Supporting Information

Chemical Space Expansion of Bromodomain Ligands Guided by In Silico Virtual Couplings (AutoCouple)

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1. Computational methods

1.1 Python scripts for AutoCouple

The scripts presented herein were written using the *Python* programming language[1] calling the following Object Oriented Libraries: *Numpy*,[2] *RDkit*.[3]
All molecular files were stored under the *structure data file* (*sdf*) format.[4]

Building-blocks library preparation
Building-blocks' libraries from various chemical providers, namely Acros Organics, AK Scientific, Alfa Aesar, ApolloChem, FluoroChem, Sigma-Aldrich, SpiroChem were retrieved under the computer-readable *sdf*-format with appended information about the molecule's Chemical Abstract Service (*CAS*) registration number (widely used by chemists), catalog number, prices and amounts.
Script Procedure:
To avoid redundancies, any building-block with the same *CAS* (hence same chemical formula) were merged. By mean of substructure-search, all the building-blocks containing the structures reported as toxic functional groups,[5] and heavy-metal containing molecules were detected and filtered-out. Considering that chemical couplings imply an increase of the molecular complexity (exception taken for cleavage reactions), and that the coupling products should preferably satisfy the Lipinski rule of 5 for druglikeliness,[6] building-blocks meeting the following criteria were discarded: (a) number of rotatable bonds larger than 5, since most non-cyclisation reactions create one to two additional rotatable bonds;[7] (b) number of heavy atoms (= non-hydrogen) smaller than 3 or larger than 35; (c) chiral centers larger than 2 (depending on the nature of the reagents and the reaction itself, additional chiral centers can be created upon coupling).
In this way, a collection of building-blocks containing ~270'000 unique molecules stored under the *sdf*-format was generated.

Reactants filters
Literature reviews estimated around ~20 reagent classes.[7-8] Those classes were redefined and merged giving 12 categories of building-blocks : (a) alcohols; (b) I- and II-amines (including anilines); (c) alkyl halides; (d) aryl/vinyl halides; (e) boronic acids/esters; (f) carboxylic acids/esters, nitriles, acylchlorides; (g) epoxides; (h) isocyanates; (i) aldehydes, ketones; (j) phophorus ylids, (k) sulfonyl chlorides, (l) terminal alkenes.
Script Procedure:
An RDkit-based Python script using substructure search parsed the building-blocks library and sorted out the molecules onto separate reactant libraries. Molecules containing several functions of the same type were saved in a different library than for the mono-functionalized ones (to avoid protection/deprotection steps). Ultimately, the reactant libraries contained the following information about the compounds: (a) reactivity (amine, carboxylic acid, halide, etc.) (b) position of the reactive centers (c) functional groups inducing side-reactions (see Reactions Pool, such data helps to foresee the reagent's adequacy for a single-step synthesis) (d) CAS number. Once the library was established, it was used multiple times and enriched on demand.

Reactions pool
The present collection comprises three reactions:[8-9] (a) Amide condensation : I- or II-amines/anilines addition onto carboxylic acids; (b) Suzuki coupling of boronic acids with aryl halides; (c) Buchwald-Hartwig coupling of I- or II-amines/anilines with aryl halides. Libraries or software making use of similar reaction collections were recently developed for *in-silico* drug design.[7-8,10]
Script Procedure:
The python script for virtual coupling parsed the *sdf* files of the two reaction partners retrieving information on the possible presence of undesired functionalities (if a competing functional group was present, the script would discard the building block). Subsequently it generated a new *sdf* file of the coupling product. Relying on the robustness of the used reaction and on the fact that compounds were generated in one step from the building-blocks, no assessment of the synthetic accessibility score[11-12] was needed for the product.

The python scripts used in AutoCouple were released on GitHub in the following repository: https://github.com/Caflisch-Group/AutoCouple_Python-based.

1.2 Conformers and protonation states

The software suite *ChemAxon* (*Marvins Beans*)[13] and the chemical toolbox *OpenBabel*[14] were used for preparation of the ligand libraries before docking. The command line program *cxcalc* within *Marvins Beans* performed various calculations such as lowest conformer generation (*leconformer*), generation of multiple conformers (*conformers*), major microspecies at given pH (*majormicrospecies*), microspecies list with distributions at given pH (*microspeciesdistribution*). *OpenBabel* was used for conversion between different chemical data formats.

1.3 Flexible ligand docking and binding energy evaluation

Target Preparation

The 3D coordinates of CBP, that were used for docking, originated from the crystallographic structures of the CBP bromodomain in complex with three different ligands, viz., 3P1C, CBP bromodomain in complex with the endogenous acetylated lysine ligand; 4TQN, CBP bromodomain in complex with our previously reported acetylbenzene ligand **1**;[15-16] 4NYX, CBP bromodomain in complex with a dihydroquinoxalinone ligand.[17] Only one structure of BRD4(1) was used for docking, from the complex with benzodiazepin-2-one (4PCI).[18] To do so, the target coordinates were extracted from the crystal structure. Protons and missing side-chains were added to the coordinates using the module AutoPSF of VMD based on the topology from CHARMM param36 force field for protein. The hereby prepared crystal structure in complex with the ligand and either 5, 6 or 7 structural water molecules was used for optimization of the positions of the hydrogen atoms by steepest descent and conjugate gradient methods implemented in the CHARMM program (version 38b1).[19]

Flexible ligand docking with tethered head group

The subsequently extracted bromodomain's coordinates as well as the optimized structural water molecules were used for flexible docking with the open-source software *rDock*.[20] During flexible ligand docking, the head groups were tethered in the binding site (command *sdtether*) to mimic the KAc residue.

Pose minimization

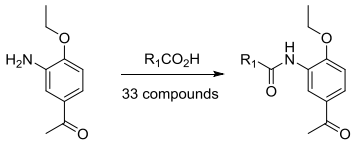
Atom typing, assignment of parameters and charges for the ligand were performed with the CHARMM General Force Field (CGenFF) program using the CHARMM param36 force field topology.[21,22] The minimization of the ligand's poses within the binding site was performed successively by steepest descent and conjugate gradient methods implemented in the CHARMM program (version 38b1).[19] All target's atoms were fixed during optimization.

Binding energy evaluation

The binding energy is the sum of protein/ligand van der Waals and electrostatic contribution. The electrostatic energy is the sum of bromodomain desolvation, ligand desolvation, and intermolecular interaction screened by the solvent which is treated implicitly by the finite-difference Poisson-Boltzmann method using the PBEQ module in CHARMM.[23] The dielectric constant of the solute was set to 4.0 and for the solvent to 78.5.

2. Molecules suggested by AutoCouple for CBP

- **Amide linker (Amide coupling):**



2 (LE = 0.45)
CBP: K_d = 53 μM

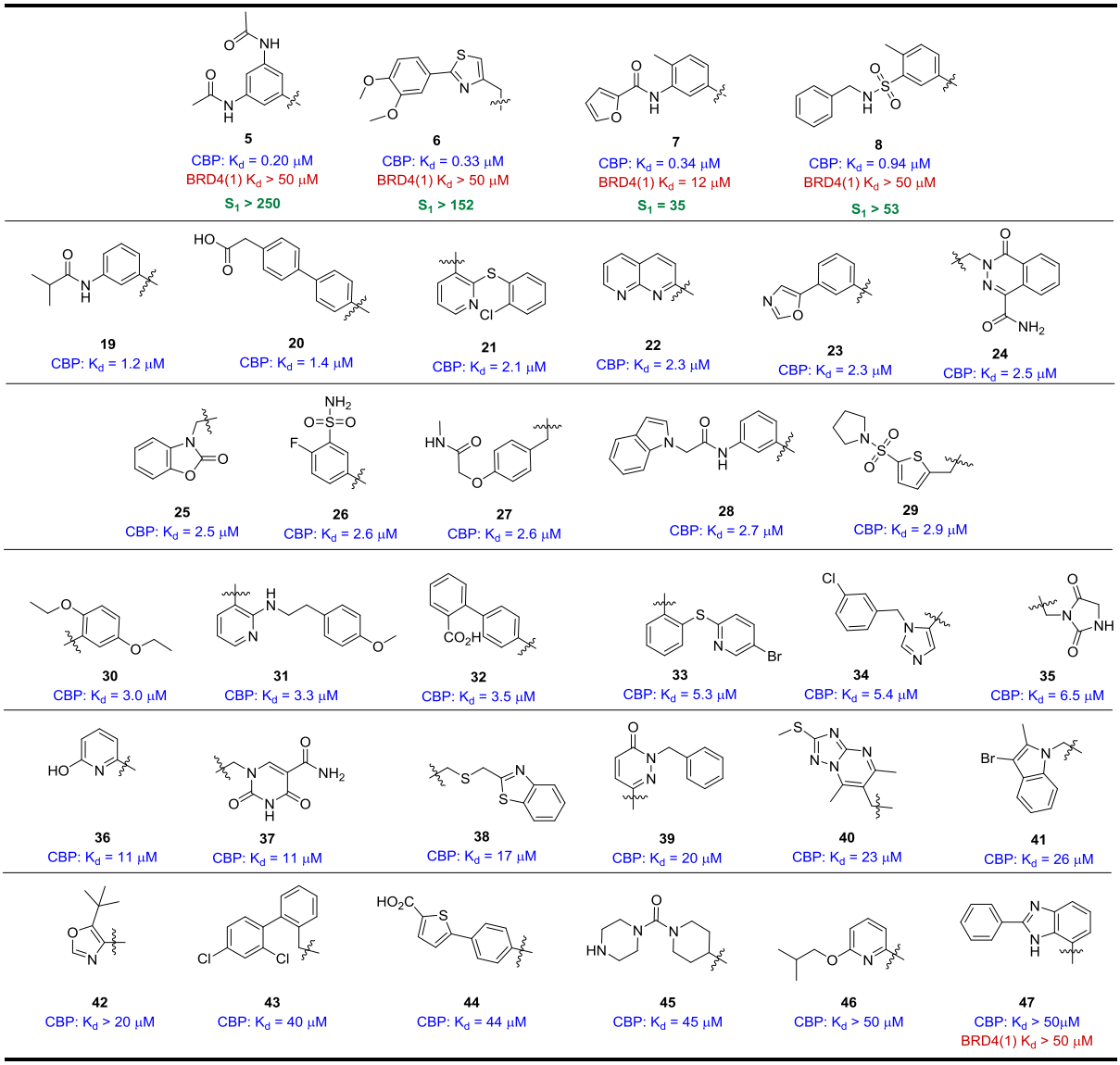


Figure S1. CBP inhibitors with an amide linker that originate from the virtual chemical reaction campaign by AutoCouple. The molecules are ordered from lowest to highest K_d for binding on CBP bromodomain. The K_d was determined in a competition binding assay (see section 6 for further details) onto CBP bromodomain (blue) or BRD4(1) bromodomain (red). Selectivity (S_1) for CBP bromodomain over BRD4(1) bromodomain determined by the ratio of K_d values.

- **Amine linker (Buchwald-Hartwig coupling)**

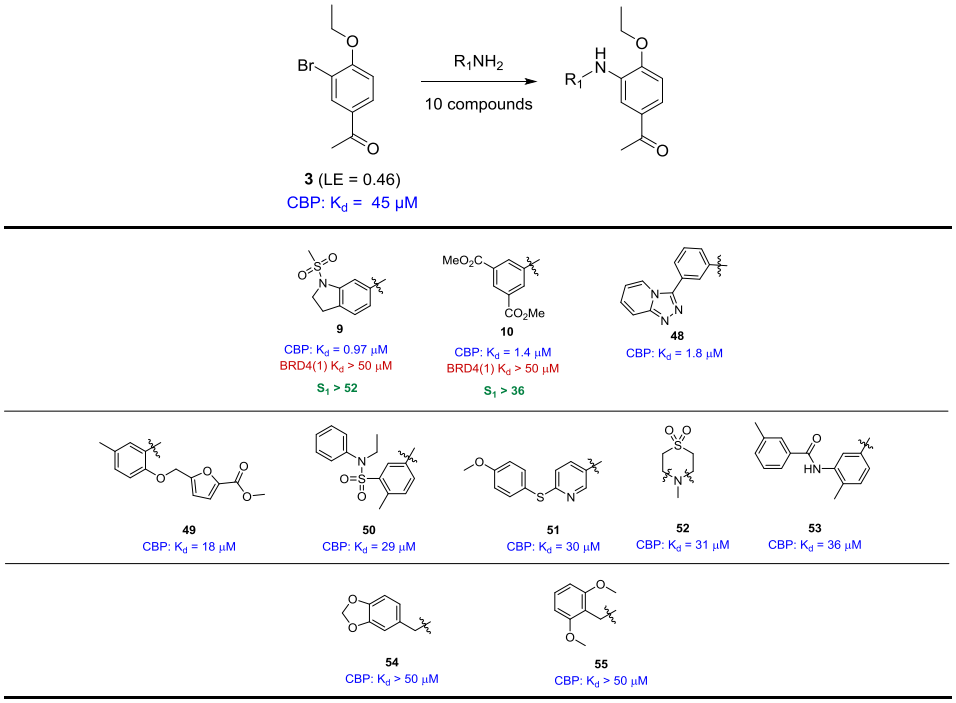


Figure S2. same as Figure S1 - synthesized CBP inhibitors containing an amine linker.

- **No linker (Suzuki cross-coupling)**

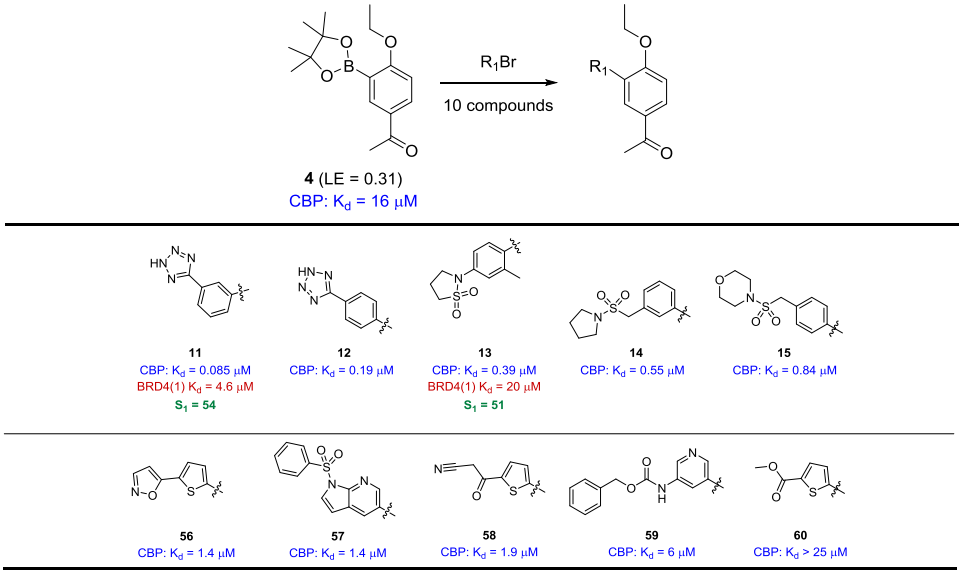


Figure S3. same as Figure S1 - synthesized CBP inhibitors without a linker (Suzuki coupling).

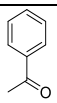
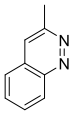
3. Molecules suggested by SEED and AutoCouple for BRD4(1)

3.1 Selective ligands of BRD4(1) identified by SEED

3.1.1 Fragment docking (SEED)

To further validate AutoCouple, we decided to focus on alternative KAc mimic fragments that, in contrast with the acetyl benzene moiety **61**, would exhibit higher affinity for BRD4(1) than for CBP. Preceding the present work, alternative "head-group" fragments (Table S1) had been identified by the fragment-docking program SEED (version 3.3.6):[24-25] A library of 419 heteroaromatics[22] was docked to the crystal structure of the CBP bromodomain (PDB code 3P1C) and the BRD4(1) bromodomain (PDB code 3MXF). The SEED docking of 419 fragments required about 15 minutes of a single core of a Xeon® Processor E3-1245 at 3.5 GHz. The CHARMM36[21] and CGenFF force fields[22] were used for the protein and fragments, respectively. The electrostatic energy is the sum of bromodomain desolvation, fragment desolvation, and intermolecular interaction screened by the solvent which is treated implicitly by the generalized Born approximation.

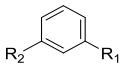
Table S1. Fragments with favorable binding energy as predicted by SEED.

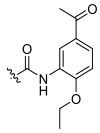
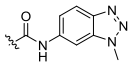
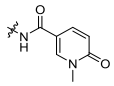
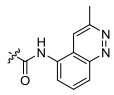
	Fragment	CBP			BRD4(1)		
		van der Waals	electrostatic	total	van der Waals	electrostatic	total
61		-14.0	-2.3	-16.3	-14.6	0.5	-14.0
62		-18.5	-1.4	-19.9	-17.5	-0.8	-18.3
63		-17.5	-1.9	-19.4	-16.6	2.1	-14.5
64		-15.3	-4.6	-19.9	-17.7	1.1	-16.5

3.1.2 Molecules suggested by SEED for BRD4(1)

Compounds **65-67** (Table S2) are analogs of compound **1** bearing a benzoic acid moiety as tail group and are connected via an amide linker to those SEED-identified hit fragments as KAc mimic (head group, see Table S1). Although these three compounds had high affinity for CBP (blue column in Table S2), compound **65** turned out to be slightly more potent towards BRD4(1) (Kd of 6.9 μM) than CBP (Kd of 17 μM), suggesting that the selectivity can possibly arise from the KAc mimic moiety. The benzotriazole moiety of compound **65** thus appeared as an alternative KAc mimic head group for targeting preferentially BRD4(1). We therefore set out to generate novel ligands via AutoCouple that would bear the benzotriazole moiety **65** as a KAc mimic.

Table S2. Affinity of compounds **1**, **65-67** for the CBP and BRD4(1) bromodomains.



Cmpd	R_1	R_2	LE CBP	K_d (μM)[a] CBP	K_d (μM)[a] BRD4(1)	S_1[b]	S_2[b]	ΔT_m(°C)[c] CBP	ΔT_m(°C)[c] BRD4(1)
1		CO_2H	0.35	0.77	> 50	> 65	< 0.02	3.8	0.4
65		CO_2H	0.30	17	6.9	0.4	2.5	2.0	2.8
66		CO_2H	0.37	4.1	33	8.0	0.1	1.9	0.9
67		CO_2H	0.35	1.1	41	37	0.03	4.0	1.4

[a] K_d values were determined by a competition binding assay[26] in duplicates for CBP (blue) and BRD4(1) (red). [b] Selectivity (S_1) for CBP bromodomain over BRD4(1) bromodomain and selectivity (S_2) for BRD4(1) bromodomain over CBP bromodomain as determined by the ratio of K_d values obtained via the competition binding assay.[26] [c] Median value of the shift in the melting temperature (number of measurements > 12). The thermal shift assay was carried out with a 2 μM concentration of the bromodomain and 100 μM compound concentration (see section 5: Thermal shift measurements).

3.2 Molecules suggested by AutoCouple for BRD4(1)

Following the same strategy as described for CBP in the main text, virtual libraries were generated in silico by coupling of the benzotriazole moiety with commercially-available reactants. Two campaigns involving amide condensation and Suzuki cross-coupling reactions on the benzotriazole head groups **68** (see Figure S5) and **69** (see Figure S6) provided 32'000 amides and 19'000 C−C coupled compounds, respectively. A crystal structure of BRD4(1) in complex with a low micromolar benzodiazepine-2-one ligand previously resolved in our groups was used as the target[18] for flexible ligand docking. During the latter, the benzotriazole was tethered in the binding site (command *sdtether*) to mimic the KAc residue as observed in SEED pose (for BRD4(1), see Figure S4).

A total of 20 compounds were prioritized and synthesized (10 for the amide condensation and 10 for the Suzuki coupling). Nine of these compounds (**70-74** with amide linkers and **80-83** via direct C-C coupling) presented a K_d lower than 10 μM with promising LE values (up to 0.37 kcal mol^{-1} per non-hydrogen atom for compound **81**; see Figure S6). Furthermore, the selectivity towards BRD4(1) was improved from 2.5 fold for compound **65** up to 11 and 12 fold for pyridine **71** and sulfonamide **70**, respectively. Interestingly, compound **70** is 26 times more potent than the original fragment **68**. As in the previous campaign, AutoCouple offered significant structural diversity with a broad range of functional groups, including sulfonamides (**70**, **74**, **83**), pyridines (**71**, **80**), and diverse five membered ring heterocycles (**72**, **73**, **82**) among others, thus demonstrating the ability of this in silico tool to identify alternative motifs streamlining hit-optimization efforts.

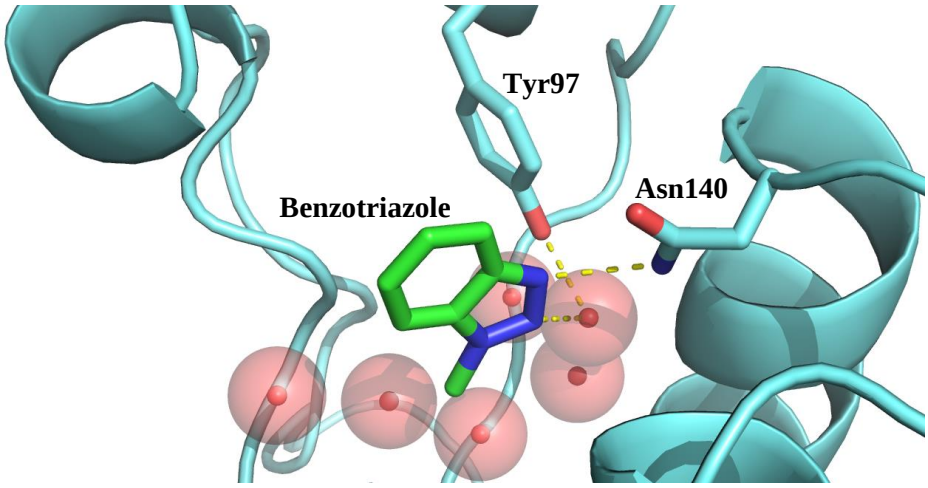


Figure S4: SEED pose of the Benzotriazole fragment (green) in BRD4(1) – During the docking of ligands generated by virtual couplings, the benzotriazole head groups were tethered to reproduce the pose within the binding site (*sdtether* command).

- **Amide linker (Amide coupling)**

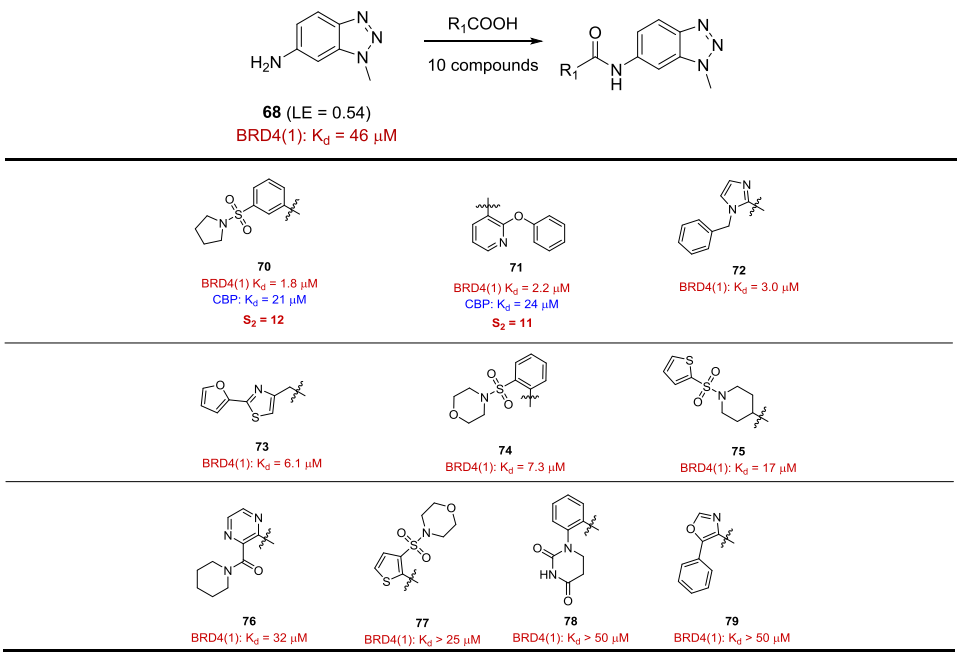


Figure S5. BRD4(1) inhibitors with an amide linker that originate from the virtual chemical reaction campaign by AutoCouple. The molecules are ordered from lowest to highest K_d for binding on BRD4(1) bromodomain. The K_d was determined in a competition binding assay (see section 6 for further details) onto CBP bromodomain (blue) or BRD4(1) bromodomain (red). Selectivity (S_2) for BRD4(1) bromodomain over CBP bromodomain determined by the ratio of K_d values.

- **No linker (Suzuki cross-coupling)**

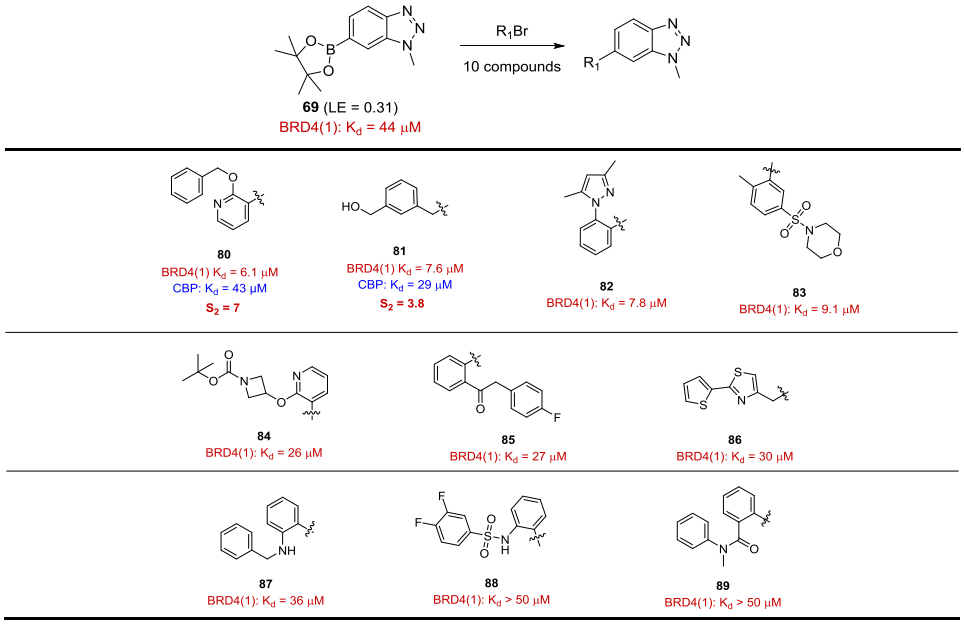


Figure S6. same as Figure S5 - synthesized BRD4(1) inhibitors without a linker (Suzuki cross-couplings).

4. Bromodomain expression and purification

Proteins were purified as described previously.[27] Briefly, Poly-Histidine-tagged (His-tag) bromodomains were expressed in *Escherichia coli* BL21(DE3) cells upon induction with isopropyl thio-beta-D-galactoside (IPTG, final concentration 0.1 mM) for 16 h at 18 °C. Bacteria were lysed and (when required) the resulting extract was treated to remove DNA, and 0.15% polyethylenimine (PEI) was added. The His-tagged proteins were purified on HisTrap columns (GE Healthcare) and eluted using a step gradient of imidazole. The His-tags were removed by overnight incubation with His-tagged tobacco etch virus (TEV) protease purified in-house (if required by the purification protocol, in the meantime the sample was exchanged via dialysis). A size-exclusion chromatography step (HiLoad 16/600 Superdex75 column) and a Ni-affinity chromatography step were subsequently performed to finally purify the cleaved bromodomains. Samples were then concentrated, flash frozen and stored at –80 °C.

5. Thermal shift measurements

Thermal shift measurements were performed using a 2 μM and 100 μM concentration for the bromodomains and ligands, respectively, as precedently described.[28] The reported values (ΔTm) were calculated as the difference between the transition midpoints of an individual sample and the average of the reference wells (containing the protein and the DMSO only) in the same plate. DMSO concentration was kept at 0.2% (v/v).

6. BROMOscan assays[26]

The binding constant (K_d) determinations by means of BROMOscan technology were carried out at DiscoverX. An E. *coli* strain derived from BL21 was used as the host to grow T7 phage strains displaying the bromodomains. E. *coli*, grown to log-phase, were infected with T7 phage (from a frozen stock, being the multiplicity of infection 0.4) and incubated while shaking at 32 °C for 90-150 minutes until lysis. In order to remove cell debris, lysates were centrifuged at 5,000 x g and filtered (0.2 μm). Affinity resins were obtained by treating streptavidin-coated magnetic beads with biotinylated acetylated peptide ligands for 30 minutes at 25°C. Those beads were then blocked with excess of biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % bovine serum albumin (BSA), 0.05 % Tween 20, 1 mM dithiothreitol (DTT)) to remove the unbound ligand and reduce non-specific phage binding.

During the experiment, the bromodomain, ligand-bound affinity beads and test compounds were combined in a buffer composed of 17% SeaBlock, 33% phosphate-buffered solution (PBS), 0.04% Tween 20, 0.02% BSA, 0.004% sodium azide and 7.4 mM DTT. Test compounds were prepared as 50 mM in pure DMSO and diluted to 5 mM with monoethylene gycol, MEG (100× concentrated in respect to the top screening concentration 50 μM). During the assay the DMSO and MEG final concentrations were 0.1% and 0.9%, respectively. The assays were carried out in polystyrene 96-well plates in a final volume of 0.135 mL. The assay plates were incubated at 25 °C with shaking for 1 hour and the affinity beads were washed with a buffer composed of 0.05% Tween 20 in PBS. The beads were then re-suspended in the elution buffer (1x PBS, 0.05% Tween 20, 2 μM non-biotinylated affinity ligand) and incubated at 25°C with shaking for 30 minutes. The bromodomain concentration in the elutes was measured by qPCR. K_d values were calculated with a standard dose-response curve using the Hill equation and curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

7. Alpha Screen assays[29]

IC_{50} determinations by means of Amplified Luminescent Proximity Homogeneous Assay (Alpha) Screen technology were carried out at Reaction Biology. Compounds were tested in 10-dose IC_{50} mode with 2 or 3-fold serial dilution starting at varying concentrations. The competitive ligand was H4/4Ac: Histone H4 peptide (1-21) K5/8/12/16Ac-Biotin. The detection was performed by the AlphaScreen

Binding assay in Envision (Ex/Em=680/520-620 nm). Data include raw data (signal-Background, Background was measured without BRD but all other components.), % binding (relative to DMSO controls), and curve fits. An IC_{50} value higher than the starting compound concentration was estimated based on the best curve fitting available.

Compound **16**

Bromodomain	**IC_{50} (µM)**
CBP	0.019
BRD4(1)	>200
Selectivity	>10526

Table S3. Half maximal inhibitory concentration (IC_{50}) as determined by Alpha Screen assays for compound **16** with BRD4(1) and the bromodomain of CBP. The selectivity is calculated as the ratio of the IC_{50} values.

8. Target engagement in cells and preliminary biological evaluation

8.1 FRAP assays[30]

In order to determine if our inhibitors engage CBP bromodomain within a cellular setting, we conducted a fluorescence recovery after photo-bleaching (FRAP) assay for the most potent and chemically diverse inhibitors. Compounds **6**, **7**, **13**, **16** and **17** were able to displace the CBP bromodomain from chromatin at concentration of 1 µM (Figure S8 and Scheme 1D in the main text). The half times ($t_{1/2}$) required to recover the fluorescence in a photobleach area of U2OS cells expressing GFP-tagged multimerized (3X) CBP bromodomains were measured (Figure 4A, 4B in the main text and Figure S7). The presence of our inhibitors reduced the recovery $t_{1/2}$ compared to cells without compound treatment, in the presence of 2.5 µM of the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA). Moreover, in the case of compound **16**, the $t_{1/2}$ value resembles that of the N1168F mutant, indicating that our compound interacts with the KAc binding site of the CBP bromdomain efficiently, displacing it from chromatin (Figure 4A, 4B in the main text and Figure S7).

Plasmids:

The GFP-BRD4 plasmid was a gift from Kyle Miller (Addgene plasmid # 65378).[55]

CBP Plasmid cloning

The CBP multimerised bromodomain construct was made as previously reported.[30] Plasmids containing the fragments shown below were purchased from GenScript and their PCR products were cloned with Gateway BP Clonase II enzyme mix (MultiSite Gateway System, ThermoFisher) into either pDONR221 P4r-P3r, pDONR221 P3-P2 or pDONR221 P1-P4 to create entry clones.

pENTR221 P4r-P3r **CBP aa868-1341**	GGGGACAACTTTTCTATACAAAGTTGCTCTCCAGCACACGACACCACCTGGGATGACTCCTCCC CAGCCAGCAGCTCCCACTCAGCCATCAACTCCTGTGTCGTCTTCCGGGCAGACTCCCACCCCGA CTCCTGGCTCAGTGCCCAGTGCTACCCAAACCCAGAGCACCCCTACAGTCCAGGCAGCAGCCC AGGCCCAGGTGACCCCGCAGCCTCAAACCCCAGTTCAGCCCCCGTCTGTGGCTACCCCTCAGTC ATCGCAGCAACAGCCGACGCCTGTGCACGCCCAGCCTCCTGGCACACCGCTTTCCCAGGCAGC AGCCAGCATTGATAACAGAGTCCCTACCCCCTCCTCGGTGGCCAGCGCAGAAACCAATTCCCA GCAGCCAGGACCTGACGTACCTGTGCTGGAAATGAAGACGGAGACCCAAGCAGAGGACACTG AGCCCGATCCTGGTGAATCCAAAGGGGAGCCCAGGTCTGAGATGATGGAGGAGGATTTGCAAG GAGCTTCCCAAGTTAAAGAAGAAACAGACATAGCAGAGCAGAAATCAGAACCAATGGAAGTG GATGAAAAGAAACCTGAAGTGAAAGTAGAAGTTAAAGAGGAAGAAGAGAGTAGCAGTAACG GCACAGCCTCTCAGTCAACATCTCCTTCGCAGCCGCGCAAAAAAATCTTTAAACCAGAGGAGT TACGCCAGGCCCTCATGCCAACCCTAGAAGCACTGTATCGACAGGACCCAGAGTCATTACCTTT CCGGCAGCCTGTAGATCCCCAGCTCCTCGGAATTCCAGACTATTTTGACATCGTAAAGAATCCC ATGGACCTCTCCACCATCAAGCGGAAGCTGGACACAGGGCAATACCAAGAGCCCTGGCAGTAC GTGGACGACGTCTGGCTCATGTTCAACAATGCCTGGCTCTATAATCGCAAGACATCCCGAGTCT ATAAGTTTTGCAGTAAGCTTGCAGAGGTCTTTGAGCAGGAAATTGACCCTGTCATGCAGTCCCT TGGATATTGCTGTGGACGCAAGTATGAGTTTTCCCCACAGACTTTGTGCTGCTATGGGAAGCAG

	CTGTGTACCATTCCTCGCGATGCTGCCTACTACAGCTATCAGAATAGGTATCATTTCTGTGAGA AGTGTTTCACAGAGATCCAGGGCGAGAATGTGACCCTGGGTGACGACCCTTCACAGCCCCAGA CGACAATTTCAAAGGATCAGTTTGAAAAGAAGAAAAATGATACCTTAGACCCCGAACCTTTCG TTGATTGCAAGGAGTGTGGCCGGAAGATGCATCAGATTTGCGTTCTGCACTATGACATCATTTG GCCTTCAGGTTTTGTGTGCGACAACTGCTTGAAGAAAACTGGCAGACCTCGAAAAGAAAACAA ATTCAGTGCTAAGAGGCTGCAGACCACAAGACTGGGAAACCACTTGGAAGACCGAACAACTTT GTATAATAAAGTTGTCCCC
pENTR221 P3-P2 **CBP aa868-1341**	GGGGACAACTTTGTATAATAAAGTTGCTCTCCAGCACACGACACCACCTGGGATGACTCCTCCC CAGCCAGCAGCTCCCACTCAGCCATCAACTCCTGTGTCGTCTTCCGGGCAGACTCCCACCCCGA CTCCTGGCTCAGTGCCCAGTGCTACCCAAACCCAGAGCACCCCTACAGTCCAGGCAGCAGCCC AGGCCCAGGTGACCCCGCAGCCTCAAACCCCAGTTCAGCCCCCGTCTGTGGCTACCCCTCAGTC ATCGCAGCAACAGCCGACGCCTGTGCACGCCCAGCCTCCTGGCACACCGCTTTCCCAGGCAGC AGCCAGCATTGATAACAGAGTCCCTACCCCCTCCTCGGTGGCCAGCGCAGAAACCAATTCCCA GCAGCCAGGACCTGACGTACCTGTGCTGGAAATGAAGACGGAGACCCAAGCAGAGGACACTG AGCCCGATCCTGGTGAATCCAAAGGGGAGCCCAGGTCTGAGATGATGGAGGAGGATTTGCAAG GAGCTTCCCAAGTTAAAGAAGAAACAGACATAGCAGAGCAGAAATCAGAACCAATGGAAGTG GATGAAAAGAAACCTGAAGTGAAAGTAGAAGTTAAAGAGGAAGAAGAGAGTAGCAGTAACG GCACAGCCTCTCAGTCAACATCTCCTTCGCAGCCGCGCAAAAAAATCTTTAAACCAGAGGAGT TACGCCAGGCCCTCATGCCAACCCTAGAAGCACTGTATCGACAGGACCCAGAGTCATTACCTTT CCGGCAGCCTGTAGATCCCCAGCTCCTCGGAATTCCAGACTATTTTGACATCGTAAAGAATCCC ATGGACCTCTCCACCATCAAGCGGAAGCTGGACACAGGGCAATACCAAGAGCCCTGGCAGTAC GTGGACGACGTCTGGCTCATGTTCAACAATGCCTGGCTCTATAATCGCAAGACATCCCGAGTCT ATAAGTTTTGCAGTAAGCTTGCAGAGGTCTTTGAGCAGGAAATTGACCCTGTCATGCAGTCCCT TGGATATTGCTGTGGACGCAAGTATGAGTTTTCCCCACAGACTTTGTGCTGCTATGGGAAGCAG CTGTGTACCATTCCTCGCGATGCTGCCTACTACAGCTATCAGAATAGGTATCATTTCTGTGAGA AGTGTTTCACAGAGATCCAGGGCGAGAATGTGACCCTGGGTGACGACCCTTCACAGCCCCAGA CGACAATTTCAAAGGATCAGTTTGAAAAGAAGAAAAATGATACCTTAGACCCCGAACCTTTCG TTGATTGCAAGGAGTGTGGCCGGAAGATGCATCAGATTTGCGTTCTGCACTATGACATCATTTG GCCTTCAGGTTTTGTGTGCGACAACTGCTTGAAGAAAACTGGCAGACCTCGAAAAGAAAACAA ATTCAGTGCTAAGAGGCTGCAGACCACAAGACTGGGAAACCACTTGGAAGACCGATAGTACCC AGCTTTCTTGTACAAAGTGGTCCCC
pENTR221 P1-P4 **NLS/CBP aa868-1341**	GGGGACAAGTTTGTACAAAAAAGCAGGCTTAATGCCCAAGAAGAAGAGGAAAGTCTCTCTCCA GCACACGACACCACCTGGGATGACTCCTCCCCAGCCAGCAGCTCCCACTCAGCCATCAACTCCT GTGTCGTCTTCCGGGCAGACTCCCACCCCGACTCCTGGCTCAGTGCCCAGTGCTACCCAAACCC AGAGCACCCCTACAGTCCAGGCAGCAGCCCAGGCCCAGGTGACCCCGCAGCCTCAAACCCCAG TTCAGCCCCCGTCTGTGGCTACCCCTCAGTCATCGCAGCAACAGCCGACGCCTGTGCACGCCCA GCCTCCTGGCACACCGCTTTCCCAGGCAGCAGCCAGCATTGATAACAGAGTCCCTACCCCCTCC TCGGTGGCCAGCGCAGAAACCAATTCCCAGCAGCCAGGACCTGACGTACCTGTGCTGGAAATG AAGACGGAGACCCAAGCAGAGGACACTGAGCCCGATCCTGGTGAATCCAAAGGGGAGCCCAG GTCTGAGATGATGGAGGAGGATTTGCAAGGAGCTTCCCAAGTTAAAGAAGAAACAGACATAG CAGAGCAGAAATCAGAACCAATGGAAGTGGATGAAAAGAAACCTGAAGTGAAAGTAGAAGTT AAAGAGGAAGAAGAGAGTAGCAGTAACGGCACAGCCTCTCAGTCAACATCTCCTTCGCAGCCG CGCAAAAAAATCTTTAAACCAGAGGAGTTACGCCAGGCCCTCATGCCAACCCTAGAAGCACTG TATCGACAGGACCCAGAGTCATTACCTTTCCGGCAGCCTGTAGATCCCCAGCTCCTCGGAATTC CAGACTATTTTGACATCGTAAAGAATCCCATGGACCTCTCCACCATCAAGCGGAAGCTGGACA CAGGGCAATACCAAGAGCCCTGGCAGTACGTGGACGACGTCTGGCTCATGTTCAACAATGCCT GGCTCTATAATCGCAAGACATCCCGAGTCTATAAGTTTTGCAGTAAGCTTGCAGAGGTCTTTGA GCAGGAAATTGACCCTGTCATGCAGTCCCTTGGATATTGCTGTGGACGCAAGTATGAGTTTTCC CCACAGACTTTGTGCTGCTATGGGAAGCAGCTGTGTACCATTCCTCGCGATGCTGCCTACTACA GCTATCAGAATAGGTATCATTTCTGTGAGAAGTGTTTCACAGAGATCCAGGGCGAGAATGTGA CCCTGGGTGACGACCCTTCACAGCCCCAGACGACAATTTCAAAGGATCAGTTTGAAAAGAAGA AAAATGATACCTTAGACCCCGAACCTTTCGTTGATTGCAAGGAGTGTGGCCGGAAGATGCATC AGATTTGCGTTCTGCACTATGACATCATTTGGCCTTCAGGTTTTGTGTGCGACAACTGCTTGAA GAAAACTGGCAGACCTCGAAAAGAAAACAAATTCAGTGCTAAGAGGCTGCAGACCACAAGAC TGGGAAACCACTTGGAAGACCGACACCCAACTTTTCTATACAAAGTTGTCCCC

The three entry clones were then combined by LR cloning (MultiSite Gateway System, ThermoFisher) into the pcDNA6.2/N-EmGFP-DEST vector creating an expression clone for three tandem repeats of the CBP bromodomain fused to an N-terminal GFP.

The N1168F CBP bromodomain mutant plasmid was generated using the QuikChange Lightning Multi Site-Directed Mutagenesis Kit (Agilent Technologies) starting from the non-mutagenic plasmid. The mutagenic primer was designed in the Agilent Technologies' website:
5'- GGATGTCTTGCGAAAATAGAGCCAGGCATTGTTGAACATG-3'

Cell culture

U2OS cells are kind gift from Dr. Sander Botter (Balgrist University Hospital, Zurich, Switzerland). Cells were grown at 37°C with 5% CO2 in a humidified incubator in Dulbecco's modified medium (DMEM) (GibcoTM, ThermoFischer Scientific). The medium contained 10% FCS, 100U/ml penicillin and 100mg/ml streptomycin.

FRAP assay

FRAP studies were performed according to a published protocol,[30] with slight modifications. In brief, U2OS cells in a 8-well chamber (ibidi) were transfected (Lipofectamine 2000, ThermoFisher) with the GFP-CBP-bromodomain plasmid (WT), GFP-CBP mutant plasmid (N1168F) or GFP-BRD4 plasmid. Six hours after transfection, culture medium was replaced with or without 2.5 μM SAHA (only for CBP plasmids), and the inhibitors (1 μM for CBP compounds and 0.1 μM for JQ1) were added 23 hours after transfection. Cells were then imaged 24 hours after transfection.

The FRAP experiments were conducted with a Leica SP5 confocal microscope (Leica microsystems GmbH, Wetzla, Germany) equipped with a HCX PL APO 40× Objective (NA 1.25) (Leica) and a controlled chamber set at 37°C and 5% CO_2. Bleaching and GFP fluorescence imaging were carried out with an argon laser (488 nm) and a detector set to detect fluorescence between 500 and 550 nm. Cells with nuclei just below saturation within the gain range of 650 to 850 were bleached. A square region (16 μm^2) of a GFP-positive nucleus was selected, and, after five prescans, the region was bleached. A time-lapse series was then taken to record GFP recovery. During the time-lapse series, images were acquired with a frame size of 256 pixels × 256 pixels with line-stepping of 2, bidirectional scanning and a zoom factor of 6, which allowed for a time interval time of 0.1-0.2 seconds. The laser power was set to 100% for photobleaching and attenuated to 2% for acquisition.

Data analysis

The fluorescence signal was measured with FIJI and normalized according to a published method.[30] All experiments were transferred to Prism (GraphPad) and fit on an exponential FRAP curve (one-way association). Different groups were compared by determining the half time ($t_{½}$) of the fluorescence recovery to reach a plateau level.

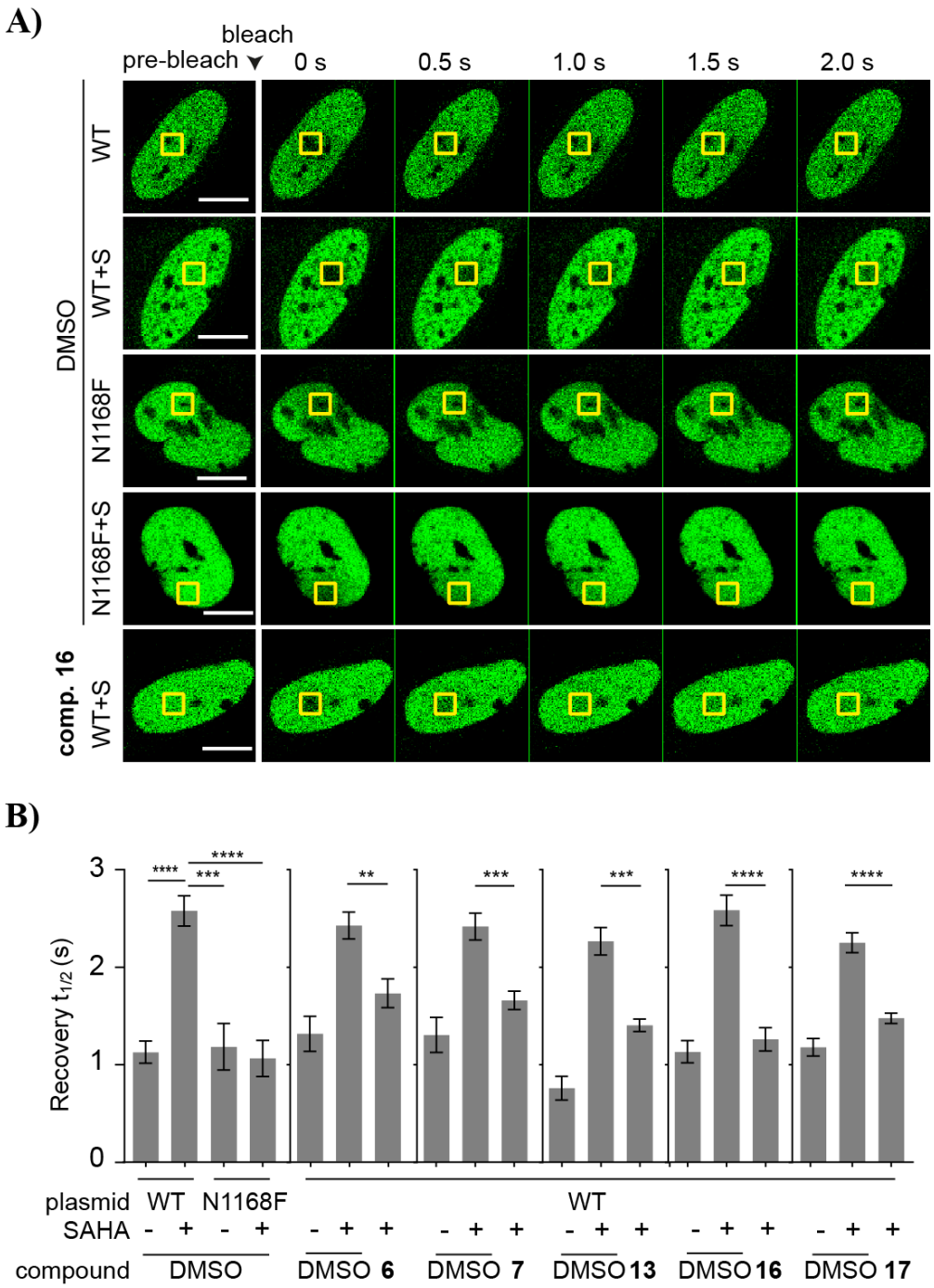


Figure S7. Fluorescence recovery after photo-bleaching (FRAP) demonstrating the displacement of CBP bromodomain from chromatin. U2OS cells were transfected with plasmids encoding GFP fused to wild-type (WT) or mutant (N1168F) multimerised CBP bromodomain, with or without 2.5 μM suberoylanilide hydroxamic acid (SAHA) and indicated compounds (1 μM). A) Representative images of the nuclei of cells treated with DMSO or compound **16**, with the presence of SAHA. The bleached area (16 μm^2) is indicated by a square. B) Half-times of fluorescence recovery ($t_{½}$) in the FRAP assays. Bars represent the mean $t_{½}$ calculated from individual recovery curves of at least 7 cells per group, and error bars represent the standard error of the mean. (statistics: Man-Whitney, always compared to SAHA-treated cells within the same experiment setup (significance: **P< 0.01, ***P<0.001 and ****P < 0.0001.)

8.2 Proliferation assays and Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR)

Cell proliferation assays

Cellular proliferation was assessed by Resazurin assay. Cells were plated at 10^4 cells/well of a 96-well plate for 24 h prior to incubation for three or six days with two-fold compound dilutions from 50µM or DMSO 1% control. Resazurin at 86µM (#R12204, ThermoFisher) was added and the metabolic activity was measured after six hours incubation at excitation of 560nM and detecting emission at 590nM. Procedures referred to Conery et al.[31]

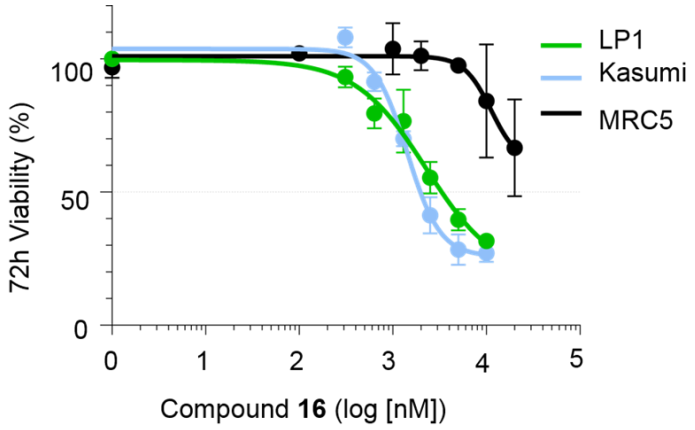


Figure S8. Proliferation assay of compound **16** in cells: LP1, Kasumi and non-transformed fibroblast MRC5, resazurin assay, 72 h incubation. Curves represent non-linear fit by a four-parameter logistic function; data points are mean values of at least three independent experiments; error bars: S.D. Hill coefficients for LP1 = -1.2, Kasumi = -2.5, MRC5 = -3.0.

6-DAYS ASSAY:

	GI_{50} (µM)
LP1	1.1 ± 0.4
Kasumi	1.8 ± 0.2
HL-60	3.2 ± 0.3

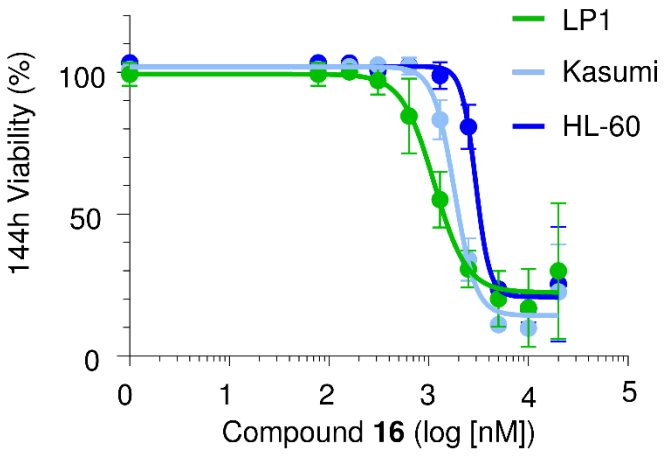


Figure S9. Same as Figure S8 with 144 h incubation and an additional cell line, the leukemia cell line HL-60. Hill coefficients for LP1 = -2.7, Kasumi = -4.1, HL-60 = -6.2.

Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR)

LP1 cells were incubated with compounds or DMSO control at 0.1% for six hours. RNA was isolated with an RNeasy kit (#74104, Qiagen) or by consistent quality with TRIzol reagent (#15596026, ThermoFisher) following manufacturer's instructions. RNA was converted to cDNA by Applied Biosystems' reverse transcriptase (#4368814, ThermoFisher). qPCR was operated in a Roche LightCycler®480 and performed by fluorescence detection of SYBRgreen® (#4368577, ThermoFisher) cycled from 1µg converted cDNA. Transcript specific primers are: IRF4: 5'-GCCAAGATTCCAGGTGACTC 3'-CTGGCTAGCAGAGGTTCTACG; cMYC: 5'-TACAACACCCGAGCAAGGAC 3'-GAGGCTGCTGGTTTTCCACT; and control transcript GAPDH: 5'-AGCCACATCGCTCAGACAC 3'-GCCCAATACGACCAAATCC.

9. Synthetic methods

All reactions, unless otherwise stated, were carried out under a nitrogen atmosphere using standard Schlenk-techniques. All reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh). NMR spectra were recorded on AV 300, AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Melting points were determined on a Mettler Toledo MP70 melting point instrument. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA, USA) double-focusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 µL PEG200, 2 µL PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, Buchs, Switzerland) dissolved in 100 mL MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard.

General procedure A for amide formation

The desired aniline (1.0 eq) and carboxylic acid (1.2 or 1.3 eq) were dissolved in dimethylformamide (0.10 M) and EDC·HCl (1.5-2.0 eq), DIPEA (1.5 eq) and HOBt (1.5-2.0 eq) were added at 25 ºC. The reaction mixture was stirred for 12-48 h at 25 ºC and was subsequently concentrated to half of the volume of dimethylformamide under reduced pressure. Water was added and then the obtained precipitate was filtered off furnishing the amides in pure form.

When no precipitate was observed, the mixture was diluted with ethylacetate. The organic phase was subsequently washed with $NaHCO_3$ saturated aqueous solution, HCl (1 M) and brine. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography affording the desired amides in pure form.

General procedure B for amide formation

To a solution of the carboxylic acid (1.0 eq) in dry toluene (1.0 M) under a nitrogen atmosphere, thionyl chloride (2.0 eq) and one drop of dry dimethylformamide were added. The solution was refluxed for 3 h, concentrated under reduced pressure and dissolved in dry dichloromethane (0.5 M). The corresponding aniline (1.2 eq) was added and the reaction mixture was stirred at 25 °C for 12 h under a nitrogen atmosphere. The reaction mixture was concentrated undr reduced pressure and purified by flash column chromatography furnishing the desired amides in pure form.

General procedure for ester hydrolysis

To a solution of the methyl ester (1.0 eq) in tetrahydrofuran (0.1 M), a 1M LiOH solution (5.0 eq.) was added. The reaction mixture was stirred at 25 °C for 2-12 h and was then subsequently concentrated under reduced pressure. HCl (1 M) was added and the obtained precipitate was washed with hexanes, diethylether and cold dichloromethane, affording the desired carboxylic acids in pure form.

General procedure for the reduction of nitro arenes

To a solution of nitro arene (1.0 eq) in methanol (0.3 M), Pd/C (10 mol%, 10% wt) was added. The reaction mixture was stirred at 25 °C under a hydrogen balloon for 4-12 h. The reaction mixture was filtered through a pad of celite, washed with methanol and concentrated under reduced pressure.

General procedure for Buchwald Hartwig aminations

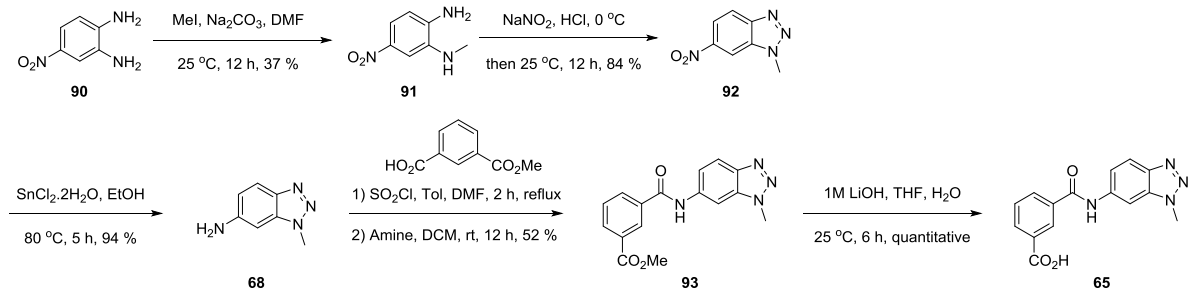
To a solution of 1-(3-bromo-4-ethoxyphenyl)ethan-1-one (1.0 eq) in toluene (0.1 M), the corresponding amine (1.5 eq), Cs_2CO_3 (3.3 eq), $Pd_2(dba)_3$ (3 mol%) and racemic BINAP (4 mol%) were added. The reactions were stirred at 100 °C for 12 h, concentrated under reduced pressure and purified by flash column chromatography to produce the desired amines in pure form.

General procedure for Suzuki cross-coupling reactions

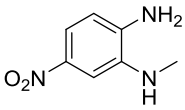
To a solution of the corresponding pinacol boronic ester (1 eq.) in dioxane (0.2 M) and water (25.0 eq.), the corresponding halide (2.0 eq.), Cs_2CO_3 (3.0 eq.) and $Pd(PPh_3)_4$ (10 mol%) were added. Nitrogen gas was bubbled through the reaction for five minutes and the reaction mixture was stirred at 100 °C for 1-21 h and diluted with dichloromethane. It was then concentrated under reduced pressure and purified by flash column chromatography furnishing the desired products in pure form. In the case of the BRD4(1) inhibitors, the organic phase was washed with water and dried over $MgSO_4$ prior to concentration under reduced pressure.

9.1 Synthesis of benzoic acid containing novel bromodomain ligands based on docking studies (65-67)

Synthesis of compound 65:

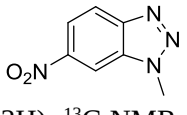


***N*-Methyl-5-nitrobenzene-1,2-diamine (91)[32]**



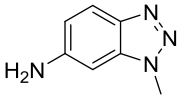
Aniline **91** was prepared according to the previously reported procedure. Off-white solid; Yield: 37 %; mp 176-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.49 (dd, J = 8.6, 2.6 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.10 (s, 2H), 5.19 (q, J = 4.8 Hz, 1H), 2.78 (d, J = 4.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 143.6, 137.3, 135.5, 115.6, 110.6, 102.7, 29.8; IR (neat): ῡ = 3399, 3327, 3246, 1579, 1525, 1483, 1346, 1276, 1156, 1080, 847, 743 cm^{-1}; MS (ESI), *m/z*: calcd for $C_7H_{10}N_3O_2^+$, 168.1; found, 167.9.

1-Methyl-6-nitro-1*H*-benzo[*d*][1,2,3]triazole (92)[32]



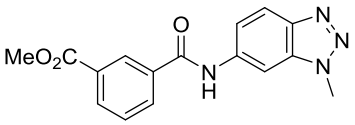
Nitro arene **92** was prepared according to the previously reported procedure. Off-white solid; Yield: 84 %; mp 137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (dd, J = 2.1, 0.7 Hz, 1H), 8.29 (dd, J = 9.1, 0.7 Hz, 1H), 8.22 (dd, J = 9.1, 2.1 Hz, 1H), 4.45 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 147.2, 146.2, 132.8, 120.2, 118.6, 108.8, 35.0; IR (neat): ῡ = 3107, 1670, 1522, 1455, 1345, 1254, 1196, 1142, 1057, 1021, 878, 852, 833, 797, 751, 735 cm^{-1}; MS (ESI), *m/z*: calcd for $C_7H_7N_4O_2^+$, 179.1; found, 178.9.

1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-amine (68)



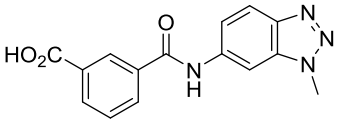
Aniline **68** was obtained following the general procedure for the reduction of nitro arenes and further purified by flash column chromatography (hexane/EtOAc = 1:1). Off-white solid; Yield: 94 %; mp 163-167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62 (d, J = 8.9 Hz, 1H), 6.72 (dd, J = 8.9, 2.0 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 5.62 (br, 2H), 4.06 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 148.4, 139.0, 135.2, 119.3, 115.7, 88.9, 33.4; IR (neat): ῡ = 3385, 3327, 3226, 1625, 1520, 1469, 1234, 1205, 1129, 1101, 1028, 802, 780, 716 cm^{-1}; MS (ESI), *m/z*: calcd for $C_7H_9N_4^+$, 149.1; found, 148.9.

Methyl 3-((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)carbamoyl)benzoate (93)



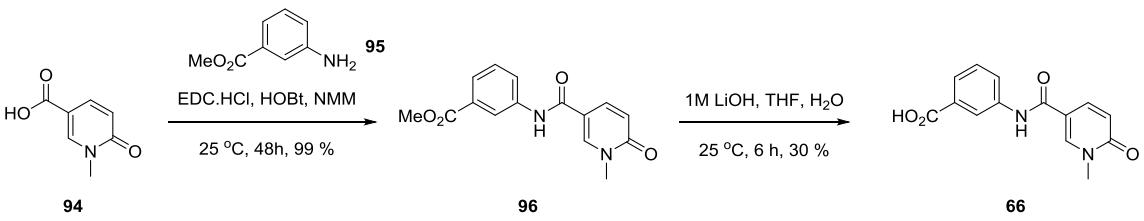
Amide **93** was obtained following the general procedure B for amide formation (chromatography: hexane/EtOAc = 1:1). Light red solid; Yield: 52 %; mp 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 8.38 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.30 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.2, 165.1, 165.0, 143.0, 137.1, 137.0, 134.8, 134.7, 134.2, 133.0, 132.1, 130.7, 129.3, 127.6, 120.3, 117.9, 117.8, 99.6, 99.5, 52.6, 34.3; IR (neat): ῡ = 3259, 1726, 1643, 1532, 1502, 1457, 1310, 1254, 1215, 1196, 1138, 1100, 1077, 1011, 959, 846, 828, 805, 780 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{16}H_{15}N_4O_3^+$, 311.1139; found, 311.1139.

3-((1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)carbamoyl)benzoic acid (65)

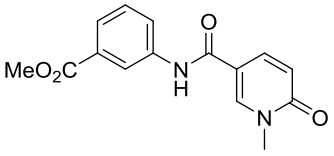


Benzoic acid **65** was obtained following the general procedure for ester hydrolysis. light red solid; Yield: quantitative; mp 294-300 °C; ^{1}H NMR (400 MHz, MeOD): δ = 8.64 (t, J = 1.6 Hz, 1H), 8.48 – 8.46 (m, 1H), 8.27 – 8.24 (m, 1H), 8.20 (ddd, J = 7.7, 1.8, 1.1 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 8.1 Hz, 1H), 7.61 (dd, J = 8.9, 1.9 Hz, 1H), 4.34 (s, 3H); ^{13}C NMR (126 MHz, MeOD): δ = 168.8, 168.2, 143.4, 139.8, 136.6, 135.4, 134.0, 133.0, 132.7, 130.0, 120.7, 120.0, 111.4, 101.7, 34.6; IR (neat): ῡ = 3283, 2829, 1704, 1625, 1556, 1505, 1449, 1248, 804, 717 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{15}H_{13}N_4O_3^+$, 297.0982; found, 297.0983.

<u>Synthesis of compound 66:</u>



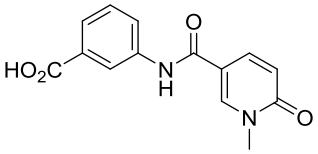
Methyl 3-(1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamido)benzoate (96)



To a solution of the carboxylic acid **94** (1.2 eq) and the amine **95** (1.0 eq) in dimethylformamide (0.16 M), a catalytic amount of HOBt (0.3 eq), NMM (2.0 eq) and EDC·HCl (1.4 eq) were added. The reaction mixture was stirred at 25 °C for 48 h and it was concentrated under reduced pressure. The corresponding amide was purified by flash column chromatography (10 % MeOH in EtOAc) obtaining the final product as a white solid in 99 % yield. mp 222-225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 1H), 8.55 (d, J = 2.6 Hz, 1H), 8.34 (t, J = 1.8 Hz, 1H), 8.03 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.98 (dd, J = 9.5, 2.7 Hz, 1H), 7.68 (ddd, J = 7.7, 1.6,

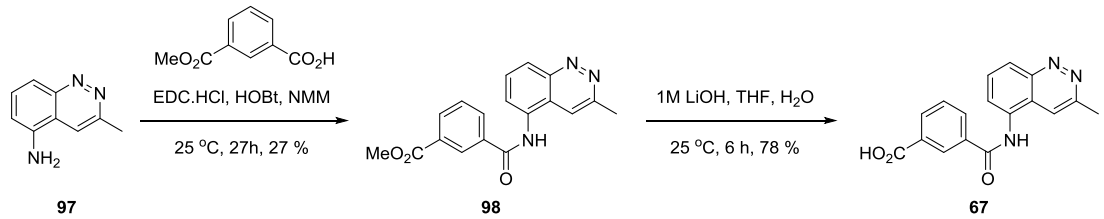
1.1 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 6.48 (d, *J* = 9.4 Hz, 1H), 3.87 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.1, 162.7, 161.7, 142.9, 139.4, 138.9, 130.0, 129.1, 124.5, 124.0, 120.6, 117.9, 112.2, 52.2, 37.4; IR (neat): $\tilde{\upsilon}$ = 3322, 3061, 2951, 1717, 1678, 1634, 1600, 1546, 1487, 1438, 1305, 1289, 1273, 1213, 1150, 1089, 1058, 943, 819, 753 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{15}H_{15}N_2O_4^+$, 287.1026; found, 287.1030.

3-(1-Methyl-6-oxo-1,6-dihydropyridine-3-carboxamido)benzoic acid (66)

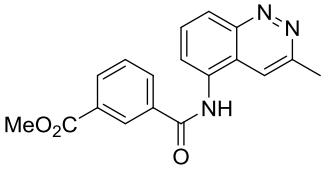


Benzoic acid **66** was obtained following the general procedure for ester hydrolysis. White solid; Yield: 30 %; mp 280-284 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.98 (s, 1H), 10.14 (s, 1H), 8.55 (s, 1H), 8.30 (s, 1H), 8.00-7.97 (m, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 9.4 Hz, 1H), 3.53 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.2, 162.7, 161.8, 142.9, 139.3, 138.1, 131.2, 128.9, 124.3, 124.2, 120.9, 117.9, 112.3, 37.4; IR (neat): $\tilde{\upsilon}$ = 3460, 3336, 1645, 1584, 1542, 1483, 1444, 1353, 1326, 1291, 1255, 1164, 1142, 1123, 924, 906, 836, 757 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{14}H_{13}N_2O_4^+$, 273.08698; found, 273.08670.

<u>Synthesis of compound 67:</u>

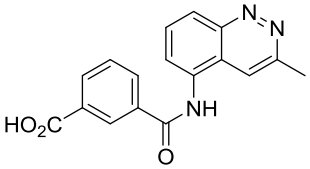


Methyl 3-((3-methylcinnolin-5-yl)carbamoyl)benzoate (98)



Amide **98** was prepared from amine **97** in an analogous manner to compound **96**. Green solid; Yield: 27 %; mp 155-159 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.79 (s, 1H), 8.66 (s, 1H), 8.37 (s, 1H), 8.35 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.07 (s, 1H), 7.96 – 7.88 (m, 2H), 7.75 (t, *J* = 7.8 Hz, 1H), 3.93 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.8, 165.5, 153.3, 149.0, 134.6, 133.0, 132.7, 132.3, 130.0, 129.6, 129.1, 128.7, 127.2, 126.9, 122.5, 117.6, 52.4, 21.7; IR (neat): $\tilde{\upsilon}$ = 3217, 3034, 1726, 1668, 1589, 1531, 1434, 1302, 1244, 1137, 1097, 814, 751, 718 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{18}H_{16}N_3O_3^+$, 322.1186; found, 322.1189.

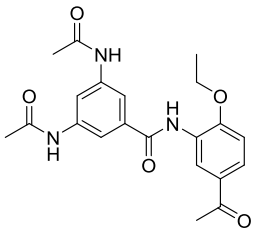
3-((3-Methylcinnolin-5-yl)carbamoyl)benzoic acid (67)



Benzoic acid **67** was obtained following the general procedure for ester hydrolysis but it was futher purified by flash column chromatography (EtOAc/ MeOH/AcOH = 90:9:1). Yellow solid; Yield: 78 %; mp 228-233 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.86 (s, 1H), 8.66 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.23-8.17 (m, 2H), 7.98-7.94 (m, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.9, 165.7, 153.1, 148.8, 134.4, 133.2, 132.6, 132.4, 131.1, 130.3, 129.0, 129.0, 127.8, 126.7, 123.1, 119.3, 21.3; IR (neat): $\tilde{\upsilon}$ = 3471, 2625, 1711, 1666, 1627, 1614, 1570, 1529, 1389, 1317, 1254, 906, 808, 734 cm^{-1}; HRMS (ESI), *m/z*: calcd for $C_{17}H_{14}N_3O_3^+$, 308.1030; found, 308.1030.

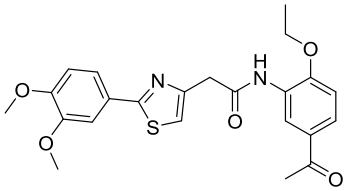
9.2 Virtual chemical reactions: synthesis of CBP inhibitors bearing an amide linker (5-8, 19-47)

***N,N'*-(5-((5-Acetyl-2-ethoxyphenyl)carbamoyl)-1,3-phenylene)diacetamide (5)**



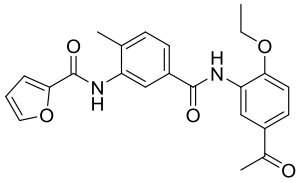
Amide **5** was obtained following the general procedure A for amide formation. White solid; mp 301-305 °C; Yield: 28 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.15 (s, 2H), 9.25 (s, 1H), 8.55 (d, J = 2.2 Hz, 1H), 8.05 (s, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.81 (dd, J = 8.6, 2.2 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.54 (s, 3H), 2.07 (s, 6H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.3, 168.6, 164.9, 153.5, 139.9, 135.4, 129.5, 127.1, 126.6, 121.9, 112.5, 111.5, 64.6, 26.4, 24.0, 14.4; IR (neat): ῡ = 3412, 3327, 1670, 1565, 1525, 1421, 1364, 1262, 1224, 1044, 874, 801, 589 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{24}N_3O_5^+$: 398.1712, found: 398.1711.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(2-(3,4-dimethoxyphenyl)thiazol-4-yl)acetamide (6)**



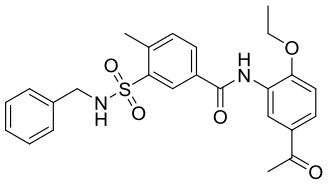
Amide **6** was obtained following the general the procedure A for amide formation (chromatography: hexane/EtOAc = 1:2). Off-white solid; mp 154-157 °C; Yield: 58 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 1H), 8.98 (s, 1H), 7.73 (s, 1H), 7.71 (dd, J = 8.6, 2.2 Hz, 1H), 7.57 (dd, J = 8.4, 2.1 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 4.10 (s, 2H), 4.05 (q, J = 7.0 Hz, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 2.57 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 169.4, 167.1, 151.5, 151.3, 149.4, 130.2, 127.4, 124.7, 120.8, 120.2, 115.8, 111.1, 110.5, 109.7, 64.6, 56.3, 56.1, 40.1, 26.5, 14.3; IR (neat): ῡ = 3278, 2928, 1664, 1603, 1584, 1537, 1519, 1498, 1475, 1420, 1355, 1271, 1227, 1204, 1169, 1126, 1040, 1014, 835, 628, 588, 525 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{23}H_{25}N_2O_5S^+$: 441.1479, found: 441.1484.

***N*-(5-((5-Acetyl-2-ethoxyphenyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide (7)**



Amide **7** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:1). Off-white solid; mp 183-189 °C; Yield: 44 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.94 (s, 1H), 9.47 (s, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 9.8, 1.2 Hz, 2H), 7.97 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.0 Hz, 1H), 7.78 (dd, J = 7.9, 1.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 3.4 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.71 (dd, J = 3.4, 1.7 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 2.54 (s, 3H), 2.31 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 164.5, 156.4, 154.7, 147.4, 145.7, 137.8, 135.8, 132.3, 130.6, 129.4, 127.0, 126.9, 125.7, 124.9, 124.0, 114.7, 112.1, 111.7, 64.4, 26.4, 18.0, 14.4; IR (neat): ῡ = 3439, 3296, 2923, 1672, 1648, 1591, 1543, 1521, 1483, 1431, 1335, 1258, 1135, 1033, 741, 584 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{23}H_{21}N_2O_5$: 405.1456, found: 405.1456.

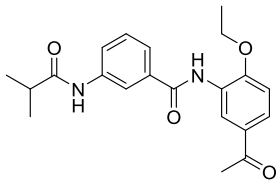
***N*-(5-Acetyl-2-ethoxyphenyl)-3-(*N*-benzylsulfamoyl)-4-methylbenzamide (8)**



Amide **8** was obtained following the general procedure B for amide formation (chromatography: hexane/EtOAc = 1:1). Off-white solid; mp 165-170 °C; Yield: 28 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 7.9, 2.0 Hz, 1H), 7.79 (dd, J = 8.6, 2.2 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.18 – 7.14 (m, 2H), 6.97 (d, J = 8.7 Hz, 1H), 5.07 (t, J = 5.7 Hz, 1H), 5.07 (t, J = 5.7 Hz, 1H), 4.19 (d, J = 5.6 Hz, 2H), 2.69 (s, 3H), 2.61 (s, 3H), 1.55 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz,

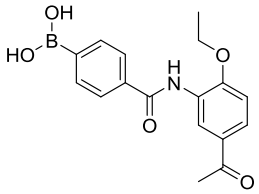
$CDCl_3$): δ = 197.1, 163.5, 151.2, 141.2, 138.9, 135.9, 133.3, 132.9, 131.4, 130.4, 128.7, 128.1, 127.9, 127.5, 127.1, 125.1, 120.5, 110.5, 64.9, 47.3, 26.5, 20.4, 14.7; IR (neat): ῡ = 3348, 3277, 1665, 1590, 1536, 1421, 1329, 1271, 1155, 1139, 1066, 804, 758, 705, 586, 507 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{25}N_2O_5S^-$: 465.1490, found: 465.1492.

_N_-(5-Acetyl-2-ethoxyphenyl)-3-isobutyramidobenzamide (19)



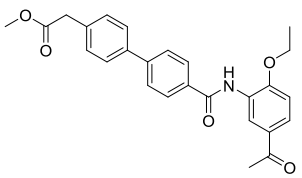
Amide **19** was obtained following the general procedure A for amide formation. White solid; mp 167-170 °C; Yield: 67 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (d, *J* = 2.2 Hz, 1H), 8.64 (s, 1H), 8.12 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.34 (s, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 2.62 (s, 3H), 2.60 – 2.51 (m, 1H), 1.55 (t, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.2, 175.4, 167.2, 165.0, 154.3, 139.8, 139.6, 131.2, 128.9, 128.9, 126.9, 123.7, 123.3, 123.2, 122.2, 121.6, 119.9, 118.4, 111.7, 64.5, 34.9, 26.4, 19.4, 14.4; IR (neat): ῡ = 3279, 2970, 1682, 1657, 1587, 1535, 1426, 1272, 1210, 1134, 948, 753, 686 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{25}N_2O_4^+$: 369.1809, found: 369.1809.

(4-((5-Acetyl-2-ethoxyphenyl)carbamoyl)phenyl)boronic acid (99)



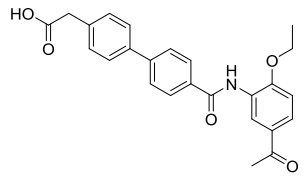
To a solution of 4-boronobenzoic acid (305.7 mg, 1.842 mmol) in dimethylformamide (8.4 mL), 1-(3-amino-4-ethoxyphenyl)ethan-1-one (**2**, 300.0 mg, 1.674 mmol), PyBOP (1.05 g, 2.018 mmol) and DIPEA (360 µL) were added. The reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, HCl (1 M) was added and the obtained precipitate was filtered off. The obtained pale brown solid was used in the next step without further purification.

Methyl 2-(4'-((5-acetyl-2-ethoxyphenyl)carbamoyl)-[1,1'-biphenyl]-4-yl)acetate (100)



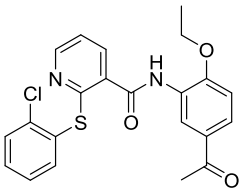
To a solution of (4-((5-acetyl-2-ethoxyphenyl)carbamoyl)phenyl)boronic acid (**99**, 150 mg, 0.458 mmol) in toluene (2.00 mL) and methanol (0.13 mL) $Pd(PPh_3)_4$ (40 mg, 0.045 mmol), methyl 2-(4-bromophenyl)acetate (157 mg, 0.687 mmol) and K_2CO_3 (290 mg, 2.098 mmol) were added.. The reaction mixture was refluxed for 12 h. It was filtered over a pad of celite and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:1, hexane:EtOAc), obaining the desired methyl ester in pure form as a yellow solid (36.4 mg, 18 % yield over two steps). mp 132-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.22 (d, *J* = 2.1 Hz, 1H), 8.64 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.79 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 3H), 3.70 (s, 2H), 2.63 (d, *J* = 7.3 Hz, 3H), 1.55 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2, 171.8, 164.9, 151.0, 144.4, 138.7, 134.0, 133.5, 130.5, 129.9, 127.5, 127.5, 127.4, 124.6, 120.5, 110.4, 64.7, 52.1, 40.8, 26.6, 14.8; IR (neat): ῡ = 3432, 2924, 2853, 1736, 1681, 1606, 1590, 1541, 1432, 1262, 1228, 1146, 1039, 1003, 902, 799, 750, 590, 576 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{26}H_{26}NO_5^-$: 432.1806, found: 432.1808.

2-(4'-((5-Acetyl-2-ethoxyphenyl)carbamoyl)-[1,1'-biphenyl]-4-yl)acetic acid (20)



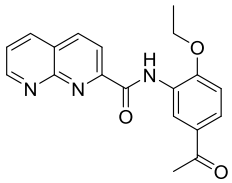
Acid **20** was obtained following the general procedure for ester hydrolysis. Pale brown solid; mp 200-206 °C; Yield: quantitative; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.55 (s, 1H), 8.43 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 3H), 7.71 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.7 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.63 (s, 2H), 2.55 (s, 3H), 1.40 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 169.2, 168.0, 164.8, 159.0, 154.7, 153.1, 150.1, 149.4, 144.4, 140.3, 133.0, 129.3, 128.5, 127.3, 127.0, 116.8, 115.9, 112.9, 111.7, 111.3, 64.4, 26.4, 20.5, 14.4; IR (neat): ῡ = 3432, 2922, 1708, 1676, 1589, 1537, 1486, 1432, 1262, 1148, 1037, 812, 749, 587 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{22}NO_5^-$: 416.1504, found: 416.1503.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-((2-chlorophenyl)thio)nicotinamide (21)**



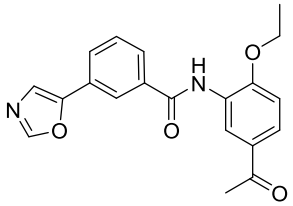
Amide **21** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 2:1). Off-white solid ; mp 133-138 °C; Yield: 44 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (d, J = 1.8 Hz, 1H), 8.99 (s, 1H), 8.44 (dd, J = 4.8, 1.8 Hz, 1H), 8.04 (dd, J = 7.7, 1.8 Hz, 1H), 7.81 (dd, J = 8.6, 2.2 Hz, 1H). 7.68 – 7.56 (m, 1H), 7.51 – 7.44 (m, 1H), 7.36 (td, J = 7.7, 1.9 Hz, 1H), 7.30 (td, J = 7.5, 1.6 Hz, 1H), 7.20 (dd, J = 7.7, 4.8 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 2.63 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 163.9, 156.0, 151.3, 151.0, 138.8, 137.5, 136.9, 130.7, 130.4, 130.4, 130.3, 129.8, 127.5, 127.0, 125.3, 120.8, 120.7, 110.5, 64.8, 26.6, 14.7; IR (neat): ῡ = 2925, 1678, 1659, 1602, 1592, 1533, 1493, 1425, 1392, 1357, 1327, 1272, 1119, 1066, 1037, 751, 586, 419 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{20}ClN_2O_3S^+$: 427.0878, found: 427.0887.

***N*-(5-Acetyl-2-ethoxyphenyl)-1,8-naphthyridine-2-carboxamide (22)**



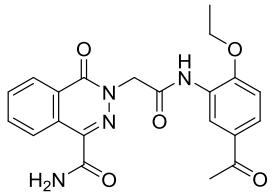
Amide **22** was obtained following the general procedure A for amide formation. Pale yellow solid; mp 216-219 °C; Yield: 79 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.82 (s, 1H), 9.27 (dd, J = 4.1, 1.9 Hz, 1H), 9.09 (d, J = 2.1 Hz, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.64 (dd, J = 8.2, 1.9 Hz, 1H), 8.42 (d, J = 8.3 Hz, 1H), 7.93 – 7.71 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 4.37 (q, J = 6.9 Hz, 2H), 2.57 (s, 3H), 1.53 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.3, 161.3, 155.4, 153.6, 151.7, 151.6, 140.6, 137.7, 129.8, 126.9, 126.0, 124.4, 123.9, 119.2, 118.4, 111.5, 64.9, 26.4, 14.5; IR (neat): ῡ = 3341, 3072, 2996, 1683, 1601, 1590, 1531, 1485, 1433, 1263, 1150, 1112, 1035, 882, 787, 716, 642, 588 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{18}N_3O_3^+$: 336.1339, found: 336.1343.

***N*-(5-Acetyl-2-ethoxyphenyl)-3-(oxazol-5-yl)benzamide (23)**



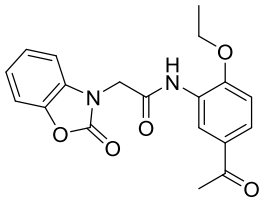
Amide **23** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:2). Off-white solid; mp 147-153 °C; Yield: 38 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.73 (s, 1H), 8.52 (s, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.30 (t, J = 1.6 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.86 (dd, J = 8.6, 2.3 Hz, 1H), 7.81 (s, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 2.54 (s, 3H), 1.39 (t, J = 7.0 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.2, 164.7, 155.0, 152.2, 149.9, 135.3, 129.5, 129.3, 127.7, 127.5, 127.3, 127.1, 126.7, 124.5, 123.2, 122.8, 111.8, 64.4, 26.4, 14.4; IR (neat): ῡ = 3432, 3120, 1679, 1670, 1590, 1534, 1489, 1429, 1360, 1334, 1269, 1256, 1110, 1038, 881, 806, 749, 685, 642, 586, 550, 458 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{19}N_2O_4^+$: 351.1339, found: 351.1344.

3-(2-((5-Acetyl-2-ethoxyphenyl)amino)-2-oxoethyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (24)



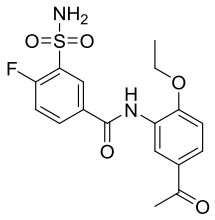
Amide **24** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). White solid; mp 215-219 °C; Yield: 29 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.57 (s, 1H), 8.74 (d, J = 8.1 Hz, 1H), 8.58 (s, 1H), 8.32 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.99 (t, J = 7.7 Hz, 1H), 7.92 (t, J = 7.6 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.17 (d, J = 8.7 Hz, 1H), 5.13 (s, 2H), 4.23 (q, J = 6.9 Hz, 2H), 2.47 (s, 3H), 1.40 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.2, 165.6, 165.1, 158.7, 152.4, 138.0, 133.9, 133.5, 132.1, 129.3, 127.6, 127.2, 126.9, 126.2, 125.8, 121.2, 111.5, 64.4, 26.3, 14.3; IR (neat): ῡ = 3409, 3305, 2923, 1659, 1603, 1594, 1536, 1427, 1273, 1257, 1125, 1035, 809, 590 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{21}N_4O_5^+$: 409.1507, found: 409.1509.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(2-oxobenzo[d]oxazol-3(2*H*)-yl)acetamide (25)**



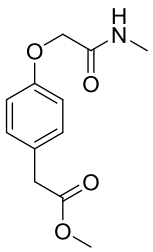
To a solution of 2-(2-oxobenzo[d]oxazol-3(2*H*)-yl)acetic acid (64.7 mg, 0.335 mmol) in dry dichloromethane (1.5 mL) at 0 °C under a nitrogen atmosphere, one drop of dry dimethylformamide and oxalyl chloride (29 µL, 0.335 mmol) were added. The solution was stirred for 1.5 hours at 0 °C, it was concentrated under reduced pressure and dry dichloromethane (1.5 mL) was added. 1-(3-amino-4-ethoxyphenyl)ethan-1-one (**2**, 50.0 mg, 0.279 mmol) and dry triethylamine (55 µL, 0.391 mmol) were added. The reaction mixture was stirred at room temperature for 12 h, concentrated under reduced pressure and the residue was then purified by flash column chromatography (hexane:EtOAc = 1:1). The desired amide was obtained as a pale yellow solid in pure form (28 mg, 29 % yield). mp 88-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.92 (d, J = 1.9 Hz, 1H), 8.29 (s, 1H), 7.75 (dd, J = 8.6, 2.2 Hz, 1H), 7.29-7.26 (m, 1H), 7.24 – 7.16 (m, 2H), 7.13 – 7.07 (m, 1H), 6.88 (d, J = 8.6 Hz, 1H), 4.66 (s, 2H), 4.09 (q, J = 7.0 Hz, 2H), 2.56 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.9, 163.7, 154.6, 150.9, 142.7, 130.4, 130.3, 126.3, 125.5, 124.5, 123.4, 120.4, 110.4, 110.4, 108.9, 64.7, 46.5, 26.5, 14.3; IR (neat): ῡ = 3161, 2943, 1746, 1682, 1587, 1486, 1435, 1394, 1366, 1269, 1236, 1110, 1025, 924, 752, 684, 603, 537 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{19}N_2O_5^+$: 355.1289, found: 355.1289

***N*-(5-Acetyl-2-ethoxyphenyl)-4-fluoro-3-sulfamoylbenzamide (26)**



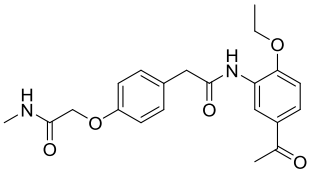
Amide **26** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Off-white solid; Yield: 6 %; ^{1}H NMR (300 MHz, DMSO-δ_6): δ = 9.81 (s, 1H), 8.44 (dd, J = 6.9, 2.2 Hz, 1H), 8.38 (dd, J = 7.4, 2.1 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H), 8.09 (ddd, J = 8.0, 4.7, 2.0 Hz, 2H), 7.85 (dd, J = 8.6, 2.2 Hz, 1H), 7.71 (s, 2H), 7.38 (td, J = 9.8, 3.4 Hz, 2H), 7.21 (d, J = 8.7 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.54 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.2, 163.3, 159.86 (d, J = 257.8 Hz), 155.3, 133.57 (d, J = 9.3 Hz), 131.75 (d, J = 15.6 Hz), 130.74 (d, J = 3.3 Hz), 129.3, 128.4, 127.6, 126.5, 125.0, 117.38 (d, J = 22.0 Hz), 112.0, 64.4, 26.4, 14.4; IR (neat): ῡ = 2923, 2853, 1731, 1666, 1601, 1538, 1465, 1262, 1126, 1071, 800 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{18}FN_2O_5S^+$: 381.0915, found: 381.0913.

Methyl 2-(4-(2-(methylamino)-2-oxoethoxy)phenyl)acetate (101)



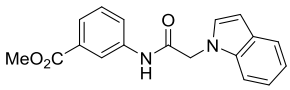
To a solution of methyl 2-(4-hydroxyphenyl)acetate (300 mg, 1.81 mmol) in dimethylformamide (6.2 mL), NaI (541 mg, 3.61 mmol), 2-chloro-*N*-methylacetamide (388 mg, 3.61 mmol) and K_2CO_3 (998 mg, 7.22 mmol) were added. The reaction mixture was stirred at 80 °C for 24 h. It was concentrated under reduced pressure and diluted with water and dichloromethane. The aqueous layer was extracted with dichloromethane three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by flash column chromatography (EtOAc = 100 %), furnishing the desired product in 34 % yield (146 mg). White solid; mp 86-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.48 (s, 2H), 3.69 (s, 3H), 3.58 (s, 2H), 2.91 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 168.7, 156.3, 130.6, 127.6, 114.7, 67.4, 52.0, 40.2, 25.7; IR (neat): ῡ = 3296, 2958, 1725, 1650, 1549, 1509, 1439, 1309, 1276, 1258, 1223, 1179, 1140, 1055, 1010, 820, 585, 532 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{16}NO_4^+$: 238.1074, found: 238.1074.

_N_-(5-Acetyl-2-ethoxyphenyl)-2-(4-(2-(methylamino)-2-oxoethoxy)phenyl)acetamide (27)



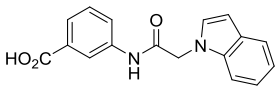
Amide **27** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). White solid; Yield: 20 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.00 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.44 (s, 2H), 4.15 (q, *J* = 6.9 Hz, 2H), 3.69 (s, 2H), 2.65 (d, *J* = 4.6 Hz, 3H), 2.48 (s, 3H), 1.34 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.3, 169.6, 168.0, 156.6, 152.5, 130.4, 129.3, 128.4, 127.2, 125.9, 121.1, 114.7, 111.3, 67.1, 64.4, 42.3, 26.3, 25.3, 14.4; IR (neat): ῡ = 3287, 2924, 2853, 1656, 1604, 1543, 1511, 1427, 1331, 1262, 1224, 1038, 800, 709, 695, 575, 547 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{25}N_2O_5^+$: 385.1758, found: 385.1754.

Methyl 3-(2-(1*H*-indol-1-yl)acetamido)benzoate (102)



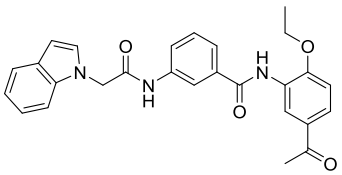
Amide **102** was obtained following the general procedure A for amide formation. Pink solid; mp 170-174 °C; Yield: 46 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 – 7.74 (m, 2H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 7.24 – 7.19 (m, 1H), 7.16 (d, *J* = 3.1 Hz, 1H), 7.04 (s, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 4.95 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 166.4, 136.7, 136.2, 130.9, 129.1, 128.9, 128.0, 126.1, 124.7, 123.2, 121.6, 121.1, 120.9, 109.1, 104.4, 52.3, 50.6; IR (neat): ῡ = 3274, 1720, 1671, 1548, 1487, 1295, 1240, 1201, 1107, 1079, 758, 744, 684, 425 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{17}N_2O_3^+$: 309.1234, found: 309.1234.

3-(2-(1*H*-Indol-1-yl)acetamido)benzoic acid (103)



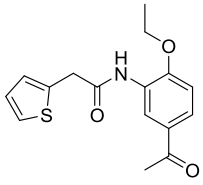
Benzoic acid **103** was obtained following the general procedure for ester hydrolysis. Pink solid; mp 245-250 °C; Yield: 85 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.94 (s, 1H), 10.58 (s, 1H), 8.23 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 3.1 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 2.9 Hz, 1H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.0, 166.6, 138.9, 136.4, 131.4, 129.9, 129.1, 128.1, 124.2, 123.2, 121.1, 120.3, 119.9, 119.1, 109.7, 100.8, 49.1; IR (neat): ῡ = 3265, 1672, 1590, 1542, 1454, 1421, 1318, 1273, 1252, 1204, 947, 756, 733, 714, 680, 426 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{15}N_2O_3^+$: 295.1077, found: 295.1076.

3-(2-(1*H*-Indol-1-yl)acetamido)-*N*-(5-acetyl-2-ethoxyphenyl)benzamide (28)



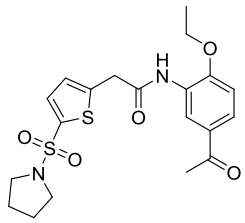
Amide **28** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Pale brown solid; mp 212-215 °C; Yield: 26 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.59 (s, 1H), 9.45 (s, 1H), 8.39 (s, 1H), 8.18 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.47 (s, 1H), 5.09 (s, 2H), 4.19 (q, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 1.35 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 166.7, 164.9, 154.5, 139.0, 136.4, 135.1, 129.9, 129.4, 129.2, 128.1, 127.0, 126.9, 123.6, 122.2, 122.1, 121.1, 120.3, 119.1, 118.5, 111.7, 109.7, 100.8, 64.4, 49.2, 26.4, 14.4; IR (neat): ϋ = 3439, 3278, 1682, 1592, 1531, 1434, 1258, 1145, 739, 585 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{27}H_{26}N_3O_4^+$: 456.1918, found: 456.1919.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(thiophen-2-yl)acetamide (104)**



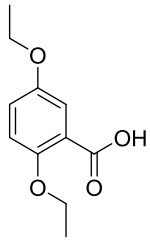
Amide **104** was obtained following the general procedure A for amide formation. Brown solid; mp 104-110 °C; Yield: 55 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (d, *J* = 2.1 Hz, 1H), 8.09 (s, 1H), 7.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.07 (s, 1H), 7.07 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 4.00 (s, 2H), 2.57 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 167.8, 150.9, 135.5, 130.3, 128.0, 127.6, 127.0, 126.1, 124.7, 120.0, 110.2, 64.5, 38.7, 26.6, 14.6; IR (neat): ϋ = 3378, 2924, 1684, 1597, 1529, 1429, 1251, 1140, 1124, 1032, 804, 702, 639, 530 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{18}NO_3S^+$: 304.1002, found: 304.1001.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(5-(pyrrolidin-1-ylsulfonyl)thiophen-2-yl)acetamide (29)**



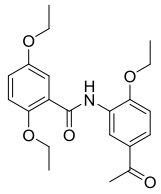
To a solution of N-(5-acetyl-2-ethoxyphenyl)-2-(thiophen-2-yl)acetamide (**104**, 50 mg, 0.165 mmol) in dichloromethane (2 mL), chlorosulfuric acid (54 µL, 0.816 mmol) was added at -78 °C. The reaction mixture was allowed to warm to room temperature over 5 hours. It was poored on ice and extracted with dichloromethane three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was re-dissolved in dimethylformamide (1.1 mL), and a solution of pyrrolidine (15 µL, 0.182 mmol) and DIEA (62 µL) in dichloromethane (2.0 mL) was added. The reaction was stirred at room temperature overnight. It was diluted with water and extracted with dichloromethane three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc, 1:1) obtaining the desired sulfonamide in 14 % yield over two steps (10 mg, 0.024 mmol). White solid; mp 106-110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.96 (d, *J* = 2.0 Hz, 1H), 7.95 (s, 1H), 7.75 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.52 (d, *J* = 3.7 Hz, 1H), 7.09 (d, *J* = 3.7 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.01 (s, 2H), 3.40 – 3.23 (m, 4H), 2.58 (s, 3H), 1.91 – 1.73 (m, 4H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.0, 166.2, 150.9, 142.3, 137.3, 132.2, 130.4, 127.7, 126.7, 125.2, 120.2, 110.3, 64.7, 48.2, 38.9, 26.5, 25.4, 14.7; IR (neat): ϋ = 3362, 2926, 1678, 1601, 1535, 1432, 1344, 1264, 1154, 1014, 611, 430 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{25}N_2O_5S^+$: 437.1199, found: 437.1200.

2,5-Diethoxybenzoic acid (105)



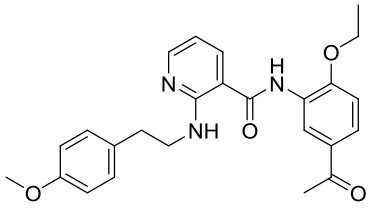
A solution of methyl 2,5-dihydroxybenzoate (1.50 g, 8.92 mmol), EtI (1.43 mL, 17.84 mmol) and K_2CO_3 (4.93 g, 35.68 mmol) in dimethylformamide (30.0 mL) was heated to 80 °C for 12 h. Water and NH_4Cl saturated aqueous solution were added to the reaction mixture and it was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:1 hexane/EtOAc) affording the desired ester in 66 % yield. The latter was then hydrolized following the general procedure for ester hydrolysis but after concentration under reduce pressure, the pH of the water phase was brought to pH 1 by addition of HCl (1 M) and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure affording the pure carboxylic acid in 96 % yield. Brown solid; mp 38-41 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.55 (s, 1H), 7.16 – 7.09 (m, 1H), 7.03 (s, 1H), 7.03 (s, 1H), 4.00 (dq, *J* = 13.8, 7.0 Hz, 4H), 1.29 (td, *J* = 7.0, 3.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.1, 151.9, 151.3, 122.7, 118.9, 115.8, 115.6, 65.0, 63.5, 14.7, 14.7; IR (neat): ῡ = 2978, 2933, 1692, 1657, 1498, 1471, 1447, 1393, 1319, 1287, 1243, 1224, 1149, 1111, 1049, 1037, 959, 810, 754, 410 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{13}O_4^-$: 209.0819, found: 209.0818.

***N*-(5-Acetyl-2-ethoxyphenyl)-2,5-diethoxybenzamide (30)**



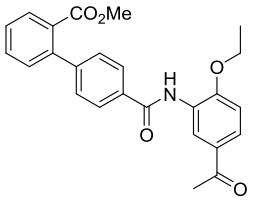
Amide **30** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 2:3). Pale brown solid; mp 69-74 °C; Yield: 62 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.51 (s, 1H), 9.11 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.23 (d, *J* = 5.3 Hz, 1H), 7.20 (d, *J* = 4.8 Hz, 1H), 7.14 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.49 – 4.22 (m, 4H), 4.03 (q, *J* = 6.9 Hz, 2H), 2.54 (s, 3H), 1.42 (t, *J* = 6.9 Hz, 6H), 1.33 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.3, 162.4, 152.6, 151.1, 150.2, 129.6, 127.7, 125.3, 122.1, 120.1, 119.7, 115.9, 115.6, 111.1, 65.6, 64.5, 63.5, 26.4, 14.6, 14.5, 14.3; IR (neat): ῡ = 3315, 2981, 2929, 1666, 1579, 1541, 1491, 1474, 1433, 1265, 1228, 1194, 1162, 1046, 827, 790, 559 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{26}NO_5^+$: 372.1806, found: 372.1812.

***N*-(5-acetyl-2-ethoxyphenyl)-2-((4-methoxyphenethyl)amino)nicotinamide (31)**



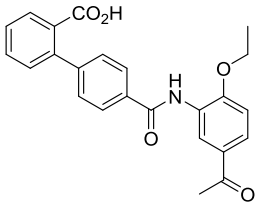
In a 100 ml round bottom flask equipped with a condenser, *N*-(5-acetyl-2-ethoxyphenyl)-2-bromonicotinamide (100 mg, 0.30 mmol, obtained using general procedure A for amide formation but used impure even after column chromatography: toluene/EtOAc = 1:1) and 4-methoxyphentylamine (136 mg, 0.90 mmol) were dissolved in isopropanol (1 ml). The reaction mixture was heated to 110 °C for 18 h and then concentrated under reduced pressure to give a crude (80 mg) which was column chromatographed (2:1 Hex/EtOAc). Further purification by column chromatography (8:1 Toluene:AcOEt) gave the desired product in pure form (14 mg, 0.03 mmol, 10 % over two steps) as orange crystals. mp 53-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.03 (d, *J* = 2.0 Hz, 1H), 8.43 (s, 1H), 8.33 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.1 Hz, 2H), 7.75 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.64 (t, *J* = 5.3 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.88 – 3.80 (m, 5H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.65 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 166.1, 158.1, 158.0, 152.2, 151.1, 135.1, 131.7, 130.4, 129.8, 127.3, 124.8, 120.4, 113.8, 110.5, 110.3, 110.1, 64.7, 55.2, 42.9, 35.0, 26.5, 14.7; IR (neat): ῡ = 3439, 3322, 2978, 1682, 1650, 1596, 1577, 1535, 1509, 1425, 1333, 1257, 1030, 815, 765, 589 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{28}N_3O_4^+$: 434.2080, found: 434.2080.

Methyl 4'-((5-acetyl-2-ethoxyphenyl)carbamoyl)-[1,1'-biphenyl]-2-carboxylate (106)



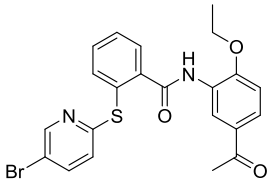
To a solution of (4-((5-acetyl-2-ethoxyphenyl)carbamoyl)phenyl)boronic acid (**99**, 150 mg, 0.458 mmol) in tetrahydrofuran (1.1 mL) $Pd(PPh_3)_2Cl_2$ (3.2 mg, 0.0046 mmol) and a solution of Na_2CO_3 (97 mg, 0.916 mmol) in 1.1 mL of water were added. The reaction mixture was stirred at room temperature for 2 minutes, and methyl 2-iodobenzoate (180 mg, 0.687 mmol) were added. The reaction mixture was stirred at 80 °C for 12 h. It was extracted three times with dichloromethane, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:1, hexane:EtOAc), obtaining the desired methyl ester in pure form as an off-white solid (88.6 mg, 46 % yield over two steps). mp 142-148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.58 (s, 1H), 8.40 (d, *J* = 2.2 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.85 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.82 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.68 (td, *J* = 7.6, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.63 (s, 3H), 2.55 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.2, 168.1, 164.8, 154.7, 143.9, 140.5, 133.1, 131.7, 130.6, 129.5, 129.3, 128.4, 128.0, 127.4, 127.1, 126.9, 124.1, 111.7, 64.4, 52.0, 26.4, 14.4; IR (neat): ῡ = 3437, 2924, 1729, 1675, 1591, 1541, 1437, 1345, 1261, 1119, 1035, 853, 810, 743, 697, 573, 530 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{22}NO_5^-$: 416.1504, found: 416.1504.

4'-((5-Acetyl-2-ethoxyphenyl)carbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (32)



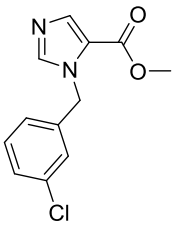
Acid **32** was obtained following the general procedure for ester hydrolysis. Off-white solid; mp 169-174 °C; Yield: 45 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.85 (br. s., 1H), 9.57 (s, 1H), 8.41 (d, *J* = 2.2 Hz, 1H), 8.20 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.56 (s, 1H), 7.54 – 7.47 (m, 3H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 4.23 (q, *J* = 6.9 Hz, 2H), 2.55 (s, 3H), 1.40 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 172.6, 164.8, 154.6, 143.1, 137.3, 135.3, 133.0, 130.1, 129.4, 128.2, 127.0, 126.7, 126.6, 123.9, 111.7, 64.4, 26.4, 14.4; IR (neat): ῡ = 3416, 3078, 1718, 1683, 1594, 1539, 1436, 1398, 1369, 1260, 1184, 1138, 1024, 906, 863, 807, 748, 632 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{22}NO_5^+$: 404.1493, found: 404.1494.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-((5-bromopyridin-2-yl)thio)benzamide (33)**



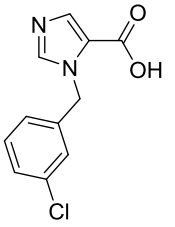
Amide **33** was obtained following the general procedure A for amide formation (chromatography: toluene/EtOAc = 10:1). Brown solid; mp 213-216 °C; Yield: 46%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.02 (d, *J* = 1.9 Hz, 1H), 8.94 (s, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 7.85 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1H), 7.51 (td, *J* = 7.5, 1.7 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 2.58 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 165.9, 157.8, 151.3, 149.9, 141.0, 140.0, 136.5, 131.4, 130.2, 130.1, 129.7, 127.7, 127.2, 125.0, 124.3, 121.1, 117.4, 110.5, 64.6, 26.6, 14.6; IR (neat): ῡ = 3412, 2925, 1672, 1588, 1525, 1427, 1253, 1150, 1002, 746, 625, 585 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{20}BrN_2O_3S^+$: 471.0373, found: 471.0372.

Methyl 1-(3-chlorobenzyl)-1*H*-imidazole-5-carboxylate (107)



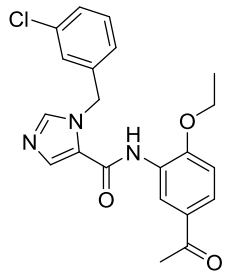
A solution of methyl 1*H*-imidazole-5-carboxylate (0.85 g, 6.71 mmol), 1-(bromomethyl)-3-chlorobenzene (0.87 mL, 6.65 mmol) and K_2CO_3 (1.10 g, 7.98 mmol) in dimethylformamide (22.0 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and redissolved in toluene and ethylacetate. The organic phase was extracted with water and dried over $MgSO_4$. It was then concentrated under reduced pressure and purified by flash column chromatography (EtOAc 100 % to 10% MeOH in EtOAc) obtaining the desired product in pure form in 30 % yield. White solid; mp 77-83 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.20 (s, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.22 (s, 1H), 7.12 – 7.05 (m, 1H), 5.53 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 159.9, 143.7, 140.0, 137.5, 133.2, 130.5, 127.6, 126.8, 125.5, 121.6, 51.4, 48.3; IR (neat): ῡ = 3104, 1716, 1542, 1475, 1428, 1363, 1292, 1259, 1230, 1195, 1129, 1110, 851, 782, 766, 688, 680, 659 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{12}ClN_2O_2^+$: 251.0582, found: 251.0578.

1-(3-Chlorobenzyl)-1*H*-imidazole-5-carboxylic acid (108)



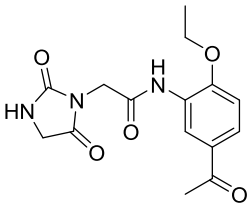
Acid **108** was obtained following the general procedure for ester hydrolysis but after concentration under reduce pressure, the pH of the water phase was brought to pH 1 by addition of HCl (1 M) and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was used without further purification. White solid; mp 265-268 °C; Yield: 30 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.78 (s, 1H), 8.00 (s, 1H), 7.43 – 7.32 (m, 2H), 7.26 (s, 1H), 7.19 – 7.07 (m, 1H), 5.60 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.3, 141.6, 139.1, 133.8, 132.0, 131.2, 128.5, 127.6, 126.4, 124.0, 49.9; IR (neat): ῡ = 3097, 2999, 1686, 1466, 1443, 1253, 1171, 1109, 862, 731, 686, 676, 642 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{10}ClN_2O_2^+$: 237.0425, found: 237.0425.

***N*-(5-Acetyl-2-ethoxyphenyl)-1-(3-chlorobenzyl)-1*H*-imidazole-5-carboxamide (34)**



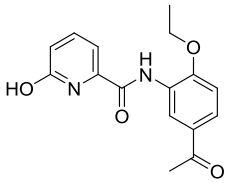
Amide **34** was obtained following the general procedure A for amide formation (chromatography: EtOAc/MeOH = 100:0 to 100:5). Pale yellow solid; mp 141-147 °C; Yield: 64 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.46 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 8.12 (s, 1H), 7.87 (s, 1H), 7.83 (dd, J = 8.6, 2.2 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.23 (s, 1H), 7.19 – 7.10 (m, 2H), 5.59 (s, 2H), 4.15 (q, J = 6.9 Hz, 2H), 2.51 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.2, 158.2, 154.9, 142.6, 140.5, 133.6, 133.1, 130.4, 129.3, 127.5, 127.3, 126.9, 126.2, 125.7, 124.8, 124.3, 111.8, 64.3, 48.0, 26.4, 14.3; IR (neat): ῡ = 3421, 3112, 1666, 1590, 1542, 1488, 1468, 1430, 1357, 1264, 1224, 1142, 1095, 1072, 1039, 869, 749, 658, 585, 556, 415 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{21}ClN_3O_3^+$: 398.1266, found: 398.1266.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(2,5-dioxoimidazolidin-1-yl)acetamide (35)**



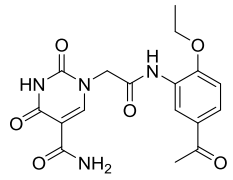
Amide **35** was obtained following the general procedure A for amide formation (chromatography: DCM/MeOH = 100:3). White solid; Yield: 37 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1H), 8.12 (s, 1H), 7.74 (dd, J = 8.6, 2.2 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 6.01 (s, 1H), 4.39 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H), 4.12 (d, J = 0.9 Hz, 2H), 2.55 (s, 3H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 170.8, 163.9, 157.3, 150.7, 130.2, 126.6, 125.1, 120.5, 110.4, 64.7, 46.7, 42.1, 26.5, 14.6; IR (neat): ῡ = 3302, 2937, 1713, 1672, 1591, 1542, 1432, 1330, 1268, 1206, 1147, 1040, 914, 804, 635, 568 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{18}N_3O_5^+$: 320.1241, found: 320.1245.

***N*-(5-Acetyl-2-ethoxyphenyl)-6-hydroxypicolinamide (36)**



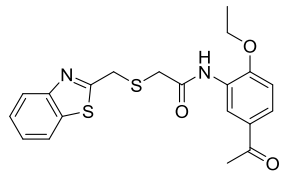
Amide **36** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Pale yellow oil; Yield: 48 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.25 (s, 1H), 10.29 (s, 1H), 9.01 (s, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 6.7 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.31 (q, J = 6.8 Hz, 2H), 2.54 (s, 3H), 1.48 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.3, 162.6, 161.5, 151.5, 141.0, 129.7, 127.0, 125.7, 118.7, 114.1, 111.4, 64.8, 26.4, 14.4; IR (neat): ῡ = 3304, 3129, 1673, 1656, 1583, 1541, 1497, 1433, 1364, 1334, 1277, 1263, 1038, 967, 892, 817, 743, 594 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{17}N_2O_4^+$: 301.1183, found: 301.11873.

1-(2-((5-Acetyl-2-ethoxyphenyl)amino)-2-oxoethyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (37)



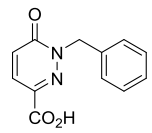
Amide **37** was obtained following the general procedure A for amide formation, but after work-up, diethylether was added to the concentrated residue and the resulting precipitate was filtered off. Pale brown solid; mp 255-260 °C; Yield: 7 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.92 (s, 1H), 9.65 (s, 1H), 8.57 (s, 2H), 8.14 (d, J = 3.7 Hz, 1H). 7.75 (dd, J = 8.6, 2.0 Hz, 1H). 7.52 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 4.86 (s, 2H), 4.23 (q, J = 7.0 Hz, 2H), 2.49 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 191.9, 165.8, 163.5, 163.0, 152.6, 150.3, 129.3, 126.7, 126.0, 121.4, 111.4, 104.7, 64.4, 50.9, 26.3, 14.4; IR (neat): ῡ = 3454, 1677, 1579, 1454, 1266, 1219, 1127, 1032, 809, 584, 419 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{19}N_4O_6^+$: 375.1299, found: 375.1300.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-((benzo[d]thiazol-2-ylmethyl)thio)acetamide (38)**



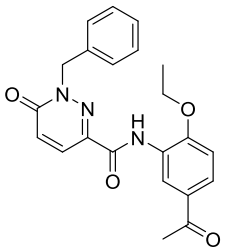
Amide **38** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:2). Light brown solid; mp 119-122 °C; Yield: 39 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 7.95 (ddd, J = 8.2, 1.1, 0.6 Hz, 1H), 7.80 (ddd, J = 8.0, 1.2, 0.6 Hz, 1H), 7.72 (dd, J = 8.6, 2.2 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.40 – 7.31 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 4.30 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.57 (s, 2H), 2.54 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 166.1, 151.3, 130.2, 126.8, 126.6, 125.8, 124.9, 122.7, 121.7, 120.7, 110.3, 64.6, 37.0, 33.7, 26.5, 14.7; IR (neat): ῡ = 3327, 2977, 1667, 1592, 1537, 1493, 1427, 1360, 1272, 1200, 1129, 1036, 808, 760, 630, 589 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{21}N_2O_3S_2^+$: 401.0988, found: 401.0990.

1-Benzyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (109)



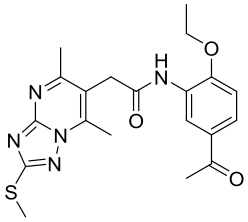
To a solution of methyl 6-oxo-1,6-dihydropyridazine-3-carboxylate (300 mg, 1.946 mmol) in dimethylformamide (4.5 mL), benzyl bromide (254 µL, 2.138 mmol) and K_2CO_3 (807 mg, 5.839 mmol) were added. The reaction was stirred at room temperature for 4 h. NaOH (1 M, 5.0 mL) was then added to the reaction mixture and it was stirred at 60 °C for 3 h. Concentrated HCl was added until pH = 1 and the resulting precipitate was filtered off yielding the desired carboxylic acid in pure form (336 mg, 75 % yield). White solid; mp 216-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.63 (s, 1H), 7.86 (d, J = 9.7 Hz, 1H), 7.40 – 7.23 (m, 5H), 7.04 (d, J = 9.7 Hz, 1H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.3, 159.3, 136.9, 136.1, 132.0, 129.1, 128.6, 127.8, 127.7, 55.0; IR (neat): ῡ = 3071, 2800, 2503, 1713, 1625, 1573, 1523, 1426, 1260, 1130, 914, 854, 762, 727, 696, 623 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{11}N_2O_3^+$: 231.0764, found: 231.0764.

***N*-(5-Acetyl-2-ethoxyphenyl)-1-benzyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (39)**



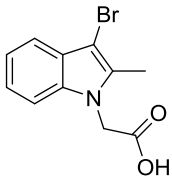
Amide **39** was obtained following the general procedure A for amide formation. Pale gray solid; mp 168-174 °C; Yield: 52 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.65 (s, 1H), 8.84 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 9.7 Hz, 1H), 7.79 (dd, J = 8.6, 2.1 Hz, 1H), 7.45 – 7.32 (m, 5H), 7.20 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 9.7 Hz, 1H), 5.35 (s, 2H), 4.24 (q, J = 6.9 Hz, 2H), 2.53 (s, 3H), 1.41 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.2, 159.2, 158.8, 151.5, 137.7, 135.9, 130.2, 129.9, 129.7, 128.6, 128.1, 128.0, 126.4, 126.1, 118.6, 111.3, 64.8, 54.8, 26.4, 14.4; IR (neat): ῡ = 3377, 1664, 1590, 1535, 1488, 1431, 1258, 1138, 1110, 1036, 740, 698, 589, 510 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{22}N_3O_4^+$: 392.1605, found: 392.1602.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(5,7-dimethyl-2-(methylthio)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)acetamide (40)**



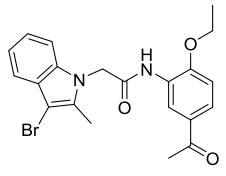
Amide **40** was obtained following the general procedure A for amide formation. Off-white solid; mp 215-218 °C; Yield: 28 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.43 (s, 1H), 8.35 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 4.04 (s, 2H), 2.78 (s, 3H), 2.65 (s, 3H), 2.62 (s, 3H), 2.48 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.2, 167.8, 166.3, 164.2, 153.7, 145.4, 129.3, 126.7, 123.0, 115.8, 111.5, 64.4, 35.0, 26.3, 23.8, 14.4, 14.2, 13.3; IR (neat): ῡ = 3263, 2975, 2931, 1673, 1605, 1530, 1514, 1432, 1343, 1293, 1260, 1143, 1038, 808, 592 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{24}N_5O_3S^+$: 414.1594, found: 414.1596.

2-(3-Bromo-2-methyl-1*H*-indol-1-yl)acetic acid (110)[33]



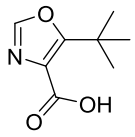
Methyl 2-(3-bromo-2-methyl-1*H*-indol-1-yl)acetate was synthesized as previously reported. The methyl ester was hydrolysed to the carboxylic acid following the general procedure for ester hydrolysis and further purified by flash column chromatography (5 % MeOH in DCM and reverse phase (MeOH)) to obtain the desired product in 76 % yield. Purple solid; mp 107-111 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.46 (dd, J = 7.1, 1.2 Hz, 1H), 7.34 (dd, J = 6.9, 1.7 Hz, 1H), 7.19-7.09 (m, 2H), 5.06 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.3, 136.0, 134.9, 126.2, 121.9, 120.3, 117.5, 109.9, 88.7, 45.0, 10.8; IR (neat): ῡ = 3029, 2916, 1711, 1460, 1398, 1248, 1210, 1167, 740, 618, 605, 424 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{11}NBrO_2^+$: 267.9968, found: 267.9969.

***N*-(5-Acetyl-2-ethoxyphenyl)-2-(3-bromo-2-methyl-1H-indol-1-yl)acetamide (41)**



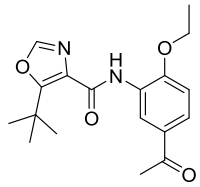
Amide **41** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Light brown solid; mp 122-130 °C; Yield: 63 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.30 (s, 1H), 8.54 (d, J = 1.9 Hz, 1H), 7.74 (dd, J = 8.6, 2.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.24 – 7.06 (m, 3H), 5.24 (s, 2H), 4.17 (q, J = 6.9 Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.1, 166.5, 152.4, 136.0, 134.9, 129.4, 126.6, 126.3, 126.2, 122.0, 120.3, 117.6, 111.4, 109.9, 88.9, 64.4, 46.9, 26.3, 14.3, 10.8; IR (neat): ῡ = 3390, 2974, 2927, 1689, 1672, 1595, 1536, 1356, 1329, 1264, 1126, 1032, 812, 740, 633, 590 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{22}BrN_2O_3^+$: 429.0808, found: 429.0816.

5-(Tert-butyl)oxazole-4-carboxylic acid (111)[34]



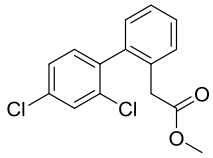
Ethyl 5-(tert-butyl)oxazole-4-carboxylate was synthesized as previously reported and the hydrolysis of the ethyl ester to the carboxylic acid was performed following the general procedure for ester hydrolysis to obtain the desired product in 91 % yield. Off-white solid; mp 114-117 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.97 (s, 1H), 8.25 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.2, 163.5, 148.5, 126.0, 32.8, 27.9; IR (neat): ῡ = 3130, 2965, 2872, 1703, 1581, 1530, 1284, 1246, 1189, 1119, 1047, 1010, 739, 645, 614 cm^{-1}; HRMS (ESI): m/z: calcd for $C_8H_{10}NO_3^-$: 168.0666, found: 168.0665.

_N_-(5-Acetyl-2-ethoxyphenyl)-5-(tert-butyl)oxazole-4-carboxamide (42)



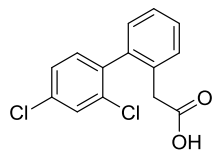
Amide **42** was obtained following the general procedure B for amide formation (chromatography: hexane/EtOAc = 5:1). Pale brown solid; mp 180-188 °C; Yield: 30 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.70 (s, 1H), 8.93 (d, J = 2.2 Hz, 1H), 8.44 (s, 1H), 7.78 (dd, J = 8.6, 2.2 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 4.27 (q, J = 6.9 Hz, 2H), 2.54 (s, 3H), 1.46 (s, 9H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.4, 163.4, 158.8, 151.3, 148.5, 129.7, 127.1, 125.8, 118.2, 111.2, 64.8, 32.8, 27.8, 26.5, 14.5; IR (neat): ῡ = 3365, 3110, 2968, 1684, 1660, 1578, 1522, 1435, 1261, 1211, 1139, 1104, 1035, 1013, 802, 650, 598 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{22}N_2O_4Na^+$: 353.1472, found: 353.1470.

Methyl 2-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)acetate (112)



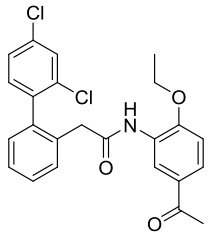
Methyl-2-bromophenyl acetate (0.50 g, 2.2 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.1 mmol) were added to dimethoxyethane (25 ml). K_2CO_3 (0.75 g, 5.5 mmol) was dissolved in water (5 ml), the solution was purged with N_2 and added to the reaction mixture. 2,4-Dichlorophenylboronic acid (6.24 g, 3.3 mmol) was dissolved in dimethoxyethane (20 ml), the solution was purged with N_2 and added to the reaction mixture which was then heated to 100 °C for 17 h. The reaction mixture was dissolved in water (50 ml), extracted with dichloromethane (2x30 ml), dried over $MgSO_4$ and the solvent was evaporated to give a crude colourless oil (425 mg). The crude was purified by column chromatography (5:95 hexane/EtOAc) to afford the desired product as a colourless oil (0.30 g, 1.0 mmol, 47 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, J = 2.1 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 7.17 – 7.12 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H). 7.03 (d, J = 7.1 Hz, 1H), 3.45 (s, 3H), 3.35 (dd, J = 34.9, 16.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 138.4, 137.9, 134.1, 134.1, 132.4, 132.3, 130.2, 129.9, 129.2, 128.5, 127.2, 126.9, 51.9, 38.6; IR (neat): ῡ = 3061, 2950, 1736, 1468, 1435, 1211, 1156, 1100, 1006, 824, 804, 761, 563 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{13}Cl_2O_2^+$: 295.0287, found: 295.0287.

2-(2',4'-Dichloro-[1,1'-biphenyl]-2-yl)acetic acid (113)



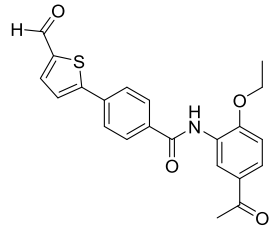
Acid **113** was obtained following the general procedure for ester hydrolysis. White solid; mp 102-104 °C; Yield: 76 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 2.0 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.30 – 7.26 (m, 1H), 7.20 (s, 1H), 7.20 – 7.15 (m, 1H), 3.49 (dd, J = 35.9, 16.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6, 138.5, 137.7, 134.2, 134.1, 132.3, 131.7, 130.3, 130.0, 129.2, 128.6, 127.5, 127.0, 38.4; IR (neat): ῡ = 3057, 3027, 1698, 1464, 1417, 1241, 1099, 932, 868, 821, 807, 763, 683 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_9Cl_2O_2^-$: 278.9985, found: 278.9983.

3-(2-(1*H*-Indol-1-yl)acetamido)-*N*-(5-acetyl-2-ethoxyphenyl)benzamide (43)



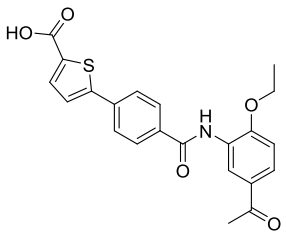
Amide **43** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:1). White solid; mp 53-55 °C; Yield: 86 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 2.2 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.69 (s, 1H), 7.49 (s, 1H), 7.48 – 7.47 (m, 2H), 7.46 – 7.38 (m, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 4.12 – 3.91 (m, 2H), 3.60 (dd, *J* = 16.5, 16.5 Hz, 2H), 2.55 (s, 3H), 1.26 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 168.5, 150.6, 138.9, 137.5, 134.4, 133.9, 132.6, 131.9, 130.6, 130.5, 130.2, 129.4, 129.1, 127.8, 127.2, 126.9, 124.5, 119.9, 110.1, 64.4, 42.6, 26.6, 14.6; IR (neat): ῡ = 2924, 1678, 1588, 1529, 1467, 1428, 1259, 1127, 1009, 806, 763, 533 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{22}Cl_2NO_3^+$: 442.0971, found: 442.0974.

_N_-(5-Acetyl-2-ethoxyphenyl)-4-(5-formylthiophen-2-yl)benzamide (114)



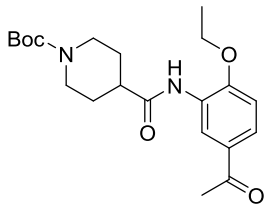
To a solution of (4-((5-acetyl-2-ethoxyphenyl)carbamoyl)phenyl)boronic acid (150 mg, 0.458 mmol) in tetrahydrofuran (1.1 mL) $Pd(PPh_3)_2Cl_2$ (3.2 mg, 0.0046 mmol) and a solution of Na_2CO_3 (97 mg, 0.916 mmol) in 1.1 mL of water were added. The reaction mixture was stirred at room temperature for 2 minutes, and methyl 5-bromothiophene-2-carbaldehyde (81.7 µL, 0.687 mmol) were added. The reaction mixture was stirred at 80 °C for 12 h. It was extracted three times with dichloromethane, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane:EtOAc = 1:1), obaining the desired methyl ester in pure form as a yellow solid (98.0 mg, 54 % yield over two steps). mp 188-191 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 9.95 (s, 1H), 9.64 (s, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 4.0 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 4.0 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 2.54 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ = 196.2, 184.3, 164.4, 154.8, 151.1, 142.9, 139.2, 135.4, 134.8, 129.4, 128.6, 127.2, 126.8, 126.5, 126.3, 124.2, 111.8, 64.4, 26.4, 14.4; IR (neat): ῡ = 3436, 2927, 1663, 1591, 1537, 1489, 1433, 1266, 1218, 1148, 1120, 1039, 803, 756, 582 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{20}NO_4S^+$: 394.1108, found: 394.1111.

5-(4-((5-Acetyl-2-ethoxyphenyl)carbamoyl)phenyl)thiophene-2-carboxylic acid (44)



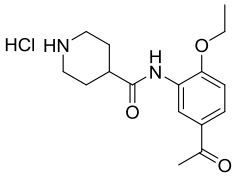
To a solution of *N*-(5-acetyl-2-ethoxyphenyl)-4-(5-formylthiophen-2-yl)benzamide (**114**, 40 mg, 0.102 mmol) in *tert*-butanol (0.51 mL) and 2-methylbut-2-ene (0.3 mL), a solution of $NaClO_2$ (83 mg, 0.918 mmol) and $NaH_2PO_4{\cdot}H_2O$ (99 mg, 0.717 mmol) in water (0.5 mL) was added. The reaction mixture was stirred at room temperature for 12 h and it was concentrated under reduced pressure. To the residue HCl (1 M) was added and the obtained precipitate was filtered off affording the desired carboxylic acid in pure form as a yellow solid (36.8 mg, 88 % yield). mp 207-210 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 9.95 (s, 1H), 9.64 (s, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 4.0 Hz, 1H), 8.07-8.03 (m, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 3.9 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 4.22 (q, *J* = 6.9 Hz, 2H), 2.54 (s, 3H), 1.39 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ = 196.2, 184.3, 164.4, 154.8, 151.1, 142.9, 139.2, 135.3, 134.8, 129.3, 128.6, 127.2, 126.8, 126.5, 126.3, 125.9, 124.2, 111.8, 64.4, 26.4, 14.4; IR (neat): ῡ = 3432, 2923, 1664, 1591, 1529, 1432, 1267, 1218, 1039, 803, 756, 583 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{20}NO_5S^+$: 410.1057, found: 410.1056.

***Tert*-butyl 4-((5-acetyl-2-ethoxyphenyl)carbamoyl)piperidine-1-carboxylate (115)**



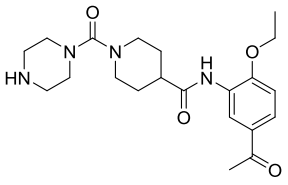
To a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (307 mg, 1.339 mmol, obtained following the general procedure A for amide formation) in dichloromethane (4.8 mL) at 0 °C, one drop of dimethylformamide and oxalyl chloride (125 µL, 1.451 mmol) were added. The solution was stirred for 1 h at 0 °C, it was concentrated under reduced pressure and dichloromethane (4.8 mL) was added. 1-(3-amino-4-ethoxyphenyl)ethan-1-one (200 mg, 1.116 mmol) and DIPEA (272 µL, 1.562 mmol) were added. The reaction mixture was stirred at room temperature for 12 h, concentrated under reduced pressure and the residue was then purified by flash column chromatography (EtOAc = 100 %). The desired amide was obtained as an off-white solid in pure form (200 mg, 46 % yield). Off-white solid; mp 97-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1H), 7.84 (s, 1H), 7.74 (dt, *J* = 8.6, 2.2 Hz, 1H), 6.92 (dd, *J* = 8.6, 1.5 Hz, 1H), 4.22 – 4.18 (m, 4H), 2.83 (t, *J* = 12.5 Hz, 2H), 2.57 (d, *J* = 1.9 Hz, 3H), 2.45 (tt, *J* = 11.4, 3.7 Hz, 1H), 1.94 (d, *J* = 12.8 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.50 (td, *J* = 7.0, 1.6 Hz, 3H), 1.47 (d, *J* = 1.5 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.2, 172.6, 154.7, 150.7, 130.4, 127.2, 124.5, 120.6, 110.4, 79.7, 77.3, 77.0, 64.6, 44.5, 28.6, 28.4, 26.5, 14.7; IR (neat): ῡ = 3327, 2934, 1678, 1664, 1603, 1583, 1532, 1493, 1421, 1366, 1358, 1274, 1239, 1165, 1128, 1037, 959, 809, 636 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{29}N_2O_5^-$: 389.2082, found: 389.2081.

