# Copper-Catalyzed Alkynylation of Hydrazides: An Easy Access to Functionalized Azadipeptides

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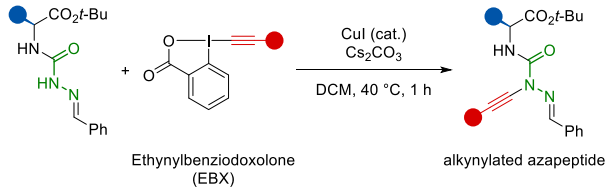
*Supporting Information Placeholder*

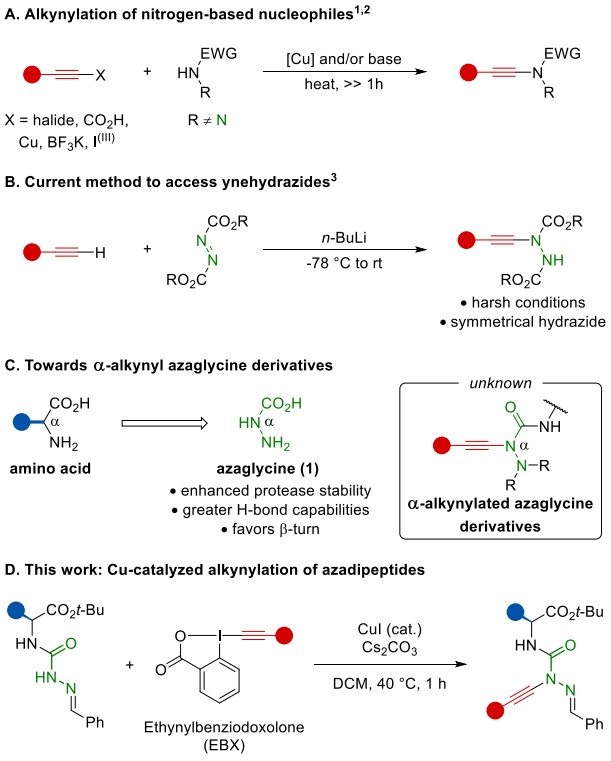



**ABSTRACT:** We report a copper-catalyzed alkynylation of azadipeptides using ethynylbenziodoxolone (EBX) reagents. Non-symmetrical ynehydrazides could be obtained in 25-97% yield using azaglycine derivatives as nucleophiles. The transformation is compatible with most functional groups naturally occurring on amino acid side-chains and allows the transfer of silyl-, alkyl- and aryl-substituted alkynes. The obtained α-alkynyl azaglycine products could be further functionalized by nucleophilic attack or cycloaddition on the triple bond.

In the last decades, the alkynylation of nitrogen-based nucleophiles has been the focus of intensive research due to the synthetic versatility of the formed ynamines/ynamides products.[1] Most methods relied on copper-catalysis with free or pre-activated alkynes (including halides, carboxylic acid, organometallic reagents and hypervalent iodine reagents (HIR), Scheme 1A).[1] Among the potential coupling partners capable of transferring alkynes, HIR particularly attracted attention as they allowed the use of milder reaction conditions.[2] While alkynylation using mononitrogen-based nucleophiles is well established, only few examples of the synthesis of ynehydrazides are reported.[3] Initial attempts to alkynylate hydrazides with alkynyl HIR or bromalkynes required harsh conditions and/or afforded the products in poor yields.[3c,d] To circumvent this issue, Batey and Beveridge followed an Umpolung strategy using azodicarboxylates as hydrazide precursors and acetylides nucleophiles (Scheme 1B).[3d] The obtained products could then be used in diverse applications.[3e-h] However, this transformation was limited to symmetrical azodicarboxylates and required a strong base. Therefore, the development of a milder protocol suitable for non-symmetrical hydrazides would be beneficial.

Among hydrazide nucleophiles, azaglycine derivatives constitute a unique class (Scheme 1C). These amino acid analogs, in which the α-carbon is replaced by a nitrogen atom, enable the fine-tuning of the structural and conformational features of bioactive peptides.[4] Notably, azapeptides exhibit enhanced protease stability,[5] greater H-bonding capability,[6] and usually favor β-turn.[7] While N-alkylation and N-arylation of azaglycine have been reported, to the best of our knowledge, N-alkynylation remains unexplored. Moreover, α-alkynyl amino acids have been shown to be irreversible enzyme inhibitors and versatile building blocks in the synthesis of bioactive compounds.[8] An easy access to their α-alkynyl azaglycine analogues would therefore be valuable.

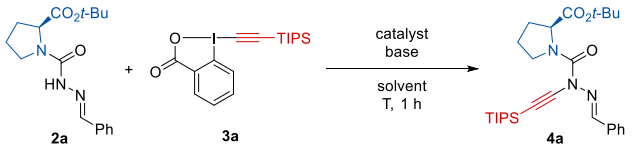
**Scheme 1. (A) Alkynylation of nitrogen-based nucleophiles, (B) Current method to access ynehydrazides, (C) Towards α-alkynyl azaglycine derivatives, (D) Our work.**



Our group and others have shown that HIR were ideal reagents for the selective functionalization of peptides.[9] Herein, we report the successful copper-catalyzed alkynylation of azadipeptides (Scheme 1D). The mild reaction conditions allowed a broad functional group tolerance on the side chain of the peptides. Various types of alkynes could be transferred and undergo further transformations, enabling an easy access to functionalized azadipeptides.

We started our investigation using azadipeptide **2a** derived from proline with the C-terminal protected with a *tert*-butyl group as a model subtrate.[10] Reaction of the later with TIPS-EBX (**3a**) for 1 hour in the presence of $Cu(CH_3CN)_4BF_4$ and potassium *tert*-butoxide led to the formation of **4a** in an encouraging 20% yield (Table 1, entry 1). A similar result could be obtained using $Cs_2CO_3$ as a milder base (entry 2). Increased formation of the desired product was observed when the reaction was heated to 40 °C (entry 3). Replacing acetonitrile by *i*-PrOH or DCE increased the yield to 48% and 60% respectively (entries 4 and 5). Several copper catalysts can promote the reaction, with the best result obtained using CuI, affording 76% of **4a** (entries 6-8). No difference could be observed when the transformation was carried out with an excess of TIPS-EBX (**3a**) (entry 9). Control reactions without base or copper catalyst resulted in, respectively, no reaction or degradation of the azapeptide (entries 10 and 11). Finally, DCM could be used as an alternative to DCE without impacting the reaction outcome (entry 12).

**Table 1. Optimization of the azapeptide alkynylation.**[a]

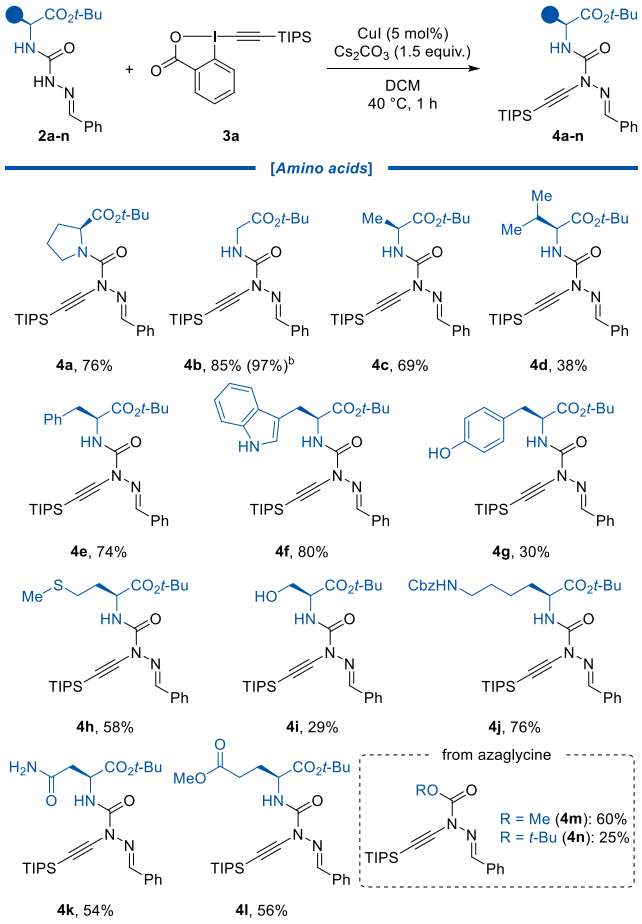



| entry | base | T | solvent | catalyst | yield |
|---|---|---|---|---|---|
| 1 | *t*-BuOK | rt | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 20% |
| 2 | $Cs_2CO_3$ | rt | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 16% |
| 3 | $Cs_2CO_3$ | 40 °C | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 32% |
| 4 | $Cs_2CO_3$ | 40 °C | *i*-PrOH | $Cu(CH_3CN)_4BF_4$ | 48% |
| 5 | $Cs_2CO_3$ | 40 °C | DCE | $Cu(CH_3CN)_4BF_4$ | 60% |
| 6 | $Cs_2CO_3$ | 40 °C | DCE | CuCl | 36% |
| 7 | $Cs_2CO_3$ | 40 °C | DCE | $CuCl_2$ | 68% |
| 8 | $Cs_2CO_3$ | 40 °C | DCE | CuI | 76% |
| 9[b] | $Cs_2CO_3$ | 40 °C | DCE | CuI | 72% |
| 10 | - | 40 °C | DCE | CuI | - |
| 11 | $Cs_2CO_3$ | 40 °C | DCE | - | - |
| **12** | **$Cs_2CO_3$** | **40 °C** | **DCM** | **CuI** | **72%** |

[a]Reaction conditions: azapeptide **2a** (1.0 equiv.), TIPS-EBX (**3a**) (1.0 equiv.), catalyst (5 mol%), base (1.5 equiv.), solvent (0.1 M), reactions were carried out under air on a 0.05 mmol scale. Isolated yields are reported. [b]TIPS-EBX (**3a**) (1.5 equiv.)

With the optimized conditions in hand we started to explore the scope of amino acids present on the urea. Carrying out the reaction on scope scale (0.3 mmol) using the model substrate afforded **4a** in 76% yield. Simple glycine or alanine gave the corresponding alkynylated azapeptides **4b** and **4c** in good yields. Product **4b** could be obtained in 97% yield on a 1 mmol scale. More sterically demanding valine only afforded 38% of **4d**. Aromatic residues are tolerated in the reaction and good yields can be obtained for phenylalanine (**2e**) and tryptophan (**2f**). However, lower efficiency was observed with tyrosine (**2g**), probably due to the presence of an unprotected phenol. Methionine derived azapeptide (**2h**) could be alkynylated in 58% yield with no side reactivity of the sulfur atom with the hypervalent iodine reagent.[11] With serine, product **4i** could be obtained in a moderate 29% yield. Amino acids bearing additional nitrogen atoms, such as protected lysine (**2j**) or asparagine (**2k**) were alkynylated selectively on the azaglycine affording **4j** and **4k** in 76% and 56% yields, respectively. Protected glutamic acid (**2l**) was well tolerated in the reaction. Finally, using a methyl carbamate protected azaglycine, we could access **4m** in 60% yield. Replacing the protecting group with a bulkier *tert*-butyl carbamate (**2n**) led to a drop in yield.

**Scheme 2. Scope of amino acids.**[a]

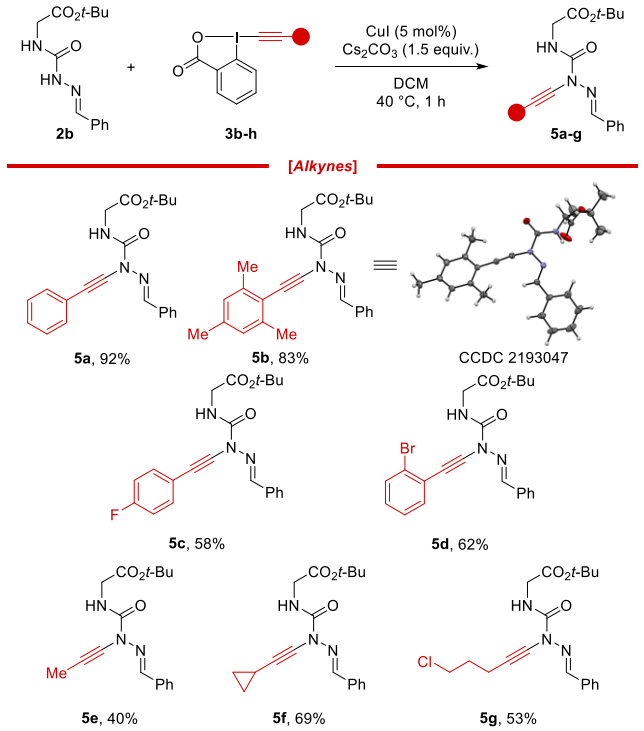



[a]Reaction conditions: azapeptide **2a-n** (1.0 equiv.), TIPS-EBX (**3a**) (1.0 equiv.), CuI (5 mol%), $Cs_2CO_3$ (1.5 equiv.), DCM (0.1 M), 40 °C, 1 h, reactions were carried out under air on a 0.3 mmol scale. [b]Reaction was performed on 1 mmol scale.

Having established the compatibility of the reaction with different amino acids, we next explored the variety of alkynes that could be transferred with azapeptide **2b** as partner. A variety of EBXs could be easily prepared by using established procedures or the most recent protocol developed by our group (1 h reaction time, no additives, no purification).[12] High yields of alkynylated azapeptides could be maintained when replacing the TIPS group by a simple phenyl (**3b**) or mesityl (**3c**) substituent. The structure of **5b** was determined by X-ray diffraction and displayed a *trans*-amide geometry in the solid state. Electron-withdrawing substituent on the aryl ring such as fluoride or bromide

were well tolerated affording **5c** and **5d** with only a slight decrease in yield. Alkyl substituted alkynes could also be transferred. Alkynylated azapeptide **5e** bearing a methyl group was obtained in 40% yield, and higher yield could be obtained with a cyclopropyl group (**5f**). Having a chloride on the alkyl chain was tolerated and **5g** could be obtained in 53% yield.

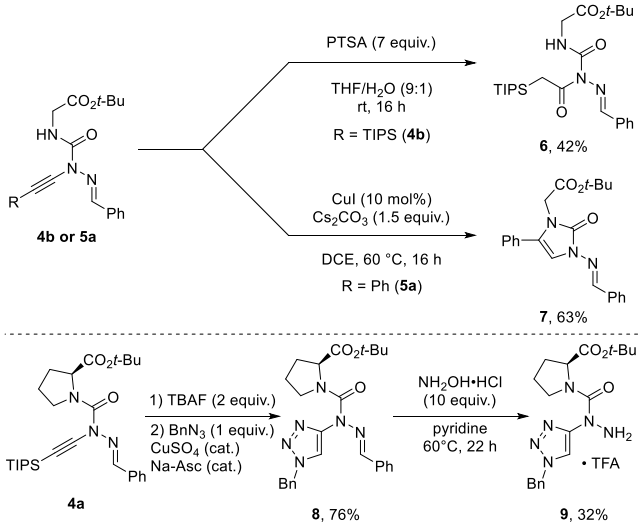
**Scheme 3. Scope of EBX reagents.**




[a]Reaction conditions: azapeptide **2b** (1.0 equiv.), EBX **3b-h** (1.0 equiv.), CuI (5 mol%), $Cs_2CO_3$ (1.5 equiv.), DCM (0.1 M), 40 °C, 1 h. Reactions were performed on 0.3 mmol scale under air.

Finally, we explored synthetic transformations of the alkynylated azapeptides. Hydration of the alkyne using PTSA afforded the corresponding amide moiety **6** bearing an α-silyl group. To the best of our knowledge, acylation of azaglycine has not been reported so far. For instance, chloroacetyl chloride has been shown to react with the hydrazone C=N bond.[13] 5-*endo-dig* Cyclization of the second nitrogen of the urea onto the alkyne afforded the product **7** in 63%. Similar cyclic scaffolds have been shown to induce β-turn conformations in peptides.[14] This type of cyclized product could only be observed as traces (<5%) during the formation of alkynylated azapeptides, which proceeded at lower reaction temperature with a shorter reaction time. Attempts to deprotect the TIPS substituted product **4a** showed that the resulting free alkyne was too unstable to be purified. To circumvent this issue, the unsubstituted alkyne was directly engaged in a copper catalyzed alkyne-azide cycloaddition affording triazole **8** in 76% yield over 2 steps. Furthermore, N-terminus deprotection using hydroxylamine afforded the free hydrazide **9** as the TFA salt in 32% isolated yield after purification by reverse-phase HPLC.

**Scheme 4. Product modification of alkynylated azadipeptides.[a]**




[a]For more detailed reaction conditions see the Supporting Information.

In summary, we have developed conditions to perform the alkynylation of azadipeptides using EBX reagents and an inexpensive copper catalyst. The reaction is selective to the nitrogen of the azaglycine residue and tolerate a large variety of amino acids affording the desired alkynylated azadipeptides in moderate to good yields. The transformation is not limited to silyl protected alkynes and both aryl and alkyl acetylenes can be transferred. The products could be further functionalized using classical alkyne reactivity affording different azadipeptide derivatives.[15]

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and analytical data for all new compounds; copy of NMR spectra (PDF).

### Accession Codes

CCDC 2193047 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Evano, G.; Coste, A.; Jouvin, K. Ynamides: Versatile Tools in Organic Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840–2859. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Ynamides: A Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110*, 5064–5106. (c) Cook, A. M.; Wolf, C. Terminal Ynamides: Synthesis, Coupling Reactions, and Additions to Common Electrophiles. *Tetrahedron Lett.* **2015**, *56*, 2377–2392. (d) Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. A Journey in the Chemistry of Ynamides: From Synthesis to Applications. *Chem. Lett.* **2016**, *45*, 574–585.

(2) Seminal work with iodonium salt: (a) Murch, P.; Williamson, B. L.; Stang, P. J. Push-Pull Ynamines via Alkynyliodonium Chemistry. *Synthesis* **1994**, 1255–1256. (b) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. Inter- and Intramolecular Addition/Cyclizations of Sulfonamide Anions with Alkynyliodonium Triflates. Synthesis of Dihydropyrrole, Pyrrole, Indole, and Tosylenamide Heterocycles. *J. Org. Chem.* **1996**, *61*, 5440–5452. (c) Witulski, B.; Stengel, T. N-Functionalized 1-Alkynylamides: New Building Blocks for Transition Metal Mediated Inter- and Intramolecular [2+2+1] Cycloadditions. *Angew. Chem. Int. Ed.* **1998**, *37*, 489–492. Recent selected examples with EBX: (d) Aubineau, T.; Cossy, J. Chemoselective Alkynylation of N-Sulfonylamides versus Amides and Carbamates – Synthesis of Tetrahydropyrazines. *Chem. Commun.* **2013**, *49*, 3303-3305. (e) Yudasaka, M.; Shimbo, D.; Maruyama, T.; Tada, N.; Itoh, A. Synthesis, Characterization, and Reactivity of an Ethynyl Benziodoxolone (EBX)–Acetonitrile Complex. *Org. Lett.* **2019**, *21*, 1098–1102. (f) Takai, R.; Shimbo, D.; Tada, N.; Itoh, A. Ligand-Enabled Copper-Catalyzed *N* -Alkynylation of Sulfonamide with Alkynyl Benziodoxolone: Synthesis of Amino Acid-Derived Ynamide. *J. Org. Chem.* **2021**, *86*, 4699–4713.

(3) (a) Löffler, A.; Himbert, G. (1,3-Butadiynyl)Hydrazines: A New Class of Electron-Rich Alkadiynes. *Synthesis* **1994**, 383–386. (b) Himbert, G.; Naßhan, H.; Gerulat, O. A Straightforward Synthesis of Silylated and Stannylated Ynamines and Ynehydrazines. *Synthesis* **1997**, 293–294. Initial attempts with iodonium salts: (c) Denonne, F.; Seiler, P.; Diederich, F. Towards the Synthesis of Azoacetylenes. *Helv. Chim. Acta* **2003**, *86*, 3096–3117. Seminal work on alkynylation of azodicarboxylate: (d) Beveridge, R. E.; Batey, R. A. Terminal Alkyne Addition to Diazodicarboxylates: Synthesis of Hydrazide Linked Alkynes (Ynehydrazides). *Org. Lett.* **2012**, *14*, 540–543. Selected examples of applications: (e) Beveridge, R. E.; Batey, R. A. Total Synthesis of the Cytotoxic Enehydrazide Natural Products Hydrazidomycins A and B by a Carbazate Addition/Peterson Olefination Approach. *Org. Lett.* **2013**, *15*, 3086–3089. (f) Beveridge, R. E.; Hu, Y.; Gregoire, B.; Batey, R. A. Di- *Tert* -Butyl Ethynylimidodicarbonate as a General Synthon for the β-Aminoethylation of Organic Electrophiles: Application to the Formal Synthesis of Pyrrolidinoindoline Alkaloids (±)-CPC-1 and (±)-Alline. *J. Org. Chem.* **2020**, *85*, 8447–8461. (g) Diana-Rivero, R.; Halsvik, B.; García Tellado, F.; Tejedor, D. Short and Modular Synthesis of Substituted 2-Aminopyrroles. *Org. Lett.* **2021**, *23*, 4078–4082. (h) Tuck, J. R.; Tombari, R. J.; Yardeny, N.; Olson, D. E. A Modular Approach to Arylazo-1,2,3-Triazole Photoswitches. *Org. Lett.* **2021**, *23*, 4305–4310.

(4) (a) Proulx, C.; Sabatino, D.; Hopewell, R.; Spiegel, J.; García Ramos, Y.; Lubell, W. D. Azapeptides and Their Therapeutic Potential. *Future Med. Chem.* **2011**, *3*, 1139–1164. (b) Chingle, R.; Proulx, C.; Lubell, W. D. Azapeptide Synthesis Methods for Expanding Side-Chain Diversity for Biomedical Applications. *Acc. Chem. Res.* **2017**, *50*, 1541–1556. (c) Proulx, C.; Zhang, J.; Sabatino, D.; Chemtob, S.; Ong, H.; Lubell, W. D. Synthesis and Biomedical Potential of Azapeptide Modulators of the Cluster of Differentiation 36 Receptor (CD36). *Biomedicines* **2020**, *8*, 241.

(5) Dutta, Anand. S.; Giles, M. B. Polypeptides. Part XIV. A Comparative Study of the Stability towards Enzymes of Model Tripeptides Containing α-Aza-Amino-Acids, L -Amino-Acids, and D -Amino-Acids. *J Chem Soc Perkin Trans 1*. **1976**, 244–248.

(6) Kasznel, A. J.; Zhang, Y.; Hai, Y.; Chenoweth, D. M. Structural Basis for Aza-Glycine Stabilization of Collagen. *J. Am. Chem. Soc.* **2017**, *139*, 9427–9430.

(7) (a) Benatalah, Z.; Aubry, A.; Boussard, G.; Marraud, M. Evidence for a β-Turn in an Azadipeptide Sequence: Synthesis and Crystal Structure of ButCO-Pro-AzaAla-NHPri. *Int. J. Pept. Protein Res.* **1991**, *38*, 603–605. (b) Thormann, M.; Hofmann, H.-J. Conformational Properties of Azapeptides. *J. Mol. Struct.* **1999**, *469*, 63–76. (c) Lee, H.-J.; Choi, K.-H.; Ahn, I.-A.; Ro, S.; Jang, H. G.; Choi, Y.-S.; Lee, K.-B. The β-Turn Preferential Solution Conformation of a Tetrapeptide Containing an Azaamino Acid Residue. *J. Mol. Struct.* **2001**, *569*, 43–54. (d) Sabatino, D.; Proulx, C.; Pohankova, P.; Ong, H.; Lubell, W. D. Structure–Activity Relationships of GHRP-6 Azapeptide Ligands of the CD36 Scavenger Receptor by Solid-Phase Submonomer Azapeptide Synthesis. *J. Am. Chem. Soc.* **2011**, *133*, 12493–12506.

(8) (a) Meffre, P.; Le Goffic, F. β,γ-Alkynyl-α-Amino Acids: A Synthetic Challenge. *Amino Acids* **1996**, *11*, 313–328. (b) Bolsakova, J.; Jirgensons, A. Synthesis of α-Ethynyl Glycines. *Eur. J. Org. Chem.* **2016**, *2016*, 4591–4602 and references cited therein.

(9) Allouche, E. M. D.; Grinhagena, E.; Waser, J. Hypervalent Iodine-Mediated Late-Stage Peptide and Protein Functionalization. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112287.

(10) Having a bulky *tert*-butyl group was essential as byproducts resulting from cyclization on the ester were observed if a methyl or a benzyl group were used.

(11) Borrel, J.; Pisella, G.; Waser, J. Copper-Catalyzed Oxyalkynylation of C–S Bonds in Thiiranes and Thiethanes with Hypervalent Iodine Reagents. *Org. Lett.* **2020**, *22*, 422–427.

(12) Borrel, J.; Waser, J. Tosyloxybenziodoxolone: A Platform for Performing the Umpolung of Alkynes in One-Pot Transformations. *Org. Lett.* **2022**, *24*, 142–146.

(13) (a) Rajasekaran, A.; Devi, K. S. Synthesis and Biological Evaluation of 1-(3-Chloro-2-Oxo-4-Phenylazetidin-1-Yl)-3-(2-Oxo-2-(10H-Phenothiazin-10-Yl)Ethyl)Urea Derivatives. *Med. Chem. Res.* **2013**, *22*, 2578–2588. (b) Jamal Gilani, S.; Zaheen Hassan, Mohd.; Sarim Imam, S.; Kala, C.; Prakash Dixit, S. Novel Benzothiazole Hydrazine Carboxamide Hybrid Scaffolds as Potential in Vitro GABA AT Enzyme Inhibitors: Synthesis, Molecular Docking and Antiepileptic Evaluation. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1825–1830.

(14) Proulx, C.; Lubell, W. D. *N* -Amino-Imidazolin-2-One Peptide Mimic Synthesis and Conformational Analysis. *Org. Lett.* **2012**, *14*, 4552–4555.

(15) A preprint of this work has appeared: Le Du, E.; Borrel, J.; Waser, J. ChemRxiv 2022, 10.26434/chemrxiv-2022-j0x08. This content is a preprint and has not been peer-reviewed.

# Copper-Catalyzed Alkynylation of Hydrazides: An Easy Access to Functionalized Azadipeptides

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## 1. General information

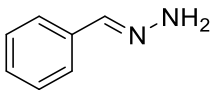
All reactions were carried out under air unless stated otherwise. Reactions requiring heating were carried out using DrySyn heating block. For flash chromatography, distilled technical grade solvents were used. THF, toluene, $Et_2O$ and $CH_2Cl_2$ were dried by passage over activated alumina under nitrogen atmosphere ($H_2O$ content <10 ppm, Karl-Fischer titration). Solvents were degassed by bubbling with a balloon of argon or by Freeze-Pump-Thaw when mentioned. All chemicals were purchased from Acros, Aldrich, Combi-blocks, Fluka, Fluorochem, Merck, TCI or VWR and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Silicycle silica 40-63 µm (230-400 mesh), using the solvents indicated as eluent with 0.1-0.5 bar pressure or using Biotage Isolera Spektra One with pre-packaged silica cartridges purchased from Buchi, models: Sepacore or GraceResolve (4 g, 12 g, 25 g, 40g, 80g, 120g). TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with UV light and potassium permanganate, *p*-anisaldehyde or ninhydrin stain. $^1$H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-$d_6$ or acetone-$d_6$. All signals are reported in ppm using the residual solvent signal as internal reference (chloroform-d: 7.26 ppm, DMSO-$d_6$: 2.50 ppm, acetone-$d_6$: 2.06 ppm). The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration, assignment). $^{13}$C-NMR spectra were recorded with {$^1$H} decoupling on a Bruker DPX-400 101 MHz spectrometer in chloroform-d, DMSO-$d_6$ or acetone-$d_6$. All signals are reported in ppm using the residual solvent signal as internal reference (chloroform-d: 77.0 ppm, DMSO-$d_6$: 39.5 ppm, acetone-$d_6$: 206.3 and 29.8 ppm). $^{19}$F-NMR spectra were recorded with {$^1$H} decoupling on a Bruker DPX-400 376 MHz spectrometer in chloroform-d, DMSO-$d_6$ or acetone-$d_6$. $^{11}$B-NMR spectra were recorded on a Bruker DPX-400 128 MHz spectrometer in DMSO-$d_6$ or acetone-$d_6$. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL. Electrospray-ionisation HRMS data were acquired on a Q-Tof Ultima mass spectrometer (Waters) or a Q-Tof 6530 Accurate mass spectrometer (Agilent) operated in the positive ionization mode and fitted with a standard Z-spray ion source equipped with the Lock-Spray interface. Data from the Lock-Spray were used to calculate a correction factor for the mass scale and provide accurate mass information of the analyte. Data were processed using the MassLynx 4.1 software. Atmospheric pressure photo-ionisation (APPI) HRMS measurements were done on a LTQ Orbitrap Elite instrument (Thermofisher) operated in the positive ionization mode. The raw data obtained from the Q-TOF Waters instrument does not take into account the mass of the electron for the ion, the obtained raw data has been corrected by removing (positive ionization) or adding (negative ionization) the mass of the electron (0.5 mDa). Optical rotations were measured on a polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated. RP-HPLC was carried out on an Agilent 1260 HPLC system with a G2260A 1260 Prep ALS Autosampler, a G1361a 1260 Prep Pump, a G1365C 1260 MWD detector and a G1364B 1260 FC-PS collector, coupled with a Waters XBridge semi-preparative C18 column (19 x 150 mm, 5 µm). Water (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% TFA, were used as the mobile phase at a flow rate of 20 mL.min$^{-1}$. The following method was used: 100% A to 100% B in 20 minutes.

## 2. Starting materials preparation

H-Pro-O*t*Bu, H-Gly-O*t*Bu, H-Tyr-O*t*Bu, H-Trp-O*t*Bu, H-Asn-O*t*Bu, H-Lys(Z)-O*t*Bu·HCl, H-Met-O*t*Bu·HCl, H-Glu(OMe)-O*t*Bu·HCl, H-Val-O*t*Bu·HCl, H-Phe-O*t*Bu·HCl, H-Ser-O*t*Bu·HCl, H-Ala-O*t*Bu·HCl, phenylacetylene, 2-ethynyl-1,3,5-trimethylbenzene, ethynyltriisopropylsilane, ethynylcyclopropane, 5-chloropent-1-yne, 1-ethynyl-3-methoxybenzene, 1-ethynyl-4-fluorobenzene and 2-bromo-1-(trimethylsilylethynyl)benzene were commercially available and used as received.

### 2.1 General procedures for aza-peptides synthesis

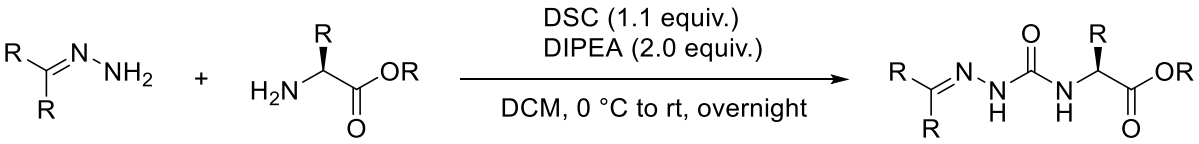
**(*E*)-benzylidenehydrazine (9)**



Following a reported procedure,[1] a microwave vial was charged under $N_2$ with hydrazine monohydrate (4.00 mL, 82.5 mmol, 4.38 equiv) and benzaldehyde (1.92 mL, 18.8 mmol, 1.00 equiv) was added dropwise at 0 °C. The reaction mixture was vigorously stirred at 100 °C for 6 h. The reaction was cooled to rt and the product was extracted with 3 X 2 mL of DCM. The combined extracts were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. (*E*)-Benzylidenehydrazine (**9**) (2.19 g, 18.2 mmol, 97% yield) was obtained as a yellowish oil and was used without further purification.[2]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, *H*C=N), 7.59-7.51 (m, 2H, Ar*H*), 7.38-7.27 (m, 3H, Ar*H*), 5.53 (br s, 2H, N*H*$_2$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.3, 135.2, 128.8, 128.7, 126.3. Spectroscopic data was consistent with the values reported in the literature.[1]

**General procedure A for the coupling of hydrazine with amino acids**




Using a slightly modified literature procedure,[3] in a flame-dried round-bottom flask, at 0 °C, a solution of *N,N'*-disuccinimidyl carbonate (DSC) (1.10 equiv.) in dry DCM (0.35 M) was treated dropwise over 20 min with a solution of the corresponding hydrazone (1.00 equiv.) in dry DCM (0.23 M). The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the mixture was cooled to 0 °C and treated dropwise with a premixed solution of the corresponding amino acid (1.00 equiv.) and DIPEA

[1] Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11* (15), 3202–3205.

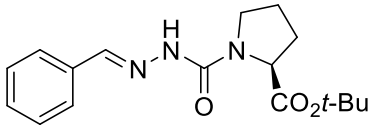
[2] For long term storage, the hydrazine was kept under $N_2$ in a -20 °C freezer in which it solidified. When needed the solid was let thawing before using it.

[3] Y. Garcia-Ramos, W. D. Lubell, *J. Pept. Sci.* **2013**, *19*, 725–729.

(2.00 equiv.) in DCM (0.8 M). The ice bath was removed. The reaction mixture was allowed to warm to room temperature and stirred overnight. The crude mixture was diluted with 20 mL of sat. $NaHCO_3$, extracted with DCM (3 x 30 mL), washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The volatiles were evaporated, and the crude was purified on a column of silica gel using flash chromatography.

**2.2 Starting amino acids and peptides characterization data**

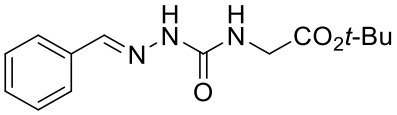
***tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (2a)**




Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Pro-OtBu (361 mg, 2.00 mmol, 1.00 equiv.), DIPEA (697 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, *tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**2a**) (400 mg, 1.26 mmol, 63% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1).

**Rf** (DCM/MeOH 20:1): 0.35. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, N*H*), 7.76 (s, 1H, *H*C=N), 7.62 (dt, *J* = 8.4, 2.2 Hz, 2H, Ar*H*), 7.43-7.28 (m, 3H, Ar*H*), 4.73-4.65 (m, 1H, NC*H*$CO_2$tBu), 3.84-3.66 (m, 2H, NC$H_2$), 2.22 (dq, *J* = 12.3, 8.5 Hz, 1H, NCHC$H_2$), 2.12-1.85 (m, 3H, NCHC$H_2$ and $NCH_2CH_2$), 1.41 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.1, 154.6, 142.0, 134.5, 129.5, 128.7, 127.2, 81.6, 61.0, 48.4, 30.5, 28.1, 23.7. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}N_3NaO_3^+$ 340.1632; Found 340.1632. **IR** ($\nu_{max}$, $cm^{-1}$) 3230 (w), 2979 (m), 2882 (w), 1737 (s), 1650 (m), 1549 (m), 1395 (s), 1365 (s), 1207 (m), 1145 (s), 1080 (m), 911 (m), 737 (s). $[\alpha]_D^{25}$ = -83.4 (c = 0.57, $CHCl_3$).

***tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (2b)**

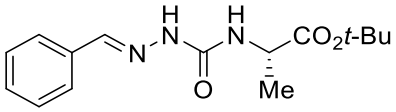



Following general procedure A and starting with DSC (1.45 g, 5.50 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (601 mg, 5.00 mmol, 1.00 equiv.), H-Gly-OtBu (690 mg, 5.00 mmol, 1.00 equiv.), DIPEA (1.74 mL, 10.0 mmol, 2.00 equiv.) and 44 mL of dry DCM, *tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (712 mg, 2.57 mmol, 51% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 20:1): 0.23. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.64 (dd, *J* = 7.6, 1.9 Hz, 2H, Ar*H*), 7.44-7.31 (m, 3H, Ar*H*), 6.64 (t, *J* = 5.4 Hz, 1H, N*H*), 4.06 (d, *J* = 5.5 Hz, 2H, C$H_2$), 1.51 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.6, 156.4, 141.7, 134.1, 129.8, 128.8, 127.0, 82.2, 42.6, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for

$C_{14}H_{19}N_3NaO_3^+$ 300.1319; Found 300.1318. **IR** ($\nu_{max}$, $cm^{-1}$) 3345 (w), 2988 (w), 1783 (m), 1733 (s), 1675 (m), 1539 (s), 1369 (s), 1224 (s), 1152 (s), 1069 (m), 757 (m).

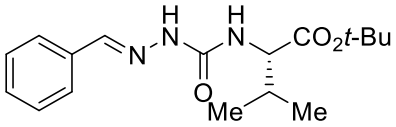
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (2c)**




Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Ala-O*t*Bu HCl (275 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (**2c**) (254 mg, 0.872 mmol, 58% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 50:1).

**Rf** (DCM/MeOH 50:1): 0.15. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.29 (s, 1H, NN*H*), 7.75 (s, 1H, *H*C=N), 7.68-7.61 (m, 2H, Ar*H*), 7.43-7.31 (m, 3H, Ar*H*), 6.70 (d, *J* = 7.8 Hz, 1H, N*H*CH), 4.51 (p, *J* = 7.2 Hz, 1H, NHC*H*), 1.55-1.42 (m, 12H, C$H_3$ and *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.7, 155.8, 141.4, 134.1, 129.8, 128.8, 127.0, 81.9, 49.3, 28.2, 19.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{15}H_{21}N_3NaO_3^+$ 314.1475; Found 314.1474. **IR** ($\nu_{max}$, $cm^{-1}$) 3400 (w), 3189 (w), 3071 (m), 2988 (m), 1737 (m), 1668 (s), 1524 (s), 1369 (s), 1141 (s), 911 (m), 846 (m), 757 (m), 732 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +58.8 (c = 0.55, $CHCl_3$).

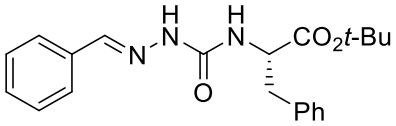
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (2d)**




Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Val-O*t*Bu HCl (321 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (**2d**) (295 mg, 0.924 mmol, 62% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 50:1): 0.21. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.33 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.63 (m, 2H, Ar*H*), 7.43-7.32 (m, 3H, Ar*H*), 6.69 (d, *J* = 9.1 Hz, 1H, N*H*CH), 4.44 (dd, *J* = 9.1, 4.6 Hz, 1H, NHC*H*), 2.30-2.16 (m, 1H, NHCHC*H*), 1.50 (s, 9H, *t*Bu), 1.02 (d, *J* = 6.9 Hz, 3H, C$H_3$), 0.99 (d, *J* = 6.9 Hz, 3H, C$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.5, 156.3, 141.4, 134.2, 129.8, 128.8, 127.0, 81.9, 58.2, 31.9, 28.2, 19.2, 17.8. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{25}N_3NaO_3^+$ 342.1788; Found 342.1781. **IR** ($\nu_{max}$, $cm^{-1}$) 3428 (w), 3215 (w), 2966 (m), 1729 (s), 1683 (s), 1524 (s), 1369 (s), 1217 (m), 1136 (s), 944 (w), 842 (m), 752 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +54.3 (c = 0.81, $CHCl_3$).

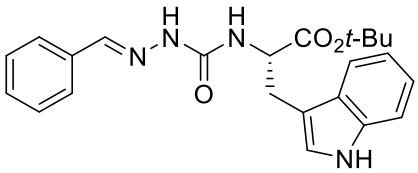
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (2e)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Phe-O*t*Bu HCl (391 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (**2e**) (262 mg, 0.713 mmol, 48% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 50:1): 0.23. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.08 (s, 1H, NN*H*), 7.70 (s, 1H, *H*C=N), 7.61-7.52 (m, 2H, Ar*H*), 7.37 (m, 3H, Ar*H*), 7.33-7.28 (m, 2H, Ar*H*), 7.27 (m, 1H, Ar*H*), 7.26-7.23 (m, 2H, Ar*H*), 6.65 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.77 (dt, *J* = 8.4, 6.0 Hz, 1H, NHC*H*), 3.26-3.09 (m, 2H, NHCHC$H_2$), 1.42 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.0, 155.7, 141.2, 136.5, 134.1, 129.8, 129.8, 128.8, 128.5, 127.1, 127.0, 82.2, 54.2, 39.0, 28.1. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{21}H_{25}N_3NaO_3^+$ 390.1788; Found 390.1786. **IR** ($\nu_{max}$, cm$^{-1}$) 3403 (w), 3087 (m), 2981 (m), 1740 (m), 1686 (s), 1527 (s), 1365 (s), 1163 (s), 1134 (s), 910 (m), 846 (m), 733 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +14.7 (c = 0.60, $CHCl_3$).

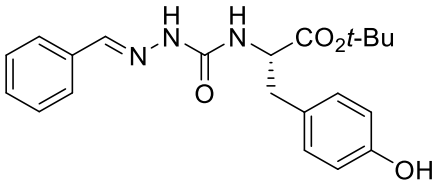
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (2f)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Trp-O*t*Bu (445 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (**2f**) (362 mg, 0.891 mmol, 59% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

**Rf** (DCM/MeOH 50:1): 0.16. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, NN*H*), 8.18 (s, 1H, N*H*), 7.69 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.60 (s, 1H, *H*C=N), 7.44-7.26 (m, 6H, Ar*H*), 7.21-7.13 (m, 1H, Ar*H*), 7.11-7.06 (m, 2H, Ar*H*), 6.71 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.85 (dt, *J* = 8.4, 5.7 Hz, 1H, NHC*H*), 3.36 (d, *J* = 5.7 Hz, 2H, NHCHC$H_2$), 1.40 (s, 9H, *t*Bu).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.6, 156.0, 141.2, 136.2, 134.1, 129.6, 128.7, 128.0, 127.0, 122.9, 122.2, 119.8, 119.1, 111.2, 110.7, 82.0, 54.1, 28.3, 28.1. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{23}H_{26}N_4NaO_3^+$ 429.1897; Found 429.1894. **IR** ($\nu_{max}$, cm$^{-1}$) 3247 (w), 2974 (w), 1729 (w), 1661 (m), 1535 (m), 1515 (m), 1369 (m), 1231 (w), 1156 (m), 1131 (m), 907 (s), 727 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -54.6 (c = 0.54, $CHCl_3$).

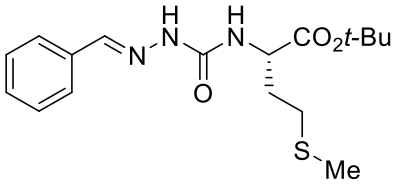
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (2g)**



Following general procedure A and starting with DSC (581 mg, 2.20 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (240 mg, 2.00 mmol, 1.00 equiv.), H-Tyr-O*t*Bu (484 mg, 2.00 mmol, 1.00 equiv.), DIPEA (696 µL, 4.00 mmol, 2.00 equiv.) and 17.6 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (**2g**) (300 mg, 0.782 mmol, 39% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

**Rf** (DCM/MeOH 20:1): 0.17. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.85 (s, 1H, NN*H*), 7.64 (s, 1H, *H*C=N), 7.57-7.51 (m, 2H, Ar*H*), 7.41-7.29 (m, 3H, Ar*H*), 7.05 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.73 (dd, *J* = 9.0, 2.4 Hz, 2H, Ar*H*), 6.65 (d, *J* = 8.5 Hz, 1H, N*H*CH), 6.33 (s, 1H, O*H*), 4.71 (dt, *J* = 8.5, 6.1 Hz, 1H, NHC*H*), 3.13-2.97 (m, 2H, NCHC$H_2$), 1.44 (s, 9H, *t*Bu).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.3, 155.7, 155.2, 141.6, 134.0, 130.8, 129.9, 128.8, 127.9, 127.1, 115.5, 82.4, 54.4, 38.1, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{25}N_3NaO_4^+$ 406.1737; Found 406.1735. **IR** ($\nu_{max}$, $cm^{-1}$) 3294 (w), 2978 (w), 1725 (w), 1672 (m), 1532 (m), 1369 (m), 1231 (w), 1156 (m), 907 (s), 730 (s). $[\alpha]_D^{25}$ = -5.4 (c = 0.54, $CHCl_3$).

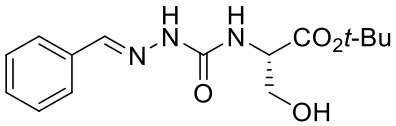
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (2h)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Met-O*t*Bu HCl (382 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (**2h**) (294 mg, 0.837 mmol, 56% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

**Rf** (DCM/MeOH 50:1): 0.13. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H, NN*H*), 7.76 (s, 1H, *H*C=N), 7.65 (m, 2H, Ar*H*), 7.45-7.31 (m, 3H, Ar*H*), 6.79 (d, *J* = 8.2 Hz, 1H, N*H*CH), 4.63 (td, *J* = 7.7, 5.0 Hz, 1H, NHC*H*), 2.70-2.52 (m, 2H, SC$H_2$), 2.22 (m, 1H, NHCHC$H_2$), 2.12 (s, 3H, SC$H_3$), 2.11 (m, 1H, NHCHC$H_2$), 1.50 (s, 9H, *t*Bu).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.4, 156.0, 141.6, 134.1, 129.9, 128.8, 127.0, 82.2, 52.8, 33.0, 30.2, 28.2, 15.6. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{17}H_{25}N_3NaO_3S^+$ 374.1509; Found 374.1502. **IR** ($\nu_{max}$, $cm^{-1}$) 3414 (w), 3202 (m), 3100 (m), 2974 (m), 1730 (m), 1668 (s), 1531 (s), 1369 (s), 1145 (s), 950 (w), 849 (w), 759 (m). $[\alpha]_D^{25}$ = -8.4 (c = 0.24, $CHCl_3$).

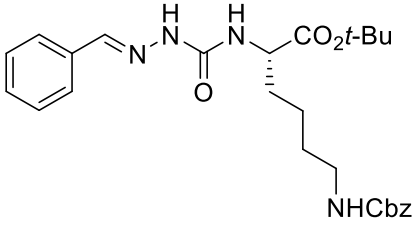
***tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (2i)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Ser-O*t*Bu HCl (312 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-Butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (**2i**) (316 mg, 1.03 mmol, 69% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

**Rf** (DCM/MeOH 20:1): 0.20. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, NN*H*), 7.74 (s, 1H, *H*C=N), 7.68-7.58 (m, 2H, Ar*H*), 7.43-7.31 (m, 3H, Ar*H*), 7.07 (d, *J* = 6.8 Hz, 1H, N*H*CH), 4.56 (ddd, *J* = 6.9, 4.8, 3.4 Hz, 1H, NHC*H*), 4.04 (ddd, *J* = 11.1, 6.0, 3.4 Hz, 1H, NHCHC$H_2$), 3.96 (ddd, *J* = 11.1, 6.2, 4.9 Hz, 1H, NHCHC$H_2$), 3.12 (t, *J* = 6.2 Hz, 1H, O*H*), 1.52 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.7, 156.7, 142.1, 133.9, 130.0, 128.8, 127.1, 83.0, 64.8, 56.4, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{15}H_{21}N_3NaO_4^+$ 330.1424; Found 330.1422. **IR** ($\nu_{max}$, $cm^{-1}$) 3407 (w), 2985 (w), 1732 (m), 1658 (m), 1527 (m), 1368 (m), 1156 (m), 1131 (m), 907 (s), 727 (s). $[\alpha]_D^{25}$ = +56.8 (c = 0.47, $CHCl_3$).

***tert*-Butyl *(E)*-N$^2$-(2-benzylidenehydrazine-1-carbonyl)-N$^6$-((benzyloxy)carbonyl)-*L*-lysinate (2j)**

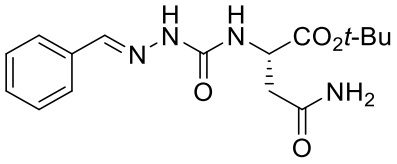


Following general procedure A and starting with DSC (291 mg, 1.10 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (120 mg, 1.00 mmol, 1.00 equiv.), H-Lys(Z)-O*t*Bu HCl (393 mg, 1.00 mmol, 1.00 equiv.), DIPEA (348 µL, 2.00 mmol, 2.00 equiv.) and 8.80 mL of dry DCM, *tert*-butyl *(E)*-N$^2$-(2-benzylidenehydrazine-1-carbonyl)-N$^6$-((benzyloxy)carbonyl)-*L*-lysinate (**2j**) (260 mg, 0.539 mmol, 54% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 50:1): 0.15. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H, NN*H*), 7.68 (s, 1H, *H*C=N), 7.63 (dd, *J* = 7.6, 1.9 Hz, 2H, Ar*H*), 7.41-7.27 (m, 8H, Ar*H*), 6.66 (d, *J* = 8.4 Hz, 1H, N*H*CH), 5.07 (s, 2H, OC$H_2$Ph), 4.90 (t, *J* = 5.0 Hz, 1H, N*H*Cbz), 4.50 (td, *J* = 7.9, 5.1 Hz, 1H, NHC*H*), 3.20 (q, *J* = 6.5 Hz, 2H, C$H_2$NHCbz), 1.96-1.85 (m, 1H, NHCHC$H_2$), 1.80-1.70 (m, 1H, NHCHC$H_2$), 1.64-1.52 (m, 2H, C$H_2$CH$_2$NHCbz), 1.50-1.40 (m, 11H, NHCHCH$_2$C$H_2$ and *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.9, 156.5, 155.8, 141.5, 136.8, 134.0, 129.9, 128.8, 128.6, 128.2, 127.0, 82.1, 66.7, 53.1, 40.9, 33.1, 29.5, 28.2, 22.5. One aromatic $^{13}$C is not resolved. **HRMS (nanochip-ESI/LTQ-Orbitrap)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{34}N_4NaO_5^+$ 505.2421; Found 505.2415. IR ($\nu_{max}$, $cm^{-1}$)

3367 (w), 2978 (m), 2934 (m), 2862 (w), 1675 (s), 1526 (s), 1368 (m), 1251 (s), 1155 (s), 1134 (s), 1023 (w), 755 (s). $[\alpha]_D^{25}$ = +1.6 (c = 0.42, $CHCl_3$).

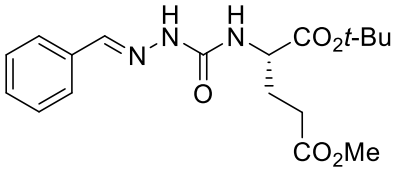
**_tert_-Butyl _(E)_-(2-benzylidenehydrazine-1-carbonyl)-_L_-asparaginate (2k)**



Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Asn-O*t*Bu (436 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, *tert*-butyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-asparaginate (**2k**) (166 mg, 0.497 mmol, 33% yield) was obtained as a white amorphous solid after purification by column chromatography on silica (DCM/MeOH 50:1 to DCM/MeOH 20:1).

**Rf** (DCM/MeOH 20:1): 0.23. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, NN*H*), 7.75 (s, 1H, *H*C=N), 7.64-7.57 (m, 2H, Ar*H*), 7.38-7.29 (m, 3H, Ar*H*), 7.19 (d, *J* = 8.1 Hz, 1H, N*H*CH), 6.21 (br s, 1H, C(O)N$H_2$), 5.99 (br s, 1H, C(O)N$H_2$), 4.71 (dt, *J* = 8.2, 5.1 Hz, 1H, NHC*H*), 2.94-2.81 (m, 2H, NHCHC$H_2$), 1.49 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.7, 170.4, 156.4, 142.0, 134.0, 129.9, 128.8, 127.1, 82.7, 50.4, 38.7, 28.1. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{16}H_{22}N_4NaO_4^+$ 357.1533; Found 357.1525. **IR** ($\nu_{max}$, $cm^{-1}$) 3379 (m), 3168 (w), 2960 (w), 1731 (m), 1669 (s), 1520 (s), 1361 (m), 1159 (s), 1127 (s), 914 (m), 730 (s). $[\alpha]_D^{25}$ = +30.6 (c = 0.51, $CHCl_3$).

**1-(_tert_-Butyl) 5-methyl _(E)_-(2-benzylidenehydrazine-1-carbonyl)-_L_-glutamate (2l)**

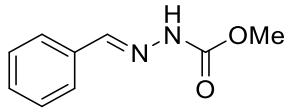


Following general procedure A and starting with DSC (436 mg, 1.65 mmol, 1.10 equiv.), (E)-benzaldehyde hydrazine (180 mg, 1.50 mmol, 1.00 equiv.), H-Glu(OMe)-O*t*Bu HCl (401 mg, 1.50 mmol, 1.00 equiv.), DIPEA (523 µL, 3.00 mmol, 2.00 equiv.) and 13.2 mL of dry DCM, 1-(*tert*-butyl) 5-methyl *(E)*-(2-benzylidenehydrazine-1-carbonyl)-*L*-glutamate (**2l**) (332 mg, 0.914 mmol, 61% yield) was obtained as a colorless oil after purification by column chromatography on silica (DCM/MeOH 200:1 to DCM/MeOH 50:1).

