Electronic Supplementary Material (ESI) for ChemComm.

Tryptophan-derived butyrylcholinesterase inhibitors as promising leads against Alzheimer's disease

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Combinatorial library preparation and virtual screening

Computer Hardware

The computations were performed on a 4 × 8 core Supermicro AMD workstation with AMD Opteron 6272 2.1 GHz processors, 32 GB RAM, four 1.5 TB hard drives and a 512 GB solid-state drive, running 64-bit Ubuntu Linux, release 14.04. Reaction modelling, compound preparation and binding mode analysis were performed on two quad-core Intel Xeon 2.2 GHz processors, 8 GB RAM, two 1 TB hard drives and a Nvidia Quadro FX 4800 graphic card, running 64-bit Ubuntu Linux.

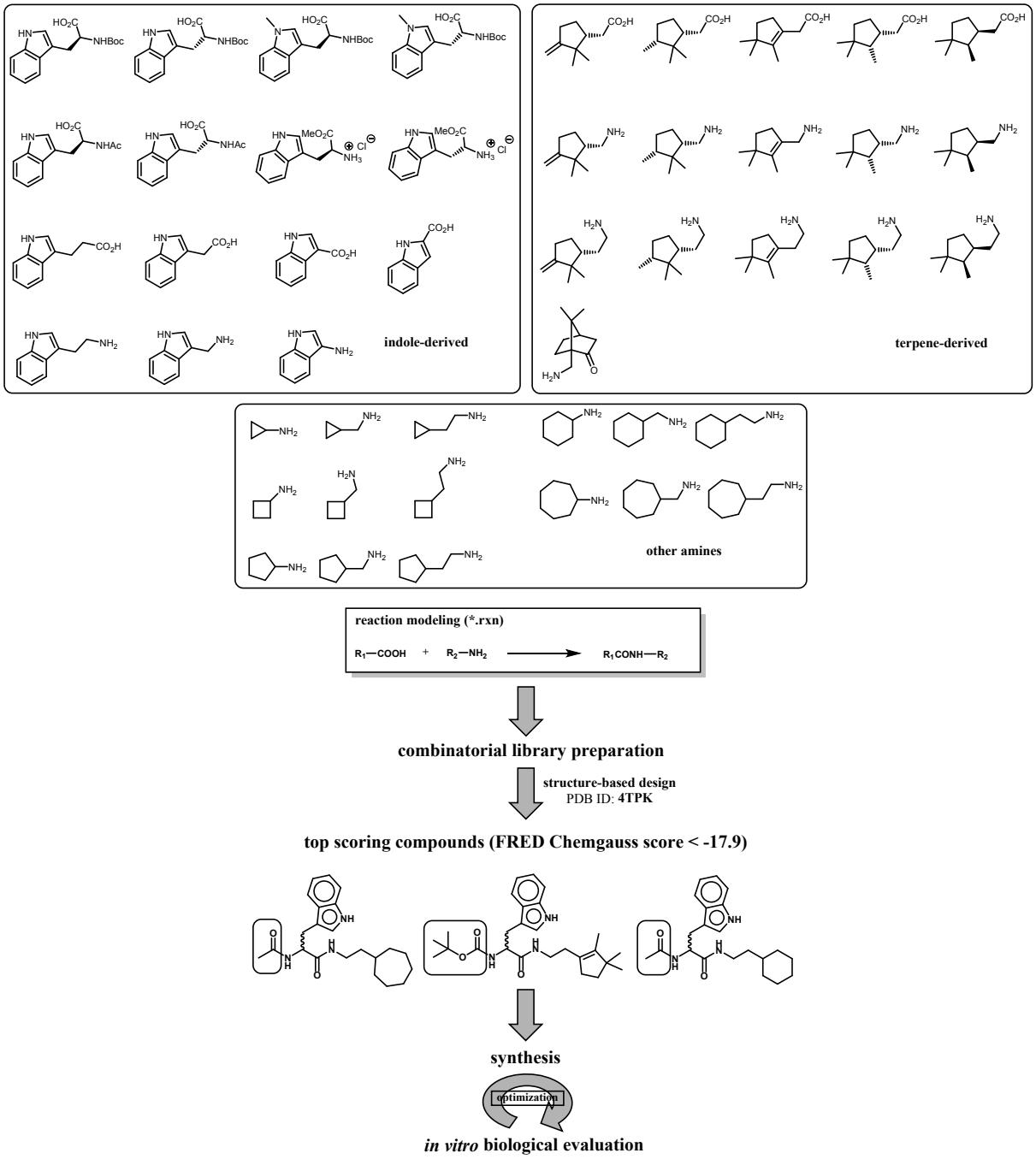
Database Preparation

The combinatorial virtual library was prepared by employing an in-house selection of available reagents (5 terpene-derived carboxylic acids, 5 indole-derived carboxylic acids, 5 terpene-derived amines, 26 other amines; *Scheme S1*). In strict accordance with future synthetic availability, suitable reagents were collected in smiles / SMARTS query string format.

Reaction modelling was performed using freely-available Accelrys Draw software (release 4.2, Dassault Systèmes Corporate, Waltham, MA, USA). *In silico* coupling of amine and carboxylic acid reagents was performed with all possible Boc-protection/deprotection schemes. Only first order of combinatorial library was calculated (no *in silico* transformations were performed on the products) and possible symmetrical conjugates were filtered off. The chemical transformations were defined as extended reaction files (*.rxn) to be exhaustively enumerated by the open-source combinatorial chemistry software Legio (release 1.1.12, Epam Life Sciences). A reaction file consisted of a REACTANT block, a PRODUCT block, AGENT block and an optional RGROUP block. An 'AGENT' is a molecular structure that does not take part in the chemical reaction, but is added to the reaction equation for informative purposes. This format can also be used for 'RGROUP' in a combinatorial chemistry scenario with moieties defined in .mol format.

The computed combinatorial library, consisting of 399 compounds was further evaluated by FILTER 2.5.1.4 software (OpenEye Scientific Software, Inc., Santa Fe, NM, USA). Predicted aggregators as well as PAINS compounds were removed. In the final step, the prepared database was processed with OMEGA2 software (release 2.5.1.4; OpenEye Scientific Software, Inc., Santa Fe, NM, USA) to construct a 3D conformer library. OMEGA2 (with a maximum of 2000 conformations per compound and an RMS of 0.5) produced a library of roughly 449 673 conformations.

Receptor for the docking experiment was generated using hBChE crystal complex[1] (PDB entry: 4TPK, 2.7 Å resolution, chain A) with MakeReceptor GUI of OEDocking software package (version 3.0.1, OpenEye Scientific Software, Inc., Santa Fe, NM, USA). Water molecules were removed and a box with the volume of 9731 Å^3 (18.7 × 22.7 × 23 Å) was defined around the central *N*-((1-(2,3-dihydro-1*H*-inden-2-yl)piperidin-3-yl)methyl)-*N*-(2-methoxyethyl)-2-naphthamide ligand. Balanced site shape potential was calculated. No constraints were used and active site residue conformation or protonation state was not modified. In the final step, prepared combinatorial virtual library was docked into the prepared receptor using FRED software (version 3.0.1, OpenEye Scientific Software, Inc., Santa Fe, NM, USA).[2] High resolution docking parameter and Chemgauss4 scoring function was used in the protocol.[3,4] Validation was executed by redocking of the receptor crystal complex ligand where FRED successfully reproduced experimentally determined inhibitor conformation. Top scoring compounds with OpenEye FRED Chemgauss scores below -17.95 were used for further synthetic optimization and biological evaluation.



Scheme S1: ***In silico*** **reagent selection, combinatorial virtual library preparation, and structure-based design**

Biological Evaluation

Inhibition of cholinesterases

The inhibitory potencies of the compounds against the ChEs were determined using the method of Ellman following the procedure described previously.[5] Briefly, compound stock solutions in DMSO were incubated with Ellman's reagent and the ChEs (final concentrations: 333 μM Ellman's reagent, 1 nM or 50 pM hBChE (human butyrylcholinesterase) or mAChE (murine acetylcholinesterase), respectively, in 0.1 M phosphate buffer pH 8.0 for 5 min at 20 °C. mAChE was chosen as the surrogate for hAChE as they are structurally highly conserved in the composition of active site amino acid residues.[6] The reactions were started by the addition of the substrate (final concentration, 500 μM butyrylthiocholine iodide or acetylthiocholine iodide for hBChE and mAChE, respectively). The final content of DMSO was always 1%. The increase in absorbance at 412 nm was monitored for 1 min using a 96-well microplate reader (Synergy H4, BioTek Instruments, VT, USA). The initial velocities in the presence (v_i) and absence (v_o) of the test compounds were calculated. The inhibitory potencies were expressed as the residual activities, according to RA = ($v_i - b$) / ($v_o - b$), where b is the blank value using phosphate buffer without ChEs. For IC_{50} determinations, at least seven different concentrations for each compound were used. The IC_{50} values were obtained by plotting the residual ChE activities against the applied inhibitor concentrations, with the experimental data fitted to a four-parameter logistic function. Tacrine and donepezil were used as positive controls.

Cell Viability Assay

Cell viability assay was performed using human neuroblastoma SH-SY5Y cell line (CRL-2266), purchased from American Type Culture Collection (Manassas, VA, USA). The cells were cultured in the Advanced Dulbecco's modified Eagle's medium (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS) (Gibco, Thermo Fisher Scientific, Waltham, MA, USA), 2 mM *L*-glutamine (Sigma, St. Louis, MO, USA), 50 U/mL penicillin and 50 μg/mL streptomycin (Sigma, St. Louis, MO, USA), in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C, and grown to 80% confluence.

For the assay, SH-SY5Y cells were seeded into 96-well culture plates (1.5×10^4/well) and assessed by the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, inner salt) assay for their response to the tested compounds. These were prepared as stock solutions at 50 mM in DMSO. SH-SY5Y cells were treated with increasing concentrations (0.5–100 μM) of the test compounds in reduced-serum medium (i.e. with 2% FBS). After 48 h treatment, the cell viability was determined using the CellTiter 96

Aqueous One Solution Cell Proliferation Assay (Promega, Madison, WI, USA), in accordance with the manufacturer's instructions. Absorbance was measured with a microplate reader (Tecan Safire², Männedorf, Switzerland) at 492 nm. The LD_{50} values are the mean ± SEM of at least two independent experiments.

***In vitro* blood-brain barrier PAMPA assay**

The *in vitro* permeability through lipid membrane was determined as follows: the compounds were dissolved in DMSO (10 mM stock solution), diluted with 10% (v/v) MeOH in PBS buffer (pH 7.4; 0.595 g $Na_2HPO_4 \times 12\ H_2O$, 0.0475 g KH_2PO_4, 2.0 g NaCl in 250 mL deionized water) to 200 µM and transferred to the donor 96-well microplate (Millipore filter plate) (300 µL/well). The acceptor 96-well microplate with a precoated filter (PAMPA Plate System from Corning, Gentest™ (Ref. 353015)) was prepared with 10% (v/v) MeOH in PBS buffer (200 µL/well). The acceptor and donor plates were then placed in a »sandwich/contact« configuration in order to provide contact of lipid filter with the acceptor solution and left undisturbed for 4 h at 25 °C. After incubation, the plates were separated, well solutions transferred to a UV-plate (UV-Star® Microplate 96 well, half area, µCLEAR®, clear, Ref. 675801, Greiner Bio-One) and concentrations measured using Biotek Synergy HT microplate reader (λ = 230–500 nm in 4 nm steps). Negative logarithm of the effective permeability ($-\log P_e$) was calculated using the in-house software.[7] Assay validation was performed by determining the experimental permeability of five commercial drugs as reference standards and traditional binning used as follows: $-\log P_e < 5.6$, high permeability; $-\log P_e > 6.2$, low permeability; intermediate was labelled as uncertain BBB permeability.

Crystallization

Recombinant human BChE (hBChE) devoid of the C-terminal end and four N-glycosylation sites was produced in eukaryotic cells as described previously.[8] The protein was purified with affinity chromatography on Hupresin (CHEMFORASE, Rouen, France), followed by a size exclusion chromatography (Superdex 200, GE Healthcare), similarly to what was described for hBChE produced in insect cells.[9] Stock solutions of ligands (0.1 M) were prepared in 100% DMSO for **6**, **8**, **10** and **13** or in water for hydrochloride of **12**. Complexes with hBChE were either obtained by co-crystallization at 1 mM final ligand concentration (0.1 M MES pH 6.5, 2.15 M $(NH_4)_2SO_4$, 1% DMSO) by the hanging drop method at 20 °C for **8** and **10**, or after crystal soaking at 0.5 mM final ligand concentration for **6**, **12** and **13**. Crystals were cryo-protected in a solution of 0.1 M MES pH 6.5, 2.15 M $(NH_4)_2SO_4$, 20% glycerol, 1 mM ligand, (1% DMSO for **6**, **8**, **10**, and **13**) before flash cooling in liquid nitrogen.

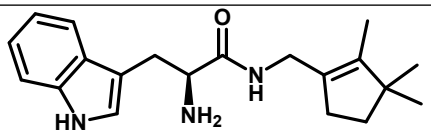
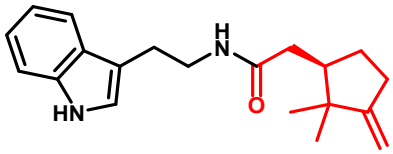
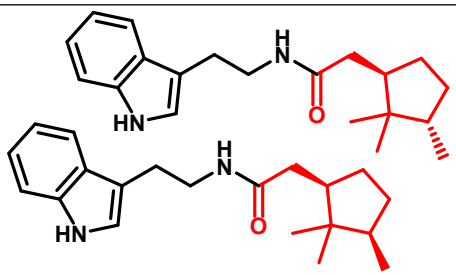
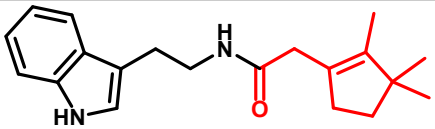
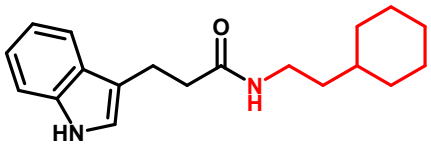
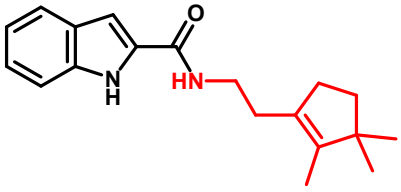
X-ray Structure Determination

X-ray diffraction data were collected at the ID29 or ID23-1 beamlines of the European Synchrotron Radiation Facility (Grenoble, France) at 100 K. Images recorded on a PILATUS 6M detector were automatically processed with autoPROC[10] for **6**, **8**, **12**, and **13**, or with EDNA[11] for **10**. Data analysis was realized using the Phenix software suite.[12] Initial models were obtained by molecular replacement using Phaser-MR and the hBChE structure (PDB entry 1P0I) devoid of any ligand, glycans or water molecules. Prominent electron densities were observed in the active site gorge and allowed unambiguous fitting of each ligand. Ligand geometry restraints were processed using Phenix eLBOW[13] and the semi-empirical quantum mechanical method (AM1). Each model was refined by iterative cycles of Phenix.refine and model building using *Coot*.[14] hBChE structures in complex with **6**, **8**, **10**, **12**, and **13** were deposited into the Protein Data Bank under accession numbers 6QAA, 6QAC, 6QAB, 6QAE and 6QAD, respectively.

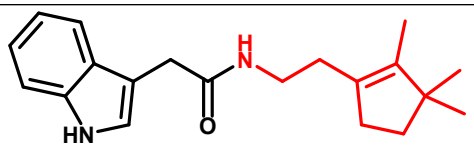
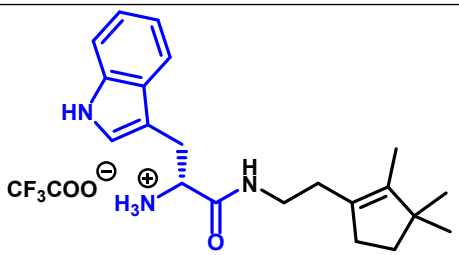
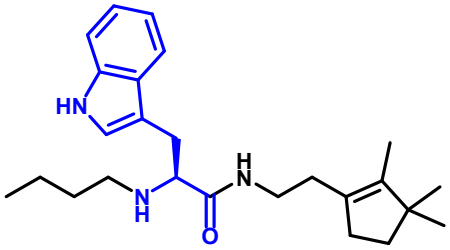
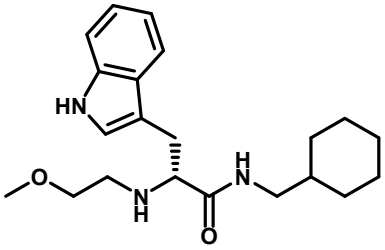
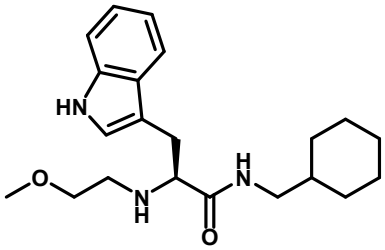
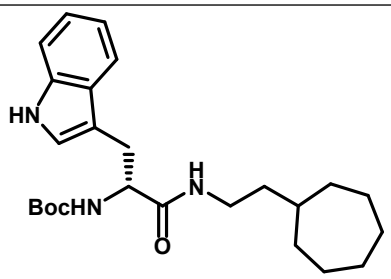
Results

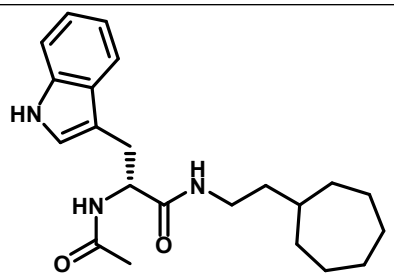
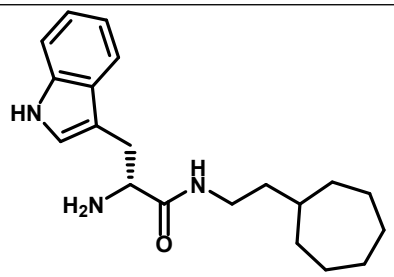
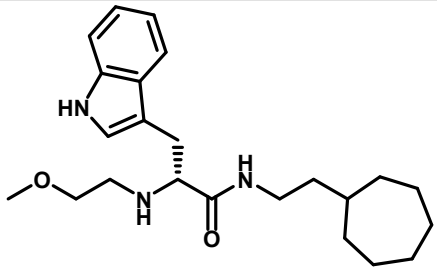
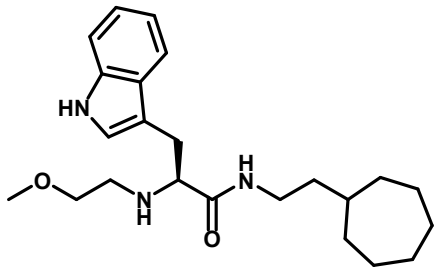
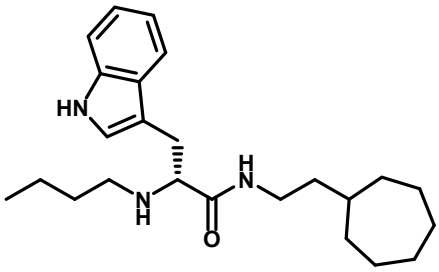
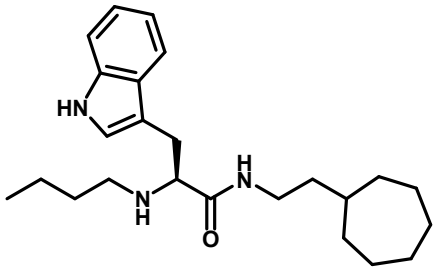
ChE inhibition

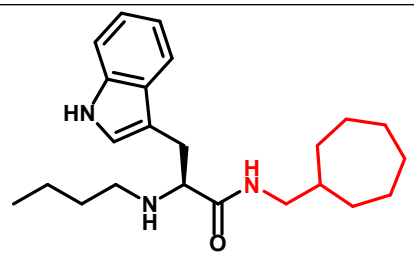
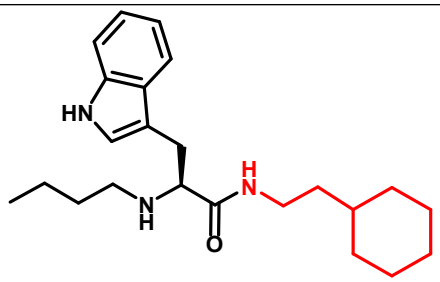
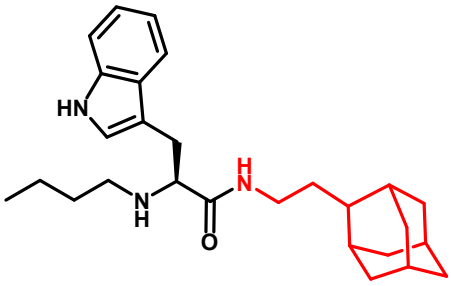
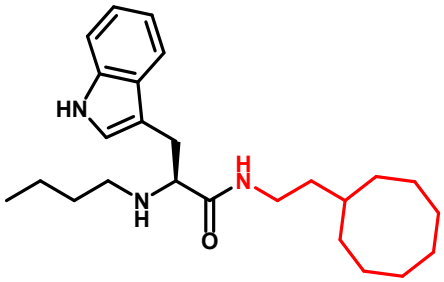
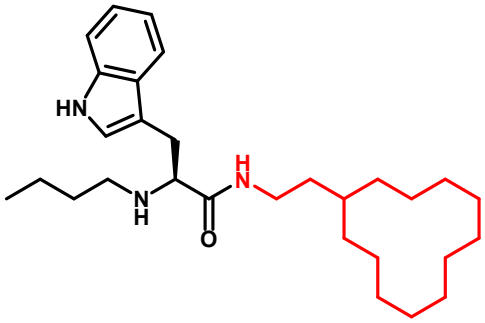
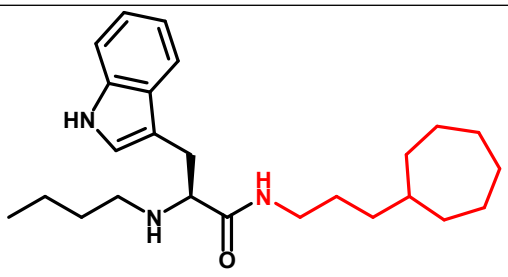
Table S1: *In vitro* ChE inhibition

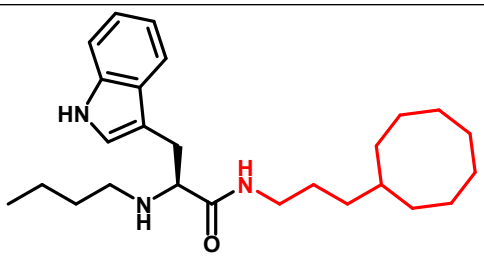
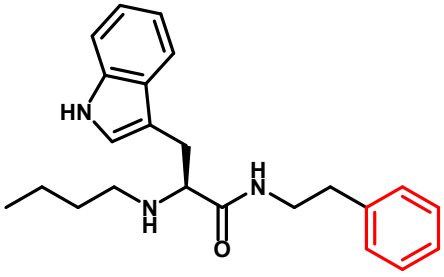
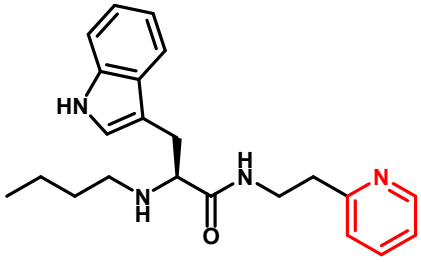
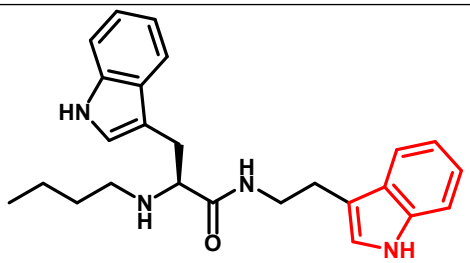
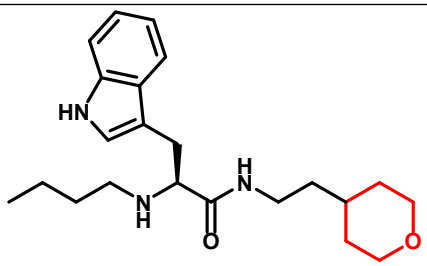
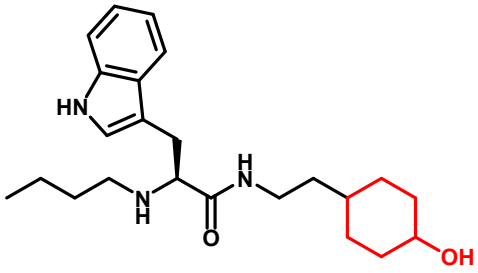
Compound[1]		hBChE IC_{50} [nM] ± SEM[a]	mAChE residual activity at 100 µM [%] *or* IC_{50} [nM] ± SEM[a]
Identified hit compound:			
1[15]		250 ± 20	not active
From terpene-derived cycles to simpler cycloalkyl rings:			
S1		18600 ± 2600	86 ± 6% not active
S2+S3[b]		12900 ± 2400	62 ± 2% not active
S4		1360 ± 90	50 ± 2% not active
S5		1400 ± 100	53 ± 2% not active
S6		10900 ± 500	53 ± 3% not active

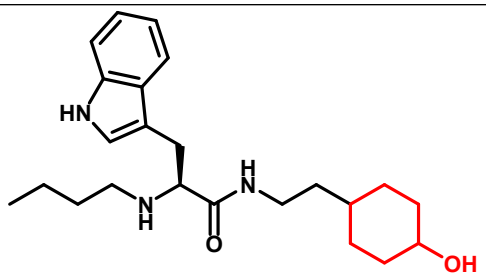
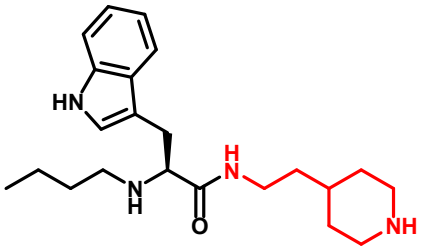
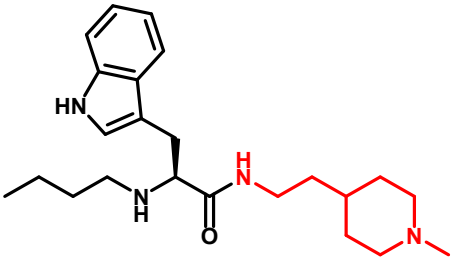
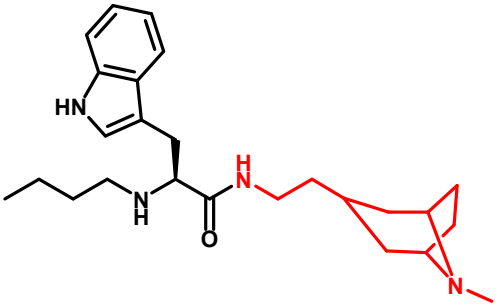
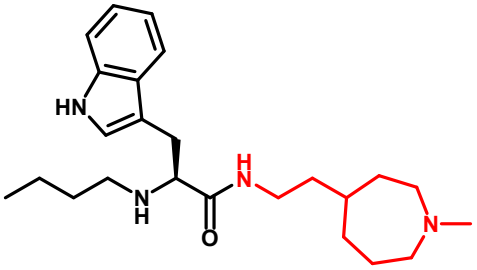
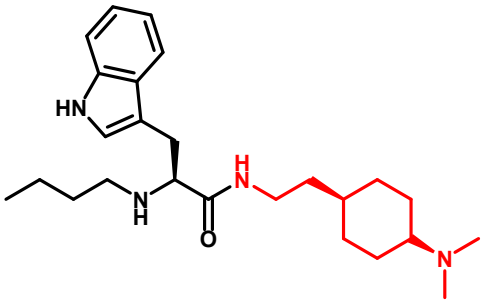
[1] Regarding compound numbering: simple Arabic numbers denote numbering used in the article and the "S"-labelled Arabic numbers denote all the rest of the compounds numbered in order of appearance in ESI.

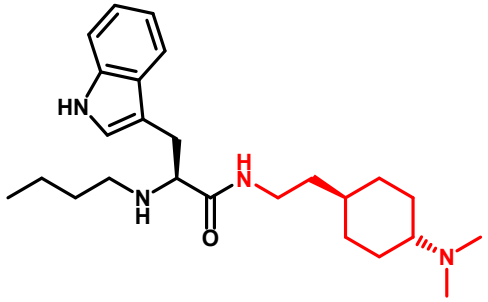
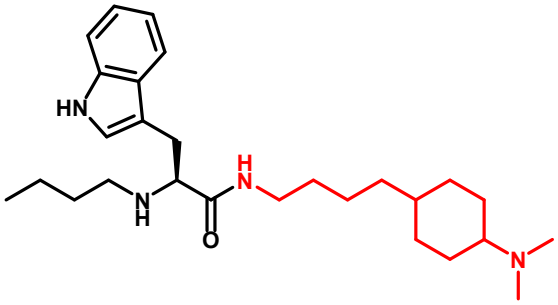
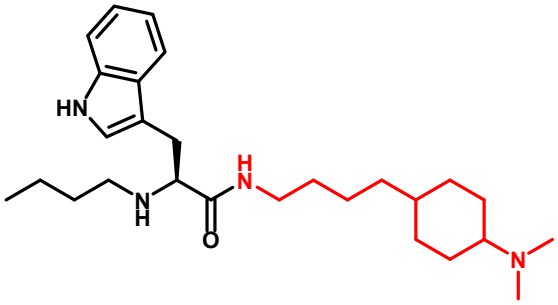
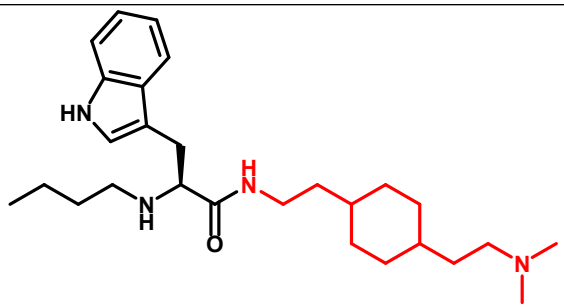
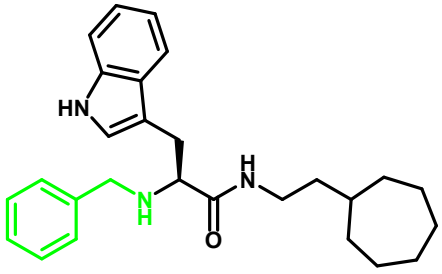
5		420 ± 50	12000 ± 2000
Back to tryptophan-based skeleton:			
S7		320 ± 10	69 ± 6% not active
S8		76 ± 3	52 ± 7% not active
Configuration at stereogenic centre explored:			
S9		990 ± 40	103 ± 4% not active
S10		610 ± 70	95 ± 2% not active
S11		1750 ± 440	52 ± 7% not active

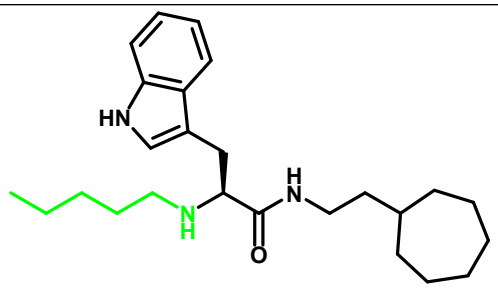
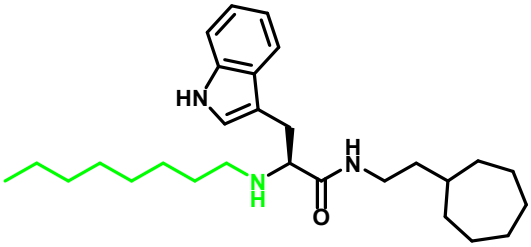
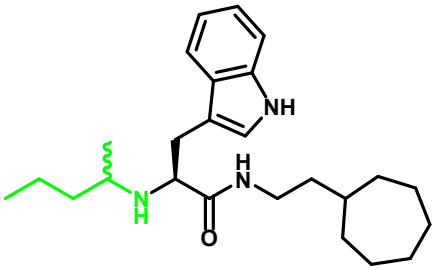
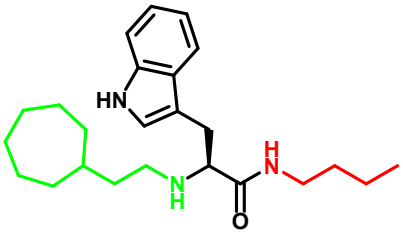
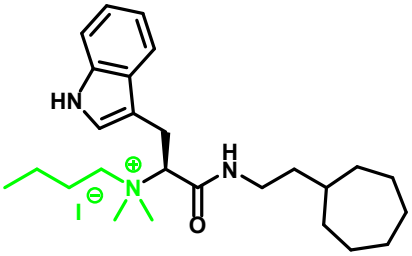
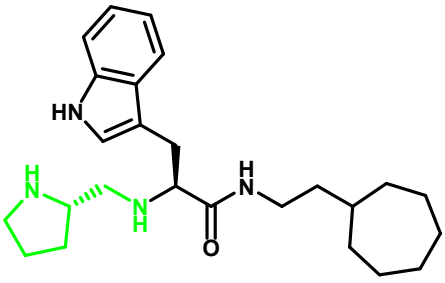
S12		730 ± 40	65 ± 7% not active
S18		340 ± 30	66 ± 5% not active
S13		46 ± 3	50 ± 3% not active
S14		45 ± 1	76 ± 6% not active
7		120 ± 10	31000 ± 7000
6		22 ± 2	52 ± 5% not active
Varying the amide chain length and ring size:			

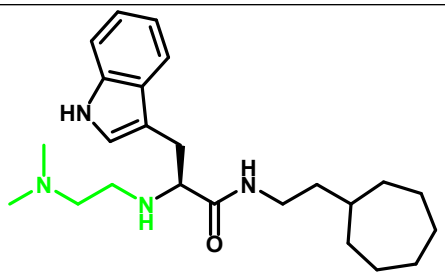
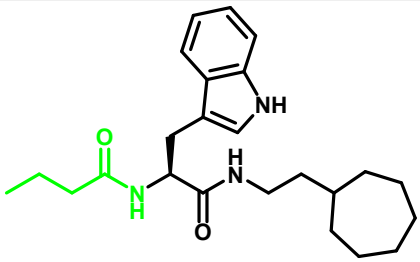
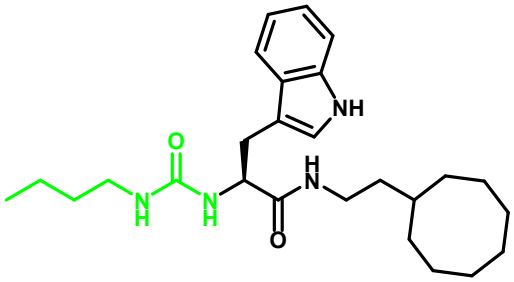
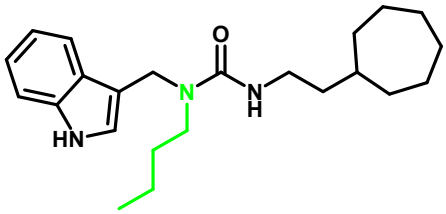
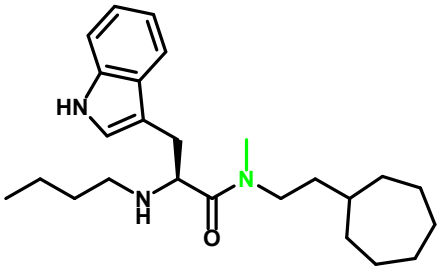
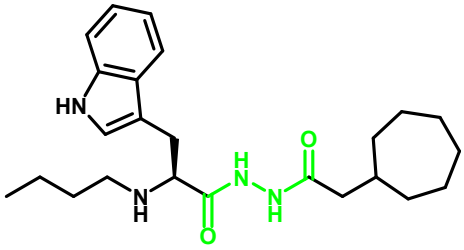
S15		52 ± 3	66 ± 6% not active
S16		47 ± 2	53 ± 4% not active
S17		25.3 ± 0.9	62 ± 2% not active
9		11.9 ± 0.6	22000 ± 14000
S19		3.1 ± 0.2	79 ± 6% not active
8		6.2 ± 0.4	58 ± 4% not active

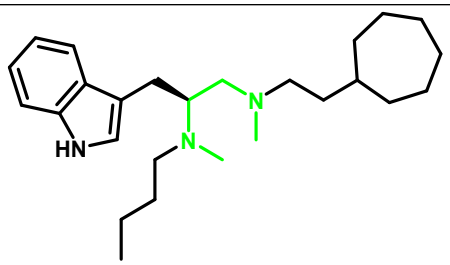
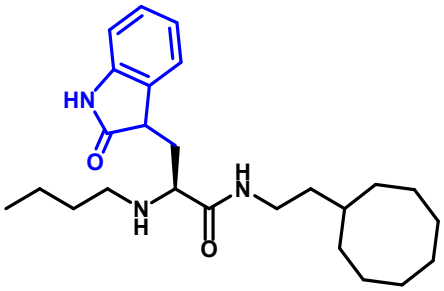
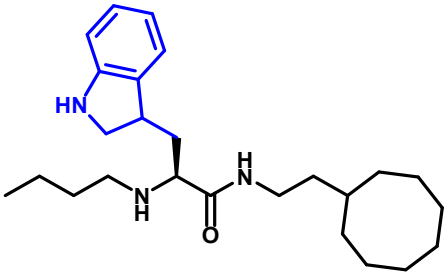
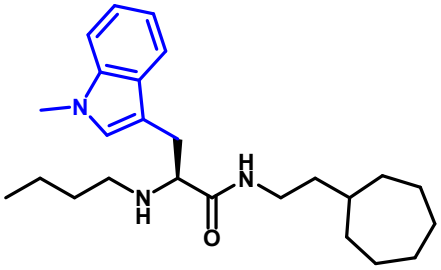
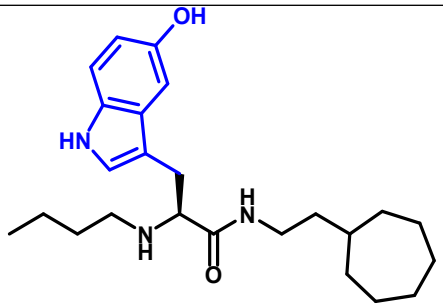
S20		4.0 ± 0.4	13300 ± 2800
Replacing cycloalkyl rings with (hetero)arenes and oxygenated rings:			
S21		270 ± 10	70 ± 6% not active
S22		2800 ± 400	92 ± 5% not active
S23		260 ± 10	60 ± 1% not active
S24		710 ± 40	93 ± 3% not active
S25[c]		240 ± 40	103 ± 5% not active

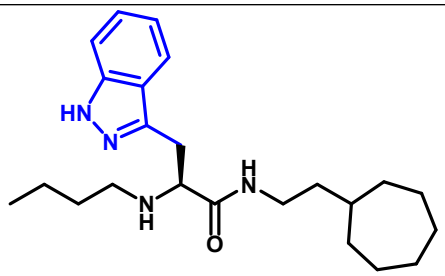
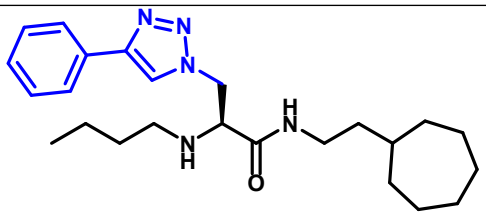
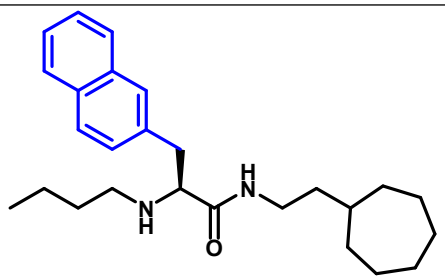
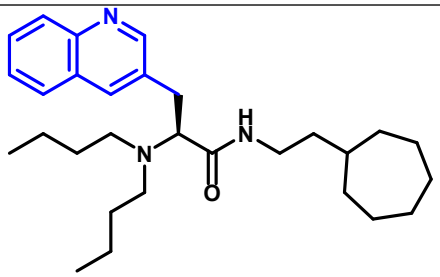
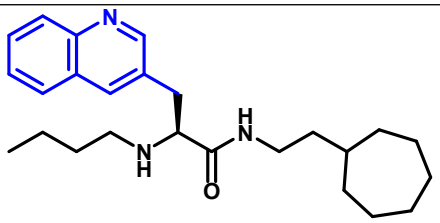
S26[c]		205 ± 9	99 ± 4% not active
Adding another basic centre in the amide chain:			
S27		75 ± 11	85 ± 5% not active
S28		88 ± 6	105 ± 6% not active
S29[b]		63 ± 3	71 ± 2% not active
S30[d]		58 ± 1	83000 ± 12000
S31		59 ± 3	65 ± 4% not active

13[e]		14 ± 1	63 ± 4% not active
S32[c]		30 ± 3	19000 ± 6000
S33[c]		39 ± 5	58000 ± 18000
S34[d]		22 ± 4	68 ± 1% not active
Different α-side chains explored:			
S35		100 ± 2	32000 ± 10000

S36		23 ± 1	58 ± 1% not active
S37		37 ± 5	52 ± 3% not active
S38[b]		110 ± 10	70 ± 7% not active
S39		470 ± 40	51.1 ± 0.4% not active
10		6.2 ± 3.4	92 ± 4% not active
S40		33 ± 1	65 ± 5% not active

S41		28 ± 4	60 ± 5% not active
11		610 ± 30	58.0 ± 0.3% not active
S42		2300 ± 900	70 ± 7% not active
S43		460 ± 60	16900 ± 4300
Modifications of the amide moiety:			
S44		8.8 ± 0.6	64 ± 4% not active
S45		1600 ± 90	101 ± 2% not active

12		3.0 ± 0.2	23400 ± 5000
Modifications of indole core:			
S46[b]		13300 ± 1500	91 ± 5% not active
S47[b]		227 ± 9	80 ± 9% not active
S48		140 ± 20	21600 ± 5900
S49		150 ± 20	50 ± 3% not active
Heterocyclic analogues of tryptophan:			

S50		140 ± 10	58 ± 3% not active
S51		290 ± 30	66 ± 3% not active
S52		8.0 ± 0.6	15000 ± 3000
S53		65 ± 16	53 ± 1% not active
S54		90 ± 7	84500 ± 9600

[a]SEM – standard error of the mean,
[b]obtained as a mixture of diastereoisomers,
[c]prepared as separated isomers, but *cis*/*trans*-configuration not determined,
[d]prepared as an inseparable *cis*/*trans*-mixture,
[e]configuration determined from X-ray structure.

Cytotoxicity assay

The cytotoxicity profiles of the compounds were determined on the neuroblastoma SH-SY5Y cell line (*Table S2*). The LD_{50} values are in micromolar range, which is significantly greater than the concentrations needed to achieve 50% *in vitro* inhibition of hBChE. For example, the most potent inhibitor **12** has the LD_{50} value 2370-fold greater than the IC_{50} value for hBChE inhibition.

Table S2: Cytotoxicity of compounds

Compounds	**LD_{50} ± SEM[a] (μM)**
S54	24 ± 2
S52	14 ± 1
S49	26 ± 5
S15	14 ± 2
S13	28 ± 2
6	7.4 ± 0.3
7	7.8 ± 0.5
8	6.8 ± 0.5
9	6.5 ± 1.1
10	75 ± 6
12	7.1 ± 1.0
13	> 100

[a]Data are expressed as mean ± SEM of at least two independent experiments.

Blood–Brain Barrier Permeability Assay

Blood–brain barrier permeability for fourteen tested compounds was assessed using the parallel artificial membrane permeability assay (PAMPA-BBB).[16] Five commercial drugs were used as references to validate the experimental system and establish the permeability range ($-\log P_e$ of 6.7–4.4). According to the results summarized in Table S3, compounds **12**–**S50** should be able to cross BBB and reach CNS.

Table S3: *In vitro* blood-brain barrier permeability prediction

Compounds	**PAMPA-BBB**	
	$-\log P_e$ (cm/s) mean ± SD	Permeabilty prediction[c]
12[a]	5.3 ± 0.1	high
S49[a]	5.3 ± 0.1	high
S54[a]	5.1 ± 0.1	high
8[a]	4.8 ± 0.5	high
S52[a]	4.5 ± 0.4	high
S48[a]	5.2 ± 0.1	high
6[a]	5.1 ± 0.1	high
9[a]	5.2 ± 0.1	high
S15[a]	5.0 ± 0.1	high
7[a]	5.2 ± 0.1	high
S13[a]	5.1 ± 0.0	high
S50[a]	5.2 ± 0.1	high
13[a]	5.9 ± 0.1	intermediate
10[a]	6.7 ± 0.1	low
Propranolol [b]	4.9 ± 0.1	high
Lidocaine [b]	4.4 ± 0.4	high
Verapamil [b]	4.9 ± 0.0	high
Quinidine [b]	5.3 ± 0.1	high
Theophylline [b]	6.2 ± 0.1	low

[a]Data are means of five replicates (n = 5).
[b]Data are means of four replicates (n = 4).
[c]$-\log Pe < 5.6$, high permeability; $-\log Pe > 6.2$, low permeability; intermediate values were labeled as intermediate BBB permeability.

X-ray structure determination

Table S4: Data collection and refinement statistics calculated using Phenix.[12]

R-work = Σ |*Fo* – |*Fc*|| / Σ |*Fo*|, *Fo* and *Fc* are observed and calculated structure factors, R-free set uses about 5% randomly chosen reflections. Statistics for the highest-resolution shell are shown in parentheses.

	hBChE 6	**hBChE 10**	**hBChE 8**	**hBChE 13**	**hBChE 12**
Data collection					
X-ray source	ESRF ID23-1	ESRF ID29	ESRF ID29	ESRF ID29	ESRF ID29
Wavelength	0.9724	1.0000	1.0000	1.0000	1.0720
Resolution range	48.89 - 1.897 (1.965 - 1.897)	47.58 - 2.49 (2.579 - 2.49)	54.49 - 2.771 (2.87 - 2.771)	61.24 - 2.497 (2.586 - 2.497)	54.36 - 2.487 (2.576 - 2.487)
Space group	I 4 2 2	I 4 2 2	I 4 2 2	I 4 2 2	I 4 2 2
Unit cell	154.597 154.597 128.214 90 90 90	153.632 153.632 128.589 90 90 90	154.113 154.113 127.619 90 90 90	155.269 155.269 129.922 90 90 90	153.744 153.744 126.94 90 90 90
Total reflections	535457 (50996)	221065 (21607)	155664 (15105)	199823 (21297)	223861 (22519)
Unique reflections	61234 (6026)	27181 (2692)	19813 (1968)	25229 (2718)	26948 (2645)
Multiplicity	8.7 (8.5)	8.1 (8.0)	7.9 (7.7)	7.9 (7.8)	8.3 (8.5)
Completeness (%)	99.90 (99.93)	99.85 (99.93)	99.82 (99.95)	90.69 (99.89)	99.86 (100.00)
Mean I/sigma(I)	17.96 (2.54)	13.33 (1.17)	16.22 (2.53)	15.41 (2.35)	19.09 (2.44)
Wilson B-factor	31.56	62.46	61.16	49.83	54.96
R-merge	0.07043 (0.8126)	0.1194 (1.445)	0.1074 (0.8093)	0.09376 (0.7896)	0.07352 (0.8433)
R-meas	0.07489 (0.8659)	0.1276 (1.544)	0.115 (0.8677)	0.1002 (0.8462)	0.07849 (0.8978)
R-pim	0.02501 (0.2939)	0.0444 (0.5386)	0.04048 (0.309)	0.03447 (0.2974)	0.02699 (0.3042)
CC1/2	0.999 (0.797)	0.997 (0.552)	0.998 (0.861)	0.998 (0.813)	0.999 (0.823)
CC*	1 (0.942)	0.999 (0.844)	1 (0.962)	1 (0.947)	1 (0.95)
Refinement statistics					
Reflections used in refinement	61233 (6026)	27177 (2691)	19802 (1967)	25224 (2718)	26944 (2645)
Reflections used for R-free	3083 (288)	1328 (115)	985 (102)	1248 (126)	1298 (135)
R-work	0.1766 (0.2477)	0.1925 (0.3024)	0.1841 (0.2169)	0.1998 (0.3037)	0.1972 (0.2626)
R-free	0.2086 (0.2747)	0.2353 (0.3250)	0.2544 (0.2518)	0.2364 (0.3840)	0.2429 (0.3303)
CC(work)	0.960 (0.847)	0.959 (0.804)	0.949 (0.907)	0.955 (0.861)	0.950 (0.876)
CC(free)	0.948 (0.734)	0.917 (0.719)	0.875 (0.894)	0.923 (0.822)	0.895 (0.805)
Number of non-hydrogen atoms	4757	4533	4487	4530	4528
macromolecules	4233	4233	4230	4233	4222
ligands	238	232	185	232	196
solvent	286	68	72	65	110

Protein residues	537	544	536	544	537
RMS(bonds)	0.008	0.006	0.010	0.004	0.004
RMS(angles)	0.90	0.82	1.19	0.81	0.72
Ramachandran favored (%)	97.14	96.18	94.08	95.61	94.85
Ramachandran allowed (%)	2.86	3.82	5.73	4.20	5.15
Ramachandran outliers (%)	0.00	0.00	0.19	0.19	0.00
Rotamer outliers (%)	0.00	0.00	0.00	0.00	0.00
Clashscore	3.86	7.97	7.95	6.49	8.76
Average B-factor	37.46	63.94	62.25	56.57	62.90
macromolecules	35.80	62.55	61.05	54.94	61.49
ligands	61.79	91.21	92.90	87.90	95.09
solvent	41.70	57.75	54.37	50.54	59.59

These ligands similarly interact with hBChE mainly through hydrophobic interactions with common binding features. The *n*-butylamine chains are protruding out the active site while the chains containing the cycloheptyl ring, or the substituted cyclohexyl ring (**13**), are interacting along a hydrophobic pocket defined by residues Trp82, Ala328, Trp430, Tyr332, Met347, His438 and Tyr440. For **6**, **8**, **10**, and **13**, the nitrogen amide atom is engaged in a hydrogen bond with the backbone carbonyl oxygen of Pro285 (3.0, 2.6, 3.3 and 2.7 Å respectively), while the equivalent tertiary amine of **12** is 3.6 Å away and can form a similar hydrogen bond or cation-π interaction towards Tyr332 upon protonation. Additionally, the indole ring of all ligands interacts through T-stacking with Phe329 (5.4, 5.4, 5.4, 6.2 and 5.6 Å for **6**, **10**, **8**, **13**, and **12**, respectively) and to a lesser extent with Trp281 (6.1, 6.0, 5.8, 7.4 and 5.7 Å for **6**, **10**, **8**, **13**, and **12**, respectively). While determining the initial structure of compound **6**, we noticed that the indole ring is flipped with endocyclic nitrogen atom in proximity to the oxygen atom of a DMSO molecule trapped between Trp82, His438 and the respective ligand (voluminous choline binding pocket, distance of 3.0 Å). We hypothesize that the presence of the DMSO can influence ligand positioning resulting in the observed indole ring orientation. Similar observation was made when analyzing crystal structures of **8**, **10**, and **13**. On the other hand, determining the crystal structure with compound **12**, prepared as a hydrochloride salt, revealed an alternative indole conformation in the absence of a trapped DMSO molecule. Here endocyclic nitrogen atom points to the hBChE acyl-loop, making hydrogen bonds with the backbone carbonyl oxygens of both Ser287 (3.3 Å) and Leu286 (3.3 Å). The binding mode in the crystal complexes with ligands dissolved in DMSO is certainly an experimental artifact and we can assume that the physiological binding mode of this type of compounds resembles

binding mode of compound **12**, while postulating that voluminous DMSO-occupied pocket could be explored by even bulkier moieties.

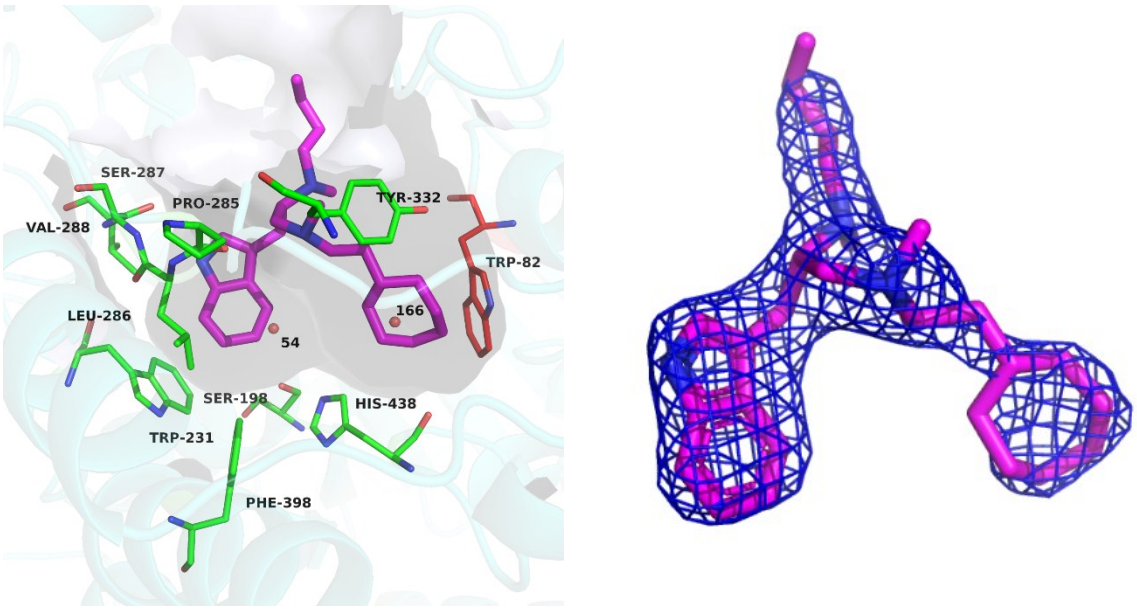


Figure S1: Left: Crystal structure of compound **12** (displayed in purple-coloured stick model) bound to hBChE (cyan-coloured ribbon model, resolution 2.4 Å). Key residues in proximity of compound **12** are coloured green and shown as sticks. **12** reaches into the acyl-binding pocket with its indole moiety while being oriented towards the choline-binding pocket with its bulky cycloheptyl ring. *N*-butyl side chain is pointing out of the active site gorge; **Right:** 2mF_o-DF_c electron density map as blue mesh, contoured at 1σ (2 Å carve), of compound **12** displayed as purple-coloured stick model at the active site of hBChE.

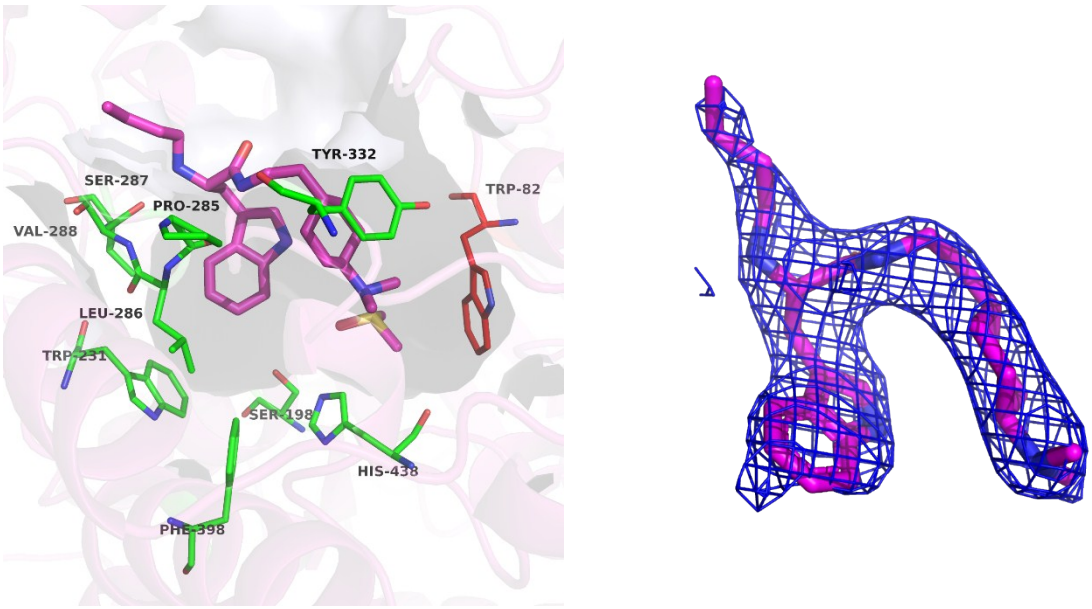


Figure S2: Left: Crystal structure of compound **13** (displayed in purple-coloured stick model) bound to hBChE (cyan-coloured ribbon model, resolution 2.5 Å) – presented as in *Figure S1*; **Right:** 2mF_o-DF_c electron density map as blue mesh, contoured at 1σ (2 Å carve), of compound **13** displayed as purple-coloured stick model at the active site of hBChE.

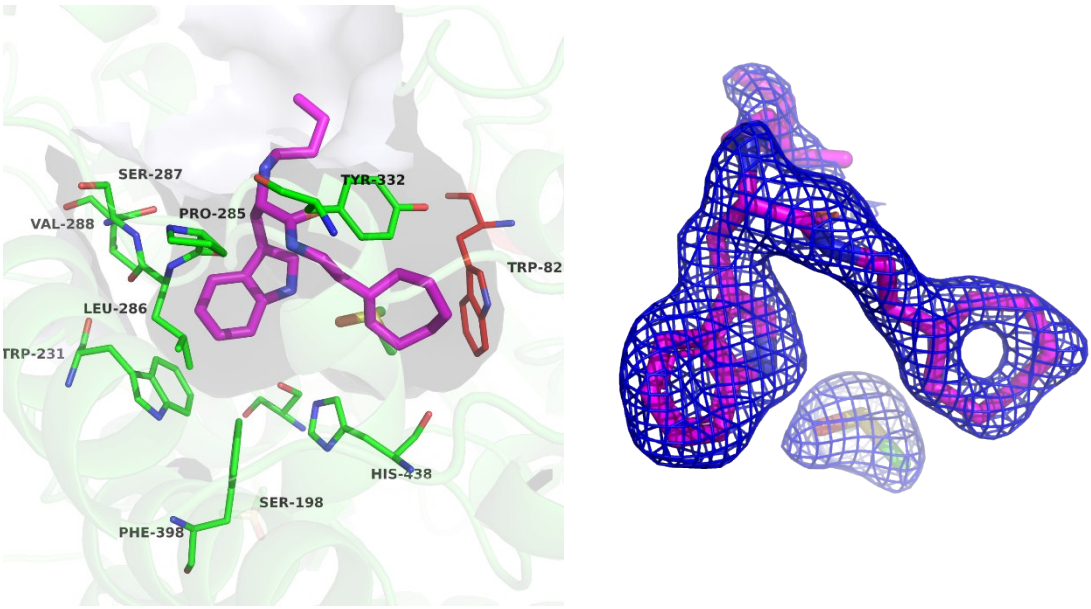


Figure S3: Left: Crystal structure of compound **6** (displayed in purple-coloured stick model) bound to hBChE (cyan-coloured ribbon model, resolution 1.9 Å). – presented as in *Figure S1*; **Right:** 2mF_o-DF_c electron density map as blue mesh, contoured at 1σ (2 Å carve), of compound **6** and the DMSO molecule displayed as purple and yellow-coloured stick model, respectively.

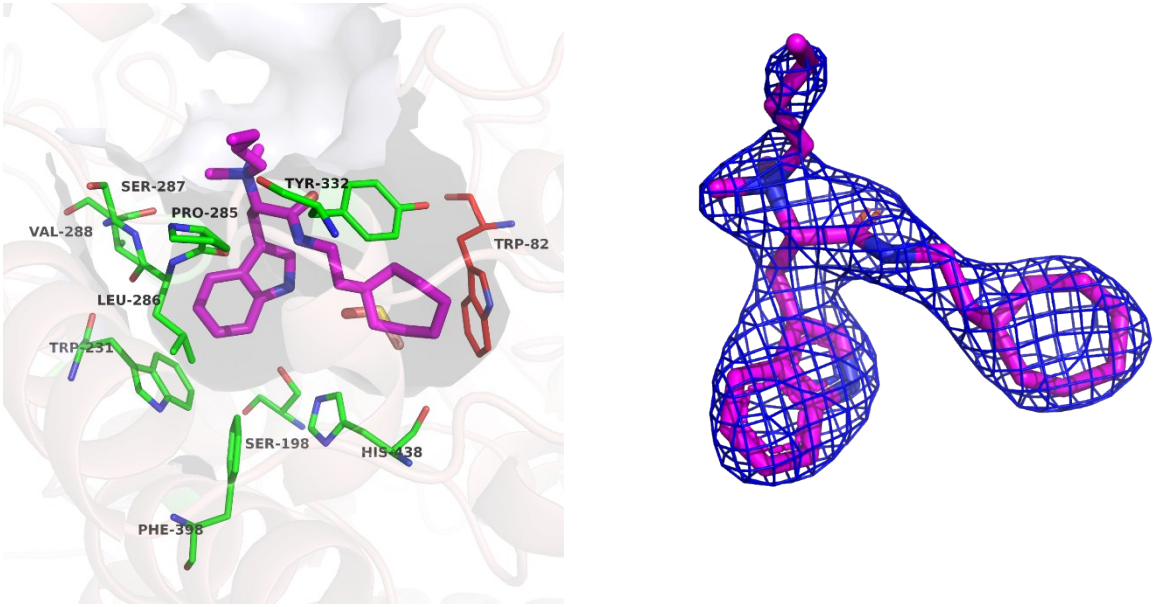


Figure S4: Left: Crystal structure of compound **10** (displayed in purple-coloured stick model) bound to hBChE (cyan-coloured ribbon model, resolution 2.5 Å) – presented as in *Figure S1*; **Right:** 2mF_o-DF_c electron density map as blue mesh, contoured at 1σ (2 Å carve), of compound **10** displayed as purple-coloured stick model at the active site of hBChE.

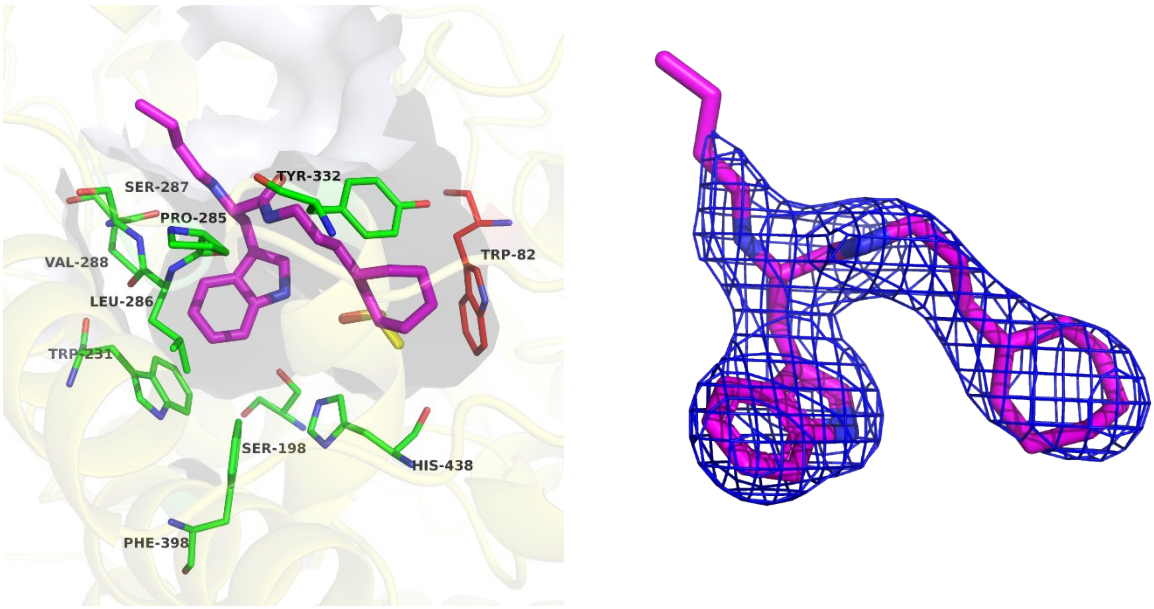


Figure S5: Left: Crystal structure of compound **8** (displayed in purple-coloured stick model) bound to hBChE (cyan-coloured ribbon model, resolution 2.8 Å) – presented as in *Figure S1*; **Right:** 2mF_o-DF_c electron density map as blue mesh, contoured at 1σ (2 Å carve), of compound **8** displayed as purple-coloured stick model at the active site of hBChE.

Chemistry

Chemistry – General Information

The reagents and solvents were used as received from commercial suppliers. For reactions that required anhydrous conditions, commercial solvents of anhydrous grade were used or dried accordingly prior to use. Glassware was flame dried with a heat gun and cooled in a dessicator, the reactants were azeotropically dried with anhydrous toluene. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Acetonitrile (MeCN) was distilled from calcium hydride and stored over 4Å molecular sieves. Anhydrous toluene was distilled from sodium and stored over sodium wire. Organic extracts were dried over anhydrous sodium sulfate. Reactions were monitored using analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} Al plates. Developed plates were inspected under UV light and if neccessary visualized with ninhydrin, vanillin/sulfuric acid, Dragendorff's or potassium permanganate stains. Melting points were determined with Stanford Research Systems OptiMelt MPA100 – Automated Melting Point System (uncorrected). Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 500 MHz, Bruker Avance III 400 MHz, or Bruker Avance DPX 300 MHz spectrometer at 500 MHz (400 MHz, 300 MHz) for ^{1}H and 126 MHz (100 MHz, 75 MHz) for ^{13}C nucleus, respectively, using DMSO-d_6 or $CDCl_3$ with TMS as the internal standard, as solvents. Chemical shifts are reported in parts per million (ppm), TMS peak was calibrated to 0 ppm, alternatively, the central peak of the residual solvent resonance was used as the internal standard *i.e.* for $CDCl_3$ at 7.27 ppm for ^{1}H and 77.16 ppm for ^{13}C and DMSO-d_6 at 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C, respectively. The multiplicities are reported as follows: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublets), *ddd* (doublet doublet of doublets), and *br* (broad), number of equivalent nuclei (by integration), coupling constants (*J*) quoted in Hertz (Hz). Mass spectra were recorded on Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on Bruker ALPHA FT-IR spectrophotometer, and elemental analyses were performed on Perkin-Elmer 2400 Series II CHNS/O Analyzer. Optical rotation was measured on Perkin Elmer 241MC Polarimeter and specific rotation values are given in 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed on silica gel (Silica gel 60, particle size: 0.035-0.070 mm, Merck) or on alumina (basic, Brockmann activity II, Fluka). UPLC analyses were performed on Thermo Scientific Dionex UltiMate 3000 modular system (Thermo Fisher Scientific Inc.). The general method used a Waters Acquity UPLC® HSS C18 SB column (2.1 × 50 mm, 1.8 µm) thermostated at 40 °C, with: injection volume, 4 µL; sample, 0.1–0.2 mg/mL in 20% $MeCN_{(aq)}$ + 0.1% TFA; flow rate,

0.4 mL/min; detector λ, 254 nm; mobile phase A: 0.1% TFA (v/v) in water; mobile phase B: MeCN. Gradient: 0–2 min, 20% B; 2–5 min, 20%–90% B; 5–8 min, 90% B. The purities of the tested compounds were established to be ≥95%, as determined by UPLC, unless indicated otherwise. Catalytic hydrogenation was performed on Parr 3916EF Hydrogenation Apparatus.

General procedure 1 (GP1) – amide formation: Carboxylic acid (1.0 eq.) was dissolved in anhydrous THF or anhydrous MeCN under argon and 1,1'-carbonyldiimidazole (CDI) (1.1 eq.) was added. After stirring the reaction mixture at r.t. for 1.5 h, amine (1.1 eq., neat) was added and stirring continued at r.t. for 12 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography to afford pure product.