***N*-(5-Acetyl-2-ethoxyphenyl)piperidine-4-carboxamide hydrochloride (116)**



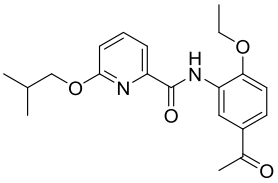
To a solution of *tert*-butyl 4-((5-acetyl-2-ethoxyphenyl)carbamoyl)piperidine-1-carboxylate (**115**, 180 mg, 0.461 mmol) in dichloromethane (4.7 mL) a 4 M HCl solution in dioxane (1.4 mL) was added. The reaction mixture was stirred at room temperature for three hours and it was concentrated under reduced pressure, obtaining the desired salt in pure form as an off-white solid (145 mg, 96 % yield). mp 208-211 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.19 (s, 1H), 8.94 (s, 1H), 8.64 (s, 1H), 8.43 (d, *J* = 1.7 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.36 (s, 3H), 3.39-3.31 (m, 2H), 2.90 (q, *J* = 12.3 Hz, 2H), 2.85 – 2.78 (m, 1H), 1.96 (d, *J* = 11.6 Hz, 2H), 1.83 (td, *J* = 14.6, 3.9 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 172.4, 153.3, 129.3, 127.0, 126.4, 122.4, 111.5, 66.3, 64.3, 42.4, 26.4, 25.2, 14.4; IR (neat): ῡ = 2923, 1686, 1585, 1526, 1423, 1254, 1147, 1035, 805, 582, 458 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{23}N_2O_3^+$: 291.1703, found: 291.1703.

***N*-(5-Aacetyl-2-ethoxyphenyl)-1-(piperazine-1-carbonyl)piperidine-4-carboxamide (45)**



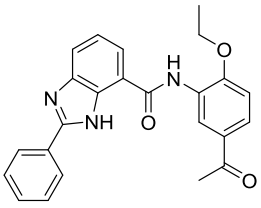
To a solution of *N*-(5-acetyl-2-ethoxyphenyl)piperidine-4-carboxamide hydrochloride (**116**, 21 mg, 0.064 mmol) in tetrahydrofuran (0.2 mL), Et_3N (21.4 µL, 0.152 mmol) and CDI (12.4 mg, 0.076 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and dimethylformamide (0.1 mL) and piperazine (60 mg, 0.697 mmol) were added. The reaction was heated at 80 °C for 24 h, concentrated under reduced pressure and purified by flash column chromatography (DCM/MeOH/Et_3N, 90:9:1), obtaining the desired urea in pure form as a yellow oil in 32 % yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.10 (s, 1H), 8.46 (s, 1H), 8.03 (s, 1H), 7.74 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.76 – 3.64 (m, 2H), 3.60 (dd, *J* = 10.3, 4.9 Hz, 2H), 3.19 – 3.00 (m, 6H), 2.81 (t, *J* = 12.4 Hz, 2H), 2.77 – 2.69 (m, 1H), 1.79 (d, *J* = 11.2 Hz, 2H), 1.65 – 1.54 (m, 2H), 1.39 (t, *J* = 6.9 Hz, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.3, 173.4, 162.6, 153.2, 129.3, 127.2, 126.1, 122.2, 111.4, 64.3, 52.0, 45.7, 43.5, 43.0, 42.4, 42.2, 41.5, 35.9, 28.2, 26.4, 14.4; IR (neat): ῡ = 3399, 2920, 1651, 1433, 1266, 1216, 1132, 1013, 804, 581 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{31}N_4O_4^+$: 403.2340, found: 403.2341.

***N*-(5-acetyl-2-ethoxyphenyl)-6-isobutoxypicolinamide (46)**



To a solution of *N*-(5-acetyl-2-ethoxyphenyl)-6-hydroxypicolinamide (**36**, 50 mg, 0.166 mmol) in dimethylformamide (0.6 mL), NaI (50 mg, 0.333 mmol), K_2CO_3 (92 mg, 0.666 mmol) and isobutyl chloride (35 µL, 0.333 mmol) were added. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with ethylacetate and washed with $NaHCO_3$ (saturated aqueous solution), HCl (1 M) and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (2:1, hexane/EtOAc) to afford the desired product in pure form (37 mg, 63 % yield). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1H), 9.31 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.80 – 7.74 (m, 2H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.95 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.20 (d, *J* = 6.4 Hz, 2H), 2.63 (s, 3H), 2.14 (dp, *J* = 13.3, 6.6 Hz, 1H), 1.56 (t, *J* = 7.0 Hz, 3H), 1.56 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 162.9, 162.3, 151.4, 147.3, 139.8, 130.4, 127.3, 124.6, 120.3, 115.6, 115.1, 110.4, 72.3, 64.6, 28.2, 26.6, 19.5, 15.1; IR (neat): ῡ = 3345, 2968, 1677, 1590, 1537, 1489, 1438, 1388, 1343, 1271, 1223, 1143, 1069, 1043, 1014, 823, 794, 769, 699, 580 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{25}N_2O_4^+$: 357.1809, found: 357.1805.

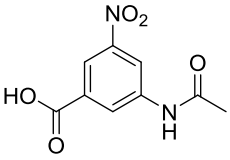
***N*-(5-Acetyl-2-ethoxyphenyl)-2-phenyl-1*H*-benzo[*d*]imidazole-7-carboxamide (47)**



Amide **47** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Pale brown solid; mp 289-293 °C; Yield: 27 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.55 (s, 1H), 12.23 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 8.34 (s, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.57 (m, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 4.46 (q, *J* = 6.6 Hz, 2H), 2.57 (s, 3H), 1.35 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.4, 163.2, 152.3, 151.6, 141.0, 135.5, 130.8, 129.6, 129.0, 128.5, 127.0, 125.2, 123.3, 122.7, 121.9, 120.2, 115.7, 111.6, 64.7, 26.5, 14.3; IR (neat): ῡ = 3202, 1655, 1589, 1553, 1478, 1420, 1297, 1264, 1250, 1205, 1121, 1036, 892, 742, 726, 700, 581, 538 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{22}N_3O_3^+$: 400.1656, found: 400.1656.

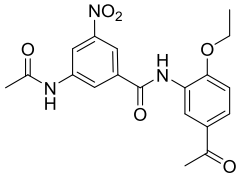
9.3 Virtual chemical reactions: synthesis of CBP inhibitors incorporating the best groups of the above compounds (16-18)

3-Acetamido-5-nitrobenzoic acid (117)[35]



Benzoic acid **117** was prepared according to the previously reported procedure. Purple solid; Yield: 61 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.69 (br, 1H), 10.63 (s, 1H), 8.80 (t, *J* = 2.1 Hz, 1H), 8.48 (s, 1H), 8.27 (t, *J* = 1.5 Hz, 1H), 2.11 (s, 3H); IR (neat): ῡ = 3364, 2932, 1715, 1654, 1542, 1426, 1336, 1263, 1208, 987, 902, 891, 740, 672, 660, 603, 506 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_7N_2O_5^-$: 223.0360, found: 223.0358.

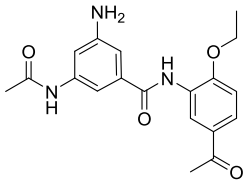
3-Acetamido-*N*-(5-acetyl-2-ethoxyphenyl)-5-nitrobenzamide (118)



Amide **118** was obtained following the general procedure B for amide formation (chromatography: DCM/EtOAc = 1:1). Pale yellow solid; mp 270-273 °C; Yield: 28 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.66 (br, 1H), 10.04 (br, 1H), 8.80 (s, 1H), 8.48 (s, 1H), 8.45 (s, 1H), 8.24 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 4.21 (q, *J* = 6.5 Hz, 2H), 2.54 (s, 3H), 2.13 (s, 3H), 1.37 (t, *J* =

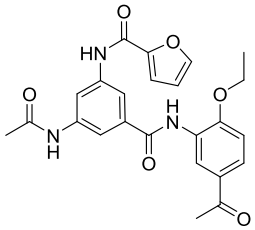
6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 169.3, 163.4, 155.5, 148.0, 140.6, 136.3, 129.4, 127.8, 126.5, 125.2, 124.0, 116.3, 115.6, 112.0, 64.4, 26.4, 24.1, 14.4; IR (neat): $\tilde{\upsilon}$ = 3344, 1701, 1678, 1655, 1592, 1532, 1430, 1350, 1338, 1267, 1254, 1133, 1039, 889, 737, 600, 588, 527 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{20}N_3O_6^+$: 386.1347, found: 386.1347.

3-Acetamido-*N*-(5-acetyl-2-ethoxyphenyl)-5-aminobenzamide (119)



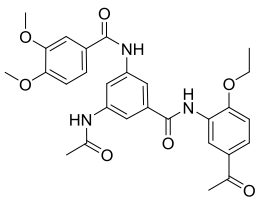
3-Acetamido-*N*-(5-acetyl-2-ethoxyphenyl)-5-nitrobenzamide (**118**, 119 mg, 0.309 mmol) was dissolved in ethanol (1.1 mL) and $SnCl_2{\cdot}2H_2O$ (234 mg, 1.038 mmol) was added. The reaction mixture was heated to 80 °C for 4 h and it was concentrated under reduced pressure. Water was added and the pH was brough to 5 by the addition of a NaOH solution (5 M). The formed precipitate was filtered off and washed extensively with dichloromethane and ethylacetate. The combined organic washes were then extracted with brine and dried over $MgSO_4$. It was then concentrated under reduced pressure and used without further purification.

***N*-(3-Acetamido-5-((5-acetyl-2-ethoxyphenyl)carbamoyl)phenyl)furan-2-carboxamide (16)**



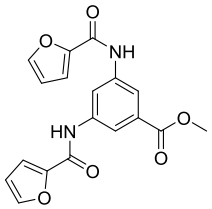
3-Acetamido-*N*-(5-acetyl-2-ethoxyphenyl)-5-aminobenzamide (**119**, 20 mg, 0.056 mmol) was dissolved in dimethylformamide (0.15 mL) at 0 °C. Et_3N (12 µL, 0.084 mmol) and 2-furoyl chloride (6.7 µL, 0.068 mmol) were added. The reaction mixture was let to warm to room temperature, stirred for 12 h and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (EtOAc = 100 %) obtaining the desired amide in pure form (15 mg, 47 % over two steps). White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 10.16 (s, 1H), 9.27 (s, 1H), 8.54 (d, J = 1.7 Hz, 1H), 8.23 (s, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.94 (s, 1H), 7.82 (dd, J = 8.5, 1.8 Hz, 1H), 7.40 (d, J = 3.3 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 3.1, 1.4 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 2.54 (s, 3H), 2.09 (s, 3H), 1.43 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.2, 168.5, 164.9, 156.3, 153.5, 147.2, 145.8, 139.8, 139.1, 135.3, 129.5, 127.1, 126.5, 122.1, 114.8, 114.1, 114.0, 113.3, 112.0, 111.6, 64.6, 26.3, 23.9, 14.3; IR (neat): $\tilde{\upsilon}$ = 3432, 3344, 1666, 1586, 1532, 1424, 1262, 1192, 879, 751, 743, 586 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{24}N_3O_6^+$: 450.1660, found: 450.1660.

***N*-(3-Acetamido-5-((5-acetyl-2-ethoxyphenyl)carbamoyl)phenyl)-3,4-dimethoxybenzamide (17)**



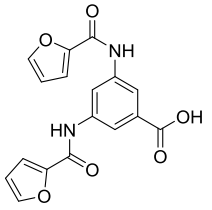
3-Acetamido-*N*-(5-acetyl-2-ethoxyphenyl)-5-aminobenzamide (**119**, 20 mg, 0.056 mmol) was dissolved in dimethylformamide (0.15 mL) at 0 °C. Et_3N (12 µL, 0.084 mmol) and 3,4-dimethoxybenzoyl chloride (14 mg, 0.068 mmol) were added. The reaction mixture was let to warm to room temperature, stirred for 12 h and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (EtOAc = 100 %) obtaining the desired amide in pure form (16 mg, 44 % over two steps). White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.26 (s, 1H), 10.15 (s, 1H), 9.28 (s, 1H), 8.55 (s, 1H), 8.27 (s, 1H), 8.02 (s, 1H), 7.94 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.59 (s, 1H), 7.21 (d, J = 9.3 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 4.25 (q, J = 6.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.09 (s, 3H), 1.44 (t, J = 6.1 Hz, 3H), three protons are missing due to overlapping with the solvent; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.3, 178.7, 168.6, 165.0, 153.7, 151.8, 148.3, 139.8, 137.6, 135.2, 129.5, 127.1, 126.7, 126.6, 122.2, 121.3, 114.4, 114.2, 113.1, 111.6, 111.1, 111.0, 64.6, 55.7, 55.6, 26.4, 24.1, 14.4. Two carbons are missing due to overlapping; IR (neat): $\tilde{\upsilon}$ = 3271, 1661, 1583, 1533, 1516, 1444, 1423, 1266, 1224, 1178, 1121, 1018, 874, 752, 584 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{28}H_{28}N_3O_7^+$: 518.1933, found: 518.1929.

Methyl 3,5-bis(furan-2-carboxamido)benzoate (120)



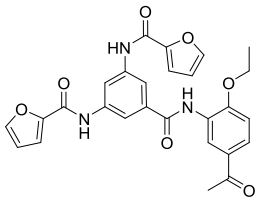
Methyl 3,5-diaminobenzoate (0.50 g, 3.01 mmol) was dissolved in dimethylformamide (5.5 mL). Et_3N (1.05 mL, 7.53 mmol) and 2-furoyl chloride (0.65 mL, 6.62 mmol) were added at 0 °C. The reaction mixture was let to warm to room temperature and stirred for 12 h. It was concentrated to half of the volume of dimethylformamide under reduced pressure and water was added. The formed precipitate was filtered off affording the desired product in pure form (0.76 g, 71 % yield). White solid; mp 235-240 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.46 (s, 2H), 8.57 (t, J = 2.0 Hz, 1H), 8.14 (d, J = 2.0 Hz, 2H), 7.97 (d, J = 1.0 Hz, 2H), 7.42 (d, J = 3.5 Hz, 2H), 6.72 (dd, J = 3.5, 1.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.0, 156.4, 147.2, 146.0, 139.2, 130.2, 116.5, 116.4, 115.0, 112.1, 52.3; IR (neat): ῡ = 3312, 3141, 1712, 1658, 1587, 1568, 1538, 1442, 1426, 1286, 1241, 1199, 1116, 1017, 998, 882, 843, 757, 606, 595 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{15}N_2O_6^+$: 355.0925, found: 355.0926.

3,5-Bis(furan-2-carboxamido)benzoic acid (121)



Benzoic acid **121** was obtained following the general procedure for ester hydrolysis. Off-white solid; mp 250-255 °C; Yield: 94 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.43 (br. s., 2H), 8.52 (br. s., 1H), 8.10 (br. s., 2H), 7.95 (br. s., 2H), 7.44 (d, J = 2.8 Hz, 2H), 6.71 (br. s., 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.0, 156.3, 147.2, 146.0, 139.0, 131.4, 116.7, 116.4, 115.0, 112.1; IR (neat): ῡ = 3120, 2832, 1582, 1539, 1455, 1295, 1267, 1195, 883, 752, 668, 424, 418 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{13}N_2O_6^+$: 341.0768, found: 341.0766.

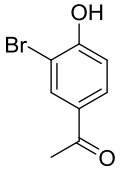
***N,N'*-(5-((5-Acetyl-2-ethoxyphenyl)carbamoyl)-1,3-phenylene)bis(furan-2-carboxamide) (18)**



Amide **18** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:2). Off-white solid; mp 284-288 °C; Yield: 52 %; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.44 (s, 2H), 9.40 (s, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 8.07 (s, 2H), 7.97 (s, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 3.1 Hz, 1H), 7.42 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.72 (s, 2H), 4.24 (q, J = 6.9 Hz, 2H), 2.55 (s, 3H), 1.42 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.2, 165.0, 156.4, 153.9, 147.2, 146.0, 139.1, 135.3, 129.5, 127.1, 126.7, 122.6, 115.5, 114.9, 112.1, 111.7, 64.6, 26.4, 14.4; IR (neat): ῡ = 3297, 3120, 2927, 1658, 1601, 1584, 1527, 1449, 1293, 1274, 1262, 1191, 862, 761, 754, 684, 590, 553, 500 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{27}H_{24}N_3O_7^+$: 502.1609, found: 502.1609.

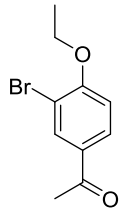
9.4 Virtual chemical reactions: synthesis of CBP inhibitors bearing an amine linker (9, 10, 48-55)

1-(3-bromo-4-hydroxyphenyl)ethan-1-one (122)[36]



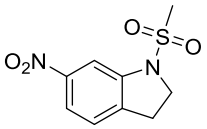
Bromo phenol **122** was prepared according to the previously reported procedure. Off-white solid; mp 96-100 °C; Yield: 35 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.5, 2.0 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 2.56 (s, 3H); IR (neat): ῡ = 3080, 2926, 1651, 1595, 1547, 1416, 1360, 1291, 1258, 1140, 823, 587 cm^{-1}; HRMS (ESI): m/z: calcd for $C_8H_8BrO_2^+$: 214.9702, found: 214.9703.

1-(3-bromo-4-ethoxyphenyl)ethan-1-one (3)



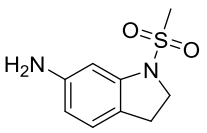
To a solution of 1-(3-bromo-4-hydroxyphenyl)ethan-1-one (**122**, 3.5 g, 16.28 mmol) in dimethylformamide (62.0 mL), ethyl iodide (1.5 mL, 19.53 mmol) and K_2CO_3 (2.9 g, 21.16 mmol) were added. The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was diluted with water and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc = 9:1), affording the pure product as a white solid in 68 % yield. mp 66-71 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 2.1 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 3H), 2.52 (s, 3H), 1.48 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 195.5, 159.0, 133.8, 130.9, 129.3, 112.1, 111.8, 65.0, 26.2, 14.4; IR (neat): ῡ = 2982, 1667, 1591, 1498, 1475, 1395, 1354, 1304, 1265, 1245, 1150, 1106, 1046, 1031, 808, 728, 585 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{10}H_{12}BrO_2^+$: 243.0015, found: 243.0017.

1-(Methylsulfonyl)-6-nitroindoline (123)[37]



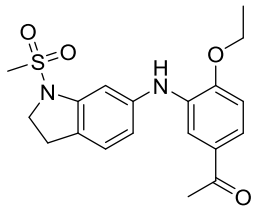
Nitro arene **123** was prepared according to the previously reported procedure. Purple solid; Yield: 55 %; mp 208-212 ˚C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.97 (d, *J* = 2.1 Hz, 1H), 7.92 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 4.06 (t, *J* = 8.6 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.13 (s, 3H);^{13}C NMR (101 MHz, DMSO-d_6): δ = 147.5, 143.1, 140.2, 126.1, 118.8, 107.4, 50.4, 34.9, 27.4; IR (neat): ῡ = 1522, 1347, 1333, 1323, 1155, 1072, 1050, 1000, 981, 960, 878, 828, 774, 735, 563, 544, 514 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{10}N_2NaO_4S^+$: 265.0254, found: 265.0253.

1-(Methylsulfonyl)indolin-6-amine (124)



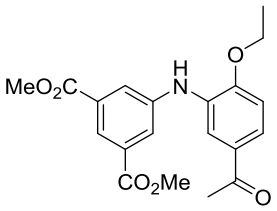
Aniline **124** was obtained following the general procedure for the reduction of nitro arenes. Light brown solid; Yield: 99 %; mp 143-146 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.87 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.09 (s, 2H), 3.83 (t, *J* = 8.3 Hz, 2H), 2.92 (s, 3H), 2.90 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 148.6, 142.7, 125.4, 118.1, 109.2, 99.6, 50.5, 33.6, 26.6; IR (neat): ῡ = 3457, 3371, 1627, 1608, 1504, 1328, 1309, 1282, 1153, 998, 983, 957, 852, 801, 764, 557, 510 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{13}N_2O_2S^+$: 213.0692, found: 213.0692.

1-(4-Ethoxy-3-((1-(methylsulfonyl)indolin-6-yl)amino)phenyl)ethan-1-one (9)



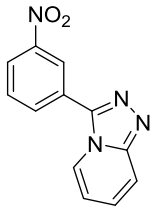
Aniline **9** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: toluene/EtOAc = 6:1). Light brown solid; Yield: 36 %; mp 120-123 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.26 – 7.25 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.94 – 6.84 (m, 2H), 6.20 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.12 (t, *J* = 8.2 Hz, 2H), 2.95 (s, 3H), 2.53 (s, 3H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.0, 151.1, 143.2, 142.1, 133.4, 130.5, 126.0, 124.5, 121.4, 114.7, 113.1, 110.3, 105.6, 64.5, 51.0, 34.8, 27.5, 26.2, 14.8; IR (neat): ῡ = 3377, 1656, 1589, 1520, 1498, 1418, 1336, 1249, 1156, 1136, 1040, 954, 806, 767, 550, 515 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{23}N_2O_4S^+$: 375.1373, found: 375.1365.

Dimethyl 5-((5-acetyl-2-ethoxyphenyl)amino)isophthalate (10)



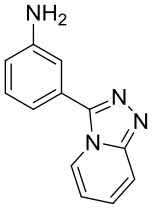
Aniline **10** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 2:1). Yellow solid; Yield: 26 %; mp 106-116 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (t, *J* = 1.5 Hz, 1H), 7.99 (d, *J* = 1.5 Hz, 2H), 7.90 (d, *J* = 2.1 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.94 (s, 6H), 2.54 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.8, 166.2, 151.9, 143.0, 131.8, 131.6, 130.3, 123.3, 122.9, 122.7, 115.0, 110.6, 64.5, 52.4, 29.7, 26.4, 14.8; IR (neat): ῡ = 3368, 2953, 2924, 1716, 1664, 1584, 1531, 1434, 1353, 1237, 1142, 1014, 753, 420 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{22}NO_6^+$: 372.1442, found: 372.1442.

3-(3-Nitrophenyl)-[*1,2,4*]triazolo[*4,3-a*]pyridine (125)[38]



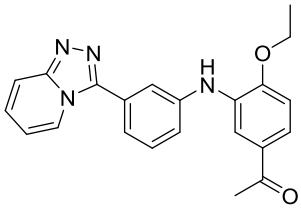
Nitro arene **125** was prepared according to the previously reported procedure. Pale yellow solid; Yield: 17 % over two steps; mp 227-231 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.70 (t, *J*= 2.0 Hz, 1H), 8.68 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.42 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 8.38 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.97 – 7.81 (m, 2H), 7.49 (ddd, *J* = 9.3, 6.6, 1.0 Hz, 1H), 7.10 (td, *J* = 6.9, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 150.3, 148.3, 144.4, 134.3, 130.9, 128.4, 128.2, 124.4, 124.1, 122.8, 115.6, 114.8; IR (neat): ῡ = 3089, 1541, 1508, 1496, 1349, 1137, 1069, 903, 870, 809, 764, 735, 697, 677, 432, 404 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_9N_4O_2^+$: 241.0720, found: 241.0721.

3-([*1,2,4*]Triazolo[*4,3-a*]pyridin-3-yl)aniline (126)



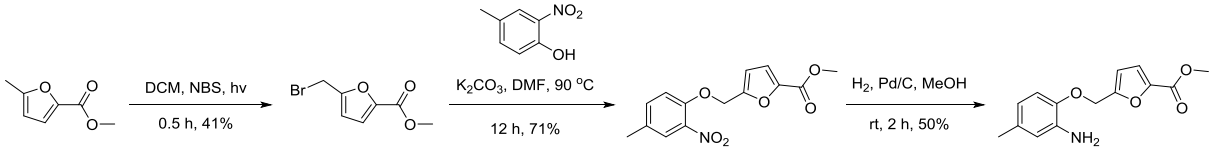
Aniline **126** was obtained following the general procedure for the reduction of nitro arenes (chromatography: EtOAc = 100 %). Pale brown solid; Yield: 59 %; mp 131-144 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.82 (dt, *J* = 9.3, 1.1 Hz, 1H), 7.40 (ddd, *J* = 9.3, 6.5, 1.1 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 1.9 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.97 (ddd, *J* = 7.5, 1.6, 1.0 Hz, 1H), 6.76 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 149.8, 149.5, 146.5, 129.7, 127.6, 127.0, 123.8, 115.7, 115.3, 114.9, 114.2, 113.0; IR (neat): ῡ = 3429, 3316, 3201, 2923, 1635, 1605, 1584, 1500, 1464, 1374, 1282, 1140, 1059, 900, 870, 791, 753, 743, 705, 419 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{11}N_4^+$: 211.0978, found: 211.0979.

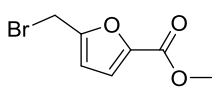
1-(3-((3-([*1,2,4*]Triazolo[*4,3-a*]pyridin-3-yl)phenyl)amino)-4-ethoxyphenyl)ethan-1-one (48)



Aniline **48** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: EtOAc/MeOH = 100:5). Light yellow solid; Yield: 53 %; mp 123-127 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 7.0 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.65 (t, *J* = 1.8 Hz, 1H), 7.58 – 7.41 (m, 3H), 6.99 (t, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.36 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.0, 151.7, 150.5, 143.0, 132.4, 130.6, 130.3, 127.7, 127.7, 127.4, 123.2, 122.5, 121.3, 120.3, 117.9, 116.6, 114.6, 113.4, 110.3, 64.5, 26.3, 14.8; IR (neat): ῡ = 3276, 1666, 1587, 1403, 1282, 1249, 1207, 1139, 1038, 881, 802, 788, 742, 707, 577, 492, 426 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{21}N_4O_2^+$: 373.1659, found: 373.1656.

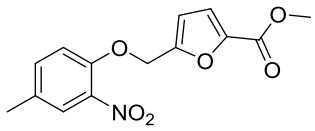
Synthesis of compound 49:





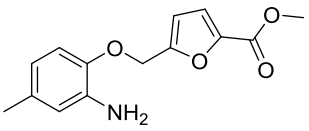
Methyl 5-(bromomethyl)furan-2-carboxylate (128)[39] Ester **128** was prepared according to the previously reported procedure. Yellow oil; Yield: 41 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 3.5 Hz, 1H), 6.50 (d, *J* = 3.5 Hz, 1H), 4.49 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 154.3, 144.8, 119.0, 111.5, 52.1, 21.9; IR (neat): ῡ = 2948, 1719, 1531, 1519, 1436, 1300, 1222, 1201, 1139, 1019, 990, 971, 811, 798, 760, 670, 563 cm^{-1}; HRMS (ESI): m/z: calcd for $C_7H_7BrNaO_3^+$: 240.9471, found: 240.9473.

Methyl 5-((4-methyl-2-nitrophenoxy)methyl)furan-2-carboxylate (129)



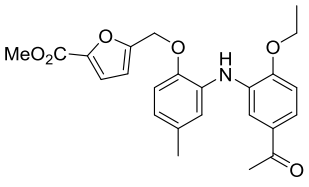
To a solution of methyl 5-(bromomethyl)furan-2-carboxylate (**128**, 300 mg, 1.37 mmol) and 4-methyl-2-nitrophenol (210 mg, 1.37 mmol) in dimethylformamide (5.2 mL) K_2CO_3 (246 mg, 1.78 mmol) was added and the reaction mixture was stirred at 90 °C for 12 h. It was then concentrated under reduced pressure, the reaction mixture was diluted with water and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc = 3:1), obtaining the desired product in pure form (282 mg, 71 % yield) as a yellow solid. mp 92-104 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 1.7 Hz, 1H), 7.33 (ddd, *J* = 8.5, 2.2, 0.6 Hz, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 5.18 (s, 2H), 3.90 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.9, 153.4, 149.1, 144.6, 140.4, 134.6, 131.9, 125.9, 118.8, 116.0, 111.7, 64.5, 52.0, 20.3; IR (neat): ῡ = 2926, 1729, 1625, 1527, 1349, 1306, 1270, 1207, 1147, 1027, 985, 816, 805, 790, 758, 674, 529 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{13}NNaO_6^+$: 314.0635, found: 314.0631.

Methyl 5-((2-amino-4-methylphenoxy)methyl)furan-2-carboxylate (130)



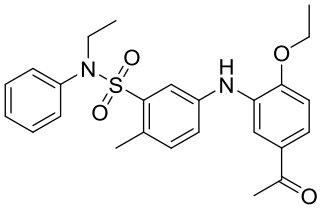
Aniline **130** was obtained following the general procedure for the reduction of nitro arenes and further purified by flash column chromatography (hexane/EtOAc = 3:1). Brown solid; Yield: 50 %; mp 111-115 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29 (d, *J* = 3.5 Hz, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 6.29 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.04 (s, 2H), 4.62 (s, 2H), 3.81 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 158.3, 155.4, 143.6, 142.7, 137.9, 130.6, 119.1, 116.4, 115.1, 113.1, 111.9, 62.4, 51.8, 20.5; IR (neat): ῡ = 3432, 3333, 2922, 1704, 1546, 1515, 1431, 1379, 1308, 1211, 1133, 1022, 963, 919, 797, 763, 645 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{16}NO_4^+$: 262.1074, found: 262.1074.

Methyl 5-((2-((5-Acetyl-2-ethoxyphenyl)amino)-4-methylphenoxy)methyl)furan-2-carboxylate (49)



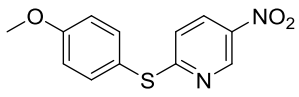
Aniline **49** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 3:1). Dark brown oil; Yield: 64 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 2.1 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.24 (d, *J* = 1.8 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 6.87 (d, *J* = 4.3 Hz, 1H), 6.85 (d, *J* = 4.5 Hz, 1H), 6.70 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.57 (s, 1H), 6.48 (d, *J* = 3.5 Hz, 1H), 5.08 (s, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.0, 158.9, 154.9, 152.0, 146.0, 144.6, 133.0, 132.6, 132.1, 130.5, 121.5, 121.4, 118.7, 117.9, 114.0, 113.8, 111.1, 110.4, 64.4, 64.0, 51.8, 26.2, 21.1, 14.6; IR (neat): ῡ = 3404, 2924, 1725, 1672, 1586, 1534, 1505, 1433, 1422, 1302, 1252, 1208, 1126, 1018, 797, 762, 587 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{26}NO_6^+$: 424.1755, found: 424.1759.

5-((5-Acetyl-2-ethoxyphenyl)amino)-*N*-ethyl-2-methyl-*N*-phenylbenzenesulfonamide (50)



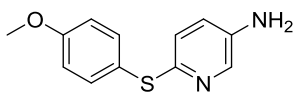
Aniline **50** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 3:1). Brown solid; Yield: 67 %; mp 108-115 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 2.1 Hz, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.21 – 7.15 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.22 (br, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.72 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 2.23 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9, 151.3, 140.1, 138.5, 137.7, 133.6, 132.5, 130.7, 130.3, 129.2, 129.1, 127.9, 122.6, 122.1, 120.7, 113.1, 110.2, 64.4, 45.9, 26.3, 19.9, 14.8, 14.0; IR (neat): ῡ = 3378, 2930, 1665, 1587, 1492, 1434, 1336, 1259, 1251, 1141, 1064, 717, 694, 594, 561, 533 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{29}N_2O_4S^+$: 453.1843, found: 453.1846.

2-((4-Methoxyphenyl)thio)-5-nitropyridine (131)[40]



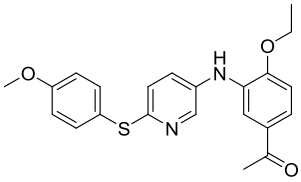
Nitro arene **131** was prepared according to the previously reported procedure. White solid; Yield: 89 %; mp 132-138 ˚C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.17 (s, 1H), 8.38 (d, *J* = 7.0 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.7, 161.0, 144.8, 141.2, 137.3, 132.1, 119.6, 118.1, 115.9, 55.4; IR (neat): ῡ = 3047, 1584, 1567, 1508, 1492, 1344, 1290, 1249, 1174, 1103, 1024, 825, 801, 748, 542, 525, 423, 402 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{11}N_2O_3S^+$: 263.0485, found: 263.0486.

6-((4-Methoxyphenyl)thio)pyridin-3-amine (132)



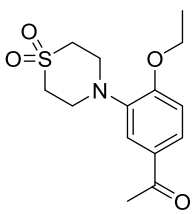
Aniline **132** was obtained following the general procedure for the reduction of nitro arenes and used impure in the next step.

1-(4-Ethoxy-3-((6-((4-methoxyphenyl)thio)pyridin-3-yl)amino)phenyl)ethan-1-one (51)



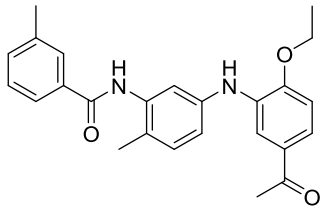
Aniline **51** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: EtOAc = 100 %). Brown oil; Yield: 36 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 2.6 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.48 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.07 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 2.50 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.7, 160.5, 154.2, 151.4, 141.8, 136.5, 135.7, 132.8, 130.6, 127.6, 122.7, 122.2, 115.3, 113.2, 110.5, 64.5, 55.4, 26.2, 14.7. One carbon is missing du to overlapping.; IR (neat): ῡ = 3382, 2933, 1656, 1584, 1455, 1436, 1293, 1245, 1212, 1141, 1031, 829, 797, 732, 518 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{23}N_2O_3S^+$: 395.1424, found: 395.1425.

1-(3-(1,1-Dioxidothiomorpholino)-4-ethoxyphenyl)ethan-1-one (52)



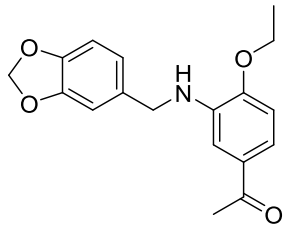
Aniline **52** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 1:2). Yellow oil; Yield: 33 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.80 – 3.45 (m, 4H), 3.34 – 3.02 (m, 4H), 2.55 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.6, 155.7, 139.7, 130.5, 126.0, 119.6, 111.3, 64.3, 52.3, 49.2, 26.2, 14.8; IR (neat): ῡ = 3583, 2981, 2927, 1670, 1591, 1505, 1309, 1251, 1221, 1120, 1028, 860, 809, 434 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{20}NO_4S^+$: 298.1108, found: 298.1110.

***N*-(5-((5-Acetyl-2-ethoxyphenyl)amino)-2-methylphenyl)-3-methylbenzamide (53)**



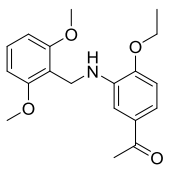
Aniline **53** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 2:1). Orange solid; Yield: 94 %; mp 69-76 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 2.3 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.75 – 7.61 (m, 3H), 7.47 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.02 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.25 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.5, 165.7, 151.0, 140.6, 138.8, 136.7, 135.1, 133.4, 132.6, 131.1, 130.4, 128.7, 127.8, 123.9, 121.5, 120.9, 115.8, 113.9, 113.1, 110.1, 64.3, 26.4, 21.4, 17.1, 14.8; IR (neat): $\tilde{\upsilon}$ = 3321, 2977, 1660, 1587, 1521, 1436, 1293, 1252, 1218, 1126, 1039, 805, 740, 697, 449 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{27}N_2O_3^+$: 403.2016, found: 403.2012.

1-(3-((Benzo[*d*][*1,3*]dioxol-5-ylmethyl)amino)-4-ethoxyphenyl)ethan-1-one (54)



To a solution of 1-(3-bromo-4-ethoxyphenyl)ethan-1-one (**3**, 50 mg, 0.21 mmol) and benzo[*d*][1,3]dioxol-5-ylmethanamine (38 µL, 0.31 mmol) in dimethylsulfoxide, CuI (4 mg, 0.021 mmol), L-proline (5 mg, 0.041 mmol) and K_3PO_4 (88 mg, 0.41 mmol) were added. The reaction mixture was stirred at 90 °C for 12 h. It was diluted with water and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc = 5:1). Yellow oil; Yield: 24 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.80 – 6.73 (m, 2H), 5.95 (s, 2H), 4.61 (s, 1H), 4.31 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 2.51 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.5, 150.1, 147.9, 146.8, 137.8, 133.0, 130.7, 120.7, 119.2, 108.9, 108.8, 108.3, 108.1, 101.0, 64.1, 47.7, 29.7, 26.3, 14.8; IR (neat): $\tilde{\upsilon}$ = 3419, 2980, 2893, 1667, 1591, 1520, 1503, 1488, 1430, 1244, 1213, 1147, 1036, 925, 799, 587 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{20}NO_4^+$: 314.1387, found: 314.1386.

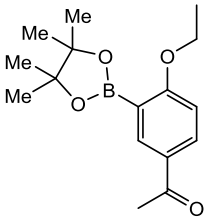
1-(3-((2,6-Dimethoxybenzyl)amino)-4-ethoxyphenyl)ethan-1-one (55)



Aniline **55** was obtained following the general procedure for Buchwald Hartwig aminations (chromatography: hexane/EtOAc = 1:1). Yellow oil; Yield: 15 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 2.1 Hz, 1H), 7.27 (dd *J* = 8.3, 2.2 Hz, 1H), 7.18 (t, *J* = 8.3 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.56 (s, 1H), 6.54 (s, 1H), 4.98 (br, 1H), 4.48 (s, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 6H), 3.88 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.7, 158.8, 150.6, 138.4, 130.7, 128.6, 118.6, 115.4, 109.9, 108.9, 103.7, 63.9, 55.8, 36.1, 26.3, 14.9. One carbon is missing due to overlapping; IR (neat): $\tilde{\upsilon}$ = 3412, 2924, 1656, 1593, 1447, 1268, 1214, 1112, 1036, 768, 724, 573 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{24}NO_4^+$: 330.1700, found: 330.1698.

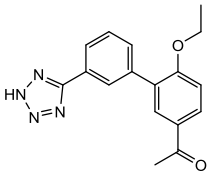
9.5 Virtual chemical reactions: synthesis of CBP inhibitors without a linker (11-15, 56-60)

1-(4-Ethoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (4)



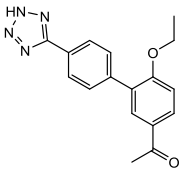
To a solution of 1-(3-bromo-4-ethoxyphenyl)ethan-1-one (**3**, 2.00 g, 8.23 mmol) in dioxane (33.6 mL), KOAc (2.42 g, 24.66 mmol), $B_2(pin)_2$ (4.18 g, 16.46 mmol) and $Pd(dppf)Cl_2$ (0.60 g, 0.82 mmol) were added. It was then stirred at 100 ºC for 23 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by flash column chromatography (hexane/EtOAc = 9:1 to 7:1), affording the desired product in pure form (2.08 g, 87 % yield). Brown solid; mp: 91-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 2.4 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.37 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.1, 167.3, 137.2, 133.2, 129.8, 111.0, 84.0, 64.3, 26.5 , 25.0, 14.7; IR (film): ῡ = 2979, 2933, 1676, 1594, 1494, 1473, 1426, 1411, 1391, 1357, 1343, 1314, 1294, 1246, 1216, 1144, 1112, 1086, 1066, 1040, 961, 927, 870, 850, 814, 757, 715, 673, 589, 541, 524; HRMS (ESI): m/z: calcd for $C_{16}H_{24}BO_4^+$: 29.1762, found: 291.1761.

1-(6-Ethoxy-3'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)ethan-1-one (11)



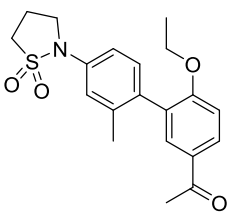
To a solution of 5'-acetyl-2'-ethoxy-[1,1'-biphenyl]-3-carbonitrile (1 eq., obtained following the general procedure for Suzuki cross-coupling reactions but contaminated with residual PPh_3O) in dimethylformamide (0.5 M), was added NaN_3 (1.5 eq.) and $ZnBr_2$ (1 eq.). The reation mixture was stirred at 130 °C for 36 h, cooled to room temperature and evaporated under reduce pressure. HCl (1 M) was added dropwise until precipitation. The solid was filtered, washed with water, washed with DCM and dry. White solid; Yield: 23 % over two steps; mp: 116-120 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.24 (s, 1H), 8.07 – 7.99 (m, 2H), 7.97 (d, *J* = 2.2 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 2.58 (s, 3H), 1.30 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 196.4, 159.2, 154.5, 138.4, 132.1, 130.7, 130.5, 129.9, 129.2, 128.5, 127.8, 125.8, 124.0, 112.3, 64.2, 26.5, 14.3. IR (neat): ῡ = 1646, 1590, 1363, 1271, 1240, 1163, 1035, 904, 808, 692 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{17}N_4O_2^+$: 309.1352 found: 309.1347.

1-(6-Ethoxy-4'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-3-yl)ethan-1-one (12)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc/AcOH = 3:2:1%), **12** was obtained in 48 % yield; Colorless solid; mp: 250-251 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.22 – 8.17 (m, 2H), 8.07 – 8.02 (m, 2H), 7.86 – 7.80 (m, 2H), 7.27 – 7.21 (m, 1H), 4.25 (q, *J* = 6.9 Hz, 2H), 2.59 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6): δ = 196.4, 160.6, 141.7, 131.8, 131.4, 131.3, 131.2, 130.0, 127.7, 124.5, 112.9, 65.2, 26.5, 14.8. One carbon is missing due to overlapping; IR (film): ῡ = 2921, 2850, 2771, 1645, 1594, 1508, 1475, 1438, 1396, 1364, 1309, 1270, 1251, 1166, 1071, 1041, 998, 972, 928, 840, 810, 741, 700, 625, 608, 597, 583, 565; HRMS (ESI): m/z: calcd for $C_{17}H_{17}N_4O_2^+$: 309.1346, found: 309.1346.

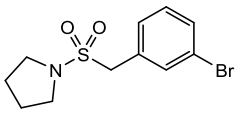
1-(4'-(1,1-Dioxidoisothiazolidin-2-yl)-6-ethoxy-2'-methyl-[1,1'-biphenyl]-3-yl)ethan-1-one (13)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:2), **13** was obtained in 65 % yield; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.22 – 7.07 (m, 3H), 6.96 (d, *J* = 8.7 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 6.5 Hz, 2H), 3.40 (t, *J* = 7.5 Hz, 2H), 2.54 (m, 5H), 2.13 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 160.0, 138.1,

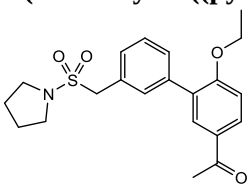
136.8, 134.2, 132.0, 130.9, 130.2, 129.8, 129.7, 120.5, 116.4, 111.0, 64.0, 48.4, 46.9, 26.3, 20.2, 18.8, 14.5; IR (neat): ϑ̃ = 1669, 1595, 1509, 1495, 1473, 1296, 1264, 1233, 1133, 1039, 806, 737, 657, 586, 515, 499, 441 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{24}NO_4S^+$: 374.1421, found: 374.1416.

1-((3-Bromobenzyl)sulfonyl)pyrrolidine (133)



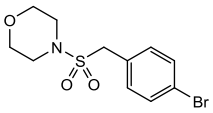
To a solution of 3-bromobenzylsulfonyl chloride (250 mg, 0.928 mmol) in dichloromethane (5 mL), pyrrolidine (160 µL, 1.948 mmol) was added. The reaction mixture was stirred at 23 °C for 24 h and concentrated under reduced pressure. Ethylacetate (25 mL) was added to the crude reaction mixture and the organic phase was washed with HCl (1 M, 2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure, obtaining the desired product in pure form (248 mg, 88 % yield). Colorless solid; mp: 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.53 (m, 1H), 7.52 – 7.48 (m, 1H), 7.38 – 7.34 (m, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 4.20 (s, 2H), 3.22 – 3.16 (m, 4H), 1.90 – 1.82 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 133.7, 131.9, 130.4, 129.5, 122.7, 56.0, 48.4, 26.0; IR (film): ϑ̃ = 3062, 2976, 2884, 1674, 1593, 1568, 1475, 1428, 1331, 1252, 1201, 1150, 1073, 1039, 1013, 891, 853, 796, 766, 731, 692, 670, 635, 612, 590, 578, 558, 538, 520, 492, 473, 457, 442, 428; HRMS (ESI): m/z: calcd for $C_{11}H_{14}BrNNaO_2S^+$: 325.9821, found: 325.9823.

1-(6-Ethoxy-3'-((pyrrolidin-1-ylsulfonyl)methyl)-[1,1'-biphenyl]-3-yl)ethan-1-one (14)



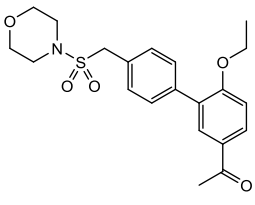
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 3:1 to 3:2), **14** was obtained in 83 % yield. Colorless solid; mp: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.60 – 7.59 (m, 1H), 7.55 – 7.51 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.36 (m, 1H), 4.30 (s, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.24 – 3.17 (m, 4H), 2.59 (s, 3H), 1.86 – 1.77 (m, 4H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.9, 159.9, 138.4, 132.0, 131.4, 130.3, 130.2, 130.1, 130.0, 129.6, 129.3, 128.5, 111.6, 64.4, 56.7, 48.4, 26.5, 26.0, 14.7. One carbons is missing due to overlapping; IR (film): ϑ̃ = 2979, 2934, 2885, 2170, 2047, 2019, 2002, 1973, 1711, 1673, 1596, 1502, 1474, 1432, 1393, 1359, 1330, 1302, 1255, 1237, 1199, 1151, 1077, 1039, 1013, 971, 899, 876, 810769, 704, 655, 626, 598, 571, 538, 507, 481, 459, 441, 419, 408; HRMS (ESI): m/z: calcd for $C_{21}H_{25}NNaO_4S^+$: 410.1397, found: 410.1392.

4-((4-Bromobenzyl)sulfonyl)morpholine (134)[41]



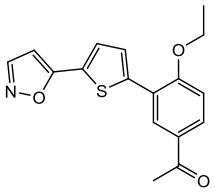
Sulfonamide **134** was prepared according to the previously reported procedure. Colorless solid; Yield: 53 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 – 7.51 (m, 2H), 7.31 – 7.26 (m, 2H), 4.16 (s, 2H), 3.70 – 3.60 (m, 4H), 3.16 – 3.11 (m, 4H).

1-(6-Ethoxy-4'-((morpholinosulfonyl)methyl)-[1,1'-biphenyl]-3-yl)ethan-1-one (15)



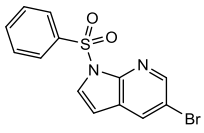
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 3:2), **15** was obtained in 71 % yield. Colorless solid; mp: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.94 (m, 2H), 7.60 – 7.56 (m, 2H), 7.48 – 7.44 (m, 2H), 7.02 – 6.98 (m, 1H), 4.28 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.67 – 3.63 (m, 4H), 3.19 – 3.15 (m, 4H), 2.59 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 278 K): δ = 197.1, 159.8, 138.4, 131.4, 130.5, 130.3, 130.1, 130.1, 129.6, 127.2, 111.4, 66.8, 64.3, 56.3, 46.2, 26.7, 14.7; IR (film): ϑ̃ = 2996, 2982, 2962, 2917, 2892, 2855, 2362, 2004, 1686, 1598, 1573, 1498, 1471, 1453, 1393, 1358, 1344, 1328, 1313, 1266, 1228, 1159, 1150, 1112, 1073, 1039, 955, 921, 895, 854, 846, 818, 775, 757, 741, 702, 645, 629, 592, 578, 543, 529, 497; HRMS (ESI): m/z: calcd for $C_{21}H_{26}NO_5S^+$: 404.1526, found: 404.1529.

1-(4-Ethoxy-3-(5-(isoxazol-5-yl)thiophen-2-yl)phenyl)ethan-1-one (56)



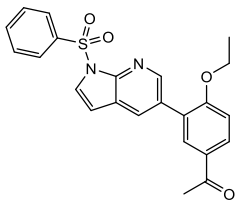
Following the general procedure for Suzuki cross-coupling reactions (reaction time was 1 h; chromatography: hexane/EtOAc = 3:1), **56** was obtained in 61 % yield. Brown solid; mp: 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 2.2 Hz, 1H), 8.27 (d, *J* = 1.9 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.51 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.41 (d, *J* = 1.9 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.61 (s, 3H), 1.61 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.7, 164.7, 158.6, 150.9, 141.3, 130.5, 130.1, 129.2, 128.7, 126.8, 126.4, 122.6, 111.8, 98.4, 65.2, 26.5, 14.8; IR (film): ῡ = 3135, 2981, 2926, 1675, 1592, 1528, 1498, 1467, 1440, 1410, 1357, 1330, 1271, 1244, 1192, 1147, 1112, 1087, 1036, 956, 915, 808, 750, 681, 636, 618, 602, 589; HRMS (ESI): m/z: calcd for $C_{17}H_{16}NO_3S^+$: 314.0845, found: 314.0845.

5-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (135)[42]



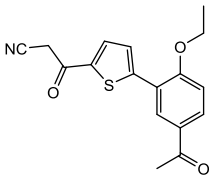
Sulfonamide **135** was prepared according to the previously reported procedure. Beige solid; Yield: 85 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 (d, *J* = 2.2 Hz, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 8.12 – 8.06 (m, 2H), 7.98 (d, *J* = 4.0 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.66 – 7.60 (m, 2H), 6.81 (d, *J* = 4.0 Hz, 1H).

1-(4-Ethoxy-3-(1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)ethan-1-one (57)



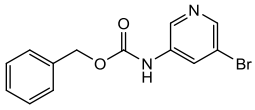
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 5:1 to 3:1), **57** was obtained in 77 % yield. Light yellow solid; mp: 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 2.1 Hz, 1H), 8.26 – 8.20 (m, 2H), 8.00 (d, *J* = 2.1 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.92 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.53 – 7.47 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.7, 159.9, 146.5, 146.1, 138.6, 134.2, 131.8, 130.5, 130.4, 129.2, 129.2, 128.2, 127.7, 127.0, 122.5, 111.6, 105.8, 64.5, 26.5, 14.7; IR (film): ῡ = 3143, 3113, 3064, 2981, 2932, 1712, 1675, 1597, 1524, 1499, 1471, 1449, 1411, 1373, 1300, 1282, 1251, 1225, 1187, 1145, 1111, 1094, 1038, 995, 813, 775, 750, 726, 686, 657, 648, 623, 609, 593, 581, 555, 530, 508, 485, 466, 428; HRMS (ESI): m/z: calcd for $C_{23}H_{21}N_2O_4S^+$: 421.1222, found: 421.1213.

3-(5-(5-Acetyl-2-ethoxyphenyl)thiophen-2-yl)-3-oxopropanenitrile (58)



Following the general procedure for Suzuki cross-coupling reactions (same reactant as the ones used for **56** but reaction time was 21 h, chromatography: hexane/EtOAc = 3:1 to 1:1), **58** was obtained in 10 % yield. Brown solid; mp: 220-221 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.44 (d, *J* = 2.2 Hz, 1H), 8.05 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.01 (d, *J* = 4.2 Hz, 1H), 7.86 (d, *J* = 4.2 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 4.53 (s, 2H), 4.41 (q, *J* = 7.0 Hz, 2H), 2.61 (s, 3H), 1.56 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, acetone-d_6): δ = 196.3, 182.4, 159.6, 148.9, 141.5, 134.7, 131.8, 131.5, 129.6, 127.7, 122.4, 115.3, 113.4, 66.2, 26.5, 14.9; IR (film): ῡ = 2922, 2851, 2362, 2216, 2186, 2005, 1666, 1640, 1594, 1523, 1494, 1445, 1412, 1352, 1337, 1280, 1255, 1233, 1153, 1100, 1032, 920, 894, 813, 794, 753, 724, 695, 638, 606, 569, 543, 488, 472, 458, 434, 409; HRMS (ESI): m/z: calcd for $C_{17}H_{16}NO_3S^+$: 314.0845, found: 314.0846.

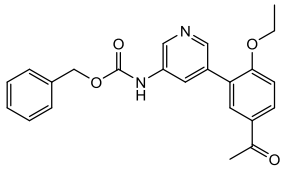
Benzyl (5-bromopyridin-3-yl)carbamate (136)



To a solution of 5-bromopyridin-3-amine (254 mg, 1.468 mmol) in dichloromethane (5 mL) benzyl carbonochloridate (310 µL, 2.172 mmol) and Et_3N (225 µL, 1.613 mmol) were added. The reaction mixture was stirred at 23

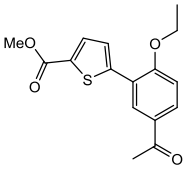
°C for 25 h. Dichloromethane (20 mL) was added to the crude reaction mixture and the organic phase was washed with water (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The obtained residue was purified by flash column chromatography (3:1 hexane/EtOAc), obtaining the desired product in pure form (184 mg, 41 % yield). Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 – 8.31 (m, 2H), 8.28 (s, 1H), 7.43 – 7.33 (m, 5H), 6.84 (br. s, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.1, 145.6, 138.2, 135.7, 135.6, 128.9, 128.8, 128.6, 128.3, 121.0, 67.8; HRMS (ESI): m/z: calcd for $C_{13}H_{12}BrN_2O_2^+$: 307.0077, found: 307.0077.

Benzyl (5-(5-acetyl-2-ethoxyphenyl)pyridin-3-yl)carbamate (59)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 3:2 to 1:1), **77** was obtained in 24 % yield. Colorless solid; mp: 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 1.9 Hz, 1H), 8.48 (d, *J* = 2.5 Hz, 1H), 8.16 (br. s, 1H), 7.99 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.43 – 7.33 (m, 5H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.78 (br. s, 1H), 5.23 (s, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.59 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.7, 160.0, 153.4, 145.4, 135.8, 134.3 133.9, 131.5, 130.8, 130.4, 128.8, 128.7, 128.6, 126.8, 111.6, 77.4, 67.6, 64.6, 26.5, 14.7. Two carbons are missing due to overlapping; IR (film): ῡ = 3281, 3062, 3034, 2982, 2934, 2158, 1989, 1731, 1676, 1598, 1548, 1499, 1445, 1393, 1358, 1249, 1217, 1156, 1072, 1042, 976, 912, 882, 814, 743, 698, 632, 606, 586, 546, 516, 498, 485, 472, 462, 452, 441, 432, 417, 405; HRMS (ESI): m/z: calcd for $C_{23}H_{23}N_2O_4^+$: 391.1652, found: 391.1648.

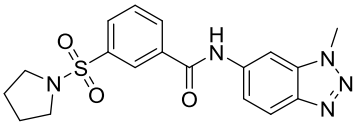
Methyl 5-(5-acetyl-2-ethoxyphenyl)thiophene-2-carboxylate (60)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 4:1 to 2:1), **60** was obtained in 66 % yield. Beige solid; mp: 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 2.2 Hz, 1H), 7.93 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.79 (d, *J* = 4.1 Hz, 1H), 7.57 (d, *J* = 4.1 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 2.61 (s, 3H), 1.59 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.5, 163.2, 158.9 145.4, 133.2, 133.1, 130.4, 130.4, 129.2, 126.1, 122.6, 111.9, 65.2, 52.3, 26.5, 14.8; IR (film): ῡ = 3090, 3075, 2982, 2952, 2357, 2178, 2159, 2039, 1981, 1702, 1677, 1666, 1599, 1575, 1533, 1499, 1446, 1399, 1359, 1315, 1283, 1255, 1232, 1187, 1137, 1110, 1040, 967, 921, 891, 819, 807, 786, 745, 694, 637, 622, 595, 547, 517, 493, 472; HRMS (ESI): m/z: calcd for $C_{16}H_{17}O_4S^+$: 305.0842, found: 305.0843.

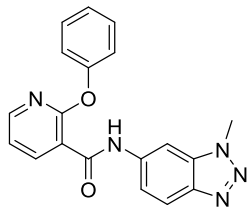
9.6 Virtual chemical reactions: synthesis of BRD4(1) inhibitors bearing an amide linker (70-79)

***N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide (70)**



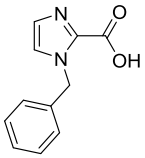
Amide **70** was obtained following general procedure A for amide formation (chromatography: EtOAc = 100 %). Light red solid; Yield: 23 %; mp 223-229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.84 (s, 1H), 8.43 (d, *J* = 1.2 Hz, 1H), 8.39 (t, *J* = 1.6 Hz, 1H), 8.35 – 8.30 (m, 1H), 8.09 – 8.00 (m, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.28 (s, 3H), 3.21 (t, *J* = 6.8 Hz, 4H), 1.81 – 1.61 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.5, 142.1, 137.9, 136.8, 135.5, 133.6, 132.1, 130.2, 129.8, 126.3, 119.2, 118.8, 100.3, 47.9, 34.0, 24.7; IR (neat): ῡ = 3328, 2926, 1649, 1538, 1498, 1348, 1264, 1159, 1127, 1012, 809, 689, 661, 610, 577, 443 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{19}N_5NaO_3S^+$: 408.1101, found: 408.1108.

***N*-(1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-phenoxynicotinamide (71)**



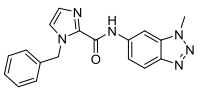
To a solution of 2-phenoxynicotinic acid (109 mg, 0.506 mmol) in dichloromethane (4.3 mL) oxalyl chloride (54 µL) and two drops of dimethylformamide were added. The solution was stirred at room temperature for one hour and it was concentrated under reduced pressure. The aniline (50 mg, 0.337 mmol) was then added in 6.4 mL of tetrahydrofuran, together with a catalytic amount of DMAP (10 mg) and Et_3N (0.43 mL). The reaction was stirred at room temperature for 12 h. It was concentrated under reduced pressure and the obtained residue was purified by flash column chromatography (EtOAc), obtaining the desired product in pure form as a white solid; Yield: 23 %; mp 209-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (s, 1H), 8.47 (d, J = 1.0 Hz, 1H), 8.26 (dd, J = 4.9, 1.9 Hz, 1H), 8.14 (dd, J = 7.4, 2.0 Hz, 1H), 7.99 (dd, J = 9.0, 0.4 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.29 (dd, J = 7.4, 4.9 Hz, 1H), 7.25 – 7.20 (m, 3H), 4.27 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.9, 159.3, 153.4, 148.9, 142.0, 139.4, 137.9, 133.7, 129.5, 124.8, 121.7, 121.0, 119.5, 118.9, 118.0, 99.0, 34.0; IR (neat): ῡ = 2922, 1697, 1581, 1419, 1271, 1251, 1190, 1144, 1122, 851, 766, 750, 741, 672, 419 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{16}N_5O_2^+$: 346.1299, found: 346.1300.

1-Benzyl-1*H*-imidazole-2-carboxylic acid (137)[43]



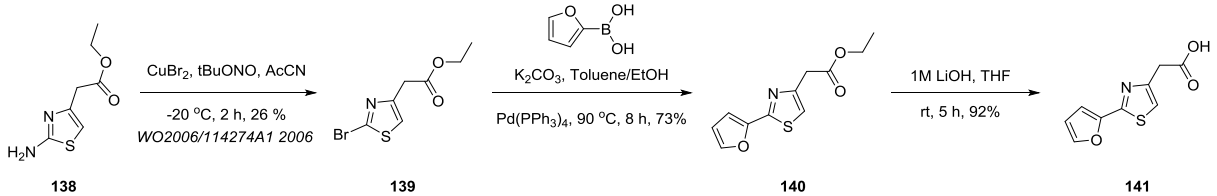
1-Benzyl-1*H*-imidazole-2-carboxylic acid was prepared according to the previously reported procedure and used in the next step without further purification.

1-Benzyl-*N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-1*H*-imidazole-2-carboxamide (72)

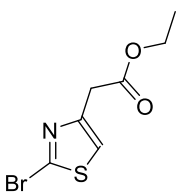


Amide **72** was obtained following the general procedure A for amide formation (chromatography: EtOAc = 100 %). Pale red solid; Yield: 29 %; mp 106-109 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.74 (s, 1H), 8.44 (d, J = 1.1 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.72 (dd, J = 9.0, 1.6 Hz, 1H), 7.62 (s, 1H), 7.42 – 7.23 (m, 5H), 7.19 (s, 1H), 5.77 (s, 2H), 4.25 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.6, 142.0, 137.9, 137.8, 137.6, 133.5, 128.6, 128.0, 127.6, 127.0, 126.4, 119.1, 118.7, 99.4, 50.3, 34.0; IR (neat): ῡ = 3341, 1673, 1593, 1541, 1498, 1456, 1238, 1218, 1112, 832, 784, 748, 710, 681, 657 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{17}N_6O^+$: 333.1448, found: 333.1454.

Synthesis of compound 73:

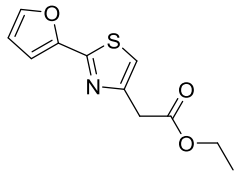


Ethyl 2-(2-bromothiazol-4-yl)acetate (139)[44]



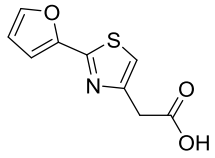
Ester **139** was prepared according to the previously reported procedure. Colourless oil; Yield: 26 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 0.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.80 (d, J = 0.9 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 149.4, 135.5, 120.1, 61.2, 36.8, 14.1; IR (neat): ῡ = 3104, 2979, 1731, 1368, 1334, 1250, 1154, 1015, 738 cm^{-1}; HRMS (ESI): m/z: calcd for $C_7H_9BrNO_2S^+$: 249.9532, found: 249.9532.

Ethyl 2-(2-(furan-2-yl)thiazol-4-yl)acetate (140)



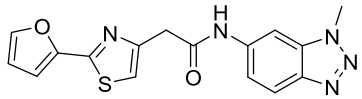
To a solution of ethyl 2-(2-bromothiazol-4-yl)acetate (**139**, 200 mg, 0.80 mmol) in 1.8 mL of toluene and 1.5 mL of ethanol, furan-2-ylboronic acid (224 mg, 2.00 mmol), K_2CO_3 (884 mg, 6.40 mmol) and $Pd(PPh_3)_4$ (55mg, 0.048mmol) was added. The reaction mixture was stirred at 80 °C for 8 h. It was then concentrated under reduced pressure and extracted with water and ethylacetate. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc = 5:1) obtaining the desired product in pure form as a brown oil in 73 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.11 (t, *J* = 0.7 Hz, 1H), 6.92 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.45 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.82 (d, *J* = 0.8 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 157.5, 149.6, 148.6, 143.3, 115.1, 112.0, 108.8, 60.8, 36.8, 14.0; IR (neat): ῡ = 3115, 2981, 1732, 1512, 1501, 1368, 1252, 1222, 1153, 1025, 875, 739, 592 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{12}NO_3S^+$: 238.0532, found: 238.0532.

2-(2-(Furan-2-yl)thiazol-4-yl)acetic acid (141)



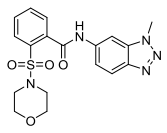
Acid **141** was obtained following the general procedure for ester hydrolysis but after concentration under reduced pressure, the mixture was diluted with water and extracted with dichloromethane three times. The pH of the water phase was then brought to pH = 1 by addition of HCl (1 M) and extracted with ethylacetate three times. The combined organic phases were dried over MgSO4 and concentrated under reduced pressure. The obtained residue was used without further purification. Light brown solid; Yield: 91 %; mp 132-136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.45 (s, 1H), 7.86 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.49 (s, 1H), 7.06 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.69 (dd, *J* = 3.5, 1.8 Hz, 1H) 3.76 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.4, 156.5, 150.6, 148.2, 144.7, 116.4, 112.6, 109.0, 36.6; IR (neat): ῡ = 3127, 2963, 2887, 1713, 1495, 1400, 1305, 1259, 1199, 1158, 1045, 967, 878, 748, 707, 699, 626, 585 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_8NO_3S^+$: 210.0219, found: 210.0220.

2-(2-(Furan-2-yl)thiazol-4-yl)-*N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)acetamide (73)



Amide **27** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:3). Pale yellow solid; Yield: 51 %; mp 165-169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.61 (s, 1H), 8.34 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.86 (d, *J* = 1.1 Hz, 1H), 7.54 (s, 1H), 7.37 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.06 (d, *J* = 3.4 Hz, 1H), 6.68 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.21 (s, 3H), 3.94 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.2, 156.5, 151.1, 148.2, 144.7, 141.7, 138.2, 133.7, 119.4, 117.6, 116.3, 112.6, 109.9, 98.4, 33.9; IR (neat): ῡ = 3250, 3111, 1677, 1601, 1552, 1503, 1456, 1241, 1126, 1033, 1012, 877, 809, 749, 590, 561, 477 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{14}N_5O_2S^+$: 340.0863, found: 340.0869.

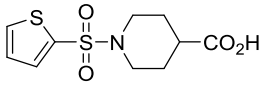
***N*-(1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-(morpholinosulfonyl)benzamide (74)**



Amide **74** was obtained following the general procedure B for amide formation (chromatography: EtOAc = 100 %). Yellow solid; Yield: 29 %; mp 90-97 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.57 (s, 1H), 7.88 (dd, *J* = 8.9, 0.6 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.43 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.21 (s, 3H), 3.77 – 3.61 (m, 4H), 3.60 – 3.45 (m, 2H), 3.15 – 3.00 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.9, 142.0, 136.8, 135.8, 133.7, 133.6, 129.7, 128.4, 127.8, 119.8, 117.8, 98.7, 65.6, 65.4, 47.0, 41.8, 33.9. One carbon is missing due to overlapping; IR (neat): ῡ = 3181, 2922, 2858, 1621, 1607, 1450, 1351, 1281, 1257, 1163, 1110, 1066, 1017, 780, 733,

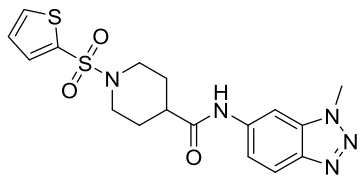
640, 598, 573, 557, 528 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{19}N_5NaO_4S^+$: 424.1050, found: 424.1050.

1-(Thiophen-2-ylsulfonyl)piperidine-4-carboxylic acid (142)[45]



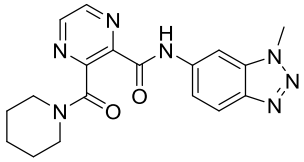
Sulfonamide **142** was prepared according to the previously reported procedure. Light purple solid; Yield: 36 %; mp 134-138 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.29 (s, 1H), 8.04 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.62 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.62 (dd, *J* = 3.7, 1.3 Hz, 1H), 3.53 – 3.40 (m, 2H), 2.37 – 2.23 (m, 1H), 1.97 – 1.84 (m, 2H), 1.68 – 1.50 (m, 2H), 2H are missing due to overlapping with the solvent.

***N*-(1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-1-(thiophen-2-ylsulfonyl)piperidine-4-carboxamide (75)**



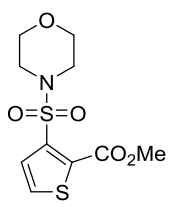
Amide **75** was obtained following the general procedure B for amide formation (chromatography: EtOAc = 100 %). Brown solid; Yield: 17 %; mp 126-133 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.21 (s, 1H), 8.31 (s, 1H), 8.06 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.67 (dd, *J* = 3.7, 1.1 Hz, 1H) 7.39 – 7.19 (m, 2H), 4.21 (s, 3H), 3.79 – 3.63 (m, 2H), 1.94 (dd, *J* = 13.9, 2.8 Hz, 2H), 1.71 (td, *J* = 15.5, 4.0 Hz, 2H), three protons are missing due to overlapping with the solvent; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.1, 141.7, 138.2, 135.5, 133.7, 133.7, 132.9, 128.3, 119.3, 117.6, 98.4, 45.3, 41.3, 33.9, 27.5; IR (neat): $\tilde{\upsilon}$ = 3255, 3209, 2847, 1690, 1596, 1550, 1503, 1347, 1226, 1165, 1022, 1007, 924, 825, 719, 598, 576 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{20}N_5O_3S_2^+$: 406.1002, found: 406.0999.

***N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-3-(piperidine-1-carbonyl)pyrazine-2-carboxamide (76)**



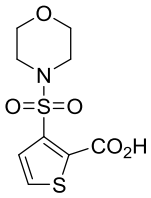
Amide **76** was obtained following the general procedure A for amide formation (chromatography: EtOAc/MeOH = 100:4). Red solid; Yield: 72 %; mp 140-146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 1H), 8.91 (d, *J* = 2.5 Hz, 1H), 8.86 (d, *J* = 2.5 Hz, 1H), 8.42 (d, *J* = 1.2 Hz, 1H), 8.02 (dd, *J* = 9.0, 0.6 Hz, 1H), 7.72 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.28 (s, 3H), 3.63 (t, *J* = 5.0 Hz, 2H), 3.21 – 3.14 (m, 2H), 1.71 – 1.38 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.8, 162.2, 150.7, 146.3, 143.2, 143.0, 142.2, 137.4, 133.5, 119.3, 118.6, 99.8, 47.1, 41.8, 34.1, 25.2, 24.9, 24.0; IR (neat): $\tilde{\upsilon}$ = 2940, 2857, 1684, 1629, 1537, 1505, 1355, 1290, 1223, 1132, 1102, 1003, 852, 816, 784, 747, 668, 628, 530 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{20}N_7O_2^+$: 366.1673, found: 366.1665.

Methyl 3-(morpholinosulfonyl)thiophene-2-carboxylate (143)



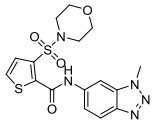
To a solution of methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (500 mg, 2.08 mmol) in dichloromethane (43.0 mL) morpholine (543 µL, 6.23 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. It was extracted with water and HCl (1 M). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The obtained solid was then washed with diethylether affording the desired product in pure form as a white solid in 59 % yield. mp 99-102 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, *J* = 5.2 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 3.85 (s, 3H), 3.69 – 3.55 (m, 4H), 3.23 – 3.02 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.1, 138.2, 134.3, 131.3, 130.1, 65.6, 53.2, 45.9; IR (neat): $\tilde{\upsilon}$ = 3126, 2971, 2957, 2919, 1733, 1434, 1355, 1343, 1235, 1145, 1113, 1065, 938, 799, 758, 717, 648, 591, 584, 506 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{10}H_{13}NNaO_5S_2^+$: 314.0127, found: 314.0126.

3-(Morpholinosulfonyl)thiophene-2-carboxylic acid (144)



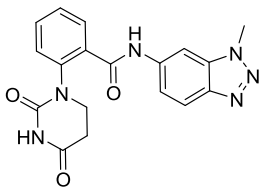
Acid **144** was obtained following the general procedure for ester hydrolysis. White solid; Yield: 87 %; mp 182-188 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.83 (br, 1H), 7.93 (d, J = 5.2 Hz, 1H), 7.40 (d, J = 5.2 Hz, 1H), 3.76 – 3.55 (m, 4H), 3.37 – 2.90 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.0, 137.5, 136.7, 130.3, 130.1, 65.6, 45.9; IR (neat): ῡ = 3432, 3108, 3088, 1693, 1426, 1339, 1274, 1259, 1179, 1146, 1107, 1071, 955, 922, 849, 781, 766, 717, 648, 597, 584 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{11}NNaO_5S_2^+$: 299.9971, found: 299.9966.

***N*-(1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-3-(morpholinosulfonyl)thiophene-2-carboxamide (77)**



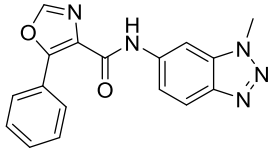
Amide **77** was obtained following the general procedure A for amide formation (chromatography: hexane/EtOAc = 1:2). Light red solid; Yield: 10 %; mp 235-241 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.08 (s, 1H), 8.33 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.42 (dd, J = 9.0, 1.7 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 4.27 (s, 3H), 3.73 – 3.53 (m, 4H), 3.10 – 3.03 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.5, 142.12 141.9, 137.5, 133.6, 132.7, 128.3, 127.1, 119.5, 118.0, 99.4, 65.4, 45.8, 34.0; IR (neat): ῡ = 3304, 3103, 2873, 1655, 1604, 1561, 1507, 1335, 1323, 1260, 1172, 1145, 1115, 943, 850, 813, 725, 646, 596, 594 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{17}N_5O_4S_2^+$: 408.0799, found: 408.0796.

2-(2,4-Dioxotetrahydropyrimidin-1(2*H*)-yl)-*N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)benzamide (78)



Amide **78** was obtained following the general procedure B for amide formation but at the end of the reaction, the mixture was diluted with ethylacetate and extracted with HCl (1 M), washed with $NaHCO_3$ (5% aq. solution) and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was triturated with ethylacetate and dichloromethane, obtaining the desired amide in pure form. White solid; Yield: 19 %; mp 286-302 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.58 (s, 1H), 10.40 (s, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.02 (dd, J = 7.9, 1.6 Hz, 1H), 7.93 (dd, J = 8.9, 0.6 Hz, 1H), 7.76 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.29 (dd, J = 9.0, 1.8 Hz, 1H), 7.29 – 7.24 (m, 1H), 4.40 (t, J = 7.4 Hz, 2H), 4.23 (s, 3H), 2.76 (t, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.4, 161.8, 150.1, 141.7, 140.8, 138.1, 135.3, 133.7, 127.7, 122.5, 119.3, 117.7, 115.8, 114.6, 98.5, 38.8, 34.5, 33.9; IR (neat): ῡ = 3578, 3359, 1668, 1606, 1501, 1485, 1401, 1332, 1320, 1228, 816, 752, 494, 486 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{17}N_6O_3^+$: 365.1357, found: 365.1361.

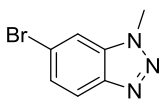
***N*-(1-Methyl-1H-benzo[*d*][1,2,3]triazol-6-yl)-5-phenyloxazole-4-carboxamide (79)**



Amide **79** was obtained following the general procedure B for amide formation (chromatography: hexane/EtOAc = 2:1). Pink solid; Yield: 32 %; mp 208-216 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.58 (s, 1H), 8.74 (s, 1H), 8.50 (s, 1H), 8.28 – 8.14 (m, 2H), 7.99 (d, J = 9.0 Hz, 1H), 7.72 (dd, J = 9.0, 1.7 Hz, 1H), 7.59 – 7.49 (m, 3H), 4.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.9, 152.3, 150.5, 142.1, 137.6, 133.6, 130.3, 128.8, 128.6, 128.0, 126.7, 119.1, 118.9, 99.9, 34.0; IR (neat): ῡ = 3341, 1665, 1596, 1564, 1530, 1503, 1492, 1221, 1194, 1057, 847, 824, 684, 640, 626 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{14}N_5O_2^+$: 320.1142, found: 320.1136.

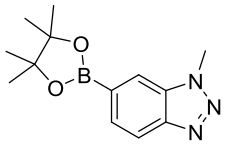
9.7 Virtual chemical reactions: synthesis of BRD4(1) inhibitors without a linker (80-89)

6-Bromo-1-methyl-1*H*-benzo[*d*][1,2,3]triazole (145)



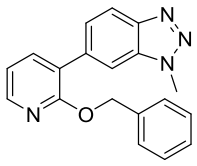
To a solution of 4-bromo-2-fluoro-1-nitrobenzene (2.0 g, 9.09 mmol) in ethanol (8.0 mL), a 40 % methylamine solution in water (2.4 mL) was added. The reaction was stirred at room temperature for 2 days, water was added (100 mL) and it was allowed to stirr for 10 min. It was diluted with brine and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue obtained was redissolved in 133 mL of ethanol. A solution of 11.3 g of $Na_2S_2O_4$ in water (107 mL) was then added dropwise and stirred at room temperature for 2 h. The solution was diluted with brine and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was dissolved in an aqueous solution of HBr (2 M, 30 mL) and cooled to 0 ºC. A solution of sodium nitrite (0.77 g) in water (9.7 mL) was added dropwise and the solution was stirred at room temperature for 4 h. It was diluted with $NaHCO_3$ (saturated aqueous solution) and extracted with ethylacetate three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/EtOAc = 3:1), obtaining the desired product in clean form (750 mg, 39 % yield over three steps). Brown solid; mp 119-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, J = 8.8, 0.7 Hz, 1H), 7.73 (dd, J = 1.6, 0.6 Hz, 1H), 7.48 (dd, J = 8.8, 1.7 Hz, 1H), 4.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.8, 134.5, 127.6, 121.7, 121.2, 112.2, 34.3; IR (neat): $\tilde{\upsilon}$ = 3083, 1606, 1454, 1341, 1259, 1193, 1013, 924, 839, 804, 795, 752 cm^{-1}; HRMS (ESI): m/z: calcd for $C_7H_7BrN_3^+$: 211.9818, found: 211.9818.

1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (69)



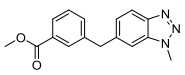
To a solution of 6-Bromo-1-methyl-1H-benzo[d][1,2,3]triazole (**145**, 100 mg, 0.47 mmol) in dioxane (3.3 mL), KOAc (96 mg, 0.98 mmol), $(Bpin)_2$ (120 mg, 0.47 mmol) and $Pd(dppf)Cl_2$ (14 mg, 0.019 mmol) were added. The solution was degassed with nitrogen for 5 min. It was then stirred at 90 ºC for 12 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by flash column chromatography (hexane/ EtOAc = 3:1), affording the desired product in pure form (116 mg, 95 % yield). Pale yellow solid; mp 119-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 – 8.00 (m, 2H), 7.79 (d, J = 8.7 Hz, 1H), 4.33 (s, 3H), 1.39 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 133.3, 129.3, 119.0, 116.3, 84.3, 34.3, 24.9; IR (neat): $\tilde{\upsilon}$ = 2984, 1504, 1359, 1341, 1308, 1190, 1145, 1126, 1054, 1011, 966, 859, 819, 783, 685 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{13}H_{19}BN_3O_2^+$: 260.1565, found: 260.1566.

6-(2-(Benzyloxy)pyridin-3-yl)-1-methyl-1*H*-benzo[*d*][1,2,3]triazole (80)



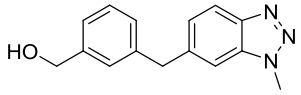
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 2:1), **80** was obtained in 60 % yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (dd, J = 4.9, 1.6 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.62 (dd, J = 7.3, 1.6 Hz, 1H), 7.45 (dd, J = 8.6, 0.7 Hz, 1H), 7.27 (s, 1H), 7.23 – 7.12 (m, 4H), 6.92 (dd, J = 7.2, 5.0 Hz, 1H), 5.36 (s, 2H), 4.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.2, 146.4, 145.3, 139.0, 137.3, 136.0, 133.6, 128.4, 127.7, 127.5, 125.8, 123.8, 119.4, 117.5, 109.7, 67.8, 34.1; IR (neat): $\tilde{\upsilon}$ = 3057, 2942, 1585, 1574, 1428, 1361, 1293, 1258, 1241, 1199, 1012, 930, 793, 729, 695, 648 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{17}N_4O^+$: 317.1397, found: 317.1399.

Methyl 3-((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)methyl)benzoate (146)



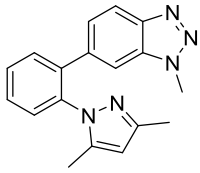
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:1), **146** was obtained in 69 % yield; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.42 – 7.36 (m, 2H), 7.26 (s, 1H), 7.21 (dd, *J* = 8.6, 1.3 Hz, 1H), 4.24 (s, 3H), 4.20 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 144.9, 140.6, 140.5, 133.9, 133.5, 130.6, 130.0, 128.7, 127.8, 125.7, 119.9, 108.6, 52.1, 41.9, 34.1; IR (neat): $\tilde{\upsilon}$ = 2950, 1715, 1445, 1433, 1279, 1199, 1106, 1082, 751, 715 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{16}N_3O_2^+$: 282.1237, found: 282.1236.

(3-((1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)methyl)phenyl)methanol (81)



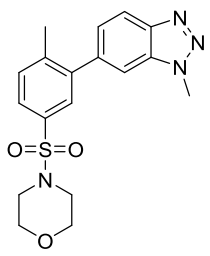
To a solution of **146** (30 mg, 0.107 mmol) in tetrahydrofuran (2.0 mL) at 0 ºC, $LiAlH_4$ (12.1 mg, 0.320 mmol) was added. The reaction was stirred at room temperature for 2 h and quenched by the sequential addition of water (0.05 mL), NaOH (5 % aqueous solution, 0.15 mL) and water (0.15 mL). It was filtered off, concentrated under reduced pressure and the obtained residue was purified by flash column chromatography (EtOAc/hexane = 3:1), delivering the desired alcohol as a colourless oil in 67 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.6 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.14 (d, *J* = 7.4 Hz, 1H), 4.67 (s, 2H), 4.23 (s, 3H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 141.4, 141.0, 140.6, 133.9, 128.9, 128.2, 127.5, 125.9, 125.1, 119.7, 108.5, 65.1, 42.1, 34.1; IR (neat): $\tilde{\upsilon}$ = 3333, 2906, 1621, 1466, 1433, 1284, 1198, 1045, 1021, 956, 882, 794, 779, 710, 694, 432 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{16}N_3O^+$: 254.1288, found: 254.1286.

6-(2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)phenyl)-1-methyl-1*H*-benzo[*d*][1,2,3]triazole (82)



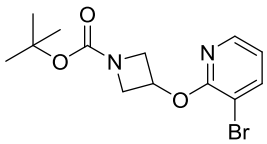
Following the general procedure for Suzuki cross-coupling reactions (chromatography: EtOAc = 100 %), **82** was obtained in 31 % yield; White solid; mp 176-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.55 – 7.51 (m, 2H), 7.28 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.11 (s, 1H), 5.75 (s, 1H), 4.15 (s, 3H), 2.31 (s, 3H), 1.59 (d, *J* = 0.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.4, 145.1, 141.0, 138.6, 137.4, 133.7, 130.6, 129.6, 129.1, 129.0, 125.0, 119.7, 109.0, 105.9, 34.0, 13.4, 11.1. One carbon is missing due to overlapping; IR (neat): $\tilde{\upsilon}$ = 2918, 1553, 1484, 1458, 1198, 1013, 828, 782, 774, 759, 698, 530 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{18}N_5^+$: 304.1557, found: 304.1564.

4-((4-Methyl-3-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)phenyl)sulfonyl)morpholine (83)



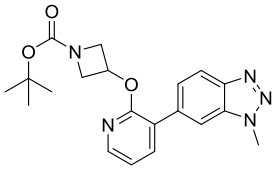
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:2), **83** was obtained in 71 % yield; Pink solid; mp 211-216 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.5 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.67 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 4.34 (s, 3H), 3.83 – 3.67 (m, 4H), 3.11 – 2.94 (m, 4H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.4, 142.3, 141.6, 139.6, 133.8, 133.0, 131.3, 129.1, 127.2, 125.5, 120.0, 109.4, 66.2, 46.1, 34.3, 20.6; IR (neat): $\tilde{\upsilon}$ = 1454, 1344, 1332, 1264, 1203, 1165, 1113, 938, 831, 737, 653, 556, 513, 505 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{21}N_4O_3S^+$: 373.1330, found: 373.1329.

***tert*-Butyl 3-((3-bromopyridin-2-yl)oxy)azetidine-1-carboxylate (147)**



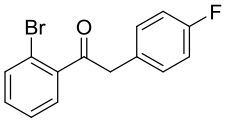
To a solution of 3-bromopyridin-2-ol (300 mg, 1.724 mmol) in dimethylformamide (5.9 mL), *tert*-butyl 3-iodoazetidine-1-carboxylate (488 mg, 1.724 mmol) and K_2CO_3 (715 mg, 5.172 mmol) were added. The solution was stirred at 80 ºC for 12 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was redissolved in ethylacetate and extracted with water. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 1:2), affording the desired product in pure form (180 mg, 32 % yield). Brown solid; mp 95-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.54 (dd, *J* = 7.0, 1.7 Hz, 1H), 6.20 (t, *J* = 7.1 Hz, 1H), 5.53 (tt, *J* = 8.1, 5.2 Hz, 1H), 4.45 – 4.31 (m, 2H), 3.98 (dd, *J* = 9.9, 5.2 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 155.9, 141.2, 132.4, 116.5, 106.9, 80.4, 55.6, 46.4, 28.2; IR (neat): $\tilde{\upsilon}$ = 2979, 2959, 1685, 1652, 1598, 1421, 1364, 1225, 1141, 1127, 1070, 989, 861, 752, 567, 549 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{13}H_{18}BrN_2O_3^+$: 329.0495, found: 329.0498.

***tert*-Butyl-3-((3-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)pyridin-2-yl)oxy)azetidine-1-carboxylate (84)**



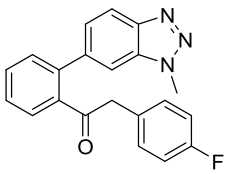
Following the general procedure for Suzuki cross-coupling reactions (chromatography: EtOAc = 100 %), **84** was obtained in 54 % yield; White solid; mp 138-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 – 8.04 (m, 2H), 7.63 (s, 1H), 7.61 (s, 1H), 7.53 (d, *J* = 10.1 Hz, 1H), 6.48 (t, *J* = 7.0 Hz, 1H), 5.68 – 5.57 (m, 1H), 4.49 (dd, *J* = 9.3, 8.5 Hz, 1H), 4.31 (s, 3H), 4.14 – 4.06 (m, 2H), 1.47 (s, 9H), one proton is missing due to overlapping with the solvent; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4, 156.1, 145.5, 138.3, 135.5, 133.6, 132.66, 130.7, 125.0, 119.6, 109.5, 107.1, 80.5, 77.2, 45.7, 34.3, 28.3; IR (neat): $\tilde{\upsilon}$ = 2979, 1686, 1650, 1595, 1547, 1421, 1280, 1131, 765, 733, 564 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{24}N_5O_3^+$: 382.1874, found: 382.1874.

1-(2-Bromophenyl)-2-(4-fluorophenyl)ethan-1-one (148)[46]



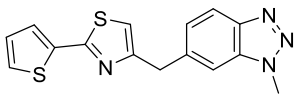
Ketone **148** was prepared according to the previously reported procedure. Yellow oil; Yield: 31%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 – 7.57 (m, 1H), 7.38 – 7.27 (m, 3H), 7.24 – 7.16 (m, 2H), 7.07 – 6.97 (m, 2H), 4.21 (s, 2H).

2-(4-Fluorophenyl)-1-(2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)phenyl)ethan-1-one (85)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:1), **85** was obtained in 60 % yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 8.5, 0.4 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.51 – 7.44 (m, 2H), 7.37 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.29 (s, 1H), 6.84 – 6.76 (m, 2H), 6.74 – 6.66 (m, 2H), 4.16 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 161.8 (d, *J* = 245.8 Hz), 145.4, 140.6, 139.9, 139.3, 133.8, 131.0, 130.8, 130.7 (d, *J* = 8.1 Hz), 129.5 (d, *J* = 3.2 Hz), 128.2, 128.2, 125.3, 120.4, 115.1 (d, *J* = 21.3 Hz), 109.5, 48.5, 34.2; IR (neat): $\tilde{\upsilon}$ = 3058, 2945, 1687, 1597, 1508, 1220, 1198, 1158, 909, 759, 728 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{17}FN_3O^+$: 346.1350, found: 346.1338.

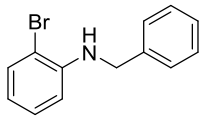
4-((1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)methyl)-2-(thiophen-2-yl)thiazole (86)



Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:1), **86** was obtained in 69 % yield; Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.6 Hz, 1H), 7.50

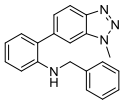
(d, *J* = 3.5 Hz, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.07 (dd, *J* = 4.7, 4.0 Hz, 1H), 6.72 (s, 1H), 4.32 (s, 2H), 4.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.9, 156.2, 145.1, 138.9, 137.3, 133.9, 127.9, 127.6, 126.6, 125.8, 119.9, 114.0, 108.9, 38.1, 34.2; IR (neat): ῡ = 3102, 2975, 2941, 1505, 1458, 1413, 1201, 977, 907, 841, 726, 703 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{13}N_4S_2^+$: 313.0576, found: 313.0583.

N-Benzyl-2-bromoaniline (149)[47]



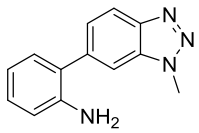
Aniline **149** was prepared according to the previously reported procedure Yellow oil; Yield: 70%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (dd, J = 7.9, 1.4 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.24 – 7.19 (m, 1H), 7.18 – 7.09 (m, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.63 (t, *J* = 7.7 Hz, 1H), 4.43 (s, 2H).

***N*-benzyl-2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)aniline (87)**



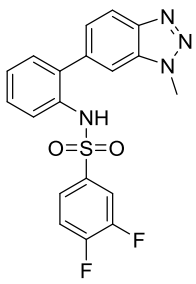
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 3:1), **87** was obtained in 83 % yield; Light yellow solid; mp 155-162 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.13 (m, 7H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 4.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.3, 139.0, 138.8, 134.2, 130.5, 129.4, 128.7, 127.3, 127.3, 125.8, 120.4, 118.0, 111.8, 109.7, 48.6, 34.2. Two carbons are missing due to overlapping; IR (neat): ῡ = 3395, 2929, 1603, 1576, 1516, 1451, 1324, 1282, 1261, 1198, 1019, 817, 742, 730, 694, 460 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{19}N_4^+$: 315.1604, found: 315.1600.

2-(1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)aniline (150)



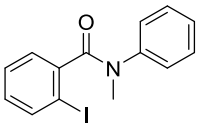
Following the general procedure for Suzuki cross-coupling reactions (chromatography: hexane/EtOAc = 1:1), **150** was obtained in 54 % yield; Grey solid; mp 123-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.6 Hz, 1H), 7.59 (s, 1H), 7.48 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.24-7.16 (m, 2H), 6.87 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 0.7 Hz, 1H), 4.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1, 143.3, 139.1, 134.0, 130.6, 129.1, 126.8, 125.7, 120.2, 118.9, 115.9, 109.3, 34.2; IR (neat): ῡ = 3449, 3358, 1616, 1486, 1450, 1300, 1285, 1258, 1202, 1018, 827, 743 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{13}H_{13}N_4^+$: 225.1135, found: 225.1135.

3,4-Difluoro-*N*-(2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)phenyl)benzenesulfonamide (88)



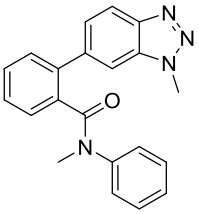
To a solution of **150** (17.5 mg, 0.078 mmol) in dichloromethane (0.2 mL) and Et_3N (19 µL) at 0 ºC, the sulfonyl chloride (13 µL, 0.094 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 12 h. It was then concentrated under reduced pressure and purified by flash column chromatography (hexane/EtAOc = 1:1), obtaining the desired sulfonamide in pure form in 76 % yield as a white solid. mp 214-217 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.46 – 7.31 (m, 3H), 7.31 – 7.18 (m, 3H), 7.13 (td, *J* = 9.4, 7.4 Hz, 1H), 6.94-6.90 (m, 2H), 4.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6 (dd, *J* = 585.5, 12.6 Hz), 151.5 (dd, *J* = 72.7, 13.0 Hz), 144.9, 136.9, 136.4 – 135.9 (m), 134.4, 133.7, 133.0, 130.7, 129.4, 126.2, 125.1, 124.3 (dd, *J* = 7.5, 4.0 Hz), 123.2, 120.4, 118.0 (d, *J* = 18.4 Hz), 117.0 (dd, *J* = 19.9, 1.4 Hz), 109.7, 34.4; IR (neat): ῡ = 3061, 2792, 1613, 1508, 1342, 1330, 1279, 1214, 1206, 1156, 1147, 1070, 947, 822, 775, 763, 675, 633, 608, 572, 529 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{15}F_2N_4O_2S^+$: 401.0878, found: 401.0879.

2-Iodo-*N*-methyl-*N*-phenylbenzamide (151)[48]



Amide **151** was prepared according to the previously reported procedure Light brown oil; Yield: 54%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.9 Hz, 1H), 7.23 – 7.15 (m, 4H), 7.14 – 7.09 (m, 2H), 7.03 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.85 (td, *J* = 7.8, 1.6 Hz, 1H), 3.51 (s, 3H).

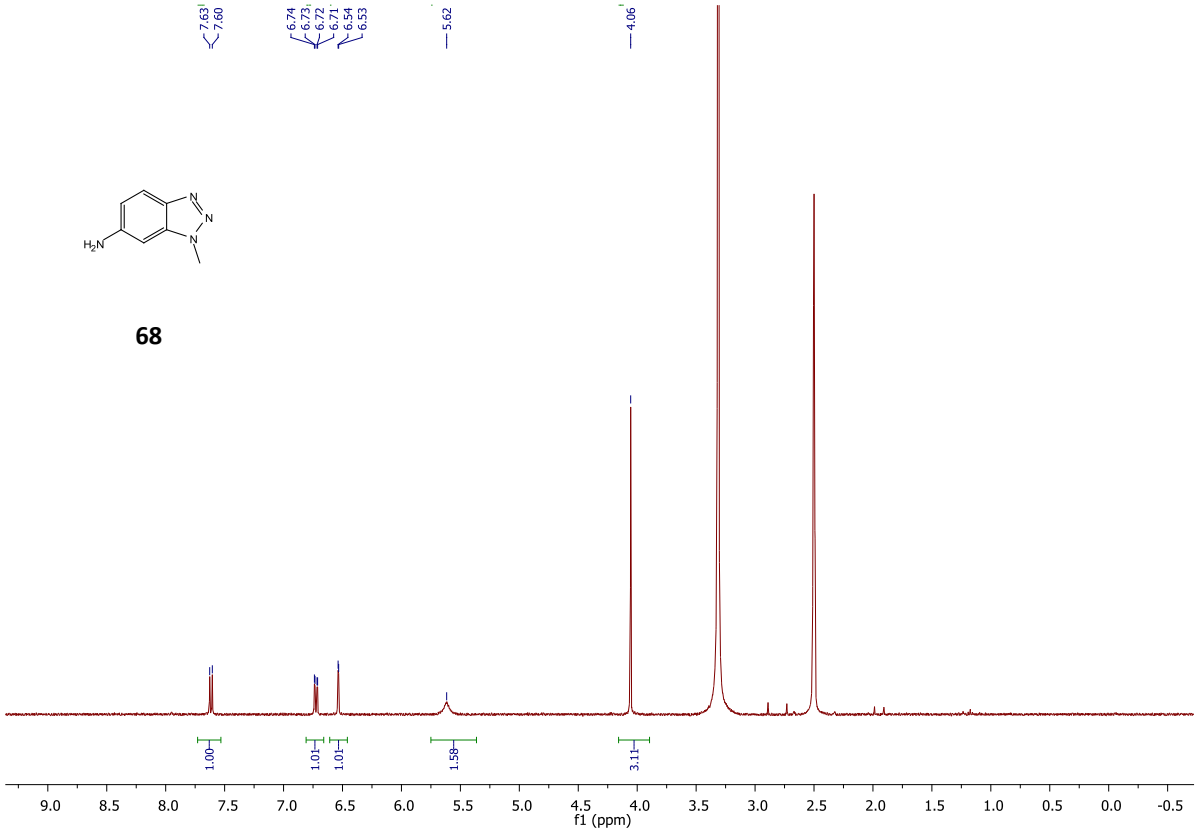
***N*-Methyl-2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-N-phenylbenzamide (89)**

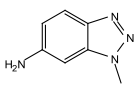


Following the general procedure for Suzuki cross-coupling reactions (chromatography: EtOAc = 100 %), **89** was obtained in 42 % yield; Orange oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.95 (t, *J* = 7.1 Hz, 1H), 6.87 – 6.78 (m, 2H), 6.09 (s, 1H), 6.08 (s, 1H), 4.27 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8, 145.2, 142.5, 139.6, 137.7, 136.4, 133.7, 129.6, 129.4, 129.3, 128.0, 127.9, 125.9, 125.7, 125.5, 119.3, 108.9, 37.0, 34.2; IR (neat): ῡ = 3060, 1631, 1594, 1495, 1368, 1201, 1111, 912, 778, 752, 731, 696, 647 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{19}N_4O^+$: 343.1553, found: 343.1553.

10. NMR traces of selected compounds

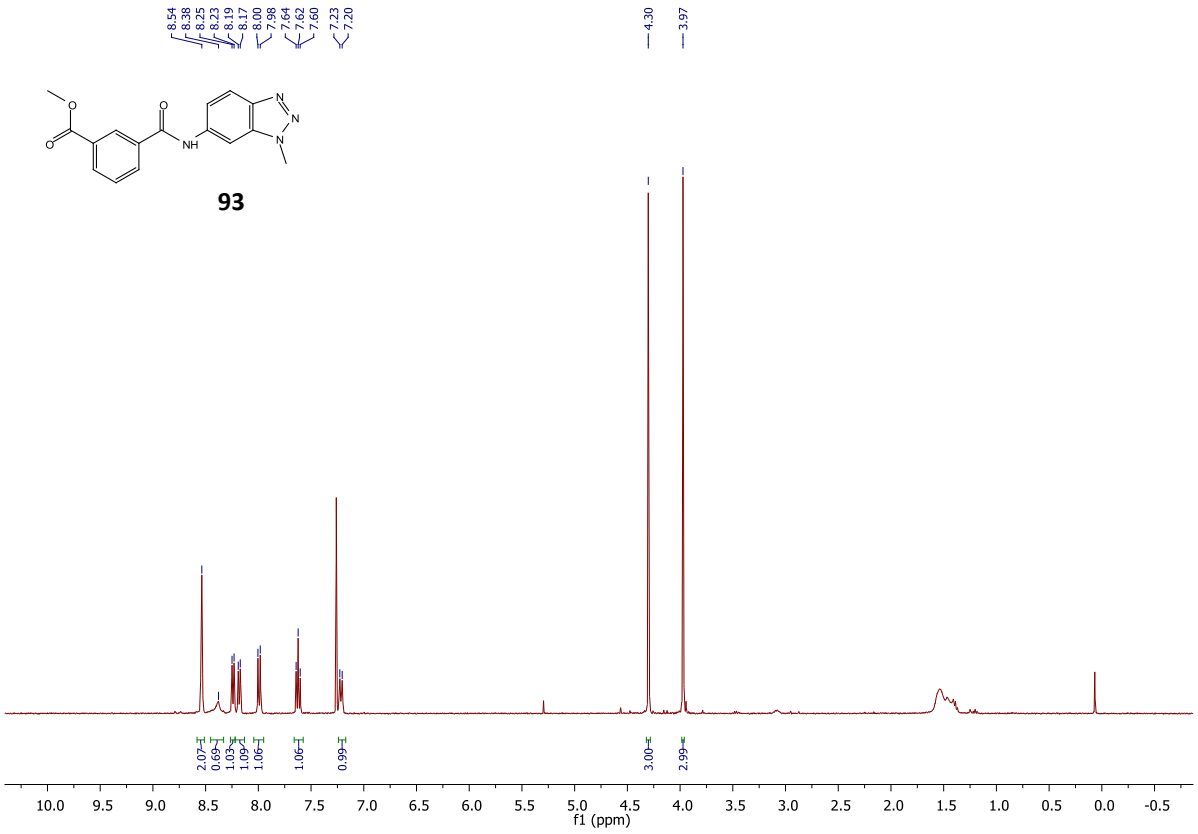
Benzoic acid containing novel bromodomain ligands:



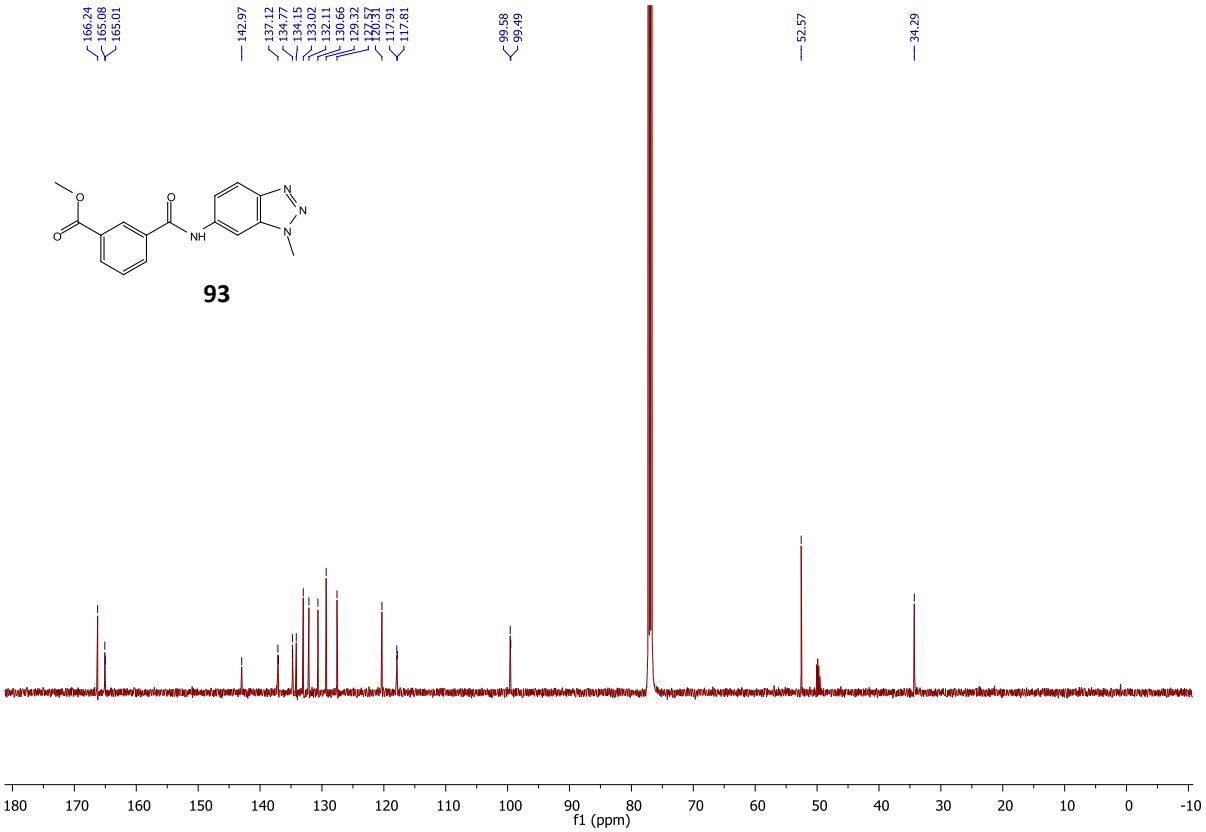


68

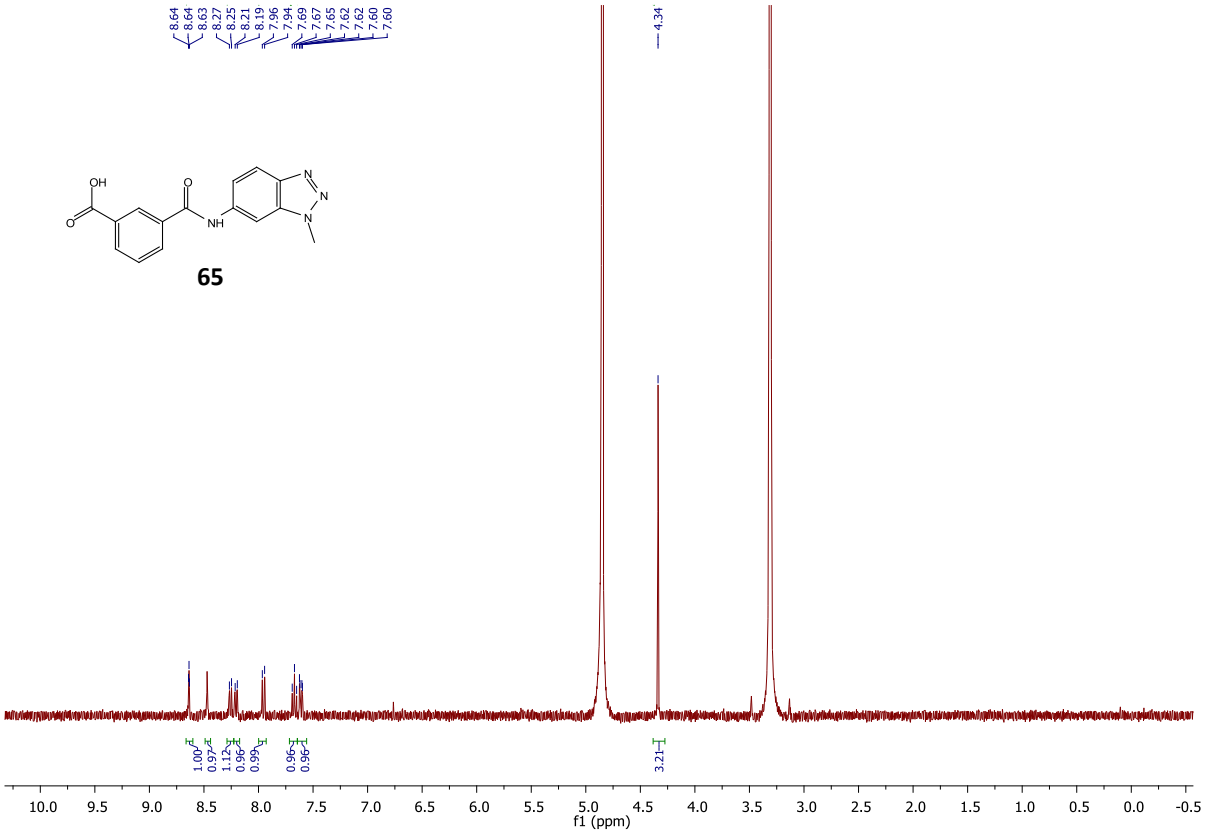
68

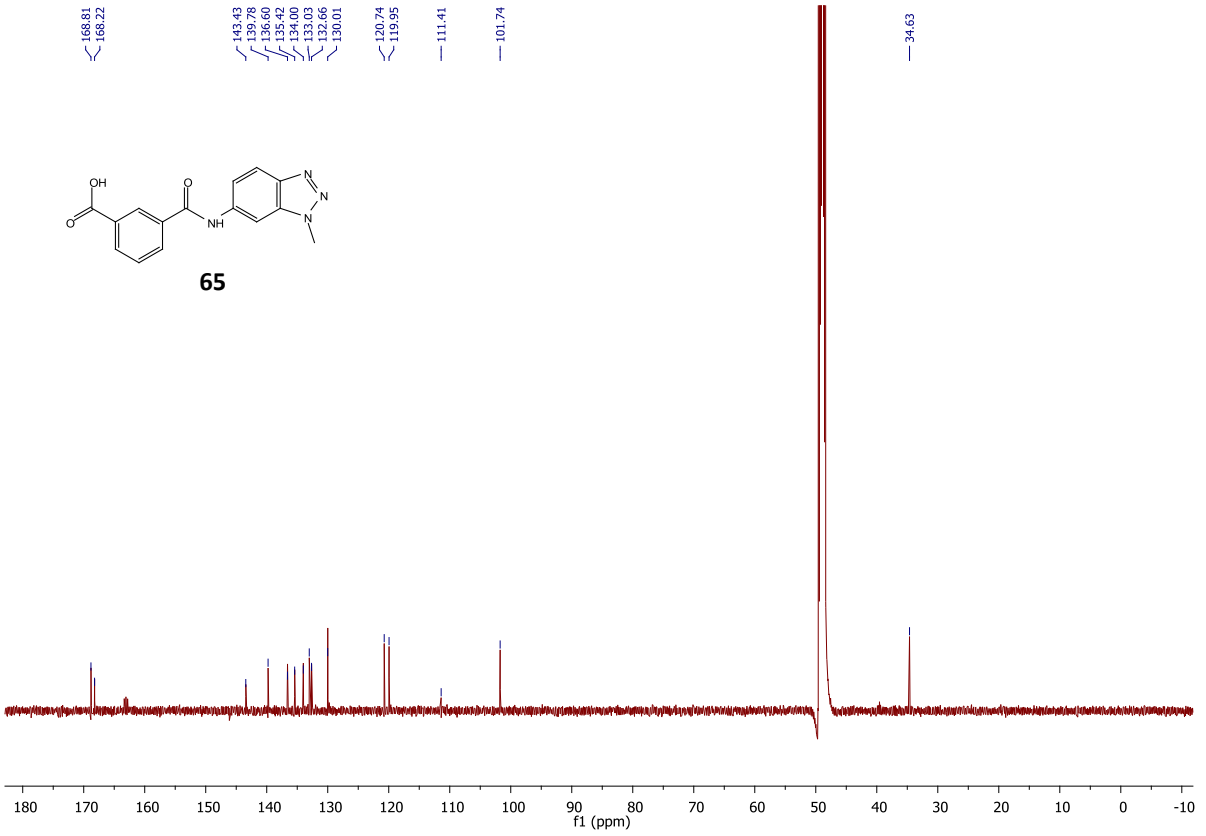

8.54
8.38
8.25
8.23
8.19
8.17
8.00
7.98
7.64
7.62
7.60
7.23
7.20
4.30
3.97
O
O
O
NH
N
N
N
2.07
0.69
1.03
1.09
1.06
1.06
0.99
3.00
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

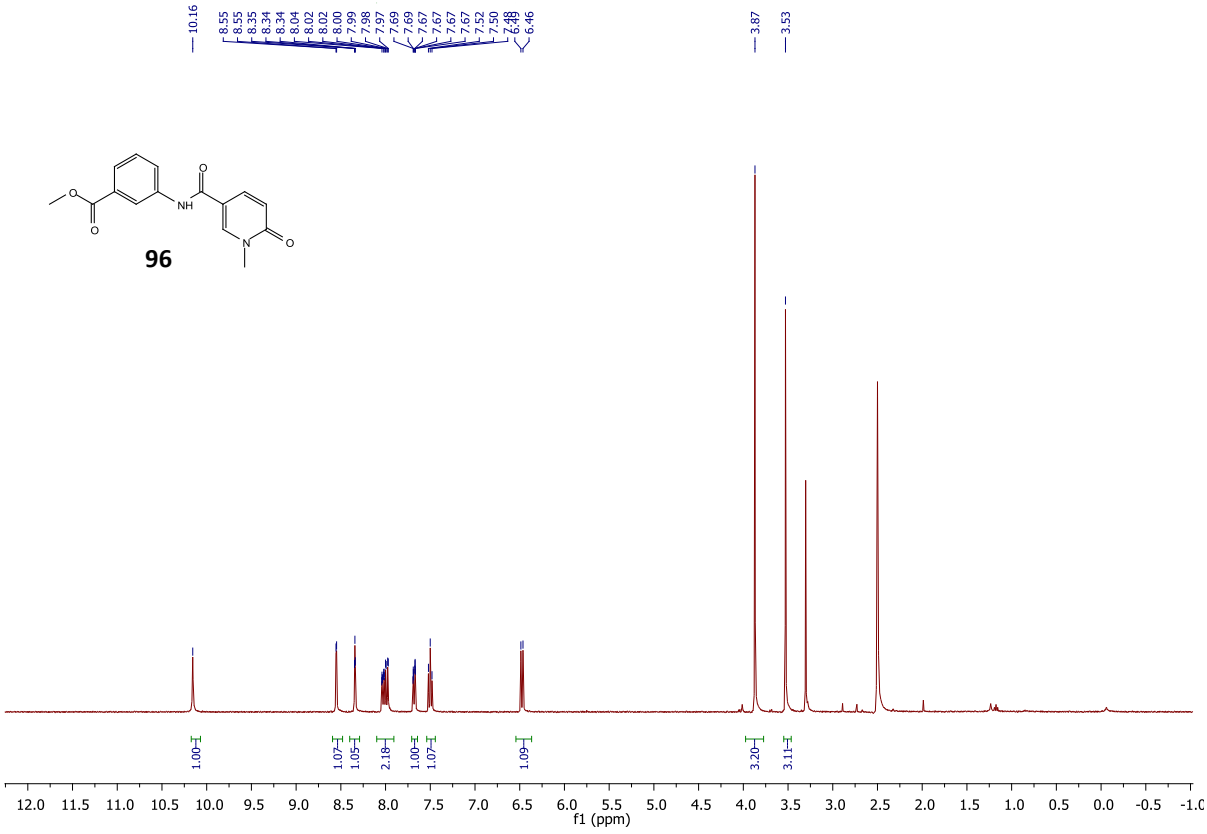
93


166.24
165.08
165.01
142.97
137.12
134.77
134.15
133.02
132.11
130.66
129.32
120.37
120.31
117.91
117.81
99.58
99.49
52.57
34.29
O
O
O
NH
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

93


8.64
8.64
8.63
8.27
8.25
8.21
8.19
7.96
7.94
7.69
7.67
7.65
7.62
7.62
7.60
7.60
4.34
OH
O
O
NH
N
N
N
65
1.00
0.97
1.12
0.96
0.99
0.96
0.96
3.21
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


168.81
168.22
143.43
139.78
136.60
135.42
134.00
133.03
132.66
130.01
120.74
119.95
111.41
101.74
34.63
OH
O
O
NH
N
N
N
65
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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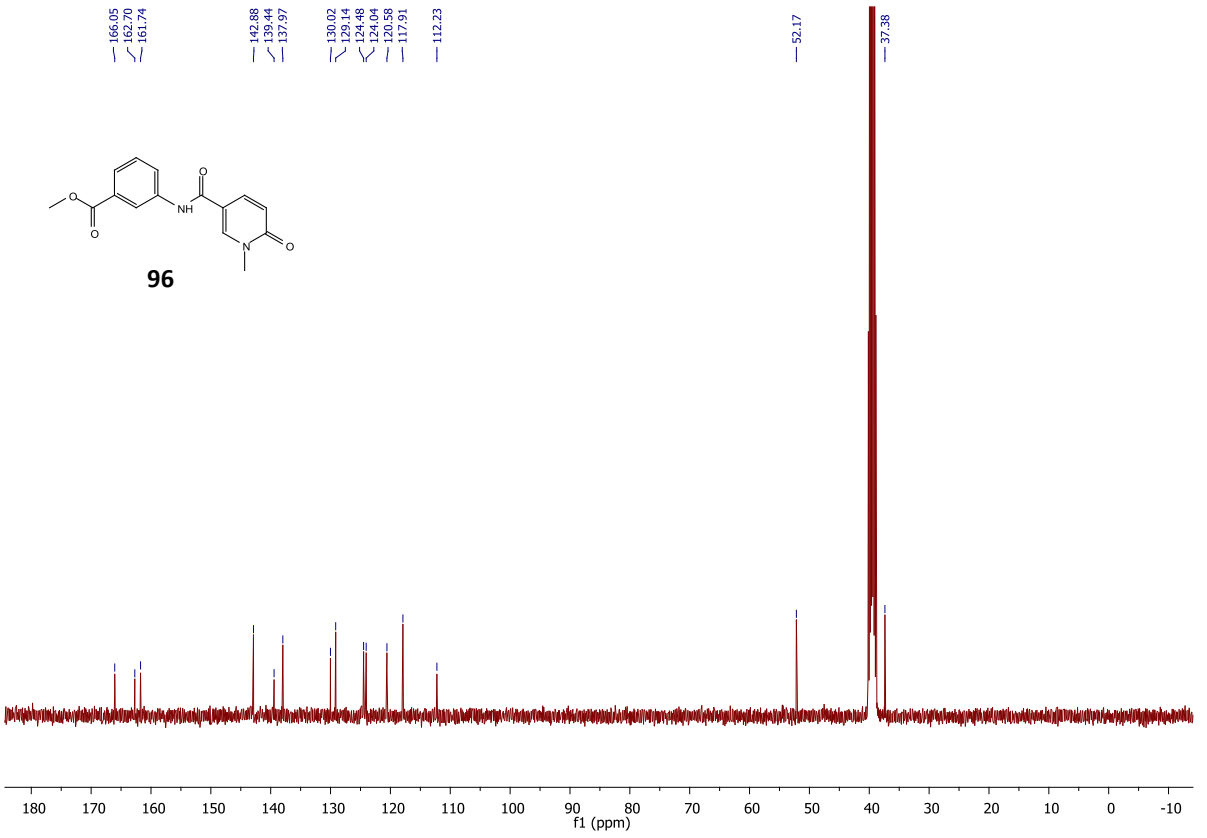
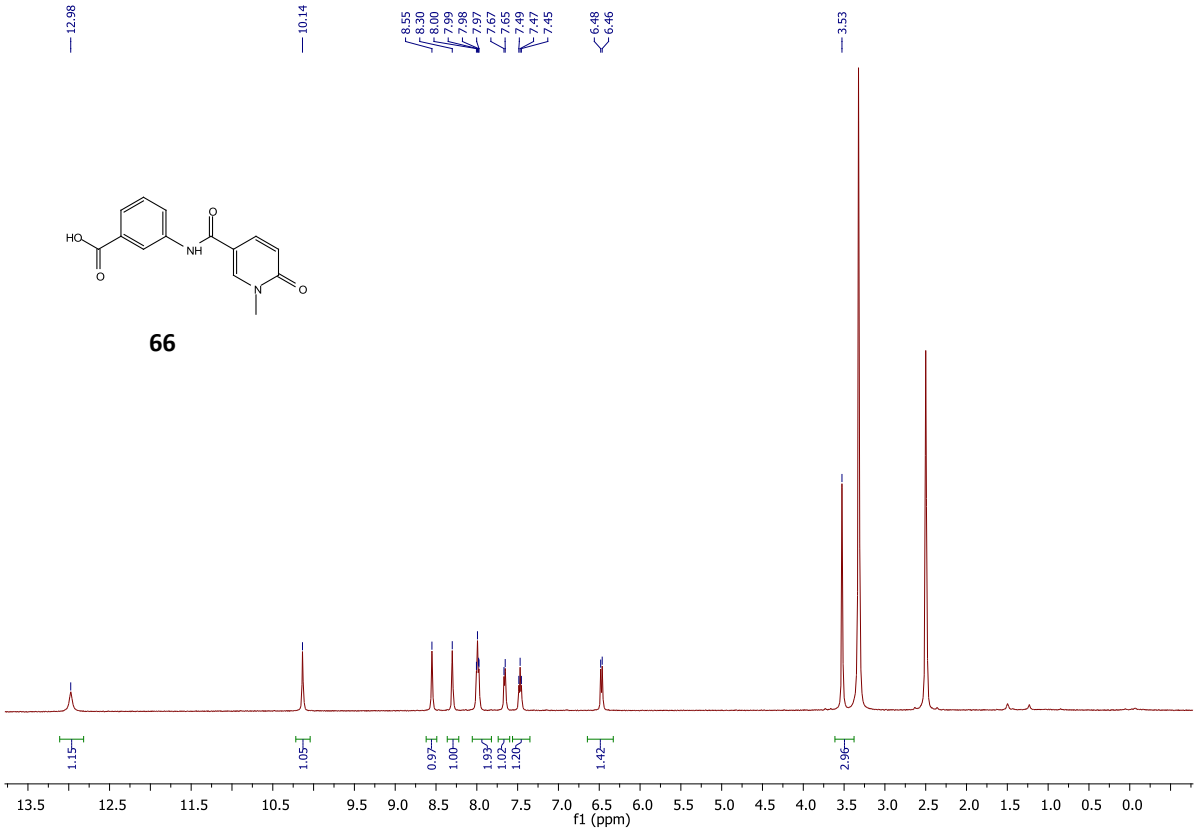
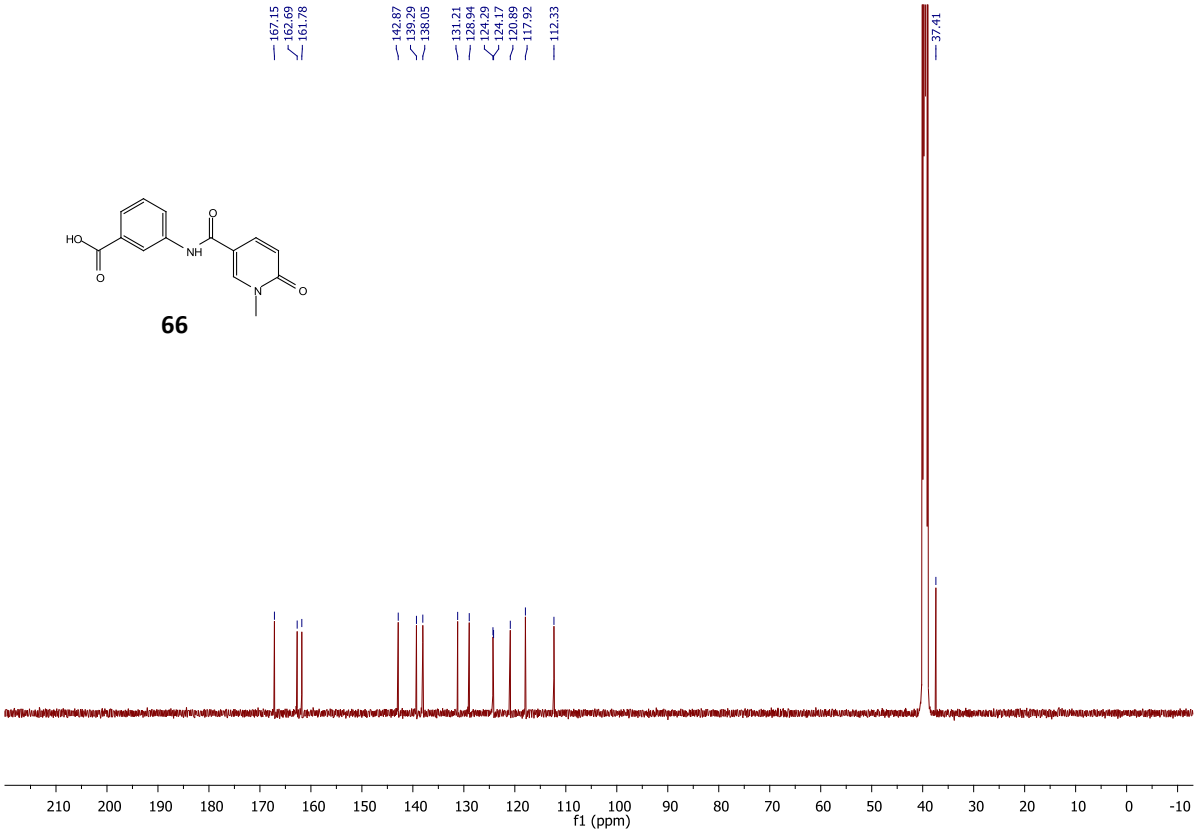
8.55
8.55
8.35
8.34
8.34
8.04
8.02
8.02
8.00
7.99
7.98
7.97
7.69
7.69
7.67
7.67
7.67
7.67
7.52
7.50
6.48
6.46
3.87
3.53
O
NH
O
N
O
O
96
1.00
1.07
1.05
2.18
1.00
1.07
1.09
3.20
3.11
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

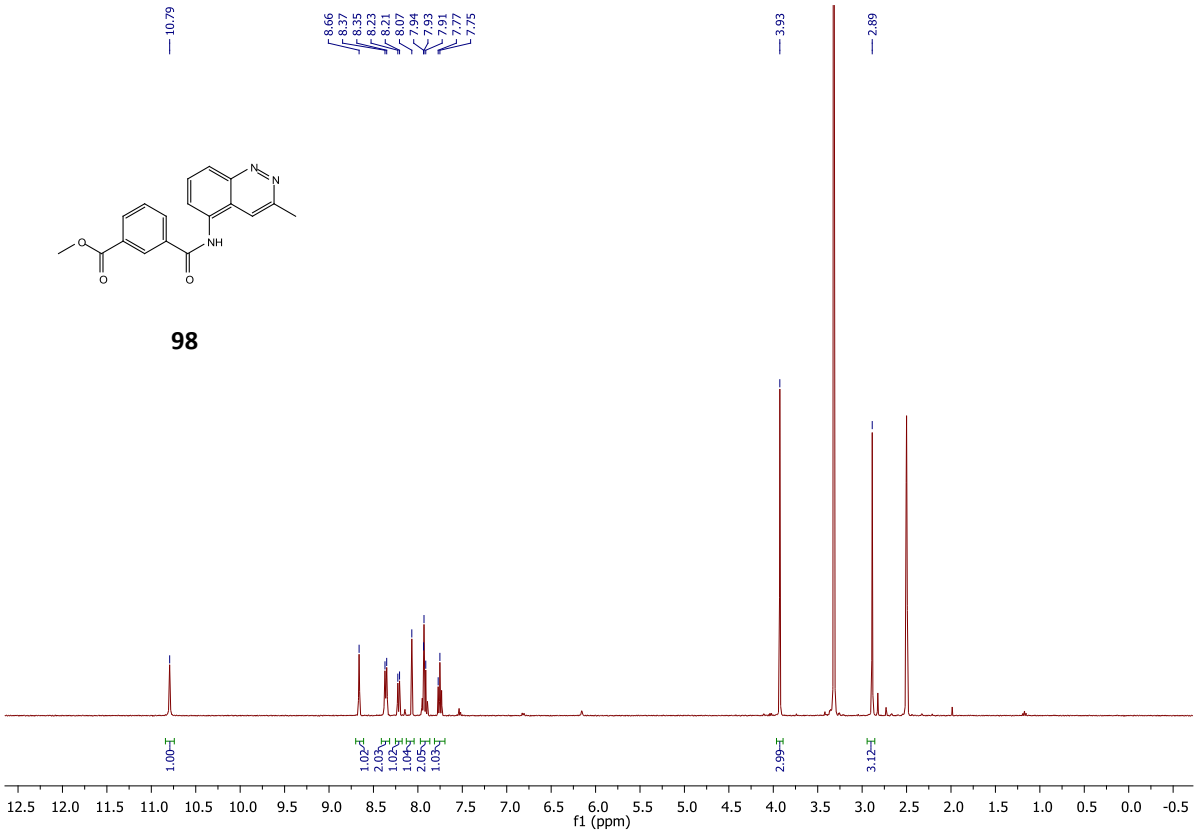

166.05
162.70
161.74
142.88
139.44
137.97
130.02
129.14
124.48
124.04
120.58
117.91
112.23
52.17
37.38
O
NH
O
N
O
O
96
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


12.98
10.14
8.55
8.30
8.00
7.99
7.98
7.97
7.67
7.65
7.49
7.47
7.45
6.48
6.46
3.53
HO
O
NH
O
N
O
1.15
1.05
0.97
1.00
1.93
1.02
1.20
1.42
2.96
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

66


167.15
162.69
161.78
142.87
139.29
138.05
131.21
128.94
124.29
124.17
120.89
117.92
112.33
37.41
HO
O
NH
O
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

66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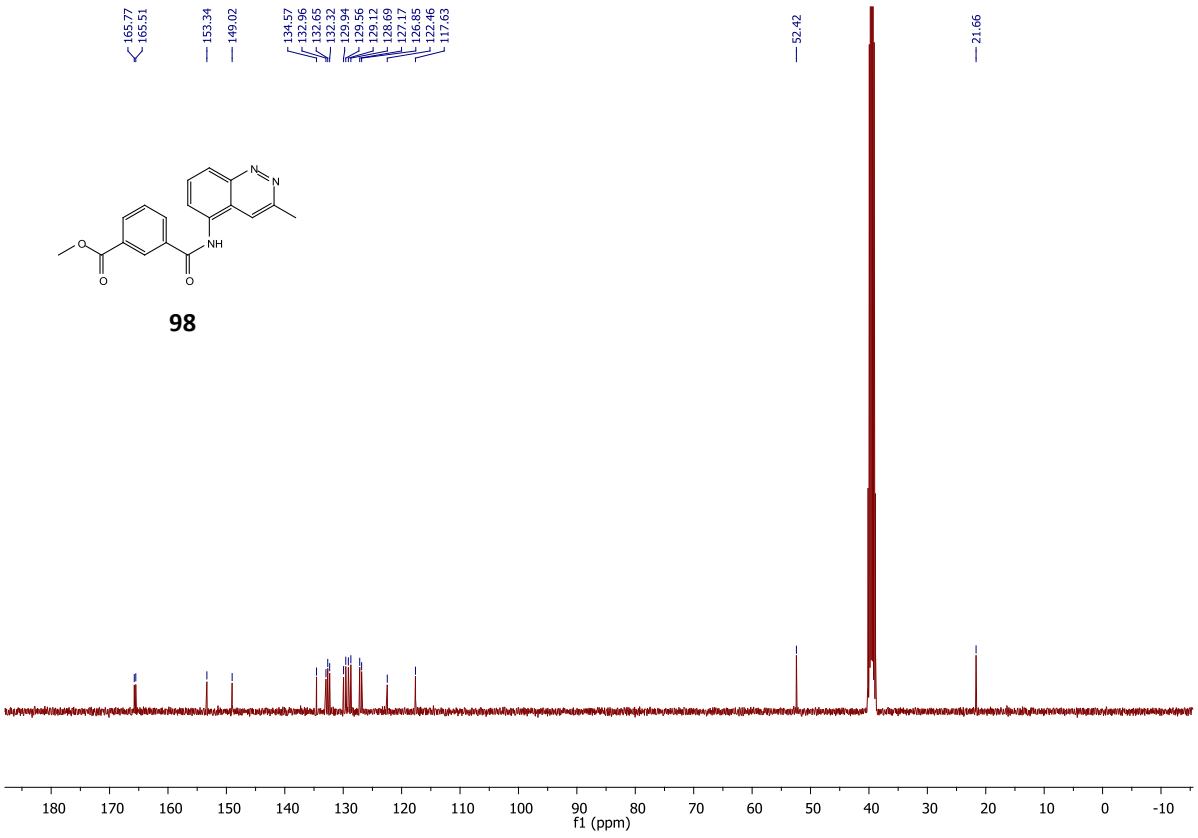
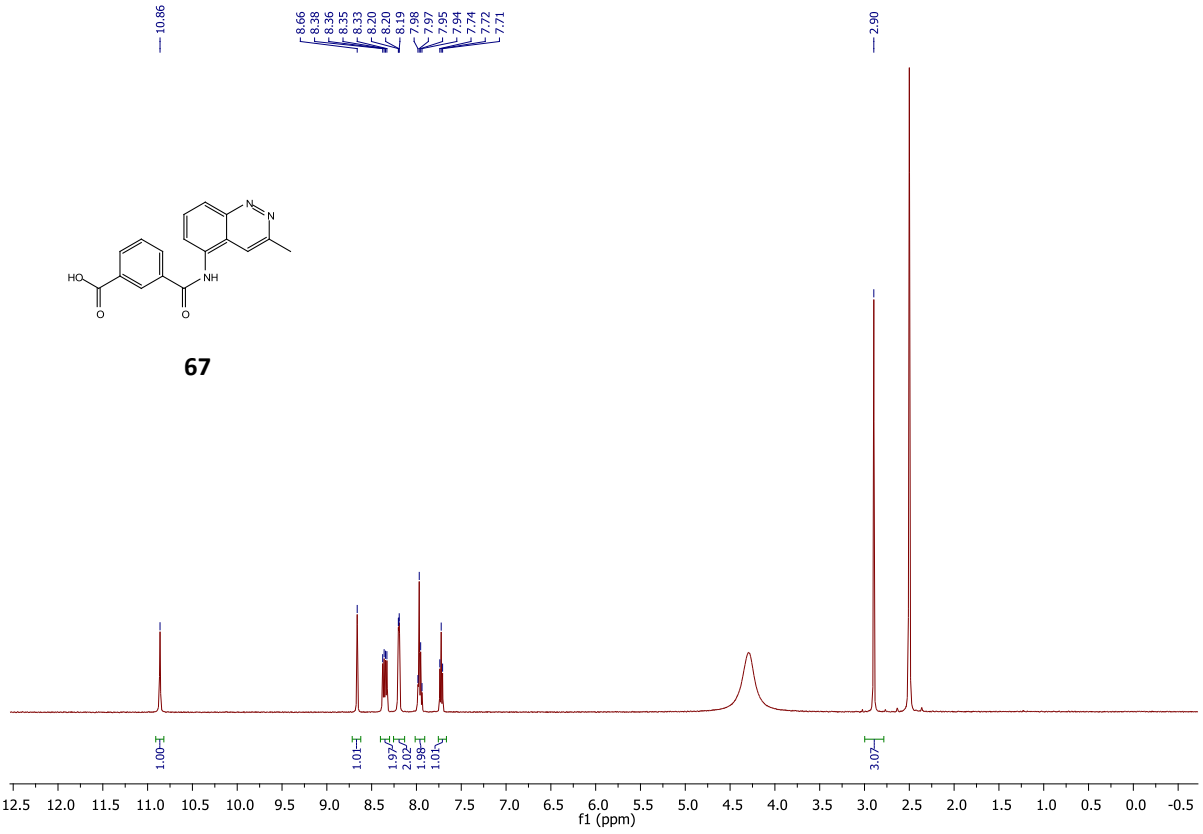
8.35
8.23
8.21
8.07
7.94
7.93
7.91
7.77
7.75
3.93
2.89
1.00
1.02
2.03
1.02
1.04
2.05
1.03
2.99
3.12
f1 (ppm)

