) was obtained as a white solid. Purification via recrystallization in acetonitrile (80 mL).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.46–8.38 (m, 1 H, Ar*H*), 8.29–8.22 (m, 1 H, Ar*H*), 7.81–7.72 (m, 2 H, Ar*H*), 7.64–7.56 (m, 2 H, Ar*H*), 7.51–7.40 (m, 3 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 166.7, 135.0, 133.0, 132.6, 131.8, 131.5, 130.9, 128.9, 126.4, 120.7, 116.3, 106.7, 50.4. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{10}IO_2^+$ 348.9720, found 348.9729. Analytical data were in agreement with the literature.[4]

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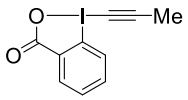
[1] D. P. Hari, P. Caramenti, L. Schouwey, M. Chang, S. Nicolai, D. Bachert, T. Wright, C. Orella, J. Waser, *Org. Process Res. Dev.* **2020**, *24*, 106.
[2] J. Cvengroš, D. Stolz, A. Togni, *Synthesis* **2009**, *16*, 2818.
[3] A. Maity, S.-M. Hyun, D. C. Powers, *Nat. Chem.* **2018**, *10*, 200.
[4] J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655.

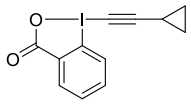
Propynyl-1,2-benziodoxol-3(1*H*)-one (17b)



Following **GP I** on 4.30 mmol scale and using trimethyl(prop-1-ynyl)silane (890 µL, 676 mg, 6.02 mmol), the EBX compound (**17b**, 354 mg, 1.24 mmol, 29%) was obtained as a white solid. Purification via column chromatography (1–5% MeOH in DCM) or MPLC (t_R = 6.0–10.8 min, gradient: 5–50% MeCN in 14 min).

TLC: R_f (DCM/MeOH = 20:1) = 0.75, R_f (DCM/MeOH = 100:1) = 0.14. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.42–8.39 (m, 1 H, Ar*H*), 8.20–8.17 (m, 1 H, Ar*H*), 7.79–7.72 (m, 2 H, Ar*H*), 2.27 (s, 3 H, CCC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 166.6, 134.8, 132.6, 131.7, 131.6, 126.3, 115.6, 105.1, 39.1, 5.7. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_8IO_2^+$ 286.9564; found 286.9577. Analytical data were in agreement with the literature.[5]

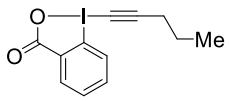
1-(Cyclopropylethynyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (17c)



1-Hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (1.50 g, 5.68 mmol, 1.0 equiv.) was dissolved in dry DCM (0.4 M, 14 mL) and the mixture was cooled down to 0 °C. Trimethylsilyl trifluoromethanesulfonate (1.13 mL, 1.39 g, 6.25 mmol, 1.1 equiv.) was added dropwise and the reaction solution was stirred for 1 h at 0 °C before being treated with 2-cyclopropylethynyl(trimethyl)silane (1.02 mL, 864 mg, 6.25 mmol, 1.1 equiv.). The reaction was allowed to warm up to room temperature and stirred for further 8 h. Saturated sodium bicarbonate (14 mL) was added and the reaction mixture was stirred vigorously over night. The two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3x20 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Final purification was performed by MPLC (t_R = 20.7–23.8 min, gradient: 5–95% MeCN in 28 min) to give EBX **17c** (320 mg, 920 µmol, 16%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42–8.36 (m, 1 H, Ar*H*), 8.16 (dd, *J* = 7.9, 1.3 Hz, 1 H, Ar*H*), 7.80–7.71 (m, 2 H, Ar*H*), 1.62 (tt, *J* = 8.3, 5.0 Hz, 1 H, C*H*), 1.06–0.99 (m, 2 H, CH_2), 0.98–0.92 (m, 2 H, CH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.7, 134.8, 132.5, 131.6, 131.6, 126.2, 115.9, 113.4, 35.2, 9.9, 1.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}IO_2^+$ 312.9720, found 312.9724. Analytical data were in agreement with the literature.[6]

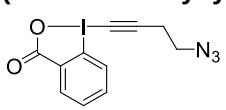
1-(Pent-1-yn-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (17d)



Following **GP I** on 40.3 mmol scale and using trimethyl(pent-1-ynyl) silane (9.61 mL, 7.35 g, 52.2 mmol), the EBX compound (**17d**, 4.94 g, 15.7 mmol, 39%) was obtained as a white solid. Purification via MPLC (t_R = 10.8–13.7 min, gradient: 5–60% MeCN in 17 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42–8.37 (m, 1 H, Ar*H*), 8.21–8.15 (m, 1 H, Ar*H*), 7.79–7.71 (m, 2 H, Ar*H*), 2.58 (t, *J* = 7.0 Hz, 2 H, CCH_2), 1.69 (h, *J* = 7.3 Hz, 2 H, CH_2CH$_3$), 1.08 (t, *J* = 7.4 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.6, 134.8, 132.5, 131.6, 131.6, 126.2, 115.7, 109.7, 39.6, 22.5, 21.9, 13.7. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}IO_2^+$ 314.9877, found 314.9883. Analytical data were in agreement with the literature.[6]

(4-Azidobut-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (17e)



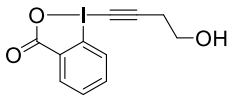
Following **GP I** on 12.9 mmol scale and using 4-azidobut-1-ynyl(trimethyl)silane (3.02 g, 18.1 mmol), the EBX compound (**17e**, 859 mg, 2.52 mmol, 20%) was obtained as a white solid. Purification via column chromatography (EtOAc/MeOH = 8:1) or MPLC (t_R = 10.3–14.8 min, gradient: 5–95% MeCN in 28 min).

TLC: R_f (EtOAc/MeOH = 9:1) = 0.41. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.41–8.38 (m, 1 H, Ar*H*), 8.22 (dd, *J* = 7.8, 1.4 Hz, 1 H, Ar*H*), 7.81–7.72 (m, 2 H, Ar*H*), 3.57 (t, *J* = 6.5 Hz, 2 H, CH$_2$CH_2N$_3$), 2.87 (t, *J* = 6.5

[5] R. Frei, M. D. Wodrich, D. P. Hari, P.-A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563.
[6] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190.

Hz, 2 H, CH_2CH$_2$N$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.6, 135.0, 132.6, 131.7, 131.5, 126.4, 115.7, 104.6, 49.5, 43.3, 21.6. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_9IN_3O_2^+$ 341.9734, found 341.9729. Analytical data were in agreement with the literature.[7]

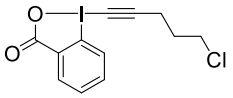
(4-Hydroxybut-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (17f)



Following **GP I** on 16.1 mmol scale and using 4-hydroxybut-1-ynyl(trimethyl)silane (3.75 mL, 3.21 g, 22.6 mmol), the EBX compound (**17f**, 275 mg, 870 µmol, 5%) was obtained as white solid. Purification via MPLC (t_R = 5.9–8.8 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.37–8.30 (m, 1 H, Ar*H*), 8.11 (dd, *J* = 7.3, 1.8 Hz, 1 H, Ar*H*), 7.88–7.81 (m, 1 H, Ar*H*), 7.81–7.73 (m, 1 H, Ar*H*), 4.99 (bs, 1 H, O*H*), 3.65 (t, *J* = 6.4 Hz, 2 H, CH$_2$CH_2OH), 2.80 (t, *J* = 6.4 Hz, 2 H, CH_2CH$_2$OH). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 166.1, 134.8, 132.3, 131.2, 131.2, 127.5, 115.7, 106.3, 59.3, 40.7, 24.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}IO_3^+$ 316.9669, found 316.9676. Analytical data were in agreement with the literature.[5]

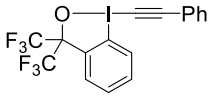
(5-Chloropent-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (17g)



Following **GP I** on 16.1 mmol scale and using 5-chloropent-1-ynyl(trimethyl)silane (4.04 mL, 3.95 g, 22.6 mmol), the EBX compound (**17g**, 2.19 g, 6.28 mmol, 39%) was obtained as a white solid. Purification via column chromatography (3% MeOH in DCM) or MPLC (t_R = 12.1–15.3 min, gradient: 5–60% MeCN in 17 min).

TLC: R_f (DCM/MeOH = 50:1) = 0.28. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.39–8.35 (m, 1 H, Ar*H*), 8.17 (dd, *J* = 7.8, 1.4 Hz, 1 H, Ar*H*), 7.79–7.70 (m, 2 H, Ar*H*), 3.70 (t, *J* = 6.2 Hz, 2 H, CH$_2$CH_2Cl), 2.81 (t, *J* = 6.9 Hz, 2 H, C≡CCH_2), 2.10 (p, *J* = 6.6 Hz, 2 H, CH_2CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 166.9, 134.9, 132.4, 131.61, 131.57, 126.4, 115.8, 107.0, 43.4, 41.2, 30.7, 18.0. **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{10}ClINaO_2^+$ 370.9306, found 370.9310. Analytical data were in agreement with the literature.[5]

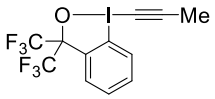
1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-3(1*H*)-1,2-benziodoxole (17h)



Following **GP II** on 11.7 mmol scale and using trimethyl(2-phenylethynyl)silane (1.65 mL, 2.02 g, 9.10 mmol), the EBX compound (**17h**, 1.65 g, 3.51 mmol, 42%) was obtained as white solid. Purification via recrystallization in acetonitrile.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32–8.25 (m, 1 H, Ar*H*), 7.88–7.82 (m, 1 H, Ar*H*), 7.74–7.66 (m, 2 H, Ar*H*), 7.56 (dd, *J* = 8.1, 1.7 Hz, 2 H, Ar*H*), 7.48–7.37 (m, 3 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 133.1, 132.8, 131.4, 130.3, 130.1, 130.0 128.8, 128.5, 123.7 (q, *J* = 290.3 Hz), 121.4, 111.6, 105.4, 82.3–81.2 (m), 54.5. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -76.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{10}F_6IO^+$ 470.9675, found 470.9683. Analytical data were in agreement with the literature.[8]

1-(Prop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-3(1*H*)-1,2-benziodoxole (17i)



Following **GP II** on 11.7 mmol scale and using trimethyl(prop-1-ynyl)silane (1.84 g, 16.4 mmol), the EBX compound (**17i**, 2.17 g, 5.32 mmol, 46%) was obtained as a yellow solid. Purification via column chromatography (*n*-pentane).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24–8.19 (m, 1 H, Ar*H*), 7.80–7.79 (m, 1 H, Ar*H*), 7.71–7.65 (m, 2 H, Ar*H*), 2.19 (s, 3 H, C≡CCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 132.9, 131.2, 130.2, 129.9 (m), 128.4, 123.8 (q, *J* = 290.5 Hz), 110.9, 103.3, 81.6 (p, *J* = 29.5 Hz), 43.0, 5.5. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -76.2. **HRMS** (nanochip-ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{12}H_8F_6IO^+$ 408.9519, found 408.9532. Analytical data were in agreement with the literature.[8]

[7] D. Abegg, R. Frei, L. Cerato, D. P. Hari, C. Wang, J. Waser, A. Adibekian, *Angew. Chem. Int. Ed.* **2015**, *54*, 10852.
[8] X. Wu, S. Shirakawa, K. Maruoka, *Org. Biomol. Chem.* **2014**, *12*, 5388.

2.2 Preparation of Peptides

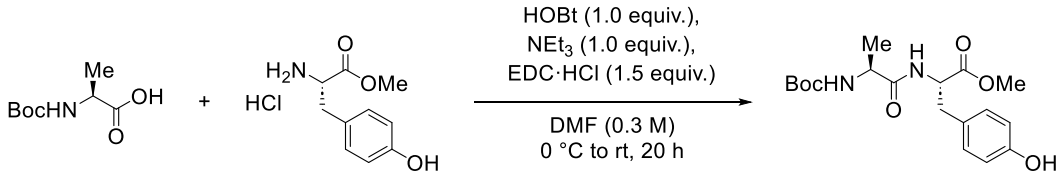
General procedure for the *N*-Boc deprotection - LPPS (GP III)

The *N*-Boc protected amino acid or peptide (1.0 equiv.) was cooled down to 0 °C and a HCl solution 4 M in dioxane (10 equiv.) was added dropwise. The mixture was stirred at 0 °C for 2 h before being concentrated in vacuo. The obtained residue was washed with MeOH (2x) and *n*-pentane (2x) to give the desired unprotected species.

General procedure for methyl ester saponification - LPPS (GP IV)

The methyl ester (1.0 equiv.) was dissolved in THF (0.5 M) and cooled down to 0 °C. A 0.1 M aqueous LiOH solution (3.0 equiv.) was added dropwise over 1 h and the reaction mixture was stirred at room temperature for 20 h. The organic solvent was removed in vacuo, the aqueous layer was extracted with diethyl ether (2x), acidified with 10% $KHSO_4$ solution and extracted again with diethyl ether (3x). The combined organic layers from the last extraction were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed to give the free carboxylic acid.

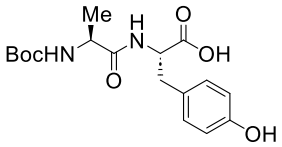
***N*-Boc-L-Ala-L-Tyr-OMe (S1)**



Following a reported procedure[9], *N*-Boc-L-Ala-OH (2.91 g, 15.4 mmol, 1.0 equiv.) and L-Tyr-OMe·HCl (3.00 g, 15.4 mmol, 1.0 equiv.) were dissolved in DMF (0.3 M, 51 mL). HOBt (2.35 g, 15.4 mmol, 1.0 equiv.) and triethylamine (2.14 mL, 1.56 g, 15.4 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 5 min at room temperature before being cooled down to 0 °C. EDC·HCl (4.42 g, 23.1 mmol, 1.5 equiv.) was added in one portion and the reaction was allowed to warm up to room temperature. After 20 h of stirring EtOAc and water were added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution, sat. NH_4Cl solution, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (EtOAc/*n*-pentane = 3:1) to give the desired dipeptide **S1** (5.25 g, 14.3 mmol, 93%) as white foam.

TLC: R_f (EtOAc/*n*-pentane = 1:1) = 0.14, R_f (EtOAc/*n*-pentane = 4:1) = 0.56. **ORD**: $[\alpha]_D^{20}$ = -11.6 (c = 0.47, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.77 (d, *J* = 7.9 Hz, 1 H, N*H*), 6.69 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.16 (d, *J* = 7.7 Hz, 1 H, N*H*), 4.81 (dt, *J* = 8.1, 5.7 Hz, 1 H, NHC*H*CH_3), 4.16 (t, *J* = 7.8 Hz, 1 H, NHC*H*CH_2), 3.71 (s, 3 H, CO_2C*H*$_3$), 3.06 (dd, *J* = 14.0, 5.5 Hz, 1 H, NHCHC*H*$_2$), 2.98 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHCHC*H*$_2$), 1.44 (s, 9 H, C(C*H*$_3$)$_3$), 1.29 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$).**^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.7, 172.0, 155.7, 155.6, 130.4, 126.9, 115.7, 80.6, 53.5, 52.5, 50.2, 37.2, 28.4, 18.4. **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{26}N_2NaO_6^+$ 389.1683, found 389.1686. Analytical data were in agreement with the literature.[9]

***N*-Boc-L-Ala-L-Tyr-OH (S2)**



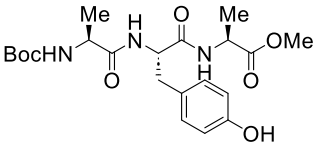
Following **GP IV** on 6.28 mmol scale and using *N*-Boc-L-Ala-L-Tyr-OMe (**S1**, 2.30 g, 6.28 mmol), *N*-Boc-L-Ala-L-Tyr-OH (**S2**, 1.95 g, 5.52 mmol, 88%) was obtained as a white foam.

ORD: $[\alpha]_D^{20}$ = +4.2 (c = 0.58, MeOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 9.21 (s, 1 H, COO*H*), 7.78 (d, *J* = 7.8 Hz, 1 H, N*H*), 6.98 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 7.8 Hz, 1 H, N*H*), 6.64 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 4.34 (td, *J* = 7.8, 5.2 Hz, 1 H, NHC*H*CH_3), 3.96 (t, *J* = 7.4 Hz, 1 H, NHC*H*CH_2), 2.91 (dd, *J* = 13.9, 5.3 Hz, 1 H, NHCHC*H*$_2$), 2.79 (dd, *J* = 13.9, 8.0 Hz, 1 H, NHCHC*H*$_2$),

[9] M. Falkenstein, D. Reiner-Link, A. Zivkovic, I. Gering, D. Willbold, H. Stark, *Bioorg. Med. Chem.* **2021**, *50*, 116462.

1.36 (s, 9 H, C(C*H*$_3$)$_3$), 1.13 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d$_6$) δ 172.9, 172.6, 156.0, 155.0, 130.2, 127.3, 115.0, 78.2, 65.0, 53.6, 36.0, 28.2, 18.2. **HRMS** (ESI/QTOF) *m/z*: [M–H]$^-$ calcd for $C_{17}H_{23}N_2O_6^-$ 351.1562, found 351.1563. Analytical data were in agreement with the literature.[9]

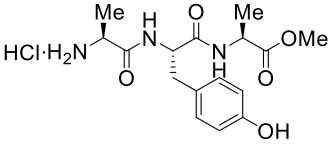
_N_-Boc-L-Ala-L-Tyr- L-Ala-OMe (S3)



Synthesized similiar to *N*-Boc-L-Ala-L-Tyr-OMe (**S1**) on 12.7 mmol scale using *N*-Boc-L-Ala-L-Tyr-OH (4.46 g, 12.7 mmol, 1.0 equiv.) and L-Ala-OMe·HCl (2.12 g, 15.2 mmol, 1.2 equiv.). Purification by column chromatography (EtOAc/*n*-pentane = 3:1) gave the protected tripeptide **S3** (4.38 g, 10.1 mmol, 79%) as a white foam.

TLC: R$_f$ (EtOAc/*n*-pentane = 3:1) = 0.49. **Mp**: 80–86 °C. **ORD**: [α]$_D^{20}$ = -41.4 (c = 0.77, MeOH). **^{1}H-NMR** (400 MHz, CDCl$_3$) δ 7.09 (d, *J* = 7.3 Hz, 1 H, N*H*), 7.02 (d, *J* = 8.0 Hz, 1 H, N*H*), 6.96 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.70 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.40 (d, *J* = 6.6 Hz, 1 H, N*H*), 4.73–4.63 (m, 1 H, NHC*H*CH$_2$), 4.47 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH$_3$), 4.20–4.08 (m, 1H, NHC*H*CH$_3$), 3.67 (s, 3 H, CO$_2$C*H*$_3$), 3.01–2.92 (m, 2 H, NHCHC*H*$_2$), 1.38 (s, 9 H, C(C*H*$_3$)$_3$), 1.31 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.26 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, CDCl$_3$) δ 173.1, 172.9, 170.9, 155.8, 155.7, 130.5, 127.2, 115.7, 80.5, 54.2, 52.6, 50.7, 48.4, 37.3, 28.3, 18.4, 17.9. **IR**: *v* 1642 (s), 1523 (w), 1455 (w), 1364 (w), 1244 (w), 1227 (w), 1162 (w), 1018 (w), 791 (w), 766 (w). **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{21}H_{31}N_3NaO_7^+$ 460.2054, found 460.2059.

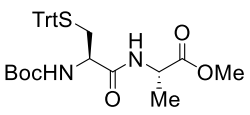
NH$_2$-L-Ala-L-Tyr- L-Ala-OMe·HCl (S4)



Following **GP III** on 2.29 mmol scale and using *N*-Boc-L-Ala-L-Tyr- L-Ala-OMe (**S3**, 1.00 g, 2.29 mmol), NH$_2$-L-Ala-L-Tyr-L-Ala-OMe·HCl (**S4**, 851 mg, 2.28 mmol, 99%) was obtained as a white solid.

Mp: 87–91 °C. **ORD**: [α]$_D^{20}$ = +68.8 (c = 0.27, MeOH). **^{1}H-NMR** (400 MHz, DMSO-d$_6$) δ 9.25 (s, 1 H, O*H*), 8.59 (d, *J* = 5.5 Hz, 1 H, N*H*), 8.57 (d, *J* = 5.1 Hz, 1 H, N*H*), 8.13 (d, *J* = 5.5 Hz, 3 H, N*H*$_3^+$), 7.09 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.67 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 4.46 (ddd, *J* = 9.8, 8.2, 4.3 Hz, 1 H, NHC*H*CH$_2$), 4.27 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH$_3$), 3.76 (p, *J* = 6.3 Hz, 1 H, NHC*H*CH$_3$), 3.61 (s, 3 H, CO$_2$C*H*$_3$), 2.93 (dd, *J* = 14.1, 4.3 Hz, 1 H, NHCHC*H*$_2$), 2.69 (dd, *J* = 14.1, 9.9 Hz, 1 H, NHCHC*H*$_2$), 1.34 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.29 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d$_6$) δ 172.9, 170.9, 169.4, 155.9, 130.1, 127.6, 115.0, 54.5, 51.9, 48.0, 47.6, 36.5, 17.3, 16.9. **IR**: *v* 2359 (m), 2294 (m), 2251 (s), 1634 (m), 1444 (m), 1376 (m), 1037 (m), 914 (w). **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{24}N_3O_5^+$ 338.1710, found 338.1704.

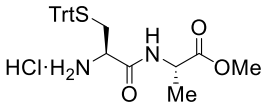
_N_-Boc-L-Cys(_S_-Trt)-L-Ala-OMe (S5)



Synthesized similiar to peptide **S1** on 15.1 mmol scale using *N*-Boc-L-Cys(*S*-Trt)-OH (7.00 g, 15.1 mmol, 1.0 equiv.) and L-Ala-OMe·HCl (2.53 g, 18.1 mmol, 1.2 equiv.). Purification by column chromatography (EtOAc/*n*-pentane = 1:1) gave the protected dipeptide **S5** (7.42 g, 13.6 mmol, 90%) as a white solid.

Mp: 202 °C. **ORD**: [α]$_D^{20}$ = -87.7 (c = 0.39, MeOH). **^{1}H-NMR** (400 MHz, DMSO-d$_6$) δ 8.12 (d, *J* = 7.2 Hz, 1 H, N*H*), 7.39–7.18 (m, 15 H, Ar*H*), 6.92 (d, *J* = 8.7 Hz, 1 H, N*H*), 4.22 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH$_2$), 4.00 (q, *J* = 7.6 Hz, 1 H, NHC*H*CH$_3$), 3.53 (s, 3 H, CO$_2$C*H*$_3$), 2.39–2.24 (m, 2 H, NHCHC*H*$_2$), 1.38 (s, 9 H, C(C*H*$_3$)$_3$), 1.24 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d$_6$) δ 172.5, 170.0, 154.9, 144.3, 129.1, 128.0, 126.7, 78.4, 65.8, 53.1, 51.8, 47.6, 34.0, 28.1, 16.9. **IR**: *v* 1655 (m), 1489 (w), 1444 (w), 1381 (w), 1366 (w), 1278 (w), 1164 (w), 1019 (m). **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{31}H_{36}N_2NaO_5S^+$ 571.2237, found 571.2250.

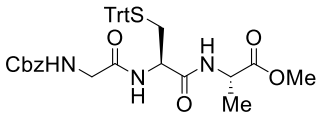
NH_2-L-Cys(*S*-Trt)-L-Ala-OMe·HCl (S6)



Following **GP III** on 11.2 mmol scale and using *N*-Boc-L-Cys(*S*-Trt)-L-Ala-OMe (**S5**, 6.15 g, 11.2 mmol), NH_2-L-Cys(*S*-Trt)-L-Ala-OMe·HCl (**S6**, 5.36 g, 11.1 mmol, 99%) was obtained as a white solid.

Mp: 84–89 °C. **ORD**: $[\alpha]_D^{20}$ = -74.2 (c = 0.38, MeOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 9.08 (d, *J* = 7.1 Hz, 1 H, N*H*), 8.51 (s, 3 H, NH_2·*H*Cl), 7.42–7.13 (m, 15 H, Ar*H*), 4.44–4.28 (m, 1 H, NHC*H*CH_2), 3.85 (bs, 1 H, NHC*H*CH_3), 3.56 (s, 3 H, CO_2CH_3), 2.48–2.43 (m, 2 H, NHCHCH_2), 1.32 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 172.1, 166.6, 143.8, 129.0, 128.2, 127.0, 66.4, 52.0, 50.6, 47.8, 32.2, 17.0. **IR**: *v* 1733 (m), 1671 (m), 1559 (m), 1544 (m), 1489 (m), 1444 (m), 1294 (w), 1221 (w), 1157 (w), 1070 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{28}N_2NaO_3S^+$ 471.1713, found 471.1712.

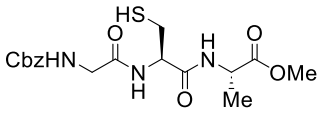
***N*-Cbz-Gly-L-Cys(*S*-Trt)-L-Ala-OMe (S7)**



Synthesized similiar to peptide **S1** on 13.4 mmol scale using NH_2-L-Cys(*S*-Trt)-L-Ala-OMe·HCl (6.50 g, 13.5 mmol, 1.0 equiv.) and *N*-CBz-Gly-OH (3.36 g, 16.1 mmol, 1.2 equiv.). Purification by column chromatography (EtOAc/*n*-pentane = 1:1) gave the protected tripeptide **S7** (6.31 g, 9.67 mmol, 72%) as white solid.

TLC: R_f (EtOAc/*n*-pentane = 1:1) = 0.35. **Mp**: 132–140 °C. **ORD**: $[\alpha]_D^{20}$ = -6.1 (c = 0.81, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.53–7.45 (m, 6 H, Ar*H*), 7.40–7.27 (m, 14 H, Ar*H*), 6.62 (d, *J* = 7.4 Hz, 1 H, N*H*), 6.44 (d, *J* = 7.9 Hz, 1 H, N*H*), 5.51 (d, *J* = 5.7 Hz, 1 H, N*H*), 5.14 (s, 2 H, CO_2CH_2Ph), 4.50 (p, *J* = 7.3 Hz, 1 H, NHC*H*CH_3), 4.16–4.10 (m, 1 H, NHC*H*CH_2), 3.84–3.80 (m, 2 H, NHCH_2), 3.74 (s, 3 H, CO_2CH_3), 2.85 (dd, *J* = 13.4, 7.3 Hz, 1 H, NHCHCH_2), 2.62 (dd, *J* = 13.3, 5.5 Hz, 1 H, NHCHCH_2), 1.39 (d, *J* = 7.2 Hz, 3 H, CH_3). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.33 (d, *J* = 7.0 Hz, 1 H, N*H*), 8.14 (d, *J* = 8.4 Hz, 1 H, N*H*), 7.47 (t, *J* = 6.2 Hz, 1 H, N*H*), 7.36–7.23 (m, 20 H, Ar*H*), 5.02 (s, 2 H, CO_2CH_2Ph), 4.42 (dd, *J* = 8.0, 7.4 Hz, 1 H, NHC*H*CH_2), 4.22 (p, *J* = 7.0 Hz, 1 H, NHC*H*CH_3), 3.69–3.60 (m, 2 H, NHCH_2), 3.52 (s, 3 H, CO_2CH_3), 2.39–2.27 (m, 2 H, NHCHCH_2), 1.24 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.8, 169.3, 168.9, 156.6, 144.5, 136.2, 129.7, 128.7, 128.3, 128.2, 128.0, 127.0, 67.4, 52.5, 52.2, 48.4, 44.5, 33.6, 18.1. **IR**: *v* 2989 (s), 2973 (s), 2899 (s), 1654 (m), 1533 (m), 1516 (m), 1411 (m), 1406 (m), 1393 (m), 1253 (m), 1249 (m), 1235 (m), 1065 (s), 1048 (s), 889 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{37}H_{40}N_3NaO_6S^+$ 662.2295, found: 662.2306.

***N*-Cbz-Gly-L-Cys-L-Ala-OMe (S8)**



Following a reported procedure[10], *N*-Cbz-Gly-L-Cys(*S*-Trt)-L-Ala-OMe (**S7**, 2.00 g, 3.13 mmol, 1.0 equiv.) was dissolved in dry DCM (0.3 M, 10 mL). Triethylsilane (599 µL, 436 mg, 3.75 mmol, 1.2 equiv.) was added, followed by the dropwise addition of trifluoroacetic acid (3.00 mL, 4.47 g, 39.2 mmol, 12.5 equiv.). The reaction was stirred 30 min at room temperature before being concentrated in vacuo. The obtained residue was purified by MPLC (t_R = 8.3–15.8 min, gradient: 5–95% MeCN in 28 min) to give the trityl deprotected tripeptide (**S8**, 855 mg, 2.15 mmol) in 69% yield.

Mp: 129–131 °C. **ORD**: $[\alpha]_D^{20}$ = +34.0 (c = 0.26, MeOH).**^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 6.9 Hz, 1 H, N*H*), 8.06 (d, *J* = 8.2 Hz, 1 H, N*H*), 7.49 (t, *J* = 6.1 Hz, 1 H, N*H*), 7.40–7.29 (m, 5 H, Ar*H*), 5.03 (s, 2 H, CO_2CH_2Ph), 4.46 (td, *J* = 7.6, 5.2 Hz, 1 H, NHC*H*CH_2), 4.27 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH_3), 3.68 (d, *J* = 6.1 Hz, 2 H, NHCH_2), 3.62 (s, 3 H, CO_2CH_3), 2.86–2.63 (m, 2 H, NHCHCH_2), 2.22 (t, *J* = 8.5 Hz, 1 H, S*H*), 1.30 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 172.8, 169.6, 169.1, 156.5, 137.0, 128.4, 127.8, 127.7, 65.5, 54.4, 51.9, 47.7, 43.4, 26.4, 16.7. **IR**: *v* 3335 (m), 3301 (m), 2982 (m), 2919 (w), 2547 (w), 1742 (s), 1670 (s), 1653 (s), 1541 (s), 1523 (s), 1455 (m), 1410 (w), 1375 (w), 1256 (s), 1213 (s), 1152 (m), 1048 (s), 970 (w), 766 (w), 727 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{24}N_3O_6S^+$ 398.1380, found 398.1374.

[10] B. V. Rao, S. Dhokale, P. R. Rajamohanan, S. Hotha, *Chem. Commun.* **2013**, *49*, 10808.

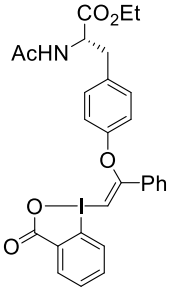
2.3 Synthesis of Vinylbenziodoxolones (VBX)

General procedure for the synthesis of protected VBX reagents (GP V)

Following a reported procedure[11], the protected amino acid (1.2 equiv.) or peptide (1.0 equiv.) and cesium carbonate (10 mol% or 1.1 equiv.) were diluted with ethanol (80 mM). The corresponding EBX reagent (1.0 equiv. for amino acid, 1.2 equiv. for peptide) was added in one portion and the reaction mixture was stirred at room temperature until TLC control indicated complete conversion of the EBX reagent (1–24 h). The mixture was concentrated in vacuo and the obtained residue was purified by column chromatography, MPLC or recrystallized in acetonitrile.

2.3.1 VBX Reagents based on single Amino Acids

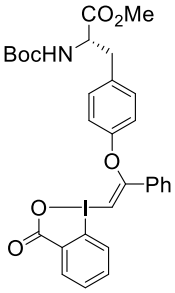
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy) phenyl)propanoate (5a)



Following **GP V** on 1.72 mmol scale and using *N*Ac-Tyr-OEt·H_2O (557 mg, 2.07 mmol, 1.2 equiv.), the VBX species (**5a**, 885 mg, 1.48 mmol, 86%) was obtained as a white solid. Purification via MPLC (t_R = 9.5–16.4 min, gradient: 5–95% MeCN in 28 min).

Mp: 111–114 °C. **ORD**: $[\alpha]_D^{20}$ = +16.6 (c = 0.85, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.43–8.37 (m, 1 H, Ar*H*), 7.67–7.55 (m, 5 H, Ar*H*), 7.45–7.35 (m, 3 H, Ar*H*), 6.96 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.79 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.73 (s, 1 H, N*H*), 6.21 (d, *J* = 7.7 Hz, 1 H, C=C*H*), 4.72 (dt, *J* = 7.6, 6.0 Hz, 1 H, NHC*H*), 4.06 (qq, *J* = 6.9, 3.6 Hz, 2 H, OCH_2CH$_3$), 3.02 (dd, *J* = 12.7, 4.8 Hz, 1 H, NHCHCH_2), 2.97 (dd, *J* = 12.7, 3.3 Hz, 1 H, NHCHCH_2), 1.92 (s, 3 H, COCH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.5, 169.9, 167.0, 165.2, 154.8, 133.8, 133.5, 133.0, 132.0, 131.6, 131.0, 130.9, 129.3, 127.9, 125.9, 117.4, 114.8, 86.8, 61.6, 53.3, 37.0, 23.2, 14.2. **IR**: *v* 3064 (m), 1740 (m), 1661 (s), 1599 (s), 1555 (s), 1507 (s), 1444 (m), 1375 (m), 1348 (m), 1297 (m), 1273 (m), 1204 (s), 1173 (s), 1131 (m), 1044 (m), 1024 (m), 745 (s), 739 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{26}INNaO_6^+$ 622.0697, found 622.0707. For a detailed assignment of the NMR signals see table **S3** (chapter 5).

Methyl (*S*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*S*)-5b)

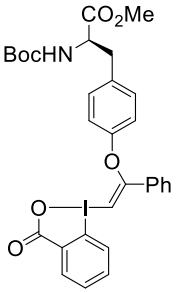


Following **GP V** on 2.30 mmol scale and using *N*Boc-L-Tyr-OMe (814 mg, 2.76 mmol, 1.2 equiv.), the VBX species (**(*S*)-5b**, 622 mg, 970 µmol, 42%) was obtained as a white solid. Purification via MPLC (t_R = 17.5–20.0 min, gradient: 5–95% MeCN in 28 min).

Mp: 122–124 °C. **ORD**: $[\alpha]_D^{20}$ = -15.8 (c = 0.94, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 6.7, 2.3 Hz, 1 H, Ar*H*), 7.65–7.55 (m, 5 H, Ar*H*), 7.44–7.34 (m, 3 H, Ar*H*), 6.94 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.77 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.74 (s, 1 H, C=C*H*), 4.96 (d, *J* = 8.3 Hz, 1 H, N*H*), 4.45 (q, *J* = 6.8 Hz, 1 H, NHC*H*), 3.58 (s, 3 H, CO_2CH_3), 2.95 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHCHCH_2), 2.89 (dd, *J* = 14.1, 6.5 Hz, 1 H, NHCHCH_2), 1.35 (s, 9 H, (CH_3)$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.2, 166.9, 165.1, 155.1, 154.7, 133.65, 133.61, 132.9, 131.8, 131.5, 130.9, 130.8, 129.2, 127.9, 125.9, 117.3, 114.7, 87.4, 80.1, 54.4, 52.3, 37.7, 28.4. **IR**: *v* 3369 (s), 2977 (m), 1690 (m), 1646 (m), 1613 (m), 1505 (w), 1440 (w), 1366 (w), 1278 (w), 1202 (w), 1171 (m), 1087 (m), 1047 (s), 881 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{31}INO_7^+$ 644.1140, found 644.1150. For a detailed assignment of the NMR signals see table **S4** (chapter 5).

[11] N. Declas, J. Waser, *Angew. Chem. Int. Ed.* **2020**, *59*, 18256.

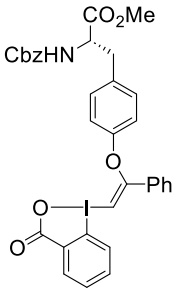
Methyl (*R*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*R*)-5b)



Following **GP V** on 2.30 mmol scale and using *N*Boc-D-Tyr-OMe (814 mg, 2.76 mmol, 1.2 equiv.), the VBX species (**(*R*)-5b**, 1.10 g, 1.72 mmol, 75%) was obtained as a white solid. Purification via MPLC (t_R = 14.8–20.3 min, gradient: 5–95% MeCN in 28 min).

Mp: 126–127 °C. **ORD**: $[\alpha]_D^{20}$ = +15.4 (c = 0.89, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.8, 2.0 Hz, 1 H, Ar*H*), 7.67–7.57 (m, 5 H, Ar*H*), 7.47–7.37 (m, 3 H, Ar*H*), 6.97 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.80 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.69 (s, 1 H, C=C*H*), 4.94 (d, *J* = 8.3 Hz, 1 H, N*H*), 4.47 (dd, *J* = 14.0, 5.8 Hz, 1 H, NHC*H*), 3.60 (s, 3 H, CO_2CH_3), 2.98 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCHCH_2), 2.91 (dd, *J* = 14.2, 6.4 Hz, 1 H, NHCHCH_2), 1.37 (s, 9 H, $(CH_3)_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.2, 167.1, 165.3, 155.1, 154.7, 133.9, 133.3, 133.2, 132.0, 131.6, 131.5, 131.0, 129.3, 128.0, 125.9, 117.4, 114.9, 86.9, 80.1, 54.5, 52.4, 37.7, 28.4. **IR**: *v* 3367 (m), 2979 (s), 2899 (m), 1675 (w), 1617 (w), 1501 (w), 1451 (w), 1407 (m), 1375 (m), 1253 (w), 1229 (w), 1166 (w), 1077 (s), 1040 (s), 878 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{31}INO_7^+$ 644.1140, found 644.1157. For a detailed assignment of the NMR signals see table **S5** (chapter 5).

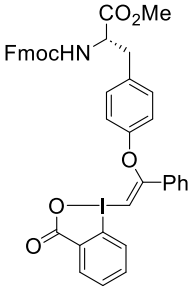
Methyl (*S*,*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(4-((2-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate (5c)



Following **GP V** on 2.87 mmol scale and using *N*CBz-L-Tyr-OMe (1.14 g, 3.44 mmol, 1.2 equiv.), the VBX species (**5c**, 1.65 g, 2.44 mmol, 85%) was obtained as a white solid. Purification via MPLC (t_R = 13.8–17.9 min, gradient: 5–95% MeCN in 25 min).

Mp: 111–114 °C. **ORD**: $[\alpha]_D^{20}$ = -5.3 (c = 1.33, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.44 (dt, *J* = 7.0, 1.5 Hz, 1 H, Ar*H*), 7.66–7.55 (m, 5 H, Ar*H*), 7.46–7.37 (m, 3 H, Ar*H*), 7.31 (qd, *J* = 5.4, 2.5 Hz, 5 H, Ar*H*), 6.93 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.75 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.65 (s, 1 H, C=C*H*), 5.24 (d, *J* = 8.3 Hz, 1 H, N*H*), 5.05 (s, 2 H, ArCH_2O), 4.54 (q, *J* = 6.4 Hz, 1 H, NHC*H*), 3.61 (s, 3 H, CO_2CH_3), 3.04–2.90 (m, 2 H, NHCHCH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.8, 166.7, 165.4, 155.7, 154.8, 136.3, 133.7, 133.6, 133.1, 131.7, 131.6, 131.0, 130.4, 129.3, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 125.6, 117.4, 115.9, 114.6, 86.9, 67.1, 54.9, 52.5, 37.5. **IR**: *v* 1717 (m), 1627 (m), 1577 (w), 1544 (w), 1512 (m), 1461 (w), 1415 (m), 1386 (m), 1251 (m), 1227 (m), 1184 (w), 1051 (s), 1019 (m), 889 (w), 829 (w), 730 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{29}INO_7^+$ 678.0983, found 678.1005.

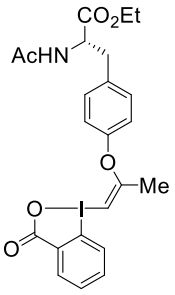
Methyl (*S*,*Z*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-((2-(3-oxo-1λ³-benzo[*d*][1,2]-iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate (5d)



Following **GP V** on 5.75 mmol scale and using *N*Fmoc-L-Tyr-OMe (2.88 g, 6.89 mmol, 1.2 equiv.), the VBX species (**5d**, 2.81 g, 3.67 mmol, 64%) was obtained as a white solid. Purification via MPLC (t_R = 17.4–21.6 min, gradient: 5–95% MeCN in 28 min). Mixture of rotamers was observed (exact ratio could not be obtained due to overlapping signals). NMR data is given for major rotamer.

Mp: 121–130 °C. **ORD**: $[\alpha]_D^{20}$ = -15.4 (c = 0.75, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.56–8.34 (m, 1 H, Ar*H*), 7.75 (dd, *J* = 7.6, 3.8 Hz, 2 H, Ar*H*), 7.66–7.50 (m, 7 H, Ar*H*), 7.43–7.34 (m, 5 H, Ar*H*), 7.33–7.26 (m, 2 H, Ar*H*), 6.92 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 6.75 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.62 (s, 1 H, C=C*H*), 5.29 (d, *J* = 8.2 Hz, 1 H, N*H*), 4.54 (q, *J* = 6.5 Hz, 1 H, NHC*H*), 4.44–4.29 (m, 2 H, CH_2O), 4.16 (t, *J* = 6.9 Hz, 1 H, C*H*CH$_2$O), 3.62 (s, 3 H, CO_2CH_3), 3.05–2.94 (m, 2 H, NHCHCH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 166.7, 165.4, 155.6, 154.8, 143.8, 141.4, 133.7, 133.1, 131.8, 131.6, 131.0, 130.4, 129.3, 127.9, 127.8, 127.2, 125.6, 125.2, 125.1, 120.1, 117.4, 114.6, 86.8, 66.9, 54.9, 52.5, 47.3, 37.5. **IR**: *v* 1716 (s), 1706 (m), 1618 (s), 1563 (m), 1534 (s), 1507 (s), 1424 (m), 1357 (m), 1210 (s), 1173 (m), 1102 (m), 1074 (m), 1044 (s), 1022 (s), 767 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{33}INO_7^+$ 766.1296, found 766.1313.

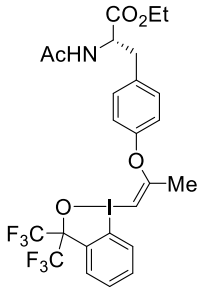
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)oxy) phenyl)propanoate (5e)



Following **GP V** on 2.10 mmol scale and using *N*Ac-Tyr-OEt·H_2O (678 mg, 2.52 mmol, 1.2 equiv.), the VBX species (**5e**, 694 mg, 1.29 mmol, 62%) was obtained as a yellowish oil. Purification via column chromatography (DCM/MeOH = 9:1).

TLC: R_f (DCM/MeOH = 9:1) = 0.39. **ORD**: $[\alpha]_D^{20}$ = +9.0 (c = 0.25, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.45–8.37 (m, 1 H, Ar*H*), 7.65-7.56 (m, 3 H, Ar*H*), 7.10 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.27 (d, *J* = 7.7 Hz, 1 H, N*H*), 5.80 (s, 1 H, C=C*H*), 4.79 (dt, *J* = 7.7, 6.0 Hz, 1 H, NHC*H*), 4.14 (qd, *J* = 7.2, 3.0 Hz, 2 H, OC$H_2$$CH_3$), 3.13 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHCHCH_2), 3.06 (dd, *J* = 14.0, 6.0, 1 H, NHCHCH_2), 2.22 (s, 3 H, HC=CCH_3), 1.97 (s, 3 H, COCH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.5, 169.9, 166.9, 166.8, 152.7, 134.2, 133.9, 133.4, 133.1 (2 C), 130.8, 125.3, 120.3, 114.0, 78.5, 61.7, 53.4, 37.3, 23.3, 19.6, 14.3. **IR**: *v* 3418 (s), 1732 (m), 1653 (m), 1595 (m), 1559 (m), 1506 (m), 1372 (w), 1315 (w), 1278 (w), 1220 (w), 1159 (w), 1120 (w), 1019 (w), 759 (m). **HRMS** (nanochip-ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{25}INO_6^+$ 538.0721, found 538.0714. For a detailed assignment of the NMR signals see table **S6** (chapter 5).

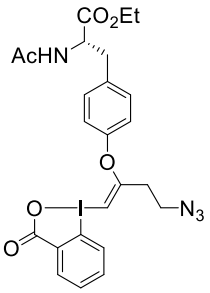
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)oxy)phenyl)propanoate (5f)



Following **GP V** on 1.23 mmol scale and using *N*Ac-Tyr-OEt·H_2O (396 mg, 1.47 mmol, 1.2 equiv.), the VBX species (**5f**, 323 mg, 490 µmol, 40%) was obtained as a white solid. Purification via MPLC (t_R = 18.5–21.1 min, gradient: 5–95% MeCN in 28 min).

Mp: 83–86 °C. **ORD:** $[\alpha]_D^{20}$ = +6.7 (c = 0.45, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.79–7.73 (m, 1 H, Ar*H*), 7.65–7.59 (m, 1 H, Ar*H*), 7.55–7.49 (m, 2 H, Ar*H*), 7.05 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 7.9 Hz, 1 H, N*H*), 6.78 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.64 (d, *J* = 1.1 Hz, 1 H, C=C*H*), 4.68 (dt, *J* = 7.8, 6.4 Hz, 1 H, NHC*H*), 4.06 (q, *J* = 7.1, 6.7 Hz, 2 H, OC$H_2$$CH_3$), 3.06 (dd, *J* = 14.0, 6.1 Hz, 1 H, NHCHCH_2), 2.99 (dd, *J* = 14.0, 6.6 Hz, 1 H, NHCHCH_2), 2.10 (d, *J* = 0.9 Hz, 3 H, HC=CCH_3), 1.88 (s, 3 H, COCH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.6, 170.2, 165.1, 153.0, 133.5, 131.9, 131.4, 130.7, 130.2, 127.0, 124.11 (q, *J* = 292.1 Hz), 119.6, 110.1, 83.2, 81.3 (p, *J* = 28.6 Hz), 61.4, 53.4, 36.8, 22.7, 19.3, 14.0. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -75.92 (t, J = 7.1 Hz), -75.98 (t, J = 7.3 Hz). **IR:** *v* 1739 (m), 1671 (m), 1512 (m), 1429 (w), 1382 (w), 1260 (s), 1180 (s), 1148 (s), 1022 (m), 965 (m), 946 (m), 822 (w), 734 (m). **HRMS** (nanochip-ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{25}F_6INO_5^+$ 660.0676, found 660.0694. For a detailed assignment of the NMR signals see table **S7** (chapter 5).

Ethyl (*S*,*Z*)-2-acetamido-3-(4-((4-azido-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)but-1-en-2-yl) oxy)phenyl)propanoate (5g)

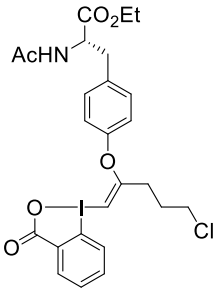


Following **GP V** on 1.47 mmol scale and using *N*Ac-Tyr-OEt·H_2O (553 mg, 2.05 mmol, 1.2 equiv.), the VBX species (**5g**, 507 mg, 860 µmol, 58%) was obtained as a white solid (96% purity). Purification via MPLC (t_R = 12.3–15.1 min, gradient: 5–95% MeCN in 28 min).

Mp: 98–101 °C. **ORD**: $[\alpha]_D^{20}$ = +8.4 (c = 0.58, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.33–8.24 (m, 1 H, Ar*H*), 7.74–7.67 (m, 1 H, Ar*H*), 7.55 (dt, *J* = 5.6, 2.1 Hz, 2 H, Ar*H*), 7.06 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 8.2 Hz, 1 H, N*H*), 6.20 (s, 1 H, C=C*H*), 4.72–4.66 (m, 1 H, NHC*H*), 4.08 (qd, *J* = 7.1, 1.8 Hz, 2 H, OC$H_2$$CH_3$), 3.50 (t, *J* = 6.3 Hz, 2 H, C$H_2$$N_3$), 3.07 (dd, *J* = 14.0, 5.7 Hz, 1 H, NHCHCH_2), 2.99 (dd, *J* = 14.0, 6.5 Hz, 1 H, NHCHCH_2), 2.77 (t, *J* = 6.3 Hz, 2 H, CH_2CH$_2$$N_3$), 1.91 (s, 3 H, COC$H_3$), 1.16 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.5, 170.3, 167.2, 165.2, 152.7, 133.9, 133.7, 132.6, 131.2, 130.6, 126.3, 119.1, 114.3, 84.3, 61.5, 53.4, 48.1, 36.9, 32.4, 23.0, 14.2. **IR**: *v* 3064

(w), 2100 (m), 1736 (m), 1660 (m), 1603 (s), 1583 (s), 1556 (m), 1505 (s), 1438 (m), 1370 (m), 1349 (m), 1296 (m), 1268 (m), 1220 (s), 1170 (m), 1127 (w), 1029 (w), 830 (w), 748 (m). **HRMS** (nanochip-ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}IN_4O_6^+$ 593.0892, found 593.0919. For a detailed assignment of the NMR signals see table **S8** (chapter 5).

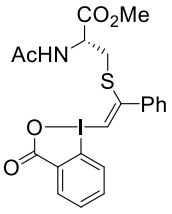
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-chloro-1-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)oxy)phenyl)propanoate (5h)



Following **GP V** on 1.72 mmol scale and using *N*Ac-Tyr-OEt·H_2O (556 mg, 2.07 mmol, 1.2 equiv.), the VBX species (**5h**, 682 mg, 1.14 mmol, 66%) was obtained as a white solid. Purification via column chromatography (DCM/MeOH = 9:1).

TLC: R_f (DCM/MeOH = 9:1) = 0.45. **Mp**: 70–73 °C. **ORD**: $[\alpha]_D^{20}$ = +7.4 (c = 0.63, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.42-8.34 (m, 1 H, Ar*H*), 7.63-7.59 (m, 3 H, Ar*H*), 7.09 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.39 (d, *J* = 7.1 Hz, 1 H, N*H*), 6.03 (s, 1 H, C=C*H*), 4.77 (dt, *J* = 7.7, 5.9 Hz, 1 H, NHC*H*), 4.14 (qd, *J* = 7.1, 2.5 Hz, 2 H, OC$H_2$$CH_3$), 3.57 (t, *J* = 6.1 Hz, 2 H, CH_2Cl), 3.14 (dd, *J* = 14.0, 5.9 Hz, 1 H, NHCHCH_2), 3.06 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHCHCH_2), 2.78-2.72 (m, 2 H, HC=CCH_2), 2.03 (p, *J* = 6.2 Hz, 2 H, C$H_2$$CH_2$Cl), 1.97 (s, 3 H, COC$H_3$), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.5, 170.1, 168.1, 166.8, 152.8, 133.9, 133.8, 133.5, 133.0, 131.4, 130.8, 125.5, 119.3, 114.3, 82.2, 61.7, 53.4, 43.6, 37.1, 30.3, 29.5, 23.2, 14.3. **IR**: *v* 1739 (m), 1609 (m), 1509 (m), 1310 (m), 1210 (m), 1159 (m), 1026 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}ClINO_6^+$ 600.0644, found 600.0649. For a detailed assignment of the NMR signals see table **S9** (chapter 5).

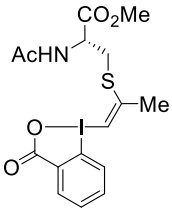
Methyl (*Z*)-*N*-acetyl-*S*-(2-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)-L-cysteinate (5i)



Following **GP V** on 4.31 mmol scale and using *N*Ac-Cys-OMe (916 mg, 5.17 mmol, 1.2 equiv.), the VBX species (**5i**, 1.58 g, 3.01 mmol, 70%) was obtained as a white solid. Purification via MPLC (t_R = 11.5–14.2 min, gradient: 5–95% MeCN in 28 min).

Mp: 106–110 °C. **ORD**: $[\alpha]_D^{20}$ = +123.9 (c = 0.55, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.3, 1.9 Hz, 1 H, Ar*H*), 7.90 (d, *J* = 7.7 Hz, 1 H, N*H*), 7.70–7.66 (m, 2 H, Ar*H*), 7.64–7.54 (m, 2 H, Ar*H*), 7.53–7.44 (m, 4 H, Ar*H*), 7.06 (s, 1 H, C=C*H*), 4.55 (td, *J* = 7.4, 3.8 Hz, 1 H, NHC*H*), 3.63 (s, 3 H, CO_2CH_3), 3.19 (dd, *J* = 14.4, 3.8 Hz, 1 H, NHCHCH_2), 3.08 (dd, *J* = 14.4, 7.3 Hz, 1 H, NHCHCH_2), 2.02 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.5, 168.2, 160.5, 135.9, 134.1, 133.4, 133.2, 131.2, 130.8, 129.5, 128.9, 126.7, 115.4, 103.8, 52.9, 52.7, 35.4, 23.2. **IR**: *v* 3054 (w), 1743 (m), 1654 (s), 1609 (s), 1552 (m), 1437 (m), 1370 (m), 1350 (m), 1264 (m), 1213 (m), 1177 (m), 1036 (w), 1004 (w), 831 (w), 749 (s), 734 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{20}INNaO_5S^+$ 547.9999, found 547.9992. For a detailed assignment of the NMR signals see table **S10** (chapter 5).

Methyl (*Z*)-*N*-acetyl-*S*-(1-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (5j)

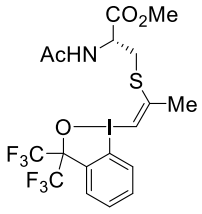


Following **GP V** on 2.10 mmol scale and using *N*Ac-Cys-OMe (446 mg, 2.52 mmol, 1.2 equiv.), the VBX species (**5j**, 804 mg, 1.74 mmol, 83%) was obtained as a white solid. Purification via column chromatography (DCM/MeOH = 9:1).

TLC: R_f (DCM/MeOH = 9:1) = 0.39. **Mp**: 91–96 °C. **ORD**: $[\alpha]_D^{20}$ = +49.2 (c = 0.78, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.1 Hz, 1 H, Ar*H*), 7.99–7.88 (m, 1 H, N*H*), 7.60–7.49 (m, 2 H, Ar*H*), 7.38 (dd, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 6.62 (s, 1 H, C=C*H*), 4.71 (td, *J* = 6.8, 4.2 Hz, 1 H, NHC*H*), 3.69 (s, 3H, CO_2CH_3), 3.50 (dd, *J* = 14.2, 4.3 Hz, 1 H, NHCHCH_2), 3.34 (dd, *J* = 14.4, 6.7 Hz, 1 H, NHCHCH_2), 2.55 (d, *J* = 1.3 Hz, 3 H, HC=CCH_3), 2.01 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.2, 170.5, 167.5, 158.9, 133.9, 133.7, 133.1, 130.7, 126.1,

113.9, 99.0, 53.1, 53.0, 33.7, 24.5, 23.0. **IR**: *v* 3436 (s), 1746 (m), 1649 (m), 1613 (s), 1559 (m), 1379 (m), 1312 (m), 1159 (m), 1058 (m), 1033 (m), 850 (m), 759 (s), 727 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{20}INNaO_5S^+$ 547.9999, found 547.9992. For a detailed assignment of the NMR signals see table **S11** (chapter 5).

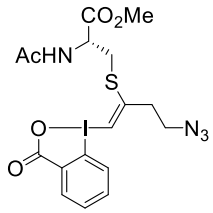
Methyl (*Z*)-*N*-acetyl-*S*-(1-(3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (5k)



Following **GP V** on 0.74 mmol scale and using *N*Ac-Cys-OMe (156 mg, 880 µmol, 1.2 equiv.), the VBX species (**5k**, 196 mg, 330 µmol, 46%) was obtained as a colorless oil (95% purity). Purification via MPLC (t_R = 16.0–17.4 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +46.6 (c =0.44 , MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (t, *J* = 8.9 Hz, 1 H, Ar*H*), 7.60–7.48 (m, 2 H, Ar*H*), 7.44–7.40 (m, 1 H, Ar*H*), 6.90 (bs, 1 H, N*H*), 6.52 (s, 1 H, C=C*H*), 4.75–4.67 (m, 1 H, NHC*H*), 3.67 (s, 3 H, CO_2CH_3), 3.37 (dd, *J* = 14.2, 5.1 Hz, 1 H, NHCHCH_2), 3.22 (dd, *J* = 14.0, 6.1 Hz, 1 H, NHCHCH_2), 2.45 (s, 3 H, HC=CCH_3), 1.97 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.6, 170.5, 154.8, 132.1, 131.5, 130.6, 130.4, 127.4, 124.2 (q, J = 291.6 Hz), 110.7, 105.1, 82.0-80.6 (m) 52.9, 52.4, 33.6, 24.5, 22.9. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -75.8 (q, J = 8.0 Hz), -76.0 (q, J = 8.6 Hz). **IR**: *v* 3274 (m), 3047 (w), 2950 (w), 2842 (w), 1750 (m), 1660 (m), 1546 (m), 1463 (w), 1443 (w), 1379 (w), 1289 (m), 1260 (s), 1213 (m), 1177 (s), 1155 (s), 1133 (m), 1033 (w), 971 (w), 943 (m), 760 (m), 730 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{18}F_6INNaO_4S^+$ 607.9798, found 607.9808. For a detailed assignment of the NMR signals see table **S12** (chapter 5).

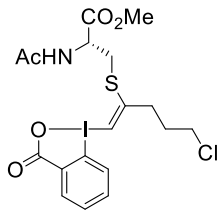
Methyl (*Z*)-*N*-acetyl-*S*-(4-azido-1-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)but-1-en-2-yl)-L-cysteinate (5l)



Following **GP V** on 0.88 mmol scale and using *N*Ac-Cys-OMe (187 mg, 1.06 mmol, 1.2 equiv.), the VBX species (**5l**, 320 mg, 620 µmol, 70%) was obtained as a white solid. Purification via MPLC (t_R = 8.5–10.5 min, gradient: 5–95% MeCN in 28 min).

Mp: 59–61 °C. **ORD:** $[\alpha]_D^{20}$ = +48.3 (c = 0.67, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.36 (dt, *J* = 7.3, 1.3 Hz, 1 H, Ar*H*), 8.23 (d, *J* = 7.2 Hz, 1 H, N*H*), 7.62–7.56 (m, 1 H, Ar*H*), 7.55 (dd, *J* = 3.5, 1.0 Hz, 2 H, Ar*H*), 6.98 (s, 1 H, C=C*H*), 4.65 (td, J = 6.8, 4.0 Hz, 1 H, NHC*H*), 3.72 (t, *J* = 6.1 Hz, 2 H, CH_2N_3), 3.71 (s, 3 H, CO_2CH_3), 3.44 (dd, *J* = 14.7, 4.1 Hz, 1 H, NHCHCH_2), 3.30 (dd, *J* = 14.6, 6.6 Hz, 1 H, NHCHCH_2), 3.04–2.87 (m, 2 H, C$H_2CH_2N_3$), 2.05 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.5, 170.3, 168.4, 157.3, 134.3, 133.2, 133.1, 130.7, 127.2, 115.0, 106.1, 53.7, 53.1, 49.6, 36.0, 33.4, 23.0. **IR**: *v* 3389 (s), 2100 (m), 1746 (m), 1643 (s), 1606 (s), 1545 (m), 1440 (m), 1361 (m), 1303 (m), 1227 (m), 1015 (w), 752 (m). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}IN_4O_5S^+$ 519.0194, found 519.0196. Analytical data were in agreement with the literature.[12]

Methyl (*Z*)-*N*-acetyl-*S*-(5-chloro-1-(3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)-L-cysteinate (5m)



Following **GP V** on 1.72 mmol scale and using *N*Ac-Cys-OMe (366 mg, 2.07 mmol, 1.2 equiv.), the VBX species (**5m**, 816 mg, 1.55 mmol, 90%) was obtained as a white solid. Purification via column chromatography (DCM/MeOH = 9:1).

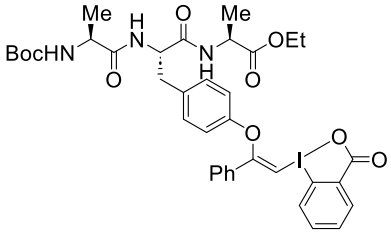
TLC: R_f (DCM/MeOH = 9:1) = 0.39. **Mp**: 163–165 °C. **ORD**: $[\alpha]_D^{20}$ = +43.3 (c =0.40 , MeOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.43 (d, *J* = 7.7 Hz, 1 H, N*H*), 8.15-8.09 (m, 1 H, Ar*H*), 7.68-7.61 (m, 2 H, Ar*H*), 7.53-7.46 (m, 1 H, Ar*H*), 7.10 (s, 1 H, C=C*H*), 4.37 (td, *J* = 8.1, 5.2 Hz, NHC*H*), 3.76 (t, *J* = 6.4 Hz, 2 H, CH_2Cl), 3.54 (s, 3 H, CO_2CH_3),

[12] R. Tessier, J. Cellabos, N. Guidotti, R. Simonet-Davin, B. Fierz, J. Waser, *Chem* **2019**, *5*, 2243.

3.26 (dd, *J* = 13.9, 5.4 Hz, 1 H, NHCHC*H*$_2$), 3.07 (dd, *J* = 13.9, 8.3 Hz, 1 H, NHCHC*H*$_2$), 2.92-2.87 (m, 2 H, CH=CC*H*$_2$), 2.10 (p, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_2$Cl), 1.74 (s, 3 H, COC*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 170.5, 169.5, 165.6, 158.0, 134.5, 133.3, 131.6, 130.2, 127.1, 113.9, 104.3, 52.2, 52.2, 44.3, 33.2, 32.4, 31.2, 22.2. **IR**: *v* 2363 (s), 1750 (m), 1737 (m), 1663 (m), 1609 (s), 1315 (m), 1156 (m), 1029 (m). **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{22}ClINO_5S^+$ 525.9946, found 525.9947. For a detailed assignment of the NMR signals see table **S13** (chapter 5).

2.3.2 VBX Reagents based on Peptides

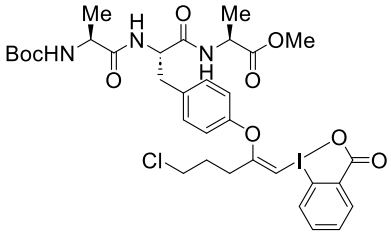
_N_-Boc-L-Ala-L-Tyr(_O_-Ph-VBX)-L-Ala-OEt (5n)



Following **GP V** on 1.14 mmol scale and using tripeptide *N*-Boc-L-Ala-L-Tyr-L-Ala-OMe (**S3**, 500 mg, 1.14 mmol, 1.0 equiv.) and EBX **17a** (478 mg, 1.37 mmol, 1.2 equiv.), the VBX species (**5n**, 833 mg, 1.04 mmol, 91%) was obtained as a white solid. Purification via MPLC (t_R = 15.8–19.2 min, gradient: 5–95% MeCN in 28 min). Full transesterification to the the ethyl ester was observed

Mp: 131–136 °C. **ORD**: $[\alpha]_D^{20}$ = -11.7 (c = 0.50, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 6.0, 3.1 Hz, 1 H, Ar*H*), 7.69–7.58 (m, 5 H, Ar*H*), 7.47–7.34 (m, 3 H, Ar*H*), 7.17 (d, *J* = 8.2 Hz, 1 H, N*H*), 7.07 (d, *J* = 8.6 Hz, 1 H, N*H*), 7.05 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.79 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.75 (s, 1 H, C=C*H*), 5.38 (bs, 1 H, N*H*), 4.60 (td, *J* = 8.0, 5.8 Hz, 1 H, NHC*H*CH$_2$), 4.40 (p, *J* = 7.1 Hz, 1 H, NHC*H*CH$_3$), 4.12 (qd, *J* = 7.1, 1.1 Hz, , $CO_2CH_2CH_3$.07–4.00 (m, 1 H, NHC*H*CH$_3$), 3.05 (dd, *J* = 14.2, 5.7 Hz, 1 H, NHCHC*H*$_2$), 2.91 (dd, *J* = 14.2, 8.0 Hz, 1 H, NHCHC*H*$_2$), 1.36 (s, 9 H, C(C*H*$_3$)$_3$), 1.31 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.21 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.15 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.2, 172.5, 170.6, 168.0, 165.8, 155.8, 154.5, 134.3, 133.2, 133.1, 133.0, 131.7, 131.6, 131.2, 130.9, 129.3, 128.1, 126.7, 117.8, 114.7, 84.5, 80.1, 61.5, 54.1, 50.7, 48.5, 36.9, 28.4, 18.3, 17.9, 14.2. **IR**: *v* 1645 (m), 1509 (w), 1364 (w), 1216 (w), 1159 (w), 1019 (w). **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{37}H_{43}IN_3O_9^+$ 800.2039, found 800.2066. For a detailed assignment of the NMR signals see table **S14** (chapter 5).

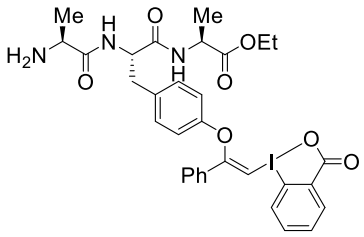
_N_-Boc-L-Ala-L-Tyr(_O_-Cl-VBX)-L-Ala-OMe (5o)



Following **GP V** on 0.86 mmol scale and using tripeptide *N*-Boc-L-Ala-L-Tyr-L-Ala-OMe (**S3**, 377 mg, 860 µmol, 1.0 equiv.) and EBX **17g** (300 mg, 860 µmol, 1.0 equiv.), the VBX species (**5o**, 345 mg, 440 µmol, 51%) was obtained as a white solid. Purification via MPLC (t_R = 15.2–28.2 min, gradient: 5–95% MeCN in 28 min).

Mp: 116–121°C. **ORD**: $[\alpha]_D^{20}$ = +19.4 (c = 0.47, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.35–8.29 (m, 1 H, Ar*H*), 7.67 (d, *J* = 8.0 Hz, 1 H, N*H*), 7.62–7.57 (m, 3 H, Ar*H*), 7.53 (d, *J* = 7.2 Hz, 1 H, N*H*), 7.15 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.79 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.99 (s, 1 H, C=C*H*), 5.59 (d, *J* = 7.2 Hz, 1 H, N*H*), 4.64 (td, *J* = 8.0, 5.7 Hz, 1 H, NHC*H*CH$_2$), 4.44 (p, *J* = 7.1 Hz, 1 H, NHC*H*CH$_3$), 4.20–4.08 (m, 1 H, NHC*H*CH$_3$), 3.65 (s, 3 H, CO_2CH_3), 3.56 (t, *J* = 6.1 Hz, 2 H, C*H*$_2$Cl), 3.13 (dd, *J* = 14.2, 5.7 Hz, 1 H, NHCHC*H*$_2$), 3.00 (dd, *J* = 14.1, 8.0 Hz, 1 H, NHCHC*H*$_2$), 2.73 (t, *J* = 7.4 Hz, 2 H, C=CHC*H*$_2$), 2.07–1.96 (m, 2 H, C*H*$_2$CH$_2$Cl), 1.36–1.30 (m, 12 H, C*H*$_3$, C(C*H*$_3$)$_3$), 1.24 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.4, 173.1, 170.8, 168.7, 167.4, 155.7, 152.4, 135.1, 133.7, 133.5, 133.0, 131.5, 130.8, 125.9, 119.6, 114.4, 79.8, 79.6, 54.3, 52.4, 50.6, 48.4, 43.6, 36.8, 30.6, 29.5, 28.4, 18.6, 17.7. **IR**: *v* 3671 (w), 2980 (s), 2892 (s), 1750 (w), 1663 (m), 1609 (m), 1505 (m), 1451 (w), 1407 (m), 1379 (m), 1242 (m), 1227 (m), 1163 (m), 1051 (s), 896 (w), 737 (m). **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{33}H_{42}ClIN_3O_9^+$ 786.1649, found 786.1670. For a detailed assignment of the NMR signals see table **S15** (chapter 5).

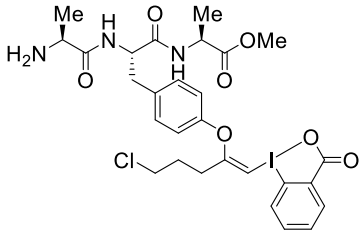
NH_2-L-Ala-L-Tyr(*O*-Ph-VBX)-L-Ala-OEt (5p)



Following **GP V** on 1.07 mmol scale and using tripeptide NH_2-L-Ala-L-Tyr-L-Ala-OMe·HCl (**S4**, 400 mg, 1.07 mmol, 1.0 equiv.), EBX **17a** (447 mg, 1.28 mmol, 1.2 equiv.) and Cs_2CO_3 (384 mg, 1.18 mmol, 1.1 equiv.), the VBX species (**5p**, 416 mg, 610 µmol, 57%) was obtained as a white solid (93% purity). Purification via MPLC (t_R = 12.0–16.2 min, gradient: 5–95% MeCN in 28 min). Full transesterification to the the ethyl ester was observed. One ^{13}C signal could not be extracted due to signal overlapping with MeOD.

Mp: 127 °C (decomposition). **ORD**: $[\alpha]_D^{20}$ = +65.7 (c = 0.38, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 8.26 (dd, *J* = 7.3, 2.0 Hz, 1 H, Ar*H*), 7.88 (dd, *J* = 7.9, 1.3 Hz, 1 H, Ar*H*), 7.77–7.64 (m, 4H, Ar*H*), 7.48–7.41 (m, 3 H, Ar*H*), 7.15 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.12 (s, 1 H, C=C*H*), 6.88 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.60–4.51 (m, 1 H, NHC*H*CH_2), 4.32 (q, *J* = 7.3 Hz, 1 H, NHC*H*CH_3), 4.12 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.95 (q, *J* = 7.1 Hz, 1 H, NHC*H*CH_3), 3.06 (dd, *J* = 14.3, 4.5 Hz, 1 H, NHCHCH_2), 2.79 (dd, *J* = 14.2, 9.0 Hz, 1 H, NHCHCH_2), 1.33 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.31–1.24 (m, 3 H, CH_3), 1.22 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 173.8, 172.9, 170.1, 166.8, 156.0, 135.5, 134.1, 133.4, 132.9, 132.6, 131.9, 130.2, 130.1, 129.4, 129.3, 128.8, 118.7, 115.1, 86.8, 62.3, 55.6, 49.6, 38.0, 17.4, 14.5. **IR**: *v* 2979 (w), 1645 (m), 1458 (w), 1338 (w), 1288 (w), 1089 (w), 1044 (m), 1019 (w), 880 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{35}IN_3O_7^+$ 700.1514, found 700.1518. For a detailed assignment of the NMR signals see table **S16** (chapter 5).

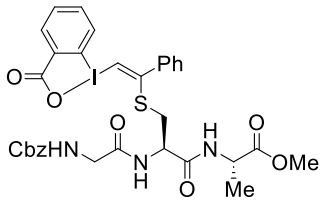
NH_2-L-Ala-L-Tyr(*O*-Cl-VBX)-L-Ala-OMe (5q)



Following **GP V** on 1.07 mmol scale and using tripeptide NH_2-L-Ala-L-Tyr-L-Ala-OMe·HCl (**S4**, 400 mg, 1.07 mmol, 1.0 equiv.), EBX **17g** (448 mg, 1.28 mmol, 1.2 equiv.) and Cs_2CO_3 (384 mg, 1.18 mmol, 1.1 equiv.), the VBX species (**5q**, 207 mg, 300 µmol, 28%) was obtained as a colorless oil. Purification via MPLC (t_R = 9.0–10.5 min, gradient: 5–95% MeCN in 28 min). One ^{13}C signal could not be extracted due to signal overlapping with MeOD.

ORD: $[\alpha]_D^{20}$ = -3.9 (c = 2.25, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 8.27 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar*H*), 7.91 (dd, *J* = 8.2, 1.1 Hz, 1 H, Ar*H*), 7.80 (td, *J* = 8.1, 7.7, 1.7 Hz, 1 H, Ar*H*), 7.73 (td, *J* = 7.3, 1.1 Hz, 1 H, Ar*H*), 7.29 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.97 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.40 (s, 1 H, C=C*H*), 4.62 (dd, *J* = 8.9, 5.7 Hz, 1 H, NHC*H*CH_2), 4.37 (qt, *J* = 7.2, 3.6 Hz, 1 H, NHC*H*CH_3), 3.88 (q, *J* = 7.0 Hz, 1 H, NHC*H*CH_3), 3.66 (s, 3 H, CO_2CH_3), 3.65 (t, *J* = 6.3 Hz, 2 H, CH_2Cl), 3.14 (dd, *J* = 14.2, 5.7 Hz, 1 H, NHCHCH_2), 2.98 (dd, *J* = 14.2, 9.1 Hz, 1 H, NHCHCH_2), 2.90 (t, *J* = 7.3 Hz, 2 H, C=CHCH_2), 2.10 (p, *J* = 6.4 Hz, 1 H, CH_2CH_2Cl), 1.47 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.36 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 174.3, 172.7, 171.0, 170.9, 170.2, 154.1, 135.8, 135.7, 133.6 (2 C), 132.2, 132.0, 128.9, 120.7, 114.5, 80.0, 55.9, 52.8, 50.0, 44.5, 38.1, 31.1, 30.8, 17.6, 17.4. **IR**: *v* 3378 (s), 2979 (m), 1654 (m), 1461 (w), 1387 (w), 1159 (w), 1091 (m), 1044 (s), 881 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{34}ClIN_3O_7^+$ 686.1125, found 686.1137. For a detailed assignment of the NMR signals see table **S17** (chapter 5).

***N*-Cbz-Gly-L-Cys(*S*-Ph-VBX)-L-Ala-OMe (5r)**

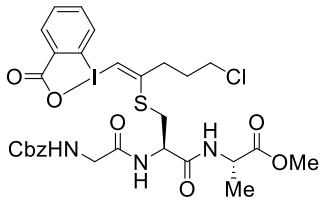


Following **GP V** on 0.86 mmol scale and using tripeptide *N*-Cbz-Gly-L-Cys-L-Ala-OMe (**S8**, 343 mg, 860 µmol, 1.0 equiv.) and EBX **17a** (300 mg, 860 µmol, 1.0 equiv.), the VBX species (**5r**, 210 mg, 280 µmol, 33%) was obtained as a white solid. Purification via MPLC (t_R = 15.8–17.9 min, gradient: 5–95% MeCN in 28 min).

Mp: 86–88°C. **ORD**: $[\alpha]_D^{20}$ = +154.4 (c = 0.12, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 8.19 (d, *J* = 8.6 Hz, 1 H, N*H*), 8.04 (d, *J* = 6.9 Hz,

1 H, N*H*), 7.65–7.61 (m, 1 H, Ar*H*), 7.61–7.56 (m, 1 H, Ar*H*), 7.53 (td, *J* = 7.7, 1.9 Hz, 1 H, Ar*H*), 7.49–7.46 (m, 2 H, Ar*H*), 7.38–7.34 (m, 2 H, Ar*H*), 7.34–7.31 (m, 1 H, Ar*H*), 7.30–7.26 (m, 2 H, Ar*H*), 7.25–7.20 (m, 2 H, Ar*H*), 7.21–7.17 (m, 1 H, Ar*H*), 6.80 (s, 1 H, C=C*H*), 6.59 (bs, 1 H, N*H*), 5.06 (s, 2 H, CO_2CH_2Ph), 4.68 (td, *J* = 8.5, 4.2 Hz, 1 H, NHC*H*CH_2), 4.37 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH_3), 4.01 (dd, *J* = 16.5, 6.8 Hz, 1 H, NHCH_2), 3.89 (dd, *J* = 17.1, 5.1 Hz, 1 H, NHCH_2), 3.63 (s, 3 H, CO_2CH_3), 3.16 (dd, *J* = 14.5, 4.3 Hz, 1 H, NHCHCH_2), 3.01 (dd, *J* = 14.5, 8.2 Hz, 1 H, NHCHCH_2), 1.35 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.3, 170.4, 169.3, 168.5, 161.6, 157.2, 136.6, 135.8, 134.1, 133.2, 131.3, 130.8, 129.5, 128.9, 128.7, 128.6, 128.2, 128.1, 126.8, 114.9, 102.7, 67.0, 53.9, 52.4, 48.6, 44.9, 35.5, 17.4. **IR**: *v* 3674 (m), 2986 (s), 2910 (s), 1735 (m), 1668 (m), 1631 (w), 1539 (m), 1455 (m), 1411 (m), 1380 (m), 1242 (m), 1231 (m), 1066 (s), 880 (w), 746 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{33}IN_3O_8S^+$ 746.1028, found 746.1030. For a detailed assignment of the NMR signals see table **S18** (chapter 5).

***N*-Cbz-Gly-L-Cys(*S*-Cl-VBX)-L-Ala-OMe (5s)**

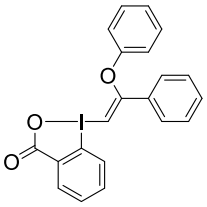


Following **GP V** on 0.86 mmol scale and using tripeptide *N*-Cbz-Gly-L-Cys-L-Ala-OMe (**S8**, 343 mg, 860 µmol, 1.0 equiv.) and EBX **17g** (300 mg, 860 µmol, 1.0 equiv.), the VBX species (**5s**, 429 mg, 580 µmol, 67%) was obtained as a white solid. Purification via MPLC (t_R = 15.8–17.6 min, gradient: 5–95% MeCN in 28 min).

Mp: 72–75 °C. **ORD**: $[\alpha]_D^{20}$ = +38.6 (c = 0.31, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.3 Hz, 1 H, N*H*), 8.34–8.28 (m, 2 H, N*H*, Ar*H*), 7.60–7.50 (m, 2 H, Ar*H*), 7.37–7.27 (m, 3 H, Ar*H*), 7.26–7.19 (m, 3 H, Ar*H*), 6.64 (t, *J* = 5.9 Hz, 1 H, N*H*), 6.59 (s, 1 H, C=C*H*), 5.09–4.98 (m, 2 H, CO_2CH_2Ph), 4.84 (td, *J* = 8.5, 4.3 Hz, 1 H, NHC*H*CH_2), 4.43 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH_3), 3.96–3.83 (m, 2 H, CH_2Cl), 3.66 (s, 3 H, CO_2CH_3), 3.60 (td, *J* = 6.3, 2.1 Hz, 2 H, NHCH_2), 3.44 (dd, *J* = 15.0, 4.4 Hz, 1 H, NHCHCH_2), 3.21 (dd, *J* = 14.7, 8.8 Hz, 1 H, NHCHCH_2), 2.91 (t, *J* = 7.2 Hz, 2 H, CH=CCH_2), 2.14–2.05 (m, 2 H, CH_2CH_2Cl), 1.39 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.2, 170.8, 169.5, 168.3, 160.6, 157.2, 136.5, 134.0, 133.6, 133.1, 130.8, 128.7, 128.6, 128.1, 126.6, 114.2, 103.3, 67.0, 54.1, 52.5, 48.7, 45.0, 43.6, 33.9, 33.6, 30.9, 17.3. **IR**: *v* 3678 (w), 2989 (s), 2901 (s), 1742 (m), 1653 (w), 1607 (m), 1532 (w), 1451 (w), 1440 (w), 1404 (m), 1375 (m), 1275 (s), 1267 (s), 1154 (w), 1055 (s), 871 (w), 838 (w), 755 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{34}ClIN_3O_8S^+$ 746.0794, found 746.0812. For a detailed assignment of the NMR signals see table **S19** (chapter 5).

2.3.3 VBX Reagents based on Vinyl (Thio) Ethers and Enamides

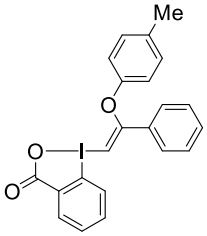
(*Z*)-1-(2-phenoxy-2-phenylvinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6a)



Following **GP V** on 5.75 mmol scale and using phenol (648 mg, 6.89 mmol, 1.2 equiv.), the VBX species (**6a**, 1.80 g, 4.07 mmol, 71%) was obtained as a white solid. Purification via recrystallization in ethanol (15 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 6.9, 2.2 Hz, 1 H, Ar*H*), 7.67–7.57 (m, 5 H, Ar*H*), 7.46–7.36 (m, 3 H, Ar*H*), 7.19 (dd, *J* = 8.7, 7.4 Hz, 2 H, Ar*H*), 6.99 (t, *J* = 7.4 Hz, 1 H, Ar*H*), 6.90–6.80 (m, 2 H, Ar*H*), 6.72 (s, 1 H, C=C*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.7, 165.3, 155.8, 133.7, 133.6, 133.1, 131.6, 130.9, 130.1, 129.3, 127.9, 125.7, 124.0, 117.2, 114.6, 87.3. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{16}IO_3^+$ 443.0139, found 443.0145. Analytical data were in agreement with the literature.[11]

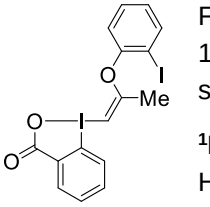
(*Z*)-1-(2-Phenyl-2-(*p*-tolyloxy)vinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6b)



Following **GP V** on 1.44 mmol scale and using *p*-cresol (186 mg, 1.72 mmol, 1.2 equiv.), the VBX species (**6b**, 378 mg, 830 µmol, 58%) was obtained as a white solid. Purification via recrystallization in acetonitrile (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49–8.42 (m, 1 H, Ar*H*), 7.70–7.58 (m, 5 H, Ar*H*), 7.47–7.36 (m, 3 H, Ar*H*), 6.98 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.78 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.67 (s, 1 H, C=C*H*), 2.21 (s, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.4, 165.5, 153.6, 134.0, 133.7, 133.3, 133.2, 131.7, 131.5, 130.9, 130.5, 129.2, 128.1, 126.3, 117.3, 115.2, 86.3, 20.7. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{18}IO_3^+$ 457.0295, found 457.0298. Analytical data were in agreement with the literature.[11]

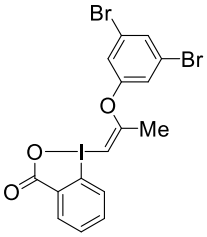
(*Z*)-1-(2-(2-Iodophenoxy)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6c)



Following **GP V** on 1.75 mmol scale and using 2-iodophenol (461 mg, 2.10 mmol, 1.2 equiv.), the VBX species (**6c**, 373 mg, 740 µmol, 42%) was obtained as a white solid. Purification via MPLC (t_R = 13.4–16.2 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 7.1, 2.2 Hz, 1 H, Ar*H*), 7.81 (dd, *J* = 8.2, 1.6 Hz, 1 H, Ar*H*), 7.73–7.70 (m, 1 H, Ar*H*), 7.67–7.59 (m, 2 H, Ar*H*), 7.39–7.32 (m, 1 H, Ar*H*), 7.02–6.95 (m, 2 H, Ar*H*), 5.78 (d, *J* = 1.0 Hz, 1 H, C=C*H*), 2.17 (d, *J* = 1.0 Hz, 3 H) , C*H*$_3$. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.8, 166.3, 153.4, 140.2, 133.9, 133.3, 133.1, 130.9, 130.1, 128.1, 125.7, 122.0, 114.1, 90.4, 77.8, 20.0. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{13}I_2O_3^+$ 506.8949, found 506.8952. Analytical data were in agreement with the literature.[11]

(*Z*)-1-(2-(3,5-Dibromophenoxy)prop-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6d)

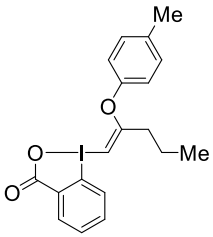


Following **GP V** on 0.52 mmol scale and using 3,5-dibromophenol (159 mg, 630 µmol, 1.2 equiv.), the VBX species (**6d**, 239 mg, 440 µmol, 85%) was obtained as a white solid. Purification via recrystallization in ethanol (8.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44–8.35 (m, 1 H, Ar*H*), 7.66–7.61 (m, 2 H, Ar*H*), 7.58–7.55 (m, 1 H, Ar*H*), 7.48 (t, *J* = 1.7 Hz, 1 H, Ar*H*), 7.06–7.05 (m, 2 H, Ar*H*), 5.99 (d, *J* = 1.1 Hz, 1 H, C=C*H*), 2.26 (d, *J* = 1.0 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.6, 165.4, 154.6, 133.8, 133.5, 133.2, 131.6, 131.0, 125.7, 123.7, 122.9, 122.2, 118.4, 114.0, 82.2, 19.4. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}Br_2IO_3^+$ 536.8192, found 536.8201. Analytical data were in agreement with the literature.[13]

[13] P. Caramenti, N. Declas, R. Tessier, M. D. Wodrich, J. Waser, *Chem. Sci.* **2019**, *10*, 3223.

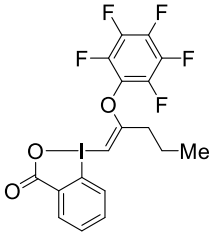
(*Z*)-1-(2-(*p*-Tolyloxy)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6e)



Following **GP V** on 1.59 mmol scale and using *p*-cresol (207 mg, 1.91 mmol, 1.2 equiv.), the VBX species (**6e**, 151 mg, 360 µmol, 22%) was obtained as a white solid. Purification by recrystallization in acetonitrile (9.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44–8.36 (m, 1 H, Ar*H*), 7.64–7.55 (m, 3 H, Ar*H*), 7.09 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 6.78 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.88 (s, 1 H, C=C*H*), 2.47 (t, *J* = 7.6 Hz, 2 H, C=CHC*H*$_2$), 2.29 (s, 3 H, ArC*H*$_3$), 1.60 (h, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 0.96 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.5, 166.8, 151.6, 135.1, 134.0, 133.2, 132.9, 130.7, 130.6, 125.3, 119.2, 114.0, 80.2, 34.5, 20.8, 20.6, 13.6. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{20}IO_3^+$ 423.0452, found 423.0458. Analytical data were in agreement with the literature.[11]

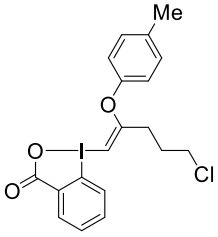
(*Z*)-1-(2-(Perfluorophenoxy)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6f)



Following **GP V** on 1.91 mmol scale and using pentafluorophenol (422 mg, 2.29 mmol, 1.2 equiv.), the VBX species (**6f**, 233 mg, 470 µmol, 25%) was obtained as a white solid.

^{1}H-NMR (400 MHz, MeOD-d_4) δ 8.30–8.22 (m, 1 H, Ar*H*), 7.81 (dd, *J* = 7.6, 1.6 Hz, 1 H, Ar*H*), 7.77–7.68 (m, 2 H, Ar*H*), 6.40 (s, 1 H, C=C*H*), 2.58 (t, *J* = 7.5 Hz, 2 H, C=CHC*H*$_2$), 1.69 (h, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.05 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 170.3, 170.1, 144.4–143.9 (m), 141.9–140.4 (m), 139.7–138.0 (m), 135.2, 134.5, 133.4, 131.9, 129.4–128.9 (m), 128.6, 114.2, 80.3, 34.2, 21.3, 13.6. **^{19}F-NMR** (376 MHz, MeOD-d_4) δ -157.0 (d, *J* = 16.9 Hz, 2 F), -161.3 (t, *J* = 21.1 Hz, 1 F), -164.4 (dd, *J* = 21.1, 16.9 Hz, 2 F). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{13}F_5IO_3^+$ 498.9824, found 498.9831. Analytical data were in agreement with the literature.[11]

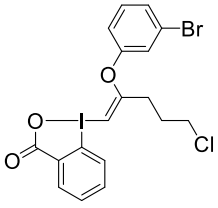
(*Z*)-1-(5-Chloro-2-(*p*-tolyloxy)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6g)



Following **GP V** on 0.57 mmol scale and using *p*-cresol (74.5 mg, 690 µmol, 1.2 equiv.), the VBX species (**6g**, 64.0 mg, 140 µmol, 24%) was obtained as a white solid. Purification via recrystallization in ethanol (5.0 ml).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46–8.36 (m, 1 H, Ar*H*), 7.68–7.54 (m, 3 H, Ar*H*), 7.11 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.80 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.00 (s, 1 H, C=C*H*), 3.56 (t, *J* = 6.1 Hz, 2 H, C*H*$_2$Cl), 2.77–2.61 (m, 2 H, CH=CC*H*$_2$), 2.30 (s, 3 H, ArC*H*$_3$), 2.02 (dq, *J* = 9.7, 6.5 Hz, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 168.5, 166.8, 151.5, 135.3, 133.8, 133.4, 133.1, 130.8, 130.8, 125.4, 119.0, 114.2, 82.1, 43.5, 29.8, 29.5, 20.9. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}ClIO_3^+$ 457.0062, found 457.0069. Analytical data were in agreement with the literature.[11]

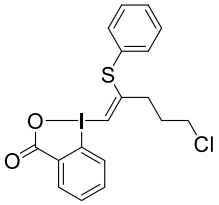
(*Z*)-1-(2-(3-Bromophenoxy)-5-chloropent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6h)



Following **GP V** on 0.57 mmol scale and using 3-bromophenol (119 mg, 690 µmol, 1.2 equiv.), the VBX species (**6h**, 88.0 mg, 170 µmol, 29%) was obtained as a white solid. Purification via recrystallization in ethanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43–8.37 (m, 1 H, Ar*H*), 7.62 (td, *J* = 5.9, 3.9 Hz, 3 H, Ar*H*), 7.26 (ddd, *J* = 7.9, 1.7, 0.9 Hz, 1 H, Ar*H*), 7.17 (t, *J* = 8.1 Hz, 1 H, Ar*H*), 7.08 (t, *J* = 2.1 Hz, 1 H, Ar*H*), 6.89 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1 H, Ar*H*), 6.22 (s, 1 H, C=C*H*), 3.59 (t, *J* = 6.1 Hz, 2 H, C*H*$_2$Cl), 2.77 (t, *J* = 7.4 Hz, 2 H, CH=CC*H*$_2$), 2.11–1.96 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.02, 167.98, 154.5, 133.8, 133.6, 133.0, 131.4, 130.8, 128.4, 125.7, 123.4, 122.1, 117.5, 114.5, 86.0, 43.5, 29.7, 29.4. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}BrClIO_3^+$ 520.9011, found 520.9016. Analytical data were in agreement with the literature.[11]

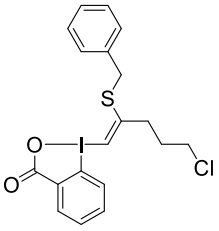
(*Z*)-1-(5-Chloro-2-(phenylthio)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6i)



Following **GP V** on 0.46 mmol scale and using thiophenol (56.2 µL, 60.7 mg, 550 µmol, 1.2 equiv.), the VBX species (**6i**, 94.0 mg, 200 µmol, 45%) was obtained as a white solid. Purification via recrystallization in acetonitrile (7.0 mL).

^{1}H-NMR (400 MHz, MeOD-d$_4$) δ 8.31 (dt, *J* = 6.8, 1.4 Hz, 1 H, Ar*H*), 7.80–7.70 (m, 3H, Ar*H*), 7.49 (dd, *J* = 7.6, 2.0 Hz, 2 H, Ar*H*), 7.47–7.39 (m, 3 H, Ar*H*), 7.06 (s, 1 H, C=C*H*), 3.54 (t, *J* = 6.3 Hz, 2 H, C*H*$_2$Cl), 2.78–2.67 (m, 2 H, CH=CC*H*$_2$), 2.09–1.99 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, MeOD-d$_4$) δ 170.1, 164.0, 135.5, 135.3, 134.7, 133.7, 131.9, 131.1, 130.9, 128.6, 114.5, 100.5, 44.4, 35.5, 32.6. **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}ClIO_2S^+$ 458.9677, found 458.9684. Analytical data were in agreement with the literature.[12]

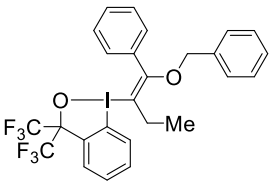
(*Z*)-1-(2-(Benzylthio)-5-chloropent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6j)



Following **GP V** on 0.57 mmol scale and using benzylthiol (67.4 µL, 71.3 mg, 570 µmol, 1.0 equiv.), the VBX species (**6j**, 100 mg, 210 µmol, 37%) was obtained as a white solid. Purification via recrystallization in acetonitrile (6.0 mL).

^{1}H-NMR (400 MHz, MeOD-d$_4$) δ 8.26 (dd, *J* = 7.5, 1.7 Hz, 1 H, Ar*H*), 7.67 (td, *J* = 7.4, 1.0 Hz, 1 H, Ar*H*), 7.58 (ddd, *J* = 8.9, 7.2, 1.8 Hz, 1 H, Ar*H*), 7.38 (dd, *J* = 8.2, 1.0 Hz, 1 H, Ar*H*), 7.32–7.13 (m, 5 H, Ar*H*), 6.94 (s, 1 H, C=C*H*), 4.15 (s, 2 H, SC*H*$_2$), 3.71 (t, *J* = 6.2 Hz, 2 H, C*H*$_2$Cl), 3.02 (td, *J* = 7.3, 1.0 Hz, 2 H, CH=CC*H*$_2$), 2.27–2.12 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, MeOD-d$_4$) δ 170.1, 163.4, 138.2, 135.2, 133.5, 131.6, 129.9, 129.8, 129.4, 128.7, 128.5, 114.4, 102.5, 44.7, 37.6, 35.4, 32.9. **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{18}ClINaO_2S^+$ 494.9653, found 494.9664. Analytical data were in agreement with the literature.[12]

(*E*)-1-(1-(benzyloxy)-1-phenylbut-1-en-2-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (6k)

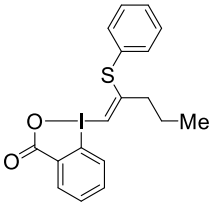


Following a reported procedure[14], but-1-ynylbenzene (54.5 µL, 50.0 mg, 380 µmol, 1.0 equiv.) and benzylalcohol (200 µL, 208 mg, 1.92 mmol, 5.0 equiv.) were dissolved in acetonitrile (2.0 mL). [3,3-Bis(trifluoromethyl)-1λ^3-2-benziodoxol-1-yl] trifluoromethanesulfonate (398 mg, 770 µmol, 2.0 equiv.) was added and the reaction was stirred at room temperature for 24 h before being treated with a sat. Na$_2$CO$_3$ solution (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted two more times with EtOAc (2x 10 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 2:1) to give the desired product **6k** (128 mg, 210 µmol, 55%) as colorless oil.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.83–7.76 (m, 1 H, Ar*H*), 7.59–7.53 (m, 1 H, Ar*H*), 7.44 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1 H, Ar*H*), 7.41–7.35 (m, 4 H, Ar*H*), 7.33–7.28 (m, 2 H, Ar*H*), 7.26–7.19 (m, 3 H, Ar*H*), 7.11–7.07 (m, 2 H, Ar*H*), 4.70 (s, 2 H, C*H*$_2$O), 2.78 (bs, 2 H, C*H*$_2$), 1.10 (*t*, J = 7.4 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, CDCl$_3$) δ 163.8, 136.7, 134.1, 132.0, 131.9, 130.4 (two signals overlapped), 130.2, 129.2, 128.8, 128.74, 128.68, 128.6, 126.9, 124.2 (q, *J* = 292.0 Hz), 111.5, 110.9, 81.5–81.0 (m), 72.5, 26.9, 14.5. **^{19}F-NMR** (376 MHz, CDCl$_3$) δ -76.2. **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{26}H_{22}F_6IO_2^+$ 607.0563, found 607.0546. Analytical data were in agreement with the literature.[14]

[14] W. Ding, J. Chai, C. Wang, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2020**, *142*, 8619.

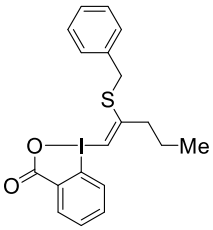
(*Z*)-1-(2-(Phenylthio)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6l)



Following **GP V** on 1.91 mmol scale and using thiophenol (234 µL, 253 mg, 2.29 mmol, 1.2 equiv.), the VBX species (**6l**, 602 mg, 1.42 mmol, 74%) was obtained as a white solid. Purification via recrystallization in acetontrile.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 6.7, 2.3 Hz, 1 H, Ar*H*), 7.69–7.60 (m, 2 H, Ar*H*), 7.50 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar*H*), 7.44–7.34 (m, 5 H, Ar*H*), 6.64 (d, *J* = 1.0 Hz, 1 H, C=C*H*), 2.43 (t, *J* = 7.5 Hz, 2 H, CH=CCH_2), 1.61 (h, *J* = 7.4 Hz, 2 H, $CCH_2CH_2CH_3$), 0.90 (t, *J* = 7.3 Hz, 3 H, $CCH_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.7, 163.9, 134.2, 134.0, 133.5, 133.4, 131.0, 130.0, 129.8, 125.3, 114.2, 98.8, 39.9, 22.3, 13.5. **IR**: *v* 2979 (s), 2896 (s), 1608 (s), 1556 (m), 1476 (m), 1439 (m), 1397 (m), 1382 (m), 1343 (m), 1251 (m), 1058 (s), 1029 (s), 892 (w), 828 (w), 759 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{18}IO_2S^+$ 425.0067, found 425.0077.

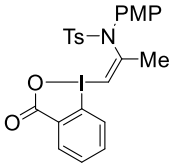
(*Z*)-1-(2-(Benzylthio)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6m)



Following **GP V** on 1.91 mmol scale and using benzylthiol (269 µL, 285 mg, 2.29 mmol, 1.2 equiv.), the VBX species (**6m**, 547 mg, 1.25 mmol, 65%) was obtained as a white solid. Purification via recrystallization in acetontrile.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar*H*), 7.62 (t, *J* = 7.3 Hz, 1 H, Ar*H*), 7.51 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1 H, Ar*H*), 7.33–7.20 (m, 6 H, Ar*H*), 6.61 (s, 1 H, C=C*H*), 4.04 (s, 2 H, SCH_2), 2.70 (t, *J* = 7.5 Hz, 2 H, CH=CCH_2), 1.77 (h, *J* = 7.4 Hz, 2 H, $CCH_2CH_2CH_3$), 1.08 (t, *J* = 7.3 Hz, 3 H, $CCH_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.7, 161.9, 136.0, 133.9, 133.3, 133.2, 130.7, 129.1, 128.8, 128.1, 125.4, 114.0, 102.3, 40.0, 37.3, 22.2, 13.7. **IR**: *v* 2988 (s), 2899 (s), 1605 (m), 1406 (m), 1393 (m), 1379 (m), 1249 (m), 1058 (s), 892 (w), 875 (w), 741 (w).**HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{20}IO_2S^+$ 439.0223, found 439.0228.

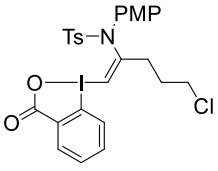
(*Z*)-*N*-(4-Methoxyphenyl)-4-methyl-*N*-(1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)benzenesulfonamide (6o)



Following **GP V** on 0.87 mmol scale and using *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (291 mg, 1.05 mmol, 1.2 equiv.), the VBX species (**6o**, 135 mg, 240 µmol, 27%) was obtained as a white solid. Purification via MPLC (t_R = 16.8–19.3 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.58 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.56 (td, *J* = 7.3, 1.2 Hz, 1 H, Ar*H*), 7.50 (td, *J* = 7.6, 7.2, 1.9 Hz, 1 H, Ar*H*), 7.34 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.31–7.26 (m, 2 H, Ar*H*), 6.95 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 1.3 Hz, 1 H, C=C*H*), 6.73 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 3.72 (s, 3 H, ArOCH_3), 2.42 (s, 3 H, ArCH_3), 2.20 (d, *J* = 1.2 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.1, 160.1, 152.6, 145.3, 135.5, 133.9, 133.5, 132.8, 130.7, 130.4, 130.1, 129.9, 128.1, 126.2, 115.0, 114.7, 105.6, 55.6, 23.0, 21.8. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{23}INO_5S^+$ 564.0336, found 564.0346. Analytical data were in agreement with the literature.[13]

(*Z*)-*N*-(5-Chloro-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (6p)

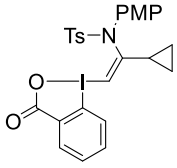


Following **GP V** on 1.15 mmol scale and using *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (318 mg, 1.15 mmol, 1.0 equiv.), the VBX species (**6p**, 216 mg, 350 µmol, 30%) was obtained as a white solid. Purification via MPLC (t_R = 22.5–27.1 min, gradient: 5–95% MeCN in 28 min). One aromatic carbon signal was not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.64 (td, *J* = 7.3, 1.1 Hz, 1 H, Ar*H*), 7.59–7.56 (m, 4 H, Ar*H*), 7.39 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.27 (d, *J* = 6.6 Hz, 2 H, Ar*H*), 7.03 (d, *J*

= 9.0 Hz, 1 H, Ar*H*), 6.86 (s, 1 H, C=C*H*), 6.77 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 3.76 (s, 3 H, OCH_3), 3.60 (t, *J* = 6.0 Hz, 2 H, CH_2Cl), 2.67–2.58 (m, 2 H, CH=CCH_2), 2.41 (s, 3 H, ArCH_3), 2.10–2.01 (m, 2 H, CH_2CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.2, 160.3, 155.0, 145.5, 136.3, 134.9, 133.7, 133.2, 131.0, 130.5, 130.1, 129.7, 128.4, 126.2, 115.2, 105.5, 55.7, 43.7, 33.4, 30.1, 21.8. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{26}ClINO_5S^+$ 626.0259, found 626.0271. Analytical data were in agreement with the literature.[13]

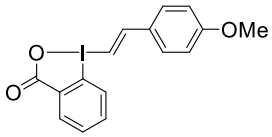
(*Z*)-*N*-(1-Cyclopropyl-2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)vinyl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (6q)



Following **GP V** on 0.80 mmol scale and using *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (267 mg, 960 µmol, 1.2 equiv.), the VBX species (**6q**, 273 mg, 460 µmol, 58%) was obtained as a white solid. Purification via recrystallization in acetontrile (16 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar*H*), 7.64–7.58 (m, 3 H, Ar*H*), 7.52 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1 H, Ar*H*), 7.28 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.17 (dd, *J* = 8.2, 0.9 Hz, 1 H, Ar*H*), 7.07 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.74 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.57 (d, *J* = 0.9 Hz, 1 H, C=C*H*), 3.75 (s, 3 H, COCH_3), 2.43 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.60–1.52 (m, 1 H, C*H*), 0.96–0.88 (m, 2 H, CH_2), 0.70 (dt, *J* = 6.9, 5.0 Hz, 2 H, CH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 167.0, 160.0, 159.1, 145.2, 135.6, 134.1, 133.4, 133.2, 130.8, 130.6, 130.6, 130.0, 128.4, 125.6, 115.0, 114.8, 101.9, 55.6, 21.8, 17.1, 10.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{25}INO_5S^+$ 590.0493, found 590.0508. Analytical data were in agreement with the literature.[13]

1-Methoxy-4-[(*E*)-3,3,3-trifluoroprop-1-enyl]benzene (6r)



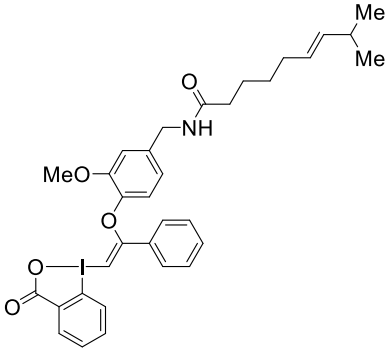
Following a reported procedure[15], 2-iodobenzoic acid (250 mg, 1.01 mmol, 1.0 equiv.) was dissolved in dry DCM (7.0 mL). The reaction solution was cooled down to 0 °C and treated with *m*CBPA (191 mg, 1.11 mmol, 1.1 equiv.) and TfOH (134 µL, 227 mg, 1.51 mmol, 1.5 equiv.). The reaction mixture was allowed to warm up to room temperature and stirred for 15 min before being cooled down again to 0 °C. [(E)-2-(4-methoxyphenyl)ethenyl]boronic acid (251 mg, 1.41 mmol, 1.4 equiv.) was added and the mixture was stirred for 1 h at room temperature before being treated with a sat. Na_2CO_3 solution (10 mL). The reaction mixture was stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted three more times with DCM (3x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was treated with Et_2O (50 mL) and stirred vigorously at rt for approx. 30 min. The solid was filtered off and washed with Et_2O to obtain 1-methoxy-4-[(*E*)-3,3,3-trifluoroprop-1-enyl]benzene (**6r**, 154 mg, 0.41 mmol, 40%) as beige solid.

^{1}H-NMR (400 MHz, MeOD-d_4) δ 8.28 (dd, *J* = 5.9, 3.3 Hz, 1 H, Ar*H*), 7.89 (d, *J* = 15.4 Hz, 1 H, HC=C*H*), 7.74 (dt, *J* = 7.3, 3.7 Hz, 1 H, Ar*H*), 7.71–7.62 (m, 4 H, Ar*H*), 7.45 (d, *J* = 15.3 Hz, 1 H, HC=C*H*), 7.03 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 3.87 (s, 3H, ArOCH_3). **HRMS** (APCI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{13}INaO_3^+$ 402.9802, found 402.9799. Analytical data were in agreement with the literature.[15]

[15] A. Boelke, L. D. Caspers, B. J. Nachtsheim, *Org. Lett.* **2017**, *19*, 5344.

2.3.4 VBX Reagents based on Special Scaffolds

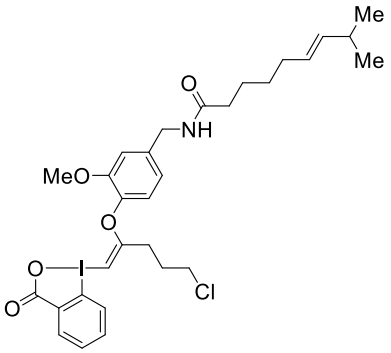
(*Z*)-1-(2-Phenylvinyl)-2-capsaicin-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7a)



Following **GP V** on 0.78 mmol scale and using capsaicin (263 mg, 860 µmol, 1.2 equiv.), the VBX species (**7a**, 182 mg, 280 µmol, 39%) was obtained as a white solid. Purification via MPLC (t_R = 20.7–22.6 min, gradient: 5–95% MeCN in 28 min). Mixture of rotamers was observed (ratio = 5:1, based on the methoxy signal). The NMR data is given for major rotamer. One carbonyl carbon signal was not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40–8.34 (m, 1 H, Ar*H*), 7.70–7.56 (m, 5 H, Ar*H*), 7.47–7.35 (m, 3 H, Ar*H*), 6.81 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 6.70 (d, *J* = 1.8 Hz, 1 H, Ar*H*), 6.60 (dd, *J* = 8.3, 1.8 Hz, 1 H, Ar*H*), 6.37 (s, 1 H, C=C*H*), 6.33 (bs, 1 H, N*H*), 5.39–5.25 (m, 2 H, *H*C=C*H*), 4.28 (d, *J* = 5.5 Hz, 2 H, ArCH_2NHCO), 3.67 (s, 3 H, OCH_3), 2.27–2.17 (m, 3 H, NHCOCH_2, C*H*$(CH_3)_2$), 1.97 (q, *J* = 6.8 Hz, 2 H, CH_2CH=CH), 1.63 (p, *J* = 7.6 Hz, 2 H, NHCOCH$_2$CH_2), 1.44–1.32 (m, 2 H, NHCOCH$_2$CH$_2$CH_2), 0.93 (d, *J* = 6.8 Hz, 5 H, CH_3), 0.87–0.82 (m, 1 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.5, 167.4, 150.3, 142.9, 138.1, 137.1, 133.6, 132.9, 132.3, 131.5, 130.9, 129.0, 127.9, 126.7, 126.2, 120.3, 120.2, 115.3, 112.4, 80.0, 55.9, 43.0, 36.6, 32.4, 31.1, 29.5, 25.5, 22.8. **IR**: *v* 3289 (m), 3060 (w), 2955 (m), 2930 (m), 2859 (w), 1739 (w), 1640 (s), 1607 (s), 1559 (m), 1509 (s), 1465 (m), 1437 (m), 1421 (m), 1347 (m), 1274 (m), 1208 (m), 1156 (m), 1130 (m), 1037 (m), 1024 (m), 1006 (w), 971 (w), 829 (m), 744 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{37}INO_5^+$ 654.1711, found 654.1722. For a detailed assignment of the NMR signals see table **S20** (chapter 5).

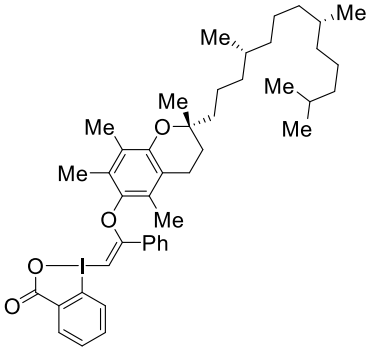
(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-capsaicin-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7b)



Following **GP V** on 0.43 mmol scale and using capsaicin (158 mg, 520 µmol, 1.2 equiv.), the VBX species (**7b**, 90.0 mg, 140 µmol, 32%) was obtained as a white solid. Purification via MPLC (t_R = 21.4–23.6 min, gradient: 5–95% MeCN in 28 min). Mixture of rotamers was observed (ratio = 3:1, based on the methoxy signal). NMR data is given for major rotamer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33–8.26 (m, 1 H, Ar*H*), 7.64–7.53 (m, 3 H, Ar*H*), 6.92 (bs, 1 H, N*H*), 6.84–6.71 (m, 3 H, Ar*H*), 5.70 (s, 1 H, C=C*H*), 5.38–5.23 (m, 2 H, *H*C=C*H*), 4.36 (d, *J* = 6.0 Hz, 2 H, ArCH_2NHCO), 3.60 (s, 3 H, OCH_3), 3.57 (t, *J* = 6.2 Hz, 2 H, CH_2Cl), 2.62 (t, *J* = 7.4 Hz, 2 H, C=CCH_2), 2.28 (t, *J* = 7.5 Hz, 2 H, NHCOCH_2), 2.23–2.14 (m, 1 H, C*H*$(CH_3)_2$), 2.04–1.99 (m, 2 H, CH_2CH=CH), 1.95 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_2$Cl), 1.70–1.59 (m, 2 H, NHCOCH$_2$CH_2), 1.41–1.32 (m, 2 H, NHCOCH$_2$CH$_2$CH_2), 0.92 (d, *J* = 6.8 Hz, 5 H, CH_3), 0.82 (dd, *J* = 6.6, 5.2 Hz, 1 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.7, 169.9, 167.0, 151.2, 140.5, 139.0, 138.0, 133.7, 133.2, 132.7, 130.7, 126.7, 125.9, 122.1, 120.4, 114.4, 112.2, 74.7, 55.8, 43.5, 42.9, 36.5, 32.4, 31.1, 30.5, 29.6, 29.4, 25.5, 22.8. **IR**: *v* 3075 (w), 2968 (m), 2928 (m), 2856 (w), 1603 (s), 1552 (m), 1507 (s), 1463 (m), 1440 (m), 1356 (m), 1280 (s), 1213 (m), 1156 (m), 1130 (m), 1029 (m), 1005 (w), 971 (w), 830 (m), 745 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{38}ClINO_5^+$ 654.1478, found 654.1494. For a detailed assignment of the NMR signals see table **S21** (chapter 5).

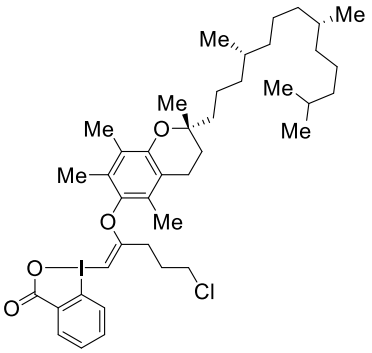
(*Z*)-1-(2-Phenylvinyl)-2-α-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7c)



Following **GP V** on 1.44 mmol scale and using tocopherol (742 mg, 1.72 mmol, 1.2 equiv.), the VBX species (**7c**, 1.05 g, 1.35 mmol, 94%) was obtained as a white solid. Purification via column chromatography (DCM/MeOH = 12:1). A mixture of rotamers was observed (ratio = 5:4, based on the aromatic methyl signal). The NMR data is given for major rotamer. Not all carbon signals were resolved in the ^{13}C-NMR.

TLC: R_f (DCM/MeOH = 9:1) = 0.53. **ORD**: $[\alpha]_D^{20}$ = -116.1 (c = 1.33, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.40 (ddd, *J* = 11.7, 5.9, 3.4 Hz, 1 H, Ar*H*), 7.74–7.68 (m, 1 H, Ar*H*), 7.68–7.54 (m, 4 H, Ar*H*), 7.51–7.37 (m, 3 H, Ar*H*), 5.95 (s, 1 H, C=C*H*), 2.45 (t, *J* = 7.5 Hz, 2 H, ArCH_2), 2.04 (s, 3 H, ArCH_3), 2.00 (s, 3 H, ArCH_3), 1.98 (s, 3 H, ArCH_3), 1.83-1.66 (m, 2 H, ArCH$_2$CH_2), 1.57–1.47 (m, 3 H, aliphatic tail), 1.46–0.99 (m, 21 H, aliphatic tail), 0.86 (s, 3 H, CH_3), 0.85 (s, 6 H, CH_3), 0.83 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 166.7, 165.5, 150.7, 142.7, 134.2, 133.9, 133.1, 132.9, 131.1, 130.6, 128.9, 127.4, 127.1, 126.2, 125.3, 125.2, 119.2, 115.2, 75.8, 70.0, 40.7, 40.0, 39.5, 37.6, 32.9, 31.1, 28.1, 24.9, 24.6, 22.8 (2 C), 21.0, 20.7, 19.9, 19.8, 13.3, 12.5, 12.0. **IR**: *v* 3059 (w), 2953 (m), 2925 (s), 2856 (m), 1742 (w), 1599 (s), 1552 (m), 1494 (w), 1461 (m), 1410 (m), 1375 (m), 1343 (m), 1294 (m), 1245 (s), 1162 (w), 1091 (s), 1022 (m), 1000 (w), 928 (w), 828 (m), 777 (m), 748 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{44}H_{60}IO_4^+$ 779.3531, found 779.3515. For a detailed assignment of the NMR signals see table **S22** (chapter 5).

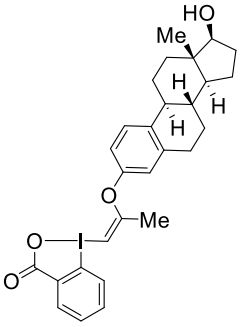
(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-α-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7d)



Following **GP V** on 0.57 mmol scale and using tocopherol (270 mg, 690 µmol, 1.2 equiv.), the VBX species (**7d**, 282 mg, 360 µmol, 63%) was obtained as a white solid. Purification via recrystallization in acetonitrile (17 mL). A mixture of rotamers was observed (ratio = 11:10, based on the aromatic methyl signal). The NMR data is given for major rotamer. Not all carbon signals were resolved in the ^{13}C-NMR.

ORD: $[\alpha]_D^{20}$ = +3.6 (c = 0.74, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.48–8.36 (m, 1 H, Ar*H*), 7.67–7.50 (m, 3 H, Ar*H*), 5.54 (d, *J* = 14.1 Hz, 1 H, C=C*H*), 3.57 (dt, *J* = 10.9, 5.8 Hz, 2 H, CH_2Cl), 2.57–2.48 (m, 3 H, CH=CCH_2, ArCH_2), 2.44 (t, *J* = 7.7 Hz, 1 H, ArCH_2), 2.16–1.99 (m, 2 H, CH_2CH$_2$Cl), 2.05 (d, *J* = 4.0 Hz, 3 H, ArCH_3), 1.97 (s, 3 H, ArCH_3), 1.93 (s, 3 H, ArCH_3), 1.84–1.73 (m, 2 H, ArCH$_2$CH_2), 1.59–1.47 (m, 3 H, aliphatic tail), 1.42–1.00 (m, 21 H, aliphatic tail), 0.87 (d, *J* = 3.3 Hz, 3 H), 0.85 (d, *J* = 3.0 Hz, 6 H), 0.83 (d, *J* = 1.9 Hz, 3 H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.8, 166.7, 150.2, 142.3, 134.1, 133.1, 130.7, 127.2, 125.7, 125.1, 124.4, 118.7, 114.1, 75.7, 71.9, 43.6, 40.9, 39.5, 37.6, 32.8, 31.1, 30.6, 29.8, 28.1, 24.9, 24.6, 22.9, 22.8, 21.2, 20.7, 19.9, 13.3, 12.4, 12.0. **IR**: *v* 2946 (m), 2918 (m), 2867 (m), 1596 (s), 1555 (m), 1463 (m), 1359 (m), 1299 (m), 1248 (m), 1147 (m), 1105 (m), 833 (w), 769 (m), 738 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{61}ClIO_4^+$ 779.3298, found 779.3307. For a detailed assignment of the NMR signals see table **S23** (chapter 5). Analytical data were in agreement with the literature.[13]

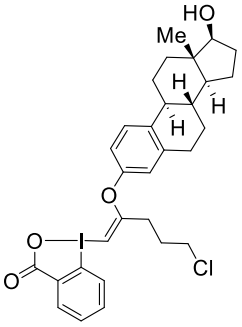
(*Z*)-1-(Prop-1-en-2-yl)-2-ß-estradiol-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7e)



Following **GP V** on 0.87 mmol scale and using ß-estradiol (238 mg, 870 µmol, 1.0 equiv.), the VBX species (**7e**, 200 mg, 360 µmol, 41%) was obtained as a white solid. Purification via MPLC (t_R = 21.8–24.0 min, gradient: 5–70% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +72.0 (c = 1.35, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.88 (dd, *J* = 8.1, 1.2 Hz, 1 H, Ar*H*), 7.78–7.73 (m, 1 H, Ar*H*), 7.70 (td, *J* = 7.3, 1.1 Hz, 1 H, Ar*H*), 7.26 (dd, *J* = 8.7, 1.0 Hz, 1 H, Ar*H*), 6.76 (dd, *J* = 8.5, 2.7 Hz, 1 H, Ar*H*), 6.70 (d, *J* = 2.6 Hz, 1 H, Ar*H*), 6.07 (d, *J* = 1.1 Hz, 1 H, C=C*H*), 3.65 (t, *J* = 8.6 Hz, 1 H, C*H*OH), 2.80–2.73 (m, 2 H, CH_2), 2.32–2.28 (m, 1 H, CH_2), 2.27 (d, *J* = 0.8 Hz, 3 H, HC=CCH_3), 2.20–2.11 (m, 1 H, C*H*), 2.08–1.99 (m, 1 H, CH_2), 1.95 (dt, *J* = 12.6, 3.5 Hz, 1 H, CH_2), 1.89–1.82 (m, 1 H, CH_2), 1.73–1.63 (m, 1 H, CH_2), 1.56–1.22 (m, 5 H, CH_2, C*H*), 1.21–1.13 (m, 1 H, C*H*), 0.76 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.1, 169.4, 152.8, 140.2, 139.4, 135.1, 134.7, 133.4, 131.7, 128.4, 128.0, 121.6, 118.8, 114.2, 82.4, 76.3, 51.3, 45.4, 44.3, 40.0, 37.9, 30.7, 30.5, 28.1, 27.4, 24.0, 19.2, 11.6. **IR**: *v* 2944 (m), 2860 (m), 1721 (m), 1599 (s), 1584 (m), 1555 (m), 1492 (m), 1454 (m), 1435 (m), 1350 (m), 1273 (s), 1264 (s), 1227 (m), 1181 (m), 1152 (m), 1133 (s), 1065 (w), 1008 (m), 965 (m), 953 (m), 817 (m), 748 (m), 738 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{32}IO_4^+$ 559.1340, found 559.1356. For a detailed assignment of the NMR signals see table **S24** (chapter 5).

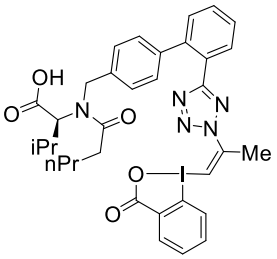
(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-ß-estradiol-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7f)



Following **GP V** on 0.87 mmol scale and using ß-estradiol (238 mg, 870 µmol, 1.0 equiv.), the VBX species (**7f**, 361 mg, 580 µmol, 67%) was obtained as a white solid. Purification via recrystallization in acetonitrile (15 mL).

ORD: $[\alpha]_D^{20}$ = +68.8 (c = 1.30, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 8.26 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.86 (dd, *J* = 8.1, 1.2 Hz, 1 H, Ar*H*), 7.76 (td, *J* = 8.1, 1.9 Hz, 1 H, Ar*H*), 7.70 (td, *J* = 7.3, 1.2 Hz, 1 H, Ar*H*), 7.25 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 6.78 (dd, *J* = 8.5, 2.7 Hz, 1 H, Ar*H*), 6.70 (d, *J* = 2.7 Hz, 1 H, Ar*H*), 6.29 (s, 1 H, C=C*H*), 3.69–3.56 (m, 3 H, CH_2Cl, C*H*OH), 2.85–2.77 (m, 2 H, CH_2), 2.72 (d, *J* = 7.1 Hz, 2 H, CH_2), 2.29 (dd, *J* = 13.6, 3.7 Hz, 1 H, CH_2), 2.16 (dt, *J* = 11.0, 4.0 Hz, 1 H, C*H*), 2.12–1.99 (m, 3 H, CH_2CH$_2$Cl, CH_2), 1.95 (dt, *J* = 12.6, 3.6 Hz, 1 H, CH_2), 1.88–1.81 (m, 1 H, CH_2), 1.73–1.63 (m, 1 H, CH_2), 1.56–1.22 (m, 7 H, CH_2, C*H*), 1.18 (t, *J* = 7.0 Hz, 1 H, C*H*), 0.76 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 170.9, 170.1, 152.8, 140.3, 139.1, 135.1, 134.6, 133.4, 131.8, 128.5, 128.1, 120.7, 118.0, 114.6, 82.4, 80.1, 58.3, 51.3, 45.4, 44.5, 40.0, 37.9, 30.9, 30.9, 30.7, 30.4, 28.1, 27.4, 24.0, 11.6. **IR**: *v* 2966 (m), 2936 (m), 2860 (m), 2842 (m), 1636 (m), 1607 (m), 1491 (w), 1458 (w), 1346 (w), 1134 (w), 1056 (s), 1044 (m), 1008 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{35}ClIO_4^+$ 621.1263, found 621.1270. For a detailed assignment of the NMR signals see table **S25** (chapter 5).

(*Z*)-1-(Prop-1-en-2-yl)-2-valsartan-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7g)

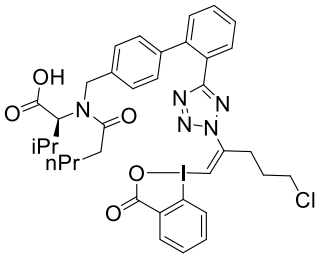


Following **GP V** on 1.44 mmol scale and using valsartan (457 mg, 1.05 mmol, 1.2 equiv.), the VBX species (**7g**, 285 mg, 400 µmol, 45%) was obtained as a white solid. Purification via MPLC (t_R = 19.6–22.0 min, gradient: 5–95% MeCN in 28 min). A mixture of rotamers was observed (ratio = 2:1, based on the CH_2 group in α position to the amide). NMR data is given for major rotamer.

ORD: $[\alpha]_D^{20}$ = +98.1 (c = 0.64, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 8.25 (td, *J* = 7.2, 1.9 Hz, 1 H, Ar*H*), 7.96–7.87 (m, 2 H, Ar*H*), 7.79–7.68 (m, 2 H, Ar*H*), 7.67–7.60 (m, 1 H, Ar*H*), 7.59–7.47 (m, 2 H, Ar*H*), 7.27–7.06 (m, 5 H, Ar*H,* C=C*H*), 4.61–4.41 (m, 2 H, ArCH_2N), 4.35–4.03 (m, 1 H, NC*H*CO$_2$H), 2.82 (d, *J* = 1.2 Hz, 3 H, HC=CCH_3), 2.32–2.18 (m, 1 H, NCOCH_2), 2.17–2.06 (m, 2 H, NCOCH_2, C*H*(CH$_3$)$_2$), 1.57–1.48 (m, 1 H, NCOCH$_2$CH_2), 1.48–1.36 (m,

1 H, NCOCH$_2$CH_2), 1.34–1.25 (m, 1 H, NCOCH$_2$CH$_2$CH_2), 1.16 (h, *J* = 7.5 Hz, 1 H, NCOCH$_2$CH$_2$CH_2), 1.04–0.88 (m, 5 H, CH_3), 0.81–0.75 (m, 4 H, CH_3). **^{13}C-NMR** (101 MHz, MeOD-d$_4$) δ 177.0, 173.4, 170.2, 165.9, 143.8, 141.0, 140.1, 138.1, 135.6, 134.5, 133.3, 132.3, 132.0, 131.7, 131.5 130.4, 129.9, 129.1, 128.5, 125.7, 116.6, 92.6, 64.8, 50.5, 34.5, 29.0, 28.5, 23.4, 20.9, 20.6, 14.2. **IR**: *v* 3707 (m), 3656 (m), 2973 (s), 2936 (s), 2863 (m), 2845 (m), 1635 (w), 1472 (w), 1455 (w), 1346 (w), 1321 (w), 1213 (w), 1123 (w), 1054 (s), 1033 (s), 1014 (s). **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{34}H_{36}IN_5NaO_5^+$ 744.1653, found 744.1664; [M-H]$^-$ calcd for $C_{34}H_{35}IN_5O_5^-$ 720.1688, found 720.1688. For a detailed assignment of the NMR signals see table **S26** (chapter 5).

(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-valsartan-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7h)



Following **GP V** on 0.57 mmol scale and using valsartan (300 mg, 690 µmol, 1.2 equiv.), the VBX species (**7h**, 321 mg, 410 µmol, 71%) was obtained as a white solid. Purification via MPLC (t_R = 21.8–25.2 min, gradient: 5–95% MeCN in 28 min). A mixture of rotamers was observed observed (ratio = 2:1, based on the CH$_2$ group in α position to the amide). The NMR data is given for major rotamer.

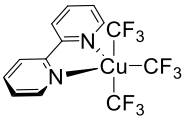
ORD: $[\alpha]_D^{20}$ = +227.8 (c = 0.38, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d$_4$) δ 8.23 (ddd, *J* = 7.4, 5.5, 1.8 Hz, 1 H, Ar*H*), 7.96–7.87 (m, 1 H, Ar*H*), 7.89–7.84 (m, 1 H, Ar*H*), 7.76 (td, *J* = 7.7, 1.8 Hz, 1 H, Ar*H*), 7.71–7.66 (m, 1 H, Ar*H*), 7.62 (dtd, *J* = 9.3, 7.5, 1.4 Hz, 1 H, Ar*H*), 7.57–7.51 (m, 1 H, Ar*H*), 7.47 (ddd, *J* = 10.4, 7.6, 1.3 Hz, 1 H, Ar*H*), 7.33 (d, *J* = 6.1 Hz, 1 H, C=C*H*), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.19–7.12 (m, 2 H, Ar*H*), 7.05 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 4.62–4.49 (m, 1 H, ArCH_2N), 4.48–4.31 (m, 2 H, ArCH_2N, NC*H*COOH), 3.70 (t, *J* = 6.2 Hz, 2 H, CH_2Cl), 3.37–3.32 (m, 2 H, C=CCH_2), 2.60–2.37 (m, 1 H, NCOCH_2), 2.31–2.06 (m, 4 H, NCOCH_2, CH_2CH$_2$Cl, C*H*(CH$_3$)$_2$), 1.54 (dtd, *J* = 8.4, 6.5, 4.4 Hz, 1 H, NCOCH$_2$CH_2), 1.49–1.38 (m, 1 H, NCOCH$_2$CH_2), 1.32 (h, *J* = 7.5 Hz, 1 H, NCOCH$_2$CH$_2$CH_2), 1.16 (h, *J* = 7.4 Hz, 1 H, NCOCH$_2$CH$_2$CH_2), 1.00–0.73 (m, 9 H, CH_3). **^{13}C-NMR** (101 MHz, MeOD-d$_4$) δ 176.9, 173.4, 170.2, 165.9, 146.5, 143.2, 140.9, 138.1, 135.6, 135.5, 134.4, 133.3, 132.3, 132.0, 131.7, 130.4, 129.9, 129.1, 128.4, 125.7, 116.7, 94.8, 64.9, 50.6, 44.6, 34.5, 33.1, 31.3, 29.1, 28.5, 23.4, 20.6, 14.2. **IR**: *v* 2963 (m), 2873 (m), 1721 (m), 1638 (m), 1605 (m), 1555 (m), 1471 (m), 1425 (m), 1375 (m), 1266 (m), 1202 (m), 1058 (m), 1011 (m), 831 (w), 734 (s). **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{36}H_{39}ClIN_5NaO_5^+$ 806.1577; Found 806.1586. For a detailed assignment of the NMR signals see table **S27** (chapter 5). Analytical data were in agreement with the literature.[13]

2.4 Preparation of Copper Species

$CuCF_3$

Following a reported procedure[16], to a solution of silver(I) fluoride (250 mg, 1.97 mmol, 1.0 equiv.) in DMF (14.0 mL, 0.14 M) was slowly added trimethyl(trifluormethyl)silane (378 µL, 364 mg, 2.56 mmol, 1.3 equiv.) or triethyl(trifluoromethyl)silane (481 µL, 472 mg, 2.56 mmol, 1.3 equiv.). The mixture was stirred for 20 min at room temperature and copper powder (200 mg, 3.15 mmol, 1.6 equiv.) was added. After further 4 h of stirring ^{19}F-NMR showed that the formation of $CuCF_3$ was complete. The synthesized $CuCF_3$ (0.14 M in DMF) was used directly for the trifluoromethylation. Reaction with $TMSCF_3$ leads to green solution, whereas reaction with $TESCF_3$ leads to blue solution.

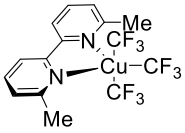
$(bpy)Cu(CF_3)_3$ (I)



Following a reported procedure[17], copper(I) iodide (2.00 g, 10.5 mmol, 1.0 equiv.), 2,2'-bipyridine (1.62 g, 10.5 mmol, 1.0 equiv.) and silver(I) fluoride (5.33 g, 42.0 mmol, 4.0 equiv.) were added to an oven-dried 50 mL flask in the glove box. Outside the glove box, dry DMF (28.0 mL, 0.38 M) was added and the flask was wrapped with alumina foil. After 30 min of stirring at room temperature, $TMSCF_3$ (9.30 mL, 8.96 g, 63.0 mmol, 6.0 equiv.) was slowly added over 1 h using a syringe pump. The reaction solution was stirred for further 18 h at room temperature before being filtered through a pad of celite. After washing with acetone, the obtained filtrate was concentrated under reduced pressure. Methanol (100 mL) was added and the resulting residue was allowed to crystallize overnight in the freezer at -20 °C. The yellow solid was filtered off and dried under vacuum. $(bpy)Cu(CF_3)_3$ (**I**, 2.34 g, 5.48 mmol, 52%) was obtained as yellow solid. CF_3 groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.23 (dt, *J* = 5.1, 1.2 Hz, 2 H, Ar*H*), 8.80 (dd, *J* = 8.1, 1.1 Hz, 2 H, Ar*H*), 8.38 (td, *J* = 7.9, 1.6 Hz, 2 H, Ar*H*), 7.92 (ddd, *J* = 7.6, 5.2, 1.2 Hz, 2 H, Ar*H*). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 149.2, 148.9, 141.0, 127.2, 123.3. **^{19}F-NMR** (376 MHz, DMSO-d_6) δ = -24.0 (h, *J* = 9.1 Hz, 3 F), -36.1 (q, *J* = 9.3 Hz, 6 F). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_8CuF_9N_2Na^+$ 448.9732, found 448.9733. Analytical data were in agreement with the literature.[17,18]

$(Me_2bpy)Cu(CF_3)_3$ (II)

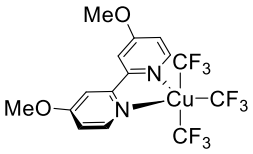


Synthesized similarly to $(bpy)Cu(CF_3)_3$ on 4.20 mmol scale using 2-methyl-6-(6-methylpyridin-2-yl)pyridine (774 mg, 4.20 mmol, 1.0 equiv.). Purification by column chromatography (acetone) gave $(Me_2bpy)Cu(CF_3)_3$ (**II**, 1.02 g, 2.23 mmol, 53%) as a yellow solid. CF_3 groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.60 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 8.24 (t, *J* = 7.9 Hz, 2 H, Ar*H*), 7.82 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 3.06 (s, 6 H, ArC*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 158.1, 148.9, 141.1, 127.2, 120.7, 23.7. **^{19}F-NMR** (376 MHz, DMSO-d_6) δ = -26.0 (h, *J* = 9.4 Hz, 3 F), -33.3 (q, *J* = 9.5 Hz, 6 F). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{13}CuF_9N_2^+$ 455.0226, found 455.0228; $[M-H]^-$ calcd for $C_{15}H_{11}CuF_9N_2^-$ 453.0080; Found 453.0075.

[16] Y. Xia, T. Guo, K. K. Baldrige, J. S. Siegel, *Eur. J. Org. Chem.* **2017**, 875.
[17] M. Paeth, W. Carson, J.-H. Luo, D. Tierney, Z. Cao, M.-J. Cheng, W. Liu, *Chem. Eur. J.* **2018**, *24*, 11559.
[18] S.-L. Zhang, W.-F. Bie, *RSC Adv.* **2016**, *6*, 70902.

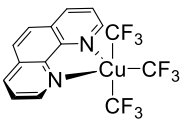
[(MeO)$_2$bpy]Cu(CF$_3$)$_3$ (III)



Synthesized similarly to (bpy)Cu(CF$_3$)$_3$ on 4.20 mmol scale using 4-methoxy-2-(4-methoxypyridin-2-yl)pyridine (908 mg, 4.20 mmol, 1.0 equiv.). Purification by column chromatography (acetone) gave [(MeO)$_2$bpy]Cu(CF$_3$)$_3$ (**III**, 872 mg, 1.79 mmol, 43%) as yellow solid. CF$_3$ groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.96 (d, *J* = 6,1 Hz, 2 H, Ar*H*), 8.35 (d, *J* = 2.5 Hz, 2 H, Ar*H*), 7.44 (dd, *J* = 6.2, 2.5 Hz, 2 H, Ar*H*), 4.06 (s, 6 H, ArOC*H*$_3$). **^{13}C-NMR** (101 MHz, DMSO-d$_6$) δ 168.4, 151.1, 149.8, 112.6, 109.9, 56.8. **^{19}F-NMR** (376 MHz, DMSO-d$_6$) δ = -24.2 (h, *J* = 9.1 Hz, 3 F), -36.0 (q, *J* = 9.1 Hz, 6 F). **HRMS** (ESI/QTOF) *m/z*: [M+H]$^+$ calcd for $C_{15}H_{12}CuF_9N_2NaO_2^+$ 508.9943, found 508.9945.

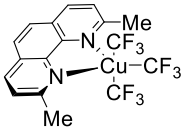
(phen)Cu(CF$_3$)$_3$ (IV)



Synthesized similarly to (bpy)Cu(CF$_3$)$_3$ on 7.88 mmol scale using 1,10-phenanthroline (1.42 g, 7.88 mmol, 1.0 equiv.). Purification by column chromatography (acetone) gave (phen)Cu(CF$_3$)$_3$ (**IV**, 2.02 g, 4.73 mmol, 60%) as anorange solid. CF$_3$ groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DCM-d$_2$) δ 9.43 (dd, *J* = 4.8, 1.5 Hz, 2 H, Ar*H*), 8.63 (dd, *J* = 8.3, 1.5 Hz, 2 H, Ar*H*), 8.06 (s, 2 H, Ar*H*), 8.02 (dd, *J* = 8.2, 4.8 Hz, 2 H, Ar*H*). **^{13}C-NMR** (101 MHz, DCM-d$_2$) δ 149.3, 141.9, 138.8, 129.7, 127.2, 125.3. **^{19}F-NMR** (376 MHz, DCM-d$_2$) δ = -24.5 (h, *J* = 9.6 Hz, 3 F), -37.4 (q, *J* = 9.6 Hz, 6 F). Analytical data were in agreement with the literature.[17,18] HRMS signal was not found with ESI+.

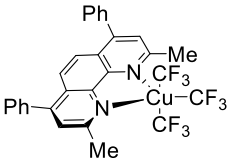
(Me$_2$phen)Cu(CF$_3$)$_3$ (V)



Synthesized similarly to (bpy)Cu(CF$_3$)$_3$ on 2.63 mmol scale using 2,9-dimethyl-1,10-phenanthroline/neocuproine (547 mg, 2.63 mmol, 1.0 equiv.). Purification by crystallization in methanol gave (Me$_2$phen)Cu(CF$_3$)$_3$ (**V**, 63.2 mg, 130 µmol, 5%) as a yellow solid. CF$_3$ groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DCM-d$_2$) δ 8.46 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.94 (s, 2 H, Ar*H*), 7.83 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 3.33 (s, 6 H, ArC*H*$_3$). **^{13}C-NMR** (101 MHz, DCM-d$_2$) δ 160.5, 141.4, 139.2, 128.1, 126.5, 126.4, 54.0, 25.5. **^{19}F-NMR** (376 MHz, DCM-d$_2$) δ -25.8 (h, *J* = 9.0 Hz, 3 F), -34.7 (q, *J* = 9.8 Hz, 6 F). HRMS signal was not found with ESI+.

(Me$_2$Ph$_2$phen)Cu(CF$_3$)$_3$ (VI)



Synthesized similarly to (bpy)Cu(CF$_3$)$_3$ on 1.31 mmol scale using 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (473 mg, 1.31 mmol, 1.0 equiv.). Purification by crystallization in methanol gave (Me$_2$Ph$_2$phen)Cu(CF$_3$)$_3$ (**VI**, 90.8 mg, 140 µmol, 11%) as yellow solid. CF$_3$ groups were not resolved in the ^{13}C-NMR.

^{1}H-NMR (400 MHz, DCM-d$_2$) δ 7.94 (s, 2 H, Ar*H*), 7.79 (s, 2 H, Ar*H*), 7.62–7.56 (m, 10 H, Ar*H*), 3.38 (s, 6 H, ArC*H*$_3$). **^{13}C-NMR** (101 MHz, DCM-d$_2$) δ 159.7, 152.0, 142.1, 136.8, 130.2, 129.9, 129.5, 126.8, 126.2, 124.3, 25.6. **^{19}F-NMR** (376 MHz, DCM-d$_2$) δ -25.8 (h, *J* = 9.8 Hz, 3 F), -34.4 (q, *J* = 9.7 Hz, 6 F). **HRMS** (ESI/QTOF) *m/z*: [M+Na]$^+$ calcd for $C_{29}H_{20}CuF_9N_2Na^+$ 653.0671, found 653.0666.

3 Trifluoromethylation

3.1 Small-Scale Screening and Optimization

General procedure for the trifluormethylation under thermal conditions (GP VI)

The thermal reactions were performed in Biotage® microwave reaction vials (size: 2.0-5.0 mL) using Carl Roth crimp caps ROTILABO® ND20 with borehole and Butyl/PTFE septum and 10 mm long stirring bars. The high-valent copper species (1.5 equiv.) and the vinylbenziodoxolone (1.0 equiv.) was balanced (outside glove box) into the reaction vial before being capped. The vial was evacuated (under 0.5 mbar) and flushed with nitrogen. This procedure was repeated three times before dry DMF (25 mM) was added under nitrogen atmosphere. The reaction vial was transferred to a preheated aluminium block (120 °C) and stirred for 1 h with 900 rpm. After 1 h, the reaction mixture was allowed to cool down to room temperature. Diethyl ether (twice the volume of DMF) was added and the organic layer was washed three times with 5% ammonia solution (removal of copper complexes). The combined organic layers were washed with brine, dried over sodium sulfate, filtrered and evaporated under reduced pressure. For qNMR analysis, the remaining residue was dissolved in deuterated chloroform and internal standard(s) was/were added (1,3-dinitrobenzene: δ_H = 9.08 ppm, trifluorotoluene: δ_F = -63.72 ppm). The substrates were integrated on the characteristic olefinic signal (quartet around 5.00-6.00 ppm) for ^{1}H-NMR and/or the CF_3 signal for ^{19}F-NMR (singlet around -50.0 - -60.0 ppm). For optimization both internal standards were used (mean value formation), whereas for the scope only ^{19}F-qNMR was used. For isolation, the remaining residue was purified by column chromatography (standard flash or MPLC) to give the desired product.

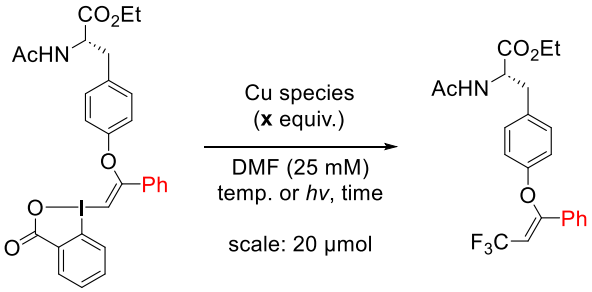
General procedure for the trifluormethylation under UV conditions (GP VII)

The light-mediated reactions were performed in KIMBLE® ASTM Type 1 test tubes (Borosilicate Glass, 12x75mm) using turn-over flange stoppers and 7 mm long stirring bars. The high-valent copper species (1.5 equiv.) and the vinylbenziodoxolone (1.0 equiv.) was balanced into the test tube before being closed and sealed with parafilm® tape. The test tube was evacuated (under 0.5 mbar) and flushed with nitrogen. This procedure was repeated three times before dry DMF (25 mM) was added under nitrogen atmosphere. The test tube was transferred to a Rayonet® Photochemical Reactor with 16 lamps (365 nm) and fan (operating temperature approximately 35 °C) and stirred for 18 h. The workup was performed in the same way as for the approach under thermal conditions.

In general, the reaction was performed on different scales:

- Optimization with the vinylbenziodoxolones **5a** and **6b**: 20 µmol
- Scope: 80–100 µmol
- Ligand analysis for visible light transformation: 10 µmol
- Upscaling experiments: 1.0 mmol

Table S1. Detailed optimization of trifluoromethylation using ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate (**5a**).[a]



5a **8a**

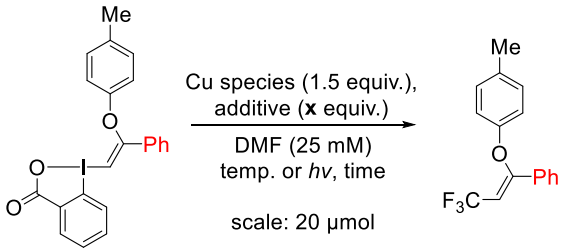
Detailed optimization of trifluoromethylation using ethyl

Entry	Cu species	x	solvent	concentration [mM]	temperature or irradiation	time	NMR yield
1	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	120 °C	1 h	84±3%
2	(bpy)Cu(CF_3)$_3$	1.0	DMF	25	120 °C	1 h	43±1%
3	(bpy)Cu(CF_3)$_3$	3.0	DMF	25	120 °C	1 h	70±2%
4	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	60 °C	1 h	1±2%
5	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	90 °C	1 h	78±3%
6	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	100 °C	1 h	75±1%
7	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	110 °C	1 h	74±4%
8	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	130 °C	1 h	84±3%
9	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	120 °C	0.5 h	73±2%
10	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	120 °C	2 h	75±4%
11	(bpy)Cu(CF_3)$_3$	1.5	DMF	100	120 °C	1 h	82±1%
12	(bpy)Cu(CF_3)$_3$	1.5	DMF	50	120 °C	1 h	78±1%
13	(bpy)Cu(CF_3)$_3$	1.5	DMF	10	120 °C	1 h	75±2%
14	(bpy)Cu(CF_3)$_3$	1.5	DMA	25	120 °C	1 h	74±2%
15	(bpy)Cu(CF_3)$_3$	1.5	NMP	25	120 °C	1 h	83±3%
16	(bpy)Cu(CF_3)$_3$	1.5	DMSO	25	120 °C	1 h	25±5%
17	(bpy)Cu(CF_3)$_3$	1.5	MeCN	25	120 °C	1 h	80±2%
18	(bpy)Cu(CF_3)$_3$	1.5	DMF	25	365 nm	18 h	66±4%
19	(phen)Cu(CF_3)$_3$	1.5	DMF	25	365 nm	18 h	75±2%
20	(phen)Cu(CF_3)$_3$	1.5	DMF	25	365 nm	1 h	0±0%
21	(phen)Cu(CF_3)$_3$	1.5	DMF	25	365 nm	2 h	0±0%
22	(phen)Cu(CF_3)$_3$	1.5	DMF	25	365 nm	4 h	0±0%

[a] Yield was determined by combined ^{1}H and ^{19}F qNMR. Error is obtained from standard deviation.

The usage of (PPh_3)$_3$CuCF$_3$ and trifluoromethylator™ ((phen)CuCF$_3$) under various conditions led to low formation (5-10%) of **8a**.

Table S2. Detailed optimization of trifluoromethylation using (*Z*)-1-(2-phenyl-2-(*p*-tolyloxy)vinyl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**6b**).[a]



6b **9b**

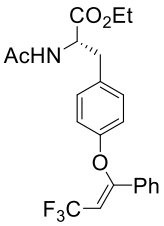
Entry	Cu species	additive	**x**	temperature or irradiation	time	NMR yield
1	(bpy)Cu(CF_3)$_3$	/	/	120 °C	1 h	47%
2	(bpy)Cu(CF_3)$_3$	/	/	120 °C	0.5 h	43%
3	(bpy)Cu(CF_3)$_3$	/	/	90 °C	1 h	34%
4	(bpy)Cu(CF_3)$_3$	Et_3SiH	1.5	120 °C	1 h	36%
5	(bpy)Cu(CF_3)$_3$	iPr_3SiH	1.5	120 °C	1 h	26%
6	(bpy)Cu(CF_3)$_3$	$tBuMe_2SiH$	1.5	120 °C	1 h	47%
7	(bpy)Cu(CF_3)$_3$	Hantzsch ester	1.5	120 °C	1 h	43%
5	(bpy)Cu(CF_3)$_3$	Hünigs base	1.5	120 °C	1 h	69%
6	(bpy)Cu(CF_3)$_3$	Hünigs base	1.5	120 °C	0.5 h	51%
7	(bpy)Cu(CF_3)$_3$	Hünigs base	3.0	120 °C	1 h	61%
8	(bpy)Cu(CF_3)$_3$	Hünigs base	0.5	120 °C	1 h	42%
9	(bpy)Cu(CF_3)$_3$	Hünigs base	1.5	365 nm	18 h	34%
10	(phen)Cu(CF_3)$_3$	Hünigs base	1.5	365 nm	18 h	21%
11	(phen)Cu(CF_3)$_3$	/	/	365 nm	18 h	67%

[a] Yield was determined by ^{19}F qNMR.

3.2 Scope

3.2.1 Trifluoromethylation of Single Amino Acid based VBX Reagents

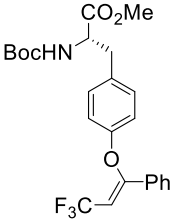
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8a)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **8a** (48.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8a** (27.0 mg, 64.0 µmol, 80%, NMR yield: 86%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8a** (24.2 mg, 57.4 µmol) in 72% yield (NMR yield: 83%). Purification via MPLC (t_R = 21.1–22.6 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +28.5 (c = 0.61, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.9, 1.7 Hz, 2 H, Ar*H*), 7.37–7.28 (m, 3 H, Ar*H*), 6.95 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.92 (d, *J* = 7.8 Hz, 1 H, N*H*), 5.82 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 4.76 (dt, *J* = 7.8, 6.1 Hz, 1 H, NHC*H*), 4.07 (qd, *J* = 7.1, 4.7 Hz, 2 H, O$C\mathit{H}_2CH_3$), 2.99 (dd, *J* = 6.0, 2.8 Hz, 2 H, NHCHCH_2), 1.94 (s, 3 H, COCH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\mathit{H}_3$).**^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.7, 158.9 (q, *J* = 5.7 Hz). 155.3, 132.8, 130.6, 130.53, 130.50, 128.9, 127.3, 123.0 (q, *J* = 269.6 Hz), 117.2, 105.3 (q, *J* = 34.9 Hz), 61.6, 53.2, 37.3, 23.2, 14.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 2935 (w), 1742 (w), 1660 (s), 1508 (m), 1447 (w), 1440 (m), 1408 (w), 1386 (m), 1343 (m), 1274 (m), 1258 (m), 1216 (m), 1137 (m), 1101 (m), 1063 (w), 1025 (w), 889 (w), 856 (w), 752 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{22}F_3NNaO_4^+$ 444.1393, found 444.1395. For a detailed assignment of the NMR signals see table **S28** (chapter 5).

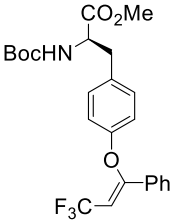
Methyl (*S*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*S*)-8b)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species (*S*)-**8b** (51.5 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound (*S*)-**8b** (24.0 mg, 51.5 µmol, 64%, NMR yield: 84%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound (*S*)-**8b** (29.7 mg, 63.8 µmol) in 80% yield (NMR yield: 90%). Purification via MPLC (t_R = 23.9–25.2 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = -17.9 (c = 2.72, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2 H, Ar*H*), 7.38–7.27 (m, 3 H, Ar*H*), 6.97 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.81 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 4.93 (d, *J* = 8.4 Hz, 1 H, N*H*), 4.50 (q, *J* = 6.9 Hz, 1 H, NHC*H*), 3.60 (s, 3 H, $CO_2C\mathit{H}_3$), 2.98 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHCHCH_2), 2.96–2.86 (m, 1 H, NHCHCH_2), 1.38 (s, 9 H, $(C\mathit{H}_3)_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.4, 158.9 (q, *J* = 5.5 Hz), 155.3, 155.1, 132.8, 130.6, 130.5, 128.9, 127.3, 123.0 (q, *J* = 269.9 Hz), 117.3, 105.3 (q, *J* = 34.7 Hz), 80.1, 54.5, 52.3, 37.8, 28.4. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 3375 (w), 2996 (w), 1742 (m), 1712 (s), 1667 (m), 1608 (w), 1509 (s), 1451 (m), 1366 (m), 1342 (s), 1267 (s), 1220 (s), 1169 (s), 1126 (s), 1056 (m), 1018 (m), 890 (m), 856 (m), 759 (w), 737 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{26}F_3NNaO_5^+$ 488.1655, found 488.1662. For a detailed assignment of the NMR signals see table **S29** (chapter 5).

Methyl (*R*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*R*)-8b)

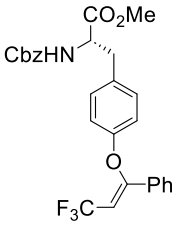


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species (*R*)-**8b** (51.5 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound (*R*)-**8b** (24.5 mg, 41.8 µmol, 52%, NMR yield: 73 %) was obtained as colorless oil. Purification via MPLC (t_R = 23.6–25.2 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +16.6 (c = 0.80, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.51–7.40 (m, 2 H, Ar*H*), 7.37–7.27 (m, 3 H, Ar*H*), 6.97 (d, J = 8.5 Hz, 2 H, Ar*H*), 6.84 (d, J = 8.6 Hz, 2 H, Ar*H*), 5.81 (q, J = 7.5 Hz, 1 H, C=C*H*CF_3), 4.93 (d, J = 8.4 Hz, 1 H, N*H*), 4.49 (q, J = 6.8 Hz, 1 H, NHC*H*), 3.60 (s, 3 H, $CO_2C\mathit{H}_3$), 2.98 (dd, J = 14.0, 6.0 Hz, 1 H, NHCHCH_2), 2.96–2.86 (m, 1 H,

NHCHCH_2), 1.38 (s, 9 H, (CH_3)$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.4, 158.9 (q, *J* = 5.6 Hz), 155.3, 155.1, 132.8, 130.6, 130.5, 128.9, 127.3, 123.0 (q, *J* = 269.8 Hz), 117.3, 105.3 (q, *J* = 35.1 Hz), 80.1, 54.5, 52.3, 37.8, 28.4. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 3371 (w), 2980 (m), 1743 (s), 1721 (s), 1653 (w), 1606 (w), 1509 (s), 1455 (m), 1393 (m), 1368 (m), 1344 (s), 1273 (s), 1217 (s), 1170 (s), 1130 (s), 1055 (m), 1022 (m), 891 (m), 856 (m), 773 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{26}F_3NNaO_5^+$ 488.1655, found 488.1663. For a detailed assignment of the NMR signals see table **S30** (chapter 5).

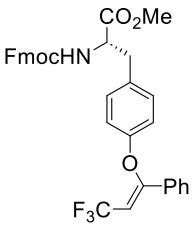
Methyl (*S*,*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8c)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5c** (54.2 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8c** (16.1 mg, 32.2 µmol, 40%, NMR yield: 46%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8c** (22.1 mg, 44.2 µmol) in 55% yield (NMR yield: 58%, 96% purity). Purification via MPLC (t_R = 22.2–23.2 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = -8.3 (c = 0.81, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.8, 1.7 Hz, 2 H, Ar*H*), 7.38–7.27 (m, 8H, Ar*H*), 6.94 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.82 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 5.16 (d, *J* = 8.3 Hz, 1 H, N*H*), 5.06 (s, 2 H, ArCH_2O), 4.57 (q, *J* = 6.2 Hz, 1 H, NHC*H*), 3.61 (s, 3 H, CO_2CH_3), 2.98 (d, *J* = 6.0 Hz, 2 H, NHCHCH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.0, 158.9 (q, *J* = 5.6 Hz), 155.7, 155.4, 136.3, 132.8, 130.6, 130.5, 130.3, 128.9, 128.7, 128.4, 128.3, 127.3, 123.0 (q, *J* = 269.7 Hz), 117.4, 105.3 (q, *J* = 35.0 Hz), 67.1, 54.9, 52.4, 37.6. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 2971 (s), 2889 (m), 1706 (m), 1667 (m), 1509 (m), 1447 (w), 1411 (m), 1379 (w), 1339 (m), 1272 (m), 1217 (m), 1130 (s), 1069 (s), 1058 (s), 1015 (m), 892 (w), 744 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{24}F_3NNaO_5^+$ 522.1499, found 522.1496.

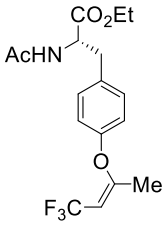
Methyl (*S*,*Z*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8d)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5d** (61.3 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8d** (26.8 mg, 45.6 µmol, 57%, NMR yield: 63%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8d** (33.5 mg, 57.0 µmol) in 71% yield (NMR yield: 73%, purity: 96%). Purification via MPLC (t_R = 24.5–25.5 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = -16.1 (c = 1.57, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.81–7.71 (m, 2 H, Ar*H*), 7.55 (t, *J* = 7.3 Hz, 2 H, Ar*H*), 7.46 (dd, *J* = 7.6, 2.0 Hz, 2 H, Ar*H*), 7.44–7.37 (m, 2 H, Ar*H*), 7.35–7.27 (m, 5 H, Ar*H*), 6.93 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.82 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 5.20 (d, *J* = 8.3 Hz, 1 H, N*H*), 4.57 (dt, *J* = 8.6, 6.0 Hz, 1 H, NHC*H*), 4.44–4.30 (m, 2 H, CH_2O), 4.18 (t, *J* = 7.0 Hz, 1 H, C*H*CH_2O), 3.62 (s, 3 H, CO_2CH_3), 2.99 (d, *J* = 6.0 Hz, 2 H, NHCHCH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.9, 158.9 (q, *J* = 5.6 Hz), 155.6, 155.4, 144.0, 143.8, 141.5, 132.7, 130.6, 130.5, 130.3, 128.9, 127.9, 127.3, 127.2, 125.2, 125.1, 123.0 (q, *J* = 269.8 Hz), 120.13, 120.11, 117.3, 105.3 (q, *J* = 35.1 Hz), 67.0, 54.9, 52.4, 47.3, 37.6. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.7. **IR**: *v* 2972 (s), 2903 (s), 1715 (w), 1703 (w), 1674 (w), 1505 (w), 1450 (w), 1407 (m), 1382 (m), 1346 (w), 1251 (m), 1227 (m), 1119 (m), 1112 (m), 1075 (s), 1058 (s), 1019 (m), 878 (w), 763 (w), 744 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{28}F_3NNaO_5^+$ 610.1812, found 610.1827. For a detailed assignment of the NMR signals see table **S31** (chapter 5).

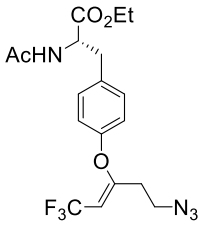
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((4,4,4-trifluorobut-2-en-2-yl)oxy)phenyl)propanoate (8e)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5e** (43.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8e** (16.3 mg, 45.1 µmol, 57% NMR yield: 62%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8e** (10.4 mg, 28.9 µmol) in 36% yield (NMR yield: 41%) . Purification via MPLC (t_R = 23.2–25.0 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = 14.7 (c = 0.64, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.97 (d, *J* = 7.7 Hz, 1 H, N*H*), 5.14 (qd, *J* = 7.5, 1.1 Hz, 1 H C=C*H*CF_3), 4.83 (dt, *J* = 7.8, 5.8 Hz, 1 H, NHC*H*), 4.16 (qd, *J* = 7.2, 1.9 Hz, 2 H, OCH_2CH_3), 3.15–3.04 (m, 2 H, NHCHCH_2), 1.99 (s, 3 H, COCH_3), 1.82 (dd, *J* = 2.1, 1.1 Hz, 3 H, HC=CCH_3), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.7, 159.3 (q, *J* = 5.8 Hz), 153.6, 132.1, 130.7, 122.9 (q, *J* = 269.3 Hz), 119.5, 102.6 (q, *J* = 34.6 Hz), 61.7, 53.3, 37.4, 23.3, 18.6, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 3678 (m), 3661 (m), 2986 (s), 2971 (s), 2899 (s), 1736 (w), 1682 (w), 1658 (w), 1508 (w), 1451 (w), 1406 (m), 1393 (m), 1386 (m), 1253 (m), 1241 (m), 1220 (m), 1079 (s), 1065 (s), 1048 (s), 1026 (s), 892 (w), 878 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{20}F_3NNaO_4^+$ 382.1237, found 382.1237. For a detailed assignment of the NMR signals see table **S32** (chapter 5).

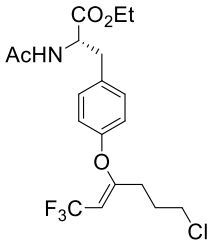
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-azido-1,1,1-trifluoropent-2-en-3-yl)oxy)phenyl)propanoate (8f)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5g** (47.4 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8f** (22.3 mg, 53.9 µmol, 67%, NMR yield: 70%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8f** (11.3 mg, 27.2 µmol) in 34% yield (NMR yield: 44%). Purification via MPLC (t_R = 20.2–21.8 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +78.3 (c = 0.15, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.97 (d, *J* = 7.7 Hz, 1 H, N*H*), 5.38 (q, *J* = 7.3 Hz, 1 H, C=C*H*CF_3), 4.83 (dt, *J* = 7.8, 5.8 Hz, 1 H, NHC*H*), 4.17 (qd, *J* = 7.2, 1.8 Hz, 2 H, OCH_2CH_3), 3.38 (t, *J* = 6.7 Hz, 2 H, CH_2N_3), 3.10 (dd, *J* = 14.2, 6.3 Hz, 1 H, NHCHCH_2), 3.09 (dd, *J* = 14.2, 5.6 Hz, 1 H, NHCHCH_2) 2.44 (t, *J* = 6.8 Hz, 2 H, $CH_2CH_2N_3$), 1.99 (s, 3 H, COCH_3), 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.6, 169.7, 158.5 (q, *J* = 5.6 Hz), 153.6, 132.1, 131.0, 122.4 (q, *J* = 270.0 Hz), 118.3, 106.4 (q, *J* = 34.9 Hz), 61.8, 53.3, 47.9, 37.3, 31.6, 23.3, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -58.2. **IR**: *v* 2106 (m), 1742 (m), 1685 (m), 1663 (m), 1541 (m), 1507 (s), 1436 (w), 1422 (w), 1375 (m), 1264 (s), 1209 (s), 1119 (s), 1095 (s), 1026 (w), 950 (w), 903 (w), 852 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{21}F_3N_4NaO_4^+$ 437.1407, found 437.1407. For a detailed assignment of the NMR signals see table **S33** (chapter 5).

Ethyl (*S*,*Z*)-2-acetamido-3-(4-((6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)phenyl)propanoate (8g)

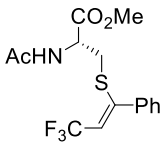


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5h** (48.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8g** (21.8 mg, 51.6 µmol, 65%, NMR yield: 77%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8g** (23.4 mg, 55.4 µmol) in 69% yield (NMR yield: 74%). Purification via MPLC (t_R = 24.0–26.2 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +122.8 (c = 0.09, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.96 (d, *J* = 7.5 Hz, 1 H, N*H*), 5.31 (q, *J* = 7.4 Hz, 1 H, C=C*H*CF_3), 4.83 (dt, *J* = 7.8, 5.8 Hz, 1 H, NHC*H*), 4.16 (qd, *J* = 7.2, 1.6 Hz, 2 H, OCH_2CH_3), 3.50 (t, *J* = 6.3 Hz, 2 H, CH_2Cl), 3.09 (t, *J* = 5.5 Hz, 2 H, NHCHCH_2), 2.39–2.30 (m, 2 H, CH=CCH_2), 1.99 (s, 3 H, COCH_3), 1.90 (p, *J* = 6.5 Hz, 2 H, CH_2CH_2Cl), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.7, 161.0 (q, *J* = 5.6 Hz), 153.7, 131.8, 130.8, 122.6 (q, *J* = 269.8 Hz), 118.5, 105.0

(q, *J* = 34.6 Hz), 61.8, 53.3, 43.5, 37.4, 29.1, 28.9, 23.3, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.9. **IR**: *v* 1743 (m), 1685 (s), 1669 (m), 1541 (m), 1507 (s), 1444 (m), 1375 (m), 1271 (m), 1216 (s), 1123 (s), 1094 (s), 1037 (w), 1018 (w), 946 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{23}ClF_3NNaO_4^+$ 444.1160, found 444.1164. For a detailed assignment of the NMR signals see table **S34** (chapter 5).

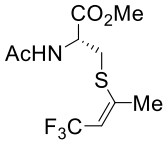
Methyl (*Z*)-*N*-acetyl-*S*-(3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinate (8h)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5i** (48.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8h** (10.0 mg, 28.7 µmol, 36%, NMR yield: 47%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8h** (13.8 mg, 39.7 µmol) in 50% yield (NMR yield: 50%). Purification via MPLC (t_R = 19.0–21.1 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +229.2 (c = 0.05, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47–7.40 (m, 5 H, Ar*H*), 6.21 (d, *J* = 7.5 Hz, 1 H, N*H*), 5.90 (q, *J* = 7.9 Hz, 1 H, C=C*H*CF_3), 4.65 (dt, *J* = 7.5, 4.6 Hz, 1 H, NHC*H*), 3.71 (s, 3 H, CO_2CH_3), 2.99 (dd, J = 14.2, 4.7 Hz, 1 H, NHCHCH_2), 2.92 (dd, *J* = 14.2, 4.6 Hz, 1 H, NHCHCH_2), 2.01 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.4, 169.7, 150.7 (q, *J* = 5.4 Hz), 136.8, 130.4, 129.1, 128.3, 122.7 (q, *J* = 270.9 Hz), 119.1 (q, *J* = 34.8 Hz), 52.9, 52.4, 34.5, 23.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.3. **IR**: *v* 1749 (s), 1684 (s), 1562 (m), 1528 (m), 1506 (m), 1439 (m), 1411 (m), 1386 (m), 1311 (m), 1270 (s), 1215 (s), 1130 (s), 939 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{16}F_3NNaO_3S^+$ 370.0695, found 370.0698. For a detailed assignment of the NMR signals see table **S35** (chapter 5).

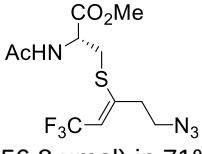
Methyl (*Z*)-*N*-acetyl-*S*-(4,4,4-trifluorobut-2-en-2-yl)-L-cysteinate (8i)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5j** (37.1 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8i** (10.6 mg, 37.1 µmol, 46%, NMR yield: 59%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8i** (12.2 mg, 42.7 µmol) in 54% yield (NMR yield: 60%). Purification via MPLC (t_R = 19.3–21.5 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +44.0 (c = 0.33, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.28 (d, *J* = 7.2 Hz, 1 H, N*H*), 5.65 (qd, *J* = 8.2, 1.5 Hz, 1 H, C=C*H*CF_3), 4.84 (dt, *J* = 7.3, 4.7 Hz, 1 H, NHC*H*), 3.78 (s, 3 H, CO_2CH_3), 3.37 (dd, *J* = 14.2, 5.0 Hz, 1 H, NHCHCH_2), 3.28 (dd, *J* = 14.1, 4.3 Hz, 1 H, NHCHCH_2), 2.15 (dd, *J* = 2.3, 1.5 Hz, 3 H, HC=CCH_3), 2.03 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.4, 170.0, 145.8 (q, *J* = 5.3 Hz), 122.6 (q, *J* = 270.6 Hz), 116.9 (q, *J* = 34.7 Hz), 53.0, 52.7, 32.3, 23.7, 23.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.9. **IR**: *v* 3670 (w), 2978 (s), 2892 (m), 1746 (m), 1658 (m), 1536 (w), 1509 (m), 1447 (w), 1439 (w), 1407 (m), 1394 (m), 1382 (m), 1275 (s), 1263 (s), 1221 (m), 1166 (m), 1116 (m), 1076 (s), 1056 (s), 896 (w), 867 (w), 752 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{14}F_3NNaO_3S^+$ 308.0539, found 308.0538. For a detailed assignment of the NMR signals see table **S36** (chapter 5).

Methyl (*Z*)-*N*-acetyl-*S*-(5-azido-1,1,1-trifluoropent-2-en-3-yl)-L-cysteinate (8j)

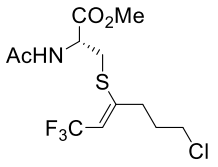


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5l** (41.5 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8j** (16.0 mg, 47.1 µmol, 60%, NMR yield: 63%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8j** (19.3 mg, 56.8 µmol) in 71% yield (NMR yield: 73%). Purification via MPLC (t_R = 26.6–28.5 min, gradient: 5–55% MeCN in 36 min).

ORD: $[\alpha]_D^{20}$ = +67.6 (c = 0.30, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 7.0 Hz, 1 H, N*H*), 5.84 (q, *J* = 7.8 Hz, 1 H, C=C*H*CF_3), 4.79 (dt, *J* = 6.9, 4.5 Hz, 1 H, NHC*H*), 3.77 (s, 3 H, CO_2CH_3), 3.50 (t, *J* = 6.6 Hz, 2 H, CH_2N_3), 3.31 (dd, *J* = 14.2, 5.1 Hz, 1 H, NHCHCH_2), 3.23 (dd, *J* = 14.2, 4.2 Hz, 1 H, NHCHCH_2), 2.63 (tq, *J* = 5.1, 1.6 Hz, 2 H, CH=CCH_2), 2.02 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$)

δ 170.24, 170.16, 146.1 (q, *J* = 5.4 Hz),122.2 (q, *J* = 271.3 Hz), 120.9 (q, *J* = 34.8 Hz), 53.1, 52.8, 49.2, 35.5, 32.5, 23.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 3678 (m), 2976 (s), 2899 (s), 2103 (m), 1750 (m), 1656 (m), 1535 (w), 1450 (w), 1407 (m), 1393 (m), 1379 (m), 1261 (s), 1224 (m), 1152 (m), 1119 (m), 1052 (s), 880 (w), 763 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{15}F_3N_4NaO_3S^+$ 363.0709, found 363.0713. For a detailed assignment of the NMR signals see table **S37** (chapter 5).

Methyl (*Z*)-*N*-acetyl-*S*-(6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinate (8k)

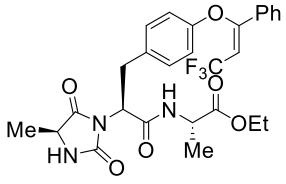


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5m** (42.1 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8k** (12.1 mg, 34.7 µmol, 43%, NMR yield: 59%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8k** (15.6 mg, 44.8 µmol) in 56% yield (NMR yield: 70%). Purification via MPLC (t_R = 22.7–24.6 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +76.9 (c = 0.51, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 7.1 Hz, 1 H, N*H*), 5.79 (q, *J* = 7.8 Hz, 1 H, C=C*H*CF_3), 4.81 (dt, *J* = 7.3, 4.6 Hz, 1 H, NHC*H*), 3.77 (s, 3 H, CO_2CH_3), 3.54 (t, *J* = 6.2 Hz, 2 H, CH_2Cl), 3.32 (dd, *J* = 14.2, 5.0 Hz, 1 H, NHCHCH_2), 3.23 (dd, *J* = 14.2, 4.2 Hz, 1 H, NHCHCH_2), 2.61–2.51 (m, 2 H, CH=CCH_2), 2.02 (s, 3 H, COCH_3), 2.00 (p, *J* = 6.5 Hz, 2 H, CH_2CH_2Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 170.3, 170.1, 148.6 (q, *J* = 5.4 Hz), 122.4 (d, *J* = 271.0 Hz), 119.0 (q, *J* = 34.7 Hz), 53.0, 52.8, 43.4, 32.7, 32.3, 30.7, 23.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.5. **IR**: *v* 3692 (m), 3662 (m), 2993 (s), 2971 (s), 2901 (s), 1750 (m), 1660 (m), 1634 (m), 1544 (w), 1443 (m), 1407 (m), 1394 (s), 1386 (m), 1274 (m), 1261 (s), 1227 (m), 1172 (w), 1110 (s), 1079 (s), 1052 (s), 885 (m), 765 (s), 752 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{17}ClF_3NNaO_3S^+$ 370.0462, found 370.0465. For a detailed assignment of the NMR signals see table **S38** (chapter 5).

3.2.2 Trifluoromethylation of Peptide based VBX Reagents

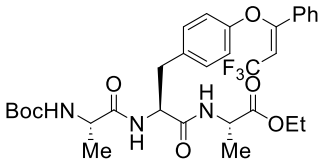
Ethyl ((*S*)-2-((*S*)-4-methyl-2,5-dioxoimidazolidin-1-yl)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (8l)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5n** (64.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8l** (19.1 mg, 34.8 µmol, 44%, NMR yield: 48%) was obtained as colorless oil. Purification via MPLC (t_R = 19.9–21.1 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +269.9 (c = 0.03, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2 H, Ar*H*), 7.36–7.27 (m, 3 H, Ar*H*), 7.24 (bs, 1 H, N*H*), 7.05 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.82 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 5.54 (bs, 1 H, N*H*), 4.86 (dd, *J* = 11.9, 5.6 Hz, 1 H, NHC*H*CH_2), 4.53 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH_3), 4.17 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.89–3.80 (m, 1 H, NHC*H*CH_3), 3.40 (dd, *J* = 14.1, 11.9 Hz, 1 H, NHCHCH_2), 3.29 (dd, *J* = 14.1, 5.7 Hz, 1 H, NHCHCH_2), 1.40 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.87 (d, *J* = 6.9 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.3, 172.9, 168.1, 158.7 (q, *J* = 5.6 Hz), 156.8, 155.4, 132.7, 130.7, 130.6, 130.5, 129.0, 127.2, 122.9 (q, *J* = 269.7 Hz), 117.2, 105.6 (q, *J* = 34.9 Hz), 61.7, 56.1, 52.8, 48.7, 34.0, 18.4, 17.4, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.9. **IR**: *v* 1771 (m), 1744 (m), 1714 (s), 1666 (s), 1562 (m), 1541 (m), 1507 (s), 1423 (m), 1375 (m), 1349 (w), 1274 (s), 1263 (s), 1216 (s), 1133 (s), 1079 (m), 1057 (m), 1046 (m), 892 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{28}F_3N_3NaO_6$ 570.1822, found: 570.1821. For a detailed assignment of the NMR signals see table **S39** (chapter 5).

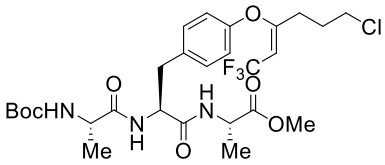
Ethyl ((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (8m)



Following **GP VII** (B, 365 nm) on 80.0 µmol scale and using VBX species **5n** (64.0 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8m** (31.3 mg, 50.3 µmol, 63%, NMR yield: 66%) was obtained as colorless oil. Purification via MPLC (t_R = 22.2–24.8 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = -16.6 (c = 1.04, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2 H, Ar*H*), 7.35–7.27 (m, 3 H, Ar*H*), 7.05 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 6.63 (d, *J* = 7.4 Hz, 1 H, N*H*), 6.55 (bs, 1 H, N*H*), 5.80 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 4.77 (bs, 1 H, N*H*), 4.62–4.54 (m, 1 H, NHC*H*CH_2), 4.40 (p, *J* = 7.0 Hz, 1 H, NHC*H*CH_3), 4.15 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.05 (d, *J* = 7.6 Hz, 1 H, NHC*H*CH_3), 2.97 (d, *J* = 6.7 Hz, 2 H, NHCHCH_2), 1.40 (s, 9 H, $(CH_3)_3$), 1.28 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.25 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.19 (d, *J* = 7.1 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.5, 172.3, 170.2, 158.9 (q, J = 5.8 Hz), 155.7, 155.3, 132.7, 131.0, 130.6 (2 C), 128.9, 127.3, 123.0 (q, J = 269.9 Hz), 117.4, 105.2 (q, J = 35.1 Hz), 80.6, 61.6, 53.9, 50.7, 48.4, 37.1, 28.4, 18.1 (2 C), 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.7. **IR**: *v* 3684 (m), 3656 (m), 2979 (s), 2908 (s), 2899 (s), 1653 (m), 1505 (w), 1451 (w), 1406 (m), 1401 (m), 1382 (m), 1249 (m), 1242 (m), 1227 (m), 1075 (s), 1073 (s), 1056 (s), 1028 (s), 889 (w), 878 (w), 871 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{31}H_{38}F_3N_3NaO_7^+$ 644.2554, found 644.2563. For a detailed assignment of the NMR signals see table **S40** (chapter 5).

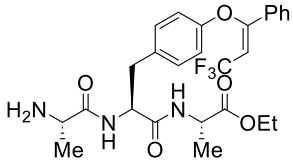
Methyl ((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)phenyl)propanoyl)-L-alaninate (8n)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5o** (62.9 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8n** (27.0 mg, 44.4 µmol, 56%, NMR yield: 63%) was obtained as white solid. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8n** (18.7 mg, 30.1 µmol) in 38% yield (NMR yield: 53%). Purification via MPLC (t_R = 20.9–23.6 min, gradient: 5–95% MeCN in 28 min).

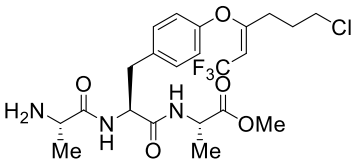
ORD: $[\alpha]_D^{20}$ = -11.1 (c = 1.08, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 6.71 (bs, 1 H, N*H*), 6.58 (bs, 1 H, N*H*), 5.30 (q, *J* = 7.4 Hz, 1 H, C=C*H*CF_3), 4.90 (bs, 1 H, N*H*), 4.65 (q, *J* = 7.0 Hz, 1 H, NHC*H*CH_2), 4.47 (p, *J* = 7.2 Hz, 1 H, NHC*H*CH_3), 4.16–4.04 (m, 1 H, NHC*H*CH_3), 3.71 (s, 3 H, CO_2CH_3), 3.50 (t, *J* = 6.3 Hz, 2 H, CH_2Cl), 3.10 (dd, *J* = 14.1, 6.0 Hz, 1 H, NHCHCH_2), 3.03 (dd, *J* = 13.9, 6.9 Hz, 1 H, NHCHCH_2), 2.34 (t, *J* = 7.2 Hz, 2 H, CH=CCH_2), 1.89 (p, *J* = 6.7 Hz, 2 H, CH_2CH_2Cl), 1.40 (s, 9 H, $(CH_3)_3$), 1.34 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.30 (d, *J* = 7.1 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.8, 172.6, 170.1, 161.1 (q, *J* = 5.6 Hz), 155.7, 153.6, 132.2, 130.9, 122.7 (q, *J* = 269.8 Hz), 118.7, 104.8 (q, *J* = 34.3 Hz), 80.7, 54.1, 52.6, 50.8, 48.4, 43.5, 37.3, 29.1, 28.8, 28.3, 18.2 (2xC). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 3678 (m), 2989 (s), 2919 (s), 1744 (m), 1688 (m), 1653 (m), 1509 (m), 1461 (w), 1397 (m), 1394 (s), 1253 (m), 1224 (m), 1163 (m), 1066 (s), 880 (m), 750 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{37}ClF_3N_3NaO_7^+$ 630.2164, found 630.2157. For a detailed assignment of the NMR signals see table **S41** (chapter 5).

Ethyl ((*S*)-2-((*S*)-2-aminopropanamido)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)-phenyl)propanoyl)-L-alaninate (8o)



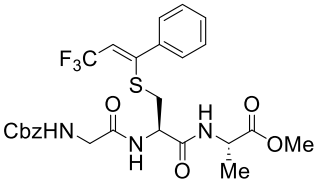
Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5p** (54.8 mg, 80 µmol, 1.0 equiv.). Trifluoromethylated compound **8o** was not isolated but qNMR indicated 20% yield. Following **GP VII** (B, 365 nm) on the same scale, qNMR indicated a yield of 13%.

Methyl ((*S*)-2-((*S*)-2-aminopropanamido)-3-(4-(((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-phenyl)propanoyl)- L-alaninate (8p)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5q** (54.9 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8p** was not isolated but qNMR indicated 2% yield. Following **GP III** (B, 365 nm) on the same scale, qNMR indicated a yield of 2%.

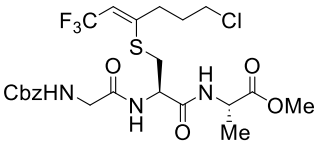
Methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinyl-L-alaninate (8q)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5r** (59.6 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8q** was not isolated but qNMR indicated 22% yield. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8q** (20.2 mg, 35.4 µmol) in 44% yield (NMR yield: 54%). Purification via MPLC (t_R = 22.1–23.3 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +26.5 (c = 0.40, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2 H, Ar*H*), 7.46–7.40 (m, 3 H, Ar*H*), 7.39–7.31 (m, 5 H, Ar*H*), 6.64 (bs, 2 H, N*H*), 5.94 (q, *J* = 8.0 Hz, 1 H, C=C*H*CF_3), 5.34 (bs, 1 H, N*H*), 5.13 (s, 2 H, CO_2CH_2Ph), 4.50–4.37 (m, 2 H, NHC*H*CH_2, NHC*H*CH_3), 3.85 (d, *J* = 5.5 Hz, 2 H, NHCH_2), 3.73 (s, 3 H, CO_2CH_3), 2.97–2.86 (m, 1H, NHCHCH_2), 2.80 (dd, J = 14.2, 5.8 Hz, 1 H, NHCHCH_2), 1.38 (d, *J* = 7.2 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.8, 169.0, 168.7, 156.9, 150.3 (q, *J* = 6.4 Hz), 136.7, 136.0, 130.4, 129.2, 128.7, 128.5, 128.4 (2 C), 122.7 (q, *J* = 270.8 Hz), 119.7 (q, *J* = 34.1 Hz), 67.6, 52.6 (2 C), 48.6, 44.8, 34.2, 18.0. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.0. **IR**: *v* 3343 (m), 2979 (m), 2897 (m), 1924 (w), 1671 (w), 1461 (w), 1422 (w), 1381 (w), 1334 (w), 1281 (w), 1087 (m), 1047 (s), 880 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{28}F_3N_3NaO_6S^+$ 590.1543, found 590.1550. For a detailed assignment of the NMR signals see table **S42** (chapter 5).

Methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinyl-L-alaninate (8r)

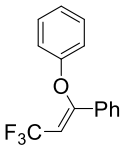


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **5s** (59.7 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8r** (28.0 mg, 49.3 µmol, 62%, NMR yield: 65%) was obtained as white solid. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **8r** (18.1 mg, 31.8 µmol) in 40% yield (NMR yield: 64%). Purification via MPLC (t_R = 20.2–22.3 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +2.9 (c = 1.12, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5 H, Ar*H*), 7.09–6.99 (m, 2 H, N*H*), 5.86 (q, *J* = 7.9 Hz, 1 H, C=C*H*CF_3), 5.44 (bs, 1 H, N*H*), 5.13 (s, 2 H, CO_2CH_2Ph), 4.55–4.44 (m, 2 H, NHC*H*CH_2, NHC*H*CH_3), 3.89 (d, *J* = 5.7 Hz, 2 H, NHCH_2), 3.74 (s, 3 H, CO_2CH_3), 3.61–3.49 (m, 2 H, CH_2Cl), 3.36 (d, *J* = 14.5 Hz, 1 H, NHCHCH_2), 2.93 (dd, *J* = 14.3, 7.4 Hz, 1 H, NHCHCH_2), 2.87–2.76 (m, 1 H, CH=CCH_2), 2.61 (dt, *J* = 15.3, 7.6 Hz, 1 H, CH=CCH_2), 2.02 (p, *J* = 7.3 Hz, 2 H, CH_2CH_2Cl), 1.41 (d, *J* = 7.3 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.7, 169.2, 168.7, 157.0, 148.3 (q, *J* = 5.0 Hz), 136.0, 128.7, 128.5, 128.3, 122.5 (q, *J* = 271.0 Hz), 119.9 (q, *J* = 33.9 Hz), 67.6, 52.7, 52.6, 48.8, 44.9, 43.5, 32.6, 32.0, 30.6, 17.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.0. **IR**: *v* 3685 (m), 2972 (s), 2903 (s), 1739 (m), 1663 (m), 1544 (w), 1447 (m), 1406 (s), 1394 (s), 1256 (s), 1235 (m), 1073 (s), 896 (m), 752 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{29}ClF_3N_3NaO_6S^+$ 590.1310, found 590.1327. For a detailed assignment of the NMR signals see table **S43** (chapter 5).

3.2.3 Trifluoromethylation of Vinyl (Thio) Ethers and Enamide based VBX Reagents

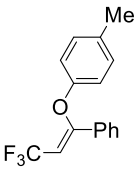
(*Z*)-(3,3,3-trifluoro-1-phenoxyprop-1-en-1-yl)benzene (9a)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6a** (44.3 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9a** (18.0 mg, 68.0 µmol, 68%) was obtained as white solid. The same approach (A, 100 µmol scale) was performed with additional Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.), giving **9a** (21.3 mg, 80.6 µmol) in 81% yield (NMR yield: 88%). Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9a** (16.0 mg, 60.5 µmol) in 61% yield (NMR yield: 75%). Purification via column chromatography (*n*-pentane).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.9, 1.8 Hz, 2 H, Ar*H*), 7.37–7.28 (m, 3 H, Ar*H*), 7.24–7.18 (m, 2 H, Ar*H*), 7.00–6.95 (m, 1 H, Ar*H*), 6.95–6.89 (m, 2 H, Ar*H*), 5.84 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.9 (q, *J* = 5.7 Hz), 156.3, 132.9, 130.6, 129.7, 128.9, 127.3, 123.0 (q, *J* = 269.7 Hz), 122.97, 117.2, 105.2 (q, *J* = 34.9 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{11}F_3O^+$ 264.0757, found 264.0754. Analytical data were in agreement with the literature.

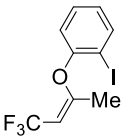
(*Z*)-1-Methyl-4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)benzene (9b)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6b** (45.6 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9b** (12.0 mg, 43.1 µmol, 43%) was obtained as colorless oil. The same approach (A, 100 µmol scale) was performed with additional Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.), giving **9b** (18.8 mg, 67.5 µmol) in 68% yield (NMR yield: 75%). Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9b** (17.6 mg, 63.1 µmol) in 63% yield (NMR yield: 72%). Purification via MPLC (t_R = 25.1–26.3 min, gradient: 5–95% MeCN in 28 min).

TLC: R_f (*n*-pentane) = 0.31. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.8, 1.8 Hz, 2 H, Ar*H*), 7.38–7.26 (m, 3H, Ar*H*), 7.00 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.79 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF_3), 2.22 (s, 3 H, ArCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 159.2 (q, *J* = 5.8 Hz), 154.1, 133.0, 132.4, 130.5, 130.1, 128.9, 127.4, 123.1 (q, *J* = 269.8 Hz), 117.0, 105.1 (q, *J* = 34.8 Hz), 20.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.7. **IR**: *v* 1666 (m), 1609 (w), 1507 (s), 1449 (m), 1343 (s), 1271 (s), 1216 (m), 1170 (m), 1127 (s), 1026 (w), 892 (w), 860 (w), 817 (w), 809 (w), 781 (w), 741 (m). **HRMS** (Sicrit plasma/LTQ) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{14}F_3O^+$ 279.0991, found 279.0990.

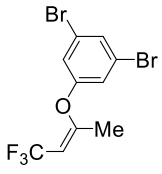
(*Z*)-1-Iodo-2-((4,4,4-trifluorobut-2-en-2-yl)oxy)benzene (9c)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6c** (50.6 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9c** (21.4 mg, 65.2 µmol, 65%) was obtained as colorless oil (NMR yield: 72%, 92% purity). Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9c** (10.1 mg, 30.7 µmol) in 31% yield (NMR yield: 37%, 90% purity). Purification via MPLC (t_R = 19.4–21.3 min, gradient: 5–95% MeCN in 25 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.9, 1.5 Hz, 1 H, Ar*H*), 7.33 (ddd, *J* = 8.9, 7.4, 1.6 Hz, 1 H, Ar*H*), 6.97 (dd, *J* = 8.1, 1.5 Hz, 1 H, Ar*H*), 6.91 (td, *J* = 7.7, 1.5 Hz, 1 H, Ar*H*), 5.14 (qd, *J* = 7.6, 1.1 Hz, 1 H, C=C*H*CF_3), 1.81 (dd, *J* = 2.1, 1.1 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.7 (q, *J* = 5.8 Hz), 153.8, 139.6, 139.6, 129.4, 126.2, 122.5 (q, *J* = 269.4 Hz), 119.8, 101.1 (q, *J* = 34.9 Hz), 18.6. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.6. **IR**: *v* 1685 (w), 1469 (m), 1443 (w), 1406 (m), 1404 (m), 1393 (m), 1339 (w), 1249 (m), 1228 (m), 1051 (s), 1022 (m), 946 (w), 900 (w), 880 (w), 759 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{10}H_8F_3IO^+$ 327.9566, found 327.9568.

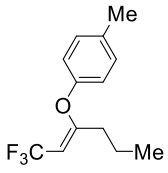
(*Z*)-1,3-Dibromo-5-((4,4,4-trifluorobut-2-en-2-yl)oxy)benzene (9d)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6d** (53.7 mg, 100 µmol, 1.0 equiv.) with additional Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9d** (26.4 mg, 73.3 µmol, 73%, NMR yield: 74%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9d** (12.7 mg, 35.4 µmol) in 35% yield (NMR yield: 41%). Purification via column chromatography (*n*-pentane).

TLC: R_f (2% EtOAc in *n*-pentane) = 0.40. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 1.6 Hz, 1 H, Ar*H*), 7.10 (d, *J* = 1.7 Hz, 2 H, Ar*H*), 5.33–5.25 (m, 1 H, C=C*H*CF_3), 1.90 (dd, *J* = 2.1, 1.1 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 158.0 (q, *J* = 5.7 Hz), 155.7, 135.7, 130.0, 123.5, 121.0, 105.3 (q, *J* = 34.9 Hz), 18.6. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -58.2. **IR**: *v* 1699 (m), 1577 (s), 1564 (s), 1422 (m), 1379 (m), 1346 (m), 1259 (s), 1213 (s), 1116 (s), 1084 (s), 950 (m), 871 (m), 849 (m), 745 (m). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{10}H_7Br_2F_3O^+$ 357.8810, found 357.8817. ^{13}C signal of the CF_3 group was not expressed.

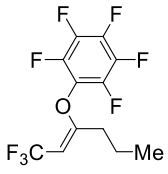
(*Z*)-1-Methyl-4-((1,1,1-trifluorohex-2-en-3-yl)oxy)benzene (9e)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6e** (42.2 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9e** (19.3 mg, 79.0 µmol, 79%, NMR yield: 80%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9e** (7.70 mg, 31.6 µmol) in 32% yield (NMR yield: 38%). Purification via MPLC (t_R = 21.4–22.3 min, gradient: 5–95% MeCN in 25 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15–7.07 (m, 2 H, Ar*H*), 6.91–6.83 (m, 2 H, Ar*H*), 5.19 (qt, *J* = 7.4, 0.9 Hz, 1 H, C=C*H*CF_3), 2.32 (s, 3 H, ArC*H*$_3$), 2.17–2.06 (m, 2 H, CH=CC*H*$_2$), 1.47 (h, *J* = 7.4 Hz, 2 H, CH=CCH$_2$C*H*$_2$), 0.89 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 163.1 (q, *J* = 5.6 Hz), 152.6, 133.5, 130.2, 123.1 (q, *J* = 269.5 Hz), 118.7, 103.0 (q, *J* = 34.3 Hz), 33.6, 20.8, 19.7, 13.4. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.6. **IR**: *v* 1685 (w), 1498 (w), 1458 (w), 1406 (m), 1382 (m), 1256 (m), 1235 (m), 1056 (s), 1022 (m), 896 (w), 878 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{13}H_{15}F_3O^+$ 244.1070, found 244.1071.

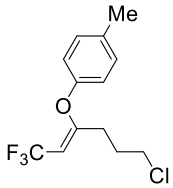
(*Z*)-1,2,3,4,5-Pentafluoro-6-((4,4,4-trifluorohex-2-en-2-yl)oxy)benzene (9f)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6f** (49.8 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9f** (22.2 mg, 52.8 µmol, 69%, NMR yield: 79%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale, qNMR indicated a yield of 22%. Purification via column chromatography (*n*-pentane).

TLC: R_f (2% EtOAc in *n*-pentane) = 0.67. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.12 (q, *J* = 7.6 Hz, 1 H, C=C*H*CF_3), 2.08 (t, *J* = 7.2 Hz, 2 H, CH=CC*H*$_2$), 1.49 (sex, *J* = 7.4 Hz, 2 H, CH=CCH$_2$C*H*$_2$), 0.94 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 161.8 (q, *J* = 5.6 Hz), 142.8 (dq, *J* = 12.0, 3.8 Hz), 140.5–139.1 (m), 137.8–136.6 (m), 122.6 (q, *J* = 269.6 Hz), 100.8 (q, *J* = 35.7 Hz), 33.2, 19.5, 13.3. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.7, -155.4 – -155.5 (m), -159.6 (tt, *J* = 21.8, 1.9 Hz), -161.8 – -161.9 (m). **IR**: *v* 1523 (m), 1407 (m), 1394 (m), 1382 (m), 1260 (m), 1227 (m), 1044 (s), 892 (m). **HRMS** (APPI/LTQ) *m/z*: $[M-H]^-$ calcd for $C_{12}H_7F_8O^-$ 319.0375, found: 319.0382.

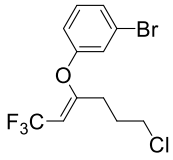
(*Z*)-1-((6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-4-methylbenzene (9g)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6g** (45.7 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9g** (7.50 mg, 26.9 µmol, 27%) was obtained as colorless oil. The same approach (A, 100 µmol scale) was performed with additional Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.), giving **9g** 21.9 mg, 78.7 µmol) in 79% yield (NMR yield: 85%). Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9g** (10.1 mg, 36.2 µmol) in 37% yield (NMR yield: 42%). Purification via MPLC (t_R = 24.7–26.2 min, gradient: 5–95% MeCN in 28 min).

TLC: R_f (2% EtOAc in *n*-pentane) = 0.53. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.17–7.06 (m, 2 H, Ar*H*), 6.87 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 5.27 (q, *J* = 7.4 Hz, 1 H, C=C*H*CF$_3$), 3.51 (t, *J* = 6.3 Hz, 2 H, C*H*$_2$Cl), 2.38–2.33 (m, 2 H, CH=CC*H*$_2$), 2.33 (s, 3 H, ArC*H*$_3$), 1.96–1.84 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 161.3 (q, *J* = 5.6 Hz), 152.3, 133.8, 130.4, 122.8 (q, *J* = 269.5 Hz), 118.5, 104.3 (q, *J* = 34.6 Hz), 43.6, 29.1, 28.8, 20.8. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 1682 (w), 1507 (m), 1404 (m), 1397 (m), 1382 (m), 1249 (m), 1217 (s), 1075 (s), 871 (w), 828 (w), 748 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{13}H_{14}ClF_3O^+$ 278.0680, found 278.0687.

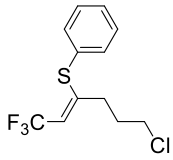
(*Z*)-1-Bromo-3-((6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)benzene (9h)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6h** (52.2 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9h** (12.8 mg, 37.2 µmol, 37%) was obtained as colorless oil. The same approach (A, 100 µmol scale) was performed with additional Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.), giving **9h** (23.9 mg, 69.5 µmol) in 70% yield (NMR yield: 86%). Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9h** (10.4 mg, 30.2 µmol) in 30% yield (NMR yield: 35%). Purification via MPLC (t_R = 25.4–27.4 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1 H, Ar*H*), 7.21 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 7.15 (t, *J* = 2.1 Hz, 1 H, Ar*H*), 6.92 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1 H, Ar*H*), 5.39 (q, *J* = 7.4 Hz, 1 H, C=C*H*CF$_3$), 3.53 (t, *J* = 6.2 Hz, 2 H, C*H*$_2$Cl), 2.39 (t, *J* = 7.1 Hz, 2 H, CH=CC*H*$_2$), 1.97–1.89 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 160.3 (q, *J* = 5.6 Hz), 155.3, 131.1, 127.3, 123.2, 122.4 (q, *J* = 270.0 Hz), 121.6, 116.9, 106.2 (q, *J* = 34.8 Hz), 43.4, 29.0, 28.9. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -58.1. **IR**: *v* 1688 (w), 1595 (w), 1469 (m), 1394 (m), 1249 (m), 1213 (m), 1076 (s), 949 (w), 885 (w), 781 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{12}H_{11}BrClF_3O^+$ 341.9628, found 341.9633.

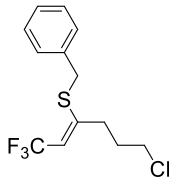
(*Z*)-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)(phenyl)sulfane (9i)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6i** (45.9 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9i** (20.7 mg, 73.7 µmol, 74%, NMR yield: 81%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9i** (11.3 mg, 40.2 µmol) in 40% yield (NMR yield: 49%). Purification via MPLC (t_R = 24.0 min, gradient: 5–95% MeCN in 28 min). One carbon signal was not resolved in the ^{13}C-NMR.

TLC: R_f (2% EtOAc in *n*-pentane) = 0.54. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2 H, Ar*H*), 7.39–7.33 (m, 3 H, Ar*H*), 5.83 (q, *J* = 8.0 Hz, 1 H, C=C*H*CF$_3$), 3.40 (t, *J* = 6.3 Hz, 2 H, C*H*$_2$Cl), 2.29 (t, *J* = 7.3 Hz, 1 H, CH=CC*H*$_2$), 1.94–1.82 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 149.7 (q, *J* = 5.3 Hz), 134.2, 129.5, 129.1, 122.7 (q, *J* = 271.0 Hz), 117.8 (q, *J* = 34.7 Hz), 43.5, 33.4, 30.8. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.3. **IR**: *v* 1394 (m), 1383 (m), 1260 (m), 1235 (m), 1079 (s), 1004 (w), 878 (w), 867 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{12}H_{12}ClF_3S^+$ 280.0295, found 280.0297.

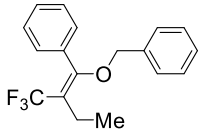
(*Z*)-Benzyl(6-chloro-1,1,1-trifluorohex-2-en-3-yl)sulfane (9j)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6j** (47.3 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9j** (11.7 mg, 39.7 µmol, 40%, NMR yield: 50%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9j** (13.2 mg, 44.7 µmol) in 45% yield (NMR yield: 61%). Purification via MPLC (t_R = 25.4–27.0 min, gradient: 5–95% MeCN in 28 min).

TLC: R_f (2% EtOAc in *n*-pentane) = 0.49. **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 7.39–7.35 (m, 2 H, Ar*H*), 7.32 (t, *J* = 7.4 Hz, 2 H, Ar*H*), 7.27–7.21 (m, 1 H, Ar*H*), 5.77 (q, *J* = 8.4 Hz, 1 H, C=C*H*CF$_3$), 4.08 (s, 2 H, SC*H*$_2$), 3.59 (t, *J* = 6.3 Hz, 2 H, C*H*$_2$Cl), 2.62–2.50 (m, 2 H, CH=CC*H*$_2$), 2.08–1.97 (m, 2 H, C*H*$_2$CH$_2$Cl). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 152.1 (q, *J* = 5.5 Hz), 138.3, 129.8, 129.7, 128.5, 124.2 (q, *J* = 269.9 Hz), 117.0 (q, *J* = 34.5 Hz), 44.6, 36.0, 34.3, 32.5. **^{19}F-NMR** (376 MHz, MeOD-d_4) δ -59.1. **IR**: *v* 1627 (m), 1465 (m), 1406 (m), 1394 (m), 1379 (m), 1260 (s), 1173 (m), 1108 (s), 1057 (s), 900 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{13}H_{14}ClF_3S^+$ 294.045, found 294.0447.

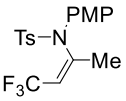
(*E*)-(1-(benzyloxy)-2-(trifluoromethyl)but-1-en-1-yl)benzene (9k)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6k** (60.6 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9k** (25.2 mg, 82.2 µmol, 82%, NMR yield: 92%) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45–7.36 (m, 3 H, Ar*H*), 7.36–7.26 (m, 5 H, Ar*H*), 7.23–7.16 (m, 2 H, Ar*H*), 4.48 (s, 2 H, OC*H*$_2$Ph), 2.41 (q, *J* = 7.5 Hz, 2 H, C*H*$_2$CH$_3$), 1.10 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 157.8 (q, *J* = 4.5 Hz), 137.2, 133.4, 129.6 (d, *J* = 2.4 Hz), 129.4, 128.6, 128.2, 128.1, 127.7, 125.6 (q, *J* = 271.8 Hz), 114.5 (q, *J* = 28.5 Hz) 70.6, 19.5, 13.9. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -56.0. **IR**: *v* 2975 (w), 2939 (w), 2888 (w), 1724 (w), 1663 (w), 1605 (w), 1505 (w), 1455 (w), 1372 (w), 1344 (m), 1261 (m), 1187 (m), 1130 (m), 1091 (s), 1069 (m), 1051 (w), 1029 (w), 989 (w), 939 (w), 907 (w), 777 (w), 741 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{18}H_{17}F_3O^+$ 306.1226, found 306.1227. For a detailed assignment of the NMR signals see table **S44** (chapter 5).

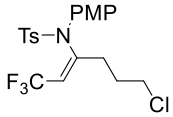
(*Z*)-*N*-(4-Methoxyphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-2-yl)benzenesulfonamide (9l)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6o** (56.3 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9l** (20.9 mg, 54.2 µmol, 54%, NMR yield: 63%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9l** (18.8 mg, 48.7 µmol) in 49% yield (NMR yield: 57%). Purification via MPLC (t_R = 23.5–24.5 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.24–7.19 (m, 2 H, Ar*H*), 7.16 (d, *J* = 9.0 Hz, 2 H), 6.80 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 5.60 (qd, *J* = 7.8, 1.3 Hz, 1 H, C=C*H*CF$_3$), 3.79 (s, 3 H, OC*H*$_3$), 2.40 (s, 3 H, ArC*H*$_3$), 2.13 (dd, *J* = 2.3, 1.3 Hz, 3 H, HC=CC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 159.6, 146.0 (q, *J* = 5.7 Hz), 144.0, 136.5, 131.4, 130.7, 129.5, 128.3, 121.5 (q, *J* = 270.4 Hz), 118.1 (q, *J* = 34.1 Hz), 114.4, 55.6, 23.4, 21.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -59.3. **IR**: *v* 1681 (m), 1603 (w), 1505 (s), 1444 (m), 1407 (m), 1386 (m), 1361 (m), 1289 (m), 1252 (s), 1239 (s), 1195 (s), 1162 (s), 1106 (s), 1088 (s), 1055 (s), 1047 (s), 982 (m), 932 (w), 863 (m), 832 (m), 817 (m), 795 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{18}F_3NNaO_3S^+$ 408.0852, found 408.0859.

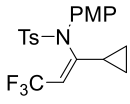
(*Z*)-*N*-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (9m)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6p** (63.0 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **8b** (32.4 mg, 73.0 µmol, 73%, NMR yield: 84%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the formation of the trifluoromethylated compound **8b** in 44% yield (NMR yield: 54%). Purification via MPLC (t_R = 23.8–25.8 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.20 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 7.19 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 5.61 (qt, *J* = 7.9, 1.3 Hz, 1 H, C=C*H*CF_3), 3.80 (s, 3 H, OCH_3), 3.61 (t, *J* = 6.1 Hz, 2 H, CH_2Cl), 2.50 (t, *J* = 7.4 Hz, 1 H, CH=CCH_2), 2.39 (s, 3 H, ArCH_3), 2.09–2.01 (m, 2 H, CH_2CH_2Cl). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 159.7, 147.7 (q, *J* = 5.6 Hz), 144.1, 136.3, 131.0, 130.7, 129.4, 128.3, 121.7 (q, *J* = 270.4 Hz), 117.3 (q, *J* = 34.3 Hz), 114.6, 55.6, 43.8, 33.2, 29.7, 21.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -59.2. **IR**: *v* 3392 (s), 2979 (m), 2902 (m), 1674 (m), 1655 (m), 1512 (m), 1451 (m), 1361 (m), 1281 (w), 1263 (w), 1164 (m), 1091 (m), 1046 (s), 879 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{21}ClF_3NNaO_3S^+$ 470.0775; Found 470.0773. For a detailed assignment of the NMR signals see table **S45** (chapter 5).

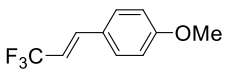
(*Z*)-*N*-(1-cyclopropyl-3,3,3-trifluoroprop-1-en-1-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (9n)



Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6q** (58.9 mg, 100 µmol, 1.0 equiv.). Trifluoromethylated compound **9n** (24.0 mg, 58.3 µmol, 58%, NMR yield: 68%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9n** (20.6 mg, 50.0 µmol) in 50% yield (NMR yield: 55%). Purification via MPLC (t_R = 22.7–24.8 min, gradient: 5–95% MeCN in 28 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.23 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.20 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.79 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 5.38 (qd, *J* = 7.8, 0.8 Hz, 1 H, C=C*H*CF_3), 3.80 (s, 3 H, OCH_3), 2.40 (s, 3 H, ArCH_3), 1.57–1.50 (m, 1 H, C*H*), 0.91–0.84 (m, 2 H, CH_2), 0.65 (dt, *J* = 6.8, 4.9 Hz, 2 H, CH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 159.5, 151.7 (q, *J* = 5.5 Hz), 143.9, 136.8, 131.7, 130.8, 129.4, 128.4, 122.2 (q, *J* = 270.2 Hz), 114.3, 113.3 (q, *J* = 34.3 Hz), 55.5, 21.7, 17.0, 9.7. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -58.4. **IR**: *v* 1664 (w), 1601 (w), 1505 (s), 1465 (w), 1444 (w), 1383 (m), 1358 (m), 1324 (m), 1290 (m), 1256 (m), 1237 (m), 1211 (m), 1166 (s), 1116 (s), 1091 (s), 1033 (m), 981 (w), 874 (w), 831 (w), 813 (w), 798 (w), 727 (w), 708 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{20}F_3NNaO_3S^+$ 434.1008, found 434.1013.

1-Methoxy-4-[(*E*)-3,3,3-trifluoroprop-1-enyl]benzene (9o)



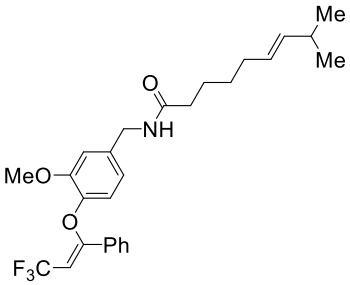
Following **GP VI** (A, 120 °C) on 100 µmol scale and using VBX species **6r** (38.0 mg, 100 µmol, 1.0 equiv.) and Hünigs base (26.1 µL, 19.4 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **9o** (11.1 mg, 54.6 µmol, 55%, NMR yield: 66%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the synthesis of the trifluoromethylated compound **9o** (10.1 mg, 50.0 µmol) in 50% yield (NMR yield: 58%). Purification via short path column chromatography (*n*-pentane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.09 (dq, *J* = 16.4, 2.0 Hz, 1 H, HC=C*H*), 6.91 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.06 (dq, *J* = 16.3, 6.6 Hz, 1 H, HC=C*H*), 3.84 (s, 3 H, ArOCH_3). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -63.0. **HRMS** (Sicrit plasma) *m/z*: $[M+K]^+$ calcd for $C_{19}H_9F_3KO^+$ 241.0237, found: 241.0228. Analytical data were in agreement with the literature.[19]

[19] G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Org. Lett.* **2012**, *14*, 1146.

3.2.4 Trifluoromethylation of Special Scaffolds

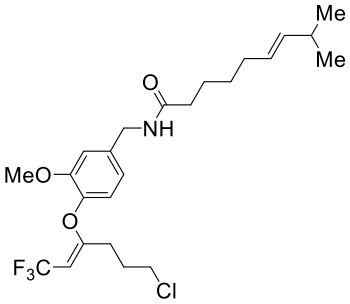
(*E*)-*N*-(3-Methoxy-4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)benzyl)-8-methylnon-6-enamide (10a)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7a** (52.3 mg, 80.0 µmol, 1.0 equiv.) and additional Hünigs base (20.9 µL, 15.5 mg, 120 µmol, 1.5 equiv.). Trifluoromethylated compound **10a** (26.2 mg, 55.0 µmol, 69%, NMR yield: 75%) was obtained as colorless oil. Purification via MPLC (t_R = 21.7–23.2 min, gradient: 5–95% MeCN in 25 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.1, 1.6 Hz, 2 H, Ar*H*), 7.35–7.27 (m, 3 H, Ar*H*), 6.80 (d, *J* = 1.9 Hz, 1 H, Ar*H*), 6.69 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 6.60 (dd, *J* = 8.2, 1.9 Hz, 1 H, Ar*H*), 5.72 (q, *J* = 7.6 Hz, 1 H, C=C*H*CF_3), 5.65 (t, *J* = 6.1 Hz, 1 H, N*H*), 5.42–5.24 (m, 2 H, *H*C=C*H*), 4.29 (d, *J* = 5.7 Hz, 2 H, ArCH_2NHCO), 3.90 (d, *J* = 1.2 Hz, 3 H, OCH_3), 2.25–2.12 (m, 3H, NHCOCH_2, C*H*$(CH_3)_2$), 2.02–1.92 (m, 2 H, CH_2CH=CH), 1.63 (p, *J* = 7.5 Hz, 2 H, NHCOCH$_2$CH_2), 1.36 (p, *J* = 7.6 Hz, 1 H, NHCOCH$_2$CH$_2$CH_2), 1.31–1.24 (m, 1 H, NHCOCH$_2$CH$_2$CH_2), 0.94 (d, *J* = 6.7 Hz, 5 H, CH_3), 0.85 (d, *J* = 6.6 Hz, 1 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.0, 159.8 (q, *J* = 5.7 Hz), 149.8, 144.6, 138.2, 134.3, 132.8, 130.6, 128.8, 127.2, 126.6, 123.1 (q, *J* = 269.6 Hz), 120.0, 118.0, 112.5, 112.5, 104.2 (q, *J* = 34.9 Hz), 56.3, 43.3, 36.8, 32.3, 31.1, 29.4, 25.4, 22.8. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.5. **IR**: *v* 1671 (w), 1660 (w), 1584 (w), 1559 (w), 1501 (w), 1458 (w), 1404 (m), 1393 (m), 1350 (w), 1263 (m), 1231 (m), 1145 (w), 1051 (s), 1033 (m), 885 (w), 758 (w). **HRMS** (ESI/TOF) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{32}F_3NNaO_3^+$ 498.2226, found 498.2228. For a detailed assignment of the NMR signals see table **S46** (chapter 5).