General procedure 2 (GP2) – double bond isomerization and/or Boc-deprotection: Starting compound was dissolved in dichloromethane (DCM) (approx. 4 mL/mmol reactant), cooled on an icebath and then trifluoroacetic acid (TFA) (0.5–1 eq. by volume) was slowly added. The icebath was then removed and the resulting mixture was stirred at r.t. for 2 h or until total conversion was achieved (monitored by TLC).

For double bond isomerization: Volatile components were evaporated *in vacuo*. Last traces of trifluoroacetic acid were removed by azeotropic evaporation with anhydrous toluene. The product was purified by column chromatography.

For Boc-deprotection: Reaction mixture was made alkaline with 1 M $NaOH_{(aq)}$ and the product extracted into DCM (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was purified by column chromatography.

General procedure 3 (GP3) – reductive alkylation: Primary amine (1.0 mmol) and an appropriate aldehyde (1.1 eq.) were dissolved in DCM (10 mL) and stirred at r.t. for 10 min before sodium triacetoxyborohydride (1.5 eq.) was added. Reaction mixture was stirred for 6 h at r.t. before $NaHCO_{3(aq., sat.)}$ (5 mL) was added and the resulting mixture extracted with DCM (2 x 20 mL). Organic phase was dried over anhydrous sodium sulfate, filtered and volatile components evaporated *in vacuo*. The product was isolated by column chromatography.

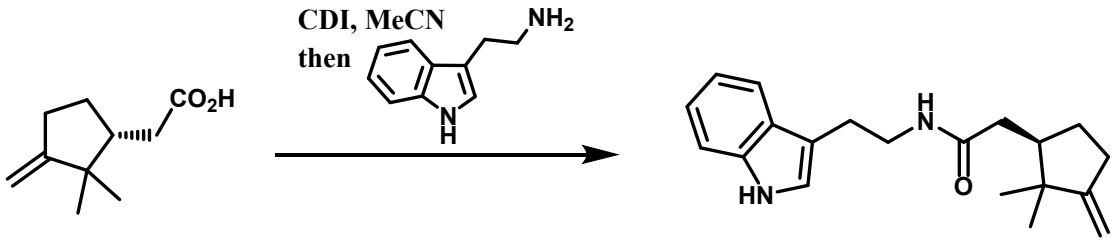
General procedure 4 (GP4) – catalytic hydrogenation of double bonds: Alkene (5.0 mmol) was dissolved in MeOH (25 mL), flushed with Ar, then 10% Pd/C (50 mg) was added and the resulting mixture hydrogenated at r.t. under H_2 (4 bar) for 12 h. The catalyst was removed by filtration, washed with MeOH and volatile components evaporated *in vacuo* to afford the saturated product.

General procedure 5 (GP5) – reduction with lithium aluminum hydride: To a solution of the starting compound (amide, nitrile, ester) (1.0 mmol) in anhydrous THF (1 mL), lithium aluminum hydride solution (2.4M in THF, 3.0 eq. (1.25 mL) for amides and nitriles or 1.0 eq. (0.42 mL) for esters) was added slowly with stirring under argon. The reaction mixture was stirred at 50 °C for 12 h and then while being cooled on an icebath, cautiously quenched with brine. The resulting grey solids were suspended in Et_2O (10 mL), filtered and washed with Et_2O (2 x 5 mL). The ethereal extracts were dried over sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford the product (amine or alcohol).

General procedure 6 (GP6) – Negishi coupling: Zinc dust (2.4 eq.) was activated as described by Jackson and Perez-Gonzalez.[17] Anhydrous DMF (1 mL/mmol alkyl iodide) was added to the activated Zn dust under argon to produce a suspension to which methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (1.2 eq.) was added and the resulting mixture was vigorously stirred for 2 h at r.t. to produce the organozinc reagent. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (2.5 mol%), SPhos (10 mol%) and aryl halide (1.0 eq.) were added to this suspension and stirring was continued for 12 h at 50°C. Reaction mixture was then poured into 5% aqueous citric acid (50 mL) and extracted with Et_2O (2 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and volatile components evaporated *in vacuo*. The product was isolated by column chromatography.

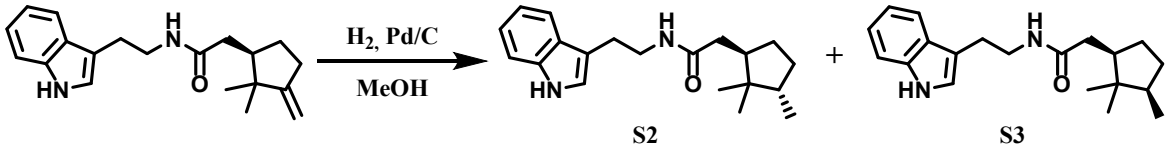
General procedure 7 (GP7) – RP-CC purification: Compounds were purified by reversed-phase column chromatography (RP-CC) (Isolera Biotage One Flash Chromatography system, SNAP Biotage KP-C18-HS column, 12 g) using a gradient of 0.1% TFA in deionized water and MeCN as eluent (gradient 10–90% MeCN in 15 column volumes (300 mL); 90% MeCN for 5 column volumes (100 mL)). After the RP-CC, fractions containing the product were combined and organic volatiles were evaporated *in vacuo*. The remaining aqueous solution was made alkaline (pH 10) with 1 M $NaOH_{(aq)}$ and extracted with DCM (2 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford pure product.

(*R*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(2,2-dimethyl-3-methylenecyclopentyl)acetamide (S1)



Prepared from (*R*)-2-(2,2-dimethyl-3-methylenecyclopentyl)acetic acid[15] (515 mg, 3.06 mmol), CDI (1.1 eq., 546 mg) and tryptamine (1.1 eq., 539 mg) in MeCN following *GP1*. The product was isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 690 mg (2.22 mmol, 73%) of orange oil. ESI-HRMS: *m/z* = 311.2121 (MH^+); $C_{20}H_{27}N_2O$ requires: *m/z* = 311.2118 (MH^+). ν_{max} 3405, 3274, 3069, 2957, 1726, 1645, 1523, 1457, 1433, 1362, 1338, 1305, 1248, 1149, 1096, 1044, 1010, 879, 806, 739, 609 cm^{-1}. $[\alpha]_D^{r.t.}$ = +11.6 (*c* 0.225, DCM). Purity: UPLC (254 nm): t_r = 4.747 min, 96.3% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78 (*s*, 3H); 1.04 (*s*, 3H); 1.21 – 1.31 (*m*, 1H); 1.73 – 1.87 (*m*, 2H); 1.94 – 2.02 (*m*, 1H); 2.24 (*dd*, *J* = 3.9; 13.8 Hz, 1H); 2.27 – 2.34 (*m*, 1H); 2.35 – 2.45 (*m*, 1H); 2.97 (*t*, *J* = 6.7 Hz, 2H); 3.61 (*q*, *J* = 6.6 Hz, 2H); 4.75 (*t*, *J* = 2.5 Hz, 1H); 4.77 (*t*, *J* = 1.7 Hz, 1H); 5.57 (*s*, 1H); 7.01 (*d*, *J* = 2.2 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.18 – 7.23 (*m*, 1H); 7.37 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.60 (*dd*, *J* = 1.1; 7.9 Hz, 1H); 8.29 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 23.64, 25.53, 26.76, 28.39, 30.54, 37.79, 39.88, 43.95, 47.18, 103.63, 111.42, 113.09, 118.82, 119.59, 122.17, 122.31, 127.47, 136.58, 161.50, 172.89.

_N_-(2-(1_H_-Indol-3-yl)ethyl)-2-((1_R_,3_S_)-2,2,3-trimethylcyclopentyl)acetamide (S2) and _N_-(2-(1_H_-indol-3-yl)ethyl)-2-((1_R_,3_R_)-2,2,3-trimethylcyclopentyl)acetamide (S3)



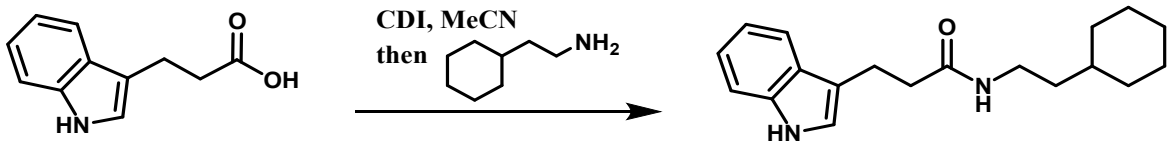
Prepared from **S1** (420 mg, 1.35 mmol) following *GP4*. The product was purified by column chromatography on silica (PE/EtOAc = 1:1) to afford a mixture of diastereomers **S3**:**S2** in a ratio of 83:17. Yield: 85.6 mg (0.274 mmol, 20.3%) of orange oil. ESI-HRMS: *m/z* = 313.2273 (MH^+); $C_{20}H_{29}N_2O$ requires: *m/z* = 313.2274 (MH^+). ν_{max} 3407, 3275, 3057, 2951, 2868, 1639, 1523, 1456, 1435, 1366, 1340, 1295, 1228, 1198, 1168, 1096, 1010, 908, 737 cm^{-1}. $[\alpha]_D^{r.t.}$ = +6.73 (*c* 0.077, DCM). Purity: UPLC (254 nm): t_r = 4.883 min, 98.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for **S3**: δ 0.46 (*s*, 3H); 0.82 (*d*, *J* = 6.8 Hz, 3H); 0.85 (*s*, 3H); 1.08 – 1.22 (*m*, 2H); 1.46 – 1.61 (*m*, 1H); 1.67 – 1.90 (*m*, 4H); 2.20 – 2.27 (*m*, 1H); 2.97 (*t*, *J* = 6.8 Hz, 2H); 3.56 –

3.64 (*m*, 2H); 5.53 (*t*, *J* = 5.9 Hz, 1H); 7.02 (*d*, *J* = 2.2 Hz, 1H); 7.09 – 7.15 (*m*, 1H); 7.18 – 7.23 (*m*, 1H); 7.37 (*dt*, *J* = 0.9; 8.2 Hz, 1H); 7.61 (*dd*, *J* = 1.1; 8.0 Hz, 1H); 8.24 (*s*, 1H). ^{1}H-NMR (500 MHz, $CDCl_3$) for **S2**: δ 0.74 (*s*, 3H); 0.81 (*s*, 3H); 0.83 (*d*, *J* = 7.0 Hz, 3H); 1.94 – 2.02 (*m*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for **S3**: δ 14.06, 14.68, 25.42, 25.53, 28.26, 30.09, 38.31, 39.84, 42.41, 44.82, 47.64, 111.39, 113.19, 118.86, 119.59, 122.16, 122.31, 127.51, 136.57, 173.30. ^{13}C-NMR (126 MHz, $CDCl_3$) for **S2**: δ 23.56, 24.09, 25.56, 29.27, 31.39, 38.99, 39.82, 42.18, 43.60, 45.29, 53.55, 173.42.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(2,3,3-trimethylcyclopent-1-en-1-yl)acetamide (S4)**

Prepared from amide **S1** (170 mg, 0.548 mmol) following *GP2*. The product was isolated by column chromatography on silica (PE/EtOAc = 1:2). Yield: 31.5 mg (0.101 mmol, 19%) of orange oil. ESI-HRMS: *m/z* = 311.2116 (MH^+); $C_{20}H_{27}N_2O$ requires: *m/z* = 311.2118 (MH^+). ν_{max} 3405, 3282, 3068, 2957, 1645, 1522, 1456, 1433, 1361, 1338, 1306, 1227, 1149, 1096, 1010, 879, 805, 738 cm^{-1}. Purity: UPLC (254 nm): t_r = 4.877 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.83 (*s*, 6H); 1.38 (*t*, *J* = 2.1 Hz, 3H); 1.48 (*t*, *J* = 7.2 Hz, 2H); 2.07 – 2.13 (*m*, 2H); 2.92 (*s*, 2H); 2.94 (*t*, *J* = 6.7 Hz, 2H); 3.62 (*q*, *J* = 6.4 Hz, 2H); 5.71 (*s*, 1H); 6.97 (*d*, *J* = 2.3 Hz, 1H); 7.08 – 7.13 (*m*, 1H); 7.17 – 7.21 (*m*, 1H); 7.35 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.58 (*dd*, *J* = 1.1; 7.9 Hz, 1H); 8.37 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.54, 25.37, 26.30, 33.36, 37.22, 38.72, 39.45, 46.94, 111.40, 112.73, 118.74, 119.54, 122.06, 122.26, 127.37, 127.52, 136.63, 144.60, 170.71.

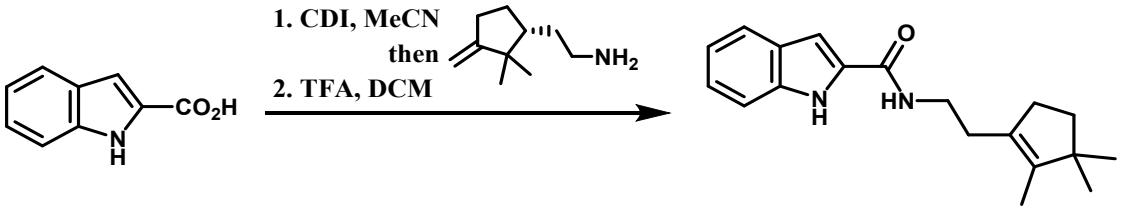
***N*-(2-Cyclohexylethyl)-3-(1*H*-indol-3-yl)propanamide (S5)**



Prepared from 3-(1*H*-indol-3-yl)propanoic acid (283 mg, 1.50 mmol), CDI (1.1 eq., 268 mg), 2-cyclohexylethan-1-amine (1.1 eq., 210 mg) in MeCN following *GP1*. The product was isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 362 mg (1.21 mmol, 80.9%) of white solid; mp 122.4–123.3 °C. ($C_{19}H_{26}N_2O$ requires: C, 76.47; H, 8.78; N, 9.39., found C 76.42, H 8.89, N 9.33); ESI-HRMS: *m/z* = 299.2117 (MH^+); $C_{19}H_{27}N_2O$ requires: *m/z* = 299.2118 (MH^+). ν_{max} 3281, 2921, 2851, 2064, 1610, 1562, 1446, 1367, 1340, 1275, 1247,

1227, 1205, 1101, 1011, 923, 888, 846, 773, 740, 672, 609 cm^{-1}. Purity: UPLC (254 nm): t_r = 4.840 min, 100% total area. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.78 – 0.90 (*m*, 2H); 1.05 – 1.31 (*m*, 6H); 1.55 – 1.70 (*m*, 5H); 2.43 (*dd*, *J* = 6.9; 8.5 Hz, 2H); 2.92 (*t*, *J* = 7.7 Hz, 2H); 3.02 – 3.11 (*m*, 2H); 6.94 – 7.00 (*m*, 1H); 7.03 – 7.10 (*m*, 2H); 7.33 (*dd*, *J* = 0.9; 8.0 Hz, 1H); 7.52 (*d*, *J* = 7.9 Hz, 1H); 7.76 (*t*, *J* = 5.6 Hz, 1H); 10.74 (*s*, 1H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 21.11, 25.77, 26.15, 32.68, 34.59, 36.20, 36.37, 36.70, 111.29, 113.92, 118.10, 118.35, 120.87, 122.05, 127.07, 136.25, 171.68.

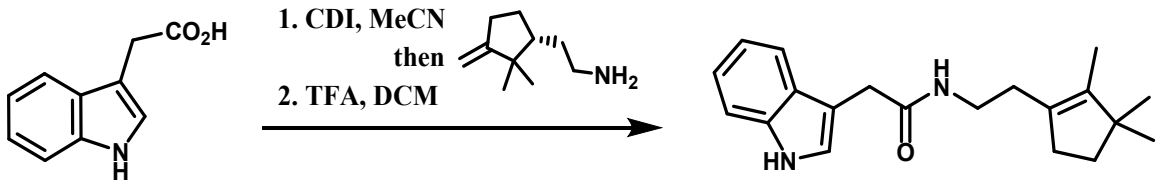
_N_-(2-(2,3,3-Trimethylcyclopent-1-en-1-yl)ethyl)-1_H_-indole-2-carboxamide (S6)



(*R*)-*N*-(2-(2,2-Dimethyl-3-methylenecyclopentyl)ethyl)-1*H*-indole-2-carboxamide was prepared following *GP1* from indole-2-carboxylic acid (322 mg, 2.00 mmol), CDI (1.1 eq., 357 mg), and (*R*)-2-(2,2-dimethyl-3-methylenecyclopentyl)ethan-1-amine[15] (1.1 eq., 337 mg) in MeCN, and isolated by column chromatography on silica (EtOAc). Yield: 489 mg (1.65 mmol, 82.6%) of yellow solid.

The title product was prepared from (*R*)-*N*-(2-(2,2-dimethyl-3-methylenecyclopentyl)ethyl)-1*H*-indole-2-carboxamide (118 mg, 0.398 mmol) following *GP2* and isolated by column chromatography on silica (PE/EtOAc = 1:2). Yield: 49.5 mg (0.167 mmol, 42%) of dark orange solid; mp 229.2–237.9 °C. ESI-HRMS: *m/z* = 297.1967 (MH^+); $C_{19}H_{25}N_2O$ requires: *m/z* = 297.1961 (MH^+). ν_{max} 3420, 3242, 2932, 2857, 1641, 1575, 1548, 1492, 1376, 1359, 1342, 1314, 1261, 1231, 1216, 1147, 1132, 1107, 1048, 999, 947, 933, 842, 810, 773, 747 cm^{-1}. Purity: UPLC (254 nm): t_r = 5.077 min, 97.7% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01 (*s*, 6H); 1.56 (*t*, *J* = 2.1 Hz, 3H); 1.67 (*t*, *J* = 7.1 Hz, 2H); 2.23 – 2.31 (*m*, 2H); 2.39 (*t*, *J* = 6.8 Hz, 2H); 3.56 (*q*, *J* = 6.7 Hz, 2H); 6.11 (*t*, *J* = 5.7 Hz, 1H); 6.69 (*d*, *J* = 1.1 Hz, 1H); 7.10 – 7.17 (*m*, 1H); 7.24 – 7.31 (*m*, 1H); 7.46 (*dd*, *J* = 1.0; 8.3 Hz, 1H); 7.64 (*d*, *J* = 8.1 Hz, 1H); 9.68 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.73, 26.66, 28.76, 32.41, 37.72, 38.95, 47.18, 101.42, 112.19, 120.72, 121.96, 124.49, 127.78, 129.96, 131.06, 136.44, 142.80, 161.63.

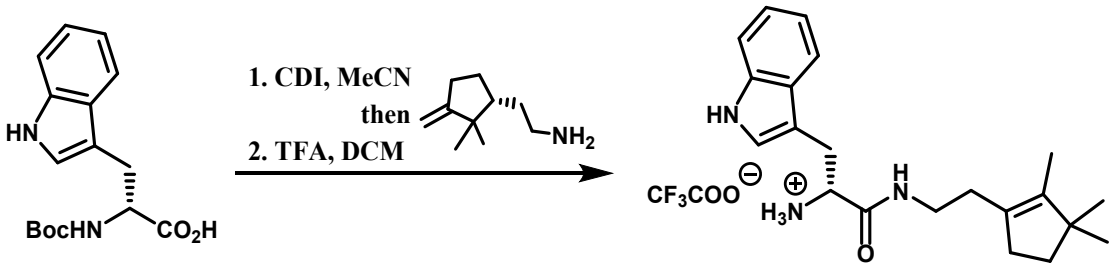
2-(1*H*-Indol-3-yl)-*N*-(2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)acetamide (5)



(*R*)-*N*-(2-(2,2-Dimethyl-3-methylenecyclopentyl)ethyl)-2-(1*H*-indol-3-yl)acetamide was prepared following *GP1* from indole-3-acetic acid (350 mg, 2.00 mmol), CDI (1.1 eq., 357 mg) and (*R*)-2-(2,2-dimethyl-3-methylenecyclopentyl)ethan-1-amine[15] (1.1 eq., 337 µL) in MeCN and isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 528 mg (1.70 mmol, 85%) of orange oil.

The title product was prepared from (*R*)-*N*-(2-(2,2-dimethyl-3-methylenecyclopentyl)ethyl)-2-(1*H*-indol-3-yl)acetamide (204 mg, 0.657 mmol) following *GP2*, isolated by column chromatography on silica (PE/EtOAc = 1:2) and additionally purified following *GP7*. Yield: 42.3 mg (0.136 mmol, 21%) of orange semisolid. ESI-HRMS: *m/z* = 311.2129 (MH^+); $C_{20}H_{27}N_2O$ requires: *m/z* = 311.2118 (MH^+). ν_{max} 3394, 3272, 2950, 2860, 1635, 1525, 1456, 1434, 1379, 1357, 1339, 1202, 1170, 1104, 1010, 926, 878, 800, 778, 739 cm^{-1}. Purity: UPLC (254 nm): t_r = 4.850 min, 93.5% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*s*, 6H); 1.12 (*t*, *J* = 2.1 Hz, 3H); 1.42 (*t*, *J* = 7.1 Hz, 2H); 1.95 – 2.02 (*m*, 2H); 2.07 (*t*, *J* = 6.7 Hz, 2H); 3.26 (*q*, *J* = 6.3 Hz, 2H); 3.74 (*s*, 2H); 5.66 (*s*, 1H); 7.10 (*d*, *J* = 2.4 Hz, 1H); 7.13 – 7.18 (*m*, 1H); 7.21 – 7.25 (*m*, 1H); 7.39 (*dt*, *J* = 0.9; 8.2 Hz, 1H); 7.53 (*d*, *J* = 7.9 Hz, 1H); 8.30 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.00, 26.37, 28.19, 32.02, 33.26, 37.81, 38.72, 46.89, 108.89, 111.54, 118.81, 120.38, 122.88, 123.86, 127.13, 129.58, 136.54, 142.23, 172.06.

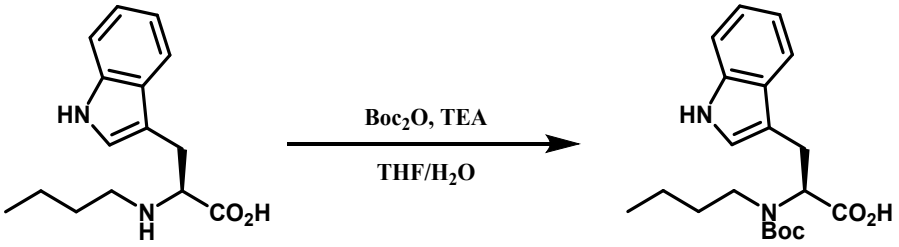
(*R*)-3-(1*H*-Indol-3-yl)-1-oxo-1-((2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)amino)propan-2-aminium 2,2,2-trifluoroacetate (S7)



tert-Butyl ((*R*)-1-((2-((*R*)-2,2-dimethyl-3-methylenecyclopentyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*tert*-butoxycarbonyl)-*D*-tryptophan (608 mg, 2.00 mmol), CDI (1.1 eq., 357 mg), and (*R*)-2-(2,2-dimethyl-3-methylenecyclopentyl)ethan-1-amine[15] (1.1 eq., 337 mg) in MeCN and isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 701 mg (1.59 mmol, 80%) of orange oil.

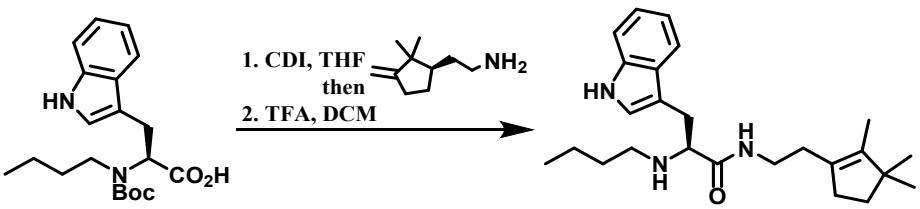
The title product was prepared from *tert*-butyl ((*R*)-1-((2-((*R*)-2,2-dimethyl-3-methylenecyclopentyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (667 mg, 1.52 mmol) following modified *GP2* – basic work-up was omitted and volatile components were evaporated *in vacuo*. Thus obtained trifluoroacetate salt (**S7**) was thoroughly dried in high vacuum. Yield: 669 mg (1.48 mmol, 97%) of dark orange oil. ESI-HRMS: *m/z* = 340.2377 (MH^+); $C_{21}H_{30}N_3O^+$ requires: *m/z* = 340.2383 (MH^+). ν_{max} 3412, 2952, 2862, 1777, 1663, 1537, 1495, 1458, 1435, 1359, 1339, 1166, 1141, 1011, 838, 798, 741, 724 cm^{-1}. $[\alpha]_D^{r.t.}$ = –16.3 (*c* 0.22, DCM). Purity: UPLC (254 nm): t_r = 4.343 min, 93.4% total area. ^{1}H-NMR (500 MHz,$CDCl_3$): δ 0.88 (*s*, 3H); 0.90 (*s*, 3H); 1.38 (*t*, *J* = 2.0 Hz, 3H); 1.47 – 1.59 (*m*, 2H); 1.91 – 2.09 (*m*, 4H); 2.96 – 3.05 (*m*, 1H); 3.06 – 3.16 (*m*, 1H); 3.18 – 3.28 (*m*, 2H); 4.17 (*t*, *J* = 7.3 Hz, 1H); 6.62 (*t*, *J* = 5.5 Hz, 1H); 7.06 (*t*, *J* = 7.5 Hz, 1H); 7.09 – 7.20 (*m*, 2H); 7.32 (*d*, *J* = 8.1 Hz, 1H); 7.48 (*d*, *J* = 7.9 Hz, 1H); 7.72 (br *s*, 3H); 8.49 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.32, 26.45, 26.50, 27.82, 28.00, 32.08, 38.46, 38.76, 46.97, 54.31, 107.37, 111.85, 114.68, 116.98, 118.19, 120.13, 122.78, 124.63, 126.75, 136.45, 142.36, 161.52 (*q*, *J* = 38.1 Hz), 168.56.

N^{α}-(*tert*-Butoxycarbonyl)-N^{α}-butyl-L-tryptophan (S8-1)



Butyl-L-tryptophan[18] (870 mg, 3.342 mmol) was dissolved in a mixture of THF (10 mL) and water (10 mL), then TEA (2.5 eq., 845 mg) and di-*tert*-butyl dicarbonate (2.5 eq., 1823 mg) were added and the reaction mixture was stirred at r.t. for 12 h. THF was then removed *in vacuo,* the residue acidified (pH 3), extracted with EtOAc (3 x 20 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was isolated by column chromatography on silica (1. PE/EtOAc = 5:1; 2. PE/EtOAc = 2:1). Yield: 910.6 mg (2.526 mmol, 75.6%) of beige semisolid. ESI-HRMS: *m/z* = 261.1598 (MH^+); $C_{20}H_{29}N_2O_4$ requires: *m/z* = 261.1598 (MH^+). ν_{max} 3341, 2977, 2931, 2251, 1713, 1673, 1495, 1455, 1420, 1394, 1366, 1334, 1248, 1157, 1096, 1075, 1030, 1011, 980, 907, 860, 806, 729, 698, 670, 647, 610 cm^{-1}. $[\alpha]_D^{r.t.}$ = –81.9 (*c* 0.41, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.73 (*t*, *J* = 7.3 Hz, 3H); 1.01 – 1.35 (*m*, 4H); 1.39 – 1.65 (*m*, 9H); 2.53 – 2.75 (*m*, 1H); 3.05 – 3.57 (*m*, 3H); 4.11 – 4.39 (*m*, 1H); 7.01 (*d*, *J* = 12.2 Hz, 1H); 7.08 – 7.15 (*m*, 1H); 7.19 (*t*, *J* = 7.5 Hz, 1H); 7.31 – 7.39 (*m*, 1H); 7.53 – 7.65 (*m*, 1H); 8.24 (s, 0.5H); 8.35 (*s*, 0.5H); 9.21 (br *s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.81, 13.86, 19.85, 20.05, 25.02, 25.94, 28.49, 28.52, 30.33, 30.78, 48.88, 49.22, 61.25, 62.71, 81.01, 111.35, 111.50, 111.68, 111.73, 118.30, 118.55, 119.54, 122.08, 123.08, 123.43, 127.30, 127.49, 136.29, 155.00, 156.60, 175.75, 177.41. Compound **S8-1** exist as a mixture of two major conformers in a 1:1 ratio.

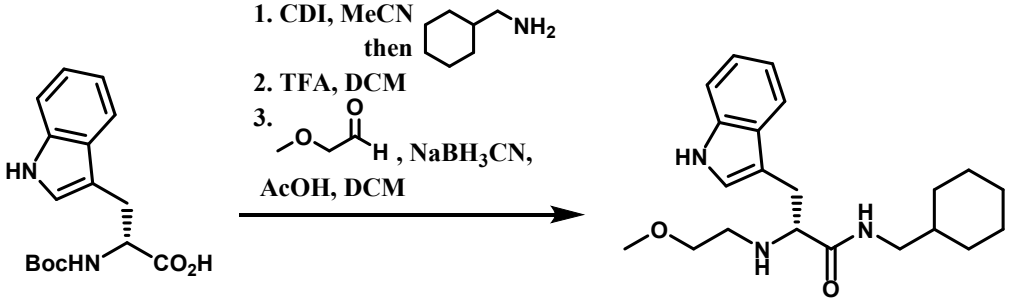
(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)propanamide (S8)



tert-Butyl butyl((2*S*)-1-((2-(2,2-dimethyl-3-methylenecyclopentyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (314.8 mg, 0.873 mmol), CDI (1.1 eq, 155.7 mg) and (*R*)-2-(2,2-dimethyl-3-methylenecyclopentyl)ethan-1-

amine[15] (1.1 eq., 147.2 mg) in THF, isolated by column chromatography on silica (1. PE/EtOAc = 5:1; 2. PE/EtOAc = 3:1) and immediately deprotected following *GP2*. **S8** was isolated by column chromatography on silica (1. PE/EtOAc = 1:1; 2. PE/EtOAc = 1:3). Yield: 59.8 mg (0.151 mmol, 17.3% over two steps) of colourless oil. ESI-HRMS: *m/z* = 396.3007 (MH^+); $C_{25}H_{38}N_3O$ requires: *m/z* = 396.3009 (MH^+). ν_{max} 3270, 2952, 2927, 2860, 1650, 1522, 1456, 1357, 1231, 1104, 1010, 739 cm^{-1}. $[\alpha]_D^{r.t.}$ = 0.0 (*c* 0.05, MeOH). Purity: UPLC (254 nm): t_r = 4.697 min, 92.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.74 (*t*, *J* = 7.2 Hz, 3H); 0.94 (*s*, 3H); 0.96 (*s*, 3H); 1.06 – 1.16 (*m*, 2H); 1.18 – 1.27 (*m*, 2H); 1.48 (*t*, *J* = 2,1 Hz, 3H); 1.56 – 1.64 (*m*, 2H); 2.11 – 2.23 (*m*, 4H); 2.34 – 2.47 (*m*, 2H); 2.88 (*dd*, *J* = 8.8; 14.1 Hz, 1H); 3.25 – 3.43 (*m*, 4H); 7.02 (*d*, *J* = 2.3 Hz, 1H); 7.07 – 7.11 (*m*, 1H); 7.15 – 7.20 (*m*, 1H); 7.33 (*t*, *J* = 5.7 Hz, 1H, NH); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.63 (*d*, *J* = 8.0 Hz, 1H); 8.72 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.53, 13.88, 20.20, 26.50, 26.56, 28.65, 29.31, 32.12, 32.17, 37.18, 38.86, 46.98, 48.74, 63.41, 111.38, 111.55, 118.87, 119.52, 122.18, 122.99, 127.59, 130.11, 136.58, 141.79, 174.60.

(*R*)-*N*-(Cyclohexylmethyl)-3-(1*H*-indol-3-yl)-2-((2-methoxyethyl)amino)propanamide (S9)

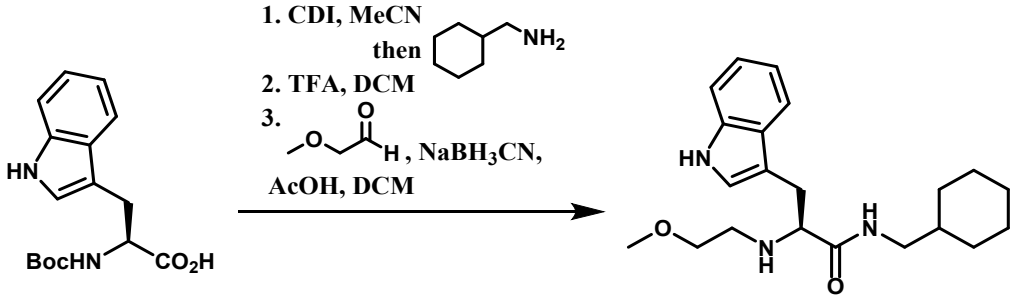


tert-Butyl (*R*)-(1-((cyclohexylmethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*tert*-butoxycarbonyl)-D-tryptophan (1.14 mmol, 347 mg), CDI (1.1 eq., 203 mg), and cyclohexylmethanamine (1.1 eq, 142 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1) and immediately deprotected following *GP2* to afford (*R*)-2-amino-*N*-(cyclohexylmethyl)-3-(1*H*-indol-3-yl)propanamide, which was used without further purification. Yield: 314.4 mg (1.05 mmol, 92% over two steps) of yellowish semisolid.

S9 was prepared following modified *GP3* from (*R*)-2-amino-*N*-(cyclohexylmethyl)-3-(1*H*-indol-3-yl)propanamide (1 mmol, 299.4 mg), ~ 50 vol.% methoxyacetaldehyde in water[19] (1000 µL), sodium cyanoborohydride (5 eq., 314 mg), acetic acid (50 µL) and anhydrous sodium sulfate (3 g) in DCM (10 mL). The reaction mixture was stirred at r.t. for 24 h, then filtered to

remove hydrated sodium sulfate, washed with DCM (2 x 20 mL), and volatile components evaporated *in vacuo*. The title product was isolated by column chromatography on silica (DCM/MeOH = 50:1) and purified following *GP7*. Yield: 156.7 mg (0.438 mmol, 43.8%) of beige oil. ESI-HRMS: *m/z* = 358.2488 (MH^+); $C_{21}H_{32}N_3O_2$ requires: *m/z* = 358.2489 (MH^+). ν_{max} 3292, 3056, 2920, 2850, 1648, 1526, 1448, 1342, 1279, 1231, 1188, 1106, 1010, 960, 927, 877, 842, 738, 683, 613 cm^{-1}. $[\alpha]_D^{r.t.}$ = +63.4 (*c* 0.10, DCM). Purity: UPLC (254 nm): t_r = 4.057 min, 95.7% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78 – 0.87 (*m*, 2H); 1.01 – 1.19 (*m*, 3H); 1.27 – 1.39 (*m*, 1H); 1.53 – 1.66 (*m*, 6H); 1.82 (*s*, 1H); 2.54 (*t*, *J* = 5.1 Hz, 2H); 2.81 (*dd*, *J* = 9.6; 14.5 Hz, 1H); 3.00 – 3.05 (*m*, 4H); 3.11 – 3.17 (*m*, 1H); 3.18 – 3.23 (*m*, 1H); 3.30 (*dd*, *J* = 3.8; 14.5 Hz, 1H); 3.37 (*dd*, *J* = 4.0; 9.6 Hz, 1H); 6.95 (*d*, *J* = 2.3 Hz, 1H); 7.00 – 7.05 (*m*, 1H); 7.08 – 7.14 (*m*, 1H); 7.28 (*d*, *J* = 8.1 Hz, 1H); 7.40 (*t*, *J* = 6.1 Hz, 1H); 7.60 (*d*, *J* = 7.9 Hz, 1H); 8.55 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.94, 26.50, 29.69, 30.89, 30.92, 37.97, 45.34, 48.26, 58.54, 63.09, 71.58, 111.35, 111.58, 119.02, 119.50, 122.17, 123.12, 127.42, 136.64, 174.40.

(*S*)-*N*-(Cyclohexylmethyl)-3-(1*H*-indol-3-yl)-2-((2-methoxyethyl)amino)propanamide (S10)

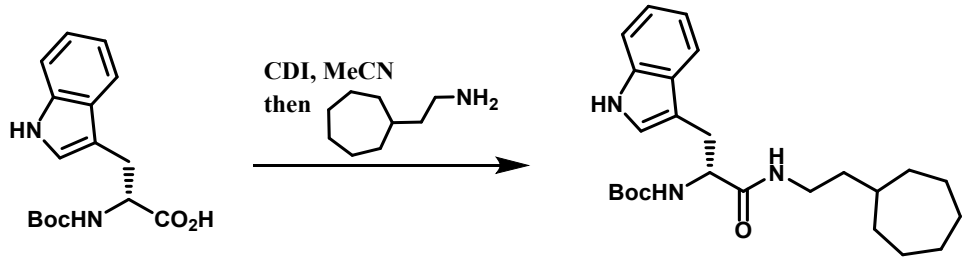


tert-Butyl (*S*)-(1-((cyclohexylmethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*tert*-butoxycarbonyl)-L-tryptophan (1.14 mmol, 347 mg), CDI (1.1 eq., 203 mg), and cyclohexylmethanamine (1.1 eq, 142 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1) and immediately deprotected following *GP2* to afford (*S*)-2-amino-*N*-(cyclohexylmethyl)-3-(1*H*-indol-3-yl)propanamide, which was used without further purification. Yield: 326.4 mg (1.09 mmol, 95.6% over two steps) of yellowish semisolid.

S10 was prepared following modified *GP3* from (*S*)-2-amino-*N*-(cyclohexylmethyl)-3-(1*H*-indol-3-yl)propanamide (1 mmol, 299.4 mg), ~ 50 vol.% methoxyacetaldehyde in water[19] (1000 µL), sodium cyanoborohydride (5 eq., 314 mg), acetic acid (50 µL) and anhydrous sodium sulfate (3 g) in DCM (10 mL). The reaction mixture was stirred at r.t. for 24 h, then filtered to

remove hydrated sodium sulfate, washed with DCM (2 x 20 mL), and volatile components evaporated *in vacuo*. The title product was isolated by column chromatography on silica (DCM/MeOH = 50:1) and purified following *GP7*. Yield: 184.8 mg (0.517 mmol, 51.7%) of beige oil. ESI-HRMS: *m/z* = 358.2495 (MH^+); $C_{21}H_{32}N_3O_2$ requires: *m/z* = 358.2489 (MH^+). ν_{max} 3292, 3056, 2920, 2850, 1648, 1526, 1448, 1342, 1279, 1231, 1188, 1106, 1010, 960, 927, 877, 842, 738, 683, 613 cm^{-1}. $[\alpha]_D^{r.t.}$ = –43.8 (*c* 0.24, DCM). Purity: UPLC (254 nm): t_r = 3.970 min, 97.8% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85 – 0.96 (*dd*, *J* = 2.9; 12.7 Hz, 2H); 1.08 – 1.28 (*m*, 3H); 1.36 – 1.48 (*m*, 1H); 1.59 – 1.85 (*m*, 7H); 2.63 (*t*, *J* = 5.0 Hz, 2H); 2.88 (*dd*, *J* = 9.5; 14.5 Hz, 1H); 3.06 – 3.12 (*m*, 1H); 3.10 (*s*, 3H); 3.20 – 3.32 (*m*, 2H); 3.38 (*dd*, *J* = 3.7; 14.3 Hz, 1H); 3.44 (*dd*, *J* = 4.0; 9.5 Hz, 1H); 7.07 (*d*, *J* = 2.3 Hz, 1H); 7.09 – 7.15 (*m*, 1H); 7.17 – 7.22 (*m*, 1H); 7.34 – 7.39 (*m*, 1H); 7.44 (*t*, *J* = 6.1 Hz, 1H); 7.71 (*dd*, *J* = 1.1; 7.9 Hz, 1H); 8.19 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.00, 26.56, 29.68, 30.95, 30.98, 38.03, 45.36, 48.30, 58.61, 63.08, 71.61, 111.27, 111.97, 119.20, 119.70, 122.37, 122.99, 127.50, 136.60, 174.27.

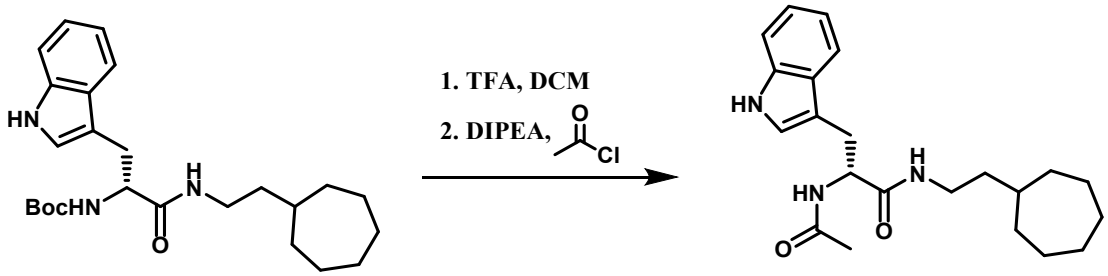
tert-Butyl (*R*)-(1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (S11)



Prepared from (*tert*-butoxycarbonyl)-*D*-tryptophan (302 mg, 0.99 mmol), CDI (1.1 eq., 177 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 154 mg) in MeCN following *GP1*, and isolated by column chromatography on silica (EtOAc). Yield: 394 mg (0.922 mmol, 93.1 %) of white solid; mp 57.9–60.4 °C. ESI-HRMS: *m/z* = 428.2921 (MH^+); $C_{25}H_{38}N_3O_3$ requires: *m/z* = 428.2908 (MH^+). ν_{max} 3295, 2916, 2851, 1698, 1648, 1541, 1522, 1508, 1490, 1457, 1389, 1364, 1246, 1162, 1063, 1010, 858, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = –20.2 (*c* 0.1, DCM). Purity: $C_{25}H_{37}N_3O_3$ requires: C, 70.23; H, 8.72; N, 9.83., found C 69.92, H 8.58, N 9.65. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01 – 1.19 (*m*, 4H); 1.29 – 1.39 (*m*, 3H); 1.39 – 1.48 (*m*, 11H); 1.49 – 1.59 (*m*, 6H); 3.00 – 3.21 (*m*, 3H); 3.31 (*dd*, *J* = 5.3; 14.6 Hz, 1H); 4.38 (*s*, 1H); 5.18 (*s*, 1H); 5.54 (*s*, 1H); 7.05 (*d*, *J* = 2.5 Hz, 1H); 7.11 – 7.16 (*m*, 1H); 7.18 – 7.23 (*m*, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.67 (*d*, *J* = 7.9 Hz, 1H); 8.11 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for a mixture of conformers: δ 25.93, 26.13, 26.32, 26.53, 27.87, 28.20, 28.51, 28.75, 28.83, 28.96, 34.09, 34.46, 36.74,

36.75, 37.24, 37.65, 37.81, 37.97, 55.45, 60.46, 80.01, 110.53, 111.26, 111.46, 118.73, 118.96, 119.48, 119.62, 122.01, 122.15, 123.28, 123.35, 127.47, 136.38, 155.58, 171.66.

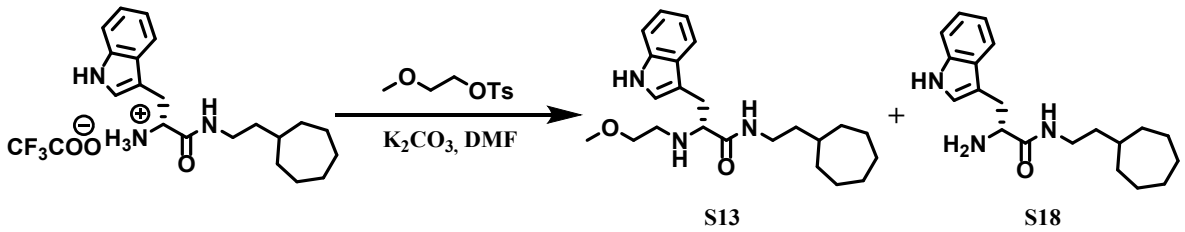
(*R*)-2-Acetamido-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (S12)



S11 (385 mg, 0.900 mmol) was deprotected following modified *GP2* – basic work-up was omitted and volatile components were removed *in vacuo* to afford (*R*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate as orange oil (360 mg, 90.6% yield).

To a solution of (*R*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (106 mg, 0.240 mmol) in anhydrous DCM (2 mL) under Ar at r.t., *N*,*N*-diisopropylethylamine (DIPEA) (4.0 eq., 167 µL) was added followed by the addition of acetyl chloride (1.5 eq., 25.7 µL). After stirring the reaction mixture at r.t. for 12 h, the reaction mixture was diluted with EtOAc (50 mL) and sequentially washed with 1 M $NaHSO_{4(aq.)}$ (2 x 5 mL), $NaHCO_{3(aq., sat.)}$ (2 x 5 mL), and brine (2 x 5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 58.2 mg (0.158 mmol, 65.6%) of white solid; mp 78.5–84.0 °C. ($C_{22}H_{31}N_3O_2$ requires: C, 71.51; H, 8.46; N, 11.37. found C 71.47, H 8.47, N 11.02); ESI-HRMS: *m/z* = 370.2496 (MH^+); $C_{22}H_{32}N_3O_2$ requires: *m/z* = 370.2489 (MH^+). ν_{max} 3271, 3078, 2916, 2850, 2178, 2138, 1631, 1536, 1456, 1435, 1370, 1286, 1233, 1098, 1010, 738 cm^{-1}. $[\alpha]_D^{r.t.} = -14.46$ (*c* 0.14, DCM). Purity: UPLC (254 nm): t_r = 4.750 min, 99.3% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.99 – 1.15 (*m*, 4H); 1.17 – 1.61 (*m*, 11H); 2.00 (*s*, 3H); 3.01 – 3.14 (*m*, 3H); 3.31 (*ddd*, *J* = 0.9; 5.2; 14.3 Hz, 1H); 4.62 – 4.72 (*m*, 1H); 5.46 (*t*, *J* = 5.2 Hz, 1H); 6.38 (*d*, *J* = 7.7 Hz, 1H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.10 – 7.19 (*m*, 1H); 7.16 – 7.25 (*m*, 1H); 7.37 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.73 (*d*, *J* = 7.9 Hz, 1H); 8.14 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 23.46, 26.37, 28.57, 28.59, 28.90, 34.34, 34.44, 36.79, 37.31, 37.93, 54.23, 111.25, 111.36, 119.10, 120.02, 122.52, 123.08, 127.51, 136.34, 170.07, 171.10.

(*R*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-((2-methoxyethyl)amino)propanamide (S13) and (*R*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (S18)



S13 **S18**

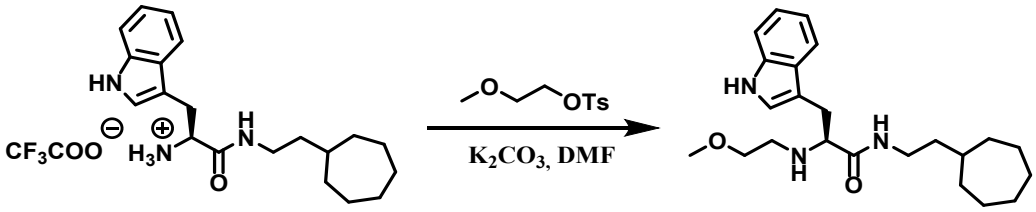
(*R*)-1-((2-Cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (prepared as described under **S12**) (676 mg, 1.53 mmol), 2-methoxyethyl tosylate (1.5 eq., 528 mg) and potassium carbonate (1.2 eq., 253 mg) in DMF (2.5 mL) were stirred at 85 °C for 16 h under Ar. Volatile components were then evaporated *in vacuo* and the residue was purified by column chromatography on silica (EtOAc/MeOH = 3:1). Fractions containing the separated pure products **S13** and **S18** were combined and volatile components evaporated *in vacuo*, respectively.

Compound **S13** eluted first from the column. Yield: 107 mg (0.278 mmol, 18.1%) of yellowish oil. ESI-HRMS: *m/z* = 386.2805 (MH^+); $C_{23}H_{36}N_3O_2$ requires: *m/z* = 386.2802 (MH^+). ν_{max} 3306, 3056, 2917, 2851, 1649, 1525, 1456, 1354, 1341, 1231, 1192, 1105, 1010, 909, 877, 737 cm^{-1}. $[\alpha]_D^{r.t.}$ = +38.7 (*c* 0.21, DCM). Purity: UPLC (254 nm): t_r = 4.450 min, 98.3% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.12 – 1.23 (*m*, 2H); 1.32 – 1.74 (*m*, 14H); 2.61 (*t*, *J* = 5.1 Hz, 2H); 2.88 (*dd*, *J* = 9.4; 14.4 Hz, 1H); 3.10 (*s*, 3H); 3.18 – 3.32 (*m*, 4H); 3.37 (*ddd*, *J* = 1.0; 4.0; 14.4 Hz, 1H); 3.42 (*dd*, *J* = 4.0; 9.5 Hz, 1H); 7.05 (*d*, *J* = 2.3 Hz, 1H); 7.08 – 7.14 (*m*, 1H); 7.16 – 7.22 (*m*, 1H); 7.31 – 7.40 (*m*, 2H); 7.64 – 7.73 (*m*, 1H); 8.36 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.48, 28.63, 29.62, 34.52, 36.99, 37.38, 37.74, 48.25, 58.59, 63.02, 71.64, 111.28, 111.94, 119.17, 119.67, 122.35, 122.99, 127.51, 136.59, 174.21.

Compound **S18** eluted second from the column. Yield: 127 mg (0.388 mmol, 25.4%) of yellowish oil. ESI-HRMS: *m/z* = 328.2382 (MH^+); $C_{20}H_{30}N_3O$ requires: *m/z* = 328.2383 (MH^+). ν_{max} 3277, 3056, 2917, 2851, 1731, 1648, 1526, 1457, 1437, 1355, 1341, 1233, 1201, 1174, 1128, 1097, 1009, 925, 879, 829, 799, 740 cm^{-1}. $[\alpha]_D^{r.t.}$ = +37.9 (*c* 0.24, DCM). Purity: UPLC (254 nm): t_r = 4.253 min, 97.8% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10 – 1.22 (*m*, 2H); 1.34 – 1.69 (*m*, 14H); 1.82 (*s*, 2H); 2.92 (*dd*, *J* = 8.9; 14.5 Hz, 1H); 3.18 – 3.29 (*m*, 2H); 3.33 – 3.41 (*m*, 1H); 3.71 (*dd*, *J* = 4.4; 8.9 Hz, 1H); 7.06 (*d*, *J* = 2.6 Hz, 1H); 7.10 – 7.14 (*m*, 1H); 7.16 – 7.23 (*m*, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.67 (*d*, *J* = 7.9 Hz, 1H); 8.34 (*s*, 1H, NH). ^{13}C-NMR

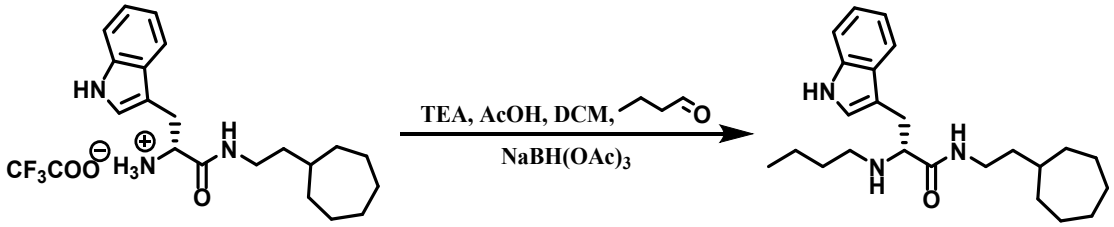
(126 MHz, $CDCl_3$): δ 26.42, 28.63, 30.88, 34.48, 34.51, 37.00, 37.53, 37.69, 55.72, 111.39, 111.86, 119.08, 119.71, 122.35, 123.23, 127.61, 136.52, 174.55.

(*S*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-((2-methoxyethyl)amino)propanamide (S14)



Prepared from (*S*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (198.2 mg, 0.449 mmol) following the procedure described under **S13**. The product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1) and purified following *GP7*. Yield: 22.4 mg (0.058 mmol, 12.9%) of yellowish oil. ESI-HRMS: *m/z* = 386.2805 (MH^+); $C_{23}H_{36}N_3O_2$ requires: *m/z* = 386.2802 (MH^+). ν_{max} (see epimer MG-33). $[\alpha]_D^{r.t.}$ = –10.2 (*c* 0.066, MeOH). Purity: UPLC (254 nm): t_r = 4.417 min, 95.3% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.07 – 1.28 (*m*, 2H); 1.33 – 1.74 (*m*, 14H); 1.80 (br *s*, 1H, NH); 2.62 (*t*, *J* = 5.1 Hz, 2H); 2.89 (*dd*, *J* = 9.2; 14.2 Hz, 1H); 3.10 (*s*, 3H); 3.18 – 3.47 (*m*, 5H); 7.04 (*s*, 1H); 7.06 – 7.14 (*m*, 1H); 7.14 – 7.23 (*m*, 1H); 7.27 – 7.40 (*m*, 2H); 7.68 (*d*, *J* = 7.7 Hz, 1H); 8.36 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (see epimer **S13**).

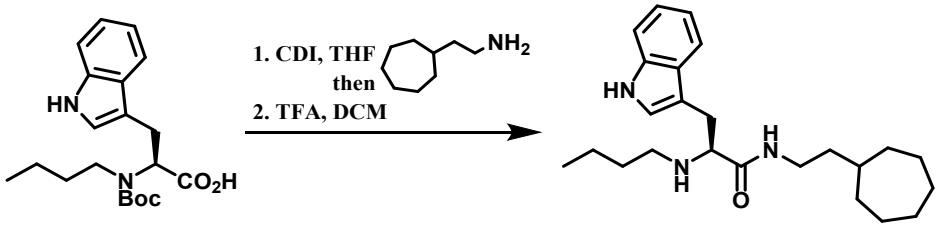
(*R*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (7)



Following modified *GP3*: (*R*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (prepared as described under **S12**) (397 mg, 0.899 mmol), TEA (1.1 eq., 138 µL), acetic acid (1 eq., 51.5 µL), and *n*-butanal (1.1 eq., 89.1 µL) in DCM (5 mL) were stirred for 1h at r.t. before sodium triacetoxyborohydride (1.5 eq., 293 mg) was added. The reaction mixture was stirred at r.t. for 16 h and worked-up as described in *GP3*. The product was isolated by column chromatography on silica (EtOAc). Yield: 87.6 mg (0.228 mmol, 25%) of yellowish semisolid. ESI-HRMS: *m/z* = 384.3008 (MH^+); $C_{24}H_{38}N_3O$ requires: *m/z* = 384.3009 (MH^+). ν_{max} 3294, 3056, 2918, 2851, 1650, 1524, 1456, 1354, 1341, 1232, 1124,

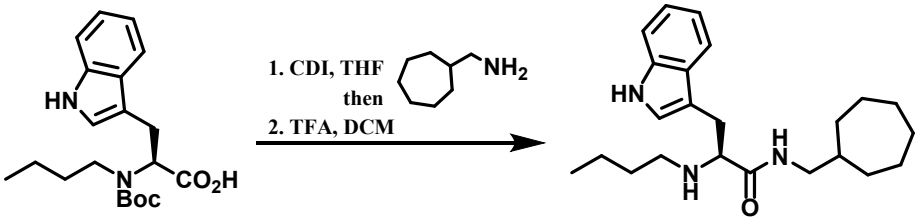
1103, 1010, 737, 670 cm^{-1}. $[\alpha]_D^{r.t.}$ = +35.8 (*c* 0.12, DCM). Purity: UPLC (254 nm): t_r = 4.630 min, 98.3% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.2 Hz, 3H); 1.09 – 1.32 (*m*, 5H); 1.33 – 1.74 (*m*, 15H); 2.37 – 2.48 (*m*, 2H); 2.88 (*dd*, *J* = 9.0; 14.1 Hz, 1H); 3.16 – 3.26 (*m*, 1H); 3.26 – 3.41 (*m*, 3H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.18 – 7.23 (*m*, 1H); 7.24 – 7.29 (*m*, 1H); 7.37 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.65 – 7.72 (*m*, 1H); 8.17 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.95, 20.33, 26.50, 28.61, 29.46, 32.31, 34.50, 34.53, 36.98, 37.24, 37.79, 48.81, 63.58, 111.31, 112.03, 119.07, 119.71, 122.36, 122.86, 127.63, 136.52, 174.46.

(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (6)



tert-Butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (150 mg, 0.416 mmol), CDI (1.1 eq., 74.2 mg), 2-cycloheptylethan-1-amine (1.05 eq., 64.6 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1) and immediately deprotected following *GP2*. The title product was purified by column chromatography on silica (DCM/MeOH = 50:1). Yield: 34.5 mg (0.09 mmol, 21.6% over two steps) of colourless oil. ESI-HRMS: *m/z* = 384.3015 (MH^+); $C_{24}H_{38}N_3O$ requires: *m/z* = 384.3009 (MH^+). ν_{max} 3273, 3057, 2919, 2852, 1651, 1525, 1457, 1354, 1232, 1124, 1103, 1010, 908, 878, 737, 666, 612 cm^{-1}. $[\alpha]_D^{r.t.}$ = –45.3 (*c* 0.29, acetone). Purity: UPLC (254 nm): t_r = 4.643 min, 94.4% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.09 – 1.29 (*m*, 6H); 1.34 – 1.72 (*m*, 14H); 2.36 – 2.47 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.3 Hz, 1H); 3.17 – 3.26 (*m*, 1H); 3.29 – 3.41 (*m*, 3H); 7.04 (*d*, *J* = 2.2 Hz, 1H); 7.08 – 7.14 (*m*, 1H); 7.19 (*d*, *J* = 1.2 Hz, 1H); 7.30 (*t*, *J* = 5.9 Hz, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.66 (*d*, *J* = 7.9 Hz, 1H); 8.56 (*br s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.92, 20.30, 26.47, 28.57, 29.47, 32.25, 34.46, 34.49, 36.94, 37.24, 37.74, 48.78, 63.57, 111.37, 111.76, 118.96, 119.59, 122.24, 122.95, 127.58, 136.57, 174.54.

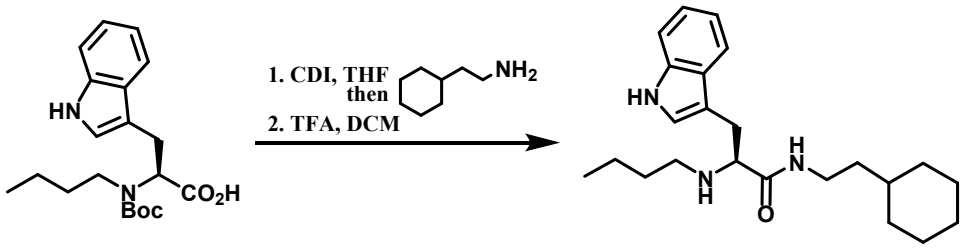
(*S*)-2-(Butylamino)-*N*-(cycloheptylmethyl)-3-(1*H*-indol-3-yl)propanamide (S15)



tert-Butyl (*S*)-butyl(1-((cycloheptylmethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared from **S8-1** (200 mg, 0.555 mmol), CDI (1.1 eq., 99 mg), and cycloheptylmethanamine (1.1 eq., 77.7 mg) in THF following *GP1* and isolated by column chromatography on silica (PE:EtOAc = 3:1). Yield: 191.8 mg (0.408 mmol, 73.5%) of colourless semisolid.

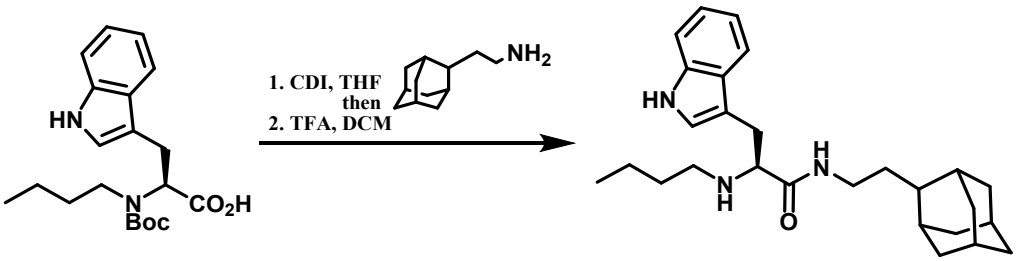
tert-Butyl (*S*)-butyl(1-((cycloheptylmethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (136.4 mg, 0.290 mmol) was deprotected following *GP2*. **S15** was purified by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1). Yield: 32.8 mg (0.089 mmol, 30.6%) of colourless oil. ESI-HRMS: *m/z* = 370.2842 (MH^+); $C_{23}H_{36}N_3O$ requires: *m/z* = 370.2853 (MH^+). ν_{max} 3277, 3057, 2920, 2853, 1652, 1521, 1456, 1355, 1302, 1247, 1152, 1125, 1101, 1046, 1010, 910, 877, 738, 613 cm^{-1}. $[\alpha]_D^{r.t.} = -57.4$ (*c* 0.42, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.453 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.76 (*t*, *J* = 7.3 Hz, 3H); 1.10 – 1.20 (*m*, 4H); 1.22 – 1.28 (*m*, 2H); 1.34 – 1.52 (*m*, 5H); 1.53 – 1.70 (*m*, 7H); 2.37 – 2.48 (*m*, 2H); 2.87 (*dd*, *J* = 9.4; 14.4 Hz, 1H); 3.01 – 3.08 (*m*, 1H); 3.16 – 3.23 (*m*, 1H); 3.32 – 3.42 (*m*, 2H); 7.04 (*d*, *J* = 2.2 Hz, 1H); 7.08 – 7.13 (*m*, 1H); 7.16 – 7.21 (*m*, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.44 (*br t*, *J* = 6.2 Hz, 1H); 7.66 (*d*, *J* = 7.9 Hz, 1H); 8.58 (br *s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.93, 20.30, 26.48, 28.42, 28.47, 29.54, 32.20, 32.22, 32.28, 39.72, 45.54, 48.83, 63.66, 111.38, 111.77, 118.96, 119.58, 122.24, 122.96, 127.56, 136.59, 174.66.

(*S*)-2-(Butylamino)-*N*-(2-cyclohexylethyl)-3-(1*H*-indol-3-yl)propanamide (S16)



tert-Butyl (*S*)-butyl(1-((2-cyclohexylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (200 mg, 0.555 mmol), CDI (1.1 eq, 99 mg) and 2-cyclohexylethan-1-amine (1.1 eq., 77.7 mg) in THF, isolated by column chromatography on silica (1. PE/EtOAc = 5:1; 2. PE/EtOAc = 3:1), and immediately deprotected following *GP2*. **S16** was isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 54.4 mg (0.147 mmol, 26.5% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 370.2851 (MH^+); $C_{23}H_{36}N_3O$ requires: *m/z* = 370.2853 (MH^+). ν_{max} 3273, 3056, 2920, 2849, 2166, 2073, 1651, 1525, 1447, 1341, 1299, 1232, 1102, 1010, 888, 739 cm^{-1}. $[\alpha]_D^{r.t.}$ = –58.75 (*c* 0.14, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.507 min, 95.0% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 0.84 – 0.96 (*m*, 2H); 1.08 – 1.30 (*m*, 9H); 1.31 – 1.41 (*m*, 2H); 1.60 – 1.73 (*m*, 5H); 2.36 – 2.47 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.3 Hz, 1H); 3.18 – 3.27 (*m*, 1H); 3.29 – 3.41 (*m*, 3H); 7.04 (*d*, *J* = 2.3 Hz, 1H); 7.07 – 7.13 (*m*, 1H); 7.15 – 7.22 (*m*, 1H); 7.31 (*t*, *J* = 6.1 Hz, 1H, NH); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.65 (*d*, *J* = 8.0 Hz, 1H); 8.63 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.92, 20.29, 26.35, 26.60, 29.48, 32.25, 33.21, 33.24, 35.46, 36.77, 37.09, 48.78, 63.58, 111.39, 111.71, 118.94, 119.56, 122.22, 122.97, 127.57, 136.58, 174.56.

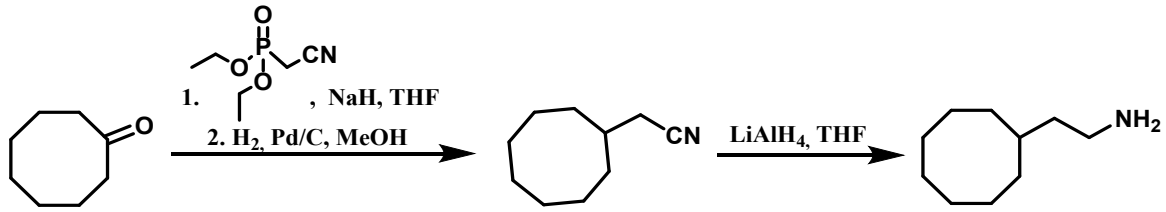
(*S*)-*N*-(2-((Adamantan-2-yl)ethyl)-2-(butylamino)-3-(1*H*-indol-3-yl)propanamide (S17)



tert-Butyl ((*S*)-1-((2-((adamantan-2-yl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (244 mg, 0.678 mmol), CDI (1.1 eq, 120.9 mg) and 2-(adamantan-2-yl)ethan-1-amine[20] (1.1 eq., 146.3 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 5:1), and immediately deprotected following *GP2*. The title product was isolated by column chromatography on silica (1. DCM; 2.

DCM/MeOH = 100:1; 3. DCM/MeOH = 20:1). Yield: 40 mg (0.0949 mmol, 14% over two steps) of yellowish semisolid. ESI-HRMS: *m/z* = 422.3168 (MH^+); $C_{27}H_{40}N_3O$ requires: *m/z* = 422.3166 (MH^+). ν_{max} 3276, 3056, 2902, 2849, 1650, 1524, 1454, 1354, 1342, 1233, 1100, 1010, 972, 908, 878, 736, 610 cm^{-1}. $[\alpha]_D^{r.t.}$ = +5.4 (*c* 0.27, MeOH). Purity: UPLC (254 nm): t_r = 4.827 min, 96.9% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.76 (*t*, *J* = 7.3 Hz, 3H); 1.10 – 1.18 (*m*, 2H); 1.20 – 1.30 (*m*, 2H); 1.48 – 1.54 (*m*, 2H); 1.57 – 1.63 (*m*, 2H); 1.64 – 1.74 (m, 8H); 1.76 – 1.89 (*m*, 6H); 2.37 – 2.47 (*m*, 2H); 2.89 (*dd*, *J* = 9.3; 14.3 Hz, 1H); 3.18 – 3.26 (*m*, 1H); 3.28 – 3.41 (*m*, 3H); 7.04 (*d*, *J* = 2.2 Hz, 1H); 7.07 – 7.12 (*m*, 1H); 7.16 – 7.21 (*m*, 1H); 7.31 – 7.39 (*m*, 2H); 7.66 (*d*, *J* = 7.9 Hz, 1H); 8.64 (br *s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.29, 28.07, 28.25, 29.48, 31.71, 31.72, 31.80, 32.24, 32.46, 37.46, 38.38, 39.22, 42.03, 48.79, 63.57, 111.38, 111.70, 118.94, 119.55, 122.21, 122.97, 127.57, 136.58, 174.61.

2-Cyclooctylethan-1-amine (9-1)



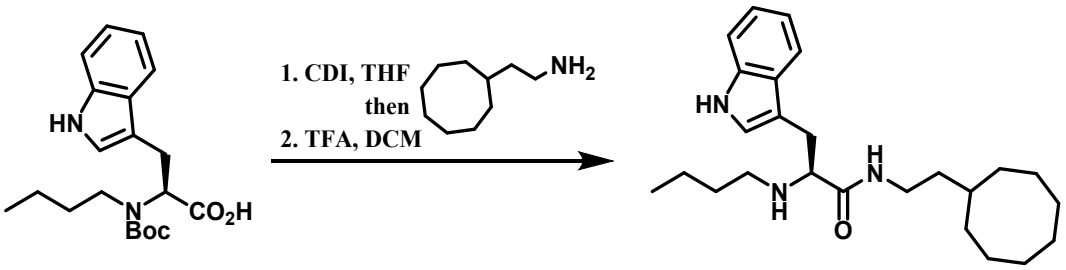
To a solution of diethyl cyanomethylphosphonate (1.3 eq., 6.7 mL) in anhydrous THF (50 mL), sodium hydride (60 wt.% dispersion in mineral oil, 1.3 eq., 1648 mg) was added portionwise. The reaction mixture was stirred for 10 min at r.t. before cyclooctanone (1.0 eq., 4000 mg, 31.7 mmol) was added and the stirring continued for 12 h at r.t.. The reaction mixture was concentrated *in vacuo*, water (50 mL) was added to dissolve the syrupy residue and extracted with Et_2O (2 x 30 mL). The organic phase was dried over anhydrous sodium sulfate, volatile components evaporated *in vacuo* and 2-cyclooctylideneacetonitrile[21] isolated by column chromatography on silica (PE). Yield: 3373 mg (22.6 mmol, 71.3%) of colourless oil.