**Rf** (DCM/MeOH 50:1): 0.10. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.07 (s, 1H, NN*H*), 7.73 (s, 1H, *H*C=N), 7.66 (m, 2H, Ar*H*), 7.44-7.32 (m, 3H, Ar*H*), 6.75 (d, *J* = 8.2 Hz, 1H, N*H*CH), 4.54 (td, *J* = 8.2, 4.9 Hz, 1H, NHC*H*), 3.66 (s, 3H, OC$H_3$), 2.58-2.37 (m, 2H, C$H_2CO_2$Me), 2.34-2.25 (m, 1H, NHCHC$H_2$), 2.07 (m, 1H, NHCHC$H_2$), 1.50 (s, 9H, *t*Bu).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.6, 171.4, 155.9, 141.5, 134.0, 129.9, 128.8, 127.1, 82.4, 52.9, 51.9, 30.4, 28.4, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{18}H_{25}N_3NaO_5^+$ 386.1686; Found 386.1680. **IR** ($\nu_{max}$, $cm^{-1}$) 3375 (w), 3201

(w), 3094 (w), 2959 (m), 1737 (s), 1672 (s), 1531 (s), 1368 (s), 1226 (m), 1153 (s), 917 (w), 849 (w), 757 (m). $[\alpha]_D^{25}$ = +11.7 (c = 0.32, $CHCl_3$).

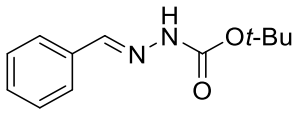
**Methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (2m)**



Following a reported procedure,[4] to a solution of methyl *N*-aminocarbamate (866 mg, 9.42 mmol, 1.00 equiv) in ethanol (23.5 mL) was added benzaldehyde (962 µL, 9.42 mmol, 1.00 equiv). The reaction mixture was stirred under reflux for 3 h. The solution was cooled to room temperature and the precipitate filtered (washed with hexane) under vacuum. Methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**2m**) (925 mg, 5.19 mmol, 55% yield) was collected as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.52-8.19 (m, 1H, NN*H*), 7.87 (s, 1H, *H*C=N), 7.73-7.61 (m, 2H, Ar*H*), 7.43-7.32 (m, 3H, Ar*H*), 3.86 (s, 3H, OC$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 154.6, 144.9, 133.7, 129.9, 128.5, 127.2, 52.8. Spectroscopic data was consistent with the values reported in the literature.[5]

***tert*-Butyl (*E*)-2-benzylidenehydrazine-1-carboxylate (2n)**



Following a reported procedure,[4] to a solution of *tert*-butylcarbazate (1.27 g, 9.42 mmol, 1.00 equiv) in ethanol (23.5 mL) was added benzaldehyde (962 µL, 9.42 mmol, 1.00 equiv). The reaction mixture was stirred under reflux for 3 h. The solution was cooled to room temperature and the precipitate filtered (washed with hexane) under vacuum. *tert*-Butyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**2n**) (1.47 g, 6.67 mmol, 71% yield) was collected as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, NN*H*), 7.83 (s, 1H, *H*C=N), 7.70-7.66 (m, 2H, Ar*H*), 7.40-7.32 (m, 3H, Ar*H*), 1.54 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.4, 143.7, 134.0, 130.0, 128.7, 127.3, 81.6, 28.4. Spectroscopic data was consistent with the values reported in the literature.[6]

## 2.3 Procedures for the synthesis of EBX

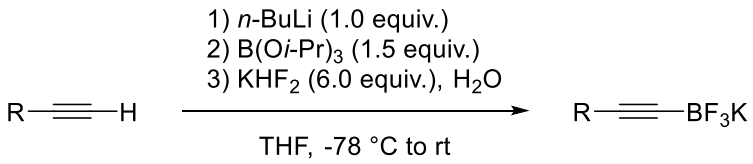
The preparation of the following $BF_3K$-alyknes and EBX reagents had been already described before. The procedures are taken here from the indicated publications to facilitate reproduction of the results by having all the data in the same file.

[4] Santos, M. S.; Nortcliffe, A.; Lewis, W.; Bradshaw, T. D.; Moody, C. J. *Chem. Eur. J.* **2018**, *24* (33), 8325–8330.
[5] He, R.; Lam, Y. *Org. Biomol. Chem.* **2008**, *6* (12), 2182-2186.
[6] Löser, R.; Schilling, K.; Dimmig, E.; Gütschow, M. *J. Med. Chem.* **2005**, *48* (24), 7688–7707.

## 2.3.1 Synthesis of Potassium Trifluoroborate Salts

General note: It is known that carbons linked to the boron atom are difficult to be observed by $^{13}C$ NMR due to a broadening of the signal caused by the quadrupole moment of $^{11}B$ nuclei. This implies that the two carbons of the alkyne (in alkynyl-$BF_3K$) are too broad to be properly visible.[7] Therefore, they are not listed in the characterization data.

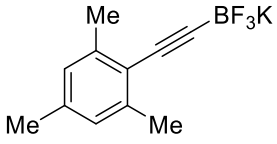
**General procedure B:**




Following a reported procedure.[8] An oven-dried round-bottom flask (PFA), charged with alkyne (1.0 equiv.) if solid, was evacuated and backfilled with $N_2$ (3x). Then, alkyne (if liquid) and dry THF (0.3 M) were added. The mixture was cooled to -78 °C and a solution of *n*-BuLi (2.5 M, 1.0 equiv.) in hexane was added dropwise under $N_2$. The reaction was stirred at -78 °C for 1 h and B(O*i*-Pr)$_3$ (1.5 equiv.) was added quickly. The reaction was stirred 10 min at -78 °C then 2 h at rt. The mixture was cooled to 0 °C and a saturated solution of $KHF_2$ (6.0 equiv.) in water (40% of THF volume + additional 40% to rinse the remaining solid) was added. The reaction was stirred at rt open to air for 2 h then concentrated *in vacuo*. The wet solid obtained was further dried by co-evaporation with acetone. To the dry solid was added acetone (~50 mL) and the resulting mixture was placed on a rotary evaporator and rotated rapidly at atmospheric pressure with the bath set at 45 °C for 15 minutes. The flask was removed and the mixture carefully filtered taking care to leave the insoluble material in the reaction flask. Acetone was once again added and the process (heating for 15 min then collection of the liquid) was repeated 2 more times. The combined acetone filtrates were concentrated *in vacuo* to approximately 1/3 of the initial volume. $Et_2O$ (~60 mL) was added causing a white solid to precipitate. The mixture was cooled to 0 °C for 10 min then filtered. The solid obtained was washed with $Et_2O$ and dried in vacuo to afford the desired potassium alkynyltrifluoroborate.

Note: This purification procedure usually affords the pure desired product. If it is not the case a more classical recrystallization from acetone followed by precipitation with $Et_2O$ can be performed.

**Potassium trifluoro(mesitylethynyl)borate (10):**

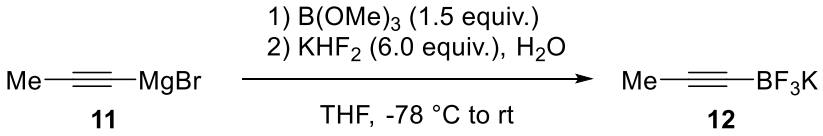



[7] R. A. Oliveira, R. O. Silva, G. A. Molander, P. H. Menezes, *Magn. Reson. Chem.* **2009**, *47*, 873–878.
[8] J. Borrel, J. Waser, *Org. Lett.* **2022**, *24*, 142–146.

Synthesized following general procedure B, starting from 2-ethynyl-1,3,5-trimethylbenzene (0.950 g, 1.03 mL, 6.3 mmol). Potassium trifluoro(mesitylethynyl)borate (**10**) (1.23 g, 4.94 mmol, 78%) was obtained as a white solid.

**$^{1}$H NMR** (400 MHz, acetone-$d_6$) δ 6.79 (s, 2H, Ar*H*), 2.34 (s, 6H, C*H*$_3$), 2.20 (s, 3H, C*H*$_3$). **$^{13}$C NMR** (101 MHz, acetone-$d_6$) δ 140.0, 135.9, 127.9, 124.0, 21.3, 21.2. **$^{19}$F NMR** (377 MHz, acetone-$d_6$) δ -134.3. **$^{11}$B NMR** (128 MHz, acetone-$d_6$) δ -1.0 (q, *J* = 37.3 Hz). Spectroscopic data was consistent with the values reported in the literature.[8]

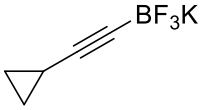
**Potassium trifluoro(prop-1-yn-1-yl)borate (12)**




Following a reported procedure.[8] An oven-dried round-bottom flask (PFA) was evacuated and backfilled with $N_2$ (3x). Then, a solution of 1-propynylmagnesium bromide (**11**) (15 mL, 7.5 mmol, 0.5 M, 1.0 equiv.) in THF and dry THF (15 mL) were added. The solution was cooled to -78 °C and $B(OMe)_3$ (1.25 mL, 11.3 mmol, 1.5 equiv.) was added quickly under $N_2$. The reaction was stirred 1 h at -78 °C then 1.5 h at -20 °C. A saturated solution of $KHF_2$ (3.5 g, 45 mmol, 6.0 equiv.) in water (10 mL + additional 10 mL to rinse the remaining solid) was added. The reaction was stirred at rt open air for 2 h then concentrated *in vacuo*. The wet solid obtained was further dried by co-evaporation with acetone. To the dry solid was added acetone (~30 mL) and the resulting mixture was placed on a rotary evaporator and rotated rapidly at atmospheric pressure with the bath set at 45 °C for 15 minutes. The flask was removed and the mixture carefully filtered taking care to leave the insoluble material in the reaction flask. Acetone was once again added and the process (heating for 15 min then collection of the liquid) was repeated 2 more times. The combined acetone filtrates were concentrated *in vacuo* to approximately 1/3 of the initial volume. $Et_2O$ (~30 mL) was added causing a white solid to precipitate. The mixture was cooled to 0 °C for 10 min then filtered. The solid obtained was washed with $Et_2O$ and dried in vacuo to afford potassium trifluoro(prop-1-yn-1-yl)borate (**12**) (0.95 g, 6.5 mmol, 87%) as a white solid.

**$^{1}$H NMR** (400 MHz, acetone-$d_6$) δ 1.64 – 1.58 (m, 3H, C*H*$_3$). **$^{13}$C NMR** (101 MHz, acetone-$d_6$) δ 4.0. **$^{19}$F NMR** (376 MHz, acetone-$d_6$) δ -134.7 (dd, *J* = 76.0, 37.4 Hz). **$^{11}$B NMR** (128 MHz, acetone-$d_6$) δ -1.7 (q, *J* = 38.2 Hz). Spectroscopic data was consistent with the values reported in the literature.[8]

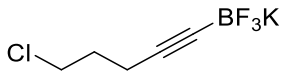
**Potassium (cyclopropylethynyl)trifluoroborate (13)**




Synthesized following general procedure B, starting from ethynylcyclopropane (0.50 g, 0.64 mL, 7.5 mmol). Potassium (cyclopropylethynyl)trifluoroborate (**13**) (0.86 g, 5.0 mmol, 67%) was obtained as a white solid.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ 1.12 – 1.01 (m, 1H, C*H*$CH_2$), 0.61 – 0.54 (m, 2H, CHC*H*$_2$), 0.42 – 0.36 (m, 2H, CHC*H*$_2$). **$^{13}$C NMR** (101 MHz, DMSO-$d_6$) δ 7.4, 0.1. **$^{19}$F NMR** (377 MHz, DMSO-$d_6$) δ -131.1. **$^{11}$B NMR** (128 MHz, DMSO-$d_6$) δ -2.1 (q, *J* = 37.5 Hz). Spectroscopic data was consistent with the values reported in the literature.[8]

**Potassium (5-chloropent-1-yn-1-yl)trifluoroborate (14)**

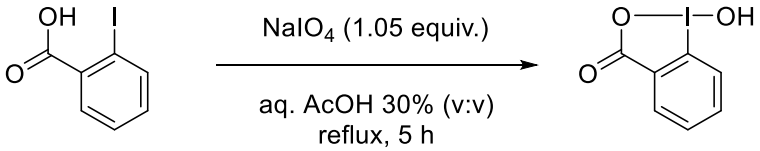



Synthesized following general procedure B, starting from 5-chloropent-1-yne (0.77 g, 0.80 mL, 7.5 mmol). Potassium (5-chloropent-1-yn-1-yl)trifluoroborate (**14**) (1.28 g, 6.14 mmol, 82%) was obtained as a white solid.

**$^1$H NMR** (400 MHz, acetone-$d_6$) δ 3.70 (t, *J* = 6.6 Hz, 2H, ClC*H*$_2$CH$_2$), 2.24 – 2.17 (m, 2H, C≡CC*H*$_2$CH$_2$), 1.85 (p, *J* = 6.7 Hz, 2H, CH$_2$C*H*$_2$CH$_2$). **$^{13}$C NMR** (101 MHz, acetone-$d_6$) δ 44.9, 33.1, 17.3. **$^{19}$F NMR** (376 MHz, acetone-$d_6$) δ -134.6. Spectroscopic data was consistent with the values reported in the literature.[9]

## 2.3.2 Procedures for the synthesis of EBX

**1-[Hydroxy]-1,2-benziodoxol-3-(1*H*)-one (16)**



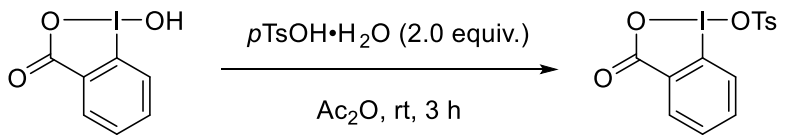

**15** **16**

Following a reported procedure.8 $NaIO_4$ (18.1 g, 84.7 mmol, 1.05 equiv) and 2-iodobenzoic acid (**15**) (20.0 g, 80.6 mmol, 1.00 equiv) were suspended in a mixture of AcOH (36 mL) and water (84 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (100 mL) and allowed to cool to room temperature protected from light. The crude product was collected by filtration, washed on the filter with ice water (3 x 50 mL) and acetone (3 x 50 mL), and air-dried in the dark to give the pure product **16** (20.0 g, 75.7 mmol, 94%) as a white solid.

**$^1$H NMR** (400 MHz, DMSO-$d_6$): δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.97 (m, 1H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*). **$^{13}$C NMR** (100 MHz, DMSO-$d_6$): δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. Spectroscopic data was consistent with the values reported in the literature.[8]

**1-[*p*-Methylbenzenesulfonyloxy]-1,2-benziodoxol-3-(1*H*)-one (17)**

[9] G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423.




**16** **17**

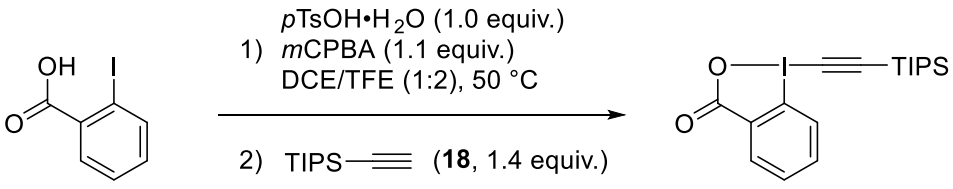
Following a reported procedure.[8] *p*TsOH•$H_2O$ (5.71 g, 30.0 mmol, 2.0 equiv.) was added portionwise to an oven-dried flask containing a suspension of 1-[Hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**16**) (3.96 g, 15.0 mmol, 1.0 equiv.) in acetic anhydride (15 mL). After 5 min, a slightly exothermic reaction began and the mixture turned into a clear slightly yellow solution. The reaction was stirred at rt under $N_2$ for 3 h. During the course of the reaction precipitation of the product as a white solid might occur. Dry $Et_2O$ (40 mL) was added and the mixture was cooled to 0 °C for 10 min. At this point precipitation of the product should have occurred. The solid was filtered and washed with dry $Et_2O$ (4 x 40 mL) then dried in vacuo to afford 1-[*p*-methylbenzenesulfonyloxy]-1,2-benziodoxol-3-(1*H*)-one (**17**) (4.75 g, 11.4 mmol, 76%) as a white solid.

Note: The product is slightly hygroscopic, when filtering it using vacuum filtration it is advised to avoid extensive drying on the frit. Just removing the ether is enough to collect it properly and further drying can be carried in vacuo.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.98 – 7.93 (m, 1H, Ar*H*), 7.83 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar*H*), 7.70 (td, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 7.15 – 7.10 (m, 2H, Ar*H*), 2.28 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 167.9, 145.2, 138.1, 134.6, 131.5, 131.2, 130.5, 128.3, 126.4, 125.6, 120.5, 20.9. Spectroscopic data was consistent with the values reported in the literature.[10]

Note: We observed a slow solubilization of **17** if dry DMSO is used. We think water present in DMSO help the solubilization and that when dry DMSO is used the solubilization happen after a couple of minutes (~5min) due to the progressive absorption of the water present in the air by the solvent.

**1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (3a)**




**15** **3a**

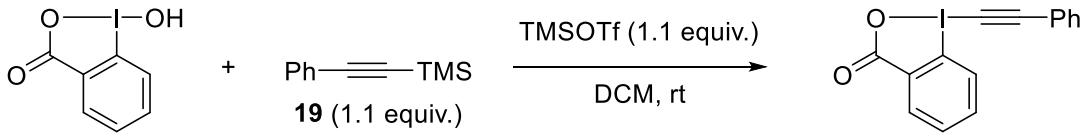
Following a reported procedure,[11] a 250 mL, three-necked, round-bottomed flask was equipped with a Teflon-coated magnetic stirrer (2 cm), a Liebig reflux condenser (open to air), and a septum. The septum was removed, and the flask was charged with *o*-iodobenzoic acid

[10] M. Nappi, C. He, W. G. Whitehurst, B. G. N. Chappell, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2018**, *57*, 3178–3182.
[11] 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*, 106–110.

(**15**) (6.00 g, 24.2 mmol, 1.00 equiv), *p*-toluenesulfonic acid monohydrate (4.60 g, 24.2 mmol, 1.00 equiv), 1,2-dichloroethane (36.3 mL), and trifluoroethanol (36.3 mL). The resulting white suspension was stirred (600 rpm) at room temperature. *m*CPBA (≤77% purity; 5.96 g, 26.6 mmol, ≤1.10 equiv) was added in portions over a period of 10 min. During the addition, the suspension slightly darkened, becoming beige. After the addition of *m*CPBA, the septum was replaced, and the flask was placed in dry-sin preheated to 55 °C and stirred (600 rpm). The mixture turned from a white suspension to a clear yellow color solution over a period of 5 min. After 1.5 h, (triisopropylsilyl)acetylene (**18**) (7.60 mL, 33.9 mmol, 1.40 equiv) was added dropwise via a 10 mL syringe over a period of 5 min and stirring was continued at 55 °C for another 24 h. After this time, the pale-yellow solution was allowed to cool down to room temperature. Saturated aq. $NaHCO_3$ (120 mL) was then added: a pinkish mixture was formed with significant bubbling. This biphasic mixture was stirred (1000 rpm) at room temperature for 1 h. The mixture was transferred to a 250 mL separatory funnel, and the reaction flask was rinsed with dichloromethane (12 mL). The two layers were separated, and the aqueous layer was extracted with additional portions of dichloromethane (3 × 40 mL). The combined organic layers were washed with water (3 × 50 mL), prior to being dried over $MgSO_4$ (ca. 3.0 g), filtered into a 250 mL round-bottomed flask, and concentrated via rotary evaporation, to provide an off-white solid. The latter was purified by recrystallization from acetonitrile (12 mL) to provide 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3a**) (8.36 g, 19.5 mmol, 81% yield) as a crystalline, white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 5.9, 3.2 Hz, 1H, Ar*H*), 8.34−8.25 (m, 1H, Ar*H*), 7.80−7.72 (m, 2H, Ar*H*), 1.27−1.06 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.5, 134.6, 132.3, 131.4, 131.4, 126.1, 115. 6, 114.0, 64.6, 18.4, 11.1. Spectroscopic data was consistent with the values reported in the literature.[11]

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




**16** **3b**

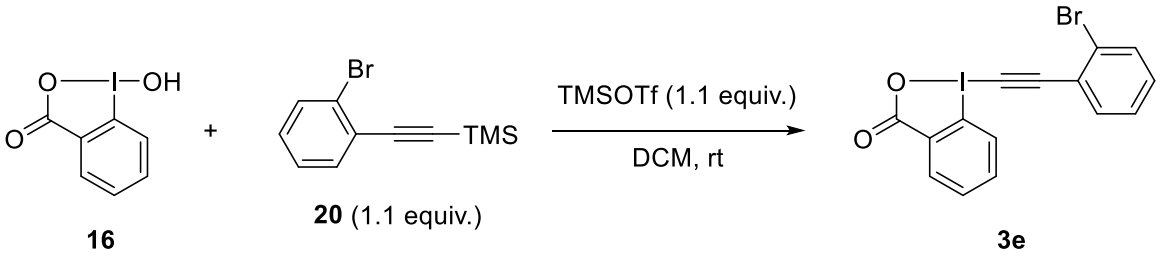
Following a reported procedure.[12] Trimethylsilyltriflate (9.1 mL, 50 mmol, 1.1 equiv) was added dropwise to a suspension of 1-[hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**16**) (12.1 g, 45.8 mmol, 1.0 equiv) in $CH_2Cl_2$ (120 mL) at 0 °C. The mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**19**) (8.8 mL, 50 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at rt, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (120 mL) was added and the mixture was stirred vigorously for 30 min. The two layers of the mother liquors were separated and the organic layer was washed with sat. $NaHCO_3$ (2x50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystalized in EtOAc:MeOH (7:3 v:v) (ca. 20 mL). The solution was left to cool to rt then in the freezer overnight, filtered and dried under

[12] S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.

high vacuum to afford 1-[phenylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3b**) (6.8 g, 25 mmol, 43% yield) as colorless crystals.

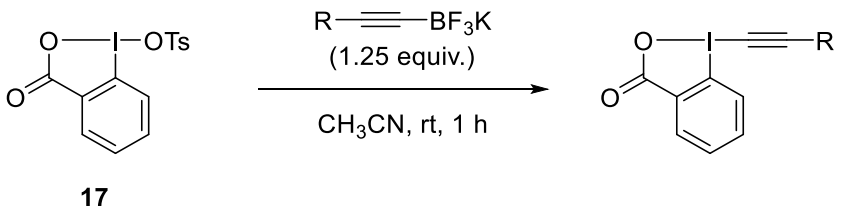
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.46 (m, 1H, Ar*H*), 8.28 (m, 1H, Ar*H*), 7.80 (m, 2H, Ar*H*), 7.63 (m, 2H, Ar*H*), 7.48 (m, 3H, Ar*H*). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3. 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2. Spectroscopic data was consistent with the values reported in the literature.[12]

**1-[(2-Bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (3e)**




Following a reported procedure.[12] Trimethylsilyl triflate (0.42 mL, 2.4 mmol, 1.1 equiv) was added to a suspension of 1-[hydroxy]-1,2-benziodoxol-3-(1*H*)-one (**16**) (0.562 g, 2.13 mmol, 1.00 equiv) in $CH_2Cl_2$ (6 mL) at rt. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((2-bromophenyl)ethynyl)trimethylsilane (**20**) (0.50 mL, 2.4 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at rt. A saturated solution of $NaHCO_3$ (10 mL) was then added and the mixture was stirred vigorously for 1 h resulting in a persistent emulsion/suspension. The mixture was diluted with $CHCl_3$ (10 mL), water (5 mL) and MeOH (ca. 2 mL) to afford 2 distinct layers. The two layers were separated, and the organic layer was washed with sat. $NaHCO_3$ (5 mL), dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure. The resulting solid was recrystallized in EtOAc:MeOH (7:3 v:v) (ca. 20 mL). The solution was left to cool to rt then was placed in the freezer (-20 °C) overnight. The crystals were filtered and washed with $Et_2O$ to afford 1-[(2-bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3e**) (1.50 g, 3.51 mmol, 70% yield) as colorless crystals.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.44 (td, *J* = 7.3, 2.1 Hz, 2 H, Ar*H*), 7.84 – 7.74 (m, 2 H, Ar*H*), 7.68 (d, *J* = 1.1 Hz, 1 H, Ar*H*), 7.61 (dd, J = 7.6, 1.7 Hz, 1 H, Ar*H*), 7.36 (m, 2 H, Ar*H*). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.6, 135.2, 134.7, 133.0, 132.7 , 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. Spectroscopic data was consistent with the values reported in the literature.[12]




**General procedure C for the purification-free synthesis of EBX reagents on 0.4 mmol scales**

Following a reported procedure.[8] A capped oven dried microwave vial charged with 1-(*p*-methylbenzenesulfonyloxy)-1,2-benziodoxol-3-(1*H*)-one (**17**) (167 mg, 0.400 mmol, 1.0

equiv.) and potassium alkynyltrifluoroborate (0.50 mmol, 1.25 equiv.) was evacuated and backfilled with $N_2$ (3x). Dry acetonitrile (4 mL) was added under $N_2$ and the reaction was stirred at rt for 1 h. To the mixture was added a sat. sol. of $NaHCO_3$ (8 mL) and the mixture was vigorously stirred open to air for 1 h. Water (10 mL) was added and the mixture was extracted with 3 x 20 mL of DCM, the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude EBX was triturated in pentane, which induced precipitation if it was an oil. The pentane layer was discarded with care to leave the solid in the flask. This process was repeated 2 more times then the solid was dried *in vacuo* to afford the desired compounds.

Note: Purity of the product obtained was determined using $^1H$ NMR by dissolving the entirety of the compound in $CDCl_3$ (~4 mL) and adding $CH_2Br_2$ (14.0 µL, 0.1975 mmol, 0.49 equiv.) as internal standard.

Purity is determined based on the signal of $CH_2Br_2$ (4.93 ppm) normalize at I = 1 and an aromatic signal of the EBX corresponding to 1 H:

$$n(EBX)_{eff} = \frac{\frac{I_{EBX}}{N_{EBX}} * n_{std} * N_{std}}{I_{std}} = \frac{\frac{I_{EBX}}{1} * 0.1975 * 2}{1} = I_{EBX} * 0.3950$$

$$p_{EBX} = \frac{n(EBX)_{eff}}{n(EBX)_{theo}} = \frac{n(EBX)_{eff}}{\frac{m_{EBX}}{MW_{EBX}}}$$

$n(EBX)_{eff}$: moles of EBX determined by NMR (in mmol).

$n(EBX)_{theo}$: moles of EBX calculated from the mass obtained if 100% pure (in mmol).

$I_{EBX}$: Integral of the EBX signal.

$I_{std}$: Integral of the standard ($CH_2Br_2$) signal.

$N_{EBX}$: Number of protons corresponding the EBX signal.

$N_{std}$: Number of protons corresponding the standard ($CH_2Br_2$) signal.

$m_{EBX}$: mass of EBX obtained at the end of the reaction (in mg).

$MW_{EBX}$: Molecular weight of the EBX (in mg/mmol)

$p_{EBX}$: purity of the EBX

**General procedure D for the purification-free synthesis of EBX reagents on 0.5 mmol scales**

Following an adapted version of a reported procedure.[8] A capped oven dried microwave vial charged with 1-(*p*-methylbenzenesulfonyloxy)-1,2-benziodoxol-3-(1*H*)-one (**17**) (209 mg, 0.500 mmol, 1.0 equiv.) and potassium alkynyltrifluoroborate (0.625 mmol, 1.25 equiv.) was evacuated and backfilled with $N_2$ (3x). Dry acetonitrile (5 mL) was added under $N_2$ and the reaction was stirred at rt for 1 h. To the mixture was added a sat. sol. of $NaHCO_3$ (8 mL) and the mixture was vigorously stirred open to air for 1 h. Water (10 mL) was added and the mixture was extracted with 3 x 20 mL of DCM, the combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The crude EBX was triturated in pentane, which induced precipitation if it was an oil. The pentane layer was discarded with care to leave the solid in the flask. This process was repeated 2 more times then the solid was dried *in vacuo* to afford the desired compounds.

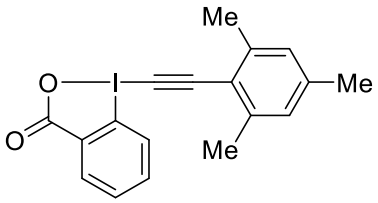
Note: Purity of the product obtained was determined using $^1$H NMR by dissolving the entirety of the compound in $CDCl_3$ (~4 mL) and adding $CH_2Br_2$ (17.5 µL, 0.2469 mmol, 0.49 equiv.) as internal standard.

Purity is determined based on the signal of $CH_2Br_2$ (4.93 ppm) normalize at I = 1 and an aromatic signal of the EBX corresponding to 1 H:

$$n(EBX)_{eff} = \frac{\frac{I_{EBX}}{N_{EBX}} * n_{std} * N_{std}}{I_{std}} = \frac{\frac{I_{EBX}}{1} * 0.2469 * 2}{1} = I_{EBX} * 0.4938$$

$$p_{EBX} = \frac{n(EBX)_{eff}}{n(EBX)_{theo}} = \frac{n(EBX)_{eff}}{\frac{m_{EBX}}{MW_{EBX}}}$$

**1-[Mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (3c)**




Synthesized following general procedure C, starting from potassium trifluoro(mesitylethynyl)borate (**10**) (125 mg, 0.500 mmol). The reaction was stirred at rt for 2 h. 1-[Mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3c**) (148.2 mg, 0.3792 mmol, 95%, 99% purity) was obtained as a white solid.

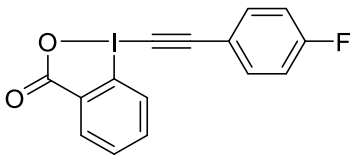
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.46 – 8.38 (m, 1H, Ar*H*), 8.33 – 8.25 (m, 1H, Ar*H*), 7.79 – 7.71 (m, 2H, Ar*H*), 6.95 (s, 2H, Ar*H*), 2.47 (s, 6H, ArC$H_3$), 2.34 (s, 3H, ArC$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7, 142.4, 141.0, 134.9, 132.7, 131.7, 131.6, 128.3, 126.2, 117.6, 116.7, 105.6, 55.7, 21.7, 21.3. Spectroscopic data was consistent with the values reported in the literature.[13]

$$n(EBX)_{eff} = 0.96 * 0.3950 = 0.3792\ mmol$$

$$p_{EBX} = \frac{0.3792}{\frac{148.2}{390.21}} = 0.9984 = 99\%\ purity$$

**1-[(4-Fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (3d)**

[13] R. Frei, M. D. Wodrich, D. P. Hari, P. A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563–16573.



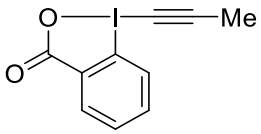

Synthesized following general procedure D, starting from potassium trifluoro((4-fluorophenyl)ethynyl)borate (141 mg, 0.625 mmol). 1-[(4-Fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3d**) (172.4 mg, 0.4592 mmol, 92%, 97% purity) was obtained as a white solid. Spectroscopic data was consistent with the values reported in the literature.[14]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.43 – 8.36 (m, 1H, Ar*H*), 8.25 – 8.18 (m, 1H, Ar*H*), 7.81 – 7.70 (m, 2H, Ar*H*), 7.64 – 7.56 (m, 2H, Ar*H*), 7.16 – 7.08 (m, 2H, Ar*H*). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.8, 164.0 (d, *J* = 253.8 Hz), 135.2 (d, *J* = 8.9 Hz), 135.0, 132.6, 131.7, 131.5, 126.5, 116.9 (d, *J* = 3.7 Hz), 116.4 (d, *J* = 22.4 Hz), 116.3, 105.5, 50.4 (d, *J* = 2.0 Hz). **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -106.0.

$$n(EBX)_{eff} = 0.93 * 0.4938 = 0.4592\, mmol$$

$$p_{EBX} = \frac{\frac{0.4592}{172.4}}{\frac{}{366.13}} = 0.9752 = 97\%\, purity$$

**1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (3f)**




Synthesized following general procedure C, starting from potassium trifluoro(prop-1-yn-1-yl)borate (**12**) (73.0 mg, 0.500 mmol). 1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**3f**) (105.9 mg, 0.3476 mmol, 87%, 94% purity) as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.41 – 8.33 (m, 1H, Ar*H*), 8.22 – 8.13 (m, 1H, Ar*H*), 7.79 – 7.67 (m, 2H, Ar*H*), 2.26 (s, 3H, C$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$)[15] δ 166.6, 134.8, 132.5, 131.6, 126.3, 115.6, 105.1, 39.0, 5.7. Spectroscopic data was consistent with the values reported in the literature.[13]

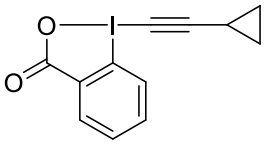
$$n(EBX)_{eff} = 0.88 * 0.3950 = 0.3476\, mmol$$

$$p_{EBX} = \frac{\frac{0.3476}{105.9}}{\frac{}{286.07}} = 0.9390 = 94\%\, purity$$

**1-[Cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (3g)**

[14] D. P. Hari, G. Pisella, M. D. Wodrich, A. V. Tsymbal, F. F. Tirani, R. Scopelliti, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 5475–5481.

[15] One aromatic carbon signal was not resolved, consistent with literature.



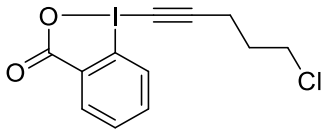
Synthesized following general procedure C, starting from potassium (cyclopropylethynyl)trifluoroborate (**13**) (86.0 mg, 0.500 mmol). 1-[Cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3g**) (115.7 mg, 0.3555 mmol, 89%, 96% purity) was obtained as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 1H, Ar*H*), 8.18 – 8.12 (m, 1H, Ar*H*), 7.79 – 7.68 (m, 2H, Ar*H*), 1.65 – 1.56 (m, 1H, C*H*$CH_2$), 1.05 – 0.97 (m, 2H, CHC$H_2$), 0.97 – 0.91 (m, 2H, CHC$H_2$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7, 134.7, 132.4, 131.6, 131.5, 126.2, 115.9, 113.4, 35.1, 9.8, 1.1. Spectroscopic data was consistent with the values reported in the literature.[13]

$$n(EBX)_{eff} = 0.90 * 0.3950 = 0.3555\, mmol$$

$$p_{EBX} = \frac{0.3555}{\frac{115.7}{312.10}} = 0.9590 = 96\%\, purity$$

**1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (3h)**



Synthesized following general procedure D, starting from potassium (5-chloropent-1-yn-1-yl)trifluoroborate (**14**) (130 mg, 0.625 mmol). 1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**3h**) (152.3 mg, 0.4345 mmol, 87%, 99% purity) was obtained as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.0, 2.2 Hz, 1H, Ar*H*), 8.22 – 8.11 (m, 1H, Ar*H*), 7.79 – 7.66 (m, 2H, Ar*H*), 3.70 (t, *J* = 6.1 Hz, 2H, ClC$H_2$$CH_2$), 2.81 (t, *J* = 6.9 Hz, 2H, C≡CC$H_2$$CH_2$), 2.10 (p, *J* = 6.6 Hz, 2H, $CH_2$C$H_2$$CH_2$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.0, 134.8, 132.4, 131.6, 131.5, 126.5, 115.8, 107.0, 43.4, 41.1, 30.7, 17.9. Spectroscopic data was consistent with the values reported in the literature.[13]

$$n(EBX)_{eff} = 0.88 * 0.4938 = 0.4345\, mmol$$

$$p_{EBX} = \frac{0.4345}{\frac{152.3}{348.56}} = 0.9944 = 99\%\, purity$$

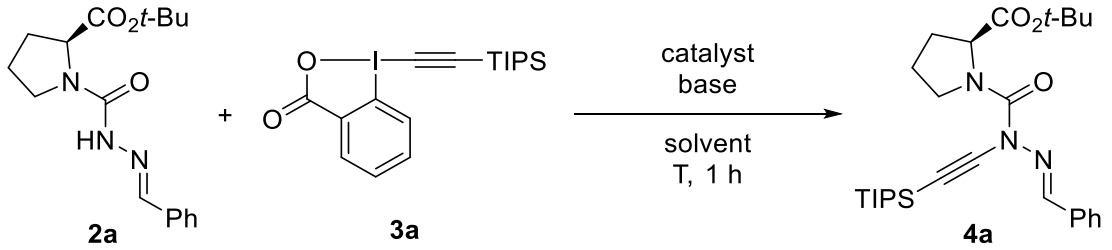
## 3. Optimization of the alkynylation of azapeptides

*tert*-Butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate **2a** was chosen as substrate on a 0.05 mmol scale.

**General method for the optimization of the reaction**

An oven-dried 5 mL microwave vial equipped with a magnetic stirring bar was charged under air with TIPS-EBX (21.4 mg, 50.0 µmol, 1.00 equiv.), the corresponding base (75.0 µmol, 1.50 equiv.), *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (15.9 mg, 50.0 µmol, 1.00 equiv.) and the corresponding catalyst (2.50 µmol, 5 mol%). The vial was capped and 500 µL of dry solvent was added. The heterogeneous mixture was vigorously stirred at the indicated temperature for 1 hour. After this time, the reaction was cooled down to room temperature, and the mixture was filtered over a pad of Celite® using DCM to rinse (≈ 10 mL) and concentrated under reduced pressure. The crude residue was then purified by preparative thin-layer chromatography (DCM/MeOH 100:1).

**Table 1. Optimization of the azapeptide alkynylation.**



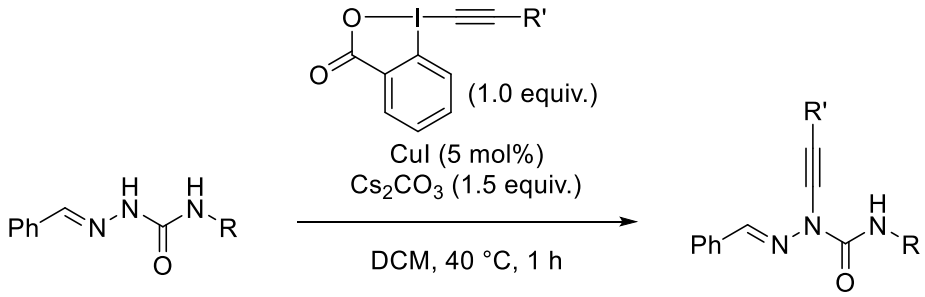

| entry | base | T | solvent | catalyst | yield |
|---|---|---|---|---|---|
| 1 | *t*-BuOK | rt | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 20% |
| 2 | $Cs_2CO_3$ | rt | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 16% |
| 3 | $Cs_2CO_3$ | 40 °C | $CH_3CN$ | $Cu(CH_3CN)_4BF_4$ | 32% |
| 4 | $Cs_2CO_3$ | 40 °C | *i*-PrOH | $Cu(CH_3CN)_4BF_4$ | 48% |
| 5 | $Cs_2CO_3$ | 40 °C | DCE | $Cu(CH_3CN)_4BF_4$ | 60% |
| 6 | $Cs_2CO_3$ | 40 °C | DCE | CuCl | 36% |
| 7 | $Cs_2CO_3$ | 40 °C | DCE | $CuCl_2$ | 68% |
| 8 | $Cs_2CO_3$ | 40 °C | DCE | CuI | 76% |
| 9[a] | $Cs_2CO_3$ | 40 °C | DCE | CuI | 72% |
| 10 | $Na_2CO_3$ | 40 °C | DCE | CuI | 8% |
| 11 | $K_2CO_3$ | 40 °C | DCE | CuI | 12% |
| 12 | - | 40 °C | DCE | CuI | - |
| 13 | $Cs_2CO_3$ | 40 °C | DCE | - | - |
| **14** | **$Cs_2CO_3$** | **40 °C** | **DCM** | **CuI** | **72%** |
| 15 | $Cs_2CO_3$ | 40 °C | DCM (not dry) | CuI | 48% |

[a]TIPS-EBX (1.5 equiv.)

## 4. Scope of the reaction

### 4.1 General procedures

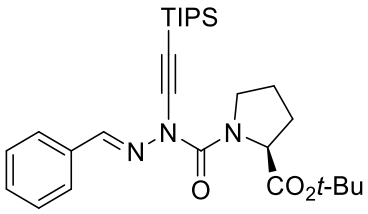
**General procedure E for the alkynylation reaction done on 0.3 mmol scale**




An oven-dried 5 mL microwave vial equipped with a magnetic stirring bar was charged under air with the corresponding EBX (0.300 mmol, 1.00 equiv.), $Cs_2CO_3$ (147 mg, 0.450 mmol, 1.50 equiv.), the chosen substrate (0.300 mmol, 1.00 equiv.) and CuI (2.90 mg, 15.0 µmol, 5 mol%). The vial was capped and 3.00 mL of dry DCM was added. The heterogeneous mixture was vigorously stirred at 40 °C for 1 hour. After this time, the reaction was cooled down to room temperature, and the mixture was filtered over a pad of Celite® using DCM to rinse (≈ 50 mL) and concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel.

### 4.2 Characterization data

***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (4a)**

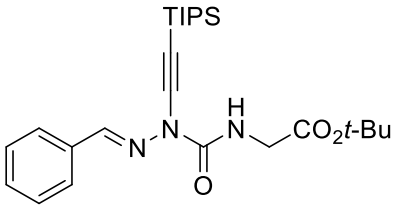


Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**2a**) (95.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (**4a**) (113 mg, 0.227 mmol, 76% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 200:1).

**Rf** (DCM/MeOH 100:1): 0.45. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.68-7.61 (m, 2H, Ar*H*), 7.48-7.34 (m, 3H, Ar*H*), 5.24-4.39 (br s, 1H, NC*H*), 4.06-3.58 (br s, 2H, NC$H_2$), 2.47-2.19 (br s, 1H, NCHC$H_2$), 2.09-1.81 (br s, 3H, NCHC$H_2$ and NCH$_2$C$H_2$), 1.54-1.23 (br s, 9H, *t*Bu), 1.21-1.04 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.4, 153.6, 144.2, 133.8, 130.2, 128.9, 127.9, 90.0, 84.2, 81.5, 62.2, 50.5, 27.9, 18.9, 11.5. (2 C not resolved)**. HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{28}H_{44}N_3O_3Si^+$ 498.3146; Found 498.3150. **IR** ($\nu_{max}$, $cm^{-1}$) 2960 (m), 2866

(m), 2156 (m), 1740 (s), 1686 (s), 1462 (m), 1404 (s), 1361 (s), 1149 (s), 882 (m), 752 (m). $[\alpha]_D^{25}$ = -66.4 (c = 0.53, $CHCl_3$).

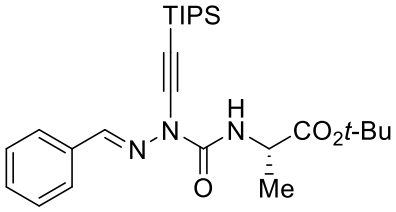
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)glycinate (4b)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)glycinate (**4b**) (117 mg, 0.256 mmol, 85% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).
The reaction was also carried out on 1 mmol scale affording (**4b**) (445 mg, 0.972 mmol, 97% yield).

**Rf** (DCM): 0.5. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.73-7.64 (m, 2H, Ar*H*), 7.47-7.40 (m, 3H, Ar*H*), 7.09 (t, *J* = 5.2 Hz, 1H, N*H*), 4.08 (d, *J* = 5.3 Hz, 2H, C$H_2$), 1.50 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.2, 145.0, 133.1, 130.7, 129.0, 127.9, 88.4, 85.1, 82.5, 43.1, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{39}N_3NaO_3Si^+$ 480.2653; Found 480.2657. **IR** ($\nu_{max}$, $cm^{-1}$) 3407 (w), 2949 (m), 2865 (m), 2152 (m), 1740 (m), 1712 (s), 1513 (s), 1369 (s), 1241 (m), 1167 (s), 1004 (w), 883 (m), 759 (s).

***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-alaninate (4c)**

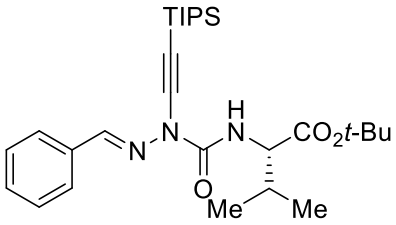



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-alaninate (**2c**) (87.4 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-alaninate (**4c**) (97.0 mg, 0.206 mmol, 69% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.61. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.73-7.64 (m, 2H, Ar*H*), 7.49-7.38 (m, 3H, Ar*H*), 7.24 (d, *J* = 7.5 Hz, 1H, N*H*CH), 4.52 (p, *J* = 7.2 Hz, 1H, NHC*H*), 1.53-1.46 (m, 12H, C$H_3$ and *t*Bu), 1.24-1.09 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.2, 152.5, 144.8, 133.2, 130.7, 129.0, 127.9, 88.6, 85.1, 82.2, 49.9, 28.1, 19.4, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_3Si^+$ 494.2809; Found 494.2806. **IR** ($\nu_{max}$, $cm^{-1}$) 3408 (w),

2949 (m), 2858 (m), 2158 (m), 1719 (s), 1498 (s), 1452 (s), 1347 (m), 1227 (m), 1156 (s), 1109 (m), 947 (m), 871 (s), 735 (s). $[\alpha]_D^{25}$ = +38.9 (c = 0.46, $CHCl_3$).

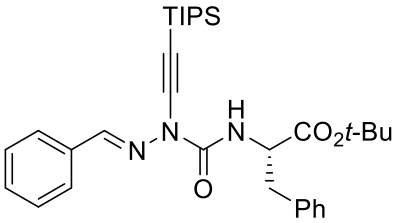
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-valinate (4d)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-valinate (**2d**) (96.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-valinate (**4d**) (57.0 mg, 0.114 mmol, 38% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.59. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.67 (m, 2H, Ar*H*), 7.49-7.40 (m, 3H, Ar*H*), 7.19 (d, *J* = 8.9 Hz, 1H, N*H*CH), 4.45 (dd, *J* = 9.0, 4.4 Hz, 1H, NHC*H*), 2.26 (pd, *J* = 6.9, 4.5 Hz, 1H, NHCHC*H*), 1.49 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS), 0.95 (d, *J* = 6.9 Hz, 3H, C$H_3$), 0.92 (d, *J* = 6.9 Hz, 3H, C$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.0, 153.0, 144.7, 133.2, 130.7, 129.1, 127.8, 88.6, 85.2, 82.2, 58.9, 31.9, 28.2, 19.0, 18.9, 17.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{28}H_{45}N_3NaO_3Si^+$ 522.3122; Found 522.3123. **IR** ($\nu_{max}$, $cm^{-1}$) 3405 (w), 2956 (m), 2869 (m), 2152 (m), 1719 (s), 1501 (s), 1369 (s), 1315 (m), 1156 (s), 1116 (s), 910 (m), 878 (s), 737 (s). $[\alpha]_D^{25}$ = +39.7 (c = 0.41, $CHCl_3$).

***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-phenylalaninate (4e)**

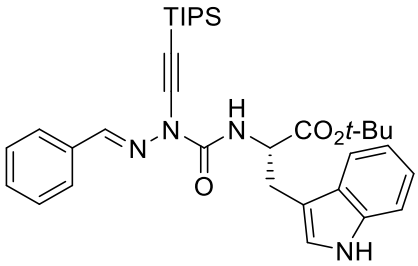



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-phenylalaninate (**2e**) (110 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-phenylalaninate (**4e**) (121 mg, 0.221 mmol, 74% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.55. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, *H*C=N), 7.62-7.53 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, Ar*H*), 7.33-7.26 (m, 3H, Ar*H*), 7.24-7.20 (m, 2H, Ar*H*), 7.12 (d, *J* = 8.4 Hz, 1H, N*H*CH), 4.81 (ddd, *J* = 8.4, 6.5, 5.1 Hz, 1H, NHC*H*), 3.26 (dd, *J* = 13.8, 5.0 Hz, 1H, NHCHC$H_2$), 3.13 (dd, *J* = 13.8, 6.5 Hz, 1H, NHCHC$H_2$), 1.41 (s, 9H, *t*Bu), 1.16 (m, 21H, TIPS). **$^{13}$C NMR** (101

MHz, $CDCl_3$) δ 170.5, 152.6, 144.7, 136.2, 133.1, 130.7, 129.8, 129.0, 128.6, 127.8, 127.1, 88.5, 85.2, 82.5, 54.6, 38.8, 28.1, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{32}H_{45}N_3NaO_3Si^+$ 570.3122; Found 570.3138. **IR** ($\nu_{max}$, $cm^{-1}$) 3410 (w), 2956 (m), 2866 (m), 2162 (m), 1737 (s), 1497 (s), 1369 (m), 1156 (s), 1105 (m), 882 (m), 755 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +11.8 (c = 0.53, $CHCl_3$).

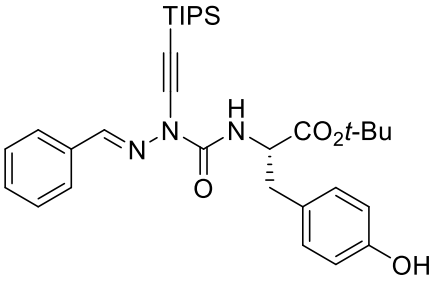
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tryptophanate (4f)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-tryptophanate (**2f**) (122 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tryptophanate (**4f**) (140 mg, 0.239 mmol, 80% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.41. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, *H*C=N), 8.10 (s, 1H, N*H*), 7.65 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.43-7.29 (m, 6H, Ar*H*), 7.22-7.12 (m, 2H, Ar*H* and N*H*CHCH$_2$), 7.10-7.00 (m, 2H, Ar*H*), 4.90 (dt, *J* = 8.5, 5.5 Hz, 1H, NHC*H*CH$_2$), 3.46-3.30 (m, 2H, NHCHC*H*$_2$), 1.37 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.0, 152.8, 144.7, 136.2, 133.1, 130.5, 128.9, 128.0, 127.9, 122.9, 122.3, 119.9, 119.2, 111.1, 110.5, 88.6, 85.1, 82.2, 54.6, 28.2, 28.1, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}N_4NaO_3Si^+$ 609.3231; Found 609.3232. **IR** ($\nu_{max}$, $cm^{-1}$) 3385 (w), 2952 (m), 2865 (m), 2156 (m), 1704 (m), 1502 (s), 1367 (m), 1153 (s), 1102 (m), 910 (m), 734 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -33.5 (c = 0.52, $CHCl_3$).

***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-tyrosinate (4g)**

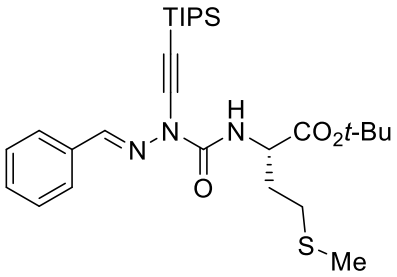



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-tyrosinate (**2g**) (115 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-

carbonyl)-*L*-tyrosinate (**4g**) (50.0 mg, 89.0 µmol, 30% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 100:1): 0.17. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, *H*C=N), 7.63-7.54 (m, 2H, Ar*H*), 7.47-7.37 (m, 3H, Ar*H*), 7.11 (d, *J* = 8.5 Hz, 1H, N*H*CH), 7.08-7.04 (m, 2H, Ar*H*), 6.79-6.71 (m, 2H, Ar*H*), 5.19 (s, 1H, O*H*), 4.80-4.71 (m, 1H, NHC*H*), 3.16 (dd, *J* = 14.0, 5.1 Hz, 1H, NHCHC$H_2$), 3.06 (dd, *J* = 14.0, 6.3 Hz, 1H, NHCHC$H_2$), 1.43 (s, 9H, *t*Bu), 1.23-1.08 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.7, 155.0, 152.7, 144.8, 133.1, 130.9, 130.7, 129.0, 128.0, 127.9, 115.5, 88.4, 85.3, 82.5, 54.7, 37.9, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{32}H_{45}N_3NaO_4Si^+$ 586.3072; Found 586.3088. **IR** ($\nu_{max}$, $cm^{-1}$) 3389 (m), 2941 (m), 2862 (m), 2152 (m), 1704 (m), 1618 (w), 1502 (s), 1369 (m), 1228 (m), 1156 (s), 907 (m), 732 (s). $[\alpha]_D^{25}$ = +3.7 (c = 0.31, $CHCl_3$).

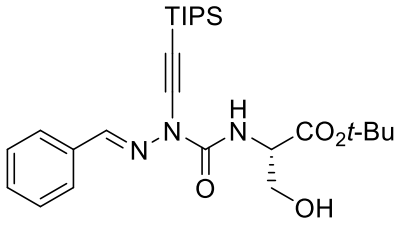
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-methioninate (4h)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-methioninate (**2h**) (105 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-methioninate (**4h**) (92.0 mg, 0.173 mmol, 58% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.62. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.74-7.65 (m, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 1H, N*H*CH), 4.62 (ddd, *J* = 7.9, 7.0, 5.1 Hz, 1H, NHC*H*), 2.67-2.50 (m, 2H, SC$H_2$), 2.24 (m, 1H, NHCHC$H_2$), 2.14-2.02 (m, 4H, SC$H_3$ and NHCHC$H_2$), 1.50 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.9, 152.9, 144.9, 133.1, 130.7, 129.1, 127.9, 88.5, 85.3, 82.7, 53.6, 32.7, 30.0, 28.2, 18.9, 15.7, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{28}H_{45}N_3NaO_3SSi^+$ 554.2843; Found 554.2840. **IR** ($\nu_{max}$, $cm^{-1}$) 3412 (w), 2938 (m), 2862 (m), 2158 (m), 1717 (s), 1502 (s), 1361 (m), 1153 (s), 1109 (m), 912 (m), 875 (m), 734 (s). $[\alpha]_D^{25}$ = +9.9 (c = 0.57, $CHCl_3$).