98


165.77
165.51
153.34
149.02
134.57
132.96
132.65
132.32
129.94
129.56
129.12
128.69
127.17
126.85
122.46
117.63
52.42
21.66
f1 (ppm)

98


10.86
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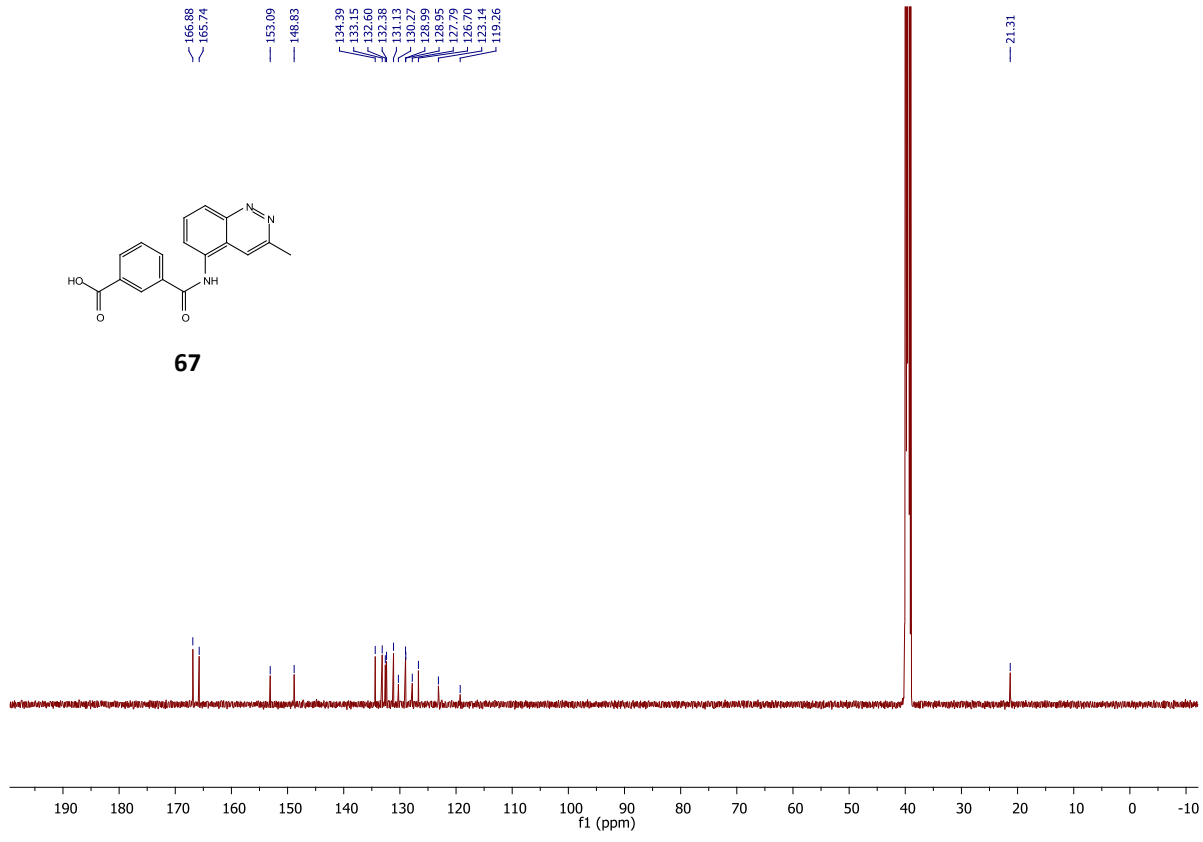
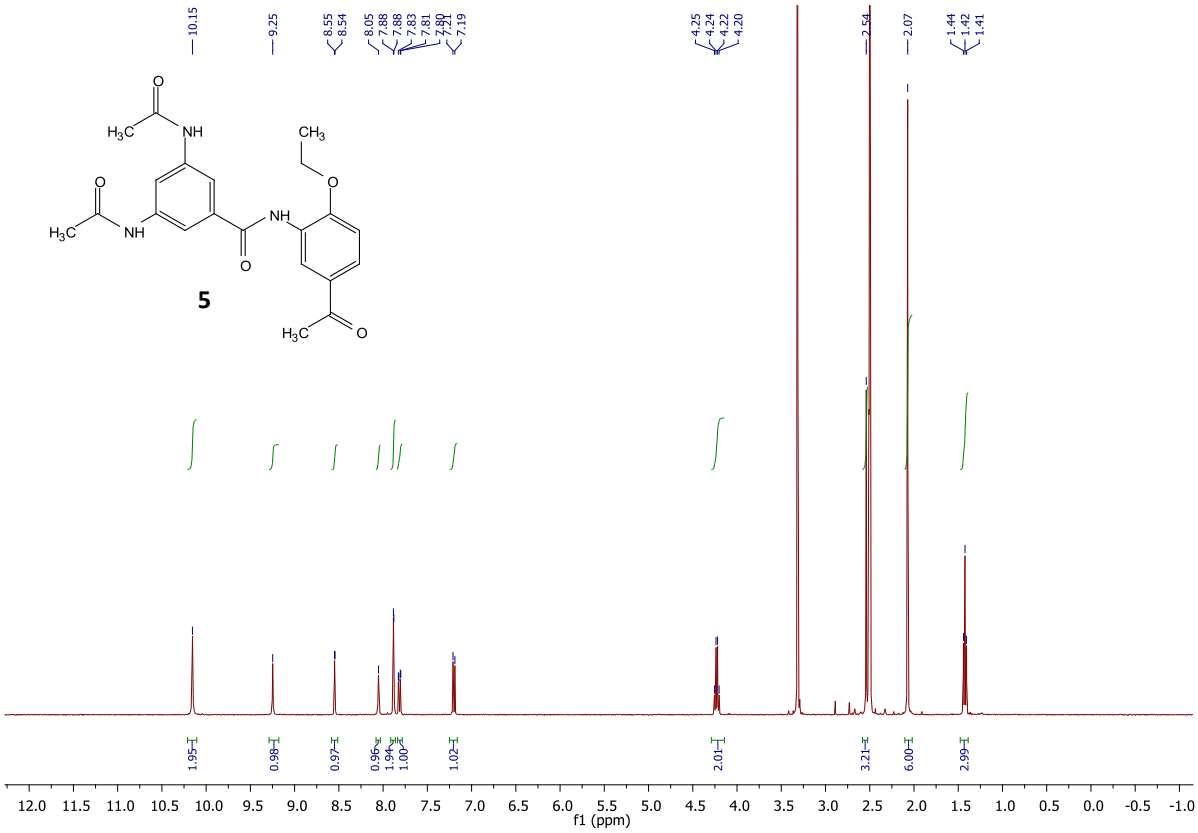
8.38
8.36
8.35
8.33
8.20
8.20
8.19
7.98
7.97
7.95
7.94
7.74
7.72
7.71
2.90
HO
O
NH
O
N
N
1.00
1.01
1.97
2.02
1.98
1.01
3.07
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

67

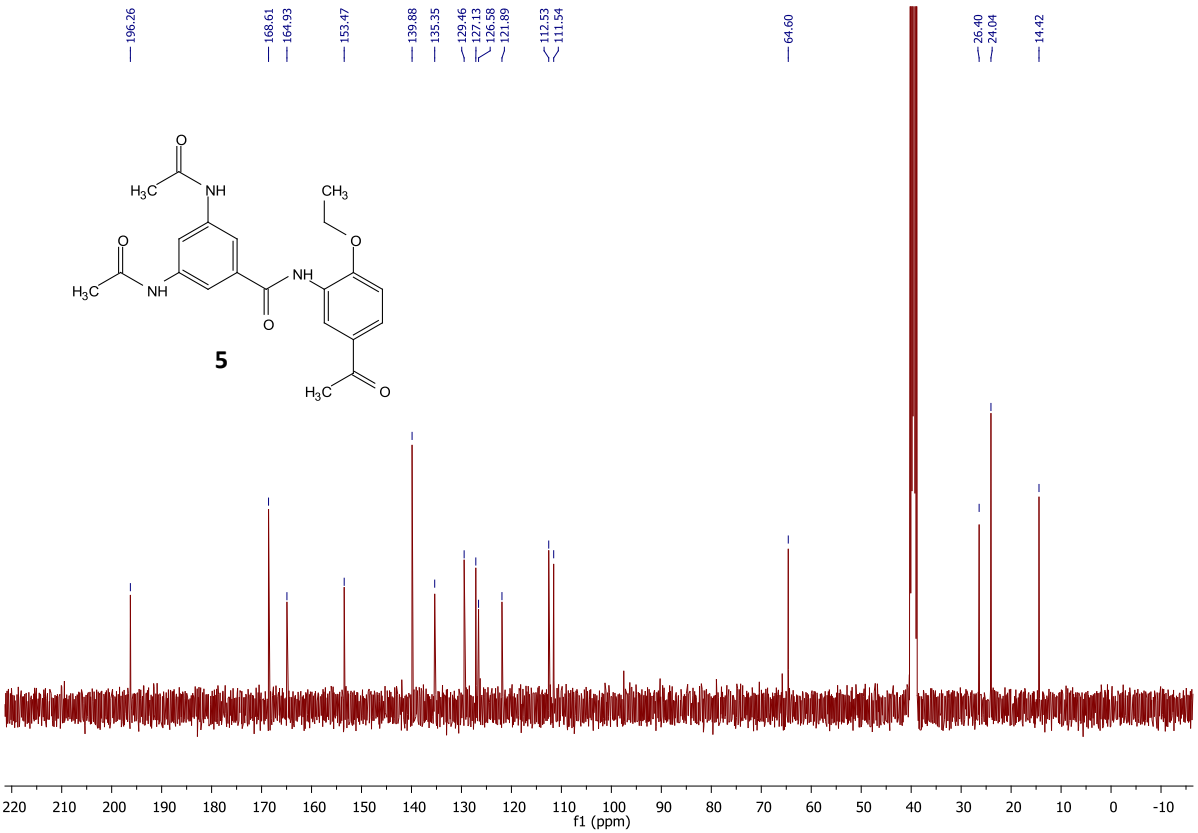

166.88
165.74
153.09
148.83
134.39
133.15
132.60
132.38
131.13
130.27
128.99
128.95
127.79
126.70
123.14
119.26
21.31
HO
O
NH
O
N
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

67

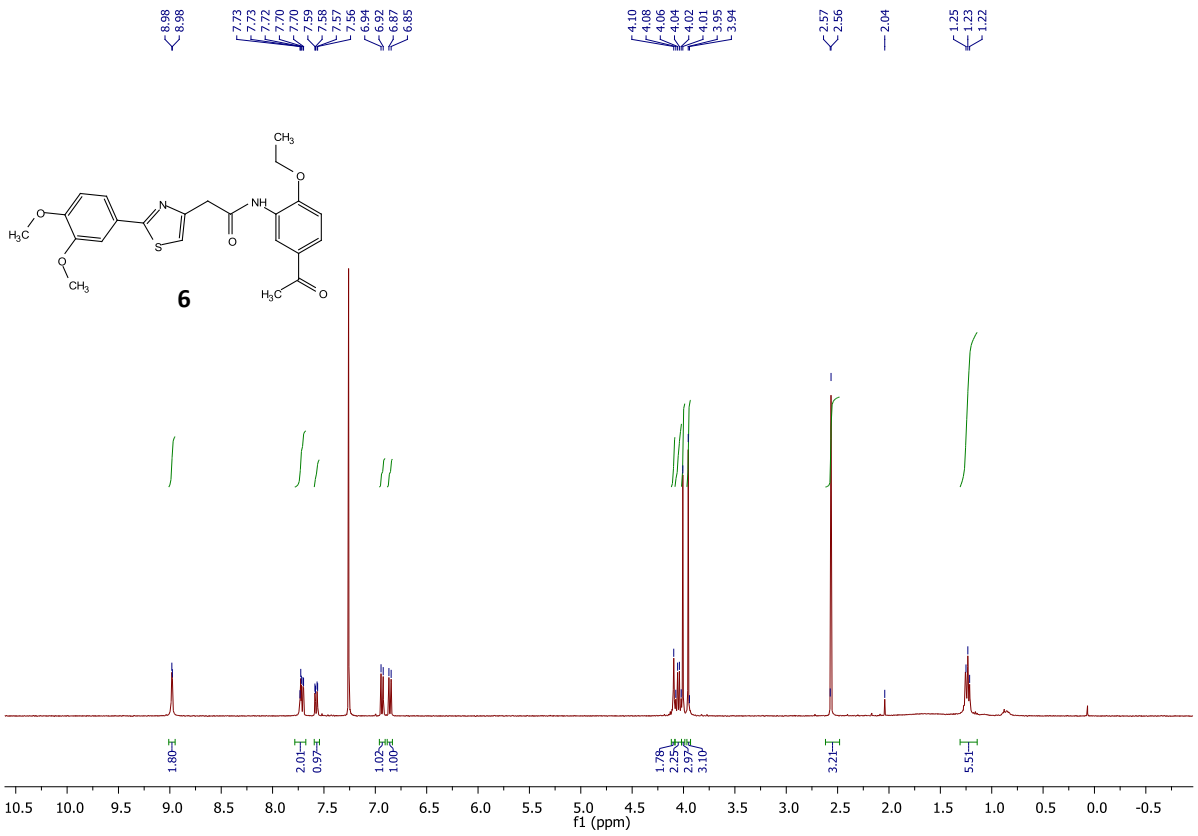
CBP inhibitors bearing an amide linker:

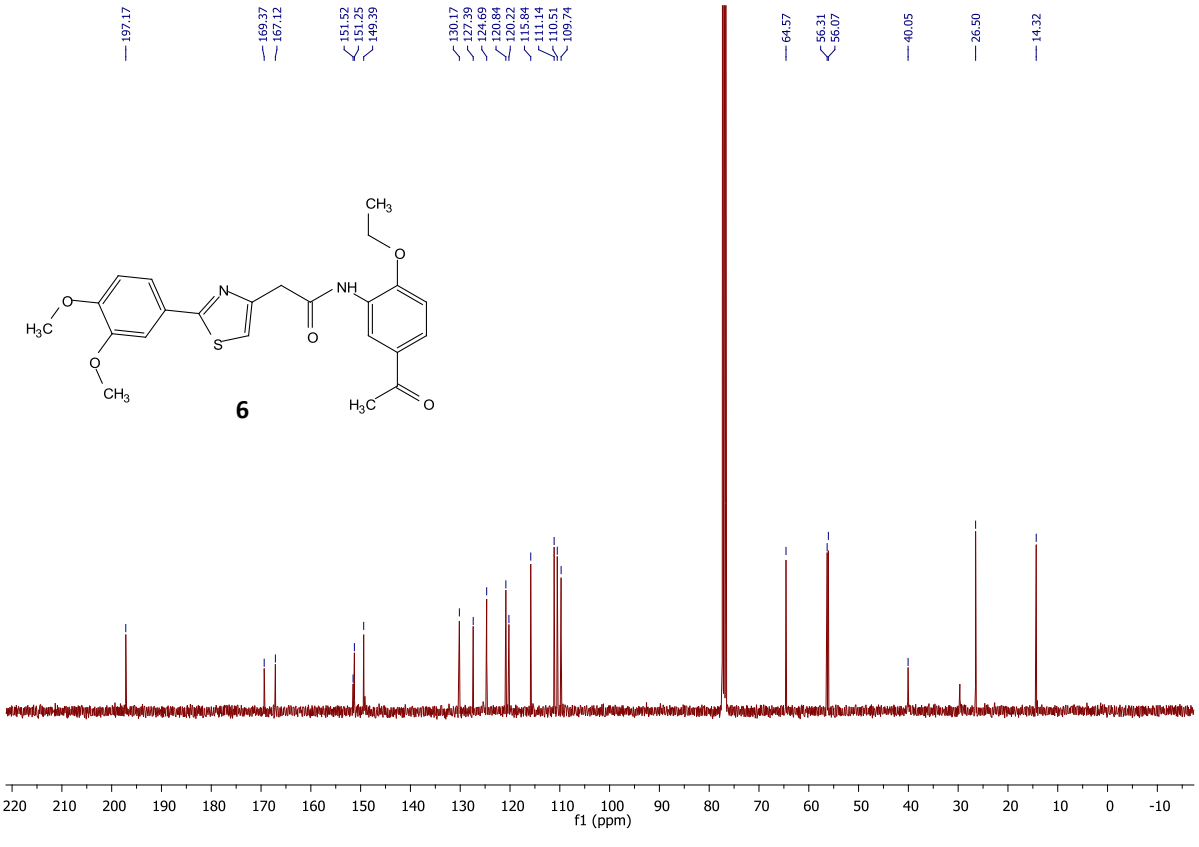


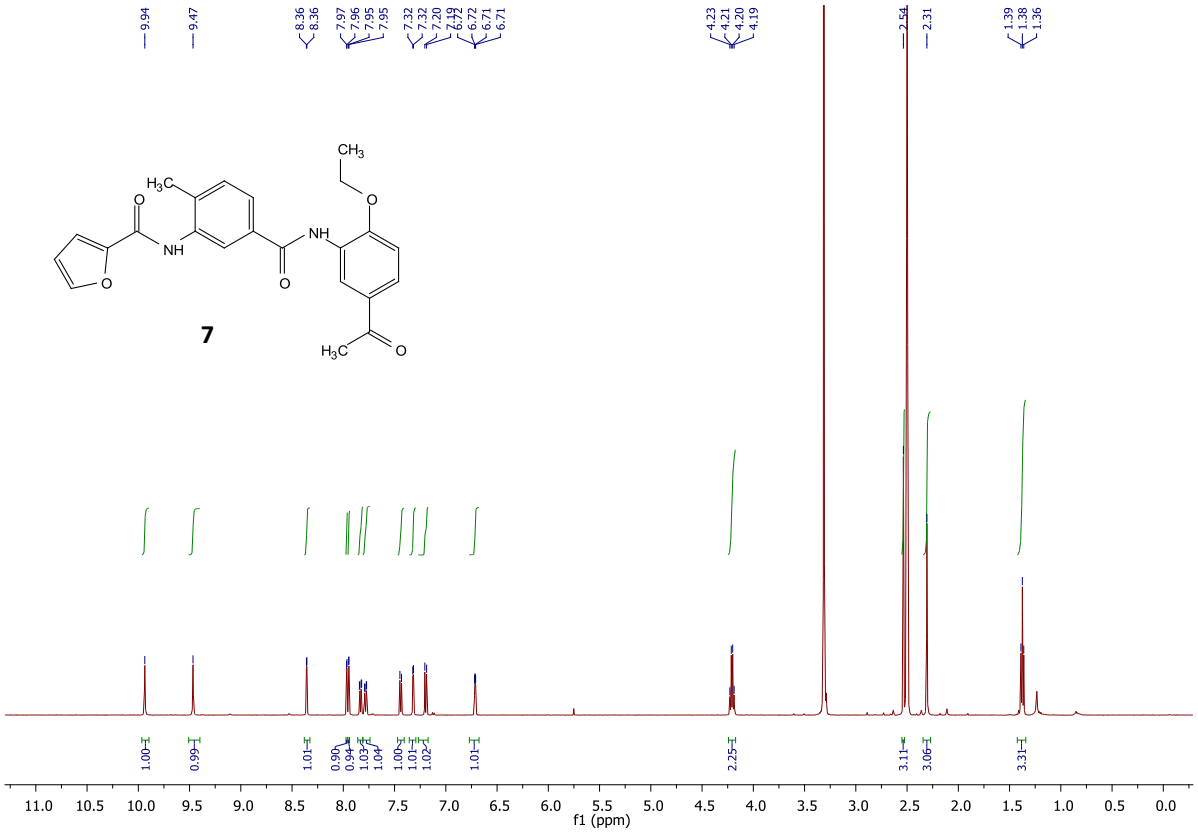
5



5


8.98
8.98
7.73
7.73
7.72
7.70
7.70
7.59
7.58
7.57
7.56
6.94
6.92
6.87
6.85
4.10
4.08
4.06
4.04
4.02
4.01
3.95
3.94
2.57
2.56
2.04
1.25
1.23
1.22
CH3
O
N
NH
S
O
H3C
O
O
CH3
6
1.80
2.01
0.97
1.02
1.00
1.78
2.25
2.97
3.10
3.21
5.51
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


197.17
169.37
167.12
151.52
151.25
149.39
130.17
127.39
124.69
120.84
120.22
115.84
111.14
110.51
109.74
64.57
56.31
56.07
40.05
26.50
14.32
CH3
O
N
NH
S
O
H3C
O
O
CH3
6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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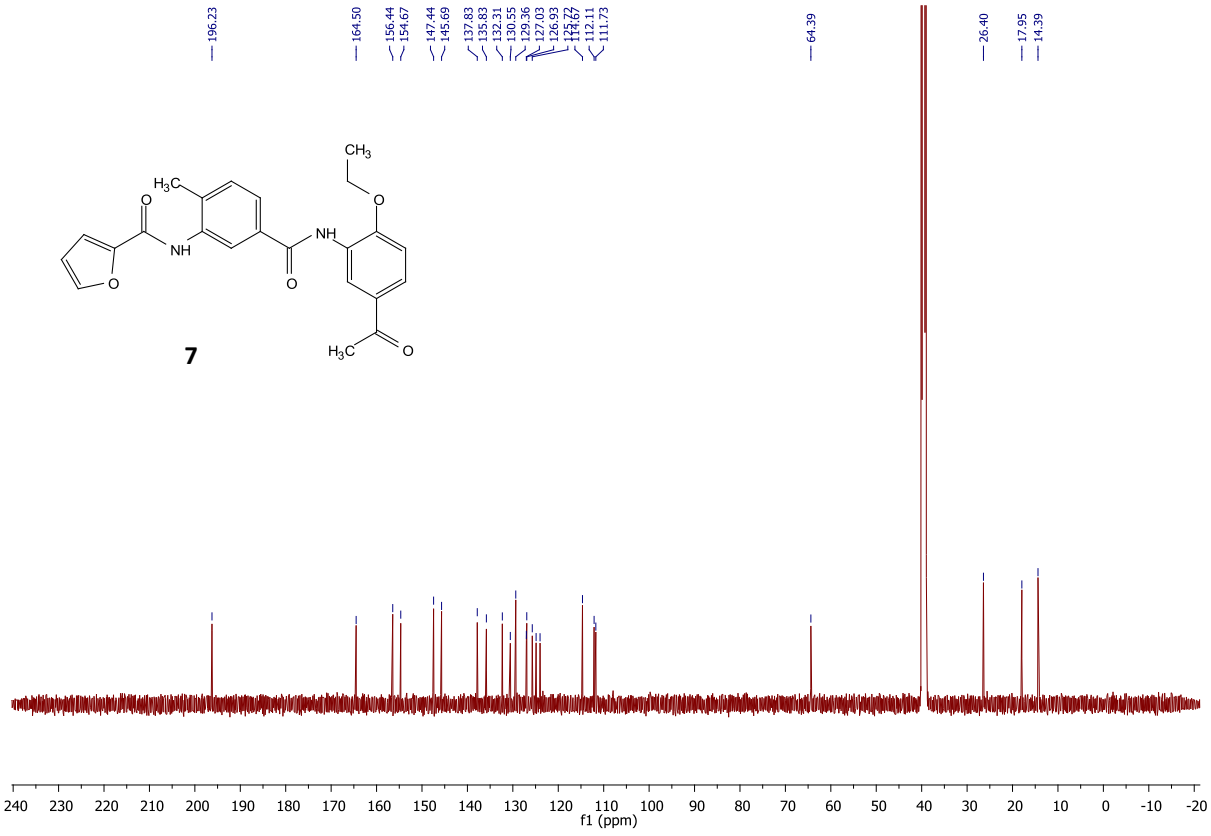
8.36
7.97
7.96
7.95
7.95
7.32
7.32
7.20
6.72
6.72
6.71
6.71
4.23
4.21
4.20
4.19
2.54
2.31
1.39
1.38
1.36
1.00
0.99
1.01
0.90
0.94
1.03
1.04
1.00
1.01
1.02
1.01
2.25
3.11
3.06
3.31
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

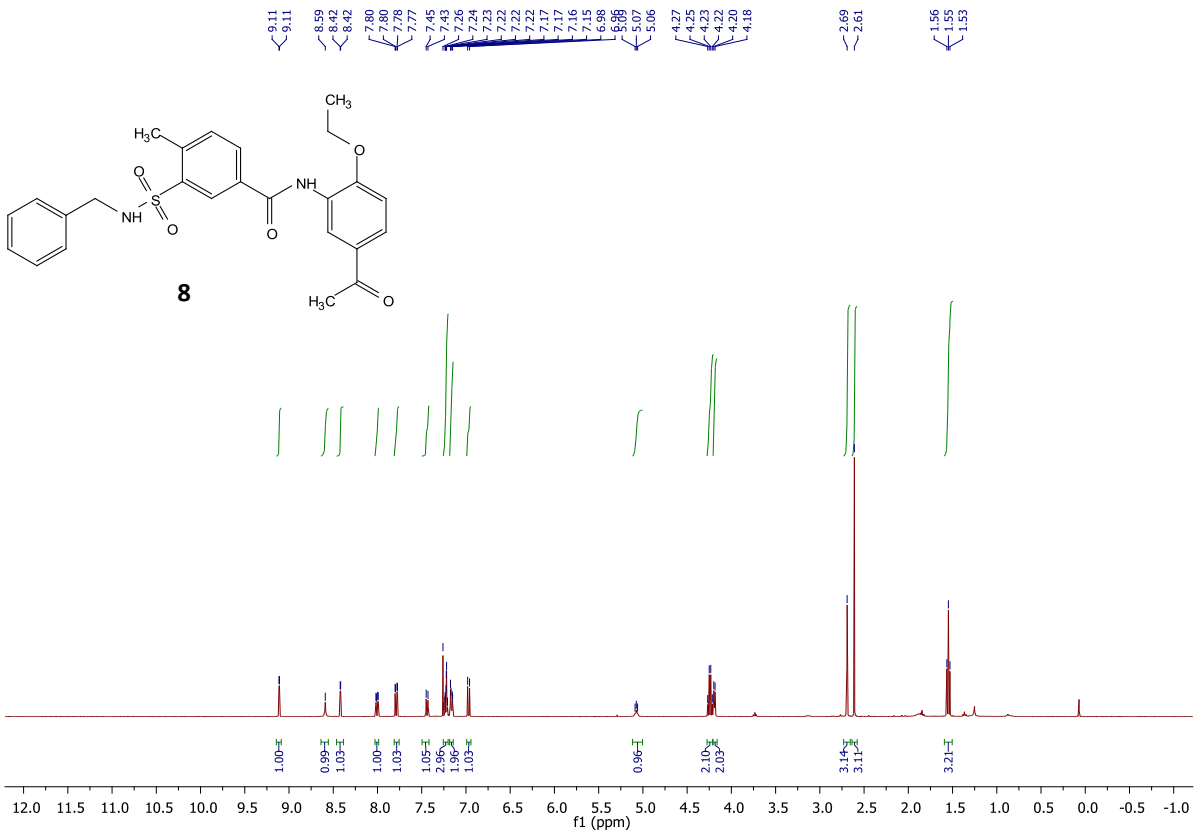
CH3
H3C
O
NH
O
NH
O
O
O
H3C
O

7


196.23
164.50
156.44
154.67
147.44
145.69
137.83
135.83
132.31
130.55
129.36
127.03
126.93
112.11
111.73
64.39
26.40
17.95
14.39
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

CH3
H3C
O
NH
O
NH
O
O
O
H3C
O

7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8.59
8.42
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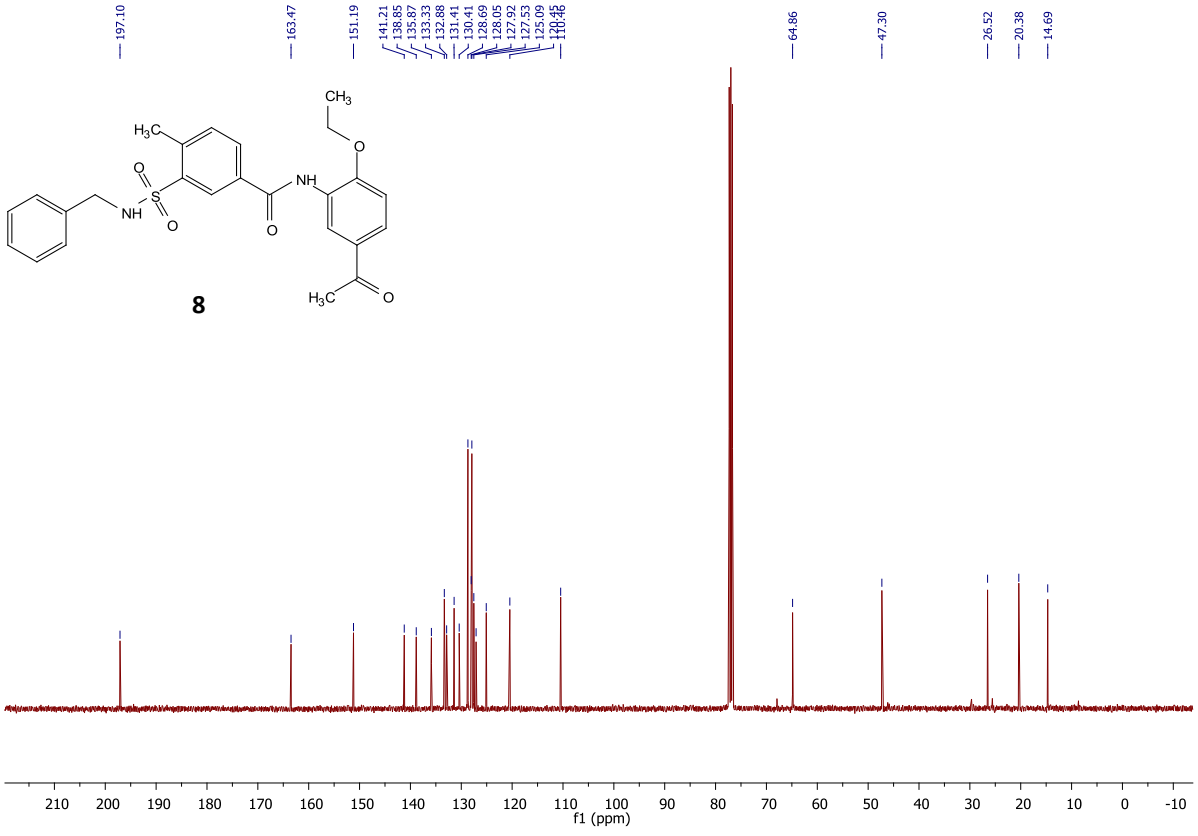
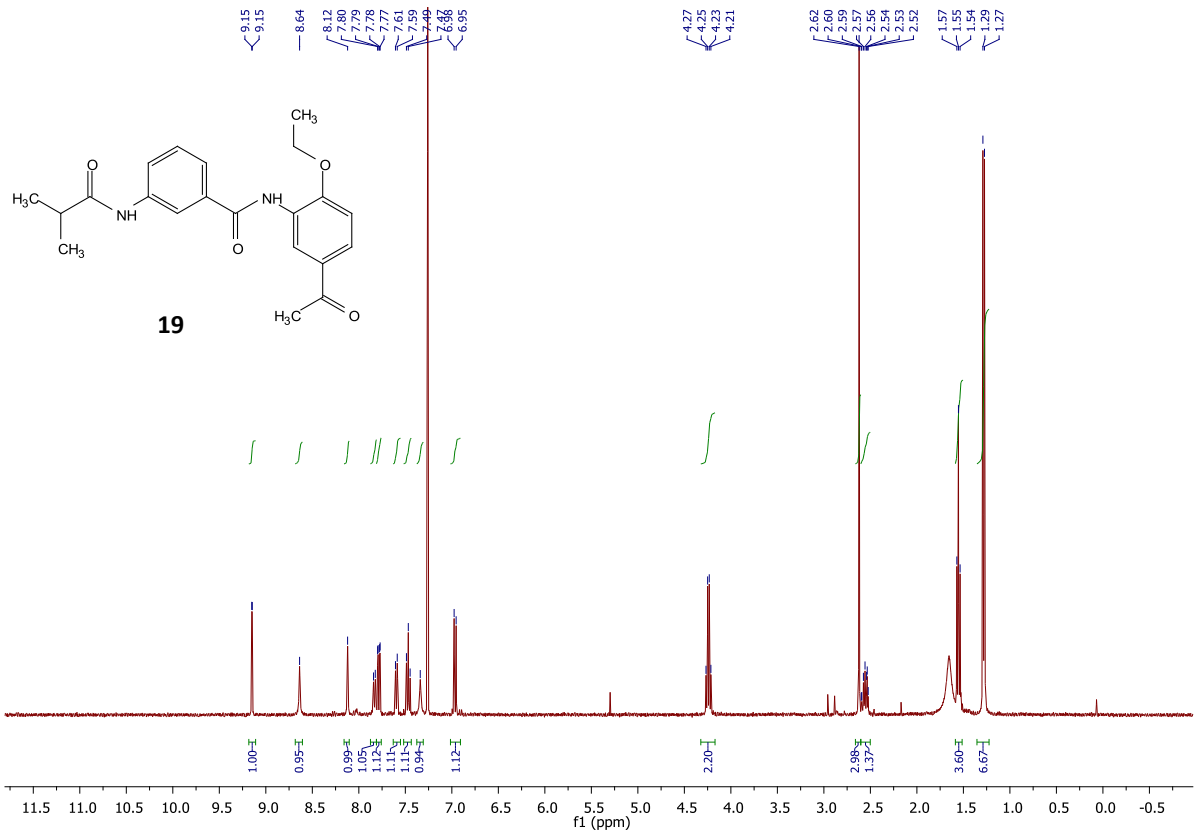
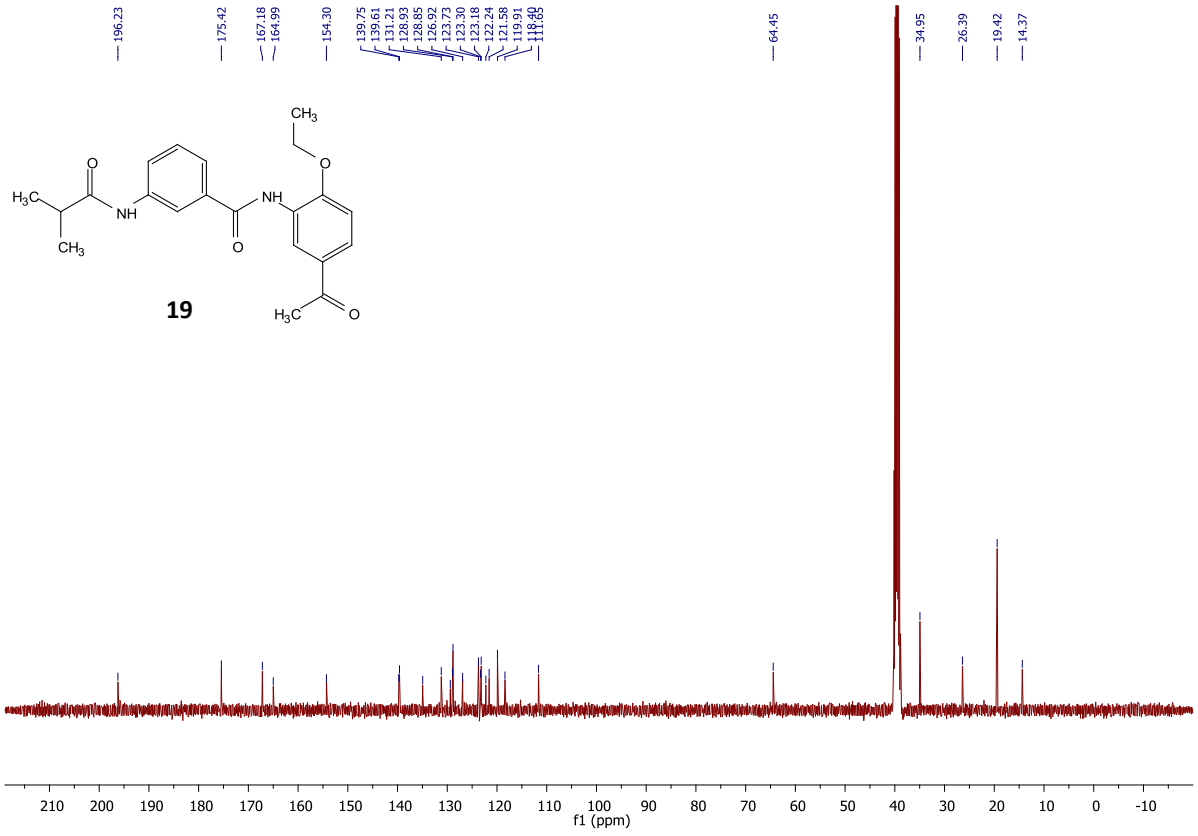
7.78
7.77
7.45
7.43
7.26
7.24
7.23
7.22
7.17
7.16
7.15
6.98
5.07
5.06
4.27
4.25
4.23
4.22
4.20
4.18
2.69
2.61
1.56
1.55
1.53
CH3
H3C
O
NH
S
O
O
NH
O
H3C
O
8
1.00
0.99
1.03
1.00
1.03
1.05
2.96
1.96
1.03
0.96
2.10
2.03
3.14
3.11
3.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


197.10
163.47
151.19
141.21
138.85
135.87
133.33
132.88
131.41
130.41
128.69
128.05
127.92
127.53
125.09
120.45
110.46
64.86
47.30
26.52
20.38
14.69
CH3
H3C
O
NH
S
O
O
NH
O
H3C
O
8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.15
9.15
8.64
8.12
7.80
7.79
7.78
7.77
7.61
7.59
7.49
7.47
6.95
4.27
4.25
4.23
4.21
2.62
2.60
2.59
2.57
2.56
2.54
2.53
2.52
1.57
1.55
1.54
1.29
1.27
CH3
O
H3C
NH
CH3
O
NH
O
H3C
O
19
1.00
0.95
0.99
1.05
1.12
1.11
1.11
0.94
1.12
2.20
2.98
1.37
3.60
6.67
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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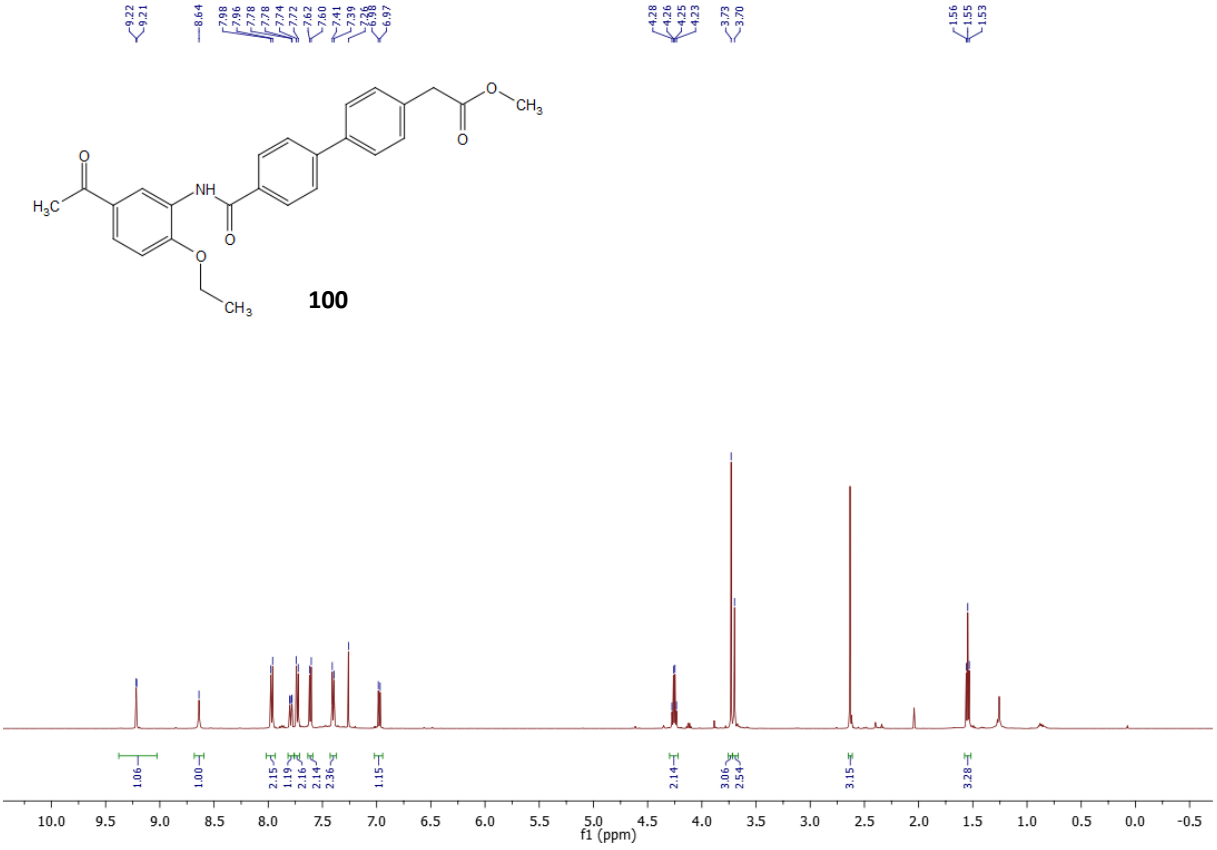
175.42
167.18
164.99
154.30
139.75
139.61
131.21
128.93
128.85
126.92
123.73
123.30
123.18
122.24
121.58
119.91
118.40
117.65
64.45
34.95
26.39
19.42
14.37
CH3
O
H3C
NH
CH3
O
NH
O
H3C
O
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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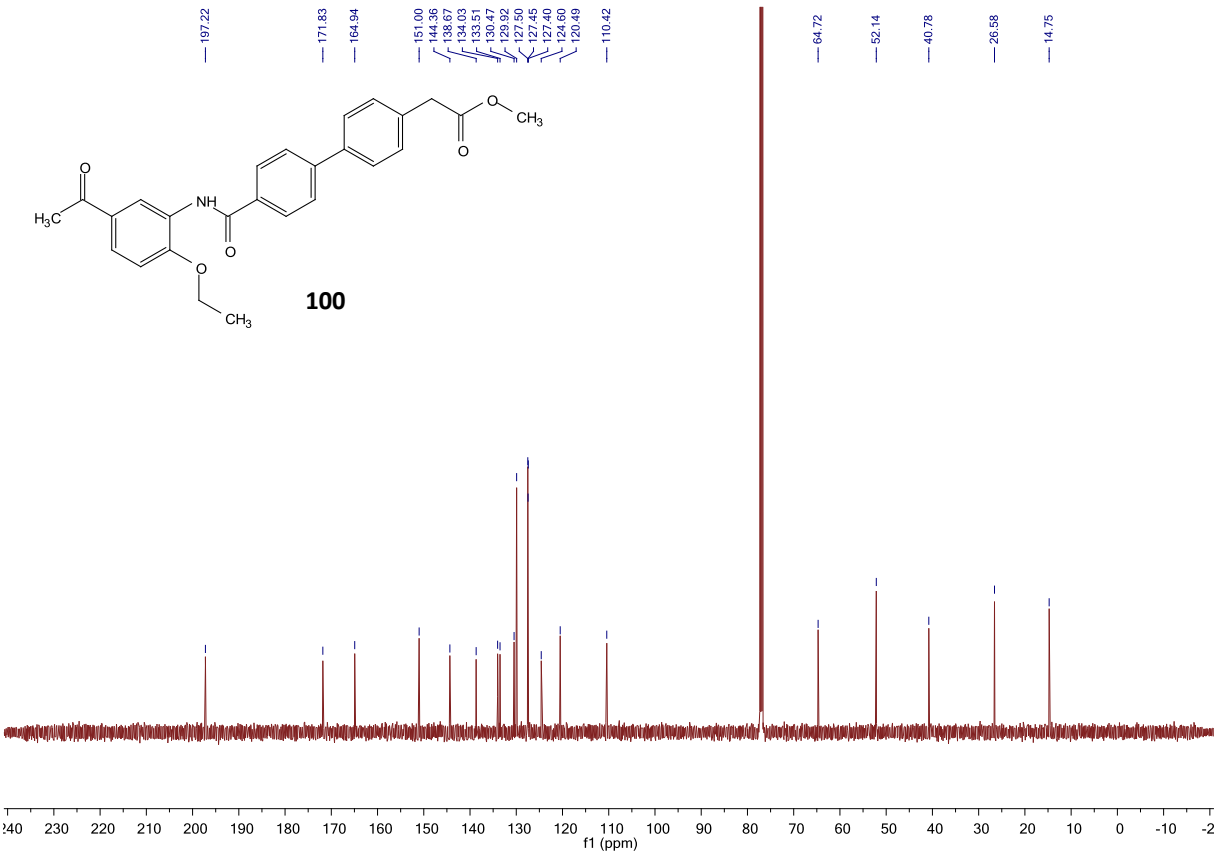
7.96
7.78
7.78
7.74
7.72
7.62
7.60
7.41
7.39
6.98
6.97
4.28
4.26
4.25
4.23
3.73
3.70
1.56
1.55
1.53
O
CH3
O
H3C
NH
O
O
CH3
1.06
1.00
2.15
1.19
2.16
2.14
2.36
1.15
2.14
3.06
2.54
3.15
3.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

100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138.67
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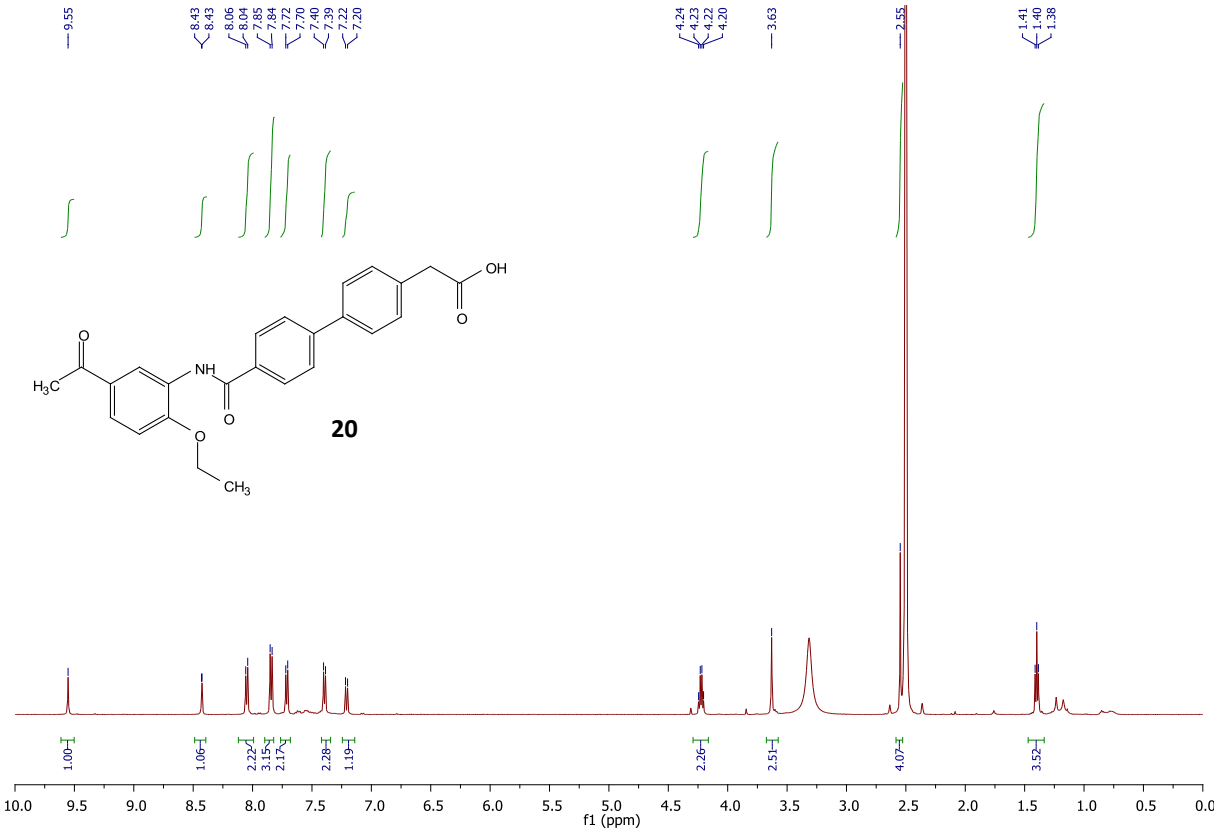
133.51
130.47
129.92
127.50
127.45
127.40
124.60
120.49
110.42
64.72
52.14
40.78
26.58
14.75
O
CH3
O
H3C
NH
O
O
CH3
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2
f1 (ppm)

100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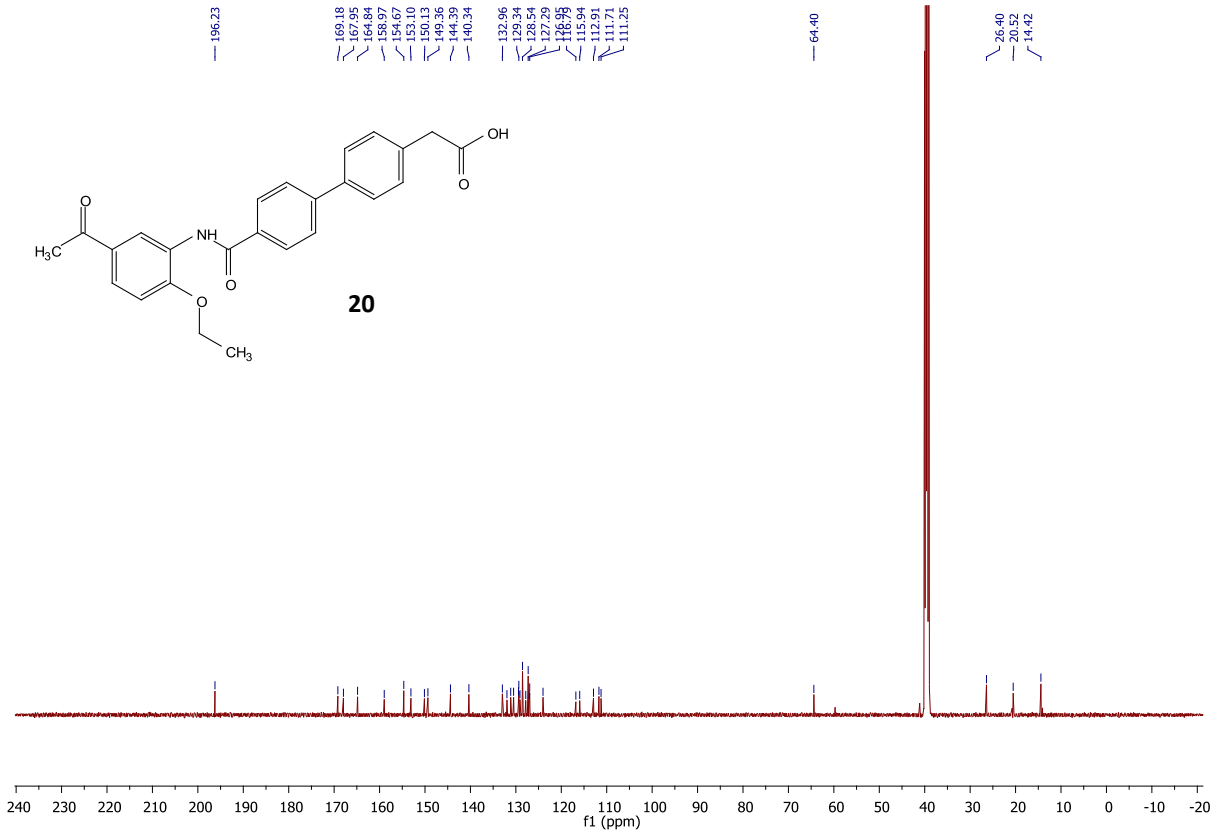
8.43
8.43
8.06
8.04
7.85
7.84
7.72
7.70
7.40
7.39
7.22
7.20
4.24
4.23
4.22
4.20
3.63
2.55
1.41
1.40
1.38
OH
O
NH
O
H3C
O
CH3
20
1.00
1.06
2.22
3.15
2.17
2.28
1.19
2.26
2.51
4.07
3.52
f1 (ppm)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153.10
150.13
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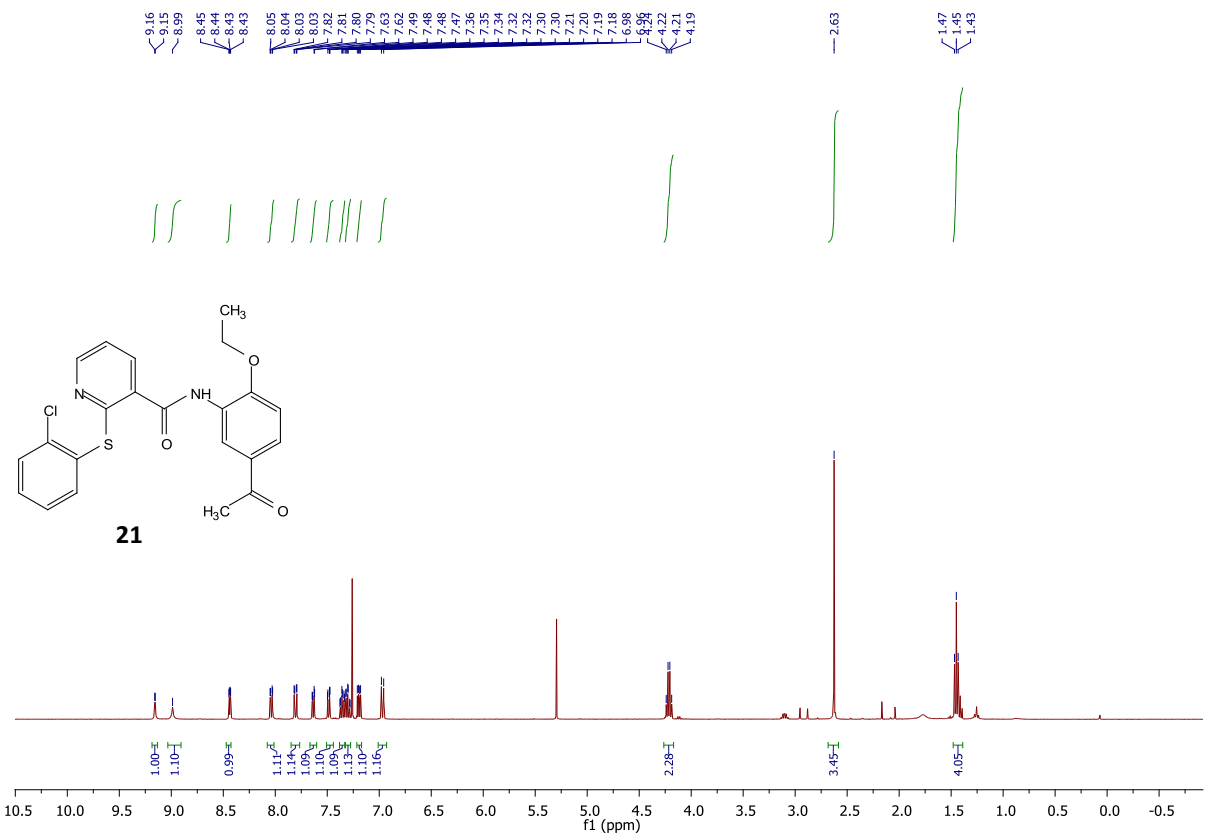
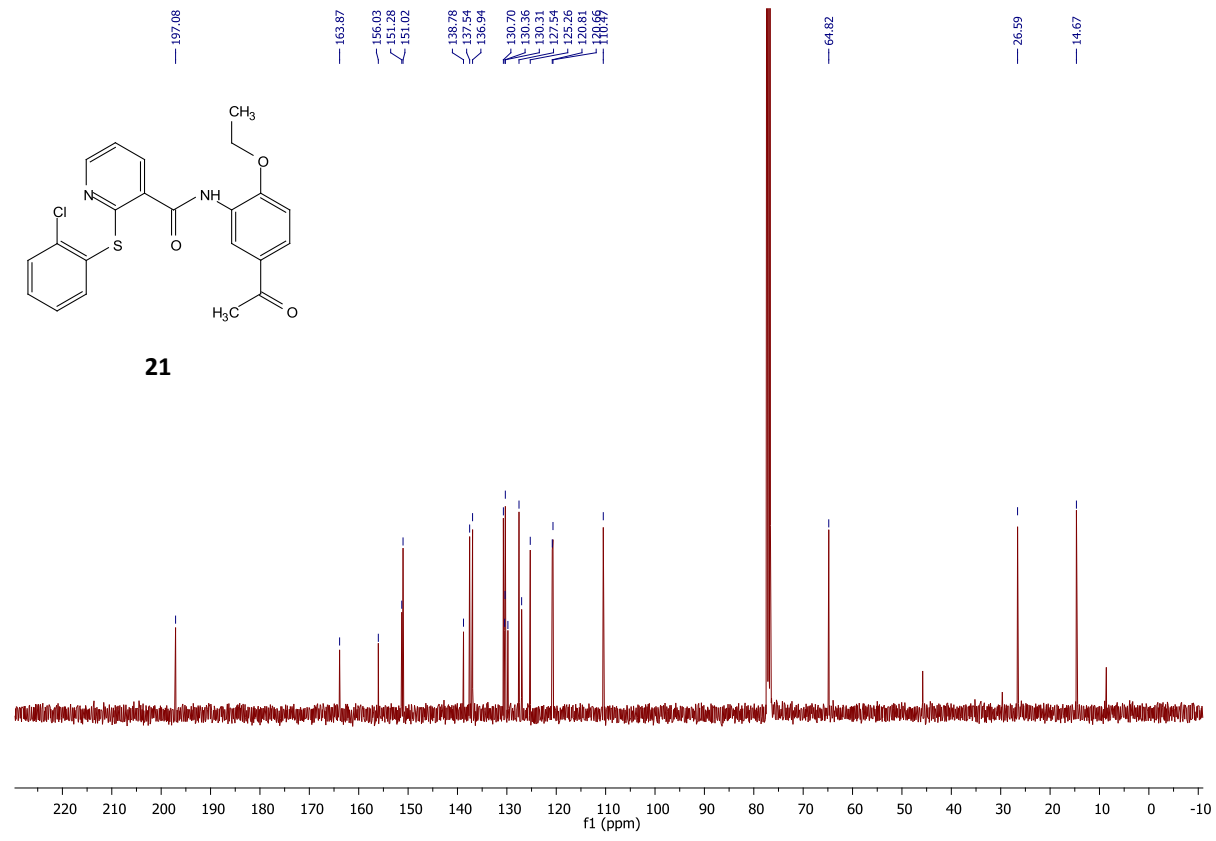
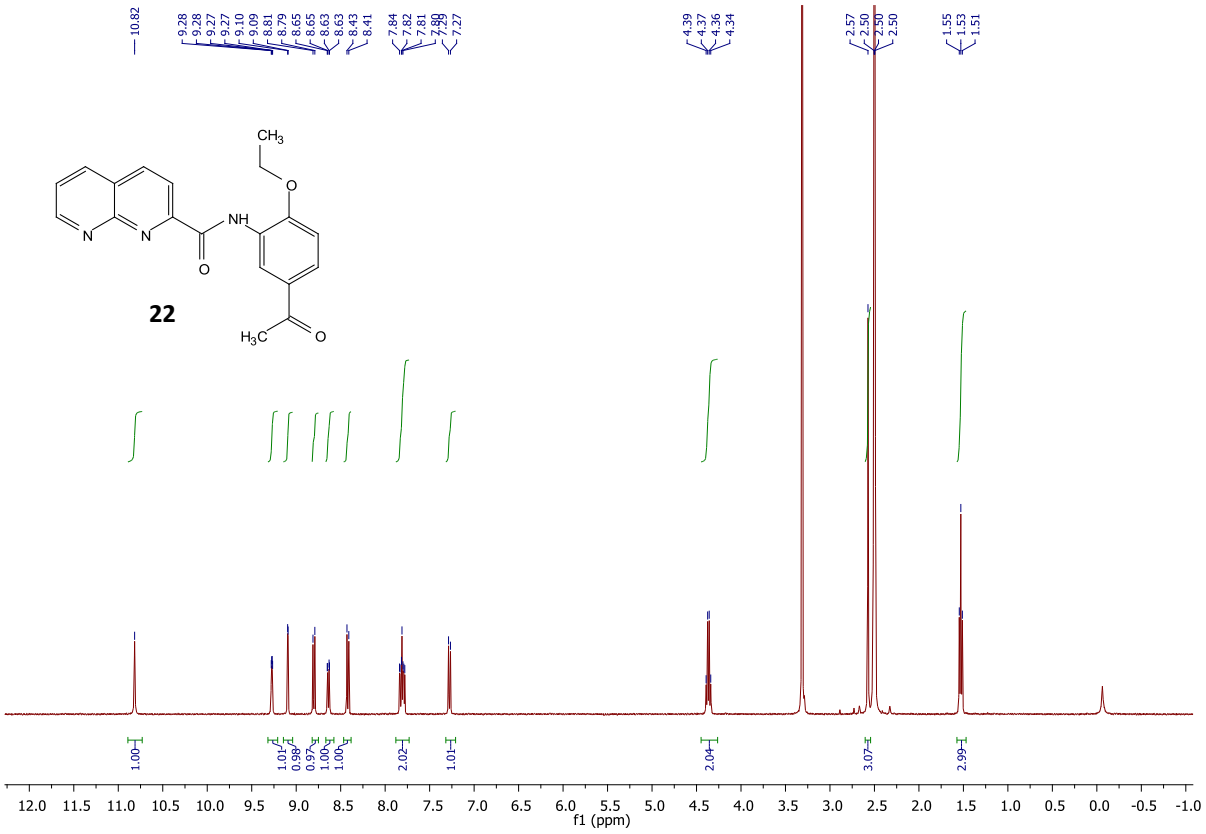
144.39
140.34
132.96
129.34
128.54
127.29
115.94
112.91
111.71
111.25
64.40
26.40
20.52
14.42
OH
O
NH
O
H3C
O
CH3
20
f1 (ppm)

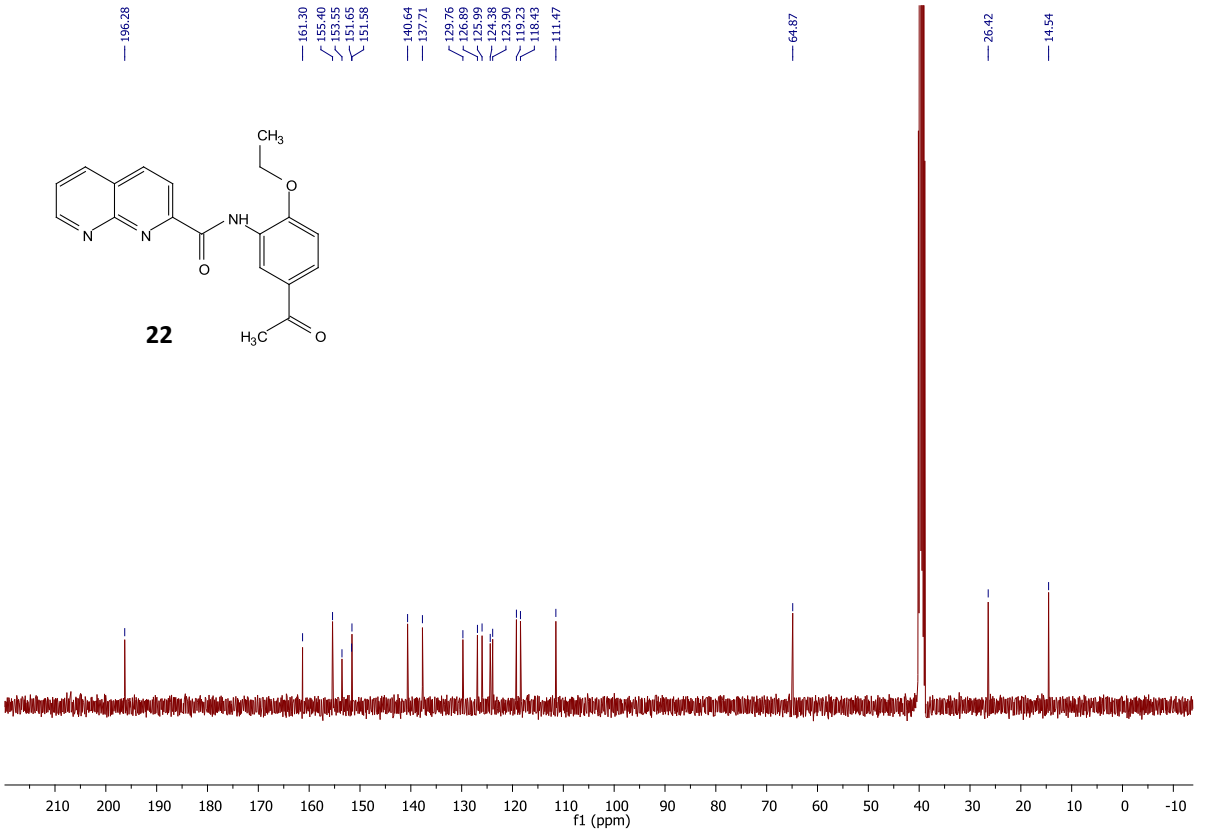

9.16
9.15
8.99
8.45
8.44
8.43
8.43
8.05
8.04
8.03
8.03
7.82
7.81
7.80
7.79
7.63
7.62
7.49
7.48
7.48
7.47
7.36
7.35
7.34
7.32
7.32
7.30
7.30
7.21
7.20
7.19
7.18
6.98
4.22
4.21
4.19
2.63
1.47
1.45
1.43
CH3
O
N
NH
Cl
S
O
H3C
O
1.00
1.10
0.99
1.11
1.14
1.09
1.10
1.09
1.13
1.10
1.16
2.28
3.45
4.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

21


197.08
163.87
156.03
151.28
151.02
138.78
137.54
136.94
130.70
130.36
130.31
127.54
125.26
120.81
120.66
110.47
64.82
26.59
14.67
CH3
O
N
NH
Cl
S
O
H3C
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

21


10.82
9.28
9.28
9.27
9.27
9.10
9.09
8.81
8.79
8.65
8.65
8.63
8.63
8.43
8.41
7.84
7.82
7.81
7.80
7.79
7.27
4.39
4.37
4.36
4.34
2.57
2.50
2.50
2.50
1.55
1.53
1.51
CH3
O
NH
N
N
O
22
H3C
O
1.00
1.01
0.98
0.97
1.00
1.00
2.02
1.01
2.04
3.07
2.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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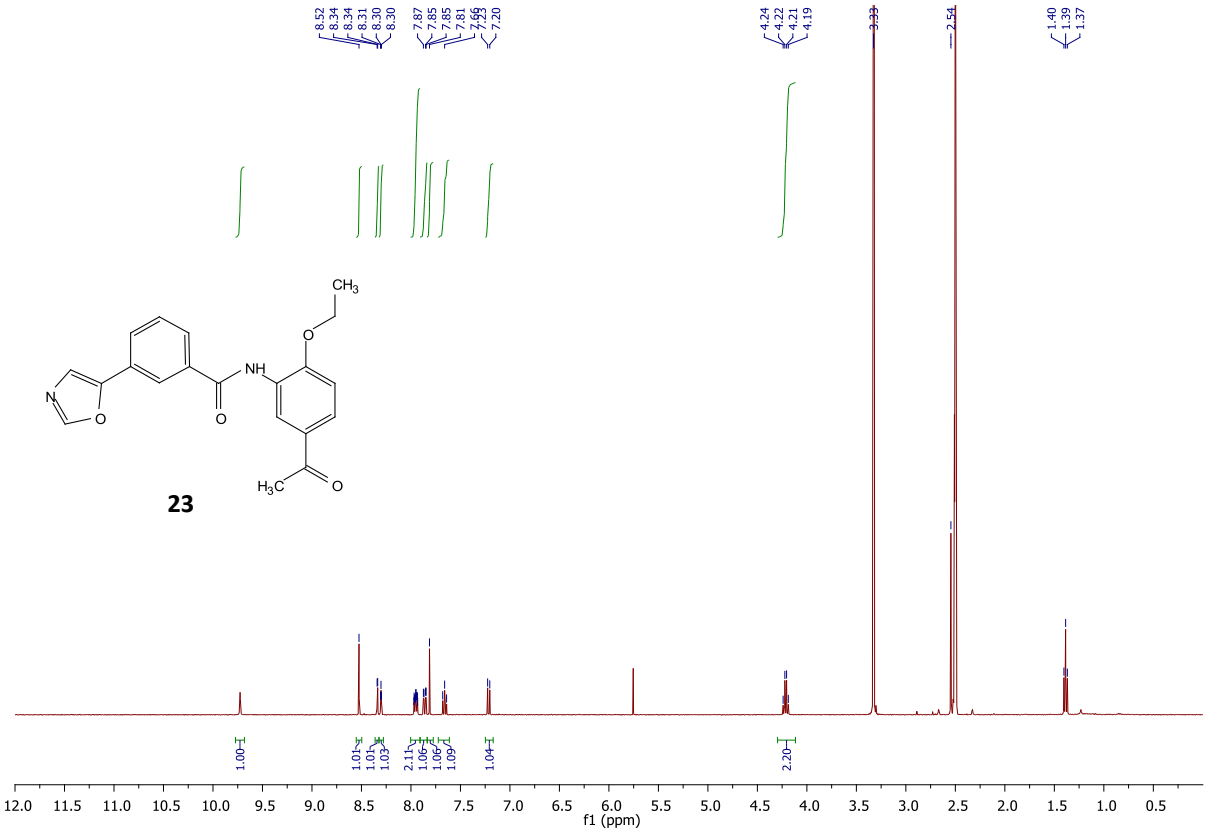
161.30
155.40
153.55
151.65
151.58
140.64
137.71
129.76
126.89
125.99
124.38
123.90
119.23
118.43
111.47
64.87
26.42
14.54
CH3
O
NH
N
N
O
22
H3C
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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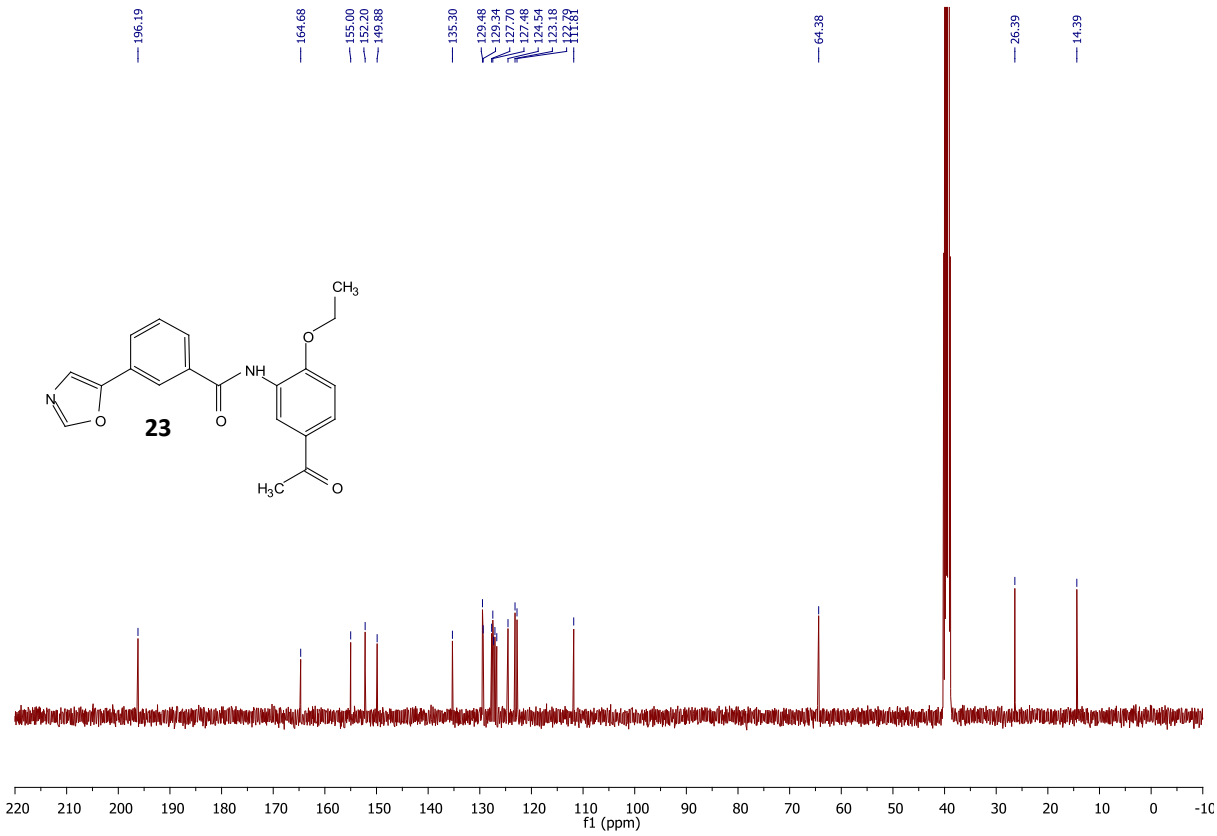
8.34
8.34
8.31
8.30
8.30
7.87
7.85
7.85
7.81
7.68
7.66
7.20
4.24
4.22
4.21
4.19
3.33
2.54
1.40
1.39
1.37
CH3
O
NH
N
O
O
O
H3C
O
23
1.00
1.01
1.01
1.03
2.11
1.06
1.06
1.09
1.04
2.20
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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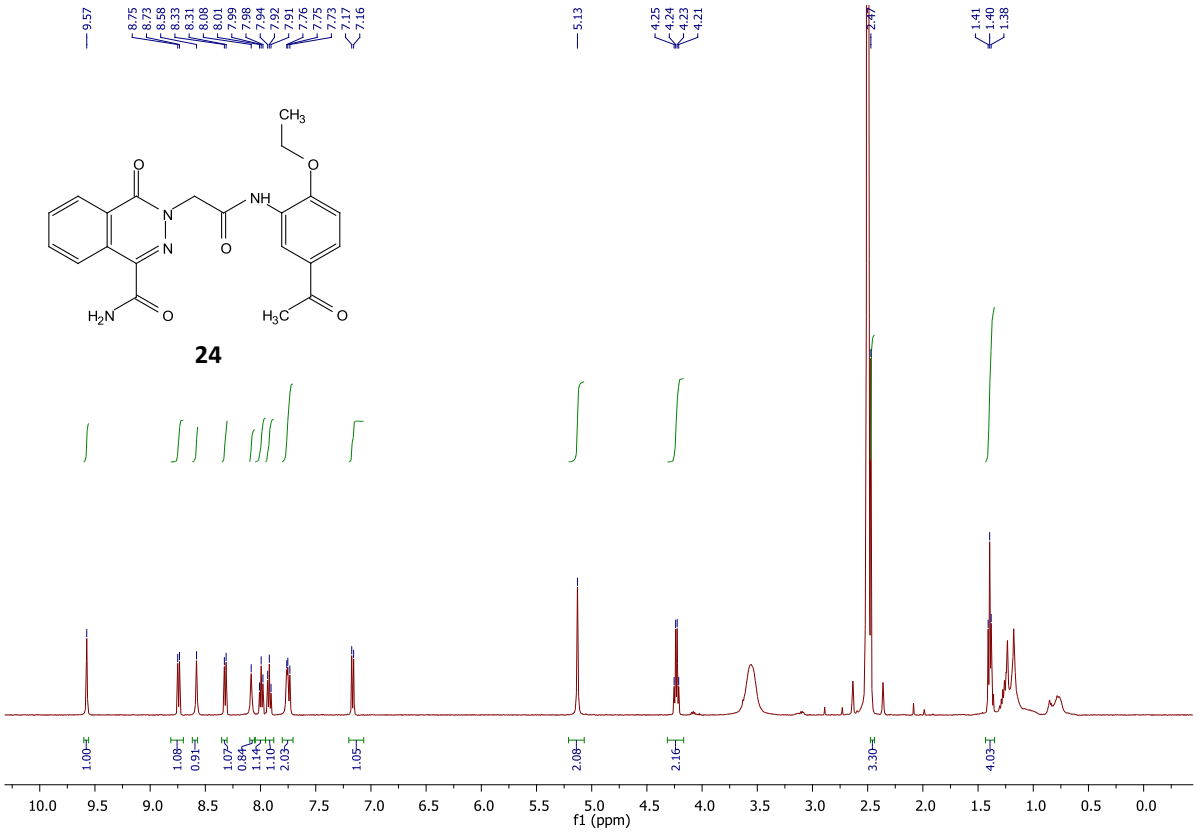
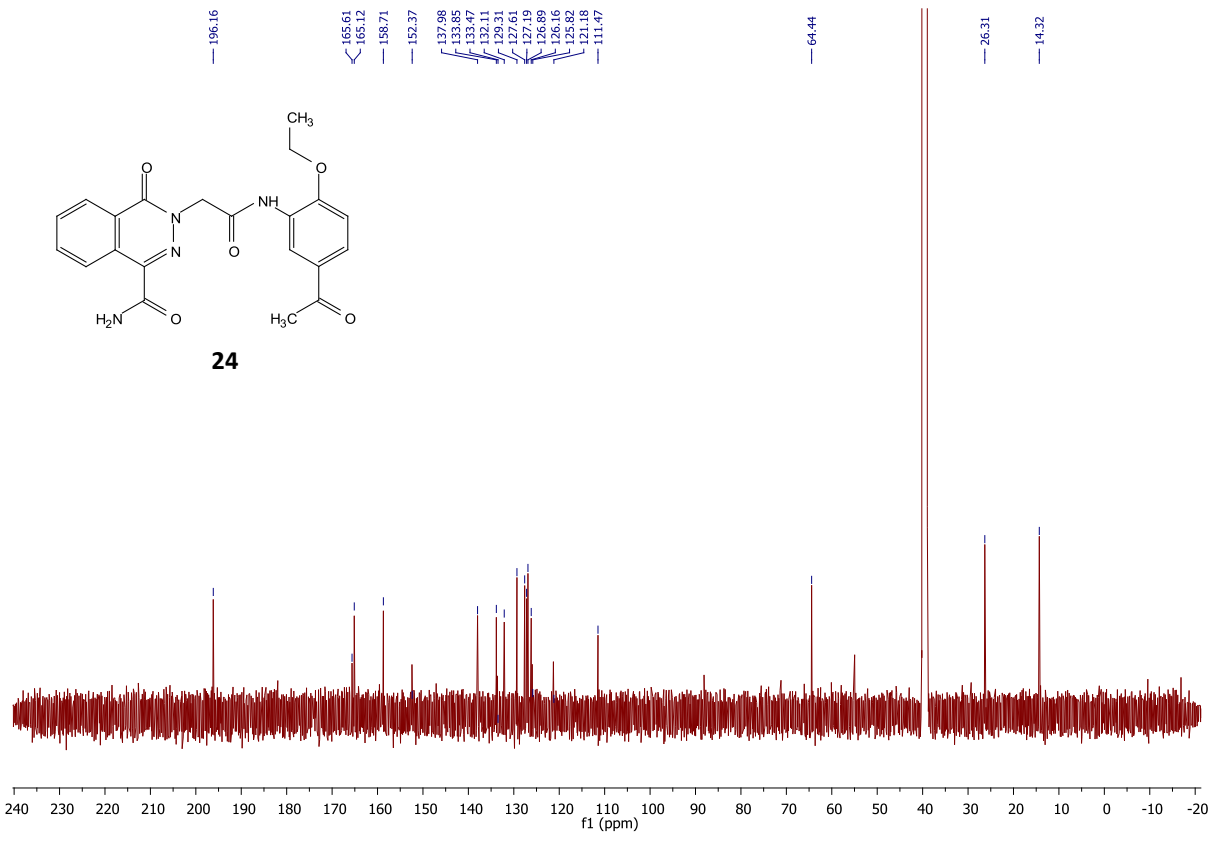
155.00
152.20
149.88
135.30
129.48
129.34
127.70
127.48
124.54
123.18
122.79
111.81
64.38
26.39
14.39
CH3
O
NH
N
O
O
O
H3C
O
23
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.57
8.75
8.73
8.58
8.33
8.31
8.08
8.01
7.99
7.98
7.94
7.92
7.91
7.76
7.75
7.73
7.17
7.16
5.13
4.25
4.24
4.23
4.21
2.47
1.41
1.40
1.38
CH3
O
NH
N
N
O
O
H2N
O
H3C
O
1.00
1.08
0.91
1.07
0.84
1.14
1.10
2.03
1.05
2.08
2.16
3.30
4.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

24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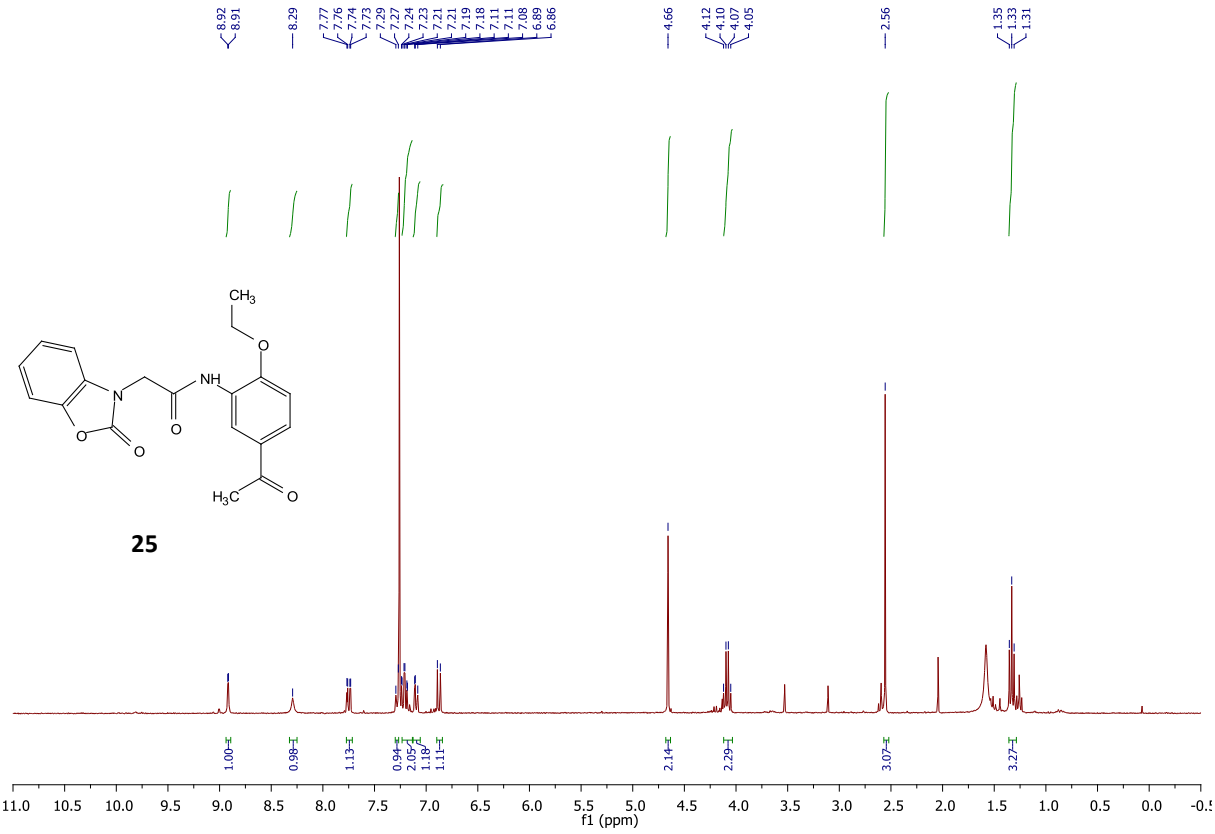
165.61
165.12
158.71
152.37
137.98
133.85
133.47
132.11
129.31
127.61
127.19
126.89
126.16
125.82
121.18
111.47
64.44
26.31
14.32
CH3
O
NH
N
N
O
O
H2N
O
H3C
O
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

24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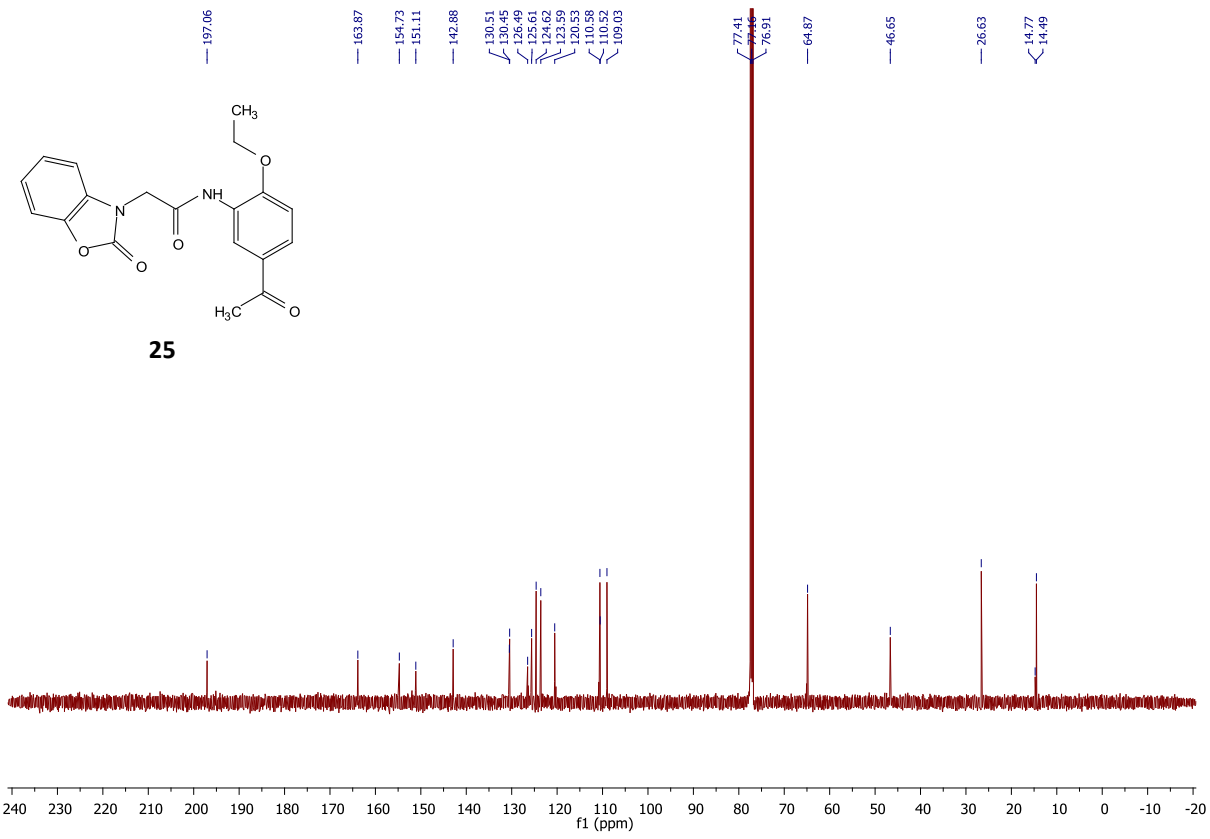
8.91
8.29
7.77
7.76
7.74
7.73
7.29
7.27
7.24
7.23
7.21
7.21
7.19
7.18
7.11
7.11
7.08
6.89
6.86
4.66
4.12
4.10
4.07
4.05
2.56
1.35
1.33
1.31
CH3
O
NH
N
O
O
O
O
H3C
O
1.00
0.98
1.13
0.94
2.05
1.18
1.11
2.14
2.29
3.07
3.27
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

25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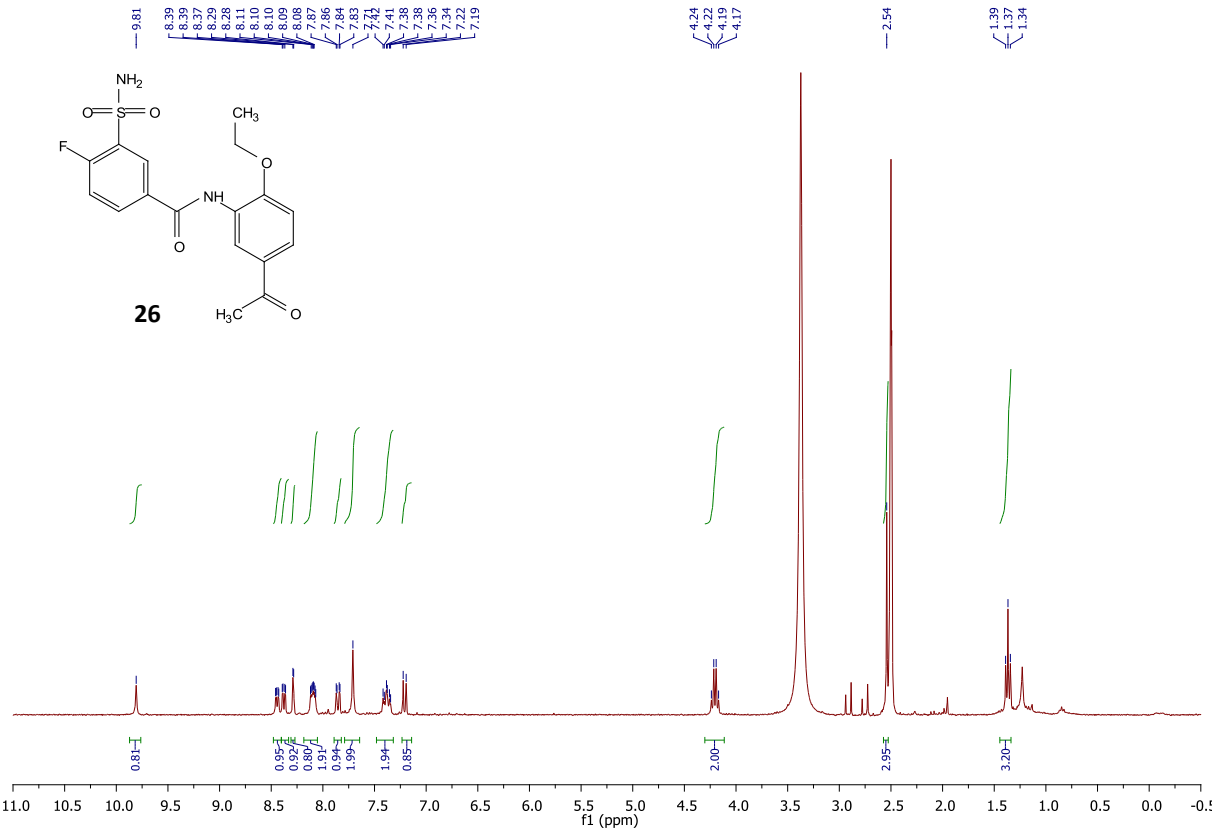
154.73
151.11
142.88
130.51
130.45
126.49
125.61
124.62
123.59
120.53
110.58
110.52
109.03
77.41
77.16
76.91
64.87
46.65
26.63
14.77
14.49
CH3
O
NH
N
O
O
O
O
H3C
O
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

25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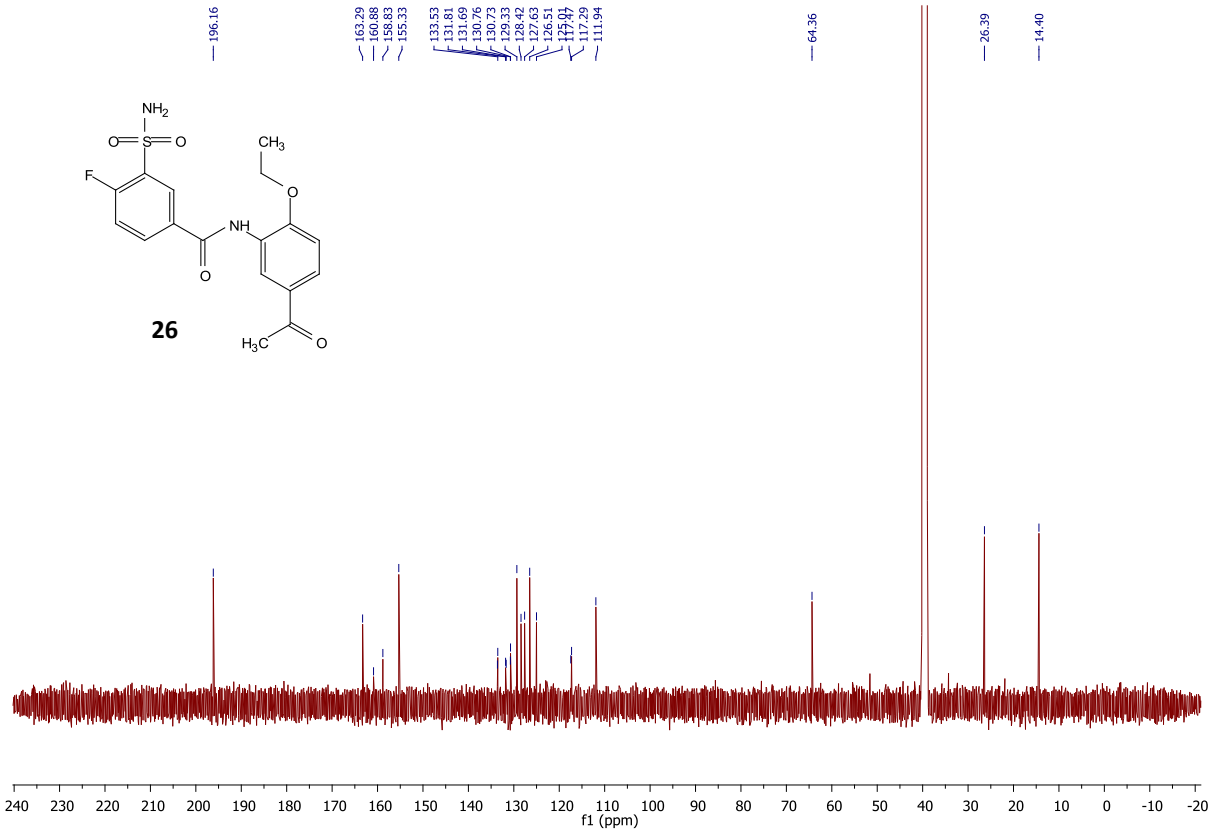
8.39
8.37
8.29
8.28
8.11
8.10
8.10
8.09
8.08
7.87
7.86
7.84
7.83
7.71
7.42
7.41
7.38
7.38
7.36
7.34
7.22
7.19
4.24
4.22
4.19
4.17
2.54
1.39
1.37
1.34
NH2
O
S
O
F
CH3
O
NH
O
O
H3C
26
0.81
0.95
0.92
0.80
1.91
0.94
1.99
1.94
0.85
2.00
2.95
3.20
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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163.29
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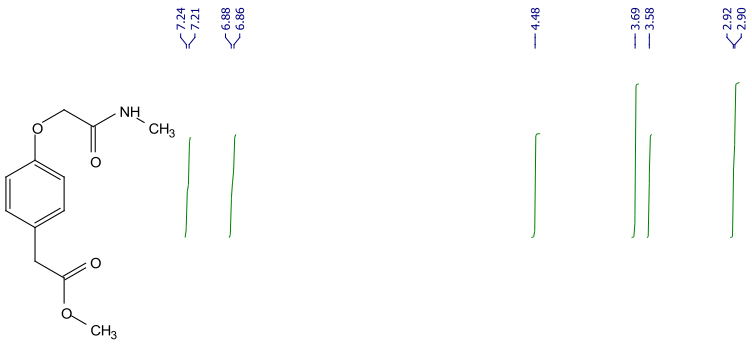
158.83
155.33
133.53
131.81
131.69
130.76
130.73
129.33
128.42
127.63
126.51
117.47
117.29
111.94
64.36
26.39
14.40
NH2
O
S
O
F
CH3
O
NH
O
O
H3C
26
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


7.24
7.21
6.88
6.86
4.48
3.69
3.58
2.92
2.90
NH
CH3
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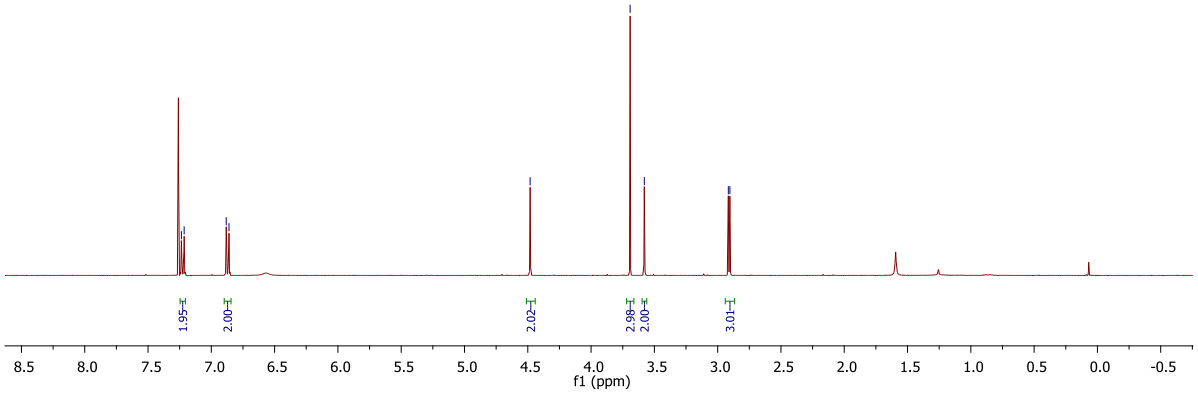
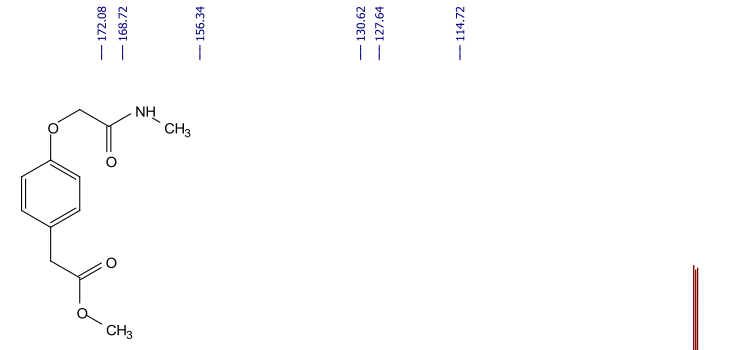
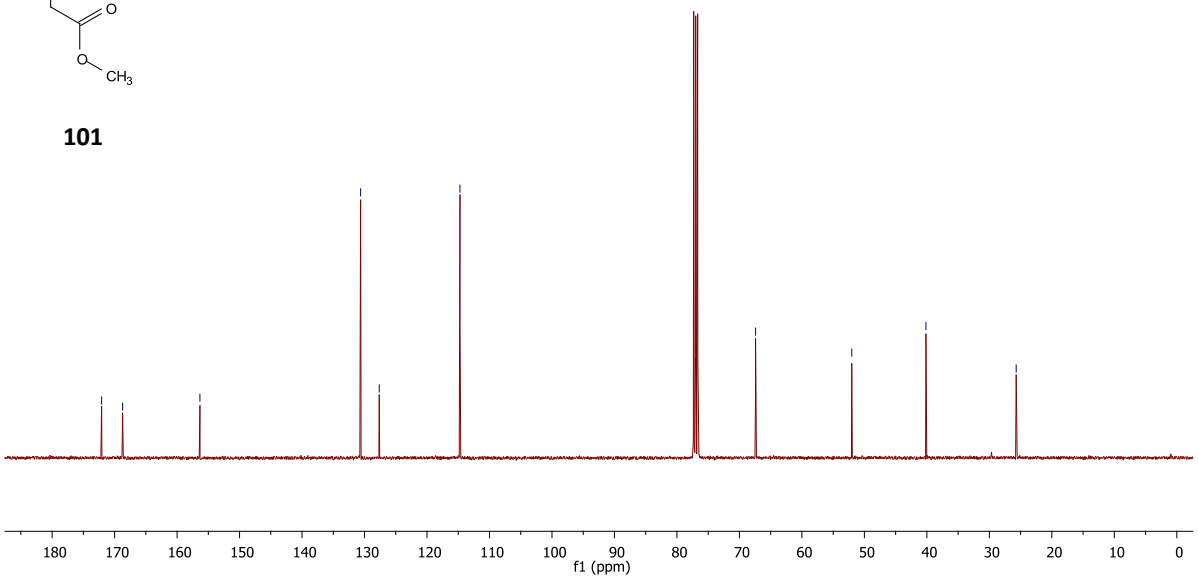
O
O
O
CH3

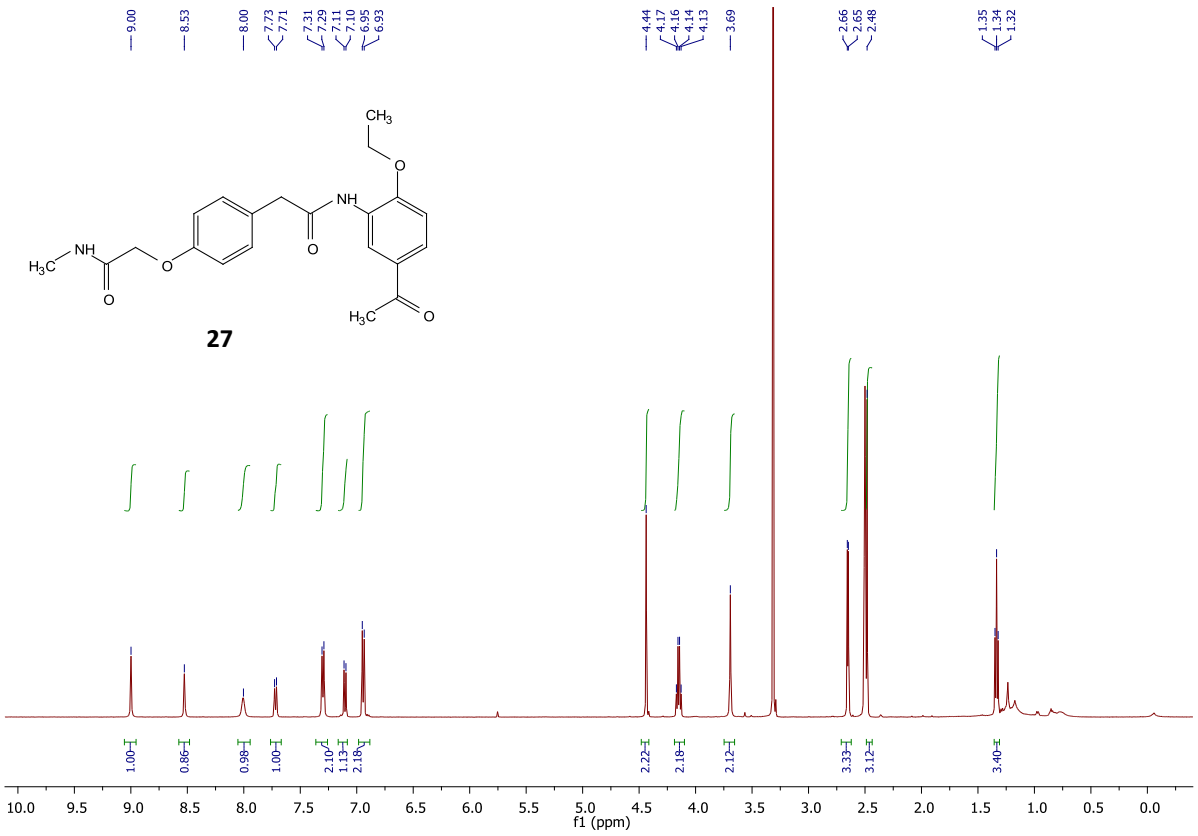
101


1.95
2.00
2.02
2.98
2.00
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


172.08
168.72
156.34
130.62
127.64
114.72
67.42
52.02
40.15
25.71
NH
CH3
O
O
O
O
CH3

101


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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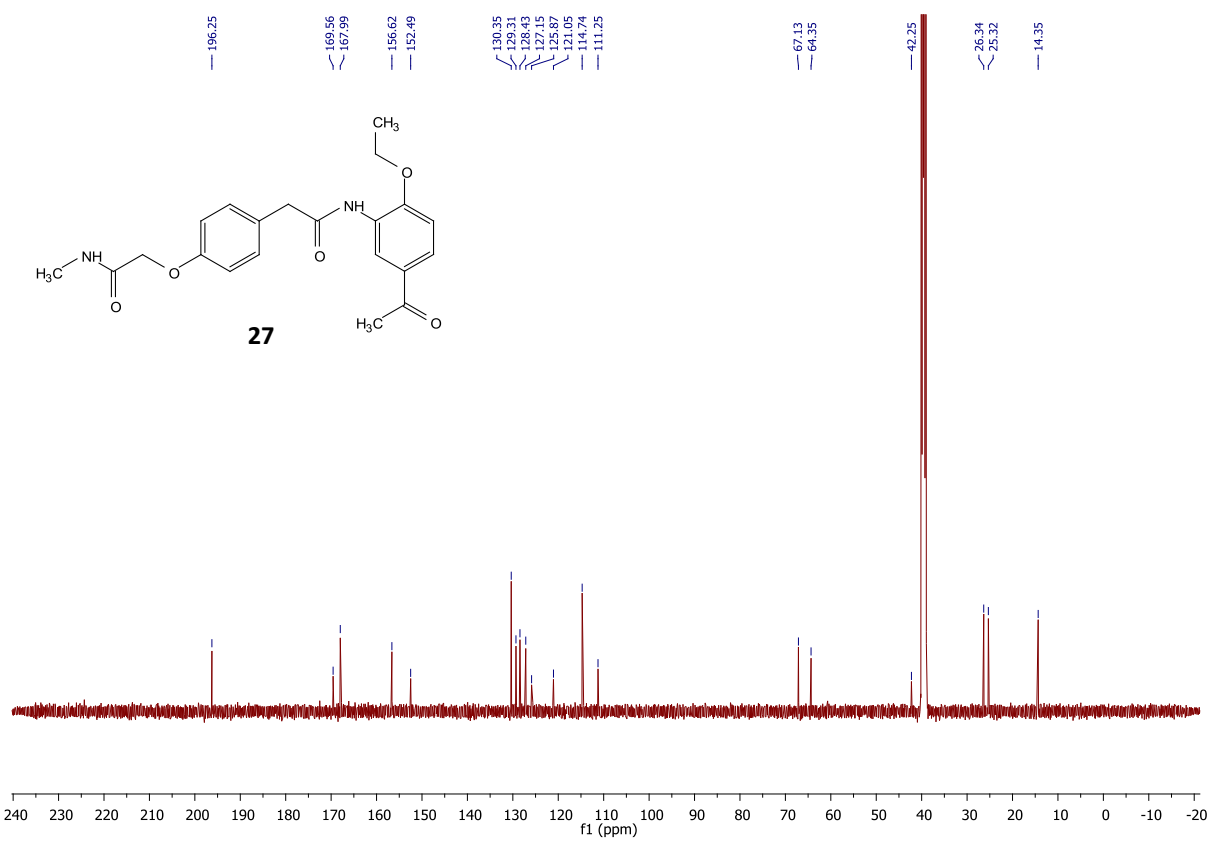
8.53
8.00
7.73
7.71
7.31
7.29
7.11
7.10
6.95
6.93
4.44
4.17
4.16
4.14
4.13
3.69
2.66
2.65
2.48
1.35
1.34
1.32
1.00
0.86
0.98
1.00
2.10
1.13
2.18
2.22
2.18
2.12
3.33
3.12
3.40
f1 (ppm)

27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156.62
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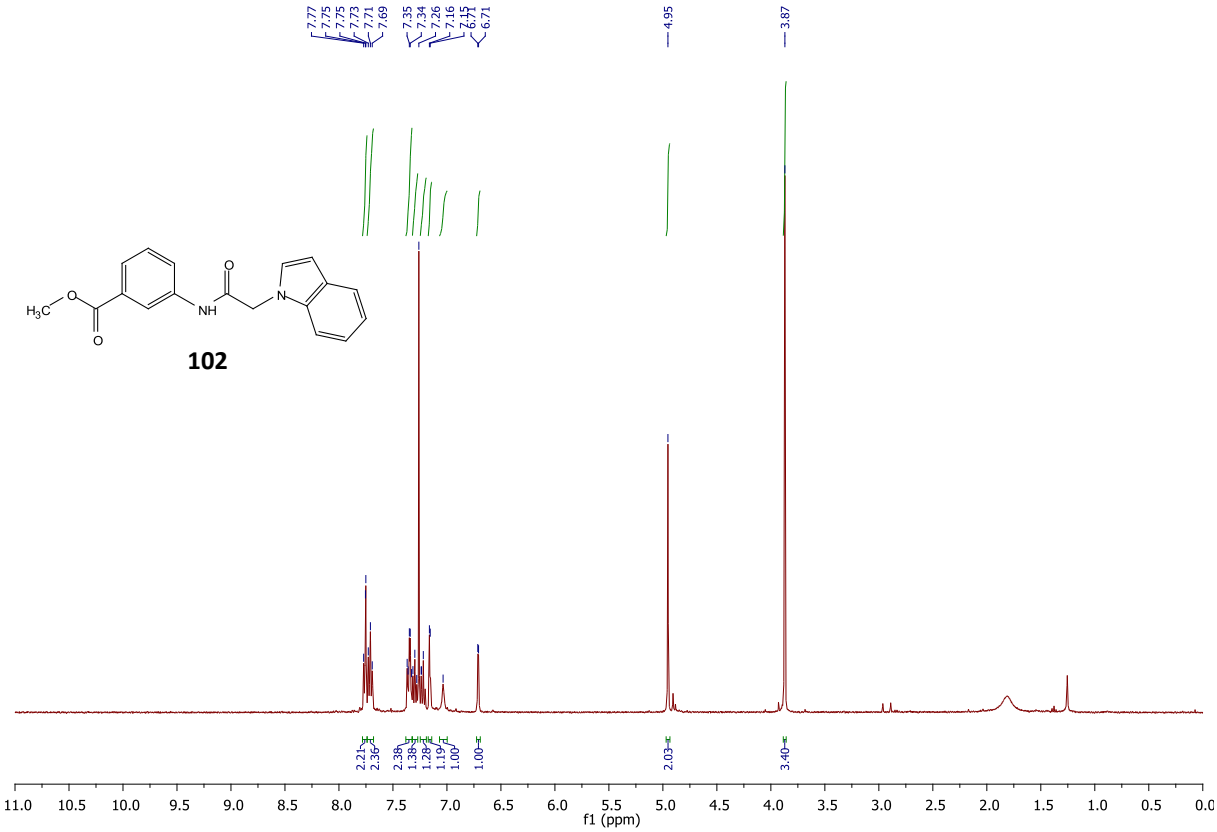
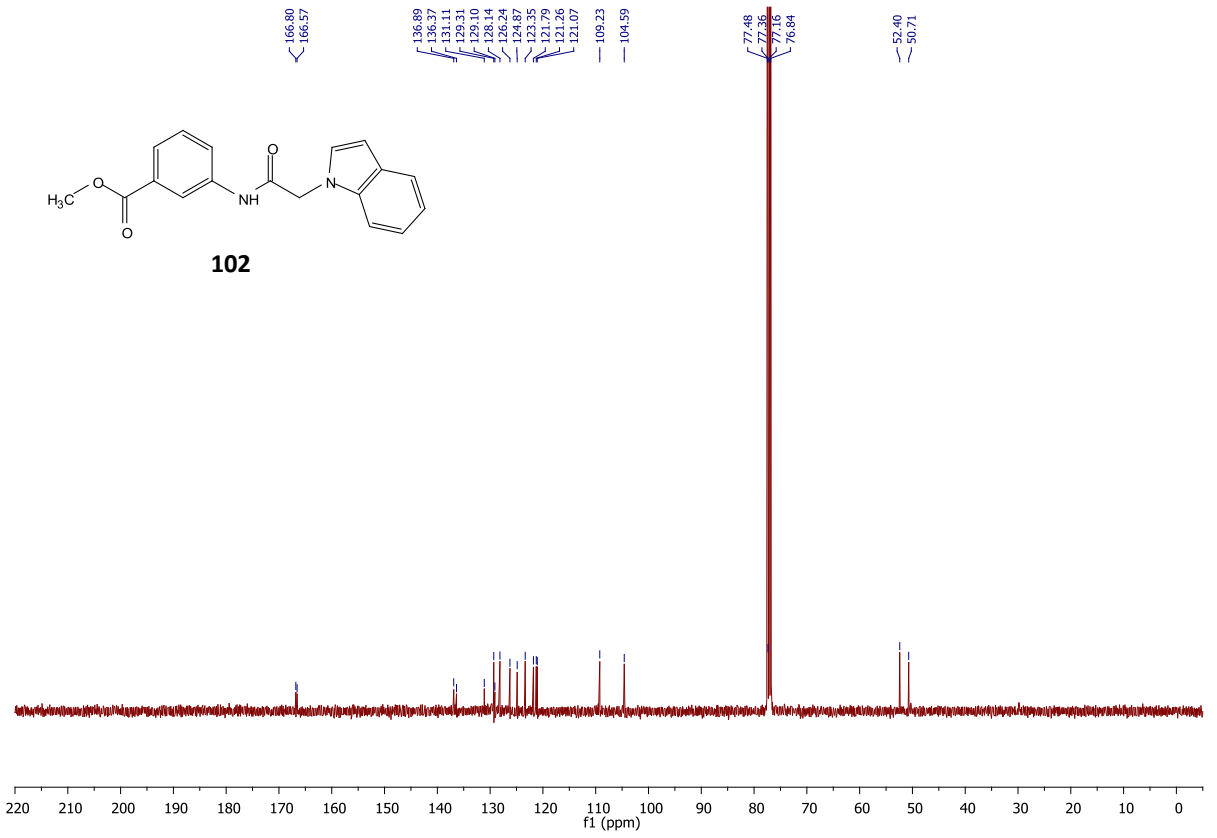
129.31
128.43
127.15
125.87
121.05
114.74
111.25
67.13
64.35
42.25
26.34
25.32
14.35
f1 (ppm)

27


7.77
7.75
7.75
7.73
7.71
7.69
7.35
7.34
7.26
7.16
6.71
4.95
3.87
2.21
2.36
2.38
1.38
1.28
1.19
1.00
1.00
2.03
3.40
f1 (ppm)

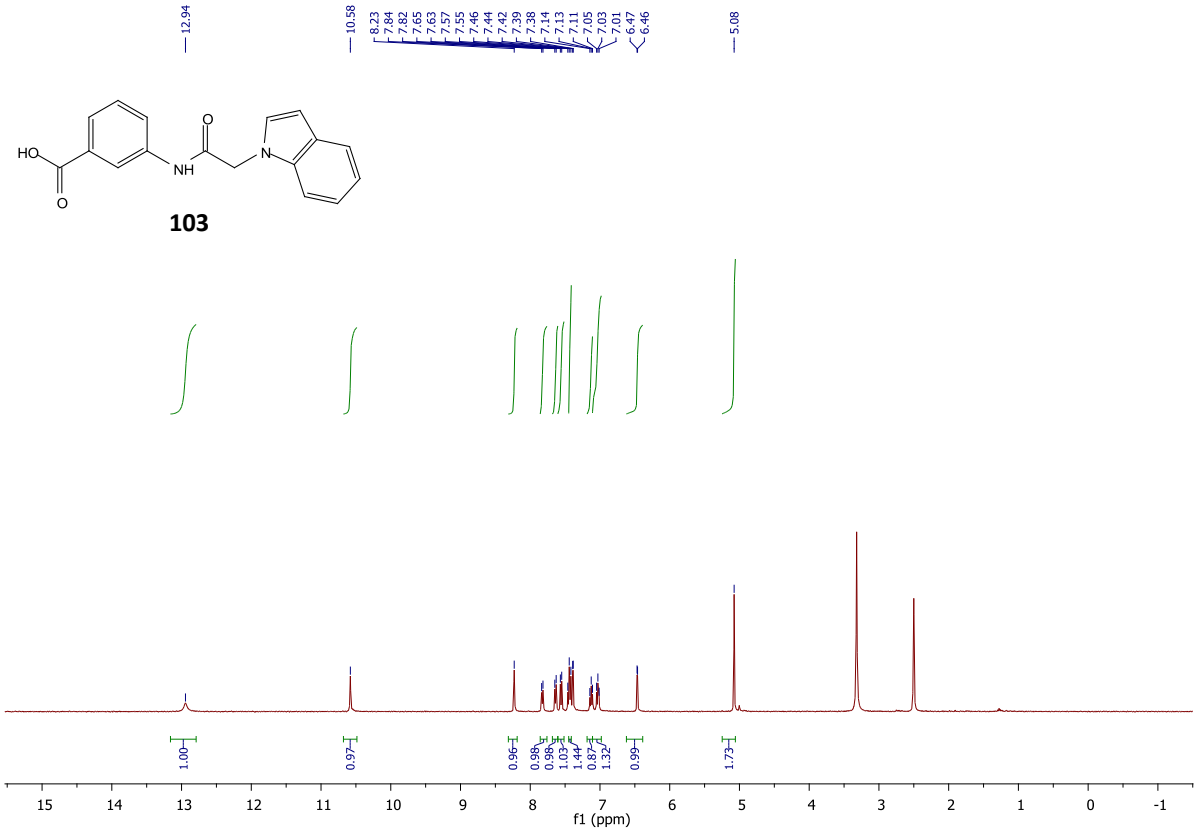
O
O
NH
N
O

102

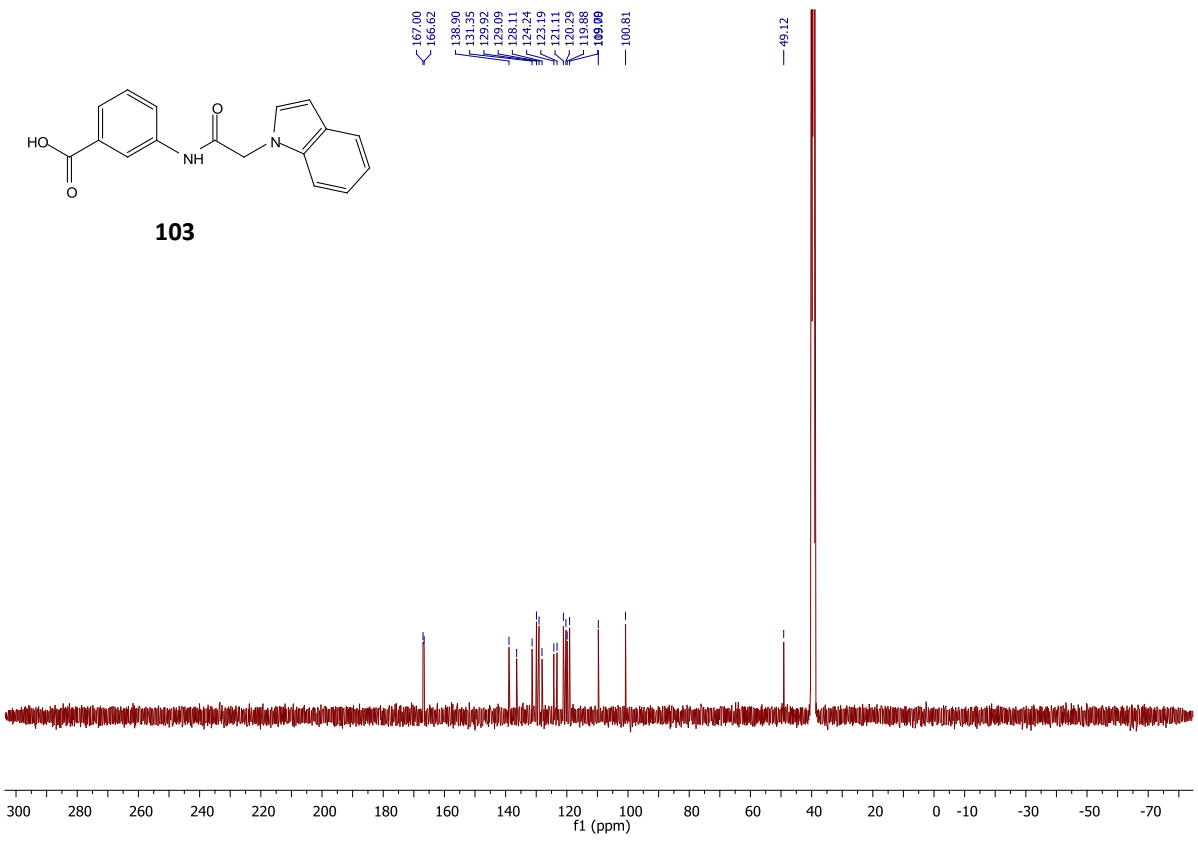

166.80
166.57
136.89
136.57
131.11
129.31
129.10
128.14
126.24
124.87
123.35
121.79
121.26
121.07
109.23
104.59
77.48
77.36
77.16
76.84
52.40
50.71
f1 (ppm)

O
O
NH
N
O

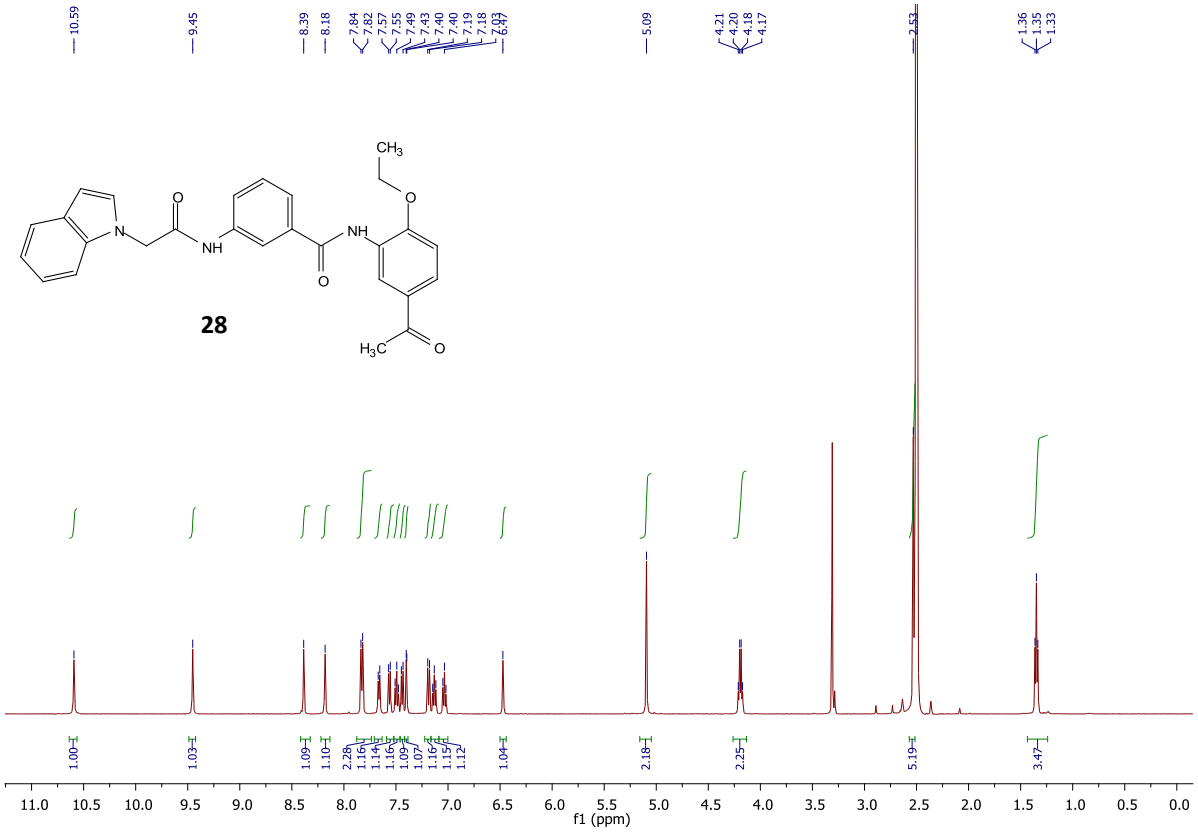
102

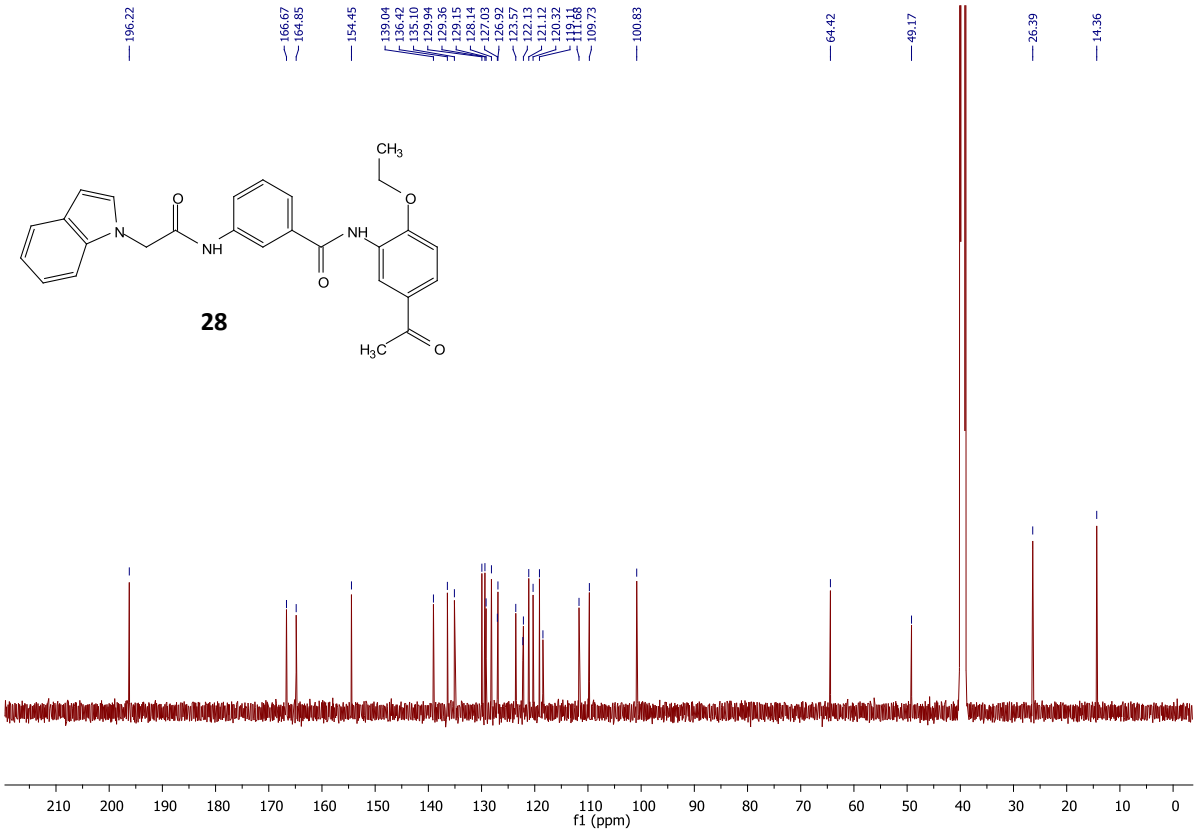

12.94
10.58
8.23
7.84
7.82
7.65
7.63
7.57
7.55
7.46
7.44
7.42
7.39
7.38
7.14
7.13
7.11
7.05
7.03
7.01
6.47
6.46
5.08
HO
O
NH
O
N
1.00
0.97
0.96
0.98
0.98
1.03
1.44
0.87
1.32
0.99
1.73
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