Following *GP4*, 2-cyclooctylideneacetonitrile (3373 mg, 22.6 mmol) was reduced to 2-cyclooctylacetonitrile.[22] Yield: 3286 mg (21.7 mmol, 68.5% over two steps) of colourless oil. ESI-HRMS: *m/z* = 152.1431 (MH^+); $C_{10}H_{18}N$ requires: *m/z* = 152.1434 (MH^+). ν_{max} 2916, 2851, 2696, 2244, 1468, 1447, 1424, 1362, 1263, 1124, 1059, 991, 951, 854, 771 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.35 – 1.82 (*m*, 14H); 1.88 – 2.03 (*m*, 1H); 2.19 – 2.30 (*m*, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.04, 25.84, 26.08, 26.85, 32.06, 34.97, 119.45.

Following *GP5*, 2-cyclooctylacetonitrile (3000 mg, 19.83 mmol) was reduced to 2-cyclooctylethan-1-amine.[23] Yield: 2069 mg (13.33 mmol, 67.2%) of colourless oil. ESI-HRMS:

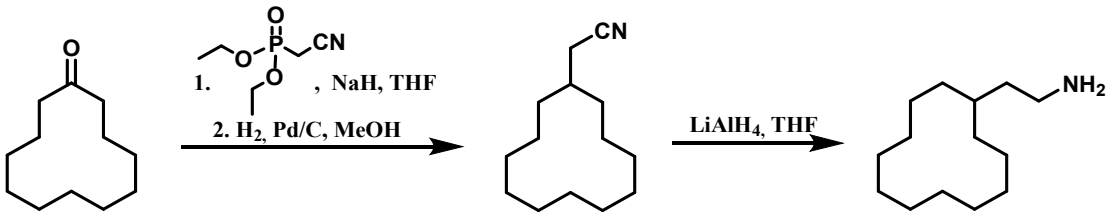
m/z = 156.1745 (MH^+); $C_{10}H_{22}N$ requires: *m/z* = 156.1747 (MH^+). ν_{max} 3292, 2911, 2847, 1589, 1468, 1445, 1362, 1066, 798 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.11 – 1.74 (*m*, 19H), 2.67 – 2.74 (*m*, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.56, 26.37, 27.43, 32.44, 34.91, 40.43, 42.47.

(*S*)-2-(Butylamino)-*N*-(2-cyclooctylethyl)-3-(1*H*-indol-3-yl)propanamide (9)



tert-Butyl (*S*)-butyl(1-((2-cyclooctylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (223 mg, 0.619 mmol), CDI (1.1 eq., 110 mg), and **9-1** (1.1 eq., 106 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 3:1), and immediately deprotected following *GP2*. The title product was purified by column chromatography on silica (1. DCM; 2. DCM/MeOH = 20:1). Yield: 74.8 mg (0.195 mmol, 31.5%) of yellowish semisolid. ESI-HRMS: *m/z* = 398.3164 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3272, 3056, 2915, 2851, 1650, 1524, 1455, 1353, 1231, 1102, 1010, 908, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = –65.8 (*c* 0.29, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.757 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.76 (*t*, *J* = 7.3 Hz, 3H); 1.10 – 1.18 (*m*, 2H); 1.21 – 1.31 (*m*, 4H); 1.33 – 1.70 (*m*, 16H); 2.36 – 2.47 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.3 Hz, 1H); 3.19 – 3.27 (*m*, 1H); 3.30 – 3.41 (*m*, 3H); 7.04 (*d*, *J* = 2.1 Hz, 1H); 7.07 – 7.12 (*m*, 1H); 7.16 – 7.21 (*m*, 1H); 7.32 (t, *J* = 5.6 Hz, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.65 (*d*, *J* = 7.9 Hz, 1H); 8.66 (br *s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.28, 25.46, 25.48, 26.38, 27.31, 29.49, 32.22, 32.24, 32.26, 34.88, 37.24, 37.76, 48.79, 63.57, 111.38, 111.69, 118.93, 119.55, 122.21, 122.97, 127.57, 136.58, 174.55.

2-Cyclododecylethan-1-amine (S19-1)

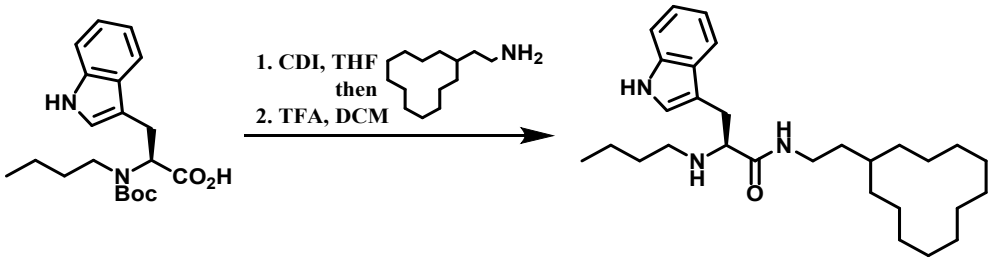


To a solution of diethyl cyanomethylphosphonate (1.3 eq., 6.7 mL) in anhydrous THF (50 mL), sodium hydride (60 wt.% dispersion in mineral oil, 1.3 eq., 1648 mg) was added portionwise. The reaction mixture was stirred for 10 min at r.t. before cyclododecanone (5779 mg, 31.7 mmol) was added and the stirring continued for 12 h at r.t.. The reaction mixture was concentrated *in vacuo*, water (75 mL) was added to dissolve the syrupy residue and extracted with Et_2O (2 x 30 mL). The organic phase was dried over sodium sulfate, filtered, volatile components evaporated *in vacuo* and 2-cyclododecylideneacetonitrile[21] isolated by column chromatography on silica (PE). Yield: 5753 mg (28.02 mmol, 88.3%) of colourless semisolid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.18 – 1.41 (*m*, 14H); 1.56 – 1.66 (*m*, 4H); 2.24 – 2.28 (*m*, 2H); 2.44 – 2.50 (*m*, 2H); 5.20 (*t*, *J* = 1.6 Hz, 1H).

Following *GP4*, 2-cyclododecylideneacetonitrile (5753 mg, 28.02 mmol) was reduced to 2-cyclododecylacetonitrile[24]. Yield: 5541 mg (26.72 mmol, 84.3% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 208.2063 (MH^+); $C_{14}H_{26}N$ requires: *m/z* = 208.206 (MH^+). ν_{max} 2930, 2900, 2860, 2847, 2668, 2242, 1471, 1446, 1422, 1346, 1313, 1211, 1156, 1046, 968, 954, 934, 903, 856, 823, 801, 735, 719, 691 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.26 – 1.44 (*m*, 20H); 1.47 – 1.58 (*m*, 2H); 1.83 – 1.92 (*m*, 1H); 2.28 (*d*, *J* = 6.7 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 21.73, 23.09, 23.41, 23.47, 23.80, 24.25, 28.96, 31.57, 119.51.

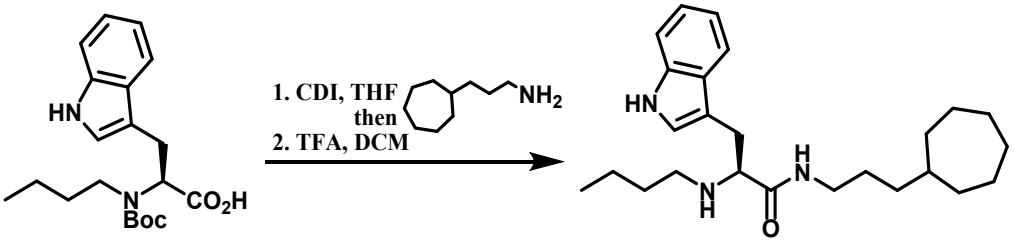
Following *GP5*, 2-cyclododecylacetonitrile (2000 mg, 9.645 mmol) was reduced to 2-cyclododecylethan-1-amine. Yield: 1413 mg (6.684 mmol, 69.3%) of colourless, viscous oil. ESI-HRMS: *m/z* = 212.2373 (MH^+); $C_{14}H_{30}N$ requires: *m/z* = 212.2373 (MH^+). ν_{max} 3286, 2926, 2859, 2847, 1571, 1469, 1444, 1346, 1316, 1059, 821, 719 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.17 – 1.53 (*m*, 27H); 2.66 – 2.73 (*m*, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 21.76, 23.37, 23.43, 24.36, 24.99, 29.19, 31.85, 39.51, 40.51.

(*S*)-2-(Butylamino)-*N*-(2-cyclododecylethyl)-3-(1*H*-indol-3-yl)propanamide (S19)



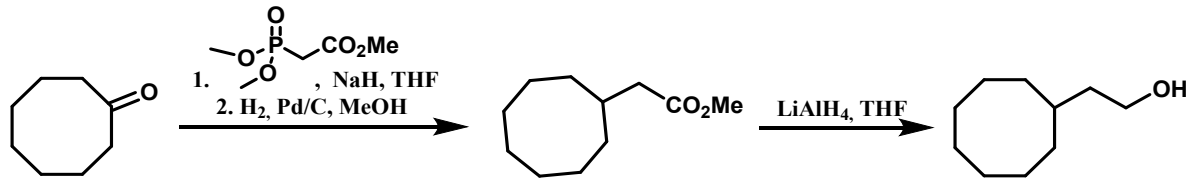
tert-Butyl (*S*)-butyl(1-((2-cyclododecylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (280 mg, 0.776 mmol), CDI (1.1 eq, 138 mg) and **S19-1** (1.1 eq., 181 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 4:1), and immediately deprotected following *GP2*. **S19** was isolated by column chromatography on silica (1. PE/EtOAc = 2:1; 1. PE/EtOAc = 1:1). Yield: 191.5 mg (0.422 mmol, 54.4% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 454.379 (MH^+); $C_{29}H_{48}N_3O$ requires: *m/z* = 454.3792 (MH^+). ν_{max} 3274, 2927, 2859, 1652, 1524, 1469, 1456, 1444, 1342, 1233, 1216, 1124, 1103, 1010, 877, 738, 665, 610 cm^{-1}. $[\alpha]_D^{r.t.}$ = –4.5 (*c* 0.11, MeOH). Purity: UPLC (254 nm): t_r = 5.243 min, 98.2% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.76 (*t*, *J* = 7.3 Hz, 3H); 1.09 – 1.18 (*m*, 2H); 1.19 – 1.48 (*m*, 28H); 2.35 – 2.48 (*m*, 2H); 2.88 (*dd*, *J* = 9.1; 14.1 Hz, 1H); 3.20 – 3.41 (*m*, 4H); 7.04 (*d*, *J* = 2.3 Hz, 1H); 7.10 (*t*, *J* = 7.5 Hz, 1H); 7.18 (*t*, *J* = 7.5 Hz, 1H); 7.34 (*t*, *J* = 5.8 Hz, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.65 (*d*, *J* = 7.9 Hz, 1H); 8.59 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.26, 21.68, 23.30, 23.33, 23.37, 23.40, 24.30, 24.89, 28.93, 28.94, 29.45, 31.87, 32.23, 34.84, 37.27, 48.78, 63.54, 111.37, 111.75, 118.95, 119.57, 122.24, 122.94, 127.59, 136.57, 174.55.

(*S*)-2-(Butylamino)-*N*-(3-cycloheptylpropyl)-3-(1*H*-indol-3-yl)propanamide (8)



tert-Butyl (*S*)-butyl(1-((3-cycloheptylpropyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (146 mg, 0.405 mmol), CDI (1.1 eq, 72.4 mg) and 3-cycloheptylpropan-1-amine (1.1 eq., 69.1 mg) in THF, isolated by column chromatography on silica (1. PE/EtOAc = 3:1; 2. PE/EtOAc = 2:1) and immediately deprotected following *GP2*. **8** was isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 43.5 mg (0.109 mmol, 28.1% over two steps) of colourless oil. ESI-HRMS: *m/z* = 398.3161 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3270, 3187, 2919, 2851, 2541, 2106, 1646, 1516, 1457, 1432, 1393, 1343, 1325, 1289, 1203, 1125, 1067, 1010, 983, 941, 873, 814, 738, 659, 615 cm^{-1}. $[\alpha]_D^{r.t.}$ = +10.0 (*c* 0.05, MeOH). Purity: UPLC (254 nm): t_r = 4.800 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.09 – 1.30 (*m*, 8H); 1.36 – 1.51 (*m*, 7H); 1.53 – 1.70 (*m*, 7H); 2.37 – 2.49 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.3 Hz, 1H); 3.13 – 3.22 (*m*, 1H); 3.24 – 3.40 (*m*, 3H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.11 – 7.16 (*m*, 1H); 7.19 – 7.24 (*m*, 1H); 7.31 (*t*, *J* = 5.9 Hz, 1H, NH); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.69 (*d*, *J* = 7.9 Hz, 1H); 8.14 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.96, 20.34, 26.60, 27.66, 28.66, 29.44, 32.30, 34.69, 35.46, 39.11, 39.32, 48.81, 63.59, 111.29, 112.13, 119.11, 119.76, 122.42, 122.83, 127.66, 136.51, 174.39.

2-Cyclooctylethan-1-ol (S20-1)

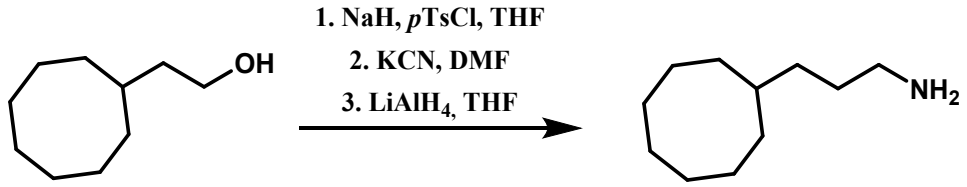


To a solution of trimethyl phosphonoacetate (1.25 eq., 6.48 mL) in anhydrous THF (200 mL), sodium hydride (60 wt% dispersion in mineral oil, 1.25 eq., 1600 mg) was added portionwise. The reaction mixture was then heated to 60 °C, stirred for 10 min (meanwhile the reaction mixture thickens considerably) before cyclooctanone (1.0 eq., 5048 mg, 31.7 mmol) was added and the stirring continued at 60 °C for 24 h. The reaction mixture was concentrated *in vacuo*, water (100 mL) was added to dissolve the syrupy residue and extracted with Et_2O (2 x 30 mL). The organic phase was dried over sodium sulfate, filtered, volatile components evaporated *in vacuo*, and methyl 2-cyclooctylideneacetate[25] isolated by column chromatography on silica (PE). Yield: 4396 mg (24.12 mmol, 60.3%) of colourless oil.

Following *GP4*, methyl 2-cyclooctylideneacetate (3793 mg, 20.81 mmol) was reduced to methyl 2-cyclooctylacetate.[26] Yield: 3707 mg (20.12 mmol, 96.7%) of colourless oil. ESI-HRMS: *m/z* = 185.1538 (MH^+); $C_{11}H_{21}O_2$ requires: *m/z* = 185.1536 (MH^+). ν_{max} 2916, 2851, 1736, 1467, 1435, 1358, 1282, 1212, 1158, 1019, 885 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 – 1.38 (*m*, 2H); 1.43 – 1.70 (*m*, 12H); 1.99 – 2.13 (*m*, 1H); 2.22 (*d*, *J* = 7.3 Hz, 2H); 3.66 (*s*, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.32, 26.27, 27.16, 32.29, 34.67, 42.74, 51.37, 173.84.

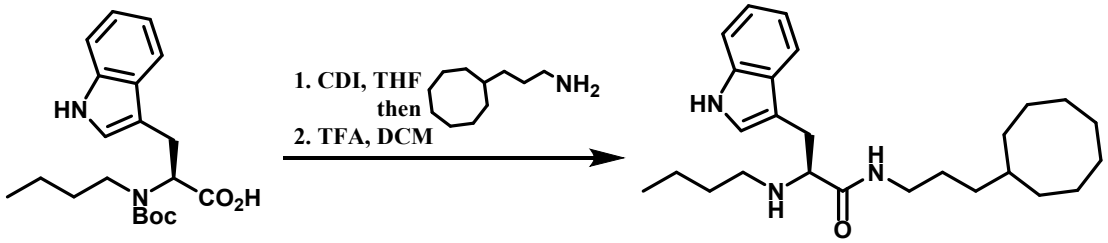
Following *GP5*, methyl 2-cyclooctylacetate (3610 mg, 19.59 mmol) was reduced to 2-cyclooctylethan-1-ol.[27] Yield: 1643 mg (10.51 mmol, 53.6%) of colourless oil. ESI-HRMS: *m/z* = 139.1478 ($(M\text{-}OH)^+$); $C_{10}H_{19}$ requires: *m/z* = 139.1481 ($(M\text{-}OH)^+$). ν_{max} 3326, 2909, 2841, 2690, 1473, 1439, 1350, 1178, 1060, 1028, 914 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.21 – 1.35 (*m*, 2H); 1.38 – 2.00 (*m*, 16H); 3.67 (*t*, *J* = 6.9 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.49, 26.32, 27.42, 32.39, 33.81, 41.09, 61.41.

3-Cyclooctylpropan-1-amine (S20-2)



To **S20-1** (1633 mg, 10.45 mmol) and tosyl chloride (1.1 eq., 2191 mg) in anhydrous THF (10 mL), sodium hydride (60 wt.% dispersion in paraffin oil, 1.1 eq., 460 mg) was slowly added and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was then concentrated *in vacuo*, the semisolid residue redissolved in anhydrous DMF (5 mL), potassium cyanide (1.2 eq., 817 mg) added and the reaction mixture stirred at r.t. for 12 h. The reaction mixture was then poured into water (50 mL), extracted with Et_2O (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford the crude nitrile[27] (1322 mg) as a yellowish oil, which was reduced following *GP5*. Ethereal extracts, which contained the title product along with some paraffin oil from the first step, were shaken with 10% $HCl_{(aq.)}$ (15 mL) and discarded. The aqueous phase was extracted again with Et_2O (30 mL), organic phase discarded, aqueous phase was made alkaline with the addition of solid sodium hydroxide and extracted with Et_2O (2 x 20 mL). Ethereal extracts were dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford pure 3-cyclooctylpropan-1-amine. Yield: 610 mg (3.603 mmol, 34.5%) of colourless oil. ESI-HRMS: *m/z* = 170.19 (MH^+); $C_{11}H_{24}N$ requires: *m/z* = 170.1903 (MH^+). ν_{max} 3356, 2914, 2850, 1602, 1446, 1378, 1058, 788 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10 – 1.26 (*m*, 6H); 1.30 – 1.65 (*m*, 17H), 2.60 (*t*, *J* = 7.1 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.56, 26.36, 27.32, 31.85, 32.46, 35.44, 37.17, 42.69.

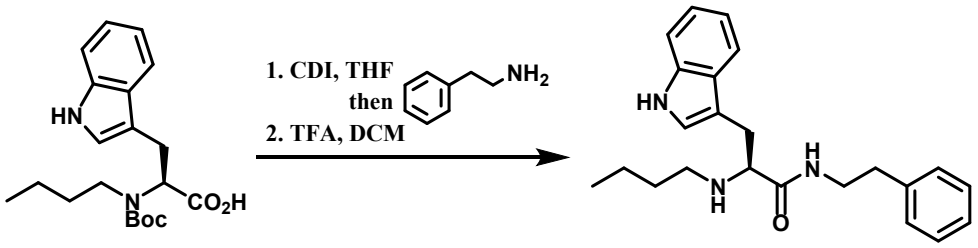
(*S*)-2-(Butylamino)-*N*-(3-cyclooctylpropyl)-3-(1*H*-indol-3-yl)propanamide (S20)



tert-Butyl (*S*)-butyl(1-((3-cyclooctylpropyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (250 mg, 0.693 mmol), CDI (1.1 eq., 124 mg), **S20-2** (1.1 eq., 129 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 3:1), and immediately deprotected following *GP2*. The product was isolated by column

chromatography on silica (EtOAc). Yield: 43.3 mg (0.105 mmol, 15.2% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 412.3323 (MH^+); $C_{26}H_{42}N_3O$ requires: *m/z* = 412.3322 (MH^+). ν_{max} 3410, 3294, 3057, 2919, 2850, 2695, 1720, 1653, 1520, 1456, 1353, 1294, 1230, 1126, 1010, 739 cm^{-1}. $[\alpha]_D^{r.t.}$ = –49.4 (*c* 0.08, acetone). Purity: UPLC (254 nm): t_r = 4.913 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.12 – 1.30 (*m*, 7H); 1.37 – 1.71 (*m*, 16H); 2.38 – 2.49 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.4 Hz, 1H); 3.14 – 3.23 (*m*, 1H); 3.25 – 3.42 (*m*, 3H); 7.05 (*d*, *J* = 2.2 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.18 – 7.23 (*m*, 1H); 7.34 (*t*, *J* = 5.9 Hz, 1H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.68 (*d*, *J* = 7.9 Hz, 1H); 8.32 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.95, 20.32, 25.61, 26.43, 27.39, 27.69, 29.46, 32.28, 32.48, 35.49, 37.10, 39.34, 48.80, 63.59, 111.33, 111.96, 119.04, 119.69, 122.35, 122.89, 127.62, 136.53, 174.50.

(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-phenethylpropanamide (S21)

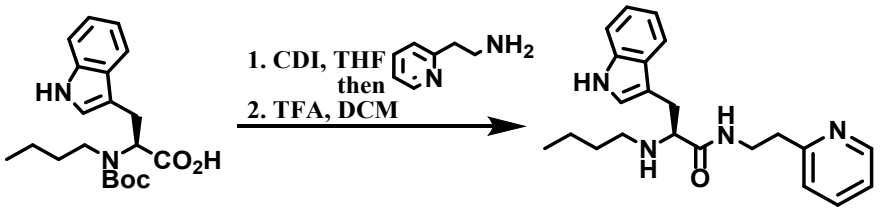


tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-(phenethylamino)propan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (150 mg, 0.416 mmol), CDI (1.1 eq., 74.2 mg) and 2-phenylethan-1-amine (1.1 eq., 55.4 mg) in THF, and isolated by column chromatography on silica (PE:EtOAc = 6:1). Yield: 99.1 mg (0.214 mmol, 51.4%) of colourless semisolid.

The title compound was prepared from *tert*-butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-(phenethylamino)propan-2-yl)(butyl)carbamate (85 mg, 0.183 mmol) following *GP2*. The product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1). Yield: 18.4 mg (0.0506 mmol, 27.6%) of colourless semisolid. ESI-HRMS: *m/z* = 364.2381 (MH^+); $C_{23}H_{30}N_3O$ requires: *m/z* = 364.2383 (MH^+). ν_{max} 3274, 3058, 2955, 2925, 2857, 1650, 1522, 1496, 1454, 1435, 1356, 1341, 1232, 1102, 1029, 1010, 738, 698 cm^{-1}. $[\alpha]_D^{r.t.}$ = –64.7 (*c* 0.793, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.143 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.73 (*t*, *J* = 7.2 Hz, 3H); 1.01 – 1.10 (*m*, 2H); 1.11 – 1.19 (*m*, 2H); 1.57 (br *s*, 1H, NH); 2.26 – 2.38 (*m*, 2H); 2.77 (*t*, *J* = 6.9 Hz, 2H); 2.86 (*dd*, *J* = 9.0; 14.4 Hz, 1H); 3.26 – 3.37 (*m*, 2H); 3.45 – 3.53 (*m*, 1H); 3.54 – 3.62 (*m*, 1H); 7.01 (*d*, *J* = 2.3 Hz, 1H); 7.08 – 7.15 (*m*, 3H); 7.16 – 7.23 (*m*, 2H); 7.24 – 7.30 (*m*, 2H); 7.31 – 7.40 (*m*, 2H); 7.66 (*d*, *J* = 7.9 Hz, 1H); 8.25 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.94, 20.22, 29.27, 32.15, 35.84, 40.04,

48.73, 63.48, 111.33, 111.89, 119.04, 119.72, 122.38, 122.88, 126.51, 127.64, 128.64, 128.86, 136.50, 139.08, 174.53.

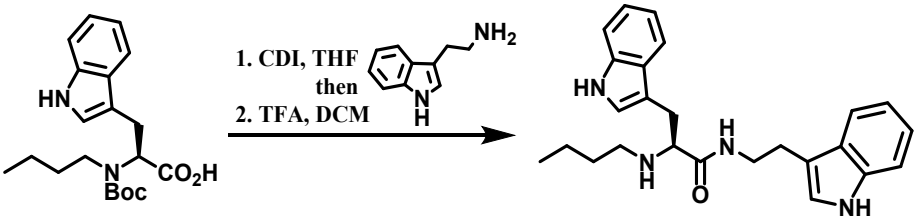
(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(pyridin-2-yl)ethyl)propanamide (S22)



tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-((2-(pyridin-2-yl)ethyl)amino)propan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (233.6 mg, 0.648 mmol), CDI (1.1 eq., 115.6 mg) and 2-(pyridin-2-yl)ethan-1-amine (1 eq., 87.1 mg) in THF, and isolated by column chromatography on silica (1. PE/EtOAc = 1:1; 2. EtOAc). Yield: 197.3 mg (0.425 mmol, 65.5%) as colourless semisolid.

tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-((2-(pyridin-2-yl)ethyl)amino)propan-2-yl)(butyl)carbamate (151 mg, 0.325 mmol) was deprotected following *GP2,* **S22** was isolated by column chromatography on silica (1. DCM/MeOH = 100:1; 2. DCM/MeOH = 10:1) and additionally purified following *GP7*. Yield: 68 mg (0.187 mmol, 57.4%) of colourless oil. ESI-HRMS: *m/z* = 365.2335 (MH^+); $C_{22}H_{29}N_4O$ requires: *m/z* = 365.2336 (MH^+). ν_{max} 3307, 3056, 2961, 2930, 2872, 1763, 1660, 1594, 1517, 1475, 1457, 1435, 1410, 1392, 1365, 1337, 1287, 1238, 1164, 1099, 1063, 1008, 961, 859, 739, 650 cm^{-1}. $[\alpha]_D^{r.t.} = -41.1$ (*c* 0.115, $CHCl_3$). Purity: UPLC (254 nm): t_r = 0.880 min, 99.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.71 (*t*, *J* = 7.2 Hz, 3H); 0.99 – 1.08 (*m*, 2H); 1.10 – 1.18 (*m*, 2H); 1.25 (*s*, 1H); 2.29 (*t*, *J* = 7.0 Hz, 2H); 2.84 (*dd*, *J* = 9.3; 14.5 Hz, 1H); 2.96 (*t*, *J* = 6.7 Hz, 2H); 3.29 (*dd*, *J* = 4.0; 14.6 Hz, 1H); 3.35 (*dd*, *J* = 4.2; 9.3 Hz, 1H); 3.61 – 3.78 (*m*, 2H); 7.01 (*d*, *J* = 2.3 Hz, 1H); 7.05 – 7.13 (*m*, 3H); 7.15 – 7.19 (*m*, 1H); 7.35 (*d*, *J* = 8.1 Hz, 1H); 7.55 (*td*, *J* = 1.9; 7.6 Hz, 1H); 7.64 (*d*, *J* = 7.9 Hz, 1H); 7.70 (*t*, *J* = 5.9 Hz, 1H); 8.49 – 8.52 (*m*, 1H); 8.87 (*br s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.94, 20.23, 29.36, 32.16, 37.62, 38.32, 48.68, 63.53, 111.31, 111.98, 119.07, 119.69, 121.58, 122.35, 122.88, 123.52, 127.62, 136.50, 136.56, 149.40, 159.44, 174.56.

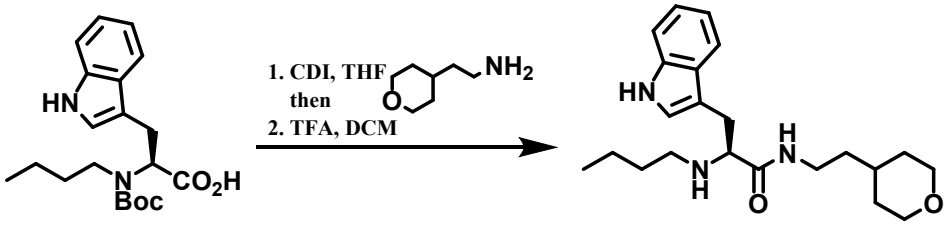
(*S*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(butylamino)-3-(1*H*-indol-3-yl)propanamide (S23)



tert-Butyl (*S*)-(1-((2-(1*H*-indol-3-yl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (233.6 mg, 0.648 mmol), CDI (1.1 eq., 115.6 mg) and tryptamine (1.1 eq., 114.2 mg) in THF, and isolated by column chromatography on silica (1. PE/EtOAc = 4:1; 2. PE/EtOAc = 1:1). Yield: 218.1 mg (0.434 mmol, 67%) of colourless semisolid.

tert-Butyl (*S*)-(1-((2-(1*H*-indol-3-yl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)(butyl)carbamate (115 mg, 0.229 mmol) was deprotected following *GP2* and the title product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1). Yield: 55.6 mg (0.138 mmol, 60.3%) of yellowish semisolid. ESI-HRMS: *m/z* = 403.2494 (MH^+); $C_{25}H_{31}N_4O$ requires: *m/z* = 403.2492 (MH^+). ν_{max} 3408, 3277, 3056, 2926, 2857, 1642, 1524, 1455, 1435, 1339, 1228, 1094, 1010, 907, 803, 733, 647 cm^{-1}. $[\alpha]_D^{r.t.}$ = +0.0 (*c* 0.29, MeOH). Purity: UPLC (254 nm): t_r = 4.137 min, 94.9% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.68 (*t*, *J* = 7.2 Hz, 3H); 0.95 – 1.05 (*m*, 2H); 1.05 – 1.14 (*m*, 2H); 1.51 (br *s*, 1H, NH); 2.24 – 2.35 (*m*, 2H); 2.81 – 2.95 (*m*, 3H); 3.26 (*dd*, *J* = 4.5; 14.5 Hz, 1H); 3.33 (*dd*, *J* = 4.5; 8.5 Hz, 1H); 3.60 (*q*, *J* = 6.6 Hz, 2H); 6.76 (*d*, *J* = 2.1 Hz, 1H); 6.87 (*d*, *J* = 2.3 Hz, 1H); 7.03 – 7.10 (*m*, 2H); 7.12 – 7.19 (*m*, 2H); 7.31 (*d*, *J* = 8.1 Hz, 2H); 7.36 (*t*, *J* = 5.9 Hz, 1H, NH); 7.52 (*d*, *J* = 7.8 Hz, 1H); 7.59 (*d*, *J* = 7.9 Hz, 1H); 8.43 (*s*, 1H, NH); 8.52 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.88, 20.14, 25.35, 29.10, 32.08, 39.23, 48.60, 63.45, 111.34, 111.35, 111.40, 112.71, 118.72, 118.84, 119.29, 119.51, 122.00, 122.13, 122.17, 123.11, 127.41, 127.60, 136.46, 174.86.

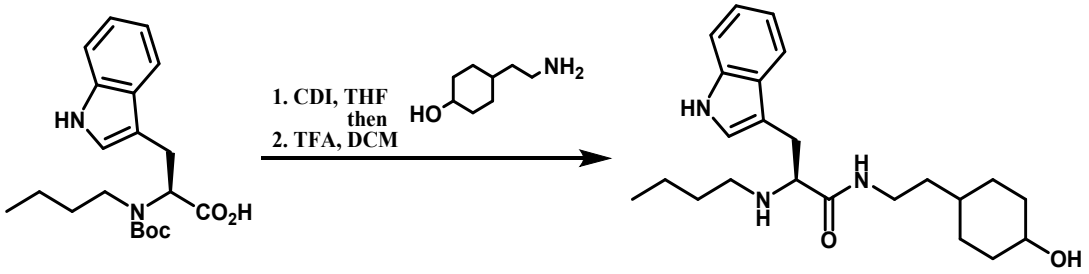
(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(tetrahydro-2*H*-pyran-4-yl)ethyl)propanamide (S24)



tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-((2-(tetrahydro-2*H*-pyran-4-yl)ethyl)amino)propan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (150 mg, 0.416 mmol), CDI (1.1 eq., 74.2 mg), and 2-(tetrahydro-2*H*-pyran-4-yl)ethan-1-amine (1.1 eq., 59.1 mg) in THF, and isolated by column chromatography on silica (PE:EtOAc = 1:1). Yield: 130 mg (0.276 mmol, 66.3%) of colourless semisolid.

tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-((2-(tetrahydro-2*H*-pyran-4-yl)ethyl)amino)propan-2-yl)(butyl)carbamate (121 mg, 0.257 mmol) was deprotected following *GP2* and **S24** was isolated by column chromatography on silica (DCM/MeOH = 20:1). Yield: 48.5 mg (0.131 mmol, 51.1%) of colourless oil. ESI-HRMS: *m/z* = 372.2645 (MH^+); $C_{22}H_{34}N_3O_2$ requires: *m/z* = 372.2646 (MH^+). ν_{max} 3273, 3056, 2954, 2924, 2845, 2244, 1649, 1524, 1456, 1437, 1355, 1341, 1297, 1234, 1141, 1092, 1012, 980, 907, 837, 810, 737, 610 cm^{-1}. $[\alpha]_D^{r.t.}$ = +8.85 (*c* 0.41, $CHCl_3$). Purity: UPLC (254 nm): t_r = 3.457 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.11 – 1.19 (*m*, 2H); 1.22 – 1.32 (*m*, 4H); 1.37 – 1.44 (*m*, 2H); 1.44 – 1.54 (*m*, 1H); 1.54 – 1.77 (*m*, 3H); 2.38 – 2.48 (*m*, 2H); 2.90 (*dd*, *J* = 14.5, 9.2 Hz, 1H); 3.20 – 3.29 (*m*, 1H); 3.30 – 3.42 (*m*, 5H); 3.94 (*ddd*, *J* = 1.8; 4.5; 11.4 Hz, 2H); 7.04 (*d*, *J* = 2.2 Hz, 1H); 7.07 – 7.13 (*m*, 1H); 7.16 – 7.22 (*m*, 1H); 7.33 (*t*, *J* = 6.0 Hz, 1H, NH); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.65 (*d*, *J* = 7.9 Hz, 1H); 8.67 (s, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.27, 29.38, 32.21, 32.78, 32.93, 32.96, 36.22, 36.68, 48.76, 63.49, 68.03, 111.37, 111.58, 118.92, 119.57, 122.23, 122.98, 127.54, 136.56, 174.61.

(*S*)-2-(Butylamino)-*N*-(2-(4-hydroxycyclohexyl)ethyl)-3-(1*H*-indol-3-yl)propanamide (S25/S26)

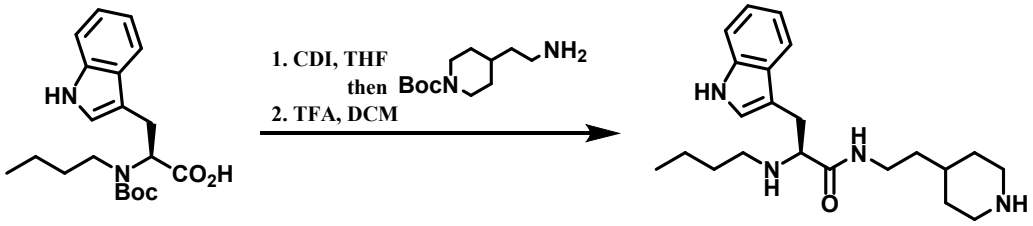


tert-Butyl (*S*)-butyl(1-((2-(4-hydroxycyclohexyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (280 mg, 0.776 mmol), CDI (1.1 eq, 138 mg) and 4-(2-aminoethyl)cyclohexan-1-ol[28] (1.1 eq., 122 mg), isolated by column chromatography on silica (PE/EtOAc = 1:1), and immediately deprotected following *GP2*. The title product was isolated by column chromatography on silica (1. PE/EtOAc = 1:1; 2. EtOAc), which furnished two isomers:

Compound **S25** eluted first from the column and was additionally purified following *GP7*. Two conformers are present in a ratio of 76:24. Yield: 126.9 mg (0.329 mmol, 42.4% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 386.2803 (MH^+); $C_{23}H_{36}N_3O_2$ requires: *m/z* = 386.2802 (MH^+). ν_{max} 3274, 2929, 2858, 1776, 1662, 1572, 1455, 1341, 1199, 1171, 1134, 1046, 1010, 956, 898, 834, 799, 742, 721, 665 cm^{-1}. $[\alpha]_D^{r.t.}$ = +24.6 (*c* 0.54, MeOH). Purity: UPLC (254 nm): t_r = 3.380–3.483 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for the major conformer: δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 0.95 – 1.87 (*m*, 15H); 2.00 – 2.08 (*m*, 2H); 2.35 – 2.49 (*m*, 2H), 2.90 (*dd*, *J* = 9.2; 14.5 Hz, 1H); 3.18 – 3.42 (*m*, 4H); 4.78 – 4.88 (*m*, 1H); 7.03 (*d*, *J* = 2.3 Hz, 1H), 7.08 (*t*, *J* = 7.5 Hz, 1H); 7.17 (*t*, *J* = 7.7 Hz, 1H); 7.31 – 7.40 (*m*, 2H); 7.63 (*d*, *J* = 7.9 Hz, 1H); 8.90 (*s*, 1H, NH). ^{1}H-NMR (500 MHz, $CDCl_3$) for the minor conformer: δ 1.89 – 1.99 (*m*, 2H); 5.16 – 5.21 (*m*, 1H); 8.92 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$) for both conformers: δ 13.82, 20.22, 26.84, 26.87, 29.05, 29.38, 29.40, 30.36, 30.38, 30.79, 32.14, 33.87, 34.00, 35.92, 36.13, 36.64, 36.80, 48.72, 63.44, 75.33, 78.22, 111.33, 111.40, 118.82, 119.46, 122.12, 123.05, 127.48, 136.59, 174.72.

Compound **S26** eluted second from the column and was additionally purified following *GP7*. Two conformers in a ratio of 80:20. Yield: 107.5 mg (0.279 mmol, 35.9% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 386.2798 (MH^+); $C_{23}H_{36}N_3O_2$ requires: *m/z* = 386.2802 (MH^+). ν_{max} 3306, 2925, 2855, 1648, 1528, 1454, 1357, 1341, 1216, 1126, 1098, 1049, 1010, 959, 898, 740, 665 cm^{-1}. $[\alpha]_D^{r.t.}$ = +6.8 (*c* 0.31, MeOH). Purity: UPLC (254 nm): t_r = 3.387–3.483 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for the major conformer: δ 0.76 (*t*, *J* = 7.3 Hz, 3H); 0.87 – 1.56 (*m*, 13H); 1.64 – 1.79 (*m*, 2H); 1.90 – 2.01 (*m*, 2H); 2.33 – 2.48 (*m*, 2H); 2.90 (*dd*, *J* = 9.1; 14.5 Hz, 1H); 3.18 – 3.40 (*m*, 4H); 3.48 – 3.59 (*m*, 1H); 7.03 (*d*, *J* = 2.3 Hz, 1H); 7.06 – 7.11 (*m*, 1H); 7.15 – 7.21 (*m*, 1H); 7.31 (*t*, *J* = 5.8 Hz, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.64 (*d*, *J* = 7.9 Hz, 1H); 8.91 (*s*, 1H, NH). ^{1}H-NMR (500 MHz, $CDCl_3$) for the minor conformer: δ 3.92 – 3.99 (*m*, 1H); 8.88 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$) for both conformers: δ 13.89, 20.24, 26.87, 26.91, 29.29, 29.39, 29.86, 31.06, 31.11, 32.17, 33.97, 34.39, 35.43, 35.68, 36.27, 36.90, 48.71, 63.48, 63.51, 66.87, 70.83, 111.36, 111.42, 118.82, 118.84, 119.46, 122.10, 123.07, 127.54, 136.56, 174.65.

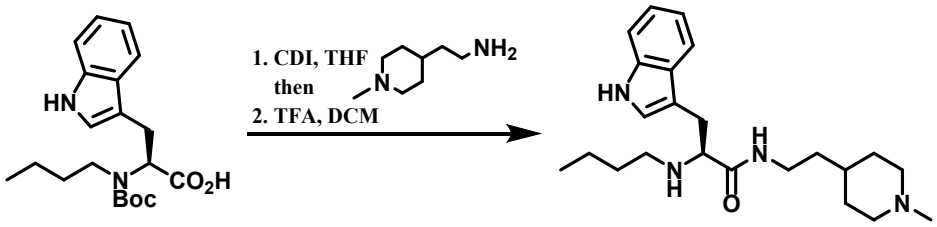
(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(piperidin-4-yl)ethyl)propanamide (S27)



tert-Butyl (*S*)-4-(2-(2-((*tert*-butoxycarbonyl)(butyl)amino)-3-(1*H*-indol-3-yl)propanamido)ethyl)piperidine-1-carboxylate was prepared following *GP1* from **S8-1** (200 mg, 0.555 mmol), CDI (1.1 eq., 99 mg) and *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (1.1 eq., 139.4 mg) in THF, and isolated by column chromatography on silica (PE:EtOAc = 3:1). Yield: 206.2 mg (0.361 mmol, 65.1%) of colourless semisolid.

tert-Butyl (*S*)-4-(2-(2-((*tert*-butoxycarbonyl)(butyl)amino)-3-(1*H*-indol-3-yl)propanamido)ethyl)piperidine-1-carboxylate (126.7 mg, 0.222 mmol) was deprotected following *GP2* and **S27** isolated following *GP7*. Yield: 121 mg (0.327 mmol, 58.8%) of colourless semisolid. ESI-HRMS: *m/z* = 371.1012 (MH^+); $C_{22}H_{35}N_4O$ requires: *m/z* = 371.2805 (MH^+). ν_{max} 3271, 2954, 2922, 2853, 1646, 1527, 1456, 1377, 1357, 1258, 1233, 1107, 1011, 974, 909, 798, 736 cm^{-1}. $[\alpha]_D^{r.t.}$ = –34.5 (*c* 0.06, acetone). Purity: UPLC (254 nm): t_r = 0.863 min, 100% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.78 (*t*, *J* = 7.3 Hz, 3H); 1.10 – 1.43 (*m*, 11H); 1.64 – 1.79 (*m*, 2H); 1.83 – 2.28 (*m*, 4H); 2.39 – 2.49 (*m*, 2H); 2.59 (*td*, *J* = 2.7; 12.3 Hz, 1H); 2.92 (*dd*, *J* = 8.9; 14.5 Hz, 1H); 3.05 – 3.13 (*m*, 1H); 3.19 – 3.42 (*m*, 4H); 7.06 (*s*, 1H); 7.10 – 7.16 (*m*, 1H); 7.17 – 7.24 (*m*, 1H); 7.38 (*d*, *J* = 8.2 Hz, 1H); 7.68 (*d*, *J* = 7.8 Hz, 1H); 8.34 (*s*, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 13.98, 20.35, 29.28, 31.97, 32.32, 32.77, 33.78, 36.35, 36.82, 46.37, 48.80, 63.51, 111.35, 111.91, 119.05, 119.74, 122.38, 122.93, 127.67, 136.51, 174.50.

(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(1-methylpiperidin-4-yl)ethyl)propanamide (S28)

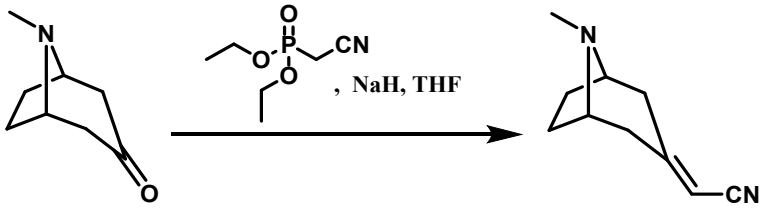


tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-((2-(1-methylpiperidin-4-yl)ethyl)amino)-1-oxopropan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (150 mg, 0.416 mmol), CDI (1.1

eq., 74.2 mg), and 2-(1-methylpiperidin-4-yl)ethan-1-amine (1.1 eq., 65.1 mg) in THF, and isolated by column chromatography on silica (1. DCM/MeOH = 10:1; 2. DCM/MeOH = 5:1). Yield: 104.2 mg (0.215 mmol, 51.7%) of colourless semisolid.

tert-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-((2-(1-methylpiperidin-4-yl)ethyl)amino)-1-oxopropan-2-yl)(butyl)carbamate (89 mg, 0.184 mmol) was deprotected following *GP2,* the title product isolated by column chromatography on basic alumina (1. Et_2O; 2. Et_2O:MeOH = 5:1) and additionally purified following *GP7*. Yield: 30.1 mg (0.0783 mmol, 42.6%) of colourless oil. ESI-HRMS: *m/z* = 385.297 (MH^+); $C_{23}H_{37}N_4O$ requires: *m/z* = 385.2962 (MH^+). ν_{max} 3247, 2925, 2854, 2792, 1649, 1524, 1455, 1377, 1356, 1342, 1278, 1233, 1103, 1072, 1010, 975, 957, 923, 878, 737, 643, 611 cm^{-1}. $[\alpha]_D^{r.t.}$ = –36.8 (*c* 0.21, $CHCl_3$). Purity: UPLC (254 nm): t_r = 0.953 min, 97.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.11 – 1.19 (*m*, 2H); 1.20 – 1.33 (*m*, 6H); 1.37 – 1.43 (*m*, 2H); 1.62 – 1.71 (*m*, 2H); 1.84 – 1.91 (*m*, 2H); 2.26 (*s*, 3H); 2.37 – 2.47 (*m*, 2H); 2.83 (br *d*, *J* = 11.1 Hz, 2H); 2.89 (*dd*, *J* = 9.2; 14.4 Hz, 1H); 3.20 – 3.28 (*m*, 1H); 3.29 – 3.40 (*m*, 3H); 7.04 (*d*, *J* = 2.3 Hz, 1H); 7.09 – 7.13 (*m*, 1H); 7.16 – 7.21 (*m*, 1H); 7.30 (*t*, *J* = 5.8 Hz, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.66 (*d*, *J* = 8.0 Hz, 1H); 8.74 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.94, 20.30, 29.42, 32.26, 32.31, 32.34, 33.01, 36.34, 36.63, 46.56, 48.79, 55.95, 63.55, 111.35, 111.73, 118.97, 119.59, 122.25, 122.97, 127.60, 136.57, 174.56.

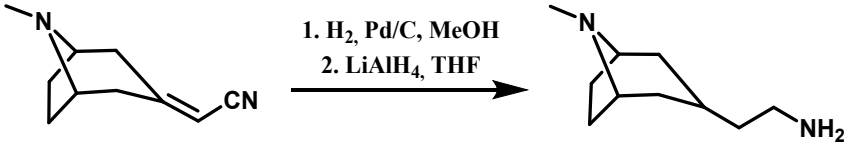
2-(8-Methyl-8-azabicyclo[3.2.1]octan-3-ylidene)acetonitrile[29] (S29-1)



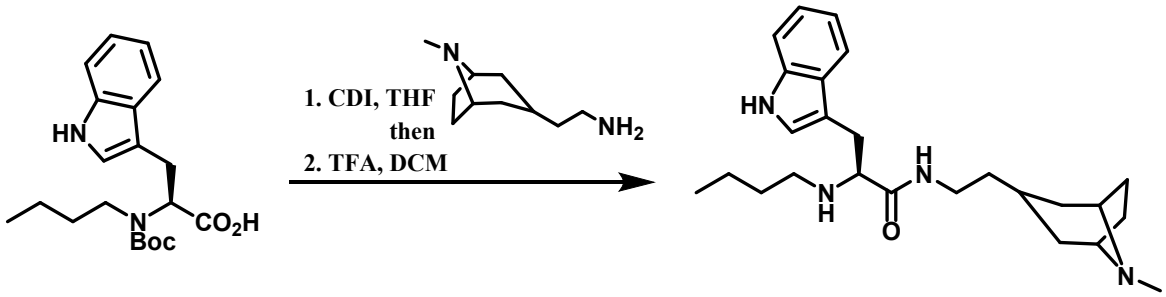
Sodium hydride (55 wt.% suspension in mineral oil) (2.0 eq., 125 mg) was added portionwise to diethyl cyanomethylphosphonate (2.0 eq., 465 µL) in anhydrous THF (20 mL) under argon at r.t. and stirred for 15 min, before tropinone (200 mg, 1.0 eq., 1.437 mmol) was added and the reaction mixture was stirred at 60 °C for 2 h. Volatile components were evaporated *in vacuo*, 1 M $HCl_{(aq)}$ (15 mL) was added, extracted with Et_2O (2 x 20 mL) and organic phase discarded. The aqueous phase was then made alkaline (pH 10) with the addition of solid sodium hydroxide and extracted with Et_2O (2 x 20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford pure product. Yield: 188.1 mg (1.159 mmol, 80.7%) of yellowish oil. ESI-HRMS: *m/z* = 163.1229 (MH^+); $C_{10}H_{15}N_2$

requires: *m/z* = 163.123 (MH^+). ν_{max} 2943, 2801, 2215, 1626, 1420, 1349, 1234, 1144, 1021, 791, 725, 653 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.42 – 1.53 (*m*, 2H); 1.93 – 2.05 (*m*, 2H); 2.08 – 2.13 (*m*, 1H); 2.39 (*s*, 3H); 2.53 – 2.68 (*m*, 3H); 3.26 – 3.30 (*m*, 1H); 3.31 – 3.36 (*m*, 1H); 5.18 (*t*, *J* = 2.3 Hz, 1H, CH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.69, 26.75, 37.58, 38.34, 39.91, 60.74, 60.88, 95.97, 116.43, 163.27.

(*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)ethyl)propanamide (S29)



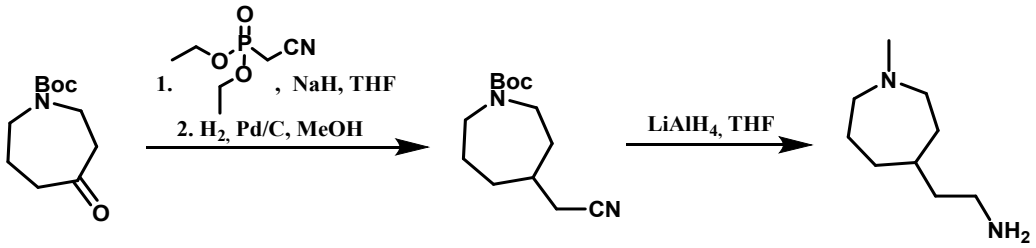
Following *GP4* and *GP5*, **S29-1**[29] (210 mg, 1.294 mmol) was reduced to afford 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)ethan-1-amine (136 mg, 0.808 mmol, 62.5% yield over two steps) as colourless oil which was used further without purification.



tert-Butyl ((*S*)-3-(1*H*-indol-3-yl)-1-((2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)ethyl)amino)-1-oxopropan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (195 mg, 0.540 mmol), CDI (1.1 eq, 96 mg) and 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)ethan-1-amine (1.1 eq., 100 mg) in THF, isolated by column chromatography on basic alumina (1. Et_2O/THF = 1:1; 2. THF), and immediately deprotected following *GP2*. The title product **S29** was isolated by column chromatography on silica (EtOAc/MeOH/TEA = 5:1:0.15). Yield: 57.2 mg (0.14 mmol, 25.8 % over two steps) of colourless oil. ESI-HRMS: *m/z* = 411.3107 (MH^+); $C_{25}H_{39}N_4O$ requires: *m/z* = 411.3118 (MH^+). ν_{max} 3274, 2924, 2871, 1649, 1525, 1455, 1339, 1232, 1121, 1050, 974, 879, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = –33.6 (*c* 0.13, acetone). Purity: UPLC (254 nm): t_r = 1.183 min, 97.3% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (*t*, *J* = 7.3 Hz, 3H); 1.13 – 1.22 (*m*, 2H); 1.23 – 1.35 (*m*, 5H); 1.50 – 1.65 (*m*, 5H); 1.99 – 2.07 (*m*, 2H); 2.09 – 2.17 (*m*, 2H); 2.27 (*s*, 3H, NMe); 2.39 – 2.51 (*m*, 2H); 2.97 (*dd*, *J* = 8.5; 14.5 Hz, 1H); 3.08 – 3.15 (*m*, 2H); 3.22 – 3.32 (*m*, 3H); 3.36 (*dd*, *J* = 4.4; 8.4 Hz, 1H); 7.05 (*d*, *J* = 2.4 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.16

– 7.22 (*m*, 2H); 7.38 (*d*, *J* = 8.1 Hz, 1H); 7.65 – 7.69 (*m*, 1H); 8.55 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.99, 20.37, 24.72, 26.64, 28.92, 30.46, 32.35, 37.67, 38.02, 40.37, 48.77, 60.63, 63.59, 111.41, 111.78, 118.91, 119.68, 122.26, 123.13, 127.80, 136.52, 174.46.

2-(1-Methylazepan-4-yl)ethan-1-amine (S30-1)



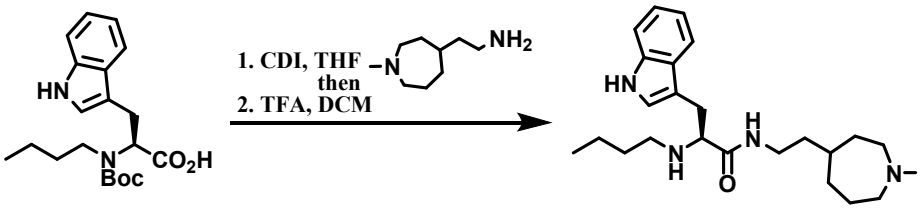
To a solution of diethyl cyanomethylphosphonate (1.3 eq., 986 µL) in anhydrous THF (10 mL), sodium hydride (60 wt.% dispersion in mineral oil, 1.3 eq., 244 mg) was added portionwise. Reaction mixture was stirred for 10 min at r.t. before *tert*-butyl 4-oxoazepane-1-carboxylate (1000 mg, 4.69 mmol, 1.0 eq.) was added and the stirring continued for 12 h at r.t.. The reaction mixture was concentrated *in vacuo*, water (20 mL) was added to dissolve the syrupy residue and extracted with Et_2O (2 x 30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, volatile components evaporated *in vacuo* and *tert*-butyl 4-(cyanomethylene)azepane-1-carboxylate isolated by column chromatography on silica (PE/EtOAc = 3:1). Yield: 901 mg (3.813 mmol, 81.3%) of colourless oil.

Following *GP4*, *tert*-butyl 4-(cyanomethylene)azepane-1-carboxylate (901 mg, 3.813 mmol) was reduced to *tert*-butyl 4-(cyanomethyl)azepane-1-carboxylate[30]. Yield: 863 mg (3.621 mmol, 77.2% over two steps) of colourless oil. ESI-HRMS: *m/z* = 139.1225 ((M-Boc)H^+); $C_8H_{15}N_2^+$ requires: *m/z* = 139.123 ((M-Boc)H^+). ν_{max} 2974, 2928, 2244, 1681, 1478, 1414, 1365, 1251, 1160, 1085, 976, 866, 772 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.32 – 1.42 (*m*, 1H); 1.43 – 1.55 (*m*, 10H); 1.56 – 1.67 (*m*, 1H); 1.79 – 2.00 (m, 4H); 2.25 – 2.38 (*m*, 2H); 3.15 – 3.52 (m, 3H), 3.53 – 3.67 (*m*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.18, 26.50, 26.73, 28.52, 32.48, 32.89, 34.36, 34.43, 35.91, 36.40, 44.17, 44.60, 45.94, 46.69, 79.43, 79.46, 118.76, 118.78, 155.45, 155.50.

tert-Butyl 4-(cyanomethyl)azepane-1-carboxylate (863 mg, 3.621 mmol) was reduced to 2-(1-methylazepan-4-yl)ethan-1-amine following *GP5* – however 6.0 eq. of lithium aluminum hydride were used. Yield: 482.3 mg (3.086 mmol, 85.2%) of colourless oil. ESI-HRMS: *m/z* = 157.1699 (MH^+); $C_9H_{21}N_2$ requires: *m/z* = 157.1699 (MH^+). ν_{max} 3273, 2920, 2851, 2797, 1638, 1567, 1450, 1383, 1295, 1201, 1100, 1019, 930, 816, 766, 713 cm^{-1}. ^{1}H-NMR (500 MHz,

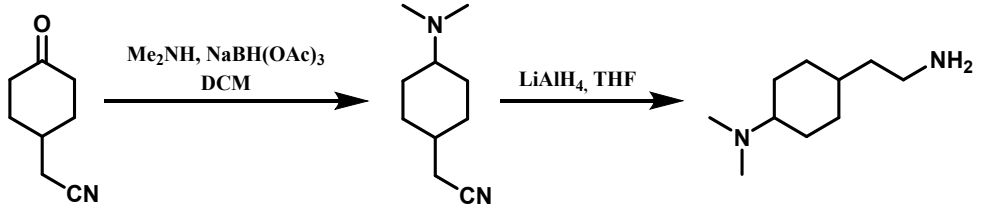
$CDCl_3$): δ 1.24 – 1.34 (*m*, 2H); 1.37 – 1.46 (*m*, 3H); 1.56 – 1.79 (*m*, 6H); 2.33 (*s*, 3H, Me); 2.45 (*ddd*, *J* = 2.7; 9.4; 12.7 Hz, 1H); 2.49 – 2.59 (*m*, 2H); 2.62 (*dddd*, *J* = 0.8; 2.9; 7.1; 13.0 Hz, 1H); 2.67 – 2.72 (*m*, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.53, 33.28, 34.33, 35.66, 40.22, 42.22, 47.51, 56.56, 58.97.

(2*S*)-2-(Butylamino)-3-(1*H*-indol-3-yl)-*N*-(2-(1-methylazepan-4-yl)ethyl)propanamide (S30)



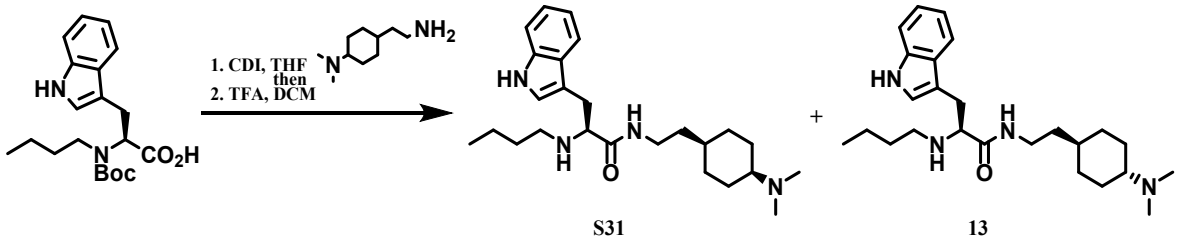
tert-Butyl ((2*S*)-3-(1*H*-indol-3-yl)-1-((2-(1-methylazepan-4-yl)ethyl)amino)-1-oxopropan-2-yl)(butyl)carbamate was prepared following *GP1* from **S8-1** (270 mg, 0.749 mmol), CDI (1.1 eq, 134 mg) and **S30-1** (1.1 eq., 128 mg) in THF, isolated by column chromatography on basic alumina (1. Et_2O/THF = 1:1; 2. THF), and immediately deprotected following *GP2*. **S30** was isolated by column chromatography on silica (EtOAc/MeOH/TEA = 5:1:0.15) and additionally purified following *GP7*. Yield: 68.8 mg (0.173 mmol, 23% over two steps) of colourless oil. Mixture of two diastereomers in a ratio of 1:1. ESI-HRMS: *m/z* = 399.3111 (MH^+); $C_{24}H_{39}N_4O$ requires: *m/z* = 399.3118 (MH^+). ν_{max} 3269, 2927, 2859, 1647, 1561, 1456, 1399, 1260, 1104, 1010, 919, 798, 741 cm^{-1}. $[\alpha]_D^{r.t.}$ = +3.5 (*c* 0.16, MeOH). Purity: UPLC (254 nm): t_r = 1.040 min, 99.4% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77 – 0.94 (*m*, 3H); 1.13 – 2.08 (*m*, 15H), 2.40 (*s*, 3H); 2.44 – 2.71 (*m*, 5H); 2.95 – 3.06 (*m*, 1H); 3.20 – 3.41 (*m*, 4H); 7.08 (*d*, *J* = 2.1 Hz, 1H); 7.12 – 7.25 (*m*, 3H); 7.39 (*d*, *J* = 8.3 Hz, 1H); 7.69 (*d*, *J* = 7.9 Hz, 1H); 8.69 (*s*, 0.5H), 8.80 (*s*, 0.5H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.98, 20.37, 23.71, 23.77, 28.56, 28.66, 30.16, 30.45, 32.32, 33.29, 33.49, 35.45, 35.61, 36.57, 36.61, 36.92, 37.12, 45.13, 45.20, 48.70, 48.70, 54.69, 54.74, 57.12, 57.24, 63.44, 63.45, 77.16, 111.10, 111.55, 111.57, 118.68, 118.72, 119.43, 121.98, 123.40, 123.42, 127.82, 127.85, 136.57, 136.59, 174.49.

(*S*)-2-(butylamino)-*N*-(2-((1*s*,4*R*)-4-(dimethylamino)cyclohexyl)ethyl)-3-(1*H*-indol-3-yl)propanamide (S31) and (*S*)-2-(butylamino)-*N*-(2-((1*s*,4*S*)-4-(dimethylamino)cyclohexyl)ethyl)-3-(1*H*-indol-3-yl)propanamide (13)



Following modified *GP3*, 2-(4-(dimethylamino)cyclohexyl)acetonitrile was prepared from 2-(4-oxocyclohexyl)acetonitrile[31] (2000 mg, 14.58 mmol), dimethylamine (33 wt.% solution in EtOH, 2.0 eq., 5.2 mL) and sodium triacetoxyborohydride (1.5 eq., 4636 mg). The reaction mixture was acidified (pH 1) with 10% $HCl_{(aq)}$, extracted with DCM (2 x 30 mL) and organic extracts discarded. While cooling on an icebath, solid sodium hydroxide was added until pH 11, extracted with Et_2O (3 x30 mL), ethereal extracts dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford pure 2-(4-(dimethylamino)cyclohexyl)acetonitrile. Yield: 1707 mg (10.27 mmol, 70.4%) of colourless oil.

Following *GP5*, 2-(4-(dimethylamino)cyclohexyl)acetonitrile (1523 mg, 9.16 mmol) was reduced to afford 4-(2-aminoethyl)-*N*,*N*-dimethylcyclohexan-1-amine (1011 mg, 5.94 mmol, 64.8% yield) as colourless oil which was used further without purification.

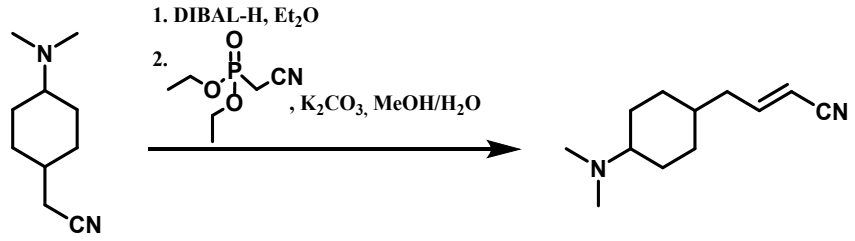


tert-Butyl (*S*)-butyl(1-((2-(4-(dimethylamino)cyclohexyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (280 mg, 0.776 mmol), CDI (1.1 eq, 138 mg) and 4-(2-aminoethyl)-*N*,*N*-dimethylcyclohexan-1-amine (1.1 eq., 146 mg) in THF, isolated by column chromatography on basic alumina (THF) and immediately deprotected following *GP2*. The title product was isolated by column chromatography on silica (EtOAc/MeOH/TEA = 5:1:0.15). Yield: 126.2 mg (0.306 mmol, 39.4% over two steps) of colourless semisolid, which could be separated into two isomers:

Compound **S31** eluted first from the column. Yield: 35.3 mg (0.0856 mmol, 11.0% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 413.3277 (MH^+); $C_{25}H_{41}N_4O$ requires: *m/z* = 413.3275 (MH^+). ν_{max} 3270, 2926, 2859, 2775, 1649, 1525, 1455, 1376, 1342, 1220, 1102, 1035, 1010, 799, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = +5.2 (*c* 0.20, MeOH). Purity: UPLC (254 nm): t_r = 1.383 min, 98.1% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78 (*t*, *J* = 7.3 Hz, 3H); 1.12 – 1.21 (*m*, 2H); 1.22 – 1.30 (*m*, 2H); 1.35 – 1.64 (*m*, 12H); 2.11 – 2.19 (*m*, 1H); 2.31 (*s*, 6H, NMe_2); 2.40 – 2.46 (*m*, 2H); 2.93 (*dd*, *J* = 8.9; 14.5 Hz, 1H); 3.17 – 3.33 (*m*, 3H); 3.37 (*dd*, *J* = 4.3; 8.9 Hz, 1H); 7.05 (*d*, *J* = 1.9 Hz, 1H); 7.08 – 7.13 (*m*, 1H); 7.16 – 7.24 (*m*, 2H); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.66 (*d*, *J* = 7.8 Hz, 1H); 8.89 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.94, 20.31, 25.58, 28.16, 28.26, 29.36, 31.96, 32.28, 33.12, 37.22, 42.41, 48.75, 63.00, 63.56, 111.42, 111.58, 118.90, 119.51, 122.14, 123.11, 127.64, 136.56, 174.52.

Compound **13** eluted second from the column. Yield: 19.1 mg (0.0463 mmol, 6.0% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 413.3271 (MH^+); $C_{25}H_{41}N_4O$ requires: *m/z* = 413.3275 (MH^+). ν_{max} 3269, 2925, 2857, 2781, 1648, 1526, 1454, 1355, 1260, 1233, 1102, 1035, 1010, 800, 739 cm^{-1}. $[\alpha]_D^{r.t.}$ = +1.9 (*c* 0.11, MeOH). Purity: UPLC (254 nm): t_r = 1.473 min, 95.5% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.72 (*t*, *J* = 7.3 Hz, 3H); 0.78 – 0.89 (*m*, 2H); 1.00 – 1.28 (*m*, 10H); 1.69 – 1.78 (*m*, 2H); 1.84 – 1.92 (*m*, 2H); 2.19 – 2.27 (*m*, 1H); 2.31 (*s*, 6H, NMe_2); 2.36 – 2.41 (*m*, 2H); 2.89 (*dd*, *J* = 8.6; 14.5 Hz, 1H); 3.16 – 3.25 (*m*, 3H); 3.30 (*dd*, *J* = 4.4; 8.5 Hz, 1H); 6.98 (*s*, 1H); 7.04 (*t*, *J* = 7.5 Hz, 1H); 7.09 – 7.14 (*m*, 1H); 7.17 (*t*, *J* = 5.9 Hz, 1H); 7.32 (*d*, *J* = 8.1 Hz, 1H); 7.59 (*dd*, *J* = 1.1; 7.9 Hz, 1H); 8.86 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.97, 20.34, 28.08, 28.14, 29.01, 31.79, 31.93, 32.32, 34.63, 36.52, 36.66, 41.26, 48.76, 63.47, 64.22, 111.46, 111.49, 118.88, 119.52, 122.13, 123.10, 127.72, 136.56, 174.45.