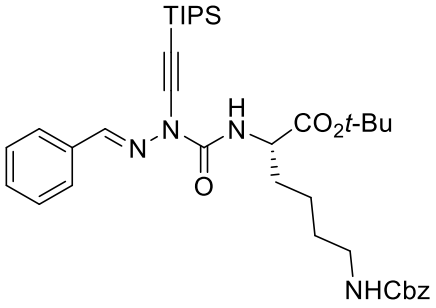
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-serinate (4i)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-serinate (**2i**) (92.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-serinate (**4i**) (43.0 mg, 88.0 µmol, 29% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

**Rf** (DCM/MeOH 50:1): 0.31. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.74-7.65 (m, 2H, Ar*H*), 7.53 (d, *J* = 6.7 Hz, 1H, N*H*CH), 7.48-7.40 (m, 3H, Ar*H*), 4.56 (dt, *J* = 7.1, 3.7 Hz, 1H, NHC*H*), 4.11-3.96 (m, 2H, NHCHC$H_2$), 2.36 (br s, 1H, O*H*), 1.52 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.3, 153.5, 145.2, 133.0, 130.8, 129.1, 128.0, 88.2, 85.4, 83.2, 64.3, 56.7, 28.2, 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{41}N_3NaO_4Si^+$ 510.2759; Found 510.2750. **IR** ($\nu_{max}$, $cm^{-1}$) 3444 (w), 2943 (m), 2862 (m), 2158 (m), 1708 (m), 1504 (s), 1347 (m), 1163 (m), 1113 (m), 1073 (m), 909 (s), 871 (m), 732 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +24.3 (c = 0.29, $CHCl_3$).

***tert*-Butyl (*E*)-N$^2$-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-N$^6$-((benzyloxy)carbonyl)-*L*-lysinate (4j)**

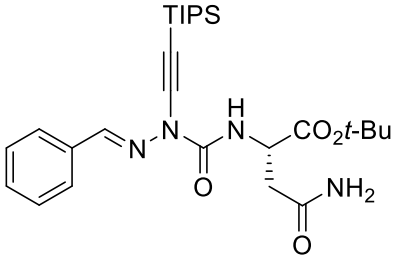



Synthesized from *tert*-butyl (*E*)-N$^2$-(2-benzylidenehydrazine-1-carbonyl)-N$^6$-((benzyloxy)carbonyl)-*L*-lysinate (**2j**) (145 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-N$^2$-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-N$^6$-((benzyloxy)carbonyl)-*L*-lysinate (**4j**) (152 mg, 0.229 mmol, 76% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM to DCM/MeOH 100:1).

**Rf** (DCM): 0.12. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, *H*C=N), 7.68 (dq, *J* = 4.8, 3.0 Hz, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 7.39-7.24 (m, 5H, Ar*H*), 7.20 (d, *J* = 8.1 Hz, 1H, N*H*CH), 5.07 (s, 2H, OC$H_2$Ph), 4.81-4.72 (m, 1H, N*H*Cbz), 4.56-4.47 (m, 1H, NHC*H*), 3.20 (q, *J* = 6.5 Hz, 2H, C$H_2$NHCbz), 2.00-1.88 (m, 1H, NHCHC$H_2$), 1.83-1.72 (m, 1H, NHCHC$H_2$), 1.58-1.40 (m, 13H, C$H_2$CH$_2$NHCbz, NHCHCH$_2$C$H_2$ and *t*Bu), 1.24-1.10 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.5, 156.5, 152.8, 144.9, 136.8, 133.1, 130.7, 129.1, 128.6, 128.2, 127.9, 88.5, 85.2, 82.5,

66.7, 53.9, 41.0, 33.0, 29.7, 28.2, 22.5, 18.9, 11.5. One aromatic $^{13}C$ is not resolved. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{37}H_{54}N_4NaO_5Si^+$ 685.3756; Found 685.3767. **IR** ($\nu_{max}$, $cm^{-1}$) 3411 (m), 2949 (m), 2862 (m), 2155 (m), 1712 (s), 1495 (s), 1365 (m), 1246 (s), 1159 (s), 910 (m), 875 (m), 734 (s). $[\alpha]_D^{25}$ = +10.1 (c = 0.62, $CHCl_3$).

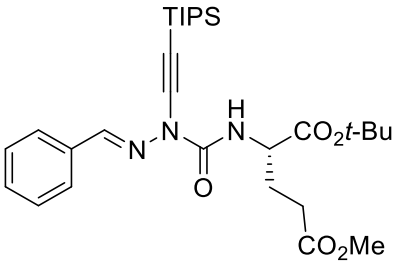
***tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-asparaginate (4k)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-asparaginate (**2k**) (100 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-asparaginate (**4k**) (84.0 mg, 0.163 mmol, 54% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM/MeOH 100:1 to DCM/MeOH 20:1).

**Rf** (DCM/MeOH 20:1): 0.27. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, *H*C=N), 7.77 (d, *J* = 7.9 Hz, 1H, N*H*CH), 7.71-7.66 (m, 2H, Ar*H*), 7.45-7.39 (m, 3H, Ar*H*), 5.90 (s, 1H, C(O)N$H_2$), 5.53 (s, 1H, C(O)N$H_2$), 4.68 (dt, *J* = 8.0, 4.6 Hz, 1H, NHC*H*), 3.02-2.85 (m, 2H, NHCHC$H_2$), 1.49 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.1, 169.8, 153.4, 145.1, 133.0, 130.7, 129.0, 128.0, 88.4, 85.1, 82.8, 51.0, 37.9, 28.0, 18.8, 11.4. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{27}H_{42}N_4NaO_4Si^+$ 537.2868; Found 537.2865. **IR** ($\nu_{max}$, $cm^{-1}$) 3425 (m), 3266 (w), 2942 (m), 2866 (m), 2152 (m), 1738 (m), 1700 (s), 1672 (s), 1520 (s), 1358 (m), 1254 (m), 1152 (s), 914 (m), 733 (s). $[\alpha]_D^{25}$ = +14.7 (c = 0.32, $CHCl_3$).

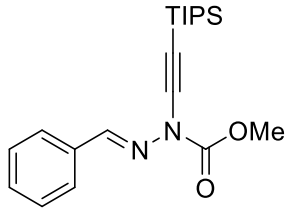
**1-(*tert*-Butyl) 5-methyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glutamate (4l)**




Synthesized from 1-(*tert*-butyl) 5-methyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)-*L*-glutamate (**2l**) (109 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. 1-(*tert*-Butyl) 5-methyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glutamate (**4l**) (92.0 mg, 0.169 mmol, 56% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.45. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.76-7.67 (m, 2H, Ar*H*), 7.44 (m, 3H, Ar*H*), 7.30-7.26 (m, 1H, N*H*CH), 4.54 (td, *J* = 7.9, 5.0 Hz, 1H, NHC*H*), 3.65 (s, 3H, OC$H_3$), 2.56-2.37 (m, 2H, C$H_2$CO$_2$Me), 2.34-2.24 (m, 1H, NHCHC$H_2$), 2.10 (m, 1H, NHCHC$H_2$), 1.49 (s, 9H, *t*Bu), 1.15 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.5, 170.9, 153.0, 145.0, 133.1, 130.7, 129.0, 128.0, 88.4, 85.2, 82.7, 53.6, 51.9, 30.3, 28.2 (X2), 18.9, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{29}H_{45}N_3NaO_5Si^+$ 566.3021; Found 566.3030. **IR** ($\nu_{max}$, $cm^{-1}$) 3403 (w), 2944 (m), 2866 (m), 2152 (m), 1722 (s), 1502 (s), 1369 (m), 1153 (s), 1109 (m), 911 (m), 882 (m), 733 (s). $[\alpha]_D^{25}$ = +9.2 (c = 0.49, $CHCl_3$).

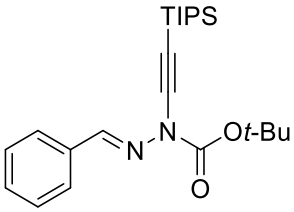
**Methyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (4m)**




Synthesized from methyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**2m**) (53.5 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. Methyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (**4m**) (65.0 mg, 0.181 mmol, 60% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.67. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.40 (s, 1H, *H*C=N), 7.79-7.70 (m, 2H, Ar*H*), 7.47-7.38 (m, 3H, Ar*H*), 3.97 (s, 3H, C$H_3$), 1.25-1.09 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 153.5, 147.3, 133.2, 130.8, 128.9, 128.2, 88.3, 85.1, 54.8, 18.8, 11.4. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{20}H_{31}N_2O_2Si^+$ 359.2149; Found 359.2149. **IR** ($\nu_{max}$, $cm^{-1}$) 2941 (s), 2862 (m), 2162 (m), 1767 (s), 1747 (s), 1441 (s), 1386 (m), 1325 (s), 1282 (s), 1228 (s), 952 (m), 882 (m), 755 (s).

***tert*-Butyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (4n)**

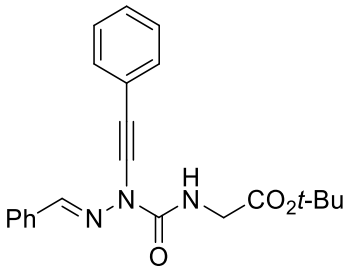



Synthesized from *tert*-Butyl (*E*)-2-benzylidenehydrazine-1-carboxylate (**2n**) (66.0 mg, 0.300 mmol, 1.00 equiv.) and TIPS-EBX (**3a**) (129 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *tert*-Butyl (*E*)-2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carboxylate (**4n**) (30.0 mg, 75.0 µmol, 25% yield) was obtained as a yellowish oil after purification by column chromatography on silica (Pentane/DCM 10:1).

**Rf** (Pentane/DCM 10:1): 0.15. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, *H*C=N), 7.78-7.70 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, Ar*H*), 1.59 (s, 9H, *t*Bu), 1.23-1.08 (m, 21H, TIPS). **$^{13}$C NMR** (101

MHz, $CDCl_3$) δ 151.1, 146.7, 133.5, 130.5, 128.8, 128.1, 88.9, 84.8, 84.1, 28.2, 18.8, 11.5. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{23}H_{36}N_2NaO_2Si^+$ 423.2438; Found 423.2434. **IR** ($\nu_{max}$, $cm^{-1}$) 2941 (m), 2869 (m), 2162 (m), 1763 (s), 1737 (m), 1462 (m), 1370 (m), 1282 (m), 1235 (s), 1152 (s), 852 (m), 755 (m).

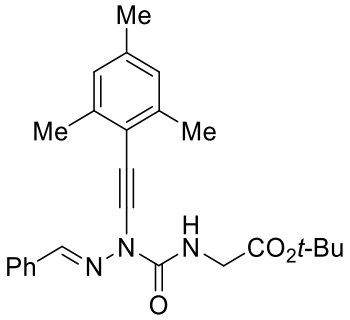
***tert*-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (5a)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.00 equiv.) and Ph-EBX (**3b**) (104 mg, 0.300 mmol, 1.00 equiv.) following general procedure E. *t*ert-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (**5a**) (104 mg, 0.276 mmol, 92% yield) was obtained as a yellowish oil after purification by column chromatography on silica (DCM).

**Rf** (DCM): 0.57. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, *H*C=N), 7.78-7.69 (m, 2H, Ar*H*), 7.60-7.51 (m, 2H, Ar*H*), 7.45-7.41 (m, 3H, Ar*H*), 7.38-7.34 (m, 3H, Ar*H*), 7.18 (t, *J* = 5.1 Hz, 1H, N*H*$CH_2$), 4.11 (d, *J* = 5.3 Hz, 2H, NHC$H_2$), 1.52 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.3, 144.5, 133.0, 131.9, 130.7, 129.0, 128.7, 128.5, 128.0, 122.3, 85.3, 82.6, 75.1, 43.2, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_3^+$ 378.1812; Found 378.1819. **IR** ($\nu_{max}$, $cm^{-1}$) 3419 (w), 2979 (w), 2931 (w), 2224 (w), 1712 (s), 1508 (s), 1365 (m), 1216 (m), 1152 (s), 1113 (m), 945 (w), 846 (w), 753 (s).

***tert*-Butyl (*E*)-(2-benzylidene-1-(mesitylethynyl)hydrazine-1-carbonyl)glycinate (5b)**

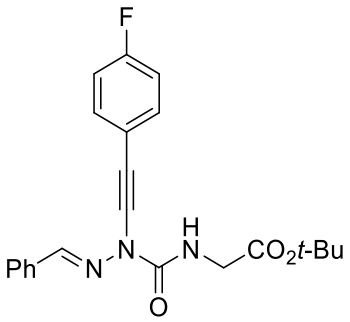



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[mesitylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3c**) (118 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(mesitylethynyl)hydrazine-1-carbonyl)glycinate (**5b**) (104 mg, 0.249 mmol, 83%) was obtained as a yellow solid after purification by column chromatography on silica (DCM).

**Rf** (Pentane/EtOAc, 85:15): 0.46. **Mp**: 148 °C. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H, *H*C=N), 7.76 – 7.68 (m, 2H, Ar*H*), 7.48 – 7.41 (m, 3H, Ar*H*), 7.22 (t, *J* = 5.3 Hz, 1H, N*H*), 6.92 (s, 2H, Ar*H*),

4.13 (d, *J* = 5.3 Hz, 2H, NHC*H*$_2$), 2.50 (s, 6H, ArC*H*$_3$), 2.31 (s, 3H, ArC*H*$_3$), 1.53 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.3, 144.1, 139.5, 137.8, 133.0, 130.5, 128.9, 127.8, 127.7, 119.2, 82.9, 82.4, 82.3, 43.1, 28.1, 21.4, 21.3. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{29}N_3NaO_3^+$ 442.2101; Found 442.2091. **IR** ($\nu_{max}$, $cm^{-1}$) 3421 (m), 2979 (m), 2920 (m), 2236 (w), 2224 (w), 1714 (s), 1502 (s), 1366 (s), 1213 (m), 1152 (s), 1113 (s), 942 (m), 852 (m), 752 (s)

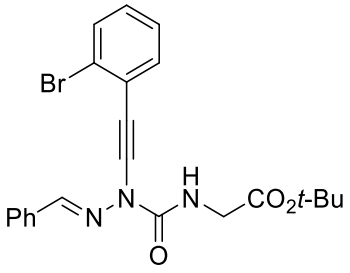
***tert*-Butyl (*E*)-(2-benzylidene-1-((4-fluorophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (5c)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[(4-fluorophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3d**) (113 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((4-fluorophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (**5c**) (68.4 mg, 0.173 mmol, 58%) was obtained as a yellow oil after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 85:15).

**Rf** (Pentane/EtOAc, 85:15): 0.35. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, *H*C=N), 7.77 – 7.69 (m, 2H, Ar*H*), 7.56 – 7.49 (m, 2H, Ar*H*), 7.47 – 7.39 (m, 3H, Ar*H*), 7.18 (t, *J* = 5.3 Hz, 1H, N*H*), 7.10 – 7.01 (m, 2H, Ar*H*), 4.10 (d, *J* = 5.3 Hz, 2H, NHC*H*$_2$), 1.51 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.0, 162.9 (d, *J* = 250.1 Hz), 153.3, 144.5, 134.1 (d, *J* = 8.5 Hz), 132.9, 130.7, 129.0, 127.9, 118.3 (d, *J* = 3.6 Hz), 115.8 (d, *J* = 22.1 Hz), 84.1, 82.5, 74.7, 43.2, 28.2. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -110.4. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}FN_3O_3^+$ 396.1718; Found 396.1712. **IR** ($\nu_{max}$, $cm^{-1}$) 3406 (w), 2980 (w), 2228 (w), 1711 (s), 1504 (s), 1366 (m), 1216 (s), 1113 (s), 836 (s), 755 (m).

***tert*-Butyl (*E*)-(2-benzylidene-1-((2-bromophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (5d)**

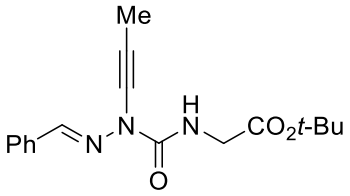



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[(2-bromophenyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3e**)

(128 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-((2-bromophenyl)ethynyl)hydrazine-1-carbonyl)glycinate (**5d**) (84.4 mg, 0.185 mmol, 62%) was obtained as a yellow amorphous solid after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 85:15).

**Rf** (Pentane/EtOAc, 85:15): 0.27. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H, *H*C=N), 7.78 – 7.72 (m, 2H, Ar*H*), 7.65-7.56 (m, 2H, Ar*H*), 7.48 – 7.41 (m, 3H, Ar*H*), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*), 7.23 – 7.14 (m, 2H, Ar*H* + N*H*), 4.11 (d, *J* = 5.3 Hz, 2H, NHC$H_2$), 1.52 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 168.9, 153.1, 145.5, 133.1, 132.8, 132.5, 130.8, 129.2, 129.0, 128.1, 127.3, 125.0, 124.2, 84.2, 82.6, 79.8, 43.2, 28.2. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{22}H_{22}BrN_3NaO_3^+$ 478.0737; Found 478.0741. **IR** ($\nu_{max}$, $cm^{-1}$) 3405 (w), 2979 (w), 2226 (m), 1712 (s), 1503 (s), 1366 (m), 1216 (m), 1148 (s), 1112 (s), 1024 (m), 949 (m), 845 (m).

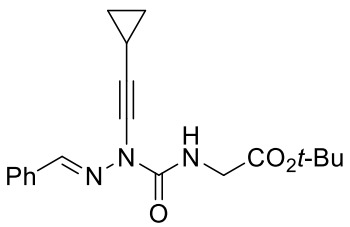
***tert*-Butyl (*E*)-(2-benzylidene-1-(prop-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (5e)**




Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[Prop-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**3f**) (91.3 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(prop-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (**5e**) (38.1 mg, 0.121 mmol, 40%) was obtained as a colorless oil after purification by column chromatography on silica (Pentane/EtOAc, 85:15 to 80:20) followed by preparative TLC (DCM/MeOH, 98:2).

**Rf** (Pentane/EtOAc, 75:25): 0.33. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, *H*C=N), 7.74 – 7.67 (m, 2H, Ar*H*), 7.45 – 7.38 (m, 3H, Ar*H*), 7.07 (t, *J* = 5.3 Hz, 1H, N*H*), 4.06 (d, *J* = 5.3 Hz, 2H, NHC$H_2$), 2.19 (s, 3H, C$H_3$), 1.50 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.9, 143.4, 133.2, 130.4, 128.9, 127.8, 82.4, 81.1, 65.5, 43.2, 28.2, 4.1. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_3^+$ 316.1656; Found 316.1647. **IR** ($\nu_{max}$, $cm^{-1}$) 3409 (w), 2979 (m), 2248 (w), 1740 (m), 1707 (s), 1509 (s), 1393 (m), 1367 (m), 1226 (m), 1152 (s), 849 (m), 753 (s), 730 (m).

***tert*-Butyl (*E*)-(2-benzylidene-1-(cyclopropylethynyl)hydrazine-1-carbonyl)glycinate (5f)**

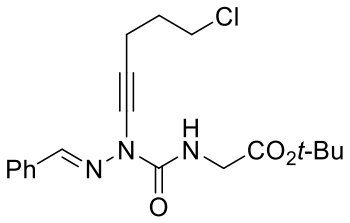



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[cyclopropylethynyl]-1,2-benziodoxol-3-(1*H*)-one (**3g**) (97.5 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(cyclopropylethynyl)hydrazine-1-carbonyl)glycinate (**5f**) (71.0 mg, 0.208 mmol, 69%) was

obtained as a yellow oil after purification by column chromatography on silica (Pentane/EtOAc, 95:5 to 80:20).

**Rf** (Pentane/EtOAc, 75:25): 0.5. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.21 (s, 1H, *H*C=N), 7.74 – 7.66 (m, 2H, Ar*H*), 7.46 – 7.38 (m, 3H, Ar*H*), 7.07 (t, *J* = 5.3 Hz, 1H, N*H*), 4.05 (d, *J* = 5.3 Hz, 2H, NHC*H*$_2$), 1.61 – 1.53 (m, 1H, C*H*CH$_2$), 1.49 (s, 9H, *t*Bu), 0.97 – 0.90 (m, 2H, CHC*H*$_2$), 0.89 – 0.82 (m, 2H, CHC*H*$_2$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.1, 153.9, 143.5, 133.2, 130.4, 128.9, 127.8, 90.0, 82.4, 61.7, 43.2, 28.2, 9.5, -0.2. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3O_3^+$ 342.1812; Found 342.1807. **IR** ($\nu_{max}$, $cm^{-1}$) 3408 (w), 2980 (m), 2246 (w), 1743 (m), 1707 (s), 1506 (s), 1367 (s), 1227 (m), 1152 (s), 1110 (m), 945 (m), 849 (m), 757 (m).

***tert*-Butyl (E)-(2-benzylidene-1-(5-chloropent-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (5g)**

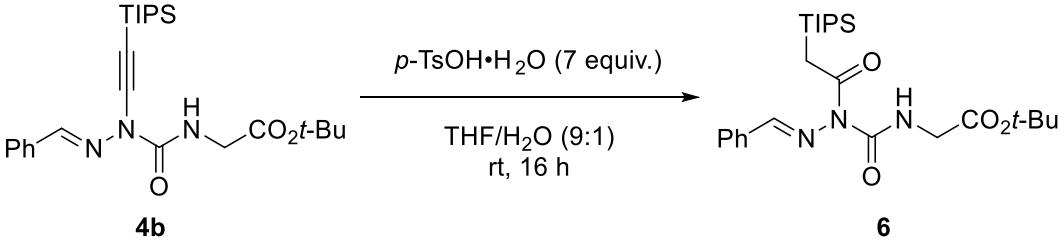



Synthesized from *tert*-butyl (*E*)-(2-benzylidenehydrazine-1-carbonyl)glycinate (**2b**) (83.2 mg, 0.300 mmol, 1.0 equiv.) and 1-[5-Chloropent-1-yn-1-yl]-1,2-benziodoxol-3-(1*H*)-one (**3h**) (106 mg, 0.300 mmol, 1.0 equiv.) following general procedure E. *tert*-Butyl (*E*)-(2-benzylidene-1-(5-chloropent-1-yn-1-yl)hydrazine-1-carbonyl)glycinate (**5g**) (60.2 mg, 159 µmol, 53% yield) was obtained as a colorless oil after purification by column chromatography on silica (Pentane/EtOAc, 85:15 to 80:20) followed by preparative TLC (DCM/MeOH, 98:2).

**Rf** (Pentane/EtOAc, 85:15): 0.27. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, *H*C=N), 7.74 – 7.68 (m, 2H, Ar*H*), 7.46 – 7.39 (m, 3H, Ar*H*), 7.09 (t, *J* = 5.3 Hz, 1H, N*H*), 4.06 (d, *J* = 5.3 Hz, 2H, NHC*H*$_2$), 3.74 (t, *J* = 6.2 Hz, 2H, ClC*H*$_2$CH$_2$), 2.78 (t, *J* = 6.7 Hz, 2H, C≡CC*H*$_2$CH$_2$), 2.08 (p, *J* = 6.6 Hz, 2H,CH$_2$C*H*$_2$CH$_2$), 1.50 (s, 9H, *t*Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.0, 153.7, 143.8, 133.1, 130.6, 129.0, 127.9, 83.5, 82.5, 67.5, 43.8, 43.2, 31.3, 28.2, 16.6. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}ClN_3O_3^+$ 378.1579; Found 378.1578. **IR** ($\nu_{max}$, $cm^{-1}$) 3404 (w), 2979 (w), 2251 (w), 1743 (m), 1708 (s), 1514 (s), 1367 (m), 1227 (m), 1153 (s), 852 (w), 754 (m).

## 5. Post-functionalizations

### 5.1 Hydration

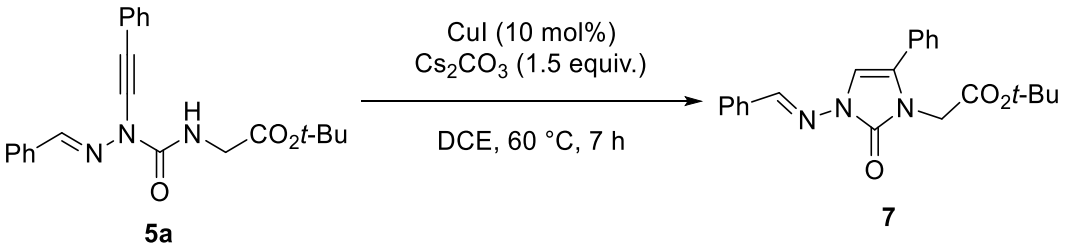



**4b** **6**

To a microwave vial containing a solution of *tert*-butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl)ethynyl)hydrazine-1-carbonyl)-*L*-glycinate (**4b**) (46 mg, 0.050 mmol, 1.0 equiv.) in a mixture of THF (1.8 mL) and $H_2O$ (0.2 mL) was added *p*TsOH•$H_2O$ (0.13 g, 0.35 mmol, 7.0 equiv.). The reaction was stirred at rt open to air for 16 h. The mixture was diluted with DCM (5 mL) and quenched with the addition of a 1 M aq. Sol. Of NaOH (10 mL). The mixture was extracted with 3 x 10 mL of DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by preparative TLC (DCM) to afford *tert*-butyl (*E*)-(2-benzylidene-1-(2-(triisopropylsilyl)acetyl)hydrazine-1-carbonyl)glycinate (**6**) (20 mg, 0.042 mmol, 42%) as a colorless oil.

**Rf** (DCM): 0.62. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.35 (t, *J* = 5.4 Hz, 1H, N*H*), 8.50 (s, 1H, *H*C=N), 7.79 – 7.74 (m, 2H, Ar*H*), 7.50 – 7.39 (m, 3H, Ar*H*), 4.00 (d, *J* = 5.3 Hz, 2H, NHC$H_2$), 2.55 (s, 2H, C(O)C$H_2$TIPS), 1.48 (s, 9H, *t*Bu), 1.22 – 1.02 (m, 21H, TIPS). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 177.8, 168.6, 162.9, 153.1, 133.5, 131.6, 128.8, 128.5, 82.2, 43.3, 28.2, 21.1, 18.5, 11.6. **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{41}N_3NaO_4Si^+$ 498.2759; Found 498.2763. **IR** ($\nu_{max}$, $cm^{-1}$) 3274 (w), 2943 (m), 2867 (m), 2254 (w), 1745 (m), 1708 (s), 1657 (m), 1512 (m), 1367 (s), 1224 (s), 1154 (s), 883 (m), 769 (m), 755 (m).

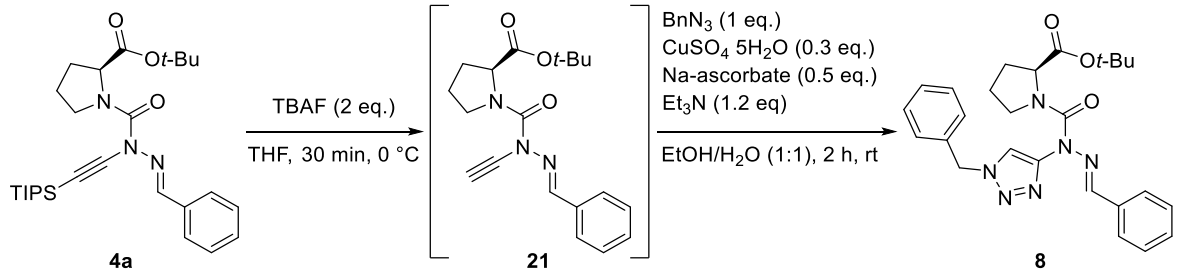
## 5.2 5-*endo-dig* Cyclization




A capped oven dried microwave vial charged with *tert*-Butyl (*E*)-(2-benzylidene-1-(phenylethynyl)hydrazine-1-carbonyl)glycinate (**5a**) (18.8 mg, 50.0 µmol, 1.0 equiv.), CuI (1.0 mg, 5.0 µmol, 0.1 equiv.) and $Cs_2CO_3$ (24.4 mg, 75.0 µmol, 1.5 equiv.) was evacuated and backfilled with $N_2$ (3x). Then, dry DCE (0.5 mL) was added and the reaction was stirred at 60 °C for 6 h. The mixture was filtered over a pad of Celite® using DCM to rinse (≈ 10 mL). The solution was concentrated in vacuo and the crude oil was purified by preparative TLC (Pentane/EtOAc, 85:15) to afford *tert*-butyl (*E*)-2-(3-(benzylideneamino)-2-oxo-5-phenyl-2,3-dihydro-1H-imidazol-1-yl)acetate (**7**) (11.8 mg, 31.3 µmol, 63%) as a yellow oil.

**Rf** (DCM): 0.59. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, *H*C=N), 7.81 – 7.72 (m, 2H, Ar*H*), 7.49 – 7.44 (m, 2H, Ar*H*), 7.43 – 7.35 (m, 5H, Ar*H*), 7.33 (s, 1H, *H*C=C), 7.31 – 7.27 (m, 1H, Ar*H*), 4.26 (s, 2H, NC$H_2$), 1.52 (s, 9H, *t*-Bu). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.6, 150.1, 148.8, 138.6, 134.7, 130.3, 128.9, 128.7, 128.2, 127.6, 127.3, 123.0, 111.7, 81.1, 49.6, 28.3. **HRMS (ESI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_3^+$ 378.1812; Found 378.1813. **IR** ($\nu_{max}$, $cm^{-1}$) 2978 (w), 2256 (w), 1743 (s), 1693 (s), 1651 (m), 1450 (m), 1405 (m), 1368 (m), 1218 (m), 1153 (s), 1022 (m), 912 (m), 754 (m).

## 5.3 Huisgen [3+2]-cycloadditions




**4a** **21** **8**

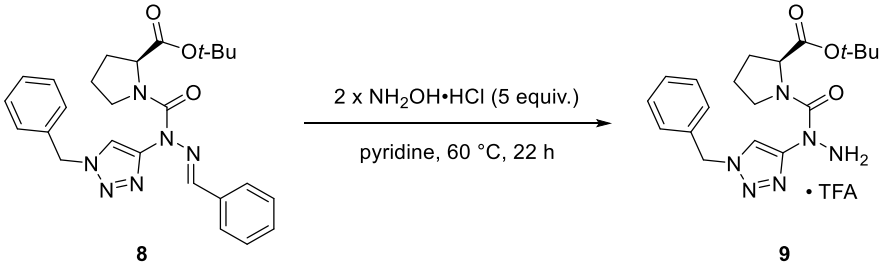
To a 0°C cooled solution of *tert*-butyl (*E*)-(2-benzylidene-1-((triisopropylsilyl) ethynyl)hydrazine-1-carbonyl)-*L*-prolinate (**4a**) (199 mg, 0.400 mmol, 1.00 equiv) in THF (4.00 mL) was added TBAF (1 M in THF, 800 µL, 0.800 mmol, 2.00 equiv) dropwise, and the reaction was stirred for 30 min. The solution was warmed to ambient temperature, poured into $H_2O$ (20 mL), and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The product was pure enough to be used in the next step without further purification.[16]

Following a reported procedure,[17] to a solution of *tert*-butyl (*E*)-(2-benzylidene-1-ethynylhydrazine-1-carbonyl)-*L*-prolinate (**21**) (137 mg, 0.400 mmol, 1.00 equiv), benzyl azide (50.0 µL, 0.400 mmol, 1.00 equiv), triethylamine (67.0 µL, 0.480 mmol, 1.20 equiv) in EtOH (0.48 mL) and $H_2O$ (0.48 mL), $CuSO_4{\cdot}5H_2O$ (30.0 mg, 0.120 mmol, 0.300 equiv) and sodium *L*-ascorbate (40.0 mg, 0.200 mmol, 0.500 equiv) were added. The mixture was allowed to stir at rt for 2 h under $N_2$ and concentrated. Then the mixture was diluted with water and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated at reduced pressure. *tert*-Butyl (*E*)-(1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**8**) (145 mg, 0.306 mmol, 76% yield) was isolated as a brownish amorphous solid after purification by column chromatography on silica (DCM/MeOH 100:1).

**Rf** (Pentane/DCM 50:1): 0.19. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, *H*C=C), 7.61-7.48 (m, 3H, *H*C=N and Ar*H*), 7.44-7.28 (m, 8H, Ar*H*), 5.56 (s, 2H, C$H_2$Ph), 5.29-4.26 (br s, 1H, NC*H*$CO_2$*t*-Bu), 4.15-3.52 (br s, 2H, NC$H_2$), 2.46-2.18 (br s, 1H, $NCH_2CH_2CH_2$), 2.07-1.79 (br s, 3H, $NCH_2CH_2CH_2$ and $NCH_2CH_2CH_2$), 1.52-1.19 (br s, 9H, *t*-Bu).**$^{13}$C NMR** $^{13}$C NMR (101 MHz, $CDCl_3$) δ 171.9, 141.6, 141.4, 134.6, 134.2, 129.6, 129.4, 129.1, 128.7, 128.4, 127.4, 122.0, 81.2, 62.2, 55.1, 50.6, 28.0 (3 C were not fully resolved). **HRMS (ESI/QTOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{30}N_6NaO_3^+$ 497.2272; Found 497.2277. **IR** ($\nu_{max}$, $cm^{-1}$) 3147 (w), 2978 (m), 2916 (w), 1737 (m), 1654 (s), 1603 (w), 1415 (s), 1358 (m), 1227 (m), 1152 (s), 911 (s), 730 (s). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -61.1 (c = 0.50, $CHCl_3$).

[16] $^1$H NMR of the crude mixture showed full conversion of the starting material. The desired deprotected compound was not isolated as initial attempts led to decomposition of the product overtime.
[17] Tuck, J. R.; Tombari, R. J.; Yardeny, N.; Olson, D. E. *Org. Lett.* **2021**, *23* (11), 4305–4310.

## 5.4 Hydrazone deprotection




8 9

A capped oven dried microwave vial charged with *tert*-butyl (*E*)-(1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-benzylidenehydrazine-1-carbonyl)-*L*-prolinate (**8**) (47.5 mg, 0.100 mmol, 1.0 equiv.) was evacuated and backfilled with $N_2$ (3x). Then, a pre-stirred solution of $NH_2OH{\cdot}HCl$ (34.7 mg, 0.500 mmol, 5.0 equiv.) in dry pyridine (0.3 mL) was added under $N_2$. The reaction was stirred at 60 °C for 6 h, then, a freshly prepared solution of $NH_2OH{\cdot}HCl$ (34.7 mg, 0.500 mmol, 5.0 equiv.) in dry pyridine (0.3 mL) was added under $N_2$. The reaction was further stirred at 60 °C for 16 h. The volatiles were evaporated *in vacuo* and the crude oil was co-evaporated with ethyl acetate to help removing pyridine. The crude compound was purified by preparative RP-HPLC ($t_R$: 11.5 min) to afford *tert*-butyl (1-(1-benzyl-1H-1,2,3-triazol-4-yl)hydrazine-1-carbonyl)-*L*-prolinate trifluoroacetic acid salt (**9**) (16.0 mg, 32.0 µmol, 32%) as a white amorphous solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, *H*C=C), 7.39 – 7.32 (m, 3H, Ar*H*), 7.31 – 7.26 (m, 2H, Ar*H*), 5.46 (s, 2H, C*H*$_2$Ph), 5.16 (s, 3H, N*H*$_3^+$), 4.63 – 4.55 (m, 1H, NC*H*CO$_2$*t*-Bu), 3.62 (t, *J* = 6.7 Hz, 2H, NC*H*$_2$), 2.23 – 2.12 (m, 1H, NCH$_2$CH$_2$C*H*$_2$), 2.00 – 1.78 (m, 3H, NCH$_2$CH$_2$C*H*$_2$), 1.43 (s, 9H, *t*-Bu). **$^{13}$C NMR (101 MHz, $CDCl_3$)**[18] δ 172.7, 159.5 (q, *J* = 41.1 Hz), 156.5, 149.5, 134.3, 129.2, 129.0, 128.3, 114.2, 81.3, 62.2, 55.1, 49.8, 30.8, 28.1, 23.5. **HRMS (ESI/QTOF)** m/z: [M + Na]$^+$ Calcd for $C_{19}H_{26}N_6NaO_3^+$ 409.1959; Found 409.1952. **IR** ($\nu_{max}$, $cm^{-1}$) 2984 (w), 1737 (m), 1644 (m), 1416 (s), 1368 (s), 1202 (s), 1155 (s), 982 (m), 763 (m). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -24.9 (c = 0.53, $CHCl_3$).

[18] The $CF_3$ carbon from the TFA was not resolved.

## 6. Crystal structure of *tert*-Butyl (*E*)-(2-benzylidene-1-(mesitylethynyl)hydrazine-1-carbonyl)glycinate (5b)

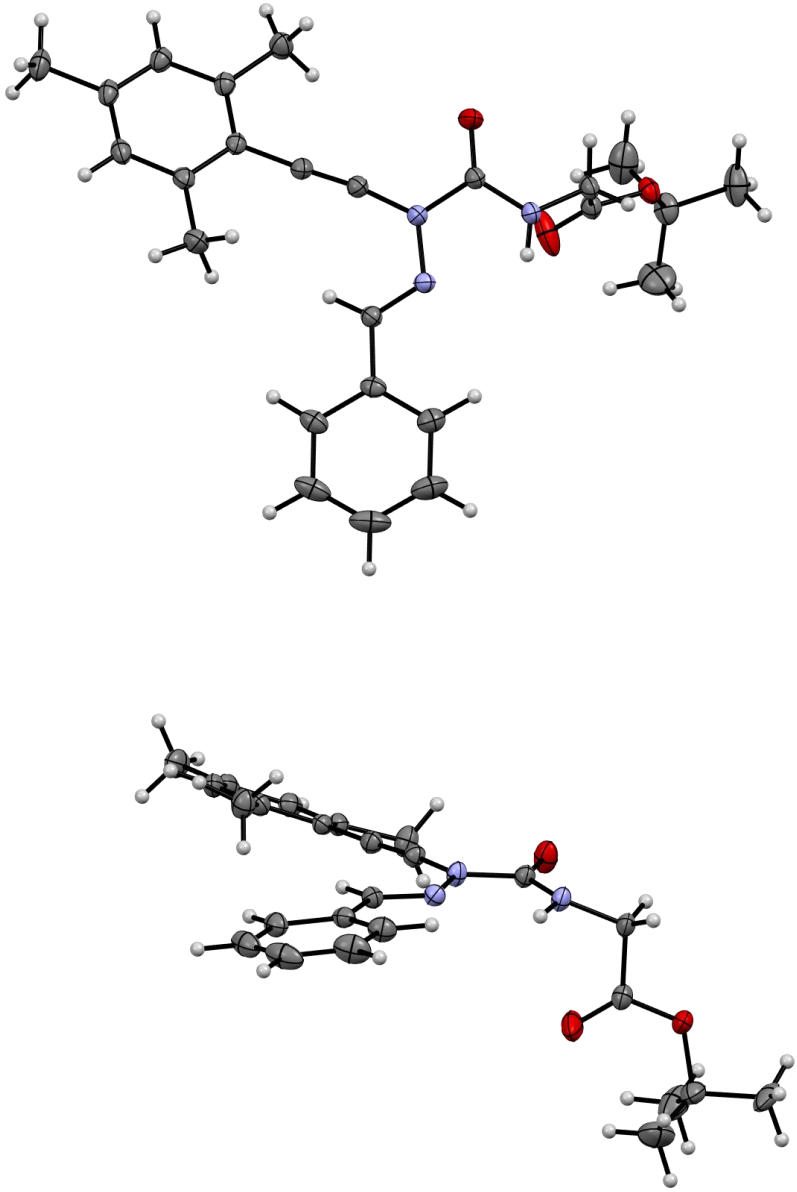


Figure S1: Ellipsoid plot (probability level 50%) of **5b**

| **Compound** | **5b** |
|---|---|
| Formula | $C_{25}H_{29}N_3O_3$ |
| $D_{calc.}$/ g cm$^{-3}$ | 1.214 |
| $\mu$/mm$^{-1}$ | 0.080 |
| Formula Weight | 419.51 |
| Colour | clear pale colourless |
| Shape | prism-shaped |
| Size/mm$^3$ | 0.95×0.28×0.21 |
| $T$/K | 140.00(10) |
| Crystal System | monoclinic |
| Space Group | $P2_1/c$ |
| $a$/Å | 9.8053(3) |
| $b$/Å | 25.9739(6) |
| $c$/Å | 9.6703(4) |
| $\alpha$/° | 90 |
| $\beta$/° | 111.234(4) |
| $\gamma$/° | 90 |
| V/Å$^3$ | 2295.64(14) |
| $Z$ | 4 |
| $Z'$ | 1 |
| Wavelength/Å | 0.71073 |
| Radiation type | Mo K$_\alpha$ |
| $\Theta_{min}$/° | 2.751 |
| $\Theta_{max}$/° | 32.745 |
| Measured Refl's. | 35274 |
| Indep't Refl's | 7912 |
| Refl's I≥2 $\sigma$(I) | 6089 |
| $R_{int}$ | 0.0271 |
| Parameters | 384 |
| Restraints | 255 |
| Largest Peak | 0.300 |
| Deepest Hole | -0.233 |
| GooF | 1.034 |
| $wR_2$ (all data) | 0.1235 |
| $wR_2$ | 0.1126 |
| $R_1$ (all data) | 0.0648 |
| $R_1$ | 0.0458 |

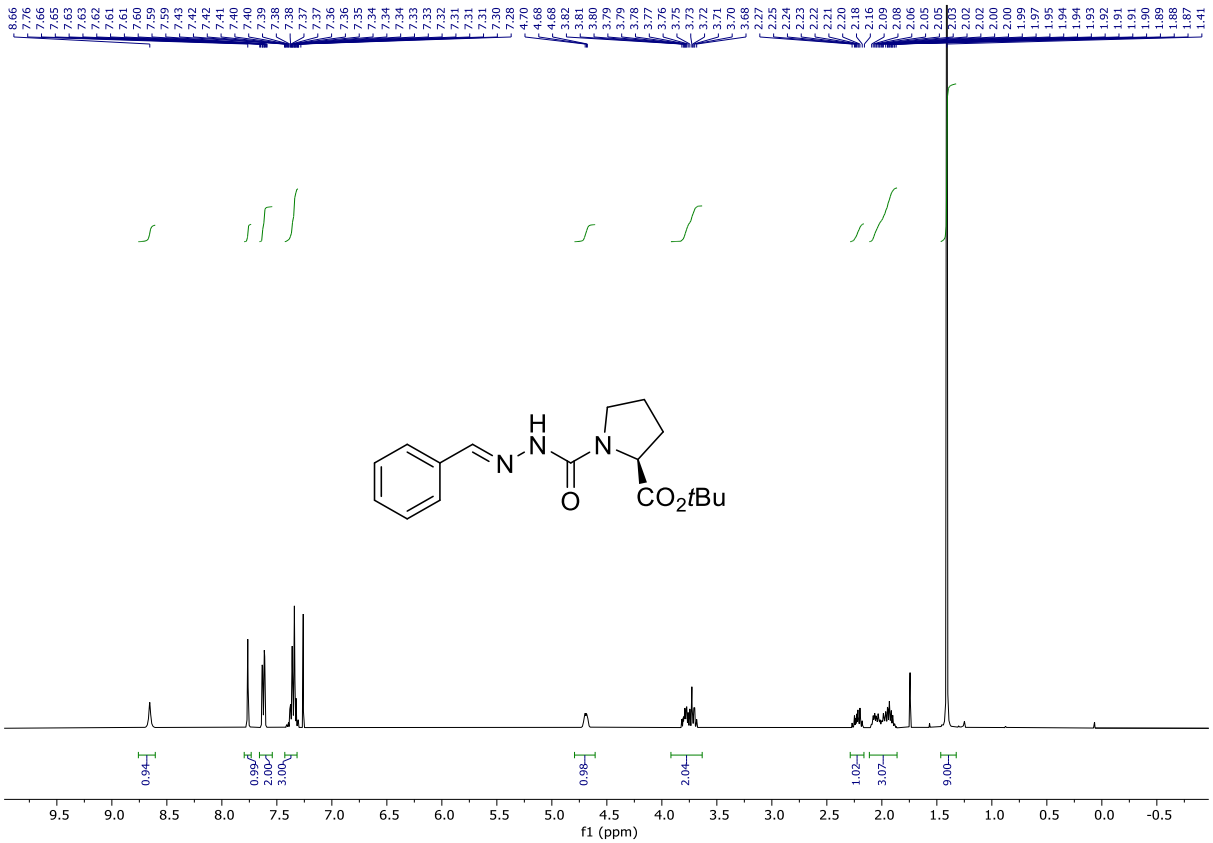
Crystals were grown by preparing a solution of **5b** in $Et_2O$, adding hexane and leaving the solution slowly evaporate over 3-4 days.

Analysis of the crystal: A suitable crystal with dimensions 0.95 × 0.28 × 0.21 mm$^3$ was selected and mounted on a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer. The crystal was kept at a steady $T$ = 140.00(10) K during data collection. The structure was solved with the **ShelXT** 2018/2 (Sheldrick, 2018) solution program using dual methods and by using **Olex2** 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on $F^2$.