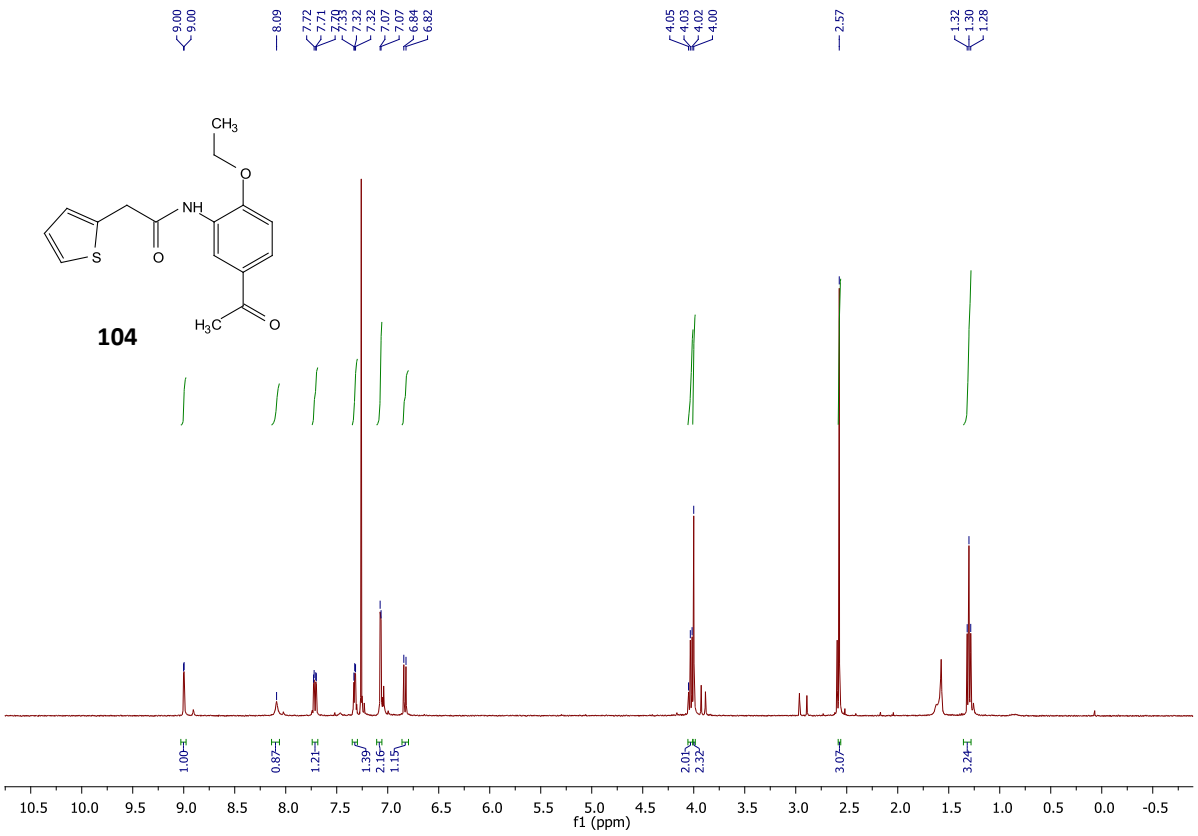
103

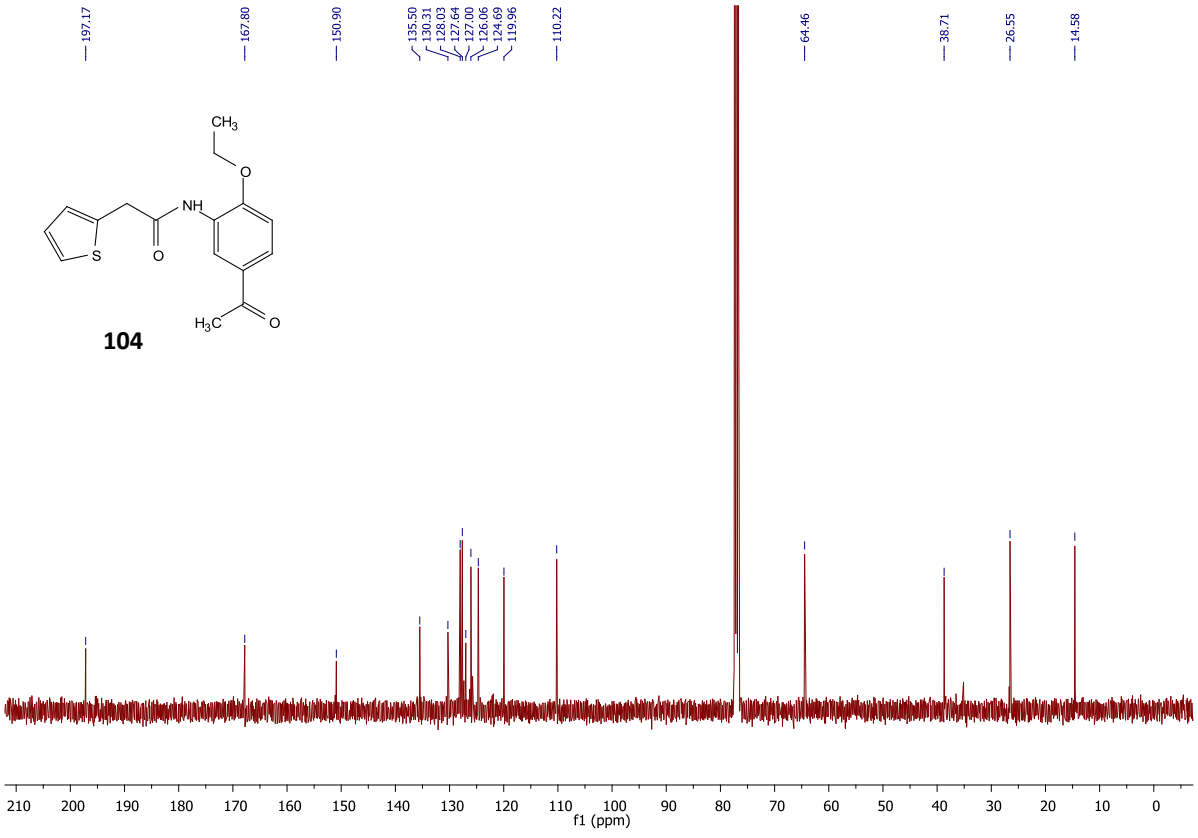

167.00
166.62
138.90
131.35
129.92
129.09
128.11
124.24
123.19
121.11
120.29
119.88
100.81
49.12
HO
O
NH
O
N
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
f1 (ppm)

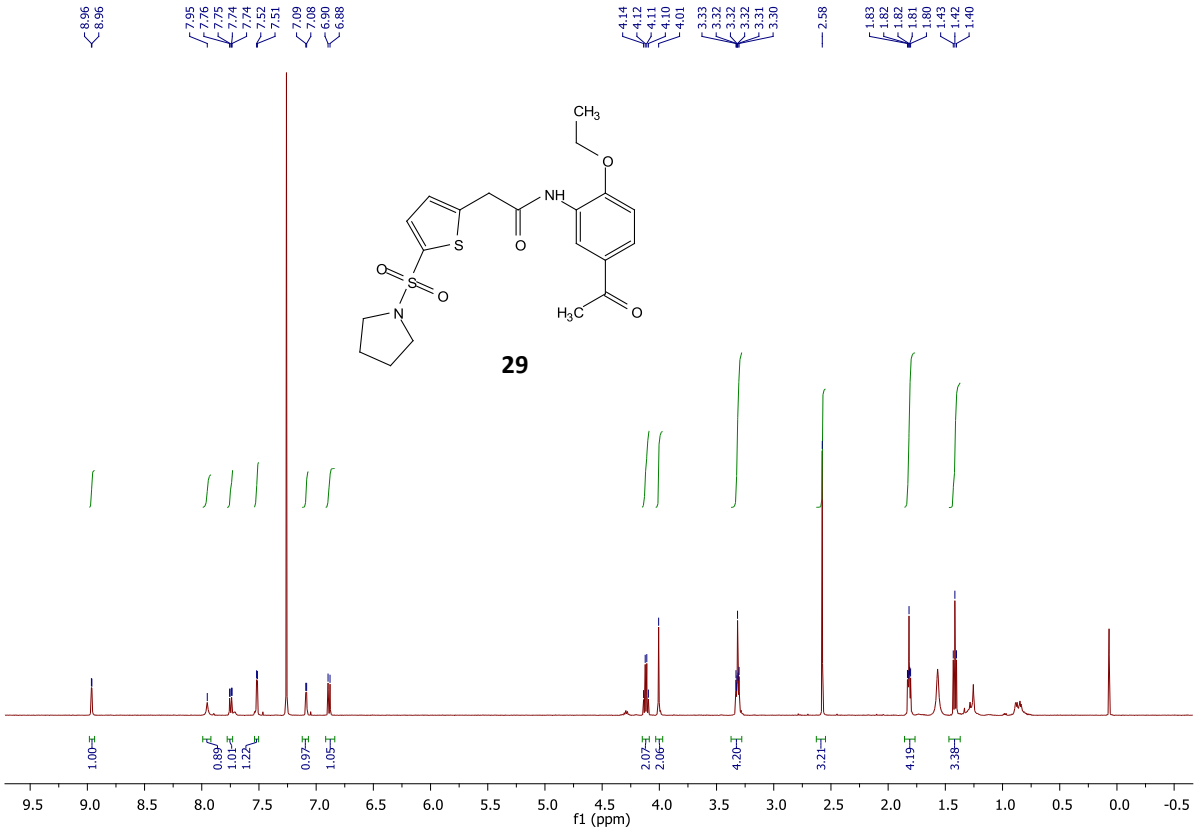
103

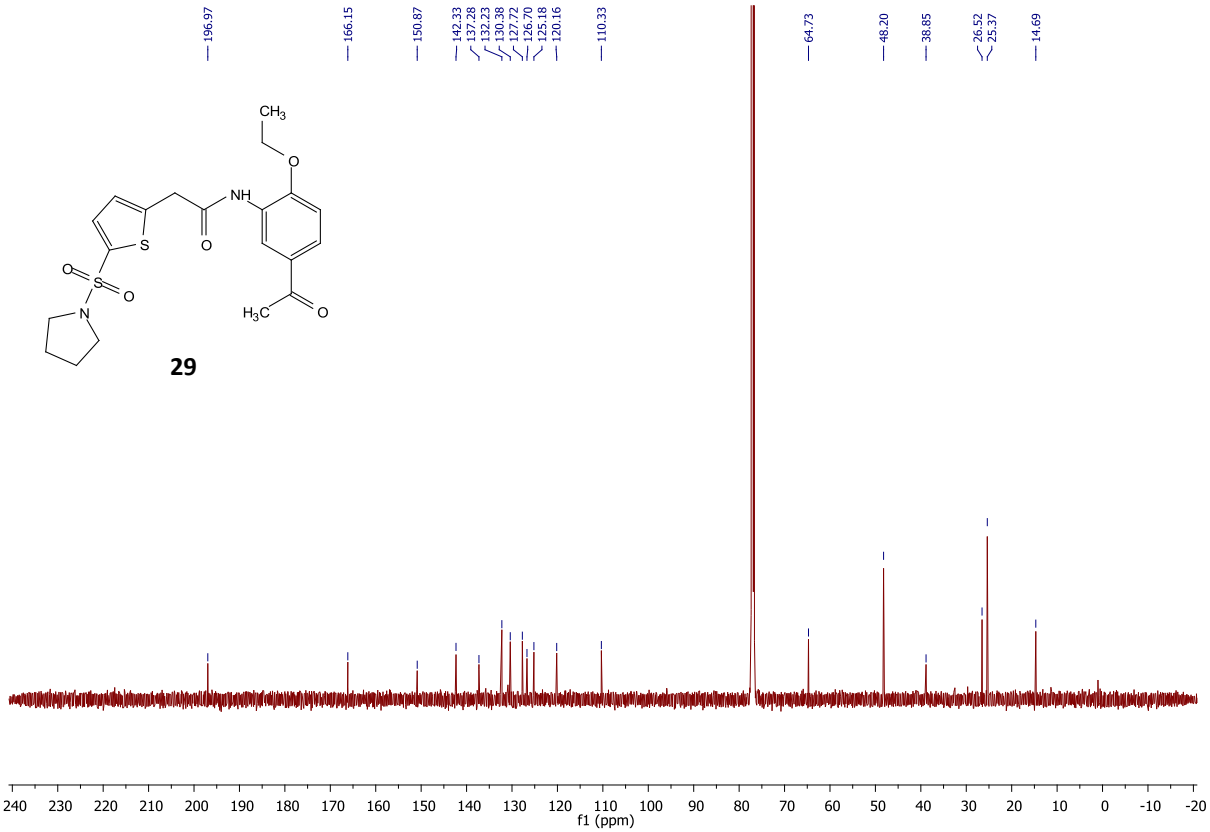

10.59
9.45
8.39
8.18
7.84
7.82
7.57
7.55
7.49
7.43
7.40
7.40
7.19
7.18
5.09
4.21
4.20
4.18
4.17
2.53
1.36
1.35
1.33
CH3
O
N
O
NH
NH
O
H3C
O
28
1.00
1.03
1.09
1.10
2.28
1.16
1.14
1.16
1.09
1.07
1.16
1.15
1.12
1.04
2.18
2.25
5.19
3.47
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

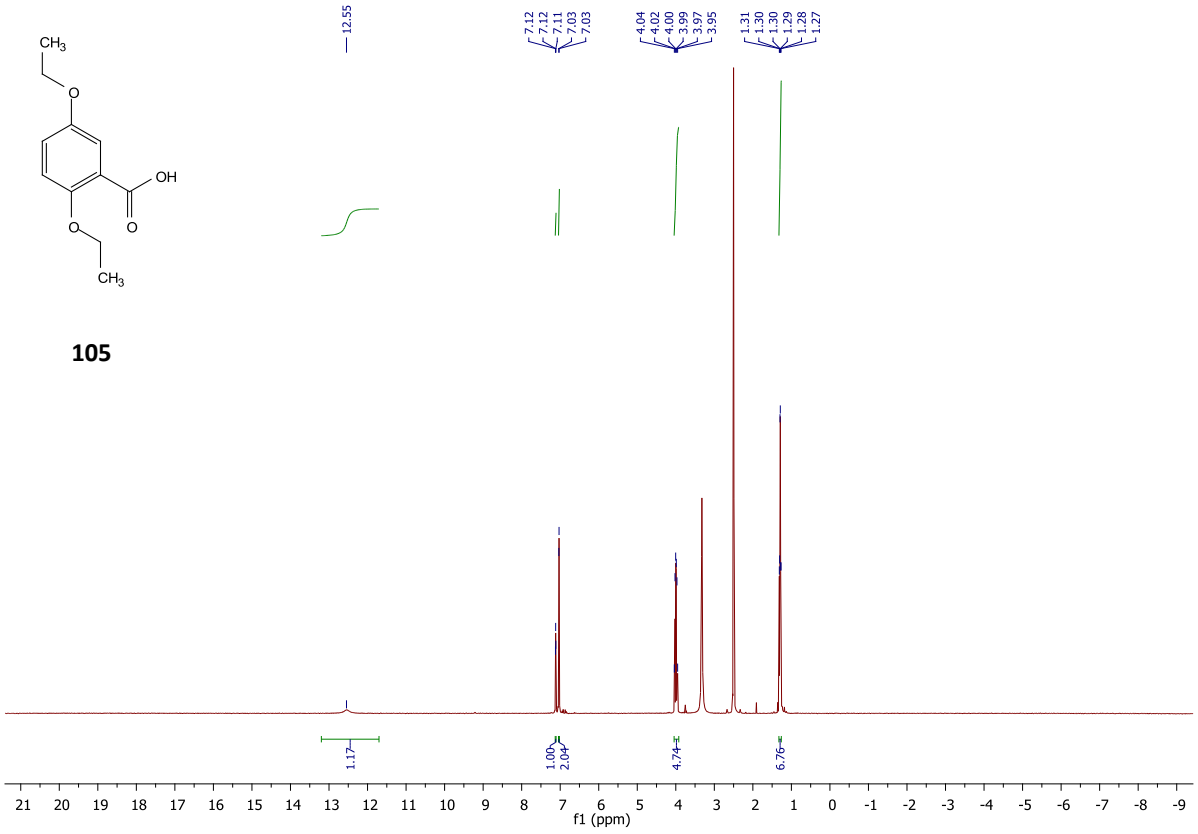

196.22
166.67
164.85
154.45
139.04
136.42
135.10
129.94
129.36
129.15
128.14
127.03
126.92
123.57
122.13
121.12
120.32
111.68
109.73
100.83
64.42
49.17
26.39
14.36
CH3
O
N
O
NH
NH
O
H3C
O
28
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.00
9.00
8.09
7.72
7.71
7.70
7.33
7.32
7.32
7.07
7.07
6.84
6.82
4.05
4.03
4.02
4.00
2.57
1.32
1.30
1.28
CH3
O
NH
S
O
H3C
O
104
1.00
0.87
1.21
1.39
2.16
1.15
2.01
2.32
3.07
3.24
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

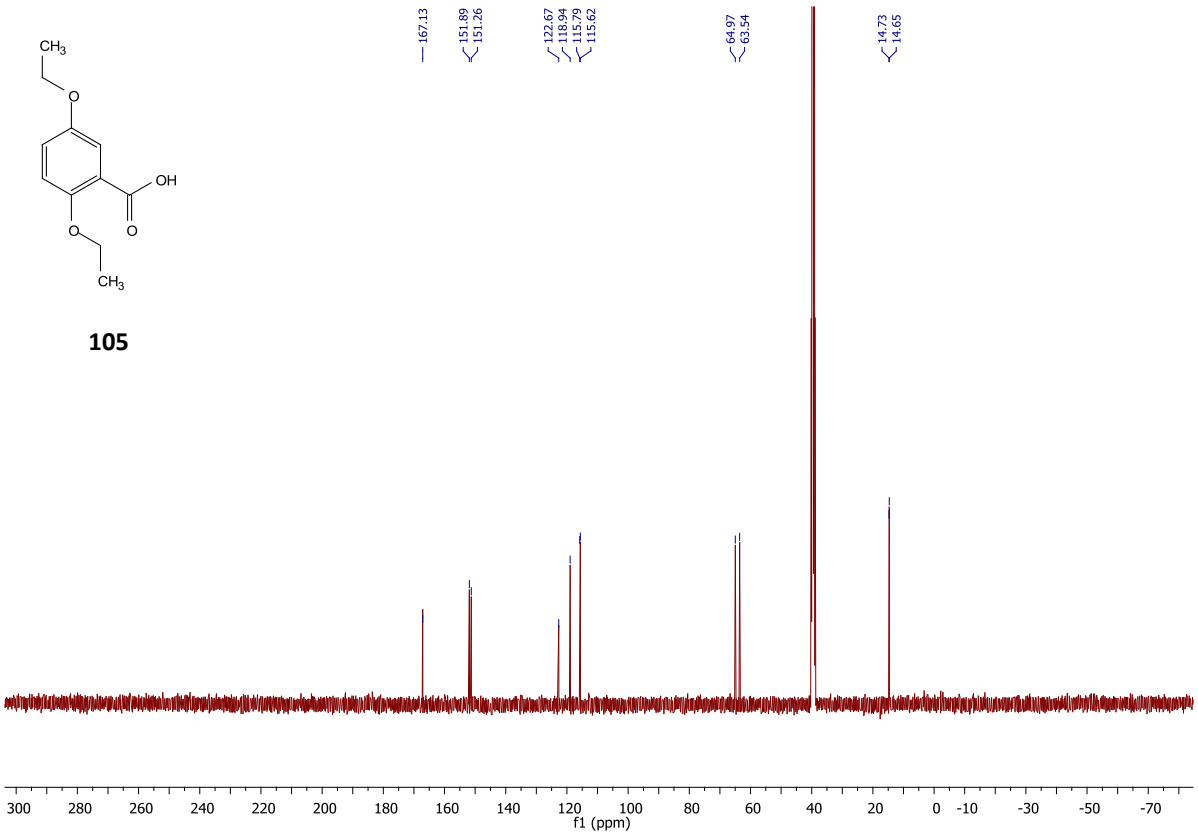

197.17
167.80
150.90
135.50
130.31
128.03
127.64
127.00
126.06
124.69
119.96
110.22
64.46
38.71
26.55
14.58
CH3
O
NH
S
O
H3C
O
104
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.96
8.96
7.95
7.76
7.75
7.74
7.74
7.52
7.51
7.09
7.08
6.90
6.88
4.14
4.12
4.11
4.10
4.01
3.33
3.32
3.32
3.32
3.31
3.30
2.58
1.83
1.82
1.82
1.81
1.80
1.43
1.42
1.40
CH3
O
NH
S
O
O
S
O
N
O
H3C
O
29
1.00
0.89
1.01
1.22
0.97
1.05
2.07
2.06
4.20
3.21
4.19
3.38
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

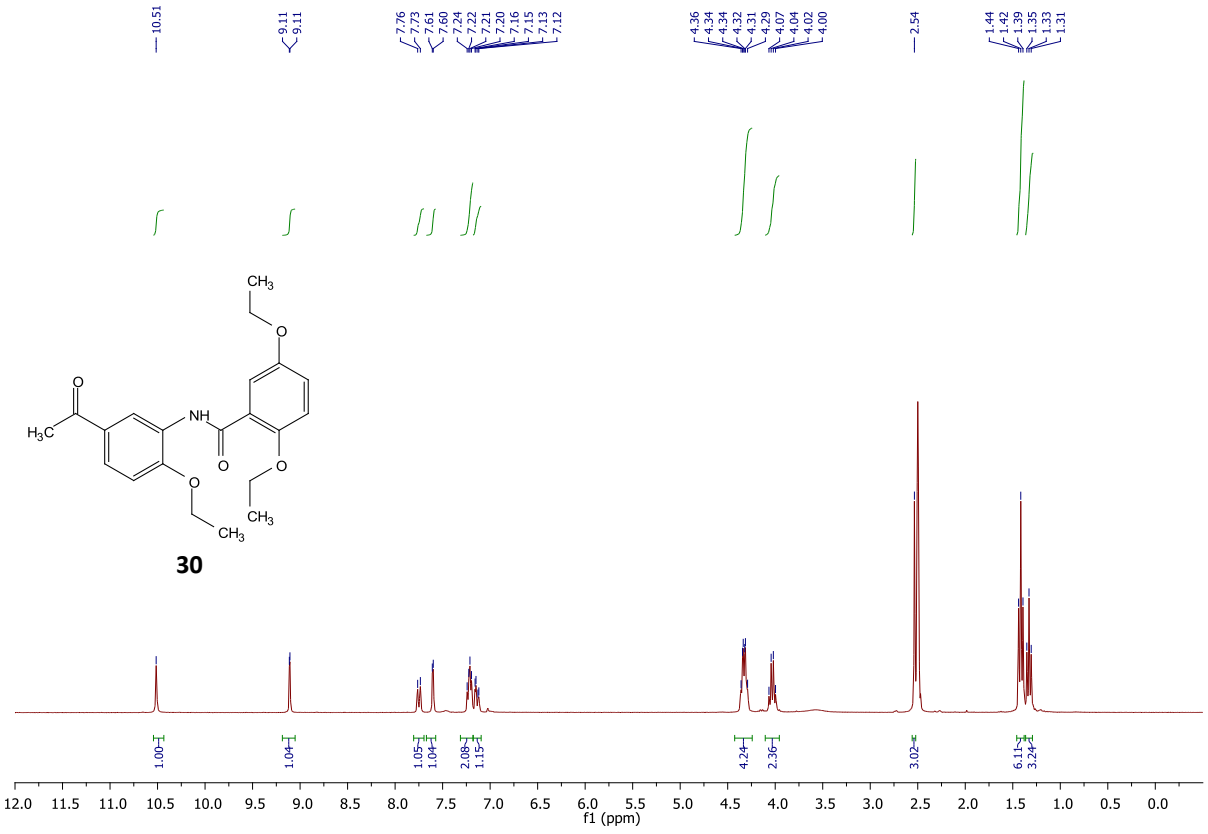

196.97
166.15
150.87
142.33
137.28
132.23
130.38
127.72
126.70
125.18
120.16
110.33
64.73
48.20
38.85
26.52
25.37
14.69
CH3
O
NH
S
O
O
S
O
N
O
H3C
O
29
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


12.55
7.12
7.12
7.11
7.03
7.03
4.04
4.02
4.00
3.99
3.97
3.95
1.31
1.30
1.30
1.29
1.28
1.27
1.17
1.00
2.04
4.74
6.76
f1 (ppm)

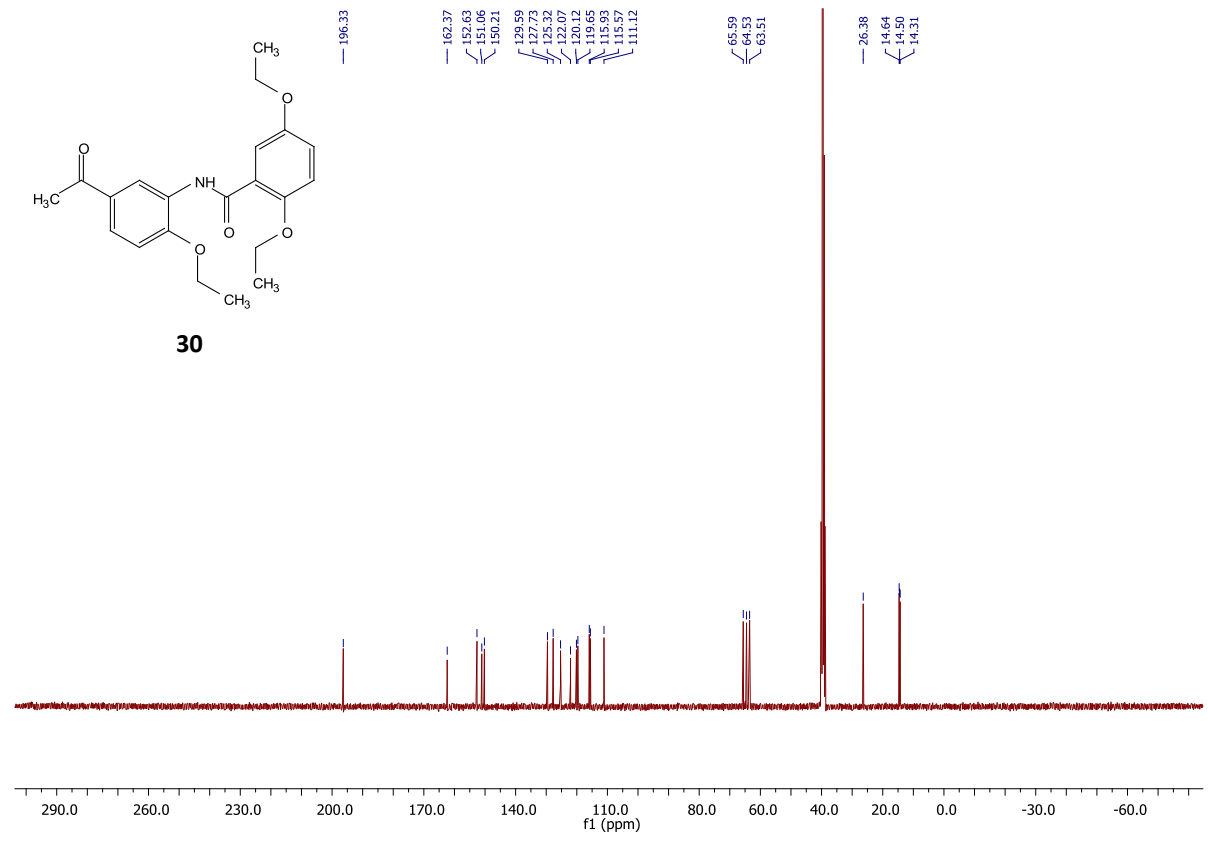
105


167.13
151.89
151.26
122.67
118.94
115.79
115.62
64.97
63.94
14.73
14.65
f1 (ppm)

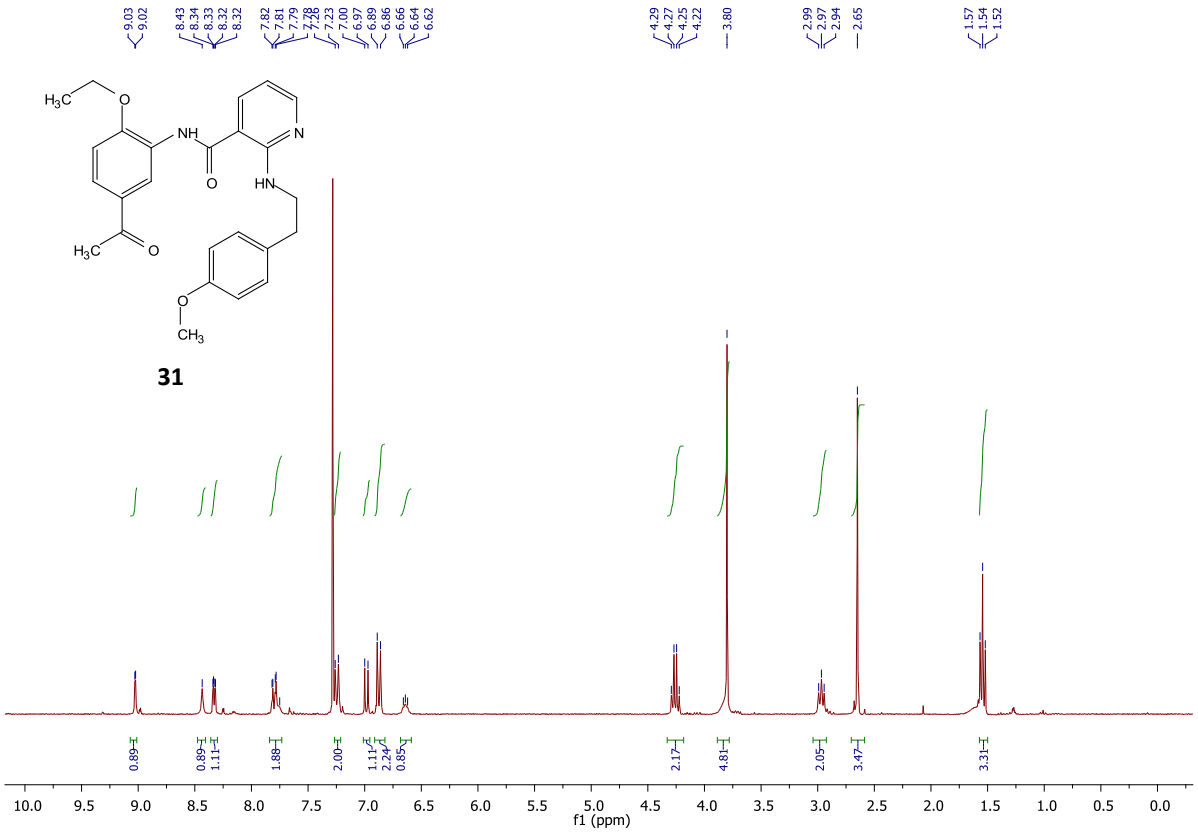
105


10.51
9.11
9.11
7.76
7.73
7.61
7.60
7.24
7.22
7.21
7.20
7.16
7.15
7.13
7.12
4.36
4.34
4.34
4.32
4.31
4.29
4.07
4.04
4.02
4.00
2.54
1.44
1.42
1.39
1.35
1.33
1.31
1.00
1.04
1.05
1.04
2.08
1.15
4.24
2.36
3.02
6.11
3.24
f1 (ppm)

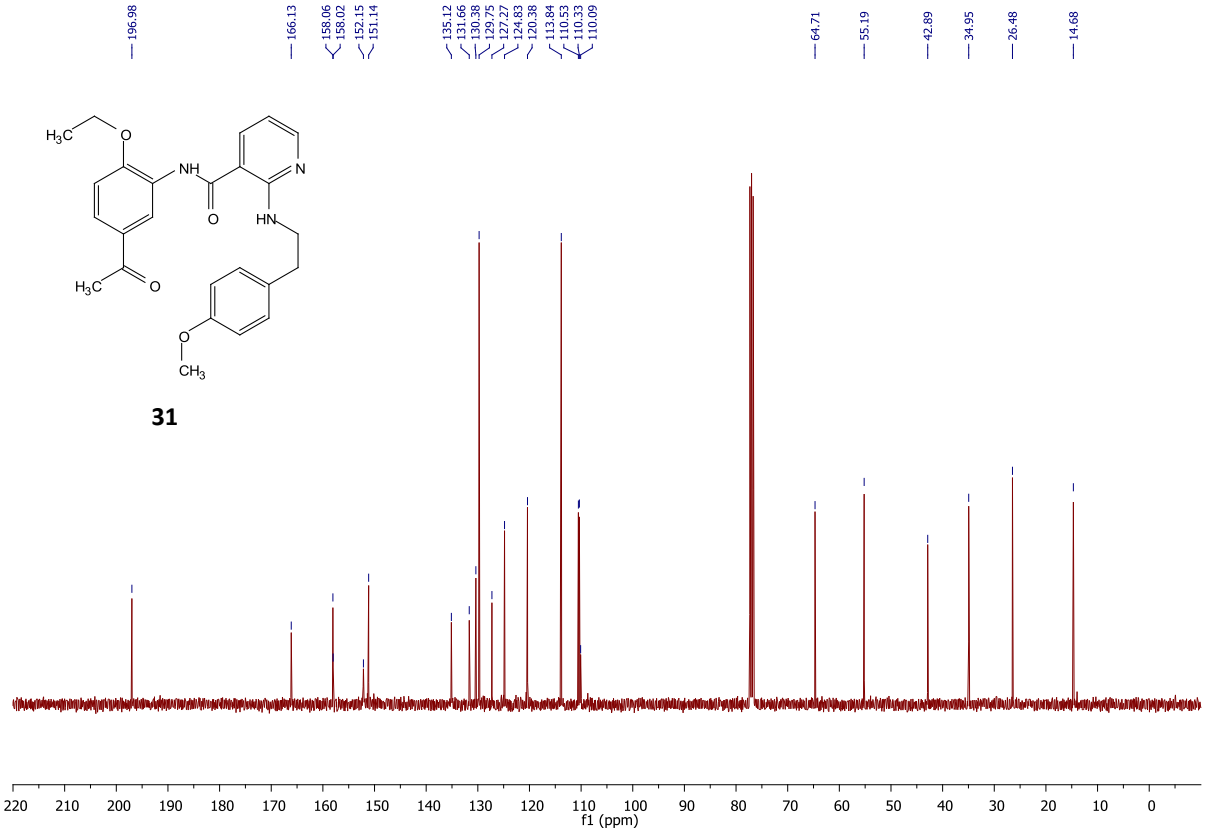
30


196.33
162.37
152.63
151.06
150.21
129.59
127.73
125.32
122.07
120.12
119.65
115.93
115.57
111.12
65.59
64.53
63.51
26.38
14.64
14.50
14.31
f1 (ppm)

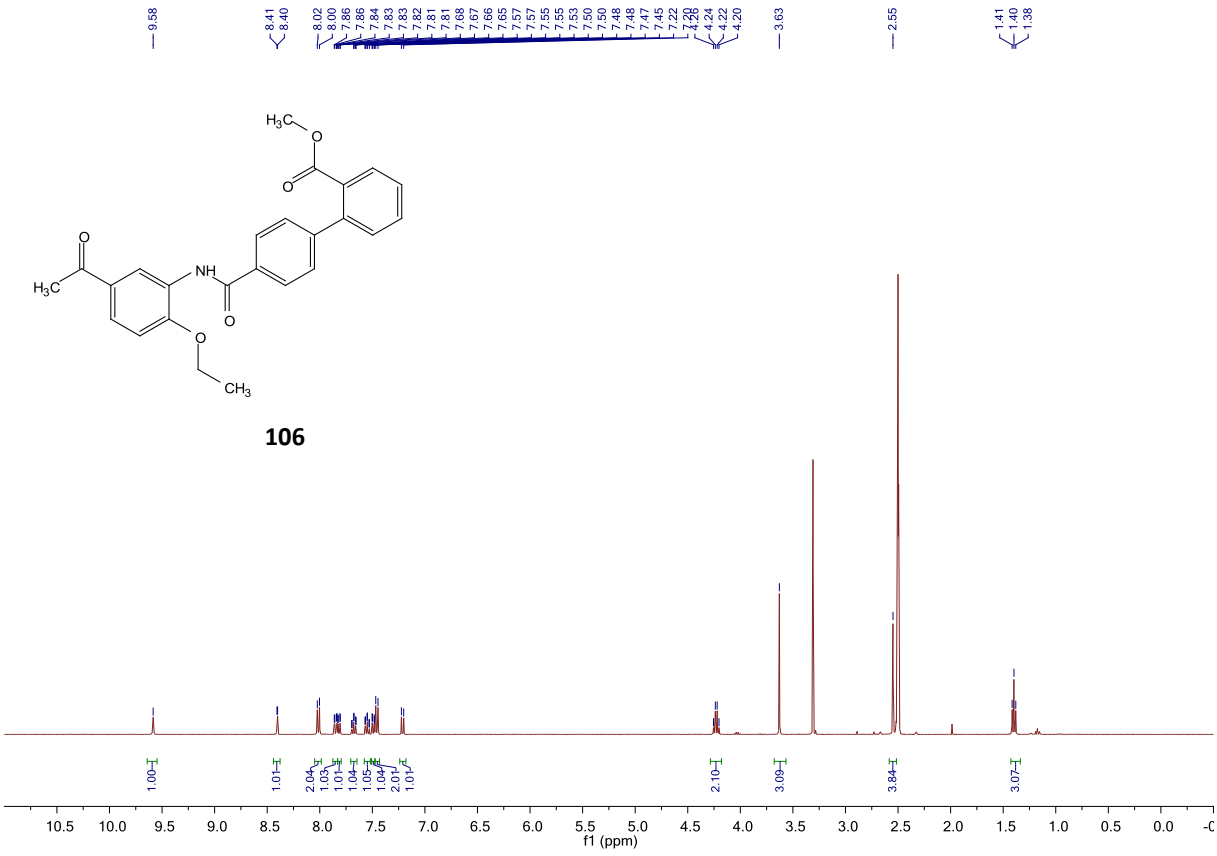
30


9.03
9.02
8.43
8.34
8.33
8.32
8.32
7.82
7.81
7.79
7.28
7.23
7.00
6.97
6.89
6.86
6.66
6.64
6.62
4.29
4.27
4.25
4.22
3.80
2.99
2.97
2.94
2.65
1.57
1.54
1.52
0.89
0.89
1.11
1.88
2.00
1.11
2.24
0.85
2.17
4.81
2.05
3.47
3.31
f1 (ppm)

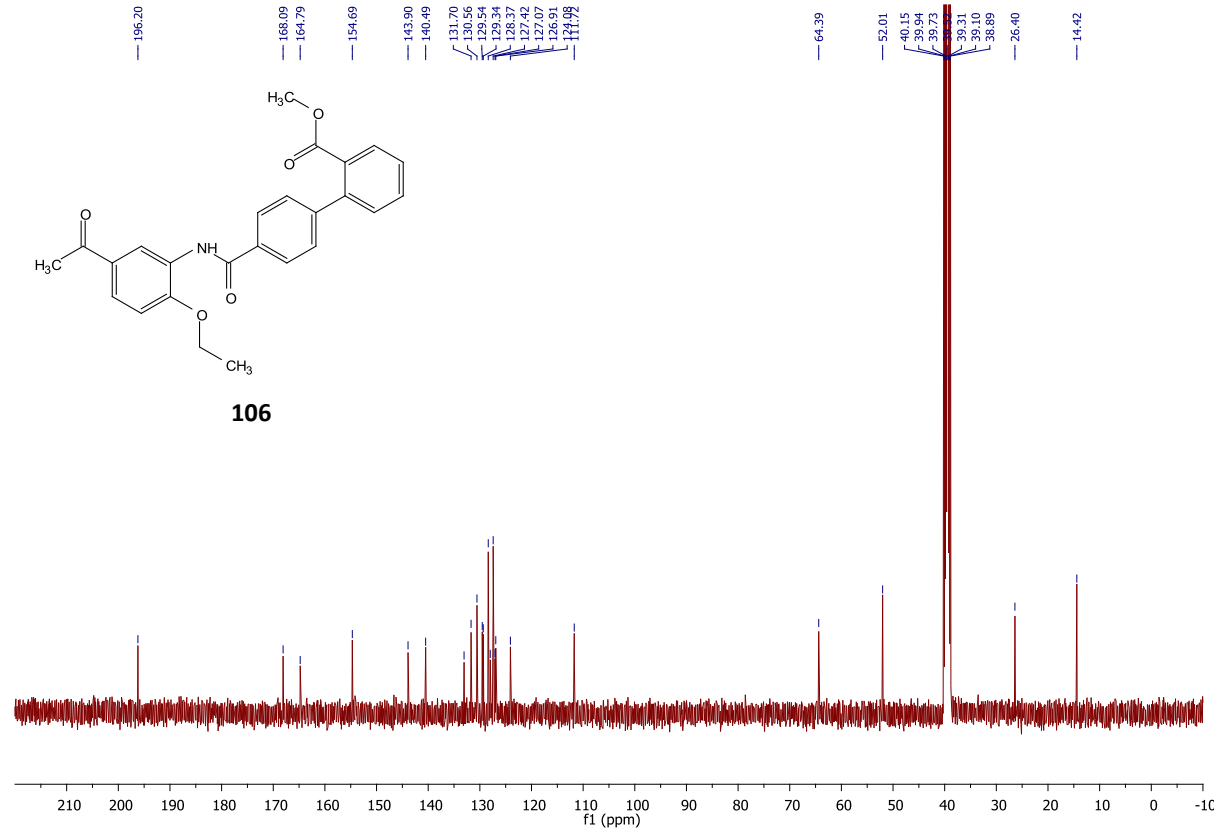
31


196.98
166.13
158.06
158.02
152.15
151.14
135.12
131.66
130.38
129.75
127.27
124.83
120.38
113.84
110.53
110.33
110.09
64.71
55.19
42.89
34.95
26.48
14.68
f1 (ppm)

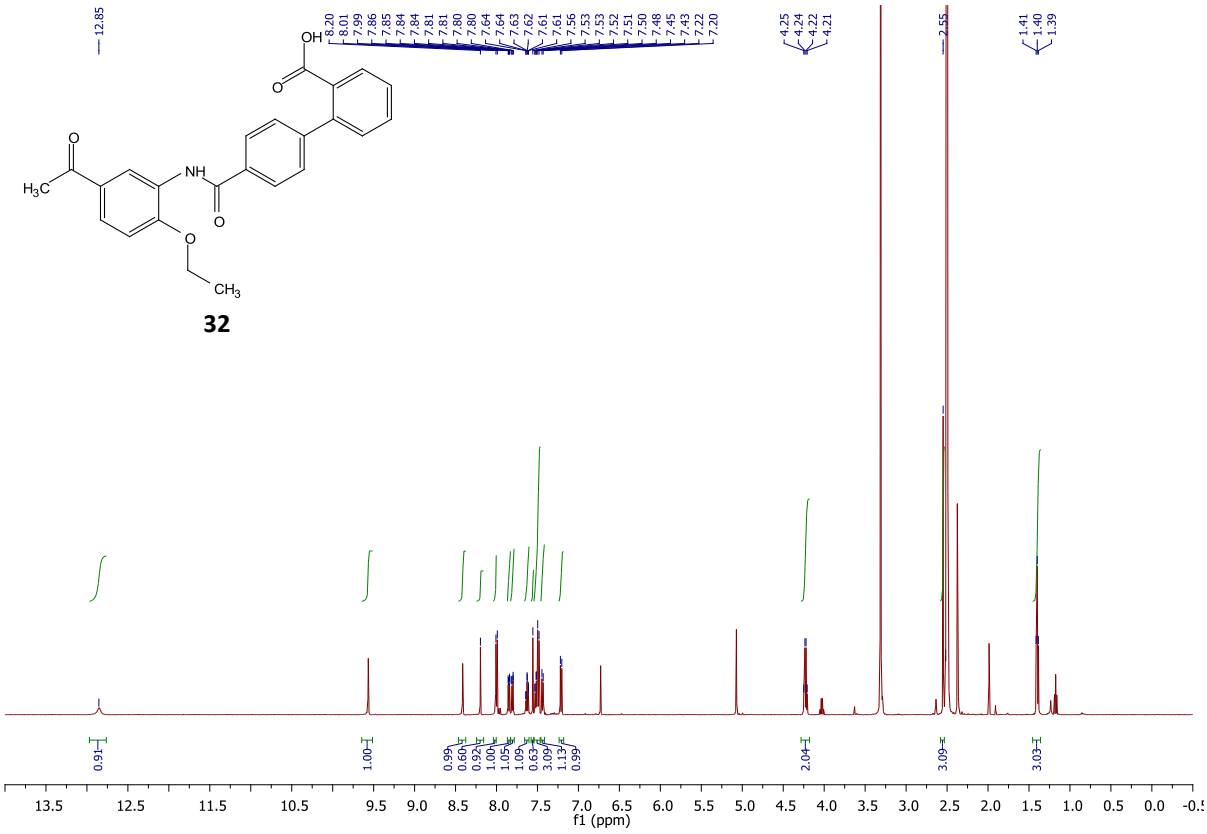
31


9.58
8.41
8.40
8.02
8.00
7.86
7.86
7.84
7.84
7.83
7.83
7.82
7.82
7.81
7.81
7.68
7.67
7.66
7.65
7.57
7.57
7.55
7.55
7.53
7.50
7.50
7.48
7.48
7.47
7.45
7.22
4.24
4.22
4.20
3.63
2.55
1.41
1.40
1.38
1.00
1.01
2.04
1.03
1.01
1.04
1.05
1.04
2.01
1.01
2.10
3.09
3.84
3.07
f1 (ppm)

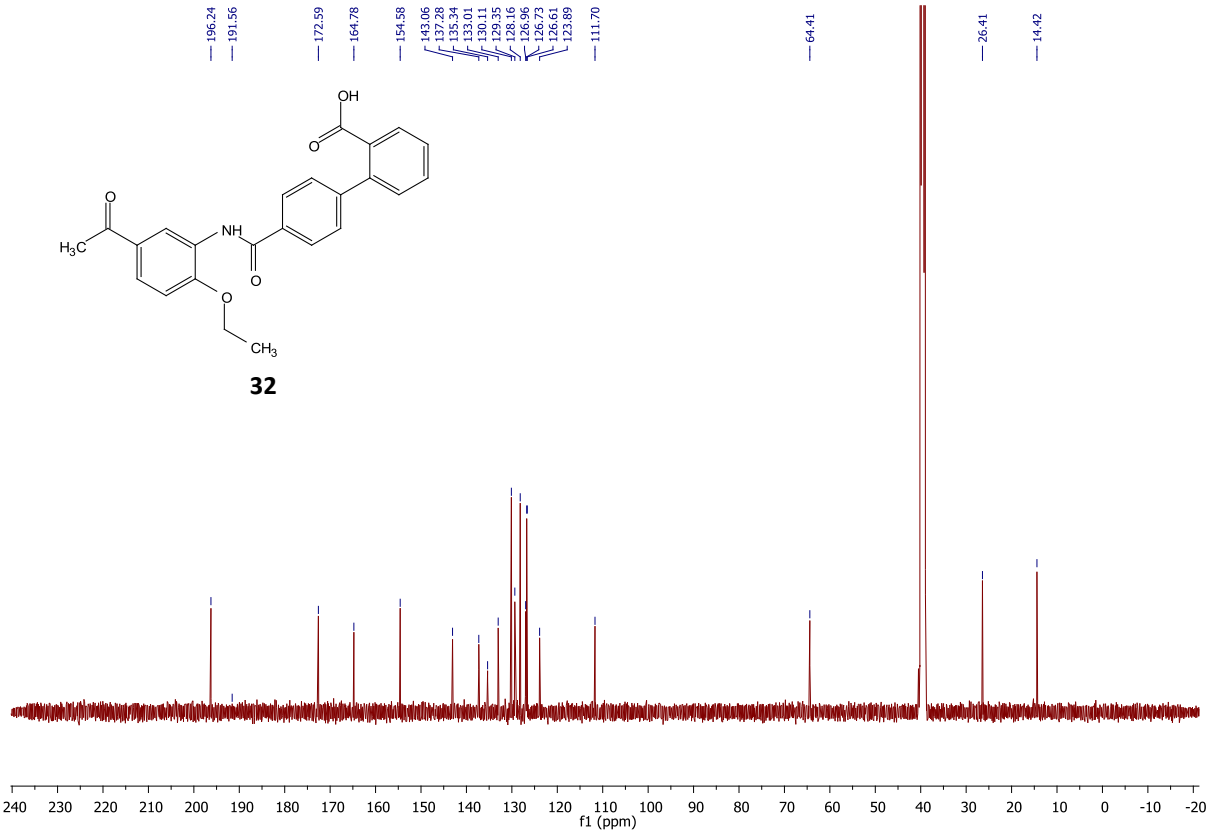
106


196.20
168.09
164.79
154.69
143.90
140.49
131.70
130.56
129.54
129.34
128.37
127.42
127.07
126.91
124.08
111.72
64.39
52.01
40.15
39.94
39.73
39.52
39.31
39.10
38.89
26.40
14.42
f1 (ppm)

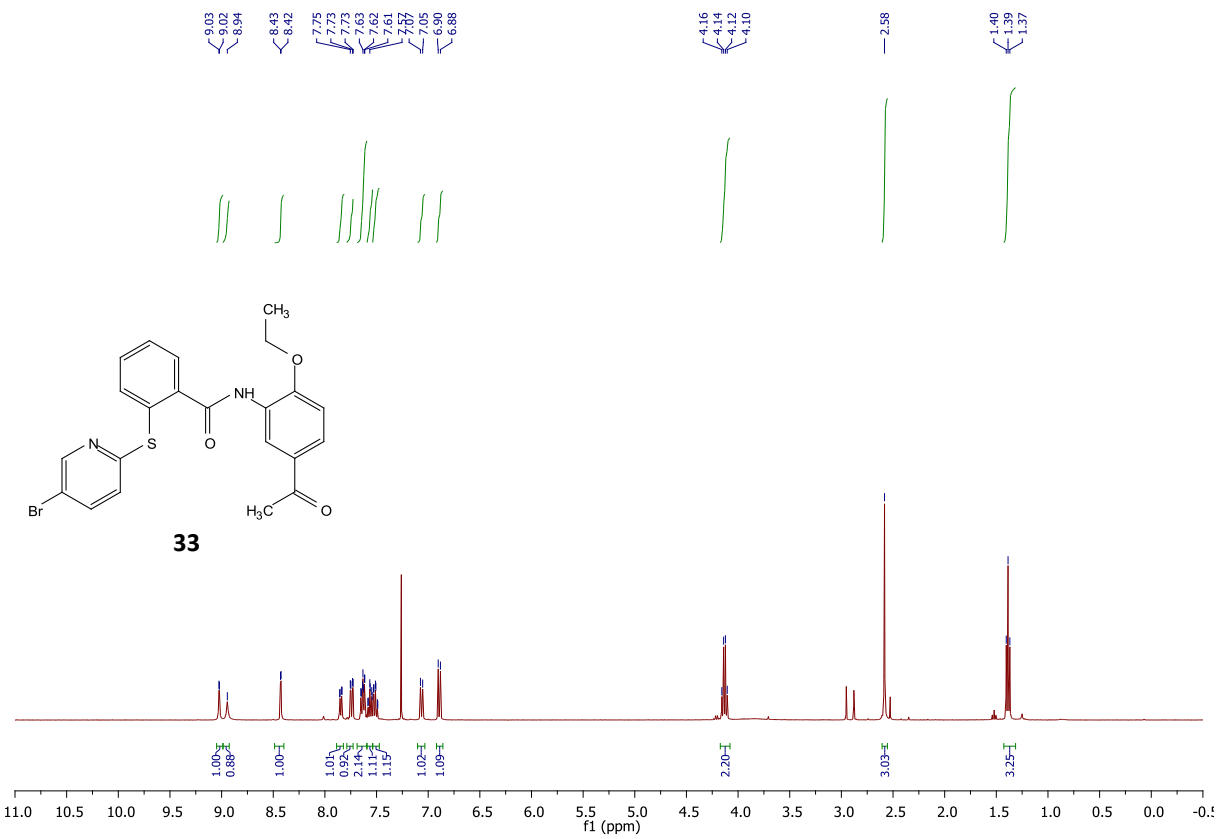
106


12.85
8.20
8.01
7.99
7.86
7.85
7.84
7.84
7.81
7.81
7.80
7.80
7.64
7.64
7.63
7.62
7.61
7.61
7.56
7.53
7.53
7.52
7.51
7.50
7.48
7.45
7.43
7.22
7.20
4.25
4.24
4.22
4.21
2.55
1.41
1.40
1.39
OH
O
O
NH
O
H3C
O
CH3
0.91
1.00
0.99
0.60
0.92
1.05
1.09
0.63
3.09
1.13
0.99
2.04
3.09
3.03
f1 (ppm)

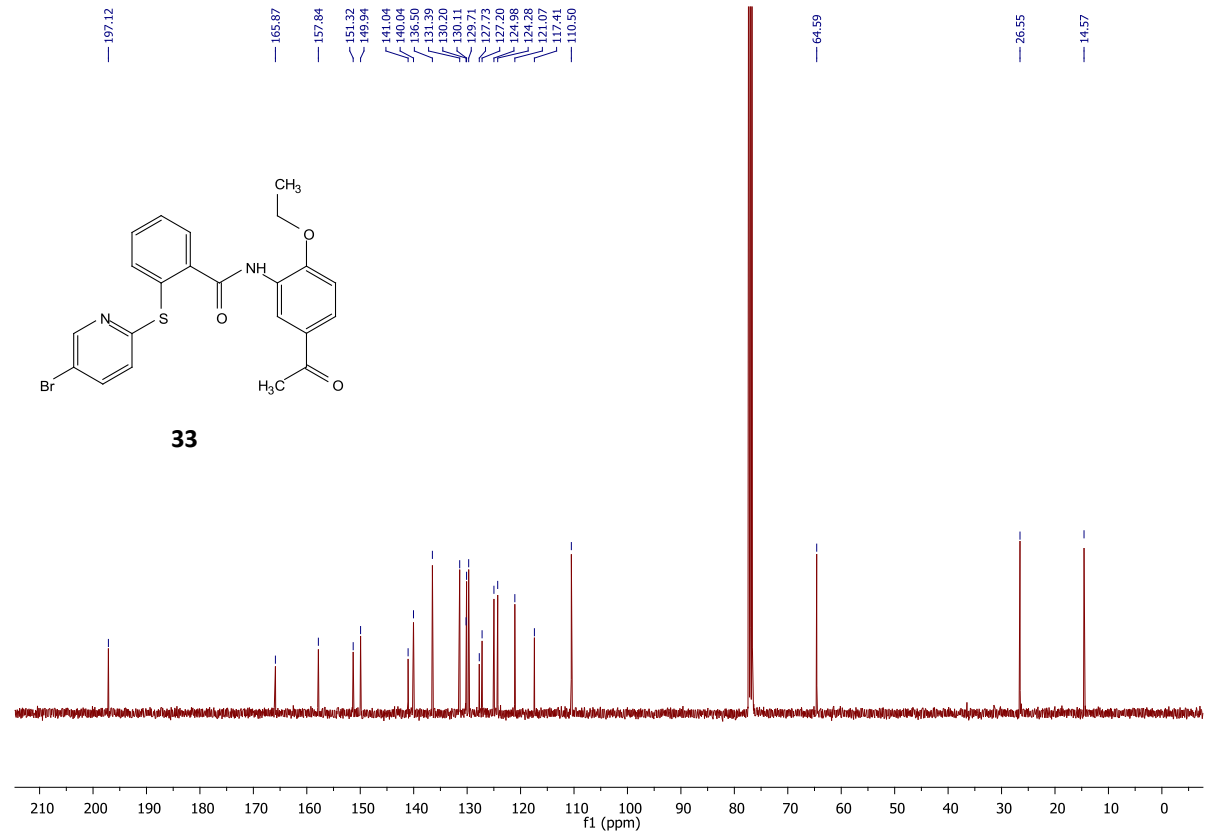
32


196.24
191.56
172.59
164.78
154.58
143.06
137.28
135.34
133.01
130.11
129.35
128.16
126.96
126.73
126.61
123.89
111.70
64.41
26.41
14.42
OH
O
O
NH
O
H3C
O
CH3
f1 (ppm)

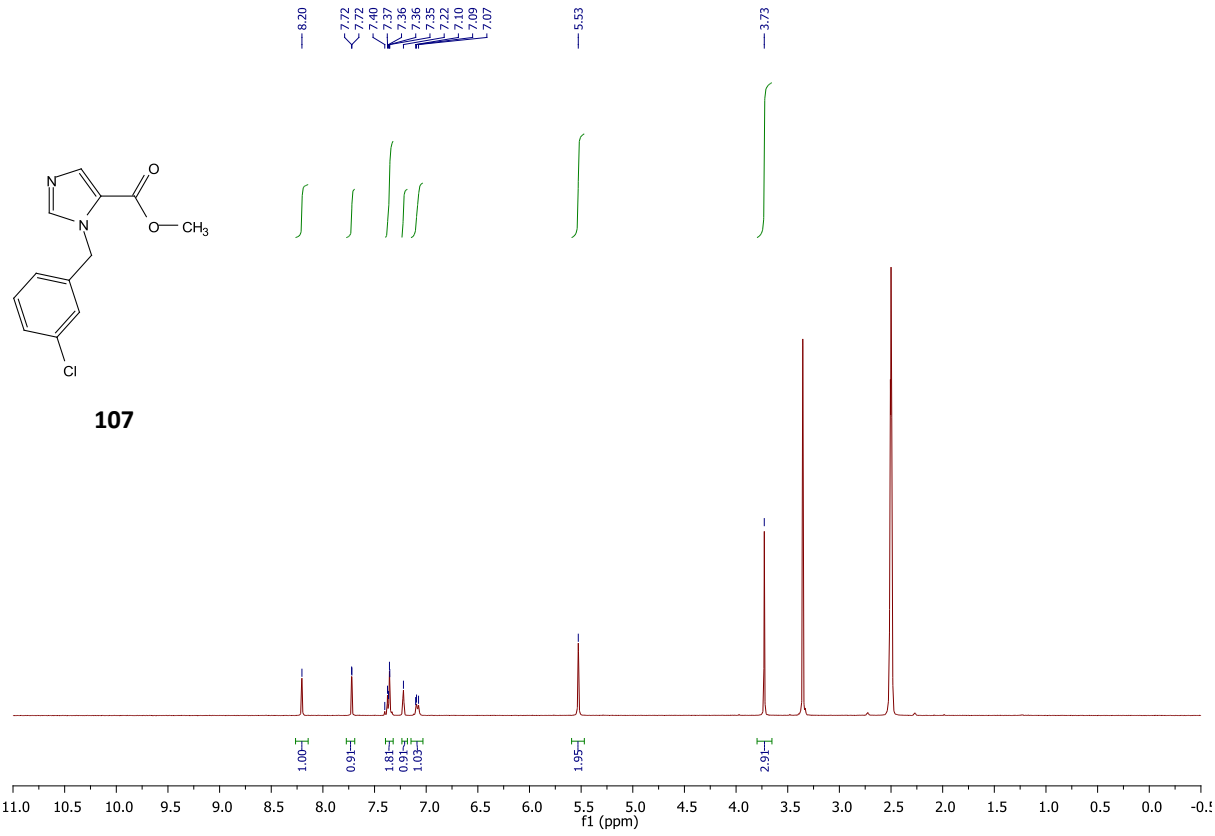
32


9.03
9.02
8.94
8.43
8.42
7.75
7.73
7.73
7.63
7.62
7.61
7.57
7.07
7.05
6.90
6.88
4.16
4.14
4.12
4.10
2.58
1.40
1.39
1.37
CH3
O
NH
O
N
S
Br
H3C
O
1.00
0.88
1.00
1.01
0.92
2.14
1.11
1.15
1.02
1.09
2.20
3.03
3.25
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

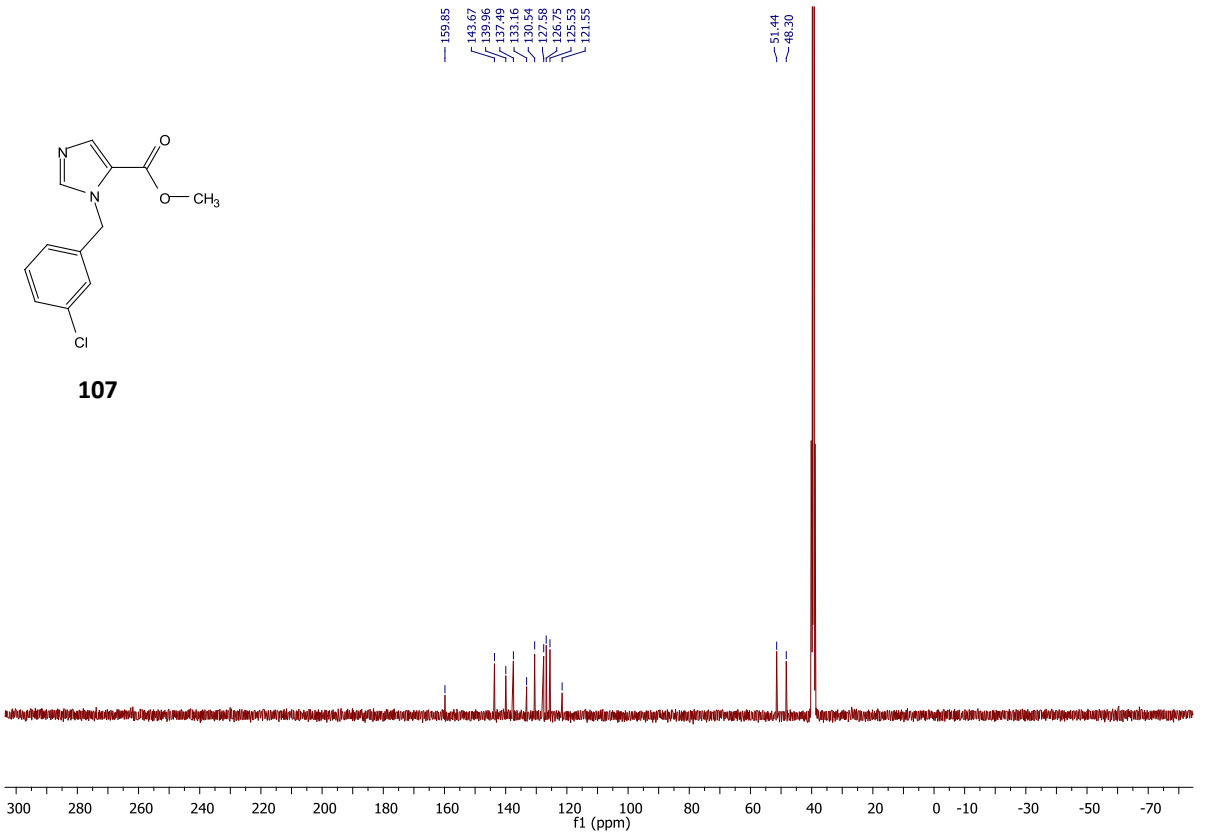
33


197.12
165.87
157.84
151.32
149.94
141.04
140.04
136.50
131.39
130.20
130.11
129.71
127.73
127.20
124.98
124.28
121.07
117.41
110.50
64.59
26.55
14.57
CH3
O
NH
O
N
S
Br
H3C
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

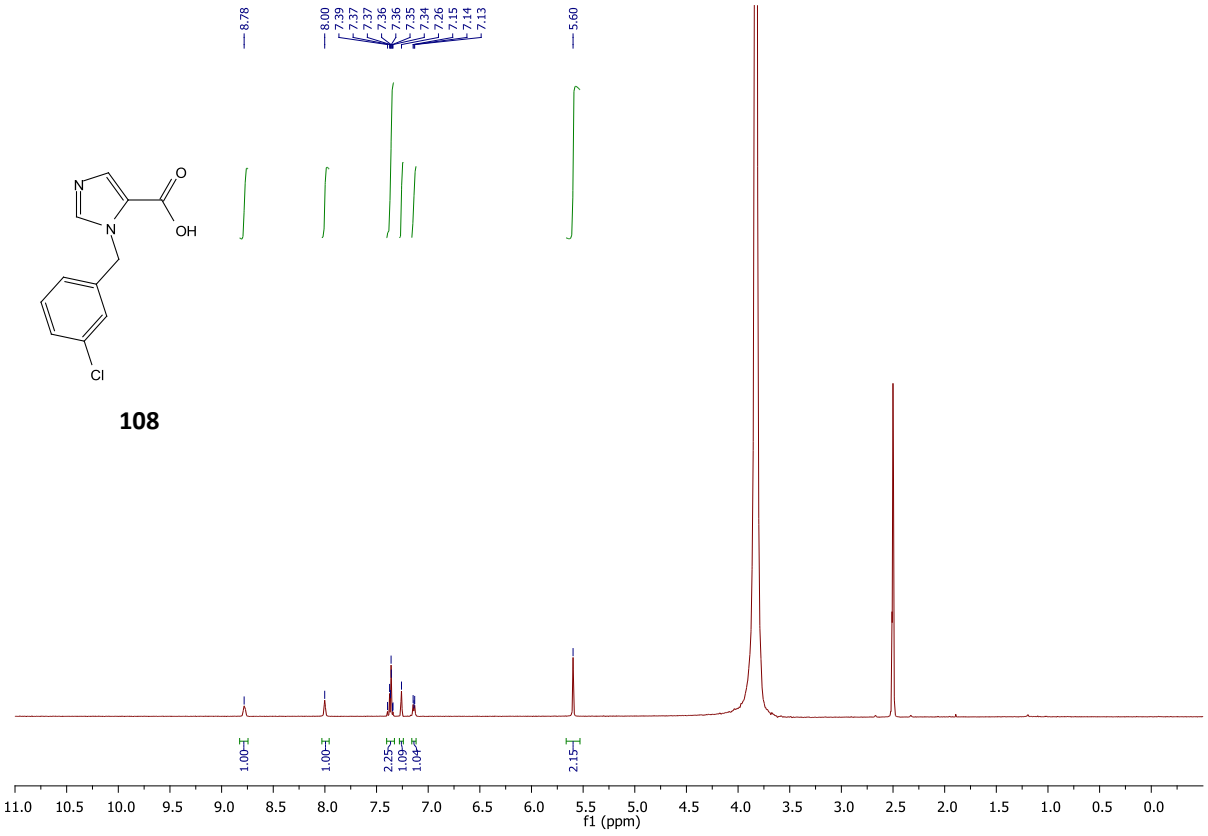
33


8.20
7.72
7.72
7.40
7.37
7.36
7.36
7.35
7.22
7.10
7.09
7.07
5.53
3.73
1.00
0.91
1.81
0.91
1.03
1.95
2.91
f1 (ppm)

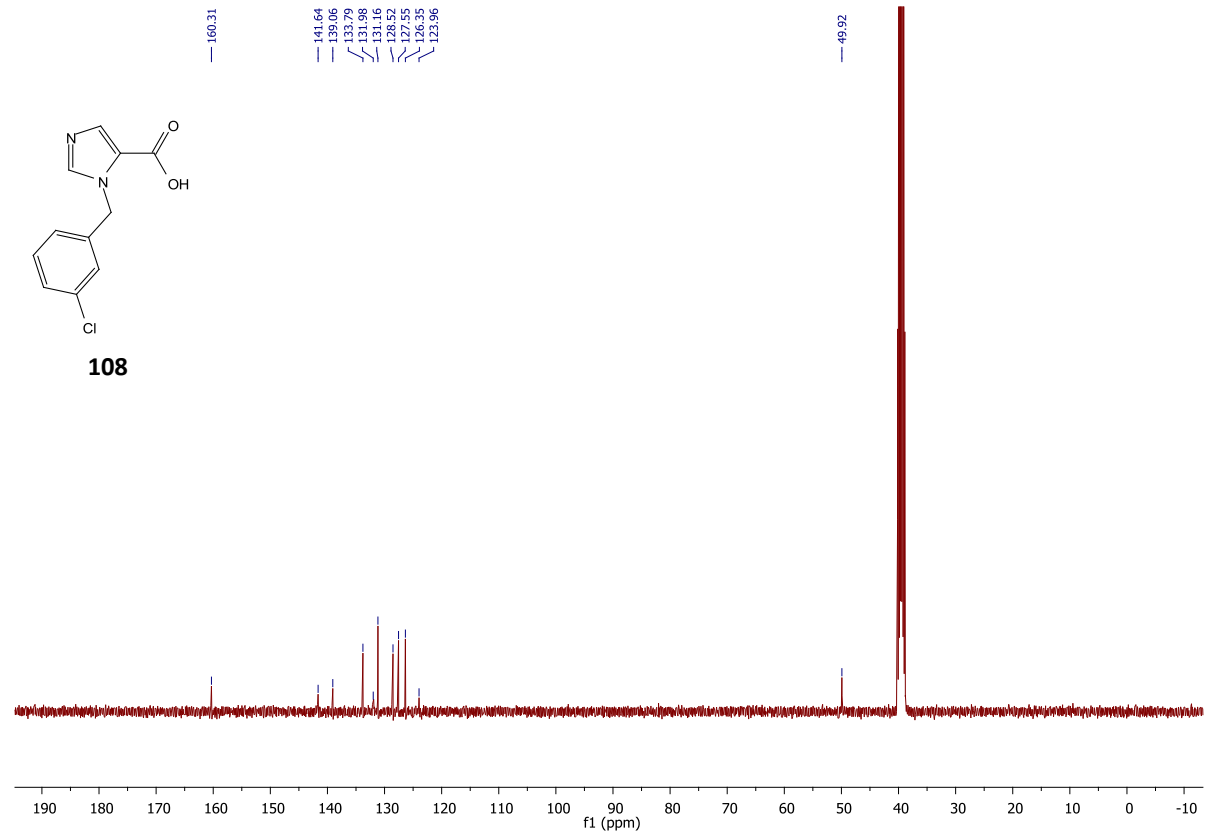
107


159.85
143.67
139.96
137.49
133.16
130.54
127.58
126.75
125.53
121.55
51.44
48.30
f1 (ppm)

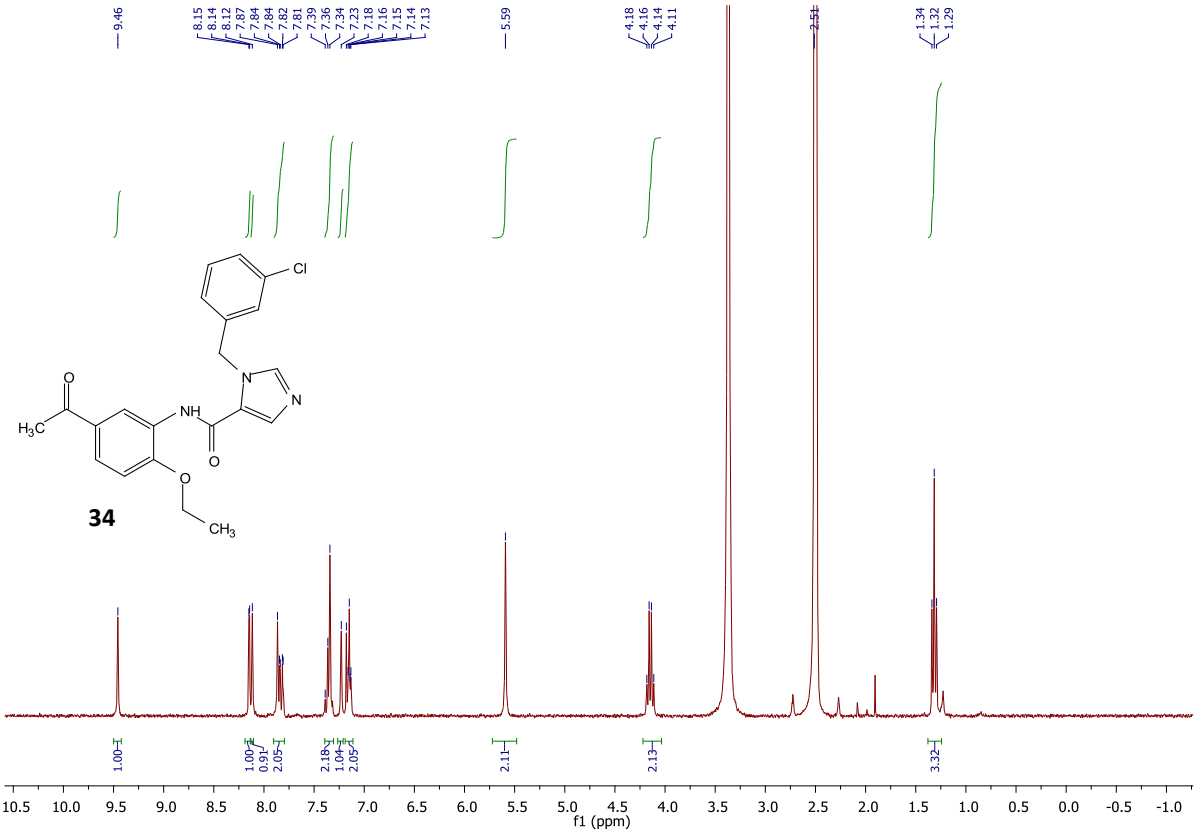
107

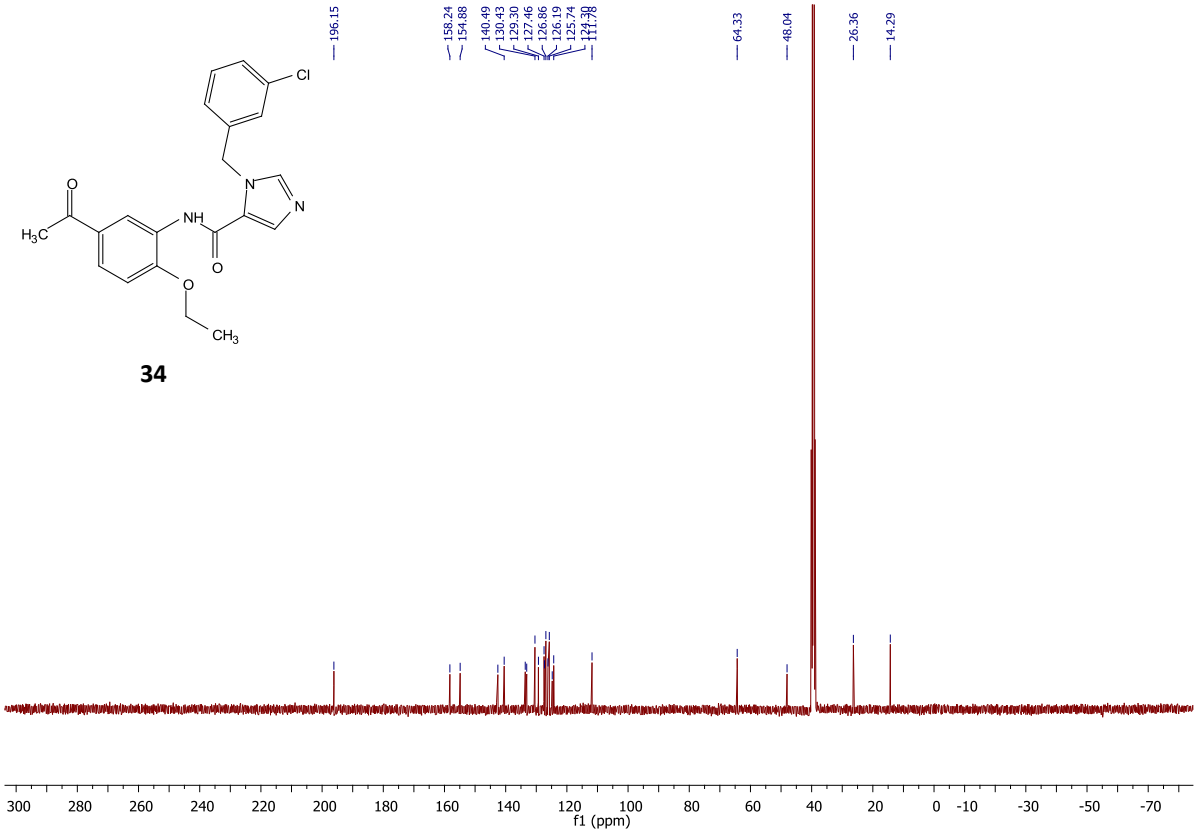

8.78
8.00
7.39
7.37
7.37
7.36
7.36
7.35
7.34
7.26
7.15
7.14
7.13
5.60
O
OH
N
N
Cl
1.00
1.00
2.25
1.09
1.04
2.15
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

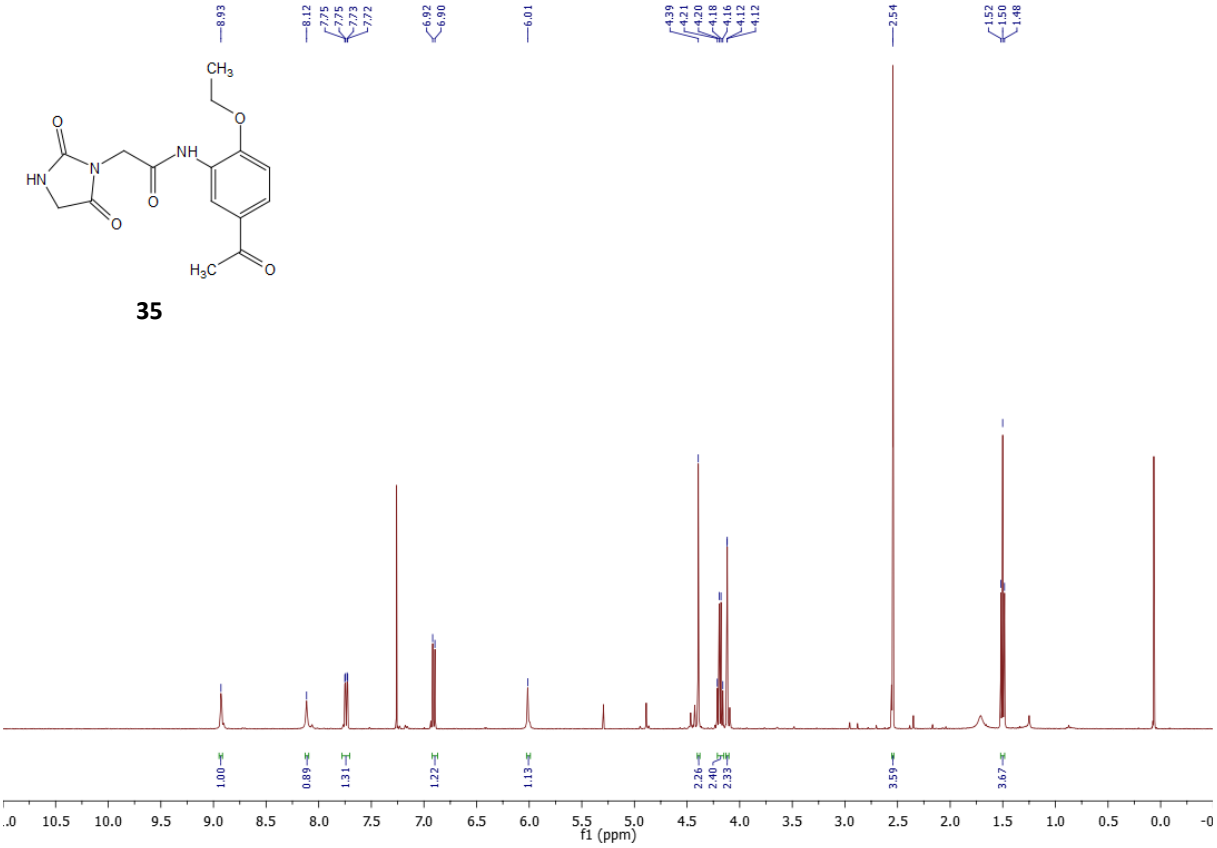
108


160.31
141.64
139.06
133.79
131.98
131.16
128.52
127.55
126.35
123.96
49.92
O
OH
N
N
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

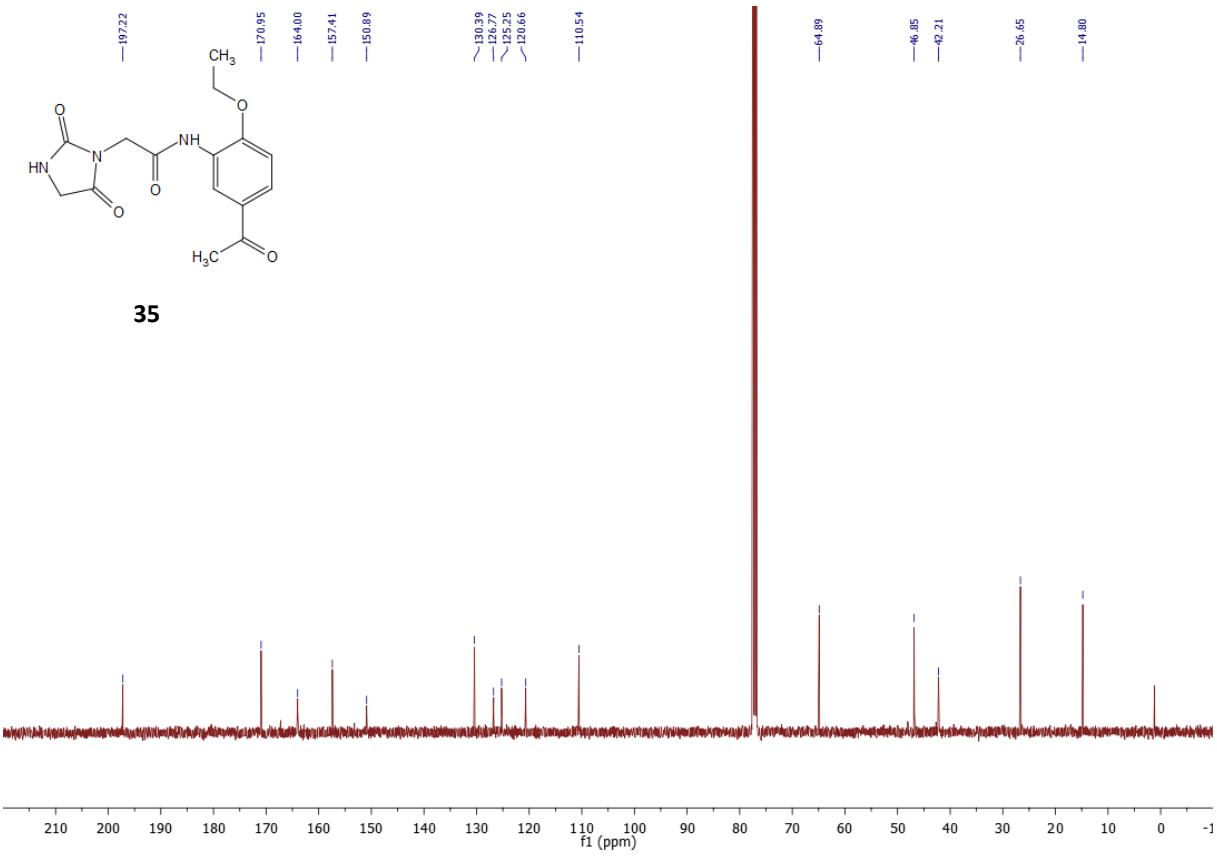
108


9.46
8.15
8.14
8.12
7.87
7.84
7.84
7.82
7.81
7.39
7.36
7.34
7.23
7.18
7.16
7.15
7.14
7.13
5.59
4.18
4.16
4.14
4.11
2.51
1.34
1.32
1.29
Cl
N
N
NH
O
O
H3C
O
CH3
34
1.00
1.00
0.91
2.05
2.18
1.04
2.05
2.11
2.13
3.32
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

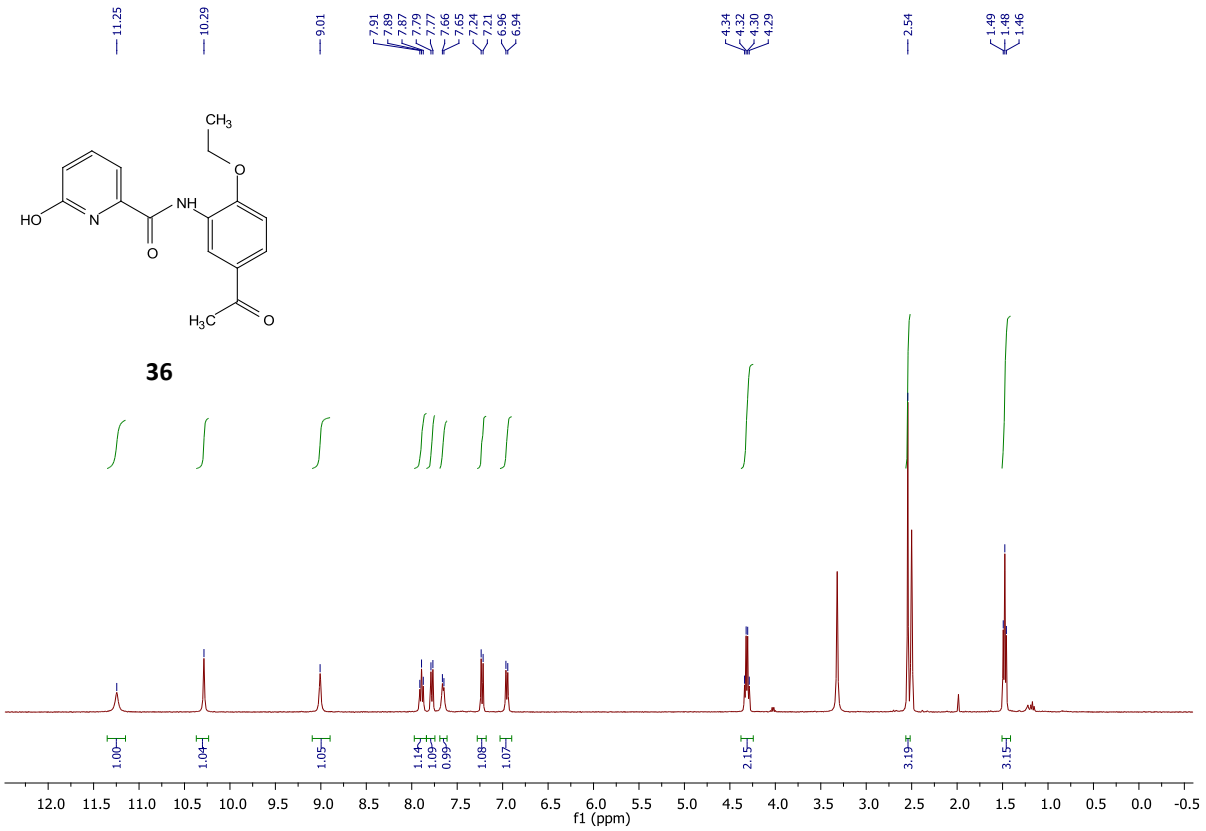

196.15
158.24
154.88
140.49
130.43
129.30
127.46
126.86
126.19
125.74
124.30
111.78
64.33
48.04
26.36
14.29
Cl
N
N
NH
O
O
H3C
O
CH3
34
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70
f1 (ppm)


8.93
8.12
7.75
7.75
7.73
7.72
6.92
6.90
6.01
4.39
4.21
4.20
4.18
4.16
4.12
4.12
2.54
1.52
1.50
1.48
1.00
0.89
1.31
1.22
1.13
2.26
2.40
2.33
3.59
3.67
f1 (ppm)

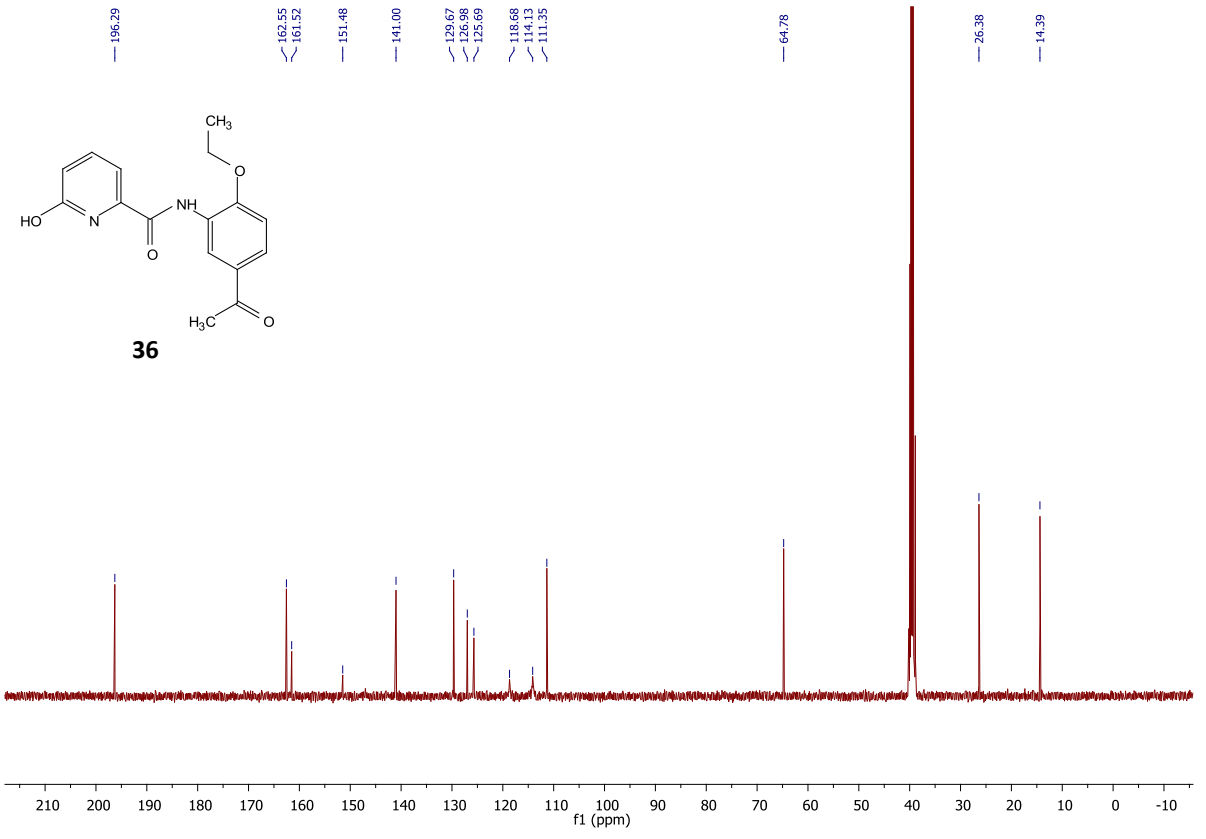
35


197.22
170.95
164.00
157.41
150.89
130.39
126.77
125.25
120.66
110.54
64.89
46.85
42.21
26.65
14.80
f1 (ppm)

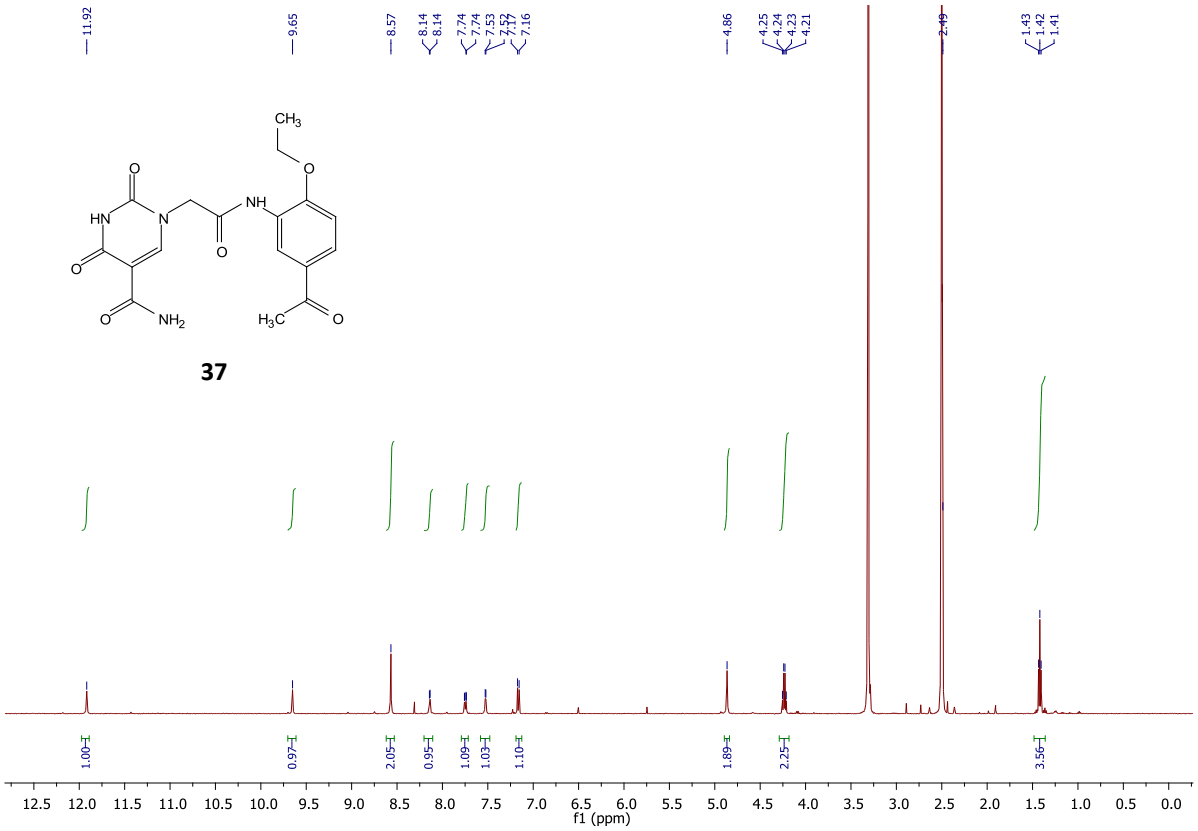
35


11.25
10.29
9.01
7.91
7.89
7.87
7.79
7.77
7.66
7.65
7.24
7.21
6.96
6.94
4.34
4.32
4.30
4.29
2.54
1.49
1.48
1.46
CH3
O
NH
HO
N
O
H3C
O
1.00
1.04
1.05
1.14
1.09
0.99
1.08
1.07
2.15
3.19
3.15
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

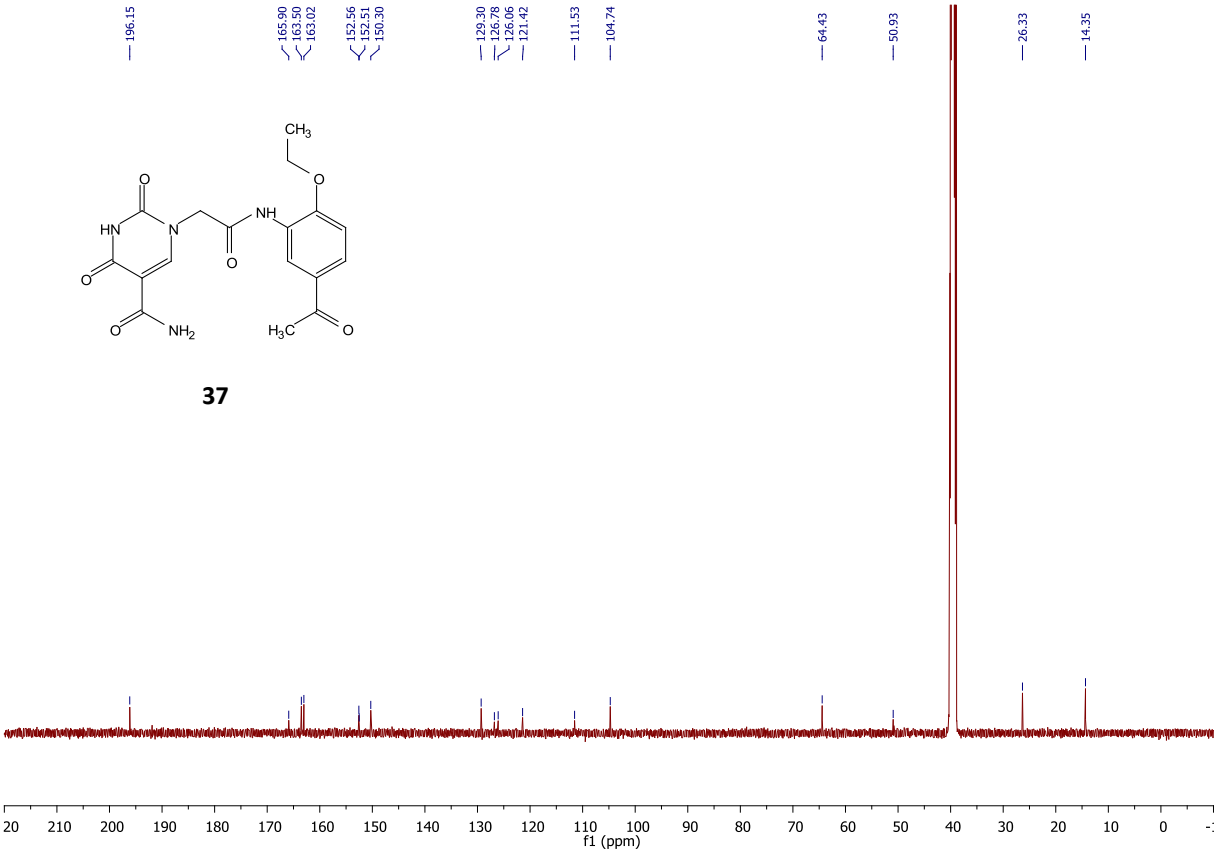
36


196.29
162.55
161.52
151.48
141.00
129.67
126.98
125.69
118.68
114.13
111.35
64.78
26.38
14.39
CH3
O
NH
HO
N
O
H3C
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

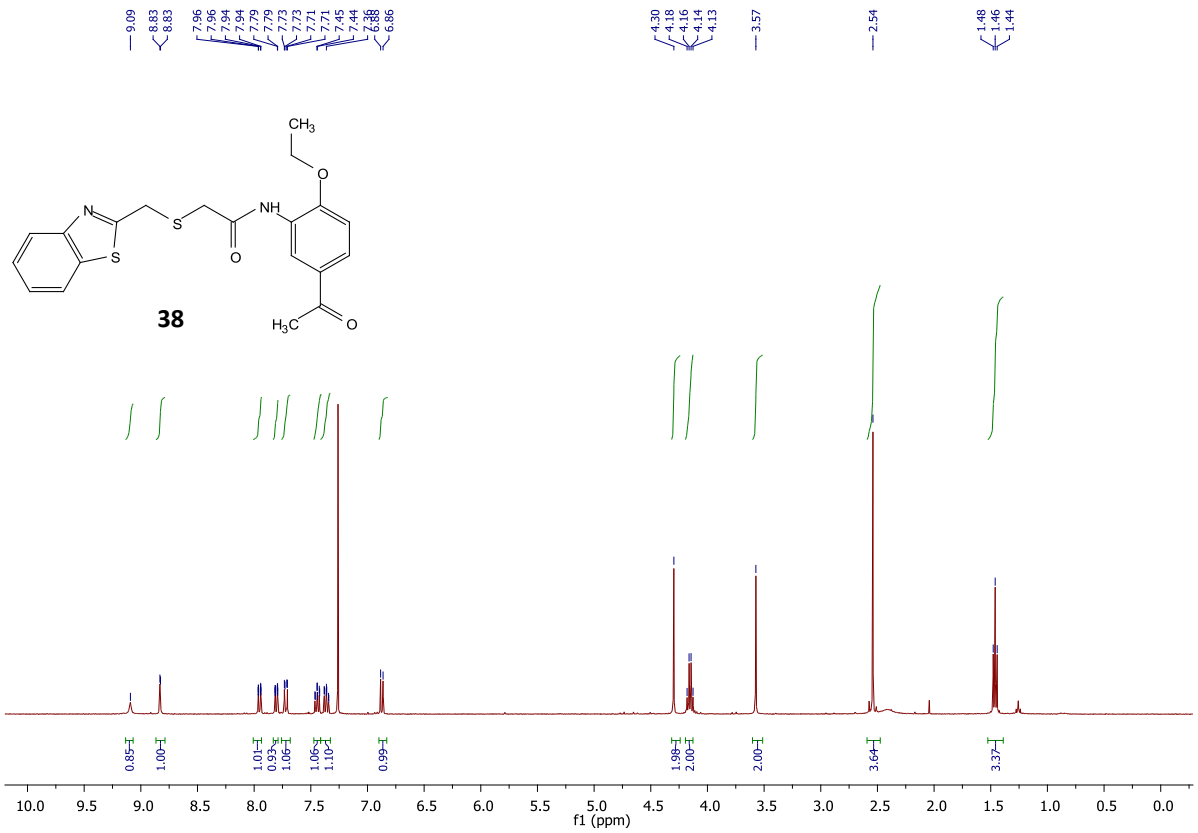
36

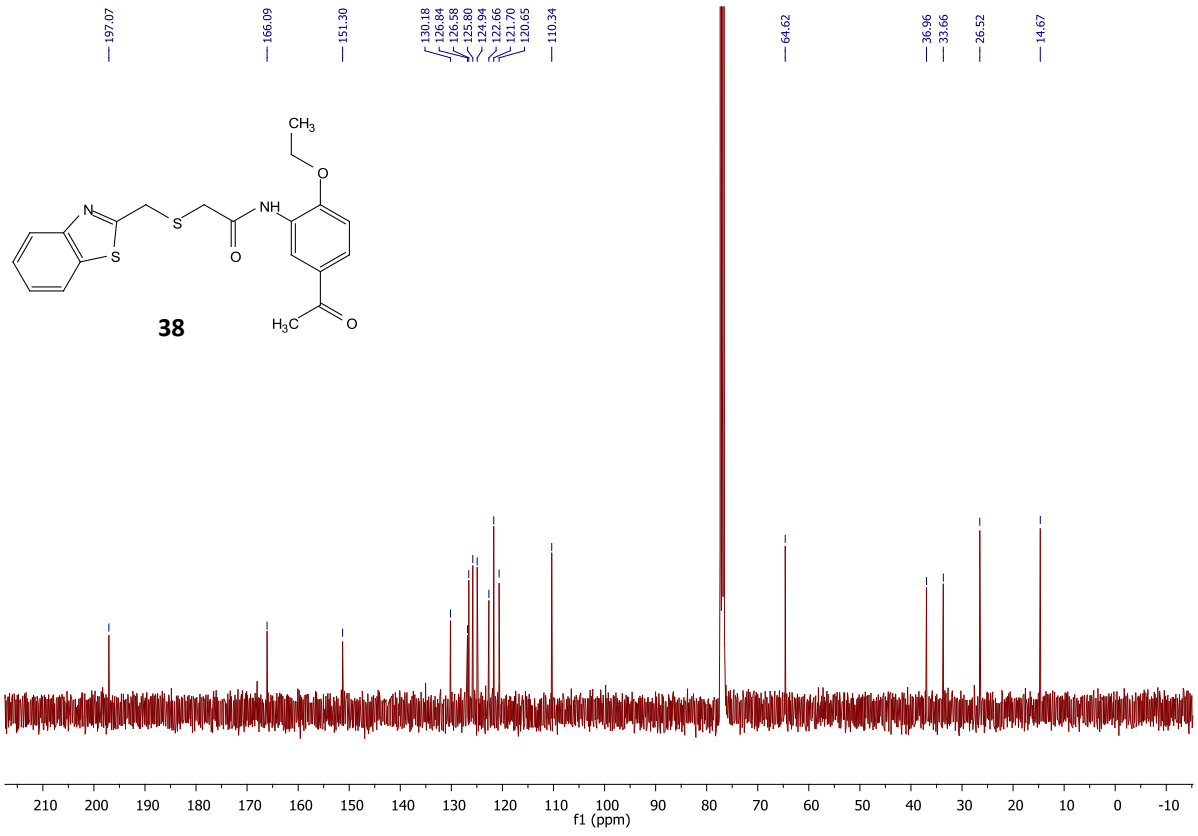

11.92
9.65
8.57
8.14
8.14
7.74
7.74
7.53
7.52
7.17
7.16
4.86
4.25
4.24
4.23
4.21
2.49
1.43
1.42
1.41
CH3
O
HN
N
NH
O
O
O
O
NH2
H3C
O
1.00
0.97
2.05
0.95
1.09
1.03
1.10
1.89
2.25
3.56
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

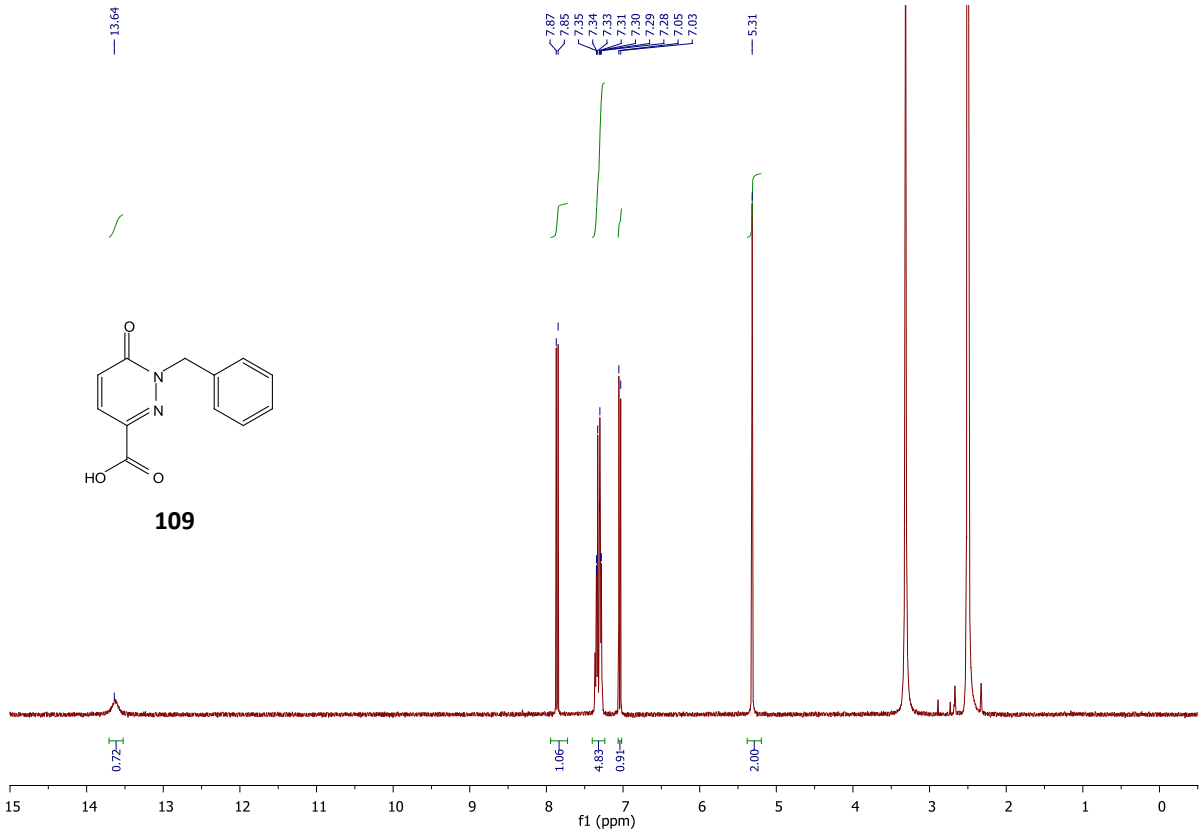
37


196.15
165.90
163.50
163.02
152.56
152.51
150.30
129.30
126.78
126.06
121.42
111.53
104.74
64.43
50.93
26.33
14.35
CH3
O
HN
N
NH
O
O
O
O
NH2
H3C
O
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

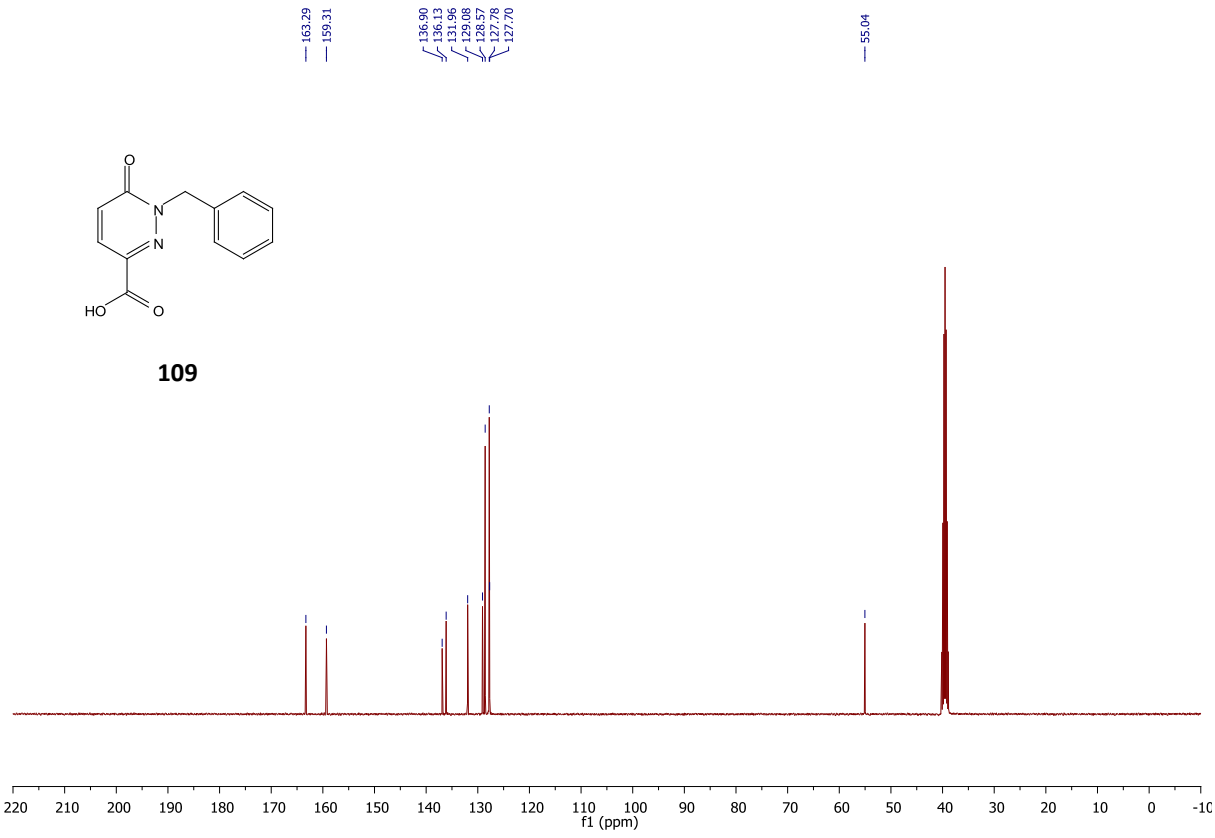
37


9.09
8.83
8.83
7.96
7.96
7.94
7.94
7.79
7.79
7.73
7.73
7.71
7.71
7.45
7.44
6.88
6.86
4.30
4.18
4.16
4.14
4.13
3.57
2.54
1.48
1.46
1.44
CH3
O
N
S
NH
S
O
H3C
O
38
0.85
1.00
1.01
0.93
1.06
1.06
1.10
0.99
1.98
2.00
2.00
3.64
3.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

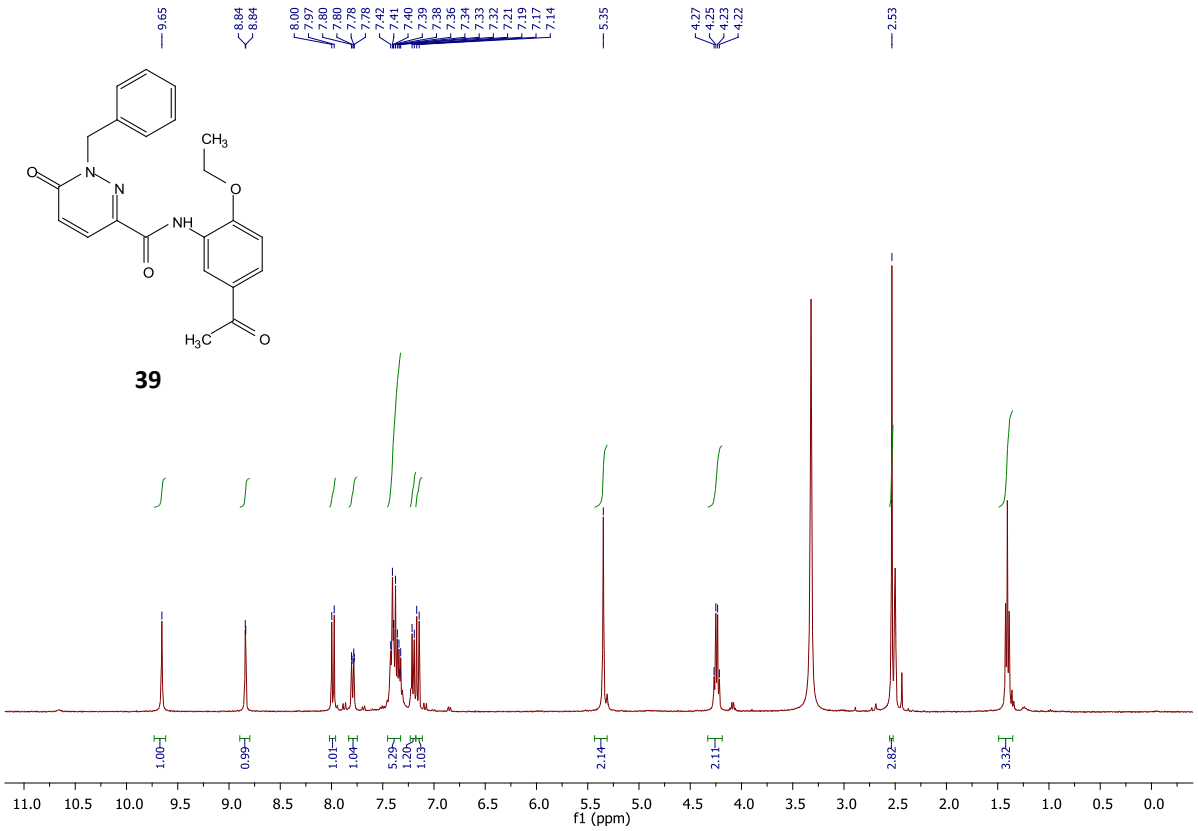

197.07
166.09
151.30
130.18
126.84
126.58
125.80
124.94
122.66
121.70
120.65
110.34
64.62
36.96
33.66
26.52
14.67
CH3
O
N
S
NH
S
O
H3C
O
38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


13.64
7.87
7.85
7.35
7.34
7.33
7.31
7.30
7.29
7.28
7.05
7.03
5.31
O
N
N
HO
O
0.72
1.06
4.83
0.91
2.00
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

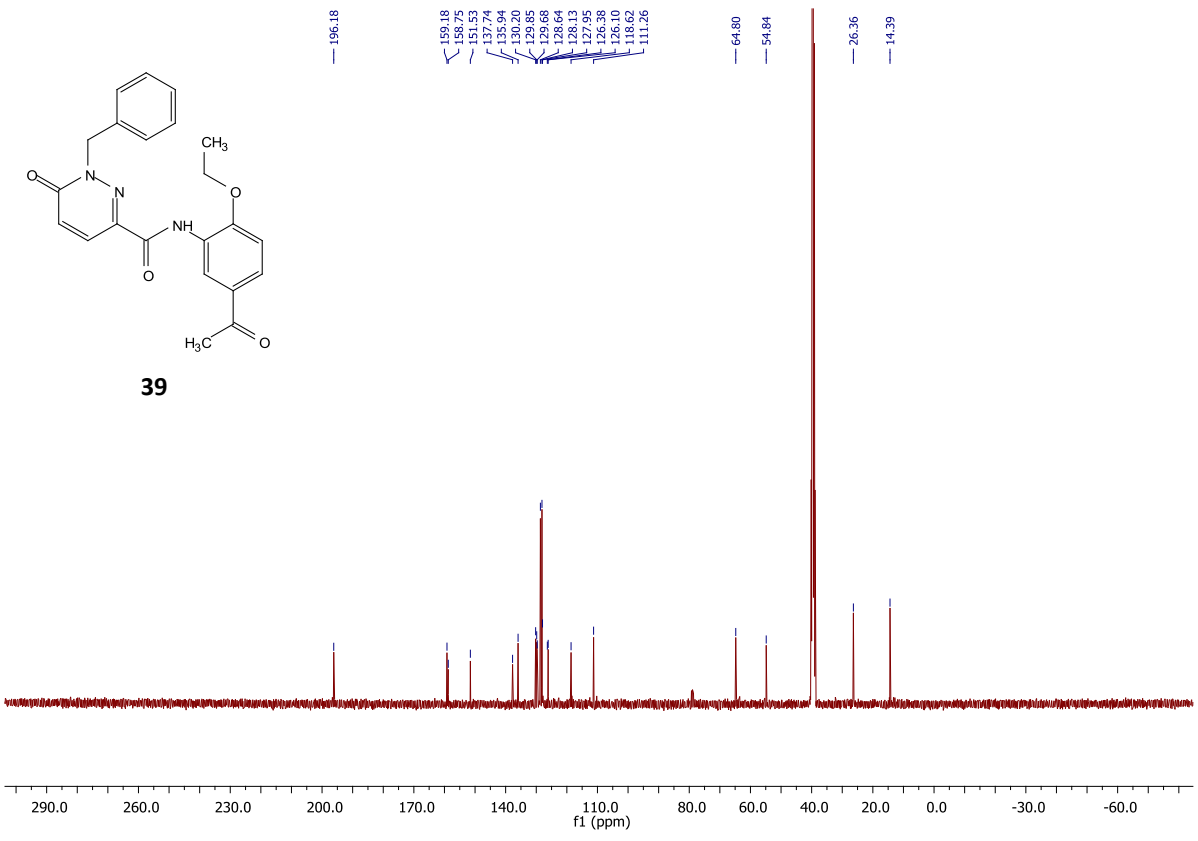
109


163.29
159.31
136.90
136.13
131.96
129.08
128.57
127.78
127.70
55.04
O
N
N
HO
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

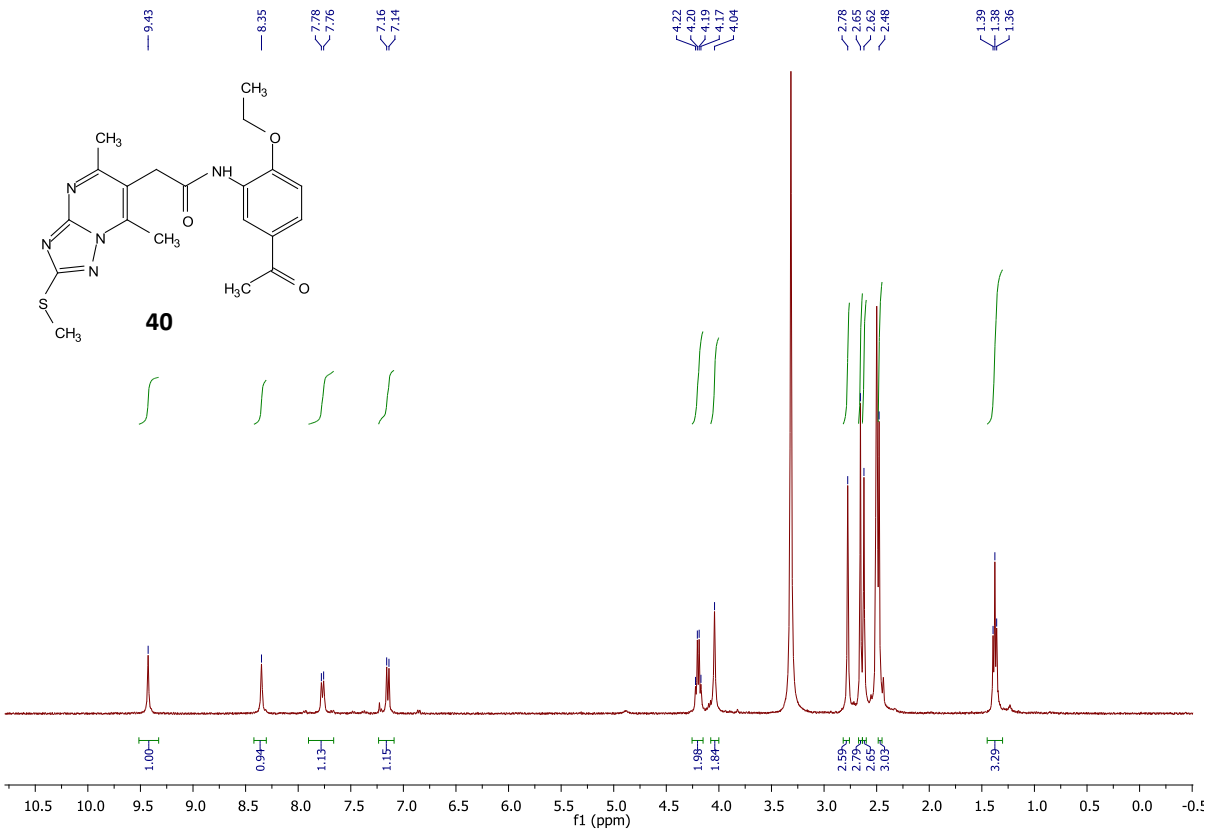
109


9.65
8.84
8.84
8.00
7.97
7.80
7.80
7.78
7.78
7.42
7.41
7.40
7.39
7.38
7.36
7.34
7.33
7.32
7.21
7.19
7.17
7.14
5.35
4.27
4.25
4.23
4.22
2.53
CH3
O
N
N
O
NH
O
H3C
O
1.00
0.99
1.01
1.04
5.29
1.26
1.03
2.14
2.11
2.82
3.32
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

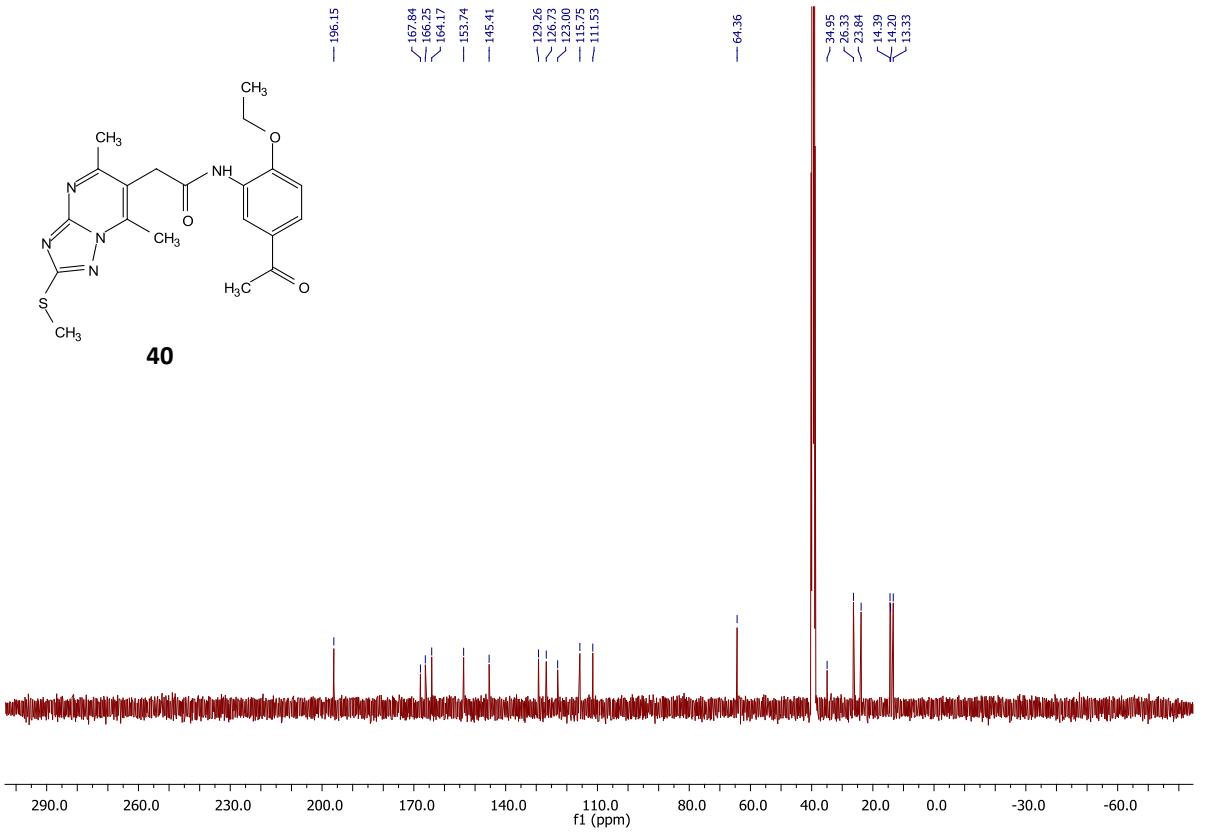
39


196.18
159.18
158.75
151.53
137.74
135.94
130.20
129.85
129.68
128.64
128.13
127.95
126.38
126.10
118.62
111.26
64.80
54.84
26.36
14.39
CH3
O
N
N
O
NH
O
H3C
O
290.0
260.0
230.0
200.0
170.0
140.0
110.0
80.0
60.0
40.0
20.0
0.0
-30.0
-60.0
f1 (ppm)

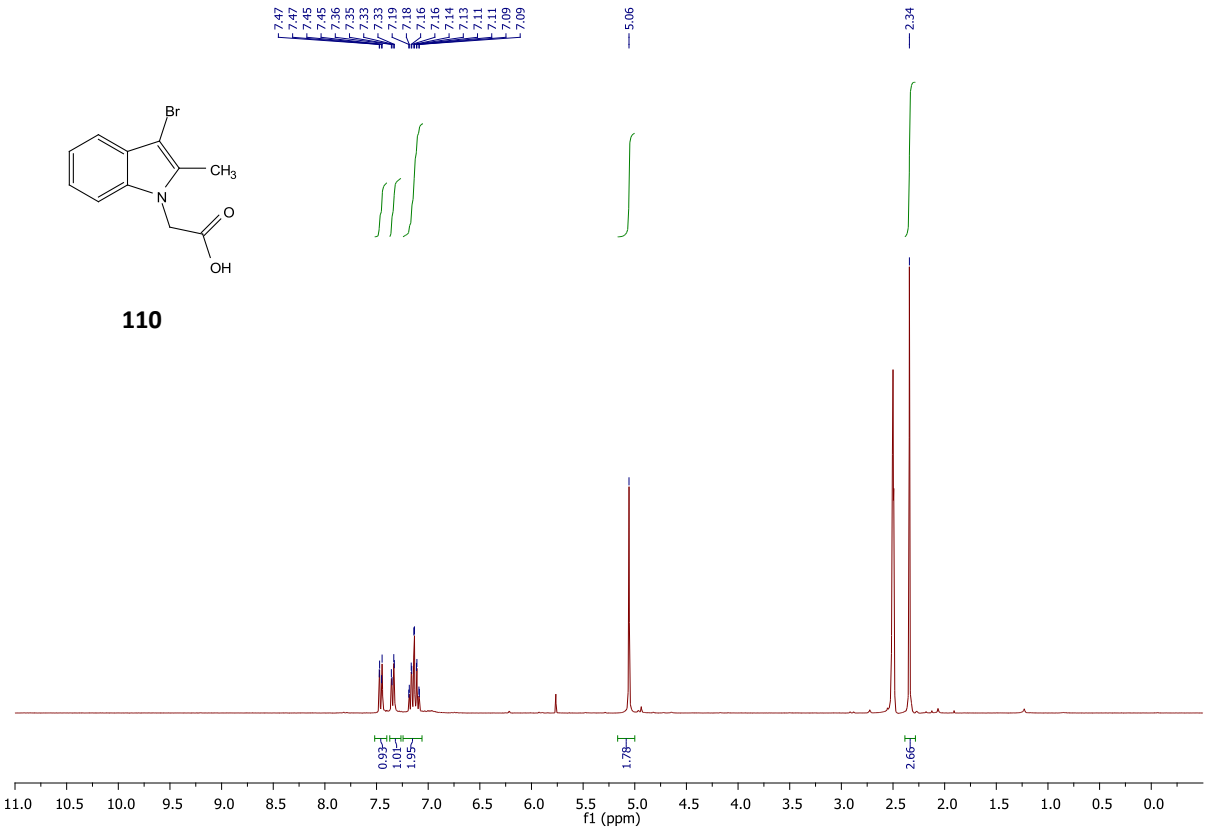
39


9.43
8.35
7.78
7.76
7.16
7.14
4.22
4.20
4.19
4.17
4.04
2.78
2.65
2.62
2.48
1.39
1.38
1.36
1.00
0.94
1.13
1.15
1.98
1.84
2.59
2.79
2.65
3.03
3.29
f1 (ppm)