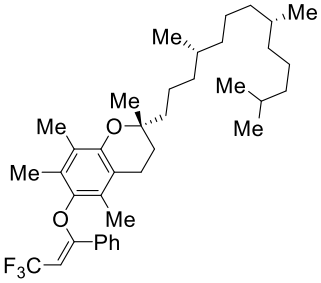
(*E*)-*N*-(4-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-3-methoxybenzyl)-8-methylnon-6-enamide (10b)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7b** (52.3 mg, 80.0 µmol, 1.0 equiv.) and additional Hünigs base (20.9 µL, 15.5 mg, 120 µmol, 1.5 equiv.). Trifluoromethylated compound **10b** (22.6 mg, 53.7 µmol, 67%, NMR yield: 70%) was obtained as colorless oil. Purification via MPLC (t_R = 20.1–21.4 min, gradient: 5–95% MeCN in 25 min).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.91–6.85 (m, 2 H, Ar*H*), 6.79 (dd, *J* = 8.1, 2.0 Hz, 1 H, Ar*H*), 5.81 (t, *J* = 5.9 Hz, 1 H, N*H*), 5.42–5.24 (m, 2 H, *H*C=C*H*), 5.10 (q, *J* = 7.6 Hz, 1 H, C=C*H*CF_3), 4.39 (d, *J* = 5.9 Hz, 2 H, ArCH_2NHCO), 3.82 (s, 3 H, OCH_3), 3.49 (t, *J* = 6.3 Hz, 2 H, CH_2CH_2Cl), 2.28–2.17 (m, 5 H, NHCOCH_2, C*H*$(CH_3)_2$, CH=CCH_2), 1.99 (q, *J* = 7.3 Hz, 2 H, CH_2CH=CH), 1.93–1.82 (m, 2 H, CH_2CH$_2$Cl), 1.66 (p, *J* = 7.3 Hz, 2 H, NHCOCH$_2$CH_2), 1.39 (p, *J* = 7.6 Hz, 2 H, NHCOCH$_2$CH$_2$CH_2), 0.94 (d, *J* = 6.8 Hz, 5 H, CH_3), 0.85 (d, *J* = 6.7 Hz, 1 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.1, 162.1 (q, *J* = 5.7 Hz), 151.2, 142.4, 138.3, 136.1, 126.5, 123.0 (q, *J* = 269.4 Hz), 120.6, 120.2, 112.7, 101.1 (q, *J* = 34.8 Hz), 56.2, 43.6, 43.3, 36.8, 32.3, 31.1, 29.4, 29.1, 28.7, 25.4, 22.8. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.4. **IR**: *v* 3685 (w), 2989 (s), 2914 (s), 1766 (w), 1674 (m), 1656 (m), 1595 (w), 1545 (m), 1505 (m), 1469 (m), 1447 (m), 1408 (m), 1382 (m), 1259 (s), 1208 (s), 1156 (m), 1116 (s), 1083 (s), 1040 (s), 968 (w), 950 (w), 892 (w), 821 (w), 741 (w). **HRMS** (ESI/TOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{33}ClF_3NNaO_3^+$ 498.1993, found 498.1994. For a detailed assignment of the NMR signals see table **S47** (chapter 5).

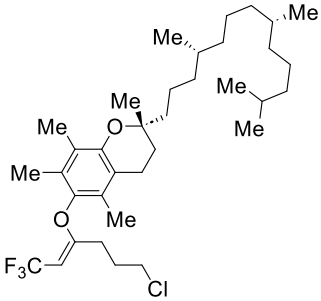
(*R*)-2,5,7,8-Tetramethyl-6-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (10c)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7c** (62.3 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **9c** (13.0 mg, 21.6 µmol, 27%) was obtained as colorless oil. The same approach (A, 80 µmol scale) was performed with additional Hünigs base (20.9 µL, 15.5 mg, 120 µmol, 1.5 equiv.), giving **10c** (34.3 mg, 57.0 µmol) in 71% yield (NMR yield: 80%). Following **GP VII** (B, 365 nm) on the same scale enabled the formation of the trifluoromethylated compound **10c** (22.0 mg, 36.6 µmol) in 46% yield (NMR yield: 51%). Purification via column chromatography (*n*-pentane). NMR data is given for major rotamer (ratio = 4:3, based on the aromatic methyl signal). Not all carbon signals were resolved in the ^{13}C-NMR.

TLC: R_f (*n*-pentane) = 0.22. **ORD**: $[\alpha]_D^{20}$ = +7.3 (c = 2.06, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25–7.13 (m, 5 H, Ar*H*), 5.04 (q, *J* = 8.0 Hz, 1 H, C=C*H*CF_3), 2.53–2.35 (m, 2 H, ArCH_2), 2.13 (s, 3 H, ArCH_3), 2.07 (s, 3 H, ArCH_3), 1.99 (s, 3 H, ArCH_3), 1.81–1.65 (m, 2 H, ArCH_2CH_2), 1.55–1.47 (m, 1 H, aliphatic tail), 1.47–1.33 (m, 6 H, aliphatic tail), 1.32–1.11 (m, 15 H, aliphatic tail), 1.10–1.00 (m, 2 H, aliphatic tail), 0.88 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 0.85 (d, *J* = 4.4 Hz, 3 H, CH_3), 0.83 (d, *J* = 4.2 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 163.6 (q, *J* = 5.7 Hz), 148.5, 144.4, 133.7, 129.7, 128.0, 127.9, 127.1, 125.2, 123.7 (q, *J* = 269.2 Hz), 123.2, 117.8, 96.9 (q, *J* = 35.3 Hz), 75.1, 39.5, 37.6, 37.4, 33.0, 32.8, 31.6, 28.1, 25.0, 24.6, 22.9, 22.8, 22.5, 20.7, 19.9, 19.8, 13.5, 12.6, 11.8. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -56.9. **IR**: *v* 1660 (m), 1465 (m), 1404 (m), 1380 (m), 1339 (m), 1274 (m), 1247 (s), 1111 (s), 1065 (s), 917 (w), 889 (w), 859 (m), 781 (w), 741 (w). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{56}F_3O_2^+$ 601.4227, found 601.4228. For a detailed assignment of the NMR signals see table **S48** (chapter 5). ^{13}C signal of the CF_3 group was not expressed.

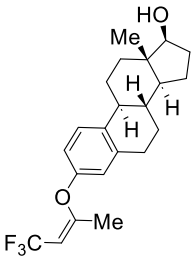
(*R*)-6-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (10d)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7d** (62.3 mg, 80.0 µmol, 1.0 equiv.). and Hünigs base (20.9 µL, 15.5 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **10d** (40.0 mg, 66.5 µmol, 83%, NMR yield: 91%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale, qNMR indicated a yield of 6%. Purification via column chromatography (*n*-pentane). NMR data is given for major rotamer (ratio = 5:4, based on the aromatic methyl signal). Not all carbon signals were resolved in the ^{13}C-NMR.

ORD: $[\alpha]_D^{20}$ = +5.5 (c = 2.67, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.78 (q, *J* = 7.8 Hz, 1 H, C=C*H*CF_3), 3.44 (td, *J* = 6.4, 2.1 Hz, 2 H, CH_2Cl), 2.58 (q, J = 6.7 Hz, 2 H, ArCH_2), 2.10 (s, 3 H, ArCH_3), 2.07 (s, 3 H, ArCH_3), 2.04 (s, 3 H, ArCH_3), 2.02–2.00 (m, 2 H, CH=CCH_2), 1.86–1.74 (m, 4 H, ArCH_2CH_2, CH_2CH_2Cl), 1.62–1.55 (m, 1 H, aliphatic tail), 1.53–1.35 (m, 6 H, aliphatic tail), 1.33–1.19 (m, 13 H, aliphatic tail), 1.17–1.12 (m, 2 H, aliphatic tail), 1.09–1.04 (m, 2 H, aliphatic tail), 0.88 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3), 0.86–0.83 (m, 6 H, 2x CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 164.0 (q, *J* = 5.8 Hz), 149.2, 142.5, 127.9, 124.0 (q, *J* = 268.9 Hz), 123.5 (2 C), 118.0, 93.9 (q, *J* = 34.9 Hz), 75.4, 43.6, 39.5, 37.6, 37.5, 33.0, 32.9, 31.5, 29.3, 28.1, 25.0, 24.6, 22.9, 22.8, 21.7, 20.8, 19.9, 19.8, 13.0, 12.1, 11.9. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -56.8. **IR**: *v* 1674 (w), 1458 (w), 1415 (m), 1404 (m), 1386 (m), 1250 (m), 1229 (m), 1048 (s), 1022 (m), 880 (m), 871 (w), 738 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+MeOH+Na]^+$ calcd for $C_{36}H_{60}ClF_3NaO_3^+$ 655.4075, found 655.4077. For a detailed assignment of the NMR signals see table **S49** (chapter 5).

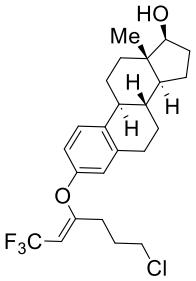
(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-3-(((*Z*)-4,4,4-trifluorobut-2-en-2-yl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (10e)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7e** (44.7 mg, 80.0 µmol, 1.0 equiv.). and Hünigs base (20.9 µL, 15.5 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **10e** (12.7 mg, 33.3 µmol, 42%, NMR yield: 44%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale, qNMR indicated a yield of 11%. Purification via MPLC (t_R = 21.2–22.6 min, gradient: 5–95% MeCN in 25 min).

ORD: $[\alpha]_D^{20}$ = +901.1 (c = 0.85, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.5, 1.1 Hz, 1 H, Ar*H*), 6.76 (dd, *J* = 8.5, 2.7 Hz, 1 H, Ar*H*), 6.71 (d, *J* = 2.6 Hz, 1 H, Ar*H*), 5.10 (qd, *J* = 7.6, 1.1 Hz, 1 H, C=C*H*CF_3), 3.74 (dd, *J* = 9.0, 8.0 Hz, 1 H, C*H*OH), 2.84 (dd, *J* = 7.5, 3.2 Hz, 2 H, CH_2), 2.32 (dtd, *J* = 13.4, 4.2, 2.7 Hz, 1 H, CH_2), 2.25–2.16 (m, 1 H, C*H*), 2.16–2.07 (m, 1 H, CH_2), 1.96 (ddd, *J* = 12.6, 3.9, 2.7 Hz, 1 H, CH_2), 1.92–1.86 (m, 1 H, CH_2), 1.84 (dd, *J* = 2.2, 1.0 Hz, 3 H, HC=CCH_3), 1.71 (dddd, *J* = 12.4, 9.9, 7.0, 3.1 Hz, 1 H, CH_2), 1.56–1.25 (m, 6 H, CH_2, C*H*), 1.20 (ddd, *J* = 12.0, 10.8, 7.2 Hz, 1 H, C*H*), 0.79 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 159.7 (q, *J* = 5.8 Hz), 152.3, 138.6, 136.6, 126.7, 123.0 (q, *J* = 269.2 Hz), 119.5, 116.7, 101.8 (q, *J* = 34.5 Hz), 82.0, 50.2, 44.2, 43.4, 38.7, 36.8, 30.7, 29.7, 27.2, 26.4, 23.3, 18.7, 11.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.6. **IR**: *v* 1685 (m), 1624 (w), 1509 (w), 1447 (w), 1404 (m), 1393 (m), 1353 (m), 1267 (m), 1231 (s), 1056 (s), 971 (w), 968 (w), 907 (m), 881 (w), 831 (w), 730 (m). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{28}F_3O_2^+$ 381.2036, found 381.2028. For a detailed assignment of the NMR signals see table **S50** (chapter 5).

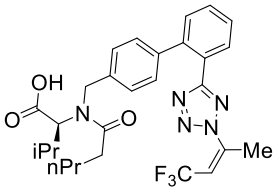
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (10f)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7f** (49.7 mg, 80.0 µmol, 1.0 equiv.). and Hünigs base (20.9 µL, 15.5 mg, 150 µmol, 1.5 equiv.). Trifluoromethylated compound **10f** (11.3 mg, 25.5 µmol, 32%, NMR yield: 38%) was obtained as colorless oil. Following **GP VII** (B, 365 nm) on the same scale enabled the formation of the trifluoromethylated compound **10f** (10.0 mg, 22.5 µmol) in 28% yield (NMR yield: 39%). Purification via MPLC (t_R = 22.4–23.8 min, gradient: 5–95% MeCN in 25 min).

ORD: $[\alpha]_D^{20}$ = +1199.9 (c = 0.62, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.6, 1.1 Hz, 1 H, Ar*H*), 6.74 (dd, *J* = 8.4, 2.8 Hz, 1 H, Ar*H*), 6.68 (d, *J* = 2.6 Hz, 1 H, Ar*H*), 5.28 (q, *J* = 7.4 Hz, 1 H, C=C*H*CF_3), 3.74 (dd, *J* = 9.0, 8.0 Hz, 1 H, C*H*OH), 3.52 (t, *J* = 6.3 Hz, 2 H, CH_2Cl), 2.84 (dd, *J* = 7.6, 3.3 Hz, 2 H, CH_2), 2.41–2.32 (m, 2 H, C=CH_2), 2.31 (dd, *J* = 13.4, 3.3 Hz, 1 H, CH_2), 2.24–2.16 (m, 1 H, CH_2), 2.12 (ddd, *J* = 13.0, 9.3, 5.4 Hz, 1 H, C*H*), 1.99–1.85 (m, 4 H, CH_2CH_2Cl, CH_2), 1.71 (dddd, *J* = 12.4, 9.9, 7.0, 3.1 Hz, 1 H, CH_2), 1.57–1.44 (m, 3 H, CH_2, C*H*), 1.42–1.26 (m, 3 H, CH_2, C*H*), 1.24–1.14 (m, 1 H, C*H*), 0.79 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 161.2 (q, *J* = 5.6 Hz), 152.3, 138.8, 136.3, 126.8, 122.8 (d, *J* = 269.7 Hz), 118.5, 115.6, 104.5 (q, *J* = 34.5 Hz), 82.0, 50.2, 44.2, 43.6, 38.7, 36.8, 30.8, 30.5, 29.8, 29.1, 28.8, 27.2, 26.4, 23.3, 11.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 1685 (w), 1617 (w), 1505 (w), 1444 (w), 1404 (m), 1393 (m), 1260 (m), 1213 (m), 1058 (s), 1026 (m), 928 (w), 881 (w), 734 (m). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{31}ClF_3O_2^+$ 443.1959, found 443.1947. For a detailed assignment of the NMR signals see table **S51** (chapter 5).

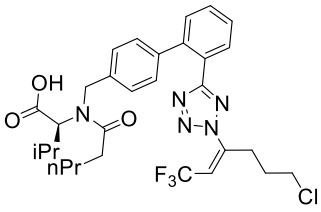
(*Z*)-*N*-Pentanoyl-*N*-((2'-(2-(4,4,4-trifluorobut-2-en-2-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-L-valine (10g)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7g** (57.7 mg, 80.0 µmol, 1.0 equiv.). and Hünigs base (20.9 µL, 15.5 mg, 150 µmol, 1.5 equiv.). qNMR indicated a yield of 9%. Following **GP VII** (B, 365 nm) on the same scale enabled the formation of the trifluoromethylated compound **10g** (16.3 mg, 29.9 µmol) as colorless oil in 37% yield (NMR yield: 47%). Purification via MPLC (t_R = 20.0–21.4 min, gradient: 5–95% MeCN in 25 min). Mixture of rotamers (ratio = 5:4, based on the CH_2 group in α position to the amide) and *Z*/*E* isomers (*Z*/*E* = 10:1) was observed. NMR data is given for major *Z*-rotamer.

ORD: $[\alpha]_D^{20}$ = -0.6 (c = 0.42, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.7, 1.5 Hz, 1 H, Ar*H*), 7.67–7.58 (m, 1 H, Ar*H*), 7.54 (td, *J* = 7.6, 1.4 Hz, 1 H, Ar*H*), 7.52–7.45 (m, 1 H, Ar*H*), 7.23 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 7.13 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.03 (d, *J* = 7.9 Hz, 1 H, Ar*H*), 6.21 (qq, *J* = 8.2, 1.6 Hz, 1 H, C=C*H*CF_3), 4.80–4.55 (m, 3 H, ArCH_2N, N*CH*CO_2H), 2.69–2.45 (m, 1 H, NCOCH_2), 2.42–2.36 (m, 1 H NCOCH_2), 2.38–2.30 (m, 3 H, HC=CCH_3), 2.29–2.18 (m, 1 H, C*H*$(CH_3)_2$), 1.73–1.63 (m, 1 H, NCOCH_2CH_2), 1.54 (dq, *J* = 14.5, 7.3 Hz, 1 H, NCOCH_2CH_2), 1.41 (q, *J* = 7.4 Hz, 1 H, NCO$CH_2CH_2CH_2$), 1.27 (h, *J* = 7.4 Hz, 1 H, NCO$CH_2CH_2CH_2$), 1.01 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.96 (t, *J* = 7.3 Hz, 1 H, CH_3), 0.89–0.76 (m, 5 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 177.2, 176.9, 166.7, 143.4, 142.3 (q, *J* = 5.8 Hz), 141.0, 138.1, 131.9, 131.6, 131.5, 130.5, 130.0, 128.8, 127.4, 122.5 (q, *J* = 269.6 Hz), 114.6 (q, *J* = 37.1 Hz), 64.9, 50.6, 34.6, 29.2, 28.5, 23.4, 21.6, 20.6, 19.4, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -60.2. **IR**: *v* 1732 (m), 1636 (m), 1509 (m), 1437 (m), 1407 (m), 1387 (m), 1353 (m), 1289 (m), 1260 (m), 1224 (m), 1195 (s), 1137 (s), 1081 (m), 1023 (m), 838 (w), 765 (m). **HRMS** (ESI/QTOF) *m/z*: $[M-H]^-$ calcd for $C_{28}H_{31}F_3N_5O_3^-$ 542.2384, found 542.2382. For a detailed assignment of the NMR signals see table **S52** (chapter 5).

(*Z*)-*N*-((2'-(2-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-pentanoyl-L-valine (10h)

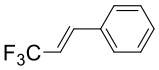


Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using VBX species **7h** (57.7 mg, 80.0 µmol, 1.0 equiv.). and Hünigs base (20.9 µL, 15.5 mg, 150 µmol, 1.5 equiv.). qNMR indicated a yield of 7%. Following **GP VII** (B, 365 nm) on the same scale enabled the formation of the trifluoromethylated compound **10h** (21.8 mg, 35.9 µmol) as colorless oil in 45% yield (NMR yield: 58%). Purification via MPLC (t_R = 21.9–22.9 min, gradient: 5–95% MeCN in 25 min). A mixture of rotamers (ratio = 5:4, based on the CH_2 group in α position to the amide) was observed. NMR data is given for major rotamer.

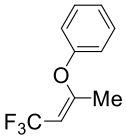
ORD: $[\alpha]_D^{20}$ = -1.4 (c = 0.39, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.91–7.75 (m, 1 H, Ar*H*), 7.62 (dtd, *J* = 8.3, 7.2, 1.5 Hz, 1 H, Ar*H*), 7.55 (td, *J* = 7.5, 1.4 Hz, 1 H, Ar*H*), 7.48 (td, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.23 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.19–7.11 (m, 2 H, Ar*H*), 7.03 (d, *J* = 7.9 Hz, 1 H, Ar*H*), 6.42–6.26 (m, 1 H, C=C*H*CF_3), 4.80–4.58 (m, 3 H, ArCH_2N, N*CH*CO_2H), 3.55 (t, *J* = 6.4 Hz, 2 H, CH_2Cl), 2.82 (dt, *J* = 11.1, 7.2 Hz, 2 H, NCOCH_2), 2.58 (ddt, *J* = 48.5, 15.1, 7.4 Hz, 1 H, C*H*$(CH_3)_2$), 2.44–2.18 (m, 2 H, HC=CCH_2), 1.86–1.64 (m, 3 H, CH_2CH_2Cl, NCOCH_2CH_2), 1.55 (dp, *J* = 14.9, 7.3, 6.6 Hz, 1 H, NCOCH_2CH_2), 1.41 (dq, *J* = 15.9, 8.5, 7.8 Hz, 1 H, NCO$CH_2CH_2CH_2$), 1.27 (h, *J* = 7.4 Hz, 1 H, NCO$CH_2CH_2CH_2$), 1.02 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.96 (t, *J* = 7.3 Hz, 1 H, CH_3), 0.89–0.78 (m, 5 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 177.2, 176.9, 166.9, 144.9 (q, *J* = 5.5 Hz), 143.3, 141.0, 138.1, 131.9, 131.8, 131.5, 130.5, 130.0, 128.8, 128.4, 127.5, 126.6, 122.4 (d, *J* = 270.1 Hz), 116.6 (q, *J* = 36.1 Hz), 65.3, 50.6, 44.1, 34.5, 33.4, 30.4, 29.2, 28.5, 23.4, 20.6, 19.4, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -60.5. **IR**: *v* 3656 (w), 2988 (s), 2968 (s), 2903 (s), 1685 (w), 1653 (w), 1505 (w), 1404 (m), 1383 (m), 1263 (m), 1242 (m), 1079 (s), 1058 (s), 1037 (s), 896 (w), 873 (w), 752 (w). **HRMS** (ESI/QTOF) *m/z*: $[M-H]^-$ calcd for $C_{30}H_{34}ClF_3N_5O_3^-$ 604.2308, found 604.2304. For a detailed assignment of the NMR signals see table **S53** (chapter 5).

3.2.5 Unsuccessful Substrates

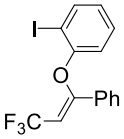
The following overview shows the unsuccessful substrates. Product formation was mainly not possible due to unsuccessful formation of the VBX species. Isolation of (*E*)-(3,3,3-trifluoroprop-1-en-1-yl)benzene (NMR yield without DIPEA: 30%) was not possible based on the low boiling point.



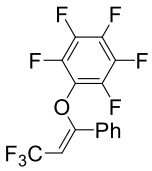
VBX: ✓
CF_3: X



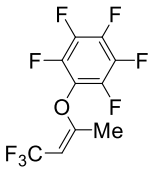
VBX: X



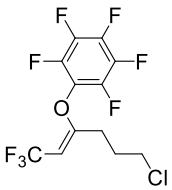
VBX: X



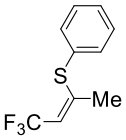
VBX: X



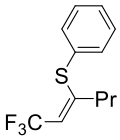
VBX: X



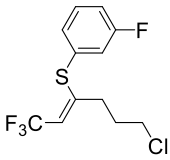
VBX: X



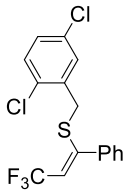
VBX: X



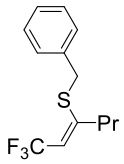
VBX: ✓
CF_3: X



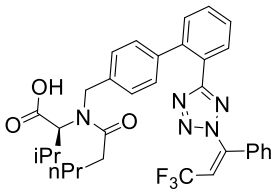
VBX: X



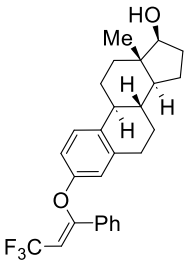
VBX: X



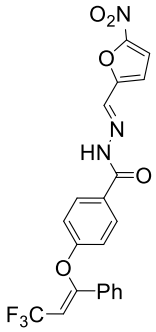
VBX: ✓
CF_3: X



VBX: X

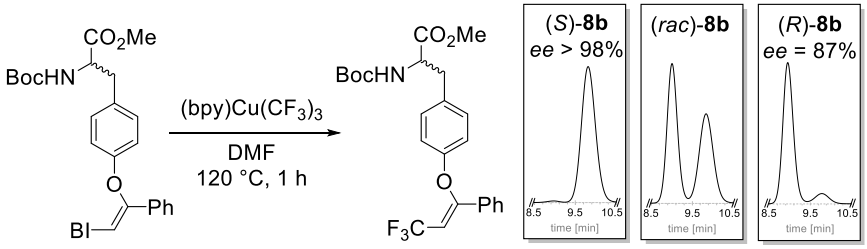


VBX: X



VBX: X

3.3 Analysis of Racemization Potential



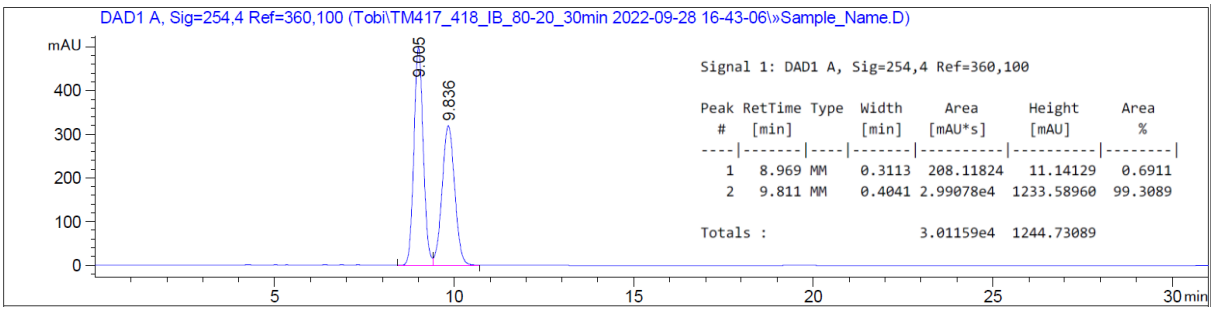
(*S*)-**5b**, *ee* = 99%
(*R*)-**5b**, *ee* = 90%

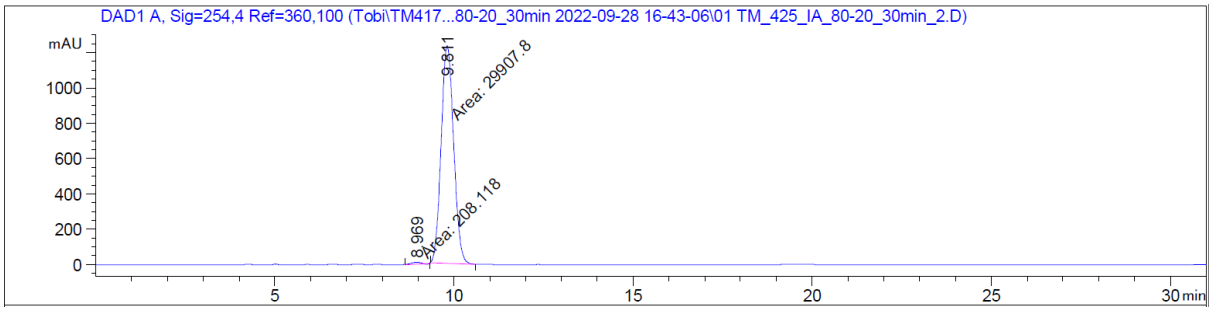
(*S*)-**8b**, 78% (64%)
(*R*)-**8b**, 73% (52%)

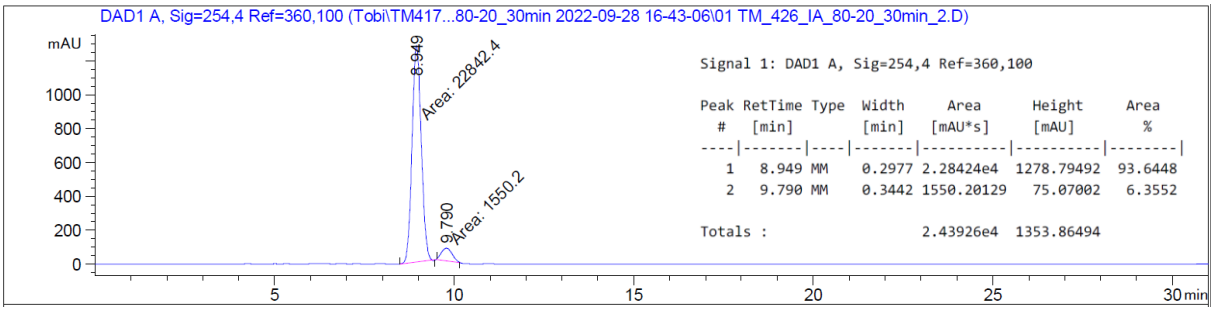
$[\alpha]_D$ = -17.9

chiral HPLC analysis

$[\alpha]_D$ = +16.6

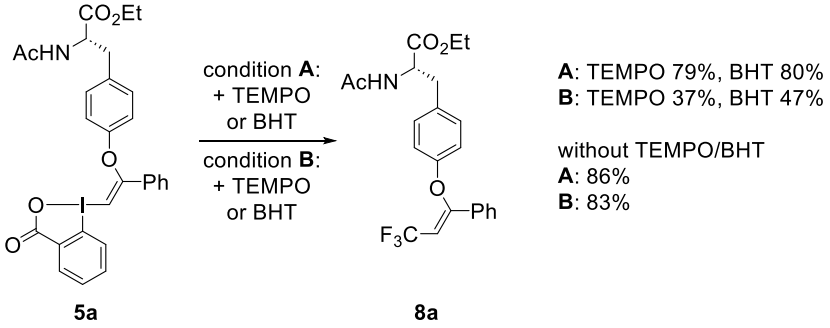






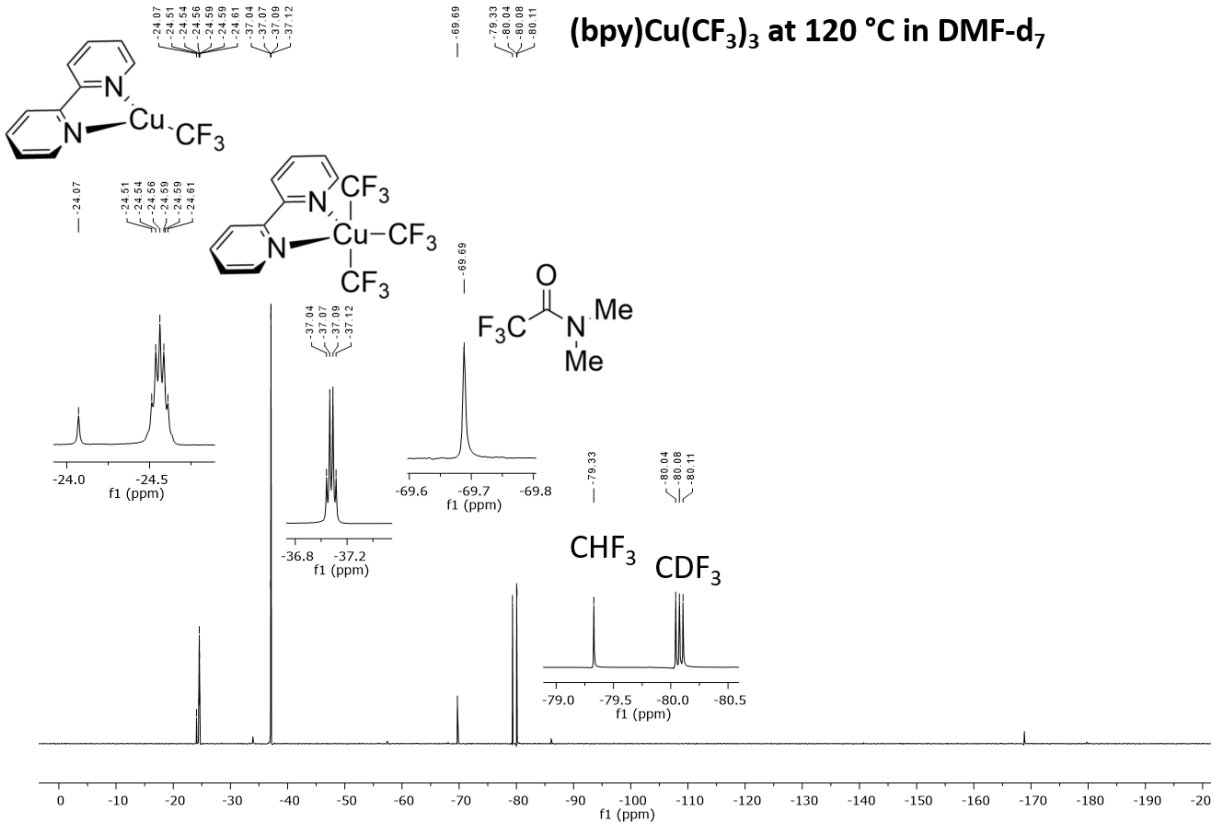
3.4 Analysis of Reaction Mechanism

Following experiments were done to investigate the reaction mechanism: NMR experiments in DMF-d_7, radical trapping approaches using BHT and TEMPO, and use of metal free CF_3 sources. The reactions were performed with starting material **5a** (scale: 15 µmol). The reactions were monitored using ^{19}F-qNMR (as described previously, Chapter: 3.1).



5a **8a**

The radical quenching experiments with BHT (5.0 equiv.) and TEMPO (5.0 equiv.) indicated that the mechanism under UV conditions is probably involving radical intermediates. On the other side, the thermal reaction is not affected at all by the radical scavengers.

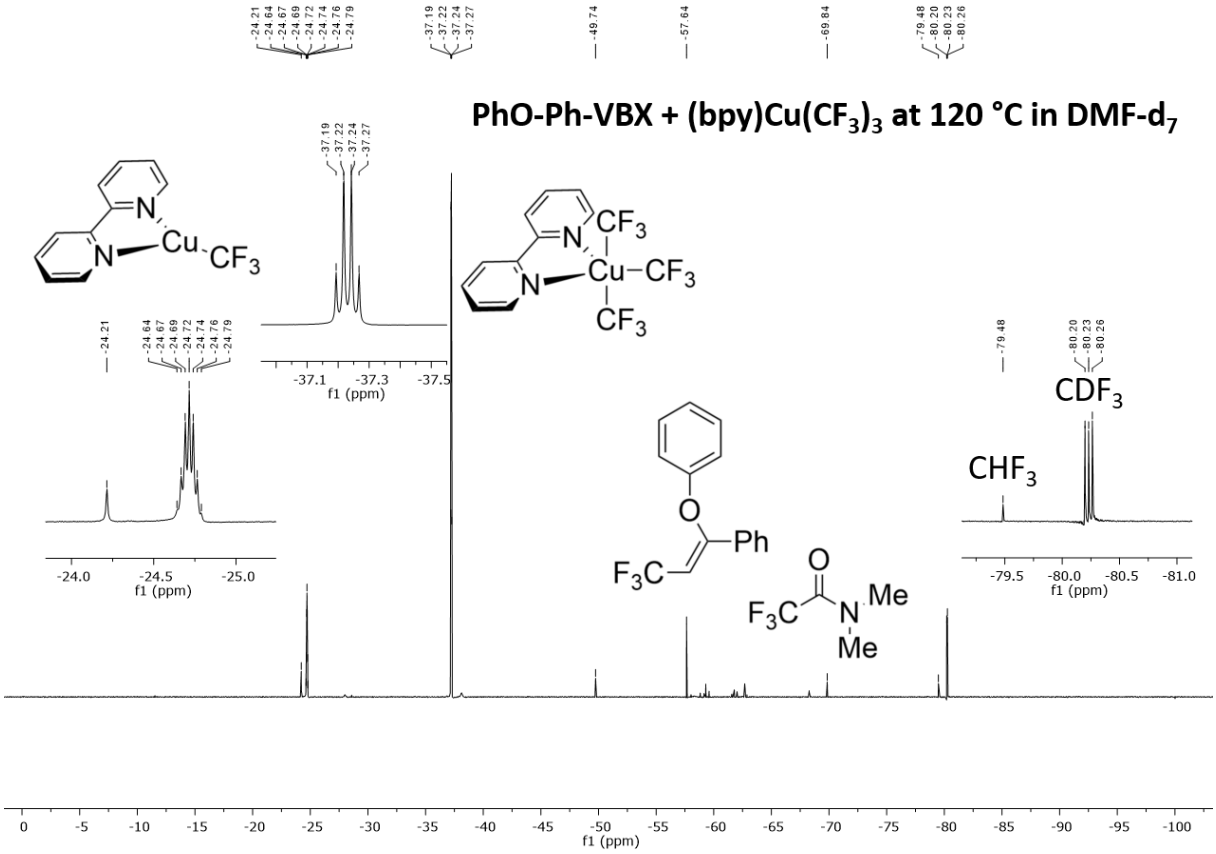


The ^{19}F-NMR of (bpy)Cu(CF_3)$_3$ in DMF-d_7 at 120 °C without the presence of starting material and Hünigs base showed the formation of (bpy)CuCF_3 (δ_F = -24.1 ppm, lit.[20]: δ_F = -23.0 – -24.5 ppm), trifluoromethylated DMF (δ_F = -69.7 ppm), fluoroform (δ_F = 79.3 ppm, lit.[21]: δ_F = -78.7 ppm), and deuterated fluorofom (δ_F = -80.1 ppm, lit.[20]: δ_F = -80.0 – -82.0 ppm).

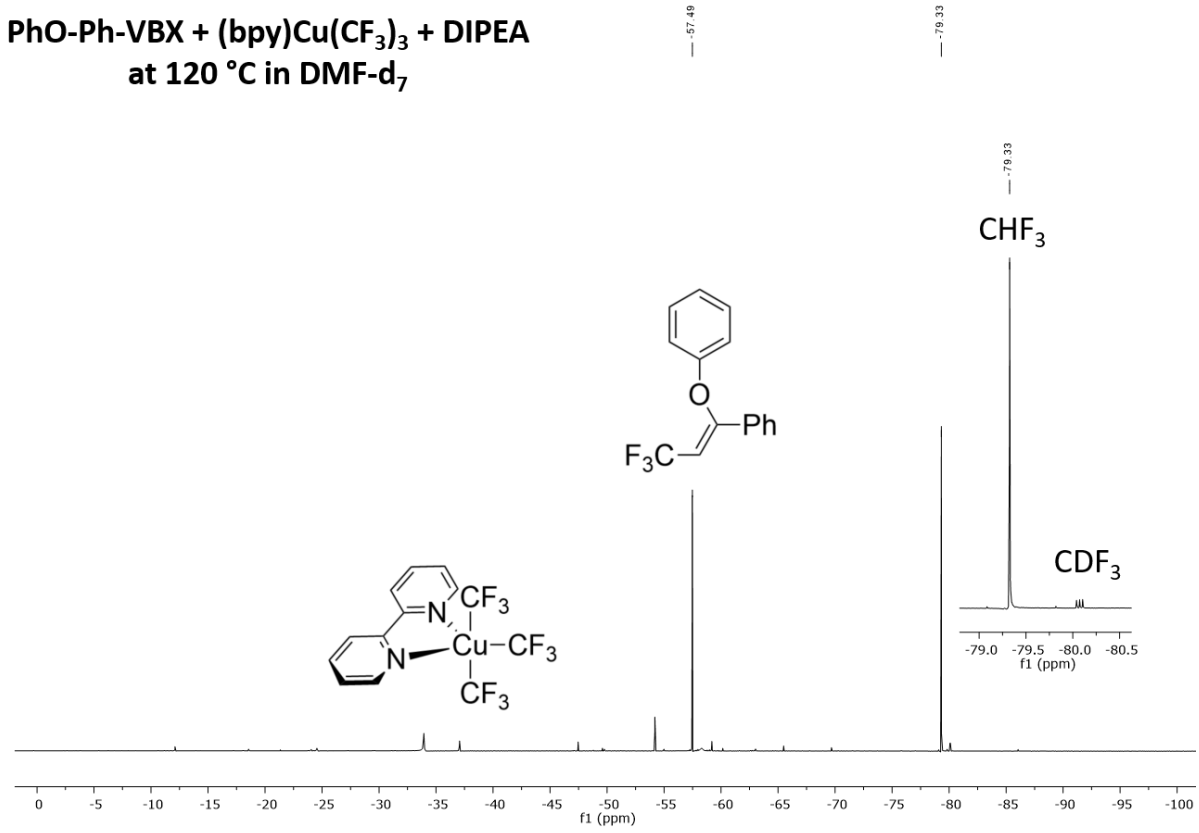
NMR data of trifluoromethylated DMF

^{1}H-NMR (400 MHz, DMF-d_7) δ 3.19 (q, *J* = 1.7 Hz, 3 H), 3.06 (d, *J* = 0.8 Hz, 3 H). **^{19}F-NMR** (376 MHz, DMF-d_7) δ -69.8.

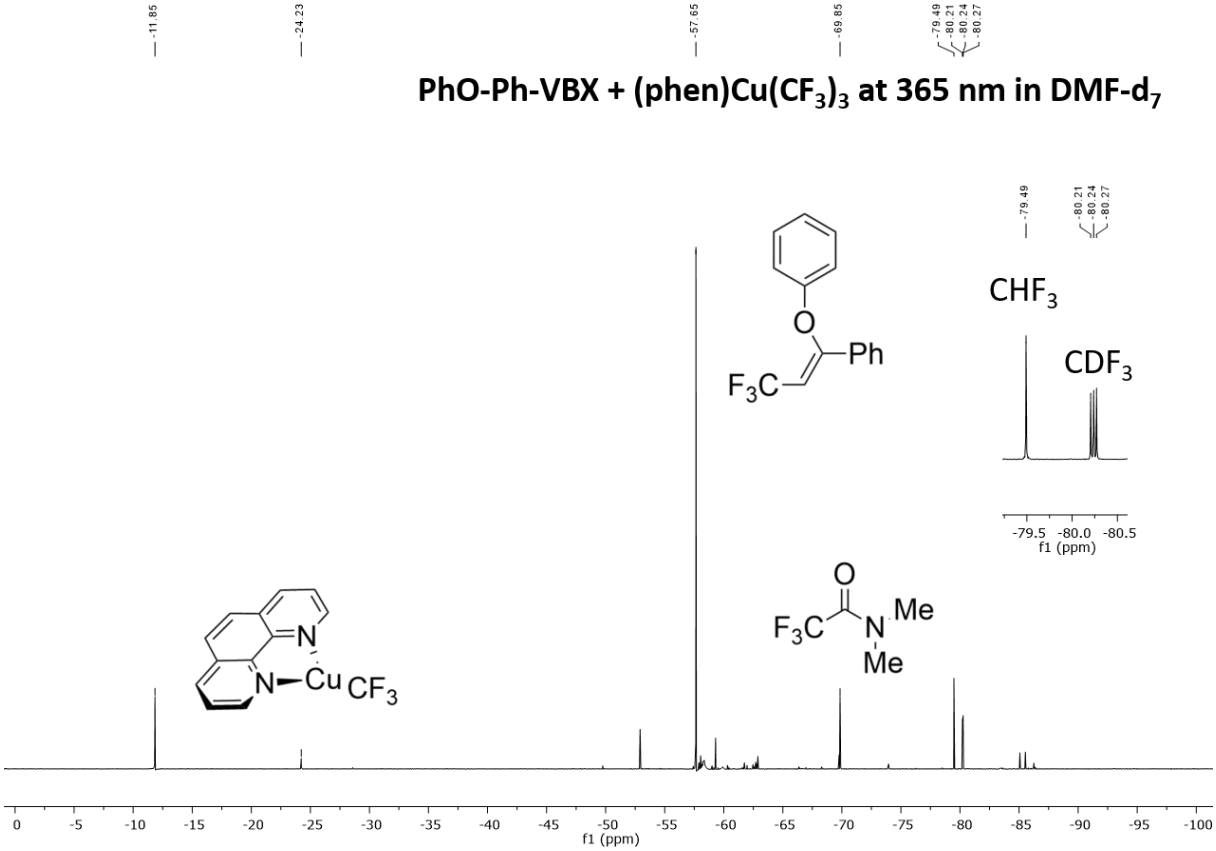
[20] N. Nebra, V. V. Grushin, *J. Am. Chem. Soc.* **2014**, *136*, 16998.
[21] C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 9516.



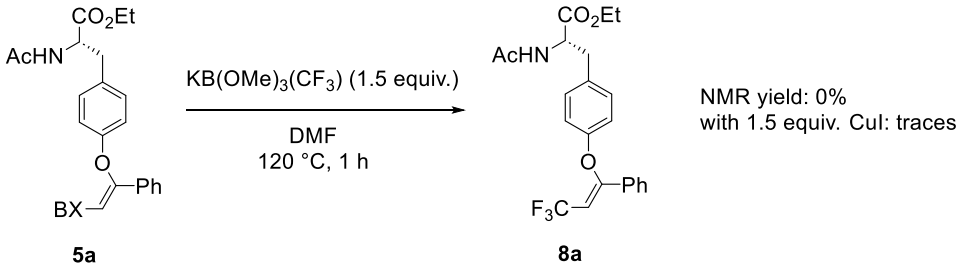
In presence of VBX species **7a** (A), the ^{19}F-NMR shows the clear formation of product **9a** (δ_F = -57.5 ppm), whereby the signals of (bpy)$CuCF_3$, trifluoromethylated DMF, fluoroform, and deuterated fluorofom still emerge. The signal of deuterated fluorofom is thereby significantly higher than the one of fluoroform. Accordingly, the deuterated fluoroform can be formed by deuterium abstraction of DMF-d_7.



Under addition of Hünigs base (A‡), the ^{19}F-NMR also shows the formation of the product **6a** and fluoroform. The signals of (bpy)$CuCF_3$, trifluoromethylated DMF, and deuterated fluorofom (traces) are not visible anymore. This observation leads to the conclusion that instead of DMF, DIPEA now abstracts a proton and is thus oxidized. Furthermore, no trifluoromethyl group is incorporated in the oxidation side product.



Under UV conditions (B), the spectrum is similar to that at 120 °C without Hünigs base. The formation of trifluoromethylated DMF, fluoroform, and deuterated fluorofom can be observed.



5a **8a**

The control experiment with potassium trimethoxy(trifluoromethyl)borate instead of (bpy)$Cu(CF_3)_3$ showed no product formation. Repeating the same reaction with addition of 1.5 equiv. copper iodide allowed the formation of traces of **8a**. Together with the fact that the reaction also works with $CuCF_3$ (see optimization table 1 in main article, entries 1–3), the conclusion can be drawn that copper(I) is involved in mechanism.

3.5 Upscaling Experiments

Batch-Δ

The upscaled batch reaction were performed similar as described in chapter 3.1 (**GP VI**). Bigger microwave reaction vials (10–20 mL) and stirring bars (10 mm, cross shape) were used.

Following **GP VI** (A, 120 °C, Batch-Δ) on 1.00 mmol scale and using VBX species **5a** (599 mg, 1.00 mmol, 1.0 equiv.) and Hünigs base (261 µL, 194 mg, 1.50 mmol, 1.5 equiv.). Trifluoromethylated compound **8a** (355 mg, 0.84 µmol, 84%) was obtained as colorless oil. Following **GP VI** (A, 120 °C, Batch-Δ) on 1.00 mmol scale and using VBX species **6a** (442 mg, 1.00 mmol, 1.0 equiv.) and Hünigs base (261 µL, 194 mg, 1.50 mmol, 1.5 equiv.). Trifluoromethylated compound **9a** (216 mg, 0.82 µmol, 82%) was obtained as colorless oil. Following **GP VI** (A, 120 °C, Batch-Δ) on 1.00 mmol scale and using VBX species **6p** (626 mg, 1.00 mmol, 1.0 equiv.) and without Hünigs base Trifluoromethylated compound **9m** (359 mg, 0.80 µmol, 80%) was obtained as colorless oil.

Batch-*hv*

The upscaled batch reaction were performed similar as described in chapter 3.1 (**GP VII**). Bigger test tubes (Corning® Pyrex 16x125mm) were used for the Rayonet® Photochemical Reactor.

Following **GP VII** (B, 365 nm, Batch-*hv*) on 1.00 mmol scale and using VBX species **5d** (766 mg, 1.00 mmol, 1.0 equiv.). Trifluoromethylated compound **8d** (456 mg, 0.77 µmol, 78%) was obtained as colorless oil.

Flow – General

The flow chemistry was performed with a vapourtec system including a R^2 C^+ pump module and R^4 reactor unit. The length of the PFA tubing from the pumps to the reactor was 70 cm and the one from the reactor to the back pressure regulator (8.0 bar) was 50 cm. All used reactors have a reactor/reaction volume of 10 cm.

Flow-Δ

For the thermal reaction, a high temperature tube reactor with metal coiling and post cooling tube was used. The reagents were pre-mixed in dry DMF and only one pump (flow rate: 0.17 mL/min) was used. The reaction was performed at 120 °C with a reaction time of 1 h ($A^‡$).

Trifluoromethylated compound **9a** (210 mg, 0.80 mmol, 79%) was synthesized from VBX species **6a** (442 mg, 1.00 mmol, 1.0 equiv.) and Hünigs base (261 µL, 194 mg, 1.50 mmol, 1.5 equiv.).

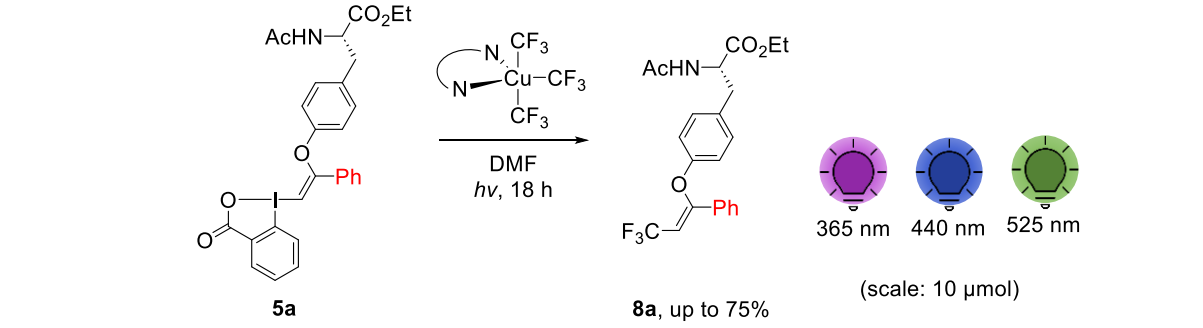
Flow-Δ/*hv*

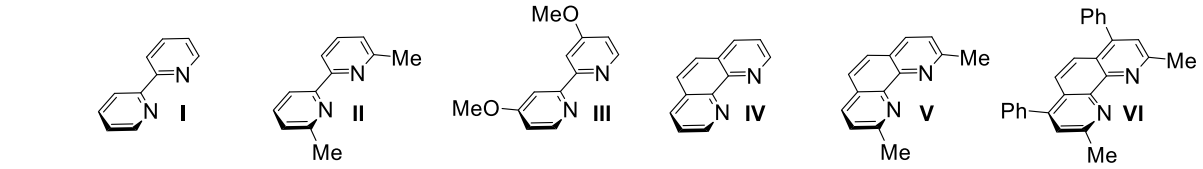
For the combined thermal/UV reaction, a UV-150 photohchemical reactor with 8 monochromatic LEDs (365 nm) was used. The reagents were not premixed and both pumps (flow rate each: 0.05 mL/min) were used. The reaction was peformed at 80 °C with a reaction time of 100 min.

Trifluoromethylated compound **8a** (322 mg, 0.76 mmol, 76%) was obtained from VBX species **5a** (442 mg, 1.00 mmol, 1.0 equiv.).

3.6 Visible Light Transformation

The reaction were performed according to **GP VII** on 10 µmol scale (B). UV reactions at 365 nm were performed in the Rayonet® Photochemical Reactor. Reactions in visible light were performed with Kessil PR160L lamps (440 nm: 2x, 100% intensity, 45W; 525 nm: 1x, 100% intensity, 44W) using compressed air for continuous cooling. The approaches were only analyzed by qNMR (as described previously, Chapter: 3.1).

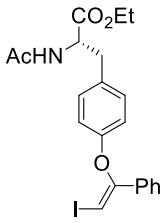




	I	II	III	IV	V	VI
Cu^{III} species:	52%	53%	43%	60%	5%	11%
yield **6a**:	75%	14%	4%	70%	17%	9%
	59%	32%	68%	63%	34%	13%
	0%	0%	0%	14%	0%	0%

4 Product Modifications

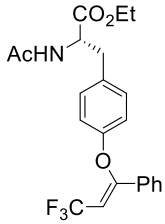
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-iodo-1-phenylvinyl)oxy)phenyl)propanoate (11)



Following a reported procedure[22], VBX species **5a** (250 mg, 420 µmol, 1.0 equiv.) was treated with copper(I) iodide (79.4 mg, 420 µmol, 1.0 equiv.) in dry THF (5.0 mL, 80 mM). The reaction mixture was stirred for 3 d under inert atmosphere at room temperature before being filtered and concentrated in vacuo. The obtained residue was purified by column chromatography or MPLC (t_R = 21.5–24.6 min, gradient: 5–95% MeCN in 28 min). The reduced compound **11** (163 mg, 340 µmol, 82%) was obtained as colorless oil.

ORD: $[\alpha]_D^{20}$ = -106.6 (c = 0.30, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2 H, Ar*H*), 7.30–7.26 (m, 3 H, Ar*H*), 6.97 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.86 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.48 (s, 1 H, C=C*H*), 6.10 (bs, 1 H, N*H*), 4.80–4.72 (m, 1 H, NHC*H*), 4.13–4.03 (m, 2 H, OCH_2CH$_3$), 2.99 (d, *J* = 6.6 Hz, 2 H, NHCHCH_2), 1.93 (s, 3 H, COCH_3), 1.14 (t, *J* = 7.2 Hz, 3 H, OCH$_2$CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.7, 157.4, 154.8, 133.8, 130.5, 129.9, 129.9, 129.2, 128.7, 126.3, 66.4, 61.4, 53.2, 37.2, 23.1, 14.1. **IR**: *v* 1653 (s), 1541 (w), 1506 (m), 1375 (w), 1296 (w), 1271 (w), 1217 (w), 1170 (w), 1133 (w), 1039 (w), 1019 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{22}INNaO_4^+$ 502.0486, found 502.0505.

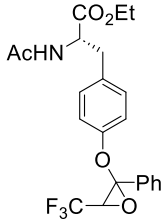
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8a)



Following **GP VI** (A, 120 °C) on 80.0 µmol scale and using ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-iodo-1-phenylvinyl)oxy)phenyl)propanoate (**11**, 38.3 mg, 80.0 µmol, 1.0 equiv.). Trifluoromethylated compound **8a** (20.4 mg, 48.4 µmol, 61%) was obtained as colorless oil. Purification via MPLC (t_R = 21.1–22.6 min, gradient: 5–95% MeCN in 28 min).

ORD: $[\alpha]_D^{20}$ = +28.5 (c = 0.61, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.9, 1.7 Hz, 2 H, Ar*H*), 7.37–7.28 (m, 3 H, Ar*H*), 6.95 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.92 (d, *J* = 7.8 Hz, 1 H, N*H*), 5.82 (q, *J* = 7.5 Hz, 1 H, C=C*H*CF$_3$), 4.76 (dt, *J* = 7.8, 6.1 Hz, 1 H, NHC*H*), 4.07 (qd, *J* = 7.1, 4.7 Hz, 2 H, OCH_2CH$_3$), 2.99 (dd, *J* = 6.0, 2.8 Hz, 2 H, NHCHCH_2), 1.94 (s, 3 H, COCH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3).**^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.7, 158.9 (q, *J* = 5.7 Hz). 155.3, 132.8, 130.6, 130.53, 130.50, 128.9, 127.3, 123.0 (q, *J* = 269.6 Hz), 117.2, 105.3 (q, *J* = 34.9 Hz), 61.6, 53.2, 37.3, 23.2, 14.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.8. **IR**: *v* 2935 (w), 1742 (w), 1660 (s), 1508 (m), 1447 (w), 1440 (m), 1408 (w), 1386 (m), 1343 (m), 1274 (m), 1258 (m), 1216 (m), 1137 (m), 1101 (m), 1063 (w), 1025 (w), 889 (w), 856 (w), 752 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{22}F_3NNaO_4^+$ 444.1393, found 444.1395. For a detailed assignment of the NMR signals see table **S53** (chapter 5).

Ethyl (2*S*)-2-acetamido-3-(4-((2-phenyl-3-(trifluoromethyl)oxiran-2-yl)oxy)phenyl)propanoate (12)



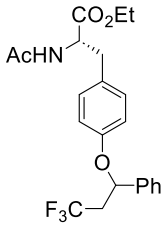
Following a reported procedure[11], compound **8a** (42.1 mg, 100 µmol, 1.0 equiv.) was treated with *m*CPBA (51.8 mg, 300 µmol, 3.0 equiv.) in a mixture of DCM (1.0 mL) and saturated $NaHCO_3$ solution (2.0 mL). The reaction mixture was stirred for 24 h before being treated with further saturated $NaHCO_3$ solution (2.0 mL). The layers were separated and the aqueous layer was extracted with DCM (3x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by MPLC (t_R = 23.5–23.9 min, gradient: 5–95% MeCN in 28 min). The corresponding epoxide **12** (25.4 mg, 58.0 µmol, 58%) was obtained as

[22] K. Mondal, S. C. Pan, *Eur. J. Org. Chem.* **2015**, *23*, 2129. D. Shimbo, A. Shibata, M. Yudasaka, T. Maruyama, N. Tada, B. Uno, A. Itoh, *Org. Lett.* **2019**, *21*, 9769.

colorless oil. A mixture of diastereomers (ratio = 1:1) was observed. NMR data is given for major diastereomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48–7.41 (m, 2 H, Ar*H*), 7.39–7.32 (m, 3 H, Ar*H*), 6.93 (d, *J* = 0.8 Hz, 4H, Ar*H*), 5.85 (d, *J* = 7.8 Hz, 1 H, N*H*), 4.77 (dq, *J* = 7.7, 5.6 Hz, 1 H, NHC*H*), 4.09 (tdd, *J* = 7.2, 6.3, 5.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.47 (qd, *J* = 4.9, 2.4 Hz, 1 H, OC*H*CF_3), 3.05–2.90 (m, 2 H, NHCHCH_2), 1.95 (s, 3 H, COCH_3), 1.15 (td, *J* = 7.2, 4.2 Hz, 3 H, $CO_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.7, 169.6, 153.4, 133.3, 130.5, 130.4, 129.9, 129.1, 126.6, 123.1–120.4 (m), 117.9, 83.6, 61.6, 61.0 (q, J = 41.3 Hz), 53.2, 37.2, 23.3, 14.2. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -68.3. **IR**: *v* 2986 (m), 2918 (m), 2250 (m), 1736 (s), 1660 (s), 1540 (m), 1510 (s), 1461 (s), 1446 (m), 1375 (m), 1294 (s), 1264 (s), 1220 (s), 1163 (s), 1126 (s), 1047 (m), 1026 (s), 961 (m), 910 (s), 881 (m), 867 (m), 759 (m), 734 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{22}F_3NNaO_5^+$ 460.1342, found 460.1354. For a detailed assignment of the NMR signals see table **S54** (chapter 5).

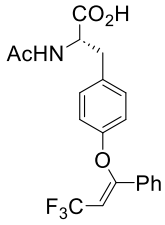
Ethyl (2*S*)-2-acetamido-3-(4-(3,3,3-trifluoro-1-phenylpropoxy)phenyl)propanoate (13)



Trifluormethylated alkene **8a** (84.3 mg, 200 µmol, 1.0 equiv.) was dissolved in EtOH (3.0 mL) and Pd/C (10% wt, 21.3 mg, 20.0 µmol, 10 mol%) was added. The reaction vial was transferred into a H_2 autoclave, in which a hydrogen pressure of 10 bar was generated. The reaction mixture was stirred under hydrogen atmosphere (10 bar) for 24 h. After removal of the overpressure, the reaction solution was filtered and concentrated in vacuo to give the desired reduced compound **13** (72.3 mg, 170 µmol, 85%) as colorless oil (dr = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4 H, Ar*H*), 7.32–7.26 (m, 1 H, Ar*H*), 6.91 (dd, *J* = 8.7, 2.1 Hz, 2 H, Ar*H*), 6.78–6.69 (m, 2 H, Ar*H*), 6.01 (d, *J* = 7.8 Hz, 1 H, N*H*), 5.38 (dd, *J* = 9.0, 3.5 Hz, 1 H, ArOC*H*Ph), 4.76 (dtd, *J* = 7.7, 5.8, 1.8 Hz, 1 H, NHC*H*), 4.16–4.03 (m, 2 H, $CO_2CH_2CH_3$), 2.98 (d, *J* = 5.9 Hz, 2 H, NHCHCH_2), 2.92–2.75 (m, 1 H, CH_2CF_3), 2.61–2.39 (m, 1 H, CH_2CF_3), 1.94 (s, 3 H, COCH_3), 1.17 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 171.8 (d, *J* = 2.4 Hz), 169.7, 156.6, 139.9 (d, J = 2.4 Hz), 130.4, 129.1, 128.9 (d, *J* = 4.5 Hz), 128.5, 125.9, 125.5 (q, *J* = 277.7 Hz), 116.3 (d, *J* = 6.6 Hz), 74.7 (dq, *J* = 6.6, 3.2 Hz), 61.5, 53.3 (d, *J* = 4.0 Hz), 42.7 (q, *J* = 27.8 Hz), 37.1, 23.2, 14.1. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -63.80, -61.81. **IR**: *v* 3692 (w), 3663 (m), 2989 (s), 2972 (s), 2892 (s), 1732 (w), 1665 (w), 1498 (w), 1405 (m), 1382 (m), 1254 (s), 1224 (m), 1133 (s), 1073 (s), 1048 (s), 1037 (s), 892 (w), 878 (w), 741 (s), 705 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{25}F_3NO_4^+$ 424.1730, found 424.1729. For a detailed assignment of the NMR signals see table **S55** (chapter 5).

(*S*,*Z*)-2-Acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoic acid (14)

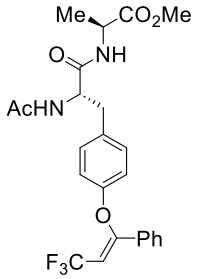


The trifluormethylated species **8a** (84.2 mg, 200 µmol, 1.0 equiv.) was dissolved in 1.0 mL THF and cooled down to 0 °C. After dropwise addition of 0.1 M LiOH solution (6.00 mL, 600 µmol, 3.0 equiv.) over 1 h, the reaction mixture was allowed to warm up to temperature and stirred for further 23 h. The organic solvent was removed in vacuo and the remaining aqueous layer was extracted with Et_2O (2x 10 mL), acidified to pH = 1 with aqueous 10% $KHSO_4$ solution and repeatedly extracted with Et_2O (2x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to give **14** (70.6 mg, 180 µmol, 90%) as slightly yellow oil. The carboxylic proton was not resolved in the ^{1}H-NMR.

ORD: $[\alpha]_D^{20}$ = +10.6 (c = 1.17 MeCN). **^{1}H-NMR** (400 MHz, CD_3CN) δ 7.56 (dd, *J* = 8.1, 1.6 Hz, 2 H, Ar*H*), 7.41–7.30 (m, 3 H, Ar*H*), 7.10 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.74 (d, *J* = 7.9 Hz, 1 H, N*H*), 6.05 (q, *J* = 7.8 Hz, 1 H, C*H*CF_3), 4.52 (td, *J* = 8.2, 5.4 Hz, 1 H, NHC*H*), 3.04 (dd, *J* = 14.2, 5.4 Hz, 1 H, NHCHCH_2), 2.84 (dd, *J* = 14.2, 8.4 Hz, 1 H, NHCHCH_2), 1.80 (s, 3 H, COCH_3). **^{13}C-NMR** (101 MHz, CD_3CN) δ 173.1, 171.6, 160.1 (q, *J* = 5.9 Hz), 155.9, 133.4, 132.9, 131.7, 131.6, 129.8, 128.4, 124.3 (q, *J* = 268.9 Hz), 118.0, 105.8 (q, *J* = 34.3 Hz), 54.5, 36.9, 22.6. **^{19}F-NMR** (376 MHz,

CD_3CN) δ -58.2. **IR**: *v* 3422 (m), 1723 (w), 1660 (m), 1624 (m), 1509 (s), 1440 (w), 1342 (s), 1274 (s), 1216 (s), 1125 (s), 1017 (w), 892 (w), 835 (w), 763 (w), 737 (w). **HRMS** (ESI/QTOF) *m/z*: $[M-H]^-$ calcd for $C_{20}H_{17}F_3NO_4^-$ 392.1115, found: 392.1110.

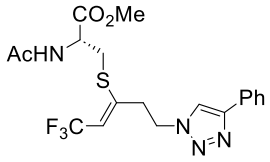
Methyl ((*S*)-2-acetamido-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (15)



Synthesized similiar to *N*-Boc-L-Ala-L-Tyr-OMe (**S1**) on 178 µmol scale using **14** (70.0 mg, 178 µmol, 1.0 equiv.) and L-Ala-OMe·HCl (24.8 mg, 178 µmol, 1.0 equiv.) Purification by MPLC (t_R = 16.4–16.9 min, gradient: 5–95% MeCN in 28 min) gave the dipeptide **15** (52.8 mg, 110 µmol, 62%) as an amorphous white solid.

ORD: $[\alpha]_D^{20}$ = +10.2 (c = 1.67, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.51–7.40 (m, 2 H, Ar*H*), 7.35–7.27 (m, 3 H, Ar*H*), 7.05 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.58–6.45 (m, 1 H, N*H*), 6.42–6.28 (m, 1 H, N*H*), 5.80 (q, *J* = 7.5 Hz, 1 H, C*H*CF_3), 4.61 (q, *J* = 7.3 Hz, 1 H, NHC*H*CH_3), 4.40 (p, *J* = 7.1 Hz, 1 H, NHC*H*CH_2), 3.68 (s, 3 H, CO_2CH_3), 2.91 (d, *J* = 7.0 Hz, 2 H, CHC*H*$_2$), 1.89 (d, *J* = 1.3 Hz, 3 H, COC*H*$_3$), 1.28 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 172.8, 170.7, 170.1, 159.0 (q, *J* = 5.7 Hz), 155.3, 132.7, 131.1, 130.6, 128.9, 127.3, 123.0 (q, *J* = 269.7 Hz), 117.3, 105.2 (q, *J* = 34.9 Hz), 54.3, 52.5, 48.3, 37.7, 23.1, 18.0. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -57.7. **IR**: *v* 3688 (m), 3678 (m), 2976 (s), 2910 (s), 1739 (w), 1663 (w), 1653 (m), 1559 (w), 1530 (w), 1512 (w), 1451 (w), 1397 (m), 1382 (m), 1350 (w), 1270 (m), 1235 (m), 1079 (s), 1048 (s), 896 (w), 871 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{25}F_3N_2NaO_5^+$ 501.1608, found 501.1617. For a detailed assignment of the NMR signals see table **S56** (chapter 5).

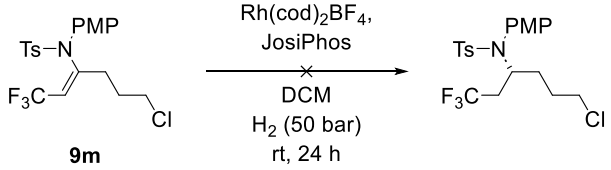
Methyl (*Z*)-*N*-acetyl-*S*-(1,1,1-trifluoro-5-(4-phenyl-1H-1,2,3-triazol-1-yl)pent-2-en-3-yl)-L-cysteinate (16)



Trifluoromethylated cysteine species **8j** (10.0 mg, 29.3 µmol, 1.0 equiv.) was dissolved in a mixture of tBuOH (1.0 mL) and water (0.5 mL). Phenylacetylene (6.45 µL, 6.00 mg, 58.7 µmol, 2.0 equiv.), copper sulphate pentahydrate (2.20 mg, 8.80 µmol, 30 mol%), tris(benzyltriazolmethyl)amine–TBTA (6.24 mg, 11.7 µmol, 40 mol%) and sodium ascorbate–NaOAsc (2.34 mg, 11.7 mmol, 40 mol%) were added and the reaction mixture was stirred for 28 h at room temperature. After addition of water (5.0 mL) and ethyl acetate (5.0 mL), the layers were separated and the and the aqueous layer was extracted with EtOAc (2x 5.0 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by MPLC (t_R = 15.6–16.7 min, gradient: 5–95% MeCN in 28 min). The corresponding cycloaddition product **16** (11.0 mg, 24.8 µmol, 85%) was obtained as colorless oil.

ORD: $[\alpha]_D^{20}$ = +7.7 (c = 0.55, MeOH). **^{1}H-NMR** (400 MHz, MeOD-d_4) δ 8.30 (s, 1 H, NC*H*=C), 7.82–7.75 (m, 2 H, Ar*H*), 7.47–7.39 (m, 2 H, Ar*H*), 7.37–7.30 (m, 1 H, Ar*H*), 5.81 (q, *J* = 8.1 Hz, 1 H, C*H*CF_3), 4.72 (t, *J* = 6.8 Hz, 2 H, C*H*$_2$N), 4.59 (dd, *J* = 8.0, 5.4 Hz, 1 H, NHC*H*), 3.74 (s, 3 H, CO_2CH_3), 3.40 (dd, *J* = 14.1, 5.4 Hz, 1 H, CHC*H*$_2$), 3.19 (dd, *J* = 14.2, 8.0 Hz, 1 H, CHC*H*$_2$), 3.16–3.11 (m, 2 H, C*H*$_2$CH$_2$N), 1.99 (s, 3 H, COC*H*$_3$). **^{13}C-NMR** (101 MHz, MeOD-d_4) δ 173.4, 171.8, 148.8, 147.1 (q, *J* = 5.5 Hz), 131.6, 130.0, 129.4, 126.7, 123.6 (q, *J* = 270.6 Hz), 122.7, 121.3 (q, *J* = 34.7 Hz), 54.0, 53.1, 49.2 (overlapping with MeOD-d_4 signal, extracted from HSQC), 37.1, 32.8, 22.3. **^{19}F-NMR** (376 MHz, MeOD-d_4) δ -59.5. **IR**: *v* 3668 (m), 2972 (s), 2901 (s), 1735 (w), 1656 (w), 1455 (w), 1401 (m), 1379 (m), 1242 (m), 1235 (m), 1076 (s), 1044 (s), 1022 (m), 896 (w), 867 (w). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{22}F_3N_4O_3S^+$ 443.1359, found 443.1364. For a detailed assignment of the NMR signals see table **S57** (chapter 5).

(*S*)-*N*-(6-Chloro-1,1,1-trifluorohexan-3-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide



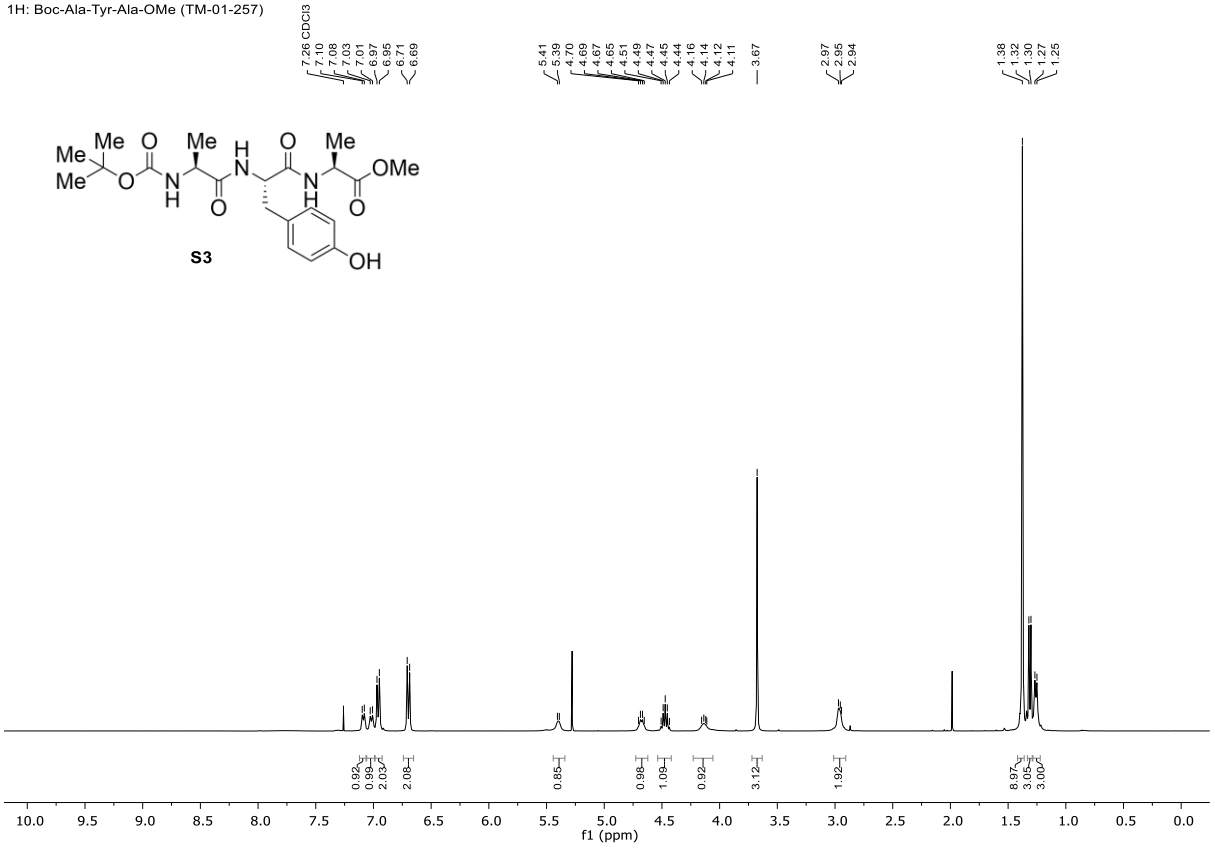
Following a reported procedure[23], $Rh(cod)_2BF_4$ (4.01 mg, 10.0 µmol, 5.0 mol%) and JosiPhos (7.16 mg, 12.0 µmol, 6.0 mol%) were dissolved in dry DCM (4.0 mL). The solution was stirred for 15 min at room temperature before the starting material **9m** (89.6 mg, 200 µmol, 1.0 equiv.) was added. The reaction mixture was transferred to an autoclave, where the reaction tube was purged and charged with hydrogen (50 bar). The mixture was stirred at room tempature for 24 h. Crude NMR analysis showed that no reaction was occurring.

[23] Z. Li, R. Xu, H. Gua, H. Yang, G. Xu, E. Shi, J. Xiao, W. Tang, *Org. Lett.* **2022**, *24*, 714.

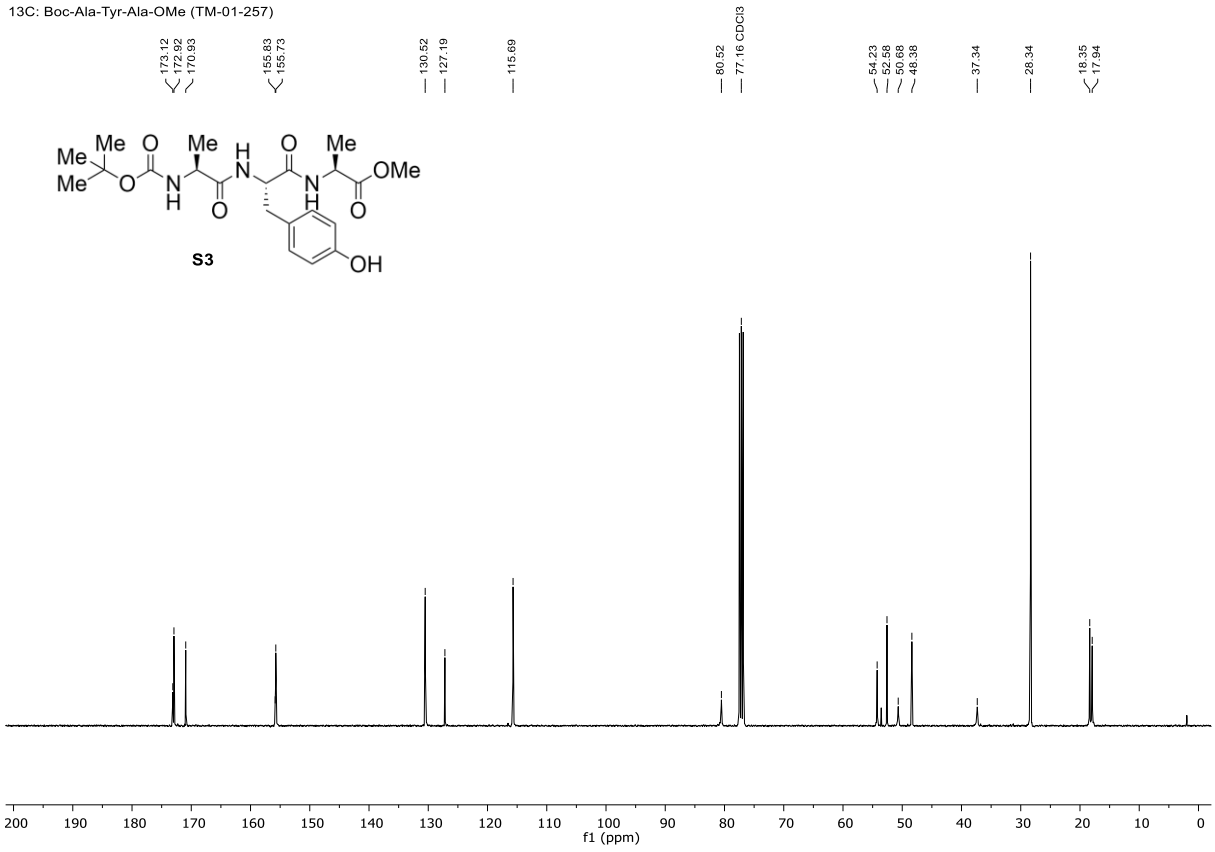
5 NMR Data

N-Boc-L-Ala-L-Tyr-L-Ala-OMe (S3)

^{1}H-NMR (400 MHz, $CDCl_3$)

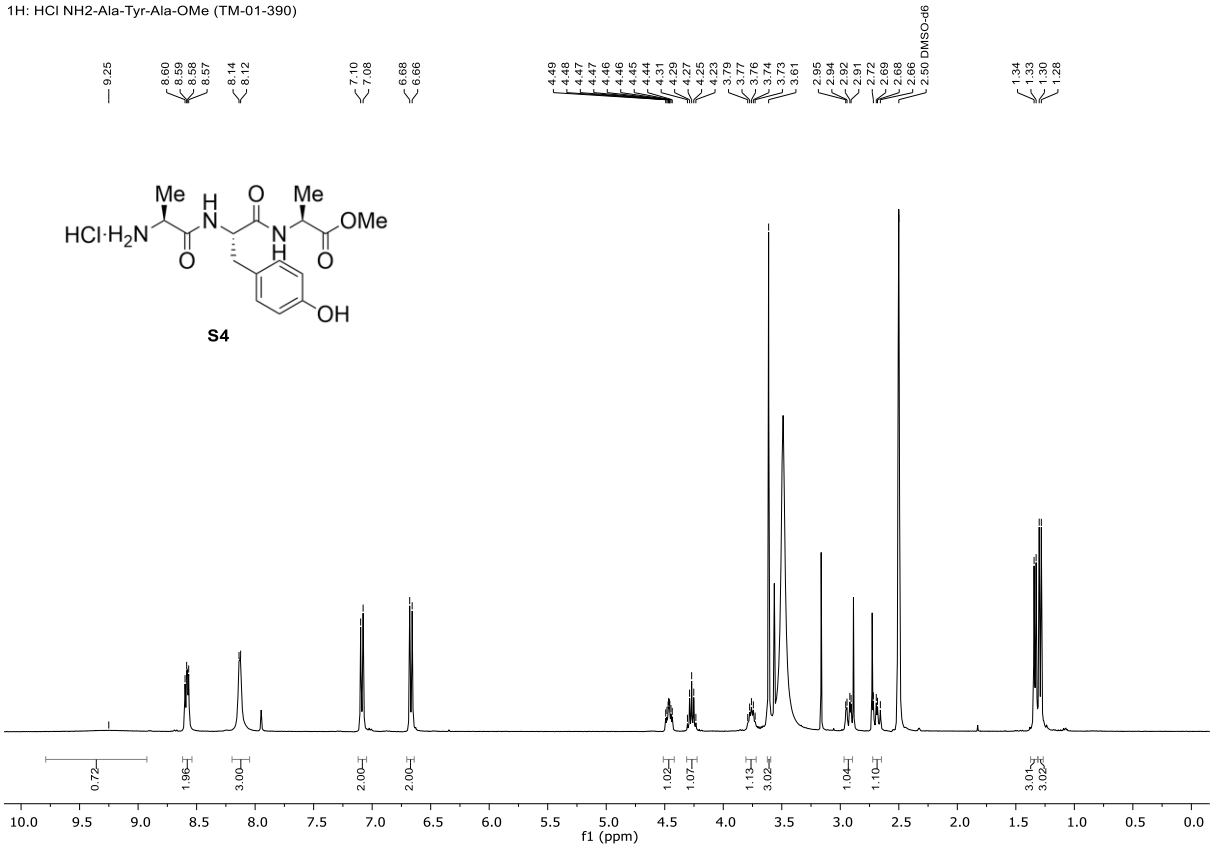


^{13}C-NMR (101 MHz, $CDCl_3$)

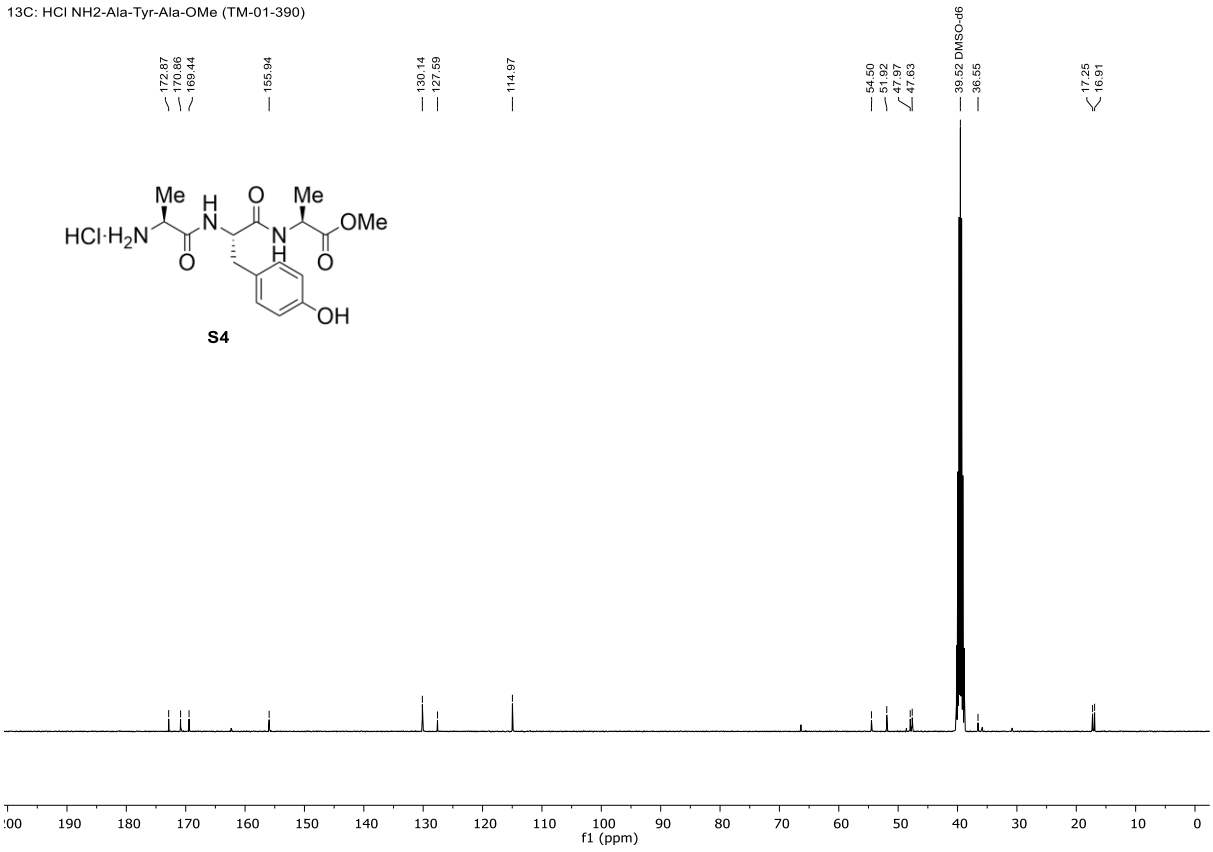


NH_2-L-Ala-L-Tyr- L-Ala-OMe·HCl (S4)

^{1}H-NMR (400 MHz, DMSO-d_6)

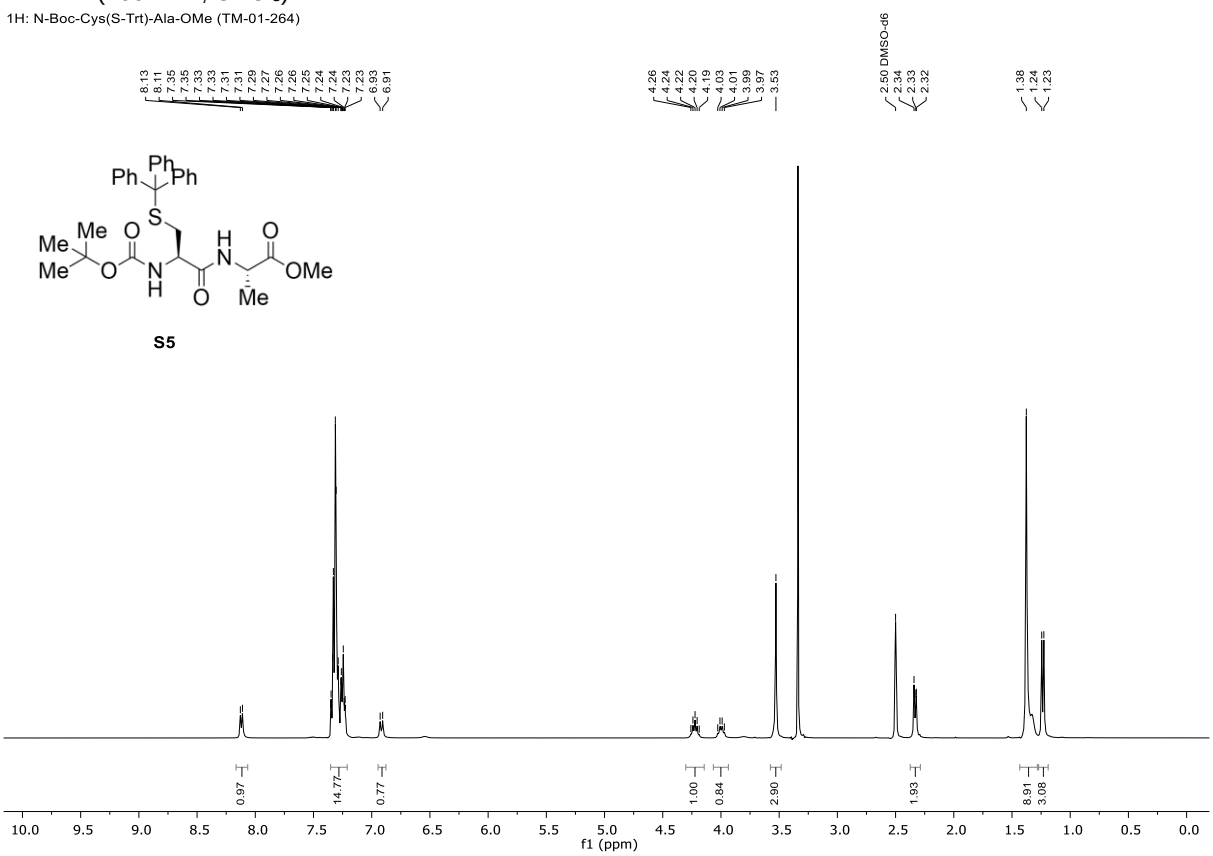


^{13}C-NMR (101 MHz, DMSO-d_6)

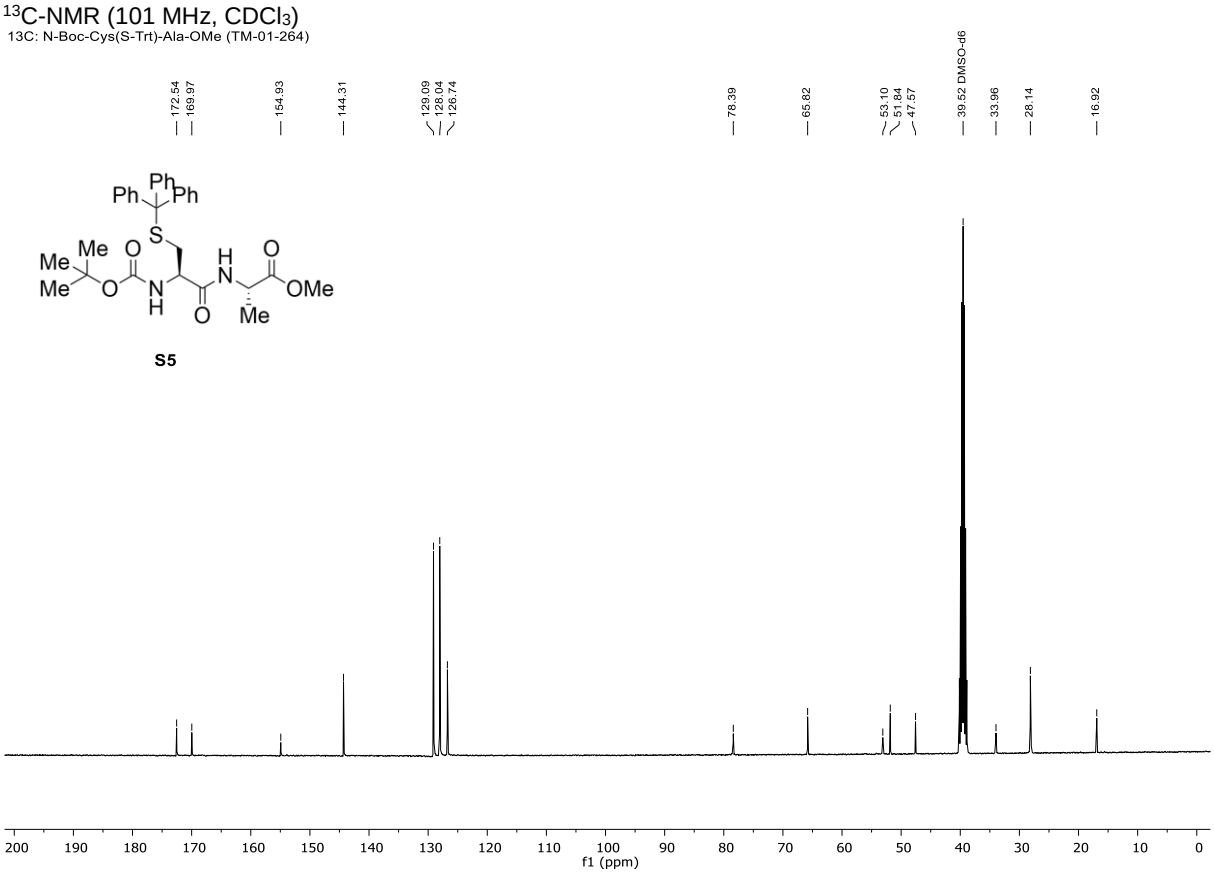


N-Boc-L-Cys(*S*-Trt)-L-Ala-OMe (S5)

^{1}H-NMR (400 MHz, $CDCl_3$)

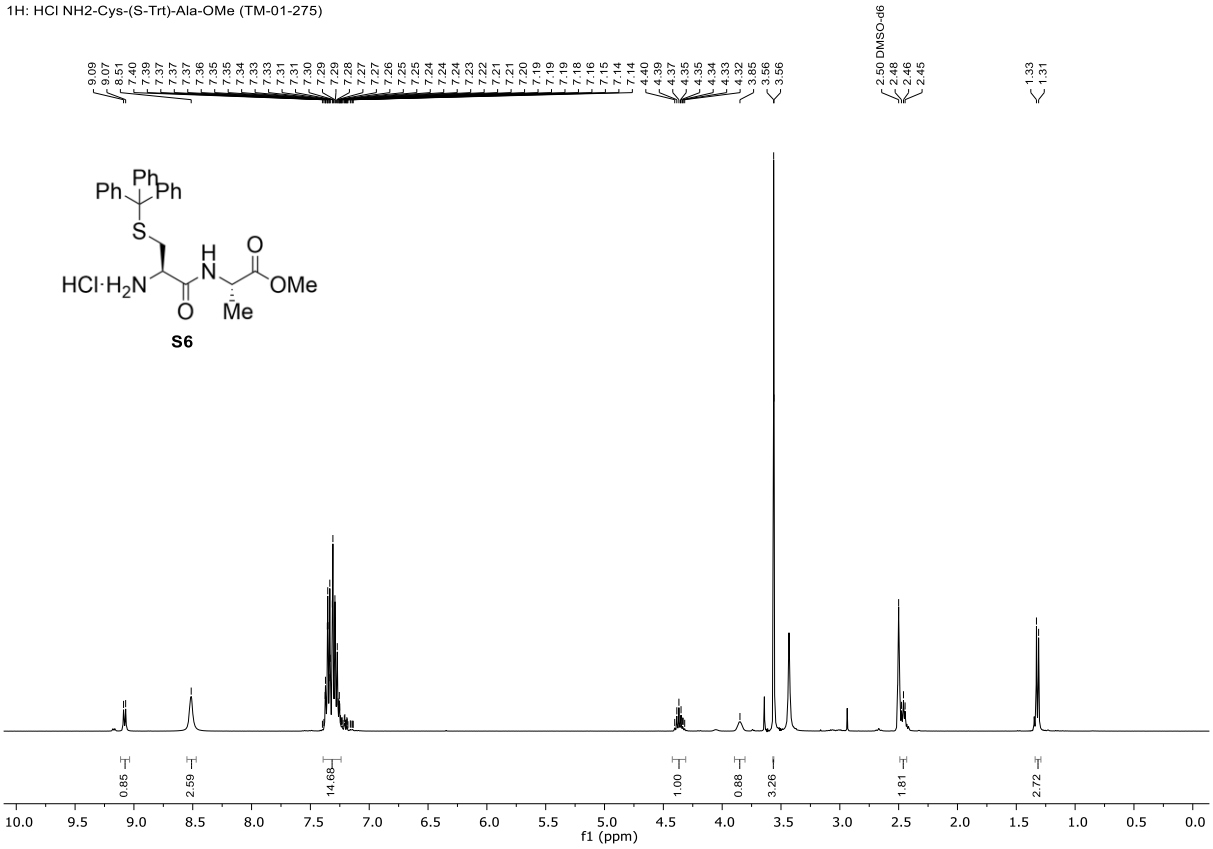


^{13}C-NMR (101 MHz, $CDCl_3$)

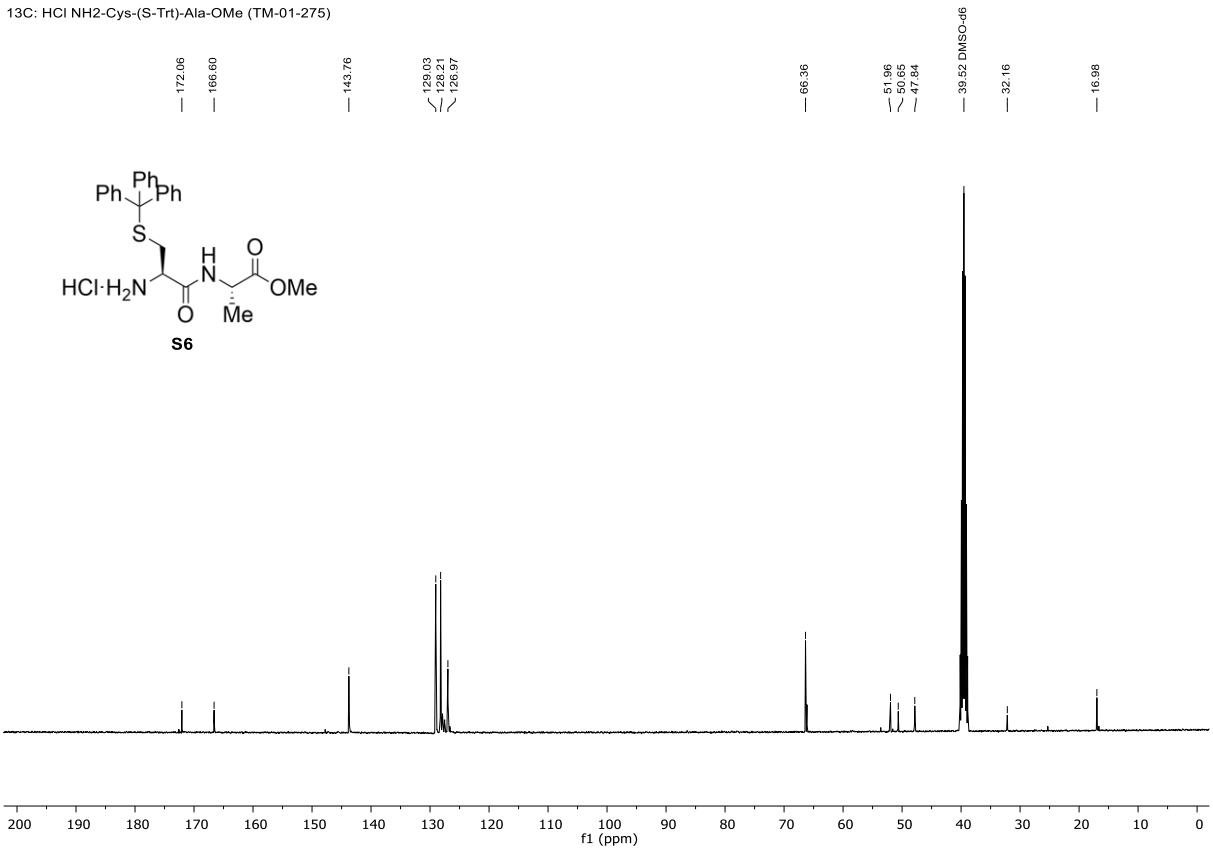


NH_2-L-Cys(*S*-Trt)-L-Ala-OMe·HCl (S6)

^{1}H-NMR (400 MHz, DMSO-d_6)

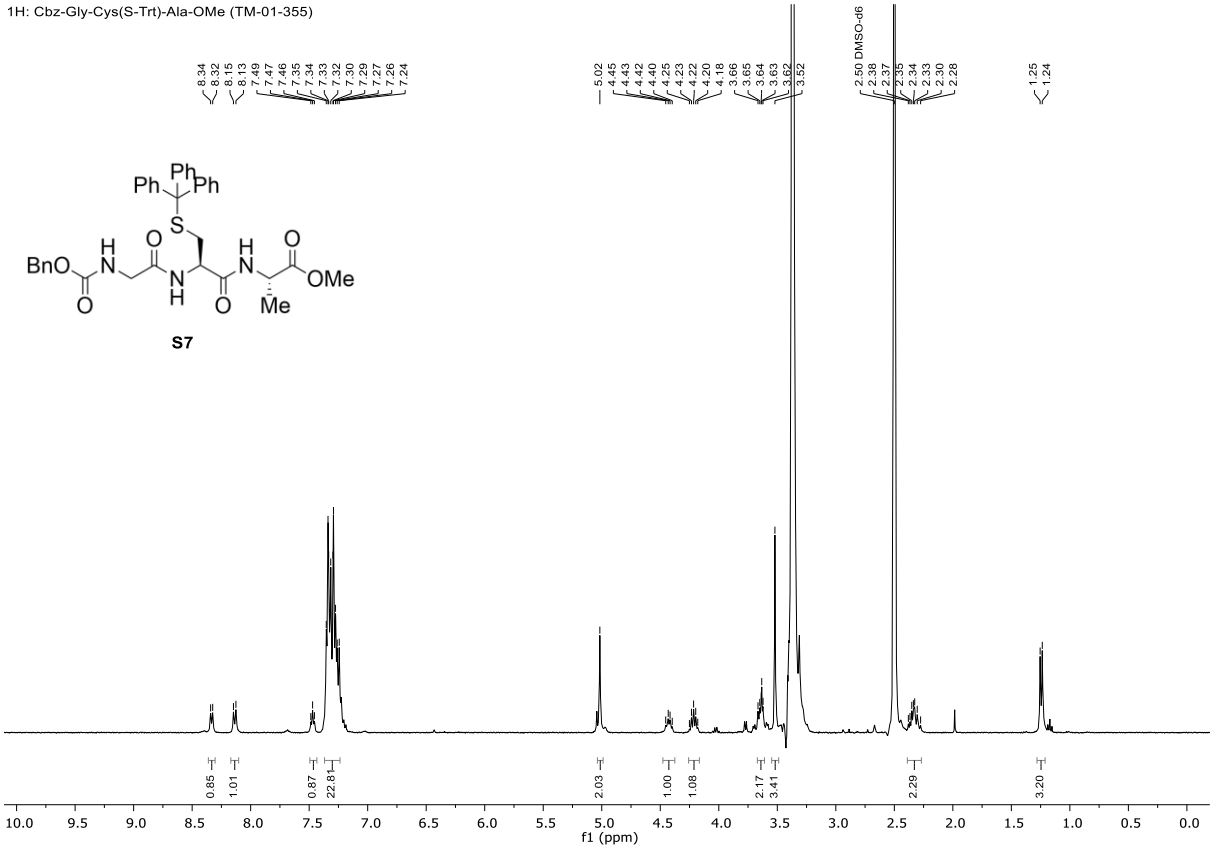


^{13}C-NMR (101 MHz, DMSO-d_6)



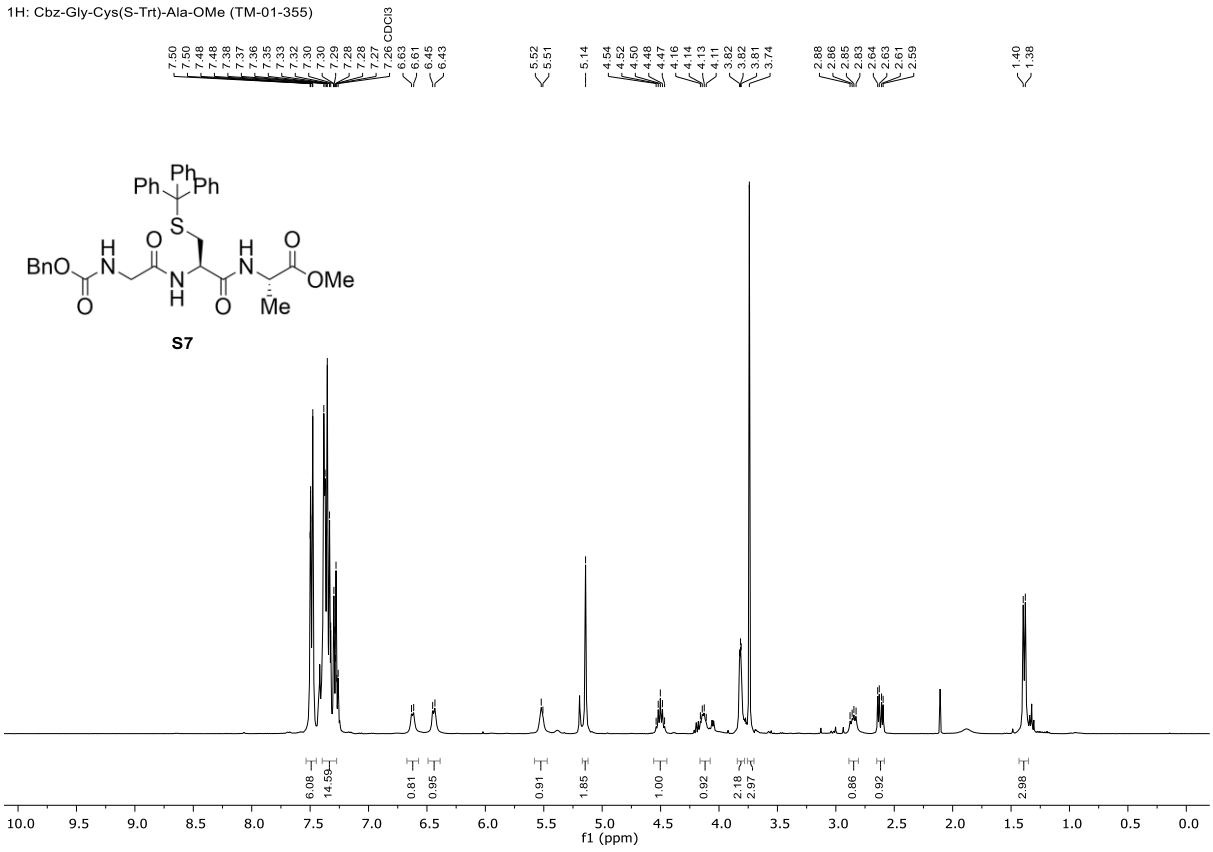
N-Cbz-Gly-L-Cys(*S*-Trt)-L-Ala-OMe (S7)

^{1}H-NMR (400 MHz, DMSO-d$_6$)



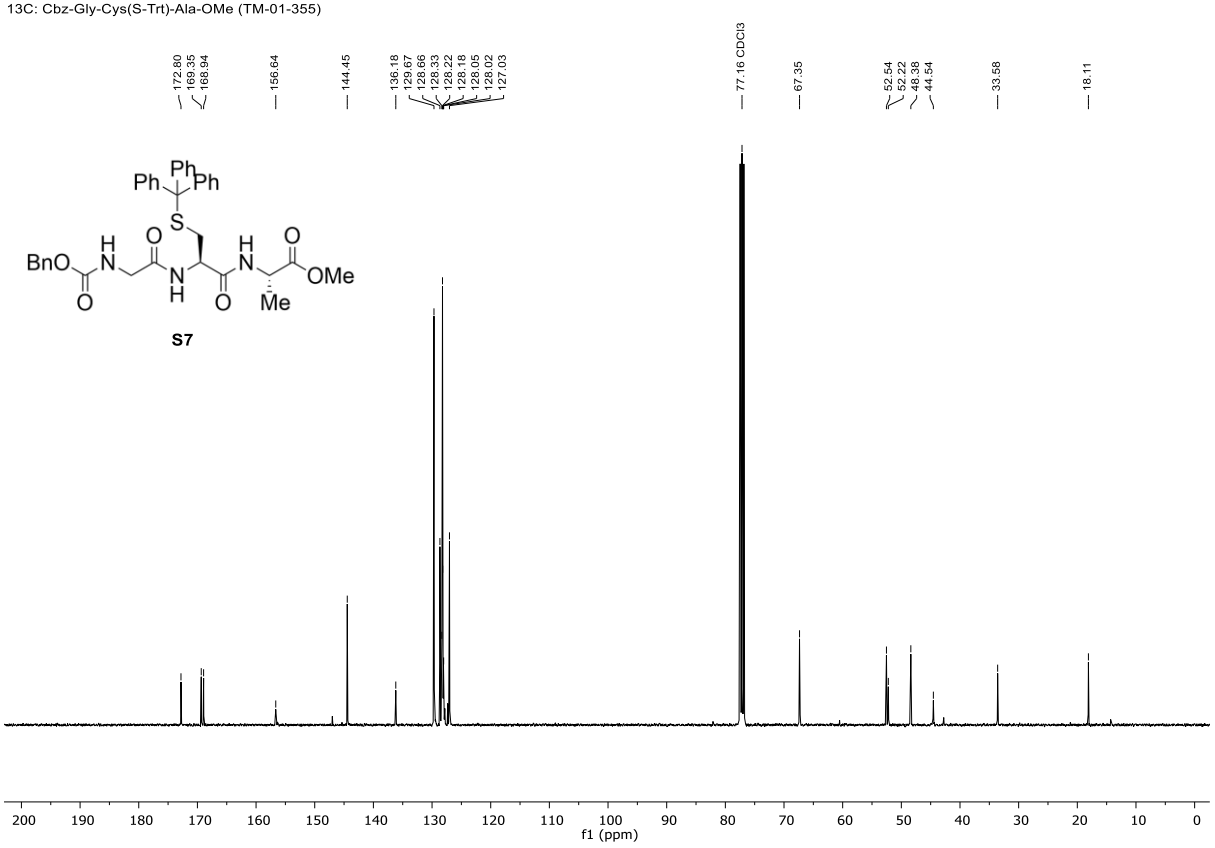
S7

^{1}H-NMR (400 MHz, CDCl$_3$)



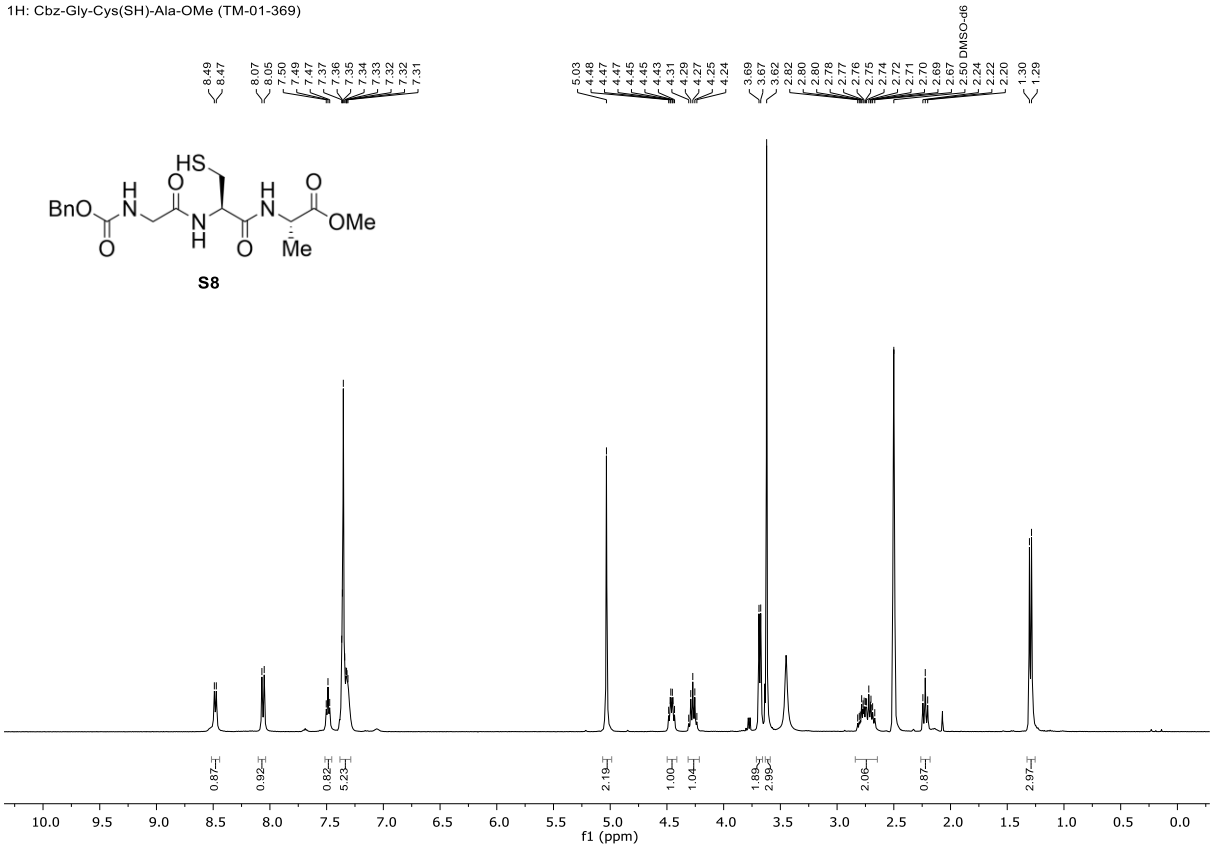
S7

^{13}C-NMR (101 MHz, $CDCl_3$)

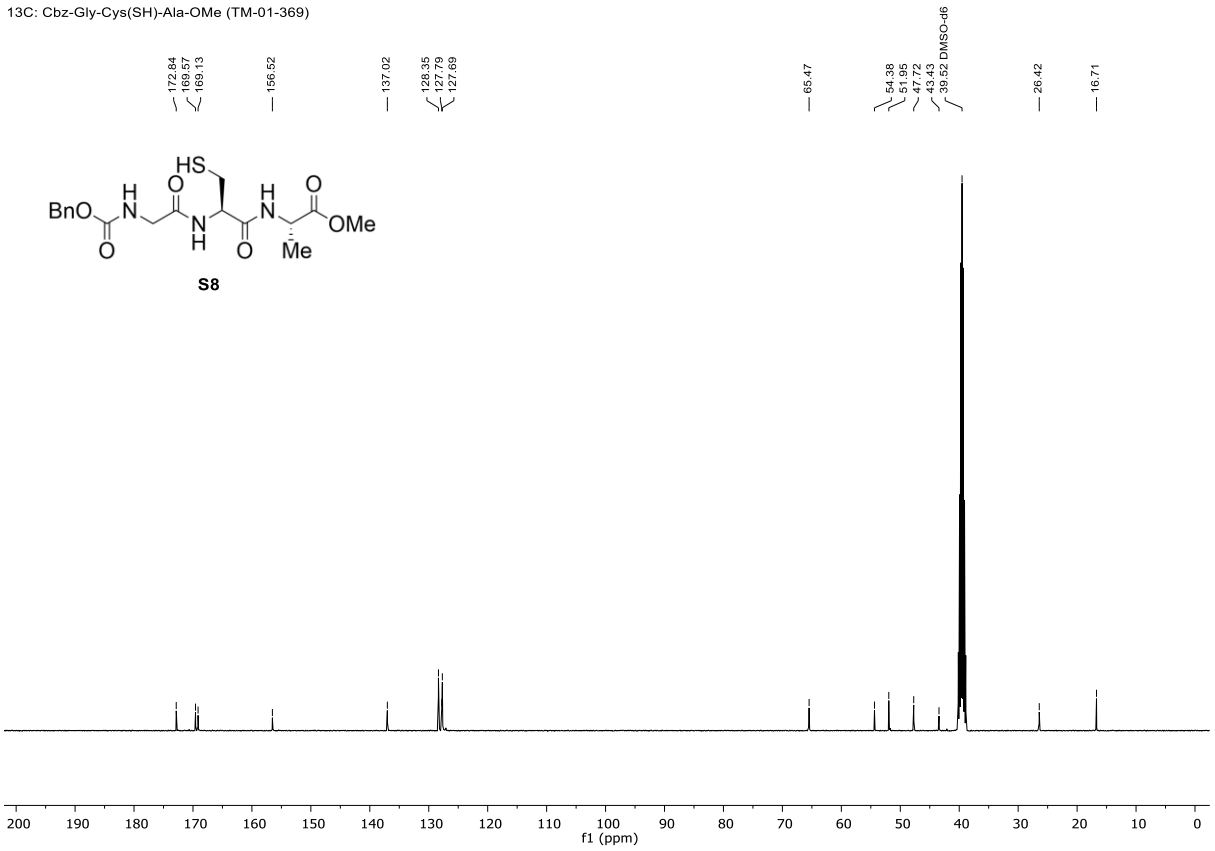


N-Cbz-Gly-L-Cys-L-Ala-OMe (S8)

^{1}H-NMR (400 MHz, DMSO-d$_6$)



^{13}C-NMR (101 MHz, DMSO-d$_6$)



Ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl) oxy)phenyl)propanoate (5a)

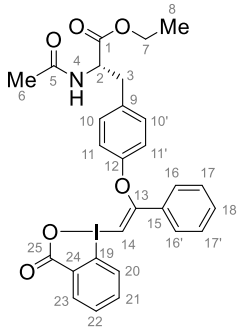
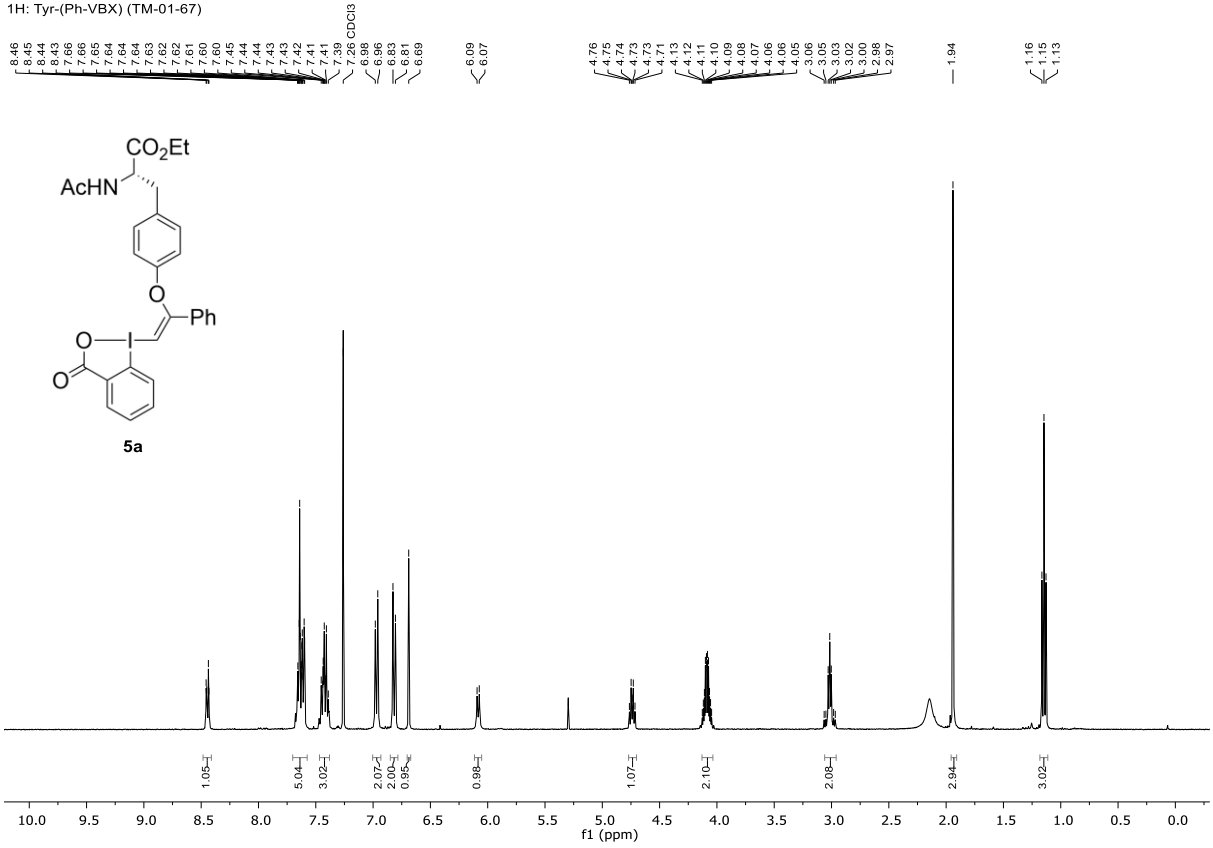


Table S3. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl) oxy)phenyl)propanoate (**5a**)

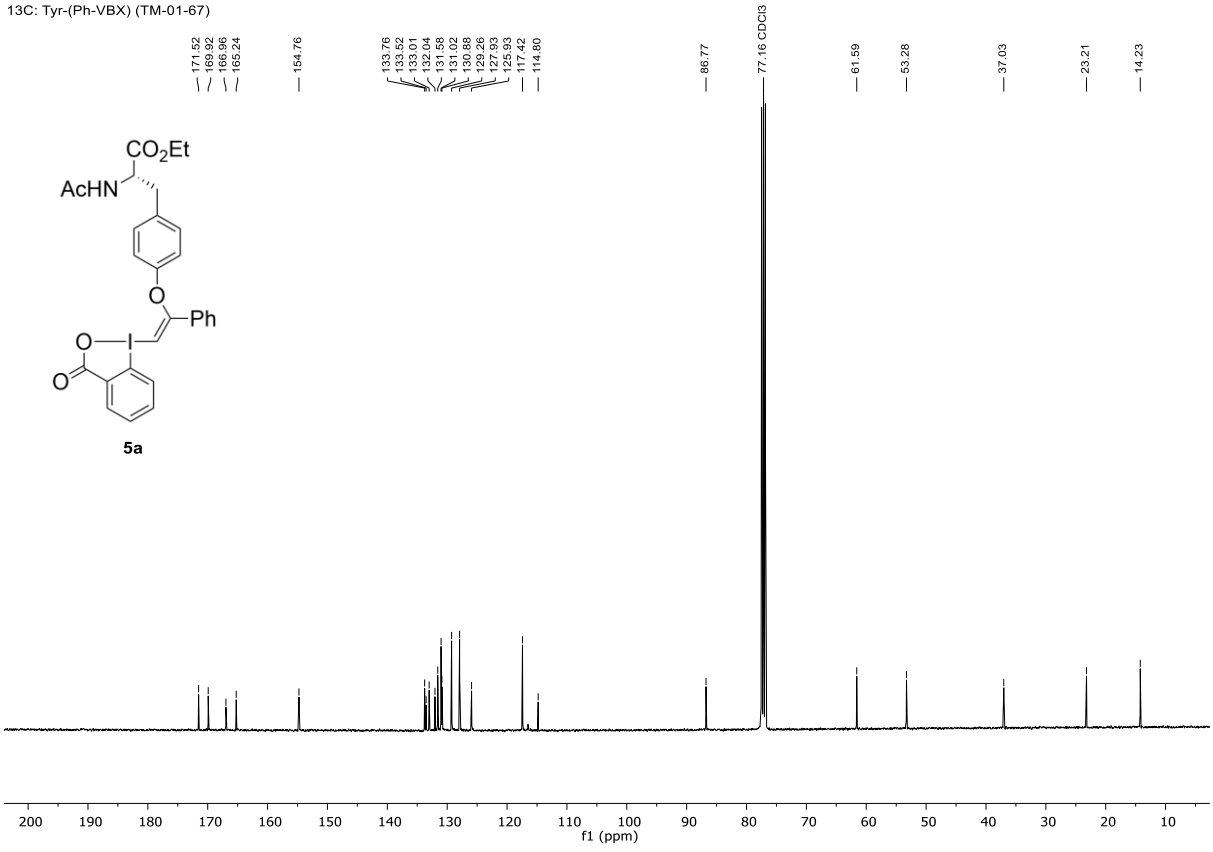
	δ_C	δ_H	COSY	HMBC (H→C)
1	171.5			
2	53.3	4.72 (dt, 7.6, 6.0 Hz)	3, 4	1, 3, 9
3	37.0	3.02 (dd, 12.7, 4.8 Hz), 2.97 (dd, 12.7, 3.3 Hz)	2	1, 2, 10/10‘
4	/	6.21 (d, 7.7 Hz)	2	2, 5
5	169.9			
6	23.2	1.92 (s)		5
7	61.6	4.06 (dq, 6.9, 3.6 Hz)	8	1, 8
8	14.2	1.12 (t, 7.1 Hz)	7	7
9	133.8			
10/10’	131.0	6.96 (d, 8.6 Hz)	11/11‘	3, 10/10‘, 12
11/11’	117.4	6.79 (d, 8.6 Hz)	10/10‘	10/10‘,12
12	154.8			
13	165.2			
14	86.8	6.72 (s)		13, 15
15	131.6			
16/16’	127.9	7.67-7.55 (m)	17/17’	13
17/17‘	129.3	7.45-7.35 (m)	16/16‘, 18	
18	129.3	7.45-7.35 (m)		
19	114.8			
20	133.0	8.43-8.37 (m)	21	19, 23, 25
21	132.0	7.67-7.55 (m)	20	19
22	125.9	7.67-7.55 (m)		
23	133.5	7.67-7.55 (m)		19
24	130.9			
25	167.0			

^{1}H-NMR (400 MHz, $CDCl_3$)

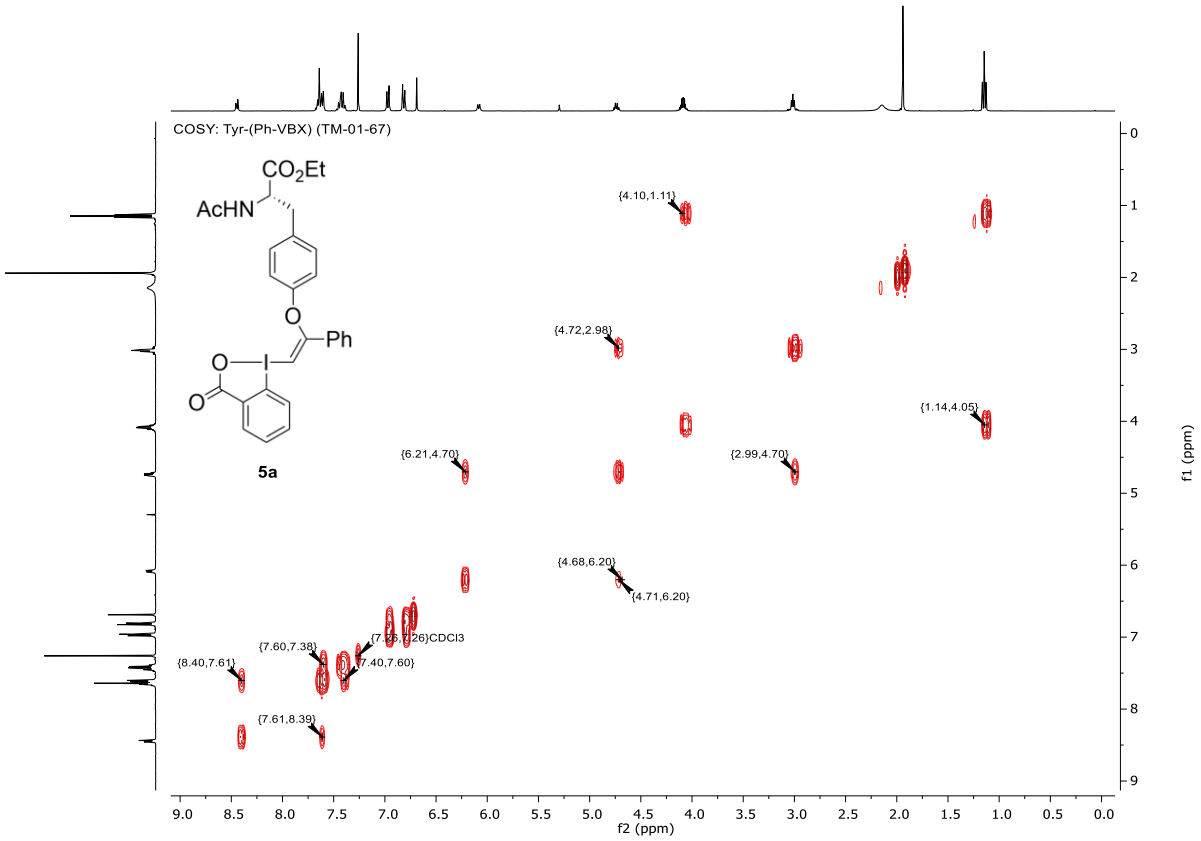


^{13}C-NMR (101 MHz, $CDCl_3$)

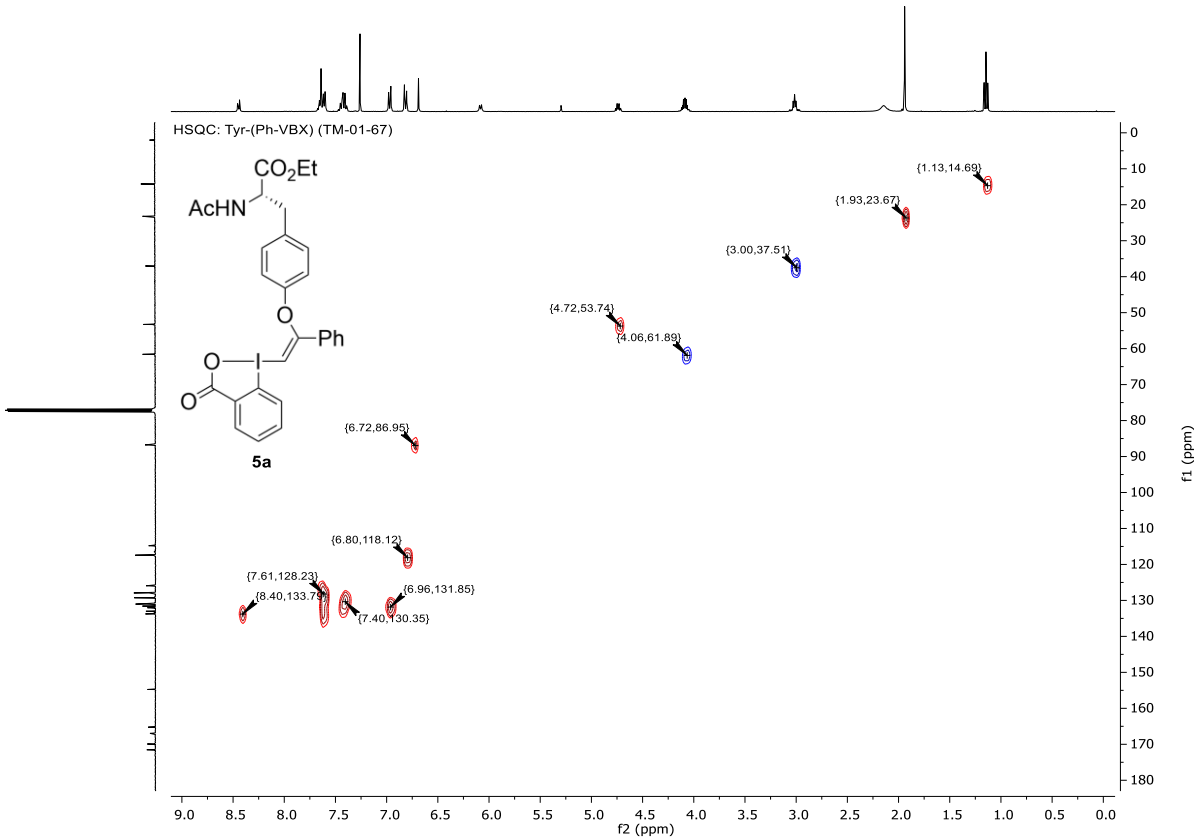
^{13}C-NMR (101 MHz, $CDCl_3$)



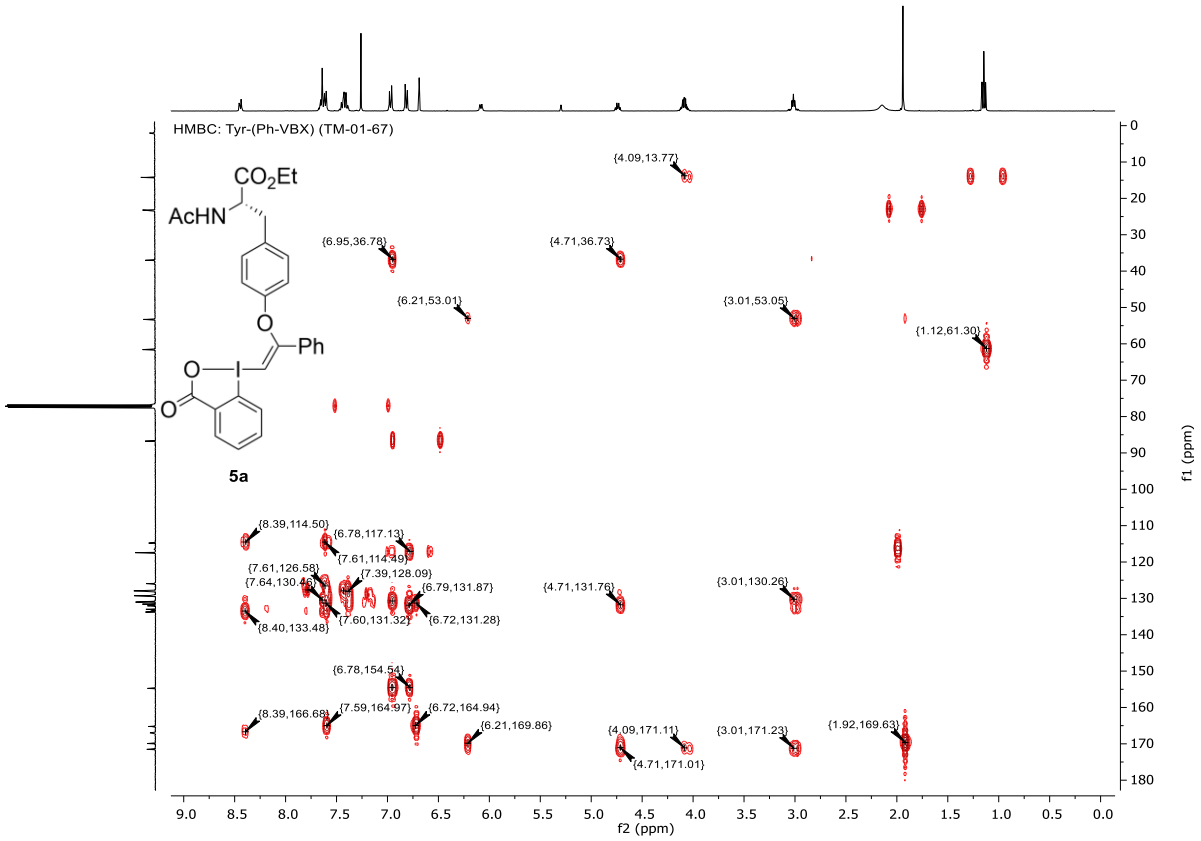
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*S*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*S*)-5b)

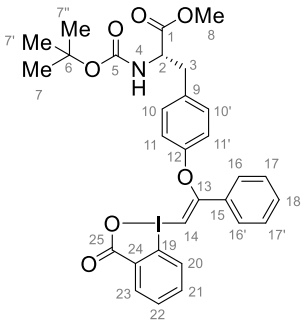
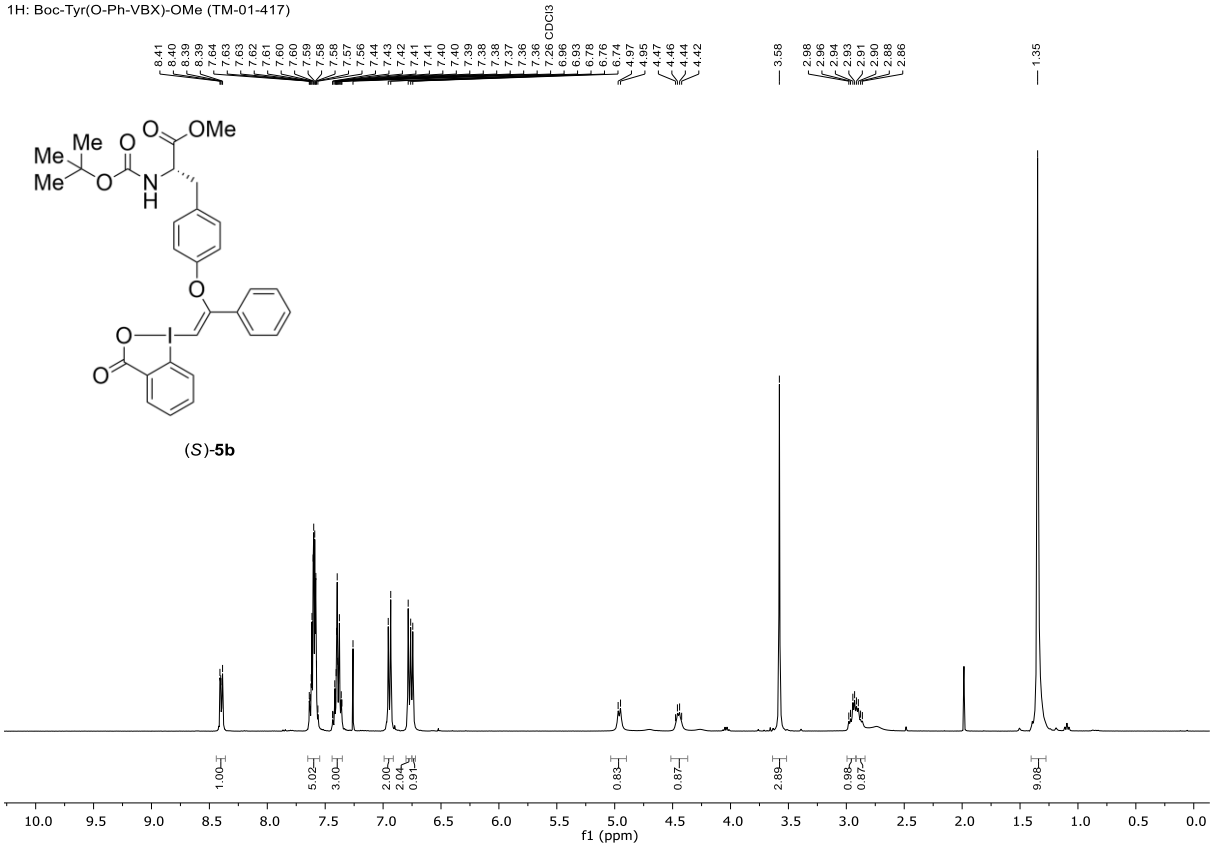


Table S4. Detailed NMR assignment of methyl (*S*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*S*)-**5b**).

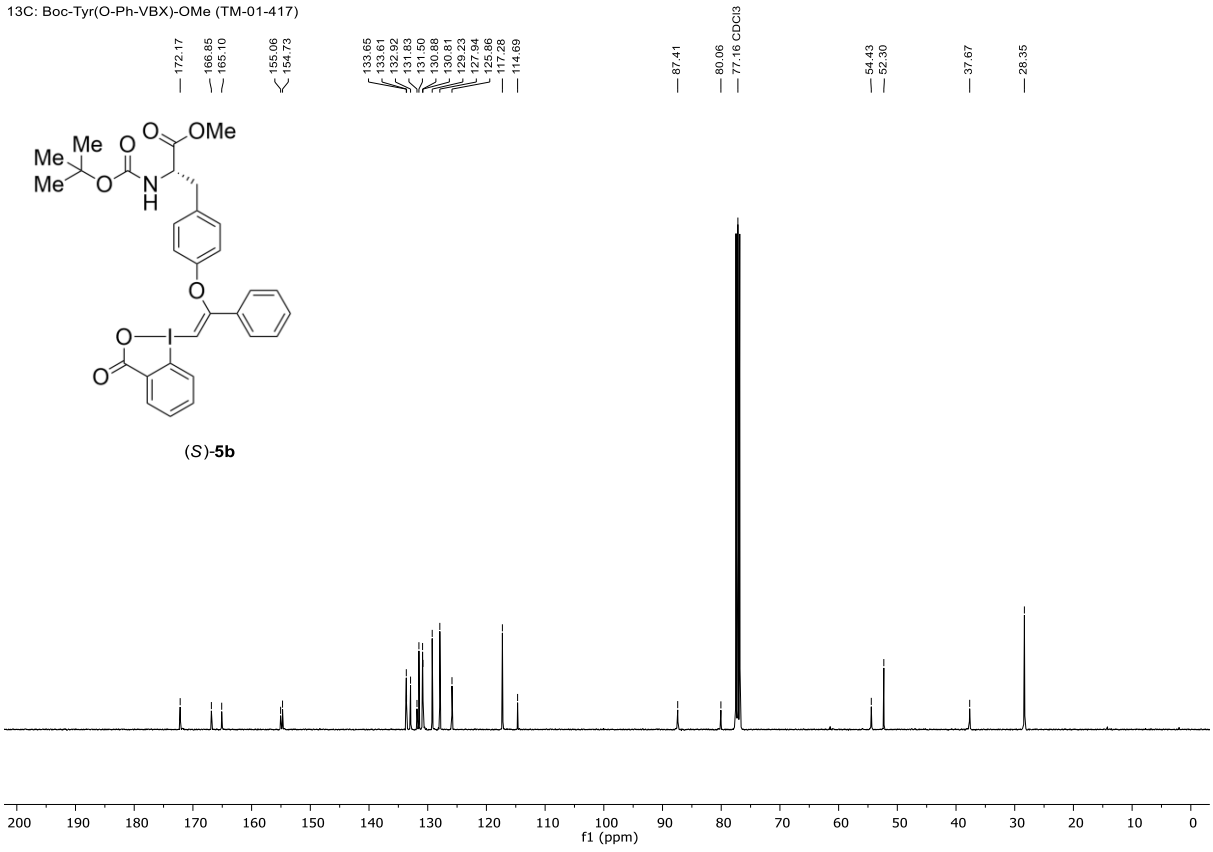
	δ_C	δ_H	COSY	HMBC (H→C)
1	172.2			
2	54.4	4.45 (q, 6.8 Hz)	3, 4	1
3	37.7	2.95 (dd, 14.0, 6.0 Hz), 2.89 (dd, 14.1, 6.5 Hz)	2	1, 2, 10/10‘
4	/	4.96 (d, 8.3 Hz)	2	
5	155.1			
6	80.1			
7/7‘/7“	28.4	1.35 (s)		6
8	52.3	3.58 (s)		1
9	131.5			
10/10’	130.8	6.94 (d, 8.6 Hz)	11/11‘	3, 11/11‘, 12
11/11’	117.3	6.77 (d, 8.6 Hz)	10/10‘	10/10‘, 12
12	154.7			
13	165.1			
14	87.4	6.74 (s)		13
15	133.6			
16/16’	127.9	7.65-7.55 (m)	17/17’, 18	
17/17‘	129.2	7.44-7.34 (m)	16/16‘	18
18	129.2	7.44-7.34 (m)	16/16‘	17/17‘
19	114.7			
20	133.6	8.40 (dd, 6.7, 2.3 Hz)	21, 22	19, 25
21	131.8	7.65-7.55 (m)	20	19, 22
22	125.9	7.65-7.55 (m)	20	21
23	132.9	7.65-7.55 (m)		21, 22, 25
24	130.9			
25	166.9			

^{1}H-NMR (400 MHz, $CDCl_3$)



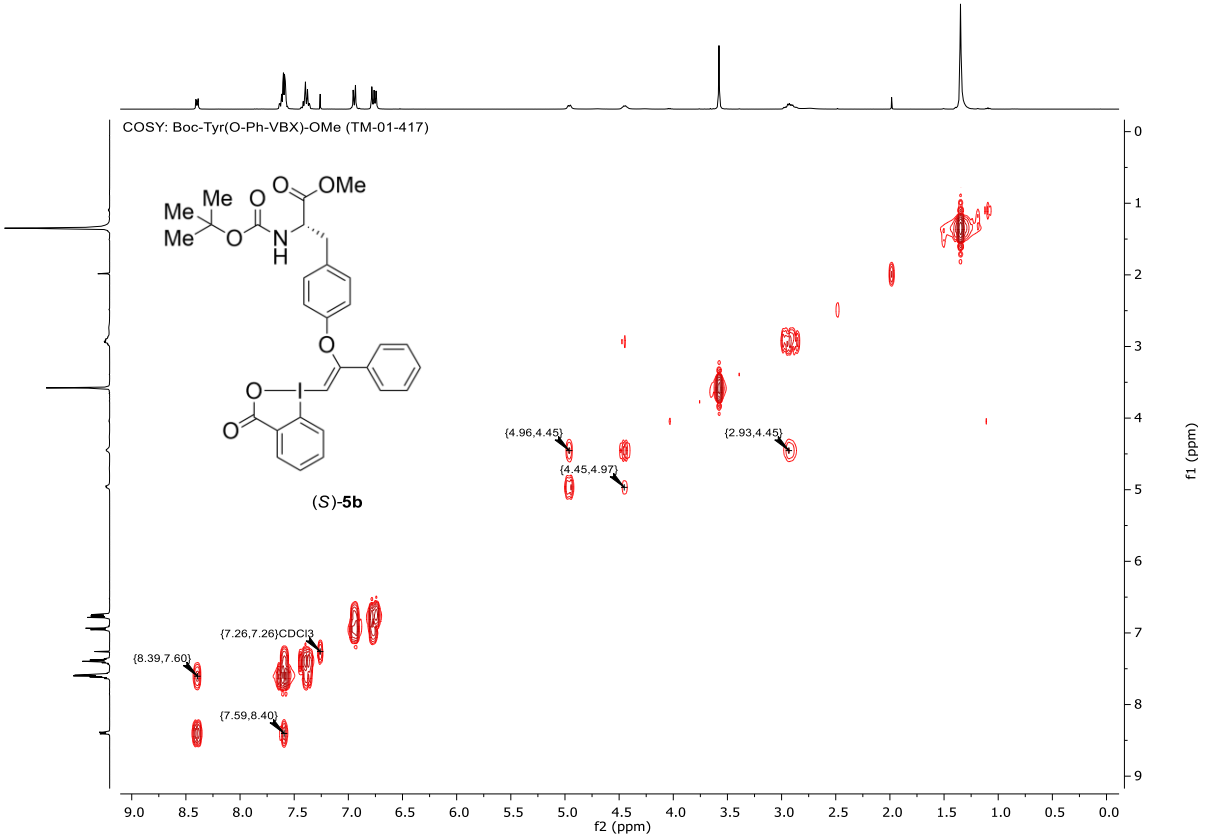
(*S*)-**5b**

^{13}C-NMR (400 MHz, $CDCl_3$)

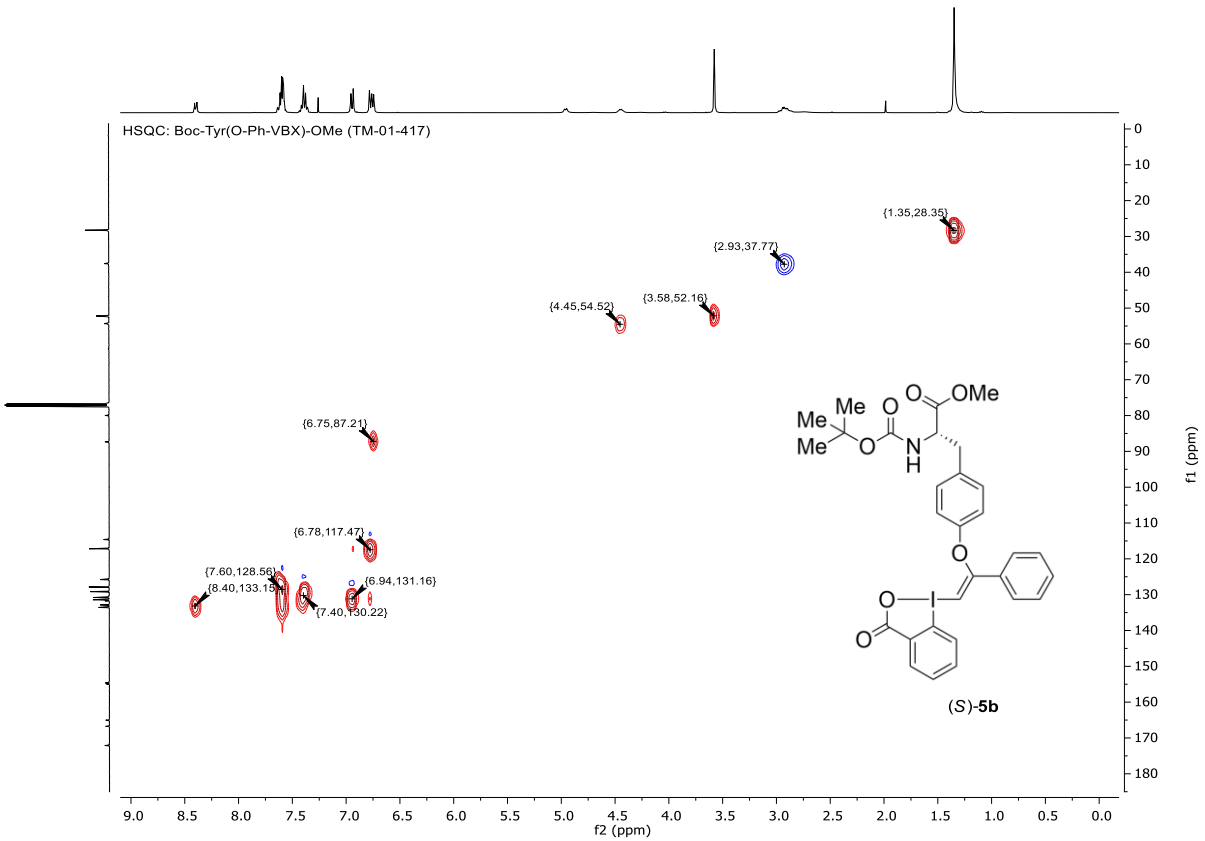


(*S*)-**5b**

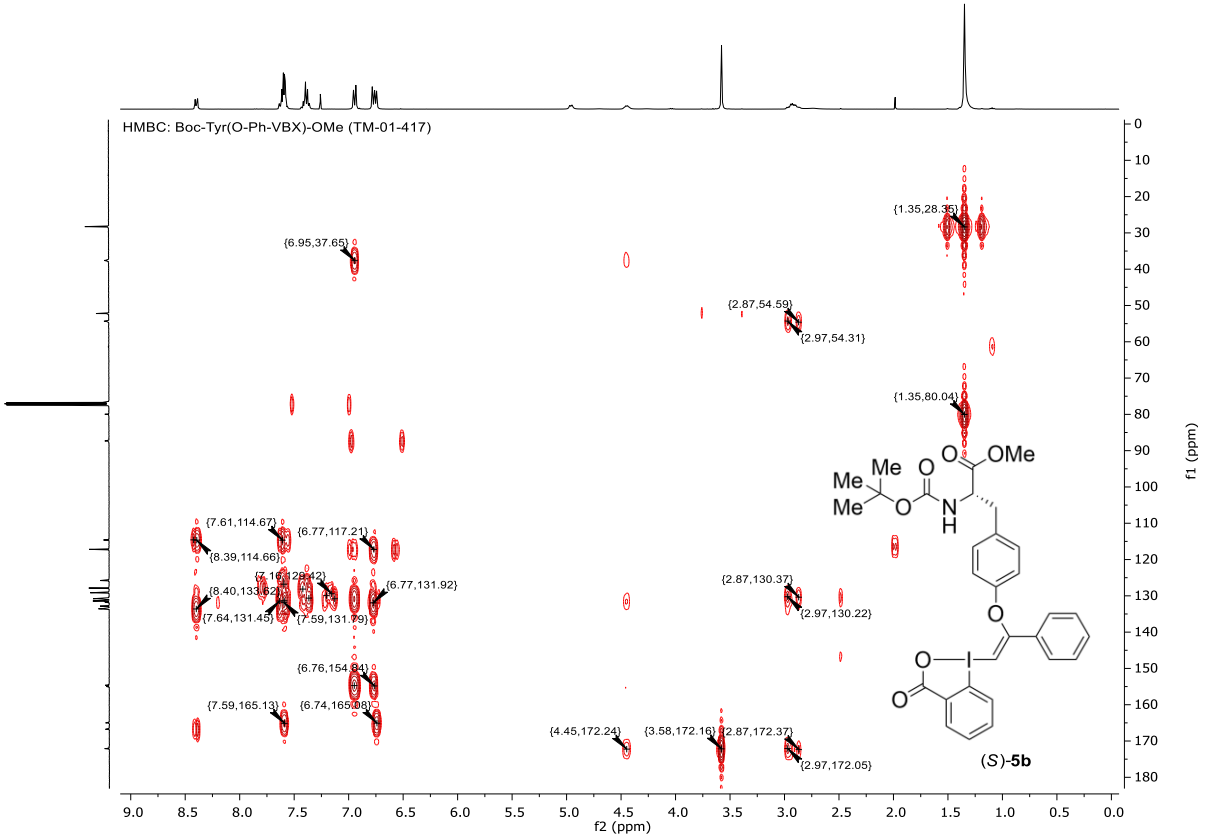
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*R*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*R*)-5b)

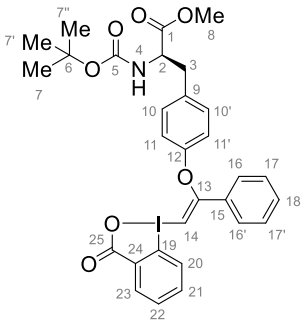
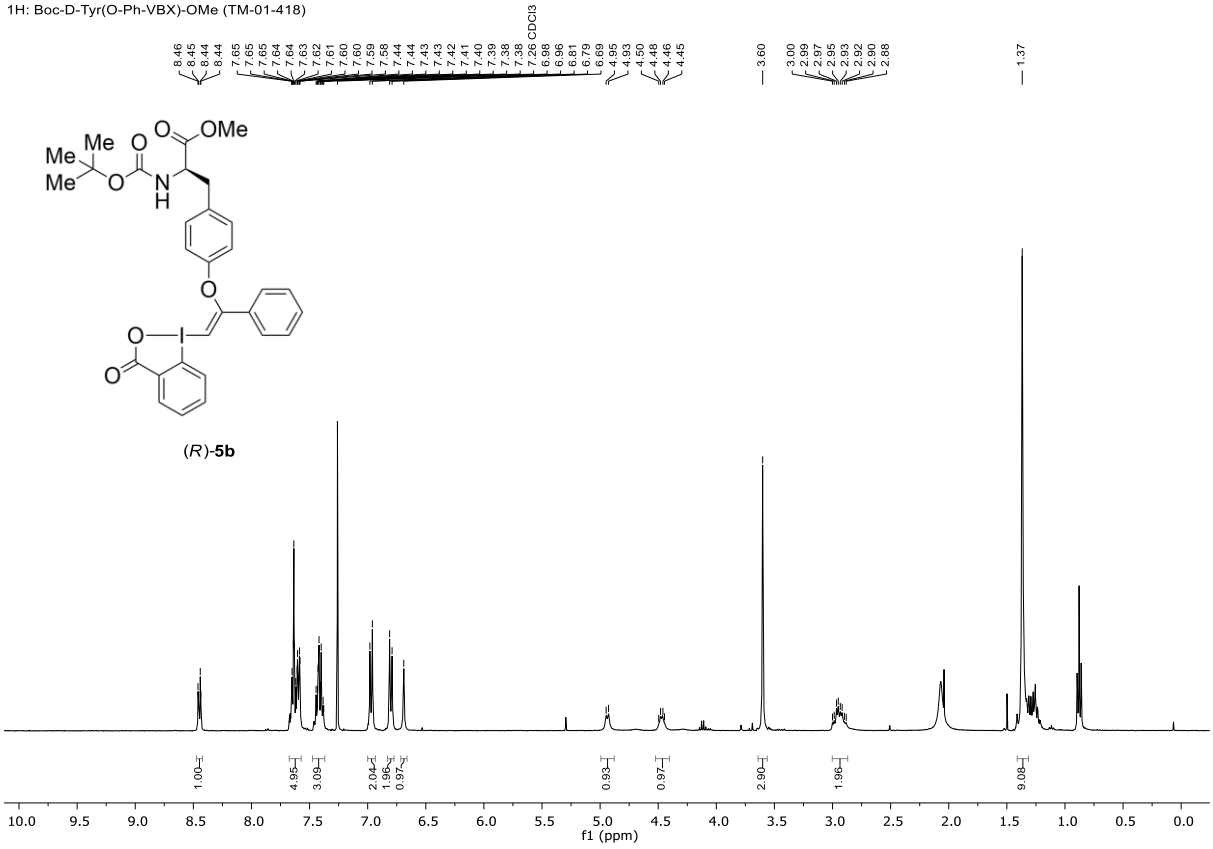


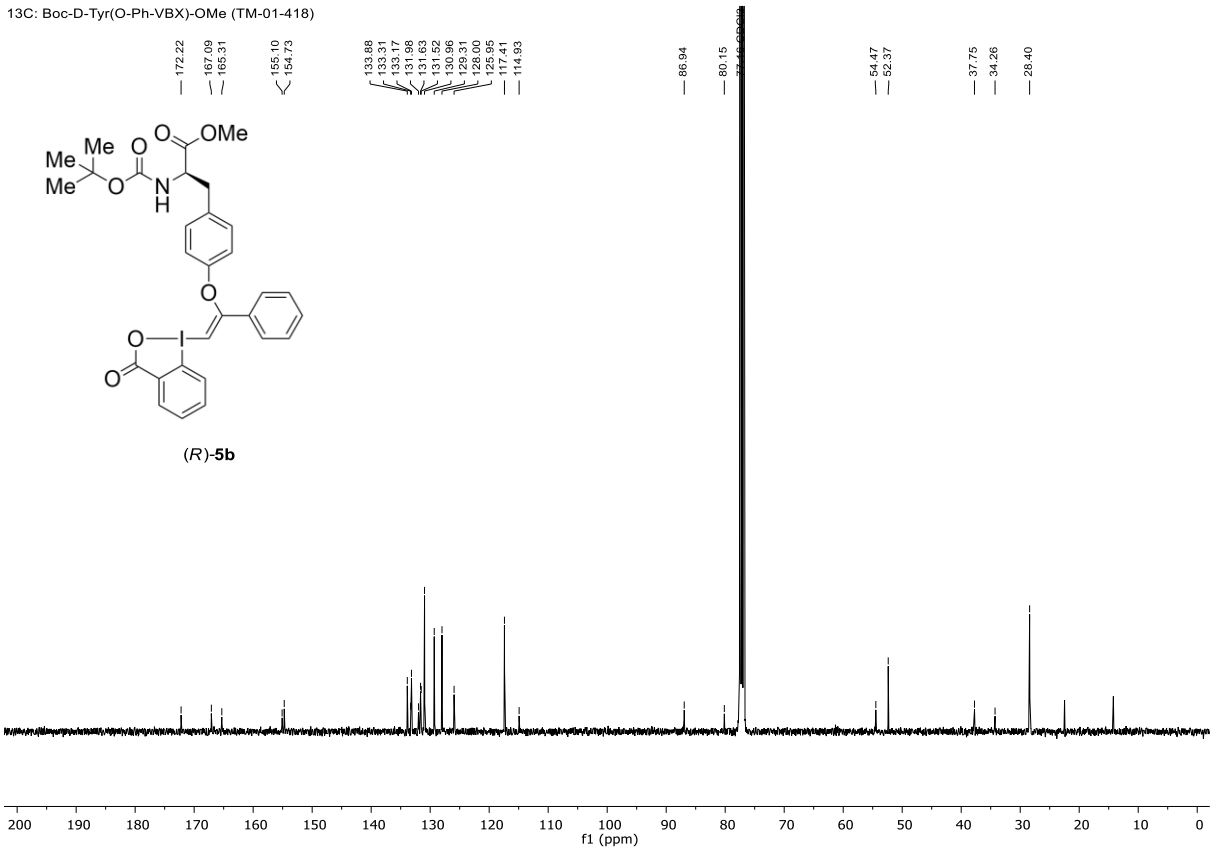
Table S5. Detailed NMR assignment of methyl (*R*,*Z*)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate ((*R*)-**5b**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	172.2			
2	54.5	4.47 (dd, 14.0, 5.8 Hz)	3, 4	1, 9
3	37.7	2.98 (dd, 13.9, 5.9 Hz), 2.91 (dd, 14.2, 6.4 Hz)	2	1, 2, 10/10‘
4	/	4.94 (d, 8.3 Hz)	2	
5	155.1			
6	80.1			
7/7‘/7“	28.4	1.37 (s)		6
8	52.4	3.60 (s)		1
9	131.6			
10/10’	131.0	6.97 (d, 8.6 Hz)	11/11‘	3, 11/11‘, 12
11/11’	117.4	6.80 (d, 8.6 Hz)	10/10‘	10/10‘, 12
12	154.7			
13	165.3			
14	86.9	6.69 (s)		13
15	133.2			
16/16’	128.0	7.67-7.57 (m)	17/17’, 18	
17/17‘	129.3	7.47-7.37 (m)	16/16‘	18
18	129.3	7.47-7.37 (m)	16/16‘	17/17‘
19	114.9			
20	133.9	8.45 (dd, 7.8, 2.0 Hz)	21, 22	19, 25
21	132.0	7.67-7.57 (m)	20	19, 22
22	125.9	7.67-7.57 (m)	20	21
23	133.3	7.67-7.57 (m)		21, 22, 25
24	131.5			
25	167.1			

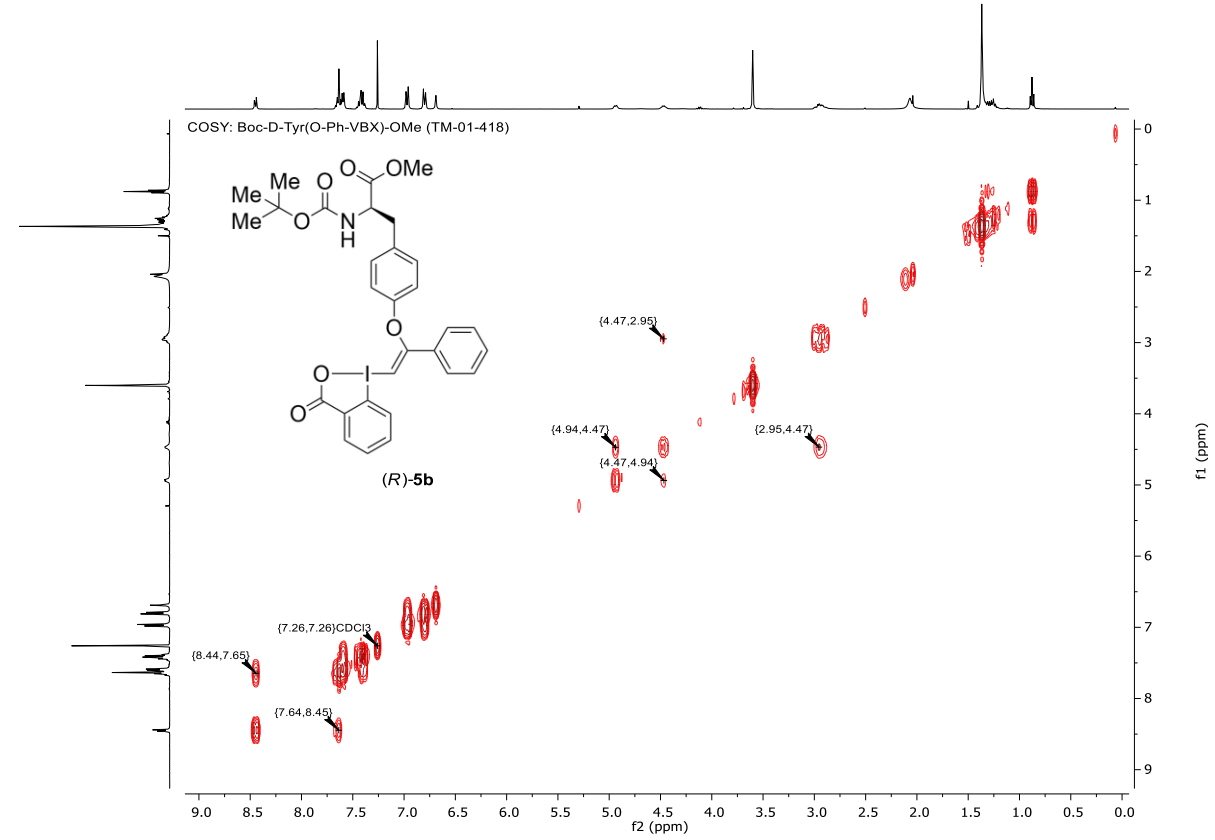
^{1}H-NMR (400 MHz, $CDCl_3$)



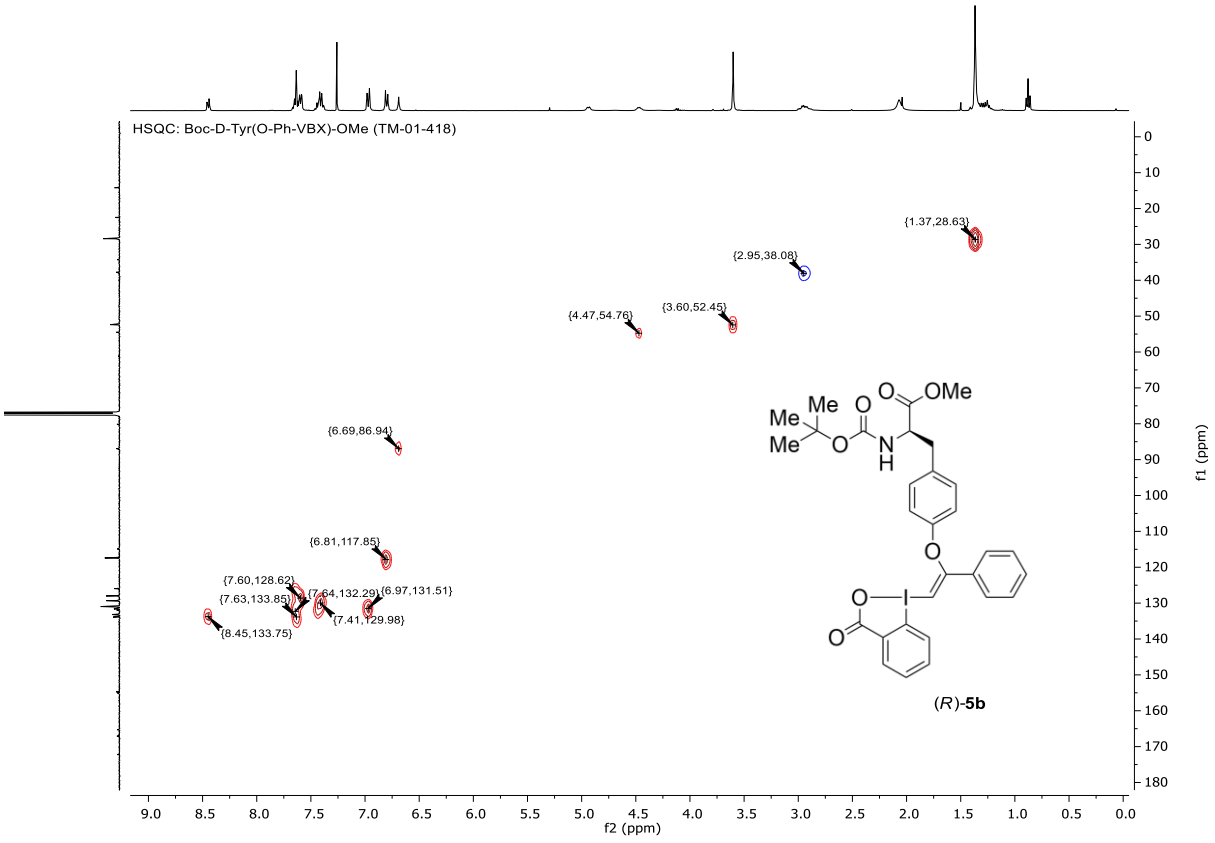
^{13}C-NMR (400 MHz, $CDCl_3$)



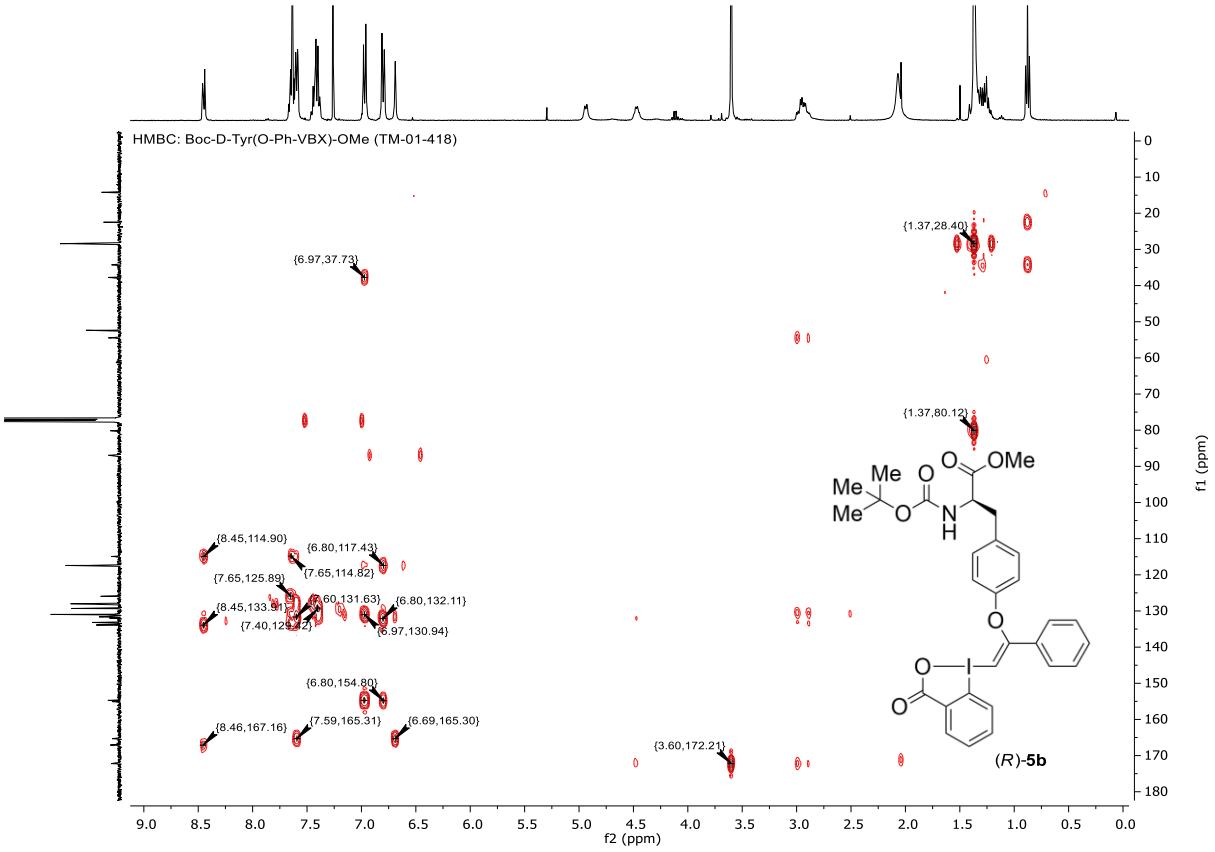
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

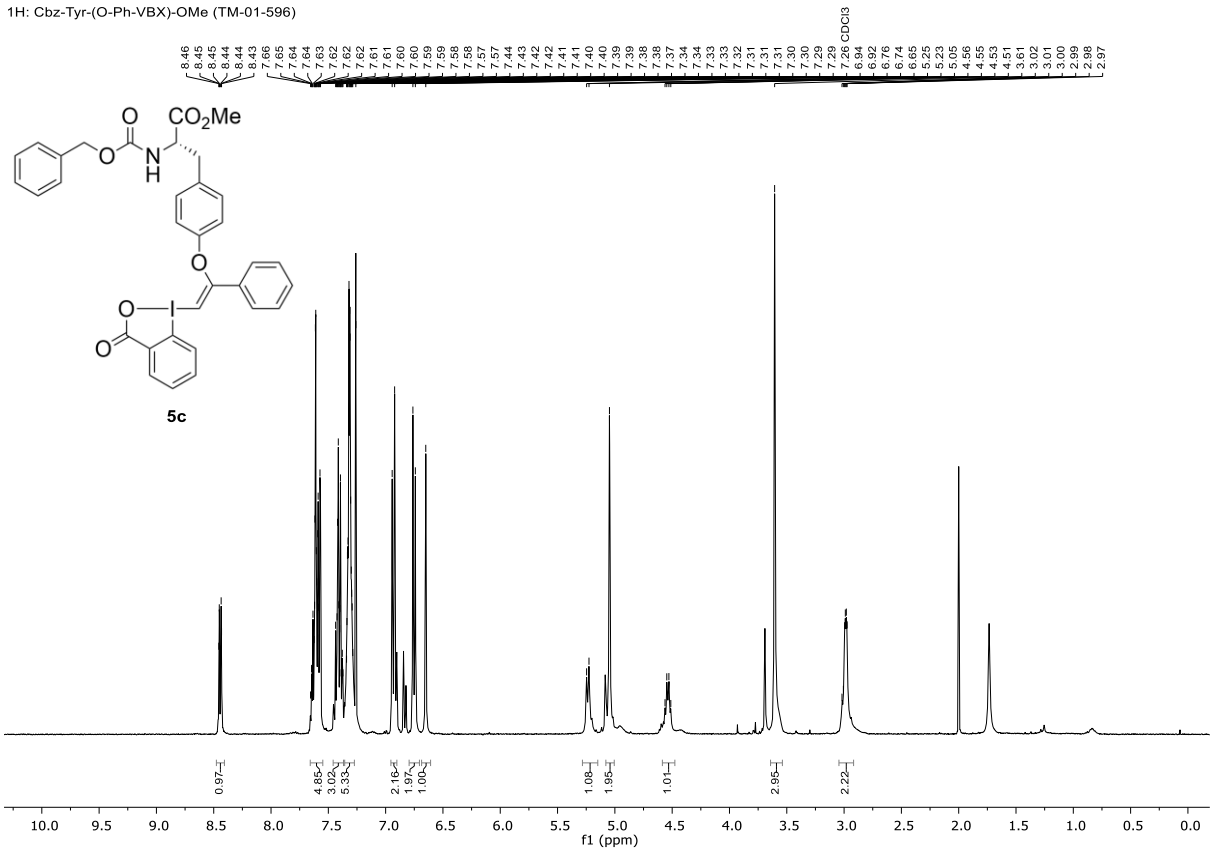


HMBC NMR ($CDCl_3$)

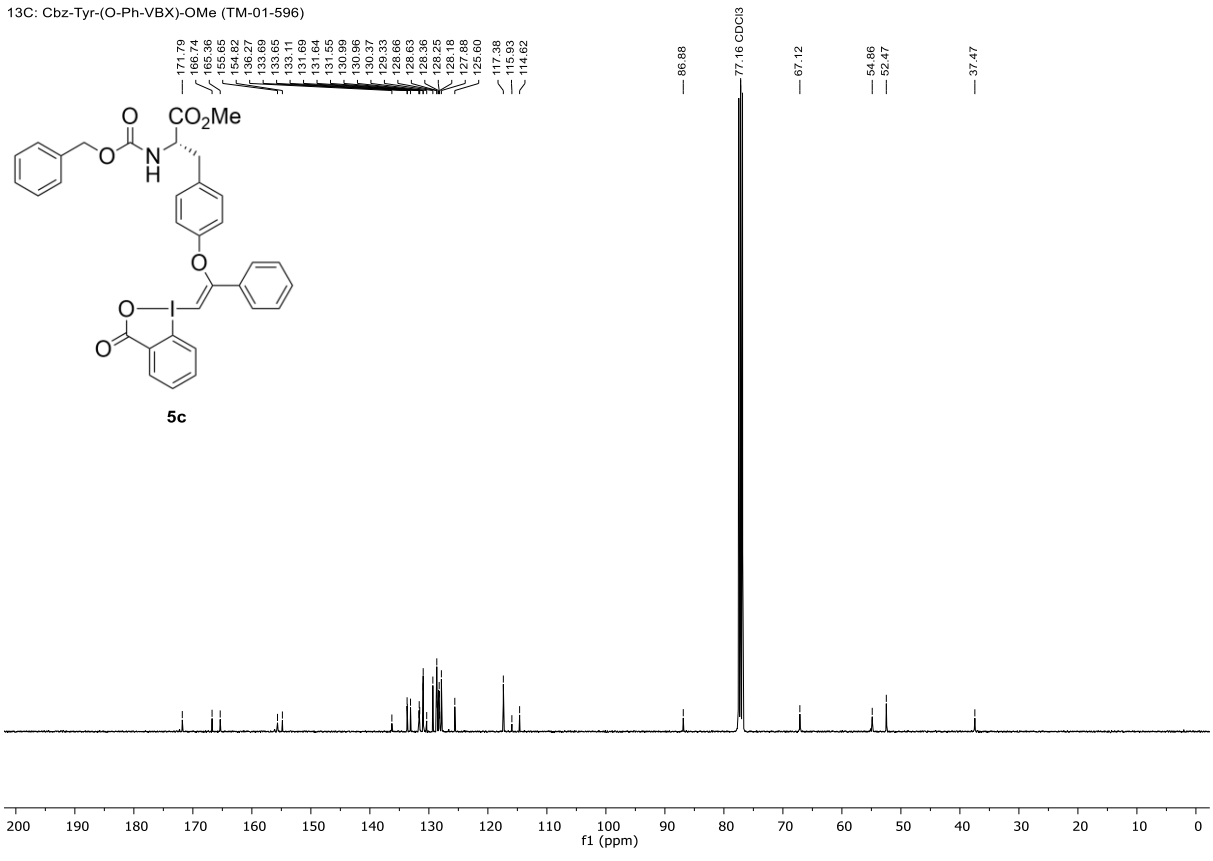


Methyl (*S*,*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate (5c)

^{1}H-NMR (400 MHz, $CDCl_3$)

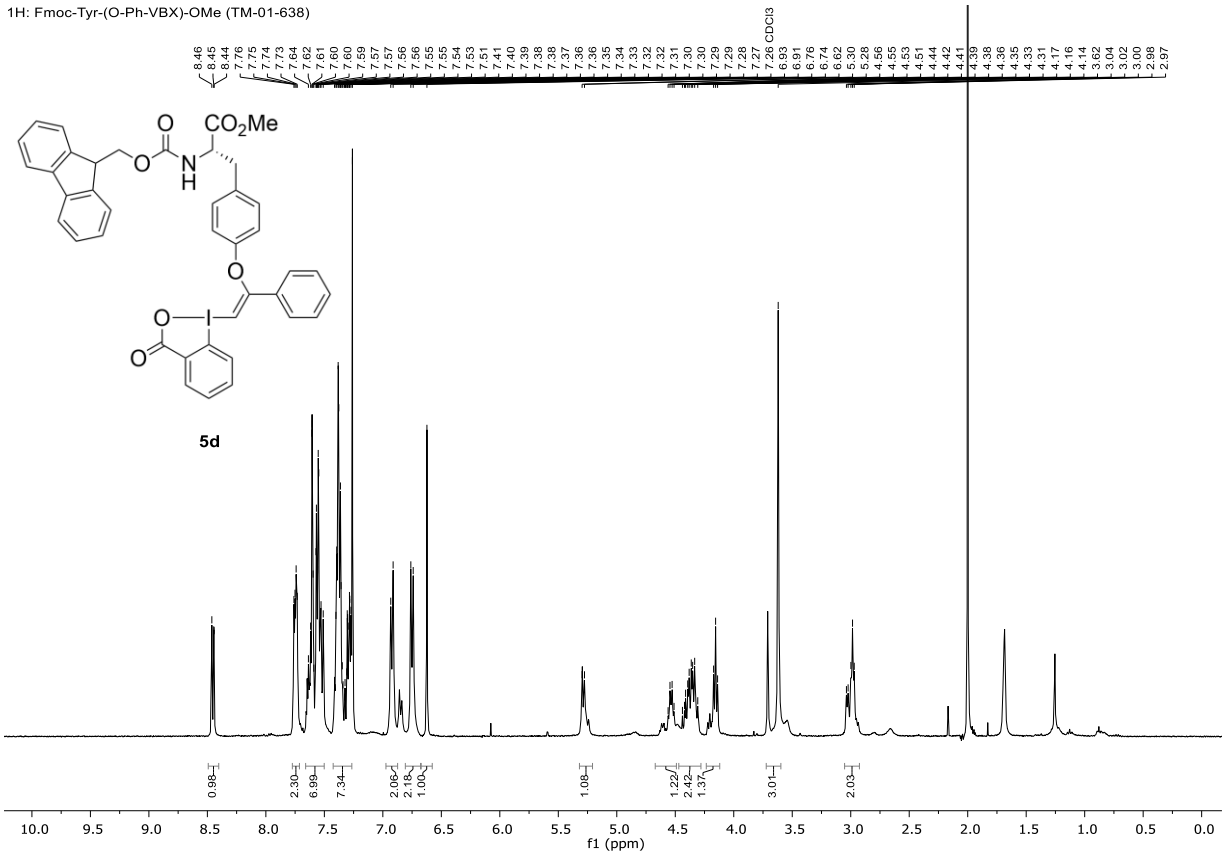


^{13}C-NMR (400 MHz, $CDCl_3$)



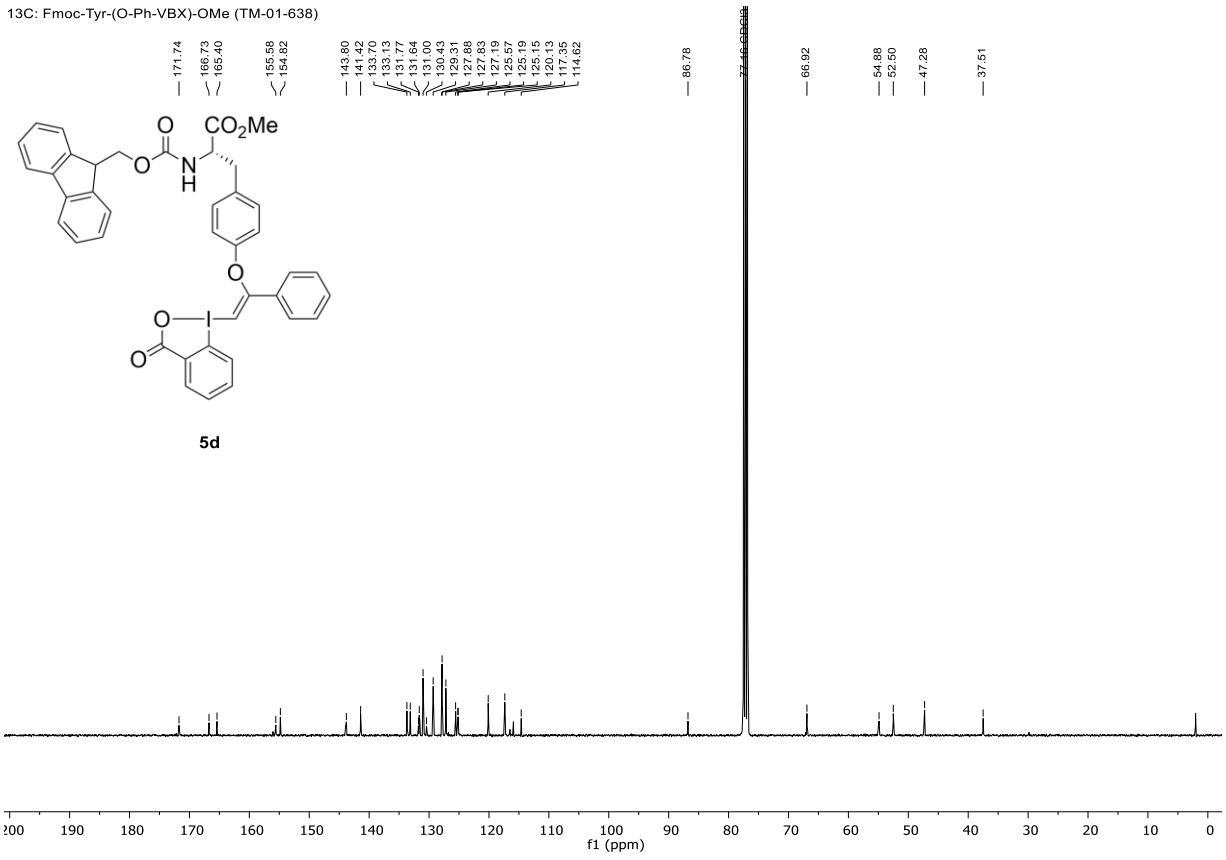
Methyl (*S*,*Z*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-((2-(3-oxo-1λ^3-benzo[*d*][1,2]-iodaoxol-1(3*H*)-yl)-1-phenylvinyl)oxy)phenyl)propanoate (5d)

^{1}H-NMR (400 MHz, $CDCl_3$)



5d

^{13}C-NMR (400 MHz, $CDCl_3$)



5d

Ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl) oxy)phenyl)propanoate (5e)

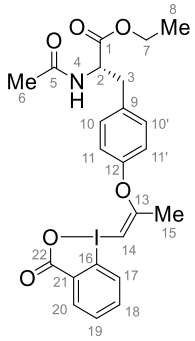
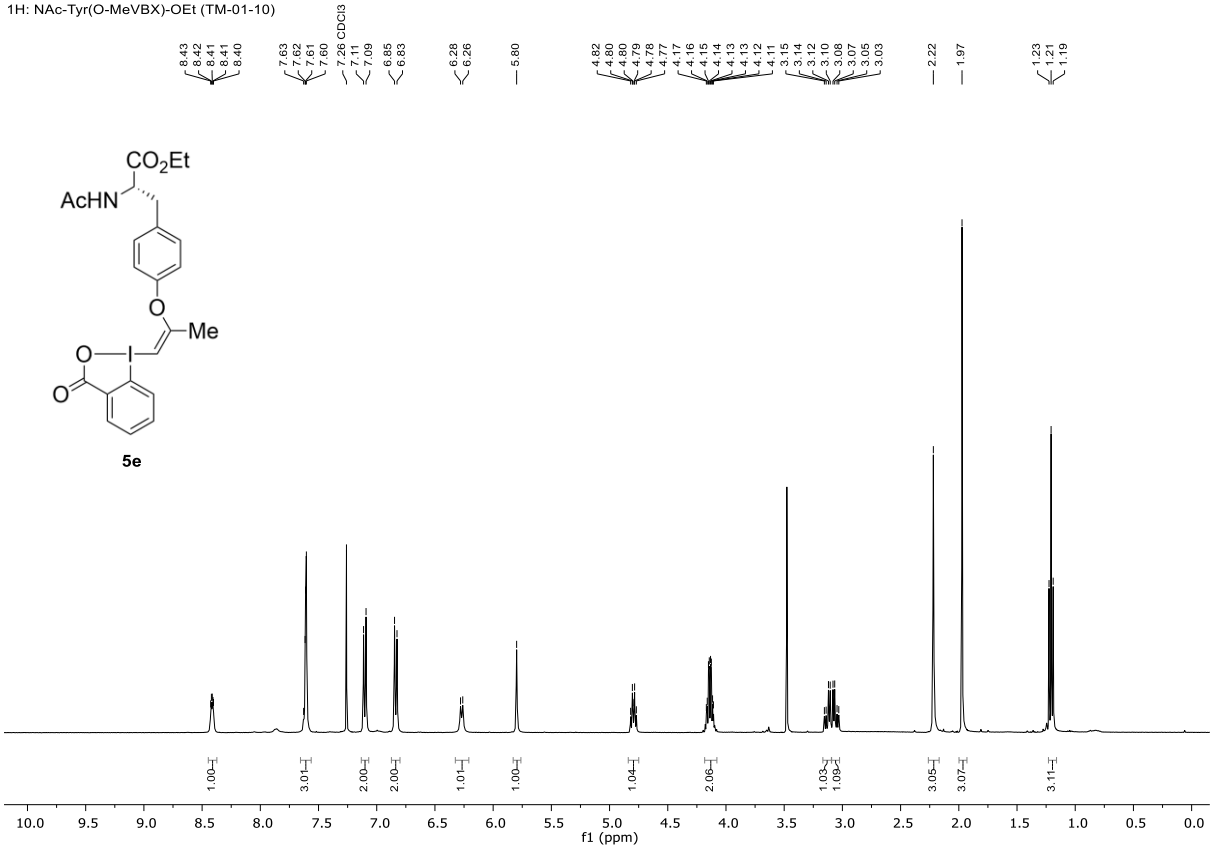


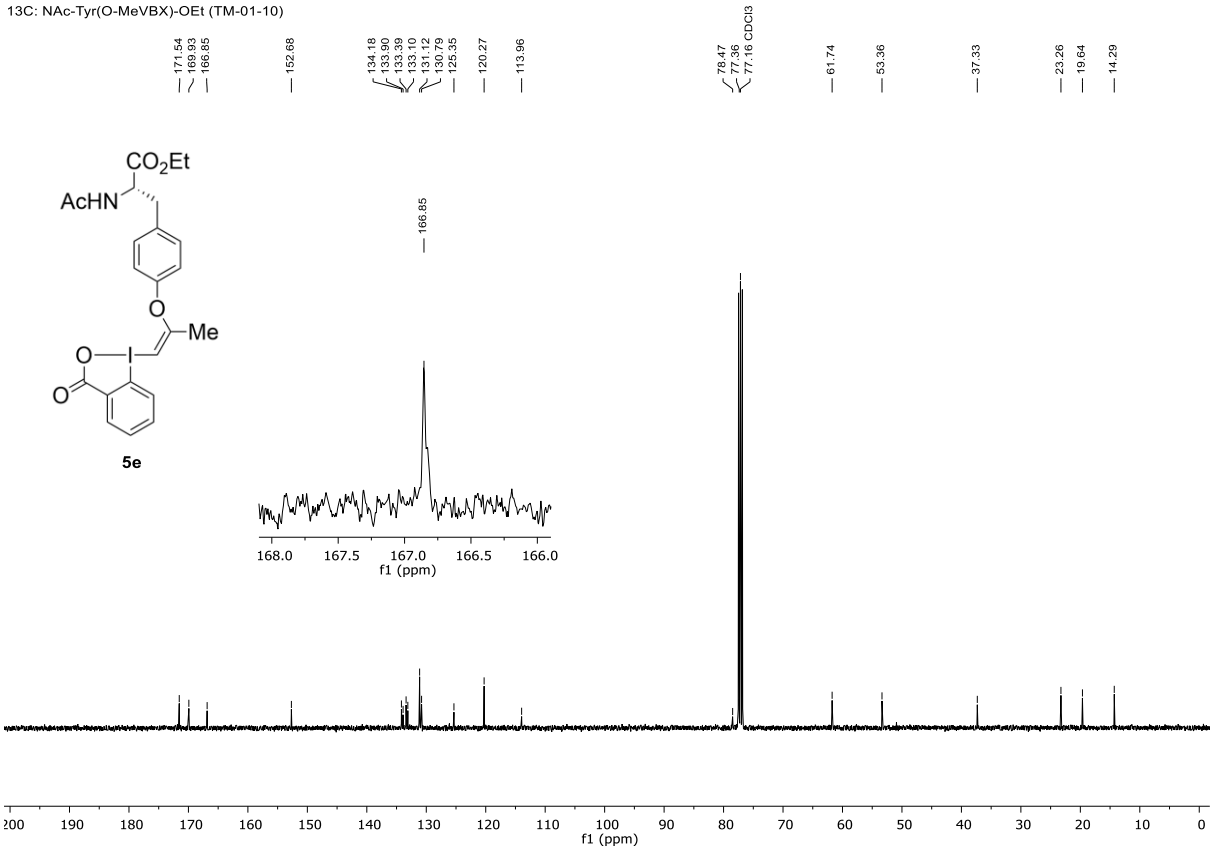
Table S6. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl) oxy)phenyl)propanoate (**5e**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.5			
2	53.4	4.79 (dt, 7.7, 6.0 Hz)	4	1, 3, 9
3	37.3	3.13 (dd, 14.0, 6.0 Hz), 3.06 (dd, 14.0 6.0 Hz)	10/10’	1, 2, 9, 10/10’
4	/	6.27 (d, 7.7 Hz)	2	5
5	169.9			
6	23.3	1.97 (s)		5
7	61.7	4.14 (qd, 7.2, 3.0 Hz)	8	1, 8
8	14.3	1.21 (t, 7.1 Hz)	7	7
9	134.2			
10/10’	131.1	7.10 (d, 8.5 Hz)	3, 11/11’	9, 12
11/11’	120.3	6.84 (d, 8.5 Hz)	10/10’	9, 12
12	152.7			
13	166.9			
14	78.5	5.80 (s)	15	13, 15
15	19.6	2.22 (s)	14	13, 14
16	114.0			
17	133.4	8.45-8-37 (m)	18	16, 18/20
18	133.1/130.8	7.65-7.56 (m)	17	16, 19, 21
19	125.3	7.65-7.56 (m)		16, 18/20, 21
20	133.1/130.8	7.65-7.56 (m)		16, 18/20, 21
21	133.9			
22	166.8			

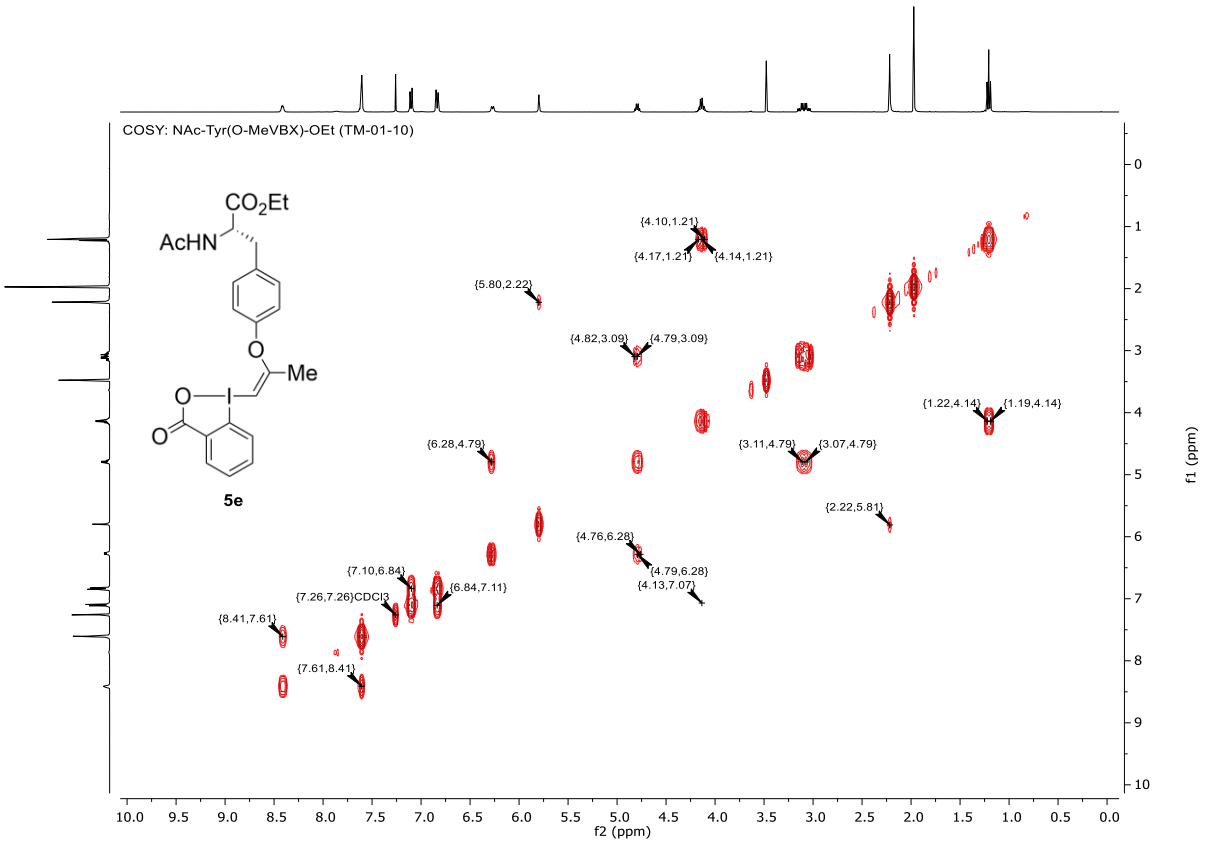
^{1}H-NMR (400 MHz, $CDCl_3$)



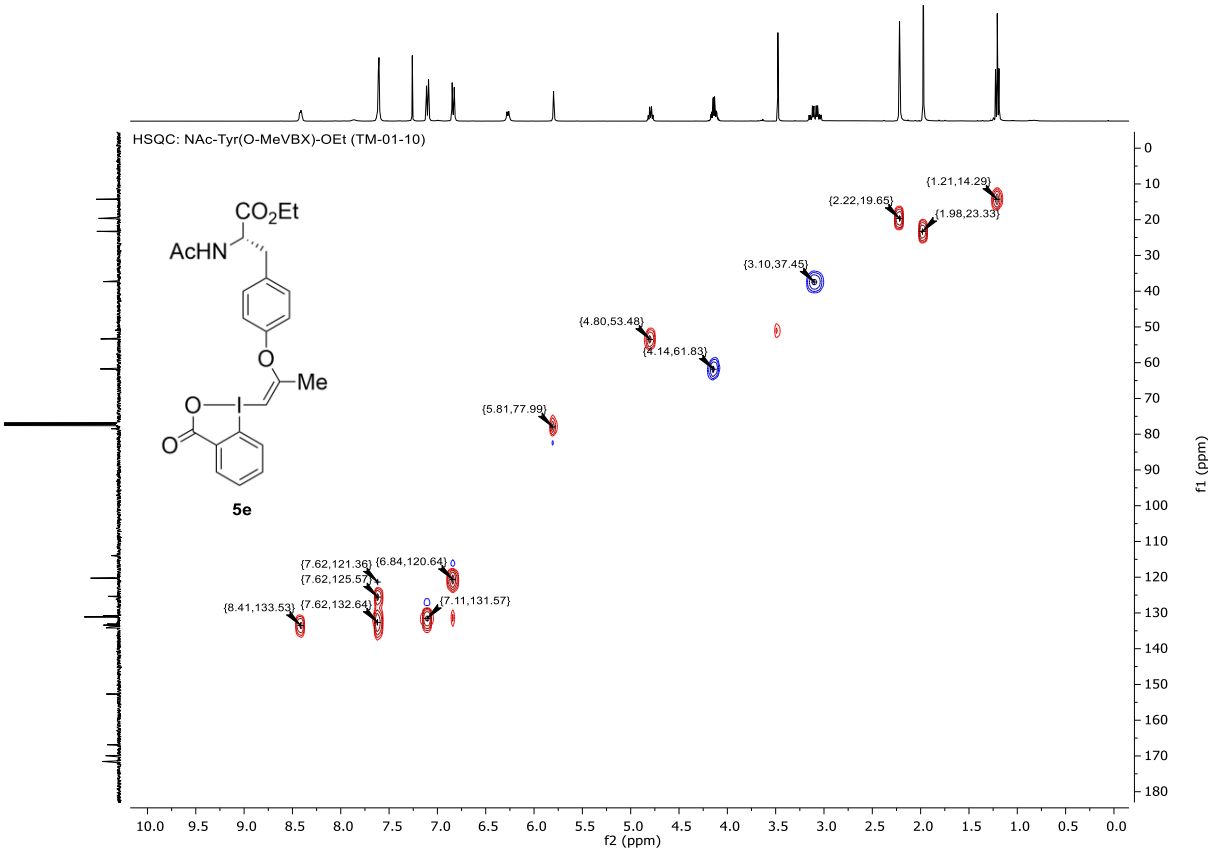
^{13}C-NMR (400 MHz, $CDCl_3$)



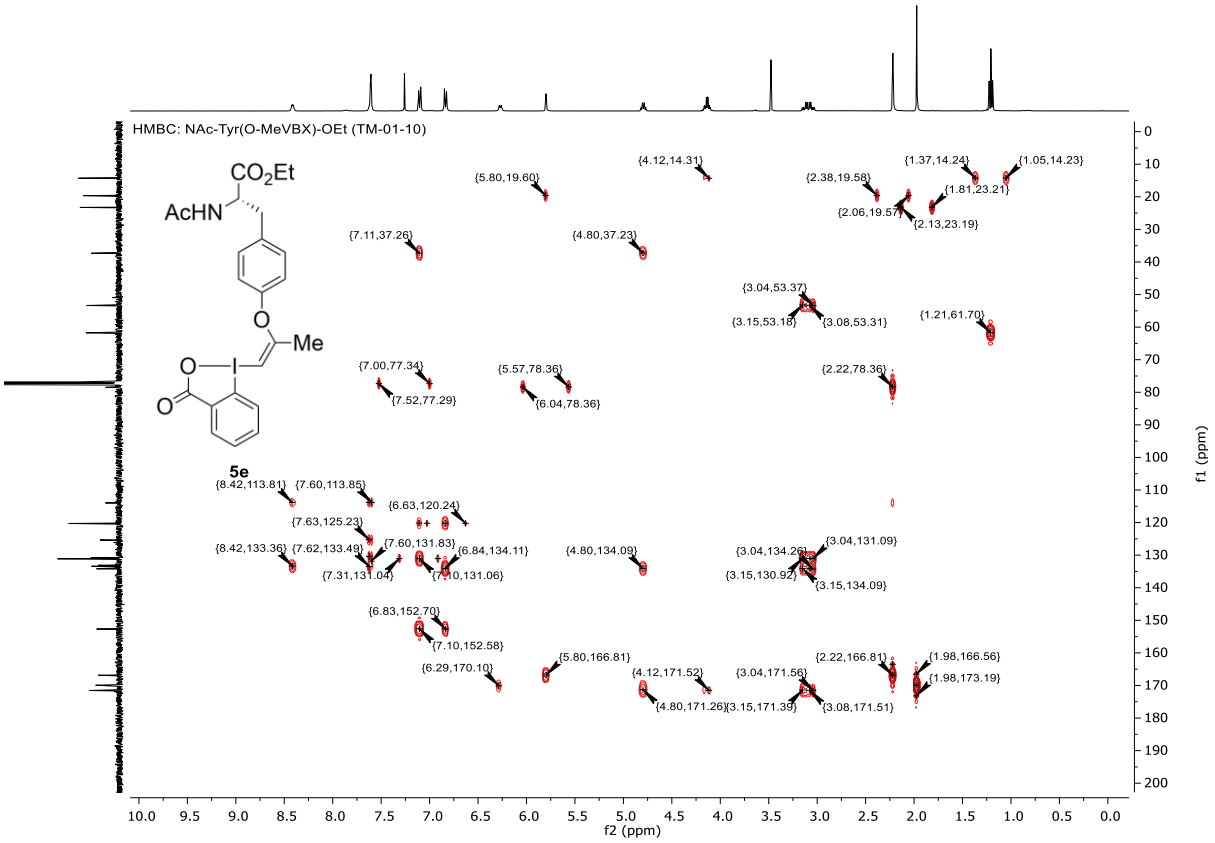
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)oxy)phenyl)propanoate (5f)

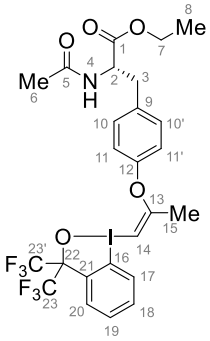
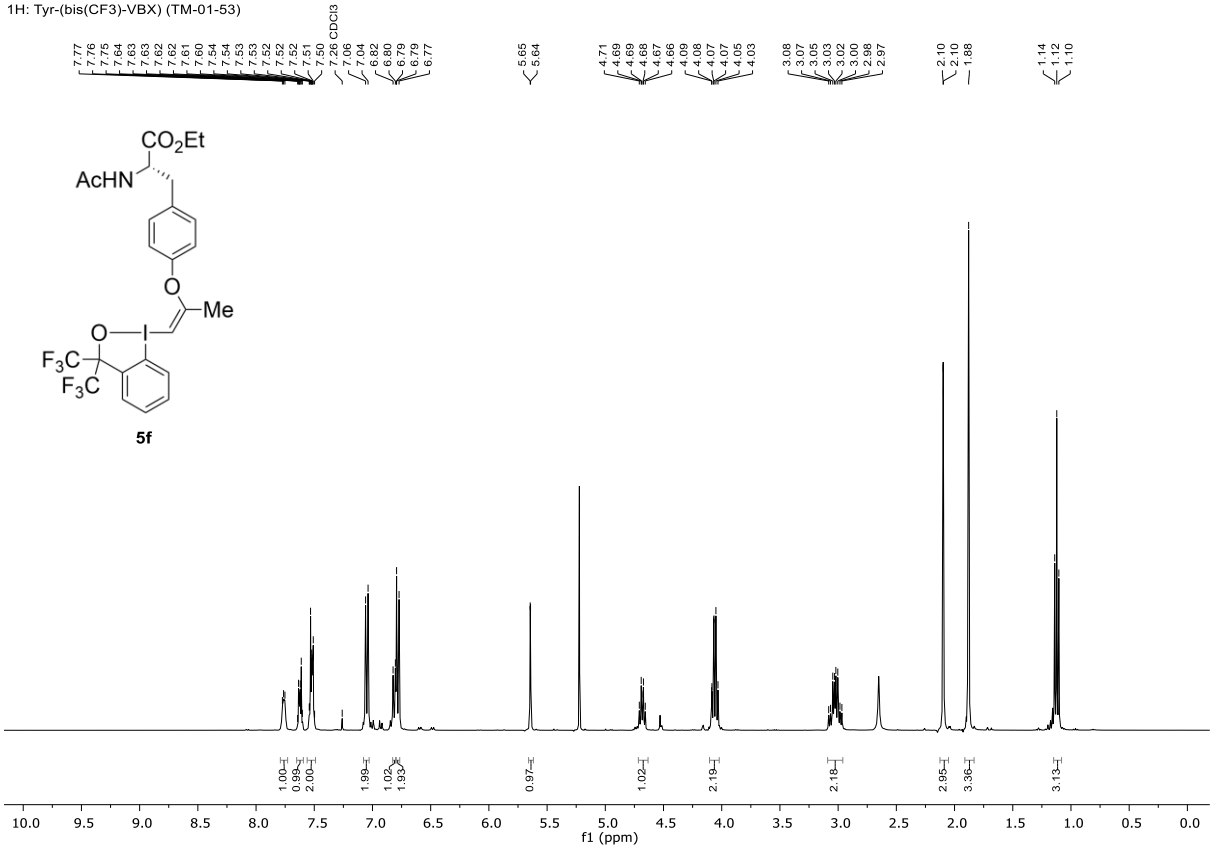


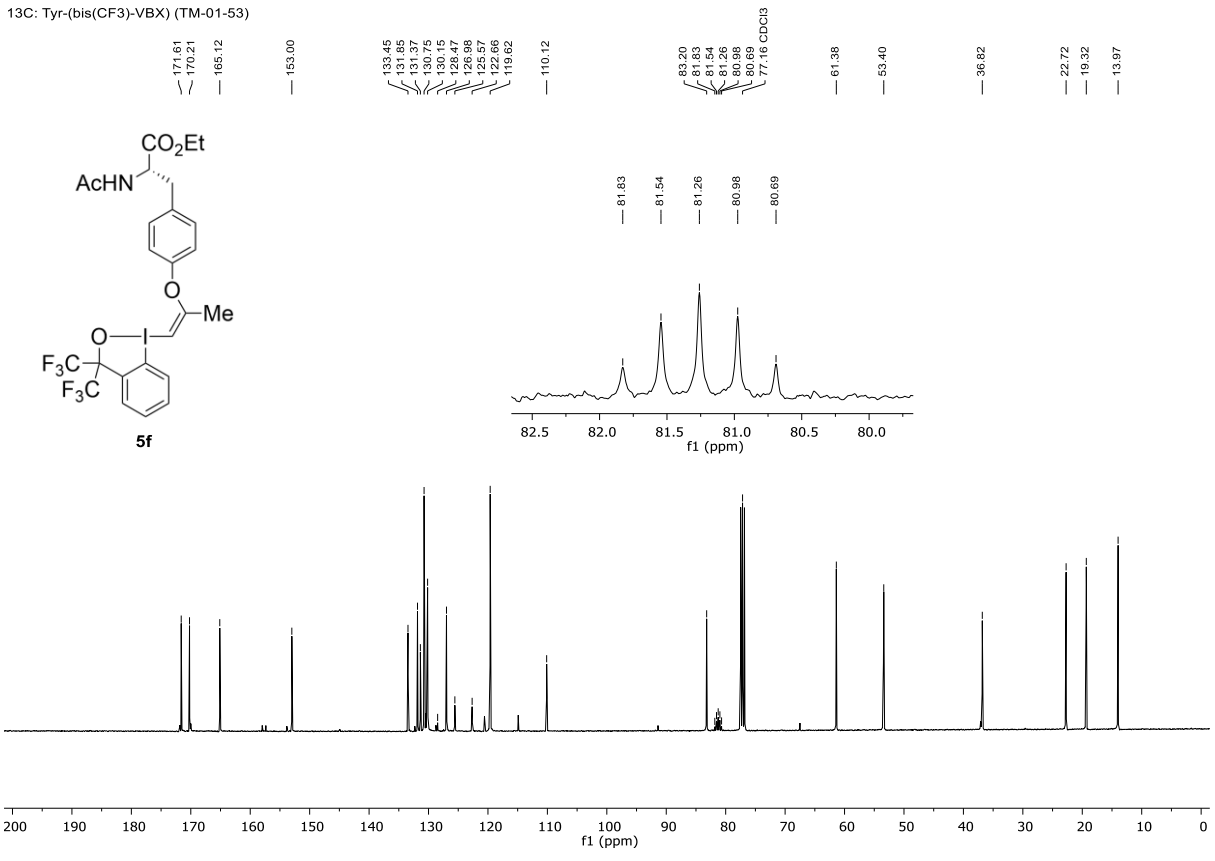
Table S7. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((1-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)oxy)phenyl)propanoate (**5f**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.6			
2	53.4	4.68 (dt, 7.8, 6.4 Hz)	3, 4	
3	36.8	3.06 (dd, 14.0, 6.1 Hz), 2.99 (dd, 14.0, 6.6 Hz)	2	1, 2, 9
4	/	6.81 (d, 7.9 Hz)	2	2, 5
5	170.2			
6	22.7	1.88 (s)		5
7	61.4	4.06 (q, 7.1 Hz)	8	1, 8
8	14.0	1.12 (t, 7.1 Hz)	7	7
9	133.5			
10/10’	130.7	7.05 (d, 8.5 Hz)	11/11‘	3, 11/11‘, 12
11/11’	119.6	6.78 (d, 8.5 Hz)	10/10‘	9, 12
12	153.0			
13	165.1			
14	83.2	5.64 (d, 1.1 Hz)	15	13, 15
15	19.3	2.10 (d, 0.9 Hz)	14	13, 14, 16
16	110.1			
17	130.2	7.79-7.73 (m)	18	16, 18
18	131.9	7.55-7.49 (m)	17	16, 17, 19
19	127.0	7.65-7.59 (m)		16, 17
20	131.9	7.55-7.49 (m)		16, 18, 22
21	131.4			
22	81.3 (p, 28.6 Hz)			
23/23’	124.1 (q, 292.1 Hz)			