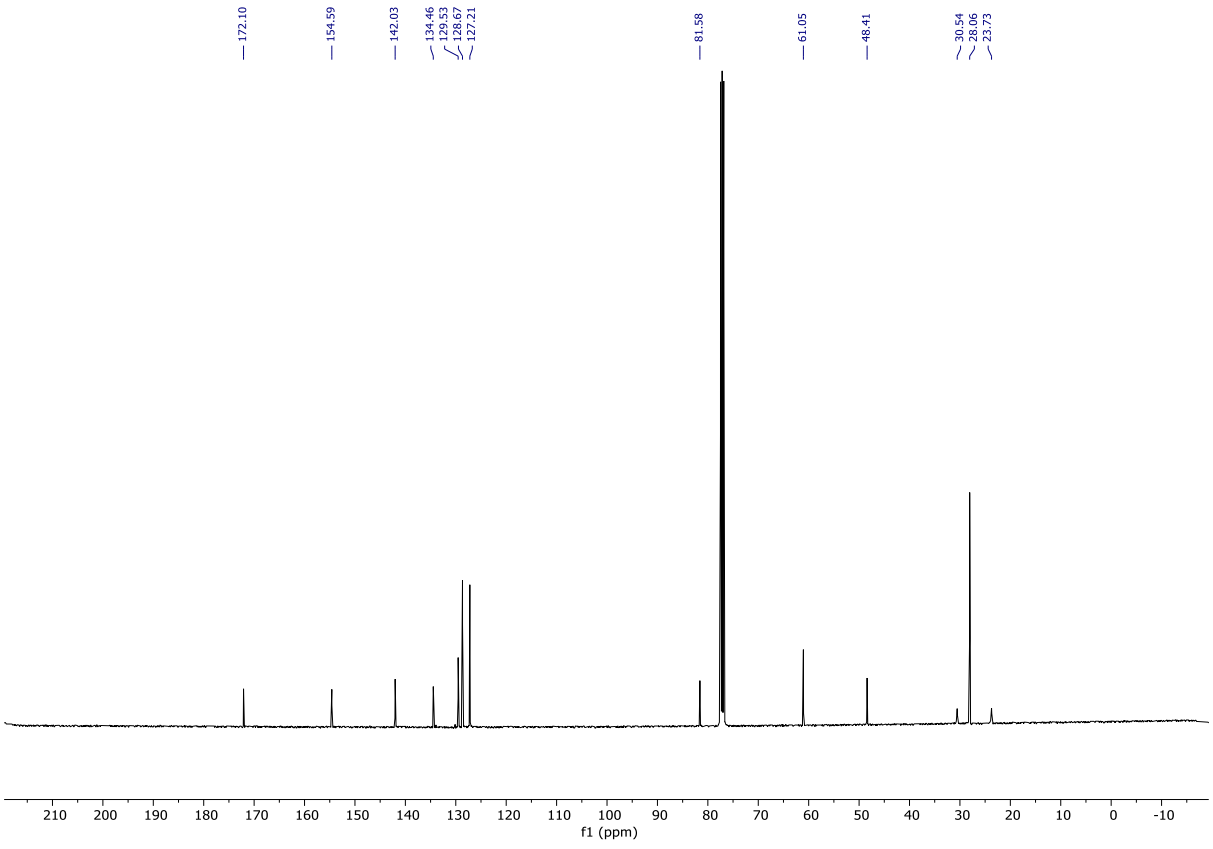
Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (CCDC 2193047) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

## 7. NMR spectra

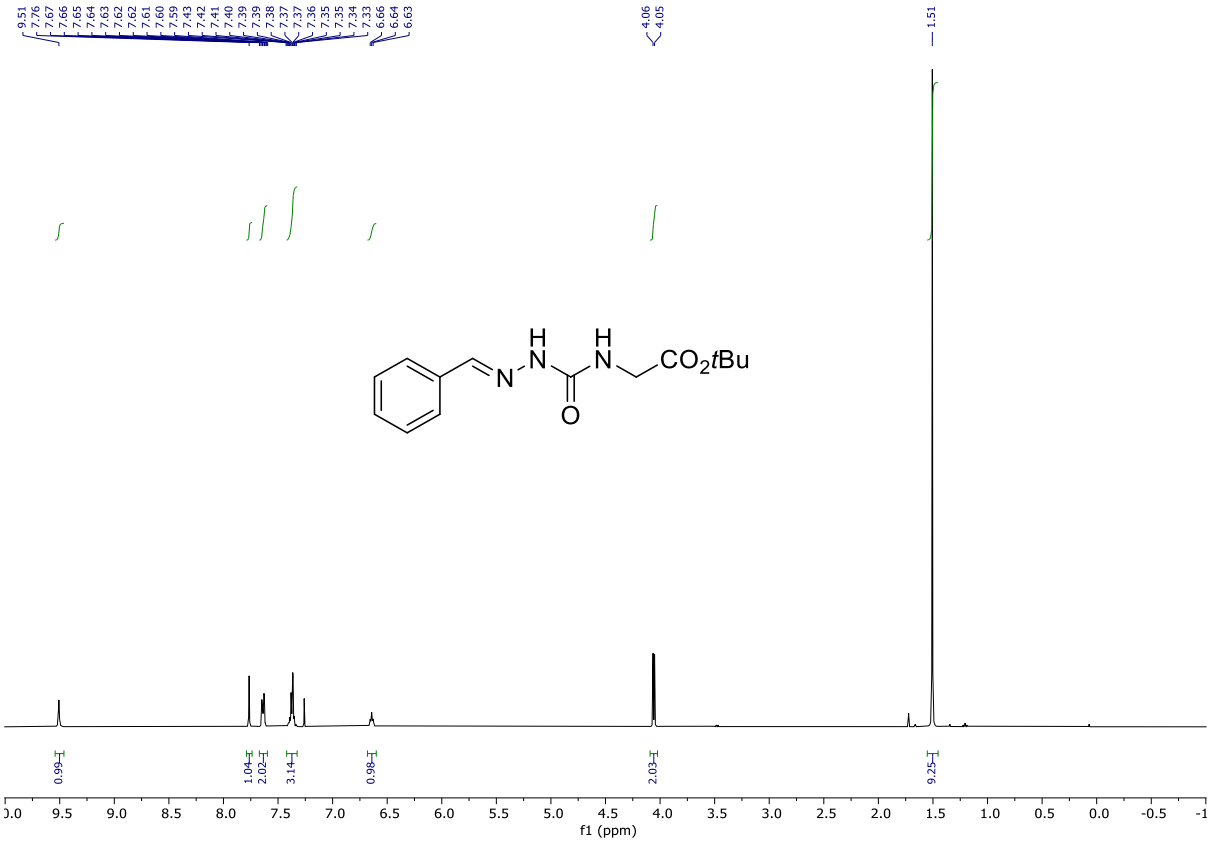
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2a**



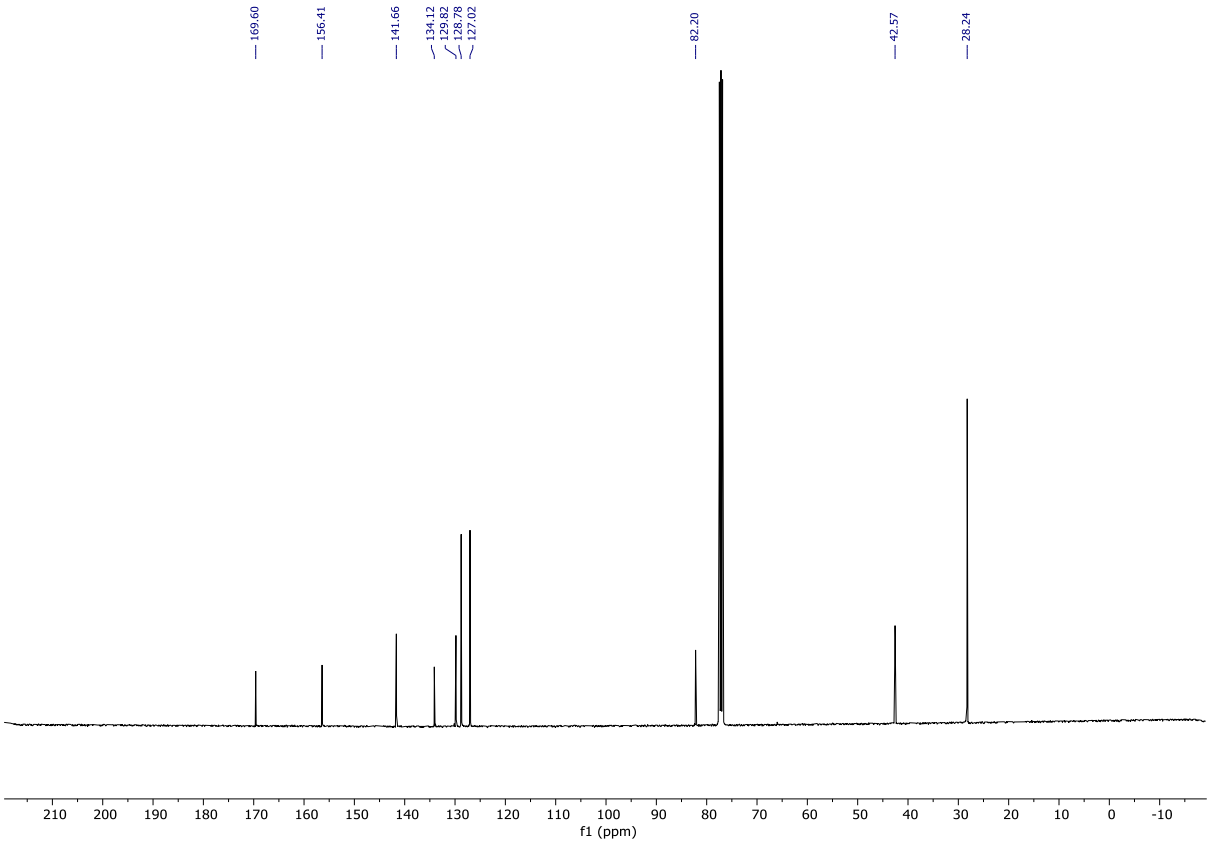

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2a**



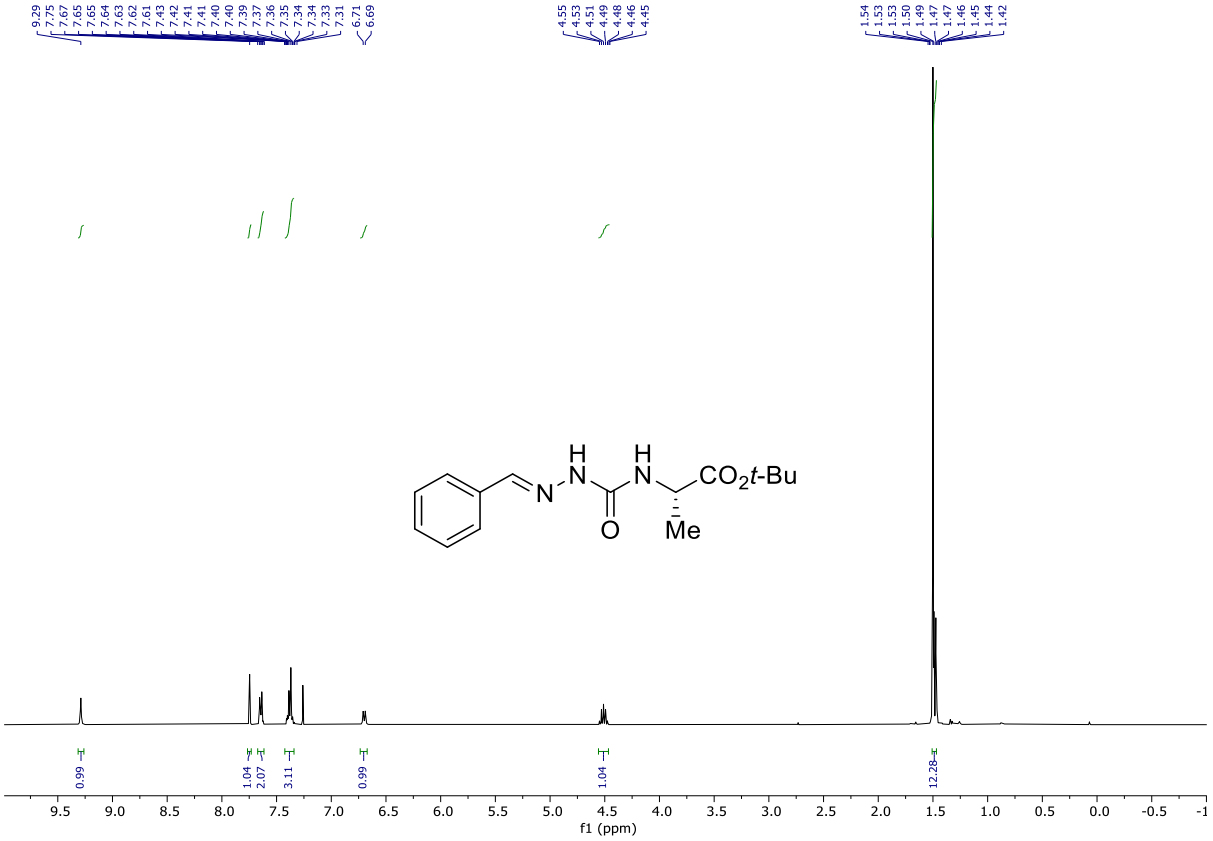
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2b**



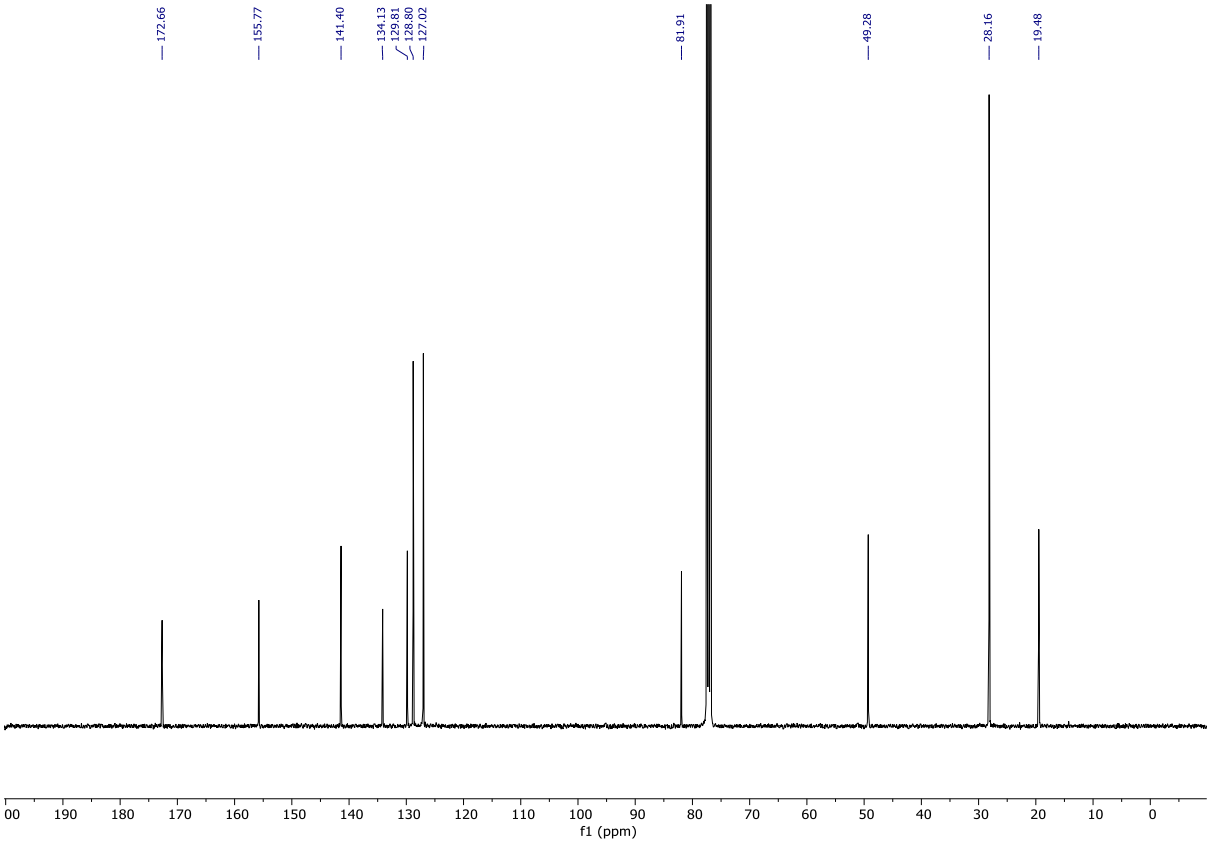

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2b**



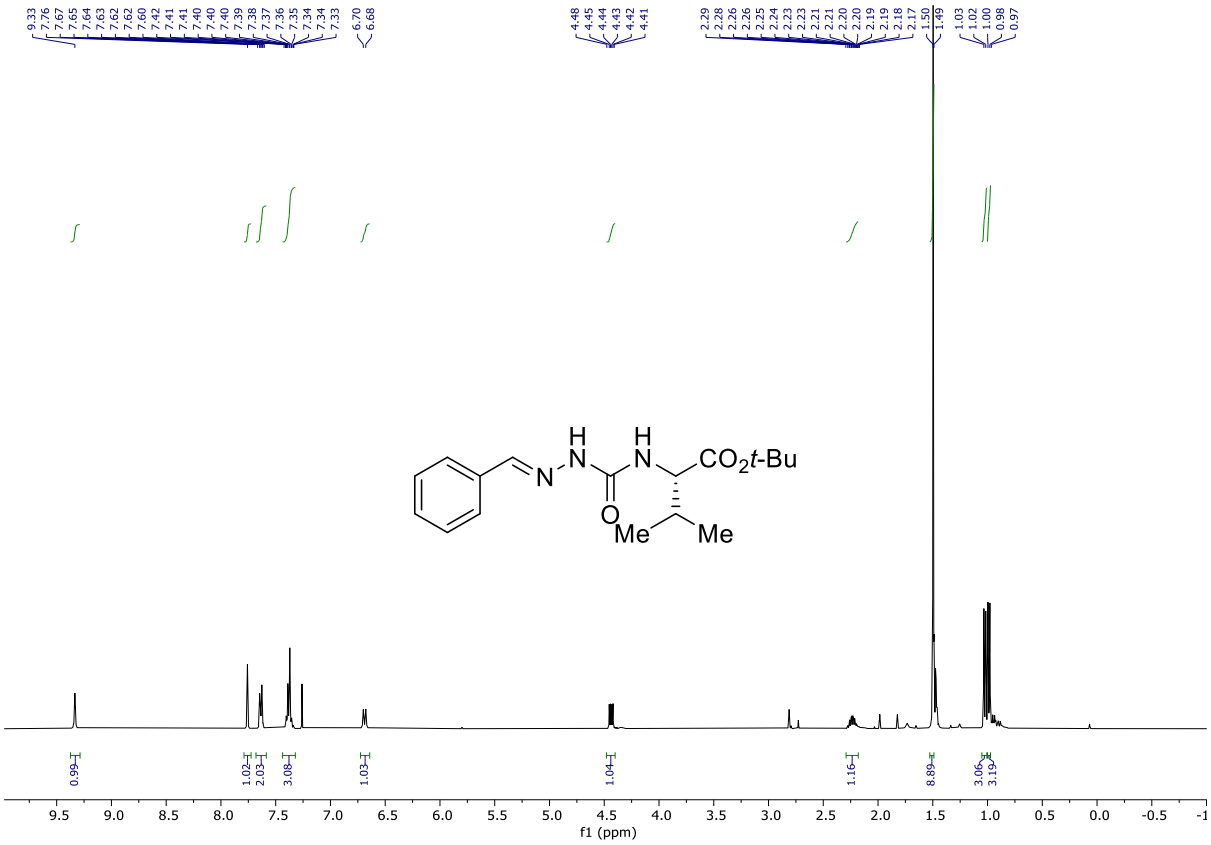
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2c**



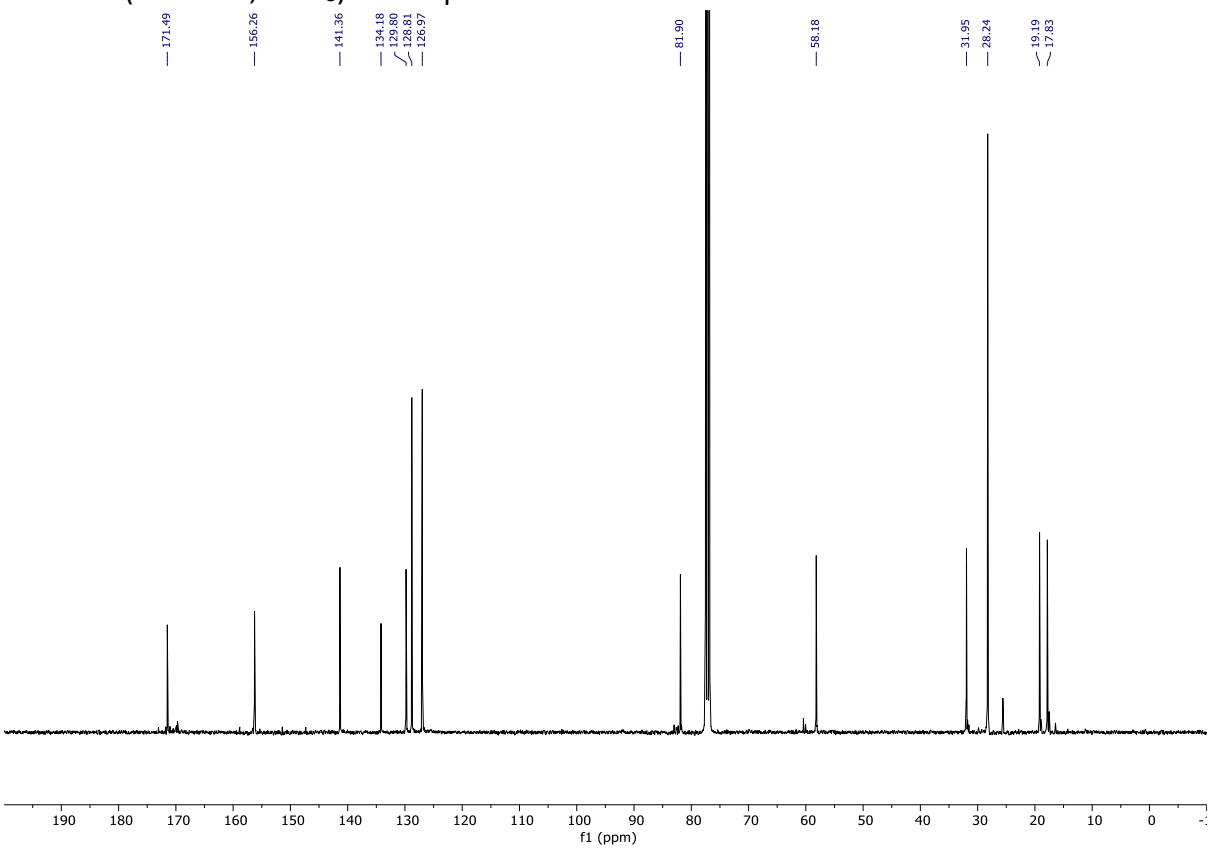

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2c**



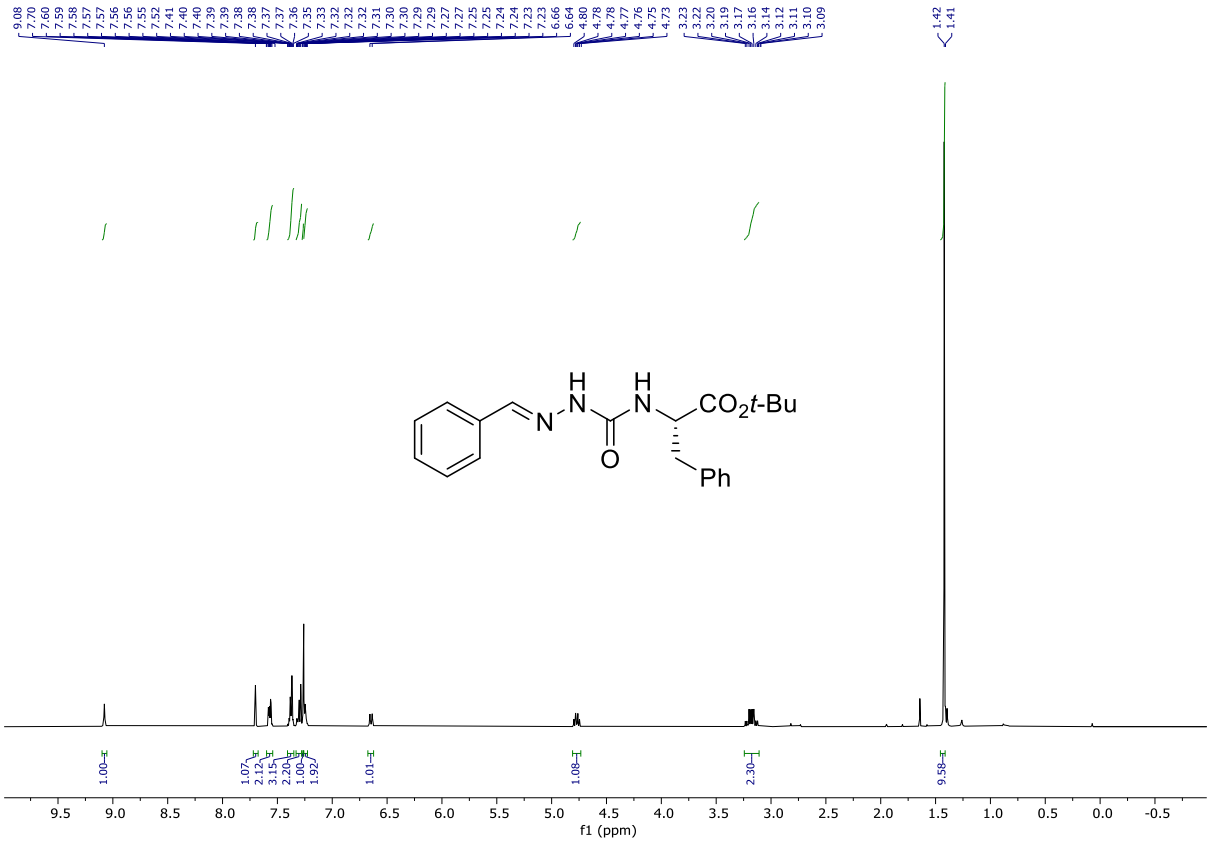
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2d**



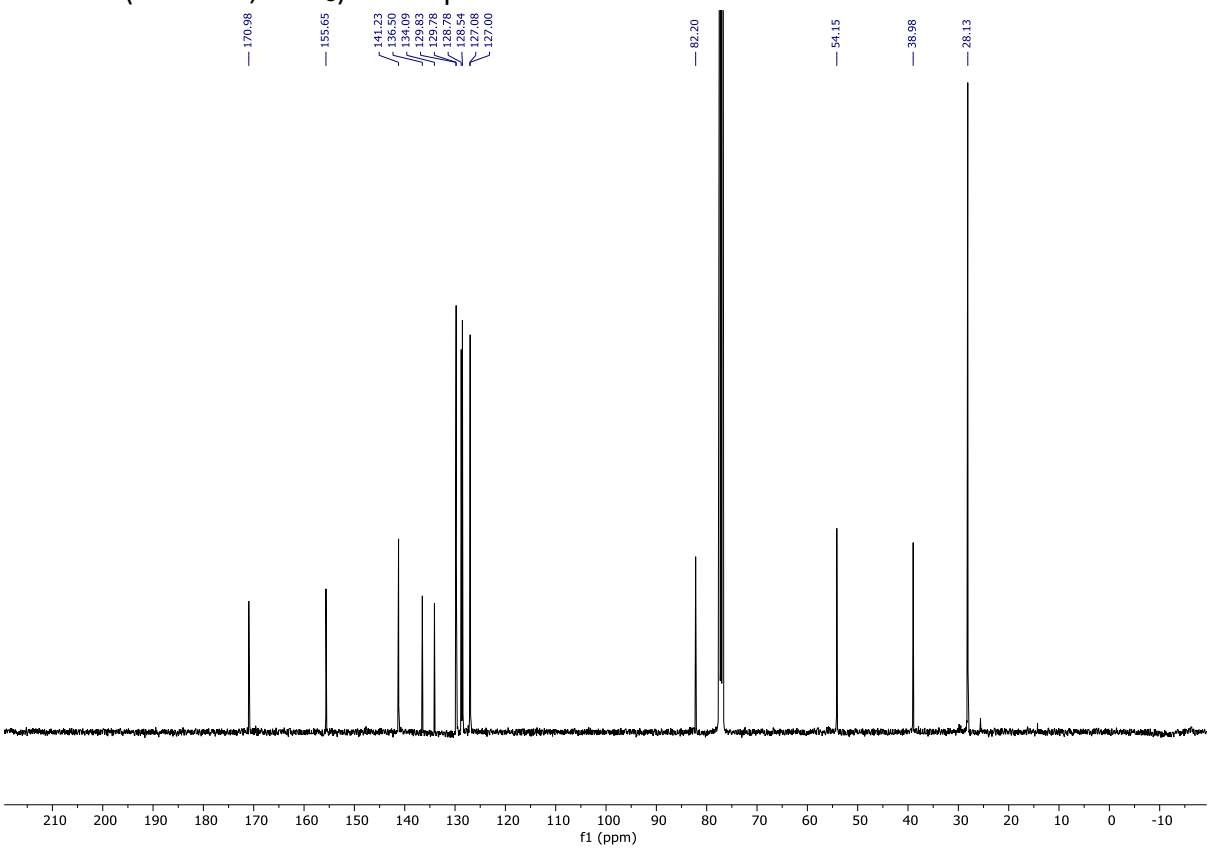

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2d**



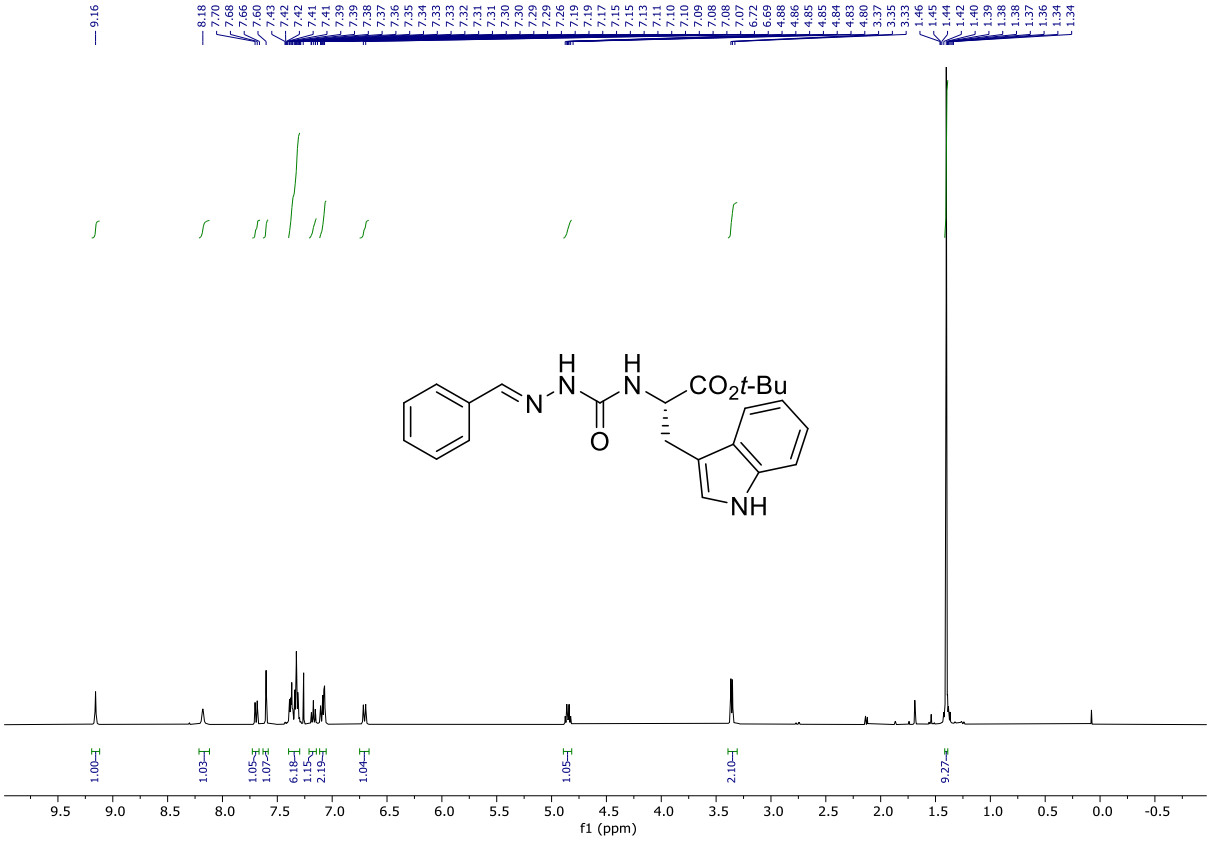
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2e**



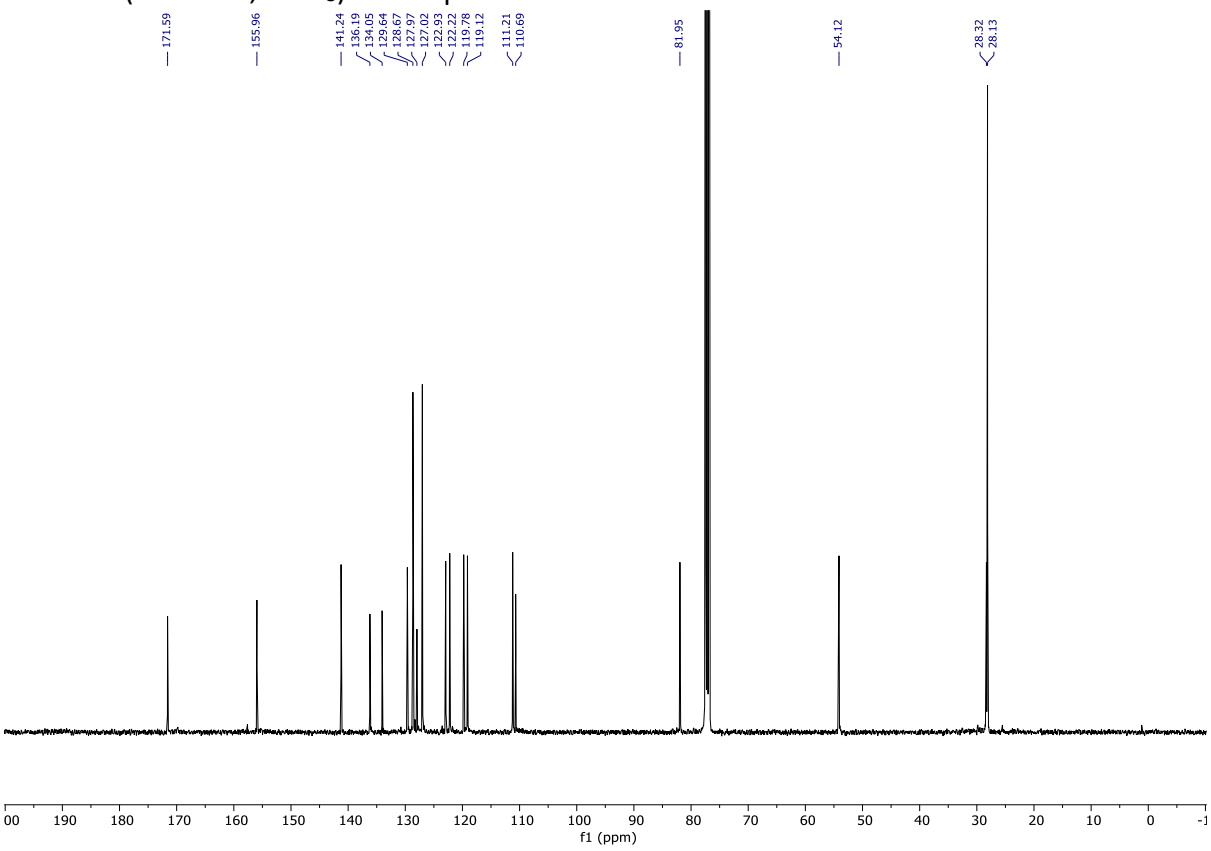

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2e**



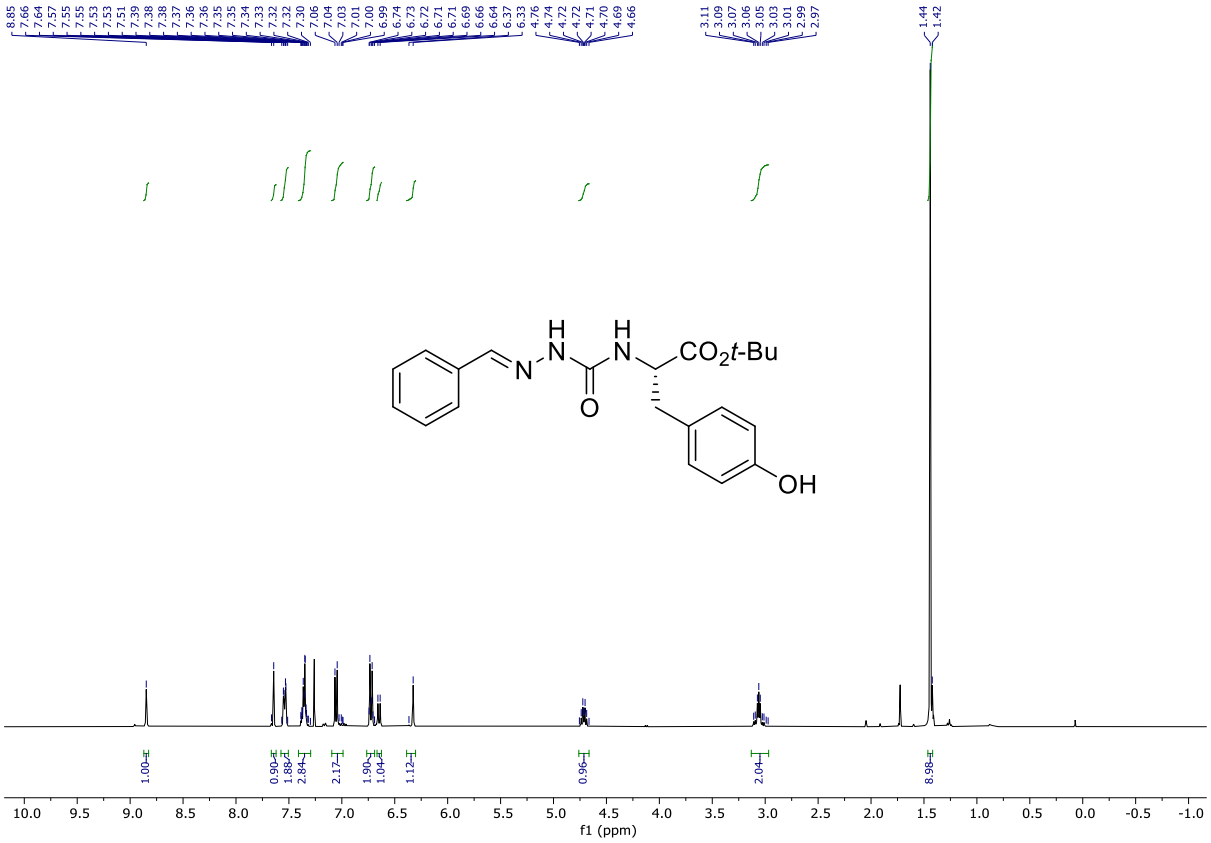
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2f**



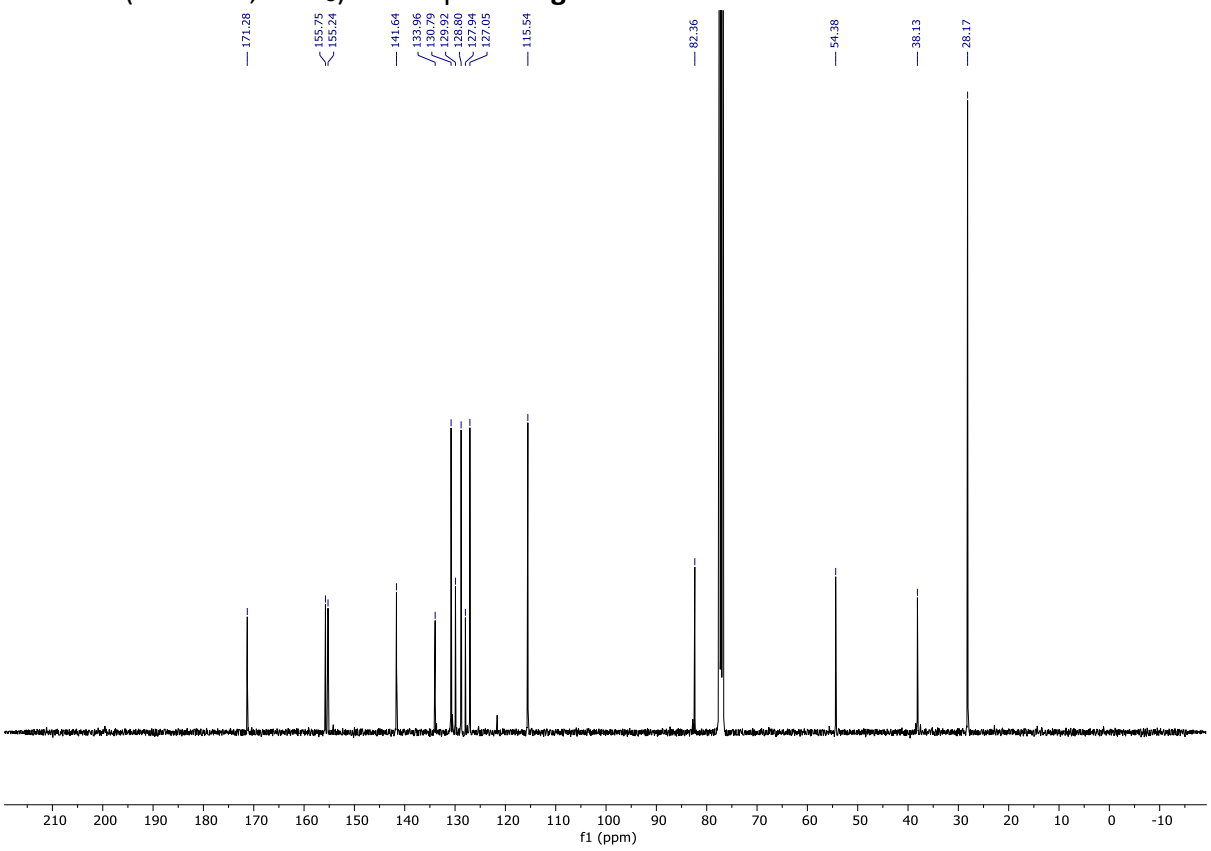

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2f**



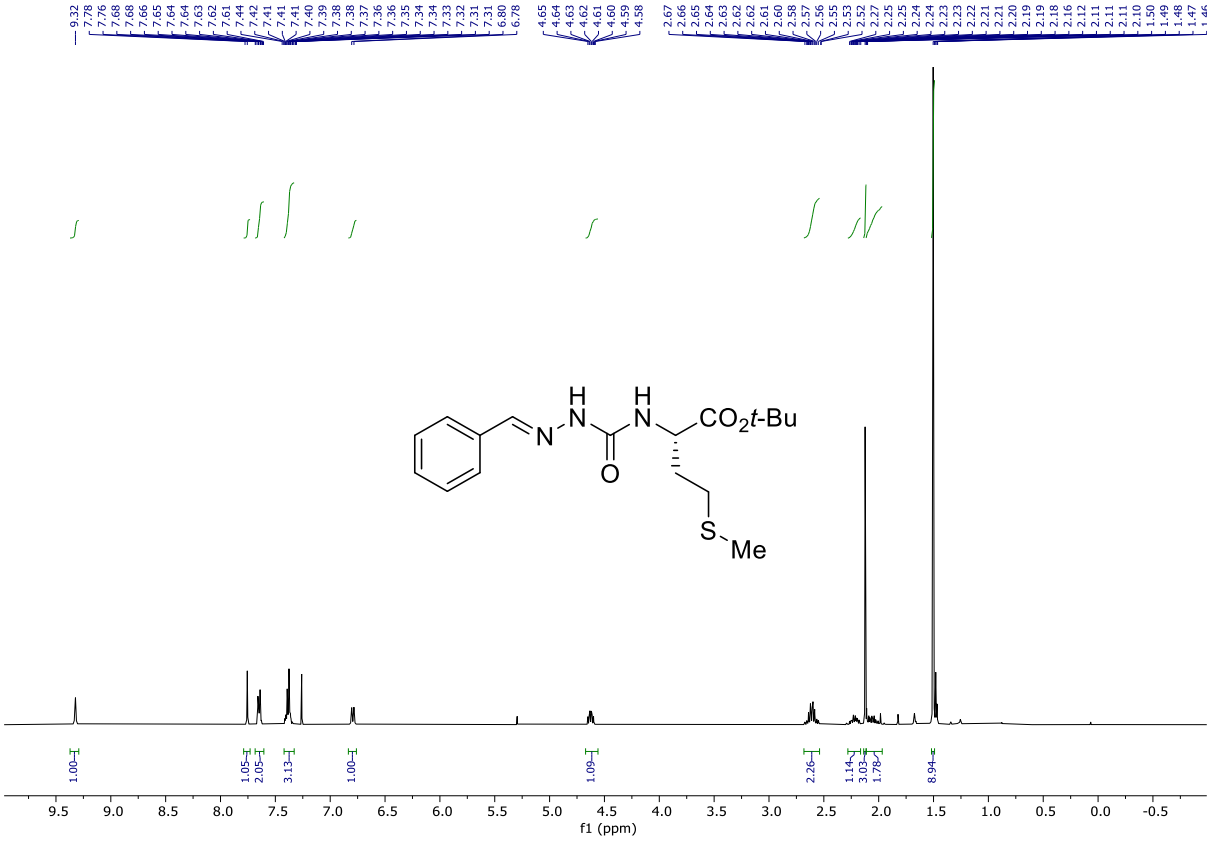
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2g**



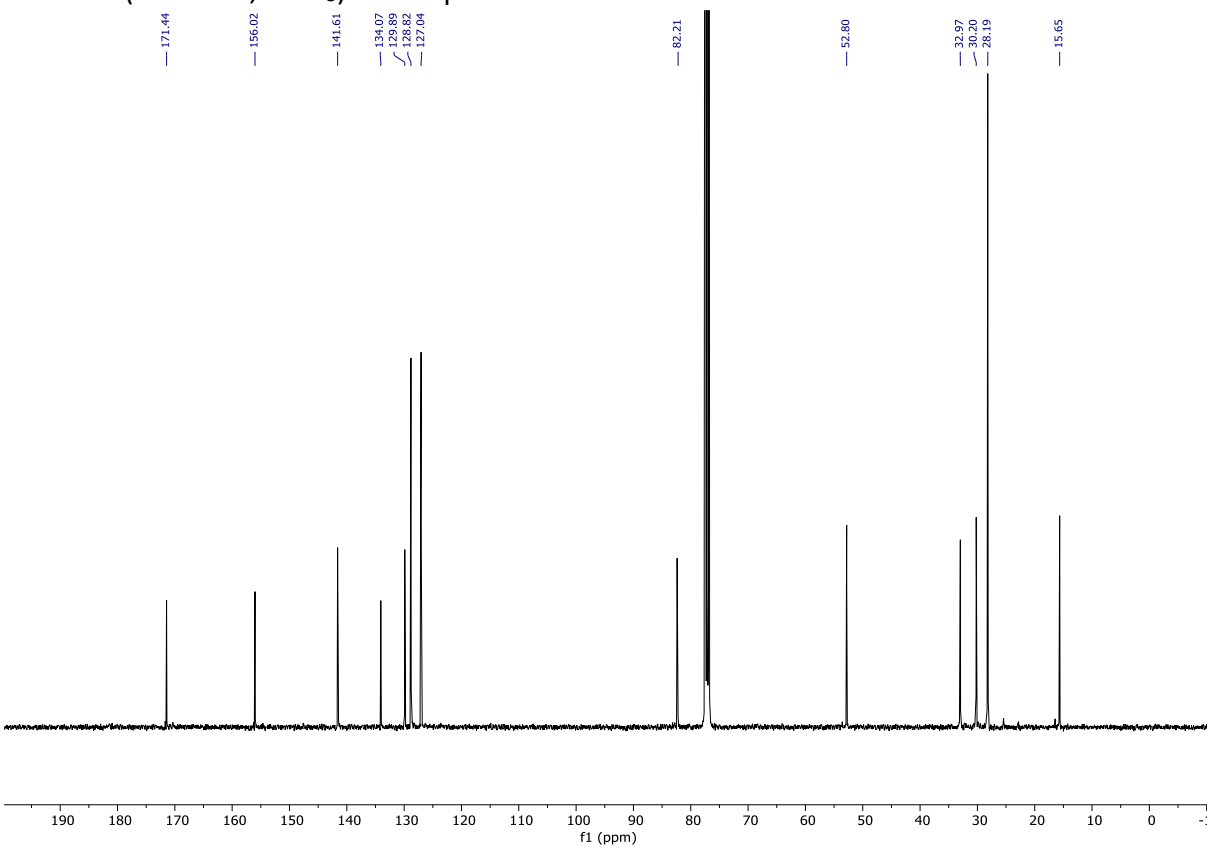

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2g**



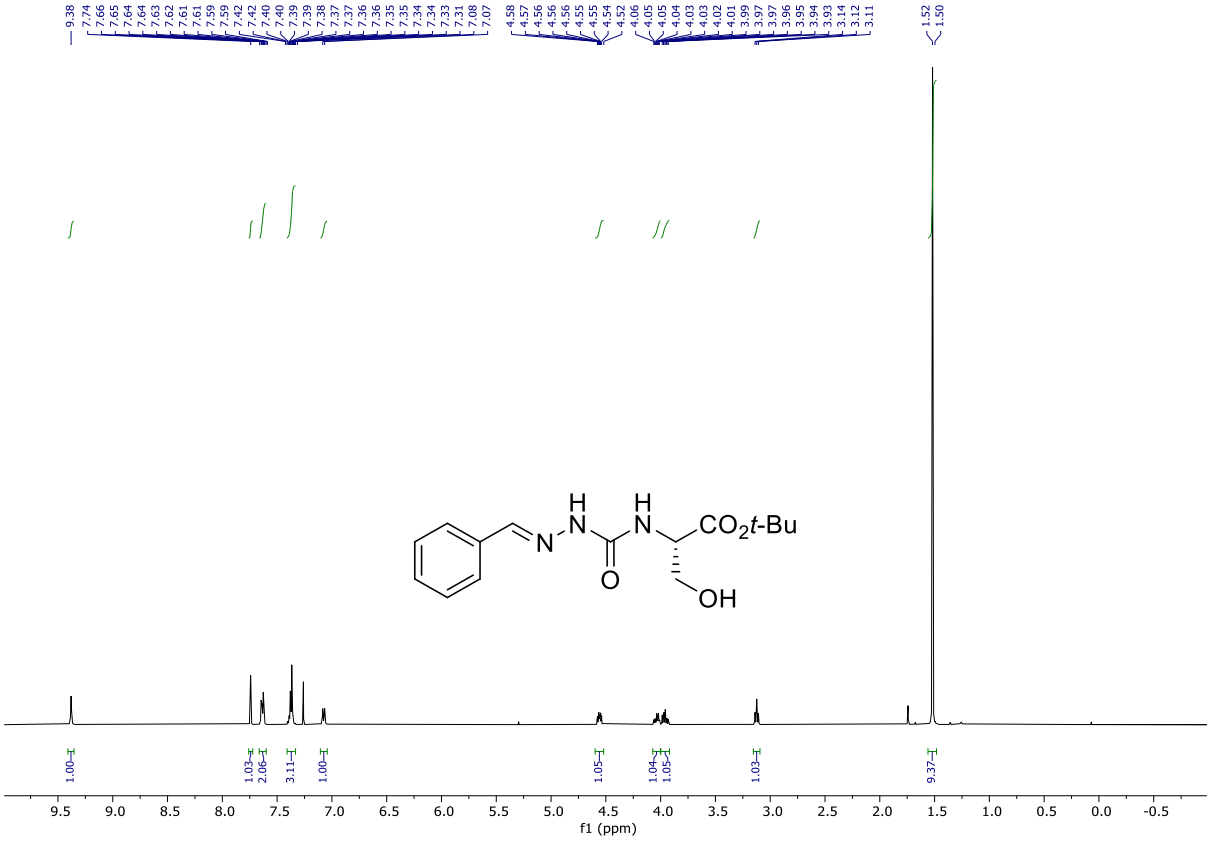
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2h**



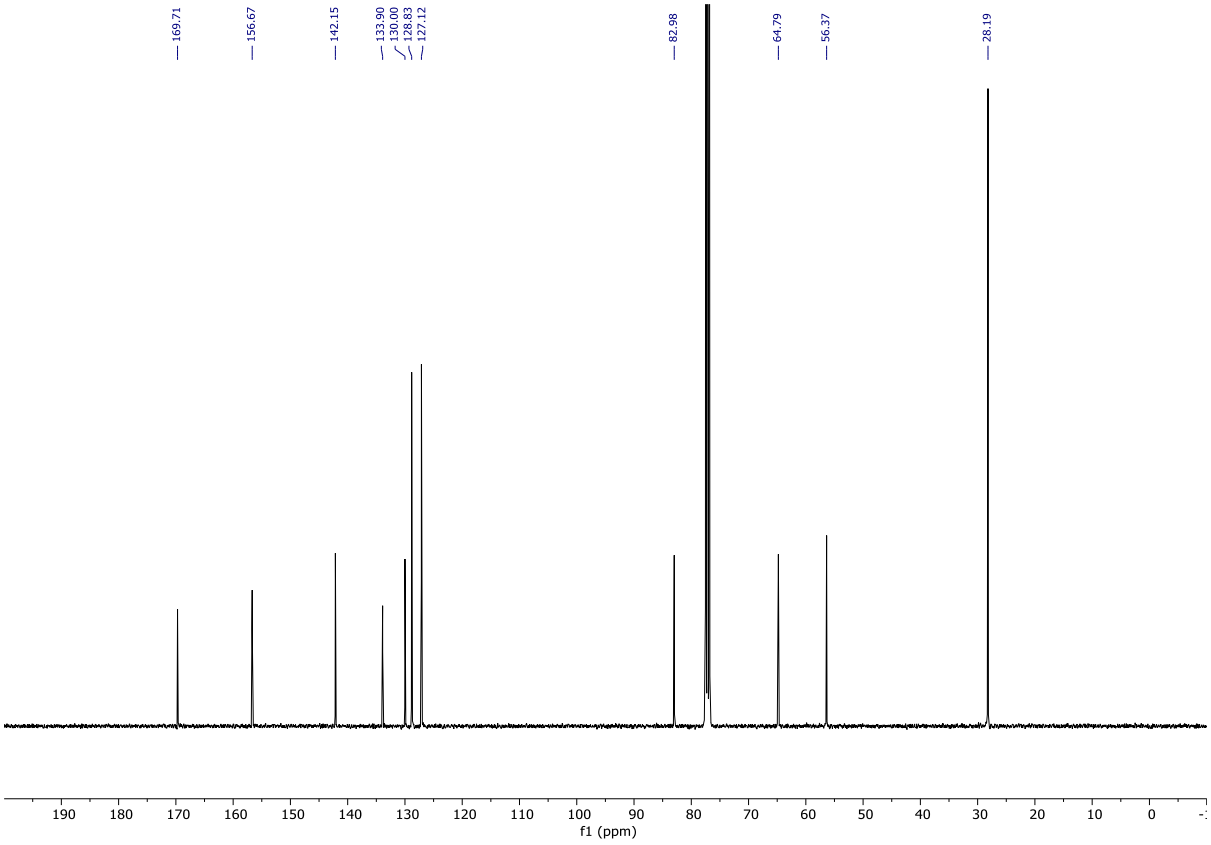

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2h**



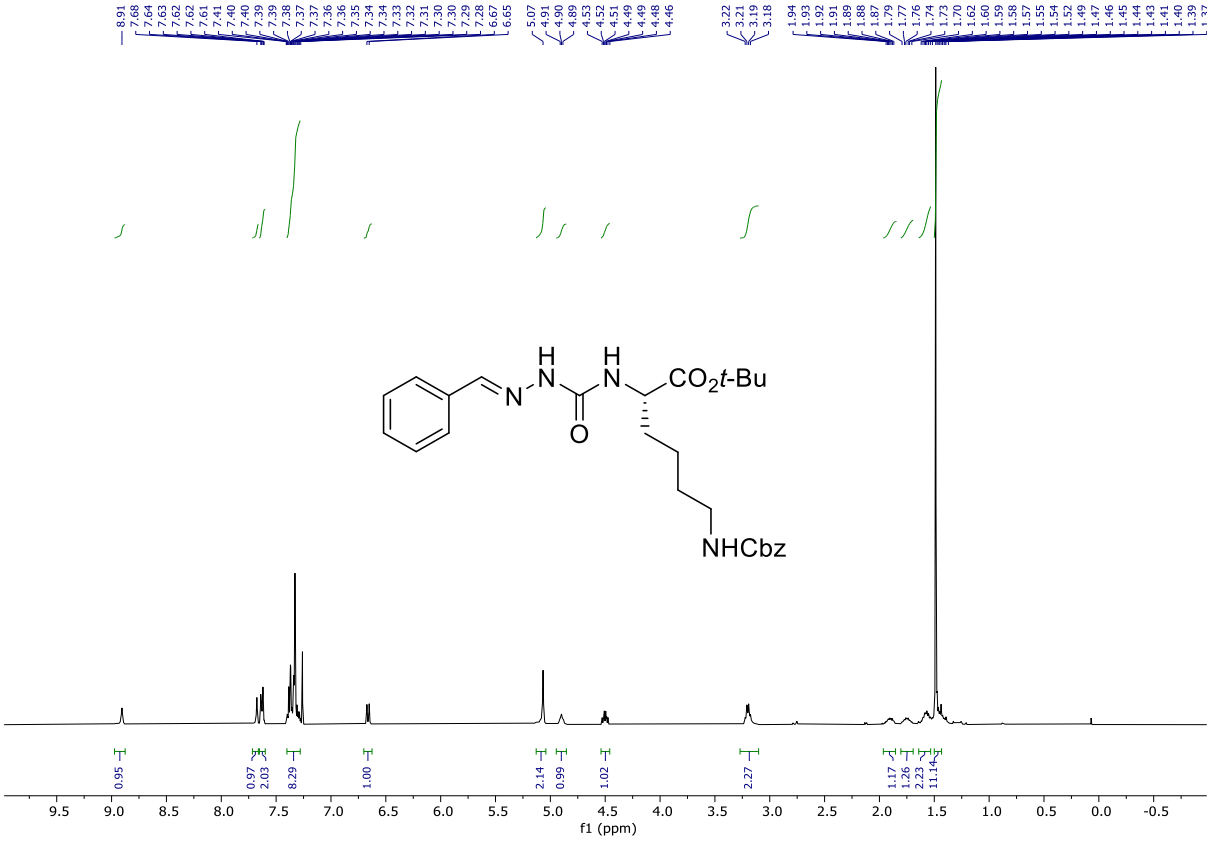
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2i**