4-(4-(Dimethylamino)cyclohexyl)but-2-enenitrile (S32-1/S33-1)



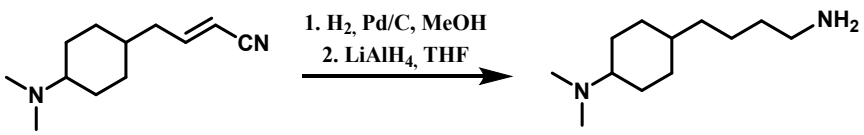
2-(4-(Dimethylamino)cyclohexyl)acetonitrile (prepared as described above under **S31**) (1707 mg, 10.27 mmol) was azeotropically dried with toluene, dissolved in anhydrous Et_2O (30 mL) and cooled to –40 °C in a cryostat. DIBAL-H (1M in hexanes, 1.0 eq., 10.27 mL) was added dropwise into the reaction mixture while stirring. After 10 min, the cryostat was turned off and

the reaction mixture was left to warm up to r.t. in 16 h. 50% $MeOH_{(aq)}$ (50 mL) was then carefully added to produce a white suspension, diethyl cyanomethylphosphonate (2.0 eq., 3.3 mL) and potassium carbonate (3.0 eq., 4250 mg) were added and the reaction mixture was vigorously stirred at 50 °C for 12 h. Afterwards, solids were removed by filtration, washed with MeOH (30 mL) and volatile components removed *in vacuo*. The viscous residue was then made alkaline with 1 M $NaOH_{(aq)}$, extracted with Et_2O (3 x 30 mL), ethereal extracts dried over anhydrous sodium sulfate, filtered, and volatile components removed *in vacuo*. The title products were isolated by column chromatography (1. PE/EtOAc/Et_3N = 1:1:0.05; 2. PE/EtOAc/Et_3N = 1:1:0.1), which furnished the two isomers:

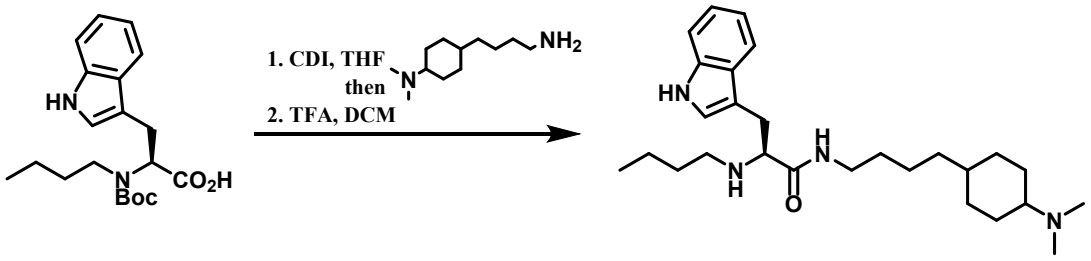
Compound **S32-1** eluted first from the column. Two major conformers in a ratio of 64:36. Yield: 710 mg (3.692 mmol, 35.9% over two steps) of colourless oil. ESI-HRMS: *m/z* = 193.1702 (MH^+); $C_{12}H_{21}N_2$ requires: *m/z* = 193.1699 (MH^+). ν_{max} 3381, 2929, 2864, 2770, 2245, 2221, 1632, 1450, 1392, 1373, 1240, 1163, 1077, 1049, 974, 945, 888, 863, 798, 766, 735 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) for both conformers: δ 1.34 – 1.76 (*m*, 9H); 1.98 – 2.12 (*m*, 1H); 2.13 – 2.27 (*m*, 8H); 2.37 – 2.45 (*m*, 1H); 5.24 – 5.37 (*m*, 1H); 6.42 – 6.75 (*m*, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) for both conformers: δ 26.15, 26.48, 27.73, 27.90, 34.71, 35.06, 36.50, 38.40, 42.60, 42.84, 61.93, 62.02, 100.15, 100.51, 116.18, 117.53, 154.30, 155.25.

Compound **S33-1** eluted second from the column. Two major conformers in a ratio of 66:34. Yield: 452 mg (2.350 mmol, 22.9% over two steps) of colourless oil. ESI-HRMS: *m/z* = 193.1703 (MH^+); $C_{12}H_{20}N_2$ requires: *m/z* = 193.1699 (MH^+). ν_{max} 3341, 2925, 2858, 2821, 2773, 2221, 1632, 1450, 1380, 1269, 1200, 1155, 1076, 1038, 1011, 963, 903, 870, 787, 740 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) for both conformers: δ 0.88 – 1.28 (*m*, 4H); 1.31 – 1.45 (*m*, 1H); 1.73 – 1.96 (*m*, 4H); 2.07 – 2.16 (*m*, 2H); 2.21 – 2.29 (*m*, 6H); 2.30 – 2.38 (*m*, 1H); 5.24 – 5.39 (*m*, 1H); 6.42 – 6.77 (*m*, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) for both conformers: δ 28.42, 28.50, 31.99, 32.06, 36.91, 37.22, 39.05, 40.80, 41.72, 41.74, 63.53, 100.41, 100.74, 116.18, 117.48, 153.78, 154.75.

(*S*)-2-(Butylamino)-*N*-(4-(4-(dimethylamino)cyclohexyl)butyl)-3-(1*H*-indol-3-yl)propanamide (S32/S33)



Following *GP4* and *GP5,* 4-(4-(dimethylamino)cyclohexyl)but-2-enenitrile isomers (710 mg, 3.692 mmol for **S32-1**; 452 mg, 2.35 mmol for **S33-1**) were reduced separately to 4-(4-aminobutyl)-*N,N*-dimethylcyclohexan-1-amine isomers (369 mg, 1.860 mmol, 50.4% yield from **S32-1**; 391 mg, 1.971 mmol, 83.9% from **S33-1**) as colourless oils which were used further without purification.



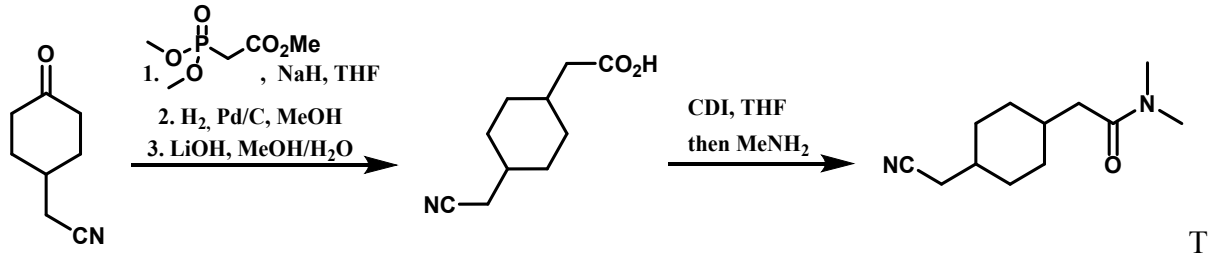
tert-Butyl (*S*)-butyl(1-((4-(4-(dimethylamino)cyclohexyl)butyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (300 mg, 0.832 mmol), CDI (1.1 eq, 148 mg) and appropriate 4-(4-aminobutyl)-*N,N*-dimethylcyclohexan-1-amine isomer (1.1 eq., 182 mg) in THF. The intermediate carbamate was not isolated, instead volatile components were evaporated *in vacuo,* and the crude reaction mixture was deprotected following *GP2*. The title products were isolated following *GP7*.

Compound **S32**: Yield: 267 mg (0.606 mmol, 72.8%) of colourless semisolid. ESI-HRMS: *m/z* = 441.3587 (MH^+); $C_{27}H_{45}N_4O$ requires: *m/z* = 441.3588 (MH^+); *m/z* = 221.1834 ($(M+2H)^{2+}$); $C_{27}H_{46}N_4O$ requires: *m/z* = 221.183 ($(M+2H)^{2+}$). ν_{max} 3264, 2925, 2856, 2768, 1651, 1523, 1455, 1355, 1221, 1125, 1036, 1010, 990, 737 cm^{-1}. $[\alpha]_D^{r.t.}$ = –40.0 (*c* 0.20, acetone). Purity: UPLC (254 nm): t_r = 3.187 min, 98.9% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.78 (*t*, *J* = 7.2 Hz, 3H); 1.10 – 1.31 (*m*, 9H); 1.37 – 1.67 (*m*, 11H); 2.04 – 2.11 (*m*, 1H); 2.27 (*s*, 6H); 2.38 – 2.51 (*m*, 2H); 2.93 (*dd*, *J* = 8.8; 14.4, Hz, 1H); 3.14 – 3.40 (*m*, 4H); 7.05 (*d*, *J* = 2.3 Hz, 1H); 7.08 – 7.14 (*m*, 1H); 7.16 – 7.22 (*m*, 1H); 7.27 (*t*, *J* = 5.8 Hz, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.67 (*dd*, *J* = 1.0; 7.8 Hz, 1H); 8.91 (*s*, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 13.95, 20.31, 24.65, 26.09, 28.26, 28.28, 29.28, 29.90, 32.29, 33.30, 34.68, 38.98, 42.69, 48.75, 62.84, 63.56, 111.37, 111.64, 118.95, 119.52, 122.16, 123.05, 127.68, 136.55, 174.52.

Compound **S33**: Yield: 249 mg (0.565 mmol, 67.9%) of colourless semisolid. ESI-HRMS: *m/z* = 441.3576 (MH^+); $C_{27}H_{45}N_4O$ requires: *m/z* = 441.3588 (MH^+); *m/z* = 221.1832 ($(M+2H)^{2+}$); $C_{27}H_{46}N_4O$ requires: *m/z* = 221.183 ($(M+2H)^{2+}$). ν_{max} 3274, 3057, 2924, 2855, 2779, 1738, 1651, 1524, 1455, 1356, 1235, 1200, 1127, 1037, 1010, 964, 898, 799, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = –42.6 (*c* 0.63, acetone). Purity: UPLC (254 nm): t_r = 3.620 min, 99.34% total area. ^{1}H-NMR (400

MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.2 Hz, 3H); 0.84 – 0.96 (*m*, 2H); 1.08 – 1.34 (*m*, 10H); 1.39 – 1.49 (*m*, 2H); 1.62 – 1.93 (*m*, 6H); 2.07 – 2.16 (*m*, 1H); 2.27 (*s*, 6H); 2.36 – 2.50 (*m*, 2H); 2.88 (*dd*, *J* = 8.9; 14.0 Hz, 1H); 3.14 – 3.40 (*m*, 4H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.10 – 7.16 (*m*, 1H); 7.18 – 7.24 (*m*, 1H); 7.31 (*t*, *J* = 5.7 Hz, 1H); 7.35 – 7.40 (*m*, 1H); 7.69 (*d*, *J* = 7.9 Hz, 1H); 8.21 (*s*, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 13.97, 20.33, 24.51, 28.71, 29.44, 30.04, 32.31, 32.43, 36.75, 37.42, 38.97, 41.78, 48.81, 63.58, 64.07, 111.30, 112.10, 119.11, 119.75, 122.41, 122.84, 127.65, 136.51, 174.46.

2-(4-(Cyanomethyl)cyclohexyl)-*N*,*N*-dimethylacetamide (S34-1)



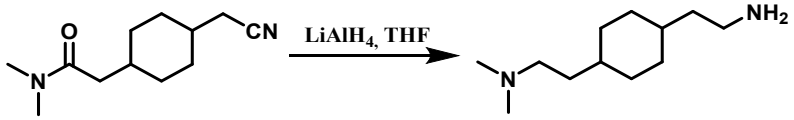
T

o a solution of trimethyl phosphonoacetate (1.5 eq., 4.70 mL) in anhydrous THF (150 mL), sodium hydride (60 wt% dispersion in mineral oil, 1.5 eq., 1161 mg) was added portionwise. The reaction mixture was then heated to 60 °C, stirred for 10 min (meanwhile the reaction mixture thickens considerably) before 2-(4-oxocyclohexyl)acetonitrile (1.0 eq., 2656 mg, 19.36 mmol) was added and the stirring continued at 60 °C for 24 h. The reaction mixture was concentrated *in vacuo*, water (100 mL) was added to dissolve the syrupy residue and extracted with Et_2O (2 x 30 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo.* Methyl 2-(4-(cyanomethyl)cyclohexylidene)acetate was isolated by column chromatography on silica (1. PE; 2. PE/EtOAc = 5:1) and immediately reduced following *GP4* to methyl 2-(4-(cyanomethyl)cyclohexyl)acetate. This intermediate was dissolved in MeOH (20 mL), 2 M $LiOH_{(aq)}$ (20 mL) was added and the reaction mixture stirred at r.t. for 6 h. MeOH was then evaporated *in vacuo*, the aqueous residue was extracted with Et_2O (2 x 20 mL, discarded), acidified (pH 1) with concentrated HCl and extracted with Et_2O (3 x 20 mL). The ethereal extracts were dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford 2-(4-(cyanomethyl)cyclohexyl)acetic acid[32] as colourless semisolid. Yield: 1190 mg (6.57 mmol, 33.9% over three steps). ESI-HRMS: *m/z* = 182.1172 (MH^+); $C_{10}H_{16}NO_2$ requires: *m/z* = 182.1181 (MH^+). ν_{max} 3449, 2924, 2855, 2671, 2244, 1705, 1456, 1424, 1397, 1299, 1240, 1200, 1178, 1109, 1065, 927, 680 cm^{-1}. Two isomers (*rel-cis*/*trans*) in a ratio of 74:26. ^{1}H-NMR (500 MHz, $CDCl_3$) for both isomers: δ 1.02 – 1.22 (*m*, 4H); 1.39 – 2.17 (*m*,

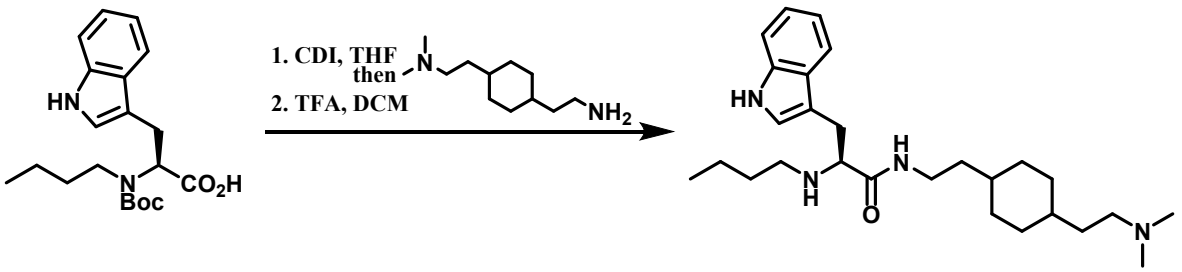
7H); 2.22 – 2.40 (*m*, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$) for both isomers: δ 22.47, 24.60, 27.74, 28.17, 31.35, 32.00, 32.11, 32.74, 33.97, 34.50, 38.51, 41.44, 118.81, 119.07, 179.21, 179.33.

2-(4-(Cyanomethyl)cyclohexyl)-*N,N*-dimethylacetamide was prepared following *GP1* from 2-(4-(cyanomethyl)cyclohexyl)acetic acid (398 mg, 2.2 mmol), CDI (1.1 eq., 392 mg) and dimethylamine (33 wt.% solution in absolute ethanol, 1.5 eq., 590 µL) in THF. The title product was isolated by column chromatography on silica (EtOAc). Yield: 450 mg (2.16 mmol, 98.2%) of colourless semisolid. ESI-HRMS: *m/z* = 209.1644 (MH^+); $C_{12}H_{21}N_2O$ requires: *m/z* = 209.1648 (MH^+). ν_{max} 3483, 2922, 2850, 2242, 1636, 1496, 1449, 1397, 1336, 1262, 1151, 1131, 1099, 1062, 964, 905, 624 cm^{-1}. Two diastereomers in a ratio of 74:26. ^{1}H-NMR (500 MHz, $CDCl_3$) for the major isomer: δ 0.96 – 1.09 (*m*, 2H); 1.09 – 1.21 (*m*, 2H); 1.58 – 1.72 (*m*, 2H); 1.84 – 1.91 (*m*, 4H); 2.23 (*dd*, *J* = 6.7; 17.9, Hz, 4H); 2.95 (*s*, 3H); 3.01 (*s*, 3H). ^{1}H-NMR (500 MHz, $CDCl_3$) for the minor isomer: δ 1.33 – 1.44 (*m*, 2H), 1.45 – 1.54 (*m*, 1H); 1.91 – 1.99 (*m*, 1H); 2.09 – 2.18 (*m*, 1H); 2.32 (*dd*, *J* = 7.2; 27.8, Hz, 4H), 3.02 (*s*, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) for both isomers: δ 24.69, 32.26, 32.62, 34.27, 34.85, 35.49, 35.53, 37.57, 37.59, 40.36, 119.00, 119.26, 172.13, 172.18.

(*S*)-2-(Butylamino)-*N*-(2-(4-(2-(dimethylamino)ethyl)cyclohexyl)ethyl)-3-(1*H*-indol-3-yl)propanamide (S34)



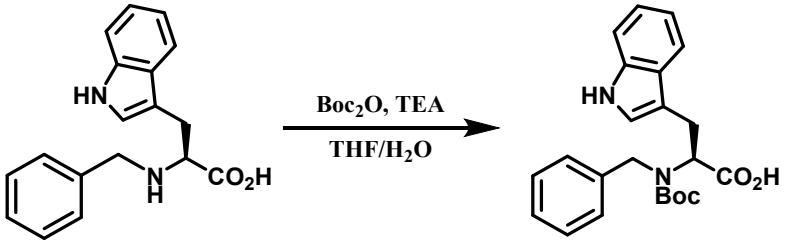
S34-1 (350 mg, 1.68 mmol) was reduced to 2-(4-(2-aminoethyl)cyclohexyl)-*N,N*-dimethylethan-1-amine following *GP5* – however 6.0 eq. of lithium aluminum hydride were used. Yield: 169 mg (0.853 mmol, 50.8% yield) as colourless oil which was used further without purification.



tert-Butyl (*S*)-butyl(1-((2-(4-(2-(dimethylamino)ethyl)cyclohexyl)ethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (255 mg, 0.707 mmol), CDI (1.1 eq, 126 mg) and 2-(4-(2-aminoethyl)cyclohexyl)-*N,N*-dimethylethan-1-amine

(1.1 eq., 153 mg), isolated by column chromatography on basic alumina (THF) and immediately deprotected following *GP2*. The title product was isolated by column chromatography on silica (EtOAc/MeOH/TEA = 5:1:0.15). Yield: 90.4 mg (0.205 mmol, 29.0%) of colourless semisolid. Diastereomers in a ratio of *ca*. 1:3. The two diastereomers could not be separated by column chromatography. ESI-HRMS: *m/z* = 441.3579 (MH^+); $C_{27}H_{45}N_4O$ requires: *m/z* = 441.3588 (MH^+). ν_{max} 3262, 3055, 2917, 2855, 2772, 1653, 1520, 1449, 1375, 1358, 1299, 1235, 1126, 1102, 1038, 1013, 922, 907, 730 cm^{-1}. $[\alpha]_D^{r.t.} = -30.4$ (*c* 0.27, acetone). Purity: UPLC (254 nm): t_r = 3.407–3.443 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for *cis*- and *trans*-isomers: δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 0.83 – 0.96 (*m*, 3H); 1.08 – 1.52 (*m*, 13H); 1.64 – 1.81 (*m*, 3H); 2.26 (*s*, 6H); 2.30 – 2.38 (*m*, 2H); 2.38 – 2.48 (*m*, 2H); 2.82 – 2.95 (*m*, 1H); 3.12 – 3.44 (*m*, 4H); 7.04 (*d*, *J* = 2.3 Hz, 1H); 7.07 – 7.13 (*m*, 1H); 7.18 (*t*, *J* = 7.6 Hz, 1H); 7.30 (*t*, *J* = 5.9 Hz, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.65 (*d*, *J* = 7.7 Hz, 1H); 9.09 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for *cis*- and *trans*-isomers: δ 13.91, 20.25, 20.27, 28.64, 28.93, 29.41, 32.22, 32.24, 32.90, 32.93, 33.21, 33.44, 33.98, 34.92, 35.49, 35.96, 36.77, 36.96, 37.14, 45.31, 45.34, 48.75, 57.55, 57.96, 63.55, 111.39, 111.48, 111.49, 118.87, 119.42, 122.08, 123.08, 127.56, 136.61, 174.56, 174.59.

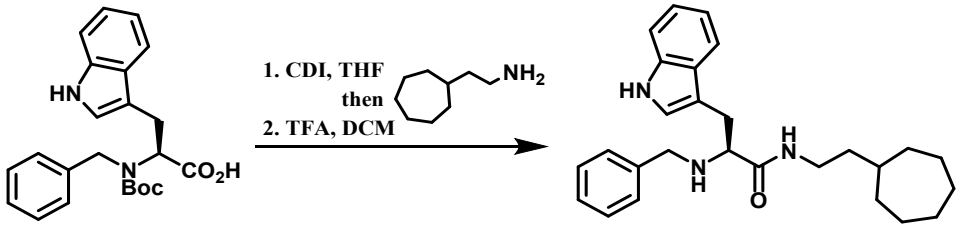
N^{α}-Benzyl-N^{α}-(*tert*-butoxycarbonyl)-*L*-tryptophan (S35-1)



Benzyl-L-tryptophan[18] (1091 mg, 3.706 mmol) was dissolved in a mixture of THF (15 mL) and water (15 mL), then TEA (2.5 eq., 938 mg) and di-*tert*-butyl dicarbonate (2.5 eq., 2022 mg) were added and the reaction mixture was stirred at r.t. for 12 h. THF was then removed *in vacuo,* the residue acidified (pH 3), extracted with EtOAc (3 x 50 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was isolated by column chromatography on silica (PE/EtOAc = 3:1). Yield: 931.6 mg (2.362 mmol, 63.7%) of beige gum. ESI-HRMS: *m/z* = 395.1955 (MH^+); $C_{23}H_{27}N_2O_4$ requires: *m/z* = 395.1965 (MH^+). ν_{max} 3413, 3347, 2976, 2930,1712, 1672, 1495, 1455, 1419, 1366, 1248, 1157, 1096, 1076, 1029, 1011, 979, 931, 860, 806, 737, 696 cm^{-1}. $[\alpha]_D^{r.t.} = -62.9$ (*c* 0.24, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.44 (*s*, 4.5H); 1.49 (*s*, 4.5H); 3.26 (*dd*, *J* = 9.3; 14.7 Hz, 0.5H); 3.36 – 3.53 (*m*, 1.5H); 3.56 (*d*, *J* = 15.1 Hz, 0.5H); 3.87 (*d*, *J* = 15.7 Hz, 0.5H); 4.10 (*dd*, *J* = 5.4; 9.4, Hz,

0.5H); 4.26 – 4.37 (*m*, 1H); 4.58 (*d*, *J* = 15.2 Hz, 0.5H); 6.87 (*s*, 0.5H); 6.93 (*s*, 0.5H); 6.98 – 7.10 (*m*, 3H); 7.12 – 7.21 (*m*, 4H); 7.29 – 7.41 (*m*, 2H); 8.14 (*s*, 0.5H); 8.23 (*s*, 0.5H); 9.30 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.27, 26.13, 28.47, 52.01, 52.83, 59.82, 61.83, 81.49, 81.56, 111.30, 111.46, 111.56, 118.42, 118.60, 119.54, 122.10, 123.18, 123.51, 127.24, 127.34, 127.71, 128.29, 128.70, 136.26, 137.13, 137.65, 155.49, 156.28, 175.66, 177.11. Compound **S35-1** exists as a mixture of two major conformers in a 1:1 ratio.

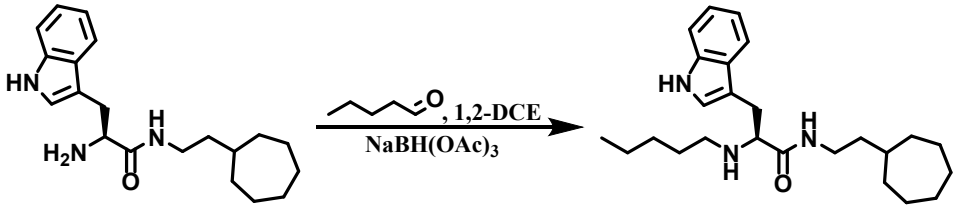
(*S*)-2-(Benzylamino)-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (S35)



tert-Butyl (*S*)-benzyl(1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S35-1** (222 mg, 0.563 mmol), CDI (1.1 eq., 100.4 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 87.3 mg) in THF and isolated by column chromatography on silica (PE/EtOAc = 2:1). Yield: 220.0 mg (0.425 mmol, 75.5%) of beige solid.

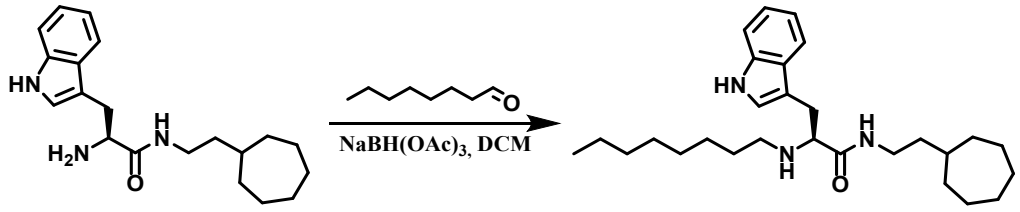
The title compound was prepared from *tert*-butyl (*S*)-benzyl(1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (155 mg, 0.299 mmol) following *GP2* and purified by column chromatography on silica (DCM/MeOH = 50:1). Yield: 102.7 mg (0.246 mmol, 82.2%) of colourless oil. ESI-HRMS: *m/z* = 418.2854 (MH^+); $C_{27}H_{36}N_3O$ requires: *m/z* = 418.2853 (MH^+). ν_{max} 3306, 2919, 2851, 1650, 1524, 1456, 1355, 1216, 1103, 1011, 738, 697, 665 cm^{-1}. $[\alpha]_D^{r.t.} = -53.0$ (*c* 0.185, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.690 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.13 – 1.21 (*m*, 2H); 1.33 – 1.71 (*m*, 13H); 1.80 (*br s*, 1H); 2.94 (*dd*, *J* = 9.3; 14.6 Hz, 1H); 3.18 – 3.32 (*m*, 2H); 3.35 (*dd*, *J* = 4.1; 14.6 Hz, 1H); 3.48 (*dd*, *J* = 4.1; 9.3 Hz, 1H); 3.55 (*d*, *J* = 13.4 Hz, 1H); 3.68 (*d*, *J* = 13.4 Hz, 1H); 6.96 (*d*, *J* = 2.1 Hz, 1H); 7.02 – 7.07 (*m*, 2H); 7.07 – 7.12 (*m*, 1H); 7.16 – 7.23 (*m*, 4H); 7.23 – 7.28 (*m*, 1H); 7.36 (*d*, *J* = 8.2 Hz, 1H); 7.63 (*d*, *J* = 7.9 Hz, 1H); 8.29 (br *s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.47, 28.59, 29.34, 34.49, 34.51, 36.98, 37.32, 37.77, 52.83, 62.72, 111.33, 111.64, 119.03, 119.73, 122.37, 122.95, 127.19, 127.59, 127.92, 128.51, 136.51, 139.54, 174.03.

(*S*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-(pentylamino)propanamide (S36)



Following *GP3*, prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (prepared as described under **S40**) (249.4 mg, 0.762 mmol), *n*-pentanal (1 eq., 89.1 µL) and sodium triacetoxyborohydride (1.5 eq., 242 mg). **S36** was isolated by column chromatography on silica (1. DCM/MeOH = 50:1; 2. DCM/MeOH = 10:1). Yield: 39.1 mg (0.098 mmol, 12.9%) of colourless oil. ESI-HRMS: *m/z* = 398.3166 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3271, 3057, 2919, 2852, 1650, 1524, 1456, 1354, 1232, 1103, 1009, 908, 877, 737, 611 cm^{-1}. $[\alpha]_D^{r.t.}$ = –61.4 (*c* 0.10, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.763 min, 95.9% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (*t*, *J* = 7.2 Hz, 3H); 1.04 – 1.31 (*m*, 8H); 1.35 – 1.72 (*m*, 14H); 2.35 – 2.48 (*m*, 2H); 2.88 (*dd*, *J* = 9.2; 14.3 Hz, 1H); 3.17 – 3.26 (*m*, 1H); 3.28 – 3.41 (*m*, 3H); 7.05 (*d*, *J* = 2.1 Hz, 1H); 7.11 (*t*, *J* = 7.5 Hz, 1H); 7.16 – 7.22 (*m*, 1H); 7.30 (*t*, *J* = 5.9 Hz, 1H, NH); 7.37 (*d*, *J* = 8.1 Hz, 1H); 7.67 (*d*, *J* = 7.9 Hz, 1H); 8.46 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.09, 22.53, 26.47, 28.60, 29.34, 29.46, 29.78, 34.47, 34.50, 36.96, 37.25, 37.75, 49.02, 63.54, 111.36, 111.84, 118.99, 119.64, 122.30, 122.93, 127.59, 136.55, 174.45.

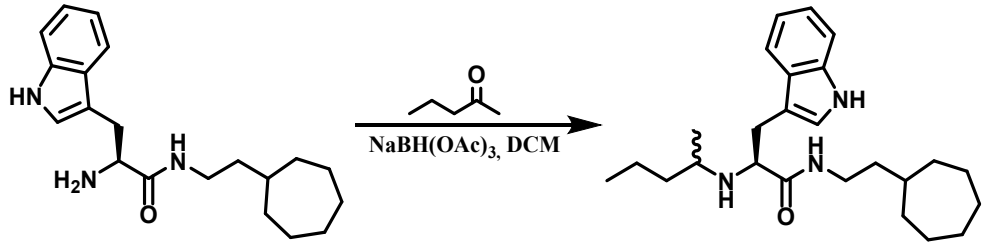
(*S*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-(octylamino)propanamide (S37)



Following *GP3*, prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (prepared as described under **S40**) (351 mg, 1.072 mmol), *n*-octanal (1.1 eq., 151.8 mg) and sodium triacetoxyborohydride (1.5 eq., 341 mg). **S37** was isolated by column chromatography on alumina (Et_2O/MeOH = 200:1) and additionally purified following *GP7*. Yield: 51.8 mg (0.118 mmol, 11.0%) of colourless oil. ESI-HRMS: *m/z* = 440.3633 (MH^+); $C_{28}H_{46}N_3O$ requires: *m/z* = 440.3635 (MH^+). ν_{max} 3294, 2920, 2852, 1651, 1525, 1457, 1354, 1232, 1102, 1010, 908, 737, 665 cm^{-1}. $[\alpha]_D^{r.t.}$ = –2.4 (*c* 0.19, MeOH). Purity: UPLC (254 nm): t_r = 5.123 min, 94.0% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.81 – 0.93 (*m*, 4H); 1.02 –

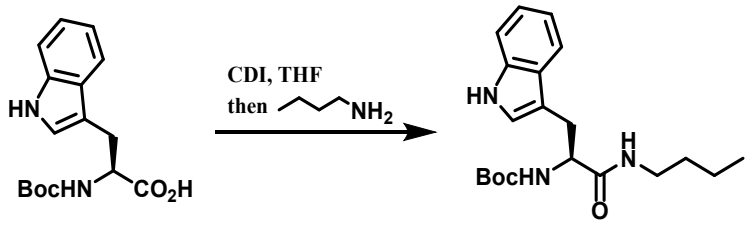
1.76 (*m*, 27H); 2.37 – 2.47 (*m*, 2H); 2.87 (*dd*, *J* = 8.8; 13.9 Hz, 1H); 3.17 – 3.26 (*m*, 1H); 3.27 – 3.41 (*m*, 3H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.11 – 7.16 (*m*, 1H); 7.19 – 7.24 (*m*, 1H); 7.24 – 7.29 (*m*, 1H); 7.35 – 7.41 (*m*, 1H); 7.69 (*d*, *J* = 7.9 Hz, 1H); 8.09 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 14.20, 22.74, 26.46, 27.16, 28.58, 29.31, 29.45, 30.08, 31.88, 34.45, 34.48, 36.94, 37.25, 37.73, 49.03, 63.55, 111.38, 111.70, 118.93, 119.57, 122.23, 122.97, 127.57, 136.56, 174.49.

(2*S*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-(pentan-2-ylamino)propanamide (S38)

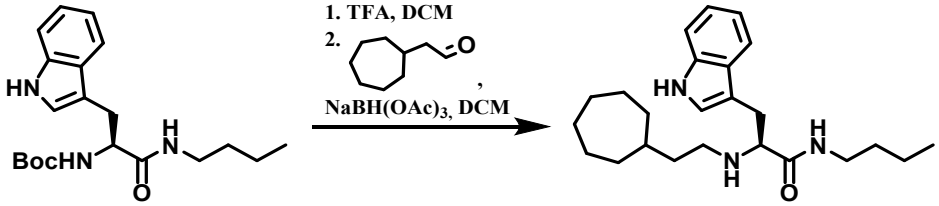


Following *GP3*, prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (prepared as described under **S40**) (214.7 mg, 0.656 mmol), methyl propyl ketone (10eq., 700 µL), and sodium triacetoxyborohydride (1.5 eq., 207.6 mg). **S38** was isolated by column chromatography on silica (PE/EtOAc = 1:2) and purified following *GP7*. Yield: 96.8 mg (0.243 mmol, 37.1%) of colourless oil. ESI-HRMS: *m/z* = 398.3162 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3293, 2919, 2852, 1649, 1523, 1456, 1377, 1354, 1232, 1102, 1010, 907, 733, 646 cm^{-1}. $[\alpha]_D^{r.t.}$ = –4.5 (*c* 0.63, MeOH). Purity: UPLC (254 nm): t_r = 4.723 min, 96.4% total area. Two diastereomers in a ratio of 61:39. ^{1}H-NMR (500 MHz, $CDCl_3$) for the major diastereomer: *δ* 0.70 (*d*, *J* = 6.2 Hz, 3H); 0.83 (*t*, *J* = 7.1 Hz, 3H); 0.92 – 1.03 (*m*, 1H); 1.07 – 1.32 (*m*, 6H); 1.34 – 1.73 (*m*, 13H); 2.36 – 2.46 (*m*, 1H); 2.86 – 2.95 (*m*, 1H); 3.13 – 3.23 (*m*, 1H); 3.28 – 3.39 (*m*, 2H); 3.49 (*dd*, *J* = 4.3; 9.0 Hz, 1H); 7.05 (*d*, *J* = 2.1 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.17 – 7.24 (*m*, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.41 (*t*, *J* = 5.9 Hz, 1H); 7.69 (*d*, *J* = 7.9 Hz, 1H); 8.15 (*s*, 1H, NH). ^{1}H-NMR (500 MHz, $CDCl_3$) for the minor diastereomer: *δ* 0.60 (*t*, *J* = 7.1 Hz, 3H); 0.89 (*d*, *J* = 6.4 Hz, 3H); 3.42 (*dd*, *J* = 4.3; 9.1 Hz, 1H); 7.47 (*t*, *J* = 6.0 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for both diastereomers: *δ* 14.00, 14.32, 18.52, 19.57, 20.18, 21.15, 26.49, 26.55, 28.61, 28.63, 28.64, 29.57, 29.67, 34.49, 34.51, 34.55, 34.58, 36.97, 37.03, 37.28, 37.32, 37.79, 37.81, 38.81, 40.29, 52.48, 53.12, 60.76, 61.41, 111.27, 112.05, 119.14, 119.17, 119.74, 122.37, 122.43, 122.91, 127.66, 127.70, 136.47, 136.54, 174.98.

(*S*)-*N*-Butyl-2-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)propanamide (S39)



tert-Butyl (*S*)-(1-(butylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*tert*-butoxycarbonyl)-L-tryptophan (500 mg, 1.643 mmol), CDI (1.1 eq., 293.1 mg), and *n*-butylamine (1.1 eq., 132.2 mg) in THF, and isolated by column chromatography on silica (PE/EtOAc = 1:1). Yield: 579.4 mg (1.612 mmol, 98.1%) of beige solid; mp 118.0–118.6 °C. ESI-HRMS: *m/z* = 360.229 (MH^+); $C_{20}H_{30}N_3O_3$ requires: *m/z* = 360.2282 (MH^+). ν_{max} 3409, 3391, 3329, 3060, 2966, 2930, 2875, 2034, 1771, 1687, 1650, 1526, 1456, 1434, 1415, 1388, 1366, 1330, 1289, 1268, 1245, 1223, 1167, 1134, 1089, 1069, 1045, 1024, 1012, 981, 930, 891, 858, 816, 796, 778, 757, 738, 694, 636 cm^{-1}. $[\alpha]_D^{r.t.}$ = +5.52 (*c* 0.61, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (*t*, *J* = 7.2 Hz, 3H); 1.02 – 1.27 (*m*, 4H); 1.42 (*s*, 9H); 2.98 – 3.32 (*m*, 4H); 4.41 (*s*, 1H); 5.28 (*s*, 1H); 5.84 (*s*, 1H); 6.98 (*d*, *J* = 2.4 Hz, 1H); 7.09 (*t*, *J* = 7.4 Hz, 1H); 7.15 – 7.19 (*m*, 1H); 7.34 (*d*, *J* = 8.1 Hz, 1H); 7.63 (*d*, *J* = 7.9 Hz, 1H); 8.67 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.73, 19.88, 28.38, 28.69, 31.30, 39.25, 55.40, 80.08, 110.60, 111.36, 118.90, 119.63, 122.16, 123.32, 127.47, 136.36, 155.61, 171.71.

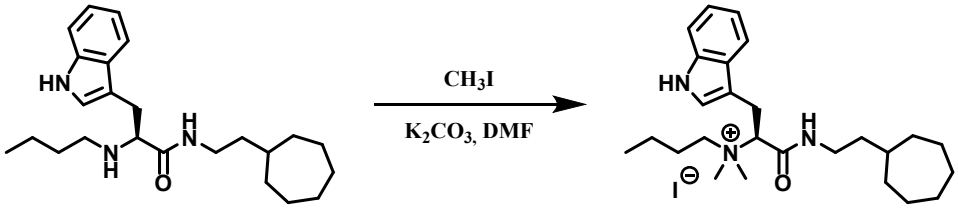


tert-Butyl (*S*)-(1-(butylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (275.6 mg, 0.767 mmol) was deprotected following *GP2* and (*S*)-2-amino-*N*-butyl-3-(1*H*-indol-3-yl)propanamide (185 mg, 93% yield) was immediately used futher.

S39 was prepared following *GP3* from (*S*)-2-amino-*N*-butyl-3-(1*H*-indol-3-yl)propanamide (185 mg, 0.713 mmol), 2-cycloheptylacetaldehyde[33] (1.1 eq., 110 mg) and sodium triacetoxyborohydride (1.5 eq., 226 mg), isolated by column chromatography on silica (DCM/MeOH = 50:1), and additionaly purified following *GP7*. Yield: 53.6 mg (0.140 mmol, 19.6%) of colourless oil. ESI-HRMS: *m/z* = 384.3009 (MH^+); $C_{24}H_{38}N_3O$ requires: *m/z* = 384.3009 (MH^+). ν_{max} 3305, 2919, 2851, 1649, 1525, 1457, 1354, 1215, 1094, 1010, 878, 740,

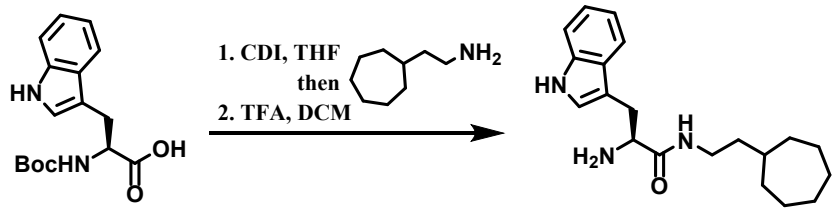
665 cm^{-1}. $[\alpha]_D^{r.t.}$ = –2.73 (*c* 0.19, MeOH). Purity: UPLC (254 nm): t_r = 4.587 min, 97.2% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (*t*, *J* = 7.3 Hz, 3H); 0.94 – 1.08 (*m*, 2H); 1.13 – 1.69 (*m*, 18H); 2.35 – 2.43 (*m*, 1H); 2.44 – 2.51 (*m*, 1H); 2.88 (*dd*, *J* = 8.8; 13.8 Hz, 1H); 3.18 – 3.40 (m, 4H); 7.06 (*d*, *J* = 2.3 Hz, 1H); 7.10 – 7.15 (*m*, 1H); 7.18 – 7.24 (*m*, 1H); 7.31 (*t*, *J* = 5.9 Hz, 1H); 7.37 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.69 (*dd*, *J* = 1.0; 7.9 Hz, 1H); 8.20 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.93, 20.23, 26.42, 26.48, 28.48, 28.53, 29.45, 31.88, 34.54, 36.85, 38.25, 38.74, 47.05, 63.70, 111.33, 112.07, 119.07, 119.77, 122.41, 122.86, 127.64, 136.53, 174.43.

(*S*)-*N*-(1-((2-Cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-*N*,*N*-dimethylbutan-1-aminium iodide (10)

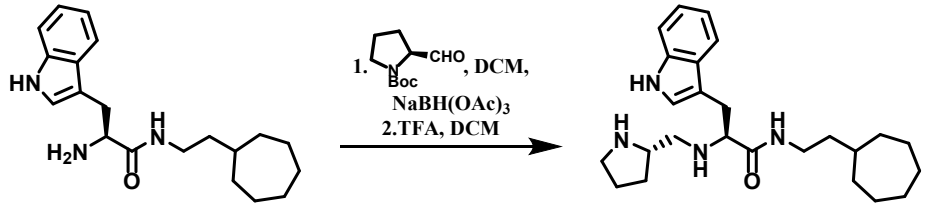


To a solution of **6** (22.5 mg, 0.0587 mmol) in MeCN (2 mL), iodomethane (2.0 eq., 16.7 mg) and potassium carbonate (6.0 eq., 48.6 mg) were added and the resulting mixture was stirred at r.t. for 48 h. Volatile components were evaporated *in vacuo* and the product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 10:1). Yield: 19.3 mg (0.0358 mmol, 60.9%) of beige solid; mp 121.4–125.8 °C. ESI-HRMS: *m/z* = 412.3312 (M^+); $C_{26}H_{42}N_3O$ requires: *m/z* = 412.3322 (MH^+). ν_{max} 3259, 3060, 2969, 2920, 2853, 2209, 1680, 1541, 1455, 1381, 1339, 1265, 1242, 1192, 1091, 1046, 1011, 987, 917, 879, 799, 745, 737, 645 cm^{-1}. $[\alpha]_D^{r.t.}$ = –21.0 (*c* 0.25, $CHCl_3$). Purity: UPLC (254 nm): t_r = 4.783 min, 95.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.72 – 0.81 (*m*, 1H); 0.82 – 0.92 (*m*, 3H); 1.00 (*t*, *J* = 7.3 Hz, 3H); 1.03 – 1.12 (*m*, 1H); 1.18 – 1.50 (*m*, 12H); 1.67 – 1.96 (*m*, 2H); 2.74 – 2.93 (*m*, 2H); 3.31 (*s*, 6H); 3.40 – 3.56 (*m*, 3H); 3.93 – 4.05 (*m*, 1H); 5.47 (*br s*, 1H); 7.07 – 7.12 (*m*, 1H); 7.13 – 7.18 (*m*, 1H); 7.38 (*d*, *J* = 7.6 Hz, 2H); 7.55 (*d*, *J* = 7.9 Hz, 1H); 7.86 (*br s*, 1H); 8.72 (*br s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.83, 19.86, 22.83, 24.87, 26.18, 26.19, 28.56, 28.57, 33.97, 34.05, 36.22, 36.50, 38.01, 48.92, 49.09, 63.22, 73.96, 106.51, 111.65, 118.53, 119.85, 122.22, 124.75, 127.06, 135.84, 165.66.

(*S*)-*N*-(2-Cycloheptylethyl)-3-(1*H*-indol-3-yl)-2-((((*S*)-pyrrolidin-2-yl)methyl)amino)propanamide (S40)



tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*tert*-butoxycarbonyl)-L-tryptophan (1.13 mmol, 344 mg), CDI (1.1 eq., 202 mg), and 2-cycloheptylethan-1-amine (1.1 eq, 176 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1), and immediately deprotected following *GP2* to afford (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide which was used further without purification. Yield: 334 mg (1.02 mmol, 90.5% over two steps) of yellowish semisolid.

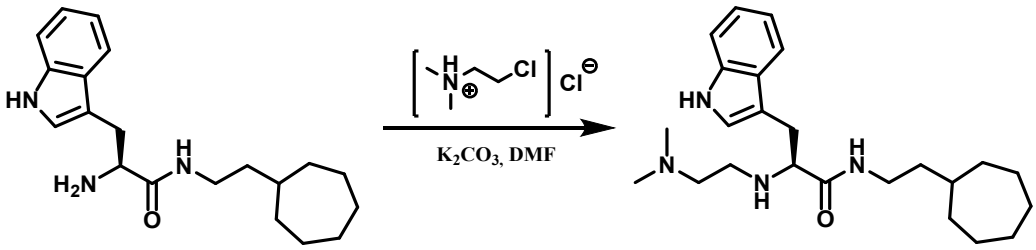


tert-Butyl (*S*)-2-((((*S*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)amino)methyl)pyrrolidine-1-carboxylate was prepared following *GP3* from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (212 mg, 0.647 mmol), *tert*-butyl (*S*)-2-formylpyrrolidine-1-carboxylate (1.1 eq., 142 mg) and sodium triacetoxyborohydride (1.5 eq., 205 mg). The product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1; 3. DCM/MeOH = 30:1). Yield: 193.6 mg (0.379 mmol, 58.6%) of beige oil, which was immediately used further.

tert-Butyl (*S*)-2-((((*S*)-1-((2-cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)amino)methyl)pyrrolidine-1-carboxylate (173 mg, 0.339 mmol) was deprotected following *GP2*, **S40** was isolated by column chromatography on basic alumina (1. Et_2O; 2. Et_2O/MeOH = 20:1; 3. Et_2O/MeOH = 10:1) and purified following *GP7*. Yield: 26.9 mg (0.066 mmol, 19.3%) of colourless oil. ESI-HRMS: *m/z* = 411.3109 (MH^+); $C_{25}H_{39}N_4O$ requires: *m/z* = 411.3118 (MH^+). ν_{max} 3272, 2917, 2850, 1647, 1524, 1456, 1355, 1231, 1104, 1010, 738 cm^{-1}. $[\alpha]_D^{r.t.} = -18.5$ (*c* 0.05, MeOH). Purity: UPLC (254 nm): t_r = 4.063 min, 88.5% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.08 – 1.23 (*m*, 3H); 1.25 (*s*, 1H); 1.32 – 1.76 (*m*, 17H); 2.37 (*dd*,

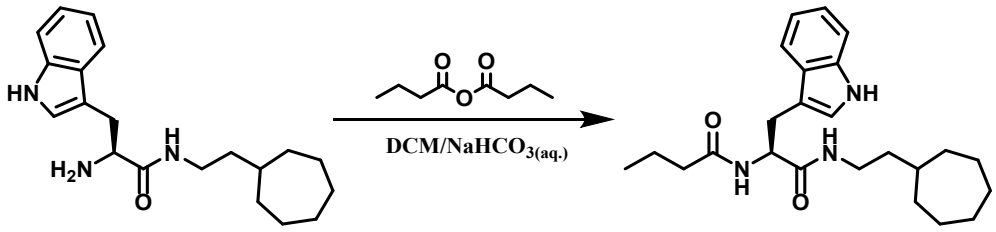
J = 7.9; 11.8 Hz, 1H); 2.49 (*dd*, *J* = 5.1; 11.7 Hz, 1H); 2.78 (*t*, *J* = 6.8 Hz, 2H); 2.91 (*dd*, *J* = 9.0; 14.4 Hz, 1H); 2.98 – 3.08 (*m*, 1H); 3.16 – 3.41 (*m*, 4H); 7.05 (*d*, *J* = 2.0 Hz, 1H); 7.09 – 7.15 (*m*, 1H); 7.16 – 7.22 (*m*, 1H); 7.32 (*t*, *J* = 5.7 Hz, 1H, NH); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.68 (*d*, *J* = 7.9 Hz, 1H); 8.33 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.64, 26.47, 28.57, 29.43, 29.74, 34.47, 34.49, 36.99, 37.32, 37.72, 46.54, 54.17, 58.82, 63.71, 111.40, 111.58, 118.97, 119.48, 122.14, 123.11, 127.56, 136.56, 174.38.

(*S*)-*N*-(2-Cycloheptylethyl)-2-((2-(dimethylamino)ethyl)amino)-3-(1*H*-indol-3-yl)propanamide (S41)



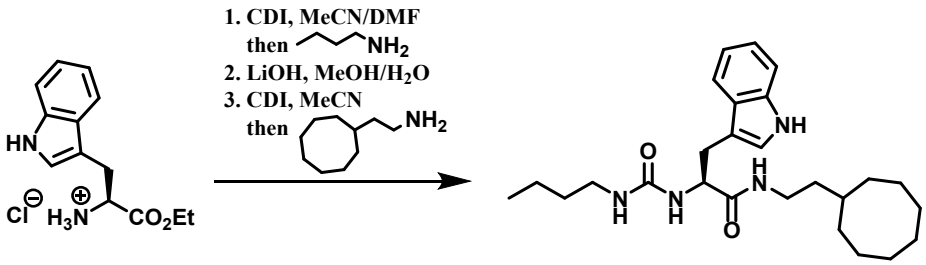
S41 was prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (prepared as described under **S40**) (270 mg, 0.823 mmol), 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (2.0 eq., 500 mg) and potassium carbonate (4.0 eq., 454 mg) in DMF (5 mL). The reaction mixture was stirred at 50 °C for 24 h, diluted with water (25 mL), extracted with Et_2O (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. **S41** was isolated by column chromatography on silica (DCM/MeOH = 10:1) and additionally purified following *GP7*. Yield: 6.0 mg (0.015 mmol, 1.8%) of colourless semisolid. ESI-HRMS: *m/z* = 399.3117 (MH^+); $C_{24}H_{39}N_4O$ requires: *m/z* = 399.3118 (MH^+). ν_{max} 3276, 3060, 2922, 2853, 2776, 1727, 1651, 1528, 1454, 1353, 1262, 1235, 1139, 1104, 1042, 1008, 949, 739, 690, 875 cm^{-1}. $[\alpha]_D^{r.t.} = -60.0$ (*c* 0.013, acetone). Purity: UPLC (254 nm): t_r = 4.067 min, 96.5% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.13 – 1.23 (*m*, 2H); 1.35 – 1.71 (*m*, 14H); 2.15 (*s*, 6H); 2.28 – 2.42 (*m*, 2H); 2.48 – 2.54 (*m*, 1H); 2.55 – 2.62 (*m*, 1H); 2.88 (*dd*, *J* = 9.4; 14.4 Hz, 1H); 3.22 – 3.29 (*m*, 2H); 3.31 – 3.43 (*m*, 2H); 7.07 (*s*, 1H); 7.10 (*t*, *J* = 7.5 Hz, 1H); 7.18 (*t*, *J* = 7.5 Hz, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.48 (*t*, *J* = 5.9 Hz, 1H); 7.68 (*d*, *J* = 7.9 Hz, 1H); 8.48 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.48, 28.63, 29.53, 34.50, 34.53, 37.05, 37.50, 37.77, 44.63, 45.63, 58.61, 63.62, 111.38, 111.65, 119.07, 119.61, 122.27, 123.35, 127.45, 136.58, 174.29.

(*S*)-*N*-(1-((2-Cycloheptylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)butyramide (11)



(*S*)-2-Amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)propanamide (prepared as described under **S40**) (241.7 mg, 0.738 mmol) was dissolved in DCM (20 mL), 0.25 M $NaOH_{(aq)}$ (20 mL) and butyric anhydride (1.2 eq., 140 mg) were added and the reaction mixture was vigorously stirred for 20 min at r.t.. Then $NaHCO_3$ (aq. sat., 10 mL) was added, the two phases were separated, the organic phase was dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was purified by column chromatography on silica (PE/EtOAc = 1:2). Yield: 190.2 mg (0.478 mmol, 64.8%) of colourless solid; mp 81.3–88.3 °C. ESI-HRMS: *m/z* = 398.2804 (MH^+); $C_{24}H_{36}N_3O_2$ requires: *m/z* = 398.2802 (MH^+). ν_{max} 3408, 3274, 3081, 2919, 2851, 1633, 1539, 1457, 1353, 1284, 1231, 1094, 1010, 738 cm^{-1}. $[\alpha]_D^{r.t.}$ = +6.82 (*c* 0.15, MeOH). Purity: UPLC (254 nm): t_r = 4.890 min, 97.0% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.89 (*t*, *J* = 7.3 Hz, 3H); 1.01 – 1.17 (*m*, 4H); 1.19 – 1.68 (*m*, 13H); 2.15 (*t*, *J* = 7.3 Hz, 2H); 3.01 – 3.17 (*m*, 3H); 3.23 – 3.36 (*m*, 1H); 4.74 (*s*, 1H); 5.79 (*s*, 1H); 6.51 (*s*, 1H); 7.02 (*s*, 1H); 7.11 (*t*, *J* = 7.4 Hz, 1H); 7.18 (*t*, *J* = 7.5 Hz, 1H); 7.35 (*d*, *J* = 8.0 Hz, 1H); 7.69 (*d*, *J* = 7.8 Hz, 1H); 8.39 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$) for both conformers: δ 13.79, 19.09, 26.31, 28.53, 28.55, 28.82, 34.30, 34.38, 36.74, 37.26, 37.89, 37.91, 38.57, 38.58, 54.06, 110.99, 111.05, 111.36, 111.37, 118.97, 119.00, 119.76, 119.81, 122.27, 122.32, 123.14, 123.17, 127.49, 127.51, 136.29, 171.43, 173.25.

(*S*)-2-(3-Butylureido)-*N*-(2-cyclooctylethyl)-3-(1*H*-indol-3-yl)propanamide (S42)



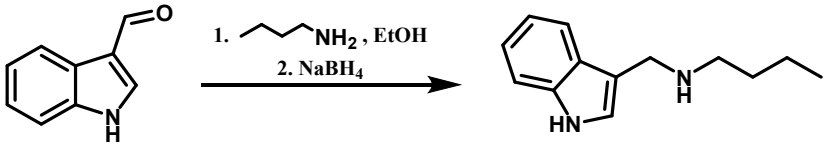
Ethyl (butylcarbamoyl)-L-tryptophanate was prepared following the procedure from Duspara et al.[34]: L-tryptophan ethyl ester hydrochloride (538.3 mg, 2.0 mmol) and CDI (1.1 eq., 357 mg) in MeCN (2 mL) and DMF (0.2 mL) were stirred at r.t. for 2 h before *n*-butylamine (2 eq.,

293 mg) was added and the stirring continued for 12 h. The reaction mixture was diluted with DCM (40 mL), extracted with 1 M $HCl_{(aq)}$ (2 x 20 mL), the organic phase was separated, dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. The product was purified by column chromatography on silica (PE/EtOAc = 1:1). Yield: 651 mg (1.964 mmol, 98.2%) of beige solid.

Ethyl (butylcarbamoyl)-*L*-tryptophanate (607 mg, 1.832 mmol) was saponified with 2M $LiOH_{(aq)}$ (5 mL) in MeOH (20 mL) at 60 °C for 8 h. The reaction mixture was then concentrated *in vacuo*, diluted with water (10 mL), extracted with EtOAc (2 x 10 mL) and organic extracts discarded. The aqueous phase was acidified (pH 1) with concentrated HCl, extracted with EtOAc (2 x 30 mL), dried over sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford (butylcarbamoyl)-L-tryptophan, which was immediately used further after azeotropical removal of water with toluene.

S42 was prepared following *GP1* from (butylcarbamoyl)-L-tryptophan (268.5 mg, 0.885 mmol), CDI (1.1 eq., 157.9 mg) and **9-1** (1.1 eq., 150.7 mg) in MeCN, and isolated by column chromatography on silica (1. PE/EtOAc = 2:1; 2. PE/EtOAc = 1:1). Yield: 218.8 mg (0.497 mmol, 24.8% over three steps) of beige solid; mp 132.7–134.7 °C. ESI-HRMS: *m/z* = 441.3229 (MH^+); $C_{26}H_{41}N_4O_2$ requires: *m/z* = 441.3224 (MH^+). ν_{max} 3345, 3285, 3109, 2917, 2851, 1622, 1561, 1456, 1429, 1345, 1308, 1263, 1231, 1094, 1069, 1013, 965, 886, 796, 766, 740, 687 cm^{-1}. $[\alpha]_D^{r.t.}$ = –0.47 (*c* 0.35, MeOH). Purity: UPLC (254 nm): t_r = 5.060 min, 100% total area. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.85 (*t*, *J* = 7.2 Hz, 3H); 1.11 – 1.69 (*m*, 21H); 2.85 – 3.06 (*m*, 6H); 4.31 – 4.39 (*m*, 1H); 5.94 (*d*, *J* = 8.3 Hz, 1H); 6.03 (*t*, *J* = 5.7 Hz, 1H); 6.90 – 6.98 (*m*, 1H); 7.00 – 7.08 (*m*, 2H); 7.30 (*dt*, *J* = 0.9; 8.1 Hz, 1H); 7.53 (*d*, *J* = 7.8 Hz, 1H); 7.80 (*t*, *J* = 5.6 Hz, 1H); 10.79 (*s*, 1H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 13.73, 19.54, 24.85, 25.76, 26.82, 29.05, 31.59, 32.12, 33.89, 36.67, 37.07, 38.81, 53.70, 110.17, 111.16, 118.08, 118.56, 120.76, 123.31, 127.55, 136.00, 157.43, 172.11.

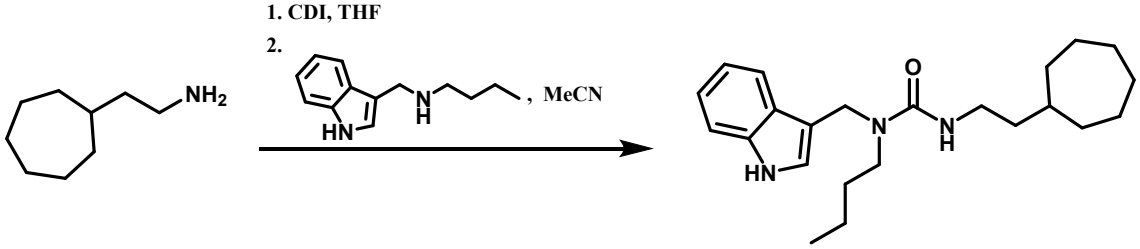
***N*-((1*H*-Indol-3-yl)methyl)butan-1-amine (S43-1)**



1*H*-Indole-3-carbaldehyde (741 mg, 5.104 mmol), *n*-butyl amine (1.5 eq., 504 µL) and anhydrous sodium sulfate (1.0 g) in absolute ethanol (10 mL) were stirred at r.t. for 12 h, before sodium borohydride (1.5 eq., 290 mg) was added, and stirring continued for 2 h. Volatile

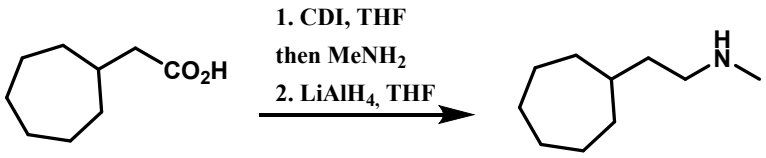
components were evaporated *in vacuo*, water (10 mL) was added, extracted with DCM (2 x 20 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. *N*-((1*H*-indol-3-yl)methyl)butan-1-amine[35] was isolated by column chromatography on silica (DCM/MeOH = 20:1). Yield: 435.8 mg (2.154 mmol, 42.2%) of yellowish oil. ESI-HRMS: *m/z* = 203.154 (MH^+); $C_{13}H_{19}N_2$ requires: *m/z* = 203.1543 (MH^+); ν_{max} 3409, 3161, 3055, 2955, 2926, 2869, 1619, 1549, 1454, 1338, 1234, 1094, 1009, 813, 737 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (*t*, *J* = 7.3 Hz, 3H); 1.28 – 1.41 (*m*, 2H); 1.49 – 1.57 (*m*, 2H); 2.03 (*s*, 1H); 2.68 – 2.76 (*m*, 2H); 3.99 (*s*, 2H); 7.07 – 7.15 (*m*, 2H); 7.16 – 7.20 (*m*, 1H); 7.28 – 7.35 (*m*, 1H); 7.64 (*d*, *J* = 7.9 Hz, 1H); 8.49 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.16, 20.67, 32.17, 44.80, 49.47, 111.36, 114.72, 118.78, 119.56, 122.12, 122.84, 127.18, 136.43.

1-((1*H*-Indol-3-yl)methyl)-1-butyl-3-(2-cycloheptylethyl)urea (S43)



2-Cycloheptylethan-1-amine (192.8 mg, 1.365 mmol) and CDI (1.05 eq., 232 mg) in anhydrous THF (1 mL) were stirred under argon at r.t. for 1 h, then **S43-1** (1 eq., 276 mg) in MeCN (2 mL) was added, and reaction mixture stirred at r.t. for 12 h. Volatile components were evaporated *in vacuo* and the product isolated by column chromatography on silica (PE/EtOAc = 2:1). Yield: 342.7 mg (0.927 mmol, 67.9%) of beige solid. mp 114–117 °C; $C_{23}H_{35}N_3O$ requires: C, 74.75; H, 9.55; N, 11.37; found: C, 74.46; H, 9.93; N, 11.31; ESI-HRMS: m/z = 370.2852 (MH^+); $C_{23}H_{36}N_3O$ requires: m/z = 370.2853 (MH^+); ν_{max} 3254, 2918, 2852, 2153, 1594, 1521, 1490, 1453, 1436, 1409, 1356, 1299, 1261, 1228, 1163, 1102, 1071, 1033, 1011, 937, 876, 827, 777, 737, 629 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (*t*, *J* = 7.3 Hz, 3H); 1.07 – 1.16 (*m*, 1H); 1.28 – 1.36 (*m*, 7H); 1.37 – 1.63 (*m*, 11H); 3.16 – 3.24 (*m*, 2H); 3.27 – 3.34 (*m*, 2H); 4.41 (*t*, *J* = 5.5 Hz, 1H); 4.62 (*s*, 2H); 7.10 (*d*, *J* = 2.4 Hz, 1H); 7.11 – 7.16 (*m*, 1H); 7.20 – 7.24 (*m*, 1H); 7.39 (*d*, *J* = 8.2 Hz, 1H); 7.63 (*d*, *J* = 7.9 Hz, 1H); 8.40 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.07, 20.39, 26.47, 28.61, 30.76, 34.52, 36.96, 38.50, 39.22, 42.77, 47.09, 111.46, 113.05, 119.08, 119.89, 122.55, 122.65, 126.47, 136.72, 158.42.

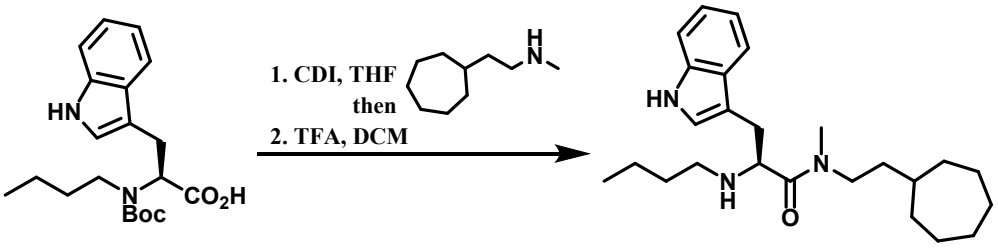
2-Cycloheptyl-*N*-methylethan-1-amine (S44-1)



2-Cycloheptyl-*N*-methylacetamide[23] was prepared following *GP1* from 2-cycloheptylacetic acid (260.6 mg, 1.668 mmol), CDI (2.0 eq., 541 mg) and methylamine solution (2.5 eq., 33 wt% in EtOH, 519 µL) in THF. The reaction mixture was concentrated *in vacuo*, diluted with DCM (30 mL) and extracted with 1 M $HCl_{(aq)}$ (2 x 15 mL) to remove imidazole and unreacted methylamine, dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford 2-cycloheptyl-*N*-methylacetamide (253.3 mg, 1.496 mmol).

Following *GP5*, 2-cycloheptyl-*N*-methylacetamide (253.3 mg, 1.496 mmol) was reduced to 2-cycloheptyl-*N*-methylethan-1-amine[36]. Yield: 142 mg (0.914 mmol, 61.1% over two steps) of colourless oil. ESI-HRMS: *m/z* = 156.1746 (MH^+); $C_{10}H_{22}N$ requires: *m/z* = 156.1747 (MH^+). ν_{max} 3307, 2915, 2850, 2794, 1624, 1542, 1459, 1383, 1304, 1264, 1115, 1040, 948, 813, 737 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.14 – 1.23 (*m*, 2H); 1.37 – 1.72 (*m*, 14H); 2.43 (*s*, 3H); 2.53 – 2.59 (*m*, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.56, 28.66, 34.86, 36.81, 37.42, 38.47, 50.51.

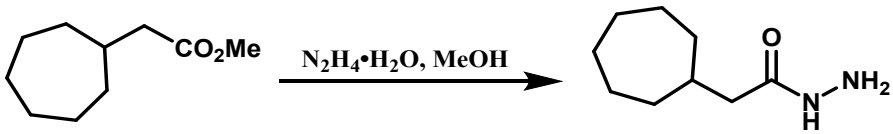
(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)-*N*-methylpropanamide (S44)



tert-Butyl (*S*)-butyl(1-((2-cycloheptylethyl)(methyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (230 mg, 0.638 mmol), CDI (1.1 eq, 114 mg), and **S44-1** (1.2 eq., 109 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 2:1) and immediately deprotected following *GP2*. **S44** was isolated by column chromatography on silica (1. PE/EtOAc = 1:1; 2. EtOAc). Yield: 79.3 mg (0.199 mmol, 31.3% over two steps) of colourless semisolid. ESI-HRMS: *m/z* = 398.3156 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3269, 3056, 2919, 2852, 1617, 1456, 1402, 1353, 1234, 1101, 1069, 1010, 970 cm^{-1}. $[\alpha]_D^{r.t.}$ = +56.9 (*c* 0.40, MeOH). Purity: UPLC (254 nm): t_r = 4.780

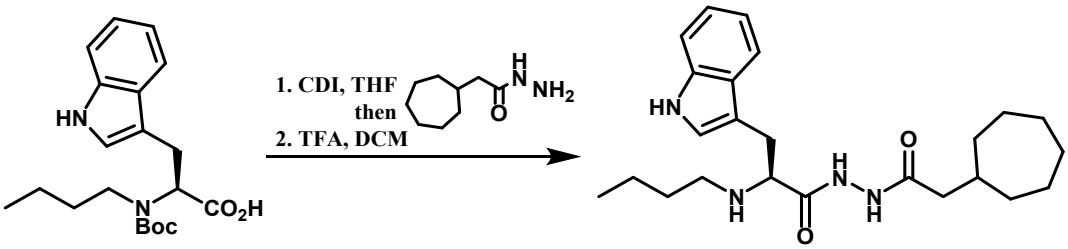
min, 97.7% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.81 – 0.96 (*m*, 5H); 0.98 – 1.69 (*m*, 17H); 2.23 (br *s*, 1H, NH); 2.36 – 2.91 (*m*, 6H); 2.95 – 3.06 (*m*, 1H); 3.09 – 3.36 (*m*, 2H); 3.77 – 3.91 (*m*, 1H); 6.98 (*dd*, *J* = 2.2; 11.4 Hz, 1H); 7.04 – 7.11 (*m*, 1H); 7.12 – 7.18 (*m*, 1H); 7.33 (*dd*, *J* = 1.7; 8.1 Hz, 1H); 7.60 (*t*, *J* = 8.8 Hz, 1H); 8.84 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.05, 14.07, 20.53, 26.26, 26.45, 26.50, 28.22, 28.29, 28.44, 28.49, 30.06, 30.40, 32.51, 32.56, 33.65, 34.13, 34.31, 34.38, 34.66, 34.67, 34.96, 36.49, 36.89, 36.95, 46.56, 47.44, 47.91, 48.04, 58.82, 58.89, 111.25, 111.28, 111.52, 111.61, 118.61, 118.68, 119.26, 119.29, 121.77, 121.84, 122.93, 123.10, 127.67, 136.22, 136.25, 174.77, 175.06. The signals in NMR spectra double due to the presence of two major conformers.