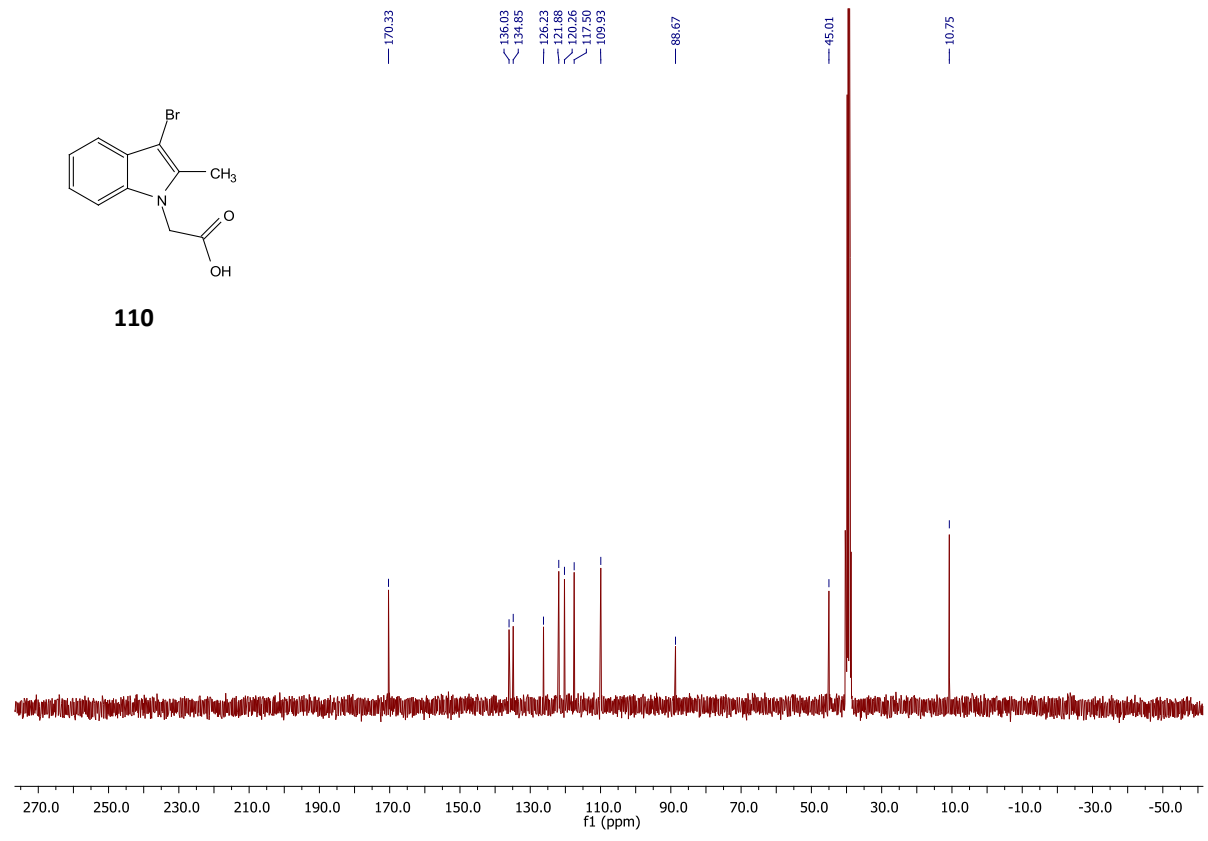
40


196.15
167.84
166.25
164.17
153.74
145.41
129.26
126.73
123.00
115.75
111.53
64.36
34.95
26.33
23.84
14.39
14.20
13.33
f1 (ppm)

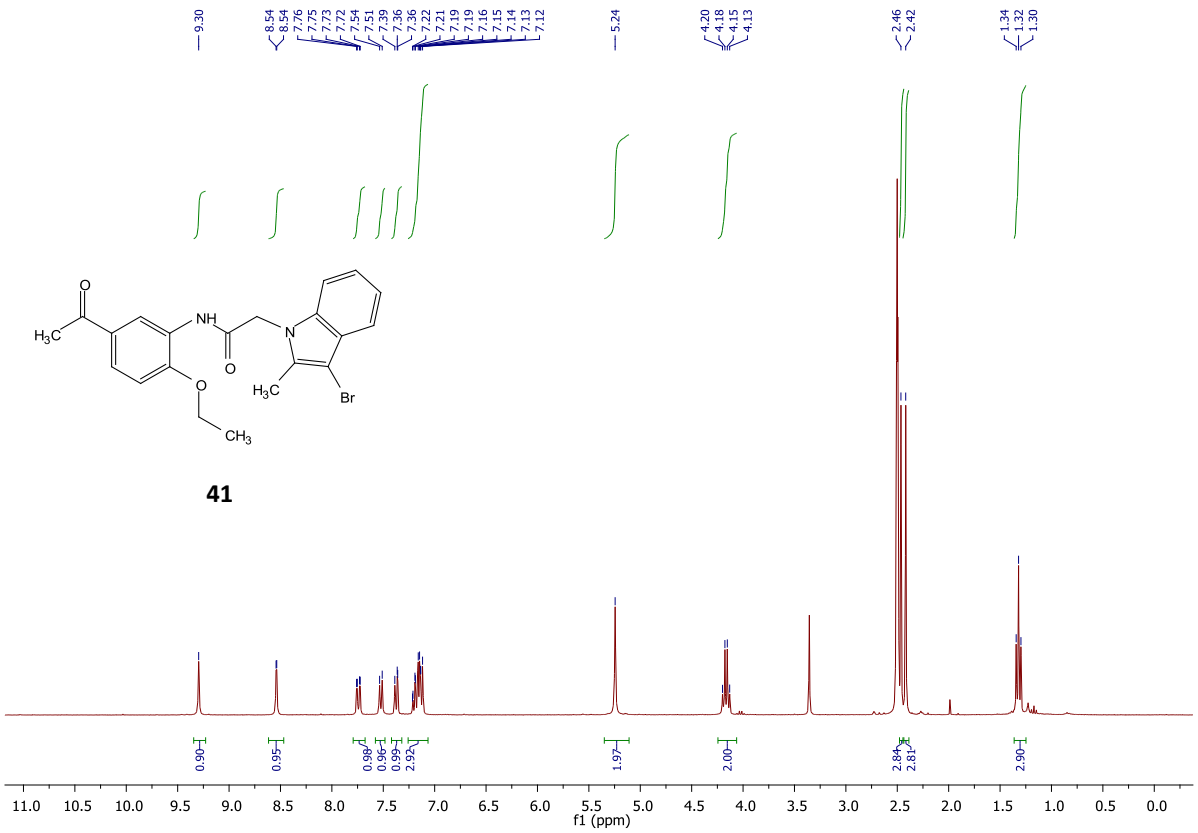
40


7.47
7.47
7.45
7.45
7.36
7.35
7.33
7.33
7.19
7.18
7.16
7.16
7.14
7.13
7.11
7.11
7.09
7.09
5.06
2.34
Br
CH3
N
O
OH
0.93
1.01
1.95
1.78
2.66
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

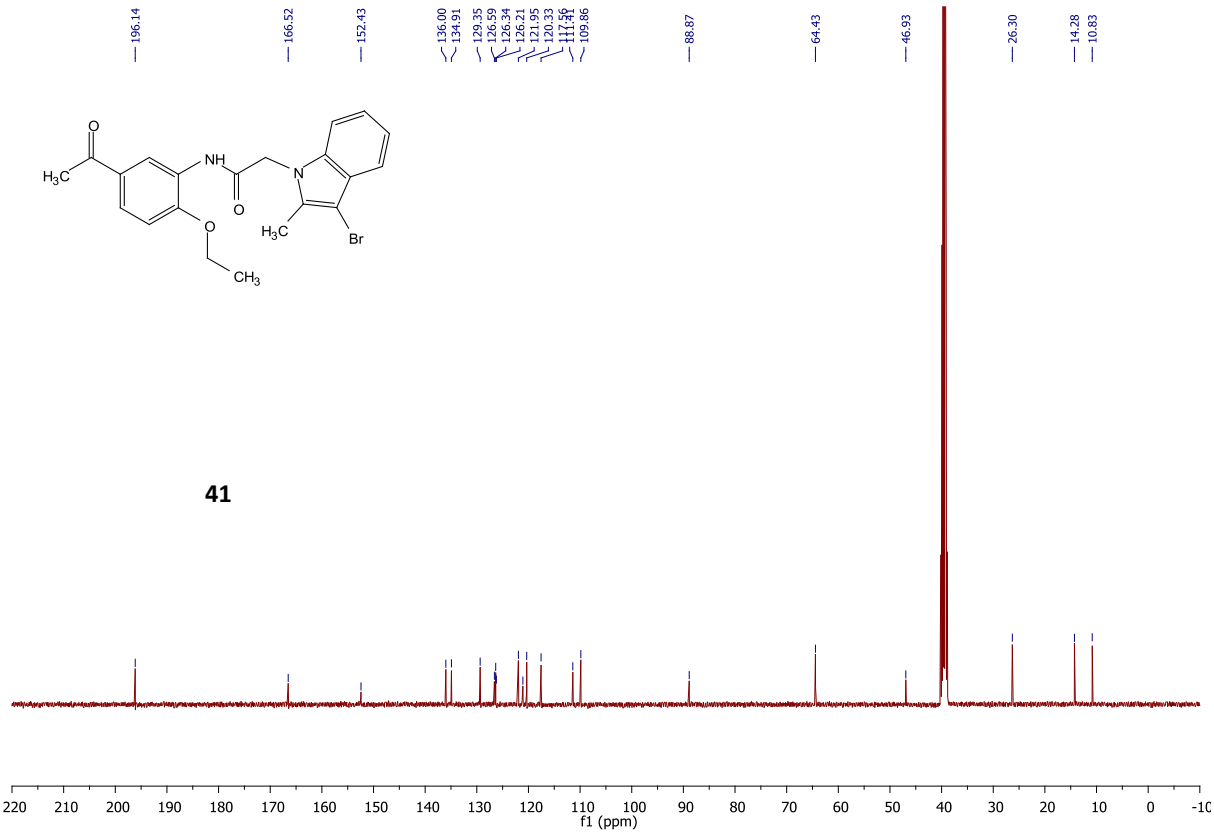
110


170.33
136.03
134.85
126.23
121.88
120.26
117.50
109.93
88.67
45.01
10.75
Br
CH3
N
O
OH
270.0 250.0 230.0 210.0 190.0 170.0 150.0 130.0 110.0 90.0 70.0 50.0 30.0 10.0 -10.0 -30.0 -50.0
f1 (ppm)

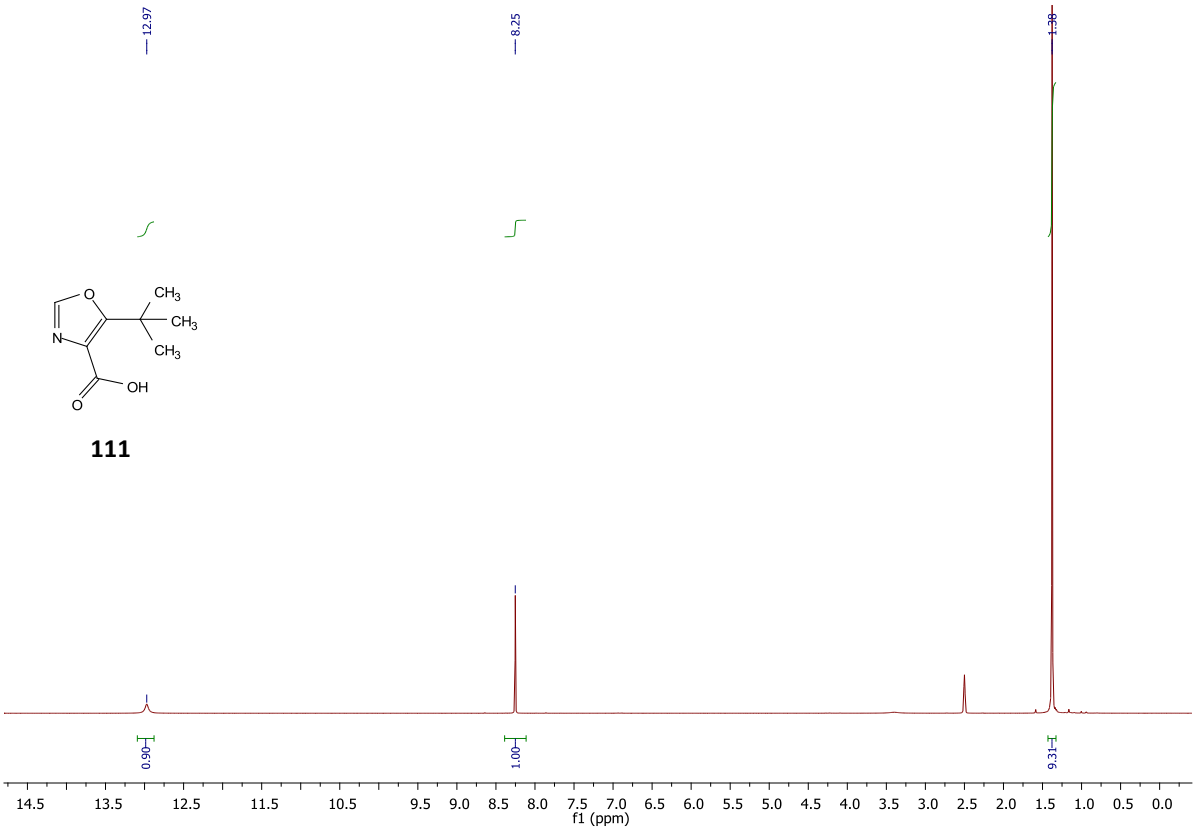
110


9.30
8.54
8.54
7.76
7.75
7.73
7.72
7.54
7.51
7.39
7.36
7.36
7.22
7.21
7.19
7.19
7.16
7.15
7.14
7.13
7.12
5.24
4.20
4.18
4.15
4.13
2.46
2.42
1.34
1.32
1.30
O
H3C
NH
O
N
H3C
Br
O
CH3
0.90
0.95
0.98
0.96
0.99
2.92
1.97
2.00
2.84
2.81
2.90
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

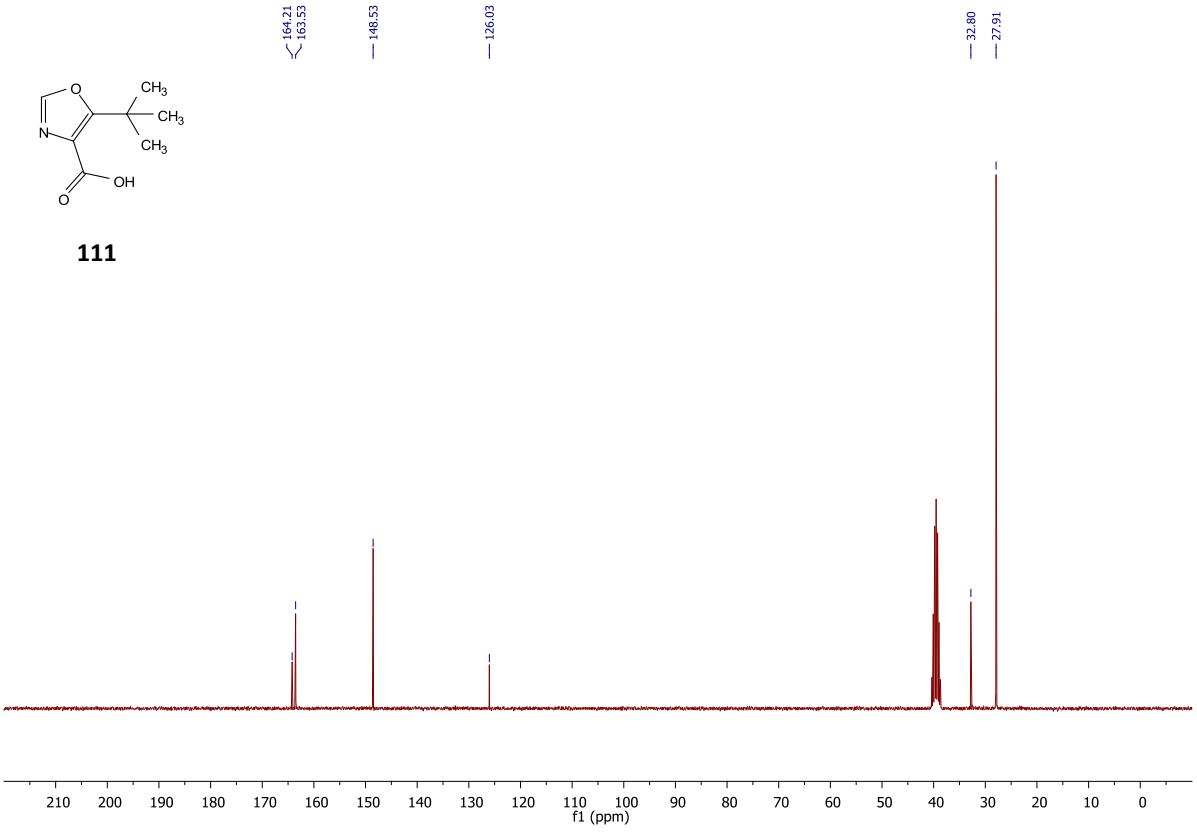
41


196.14
166.52
152.43
136.00
134.91
129.35
126.59
126.34
126.21
121.95
120.33
117.56
111.41
109.86
88.87
64.43
46.93
26.30
14.28
10.83
O
H3C
NH
O
N
H3C
Br
O
CH3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

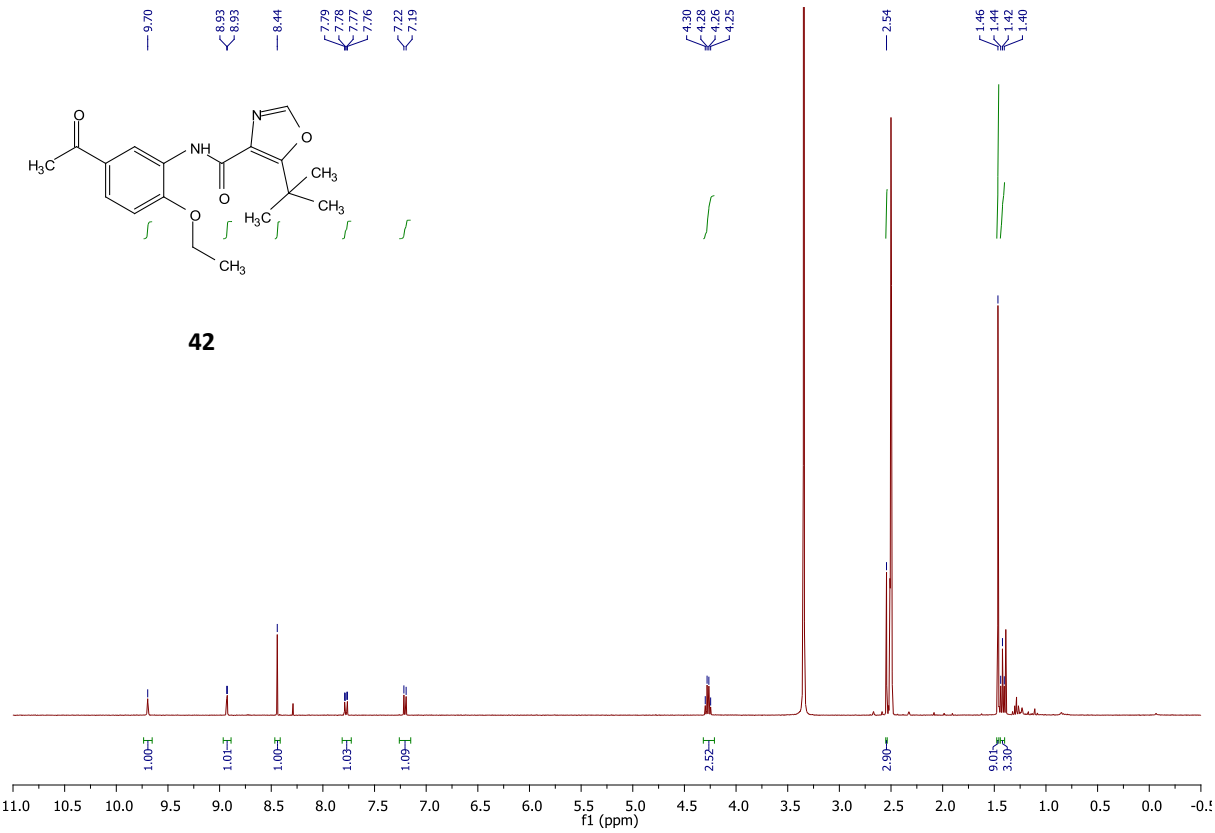
41


12.97
8.25
1.00
CH3
CH3
CH3
O
N
OH
O
0.90
1.00
9.31
14.5 13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

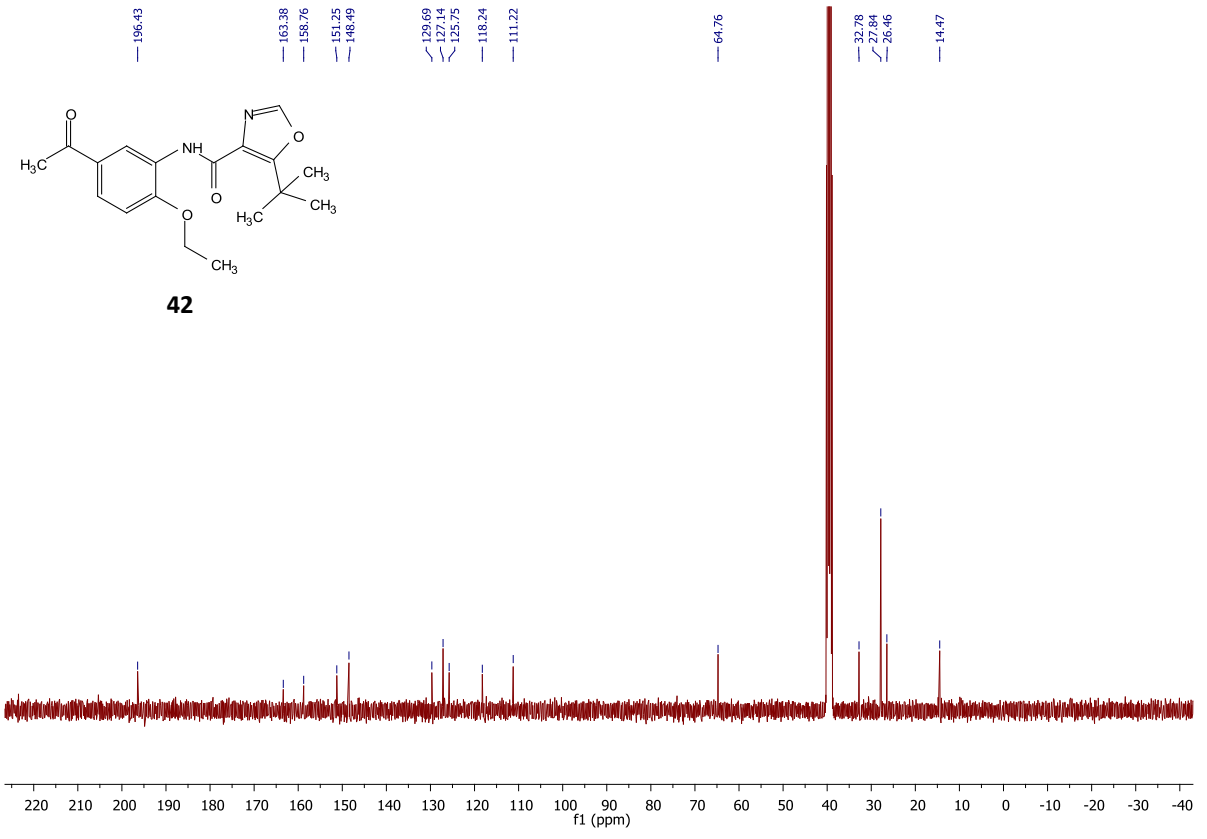
111


164.21
163.53
148.53
126.03
32.80
27.91
CH3
CH3
CH3
O
N
OH
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

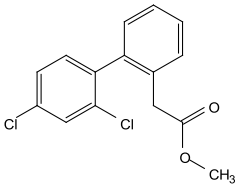
111


9.70
8.93
8.93
8.44
7.79
7.78
7.77
7.76
7.22
7.19
4.30
4.28
4.26
4.25
2.54
1.46
1.44
1.42
1.40
1.00
1.01
1.00
1.03
1.09
2.52
2.90
9.01
3.30
f1 (ppm)

42

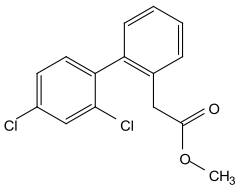

196.43
163.38
158.76
151.25
148.49
129.69
127.14
125.75
118.24
111.22
64.76
32.78
27.84
26.46
14.47
f1 (ppm)

42


Cl
Cl
O
O
CH3

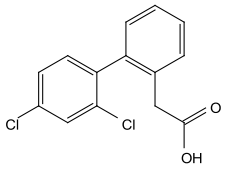
112

7.37
7.36
7.28
7.28
7.26
7.25
7.24
7.23
7.21
7.21
7.20
7.19
7.18
7.16
7.16
7.13
7.08
7.06
7.05
7.02
3.45
3.43
3.38
3.31
3.26
1.00
2.72
1.29
1.01
1.00
1.22
3.59
2.43
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Cl
Cl
O
O
CH3

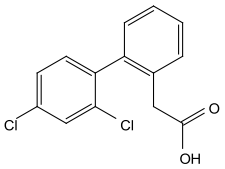
112

171.65
138.37
137.93
134.11
134.08
132.42
132.26
130.23
129.91
129.20
128.52
127.21
126.90
51.91
38.62
270.0 250.0 230.0 210.0 190.0 170.0 150.0 130.0 110.0 90.0 70.0 50.0 30.0 10.0 -10.0 -30.0 -50.0
f1 (ppm)


Cl
Cl
O
OH

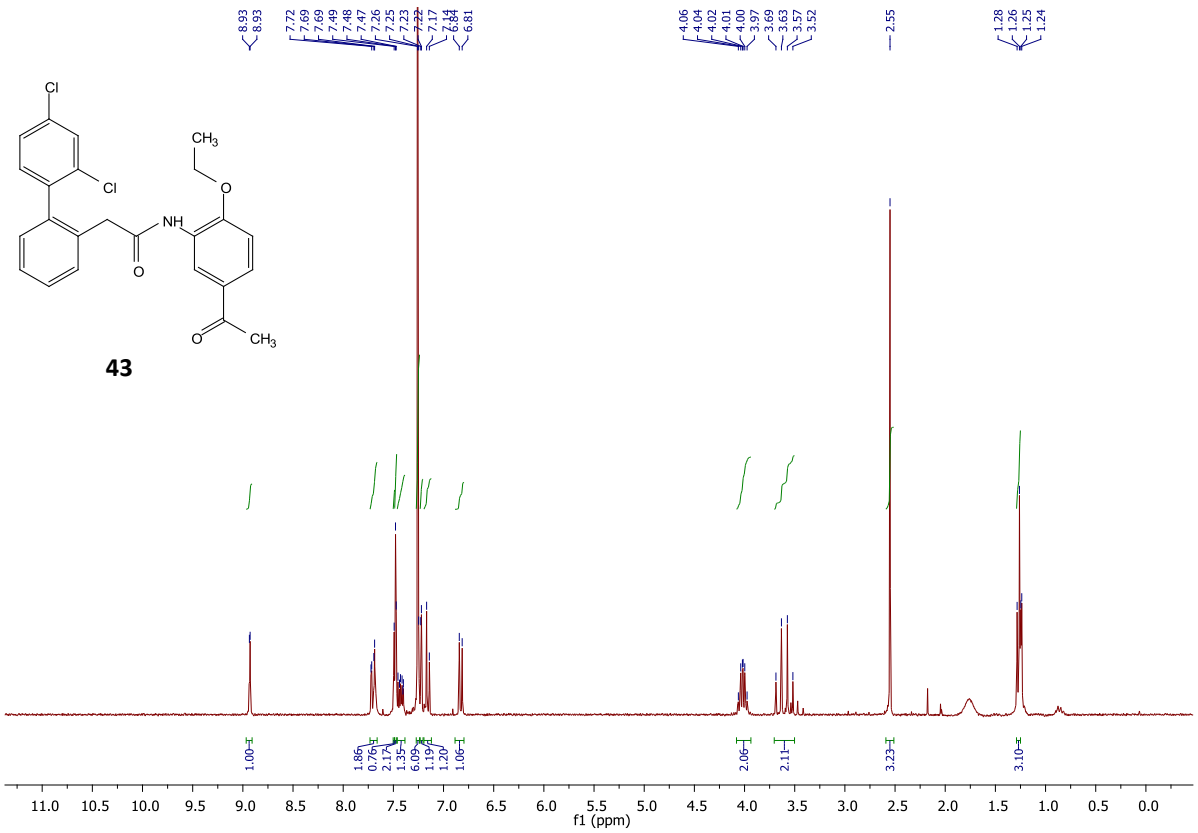
113

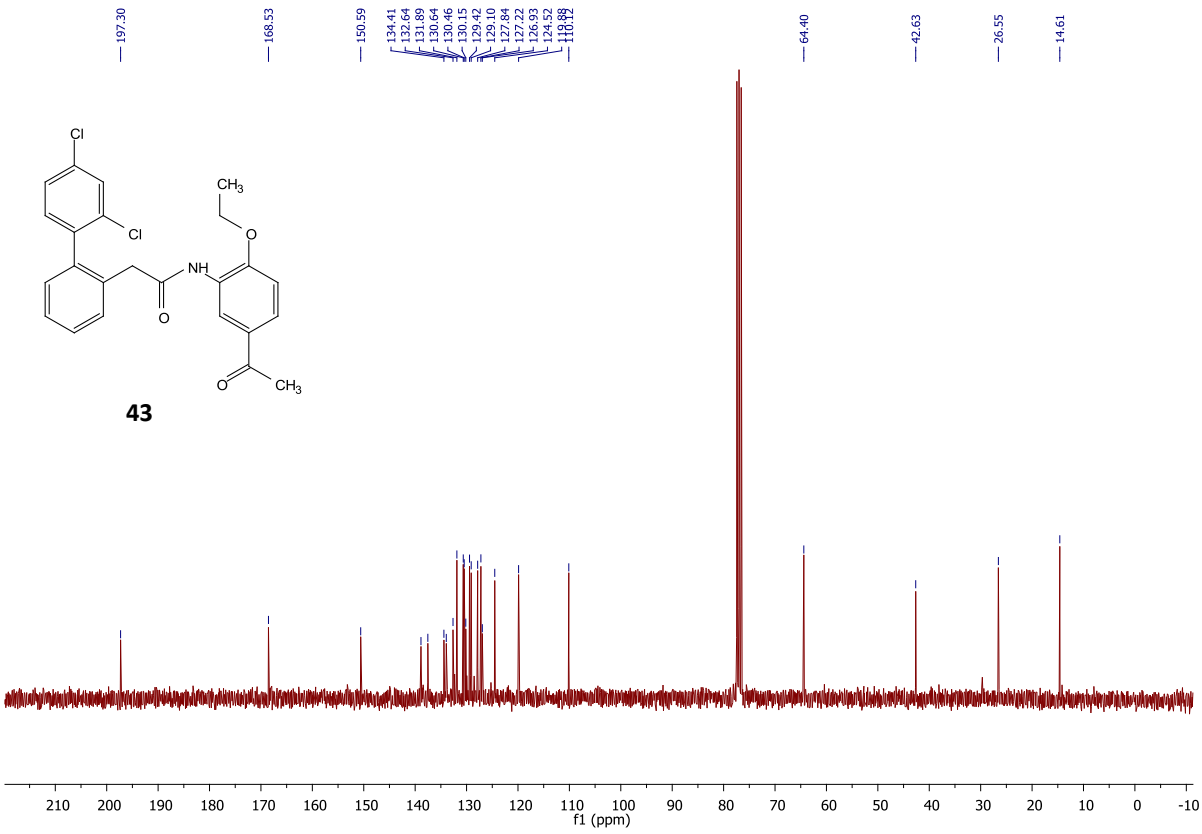
7.49
7.48
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.29
7.29
7.27
7.20
7.19
7.18
7.16
7.15
3.58
3.52
3.46
3.40
1.00
3.43
0.86
0.62
1.47
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

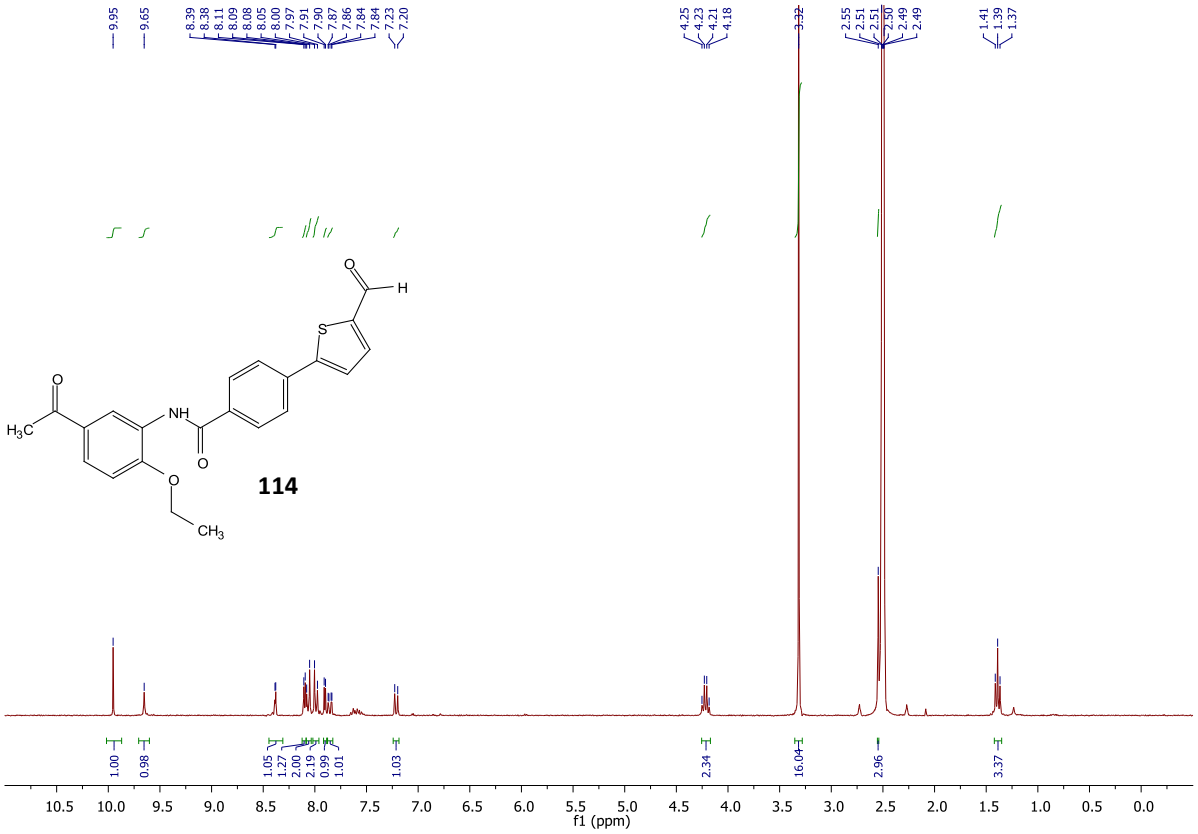

Cl
Cl
O
OH

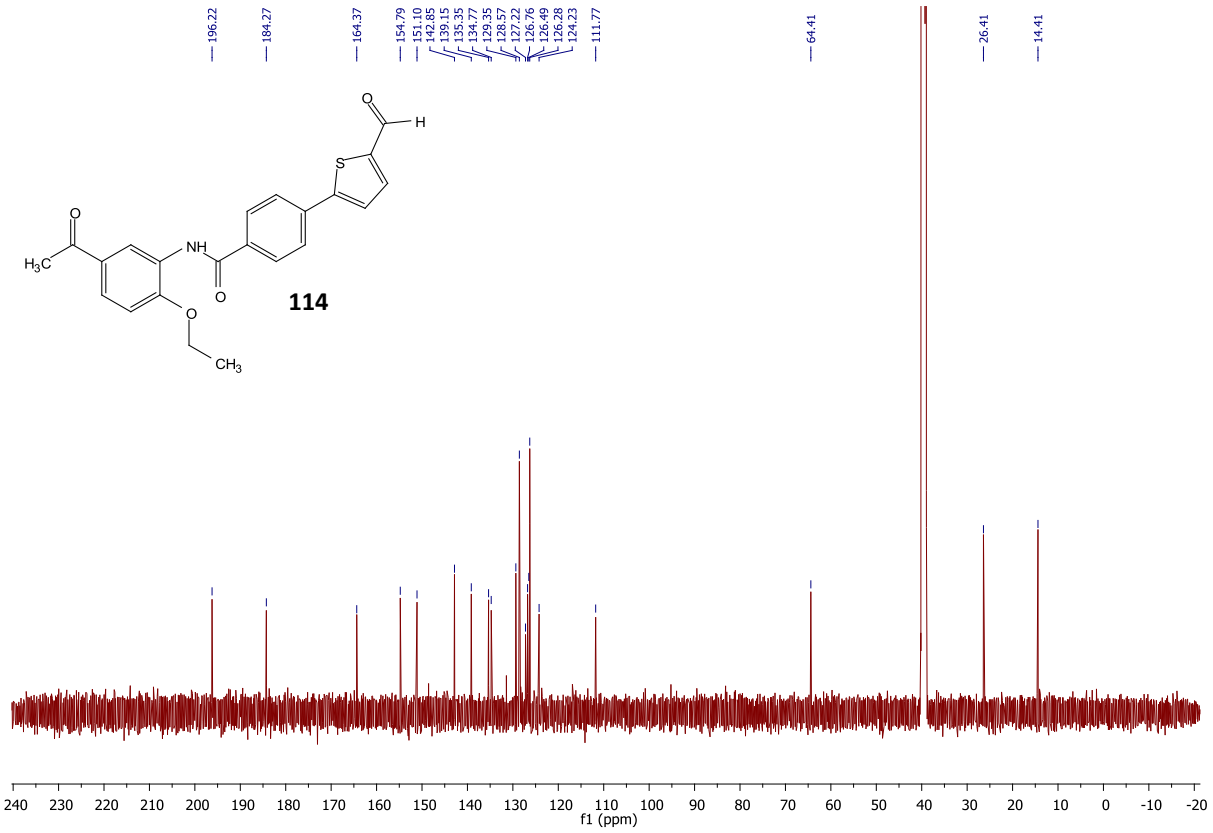
113

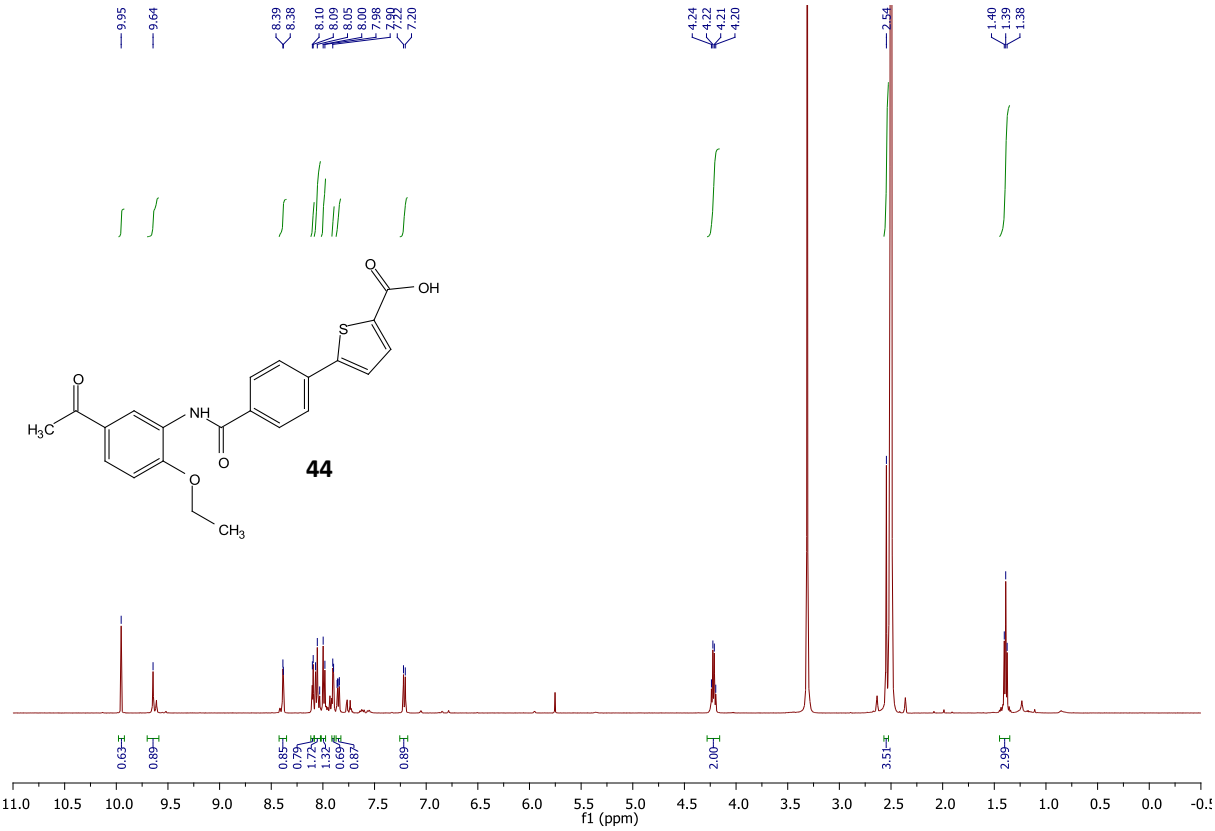
177.63
138.49
137.71
134.21
134.06
132.30
131.69
130.25
130.01
129.24
128.56
127.48
127.01
38.40
270.0
250.0
230.0
210.0
190.0
170.0
150.0
130.0
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
f1 (ppm)

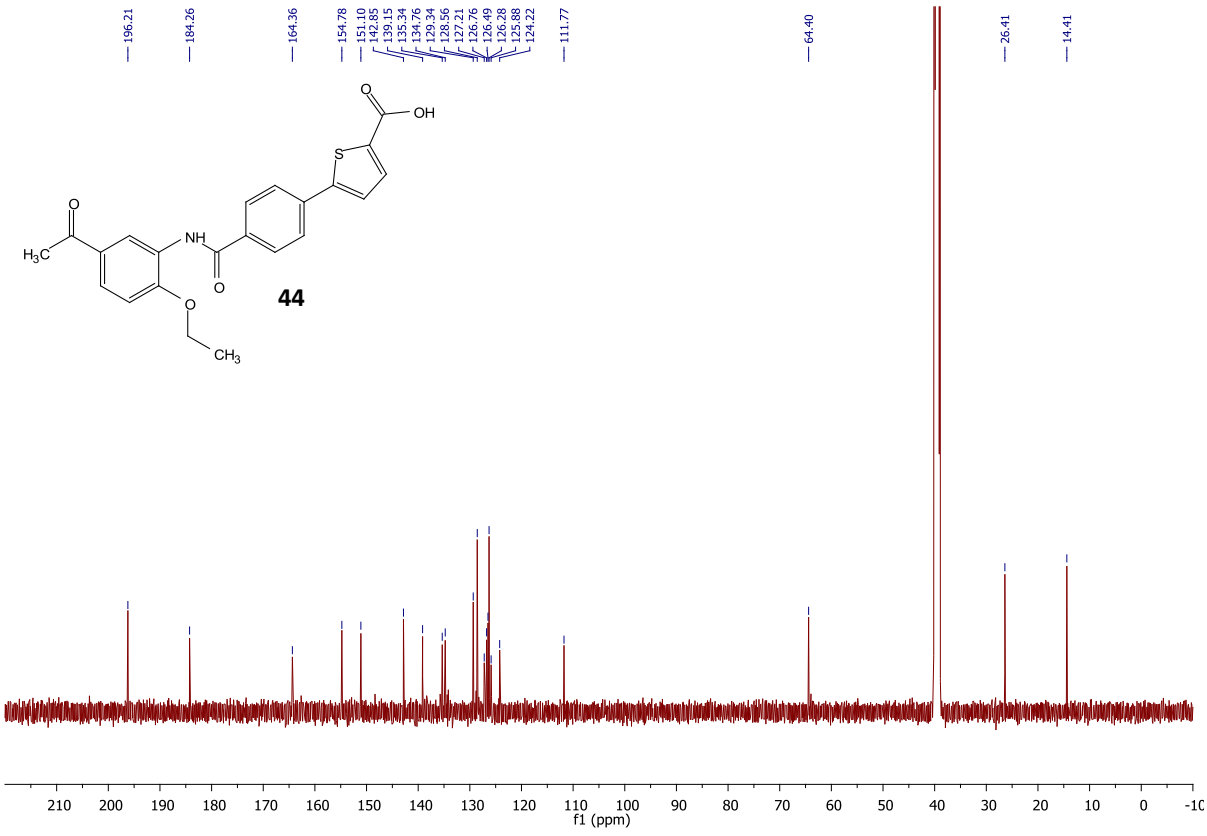

Cl
Cl
CH3
O
NH
O
O
CH3
43
8.93
8.93
7.72
7.69
7.69
7.49
7.48
7.47
7.26
7.25
7.23
7.22
7.17
7.14
6.84
6.81
4.06
4.04
4.02
4.01
4.00
3.97
3.69
3.63
3.57
3.52
2.55
1.28
1.26
1.25
1.24
1.00
1.86
0.76
2.17
1.35
6.09
1.19
1.20
1.06
2.06
2.11
3.23
3.10
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

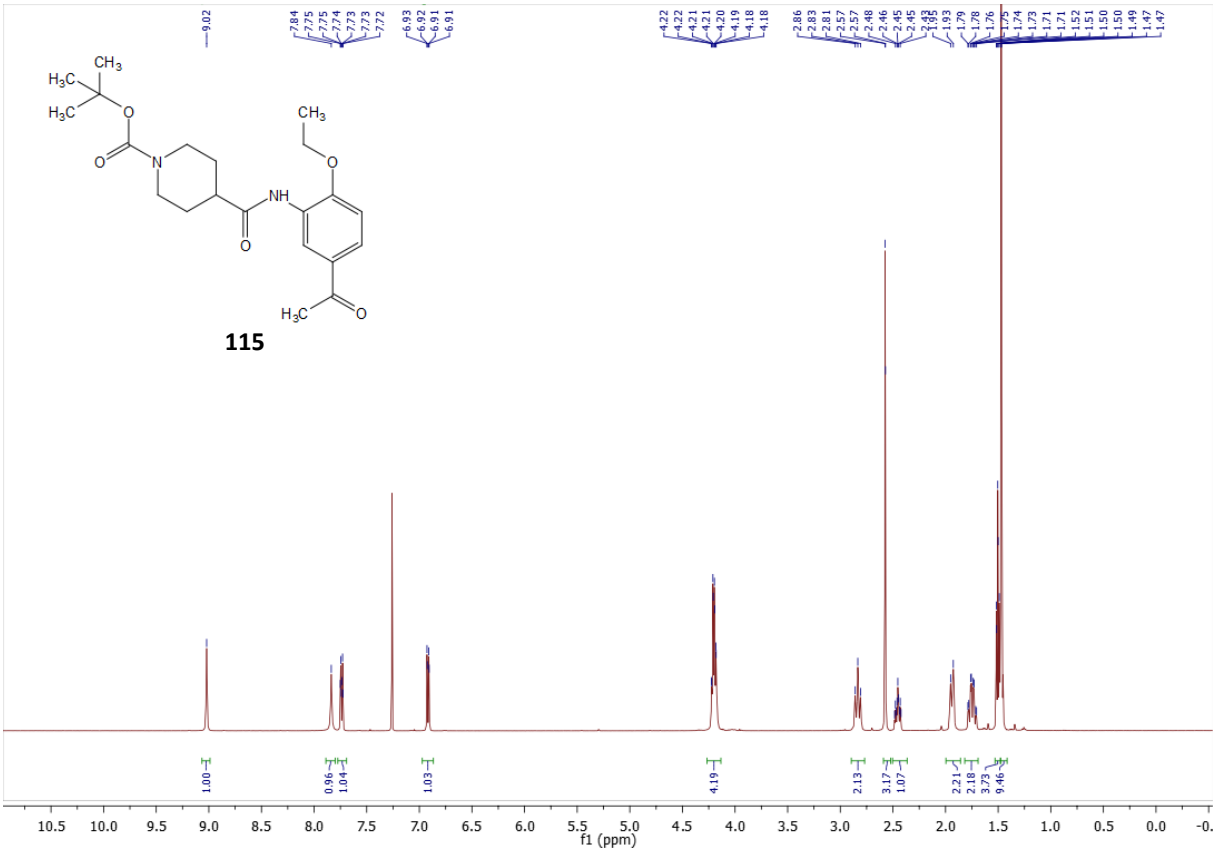

Cl
Cl
CH3
O
NH
O
O
CH3
43
197.30
168.53
150.59
134.41
132.64
131.89
130.64
130.46
130.15
129.42
129.10
127.84
127.22
126.93
124.52
64.40
42.63
26.55
14.61
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

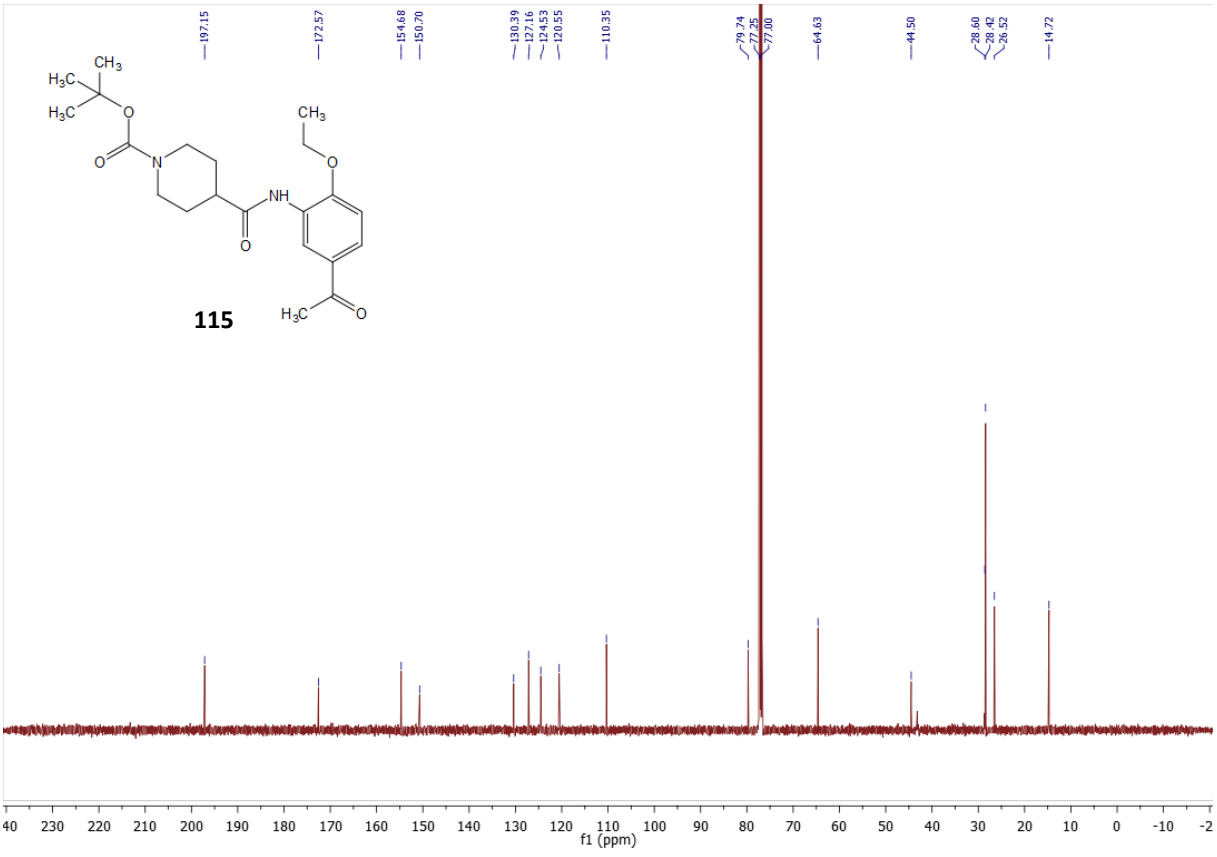

9.95
9.65
8.39
8.38
8.11
8.09
8.08
8.05
8.00
7.97
7.91
7.90
7.87
7.86
7.84
7.84
7.23
7.20
4.25
4.23
4.21
4.18
3.32
2.55
2.51
2.51
2.50
2.49
2.49
1.41
1.39
1.37
O
H
S
O
NH
H3C
O
O
CH3
114
1.00
0.98
1.05
1.27
2.00
2.19
0.99
1.01
1.03
2.34
16.04
2.96
3.37
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

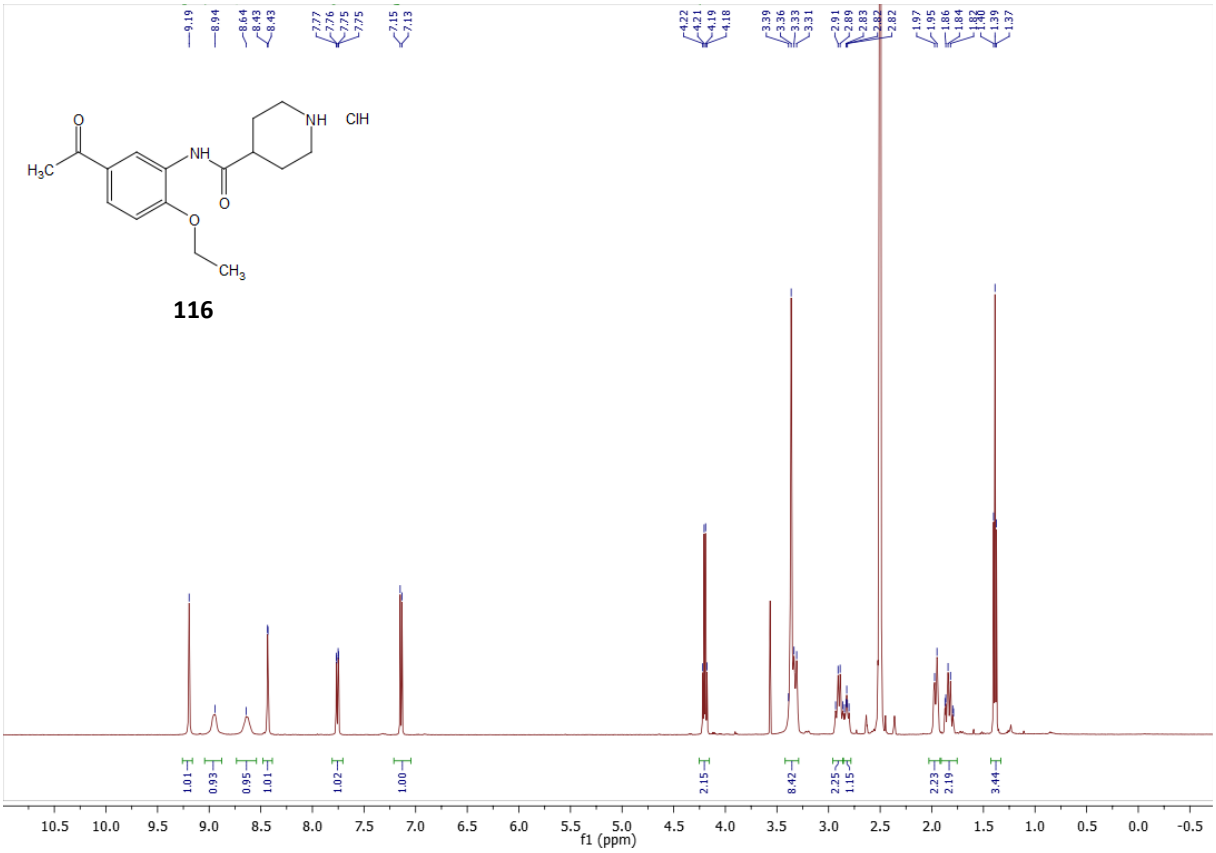

196.22
184.27
164.37
154.79
151.10
142.85
139.15
135.35
134.77
129.35
128.57
127.22
126.76
126.49
126.28
124.23
111.77
64.41
26.41
14.41
O
H
S
O
NH
H3C
O
O
CH3
114
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


9.95
9.64
8.39
8.38
8.10
8.09
8.05
8.00
7.98
7.92
7.90
7.20
4.24
4.22
4.21
4.20
2.54
1.40
1.39
1.38
OH
O
S
NH
H3C
O
O
CH3
44
0.63
0.89
0.85
0.79
1.72
1.32
0.69
0.87
0.89
2.00
3.51
2.99
f1 (ppm)

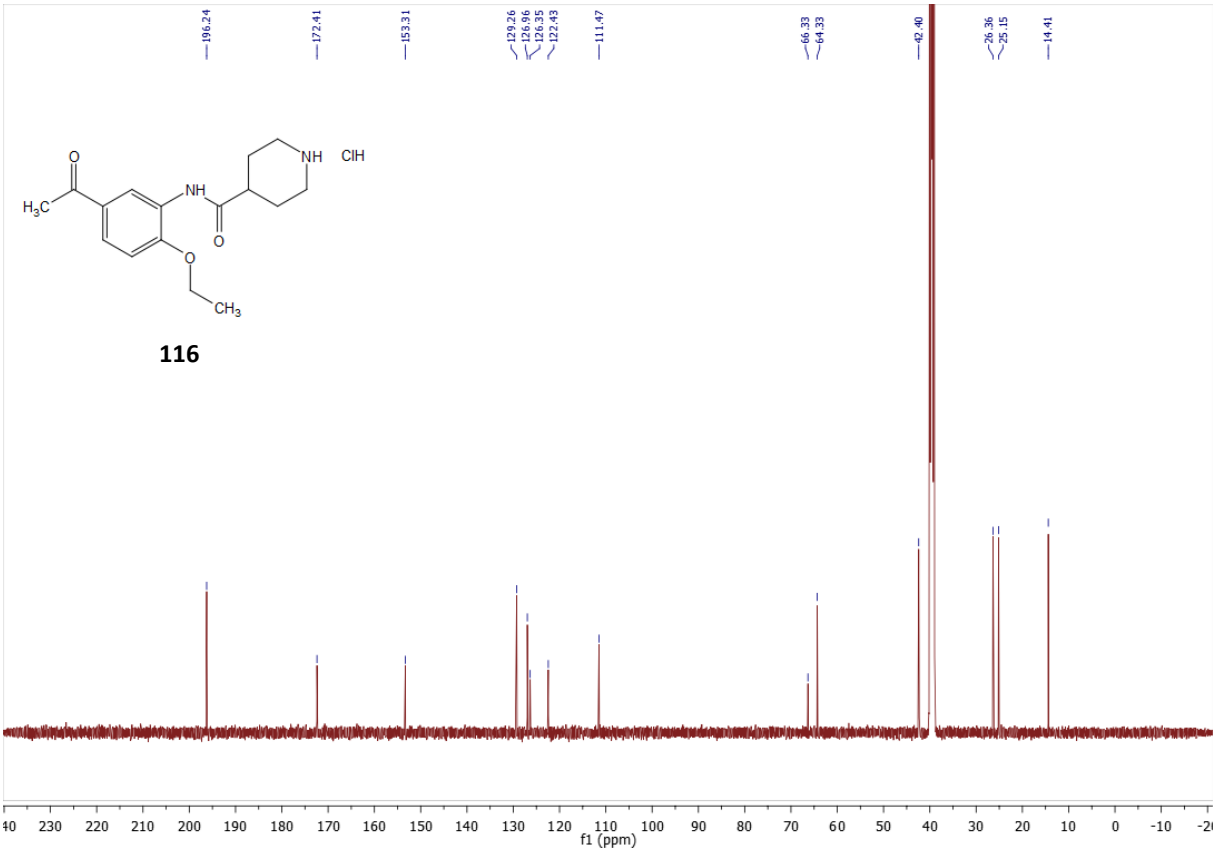

196.21
184.26
164.36
154.78
151.10
142.85
139.15
135.34
134.76
129.34
128.56
127.21
126.76
126.49
126.28
125.88
124.22
111.77
64.40
26.41
14.41
OH
O
S
NH
H3C
O
O
CH3
44
f1 (ppm)


CH3
H3C
H3C
O
O
N
NH
O
CH3
O
H3C
O
115

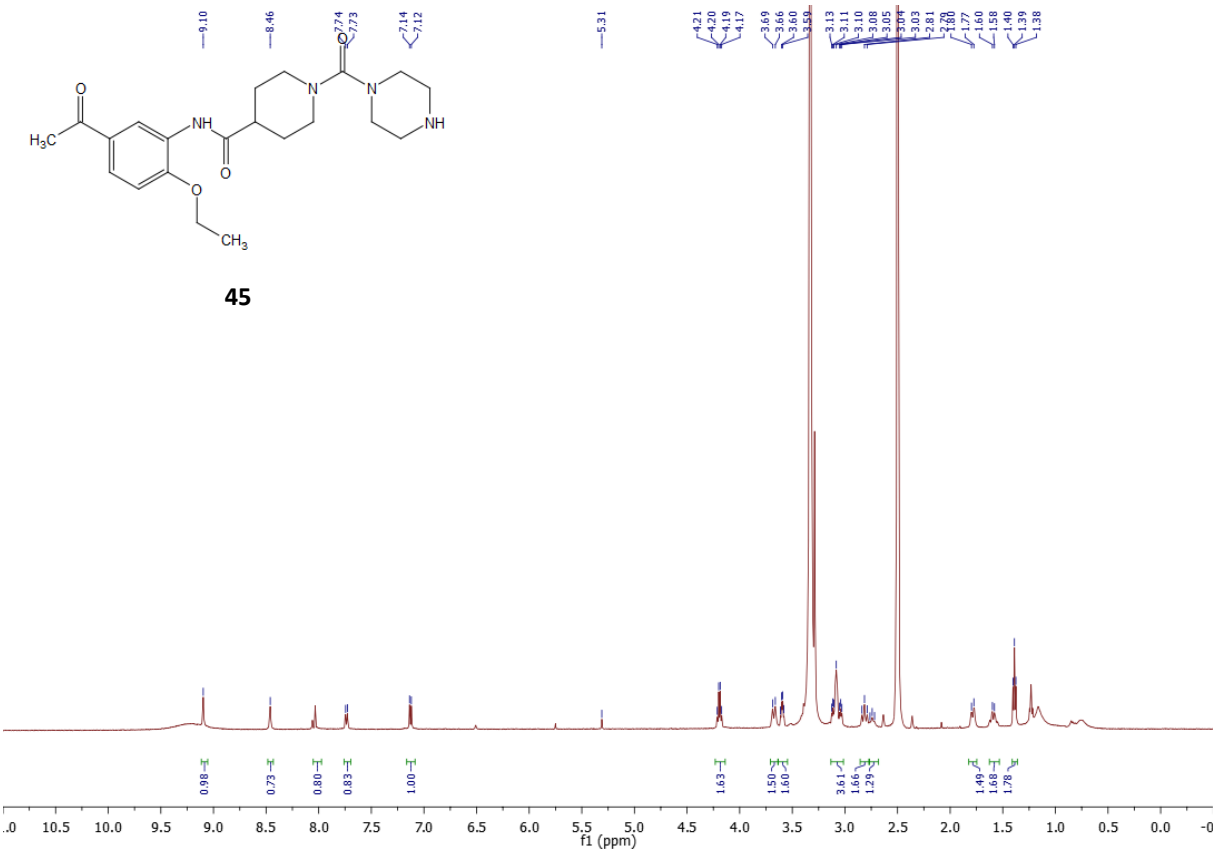

CH3
H3C
H3C
O
O
N
NH
O
CH3
O
H3C
O
115


9.19
8.94
8.64
8.43
8.43
7.77
7.76
7.75
7.75
7.15
7.13
4.22
4.21
4.19
4.18
3.39
3.36
3.33
3.31
2.91
2.89
2.83
2.82
2.82
1.97
1.95
1.86
1.84
1.82
1.40
1.39
1.37
NH
ClH
NH
O
O
O
H_3C
CH_3
1.01
0.93
0.95
1.01
1.02
1.00
2.15
8.42
2.25
1.15
2.23
2.19
3.44
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

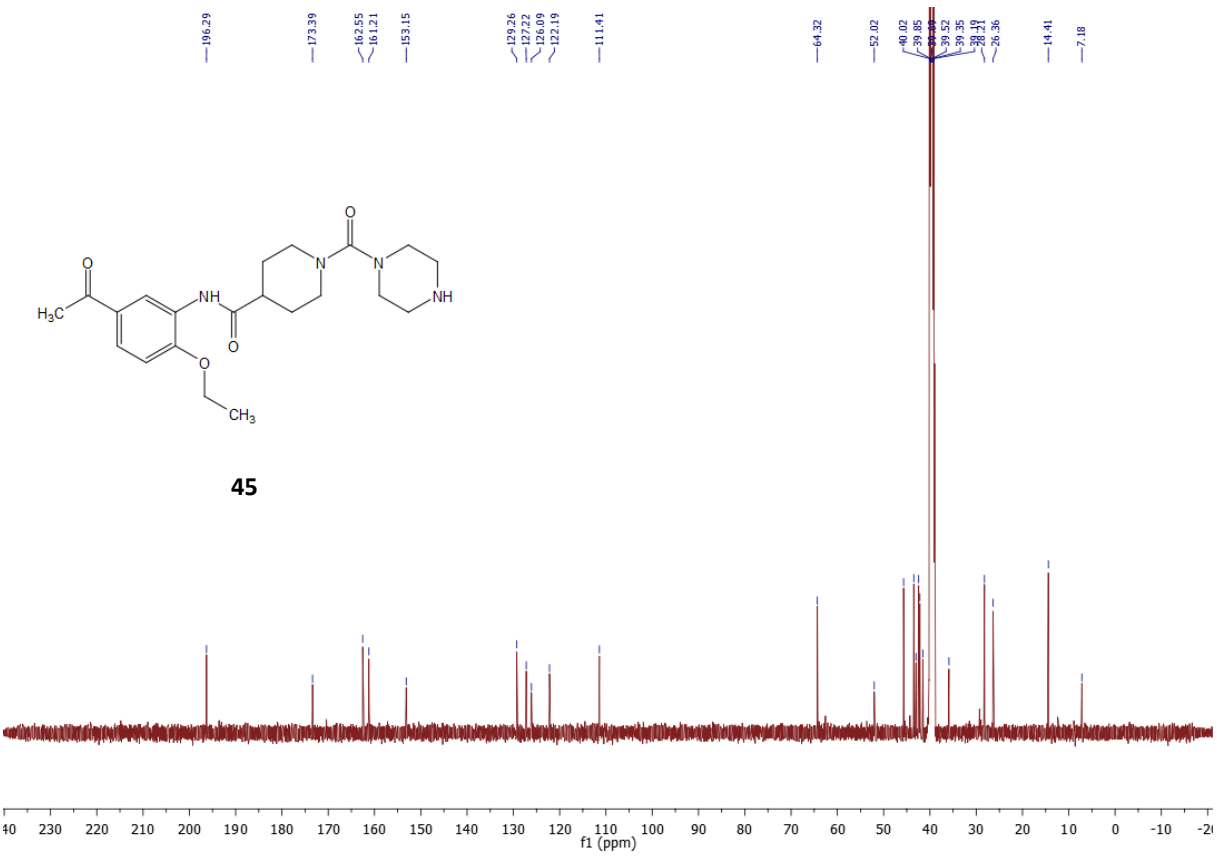
116


196.24
172.41
153.31
129.26
126.96
126.35
122.43
111.47
66.33
64.33
42.40
26.36
25.15
14.41
NH
ClH
NH
O
O
O
H_3C
CH_3
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)

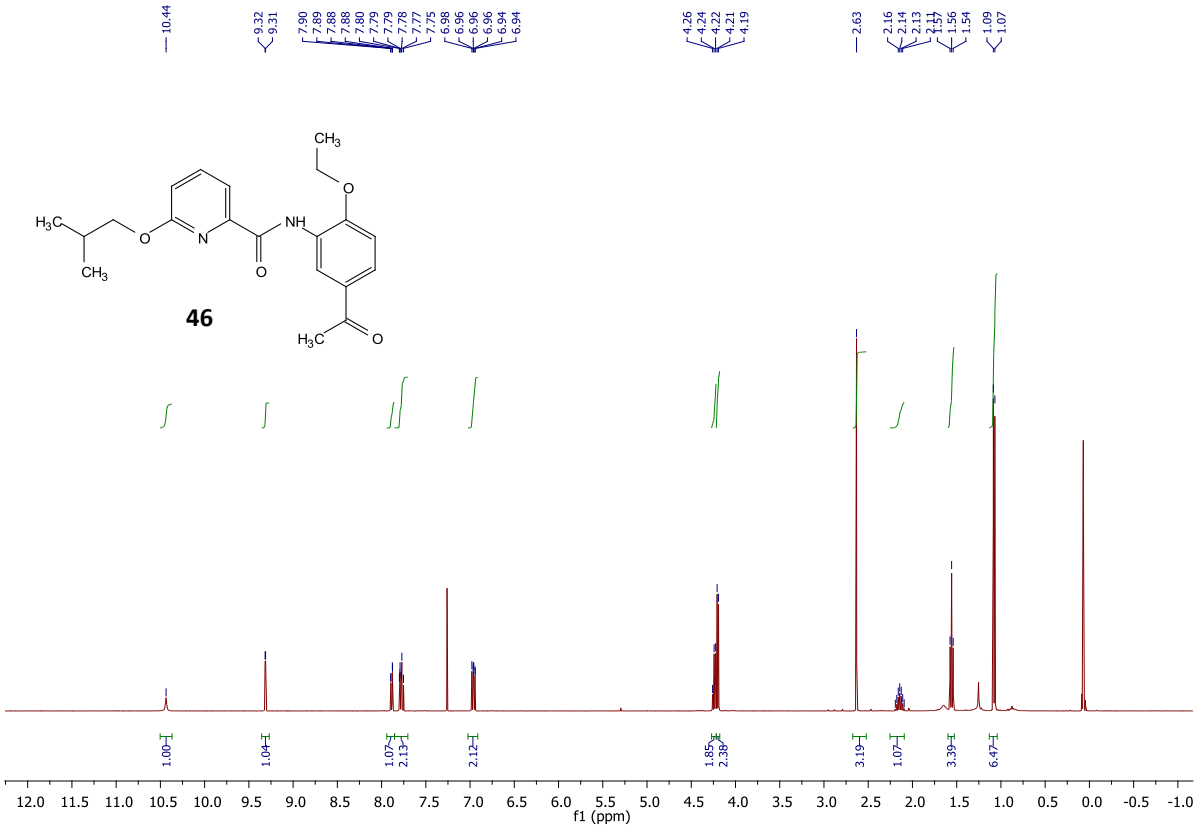
116

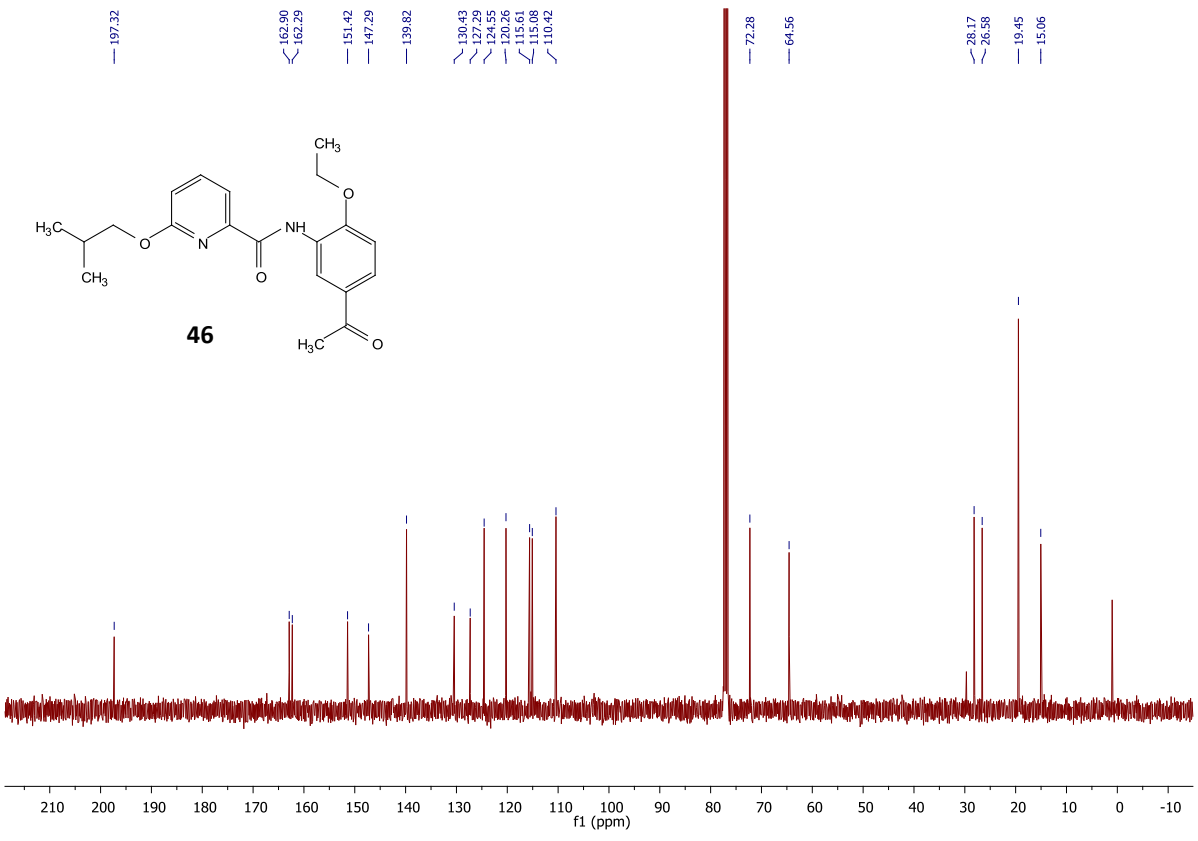

9.10
8.46
7.74
7.73
7.14
7.12
5.31
4.21
4.20
4.19
4.17
3.69
3.66
3.60
3.59
3.13
3.11
3.10
3.08
3.05
3.04
3.03
2.81
2.79
2.80
1.77
1.60
1.58
1.40
1.39
1.38
0.98
0.73
0.80
0.83
1.00
1.63
1.50
1.60
3.61
1.66
1.29
1.49
1.68
1.78
f1 (ppm)

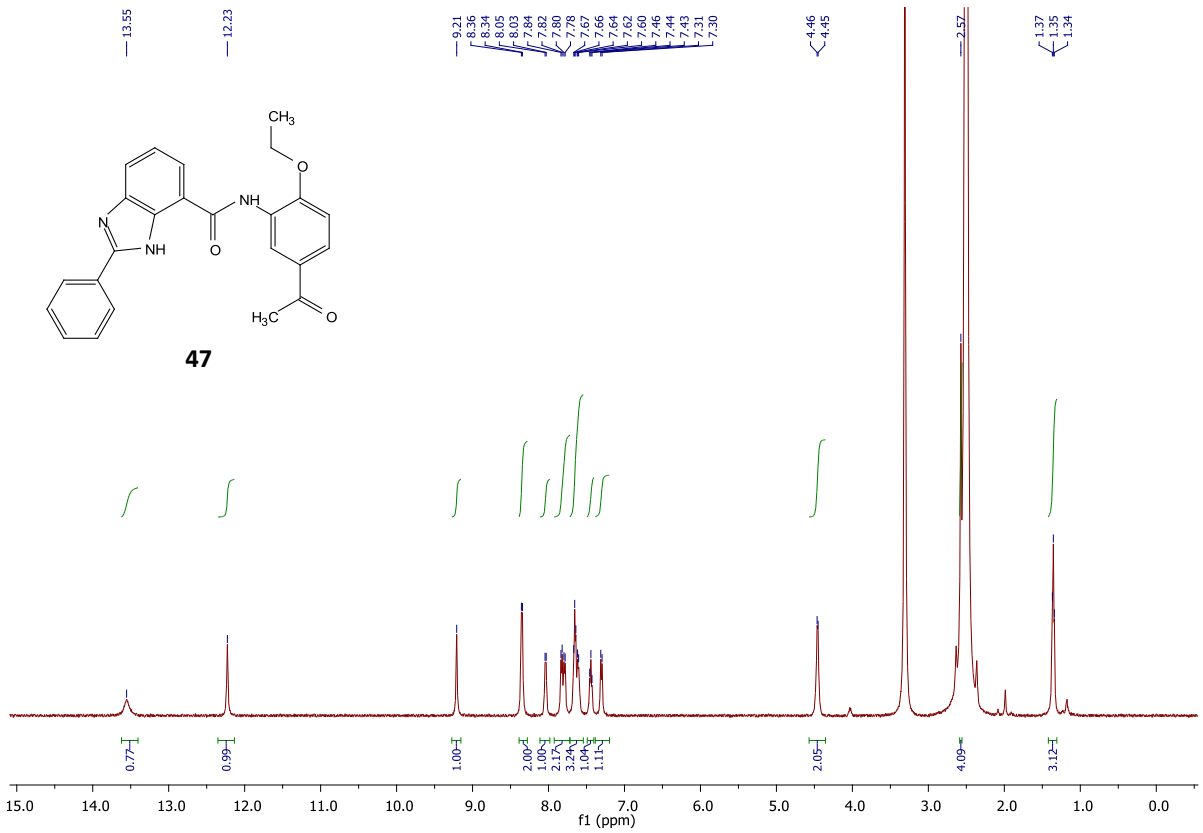
45


196.29
173.39
162.55
161.21
153.15
129.26
127.22
126.09
122.19
111.41
64.32
52.02
40.02
39.85
39.52
39.35
39.19
28.21
26.36
14.41
7.18
f1 (ppm)

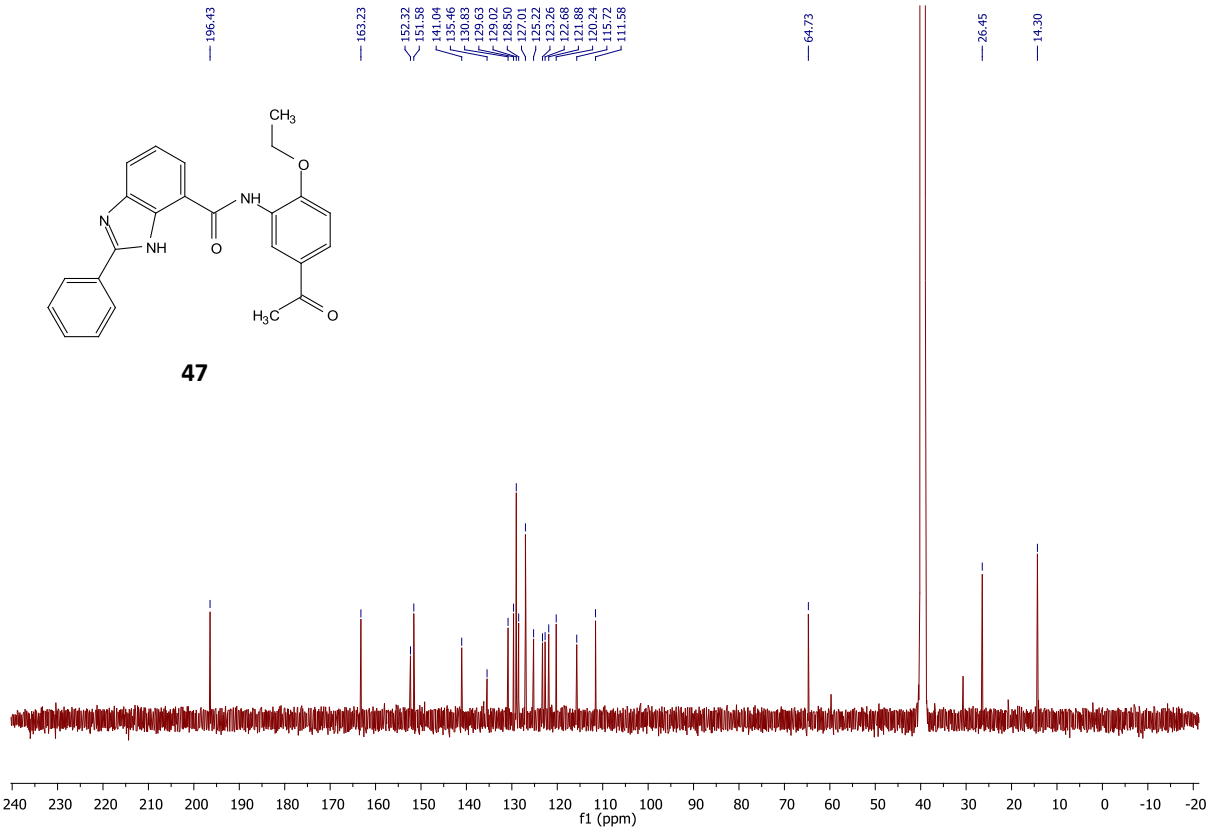
45


10.44
9.32
9.31
7.90
7.89
7.88
7.88
7.80
7.79
7.79
7.78
7.77
7.75
6.98
6.96
6.96
6.96
6.94
6.94
4.26
4.24
4.22
4.21
4.19
2.63
2.16
2.14
2.13
1.57
1.56
1.54
1.09
1.07
CH3
O
H3C
O
N
NH
CH3
O
H3C
O
46
1.00
1.04
1.07
2.13
2.12
1.85
2.38
3.19
1.07
3.39
6.47
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


197.32
162.90
162.29
151.42
147.29
139.82
130.43
127.29
124.55
120.26
115.61
115.08
110.42
72.28
64.56
28.17
26.58
19.45
15.06
CH3
O
H3C
O
N
NH
CH3
O
H3C
O
46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

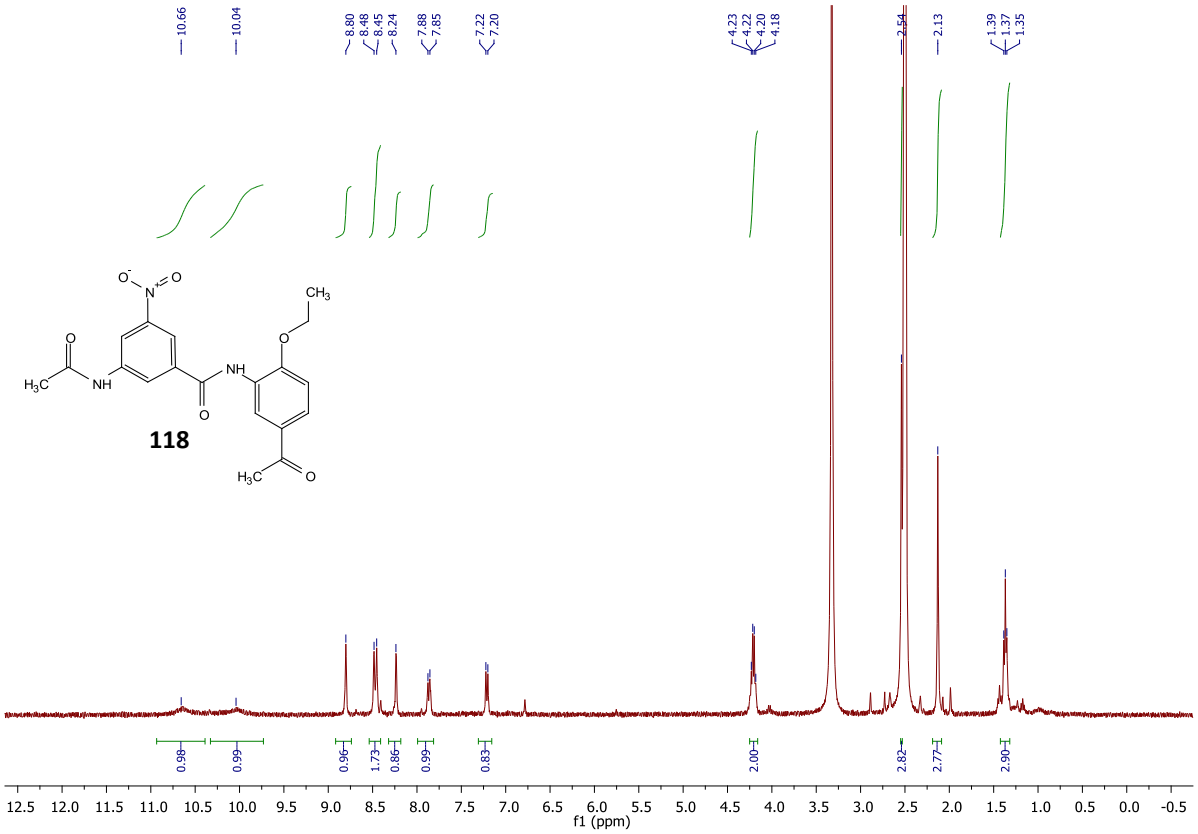

13.55
12.23
9.21
8.36
8.34
8.05
8.03
7.84
7.82
7.80
7.78
7.67
7.66
7.64
7.62
7.60
7.46
7.44
7.43
7.31
7.30
4.46
4.45
2.57
1.37
1.35
1.34
CH3
O
NH
N
NH
O
H3C
O
0.77
0.99
1.00
2.00
1.00
2.17
3.24
1.04
1.11
2.05
4.09
3.12
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

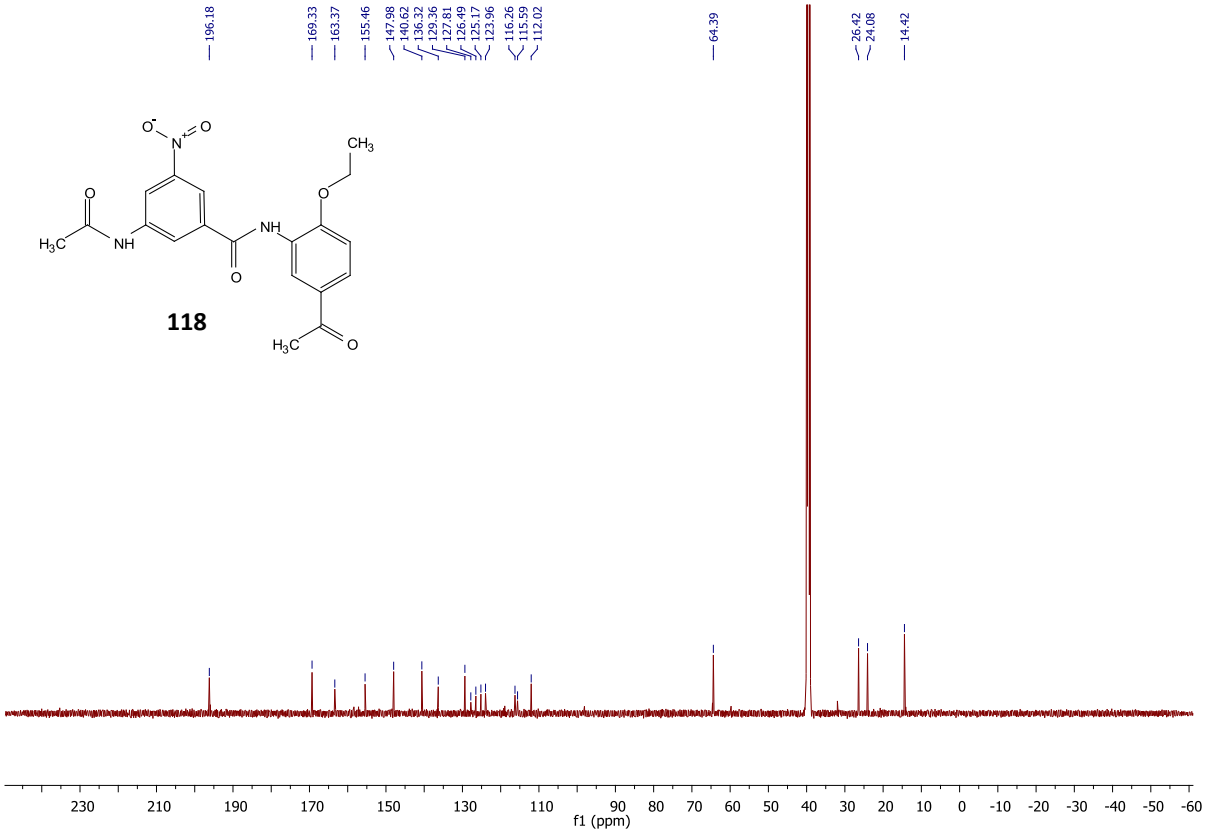
47

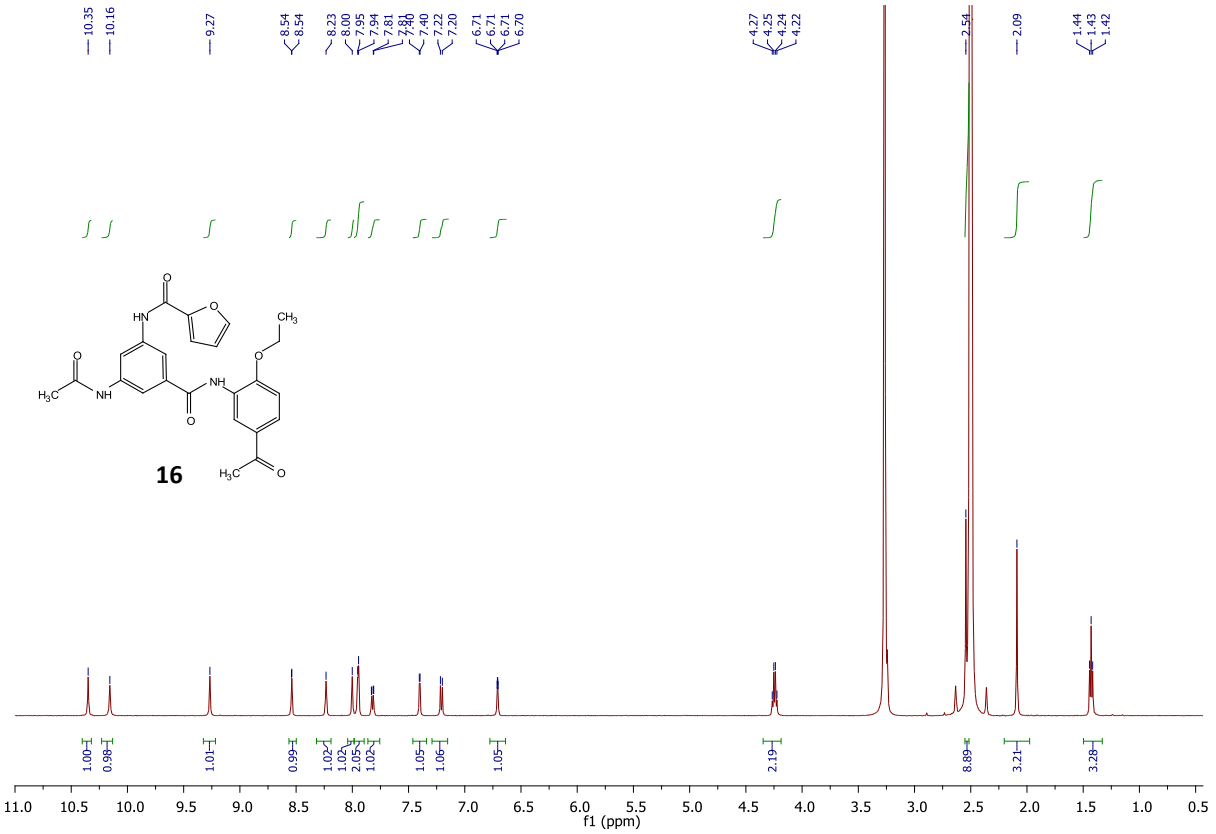

196.43
163.23
152.32
151.58
141.04
135.46
130.83
129.63
129.02
128.50
127.01
125.22
123.26
122.68
121.88
120.24
115.72
111.58
64.73
26.45
14.30
CH3
O
NH
N
NH
O
H3C
O
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

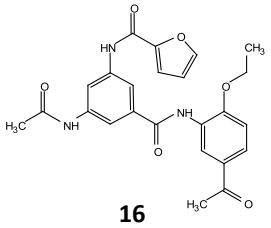
47

CBP inhibitors incorporating the best groups:





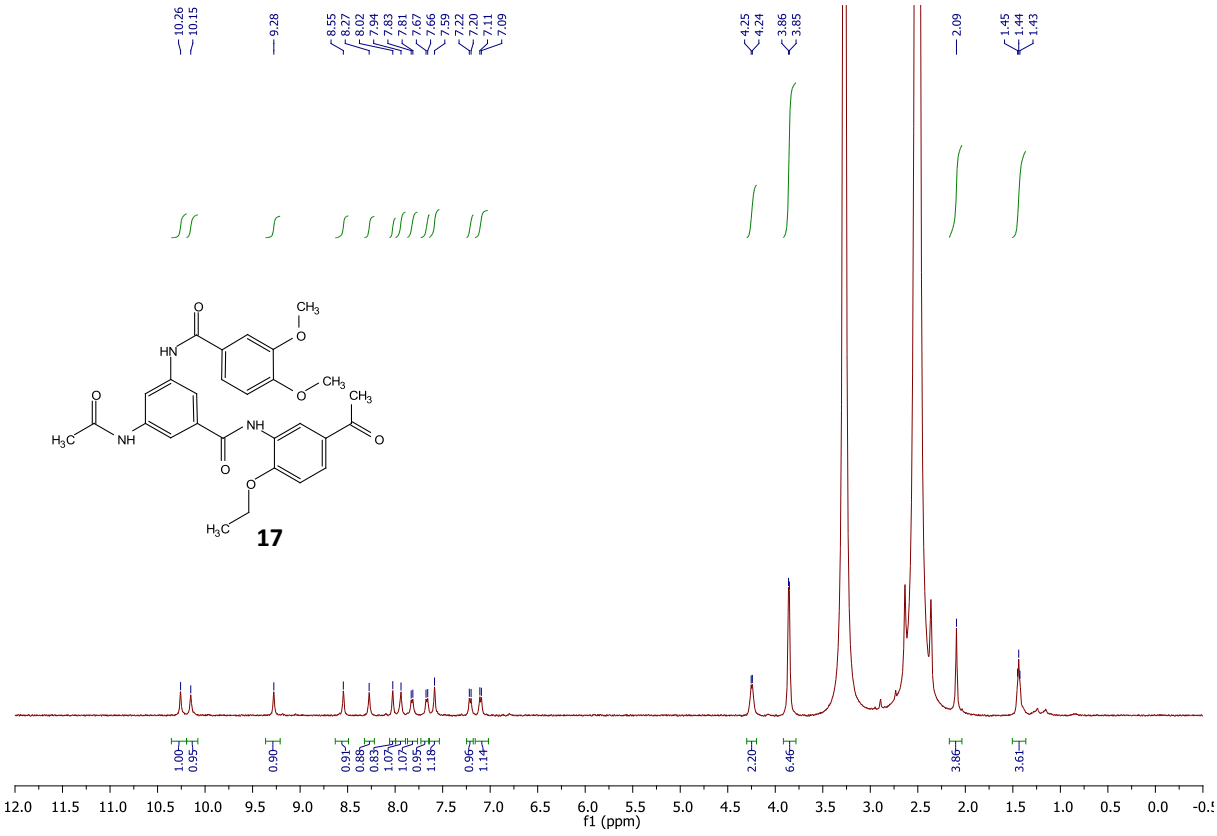

10.35
10.16
9.27
8.54
8.54
8.23
8.00
7.95
7.94
7.81
7.80
7.40
7.22
7.20
6.71
6.71
6.71
6.70
4.27
4.25
4.24
4.22
2.54
2.09
1.44
1.43
1.42
1.00
0.98
1.01
0.99
1.02
1.02
2.05
1.02
1.05
1.06
1.05
2.19
8.89
3.21
3.28
f1 (ppm)



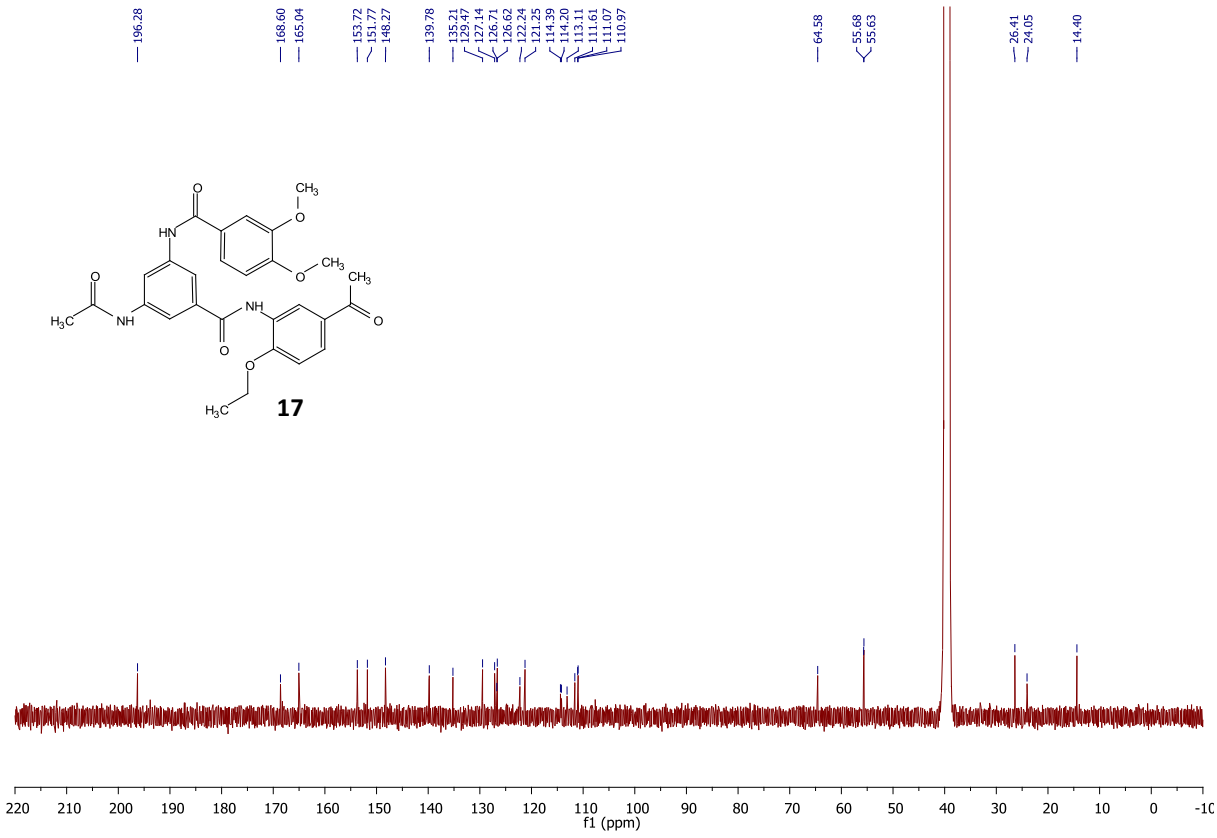
16

196.16
168.52
164.86
156.30
153.53
147.21
145.83
139.76
139.07
135.28
129.48
127.12
126.52
122.08
114.81
114.09
113.99
113.29
112.00
111.57
64.55
26.29
23.94
14.33
f1 (ppm)

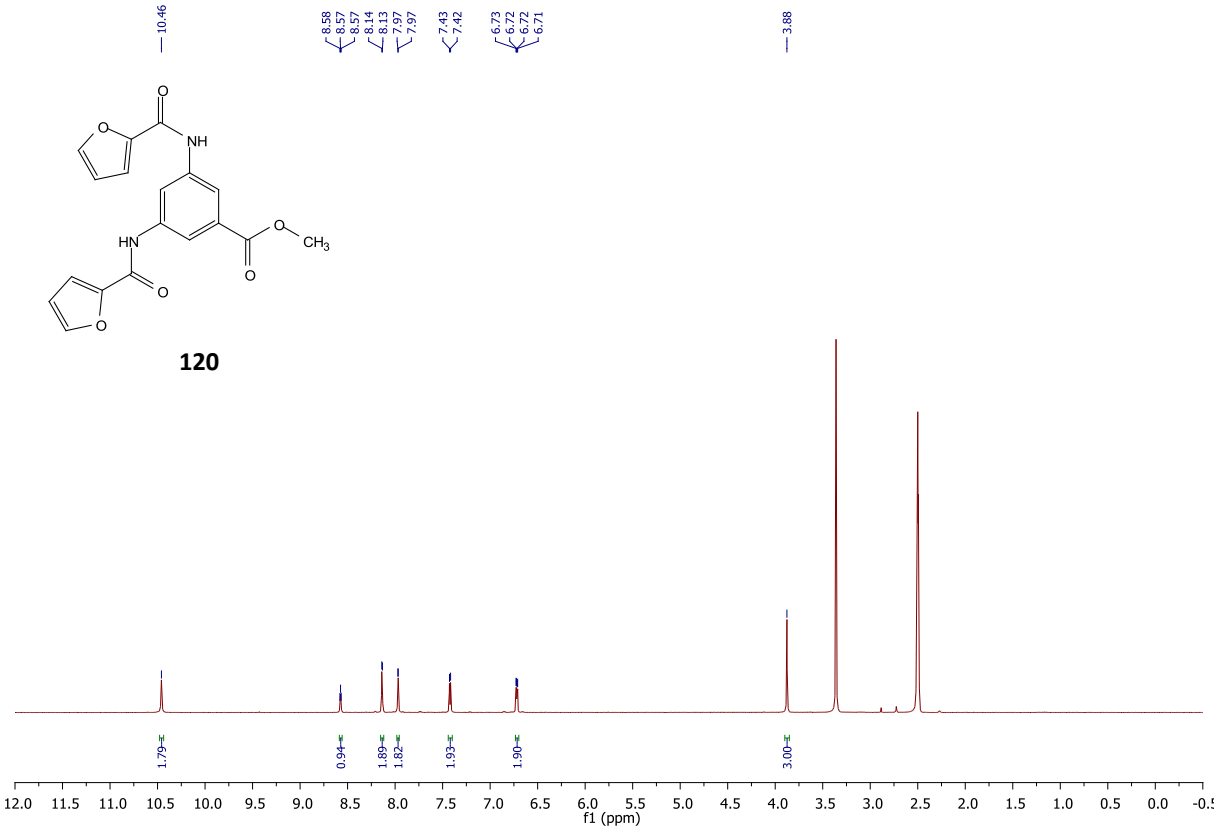
16


10.26
10.15
9.28
8.55
8.27
8.02
7.94
7.83
7.81
7.67
7.66
7.59
7.22
7.20
7.11
7.09
4.25
4.24
3.86
3.85
2.09
1.45
1.44
1.43
1.00
0.95
0.90
0.91
0.88
0.83
1.07
1.07
0.95
1.18
0.96
1.14
2.20
6.46
3.86
3.61
f1 (ppm)

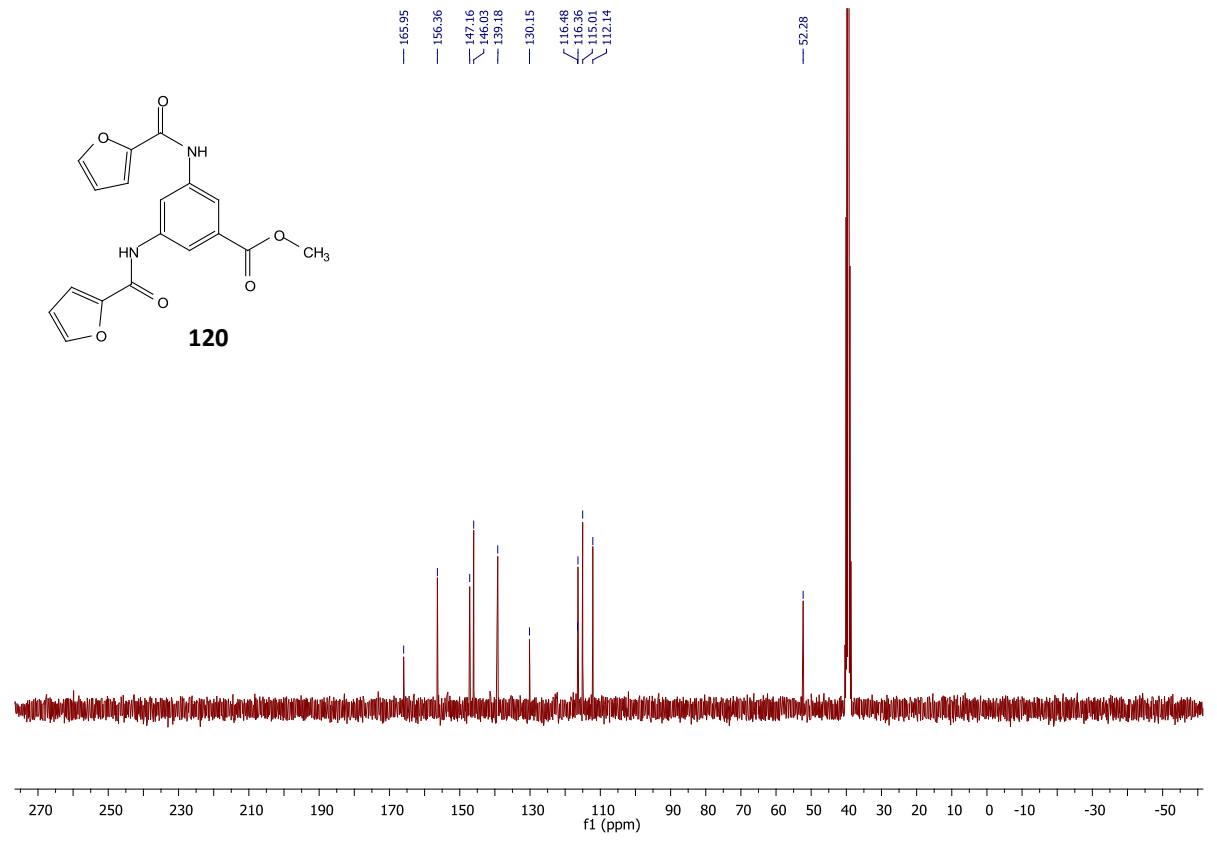
17


196.28
168.60
165.04
153.72
151.77
148.27
139.78
135.21
129.47
127.14
126.71
126.62
122.24
121.25
114.39
114.20
113.11
111.61
111.07
110.97
64.58
55.68
55.63
26.41
24.05
14.40
f1 (ppm)

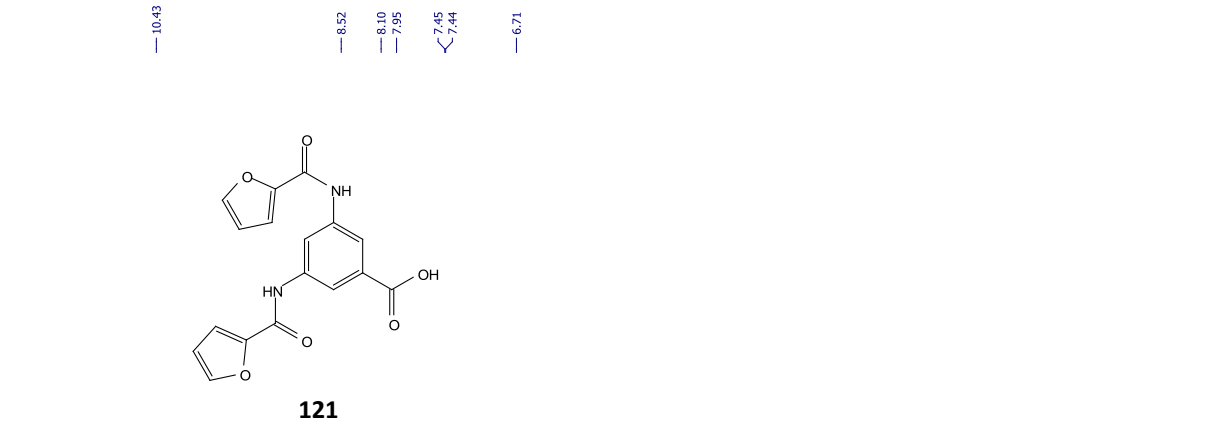
17


10.46
8.58
8.57
8.57
8.14
8.13
7.97
7.97
7.43
7.42
6.73
6.72
6.72
6.71
3.88
NH
HN
O
O
O
O
O
O
CH3
1.79
0.94
1.89
1.82
1.93
1.90
3.00
f1 (ppm)

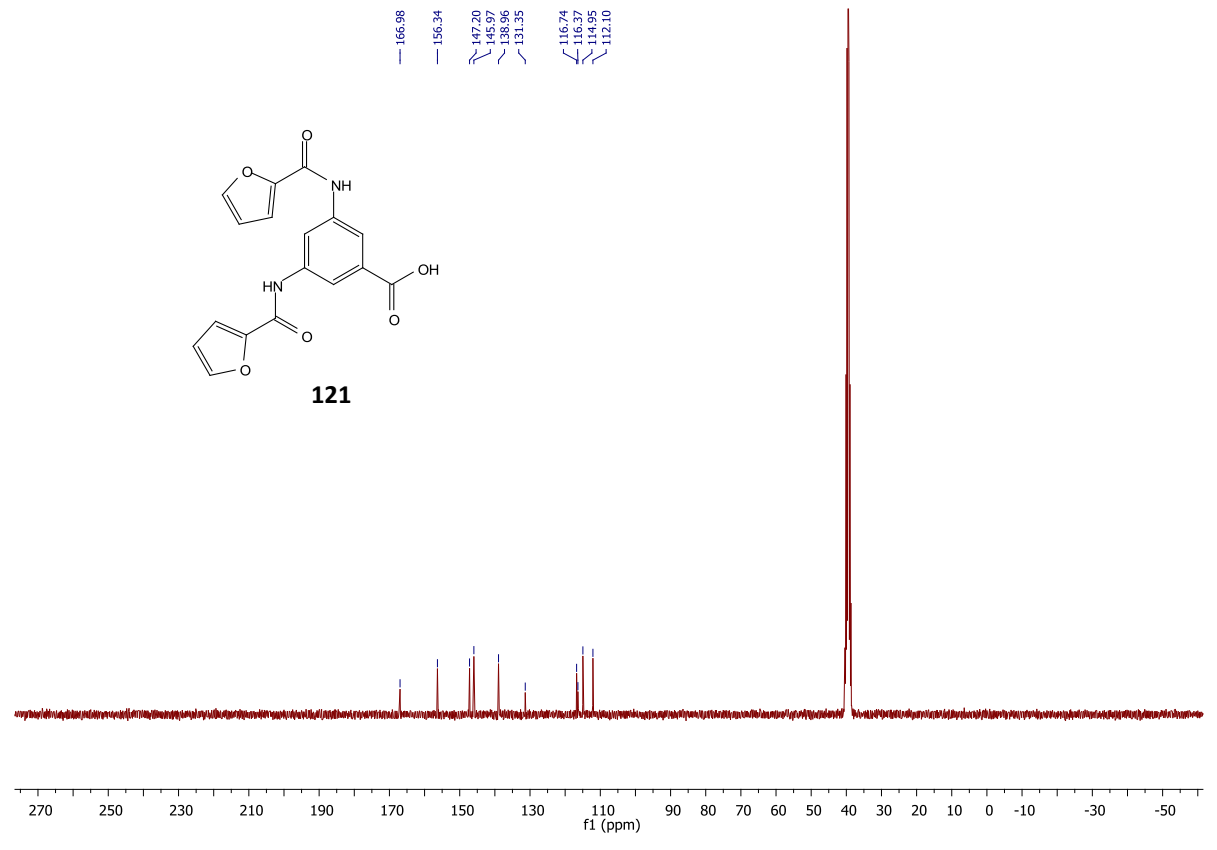
120


165.95
156.36
147.16
146.03
139.18
130.15
116.48
116.36
115.01
112.14
52.28
NH
HN
O
O
O
O
O
O
CH3
f1 (ppm)

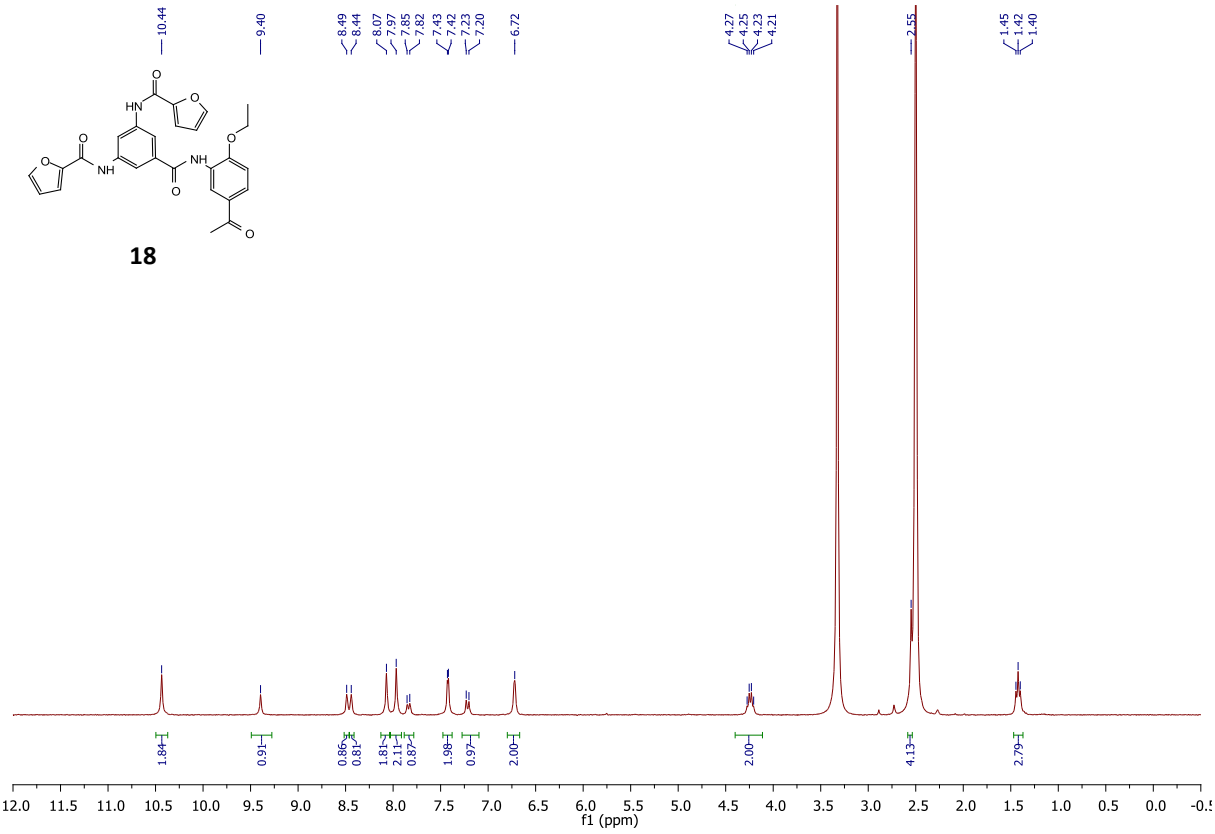
120


10.43
8.52
8.10
7.95
7.45
7.44
6.71
O
NH
OH
HN
O
O
O
O
1.85
1.00
2.06
1.96
1.98
2.05
f1 (ppm)

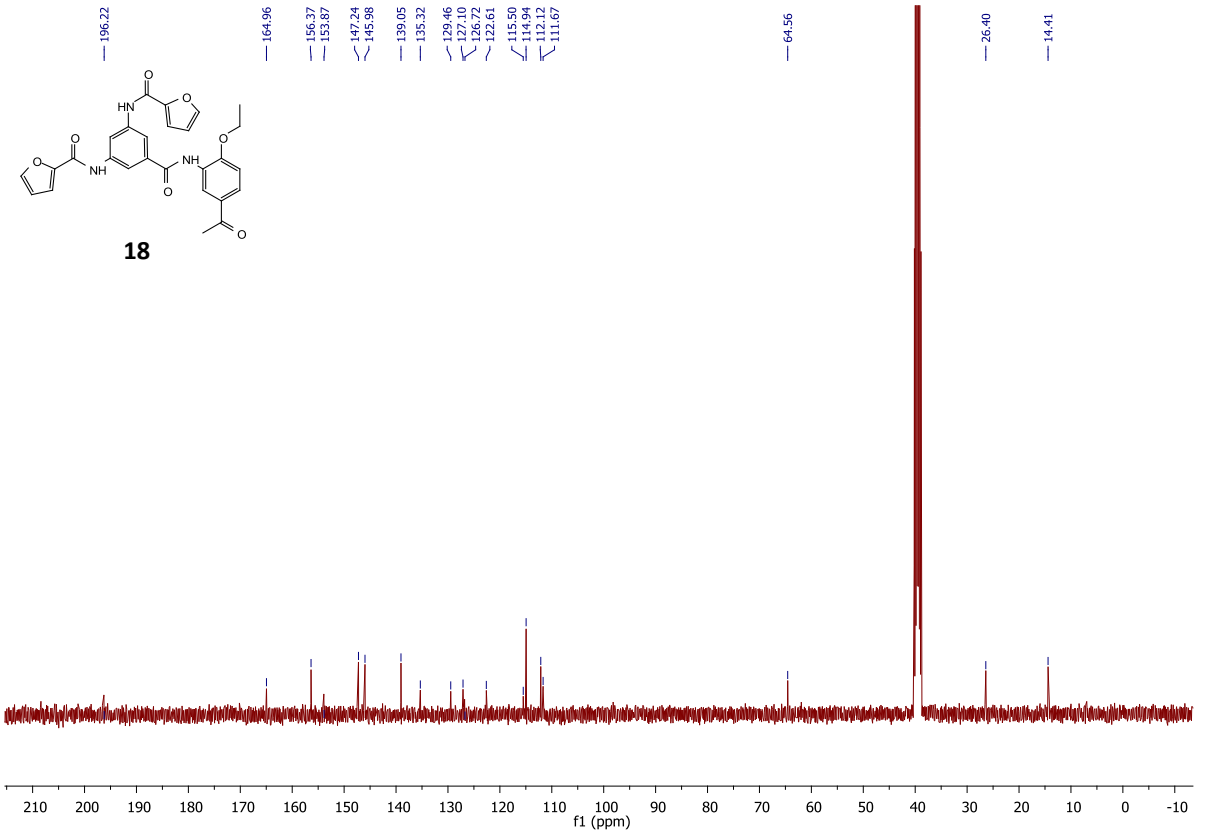
121


166.98
156.34
147.20
145.97
138.96
131.35
116.74
116.37
114.95
112.10
O
NH
OH
HN
O
O
O
O
f1 (ppm)

121

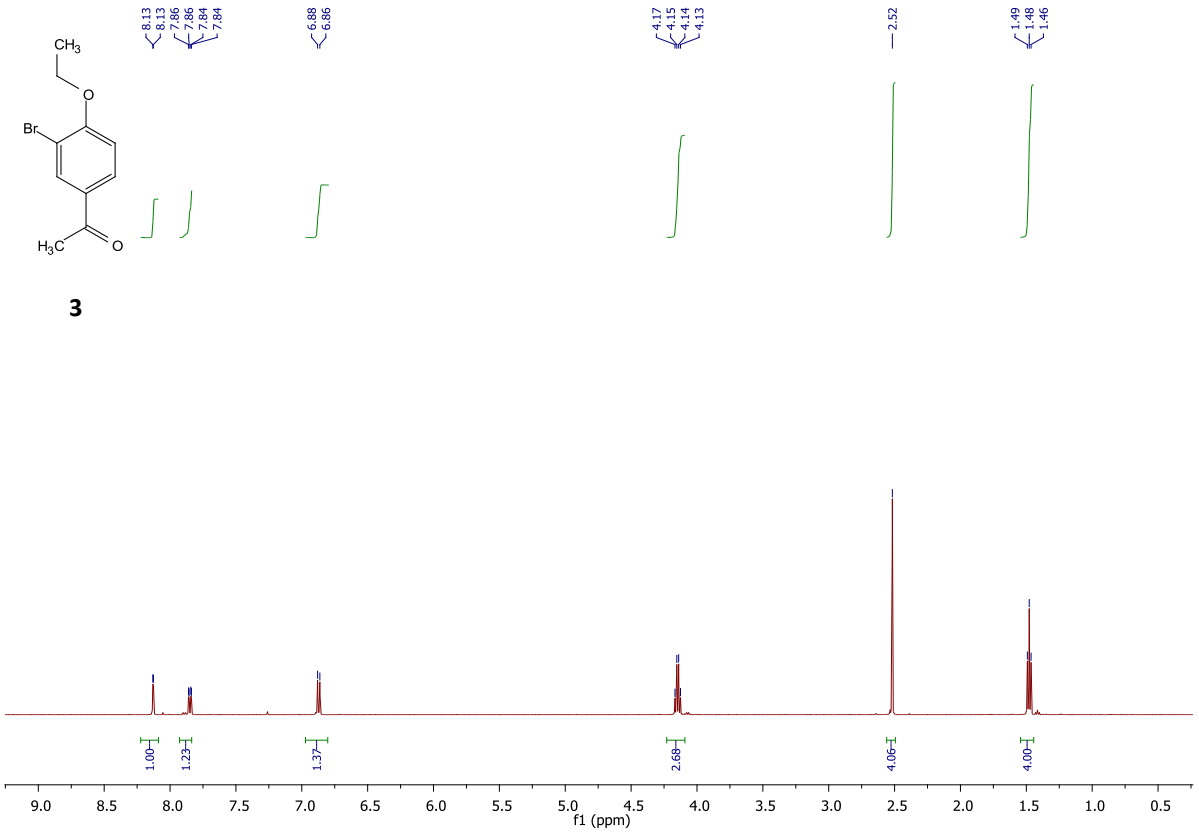

10.44
9.40
8.49
8.44
8.07
7.97
7.85
7.82
7.43
7.42
7.23
7.20
6.72
4.27
4.25
4.23
4.21
2.55
1.45
1.42
1.40
1.84
0.91
0.86
0.81
1.81
2.11
0.87
1.98
0.97
2.00
2.00
4.13
2.79
f1 (ppm)

18

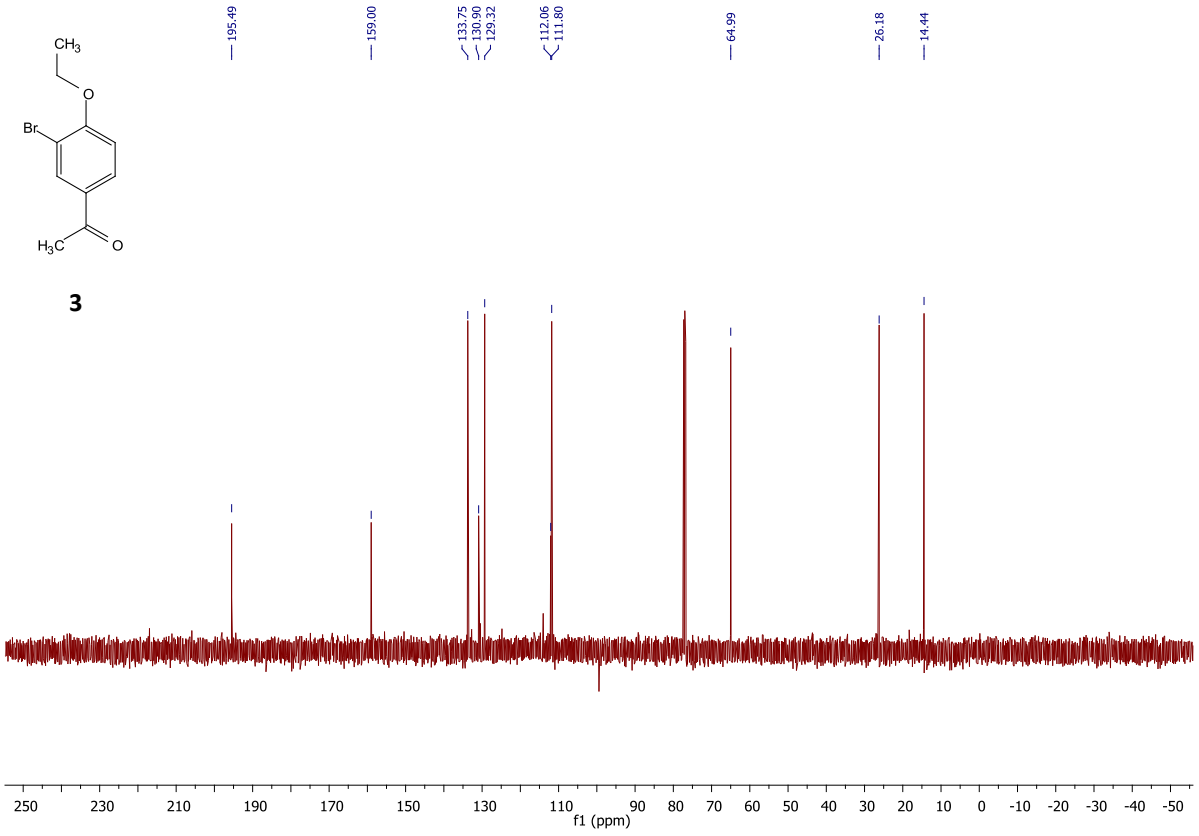

196.22
164.96
156.37
153.87
147.24
145.98
139.05
135.32
129.46
127.10
126.72
122.61
115.50
114.94
112.12
111.67
64.56
26.40
14.41
f1 (ppm)

18

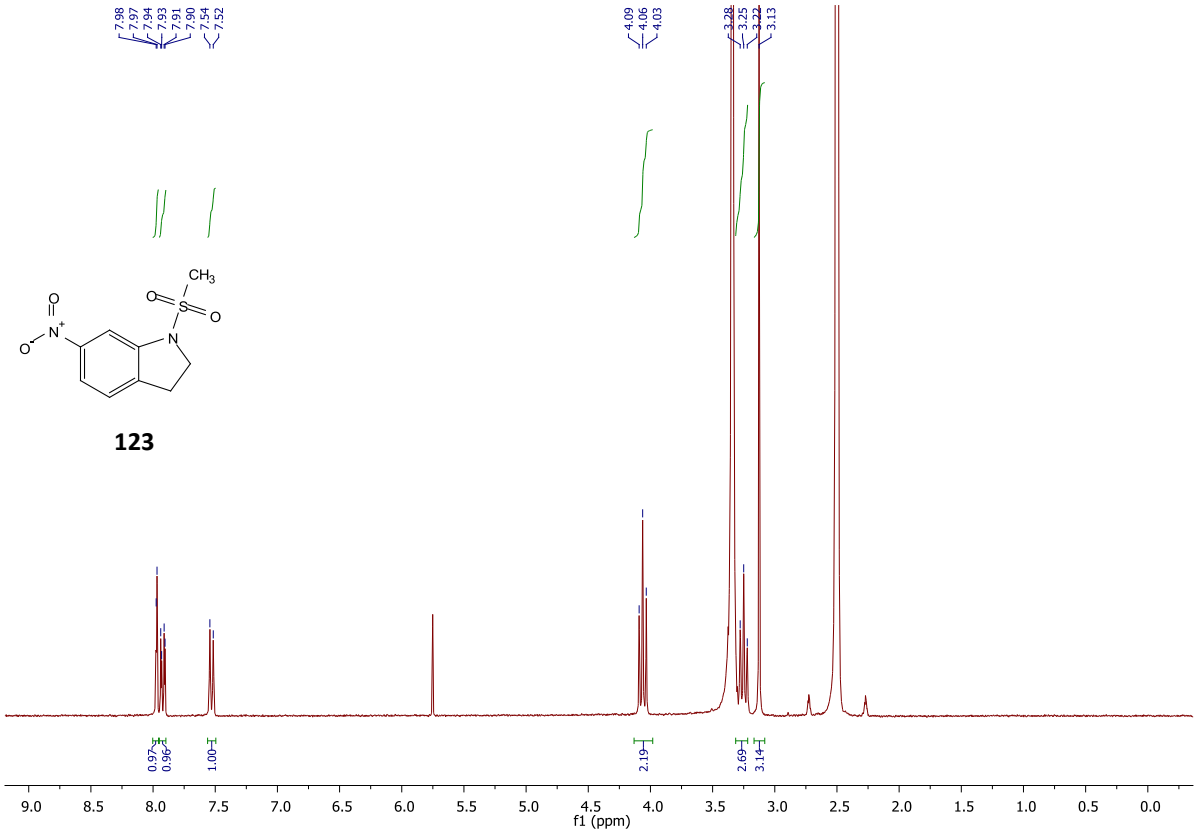
CBP inhibitors bearing an amine linker:



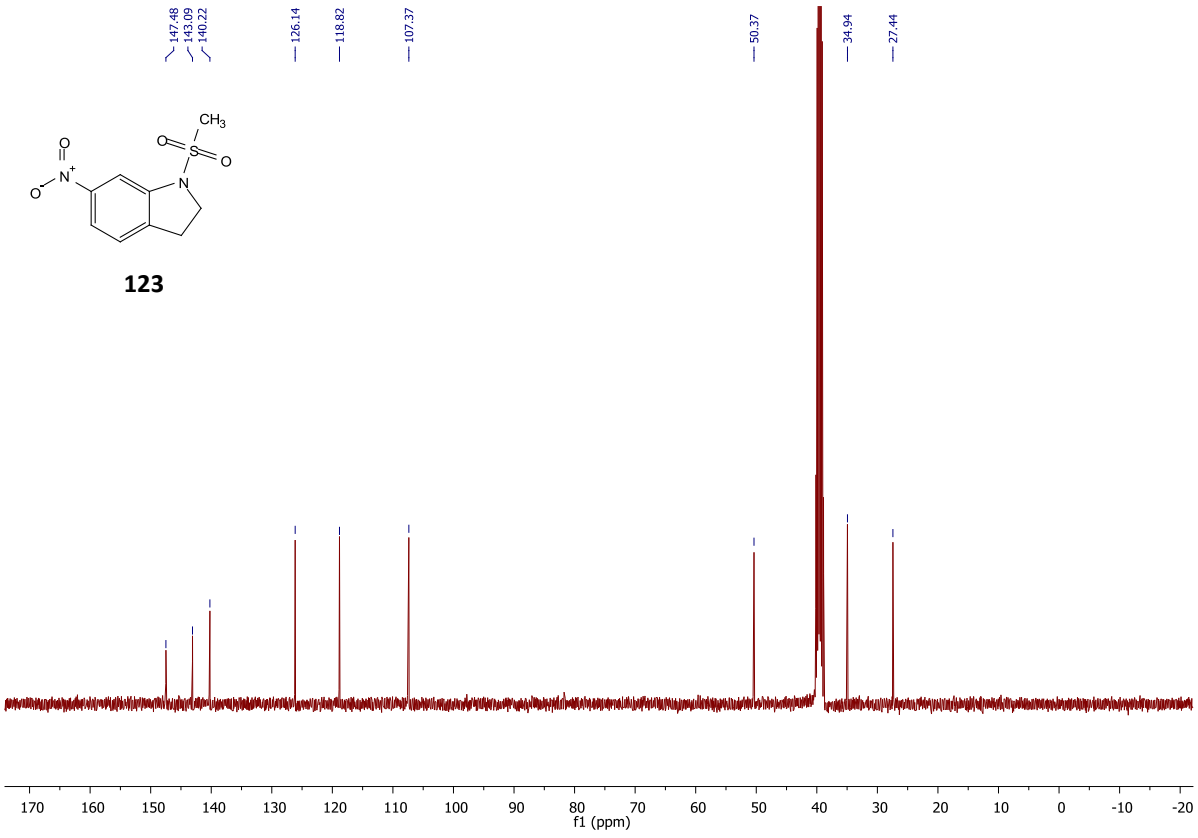
3



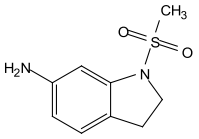
3


7.98
7.97
7.94
7.93
7.91
7.90
7.54
7.52
4.09
4.06
4.03
3.28
3.25
3.23
3.13
CH3
O
S
O
N
O
N+
O-
0.97
0.96
1.00
2.19
2.69
3.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

123

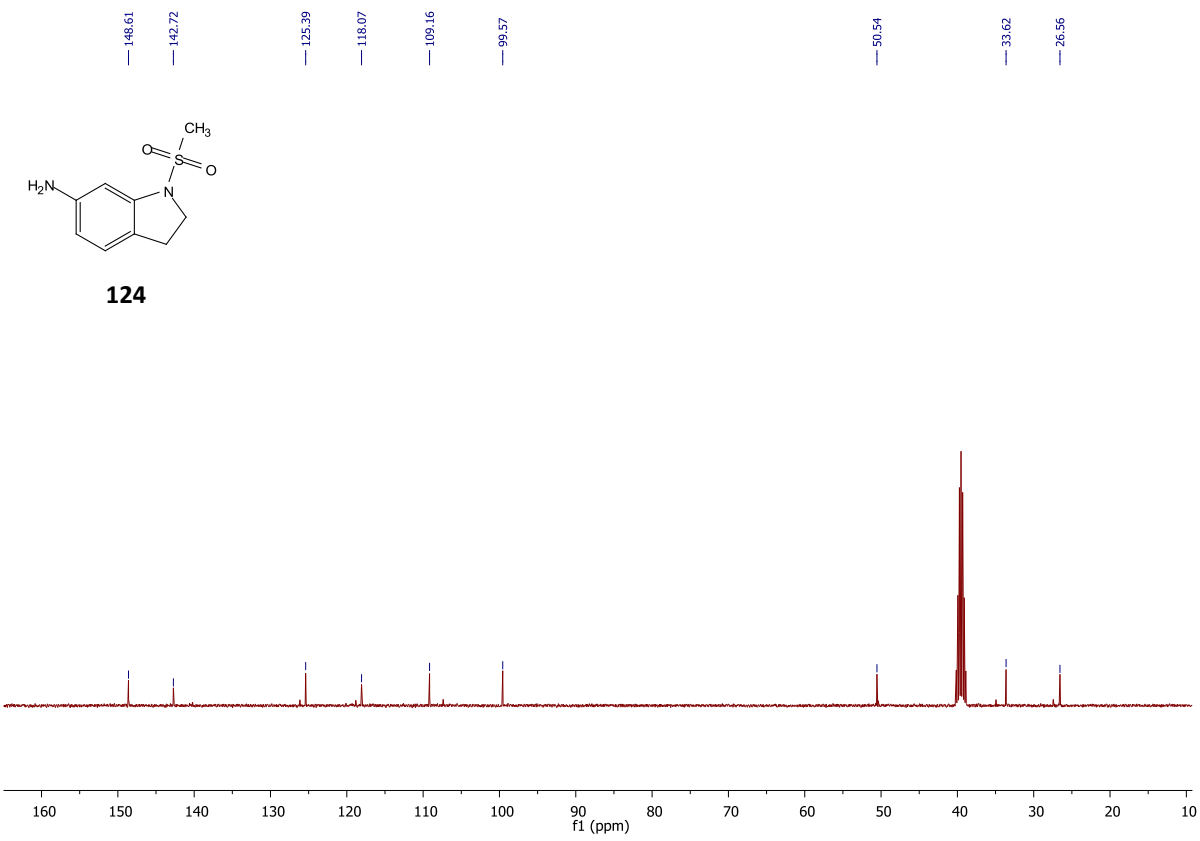

147.48
143.09
140.22
126.14
118.82
107.37
50.37
34.94
27.44
CH3
O
S
O
N
O
N+
O-
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

123


CH3
O
S
O
H2N
N

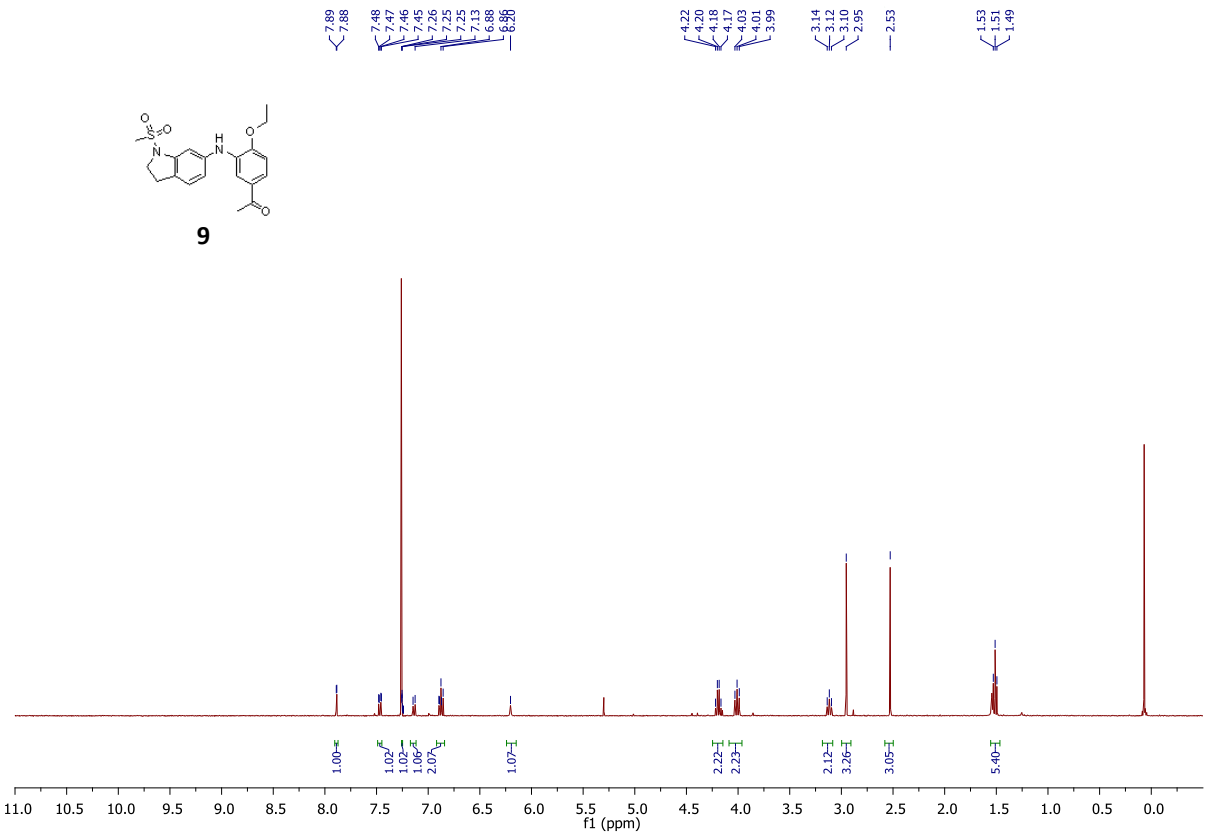
124

6.88
6.86
6.60
6.60
6.24
6.24
6.22
6.22
5.09
3.85
3.83
3.81
2.92
2.90
2.88
1.00
1.01
1.01
1.94
2.05
5.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

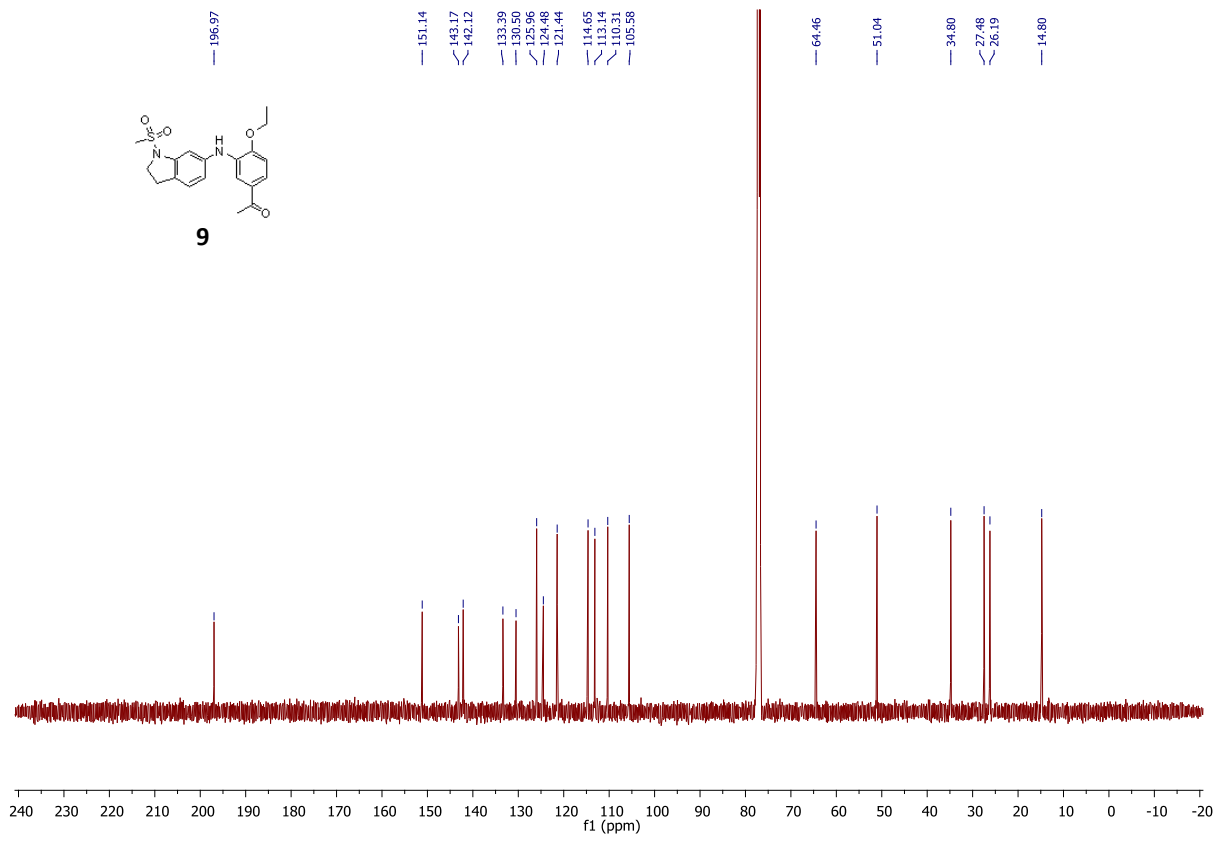

148.61
142.72
125.39
118.07
109.16
99.57
50.54
33.62
26.56
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

CH3
O
S
O
H2N
N

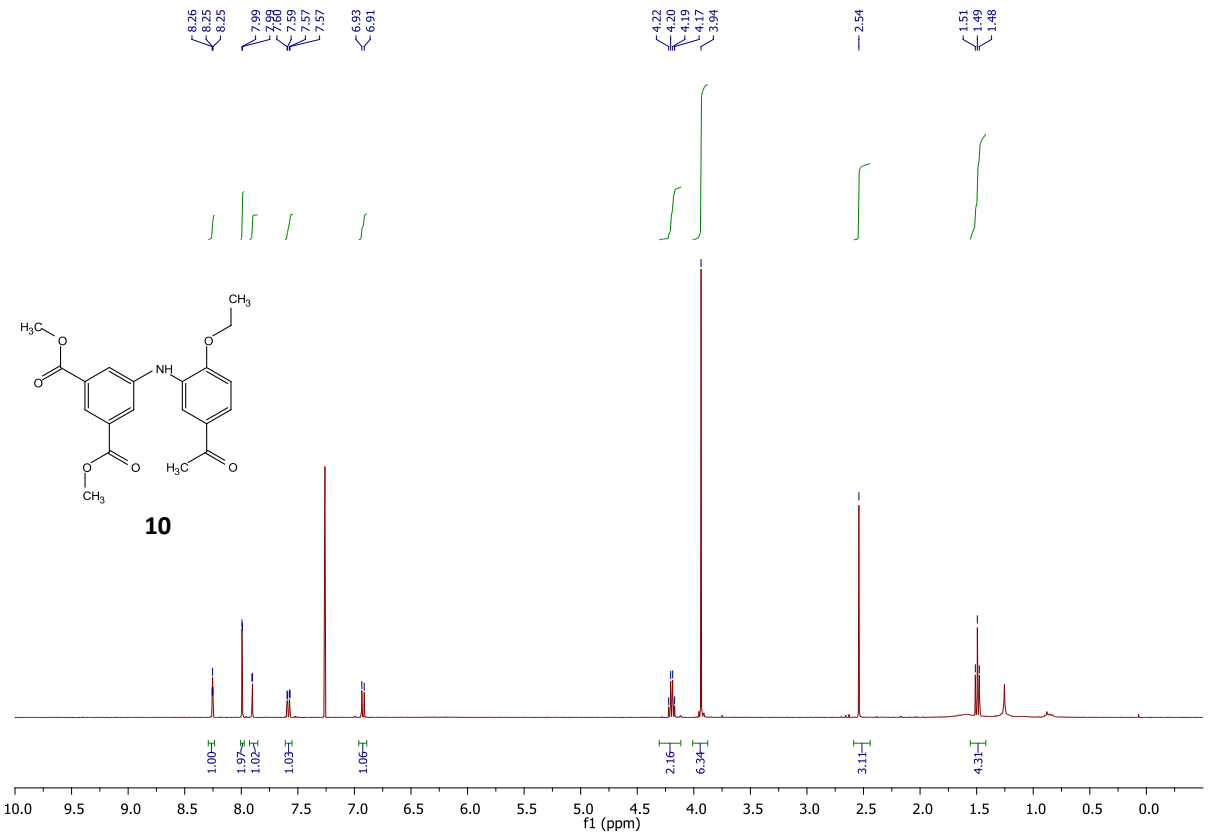
124


7.89
7.88
7.48
7.47
7.46
7.45
7.26
7.25
7.25
7.13
6.88
6.86
6.85
4.22
4.20
4.18
4.17
4.03
4.01
3.99
3.14
3.12
3.10
2.95
2.53
1.53
1.51
1.49
1.00
1.02
1.02
1.06
2.07
1.07
2.22
2.23
2.12
3.26
3.05
5.40
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

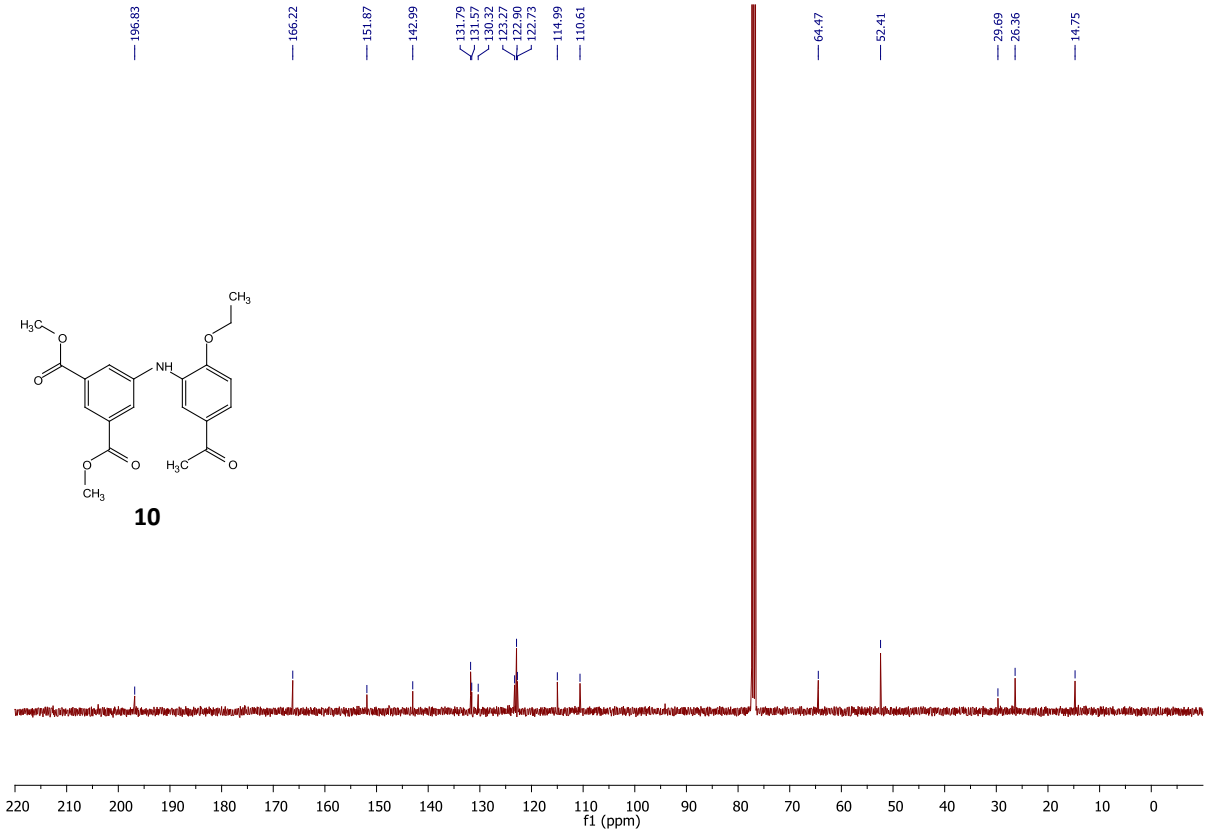
9


196.97
151.14
143.17
142.12
133.39
130.50
125.96
124.48
121.44
114.65
113.14
110.31
105.58
64.46
51.04
34.80
27.48
26.19
14.80
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

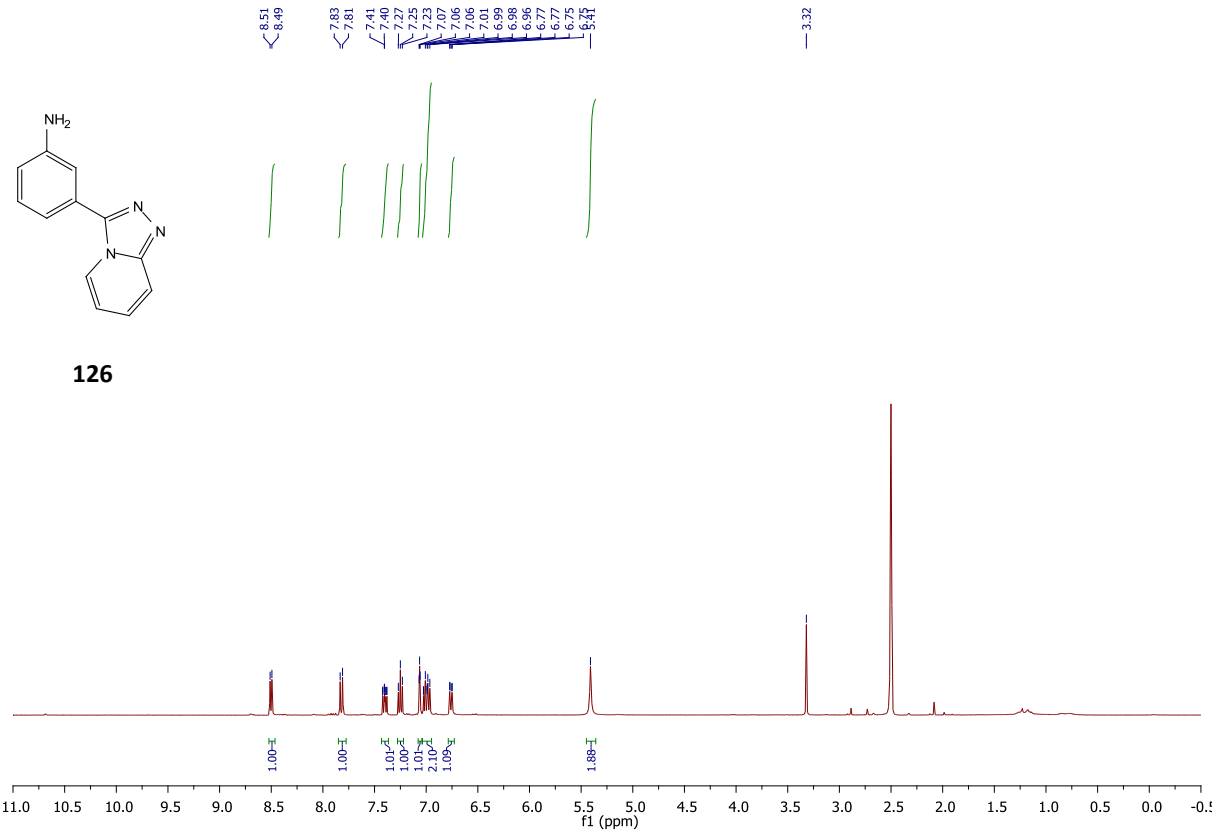
9


8.26
8.25
8.25
7.99
7.98
7.60
7.59
7.57
7.57
6.93
6.91
4.22
4.20
4.19
4.17
3.94
2.54
1.51
1.49
1.48
1.00
1.97
1.02
1.03
1.06
2.16
6.34
3.11
4.31
f1 (ppm)

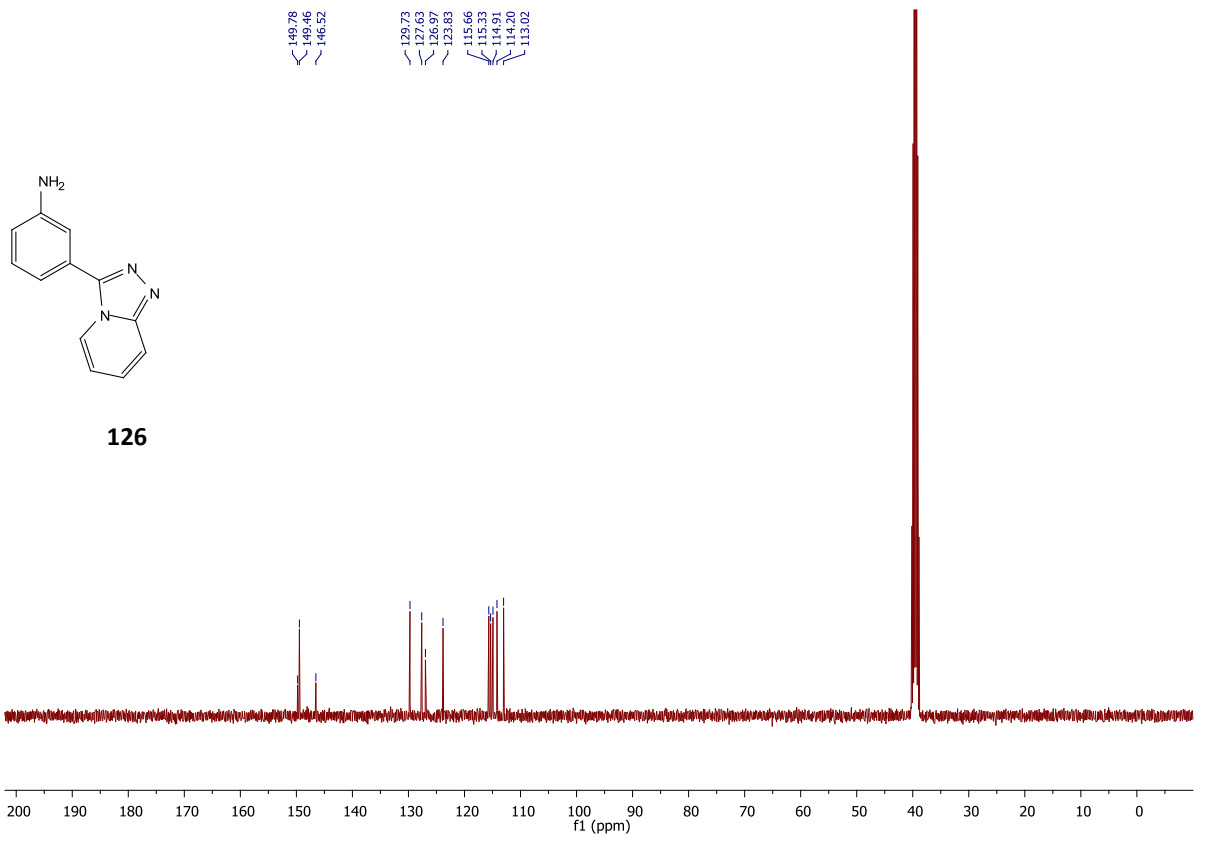
10


196.83
166.22
151.87
142.99
131.79
131.57
130.32
123.27
122.90
122.73
114.99
110.61
64.47
52.41
29.69
26.36
14.75
f1 (ppm)

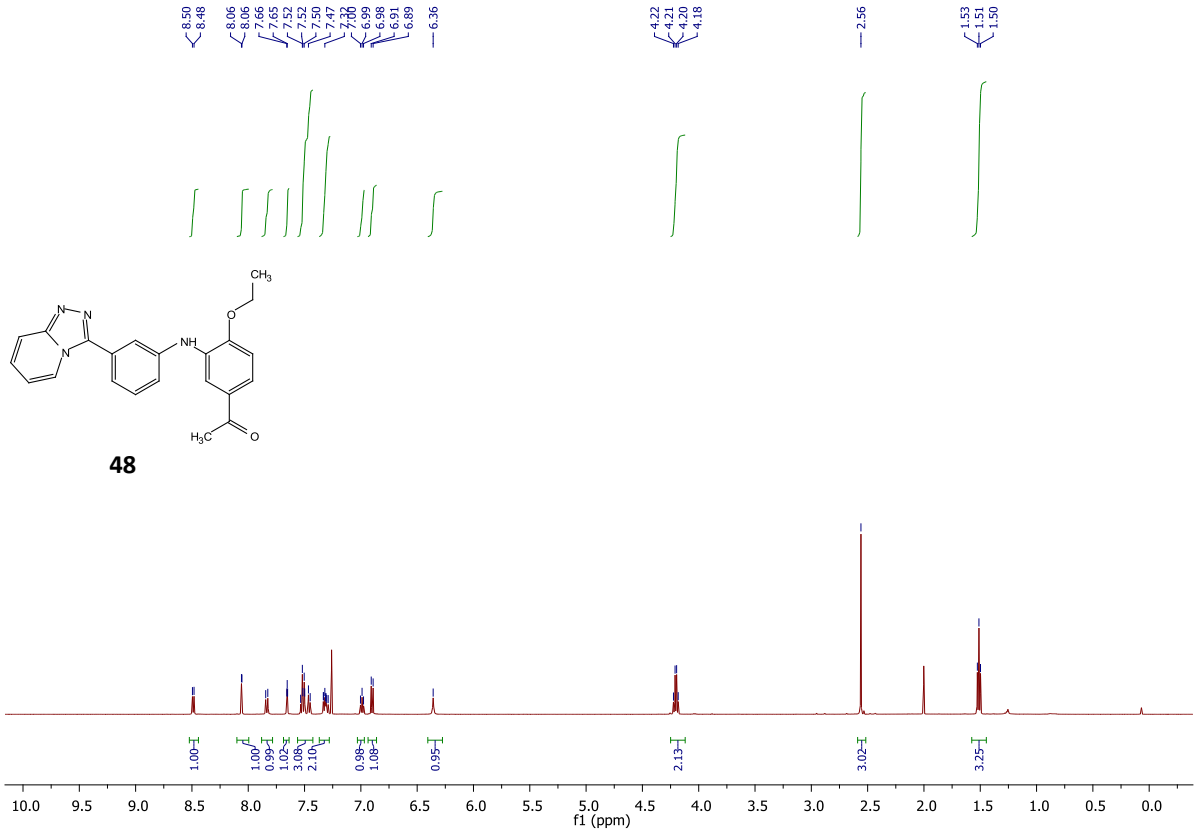
10


8.51
8.49
7.83
7.81
7.41
7.40
7.27
7.25
7.23
7.07
7.06
7.06
7.01
6.99
6.98
6.96
6.77
6.77
6.75
5.41
3.32
NH2
N
N
N
1.00
1.00
1.01
1.00
1.01
2.10
1.09
1.88
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

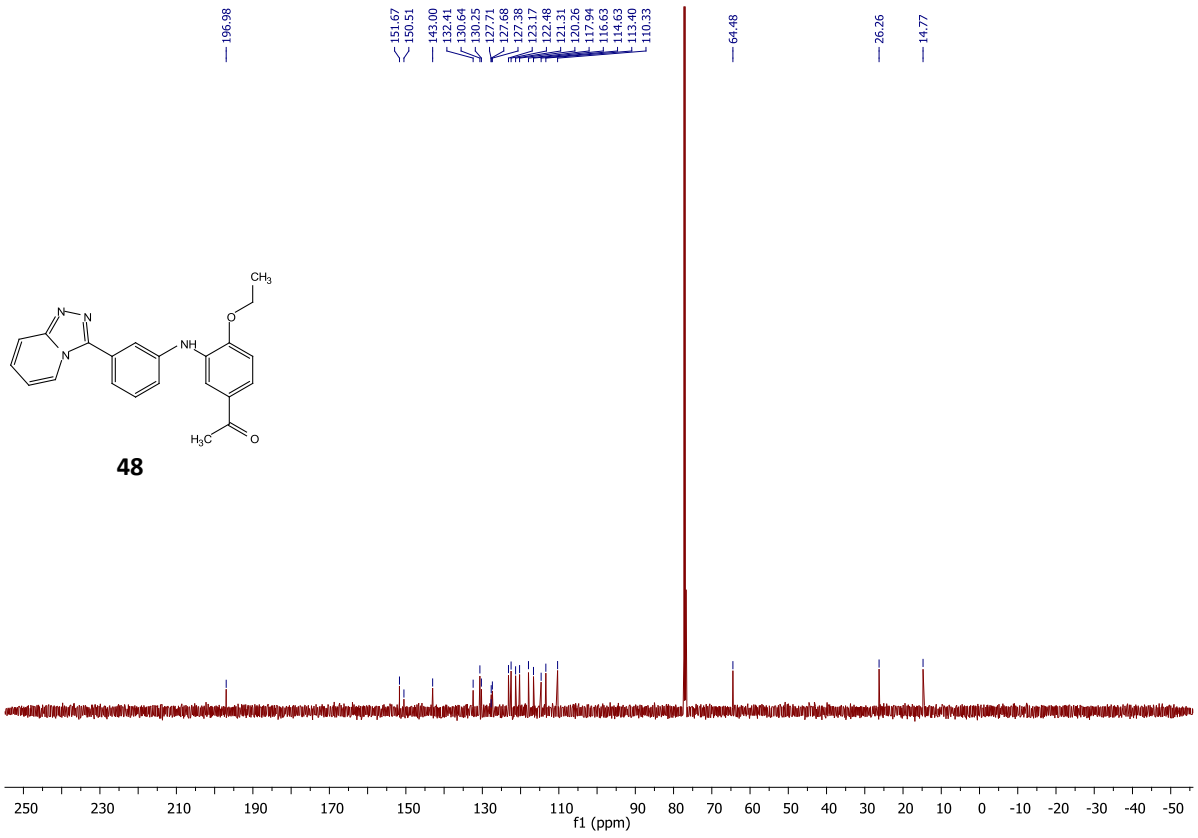
126


149.78
149.46
146.52
129.73
127.63
126.97
123.83
115.66
115.33
114.91
114.20
113.02
NH2
N
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

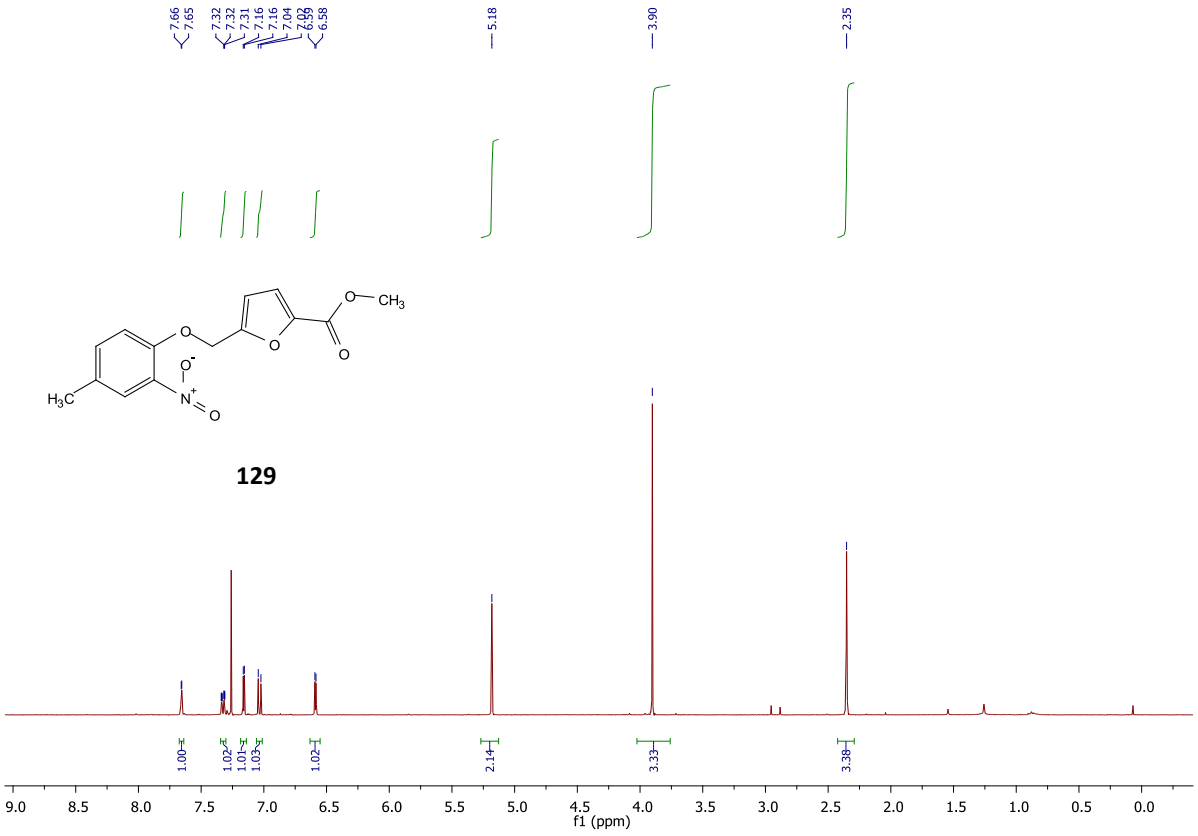
126


8.50
8.48
8.06
8.06
7.66
7.65
7.52
7.52
7.50
7.47
7.32
7.00
6.99
6.98
6.91
6.89
6.36
4.22
4.21
4.20
4.18
2.56
1.53
1.51
1.50
CH3
O
NH
N
N
N
H3C
O
1.00
1.00
0.99
1.02
3.08
2.10
0.98
1.08
0.95
2.13
3.02
3.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

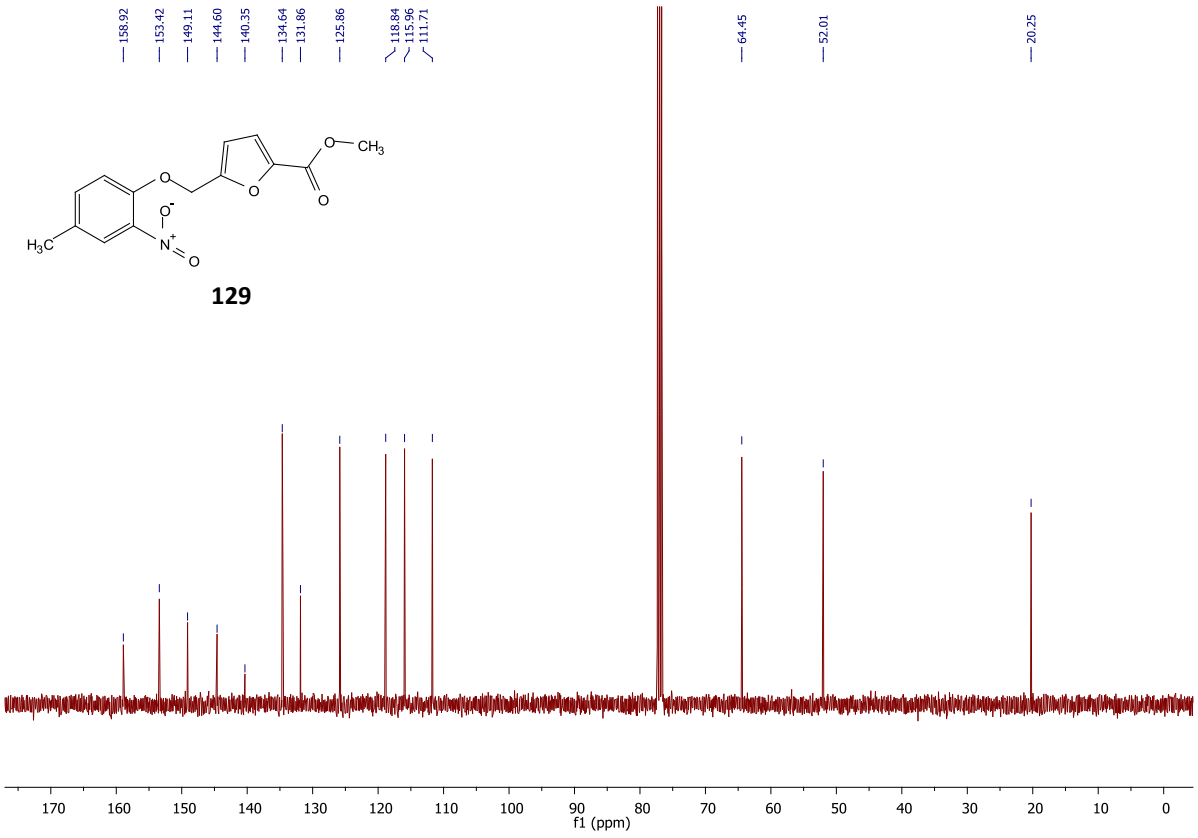
48


196.98
151.67
150.51
143.00
132.41
130.64
130.25
127.71
127.68
127.38
123.17
122.48
121.31
120.26
117.94
116.63
114.63
113.40
110.33
64.48
26.26
14.77
CH3
O
NH
N
N
N
H3C
O
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
f1 (ppm)

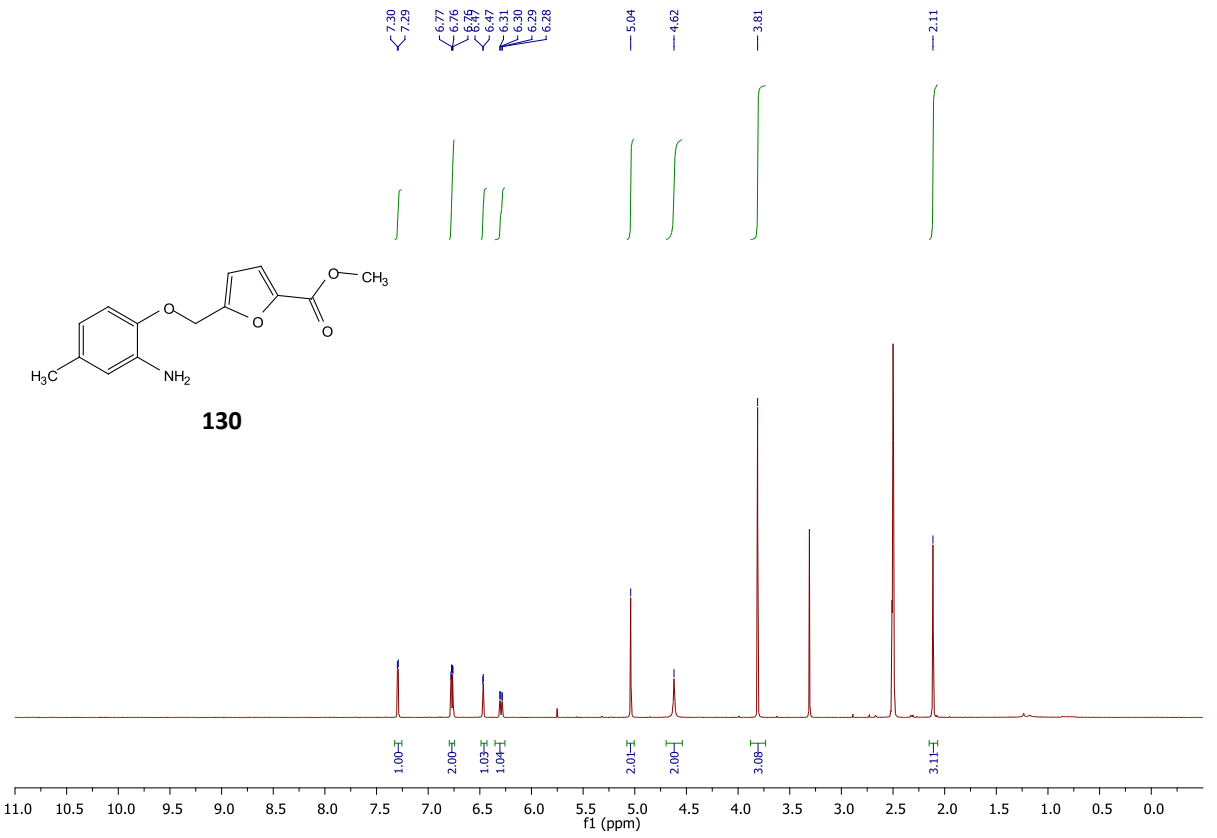
48


7.66
7.65
7.32
7.32
7.31
7.16
7.16
7.04
6.59
6.58
5.18
3.90
2.35
O
CH3
O
O
O
O
H3C
N+
O
1.00
1.02
1.01
1.03
1.02
2.14
3.33
3.38
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

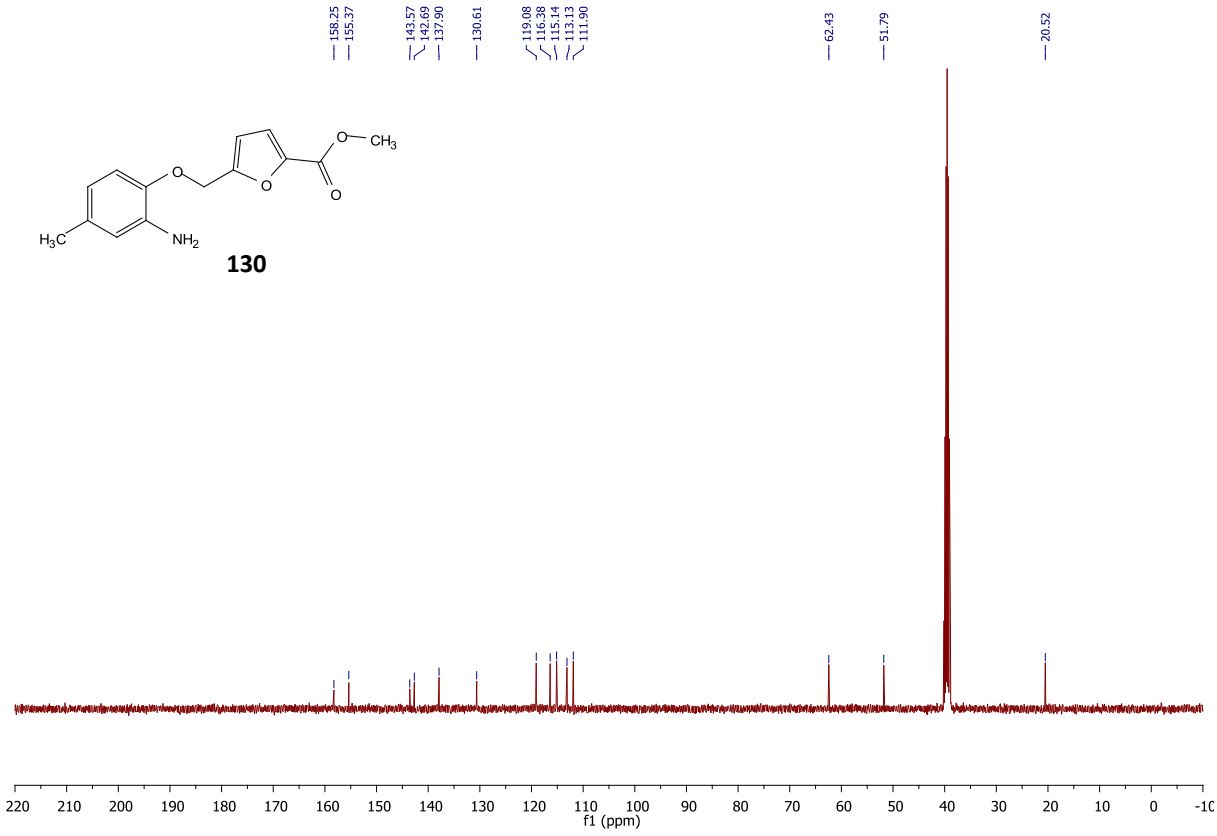
129


158.92
153.42
149.11
144.60
140.35
134.64
131.86
125.86
118.84
115.96
111.71
64.45
52.01
20.25
O
CH3
O
O
O
O
H3C
N+
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

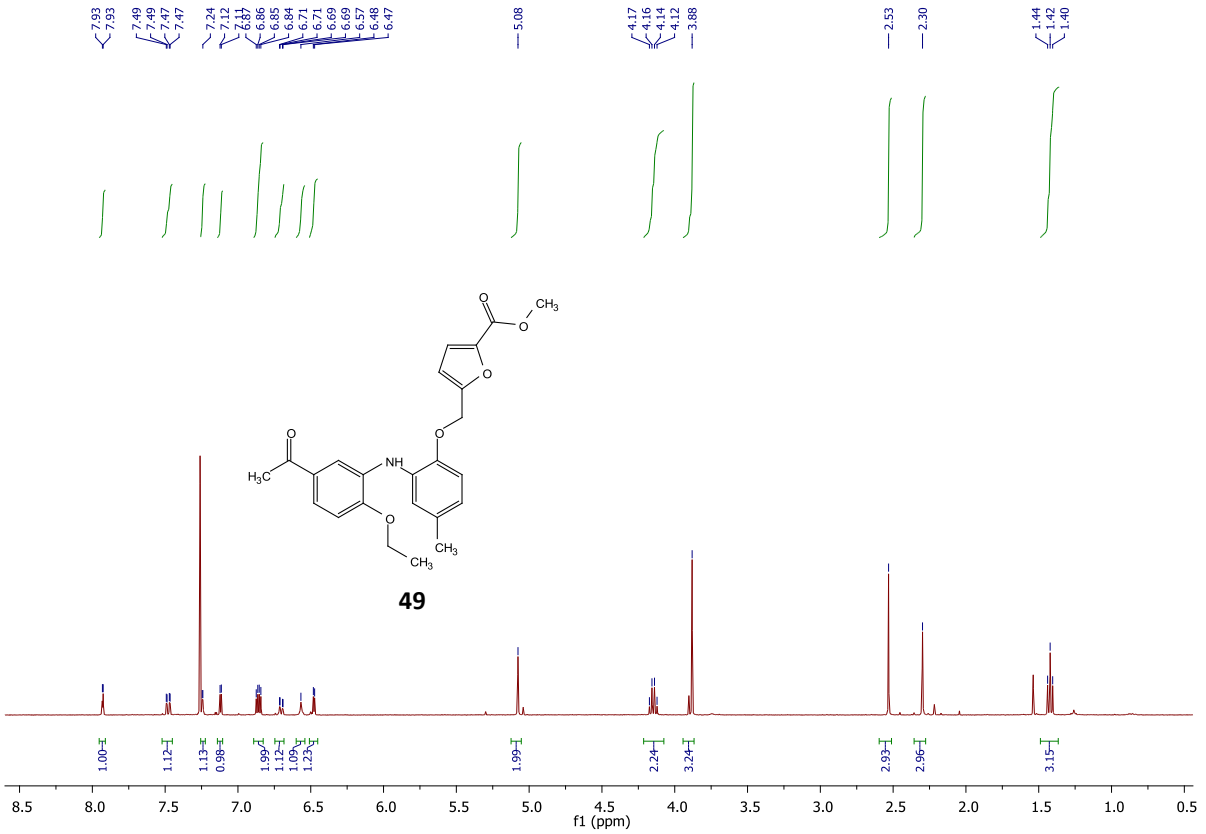
129


7.30
7.29
6.77
6.76
6.47
6.31
6.30
6.29
6.28
5.04
4.62
3.81
2.11
O
CH3
O
O
H3C
NH2
1.00
2.00
1.03
1.04
2.01
2.00
3.08
3.11
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

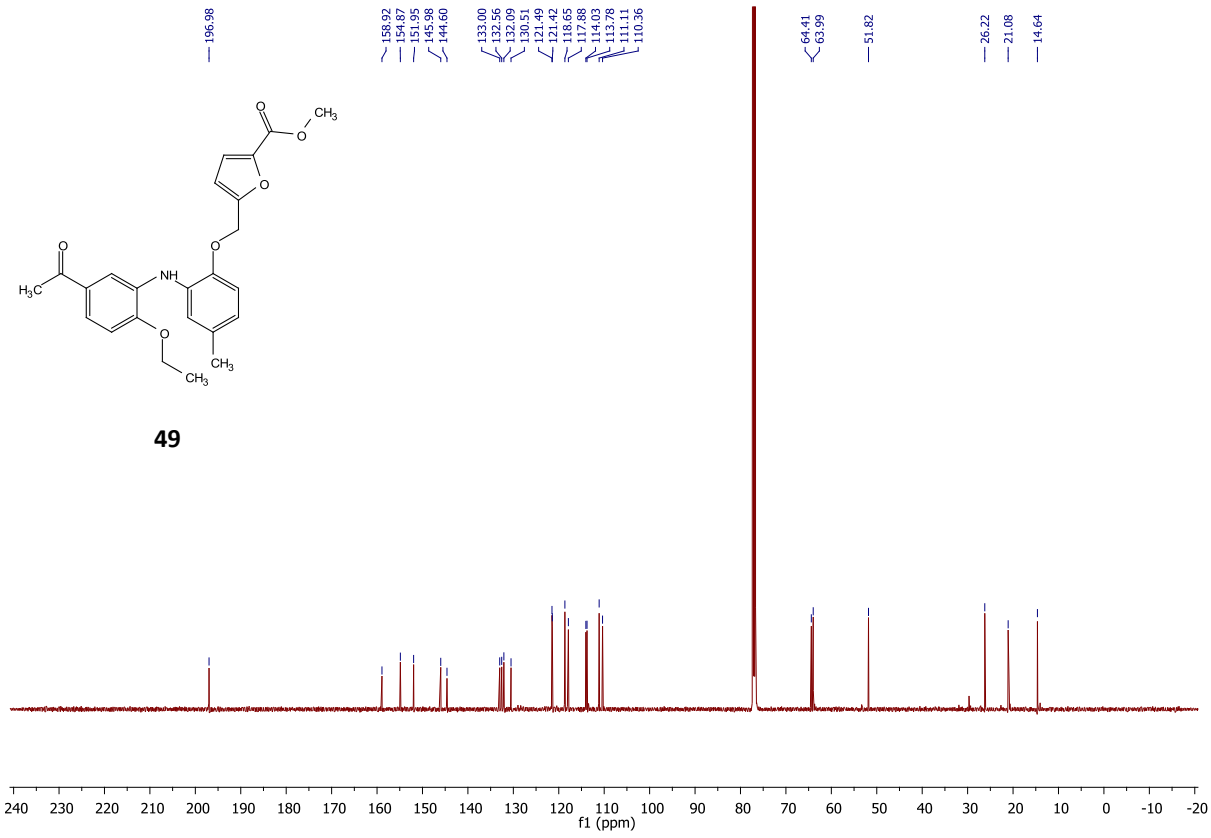
130


158.25
155.37
143.57
142.69
137.90
130.61
119.08
116.38
115.14
113.13
111.90
62.43
51.79
20.52
O
CH3
O
O
H3C
NH2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

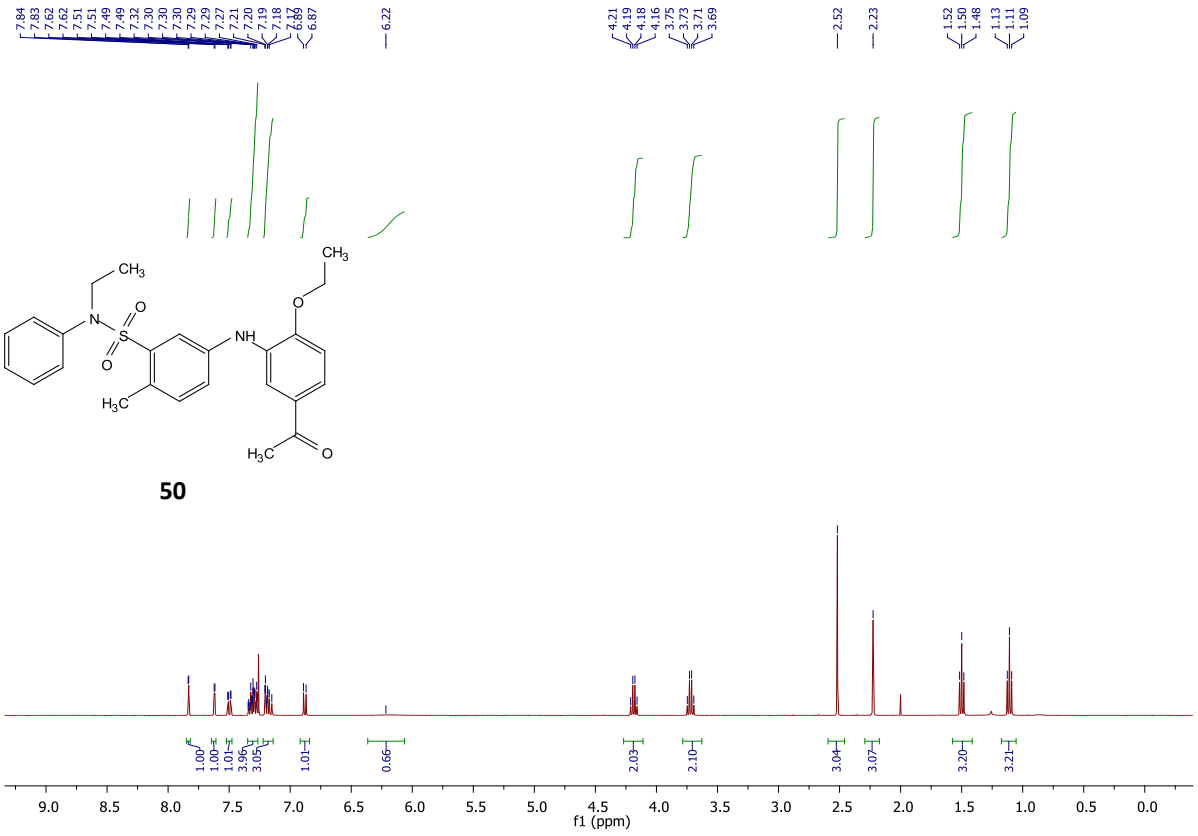
130


7.93
7.93
7.49
7.49
7.47
7.47
7.24
7.12
6.87
6.86
6.85
6.84
6.71
6.71
6.69
6.69
6.57
6.48
6.47
5.08
4.17
4.16
4.14
4.12
3.88
2.53
2.30
1.44
1.42
1.40
O
CH3
O
O
O
NH
H3C
O
CH3
CH3
1.00
1.12
1.13
0.98
1.99
1.12
1.09
1.23
1.99
2.24
3.24
2.93
2.96
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

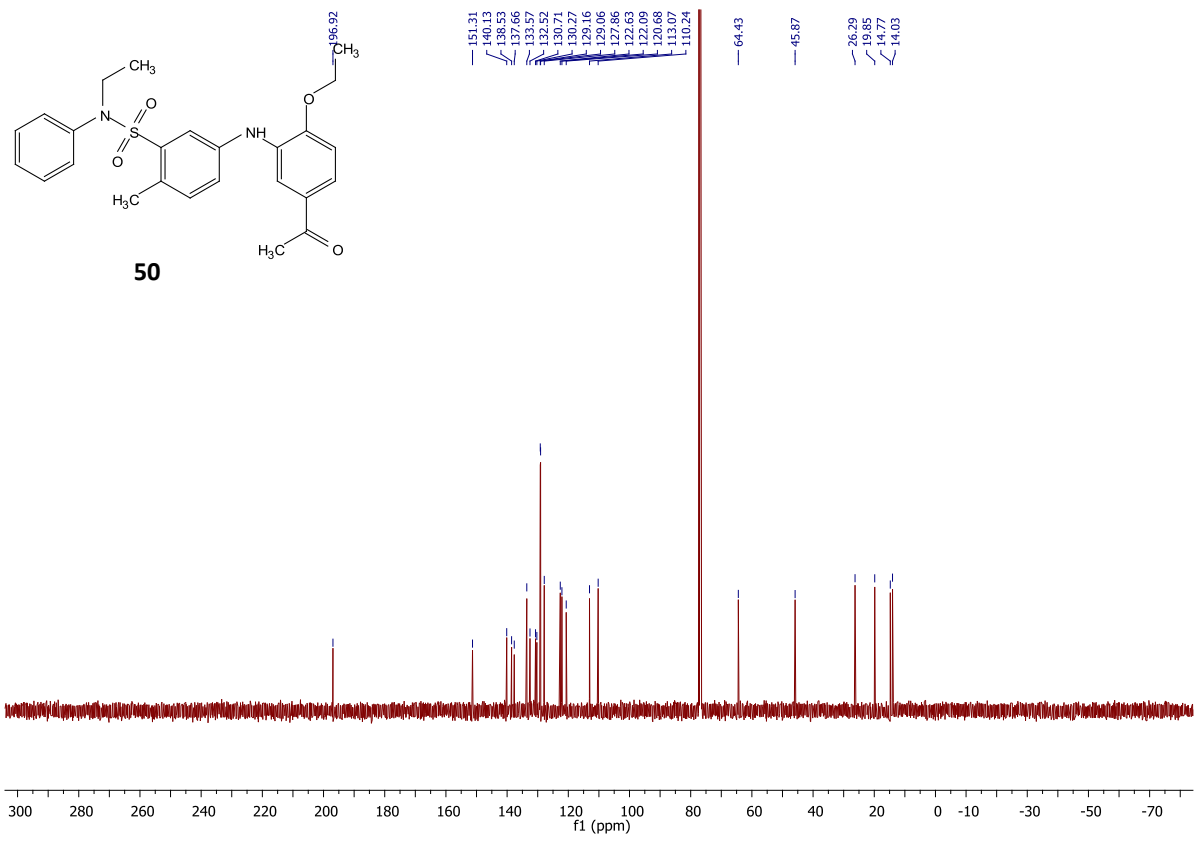
49


196.98
158.92
154.87
151.95
145.98
144.60
133.00
132.56
132.09
130.51
121.49
121.42
118.65
117.88
114.03
113.78
111.11
110.36
64.41
63.99
51.82
26.22
21.08
14.64
O
CH3
O
O
O
NH
H3C
O
CH3
CH3
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

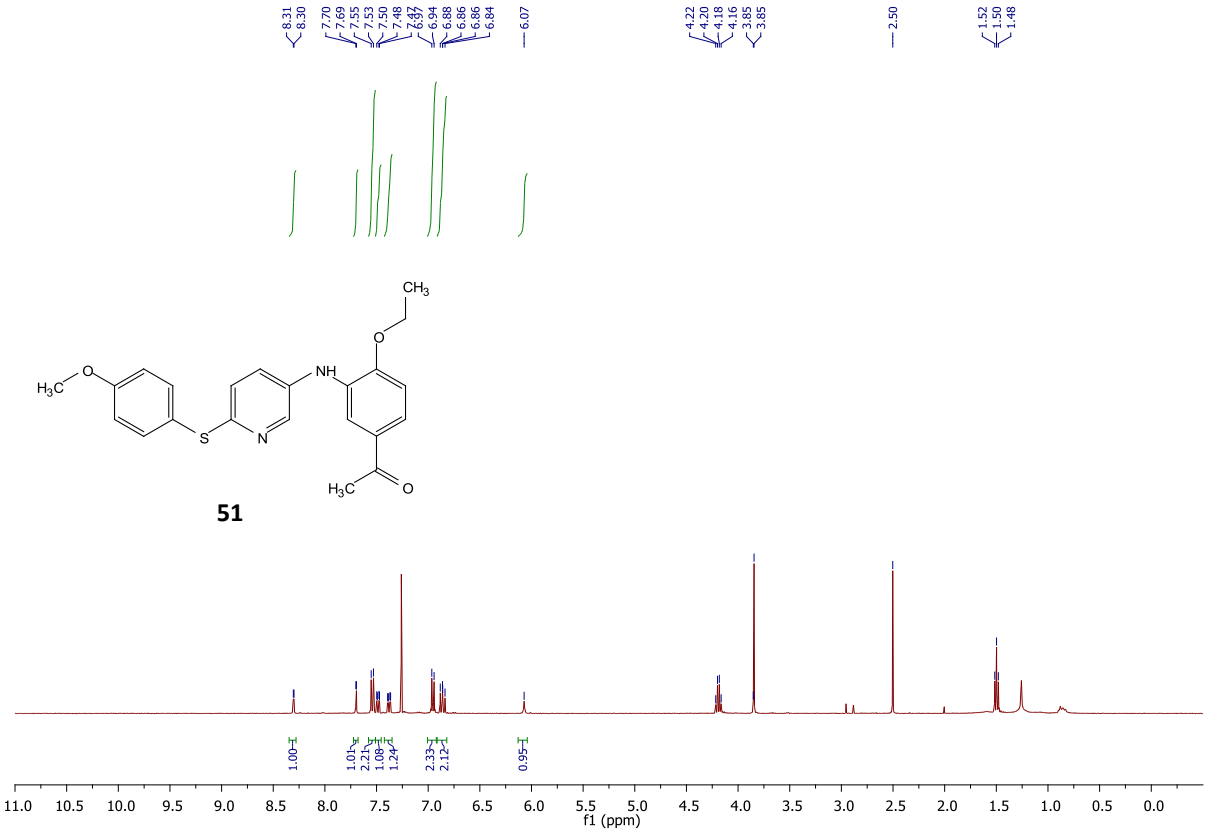
49

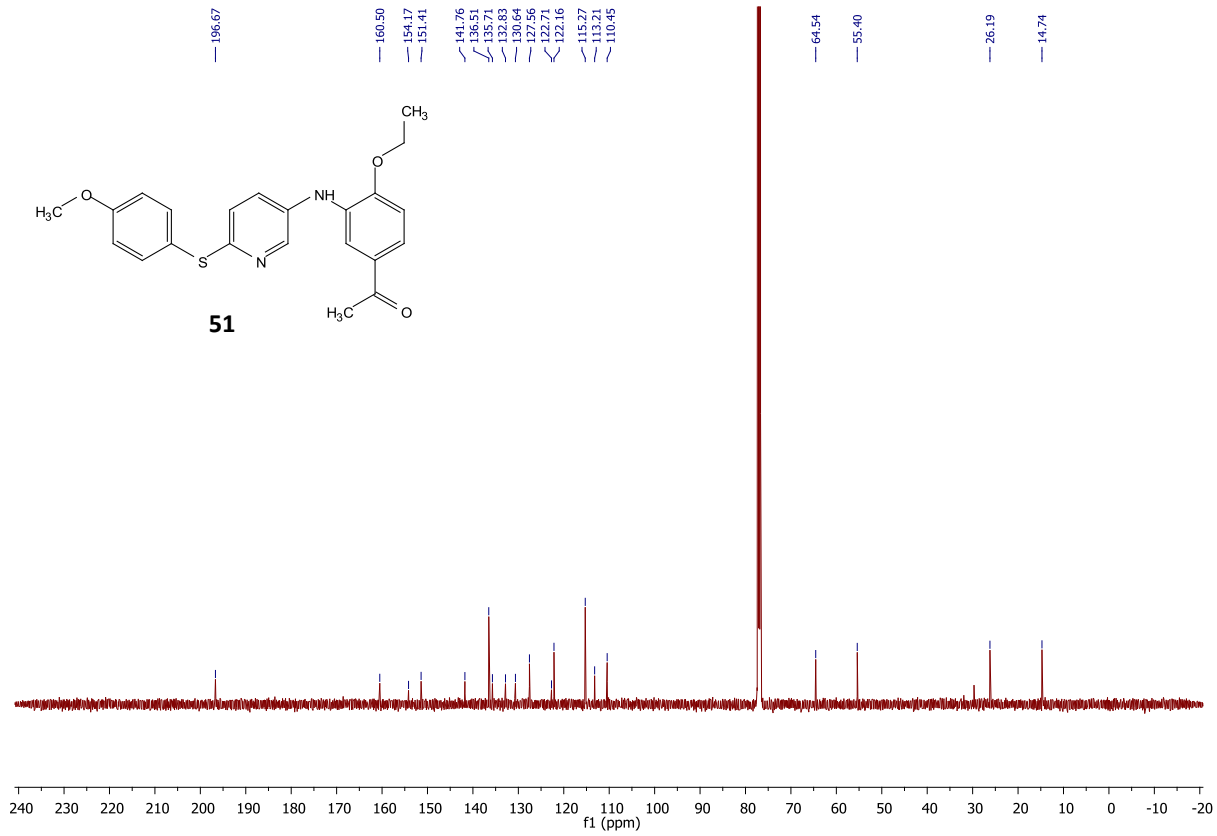

7.84
7.83
7.62
7.62
7.51
7.51
7.49
7.49
7.32
7.30
7.30
7.29
7.29
7.27
7.21
7.20
7.19
7.18
7.17
6.89
6.87
6.22
4.21
4.19
4.18
4.16
3.75
3.73
3.71
3.69
2.52
2.23
1.52
1.50
1.48
1.13
1.11
1.09
CH3
N
O
S
O
O
NH
O
CH3
H3C
H3C
O
1.00
1.00
1.01
3.96
3.05
1.01
0.66
2.03
2.10
3.04
3.07
3.20
3.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

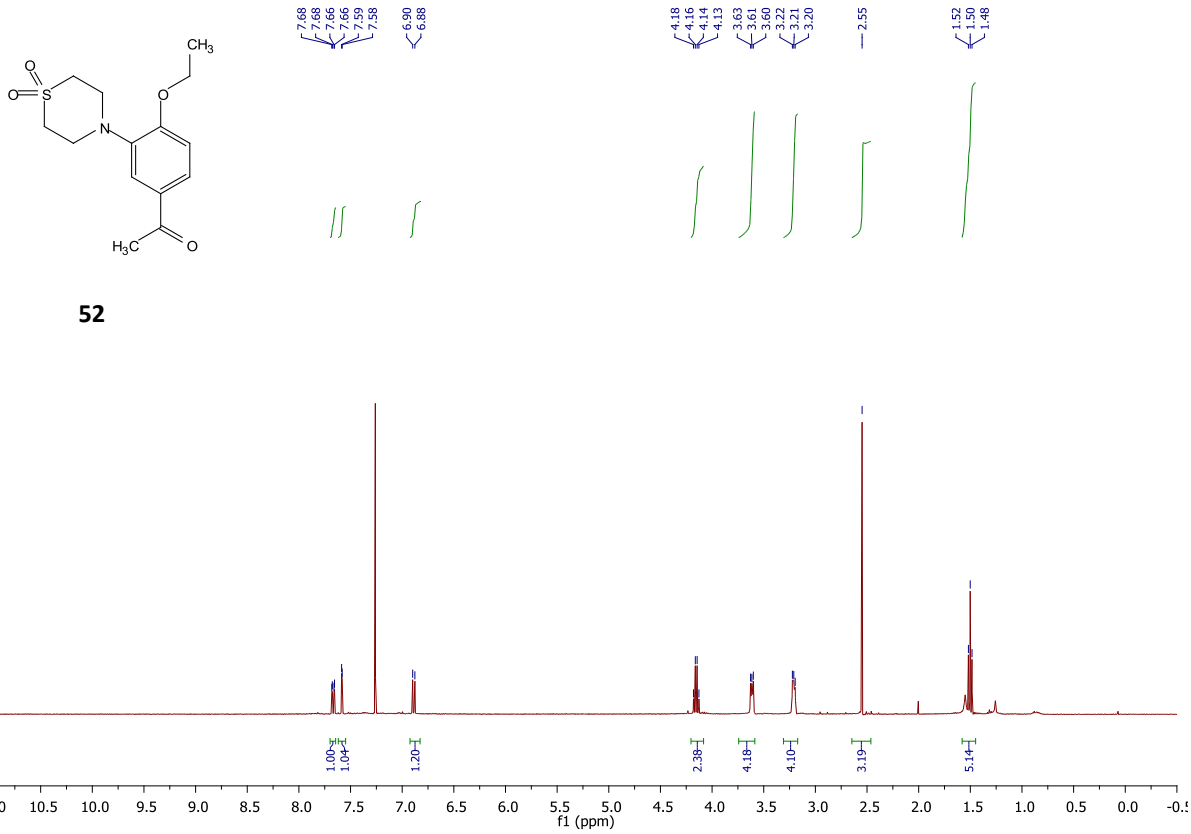
50


196.92
151.31
140.13
138.53
137.66
133.57
132.52
130.71
130.27
129.16
129.06
127.86
122.63
122.09
120.68
113.07
110.24
64.43
45.87
26.29
19.85
14.77
14.03
CH3
N
O
S
O
O
NH
O
CH3
H3C
H3C
O
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
f1 (ppm)

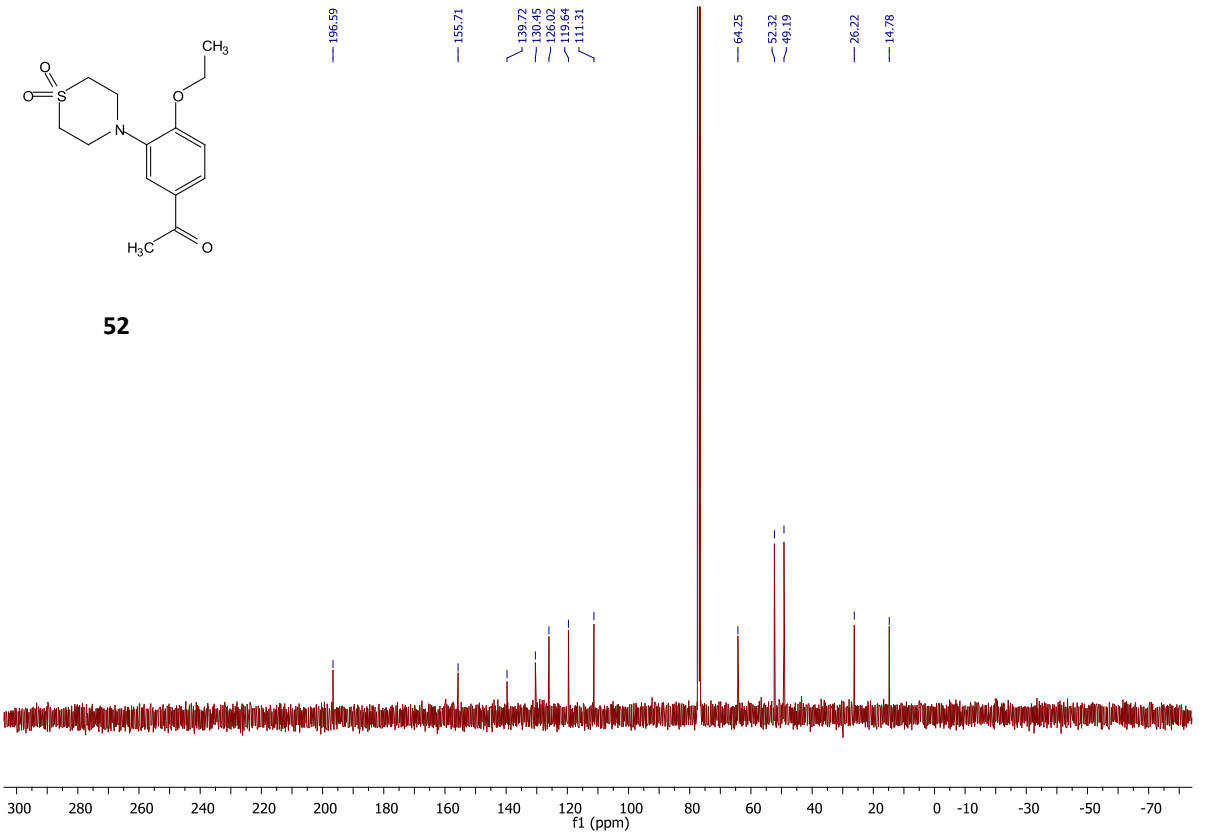
50


8.31
8.30
7.70
7.69
7.55
7.53
7.50
7.48
7.47
6.97
6.94
6.88
6.86
6.86
6.84
6.07
4.22
4.20
4.18
4.16
3.85
3.85
2.50
1.52
1.50
1.48
CH3
O
NH
H3C
O
S
N
H3C
O
51
1.00
1.01
2.21
1.08
1.24
2.33
2.12
0.95
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

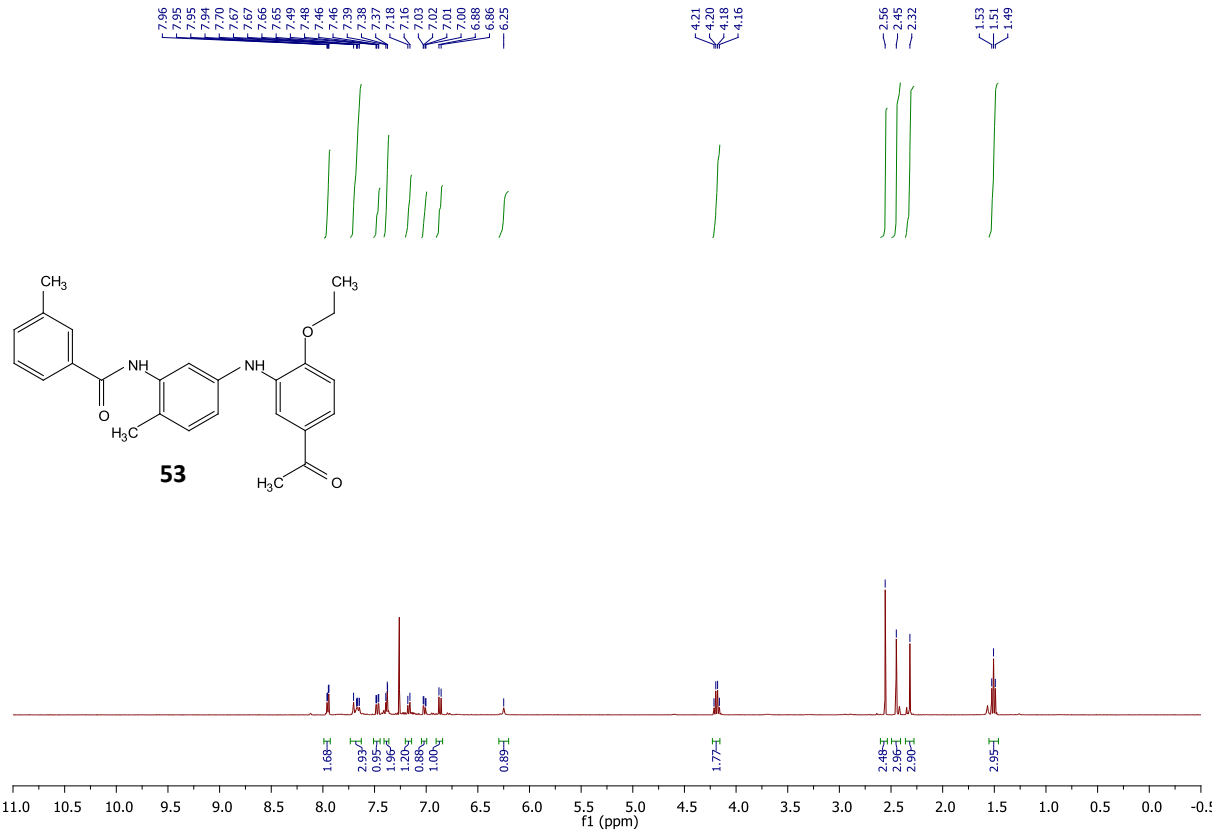

196.67
160.50
154.17
151.41
141.76
136.51
135.71
132.83
130.64
127.56
122.71
122.16
115.27
113.21
110.45
64.54
55.40
26.19
14.74
CH3
O
NH
H3C
O
S
N
H3C
O
51
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

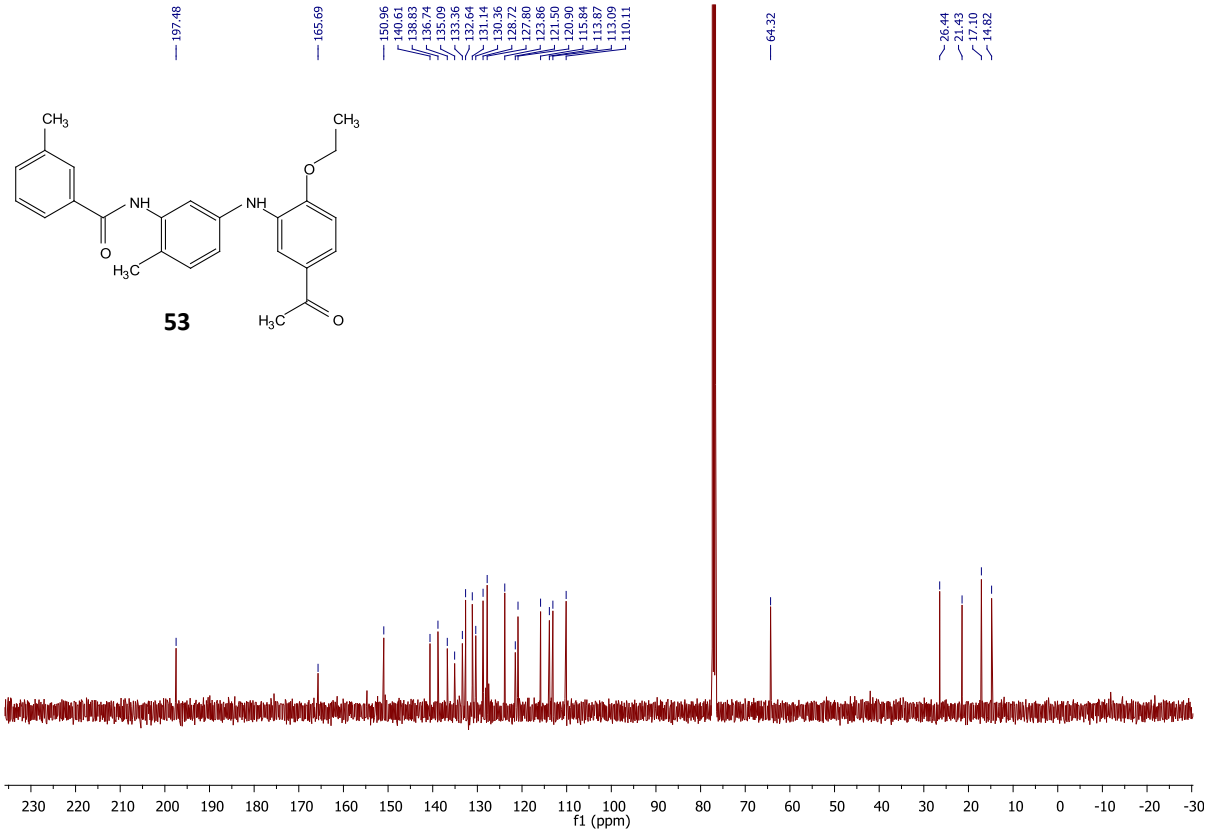

7.68
7.68
7.66
7.66
7.59
7.58
6.90
6.88
4.18
4.16
4.14
4.13
3.63
3.61
3.60
3.22
3.21
3.20
2.55
1.52
1.50
1.48
1.00
1.04
1.20
2.38
4.18
4.10
3.19
5.14
f1 (ppm)

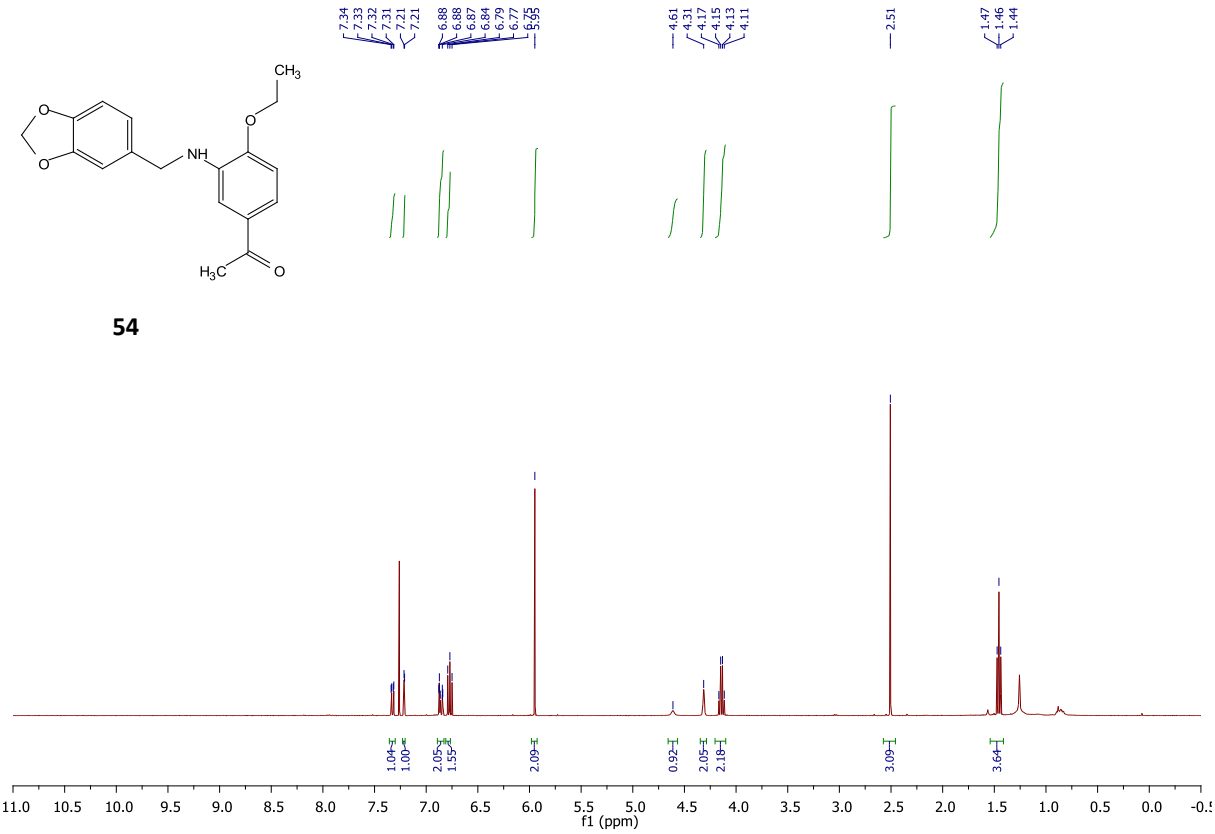
52


196.59
155.71
139.72
130.45
126.02
119.64
111.31
64.25
52.32
49.19
26.22
14.78
f1 (ppm)

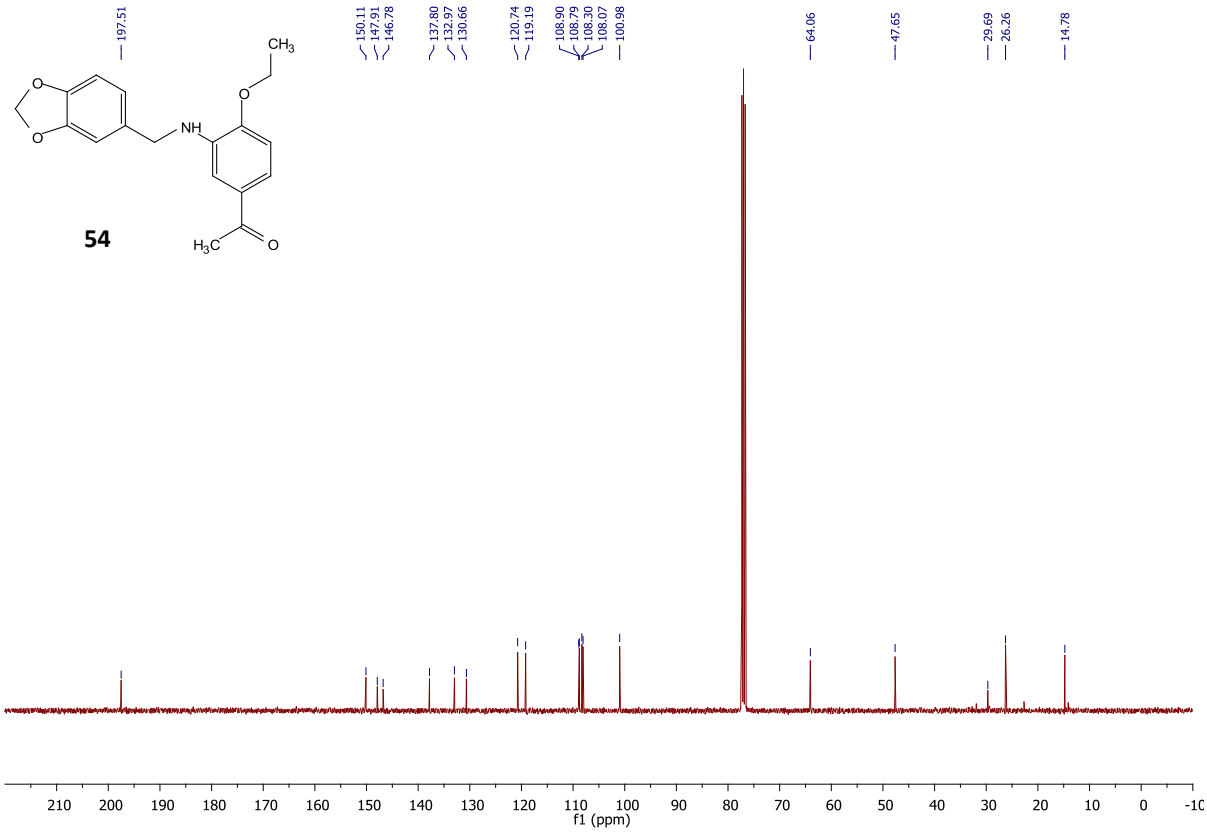
52


7.96
7.95
7.95
7.94
7.70
7.67
7.67
7.66
7.65
7.49
7.48
7.46
7.46
7.39
7.38
7.37
7.18
7.16
7.03
7.02
7.01
7.00
6.88
6.86
6.25
4.21
4.20
4.18
4.16
2.56
2.45
2.32
1.53
1.51
1.49
CH3
NH
NH
O
O
H3C
CH3
O
H3C
O
53
1.68
2.93
0.95
1.96
1.20
0.88
1.00
0.89
1.77
2.48
2.96
2.90
2.95
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

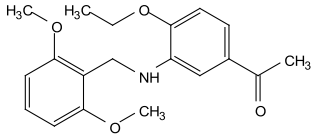

197.48
165.69
150.96
140.61
138.83
136.74
135.09
133.36
132.64
131.14
130.36
128.72
127.80
123.86
121.50
120.90
115.84
113.87
113.09
110.11
64.32
26.44
21.43
17.10
14.82
CH3
NH
NH
O
O
H3C
CH3
O
H3C
O
53
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


7.34
7.33
7.32
7.31
7.21
7.21
6.88
6.88
6.87
6.84
6.79
6.77
5.95
4.61
4.31
4.17
4.15
4.13
4.11
2.51
1.47
1.46
1.44
CH3
O
O
NH
O
H3C
O
1.04
1.00
2.05
1.55
2.09
0.92
2.05
2.18
3.09
3.64
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

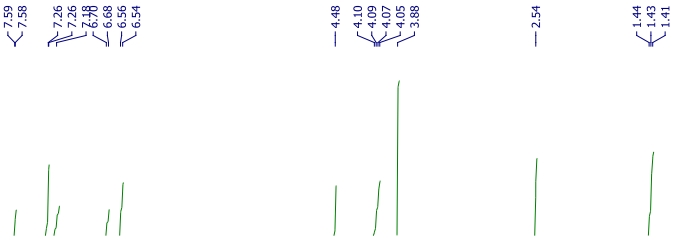
54

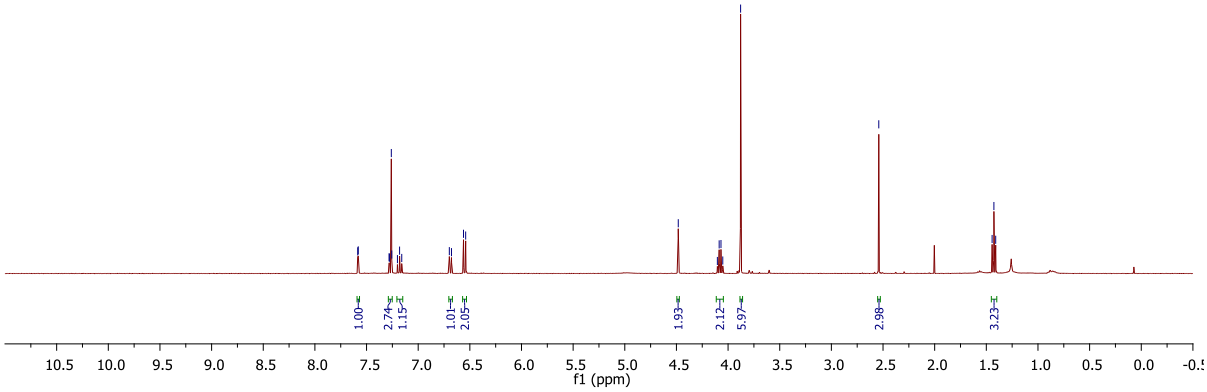

197.51
150.11
147.91
146.78
137.80
132.97
130.66
120.74
119.19
108.90
108.79
108.30
108.07
100.98
64.06
47.65
29.69
26.26
14.78
CH3
O
O
NH
O
H3C
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

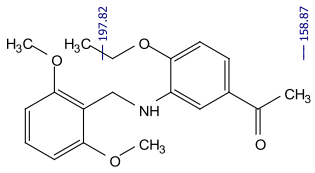
54



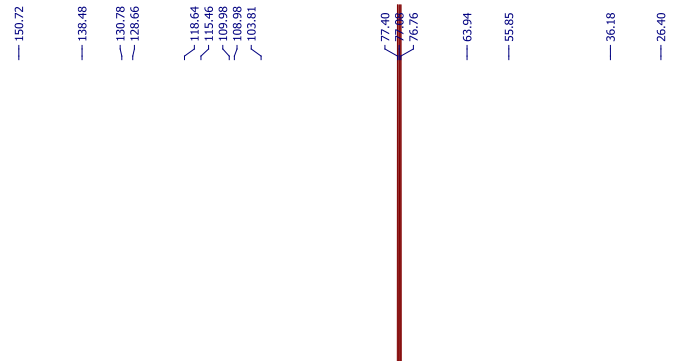
55

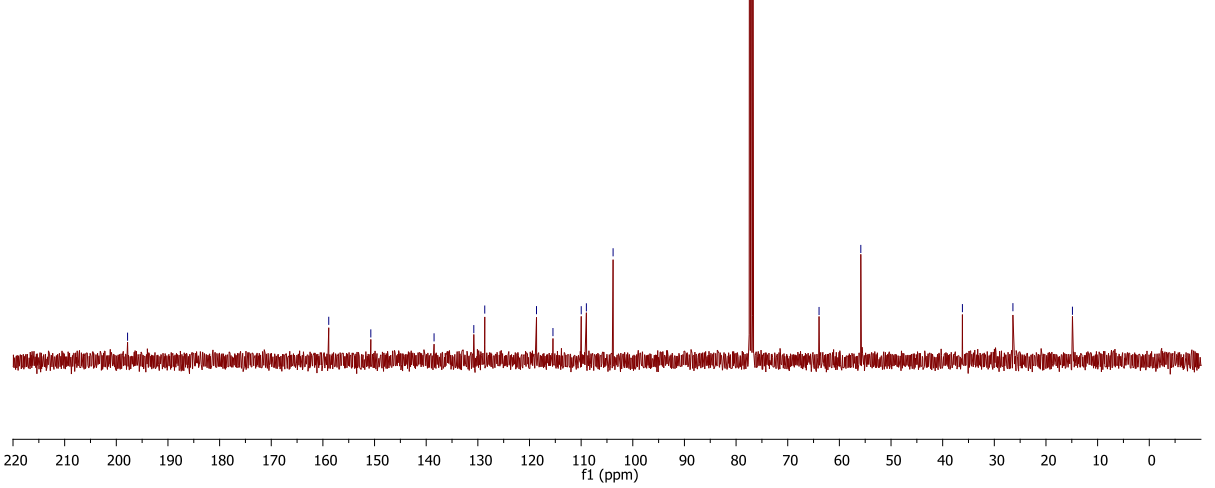

7.59
7.58
7.26
7.26
7.18
6.70
6.68
6.56
6.54
4.48
4.10
4.09
4.07
4.05
3.88
2.54
1.44
1.43
1.41


1.00
2.74
1.15
1.01
2.05
1.93
2.12
5.97
2.98
3.23
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

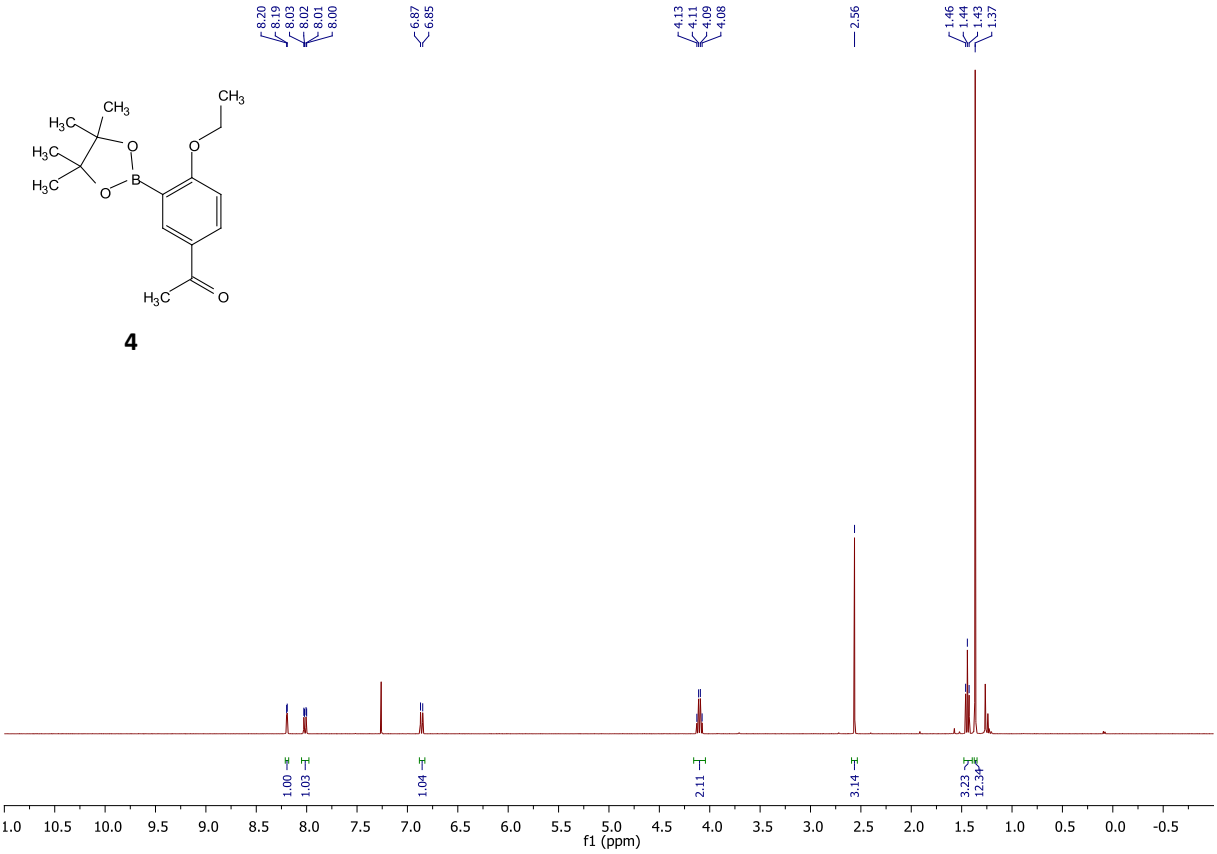


55

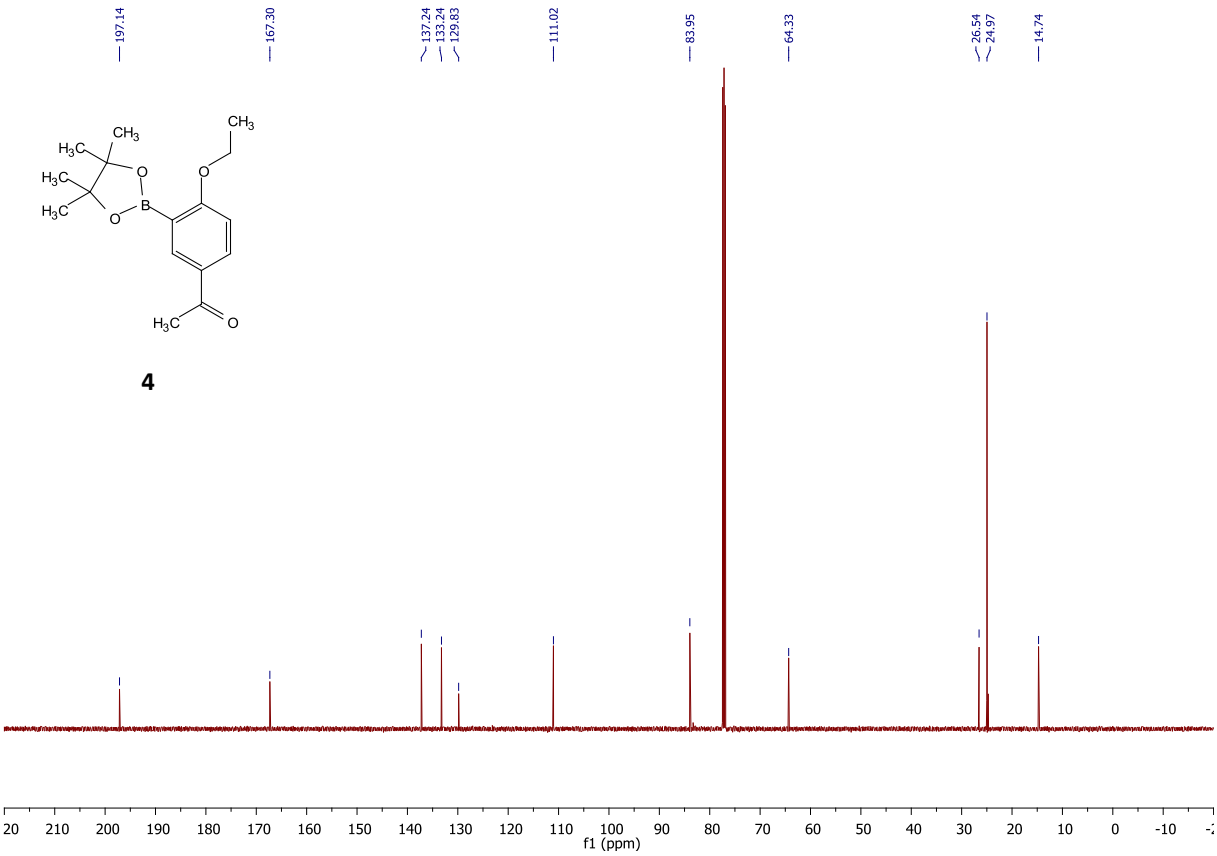

197.82
158.87
150.72
138.48
130.78
128.66
118.64
115.46
109.98
108.98
103.81
77.40
77.08
76.76
63.94
55.85
36.18
26.40
14.87


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

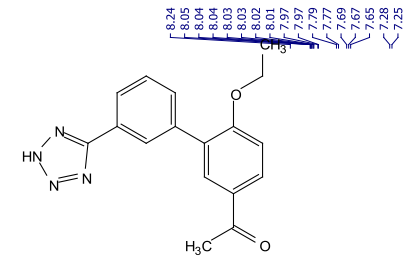
CBP inhibitors without a linker:



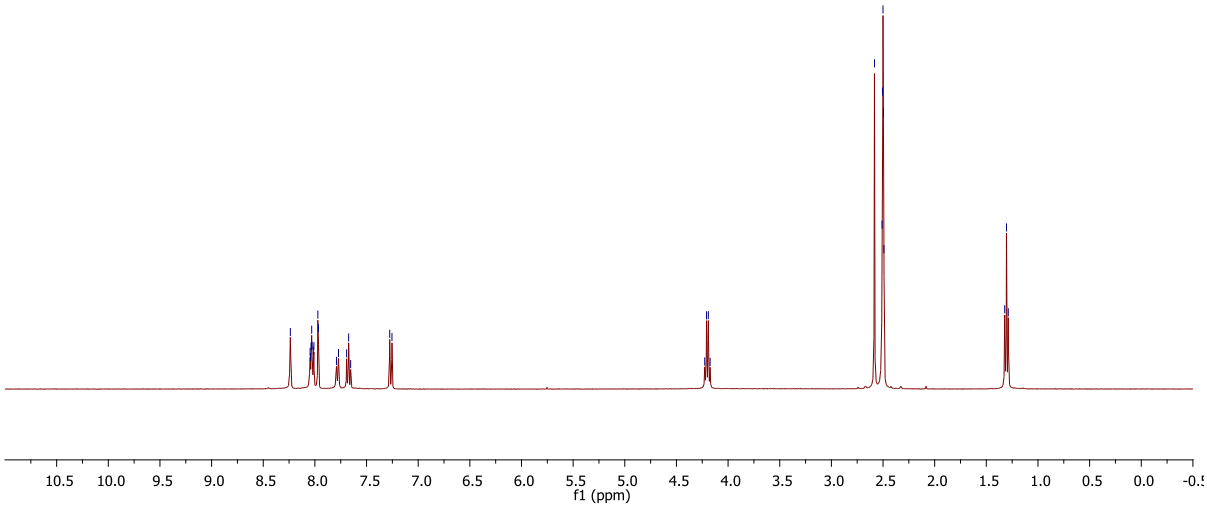
4

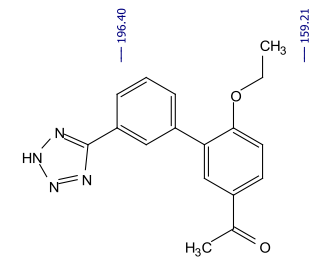


4

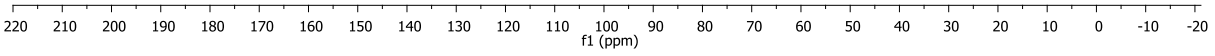

8.24
8.05
8.04
8.04
8.04
8.03
8.03
8.02
8.01
7.97
7.97
7.79
7.77
7.69
7.67
7.65
7.28
7.25
4.23
4.21
4.19
4.17
2.58
2.51
2.50
2.50
2.50
2.50
2.49
1.32
1.30
1.29
CH3
O
N
HN
N
N
H3C
O

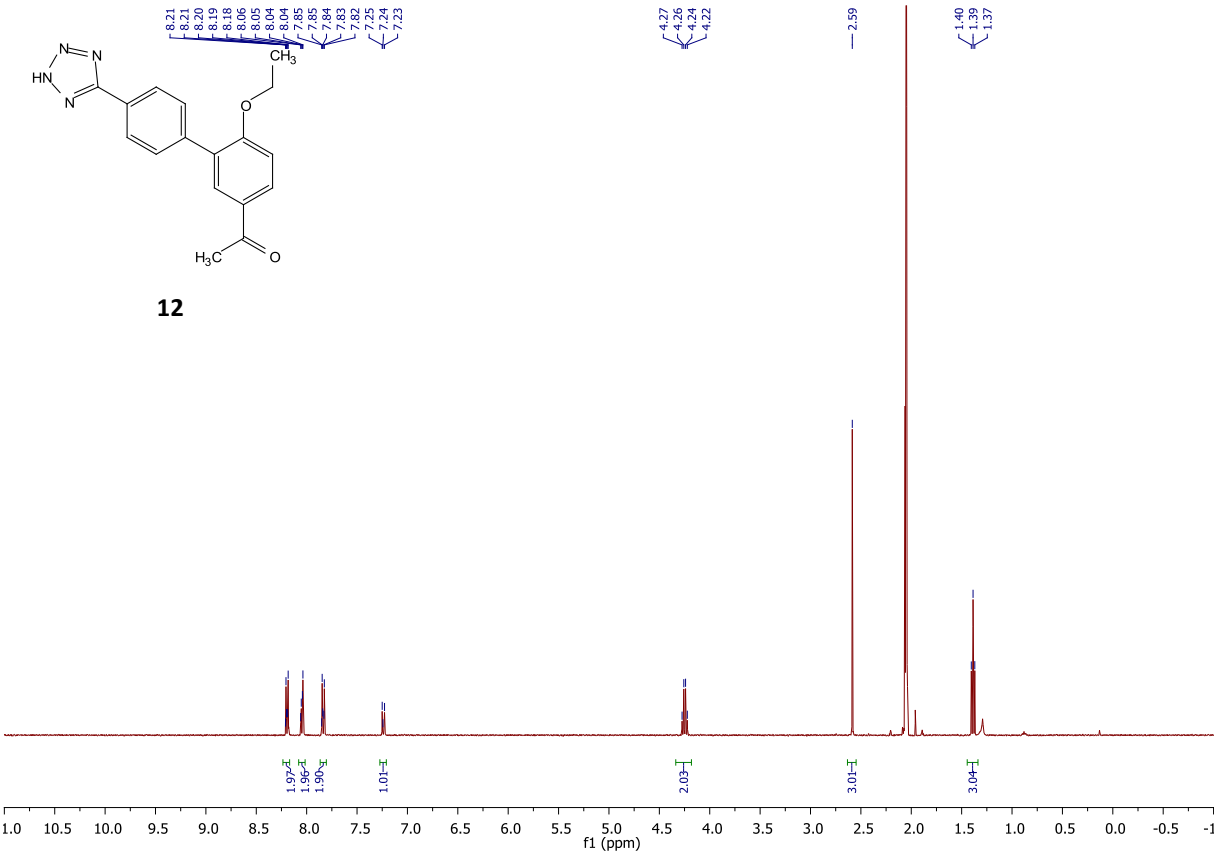
11


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

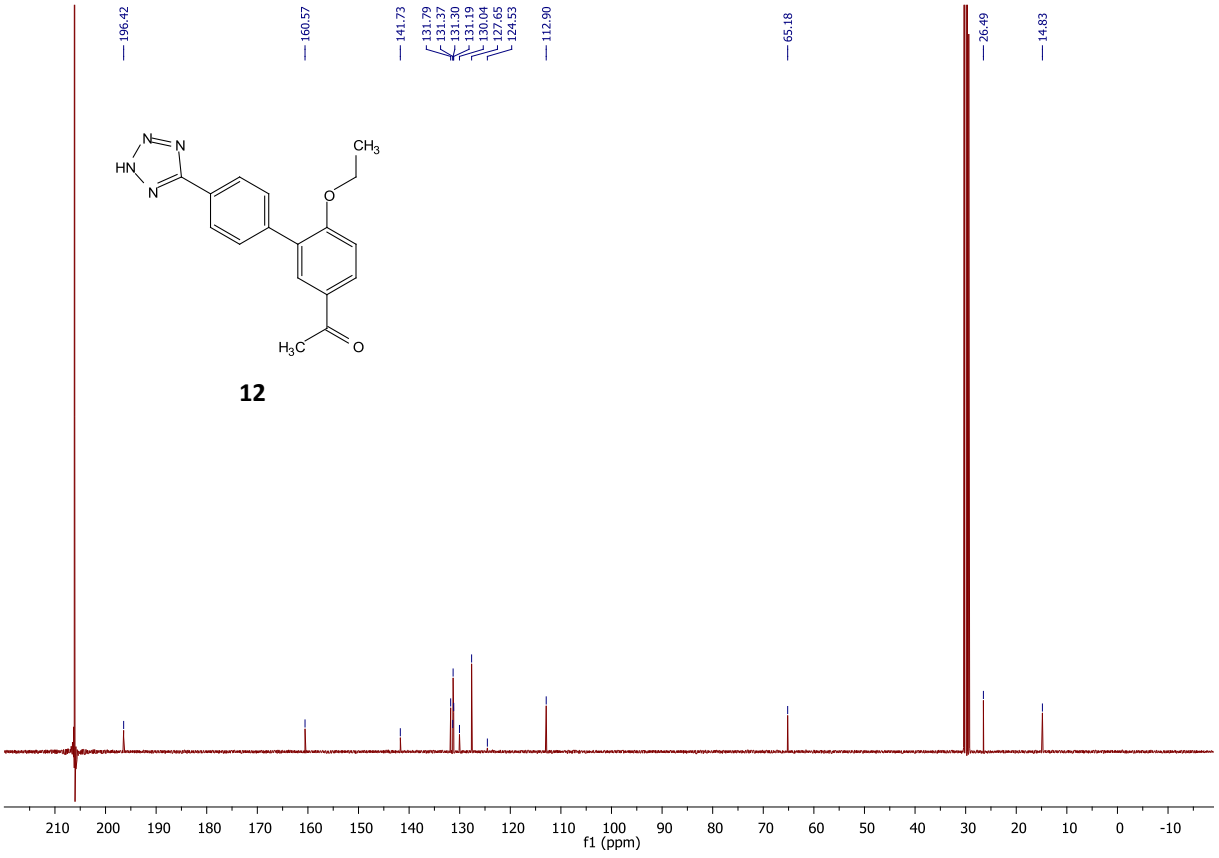

196.40
159.21
138.37
132.13
130.66
130.47
129.88
129.24
128.45
127.79
125.80
112.33
64.18
26.51
14.32
CH3
O
N
HN
N
N
H3C
O

11

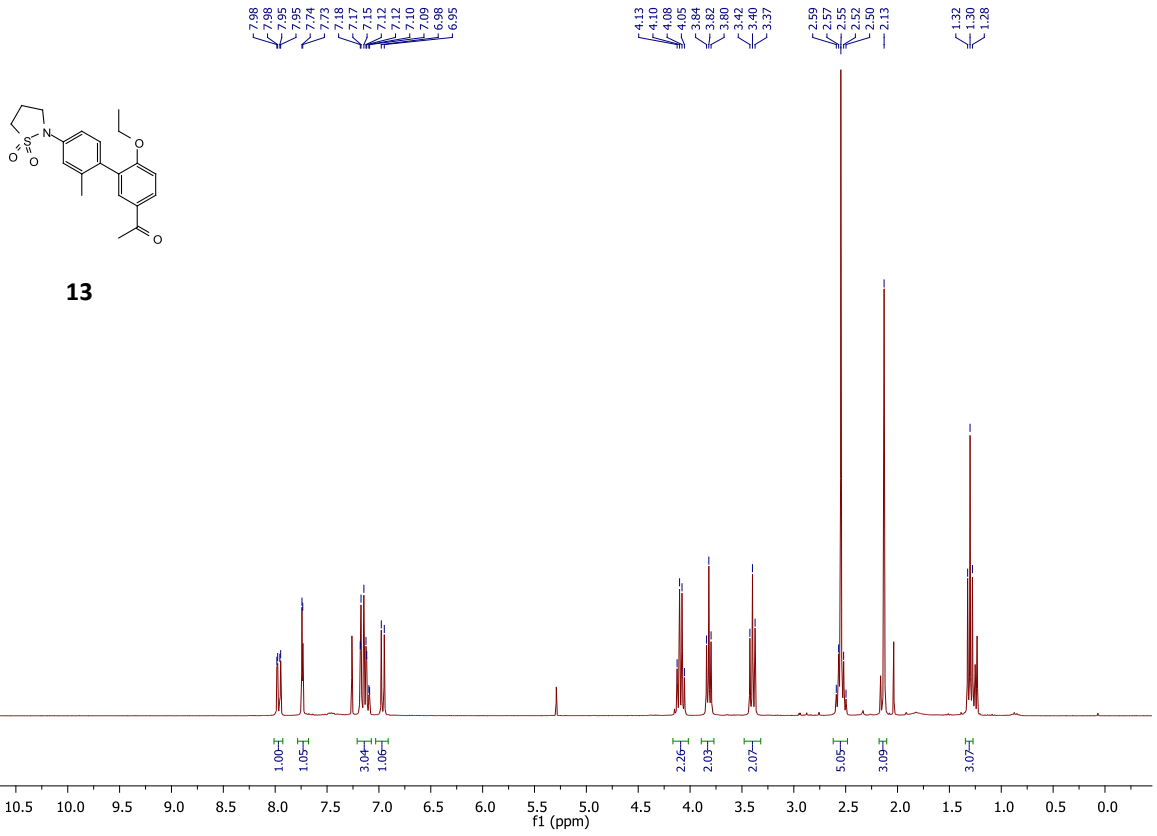

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


8.21
8.21
8.20
8.19
8.18
8.06
8.05
8.04
8.04
7.85
7.85
7.84
7.83
7.82
7.25
7.24
7.23
4.27
4.26
4.24
4.22
2.59
1.40
1.39
1.37
1.97
1.96
1.90
1.01
2.03
3.01
3.04
f1 (ppm)

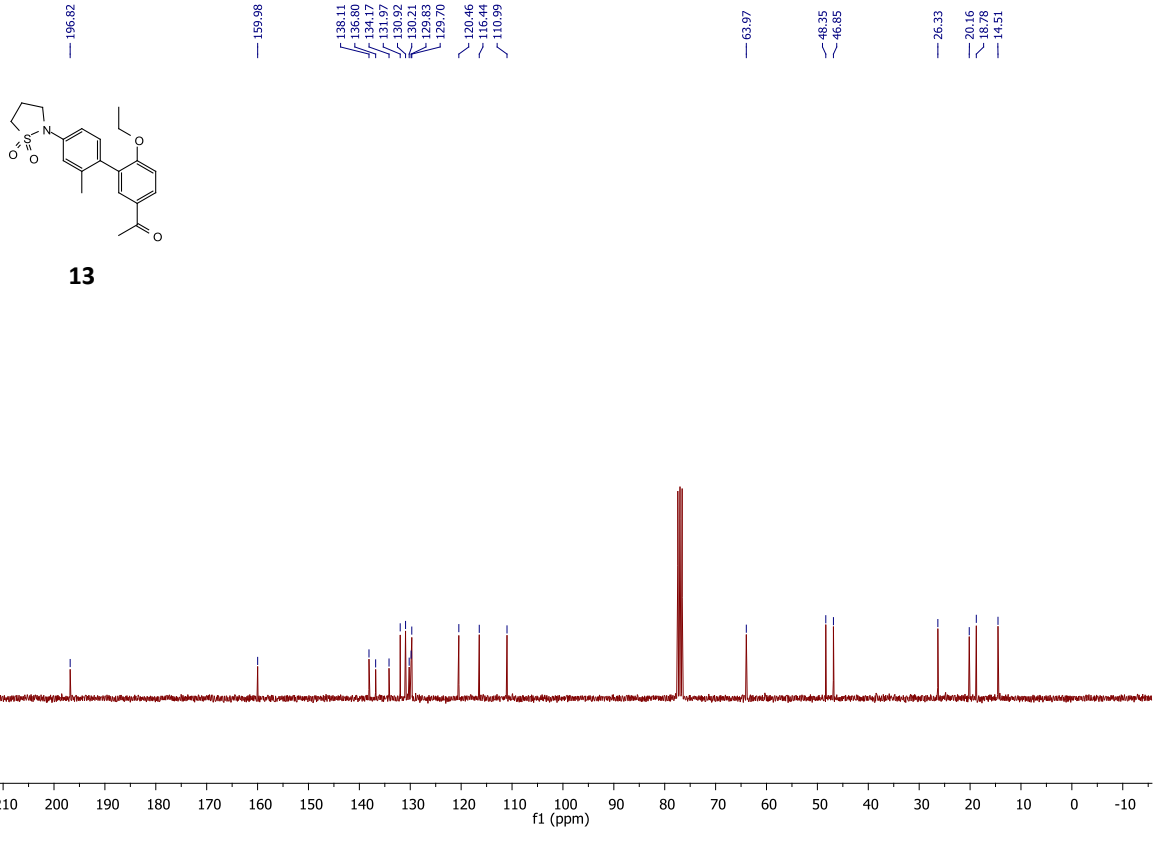
12


196.42
160.57
141.73
131.79
131.37
131.30
131.19
130.04
127.65
124.53
112.90
65.18
26.49
14.83
f1 (ppm)

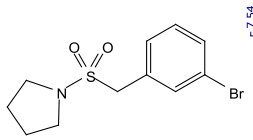
12


7.98
7.98
7.95
7.95
7.74
7.73
7.18
7.17
7.15
7.12
7.12
7.10
7.09
6.98
6.95
4.13
4.10
4.08
4.05
3.84
3.82
3.80
3.42
3.40
3.37
2.59
2.57
2.55
2.52
2.50
2.13
1.32
1.30
1.28
1.00
1.05
3.04
1.06
2.26
2.03
2.07
5.05
3.09
3.07
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

13

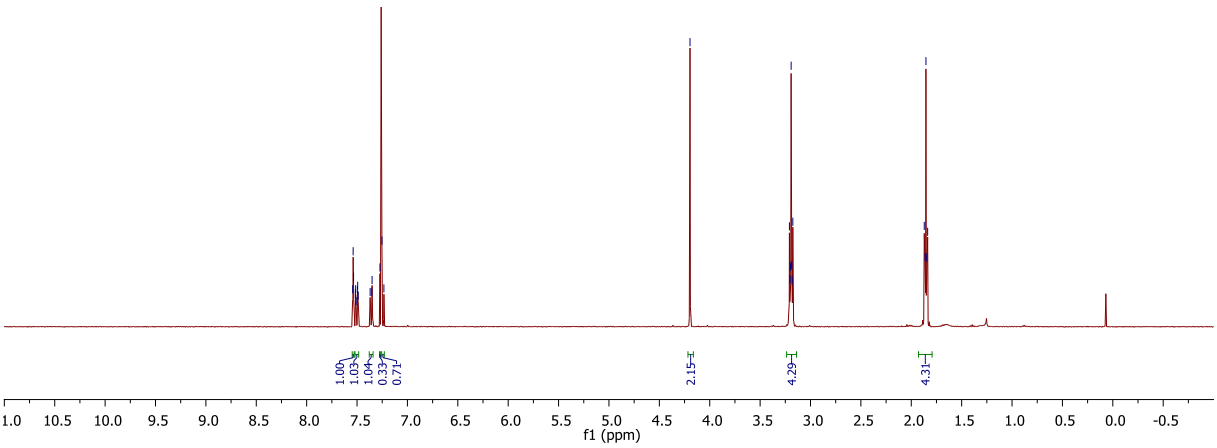

196.82
159.98
138.11
136.80
134.17
131.97
130.92
130.21
129.83
129.70
120.46
116.44
110.99
63.97
48.35
46.85
26.33
20.16
18.78
14.51
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

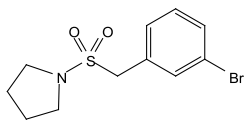
13


O
O
S
N
Br

133

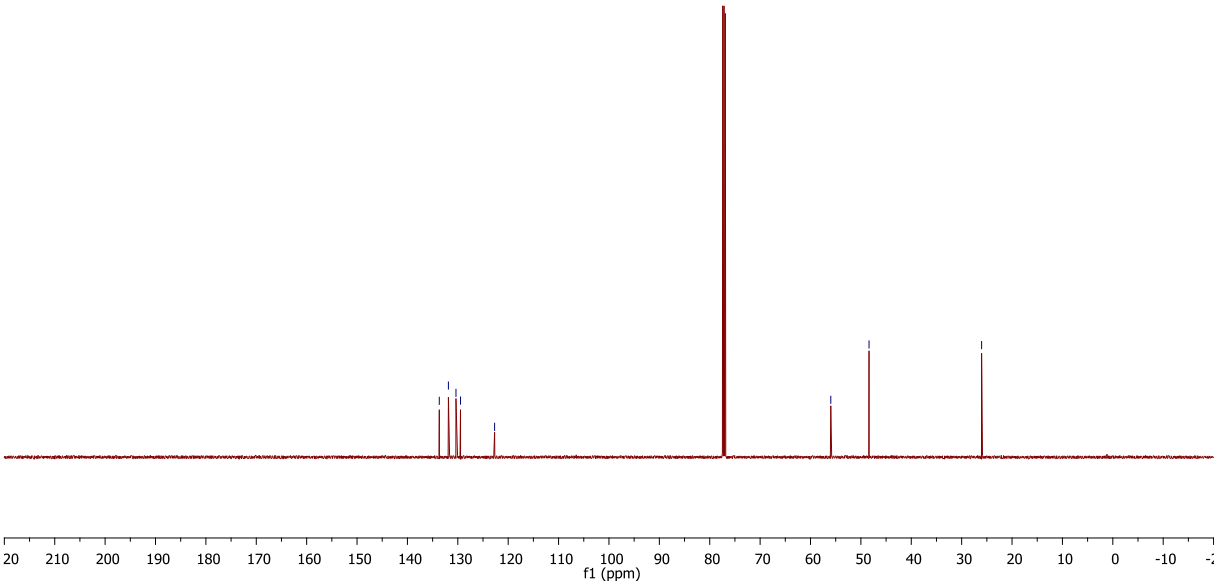

7.54
7.54
7.53
7.52
7.51
7.51
7.50
7.49
7.49
7.37
7.35
7.35
7.27
7.25
7.23
4.20
3.21
3.20
3.20
3.19
3.19
3.18
3.18
1.87
1.86
1.85
1.85
1.84

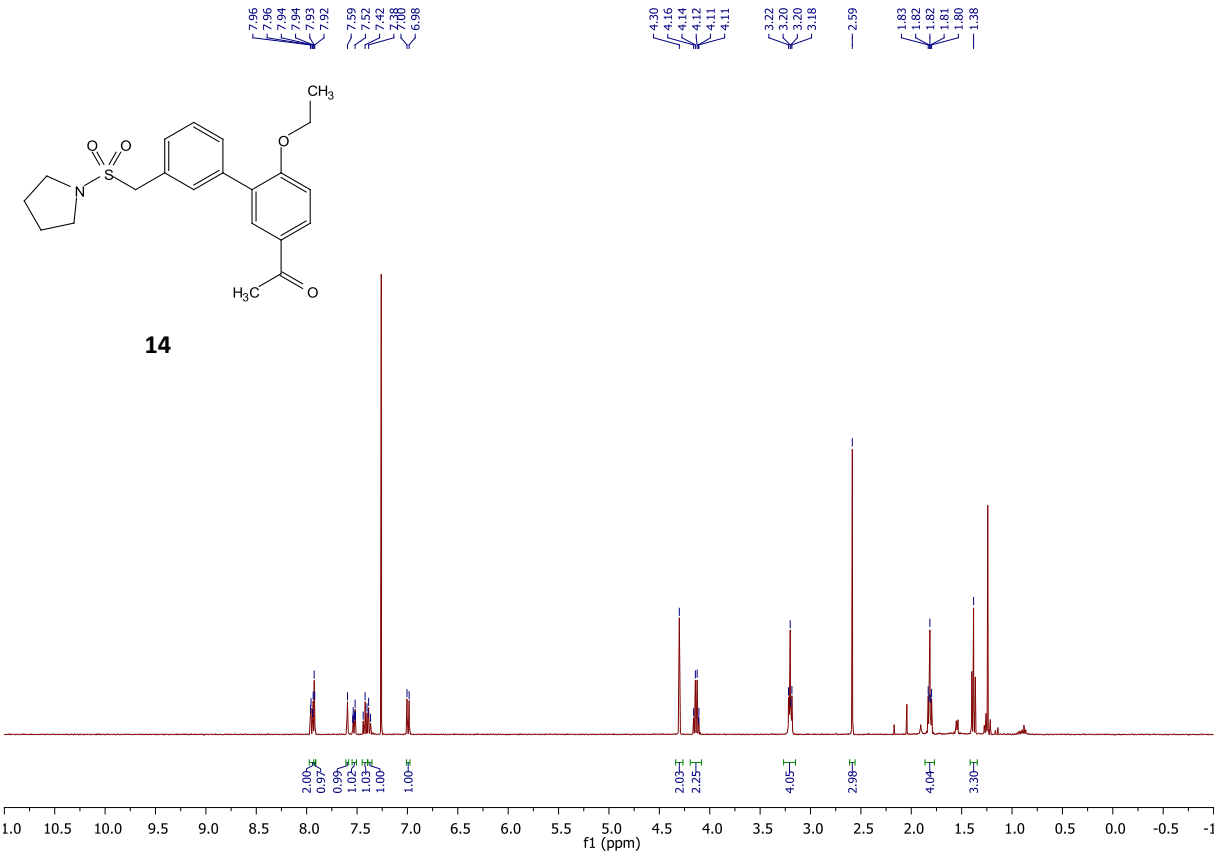

1.00
1.03
1.04
0.33
0.71
2.15
4.29
4.31
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