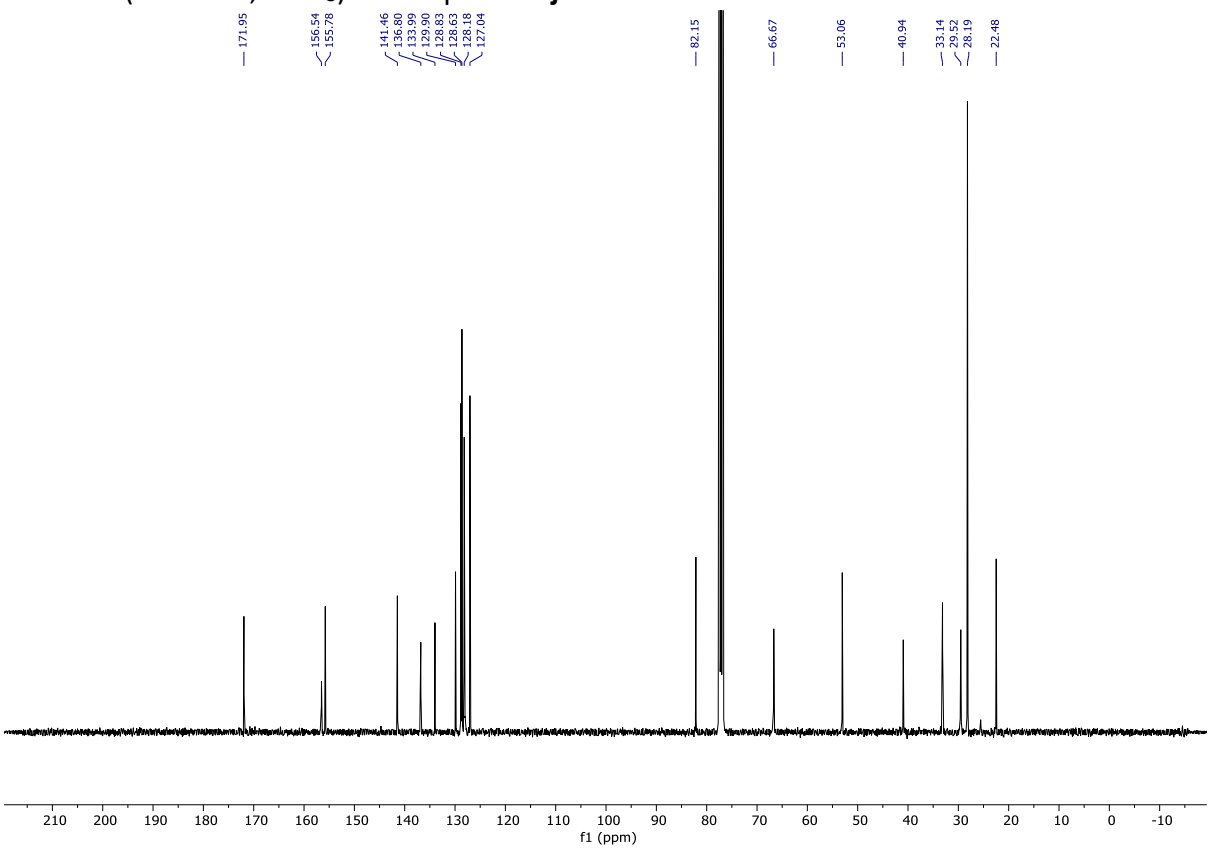

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2i**



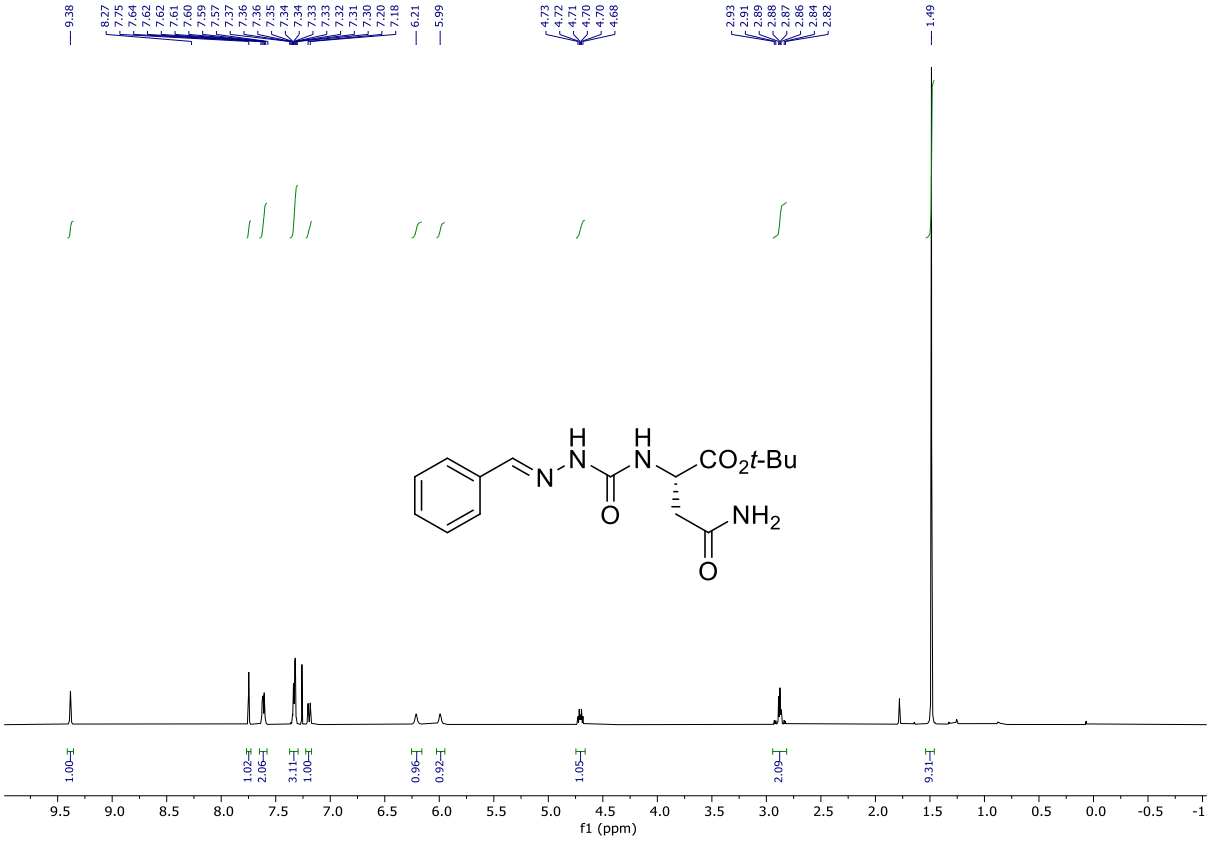
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2j**




**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2j**



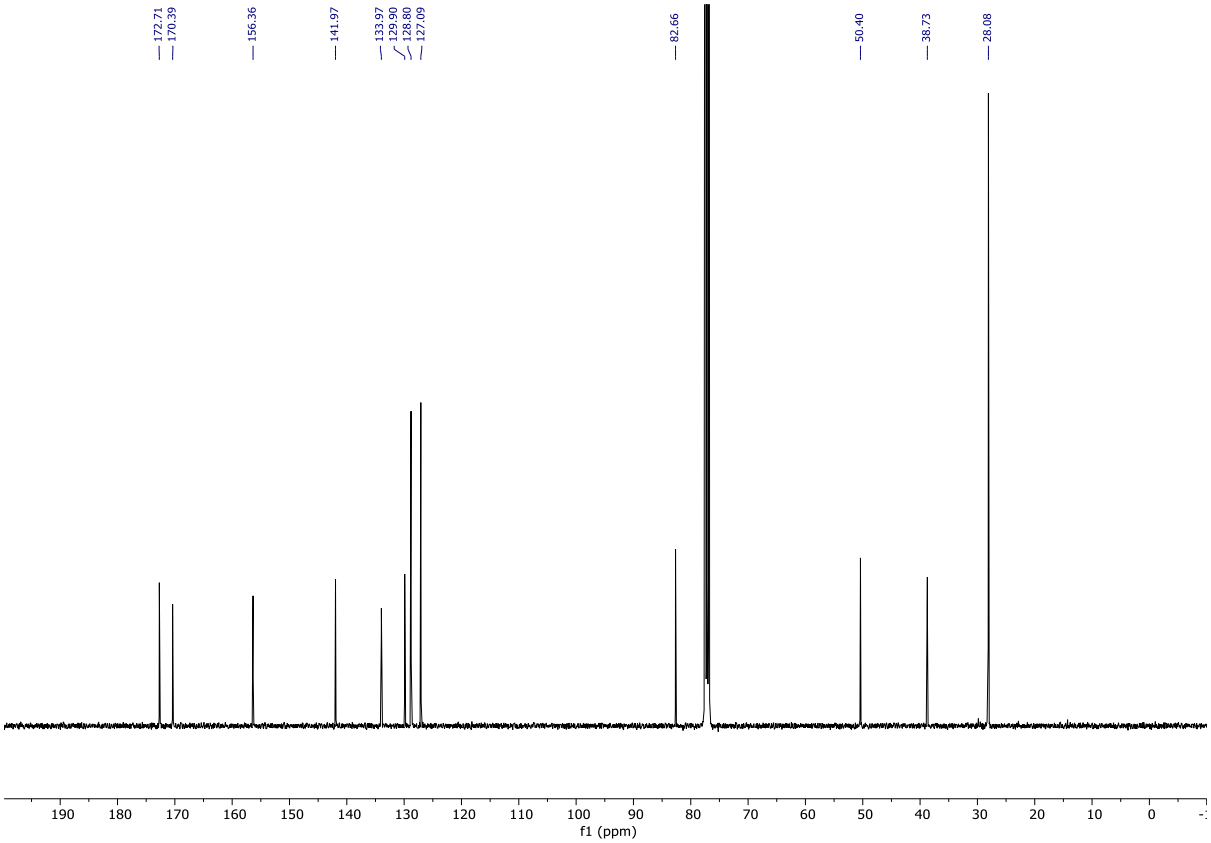
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2k**



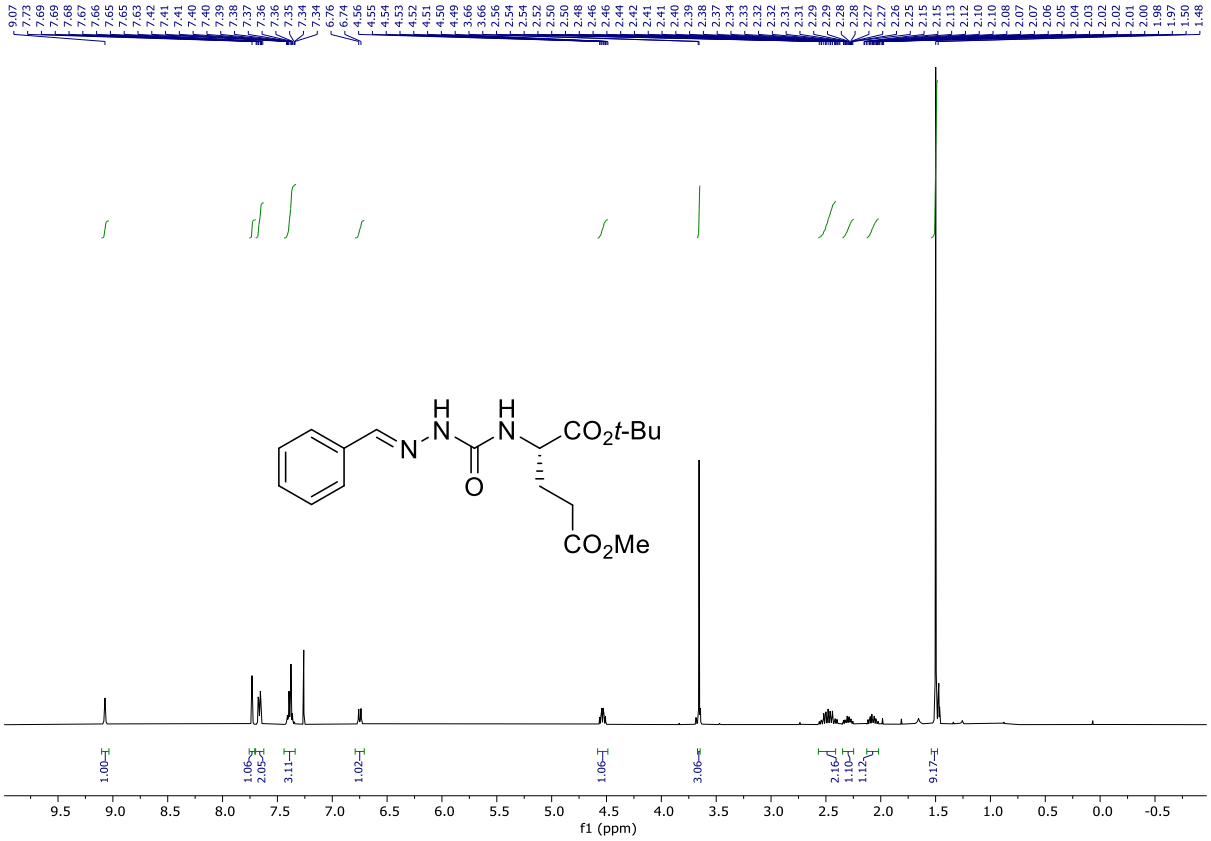




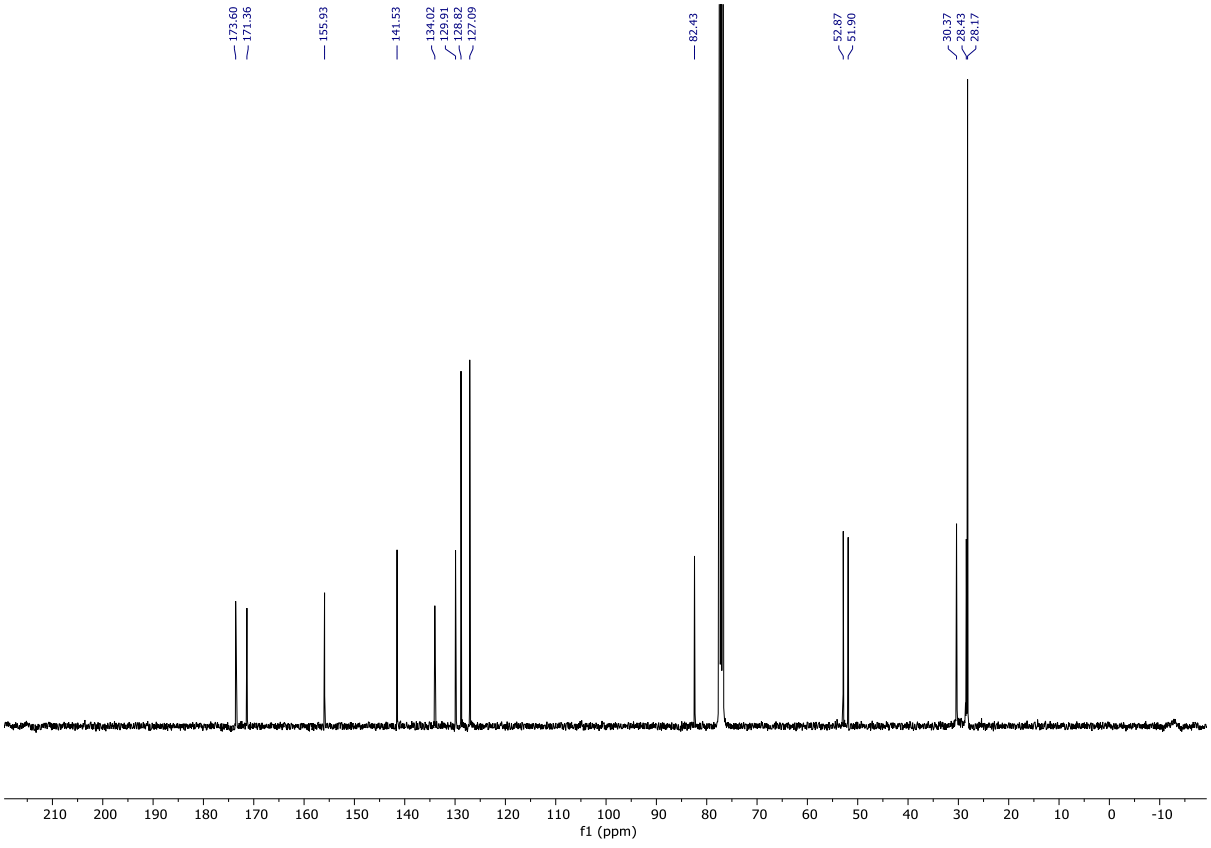
**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2k**



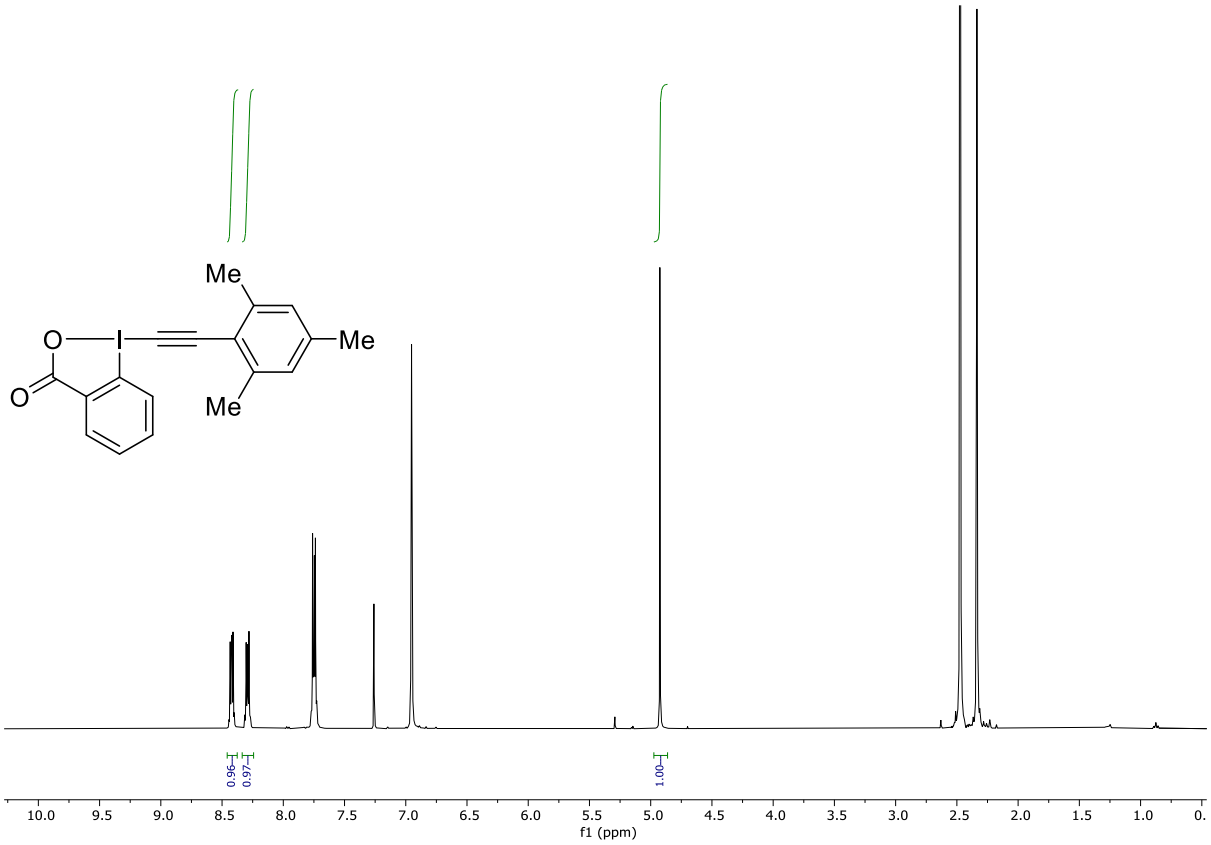
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **2l**



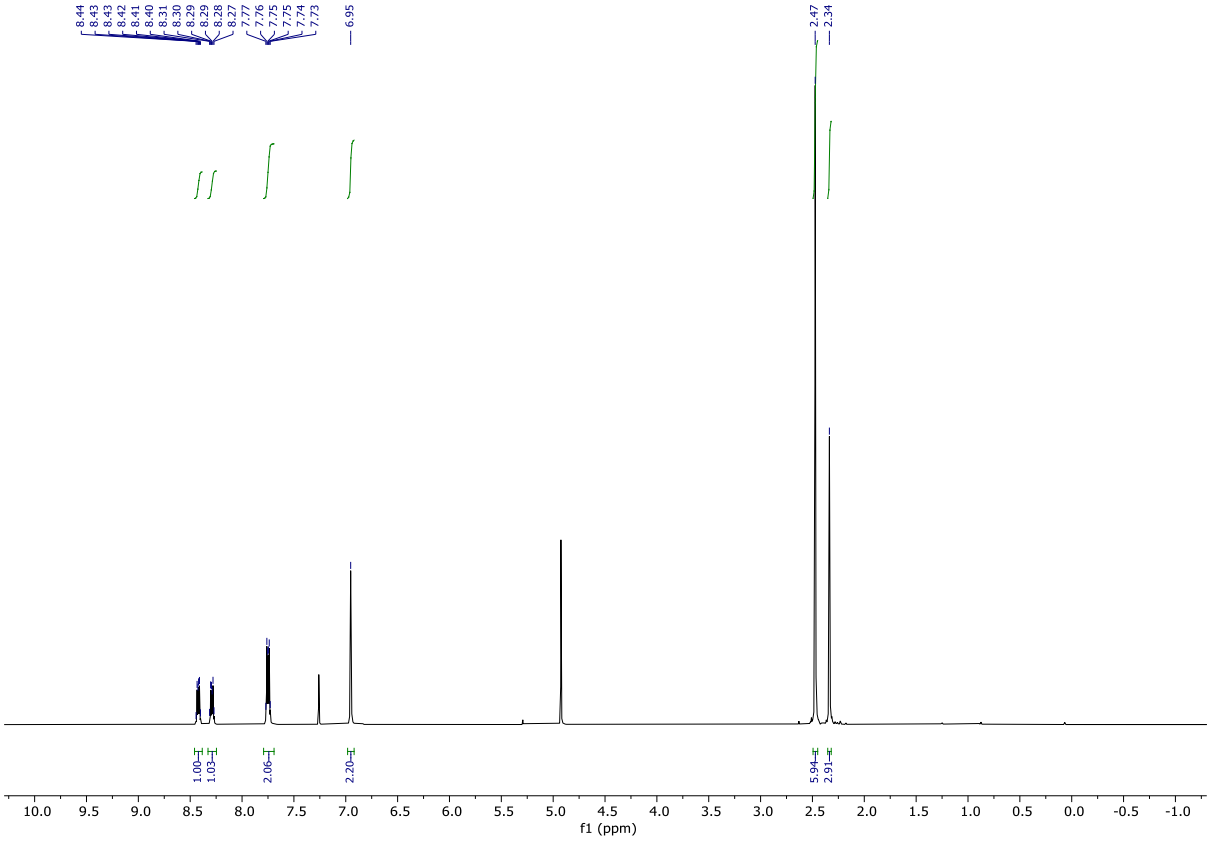

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **2l**



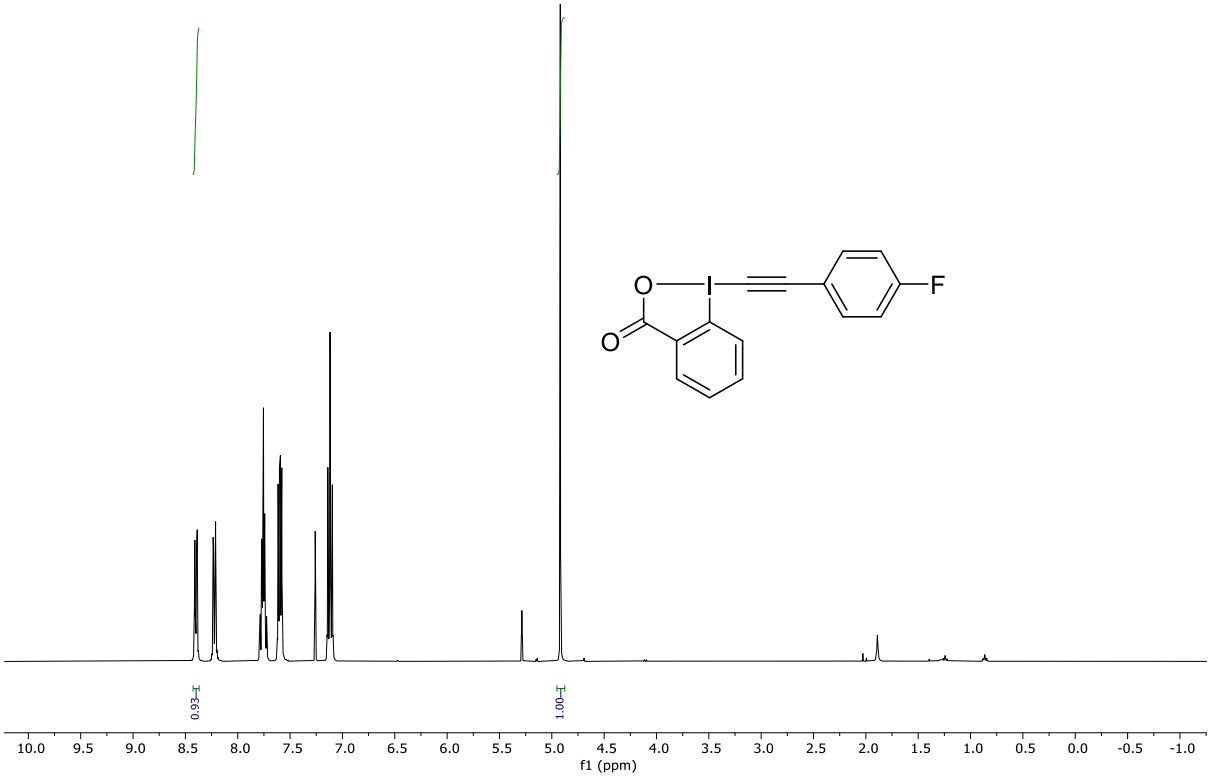
**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3c** (purity determination)



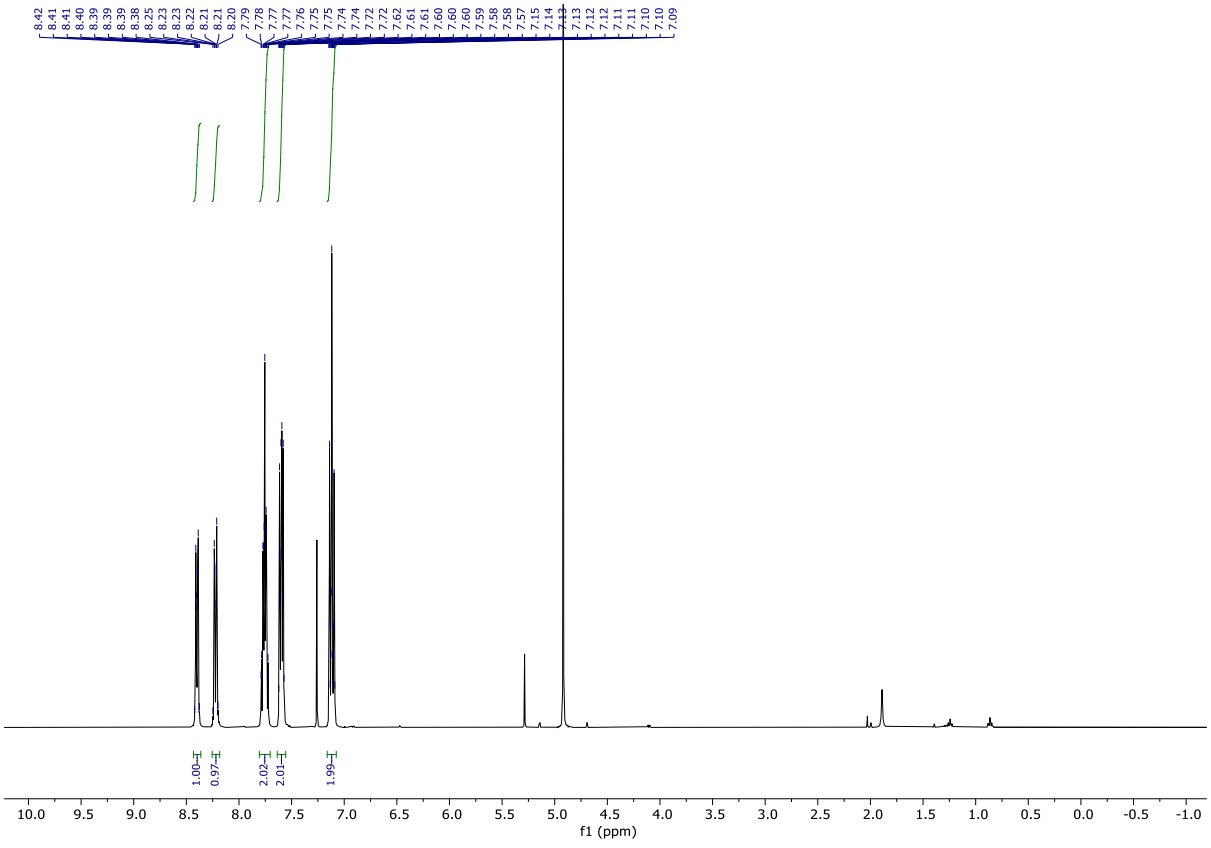

**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3c**



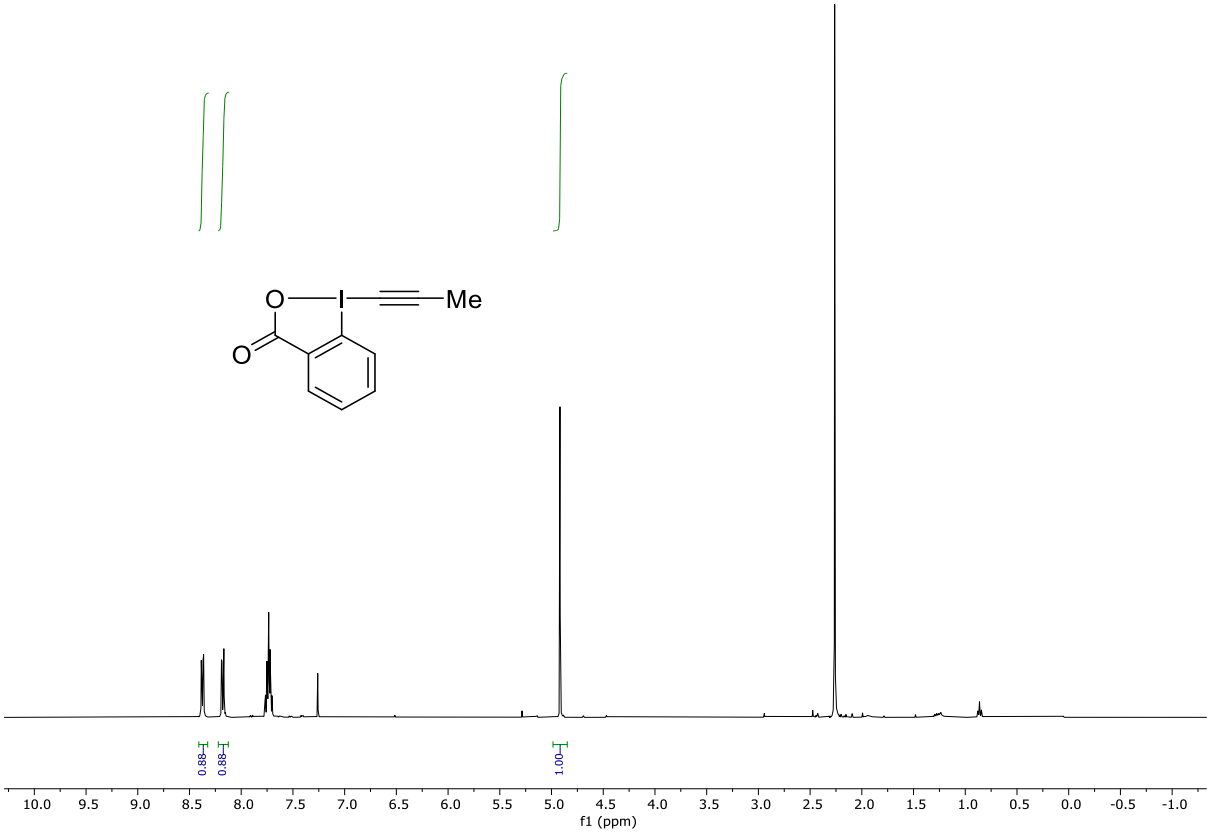
**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3d** (purity determination)



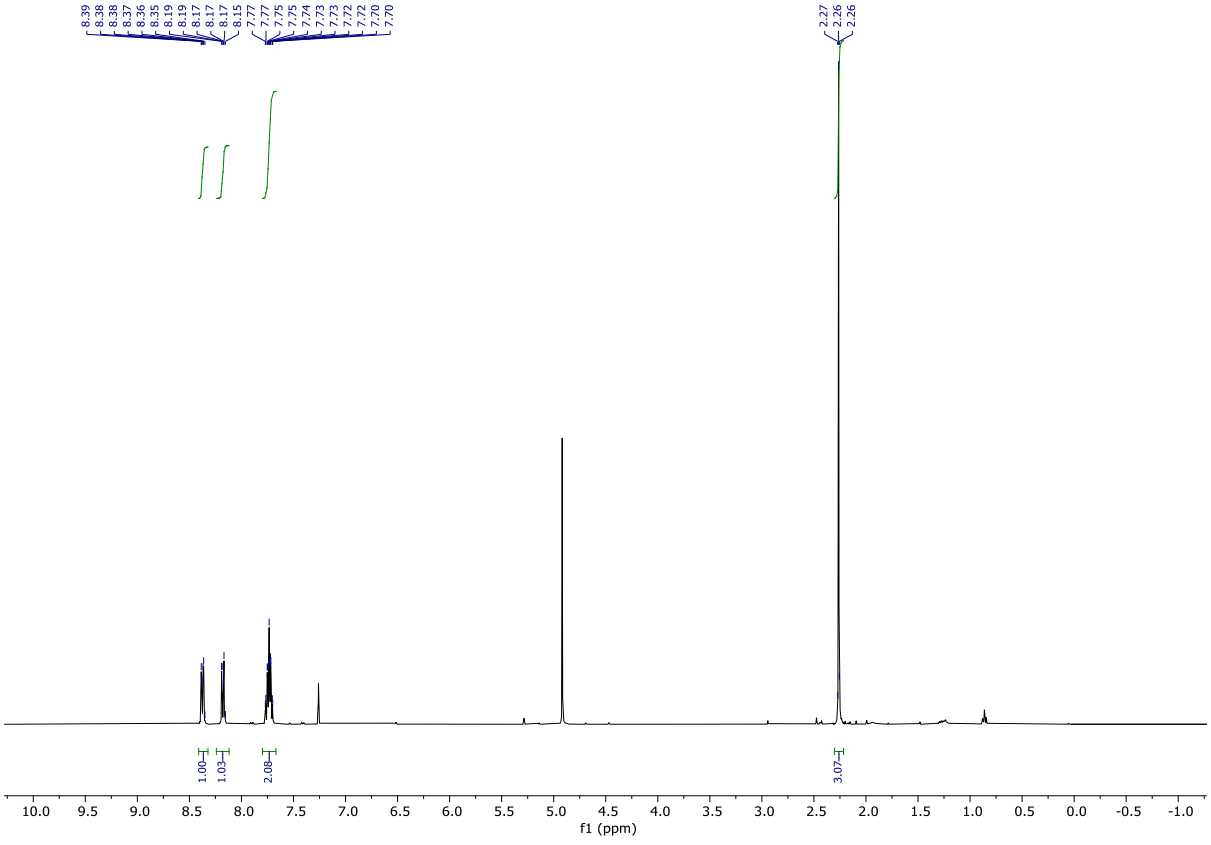

**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3d**



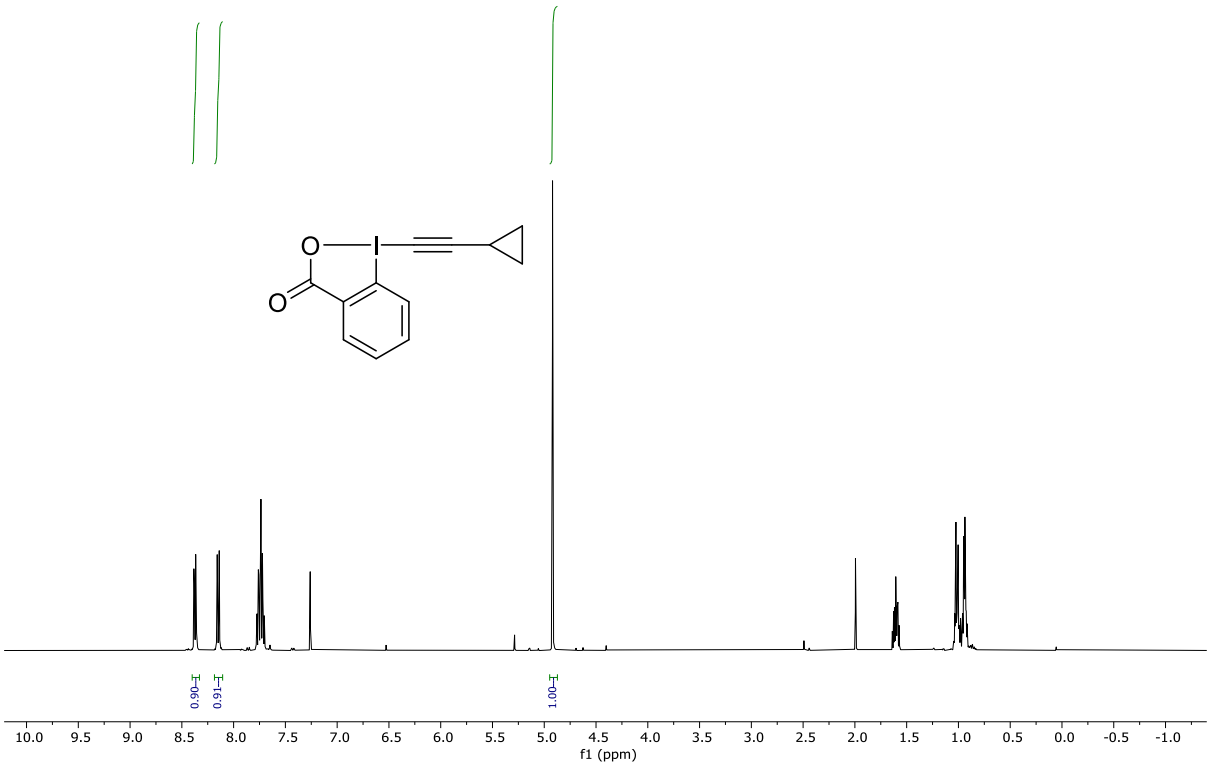
**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3f** (purity determination)



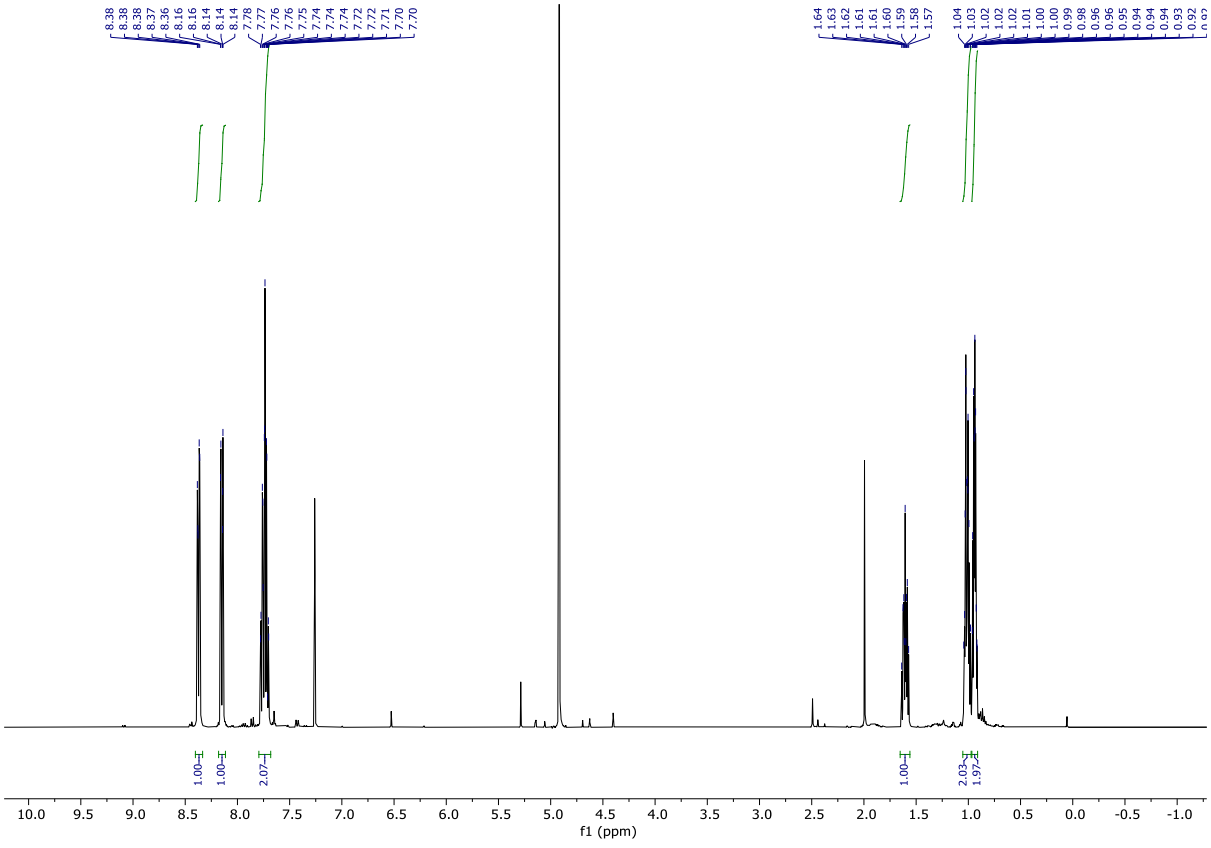

**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3f**



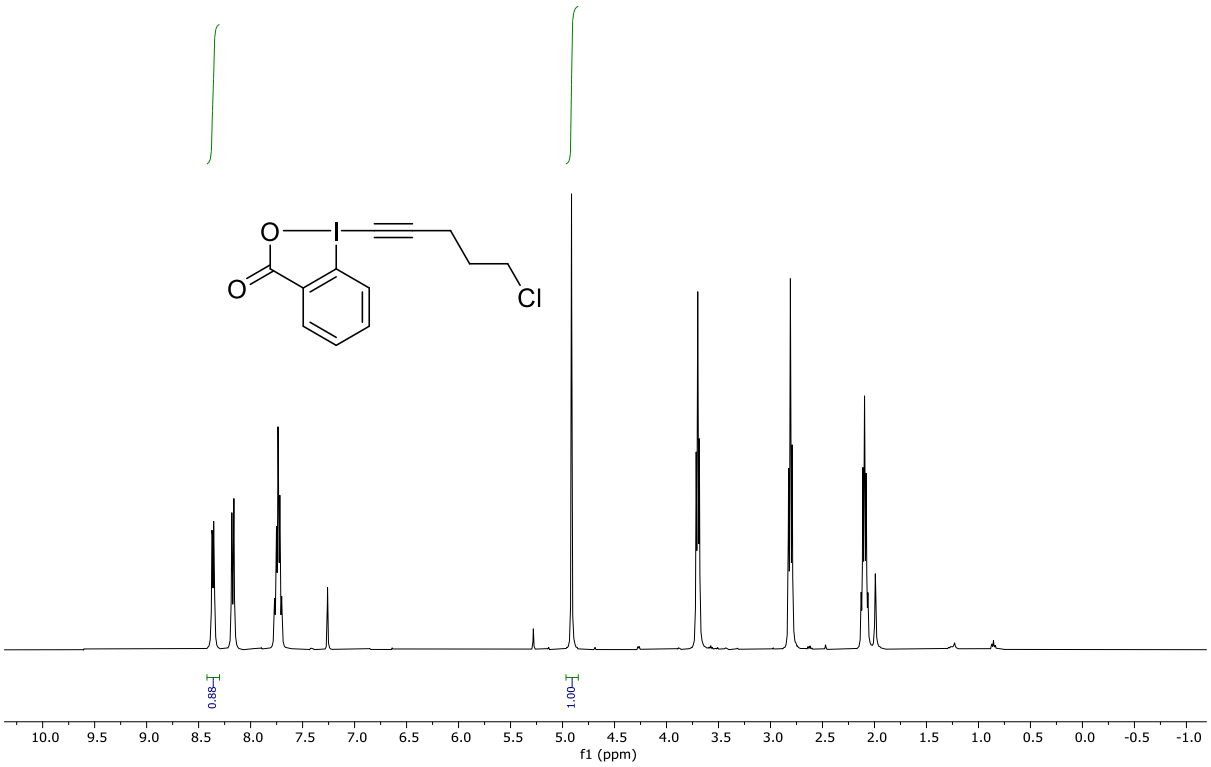
**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3g** (purity determination)



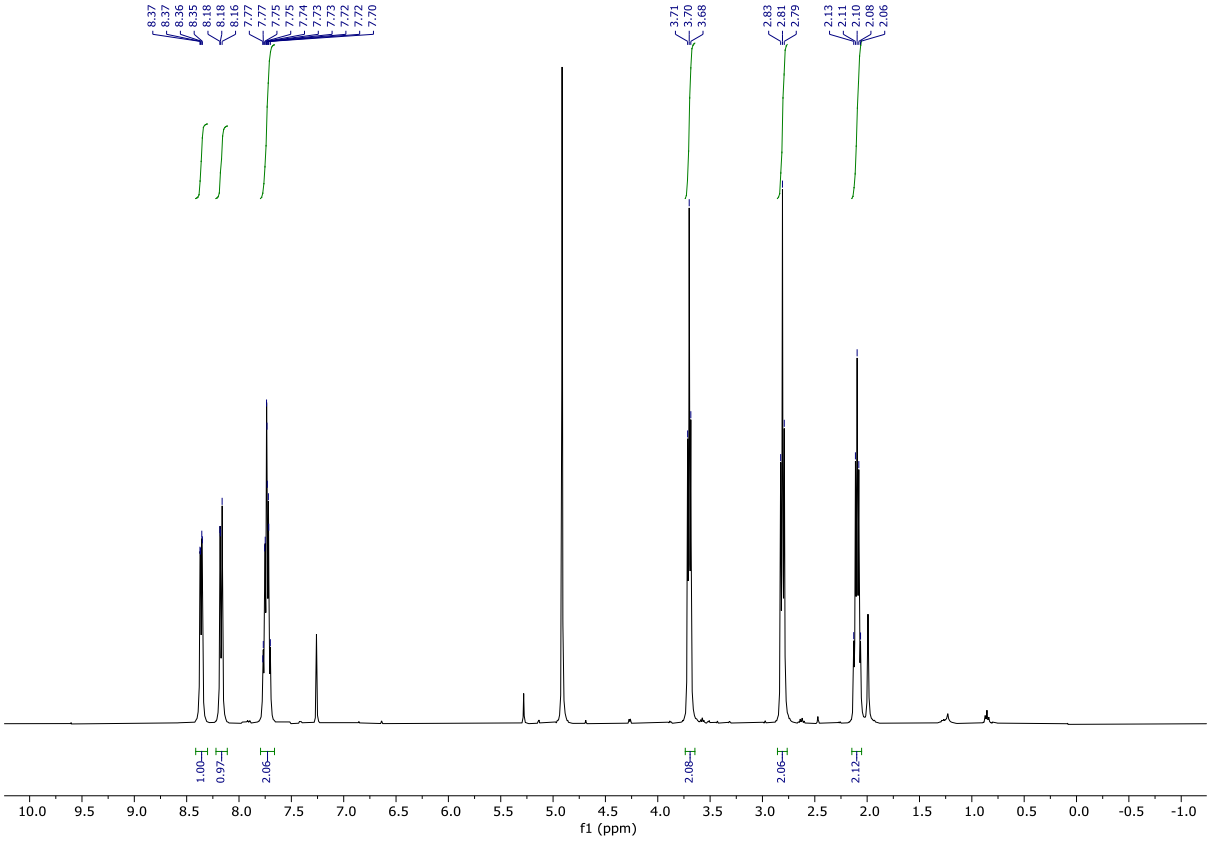

**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3g**



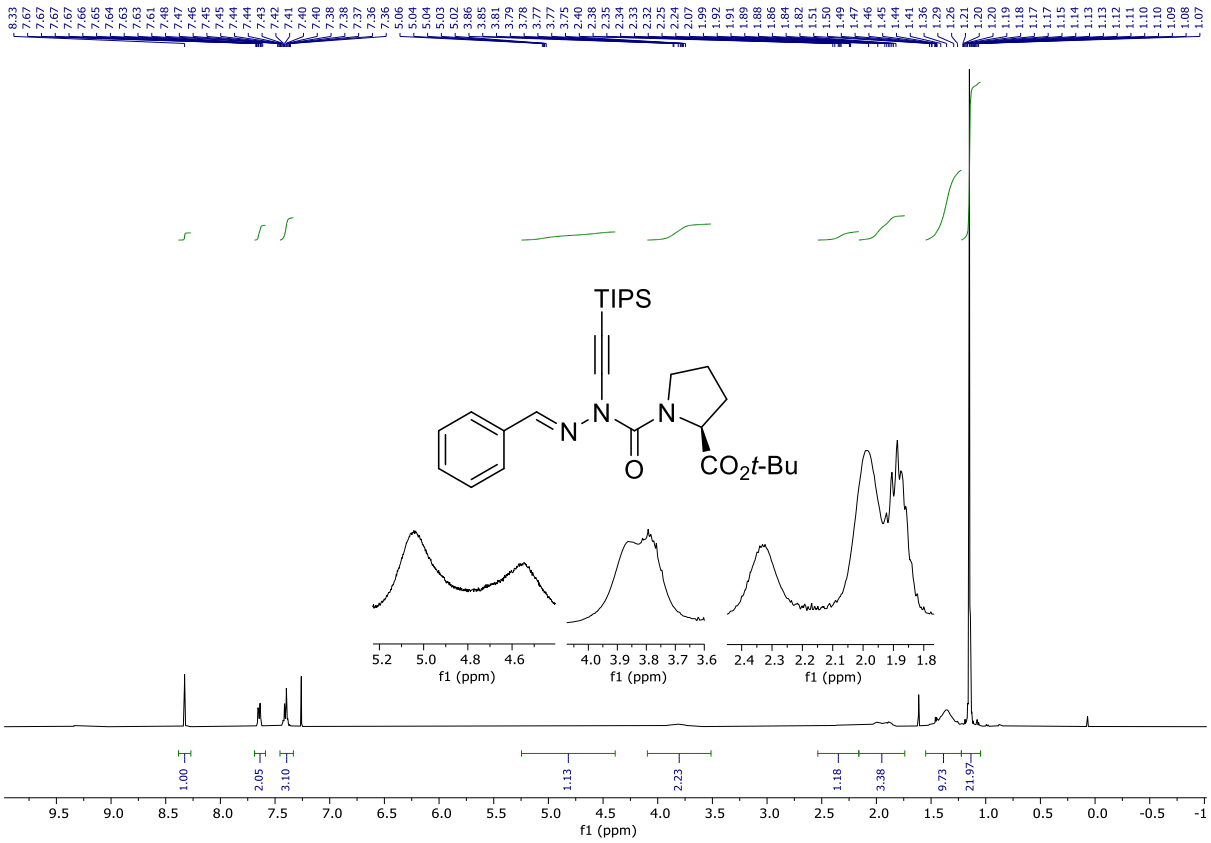
**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3h** (purity determination)