2-Cycloheptylacetohydrazide (S45-1)



Methyl 2-cycloheptylacetate[37] (561 mg, 3.295 mmol) and hydrazine hydrate (16 eq., 3 mL) in MeOH (10 mL) were stirred at 60 °C for 12 h. The reaction mixture was poured into water (50 mL), extracted with EtOAc (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford pure 2-cycloheptylacetohydrazide. Yield: 444 mg (2.608 mmol, 79%) of white solid. mp 86.1–87.9 °C. ESI-HRMS: *m/z* = 171.1489 (MH^+); $C_9H_{19}N_2O$ requires: *m/z* = 171.1492 (MH^+). ν_{max} 3334, 3259, 3041, 2918, 2851, 1630, 1529, 1448, 1372, 1305, 1214, 1165, 1047, 993, 922, 898, 772, 714, 631 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.14 – 1.25 (*m*, 2H); 1.39 – 1.53 (*m*, 4H); 1.54 – 1.67 (*m*, 4H); 1.67 – 1.75 (*m*, 2H); 1.98 – 2.09 (*m*, 3H); 3.94 (*s*, 2H); 6.96 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.28, 28.29, 34.66, 36.86, 43.19, 173.62.

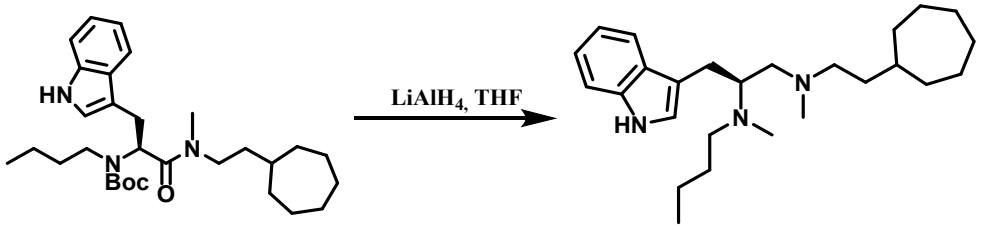
(*S*)-2-(Butylamino)-*N*′-(2-cycloheptylacetyl)-3-(1*H*-indol-3-yl)propanehydrazide (S45)



tert-Butyl (*S*)-butyl(1-(2-(2-cycloheptylacetyl)hydrazineyl)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from **S8-1** (201 mg, 0.558 mmol), CDI (1.1 eq, 99.6 mg) and **S45-1** (1.1 eq., 104.5 mg) in THF, isolated by column chromatography on silica

(PE/EtOAc = 1:1), and immediately deprotected following *GP2* – however aqueous phase was only neutralized (pH 7) prior to extraction. **S45** was isolated by column chromatography on silica (1. DCM/MeOH = 50:1, 2. DCM/MeOH = 25:1). Yield: 69.4 mg (0.168 mmol, 30.1%) of colourless semisolid. ESI-HRMS: *m/z* = 413.2914 (MH^+); $C_{24}H_{37}N_4O_2$ requires: *m/z* = 413.2911 (MH^+). ν_{max} 3321, 3051, 2920, 2850, 1599, 1475, 1451, 1341, 1226, 1202, 1120, 1063, 1012, 982, 953, 922, 893, 872, 838, 815, 795, 777, 734 cm^{-1}. $[\alpha]_D^{r.t.}$ = +7.0 (*c* 0.14, MeOH). Purity: UPLC (254 nm): t_r = 4.233 min, 95.1% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.74 (*t*, *J* = 7.3 Hz, 3H); 1.07 – 1.33 (*m*, 7H); 1.39 – 1.51 (*m*, 5H); 1.53 – 1.66 (*m*, 4H); 1.70 – 1.78 (*m*, 2H); 2.00 – 2.12 (*m*, 1H); 2.20 (*d*, *J* = 7.2 Hz, 2H); 2.41 – 2.47 (*m*, 1H); 2.51 – 2.59 (*m*, 1H); 2.99 (*dd*, *J* = 9.1; 14.6 Hz, 1H); 3.37 (*dd*, *J* = 4.2; 14.6 Hz, 1H); 3.53 (*dd*, *J* = 4.2; 9.1 Hz, 1H); 7.04 (*s*, 1H); 7.08 – 7.14 (*m*, 1H); 7.17 – 7.22 (*m*, 1H); 7.36 (*d*, *J* = 8.1 Hz, 1H); 7.63 (*d*, *J* = 7.9 Hz, 1H); 8.38 (*s*, 1H); 9.20 (br *s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.18, 26.28, 28.32, 29.01, 32.10, 34.65, 36.84, 42.60, 48.87, 62.39, 111.00, 111.47, 118.72, 119.73, 122.40, 123.17, 127.47, 136.53, 169.38, 170.77.

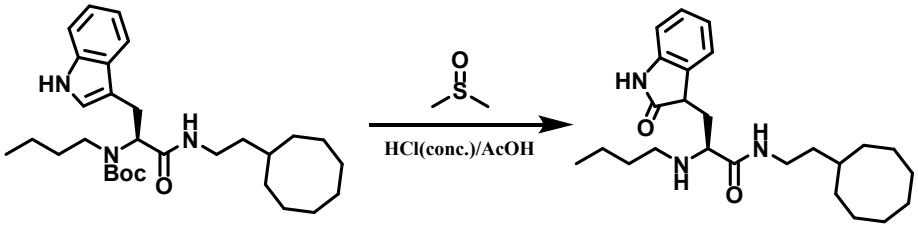
(*S*)-*N*^{2}-Butyl-*N*^{1}-(2-cycloheptylethyl)-3-(1*H*-indol-3-yl)-*N*^{1},*N*^{2}-dimethylpropane-1,2-diamine (12)



tert-Butyl (*S*)-butyl(1-((2-cycloheptylethyl)(methyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (prepared as described under **S44**) (141 mg, 0.284 mmol) was reduced following *GP5* – however 8.0 eq. of lithium aluminum hydride were used. The crude product was purified by column chromatography on silica (EtOAc/MeOH = 4:1). Yield: 21.3 mg (0.054 mmol, 18.9%) of brownish oil. ESI-HRMS: *m/z* = 398.3525 (MH^+); $C_{26}H_{44}N_3$ requires: *m/z* = 398.353 (MH^+). ν_{max} 3422, 3057, 3168, 2917, 2853, 2789, 1621, 1456, 1355, 1306, 1227, 1205, 1131, 1094, 1062, 1042, 1010, 934, 872, 828, 784, 732, 629 cm^{-1}. $[\alpha]_D^{r.t.}$ = –8.6 (*c* 0.12, acetone). Purity: UPLC (254 nm): t_r = 4.403 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.89 (*t*, *J* = 7.3 Hz, 3H); 1.03 – 1.13 (*m*, 2H); 1.22 – 1.63 (*m*, 17H); 2.14 (*s*, 3H); 2.22 – 2.31 (*m*, 3H); 2.35 (*s*, 3H); 2.50 – 2.60 (*m*, 3H); 2.66 (*dd*, *J* = 8.0; 14.6 Hz, 1H); 2.94 (*dd*, *J* = 5.4; 14.6 Hz, 1H); 3.06 – 3.15 (*m*, 1H); 7.02 (*d*, *J* = 2.0 Hz, 1H); 7.07 – 7.12 (*m*, 1H); 7.14 – 7.19 (*m*, 1H); 7.33 (*d*, *J* = 8.0 Hz, 1H); 7.62 (*d*, *J* = 7.8 Hz, 1H); 8.12 (*s*, 1H, NH). ^{13}C-NMR (126 MHz,

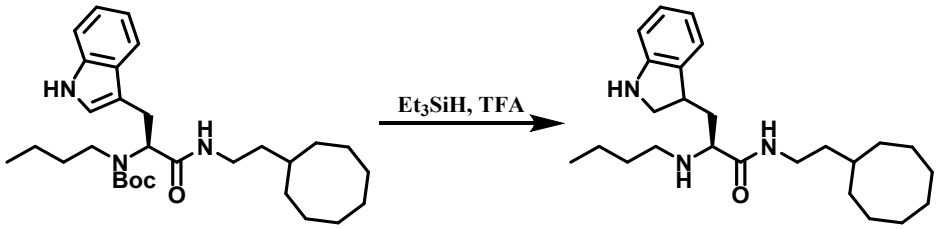
$CDCl_3$): δ 14.30, 20.84, 23.62, 26.57, 26.59, 28.61, 28.63, 30.86, 34.82, 34.86, 35.21, 37.22, 37.72, 43.07, 53.75, 56.54, 57.98, 61.45, 111.15, 114.96, 118.97, 119.13, 121.80, 122.34, 127.93, 136.35.

(2*S*)-2-(Butylamino)-*N*-(2-cyclooctylethyl)-3-(2-oxoindolin-3-yl)propanamide (S46)



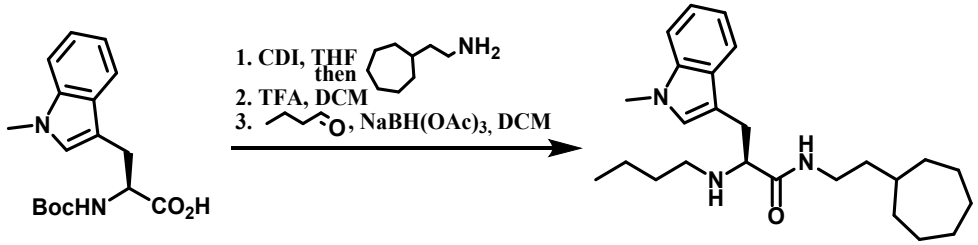
tert-Butyl (*S*)-butyl(1-((2-cyclooctylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (prepared as described under **9**) (185 mg, 0.372 mmol) was dissolved in acetic acid (2 mL), dimethyl sulfoxide (DMSO) (0.25 mL) and concentrated HCl (1 mL) were added, and the resulting dark blue solution was stirred at r.t. for 12 h. The reaction mixture was diluted with water (50 mL), neutralized with solid sodium bicarbonate, extracted with DCM (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. **S46** was isolated by column chromatography on silica (1. DCM/MeOH = 50:1; 2. DCM/MeOH = 10:1) and additionally purified following *GP7*. Yield: 45.7 mg (0.11 mmol, 29.7%) of colourless semisolid. Two diastereomers in a ratio of 1:1. ESI-HRMS: *m/z* = 414.3113 (MH^+); $C_{25}H_{40}N_3O_2$ requires: *m/z* = 414.3115 (MH^+). ν_{max} 3293, 3081, 2917, 2854, 1655, 1550, 1498, 1469, 1453, 1377, 1246, 1197, 1129, 908, 857, 746, 732, 645 cm^{-1}. $[\alpha]_D^{r.t.}$ = +8.1 (*c* 0.087, acetone). Purity: UPLC (254 nm): t_r = 4.650-4.700 min, 69.7% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for both diastereomers: δ 0.83 – 0.95 (*m*, 3H); 1.20 – 1.69 (*m*, 21H); 1.88 – 2.41 (*m*, 3H), 2.41 – 2.61 (*m*, 2H); 3.17 – 3.63 (*m*, 4H); 6.88 (*d*, *J* = 7.7 Hz, 1H); 6.98 – 7.10 (*m*, 1H); 7.16 – 7.47 (*m*, 3H); 8.59 – 8.86 (*m*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for both diastereomers: δ 14.09, 14.12, 20.49, 20.55, 25.48, 25.50, 25.51, 26.40, 27.30, 27.33, 32.26, 32.28, 32.31, 32.33, 32.50, 33.83, 34.96, 35.00, 37.46, 37.51, 37.86, 43.54, 44.29, 48.60, 48.67, 60.53, 61.53, 109.70, 109.88, 122.82, 122.84, 124.27, 124.93, 128.14, 128.23, 129.47, 129.64, 141.06, 141.32, 174.01, 174.07, 180.47, 180.85.

(2*S*)-2-(Butylamino)-*N*-(2-cyclooctylethyl)-3-(indolin-3-yl)propanamide (S47)



To a solution of *tert*-butyl (*S*)-butyl(1-((2-cyclooctylethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (prepared as described under **9**) (285 mg, 0.572 mmol) in TFA (2 mL) under argon, triethylsilane (2.0 eq., 91 µL) was added[38] and the reaction mixture was heated at 50 °C for 12 h. 1 M $NaOH_{(aq)}$ (40 mL) was added, extracted with Et_2O (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo*. **S47** was isolated by column chromatography on silica (1. DCM/MeOH = 50:1; 2. DCM/MeOH = 10:1) and purified following *GP7*. Yield: 110.8 mg (0.277 mmol, 48.5%) of colourless semisolid which quickly darkens on standing. Two diastereomers in a ratio of 60:40. ESI-HRMS: *m/z* = 400.332 (MH^+); $C_{25}H_{42}N_3O$ requires: *m/z* = 400.3322 (MH^+). ν_{max} 3271, 3050, 2920, 1660, 1571, 1467, 1432, 1179, 1131, 836, 798, 751, 721 cm^{-1}. $[\alpha]_D^{r.t.}$ = +25.0 (*c* 0.11, MeOH). Purity: UPLC (254 nm): t_r = 4.243 min, 90.6% total area. ^{1}H-NMR (500 MHz, $CDCl_3$) for both diastereomers: δ 0.85 – 0.94 (*m*, 3H); 1.22 – 1.82 (*m*, 23H); 1.90 – 2.16 (*m*, 2H); 2.40 – 2.57 (*m*, 2H); 3.04 – 3.50 (*m*, 5H); 3.66 – 3.80 (*m*, 1H); 6.60 – 6.67 (*m*, 1H); 6.68 – 6.75 (*m*, 1H); 6.99 – 7.09 (*m*, 1H); 7.12 – 7.18 (*m*, 1H); 7.22 (*t*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$) for both diastereomers: δ 14.10, 14.11, 14.28, 20.52, 22.81, 25.52, 25.54, 26.42, 26.44, 27.35, 31.74, 32.31, 32.34, 32.56, 34.96, 37.26, 37.30, 37.91, 38.85, 39.42, 39.46, 48.82, 53.25, 54.07, 61.93, 62.12, 109.75, 109.90, 118.77, 119.04, 123.92, 124.28, 127.92, 132.09, 132.32, 151.46, 174.29.

(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(1-methyl-1*H*-indol-3-yl)propanamide (S48)

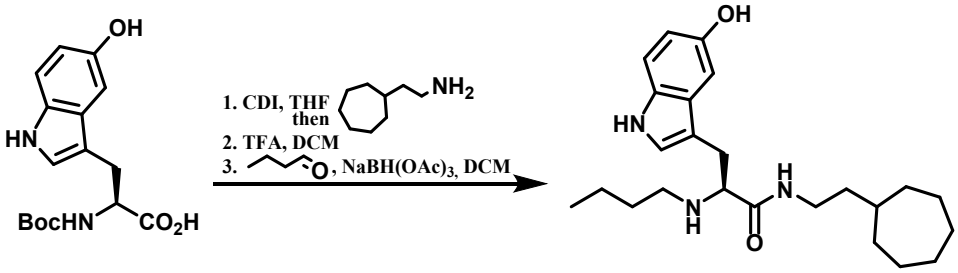


tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-3-(1-methyl-1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* fom N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*L*-tryptophan[39] (159 mg, 0.499 mmol), CDI (1.1 eq., 88.9 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 78 mg) in MeCN, isolated by column chromatography on silica (PE/EtOAc = 1:1), and immediately deprotected following *GP2* to (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1-methyl-1*H*-indol-3-yl)propanamide.

Following GP3, **S48** was prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1-methyl-1*H*-indol-3-yl)propanamide (138 mg, 0.404 mmol), *n*-butanal (1.1 eq., 40.3 µL) and sodium triacetoxyborohydride (1.5 eq., 128 mg). The title product was isolated by column

chromatography on silica (1. DCM; 2. DCM/MeOH = 100:1; 3. DCM/MeOH = 50:1). Yield: 22 mg (0.0553 mmol, 11.8%) of colourless semisolid. ESI-HRMS: *m/z* = 398.3166 (MH^+); $C_{25}H_{40}N_3O$ requires: *m/z* = 398.3166 (MH^+). ν_{max} 3322, 2919, 2852, 1654, 1520, 1461, 1375, 1327, 1249, 1129, 1013, 736 cm^{-1}. $[\alpha]_D^{r.t.} = -37.4$ (*c* 0.073, acetone). Purity: UPLC (254 nm): t_r = 4.803 min, 98.1% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.78 (*t*, *J* = 7.2 Hz, 3H); 0.82 – 0.91 (*m*, 2H); 1.13 – 1.74 (*m*, 18H); 2.43 (*t*, *J* = 7.1 Hz, 2H); 2.87 (*dd*, *J* = 8.9; 14.2 Hz, 1H); 3.15 – 3.25 (*m*, 1H); 3.26 – 3.37 (*m*, 3H); 3.76 (*s*, 3H); 6.90 (*s*, 1H); 7.09 – 7.14 (*m*, 1H); 7.21 – 7.26 (*m*, 2H); 7.28 – 7.32 (*m*, 1H); 7.65 – 7.69 (*m*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.91, 20.30, 26.49, 28.63, 28.87, 29.86, 31.84, 32.86, 34.52, 37.00, 37.44, 37.71, 48.54, 63.52, 109.41, 119.14, 119.31, 121.99, 127.82, 128.07, 137.23, 165.65.

(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(5-hydroxy-1*H*-indol-3-yl)propanamide (S49)

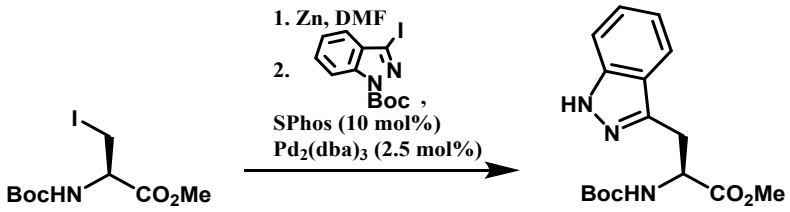


tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-3-(5-hydroxy-1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from *N*-Boc-*L*-5-hydroxytryptophan[40] (780 mg, 2.444 mmol), CDI (1.1 eq., 436 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 379 mg) in THF, and isolated by column chromatography on silica (PE/EtOAc = 3:1). Yield: 526 mg (1.186 mmol, 48.5%) of beige solid which was immediately deprotected following *GP2*.

Following *GP3*, **S49** was prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(5-hydroxy-1*H*-indol-3-yl)propanamide (333 mg, 0.972 mmol), *n*-butanal (1.1 eq., 96 µL) and sodium triacetoxyborohydride (1.5 eq., 309 mg). The title product was isolated by column chromatography on silica (1. PE/EtOAc = 2:1; 2. EtOAc), and additionally purified following *GP7*. Yield: 139 mg (0.348 mmol, 17.4% over three steps) of beige semisolid. ESI-HRMS: *m/z* = 400.2963 (MH^+); $C_{24}H_{38}N_3O_2$ requires: *m/z* = 400.2959 (MH^+). ν_{max} 3305, 2919, 2852, 1644, 1581, 1530, 1457, 1375, 1209, 1102, 935, 907, 796, 729 cm^{-1}. $[\alpha]_D^{r.t.} = -45.3$ (*c* 0.23, acetone). Purity: UPLC (254 nm): t_r = 4.257 min, 97.6% total area. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.75 (*t*, *J* = 7.3 Hz, 3H); 1.06 – 1.29 (*m*, 6H); 1.32 – 1.72 (*m*, 14H); 2.29 – 2.45 (*m*, 2H); 2.79 (*dd*, *J* = 9.3; 14.4 Hz, 1H); 3.15 – 3.43 (*m*, 4H); 6.82 (*dd*, *J* = 2.3; 8.7 Hz, 1H); 6.97 (*d*, *J* = 2.4 Hz,

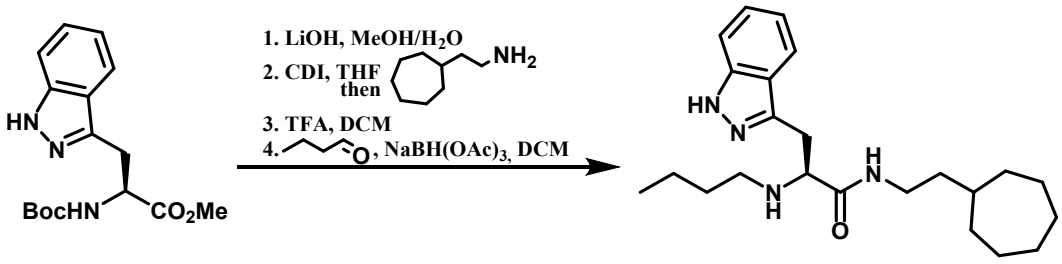
1H); 7.13 (*d*, *J* = 2.4 Hz, 1H); 7.19 (*d*, *J* = 8.7 Hz, 1H); 7.33 (*t*, *J* = 5.8 Hz, 1H); 8.21 (*d*, *J* = 1.7 Hz, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.97, 20.34, 26.47, 28.61, 29.80, 32.23, 34.47, 34.49, 36.93, 37.40, 37.64, 48.67, 62.96, 103.56, 111.04, 111.91, 112.69, 123.89, 128.06, 131.52, 150.60, 175.06.

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indazol-3-yl)propanoate (4)



Following *GP6*, prepared from zinc (2.4 eq., 573 mg), (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (1.2 eq., 1441.6 mg), *tert*-butyl 3-iodo-1*H*-indazole-1-carboxylate[41] (1256 mg, 3.65 mmol), $Pd_2(dba)_3$ (2.5 mol%, 83.5 mg) and SPhos (10 mol%, 149.8 mg) – however reaction time was prolonged to 72 h. **4** was isolated by column chromatography on silica (1. PE/EtOAc = 5:1; 2. PE/EtOAc = 1:1). Yield: 570.8 mg (1.787 mmol, 49%) of yellowish semisolid. ESI-HRMS: *m/z* = 320.1608 (MH^+); $C_{16}H_{22}N_3O_4$ requires: *m/z* = 320.1605 (MH^+). ν_{max} 3317, 2978, 1692, 1622, 1498, 1437, 1366, 1249, 1214, 1158, 1073, 1023, 907, 857, 729 cm^{-1}. $[\alpha]_D^{r.t.}$ = +19.3 (*c* 0.60, acetone). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.30 (*s*, 9H); 3.30 (*d*, *J* = 7.1 Hz, 2H); 3.57 (*s*, 3H); 4.43 (*q*, *J* = 7.2 Hz, 1H); 7.05 – 7.11 (*m*, 1H); 7.23 (*d*, *J* = 8.2 Hz, 1H); 7.29 – 7.35 (*m*, 1H); 7.43 – 7.50 (*m*, 1H); 7.69 – 7.75 (*m*, 1H); 12.80 (*s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.20, 29.07, 52.39, 52.85, 79.85, 110.31, 119.53, 120.37, 122.26, 126.60, 140.94, 141.31, 155.62, 172.80.

(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(1*H*-indazol-3-yl)propanamide (S50)



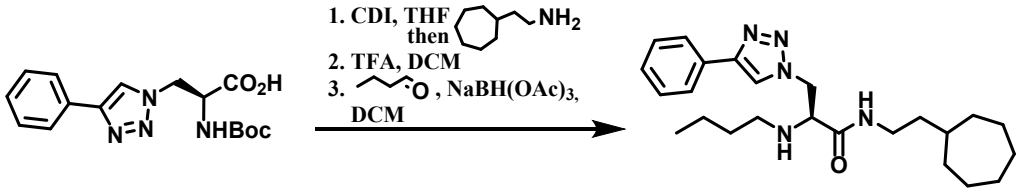
4 (530 mg, 1.66 mmol) and 2M $LiOH_{(aq)}$ (4.0 eq., 3.3 mL) in MeOH (6 mL) were stirred at r.t. until TLC indicated a complete conversion. Volatile components were evaporated *in vacuo*, the aqueous residue acidified (pH 3) with citric acid (aq., 20%), extracted with EtOAc (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to

afford (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indazol-3-yl)propanoic acid (488.2 mg, 1.599 mmol) as beige solid which was immediately used further without purification.

tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-3-(1*H*-indazol-3-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indazol-3-yl)propanoic acid (200 mg, 0.655 mmol), CDI (1.1 eq., 117 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 92 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1), and immediately deprotected following *GP2*.

Following *GP3*, **S50** was prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(1*H*-indazol-3-yl)propanamide (105.1 mg, 0.320 mmol), *n*-butanal (1.1 eq., 32 µL) and sodium triacetoxyborohydride (1.5 eq., 102 mg). The title product was isolated by column chromatography on silica (1. DCM; 2. DCM/MeOH = 50:1). Yield: 62.7 mg (0.163 mmol, 24% over 4 steps) of yellowish semisolid. ESI-HRMS: *m/z* = 385.296 (MH^+); $C_{23}H_{37}N_4O$ requires: *m/z* = 385.2962 (MH^+). ν_{max} 3218, 3079, 2920, 2852, 1651, 1622, 1527, 1497, 1459, 1348, 1251, 1129, 1077, 1004, 906, 741 cm^{-1}. $[\alpha]_D^{r.t.}$ = –6.19 (*c* 0.42, acetone). Purity: UPLC (254 nm): t_r = 4.557 min, 98.8% total area. ^{1}H-NMR (500 MHz $CDCl_3$): δ 0.71 (*t*, *J* = 7.3 Hz, 3H); 1.00 – 1.60 (*m*, 19H); 2.03 (br *s*, 1H); 2.36 (*t*, *J* = 6.9 Hz, 2H); 3.06 – 3.16 (*m*, 2H); 3.17 – 3.26 (*m*, 1H); 3.39 (*dd*, *J* = 4.0; 8.8 Hz, 1H); 3.46 (*dd*, *J* = 4.0; 14.4 Hz, 1H); 7.00 – 7.07 (*m*, 1H); 7.25 – 7.31 (*m*, 1H); 7.35 – 7.46 (*m*, 2H); 7.68 (*d*, *J* = 8.1 Hz, 1H); 10.83 (br *s*, 1H, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.94, 20.31, 26.42, 28.55, 28.56, 30.58, 32.24, 34.39, 34.44, 36.88, 37.32, 37.58, 48.63, 62.30, 109.93, 120.45, 120.63, 122.25, 126.93, 141.26, 143.60, 174.09.

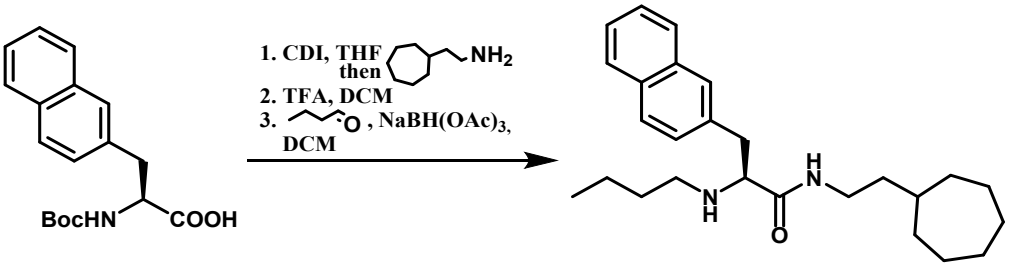
(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanamide (S51)



tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-1-oxo-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-yl)carbamate was prepared following *GP1* from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoic acid[42] (370 mg, 1.11 mmol), CDI (1.1 eq, 199 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 172 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 3:1), and immediately deprotected following *GP2*.

Following *GP3*, **S51** was prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanamide (232 mg, 0.653 mmol), *n*-butanal (1.1 eq., 65 µL) and sodium triacetoxyborohydride (1.5 eq., 208 mg). (*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanamide (**S51**) was isolated by column chromatography on silica (1. PE/EtOAc = 4:1; 2. PE/EtOAc = 3:1). Yield: 211 mg (0.513 mmol, 46.2% over three steps) of white solid; mp 64.1–65.3 °C. ESI-HRMS: *m/z* = 412.3061 (MH^+); $C_{24}H_{38}N_5O$ requires: *m/z* = 412.3071 (MH^+). ν_{max} 3305, 3085, 2921, 2853, 1646, 1544, 1463, 1442, 1358, 1302, 1223, 1176, 1140, 1088, 1048, 1028, 978, 911, 858, 787, 763, 710 cm^{-1}. $[\alpha]_D^{r.t.}$ = +0.38 (*c* 0.37, acetone). Purity: UPLC (254 nm): t_r = 4.580 min, 99.1% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.90 (*t*, *J* = 7.3 Hz, 3H); 1.06 – 1.15 (*m*, 2H); 1.27 – 1.64 (*m*, 17H); 1.80 (br *s*, 1H); 2.52 – 2.59 (*m*, 1H); 2.70 – 2.78 (*m*, 1H); 3.13 – 3.25 (*m*, 2H); 3.47 (*dd*, *J* = 3.8; 5.5 Hz, 1H); 4.74 (*dd*, *J* = 3.8; 14.0 Hz, 1H); 4.81 (*dd*, *J* = 5.5; 13.9 Hz, 1H); 7.30 – 7.35 (*m*, 1H); 7.38 – 7.45 (*m*, 2H); 7.49 (*t*, *J* = 5.9 Hz, 1H); 7.78 – 7.85 (*m*, 2H); 7.87 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.95, 20.29, 26.22, 26.25, 28.46, 28.48, 32.23, 34.26, 34.29, 36.79, 37.53, 37.57, 48.30, 50.34, 62.58, 121.06, 125.67, 128.25, 128.87, 130.36, 147.87, 170.62.

(*S*)-2-(Butylamino)-*N*-(2-cycloheptylethyl)-3-(naphthalen-2-yl)propanamide (S52)

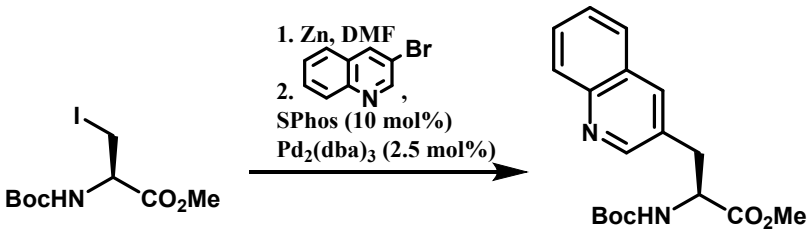


tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamate was prepared following *GP1* from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)propanoic acid (315 mg, 1.0 mmol), CDI (1.1 eq, 179 mg) and 2-cycloheptylethan-1-amine (1.2 eq., 156 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 4:1), and immediately deprotected following *GP2*.

S52 was prepared following *GP3* from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(naphthalen-2-yl)propanamide (295 mg, 0.87 mmol), *n*-butanal (1.1 eq., 86 µL) and sodium triacetoxyborohydride (1.5 eq., 277 mg). The title product was isolated by column chromatography on silica (PE/EtOAc = 3:1) and additionally purified following *GP7*. Yield: 80.3 mg (0.203 mmol, 20.3%) of colourless oil. ESI-HRMS: *m/z* = 395.3054 (MH^+); $C_{26}H_{39}N_2O$ requires: *m/z* = 395.3057 (MH^+). ν_{max} 3313, 3050, 2914, 2850, 1643, 1599, 1525,

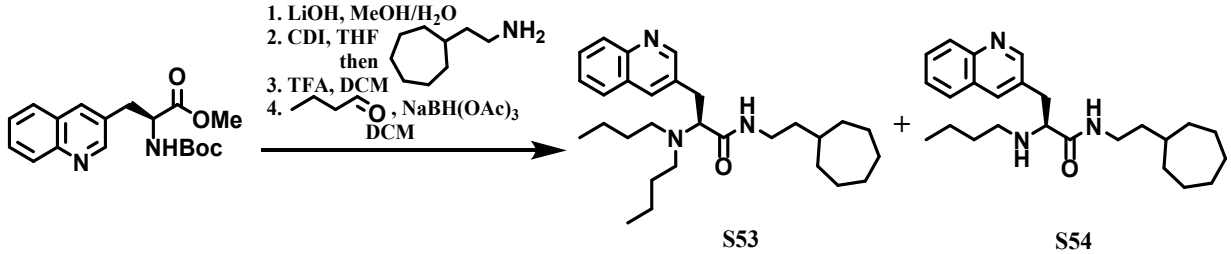
1461, 1444, 1373, 1333, 1240, 1121, 1015, 959, 895, 845, 821, 744, 643 cm^{-1}. $[\alpha]_D^{r.t.}$ = –19.3 (*c* 0.08, acetone). Purity: UPLC (254 nm): t_r = 4.823 min, 100% total area. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (*t*, *J* = 7.3 Hz, 3H); 1.10 – 1.71 (*m*, 20H); 2.36 – 2.47 (m, 2H); 2.80 – 2.88 (*m*, 1H); 3.18 – 3.40 (*m*, 4H); 7.23 – 7.29 (*m*, 1H); 7.34 – 7.39 (*m*, 1H); 7.41 – 7.49 (*m*, 2H); 7.63 (*d*, *J* = 1.7 Hz, 1H); 7.75 – 7.82 (*m*, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 13.93, 20.32, 26.47, 28.60, 32.23, 34.47, 34.49, 36.95, 37.27, 37.77, 39.79, 48.74, 64.10, 125.77, 126.31, 127.18, 127.62, 127.79, 127.91, 128.60, 132.51, 133.57, 135.44, 173.80.

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(quinolin-3-yl)propanoate (3)



Following *GP6*, prepared from zinc (2.4 eq., 365 mg), methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (919.5 mg, 1.2 eq.), 3-bromoquinoline (316 µL, 2.328 mmol), $Pd_2(dba)_3$ (2.5 mol%, 53.3 mg) and SPhos (10 mol%, 95.6 mg). **3** was isolated by column chromatography on silica (1. PE/EtOAc = 10:1; 2. PE/EtOAc = 5:1; 3. PE/EtOAc = 1:1) and additionally purified by column chromatography on silica (1. DCM/MeOH = 100:1; 2. DCM/MeOH = 50:1) to remove a fluorescent impurity. Yield: 331 mg (1.002 mmol, 43%) of beige solid; mp 90.1–91.8 °C. ESI-HRMS: *m/z* = 331.1657 (MH^+); $C_{18}H_{23}N_2O_4$ requires: *m/z* = 331.1652 (MH^+). ν_{max} 3351, 2977, 1742, 1705, 1496, 1437, 1391, 1365, 1249, 1208, 1159, 1055, 1016, 913, 851, 786, 751, 731 cm^{-1}. $[\alpha]_D^{r.t.}$ = –11.0 (*c* 0.45, acetone). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.31 (*s*, 9H); 3.15 (*dd*, *J* = 6.0; 14.1 Hz, 1H); 3.27 (*dd*, *J* = 5.7; 14.1 Hz, 1H); 3.64 (*s*, 3H); 4.59 (*q*, *J* = 6.5 Hz, 1H); 5.00 (*d*, *J* = 7.9 Hz, 1H); 7.42 – 7.48 (*m*, 1H); 7.57 – 7.62 (*m*, 1H); 7.68 (*d*, *J* = 8.1 Hz, 1H); 7.83 (*d*, *J* = 1.9 Hz, 1H); 7.99 (*d*, *J* = 8.4 Hz, 1H); 8.60 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.40, 35.89, 52.67, 54.41, 80.39, 127.02, 127.66, 128.02, 129.22, 129.30, 129.46, 136.18, 147.32, 151.88, 155.14, 171.92.

(*S*)-*N*-(2-Cycloheptylethyl)-2-(dibutylamino)-3-(quinolin-3-yl)propanamide (S53) and (*S*)-2-(butylamino)-*N*-(2-cycloheptylethyl)-3-(quinolin-3-yl)propanamide (S54)



3 (300 mg, 0.908 mmol) and 2M $LiOH_{(aq)}$ (4.0 eq., 1.8 mL) in MeOH (5 mL) were stirred at r.t. until TLC indicated a complete conversion. Volatile components were evaporated *in vacuo*, the aqueous residue acidified (pH 3) with citric acid (aq., 20%), extracted with EtOAc (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and volatile components evaporated *in vacuo* to afford (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(quinolin-3-yl)propanoic acid (279 mg, 0.882 mmol) as beige solid which was immediately used further without purification.

tert-Butyl (*S*)-(1-((2-cycloheptylethyl)amino)-1-oxo-3-(quinolin-3-yl)propan-2-yl)carbamate was prepared following *GP1* from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(quinolin-3-yl)propanoic acid (279 mg, 0.882 mmol), CDI (1.1 eq., 157 mg) and 2-cycloheptylethan-1-amine (1.1 eq., 137 mg) in THF, isolated by column chromatography on silica (PE/EtOAc = 1:1), and immediately deprotected following *GP2*.

Following *GP3*, **S53** and **S54** were prepared from (*S*)-2-amino-*N*-(2-cycloheptylethyl)-3-(quinolin-3-yl)propanamide (269.8 mg, 0.795 mmol), *n*-butanal (1.1 eq., 79 µL), and sodium triacetoxyborohydride (1.5 eq., 253 mg). The title products were isolated by column chromatography on silica (1. PE/EtOAc = 2:1; 2. PE/EtOAc = 1:1; 3. EtOAc):

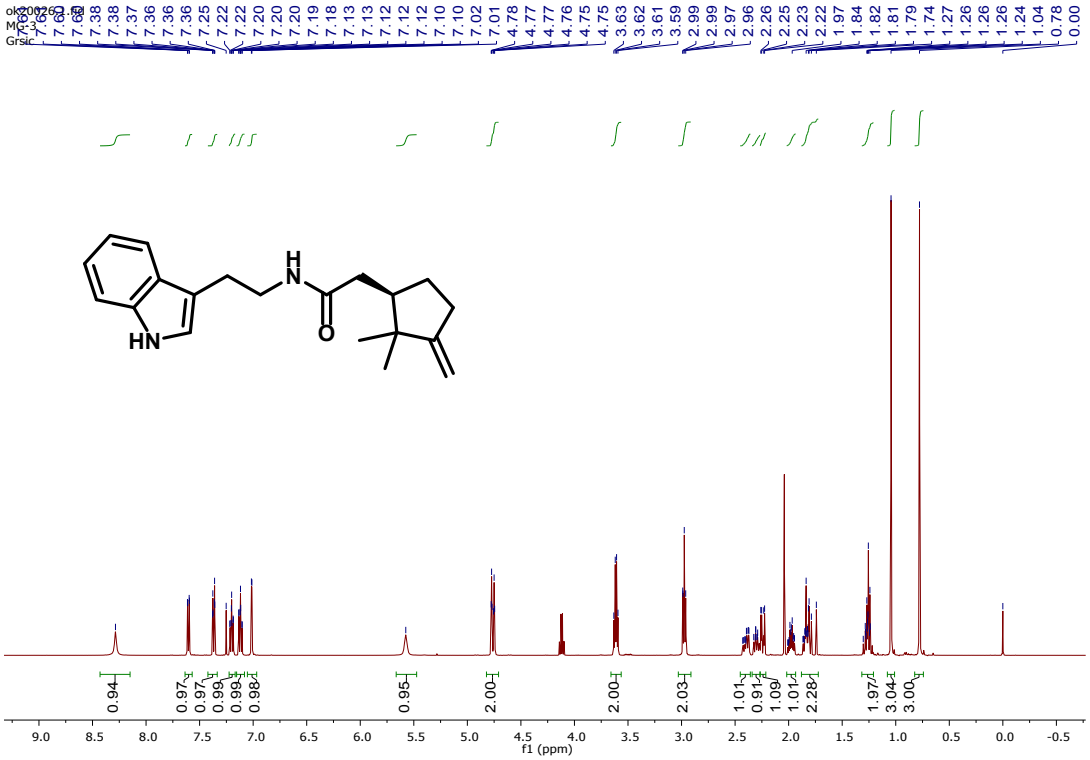
Compound **S53** eluted first from the column. Yield: 58.9 mg (0.130 mmol, 14.3% over four steps) of colourless semisolid. ESI-HRMS: *m/z* = 452.3634 (MH^+); $C_{29}H_{46}N_3O$ requires: *m/z* = 452.3635 (MH^+). ν_{max} 3306, 2921, 2853, 1649, 1524, 1495, 1459, 1378, 1244, 1125, 908, 960, 786, 749, 729 cm^{-1}. $[\alpha]_D^{r.t.}$ = +0.37 (*c* 0.27, acetone). Purity: UPLC (254 nm): t_r = 4.570 min, 98.0% total area. ^{1}H-NMR (500 MHz $CDCl_3$): δ 0.83 (*t*, *J* = 7.3 Hz, 6H); 1.05 – 1.65 (*m*, 23H); 2.35 – 2.50 (*m*, 4H); 2.89 (*dd*, *J* = 4.4; 14.0 Hz, 1H); 3.06 – 3.16 (*m*, 1H); 3.17 – 3.28 (*m*, 1H); 3.36 (*dd*, *J* = 7.5; 14.0 Hz, 1H); 3.52 (*dd*, *J* = 4.4; 7.5 Hz, 1H); 7.09 (*t*, *J* = 5.8 Hz, 1H); 7.41 (*ddd*, *J* = 1.2; 6.8; 8.1 Hz, 1H); 7.55 (*ddd*, *J* = 1.5; 6.8; 8.4 Hz, 1H); 7.69 (*dd*, *J* = 1.3; 8.2 Hz, 1H); 7.97 (*dd*, *J* = 1.0; 8.6 Hz, 1H); 8.05 (*d*, *J* = 2.1 Hz, 1H); 8.77 (*d*, *J* = 2.2 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.10, 20.62, 26.40, 28.28, 28.51, 30.96, 34.39, 34.45, 36.93, 37.42,

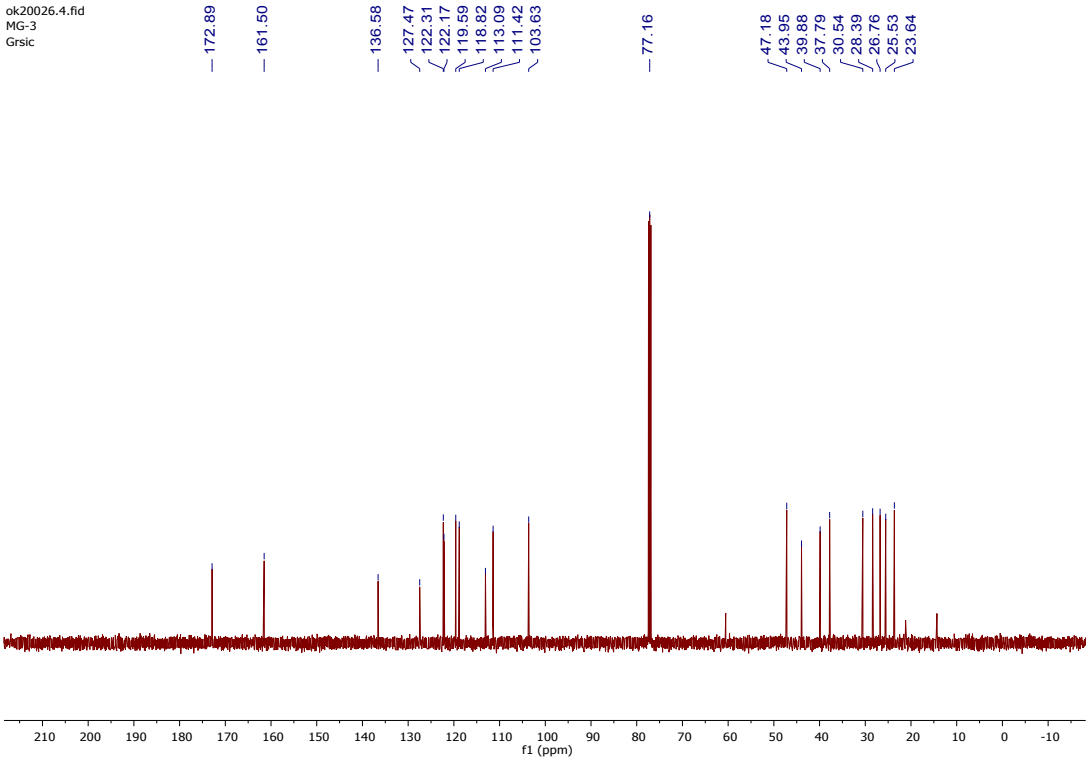
37.77, 51.00, 66.08, 126.52, 127.56, 128.15, 128.64, 129.14, 134.24, 135.90, 146.77, 152.49, 173.02.

Compound **S54** eluted second from the column. Yield: 71.4 mg (0.180 mmol, 19.9% over four steps) of colourless semisolid. ESI-HRMS: *m/z* = 396.3007 (MH^+); $C_{25}H_{38}N_3O$ requires: *m/z* = 396.3009 (MH^+). ν_{max} 3305, 2921, 2853, 1650, 1524, 1495, 1459, 1378, 1244, 1125, 908, 860, 786, 749, 728 cm^{-1}. $[\alpha]_D^{r.t.}$ = –5.4 (*c* 0.98, acetone). Purity: UPLC (254 nm): t_r = 4.167 min, 98.4% total area. ^{1}H-NMR (500 MHz $CDCl_3$): δ 0.79 (*t*, *J* = 7.3 Hz, 3H); 1.05 – 1.15 (*m*, 2H); 1.16 – 1.24 (*m*, 2H); 1.26 – 1.64 (*m*, 15H); 2.47 (*t*, *J* = 7.1 Hz, 2H); 2.79 (br *s*, 1H); 2.99 (*dd*, *J* = 8.3; 14.1 Hz, 1H); 3.13 – 3.32 (*m*, 3H); 3.41 (*dd*, *J* = 4.7; 8.3 Hz, 1H); 7.18 (*t*, *J* = 5.8 Hz, 1H); 7.52 (*ddd*, *J* = 1.1; 6.8; 8.0 Hz, 1H); 7.66 (*ddd*, *J* = 1.4; 6.8; 8.4 Hz, 1H); 7.75 (*dd*, *J* = 1.3; 8.2 Hz, 1H); 7.97 (*d*, *J* = 2.1 Hz, 1H); 8.06 (*d*, *J* = 8.4 Hz, 1H); 8.77 (*d*, *J* = 2.2 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.85, 20.25, 26.30, 28.46, 32.12, 34.29, 34.32, 36.59, 36.81, 37.25, 37.59, 48.44, 63.68, 126.92, 127.49, 127.95, 129.07, 129.24, 130.54, 135.80, 147.12, 151.65, 172.87

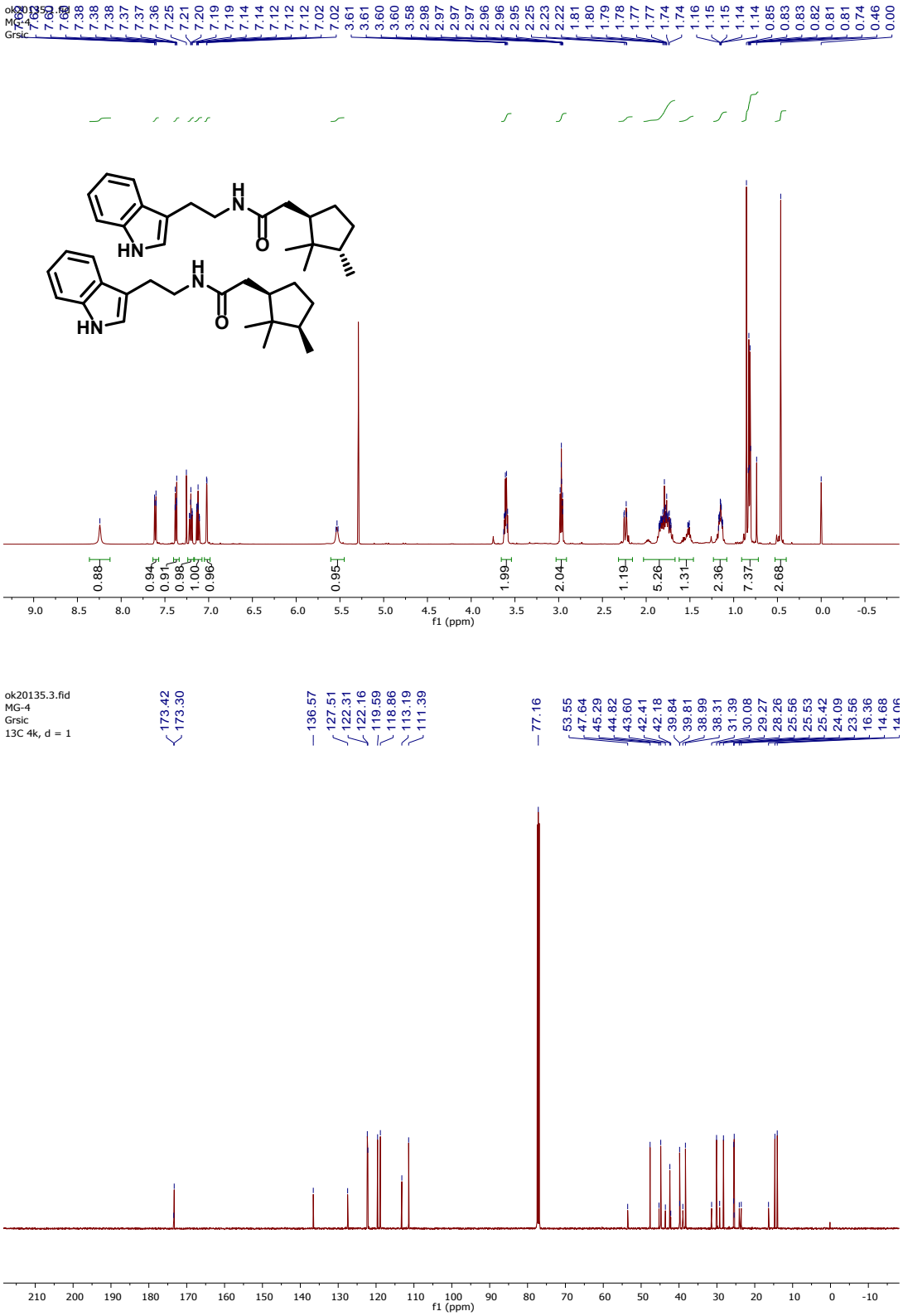
NMR spectra

S1

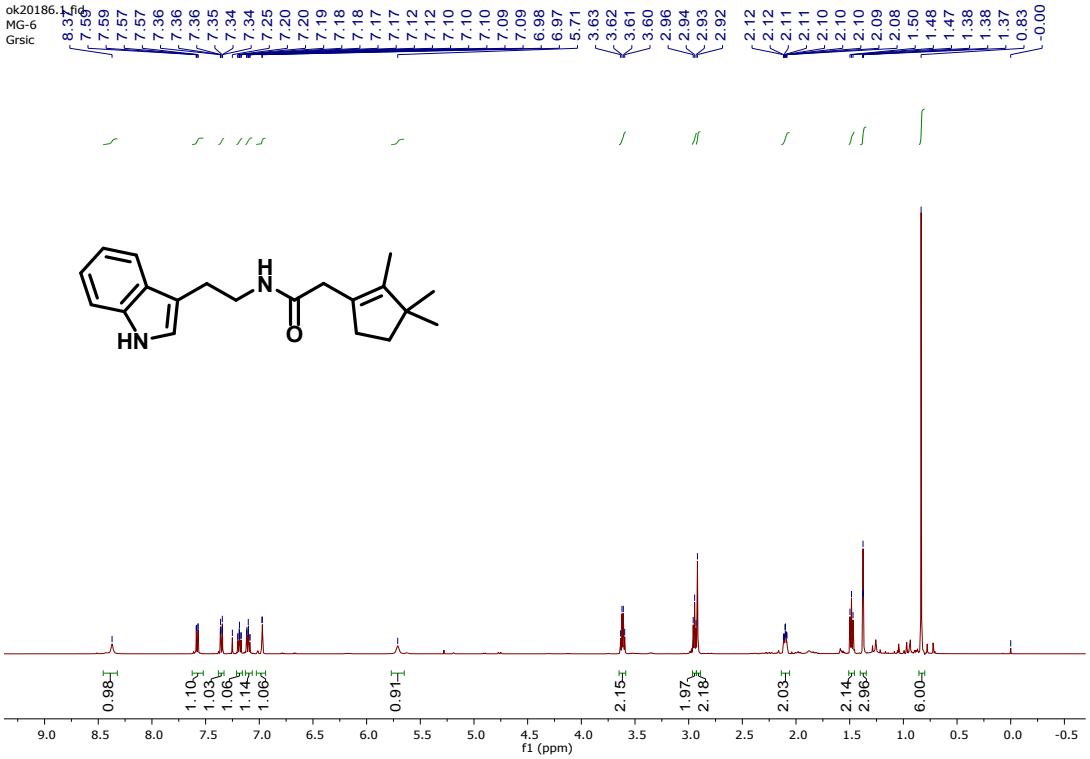




S2/S3



S4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MG-6
Grsic
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7.59
7.59
7.57
7.57
7.57
7.36
7.36
7.36
7.35
7.34
7.34
7.25
7.20
7.20
7.19
7.18
7.18
7.17
7.17
7.17
7.12
7.12
7.10
7.10
7.10
7.09
7.09
6.98
6.97
5.71
3.63
3.62
3.61
3.60
2.96
2.94
2.93
2.92
2.12
2.12
2.11
2.11
2.10
2.10
2.10
2.09
2.09
2.08
1.50
1.48
1.47
1.38
1.38
1.37
0.83
-0.00
H
N
HN
O
0.98
1.10
1.03
1.06
1.14
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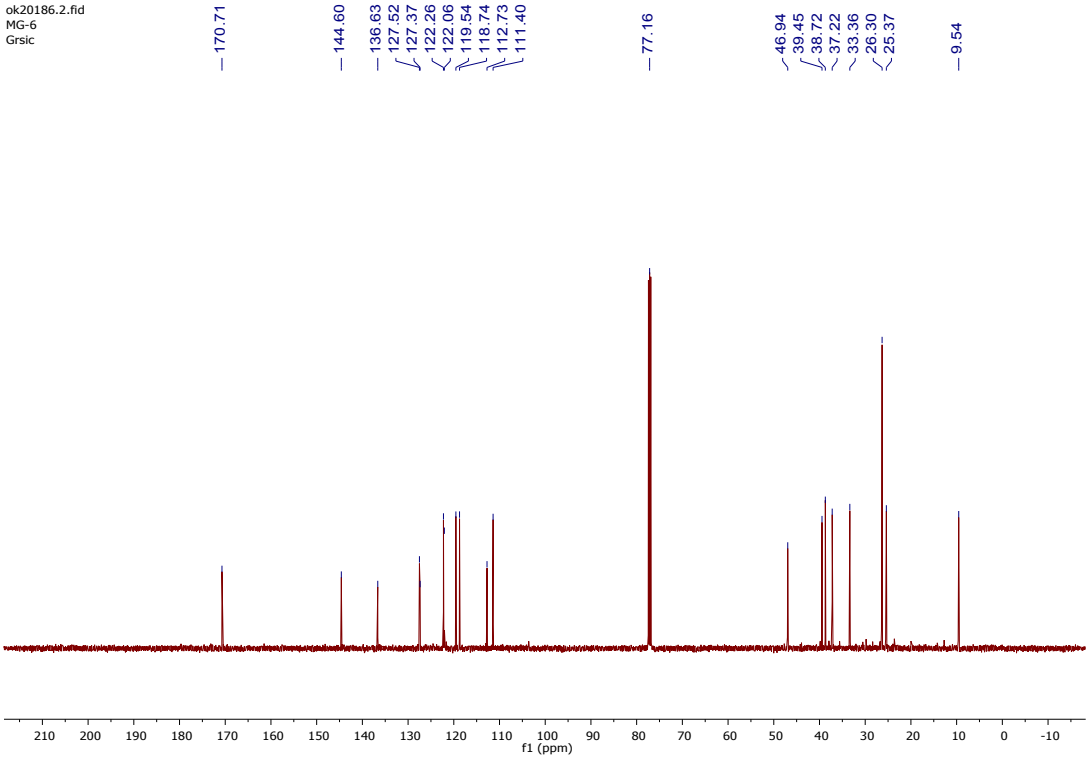
0.91
2.15
1.97
2.18
2.03
2.14
2.96
6.00
f1 (ppm)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122.06
119.54
118.74
112.73
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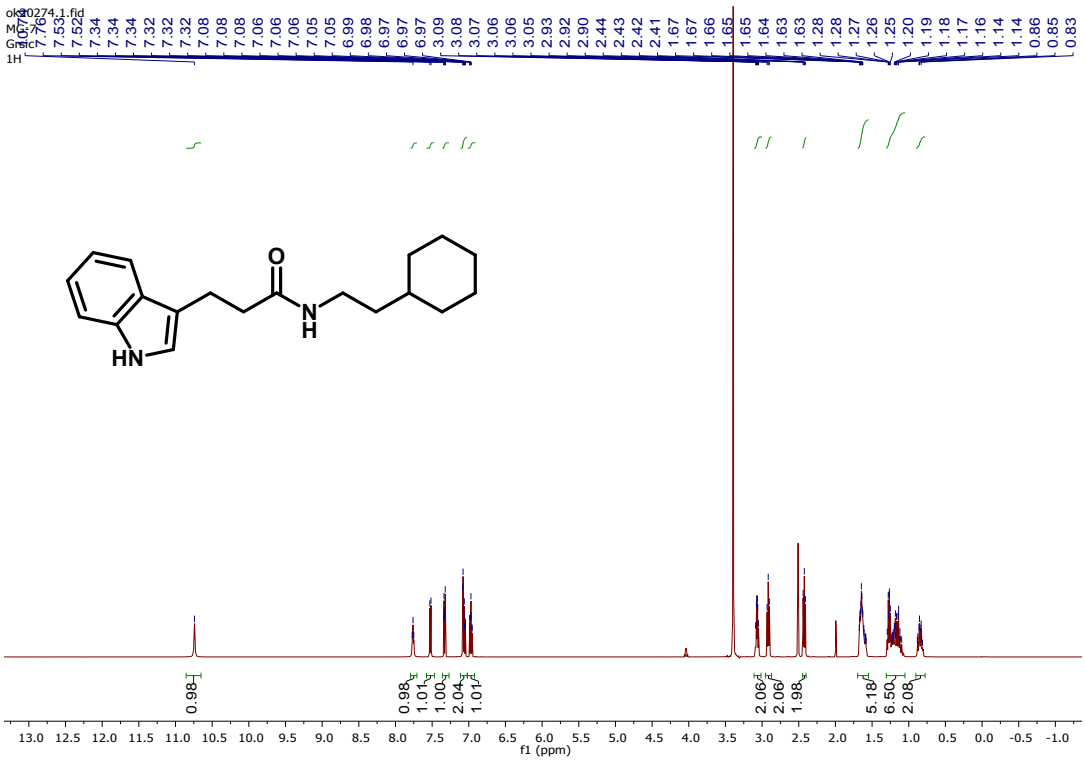
39.45
38.72
37.22
33.36
26.30
25.37
9.54
f1 (ppm)

S5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Grsic
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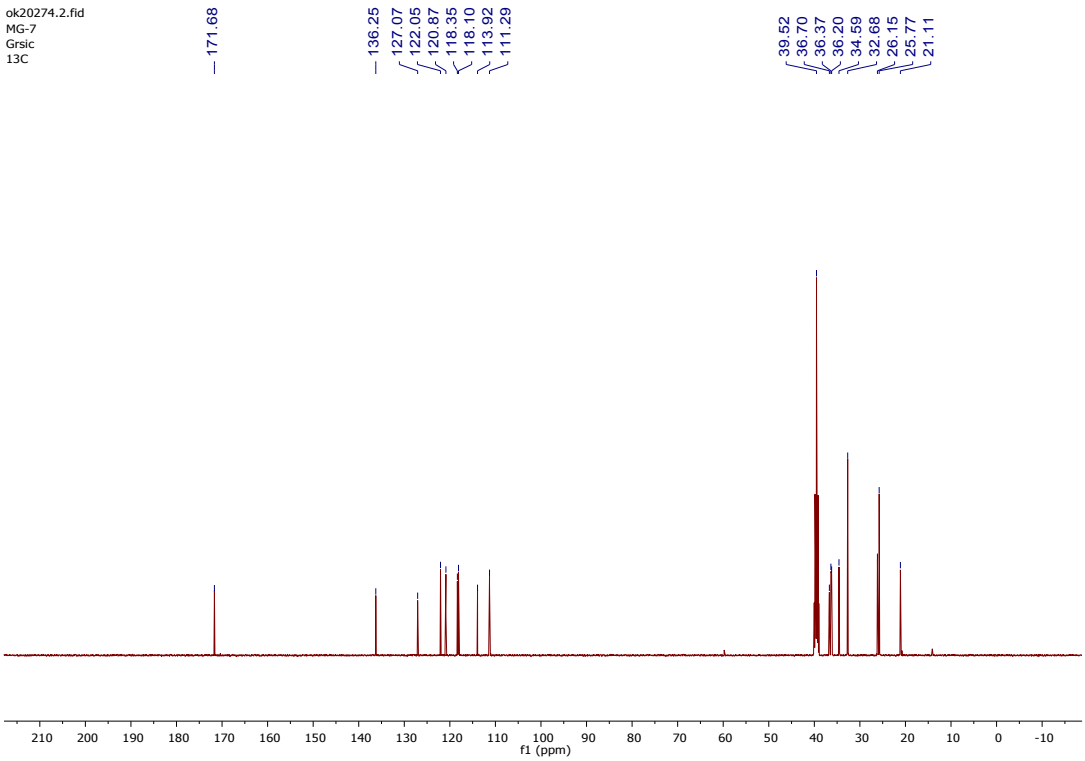
O
N
H
HN
f1 (ppm)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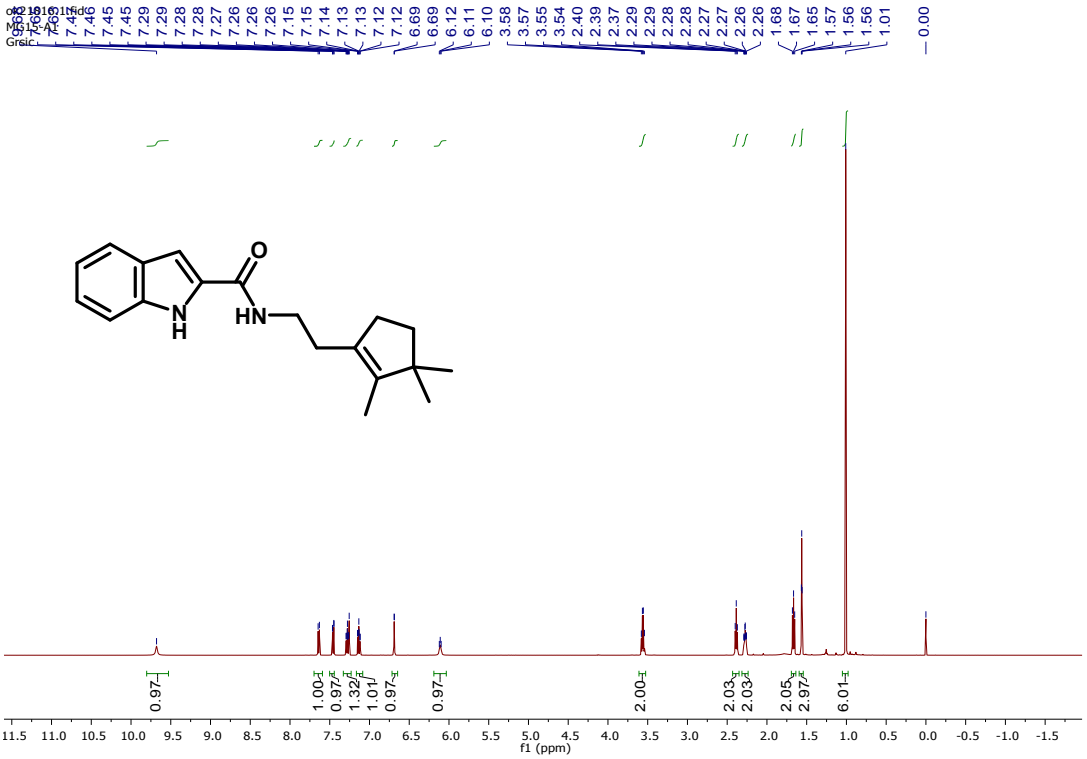
MG-7
Grsic
13C
f1 (ppm)

S6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7.45
7.29
7.28
7.27
7.26
7.15
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7.13
7.12
6.69
6.12
6.11
6.10
3.58
3.57
3.55
3.54
2.40
2.39
2.37
2.29
2.29
2.28
2.28
2.27
2.27
2.26
2.26
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1.67
1.65
1.57
1.56
1.56
1.01
0.00
O
N
H
HN
0.97
1.00
0.97
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0.97
2.00
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2.05
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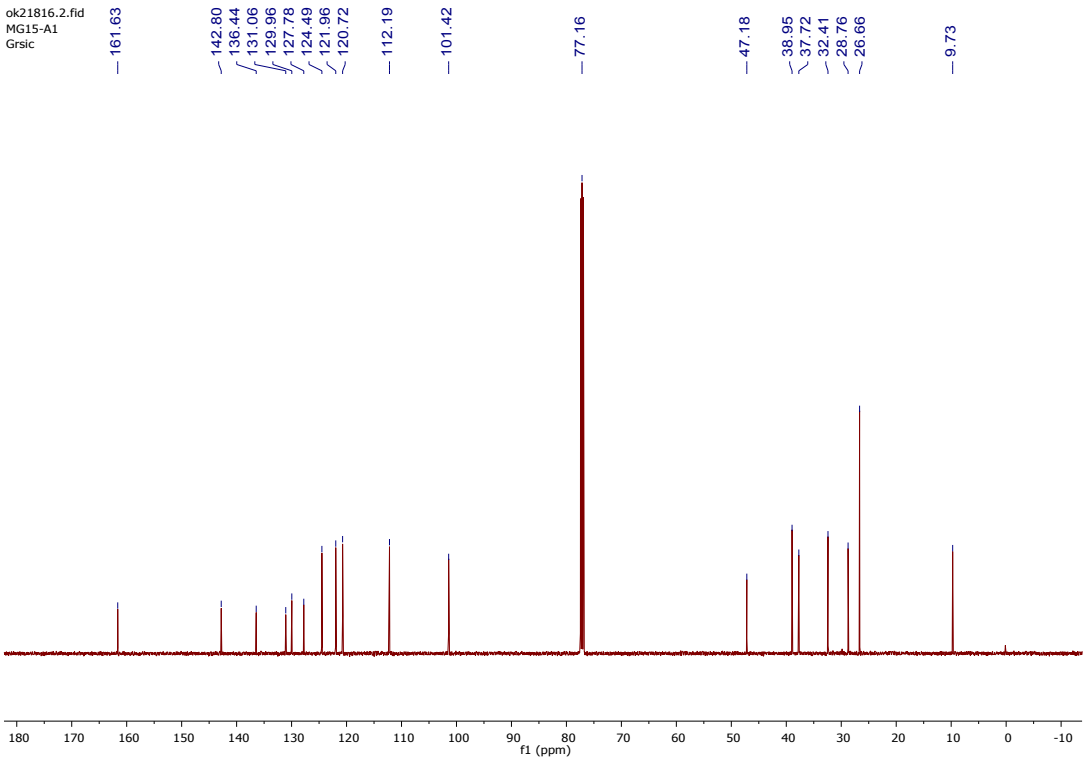
f1 (ppm)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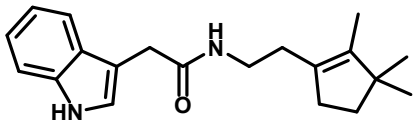
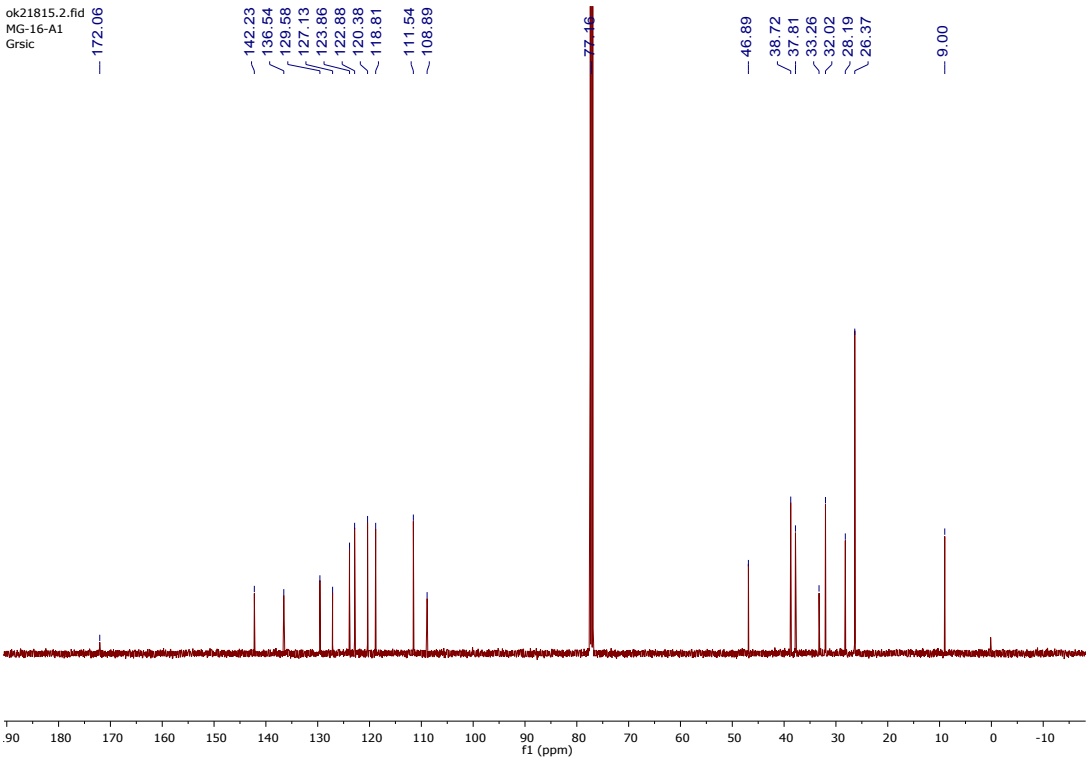
142.80
136.44
131.06
129.96
127.78
124.49
121.96
120.72
112.19
101.42
77.16
47.18
38.95
37.72
32.41
28.76
26.66
9.73
f1 (ppm)