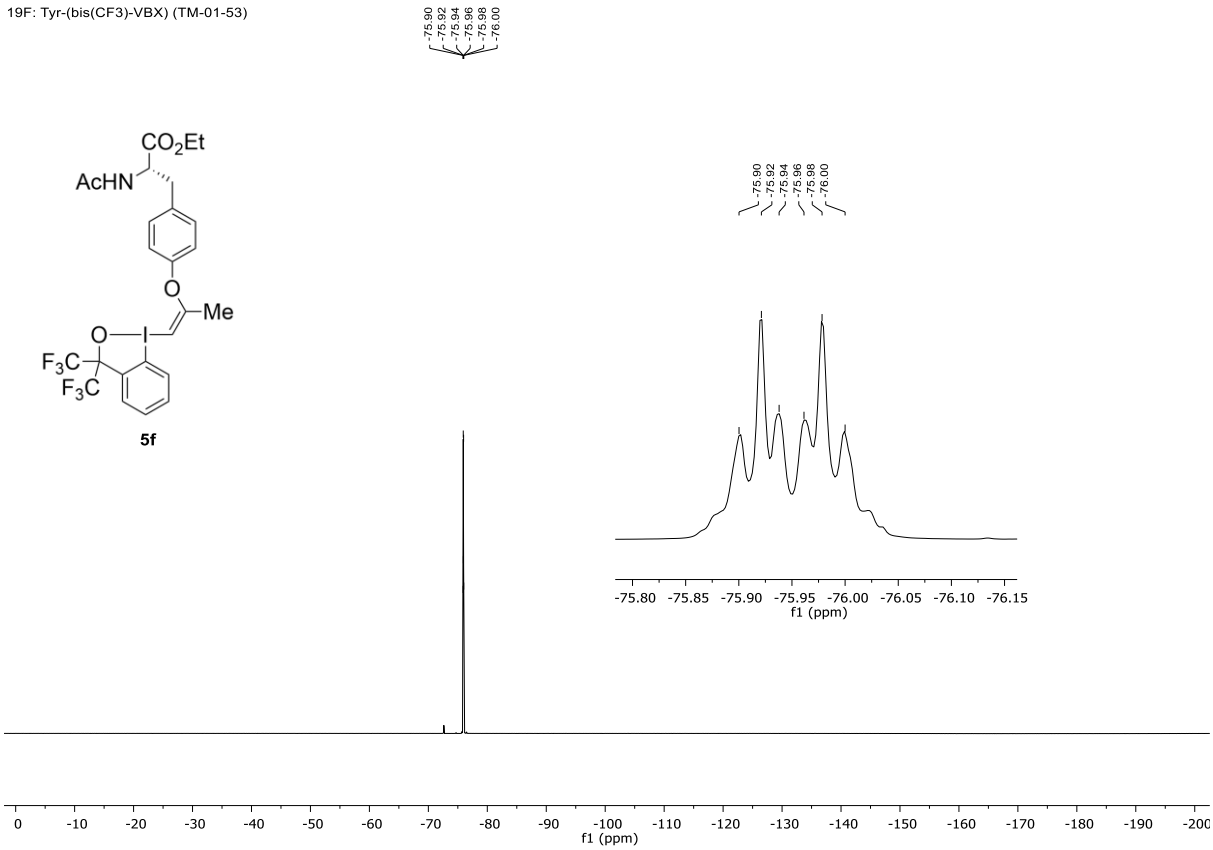
^{1}H-NMR (400 MHz, $CDCl_3$)



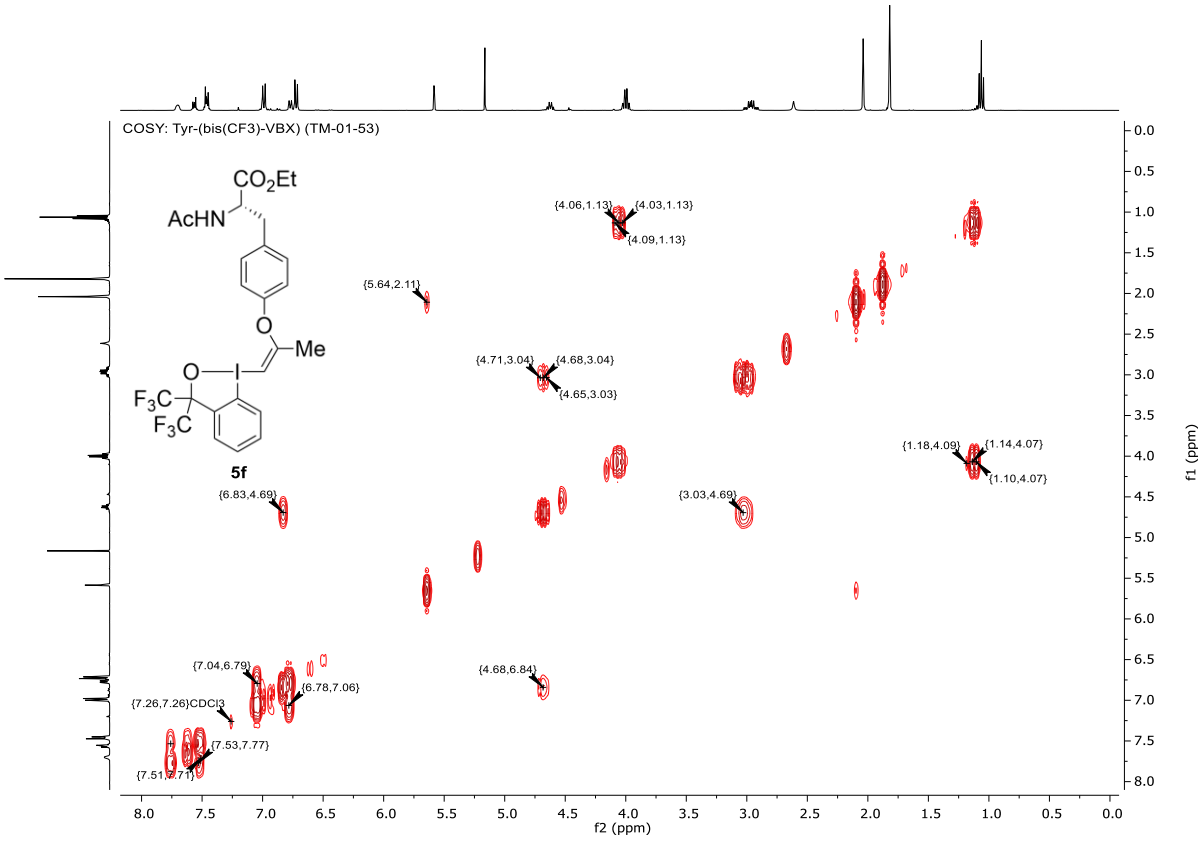
^{13}C-NMR (400 MHz, $CDCl_3$)



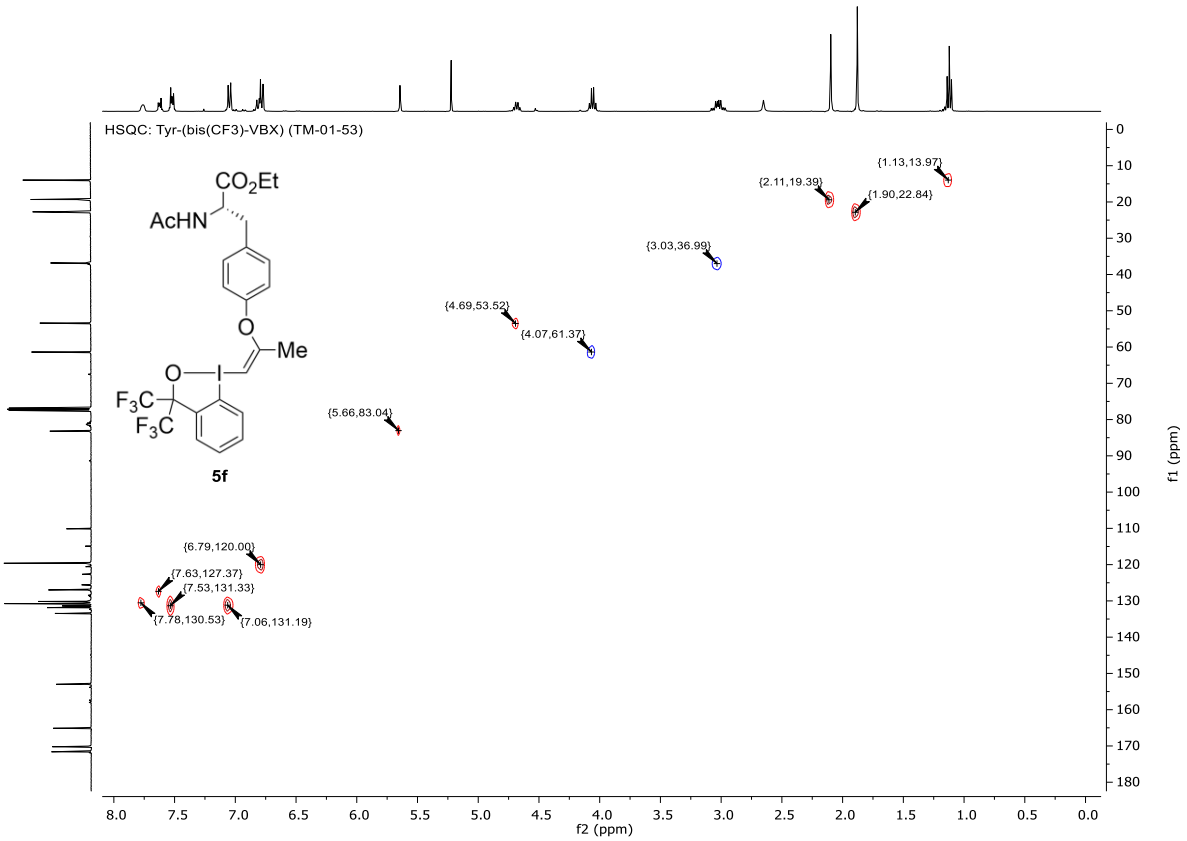
^{19}F-NMR (376 MHz, $CDCl_3$)



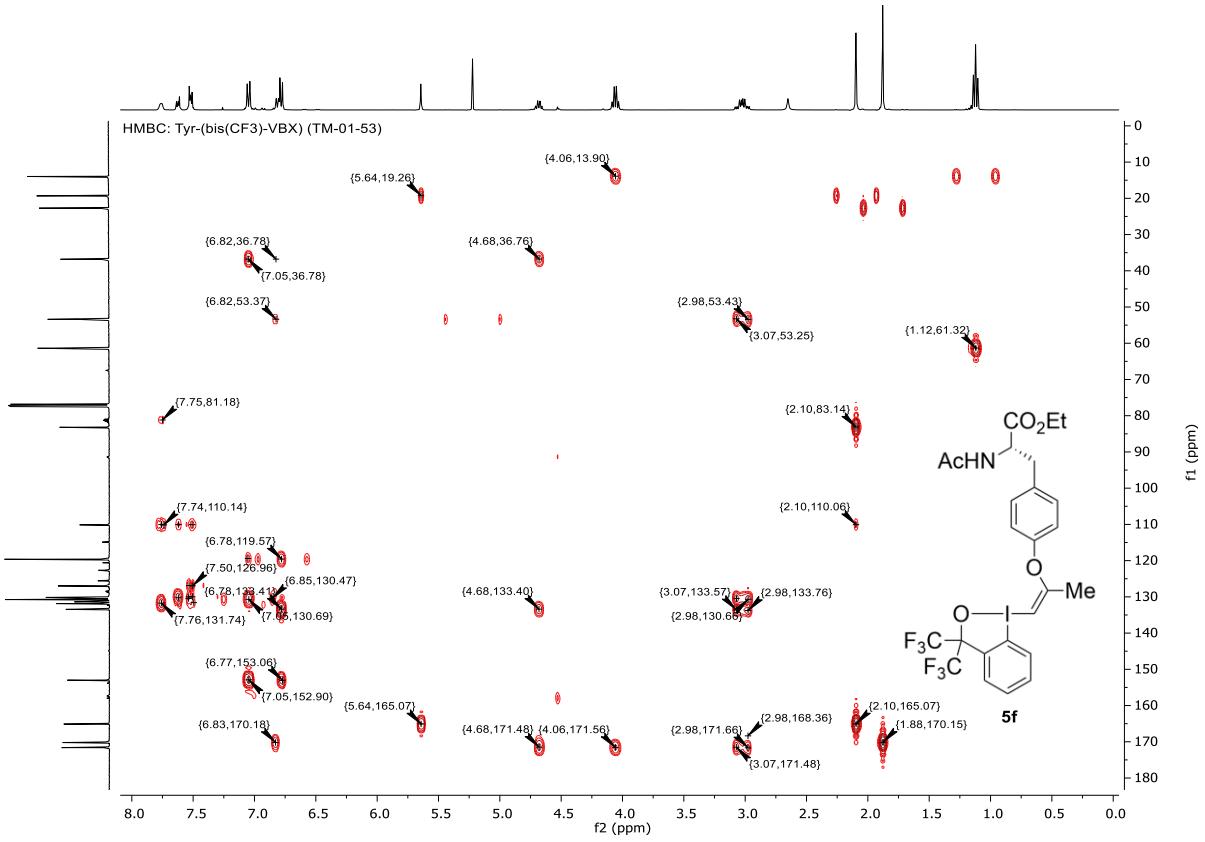
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl (*S*,*Z*)-2-acetamido-3-(4-((4-azido-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)but-1-en-2-yl)oxy)phenyl)propanoate (5g)

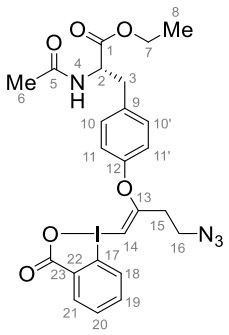
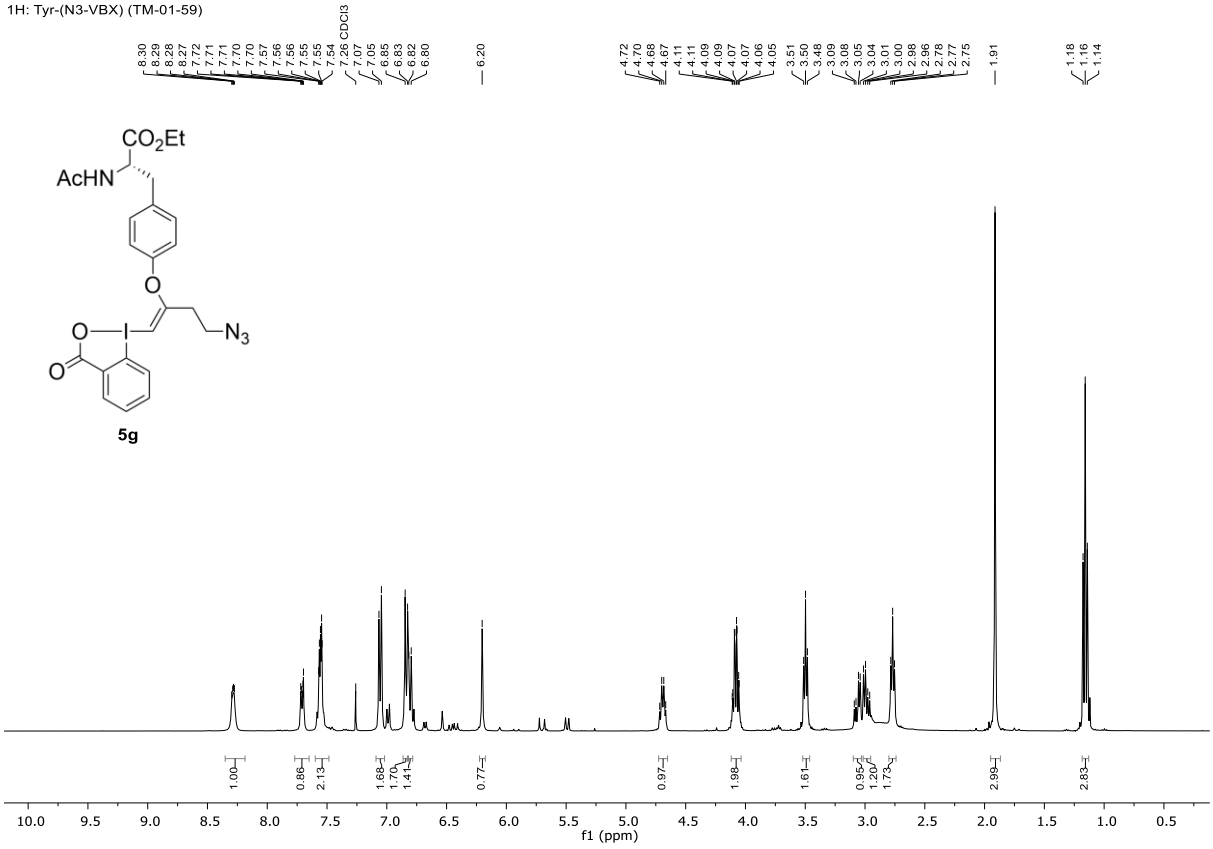


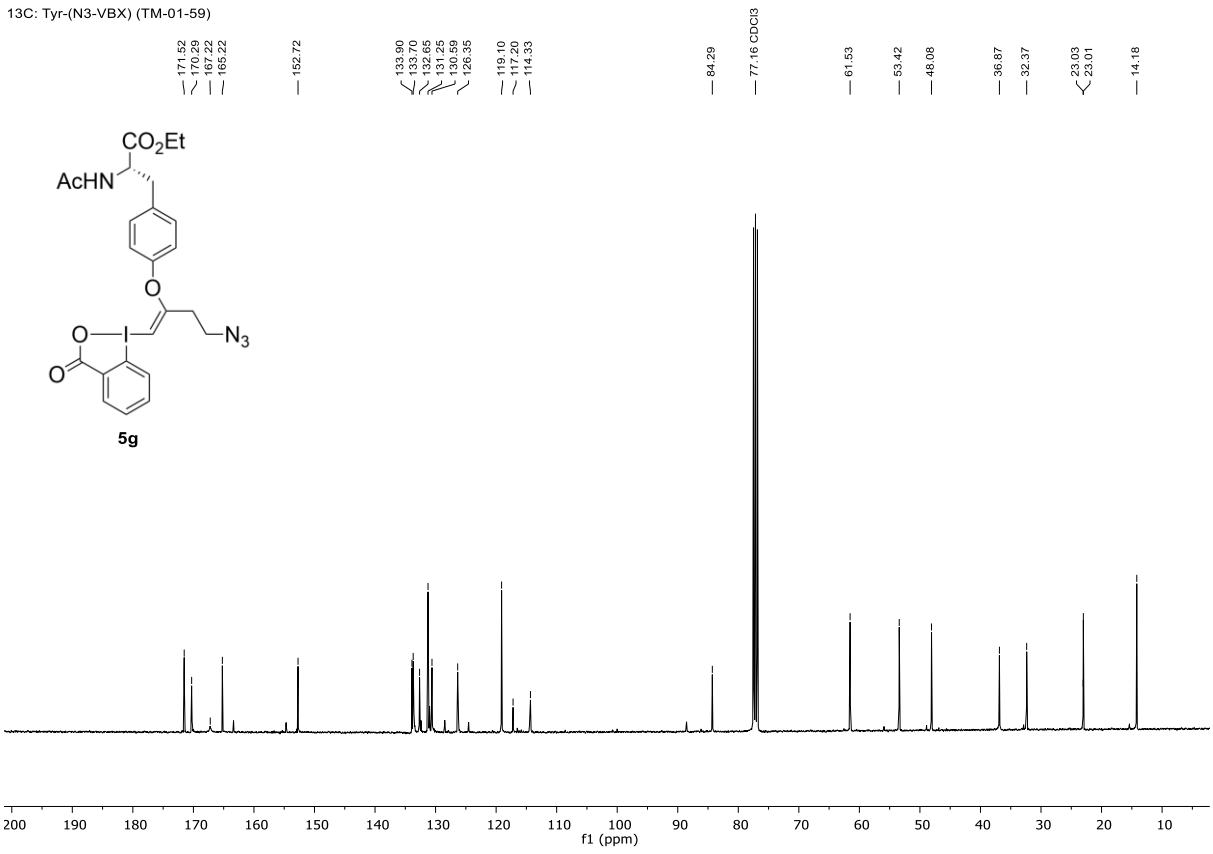
Table S8. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((4-azido-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)but-1-en-2-yl)oxy)phenyl)propanoate (**5g**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.5			
2	53.4	4.73-4.65 (m)	3, 4	1, 3, 9
3	36.9	3.07 (dd, 14.0, 5.7 Hz), 2.99 (dd, 14.0, 6.5 Hz)	2	1, 2, 9
4	/	6.81 (d, 8.2 Hz)	2	2, 5
5	170.3			
6	23.0	1.91 (s)		5
7	61.5	4.08 (qd, 7.1, 1.8 Hz)	8	1, 8
8	14.2	1.16 (t, 7.1 Hz)	7	7
9	133.9			
10/10’	131.2	7.06 (d, 8.3 Hz)	11/11’	3, 10/10’, 12
11/11’	119.1	6.84 (d, 8.1 Hz)	10/10’	9, 11/11’, 12
12	152.7			
13	165.2			
14	84.3	6.20 (s)		13, 16
15	48.1	2.77 (t, 6.3 Hz)		13, 14
16	32.4	3.50 (t, 6.3 Hz)		13
17	114.3			
18	133.7	8.33-8.24 (m)	19	17, 23
19	132.6	7.55 (dt, 5.6, 2.1 Hz)	18, 20	17, 19, 20, 21
20	126.3	7.74-7.67 (m)	19/21	17, 18, 22
21	132.6	7.55 (dt, 5.6, 2.1 Hz)	20	17, 19, 20, 21
22	130.6			
23	167.2			

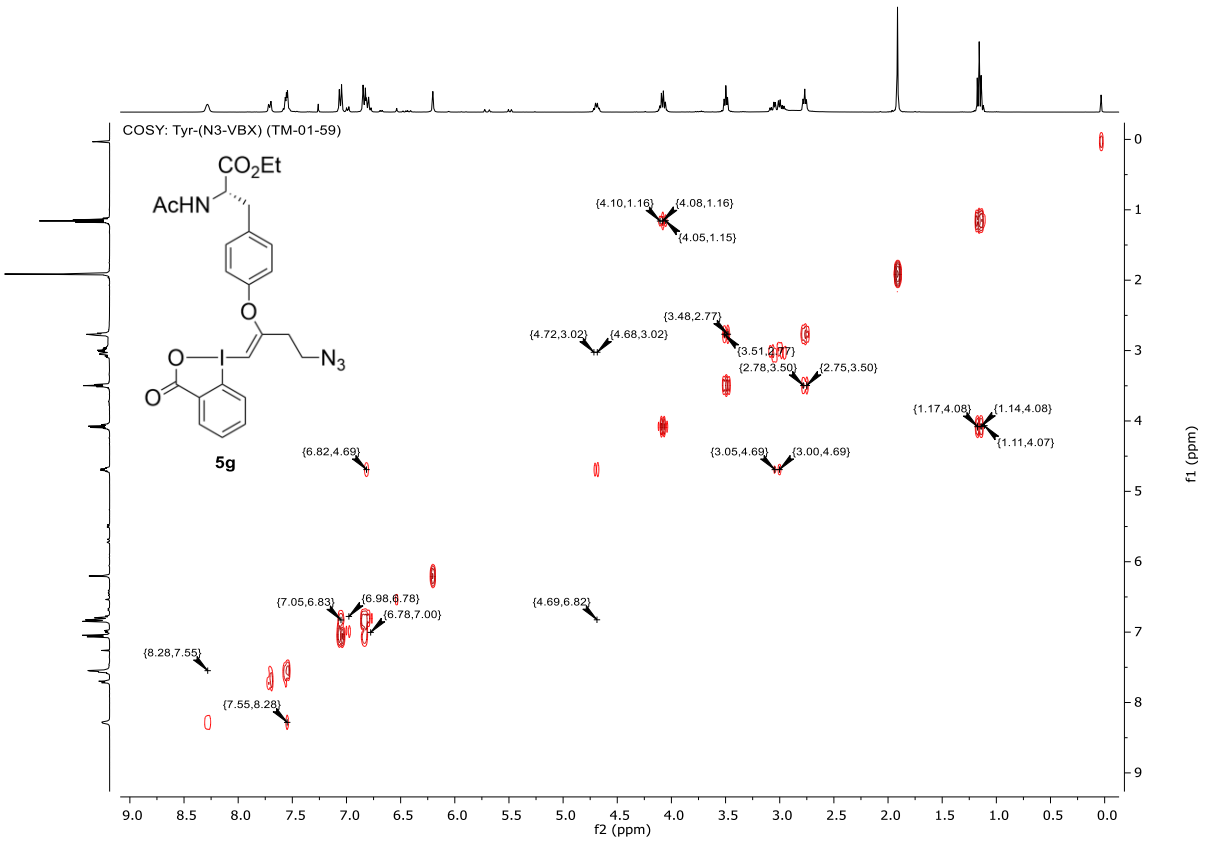
^{1}H-NMR (400 MHz, $CDCl_3$)



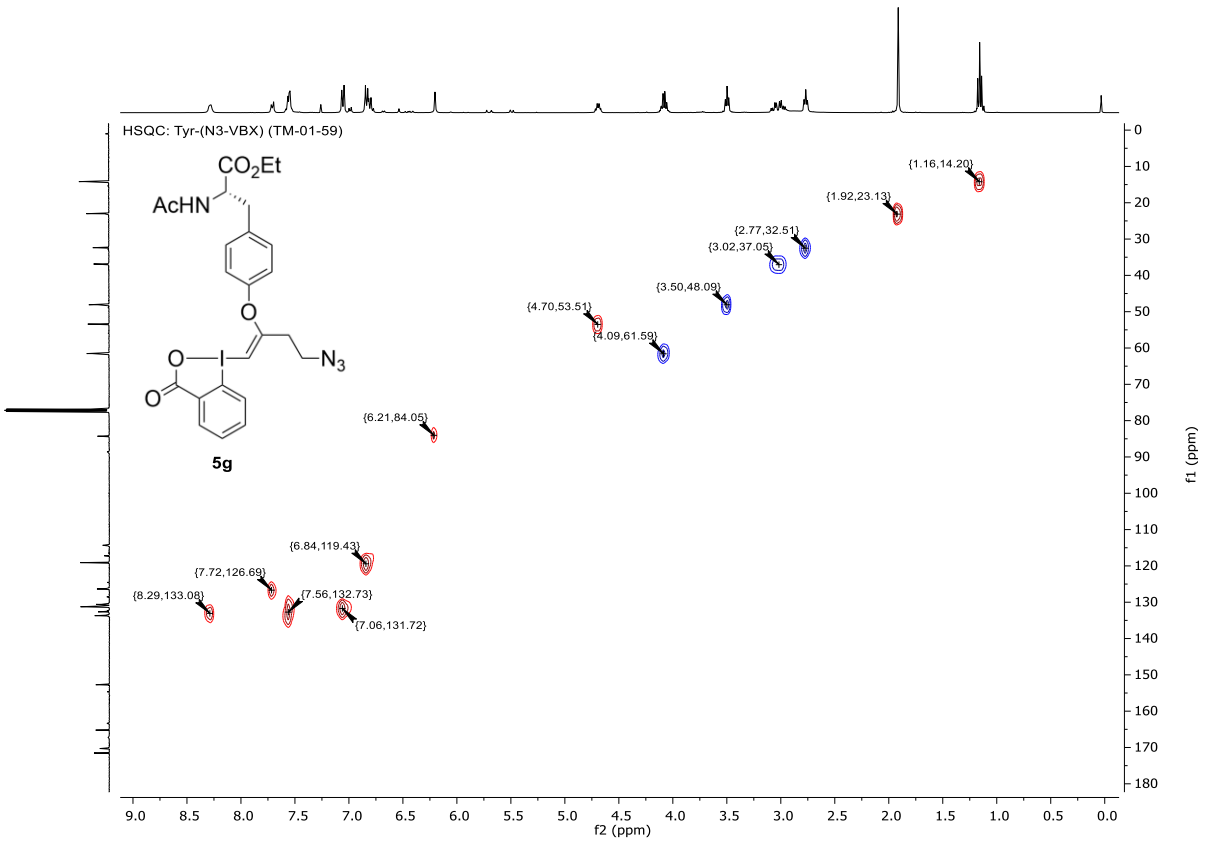
^{13}C-NMR (400 MHz, $CDCl_3$)



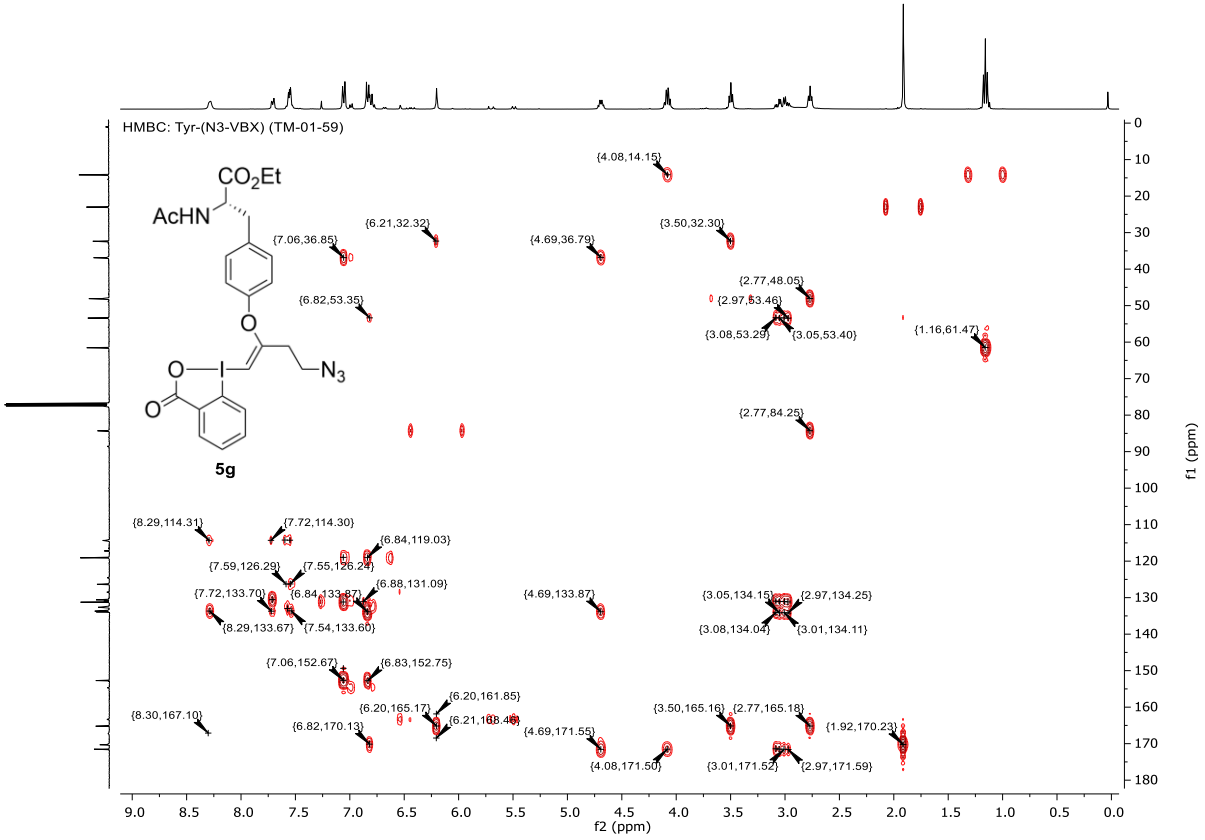
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-chloro-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)oxy)phenyl)propanoate (5h)

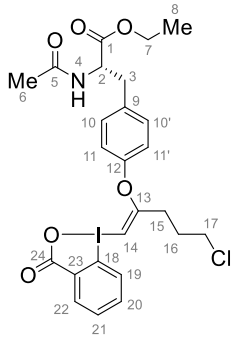
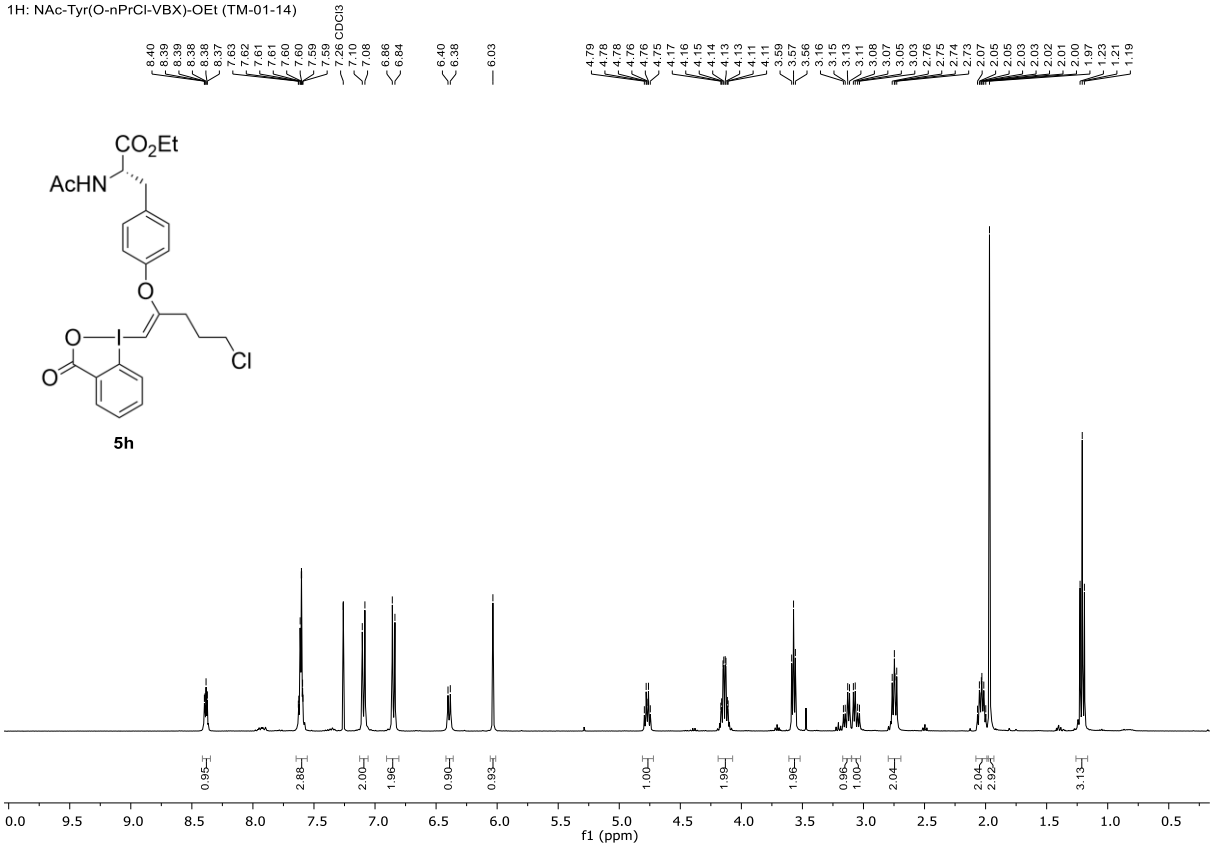


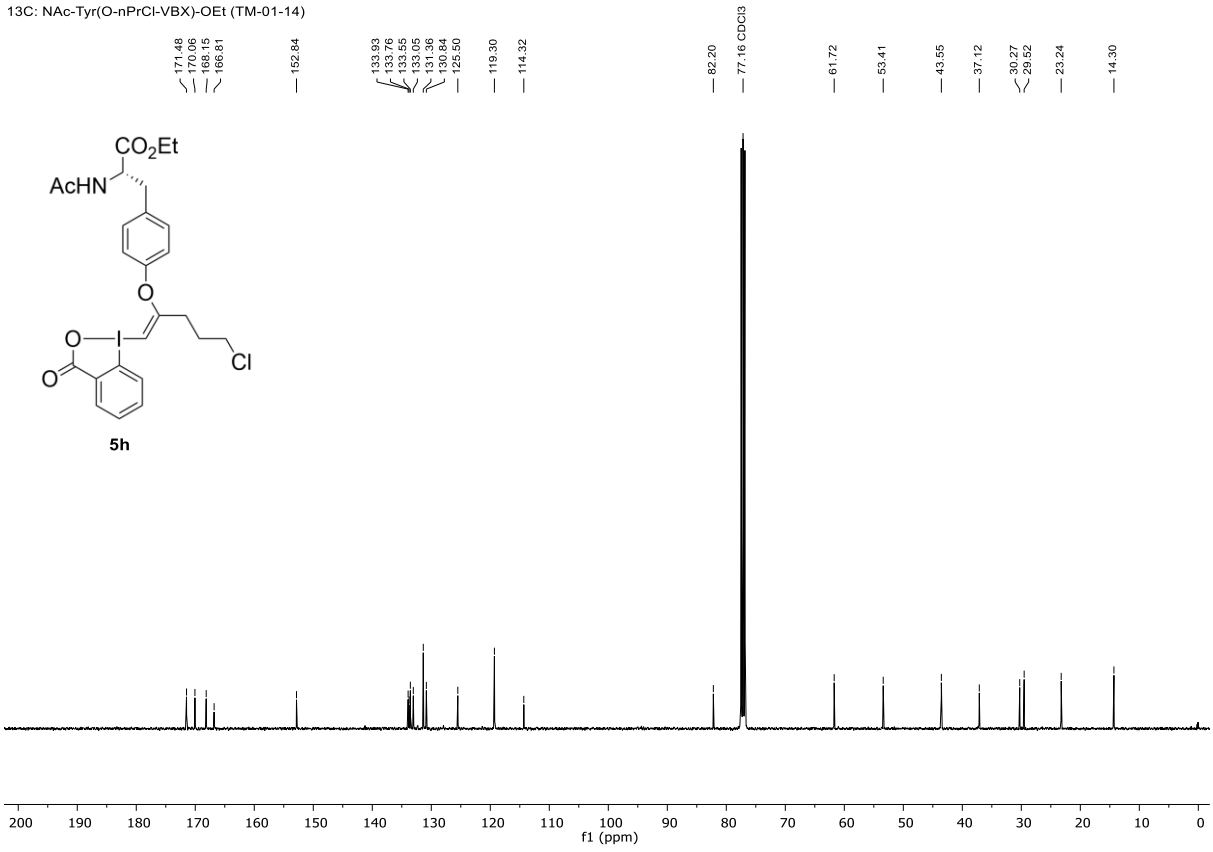
Table S9. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-chloro-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)oxy)phenyl)propanoate (**5h**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.5			
2	53.4	4.77 (dt, 7.7, 5.9 Hz)	3, 4	1, 3, 9
3	37.1	3.14 (dd, 14.0, 5.9 Hz), 3.06 (dd, 14.0, 6.0 Hz)	2	1, 2, 9, 10/10’
4	/	6.39 (d, 7.1 Hz)	2	5
5	170.1			
6	23.2	1.97 (s)		5
7	61.7	4.14 (qd, 7.1, 2.5 Hz)	8	1, 8
8	14.3	1.21 (t, 7.1 Hz)	7	
9	133.9			
10/10’	131.4	7.09 (d, 8.6 Hz)	11/11’	3, 11/11’, 12
11/11’	119.3	6.85 (d, 8.6 Hz)	10/10’	9, 12
12	152.8			
13	168.1			
14	82.2	6.03 (s)		13, 15
15	30.3	2.78-2.72 (m)	16	13, 14, 16, 17
16	29.5	2.03 (p, 6.2 Hz)	15, 17	13, 15, 17
17	43.6	3.57 (t, 6.1 Hz)	16	15
18	114.3			
19	133.5	8.42-8.34 (m)	20	18, 20/22, 24
20	133.0/130.8	7.63-7.59 (m)	19	18, 21
21	125.5	7.63-7.59 (m)		23
22	133.0/130.8	7.63-7.59 (m)		18, 21
23	133.8			
24	166.8			

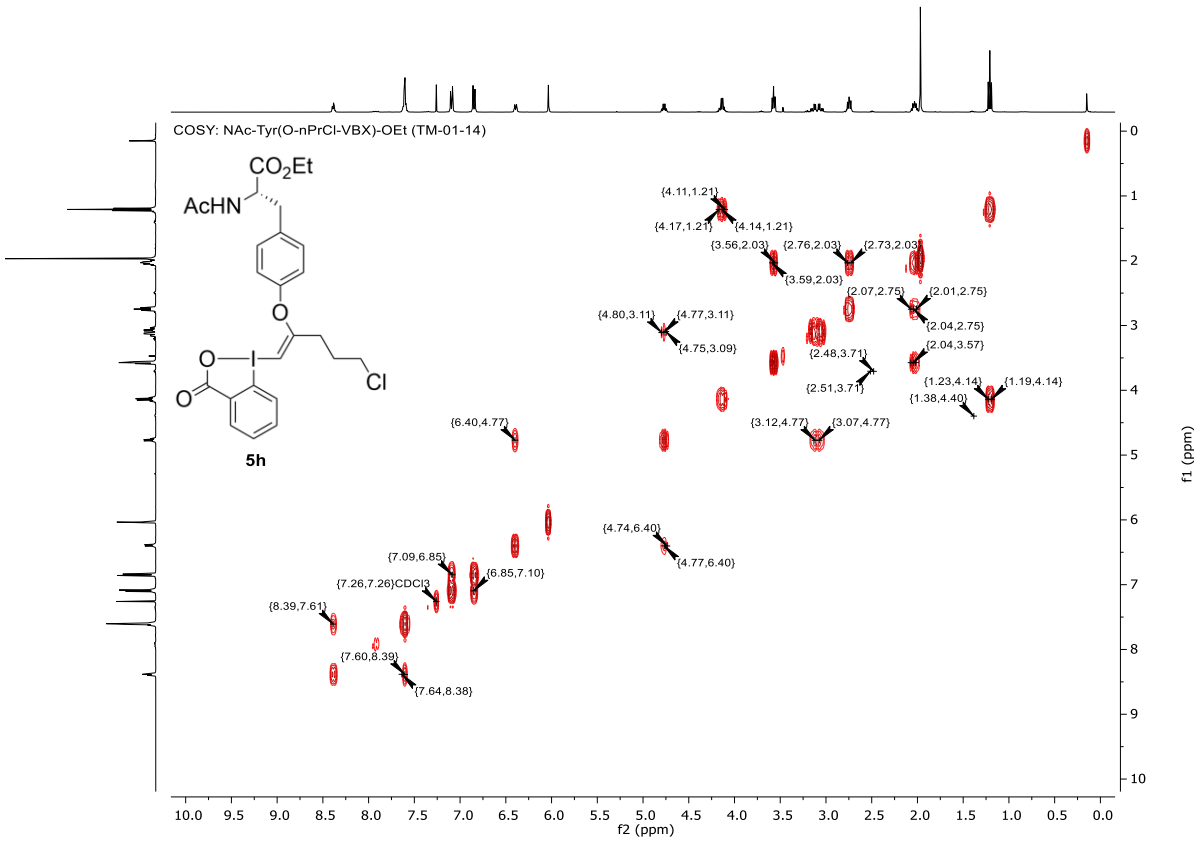
^{1}H-NMR (400 MHz, $CDCl_3$)



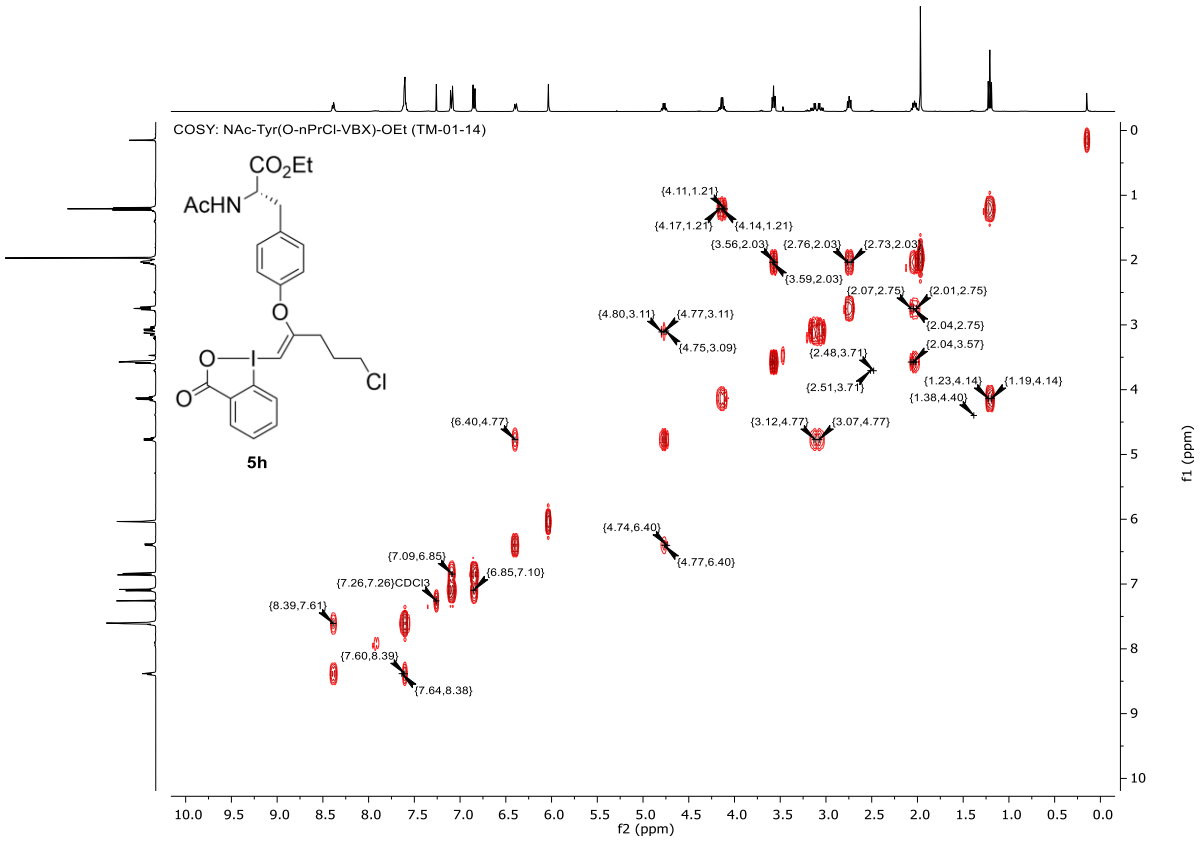
^{13}C-NMR (400 MHz, $CDCl_3$)



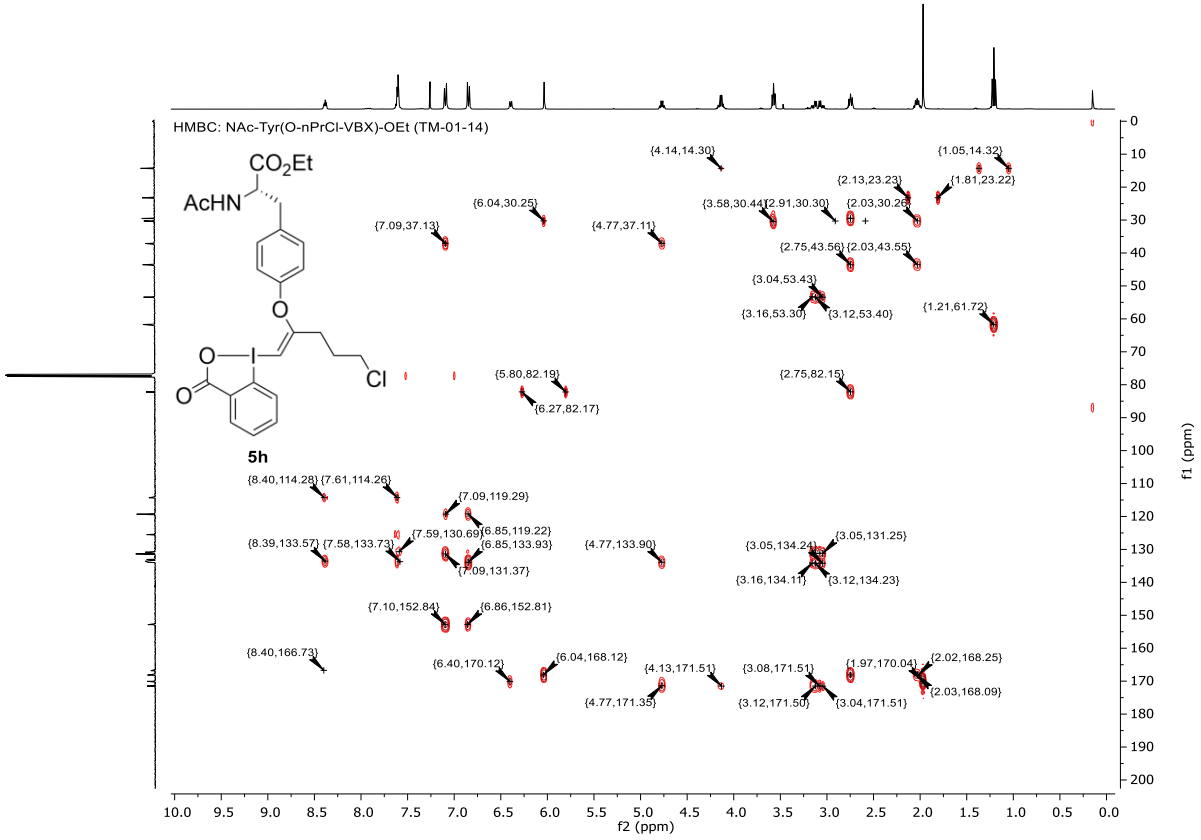
COSY ($CDCl_3$)



HSQC ($CDCl_3$)



HMBC ($CDCl_3$)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O
Cl
5h
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{3.16,134.11}
{3.12,134.23}
{7.10,152.84}
{6.86,152.81}
{8.40,166.73}
{6.40,170.12}
{6.04,168.12}
{4.13,171.51}
{4.77,171.35}
{3.08,171.51}
{3.12,171.50}
{1.97,170.04}
{3.04,171.51}
{2.02,168.25}
{2.03,168.09}
f2 (ppm)
f1 (ppm)

Methyl (*Z*)-*N*-acetyl-*S*-(2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)-L-cysteinate (5i)

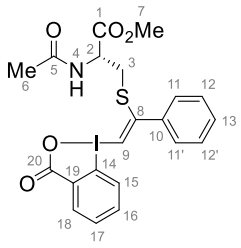
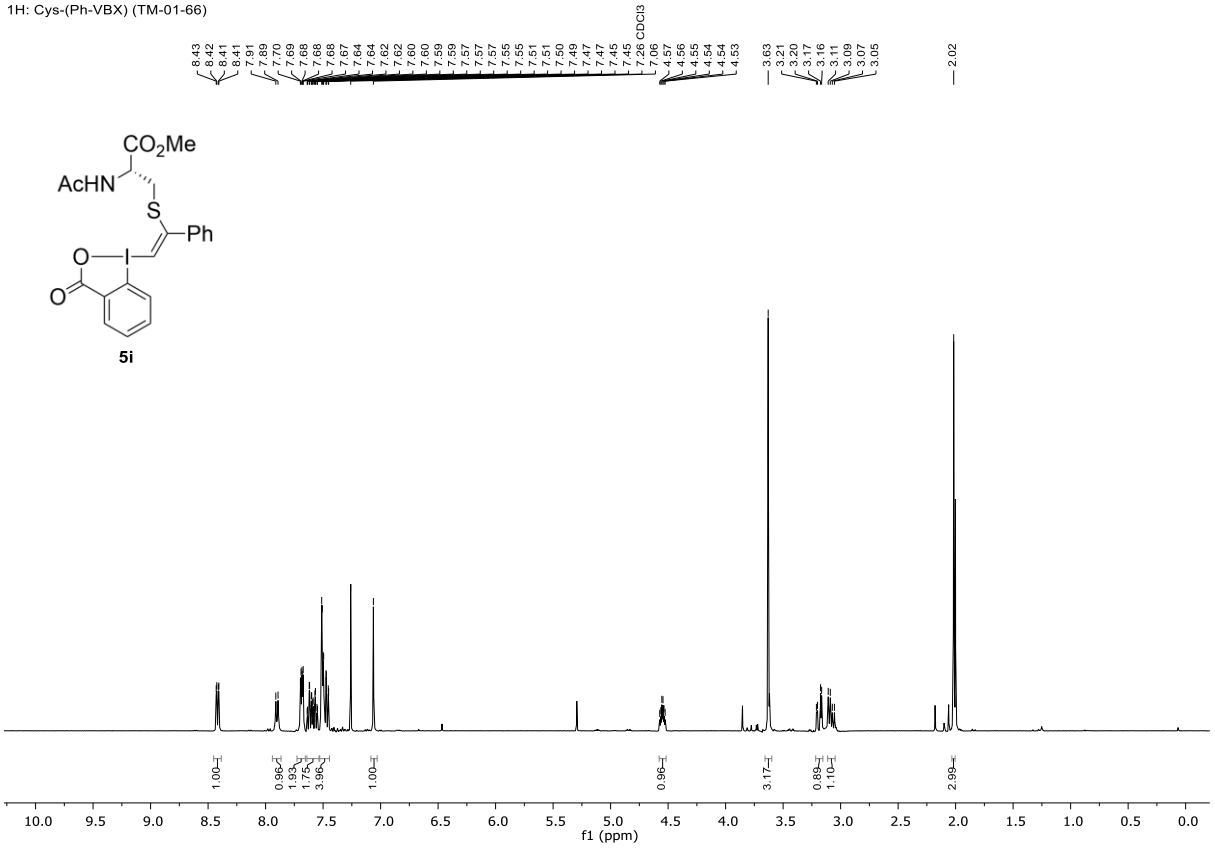


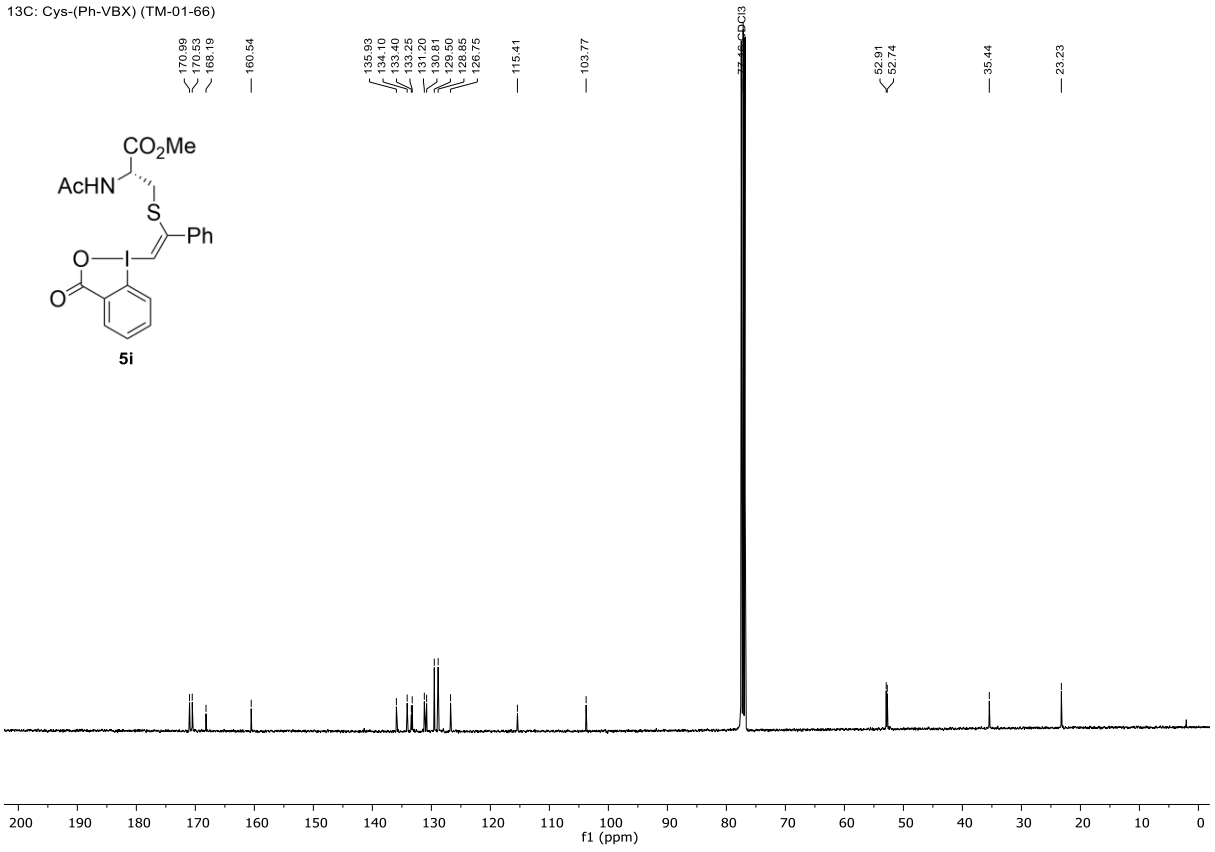
Table S10. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(2-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylvinyl)-L-cysteinate (**5i**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	170.5			
2	52.7	4.55 (td, 7.4, 3.8 Hz)	3, 4	1, 3
3	35.4	3.19 (dd, 14.4, 3.8 Hz), 3.08 (dd, 14.4, 7.3 Hz)	2	1, 2, 8
4	/	7.90 (d, 7.7 Hz)	2	2, 5
5	171.0			
6	23.2	2.02 (s)		5
7	52.9	3.63 (s)		1
8	160.5			
9	103.8	7.08 (s)		8, 10
10	135.9			
11/11’	128.9	7.70-7.66 (m)	12/12’	8
12/12’	129.5	7.53-7.44 (m)	11/11’	
13	130.8	7.53-7.44 (m)		
14	115.4			
15	133.2	8.42 (dd, 7.3, 1.9 Hz)	16	14, 18, 20
16	131.2	7.64-7.54 (m)	15, 17	
17	126.7	7.53-7.44 (m)	16, 18	14
18	134.1	7.64-7.54 (m)	17	
19	133.4			
20	168.2			

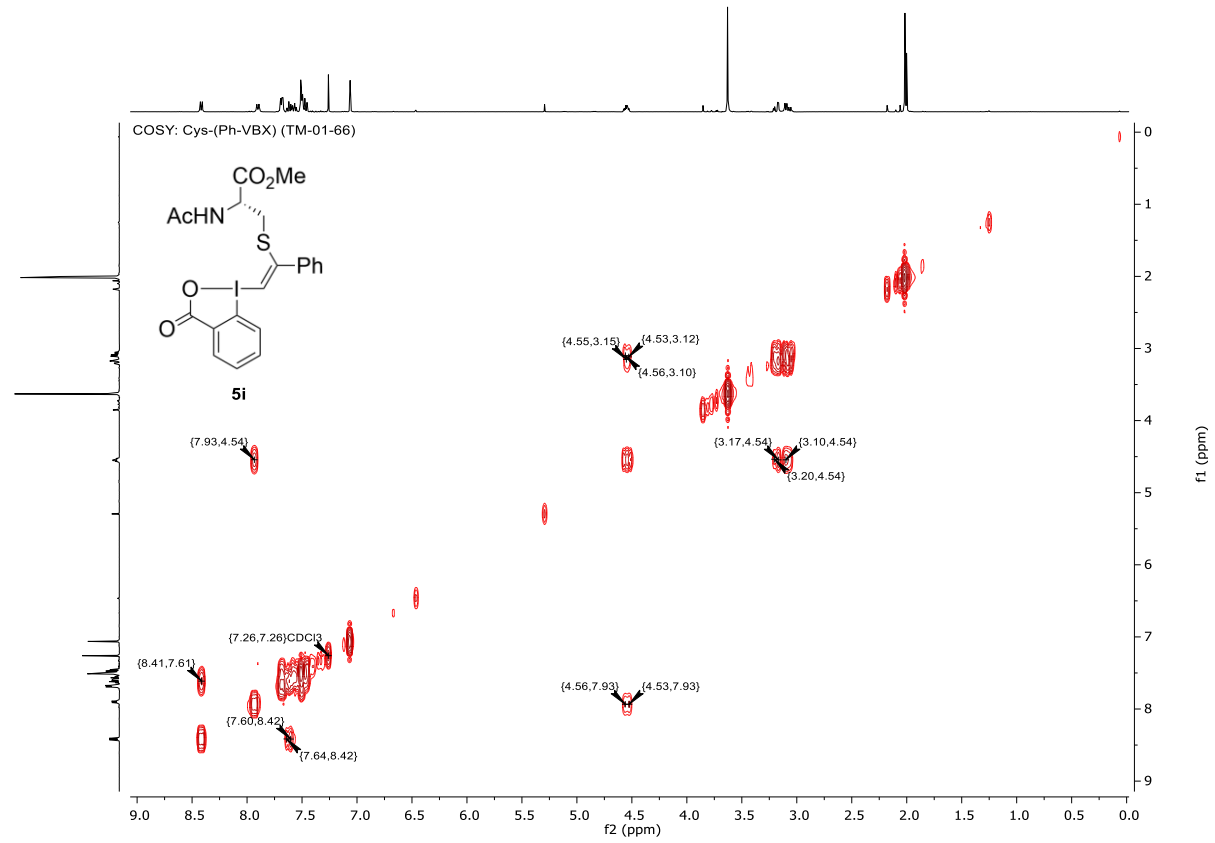
^{1}H-NMR (400 MHz, $CDCl_3$)



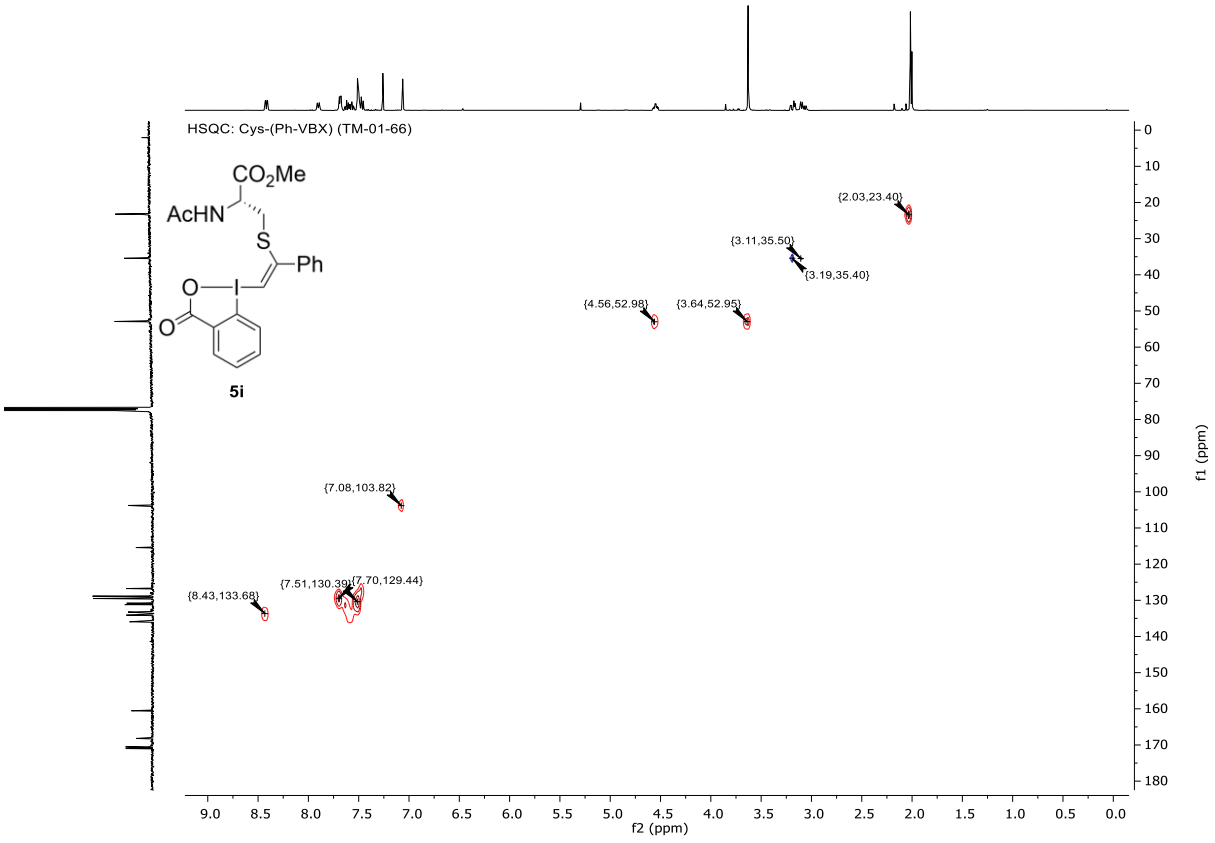
^{13}C-NMR (400 MHz, $CDCl_3$)



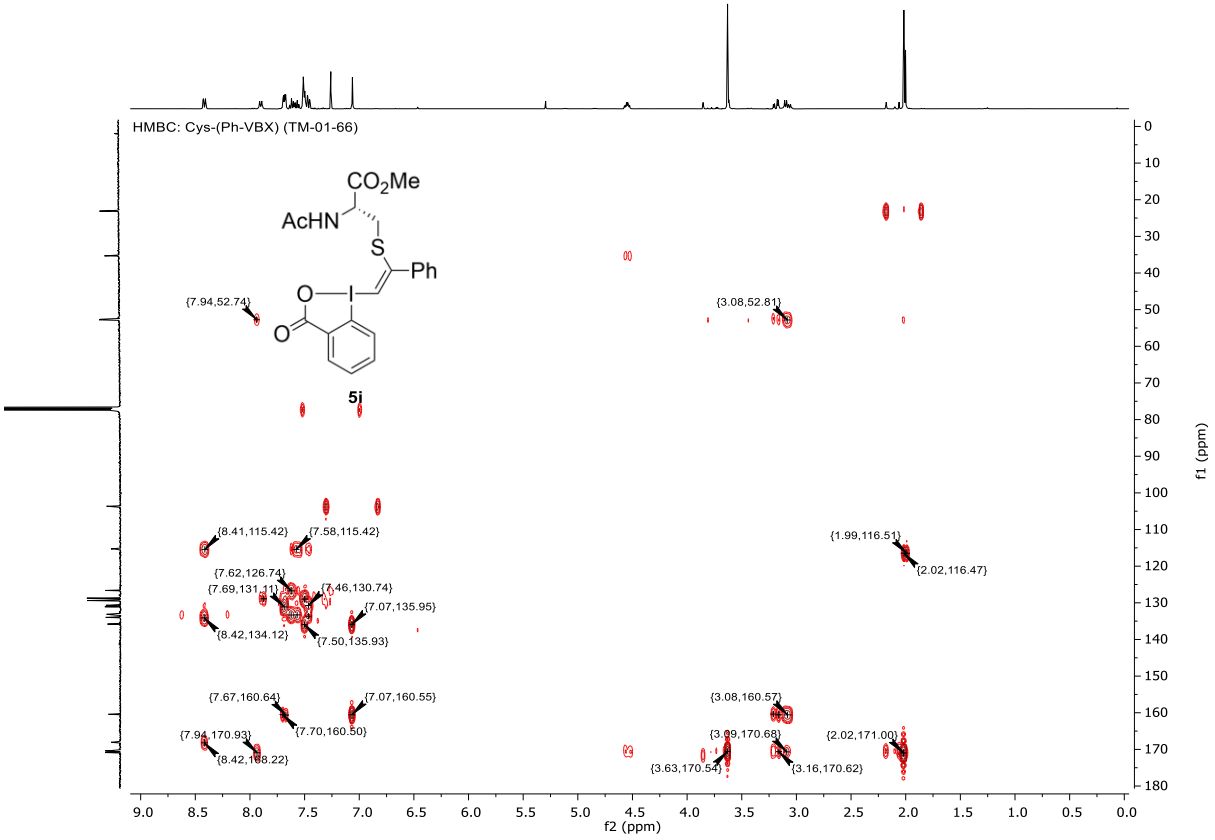
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (5j)

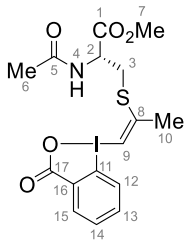
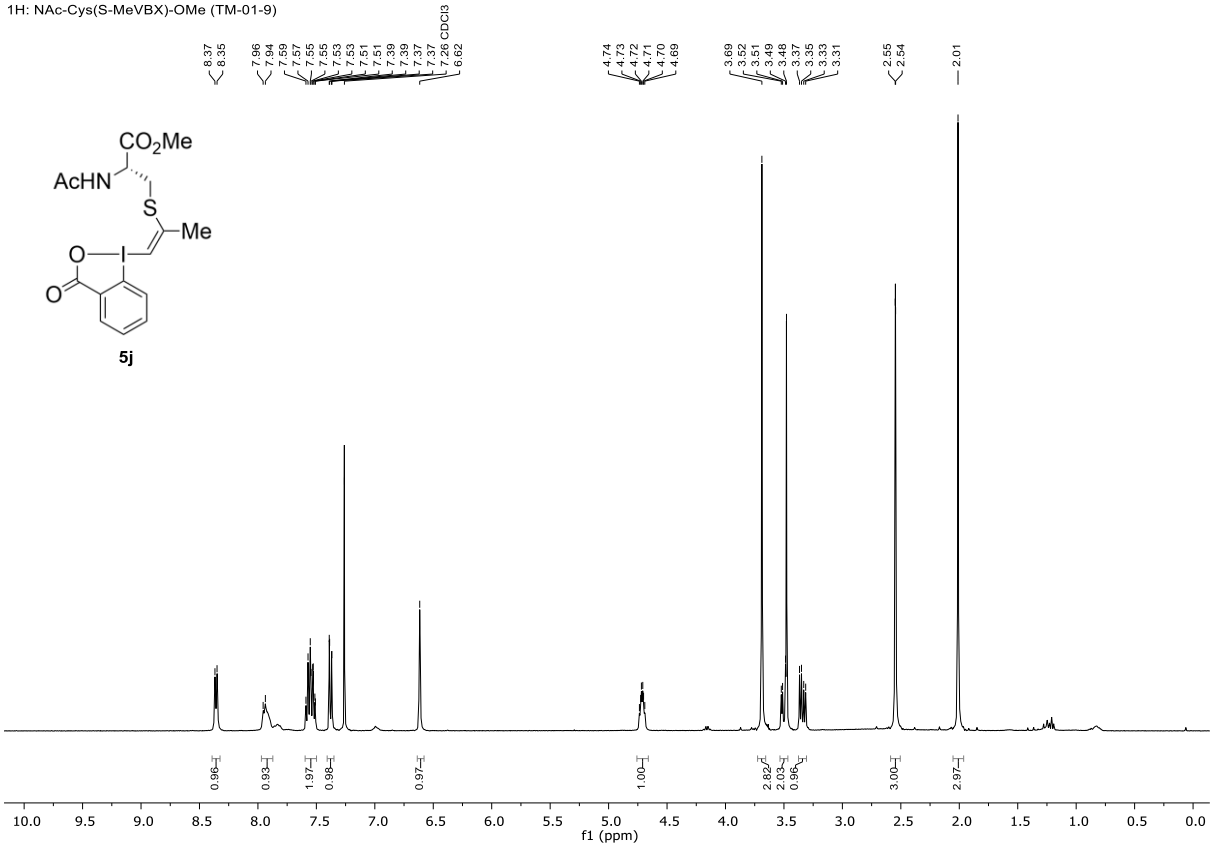


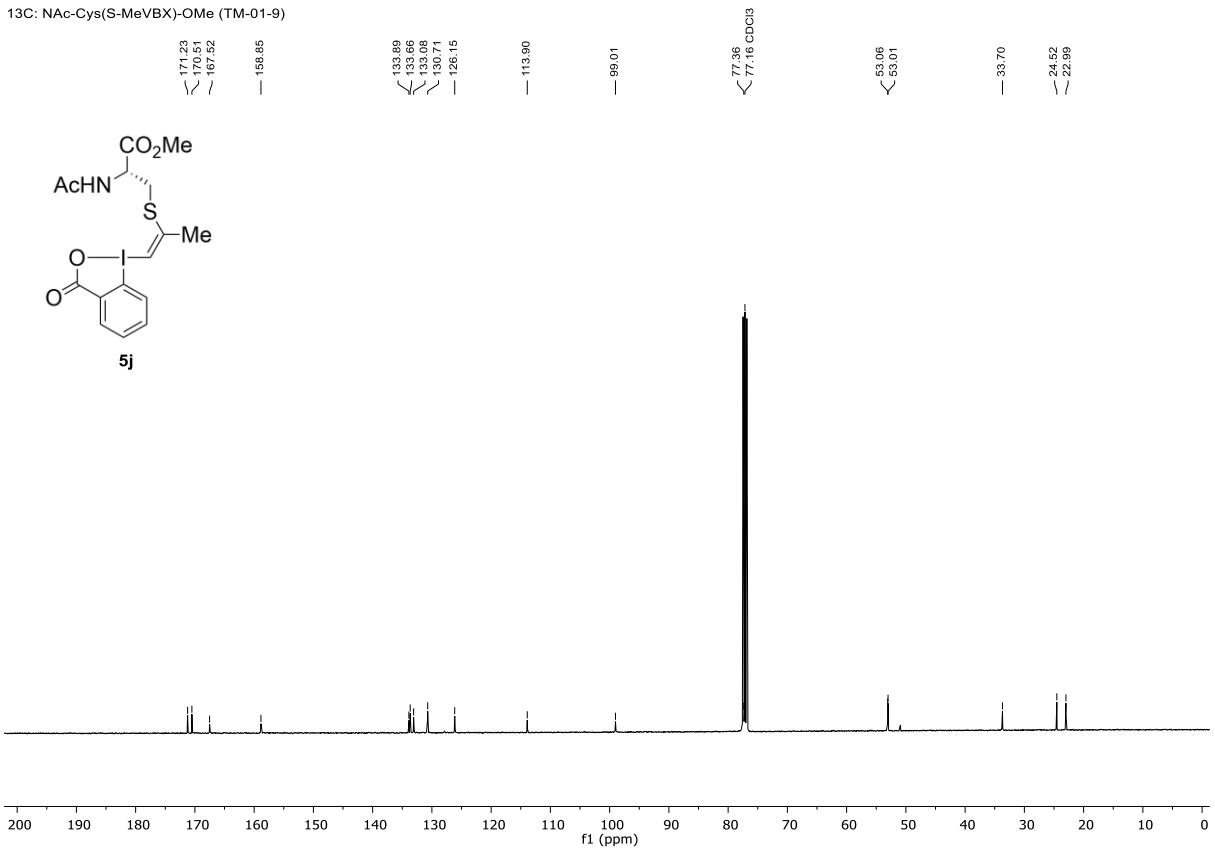
Table S11. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (**5j**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	170.5			
2	53.1	4.71 (td, 6.8, 4.2)	3, 4	1, 3
3	33.7	3.50 (dd, 14.2, 4.3 Hz), 3.34 (dd, 14.4, 6.7 Hz)	4	1, 2, 8
4	/	7.99–7.88 (m)	2	2, 5
5	171.2			
6	23.0	2.01 (s)		5
7	53.0	3.69 (s)		1
8	158.9			
9	99.0	6.62 (s)	10	8, 10
10	24.5	2.55 (d, 1.3 Hz)	9	8, 9
11	113.9			
12	133.1	8.36 (d, 7.1 Hz)	13	11, 13/15, 17
13	133.7/130.7	7.60-7.49 (m)	12, 14	11, 14, 16
14	126.1	7.38 (dd, 7.8, 1.3 Hz)	13, 15	11, 13/15, 16
15	133.7/130.7	7.60-7.49 (m)	14	11, 14, 16
16	133.9			
17	167.5			

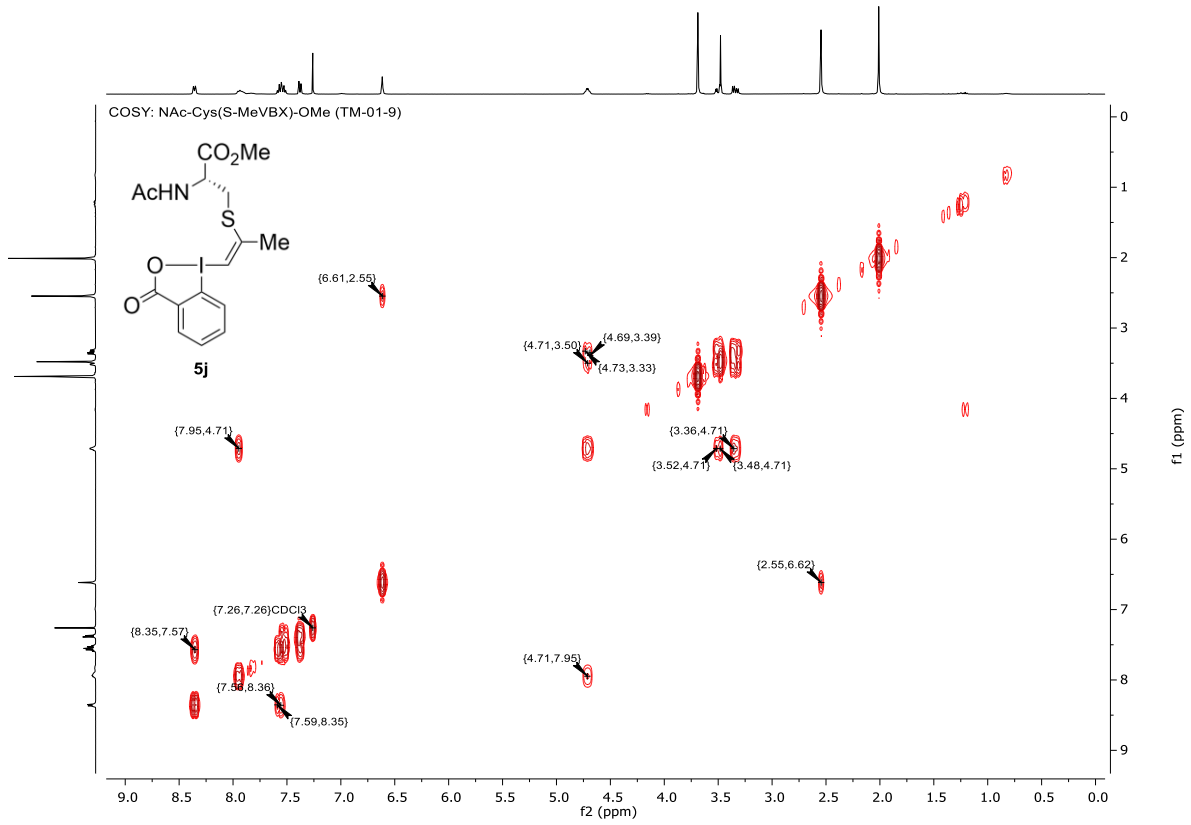
^{1}H-NMR (400 MHz, $CDCl_3$)



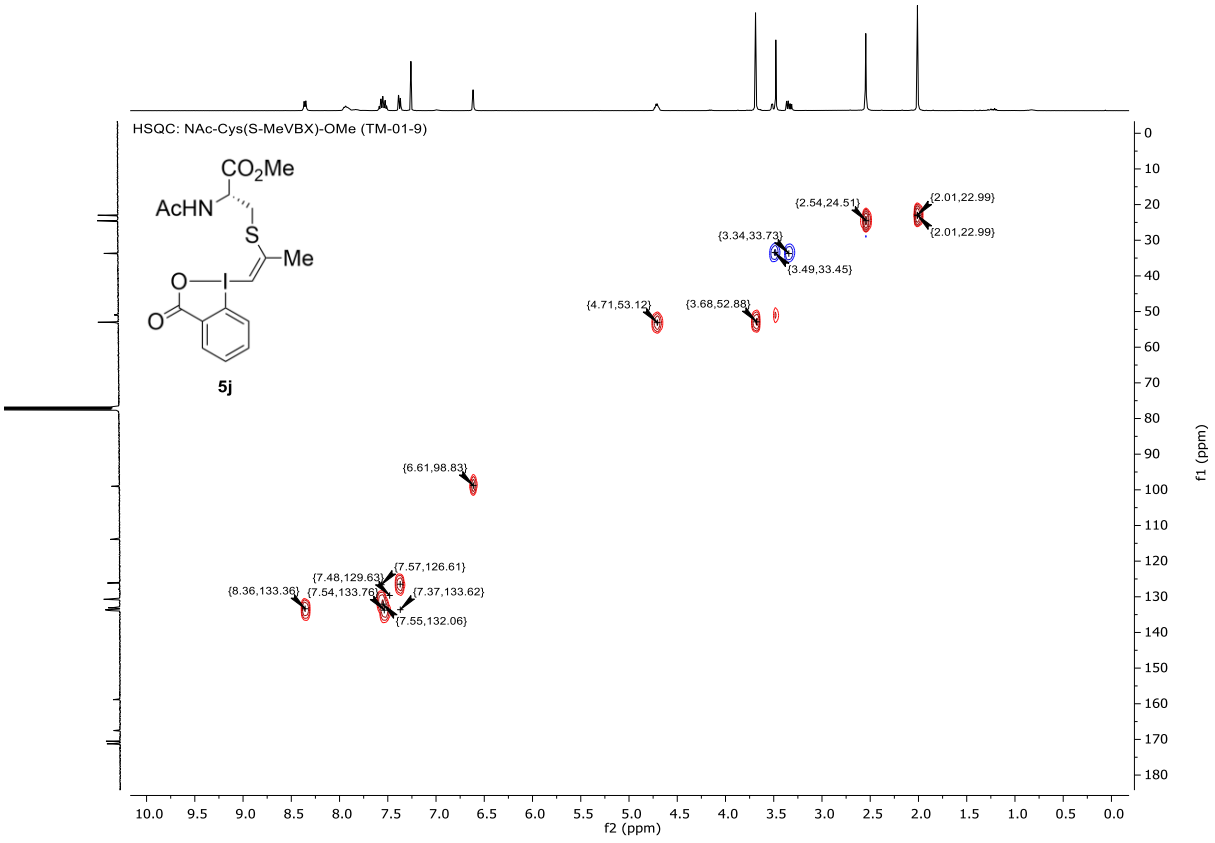
^{13}C-NMR (400 MHz, $CDCl_3$)



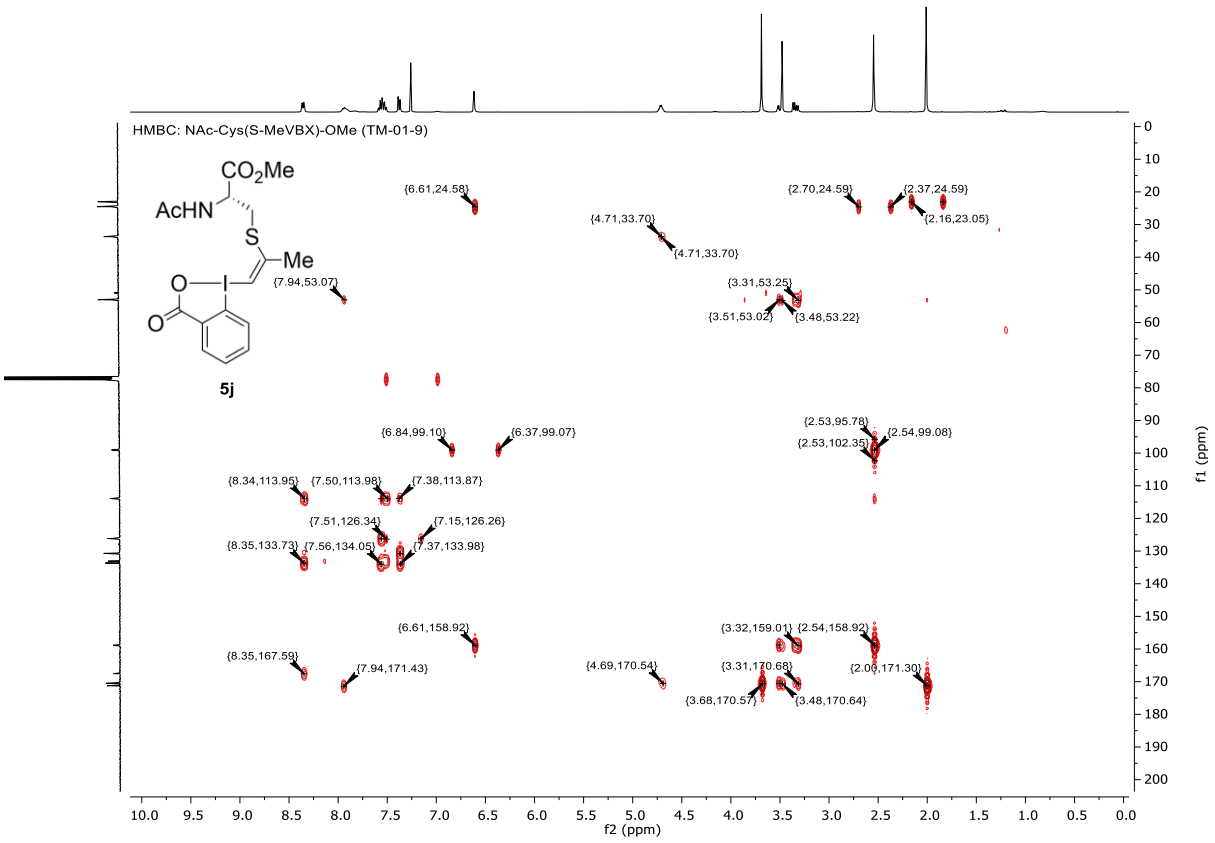
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(1-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (5k)

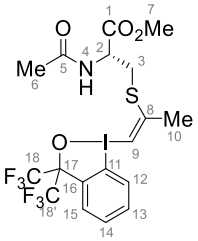
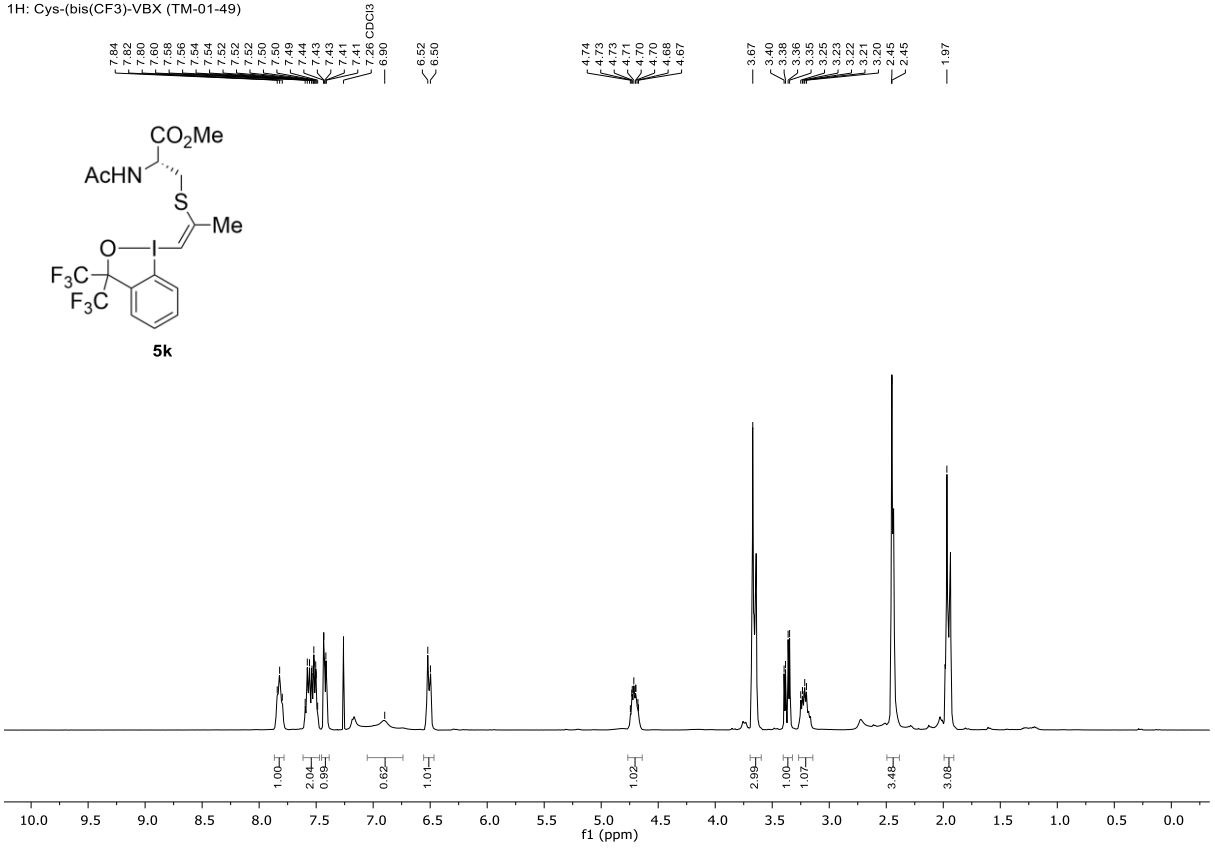


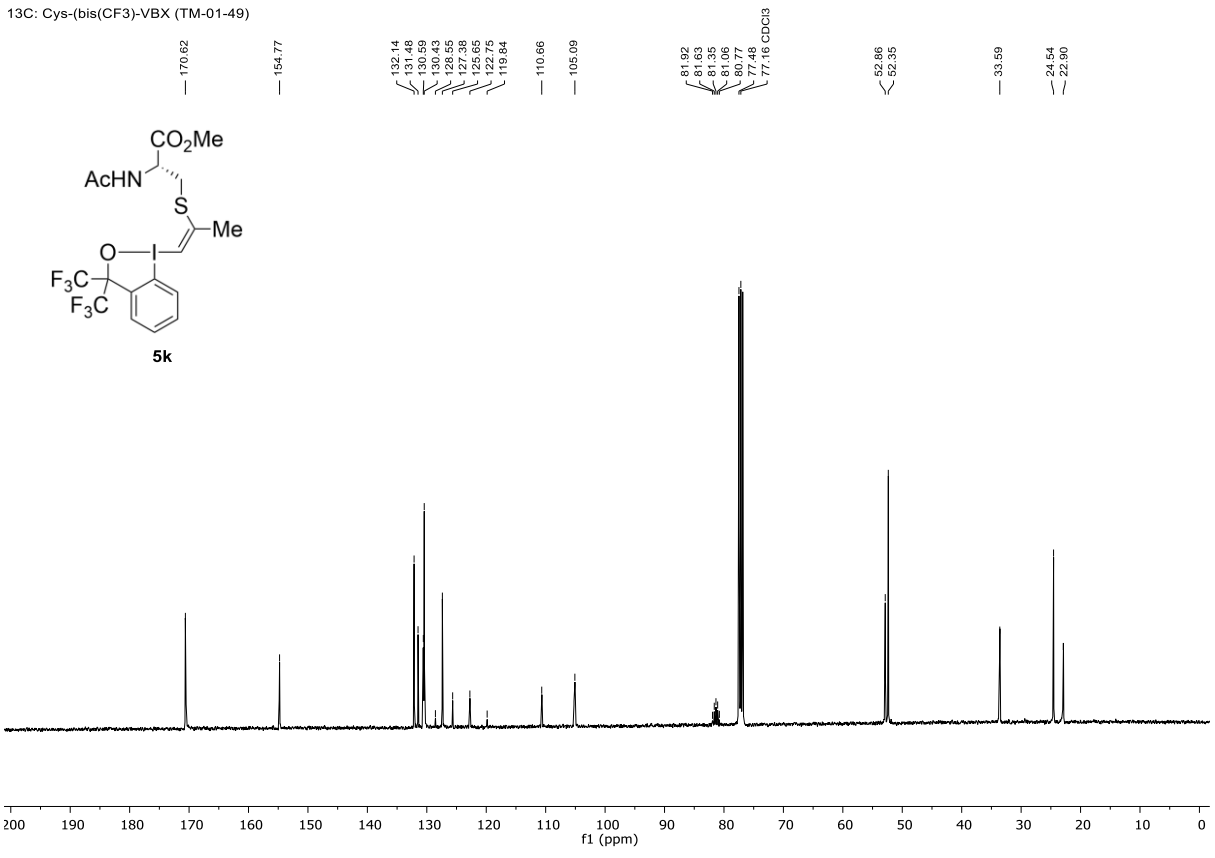
Table S12. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(1-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)prop-1-en-2-yl)-L-cysteinate (**5k**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	170.6			
2	52.4	4.75-4.67 (m)	3,4	1, 3
3	33.6	3.37 (dd, 14.2, 5.1 Hz), 3.22 (dd, 14.0, 6.1 Hz)	2	1, 2, 8
4	/	6.90 (bs)	2	1
5	170.5			
6	22.9	1.97 (s)		5
7	52.9	3.67 (s)		1
8	154.8			
9	105.1	6.52 (s)	10	8, 10
10	24.5	2.45 (s)	9	8, 9
11	110.7			
12	130.6	7.82 (t, 8.9 Hz)	13	11, 13, 17
13	132.1/130.4	7.60-7.48 (m)	12	11, 14, 15
14	127.4	7.44-7.40 (m)		11, 13/15
15	132.1/130.4	7.60-7.48 (m)		11, 13, 14
16	131.5			
17	82.0-80.6 (m)			
18/18’	124.2 (q, 291.6 Hz)			

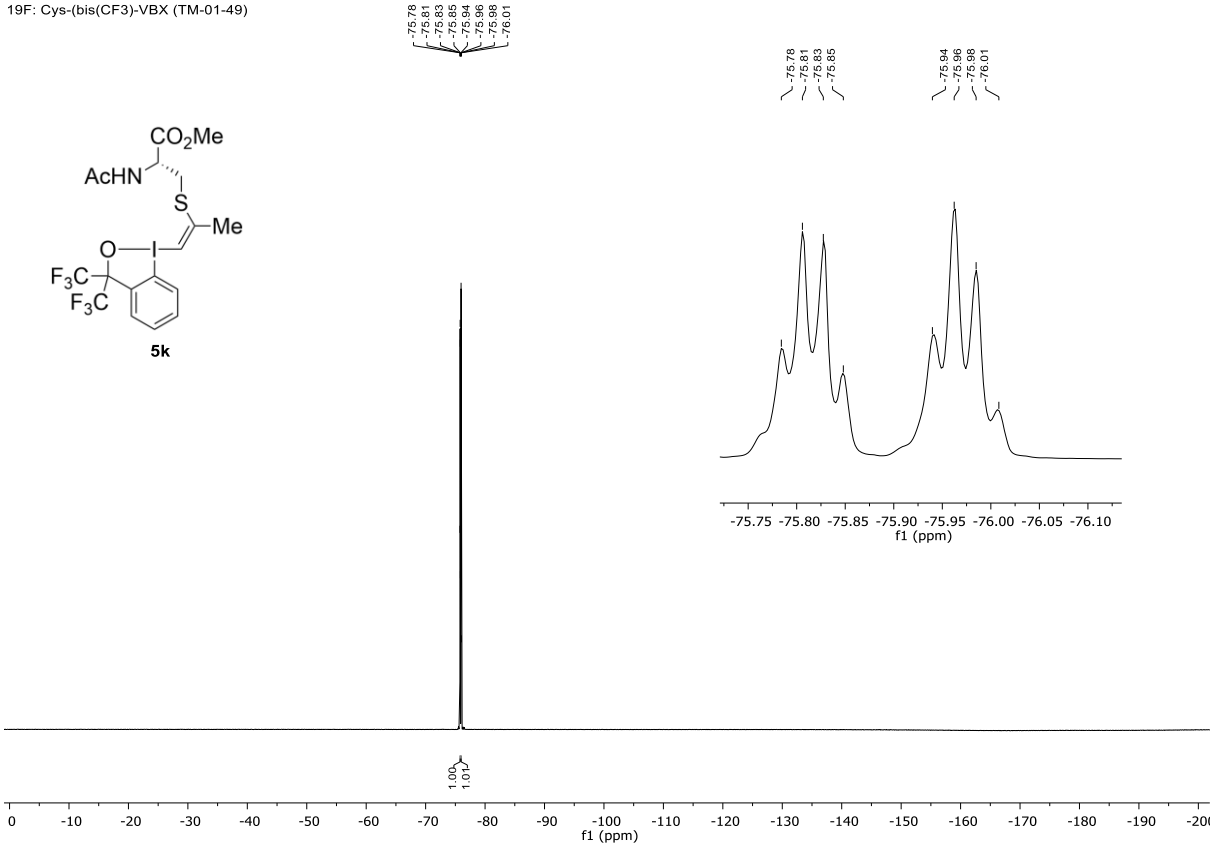
^{1}H-NMR (400 MHz, $CDCl_3$)



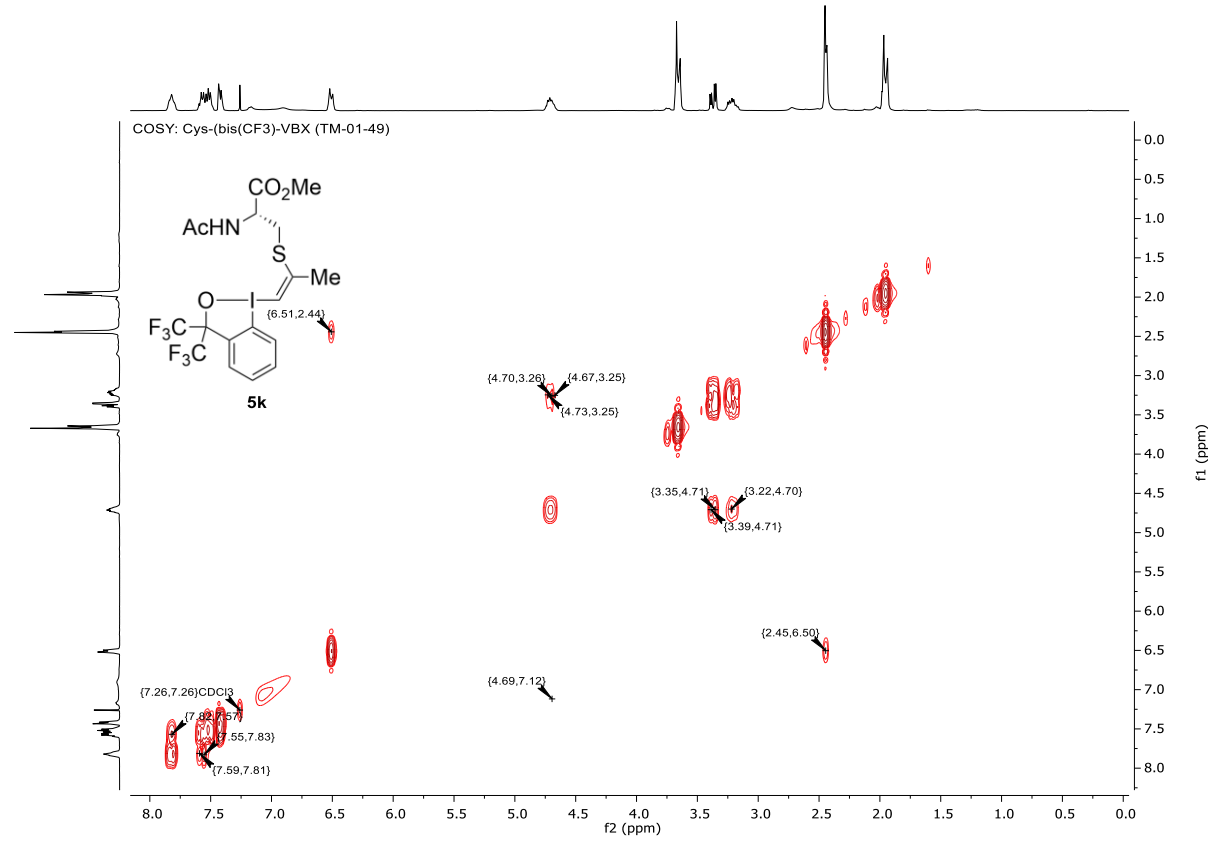
^{13}C-NMR (400 MHz, $CDCl_3$)



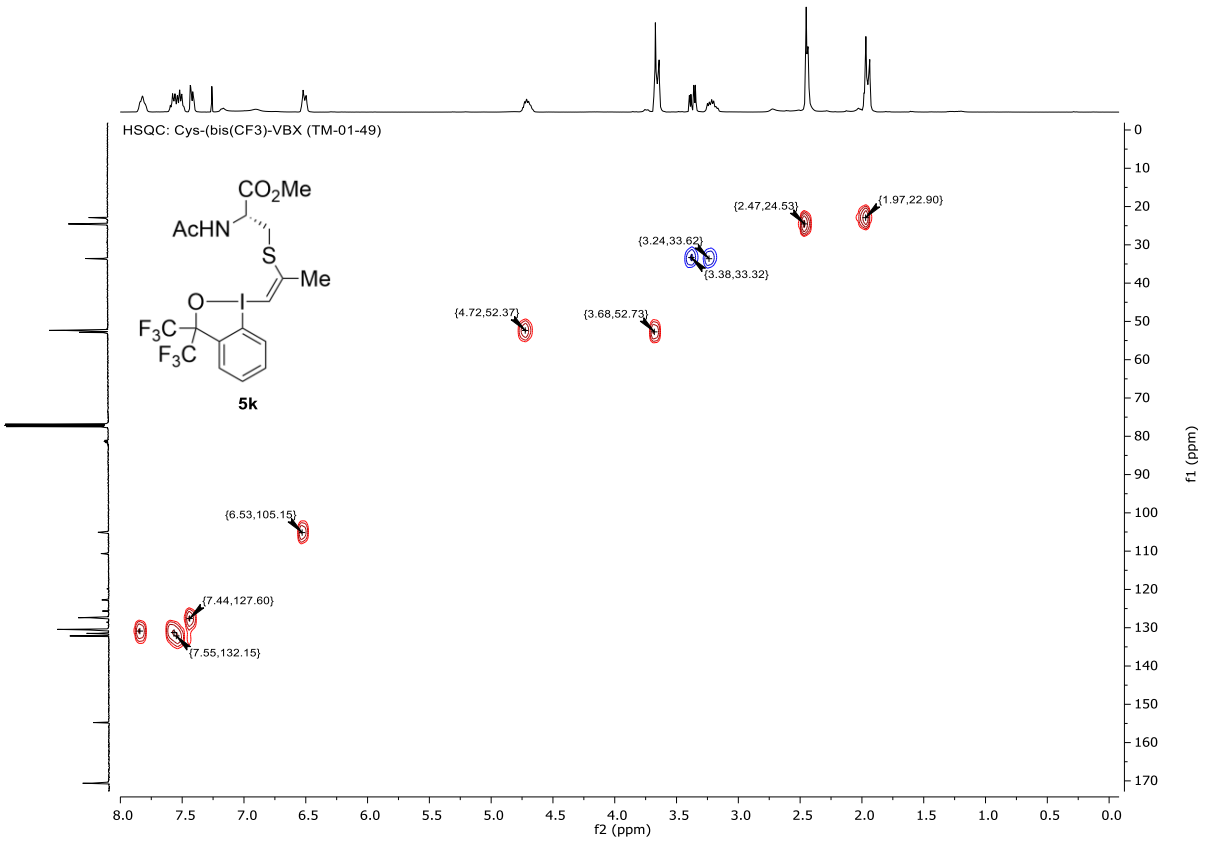
^{19}F-NMR (376 MHz, $CDCl_3$)



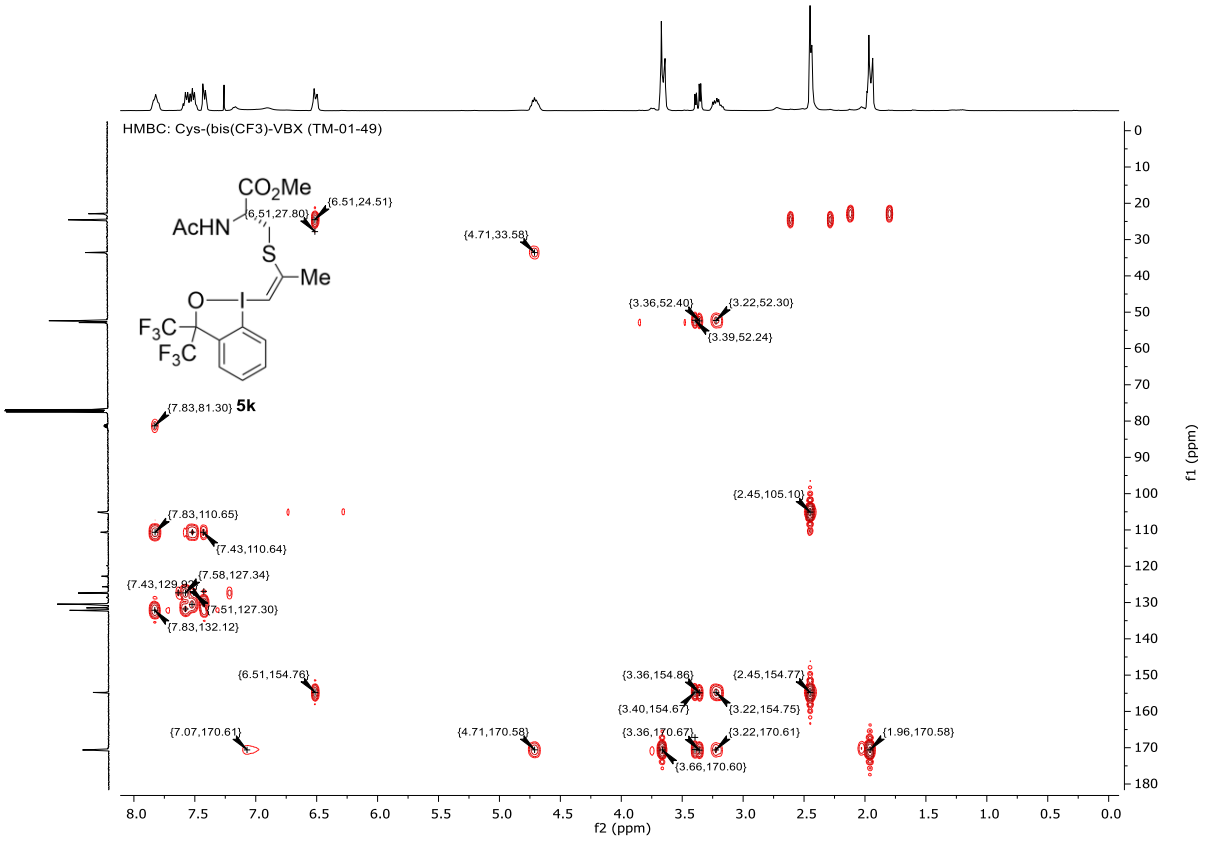
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(5-chloro-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)-L-cysteinate (5m)

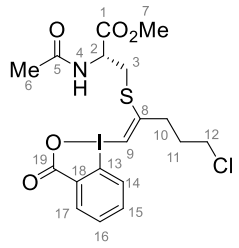
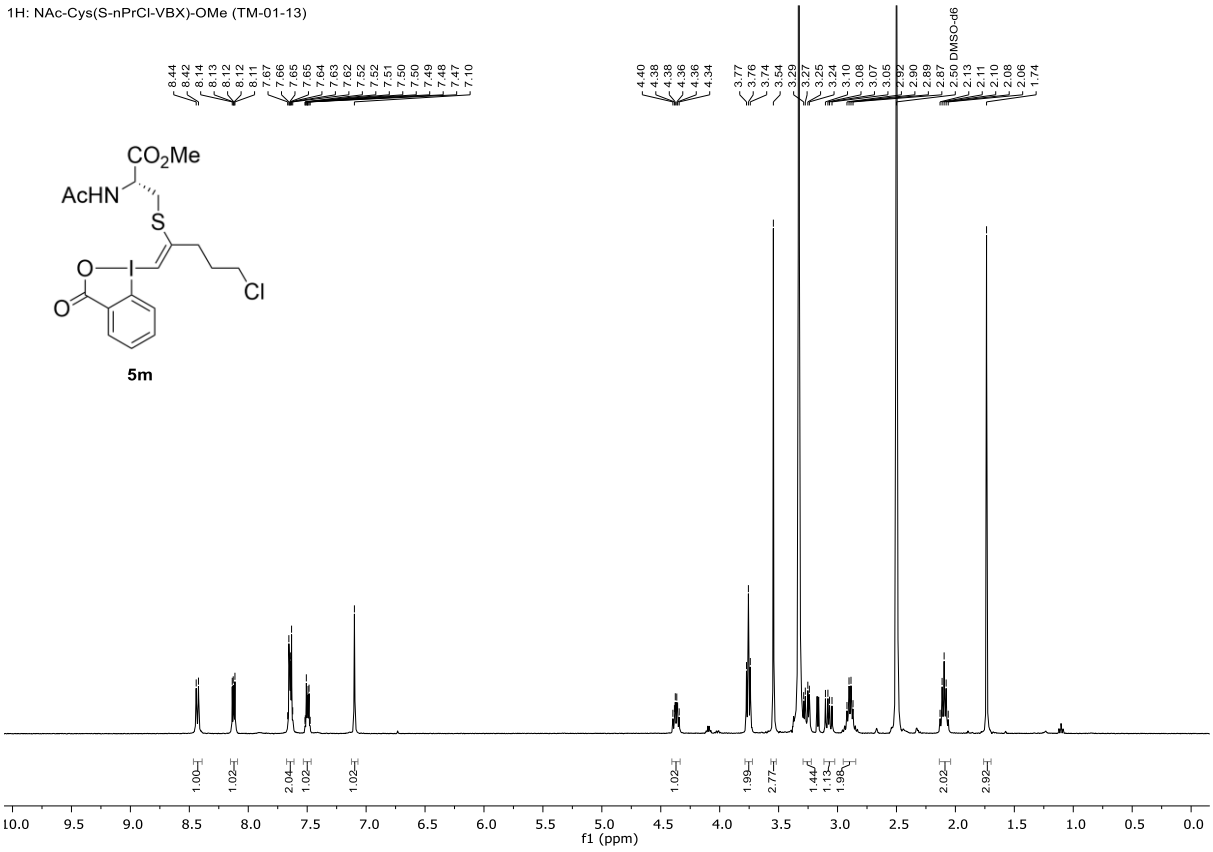


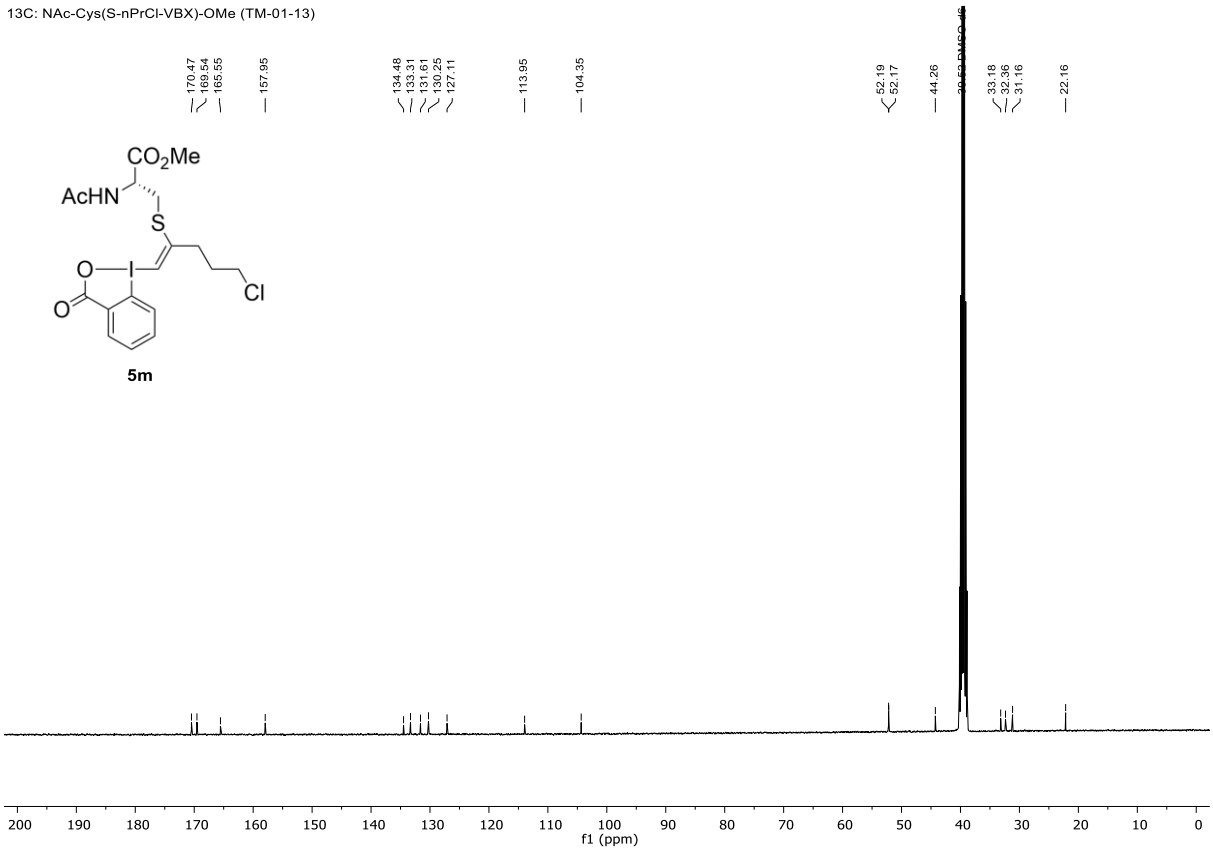
Table S13. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(5-chloro-1-(3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)pent-1-en-2-yl)-L-cysteinate (**5m**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	169.5			
2	52.19	4.37 (td, 8.1, 5.2 Hz)	3, 4	1, 3
3	32.4	3.26 (dd, 13.9, 5.4 Hz), 3.07 (dd, 13.9, 8.3 Hz)	2	1, 2, 8
4	/	8.43 (d, 7.7 Hz)	2	1, 2
5	170.5			
6	22.2	1.74 (s)		5
7	52.17	3.54 (s)		1
8	158.0			
9	104.3	7.10 (s)		8, 10
10	33.2	2.92-2.87 (m)	11	8, 9, 11, 12
11	31.2	2.10 (p, 7.0 Hz)	10, 12	8, 10, 12
12	44.3	3.76 (t, 6.4 Hz)	11	11
13	113.9			
14	131.6	8.15-8.09 (m)	15	13, 15/17, 19
15	133.3/130.2	7.68-7.61 (m)	14	13, 14, 16
16	127.1	7.53-7.46 (m)		13, 15/17, 18
17	133.3/130.2	7.68-7.61 (m)		13, 14, 16
18	134.5			
19	165.6			

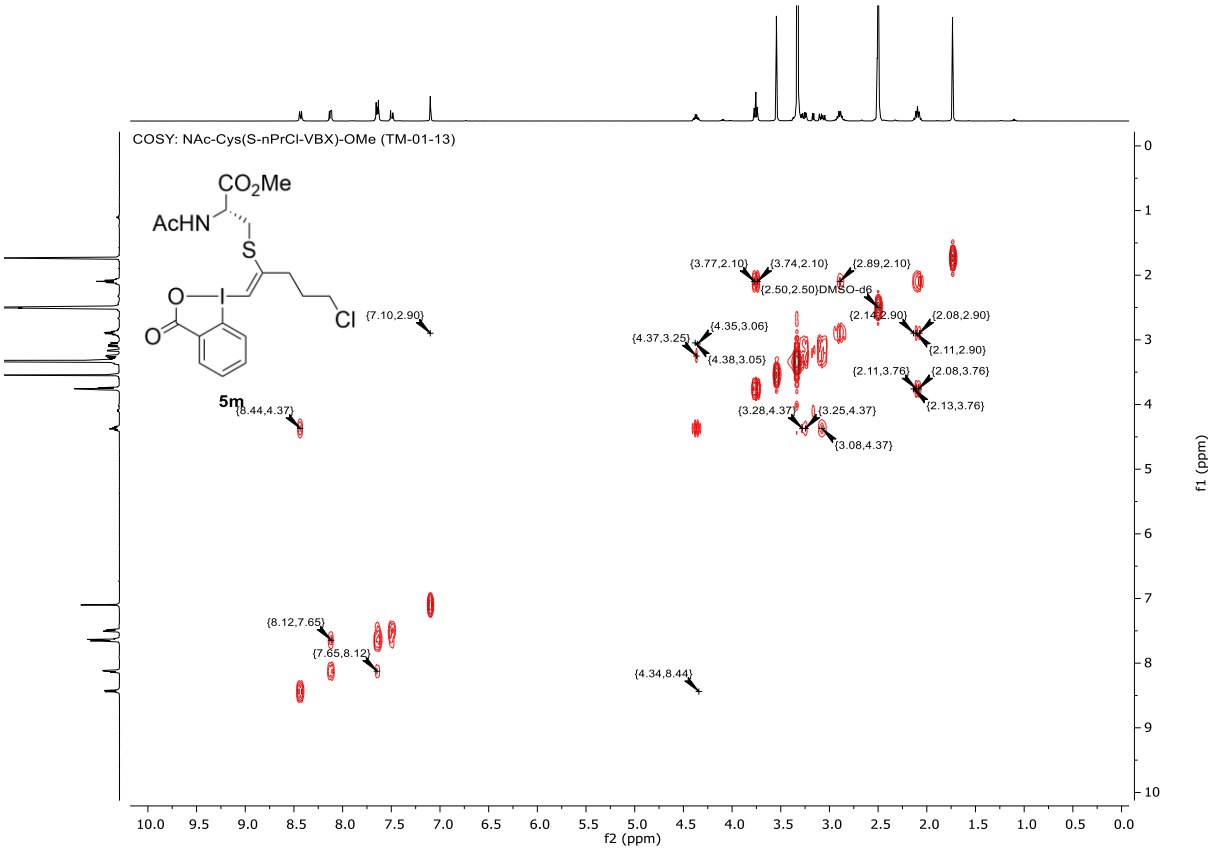
^{1}H-NMR (400 MHz, $CDCl_3$)



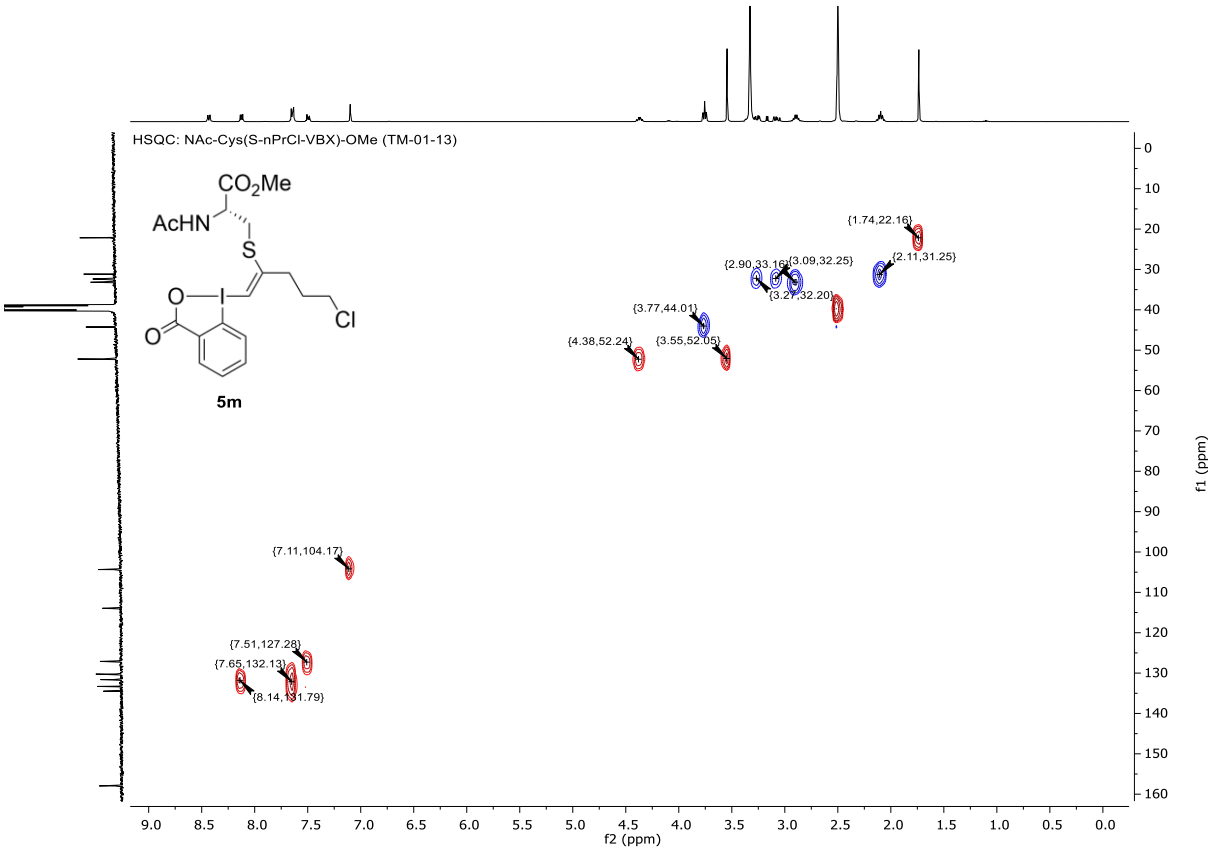
^{13}C-NMR (400 MHz, $CDCl_3$)



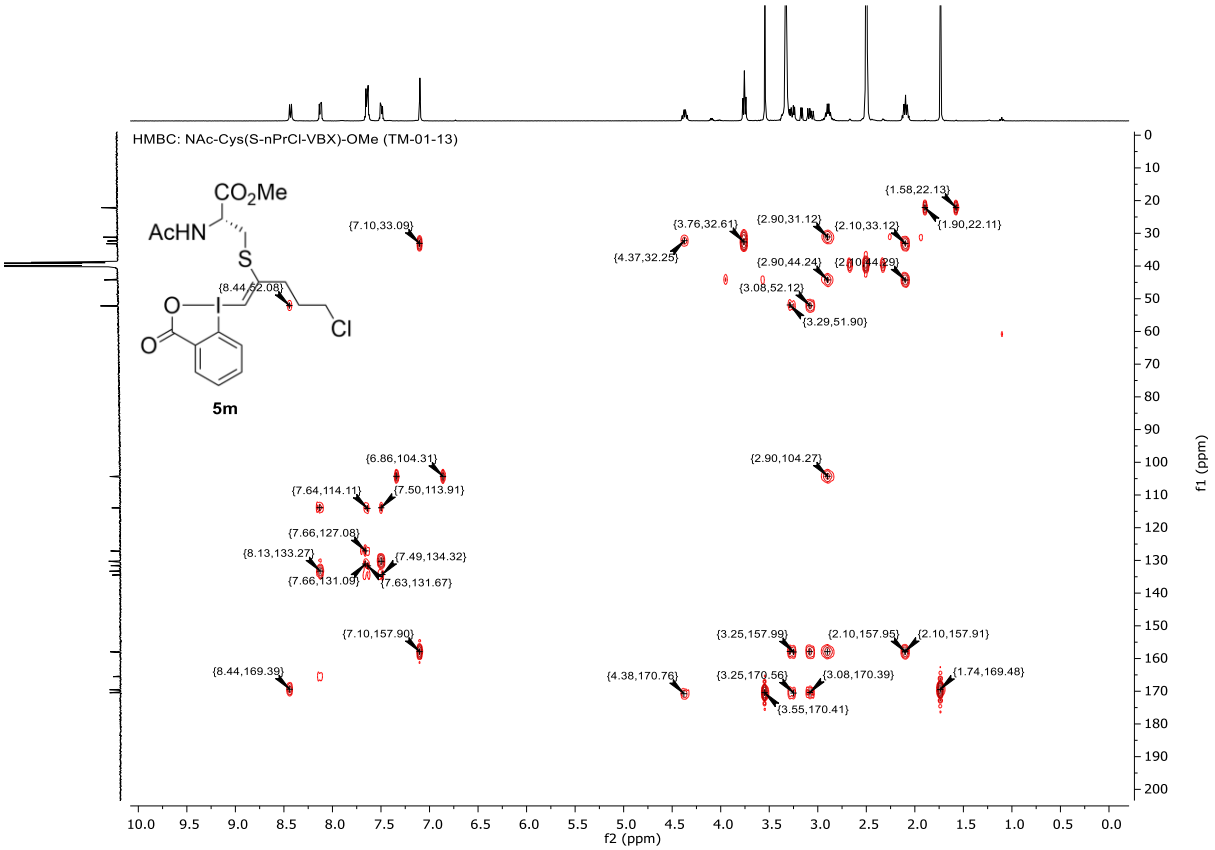
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



N-Boc-L-Ala-L-Tyr(*O*-Ph-VBX)-L-Ala-OEt (5n)

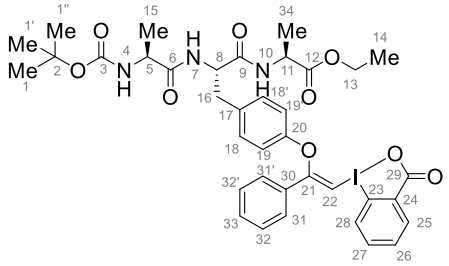
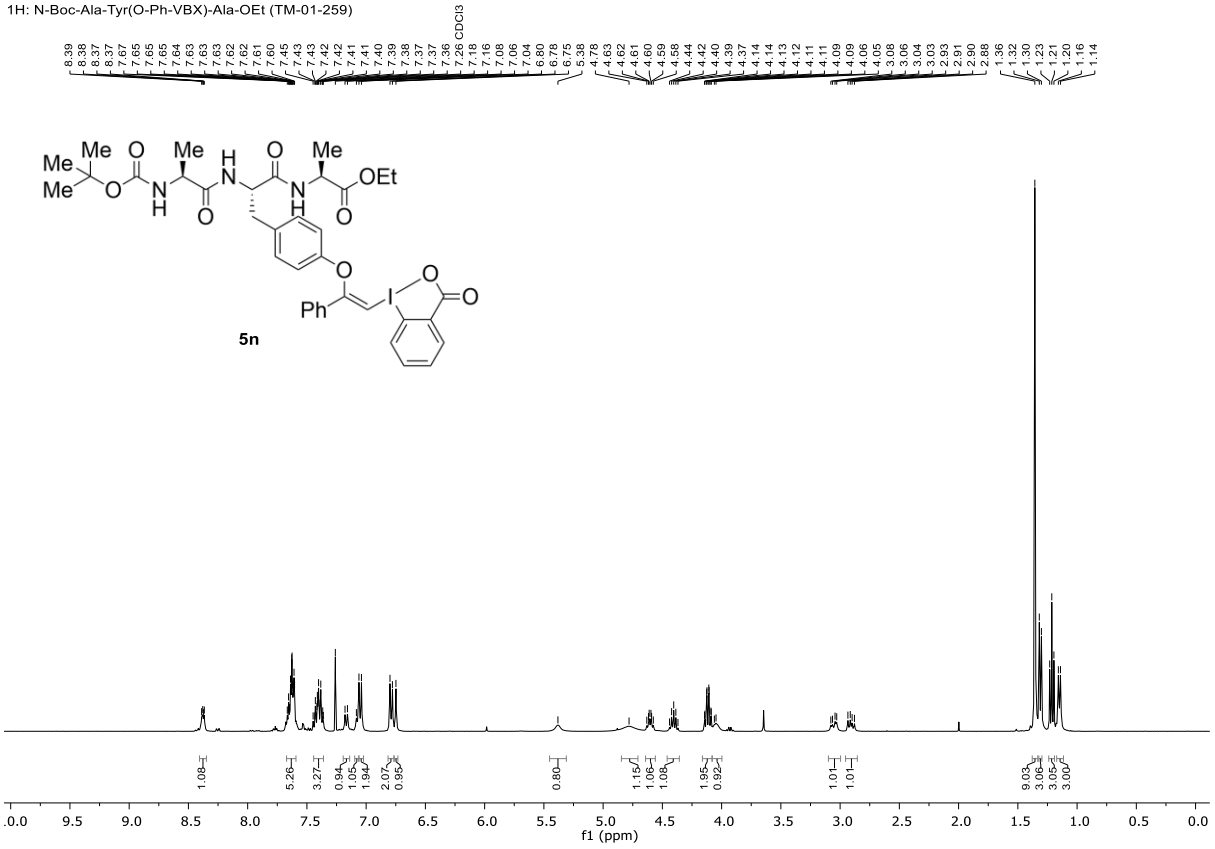


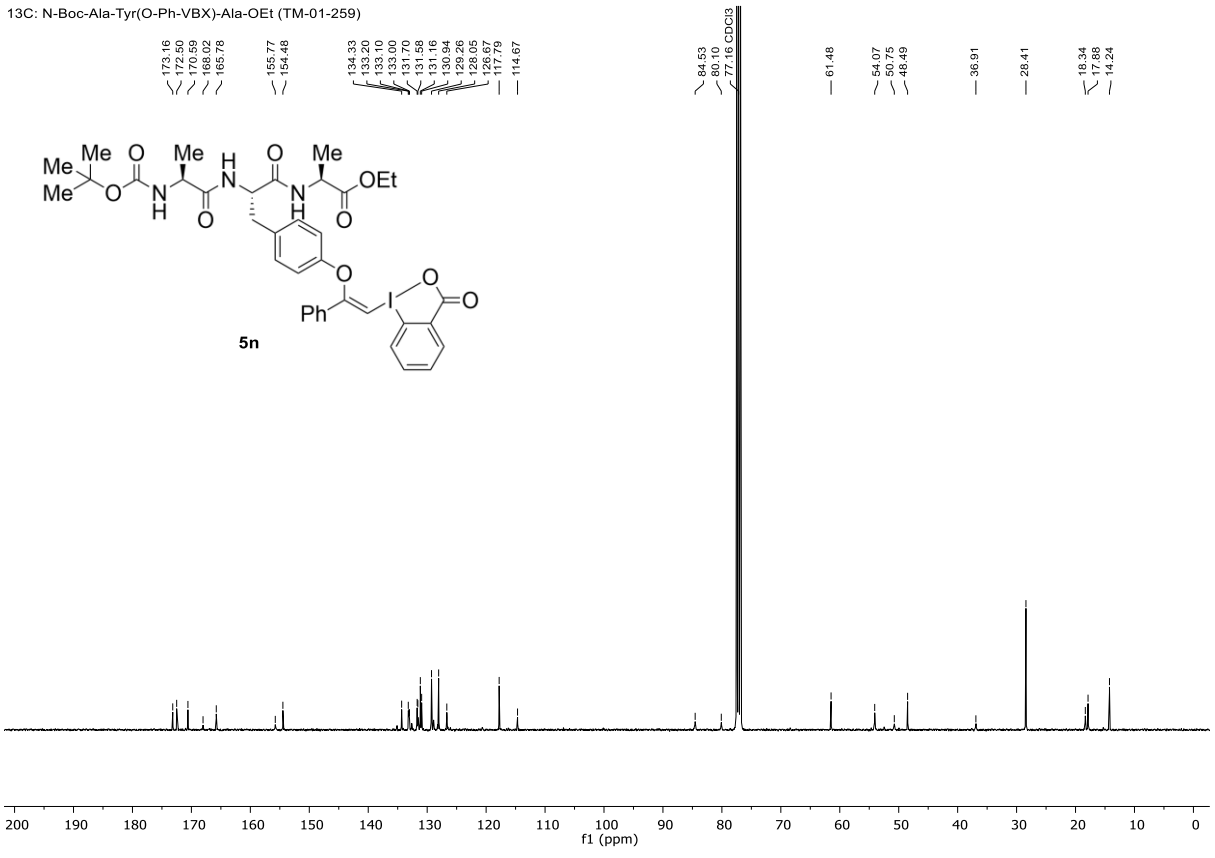
Table S14. Detailed NMR assignment of *N*-Boc-L-Ala-L-Tyr(*O*-Ph-VBX)-L-Ala-OEt (**5n**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1'/1''	28.4	1.36 (s)		2
2	80.1			
3	155.8			
4	/	5.38 (bs)		
5	50.7	4.07-4.00 (m)	15	
6	173.2			
7	/	7.17 (d, 8.2 Hz)	8	6
8	54.1	4.60 (td, 8.0, 5.8 Hz)	7, 16	9, 16, 17
9	170.6			
10	/	7.07 (d, 8.6 Hz)	11	
11	48.5	4.40 (p, 7.1 Hz)	10 ,34	12, 34
12	172.5			
13	61.5	4.12 (qd, 7.1, 1.1 Hz)	14	12, 14
14	14.2	1.21 (t, 7.1 Hz)	13	13
15	18.3	1.15 (d, 7.1 Hz)	5	5, 6
16	36.9	3.05 (dd, 14.2, 5.7 Hz), 2.91 (dd, 14.2, 8.0 Hz)	8	8, 9, 18/18'
17	133.0/133.1			
18/18'	131.2	7.05 (d, 8.5 Hz)	19/19'	16, 20
19/19'	117.8	6.79 (d, 8.2 Hz)	18/18'	17, 20
20	154.5			
21	165.8			
22	84.5	6.75 (s)		21
23	114.7			
24	130.9			
25	133.0/133.1	7.69-7.58 (m)		
26	131.7	7.69-7.58 (m)		
27	134.3	7.69-7.58 (m)	28	
28	133.2	8.38 (dd, 6.0, 3.1 Hz)	27	23, 27
29	168.0			
30	131.6			
31/31'	128.1	7.69-7.58 (m)	32/32'	
32/32'	129.3	7.47-7.37 (m)	31/31'	
33	126.7	7.47-7.37 (m)		32/32'
34	17.9	1.31 (d, 7.1 Hz)	11	11, 12

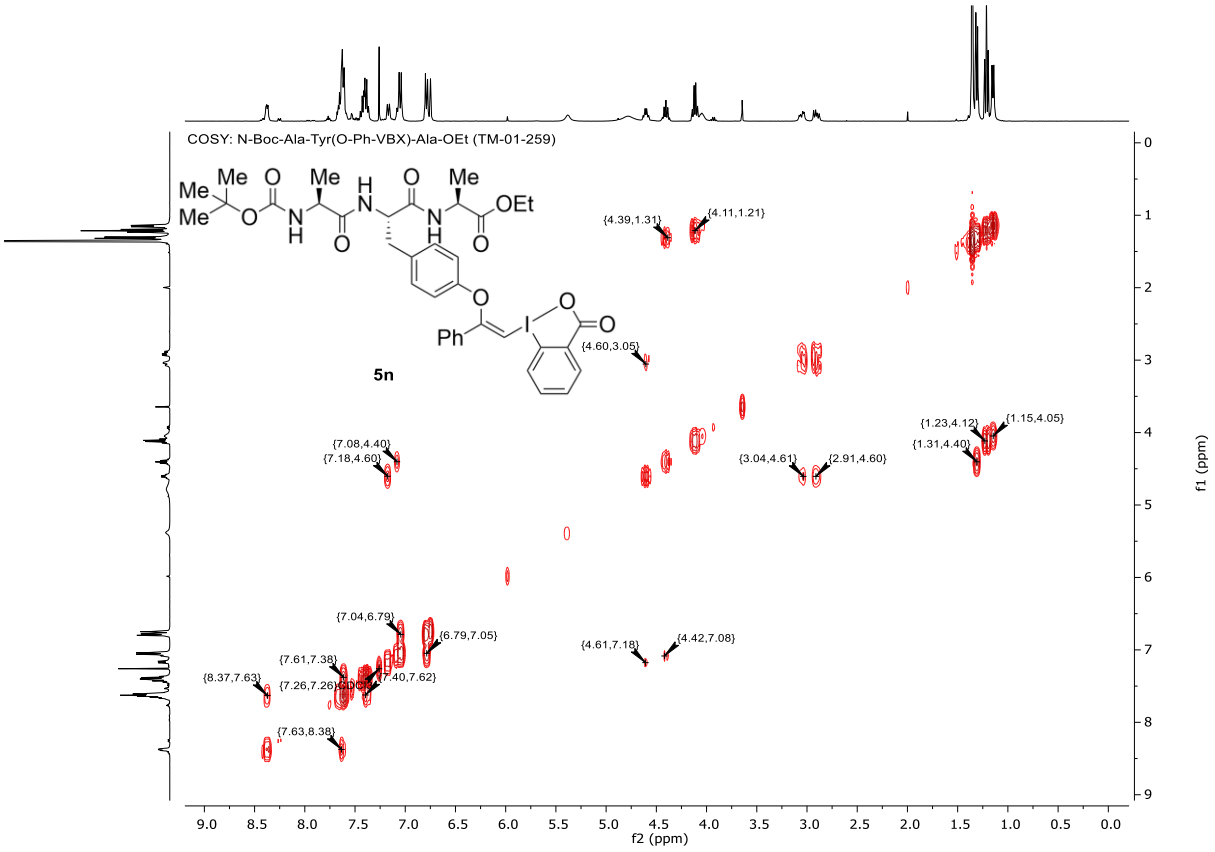
^{1}H-NMR (400 MHz, $CDCl_3$)



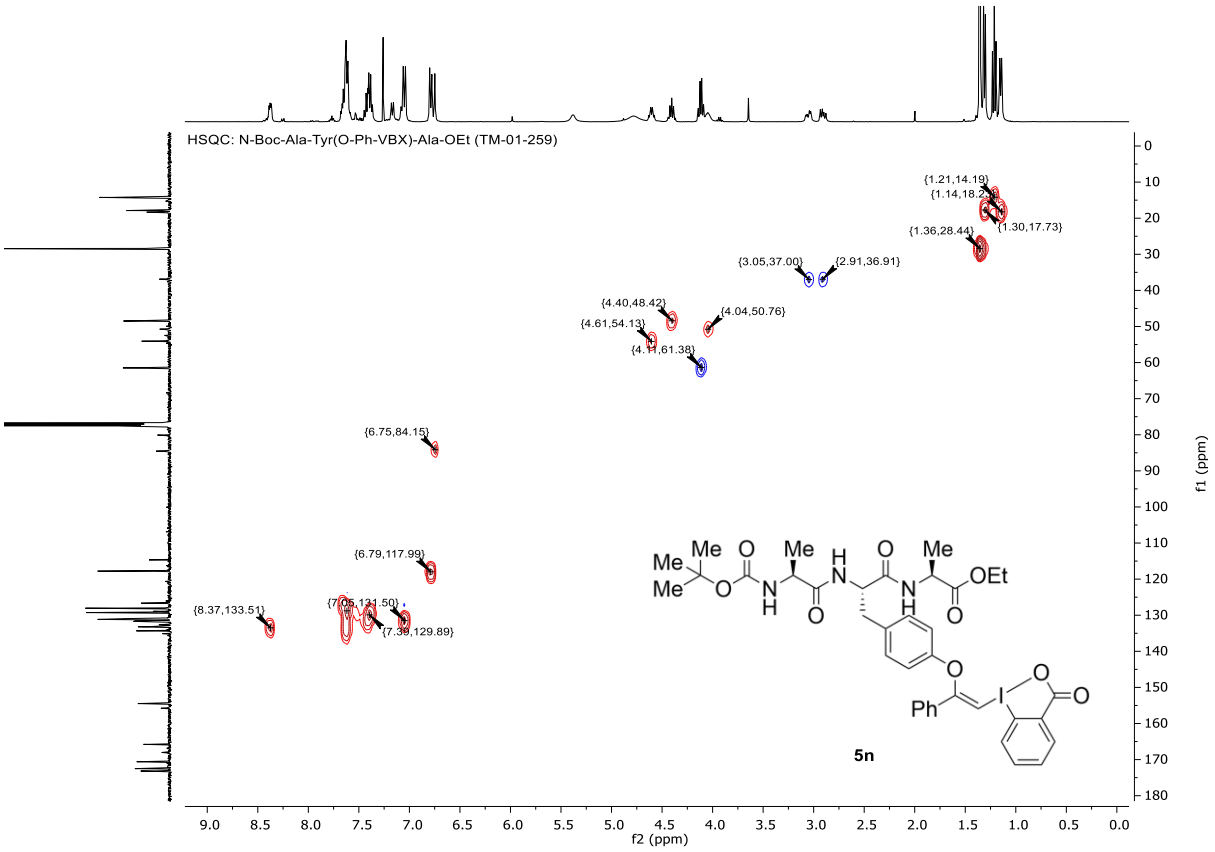
^{13}C-NMR (101 MHz, $CDCl_3$)



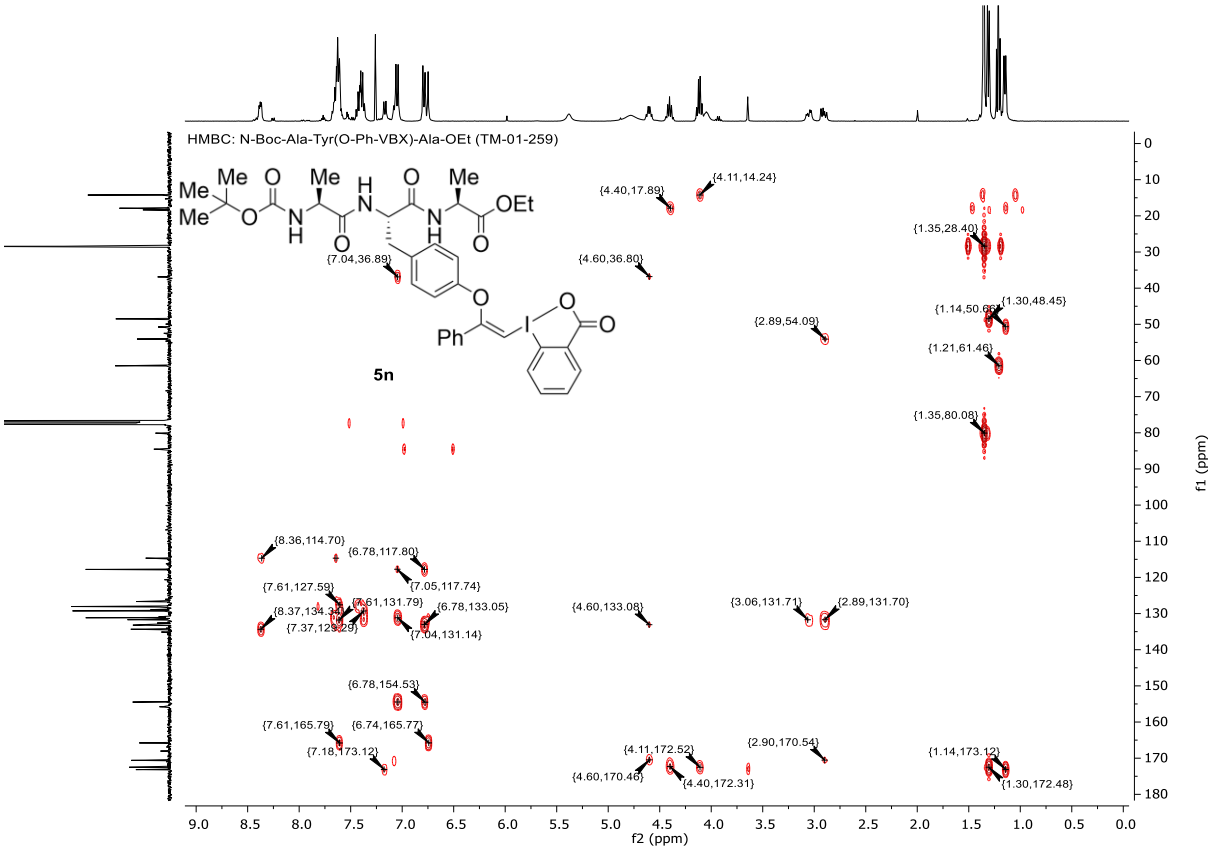
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



N-Boc-L-Ala-L-Tyr(*O*-Cl-VBX)-L-Ala-OMe (5o)

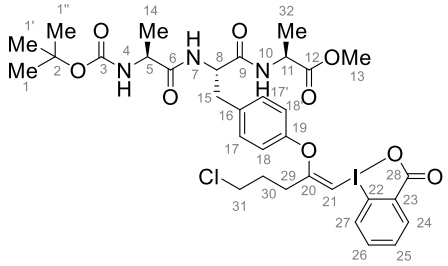
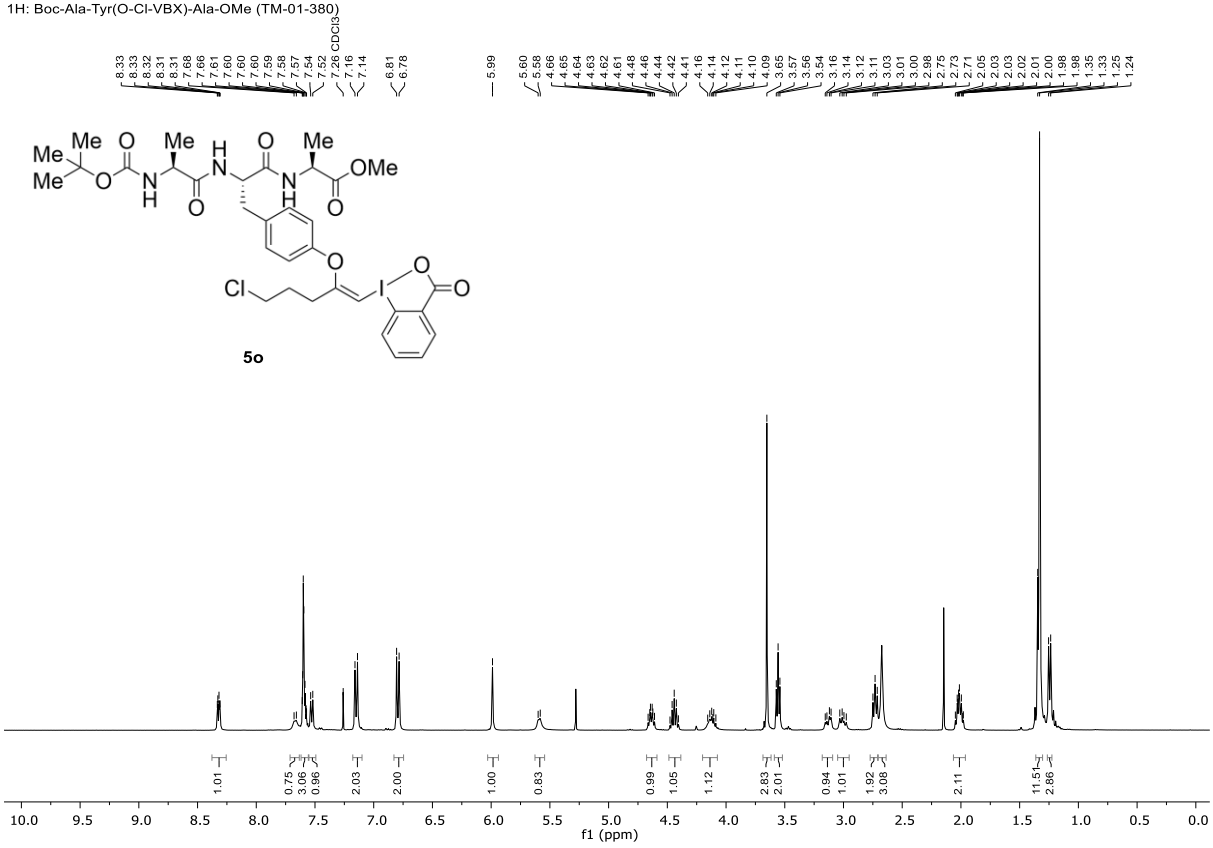


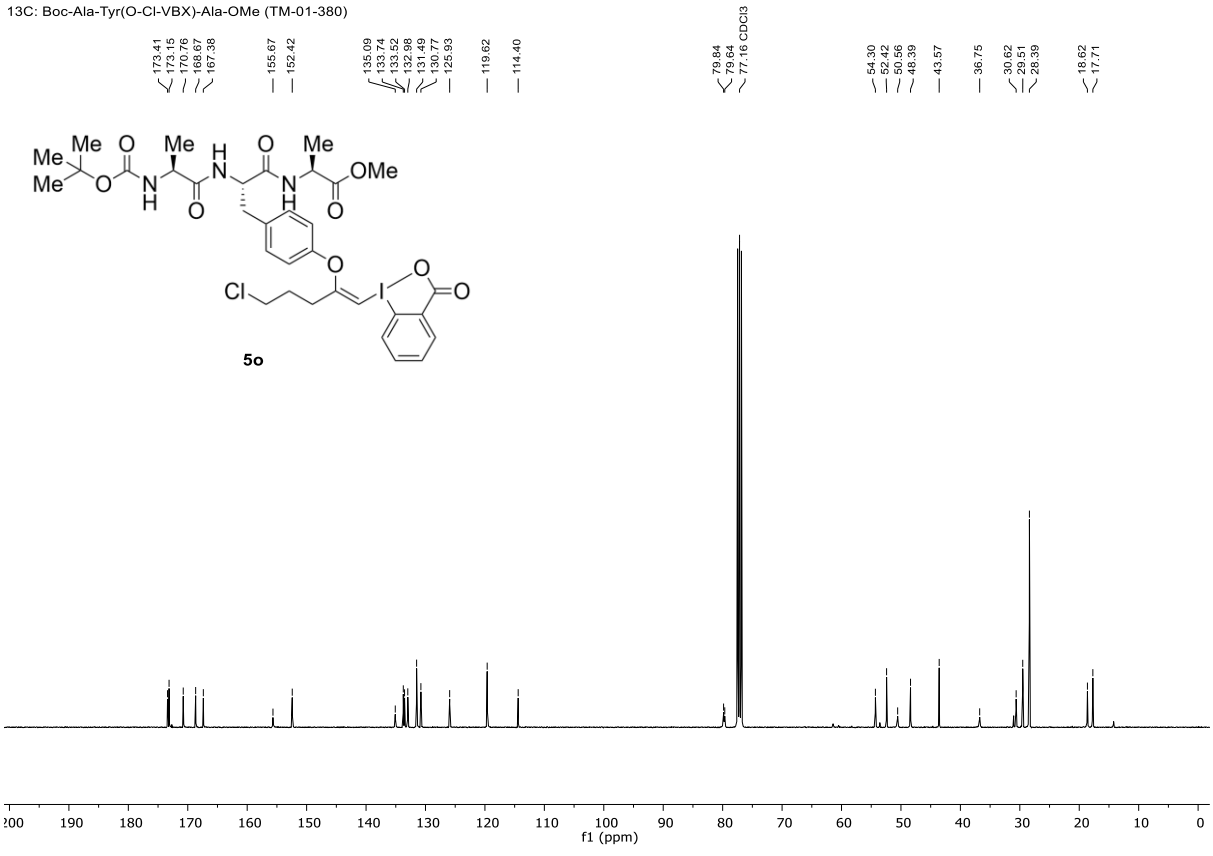
Table S15. Detailed NMR assignment of *N*-Boc-L-Ala-L-Tyr(*O*-Cl-VBX)-L-Ala-OMe (**5o**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1'/1''	28.4	1.36-1.30 (m)		2
2	79.8			
3	155.7			
4	/	5.59 (d, 7.2 Hz)		
5	50.6	4.20-4.08 (m)	14	
6	173.8			
7	/	7.67 (d, 8.0 Hz)		
8	54.3	4.64 (td, 8.0, 5.7 Hz)		9, 15, 16
9	170.8			
10	/	7.53 (d, 7.2 Hz)	11	9, 11
11	48.4	4.44 (p, 7.1 Hz)	10, 32	12, 32
12	173.1			
13	52.4	3.65 (s)		12
14	18.6	1.24 (d, 7.1 Hz)	5	5, 6
15	36.8	3.13 (dd, 14.2, 5.7 Hz), 3.00 (dd, 14.1, 8.0 Hz)		8, 9, 17/17‘
16	135.1			
17/17’	131.5	7.15 (d, 8.6 Hz)	18/18’	15, 18/18’, 19
18/18’	119.6	6.79 (d, 8.6 Hz)	17/17’	17/17’, 19
19	152.4			
20	168.7			
21	79.6	5.99 (s)		20, 29
22	114.4			
23	133.7			
24	133.0/130.8	7.62-7.57 (m)		25, 26
25	125.9	7.62-7.57 (m)	27	24, 26
26	133.0/130.8	7.62-7.57 (m)	27	24, 25
27	133.5	8.35-8.29 (m)	25, 26	22, 24/26, 28
28	167.4			
29	30.6	2.73 (t, 7.4 Hz)	30	20, 21, 30, 31
30	29.5	2.07-1.96 (m)	29, 31	20, 29, 31
31	43.6	3.56 (6.1 Hz)	30	29
32	17.7	1.36-1.30 (m)	11	11, 12

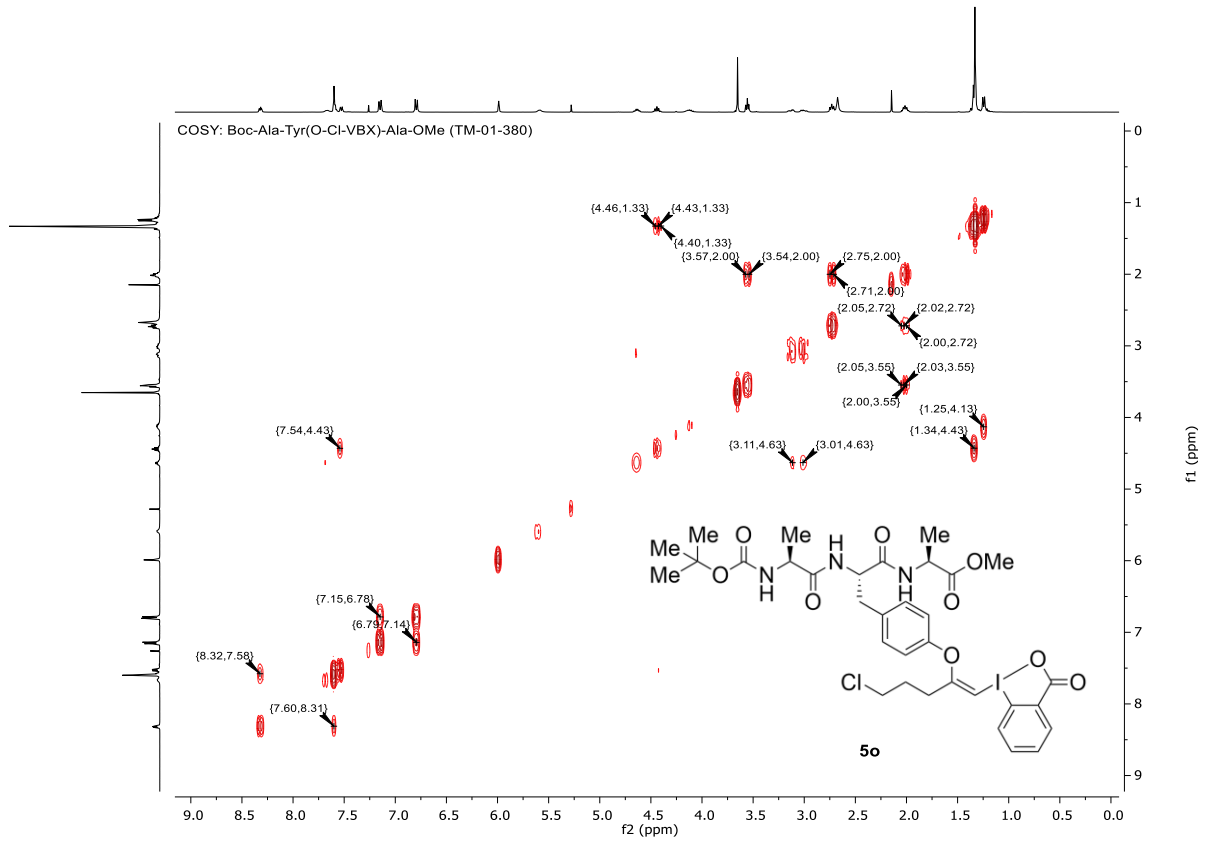
^{1}H-NMR (400 MHz, $CDCl_3$)



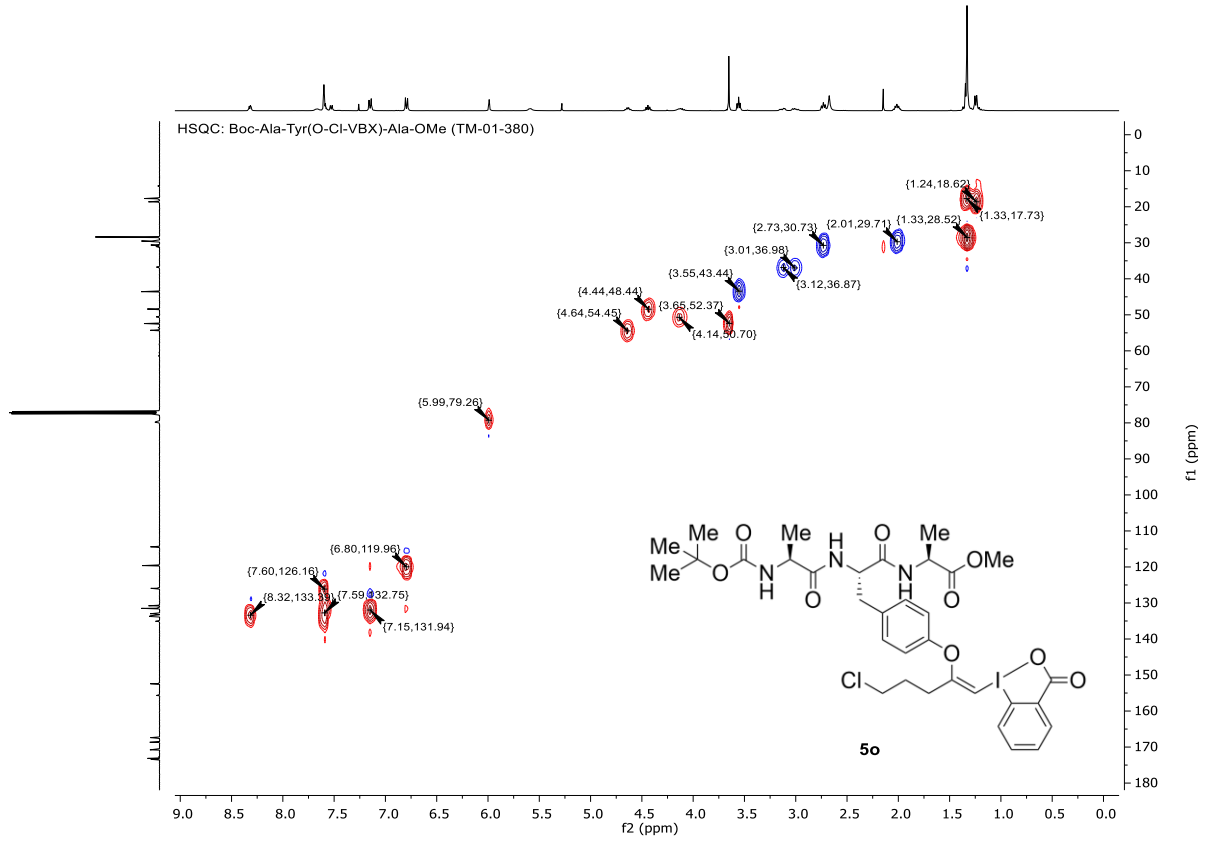
^{13}C-NMR (101 MHz, $CDCl_3$)



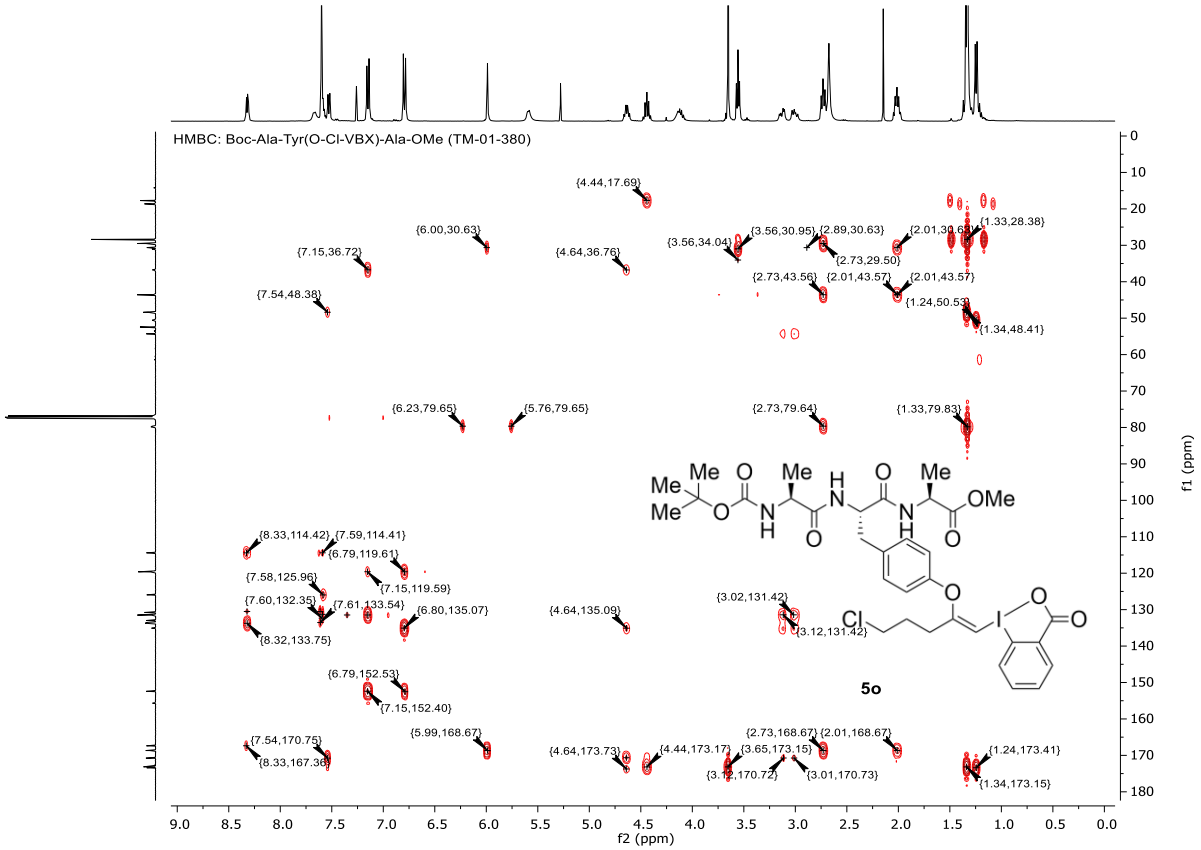
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



NH_2-L-Ala-L-Tyr(*O*-Ph-VBX)-L-Ala-OEt (5p)

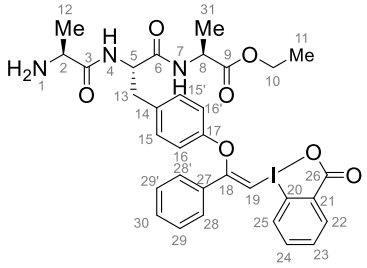
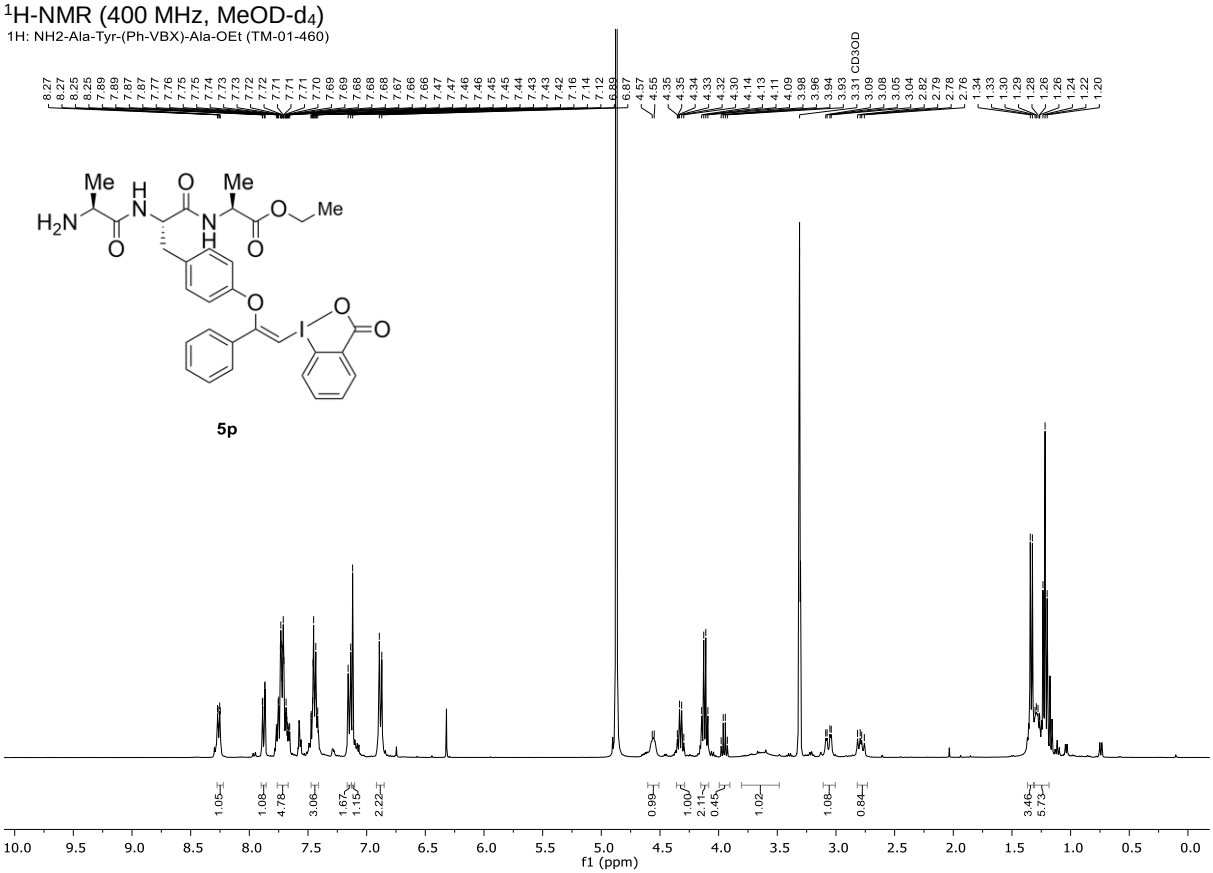


Table S16. Detailed NMR assignment of NH_2-L-Ala-L-Tyr(*O*-Ph-VBX)-L-Ala-OEt (**5p**) .

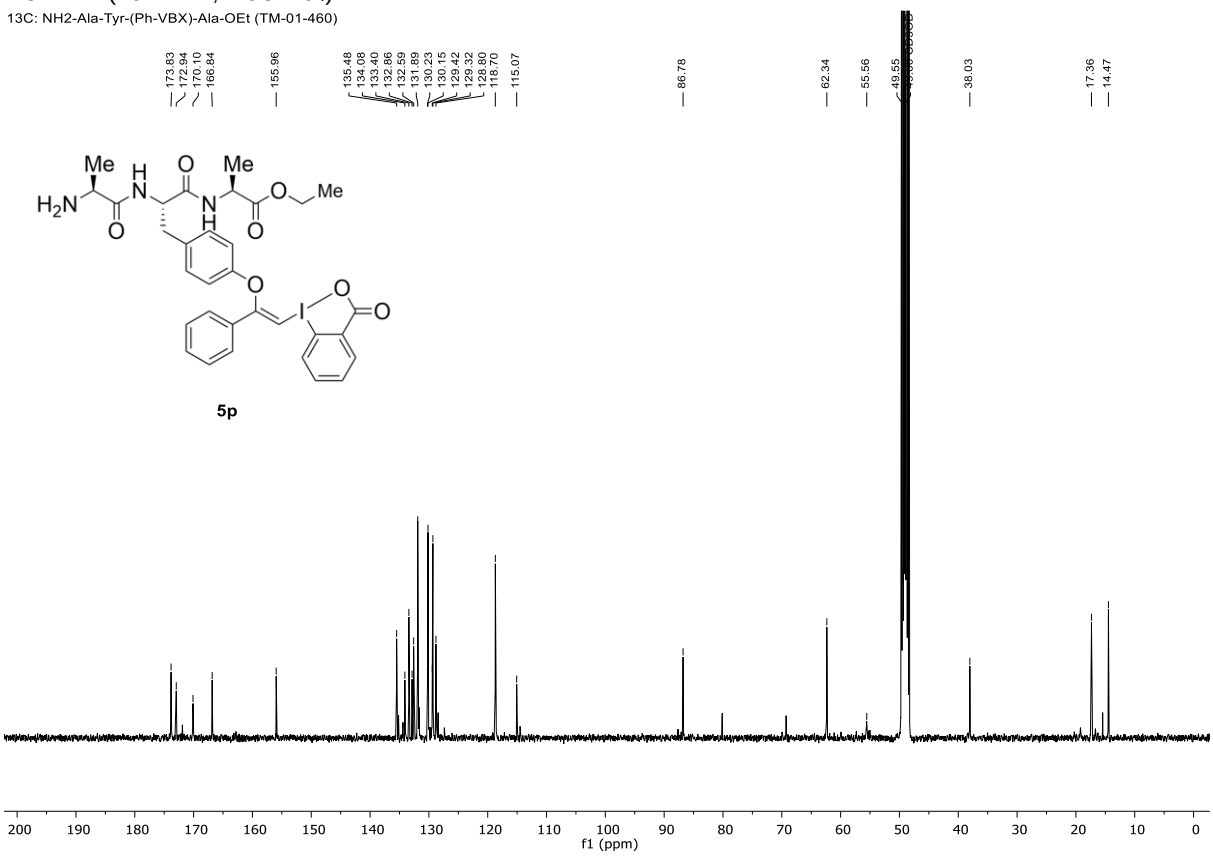
	δ_C in MeOD-d_4	δ_H in MeOD-d_4	δ_C in DMSO-d_6	δ_H in DMSO-d_6	COSY	HMBC (H→C)
1	/	exchange with solvent	/			
2	overlapping with MeOD signal	3.95 (q, 7.1 Hz)	53.1	overlapping with DMSO signal		
3	172.9		170.8			
4	/	exchange with solvent	/	7.83 (d, 8.1 Hz)		
5	55.6	4.60-4.51 (m)	53.2	4.45 (bs)	13	
6	172.9		170.8			
7	/	exchange with solvent	/	8.46 (d, 7.0 Hz)		
8	49.6	4.32 (q, 7.3 Hz)	47.7	4.20 (p, 7.2 Hz)		9, 31
9	173.8		172.3			
10	62.3	4.12 (q, 7.1 Hz)	60.5	4.03 (qd, 7.0, 2.2 Hz)	11	9, 11
11	14.5	1.22 (t, 7.1 Hz)	14.0	1.13 (t, 7.0 Hz)	10	10
12	17.4	1.31-1.24 (m)	15.0	1.06-0.98 (m)		
13	38.0	3.06 (dd, 14.3, 4.5 Hz), 2.79 (dd, 14.2, 9.0 Hz)	36.7	2.99-2.83 (m), 2.66 (dd, 14.0, 9.6 Hz)	5	15/15‘
14	132.6		132.8			
15/15‘	131.9	7.15 (d, 8.6 Hz)	130.7	7.11 (d, 8.1 Hz)	16/16‘	17
16/16’	118.7	6.88 (d, 8.4 Hz)	117.0	6.92 (d, 8.1 Hz)	15/15’	14, 17
17	156.0		154.1			
18	166.8		162.6			
19	86.8	7.12 (s)	91.2	7.41 (s)		18
20	115.1		114.6			
21	133.4		133.4			
22	128.8	7.88 (dd, 7.9, 1.3 Hz)	128.8	7.76-7.71 (m)		20, 24
23	132.9	7.77-7.64 (m)	133.7	7.71-7.63 (m)	25	
24	135.5	7.77-7.64 (m)	134,3	7.71-7.63 (m)	25	20
25	124.1	8.26 (dd, 7.4, 2.0 Hz)	131.4	8.11 (dd, 7.5, 1.9 Hz)	23, 24	20, 24, 26
26	170.1		165.7			
27	130.2		130.2			
28/28’	130.1	7.77-7.64 (m)	127.8	7.71-7.63 (m)	29/29’	18
29/29’	129.3	7.48-7.41 (m)	129.0	7.47-7.42 (m)	28/28’	27, 28/28’
30	129.4	7.48-7.41 (m)	129.1	7.47-7.42 (m)		
31	17.4	1.33 (d, 7.2 Hz)	16.8	1.24 (d, 7.3 Hz)		8, 9

^{1}H-NMR (400 MHz, MeOD-d$_4$)



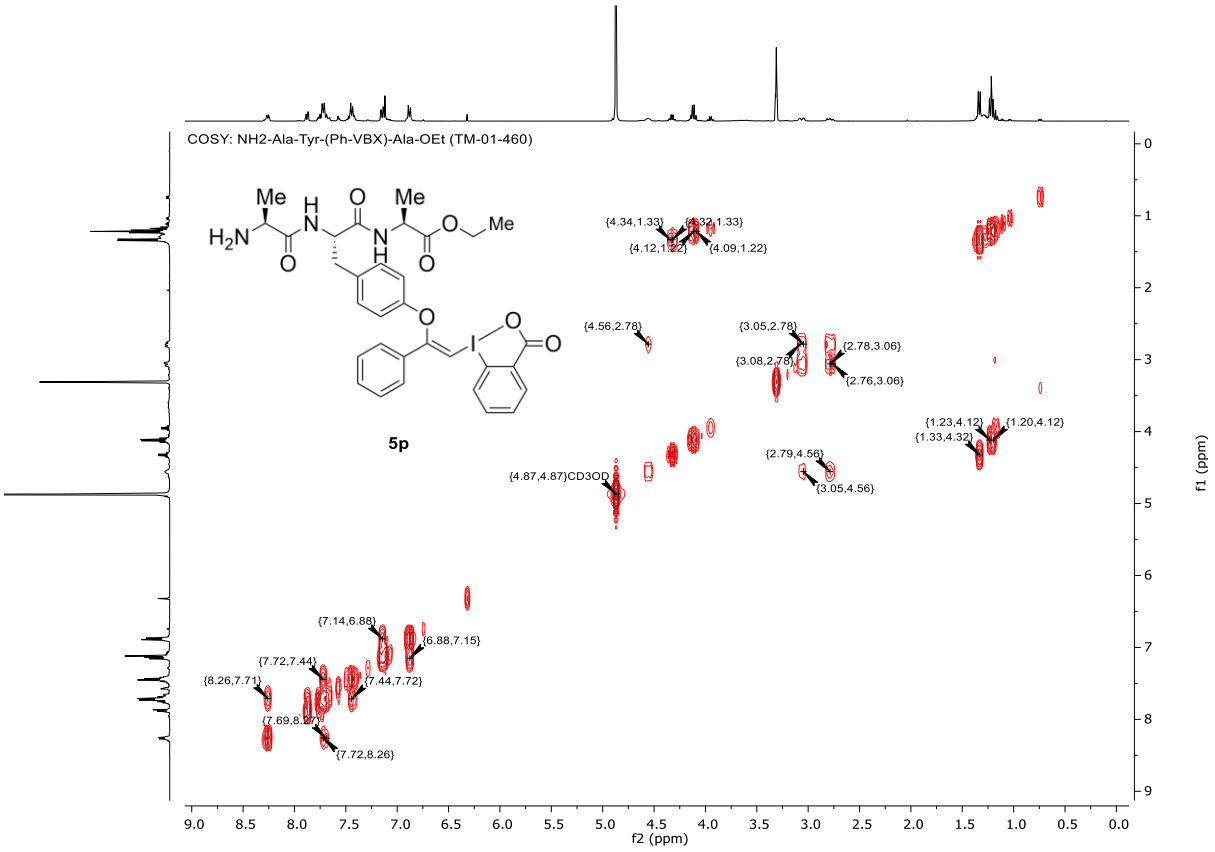
5p

^{13}C-NMR (101 MHz, MeOD-d$_4$)

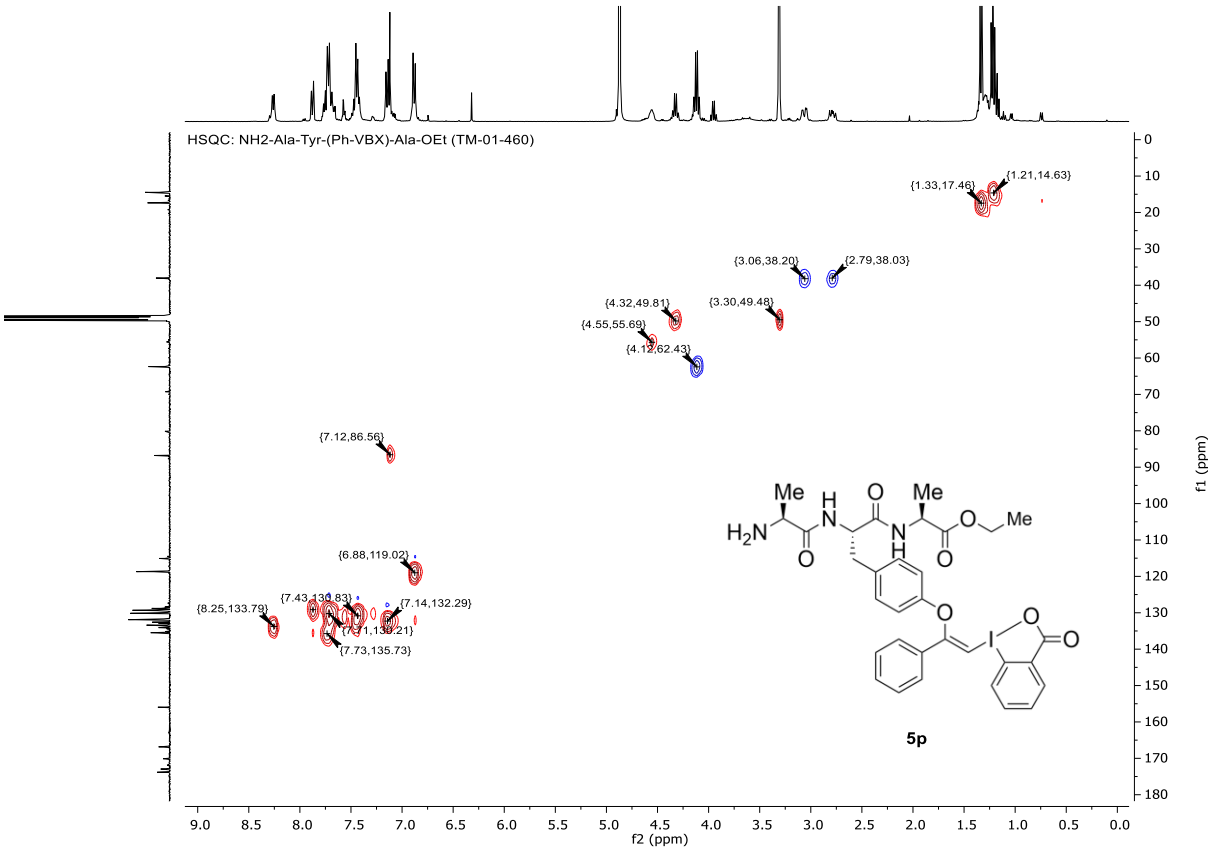


5p

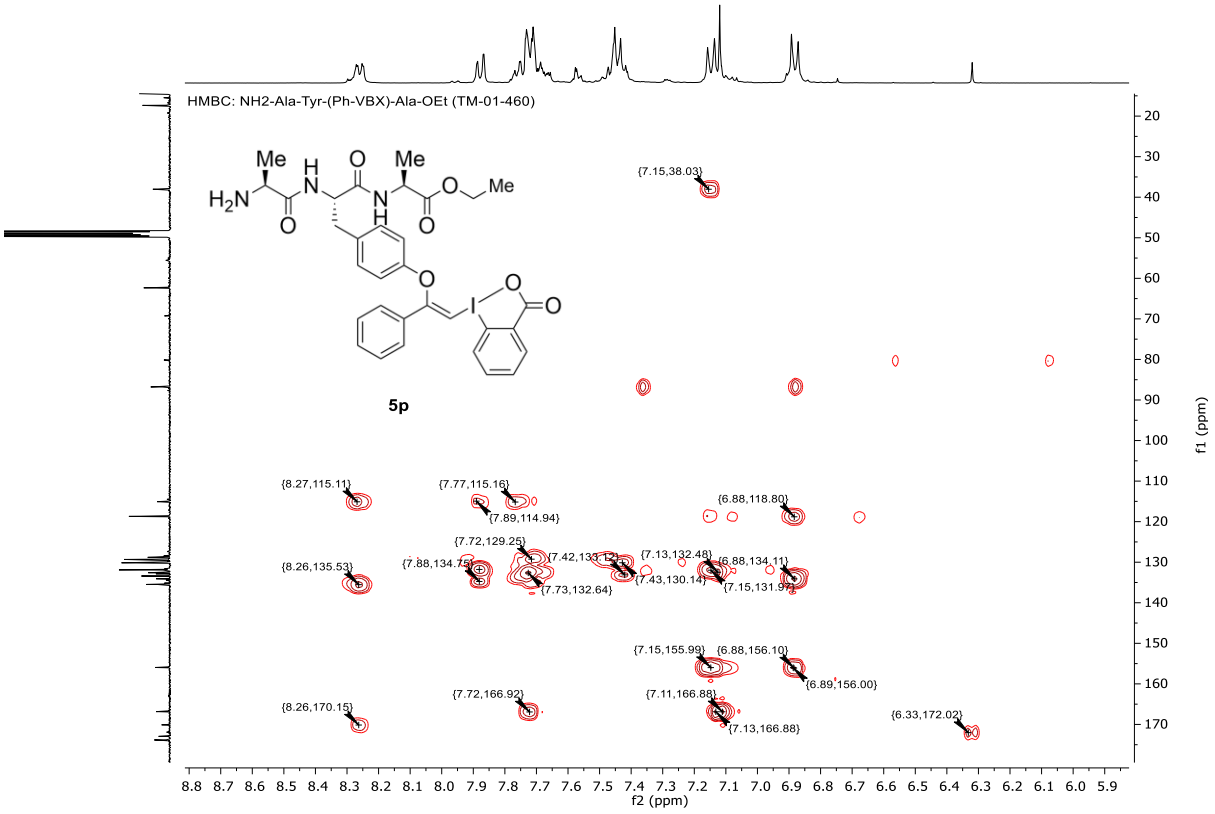
COSY NMR (MeOD-d_4)



HSQC NMR (MeOD-d_4)



HMBC NMR (MeOD-d_4)



NH_2-L-Ala-L-Tyr(*O*-Cl-VBX)-L-Ala-OMe (5q)

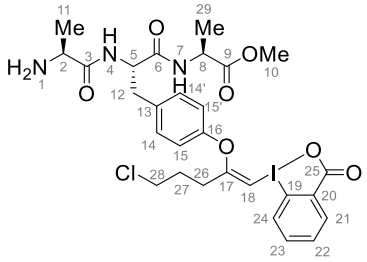
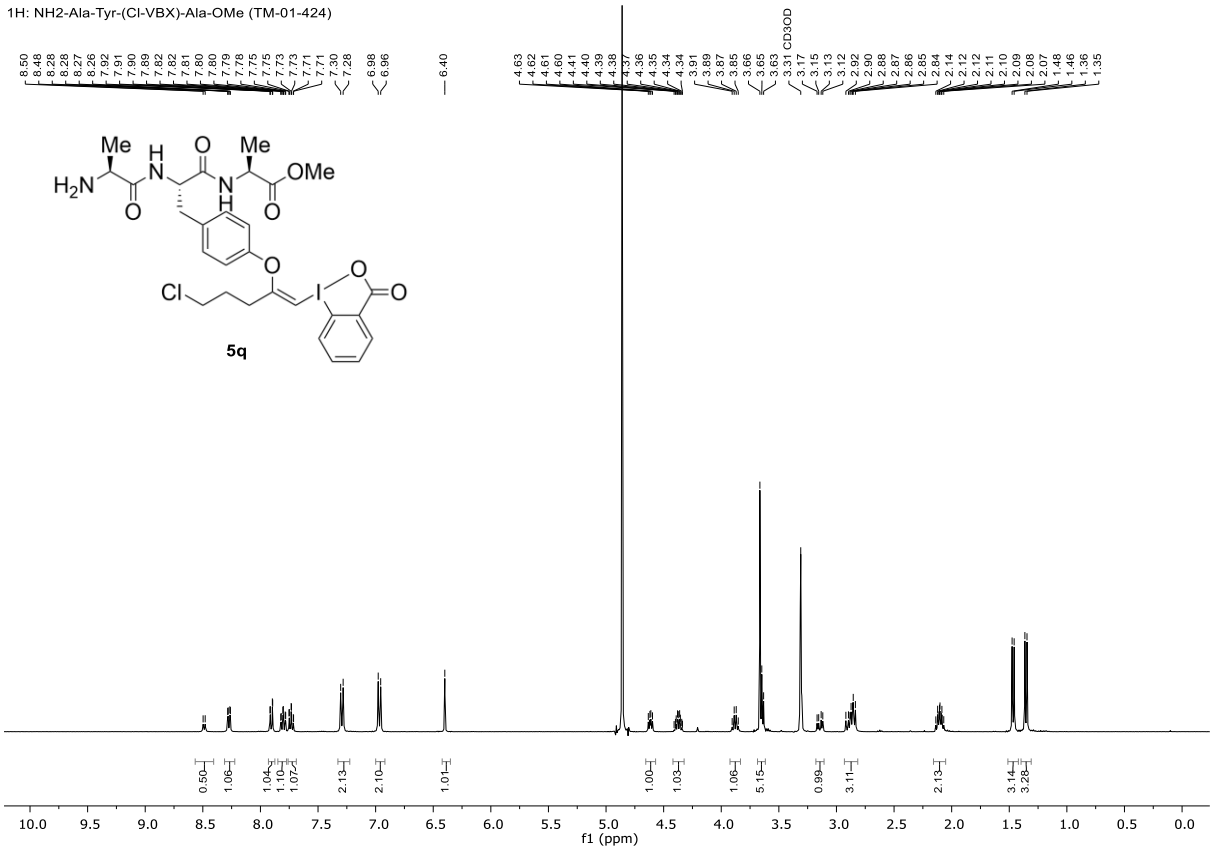


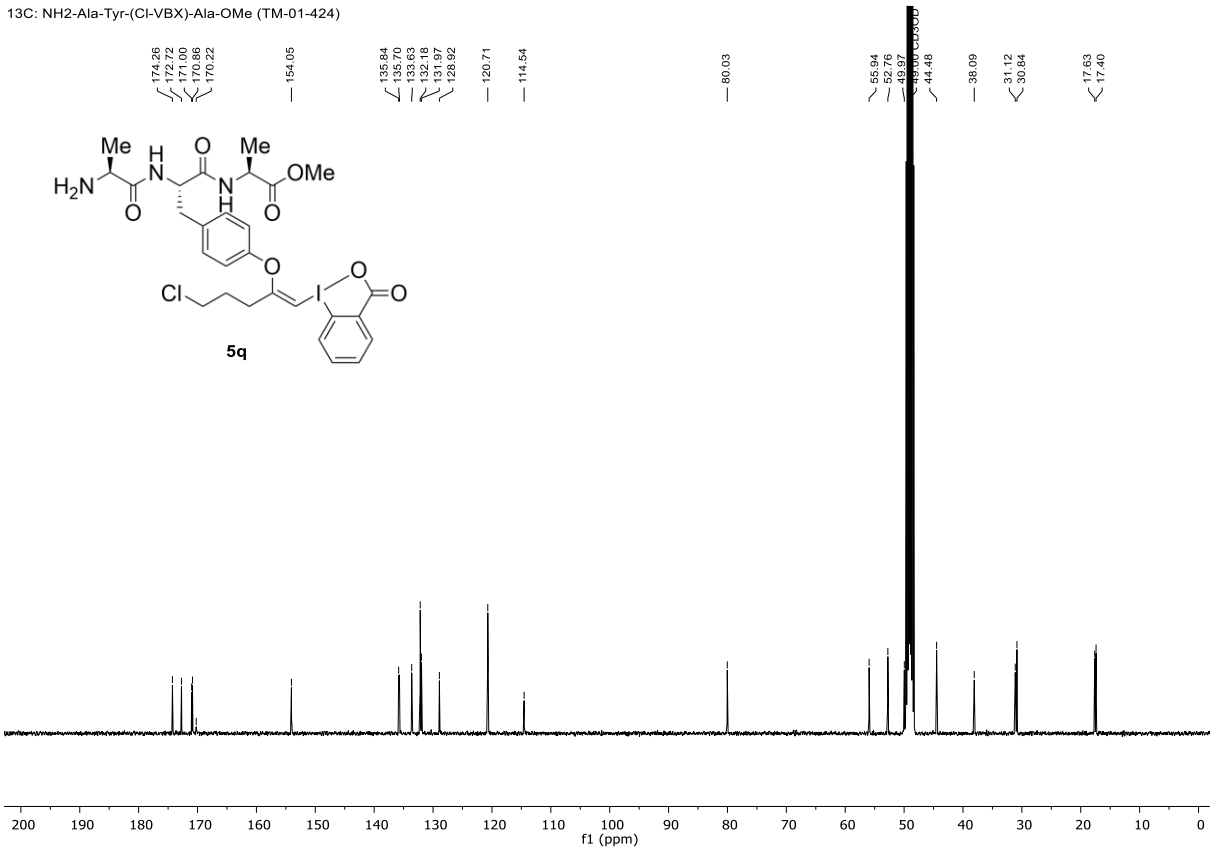
Table S17. Detailed NMR assignment of NH_2-L-Ala-L-Tyr(*O*-Cl-VBX)-L-Ala-OMe (**5q**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	50.0	3.88 (q, 7.0 Hz)	11	3, 11
3	171.0			
4	/	exchange with solvent		
5	55.9	4.62 (dd, 8.9, 5.7 Hz)	12	6, 12, 13
6	172.7			
7	/	exchange with solvent		
8	overlapping with MeOD signal	4.37 (qt, 7.2, 3.6 Hz)	29	9, 29
9	174.3			
10	52.8	3.66 (s)		9
11	17.6	1.47 (d, 7.1 Hz)	2	2, 3
12	38.1	3.14 (dd, 14.2, 5.7 Hz), 2.98 (dd, 14.2, 9.1 Hz)	5	5, 14/14‘
13	135.8			
14/14‘	132.2	7.29 (d, 8.6 Hz)	15/15‘	12, 15/15‘, 16
15/15‘	120.7	6.97 (d, 8.6 Hz)	14/14‘	14/14‘, 16
16	154.1			
17	170.9			
18	80.0	6.40 (s)		17, 26
19	114.5			
20	133.6			
21	128.9	7.91 (dd, 8.2, 1.1 Hz)	22, 23	19, 23
22	132.0	7.73 (td, 7.3, 1.1 Hz)	21, 23, 24	21, 24
23	135.7	7.80 (td, 8.1, 1.7 Hz)	21, 22	19, 20, 24
24	133.6	8.27 (dd, 7.5, 1.8 Hz)	22	19, 23, 25
25	170.2			
26	31.1	2.90 (t, 7.3 Hz)	27	17, 18, 27, 28
27	30.8	2.10 (p, 6.4 Hz)	26, 28	17, 26, 28
28	44.5	3.65 (t, 6.3 Hz)	27	26
29	17.4	1.36 (d, 7.3 Hz)	8	8, 9

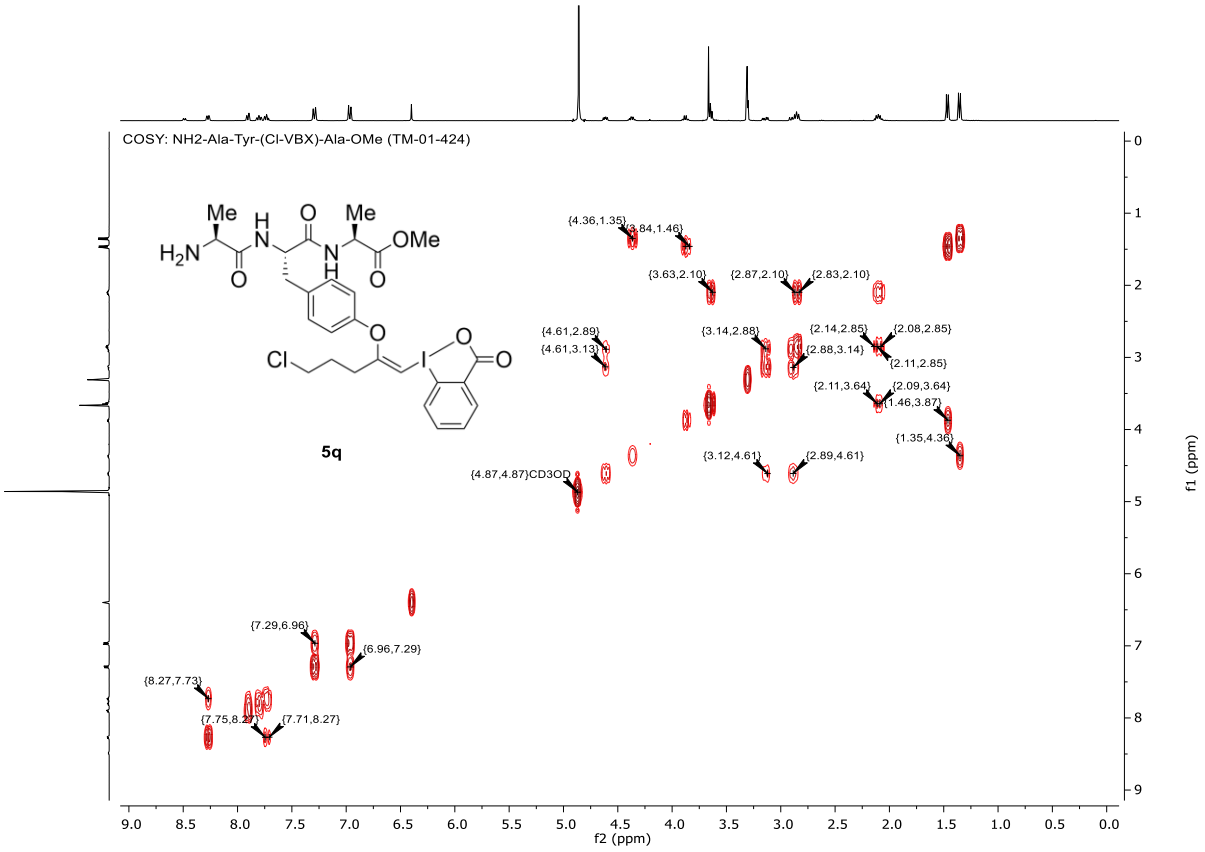
^{1}H-NMR (400 MHz, MeOD-d$_4$)



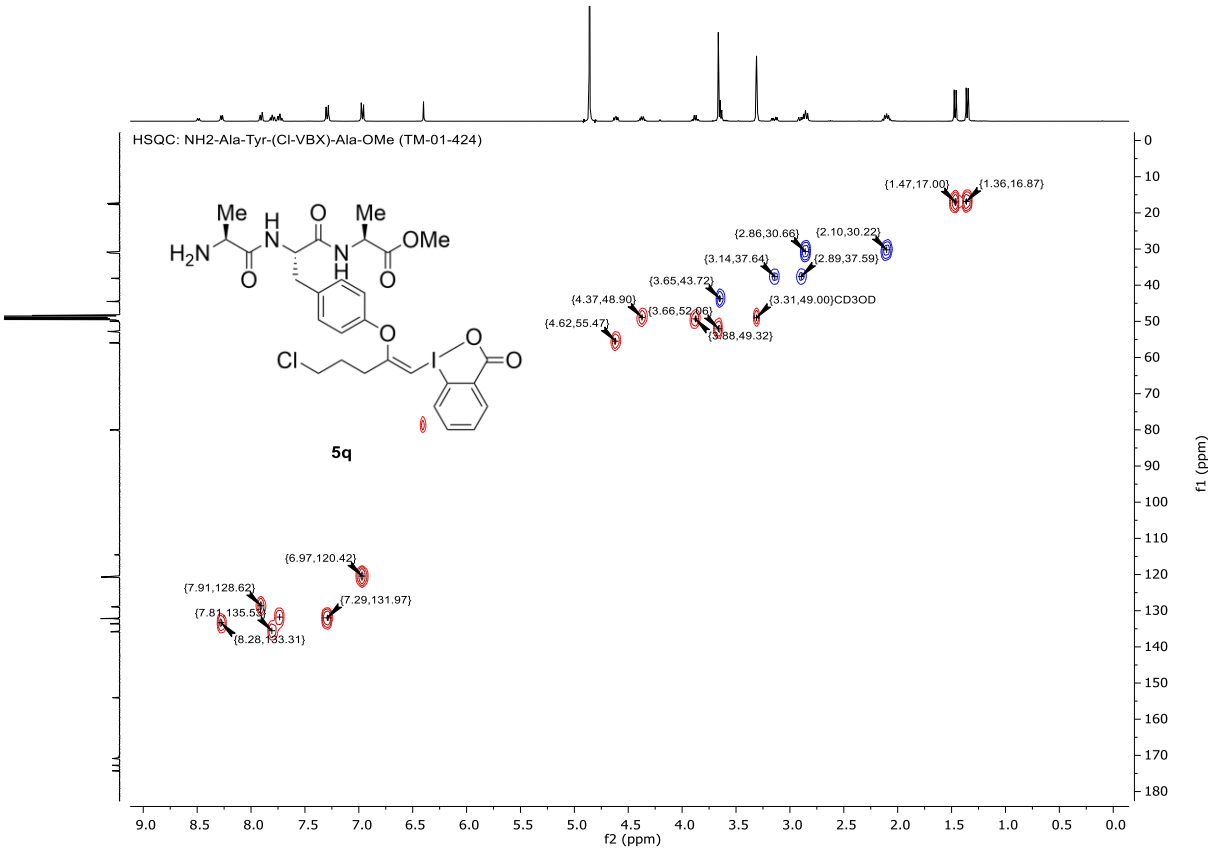
^{13}C-NMR (101 MHz, MeOD-d$_4$)



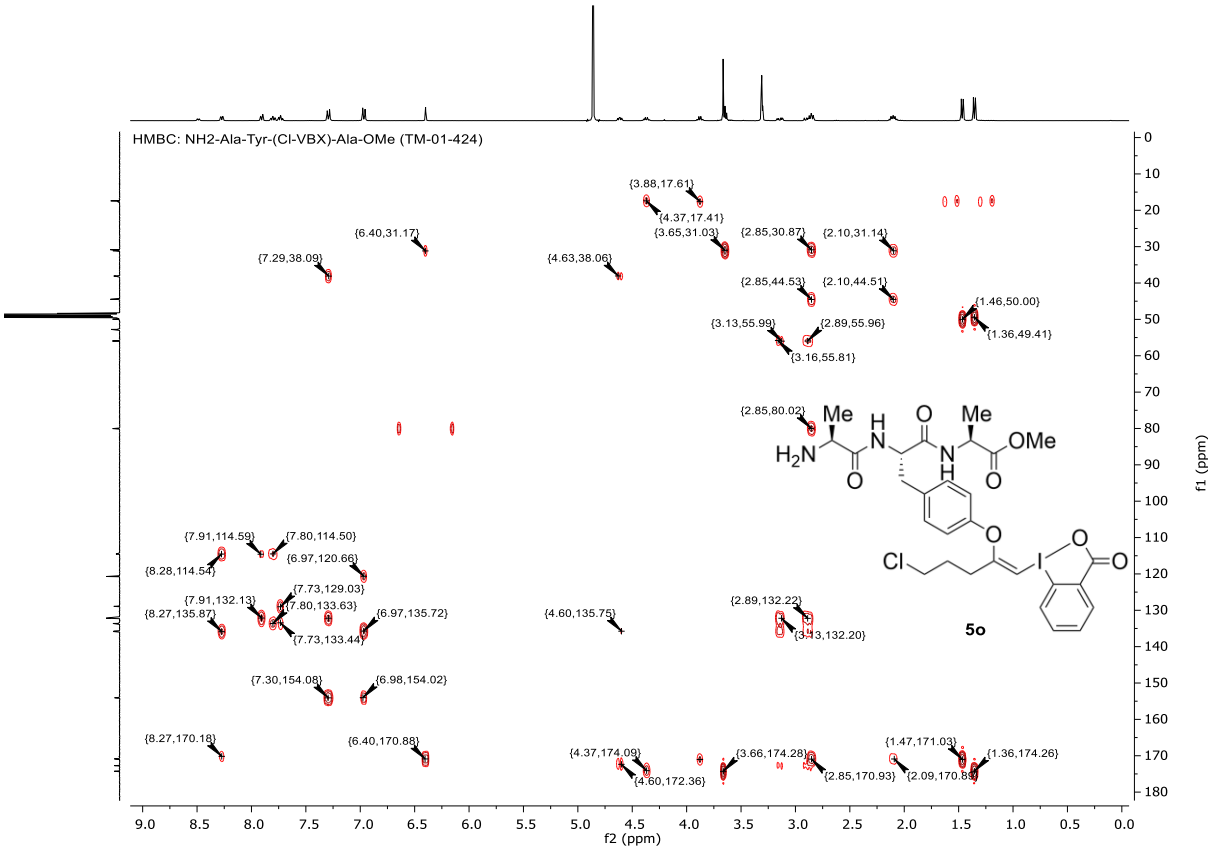
COSY NMR (MeOD-d$_4$)



HSQC NMR (MeOD-d$_4$)



HMBC NMR (MeOD-d_4)



N-Cbz-Gly-L-Cys(*S*-Ph-VBX)-L-Ala-OMe (5r)

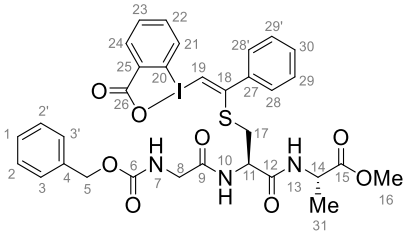
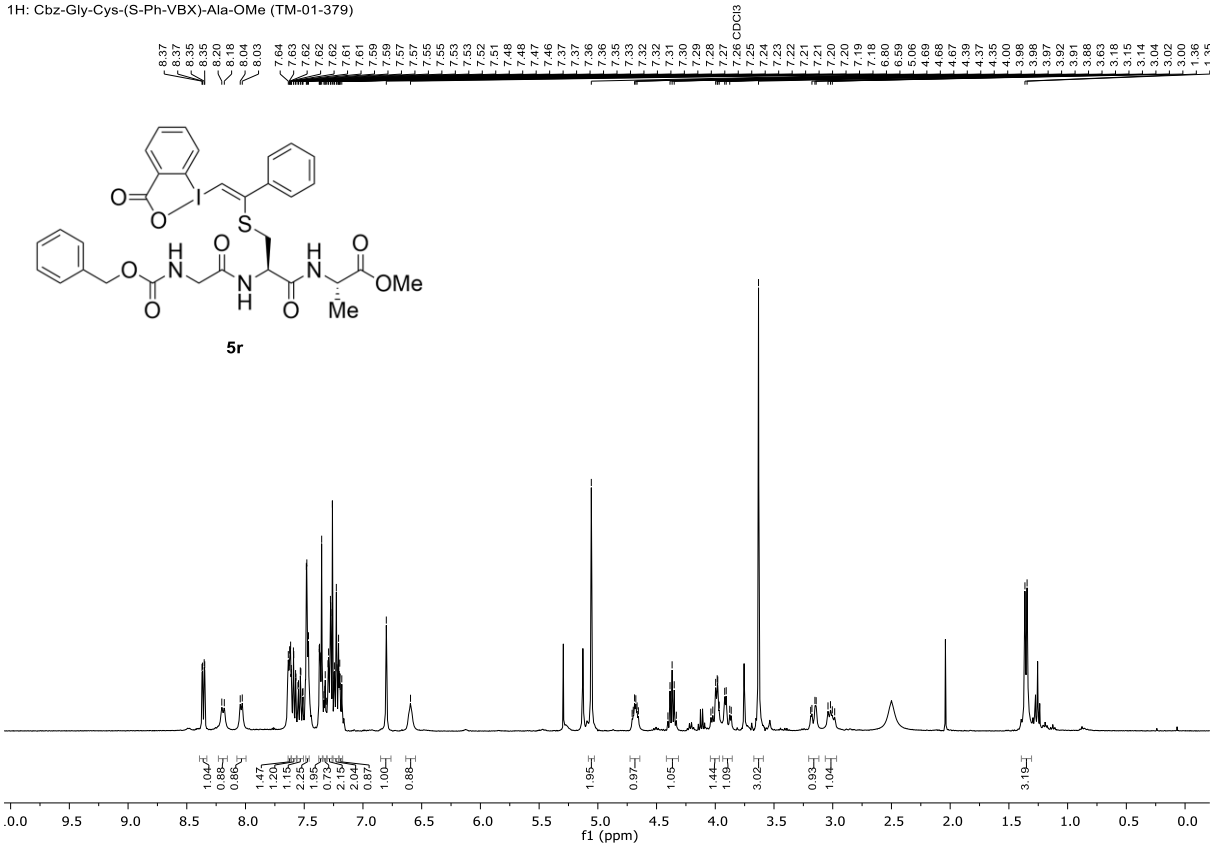


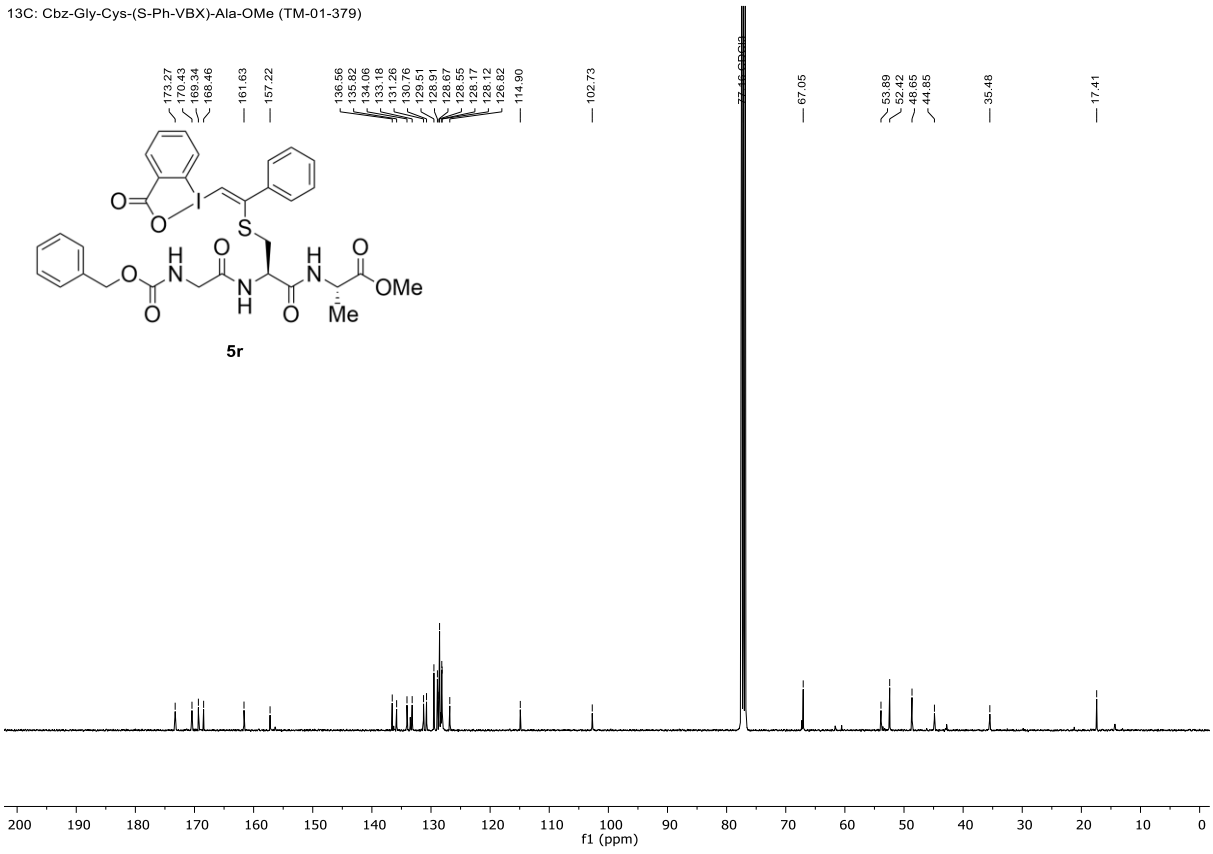
Table S18. Detailed NMR assignment of *N*-Cbz-Gly-L-Cys(*S*-Ph-VBX)-L-Ala-OMe (**5r**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	128.7	7.34-7.31 (m)		
2/2‘	126.8	7.30-7.26 (m)	1, 3/3‘	5
3/3‘	128.1	7.25-7.20 (m)	2/2‘	4
4	136.6			
5	67.0	5.06 (s)		3/3’, 4, 6
6	157.2			
7	/	6.59 (bs)		
8	44.9	4.01 (dd, 16.5, 6.8 Hz), 3.89 (dd, 17.1, 5.1 Hz)		9
9	170.4			
10	/	8.19 (d, 8.6 Hz)	11	
11	53.9	4.68 (td, 8.5, 4.2 Hz)	10	
12	169.3			
13	/	8.04 (d, 6.9 Hz)	14	
14	48.6	4.37 (p, 7.2 Hz)	13, 31	31, 15
15	173.3			
16	52.4	3.63 (s)		15
17	35.5	3.16 (dd, 14.5, 4.3 Hz), 3.01 (dd, 14.5, 8.2 Hz)		
18	161.6			
19	102.7	6.80 (s)		18, 27
20	114.9			
21	133.2	8.36 (dd, 7.4, 1.9 Hz)	23	20, 22, 26
22	134.1	7.65-7.61 (m)		
23	126.8	7.61-7.56 (m)	21	21
24	129.5	7.53 (td, 7.7, 1.9 Hz)		20
25	131.3			
26	168.5			
27	135.8			
28/28’	128.6	7.49-7.46 (m)	29/29’	
29/29’	128.9	7.38-7.34 (m)	28/28’	
30	128.2	7.21-7.17 (m)		28/28’
31	17.4	1.35 (d, 7.3 Hz)	14	14, 15