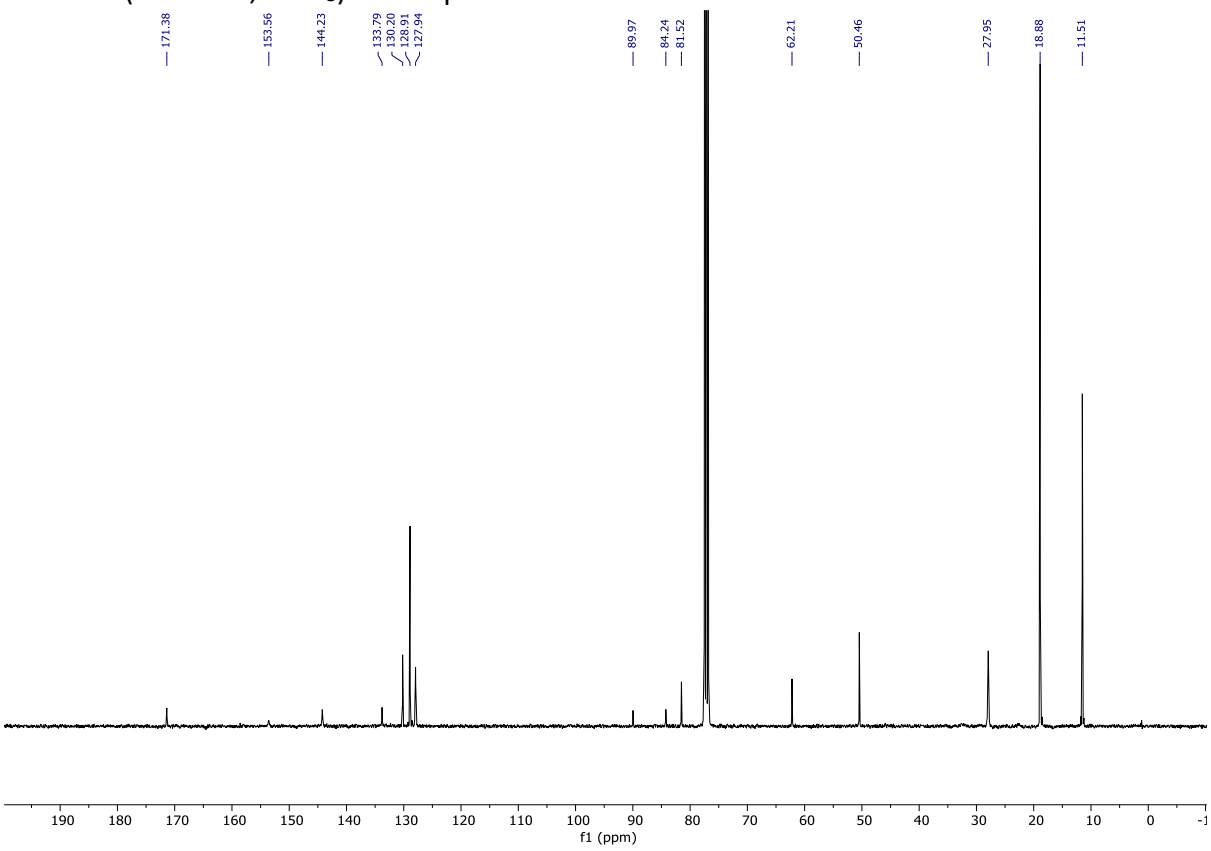

**$^1$H NMR** (400 MHz, $CDCl_3$) of compound **3h**



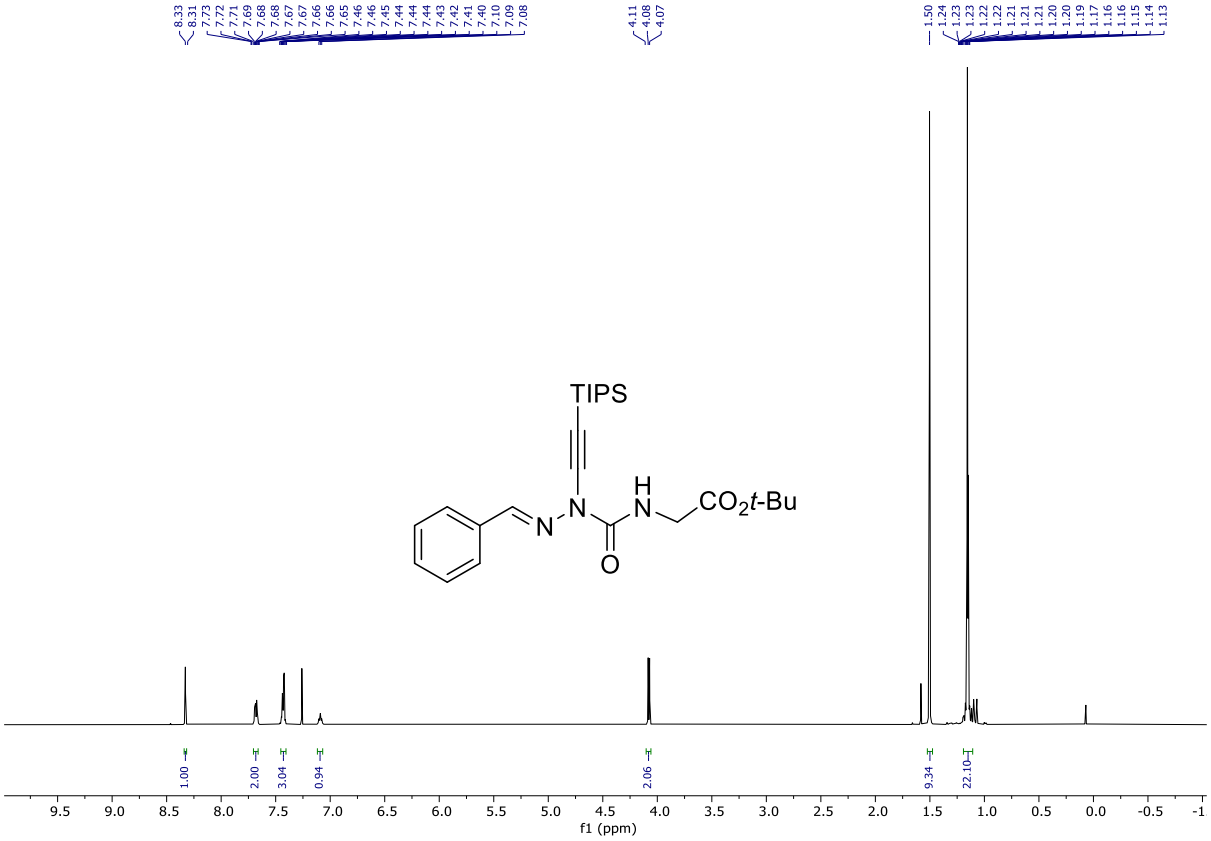
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4a**



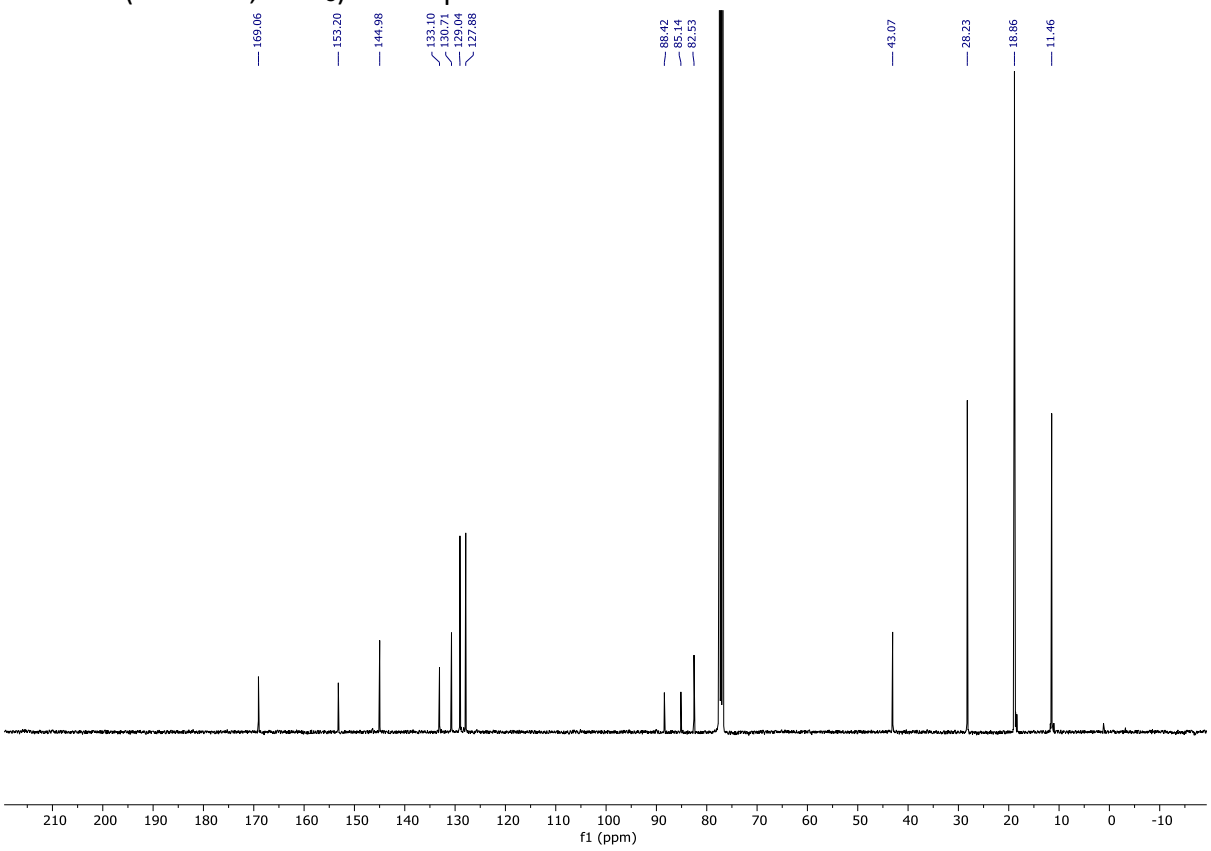

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4a**



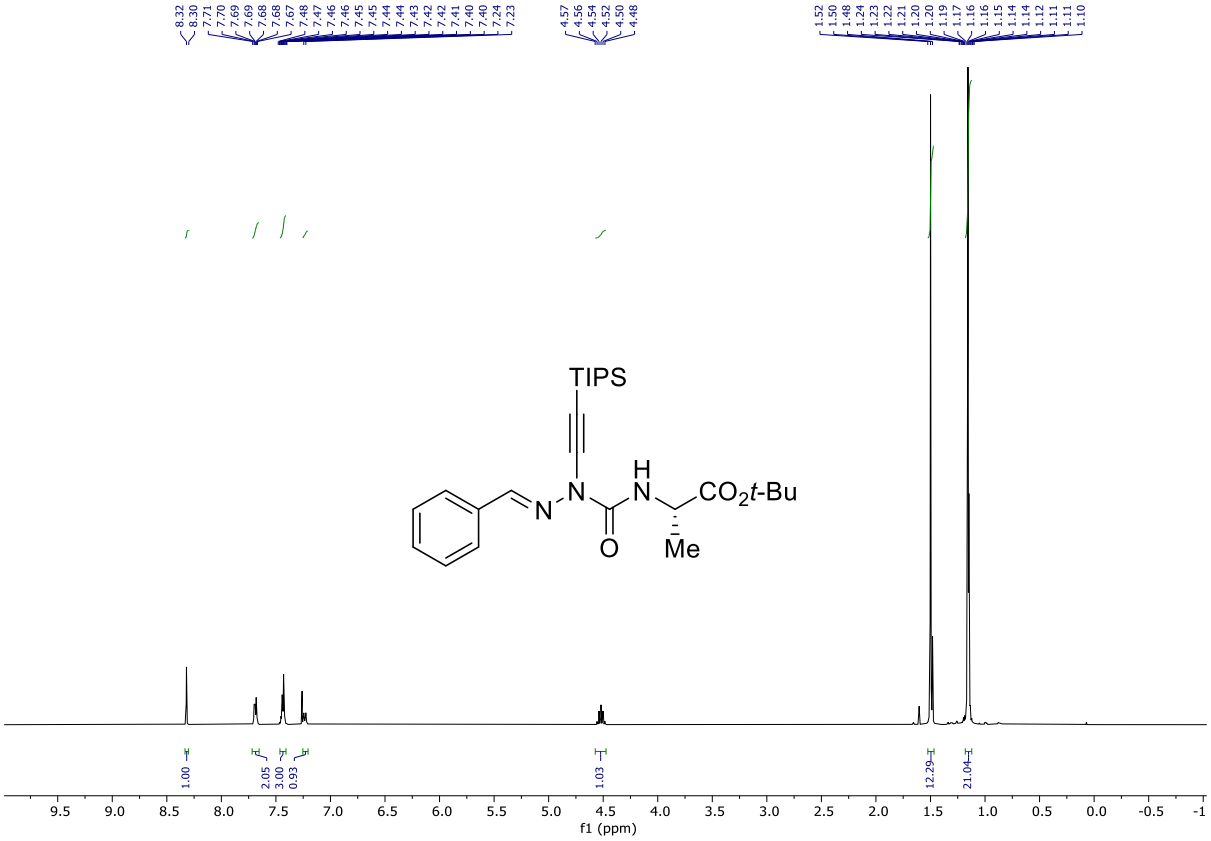
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4b**



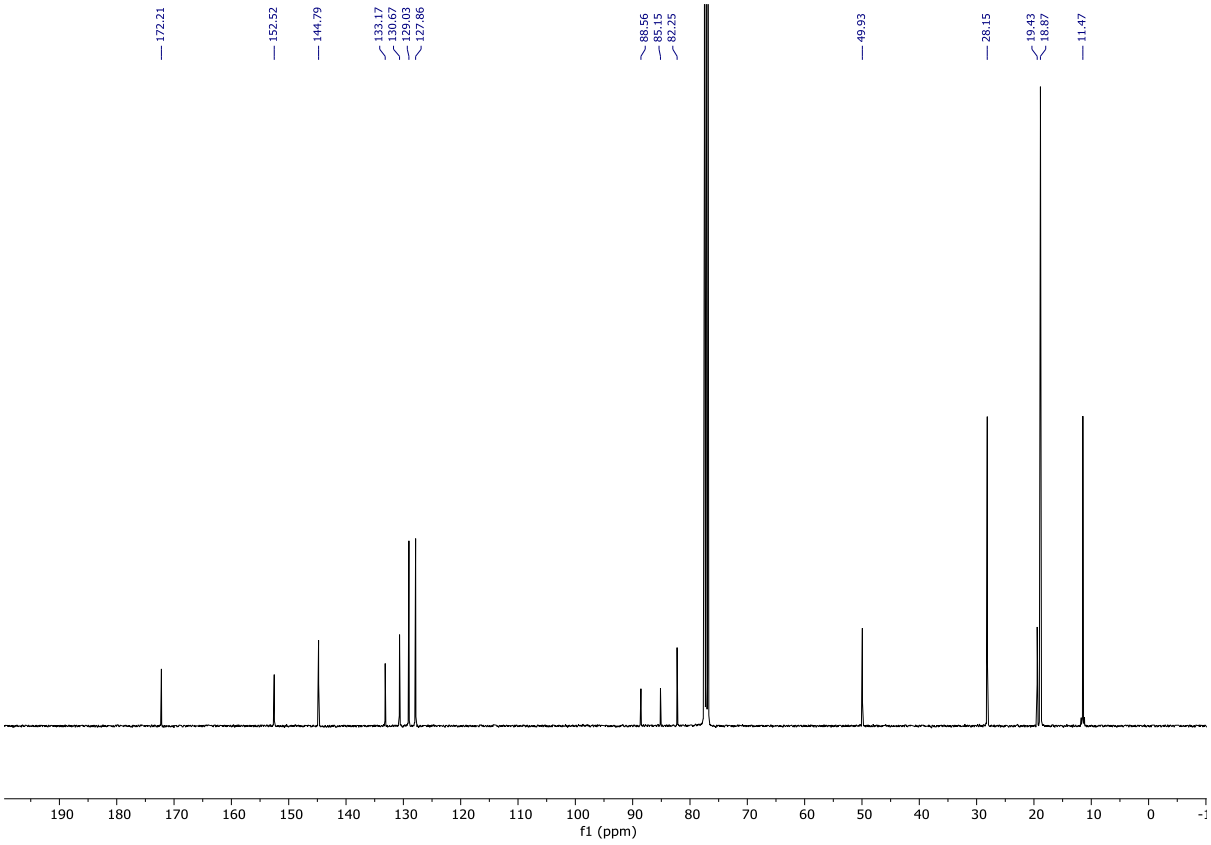

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4b**



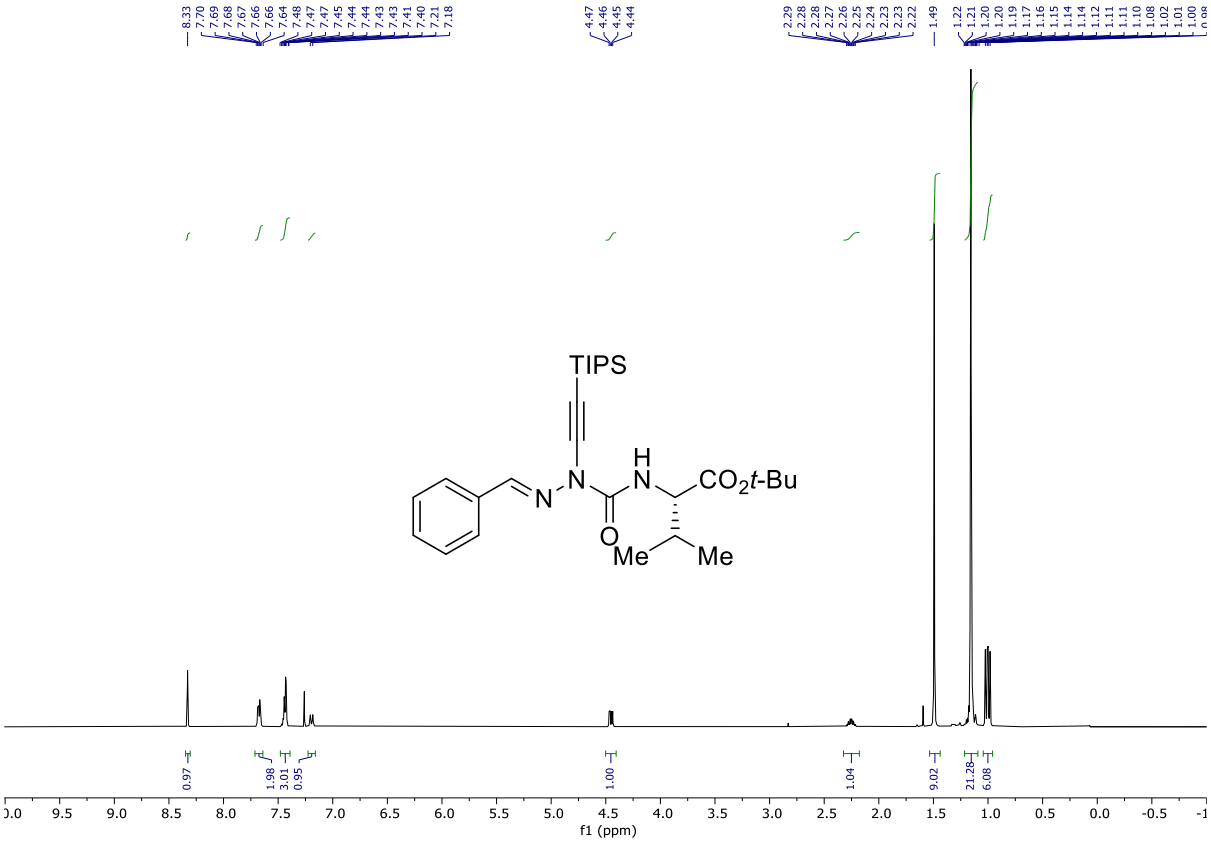
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4c**



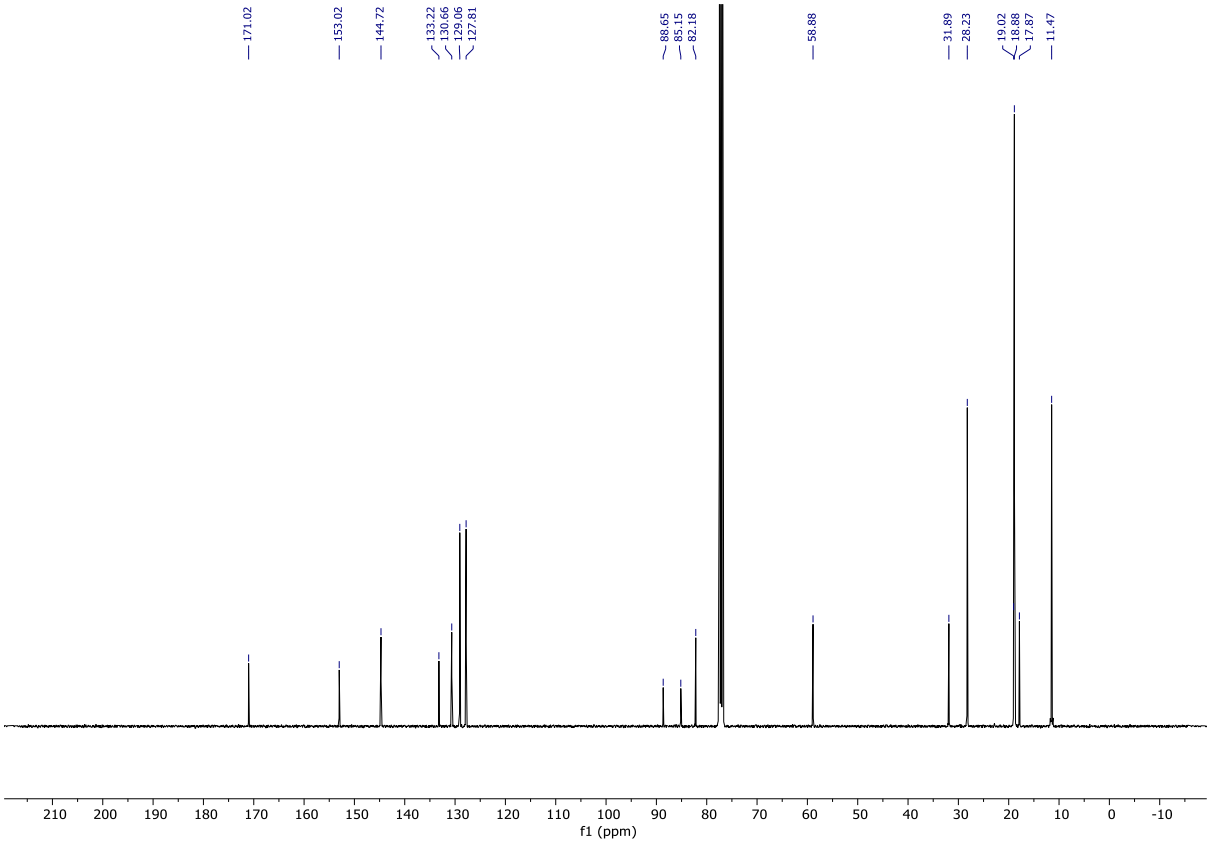

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4c**



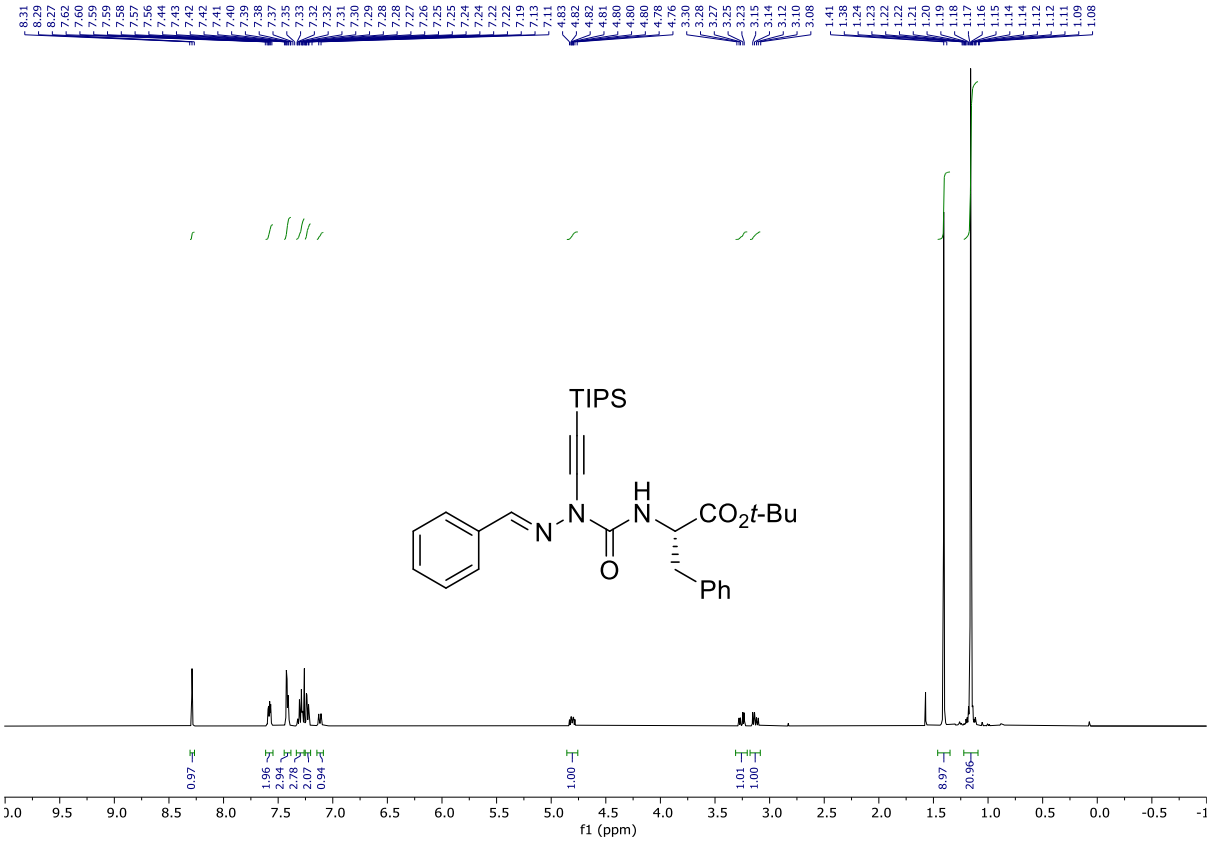
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4d**



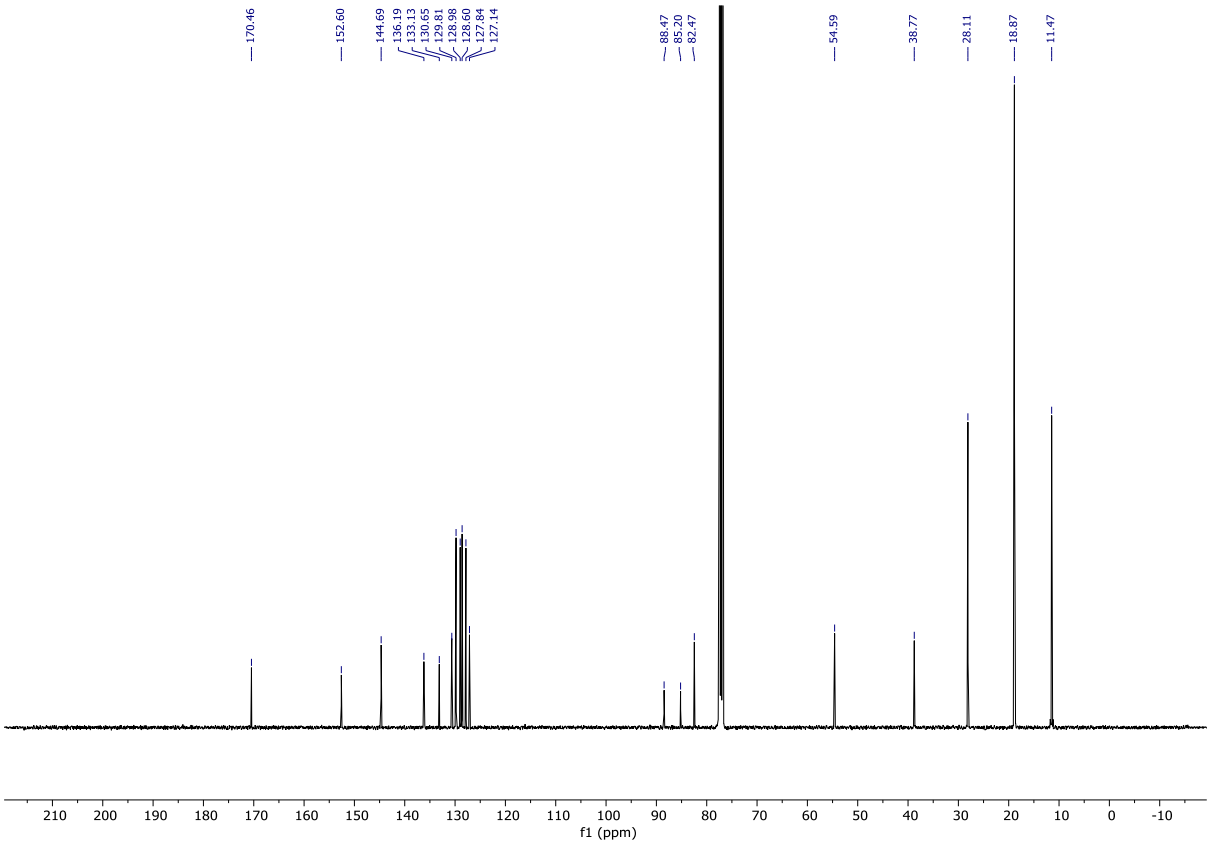

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4d**



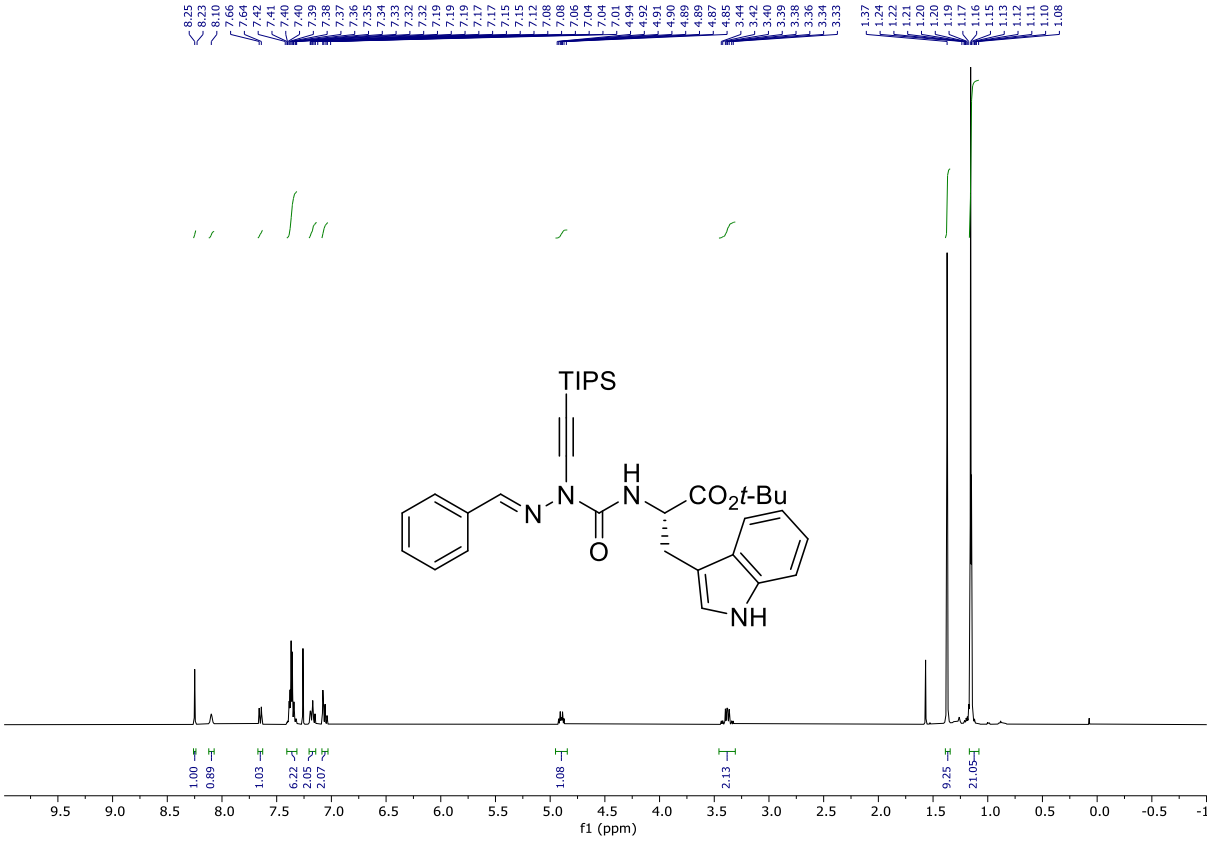
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4e**



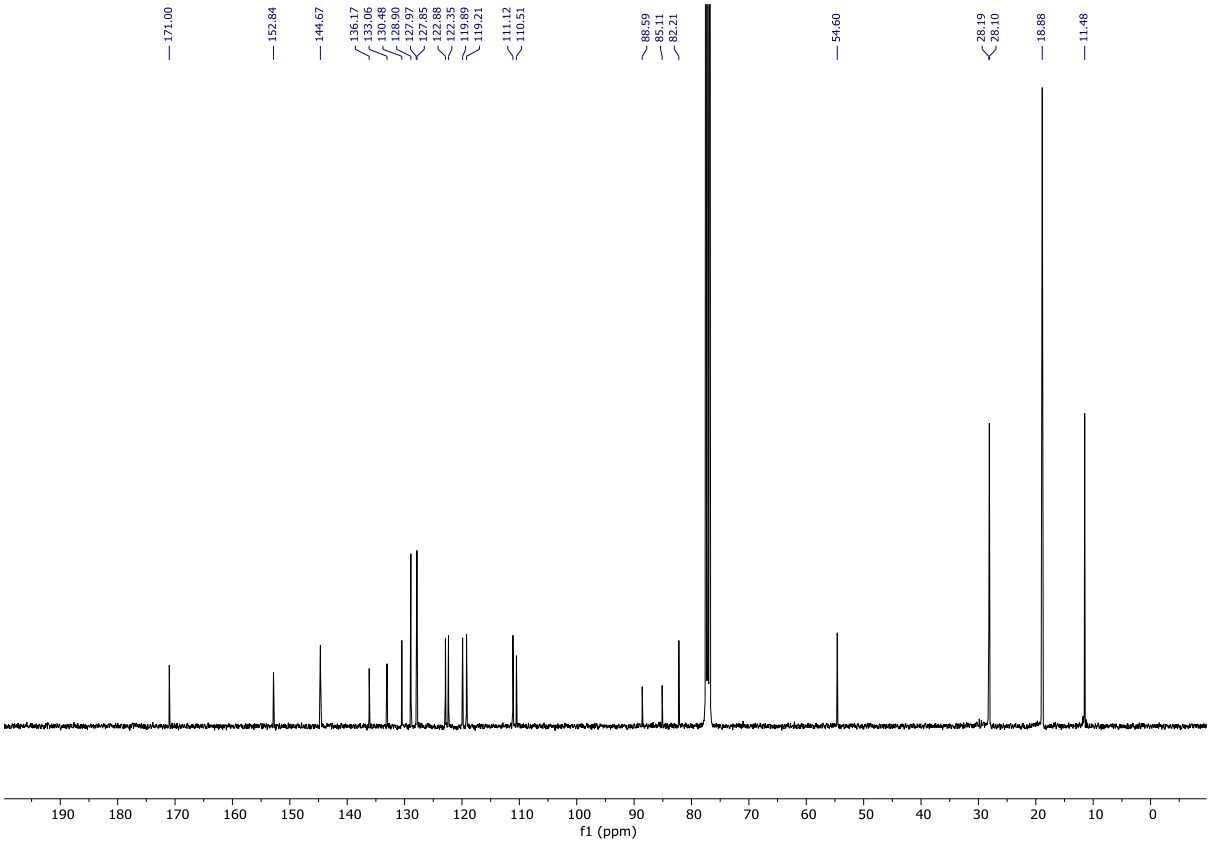

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4e**



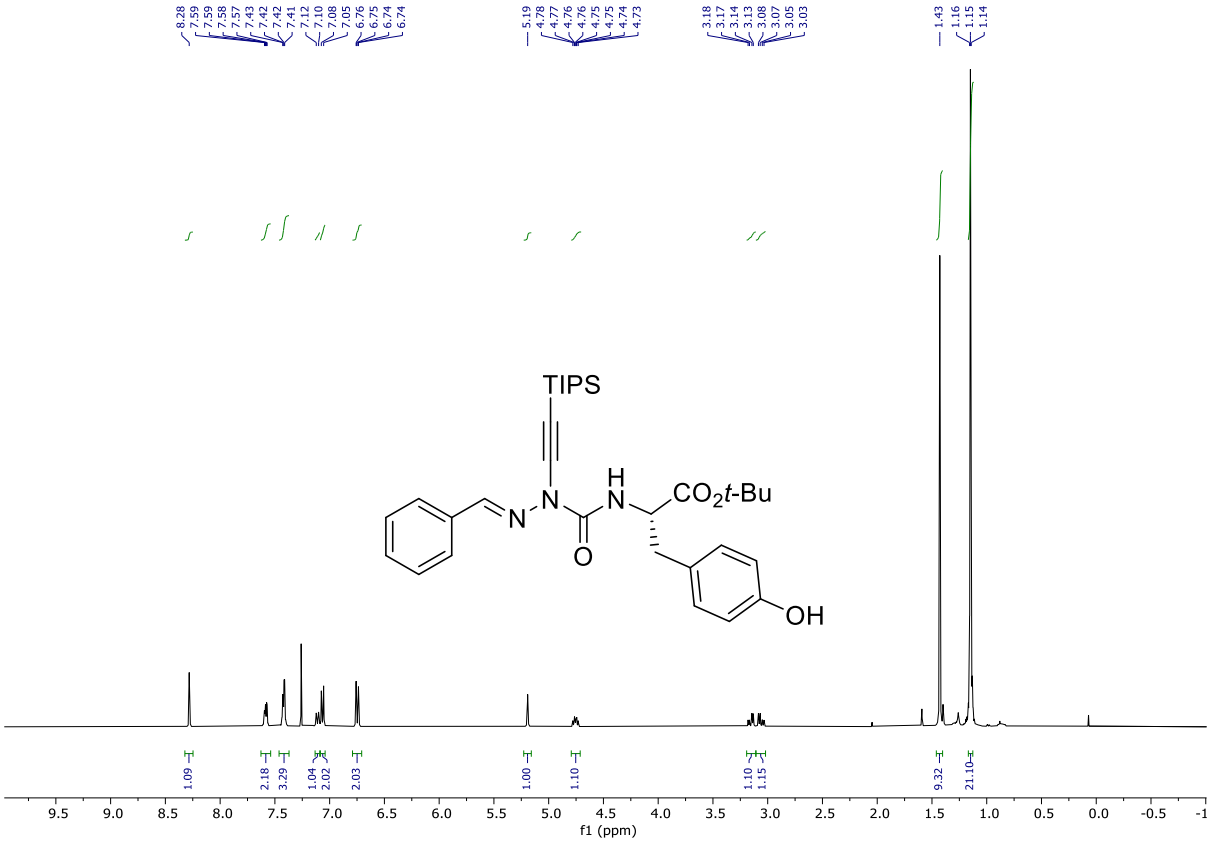
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4f**



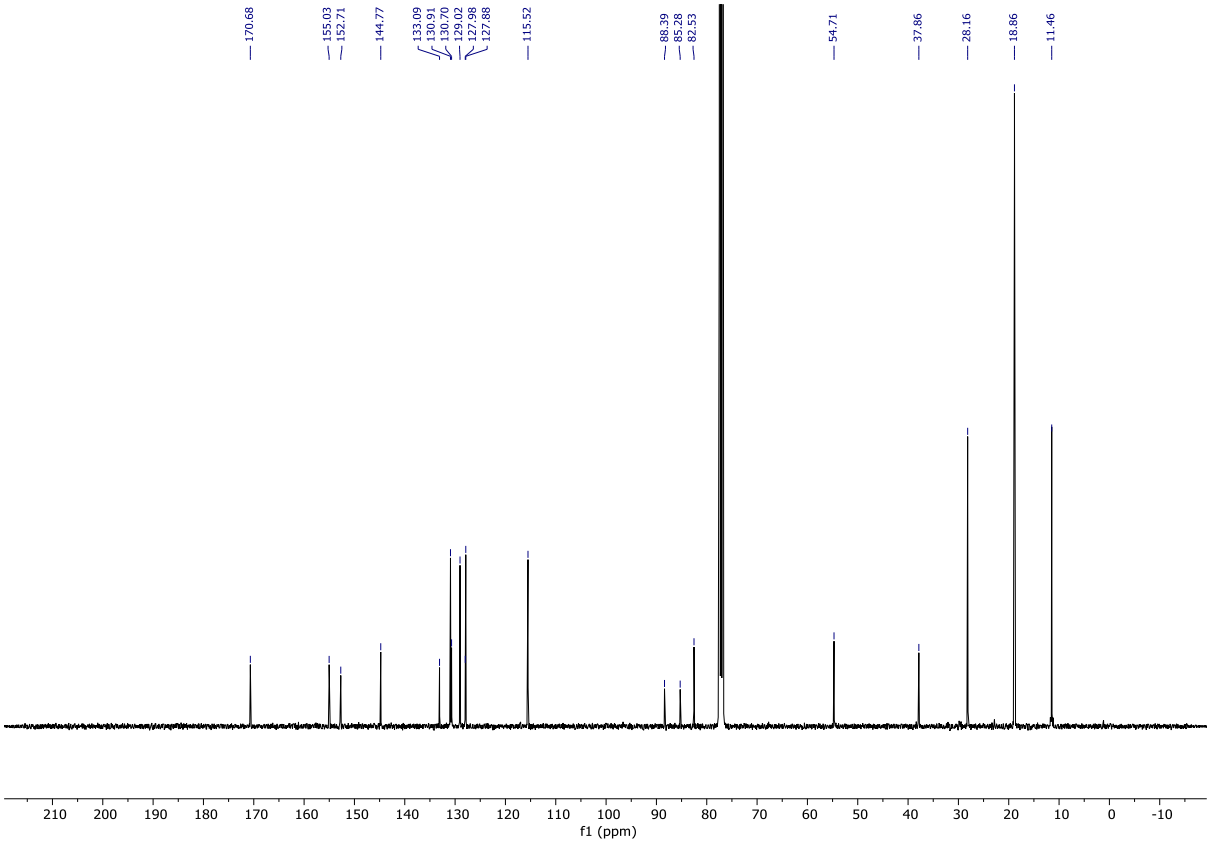

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4f**



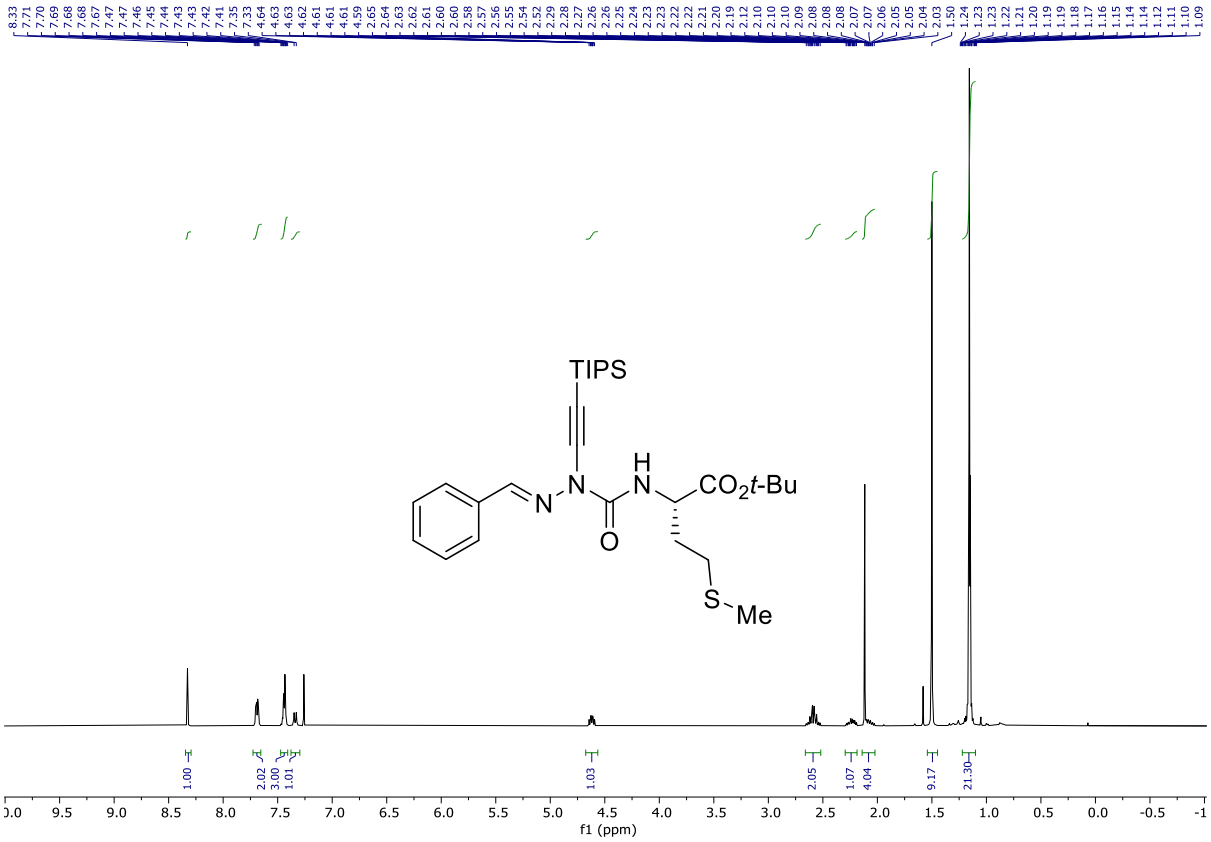
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4g**



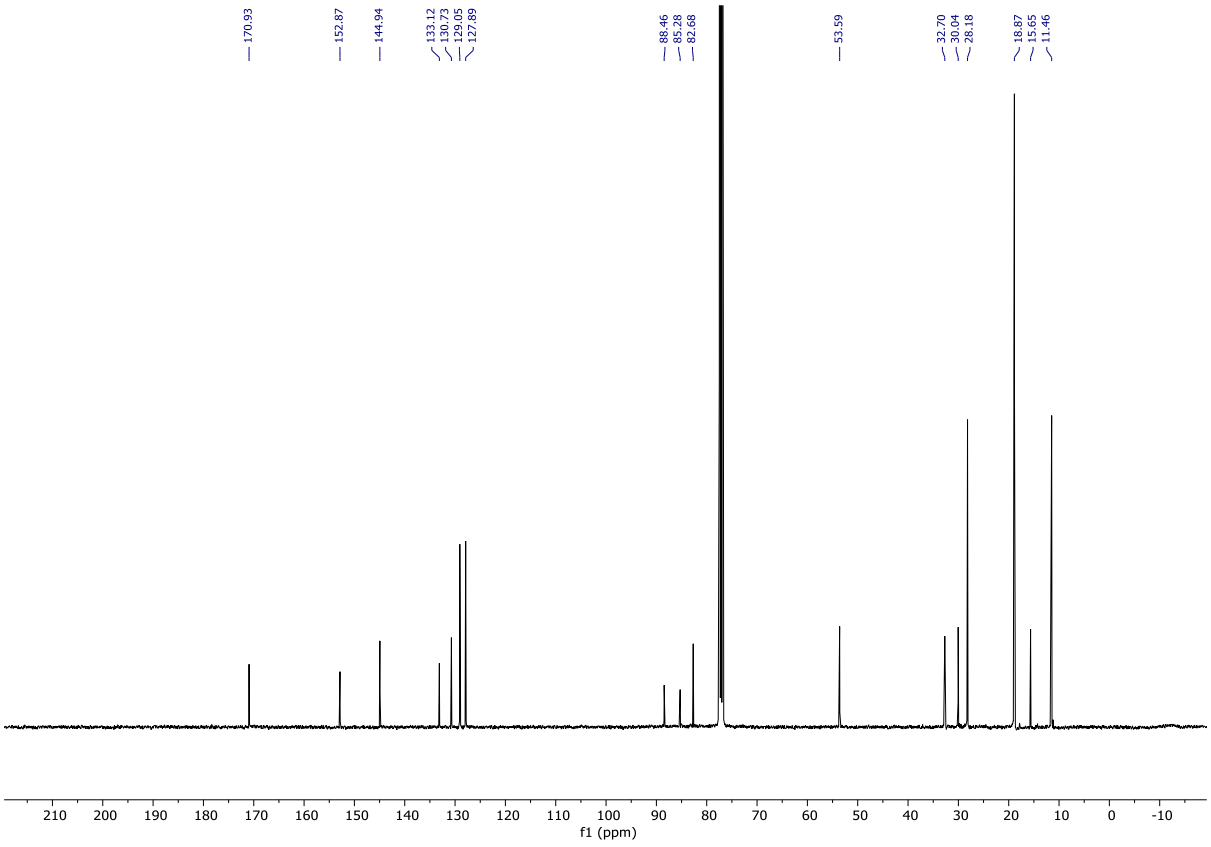

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4g**



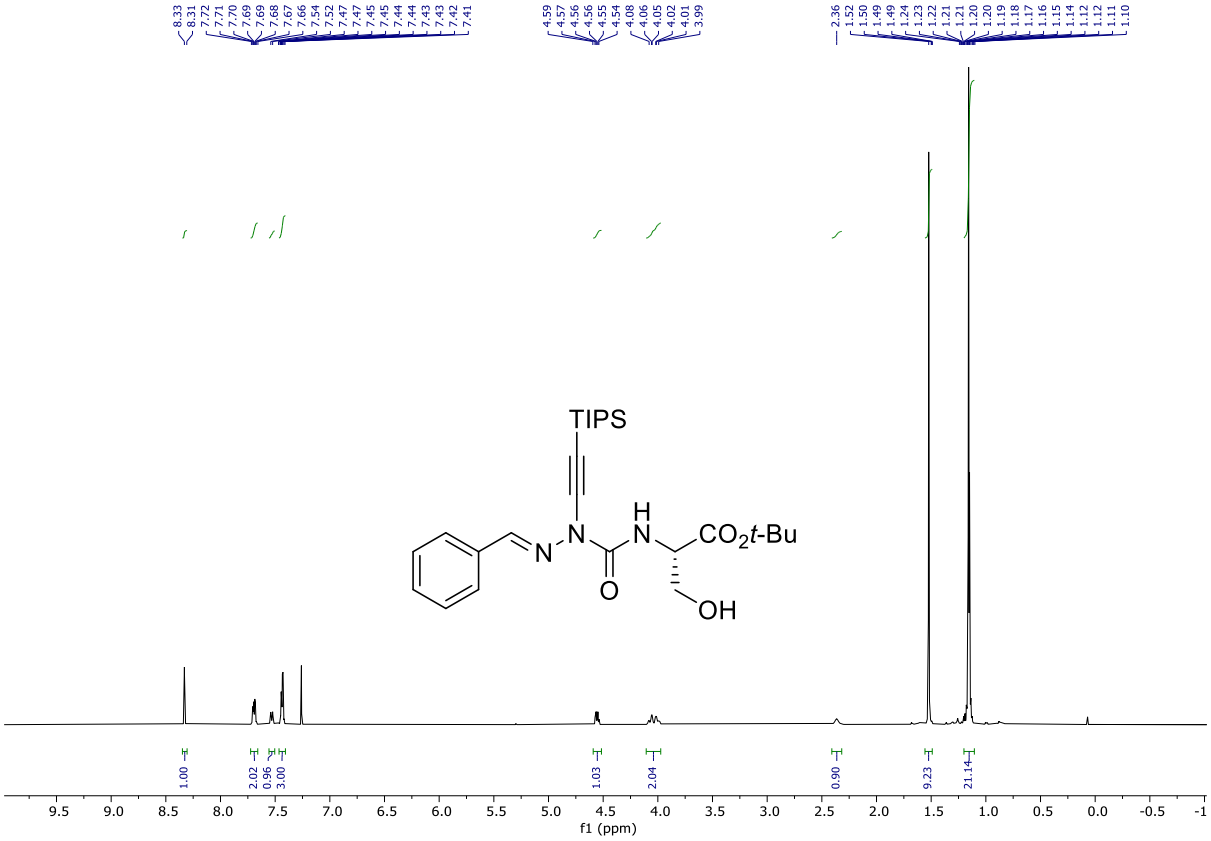
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4h**