5

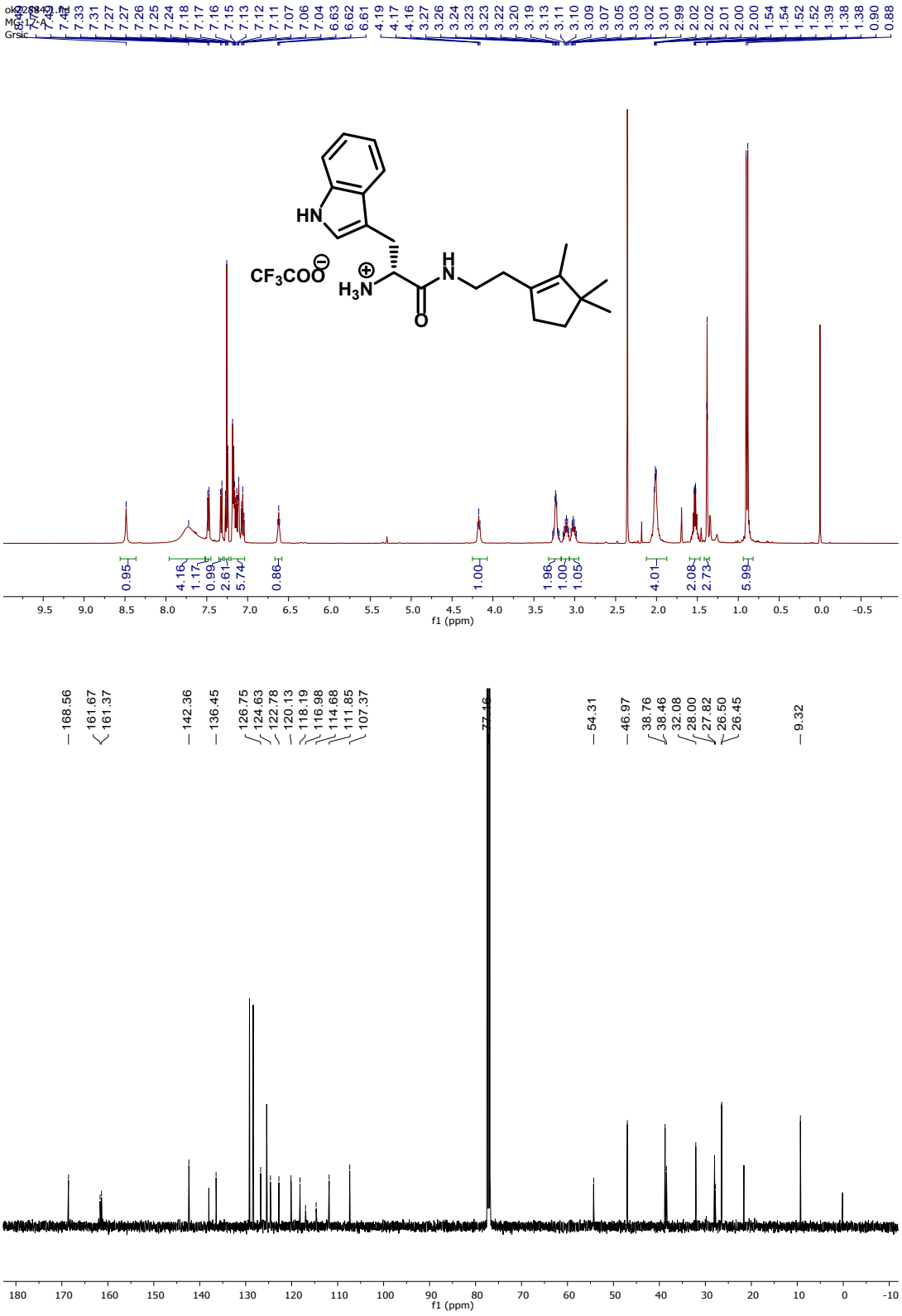

ok21815.1.fid
MG-16-A1
Grsic
8.30 7.54 7.52 7.40 7.40 7.40 7.38 7.38 7.38 7.26 7.25 7.24 7.23 7.23 7.23 7.22 7.21 7.16 7.16 7.15 7.14 7.14 7.13 7.13 7.10 7.10 6.66 3.74 3.28 3.26 3.25 3.24 2.08 2.07 2.06 2.00 2.00 1.99 1.99 1.98 1.97 1.43 1.42 1.40 1.12 1.12 1.11 0.77 -0.00


H
N
O
HN

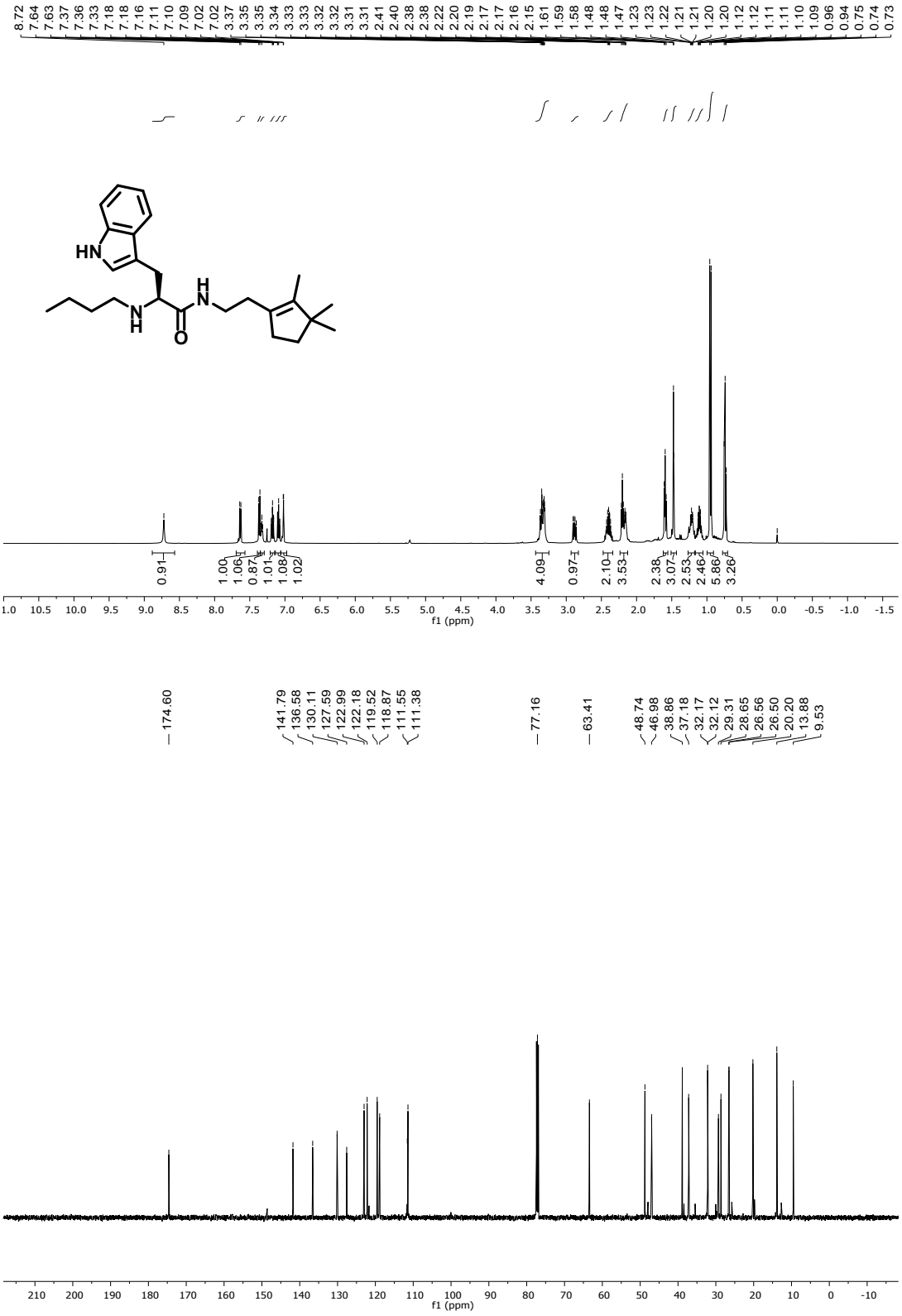
1.03 1.01 1.05 1.02 1.05 0.99 0.98 2.18 2.11 2.02 2.03 2.02 3.00 6.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


ok21815.2.fid
MG-16-A1
Grsic
172.06 142.23 136.54 129.58 127.13 123.86 122.88 120.38 118.81 111.54 108.89 77.16 46.89 38.72 37.81 33.26 32.02 28.19 26.37 9.00
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

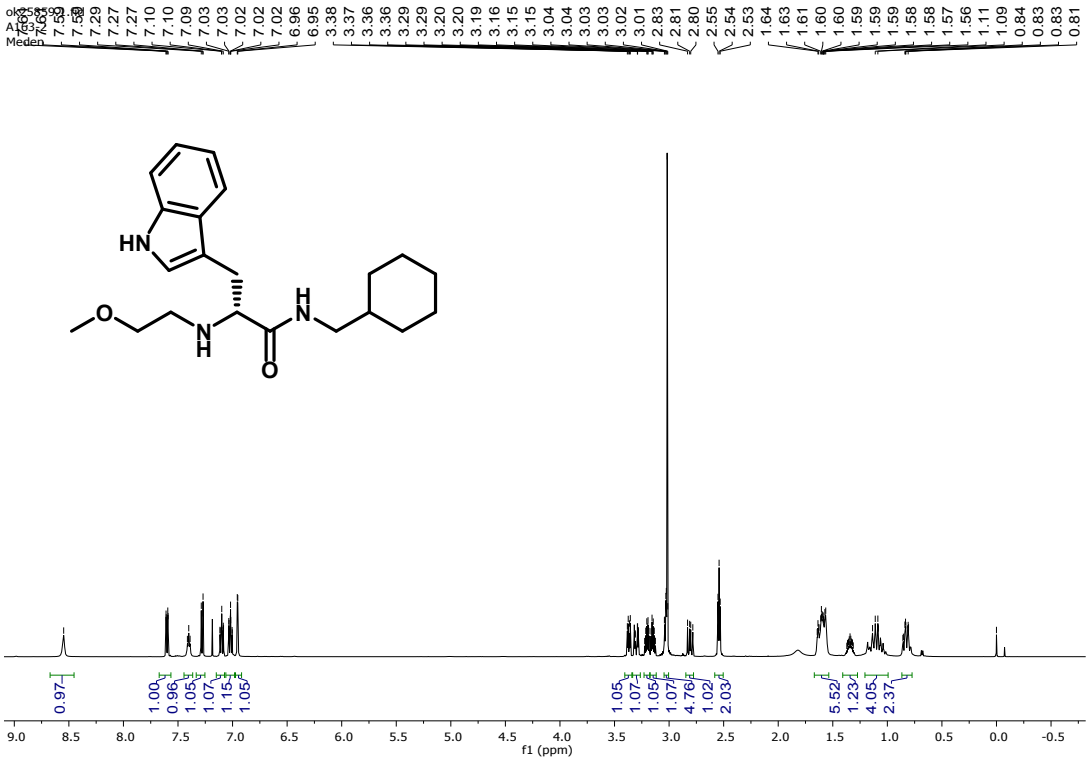
S7



S8



S9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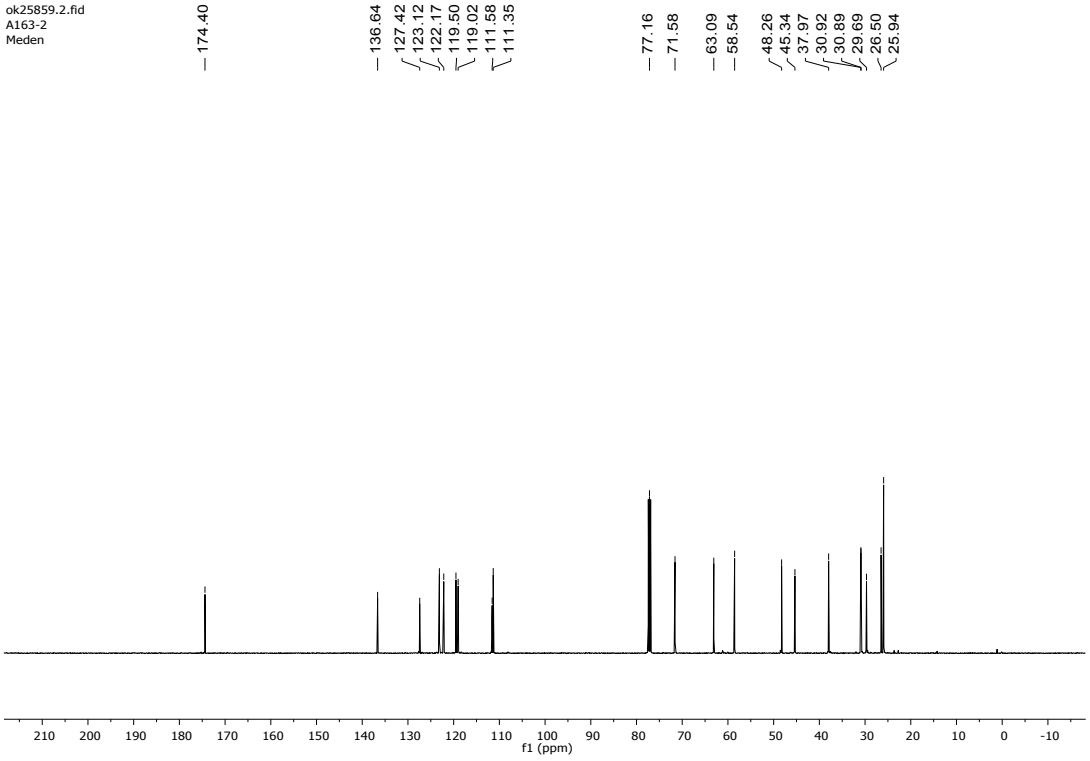
O
N
H
H
N
O
0.97
1.00
0.96
1.05
1.07
1.15
1.05
1.05
1.07
1.05
1.07
4.76
1.02
2.03
5.52
1.23
4.05
2.37
f1 (ppm)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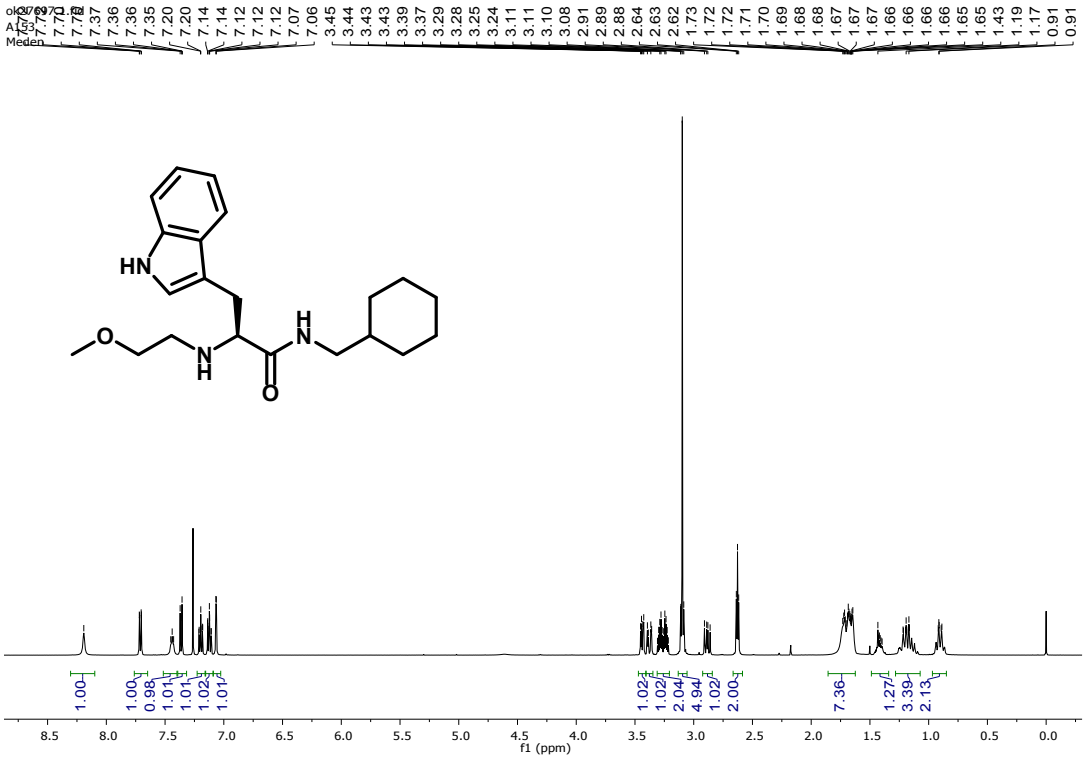
123.12
122.17
119.50
119.02
111.58
111.35
77.16
71.58
63.09
58.54
48.26
45.34
37.97
30.92
30.89
29.69
26.50
25.94
f1 (ppm)

S10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Meden
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7.76
7.37
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7.20
7.14
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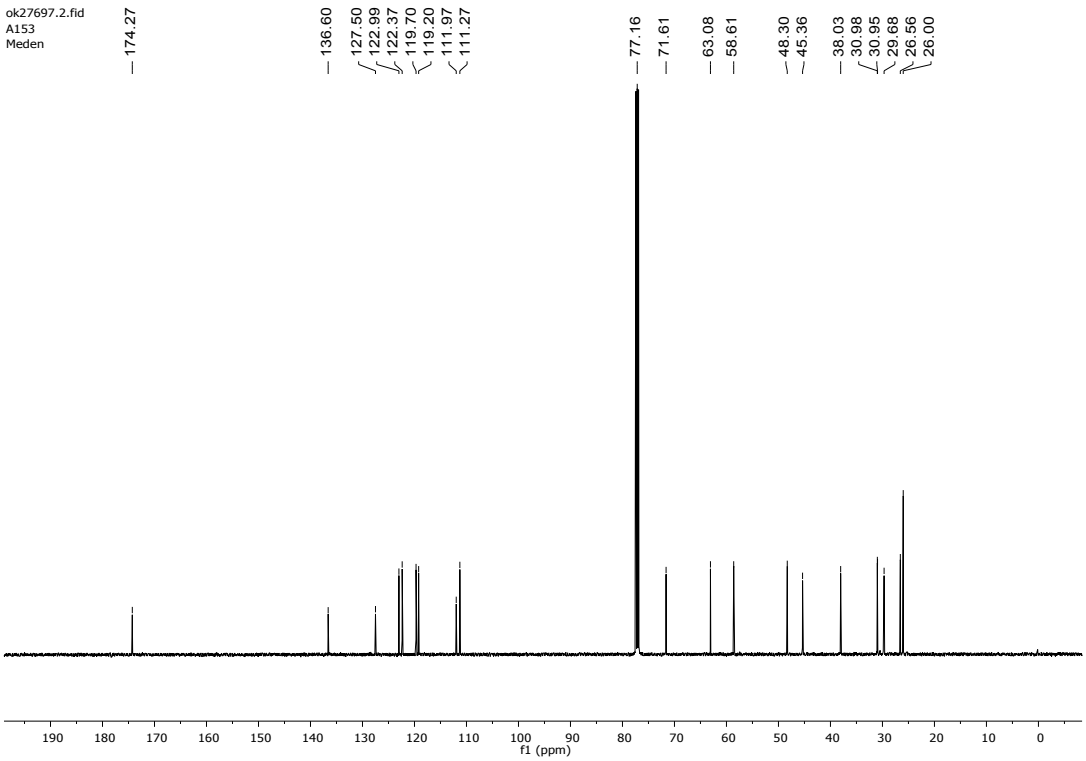
7.12
7.12
7.12
7.07
7.06
3.45
3.44
3.43
3.43
3.39
3.37
3.29
3.28
3.25
3.24
3.11
3.11
3.10
3.08
2.91
2.89
2.88
2.64
2.63
2.62
1.73
1.72
1.72
1.71
1.70
1.69
1.68
1.68
1.67
1.67
1.67
1.66
1.66
1.66
1.66
1.65
1.65
1.43
1.19
1.17
0.91
0.91
HN
O
N
H
H
N
O
1.00
1.00
0.98
1.01
1.01
1.02
1.01
1.02
1.02
2.04
4.94
1.02
2.00
7.36
1.27
3.39
2.13
f1 (ppm)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Meden
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136.60
127.50
122.99
122.37
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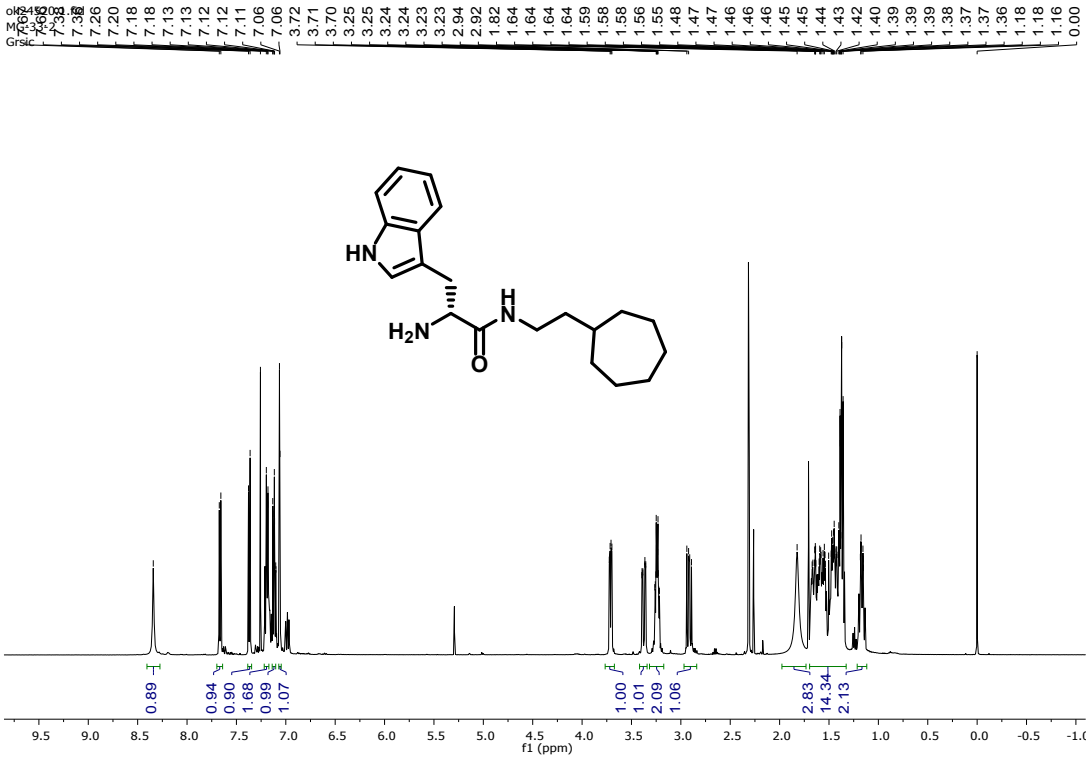
119.20
111.97
111.27
77.16
71.61
63.08
58.61
48.30
45.36
38.03
30.98
30.95
29.68
26.56
26.00
f1 (ppm)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7.18
7.13
7.12
7.12
7.11
7.06
7.06
3.72
3.71
3.70
3.25
3.25
3.24
3.24
3.23
3.23
2.94
2.92
1.82
1.64
1.64
1.64
1.64
1.59
1.58
1.58
1.56
1.55
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1.37
1.37
1.36
1.18
1.18
1.16
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HN
H
N
H2N
O
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0.94
0.90
1.68
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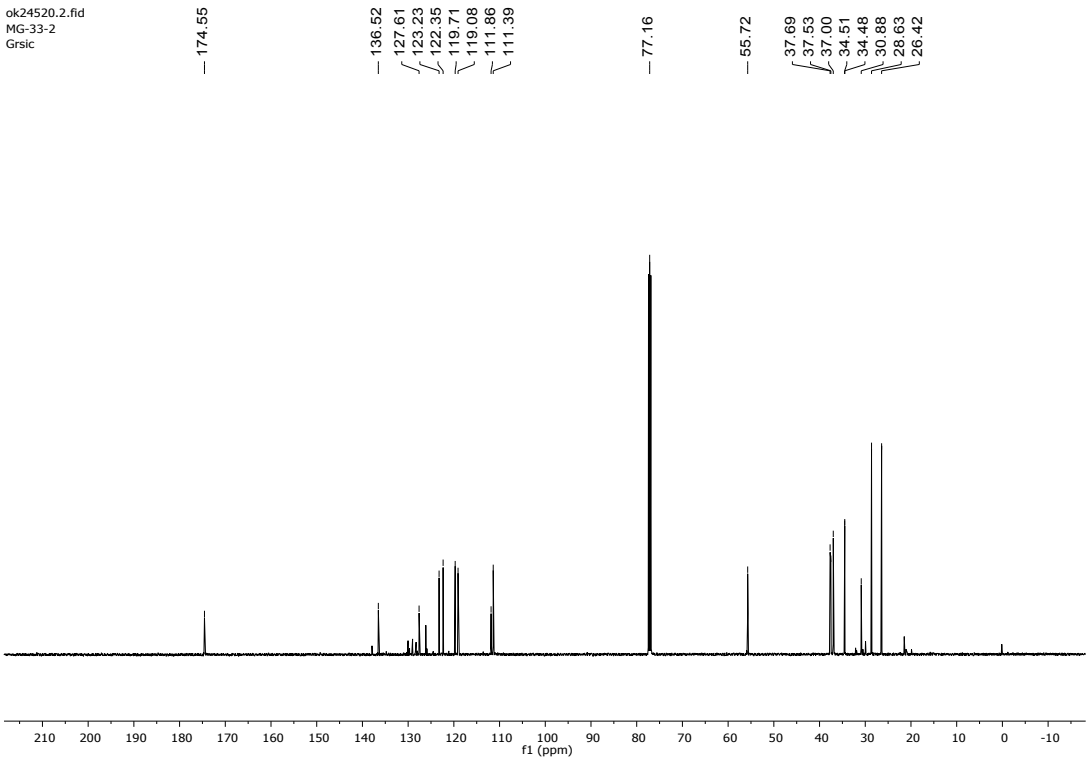
1.07
1.00
1.01
2.09
1.06
2.83
14.34
2.13
f1 (ppm)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111.39
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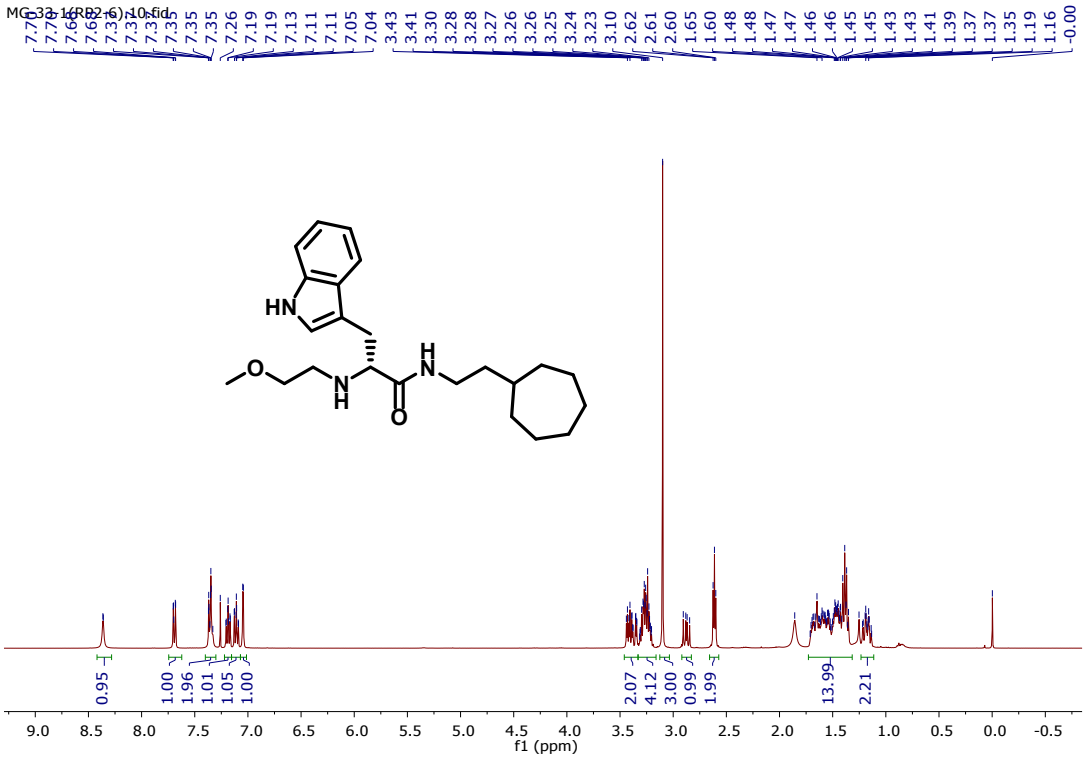
f1 (ppm)

S13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H
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O
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1.01
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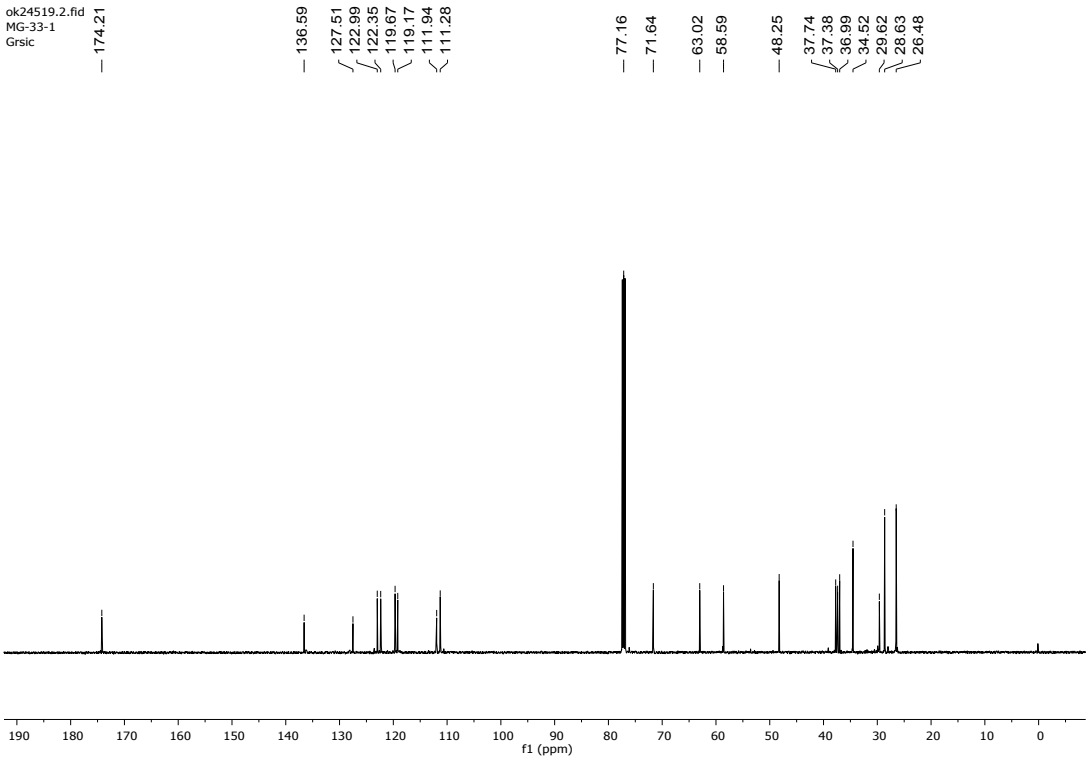
1.00
2.07
4.12
3.00
0.99
1.99
13.99
2.21
f1 (ppm)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Grsic
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127.51
122.99
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119.67
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111.28
77.16
71.64
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36.99
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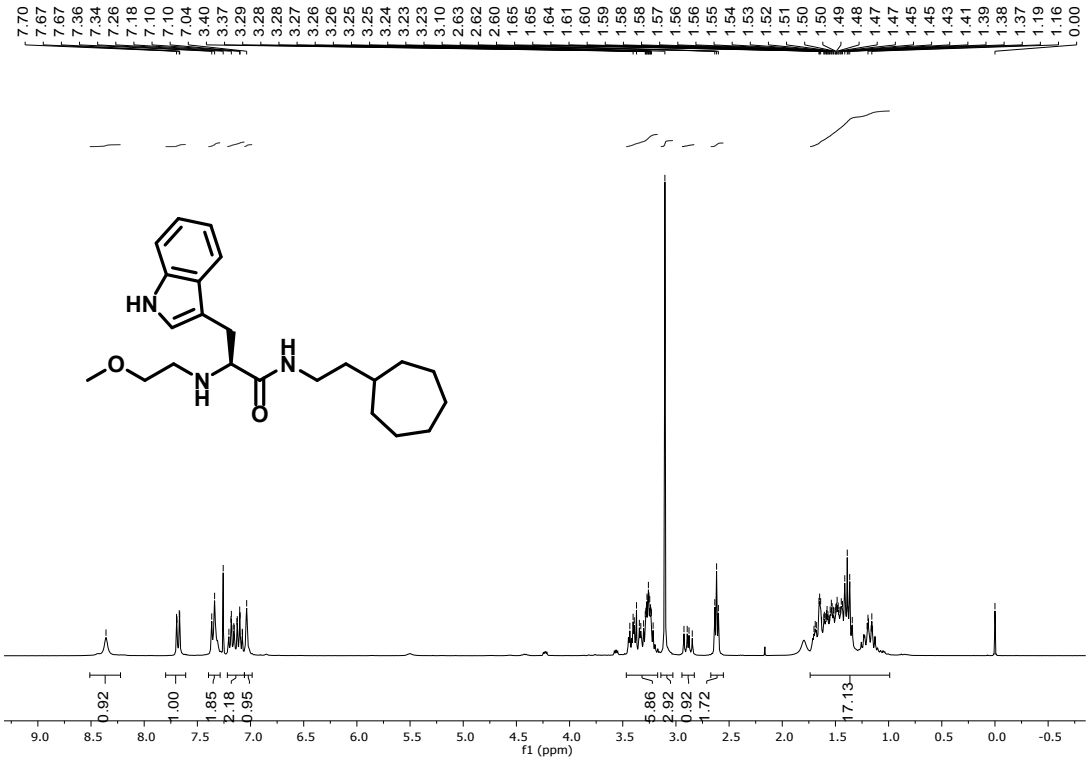
29.62
28.63
26.48
f1 (ppm)

S14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3.37
3.29
3.28
3.28
3.27
3.26
3.26
3.25
3.25
3.24
3.23
3.23
3.10
2.63
2.62
2.60
1.65
1.65
1.64
1.61
1.60
1.59
1.58
1.58
1.57
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1.43
1.41
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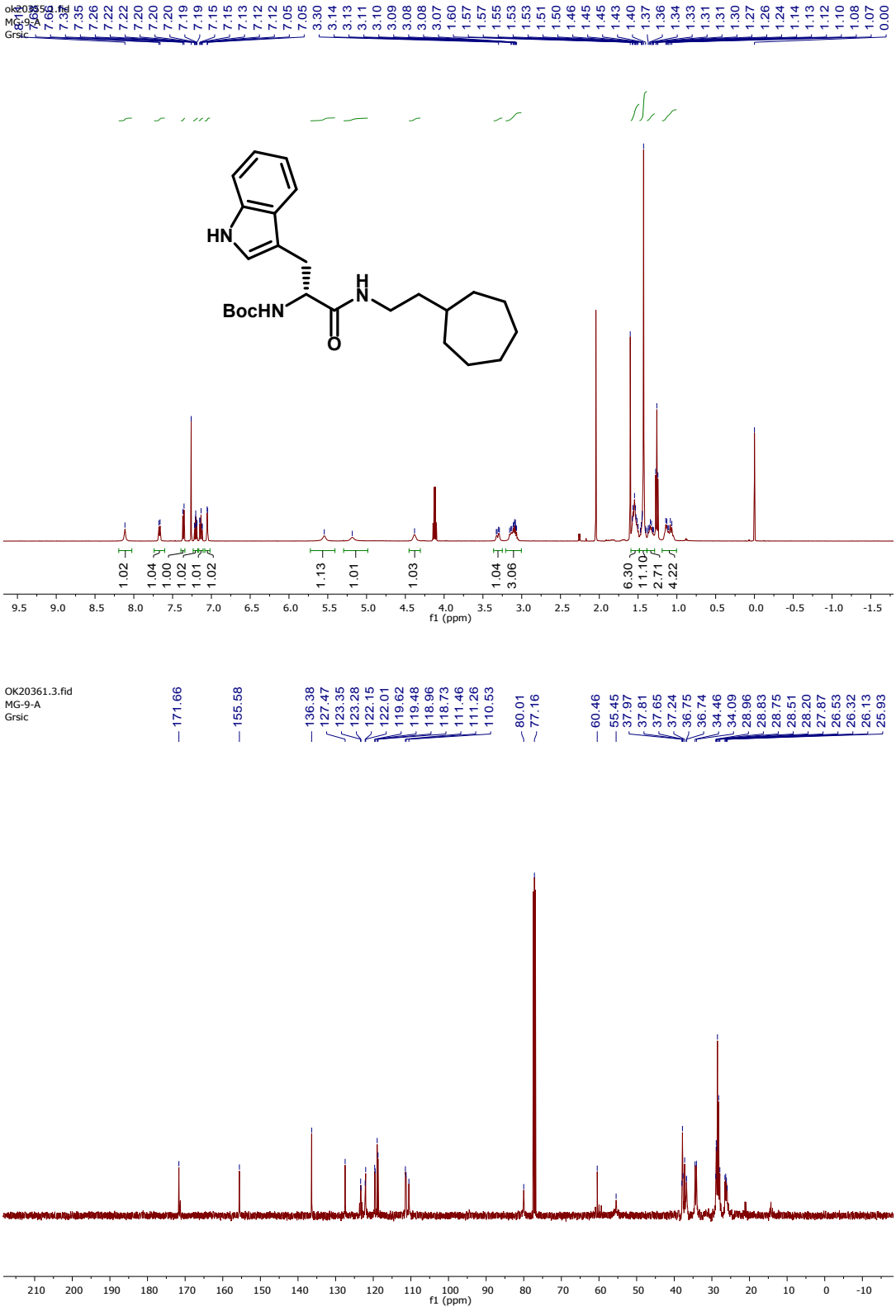
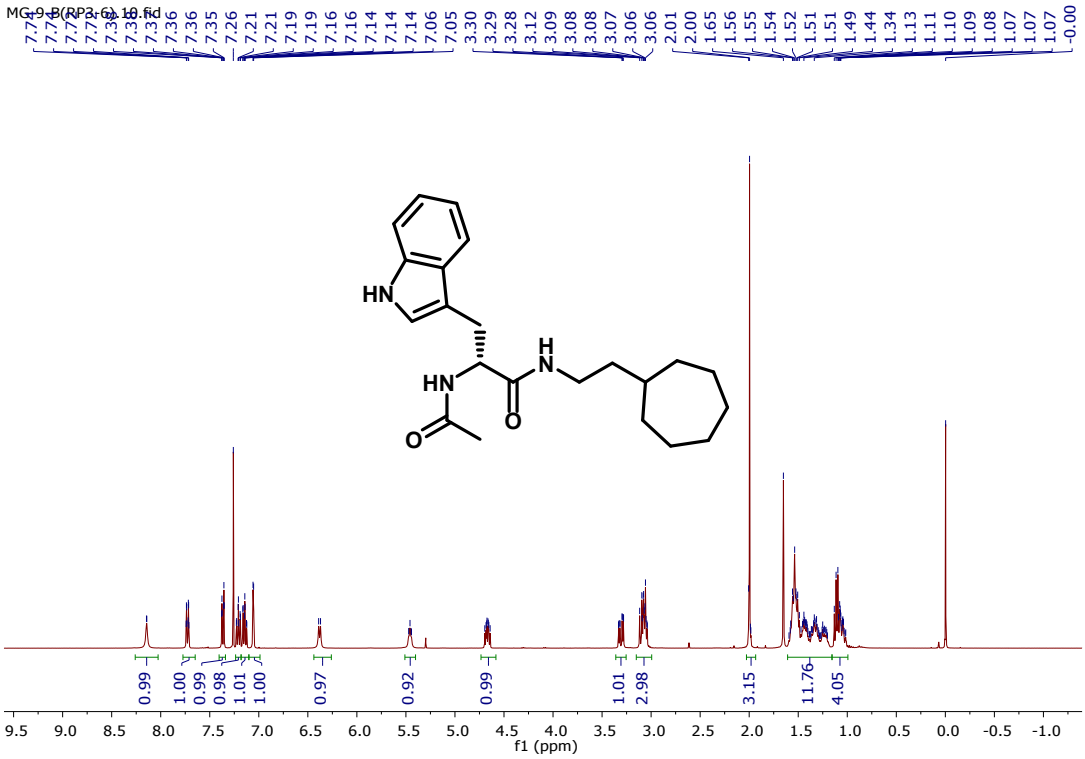
1.38
1.37
1.19
1.16
0.00
HN
O
N
H
H
N
O
0.92
1.00
1.85
2.18
0.95
5.86
2.92
0.92
1.72
17.13
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

S11



The ^{13}C-NMR spectrum is complex due to the presence of several conformers.

S12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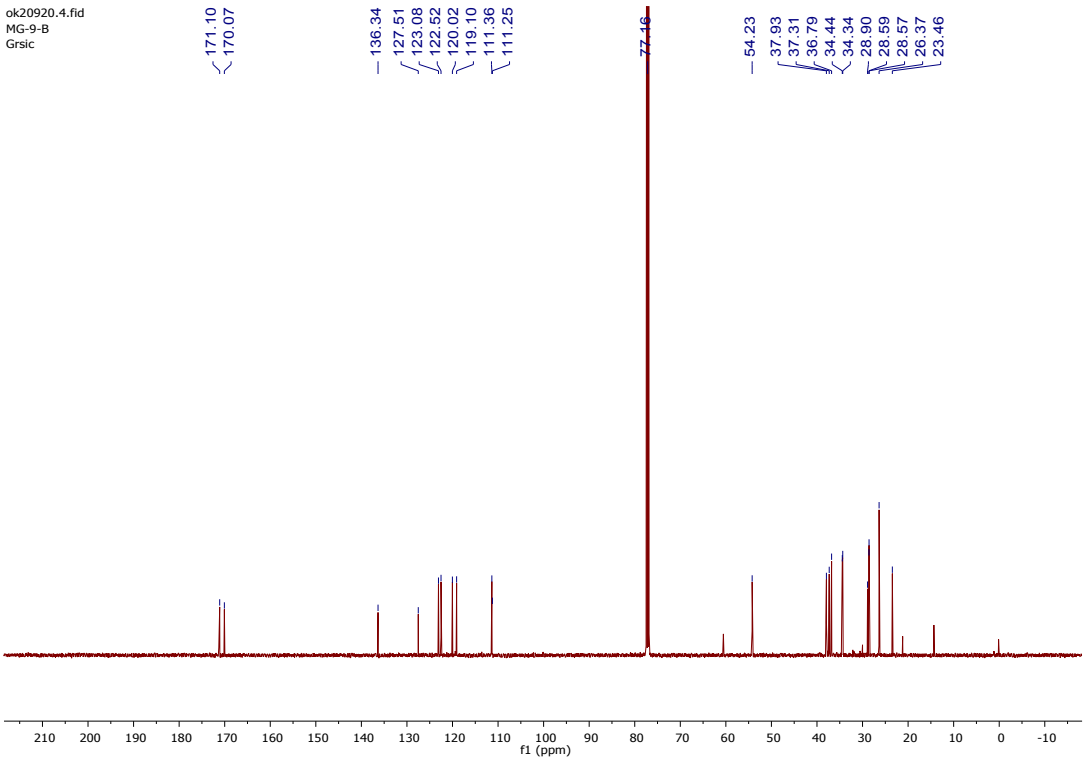
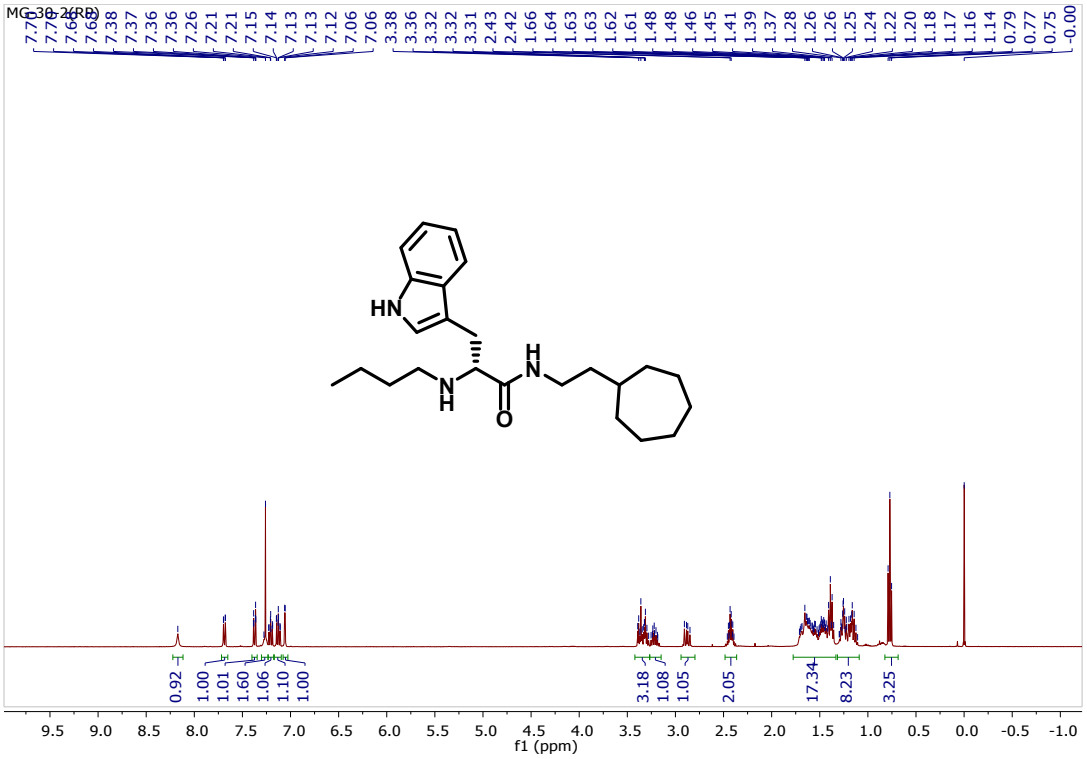
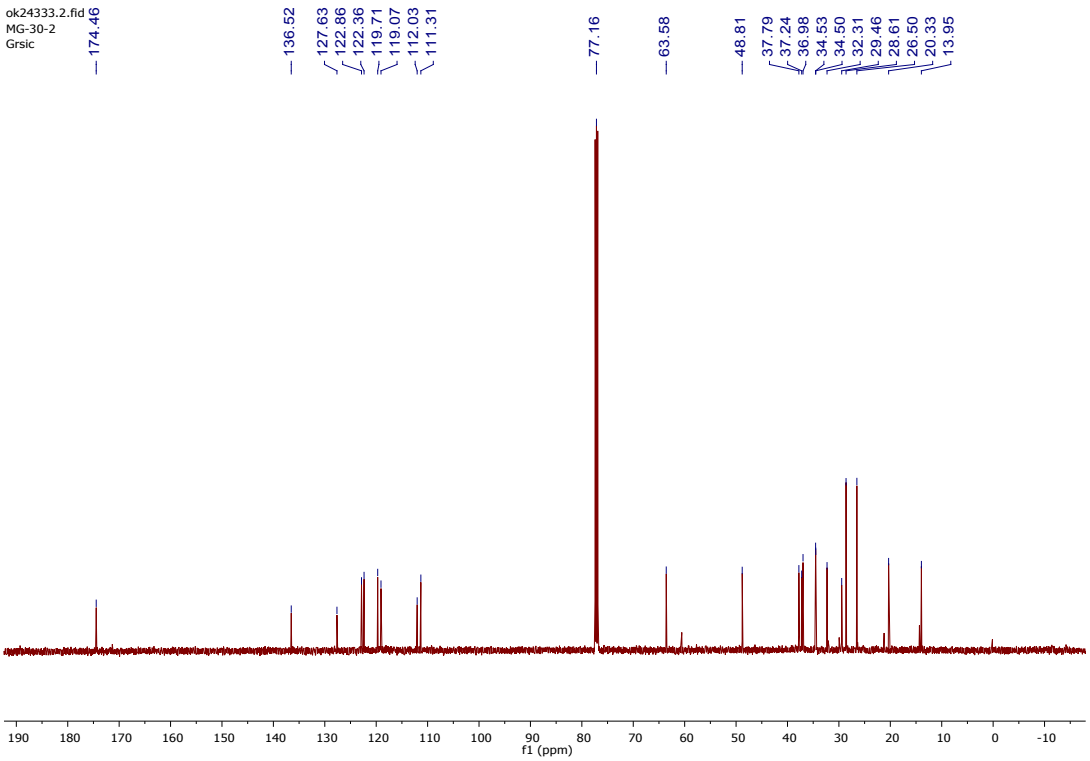
HN
O
H
N
O
0.99
1.00
0.99
0.98
1.01
1.00
0.97
0.92
0.99
1.01
2.98
3.15
11.76
4.05
f1 (ppm)

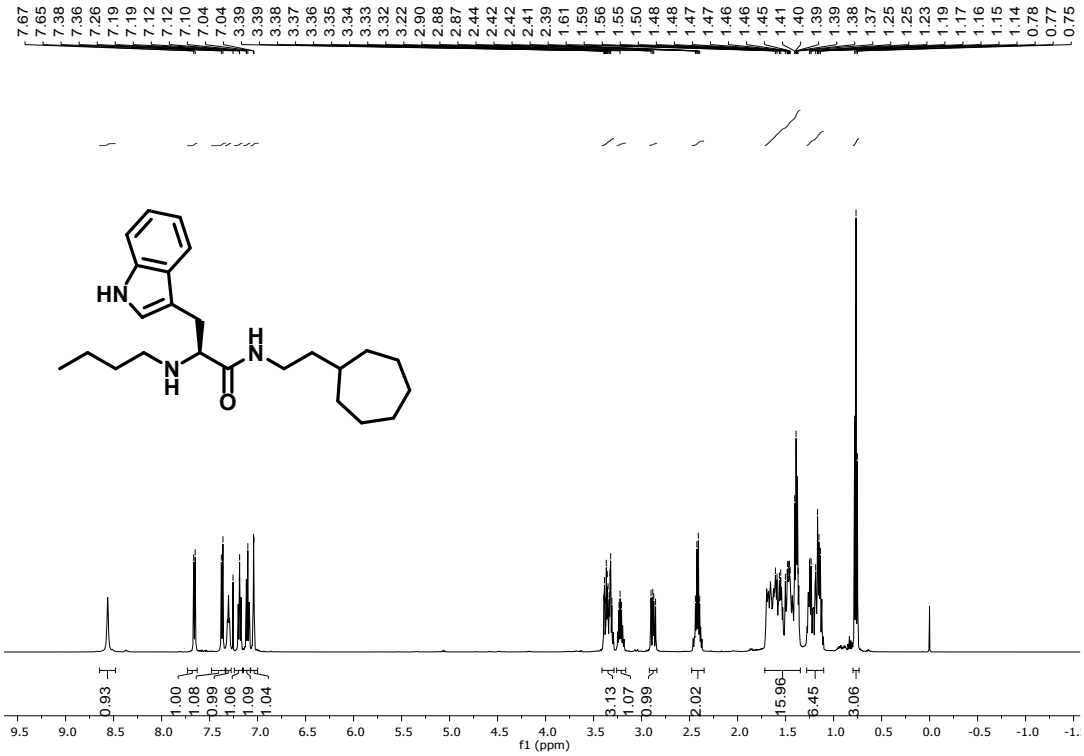

ok20920.4.fid
MG-9-B
Grsic
171.10
170.07
136.34
127.51
123.08
122.52
120.02
119.10
111.36
111.25
77.16
54.23
37.93
37.31
36.79
34.44
34.34
28.90
28.59
28.57
26.37
23.46
f1 (ppm)

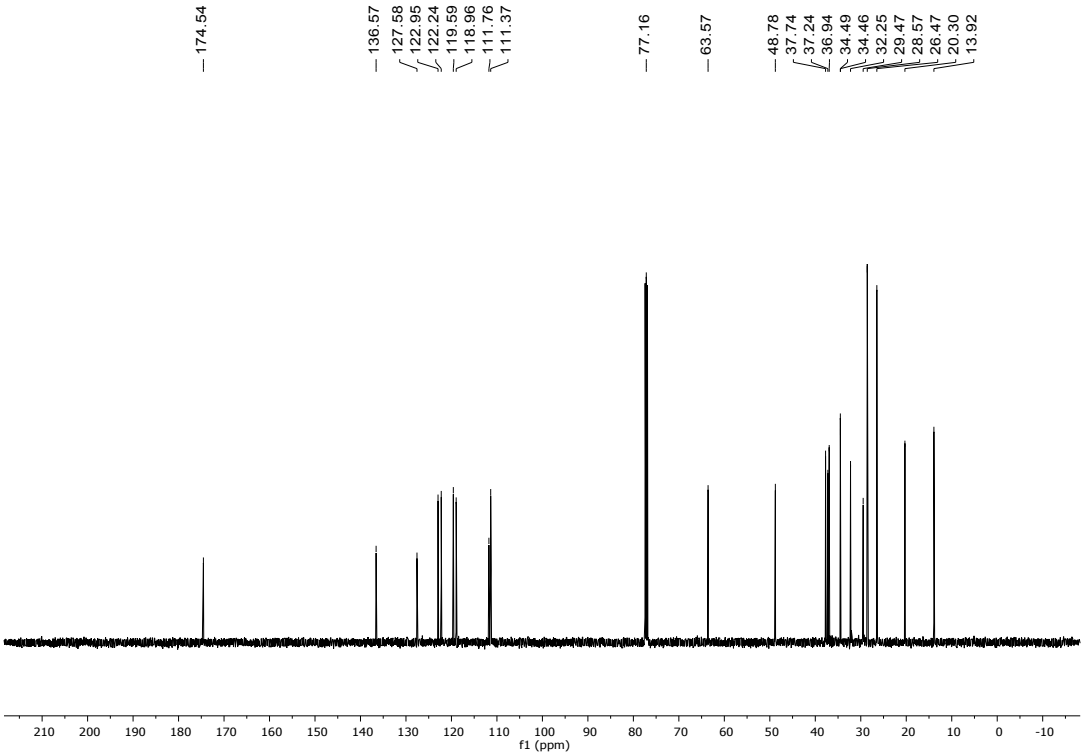
7


MG-30-2(RB)
HN
N
H
H
N
O
0.92
1.00
1.01
1.60
1.06
1.10
1.00
3.18
1.08
1.05
2.05
17.34
8.23
3.25
f1 (ppm)

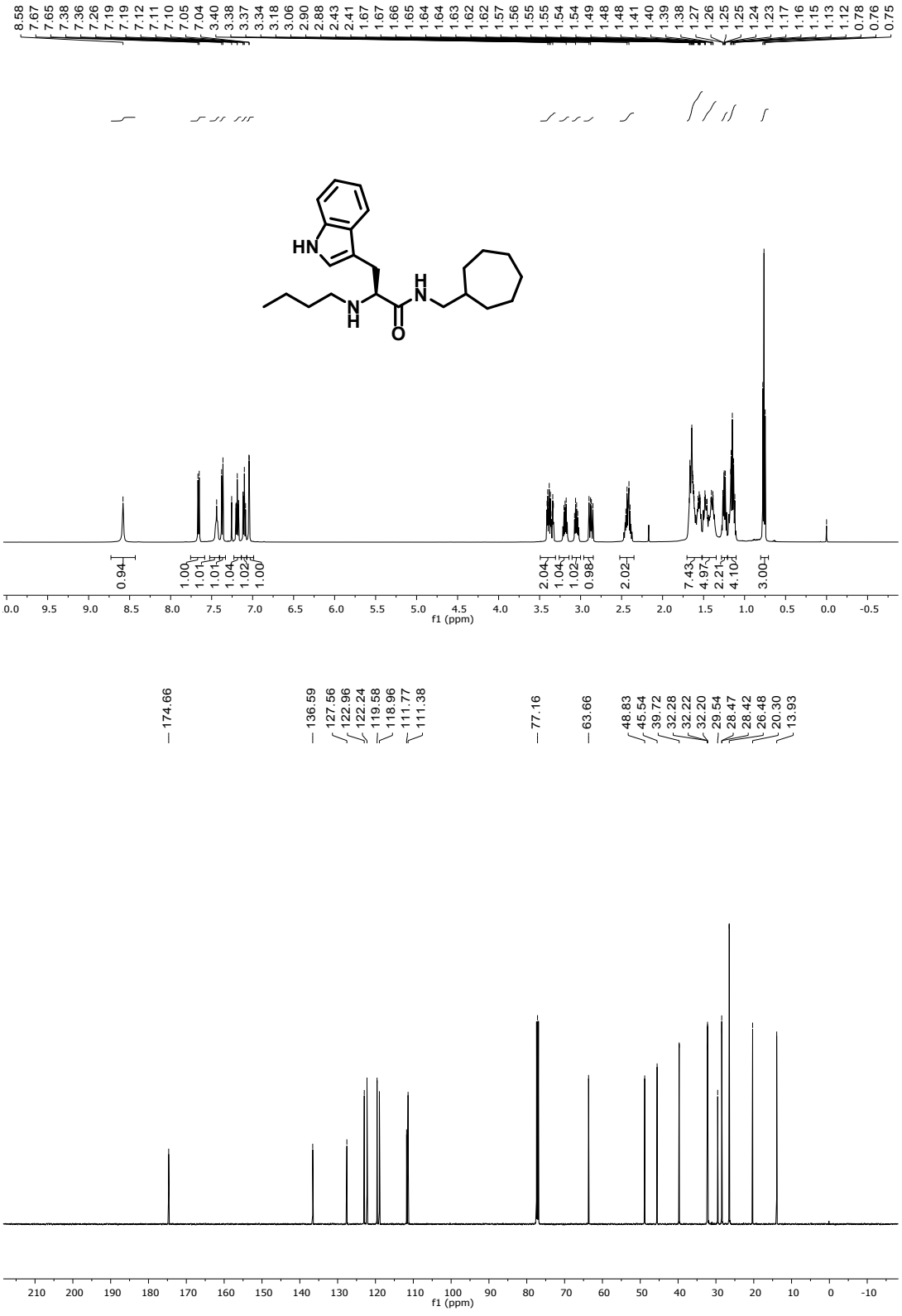

ok24333.2.fid
MG-30-2
Grsic
174.46
136.52
127.63
122.86
122.36
119.71
119.07
112.03
111.31
77.16
63.58
48.81
37.79
37.24
36.98
34.53
34.50
32.31
29.46
28.61
26.50
20.33
13.95
f1 (ppm)

6

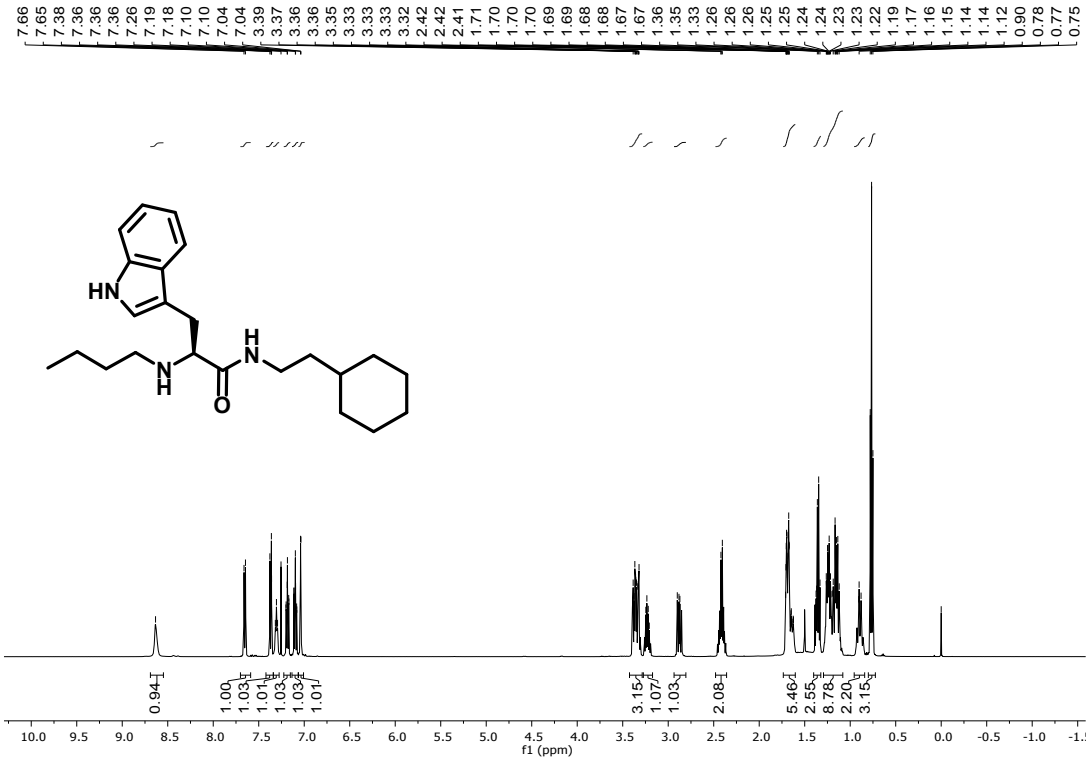

7.67
7.65
7.38
7.36
7.26
7.19
7.19
7.12
7.12
7.10
7.04
7.04
3.39
3.39
3.38
3.37
3.36
3.35
3.34
3.33
3.32
3.22
2.90
2.88
2.87
2.44
2.42
2.42
2.41
2.39
1.61
1.59
1.56
1.55
1.50
1.48
1.48
1.47
1.47
1.46
1.46
1.45
1.41
1.40
1.39
1.39
1.38
1.37
1.25
1.25
1.23
1.19
1.17
1.16
1.15
1.14
0.78
0.77
0.75
HN
H
N
N
H
O
0.93
1.00
1.08
0.99
1.06
1.09
1.04
3.13
1.07
0.99
2.02
15.96
6.45
3.06
f1 (ppm)

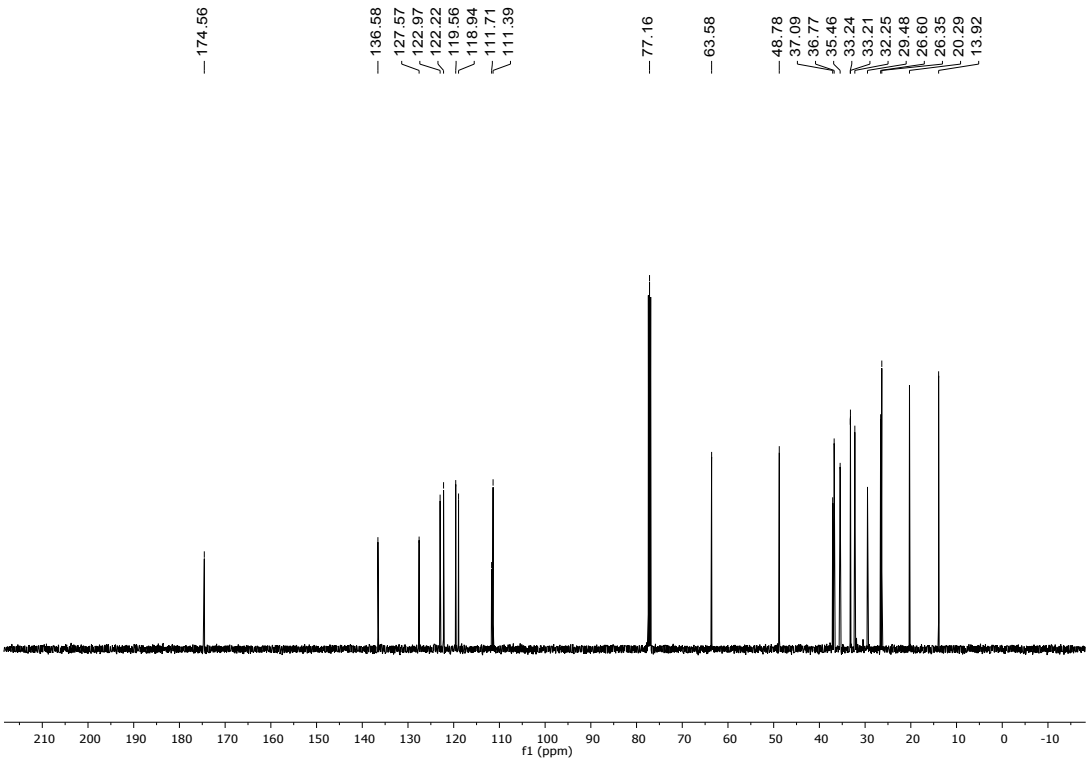

174.54
136.57
127.58
122.95
122.24
119.59
118.96
111.76
111.37
77.16
63.57
48.78
37.74
37.24
36.94
34.49
34.46
32.25
29.47
28.57
26.47
20.30
13.92
f1 (ppm)