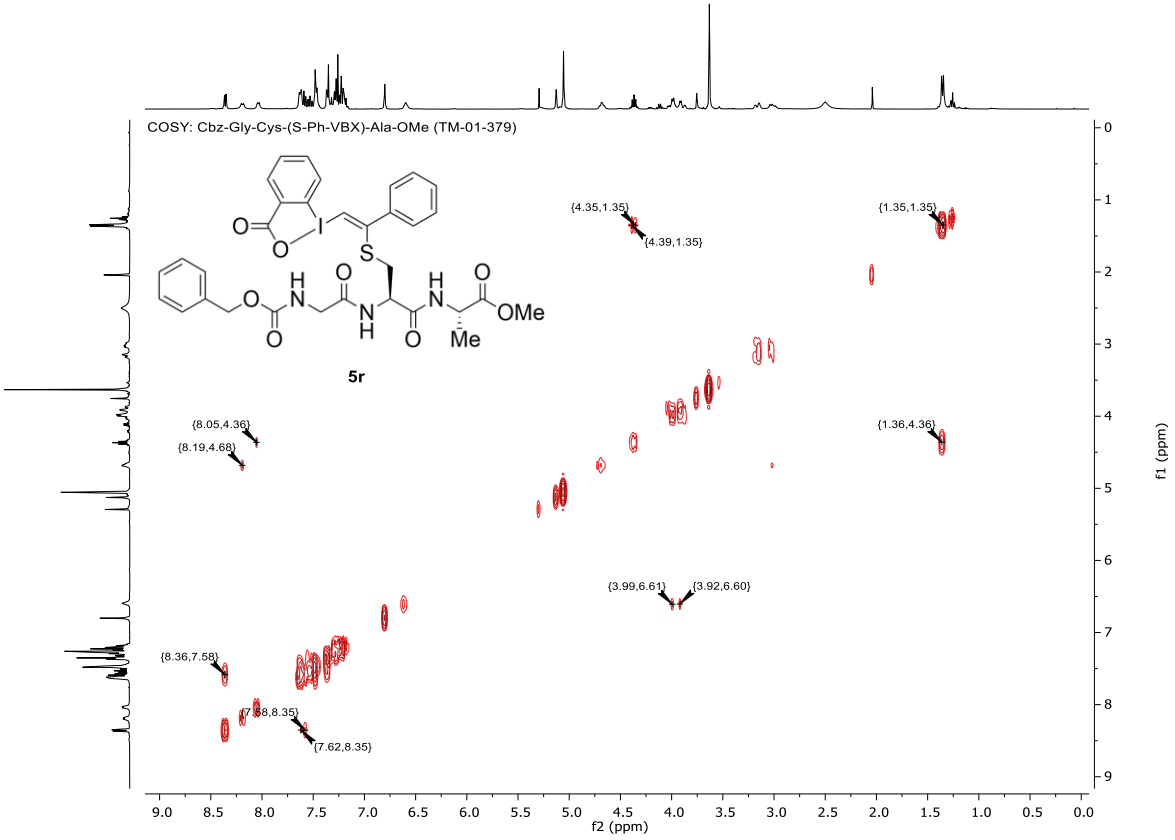
^{1}H-NMR (400 MHz, $CDCl_3$)



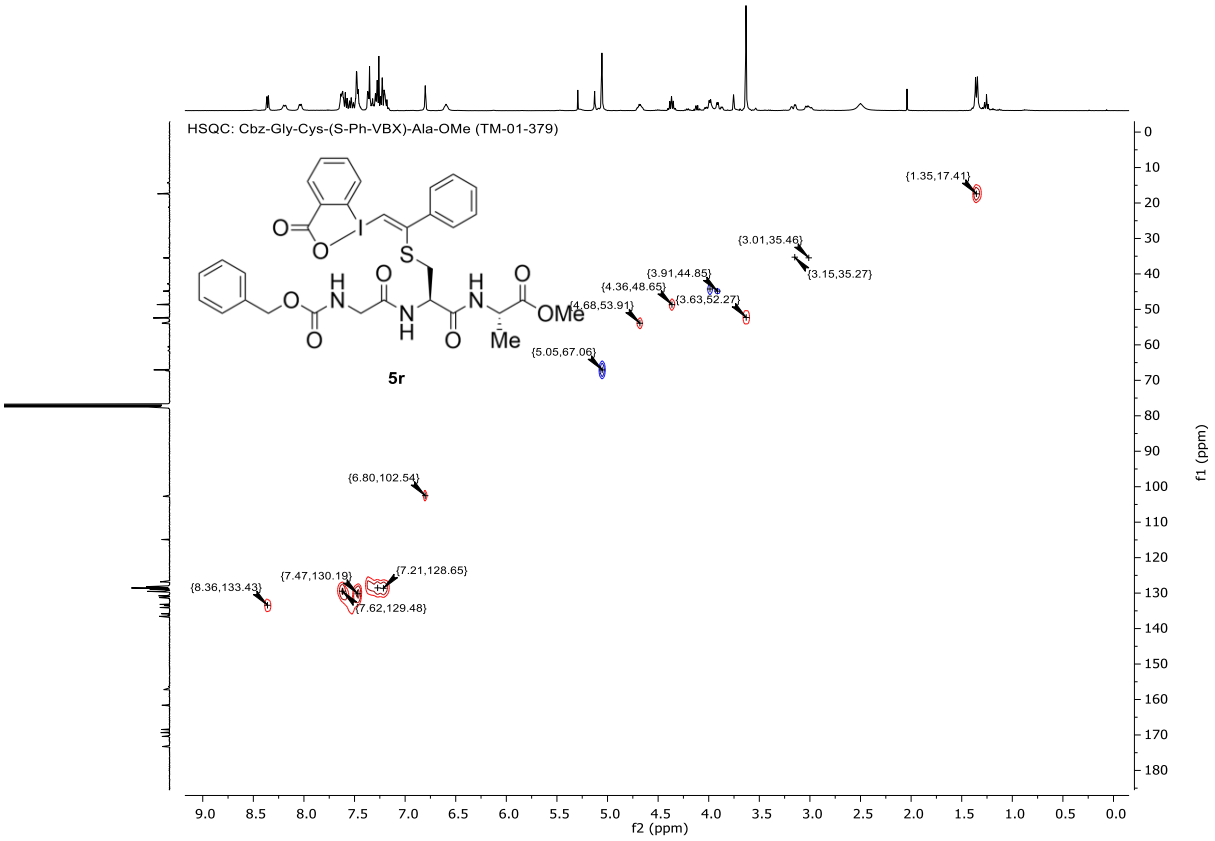
^{13}C-NMR (101 MHz, $CDCl_3$)



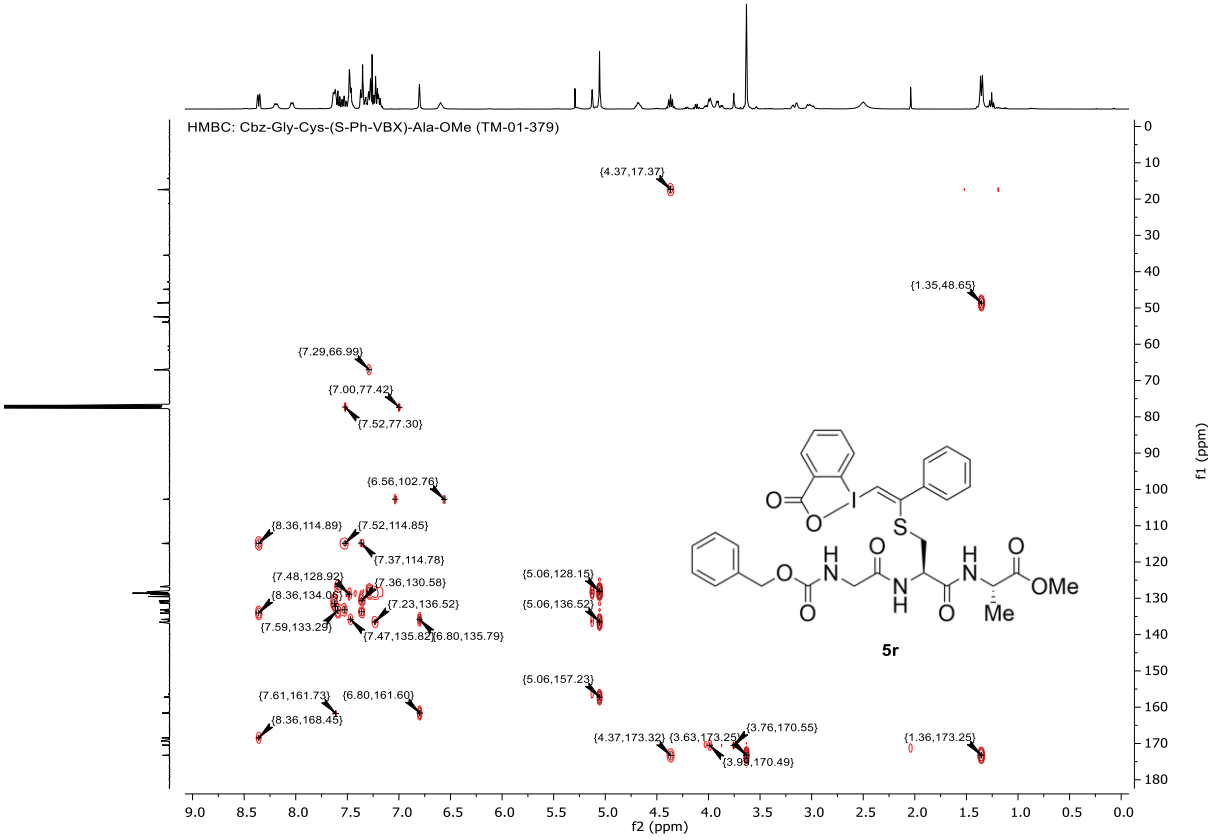
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



N-Cbz-Gly-L-Cys(*S*-Cl-VBX)-L-Ala-OMe (5s)

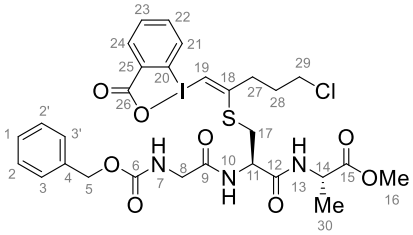
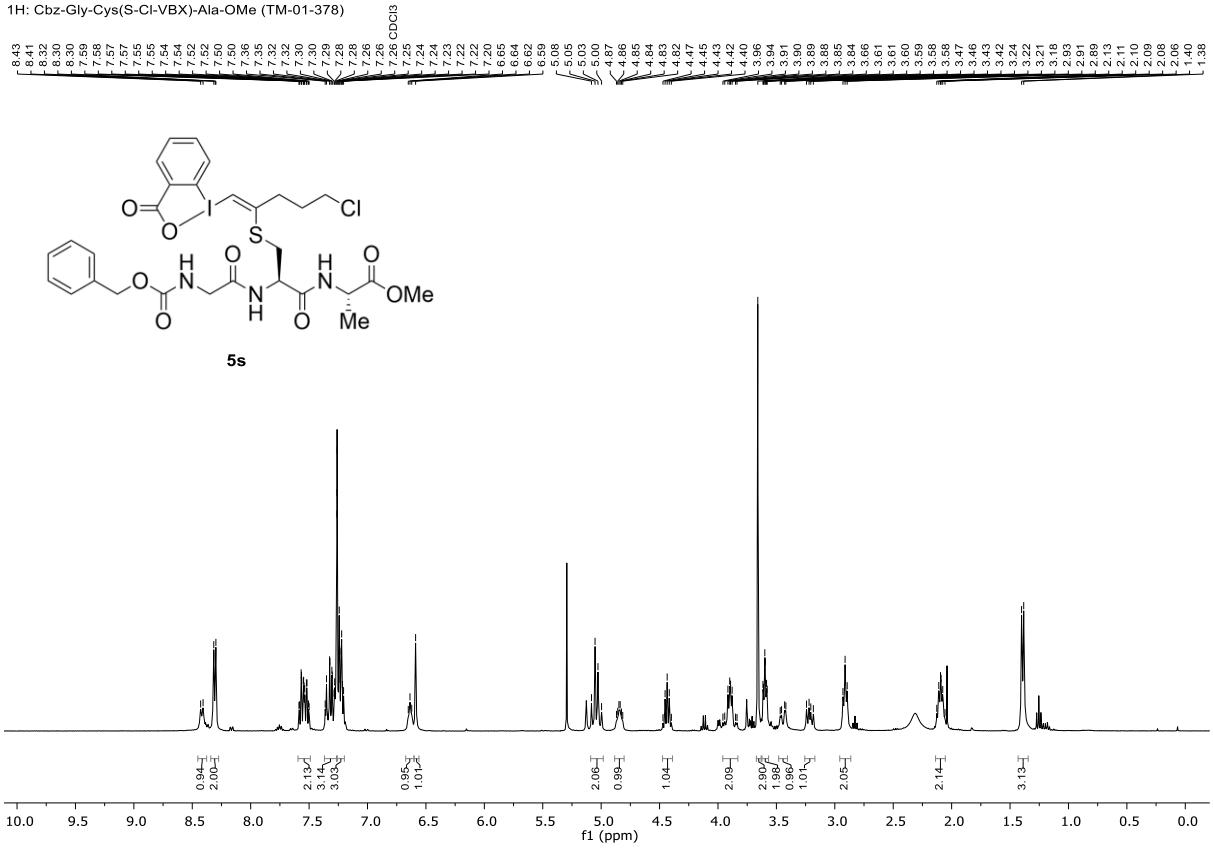


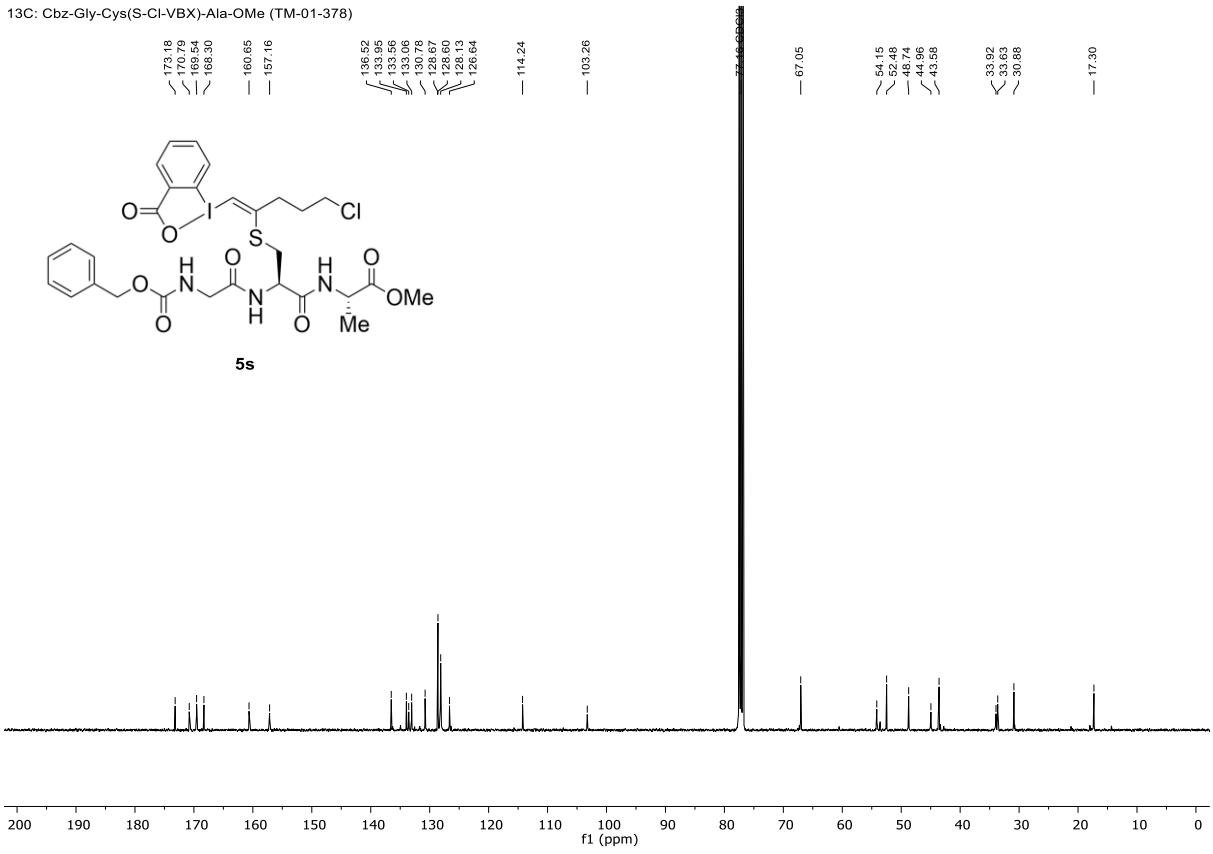
Table S19. Detailed NMR assignment of *N*-Cbz-Gly-L-Cys(*S*-Cl-VBX)-L-Ala-OMe (**5s**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	128.7	7.26-7.19 (m)	2/2‘	
2/2‘	126.6	7.26-7.19 (m)	1, 3/3‘	
3/3‘	128.1	7.37-7.27 (m)	2/2‘	6
4	136.5			
5	67.0	5.09-4.98 (m)		3/3’, 4, 6
6	157.2			
7	/	6.64 (t, 5.9 Hz)	8	
8	45.0	3.96-3.83 (m)	7	9
9	170.8			
10	/	8.42 (d, 8.3 Hz)	11	
11	54.1	4.84 (td, 8.5, 4.3 Hz)	10	
12	168.3			
13	/	8.34-8.28 (m)	14	
14	48.7	4.43 (p, 7.2 Hz)	13, 30	15, 30
15	173.2			
16	52.5	3.66 (s)		15
17	33.9	3.44 (dd, 15.0, 4.4 Hz), 3.21 (dd, 14.7, 8.8 Hz)		
18	160.6			
19	103.3	6.59 (s)		18, 27
20	114.2			
21	133.1	8.34-8.28 (m)	22, 24	20, 22, 24, 26
22	134.0/130.8	7.60-7.50 (m)		20, 23, 24
23	128.6	7.37-7.27 (m)		
24	134.0/130.8	7.60-7.50 (m)		20, 22, 23
25	133.6			
26	169.5			
27	33.6	2.91 (t, 7.2 Hz)	28	18, 19, 28, 29
28	30.9	2.14-2.05 (m)	27, 29	18, 27, 29
29	43.6	3.60 (td, 6.3, 2.1 Hz)	28	27
30	17.3	1.39 (d, 7.3 Hz)	14	14, 15

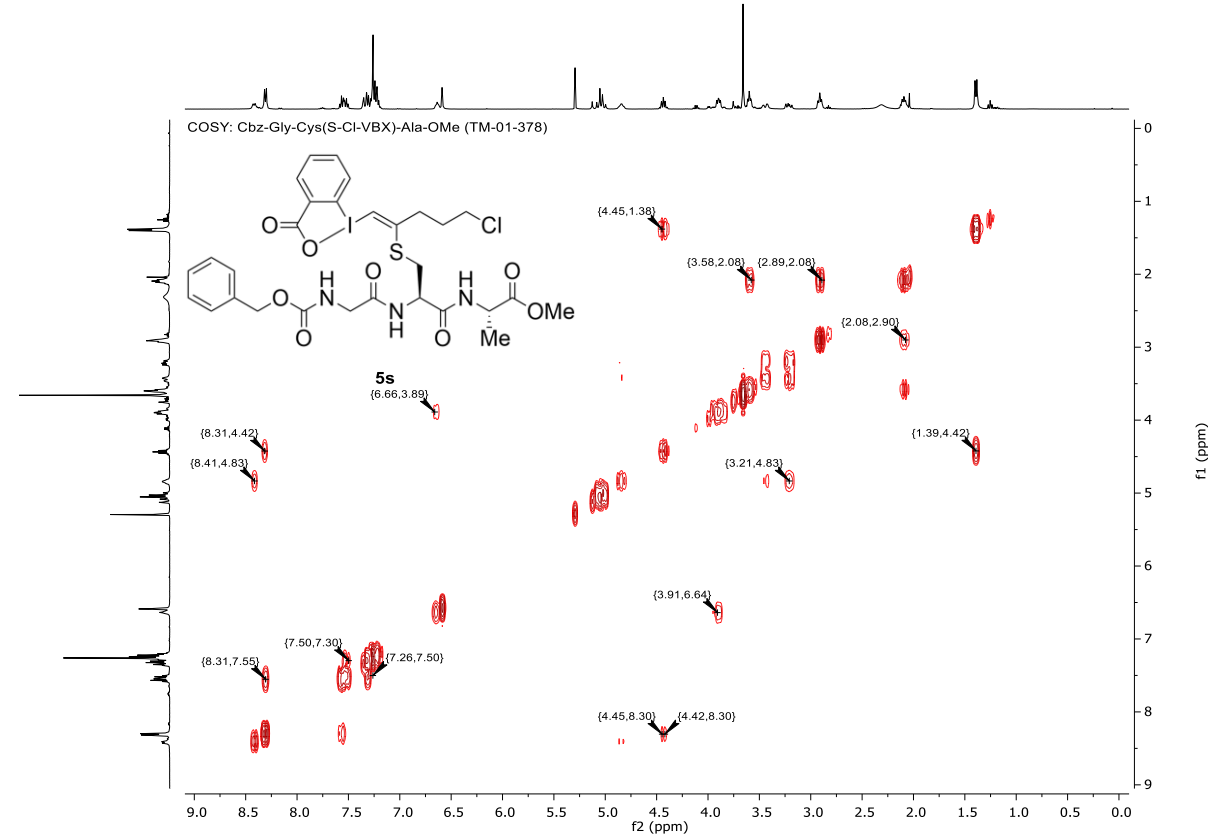
^{1}H-NMR (400 MHz, $CDCl_3$)



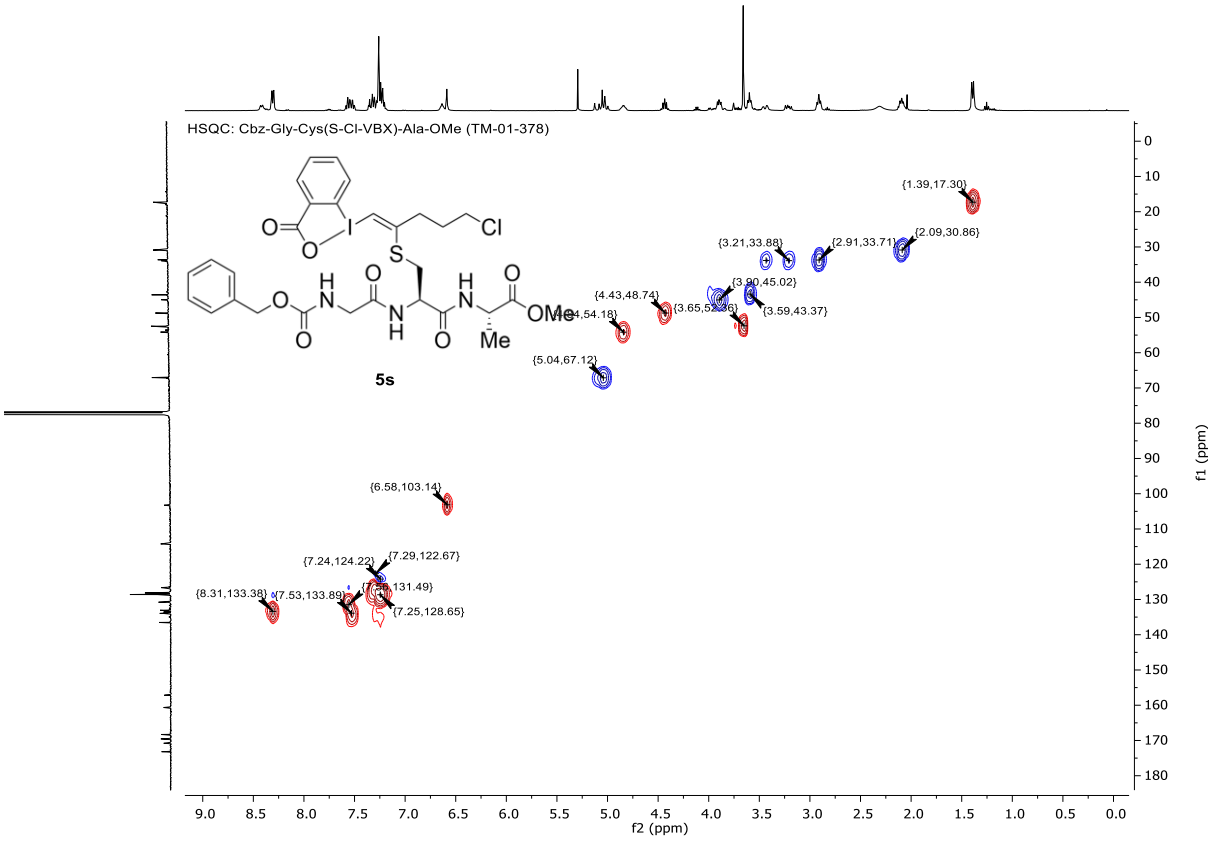
^{13}C-NMR (101 MHz, $CDCl_3$)



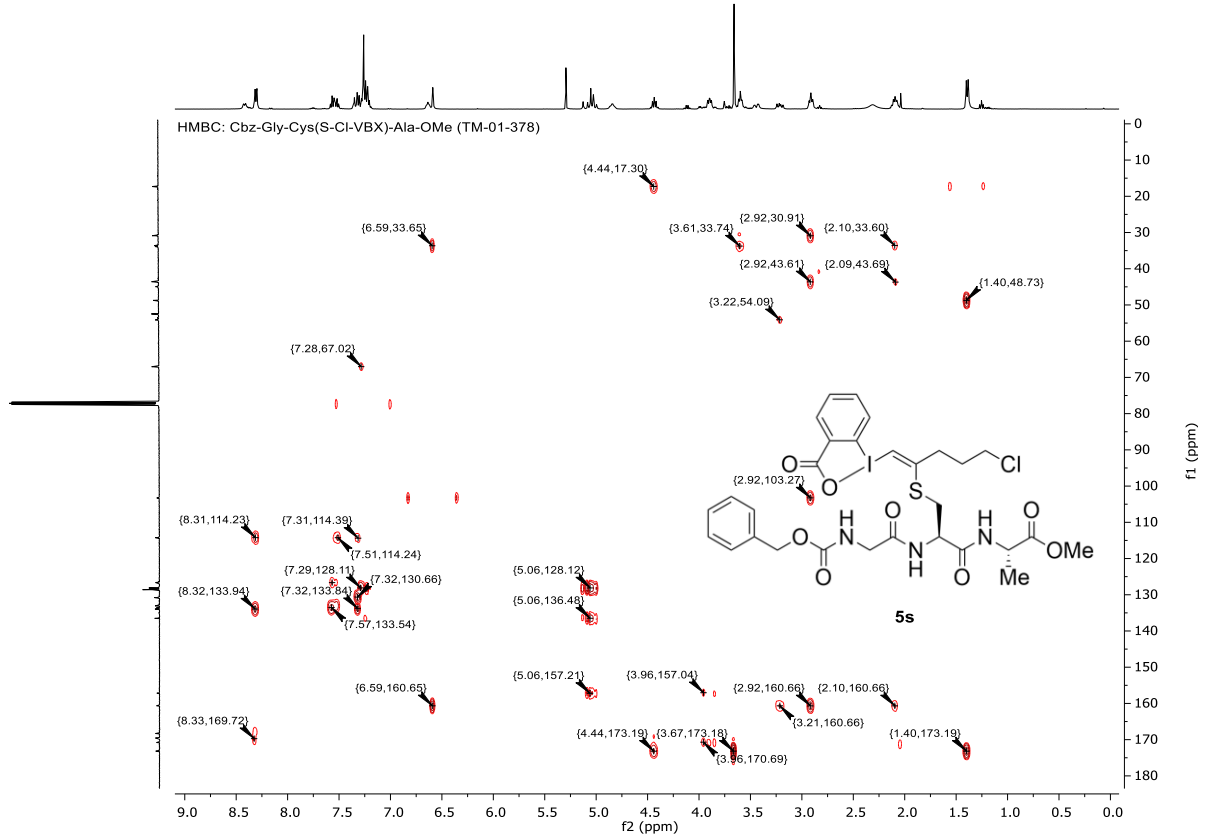
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

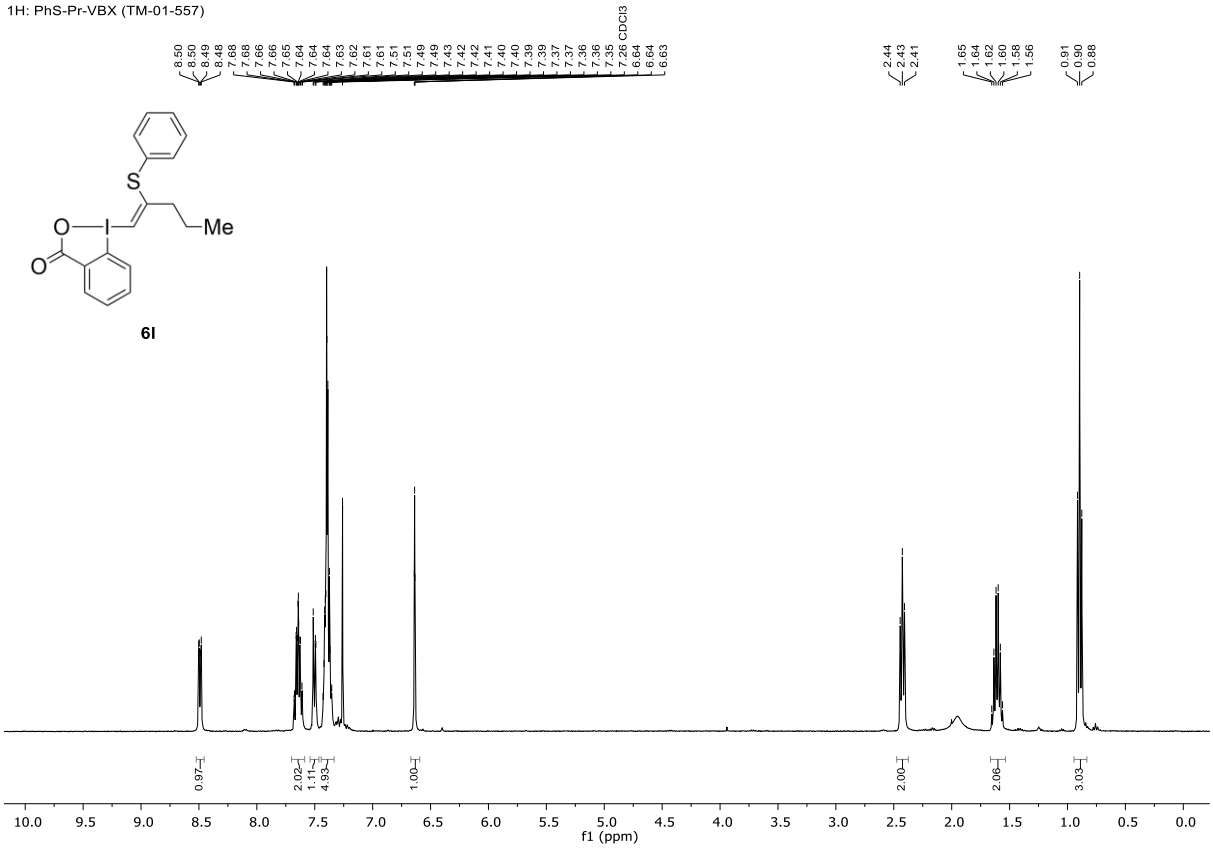


HMBC NMR ($CDCl_3$)

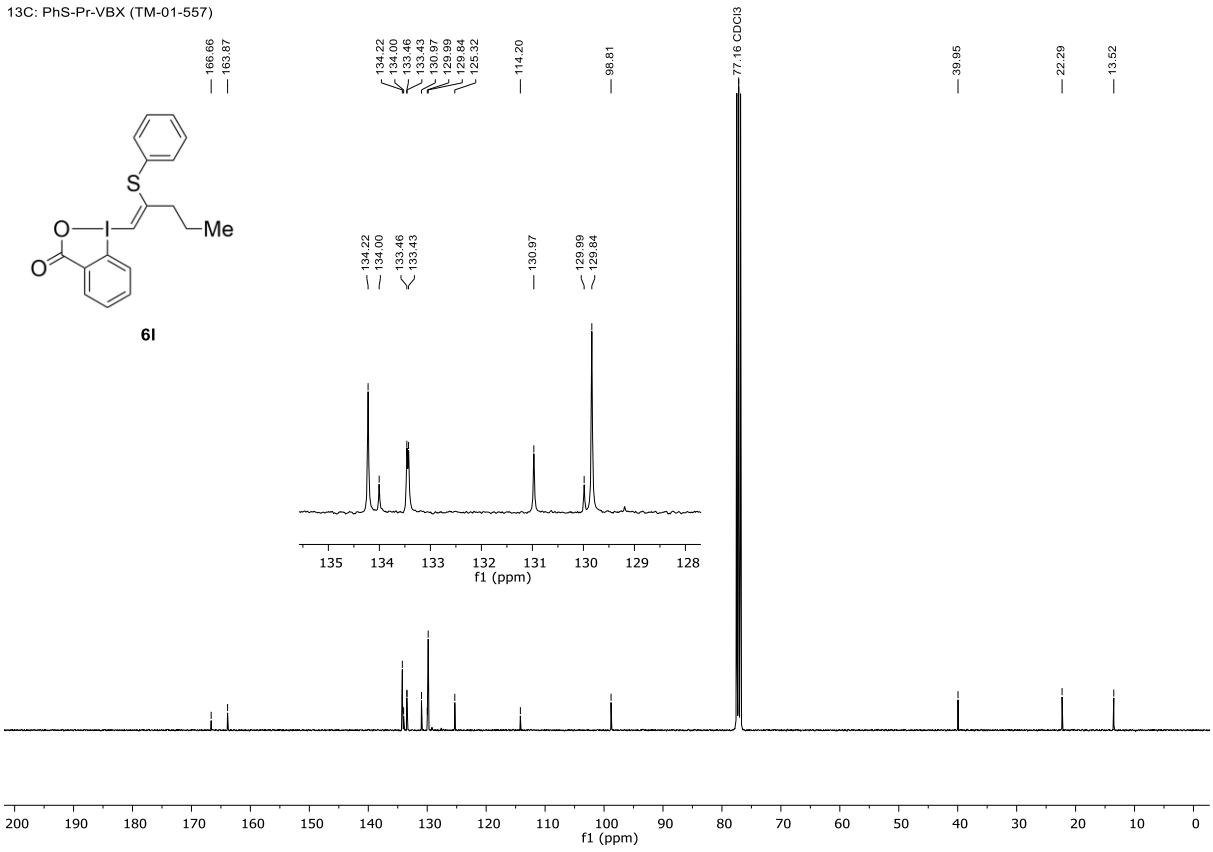


(*Z*)-1-(2-(Phenylthio)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6l)

^{1}H-NMR (400 MHz, $CDCl_3$)

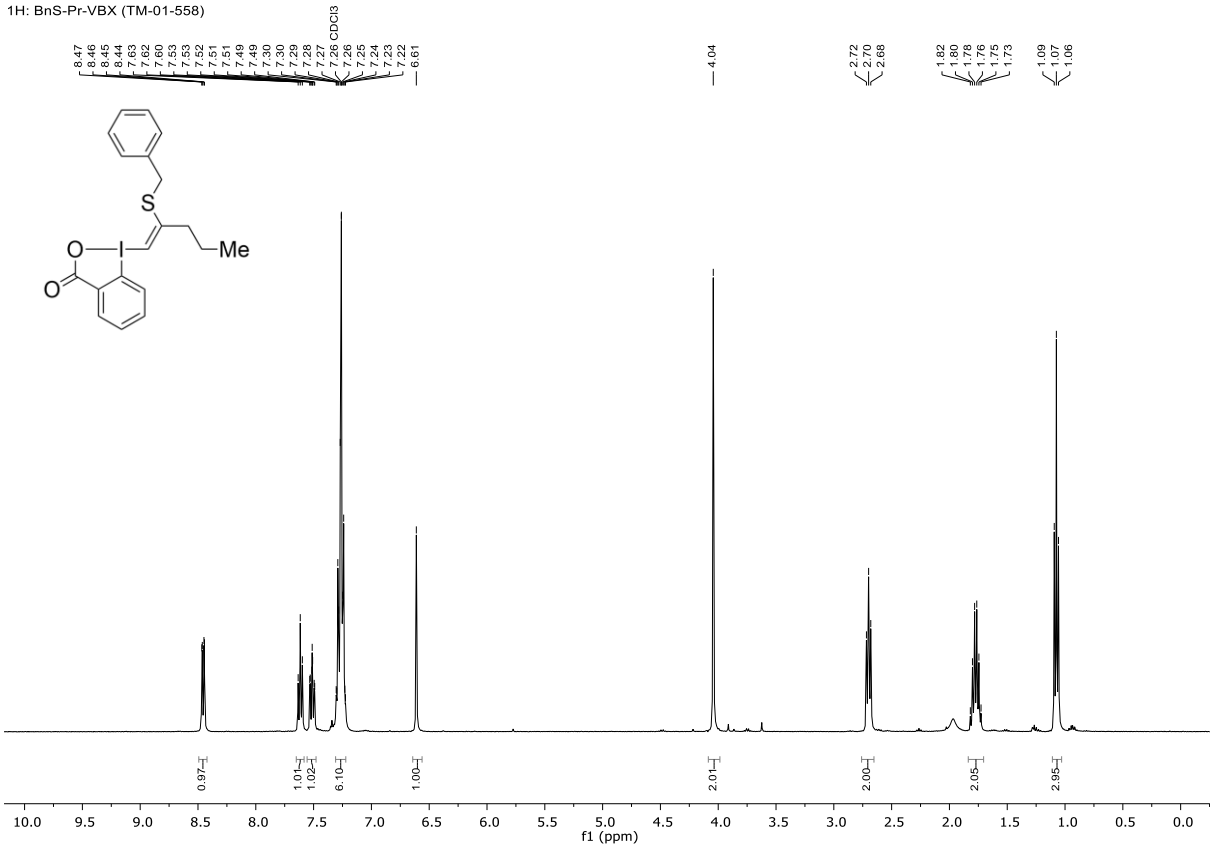


^{13}C-NMR (101 MHz, $CDCl_3$)

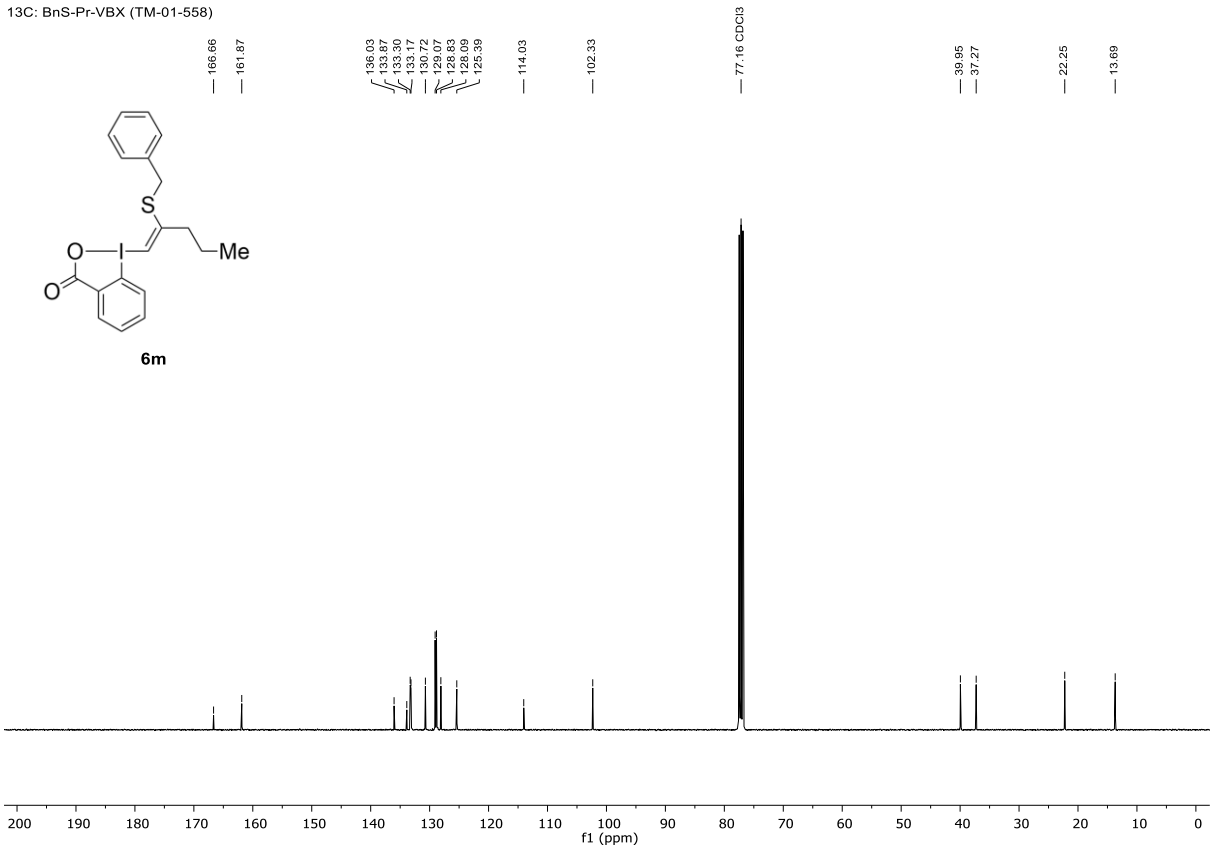


(*Z*)-1-(2-(Benzylthio)pent-1-en-1-yl)-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (6m)

^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



(*Z*)-1-(2-Phenylvinyl)-2-Capsaicin-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7a)

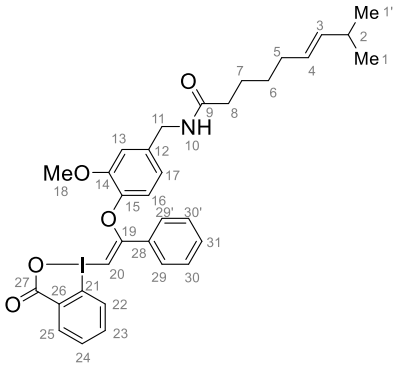
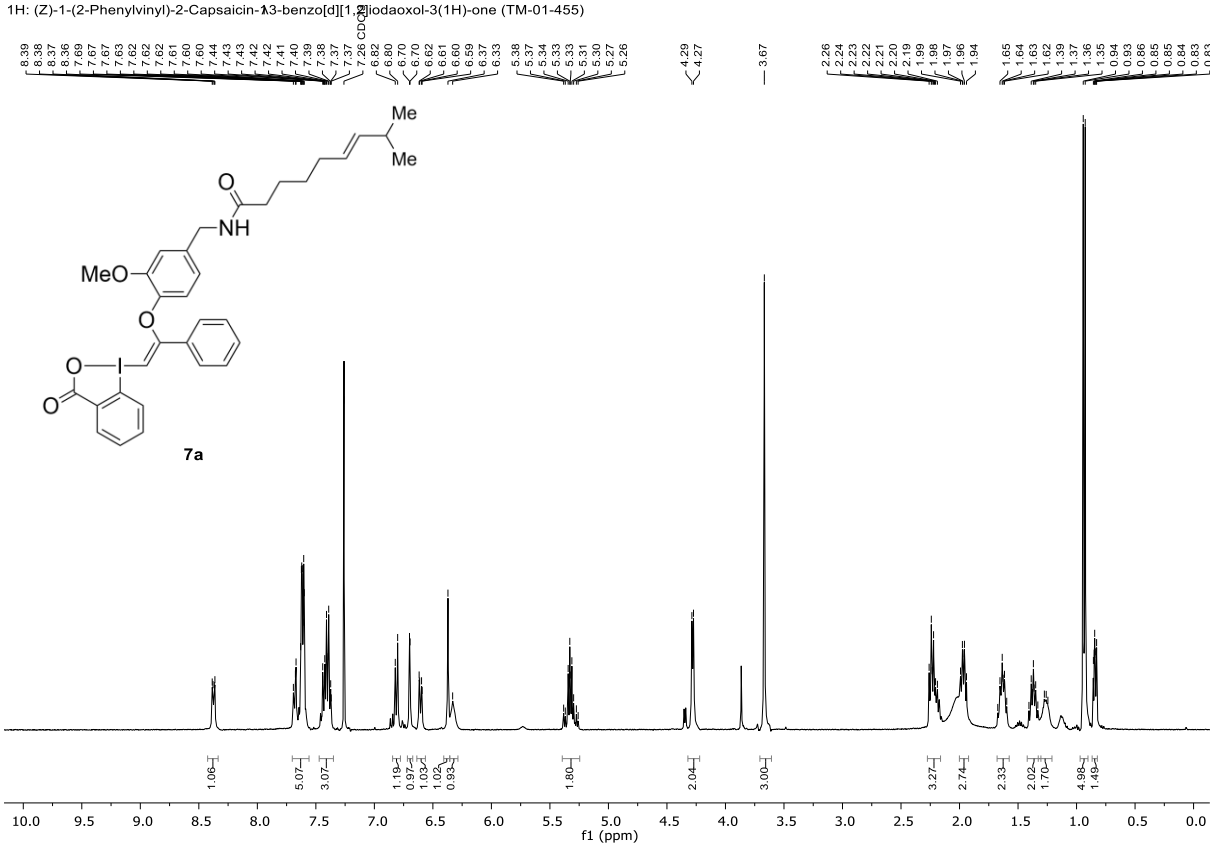


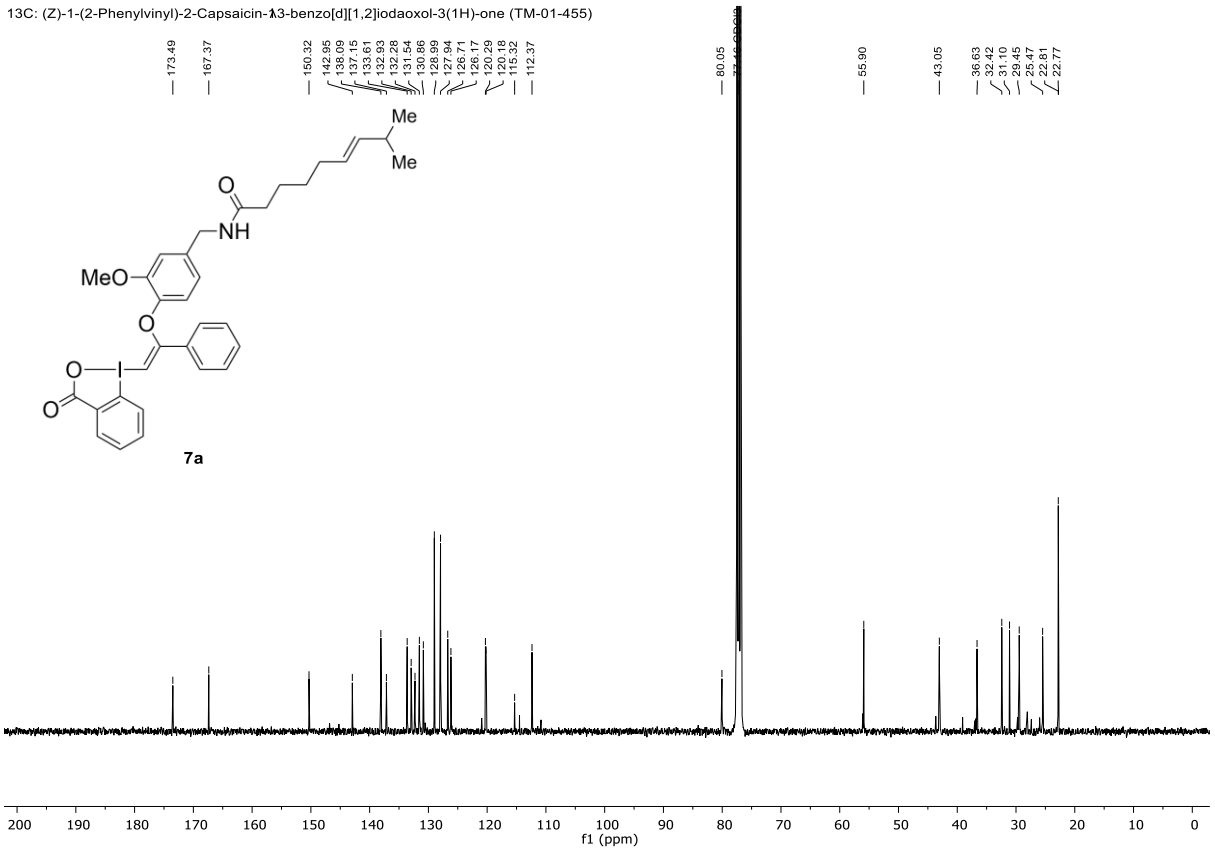
Table S20. Detailed NMR assignment of (*Z*)-1-(2-phenylvinyl)-2-Capsaicin-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7a**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	22.8	0.93 (d, 6.8 Hz),	2	2, 3
2	31.1	2.27-2.17 (m)	1/1’, 3	3, 4
3	138.1	5.39-5.25 (m)	2, 5	1/1’
4	126.7	5.39-5.25 (m)	5	5
5	32.4	1.97 (q, 6.8 Hz)	3, 4, 7	3, 4, 6,
6	29.5	1.44-1.32 (m)	5, 7	4, 5
7	25.5	1.63 (p, 7.6 Hz)	6, 8	6, 8, 9
8	36.6	2.27-2.17 (m)	7	7, 9
9	173.5			
10	/	6.33 (bs)	11	
11	43.0	4.28 (d, 5.5 Hz)	10	9, 12, 13, 16, 17
12	137.1			
13	120.2	6.81 (d, 8.1 Hz)	17	12, 14, 15
14	150.3			
15	142.9			
16	112.4	6.70 (dd, 1.8 Hz)		11, 14, 15, 17
17	120.3	6.60 (dd, 8.3, 1.8 Hz)	13	11, 15, 16
18	55.9	3.67 (s)		14
19	167.4			
20	80.0	6.37 (s)		19, 28
21	115.3			
22	133.6	8.40-8.34 (m)	23, 24	21, 22
23	131.5	7.70-7.56 (m)	22	
24	126.2	7.70-7.56 (m)	22	
25	132.5	7.70-7.56 (m)		
26	130.9			
27	not expressed			
28	132.9			
29/29’	127.9	7.70-7.56 (m)	30/30’, 31	19, 30/30’
30/30’	129.0	7.47-7.35 (m)	29/29’	28, 29/29’
31	129.0	7.47-7.35 (m)	29/29’	29/29’

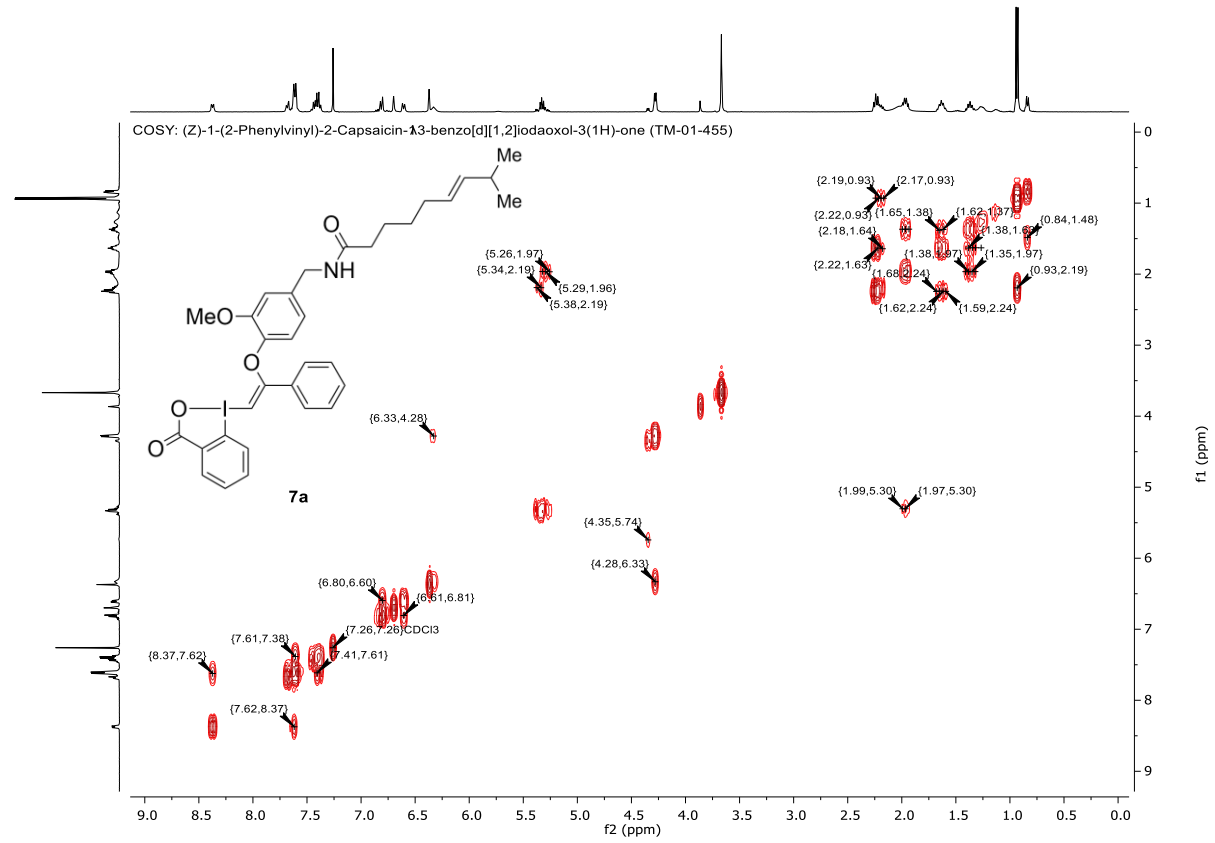
^{1}H-NMR (400 MHz, $CDCl_3$)



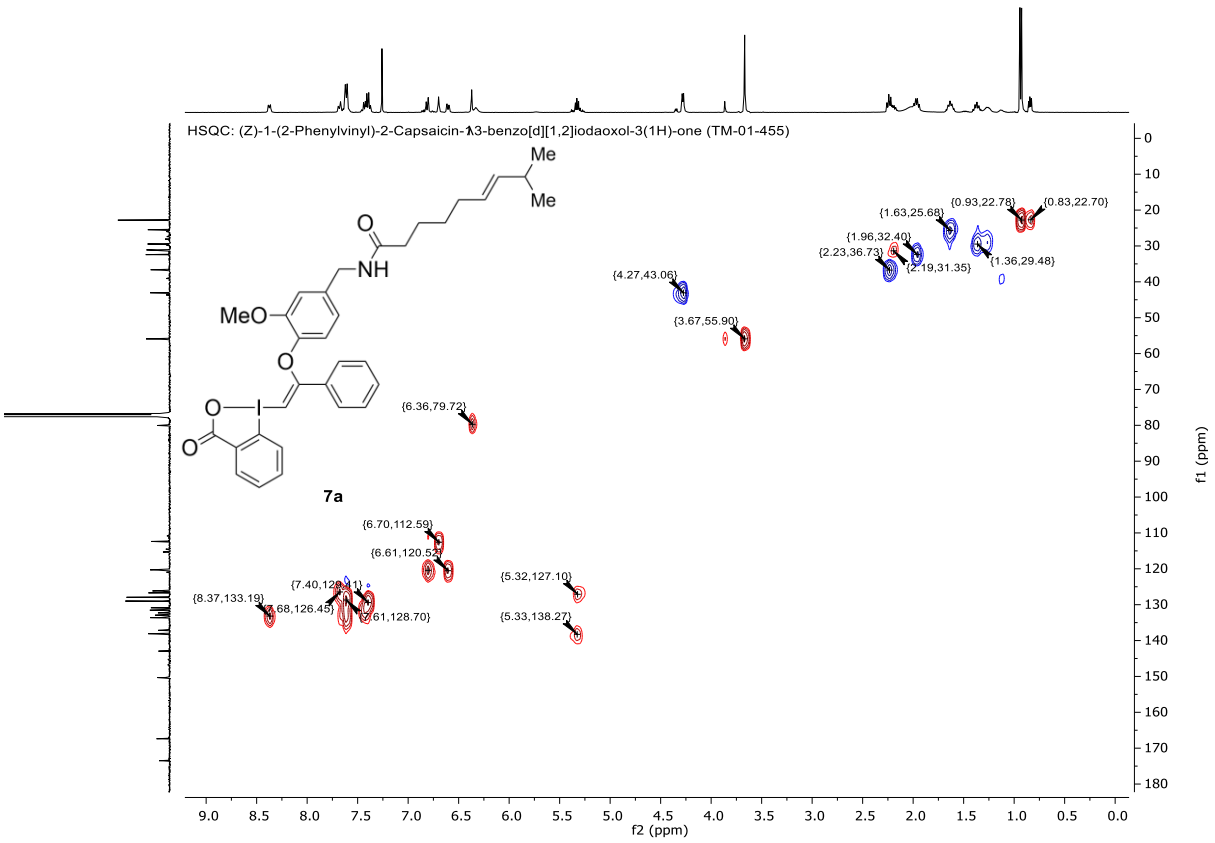
^{13}C-NMR (101 MHz, $CDCl_3$)



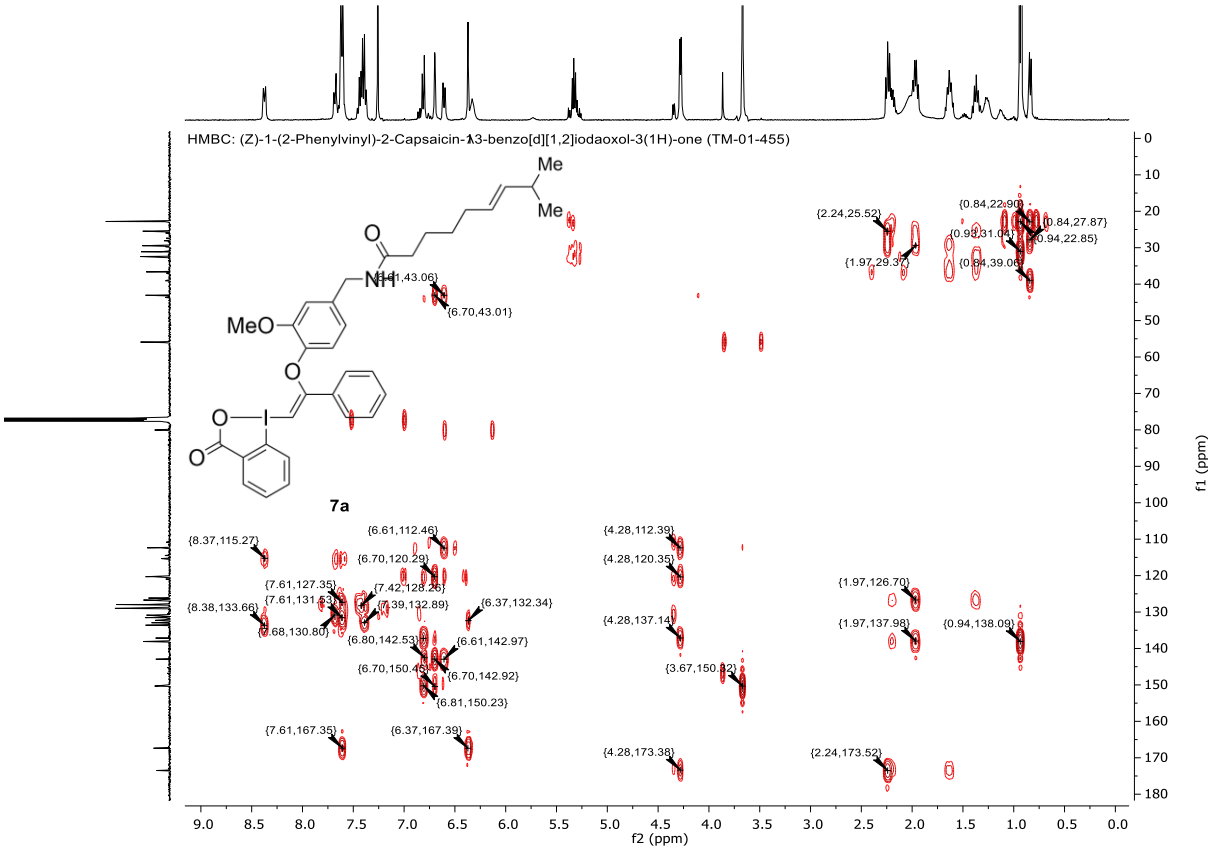
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-capsaicin-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7b)

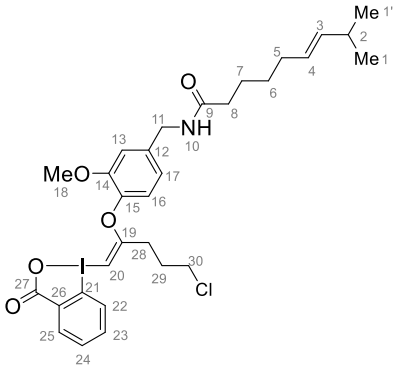
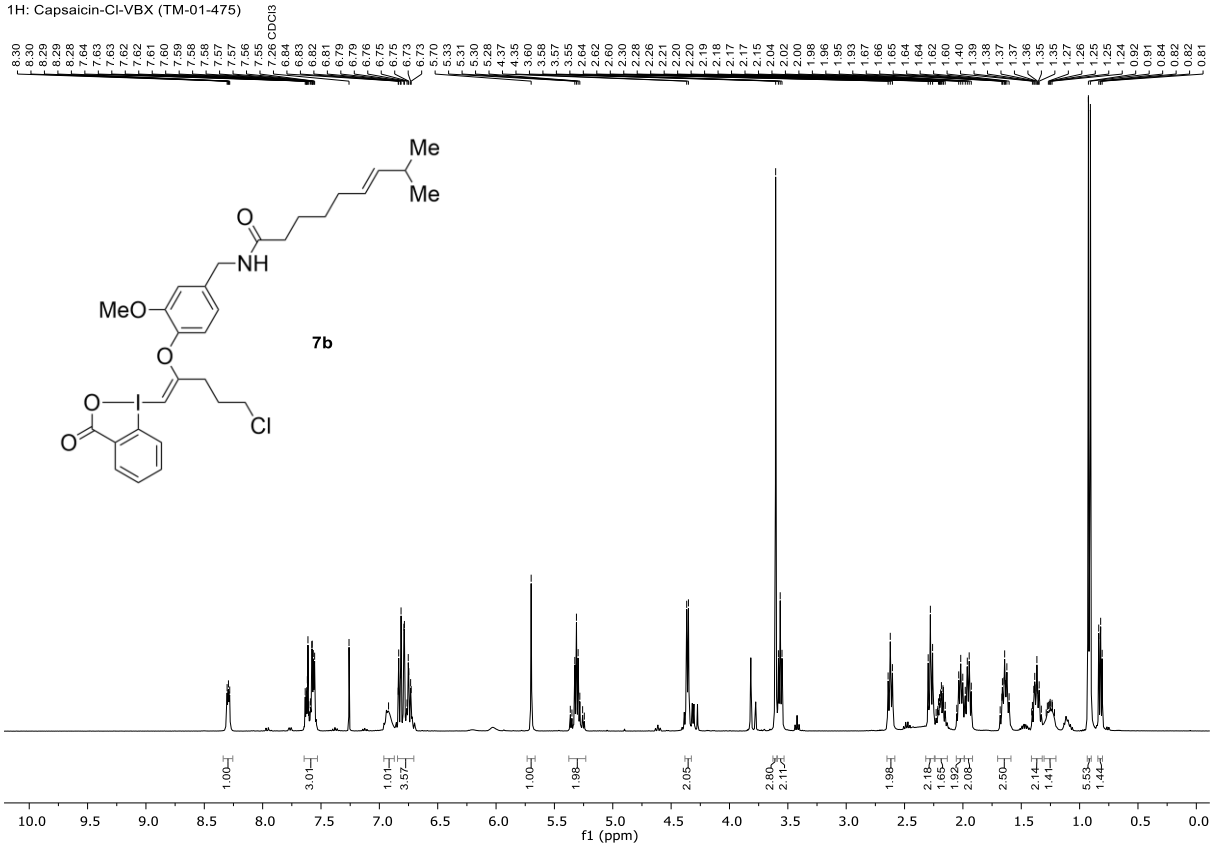


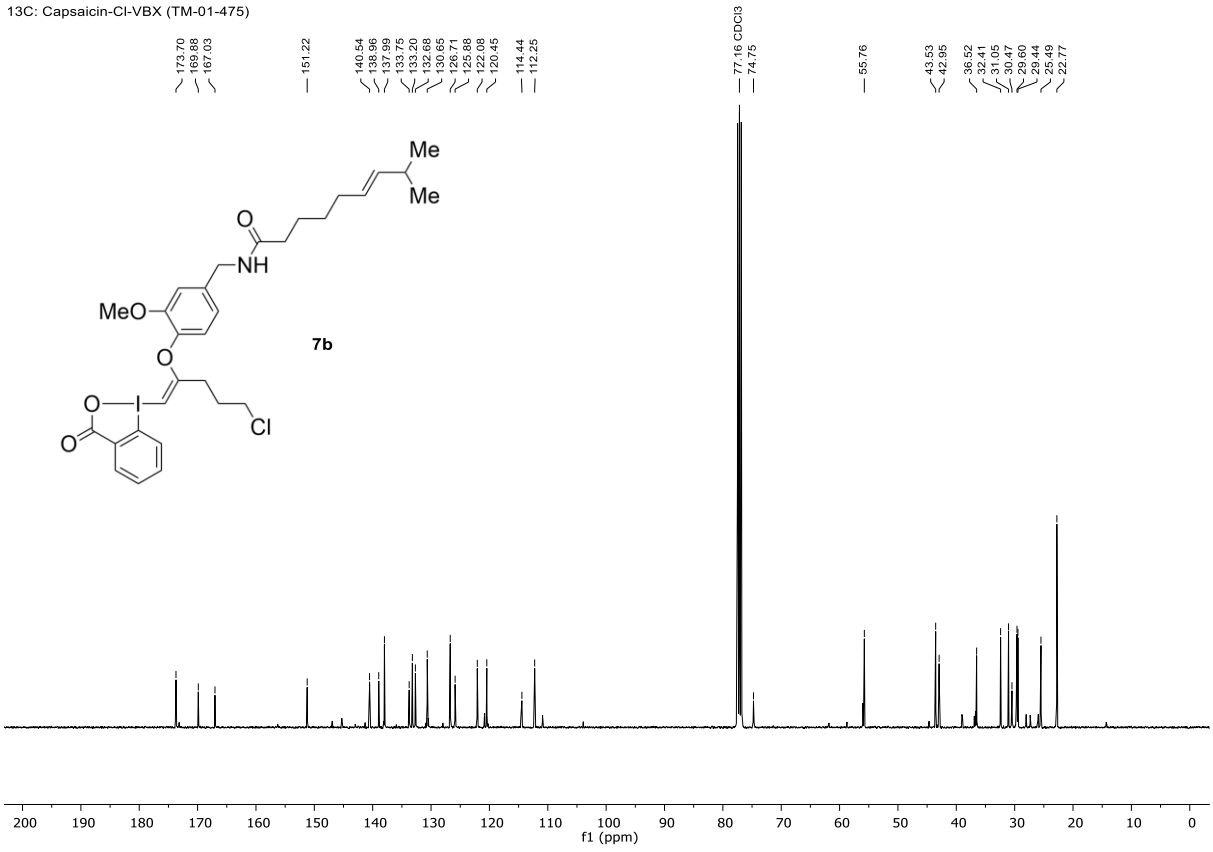
Table S21. Detailed NMR assignment of (*Z*)-(5-chloro-1-pent-1-en-2-yl)-2-capsaicin-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7b**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	22.8	0.92 (d, 6.8 Hz), 0.82 (dd, 6.6, 5.2 Hz)	2	2, 3
2	31.1	2.23-2.14 (m)	1/1’	3, 4
3	139.0	5.38-5.23 (m)	5	1/1’, 2
4	125.9	5.38-5.23 (m)	5	1/1’, 2
5	29.6	2.04-1.99 (m)	3, 4, 6	3, 4, 6, 7
6	29.4	1.41-1.32 (m)	5, 7	4, 7, 8
7	25.5	1.70-1.59 (m)	6, 8	8, 9
8	36.5	2.28 (t, 7.5 Hz)	7	6, 7, 9
9	173.7			
10	/	6.92 (bs)	11	9
11	43.5	4.36 (d, 6.0 Hz)	10	
12	138.0			
13	120.4	6.84-6.71 (m)	16	11, 16
14	151.2			
15	140.5			
16	112.2	6.84-6.71 (m)	13, 17	13, 15
17	122.1	6.84-6.71 (m)	16	11, 14
18	55.8	3.60 (s)		14
19	169.9			
20	74.7	5.70 (s)		19, 28
21	114.4			
22	133.2	8.33-8.26 (m)	23, 24, 25	21, 22, 27
23	130.7	7.64-7.53 (m)	22	24, 25
24	126.7	7.64-7.53 (m)	22	21
25	132.7	7.64-7.53 (m)	22	
26	133.7			
27	167.0			
28	30.5	2.62 (t, 7.4 Hz)	29	19, 20, 30
29	32.4	1.95 (q, 7.1 Hz)	28, 30	19, 28, 30
30	42.9	3.57 (t, 6.2 Hz)	29	28

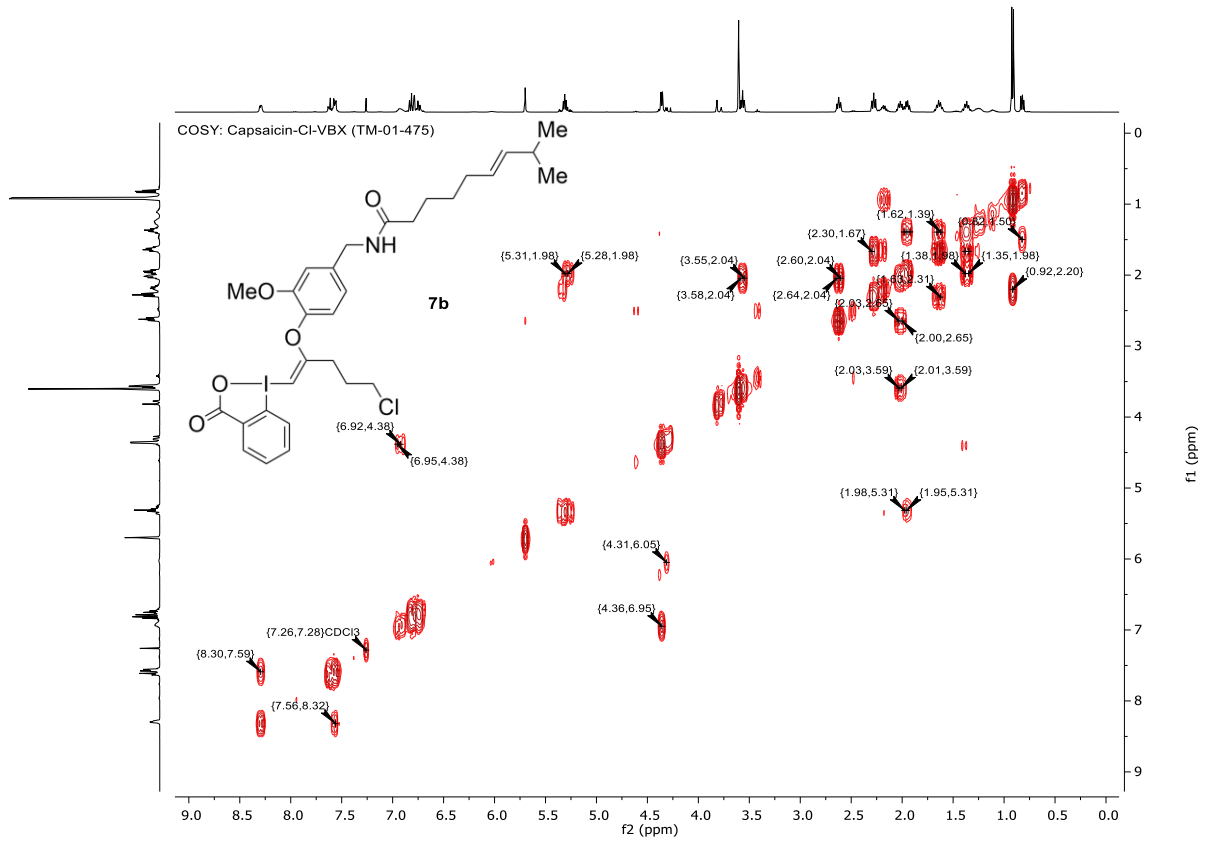
^{1}H-NMR (400 MHz, $CDCl_3$)



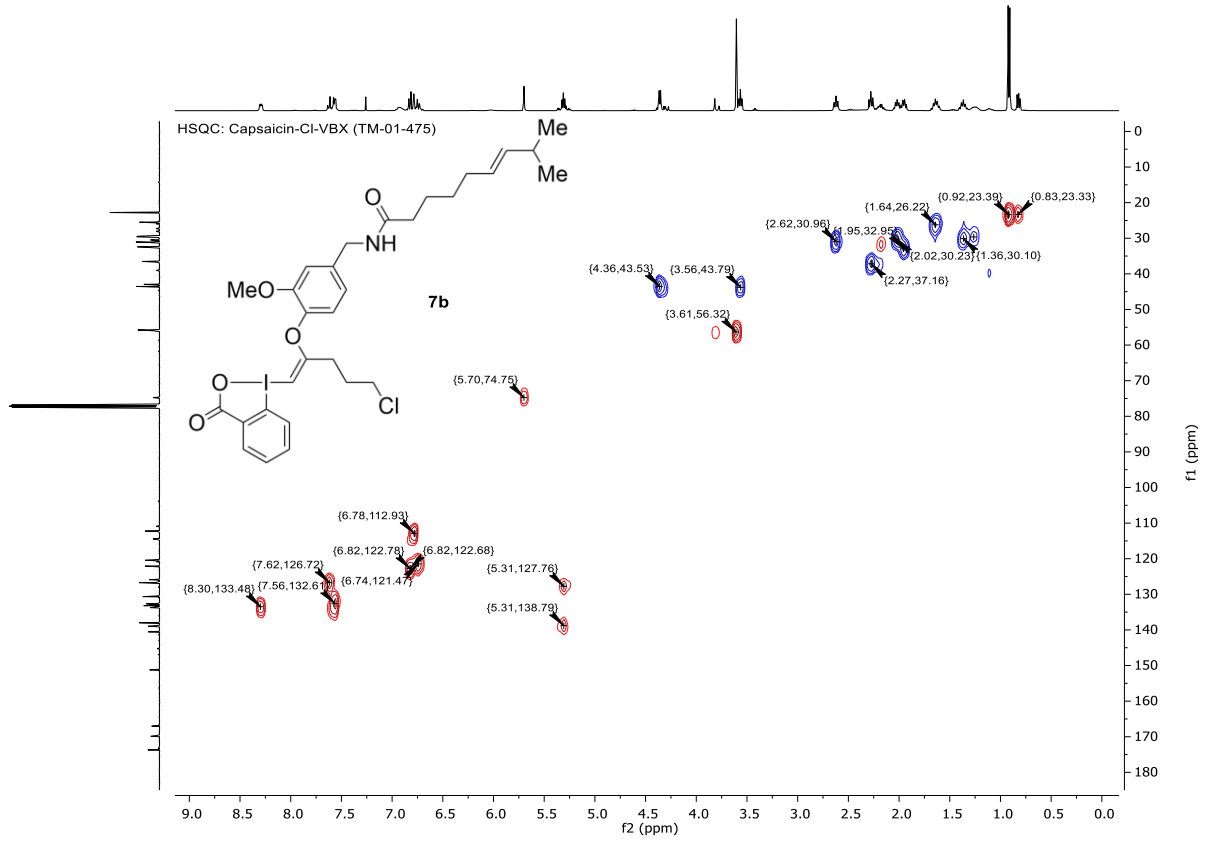
^{13}C-NMR (101 MHz, $CDCl_3$)



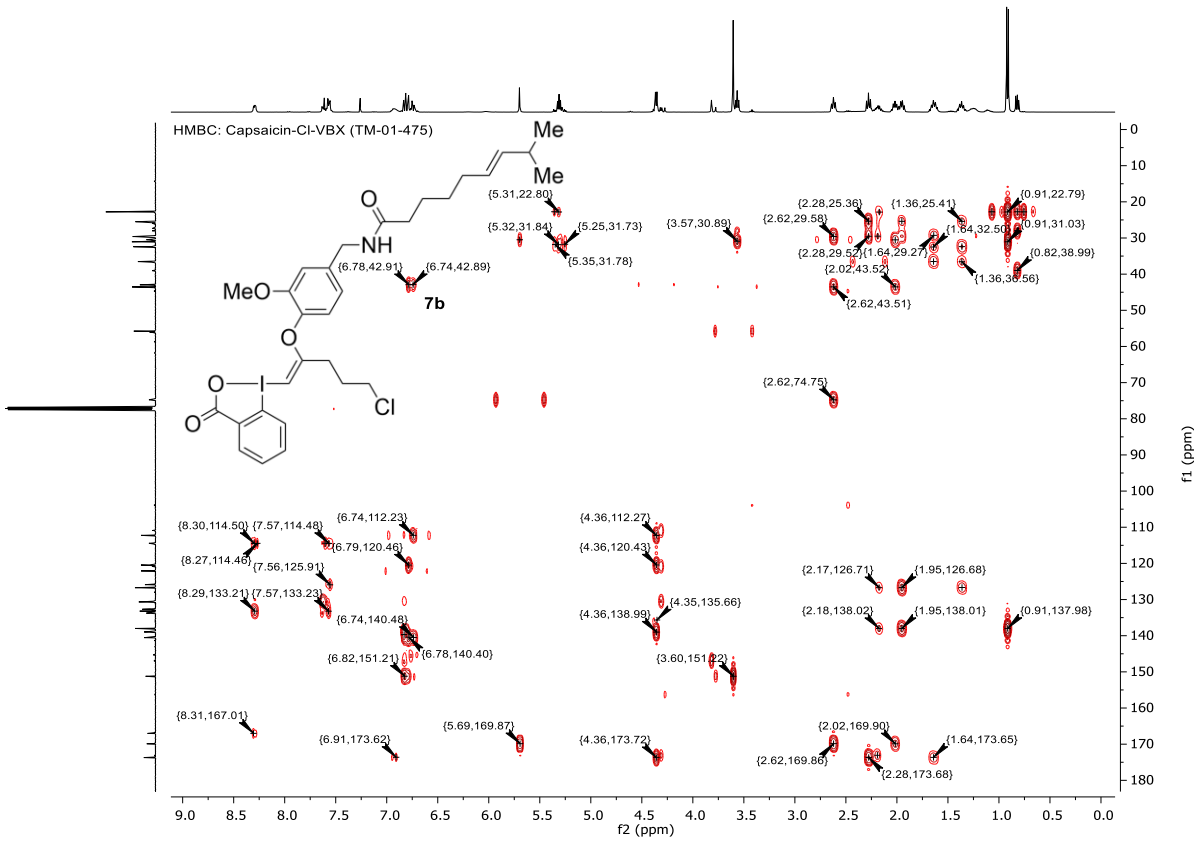
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*Z*)-1-(2-Phenylvinyl)-2-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7c)

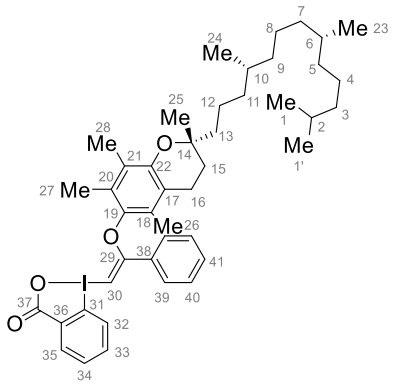
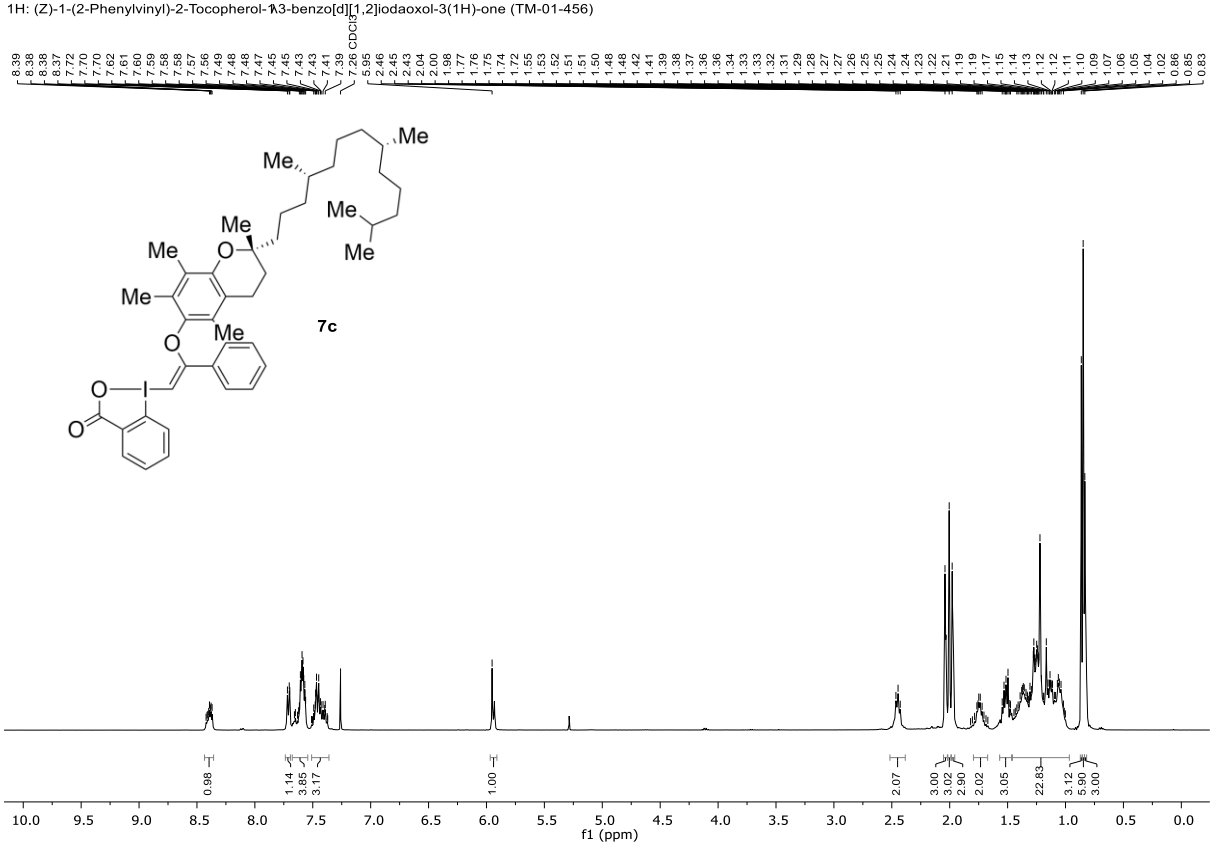


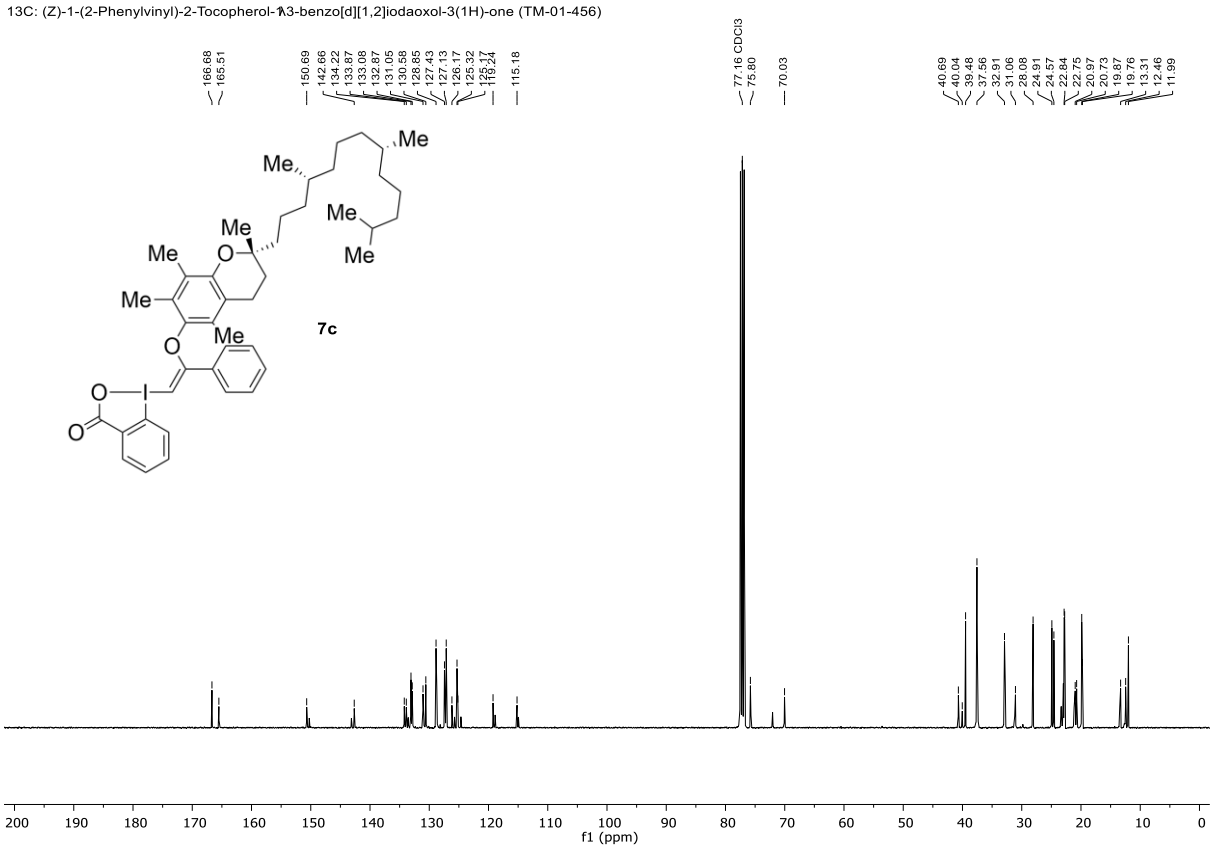
Table S22. Detailed NMR assignment of (*Z*)-1-(2-phenylvinyl)-2-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7c**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	19.8	0.85 (s)	2	3
2	28.1	1.57-1.47 (m)	1/1’	
3	40.7 or 40.0 or 39.5	1.46-0.99 (m)	overlapping	overlapping
4	24.6	1.46-0.99 (m)	overlapping	overlapping
5	37.6	1.46-0.99 (m)	overlapping	overlapping
6	32.9	1.46-0.99 (m)	overlapping	overlapping
7	37.6	1.46-0.99 (m)	overlapping	overlapping
8	24.9	1.46-0.99 (m)	overlapping	overlapping
9	37.6	1.46-0.99 (m)	overlapping	overlapping
10	32.9	1.46-0.99 (m)	overlapping	overlapping
11	40.7 or 40.0 or 39.5	1.46-0.99 (m)	overlapping	overlapping
12	22.8	1.46-0.99 (m)	overlapping	overlapping
13	40.7 or 40.0 or 39.5	1.57-1.47 (m)		12
14	75.8			
15	31.1	1.83-1.66 (m)	16	14, 16, 17
16	19.9	2.45 (t, 7.5 Hz)	15	14, 15, 17
17	119.2			
18	125.2			
19	150.7			
20	125.3			
21	126.2			
22	142.7			
23	21.0 or 20.7	0.86 (s) or 0.83 (s)		5, 6, 7
24	21.0 or 20.7	0.86 (s) or 0.83 (s)		9, 10, 11
25	22.8	1.46-0.99 (m)		
26	12.0	1.98 (s)		17, 18, 22
27	12.5	2.00 (s)		19, 20, 21
28	13.3	2.04 (s)		21, 22
29	165.5			
30	70.0	5.95 (s)		29, 38
31	115.2			
32	133.1	8.40 (ddd, 11.7, 5.9, 3.4 Hz)	33, 35	31, 33
33	131.1	7.68-7.54 (m)	32	31, 34
34	127.4	7.74-7.68 (m)		33
35	134.2 or 133.9	7.68-7.54 (m)	32	31, 34
36	130.6			
37	166.7			
38	132.9			
39/39’	127.1	7.68-7.54 (m)	40/40’	29
40/40’	128.9	7.57-7.37 (m)	39/39’	38, 39/39’
41	128.9	7.57-7.37 (m)	39/39’	39/39’

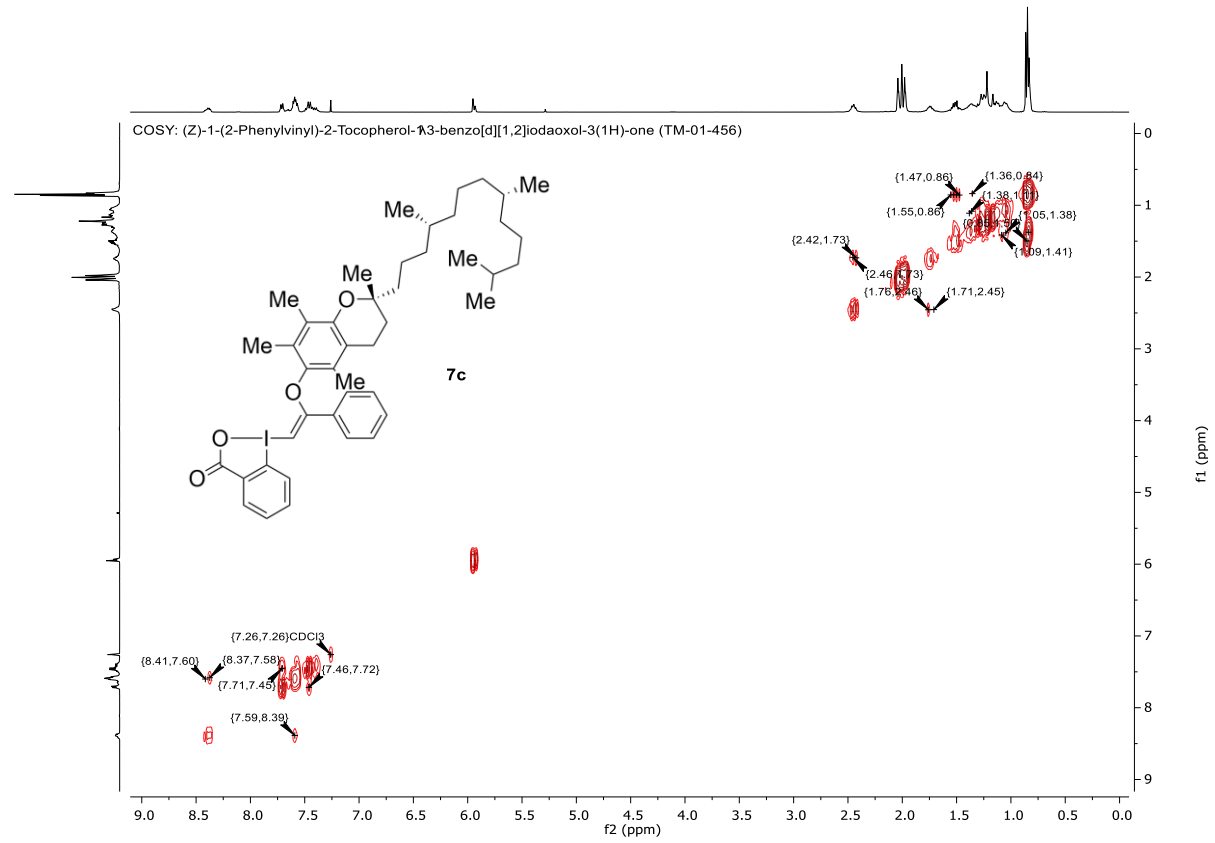
^{1}H-NMR (400 MHz, $CDCl_3$)



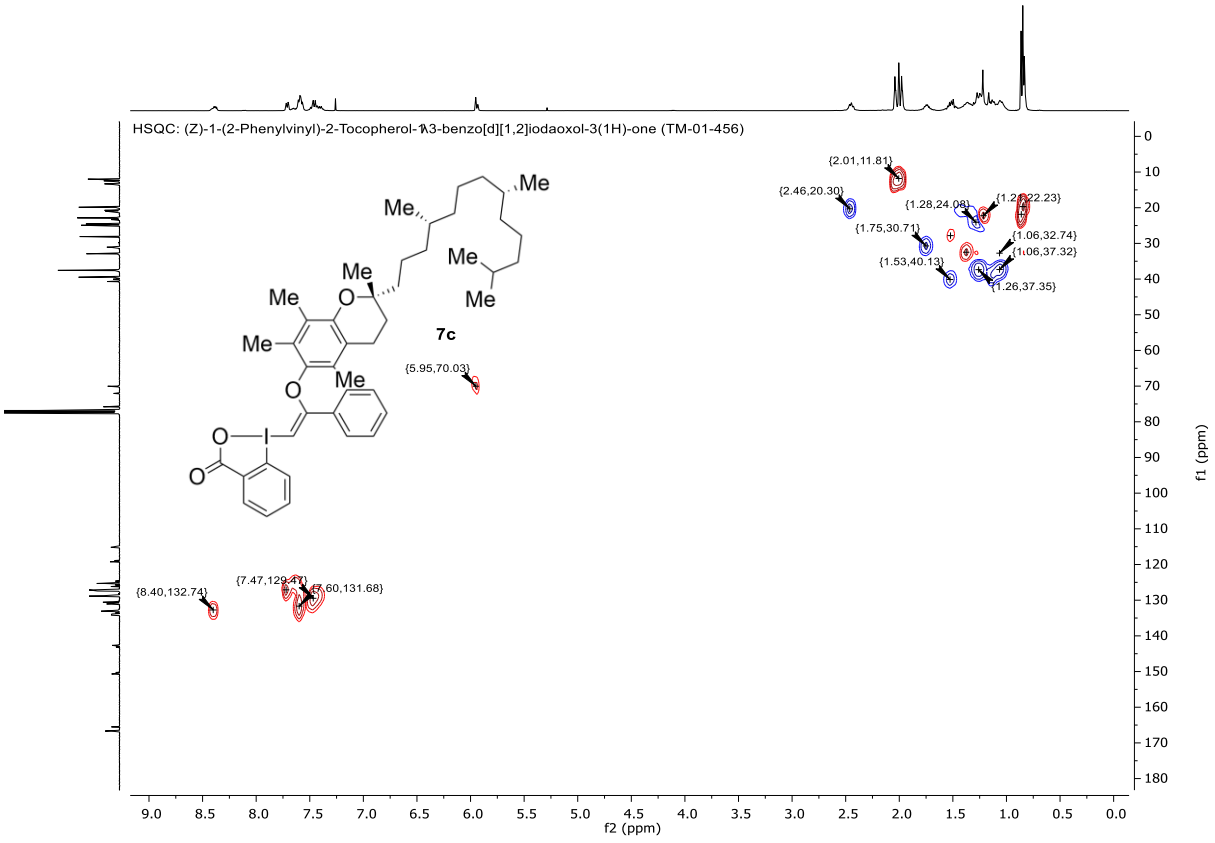
^{13}C-NMR (101 MHz, $CDCl_3$)



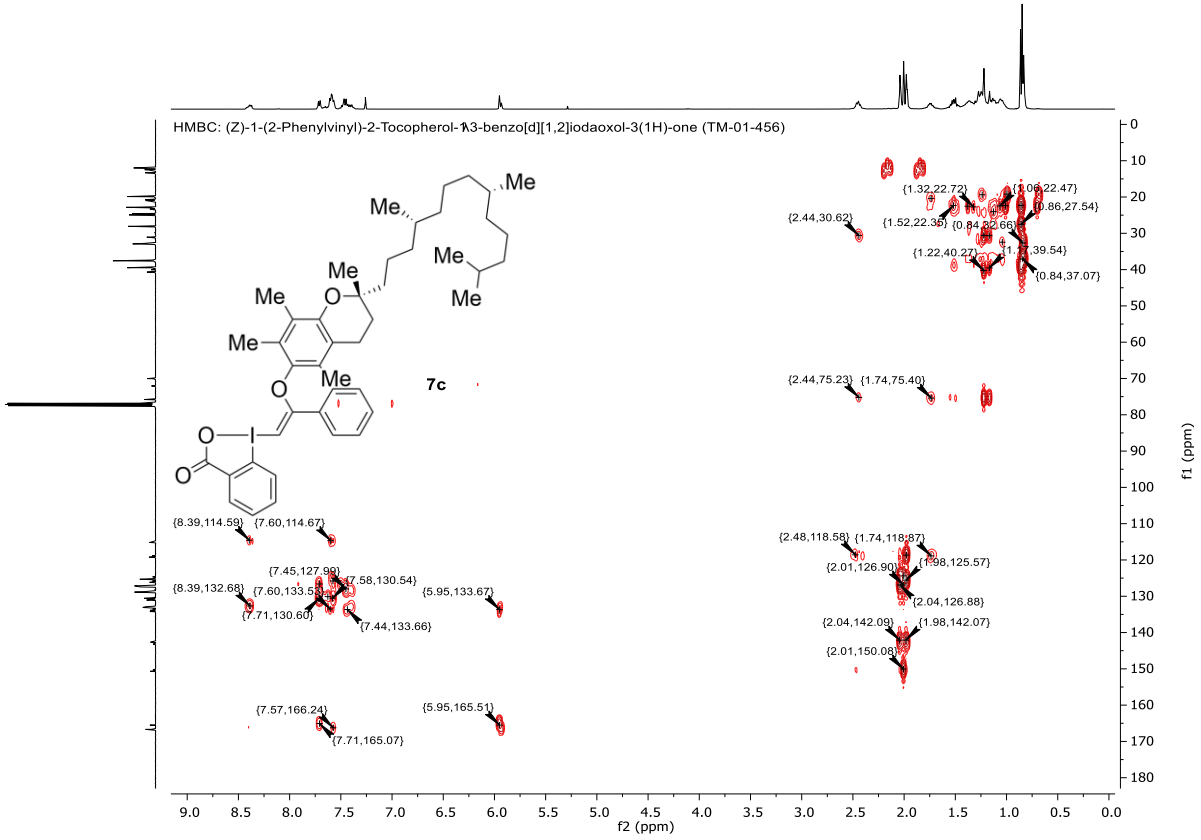
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-α-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7d)

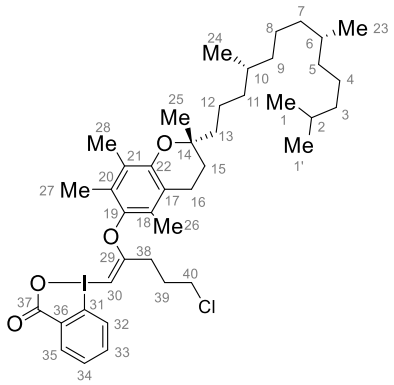
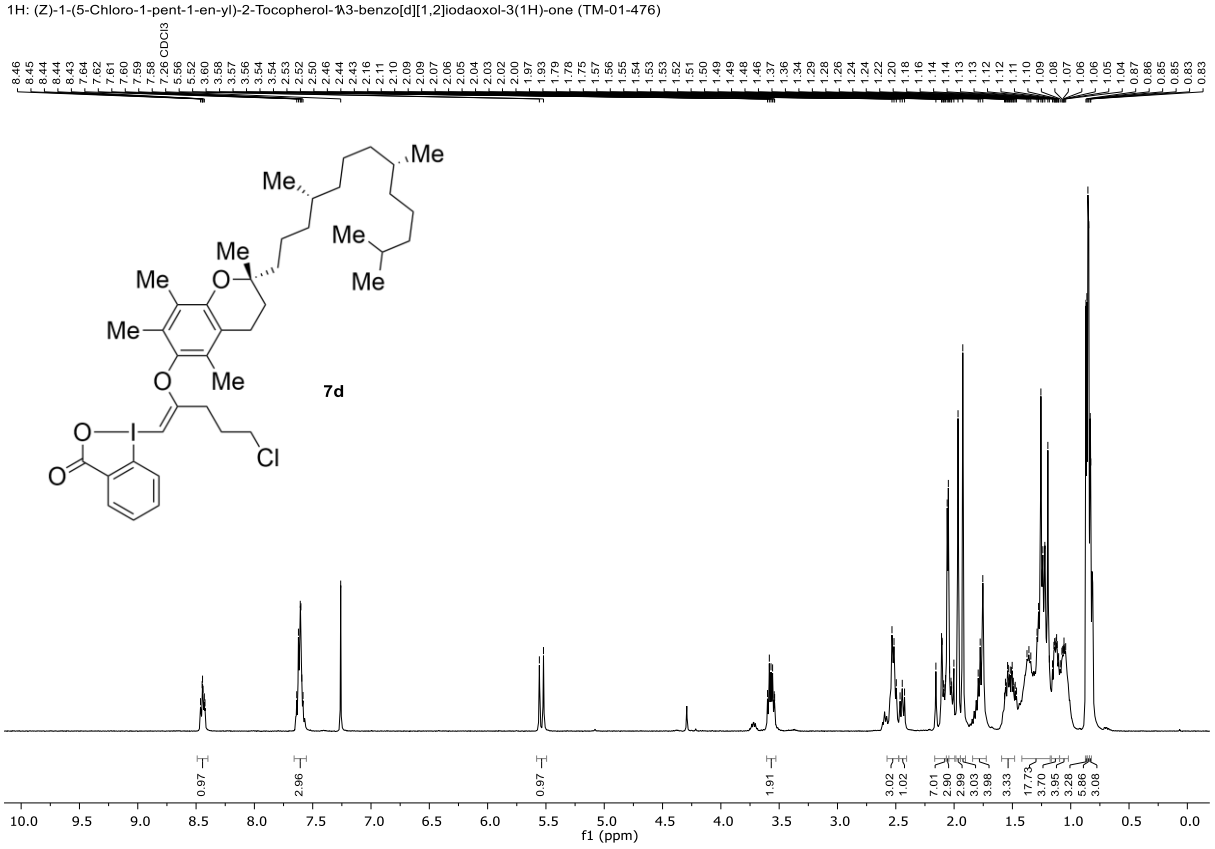


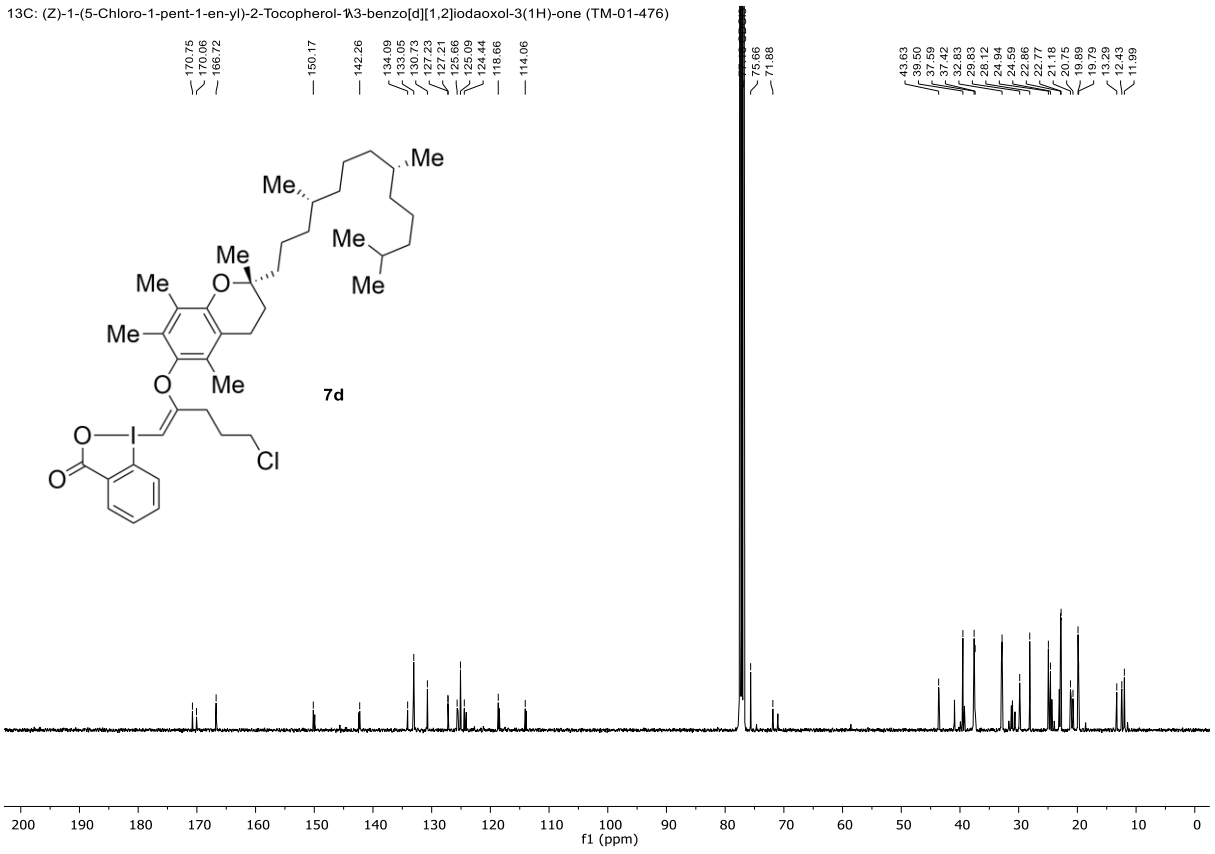
Table S23. Detailed NMR assignment of (*Z*)-1-(5-chloro-1-pent-1-en-2-yl)-2-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7d**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	19.9	0.85 (s)	2	3
2	28.1	1.59-1.47 (m)	1/1’	
3	39.5	1.42-1.00 (m)	overlapping	overlapping
4	24.6	1.42-1.00 (m)	overlapping	overlapping
5	37.6	1.42-1.00 (m)	overlapping	overlapping
6	32.8	1.42-1.00 (m)	overlapping	overlapping
7	37.6	1.42-1.00 (m)	overlapping	overlapping
8	24.9	1.42-1.00 (m)	overlapping	overlapping
9	37.6	1.42-1.00 (m)	overlapping	overlapping
10	32.8	1.42-1.00 (m)	overlapping	overlapping
11	39.5	1.42-1.00 (m)	overlapping	overlapping
12	22.9	1.42-1.00 (m)	overlapping	overlapping
13	40.9	1.59-1.47 (m)		12
14	75.7			
15	31.1	1.84-1.73 (m)	16	14, 16, 17
16	20.7	2.57-2.48 (m)	15	14, 15, 17
17	118.7			
18	124.4			
19	150.2			
20	125.1			
21	125.7			
22	142.3			
23	22.8 or 21.2	0.87 (s) or 0.83 (s)		5, 6, 7
24	22.8 or 21.2	0.87 (s) or 0.83 (s)		9, 10, 11
25	22.9	1.42-1.00 (m)		
26	12.0	1.93 (s)		17, 18, 22
27	12.4	1.97 (s)		19, 20, 21
28	13.3	2.05 (s)		21, 22
29	170.8			
30	71.9	5.54 (d, 14.1 Hz)		29, 38
31	114.1			
32	133.1	8.48-8.36 (m)	33, 35	31, 33
33	not oberserved	7.67-7.50 (m)	32	31, 34
34	127.2	7.67-7.50 (m)		33
35	134.1	7.67-7.50 (m)	32	31, 34
36	130.7			
37	166.7			
38	29.8	2.57-2.48 (m), 2.44 (t, 7.7 Hz)	39	29, 30, 40
39	30.6	2.16-1.99 (m)	38, 40	
40	43.6	3.57 (dt, 10.9, 5.8 Hz)	39	39

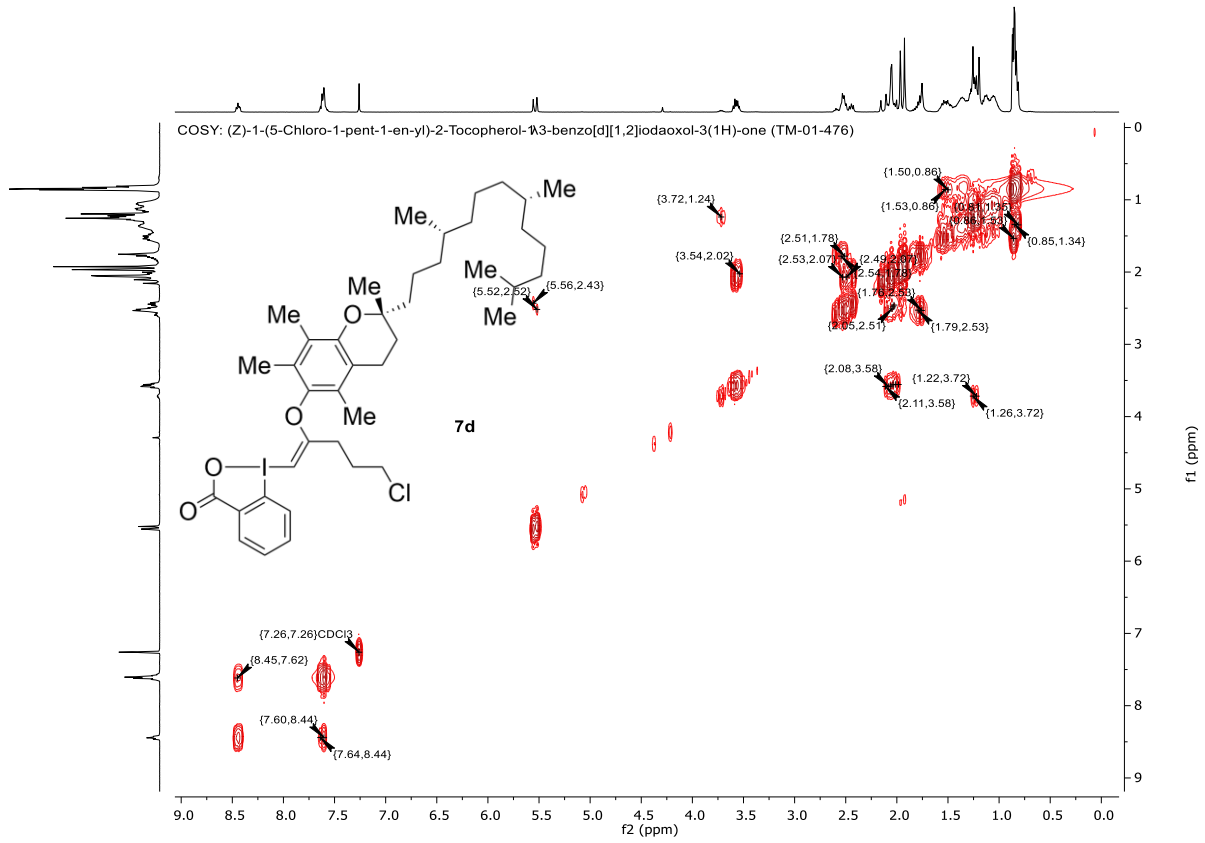
^{1}H-NMR (400 MHz, $CDCl_3$)



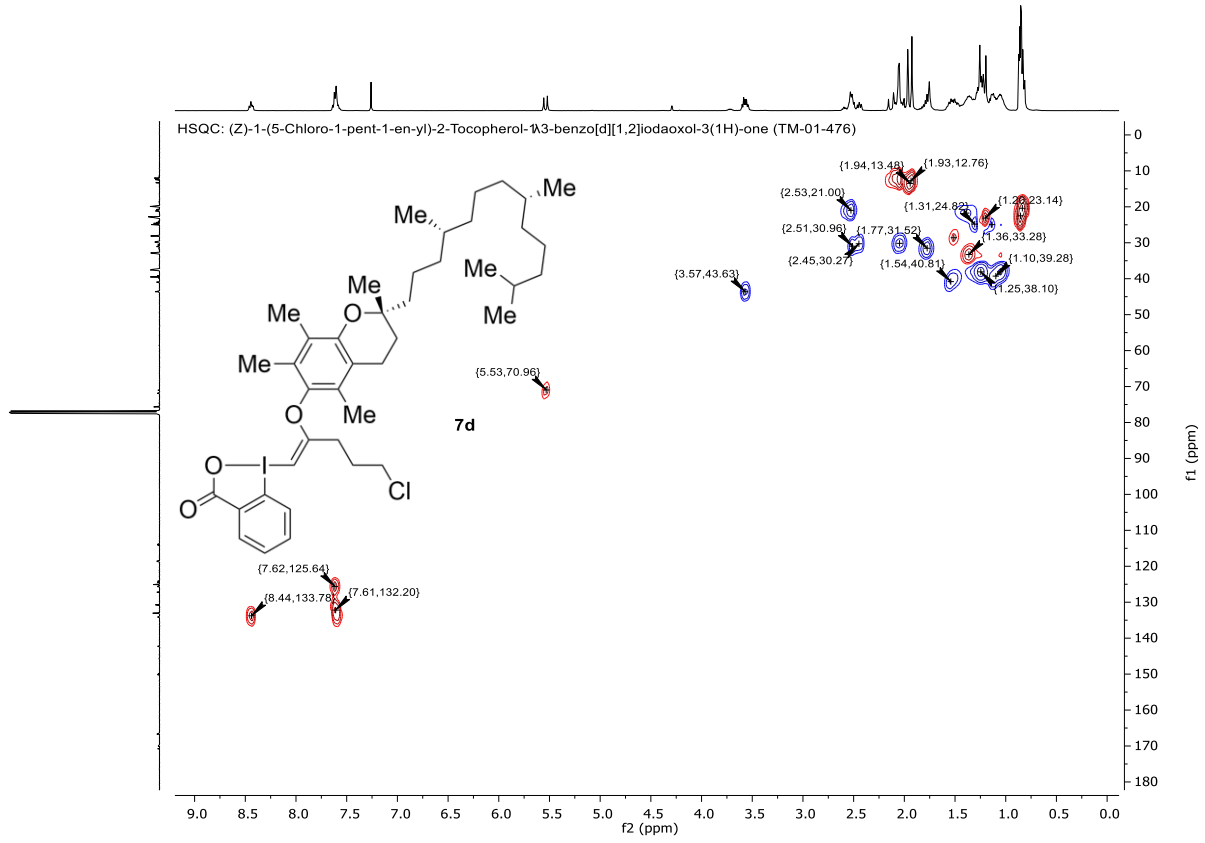
^{13}C-NMR (101 MHz, $CDCl_3$)



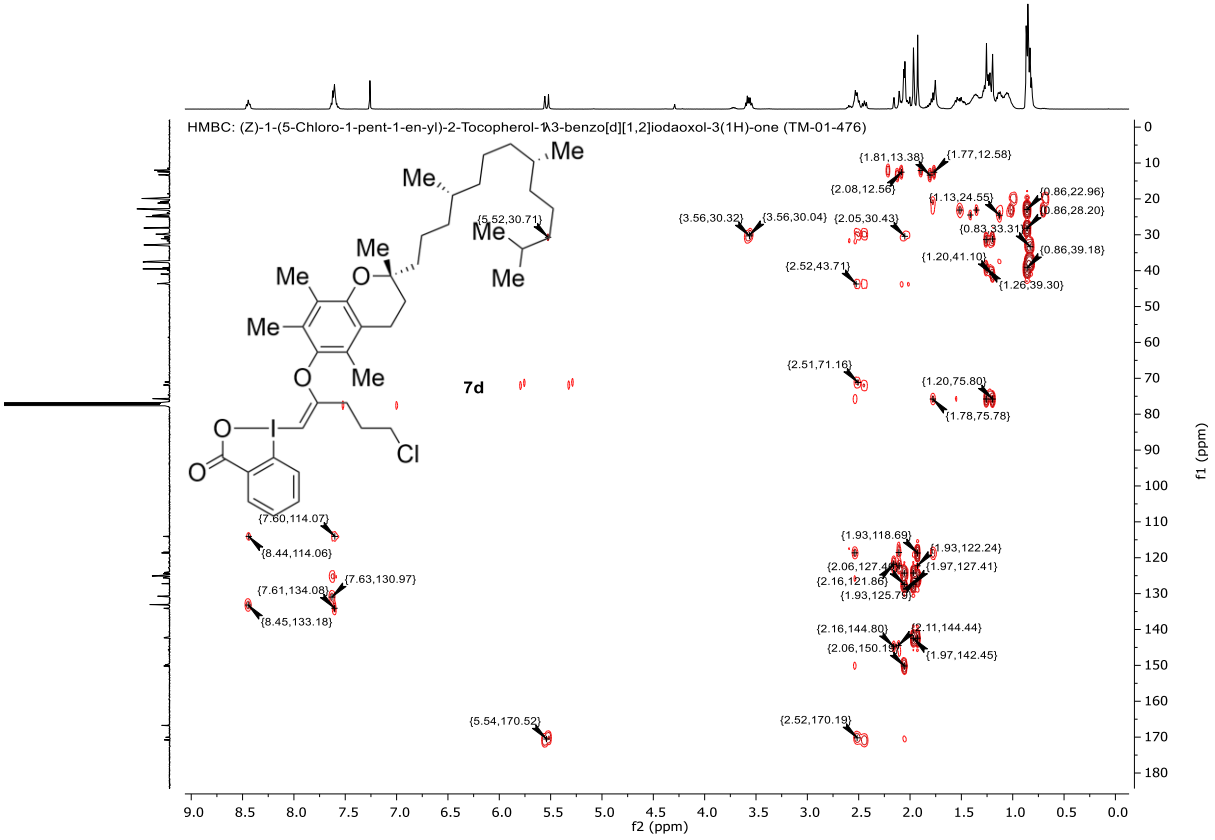
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*Z*)-1-(Prop-1-en-2-yl)-2-ß-estradiol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7e)

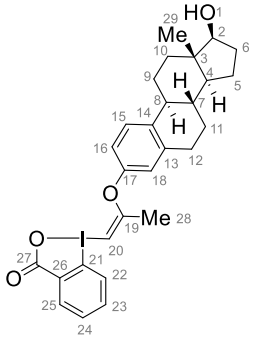
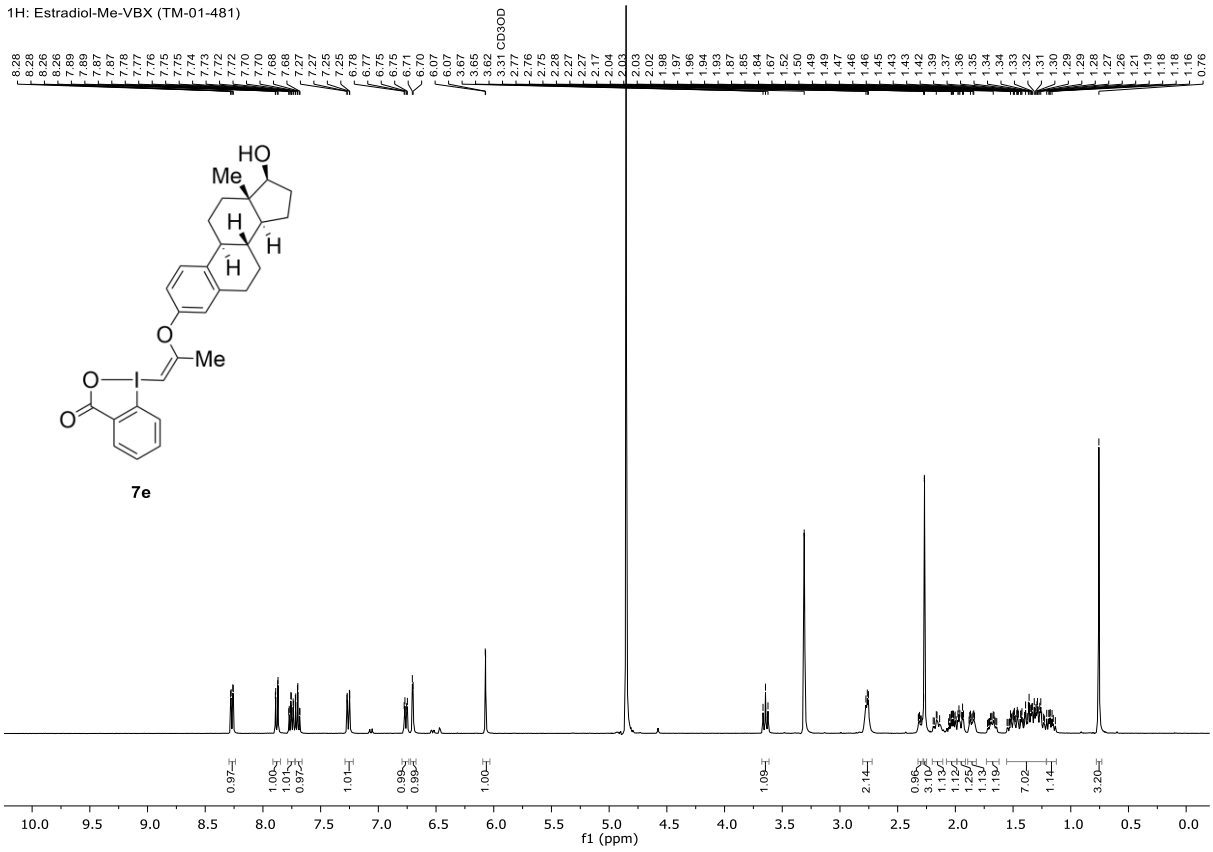


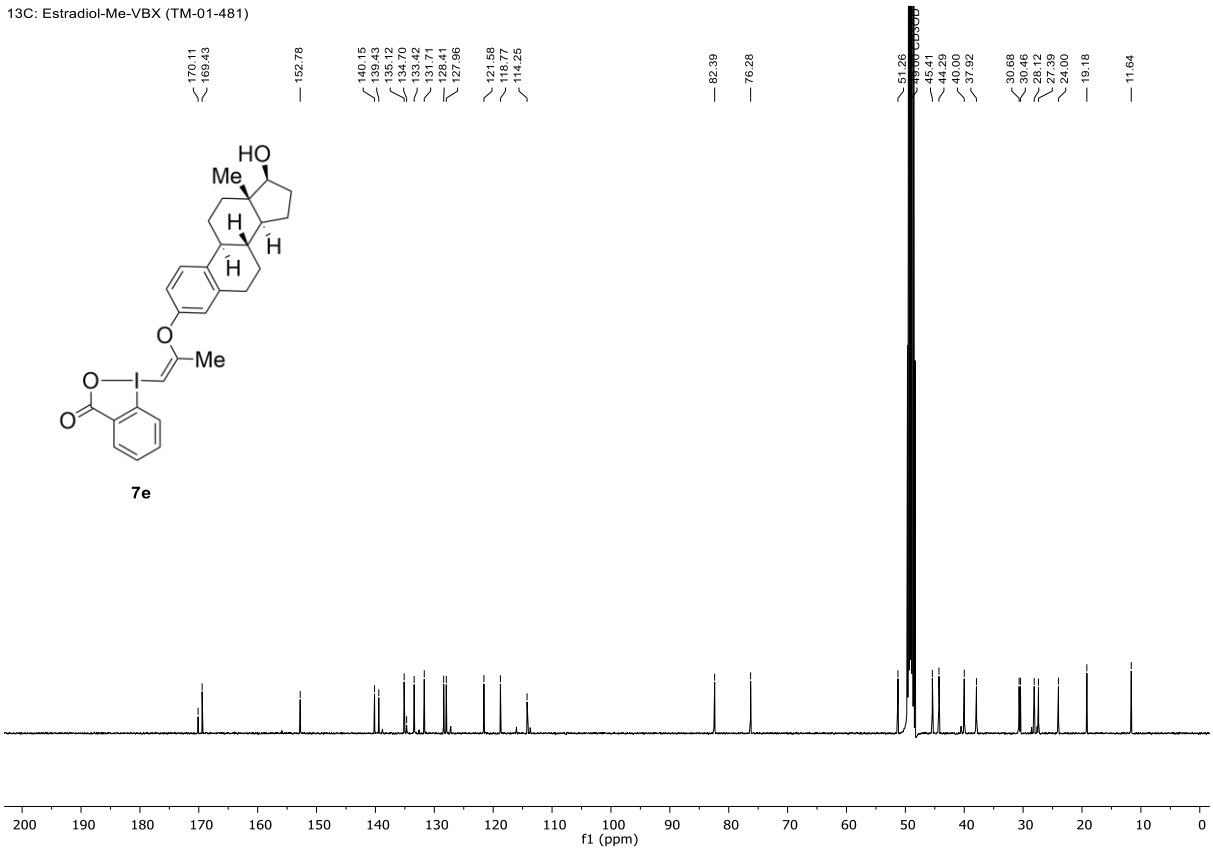
Table S24. Detailed NMR assignment of (*Z*)-1-(prop-1-en-2-yl)-2-ß-estradiol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7e**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	82.4	3.65 (t, 8.6 Hz)	6	10, 29
3	44.3			
4	51.3	1.21-1.13 (m)		3, 29
5	24.0	1.73-1.63 (m), 1.56-1.22 (m)	6	
6	30.7	2.32-2.28 (m), 1.56-1.22 (m)	2, 5	
7	40.0	1.56-1.22 (m)		
8	45.4	2.20-2.11 (m)		
9	27.4	2.08-1.99 (m), 1.56-1.22 (m)	10	
10	37.9	1.95 (dt, 12.6, 3.5 Hz), 1.56-1.22 (m)	9	
11	28.1	1.89-1.82 (m), 1.56-1.22 (m)	12	
12	30.5	2.80-2.73 (m)	11	11, 14
13	140.2			
14	139.4			
15	128.0	7.26 (dd, 8.7, 1.0 Hz)	16	8, 13, 17
16	118.8	6.76 (dd, 8.5, 2.7 Hz)	15	14, 17, 18
17	152.8			
18	121.6	6.70 (d, 2.6 Hz)		12, 14, 16, 17
19	169.4			
20	76.3	6.07 (d, 1.1 Hz)	28	19, 28
21	114.2			
22	133.4	8.27 (dd, 7.4, 1.9 Hz)	23	21, 24, 27
23	131.7	7.70 (td, 7.3, 1.1 Hz)	22	24, 25
24	135.1	7.79-7.73 (m)		21, 22
25	128.4	7.88 (dd, 8.1, 1.2 Hz)		21, 24
26	134.7			
27	170.1			
28	19.2	2.27 (d, 0.8 Hz)	20	19, 20
29	11.6	0.76 (s)		2, 3, 4, 10

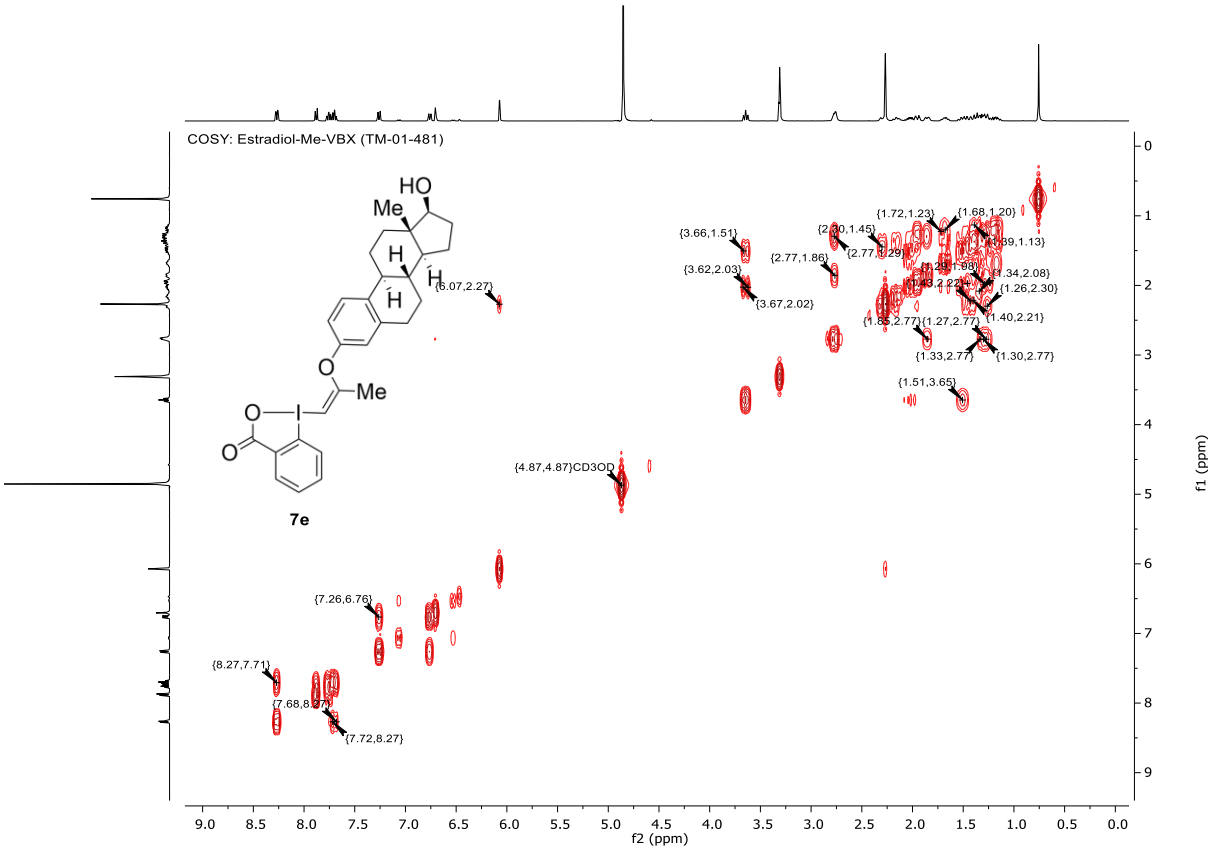
^{1}H-NMR (400 MHz, MeOD-d$_4$)



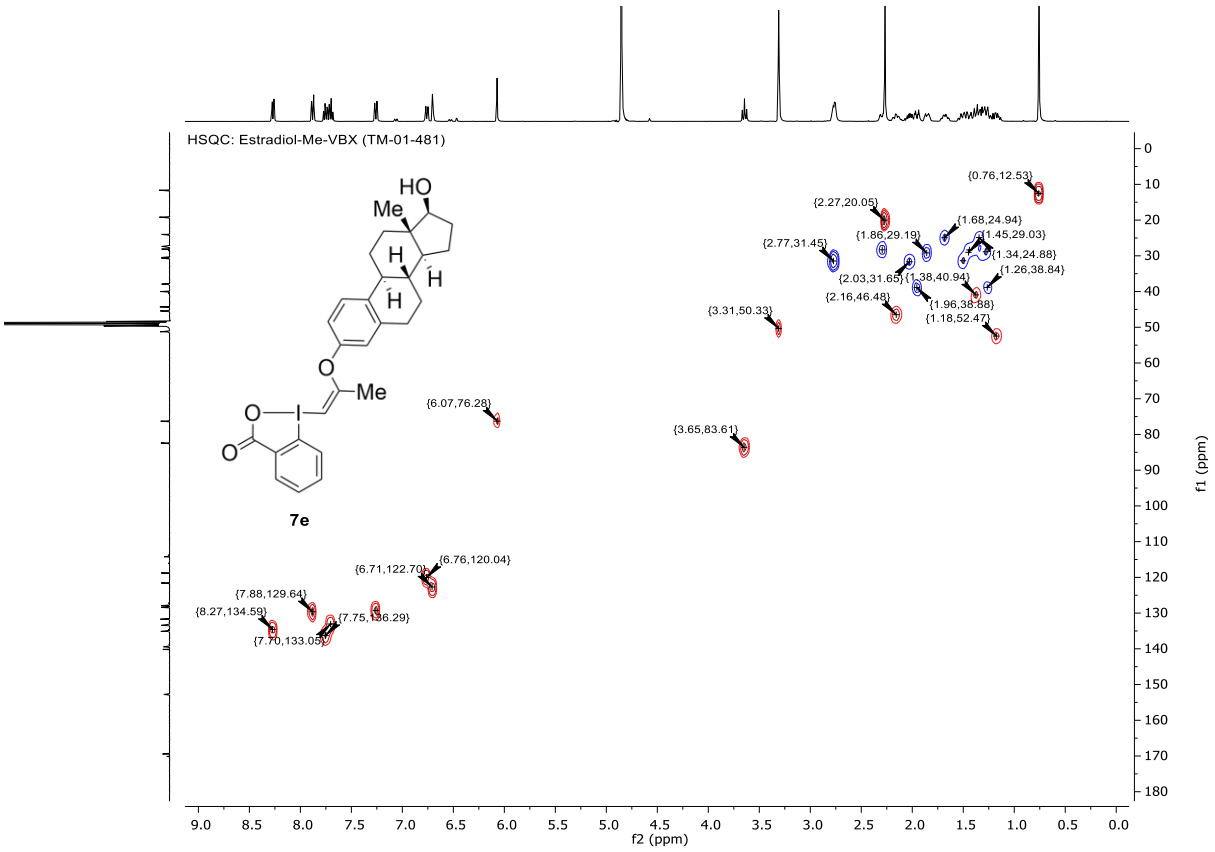
^{13}C-NMR (101 MHz, MeOD-d$_4$)



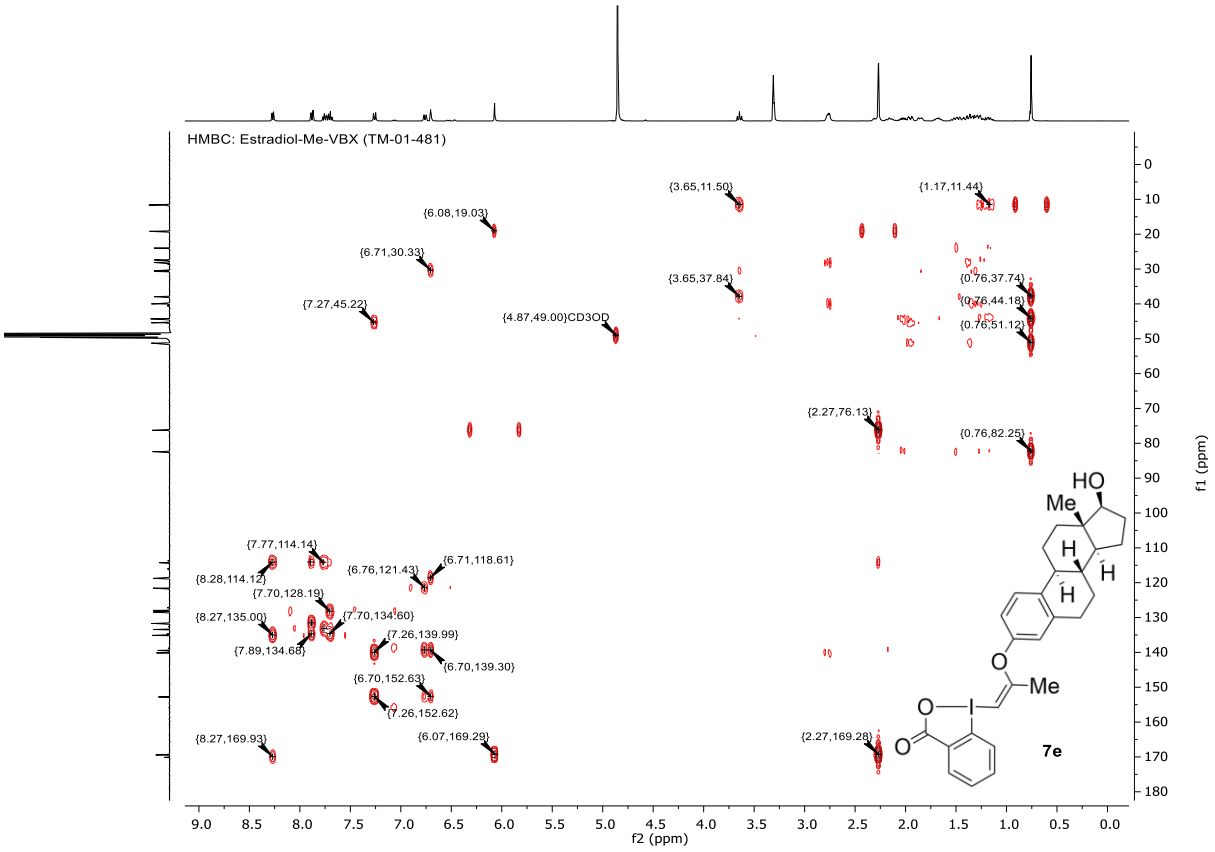
COSY NMR (MeOD-d4)



HSQC NMR (MeOD-d4)



HMBC NMR (MeOD-d_4)



(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-ß-estradiol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7f)

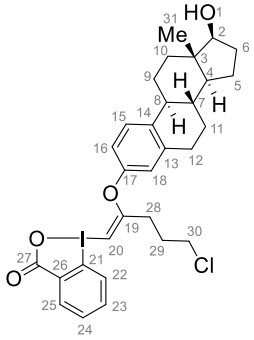
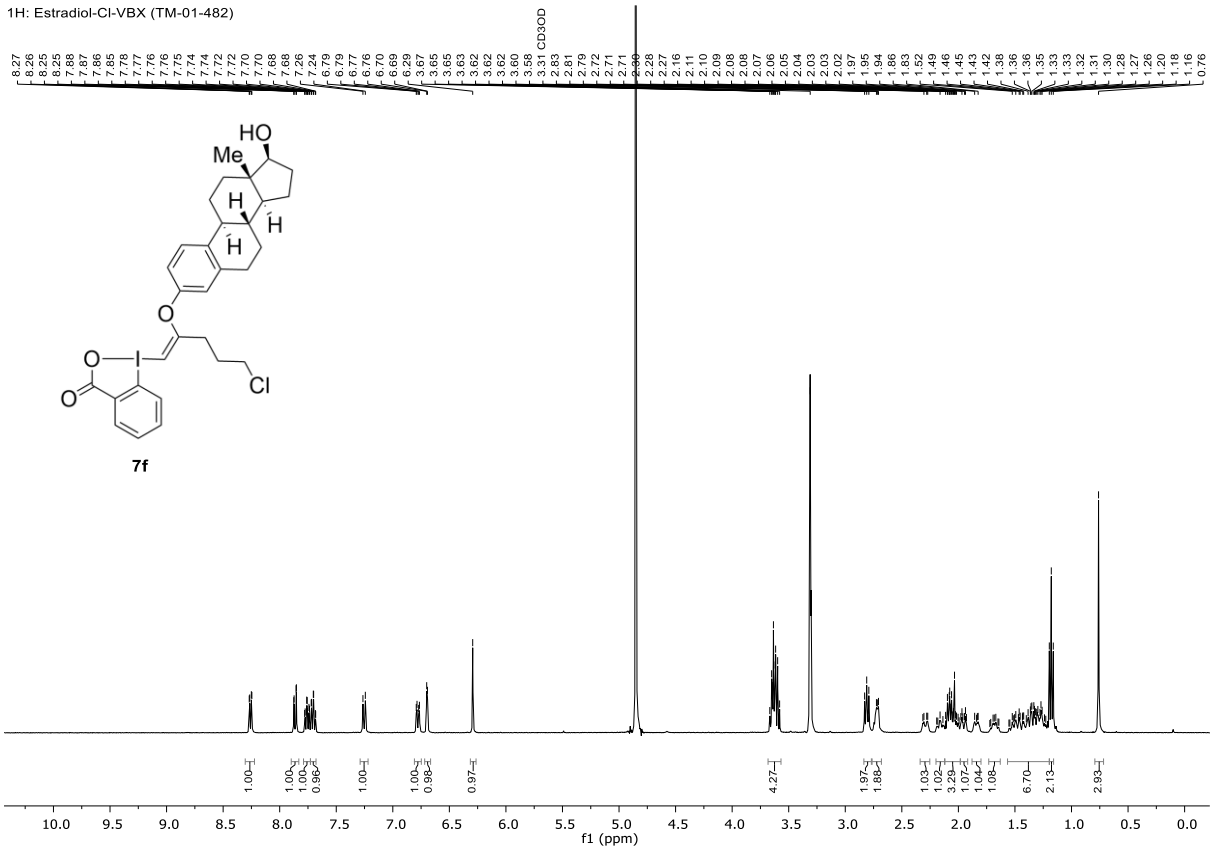


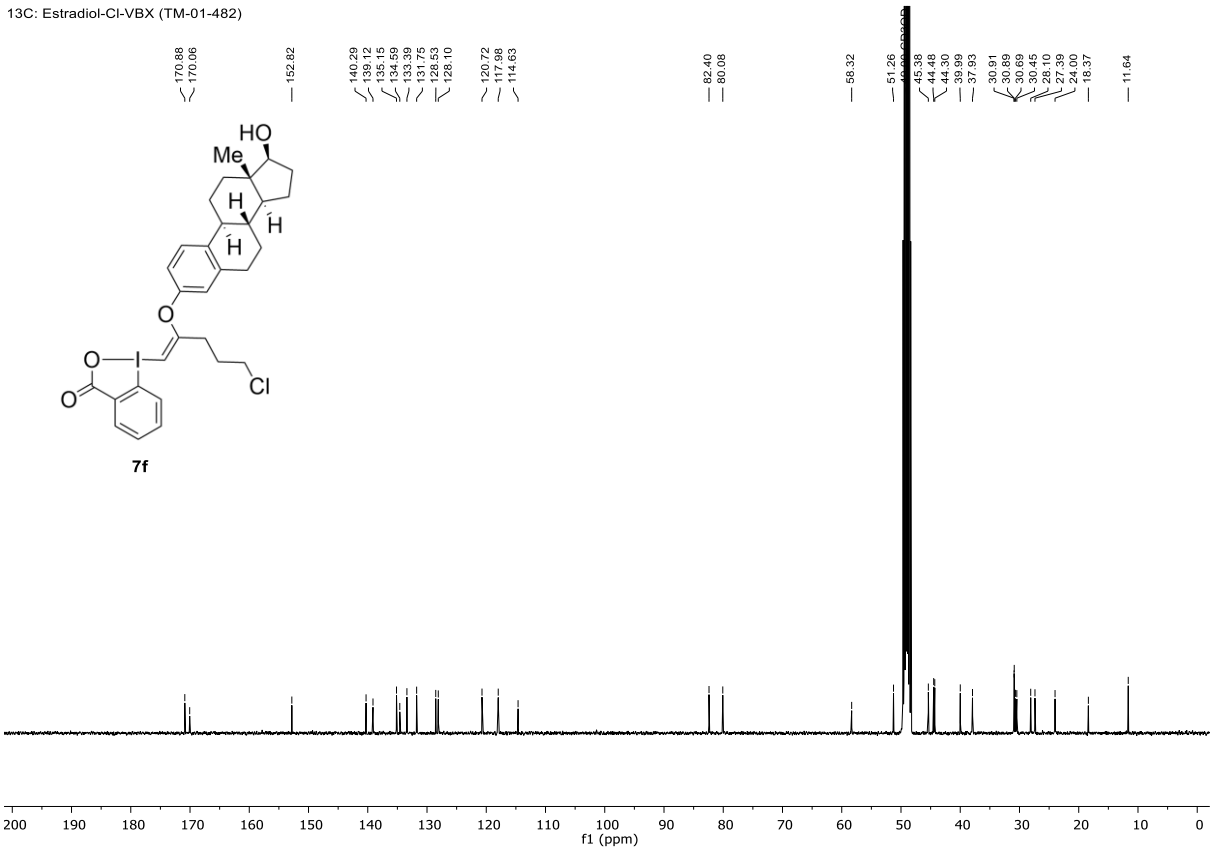
Table S25. Detailed NMR assignment of (*Z*)-1-(5-chloro-1-pent-1-en-2-yl)-2-ß-estradiol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7f**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	82.4	3.69-3.56 (m)		
3	58.3			
4	51.3	1.18 (t, 7.0 Hz)	5	
5	24.0	1.73-1.63 (m), 1.56-1.22 (m)	4, 6	
6	30.7	2.72 (d, 7.1 Hz)	5	
7	40.0	1.56-1.22 (m)		
8	45.4	2.16 (dt, 11.0, 4.0 Hz)		
9	27.4	2.29 (dd, 13.6, 3.7 Hz), 1.56-1.22 (m)	10	
10	37.9	1.95 (dt, 12.6, 3.6 Hz), 1.56-1.22 (m)	9	
11	28.1	1.88-1.81 (m), 1.56-1.22 (m)		
12	30.4	2.12-1.99 (m), 1.56-1.22 (m)		
13	140.3			
14	139.1			
15	128.1	7.25 (d, 8.5 Hz)	16	
16	118.0	6.78 (dd, 8.5, 2.7 Hz)	15	14, 18
17	152.8			
18	120.7	6.70 (d, 2.7 Hz)		12, 14, 16
19	170.9			
20	80.1	6.29 (s)		19, 28
21	114.6			
22	133.4	8.26 (dd, 7.4, 1.9 Hz)	23	21, 26, 27
23	131.8	7.70 (td, 7.3, 1.2 Hz)	22	21, 24, 25
24	135.1	7.76 (td, 8.1, 1.9 Hz)		21, 22
25	128.5	7.86 (dd, 8.1, 1.2 Hz)		21, 23, 24
26	134.6			
27	170.1			
28	30.9	2.85-2.77 (m)	29	19, 20, 29, 30
29	30.9	2.12-1.99 (m)	28, 30	19, 28, 30
30	44.5	3.69-3.56 (m)	29	28
31	11.6	0.76 (s)		2, 4, 10

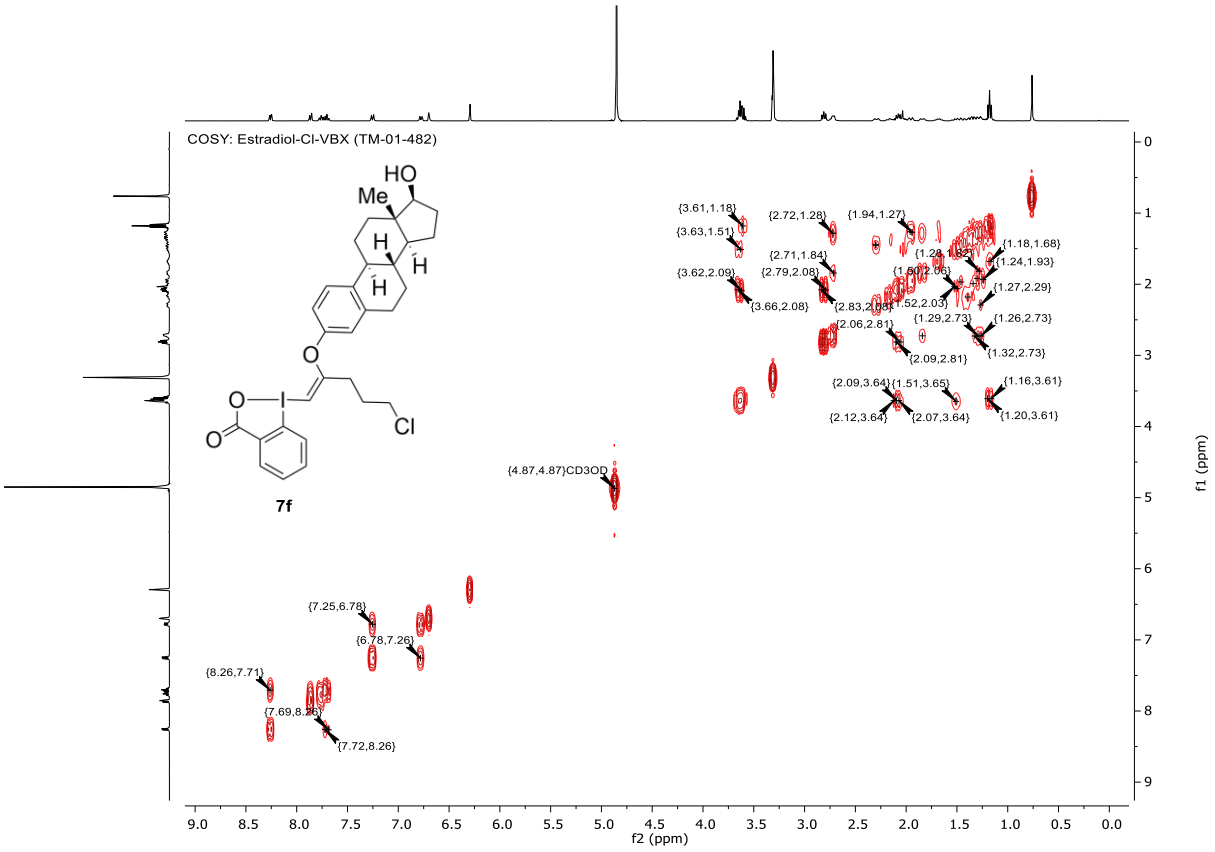
^{1}H-NMR (400 MHz, MeOD-d$_4$)



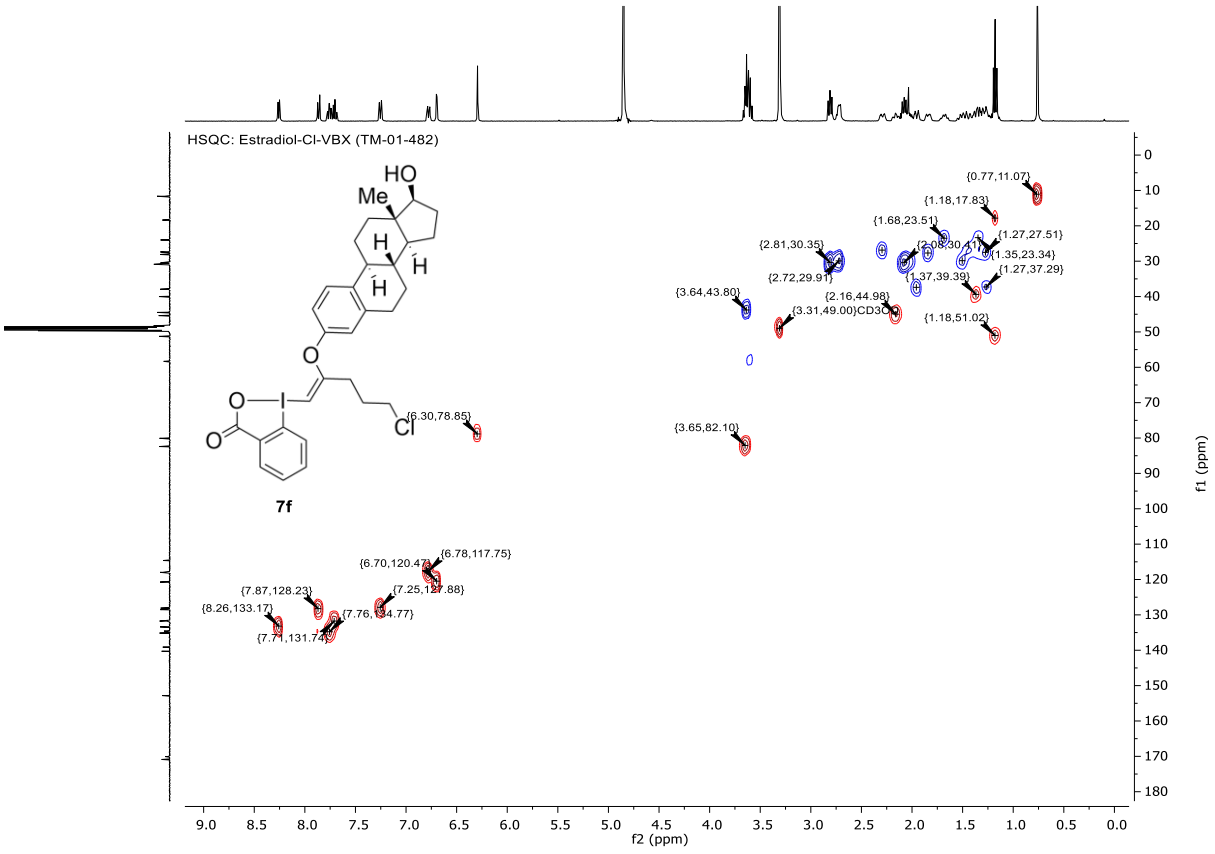
^{13}C-NMR (101 MHz, MeOD-d$_4$)



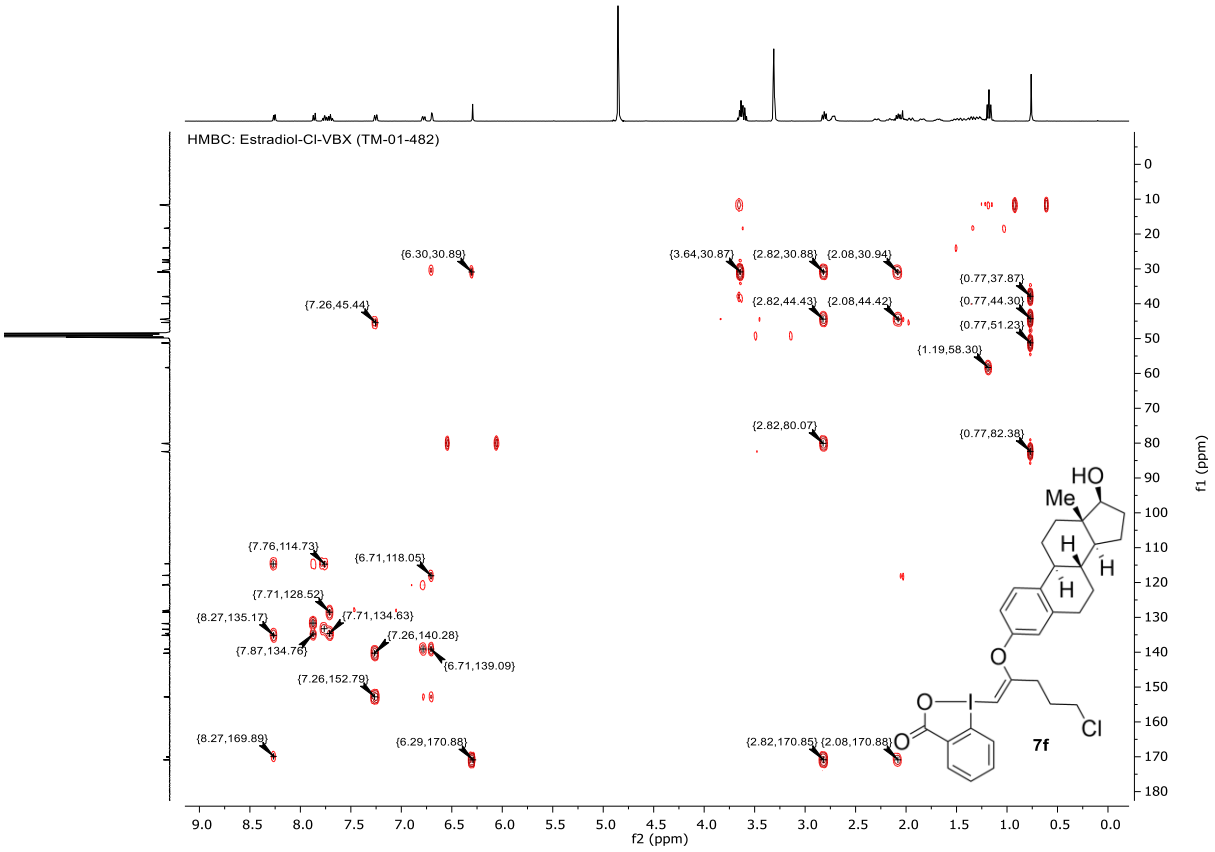
COSY NMR (MeOD-d4)



HSQC NMR (MeOD-d4)



HMBC NMR (MeOD-d_4)



(*Z*)-1-(Prop-1-en-2-yl)-2-valsartan-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7g)

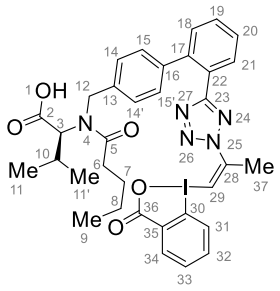
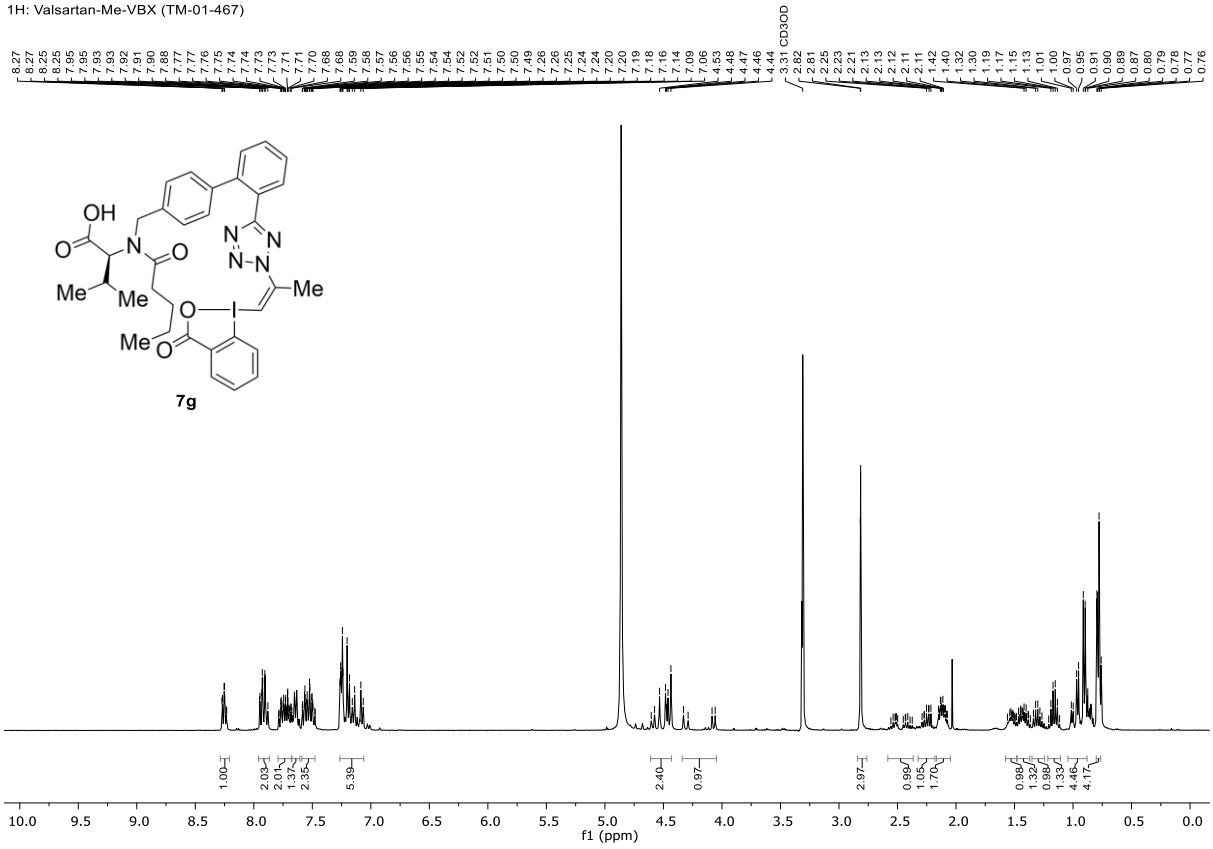


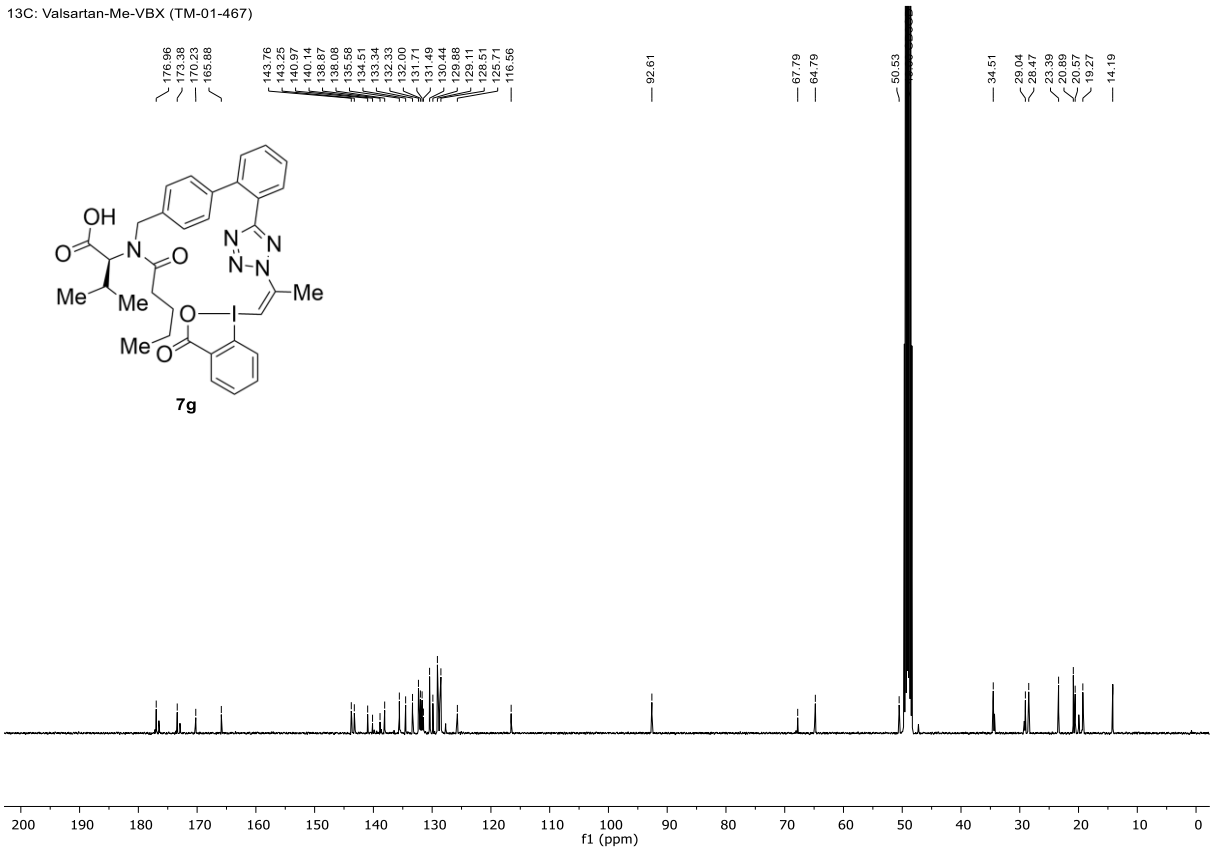
Table S26. Detailed NMR assignment of (*Z*)-1-(prop-1-en-2-yl)-2-valsartan-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7g**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	173.4			
3	64.8	4.35-4.03 (m)	10	2
4	/			
5	177.0			
6	34.5	2.32-2.18 (m), 2.17-2.06 (m)	7	5, 7, 8
7	28.5	1.57-1.48 (m), 1.48-1.36 (m)	6	
8	23.4	1.34-1.25 (m), 1.16 (h, 7.5 Hz)	9	6, 7, 9
9	14.2	1.04-0.88 (m), 0.81-0.75 (m)	8	7
10	29.0	2.17-2.06 (m)	3, 11/11’	
11/11’	20.6	1.04-0.88 (m), 0.81-0.75 (m)	10	3, 10
12	50.5	4.61-4.41 (m)		15/15’
13	138.1			
14/14’	130.4	7.27-7.06 (m)		16
15/15’	128.5	7.27-7.06 (m)		12, 13
16	141.0			
17	135.6			
18	125.7	7.96-7.87 (m)	19, 20	23
19	131.7	7.59-7.47 (m)	18, 21	18, 22
20	129.9	7.59-7.47 (m)	18, 21	18, 22
21	129.1	7.96-7.87 (m)	19, 20	
22	140.1			
23	165.9			
24	/			
25	/			
26	/			
27	/			
28	143.8			
29	92.6	7.27-7.06 (m)	37	
30	116.6			
31	133.3	8.25 (td, 7.2, 1.9 Hz)	32, 34	30, 32, 36
32	134.5	7.79-7.68 (m)	31	30, 32
33	132.0	7.67-7.60 (m)		34
34	132.3	7.79-7.68 (m)	31	30, 32
35	131.5			
36	170.2			
37	20.9	2.82 (d, 1.2 Hz)	29	28, 29

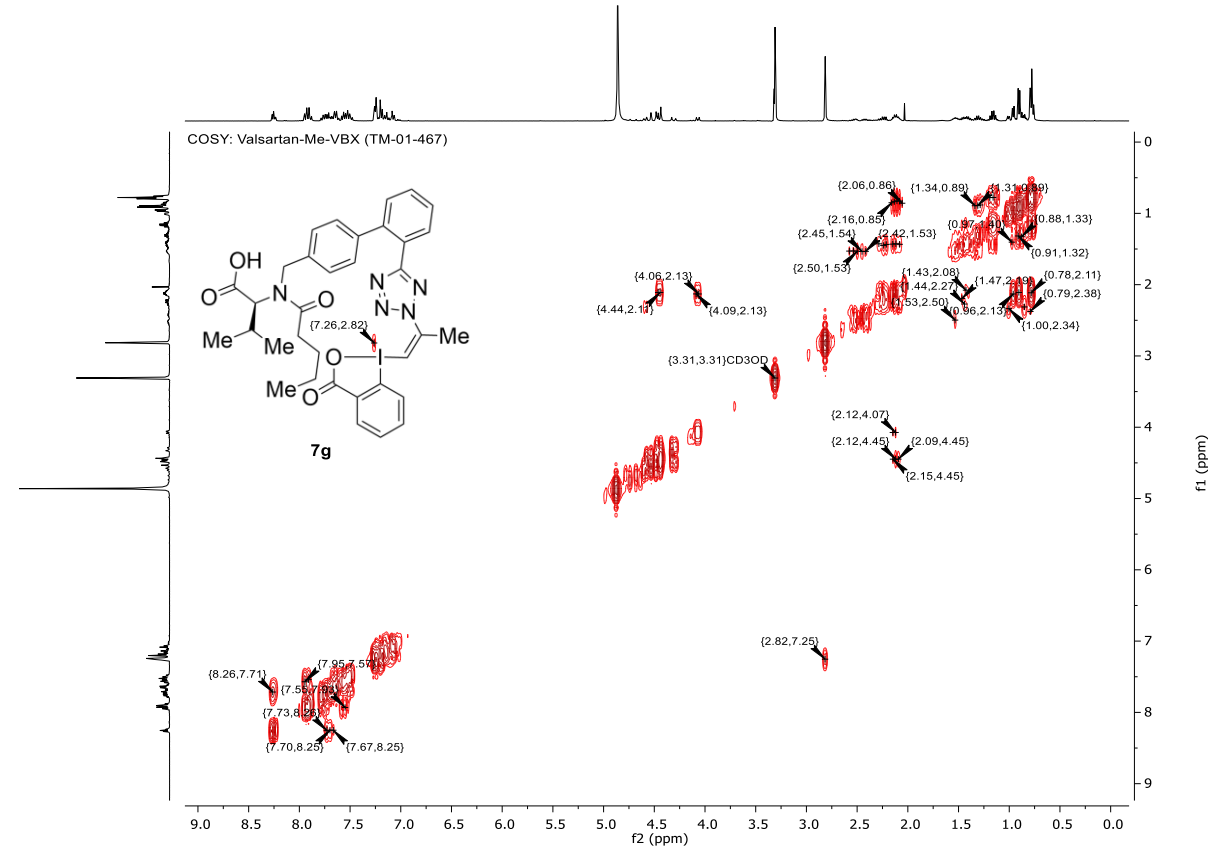
^{1}H-NMR (400 MHz, MeOD-d$_4$)



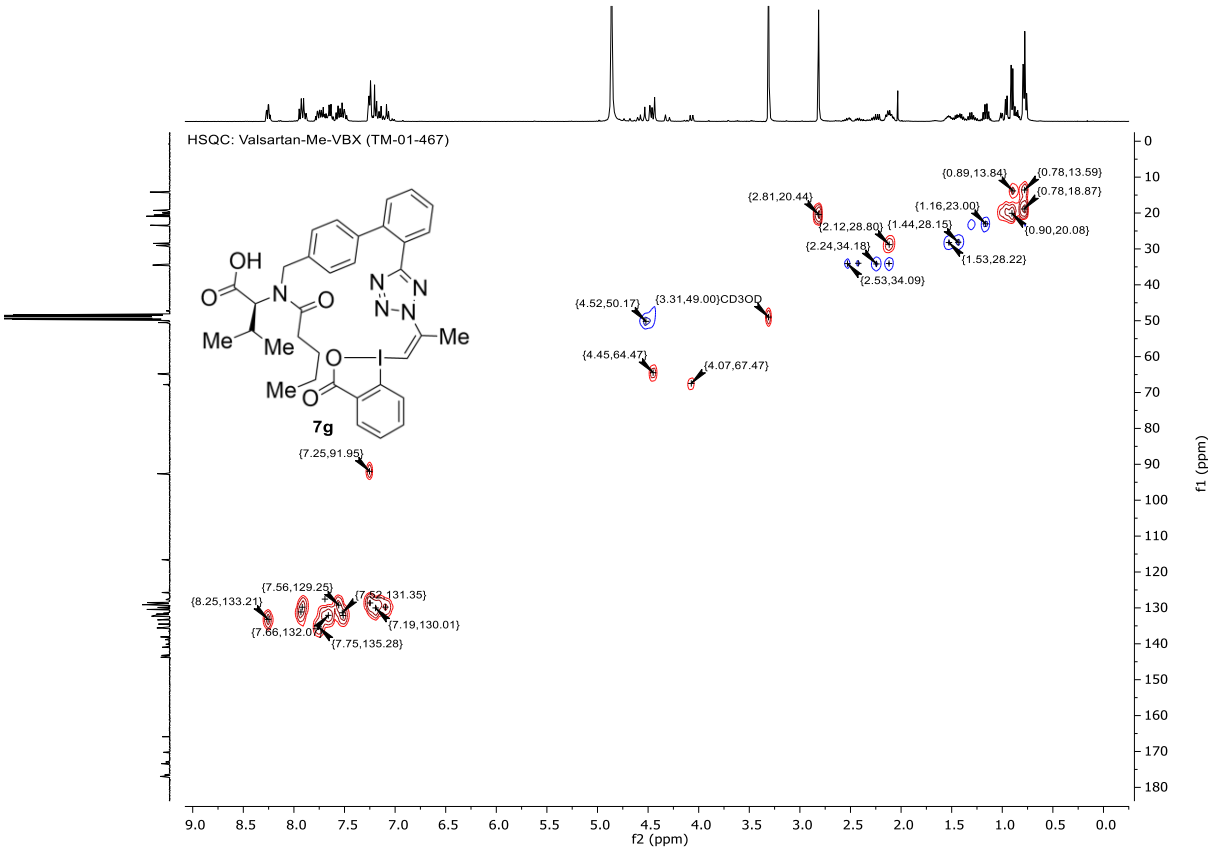
^{13}C-NMR (101 MHz, MeOD-d$_4$)



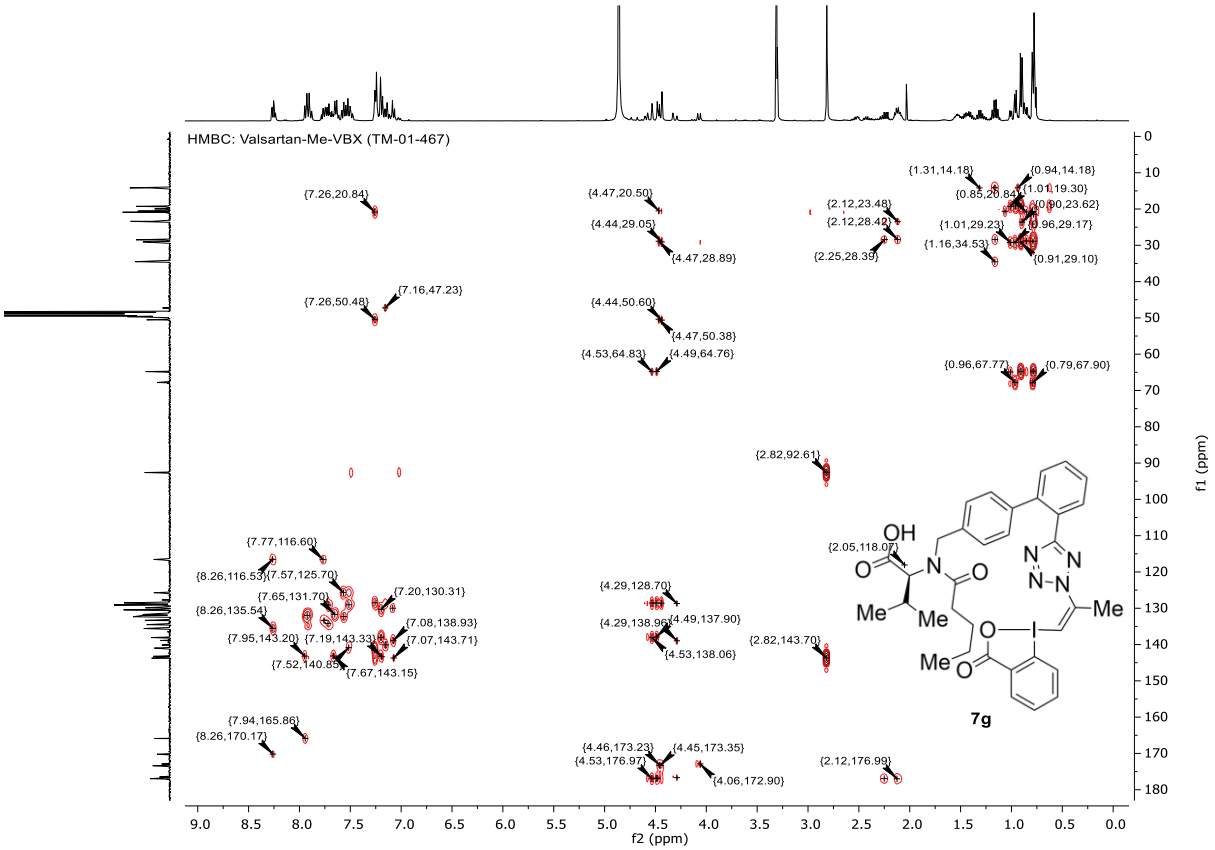
COSY NMR (MeOD-d_4)



HSQC NMR (MeOD-d_4)



HMBC NMR (MeOD-d_4)



(*Z*)-(5-Chloro-1-pent-1-en-2-yl)-2-valsartan-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (7h)

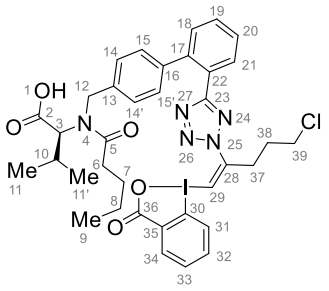
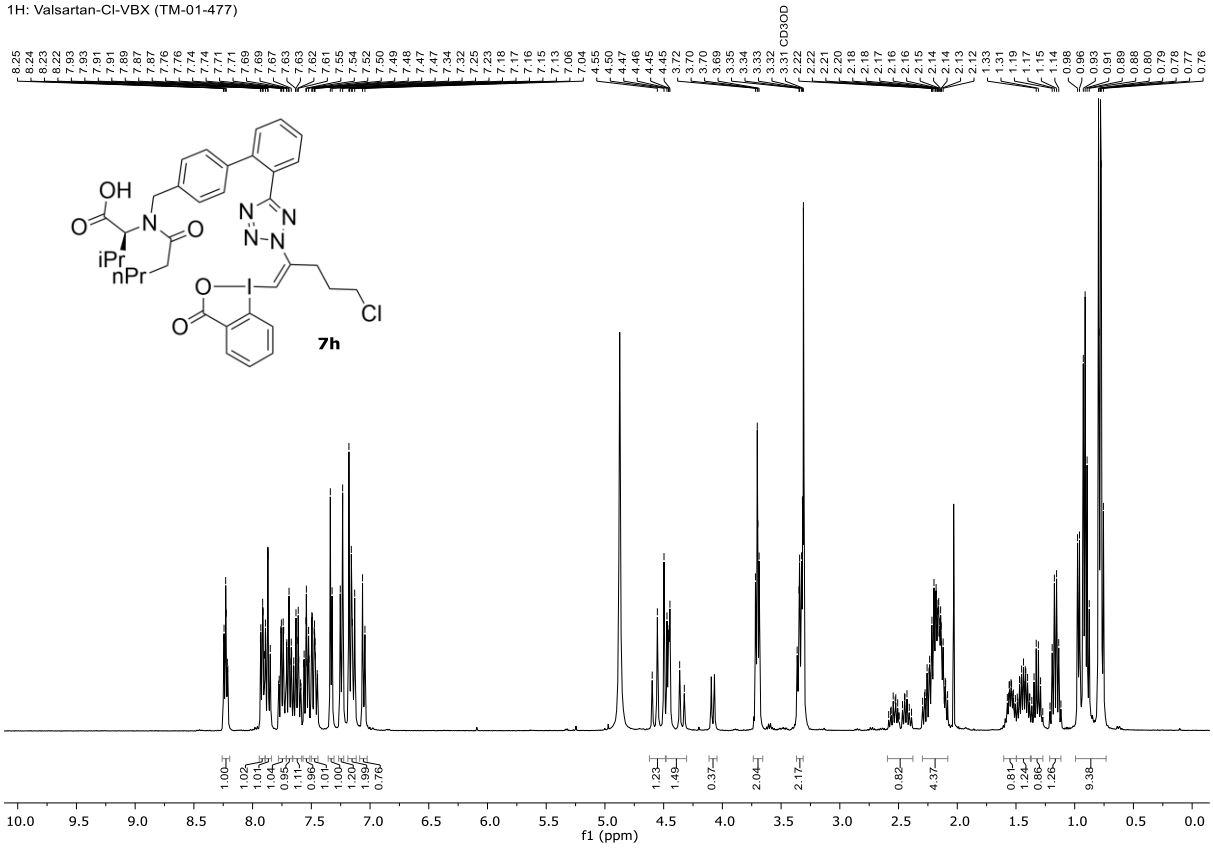


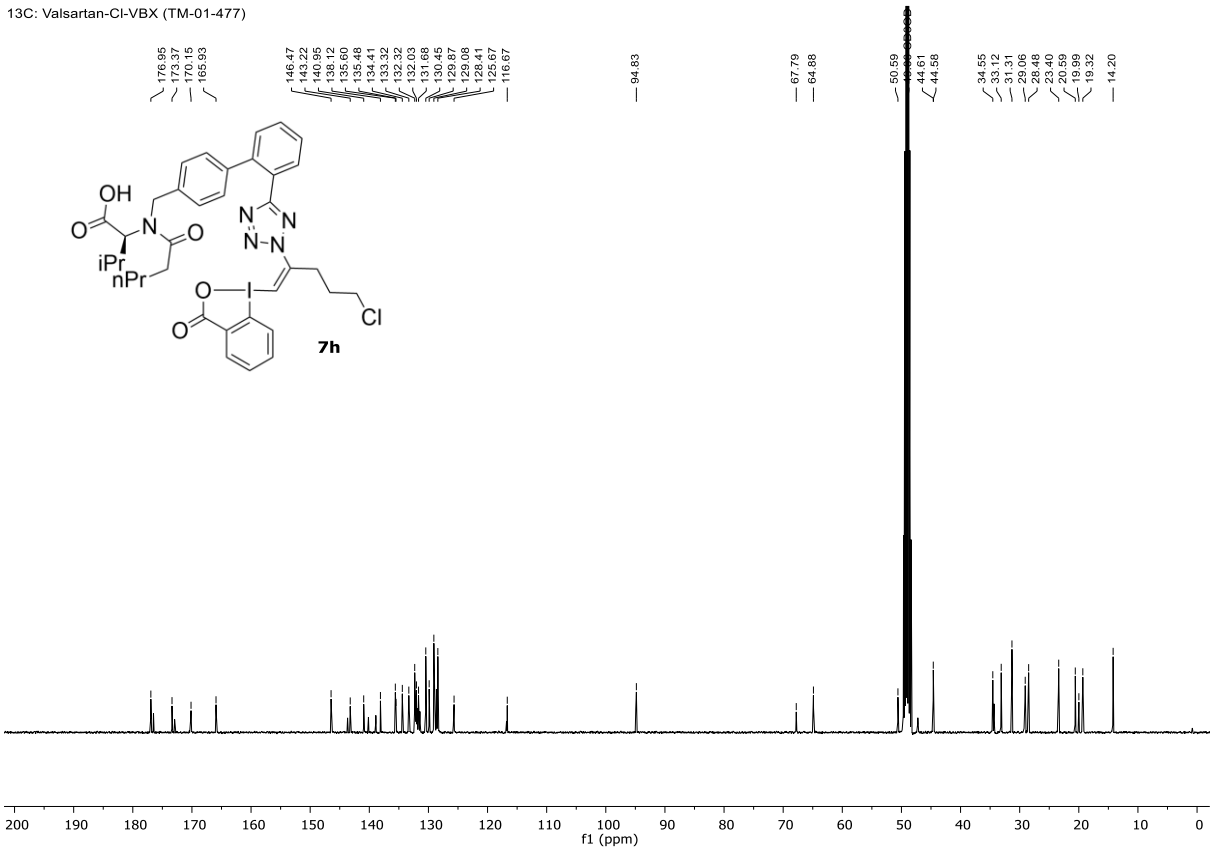
Table S27. Detailed NMR assignment of (*Z*)-1-(5-chloro-1-pent-1-en-2-yl)-2-valsartan-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**7h**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	173.4			
3	64.9	4.48-4.31 (m)	10	2
4	/			
5	176.9			
6	34.5	2.60-2.37 (m), 2.31-2.06 (m)	7	5, 7, 8
7	29.1	1.54 (dtd, 8.4, 6.5, 4.4 Hz), 1.49-1.38 (m)	6	
8	23.4	1.32 (h, 7.5 Hz), 1.16 (h, 7.4 Hz)	9	6, 7, 9
9	14.2	1.00-0.73 (m)	8	7
10	28.5	2.31-2.06 (m)	3, 11/11’	
11/11’	20.6	1.00-0.73 (m)	10	3, 10
12	50.6	4.62-4.49 (m), 4.48-4.31 (m)		15/15’
13	138.1			
14/14’	130.4	7.19-7.12 (m)		16
15/15’	128.4	7.57-7.51 (m) 7.05 (d, 8.2 Hz)		12, 13
16	143.2			
17	135.5			
18	125.7	7.47 (ddd, 10.4, 7.6, 1.3 Hz)	19, 20	23
19	131.7	7.96-7.87	18, 21	18, 22
20	129.9	7.89-7.84 (m)	18, 21	18, 22
21	129.1	7.24 (d, 8.0 Hz)	19, 20	
22	140.9			
23	165.9			
24	/			
25	/			
26	/			
27	/			
28	146.5			
29	94.8	7.33 (d, 6.1 Hz)	37	
30	116.7			
31	134.4	8.23 (ddd, 7.4, 5.5, 1.8 Hz)	32, 34	30, 32, 36
32	135.6	7.76 (td, 7.7, 1.8 Hz)	31	30, 32
33	132.0	7.62 (dtd, 9.3, 7.5, 1.4 Hz)		34
34	132.3	7.71-7.66 (m)	31	30, 32
35	133.3			
36	170.2			
37	33.1	3.37-3.32 (m)	38	28, 29, 38, 39
38	31.3	2.31-2.06 (m)	37, 39	28, 39
39	44.6	3.70 (t, 6.2 Hz)	38	37

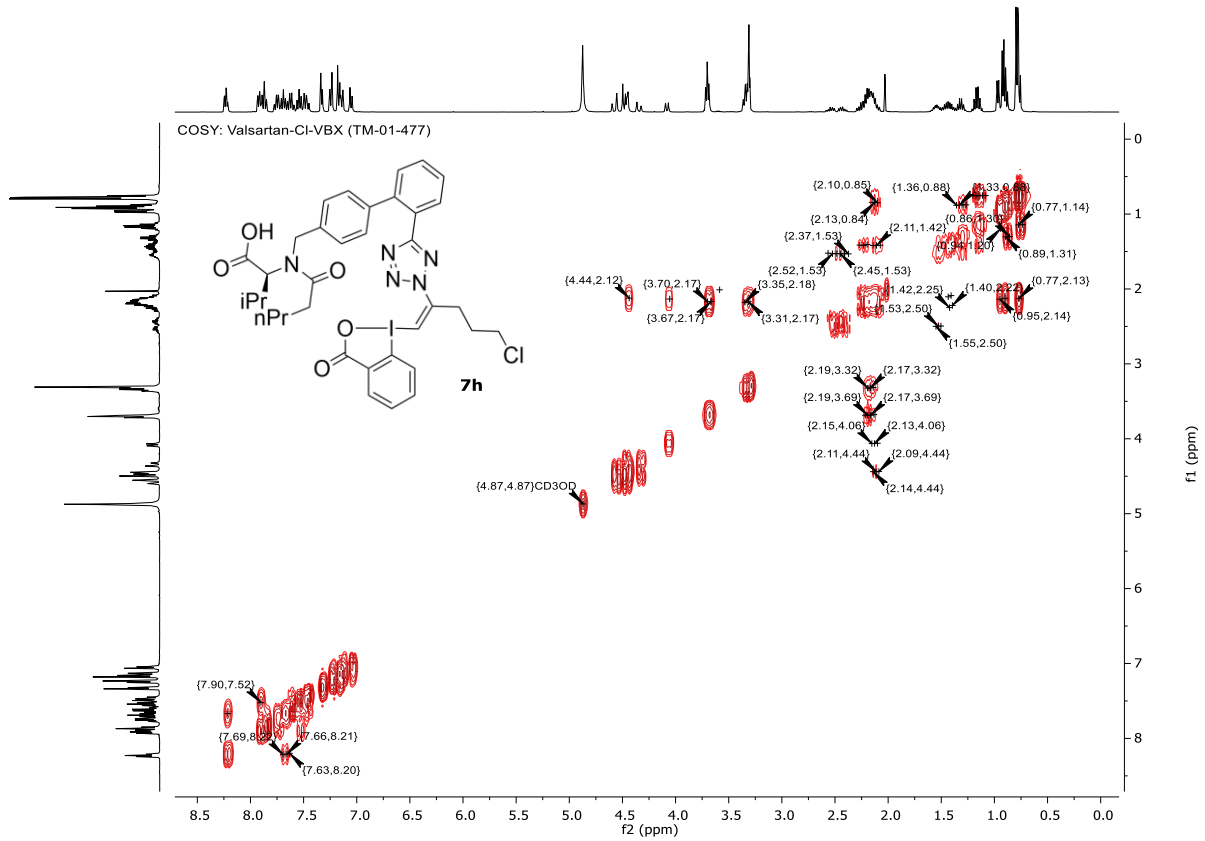
^{1}H-NMR (400 MHz, MeOD-d$_4$)



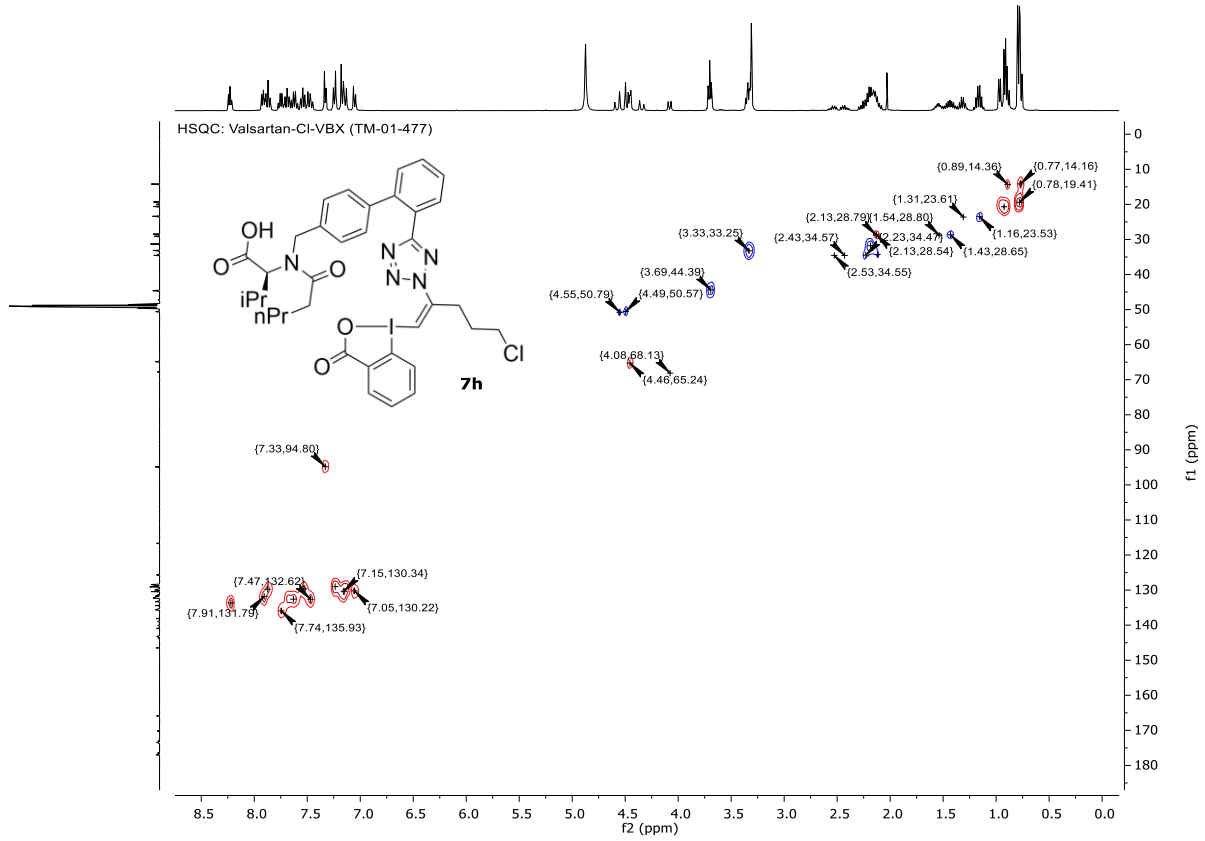
^{13}C-NMR (101 MHz, MeOD-d$_4$)



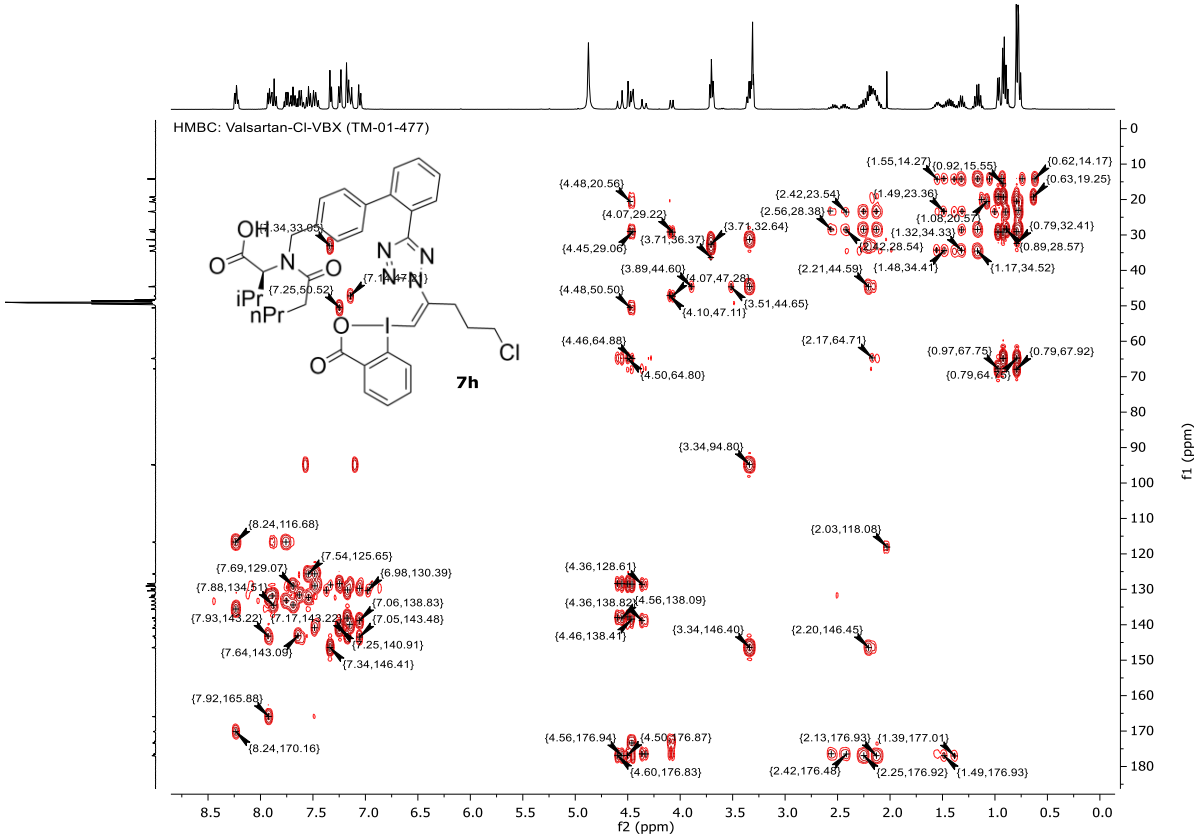
COSY NMR (MeOD-d_4)



HSQC NMR (MeOD-d_4)

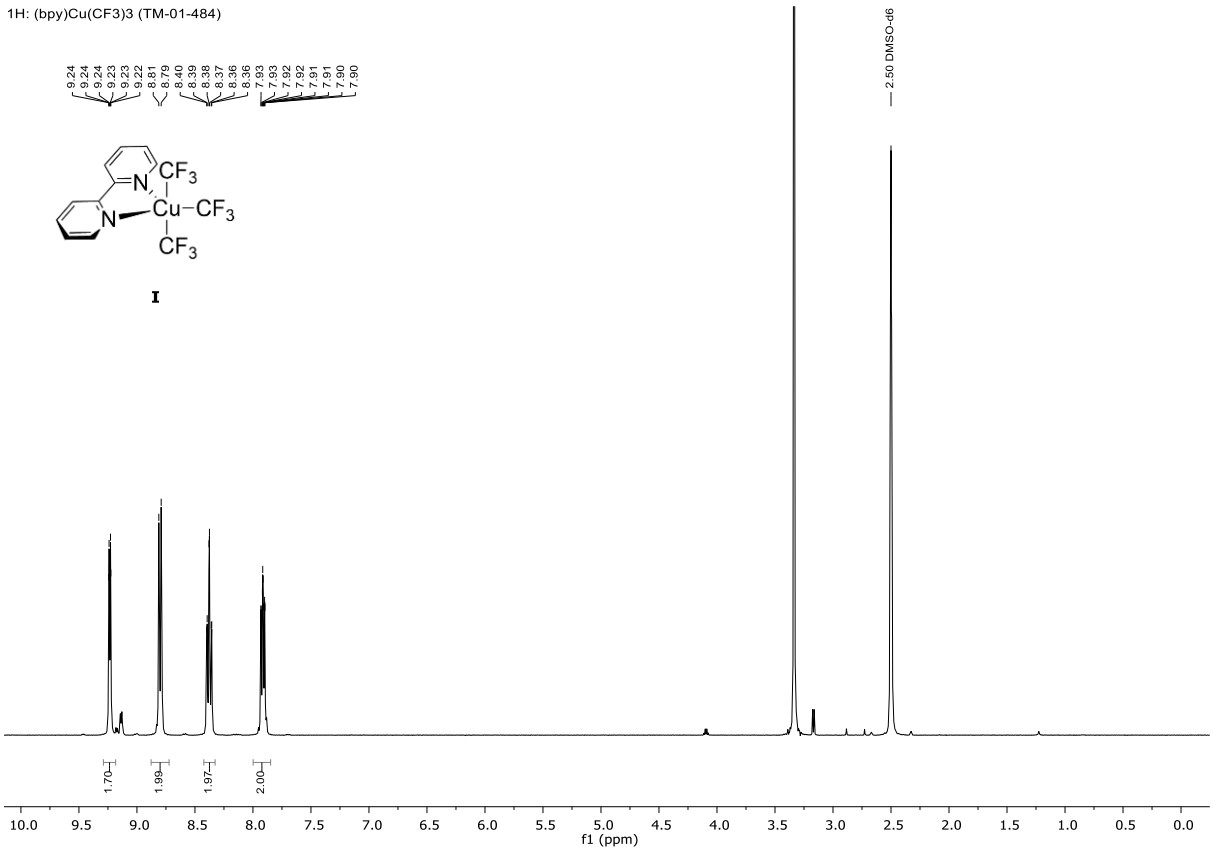


HMBC NMR (MeOD-d_4)

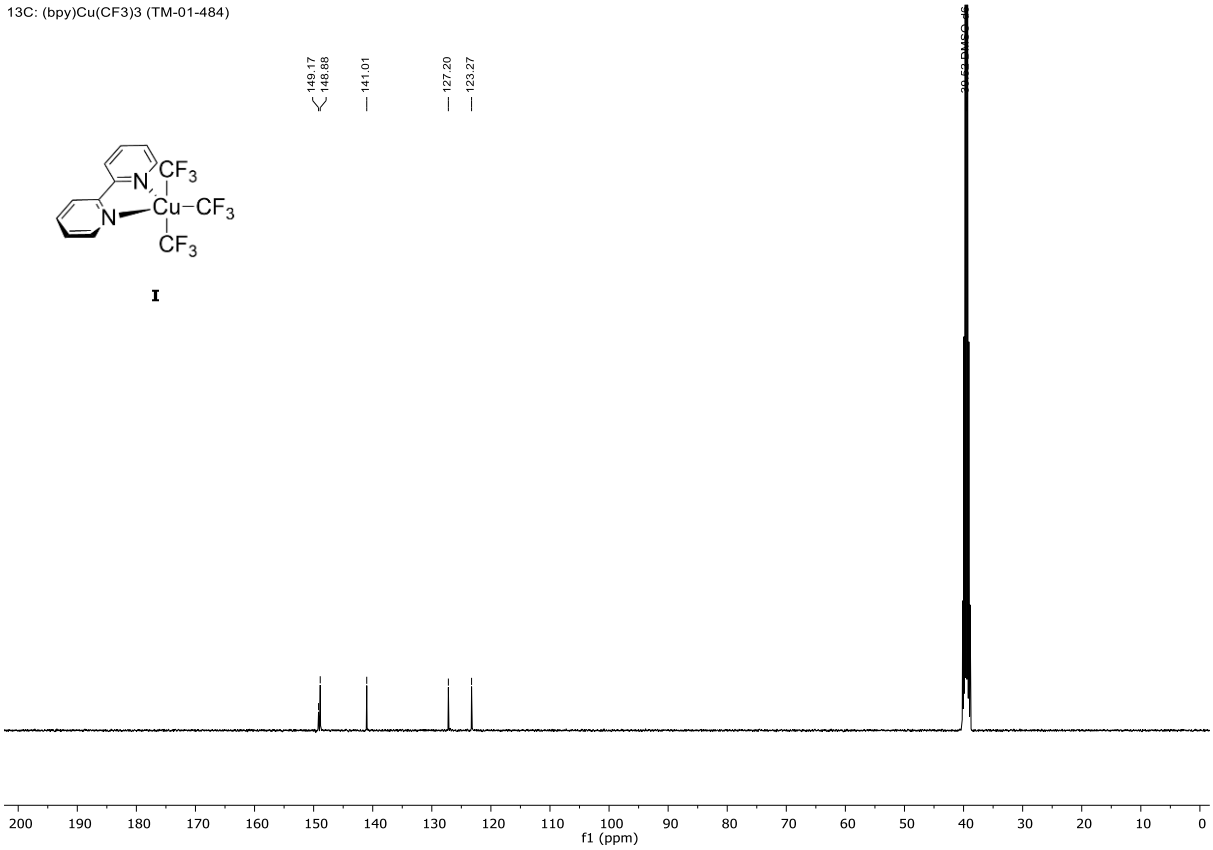


(bpy)Cu(CF_3)$_3$ (I)

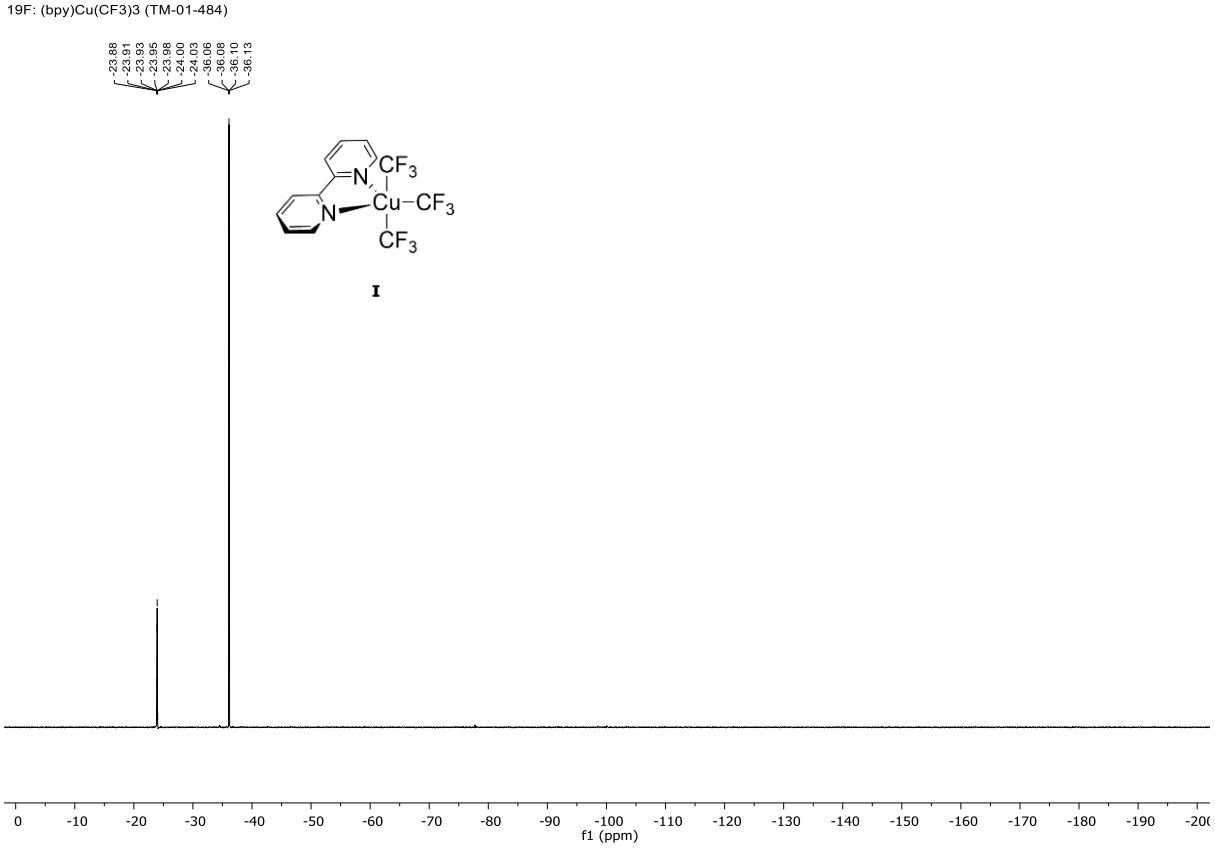
^{1}H-NMR (400 MHz, DMSO-d$_6$)



^{13}C-NMR (101 MHz, DMSO-d$_6$)

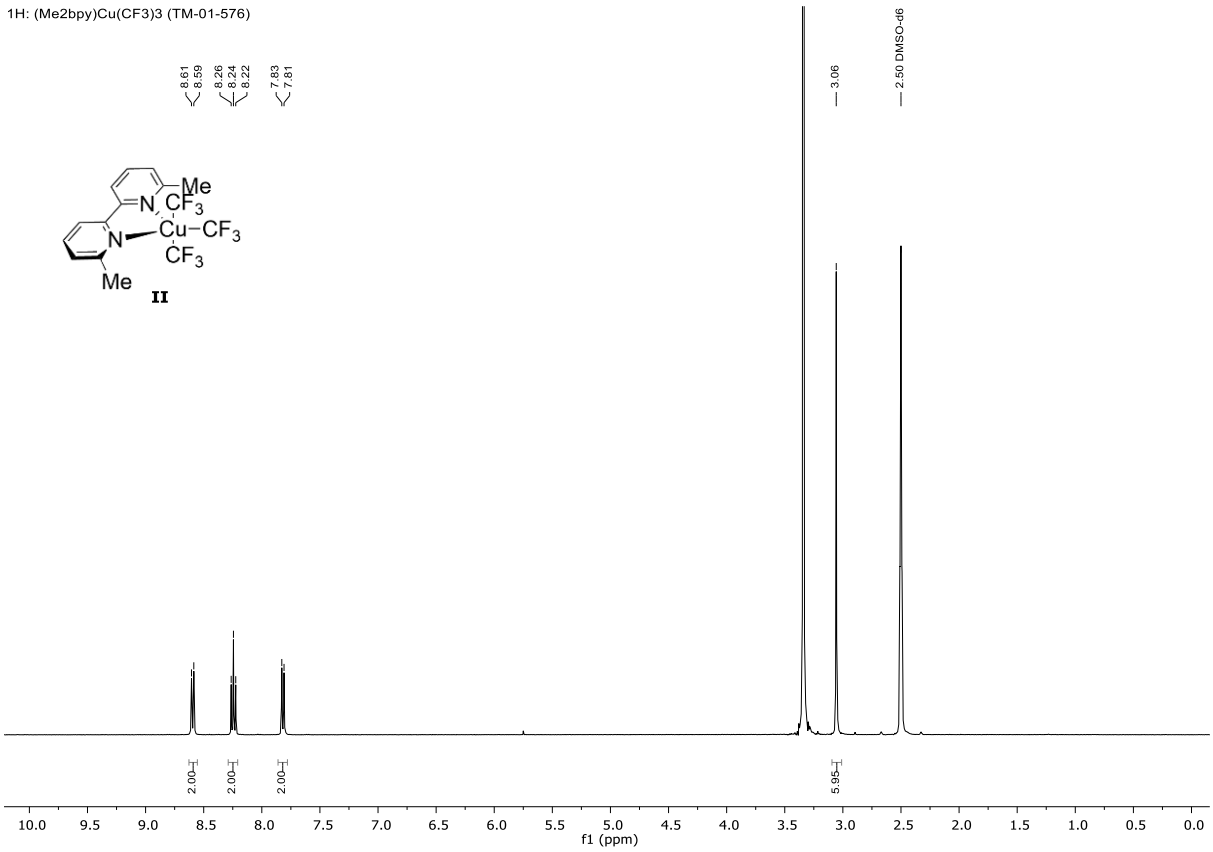


^{19}F-NMR (376 MHz, DMSO-d_6)

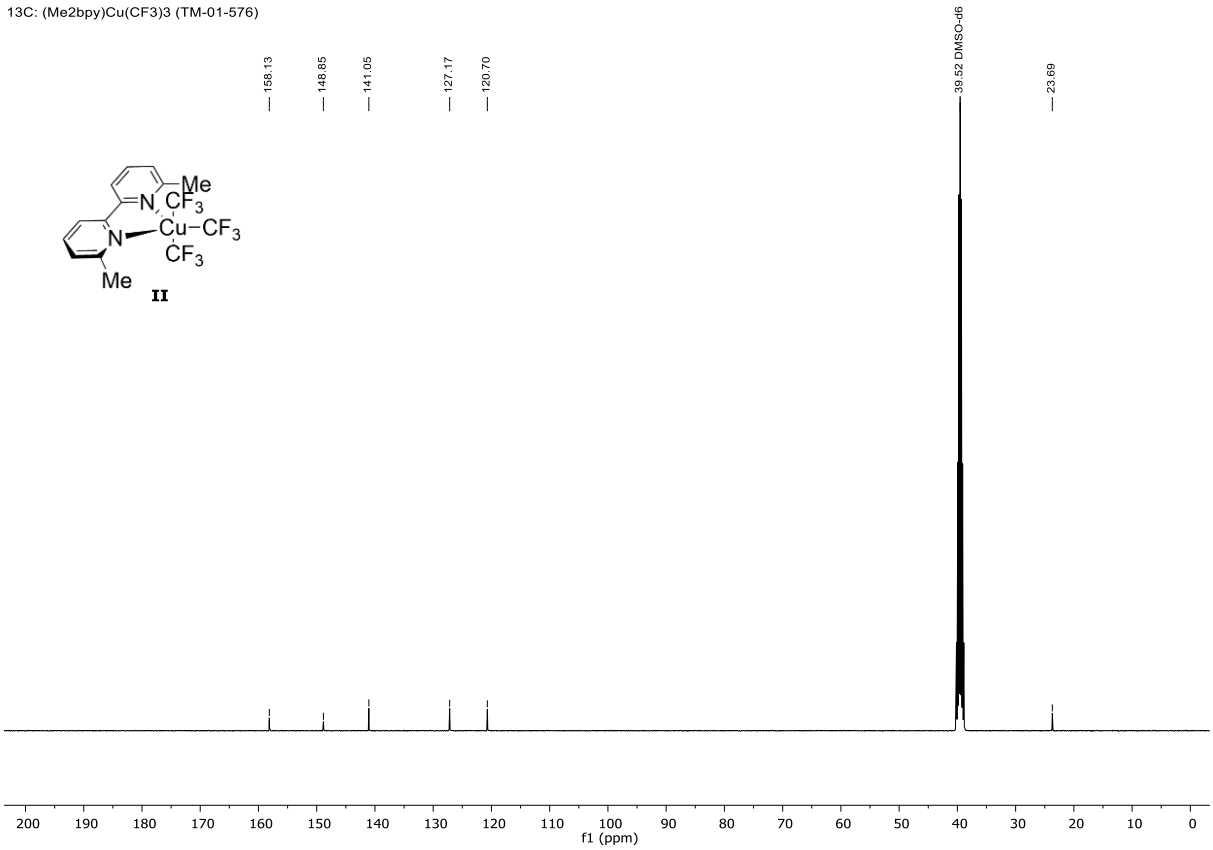


$(Me_2bpy)Cu(CF_3)_3$ (II)