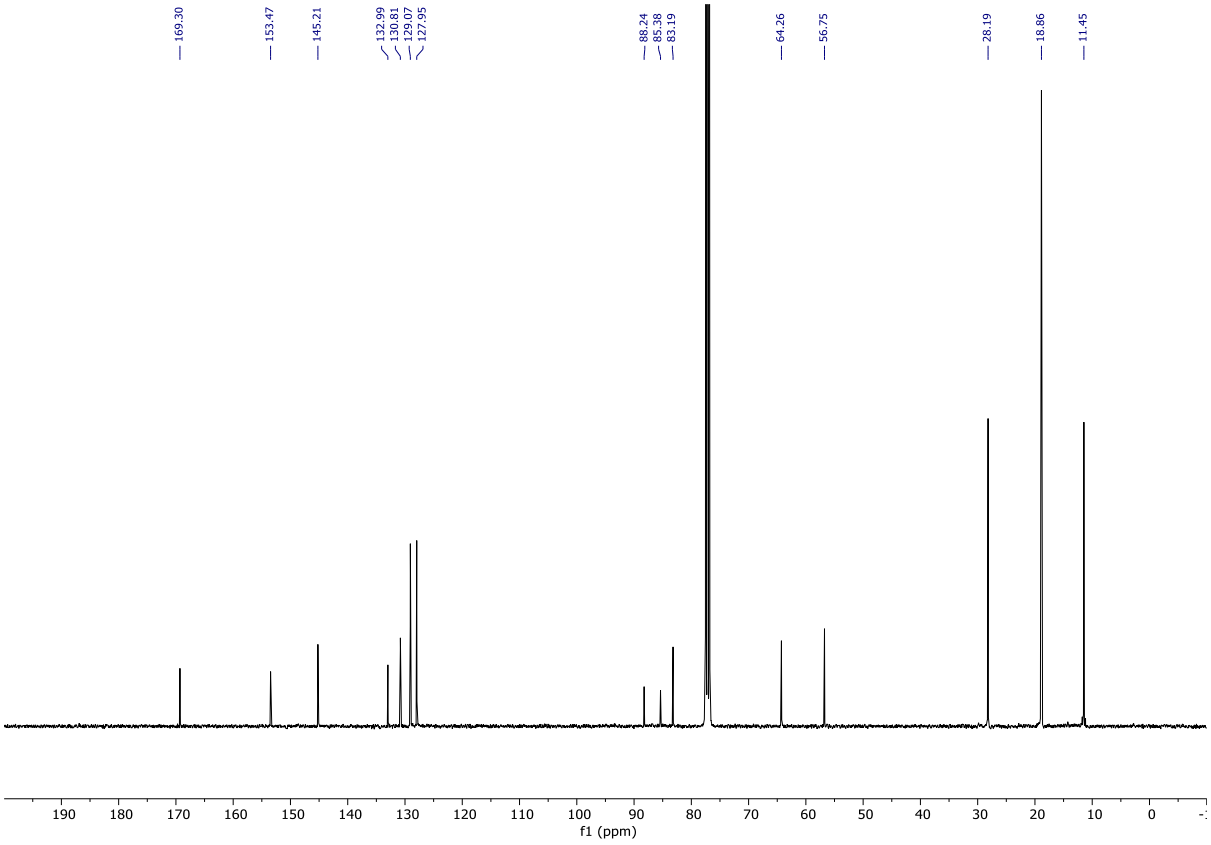

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4h**



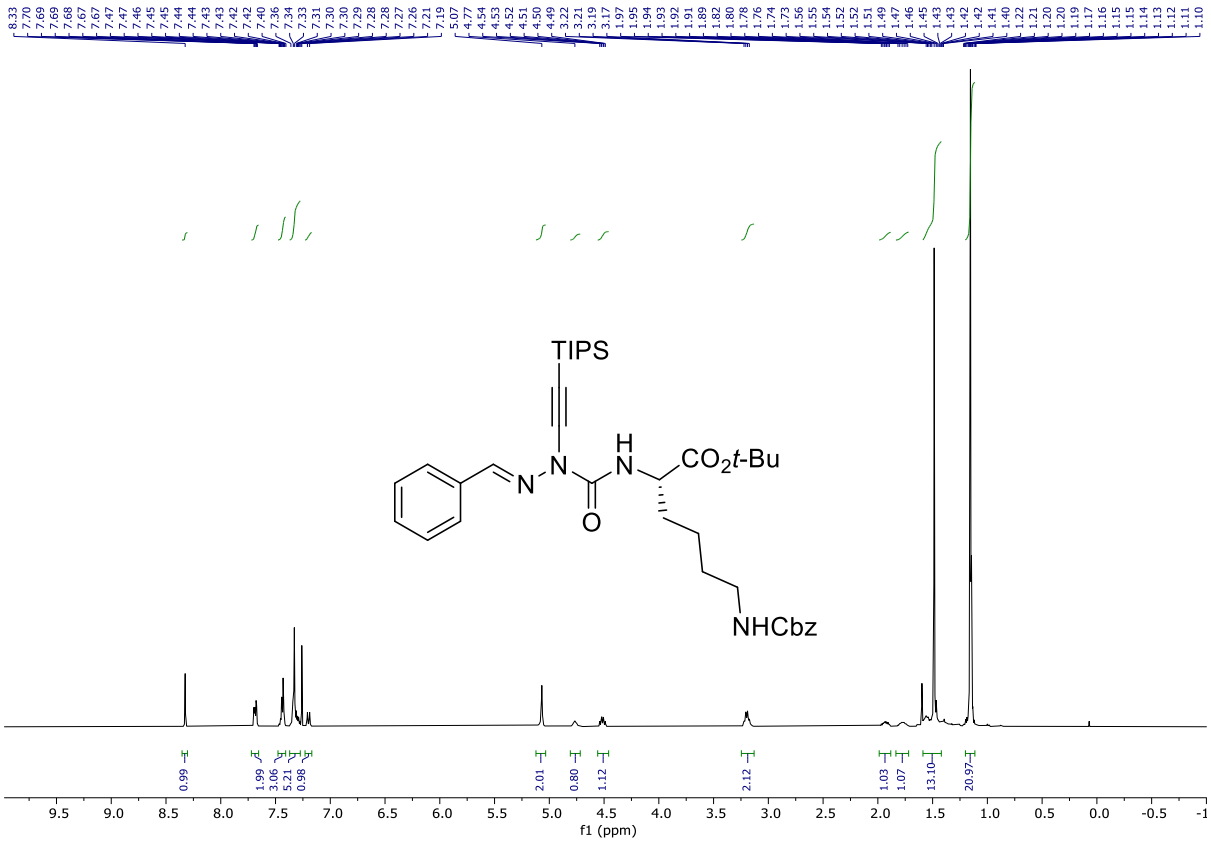
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4i**



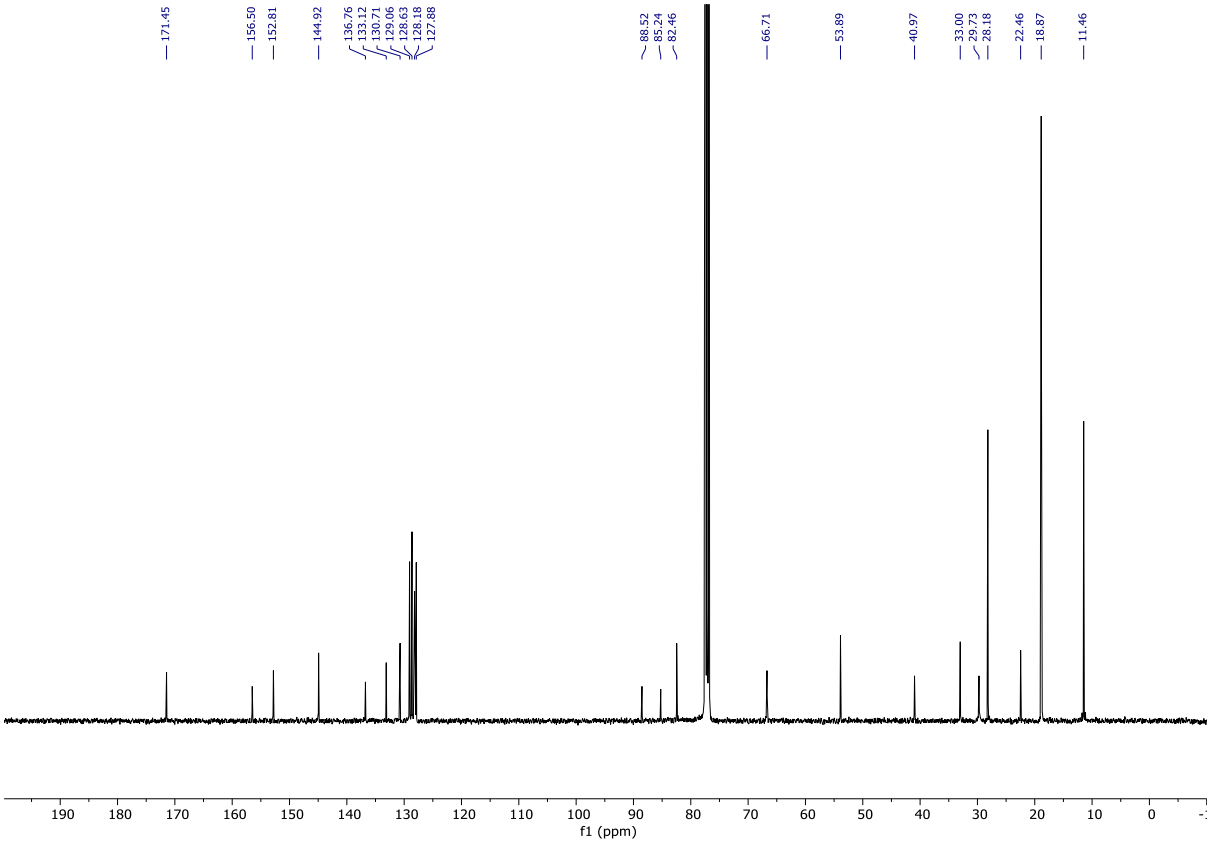

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4i**



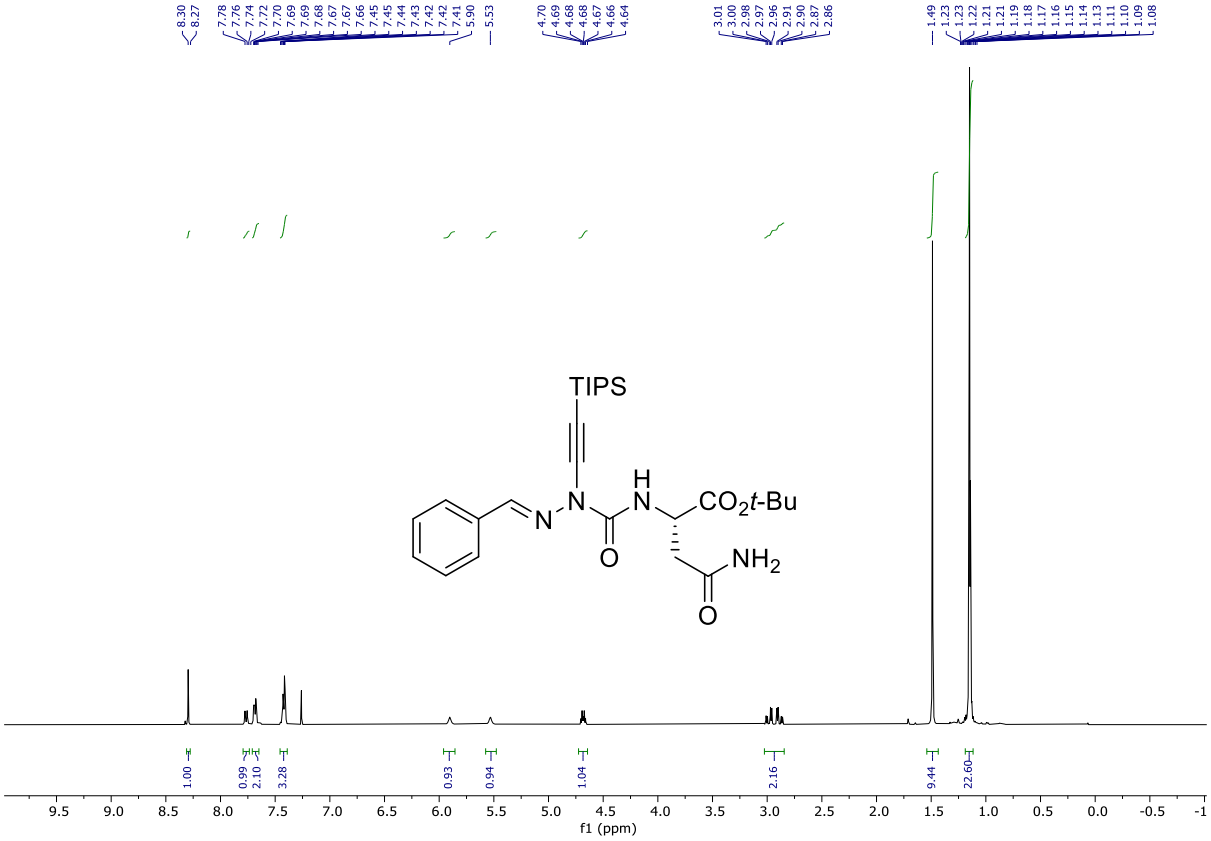
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4j**



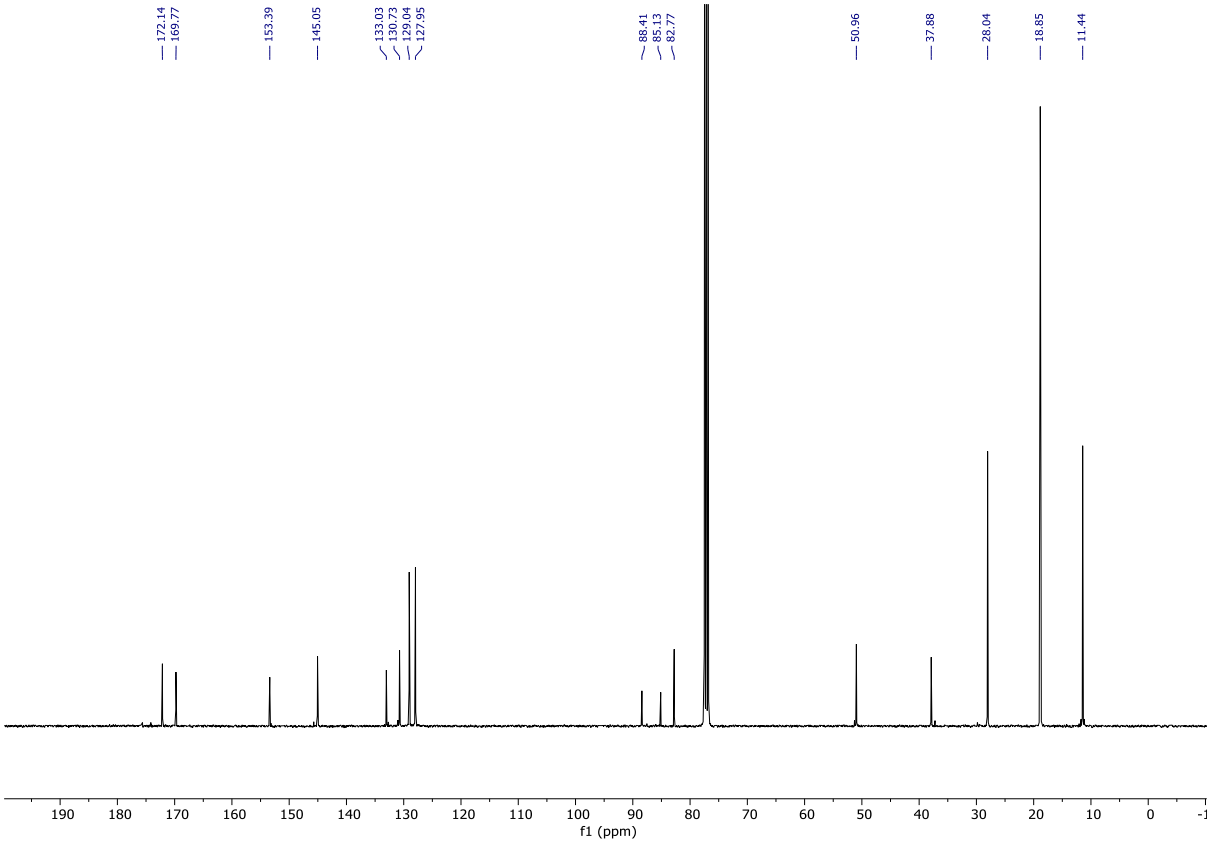

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4j**



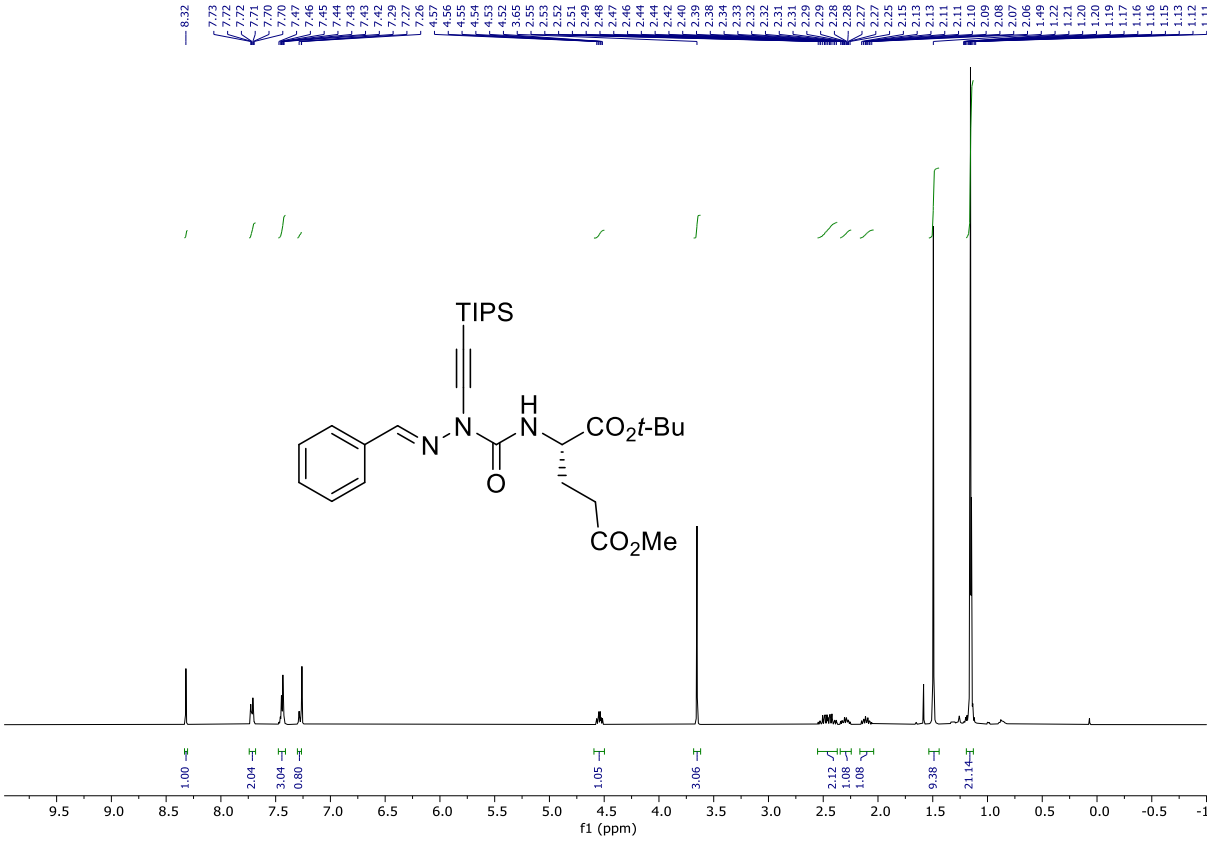
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4k**



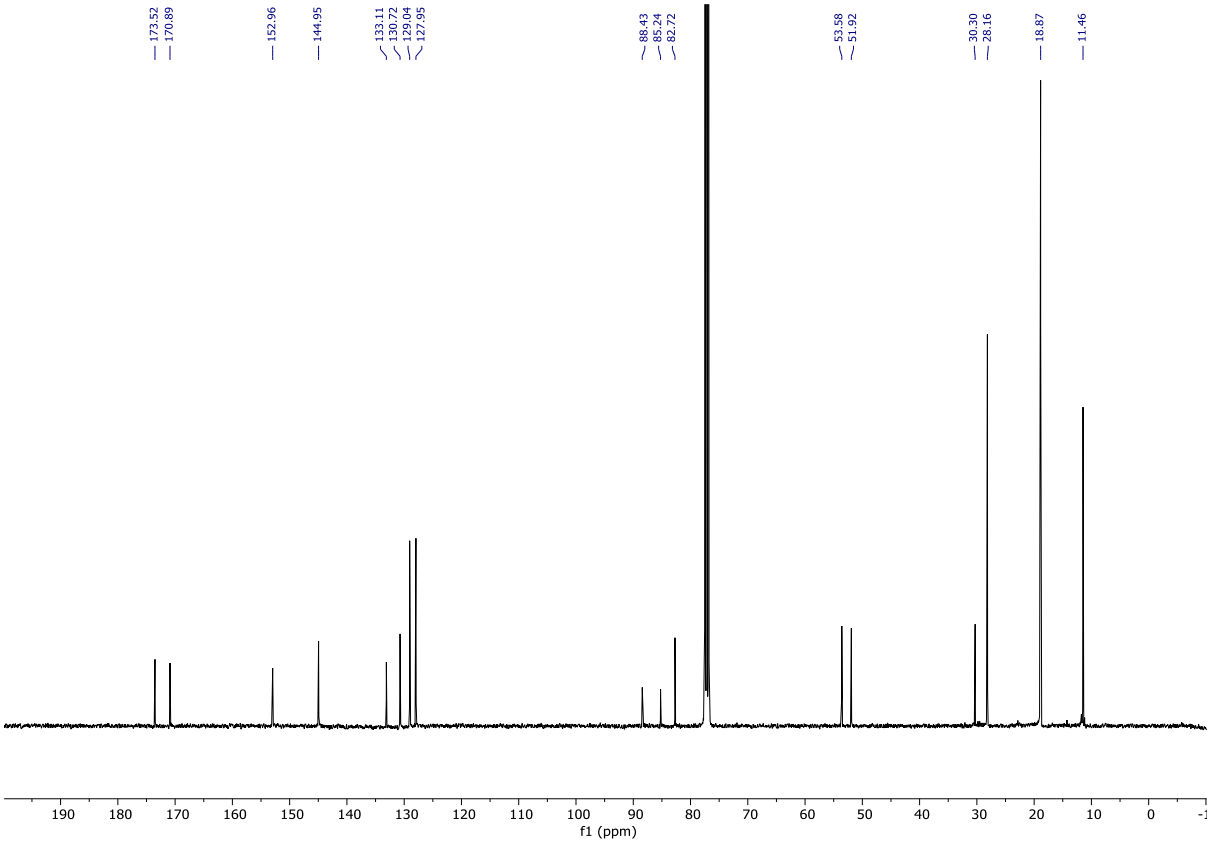

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4k**



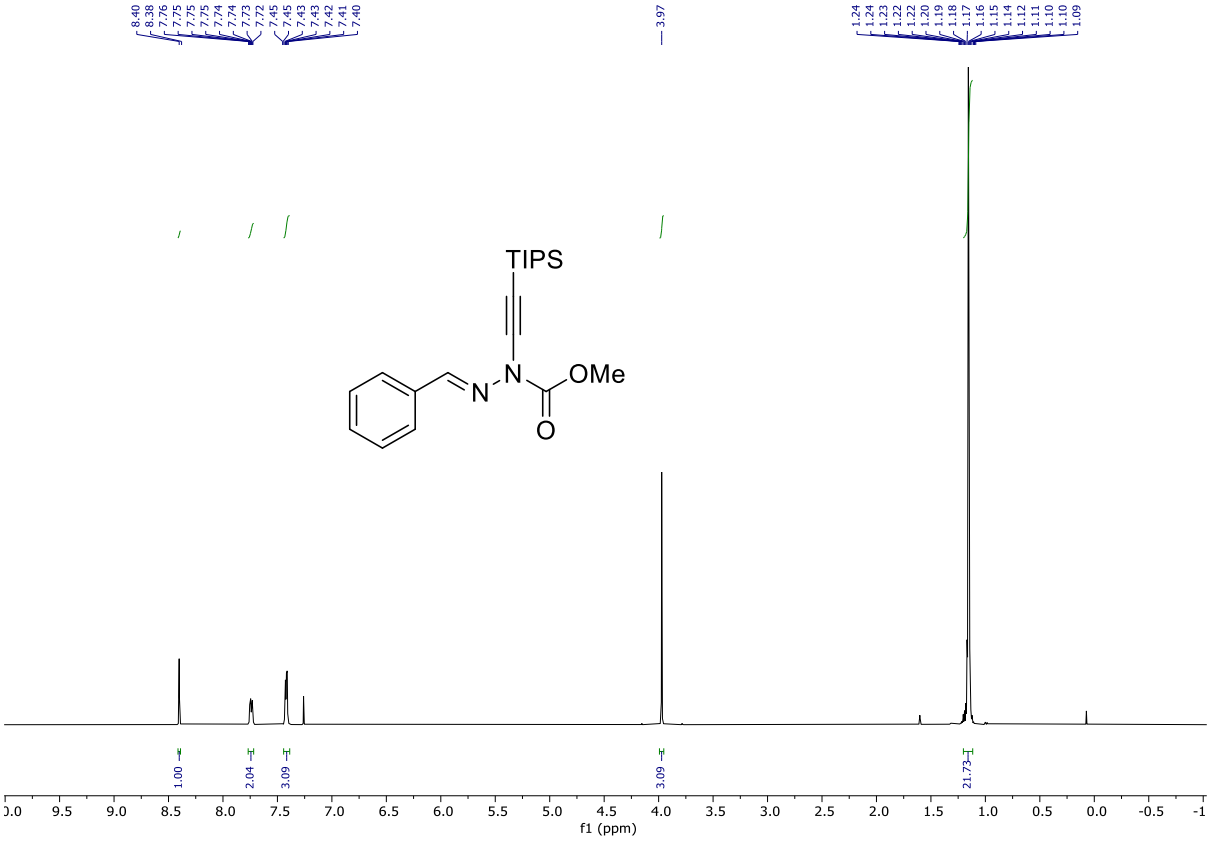
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4l**



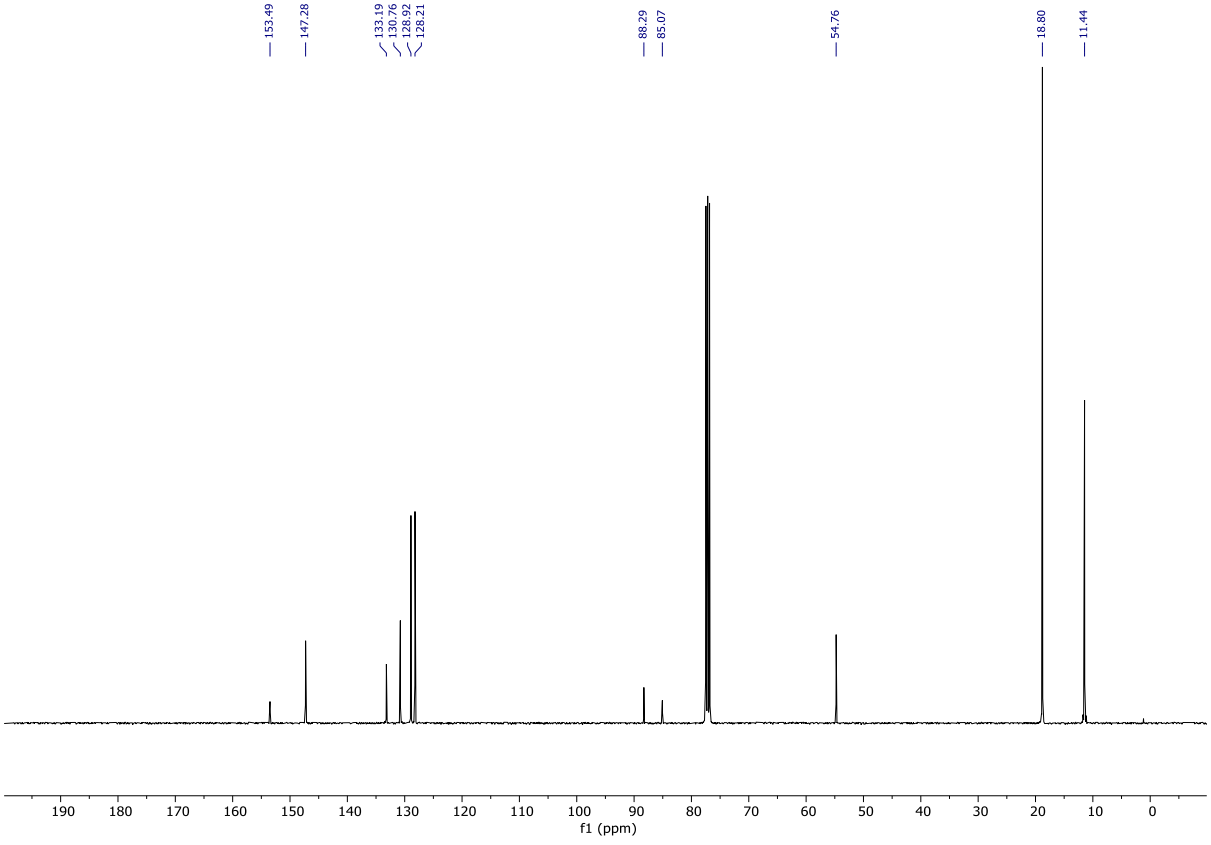

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4l**



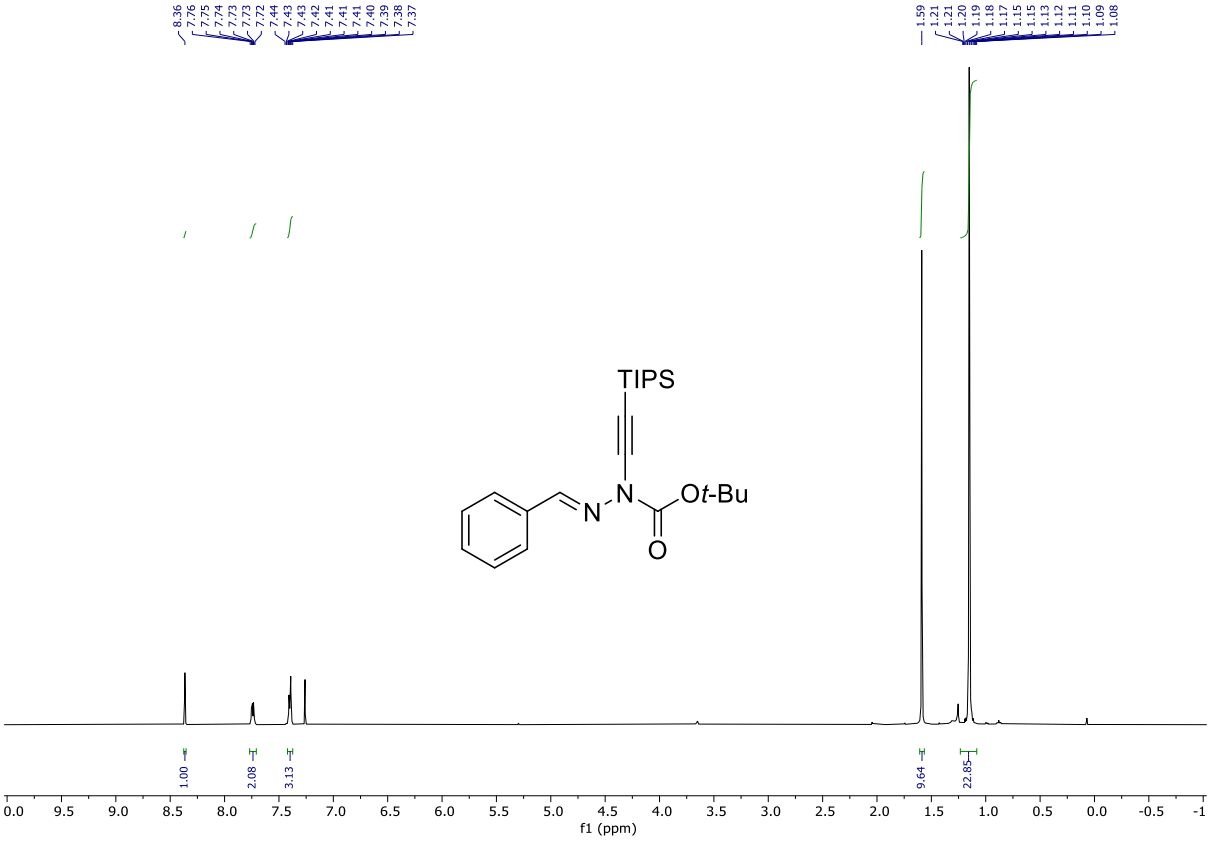
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4m**



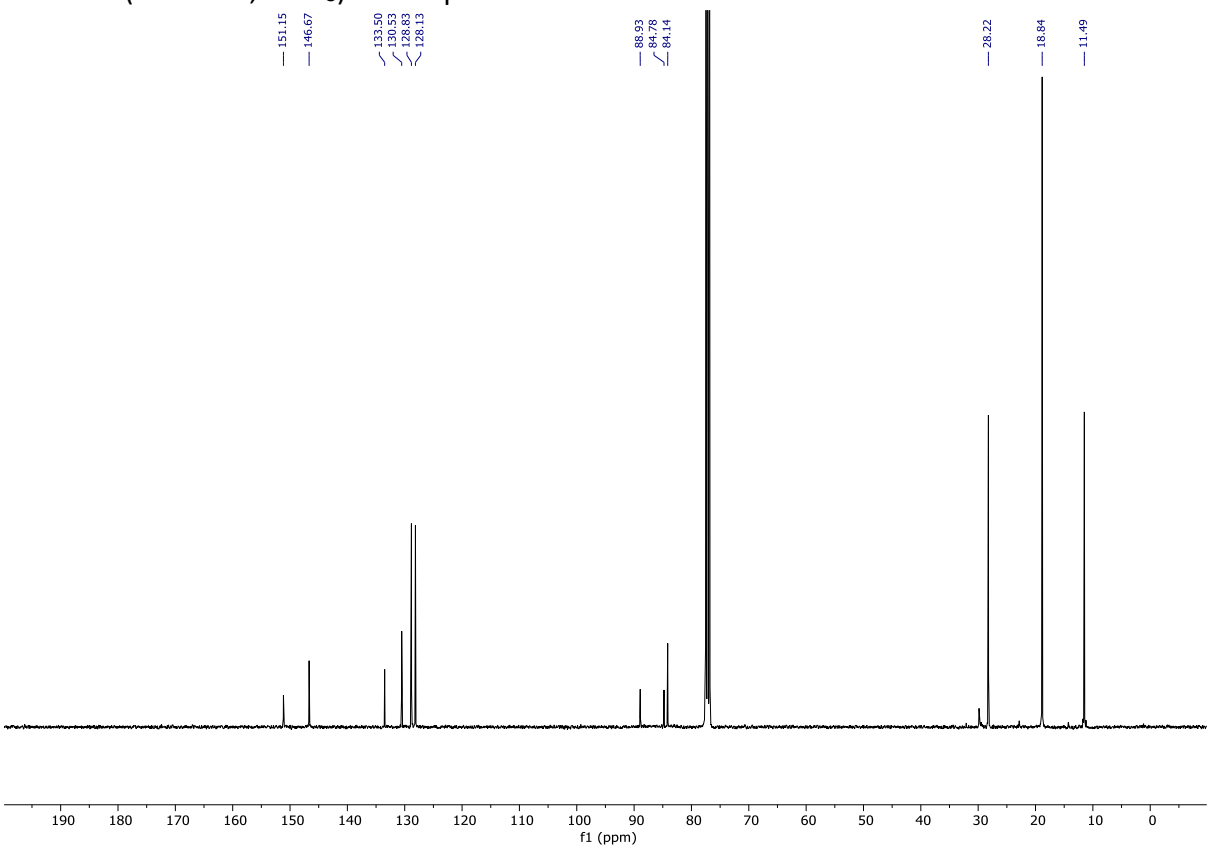

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4m**



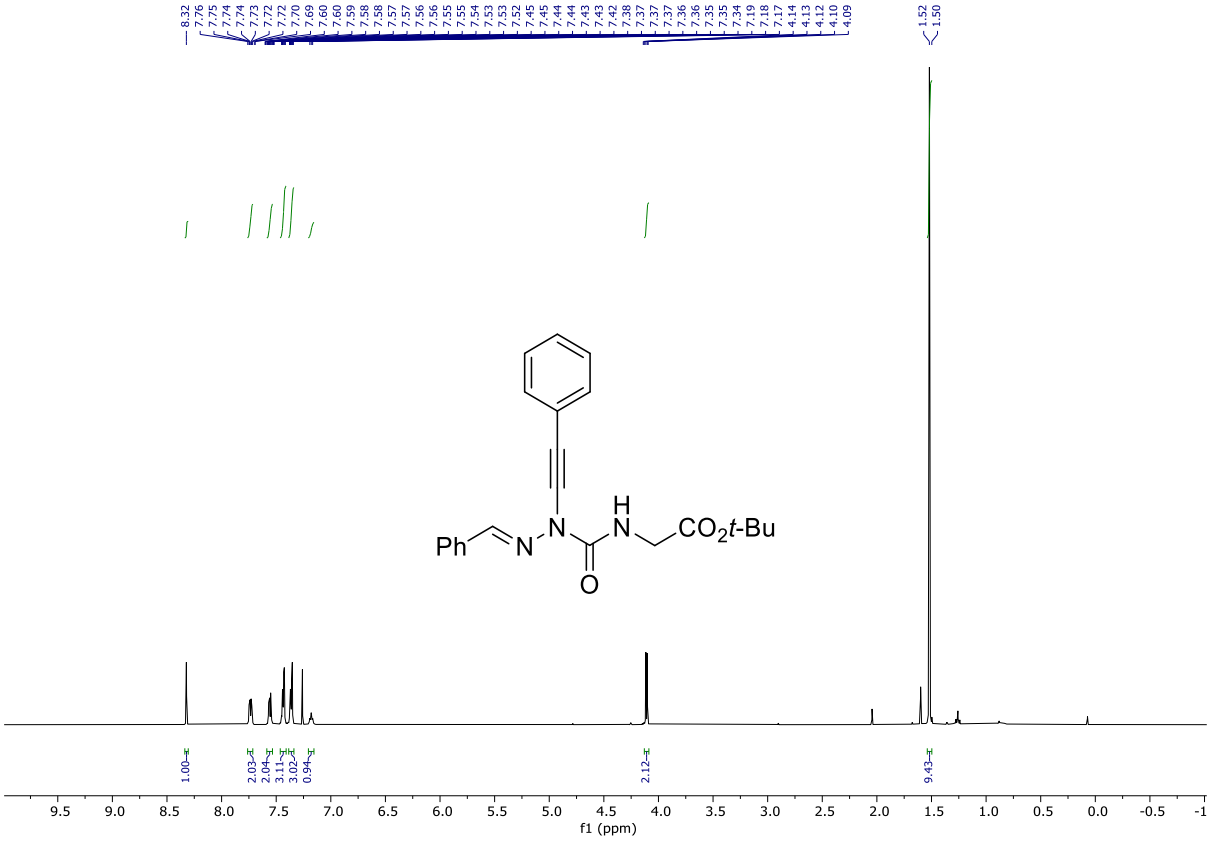
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **4n**



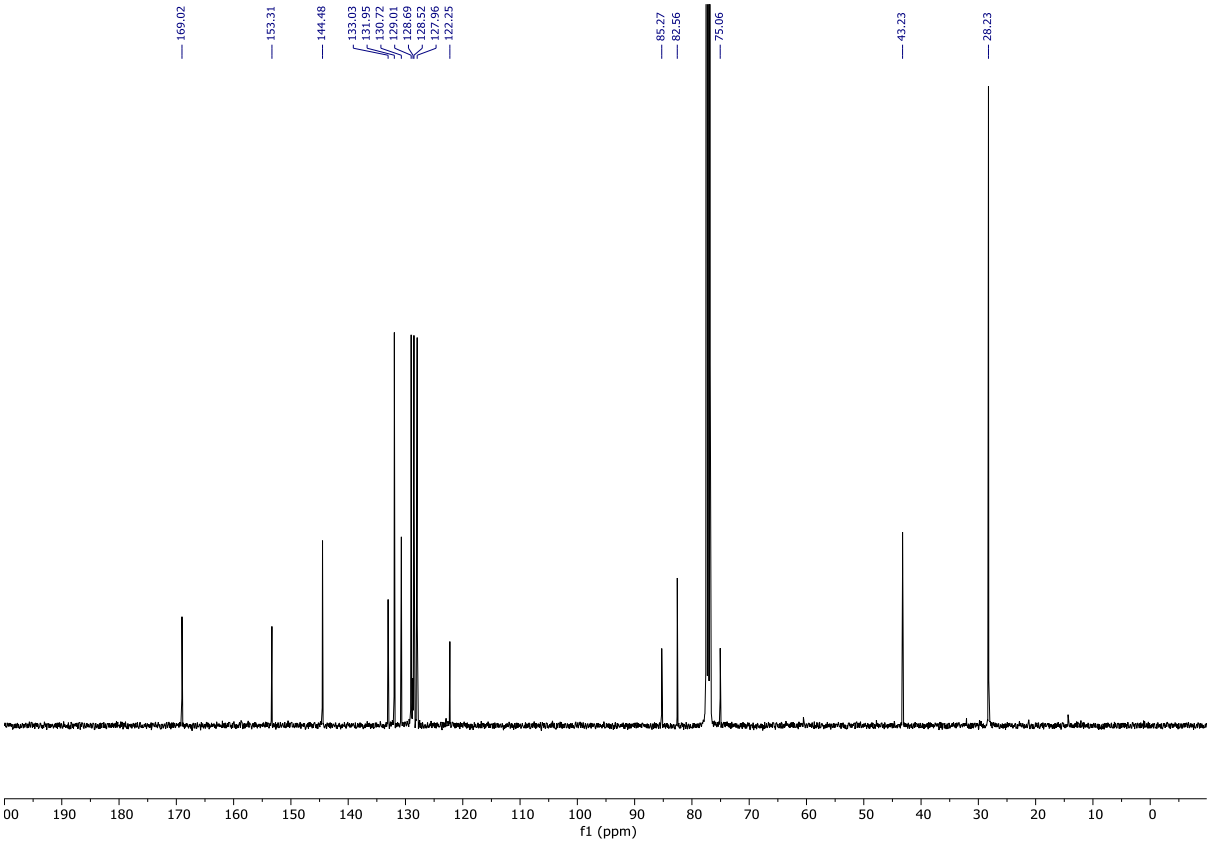

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **4n**



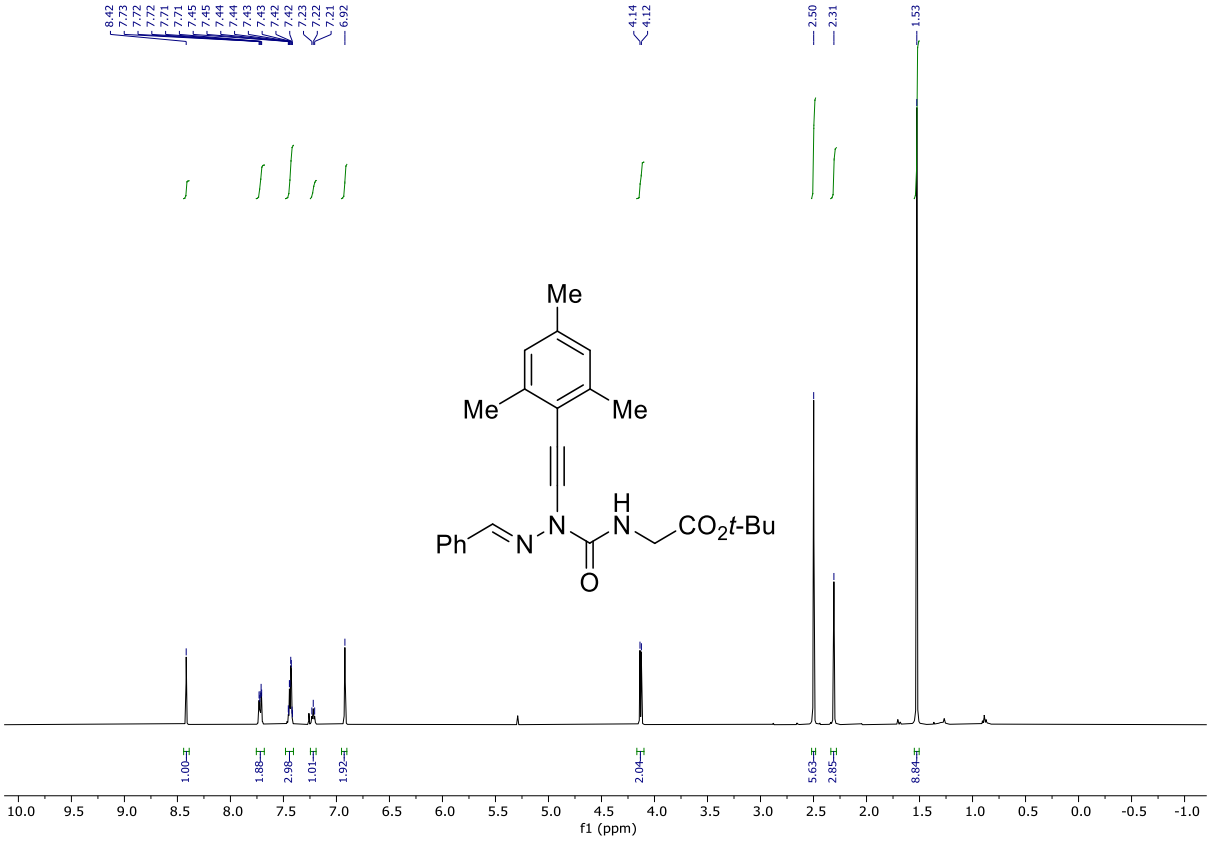
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5a**



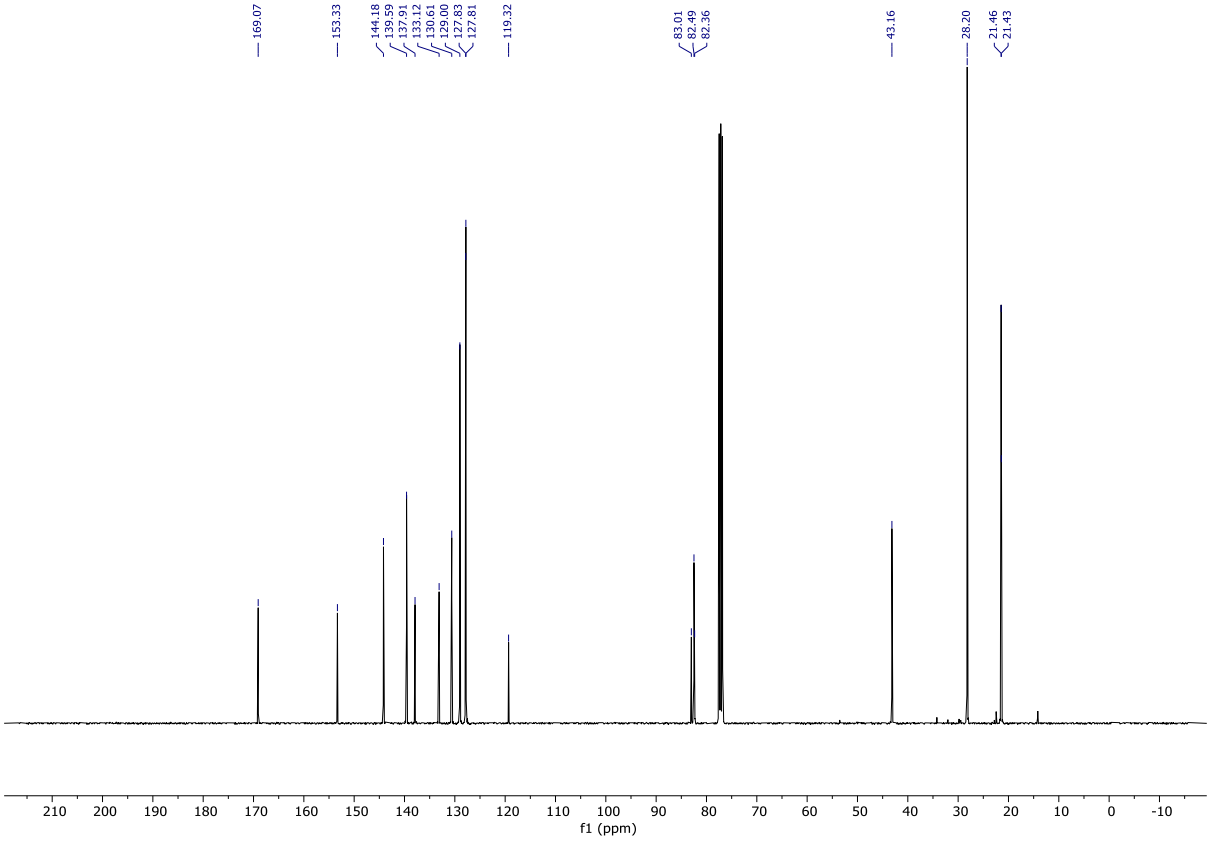

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5a**



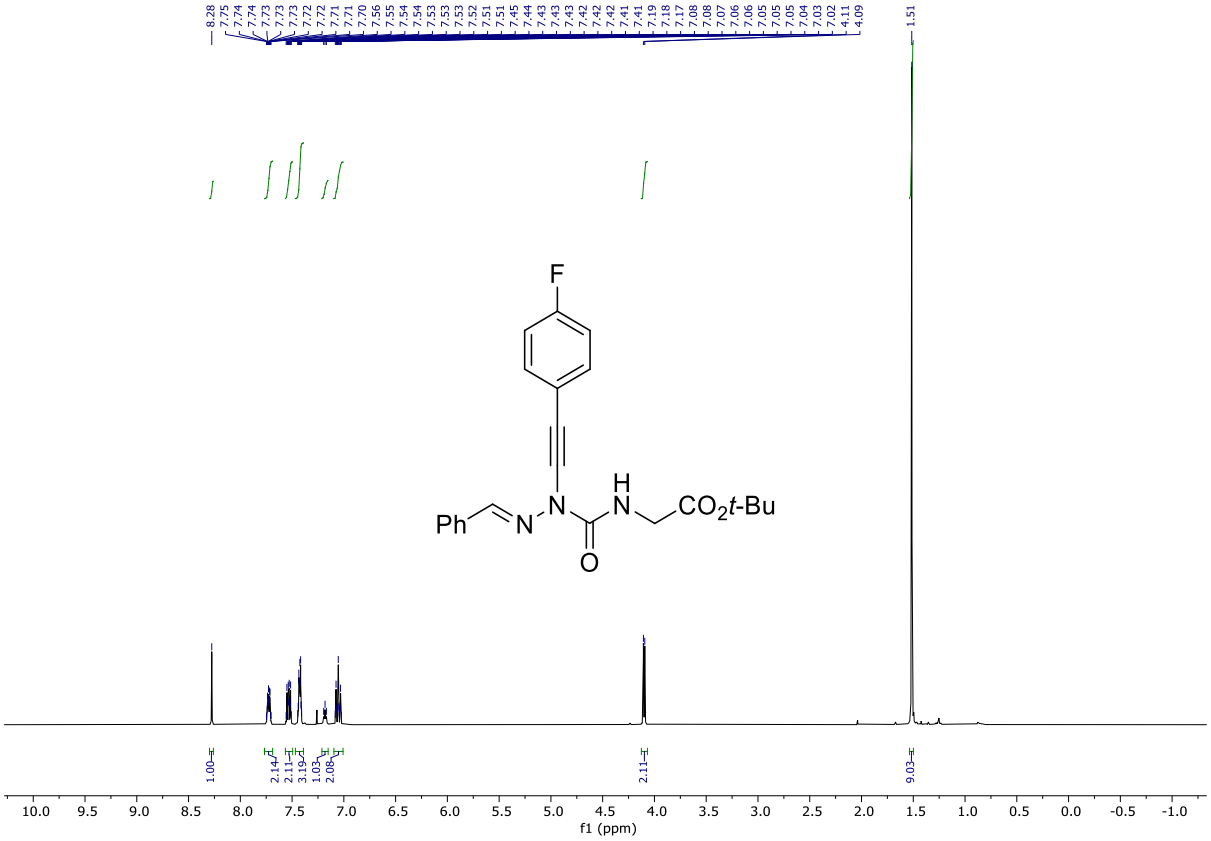
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5b**