S15

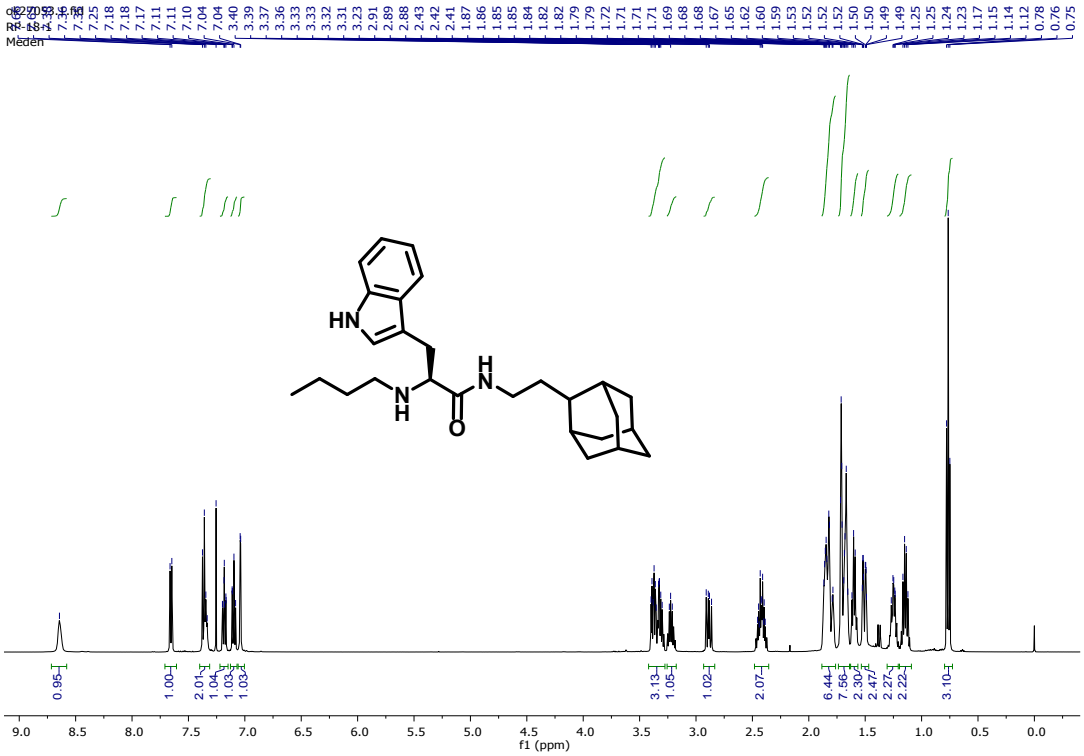

8.58 7.67 7.65 7.38 7.36 7.26 7.19 7.19 7.12 7.11 7.10 7.05 7.04 3.40 3.38 3.37 3.34 3.18 3.06 2.90 2.88 2.43 2.41 1.67 1.67 1.66 1.65 1.64 1.64 1.63 1.62 1.62 1.57 1.56 1.55 1.55 1.54 1.54 1.49 1.48 1.48 1.41 1.40 1.39 1.38 1.27 1.26 1.25 1.25 1.24 1.23 1.17 1.16 1.15 1.13 1.12 0.78 0.76 0.75
HN
H
N
N
H
O
0.94 1.00 1.01 1.01 1.04 1.02 1.00 2.04 1.04 1.02 0.98 2.02 7.43 4.97 2.21 4.10 3.00
f1 (ppm)
174.66 136.59 127.56 122.96 122.24 119.58 118.96 111.77 111.38 77.16 63.66 48.83 45.54 39.72 32.28 32.22 32.20 29.54 28.47 28.42 26.48 20.30 13.93
f1 (ppm)

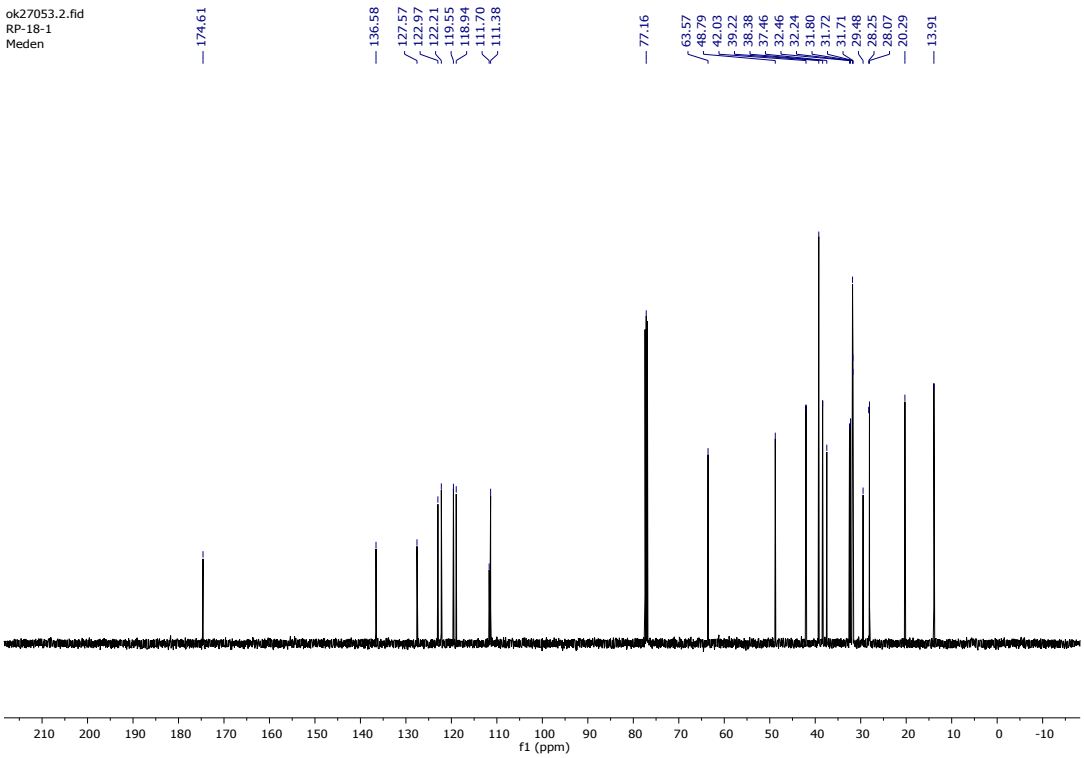
S16


7.66 7.65 7.38 7.36 7.36 7.36 7.26 7.19 7.18 7.10 7.10 7.04 7.04 3.39 3.37 3.36 3.36 3.35 3.33 3.33 3.33 3.32 2.42 2.42 2.41 1.71 1.70 1.70 1.70 1.69 1.69 1.68 1.68 1.67 1.67 1.36 1.35 1.33 1.26 1.26 1.26 1.25 1.25 1.24 1.24 1.23 1.23 1.22 1.19 1.17 1.16 1.15 1.14 1.14 1.12 0.90 0.78 0.77 0.75
HN
H
N
N
H
O
0.94 1.00 1.03 1.01 1.03 1.03 1.01 3.15 1.07 1.03 2.08 5.46 2.55 8.78 2.20 3.15
f1 (ppm)

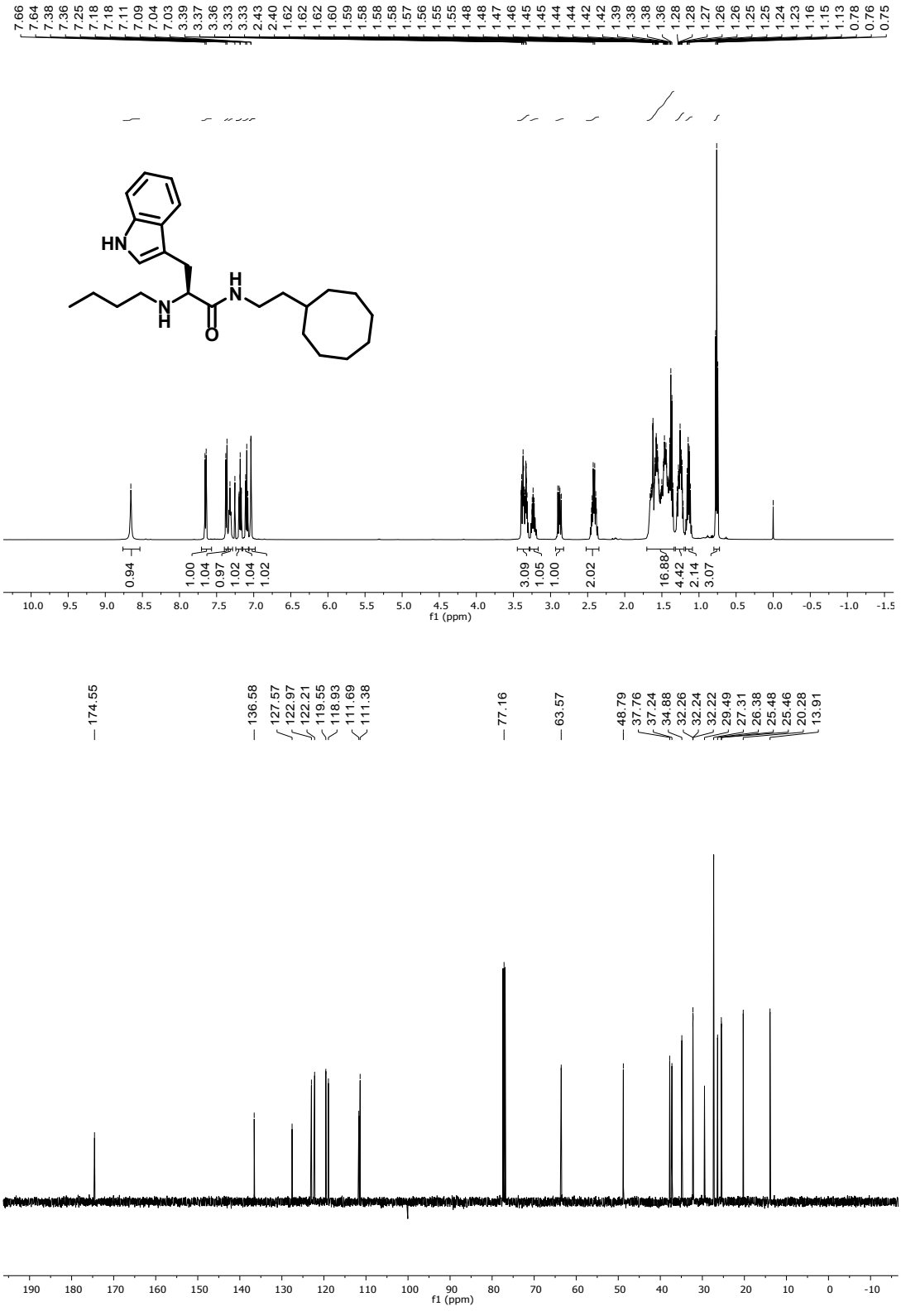

174.56 136.58 127.57 122.97 122.22 119.56 118.94 111.71 111.39 77.16 63.58 48.78 37.09 36.77 35.46 33.24 33.21 32.25 29.48 26.60 26.35 20.29 13.92
f1 (ppm)

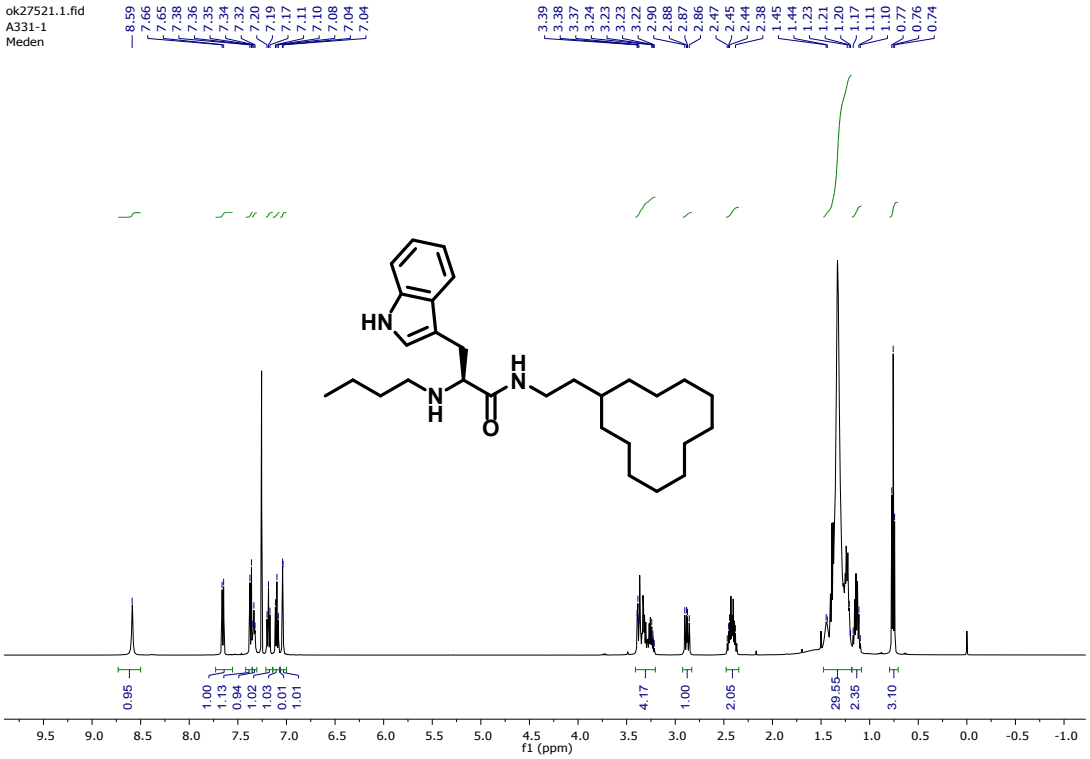
S17

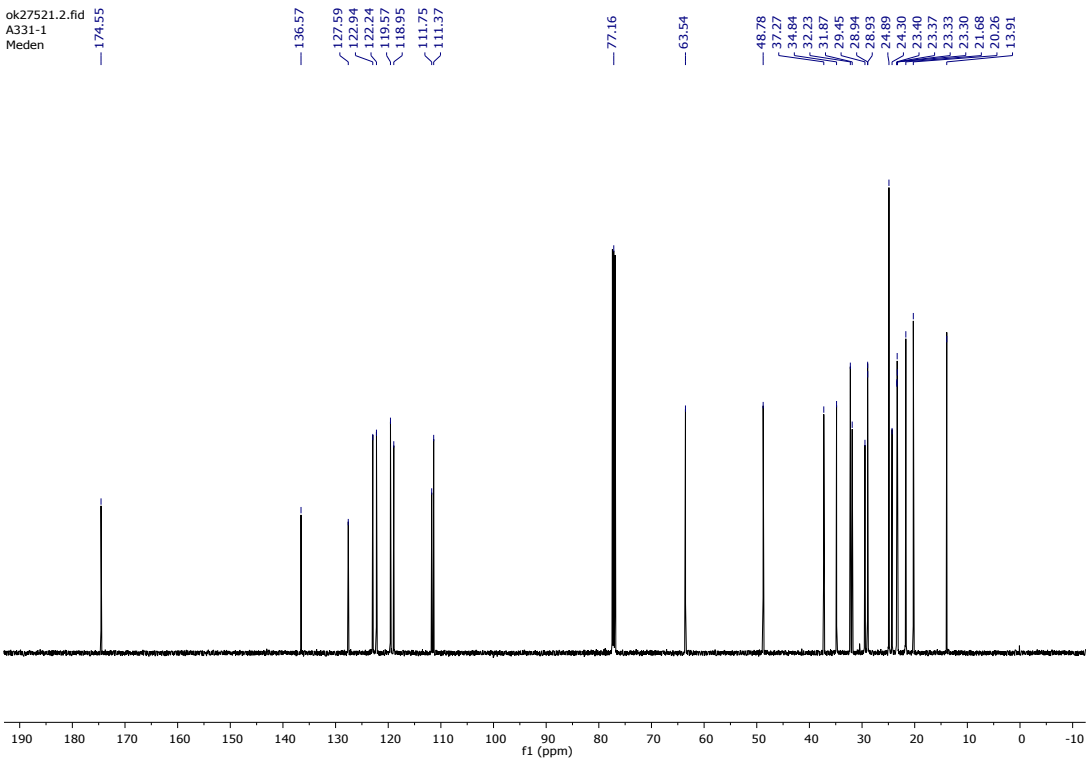

ok27053.2.fid
RP-18-1
Meden
HN
H
N
N
H
O
f1 (ppm)


ok27053.2.fid
RP-18-1
Meden
f1 (ppm)

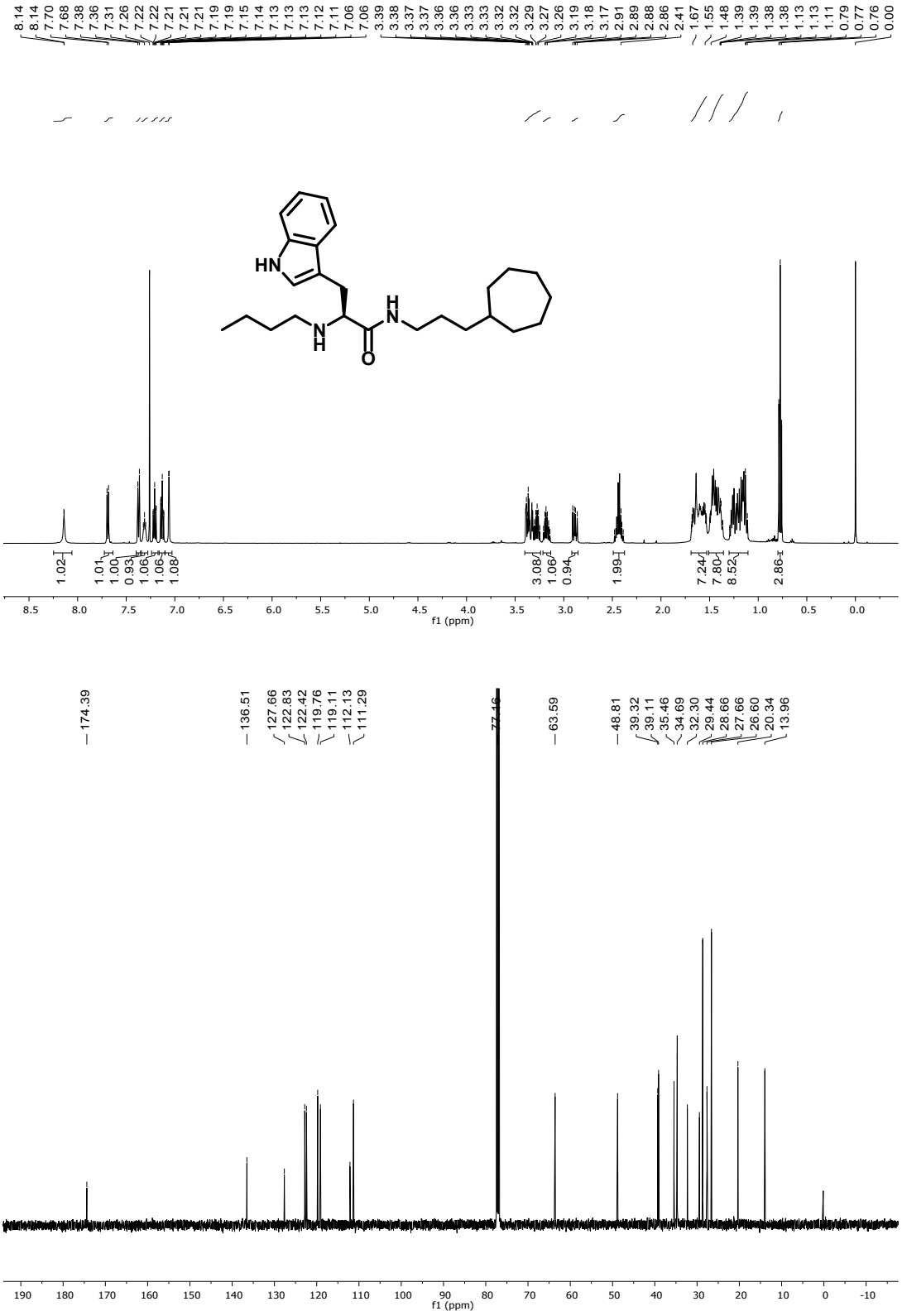
9


7.66 7.64 7.38 7.36 7.25 7.18 7.11 7.09 7.04 7.03 3.39 3.37 3.36 3.33 3.33 2.43 2.40 1.62 1.62 1.62 1.60 1.59 1.58 1.58 1.58 1.57 1.56 1.55 1.55 1.48 1.48 1.47 1.46 1.45 1.45 1.44 1.44 1.42 1.42 1.39 1.38 1.38 1.36 1.28 1.28 1.27 1.26 1.26 1.25 1.25 1.24 1.23 1.16 1.15 1.13 0.78 0.76 0.75
HN
H
N
N
H
O
0.94 1.00 1.04 0.97 1.02 1.04 1.02 3.09 1.05 1.00 2.02 16.88 4.42 2.14 3.07
f1 (ppm)
174.55 136.58 127.57 122.97 122.21 119.55 118.93 111.69 111.38 77.16 63.57 48.79 37.76 37.24 34.88 32.26 32.24 32.22 29.49 27.31 26.38 25.48 25.46 20.28 13.91
f1 (ppm)

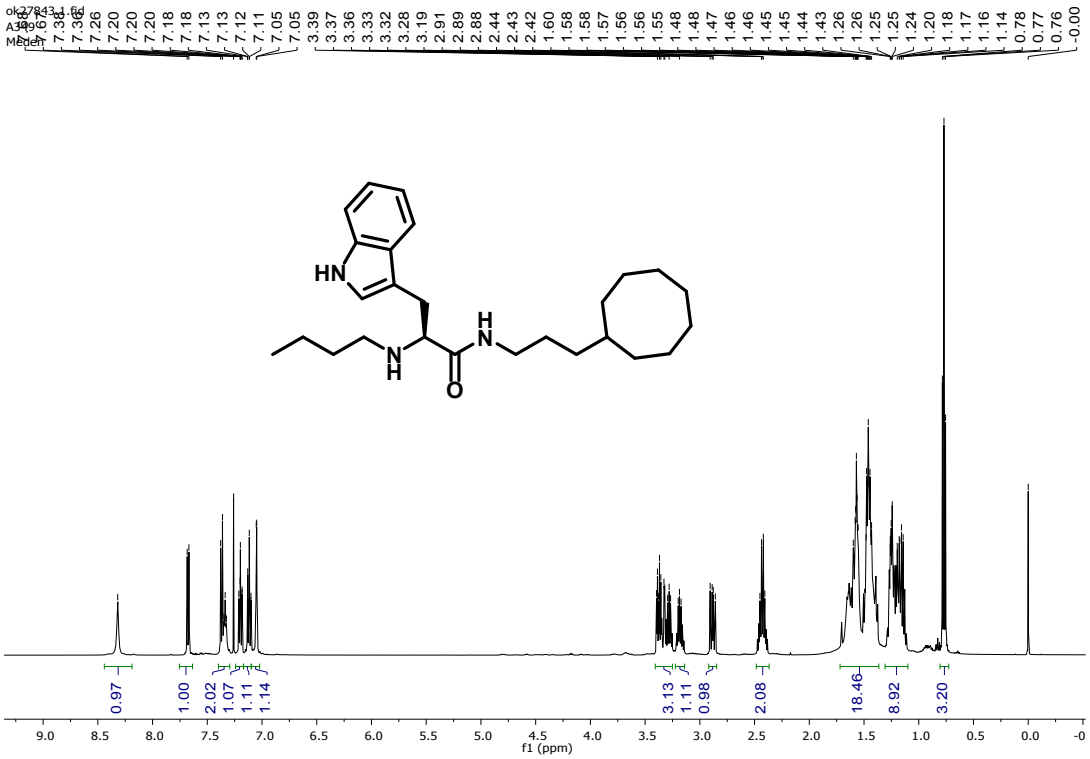

ok27521.1.fid
A331-1
Meden
8.59
7.66
7.65
7.38
7.36
7.35
7.34
7.32
7.20
7.19
7.17
7.11
7.10
7.08
7.04
7.04
3.39
3.38
3.37
3.24
3.23
3.23
3.22
2.90
2.88
2.87
2.86
2.47
2.45
2.44
2.38
1.45
1.44
1.23
1.21
1.20
1.17
1.11
1.10
0.77
0.76
0.74
HN
N
H
H
N
O
0.95
1.00
1.13
0.94
1.02
1.03
0.01
1.01
4.17
1.00
2.05
29.55
2.35
3.10
f1 (ppm)

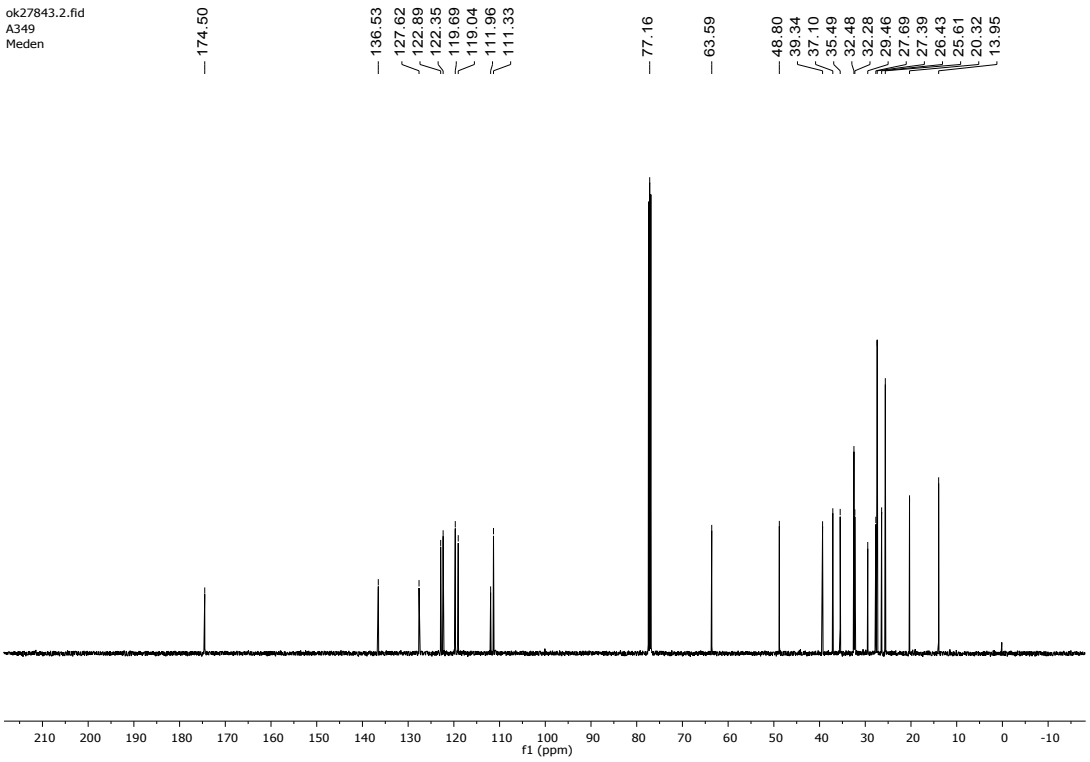

ok27521.2.fid
A331-1
Meden
174.55
136.57
127.59
122.94
122.24
119.57
118.95
111.75
111.37
77.16
63.54
48.78
37.27
34.84
32.23
31.87
29.45
28.94
28.93
24.89
24.30
23.40
23.37
23.33
23.30
21.68
20.26
13.91
f1 (ppm)

8

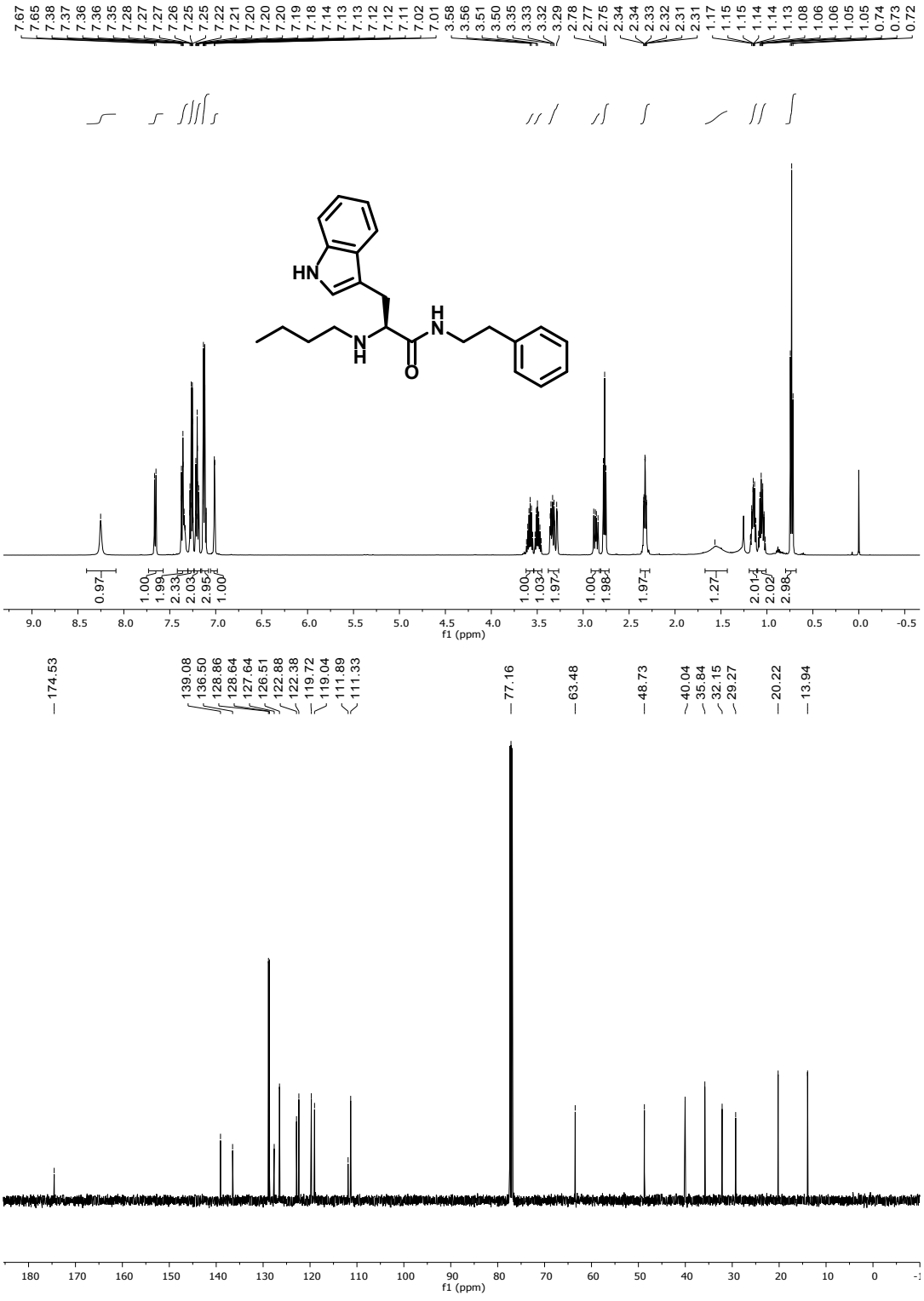

8.14 8.14 7.70 7.68 7.38 7.36 7.31 7.26 7.22 7.22 7.21 7.21 7.21 7.19 7.19 7.15 7.14 7.13 7.13 7.13 7.12 7.11 7.06 7.06 3.39 3.38 3.37 3.37 3.36 3.36 3.33 3.33 3.32 3.32 3.29 3.27 3.26 3.19 3.18 3.17 2.91 2.89 2.88 2.86 2.41 1.67 1.55 1.48 1.39 1.39 1.38 1.38 1.13 1.13 1.11 0.79 0.77 0.76 0.00
HN
N
H
H
N
O
1.02 1.01 1.00 0.93 1.06 1.06 1.08 3.08 1.06 0.94 1.99 7.24 7.80 8.52 2.86
f1 (ppm)
174.39 136.51 127.66 122.83 122.42 119.76 119.11 112.13 111.29 77.16 63.59 48.81 39.32 39.11 35.46 34.69 32.30 29.44 28.66 27.66 26.60 20.34 13.96
f1 (ppm)

S20


ok27843.1.fid
A349
Meden
HN
H
N
N
H
O
0.97
1.00
2.02
1.07
1.11
1.14
3.13
1.11
0.98
2.08
18.46
8.92
3.20
f1 (ppm)

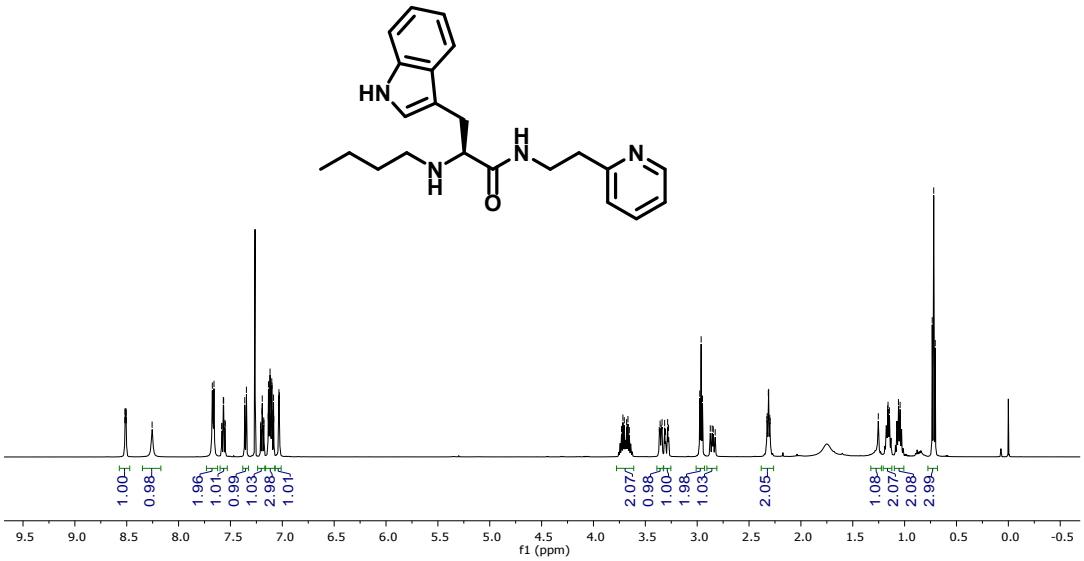

ok27843.2.fid
A349
Meden
174.50
136.53
127.62
122.89
122.35
119.69
119.04
111.96
111.33
77.16
63.59
48.80
39.34
37.10
35.49
32.48
32.28
29.46
27.69
27.39
26.43
25.61
20.32
13.95
f1 (ppm)

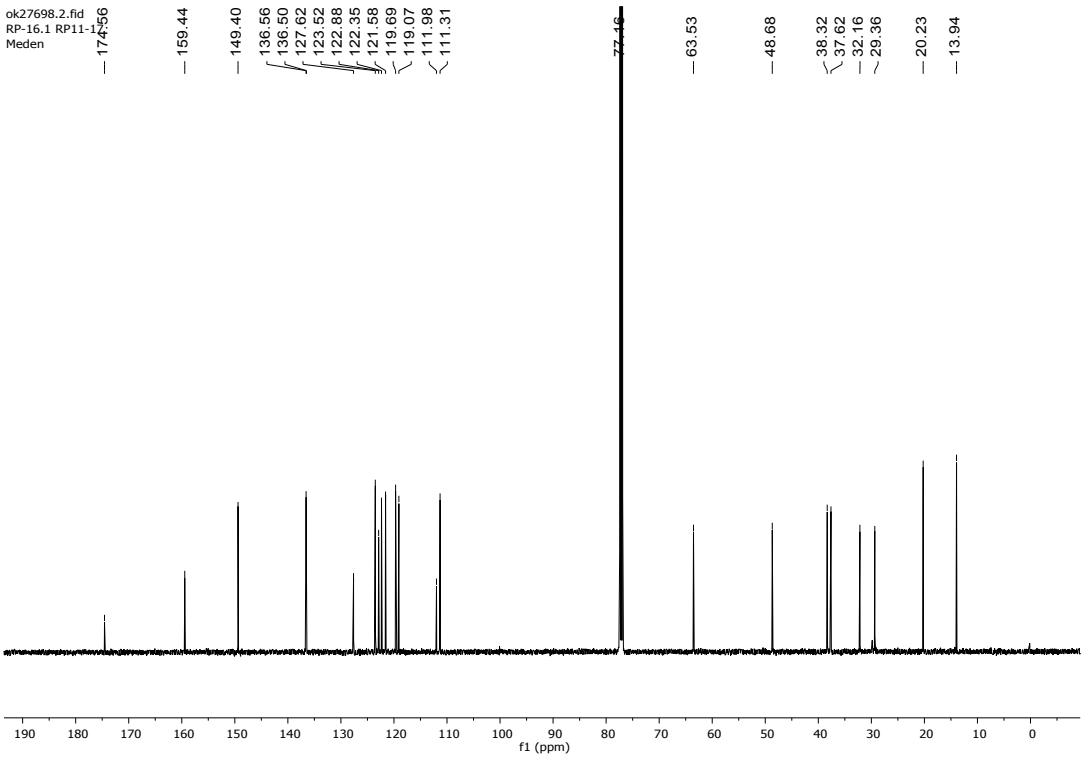
S21


7.67 7.65 7.38 7.37 7.36 7.36 7.35 7.28 7.27 7.26 7.25 7.25 7.22 7.21 7.20 7.20 7.19 7.18 7.14 7.13 7.13 7.12 7.12 7.11 7.02 7.01
3.58 3.56 3.51 3.50 3.35 3.33 3.32 3.29
2.78 2.77 2.75
2.34 2.34 2.33 2.32 2.31 2.31
1.17 1.15 1.15 1.14 1.14 1.13 1.08 1.06 1.06 1.05 1.05 0.74 0.73 0.72
HN
H
N
N
H
O
0.97 1.00 1.99 2.33 2.03 2.95 1.00 1.00 1.03 1.97 1.00 1.98 1.97 1.27 2.01 2.02 2.98
f1 (ppm)
174.53
139.08 136.50 128.86 128.64 127.64 126.51 122.88 122.38 119.72 119.04 111.89 111.33
77.16
63.48
48.73
40.04 35.84 32.15 29.27
20.22
13.94
f1 (ppm)

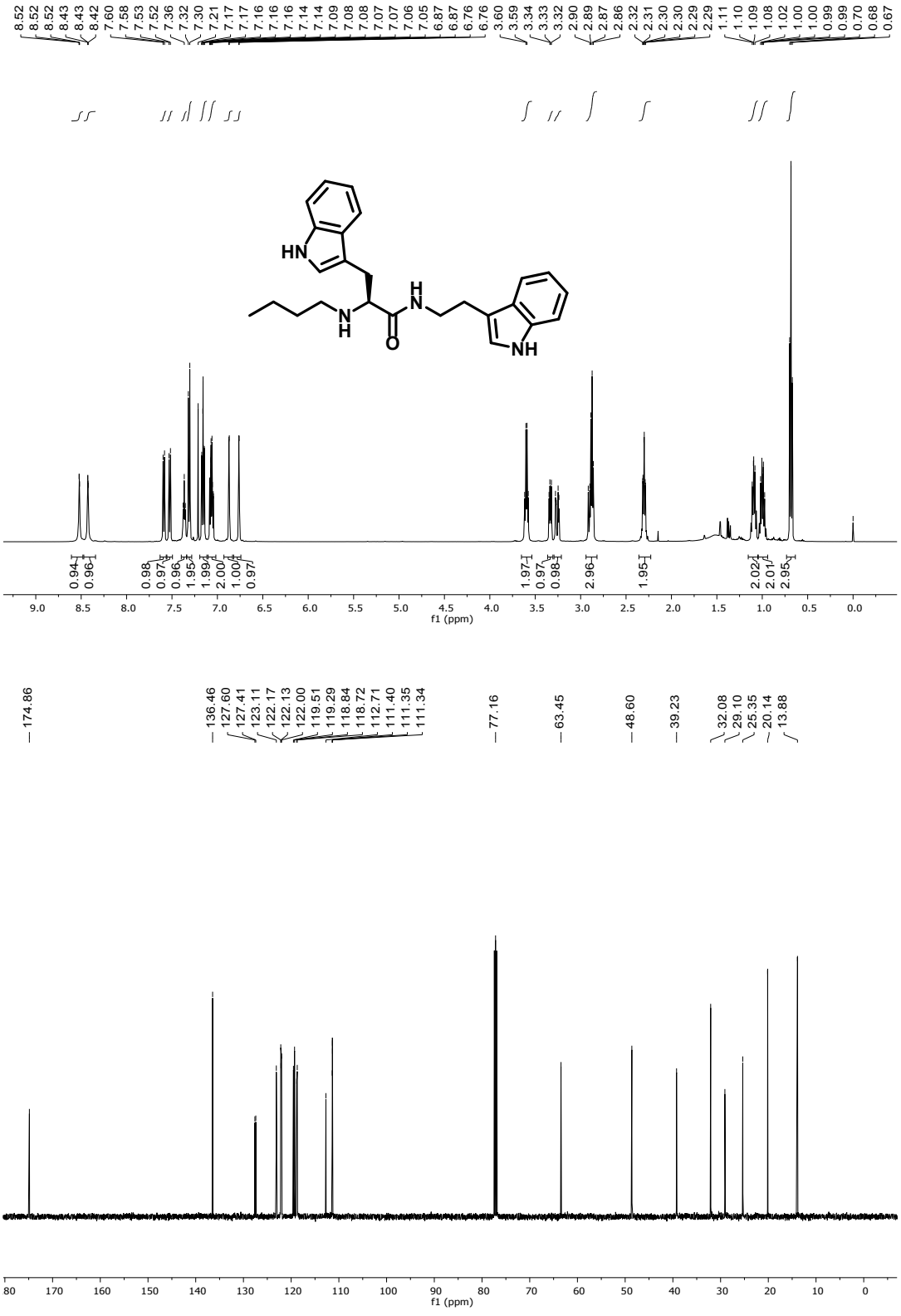
S22


ok27698.1.fid
RP-16.1 RP11-1
Meden
8.52
8.51
8.50
7.67
7.66
7.57
7.36
7.35
7.20
7.19
7.18
7.14
7.13
7.13
7.13
7.12
7.12
7.12
7.11
7.11
7.10
7.10
7.10
7.10
7.09
7.08
7.08
7.03
7.03
3.72
3.70
3.67
3.28
2.98
2.96
2.95
2.33
2.32
2.31
2.30
2.30
1.25
1.16
1.16
1.15
1.06
1.06
1.04
0.73
0.72
0.70

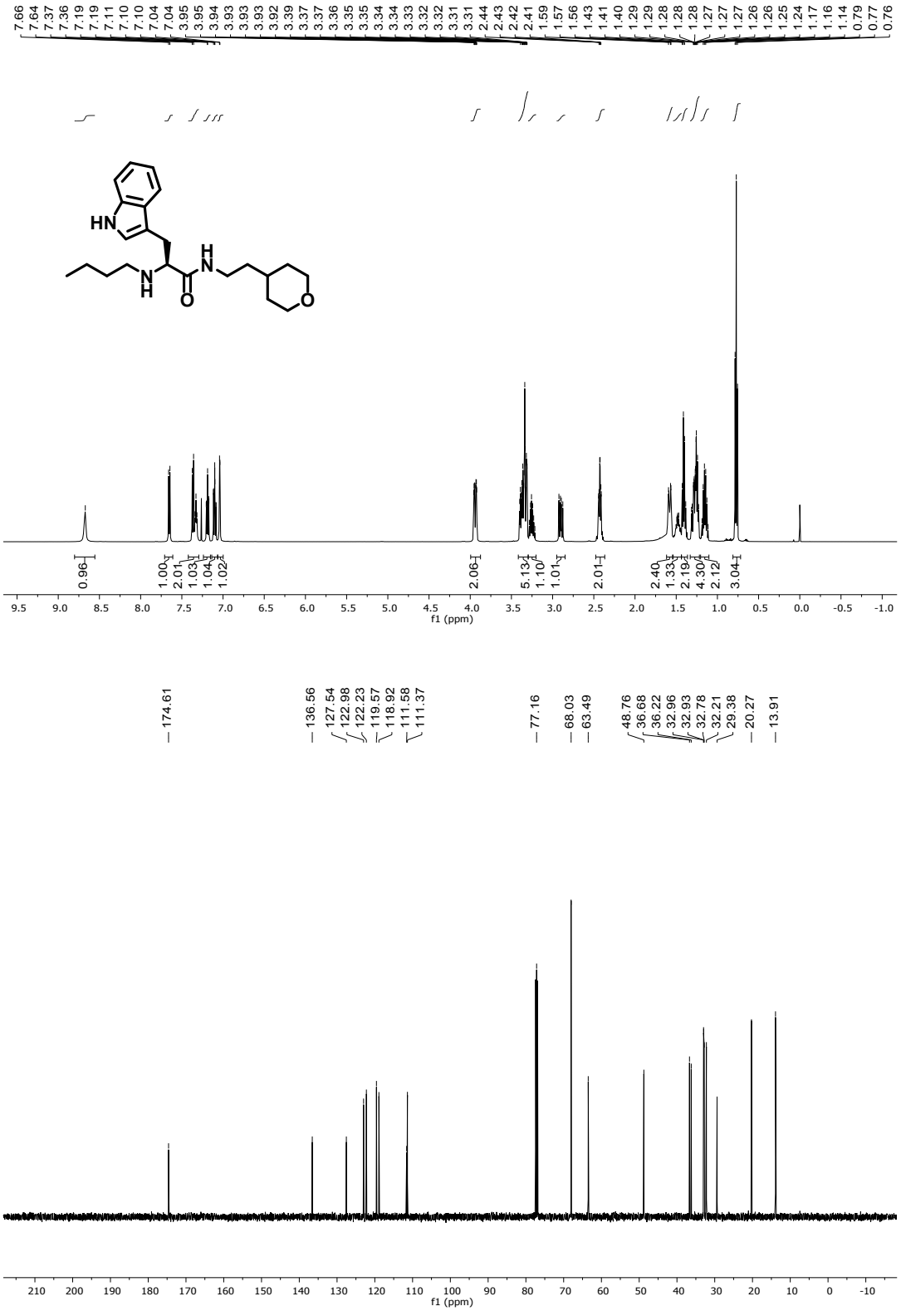

HN
H
N
N
H
O
N
1.00
0.98
1.96
1.01
0.99
1.03
2.98
1.01
2.07
0.98
1.00
1.98
1.03
2.05
1.08
2.07
2.08
2.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


ok27698.2.fid
RP-16.1 RP11-1
Meden
174.56
159.44
149.40
136.56
136.50
127.62
123.52
122.88
122.35
121.58
119.69
119.07
111.98
111.31
77.46
63.53
48.68
38.32
37.62
32.16
29.36
20.23
13.94
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

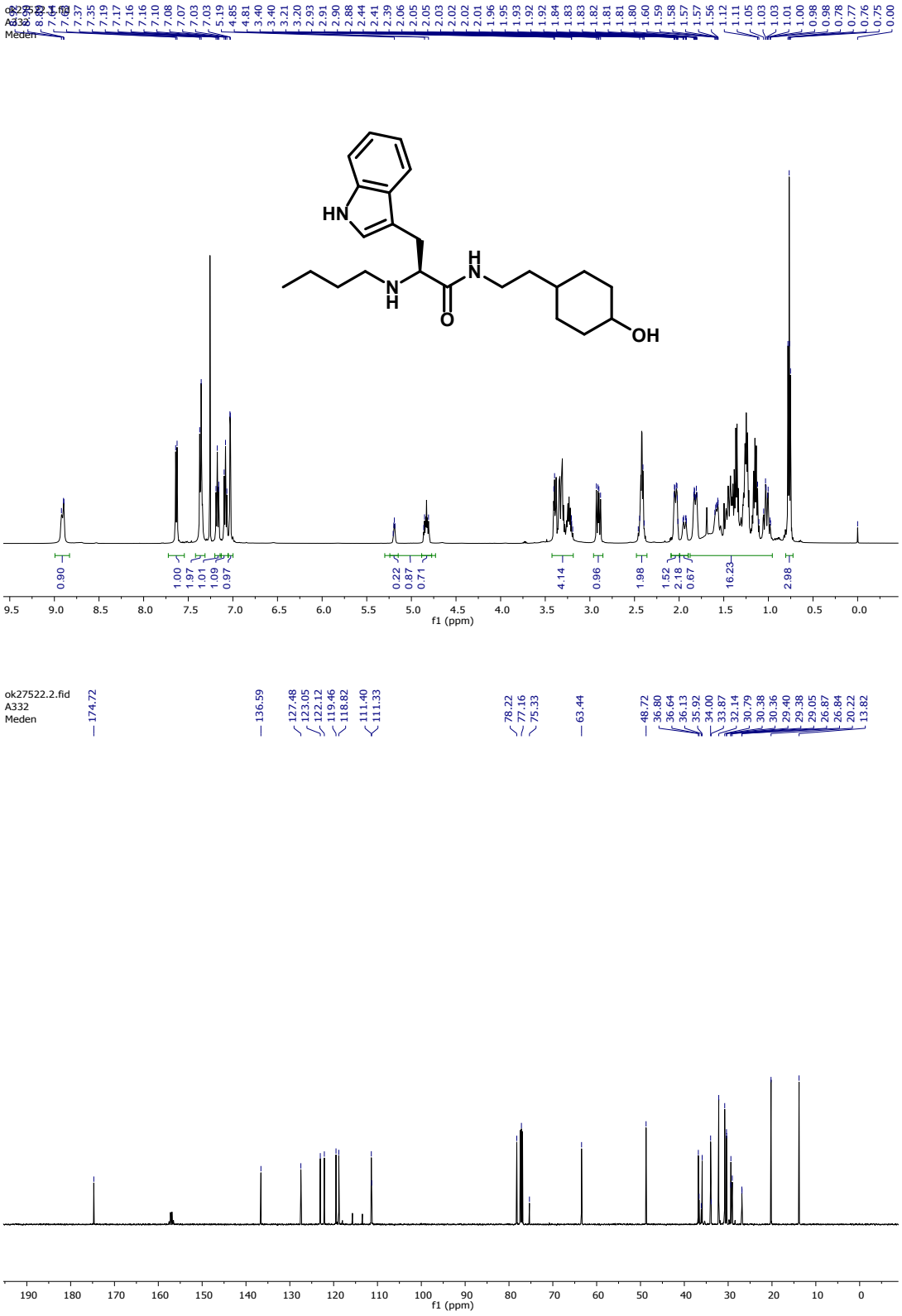
S23


8.52 8.52 8.52 8.43 8.43 8.42 7.60 7.58 7.53 7.52 7.36 7.32 7.30 7.21 7.17 7.17 7.16 7.16 7.16 7.14 7.14 7.09 7.08 7.08 7.07 7.07 7.06 7.05 6.87 6.76 6.76 3.60 3.59 3.34 3.33 3.32 2.90 2.89 2.87 2.86 2.32 2.31 2.30 2.30 2.29 2.29 1.11 1.10 1.09 1.08 1.02 1.00 1.00 0.99 0.99 0.70 0.68 0.67
HN
H
N
N
H
O
NH
0.94 0.96 0.98 0.97 0.96 1.95 1.99 2.00 0.97 1.97 0.97 0.98 2.96 1.95 2.02 2.01 2.95
f1 (ppm)
174.86 136.46 127.60 127.41 123.11 122.17 122.13 122.00 119.51 119.29 118.84 118.72 112.71 111.40 111.35 111.34 77.16 63.45 48.60 39.23 32.08 29.10 25.35 20.14 13.88
f1 (ppm)

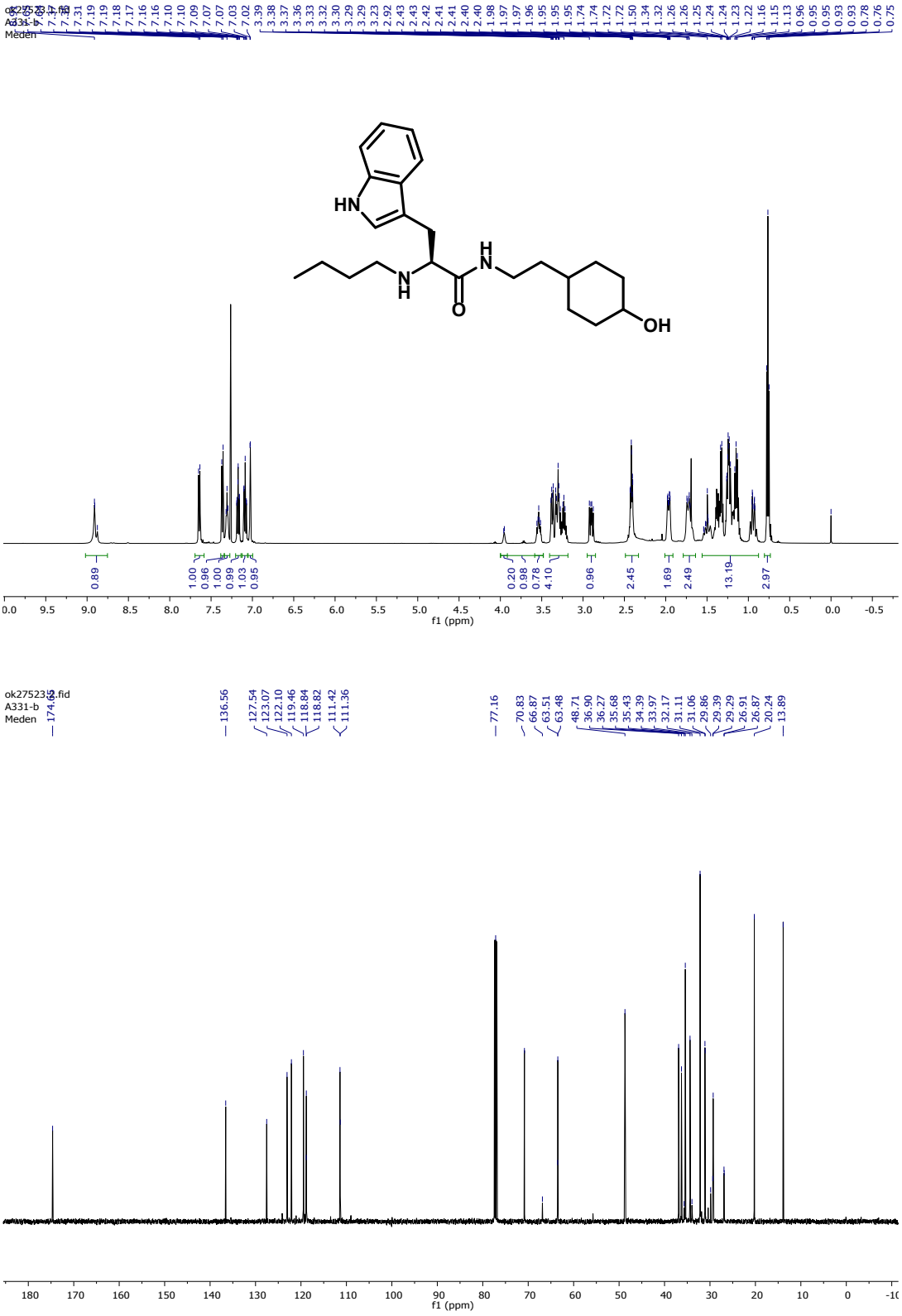
S24


7.66 7.64 7.37 7.36 7.19 7.19 7.11 7.10 7.10 7.04 7.04 3.95 3.95 3.94 3.93 3.93 3.93 3.92 3.39 3.37 3.37 3.36 3.35 3.35 3.34 3.34 3.33 3.32 3.32 3.31 3.31 2.44 2.43 2.42 2.41 1.59 1.57 1.56 1.43 1.41 1.40 1.29 1.29 1.28 1.28 1.28 1.27 1.27 1.27 1.26 1.26 1.25 1.24 1.17 1.16 1.14 0.79 0.77 0.76
HN
H
N
N
H
O
O
0.96 1.00 2.01 1.03 1.04 1.02 2.06 5.13 1.10 1.01 2.01 2.40 1.33 2.19 4.30 2.12 3.04
f1 (ppm)
174.61 136.56 127.54 122.98 122.23 119.57 118.92 111.58 111.37 77.16 68.03 63.49 48.76 36.68 36.22 32.96 32.93 32.78 32.21 29.38 20.27 13.91
f1 (ppm)

S25

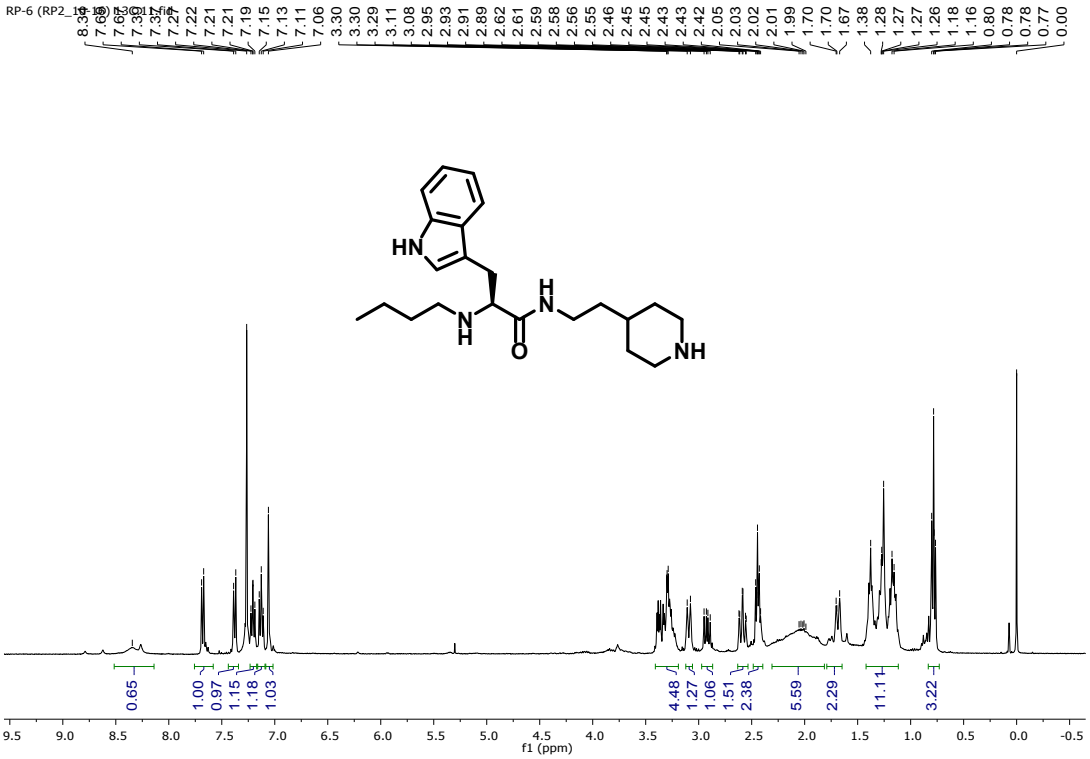


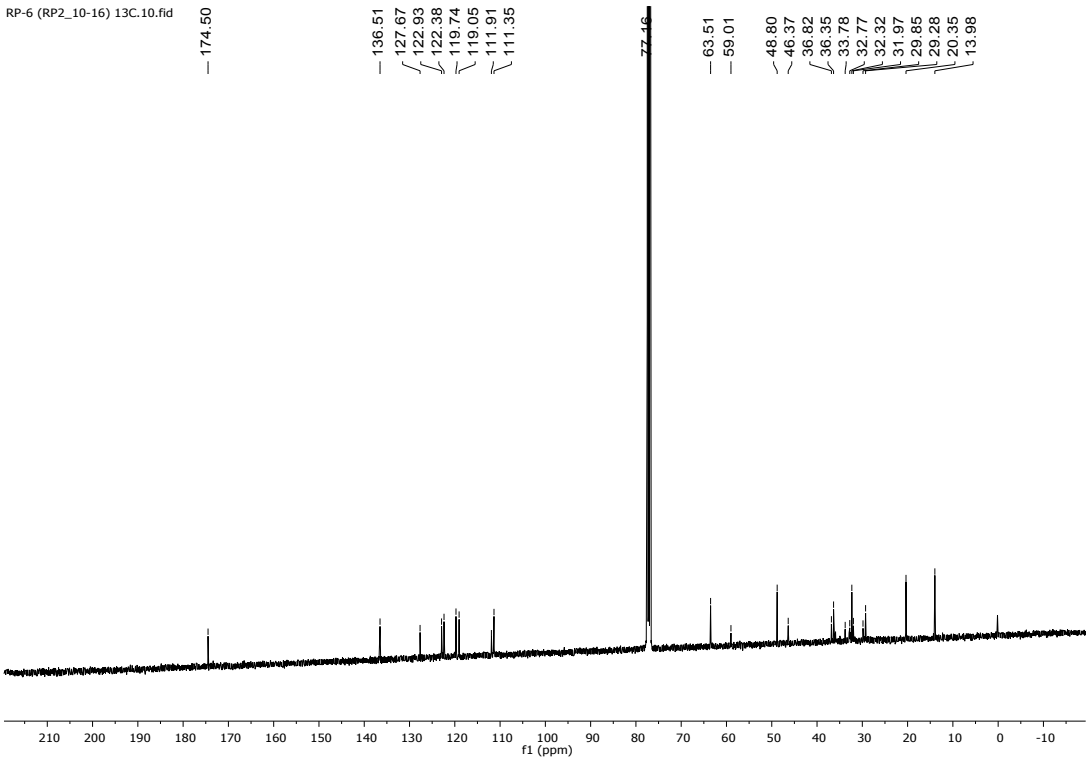
Two conformers in a ratio of 76:24.



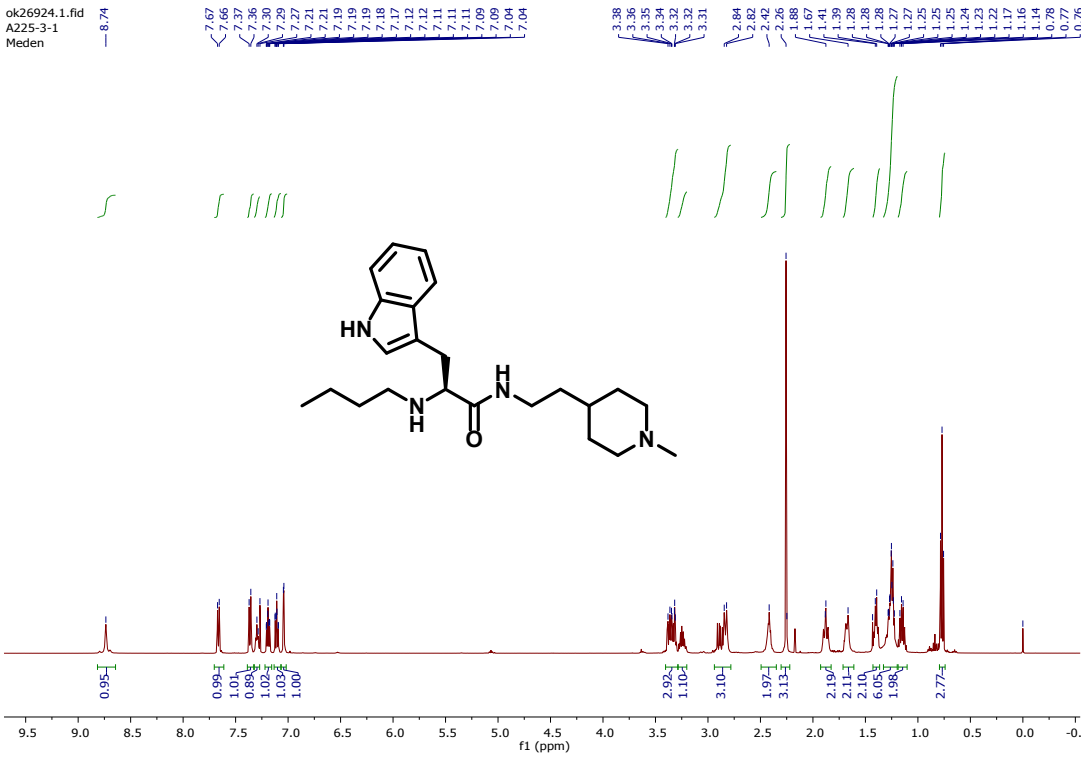
Two conformers in a ratio of 80:20.