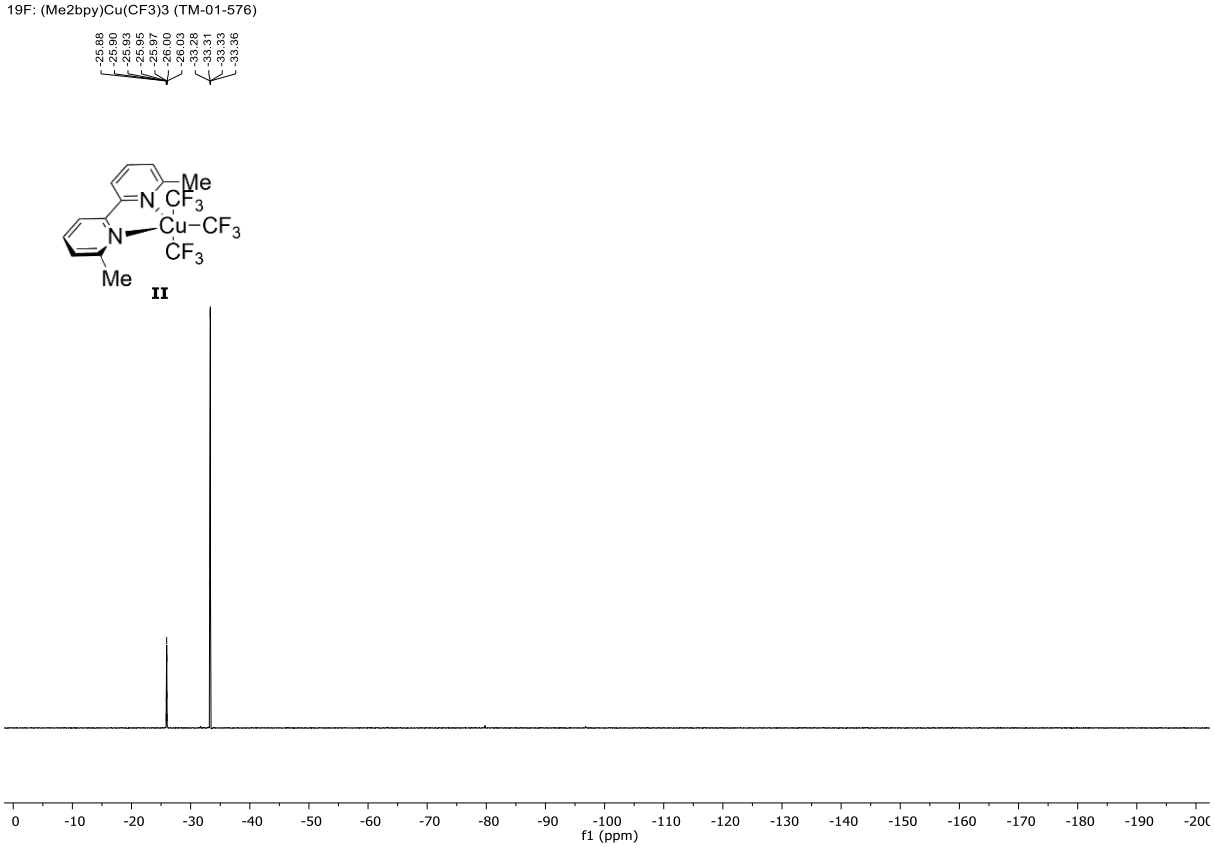
^{1}H-NMR (400 MHz, DMSO-d_6)



^{13}C-NMR (101 MHz, DMSO-d_6)

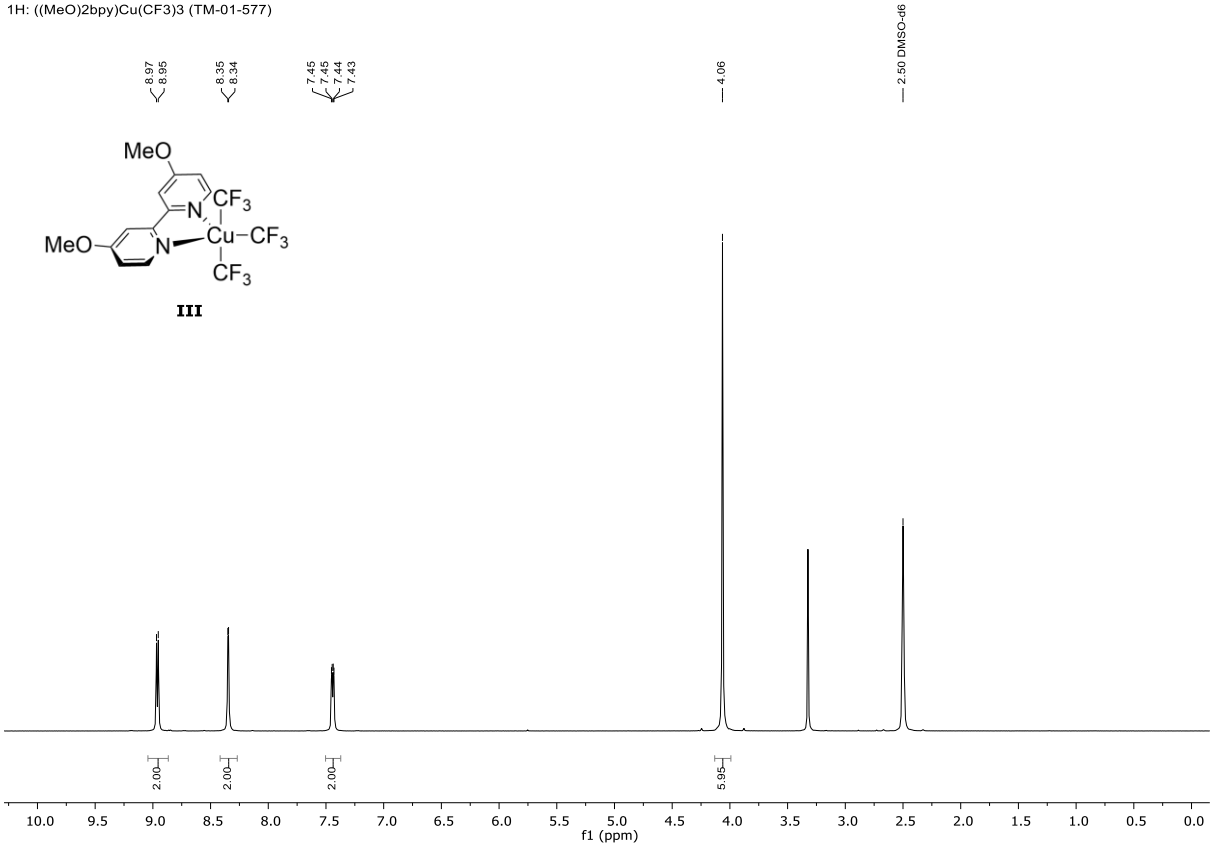


^{19}F-NMR (376 MHz, DMSO-d_6)

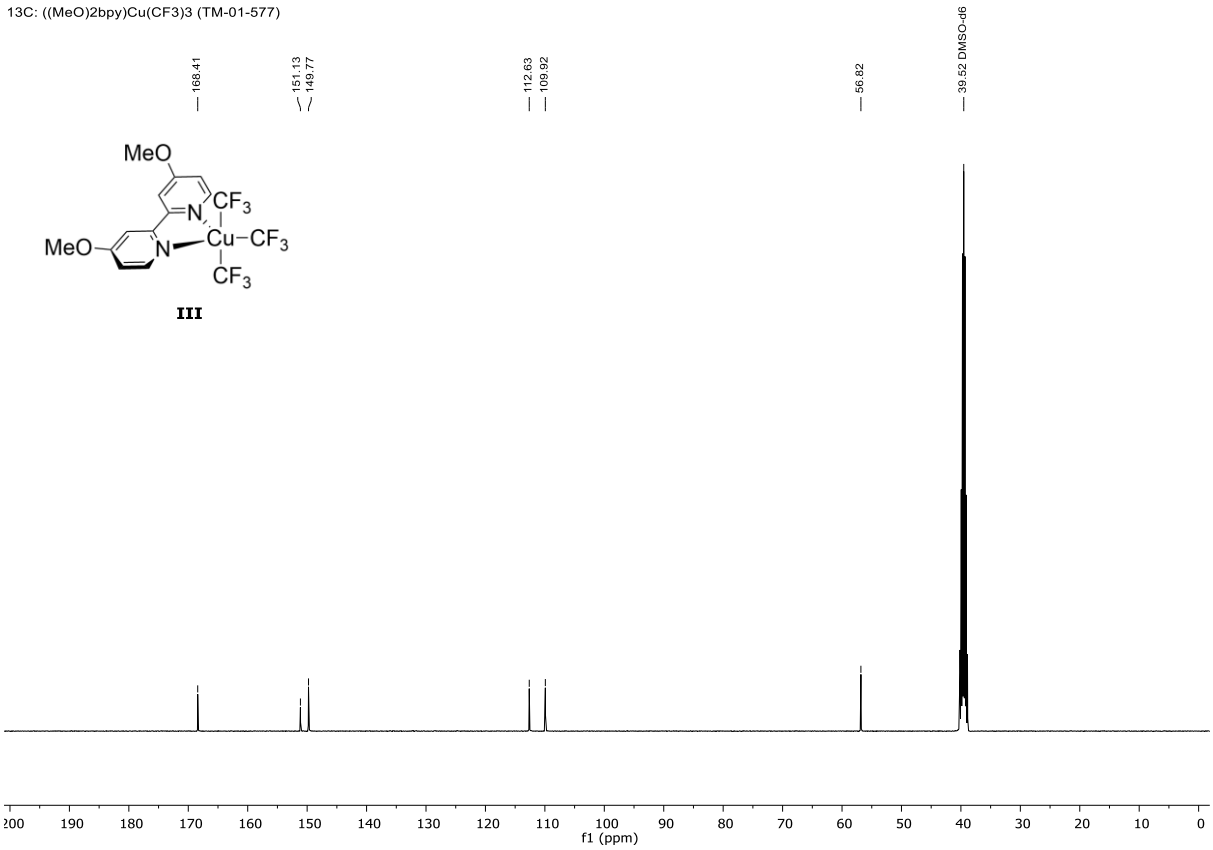


[(MeO)$_2$bpy]Cu(CF$_3$)$_3$ (III)

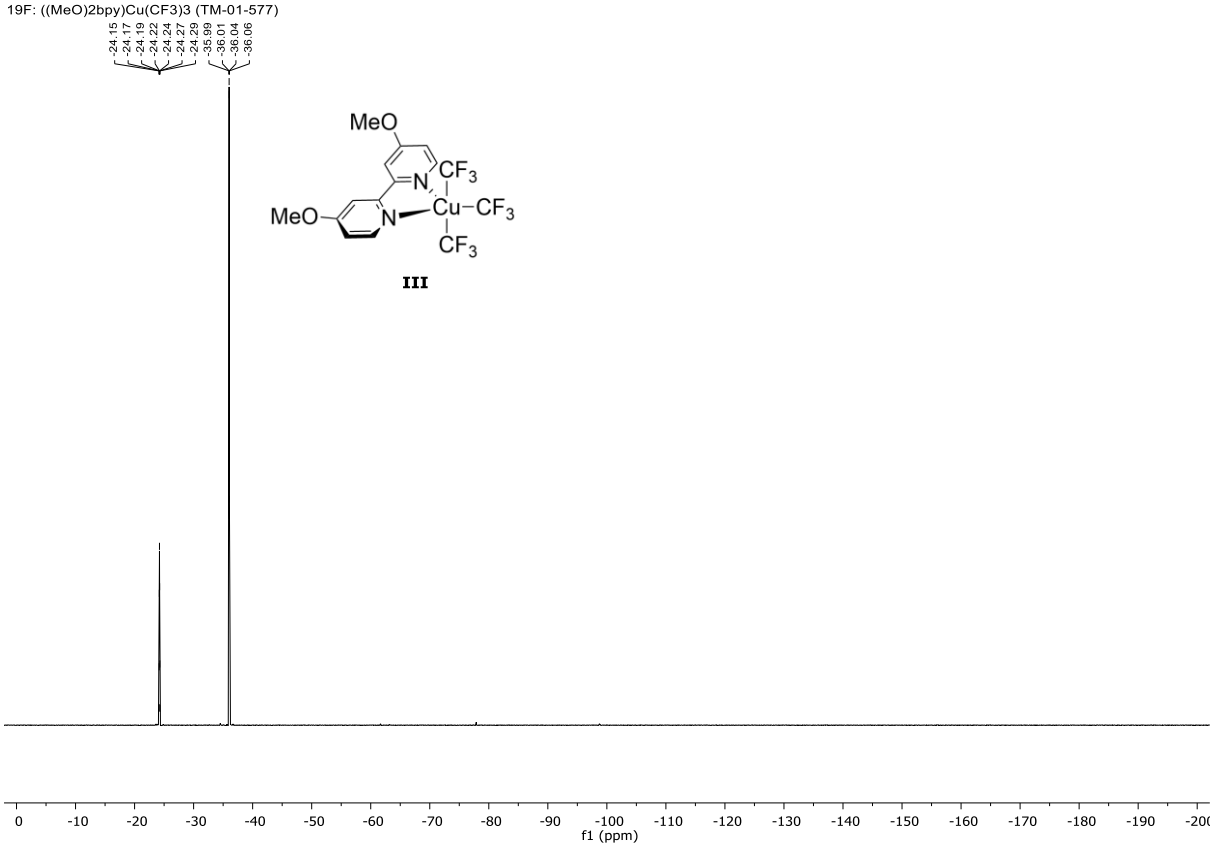
^{1}H-NMR (400 MHz, DMSO-d$_6$)



^{13}C-NMR (101 MHz, DMSO-d$_6$)



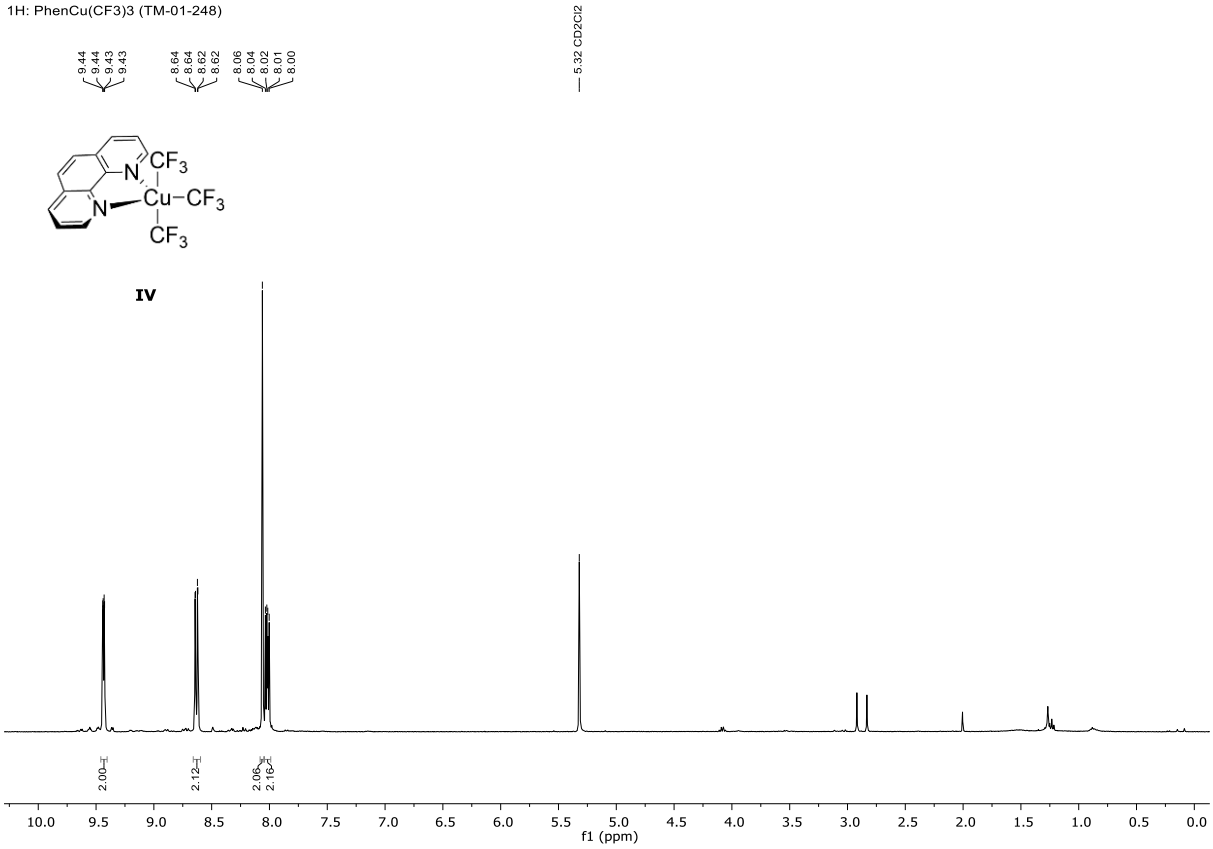
^{19}F-NMR (376 MHz, DMSO-d_6)



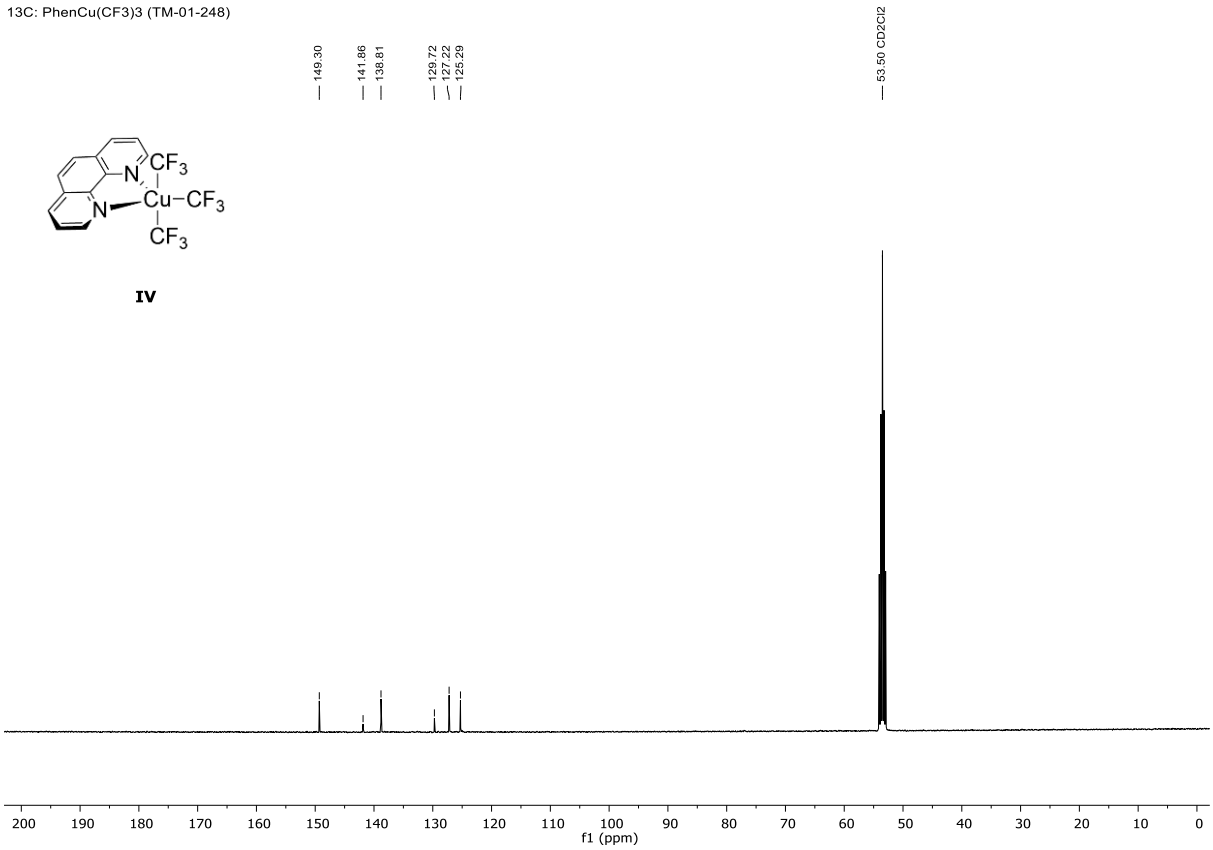
III

(phen)Cu(CF_3)$_3$ (IV)

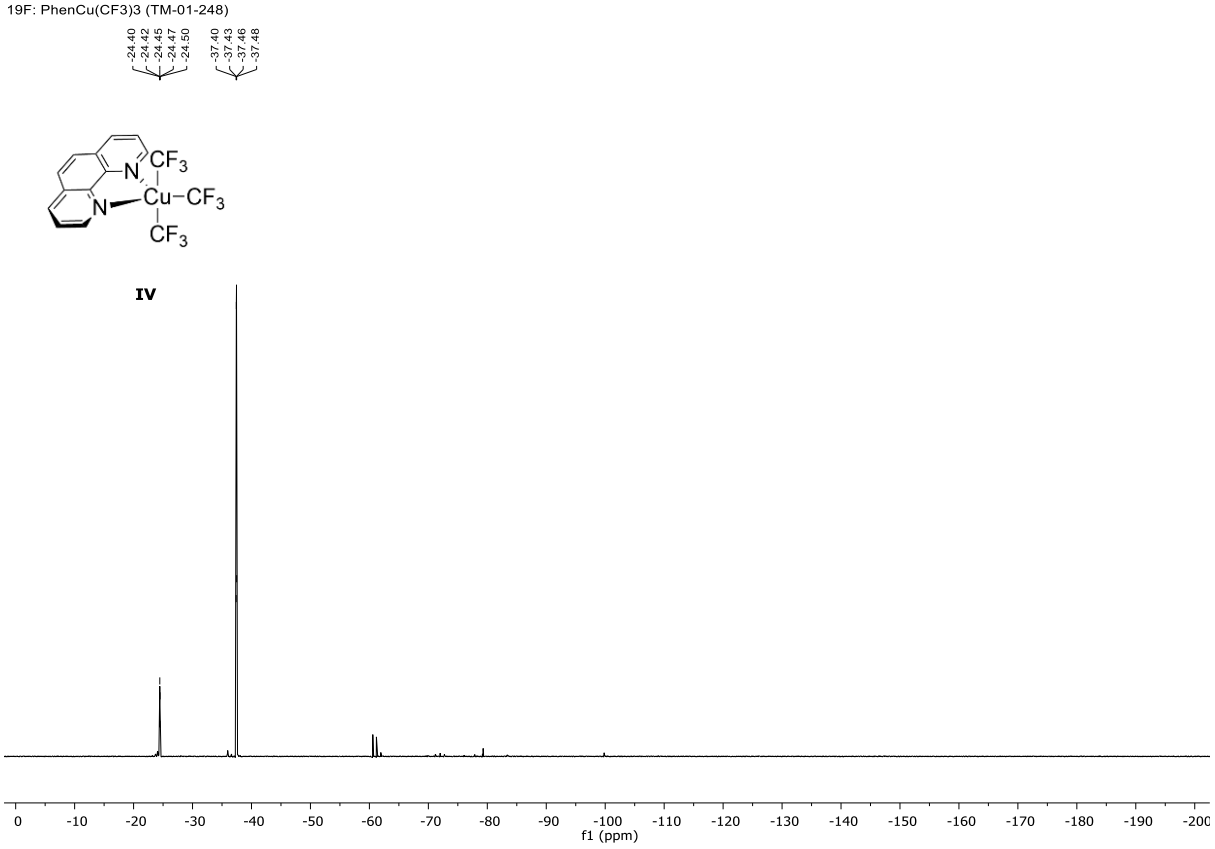
^{1}H-NMR (400 MHz, DCM-d_2)



^{13}C-NMR (101 MHz, DCM-d_2)

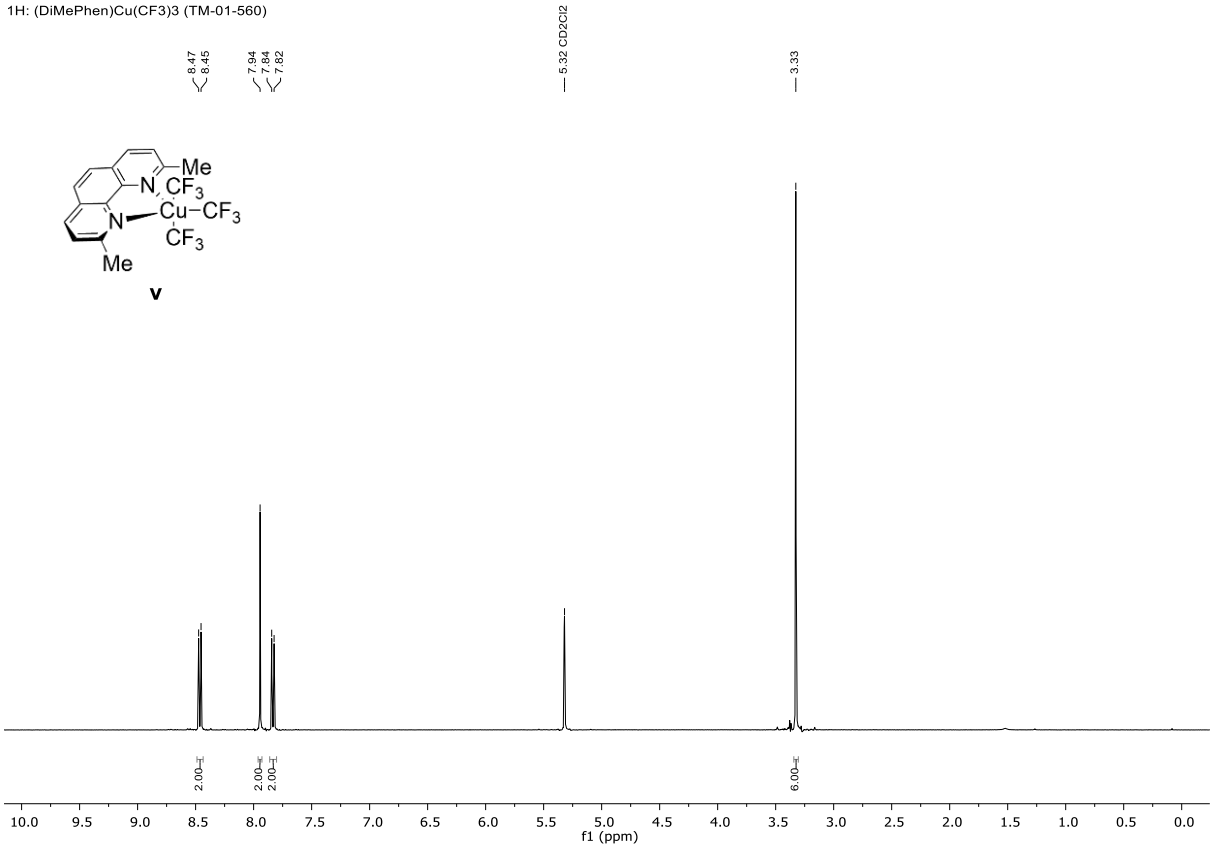


^{19}F-NMR (376 MHz, DCM-d_2)

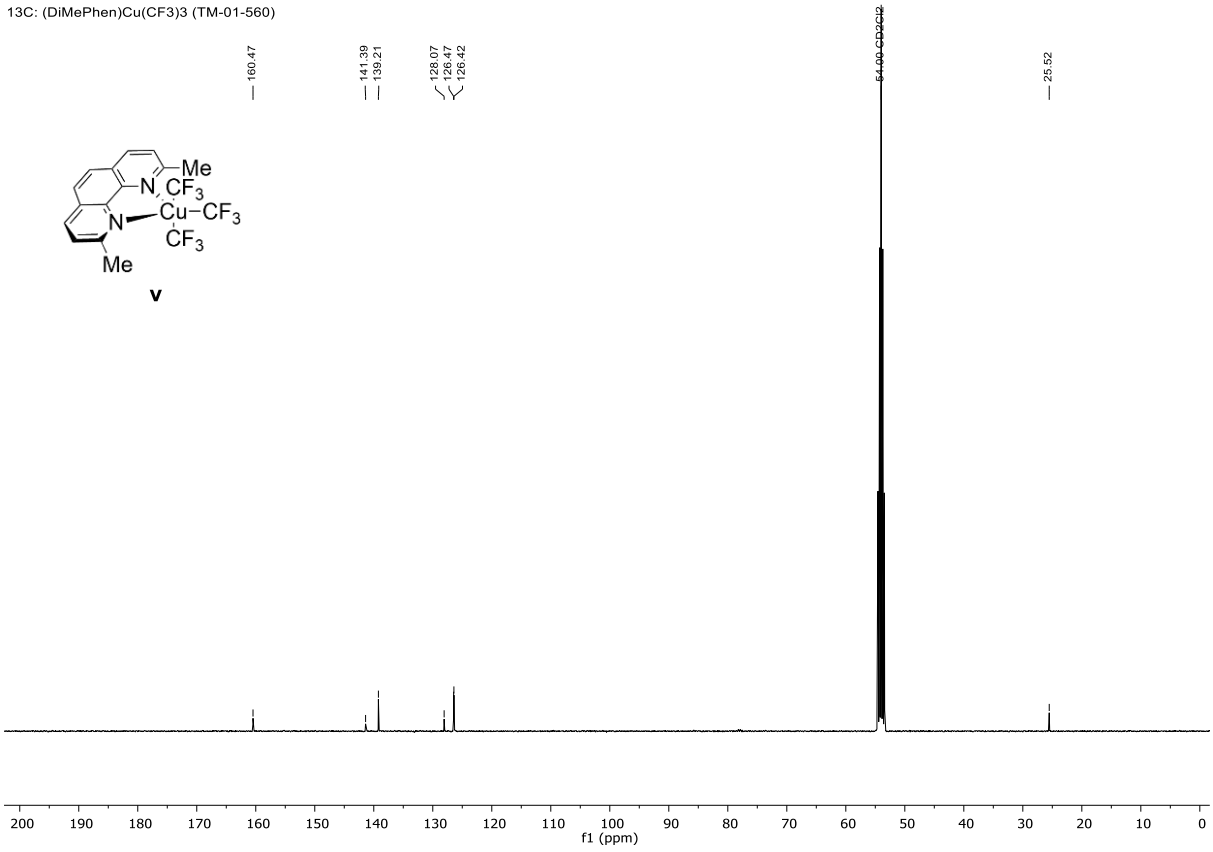


(Me$_2$phen)Cu(CF$_3$)$_3$ (V)

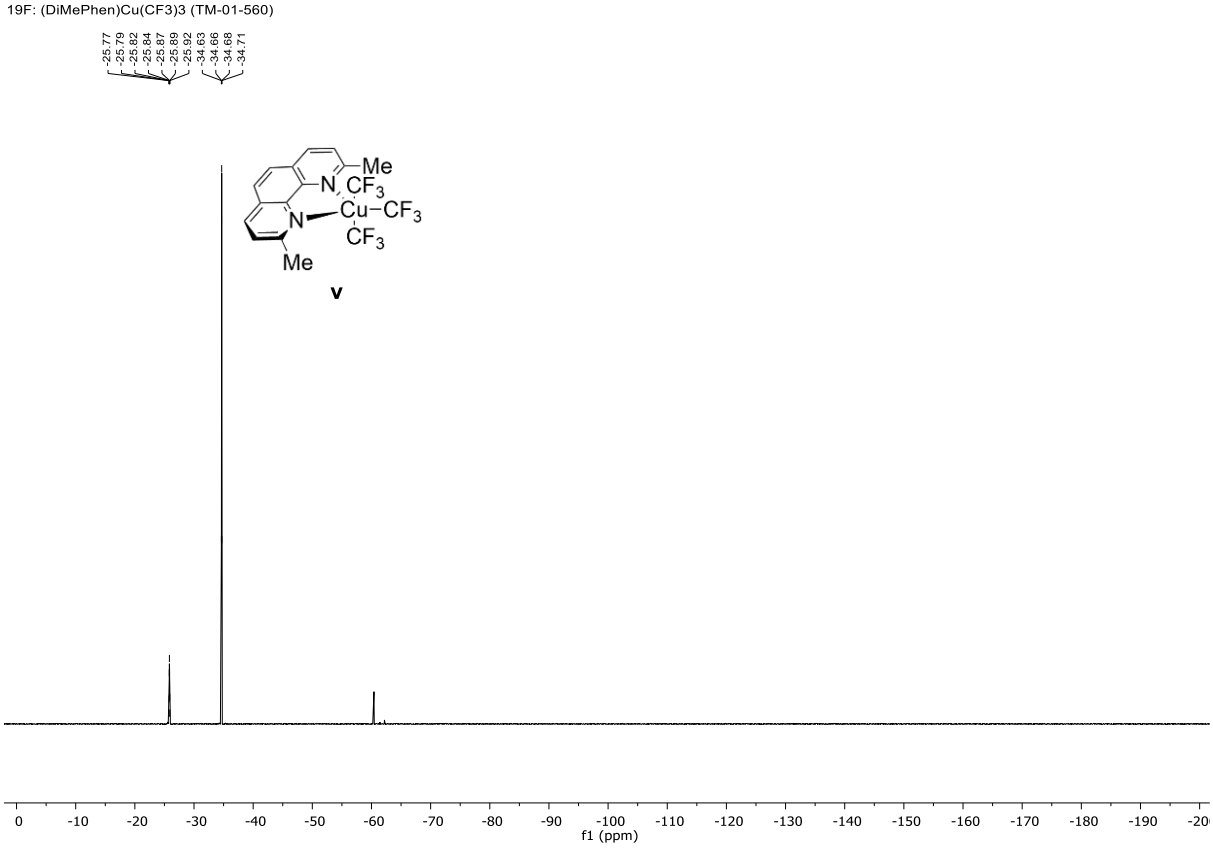
^{1}H-NMR (400 MHz, DCM-d$_2$)



^{13}C-NMR (101 MHz, DCM-d$_2$)

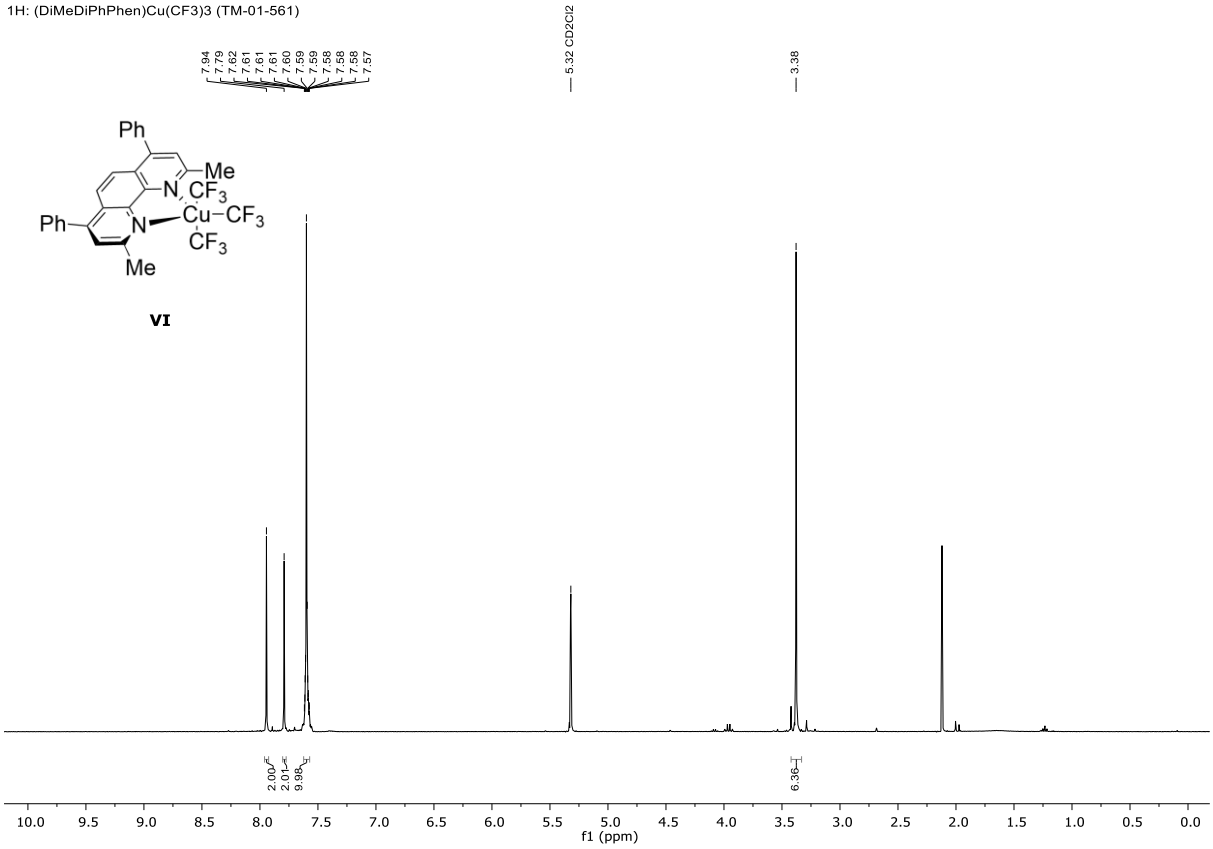


^{19}F-NMR (376 MHz, DCM-d_2)



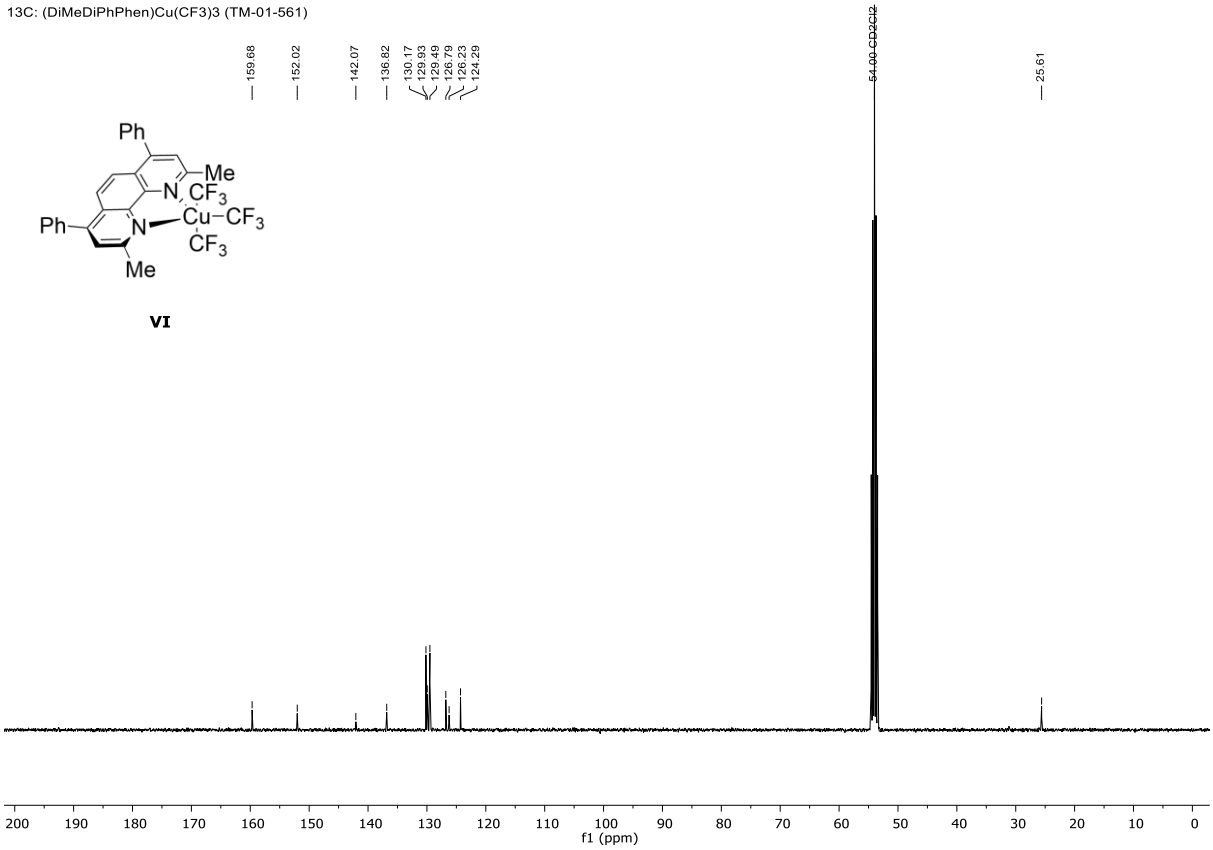
$(Me_2Ph_2phen)Cu(CF_3)_3$ (VI)

^{1}H-NMR (400 MHz, DCM-d_2)



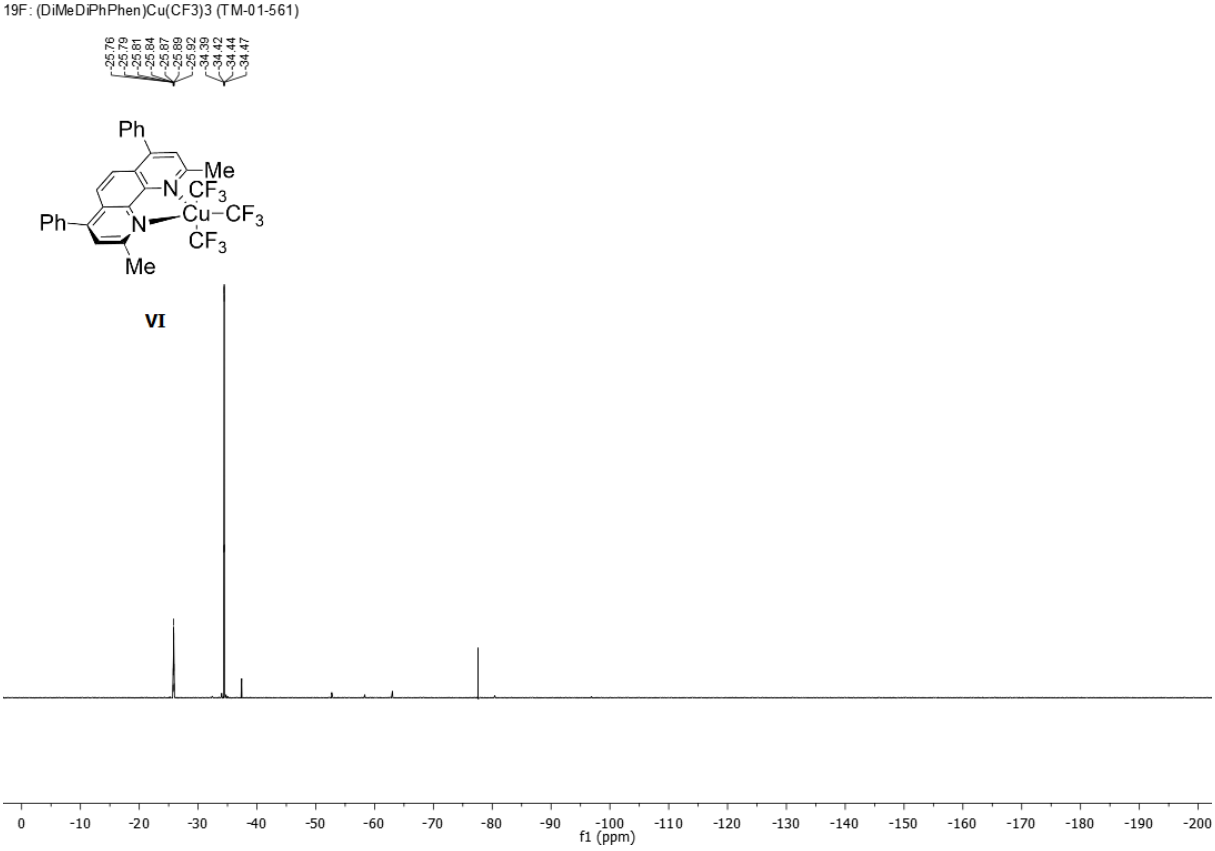
VI

^{13}C-NMR (101 MHz, DCM-d_2)



VI

^{19}F-NMR (376 MHz, DCM-d_2)



Ethyl (*S*,*Z*)-2-acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8a)

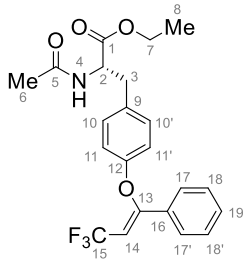
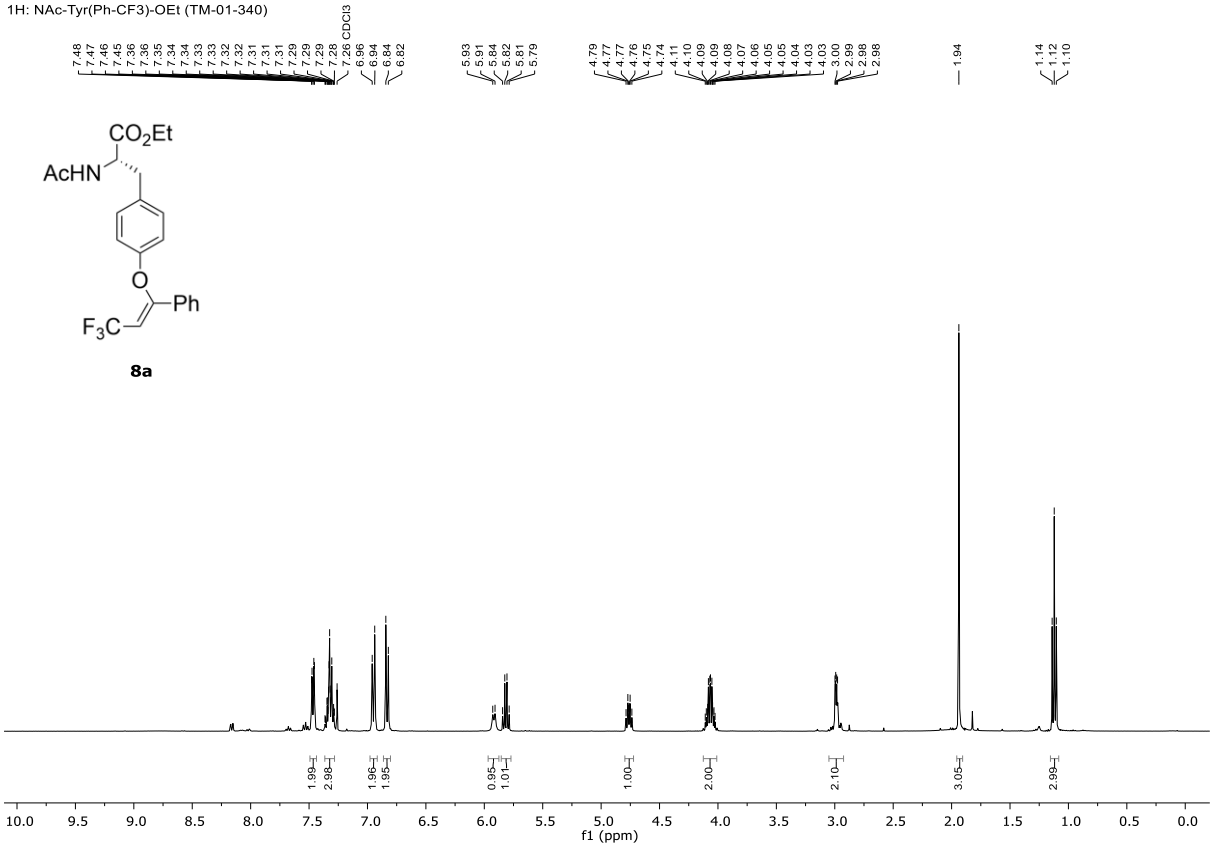


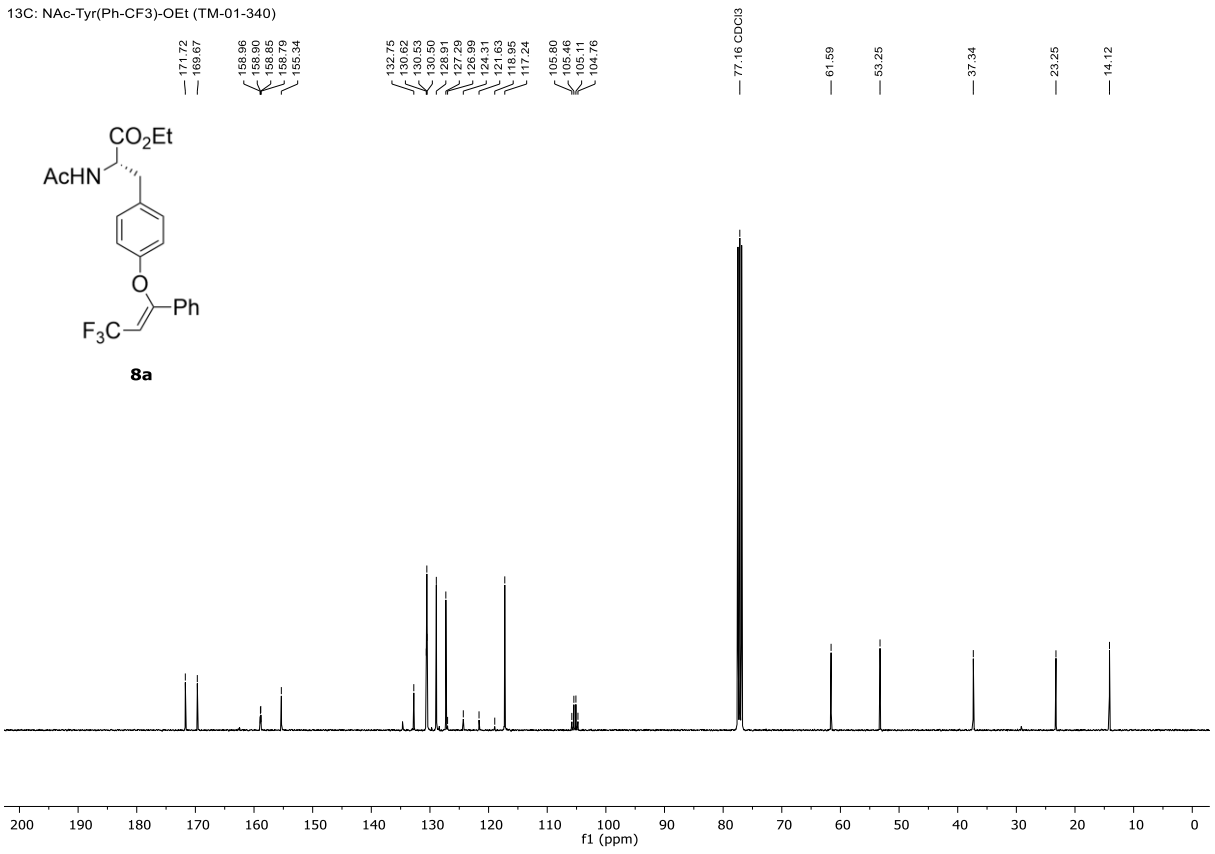
Table S28. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (**8a**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.7			
2	53.2	4.76 (dt, 7.8, 6.1 Hz)	3, 4	1, 2, 9
3	37.3	2.99 (dd, 6.0, 2.8 Hz)	2	1, 2, 9
4	/	5.92 (d, 7.8 Hz)	2	5
5	169.7			
6	23.2	1.94 (s)		5
7	61.6	4.07 (qd, 7.1, 4.7 Hz)	8	1, 8
8	14.1	1.12 (t, 7.1 Hz)	7	7
9	130.6			
10/10’	130.53	6.95 (d, 8.6 Hz)	11/11’	12
11/11’	117.2	6.83 (d, 8.6 Hz)	10/10’	9, 10/10’, 12
12	155.3			
13	158.9 (q, 5.7 Hz)			
14	105.3 (q, 34.9 Hz)	5.82 (q, 7.5 Hz)		13, 16
15	123.0 (q, 269.6 Hz)			
16	132.8			
17/17’	127.3	7.47 (dd, 7.9, 1.7 Hz)	18/18’	13, 19
18/18’	128.9	7.37-7.28 (m)	17/17’	16
19	130.50	7.37-7.28 (m)		

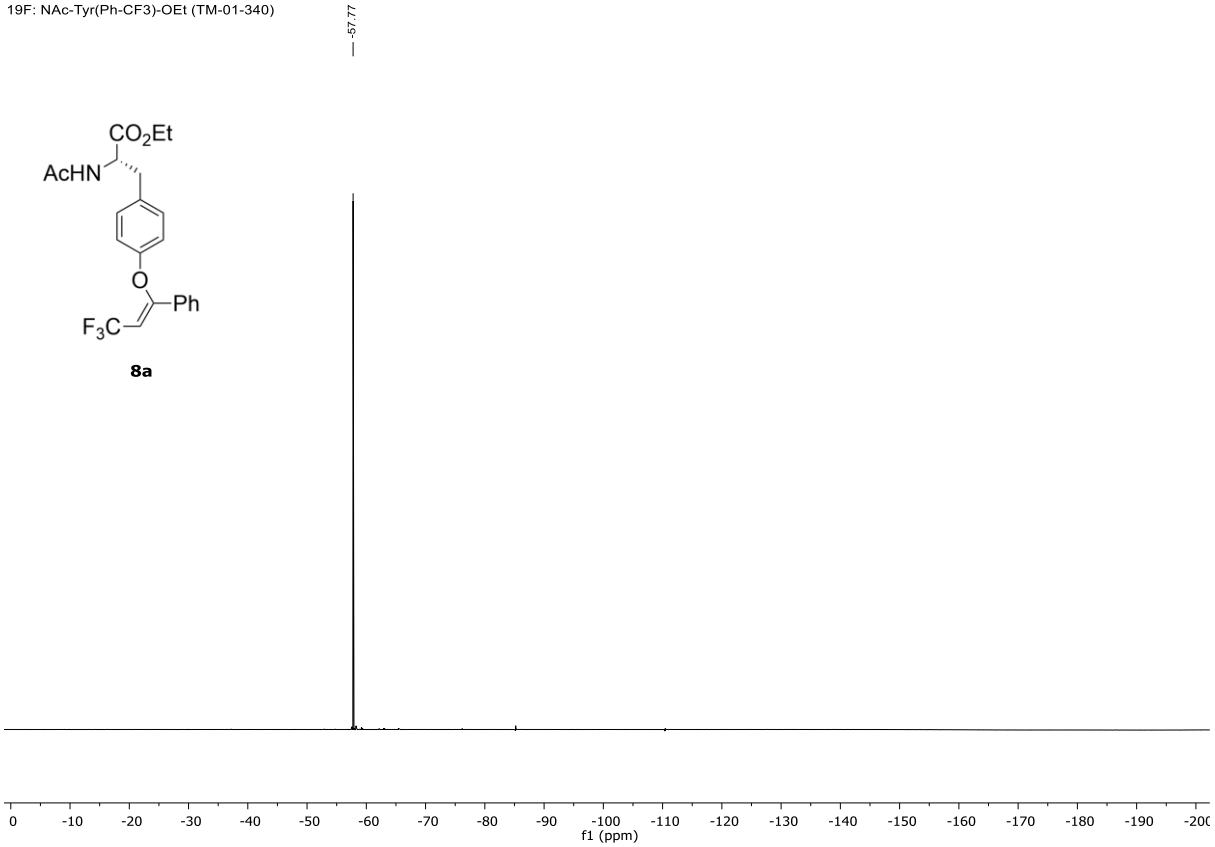
^{1}H-NMR (400 MHz, $CDCl_3$)



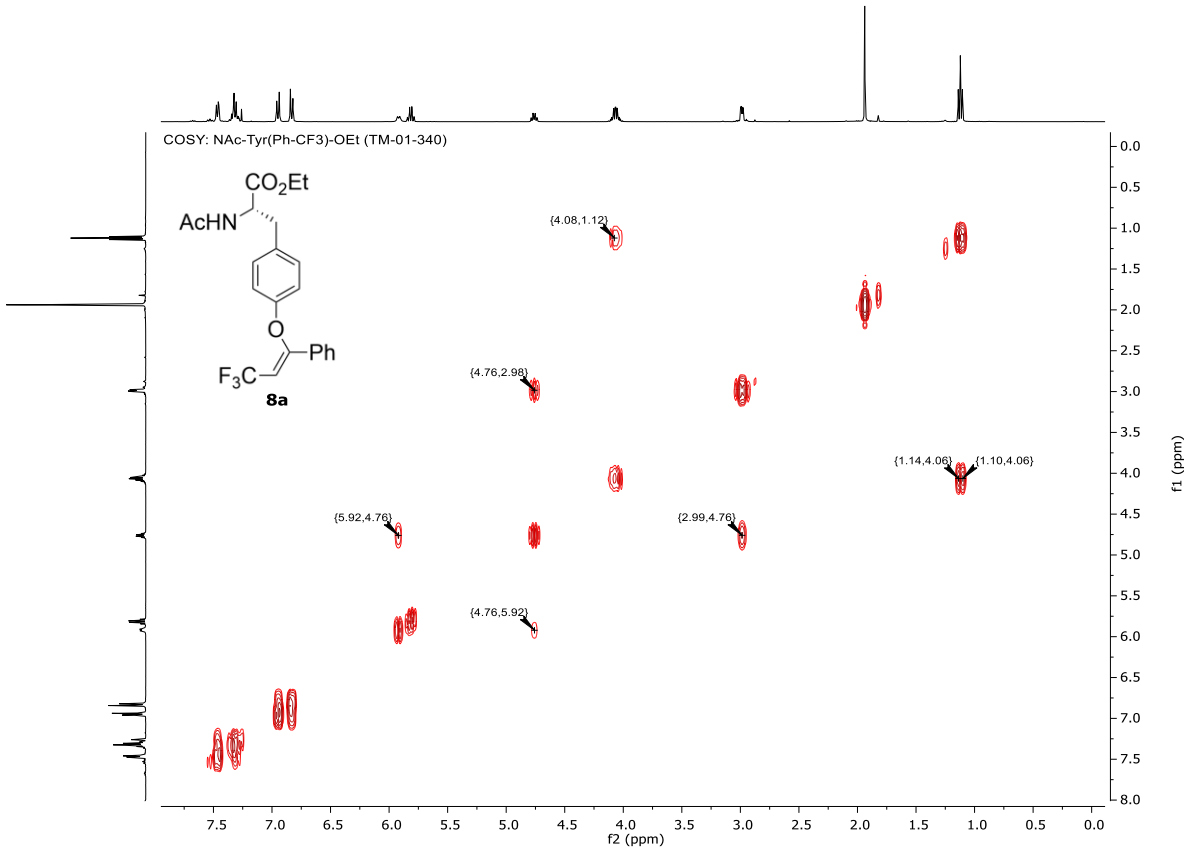
^{13}C-NMR (101 MHz, $CDCl_3$)



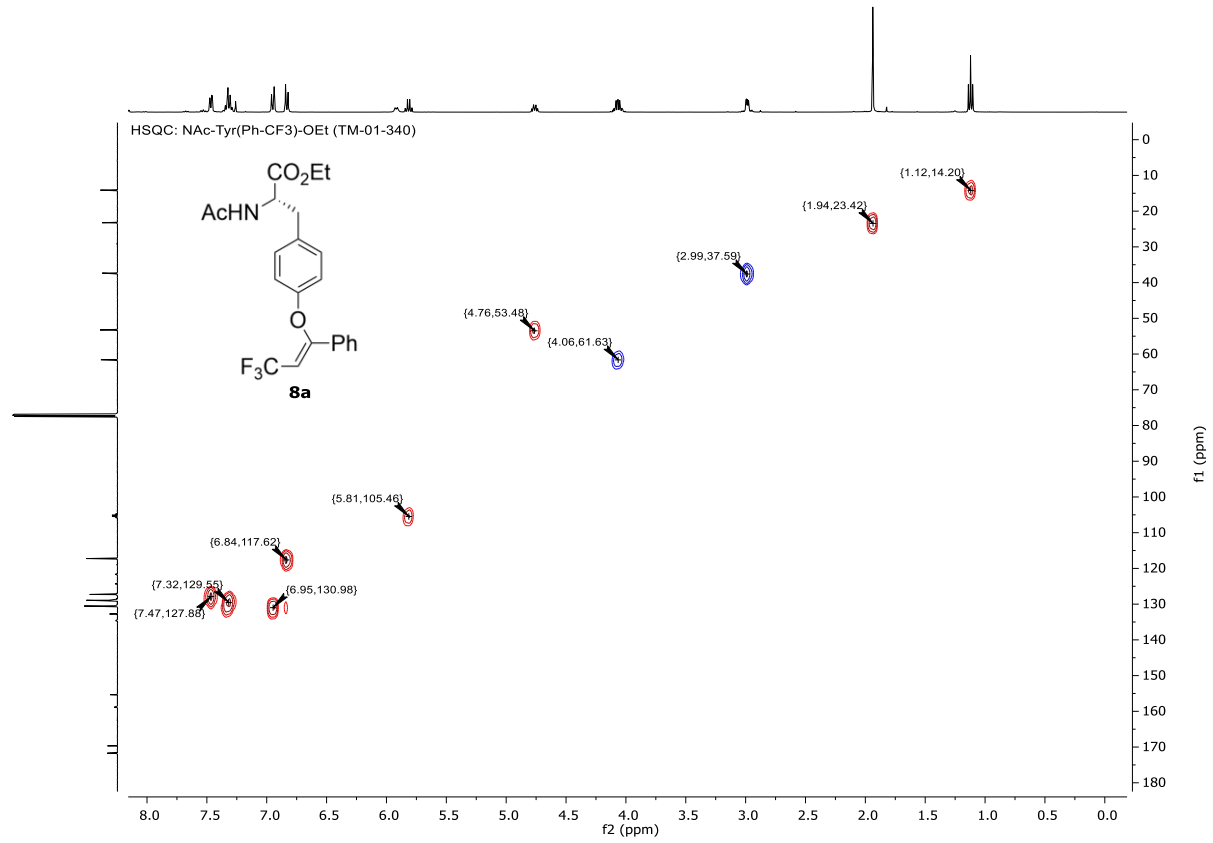
^{19}F-NMR (376 MHz, $CDCl_3$)



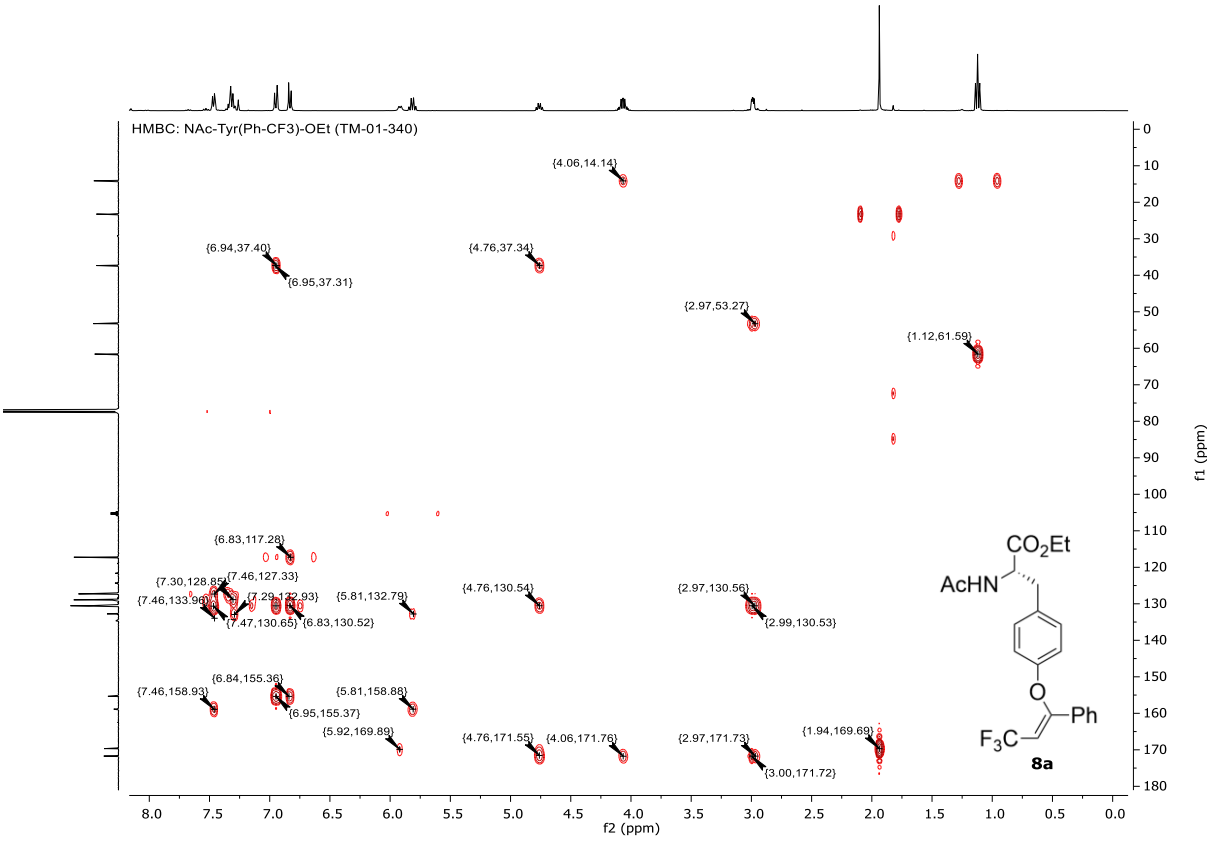
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*S*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*S*)-8b)

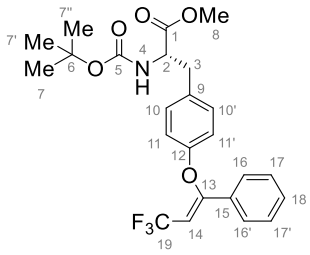
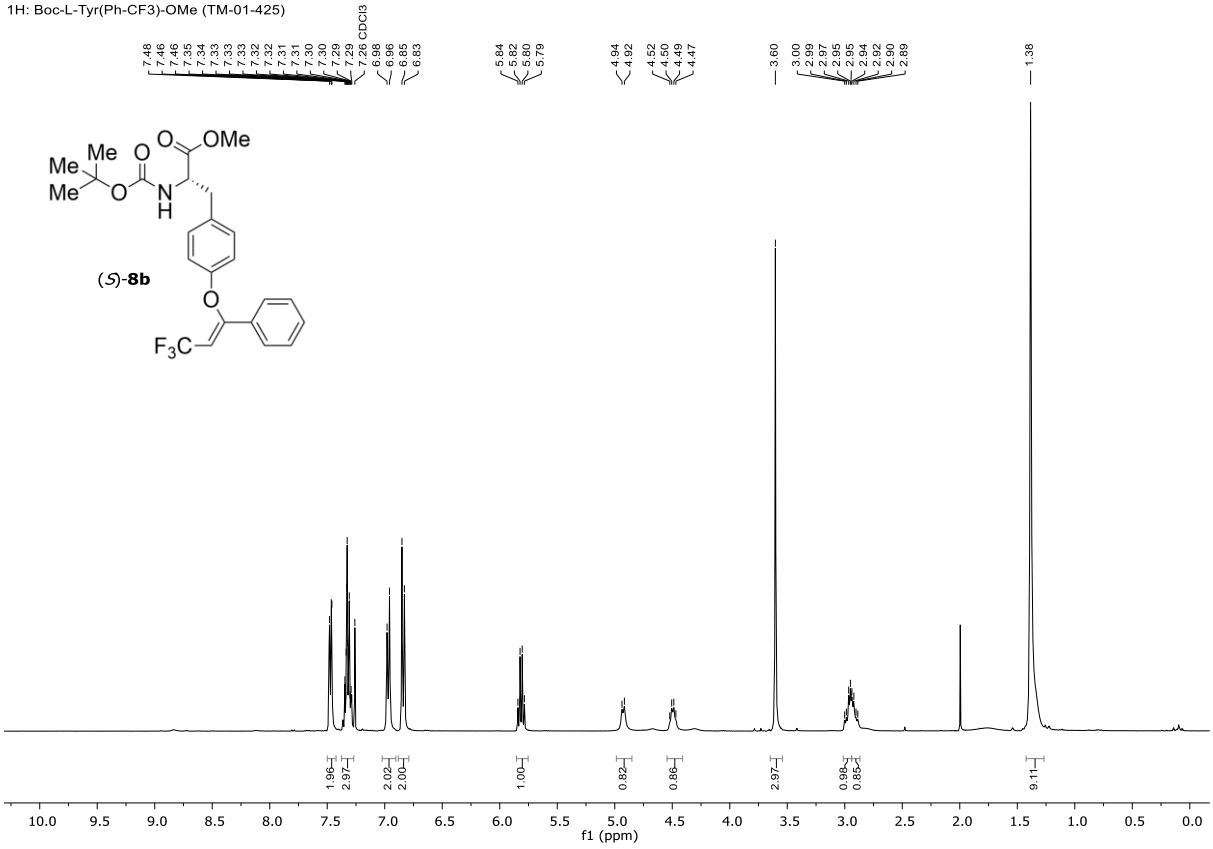


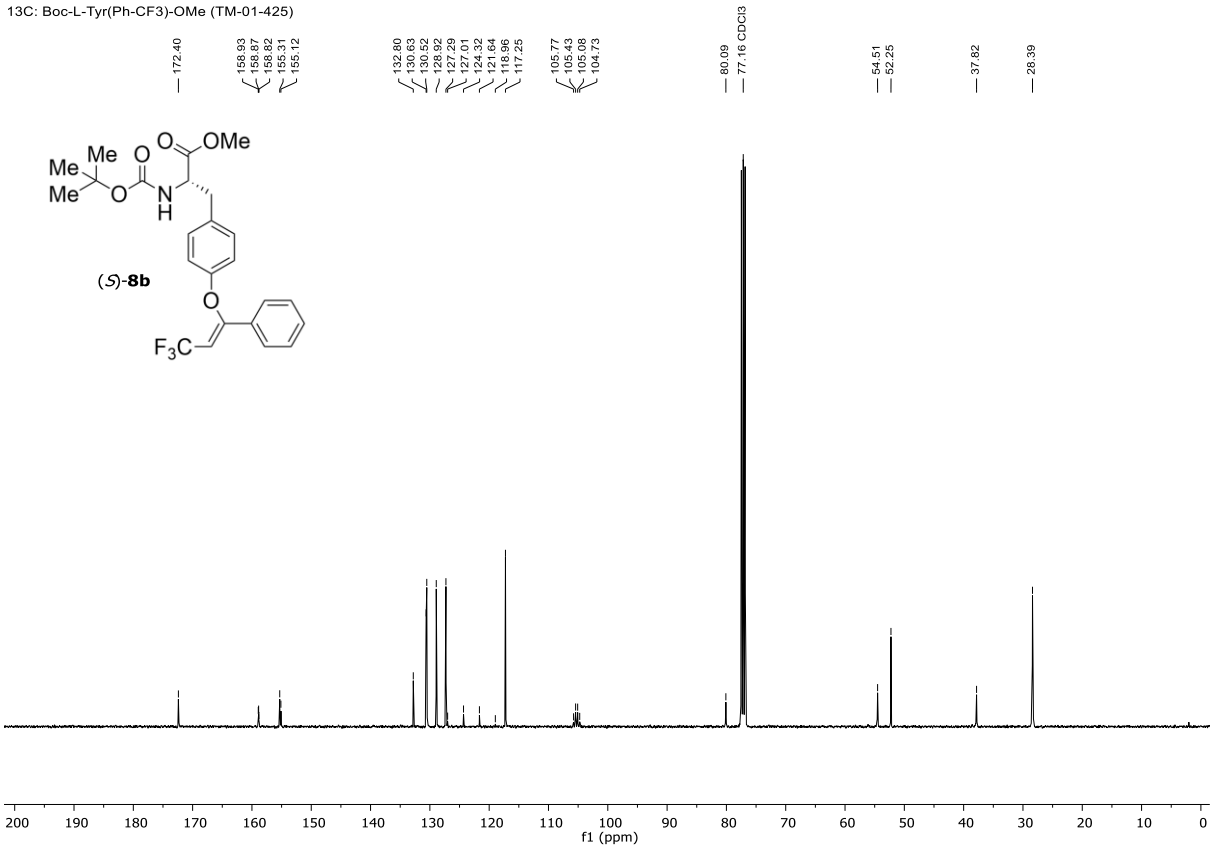
Table S29. Detailed NMR assignment of methyl (*S*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*S*)-**8b**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	172.4			
2	54.5	4.50 (q, 6.9 Hz)	3, 4	1, 3, 9
3	37.8	2.98 (dd, 14.0, 6.0 Hz), 2.96-2.86 (m)	2	1, 2, 10/10‘
4	/	4.93 (d, 8.4 Hz)	2	
5	155.1			
6	80.1			
7/7‘/7“	28.4	1.38 (s)		6
8	52.3	3.60 (s)		
9	130.6			
10/10’	130.5	6.97 (d, 8.4 Hz)	11/11‘	3, 12
11/11’	117.3	6.84 (d, 8.6 Hz)	10/10‘	10/10‘, 12
12	155.3			
13	158.9 (q, 5.5 Hz)			
14	105.3 (q, 34.7 Hz)	5.81 (q, 7.5 Hz)		13, 15, 19
15	132.8			
16/16’	127.3	7.50-7.43 (m)	17/17’, 18	13
17/17‘	128.9	7.38-7.27 (m)	16/16’	15
18	128.9	7.38-7.27 (m)	16/16’	
19	123.0 (q, 269.9 Hz)			

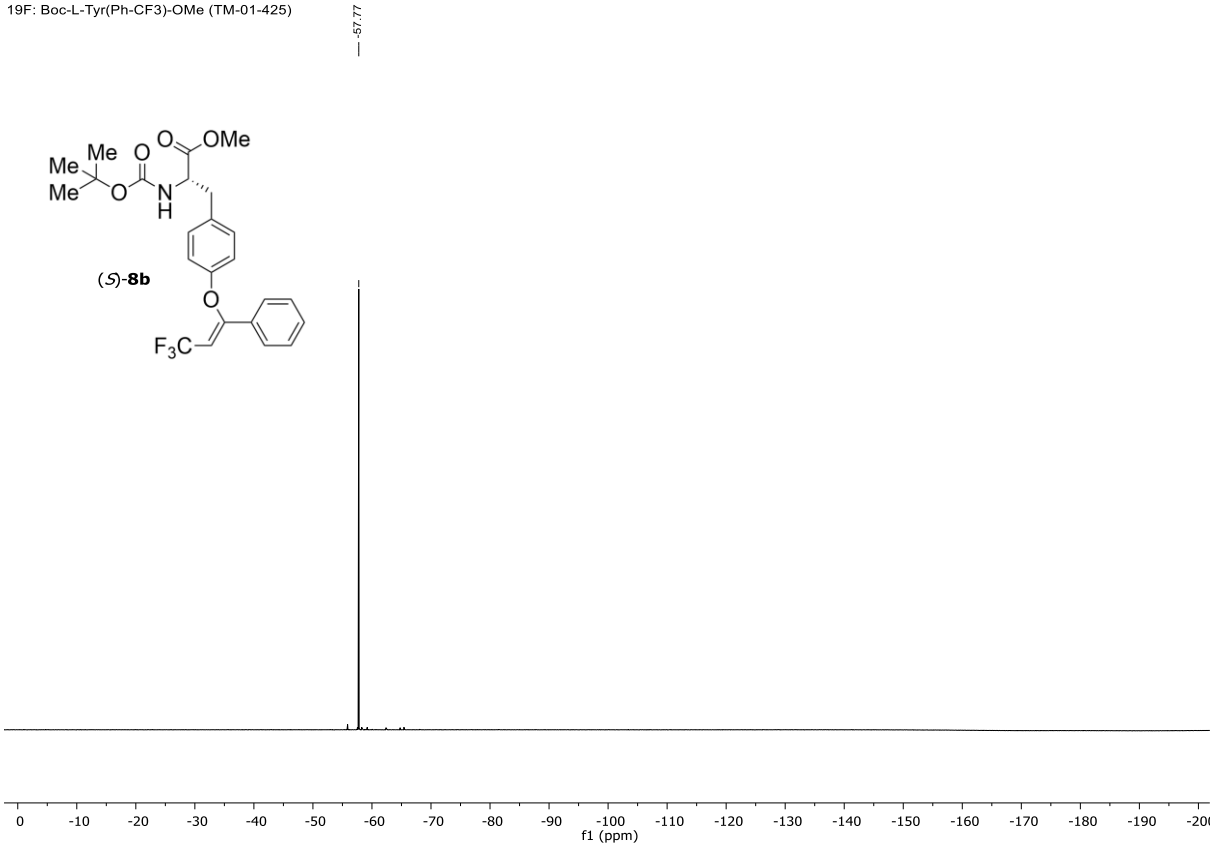
^{1}H-NMR (400 MHz, $CDCl_3$)



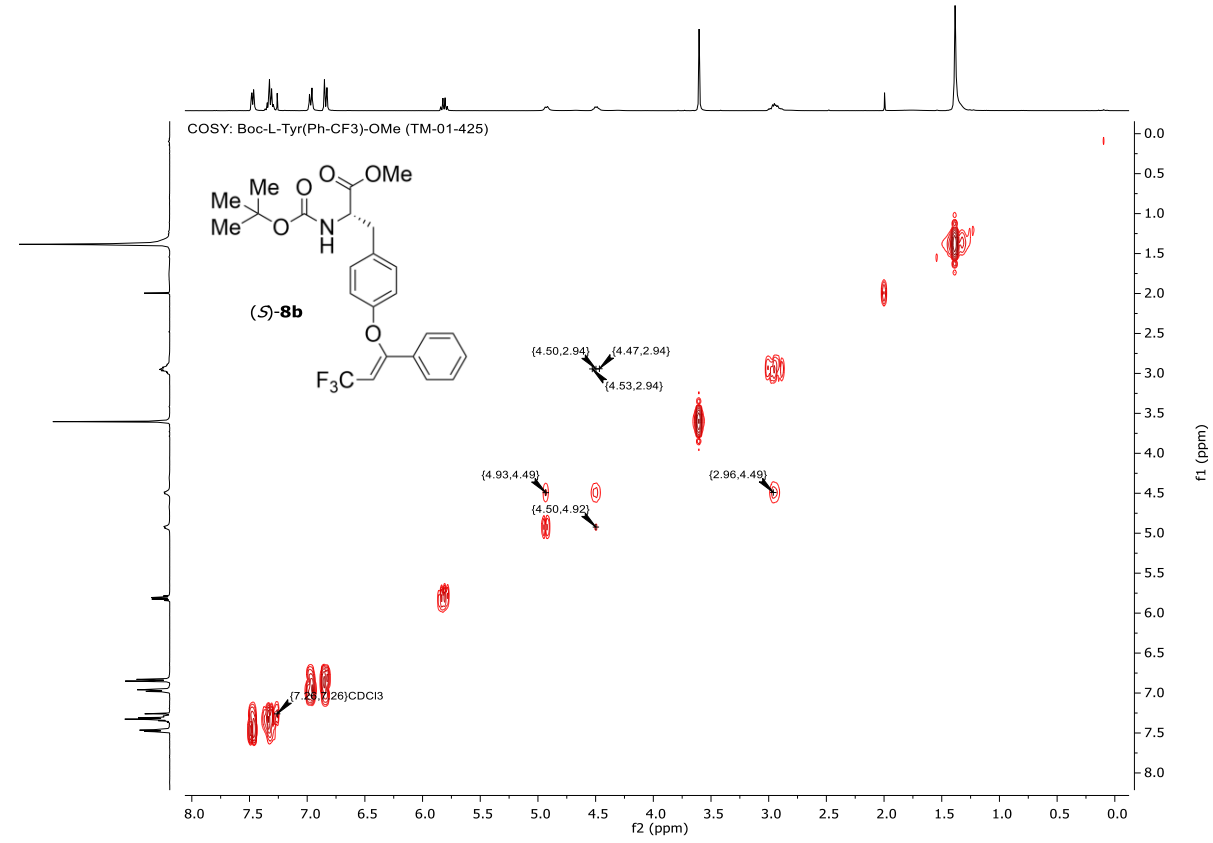
^{13}C-NMR (101 MHz, $CDCl_3$)



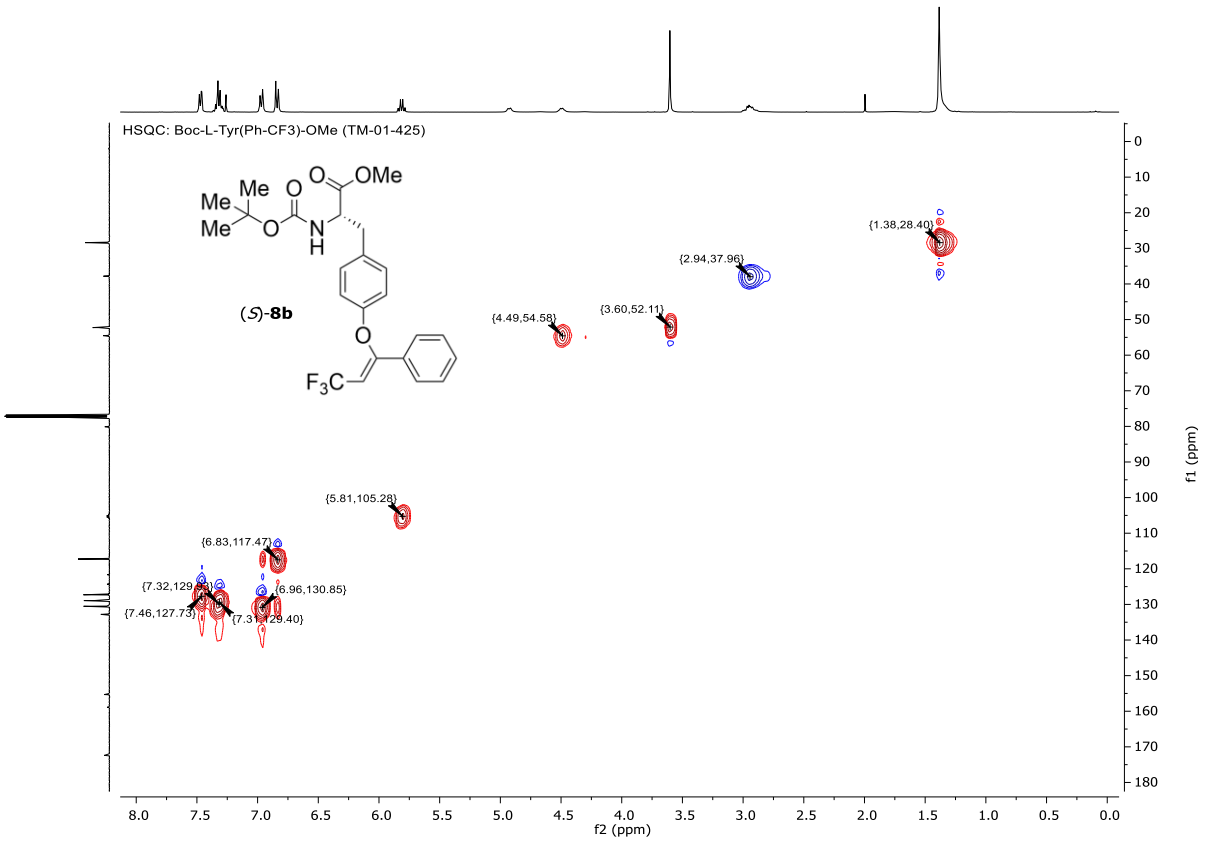
^{19}F-NMR (376 MHz, $CDCl_3$)



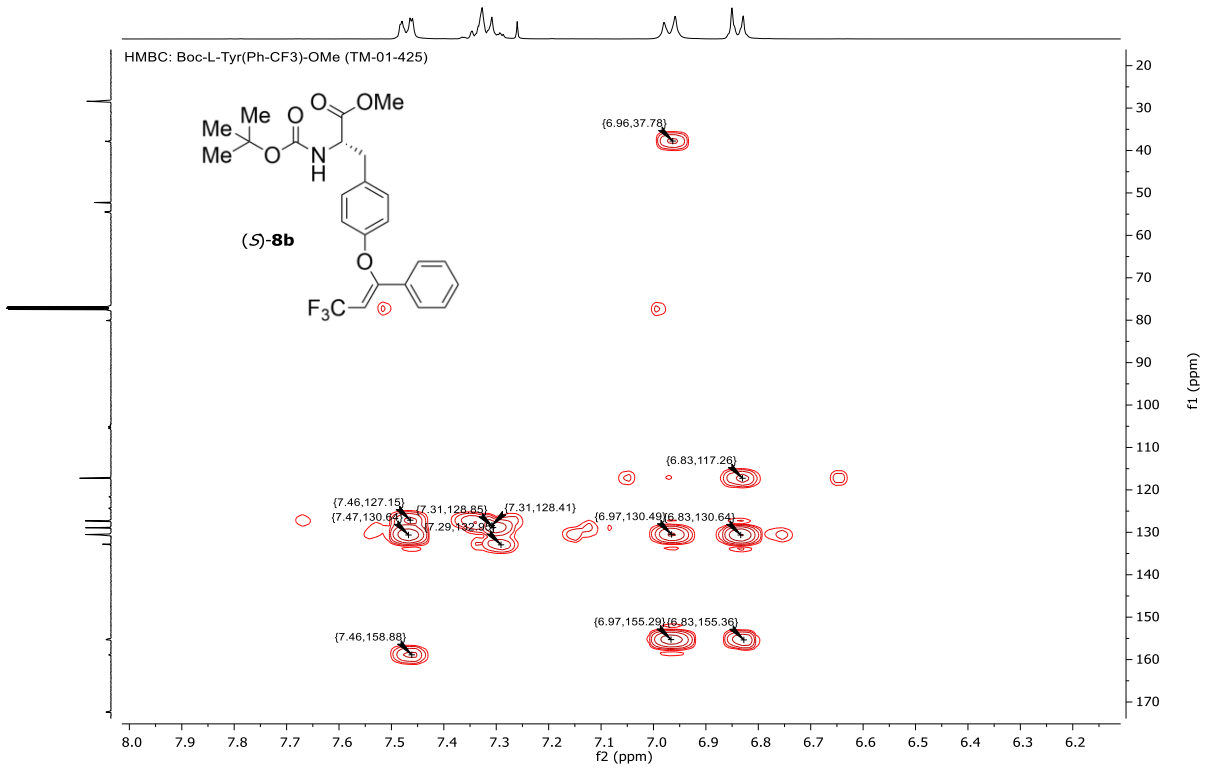
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*R*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*R*)-8b)

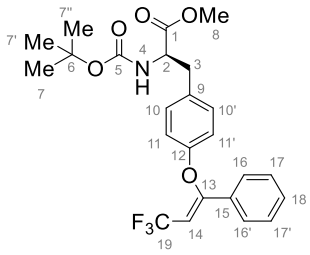
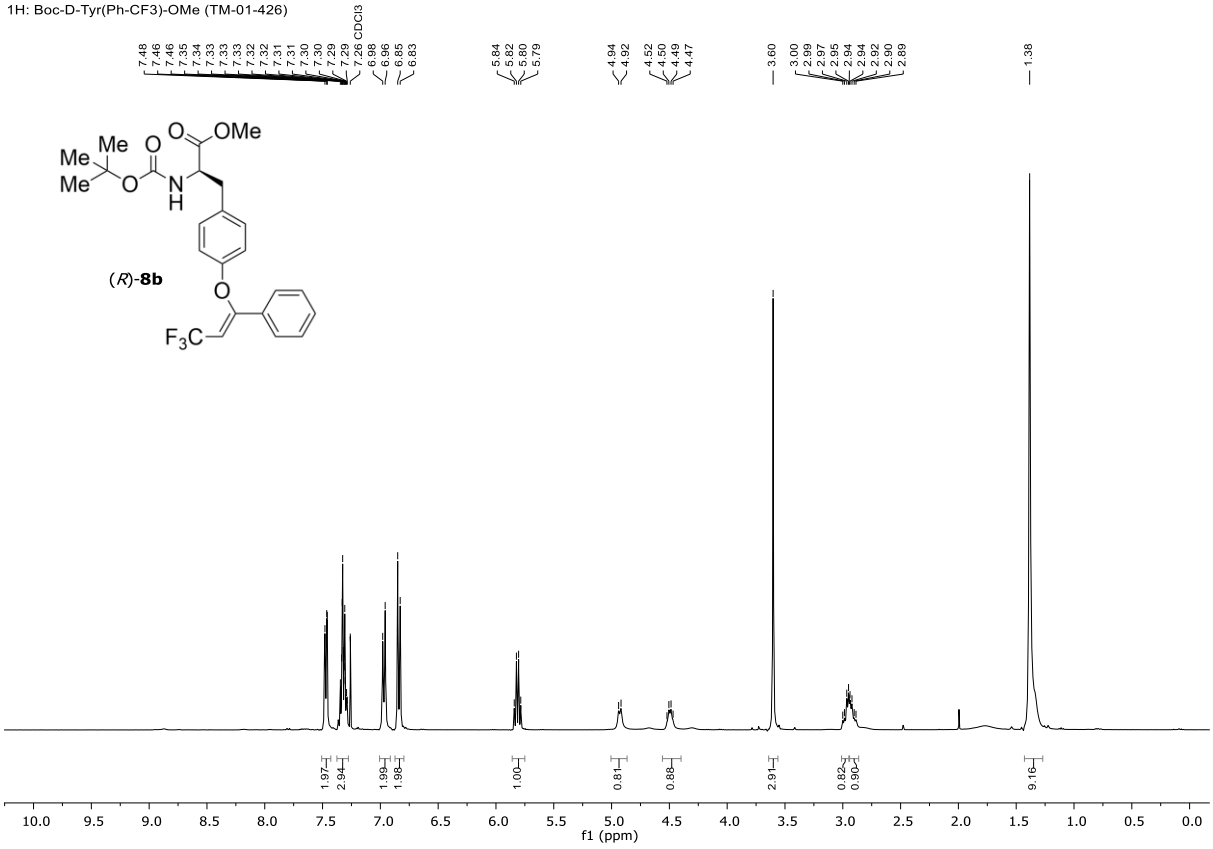


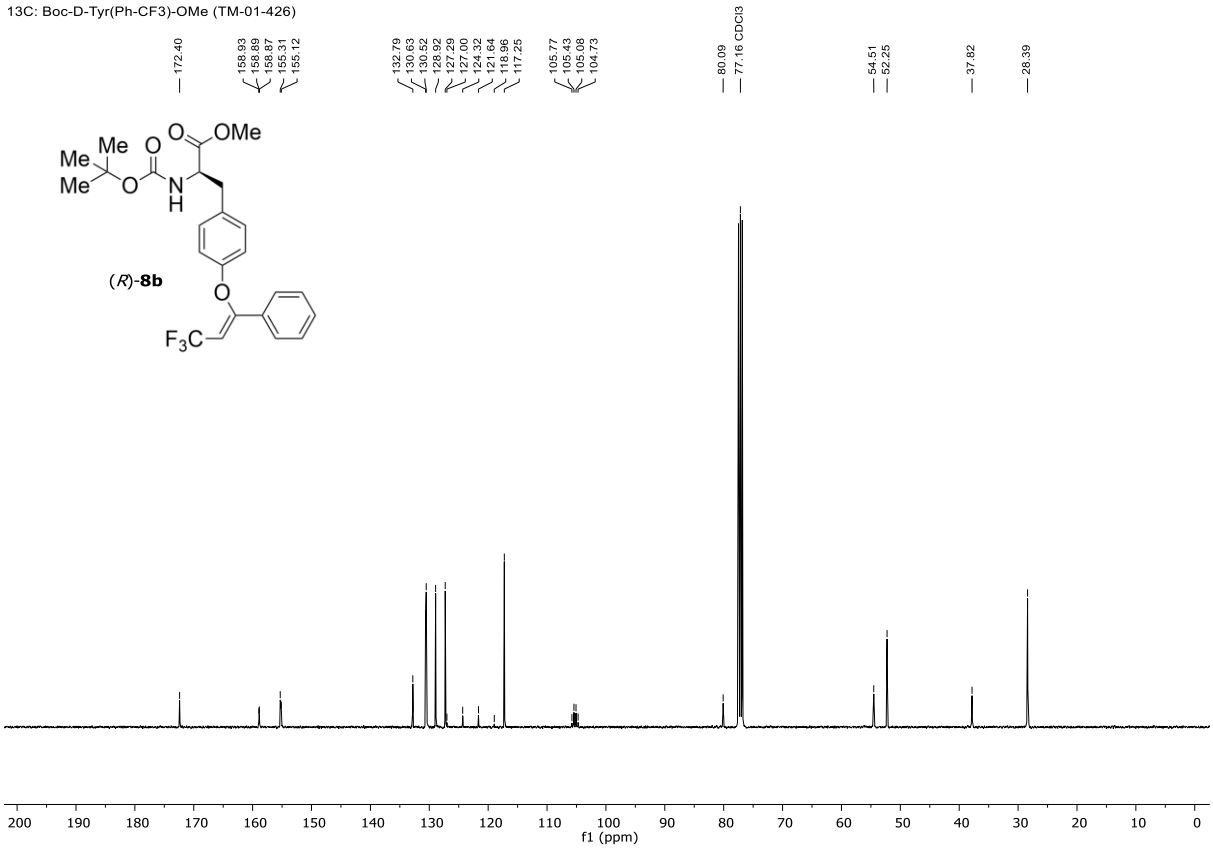
Table S30. Detailed NMR assignment of methyl (*S*,*Z*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy) phenyl)propanoate ((*S*)-**8b**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	172.4			
2	54.5	4.49 (q, 6.8 Hz)	3, 4	1, 3, 9
3	37.8	2.98 (dd, 14.0, 6.0 Hz), 2.96-2.86 (m)	2	1, 2, 10/10‘
4	/	4.93 (d, 8.4 Hz)	2	
5	155.1			
6	80.1			
7/7‘/7“	28.4	1.38 (s)		6
8	52.3	3.60 (s)		
9	130.6			
10/10’	130.5	6.97 (d, 8.5 Hz)	11/11‘	3, 12
11/11’	117.3	6.84 (d, 8.6 Hz)	10/10‘	10/10‘, 12
12	155.3			
13	158.9 (q, 5.5 Hz)			
14	105.3 (q, 34.7 Hz)	5.81 (q, 7.5 Hz)		13, 15, 19
15	132.8			
16/16’	127.3	7.51-7.40 (m)	17/17’, 18	13
17/17‘	128.9	7.37-7.27 (m)	16/16’	15
18	128.9	7.37-7.27 (m)	16/16’	
19	123.0 (q, 269.9 Hz)			

^{1}H-NMR (400 MHz, $CDCl_3$)

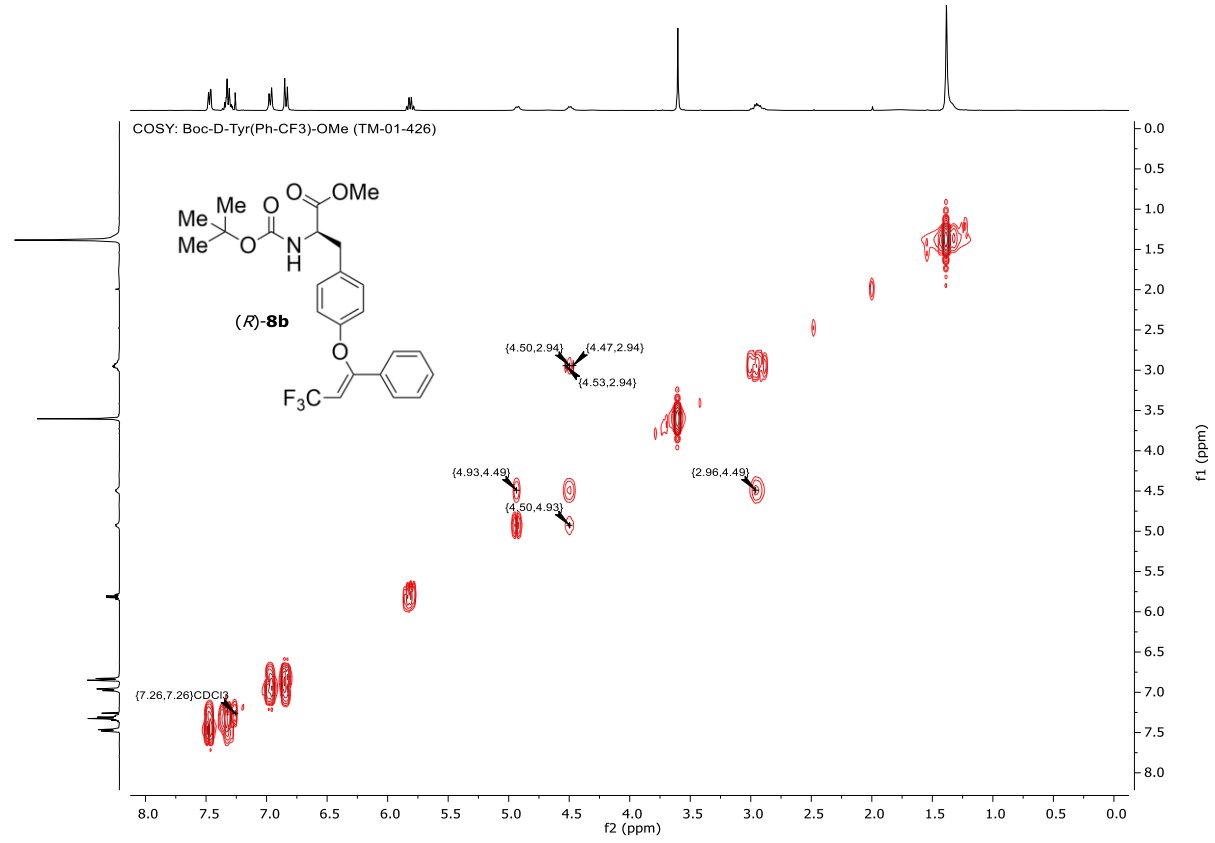


^{13}C-NMR (101 MHz, $CDCl_3$)

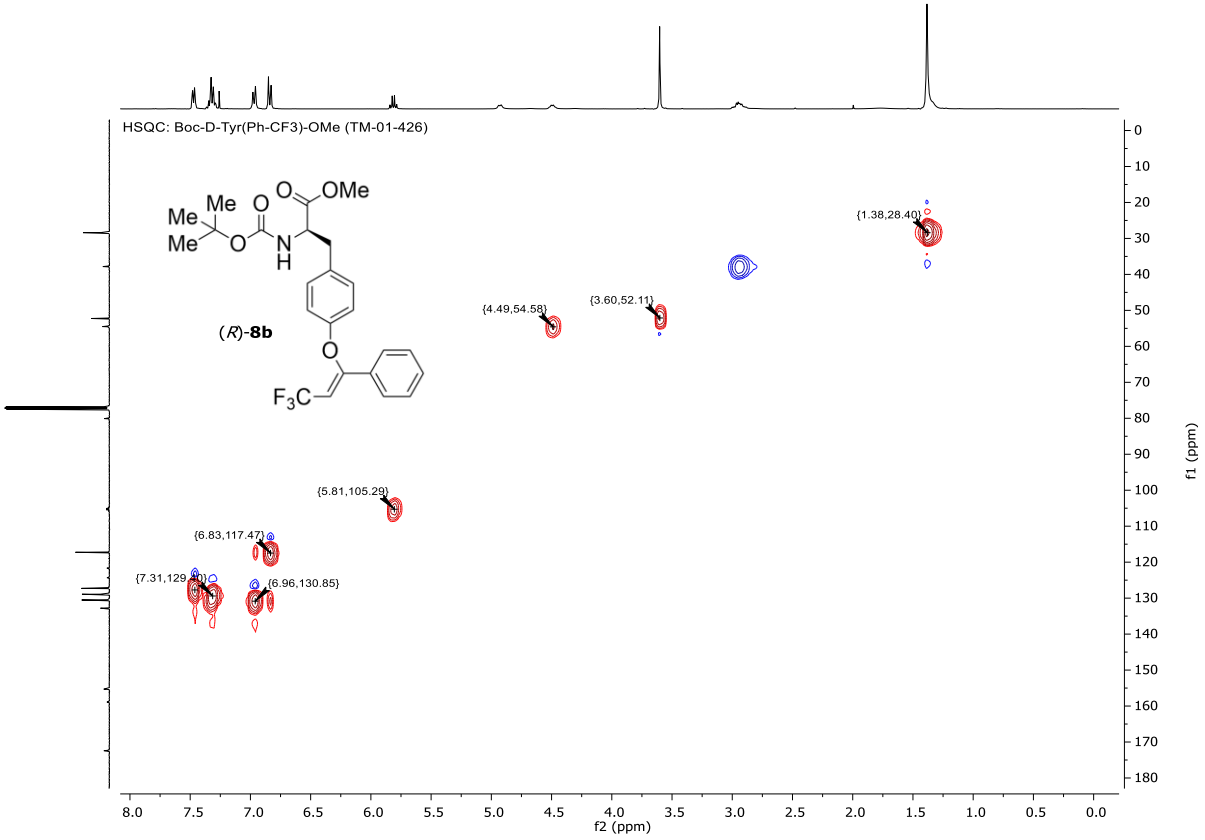


^{19}F-NMR (376 MHz, $CDCl_3$)

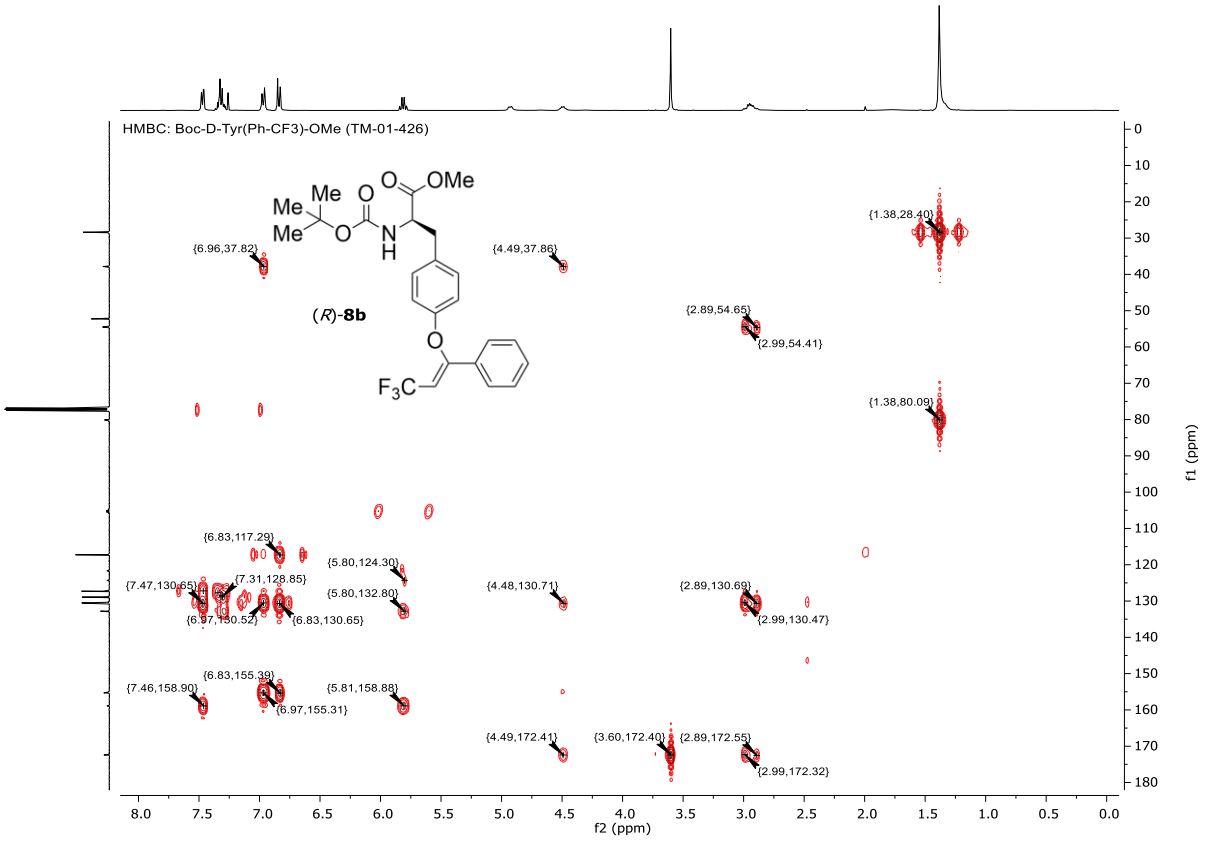
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

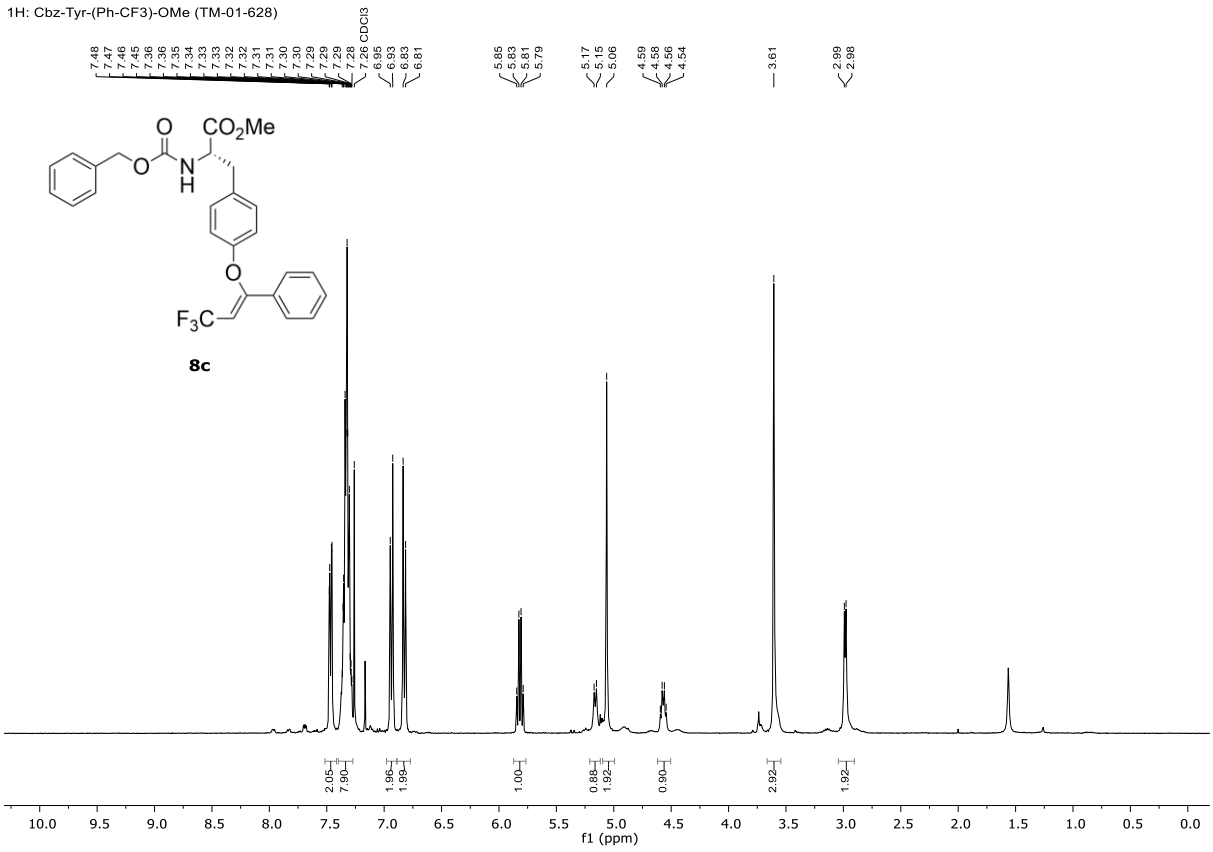


HMBC NMR ($CDCl_3$)



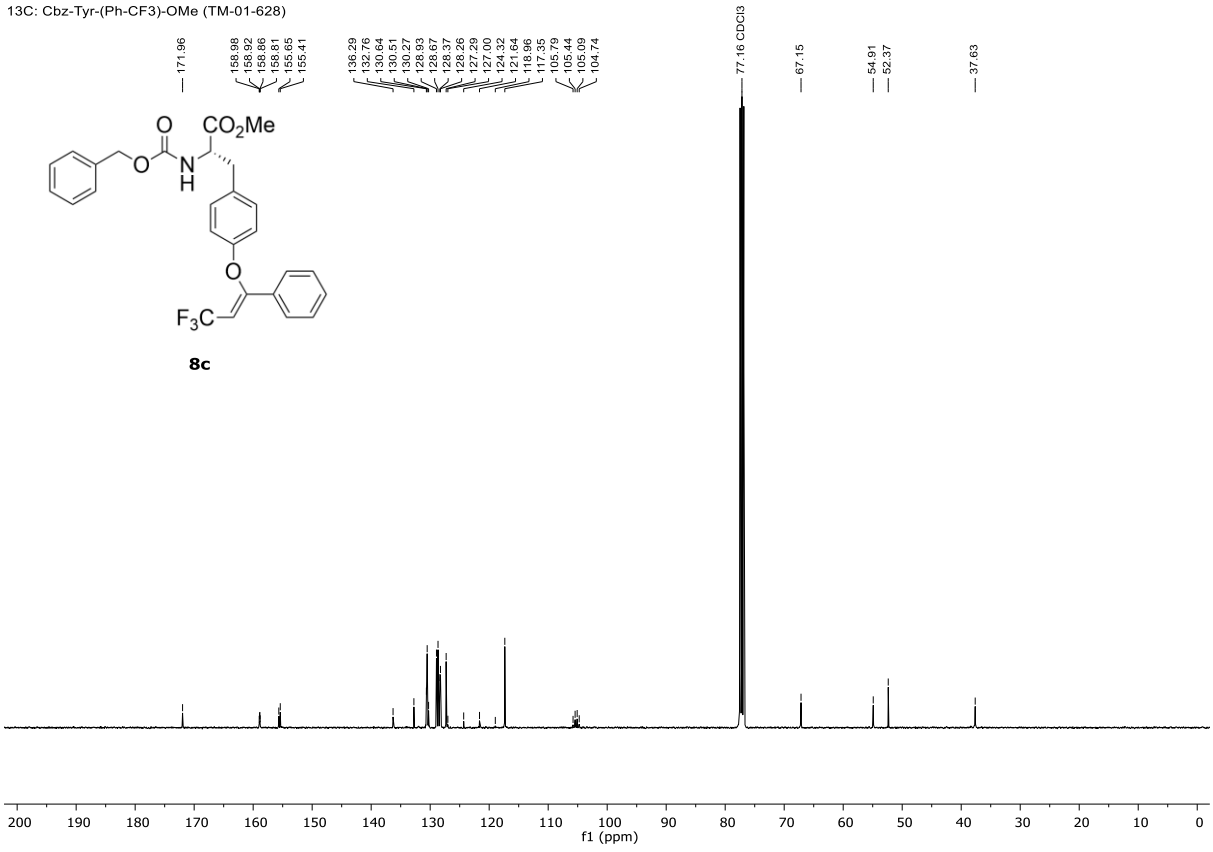
Methyl (*S*,*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8c)

^{1}H-NMR (400 MHz, $CDCl_3$)



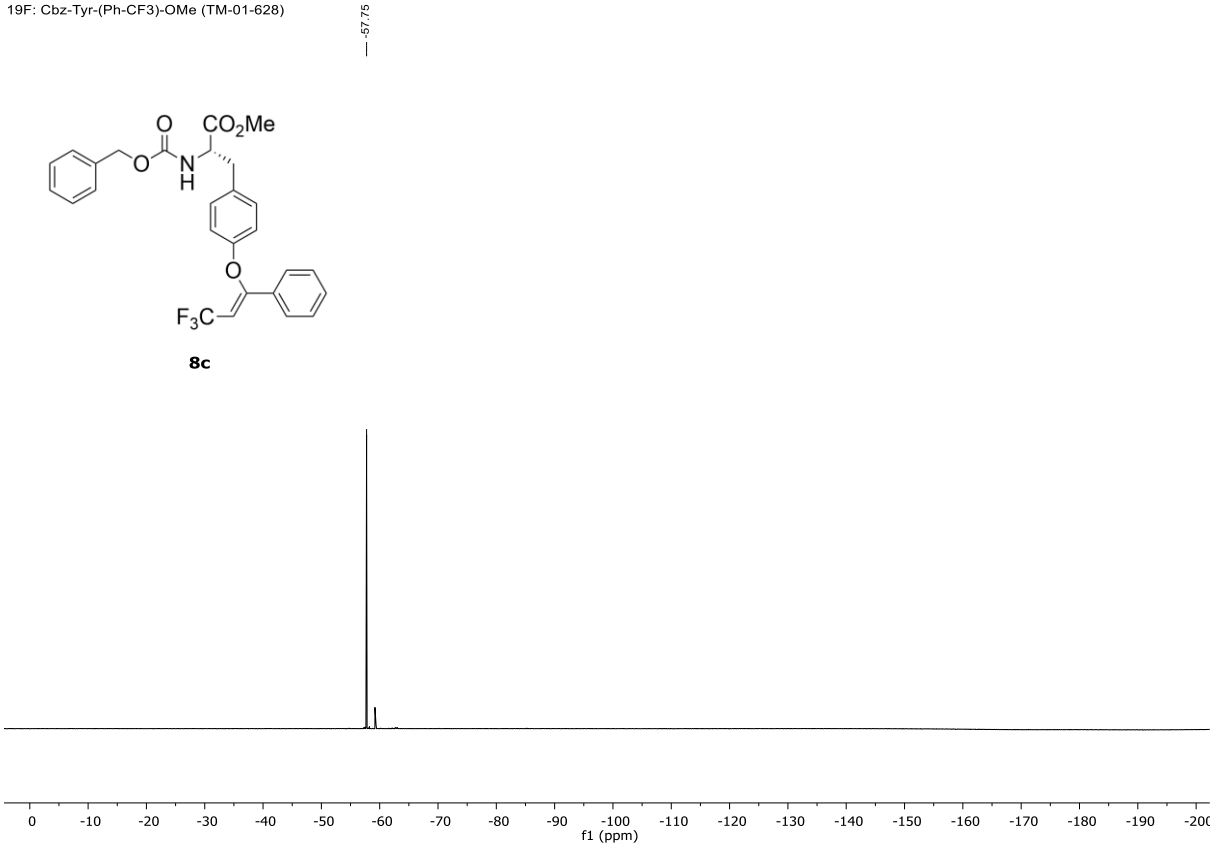
8c

^{13}C-NMR (101 MHz, $CDCl_3$)



8c

^{19}F-NMR (376 MHz, $CDCl_3$)



Methyl (*S*,*Z*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (8d)

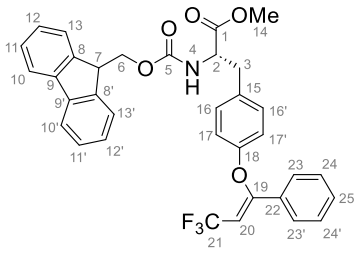
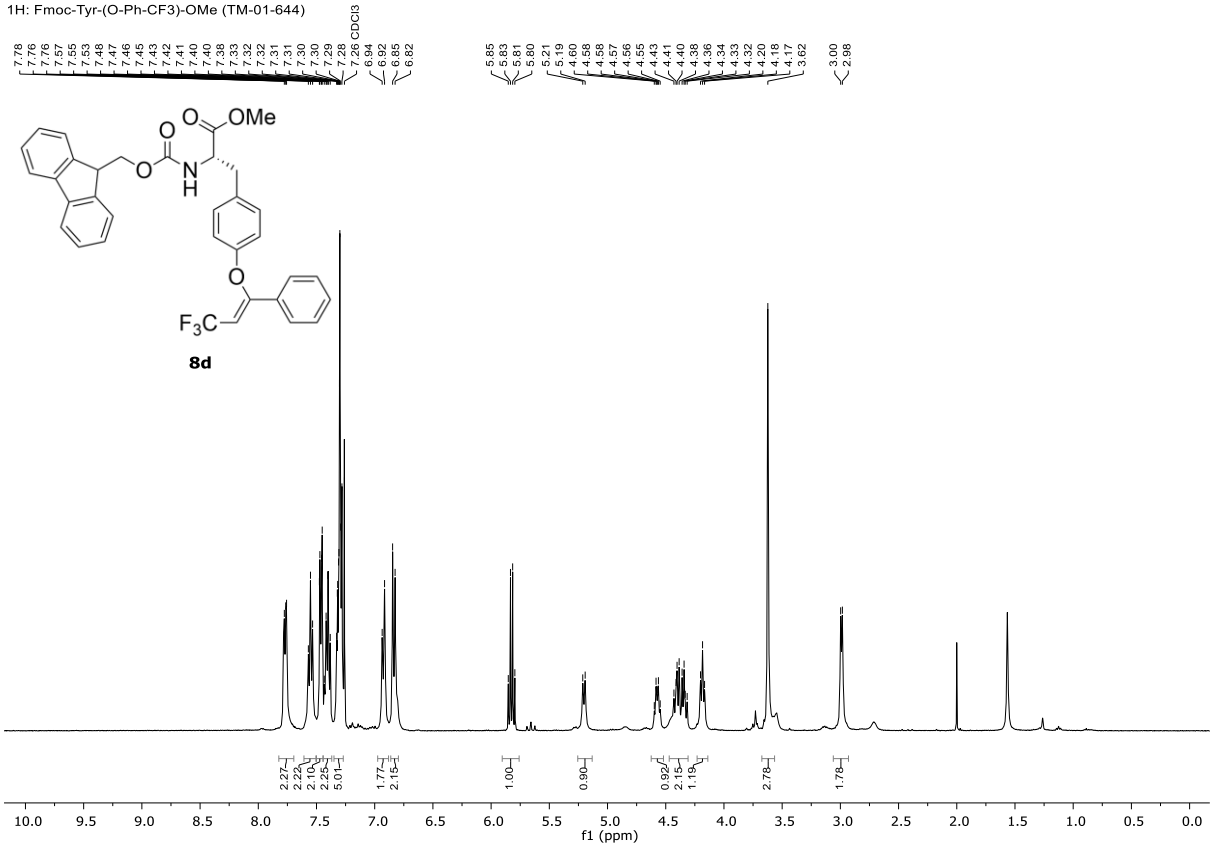


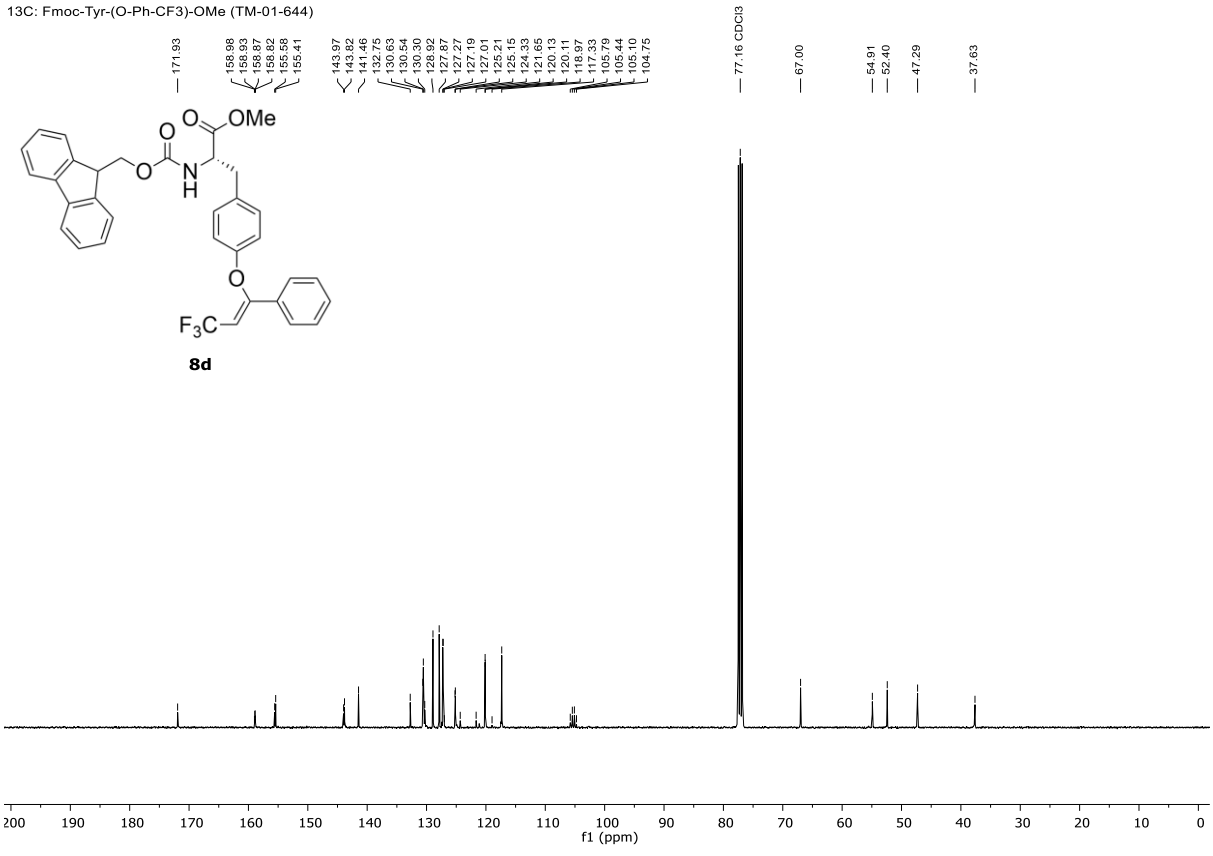
Table S31. Detailed NMR assignment of methyl (*S*,*Z*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoate (**8d**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.9			
2	54.9	4.57 (dt, 8.6, 6.0 Hz)	3, 4	1, 3, 15
3	37.6	2.99 (d, 6.0 Hz)	2	1, 2, 16/16‘
4	/	5.20 (d, 8.3 Hz)	2	
5	155.6			
6	67.0	4.44-4.30 (m)	7	5, 7, 8/8‘
7	47.3	4.18 (t, 7.0 Hz)	6	6, 8/8‘
8/8‘	144.0, 143.8			
9/9‘	141.5			
10/10’	120.13, 120.11	7.81-7.71 (m)		8/8‘, 12/12‘
11/11’	125.2, 125.1	7.55 (t, 7.3 Hz)		9/9‘, 12/12‘
12/12‘	127.9	7.44-7.37 (m)		9/9‘, 11/11‘
13/13‘	130.6	7.35-7.27 (m)		8/8‘, 11/11‘
14	52.4	3.62 (s)		1
15	130.3			
16/16’	130.5	6.93 (d, 8.3 Hz)		3, 18
17/17’	117.3	6.84 (d, 8.5 Hz)		16/16’, 18
18	155.4			
19	158.9 (q, 5.6 Hz)			
20	105.3 (q, 35.1 Hz)	5.82 (q, 7.5 Hz)		19, 22
21	123.0 (q, 269.8 Hz)			
22	132.7			
23/23’	127.3 or 127.2	7.46 (dd, 7.6, 2.0 Hz)		19
24/24’	128.9	7.35-7.27 (m)		
25	127.3 or 127.2	7.35-7.27 (m)		

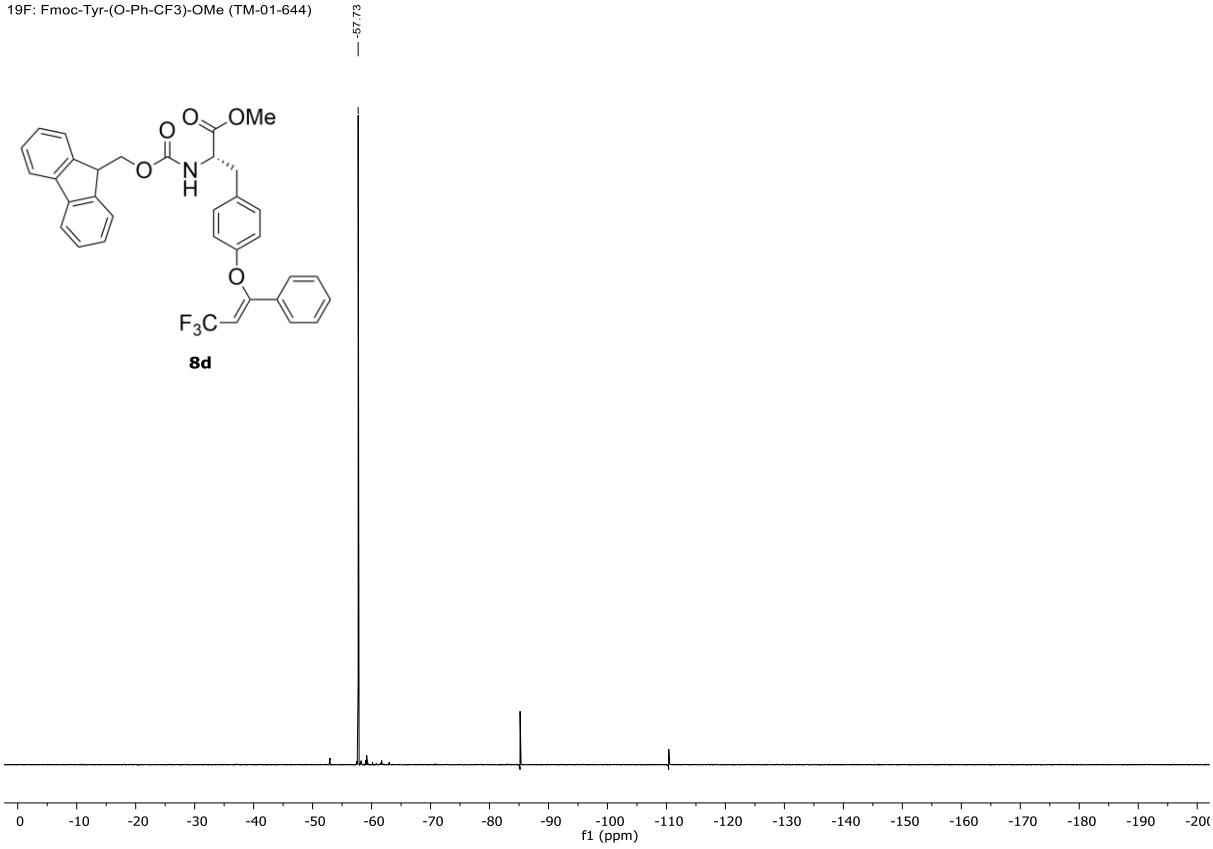
^{1}H-NMR (400 MHz, $CDCl_3$)



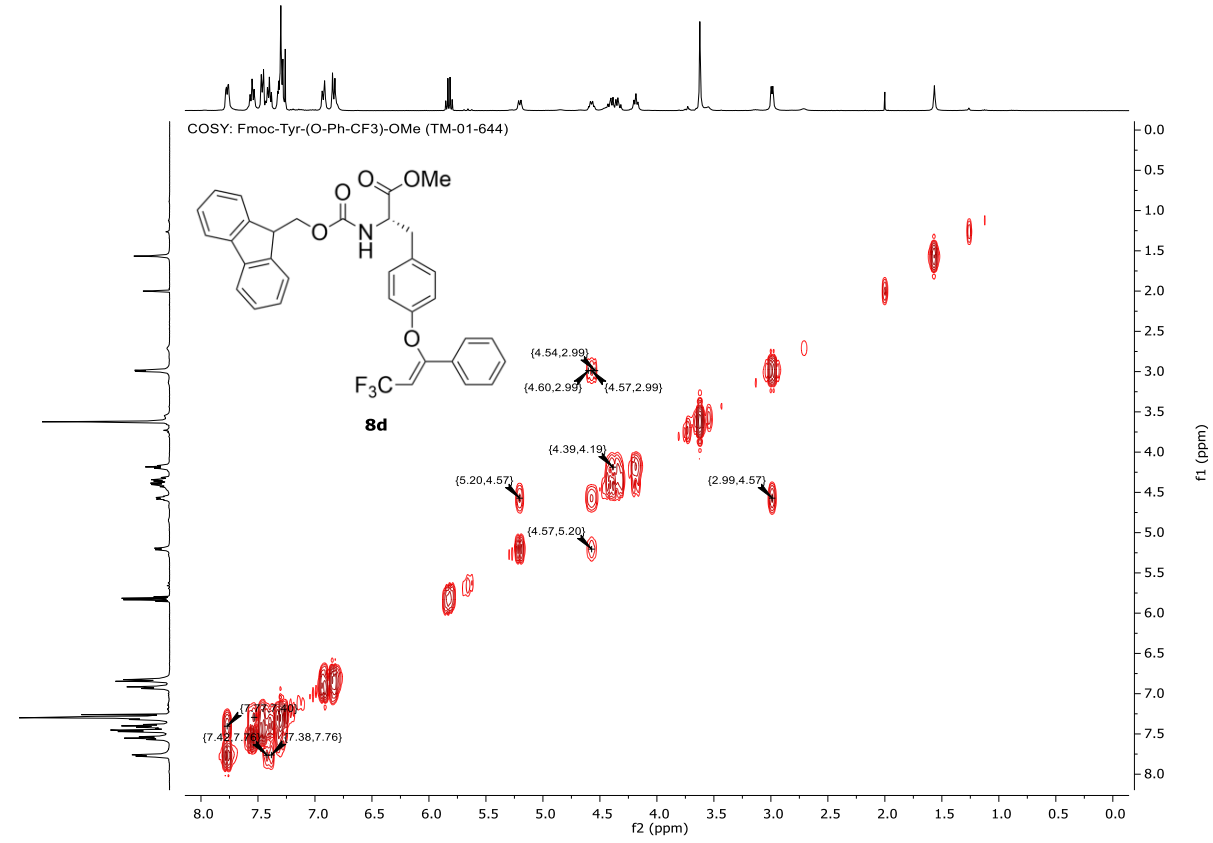
^{13}C-NMR (101 MHz, $CDCl_3$)



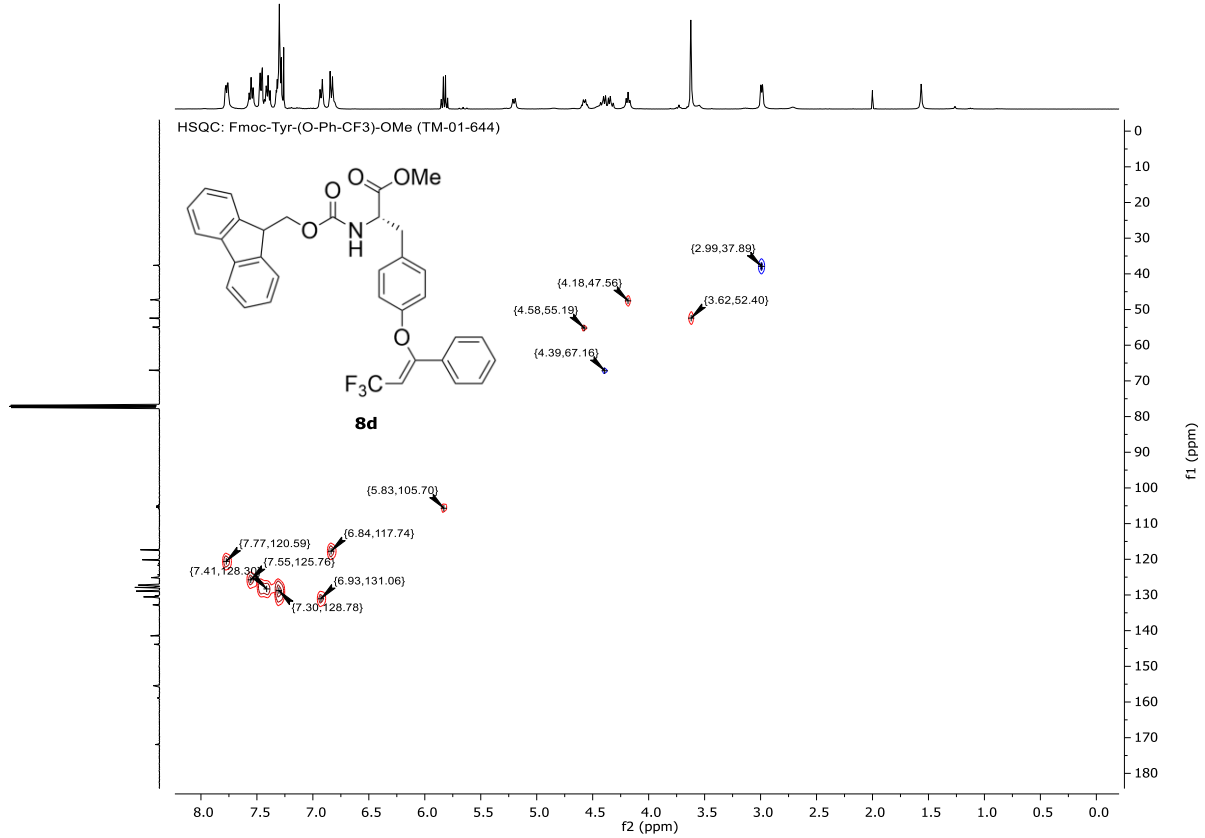
^{19}F-NMR (376 MHz, $CDCl_3$)



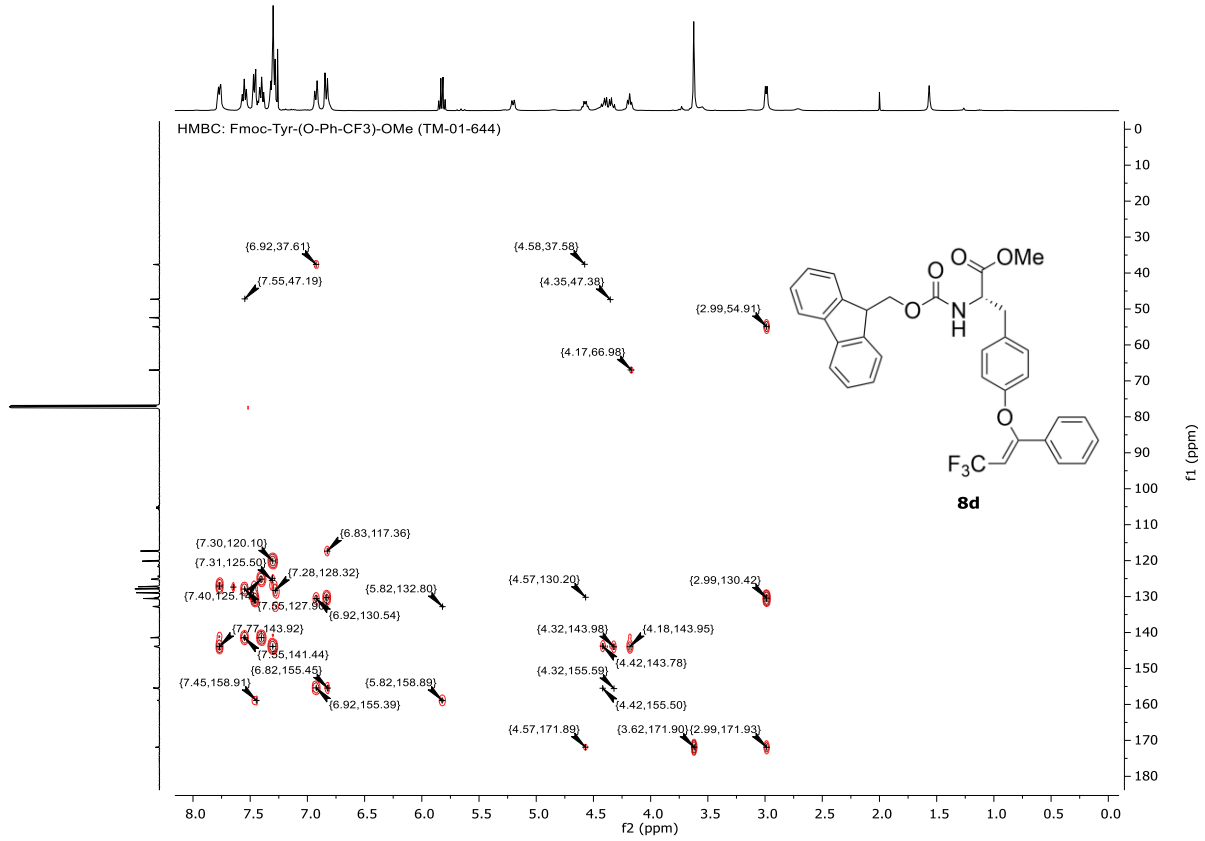
COSY NMR ($CDCl_3$)



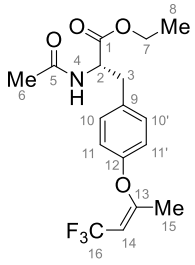
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



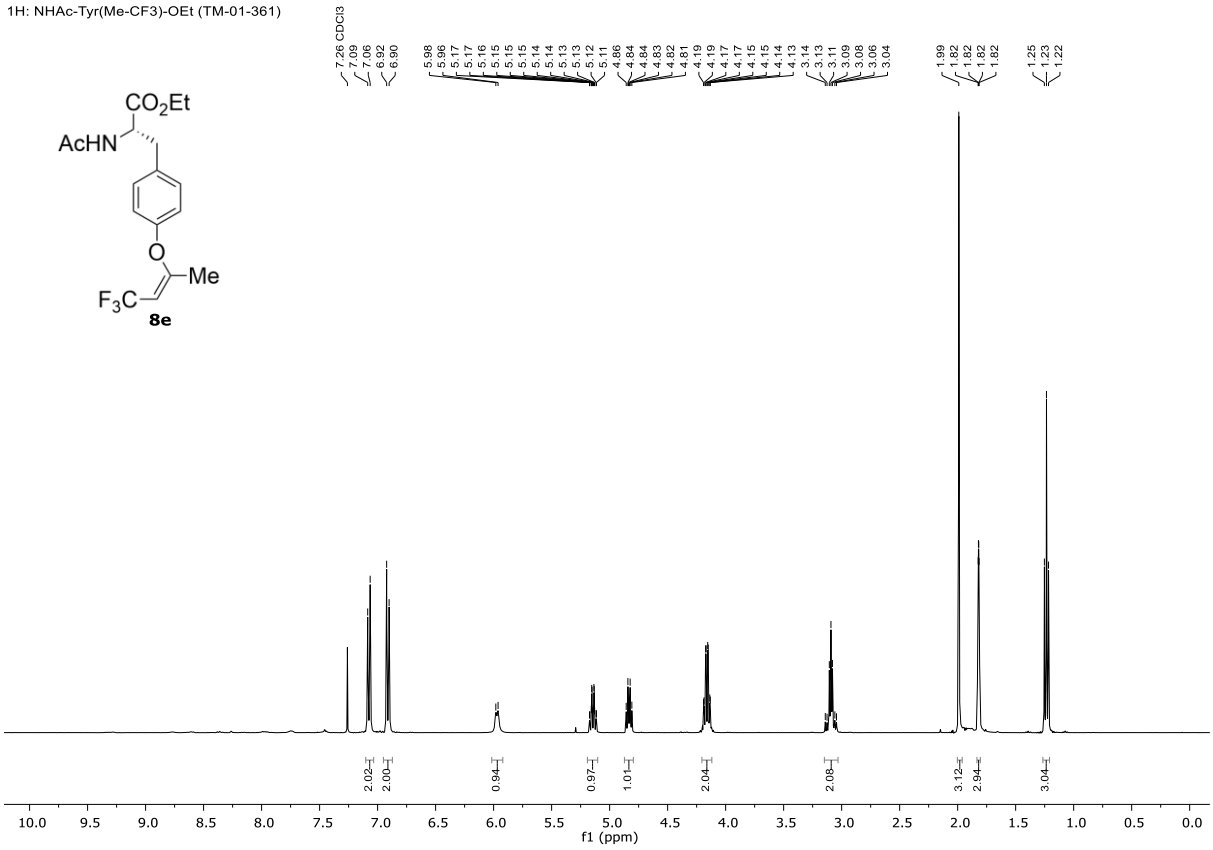
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((4,4,4-trifluorobut-2-en-2-yl)oxy)phenyl)propanoate (8e)



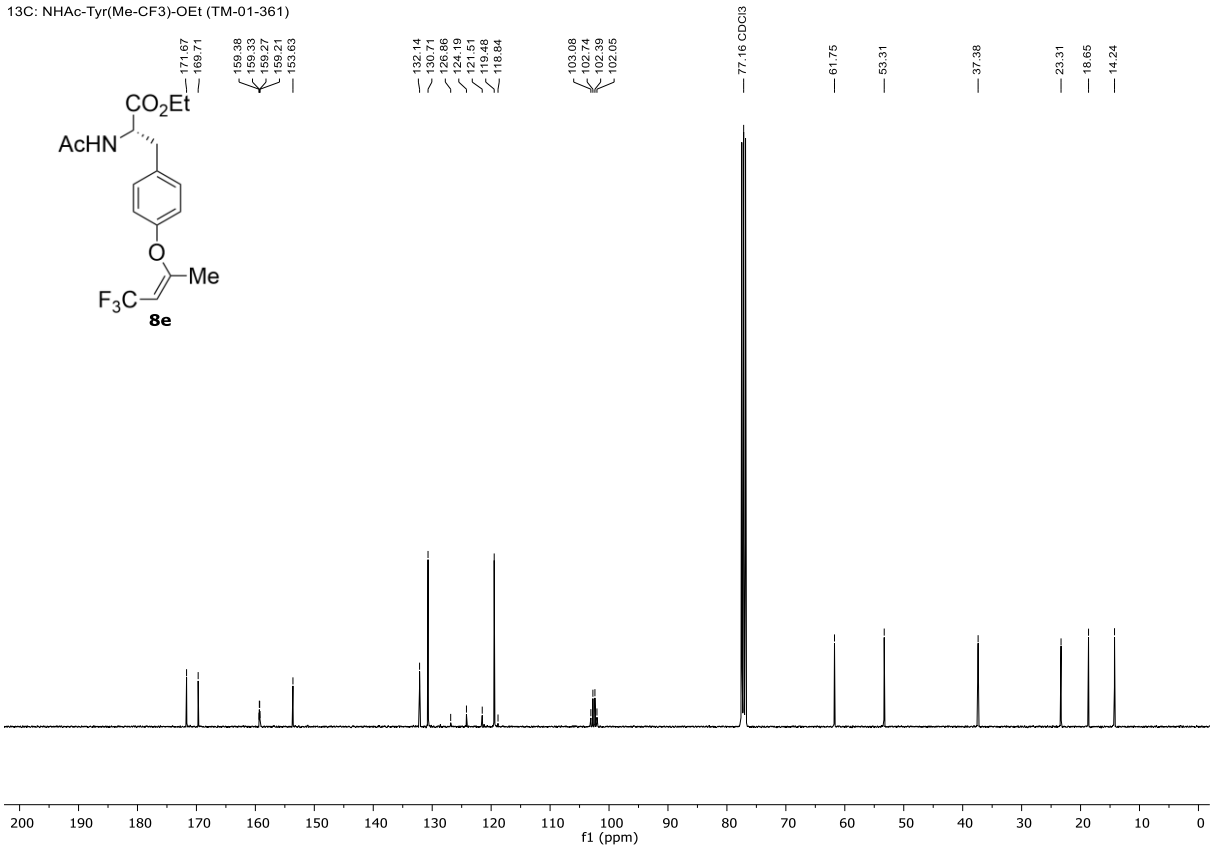
	δ_C	δ_H	COSY	HMBC (H→C)
1	171.7			
2	53.3	4.83 (7.8, 5.8 Hz)	3, 4	1, 3, 9
3	37.4	3.15-3.04 (m)	2	1, 2, 10/10‘
4	/	5.97 (d, 7.7 Hz)	2	
5	169.7			
6	23.3	1.99 (s)		5
7	61.7	4.16 (qd, 7.2, 1.9 Hz)	8	1, 8
8	14.2	1.23 (t, 7.1 Hz)	7	7
9	132.1			
10/10’	130.7	7.07 (d, 8.5 Hz)	11/11’	3, 11/11’, 12
11/11’	119.5	6.91 (d, 8.5 Hz)	10/10’	9, 10/10’, 12
12	153.6			
13	159.3 (q, 5.8 Hz)			
14	102.6 (q, 34.6 Hz)	5.14 (qd, 7.5, 1.1 Hz)		13, 15, 16
15	18.6	1.82 (dd, 2.1, 1.1 Hz)		13, 14
16	122.9 (q, 269.3 Hz)			

Table S32. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((4,4,4-trifluorobut-2-en-2-yl)oxy)phenyl)propanoate (**8e**).

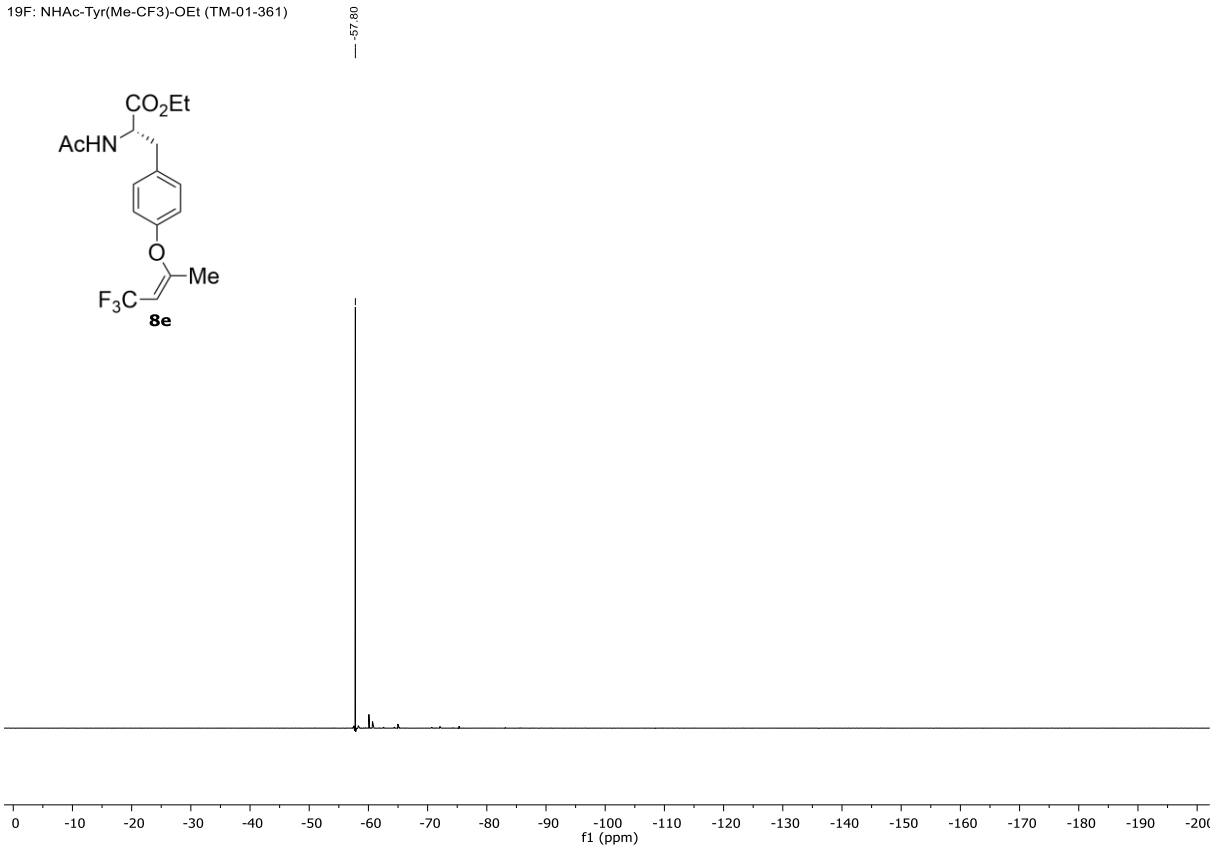
^{1}H-NMR (400 MHz, $CDCl_3$)



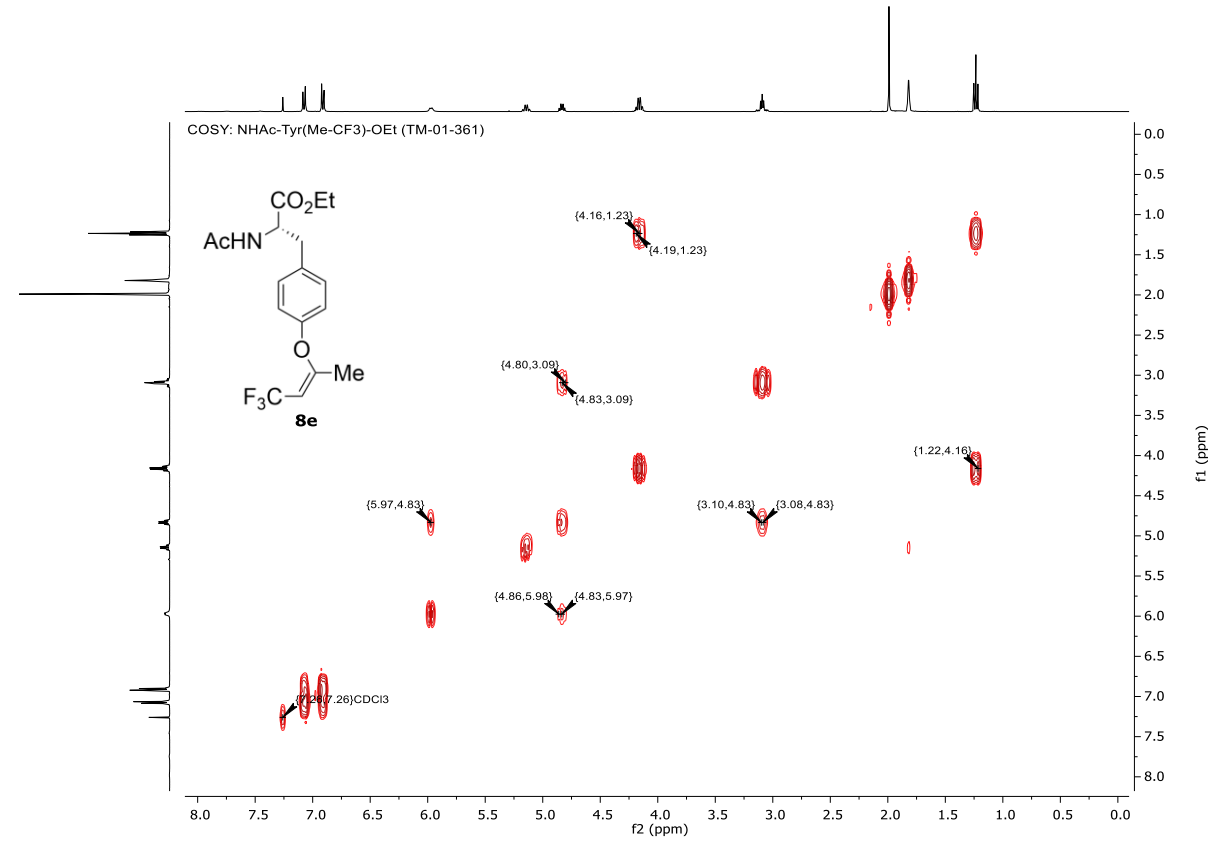
^{13}C-NMR (101 MHz, $CDCl_3$)



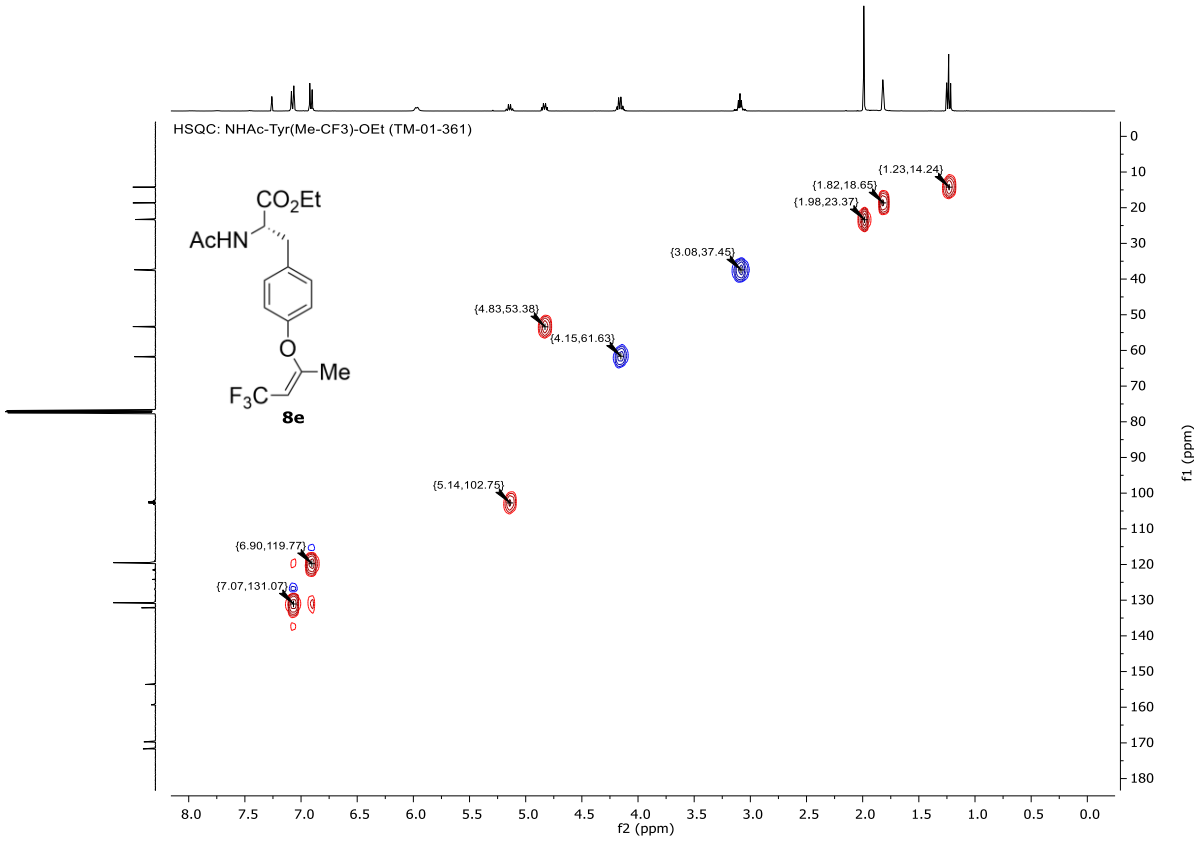
^{19}F-NMR (376 MHz, $CDCl_3$)



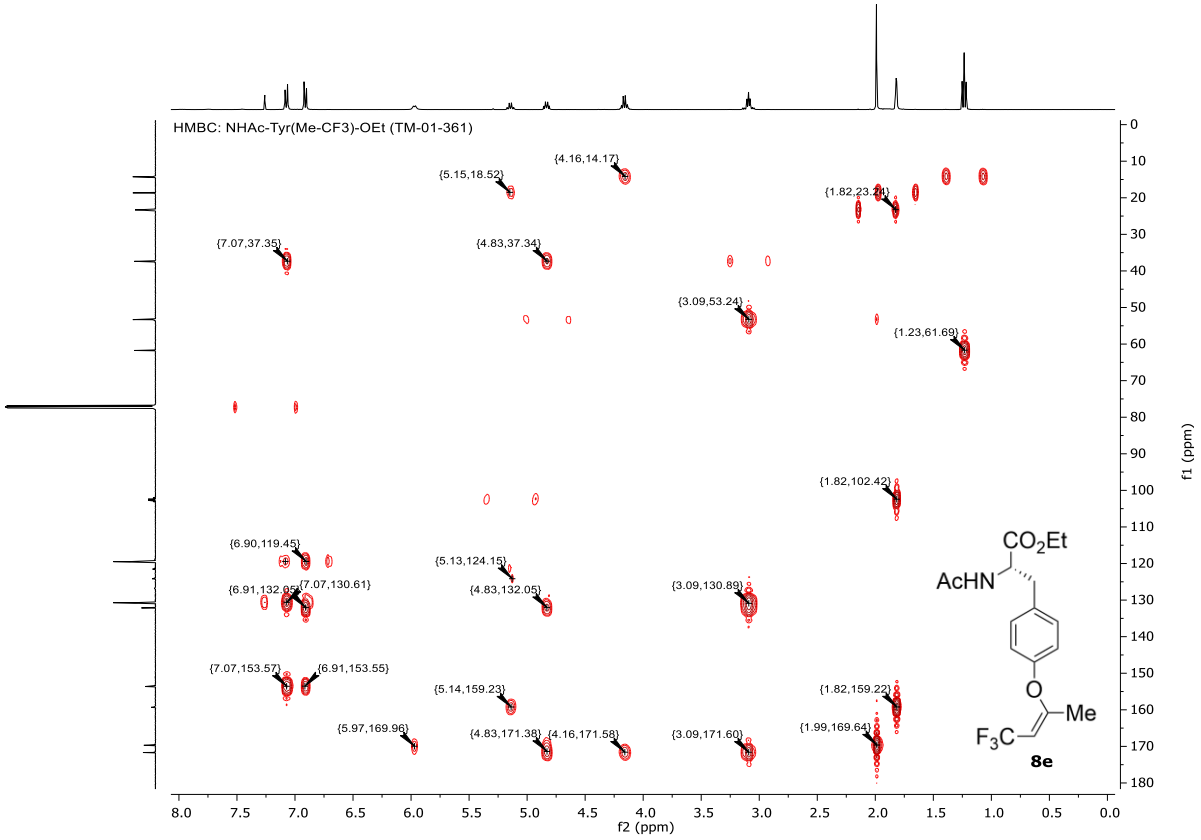
COSY NMR ($CDCl_3$)



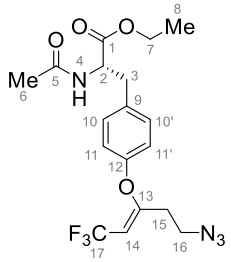
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



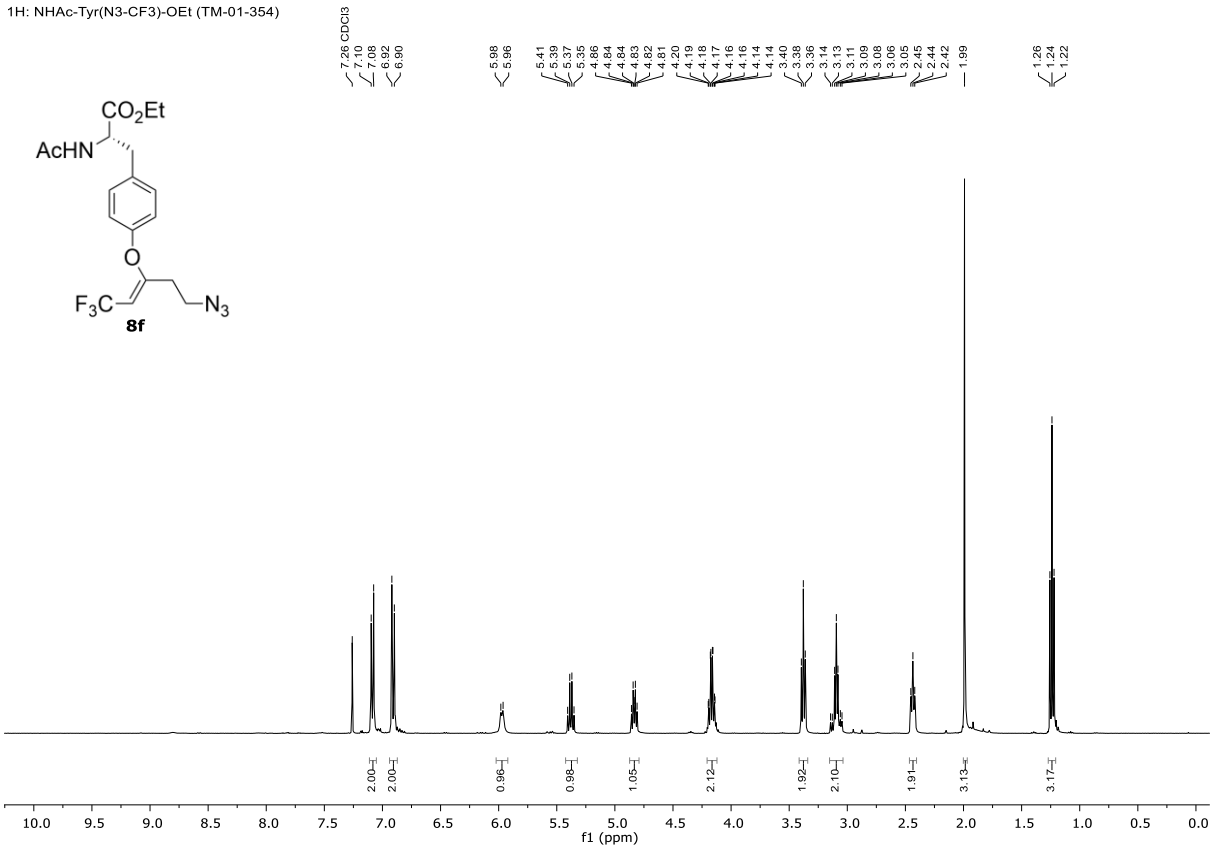
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-azido-1,1,1-trifluoropent-2-en-3-yl)oxy)phenyl)propanoate (8f)



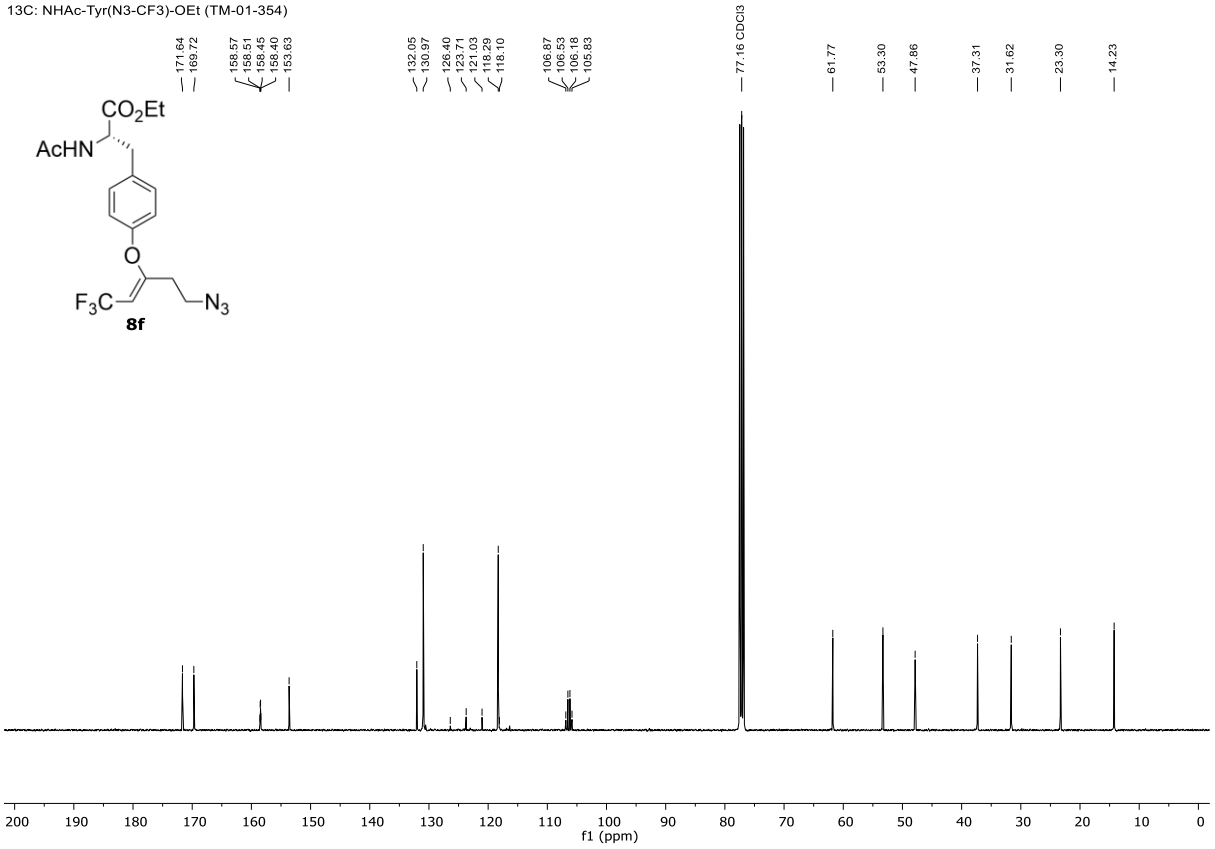
	δ_C	δ_H	COSY	HMBC (H→C)
1	171.6			
2	53.3	4.83 (dt, 7.8, 5.8 Hz)	3, 4	1, 3, 9
3	37.3	3.10 (dd, 14.2, 6.3 Hz), 3.09 (dd, 14.2, 5.6 Hz)	2	1, 2, 10/10’
4	/	5.97 (d, 7.7 Hz)	2	5
5	169.7			
6	23.3	1.99 (s)		5
7	61.8	4.17 (qd, 7.2, 1.8 Hz)	8	1, 8
8	14.2	1.24 (t, 7.1 Hz)	7	7
9	132.1			
10/10’	131.0	7.09 (d, 8.5 Hz)	11/11’	3, 11/11’, 12
11/11’	118.3	6.91 (d, 8.6 Hz)	10/10’	10/10’, 12
12	153.6			
13	158.5 (q, 5.6 Hz)			
14	106.4 (q, 34.9 Hz)	5.38 (q, 7.3 Hz)		13, 15, 17
15	31.6	2.44 (t, 6.8 Hz)	16	13, 14, 16
16	47.9	3.38 (t, 6.7 Hz)	15	13, 15
17	122.4 (q, 270.0 Hz)			

Table S33. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((5-azido-1,1,1-trifluoropent-2-en-3-yl)oxy)phenyl)propanoate (**8f**).

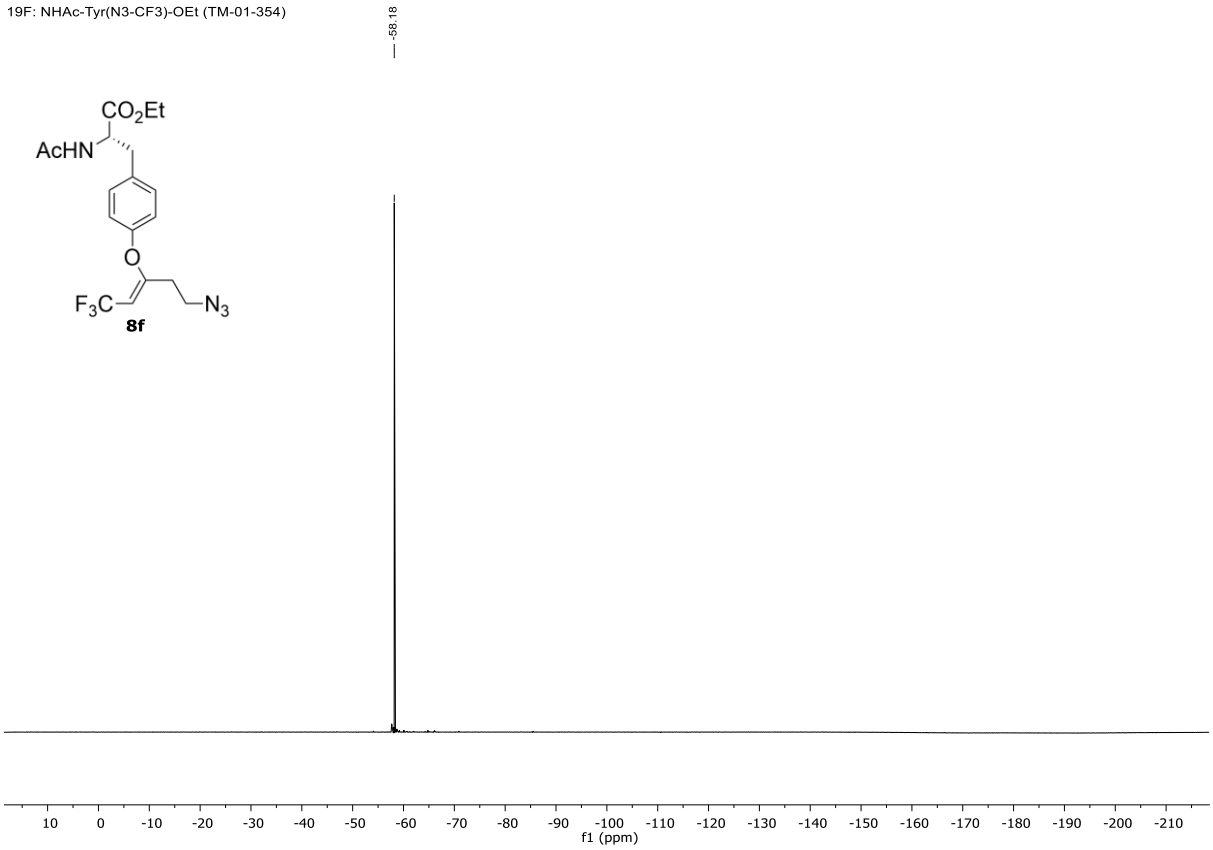
^{1}H-NMR (400 MHz, $CDCl_3$)



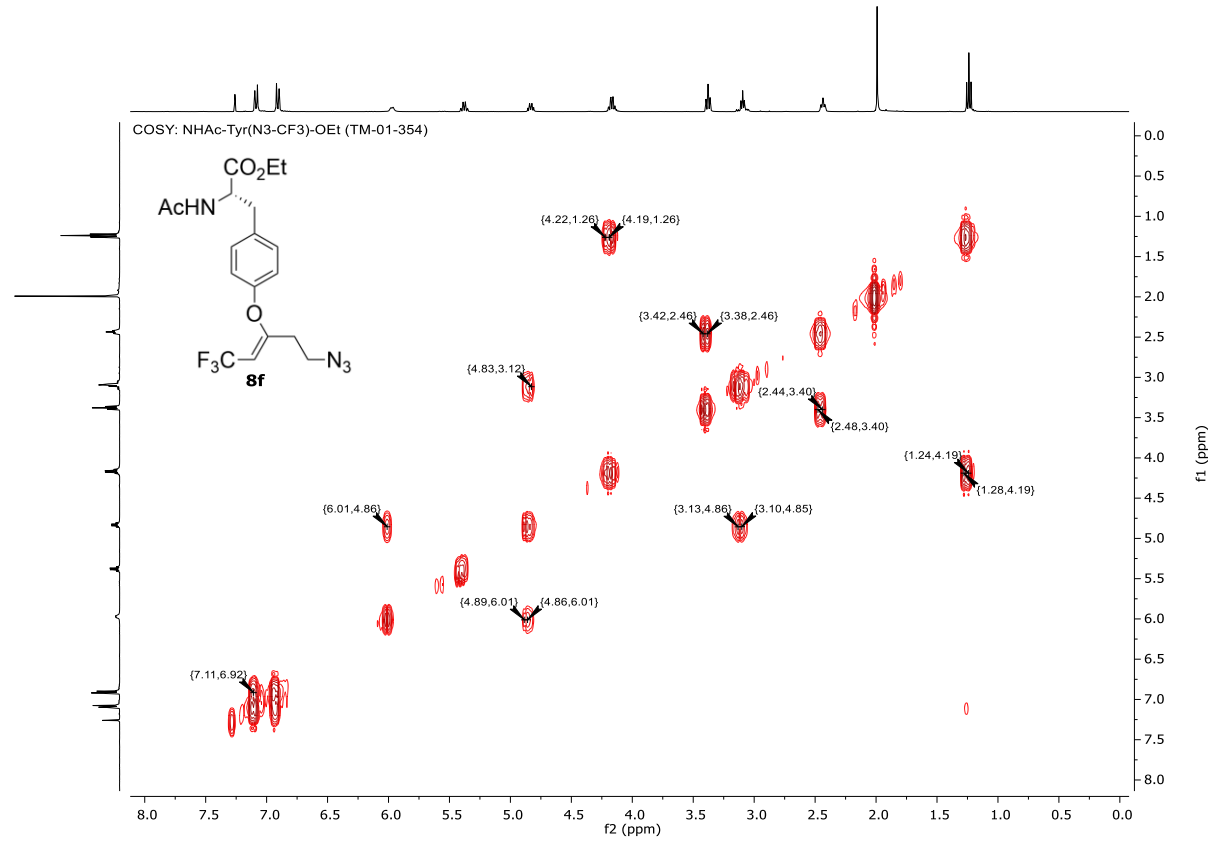
^{13}C-NMR (101 MHz, $CDCl_3$)



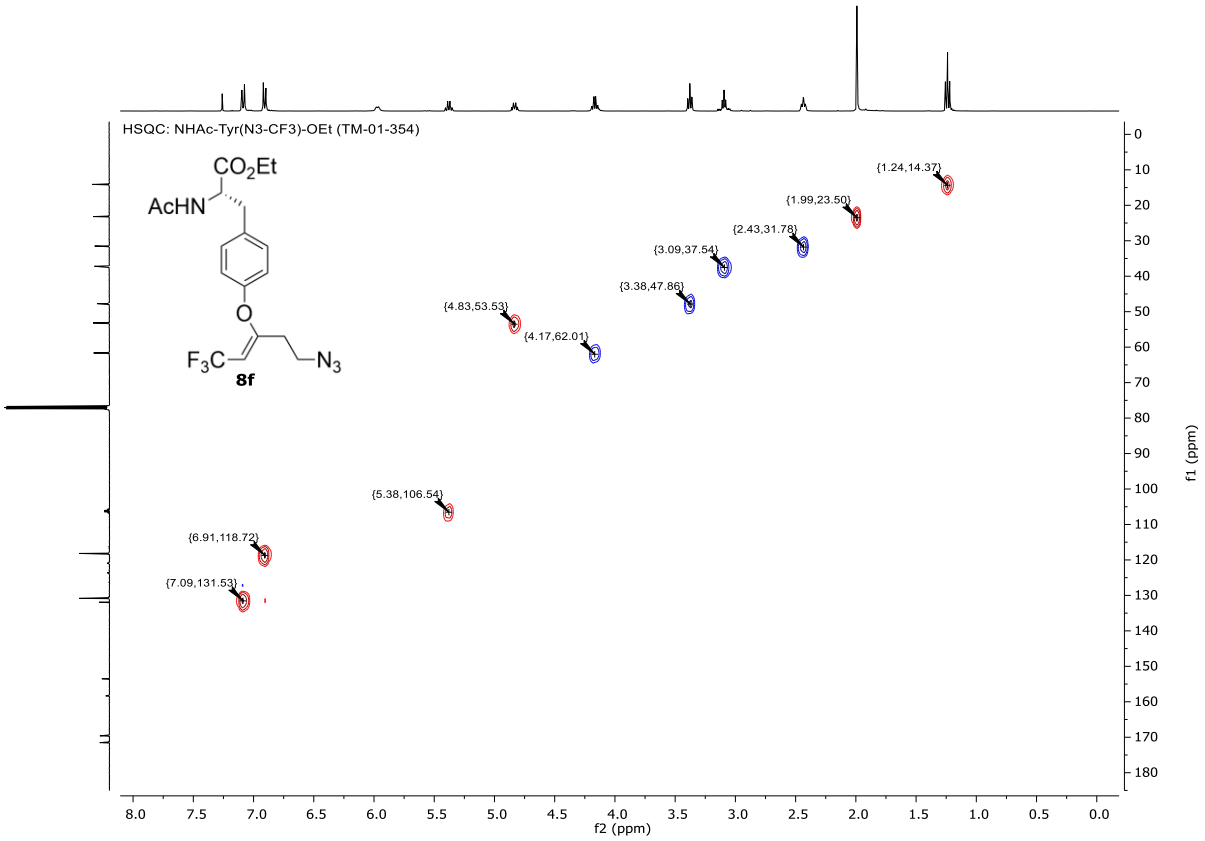
^{19}F-NMR (376 MHz, $CDCl_3$)



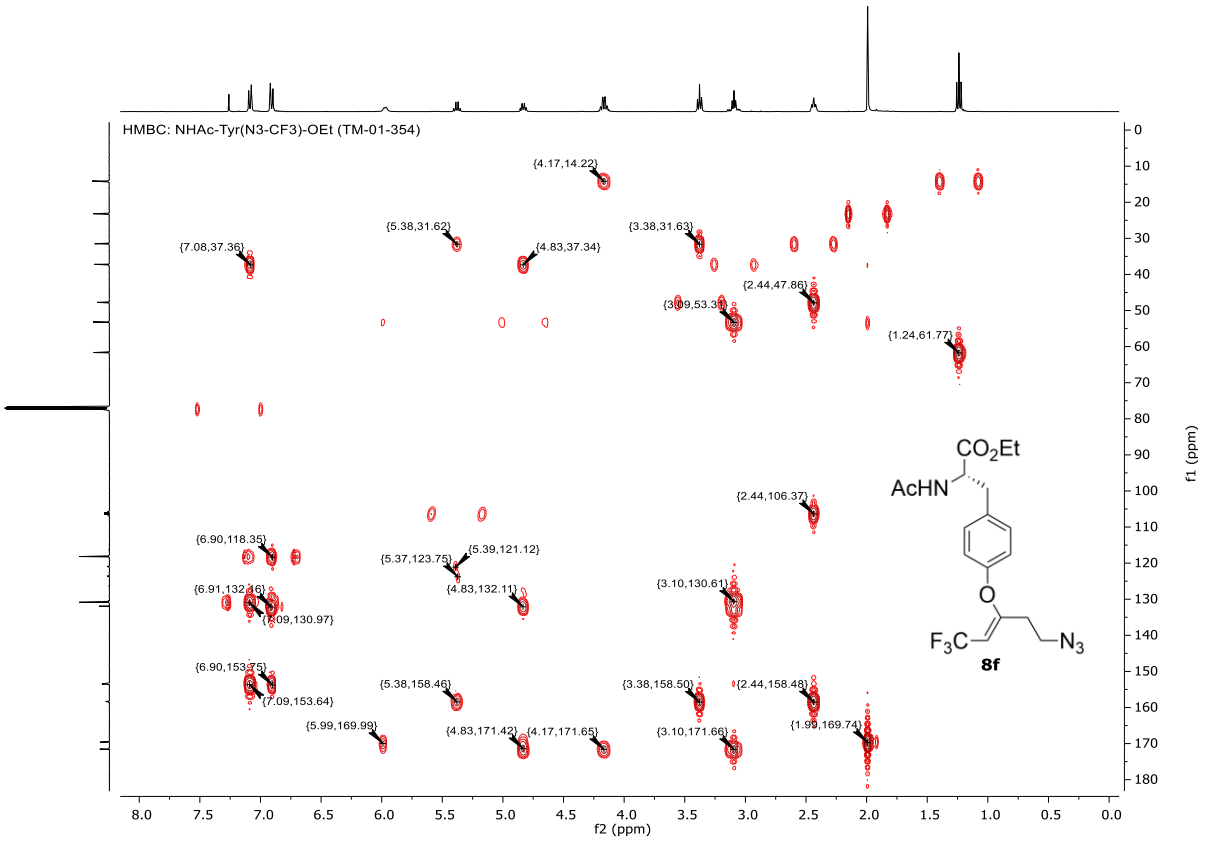
COSY NMR ($CDCl_3$)



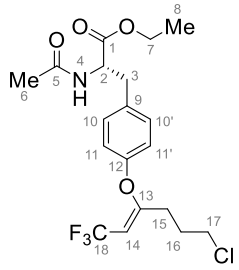
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



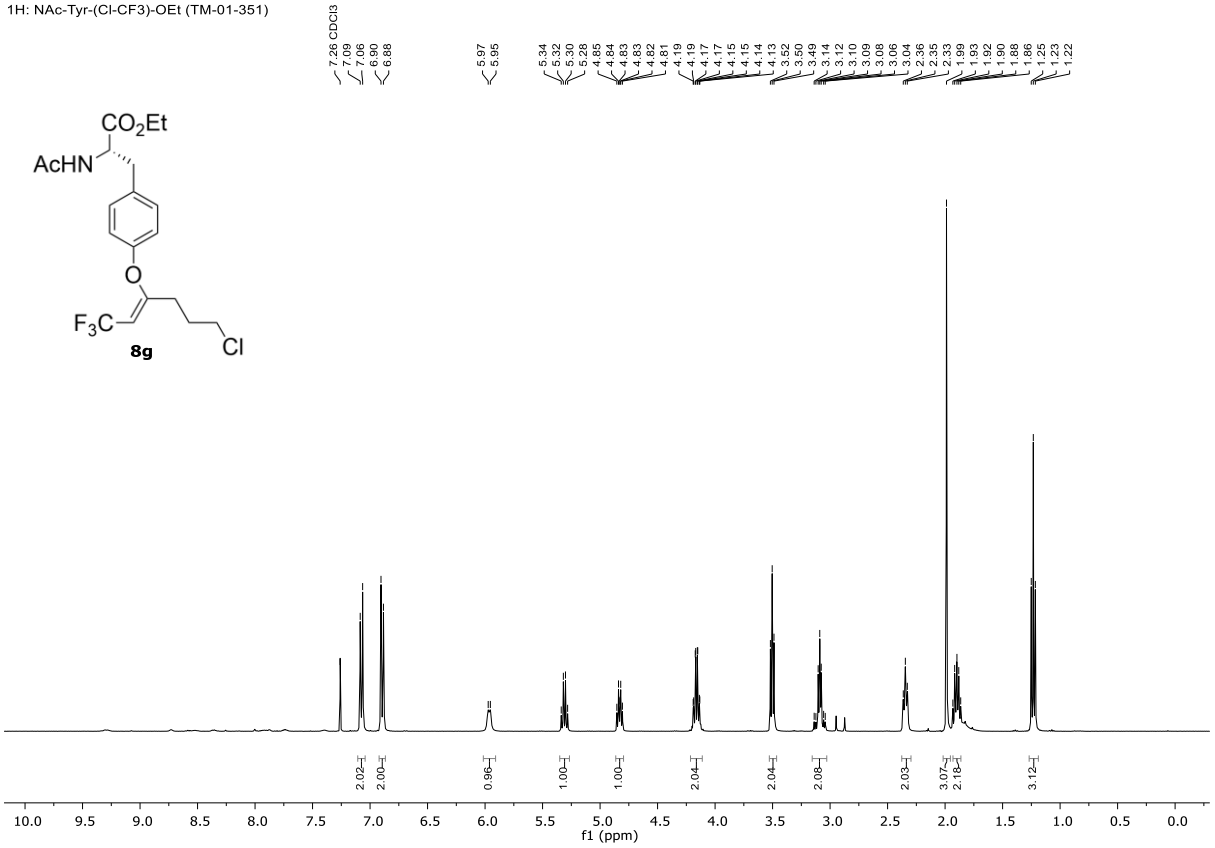
Ethyl (*S*,*Z*)-2-acetamido-3-(4-((6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)phenyl)propanoate (8g)



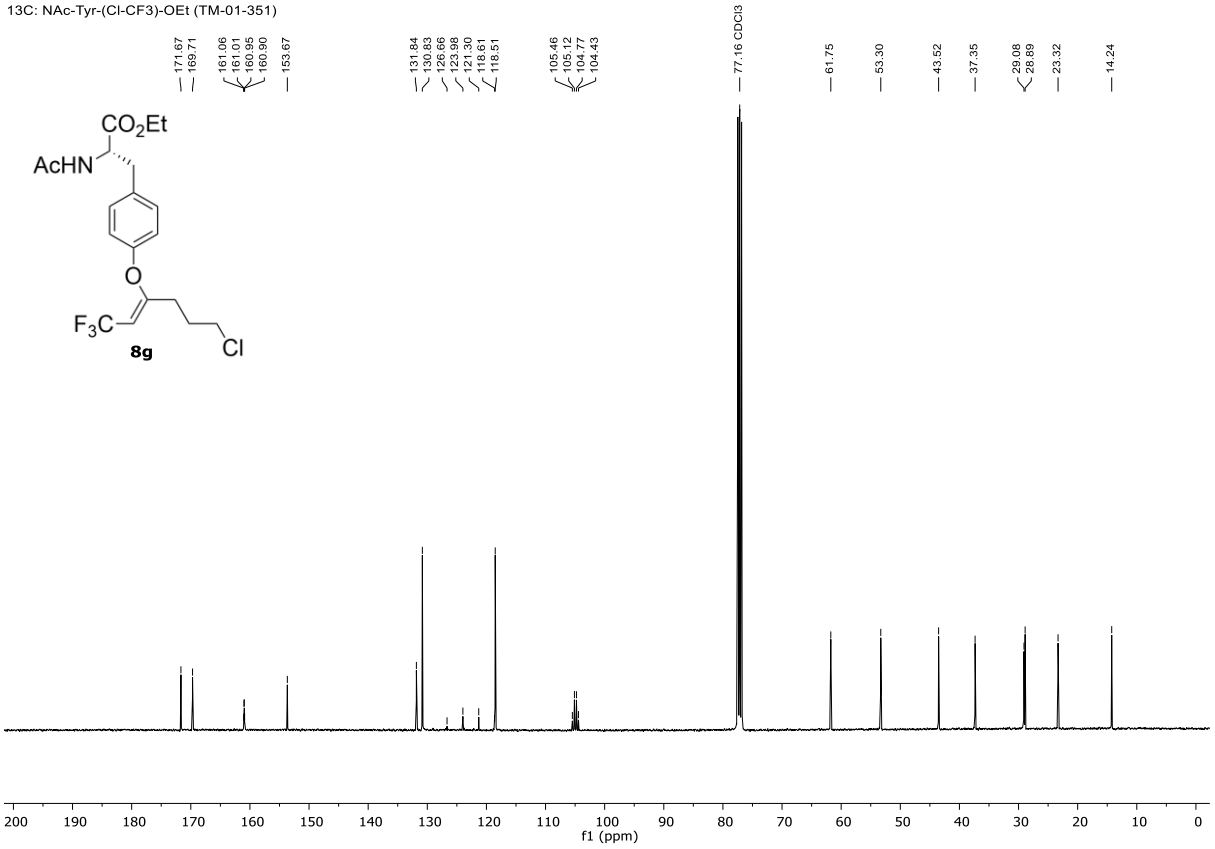
	δ_C	δ_H	COSY	HMBC (H→C)
1	171.7			
2	53.3	4.83 (dt, 7.8, 5.8 Hz)	3, 4	1, 3, 9
3	37.4	3.09 (t, 5.5 Hz)	4	1, 2, 11/11’
4	/	5.96 (d, 7.5 Hz)	2	
5	169.7			
6	23.3	1.99 (s)		5
7	61.8	4.16 (qd, 7.2, 1.6 Hz)	8	1, 8
8	14.2	1.23 (t, 7.1 Hz)	7	7
9	131.8			
10/10’	130.8	7.08 (d, 8.5 Hz)	11/11’	3, 11/11’, 12
11/11’	118.5	6.89 (d, 8.5 Hz)	10/10’	10/10’, 12
12	153.7			
13	161.0 (q, 5.6 Hz)			
14	105.0 (q, 34.6 Hz)	5.31 (q, 7.4 Hz)		13, 15, 18
15	28.9	2.39-2.30 (m)	16	13, 14, 16, 17
16	29.1	1.90 (p, 6.5 Hz)	15, 17	13, 15, 17
17	43.5	3.50 (t, 6.3 Hz)	16	15
18	122.6 (q, 269.8 Hz)			

Table S34. Detailed NMR assignment of ethyl (*S*,*Z*)-2-acetamido-3-(4-((6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)phenyl)propanoate (**8g**).

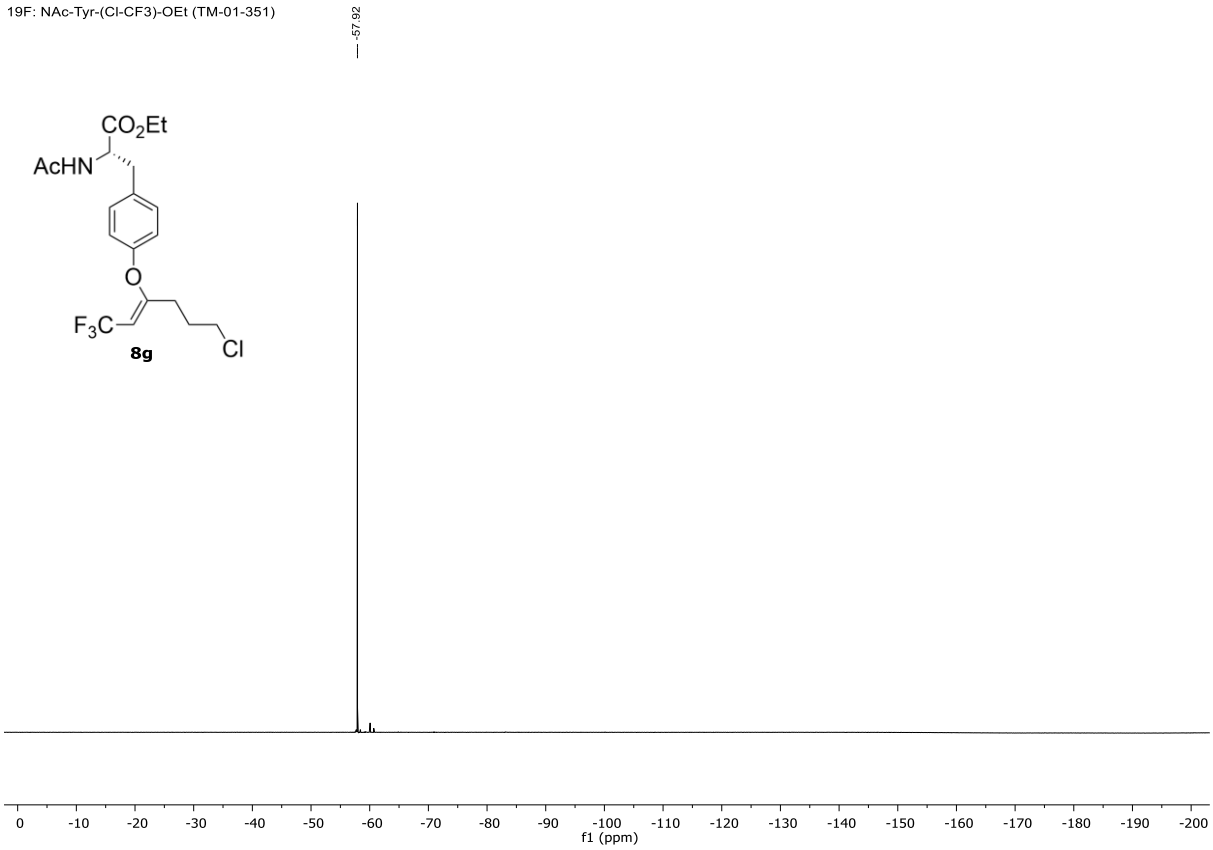
^{1}H-NMR (400 MHz, $CDCl_3$)



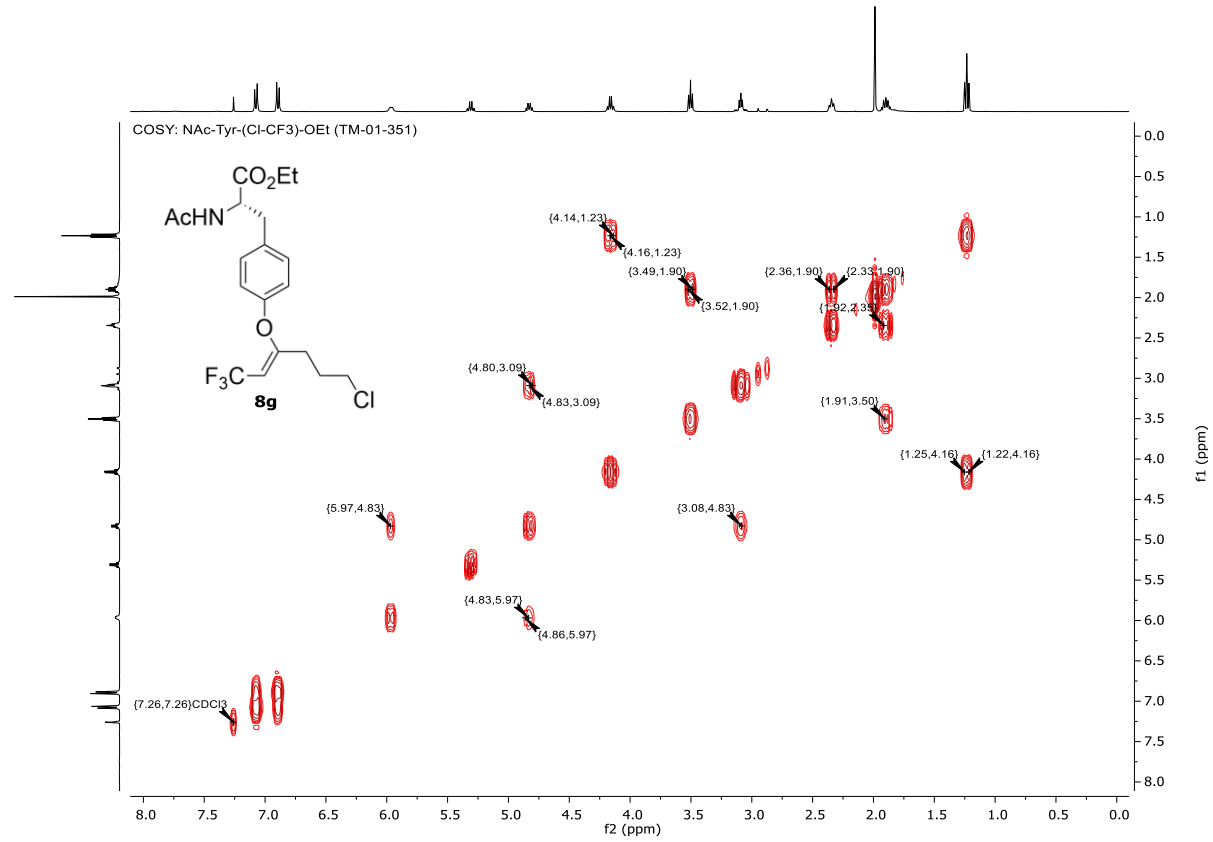
^{13}C-NMR (101 MHz, $CDCl_3$)



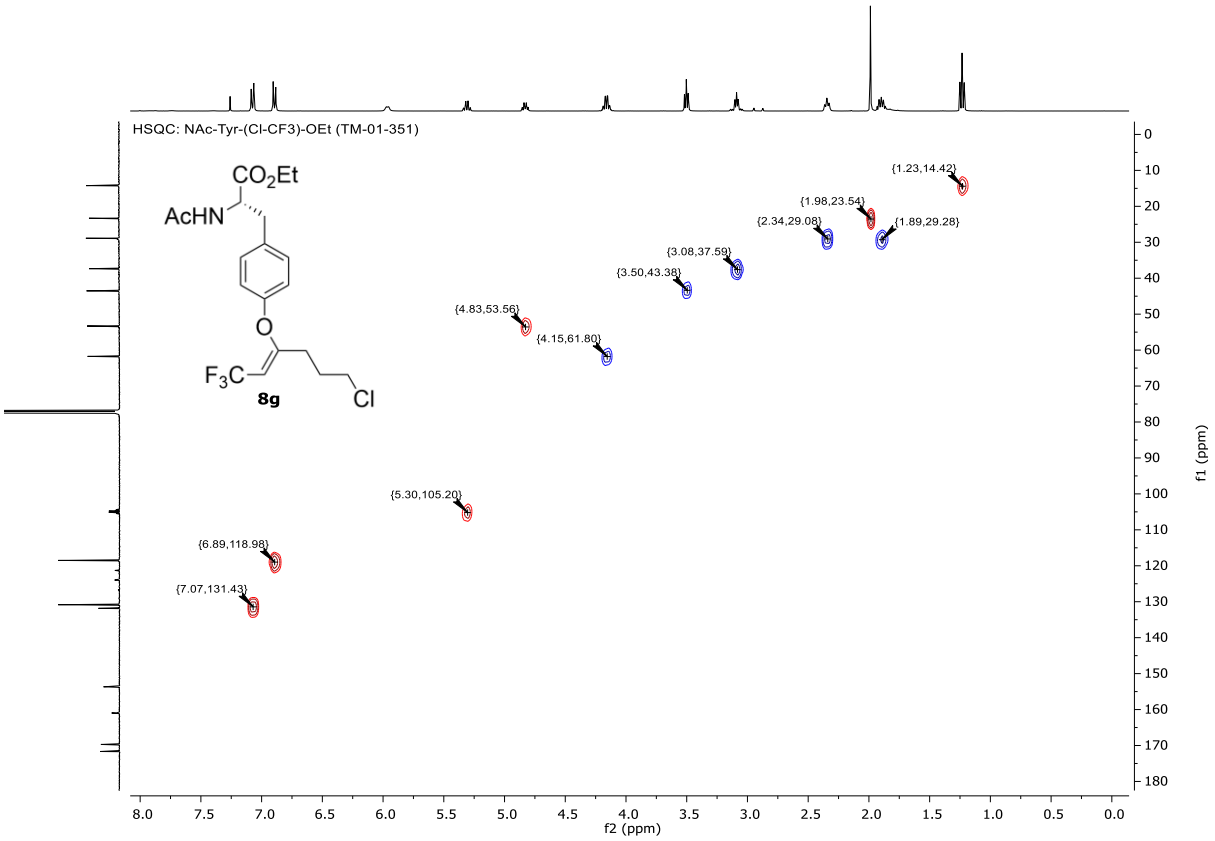
^{19}F-NMR (376 MHz, $CDCl_3$)



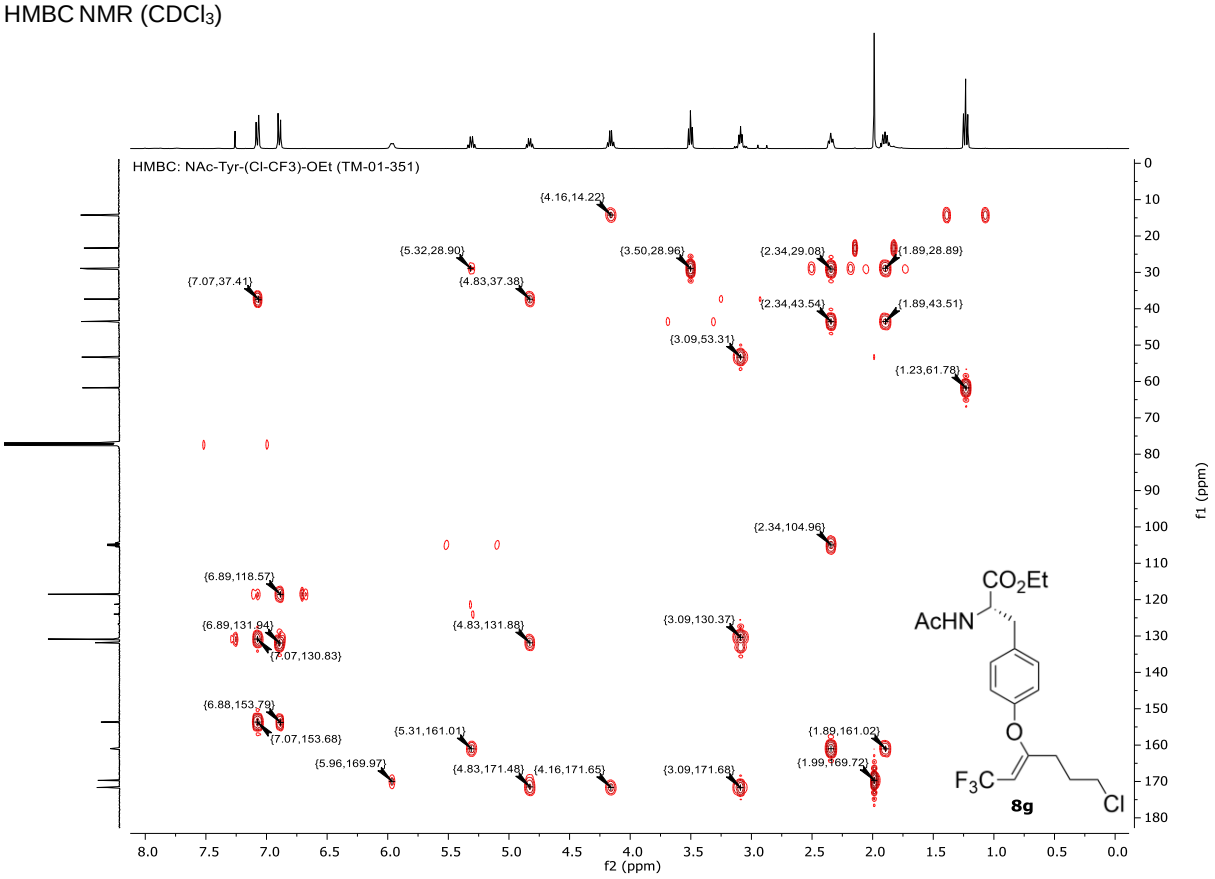
COSY NMR ($CDCl_3$)



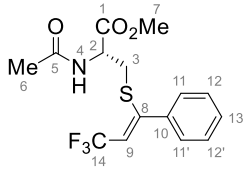
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



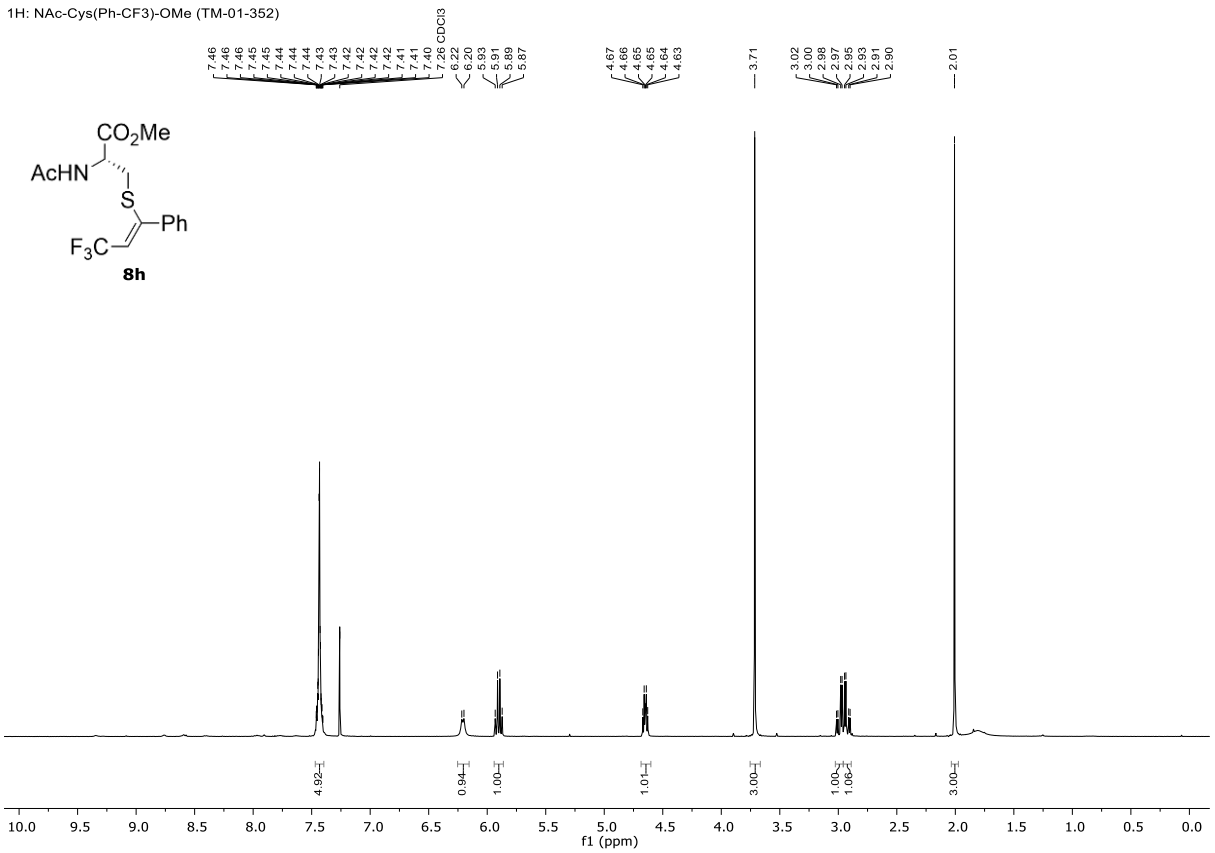
Methyl (*Z*)-N-acetyl-*S*-(3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinate (8h)



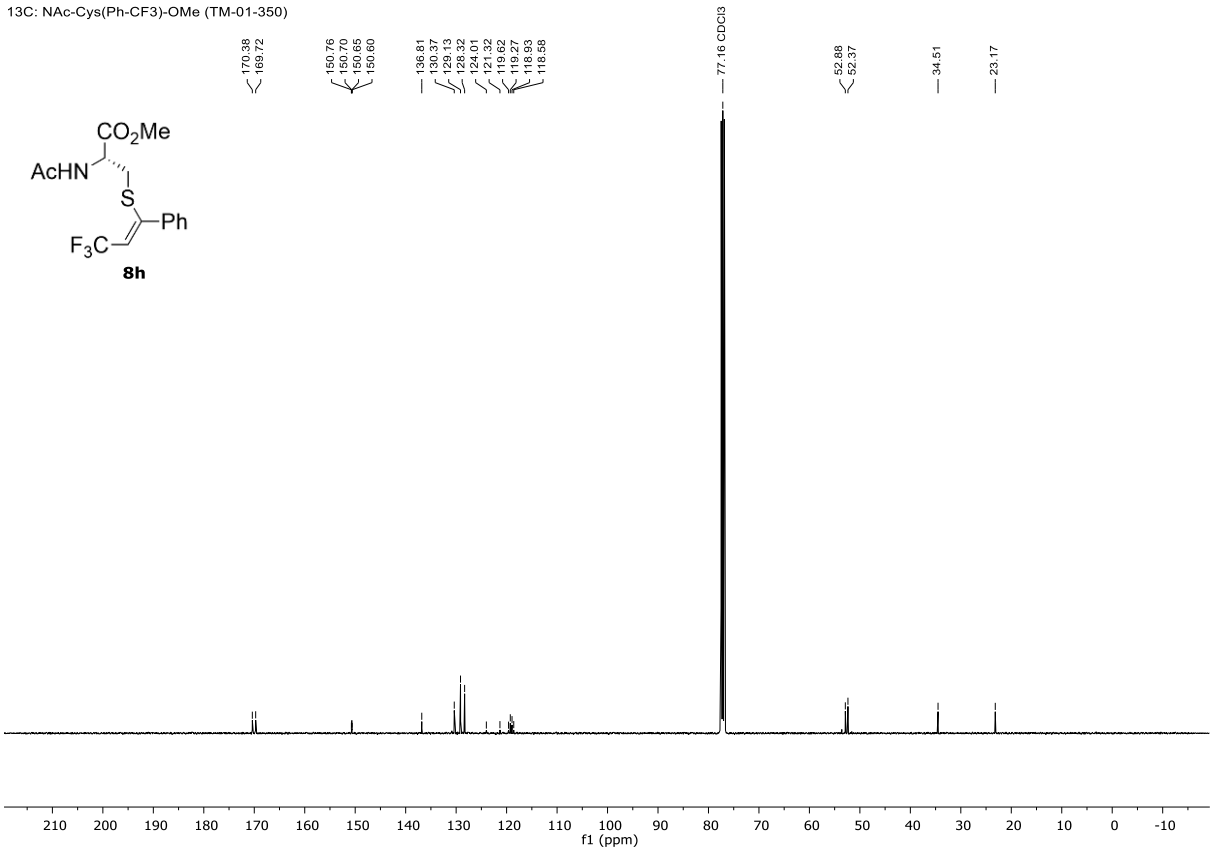
	δ_C	δ_H	COSY	HMBC (H→C)
1	170.4			
2	52.4	4.65 (dt, 7.5, 4.6 Hz)	3, 4	1, 3
3	34.5	2.99 (dd, 14.2, 4.7 Hz), 2.92 (dd, 14.2, 4.6 Hz)	2	1, 2, 8
4	/	6.21 (d, 7.5 Hz)	2	
5	169.7			
6	23.2	2.01 (s)		5
7	52.9	3.71 (s)		1
8	150.7 (q, 5.4 Hz)			
9	119.1 (q, 34.8 Hz)	5.90 (q, 7.9 Hz)		10, 14
10	136.8			
11/11’	128.3	7.47-7.40 (m)	12/12’	13
12/12’	129.1	7.47-7.40 (m)	11/11’, 13	8
13	130.4	7.47-7.40 (m)		
14	122.7 (q, 270.9 Hz)			

Table S35. Detailed NMR assignment of methyl (*Z*)-N-acetyl-*S*-(3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinate (**8h**).