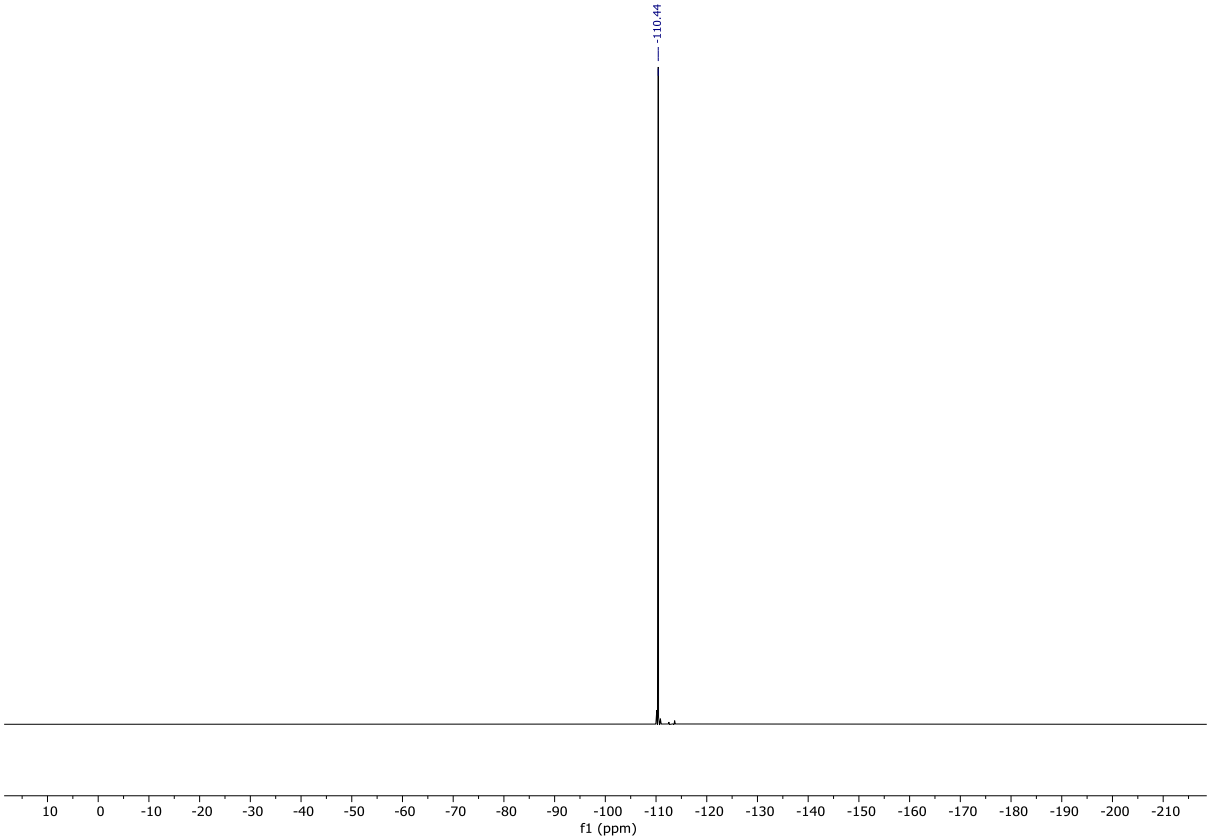

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5b**



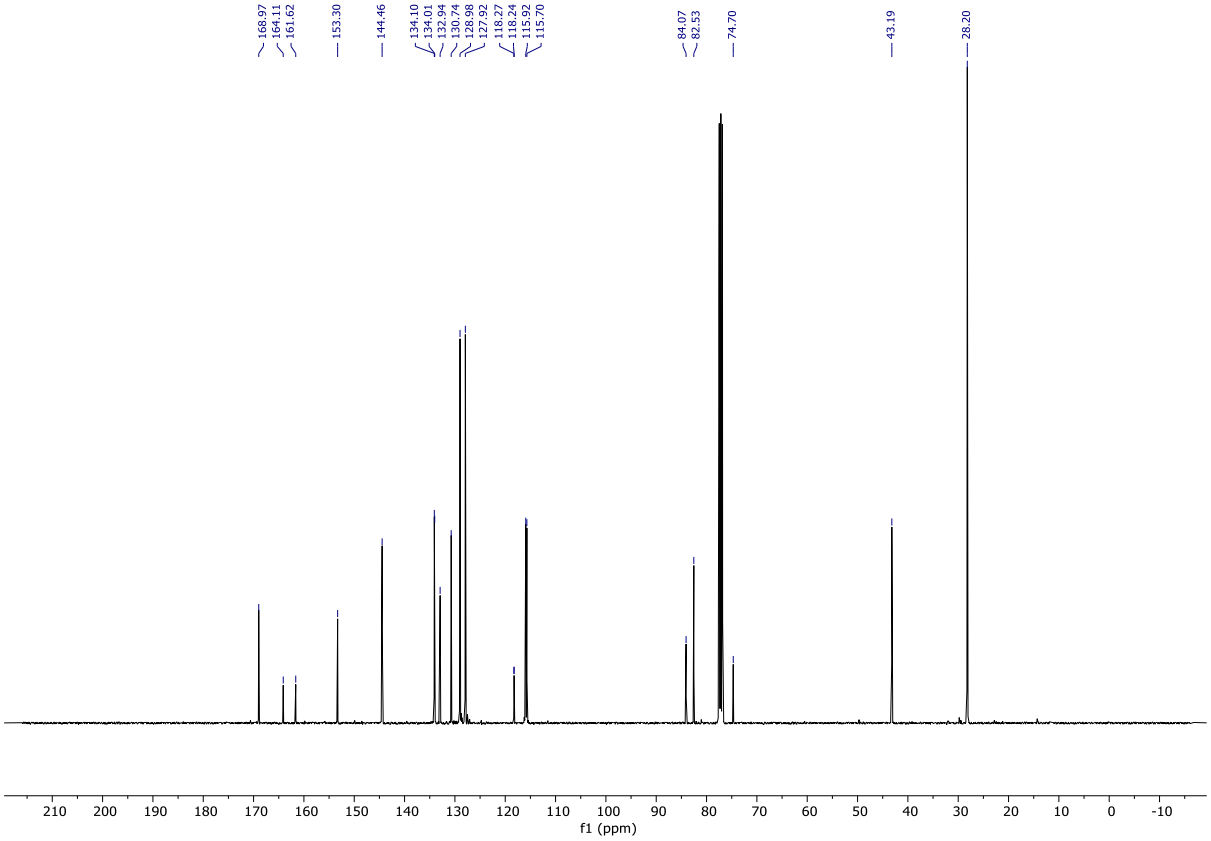
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5c**



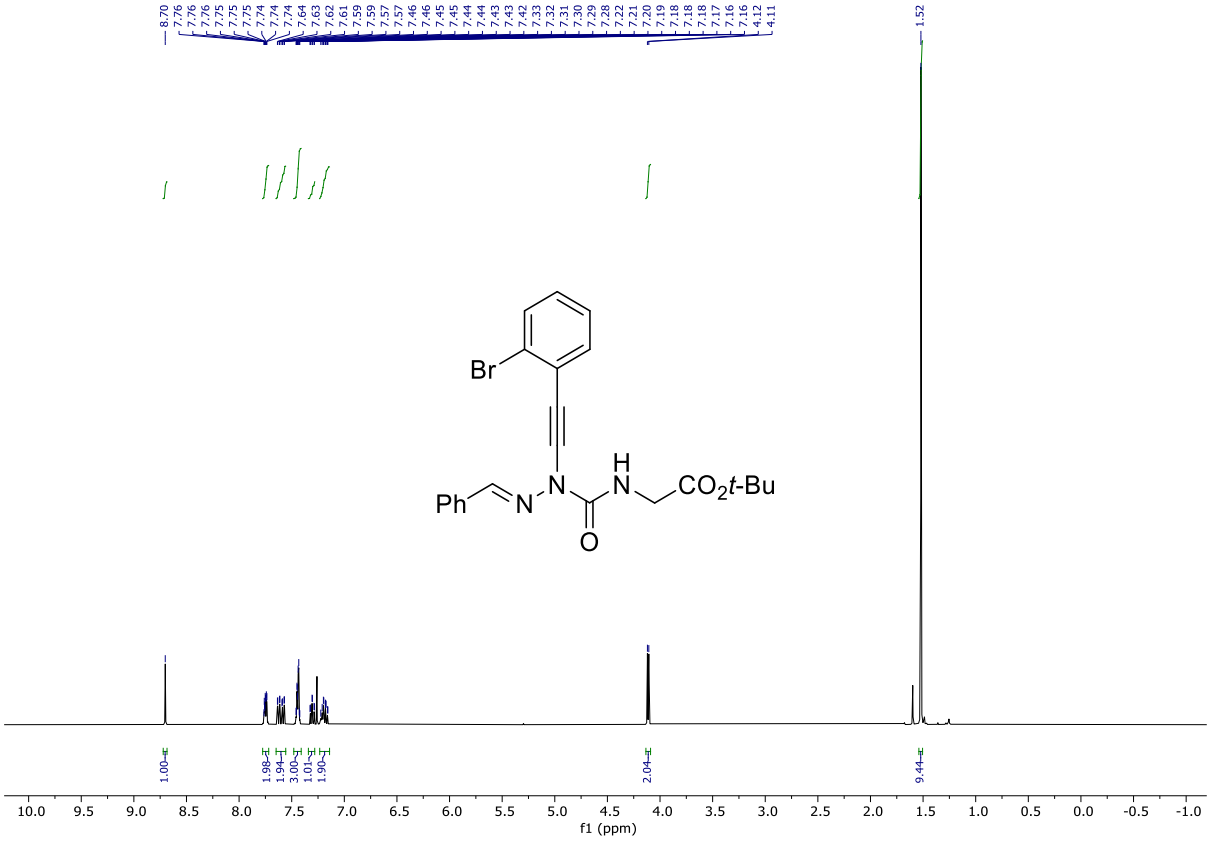

**$^{19}$F NMR** (376 MHz, $CDCl_3$) of compound **5c**



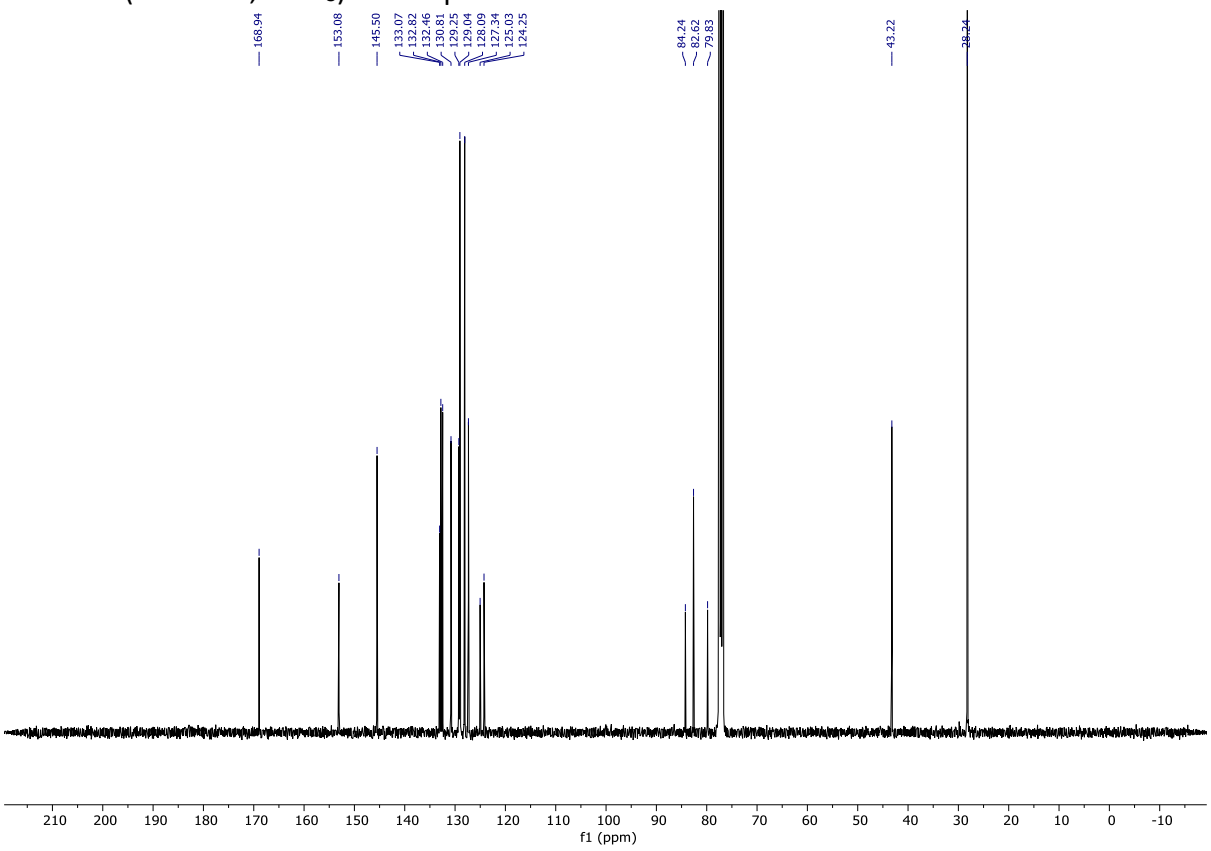
**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5c**



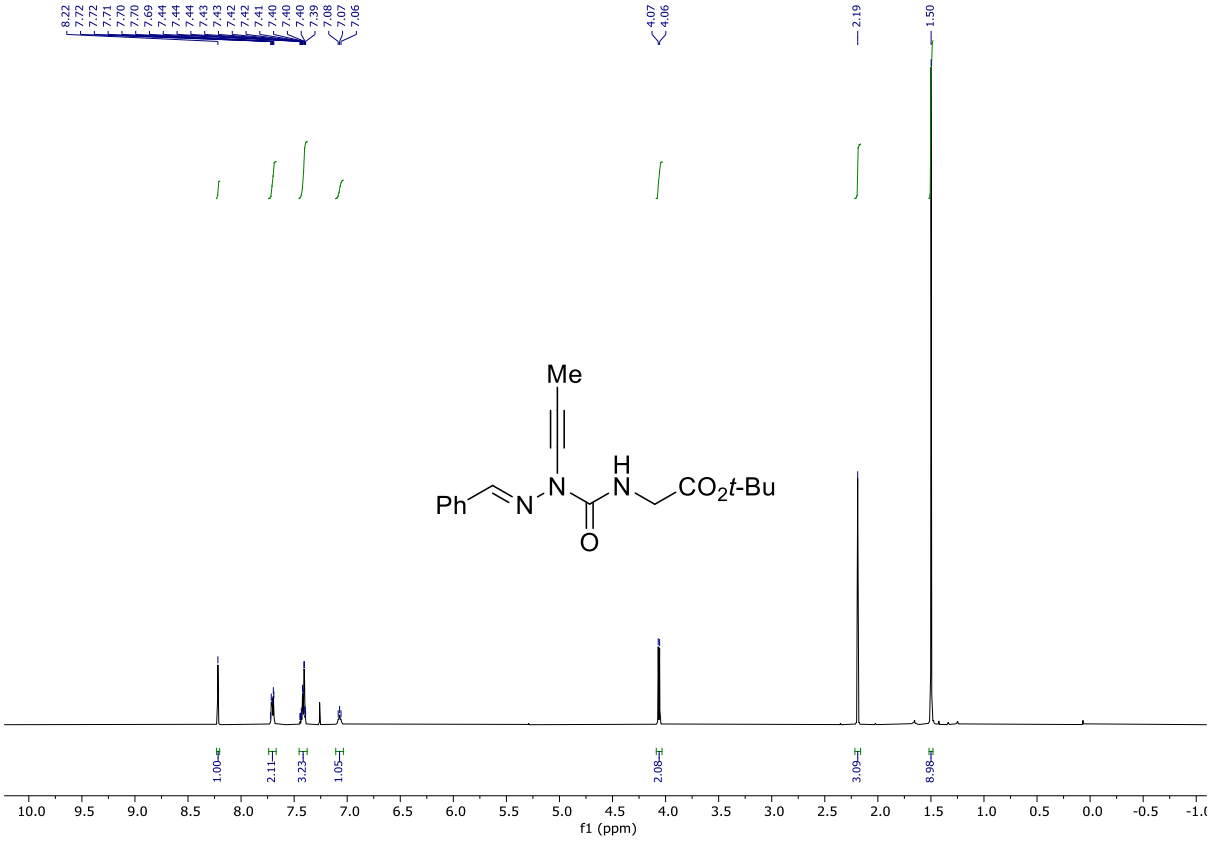
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5d**



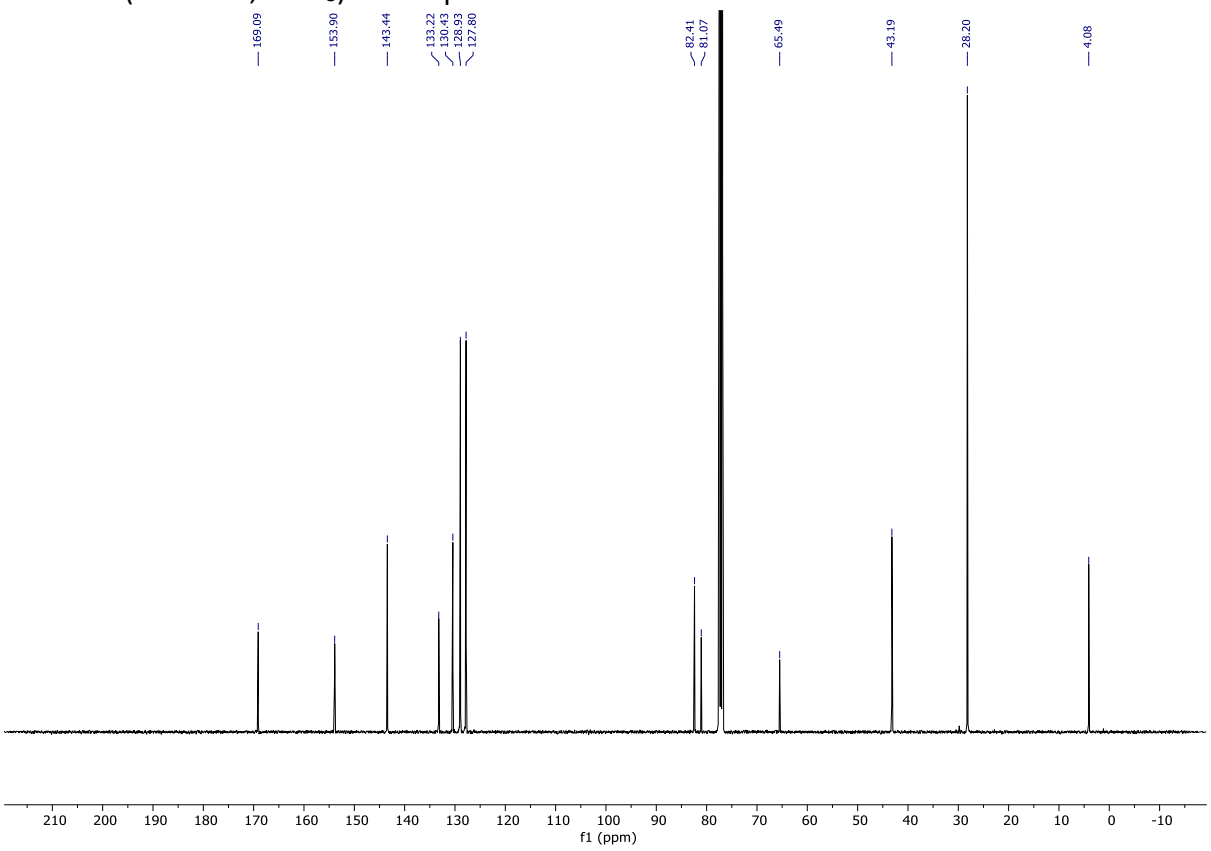

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5d**



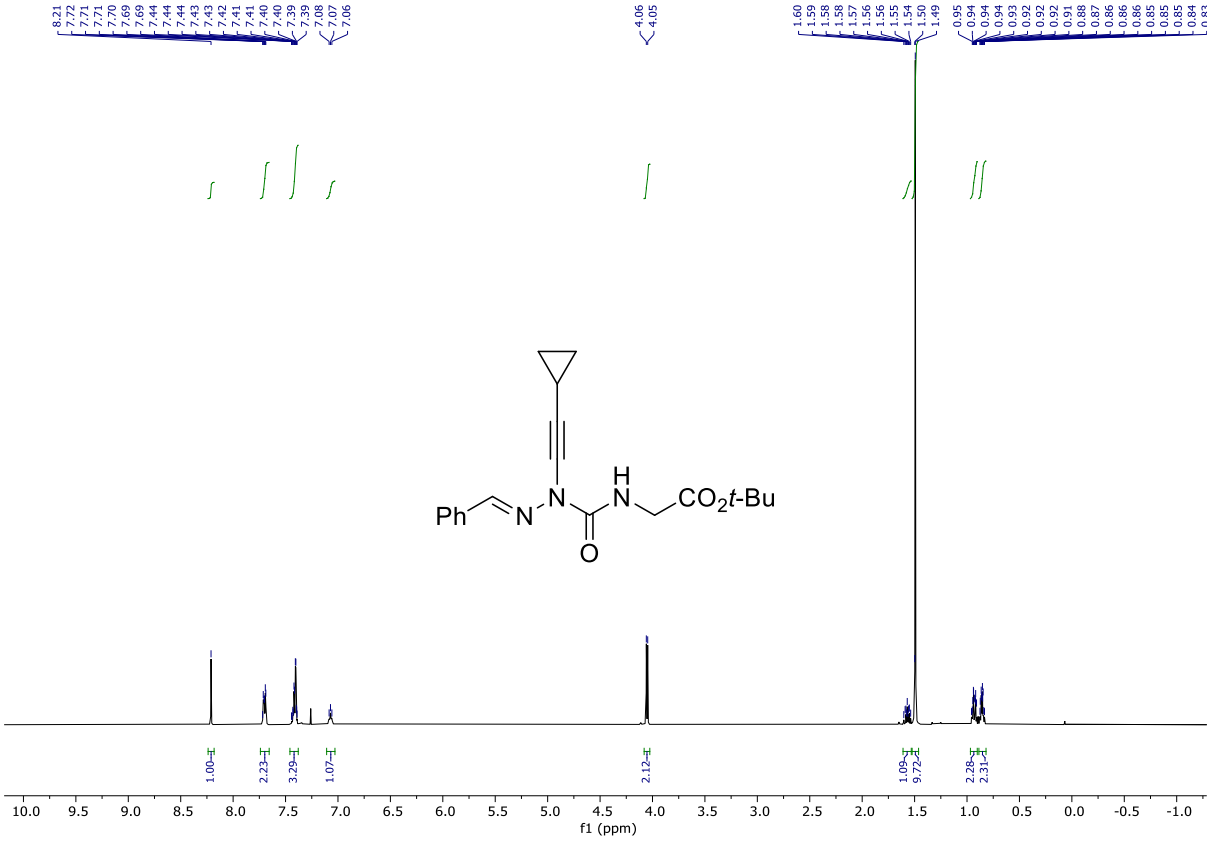
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5e**



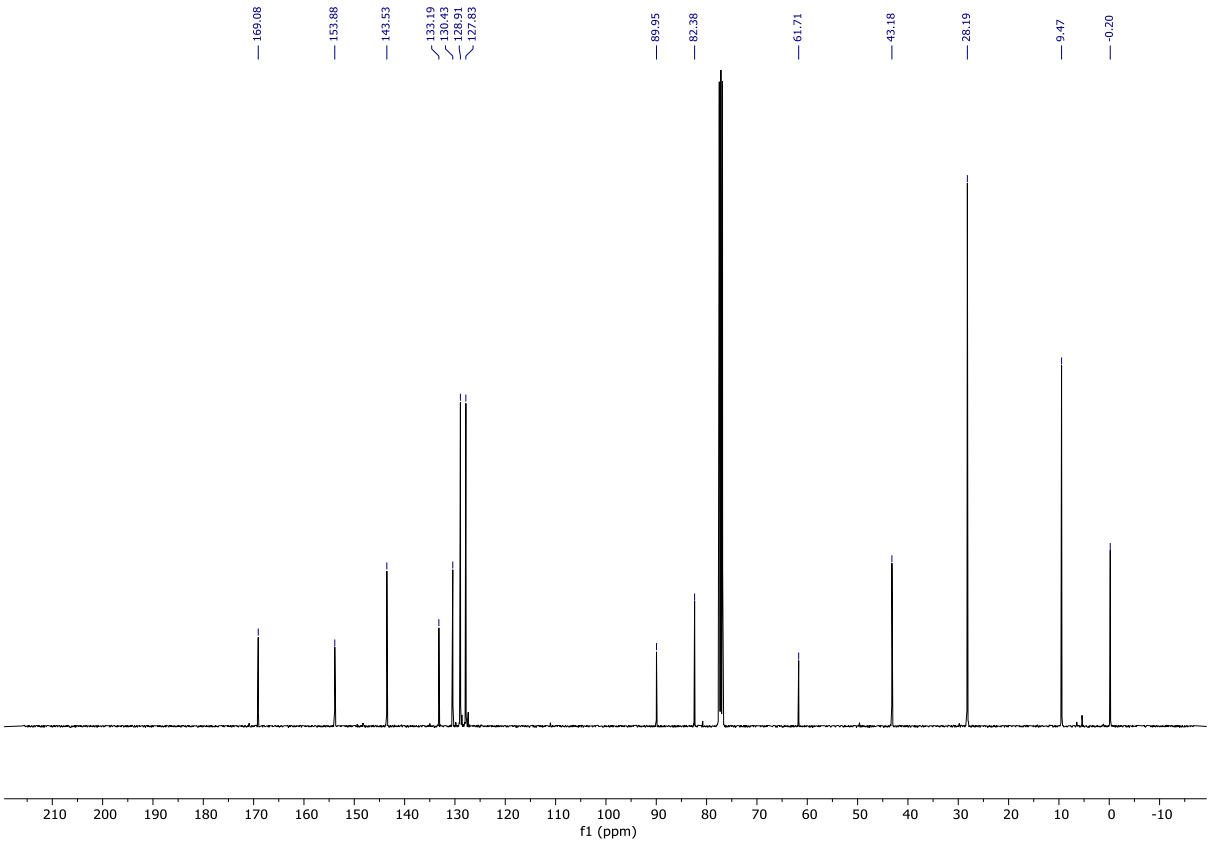

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5e**



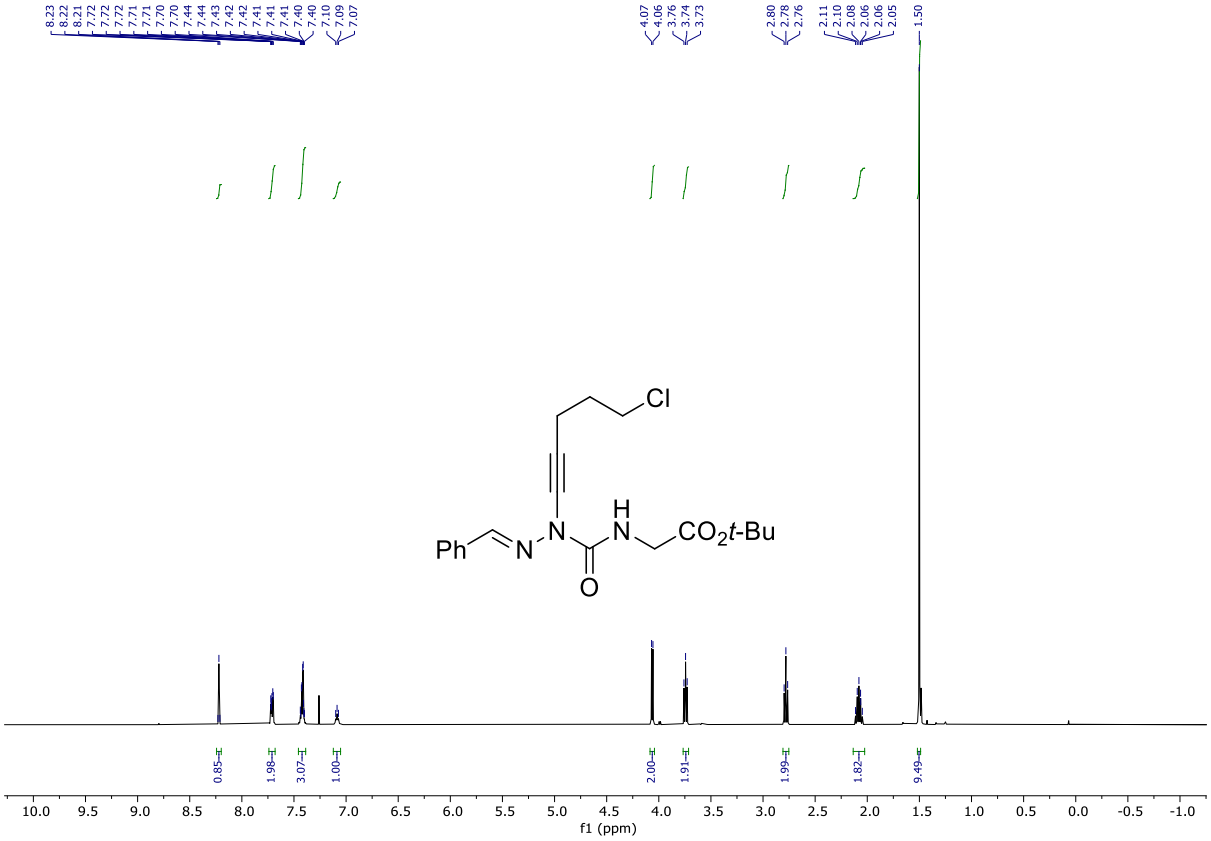
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5f**



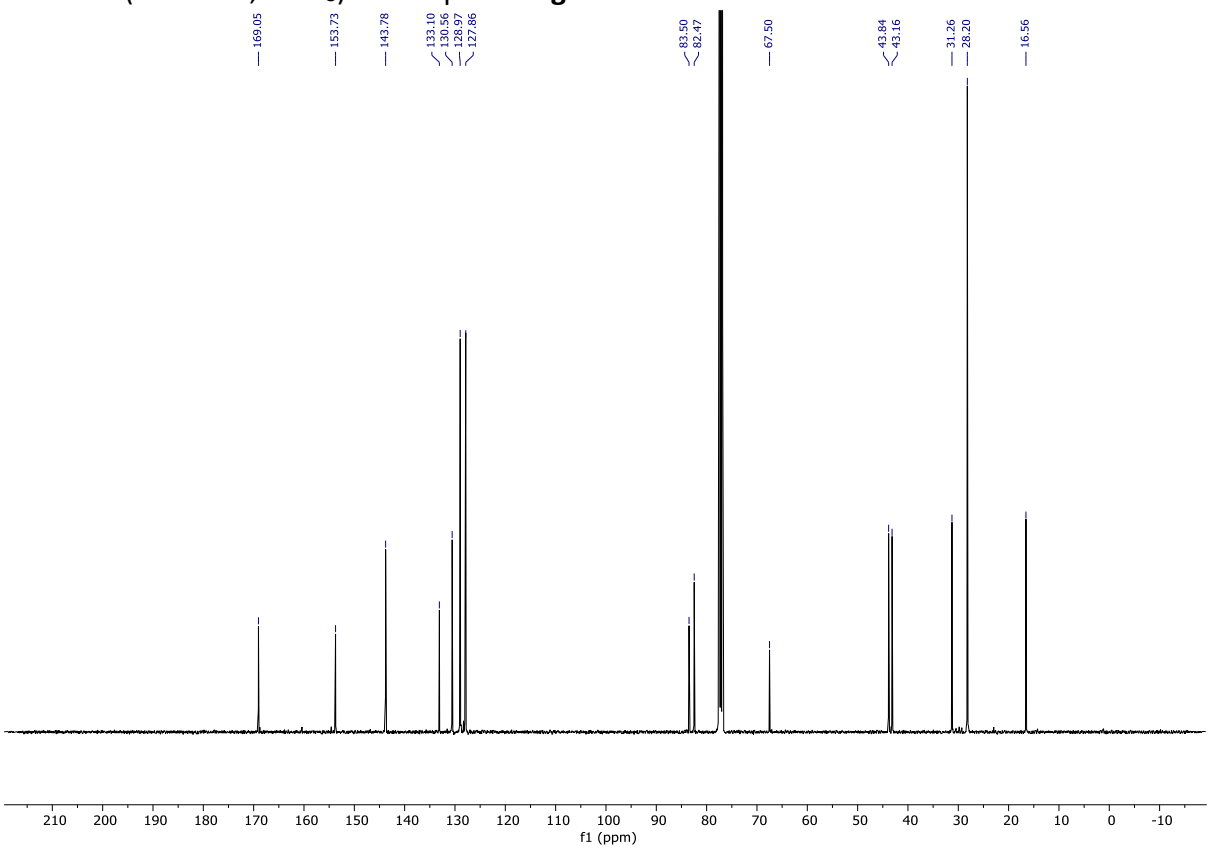

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5f**



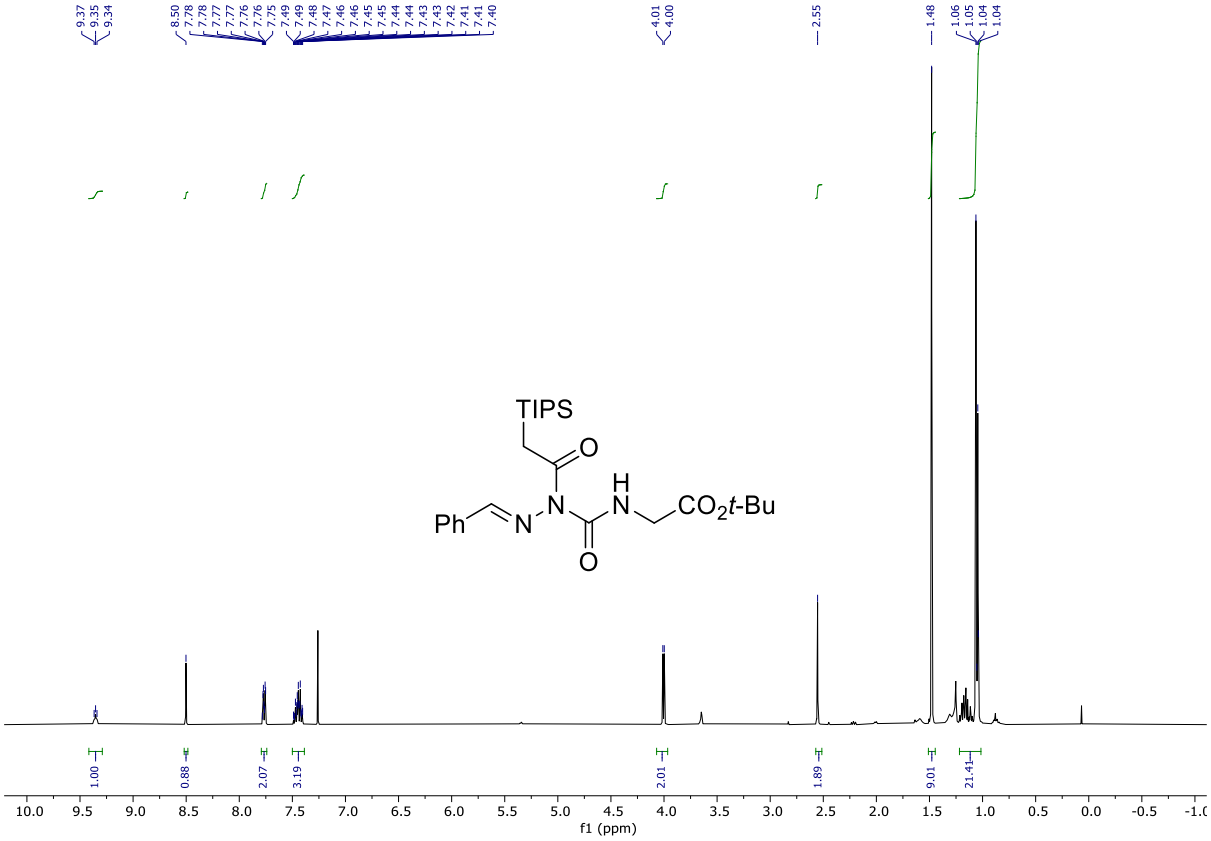
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **5g**



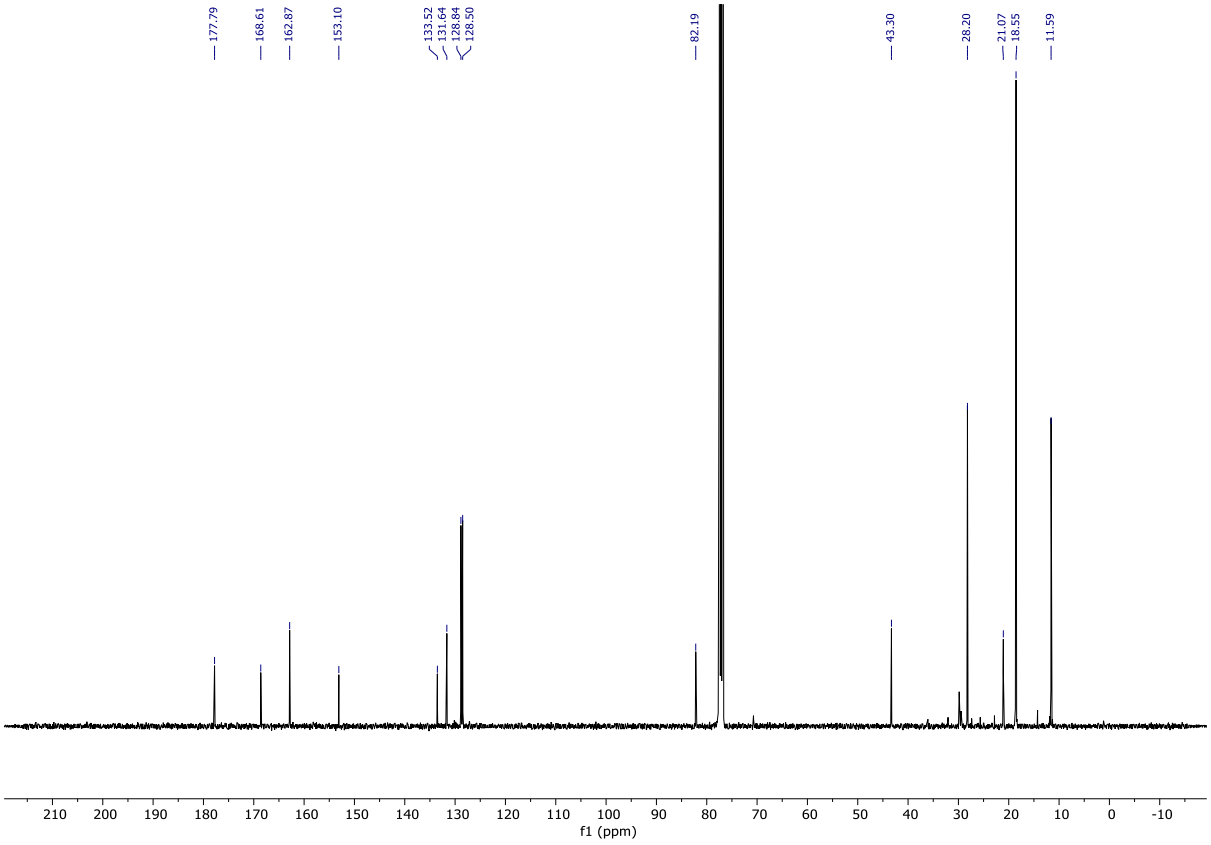

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **5g**



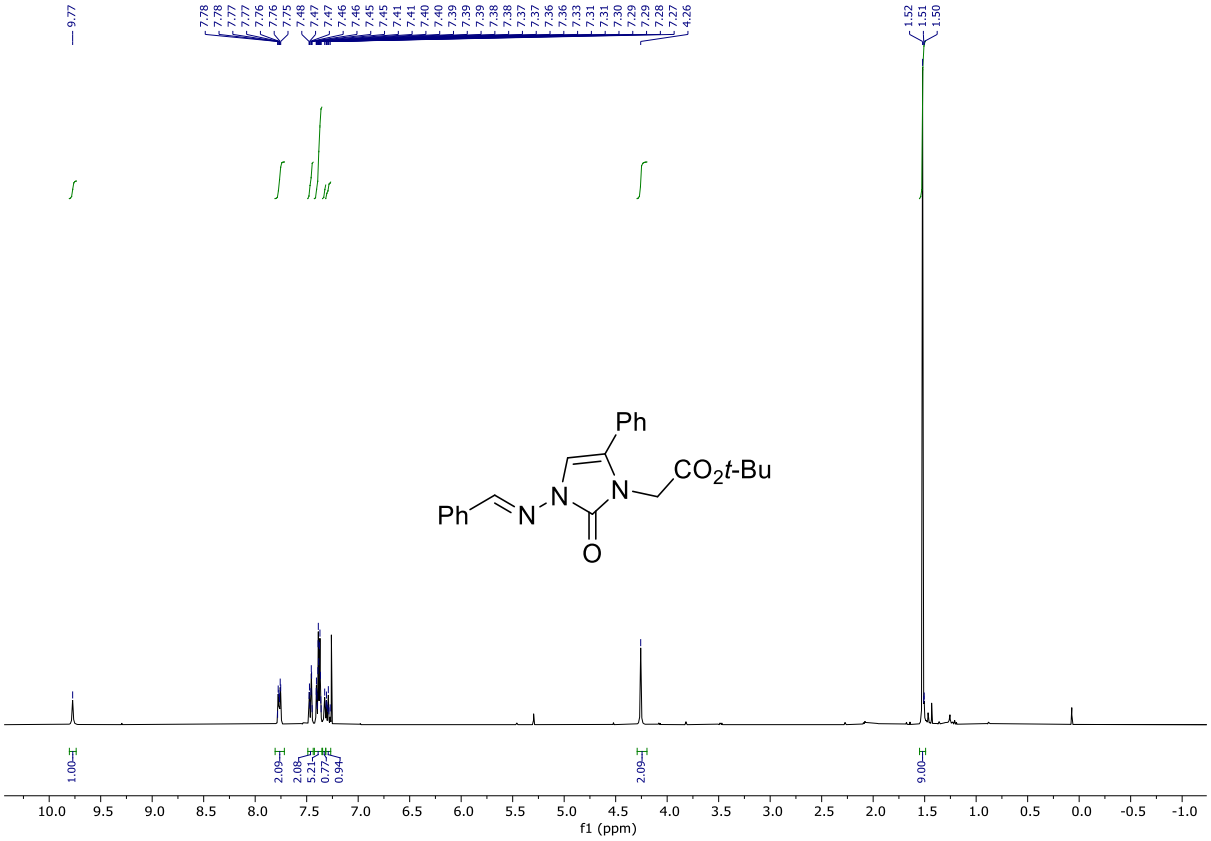
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **6**



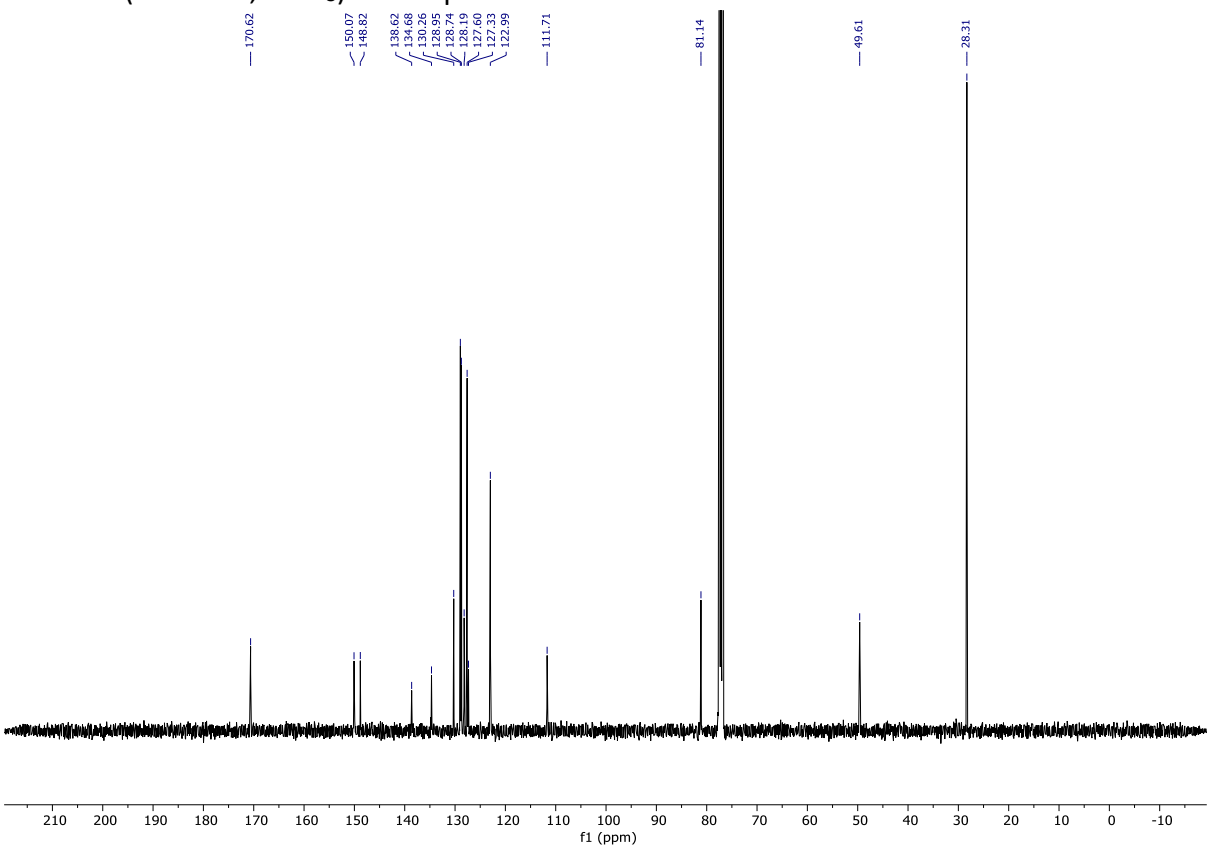

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **6**



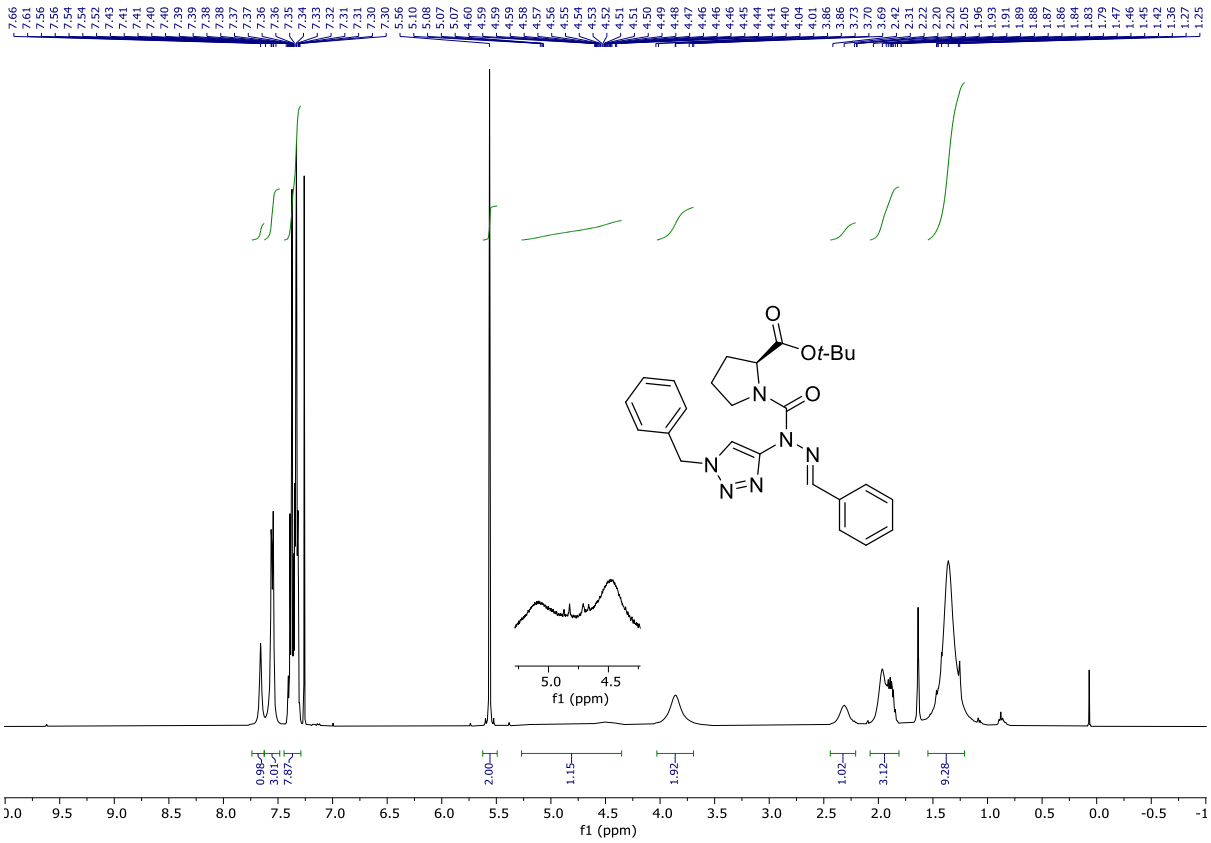
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **7**



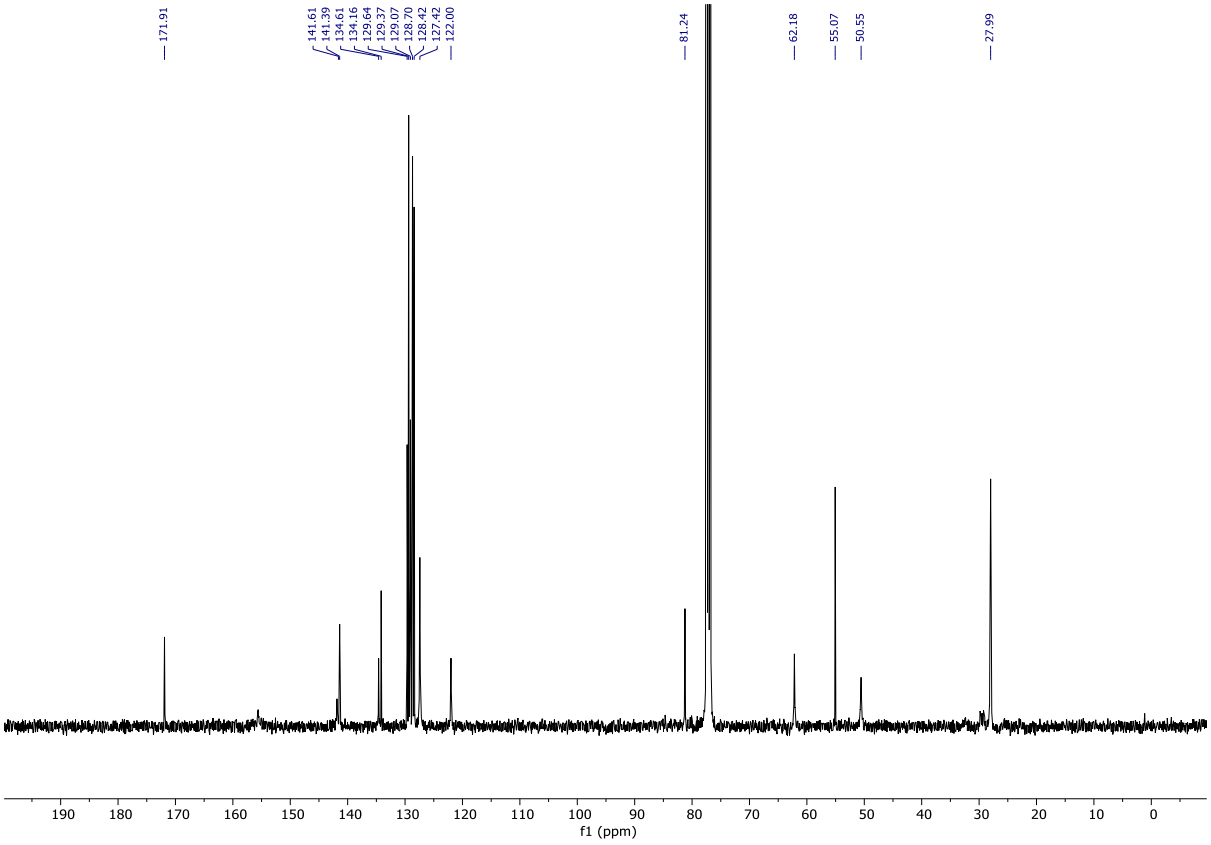

**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **7**



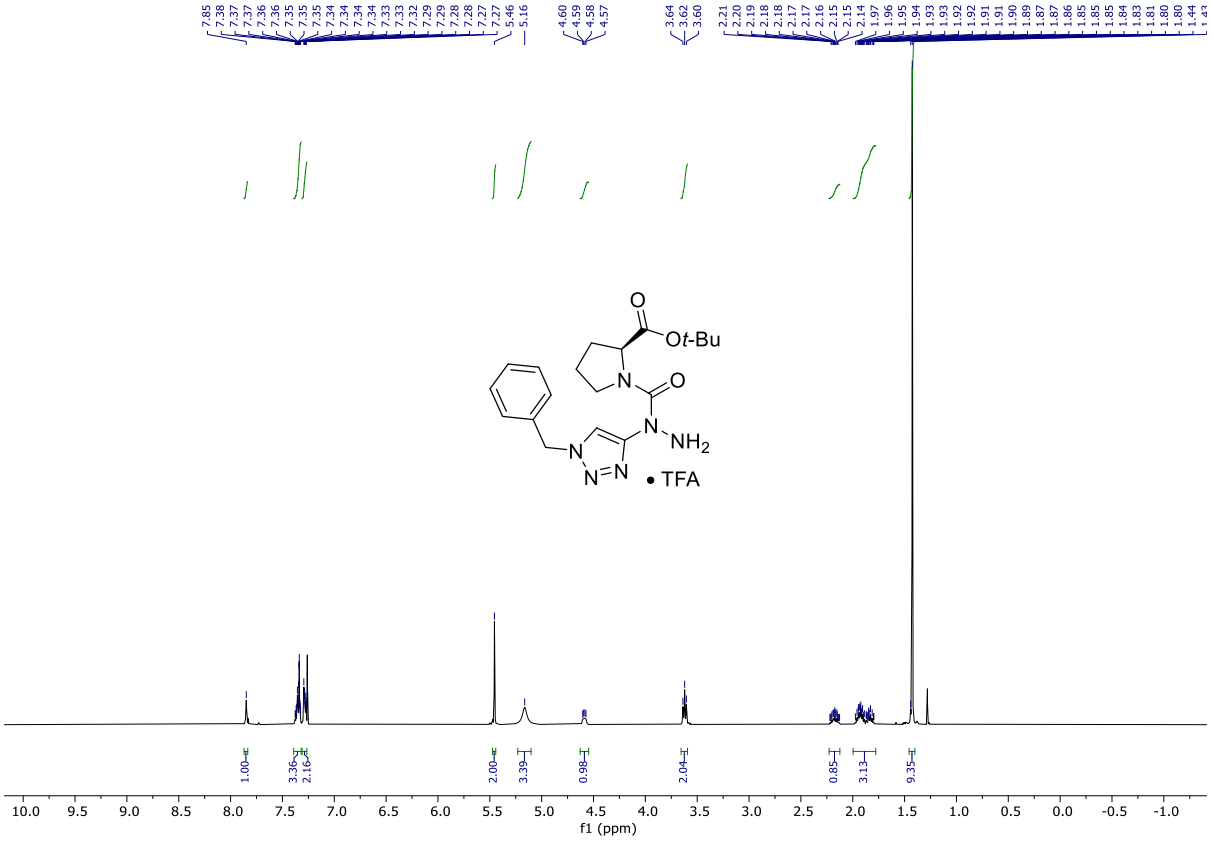
**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **8**




**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **8**



**$^{1}$H NMR** (400 MHz, $CDCl_3$) of compound **9**




**$^{13}$C NMR** (101 MHz, $CDCl_3$) of compound **9**