O
O
S
N
Br

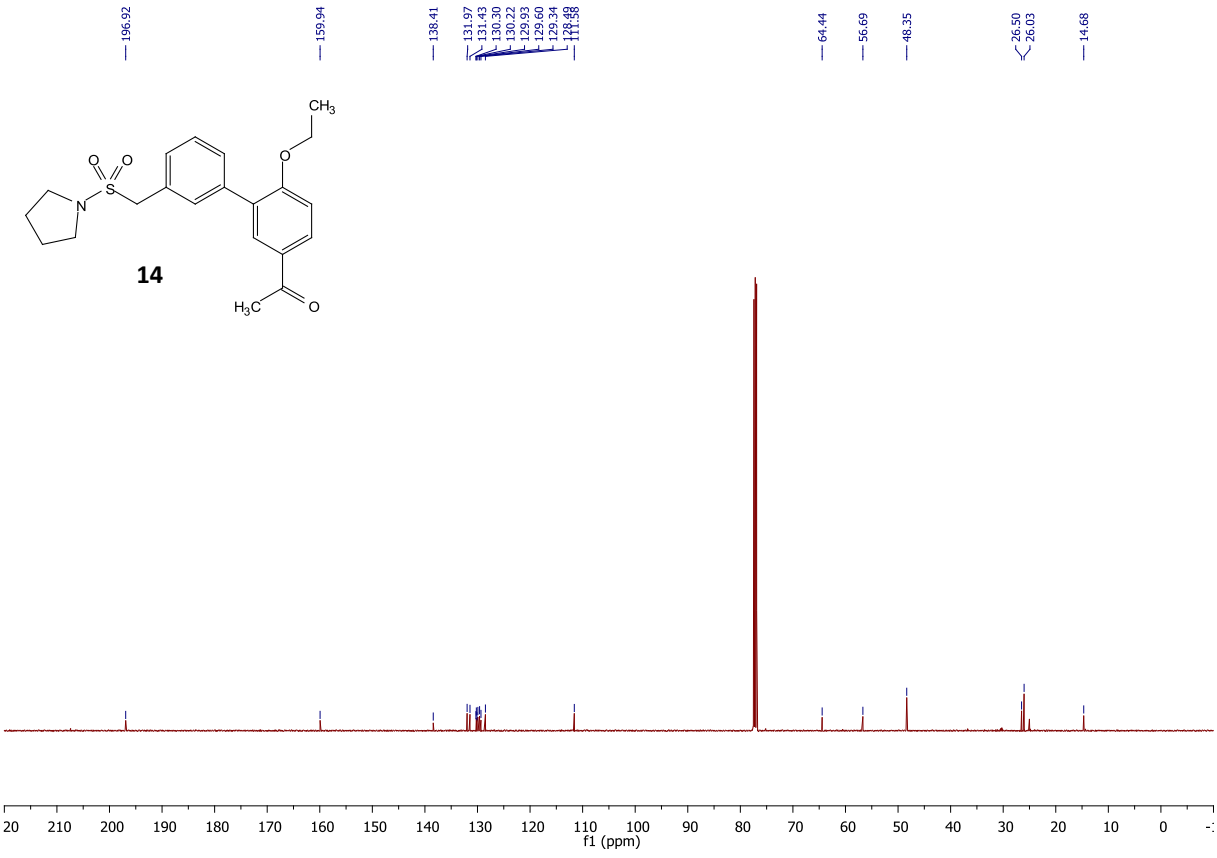
133


133.67
131.87
130.37
129.46
122.70
55.97
48.38
26.04

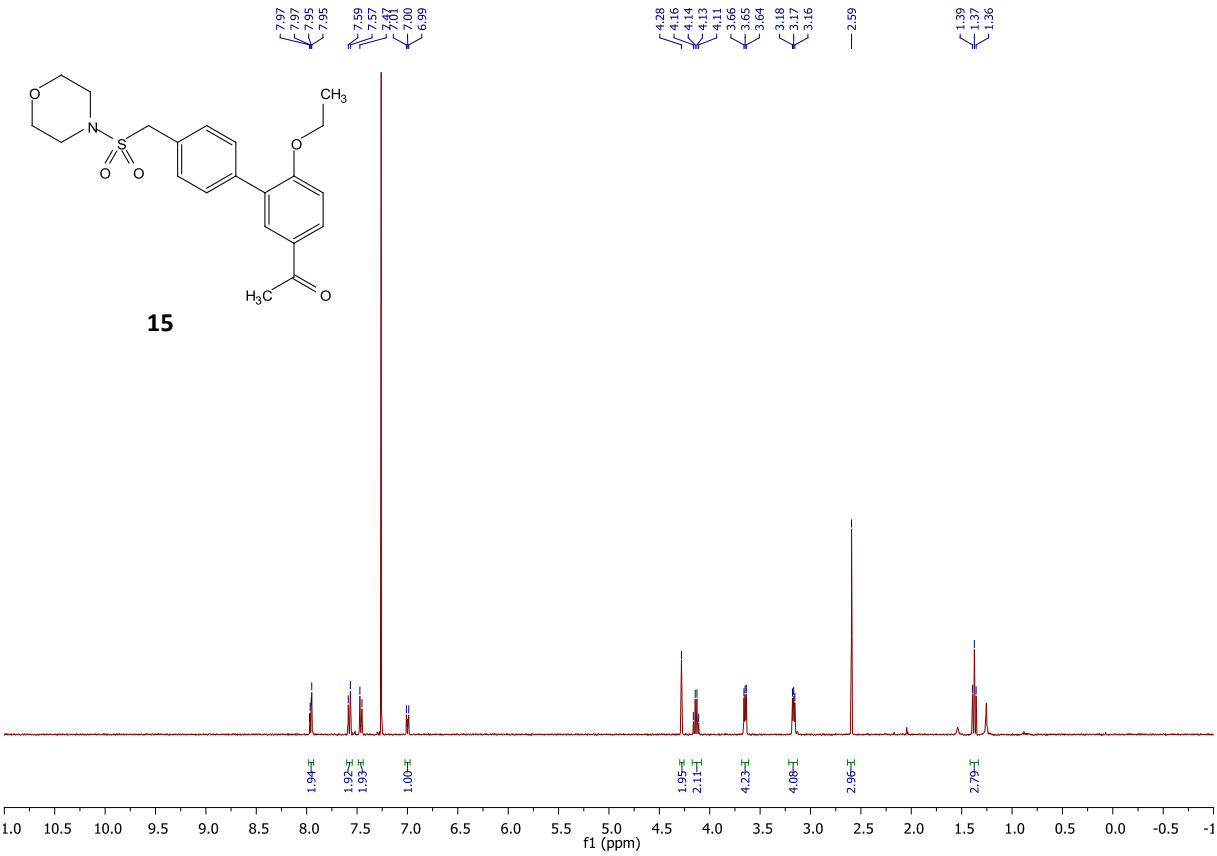

20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

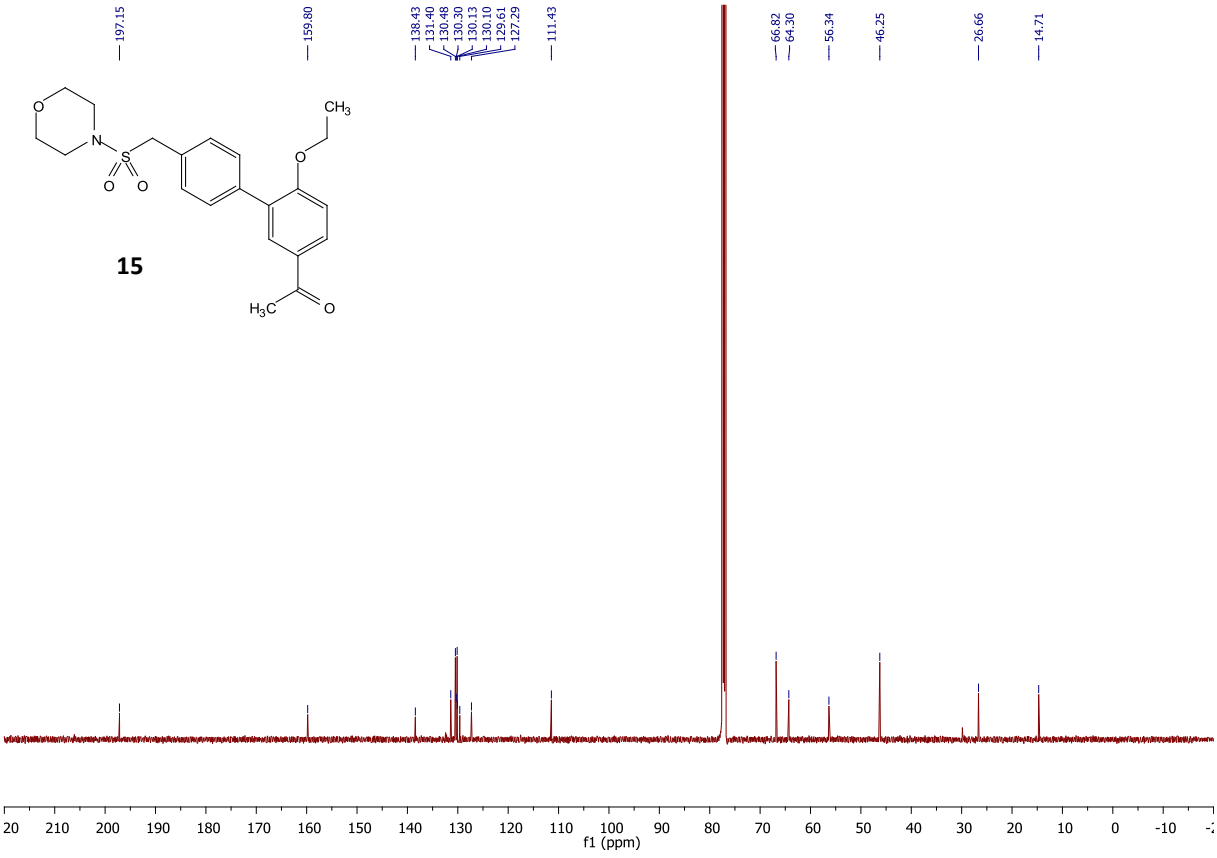

7.96
7.96
7.94
7.94
7.93
7.92
7.59
7.52
7.42
7.38
6.98
4.30
4.16
4.14
4.12
4.11
4.11
3.22
3.20
3.20
3.18
2.59
1.83
1.82
1.82
1.81
1.80
1.38
CH3
O
O
O
S
N
H3C
O
2.00
0.97
0.99
1.02
1.03
1.00
1.00
2.03
2.25
4.05
2.98
4.04
3.30
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

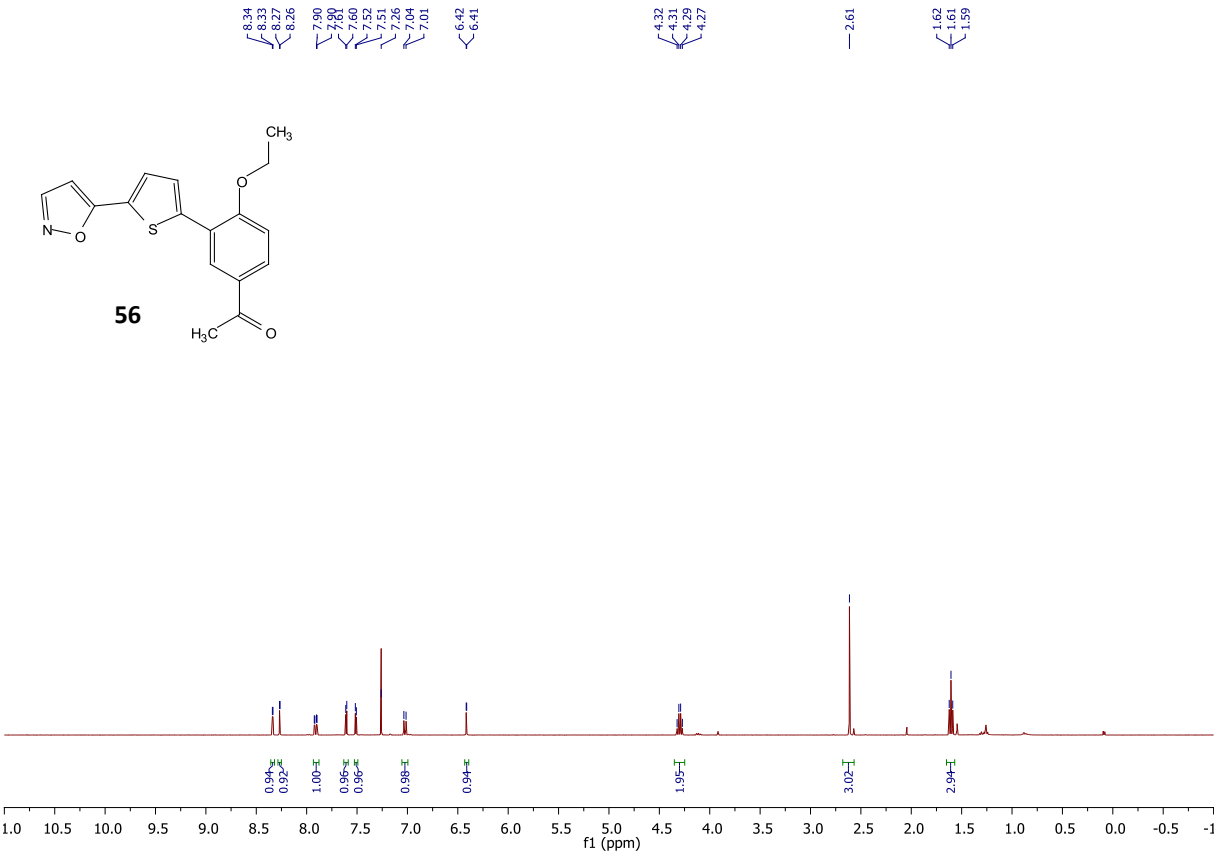
14


196.92
159.94
138.41
131.97
131.43
130.30
130.22
129.93
129.60
129.34
128.49
111.58
64.44
56.69
48.35
26.50
26.03
14.68
CH3
O
O
O
S
N
H3C
O
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

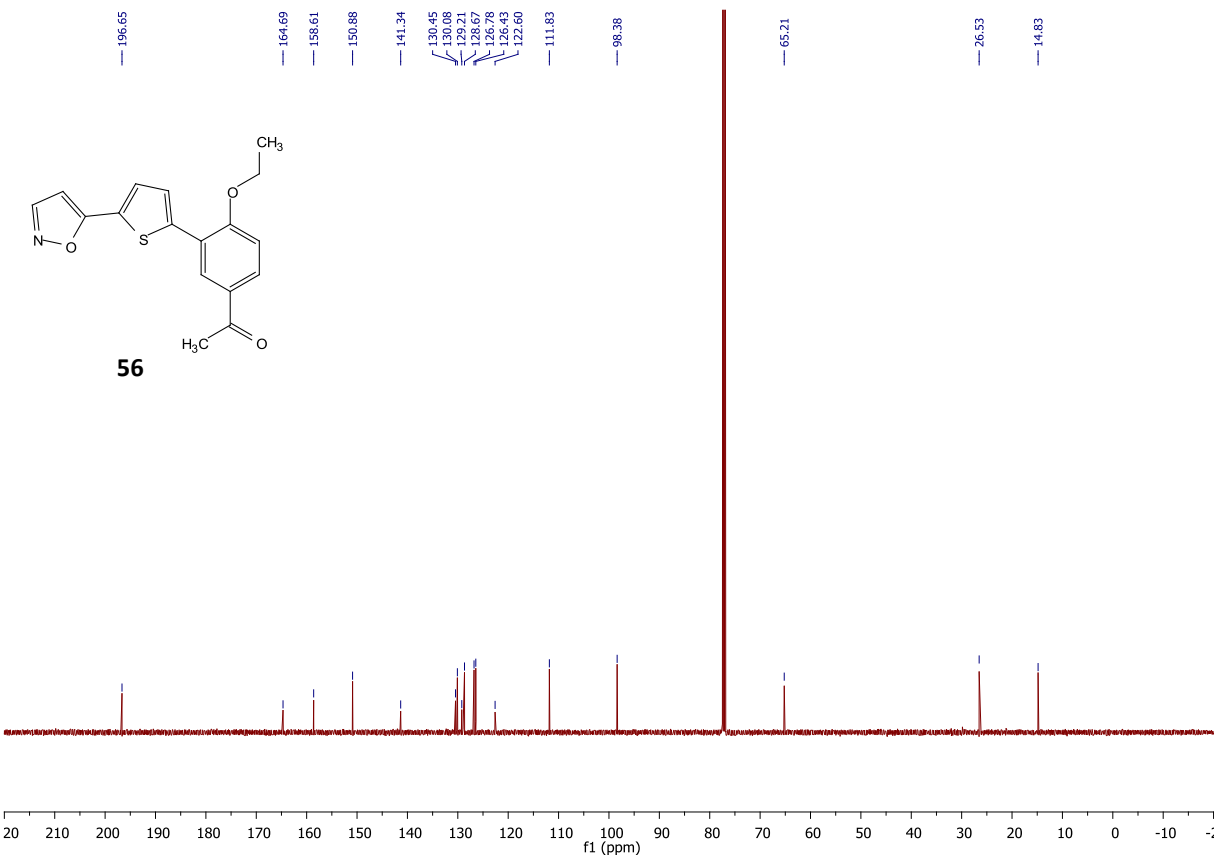
14


7.97
7.97
7.95
7.95
7.59
7.57
7.47
7.01
7.00
6.99
4.28
4.16
4.14
4.13
4.11
3.66
3.65
3.64
3.18
3.17
3.16
2.59
1.39
1.37
1.36
CH3
O
N
S
O
O
O
H3C
O
15
1.94
1.92
1.93
1.00
1.95
2.11
4.23
4.08
2.96
2.79
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

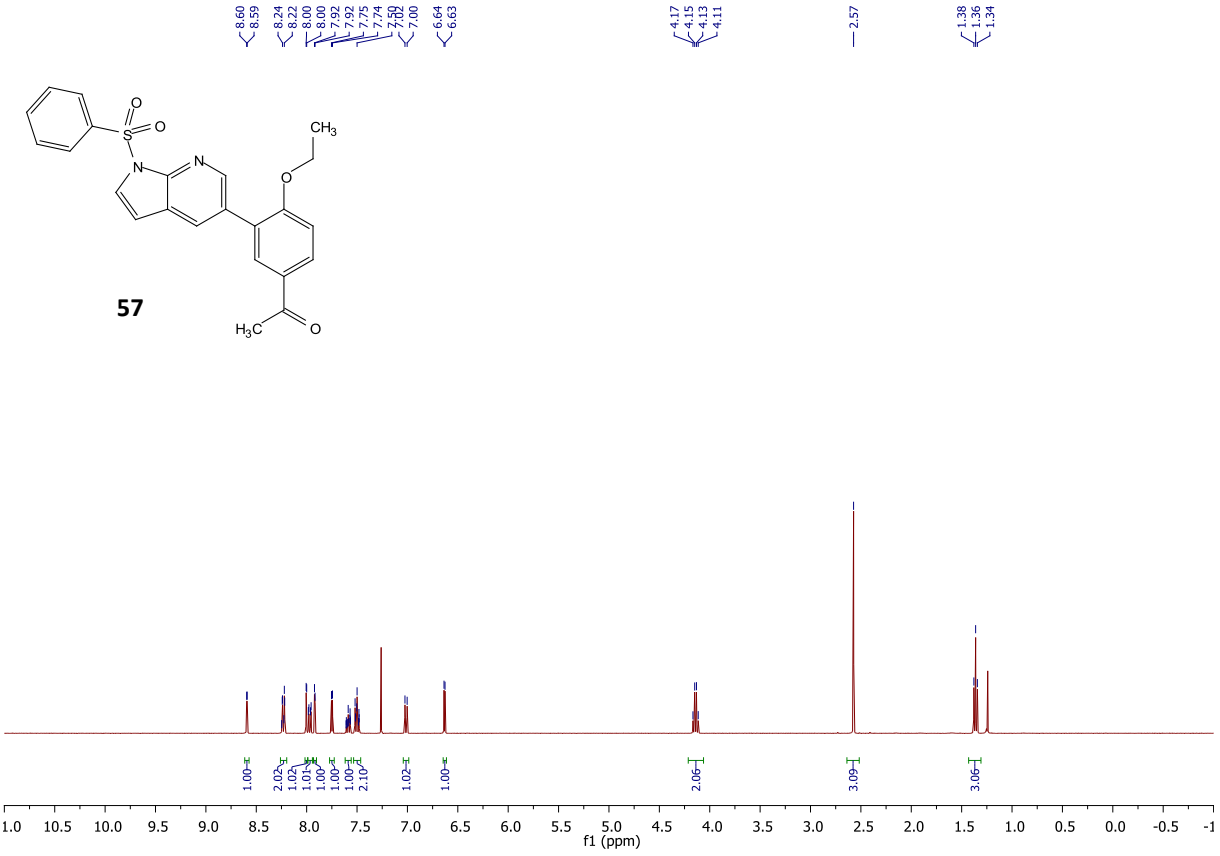

197.15
159.80
138.43
131.40
130.48
130.30
130.13
130.10
129.61
127.29
111.43
66.82
64.30
56.34
46.25
26.66
14.71
CH3
O
N
S
O
O
O
H3C
O
15
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

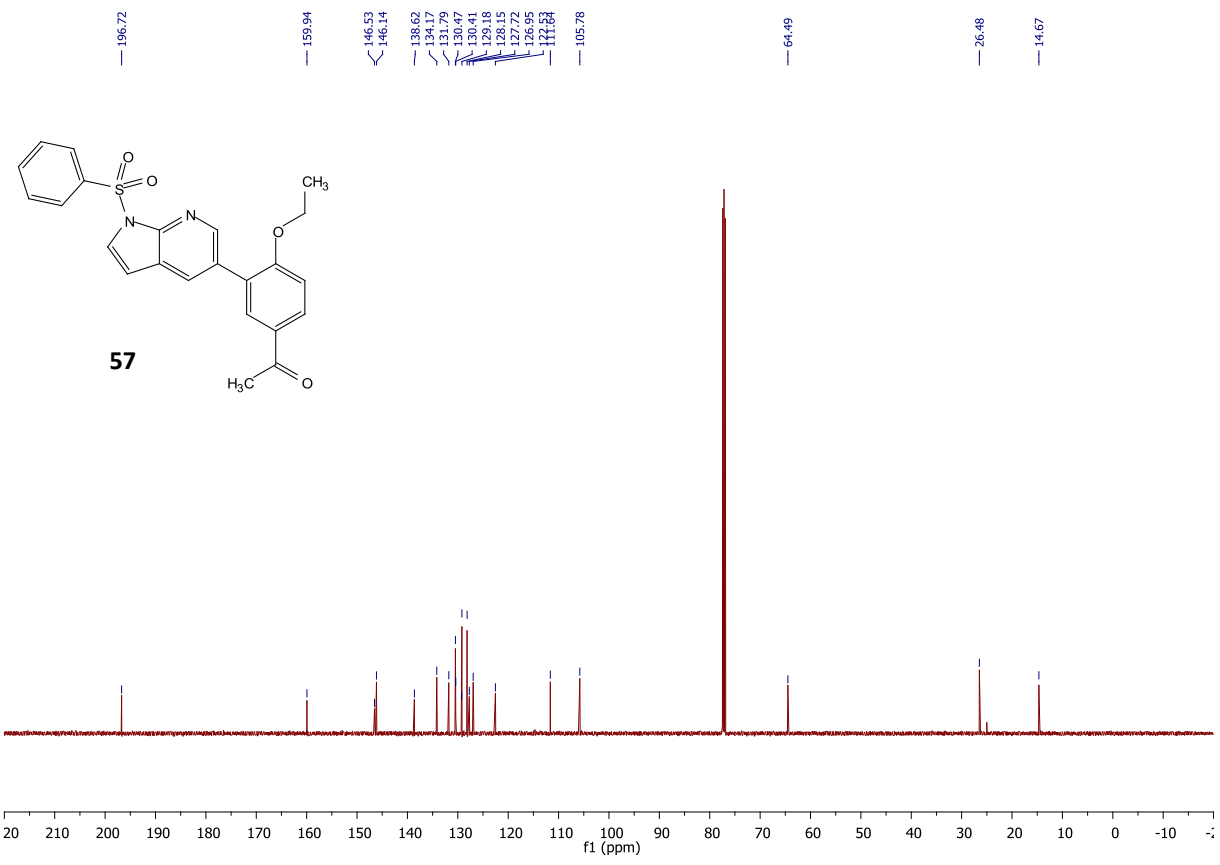

8.34
8.33
8.27
8.26
7.90
7.90
7.61
7.60
7.52
7.51
7.26
7.04
7.01
6.42
6.41
4.32
4.31
4.29
4.27
2.61
1.62
1.61
1.59
CH3
O
N
O
S
H3C
O
0.94
0.92
1.00
0.96
0.96
0.98
0.94
1.95
3.02
2.94
f1 (ppm)

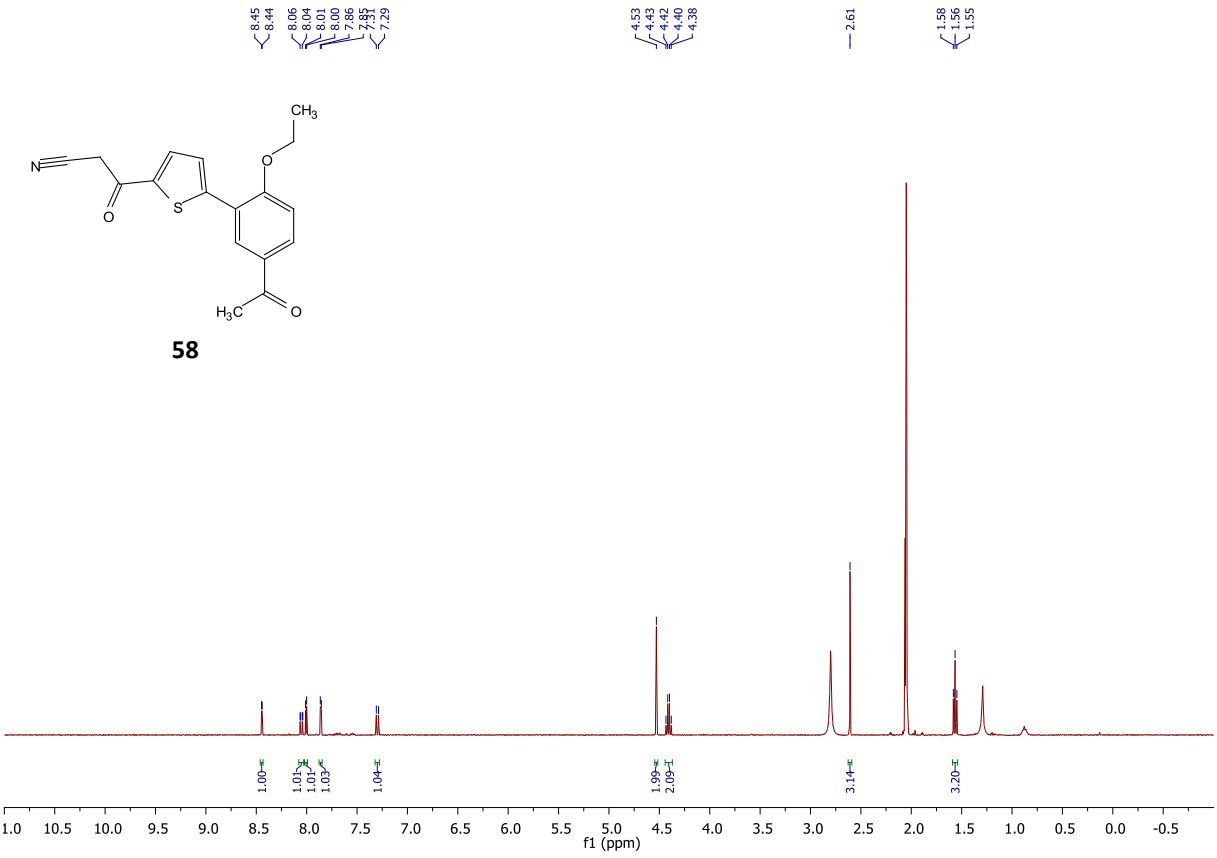
56


196.65
164.69
158.61
150.88
141.34
130.45
130.08
129.21
128.67
126.78
126.43
122.60
111.83
98.38
65.21
26.53
14.83
CH3
O
N
O
S
H3C
O
f1 (ppm)

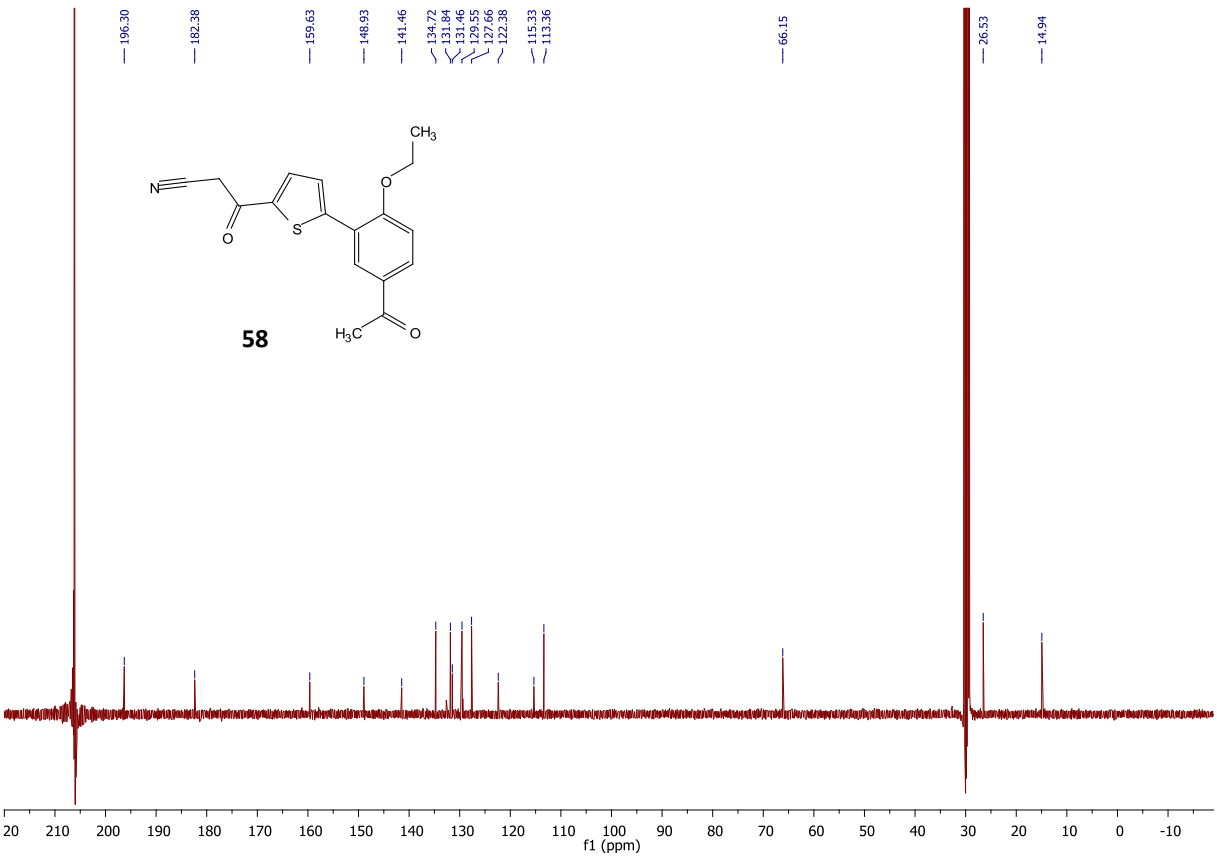
56


8.60
8.59
8.24
8.22
8.00
8.00
7.92
7.92
7.75
7.74
7.00
6.64
6.63
4.17
4.15
4.13
4.11
2.57
1.38
1.36
1.34
CH3
O
S
N
N
O
O
H3C
O
57
1.00
2.02
1.01
1.00
1.00
1.00
2.10
1.02
1.00
2.06
3.09
3.06
f1 (ppm)

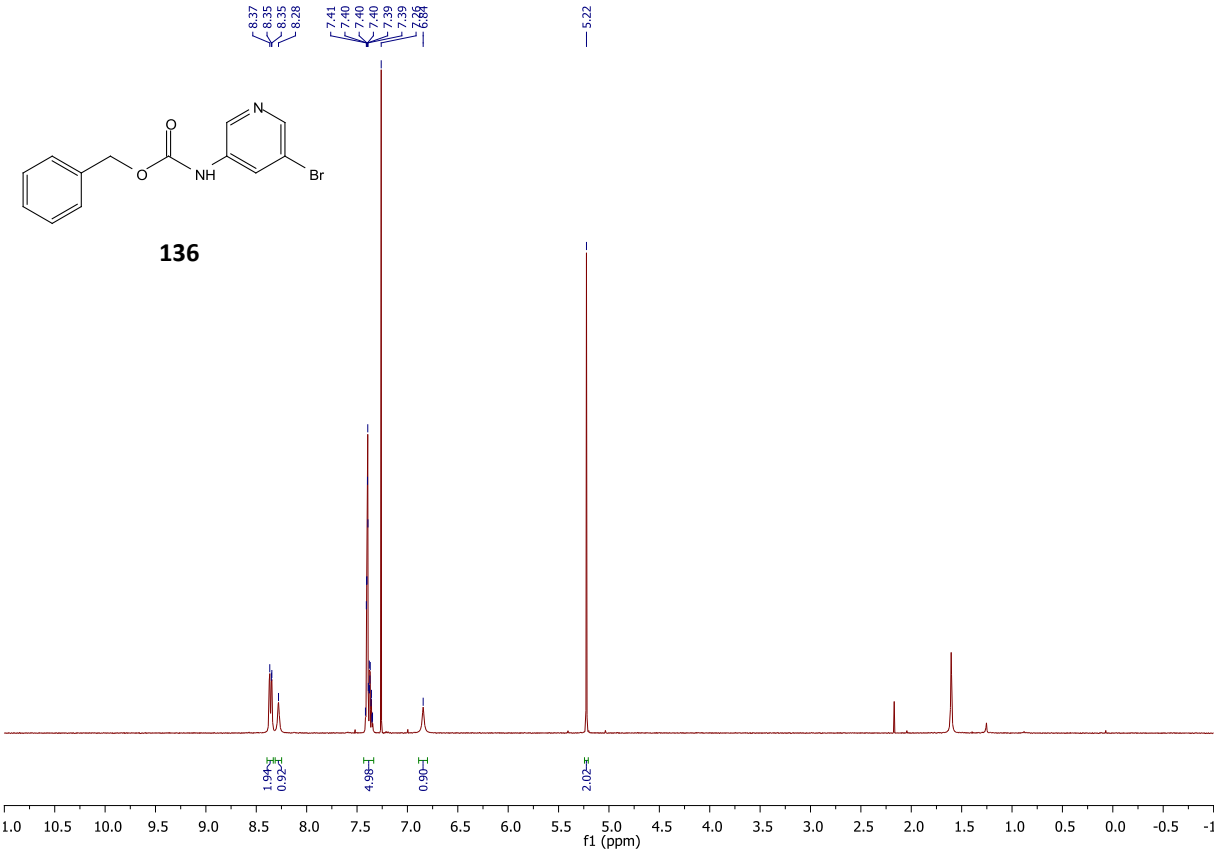

196.72
159.94
146.53
146.14
138.62
134.17
131.79
130.47
130.41
129.18
128.15
127.72
126.95
105.78
64.49
26.48
14.67
CH3
O
S
N
N
O
O
H3C
O
57
f1 (ppm)

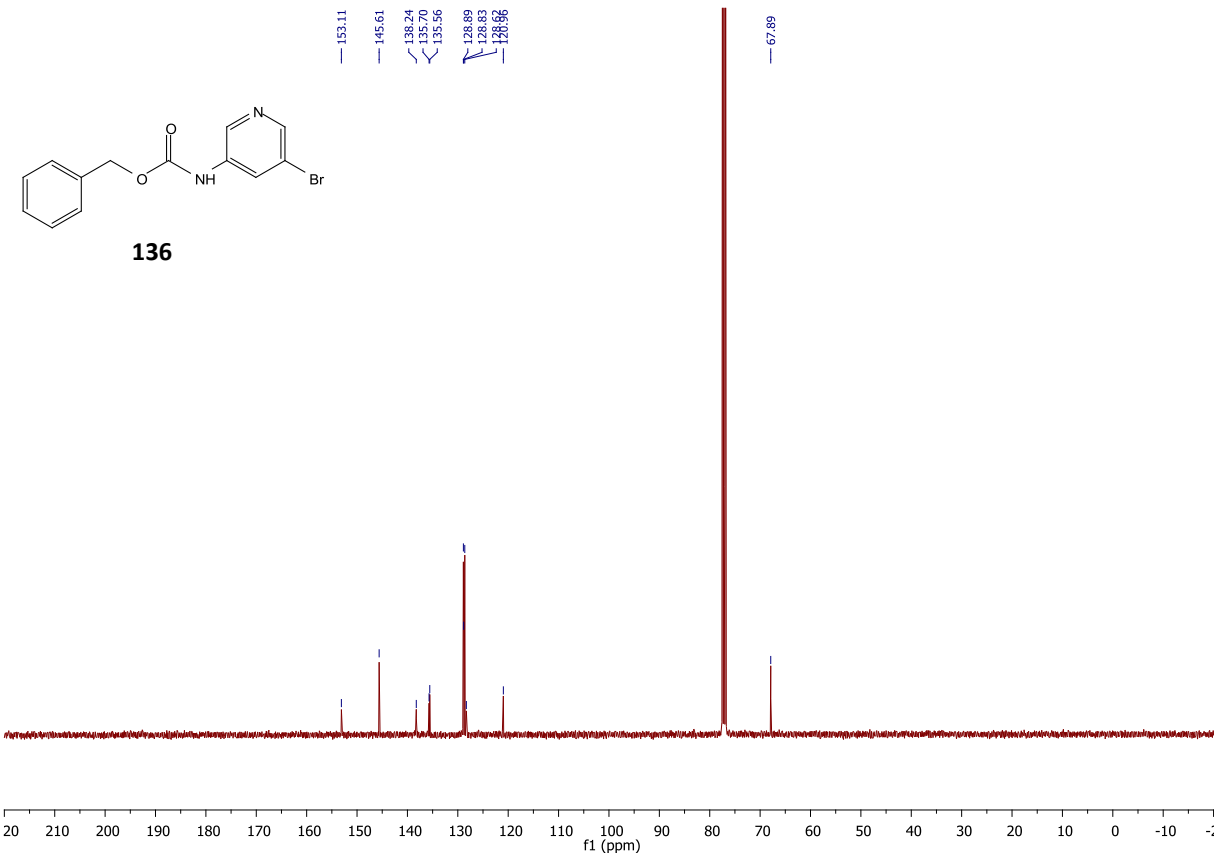

8.45
8.44
8.06
8.04
8.01
8.00
7.86
7.85
7.84
7.29
4.53
4.43
4.42
4.40
4.38
2.61
1.58
1.56
1.55
CH3
O
N
O
S
H3C
O
1.00
1.01
1.01
1.03
1.04
1.99
2.09
3.14
3.20
f1 (ppm)

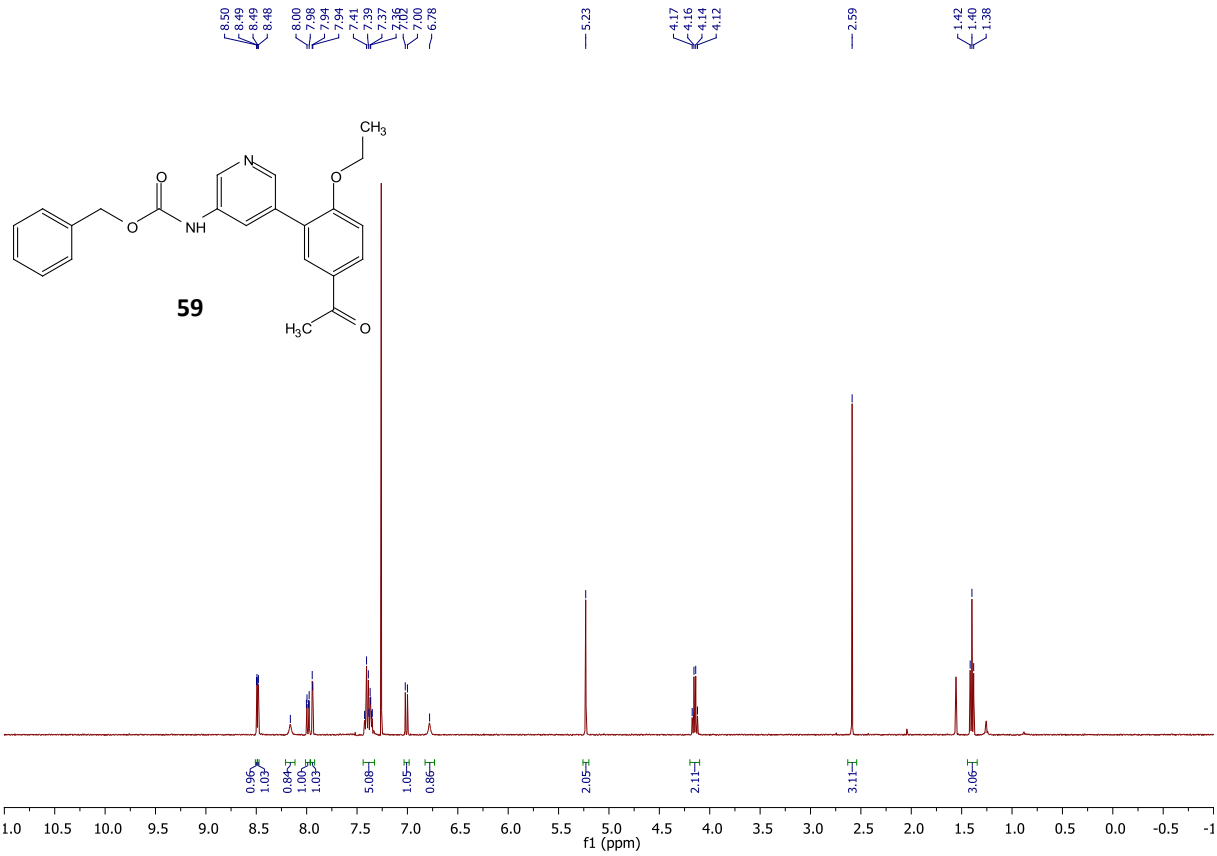
58

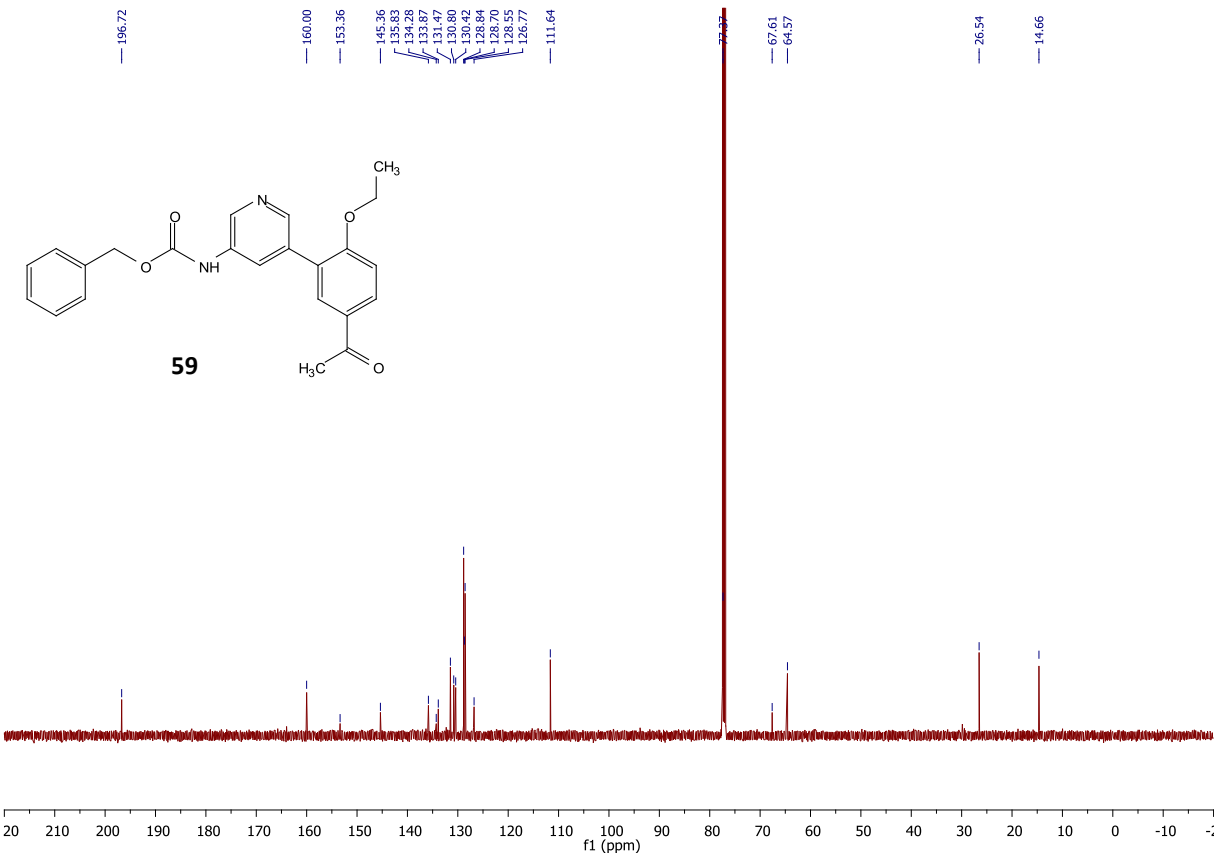

196.30
182.38
159.63
148.93
141.46
134.72
131.84
131.46
129.55
127.66
122.38
115.33
113.36
66.15
26.53
14.94
CH3
O
N
O
S
H3C
O
f1 (ppm)

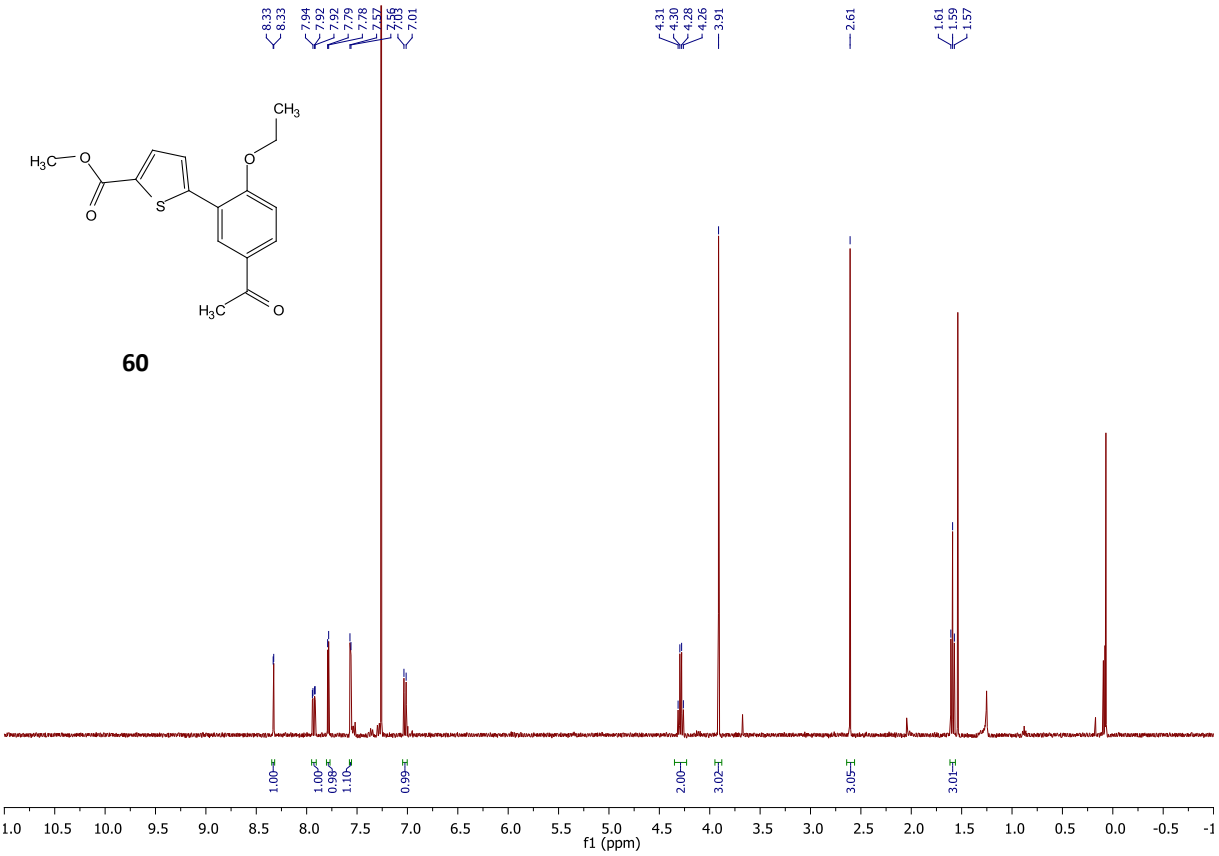
58


8.37
8.35
8.35
8.28
7.41
7.40
7.40
7.40
7.39
7.39
7.25
6.84
5.22
N
O
O
NH
Br
136
1.94
0.92
4.98
0.90
2.02
f1 (ppm)

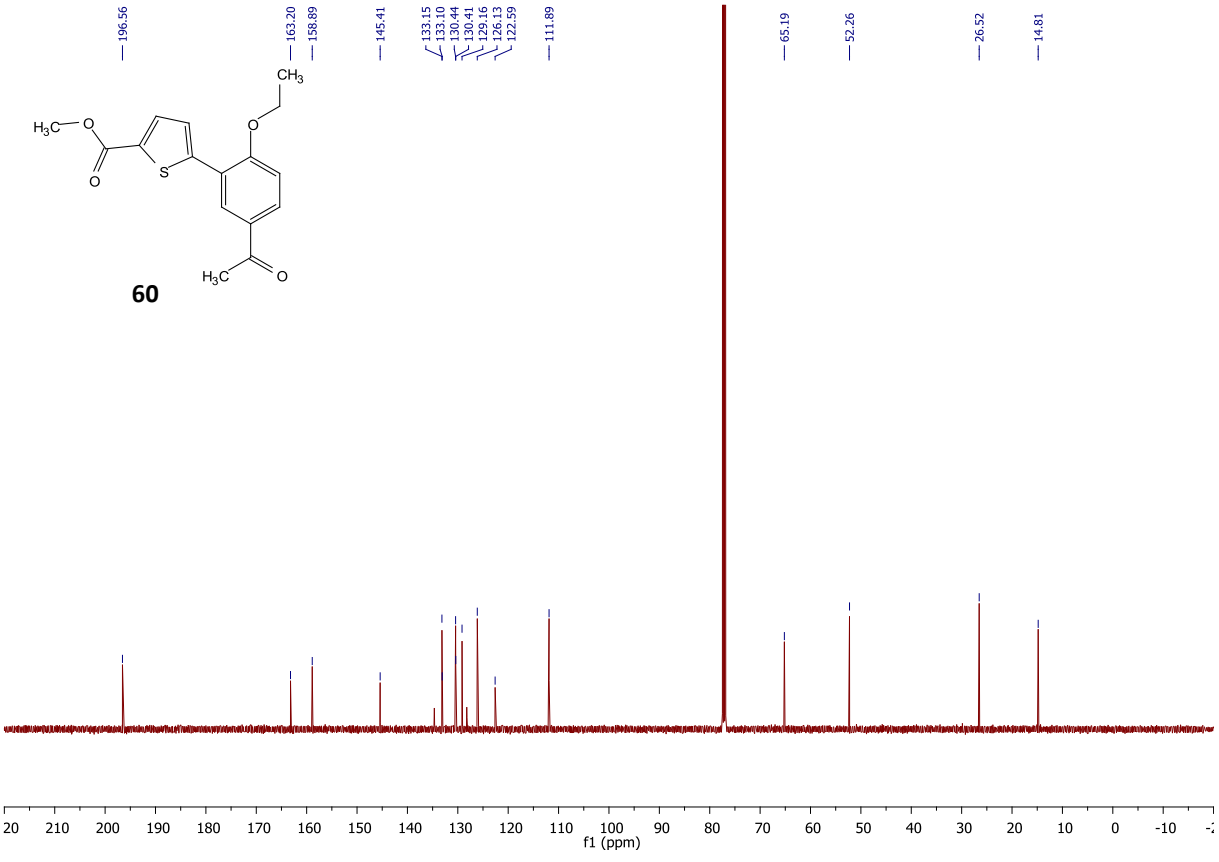

153.11
145.61
138.24
135.70
135.56
128.89
128.83
128.62
120.96
67.89
N
O
O
NH
Br
136
f1 (ppm)


8.50
8.49
8.49
8.48
8.00
7.98
7.94
7.94
7.41
7.39
7.37
7.36
7.02
7.00
6.78
5.23
4.17
4.16
4.14
4.12
2.59
1.42
1.40
1.38
CH3
N
O
O
NH
O
H3C
O
59
0.96
1.03
0.84
1.00
1.03
5.08
1.05
0.86
2.05
2.11
3.11
3.06
f1 (ppm)


196.72
160.00
153.36
145.36
135.83
134.28
133.87
131.47
130.80
130.42
128.84
128.70
128.55
126.77
111.64
77.37
67.61
64.57
26.54
14.66
CH3
N
O
O
NH
O
H3C
O
59
f1 (ppm)

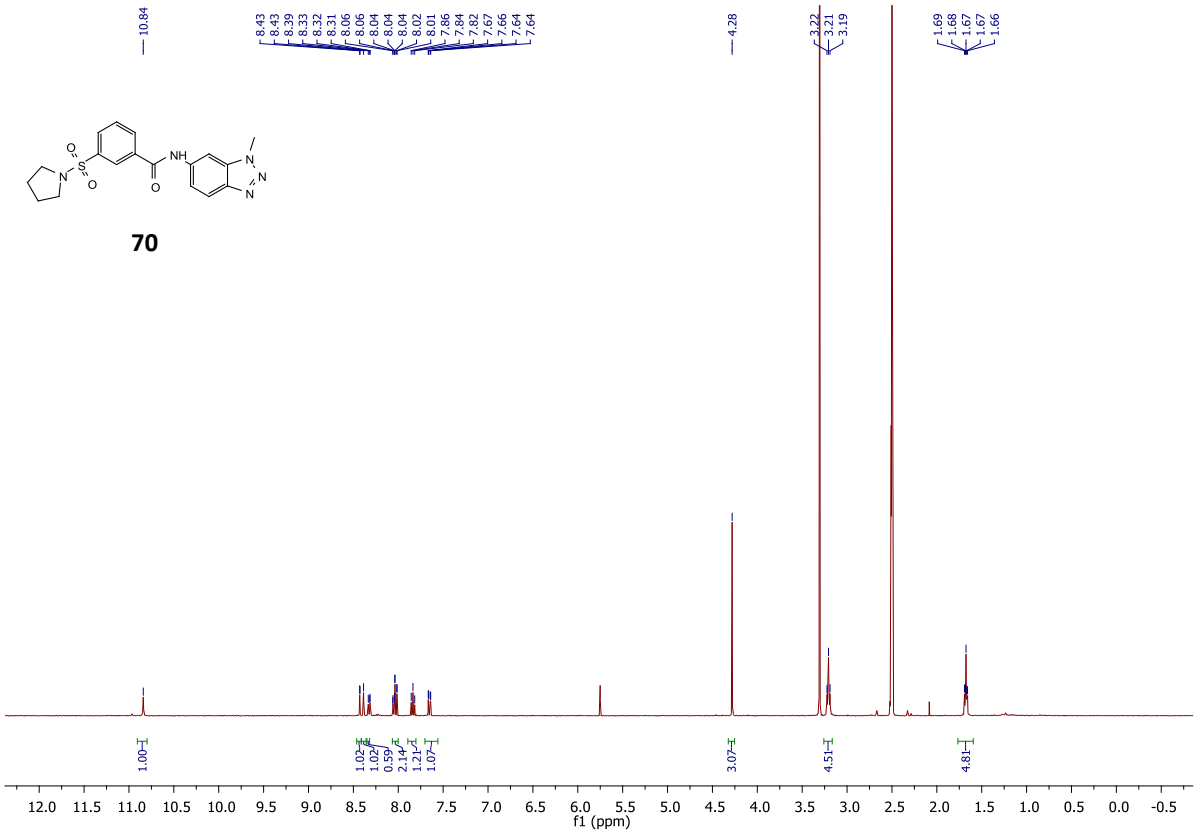

8.33
8.33
7.94
7.92
7.92
7.79
7.78
7.01
4.31
4.30
4.28
4.26
3.91
2.61
1.61
1.59
1.57
CH3
H3C
O
O
S
O
H3C
O
1.00
1.00
0.99
1.10
0.99
2.00
3.02
3.05
3.01
f1 (ppm)

60

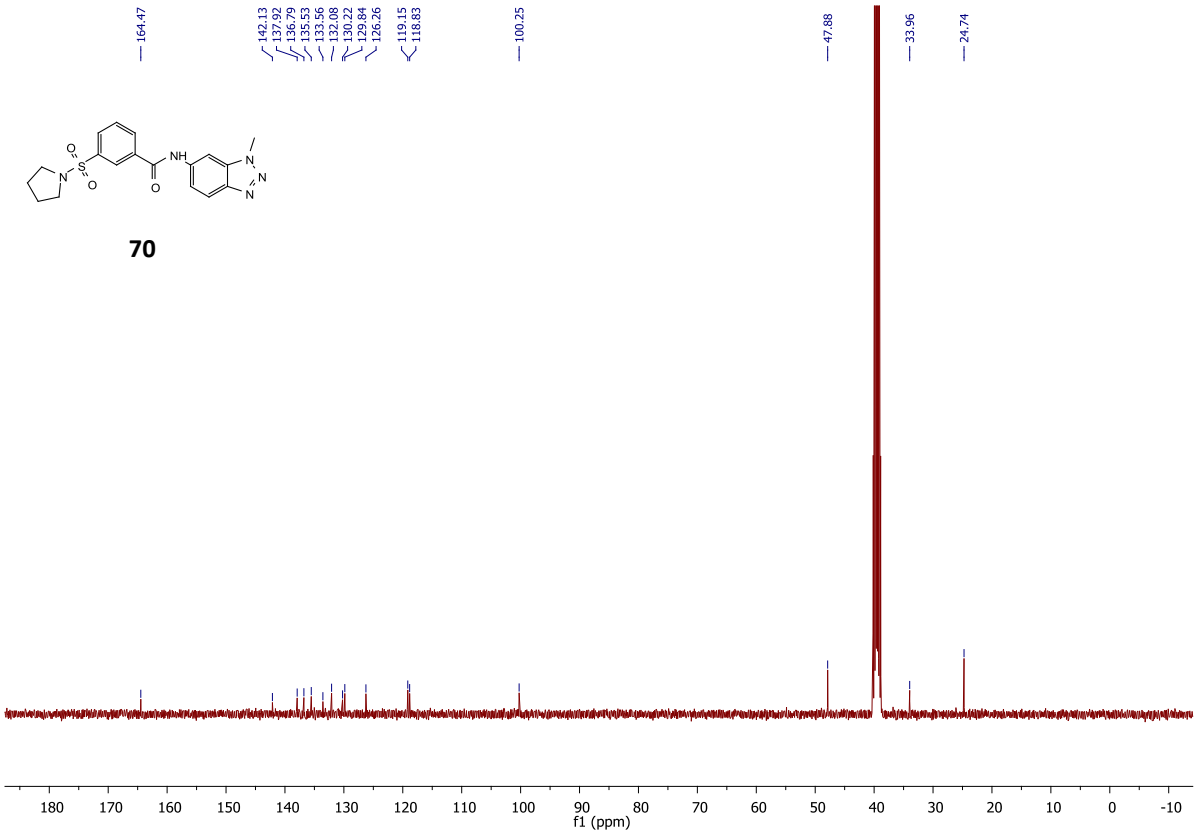

196.56
163.20
158.89
145.41
133.15
133.10
130.44
130.41
129.16
126.13
122.59
111.89
65.19
52.26
26.52
14.81
CH3
H3C
O
O
S
O
H3C
O
f1 (ppm)

60

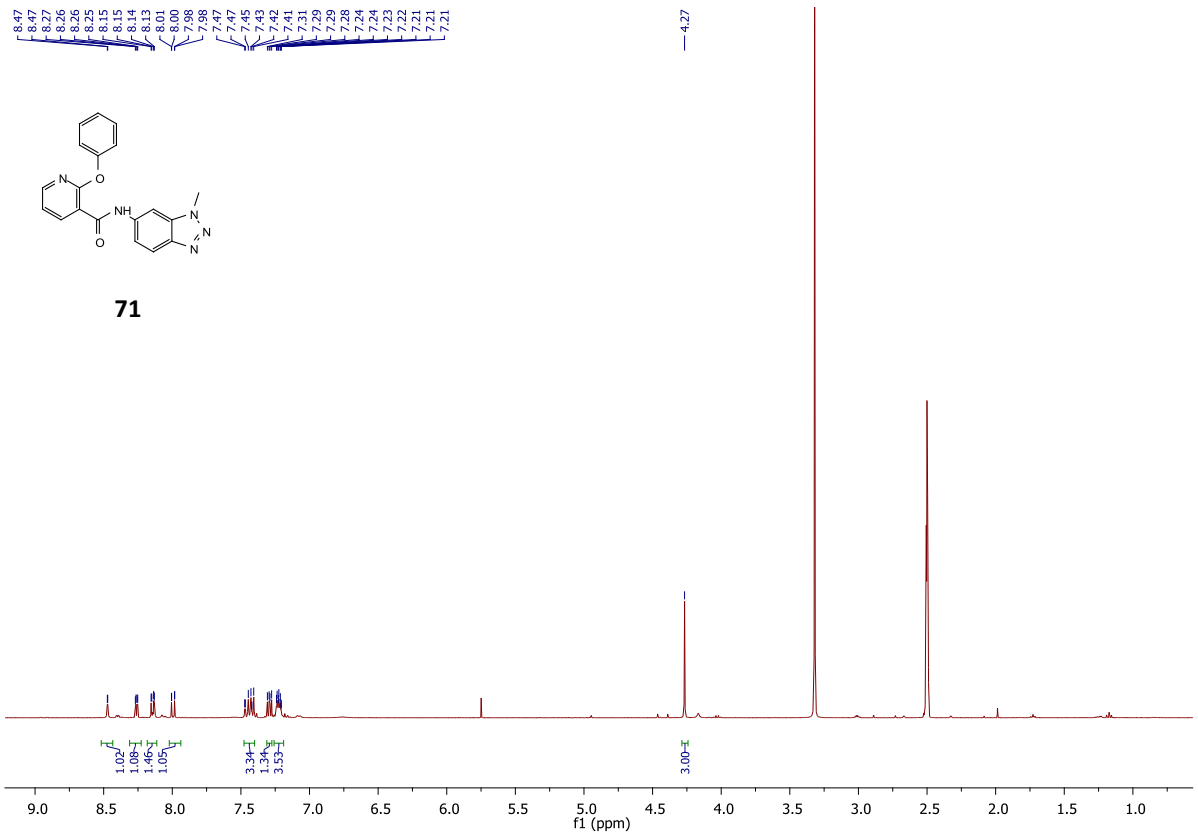
BRD4(1) inhibitors bearing an amide linker:



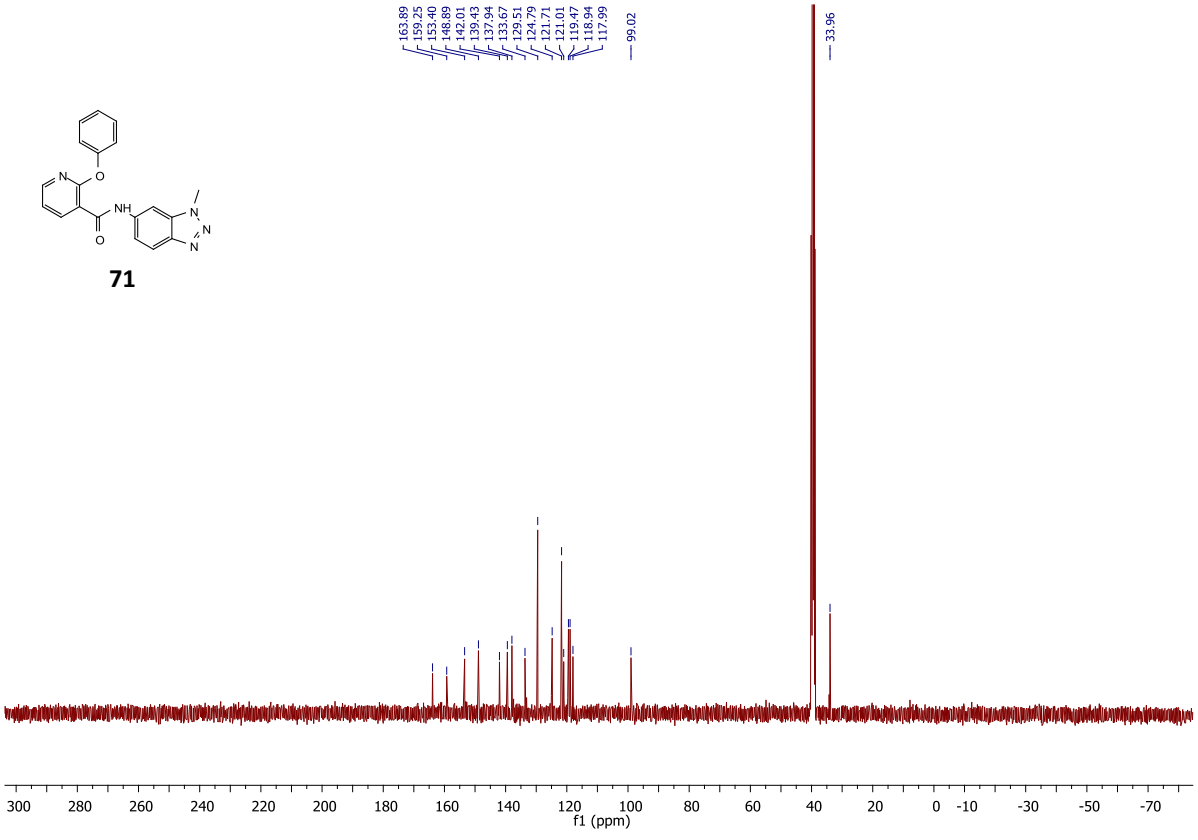
70



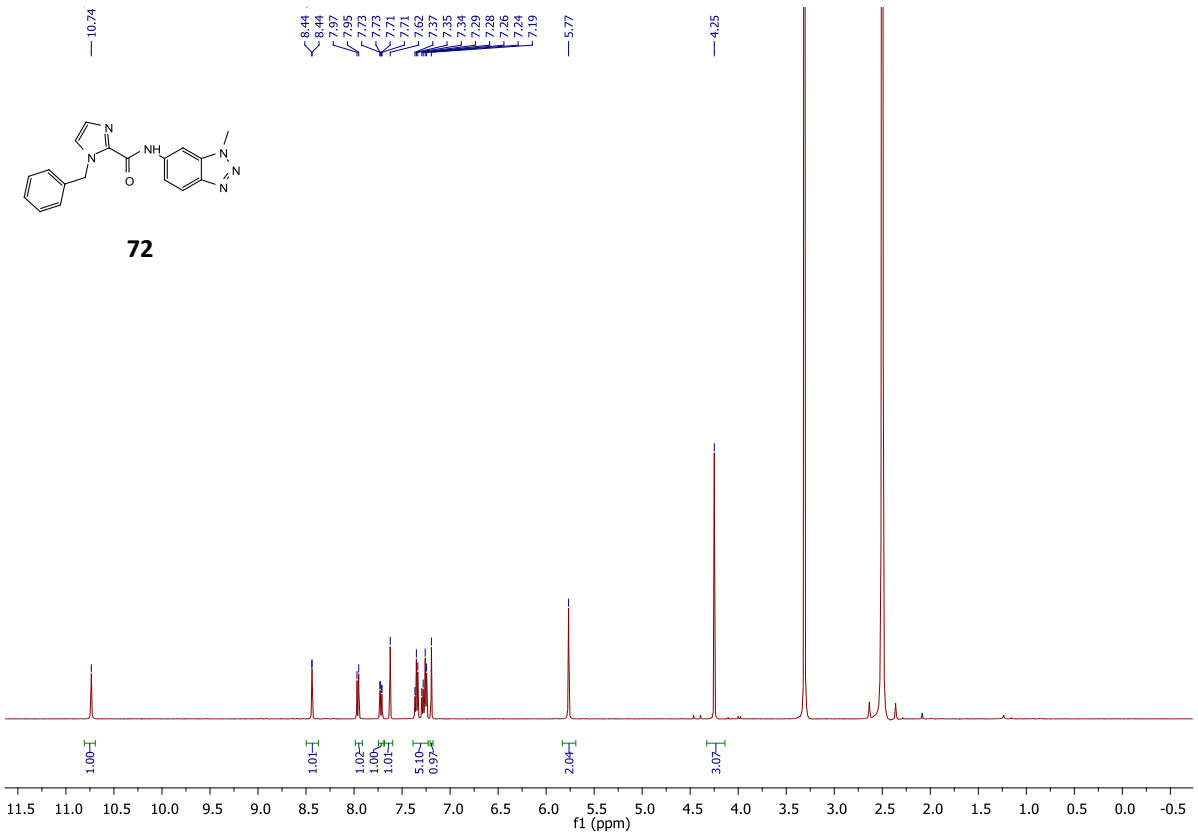
70


8.47
8.47
8.27
8.26
8.26
8.25
8.15
8.15
8.14
8.13
8.01
8.00
7.98
7.98
7.47
7.47
7.45
7.43
7.42
7.41
7.31
7.29
7.29
7.28
7.24
7.24
7.23
7.22
7.21
7.21
7.21
4.27
1.02
1.08
1.46
1.05
3.34
1.34
3.53
3.00
f1 (ppm)

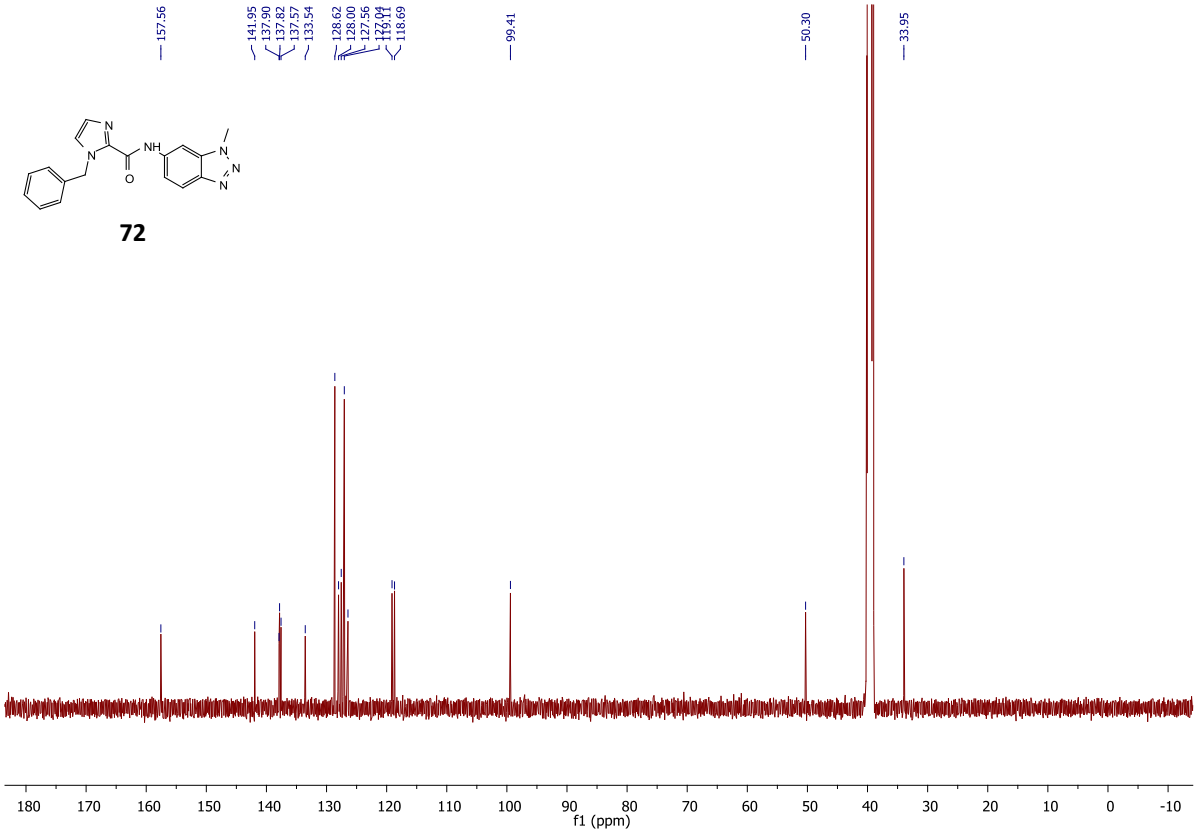
71


163.89
159.25
153.40
148.89
142.01
139.43
137.94
133.67
129.51
124.79
121.71
121.01
119.47
118.94
117.99
99.02
33.96
f1 (ppm)

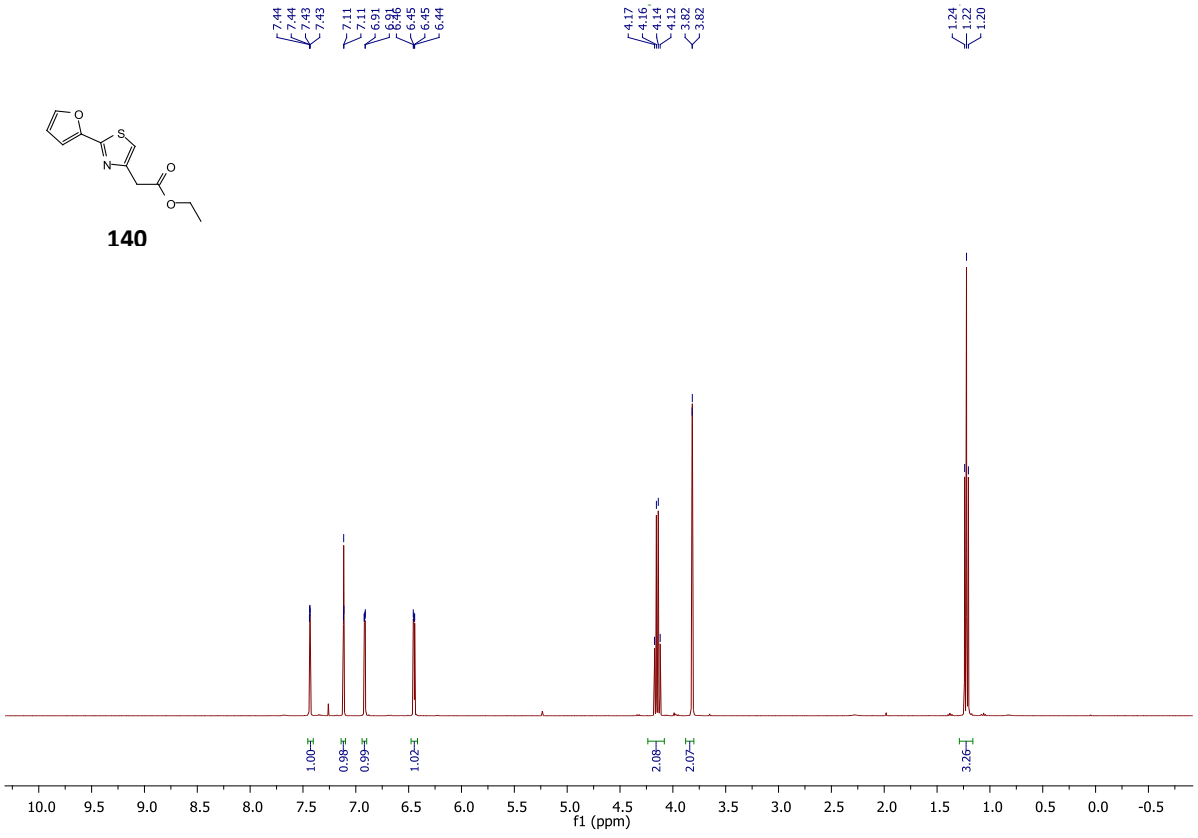
71

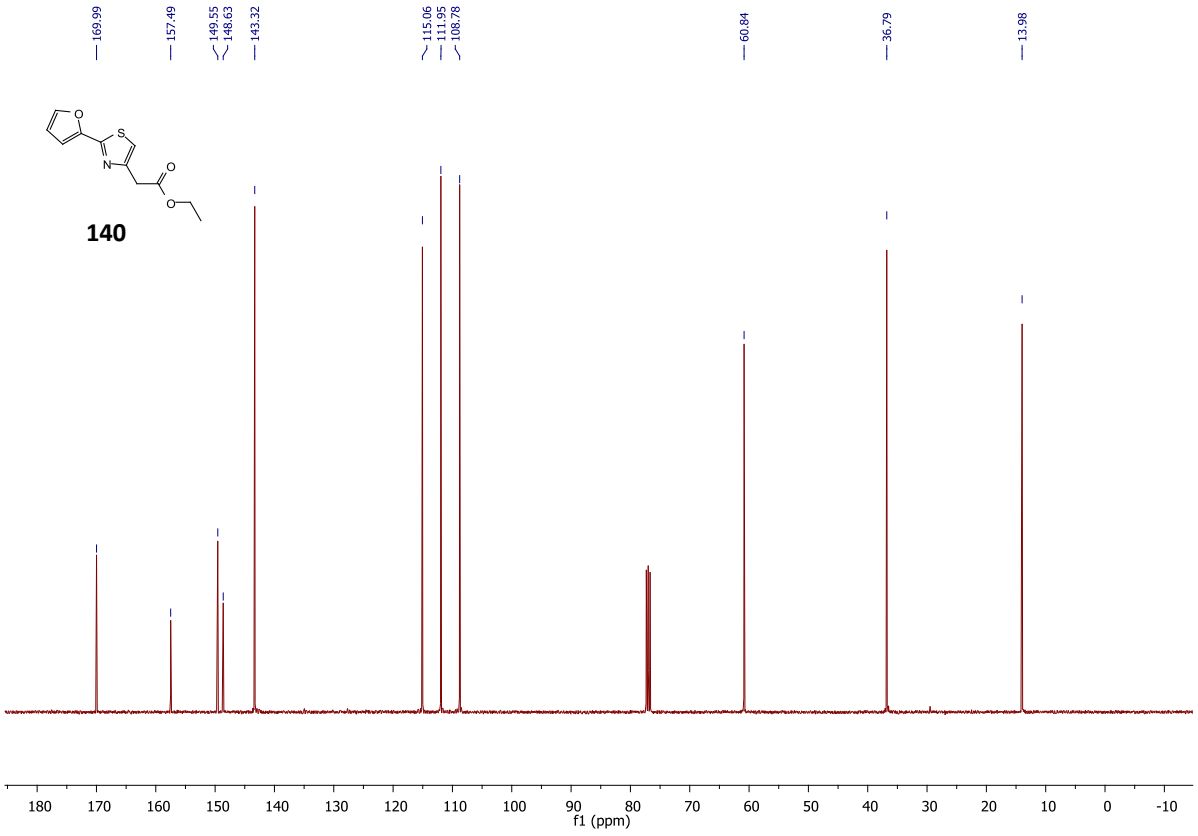

10.74
8.44
8.44
7.97
7.95
7.73
7.73
7.71
7.71
7.62
7.37
7.35
7.34
7.29
7.28
7.26
7.24
7.19
5.77
4.25
1.00
1.01
1.02
1.00
1.01
5.10
0.97
2.04
3.07
f1 (ppm)

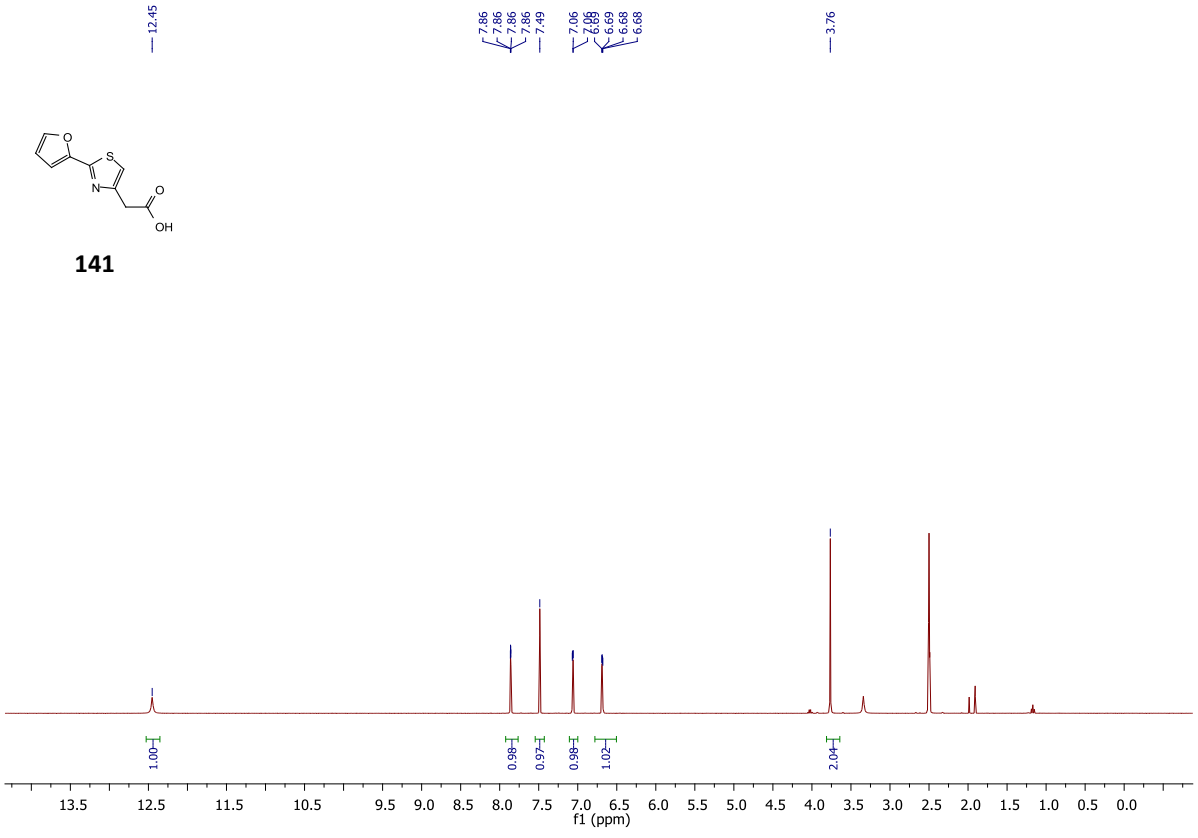
72


157.56
141.95
137.90
137.82
137.57
133.54
128.62
128.00
127.56
119.11
118.69
99.41
50.30
33.95
f1 (ppm)

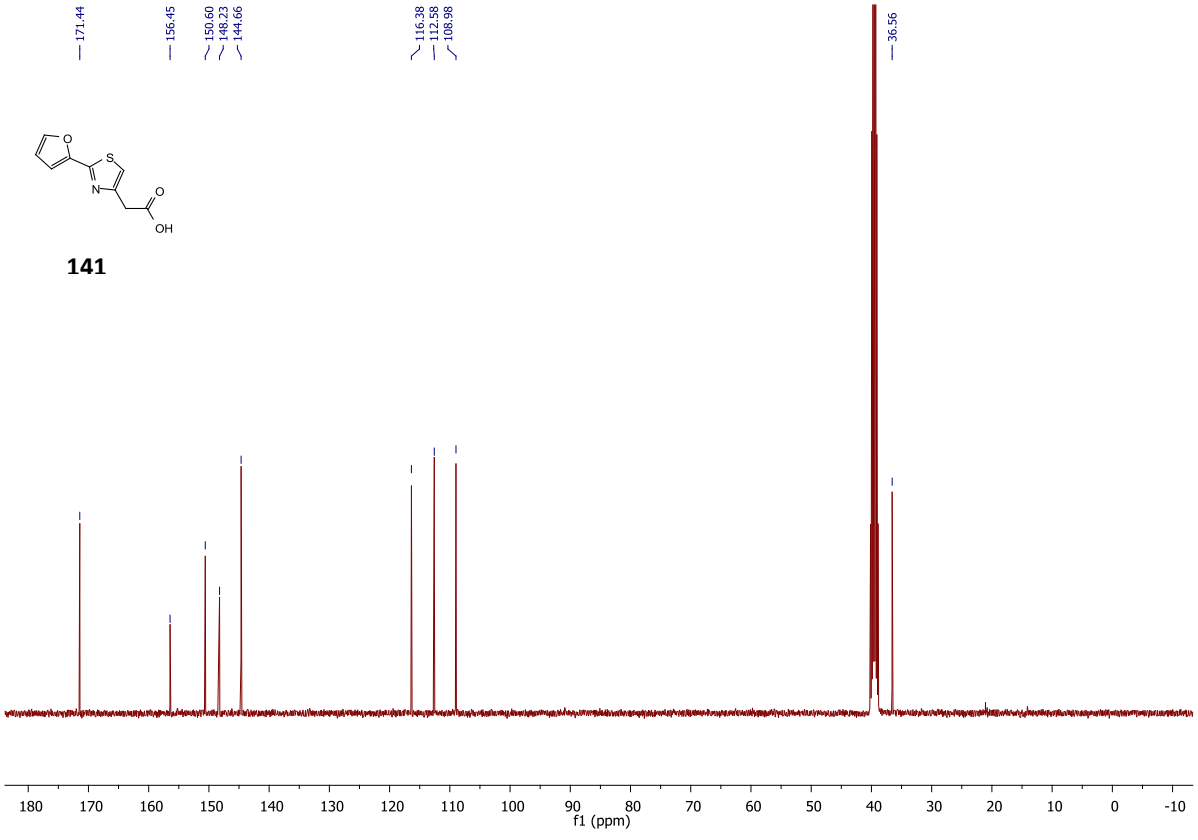
72


7.44
7.44
7.43
7.43
7.11
7.11
6.91
6.46
6.45
6.45
6.44
4.17
4.16
4.14
4.12
3.82
3.82
1.24
1.22
1.20
O
S
N
O
O
140
1.00
0.98
0.99
1.02
2.08
2.07
3.26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

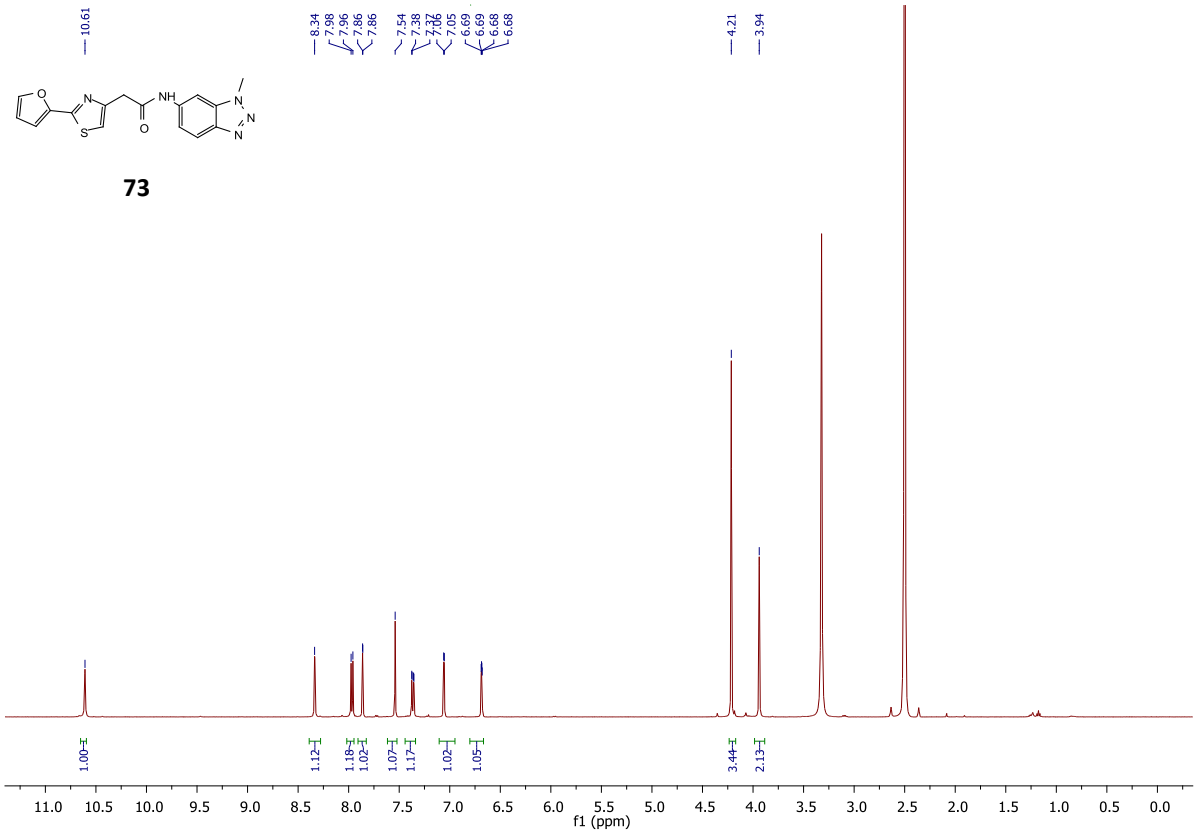

169.99
157.49
149.55
148.63
143.32
115.06
111.95
108.78
60.84
36.79
13.98
O
S
N
O
O
140
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


12.45
7.86
7.86
7.86
7.86
7.49
7.06
7.05
6.69
6.68
6.68
3.76
O
S
N
O
OH
1.00
0.98
0.97
0.98
1.02
2.04
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

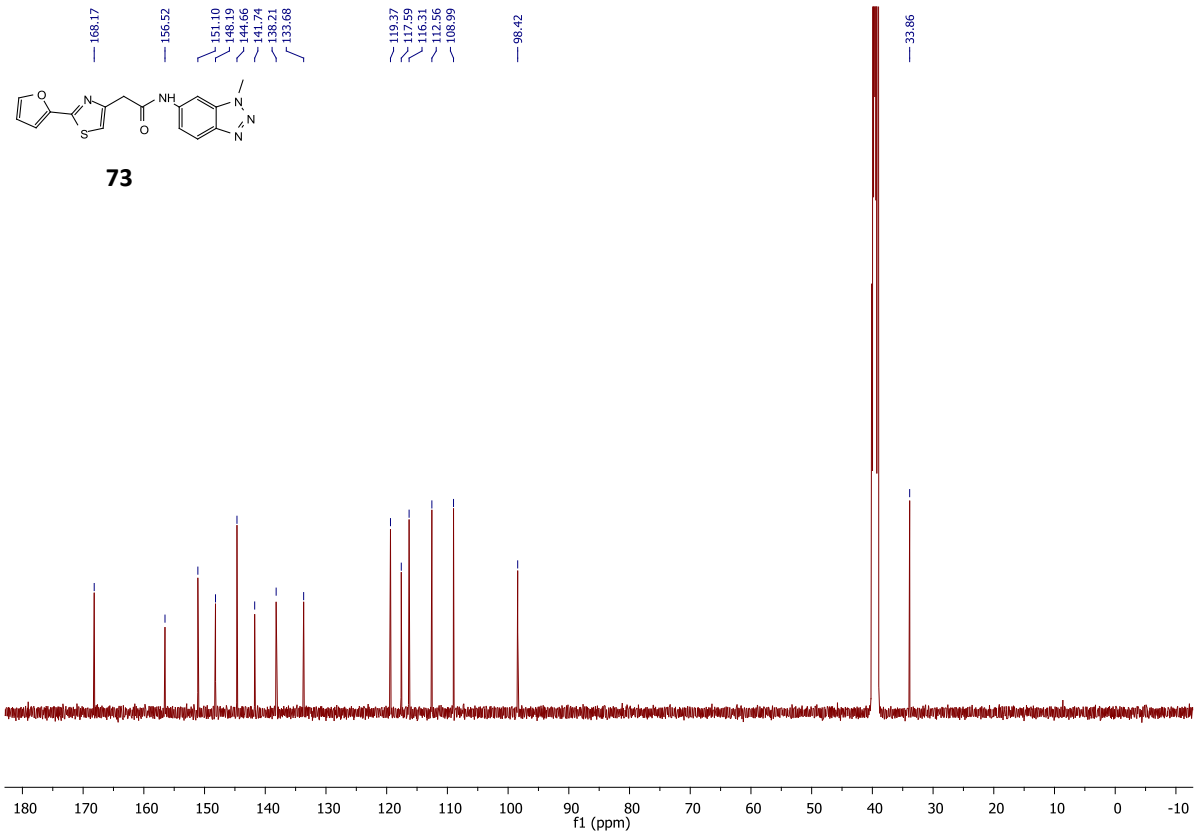
141


171.44
156.45
150.60
148.23
144.66
116.38
112.58
108.98
36.56
O
S
N
O
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

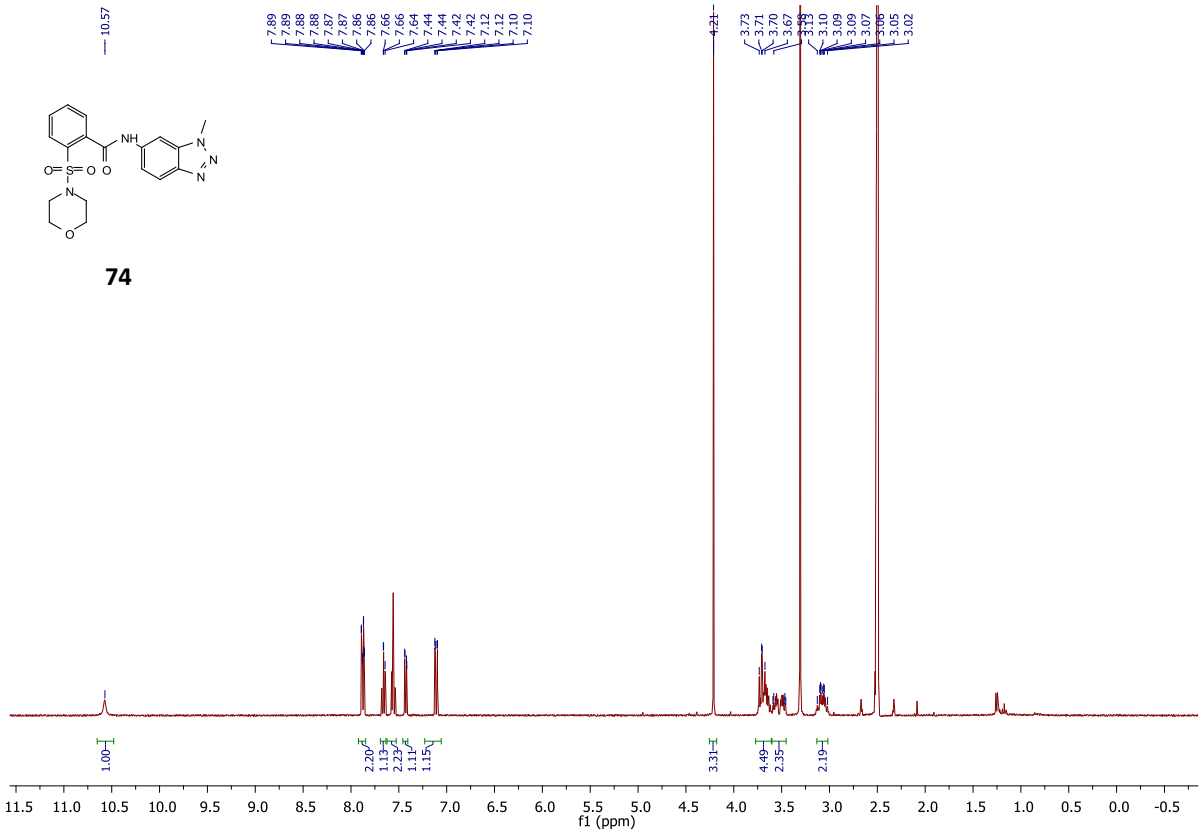
141


10.61
8.34
7.98
7.96
7.86
7.86
7.54
7.38
7.32
7.06
7.05
6.69
6.69
6.68
6.68
4.21
3.94
1.00
1.12
1.18
1.02
1.07
1.17
1.02
1.05
3.44
2.13
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

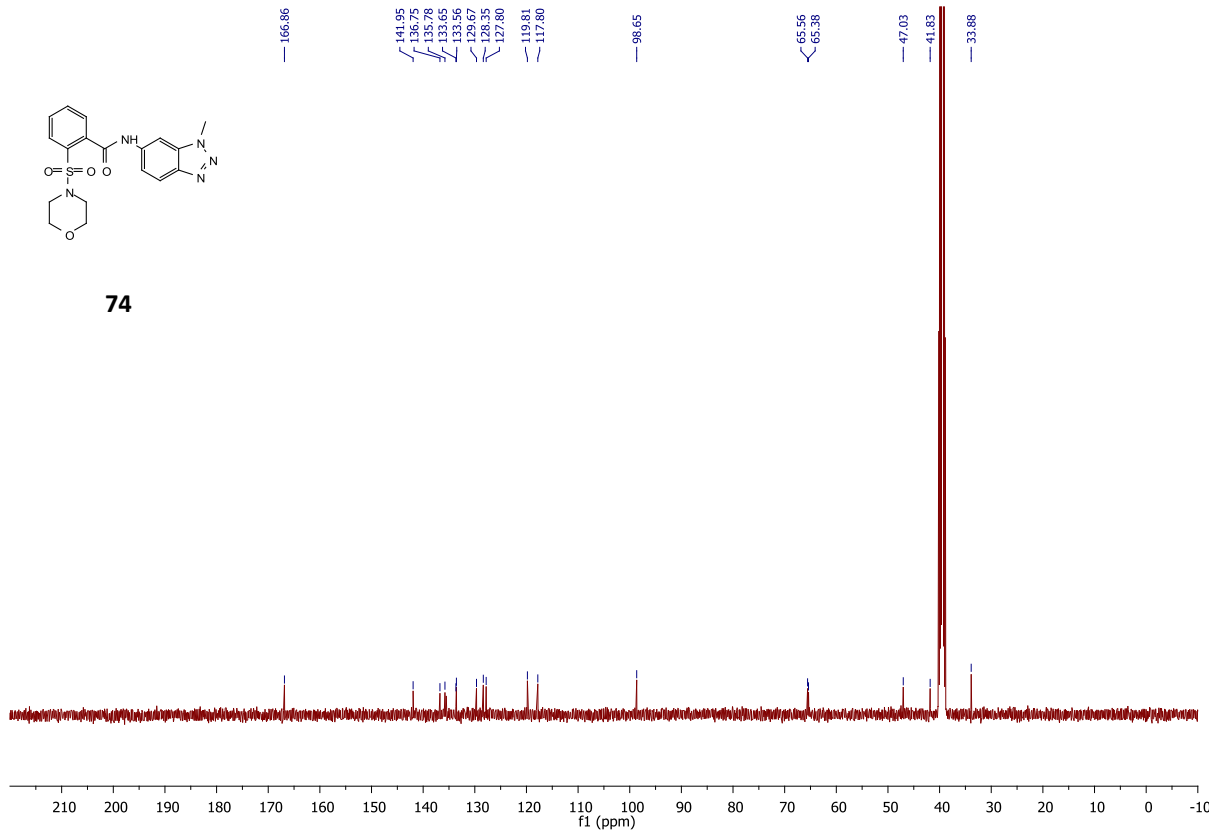
73


168.17
156.52
151.10
148.19
144.66
141.74
138.21
133.68
119.37
117.59
116.31
112.56
108.99
98.42
33.86
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

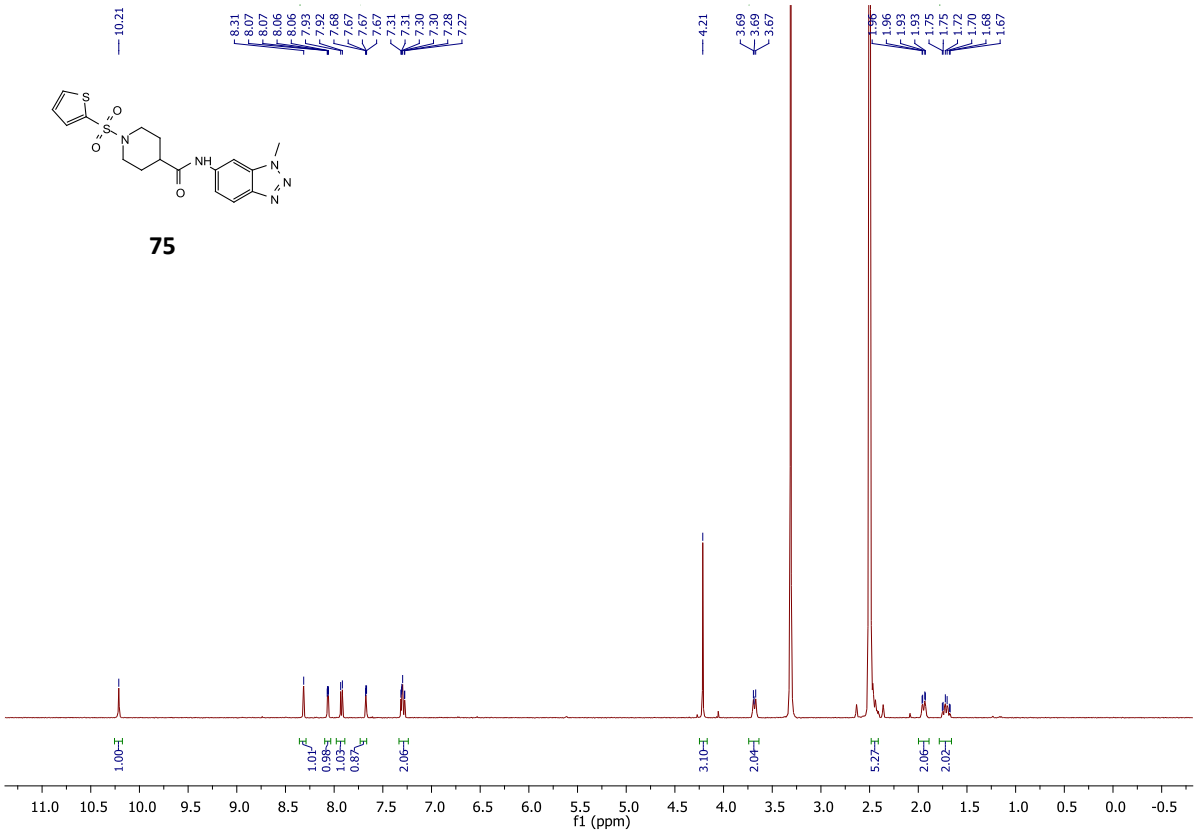
73


10.57
7.89
7.89
7.88
7.88
7.87
7.87
7.86
7.86
7.66
7.66
7.64
7.44
7.44
7.42
7.42
7.12
7.10
7.10
4.21
3.73
3.71
3.70
3.67
3.13
3.10
3.09
3.09
3.07
3.06
3.05
3.02
NH
N
N
N
O=S=O
O
N
O
1.00
2.20
1.13
2.23
1.11
1.15
3.31
4.49
2.35
2.19
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

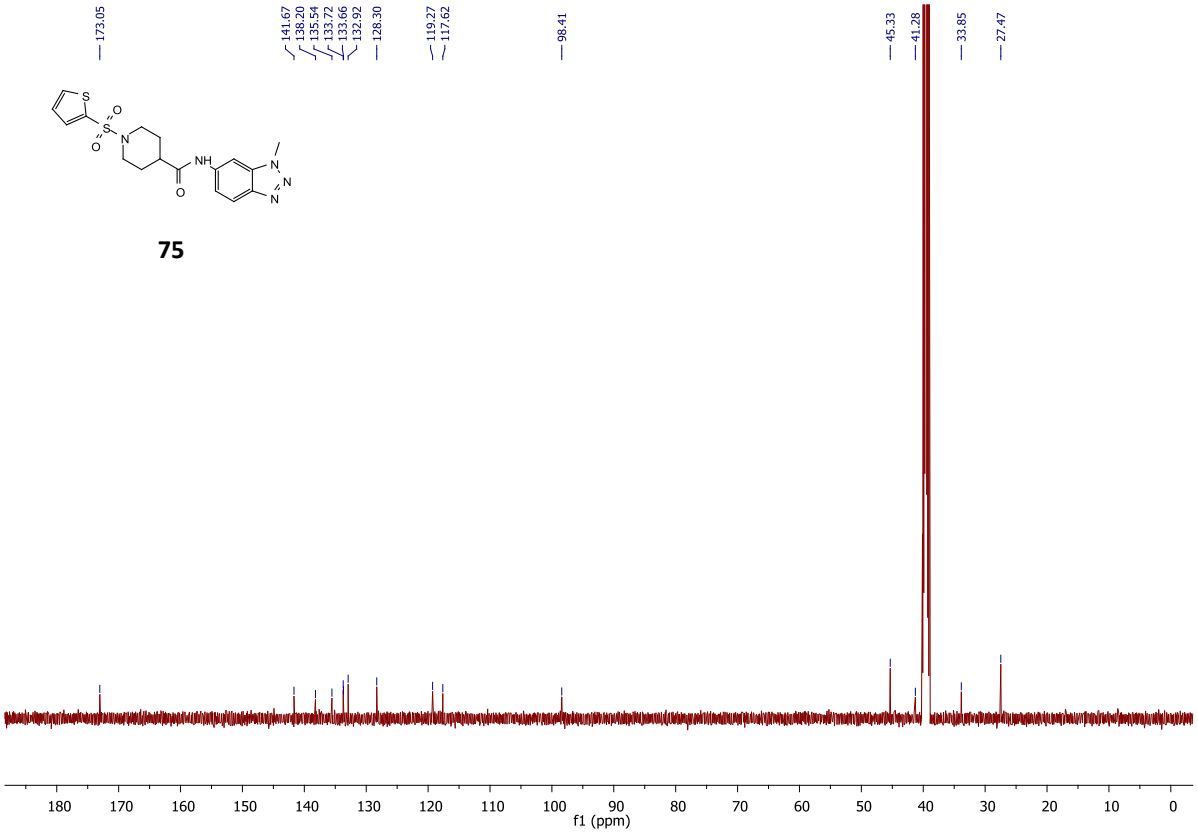
74


166.86
141.95
136.75
135.78
133.65
133.56
129.67
128.35
127.80
119.81
117.80
98.65
65.56
65.38
47.03
41.83
33.88
NH
N
N
N
O=S=O
O
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

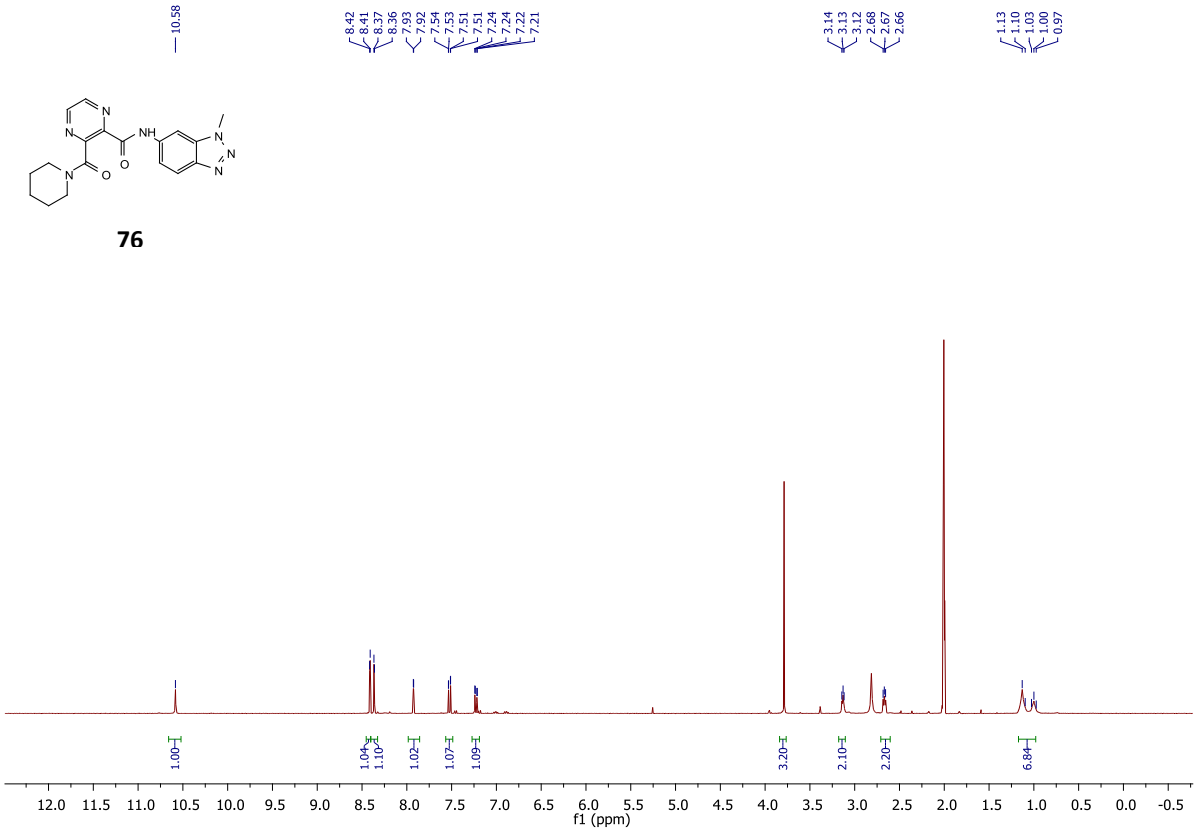
74


10.21
8.31
8.07
8.07
8.06
8.06
7.93
7.92
7.68
7.67
7.67
7.67
7.31
7.31
7.30
7.30
7.28
7.27
4.21
3.69
3.69
3.67
1.96
1.96
1.93
1.93
1.75
1.72
1.70
1.68
1.67
1.00
1.01
0.98
1.03
0.87
2.06
3.10
2.04
5.27
2.06
2.02
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

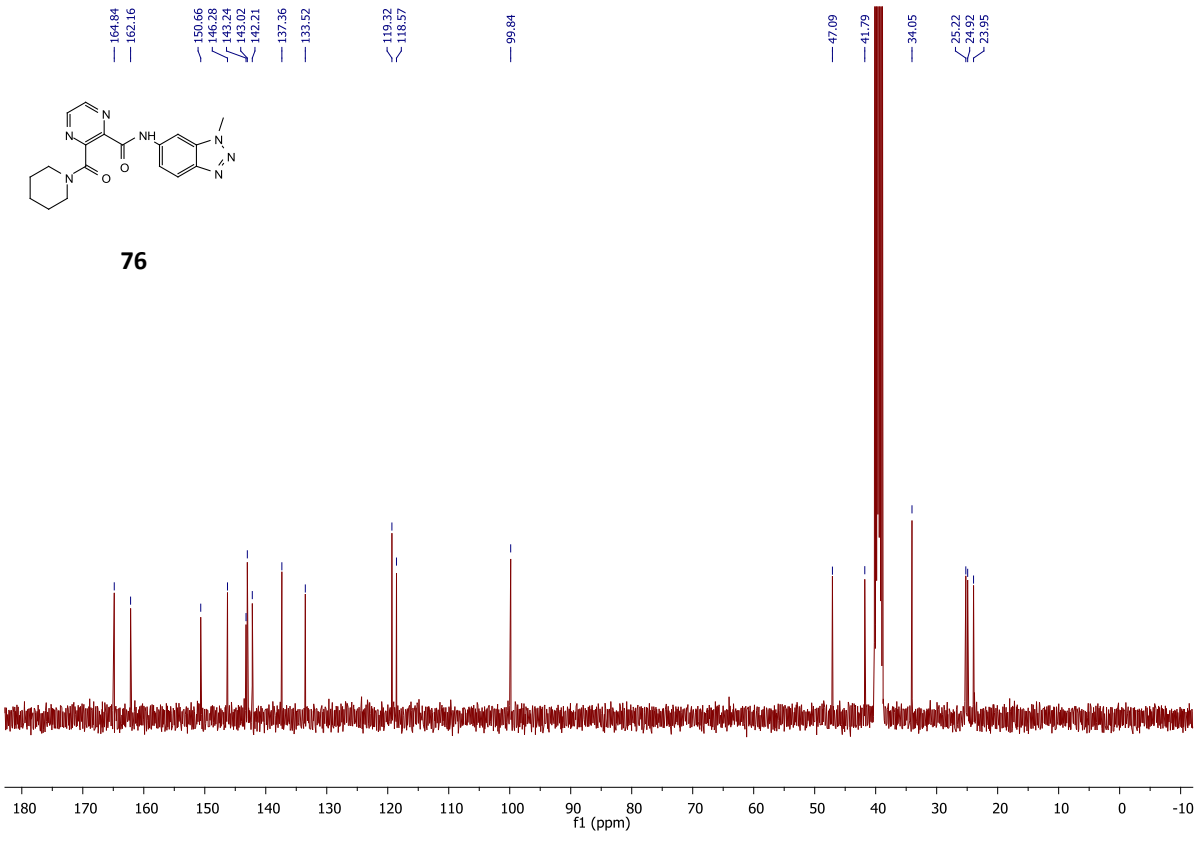
75


173.05
141.67
138.20
135.54
133.72
133.66
132.92
128.30
119.27
117.62
98.41
45.33
41.28
33.85
27.47
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

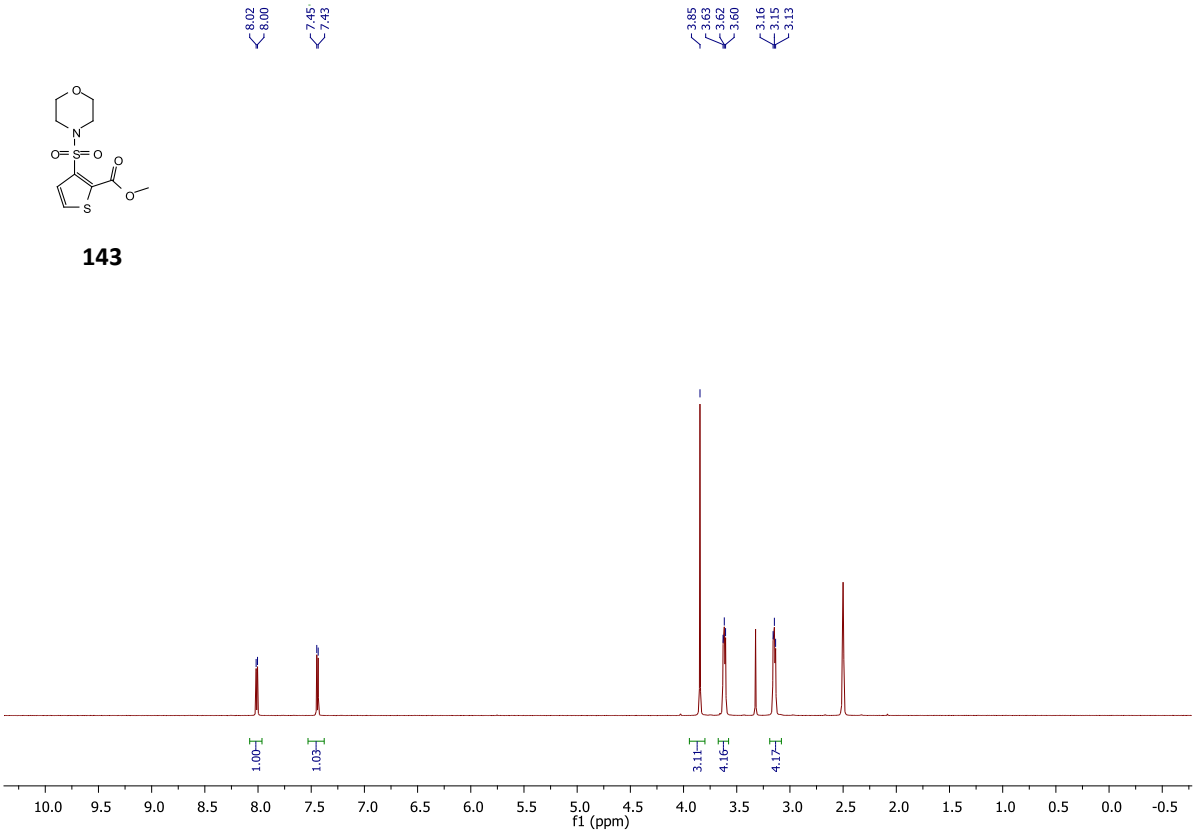
75


10.58
8.42
8.41
8.37
8.36
7.93
7.92
7.54
7.53
7.51
7.51
7.24
7.24
7.22
7.21
3.14
3.13
3.12
2.68
2.67
2.66
1.13
1.10
1.03
1.00
0.97
NH
O
O
N
N
N
N
N
1.00
1.04
1.10
1.02
1.07
1.09
3.20
2.10
2.20
6.84
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

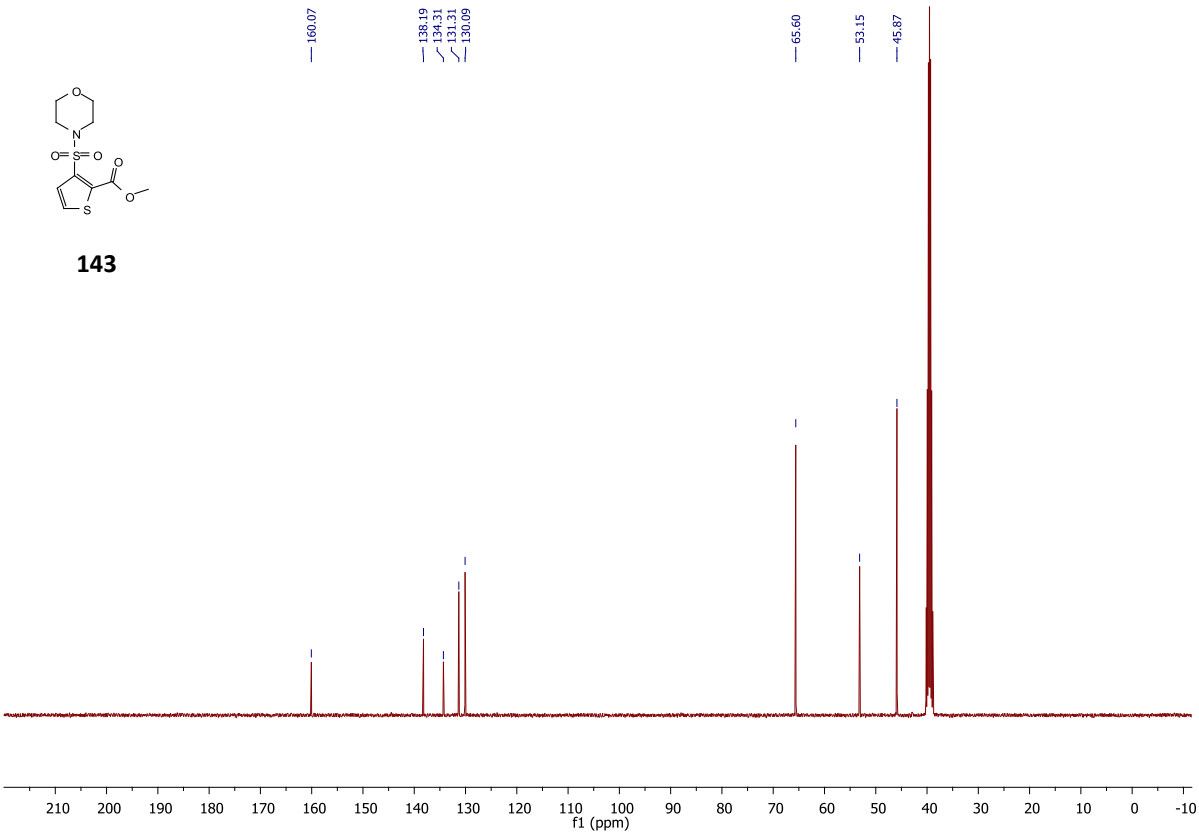
76


164.84
162.16
150.66
146.28
143.24
143.02
142.21
137.36
133.52
119.32
118.57
99.84
47.09
41.79
34.05
25.22
24.92
23.95
NH
O
O
N
N
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

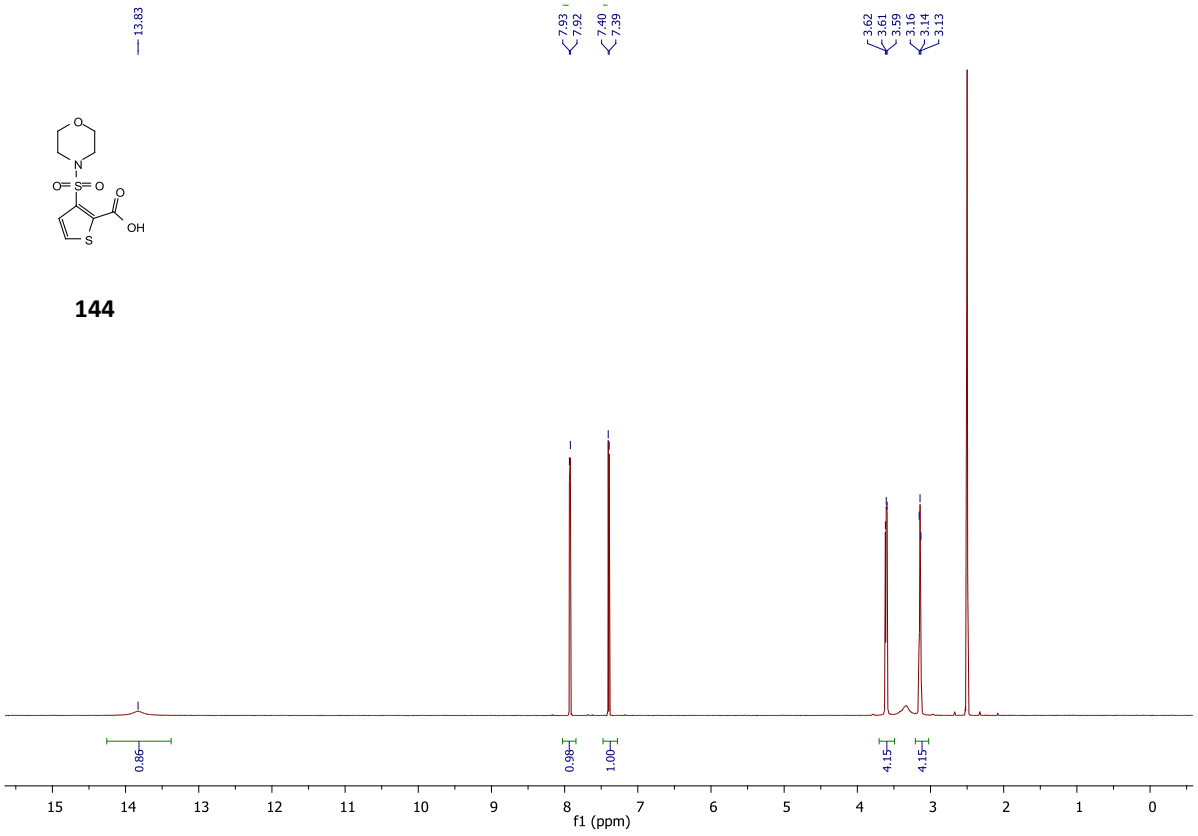
76


8.02
8.00
7.45
7.43
3.85
3.63
3.62
3.60
3.16
3.15
3.13
1.00
1.03
3.11
4.16
4.17
f1 (ppm)

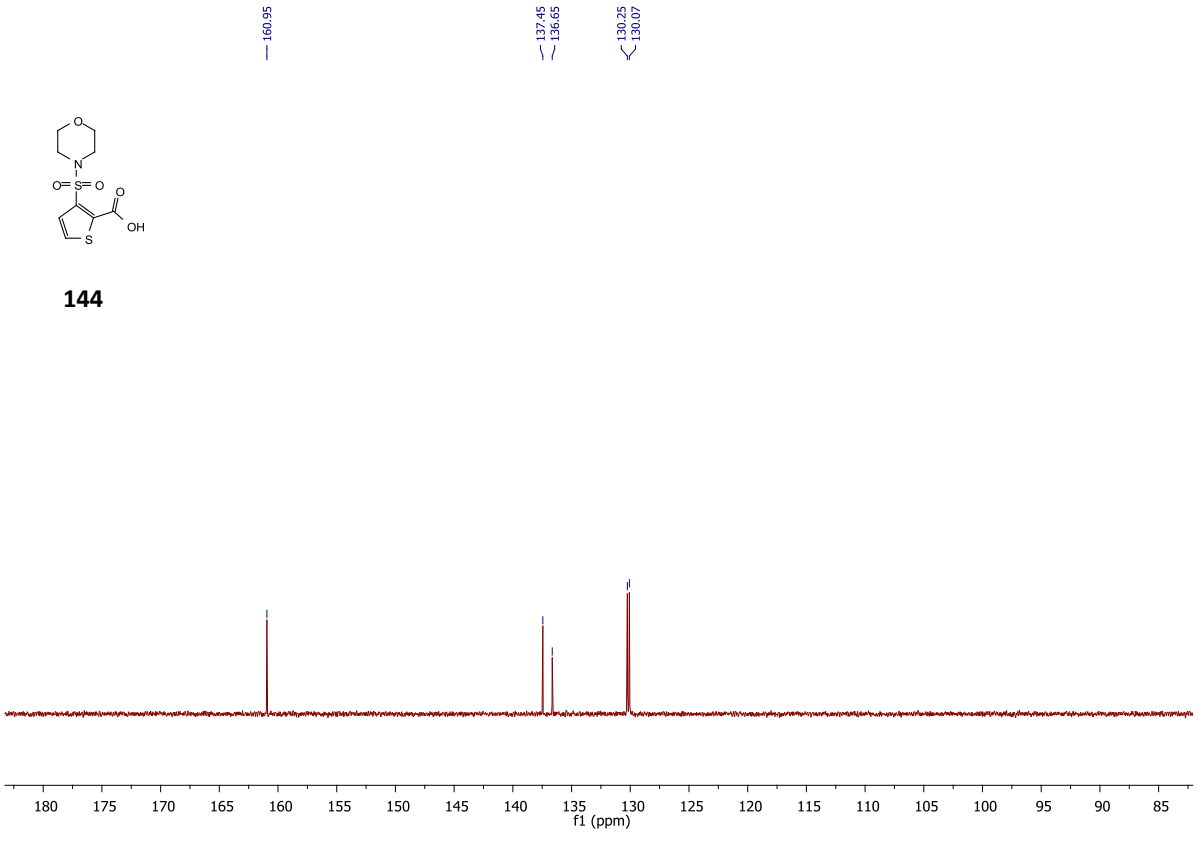
143


160.07
138.19
134.31
131.31
130.09
65.60
53.15
45.87
f1 (ppm)

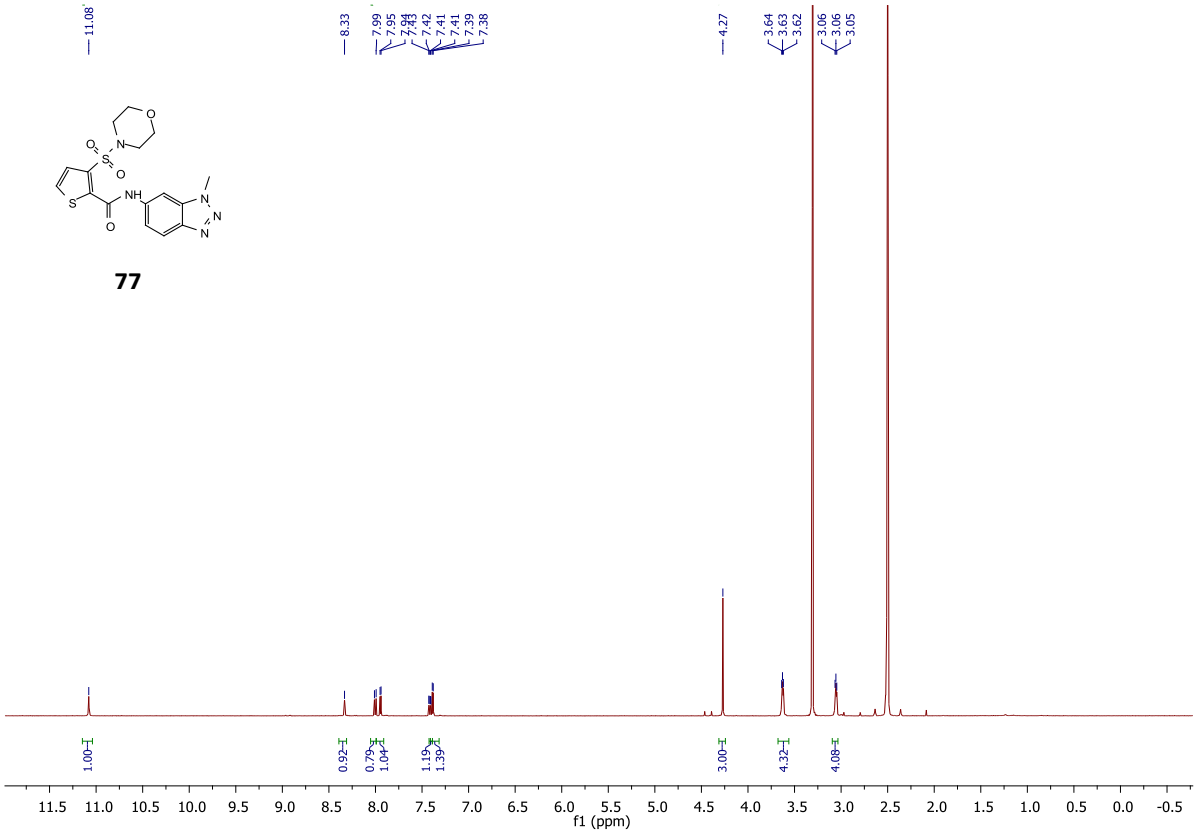
143


13.83
7.93
7.92
7.40
7.39
3.62
3.61
3.59
3.16
3.14
3.13
0.86
0.98
1.00
4.15
4.15
f1 (ppm)

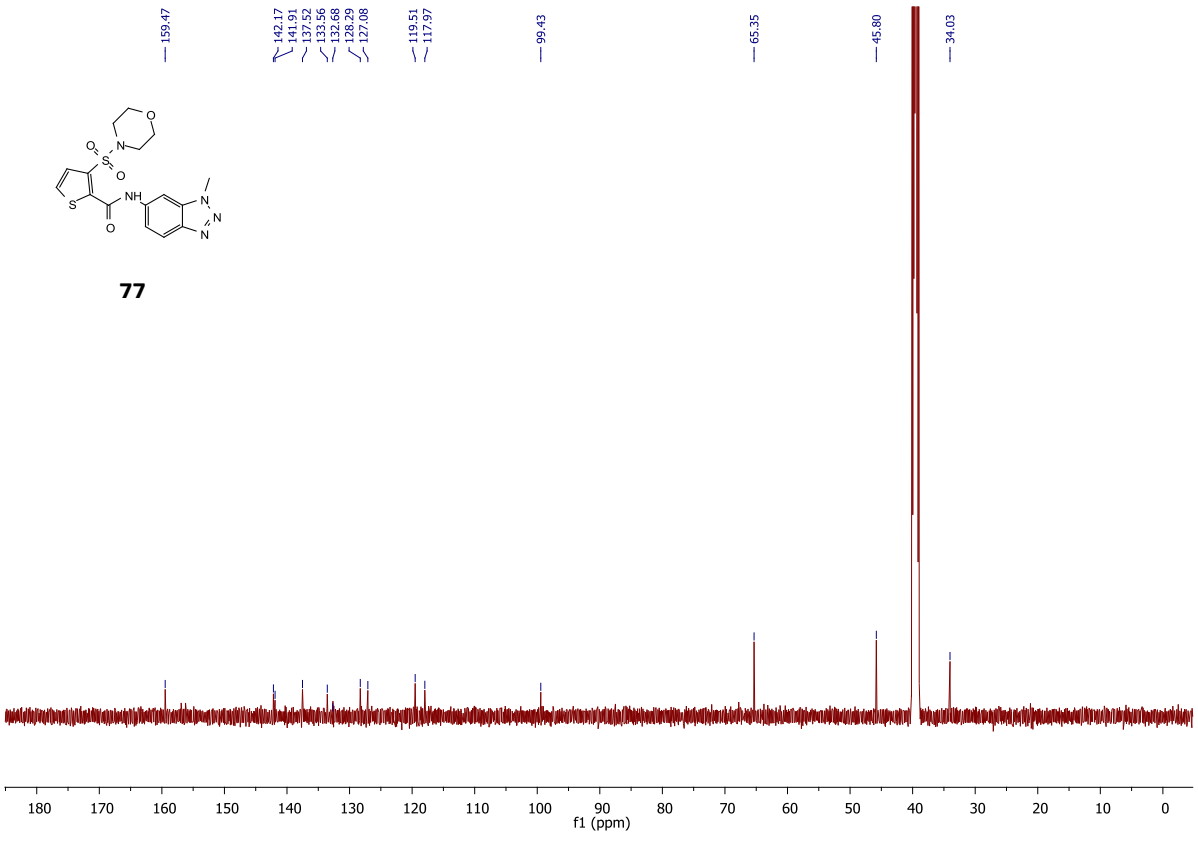
144


160.95
137.45
136.65
130.25
130.07
f1 (ppm)