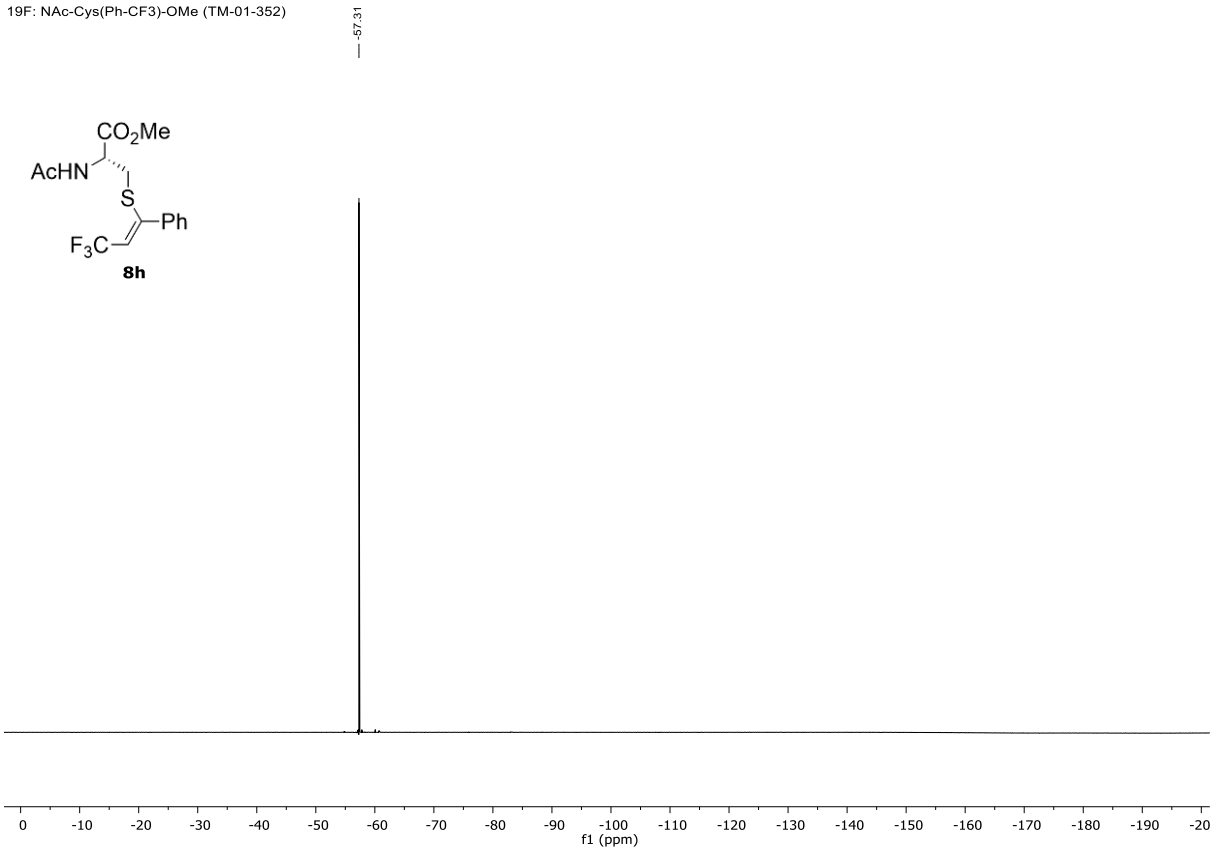
^{1}H-NMR (400 MHz, $CDCl_3$)



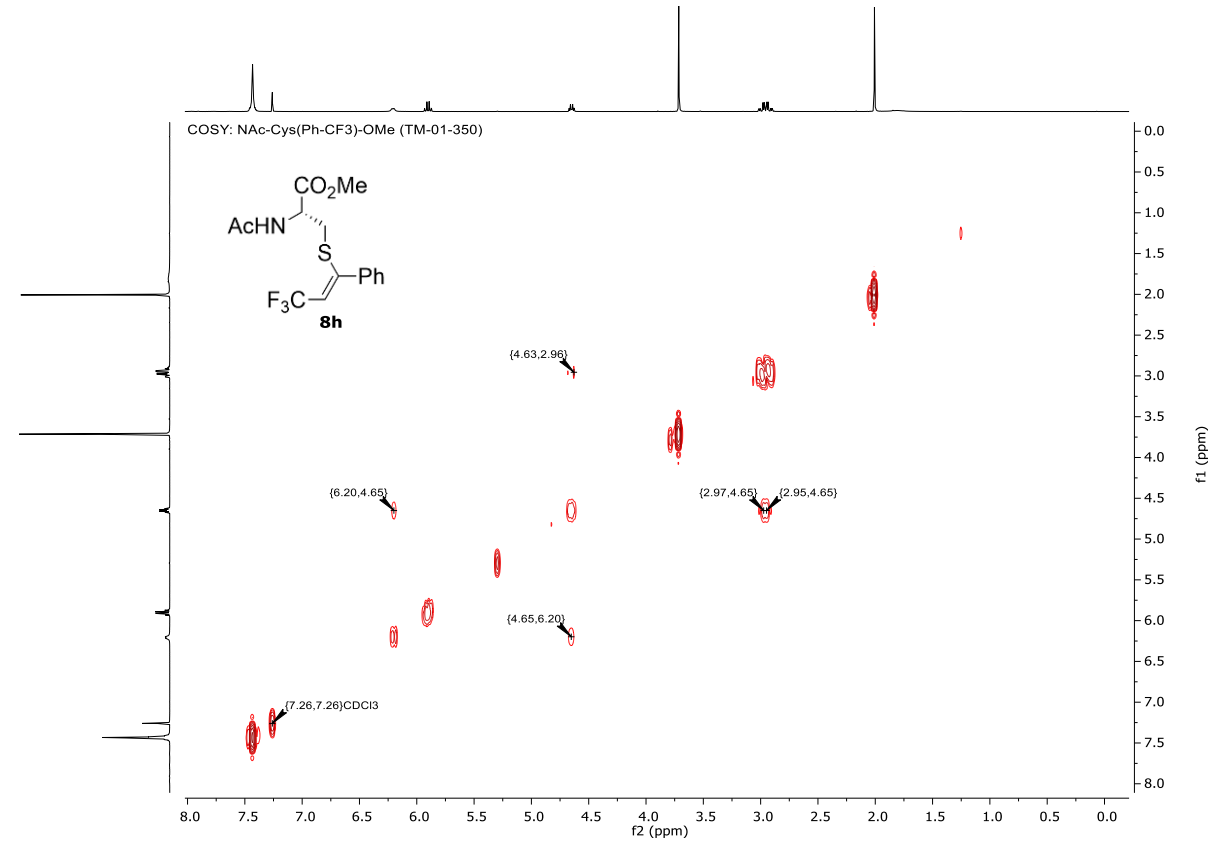
^{13}C-NMR (101 MHz, $CDCl_3$)



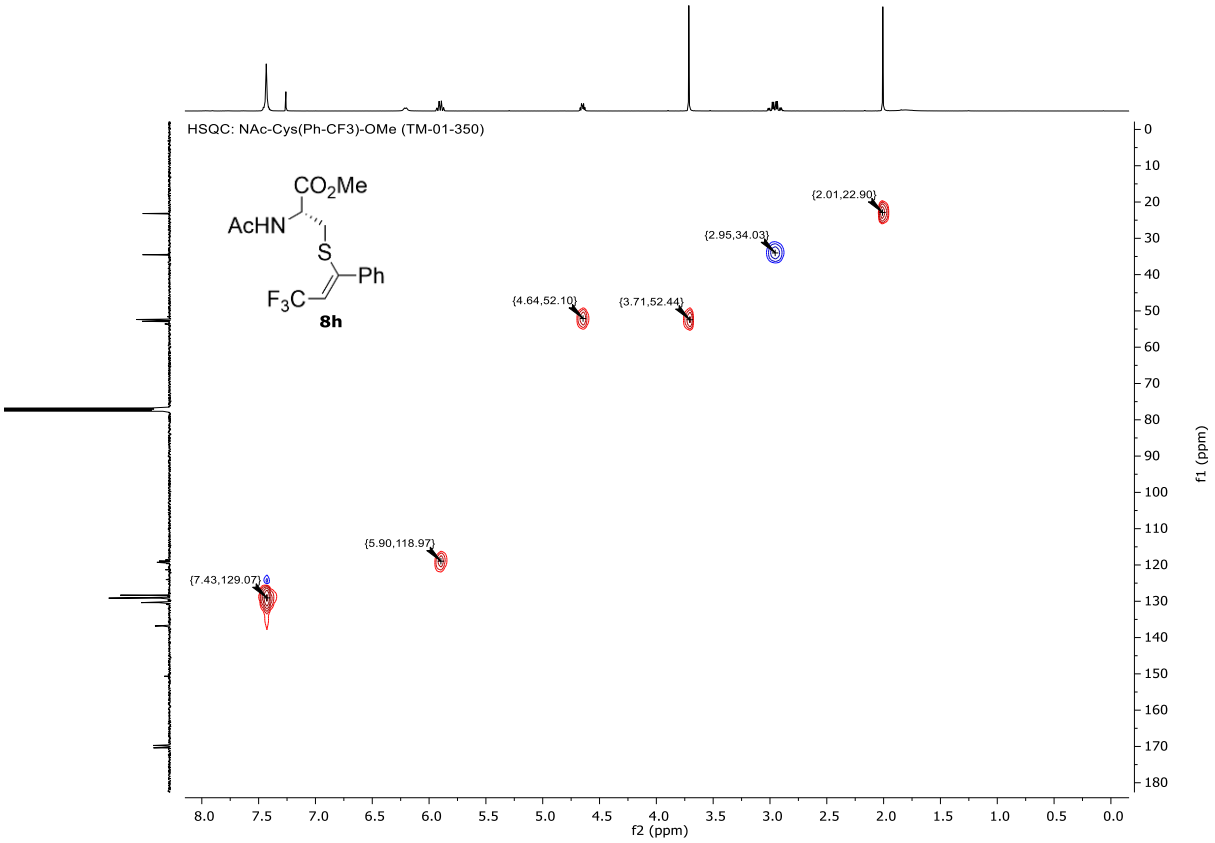
^{19}F-NMR (376 MHz, $CDCl_3$)



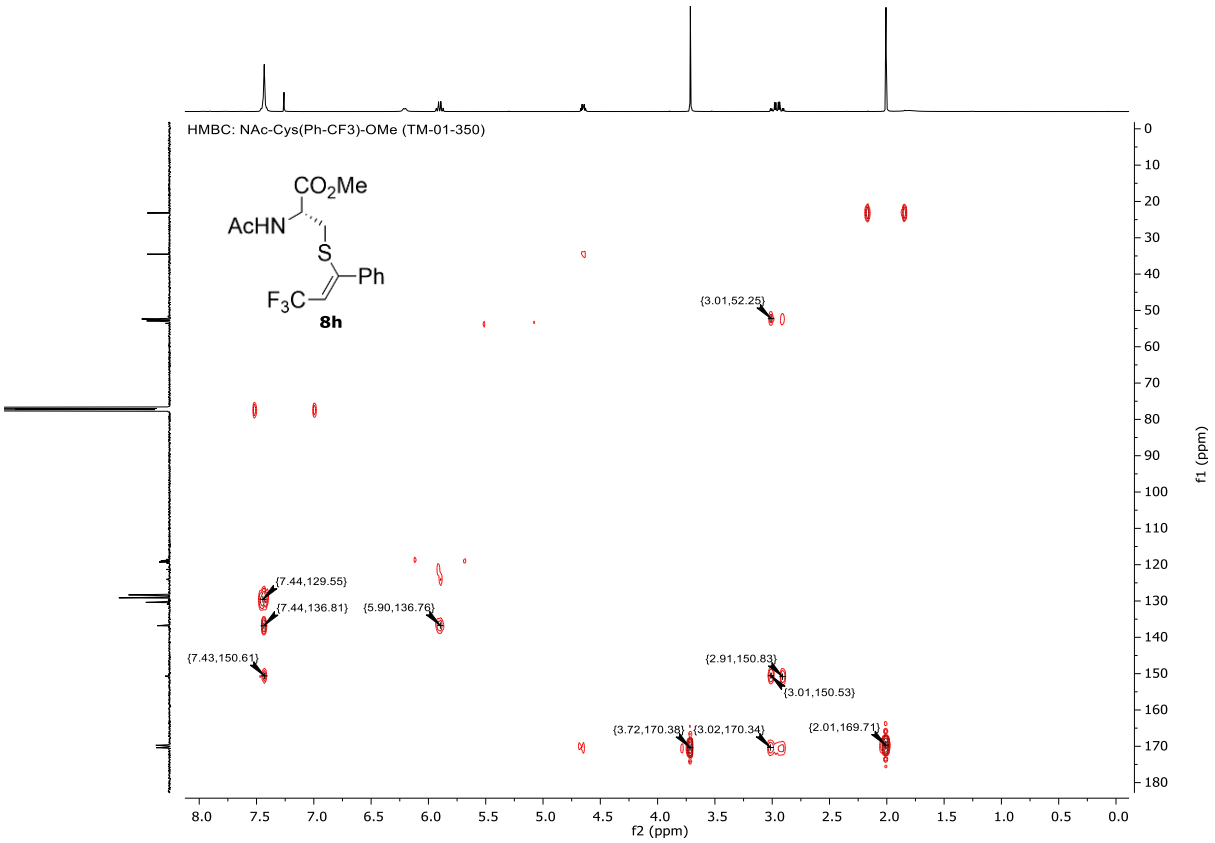
COSY NMR ($CDCl_3$)



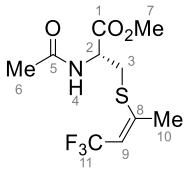
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



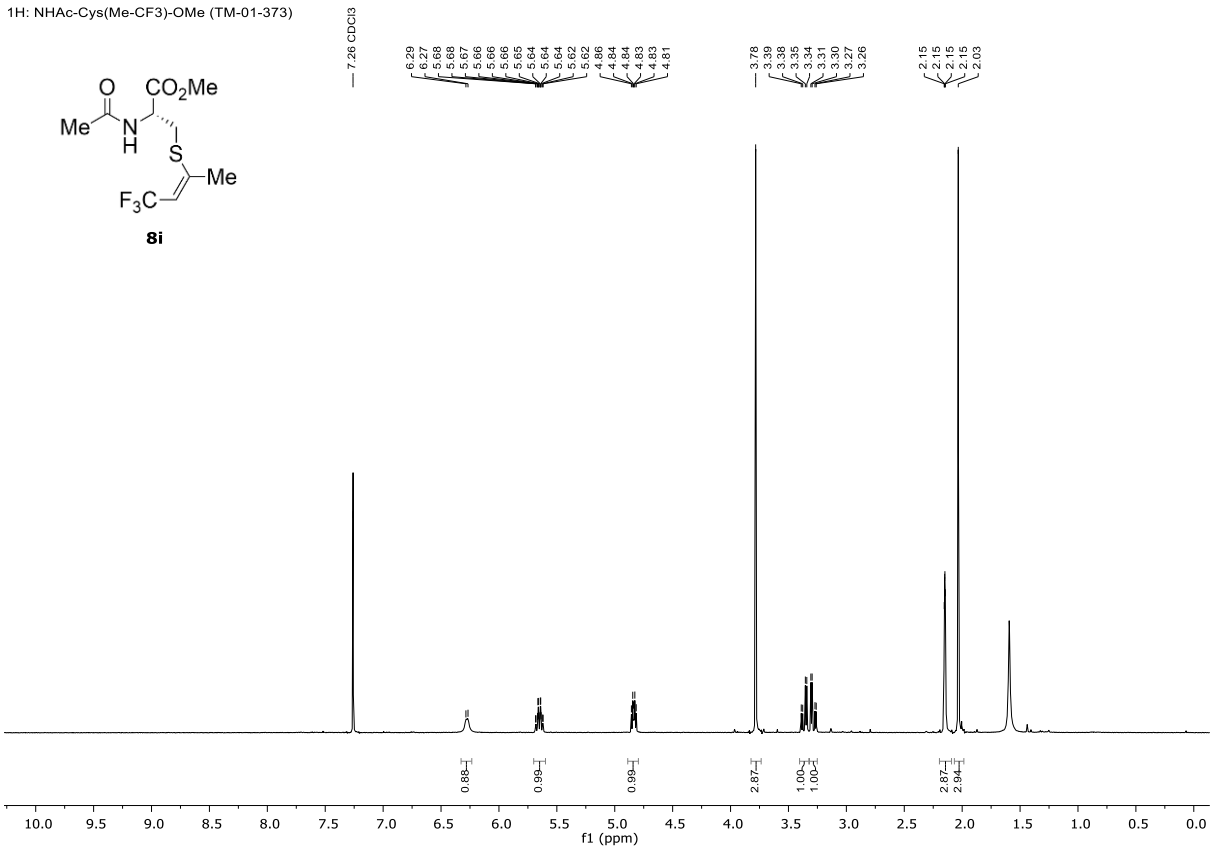
Methyl (*Z*)-*N*-acetyl-*S*-(4,4,4-trifluorobut-2-en-2-yl)-L-cysteinate (8i)



	δ_C	δ_H	COSY	HMBC (H→C)
1	170.4			
2	52.7	4.84 (dt, 7.3, 4.7 Hz)	3, 4	1, 3
3	32.3	3.37 (dd, 14.2, 5.0 Hz), 3.28 (dd, 14.1, 4.3 Hz)	2	1, 2, 8
4	/	6.28 (d, 7.2 Hz)	2	
5	170.0			
6	23.1	2.03 (s)		5
7	53.0	3.78 (s)		1
8	145.8 (q, 5.3 Hz)			
9	116.9 (q, 34.7 Hz)	5.65 (qd, 8.2, 1.5 Hz)	10	10, 11
10	23.7	2.15 (dd, 2.3, 1.5 Hz)	9	8, 9
11	122.6 (q, 270.6 Hz)			

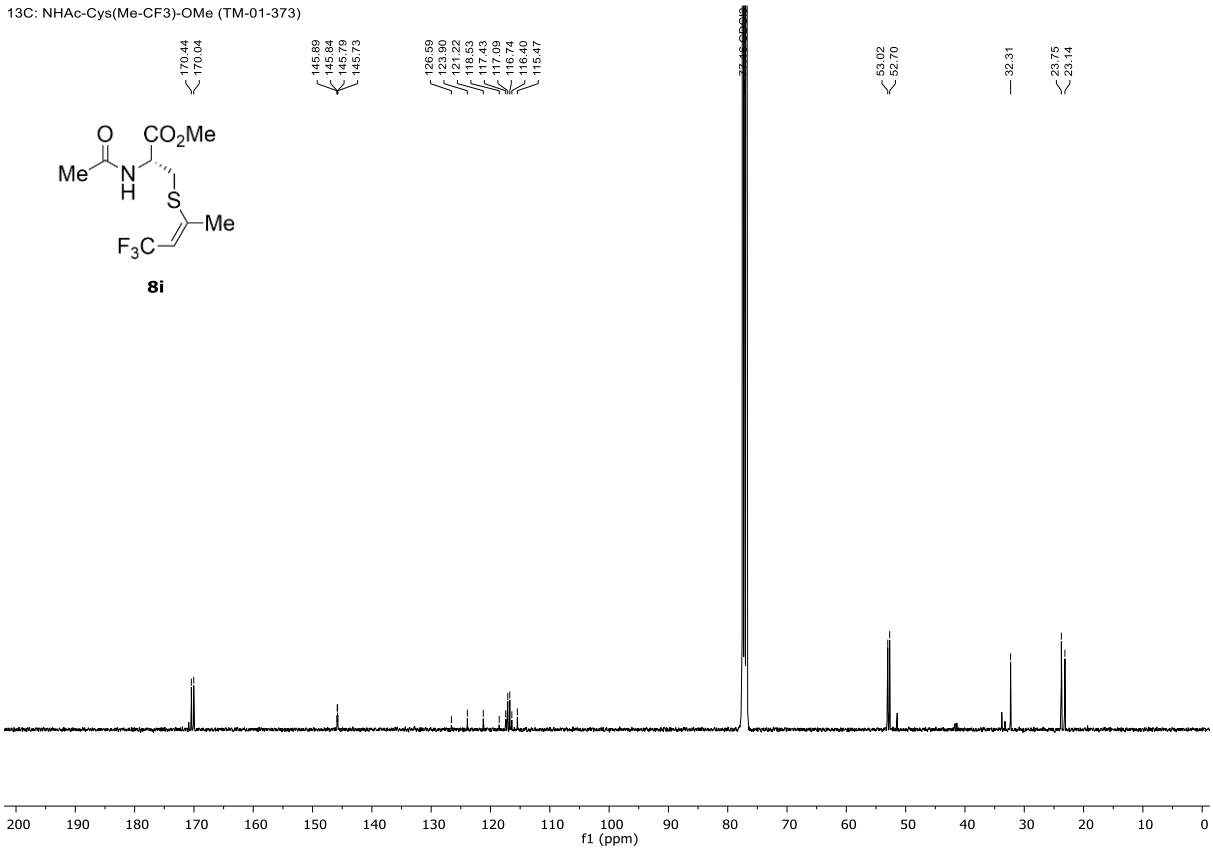
Table S36. Detailed NMR assignment of methyl methyl (*Z*)-*N*-acetyl-*S*-(4,4,4-trifluorobut-2-en-2-yl)-L-cysteinate (**8i**).

^{1}H-NMR (400 MHz, $CDCl_3$)



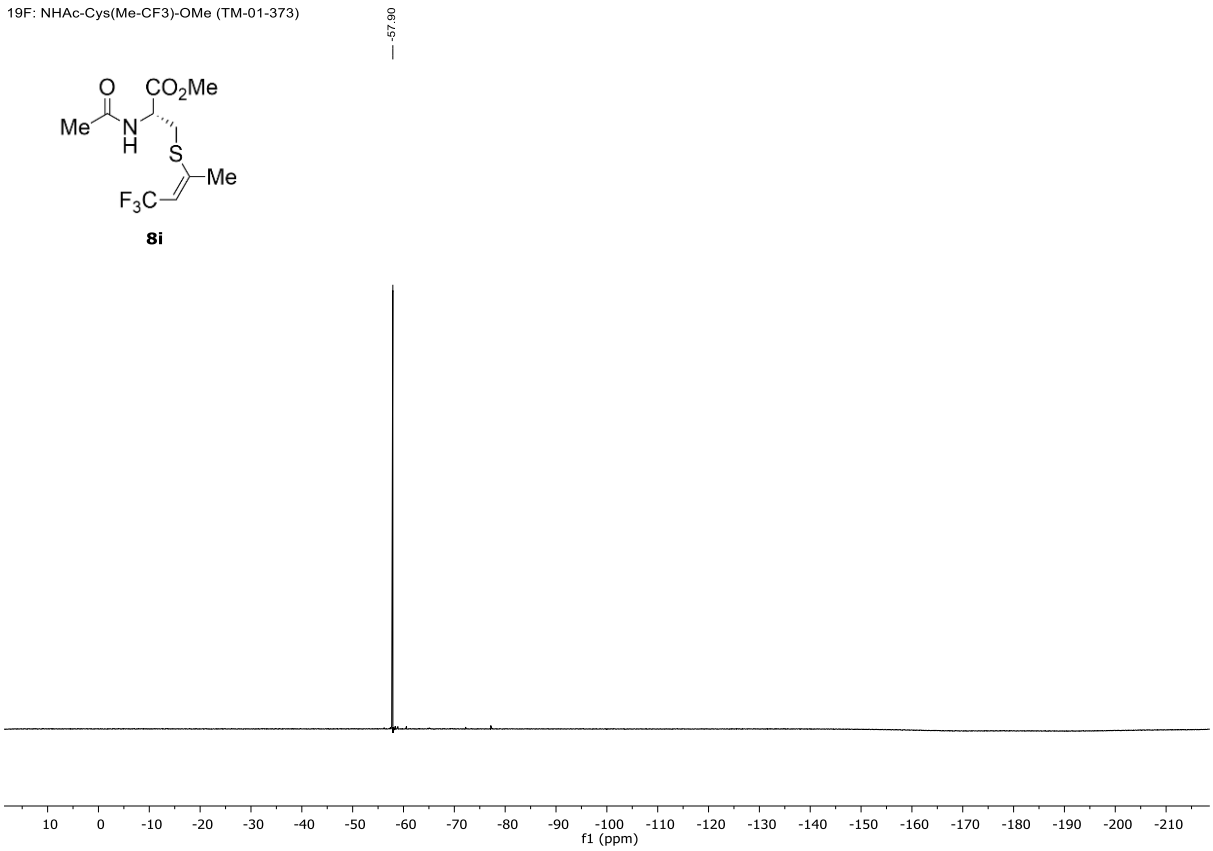
8i

^{13}C-NMR (101 MHz, $CDCl_3$)

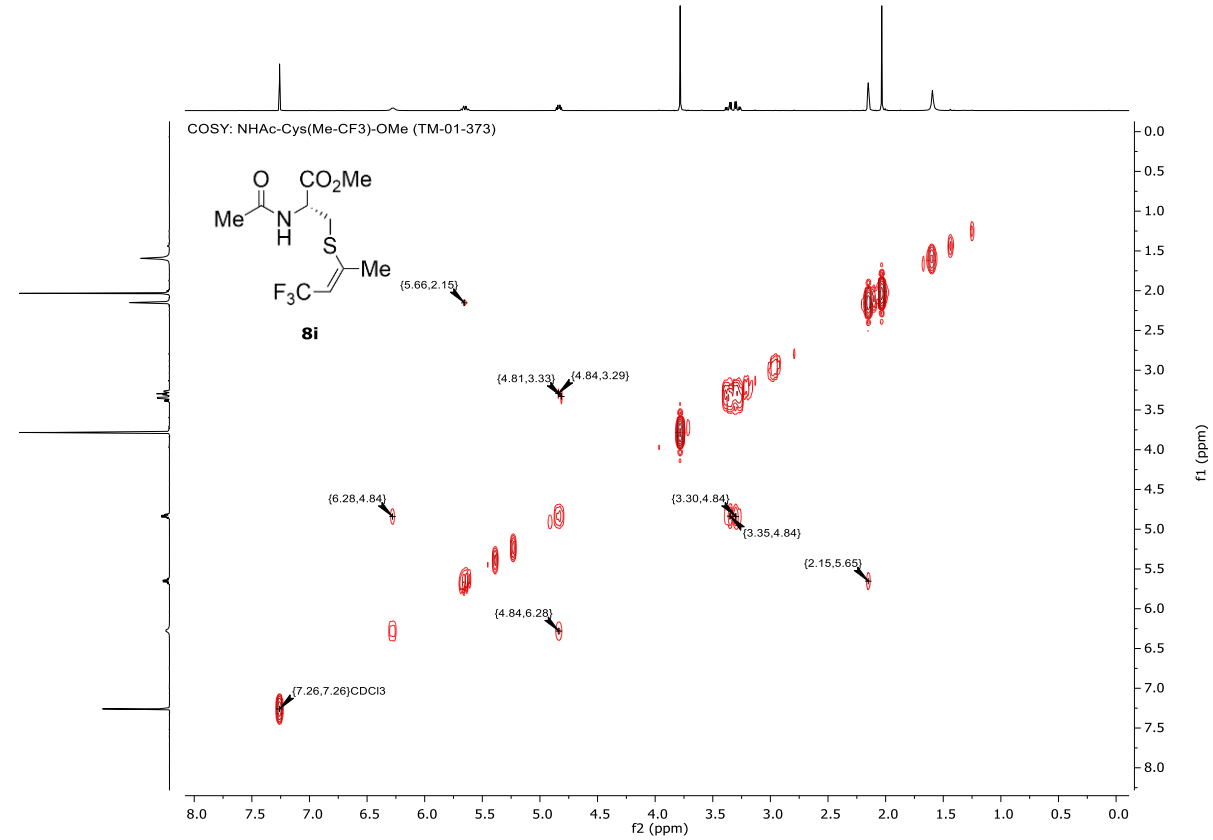


8i

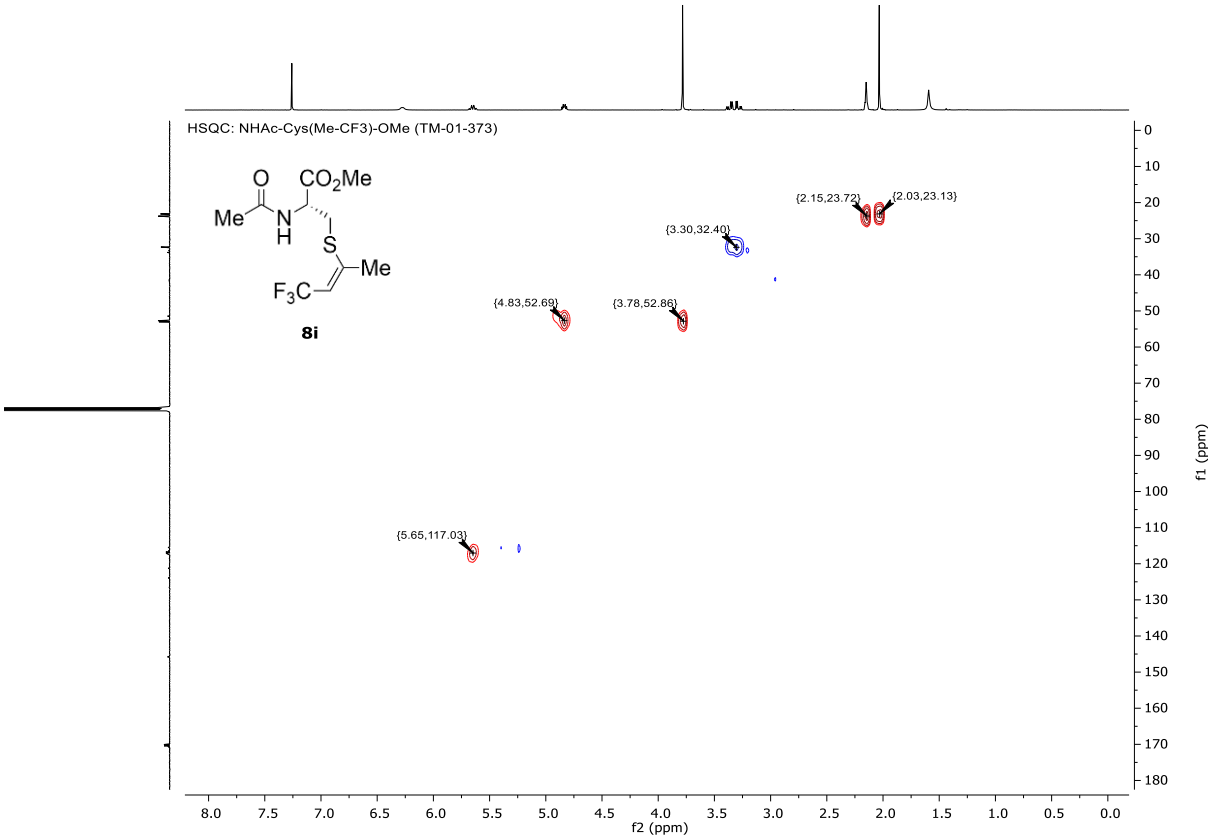
^{19}F-NMR (376 MHz, $CDCl_3$)



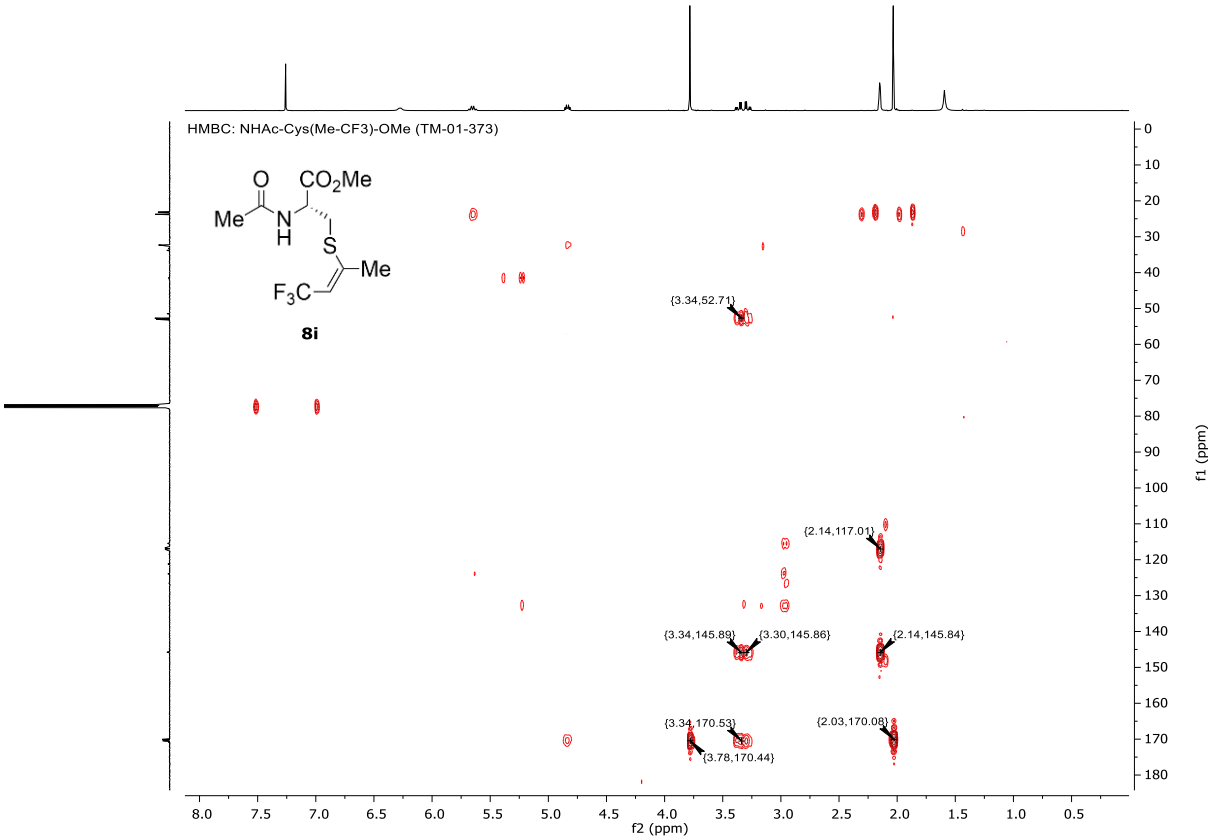
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(5-azido-1,1,1-trifluoropent-2-en-3-yl)-L-cysteinate (8j)

	δ_C	δ_H	COSY	HMBC (H→C)
1	170.24			
2	52.8	4.79 (dt, 6.9, 4.5 Hz)	3, 4	1
3	32.5	3.31 (dd, 14.2, 5.1 Hz), 3.23 (dd, 14.2, 4.2 Hz)	2	1, 2, 8
4	/	6.36 (d, 7.0 Hz)	2	
5	170.16			
6	23.1	2.02 (s)		5
7	53.1	3.77 (s)		
8	146.1 (q, 5.4 Hz)			
9	120.9 (q, 34.8 Hz)	5.84 (q, 7.8 Hz)		10
10	35.5	2.63 (tq, 5.1, 1.6 Hz)	11	8, 9, 11
11	49.2	3.50 (t, 6.6 Hz)	10	8, 10
12	122.2 (q, 271.3 Hz)			

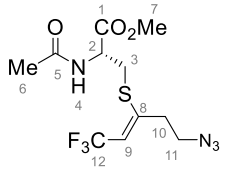
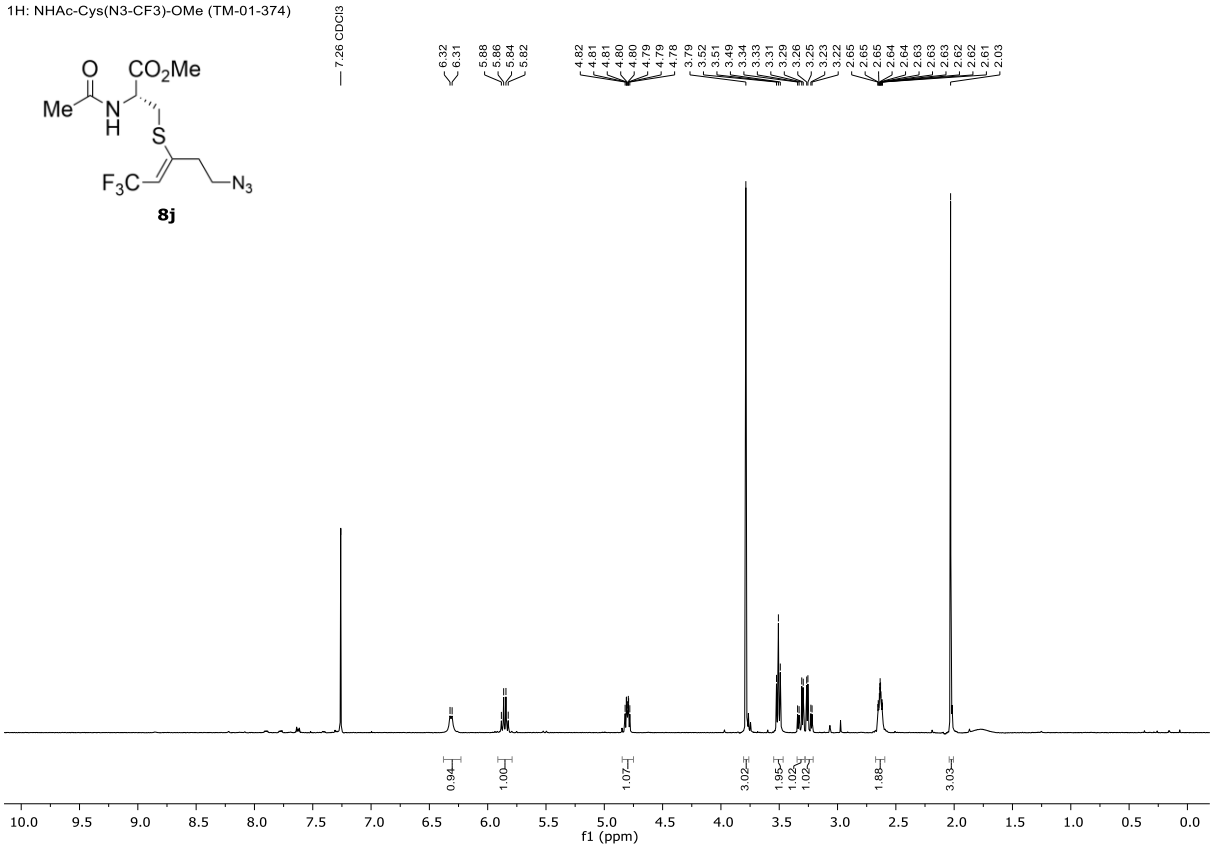


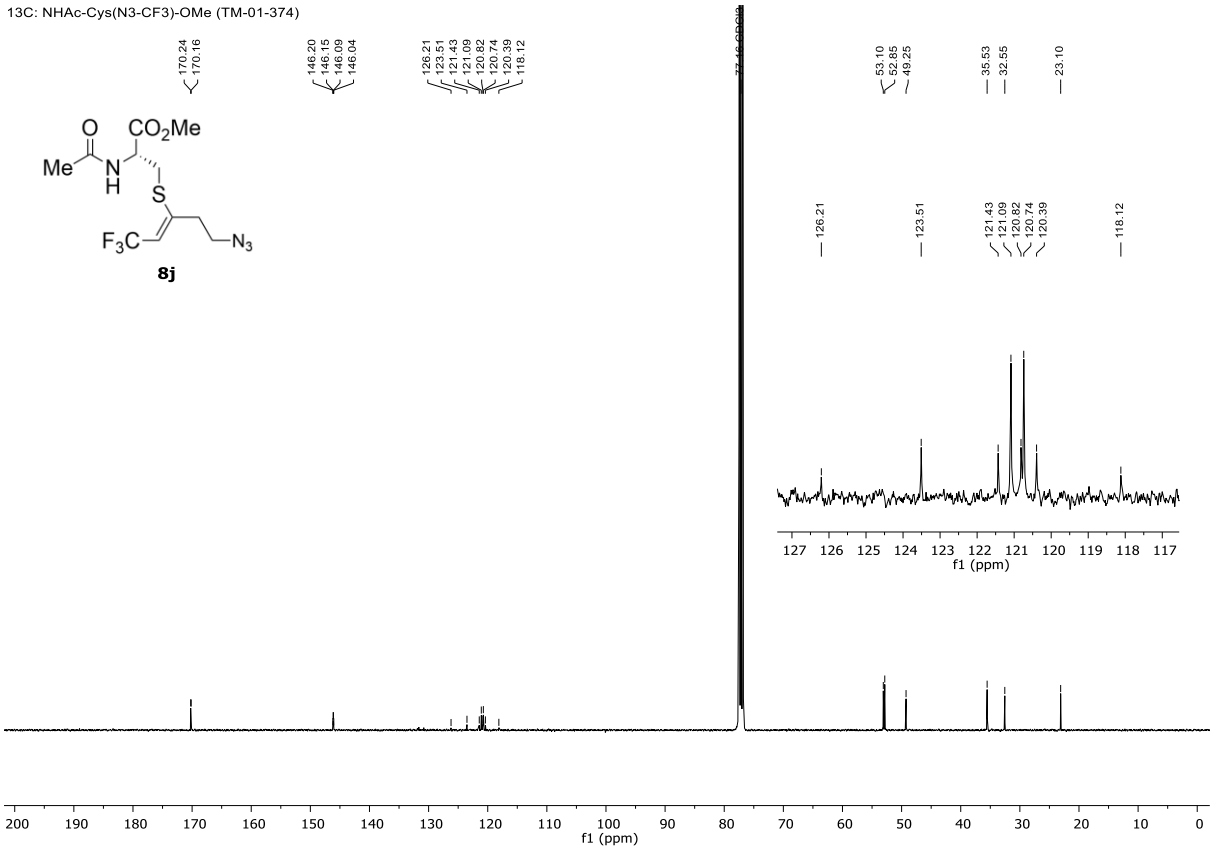
Table S37. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(5-azido-1,1,1-trifluoropent-2-en-3-yl)-L-cysteinate (**8j**).

^{1}H-NMR (400 MHz, $CDCl_3$)

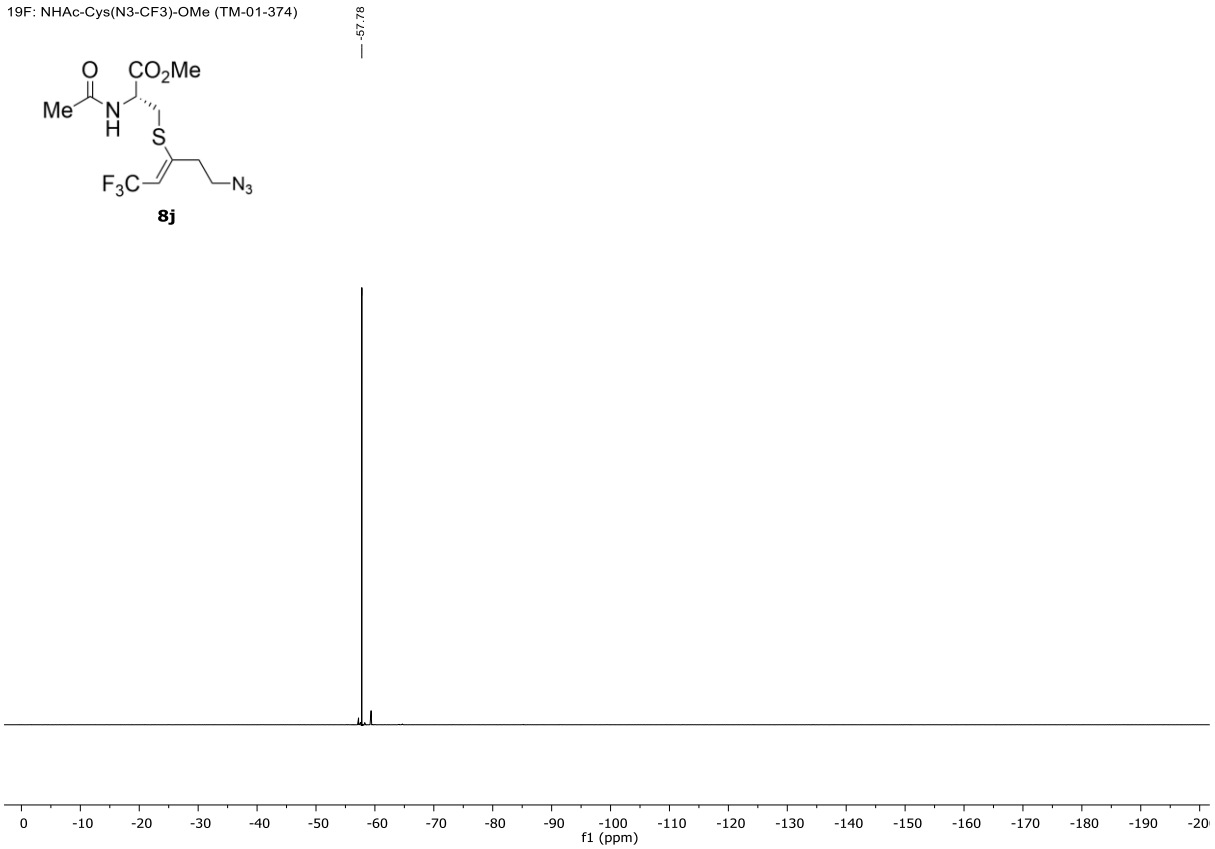


8j

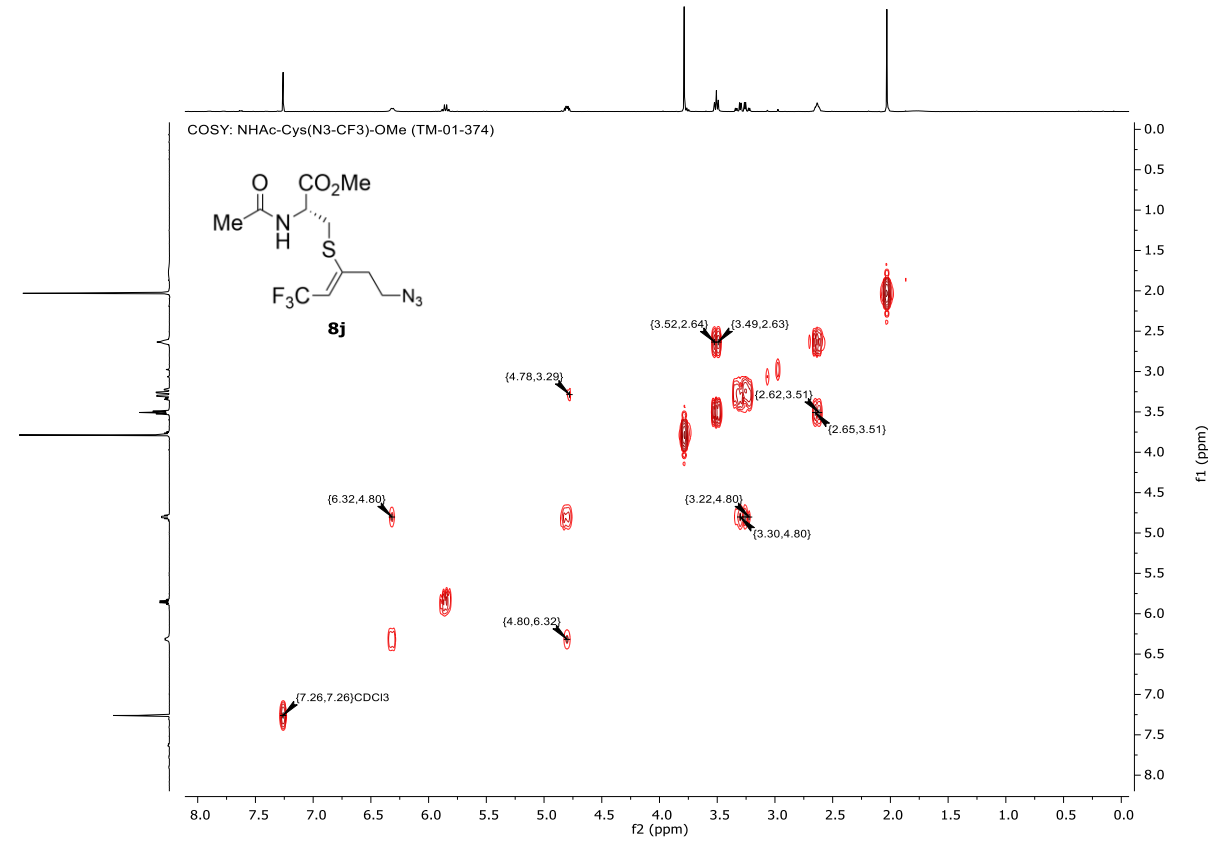
^{13}C-NMR (101 MHz, $CDCl_3$)



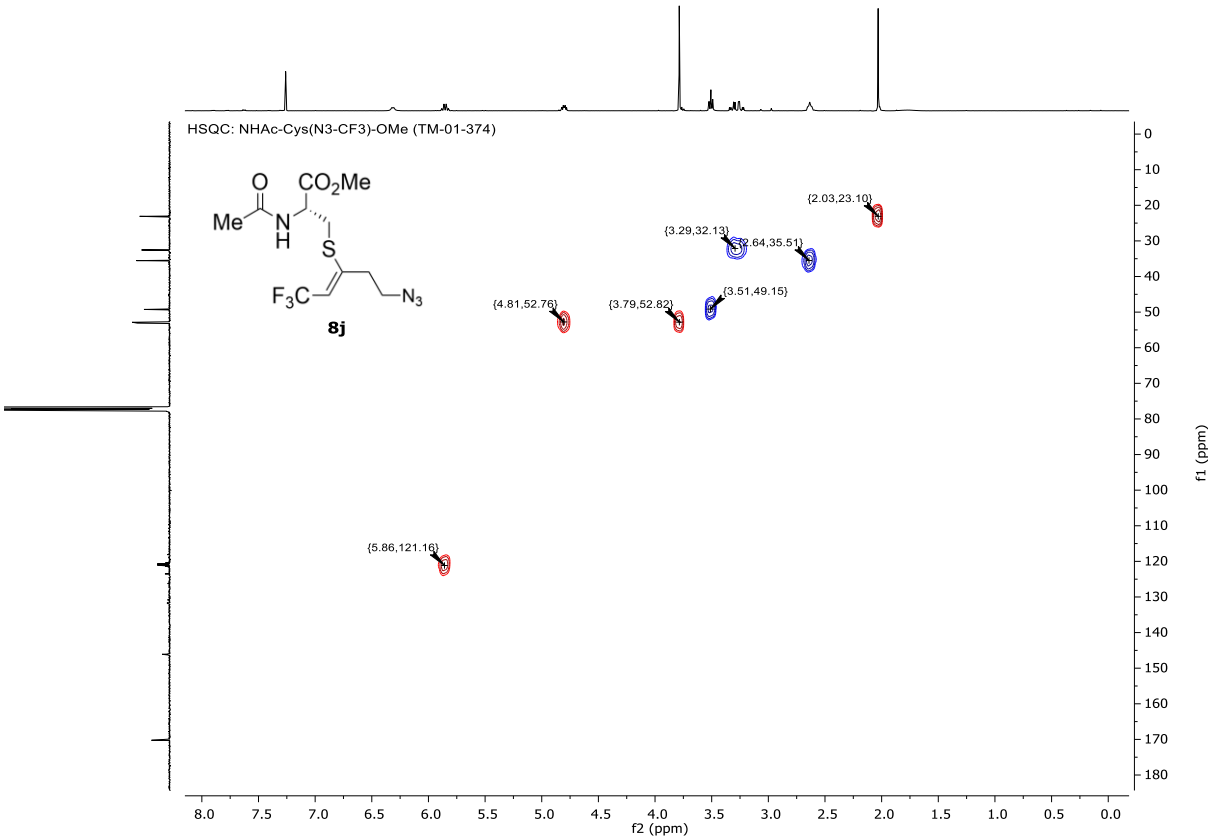
^{19}F-NMR (376 MHz, $CDCl_3$)



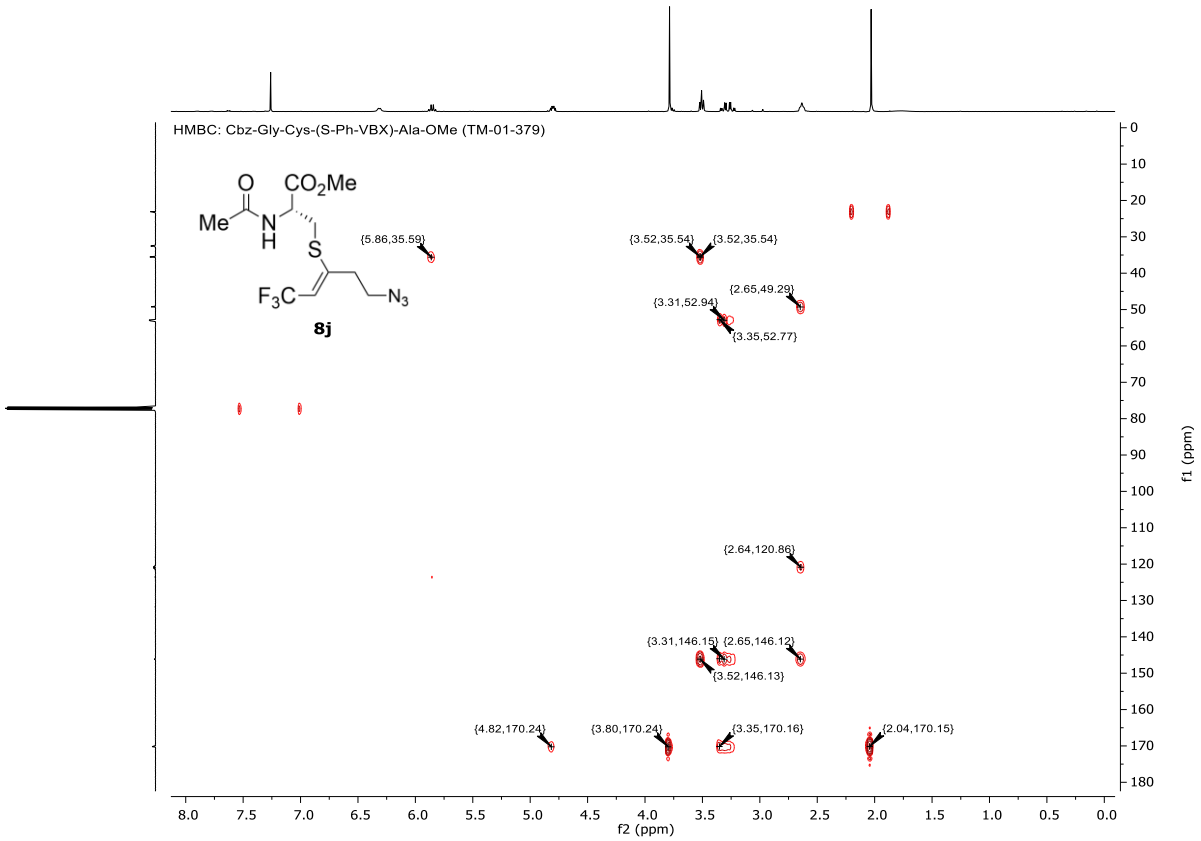
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinate (8k)

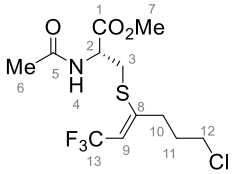
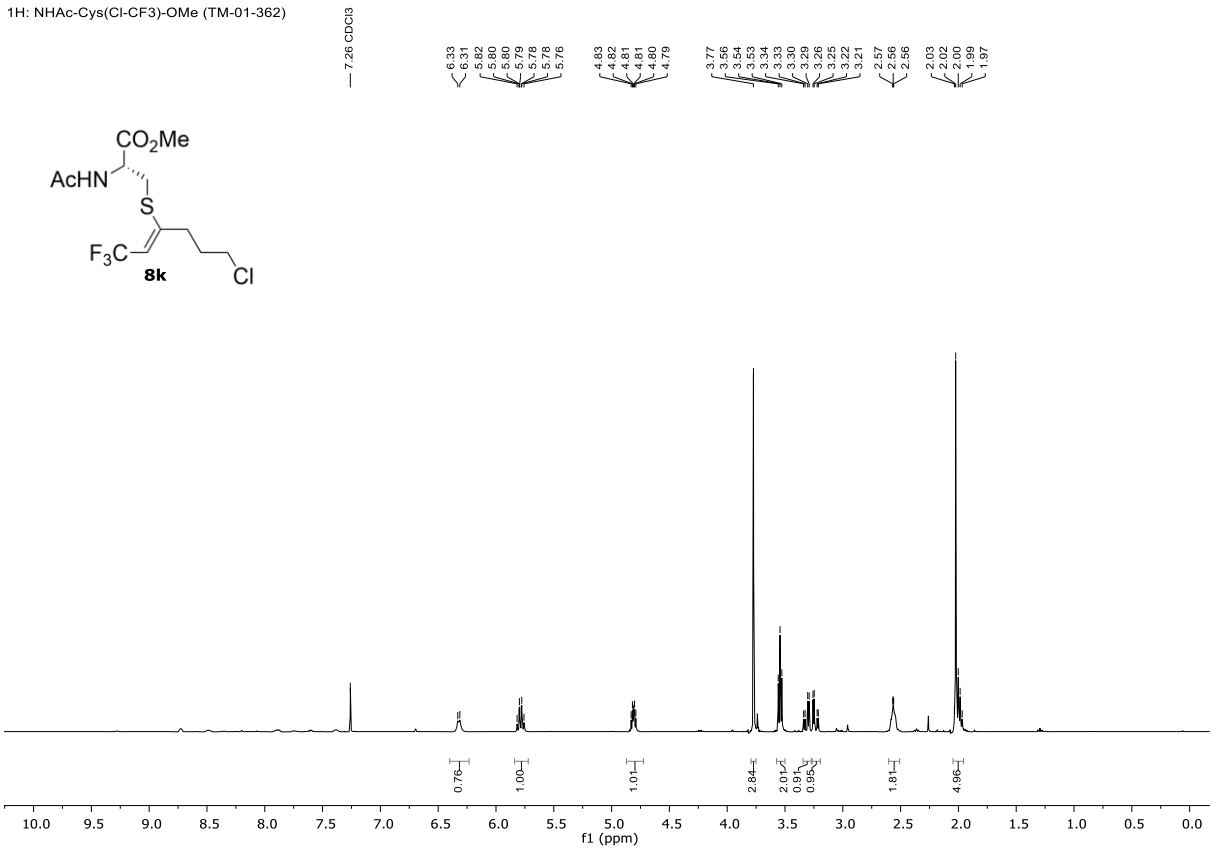


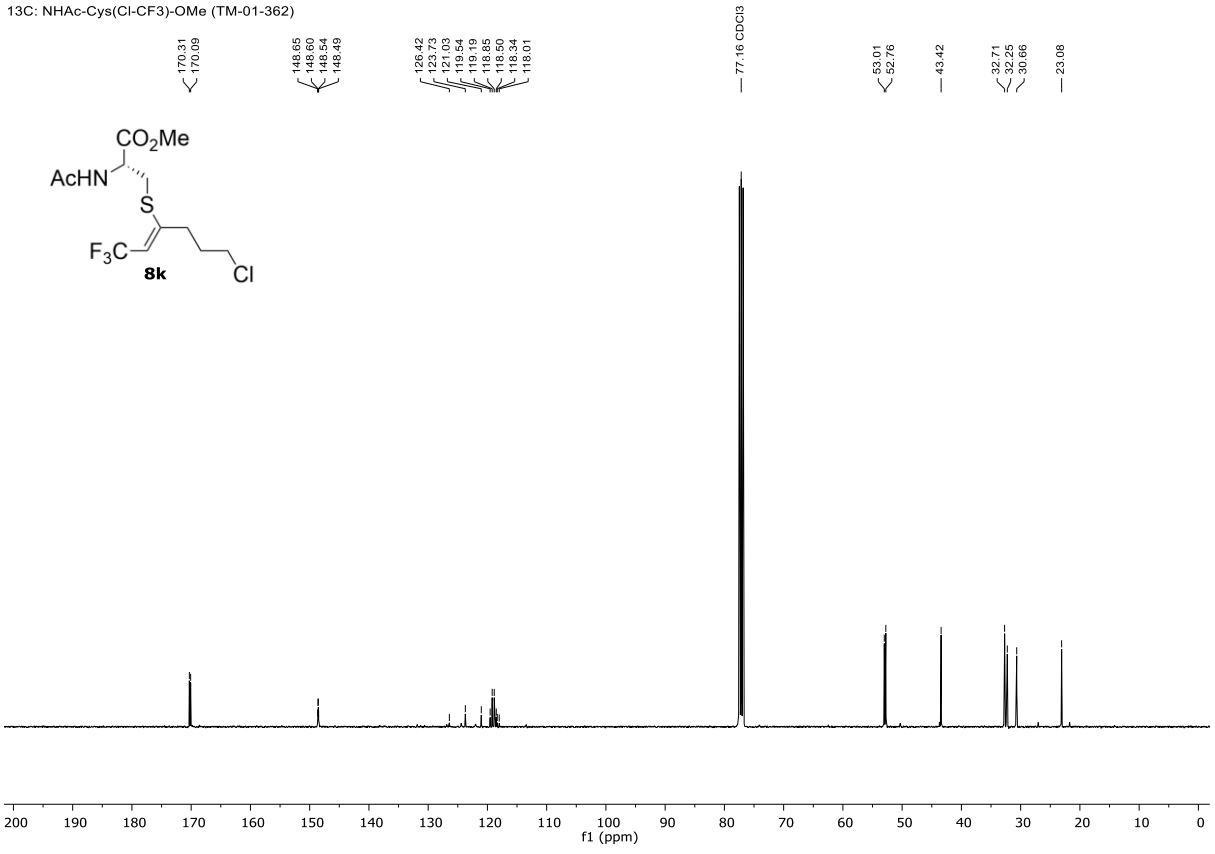
Table S38. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinate (**8k**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	170.3			
2	52.8	4.81 (dt, 7.3, 4.6 Hz)	3, 4	1, 3
3	32.3	3.32 (dd, 14.2, 5.0 Hz), 3.23 (dd, 14.2, 4.2 Hz)	2	1, 2, 8
4	/	6.32 (d, 7.1 Hz)	2	5
5	170.1			
6	23.1	2.02 (s)		5
7	53.0	3.77 (s)		1
8	148.6 (q, 5.4 Hz)			
9	119.0 (q, 34.7 Hz)	5.79 (q, 7.8 Hz)		10, 13
10	32.7	2.61-2.51 (m)	11	8, 11, 12, 13
11	30.7	2.00 (p, 6.5 Hz)	10, 12	8, 10, 12
12	43.4	3.54 (t, 6.2 Hz)	11	10
13	122.4 (q, 271.0 Hz)			

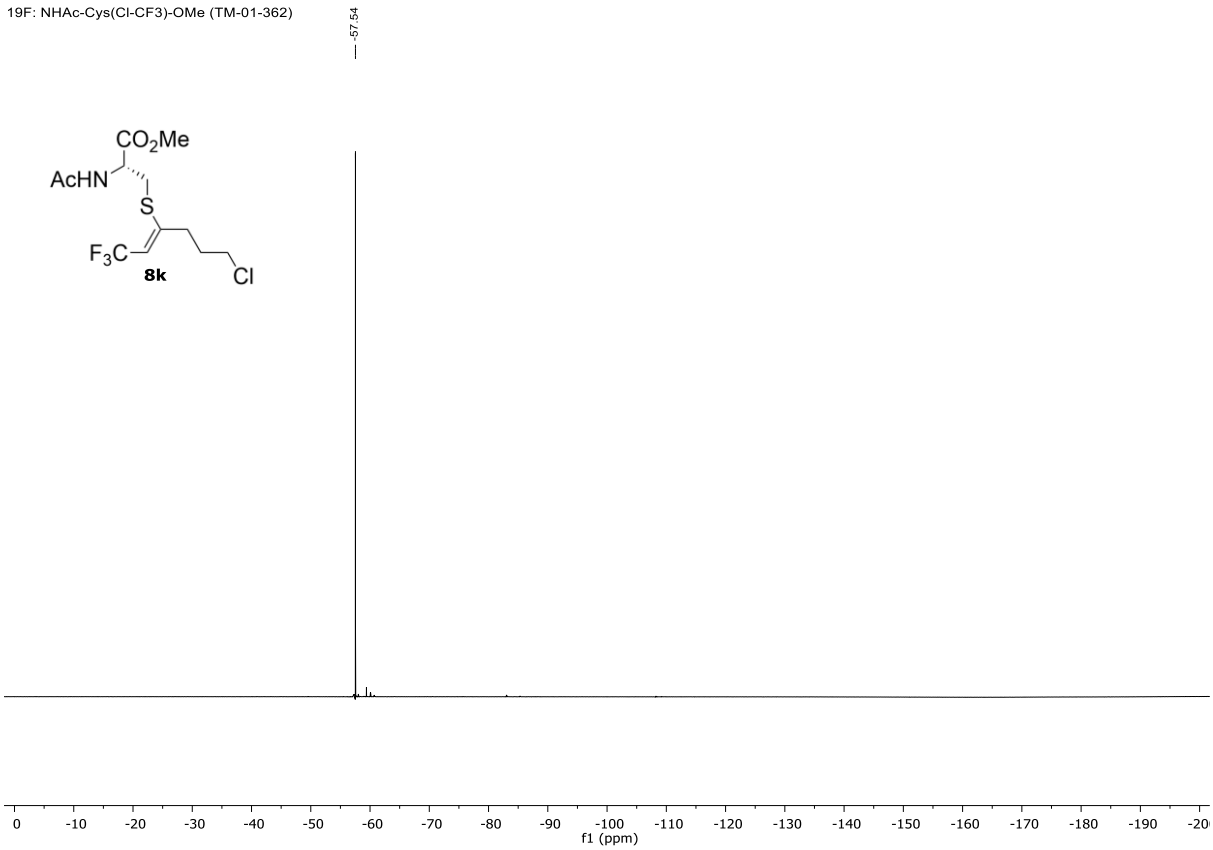
^{1}H-NMR (400 MHz, $CDCl_3$)



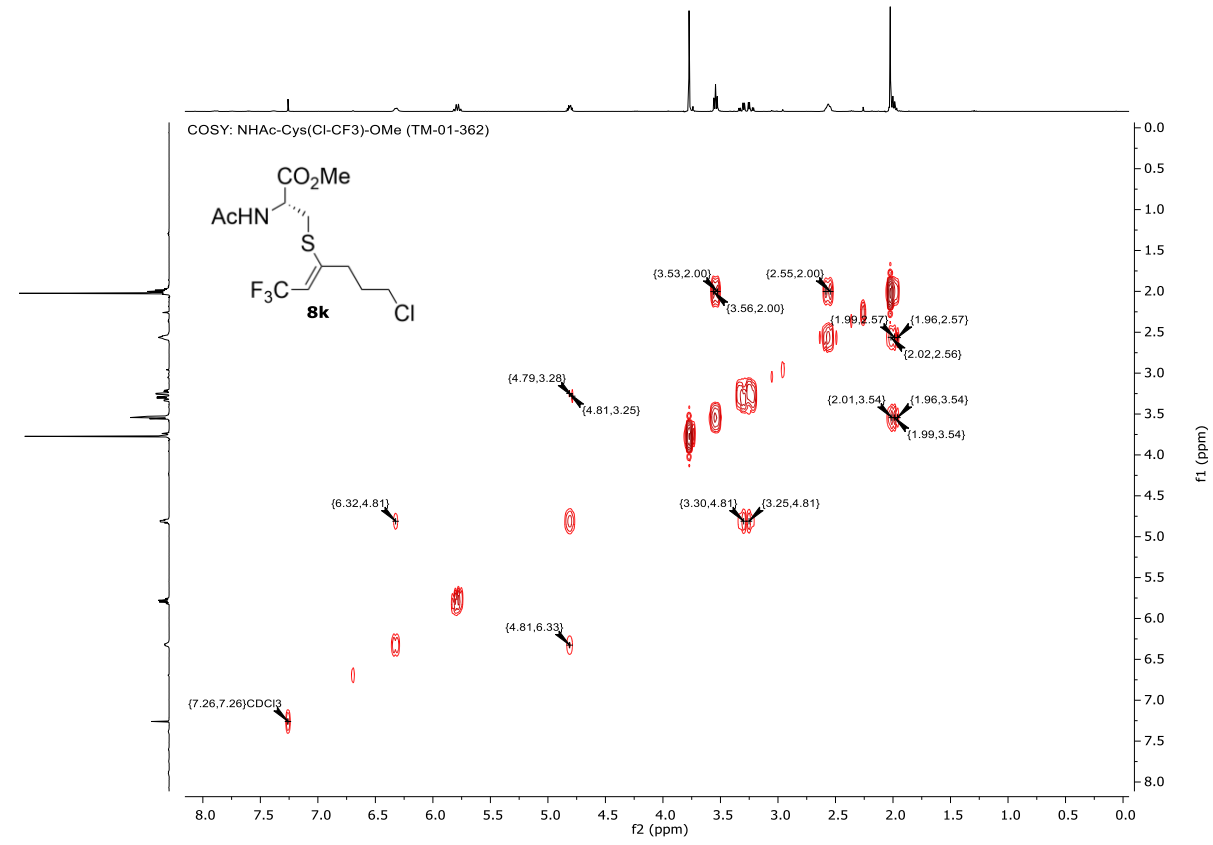
^{13}C-NMR (101 MHz, $CDCl_3$)



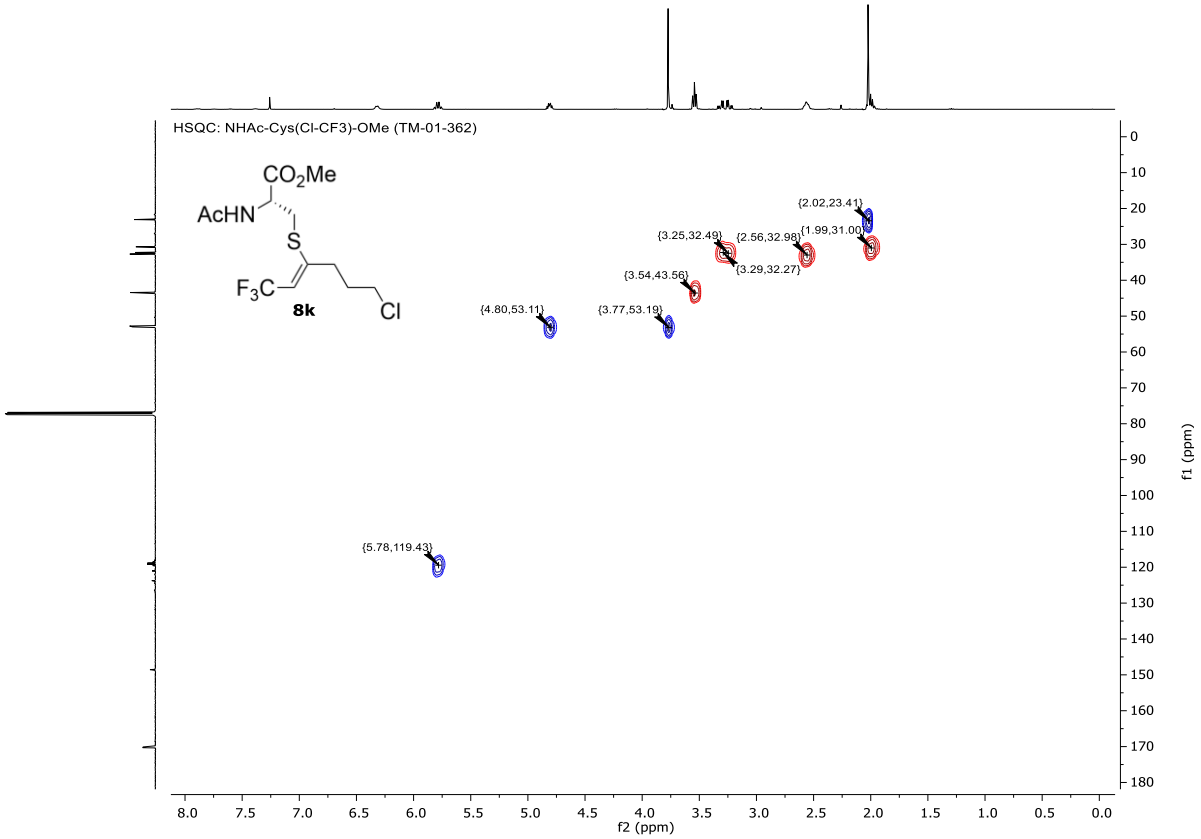
^{19}F-NMR (376 MHz, $CDCl_3$)



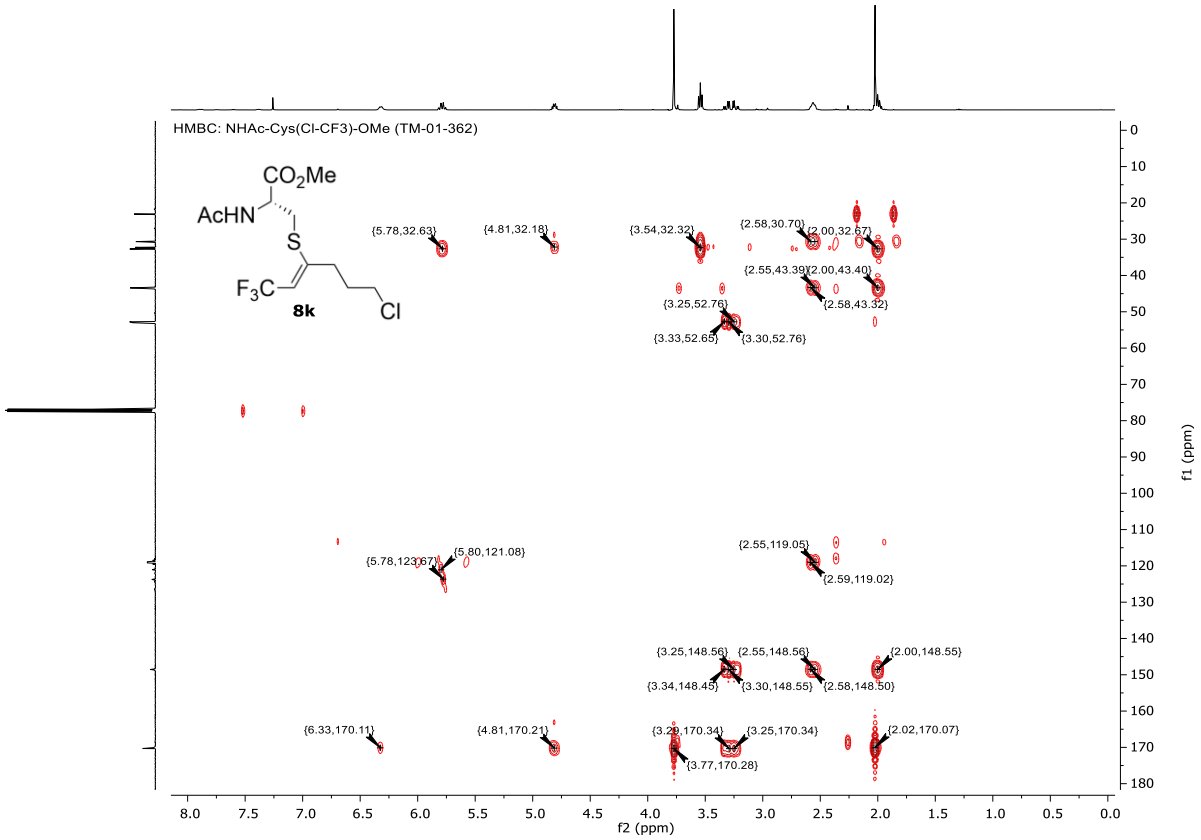
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl ((*S*)-2-((*S*)-4-methyl-2,5-dioxoimidazolidin-1-yl)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (8l)

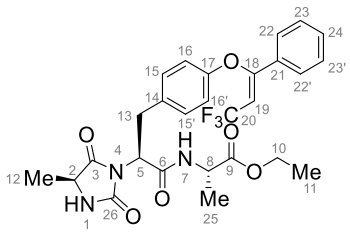
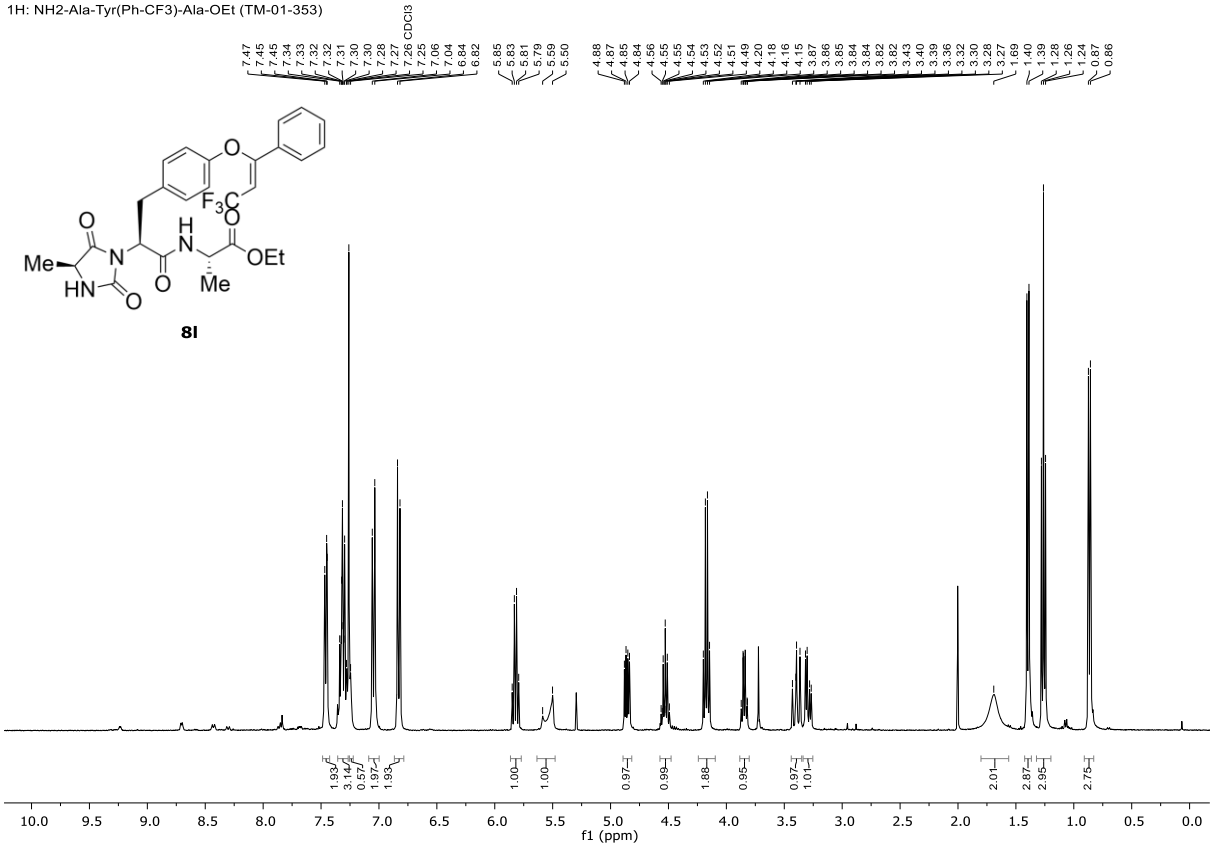


Table S39. Detailed NMR assignment of ethyl ((*S*)-2-((*S*)-4-methyl-2,5-dioxoimidazolidin-1-yl)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (**8l**).

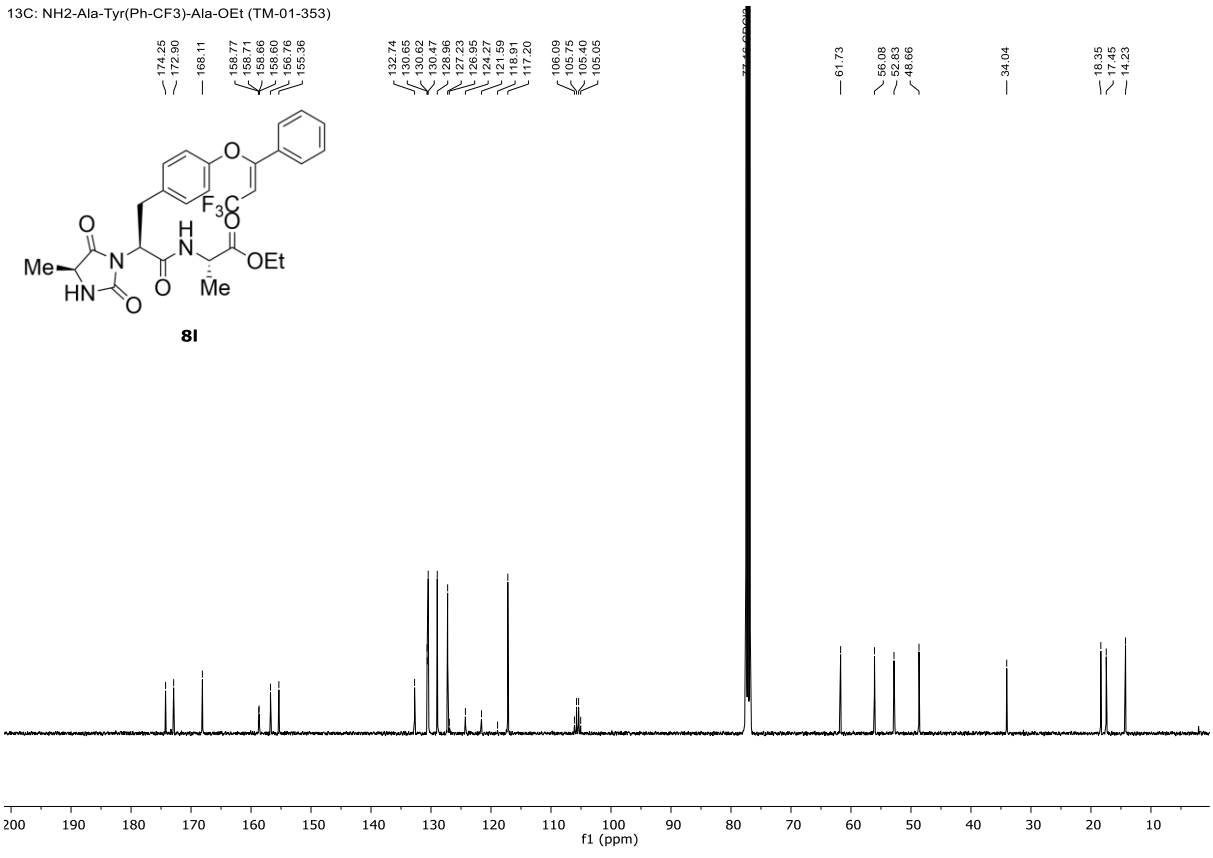
	δ_C	δ_H	COSY	HMBC (H→C)
1	/	5.54 (bs)		2, 3, 26
2	52.8	3.89-3.80 (m)	12	3, 12, 26
3	174.3			
4	/	/		
5	56.1	4.86 (dd, 11.9, 5.6 Hz)	13	3, 6, 13, 26
6	168.1			
7	/	7.24 (bs)	8	6
8	48.7	4.53 (p, 7.2 Hz)	7, 25	9, 25
9	172.9			
10	61.7	4.17 (q, 7.1 Hz)	11	9, 11
11	14.2	1.26 (t, 7.1 Hz)	10	10
12	17.4	0.87 (d, 6.9 Hz)	2	2, 3
13	34.0	3.40 (dd, 14.1, 11.9 Hz), 3.29 (dd, 14.1, 5.7 Hz)	5	5, 6, 15/15‘
14	130.7			
15/15‘	130.5	7.05 (d, 8.6 Hz)	16/16‘	13, 16/16‘, 17
16/16’	117.2	6.83 (d, 8.6 Hz)	15/15’	15/15’, 17
17	155.4			
18	158.7 (q, 5.6 Hz)			
19	105.6 (q, 34.9 Hz)	5.82 (q, 7.5 Hz)		18, 21
20	122.9 (q, 269.7 Hz)			
21	132.7			
22/22’	129.0	7.36-7.27 (m)	23/23’	24
23/23’	127.2	7.48-7.43 (m)	22/22’, 24	18, 24
24	130.6	7.36-7.27 (m)	23/23’	22/22’
25	18.4	1.40 (d, 7.1 Hz)	8	8, 9
26	156.8			

^{1}H-NMR (400 MHz, $CDCl_3$)



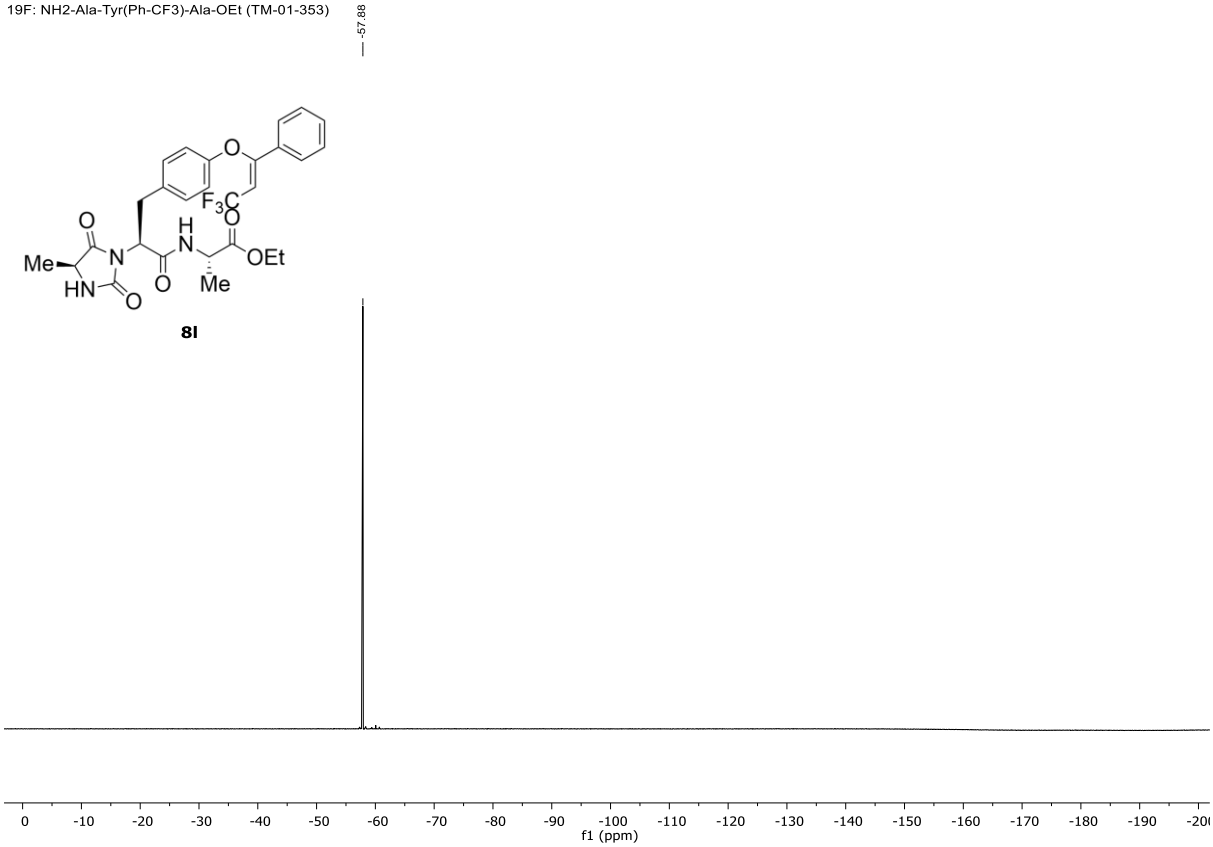
8l

^{13}C-NMR (101 MHz, $CDCl_3$)

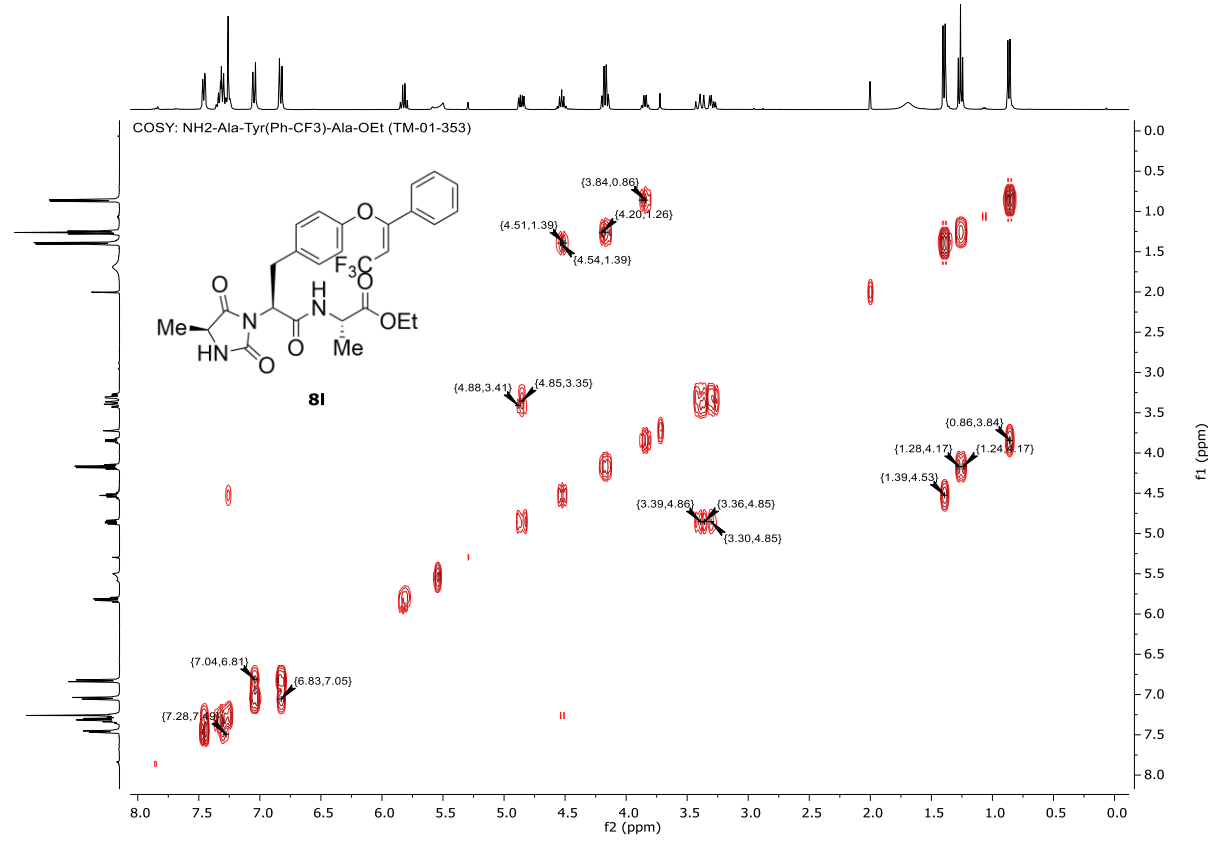


8l

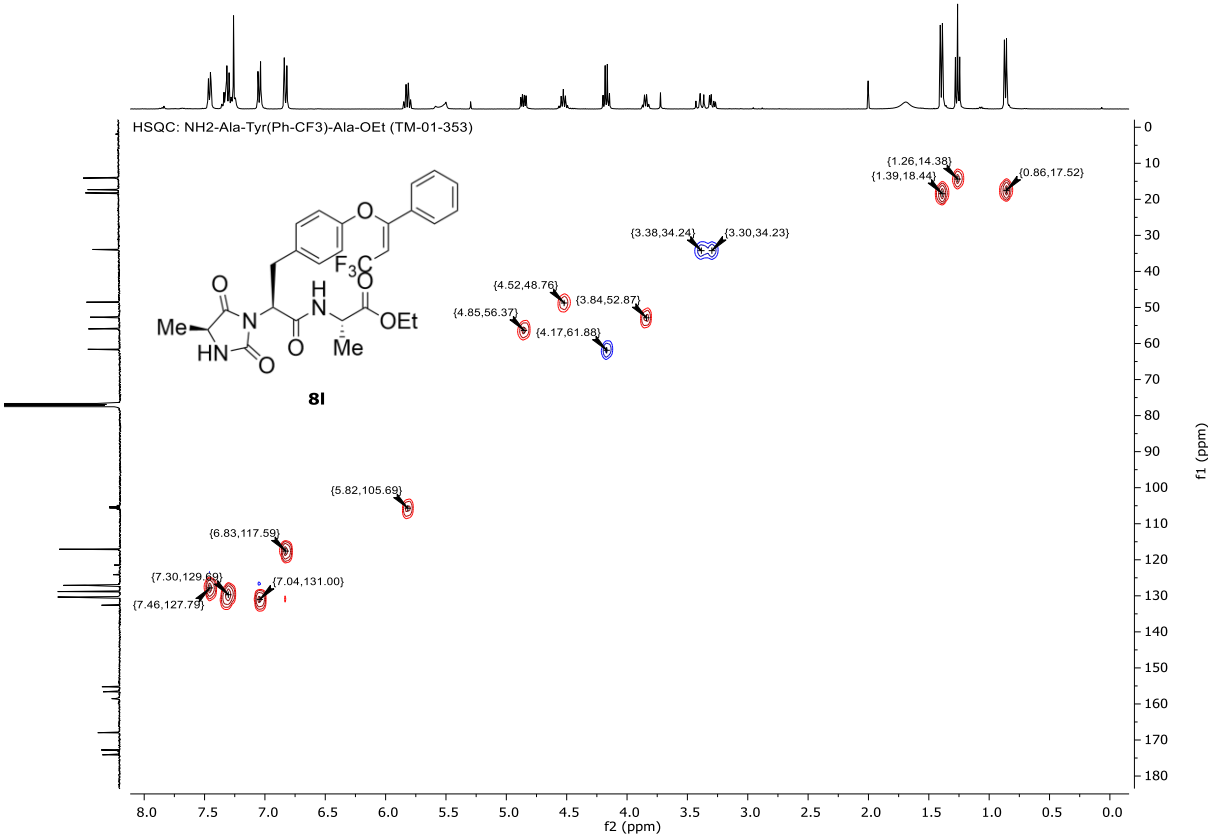
^{19}F-NMR (376 MHz, $CDCl_3$)



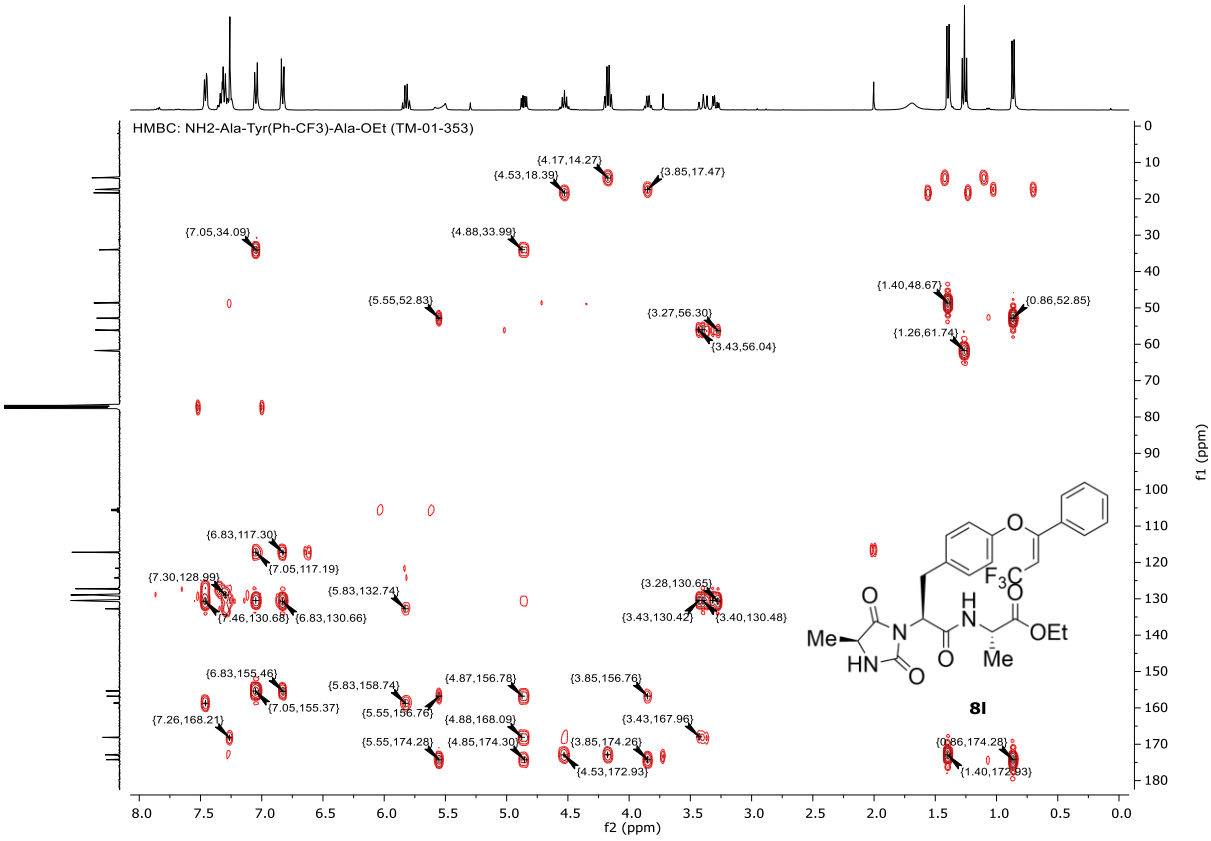
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl ((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenyl-prop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (8m)

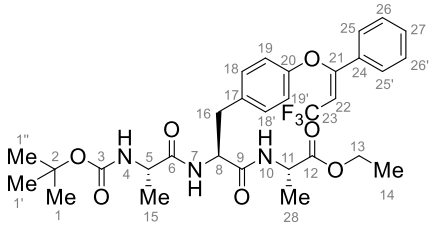
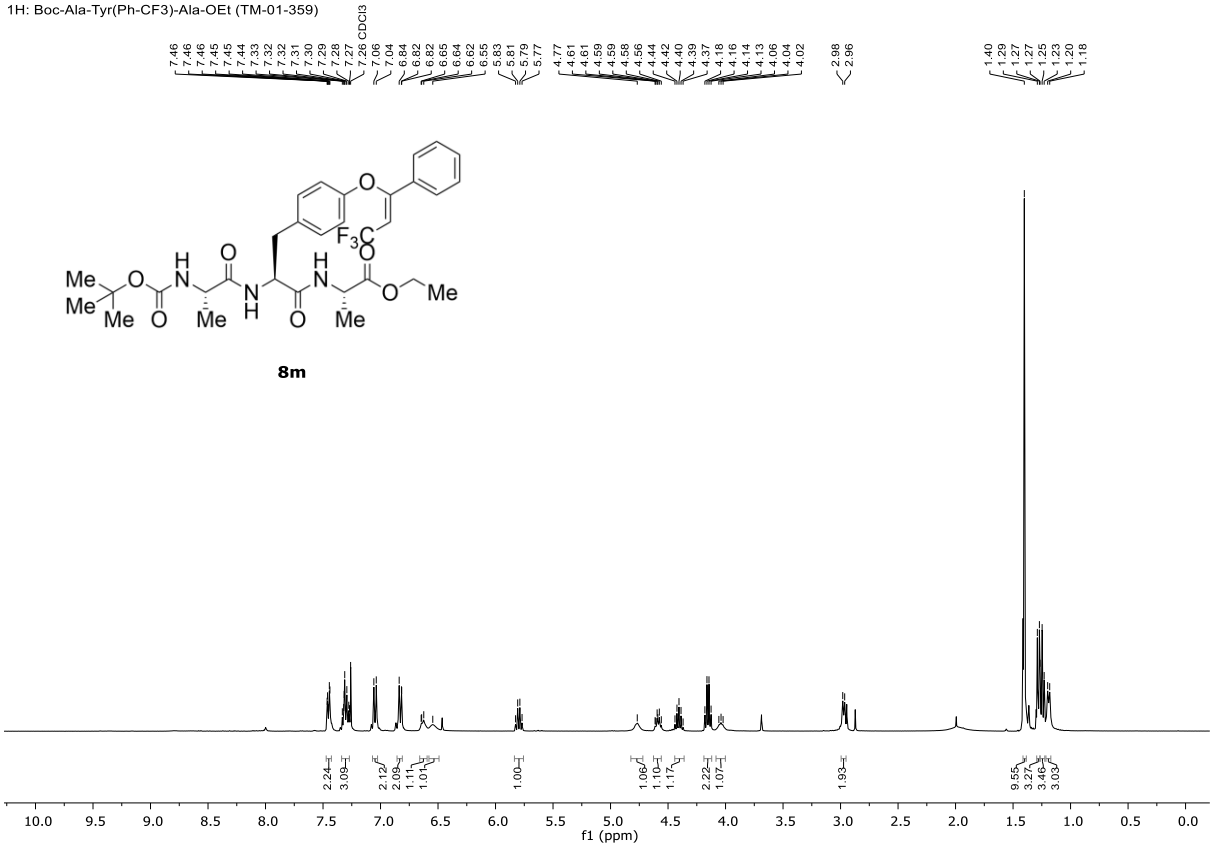


Table S40. Detailed NMR assignment of ethyl ((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenyl-prop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (**8m**).

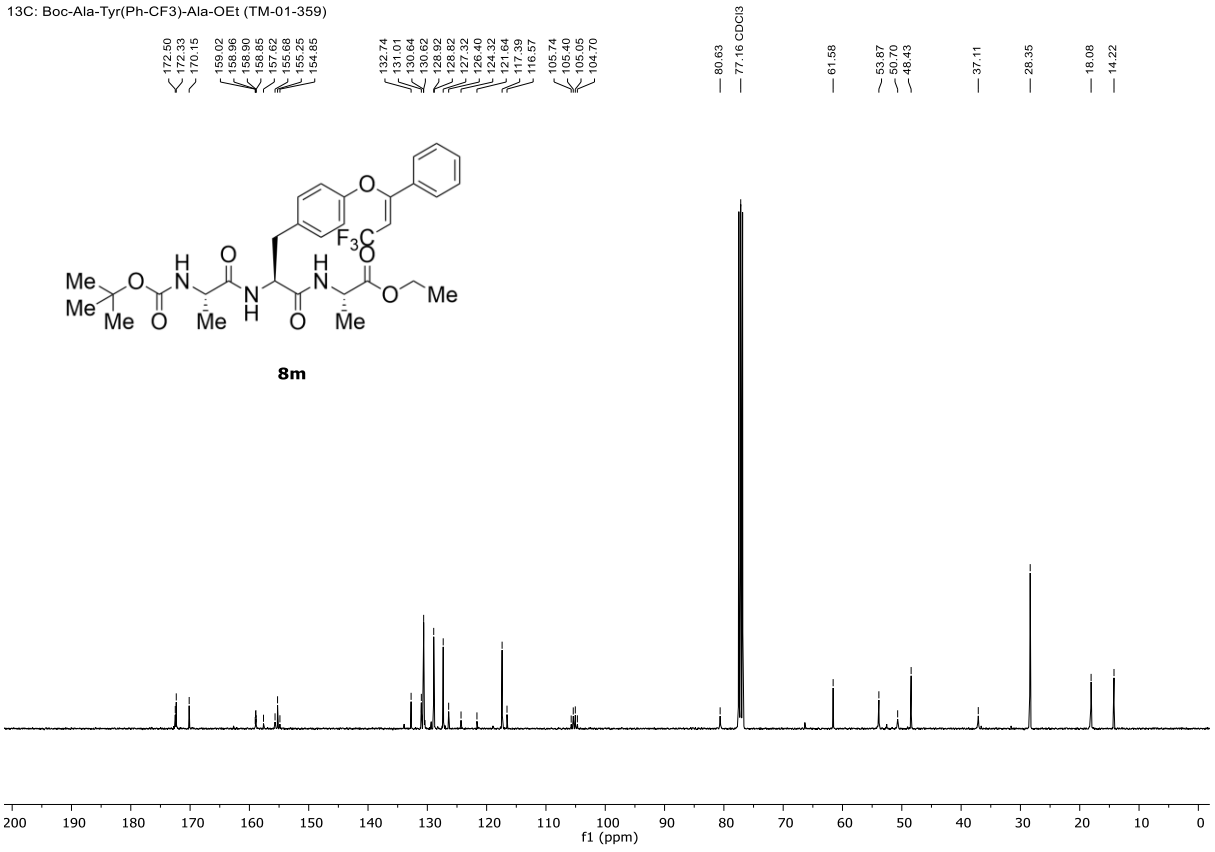
	δ_C	δ_H	COSY	HMBC (H→C)
1/1‘/1“	28.4	1.40 (s)		2
2	80.6			
3	155.7			
4	/	4.77 (bs)		
5	50.7	4.05 (d, 7.6 Hz)		6
6	172.5			
7	/	6.63 (d, 7.4 Hz)	8	6
8	53.9	4.62-4.54 (m)	7, 16	9, 16, 18/18’
9	170.2			
10	/	6.55 (bs)		
11	48.4	4.40 (p, 7.0 Hz)	28	12, 28
12	172.3			
13	61.6	4.15 (q, 7.2 Hz)	14	12, 14
14	14.2	1.25 (t, 7.2 Hz)	13	14
15	18.1	1.19 (d, 7.1 Hz)		5, 6
16	37.1	2.97 (d, 6.7 Hz)	8	8, 9, 18/18‘
17	130.6			
18/18’	130.6	7.05 (d, 8.4 Hz)	19/19’	16, 19/19’, 20
19/19’	117.4	6.83 (d, 7.9 Hz)	18/18’	18/18’, 20
20	155.3			
21	158.9 (q, 5.8 Hz)			
22	105.2 (q, 35.1 Hz)	5.80 (q, 7.5 Hz)		21, 24
23	123.0 (q, 269.9 Hz)			
24	132.7			
25/25’	128.9	7.35-7.27 (m)	26/26’	26/26’, 27
26/26’	127.3	7.48-7.42 (m)	25/25’	21, 25/25’, 27
27	131.0	7.35-7.27 (m)		
28	18.1	1.28 (d, 7.2 Hz)	11	11, 12

^{1}H-NMR (400 MHz, $CDCl_3$)



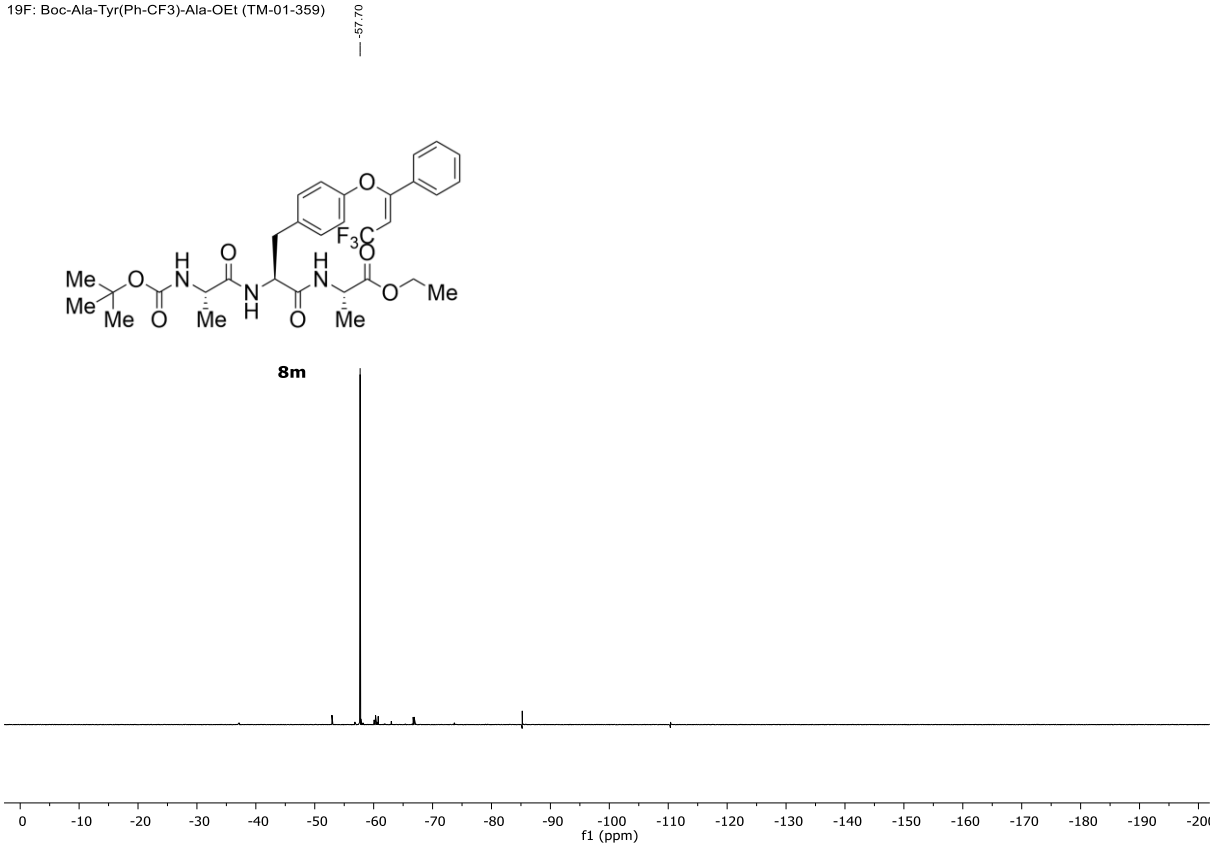
8m

^{13}C-NMR (101 MHz, $CDCl_3$)

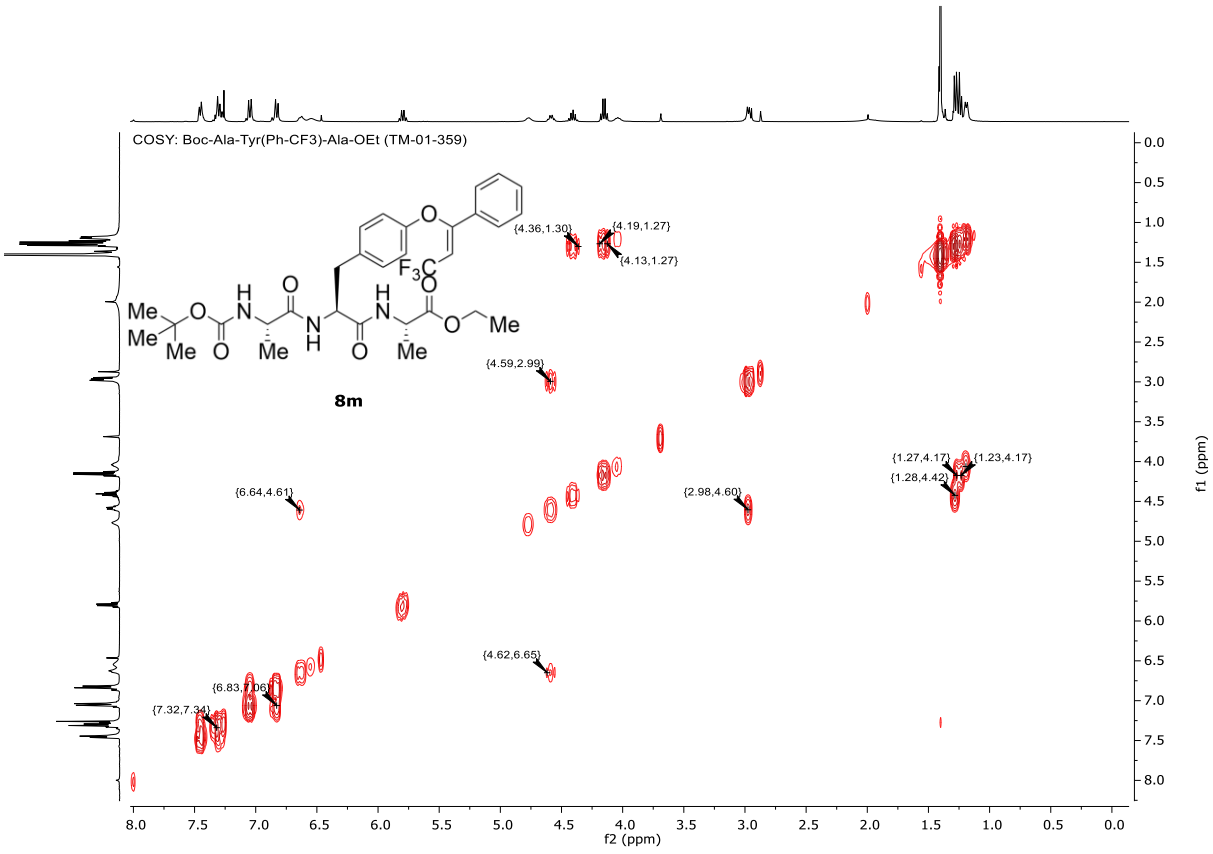


8m

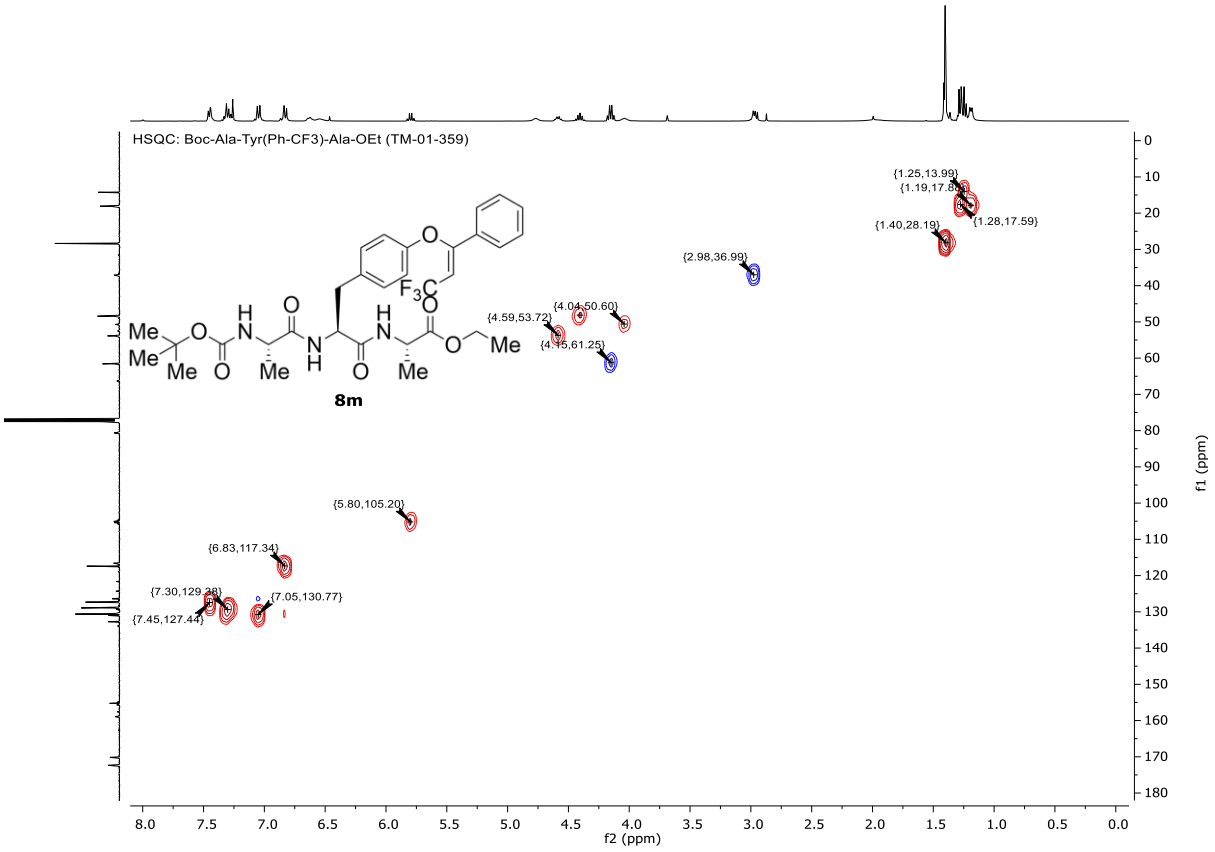
^{19}F-NMR (376 MHz, $CDCl_3$)



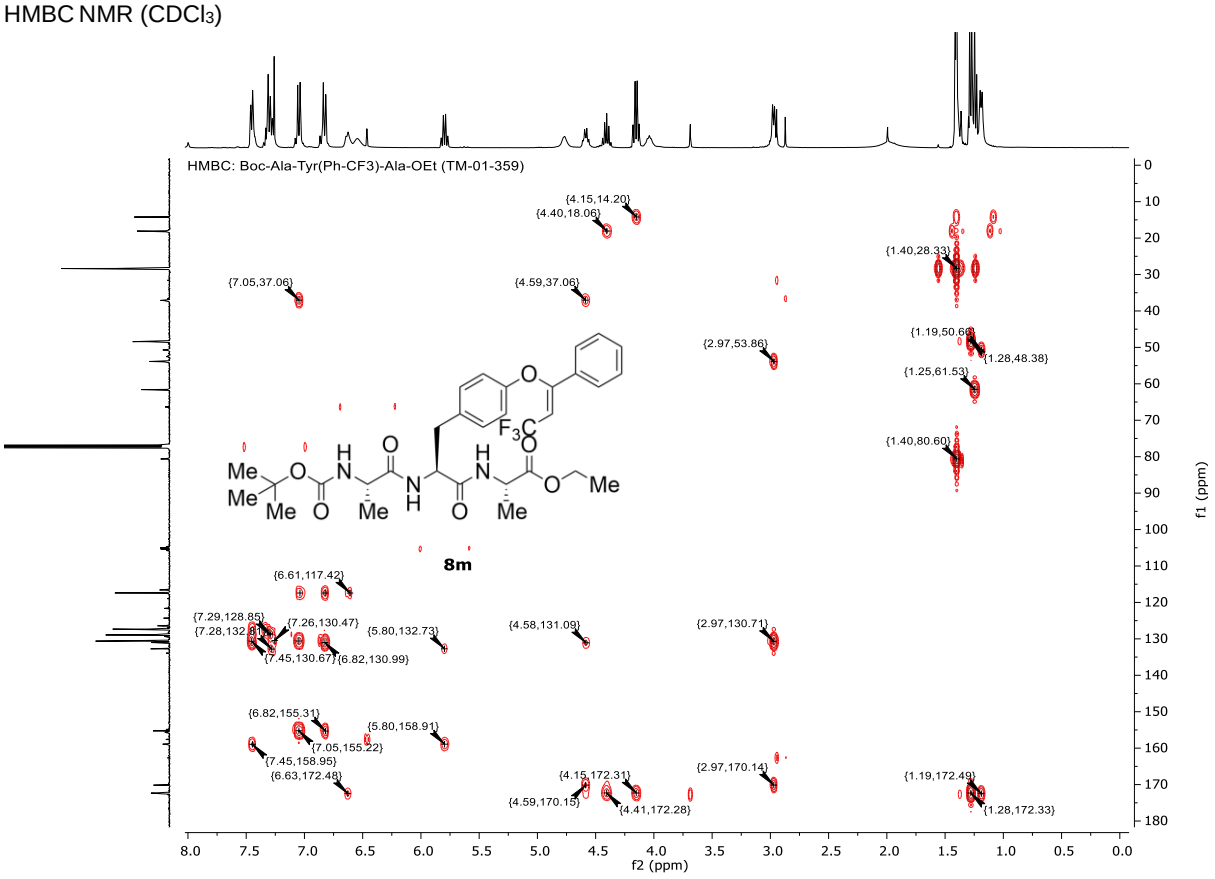
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl ((*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-6-chloro-1,1,1-trifluoro-hex-2-en-3-yl)oxy)phenyl)propanoyl)-L-alaninate (8n)

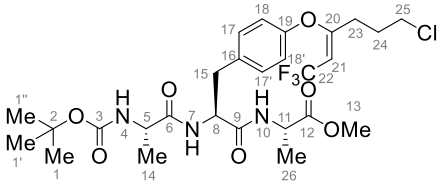
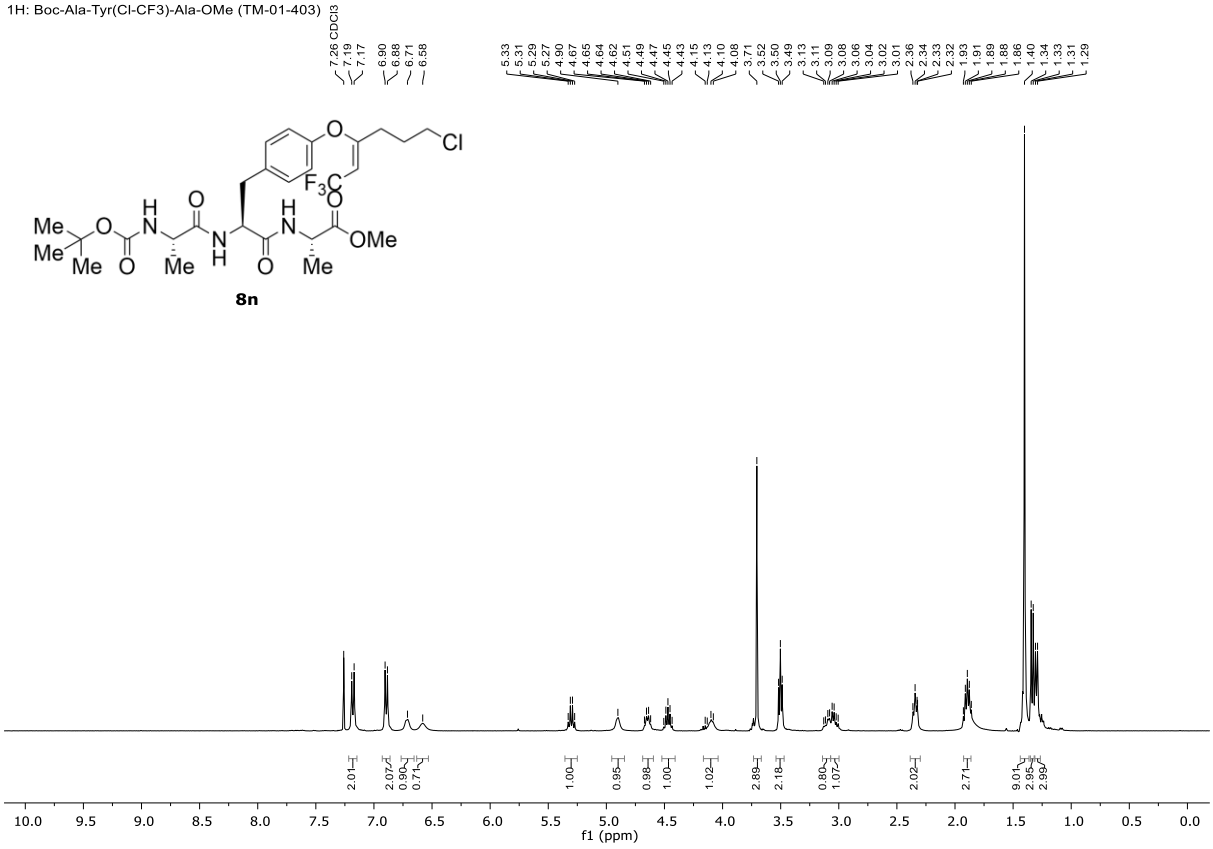


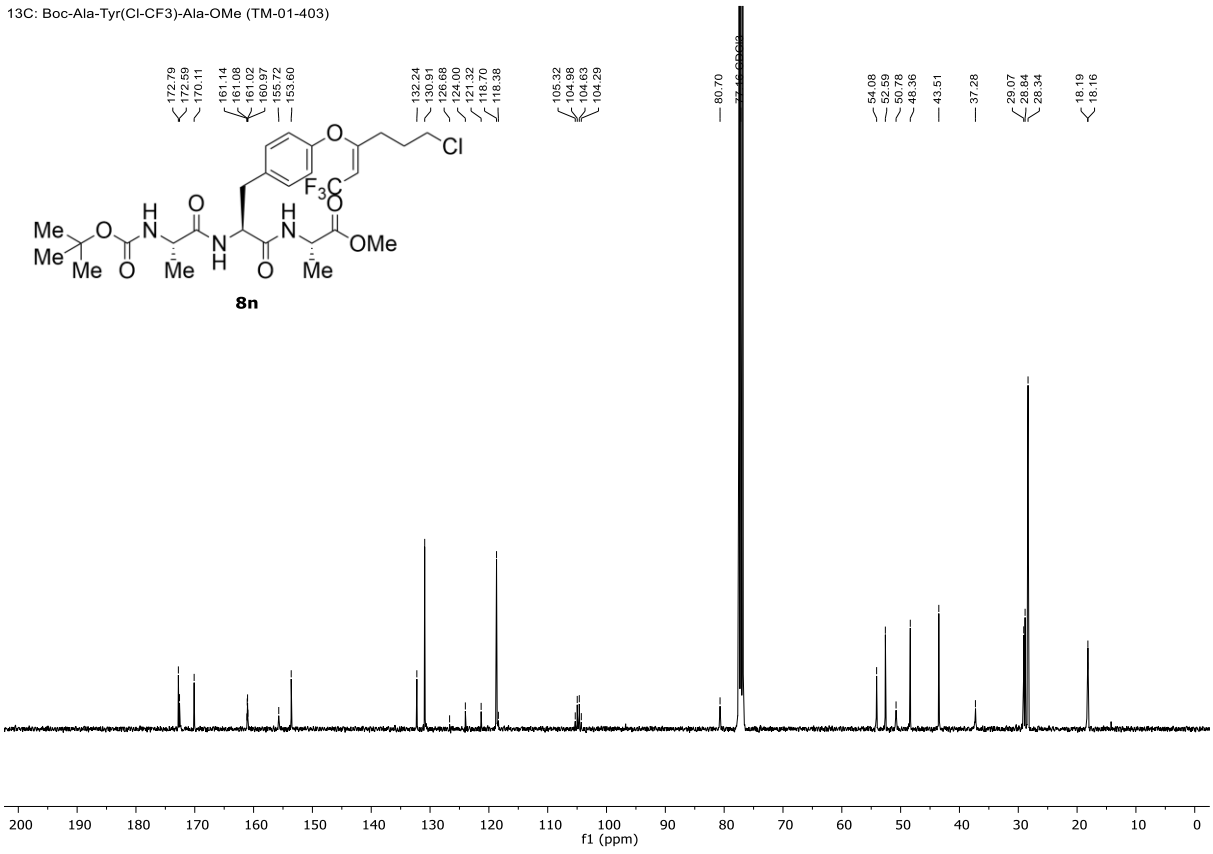
Table S41. Detailed NMR assignment of methyl ((S)-2-((S)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-(((*Z*)-6-chloro-1,1,1-trifluoro-hex-2-en-3-yl)oxy)phenyl)propanoyl)-L-alaninate (**8n**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1‘/1“	28.3	1.40 (s)		2
2	80.7			
3	155.7			
4	/	4.90 (bs)	5	
5	50.8	4.16-4.04 (m)	4, 14	
6	172.6			
7	/	6.71 (bs)	8	
8	54.1	4.65 (q, 7.0 Hz)	7, 16	9, 15, 16
9	170.1			
10	/	6.58 (bs)		
11	48.4	4.47 (p, 7.2 Hz)	26	12, 26
12	172.8			
13	52.6	3.71 (s)		12
14	18.16	1.30 (d, 7.1 hz)	5	5, 6
15	37.3	3.10 (dd, 14.1, 6.0 Hz), 3.03 (dd, 13.9, 6.9 Hz)	8	
16	132.2			
17/17’	130.9	7.18 (d, 8.2 Hz)	18/18’	15, 18/18’, 19
18/18’	118.7	6.89 (d, 8.1 Hz)	17/17’	16, 19
19	153.6			
20	161.1 (q, 5.6 Hz)			
21	104.8 (q, 34.3 Hz)	5.30 (q, 7.4 Hz)		20, 23
22	122.7 (q, 269.8 Hz)			
23	28.8	2.34 (t, 7.2 Hz)	24	20, 21, 25
24	29.1	1.89 (p, 6.7 Hz)	23, 25	20, 23, 25
25	43.5	3.50 (t, 6.3 Hz)	24	23
26	18.19	1.34 (d, 7.2 Hz)	11	11, 12

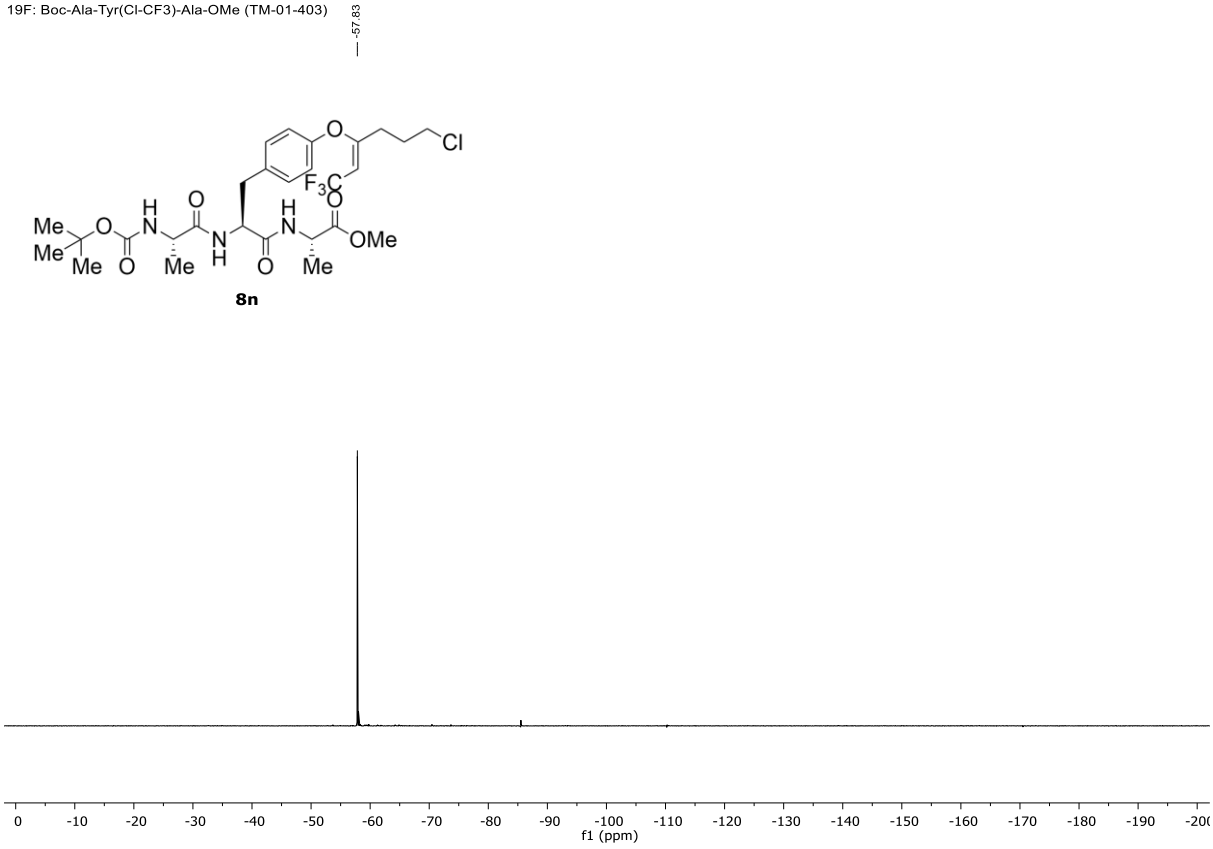
^{1}H-NMR (400 MHz, $CDCl_3$)



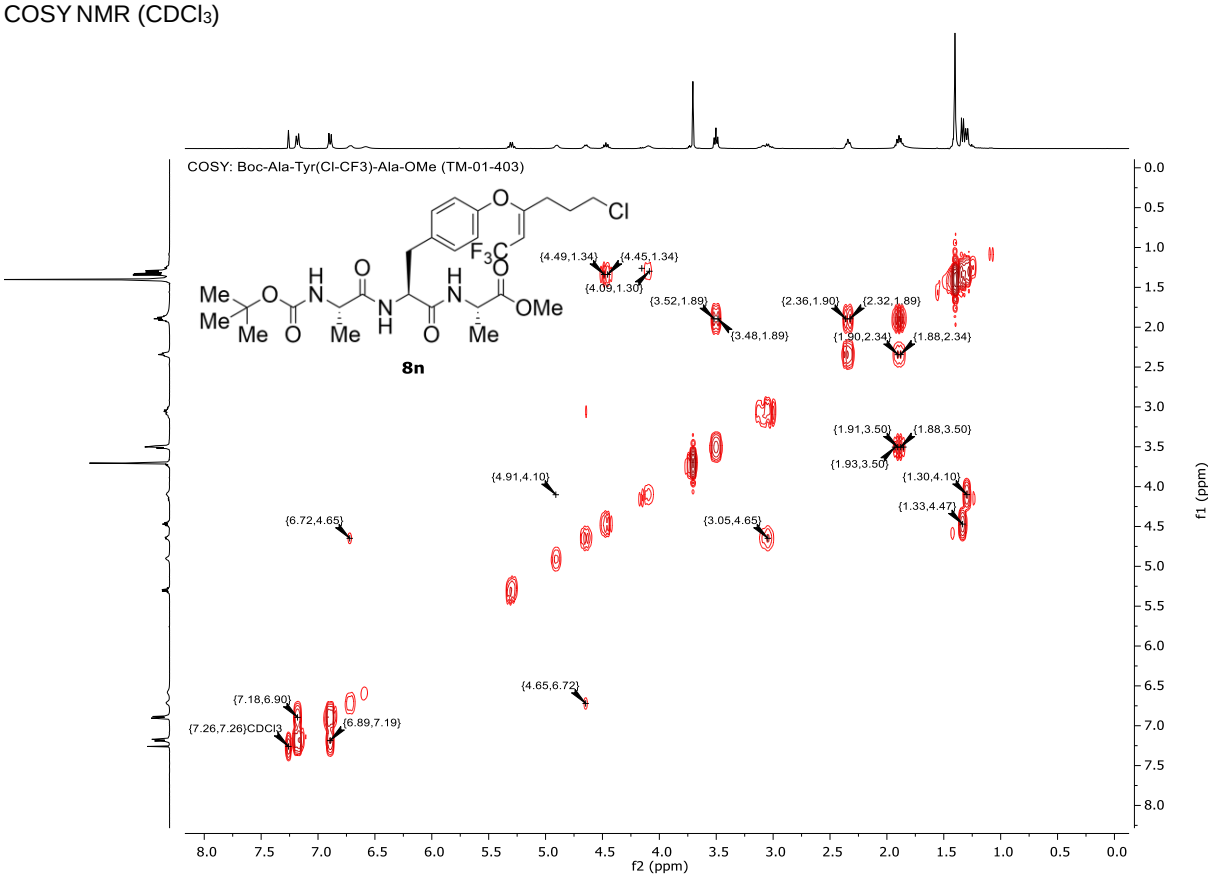
^{13}C-NMR (101 MHz, $CDCl_3$)



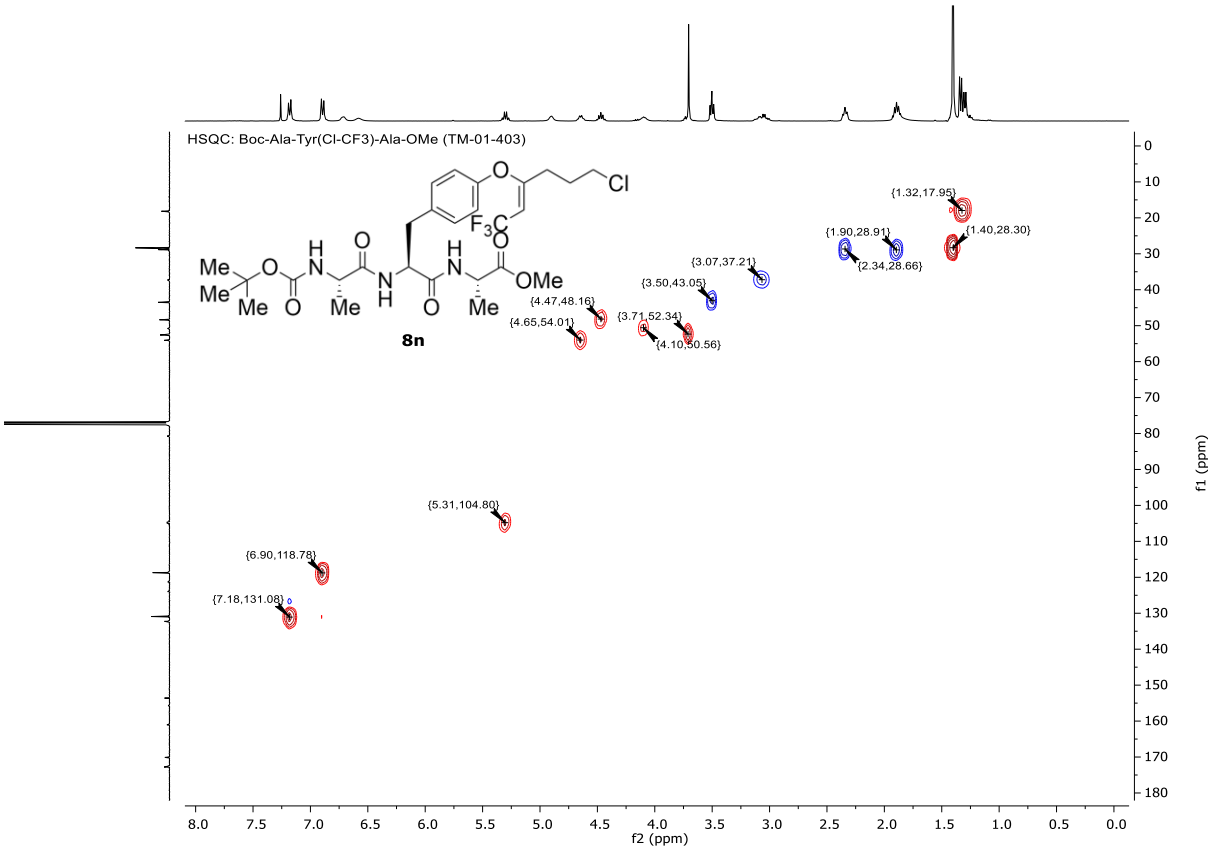
^{19}F-NMR (376 MHz, $CDCl_3$)



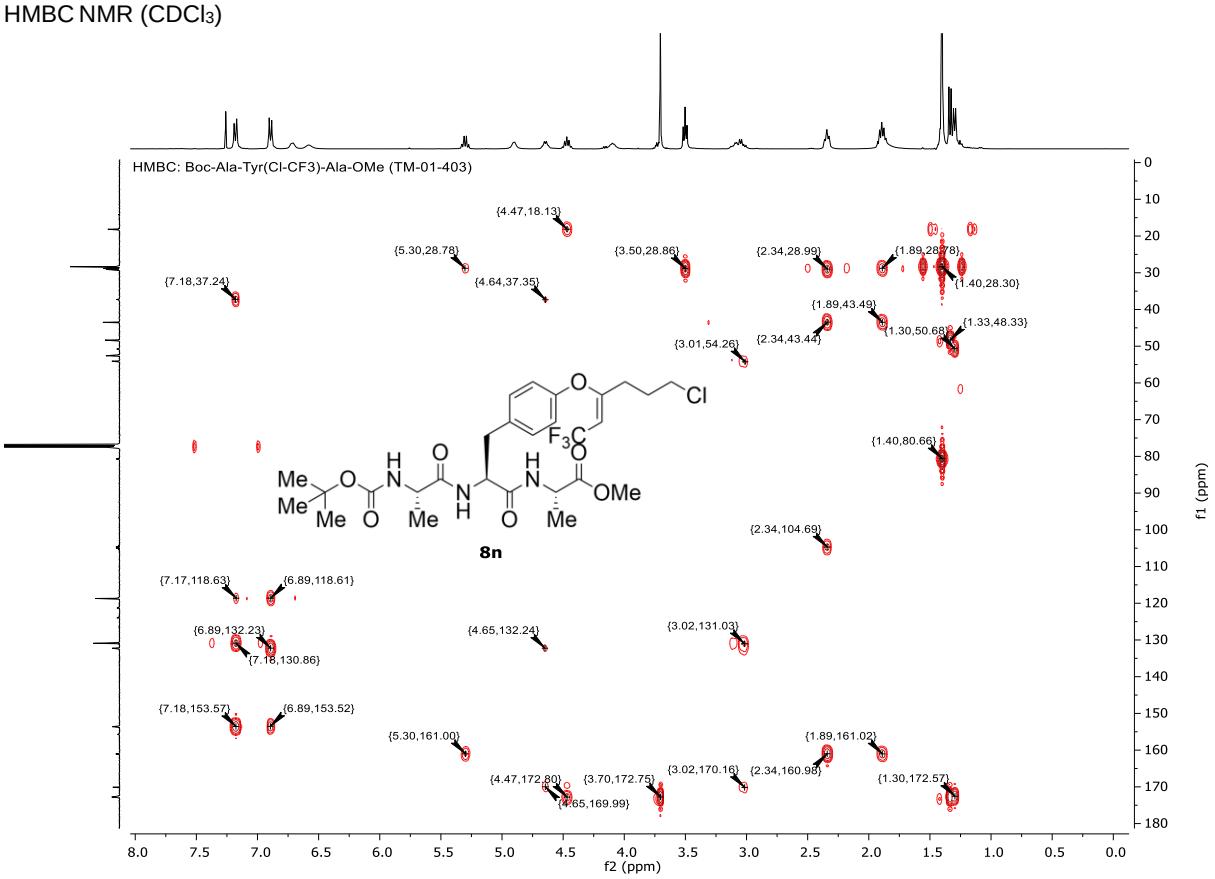
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinyl-L-alaninate (8q)

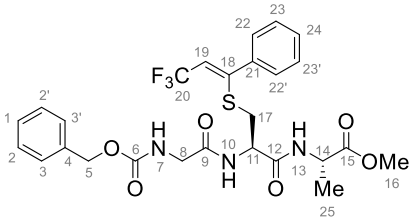
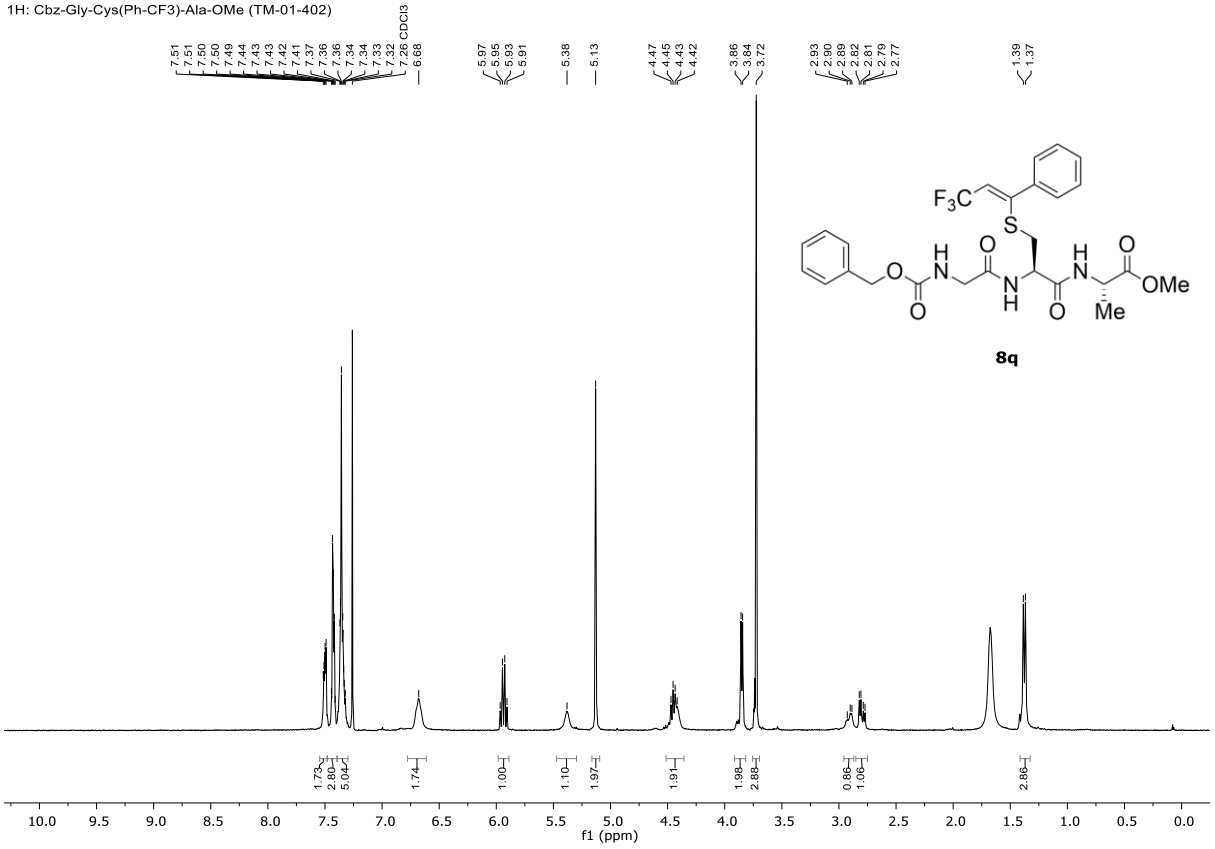


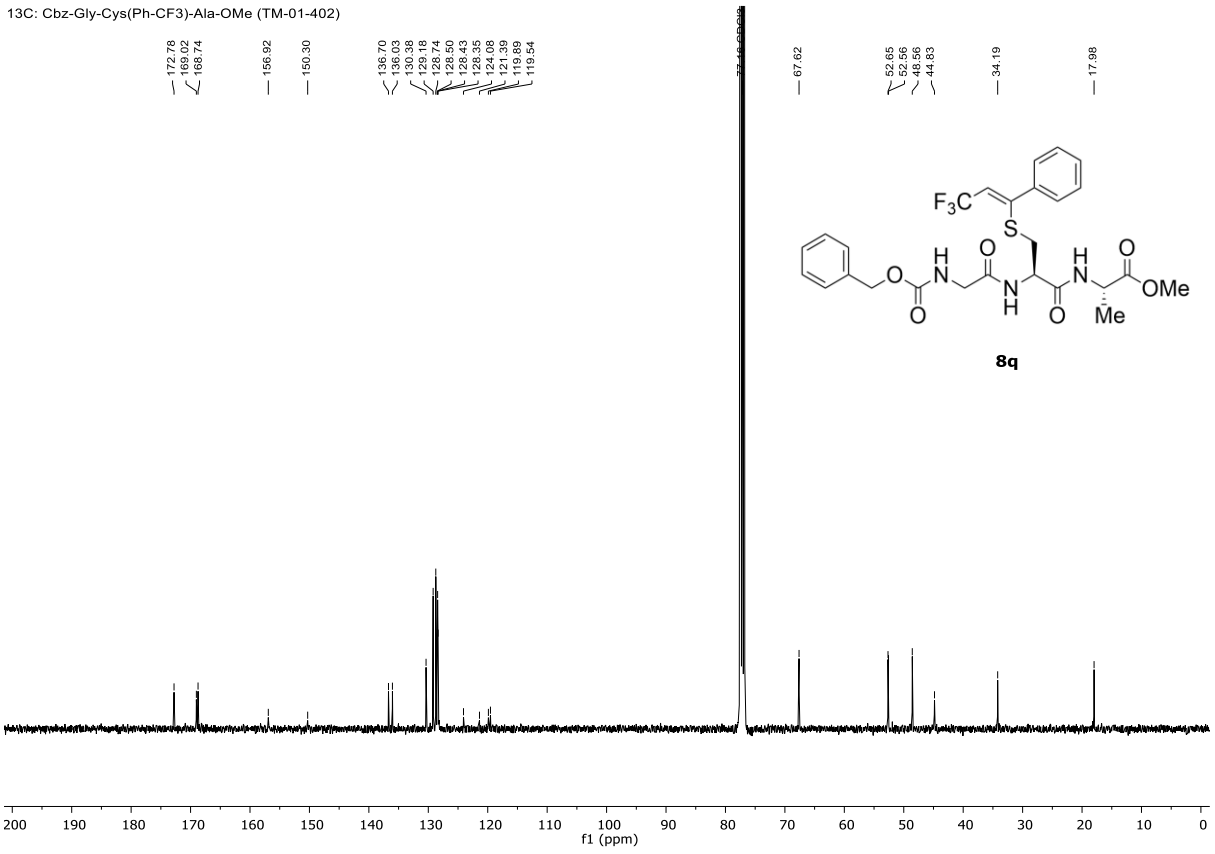
Table S42. Detailed NMR assignment of methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)-L-cysteinyl-L-alaninate (**8q**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	128.5	7.39-7.31 (m)		3/3‘
2/2‘	128.4	7.39-7.31 (m)		5
3/3‘	128.7	7.39-7.31 (m)		5
4	136.0			
5	67.6	5.13 (s)		2/2’, 4, 7
6	156.9			
7	/	5.34 (bs)	8	
8	44.8	3.85 (d, 5.5 Hz)	7	6, 9
9	169.0			
10	/	6.64 (bs)	11	
11	52.6	4.50-4.37 (m)	10, 17	12
12	168.7			
13	/	6.64 (bs)	14	
14	48.6	4.50-4.37 (m)	13, 25	15, 25
15	172.8			
16	52.6	3.73 (s)		15
17	34.2	2.97-2.86 (m), 2.80 (dd, 14.2, 5.8 Hz)	11	11, 12, 18
18	150.3 (q, 6.4 Hz)			
19	119.7 (q, 34.1 Hz)	5.94 (q, 8.0 Hz)		20, 21
20	122.7 (q, 270.8 Hz)			
21	136.7	7.46-7.40 (m)	22/22’	23/23’
22/22’	129.2	7.53-7.46 (m)	21, 23/23’	18, 23’23’
23/23’	130.4	7.46-7.40 (m)	22/22’	21
24	128.4			
25	18.0	1.38 (d, 7.2 Hz)	14	14, 15

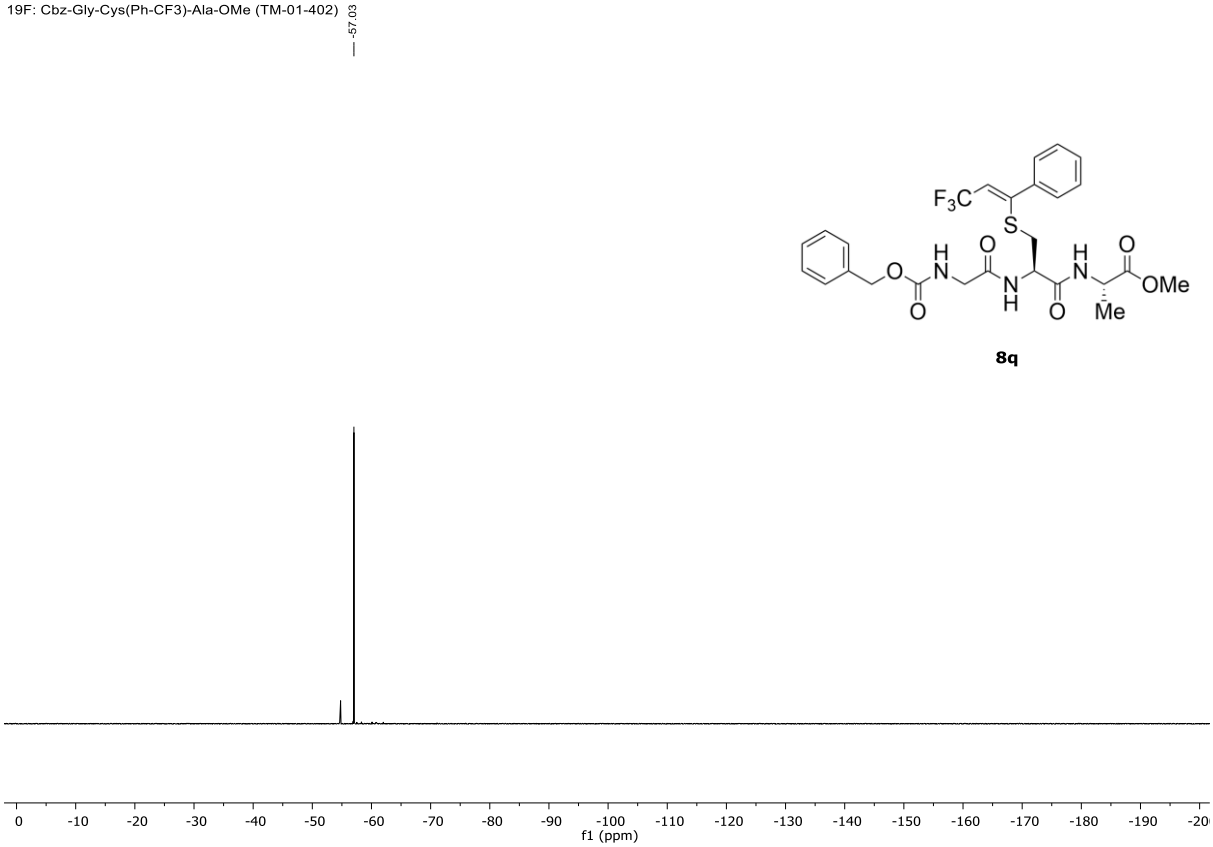
^{1}H-NMR (400 MHz, $CDCl_3$)



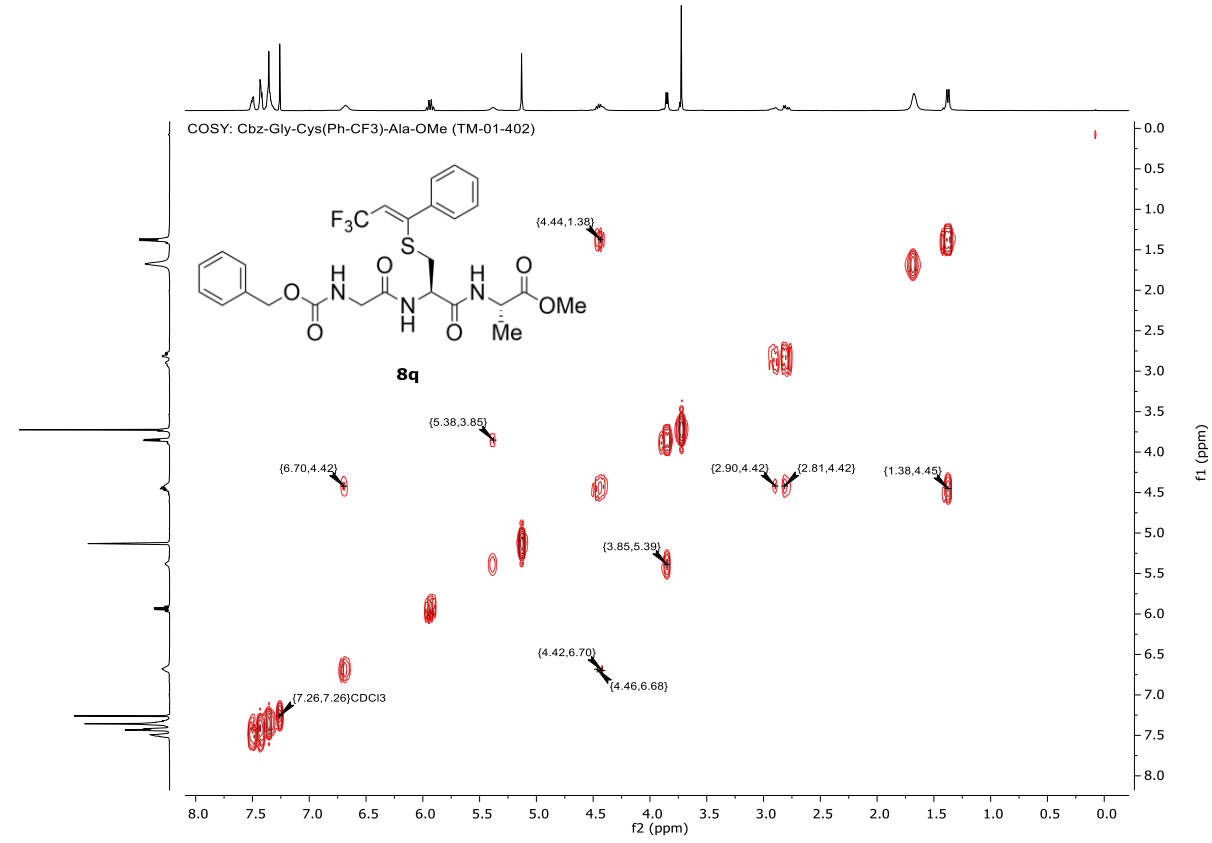
^{13}C-NMR (101 MHz, $CDCl_3$)



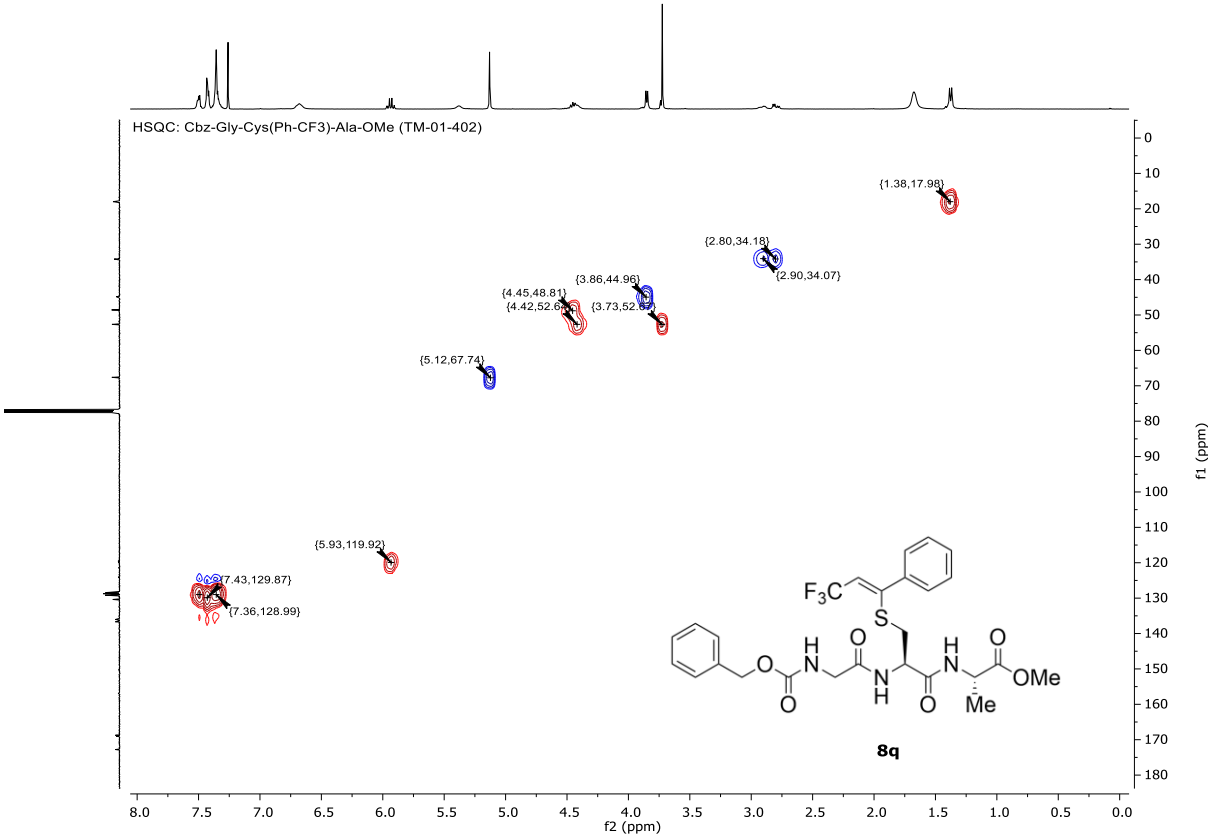
^{19}F-NMR (376 MHz, $CDCl_3$)



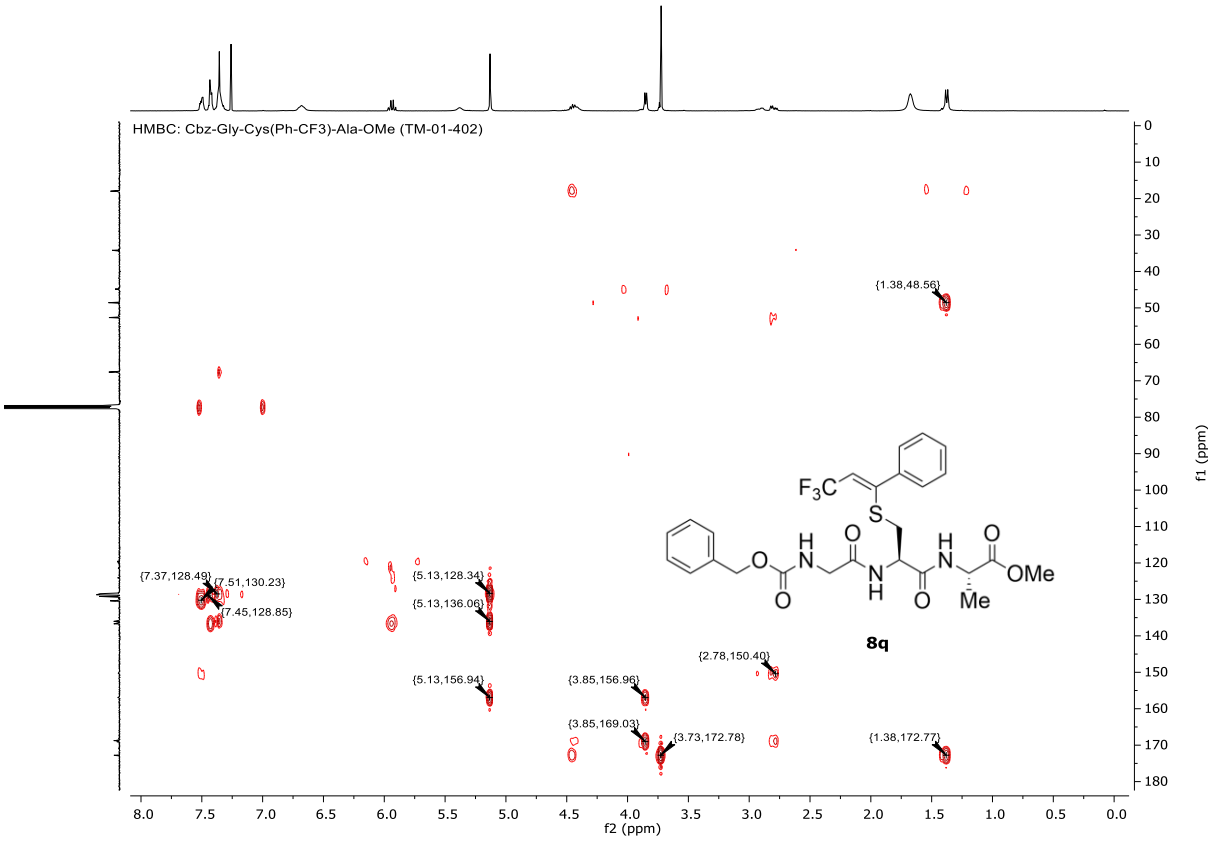
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinyl-L-alaninate (8r)

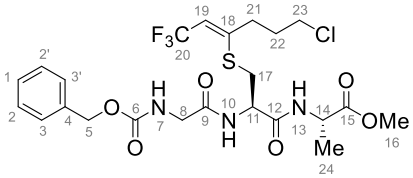
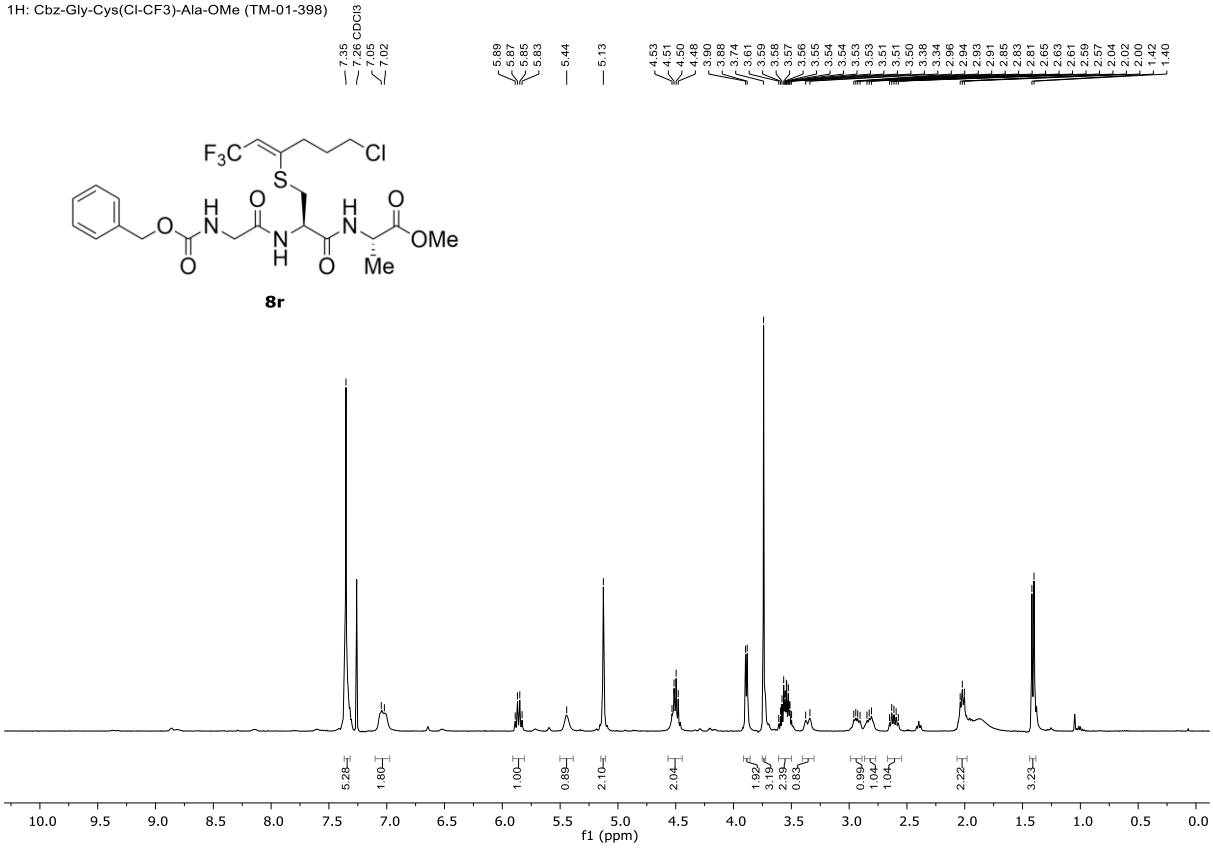


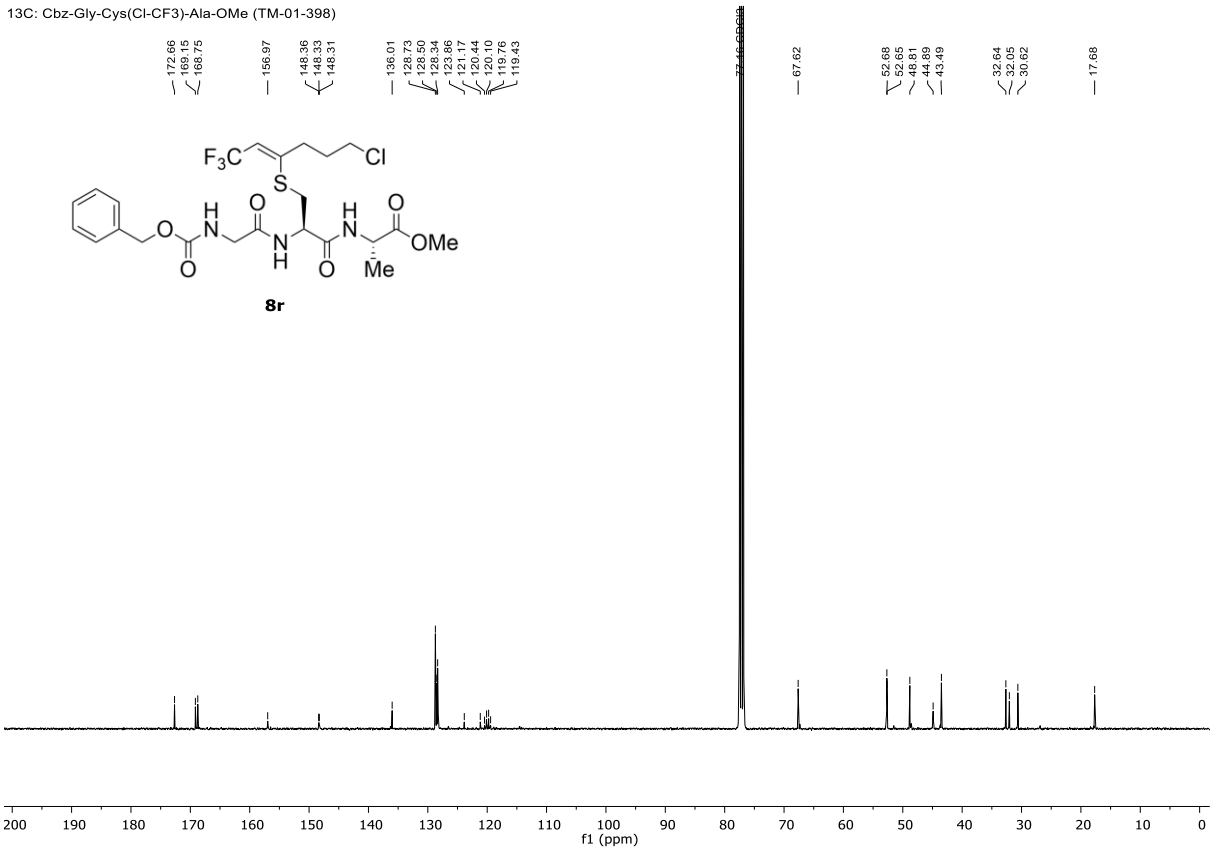
Table S43. Detailed NMR assignment of methyl *N*-(((benzyloxy)carbonyl)glycyl)-*S*-((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)-L-cysteinyl-L-alaninate (**8r**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	128.5	7.38-7.33 (m)		
2/2‘	128.3	7.38-7.33 (m)		4, 5
3/3‘	128.7	7.38-7.33 (m)		1, 5
4	136.0			
5	67.6	5.13 (s)		2/2’, 4, 6
6	157.0			
7	/	5.44 (bs)	8	
8	44.9	3.89 (d, 5.7 Hz)	7	6, 9
9	169.2			
10	/	7.09-6.99 (m)	11	9
11	52.6	4.55-4.44 (m)	10, 17	12
12	168.7			
13	/	7.09-6.99 (m)	14	12
14	48.8	4.55-4.44 (m)	13, 24	15, 24
15	172.7			
16	52.7	3.74 (s)		15
17	32.6	3.36 (d, 14.5 Hz), 2.93 (dd, 14.3, 7.4 Hz)	11	12, 18
18	148.3 (q, 5.0 Hz)			
19	119.9 (q, 33.9 Hz)	5.86 (q, 7.9 Hz)		20, 21
20	122.5 (q, 271.0 Hz)			
21	32.0	2.87-2.76 (m), 2.61 (dt, 15.3, 7.6 Hz)	22	
22	30.6	2.02 (p, 7.3 Hz)	21, 23	18, 21, 23
23	43.5	3.61-3.49 (m)	22	21
24	17.7	1.41 (d, 7.3 Hz)	14	14, 15

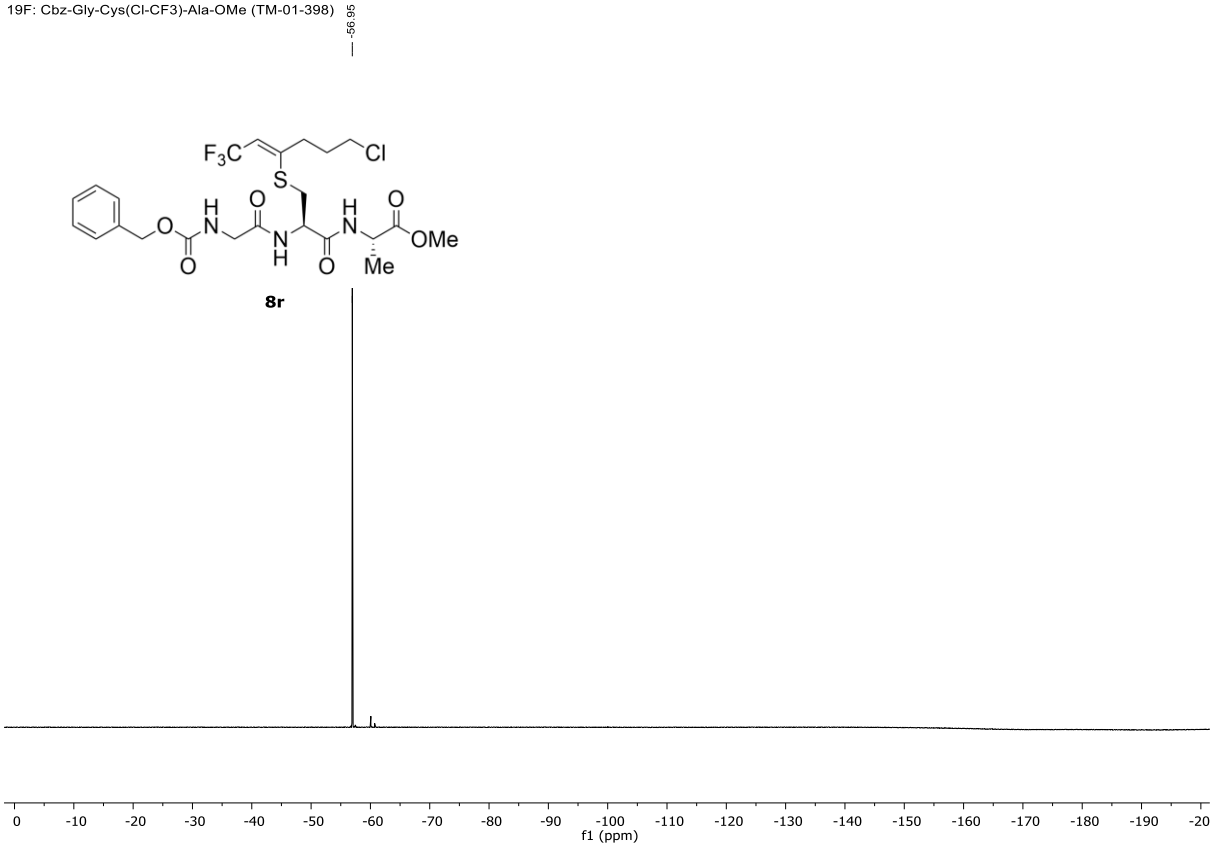
^{1}H-NMR (400 MHz, $CDCl_3$)



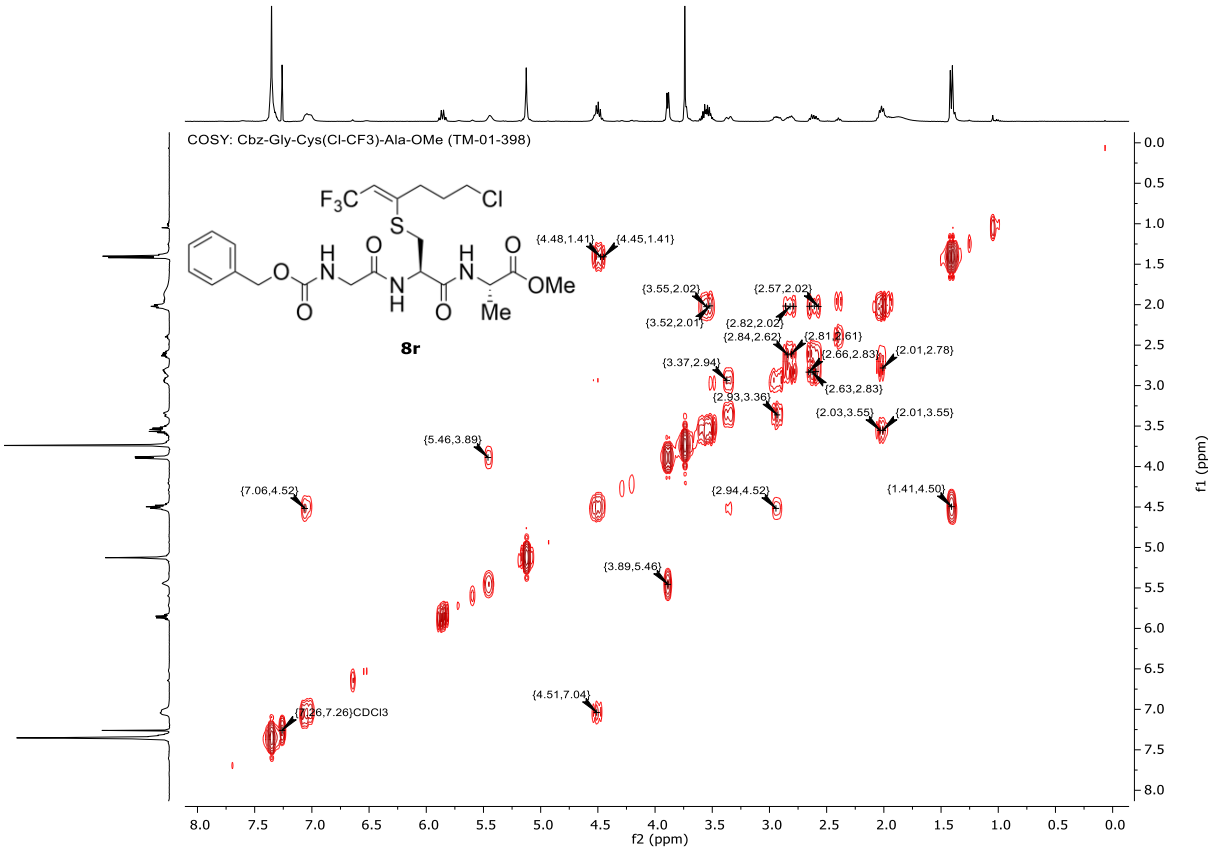
^{13}C-NMR (101 MHz, $CDCl_3$)



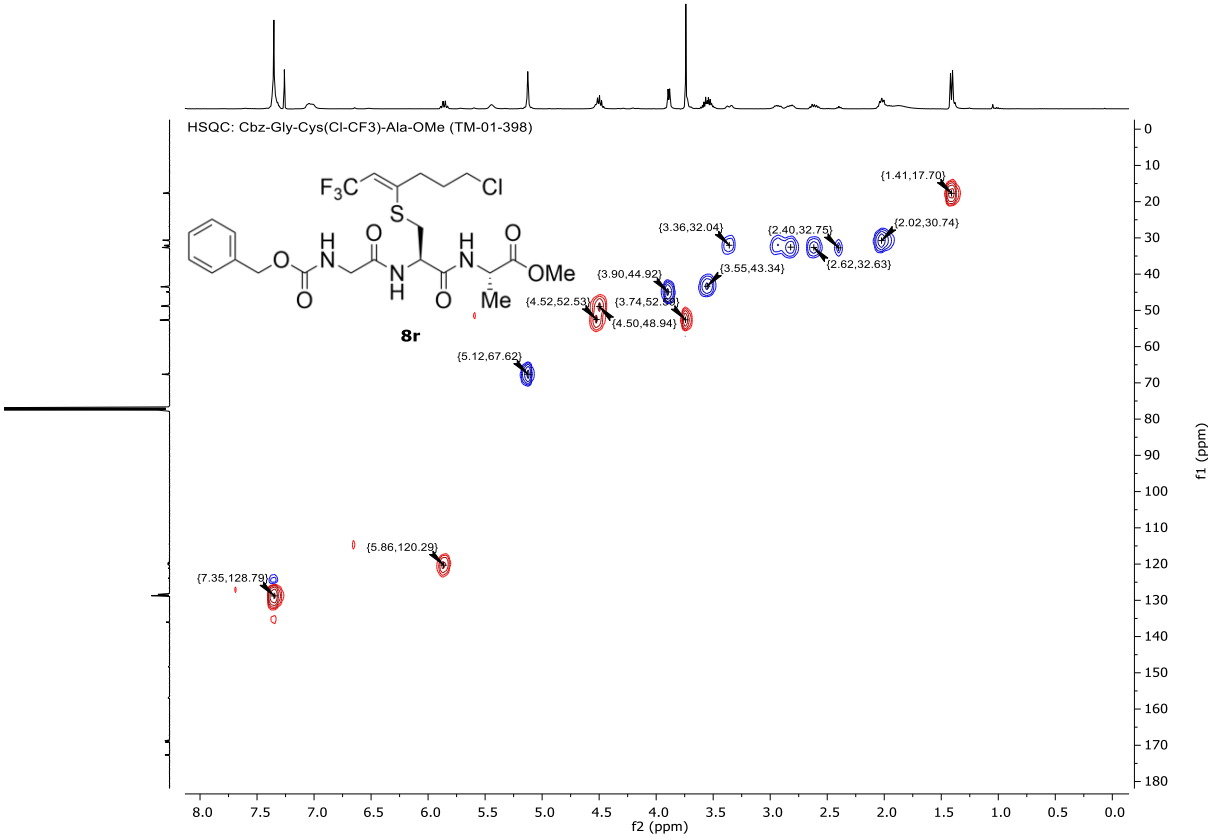
^{19}F-NMR (376 MHz, $CDCl_3$)



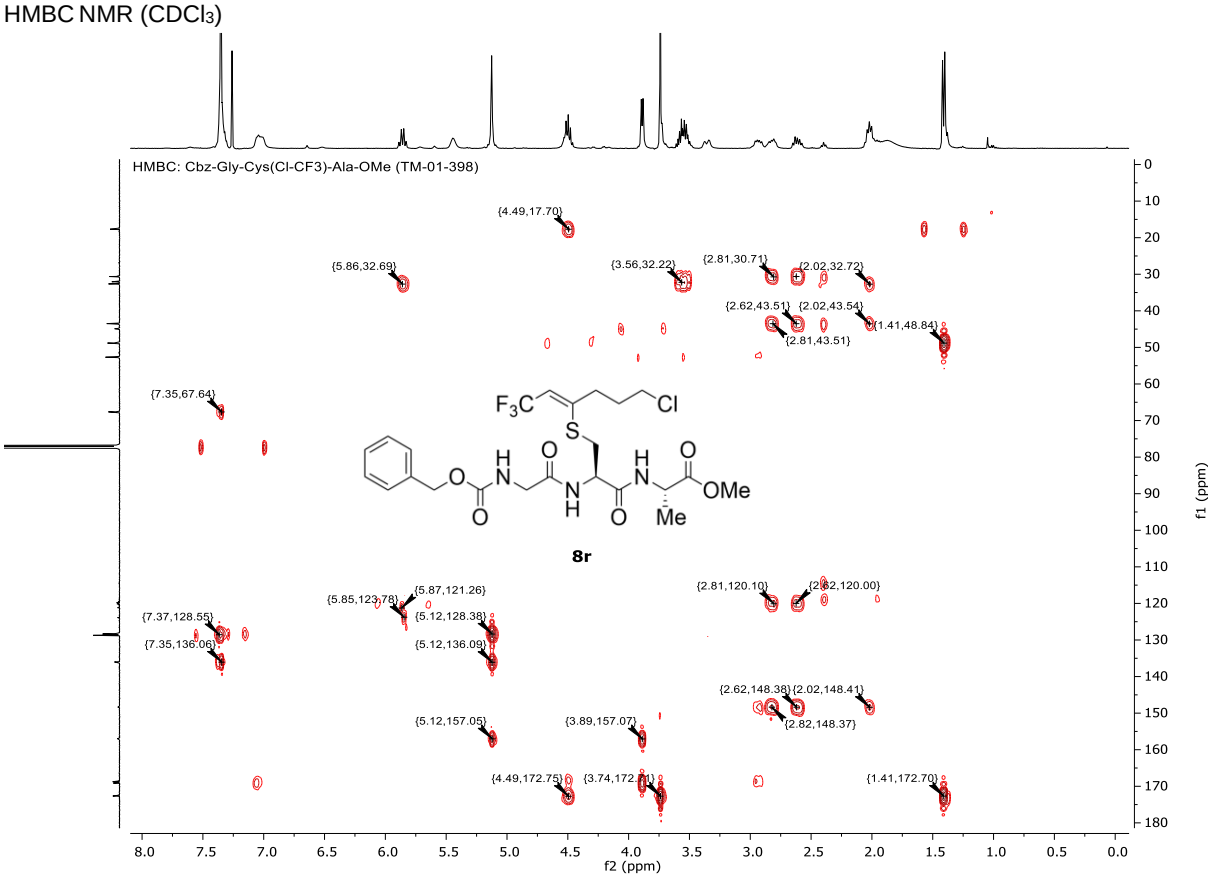
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

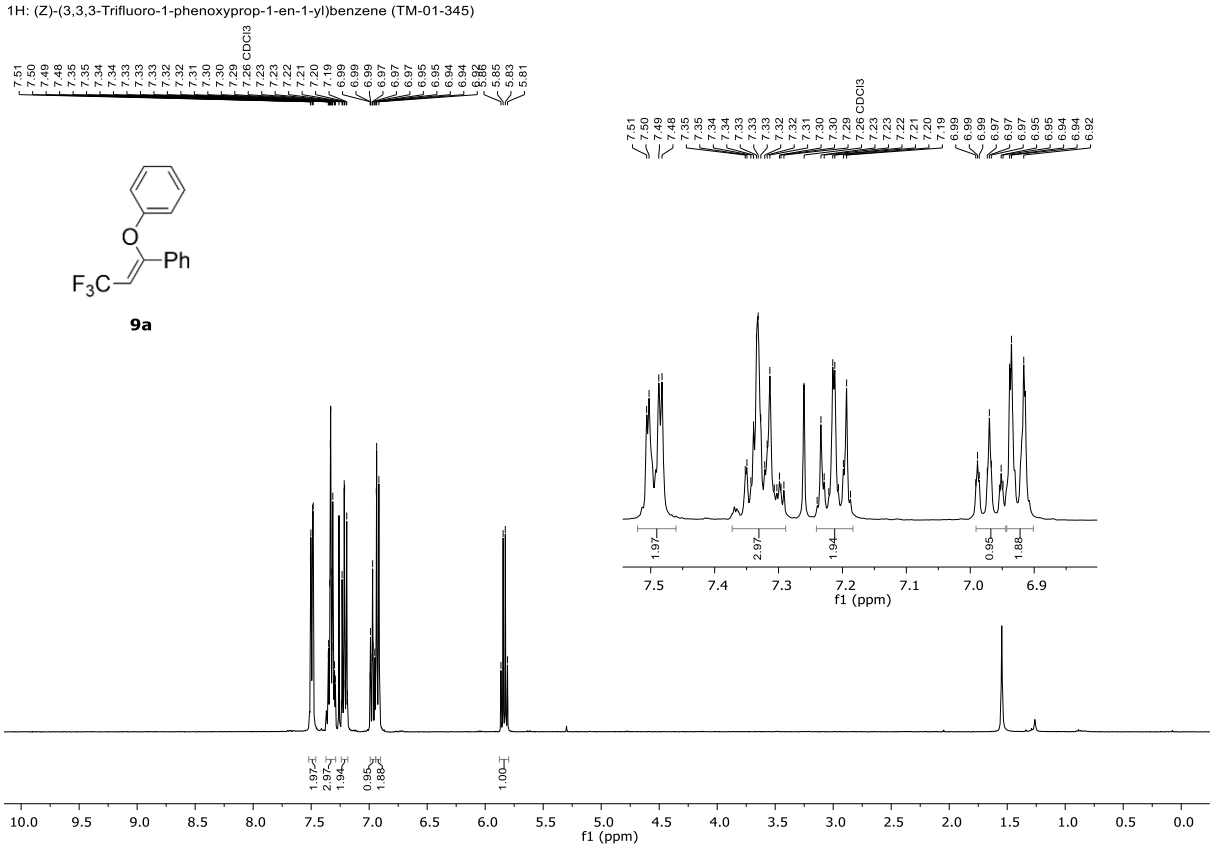


HMBC NMR ($CDCl_3$)

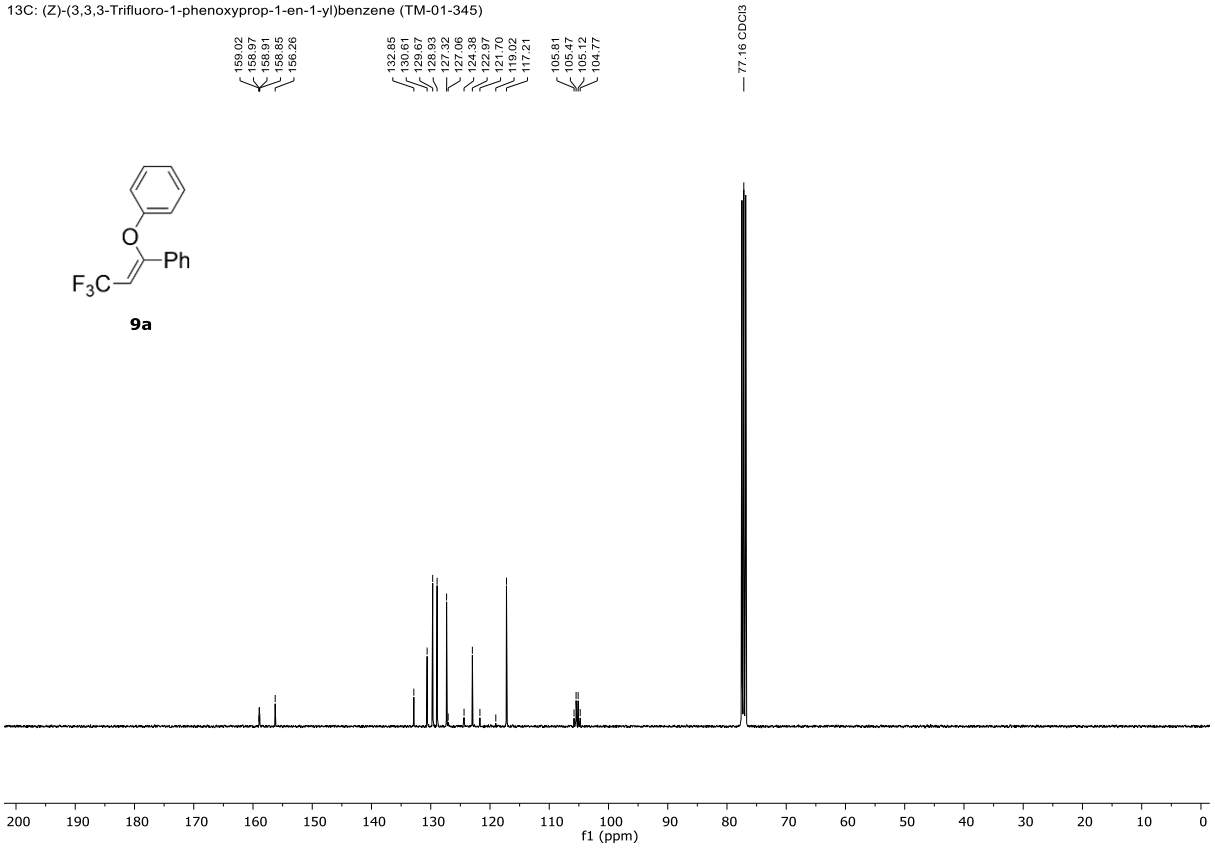


(*Z*)-(3,3,3-Trifluoro-1-phenoxyprop-1-en-1-yl)benzene (9a)

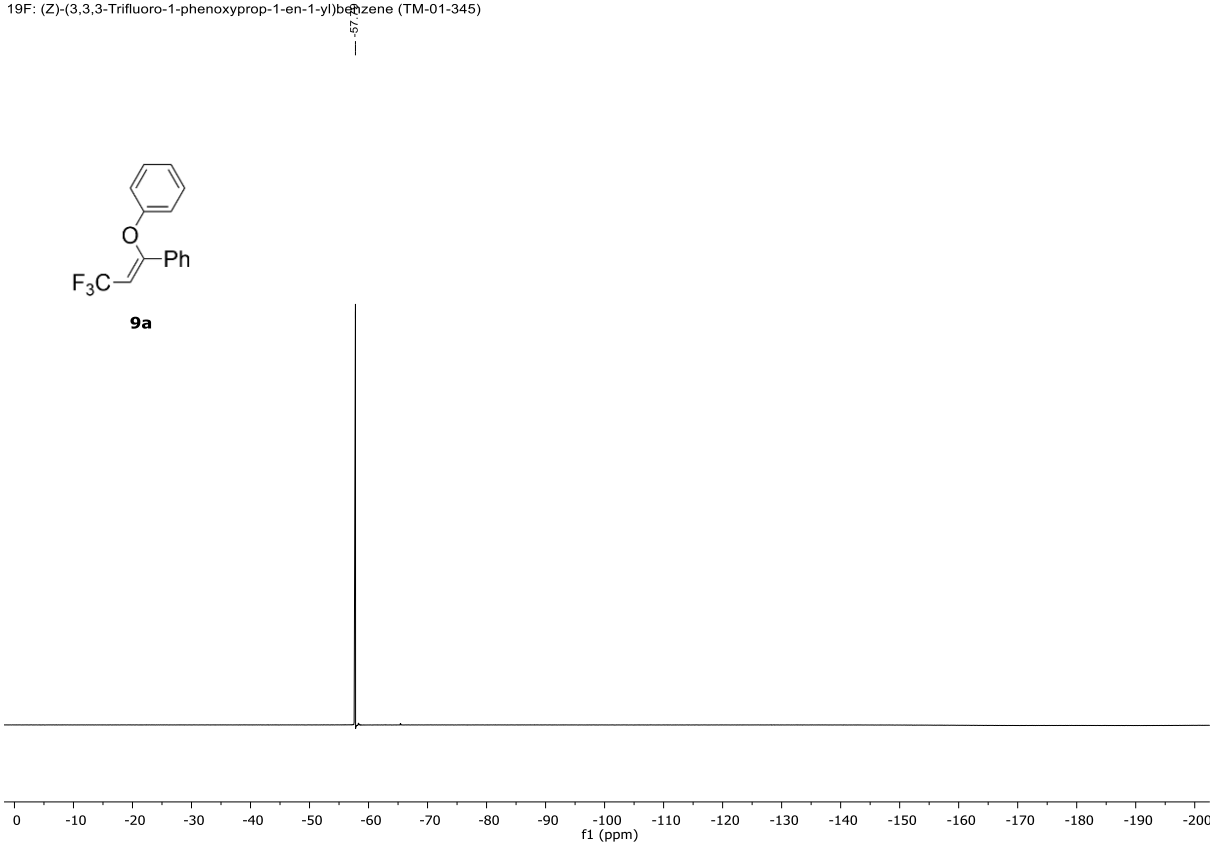
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

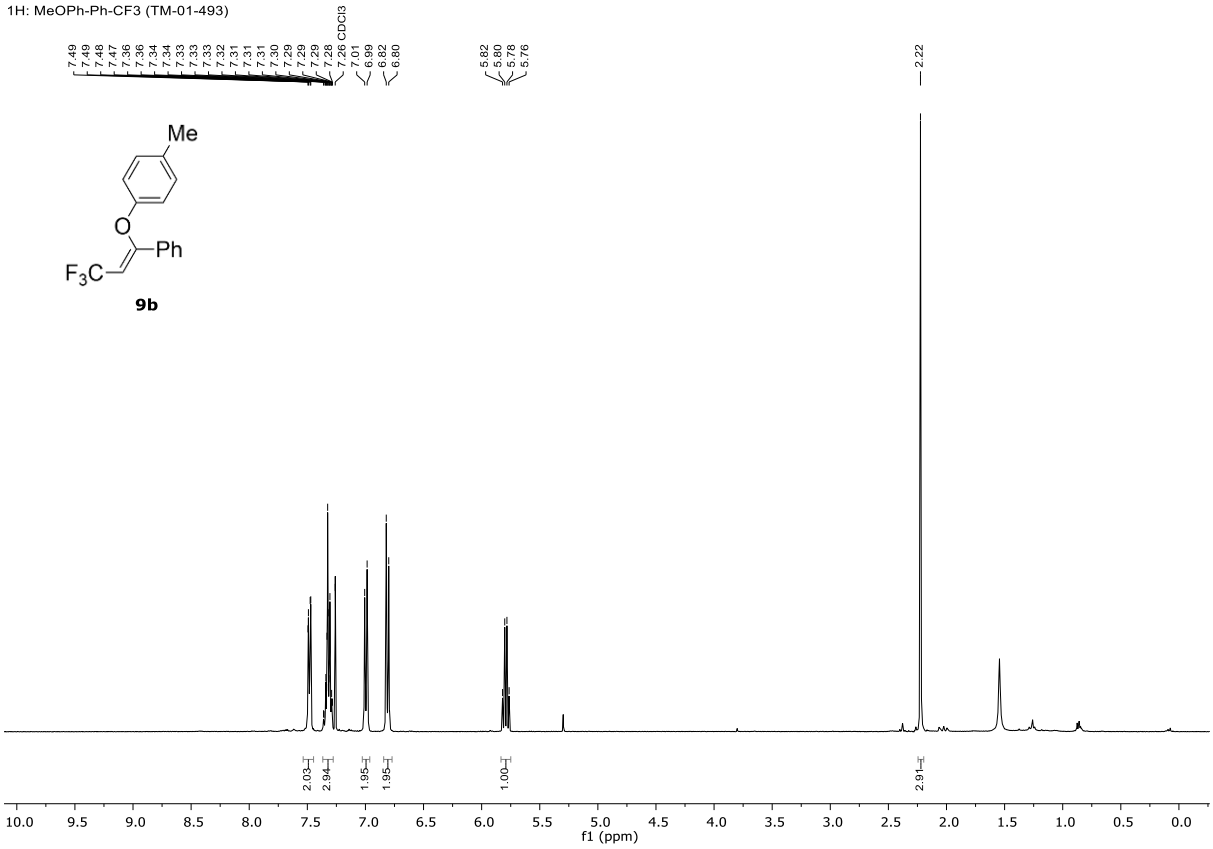


^{19}F-NMR (376 MHz, $CDCl_3$)

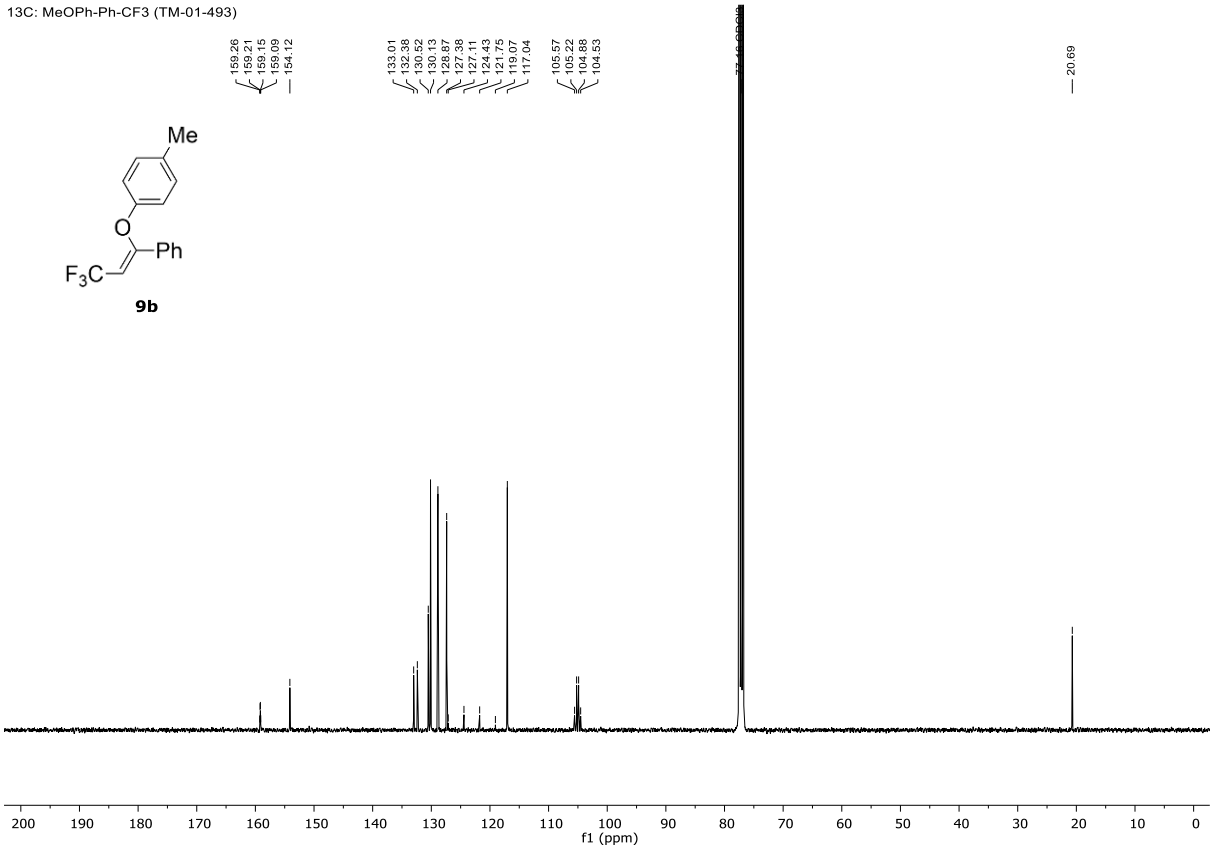


(*Z*)-1-Methyl-4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)benzene (9b)

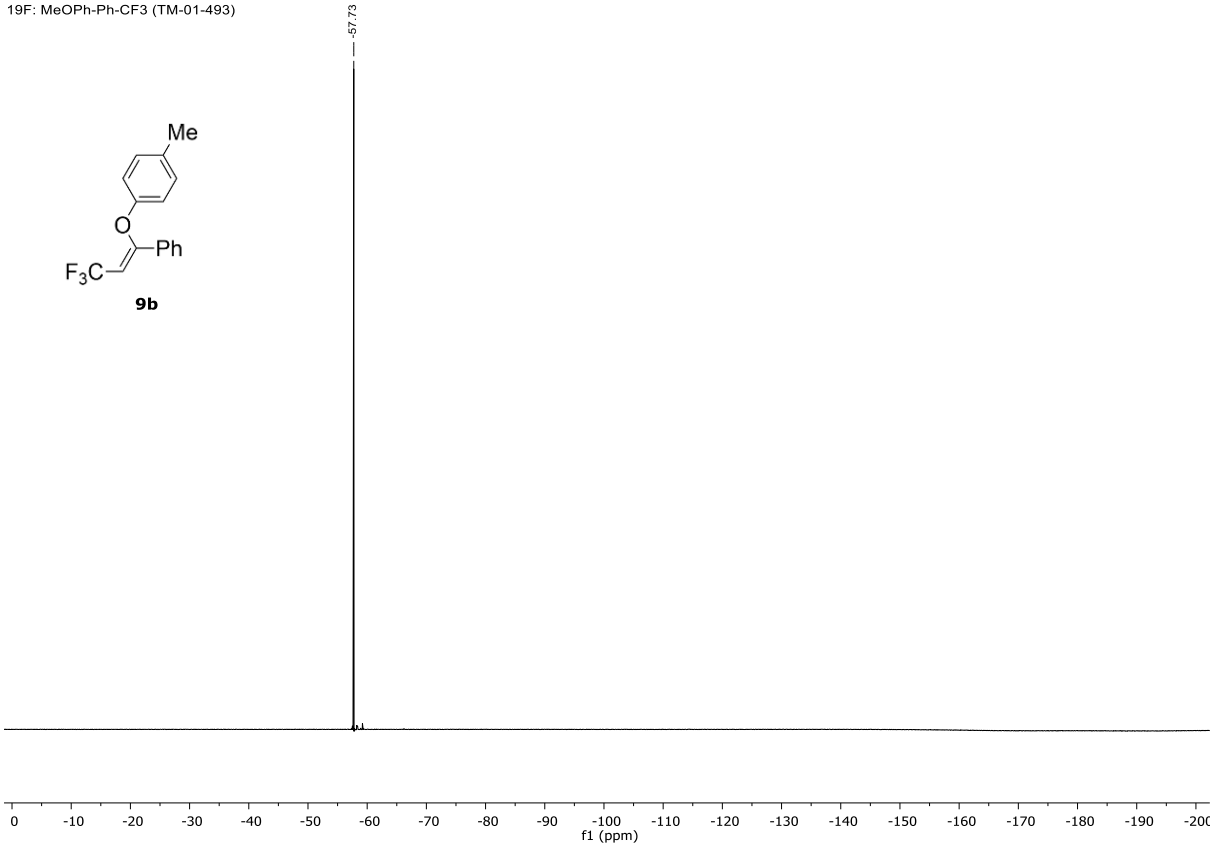
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

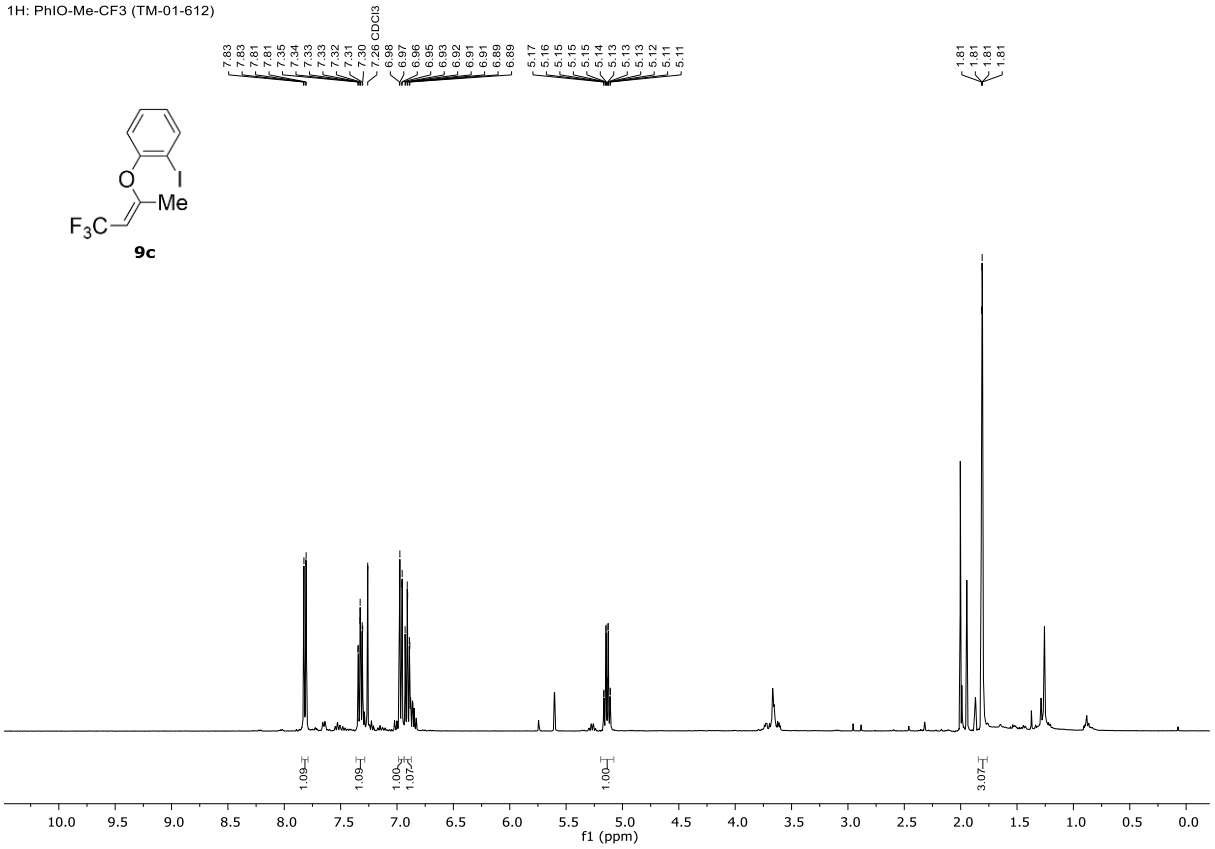


^{19}F-NMR (376 MHz, $CDCl_3$)

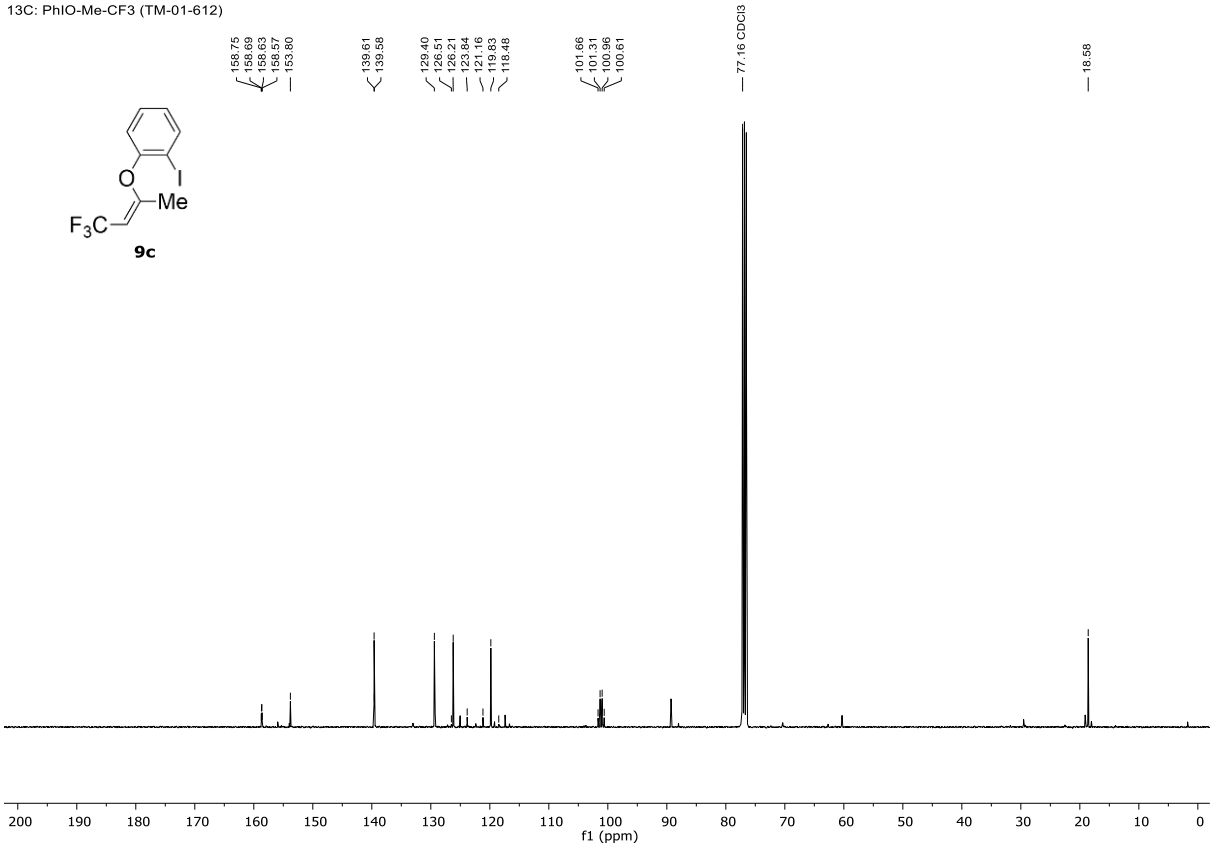


(*Z*)-1-Iodo-((4,4,4-trifluorobut-2-en-2-yl)oxy)benzene (9c)

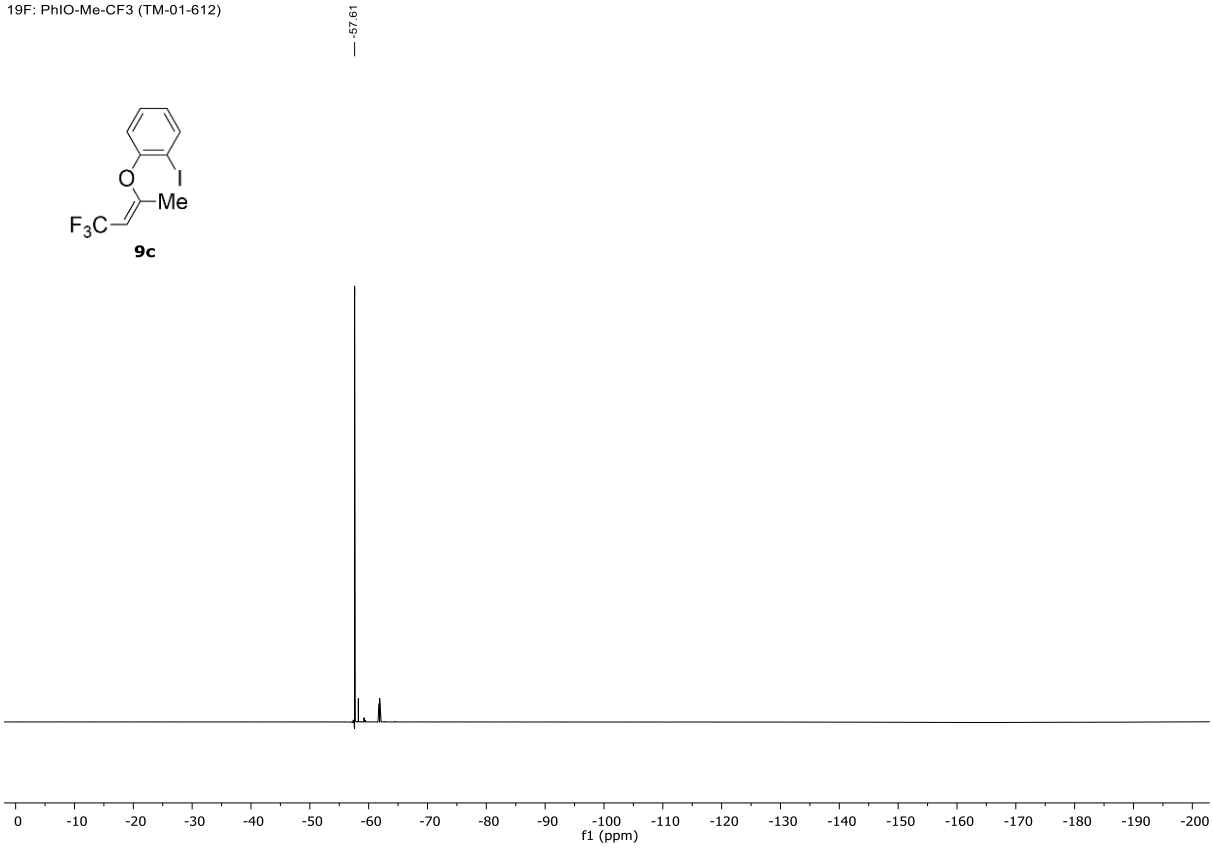
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

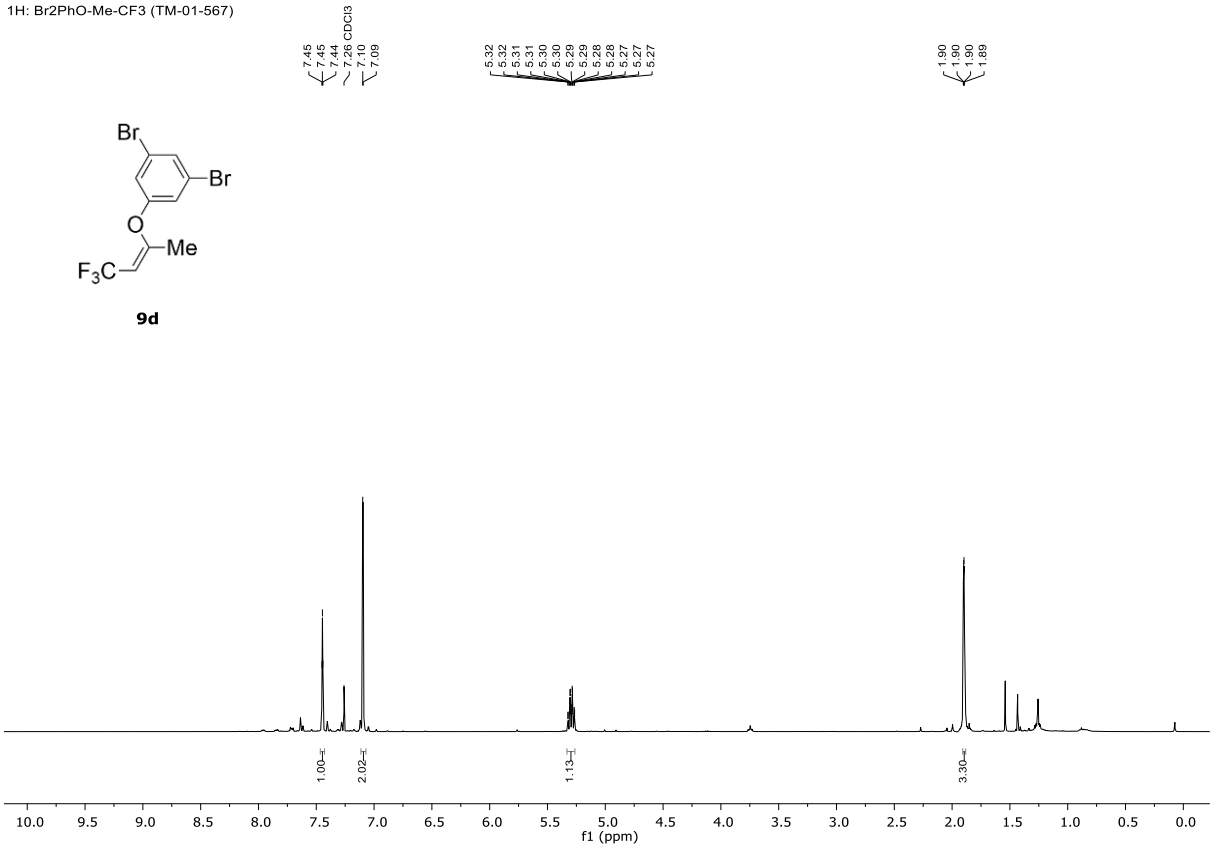


^{19}F-NMR (376 MHz, $CDCl_3$)

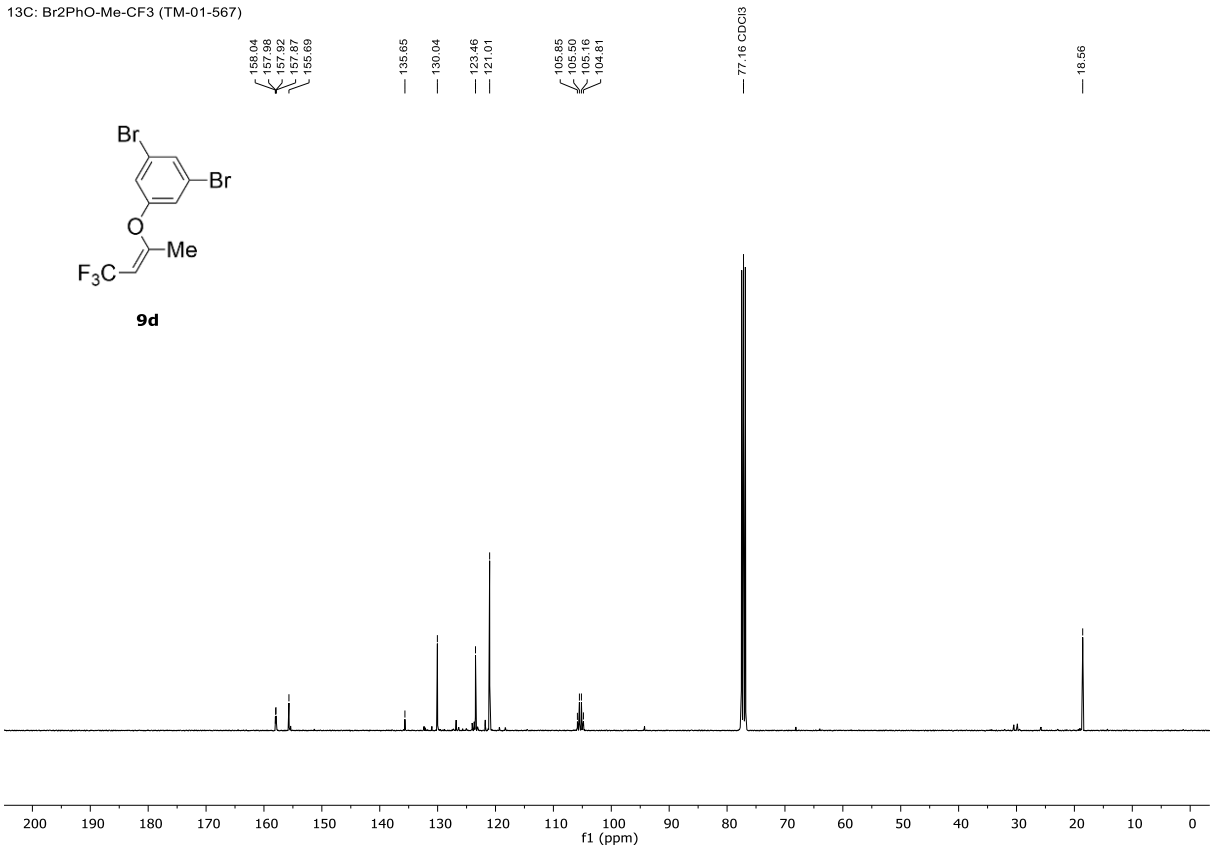


(*Z*)-1,3-Dibromo-5-((4,4,4-trifluorobut-2-en-2-yl)oxy)benzene (9d)

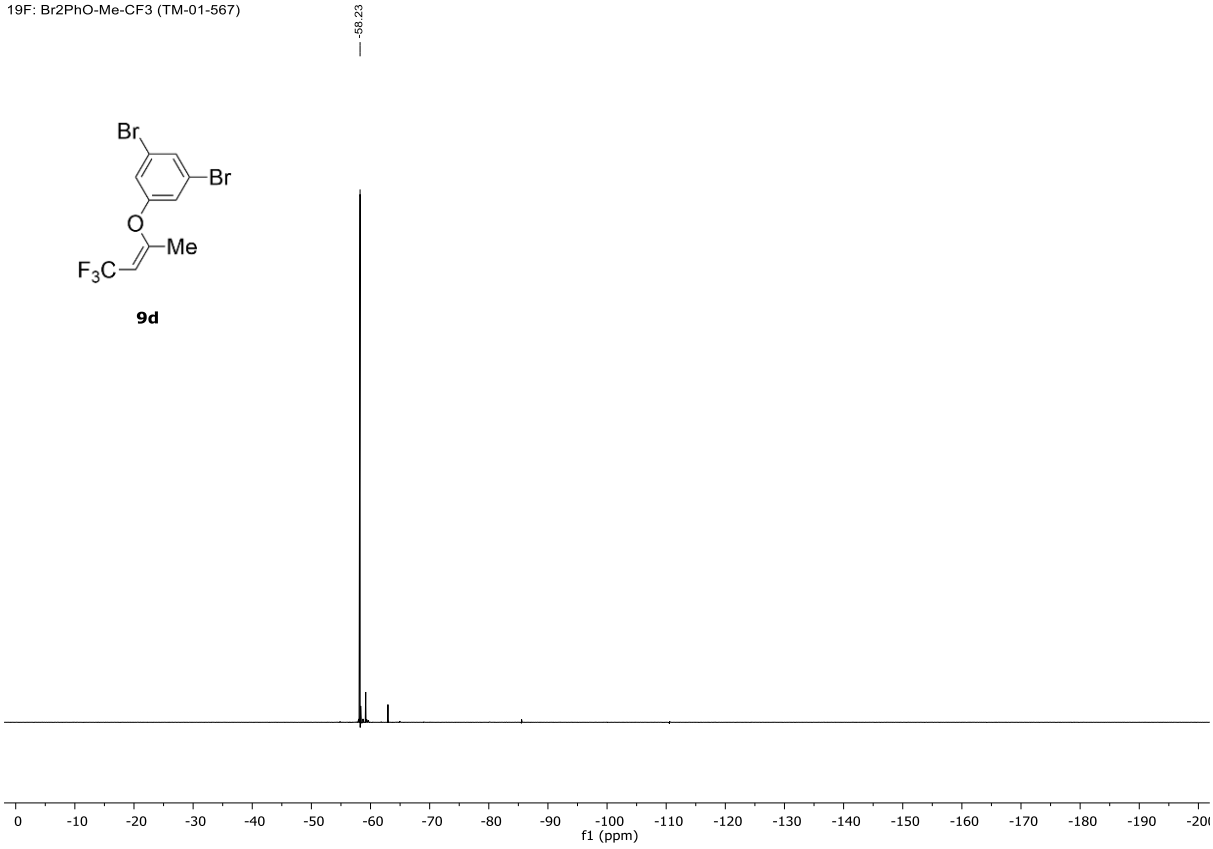
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

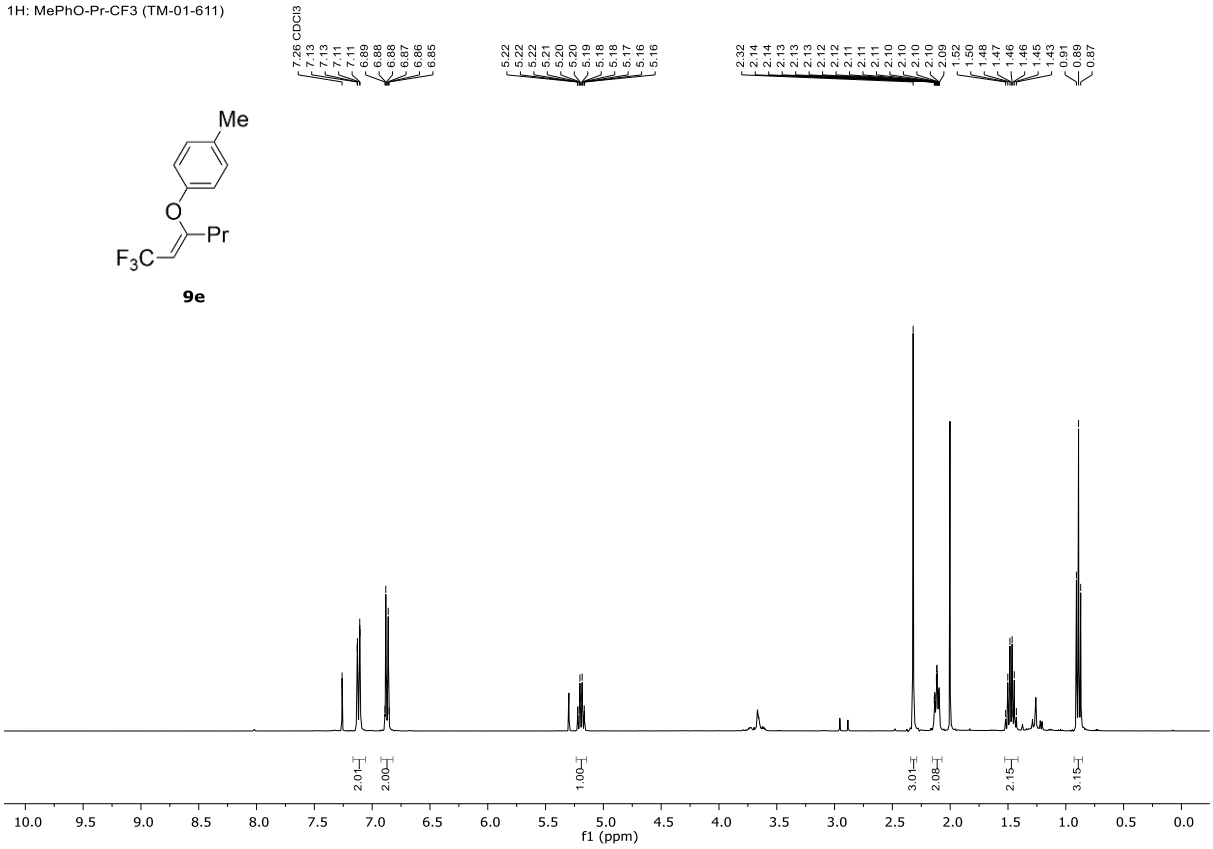


^{19}F-NMR (376 MHz, $CDCl_3$)

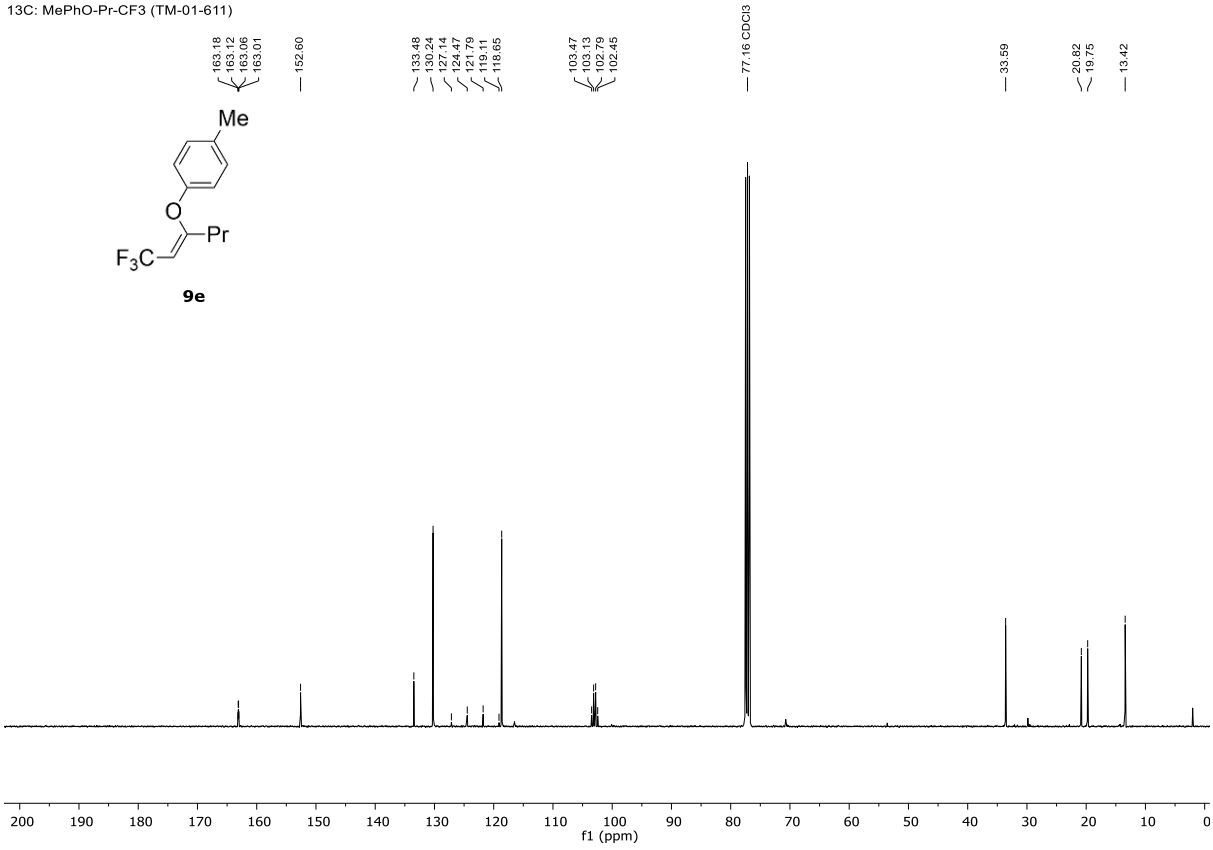


(*Z*)-1-Methyl-4-((1,1,1-trifluorohex-2-en-3-yl)oxy)benzene (9e)

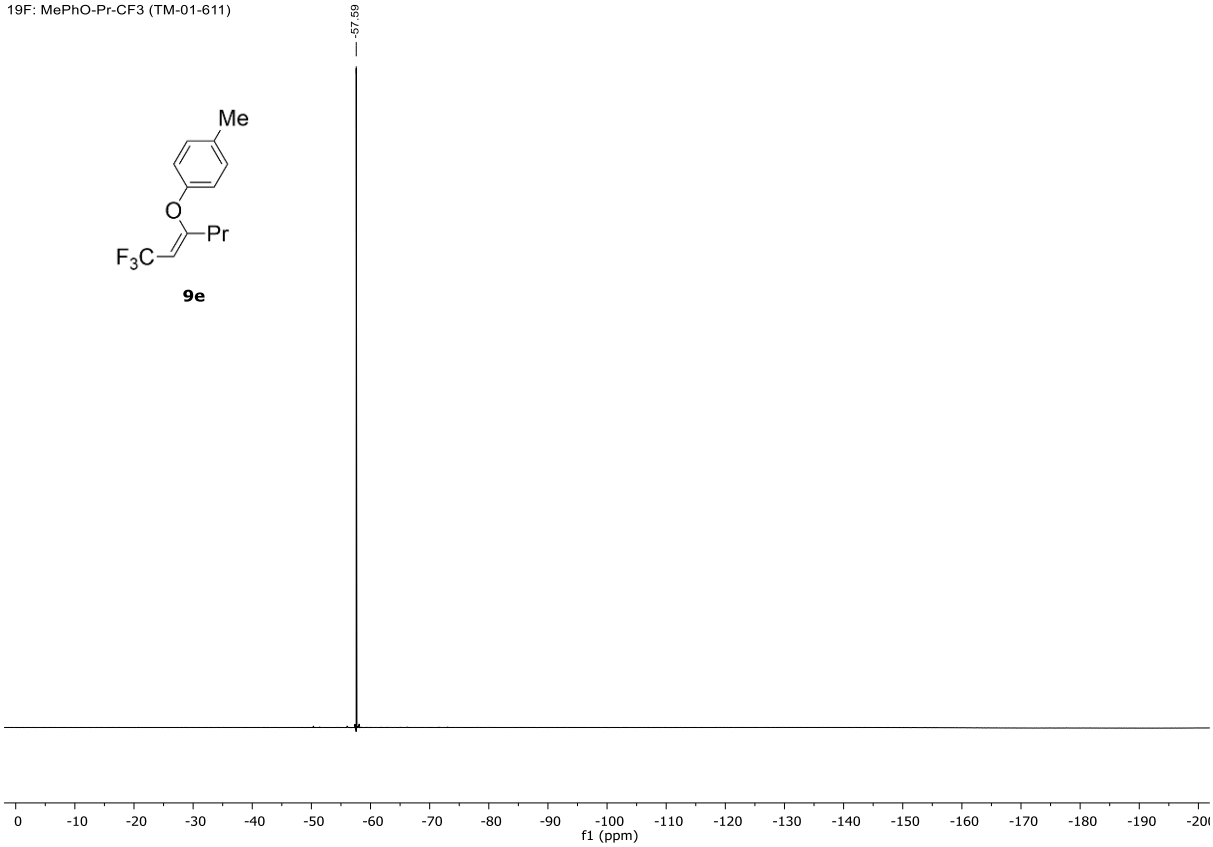
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

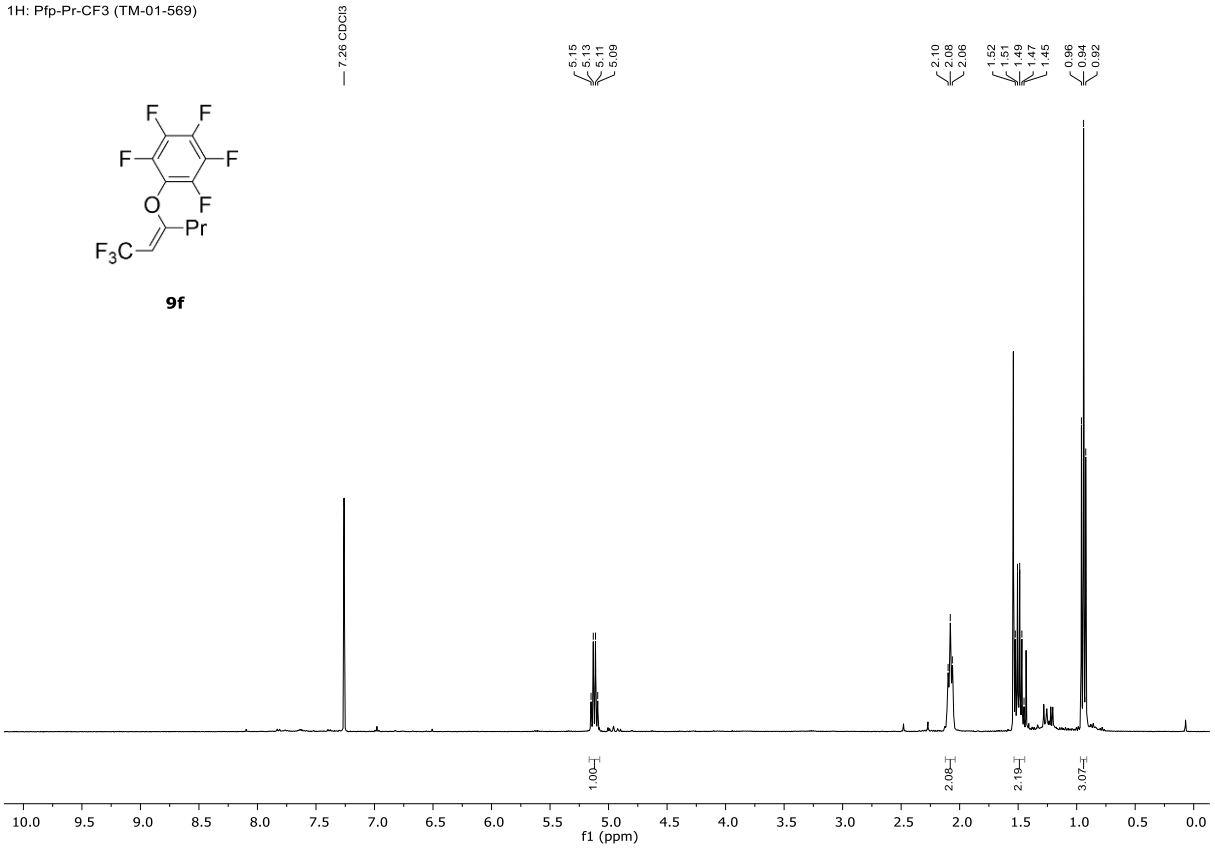


^{19}F-NMR (376 MHz, $CDCl_3$)

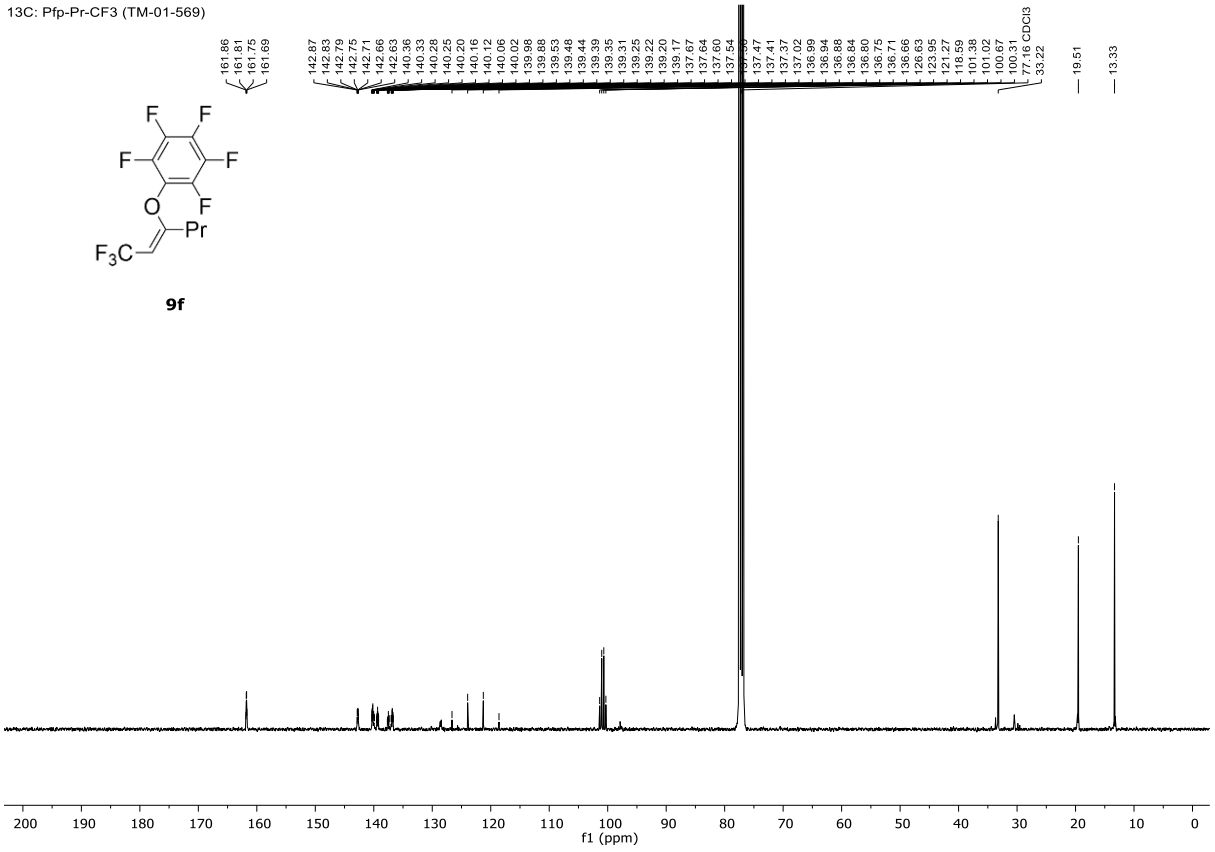


(*Z*)-1,2,3,4,5-Pentafluoro-6-((4,4,4-trifluorohex-2-en-2-yl)oxy)benzene (9f)

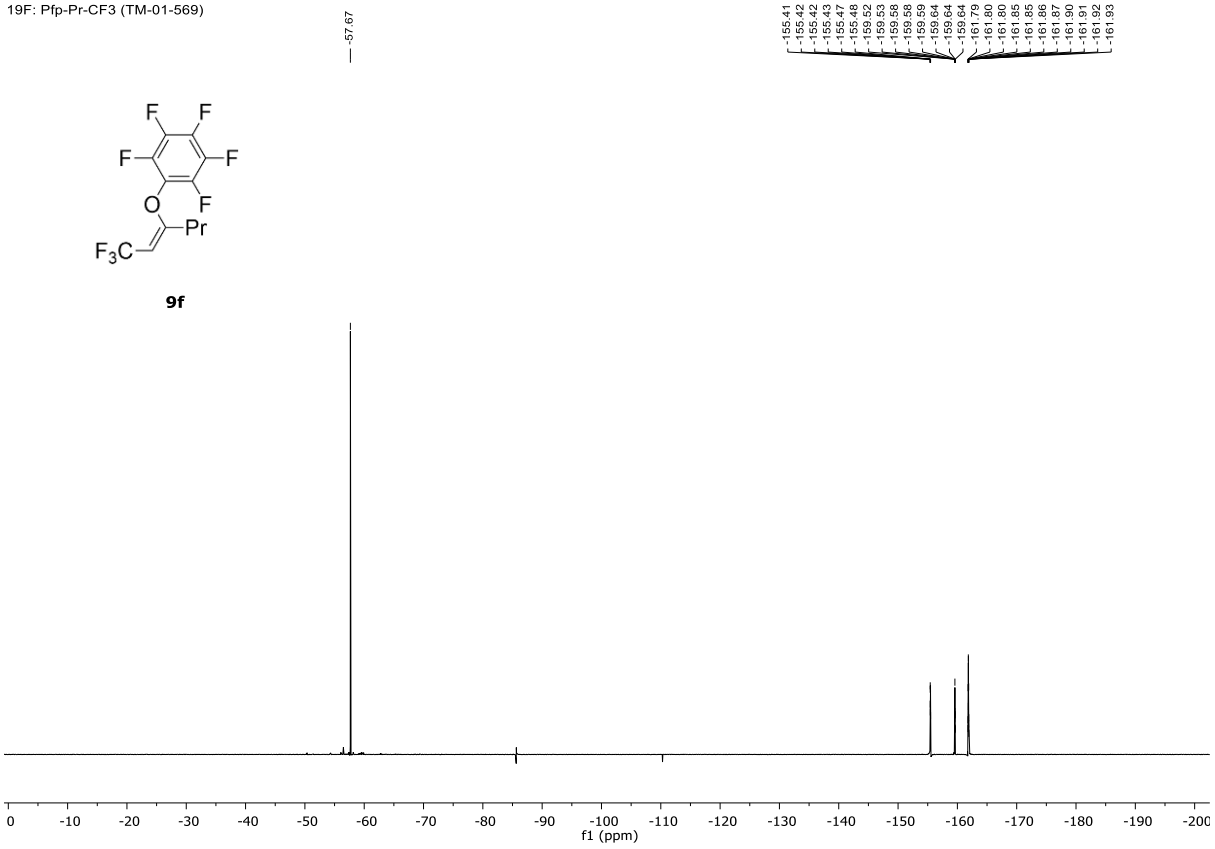
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

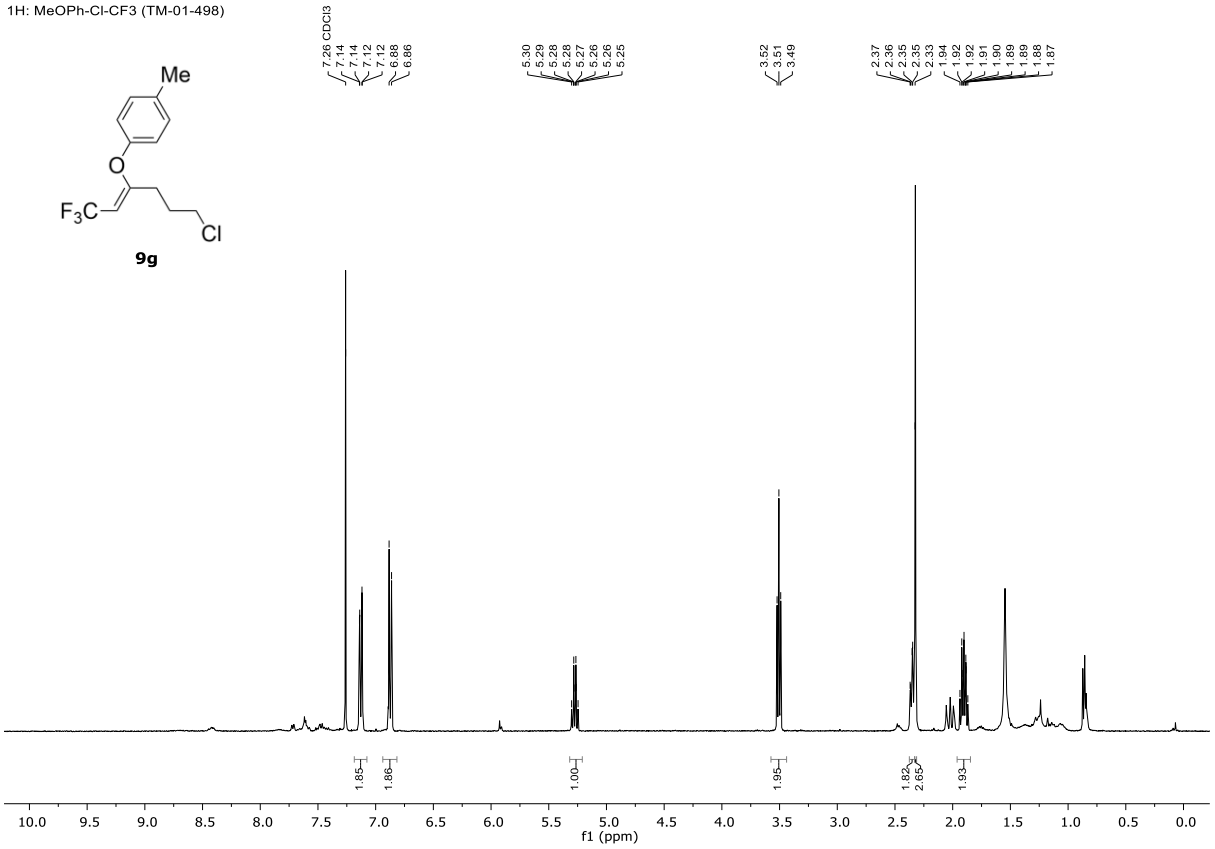


^{19}F-NMR (376 MHz, $CDCl_3$)

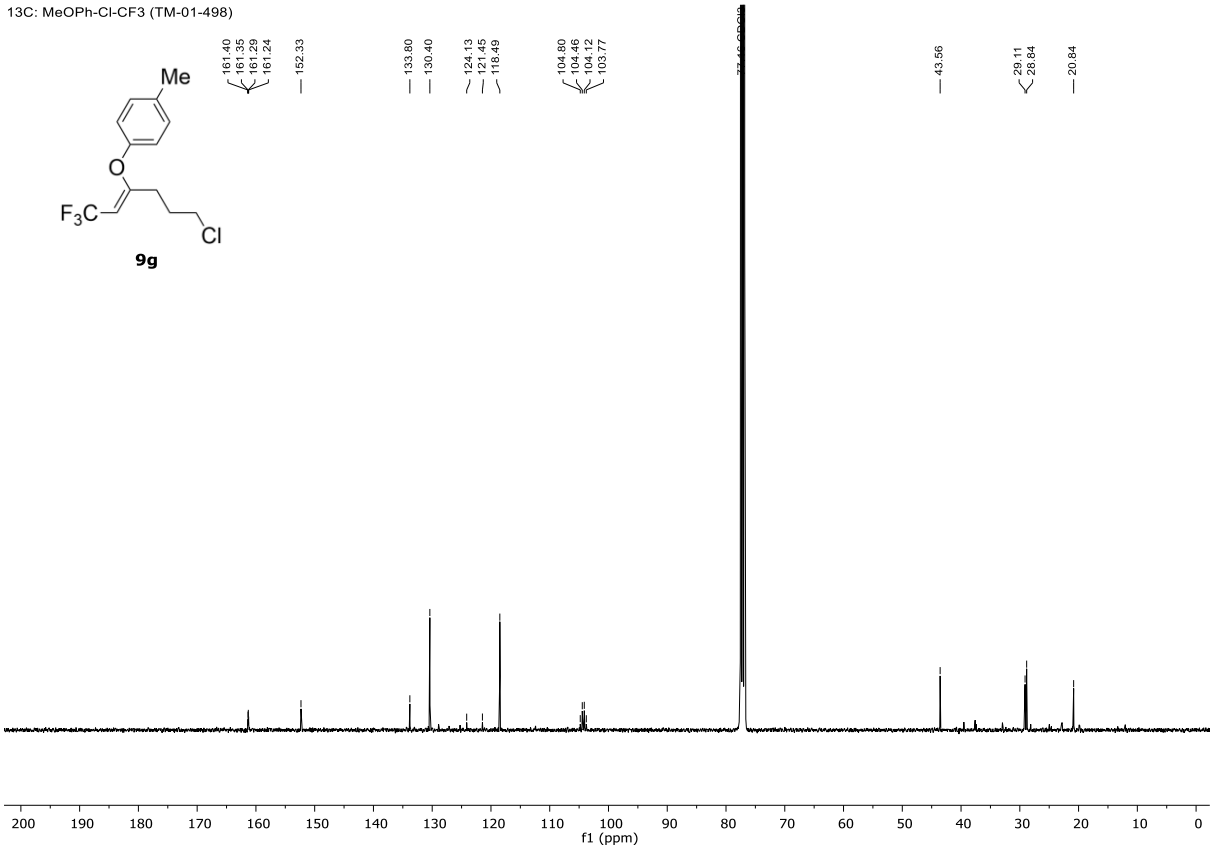


(*Z*)-1-((6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-4-methylbenzene (9g)

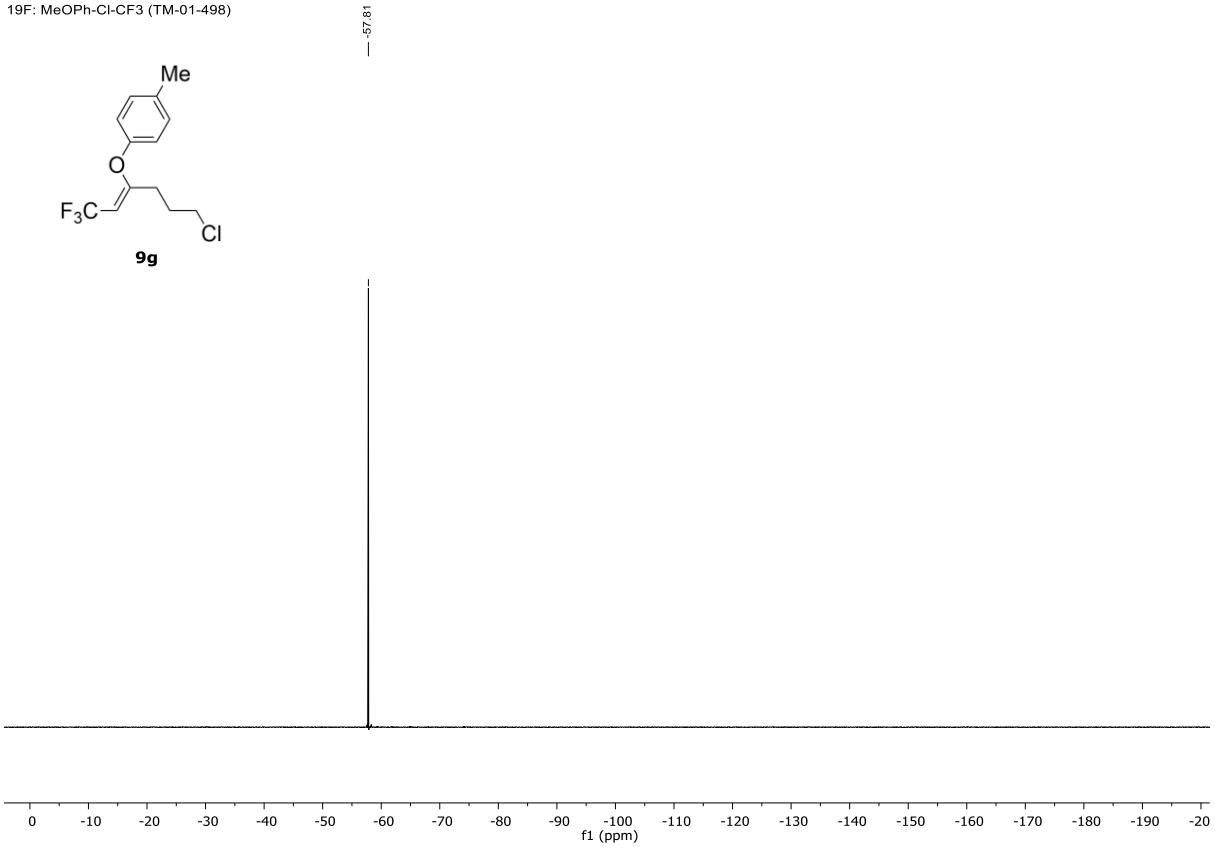
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

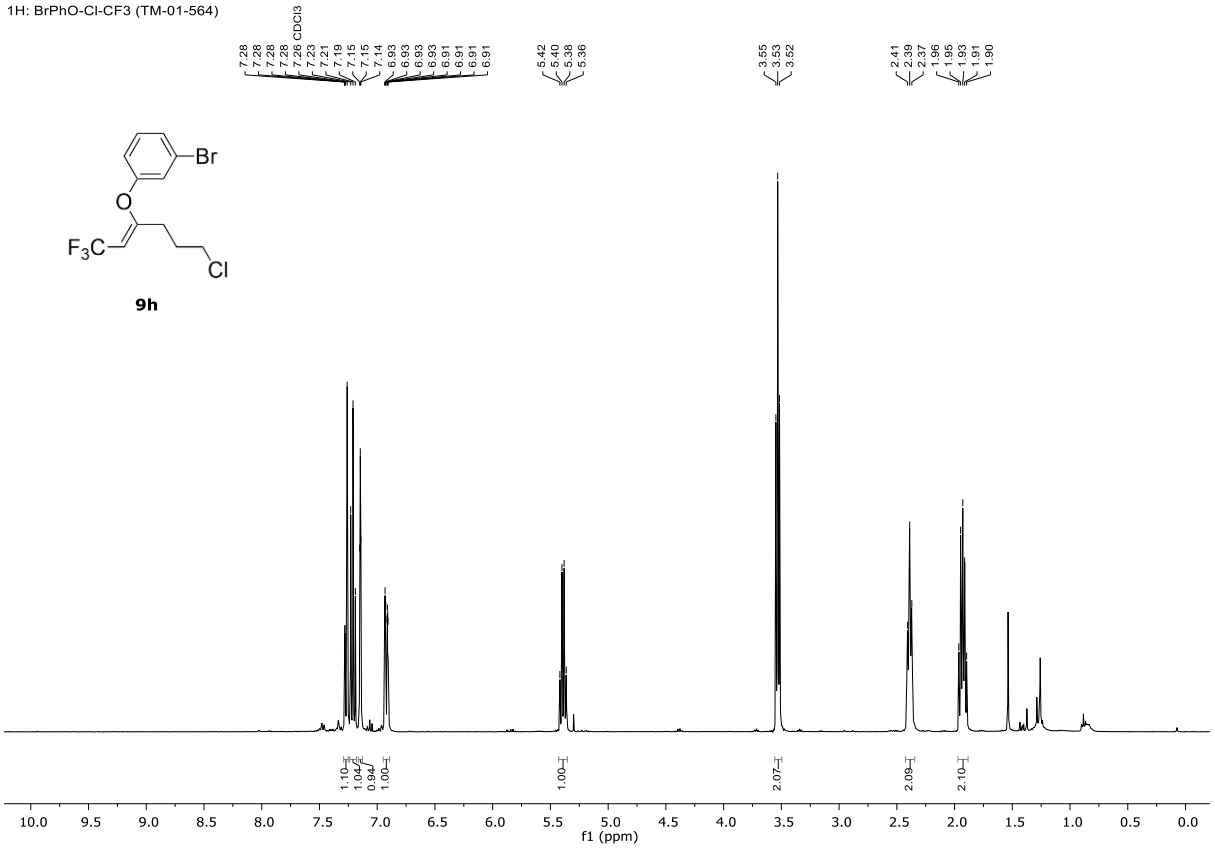


^{19}F-NMR (376 MHz, $CDCl_3$)

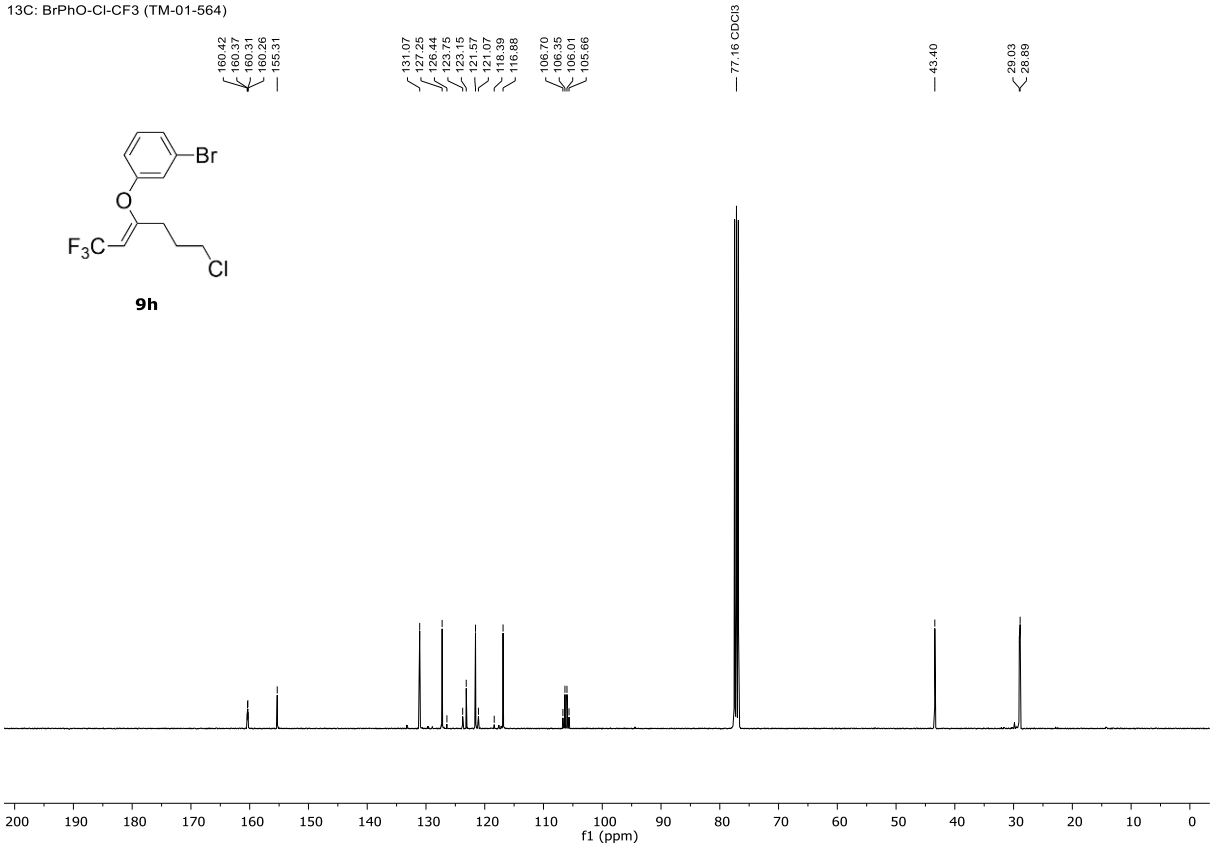


(*Z*)-1-Bromo-3-((6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)benzene (9h)

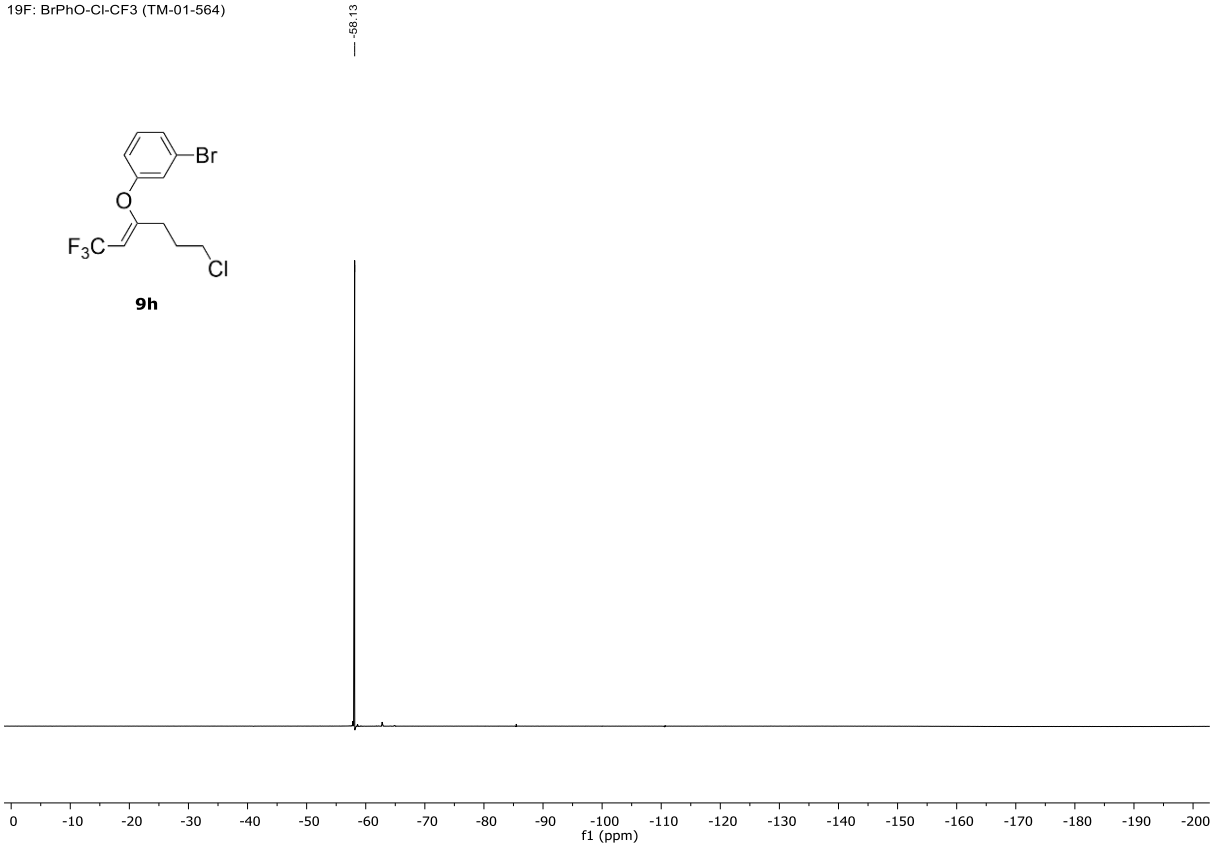
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

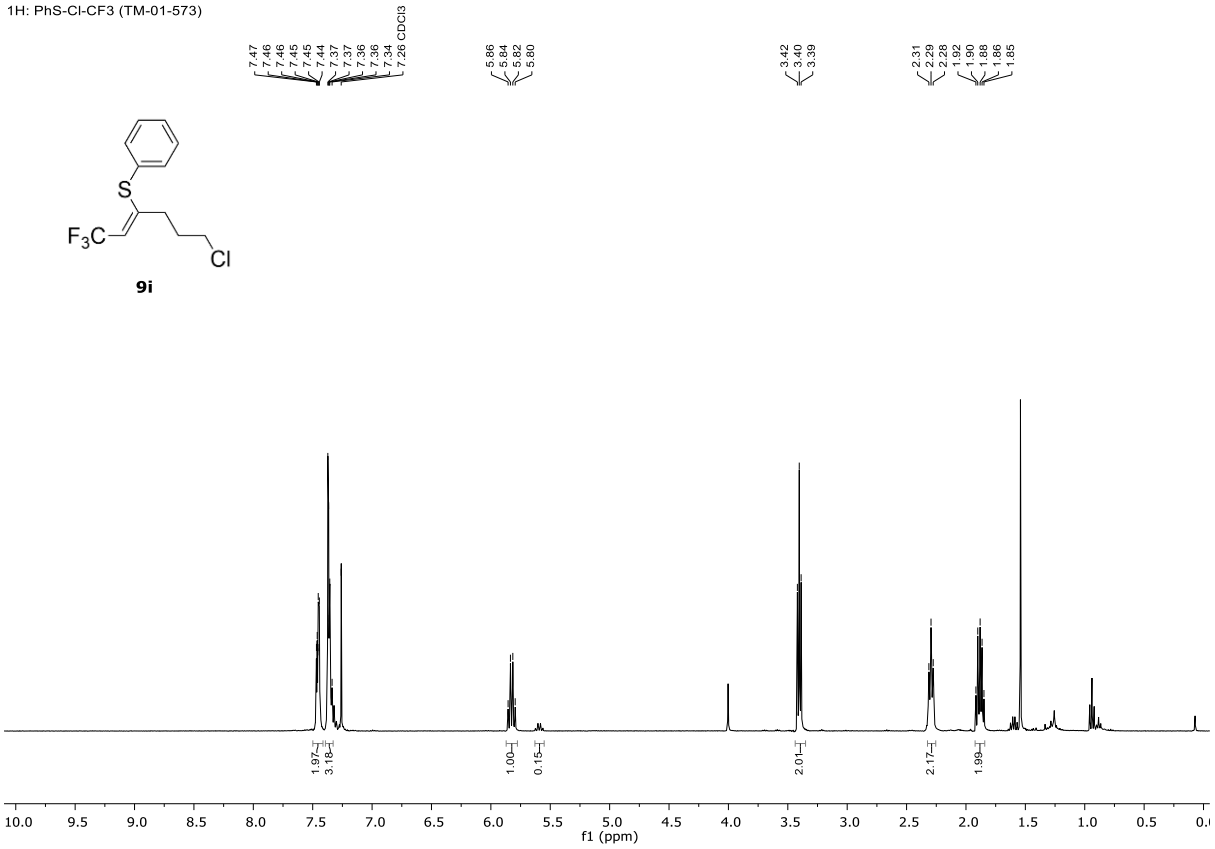


^{19}F-NMR (376 MHz, $CDCl_3$)

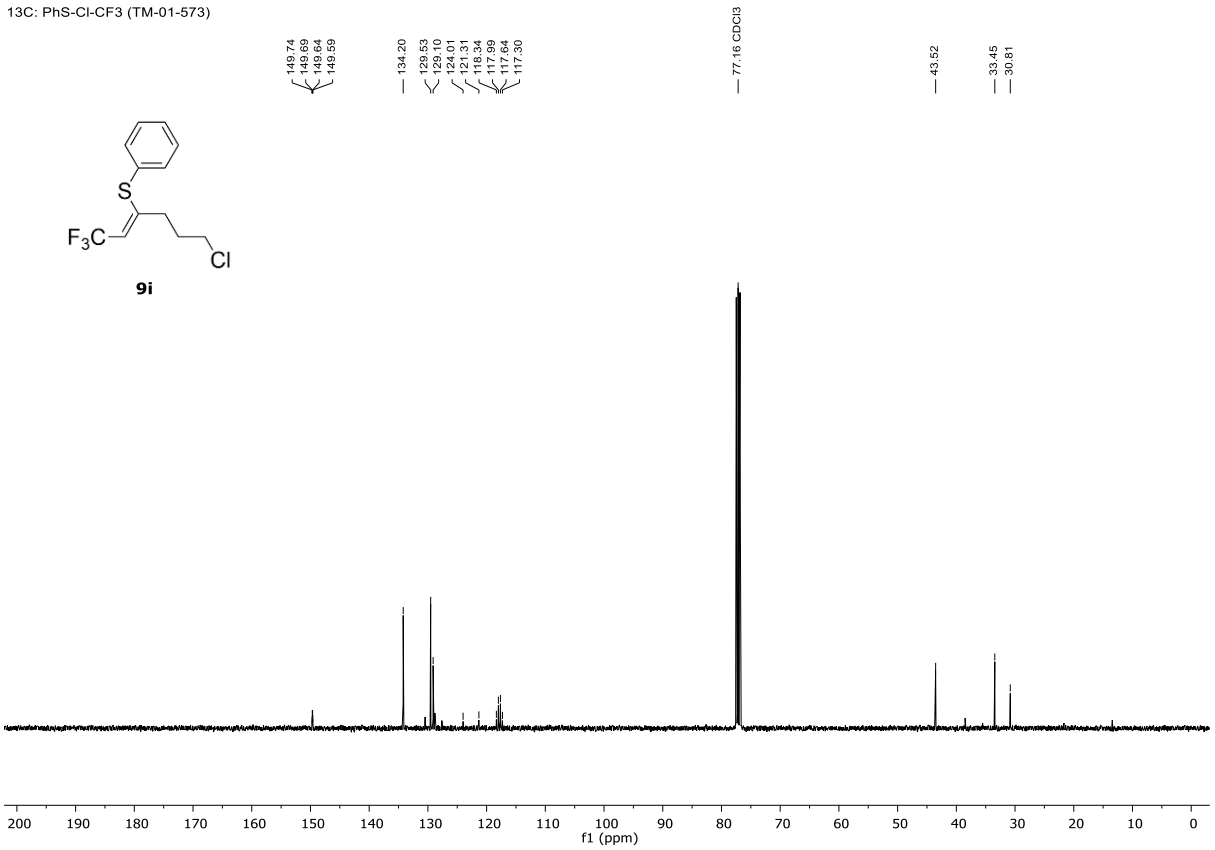


(*Z*)-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)(phenyl)sulfane (9i)

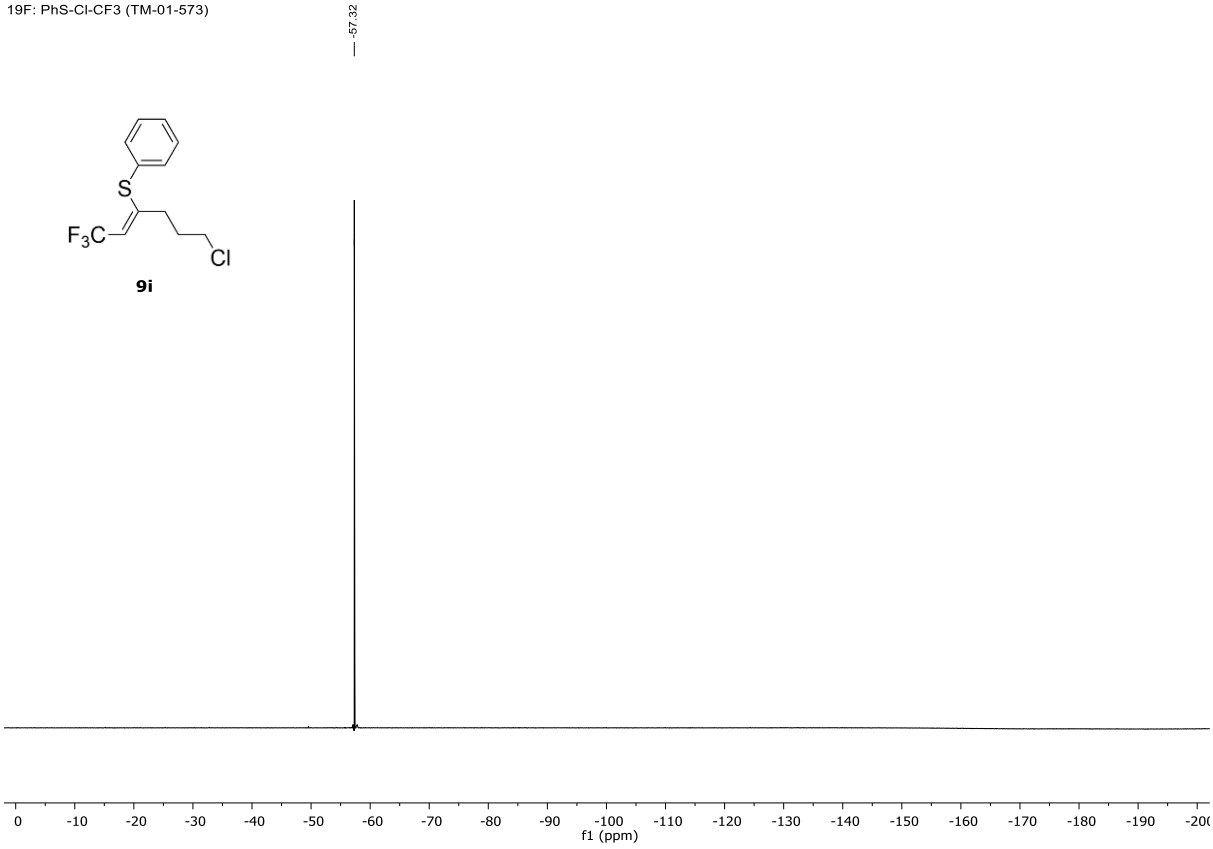
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

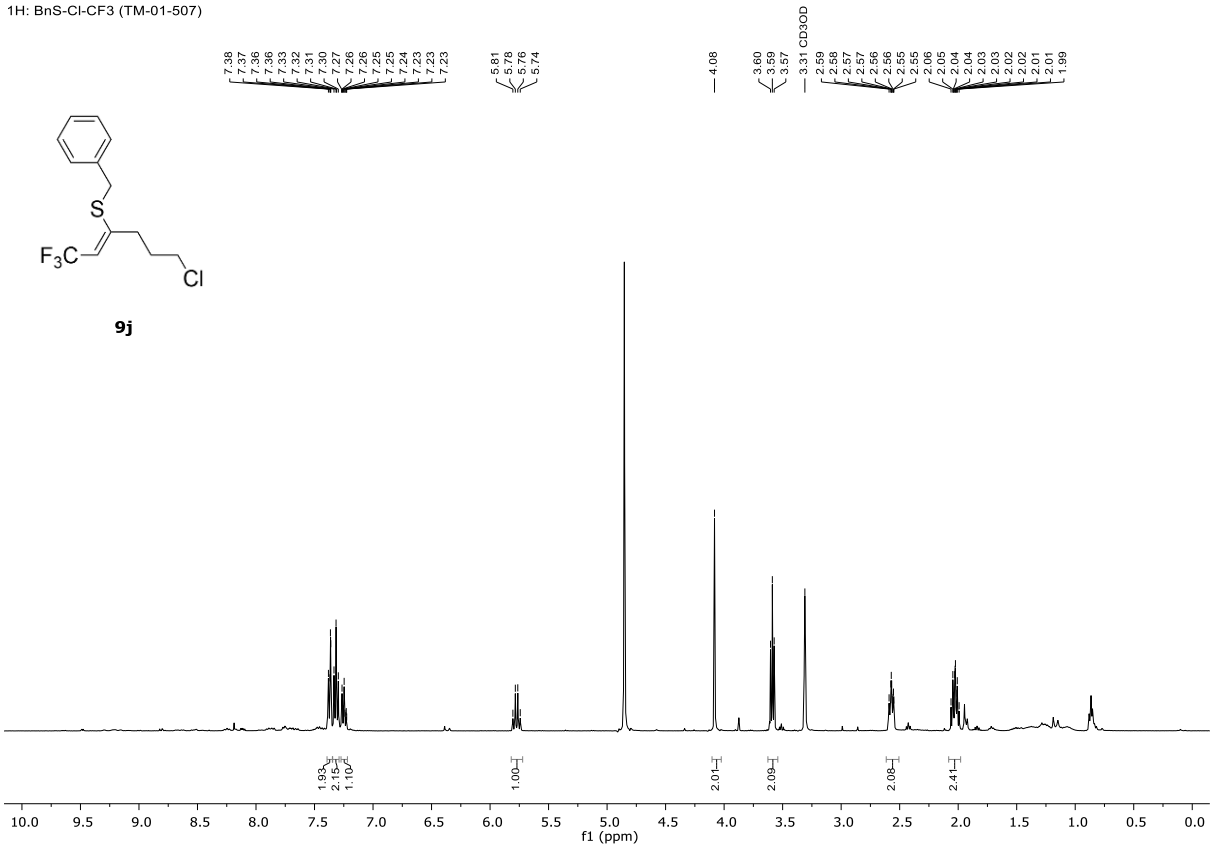


^{19}F-NMR (376 MHz, $CDCl_3$)

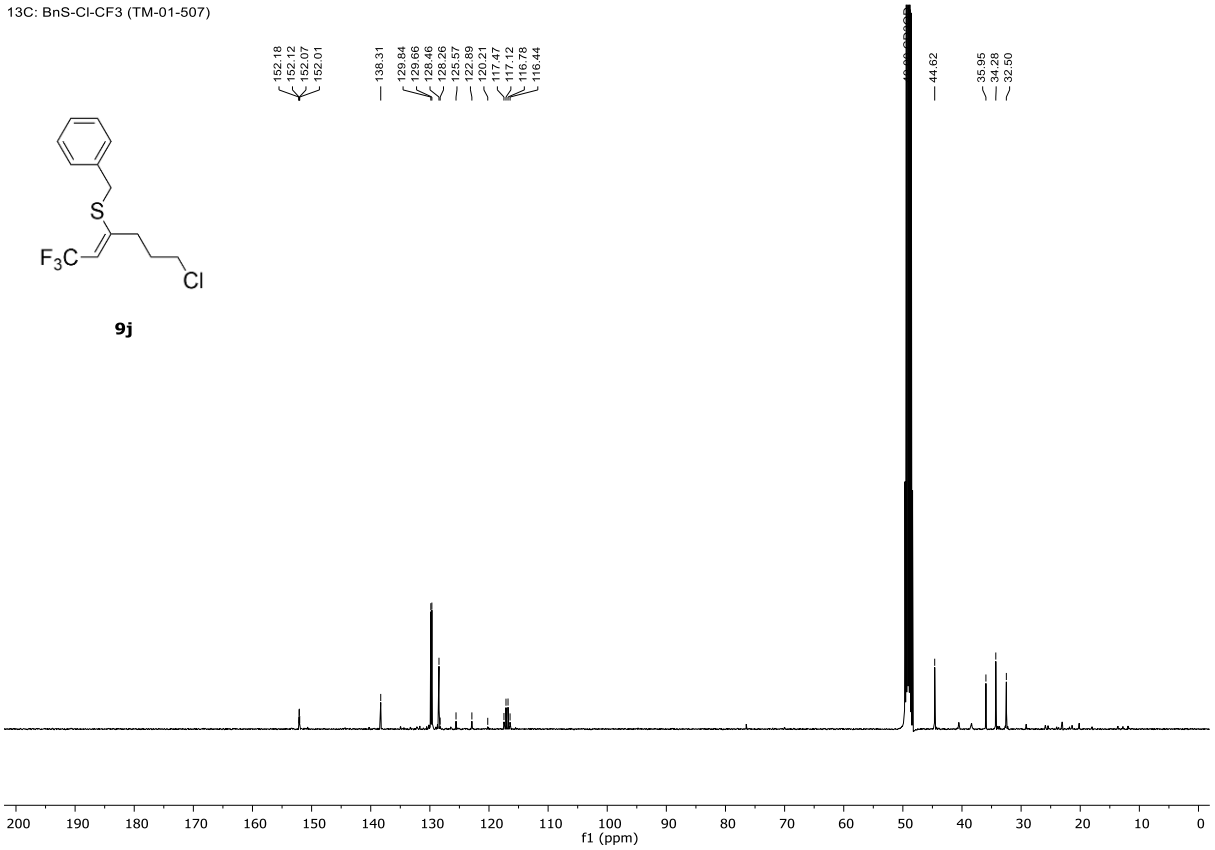


(*Z*)-Benzyl(6-chloro-1,1,1-trifluorohex-2-en-3-yl)sulfane (9j)

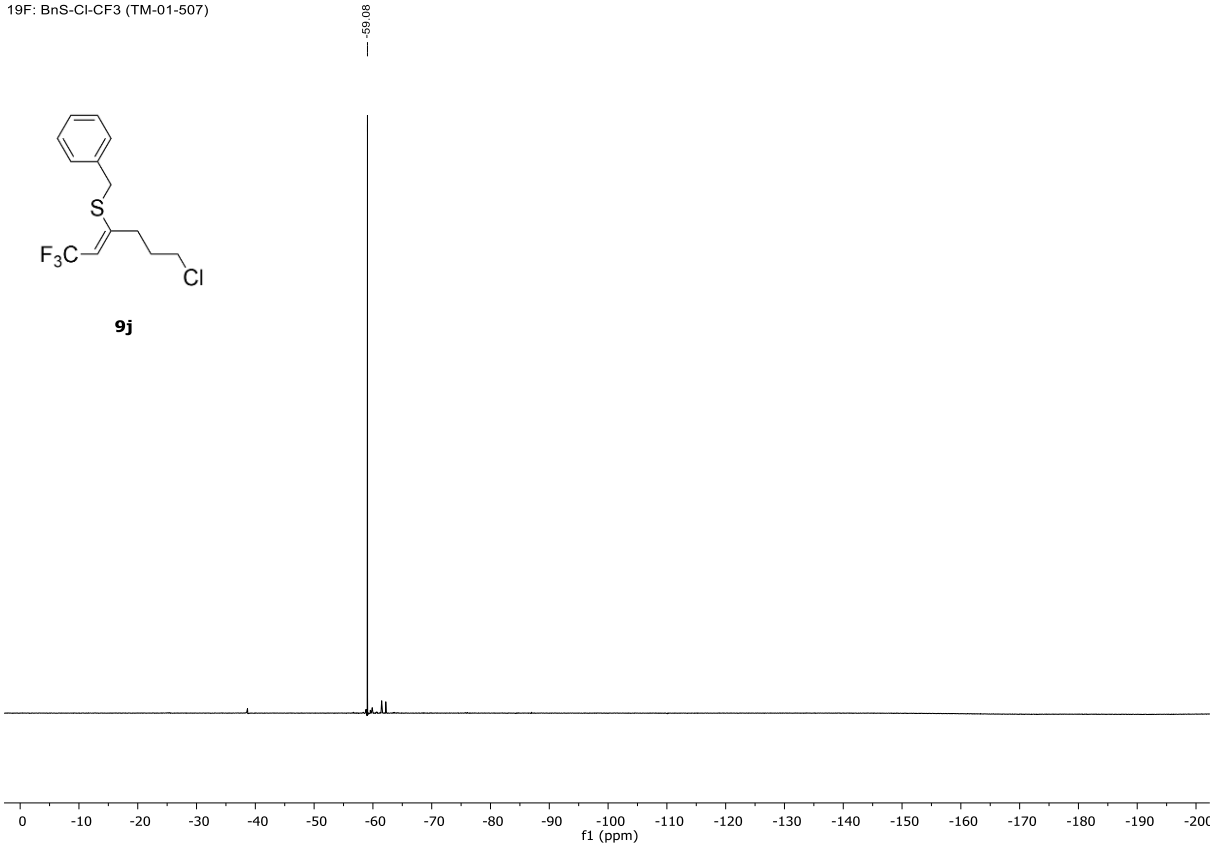
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)



(*E*)-(1-(Benzyloxy)-2-(trifluoromethyl)but-1-en-1-yl)benzene (9k)

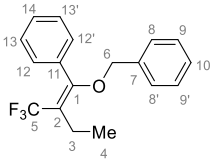
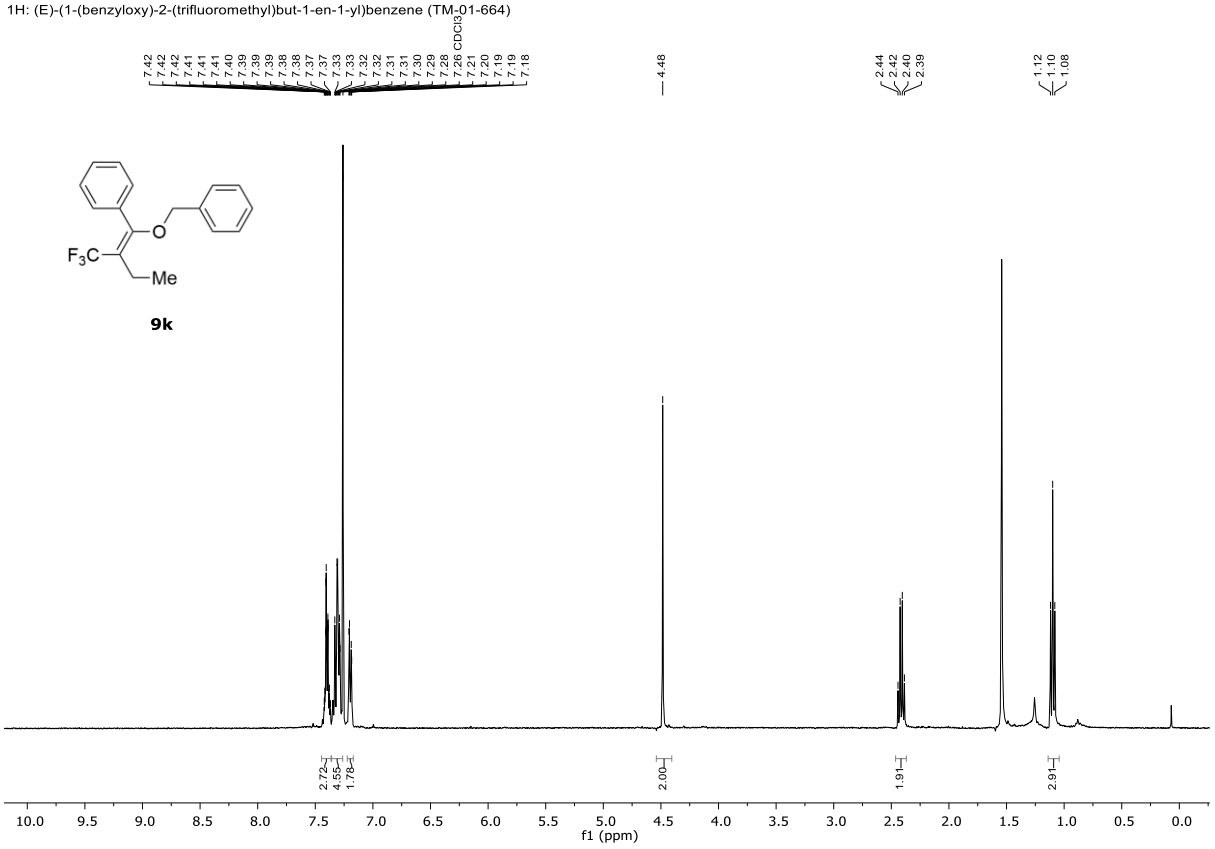


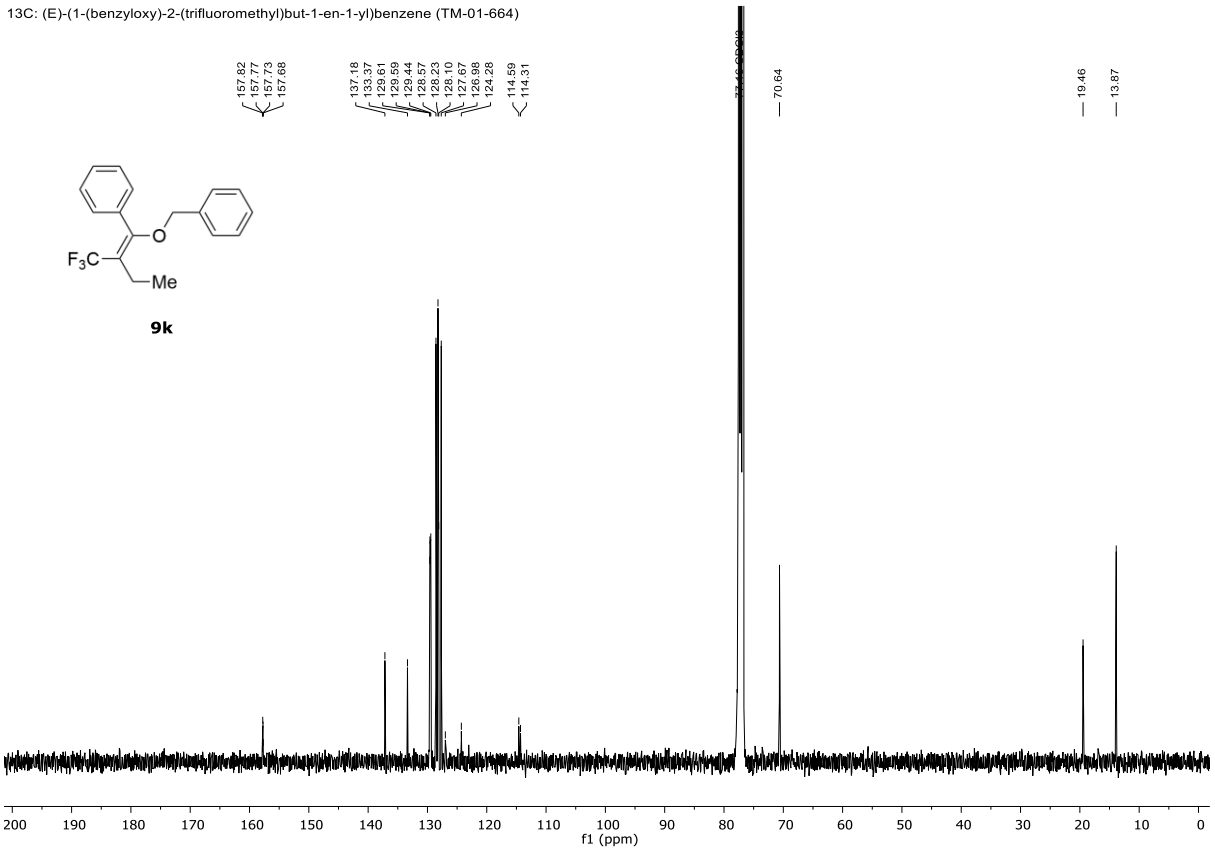
Table S44. Detailed NMR assignment of (*E*)-(1-(benzyloxy)-2-(trifluoromethyl)but-1-en-1-yl)benzene (**9k**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	157.8 (q, 4.5 Hz)			
2	114.5 (q, 28.5 Hz)			
3	19.5	2.41 (q, 7.5 Hz)	4	1, 2, 4, 5
4	13.9	1.10 (t, 7.4 Hz)	3	2, 3
5	125.6 (q, 271.8 Hz)			
6	70.6	4.48 (s)		1, 7, 8/8’
7	137.2			
8/8’	127.7	7.23-7.16 (m)		
9/9’	128.2	7.45-7.26 (m)		
10	128.1	7.45-7.26 (m)		
11	133.4			
12/12‘	129.6 (d, 2.4 Hz)	7.45-7.26 (m)		
13/13‘	128.6	7.45-7.26 (m)		
14	129.4	7.45-7.26 (m)		

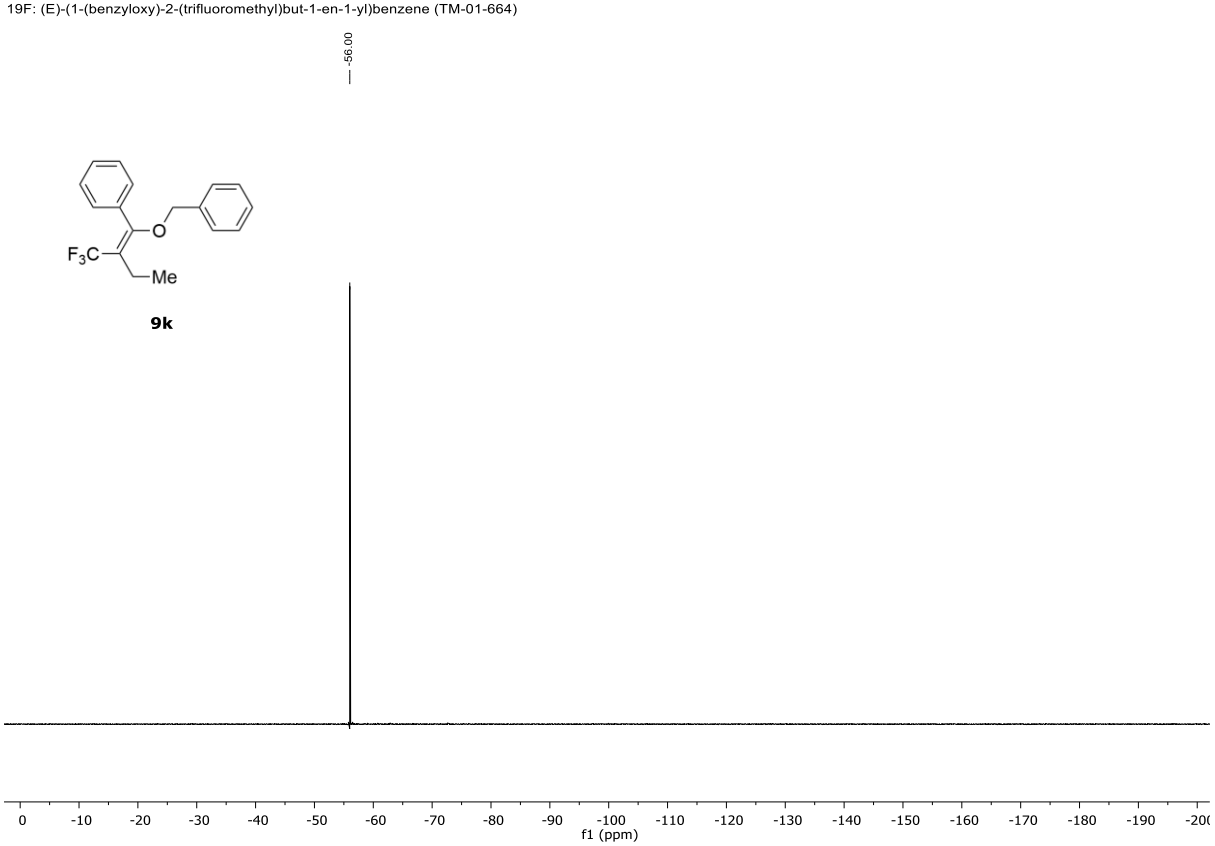
^{1}H-NMR (400 MHz, $CDCl_3$)



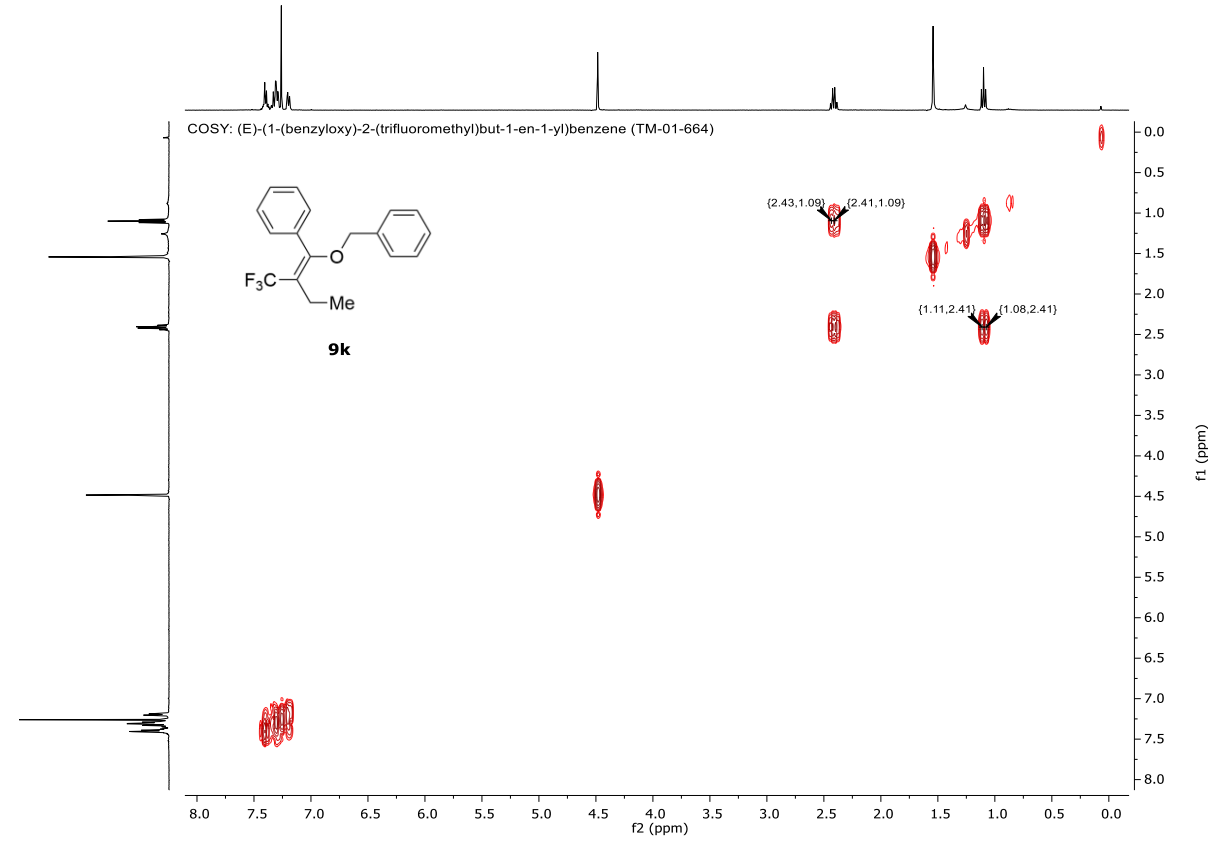
^{13}C-NMR (101 MHz, $CDCl_3$)



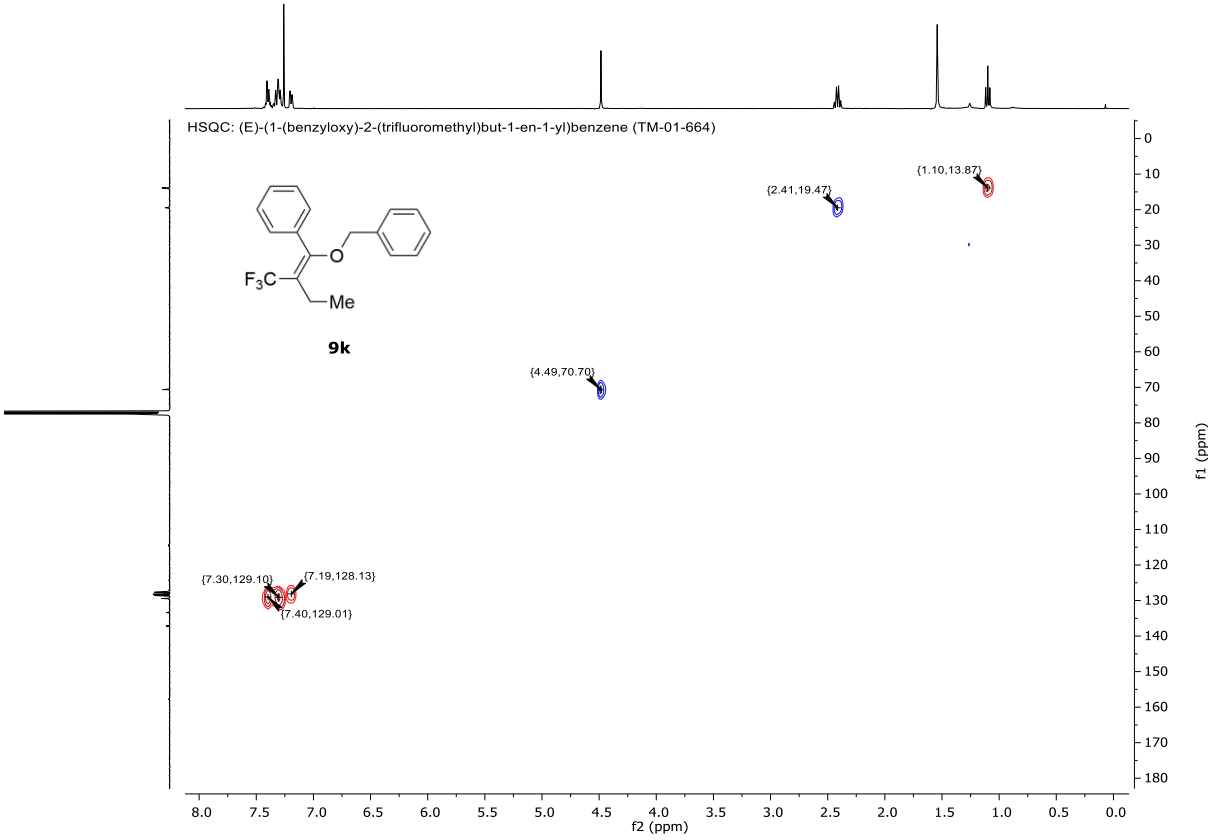
^{19}F-NMR (376 MHz, $CDCl_3$)



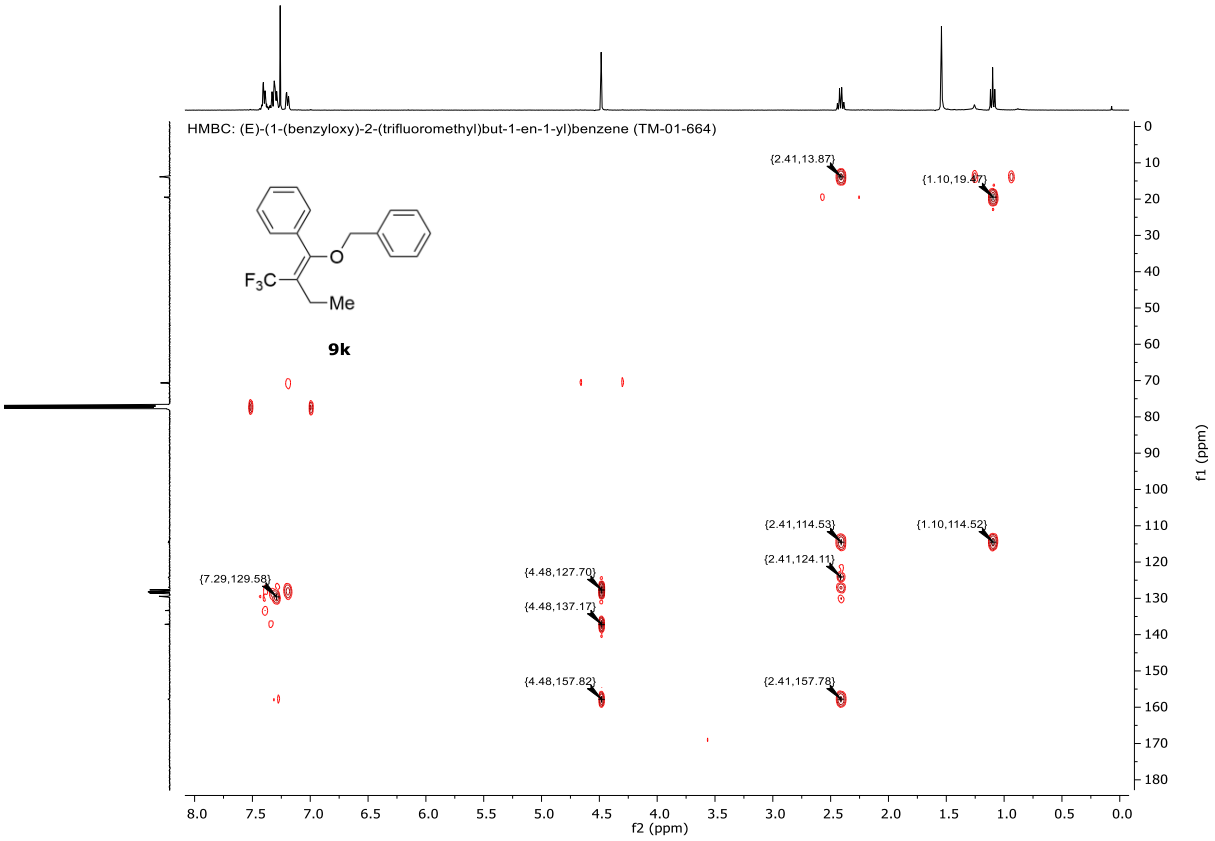
COSY NMR ($CDCl_3$)



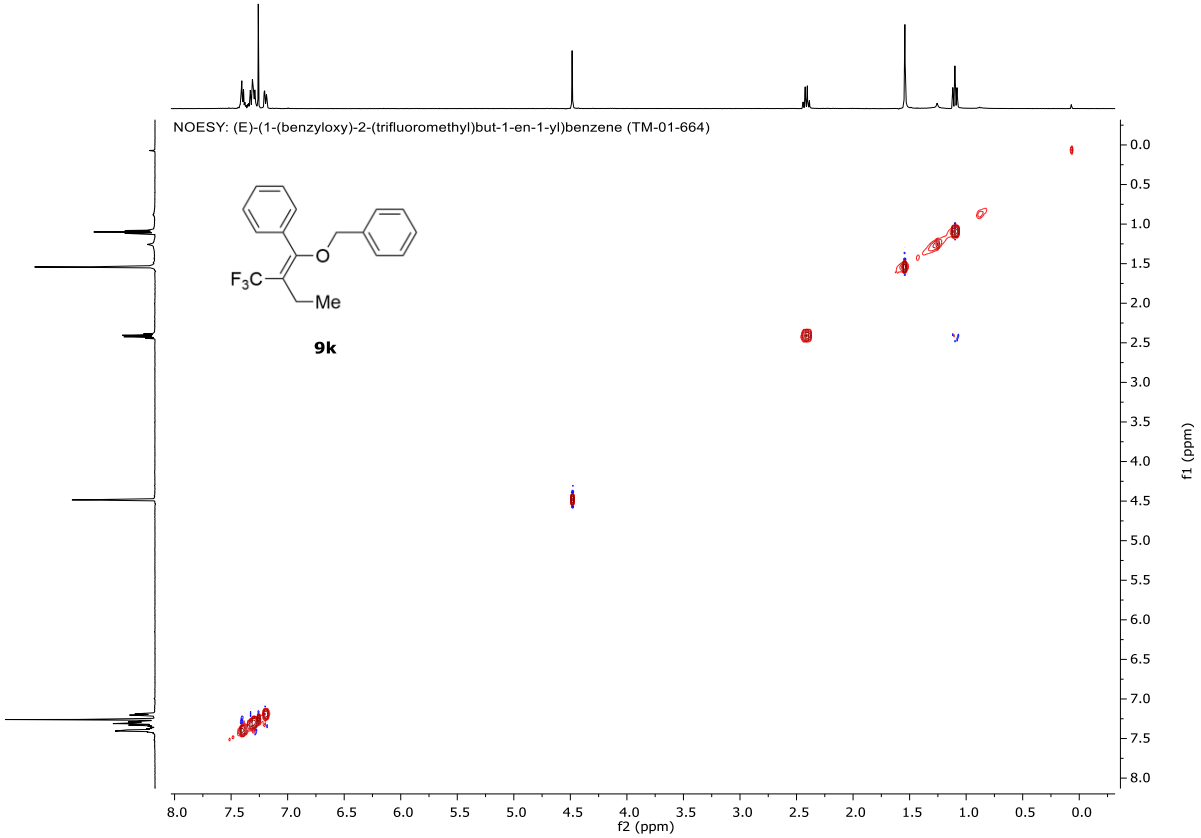
HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)

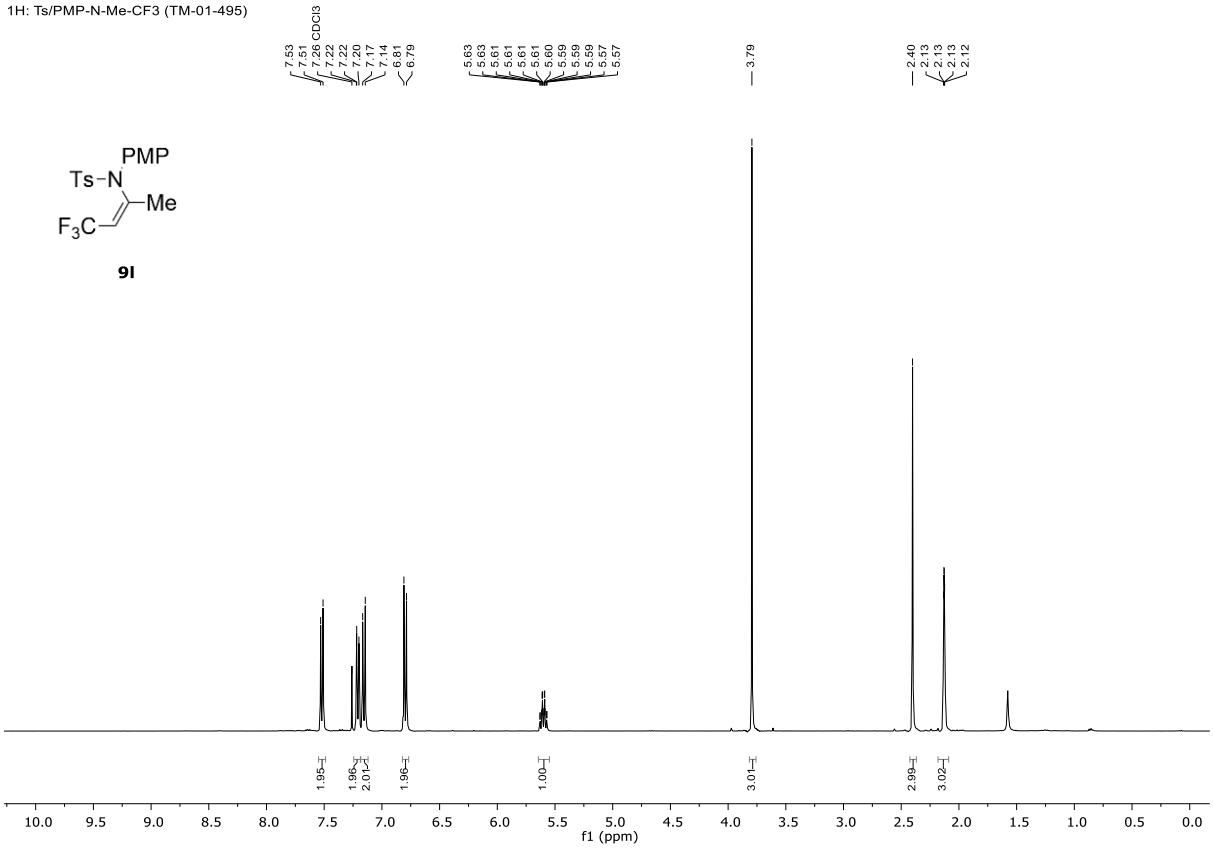


NOESY NMR ($CDCl_3$)

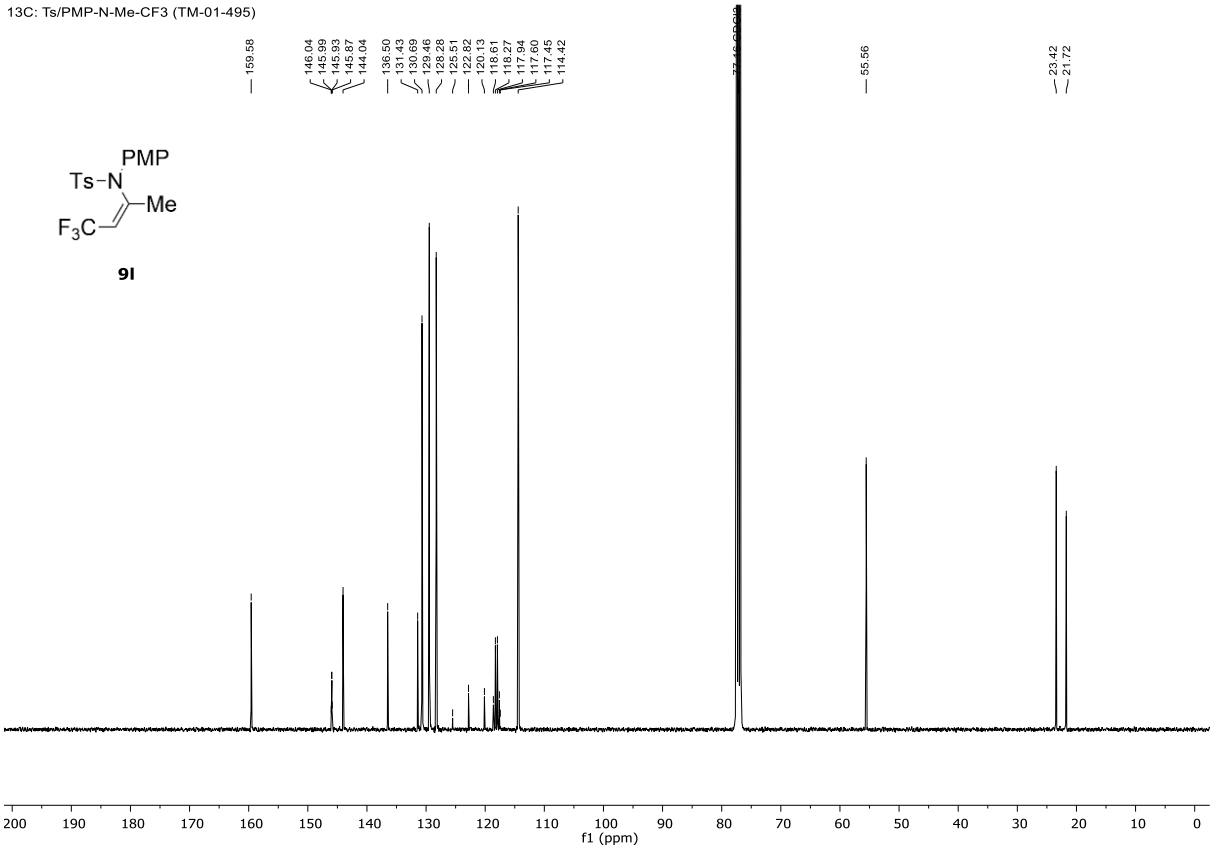


(*Z*)-*N*-(4-Methoxyphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-2-yl)benzenesulfonamide (9l)

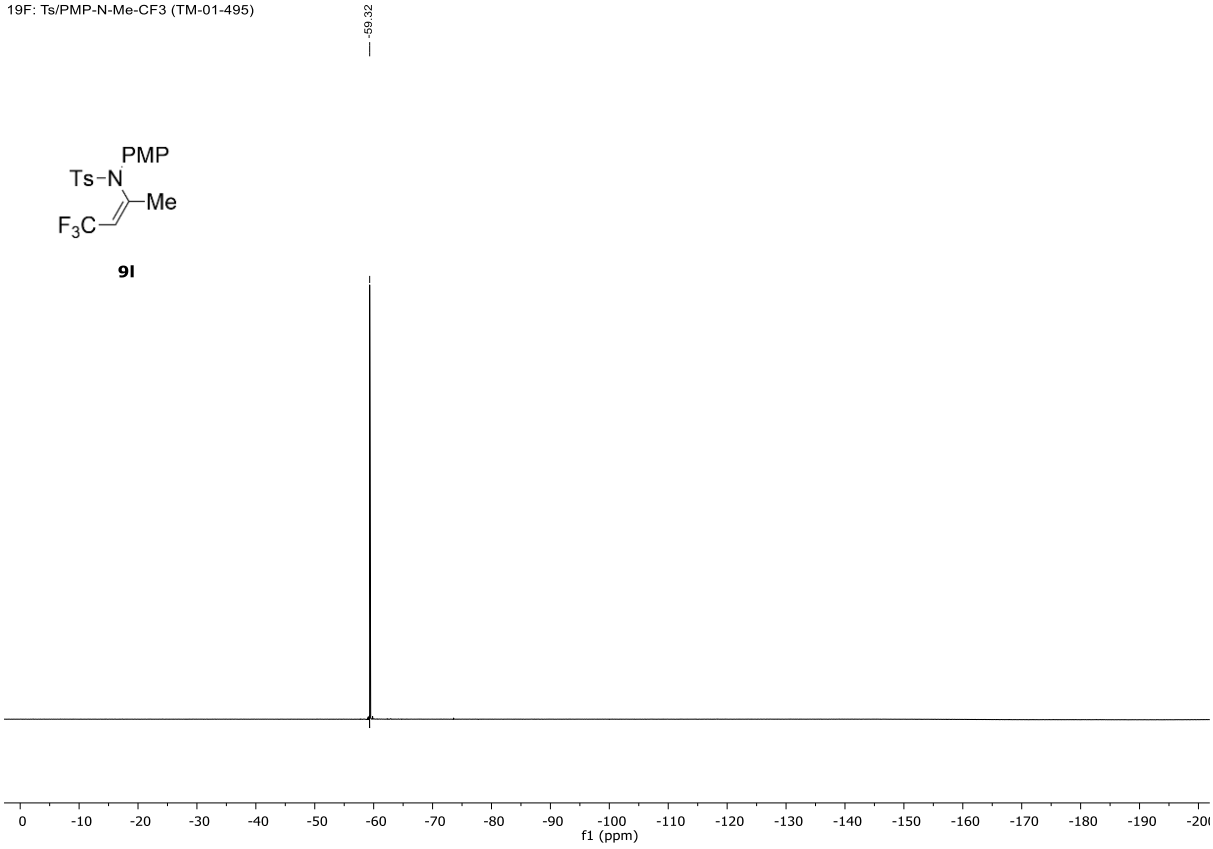
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)



(*Z*)-*N*-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (9m)

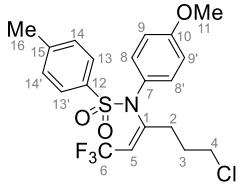
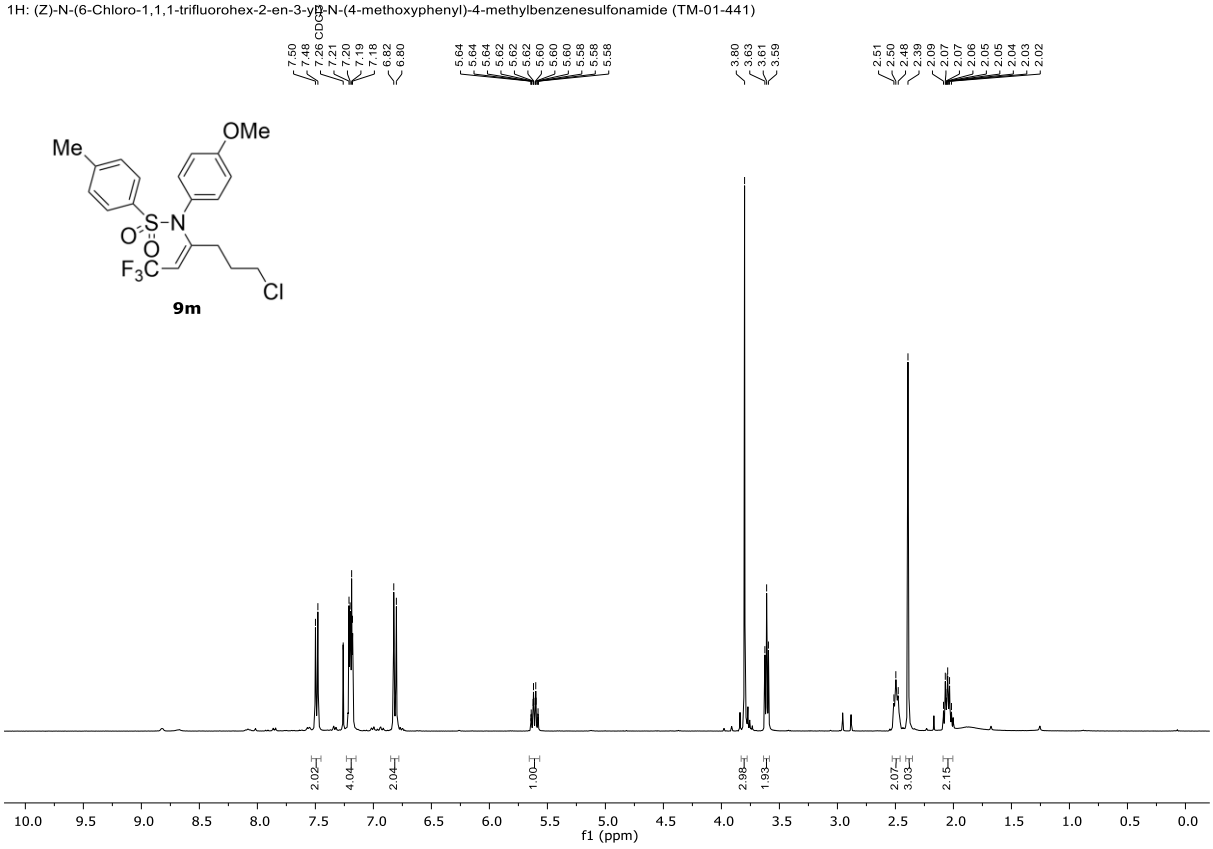


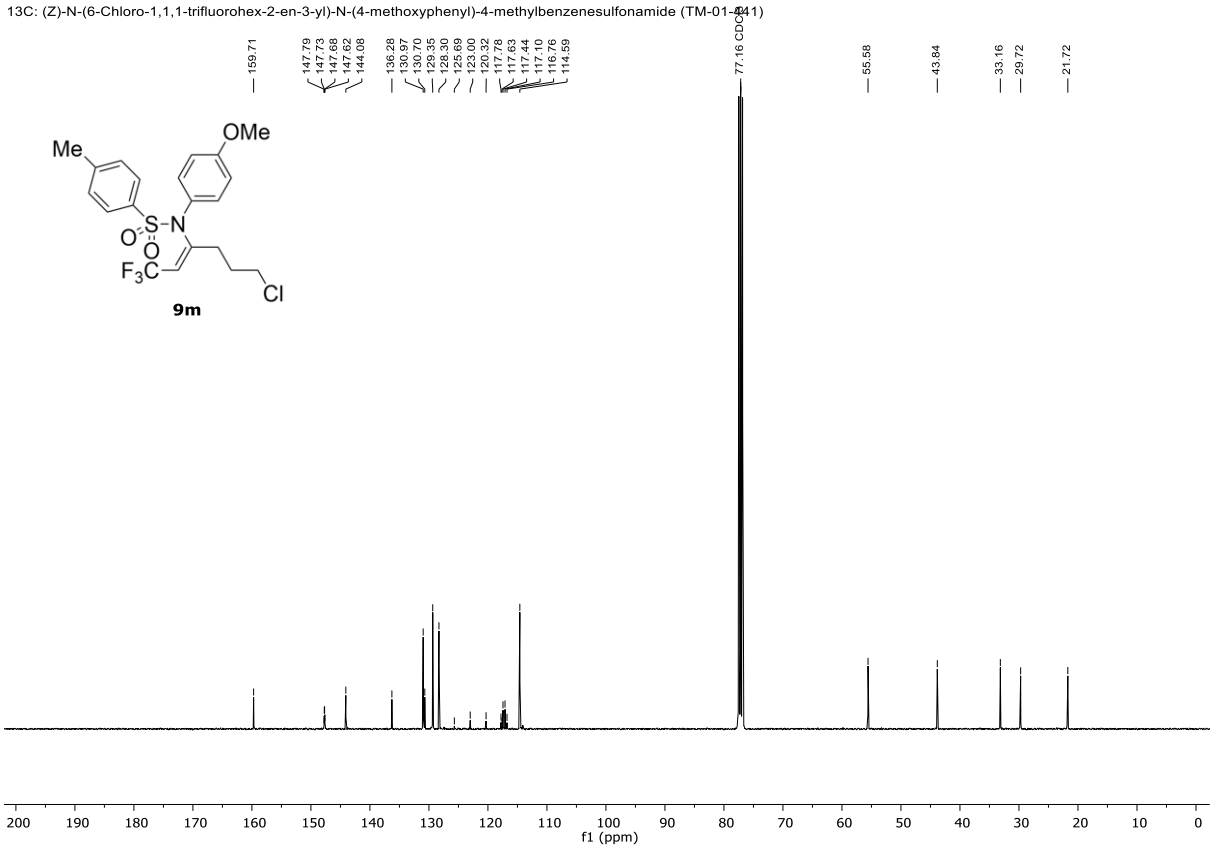
Table S45. Detailed NMR assignment of (*Z*)-*N*-(6-chloro-1,1,1-trifluorohex-2-en-3-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (**9m**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	147.7 (q, 5.6 Hz)			
2	33.2	2.50 (t, 7.4 Hz)	3	1, 3, 4, 5
3	29.7	2.09-2.01 (m)	2, 4	1, 2,4
4	43.8	3.61 (t, 6.1 Hz)	3	2, 3
5	117.3 (q, 34.3 Hz)	5.61 (qt, 7.9, 1.3 Hz)		1, 2
6	121.7 (q, 270.4 Hz)			
7	130.7			
8/8’	131.0	7.20 (d, 9.1 Hz)	9/9’	7, 10
9/9’	114.6	6.81 (d, 9.1 Hz)	8/8’	7, 8,8’, 10
10	159.7			
11	55.6	3.80 (s)		10
12	136.3			
13/13‘	128.3	7.49 (d, 8.4 Hz)	14/14‘	15
14/14‘	129.4	7.19 (d, 8.2 Hz)	13/13‘	12, 16
15	144.1			
16	21.7	2.39 (s)		14/14’, 15

^{1}H-NMR (400 MHz, $CDCl_3$)

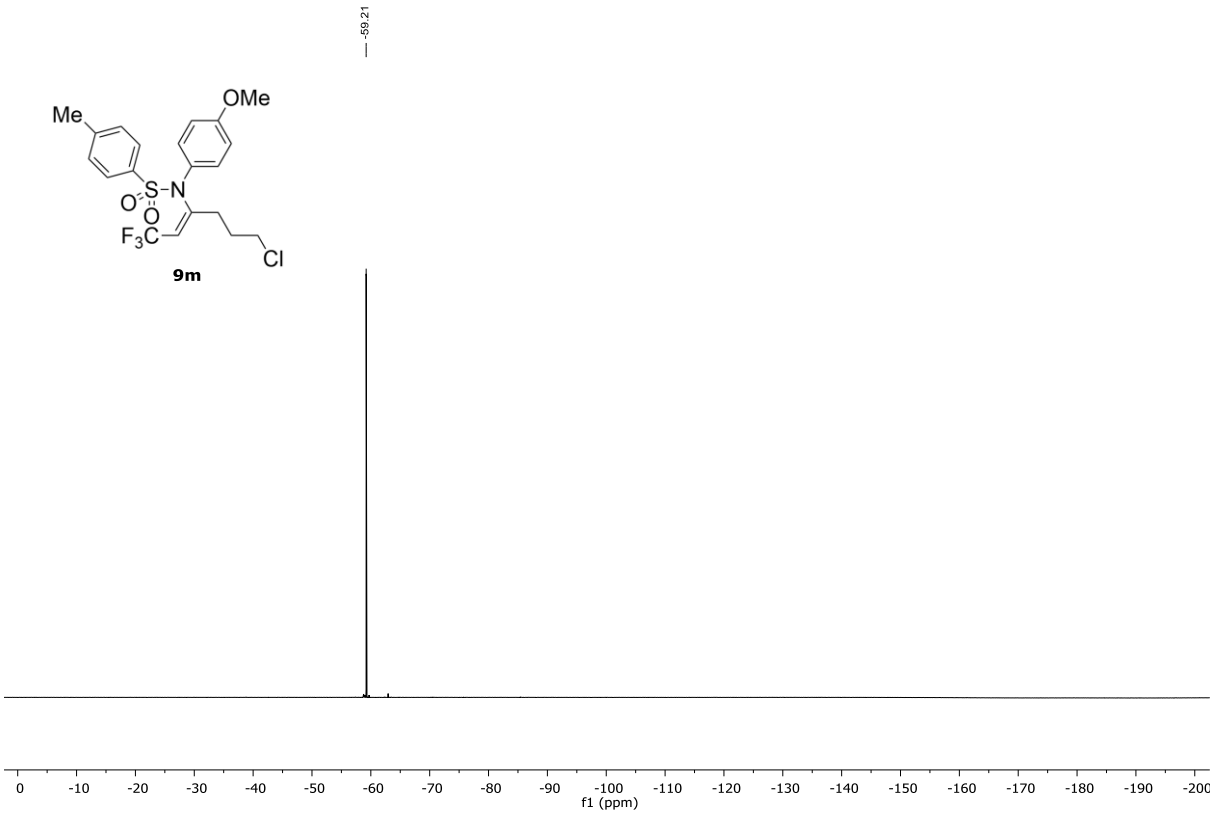


^{13}C-NMR (101 MHz, $CDCl_3$)

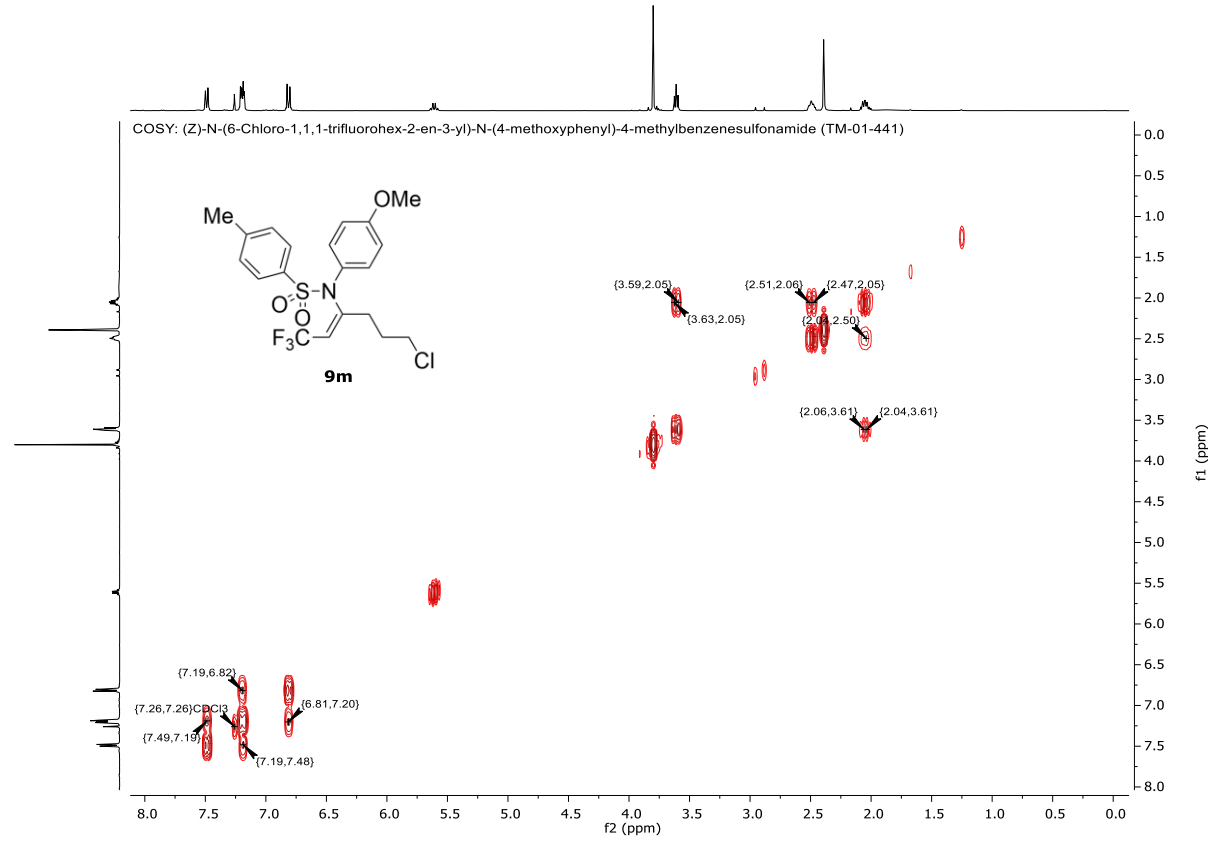


^{19}F-NMR (376 MHz, $CDCl_3$)

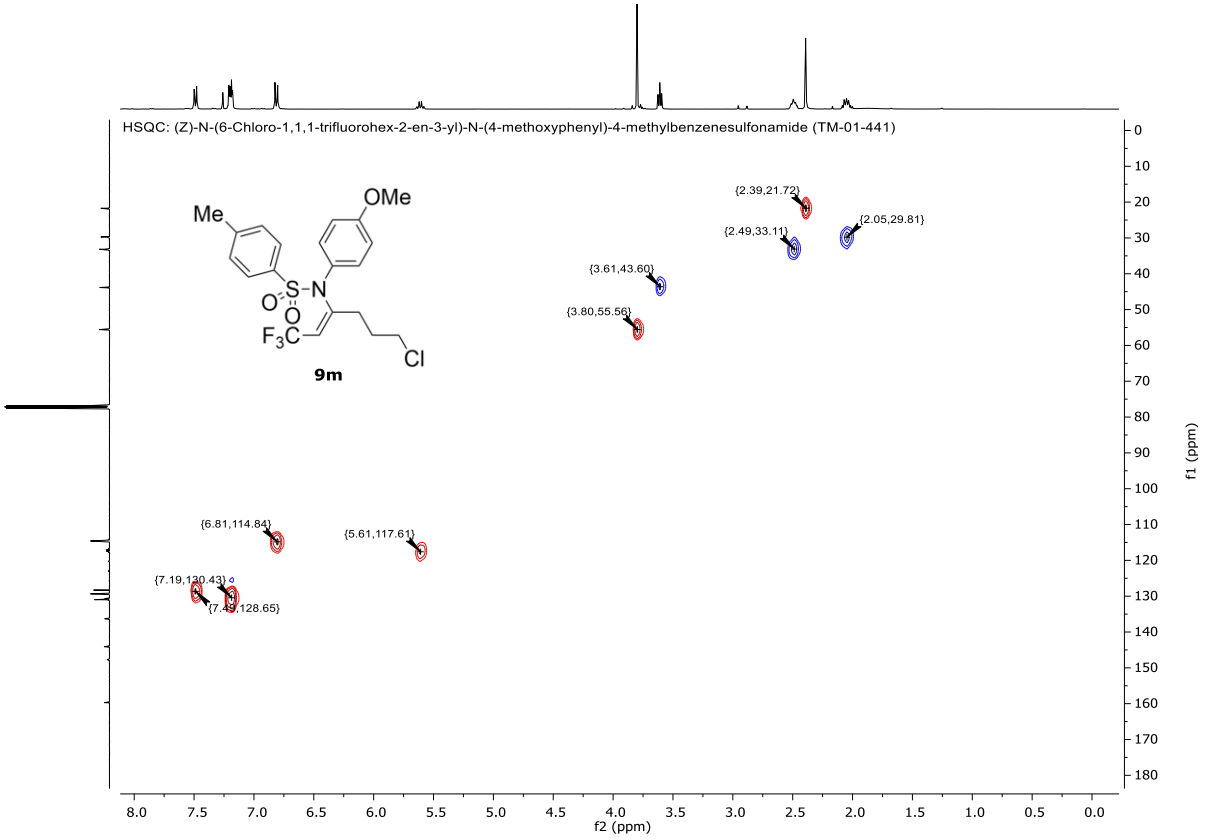
19F: (Z)-N-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)-N-(4-methoxyphenyl)-4-methylbenzenesulfonamide (TM-01-441)



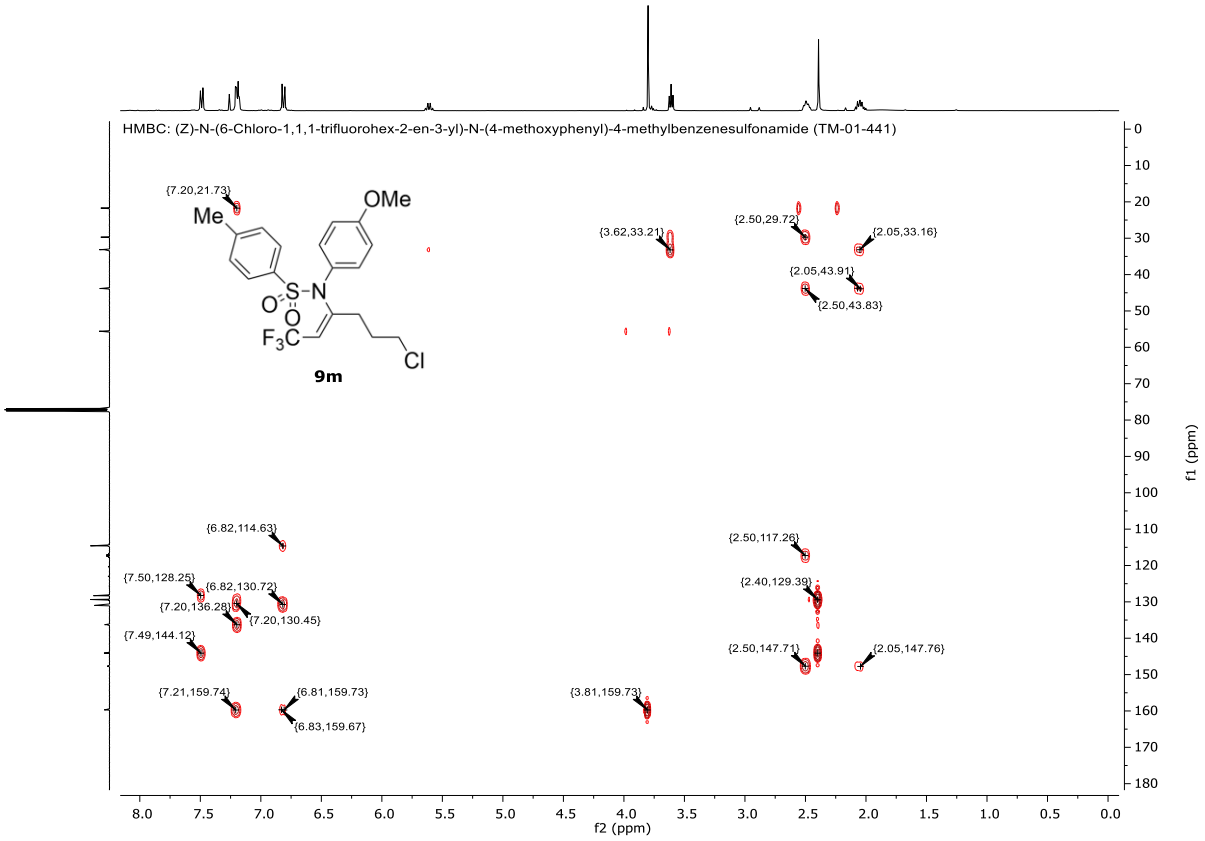
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

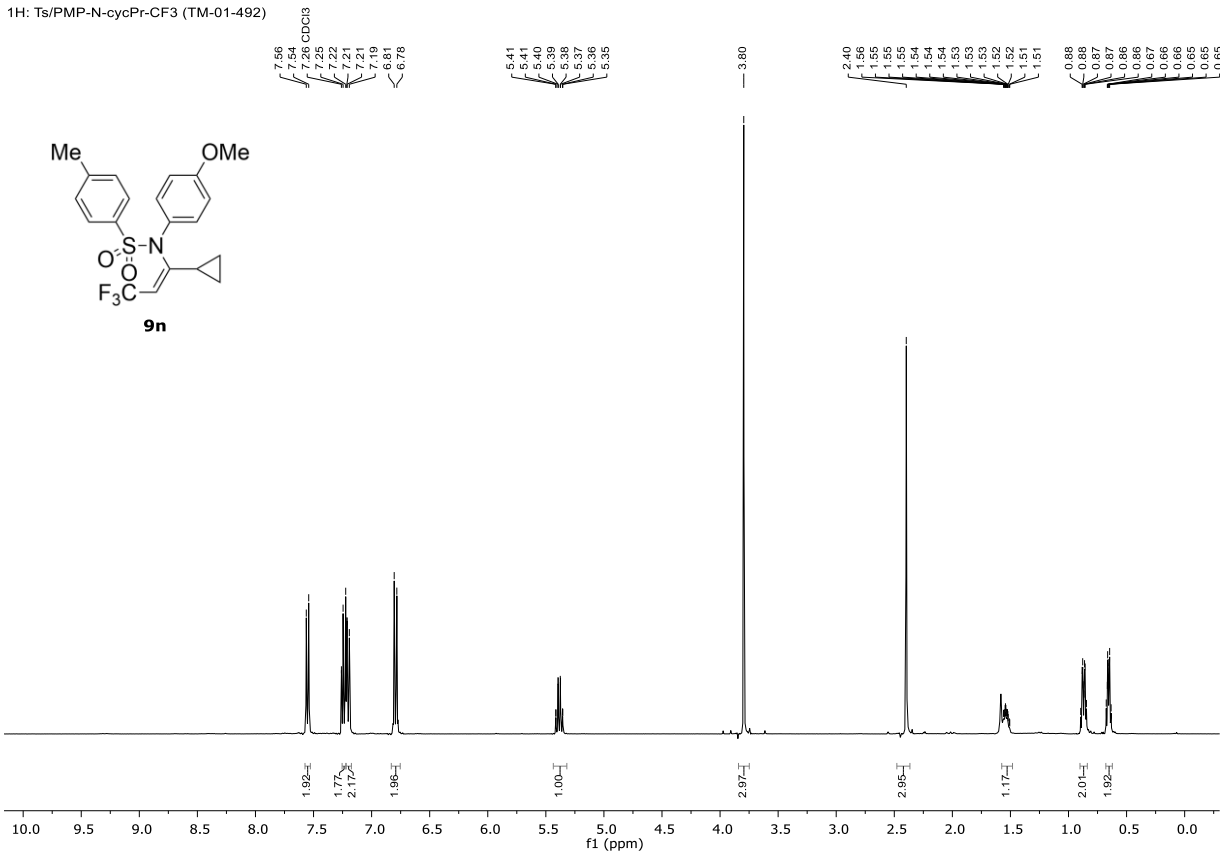


HMBC NMR ($CDCl_3$)

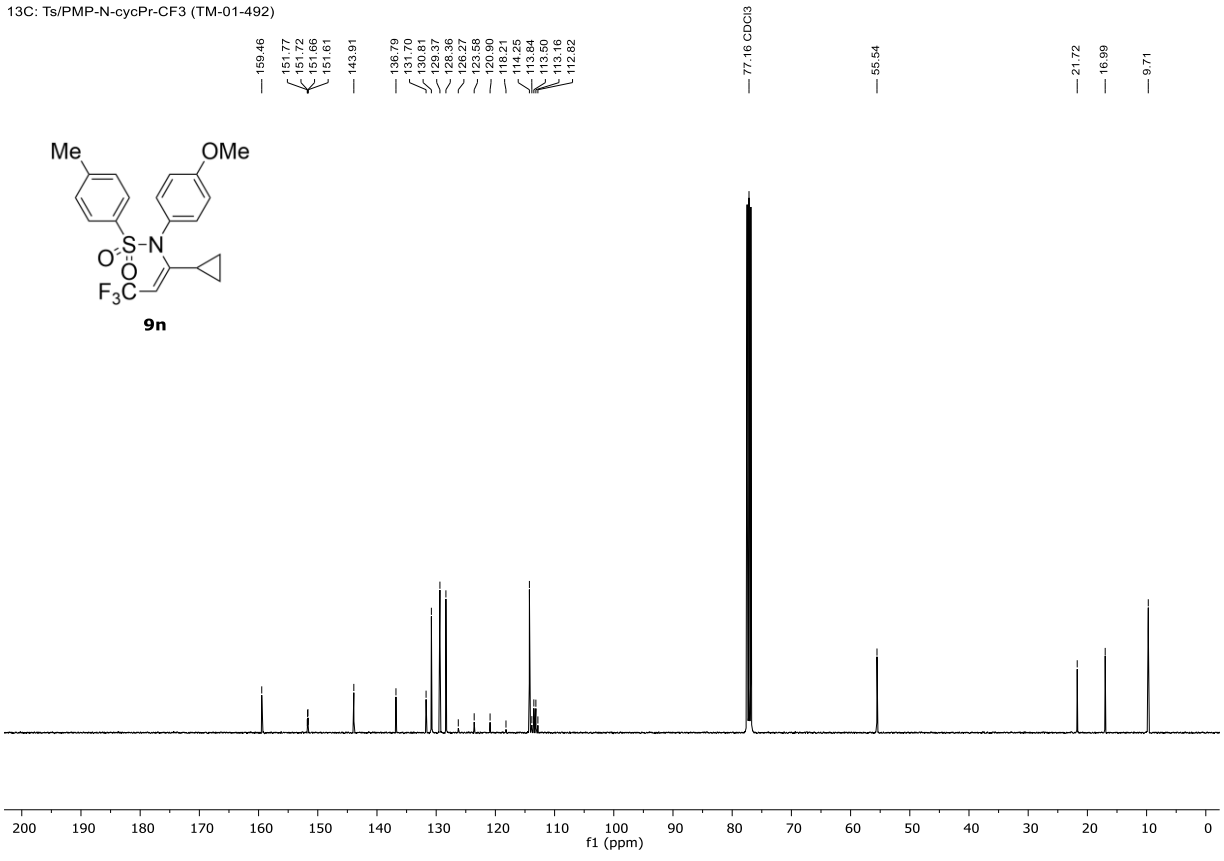


(*Z*)-*N*-(1-cyclopropyl-3,3,3-trifluoroprop-1-en-1-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (9n)

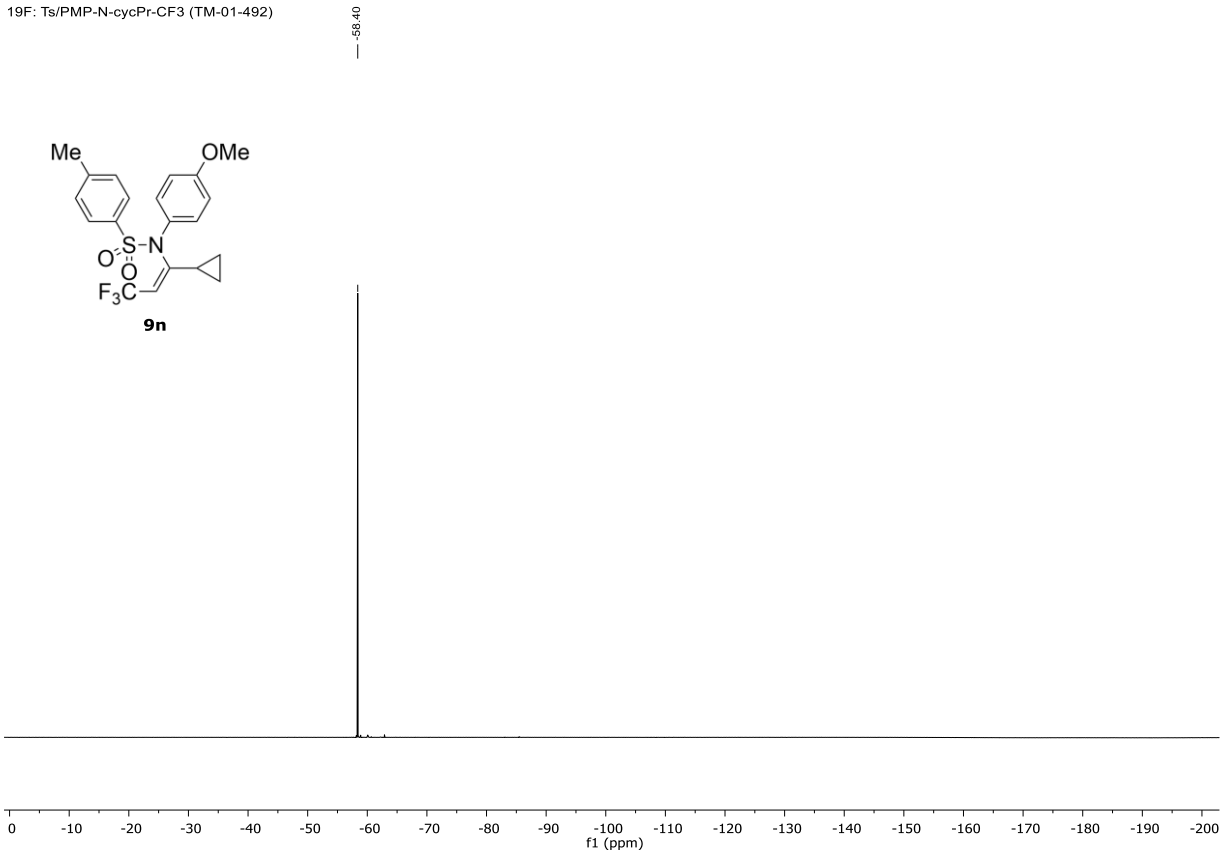
^{1}H-NMR (400 MHz, $CDCl_3$)



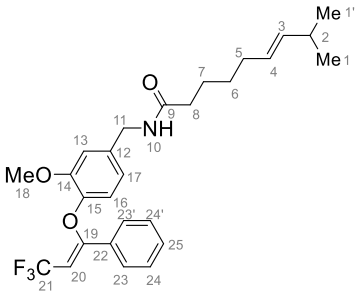
^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)



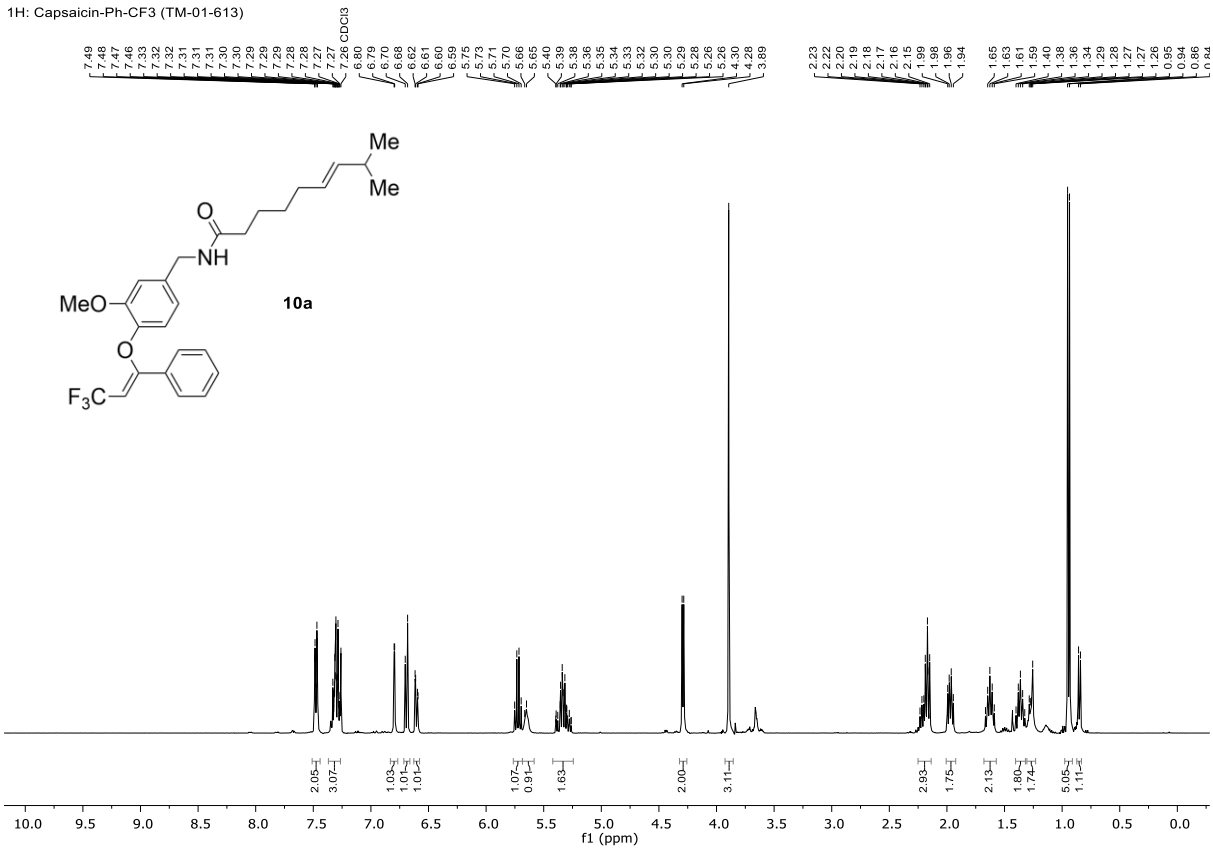
(*E*)-*N*-(3-Methoxy-4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)benzyl)-8-methylnon-6-enamide (10a)



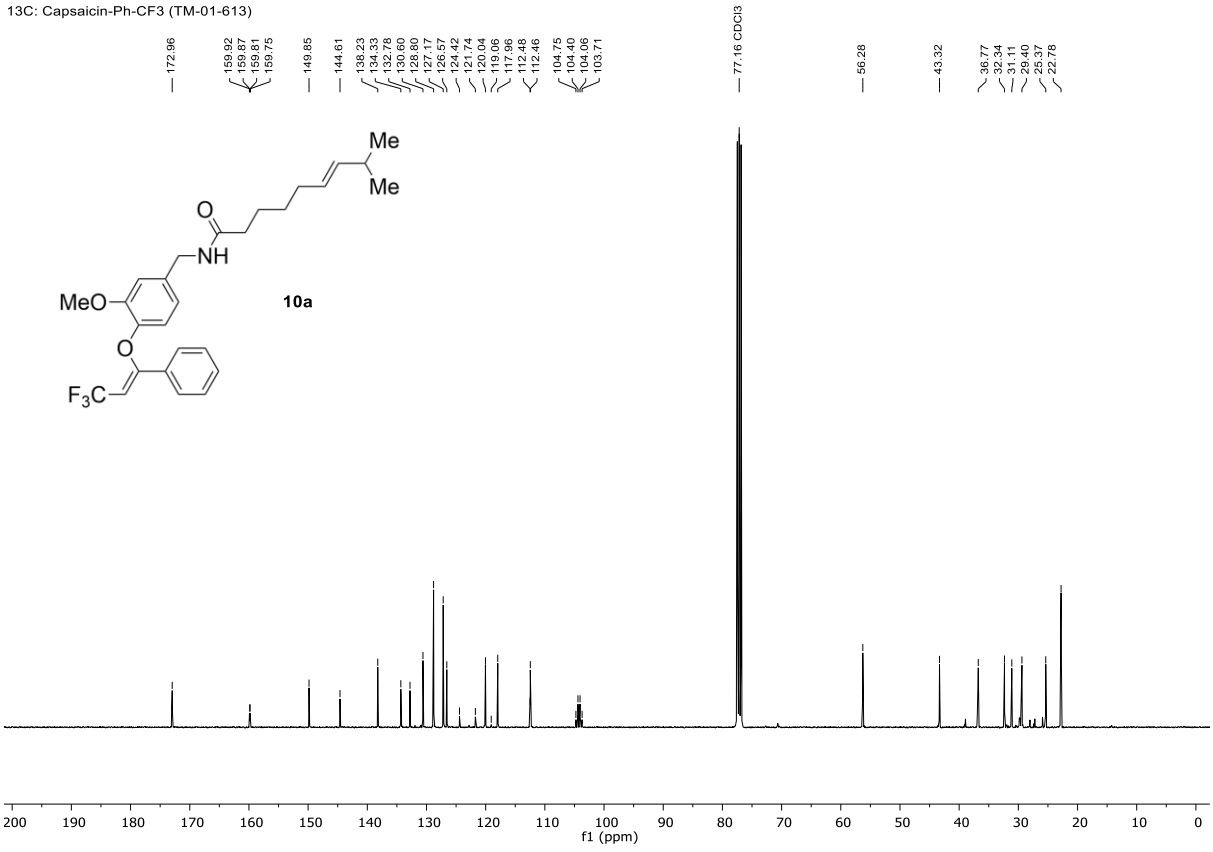
	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	22.8	0.94 (d, 6.7 Hz), 0.85 (d, 6.6 Hz)	2	2, 3
2	31.1	2.25-2.12 (m)	1/1’, 4	
3	138.2	5.42-5.24 (m)	5	
4	126.6	5.42-5.24 (m)	2	
5	32.3	2.02-1.92 (m)	3, 6	3, 4, 6, 7
6	29.4	1.36 (p, 7.6 Hz), 1.31-1.24 (m)	5	4, 5, 7, 8
7	25.4	1.63 (p, 7.5 Hz)	8	5, 8, 9
8	36.8	2.25-2.12 (m)	7	6, 9
9	173.0			
10	/	5.65 (t, 6.1 Hz)	11	
11	43.3	4.29 (d, 5.7 Hz)	10	9, 12, 13, 17
12	134.3			
13	112.5	6.80 (d, 1.9 Hz)		11, 12, 14, 15, 17
14	149.8			
15	144.6			
16	118.0	6.69 (d, 8.2 Hz)		12, 14, 15
17	120.0	6.60 (dd, 8.2, 1.9 Hz)		11, 13, 15
18	56.3	3.90 (d, 1.2 Hz)		14
19	159.8 (q, 5.7 Hz)			
20	104.2 (q, 34.9 Hz)	5.72 (q, 7.6 Hz)		19, 22
21	123.1 (q, 269.6 Hz)			
22	132.8			
23/23’	127.2	7.48 (dd, 8.1, 1.6 Hz)	24/24’, 25	19, 25
24/24’	128.8	7.35-7.27 (m)	23/23’	22
25	130.6	7.35-7.27 (m)	23/23’	24/24’

Table S46. Detailed NMR assignment of (*E*)-*N*-(3-methoxy-4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)benzyl)-8-methylnon-6-enamide (**10a**).

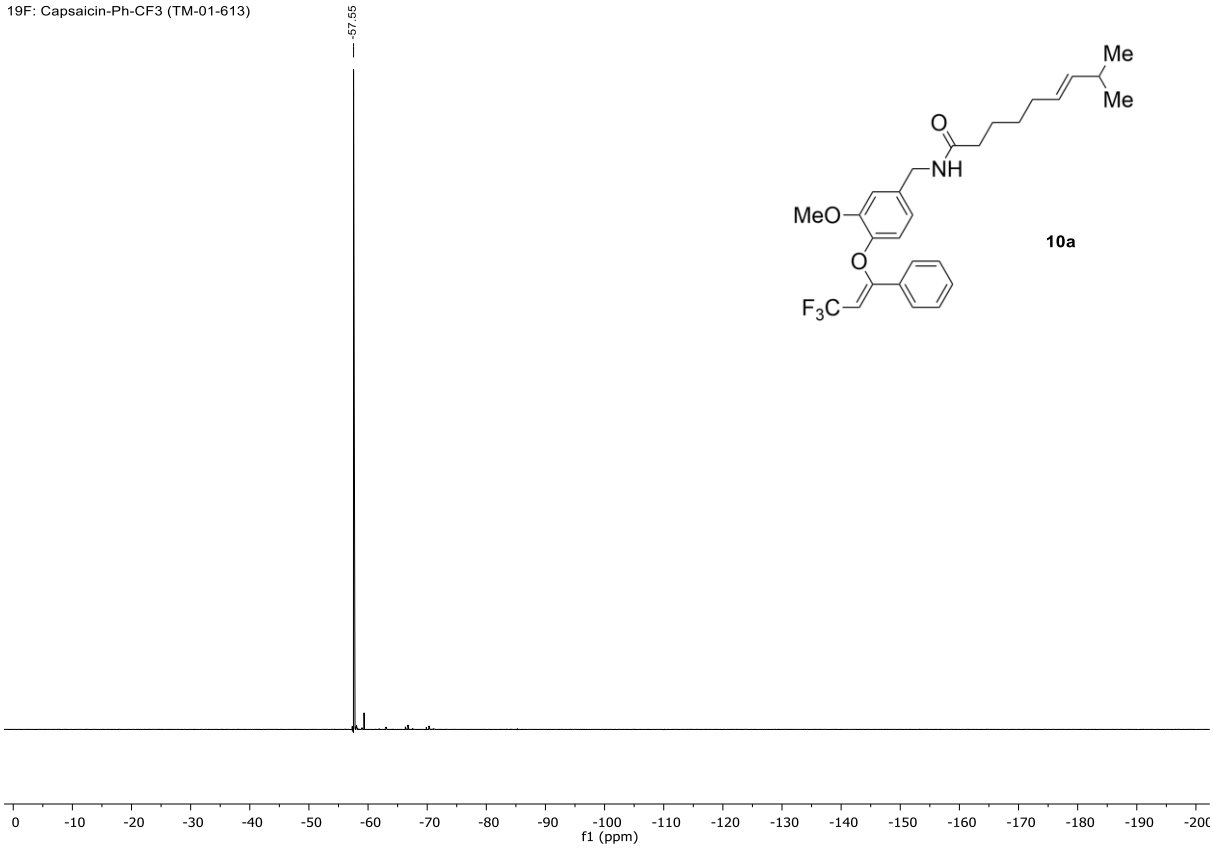
^{1}H-NMR (400 MHz, $CDCl_3$)



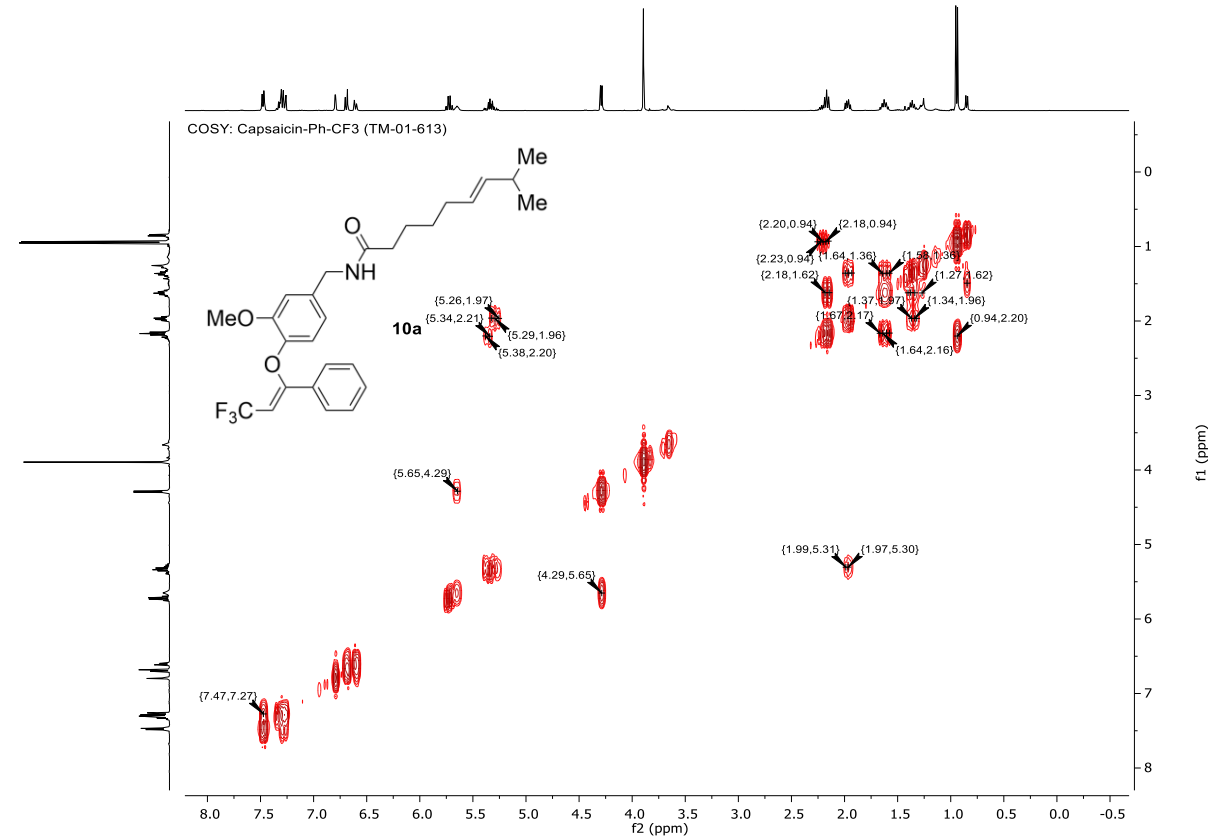
^{13}C-NMR (101 MHz, $CDCl_3$)



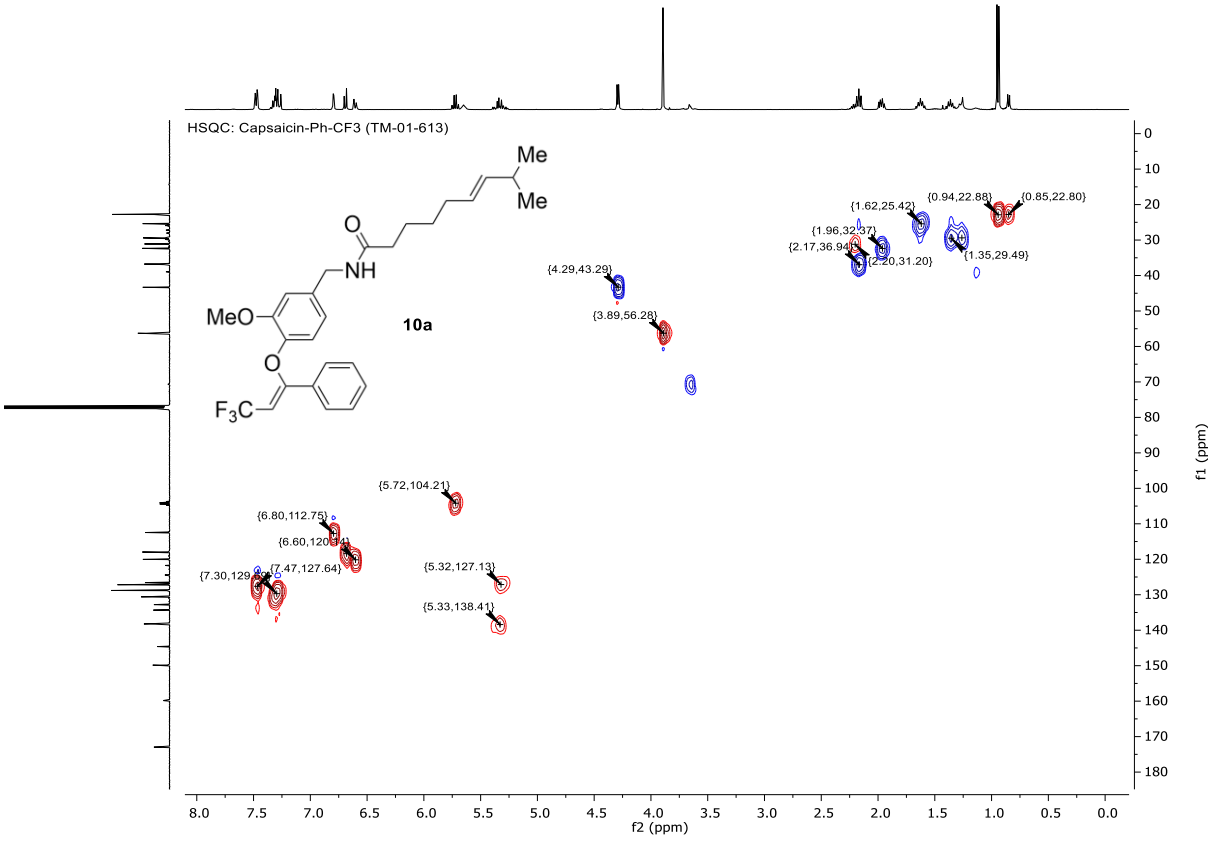
^{19}F-NMR (376 MHz, $CDCl_3$)



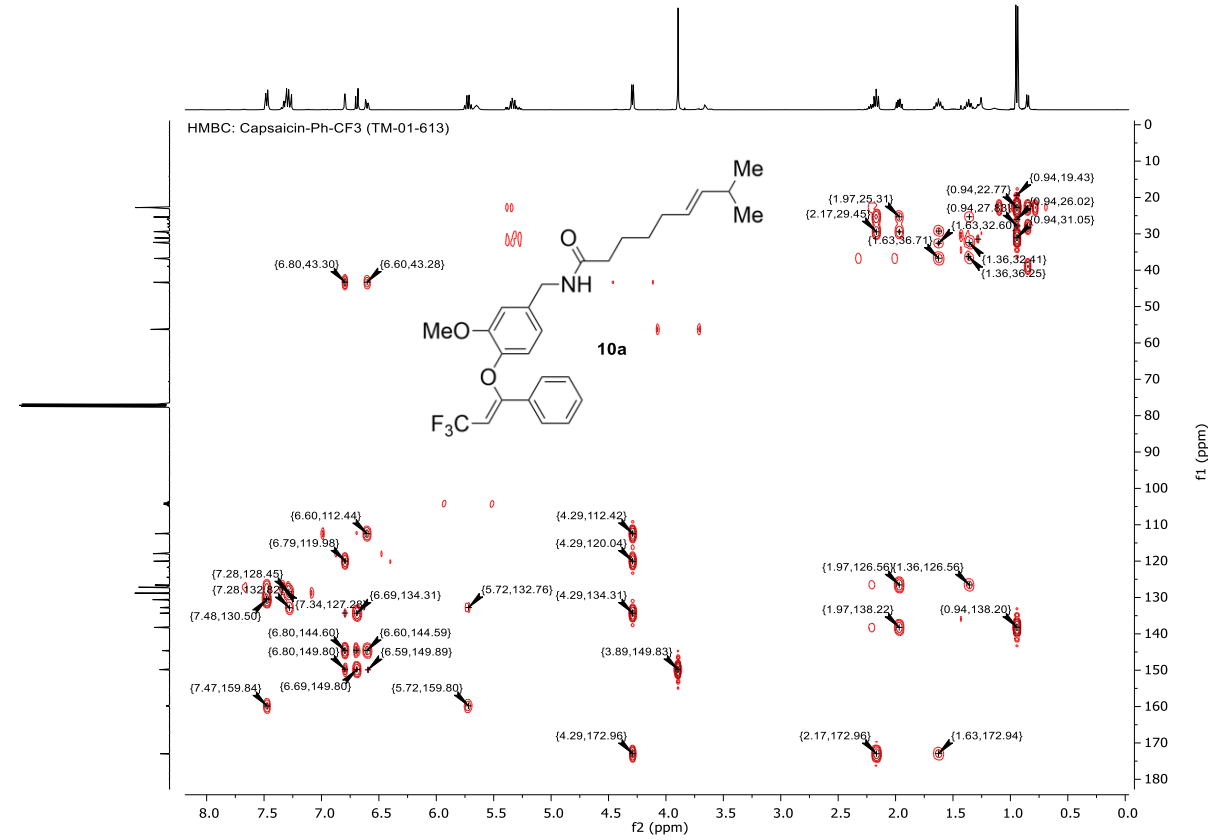
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*E*)-*N*-(4-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-3-methoxybenzyl)-8-methylnon-6-enamide (10b)

	δ_C	δ_H	COSY	HMBC (H→C)
1/1'	22.8	0.94 (d, 6.8 Hz), 0.85 (d, 6.7 Hz)	2	2, 3
2	31.1	2.28-2.17 (m)	1/1', 4	
3	138.3	5.42-5.24 (m)	5	5
4	126.5	5.42-5.24 (m)	2	2
5	32.3	1.99 (q, 7.3 Hz)	3, 6	3, 4, 6, 7
6	29.4	1.39 (p, 7.6 Hz	5	4, 5
7	25.4	1.66 (p, 7.3 Hz)	8	6, 8
8	36.8	2.28-2.17 (m)	7	6, 7, 9
9	173.1			
10	/	5.81 (t, 5.9 Hz)	11	
11	43.3	4.39 (d, 5.9 Hz)	10	9, 12, 13, 16
12	136.1			
13	112.7	6.91-6.85 (m)		11, 15, 16
14	151.2			
15	142.6			
16	120.2	6.91-6.85 (m)	17	12, 14, 15
17	120.6	6.79 (dd, 8.1, 2.0 Hz)	16	11, 13, 15
18	56.2	3.82 (s)		14
19	162.1 (q, 5.7 Hz)			
20	101.1 (q, 34.8 Hz)	5.10 (q, 7.6 Hz)		19, 22
21	123.0 (q, 269.4 Hz)			
22	29.1	2.28-2.17 (m)	23	19, 20, 23, 24
23	28.7	1.93-1.82 (m)	22, 24	19, 24
24	43.6	3.49 (t, 6.3 Hz)	23	22

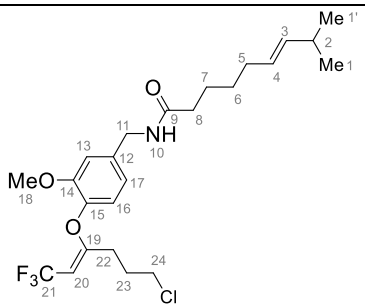
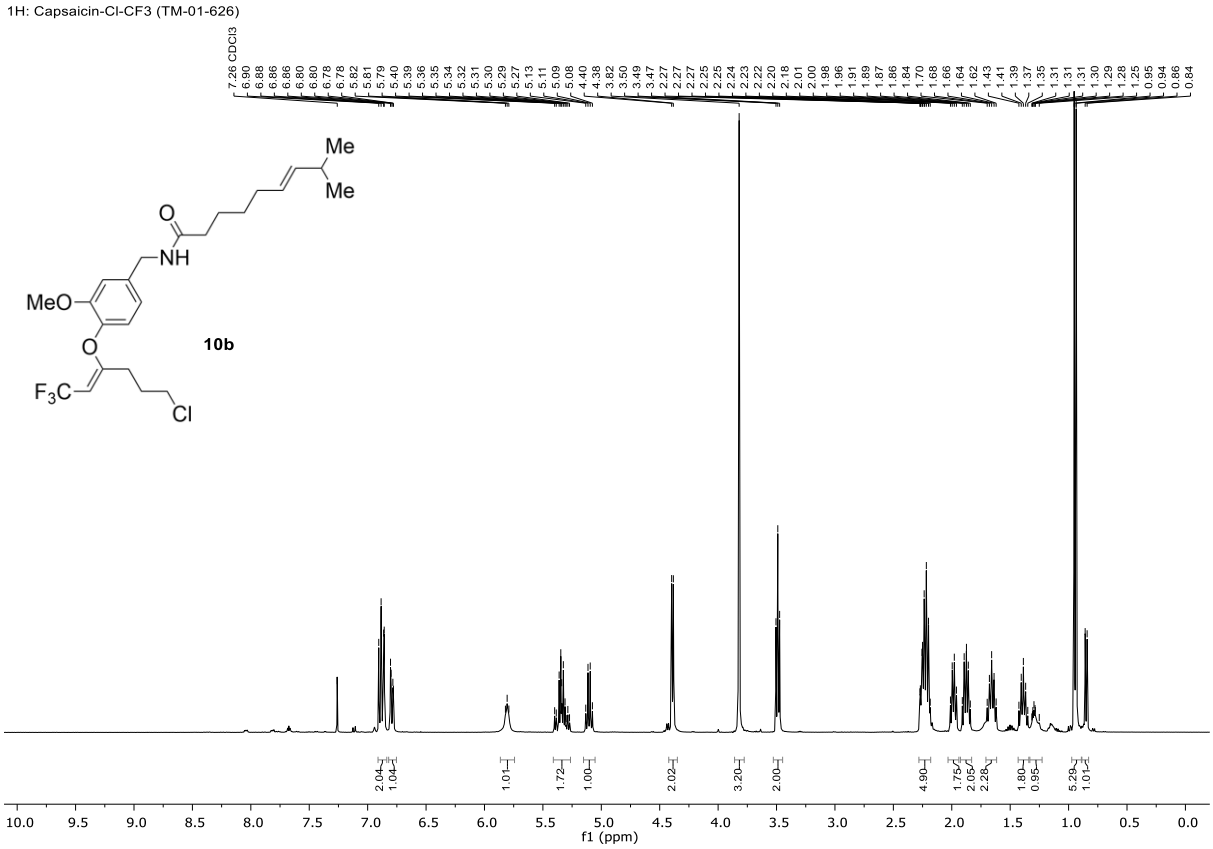
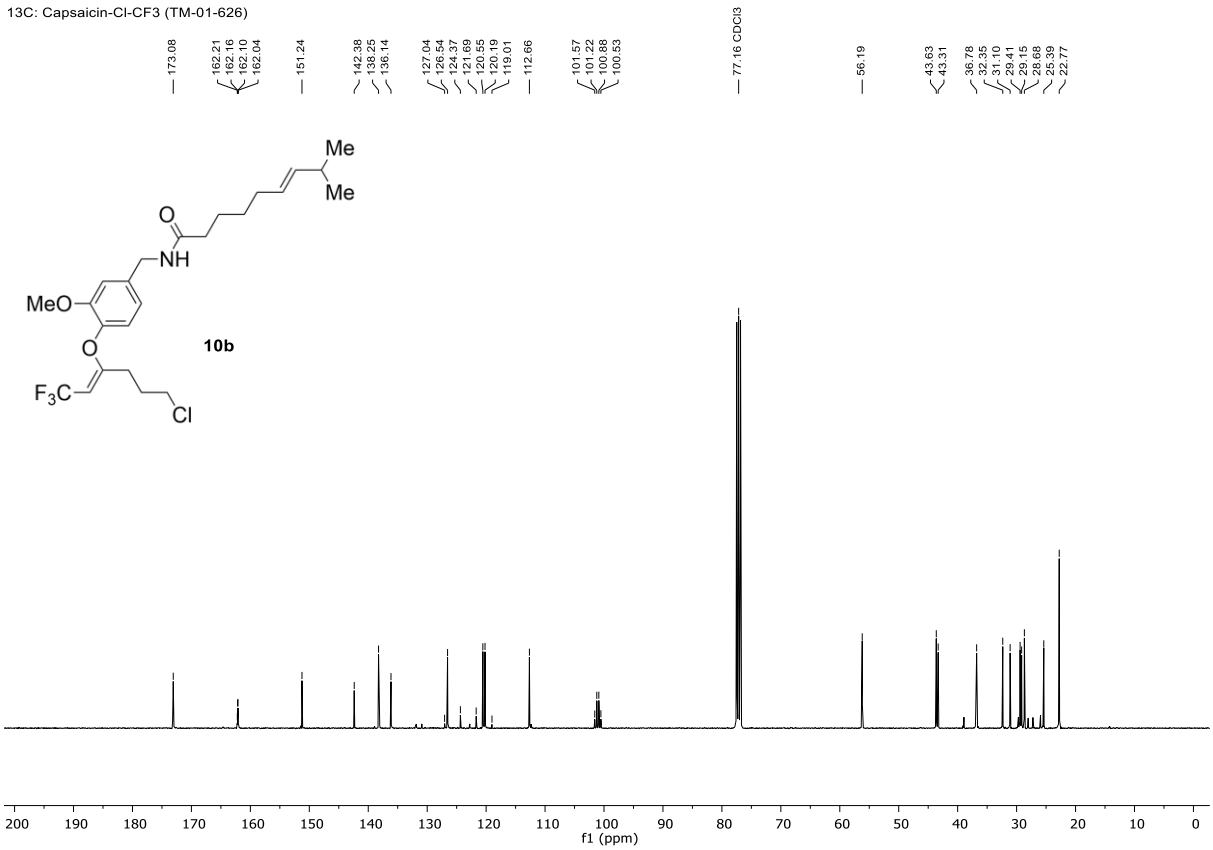


Table S47. Detailed NMR assignment of (*E*)-*N*-(4-(((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-3-methoxybenzyl)-8-methylnon-6-enamide (**10b**).

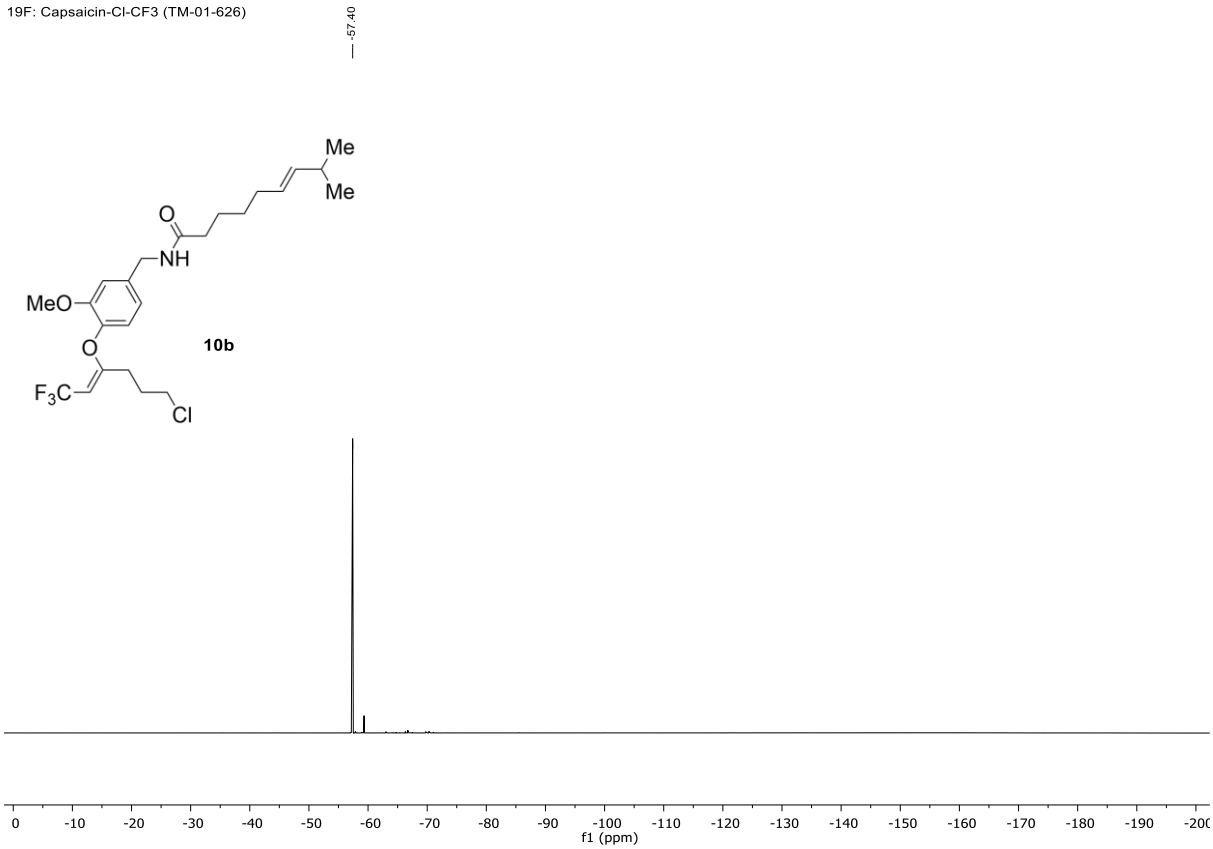
^{1}H-NMR (400 MHz, $CDCl_3$)



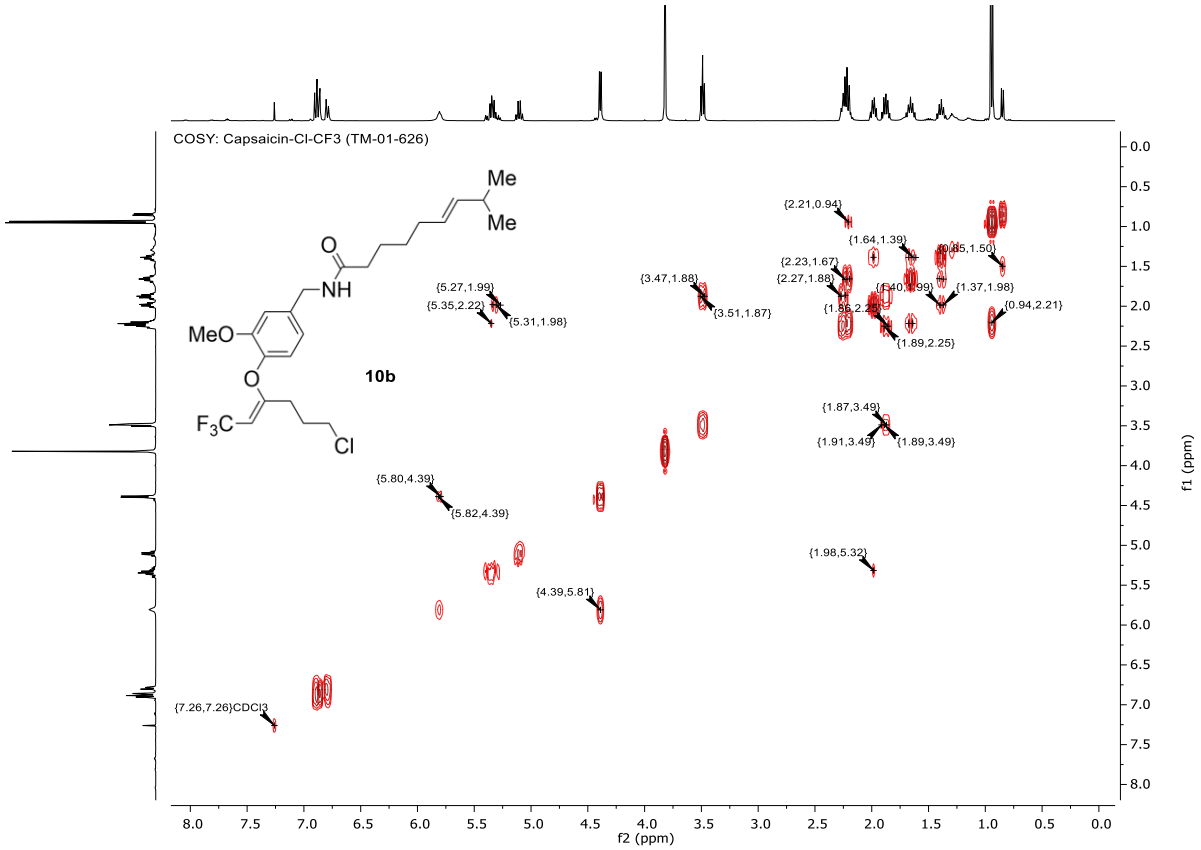
^{13}C-NMR (101 MHz, $CDCl_3$)



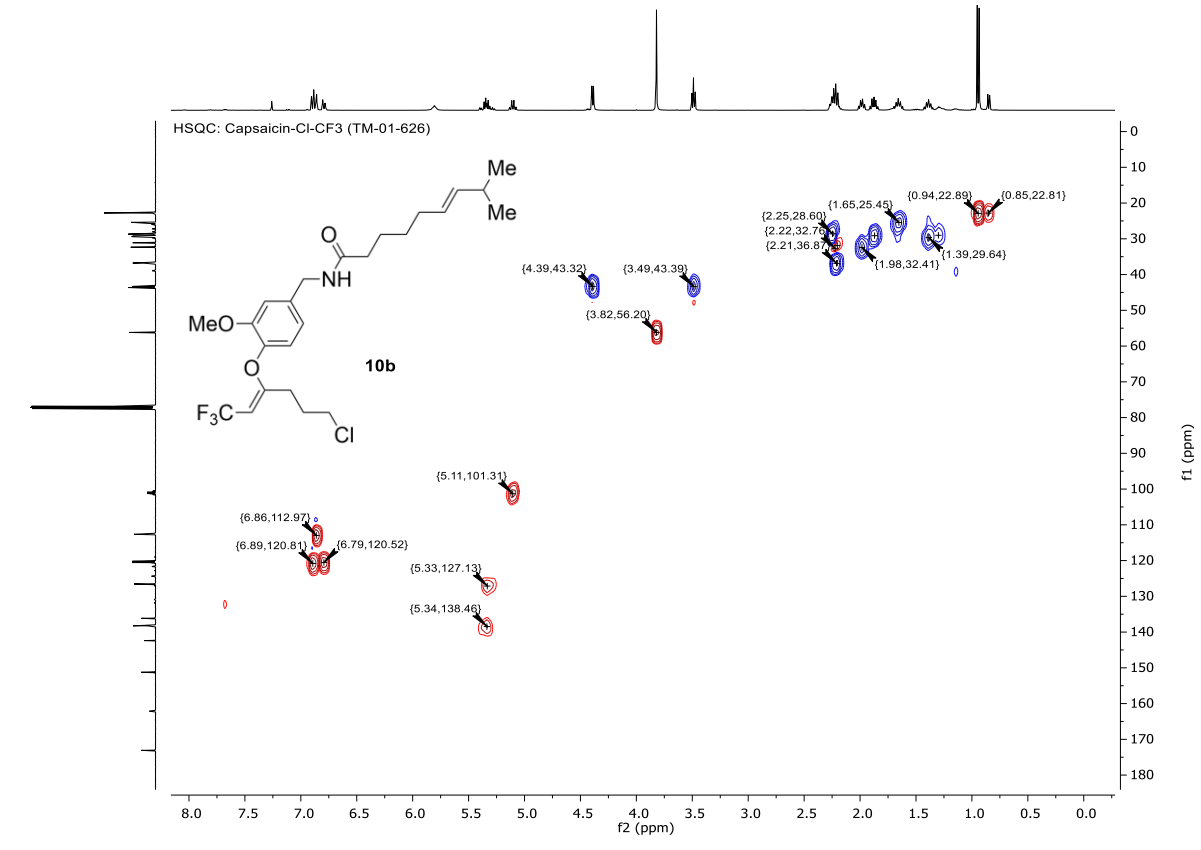
^{19}F-NMR (376 MHz, $CDCl_3$)



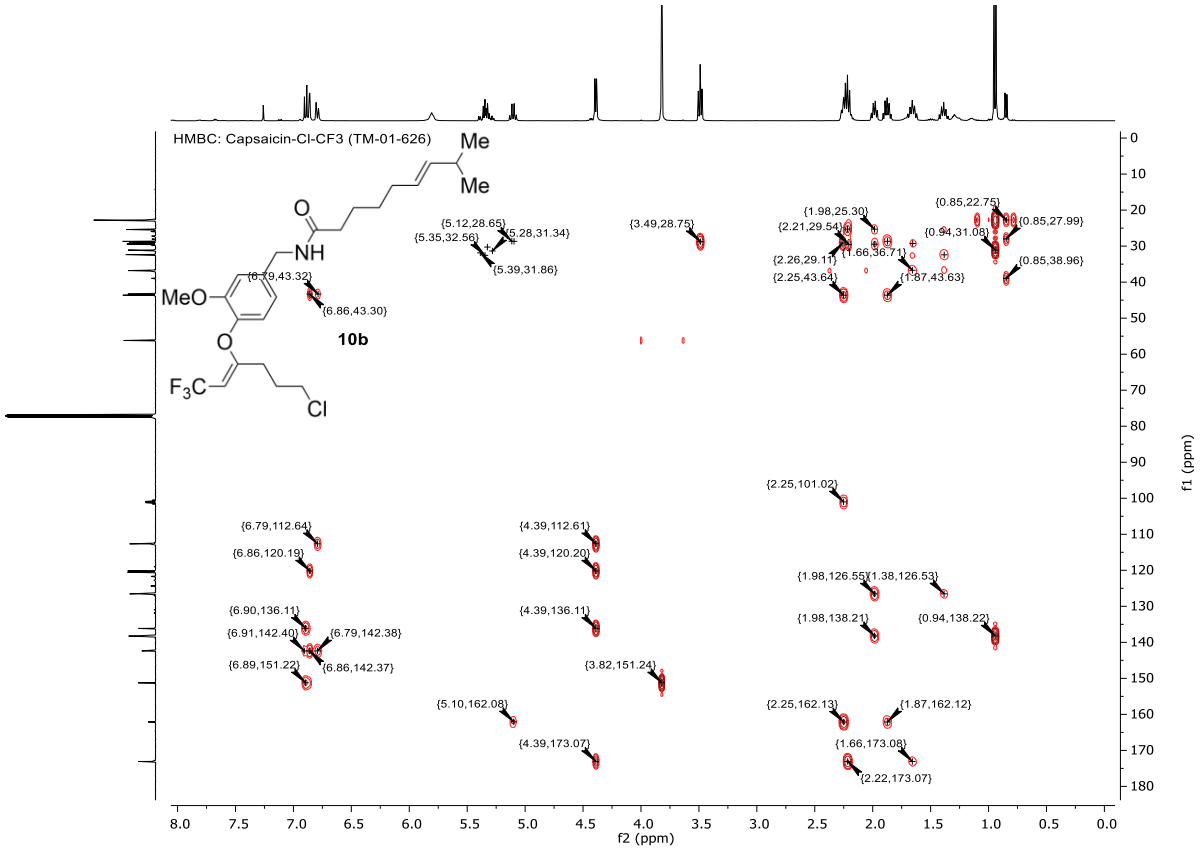
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*R*)-2,5,7,8-Tetramethyl-6-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (10c)

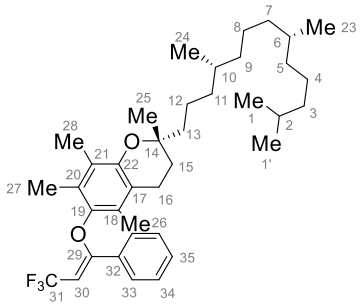
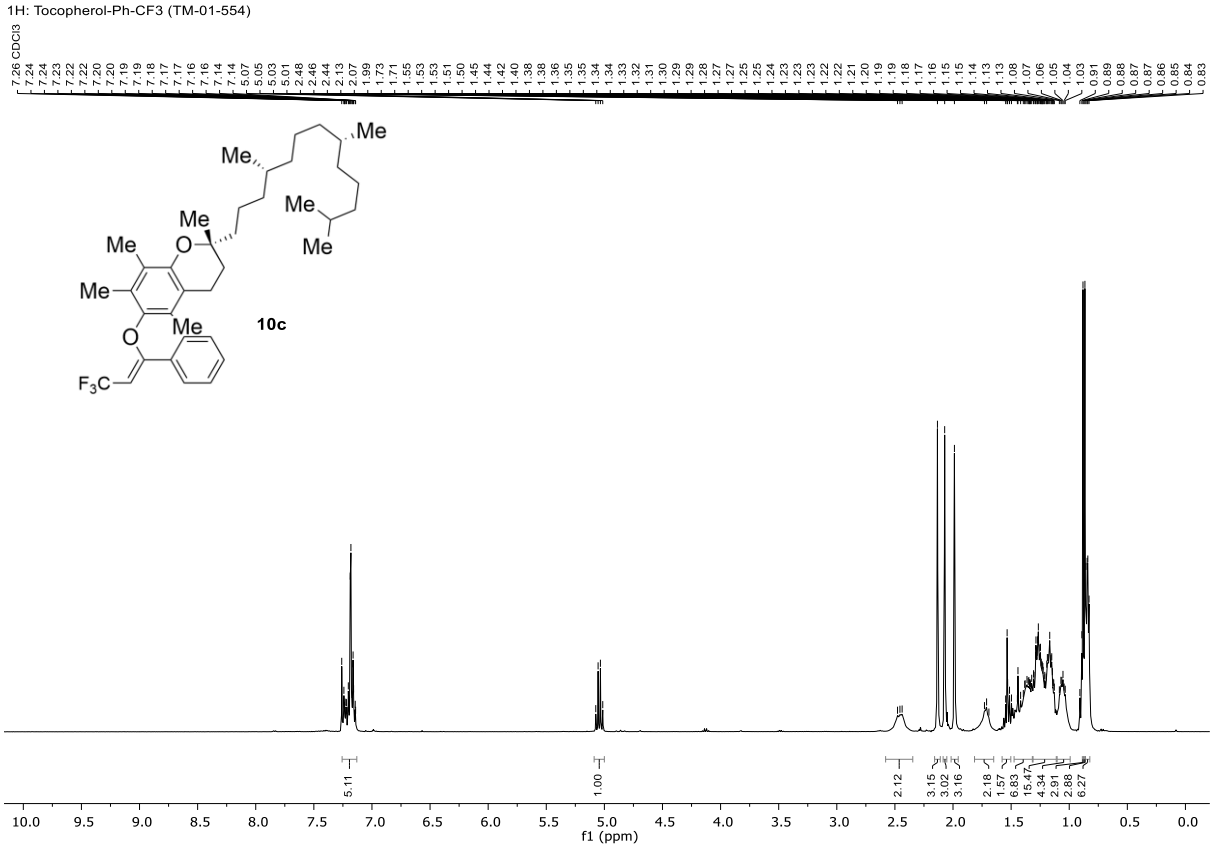


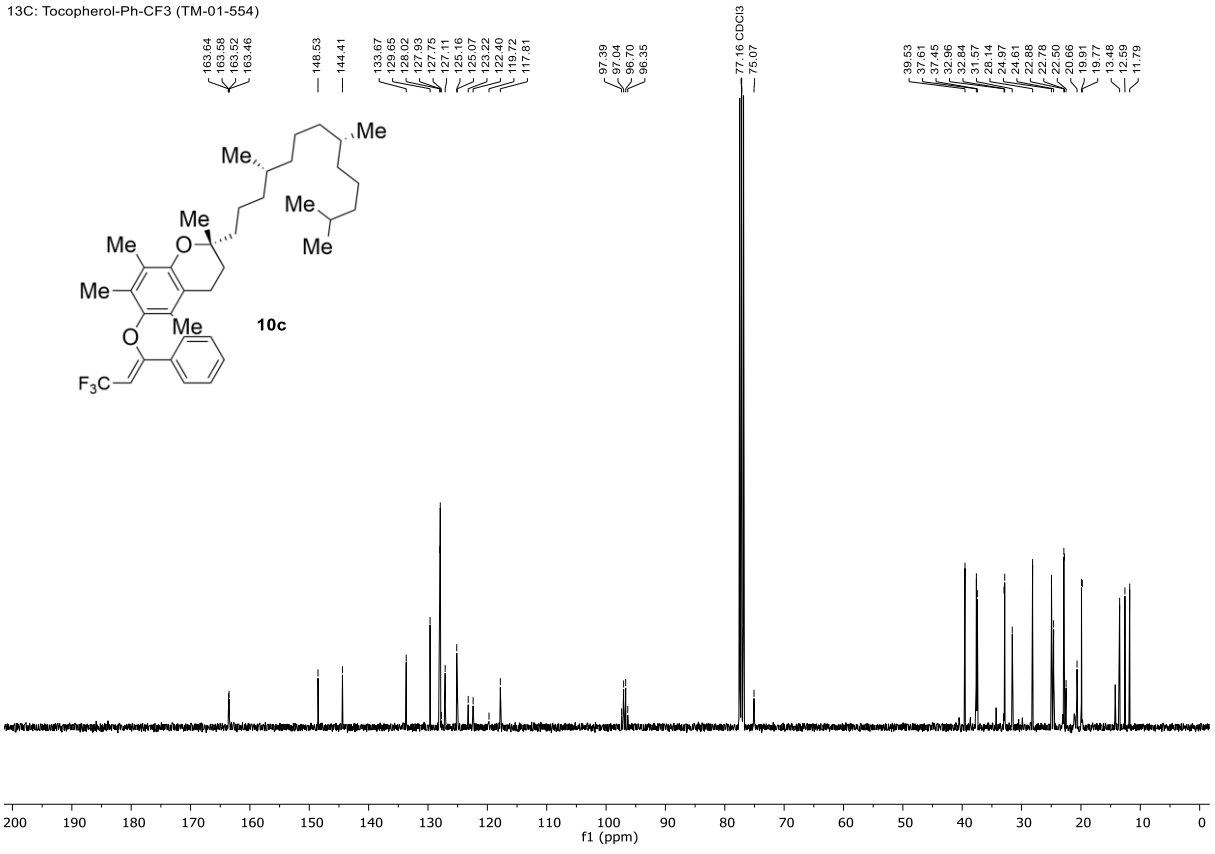
Table S48. Detailed NMR assignment of (*Z*)-1-(2-phenylvinyl)-2-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**10c**).

^{1}H-NMR (400 MHz, $CDCl_3$)

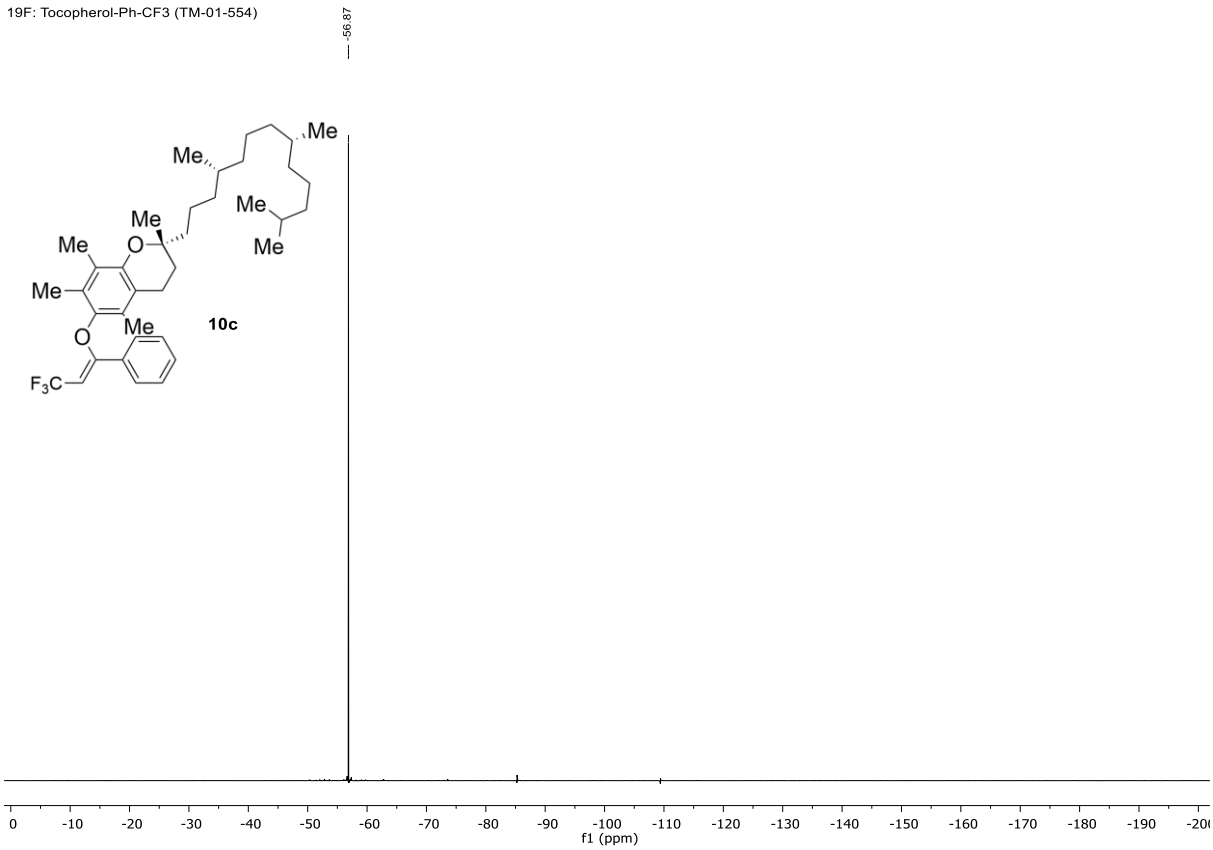
	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	19.8	0.85 (d, 4.4 Hz), 0.83 (d, 4.2 Hz)	2	
2	28.1	1.55-1.47 (m)	1/1’	
3	39.5	1.47-1.33 (m) or 1.32-1.11 (m)		
4	24.6	1.32-1.11 (m)		
5	37.6	1.32-1.11 (m)		
6	32.8	1.47-1.33 (m)		
7	37.4	1.10-1.00 (m)	8	
8	25.0	1.32-1.11 (m)	7	
9	37.6	1.32-1.11 (m)		
10	33.0	1.47-1.33 (m)		
11	39.5	1.47-1.33 (m) or 1.32-1.11 (m)		
12	22.9	1.32-1.11 (m)		
13	39.5	1.47-1.33 (m) or 1.32-1.11 (m)		
14	75.1			
15	31.6	1.81-1.65 (m)		
16	19.9	2.53-2.35 (m)		
17	117.8			
18	123.2			
19	148.5			
20	127.1			
21	129.7			
22	144.4			
23	22.5 or 20.7	0.88 (s) or 0.87 (s)		
24	22.5 or 20.7	0.88 (s) or 0.87 (s)		
25	22.8	1.32-1.11 (m)		
26	12.6	2.07 (s)		17, 22
27	11.8	1.99 (s)		19, 20
28	13.5	2.13 (s)		20, 22
29	163.6 (q, 5.7 Hz)			
30	96.9 (q, 35.3 Hz)	5.04 (q, 8.0 Hz)		29, 31, 32
31	123.7 (q, 269.2 Hz)			
32	133.7			
33/33’	125.2	7.25-7.13 (m)		29, 34/34’
34/34’	128.0	7.25-7.13 (m)		33/33’
35	127.9	7.25-7.13 (m)		



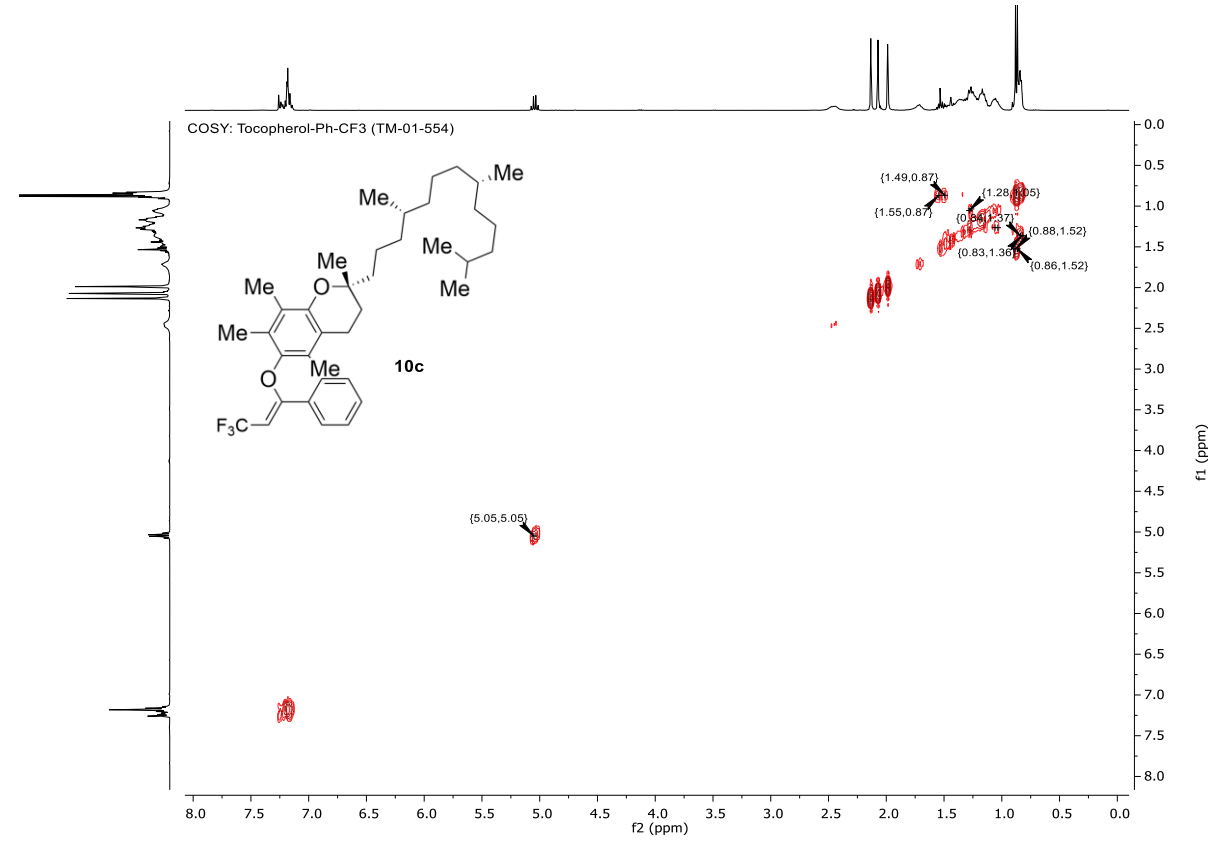
^{13}C-NMR (101 MHz, $CDCl_3$)



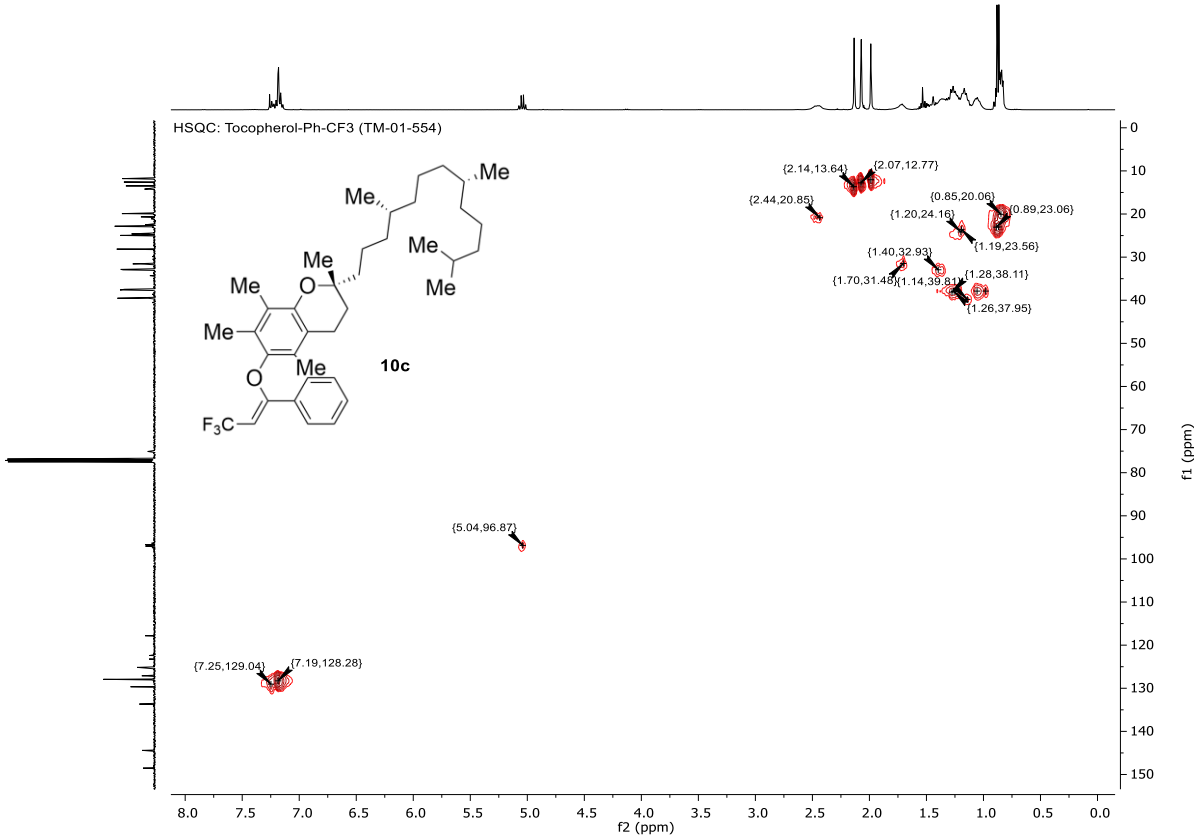
^{19}F-NMR (376 MHz, $CDCl_3$)



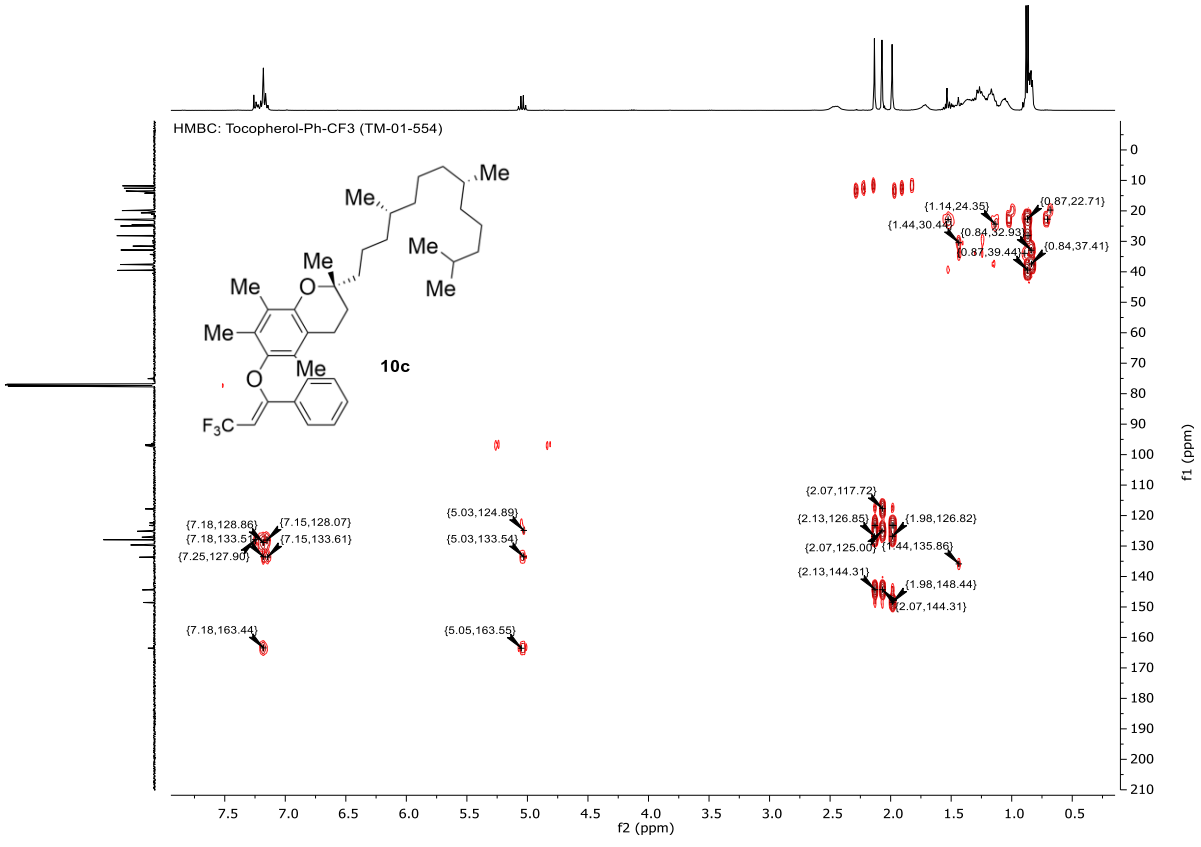
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*R*)-6-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (10d)

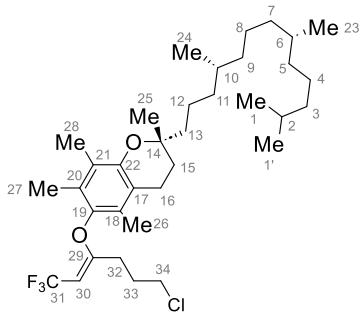
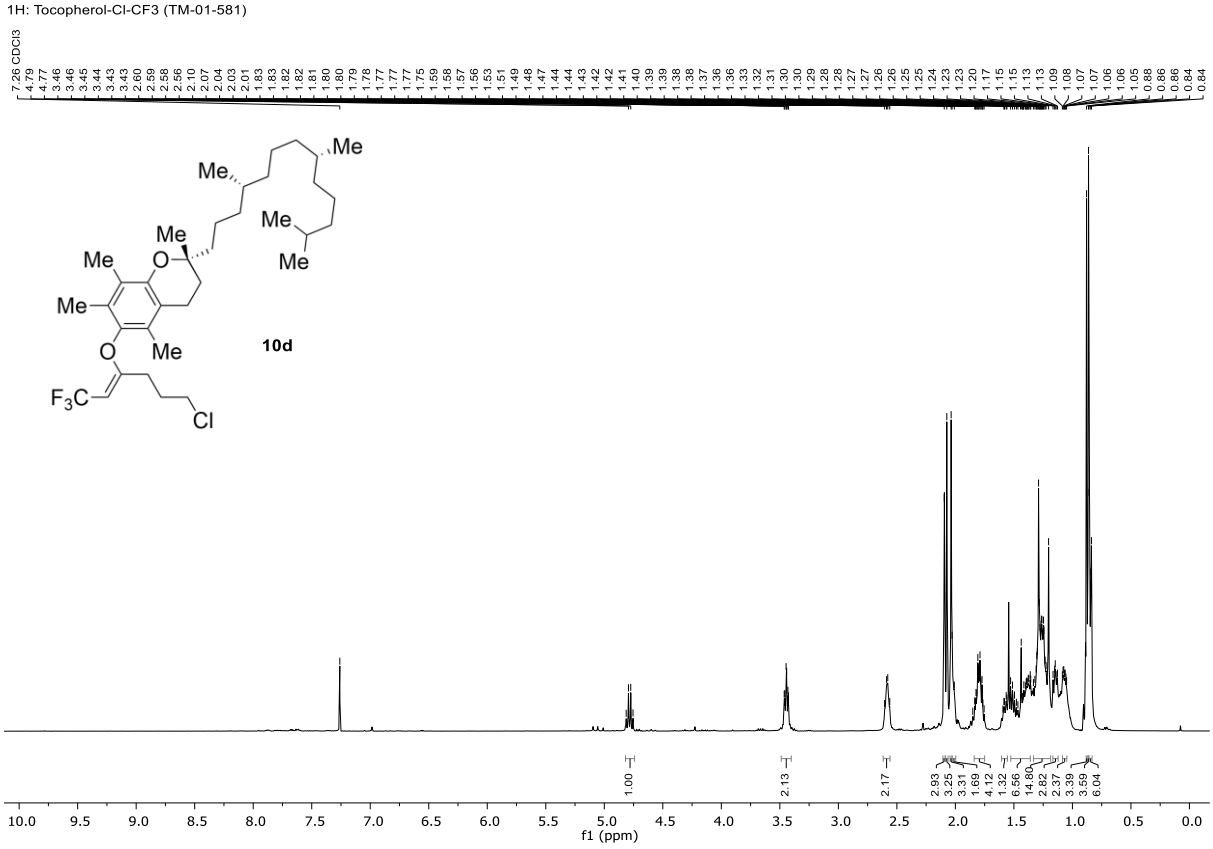


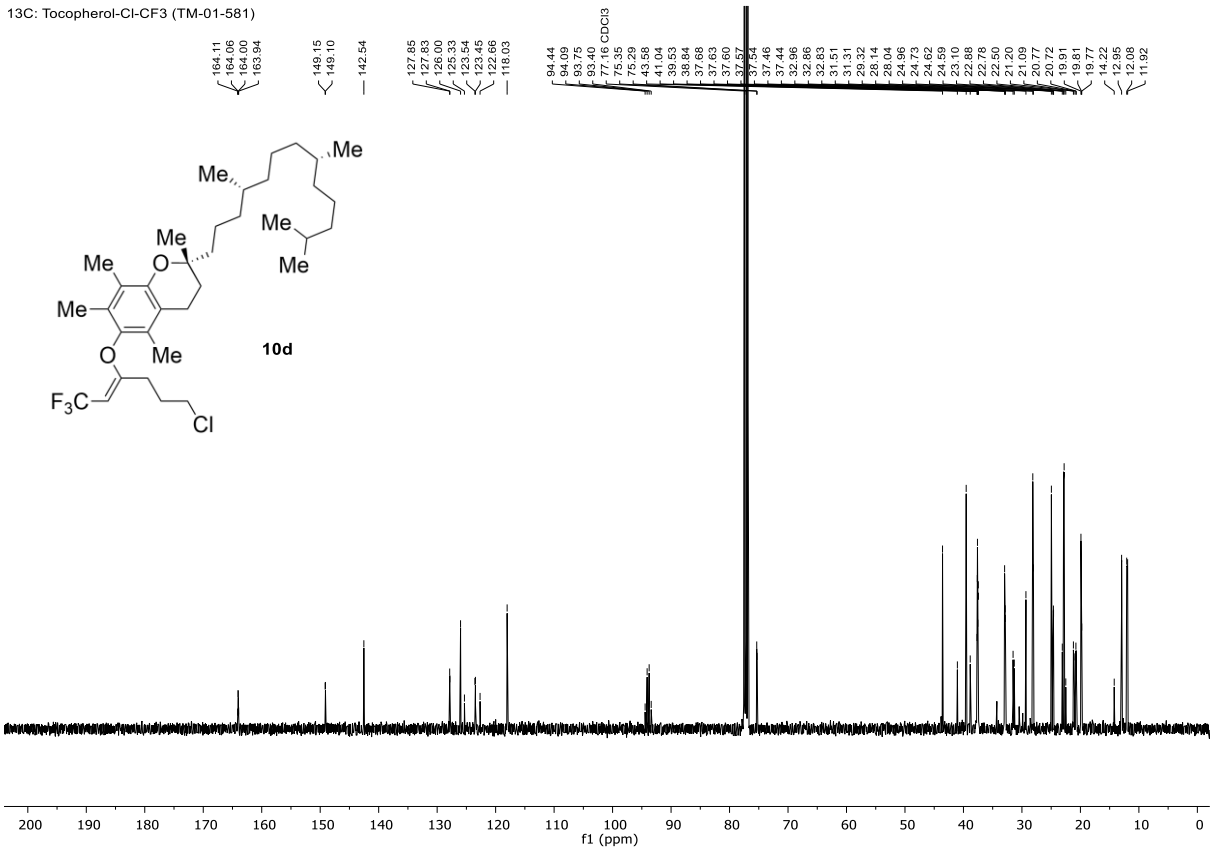
Table S49. Detailed NMR assignment of (*Z*)-1-(2-phenylvinyl)-2-tocopherol-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**10d**).