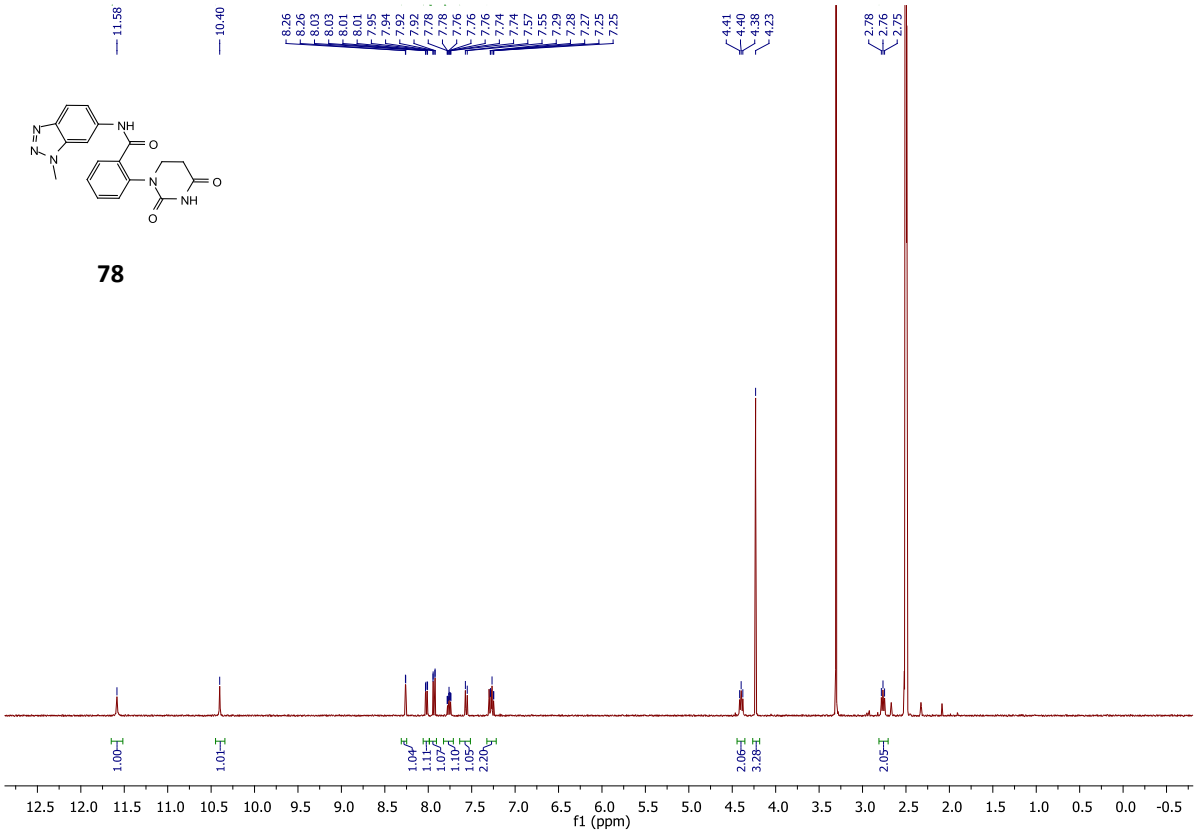
144


11.08
8.33
7.99
7.95
7.94
7.43
7.42
7.41
7.41
7.39
7.38
4.27
3.64
3.63
3.62
3.06
3.06
3.05
1.00
0.92
0.79
1.04
1.19
1.39
3.00
4.32
4.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

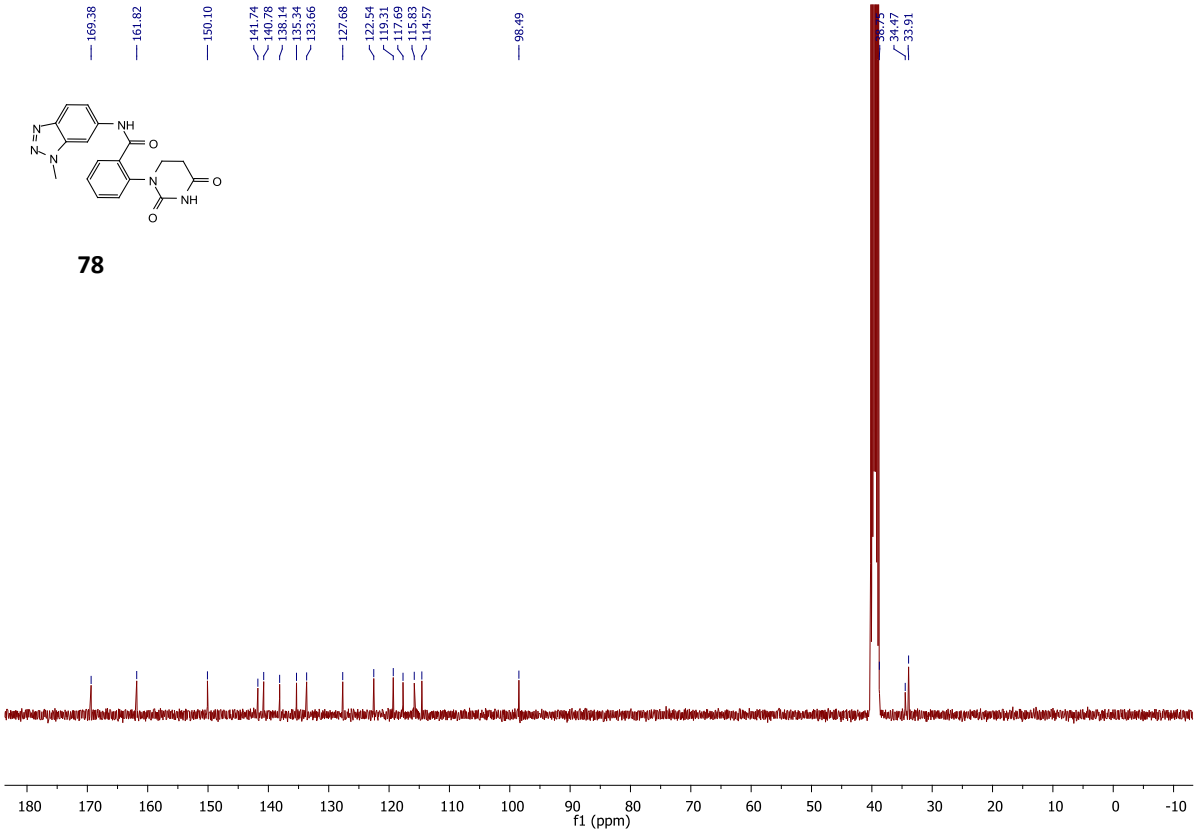
77


159.47
142.17
141.91
137.52
133.56
132.68
128.29
127.08
119.51
117.97
99.43
65.35
45.80
34.03
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

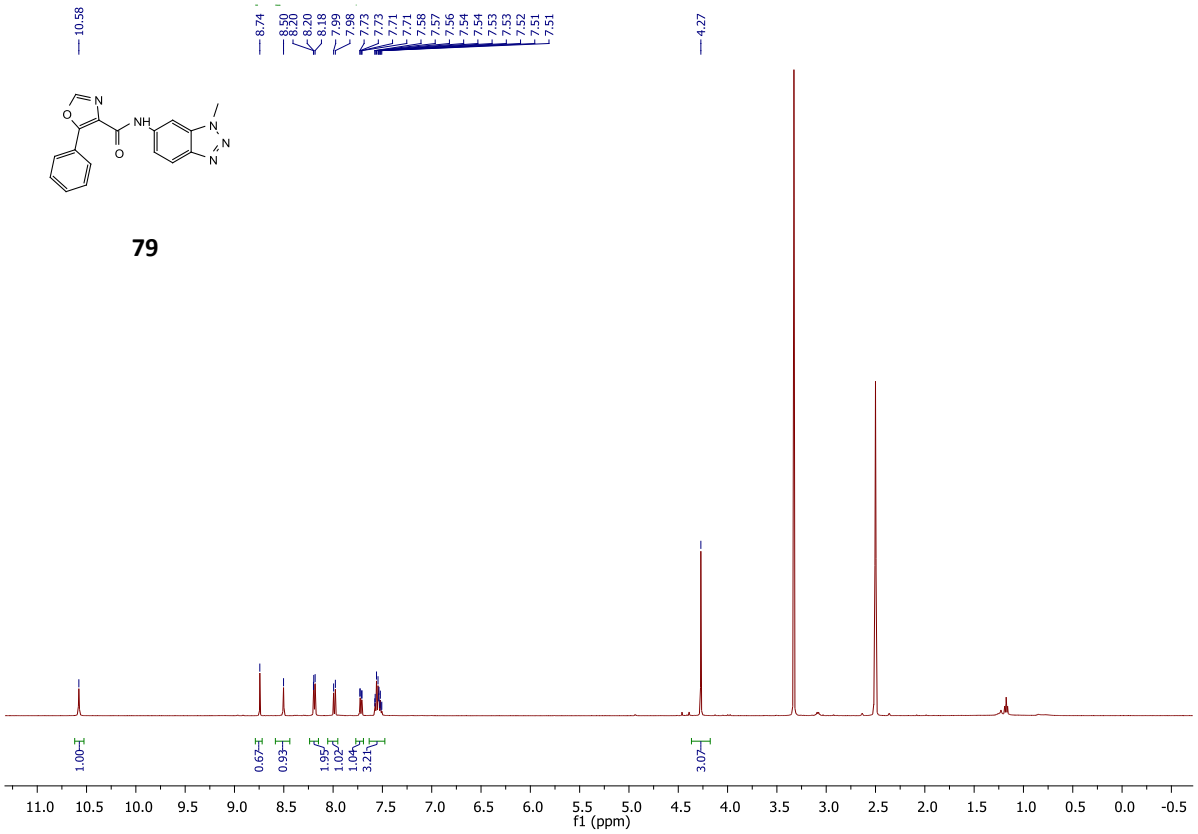
77


11.58
10.40
8.26
8.26
8.03
8.03
8.01
8.01
7.95
7.94
7.92
7.92
7.78
7.78
7.76
7.76
7.76
7.74
7.74
7.57
7.55
7.29
7.28
7.27
7.25
7.25
4.41
4.40
4.38
4.23
2.78
2.76
2.75
NH
O
N
N
N
O
NH
O
1.00
1.01
1.04
1.11
1.07
1.10
1.05
2.20
2.06
3.28
2.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

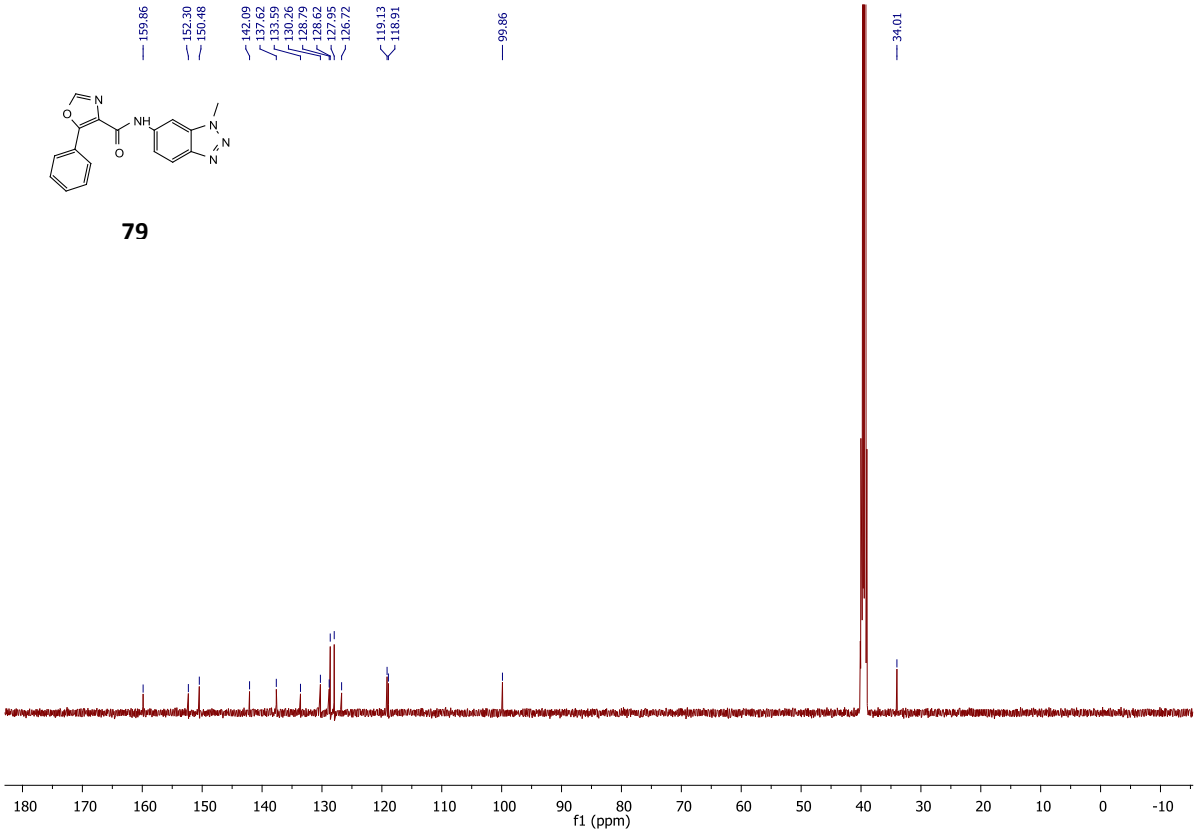
78


169.38
161.82
150.10
141.74
140.78
138.14
135.34
133.66
127.68
122.54
119.31
117.69
115.83
114.57
98.49
38.75
34.47
33.91
NH
O
N
N
N
O
NH
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

78

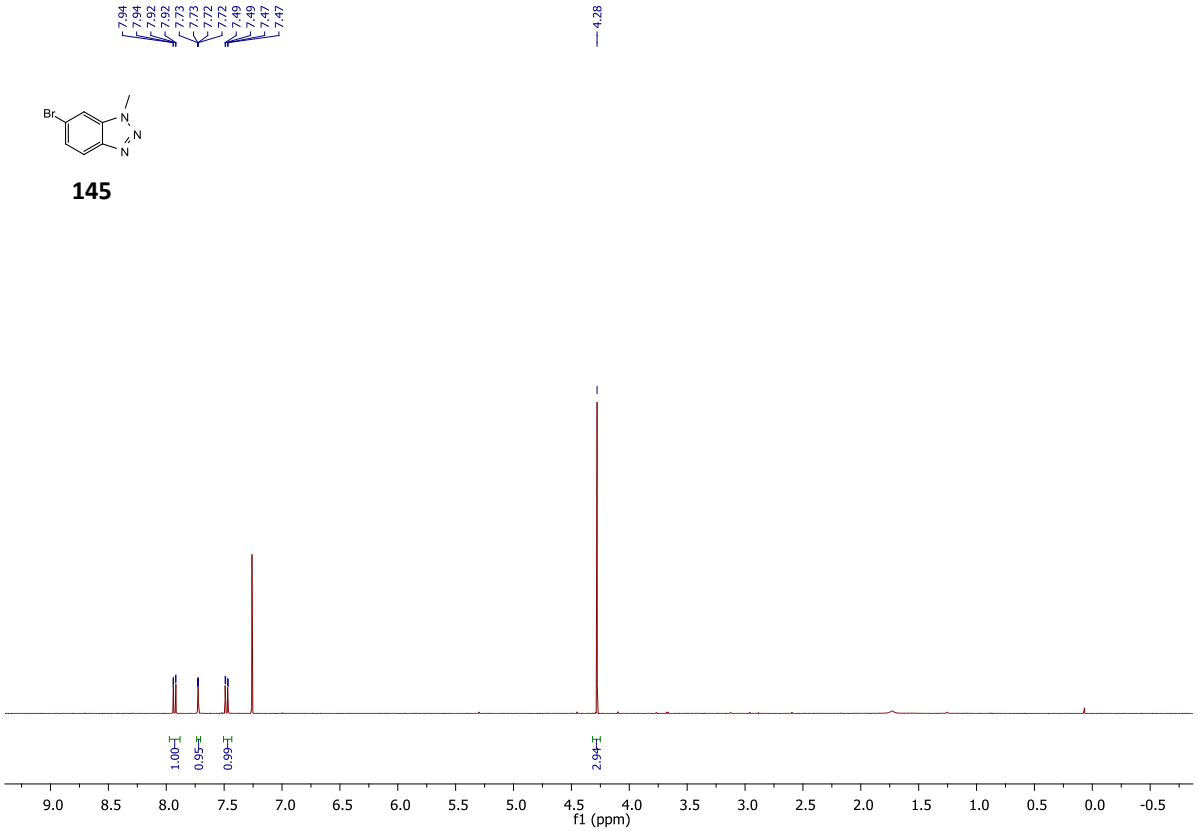

10.58
8.74
8.50
8.20
8.18
7.99
7.98
7.73
7.73
7.71
7.71
7.58
7.57
7.56
7.54
7.54
7.53
7.52
7.51
7.51
4.27
1.00
0.67
0.93
1.95
1.02
1.04
3.21
3.07
f1 (ppm)

79

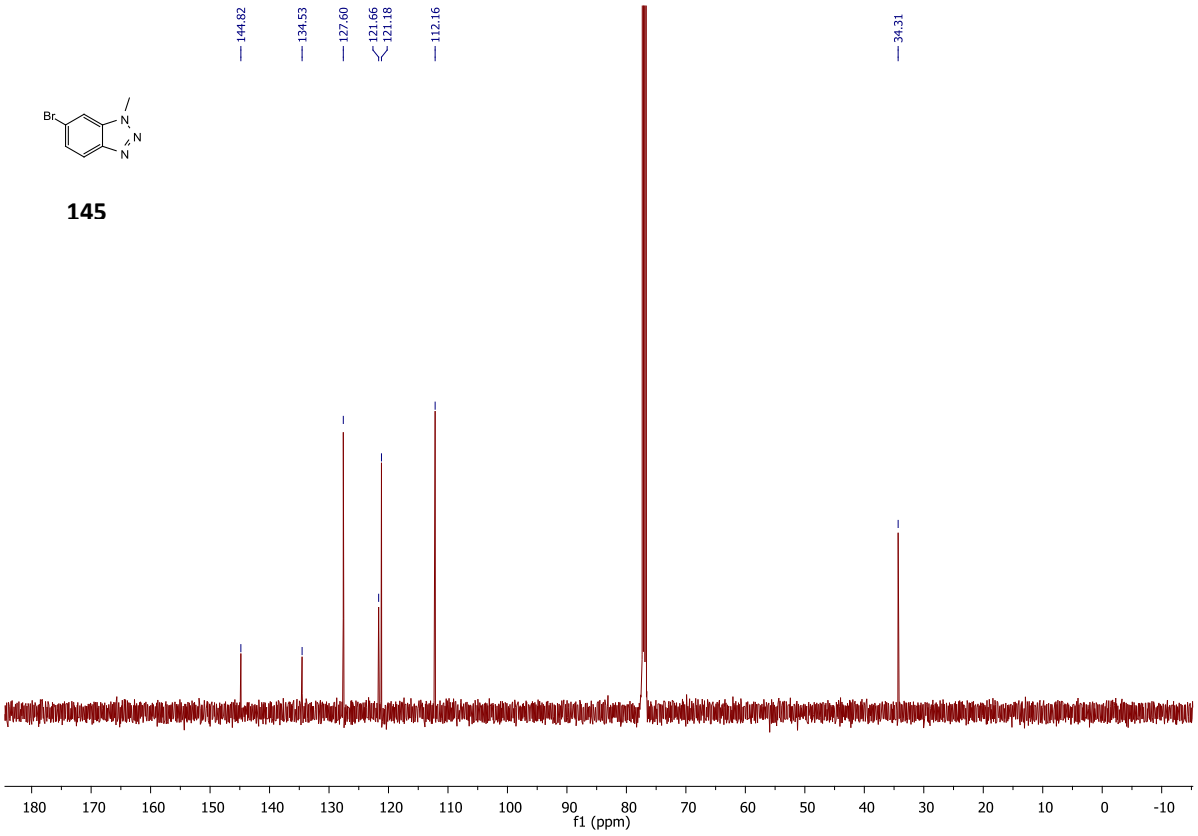

159.86
152.30
150.48
142.09
137.62
133.59
130.26
128.79
128.62
127.95
126.72
119.13
118.91
99.86
34.01
f1 (ppm)

79

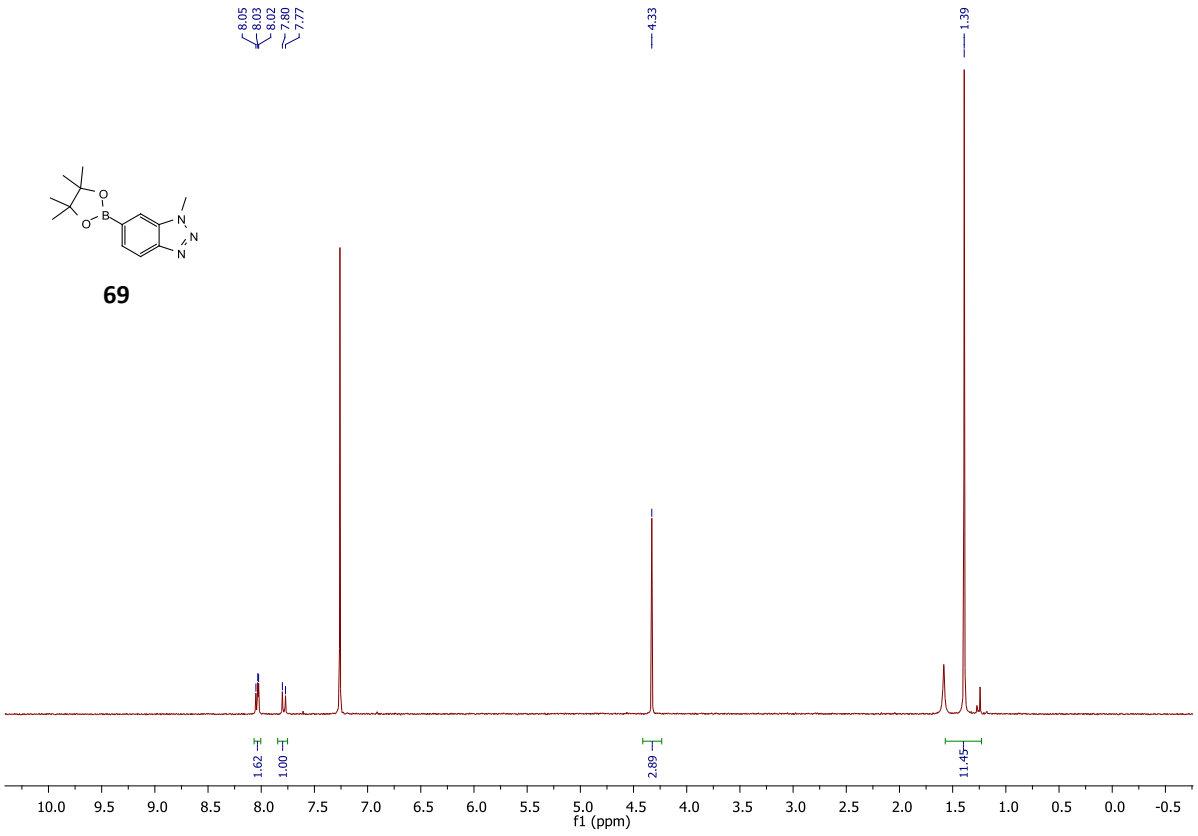
BRD4(1) inhibitors without a linker:



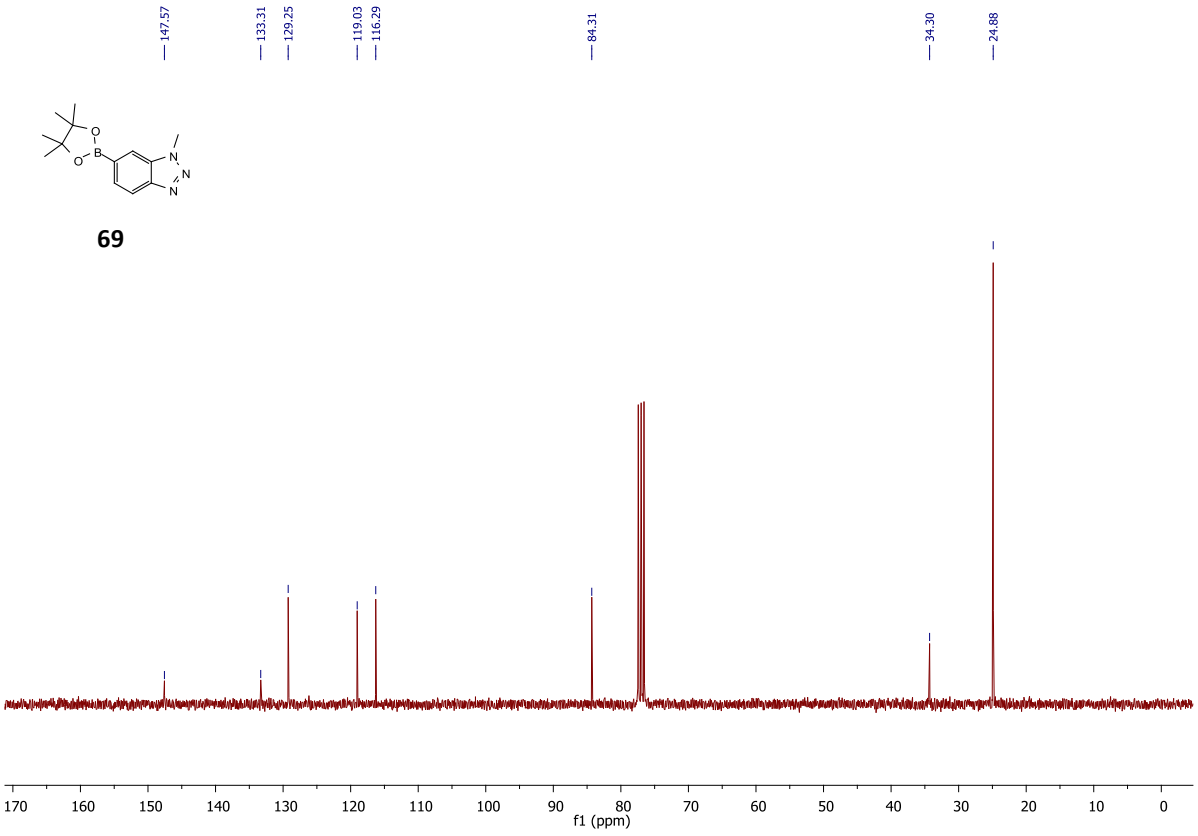
145



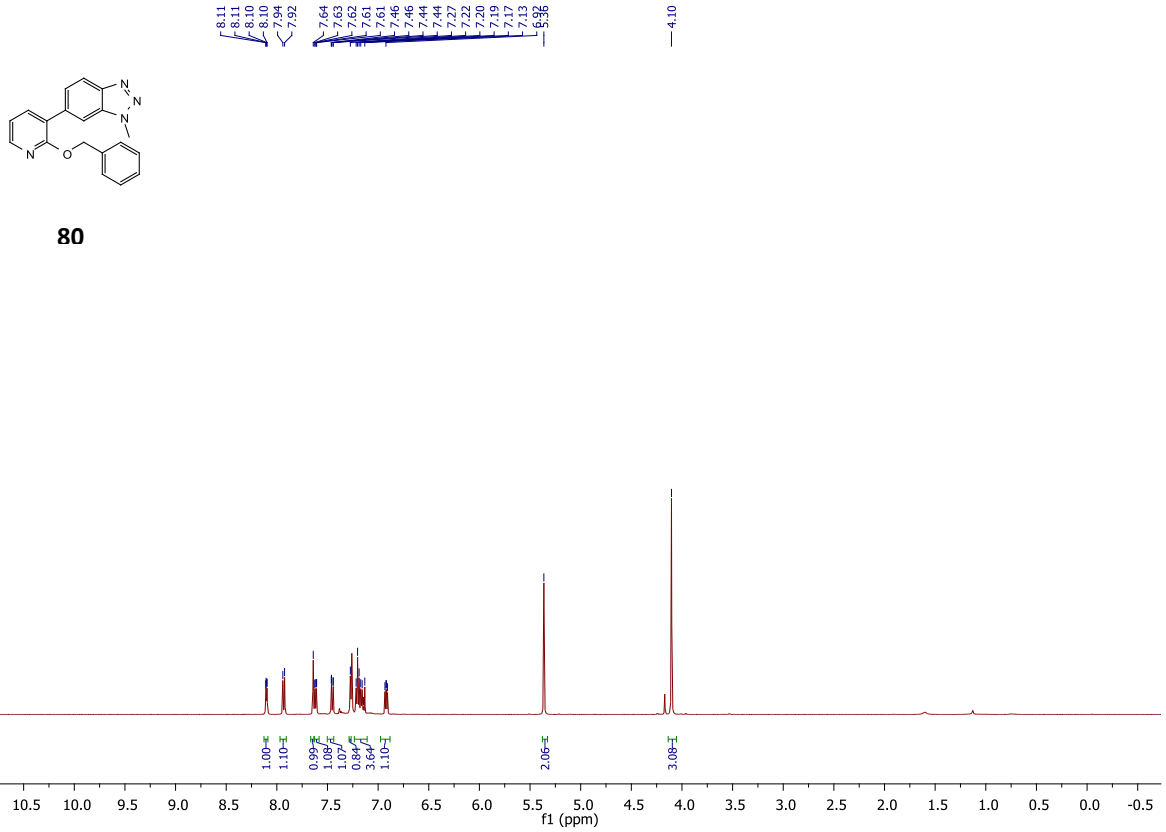
145


8.05
8.03
8.02
7.80
7.77
4.33
1.39
1.62
1.00
2.89
11.45
f1 (ppm)

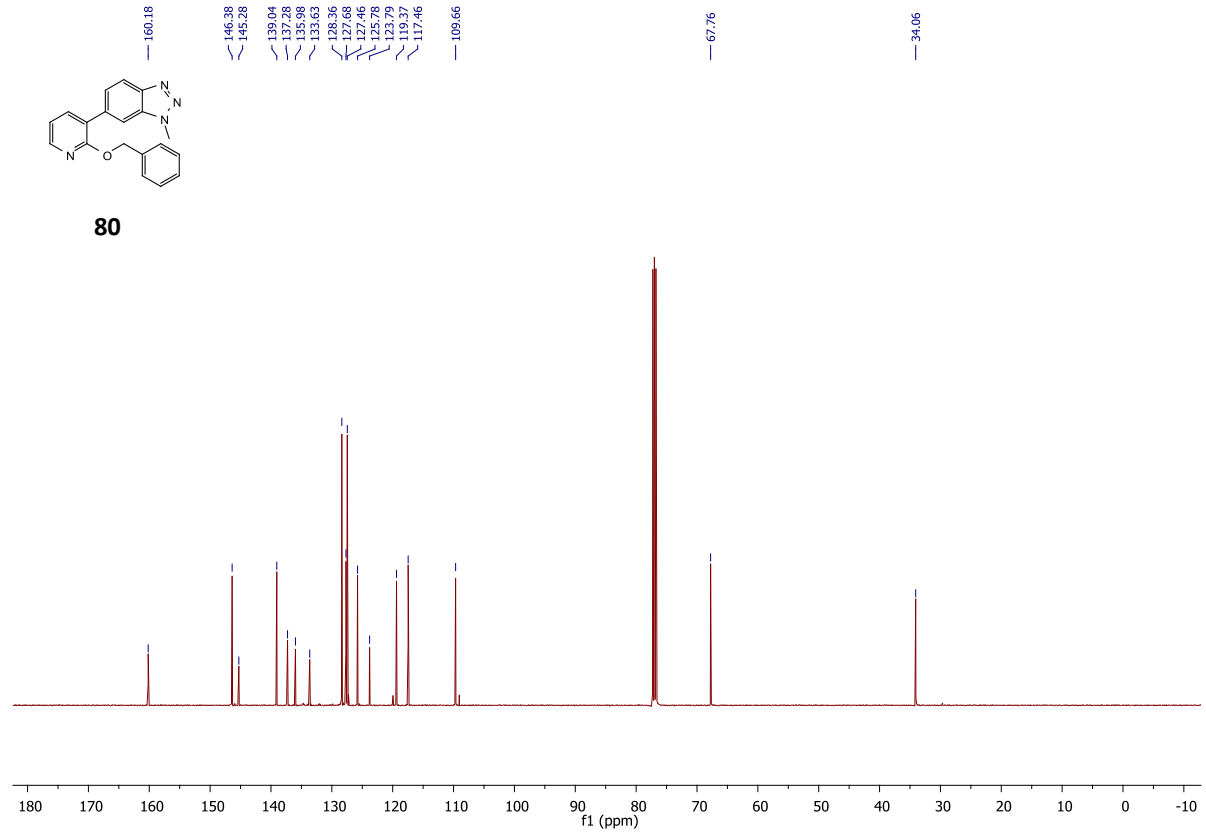
69


147.57
133.31
129.25
119.03
116.29
84.31
34.30
24.88
f1 (ppm)

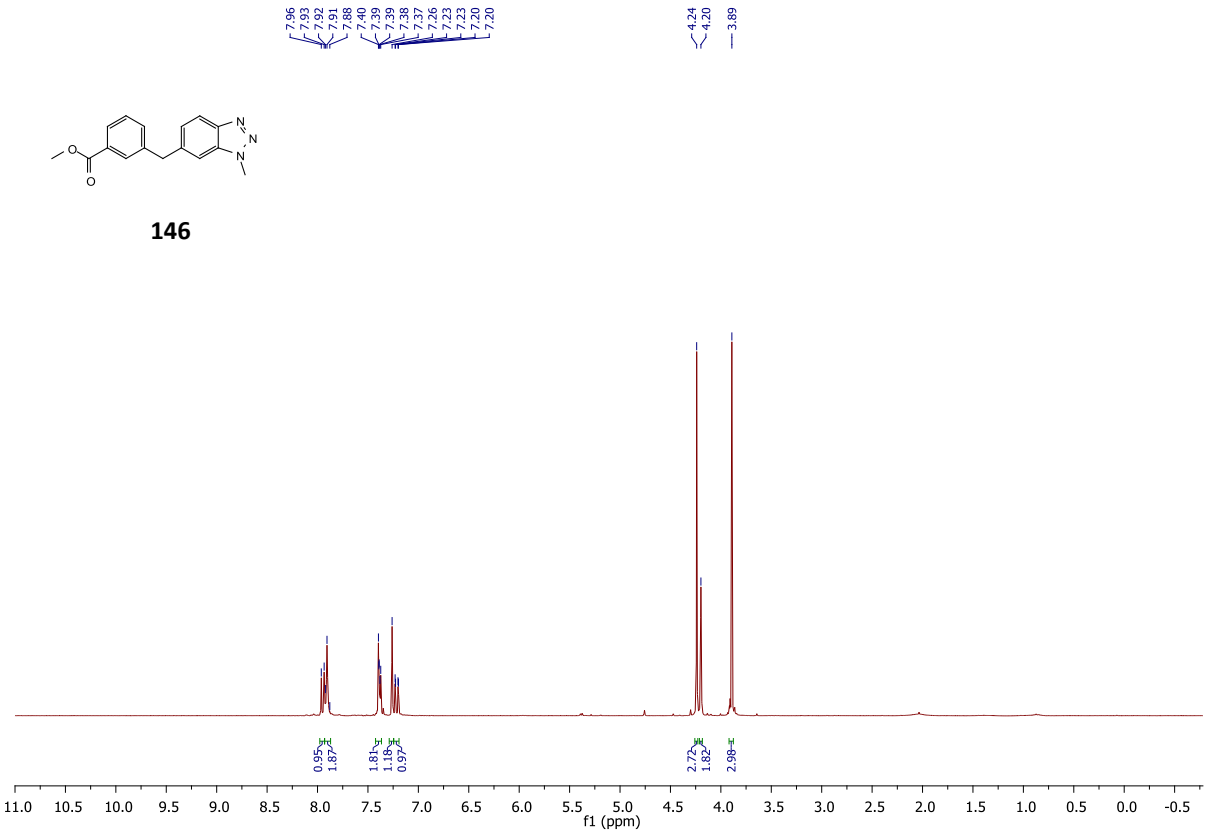
69


8.11
8.11
8.10
8.10
7.94
7.92
7.64
7.63
7.62
7.61
7.61
7.46
7.46
7.44
7.44
7.27
7.22
7.20
7.19
7.17
7.13
6.92
5.36
4.10
1.00
1.10
0.99
1.08
1.07
0.84
3.64
1.10
2.06
3.08
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

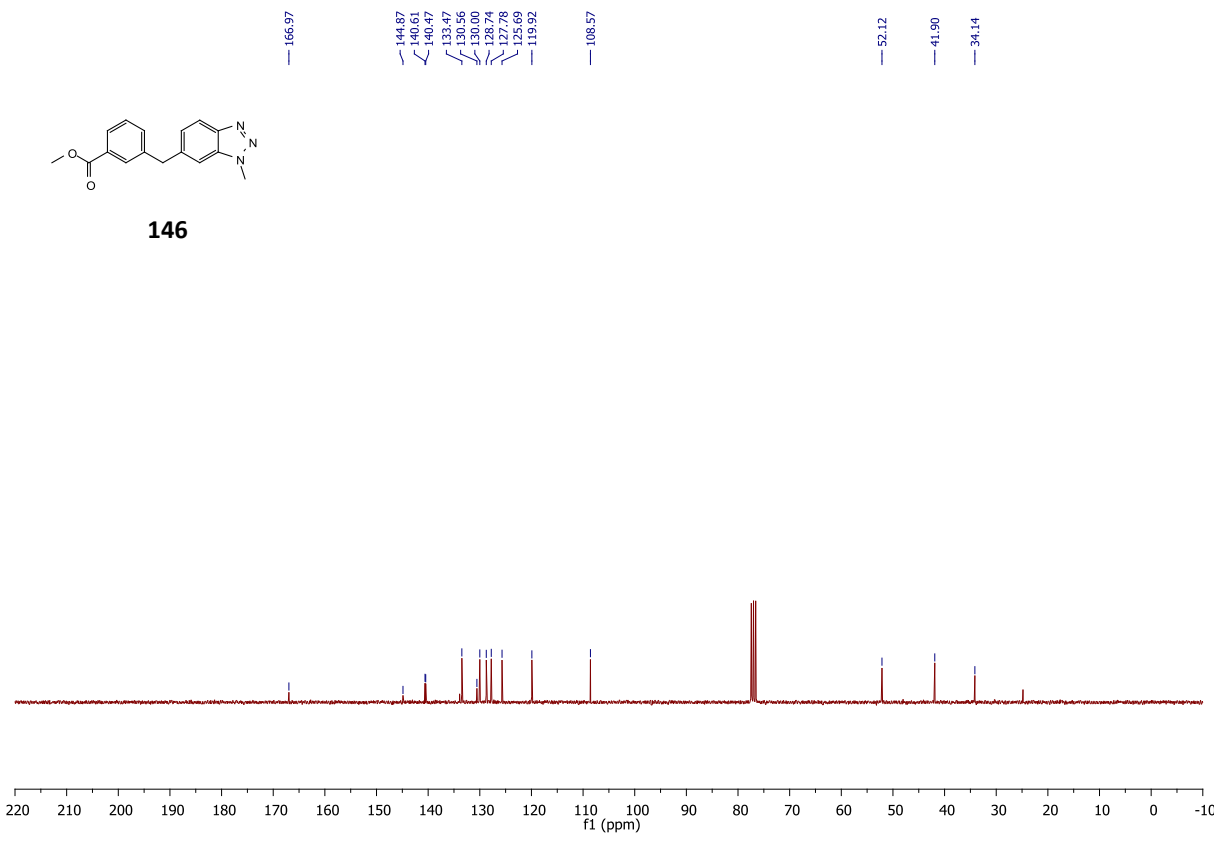
80


160.18
146.38
145.28
139.04
137.28
135.98
133.63
128.36
127.68
127.46
125.78
123.79
119.37
117.46
109.66
67.76
34.06
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

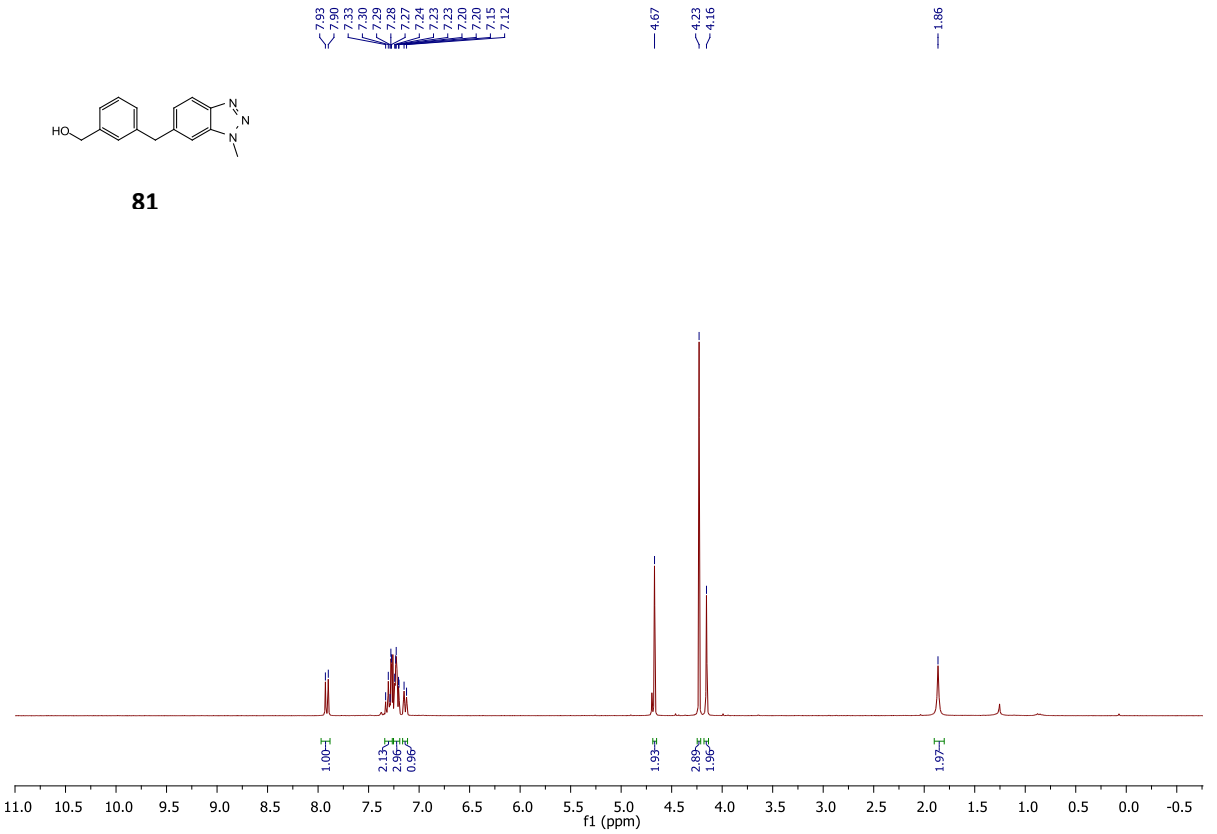
80


7.96
7.93
7.92
7.91
7.88
7.40
7.39
7.39
7.38
7.37
7.26
7.23
7.23
7.20
7.20
4.24
4.20
3.89
0.95
1.87
1.81
1.18
0.97
2.72
1.82
2.98
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

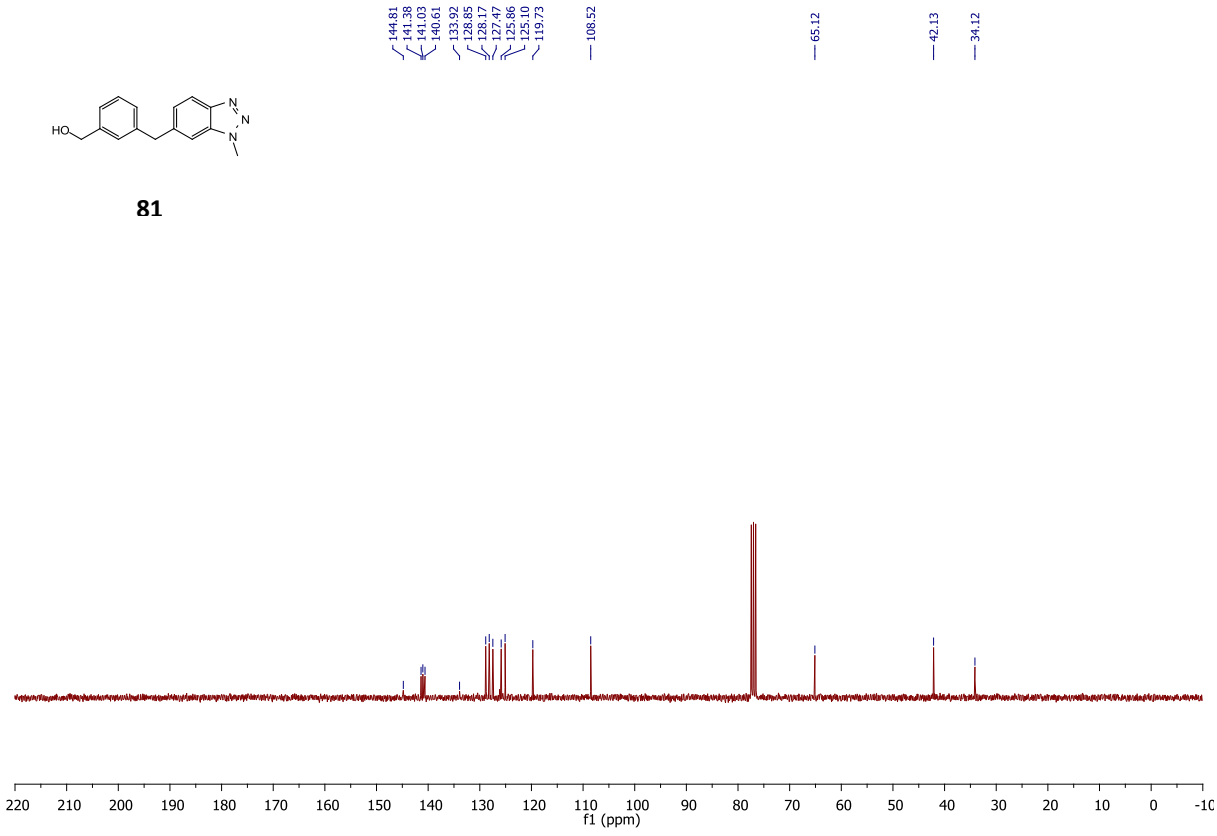
146


166.97
144.87
140.61
140.47
133.47
130.56
130.00
128.74
127.78
125.69
119.92
108.57
52.12
41.90
34.14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

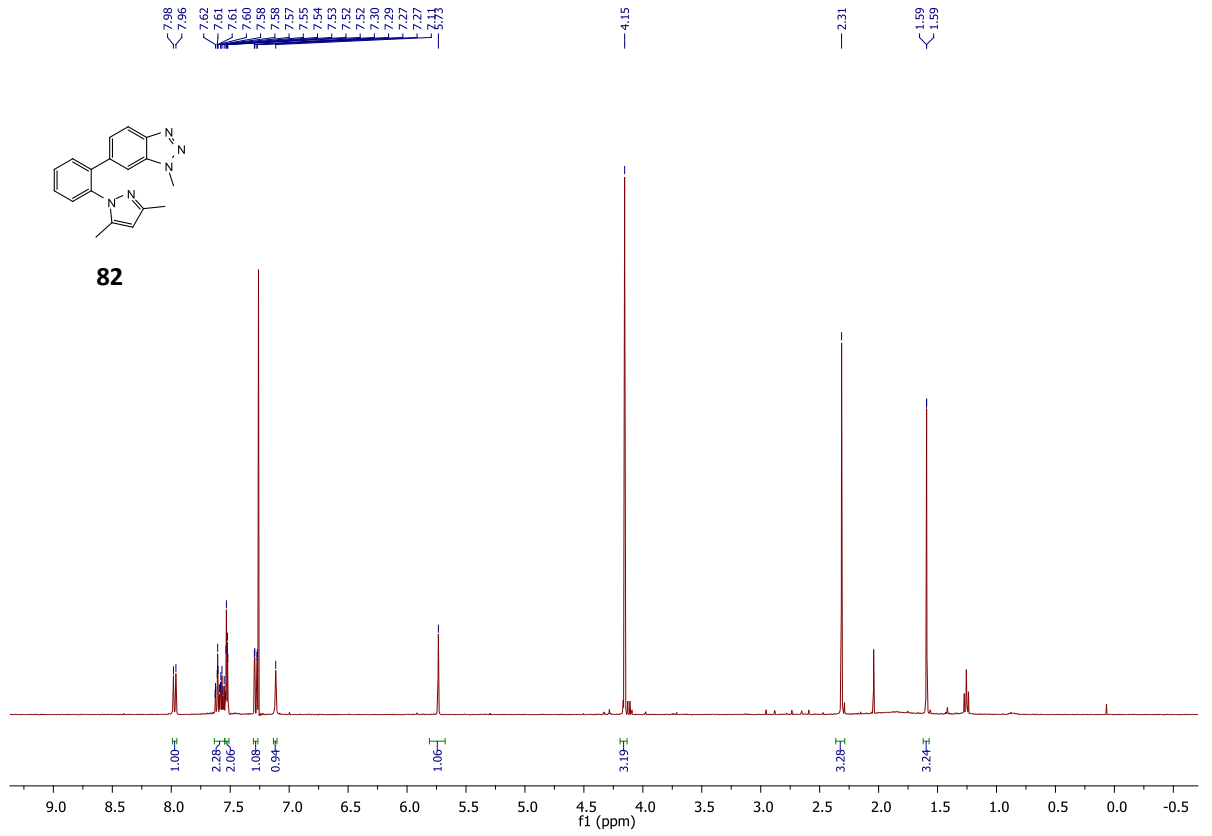
146


7.93
7.90
7.33
7.30
7.29
7.28
7.27
7.24
7.23
7.23
7.20
7.20
7.15
7.12
4.67
4.23
4.16
1.86
HO
N
N
N
1.00
2.13
2.96
0.96
1.93
2.89
1.96
1.97
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

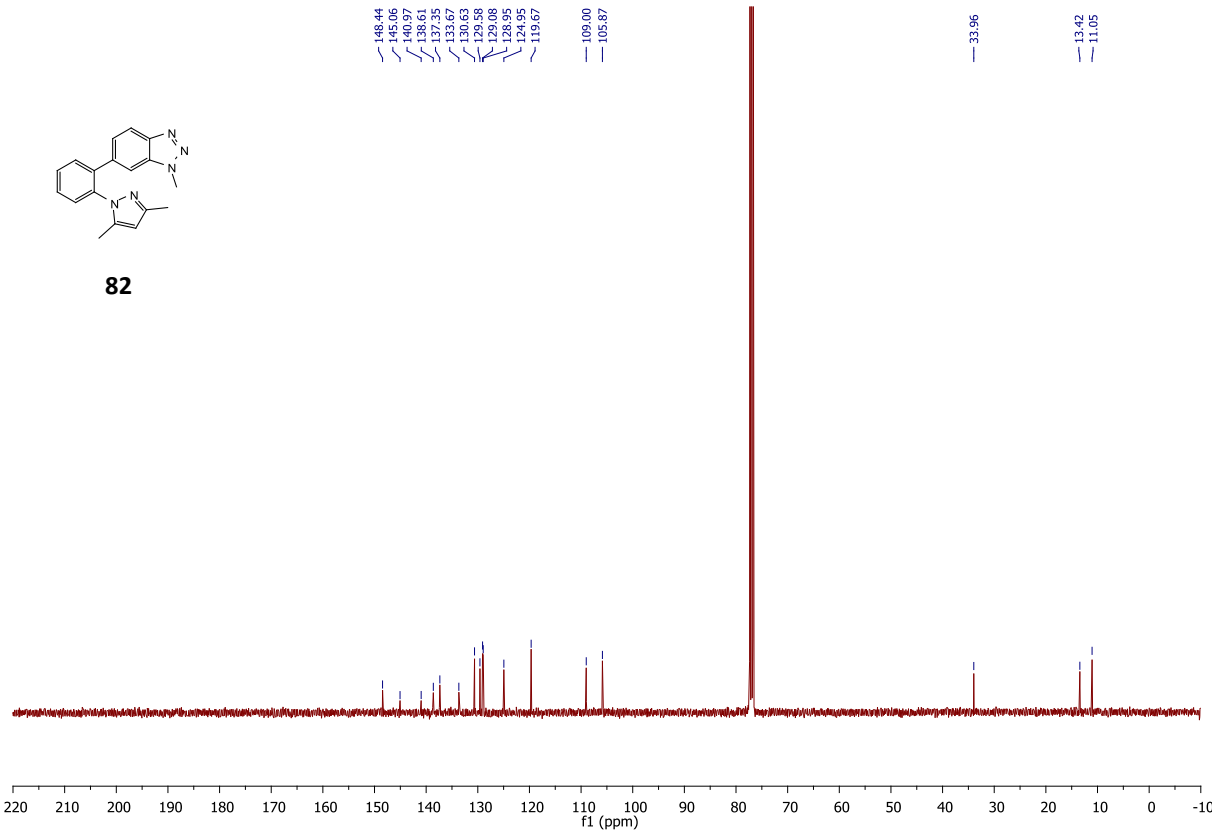
81


144.81
141.38
141.03
140.61
133.92
128.85
128.17
127.47
125.86
125.10
119.73
108.52
65.12
42.13
34.12
HO
N
N
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

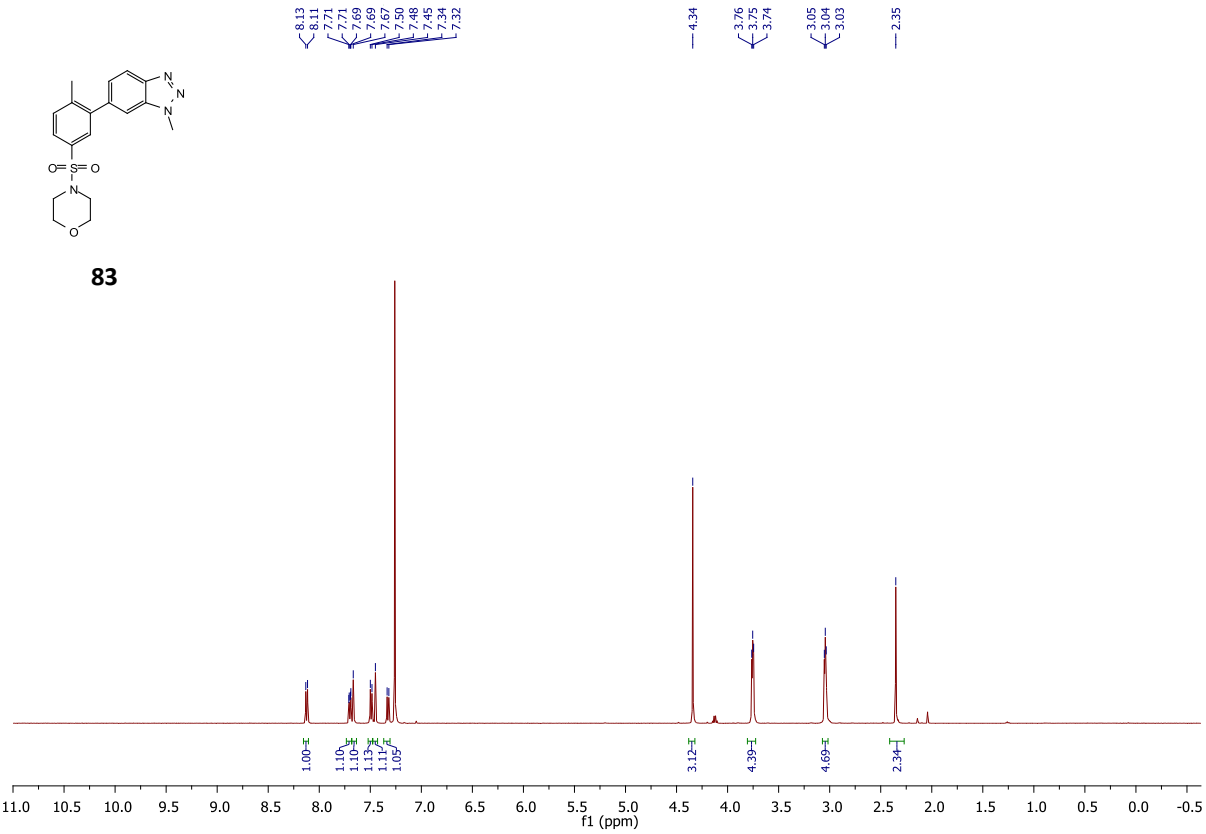
81


7.98
7.96
7.62
7.61
7.61
7.60
7.58
7.58
7.57
7.55
7.54
7.53
7.52
7.52
7.30
7.29
7.27
7.27
7.11
3.73
4.15
2.31
1.59
1.59
1.00
2.28
2.06
1.08
0.94
1.06
3.19
3.28
3.24
f1 (ppm)

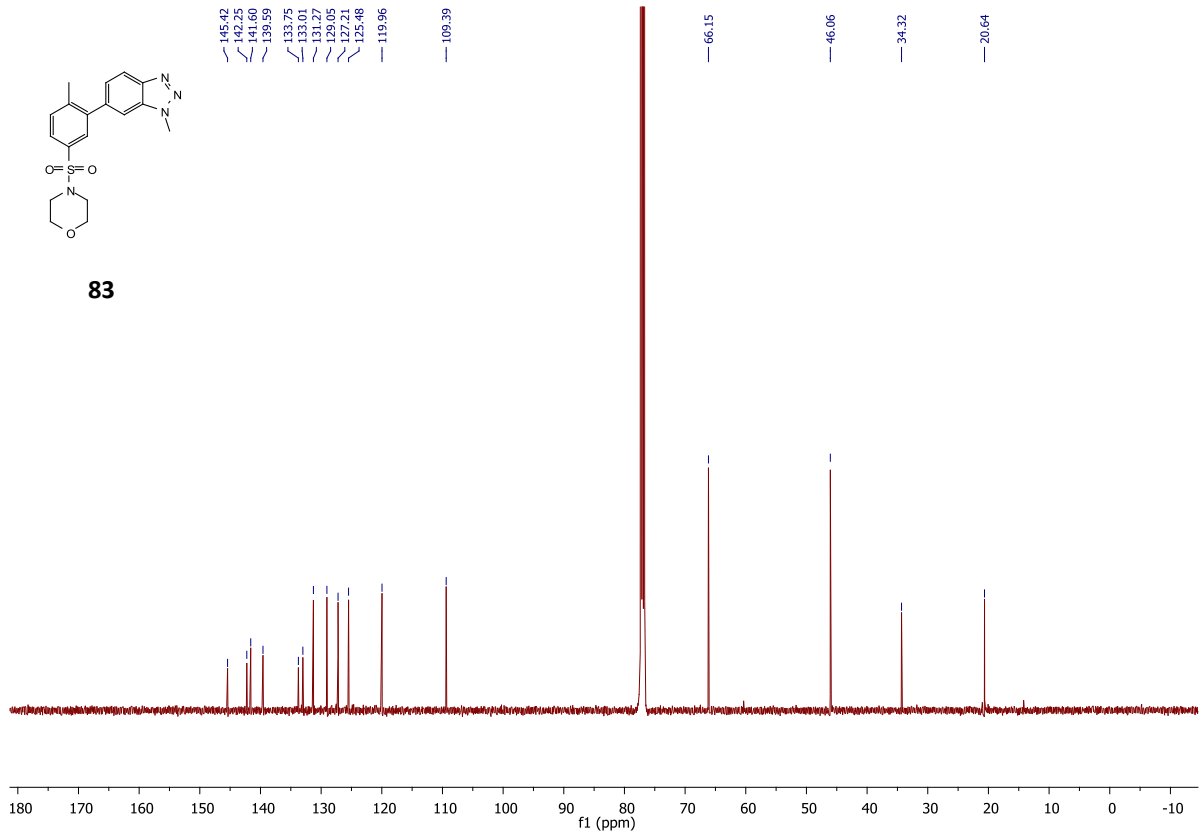
82


148.44
145.06
140.97
138.61
137.35
133.67
130.63
129.58
129.08
128.95
124.95
119.67
109.00
105.87
33.96
13.42
11.05
f1 (ppm)

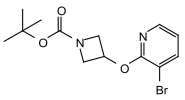
82


8.13
8.11
7.71
7.71
7.69
7.69
7.67
7.50
7.48
7.45
7.34
7.32
4.34
3.76
3.75
3.74
3.05
3.04
3.03
2.35
1.00
1.10
1.10
1.13
1.11
1.05
3.12
4.39
4.69
2.34
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

83

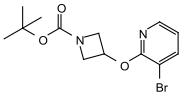

145.42
142.25
141.60
139.59
133.75
133.01
131.27
129.05
127.21
125.48
119.96
109.39
66.15
46.06
34.32
20.64
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

83



147

7.73
7.73
7.71
7.70
7.56
7.55
7.54
7.53
6.22
6.20
6.17
5.57
5.55
5.54
5.54
5.53
5.52
5.51
5.50
5.48
4.43
4.40
4.37
4.01
3.99
3.97
3.96
1.42
1.00
1.02
1.03
1.04
2.09
2.11
9.77
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



147

158.73
155.93
141.20
132.39
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106.86
80.36
55.63
46.37
28.19
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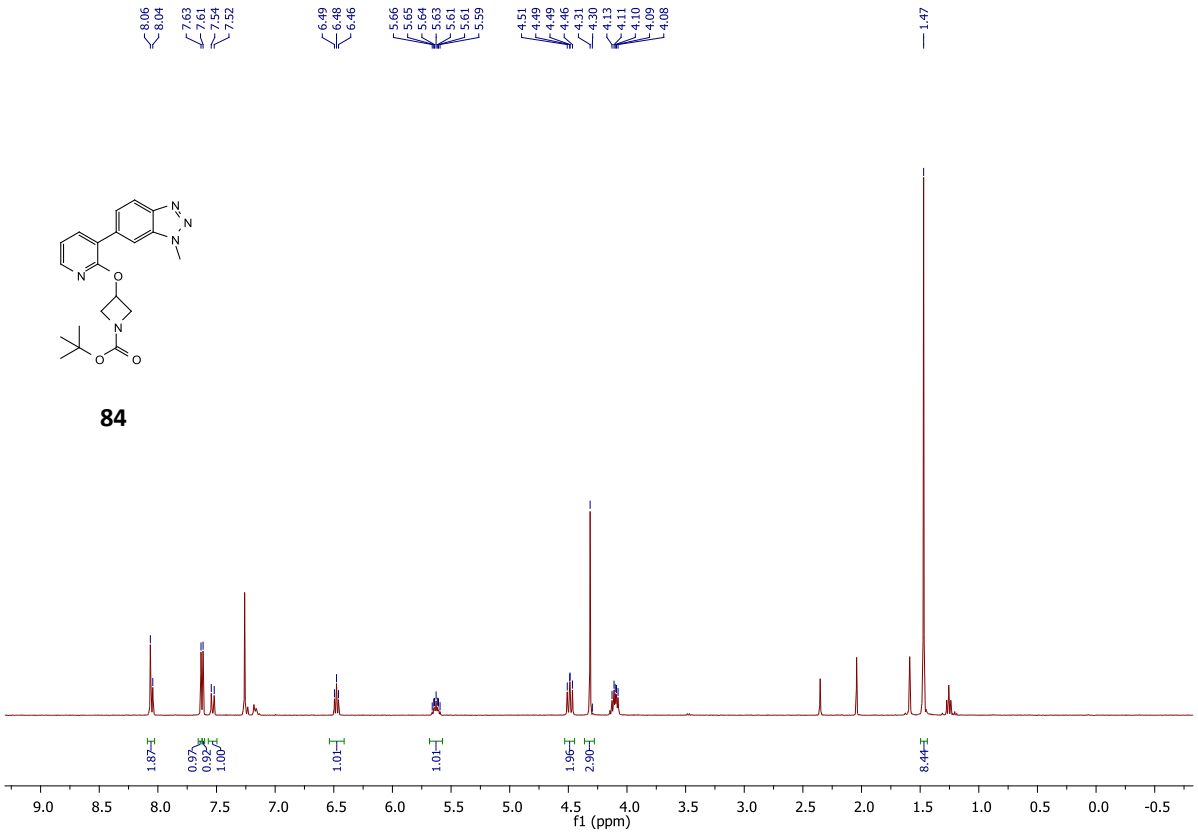
f1 (ppm)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5.61
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4.49
4.49
4.46
4.31
4.30
4.13
4.11
4.10
4.09
4.08
1.47
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0.92
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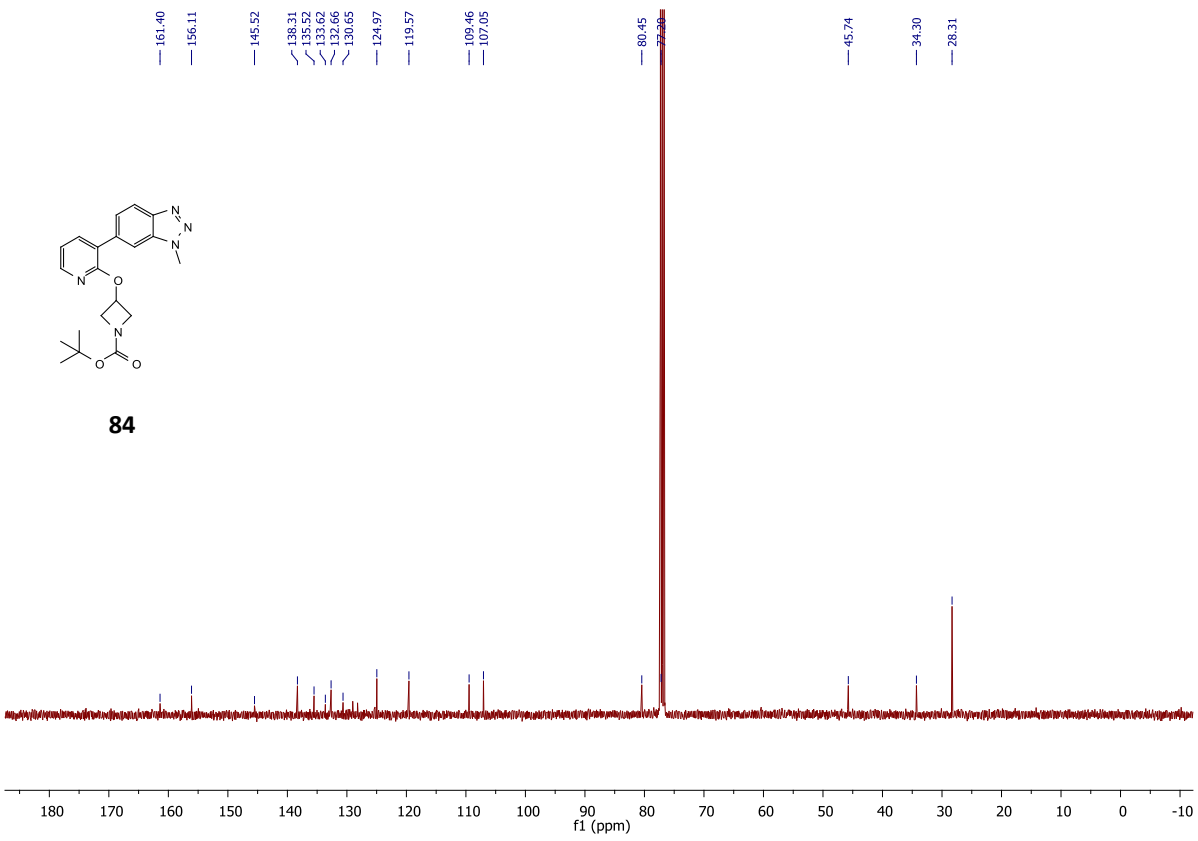
1.01
1.01
1.96
2.90
8.44
f1 (ppm)

84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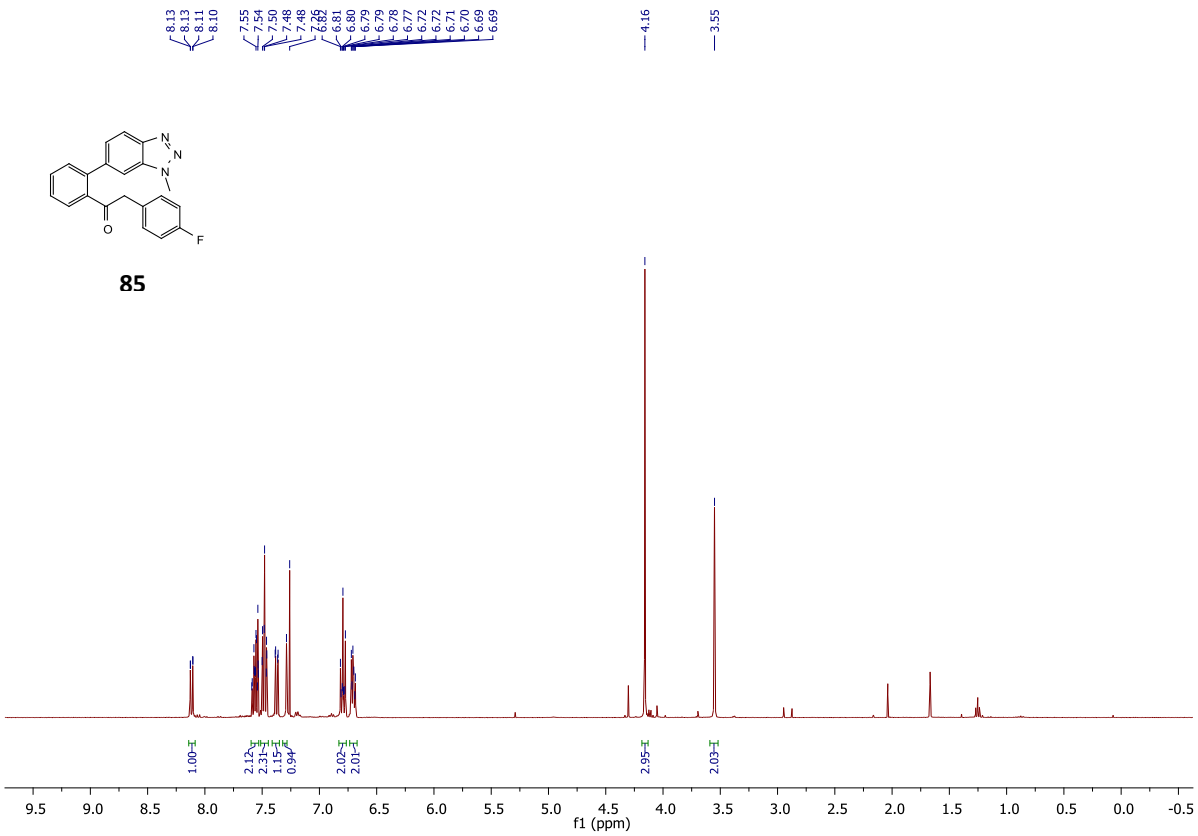
77.30
45.74
34.30
28.31
f1 (ppm)

84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8.11
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7.54
7.50
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7.48
7.02
6.81
6.80
6.79
6.79
6.78
6.77
6.72
6.72
6.71
6.70
6.69
6.69
4.16
3.55
1.00
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2.31
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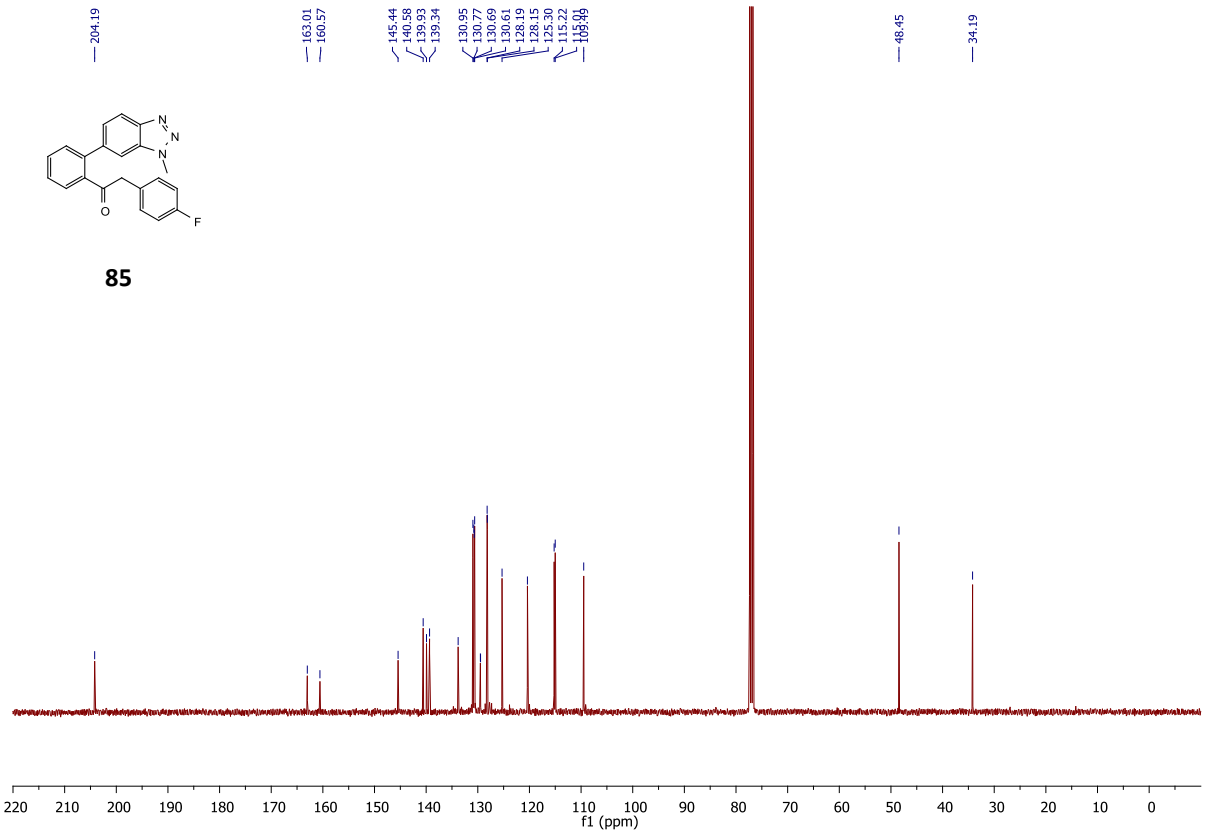
0.94
2.02
2.01
2.95
2.03
f1 (ppm)

85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139.93
139.34
130.95
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130.69
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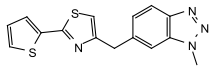
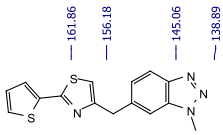
128.19
128.15
125.30
115.22
115.01
114.79
48.45
34.19
f1 (ppm)

85



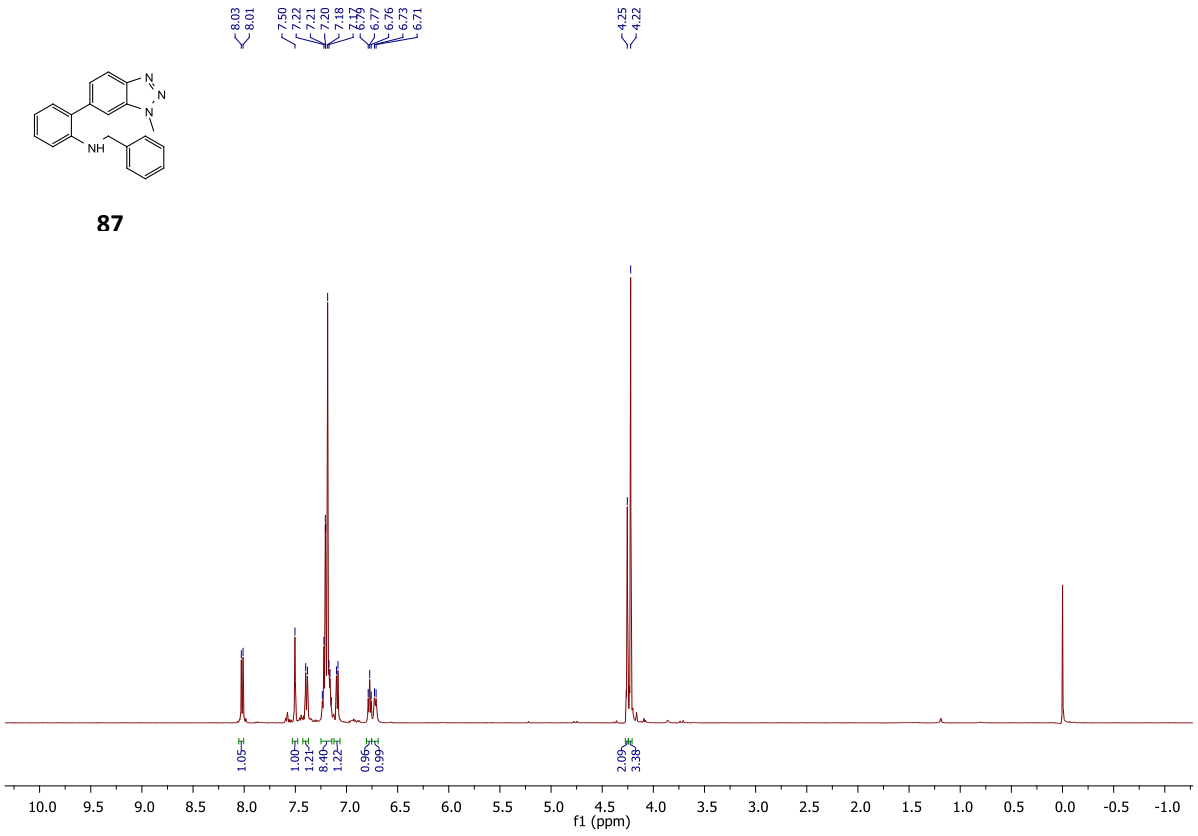
86

8.00
7.98
7.50
7.49
7.45
7.39
7.38
7.07
7.07
6.72
4.32
4.27
1.04
1.10
1.12
1.11
1.19
1.13
1.00
2.16
3.25
f1 (ppm)



86

161.86
156.18
145.06
138.89
137.25
133.93
127.86
127.62
126.57
125.80
119.85
113.98
108.91
38.05
34.15
f1 (ppm)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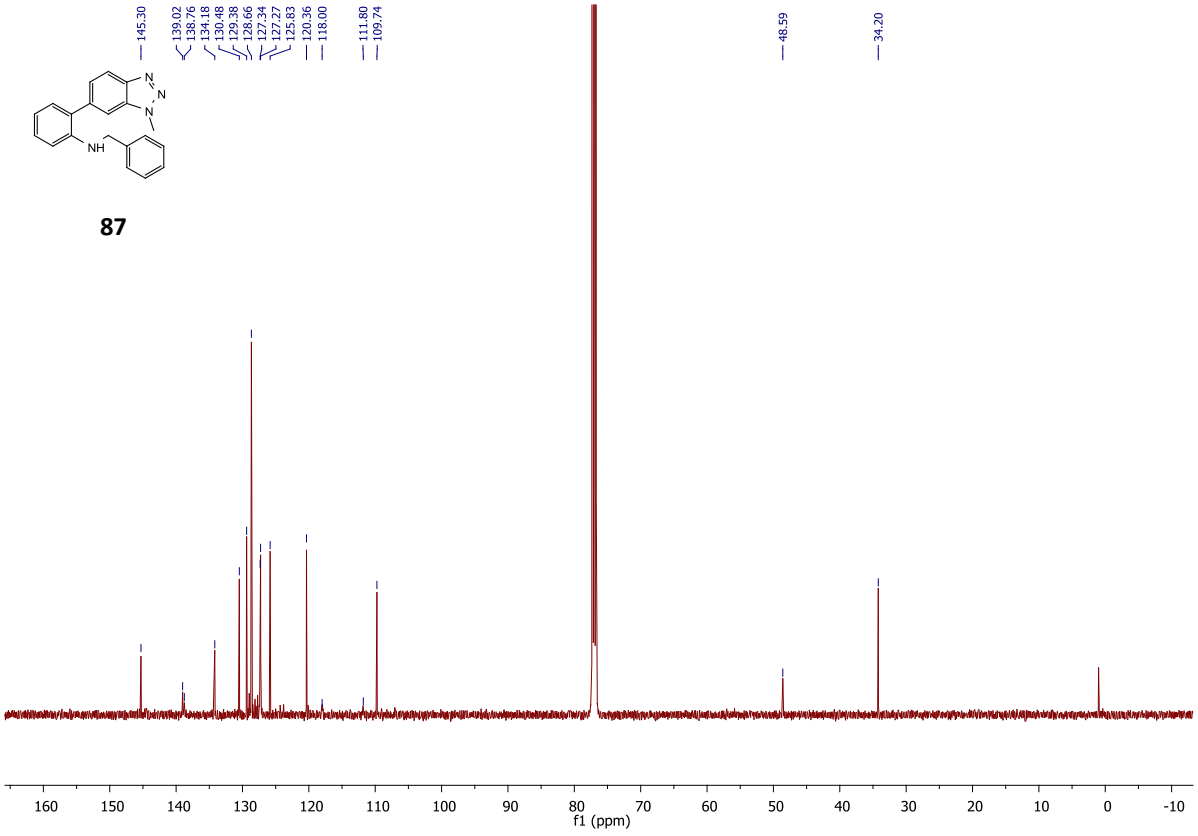
8.01
7.50
7.22
7.21
7.20
7.18
6.77
6.77
6.76
6.73
6.71
4.25
4.22
NH
1.05
1.00
1.21
8.40
1.22
0.96
0.99
2.09
3.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

87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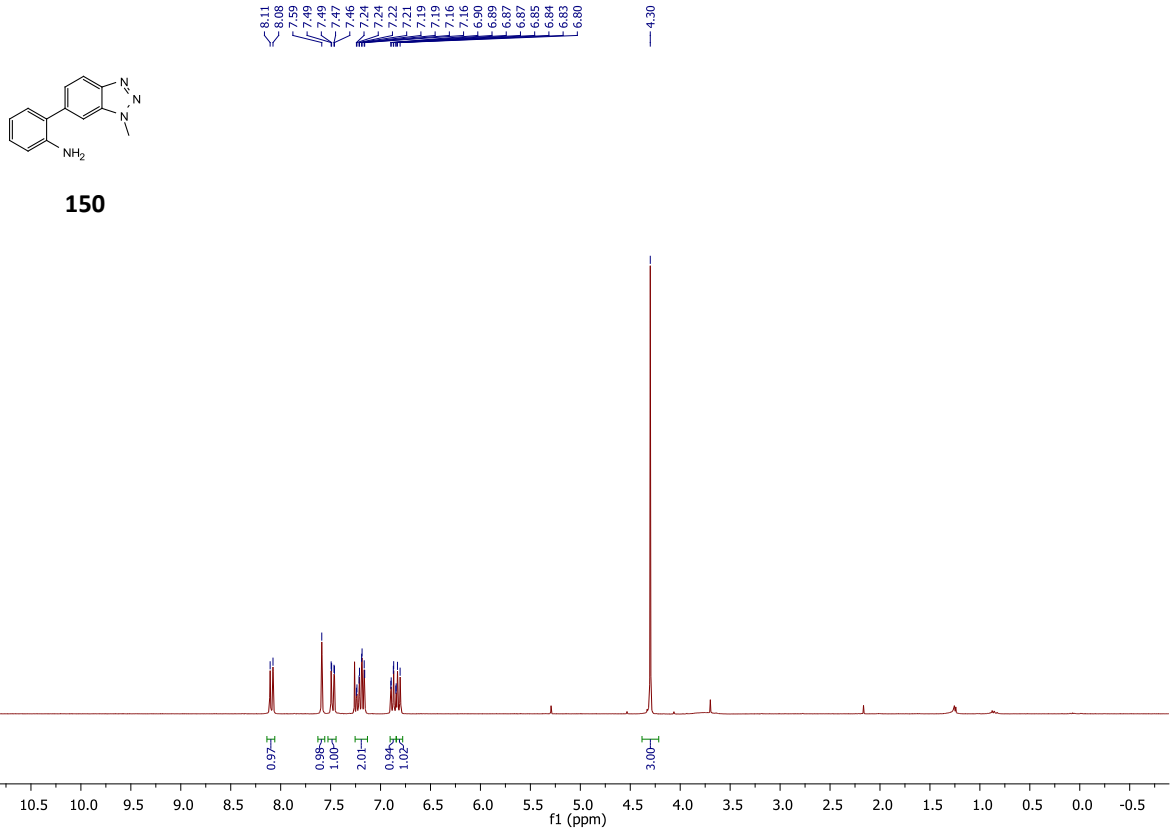
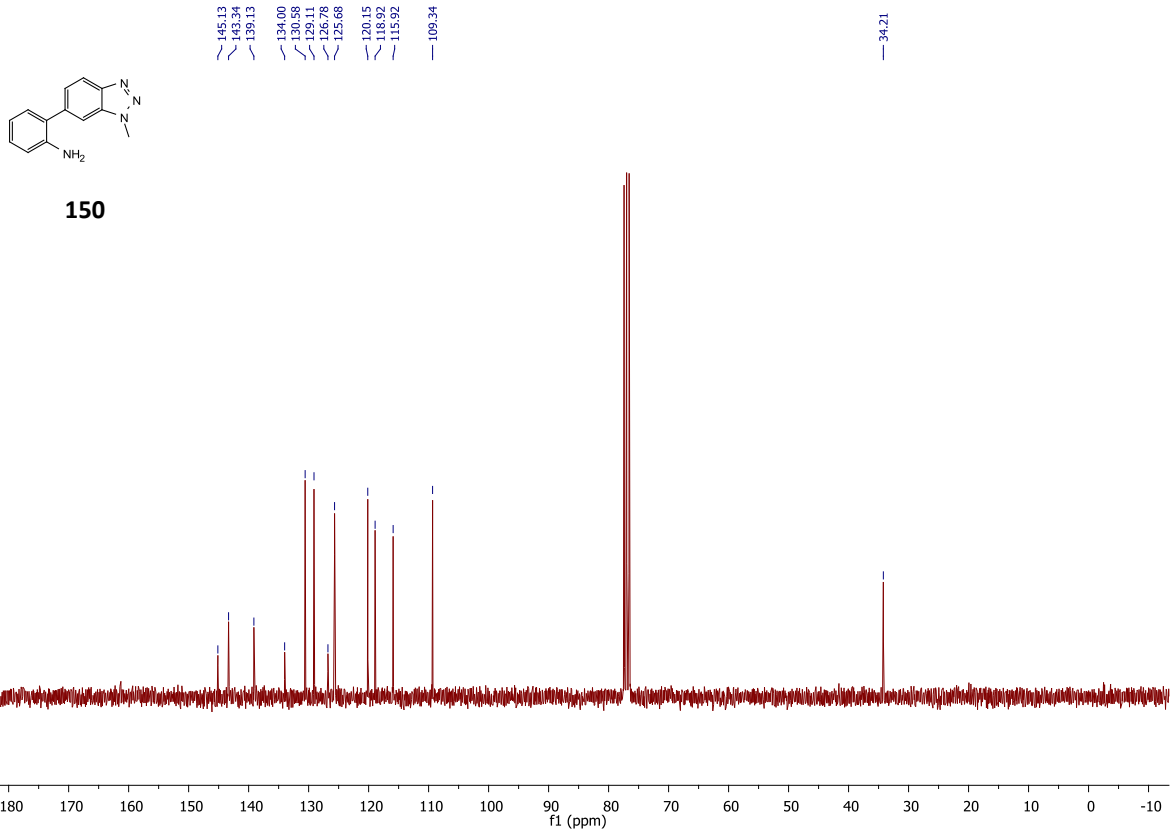
139.02
138.76
134.18
130.48
129.38
128.66
127.34
127.27
125.83
120.36
118.00
111.80
109.74
48.59
34.20
NH
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

87


8.11
8.08
7.59
7.49
7.49
7.47
7.46
7.24
7.24
7.22
7.21
7.19
7.19
7.16
7.16
6.90
6.89
6.87
6.87
6.85
6.84
6.83
6.80
4.30
NH2
0.97
0.98
1.00
2.01
0.94
1.02
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

150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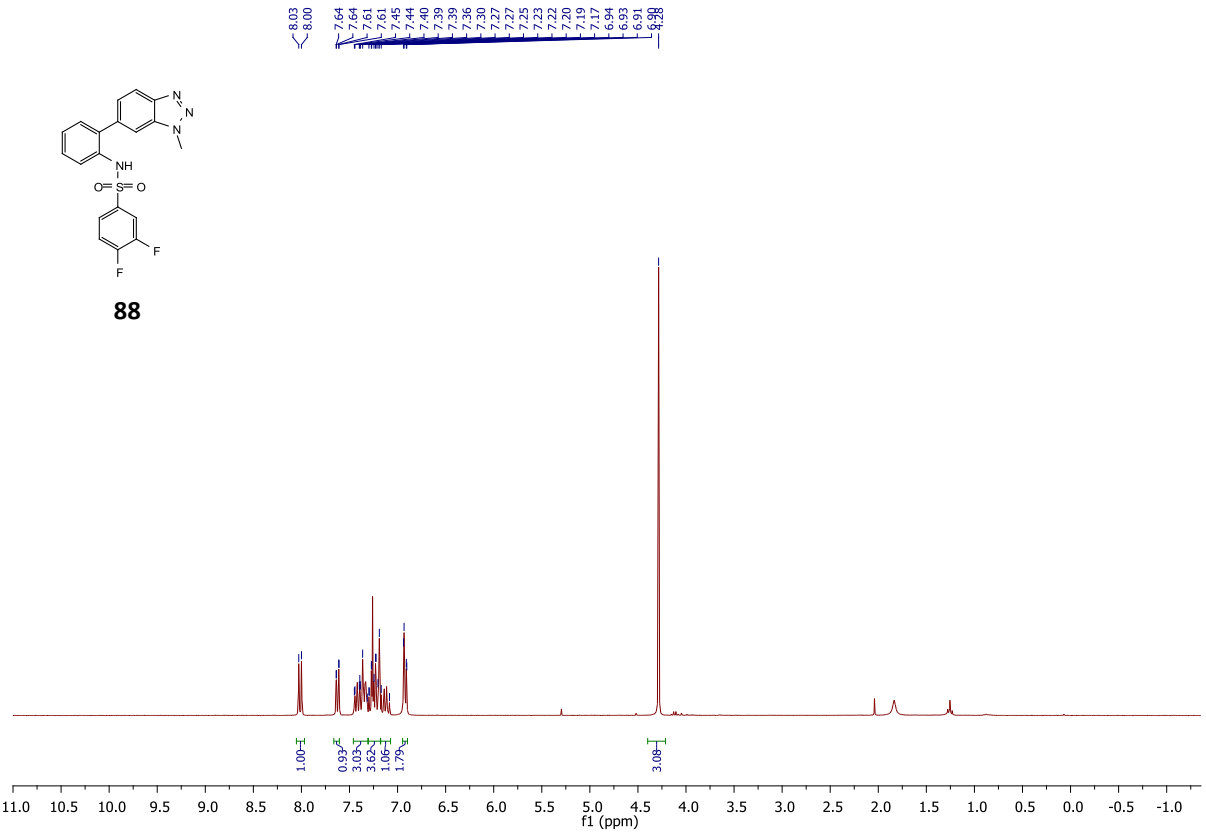
143.34
139.13
134.00
130.58
129.11
126.78
125.68
120.15
118.92
115.92
109.34
34.21
NH2
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

150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8.00
7.64
7.64
7.61
7.61
7.45
7.44
7.40
7.39
7.39
7.36
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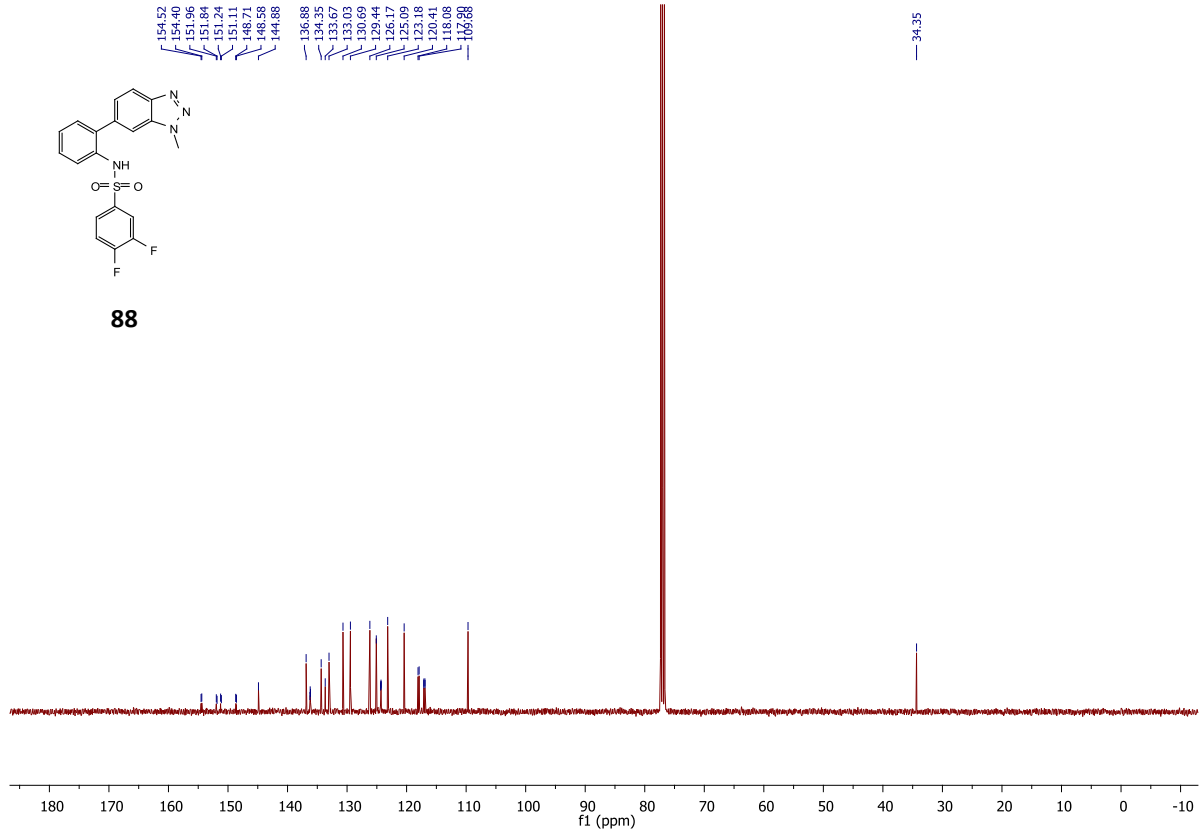
7.27
7.27
7.25
7.23
7.22
7.20
7.19
7.17
6.94
6.93
6.91
6.90
4.28
1.00
0.93
3.03
3.62
1.06
1.79
3.08
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

88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154.40
151.96
151.84
151.24
151.11
148.71
148.58
144.88
136.88
134.35
133.67
133.03
130.69
129.44
126.17
125.09
123.18
120.41
118.08
117.90
109.88
34.35
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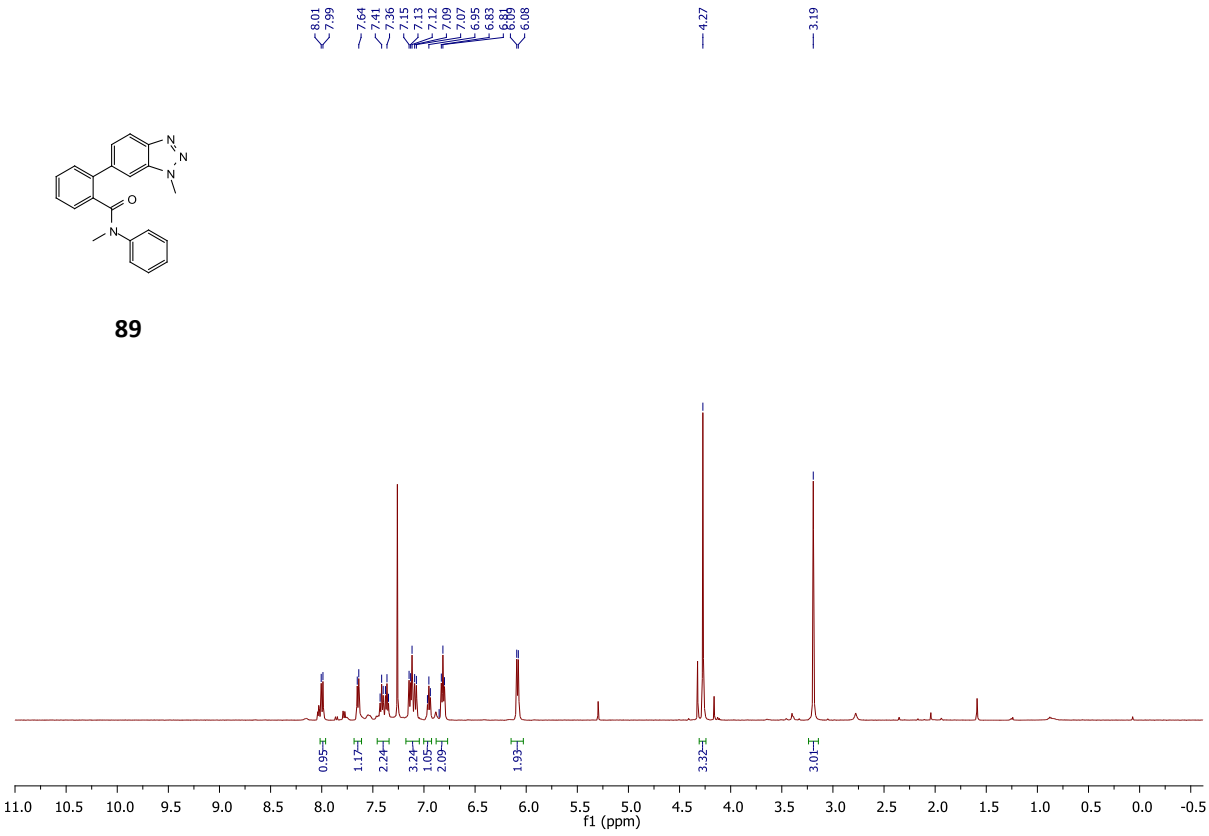
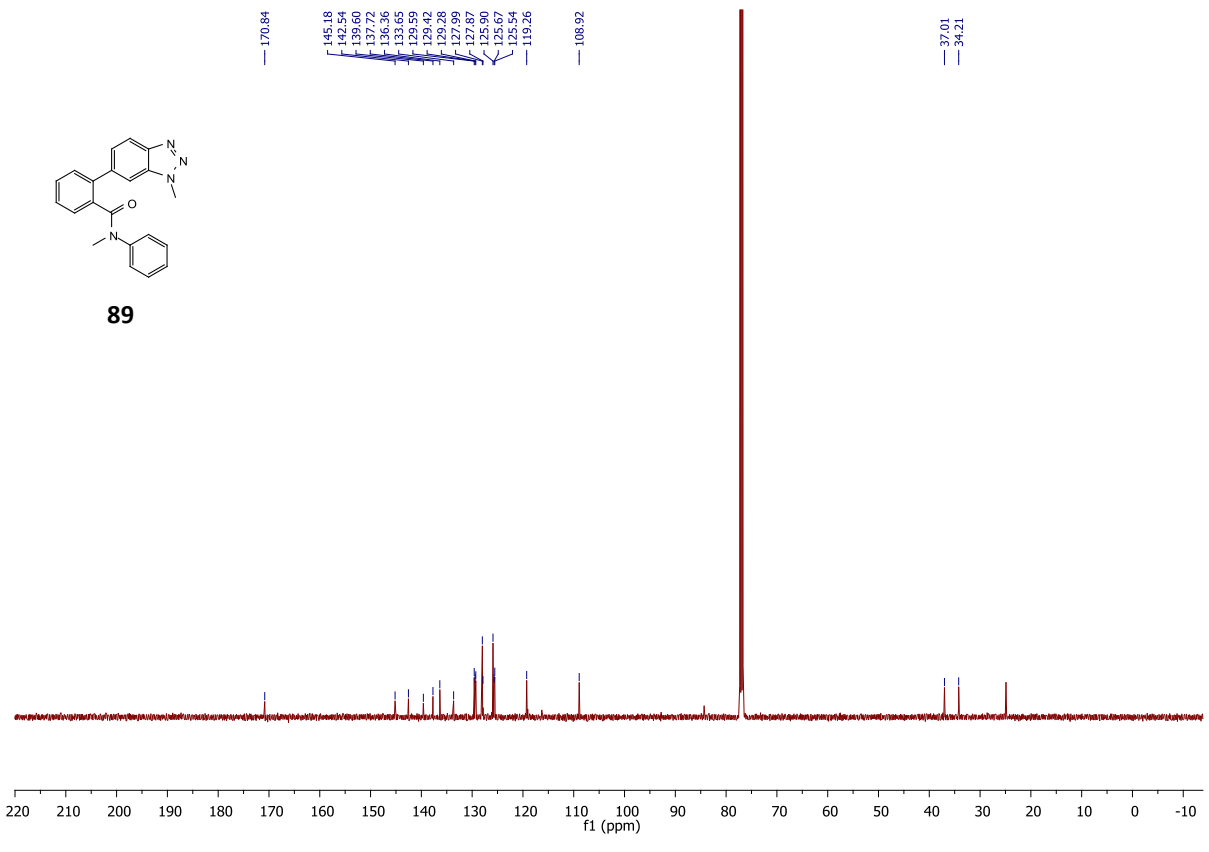
f1 (ppm)

88


8.01
7.99
7.64
7.41
7.36
7.15
7.13
7.12
7.09
7.07
6.95
6.83
6.81
6.80
6.08
4.27
3.19
0.95
1.17
2.24
3.24
1.05
2.09
1.93
3.32
3.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

89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133.65
129.59
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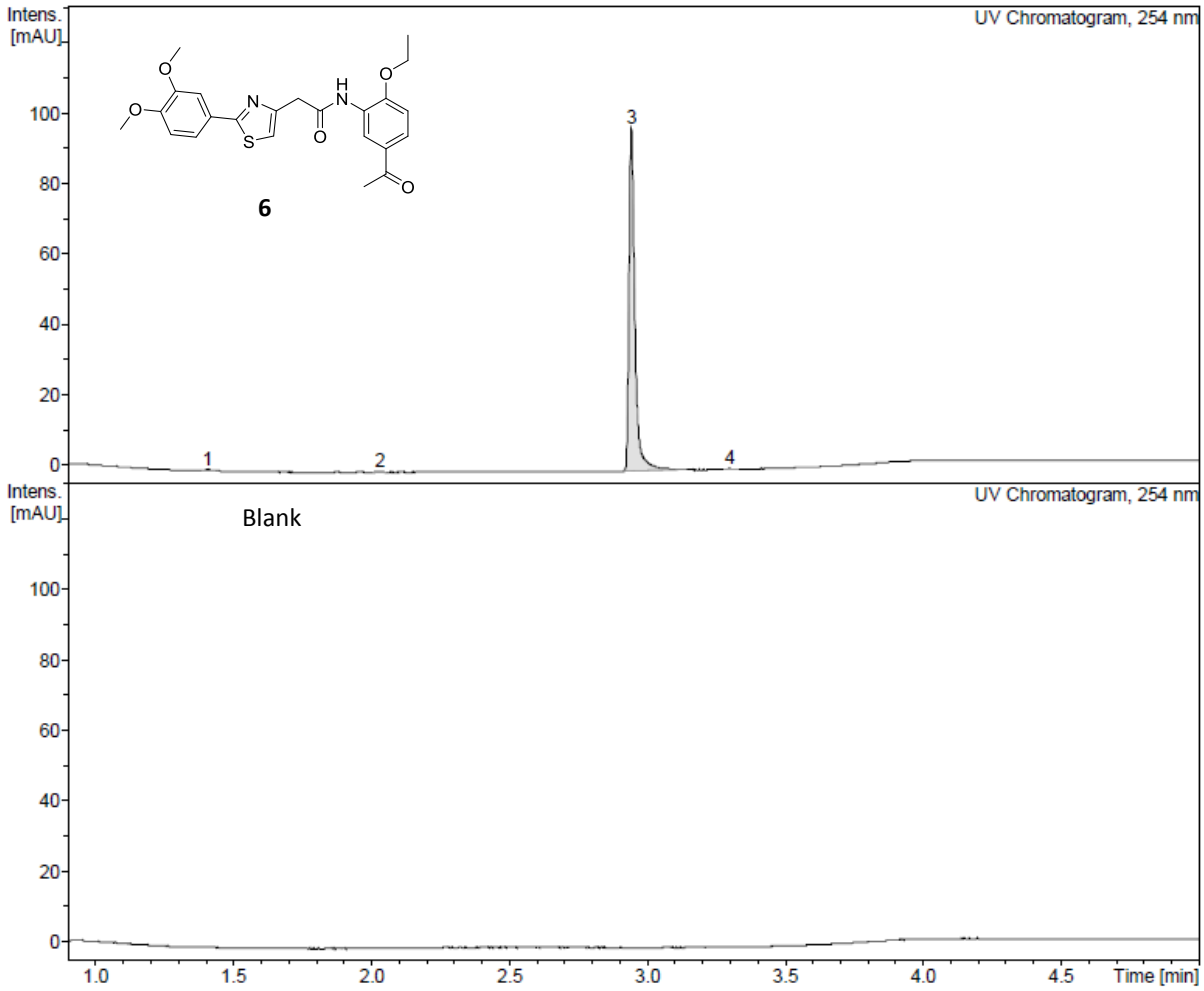
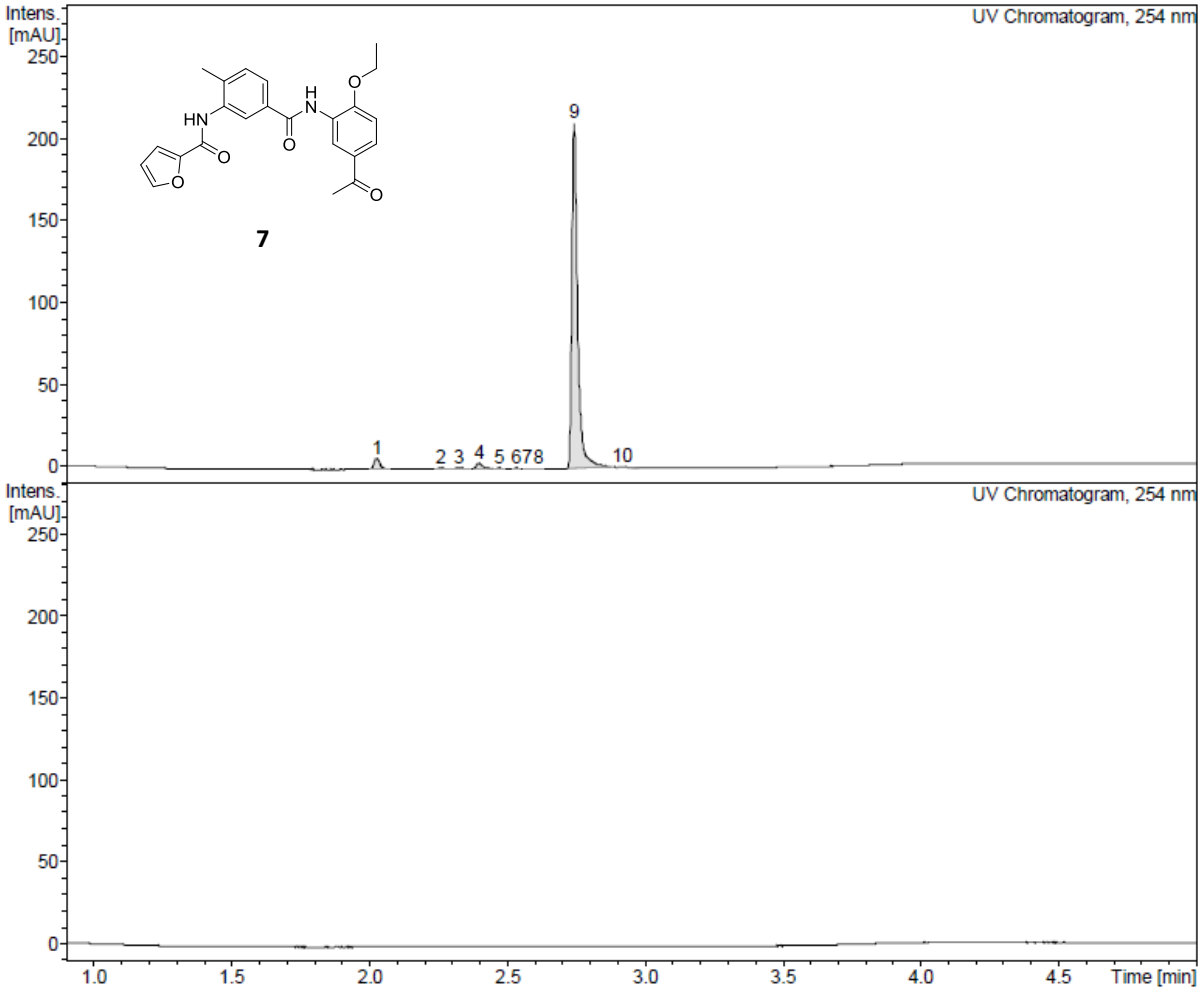
129.28
127.99
127.87
125.90
125.67
125.54
119.26
108.92
37.01
34.21
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

89

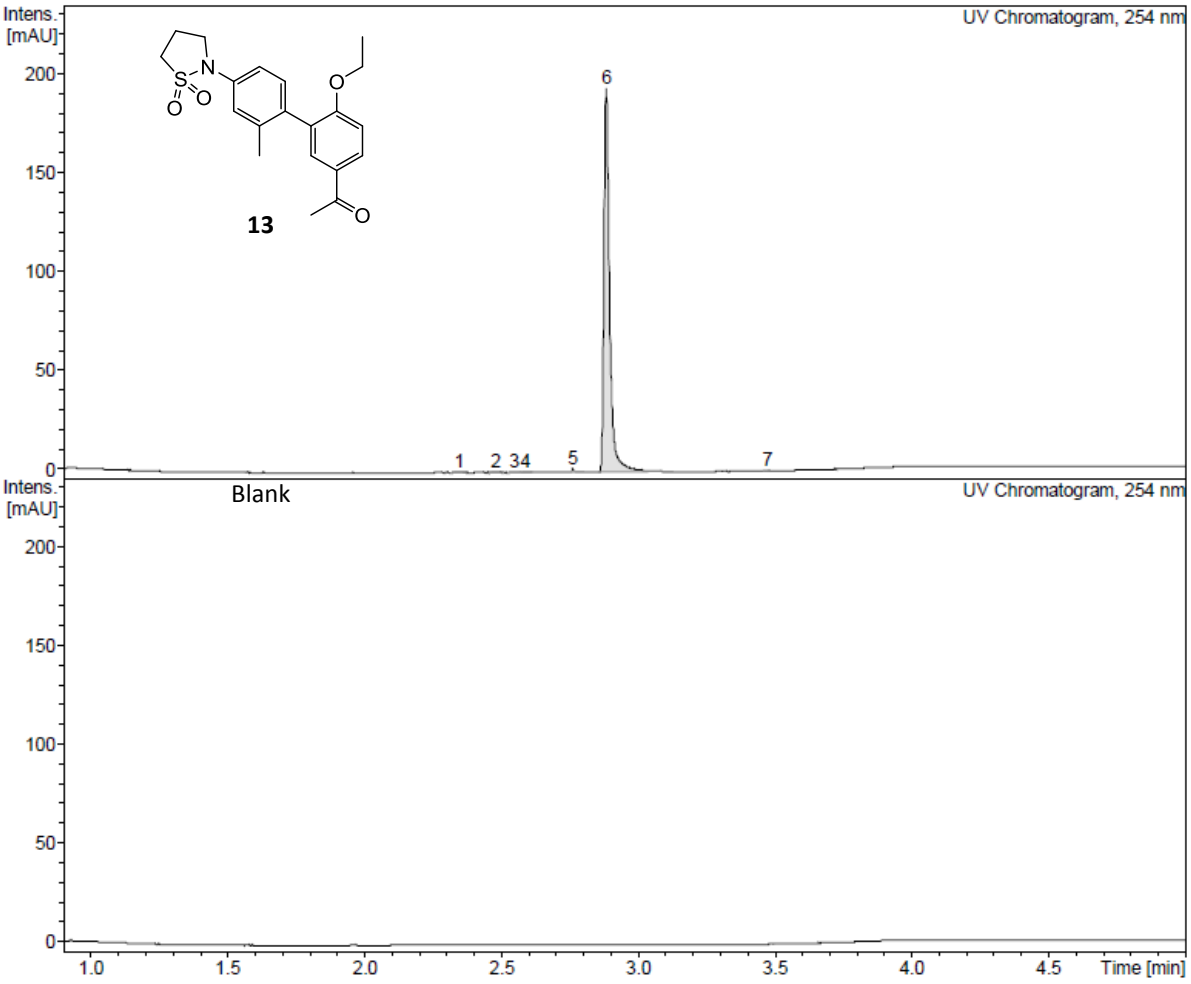
11. HPLC traces of compounds 6, 7, 13, 16 and 17



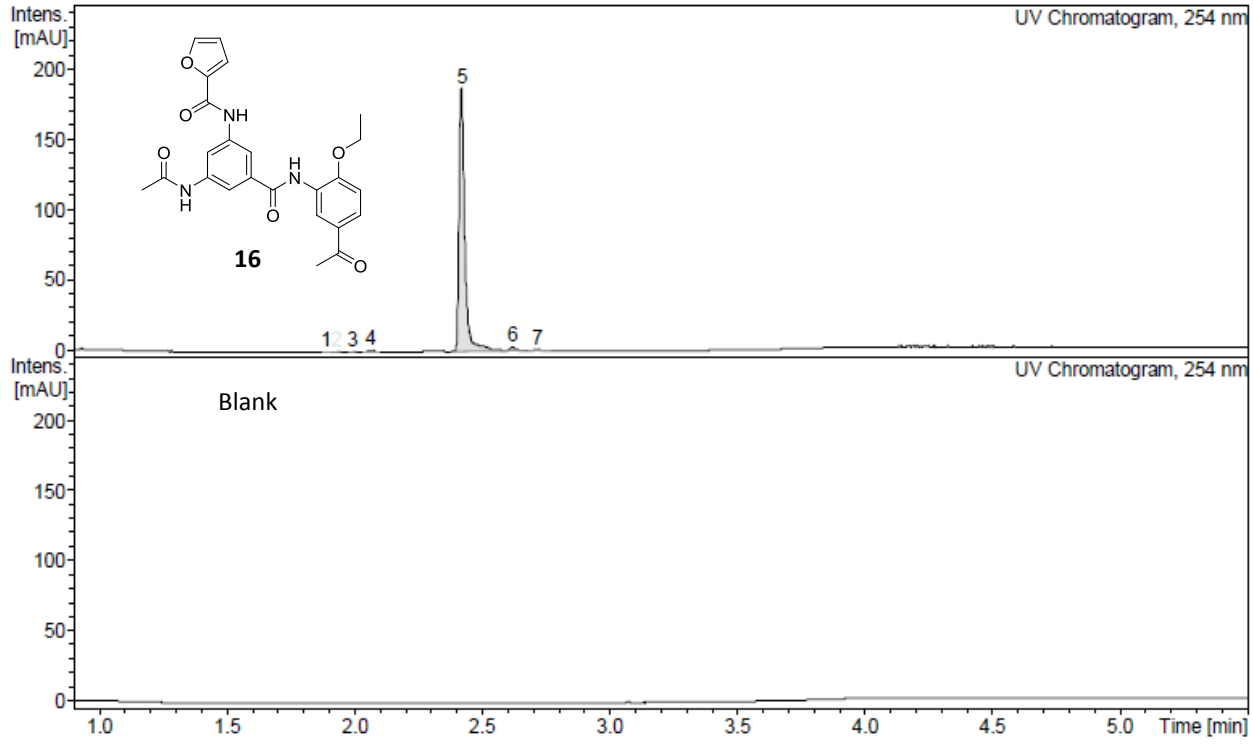
#	RT [min]	Chromatogram	Area	Area %	Area Frac. %
1	1.40	UV Chromatogram, 254 nm	0.4612	0.32	0.32
2	2.03	UV Chromatogram, 254 nm	0.4404	0.30	0.30
3	2.94	UV Chromatogram, 254 nm	145.1688	100.00	99.16
4	3.30	UV Chromatogram, 254 nm	0.3311	0.23	0.23



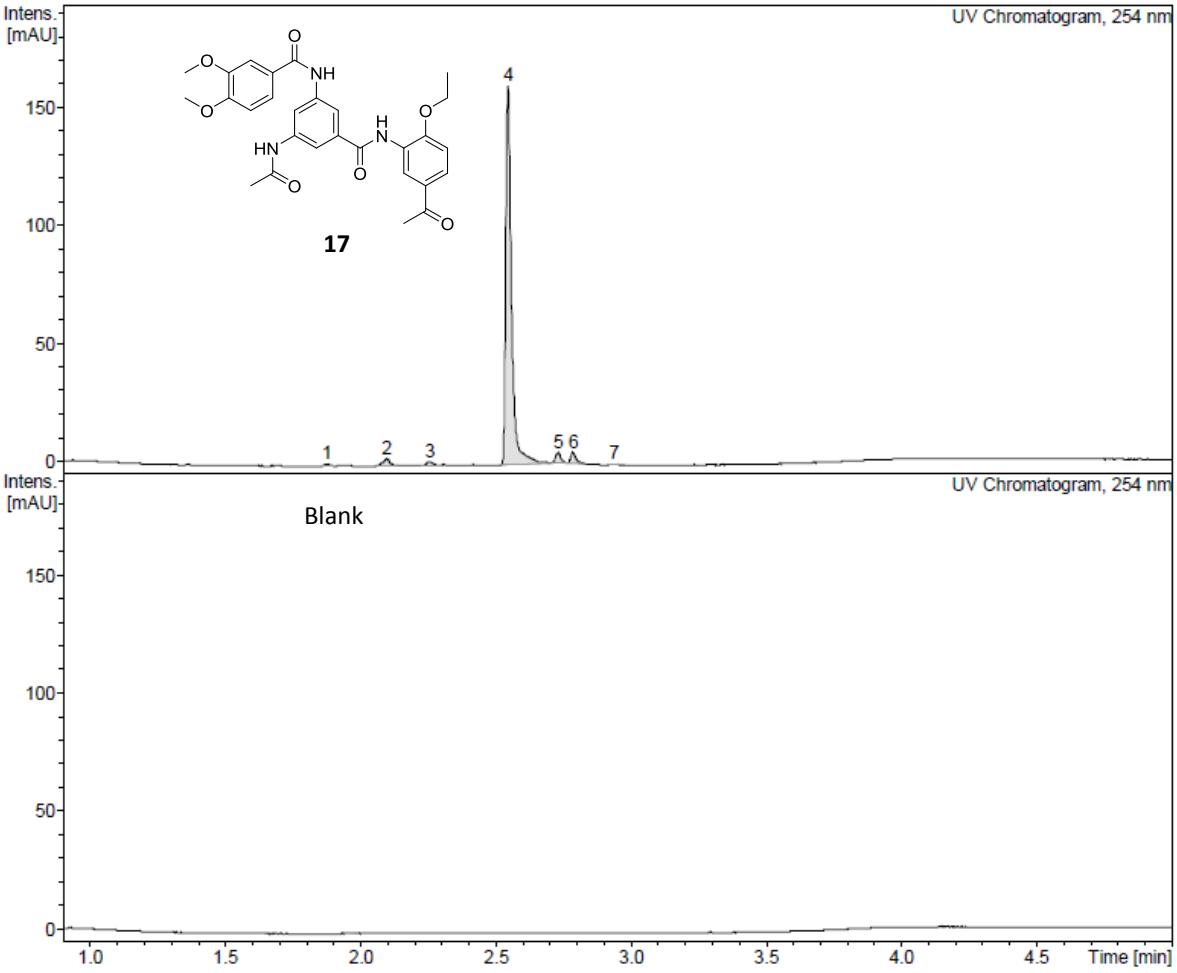
#	RT [min]	Chromatogram	Area	Area %	Area Frac. %
1	2.03	UV Chromatogram, 254 nm	9.3444	3.07	2.88
2	2.26	UV Chromatogram, 254 nm	1.0072	0.33	0.31
3	2.32	UV Chromatogram, 254 nm	1.3124	0.43	0.40
4	2.40	UV Chromatogram, 254 nm	5.7260	1.88	1.77
5	2.47	UV Chromatogram, 254 nm	0.2847	0.09	0.09
6	2.53	UV Chromatogram, 254 nm	0.2607	0.09	0.08
7	2.57	UV Chromatogram, 254 nm	0.2438	0.08	0.08
8	2.61	UV Chromatogram, 254 nm	0.2788	0.09	0.09
9	2.74	UV Chromatogram, 254 nm	304.5829	100.00	93.92
10	2.92	UV Chromatogram, 254 nm	1.2427	0.41	0.38



#	RT [min]	Chromatogram	Area	Area %	Area Frac. %
1	2.35	UV Chromatogram, 254 nm	0.26120	0.09	0.09
2	2.48	UV Chromatogram, 254 nm	0.16618	0.06	0.06
3	2.55	UV Chromatogram, 254 nm	0.38519	0.14	0.14
4	2.59	UV Chromatogram, 254 nm	0.59467	0.21	0.21
5	2.76	UV Chromatogram, 254 nm	0.61517	0.22	0.22
6	2.88	UV Chromatogram, 254 nm	281.27789	100.00	99.25
7	3.47	UV Chromatogram, 254 nm	0.09088	0.03	0.03



#	RT [min]	Chromatogram	Area	Area %	Area Frac. %
1	1.89	UV Chromatogram, 254 nm	0.1974	0.07	0.07
2	1.93	UV Chromatogram, 254 nm	0.3754	0.13	0.13
3	1.99	UV Chromatogram, 254 nm	0.2536	0.09	0.08
4	2.06	UV Chromatogram, 254 nm	1.5477	0.53	0.52
5	2.42	UV Chromatogram, 254 nm	290.6111	100.00	97.39
6	2.62	UV Chromatogram, 254 nm	3.5996	1.24	1.21
7	2.71	UV Chromatogram, 254 nm	1.8080	0.62	0.61



#	RT [min]	Chromatogram	Area	Area %	Area Frac. %
1	1.87	UV Chromatogram, 254 nm	1.0748	0.45	0.41
2	2.10	UV Chromatogram, 254 nm	4.8960	2.04	1.87
3	2.26	UV Chromatogram, 254 nm	2.3571	0.98	0.90
4	2.55	UV Chromatogram, 254 nm	240.0186	100.00	91.64
5	2.73	UV Chromatogram, 254 nm	6.1806	2.58	2.36
6	2.79	UV Chromatogram, 254 nm	6.5033	2.71	2.48
7	2.94	UV Chromatogram, 254 nm	0.8769	0.37	0.33

12. Protein purification, crystallization and structural determination

CBP bromodomain was expressed and purified by following the protocol described previously.[27] Protein was concentrated to 20 mg/ml in the buffer of 20 mM HEPES, pH 7.4, 500 mM NaCl, 5% glycerol and 0.5 mM TCEP for crystallization. The co-crystal of **16** bound to CBP bromodomain was grown by sitting-drop vapor diffusion at 277 K in 0.1 M Morpheus® Buffer System 3, pH 8.5, 37.50% v/v MPD_P1K_P3350 and 0.09 M NPS at a1:1 (v/v) ratio of protein/ligand to reservoir buffer. Crystals were cryoprotected by crystallization buffer supplemented with 20% ethylene glycol prior to freezing in liquid nitrogen. Diffraction data were collected at the X06SA beamline at the Swiss Light Source, Paul Scherrer Institut, Villigen, Switzerland. Data was integrated with XDS[49] and scaled with AIMLESS.[50] Structure was solved by molecular replacement with Phaser[51] using PDB 3DWY as a search model. Model building and refinement was performed with Coot[52] and Phenix,[53] respectively. Programs used for crystallographic data processing and analysis were supported by the SBGrid Consortium[54]. The statistics of data process and refinement are summarized in Table S3.

Table S4. X-ray data collection and refinement statistics for co-crystal structure of the CBP bromodomain with compound **16**.

Data Collection	
PDB ID	5NLK
Space group	$P2_12_12_1$
Cell dimensions	
a, b, c (Å)	37.38, 40.81, 87.38
α, β, γ (°)	90.00, 90.00, 90.00
Resolution (Å)	40.81 - 1.80
Unique observations[a]	12880(745)
Completeness[a]	99.3(99.8)
Redundancy[a]	12.6(13.5)
Rmerge[a]	0.164(0.689)
I/σI[a]	9.9(2.6)
$CC_{1/2}$[a]	0.99(0.94)
Refinement	
Rwork/Rfree[a]	0.176(0.227) /0.216(0.333)
R.m.s. deviations of bond lengths (Å)	0.005
R.m.s. deviations of bond angles (°)	0.989
Average B-factor ($Å^2$)	
Protein	35.23
Ligand	32.10
Wwater	42.50
Ramachandran	
Favored (%)	99.12
Allowed (%)	0.88
Disallowed (%)	0
[a] Highest resolution shell is shown in parentheses.	

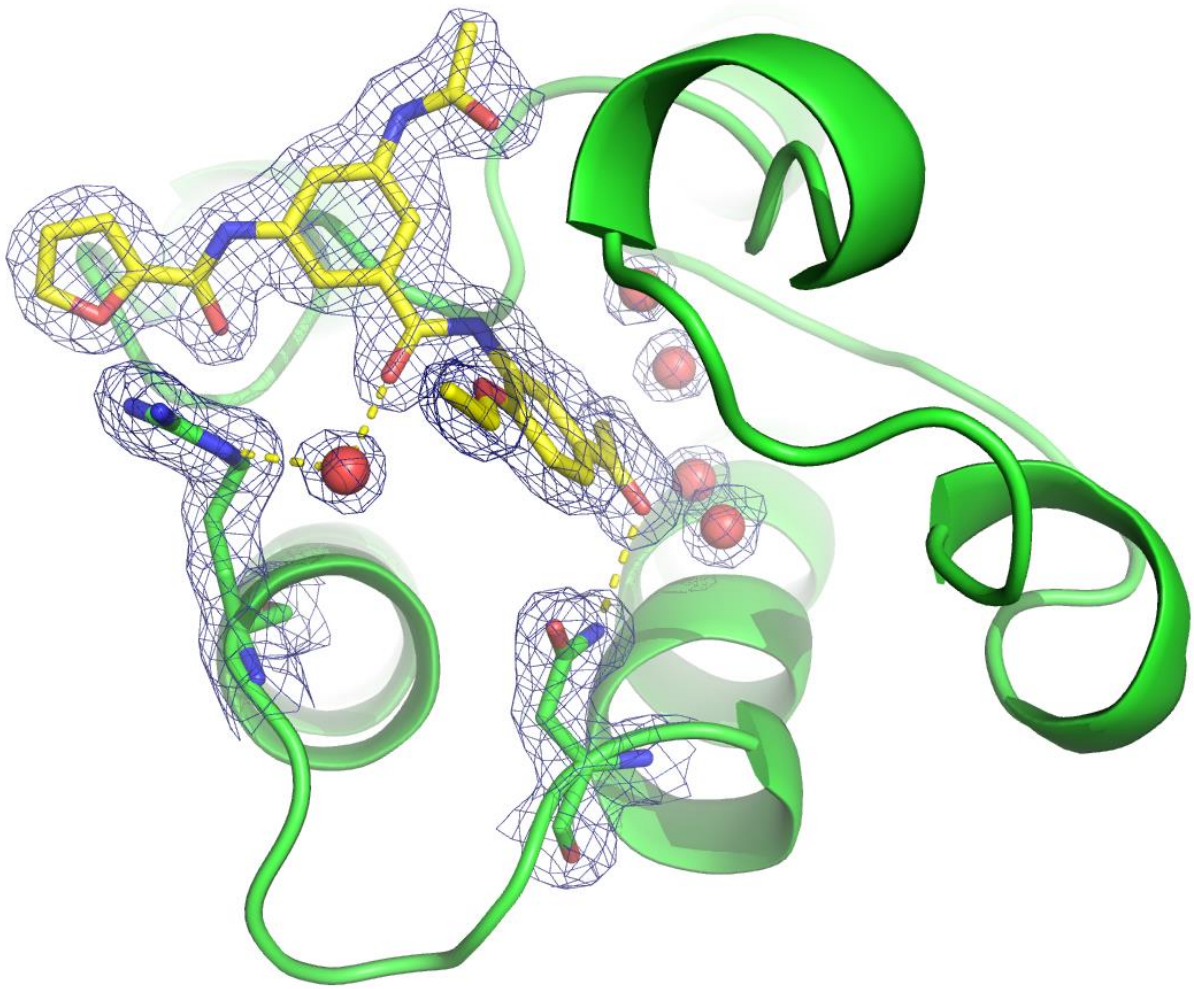


Figure S10. 2mFo – DFc electron density maps of ligand **16**, structural water molecules and key residues of the CBP bromodomain; PDB code : 5NLK

13. References

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