	δ_C	δ_H	COSY	HMBC (H→C)
1/1’	19.8	0.86-0.83 (m)	2	
2	28.1	1.62-1.55 (m)	1/1’	
3	39.5	1.53-1.35 (m) or 1.33-1.19 (m)		
4	24.6	1.33-1.19 (m)		
5	37.6	1.33-1.19 (m)		
6	32.9	1.53-1.35 (m)		
7	37.5	1.09-1.04 (m)		
8	25.0	1.33-1.19 (m)		
9	37.6	1.33-1.19 (m)		
10	33.0	1.53-1.35 (m)		
11	39.5	1.53-1.35 (m) or 1.33-1.19 (m)		
12	22.9	1.33-1.19 (m)		
13	39.5	1.53-1.35 (m) or 1.33-1.19 (m)		
14	75.4			
15	31.5	1.86-1.74 (m)		
16	19.9	2.58 (q, 6.7 Hz)		14, 15, 17, 18, 19
17	118.0			
18	123.5			
19	149.2			
20	123.5			
21	127.9			
22	142.5			
23	21.7 or 20.8	0.88 (s) or 0.86 (s)		
24	21.7 or 20.8	0.88 (s) or 0.86 (s)		
25	22.8	1.33-1.19 (m)		
26	12.1	2.07 (s)		18
27	11.9	2.04 (s)		19
28	13.0	2.10 (s)		20, 22
29	164.0 (q, 5.8 Hz)			
30	93.9 (q, 34.9 Hz)	4.78 (q, 7.8 Hz)		29, 31
31	124.0 (q, 268.9 Hz)			
32	33.0	2.02-2.00 (m)	33	33
33	29.3	1.86-1.74 (m)	32, 34	29 34
34	43.6	3.44 (td, 6.4, 2.1 Hz)	33	33

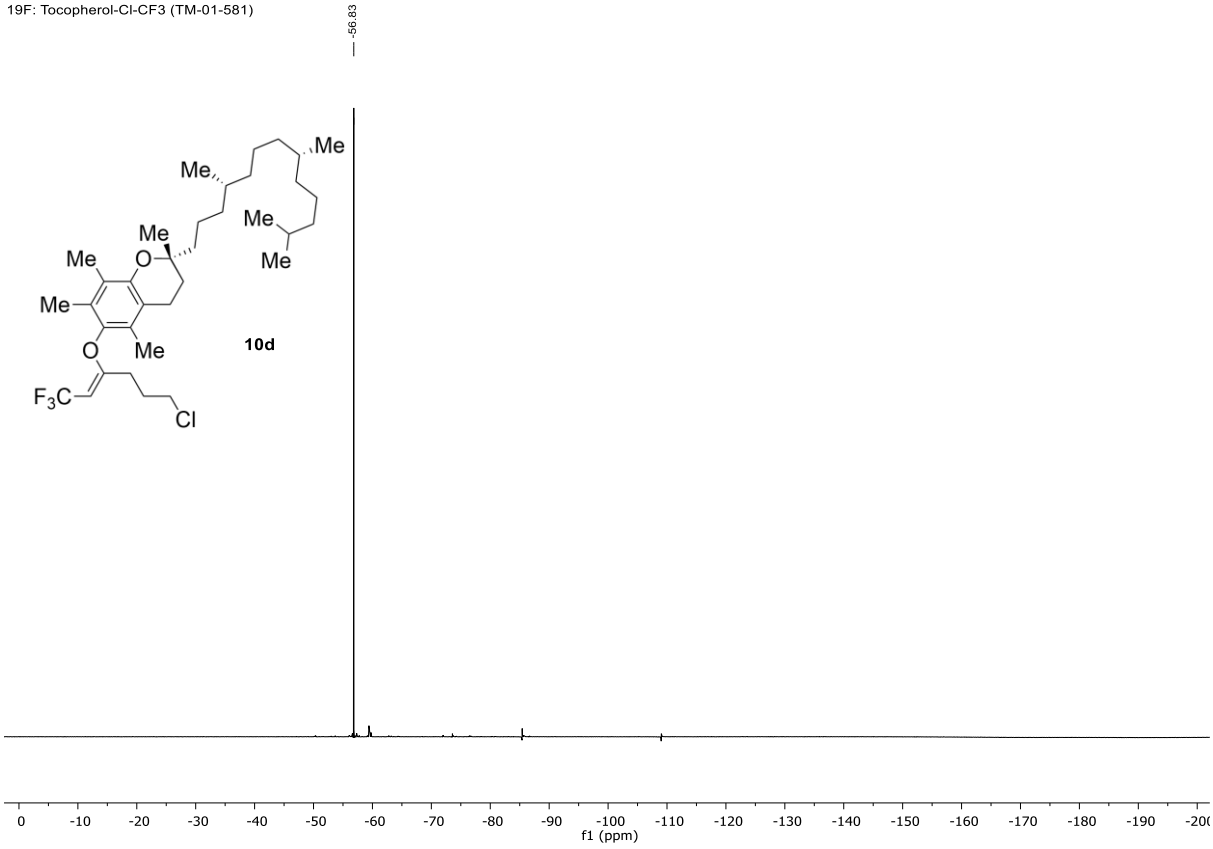
^{1}H-NMR (400 MHz, $CDCl_3$)



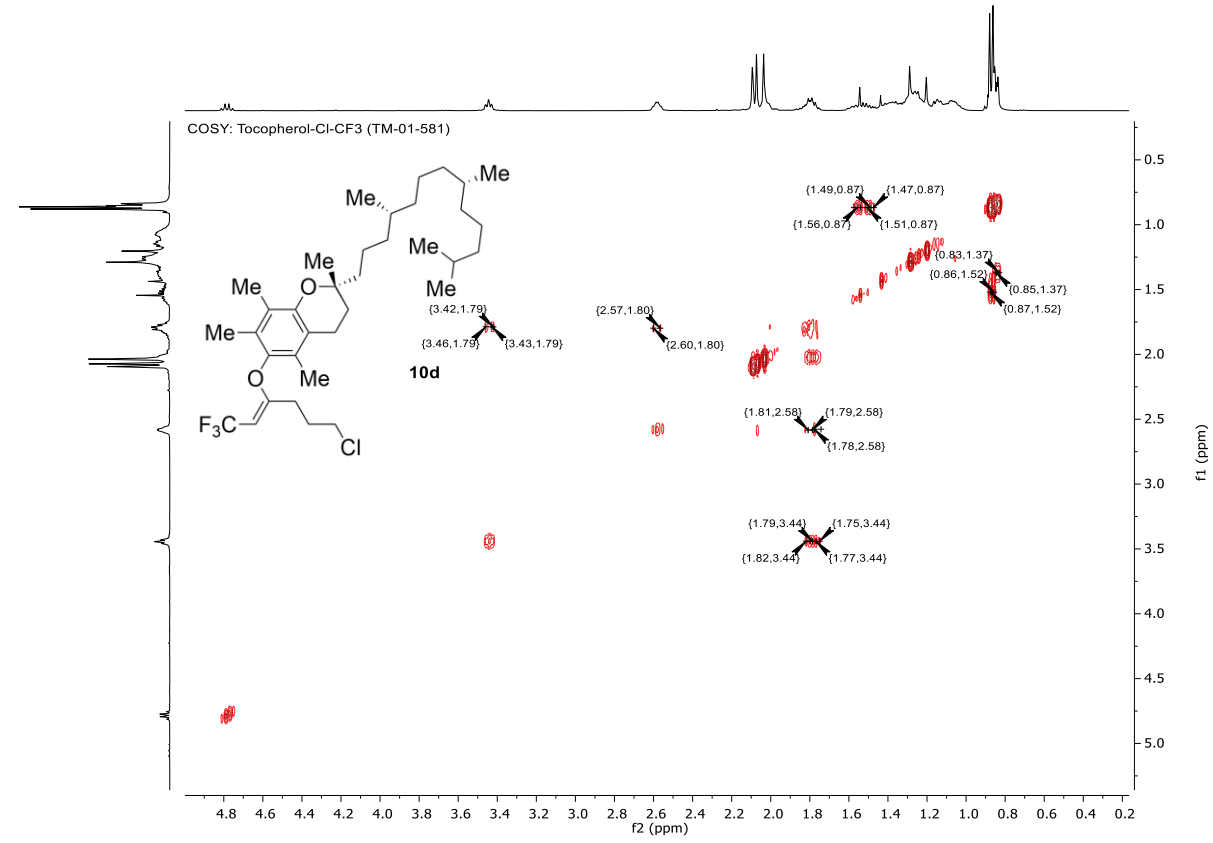
^{13}C-NMR (101 MHz, $CDCl_3$)



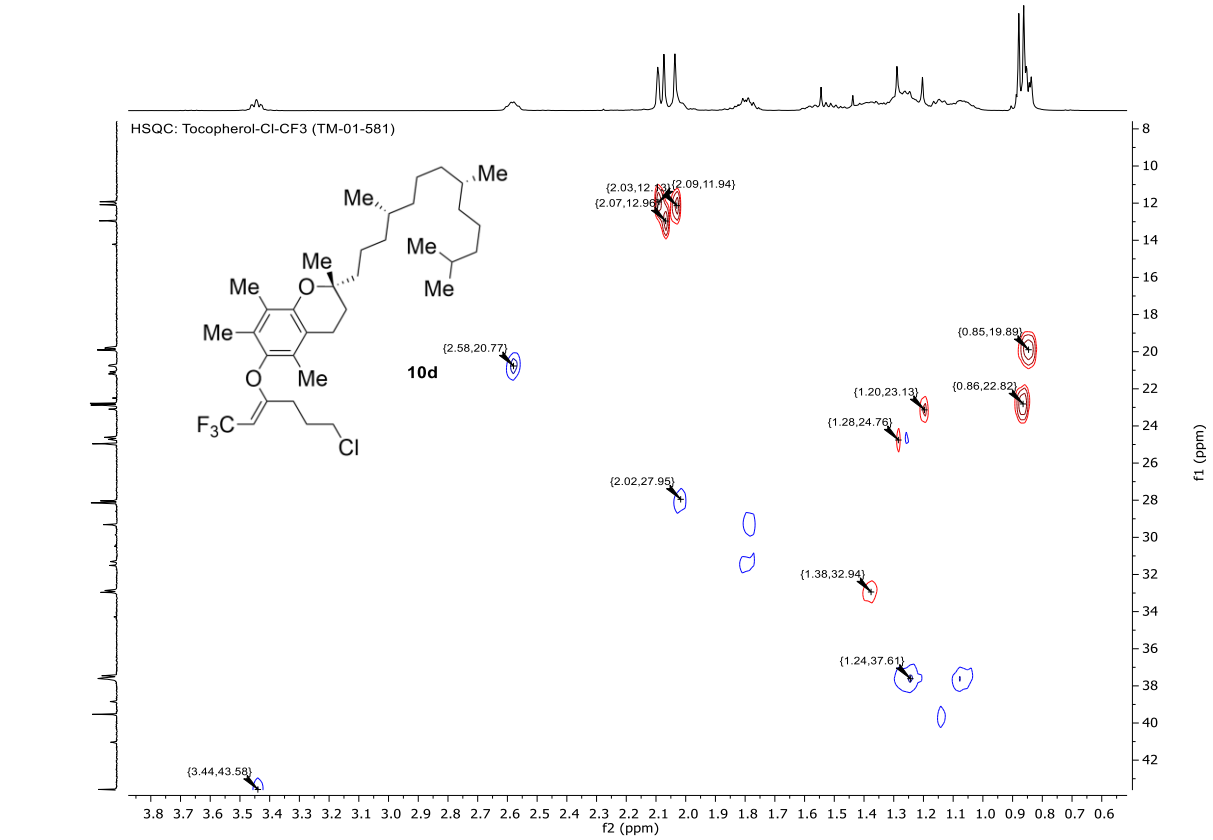
^{19}F-NMR (376 MHz, $CDCl_3$)



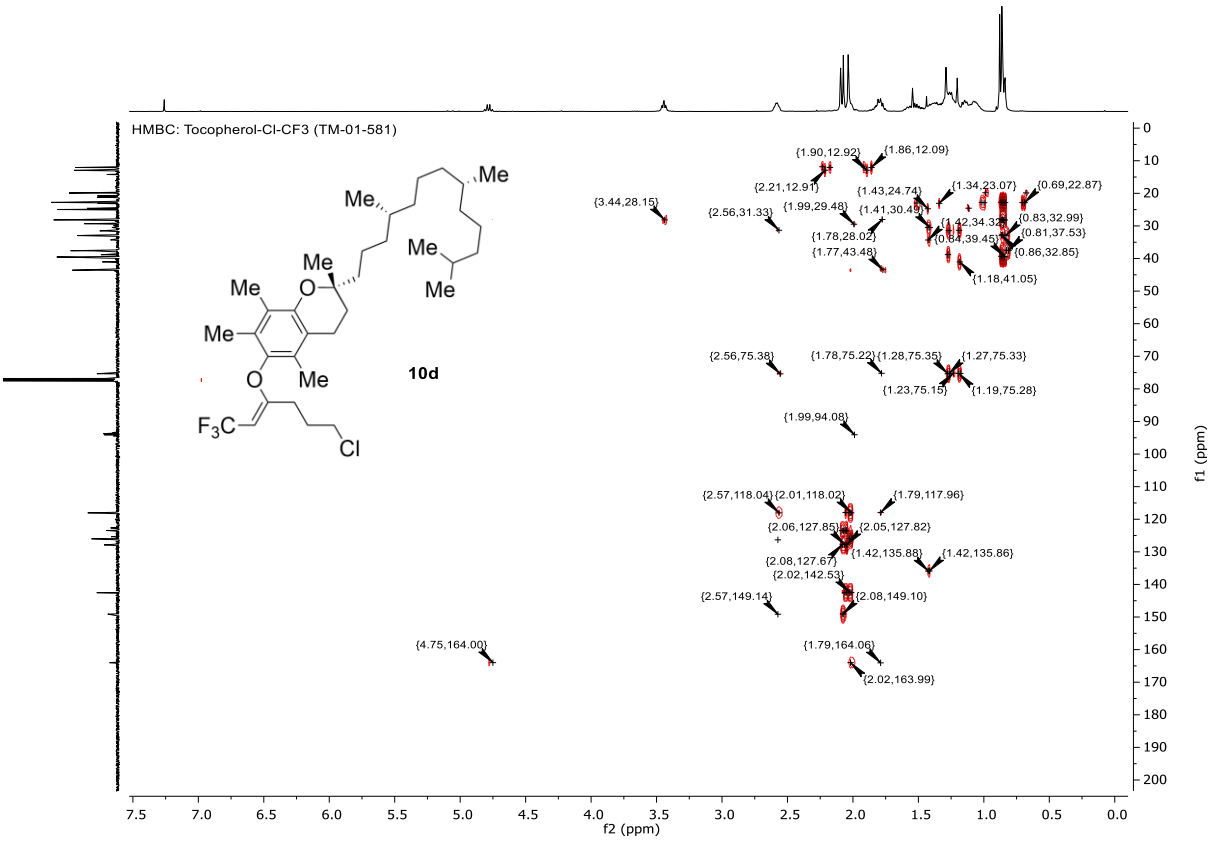
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-3-(((*Z*)-4,4,4-trifluorobut-2-en-2-yl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (10e)

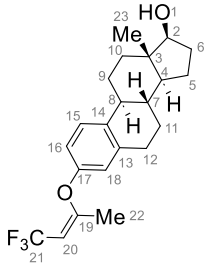
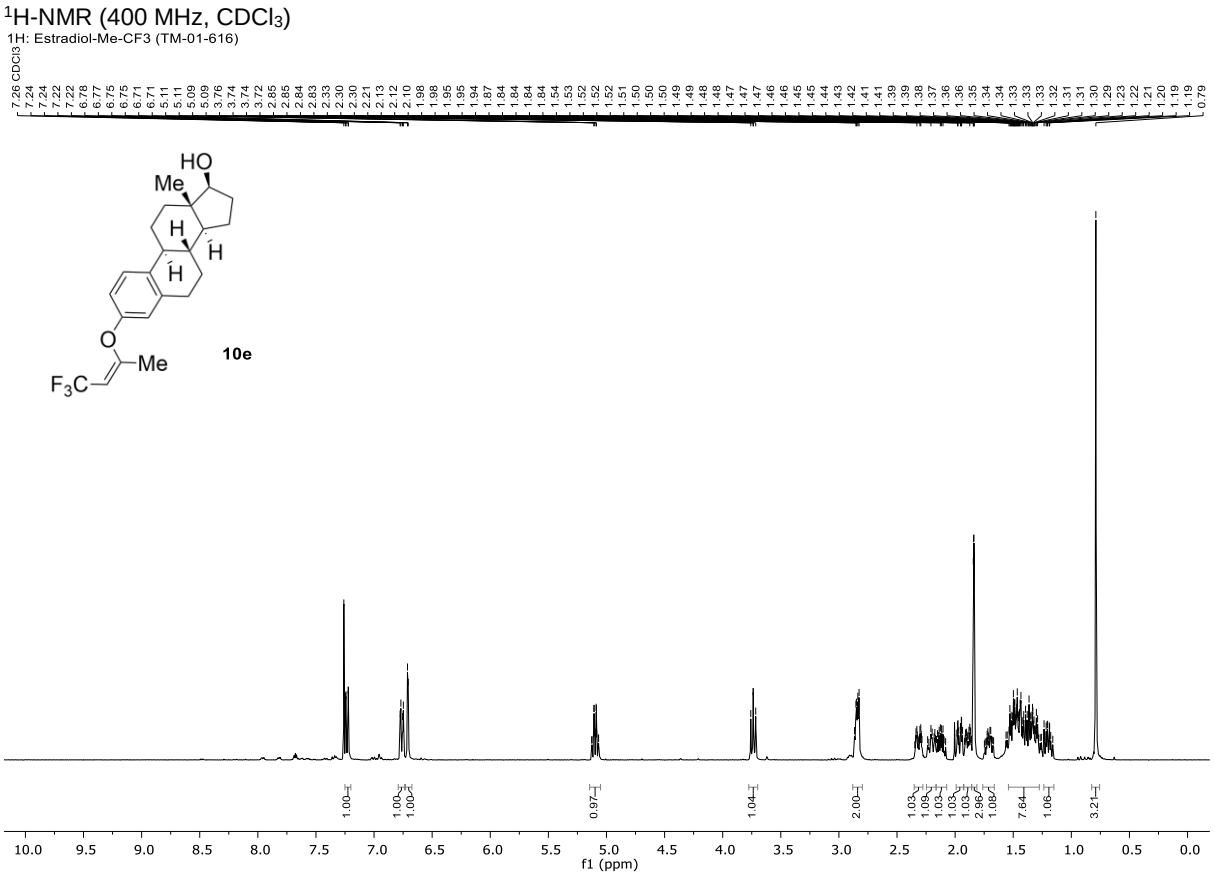


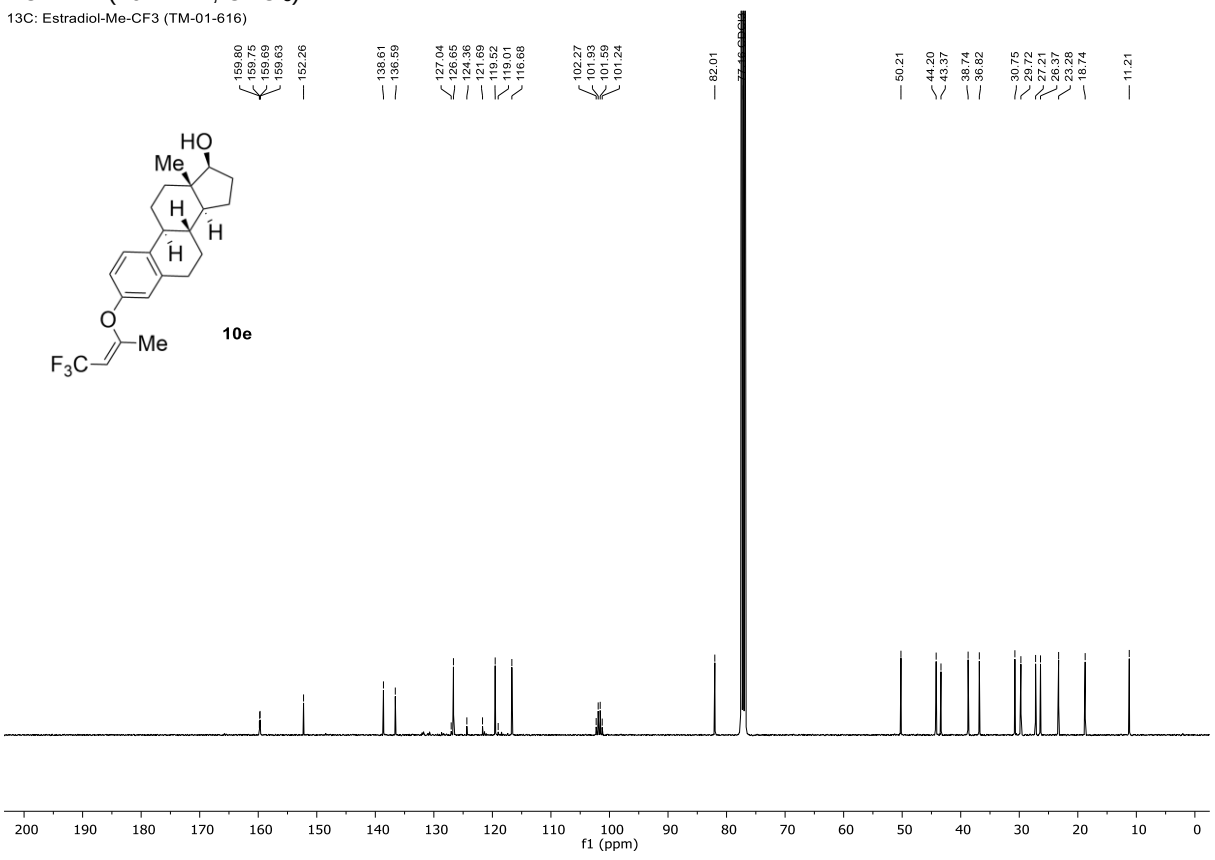
Table S50. Detailed NMR assignment of (8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-3-(((*Z*)-4,4,4-trifluorobut-2-en-2-yl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (**10e**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	not observed		
2	82.0	3.74 (dd, 9.0, 8.0 Hz)	6	10, 23
3	43.4			
4	50.2	1.20 (ddd, 12.0 10.8, 7.2 Hz)		3, 5, 7, 23
5	23.3	1.71 (dddd, 12.4, 9.9, 7.0, 3.1 Hz) 1.56-1.25 (m)	6	
6	30.7	2.16-2.07 (m), 1.56-1.25 (m)	2, 5, 7	3
7	38.7	1.56-1.25 (m)	6, 8	
8	44.2	2.25-2.16 (m)	7, 9	
9	26.4	2.32 (dtd, 13.4, 4.2, 2.7 Hz), 1.56-1.25 (m)	8	
10	36.8	1.96 (ddd, 12.6, 3.9, 2.7 Hz), 1.56-1.25 (m)		4, 8
11	27.2	1.92-1.86 (m), 1.56-1.25 (m)	12	
12	29.7	2.84 (dd, 7.5, 3.2 Hz)	11	7, 11, 13, 18
13	138.6			
14	136.6			
15	126.7	7.23 (dd, 8.5, 1.1 Hz)	16	8, 14, 17
16	116.7	6.76 (dd, 8.5, 2.7 Hz)	15	14, 17, 18
17	152.3			
18	119.5	6.71 (d, 2.6 Hz)		12, 14, 16, 17
19	159.7 (q, 5.8 Hz)			
20	101.8 (q, 34.5 Hz)	5.10 (qd, 7.6, 1.1 Hz)		19, 21, 22
21	123.0 (q, 269.2 Hz)			
22	18.7	1.84 (dd, 2.2, 1.0 Hz)		19, 20
23	11.2	0.79 (s)		2, 3, 4, 10

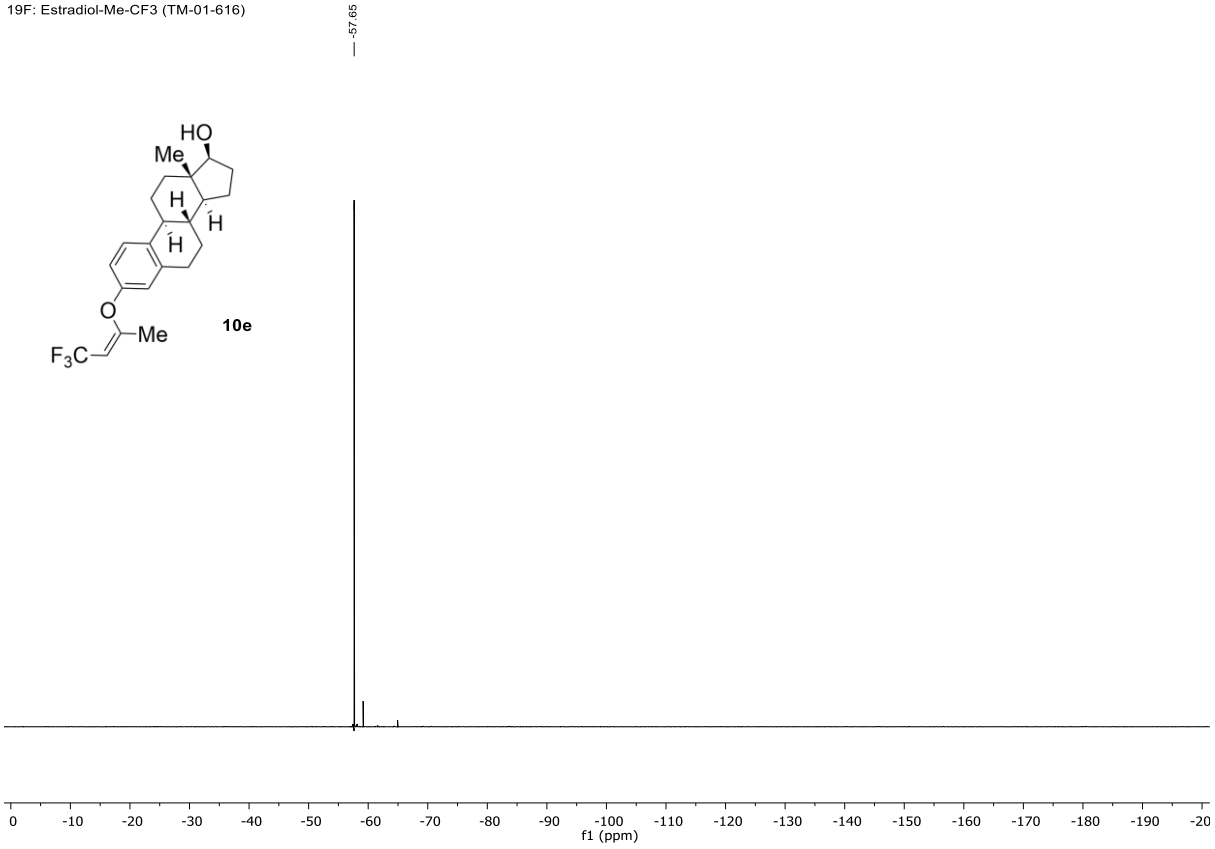
^{1}H-NMR (400 MHz, $CDCl_3$)



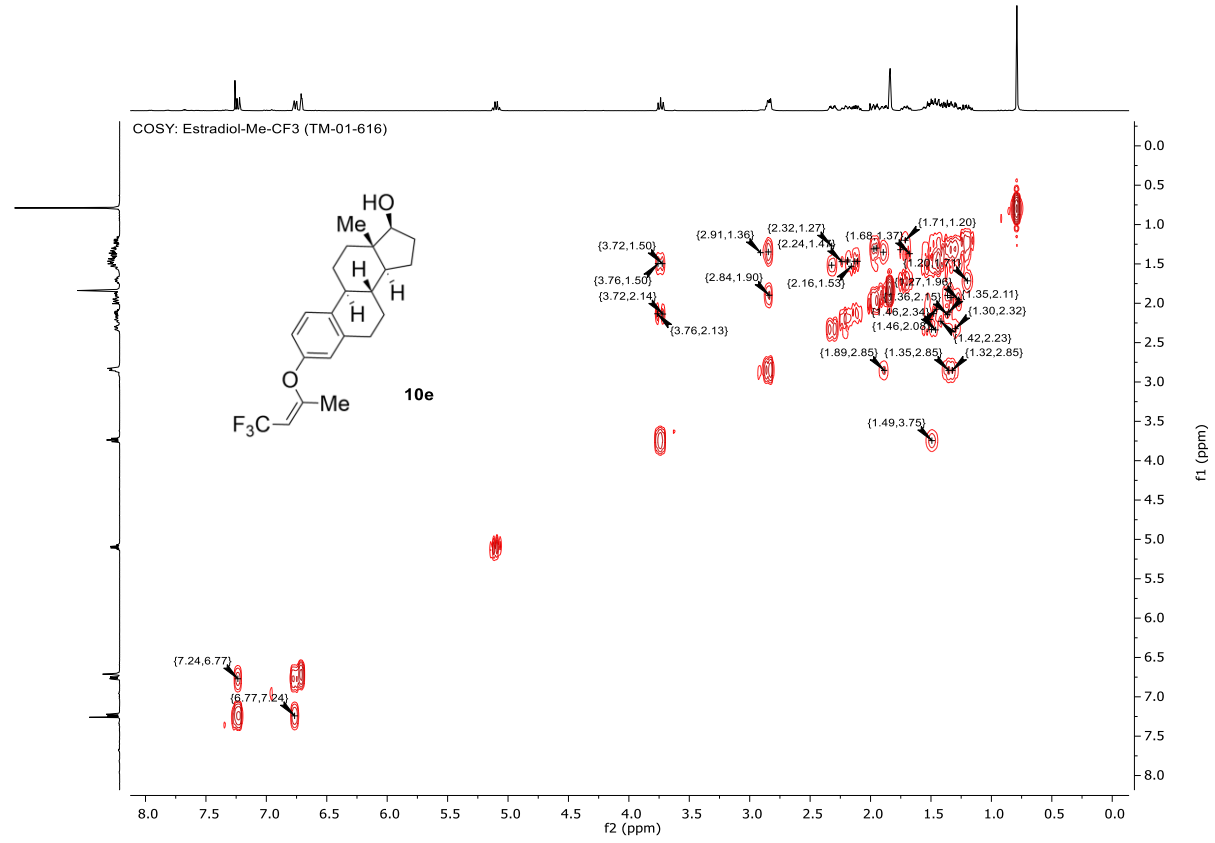
^{13}C-NMR (101 MHz, $CDCl_3$)



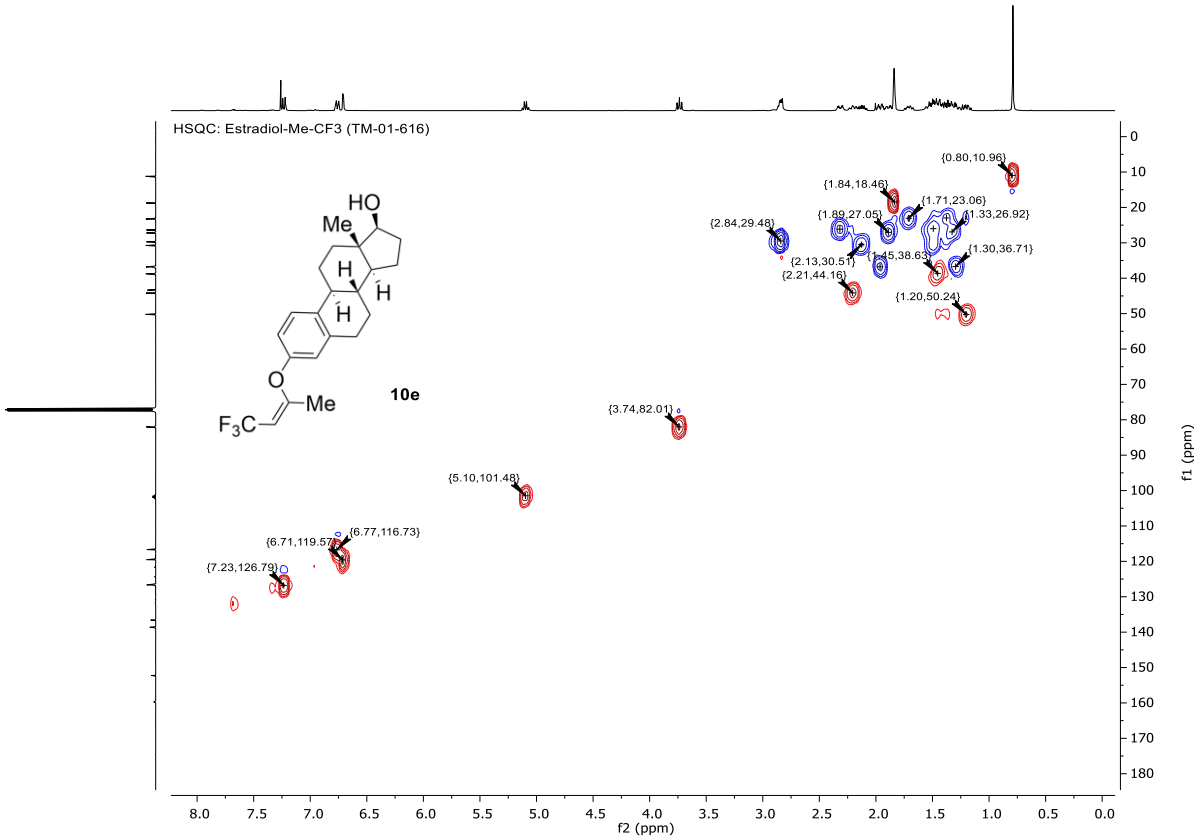
^{19}F-NMR (376 MHz, $CDCl_3$)



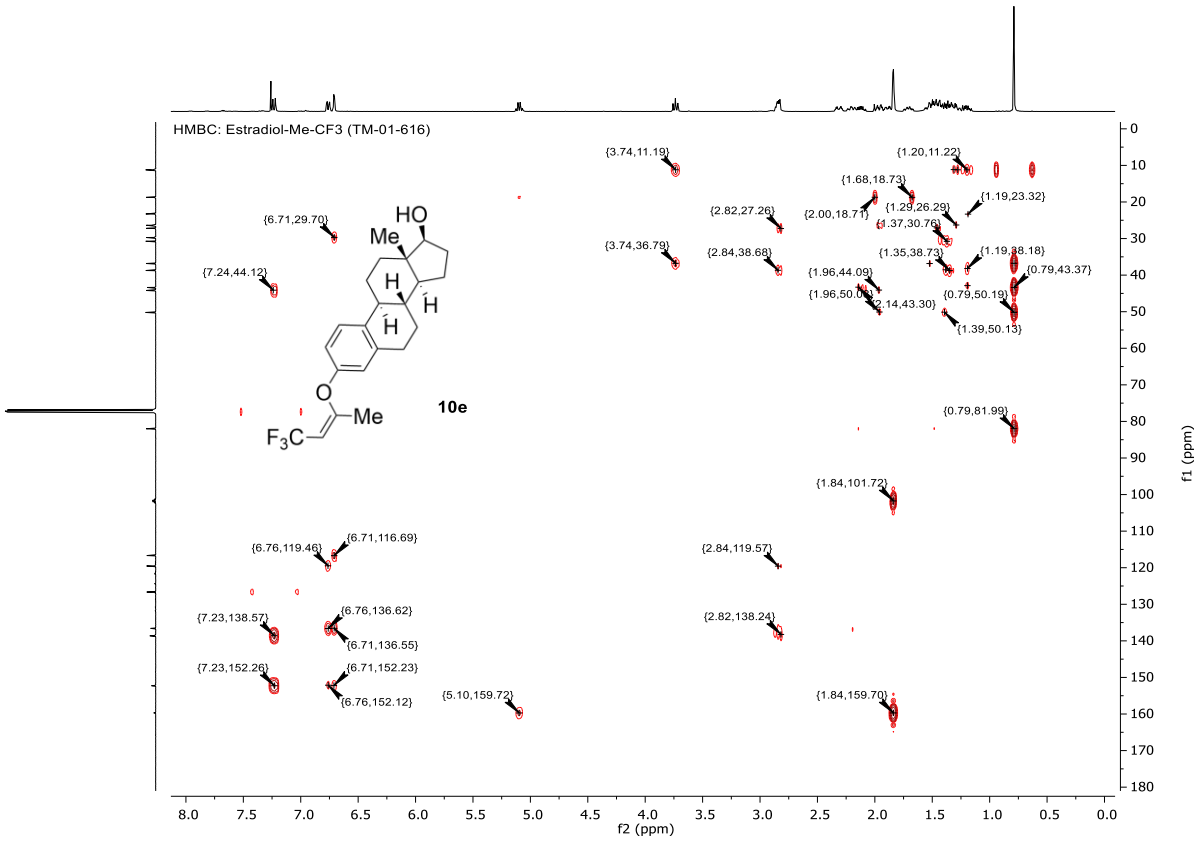
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(8*R*,9*S*,13*S*,14*S*,17*S*)-3-(((*Z*)-6-Chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (10f)

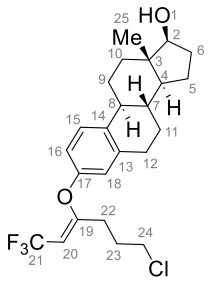
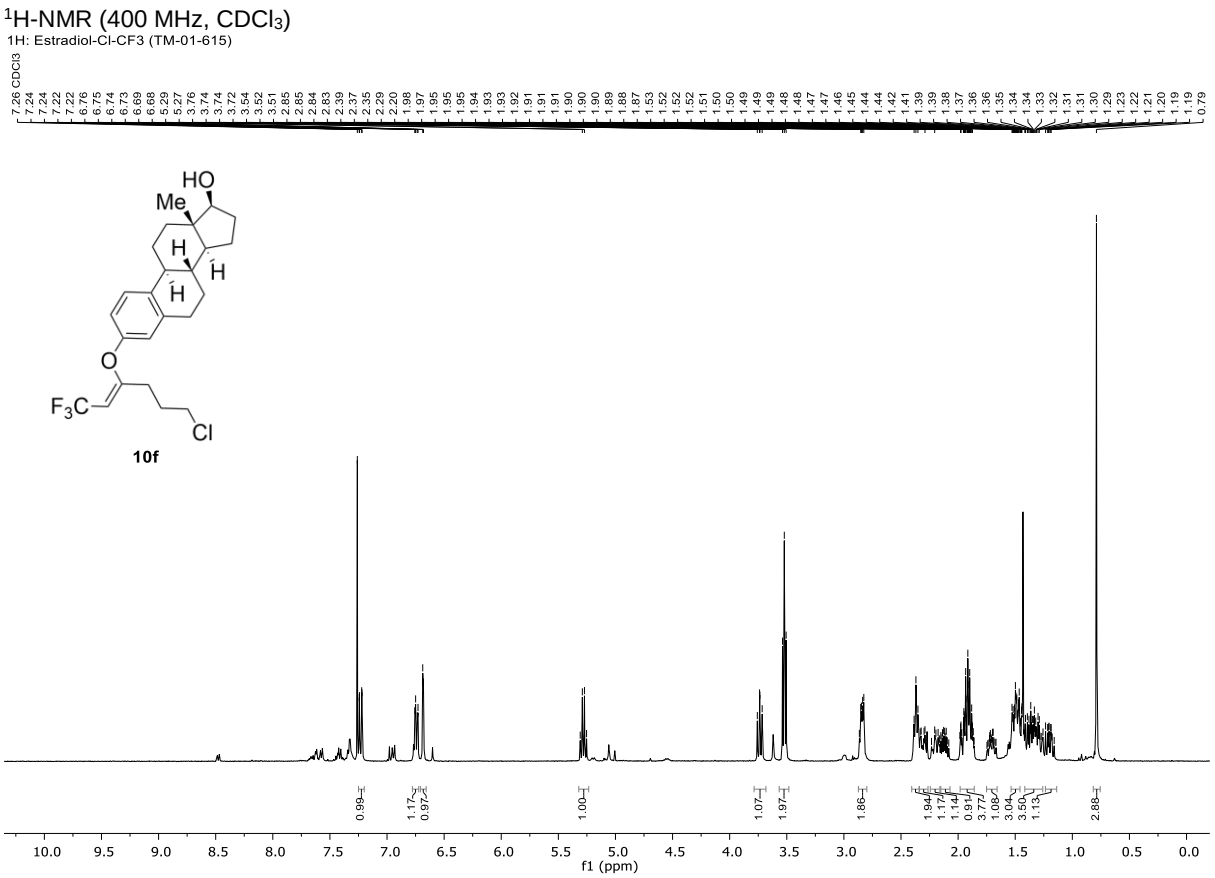


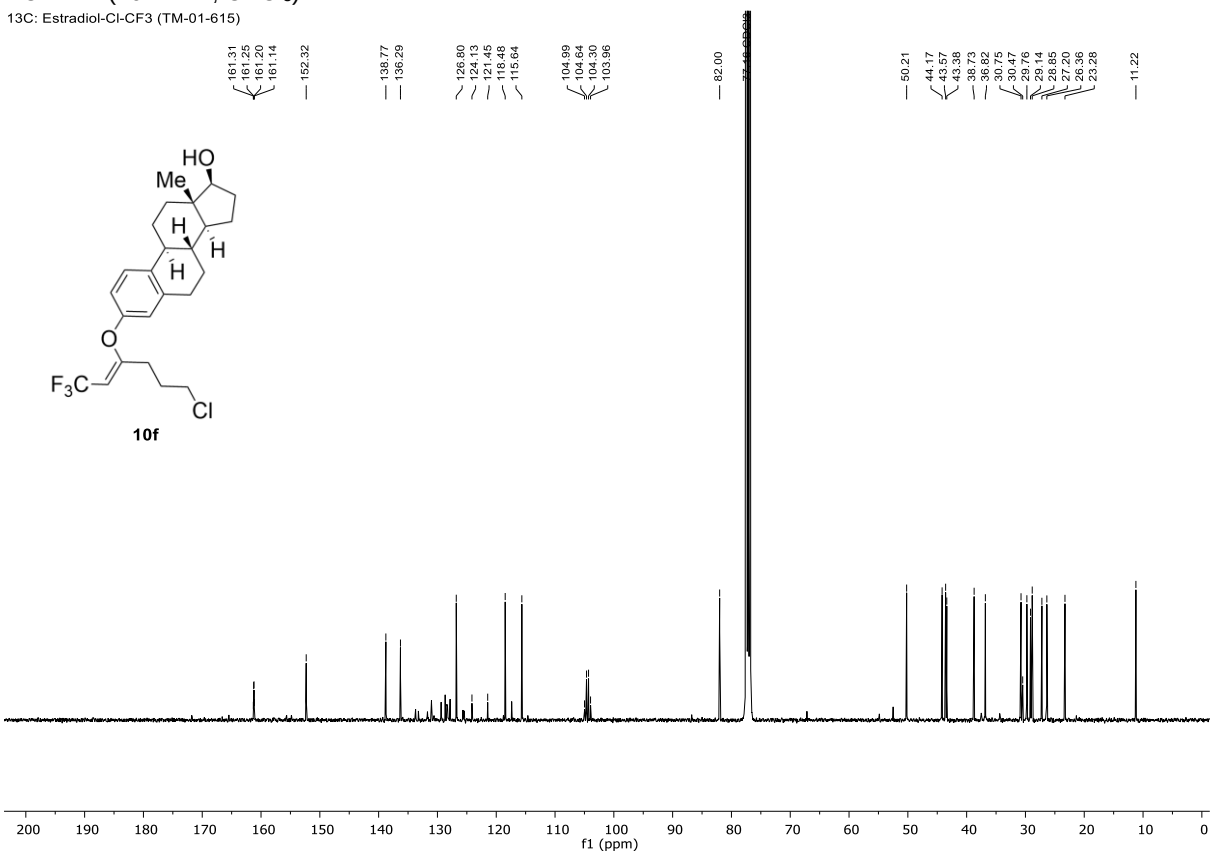
Table S51. Detailed NMR assignment of (8*R*,9*S*,13*S*,14*S*,17*S*)-3-(((*Z*)-6-chloro-1,1,1-trifluorohex-2-en-3-yl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (**10f**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	not observed		
2	82.0	3.74 (dd, 9.0, 8.0 Hz)	6	10, 25
3	43.6			
4	50.2	1.24-1.14 (m)		
5	23.3	1.71 (dddd, 12.4, 9.9, 7.0, 3.1 Hz) 1.56-1.44 (m) or 1.42-1.26 (m)		
6	30.8	2.12 (ddd, 13.0, 9.3, 5.4 Hz), 1.56-1.44 (m) or 1.42-1.26 (m)	2	
7	38.7	1.56-1.44 (m) or 1.42-1.26 (m)		
8	44.2	2.24-2.16 (m)		
9	26.4	2.31 (dd, 13.4, 3.3 Hz), 1.56-1.44 (m) or 1.42-1.26 (m)	10	
10	36.9	1.99-1.85 (m) 1.56-1.44 (m) or 1.42-1.26 (m)	9	
11	27.2	1.99-1.85 (m) 1.56-1.44 (m) or 1.42-1.26 (m)		
12	30.5	2.84 (dd, 7.6, 3.3 Hz)		
13	138.8			
14	136.3			
15	126.8	7.23 (dd, 8.56, 1.1 Hz)	16	8, 13, 17
16	115.6	6.74 (dd, 8.4, 2.8 Hz)	15	14, 17, 18
17	152.3			
18	118.5	6.68 (d, 2.6 Hz)		12, 16, 14, 17
19	161.2 (q, 5.6 Hz)			
20	104.5 (q, 34.5 Hz)	5.28 (q, 7.4 Hz)		19
21	122.8 (269.7 Hz)			
22	29.1	2.41-2.32 (m)	23	19, 20, 23
23	28.8	1.99-1.85 (m)	22, 24	19, 22, 24
24	43.4	3.52 (t, 6.3 Hz)	23	22
25	11.2	0.79 (s)		2, 3, 4, 10

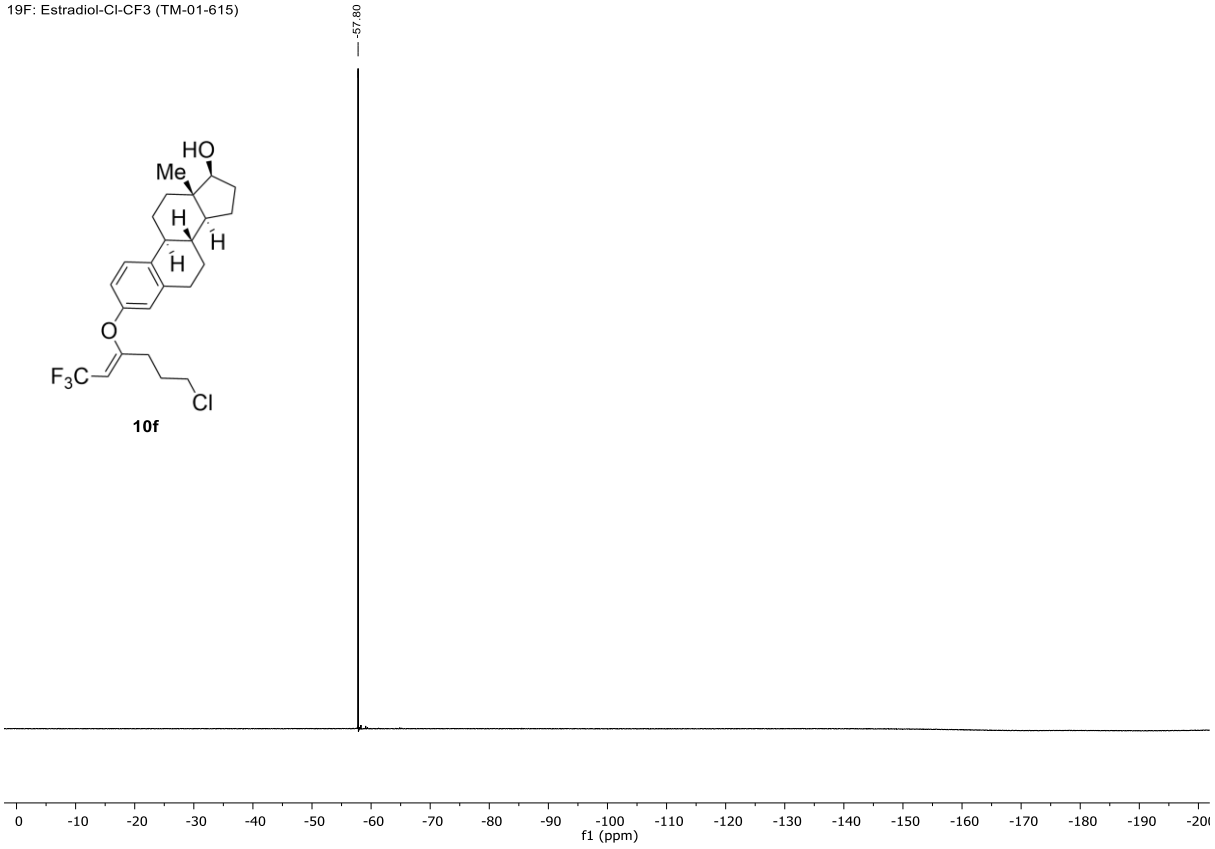
^{1}H-NMR (400 MHz, $CDCl_3$)



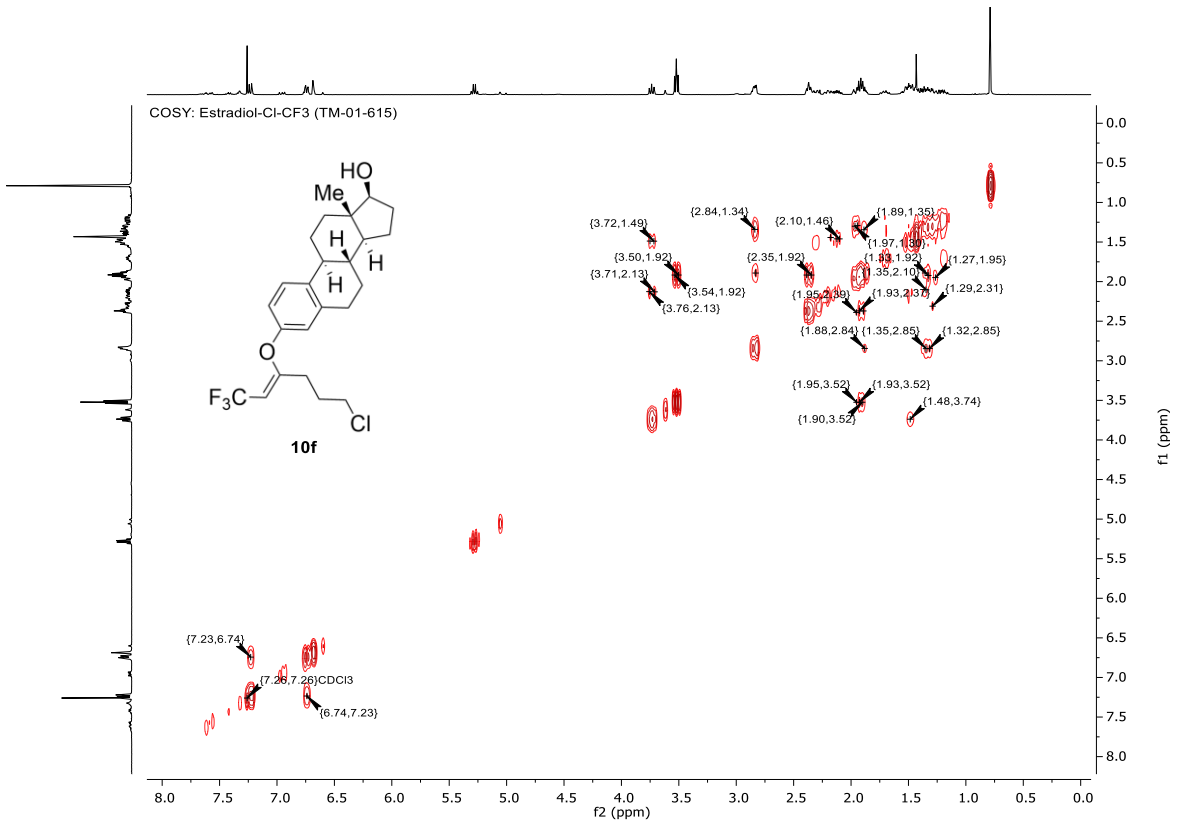
^{13}C-NMR (101 MHz, $CDCl_3$)



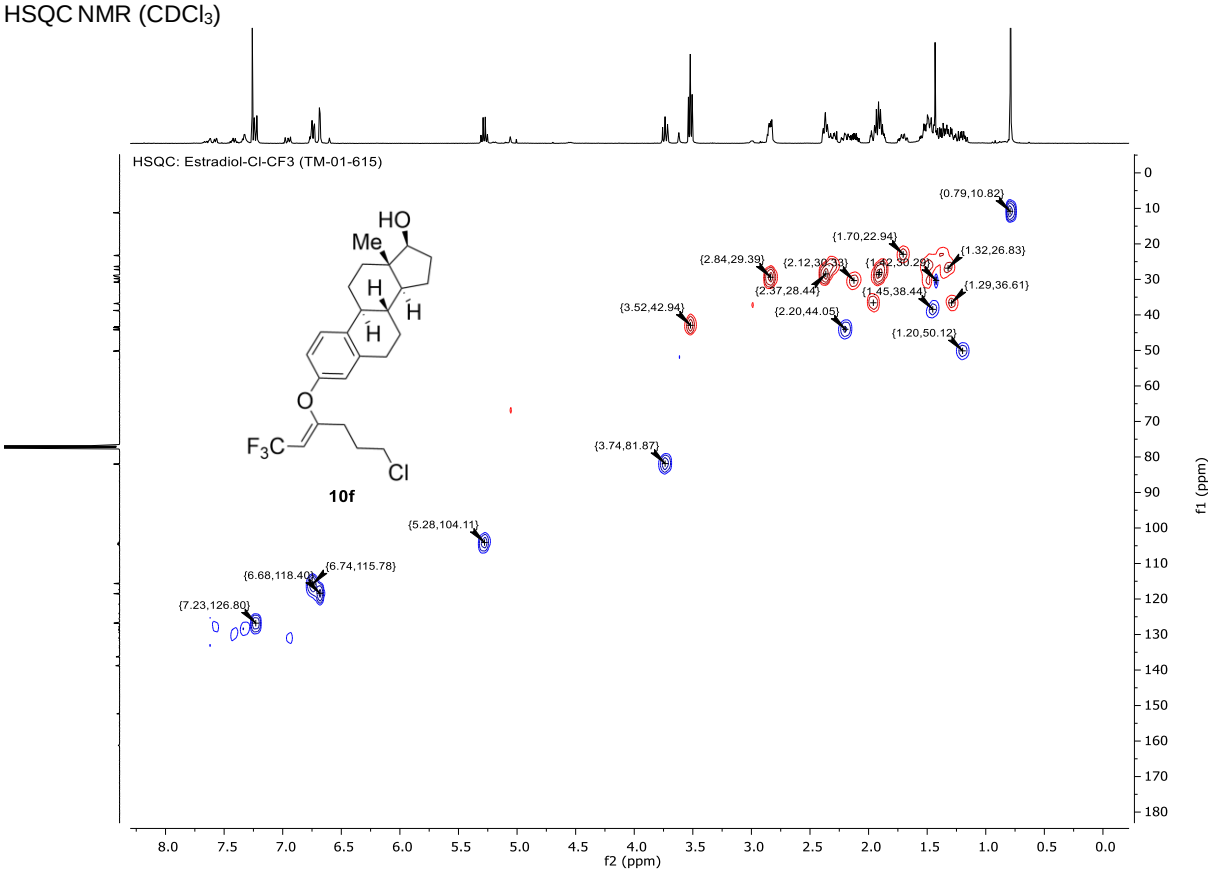
^{19}F-NMR (376 MHz, $CDCl_3$)



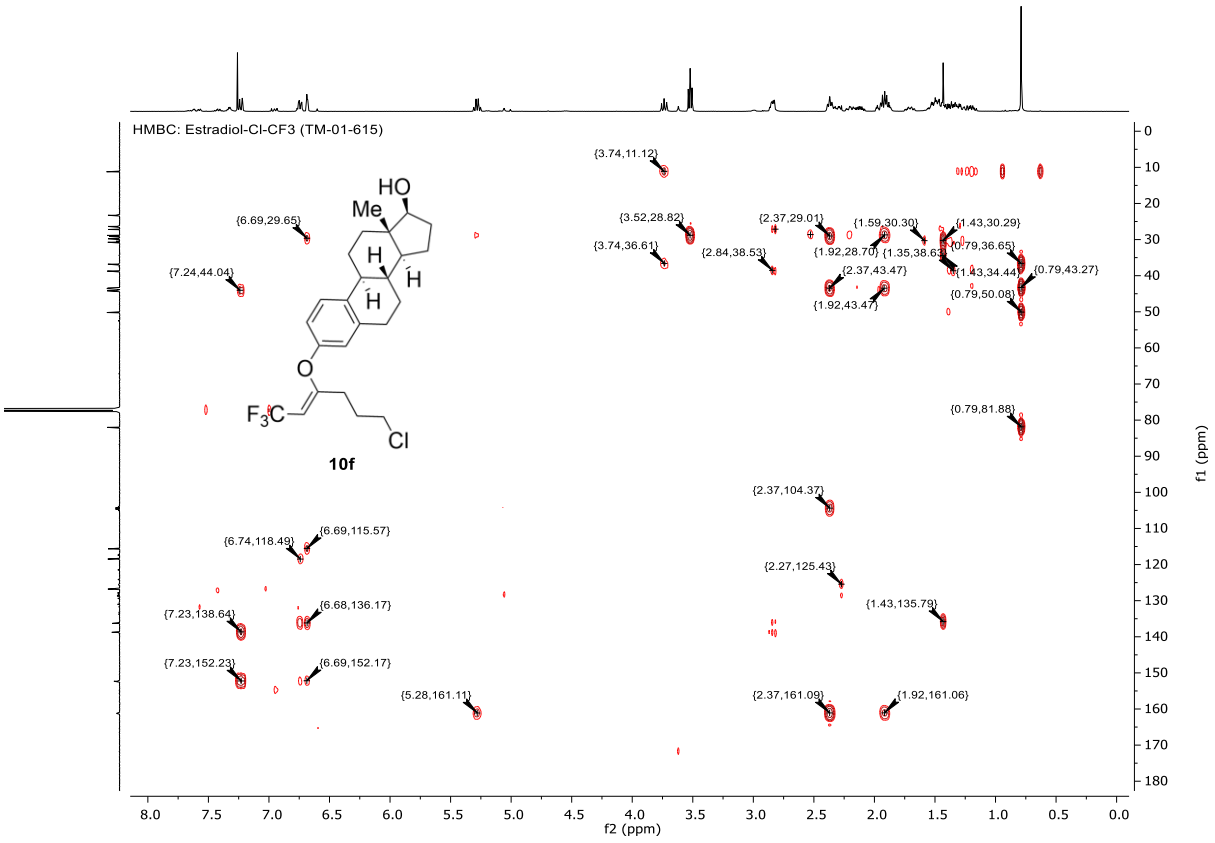
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



(*Z*)-*N*-Pentanoyl-*N*-((2'-(2-(4,4,4-trifluorobut-2-en-2-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-L-valine (10g)

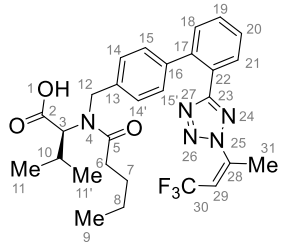
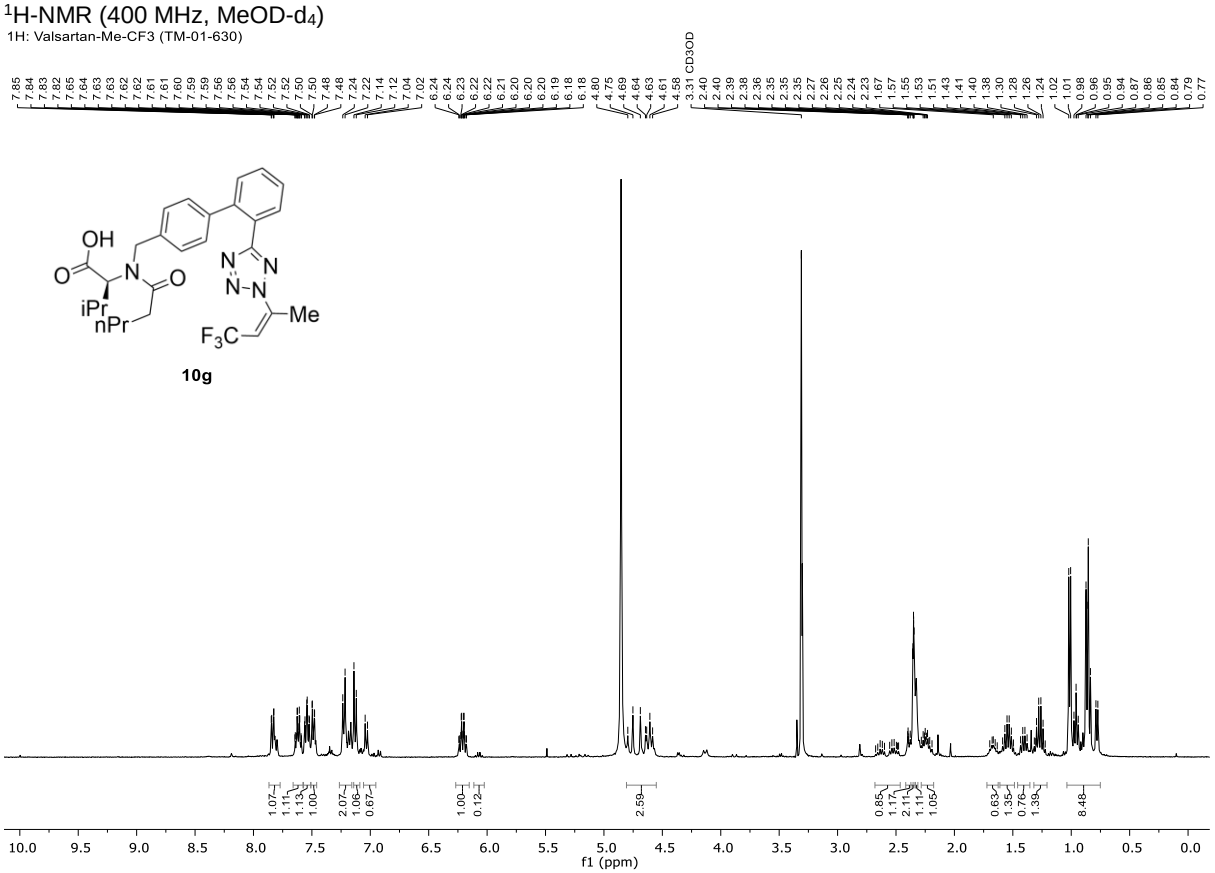


Table S52. Detailed NMR assignment of (*Z*)-*N*-Pentanoyl-*N*-((2'-(2-(4,4,4-trifluorobut-2-en-2-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-L-valine (**10g**).

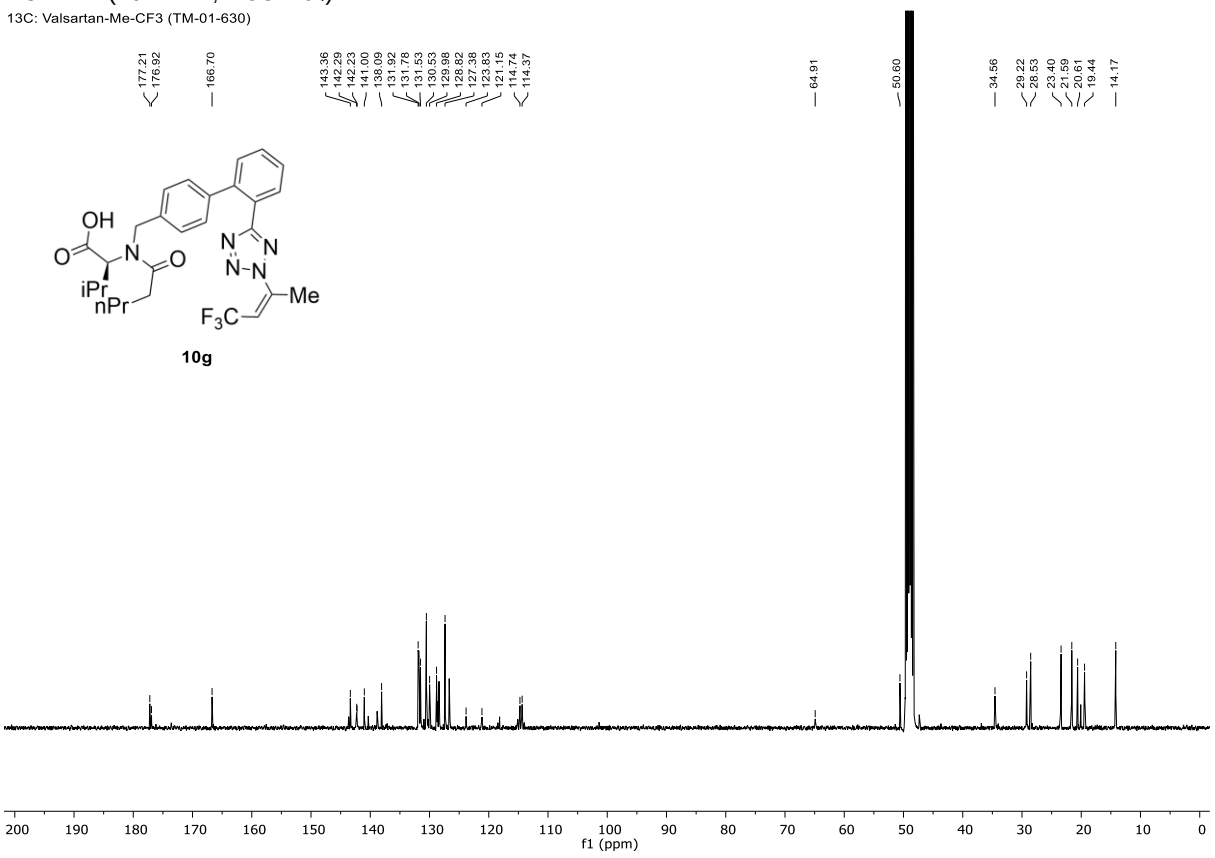
	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	176.9			
3	64.9	4.80-4.55 (m)	10	2
4	/			
5	177.2			
6	34.6	2.69-2.45 (m), 2.42-2.36 (m)		
7	28.5	1.73-1.63 (m), 1.54 (dq, 14.5, 7.3 Hz)		
8	23.4	1.41 (q, 7.4 Hz), 1.27 (h, 7.4 Hz)	9	6, 7, 9
9	14.2	0.96 (t, 7.3 Hz), 0.89-0.76 (m)	8	7, 8
10	29.2	2.29-2.18 (m)	3, 11/11‘	2
11/11’	20.6, 19.4	1.01 (d, 6.4 Hz), 0.89-0.76 (m)	10	3, 10
12	50.6	4.80-4.55 (m)		13, 14/14’
13	138.1			
14/14’	127.4	7.23 (d, 7.9 Hz)		12, 16
15/15’	130.5	7.13 (d, 8.0 Hz), 7.03 (d, 7.9 Hz)		13
16	141.0			
17	130.0			
18	128.8	7.54 (td, 7.6, 1.4 Hz)		15/15’, 20
19	131.9	7.52-7.45 (m)		16
20	131.6	7.84 (dd, 7.7, 1.5 Hz)		19, 22, 23
21	131.6	7.67-7.58 (m)		20, 22
22	143.4			
23	166.7			
24	/			
25	/			
26	/			
27	/			
28	142.3 (q, 5.8 Hz)			
29	114.6 (q, 37.1 Hz)	6.21 (qq, 8.2, 1.6 Hz)	31	
30	122.5 (q, 269.6 Hz)			
31	21.6	2.38-2.30 (m)	29	28, 29

^{1}H-NMR (400 MHz, MeOD-d$_4$)



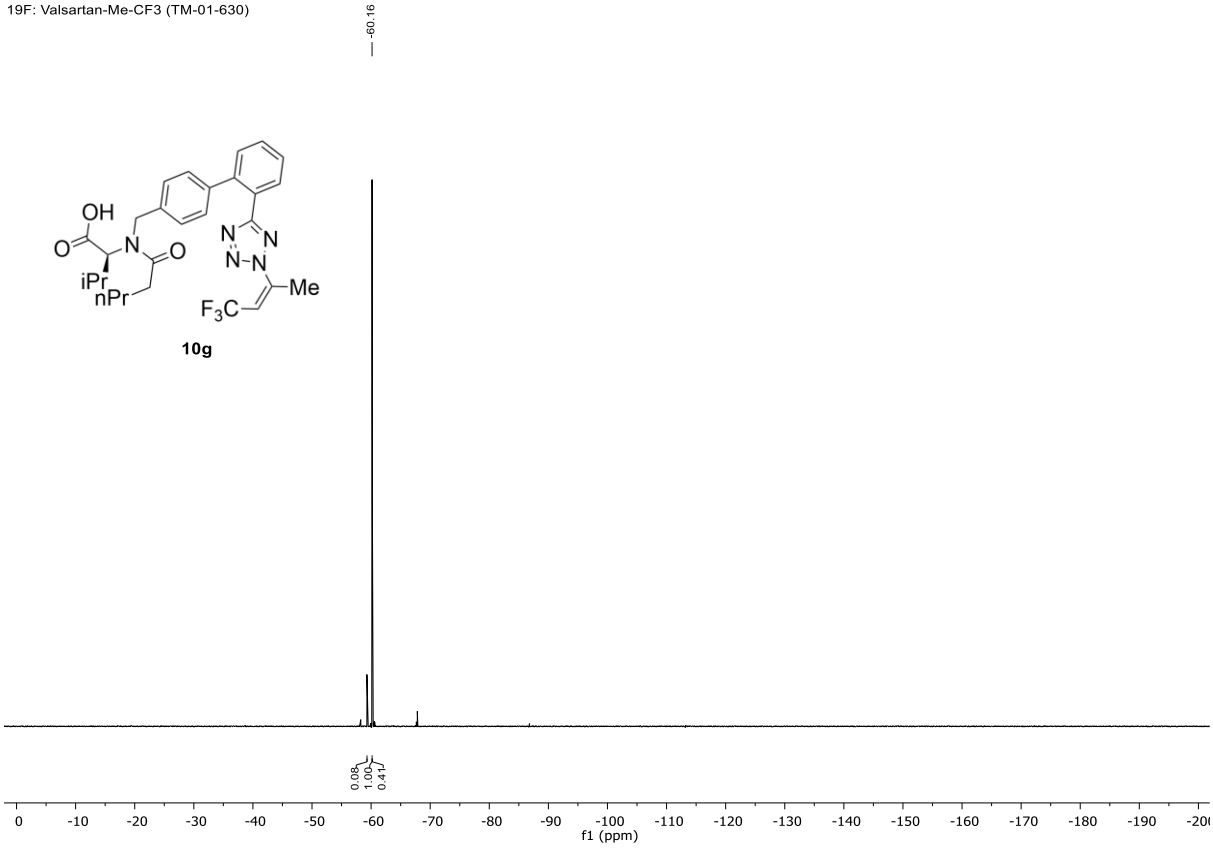
10g

^{13}C-NMR (101 MHz, MeOD-d$_4$)

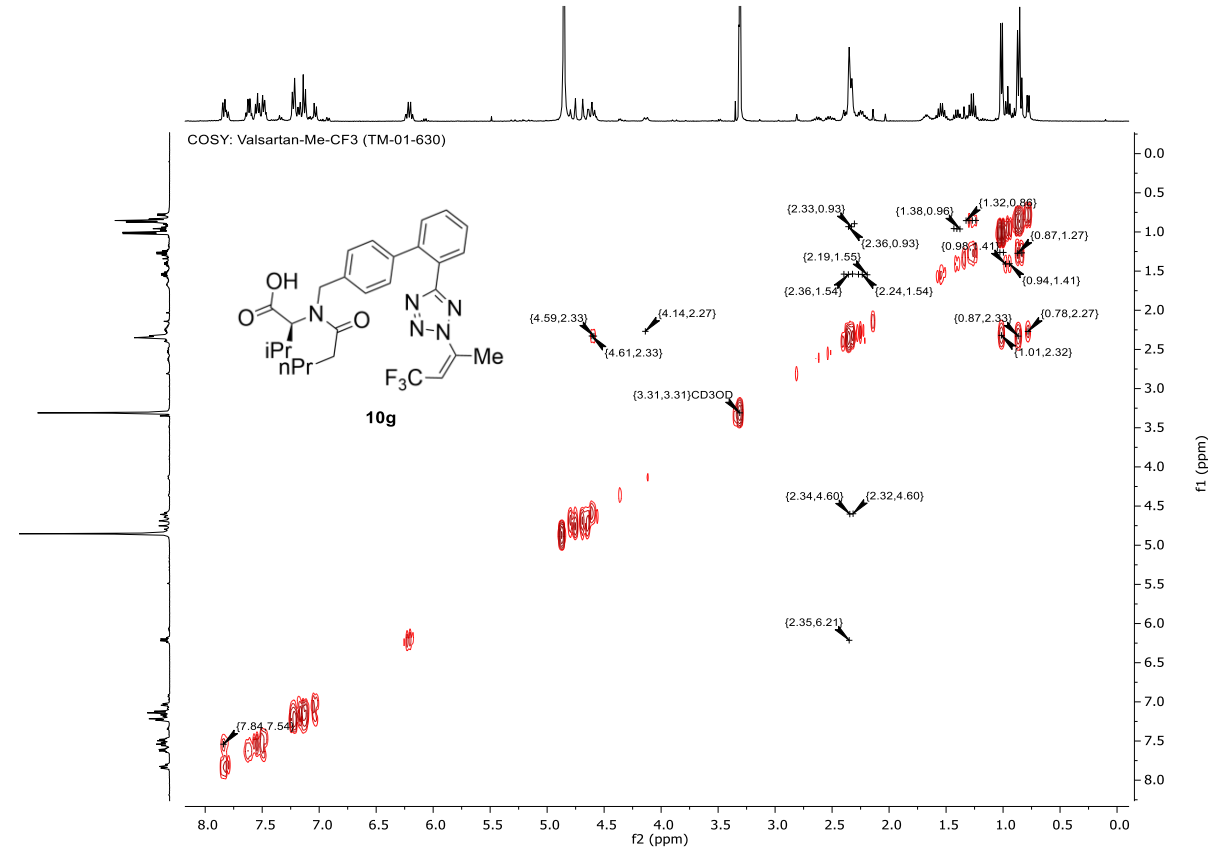


10g

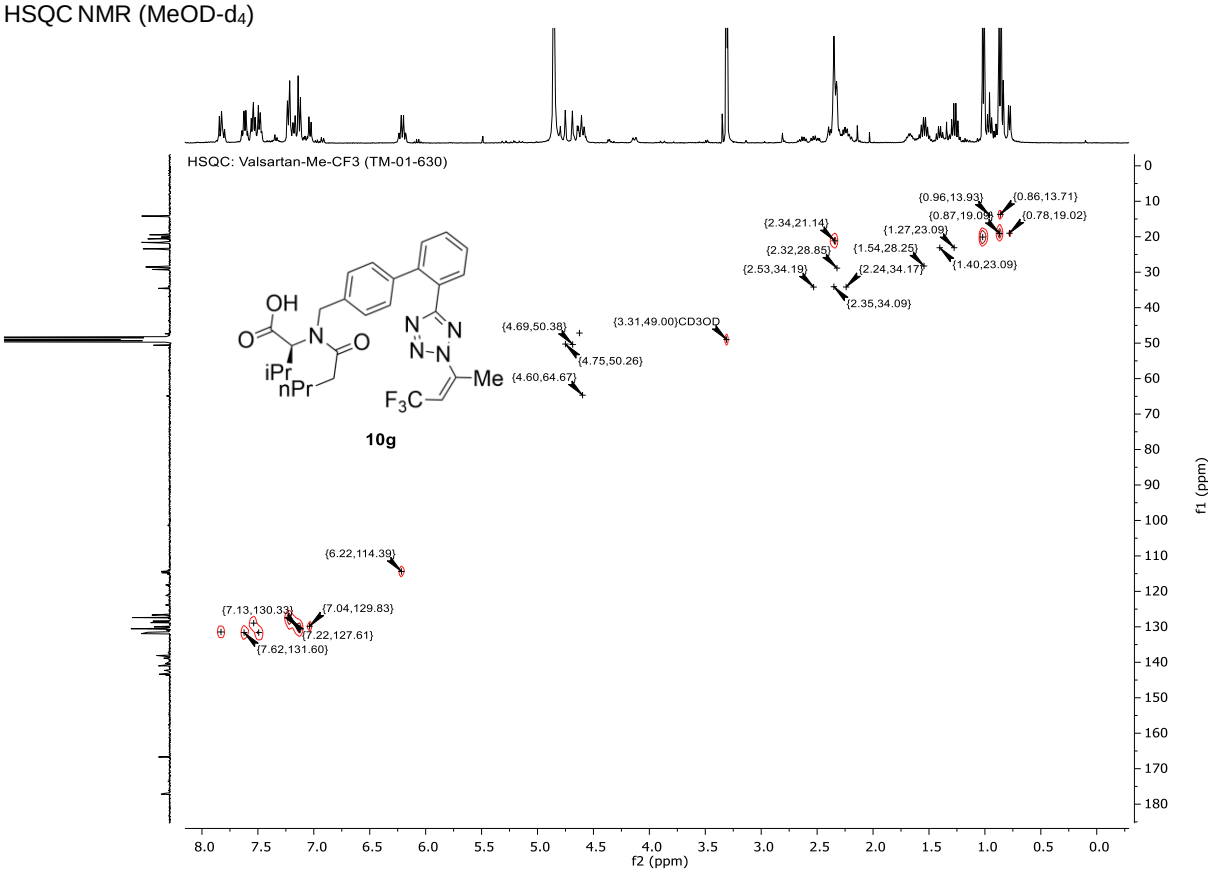
^{19}F-NMR (376 MHz, MeOD-d$_4$)



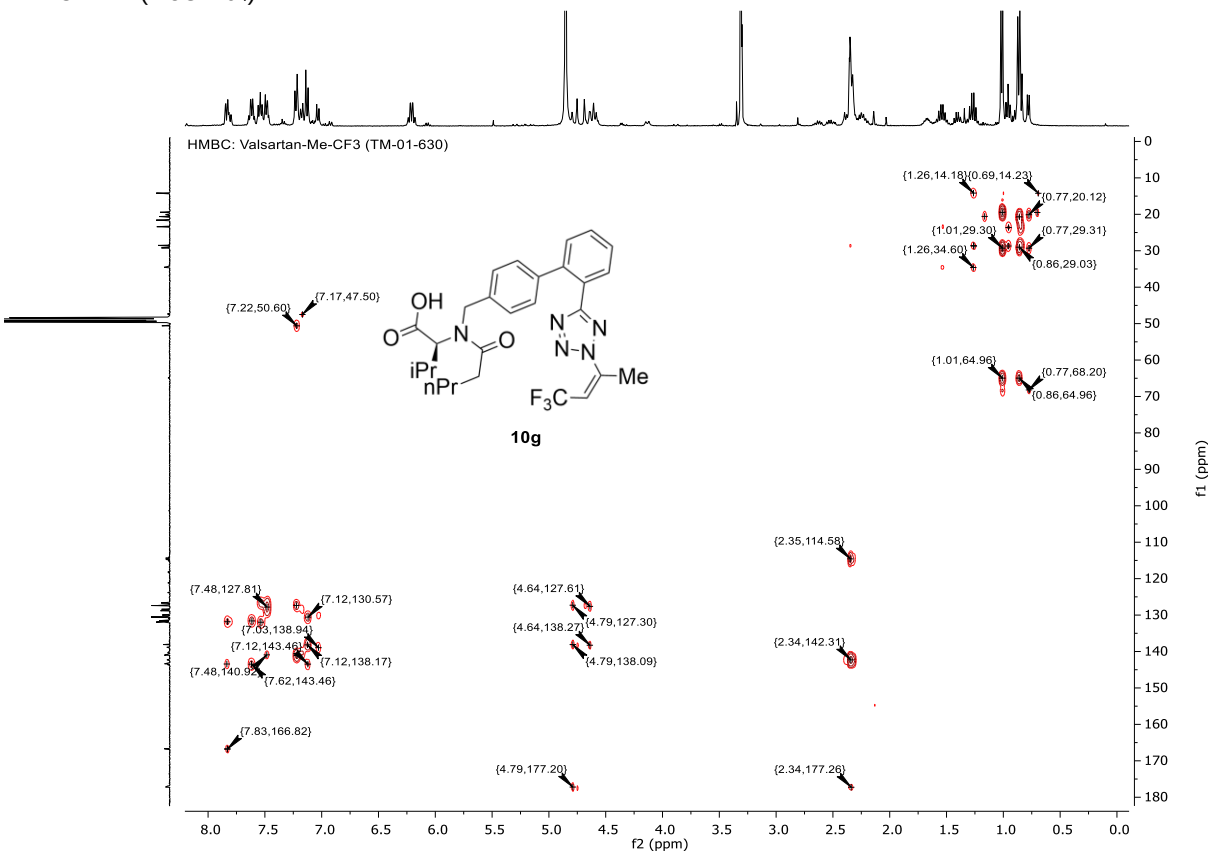
COSY NMR (MeOD-d$_4$)



HSQC NMR (MeOD-d_4)



HMBC NMR (MeOD-d_4)



(*Z*)-*N*-((2'-(2-(6-Chloro-1,1,1-trifluorohex-2-en-3-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-pentanoyl-L-valine (10h)

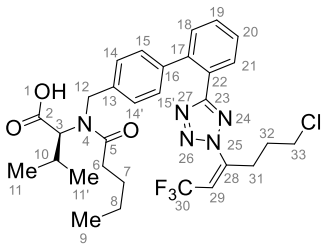
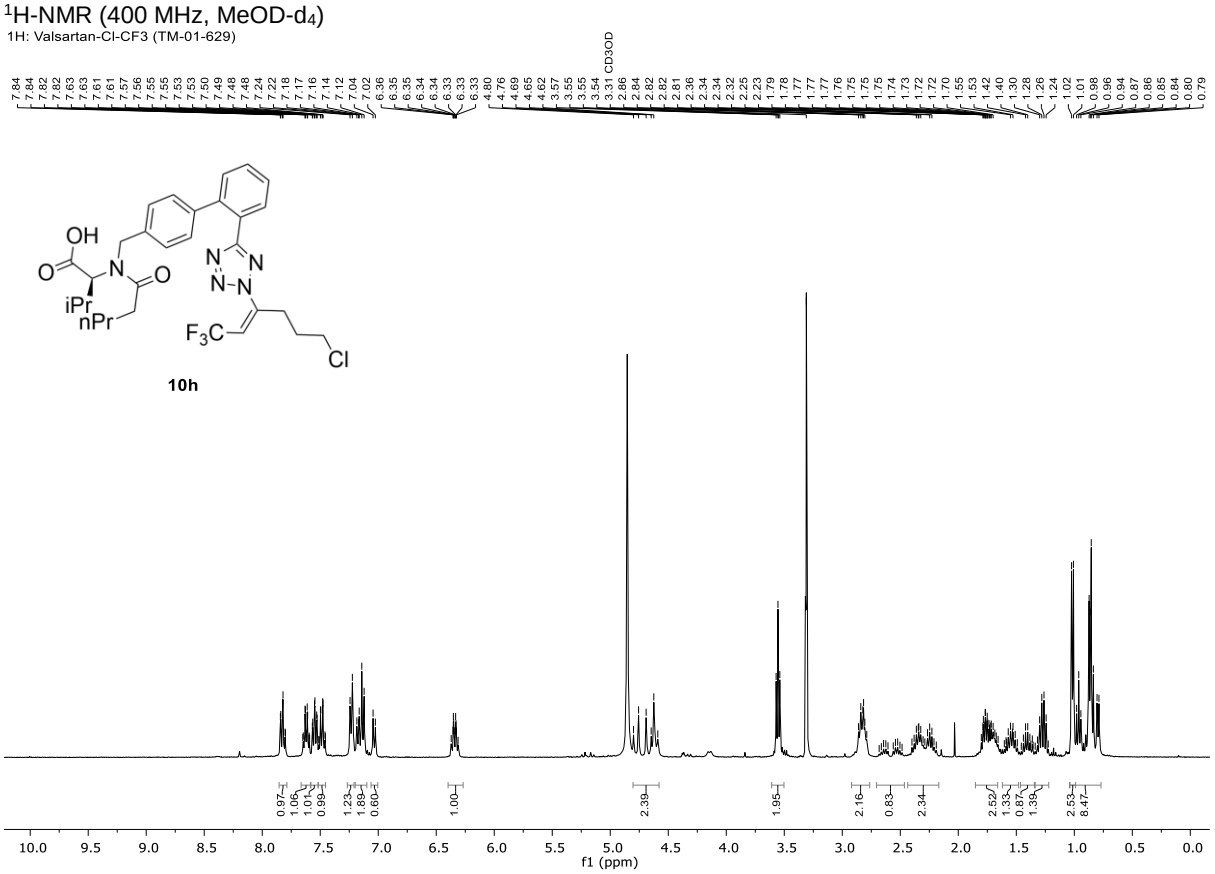


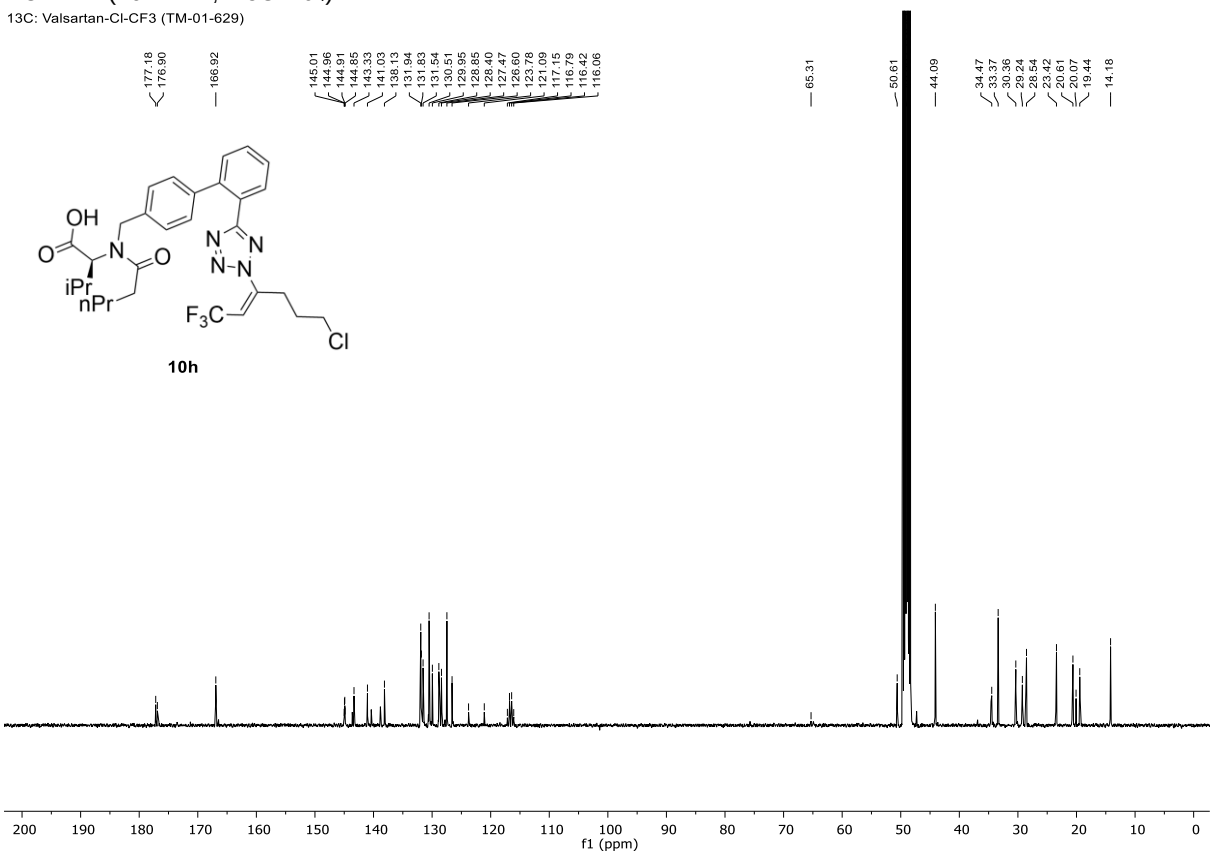
Table S53. Detailed NMR assignment of (*Z*)-*N*-((2'-(2-(6-chloro-1,1,1-trifluorohex-2-en-3-yl)-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-pentanoyl-L-valine (**10h**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	/	exchange with solvent		
2	176.9			
3	65.3	4.80-4.58 (m)		2
4	/			
5	177.2			
6	34.5	2.44-2.18 (m)		5
7	29.2	1.86-1.64 (m), 1.55 (dp, 14.9, 7.3 Hz)		
8	23.4	1.41 (dq, 15.9, 7.8 Hz), 1.27 (h, 7.4 Hz)		6, 9, 10
9	14.2	0.96 (t, 7.3 Hz), 0.89-0.78 (m)		7, 8
10	28.5	2.58 (dt, 15.1, 7.4 Hz)		
11/11'	20.6, 19.4	1.02 (d, 6.3 Hz), 0.89-0.78 (m)		3, 10
12	50.6	4.80-4.58 (m)		13, 15/15'
13	138.1			
14/14'	130.5	7.23 (d, 8.0 Hz), 7.19-7.11 (m)		12, 13, 15/15'
15/15'	127.5	7.19-7.11 (m), 7.03 (d, 7.9 Hz)		13, 14/14', 16
16	143.3			
17	128.8			
18	126.6	7.55 (td, 7.5, 1.4 Hz)	20	19
19	131.9	7.48 (td, 7.8, 1.3 Hz)	20	17, 22
20	130.0	7.91-7.75 (m)	18, 19	21, 23
21	131.8	7.62 (dtd, 8.3, 7.2, 1.5 Hz)		16, 19
22	141.0			
23	166.9			
24	/			
25	/			
26	/			
27	/			
28	144.9 (q, 5.5 Hz)			
29	116.6 (q, 36.1 Hz)	6.42-6.26 (m)		18, 31
30	122.4 (270.1 Hz)			
31	33.4	2.82 (dt, 11.1, 7.2 Hz)		28, 29, 32, 33
32	30.4	1.86-1.64 (m)	33	31, 33
33	44.1	3.55 (t, 6.4 Hz)	32	31

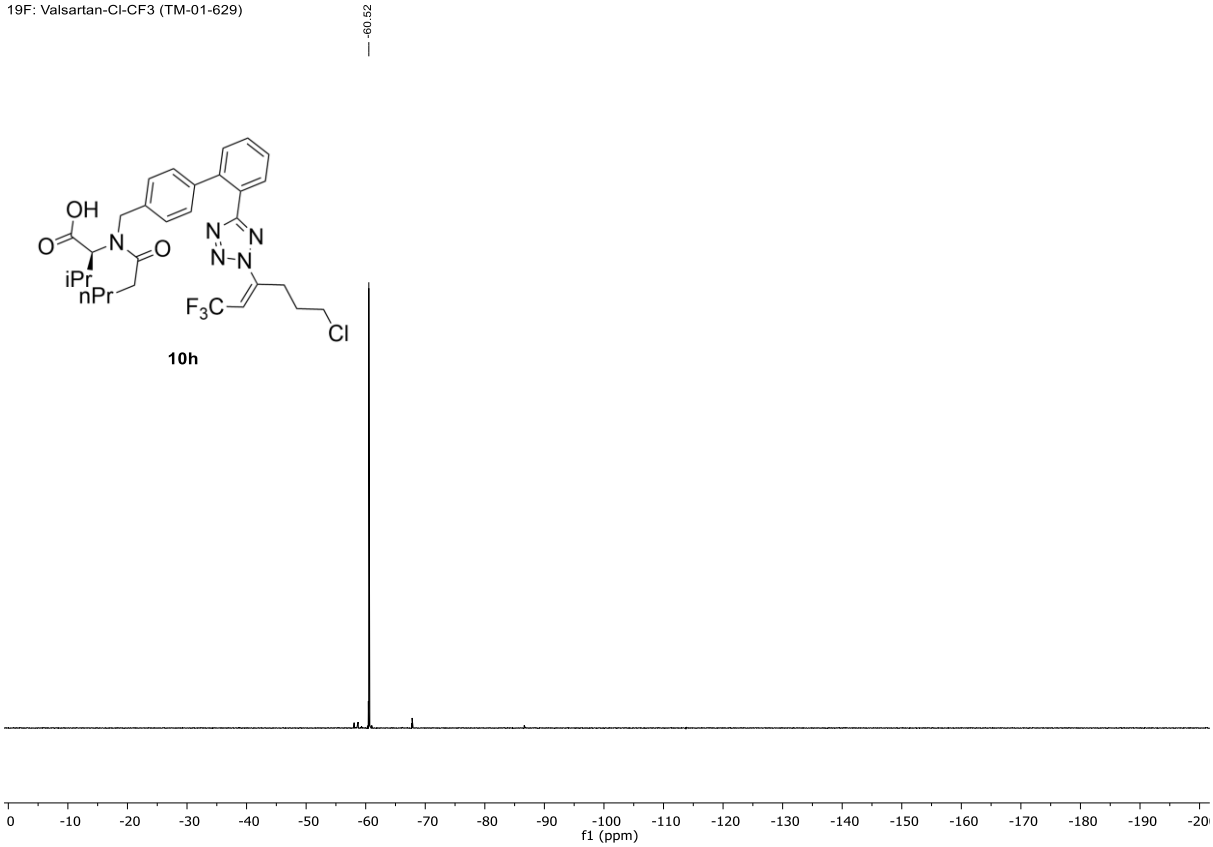
^{1}H-NMR (400 MHz, MeOD-d$_4$)



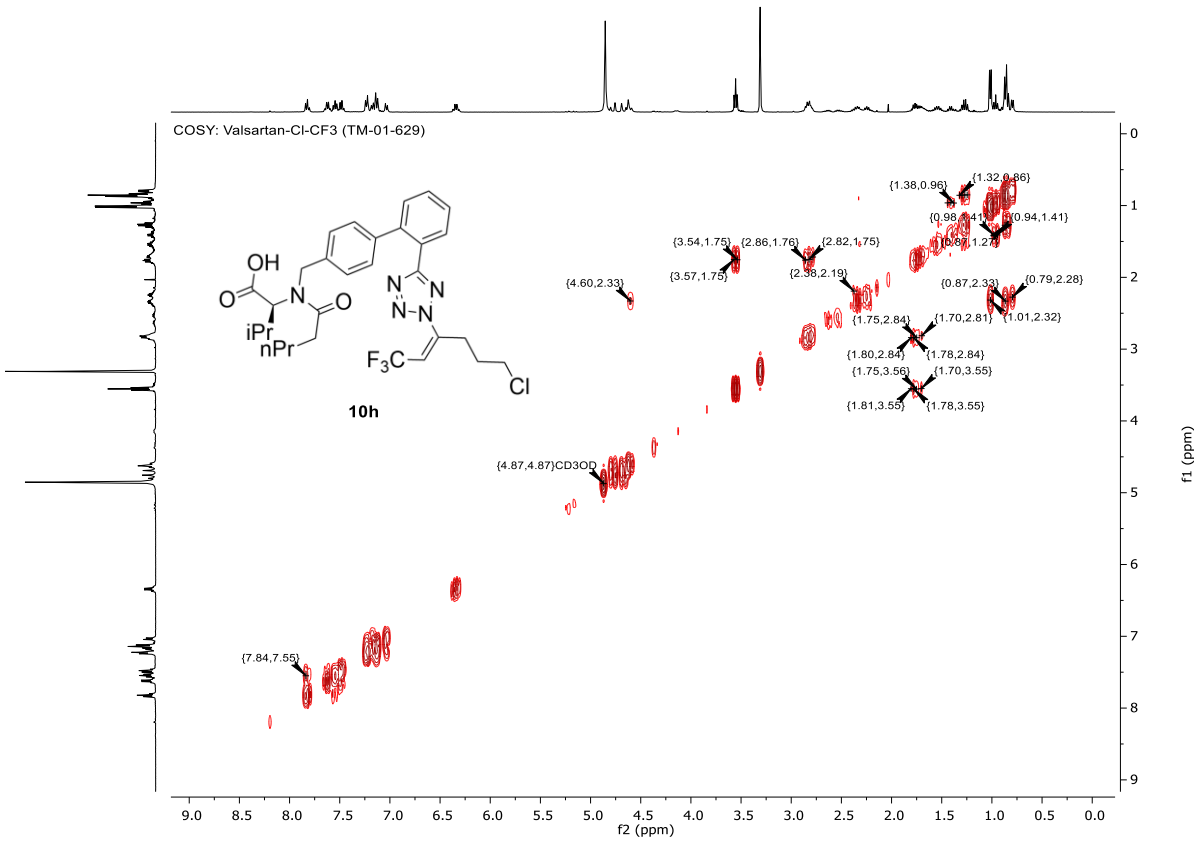
^{13}C-NMR (101 MHz, MeOD-d$_4$)



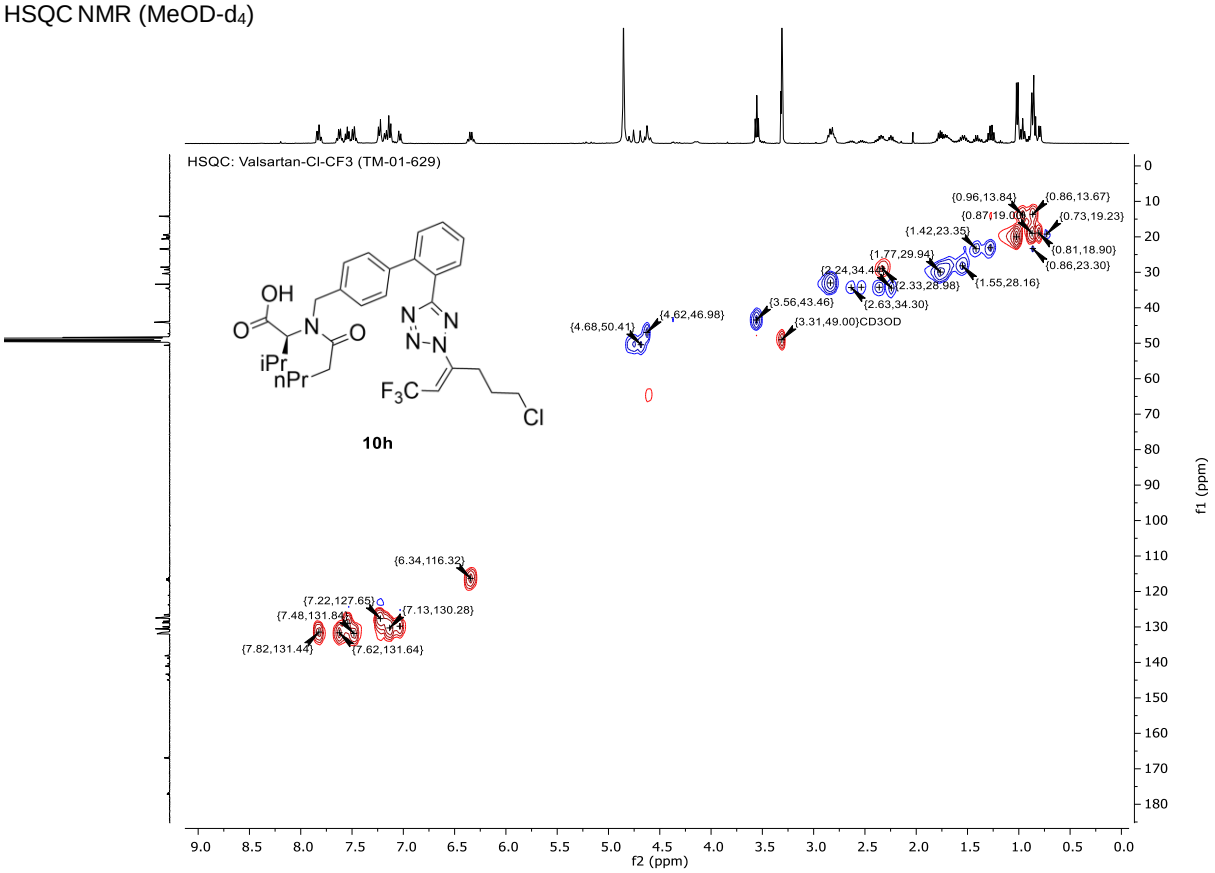
^{19}F-NMR (376 MHz, MeOD-d$_4$)



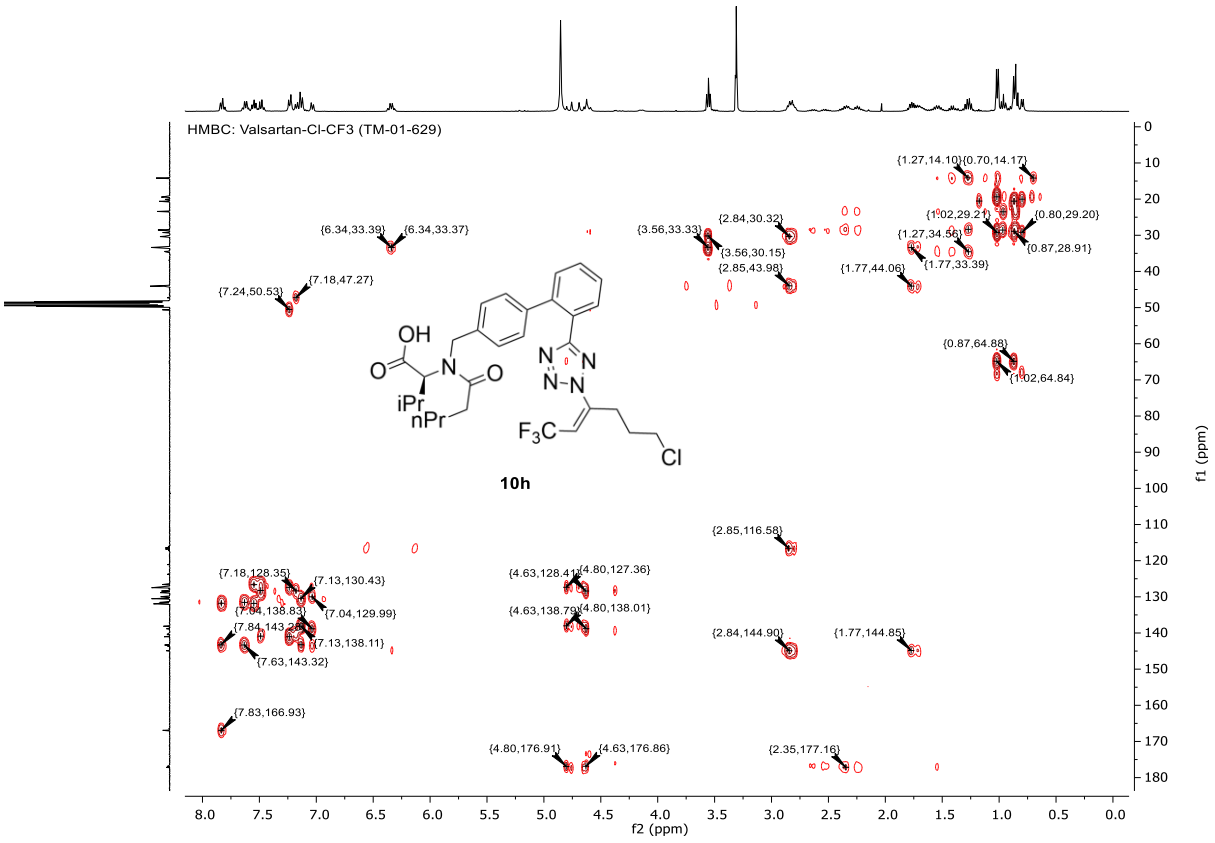
COSY NMR (MeOD-d$_4$)



HSQC NMR (MeOD-d_4)

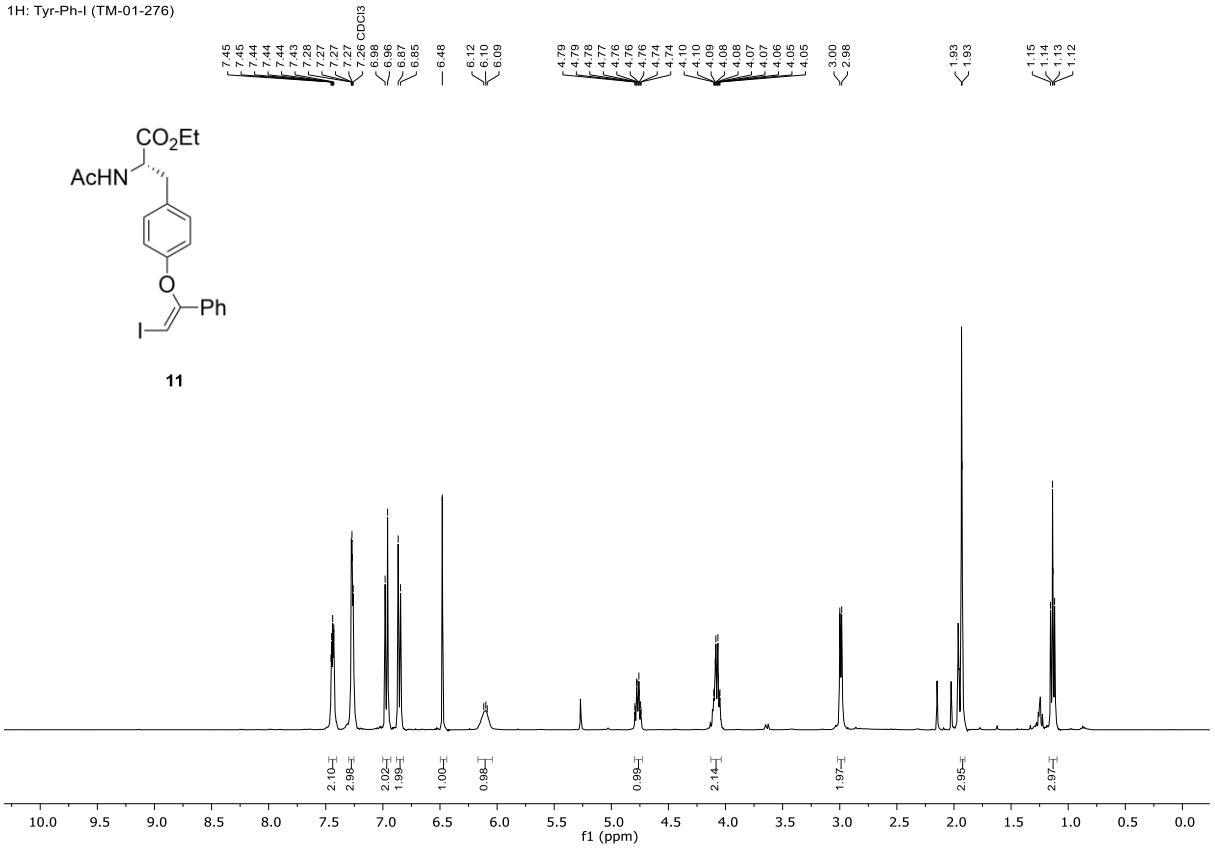


HMBC NMR (MeOD-d_4)

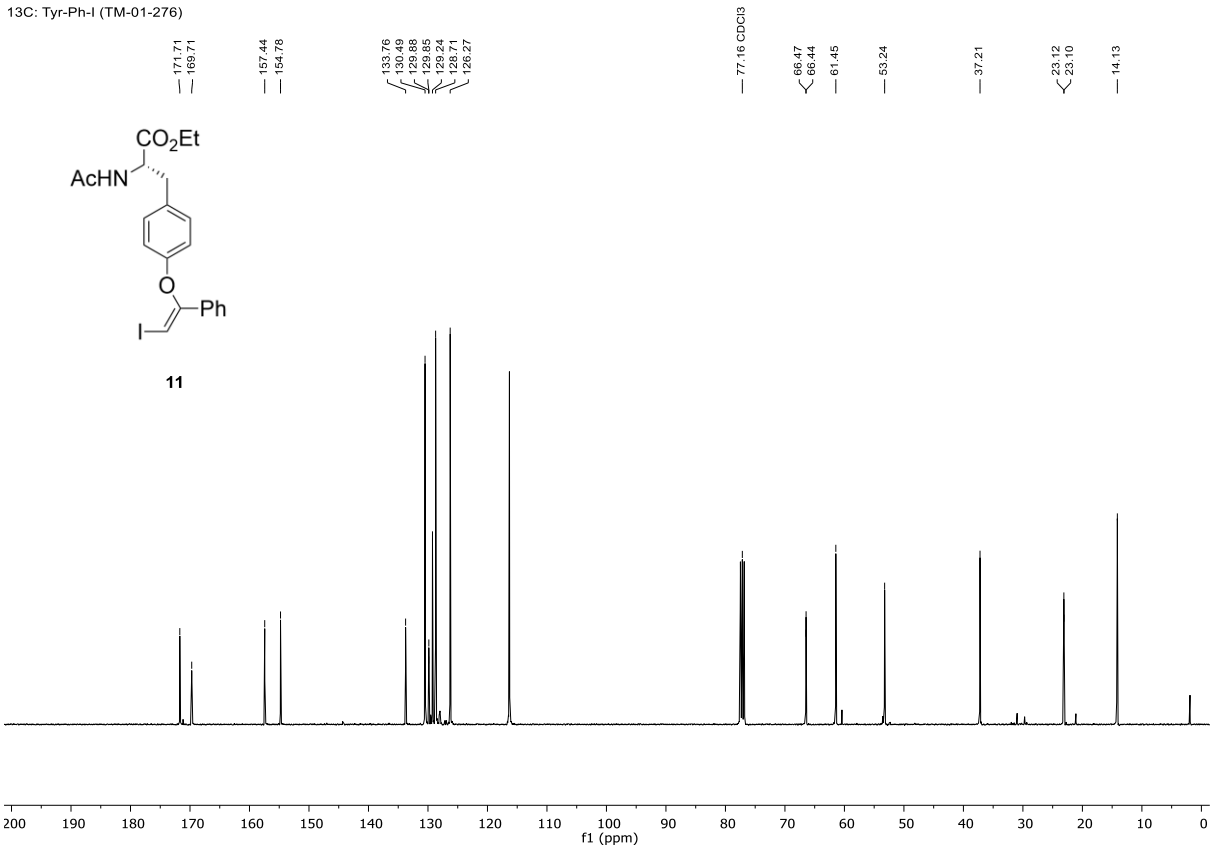


Ethyl (*S*,*Z*)-2-acetamido-3-(4-((2-iodo-1-phenylvinyl)oxy)phenyl)propanoate (11)

^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



Ethyl (2*S*)-2-acetamido-3-(4-((2-phenyl-3-(trifluoromethyl)oxiran-2-yl)oxy)phenyl)propanoate (12)

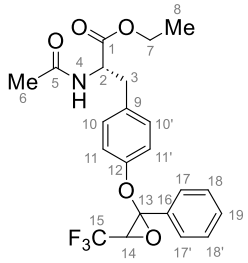
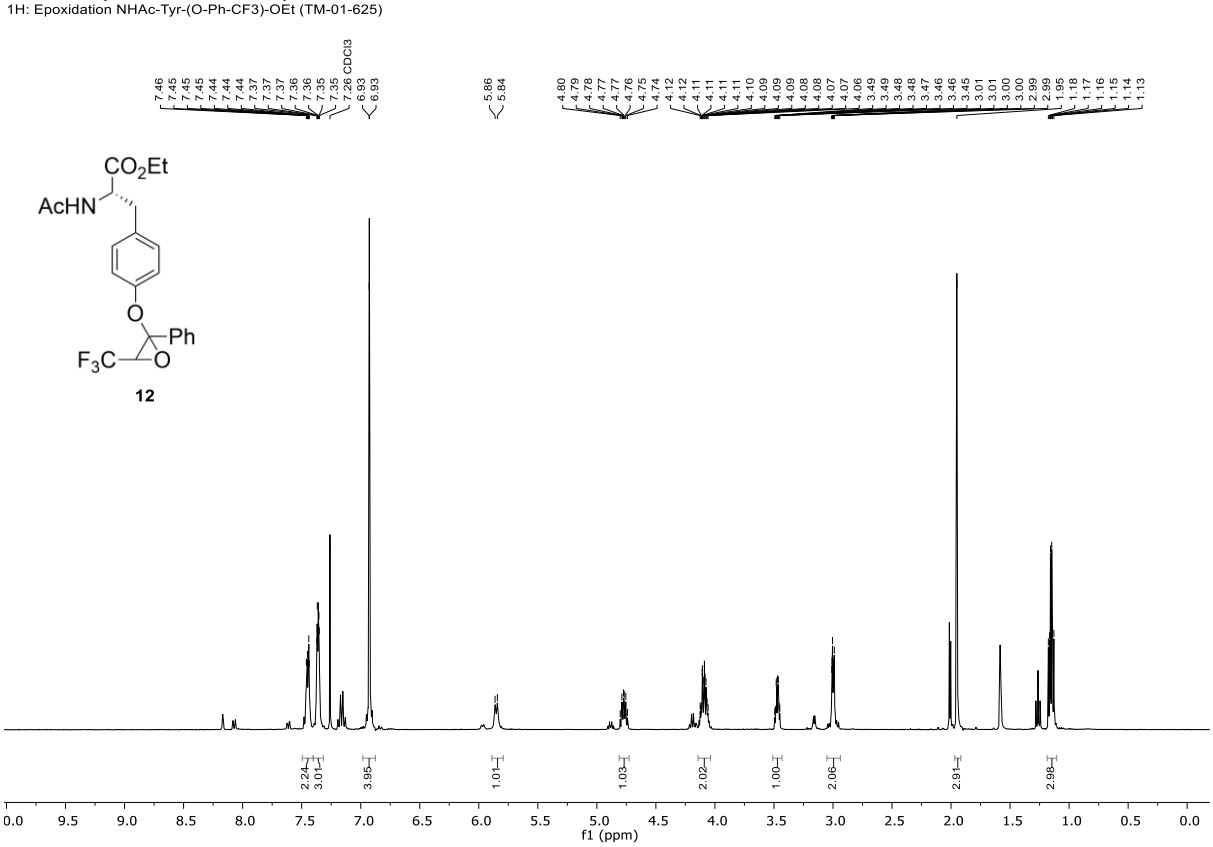


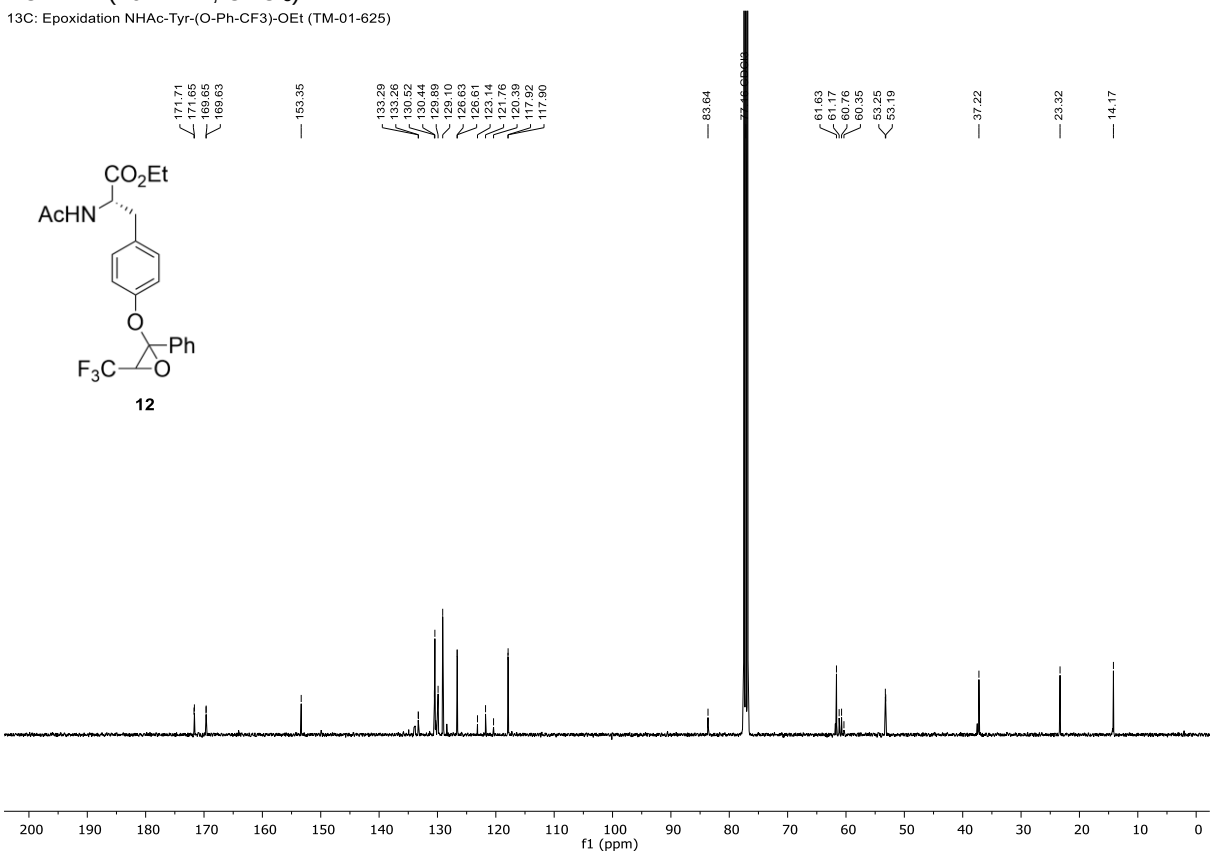
Table S54. Detailed NMR assignment of ethyl (2*S*)-2-acetamido-3-(4-((2-phenyl-3-(trifluoromethyl)oxiran-2-yl)oxy)phenyl)propanoate (**12**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.7			
2	53.2	4.77 (tdd, 7.2, 6.3, 5.1 Hz)	3, 4	1, 3, 9
3	37.2	3.05-2.90 (m)	2	1, 2, 10/10’
4	/	5.85 (d, 7.8 Hz)	2	5
5	169.6			
6	23.3	1.95 (s)		5
7	61.6	4.09 (tdd, 7.2, 6.3, 5.1 Hz)	8	1, 8
8	14.2	1.15 (td, 7.2, 4.2 Hz)	7	7
9	129.9			
10/10’	130.5	6.93 (d, 0.8 Hz)		12
11/11’	117.9	6.93 (d, 0.8 Hz)		10/10‘
12	153.5			
13	83.6			
14	61.0 (q, 41.3 Hz)	3.47 (qd, 4.9, 2.4 Hz)		15
15	123.1-120.4 (m)			
16	133.3			
17/17’	126.6	7.48-7.41 (m)		13,18/18’
18/18’	129.1	7.39-7.32 (m)		16, 17/17’
19	130.4	7.39-7.32 (m)		

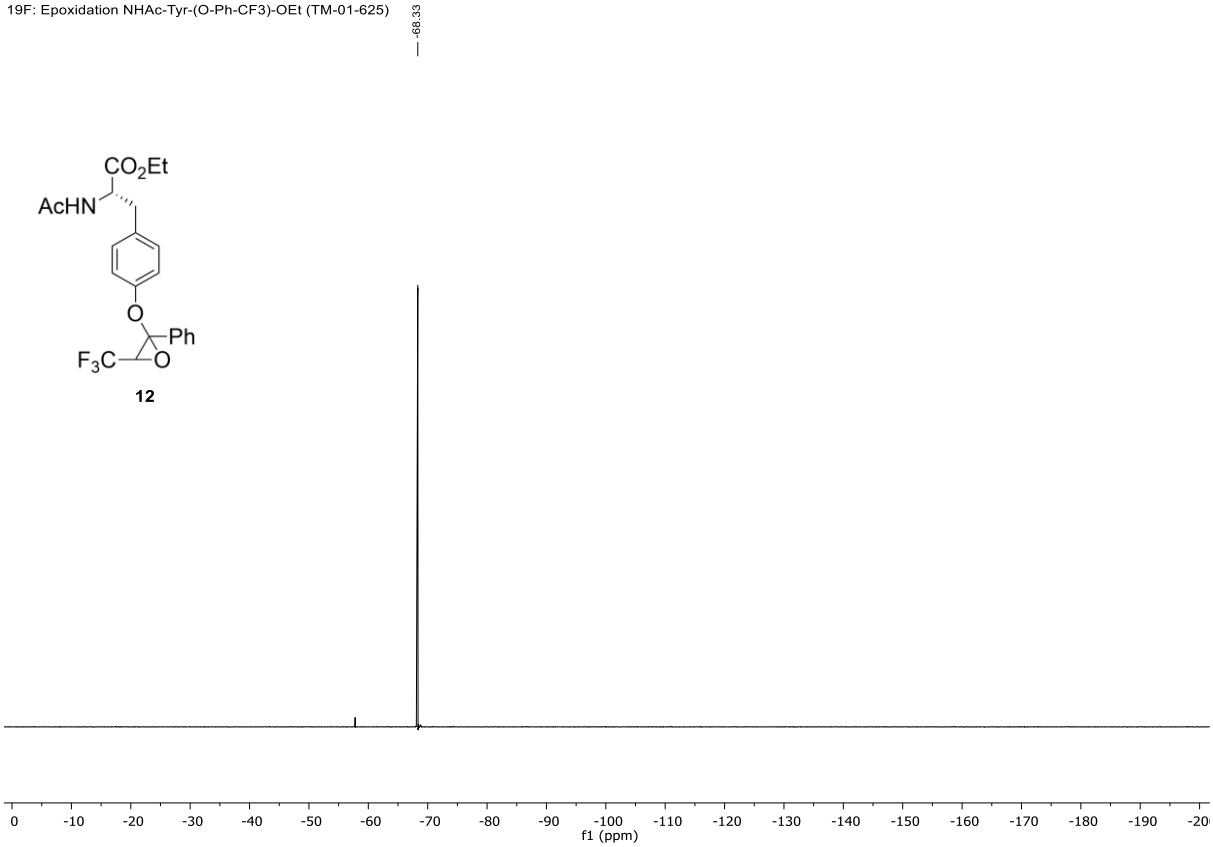
^{1}H-NMR (400 MHz, $CDCl_3$)



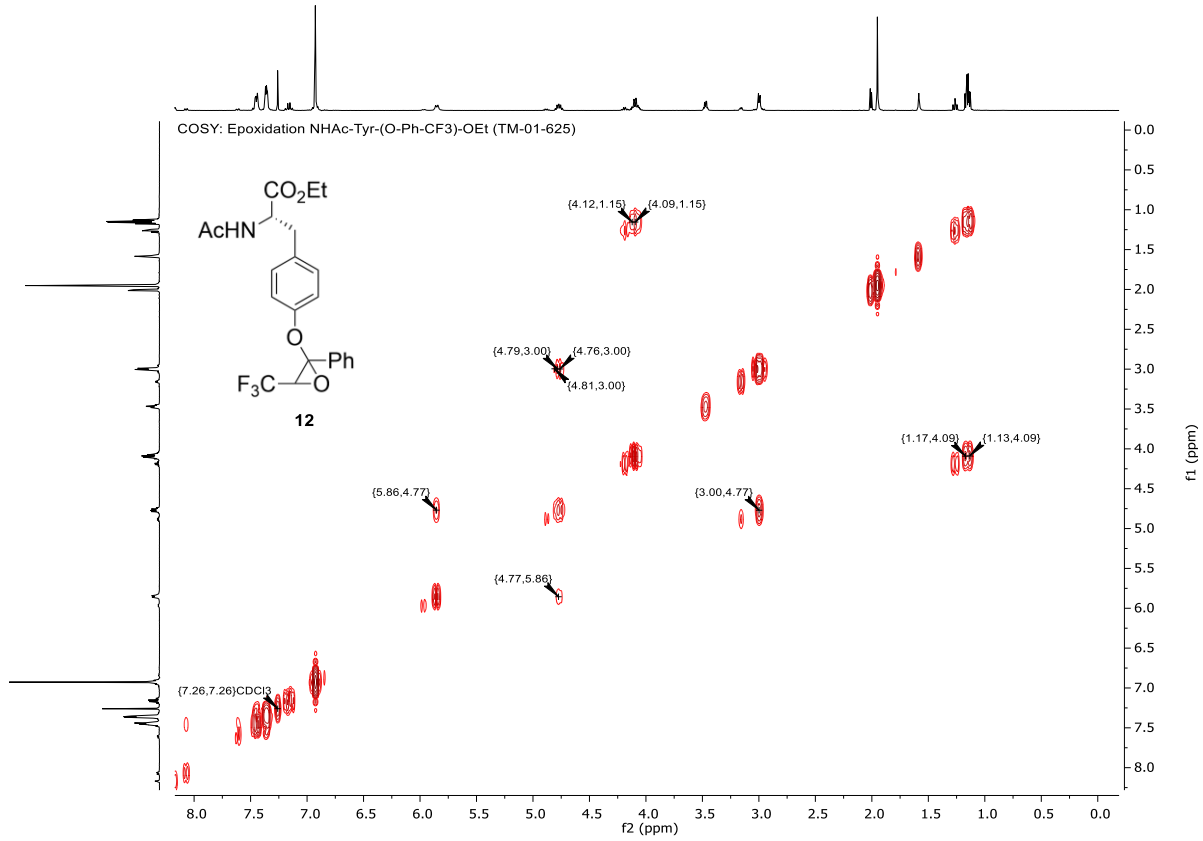
^{13}C-NMR (101 MHz, $CDCl_3$)



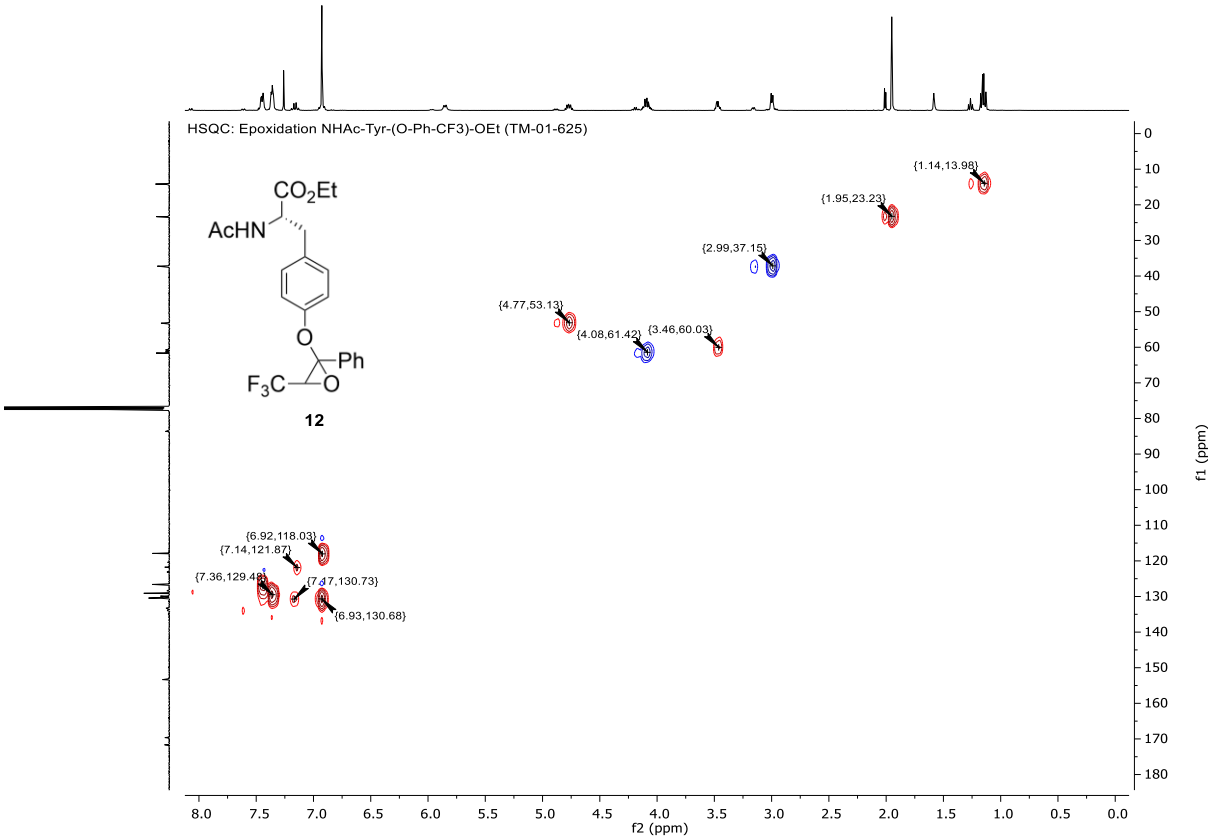
^{19}F-NMR (376 MHz, $CDCl_3$)



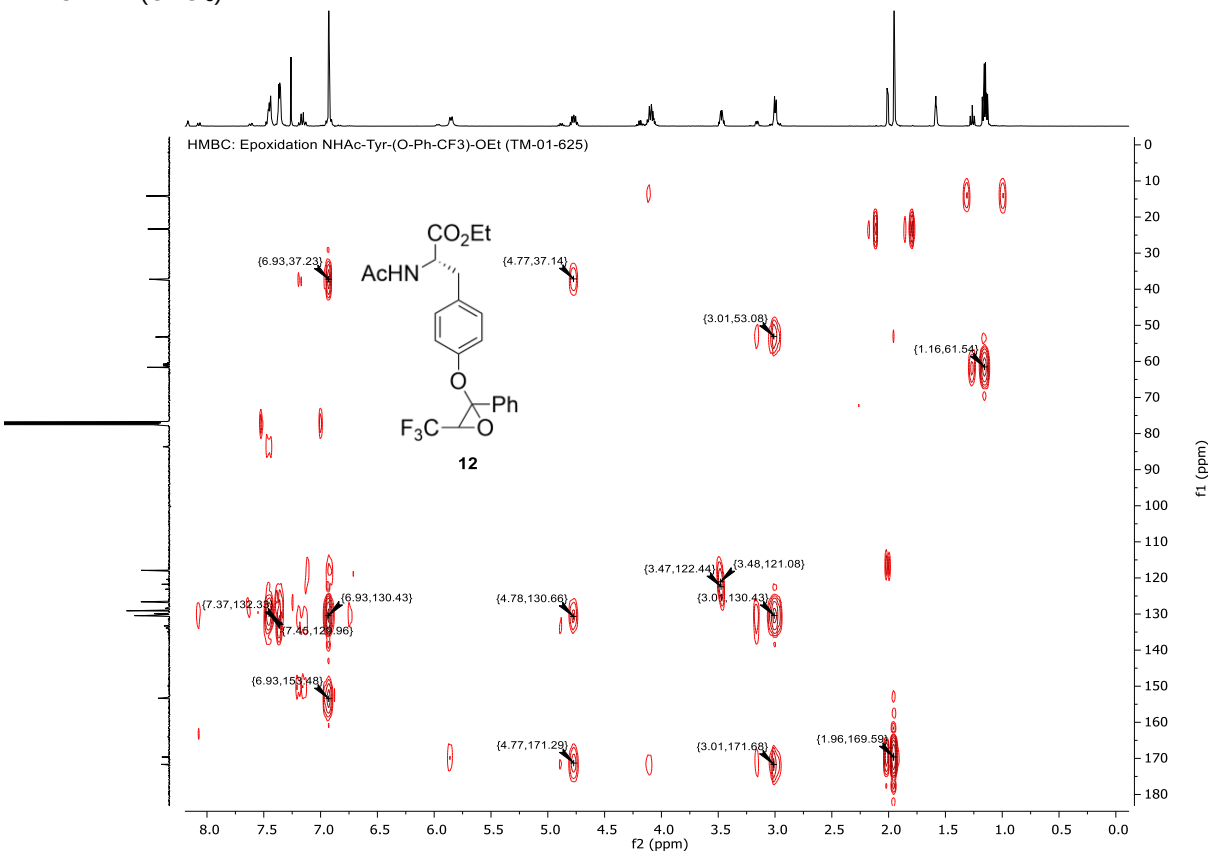
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Ethyl (2*S*)-2-acetamido-3-(4-(3,3,3-trifluoro-1-phenylpropoxy)phenyl)propanoate (13)

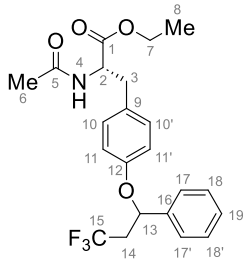
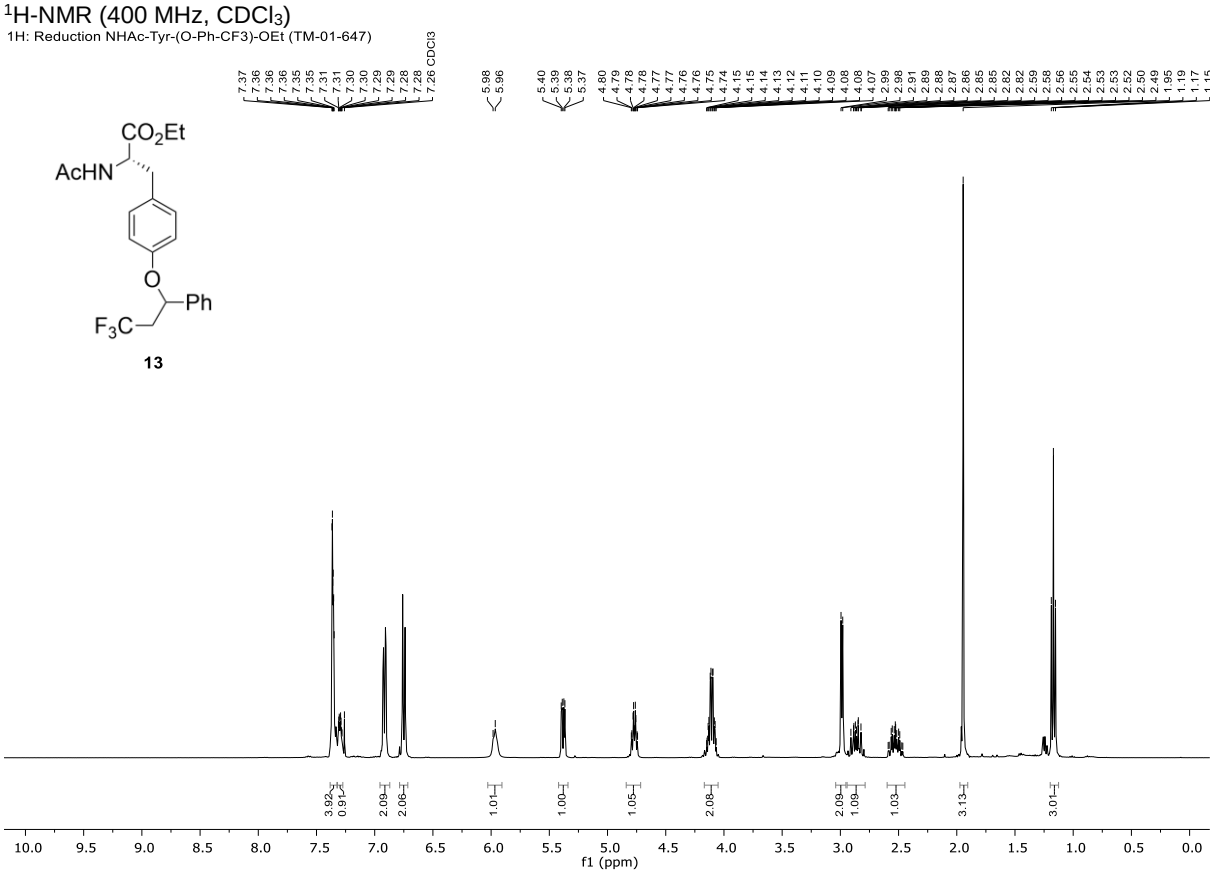


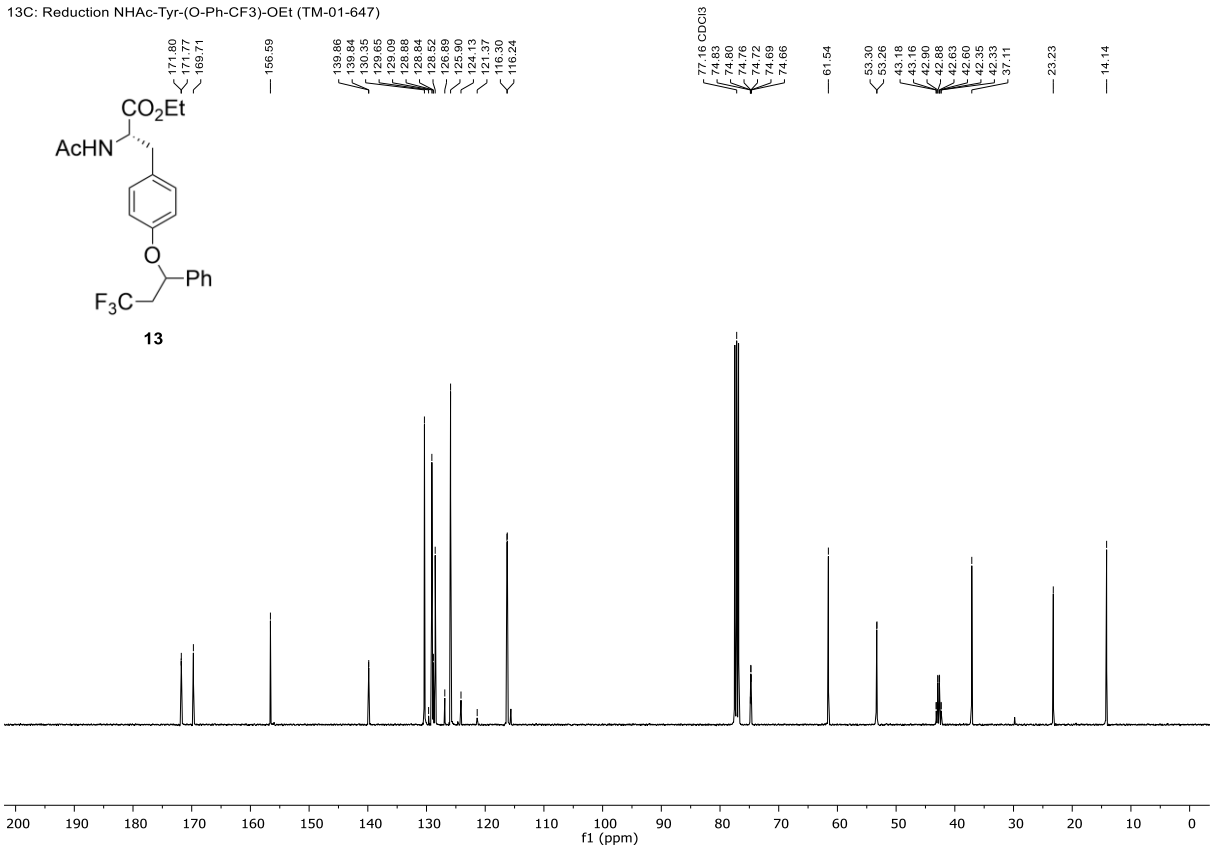
Table S55. Detailed NMR assignment of ethyl (2*S*)-2-acetamido-3-(4-(3,3,3-trifluoro-1-phenylpropoxy)phenyl)propanoate (**13**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.8 (d, 2.4 Hz)			
2	53.3 (d, 4.0 Hz)	4.76 (dtd, 7.7, 5.8, 1.8 Hz)	3, 4	1, 3, 9
3	37.1	2.98 (d, 5.9 Hz)	2	1, 2, 10/10’
4	/	6.01 (d, 7.8 Hz)	2	5
5	169.7			
6	23.2	1.94 (s)		5
7	61.5	4.16-4.03 (m)	8	1, 8
8	14.1	1.17 (t, 7.1 Hz)	7	7
9	128.9 (d, 4.5 Hz)			
10/10’	130.4	6.91 (dd, 8.7, 2.1 Hz)	11/11‘	3, 11/11‘, 12
11/11’	116.3 (d, 6.6 Hz)	6.79-6.69 (m)	10/10‘	9, 12
12	156.6			
13	74.7 (dq, 6.6, 3.2 Hz)	5.38 (dd, 9.0, 3.5 Hz)	14	12, 14, 15, 16
14	42.7 (q, 27.8 Hz)	2.92-2.75 (m), 2.61-2.39 (m)	13	13, 15, 16
15	125.5 (q, 277.7 Hz)			
16	139.9 (d, 2.4 Hz)			
17/17’	125.9	7.38-7.32 (m)		13, 19
18/18’	129.1	7.38-7.32 (m)		16
19	128.5	7.32-7.26 (m)		

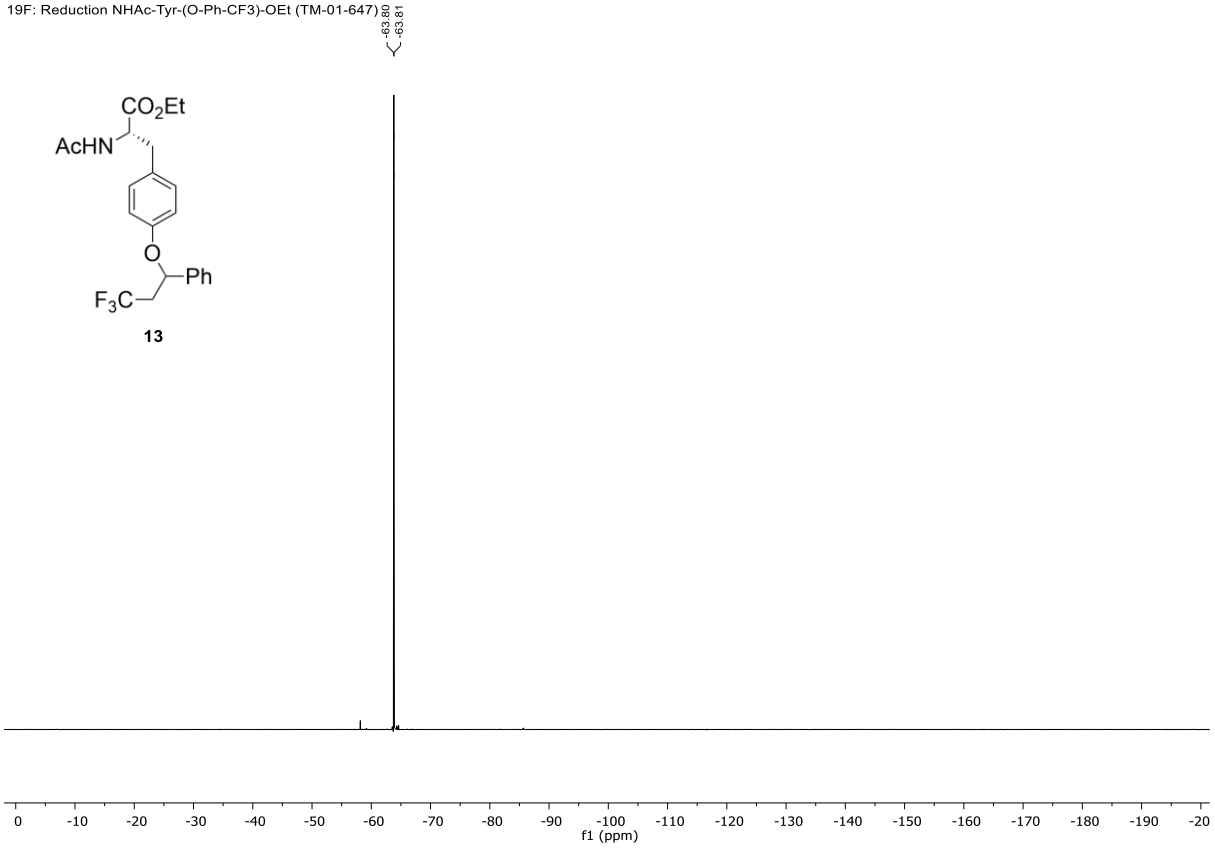
^{1}H-NMR (400 MHz, $CDCl_3$)



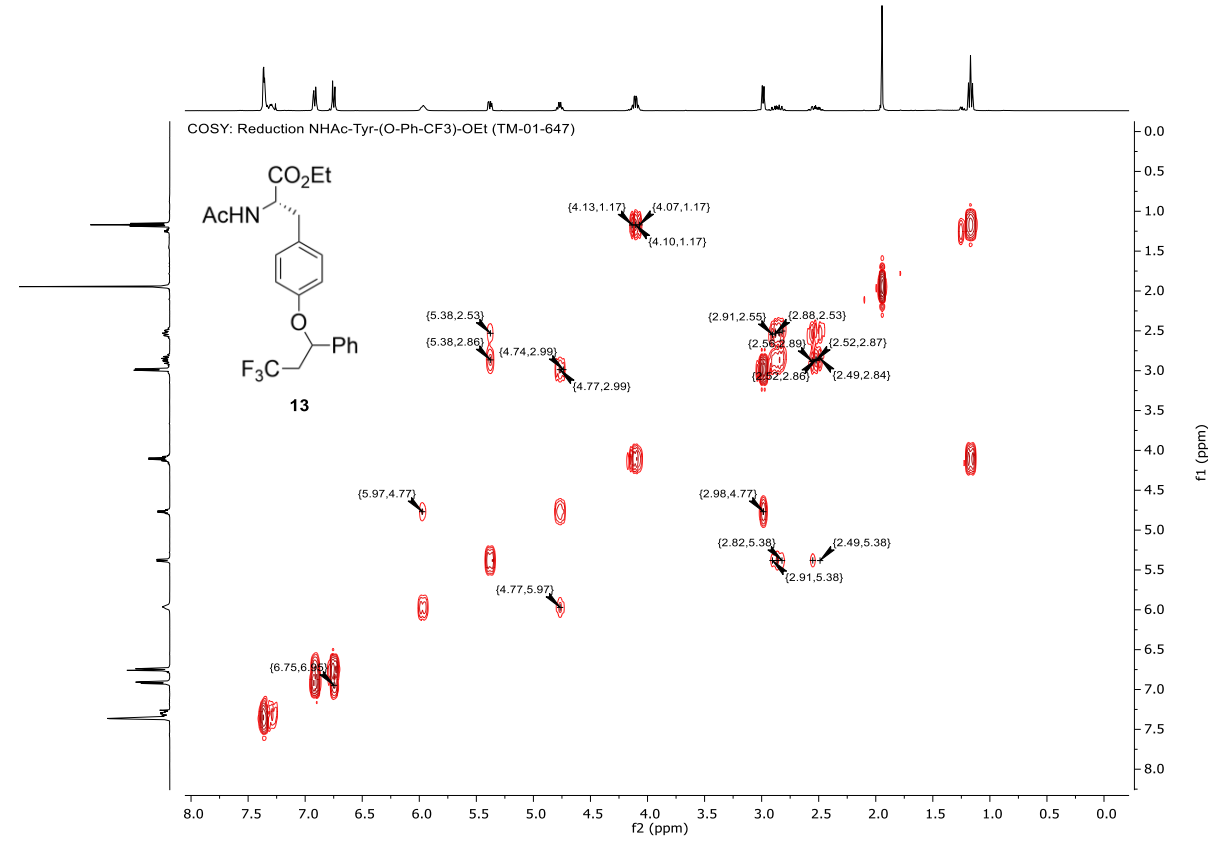
^{13}C-NMR (101 MHz, $CDCl_3$)



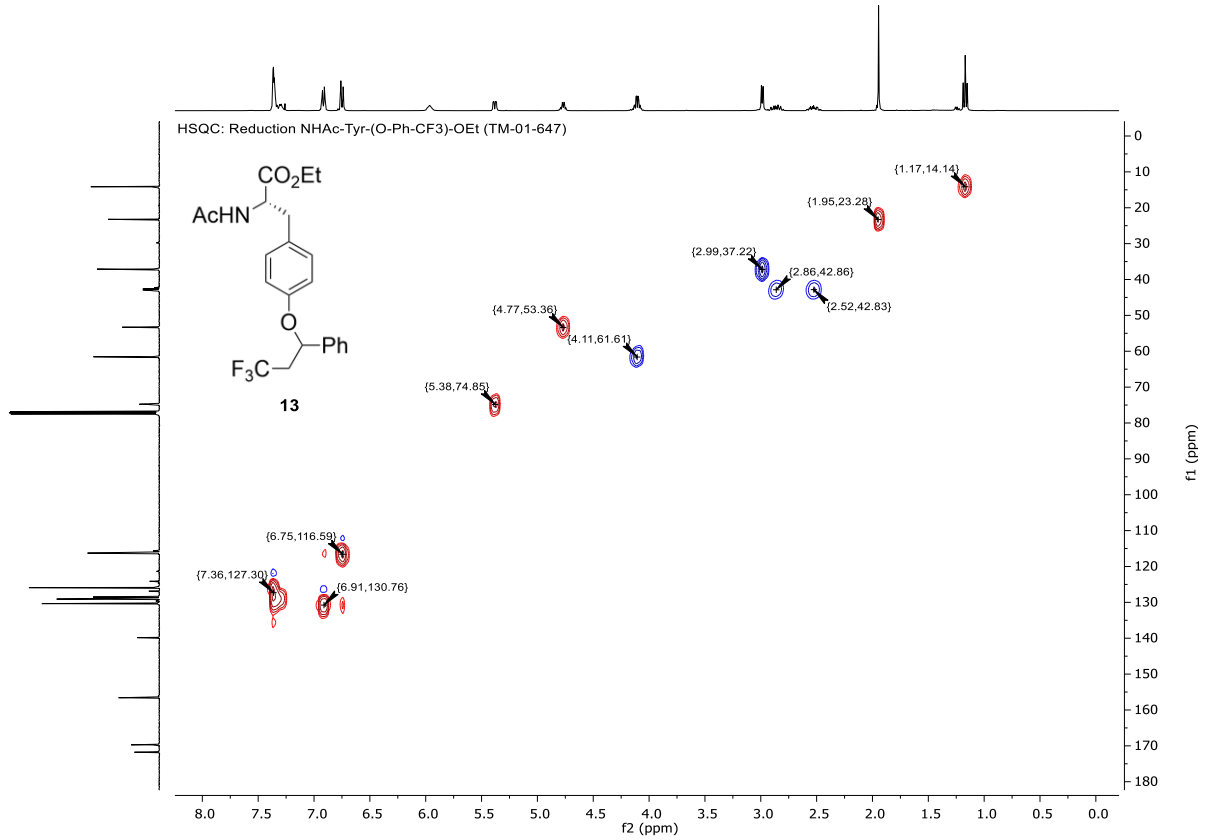
^{19}F-NMR (376 MHz, $CDCl_3$)



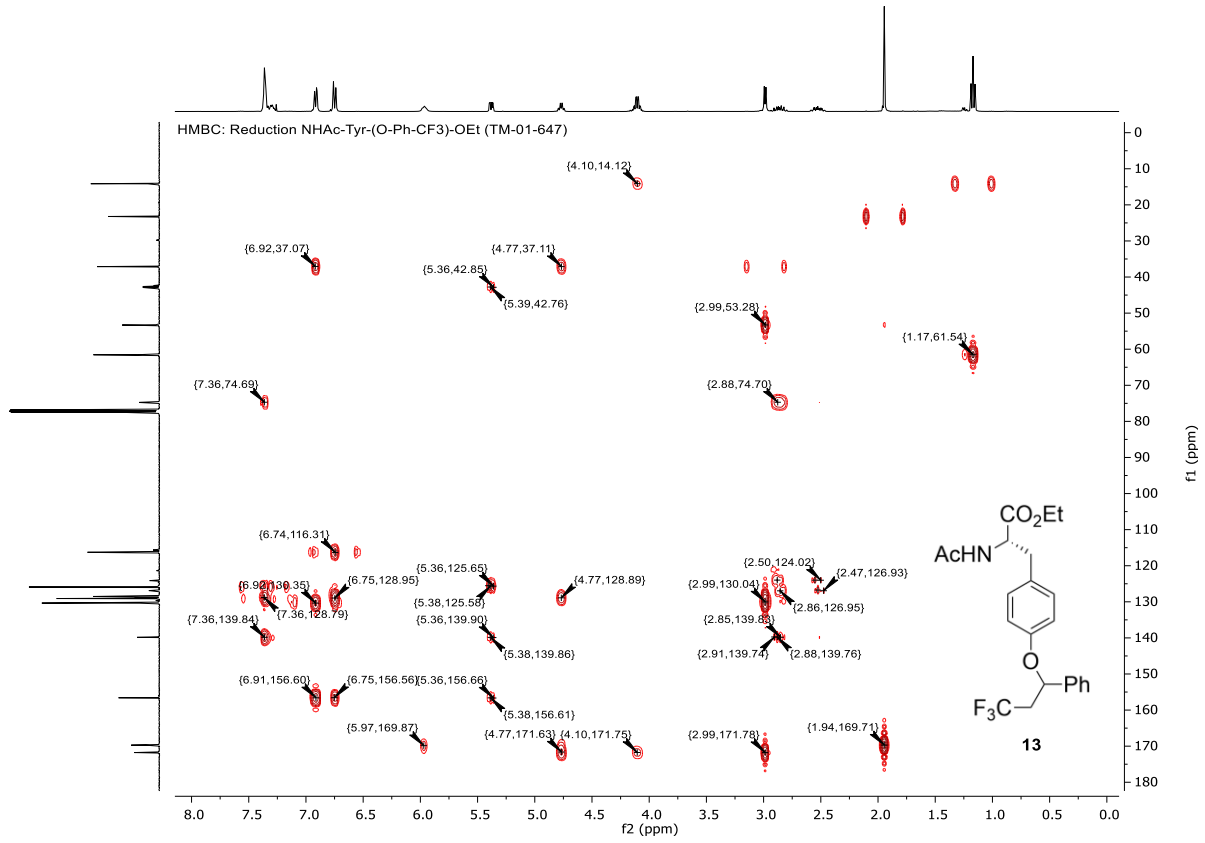
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)

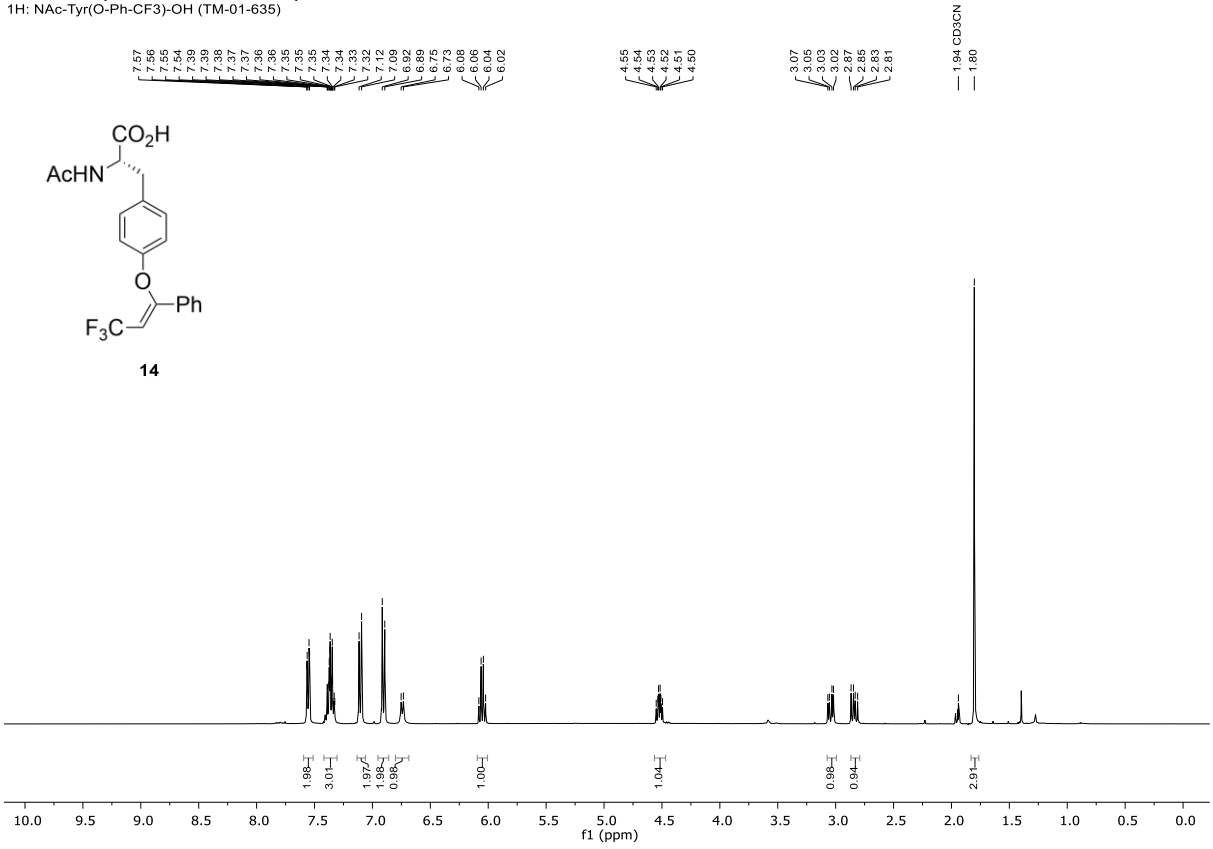


HMBC NMR ($CDCl_3$)

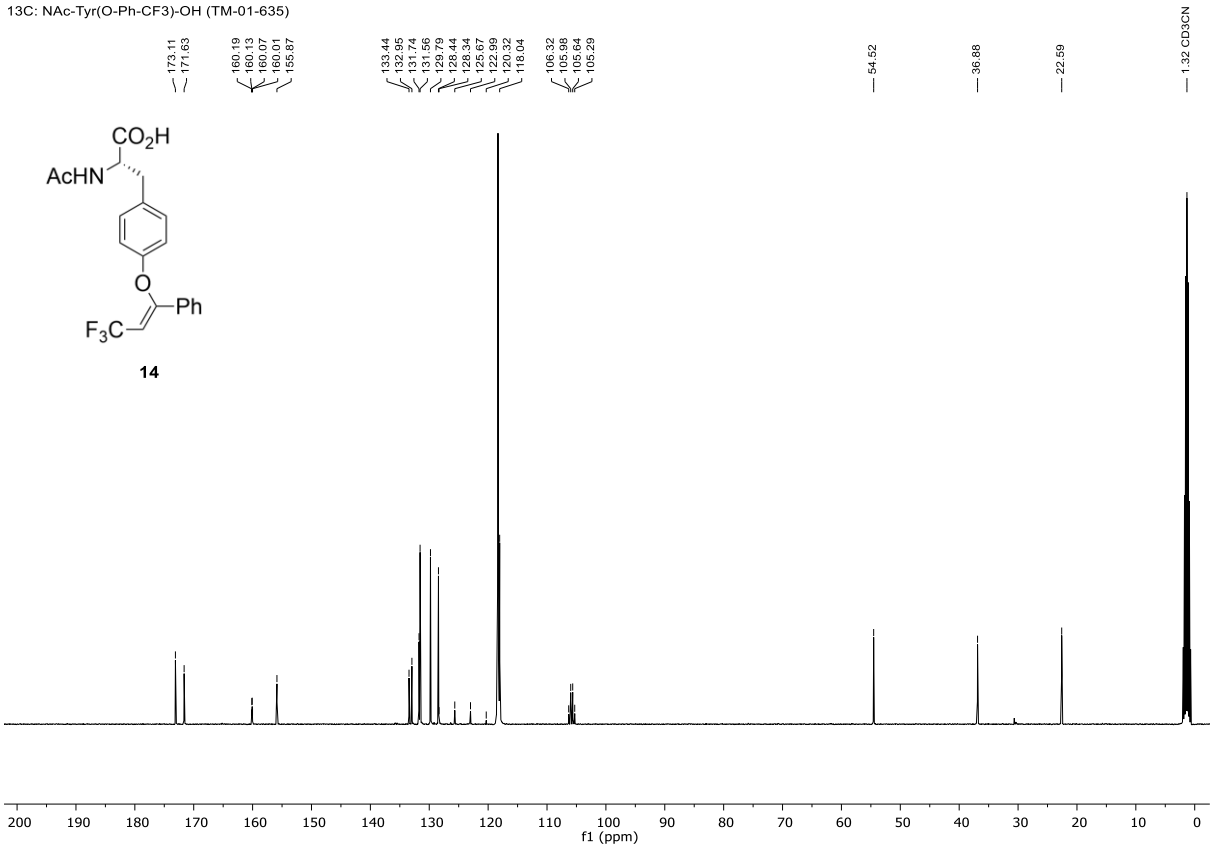


(*S*,*Z*)-2-Acetamido-3-(4-((3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoic acid (14)

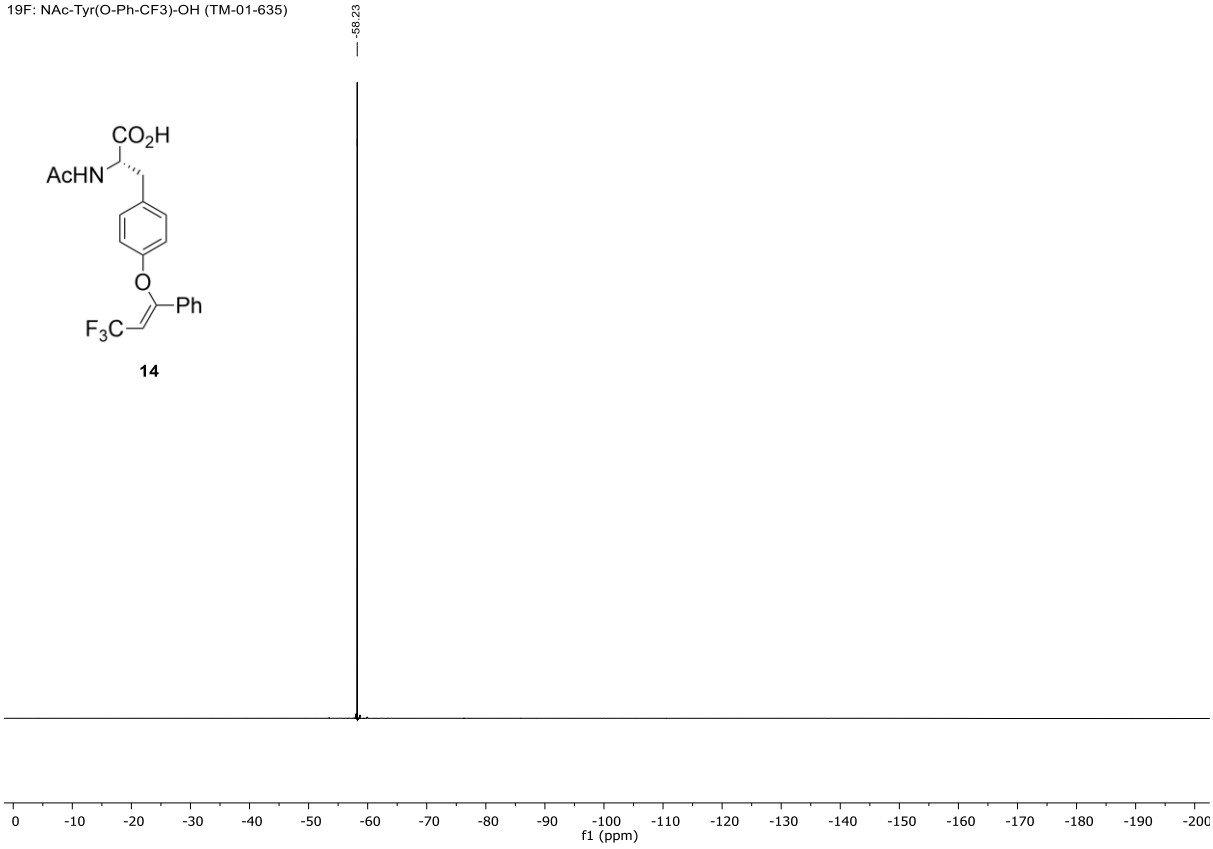
^{1}H-NMR (400 MHz, CD_3CN)



^{13}C-NMR (101 MHz, CD_3CN)



^{19}F-NMR (376 MHz, CD_3CN)



Methyl ((*S*)-2-acetamido-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (15)

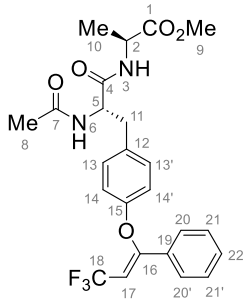
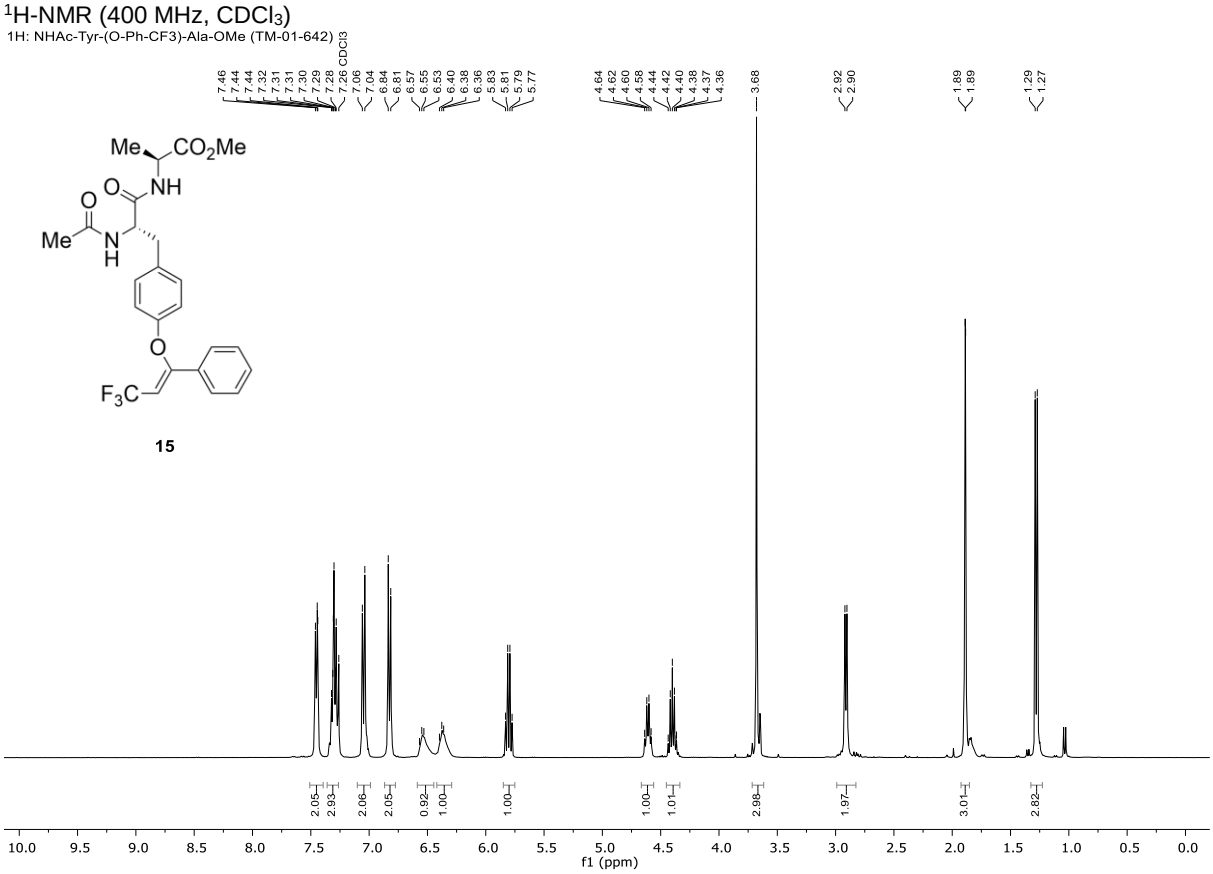


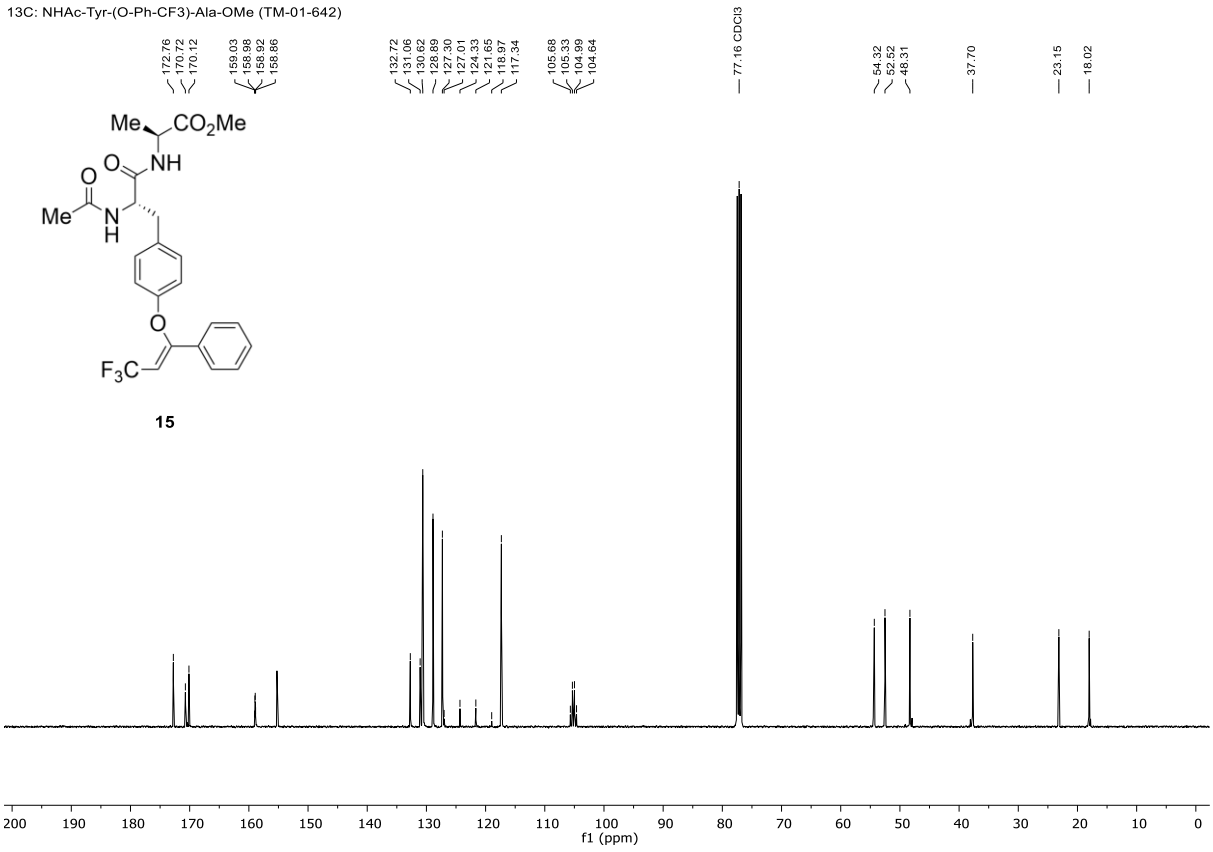
Table S56. Detailed NMR assignment of methyl ((*S*)-2-acetamido-3-(4-(((*Z*)-3,3,3-trifluoro-1-phenylprop-1-en-1-yl)oxy)phenyl)propanoyl)-L-alaninate (**15**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	172.8			
2	48.3	4.40 (p, 7.1 Hz)	3, 10	1, 10
3	/	6.58-6.45 (m)	2	4
4	170.7			
5	54.3	4.61 (q, 7.3 Hz)	6, 11	4, 11, 12
6	/	6.42-6.28 (m)	5	7
7	170.1			
8	23.1	1.89 (d, 1.3 Hz)		7
9	52.5	3.68 (s)		
10	18.0	1.28 (dd, 7.2 Hz)	2	1, 2
11	37.7	2.91 (d, 7.0 Hz)	5	4, 5, 13/13‘
12	131.1			
13/13‘	130.6	7.05 (d, 8.4 Hz)	14/14‘	11, 14/14‘, 15
14/14‘	117.3	6.83 (d, 8.6 Hz)	13/13‘	13/13‘, 15
15	155.3			
16	159.0 (q, 5.7 Hz)			
17	105.2 (q, 34.9 Hz)	5.80 (q, 7.5 Hz)		16, 18, 19
18	123.0 (q, 269.7 Hz)			
19	132.7			
20/20’	127.3	7.51-7.40 (m)		16, 22
21/21’	128.9	7.35-7.27 (m)		20/20’
22	131.1	7.35-7.27 (m)		

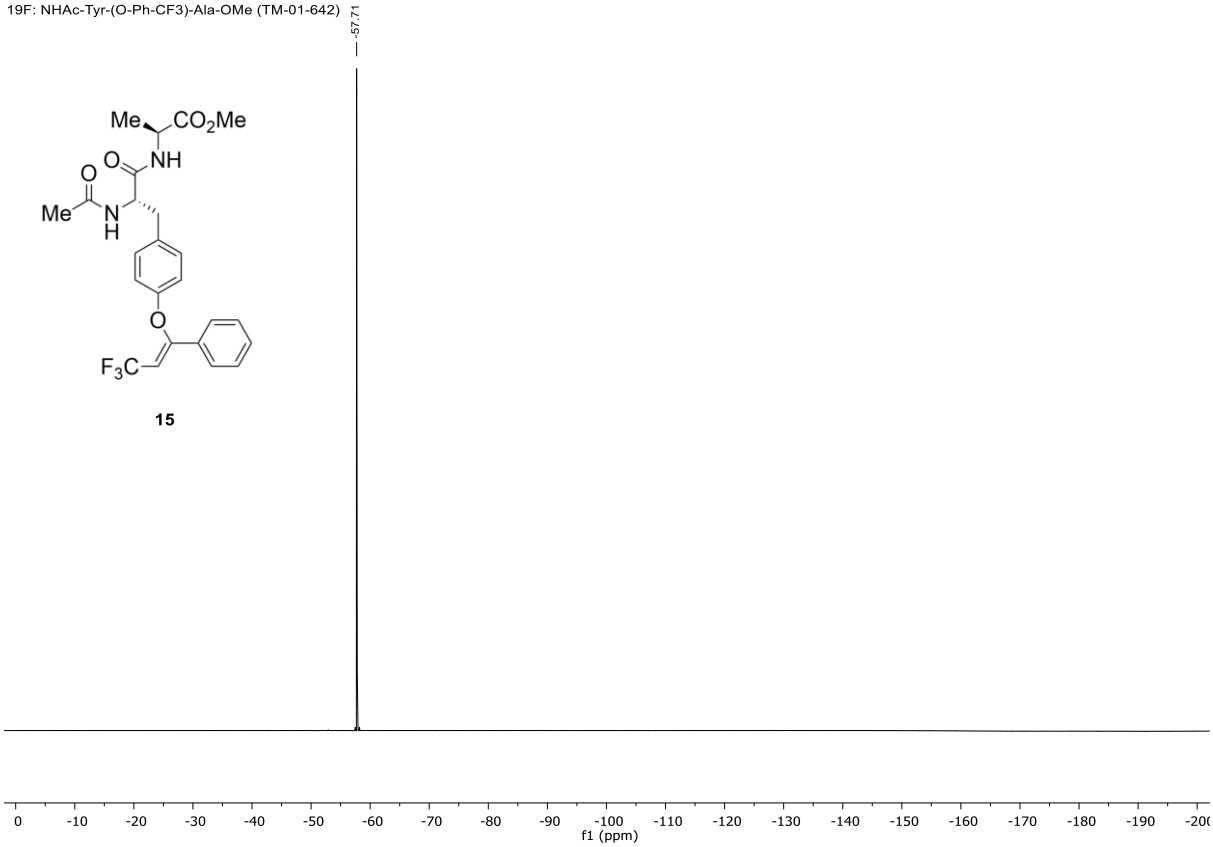
^{1}H-NMR (400 MHz, $CDCl_3$)



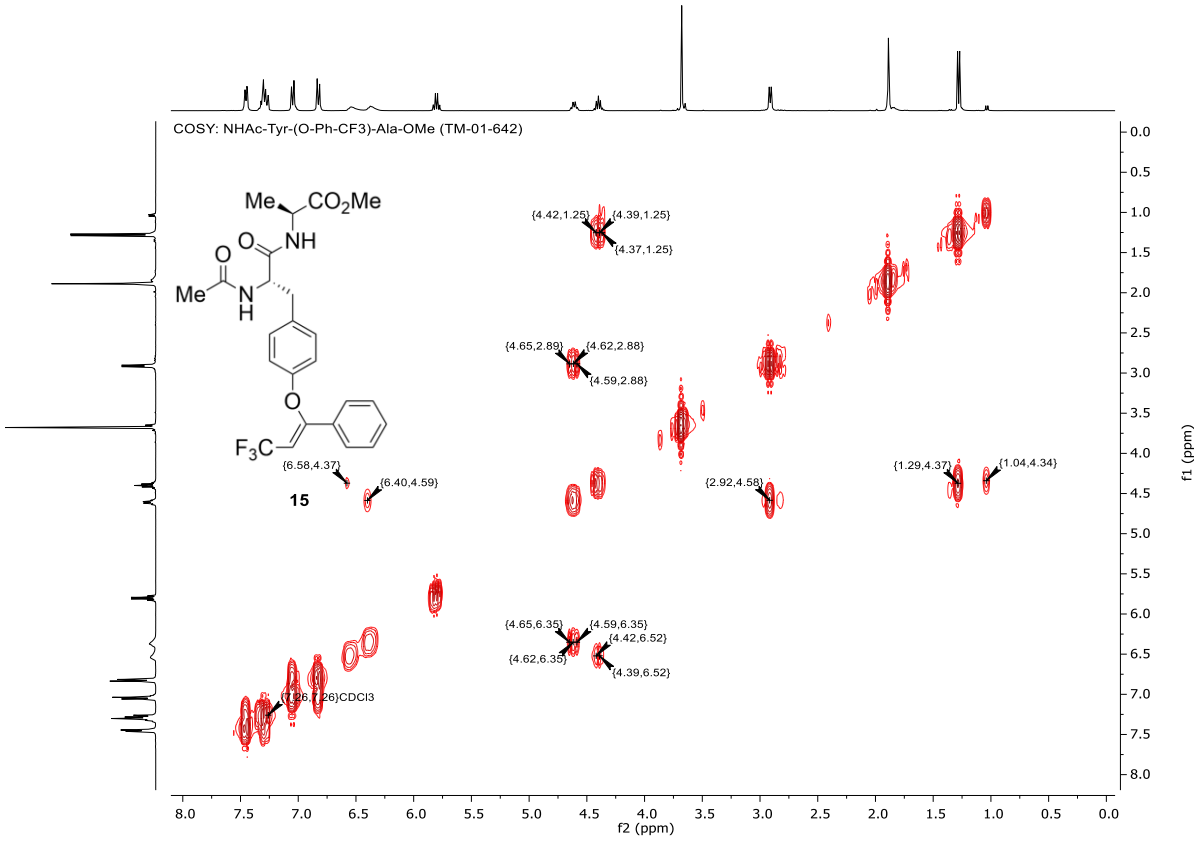
^{13}C-NMR (101 MHz, $CDCl_3$)



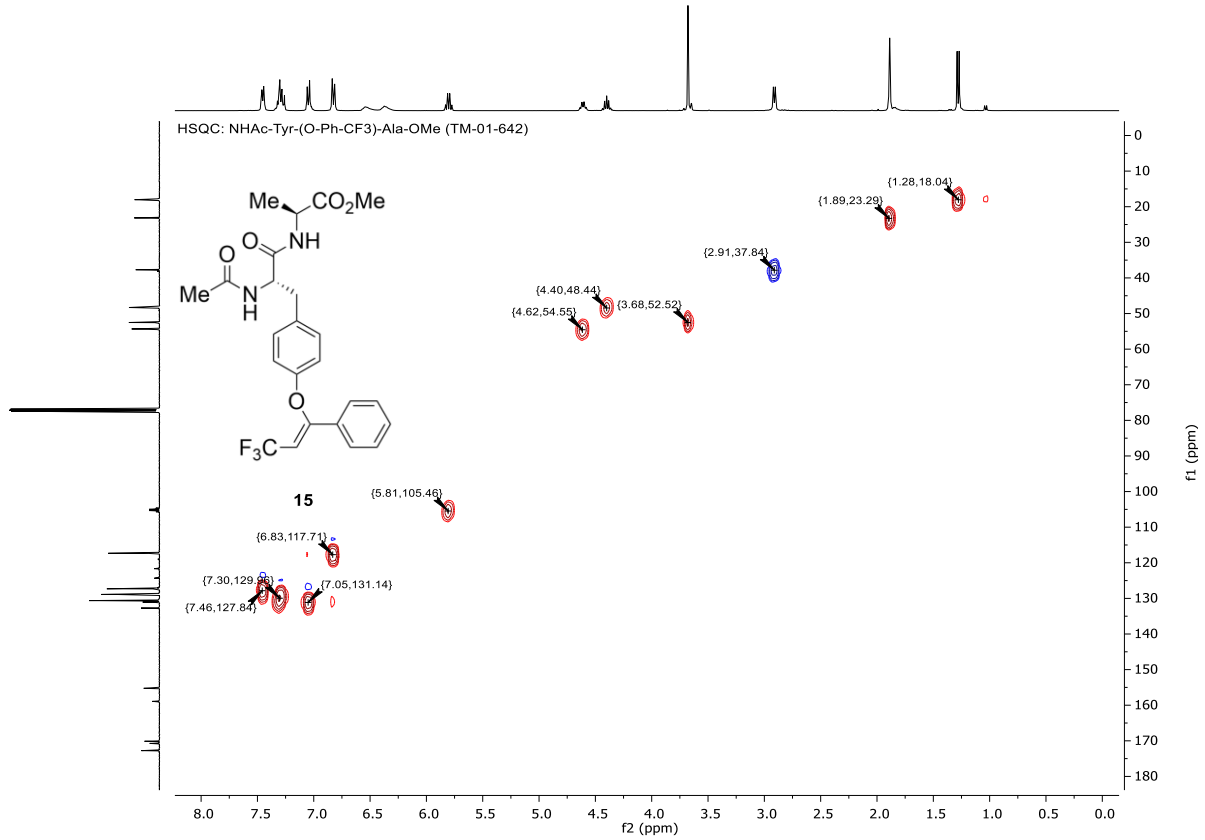
^{19}F-NMR (376 MHz, $CDCl_3$)



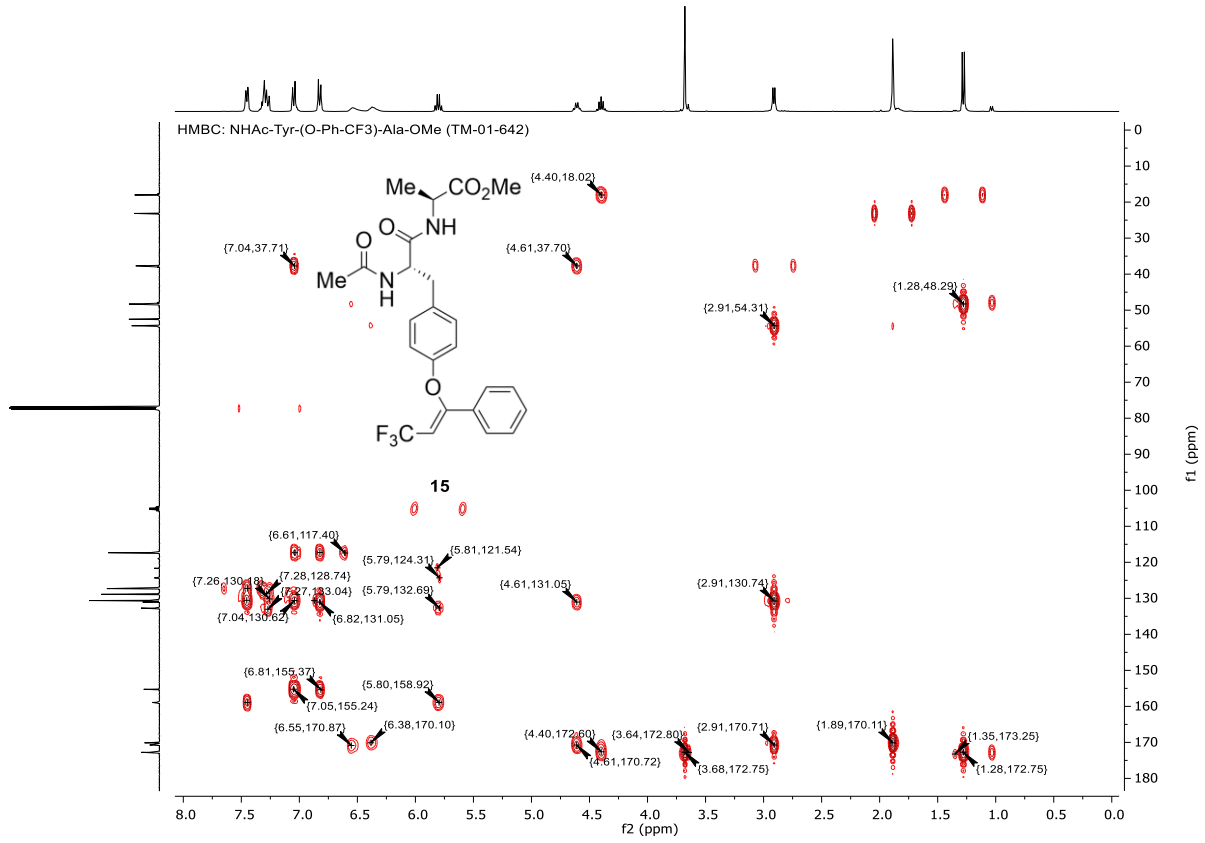
COSY NMR ($CDCl_3$)



HSQC NMR ($CDCl_3$)



HMBC NMR ($CDCl_3$)



Methyl (*Z*)-*N*-acetyl-*S*-(1,1,1-trifluoro-5-(4-phenyl-1H-1,2,3-triazol-1-yl)pent-2-en-3-yl)-L-cysteinate (16)

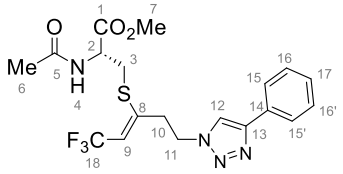
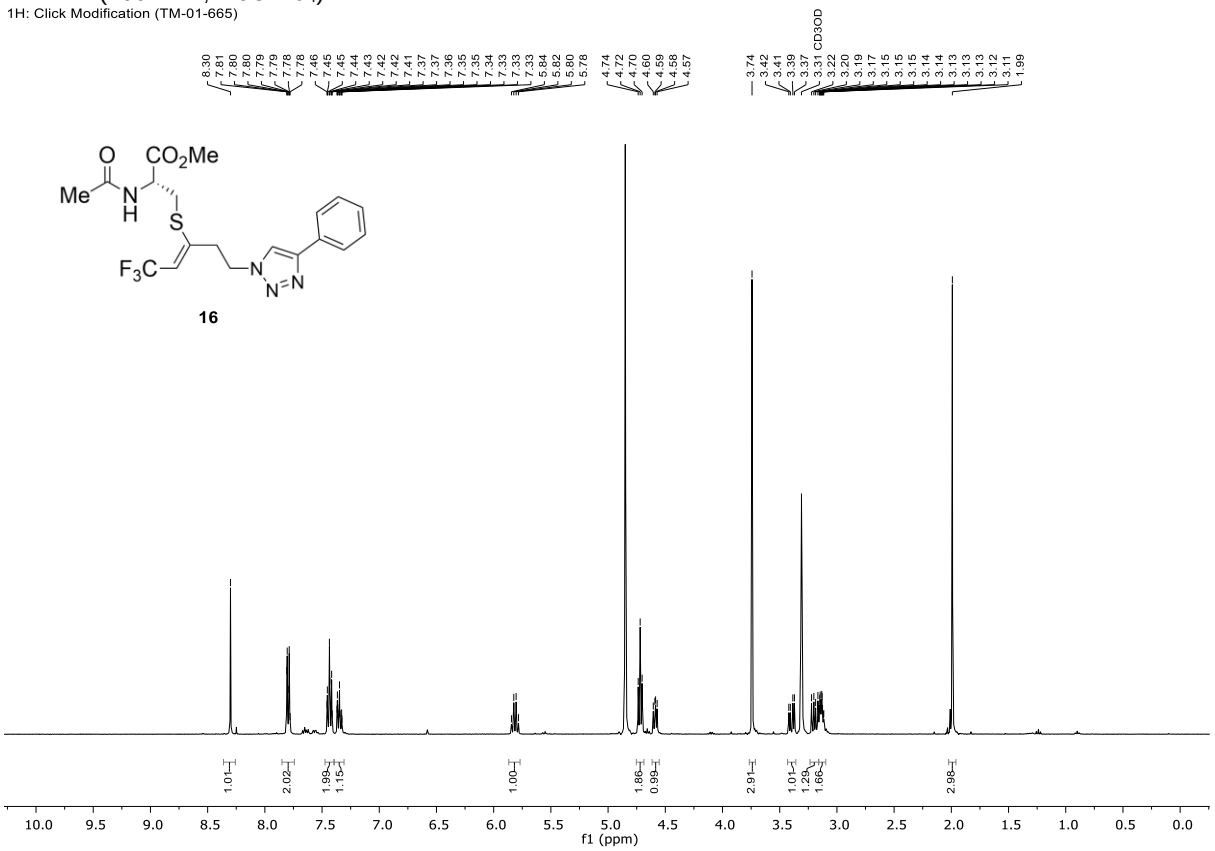


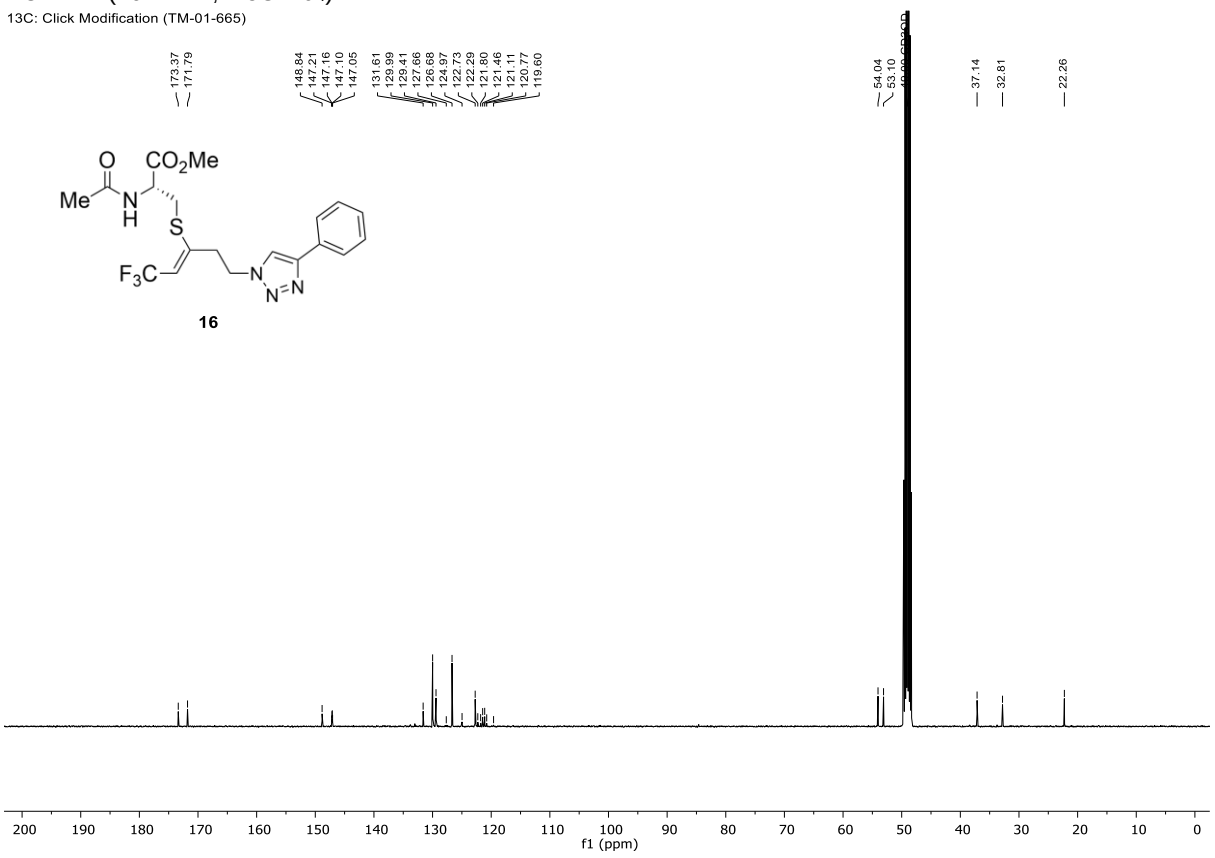
Table S57. Detailed NMR assignment of methyl (*Z*)-*N*-acetyl-*S*-(1,1,1-trifluoro-5-(4-phenyl-1H-1,2,3-triazol-1-yl)pent-2-en-3-yl)-L-cysteinate (**16**).

	δ_C	δ_H	COSY	HMBC (H→C)
1	171.8			
2	54.0	4.59 (dd, 8.0, 5.4 Hz)	3	1, 3
3	32.8	3.40 (dd, 14.1, 5.4 Hz), 3.19 (dd, 14.2, 8.0 Hz)	2	1, 2, 8
4	/	exchange with solvent		
5	173.4			
6	22.3	1.99 (s)		5
7	53.1	3.74 (s)		1
8	147.1 (q, 5.5 Hz)			
9	121.3 (q, 34.8 Hz)	5.81 (q, 8.1 Hz)		10, 18
10	37.1	3.16-3.11 (m)	11	8, 9, 11
11	49.2	4.72 (t, 6.8 Hz)	10	8, 9, 10
12	122.7	8.30 (s)		13
13	148.8			
14	131.6			
15/15’	126.7	7.82-7.75 (m)	16/16’	13, 16/16’
16/16’	130.0	7.47-7.39 (m)	15/15’	14
17	129.4	7.37-7.30 (m)		15/15’
18	123.6 (q, 270.6 Hz)			

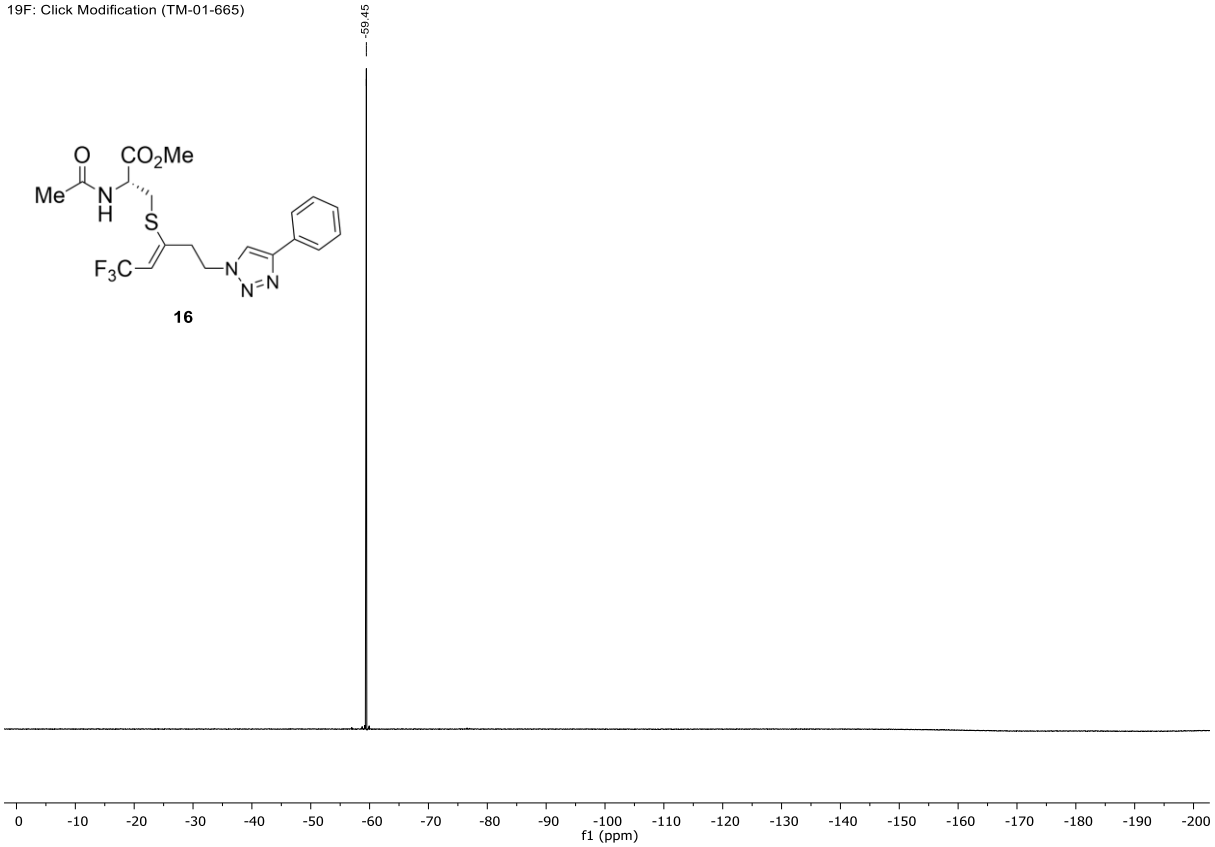
^{1}H-NMR (400 MHz, MeOD-d$_4$)



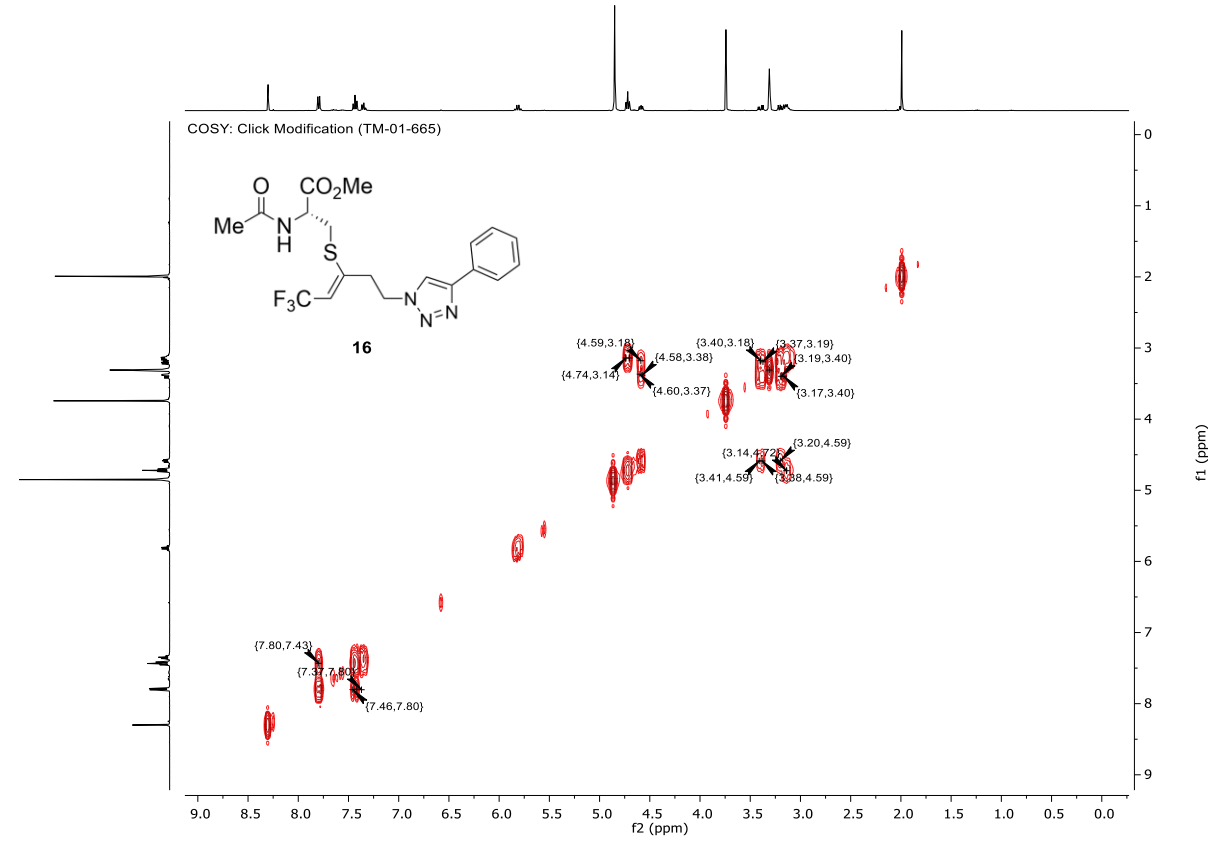
^{13}C-NMR (101 MHz, MeOD-d$_4$)



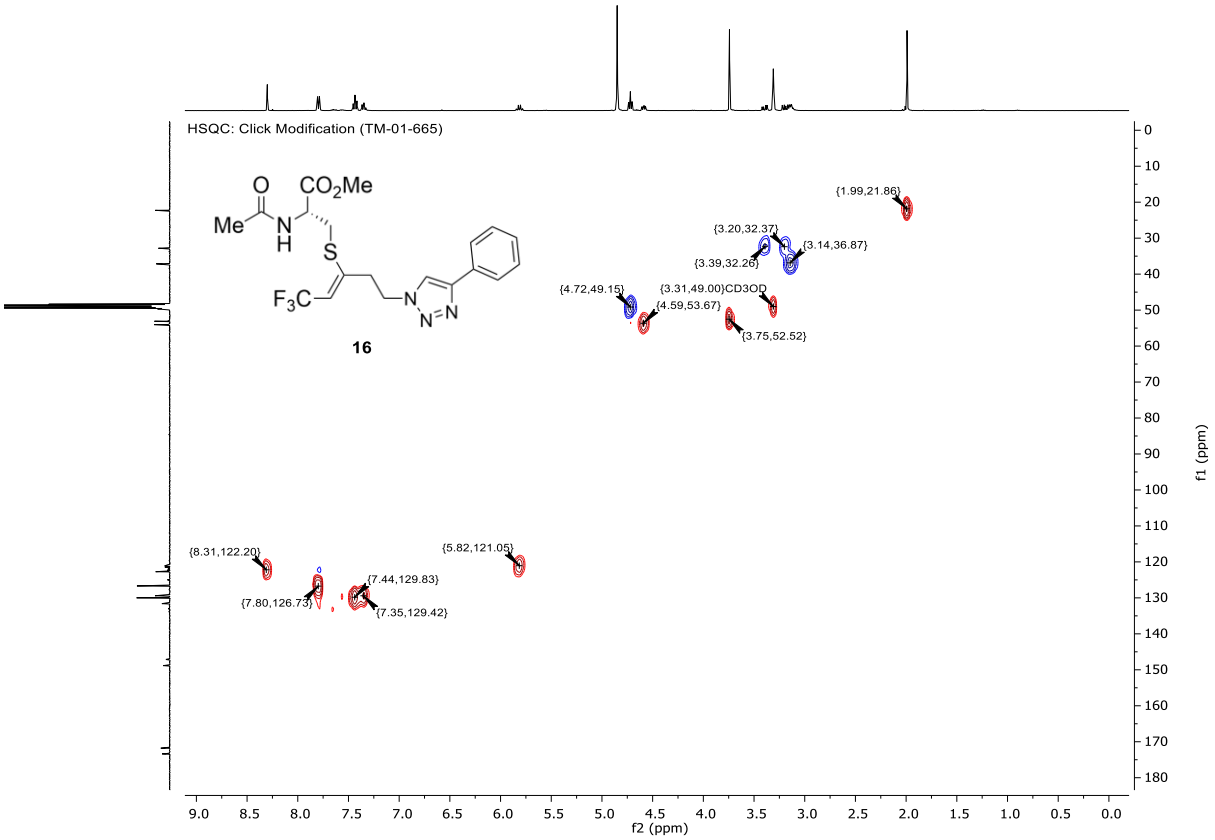
^{19}F-NMR (376 MHz, MeOD-d$_4$)



COSY NMR (MeOD-d$_4$)



HSQC NMR (MeOD-d_4)



HMBC NMR (MeOD-d_4)