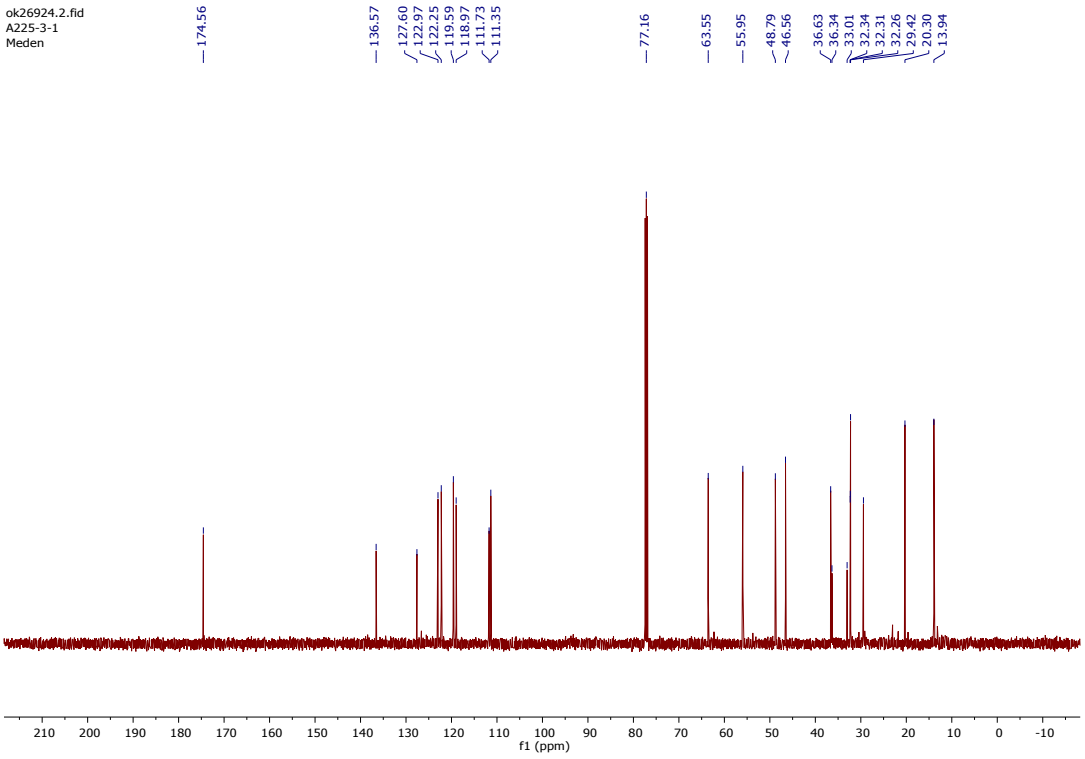
S27


RP-6 (RP2_10-16) 13C.11.fid
8.34
7.68
7.66
7.30
7.37
7.24
7.22
7.21
7.21
7.19
7.15
7.13
7.11
7.06
3.30
3.30
3.29
3.11
3.08
2.95
2.93
2.91
2.89
2.62
2.61
2.59
2.58
2.56
2.55
2.46
2.45
2.45
2.43
2.43
2.42
2.05
2.03
2.02
2.01
1.99
1.70
1.70
1.67
1.38
1.28
1.27
1.27
1.26
1.18
1.16
0.80
0.78
0.78
0.77
0.00
HN
H
N
N
H
O
NH
0.65
1.00
0.97
1.15
1.18
1.03
4.48
1.27
1.06
1.51
2.38
5.59
2.29
11.11
3.22
f1 (ppm)


RP-6 (RP2_10-16) 13C.10.fid
174.50
136.51
127.67
122.93
122.38
119.74
119.05
111.91
111.35
77.46
63.51
59.01
48.80
46.37
36.82
36.35
33.78
32.77
32.32
31.97
29.85
29.28
20.35
13.98
f1 (ppm)

S28

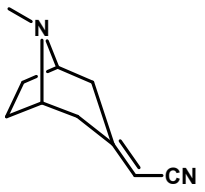

ok26924.1.fid
A225-3-1
Meden
HN
H
N
N
H
O
N
f1 (ppm)


ok26924.2.fid
A225-3-1
Meden
f1 (ppm)

S29-1

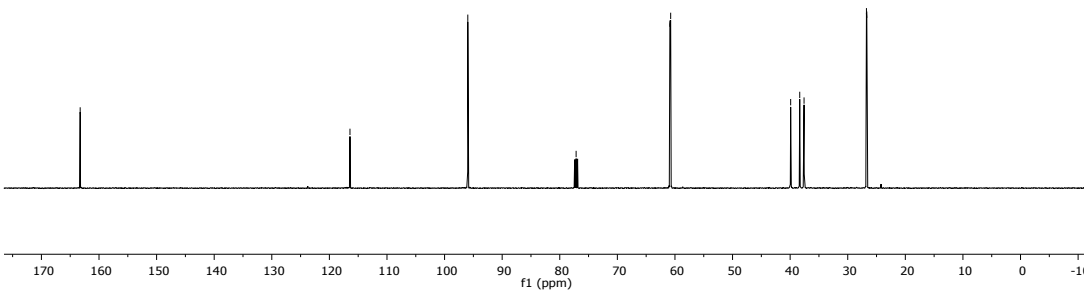
ok27276.1.fid
A300-1
Meden

5.18 5.18 5.18 3.34 3.33 3.33 3.29 3.28 3.27 2.67 2.67 2.66 2.66 2.66 2.64 2.64 2.63 2.63 2.62 2.60 2.60 2.59 2.58 2.58 2.58 2.57 2.57 2.55 2.54 2.39 2.38 2.12 2.12 2.09 2.00 2.00 1.99 1.99 1.98 1.98 1.49 1.48 1.47 1.46 -0.00

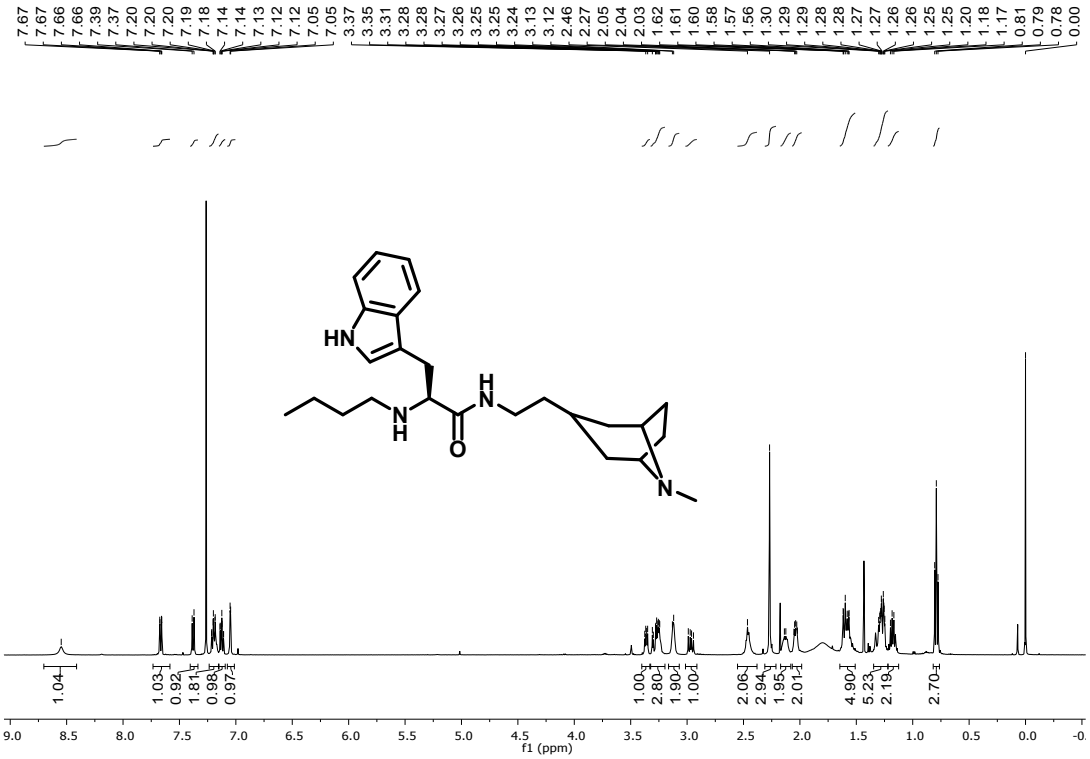


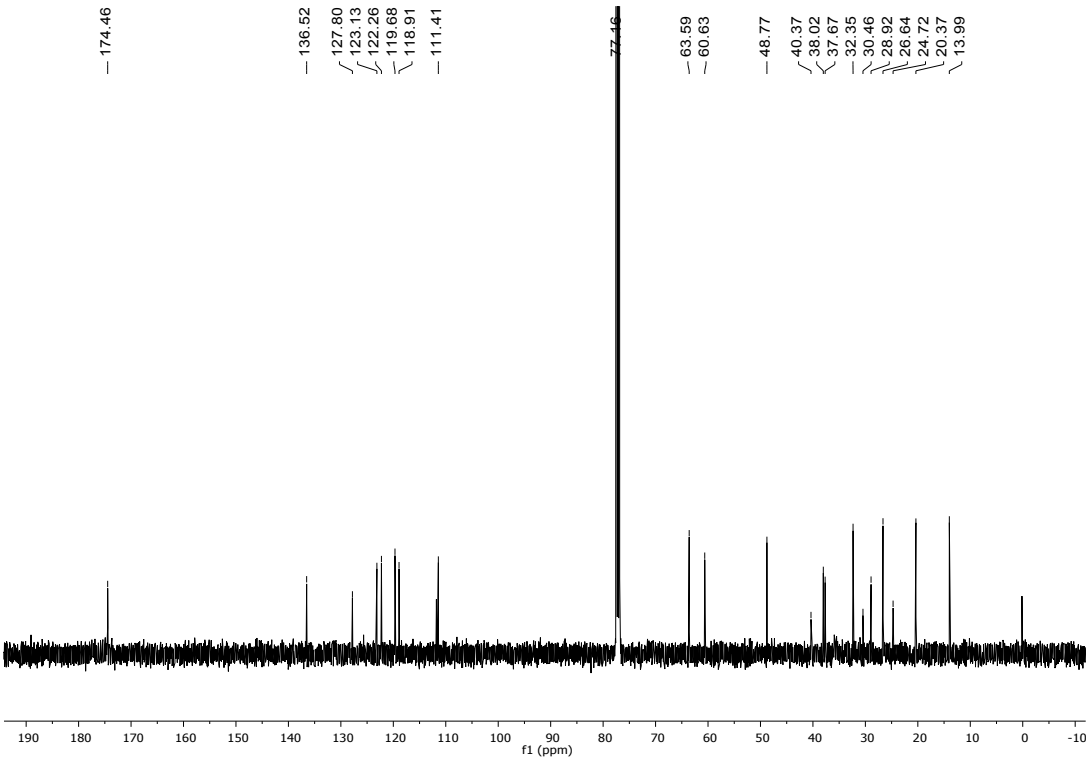
ok27276.2.fid
A300-1
Meden

163.22 116.43 95.97 77.16 60.88 60.74 39.91 38.34 37.58 26.75 26.69



S29

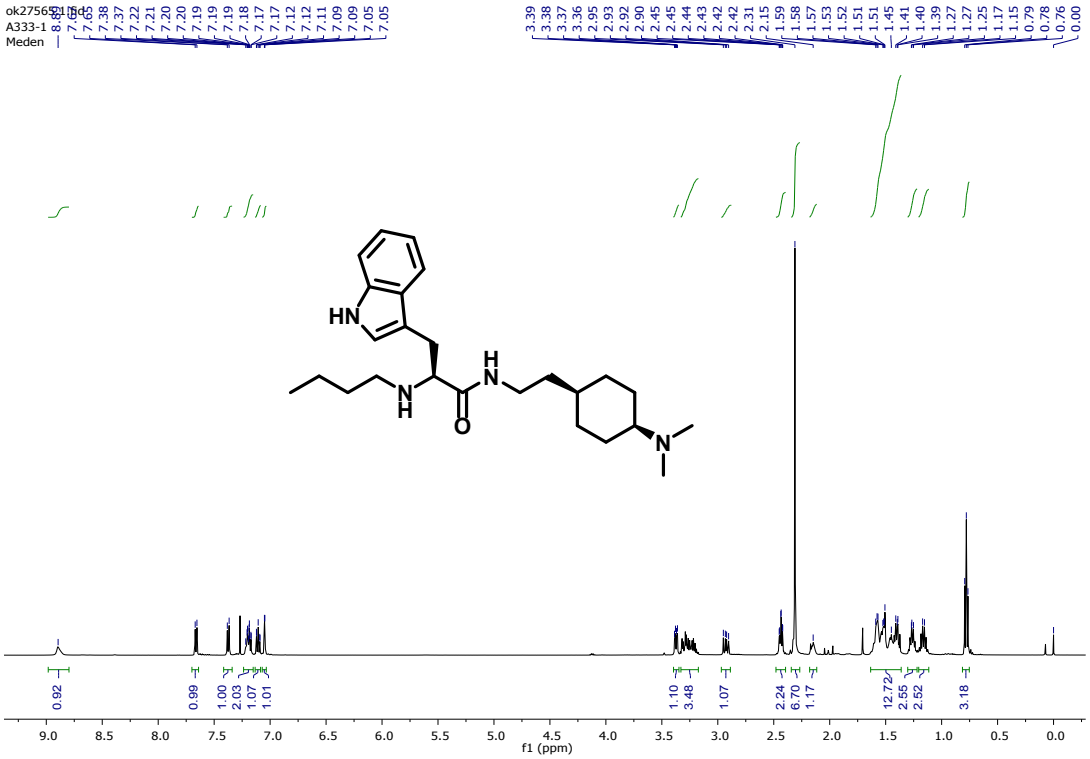

7.67 7.67 7.66 7.66 7.39 7.37 7.20 7.20 7.20 7.19 7.18 7.14 7.14 7.13 7.12 7.12 7.05 7.05
3.37 3.35 3.31 3.28 3.28 3.27 3.26 3.25 3.25 3.24 3.13 3.12 2.46 2.27 2.05 2.04 2.03 1.62 1.61 1.60 1.58 1.57 1.56 1.30 1.29 1.29 1.28 1.28 1.27 1.27 1.26 1.26 1.25 1.25 1.20 1.18 1.17 0.81 0.79 0.78 0.00
HN
H
N
N
H
O
N
1.04 1.03 0.92 1.81 0.98 0.97 1.00 2.80 1.90 1.00 2.06 2.94 1.95 2.01 4.90 5.23 2.19 2.70
f1 (ppm)

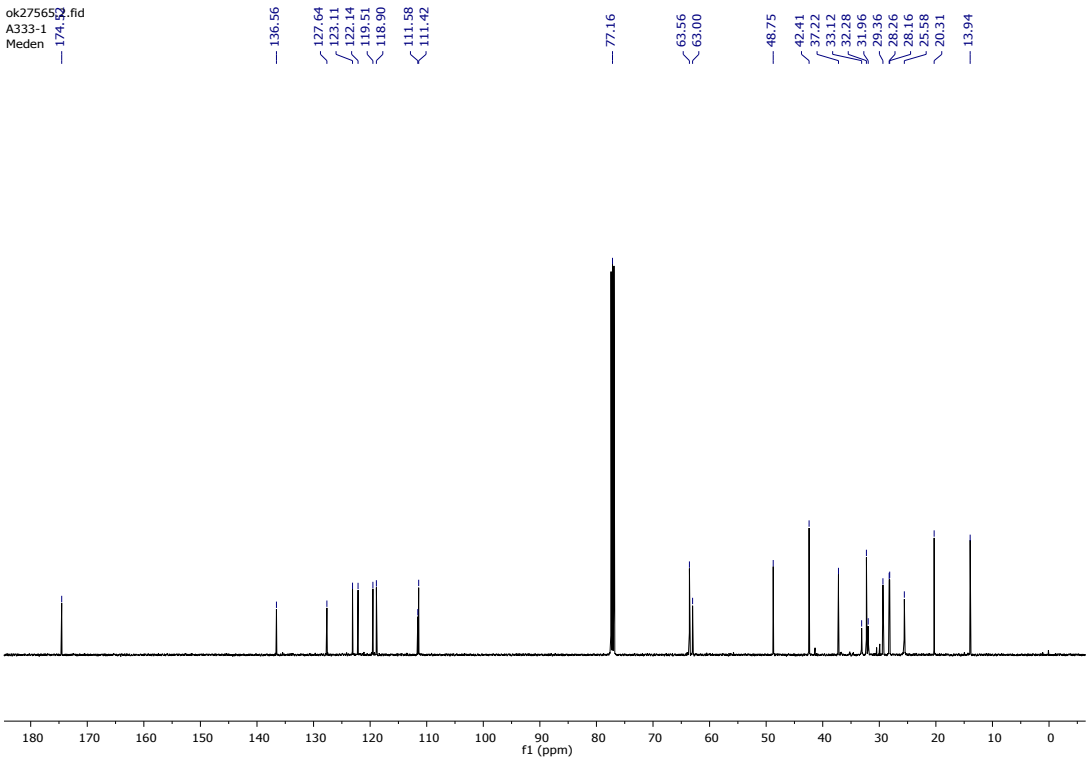

174.46 136.52 127.80 123.13 122.26 119.68 118.91 111.41 77.46 63.59 60.63 48.77 40.37 38.02 37.67 32.35 30.46 28.92 26.64 24.72 20.37 13.99
f1 (ppm)

S30

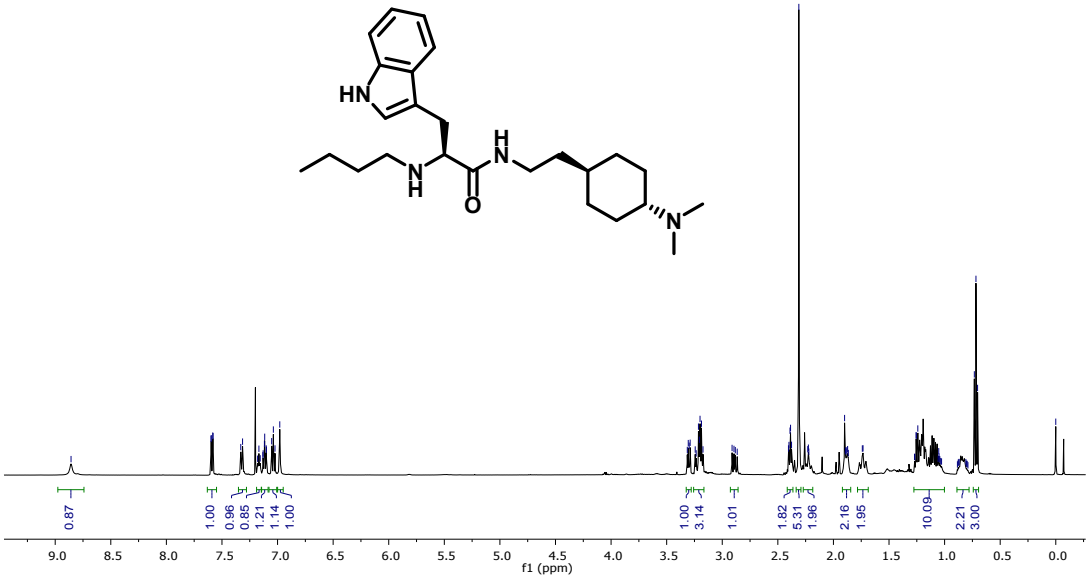
Mixture of two diastereomers in a ratio of 1:1.

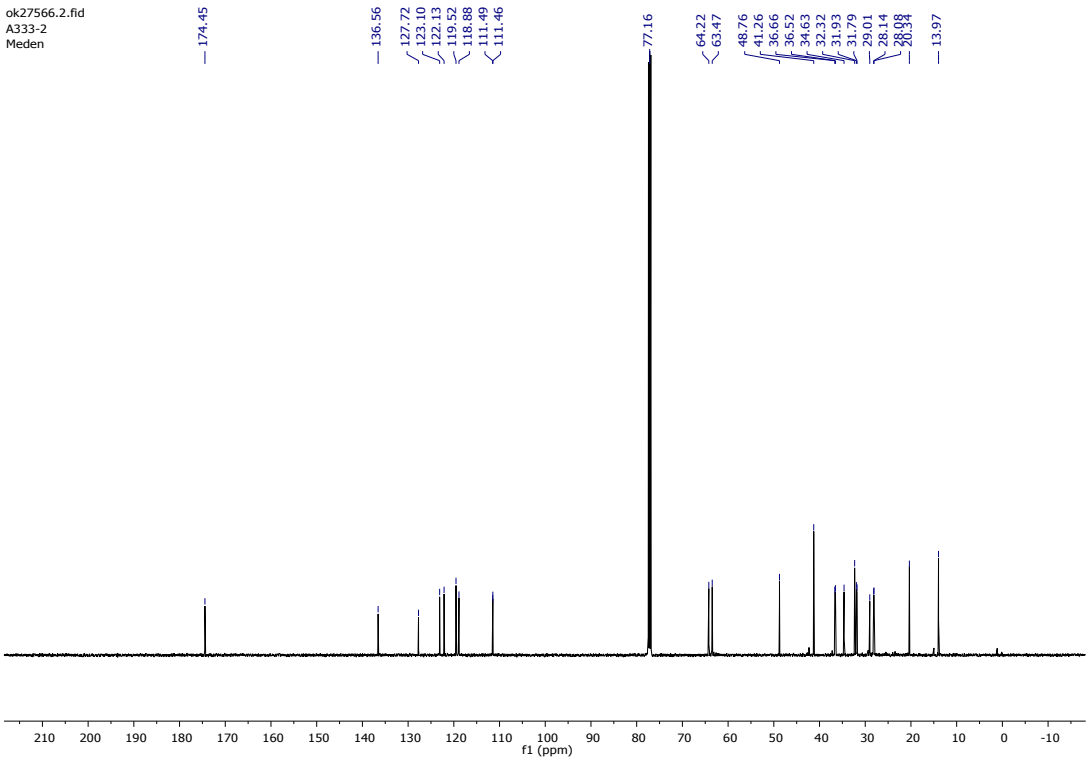
S31


ok275652.fid
A333-1
Meden
HN
H
N
N
H
O
N
f1 (ppm)

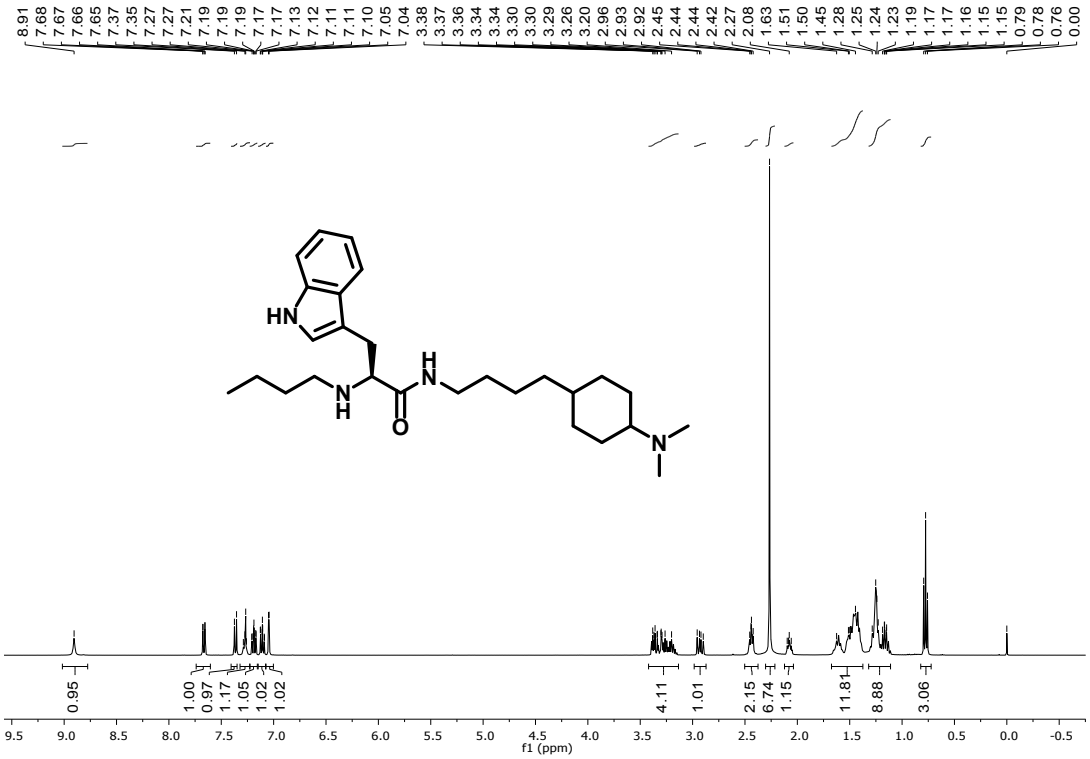

ok275652.fid
A333-1
Meden
f1 (ppm)

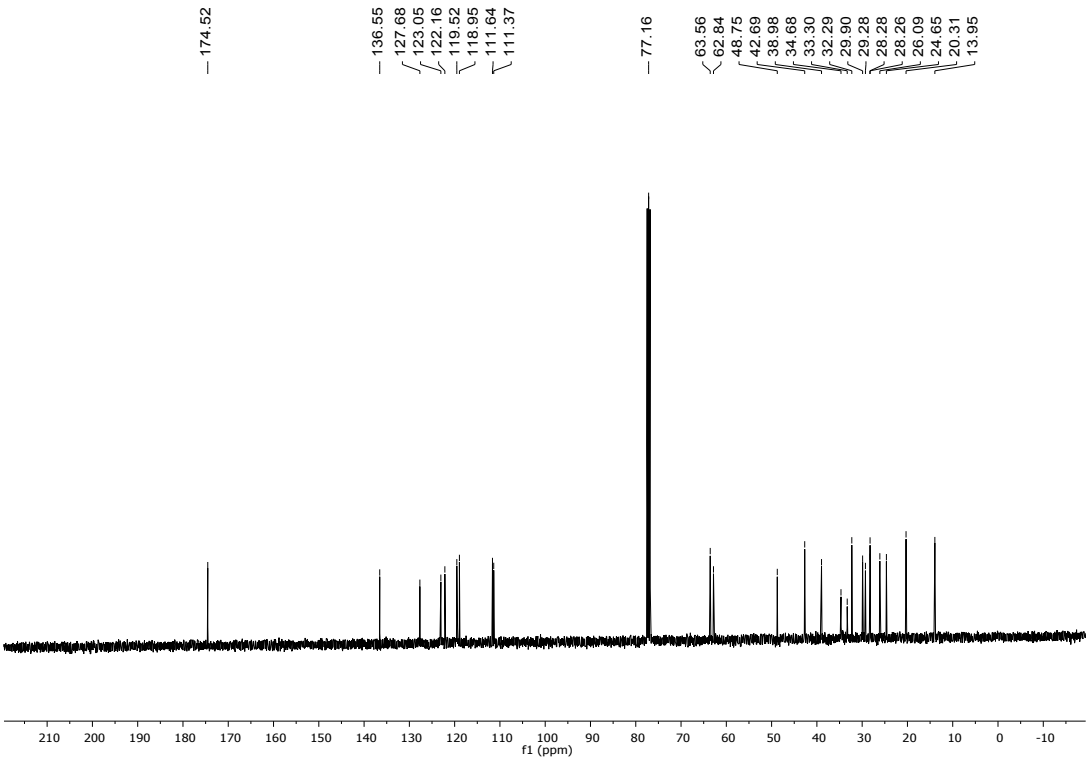
13



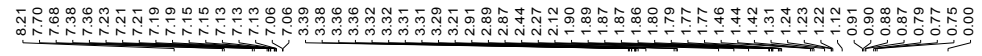


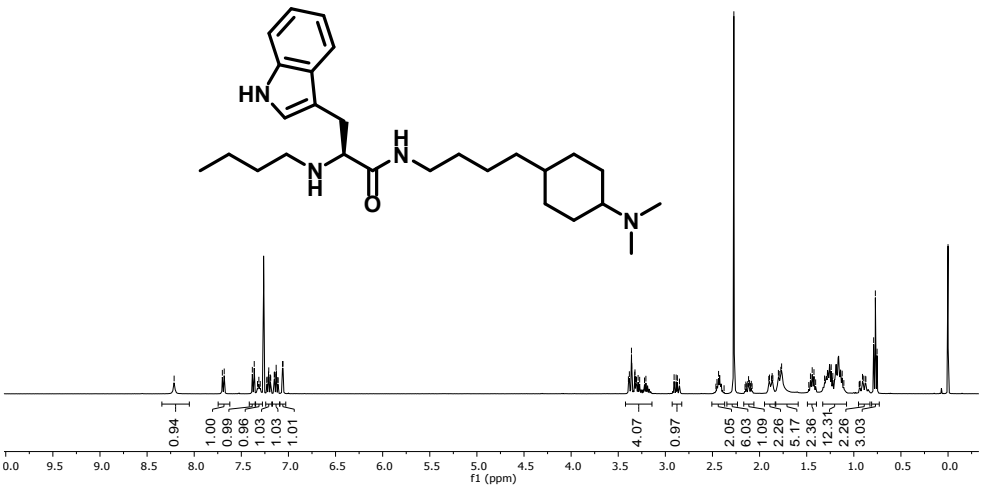
S32

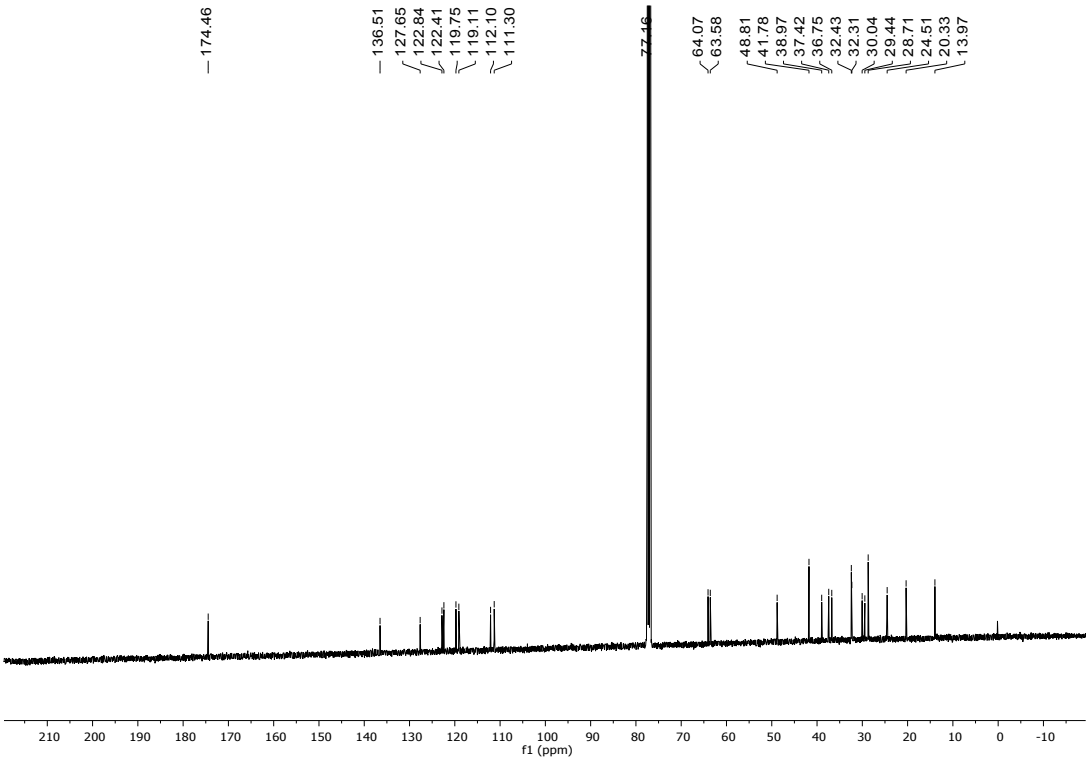

8.91
7.68
7.67
7.66
7.65
7.37
7.35
7.27
7.27
7.21
7.19
7.19
7.19
7.17
7.17
7.13
7.12
7.11
7.11
7.10
7.05
7.04
3.38
3.37
3.36
3.34
3.34
3.30
3.30
3.29
3.26
3.20
2.96
2.93
2.92
2.45
2.44
2.44
2.42
2.27
2.08
1.63
1.51
1.50
1.45
1.28
1.25
1.24
1.23
1.19
1.17
1.17
1.16
1.15
1.15
0.79
0.78
0.76
0.00
HN
H
N
N
H
O
N
0.95
1.00
0.97
1.17
1.05
1.02
1.02
4.11
1.01
2.15
6.74
1.15
11.81
8.88
3.06
f1 (ppm)


174.52
136.55
127.68
123.05
122.16
119.52
118.95
111.64
111.37
77.16
63.56
62.84
48.75
42.69
38.98
34.68
33.30
32.29
29.90
29.28
28.28
28.26
26.09
24.65
20.31
13.95
f1 (ppm)

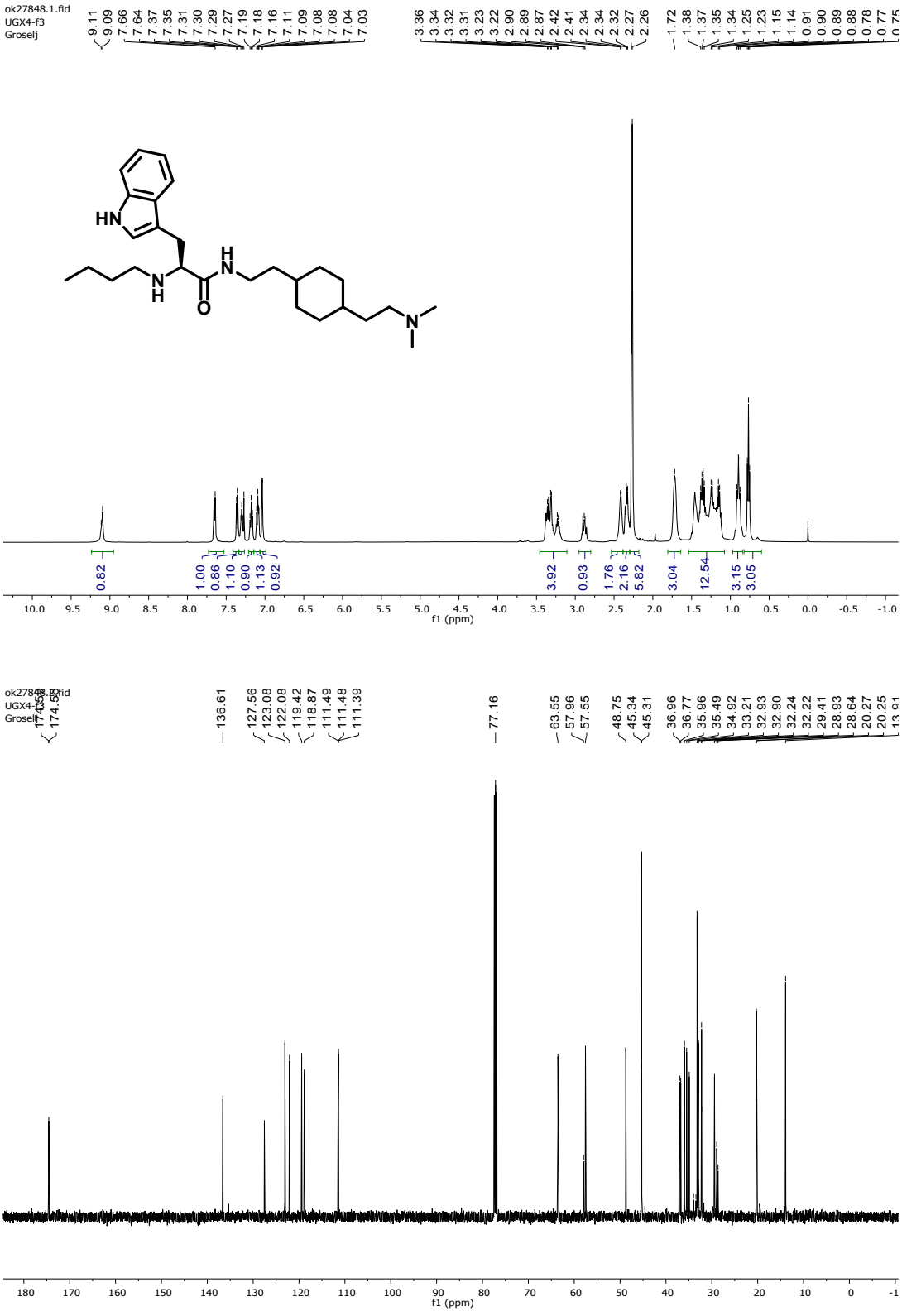
S33


8.21
7.70
7.68
7.38
7.36
7.23
7.21
7.21
7.19
7.19
7.15
7.15
7.13
7.13
7.13
7.06
7.06
3.39
3.38
3.36
3.36
3.32
3.32
3.31
3.31
3.29
3.21
2.91
2.89
2.87
2.44
2.27
2.12
1.90
1.89
1.87
1.87
1.86
1.80
1.79
1.77
1.77
1.46
1.44
1.42
1.31
1.24
1.23
1.22
1.12
0.91
0.90
0.88
0.87
0.79
0.77
0.75
0.00

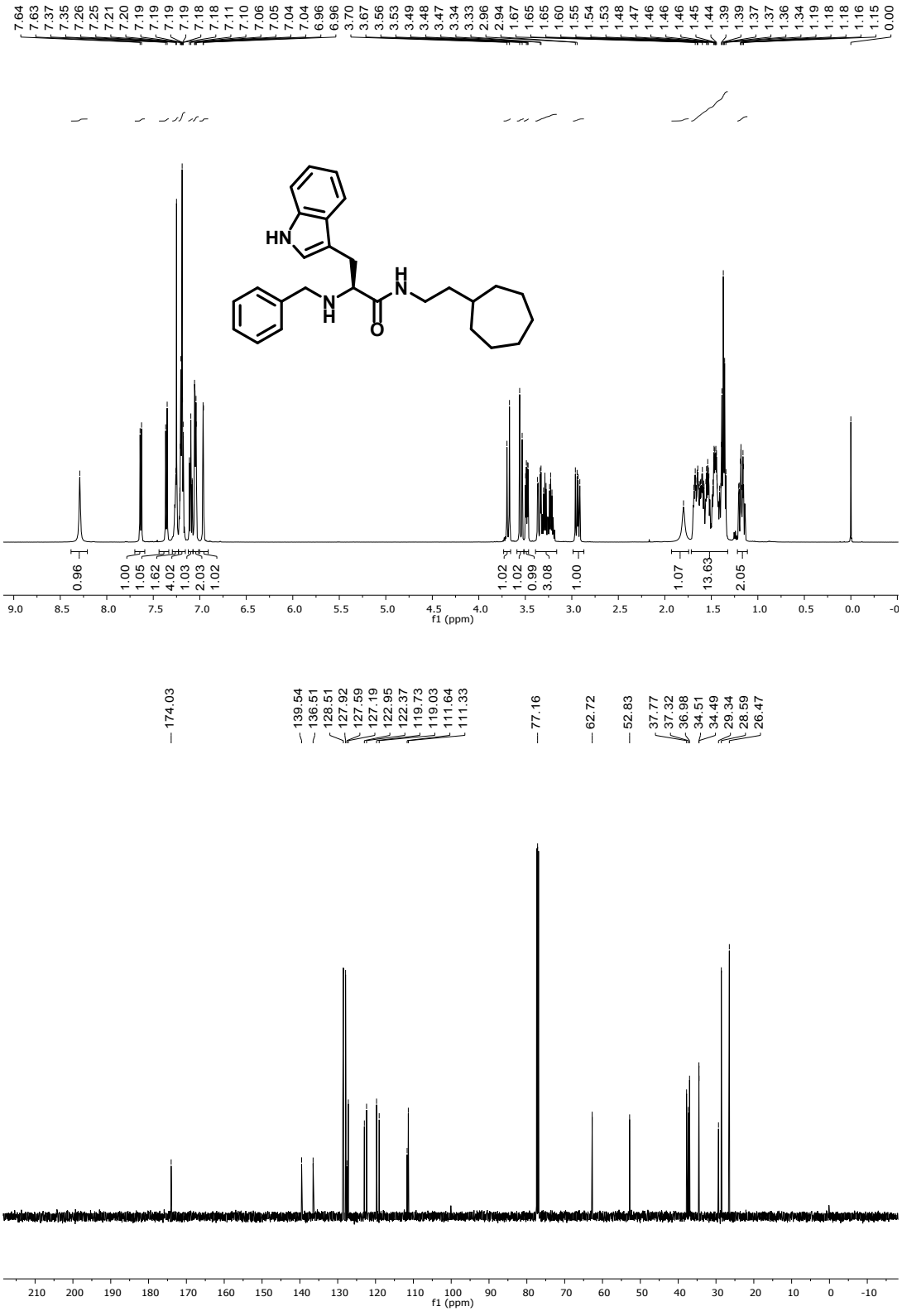

HN
H
N
N
H
O
N
0.94
1.00
0.99
0.96
1.03
1.03
1.01
4.07
0.97
2.05
6.03
1.09
2.26
5.17
2.36
12.31
2.26
3.03
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


174.46
136.51
127.65
122.84
122.41
119.75
119.11
112.10
111.30
77.46
64.07
63.58
48.81
41.78
38.97
37.42
36.75
32.43
32.31
30.04
29.44
28.71
24.51
20.33
13.97
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)

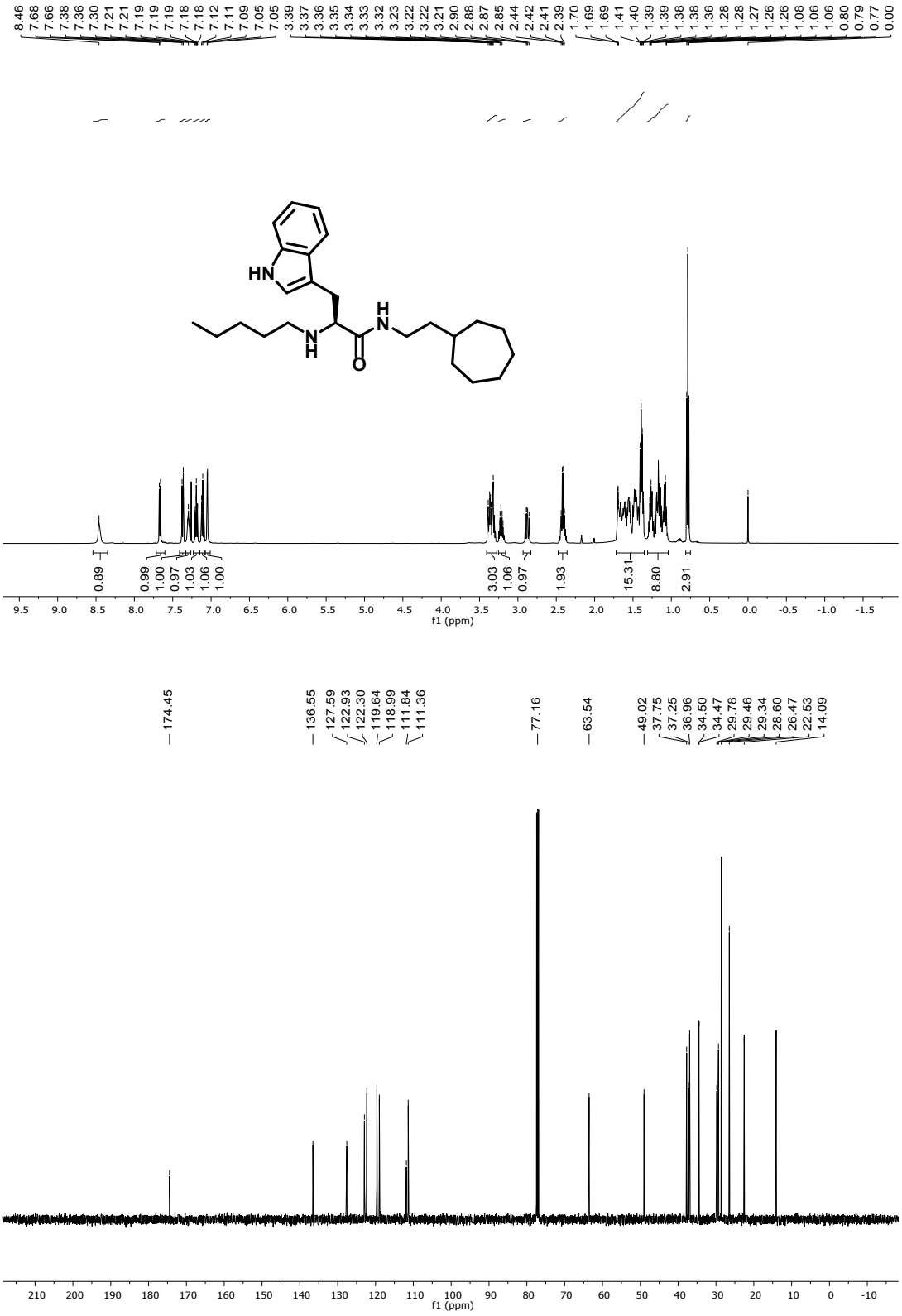
S34

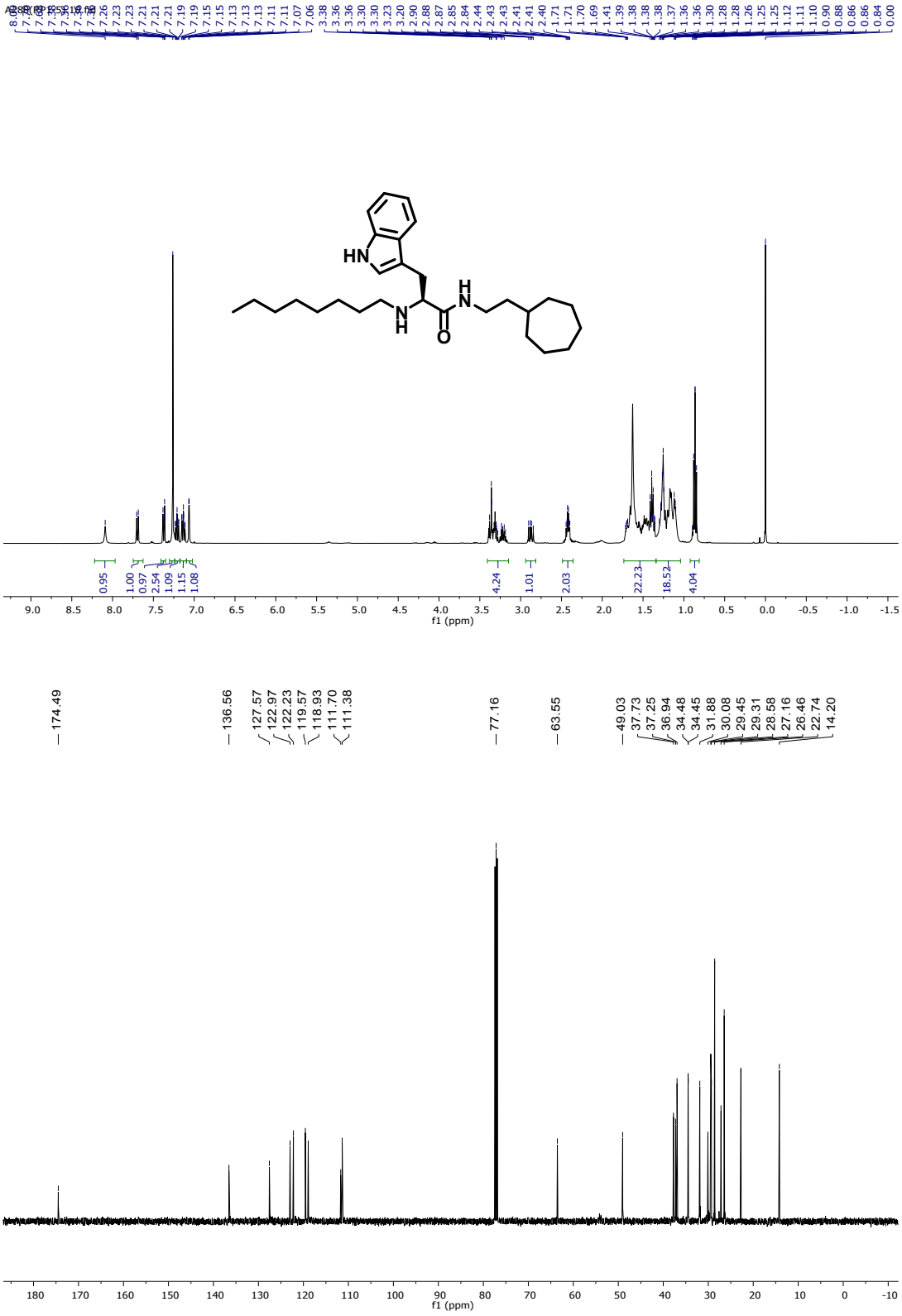


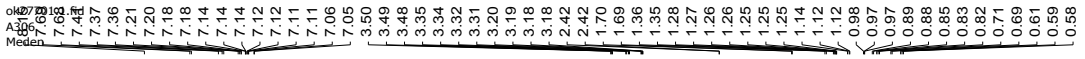
S35

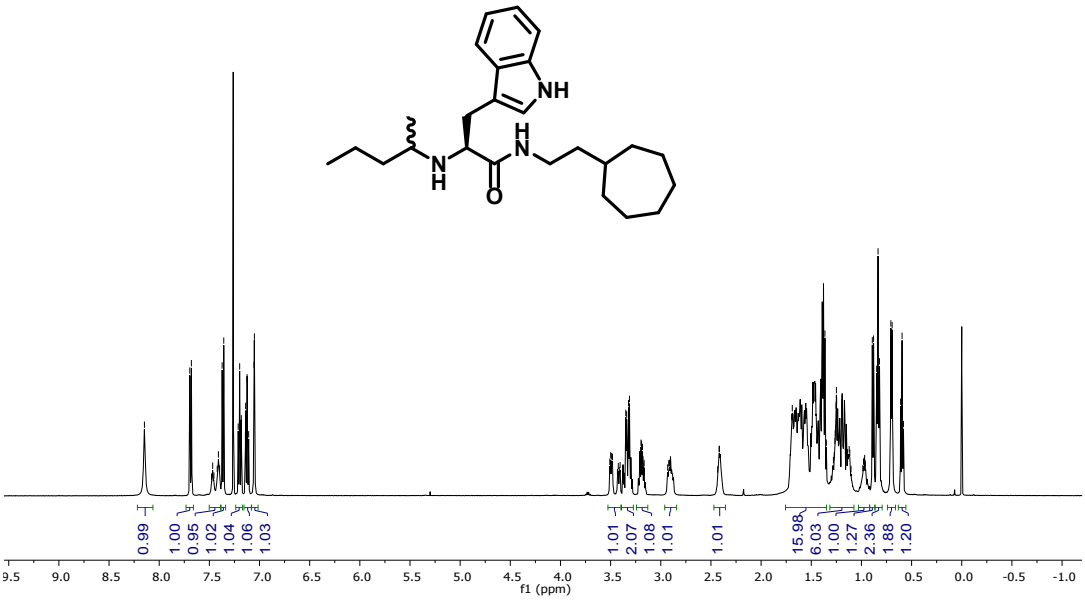

7.64 7.63 7.37 7.35 7.26 7.25 7.21 7.20 7.19 7.19 7.19 7.19 7.18 7.18 7.11 7.10 7.06 7.05 7.04 7.04 6.96 6.96
3.70 3.67 3.56 3.53 3.49 3.48 3.47 3.34 3.33 2.96 2.94 1.67 1.65 1.65 1.60 1.55 1.54 1.53 1.48 1.47 1.46 1.46 1.46 1.45 1.44 1.39 1.39 1.37 1.37 1.36 1.34 1.19 1.18 1.18 1.16 1.15 0.00
HN
H
N
N
H
O
0.96 1.00 1.05 1.62 4.02 1.03 2.03 1.02 1.02 1.02 0.99 3.08 1.00 1.07 13.63 2.05
f1 (ppm)
174.03 139.54 136.51 128.51 127.92 127.59 127.19 122.95 122.37 119.73 119.03 111.64 111.33 77.16 62.72 52.83 37.77 37.32 36.98 34.51 34.49 29.34 28.59 26.47
f1 (ppm)

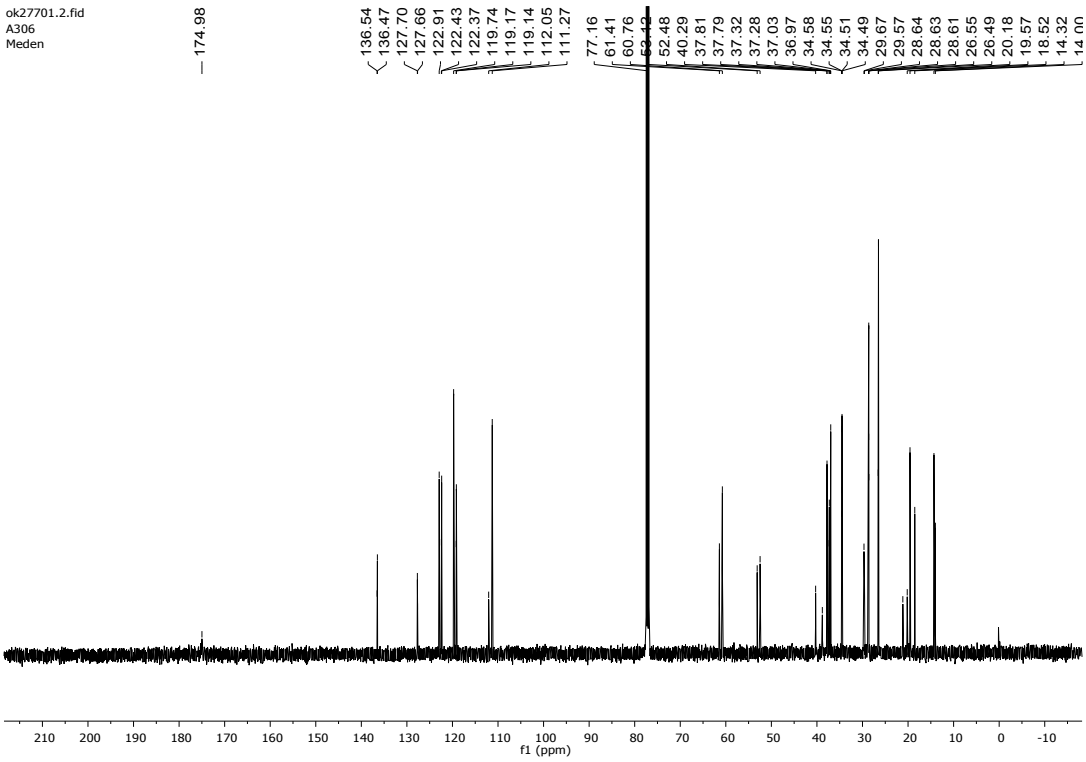
S36


8.46 7.68 7.66 7.38 7.36 7.30 7.21 7.21 7.19 7.19 7.19 7.18 7.18 7.12 7.11 7.09 7.05 7.05
3.39 3.37 3.36 3.35 3.34 3.33 3.32 3.23 3.22 3.22 3.21 2.90 2.88 2.87 2.85 2.44 2.42 2.41 2.39
1.70 1.69 1.69 1.41 1.40 1.39 1.39 1.38 1.38 1.36 1.28 1.28 1.27 1.26 1.26 1.08 1.06 1.06 0.80 0.79 0.77 0.00
HN
H
N
N
H
O
0.89 0.99 1.00 0.97 1.03 1.06 1.00
3.03 1.06 0.97 1.93 15.31 8.80 2.91
f1 (ppm)
174.45 136.55 127.59 122.93 122.30 119.64 118.99 111.84 111.36
77.16 63.54
49.02 37.75 37.25 36.96 34.50 34.47 29.78 29.46 29.34 28.60 26.47 22.53 14.09
f1 (ppm)

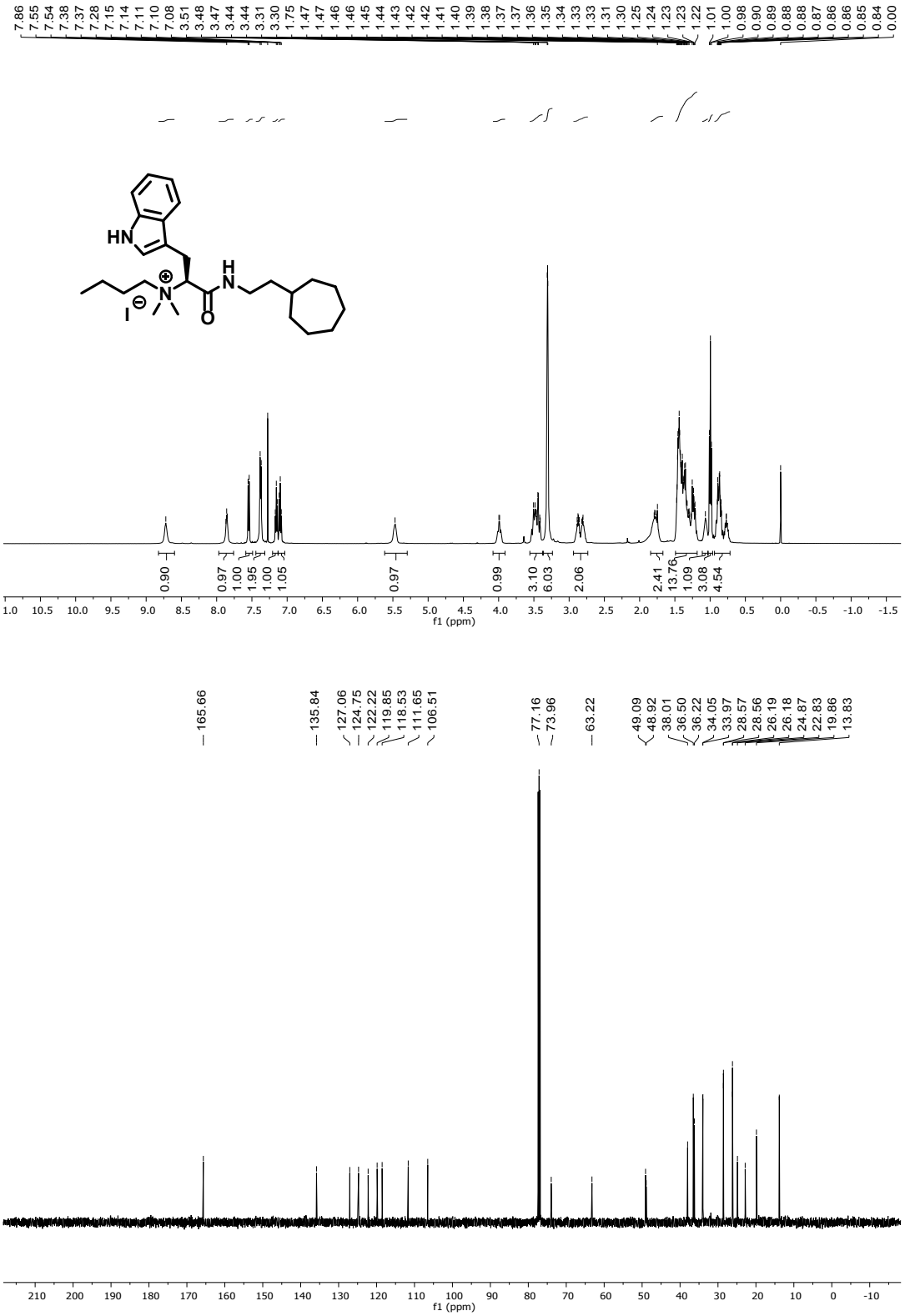

HN
H
N
N
H
O
0.95
1.00
0.97
2.54
1.09
1.15
1.08
4.24
1.01
2.03
22.23
18.52
4.04
f1 (ppm)
174.49
136.56
127.57
122.97
122.23
119.57
118.93
111.70
111.38
77.16
63.55
49.03
37.73
37.25
36.94
34.48
34.45
31.88
30.08
29.45
29.31
28.58
27.16
26.46
22.74
14.20
f1 (ppm)



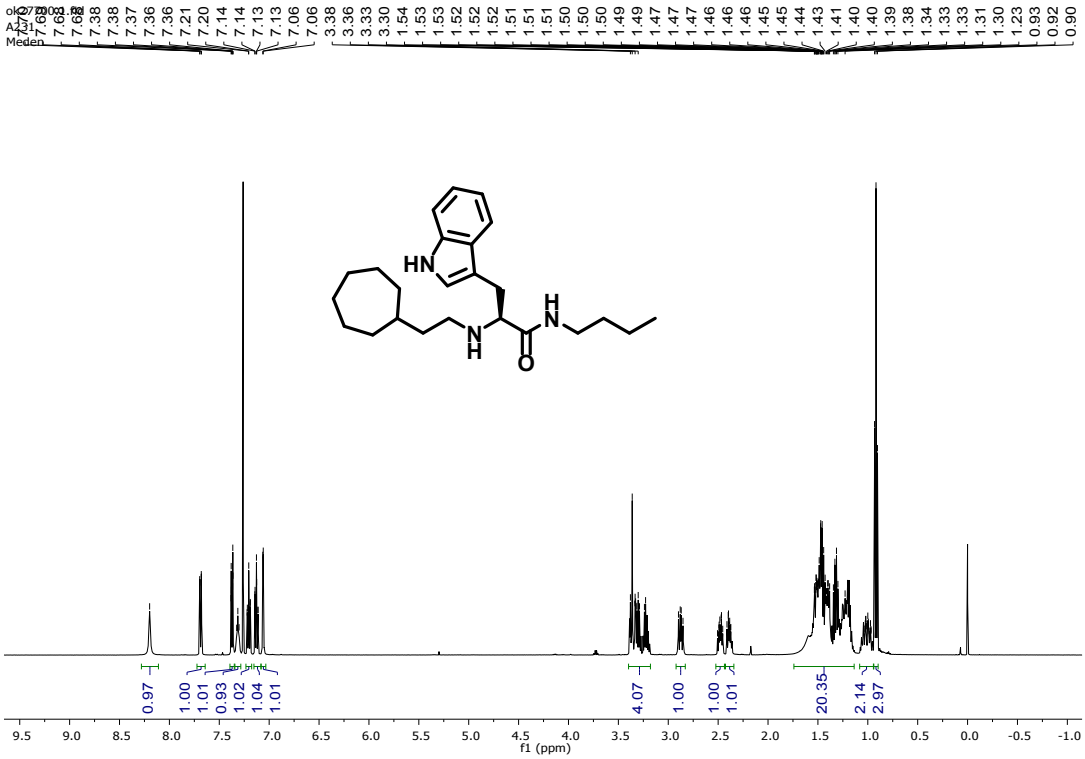

NH
H
N
N
H
O
0.99
1.00
0.95
1.02
1.04
1.06
1.03
1.01
2.07
1.08
1.01
1.01
15.98
6.03
1.00
1.27
2.36
1.88
1.20
f1 (ppm)

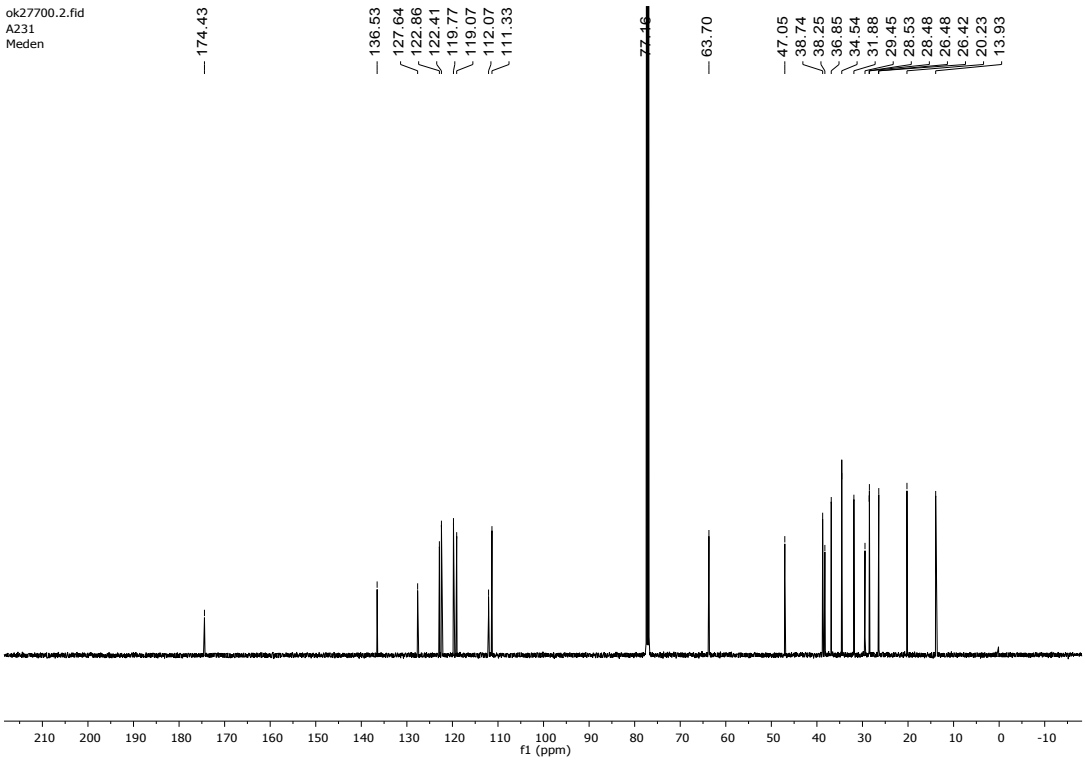

ok27701.2.fid
A306
Meden
f1 (ppm)

10

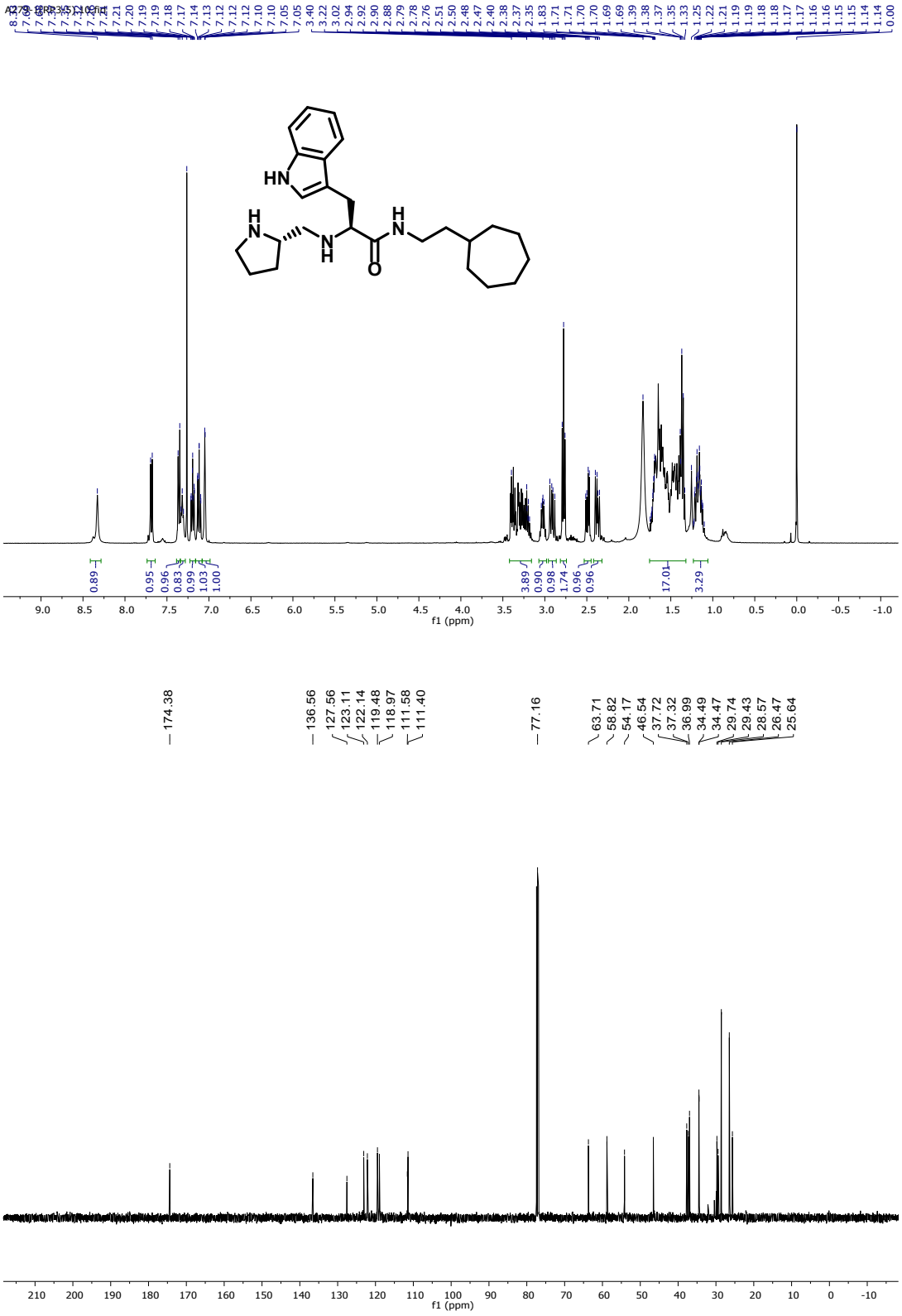

7.86 7.55 7.54 7.38 7.37 7.28 7.15 7.14 7.11 7.10 7.08 3.51 3.48 3.47 3.44 3.44 3.31 3.30 1.75 1.47 1.47 1.46 1.46 1.45 1.44 1.43 1.42 1.42 1.41 1.40 1.39 1.38 1.37 1.37 1.36 1.35 1.34 1.33 1.33 1.31 1.30 1.25 1.24 1.23 1.23 1.22 1.01 1.00 0.98 0.90 0.89 0.88 0.88 0.87 0.86 0.86 0.85 0.84 0.00
HN
H
N
N
I
O
0.90 0.97 1.00 1.95 1.00 1.05 0.97 0.99 3.10 6.03 2.06 2.41 13.76 1.09 3.08 4.54
f1 (ppm)
165.66 135.84 127.06 124.75 122.22 119.85 118.53 111.65 106.51 77.16 73.96 63.22 49.09 48.92 38.01 36.50 36.22 34.05 33.97 28.57 28.56 26.19 26.18 24.87 22.83 19.86 13.83
f1 (ppm)

S39

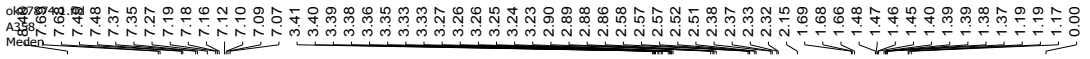

ok27700.2.fid
A231
Meden
HN
H
N
N
H
O
0.97
1.00
1.01
0.93
1.02
1.04
1.01
4.07
1.00
1.00
1.01
20.35
2.14
2.97
f1 (ppm)

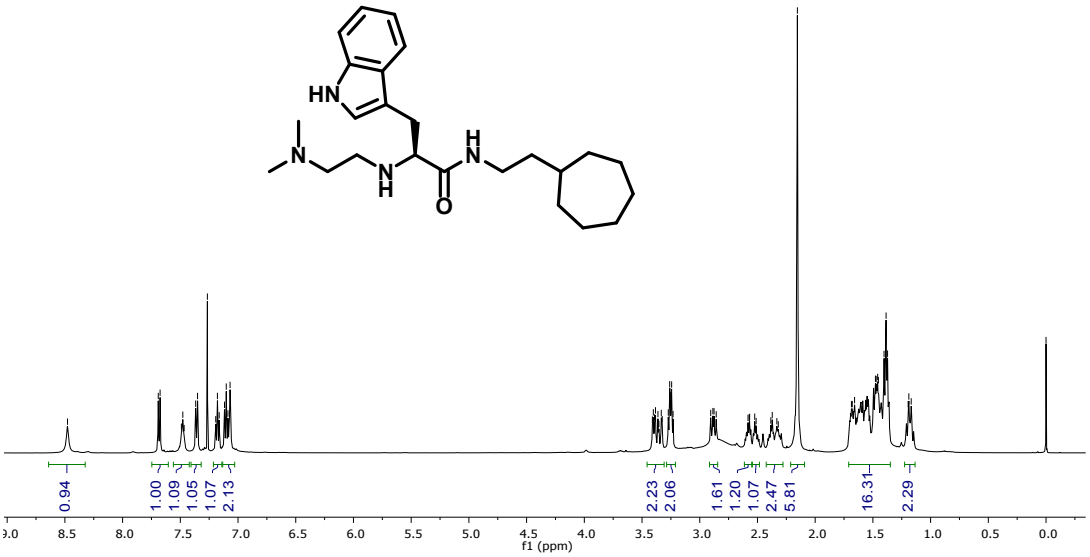

ok27700.2.fid
A231
Meden
174.43
136.53
127.64
122.86
122.41
119.77
119.07
112.07
111.33
77.16
63.70
47.05
38.74
38.25
36.85
34.54
31.88
29.45
28.53
28.48
26.48
26.42
20.23
13.93
f1 (ppm)

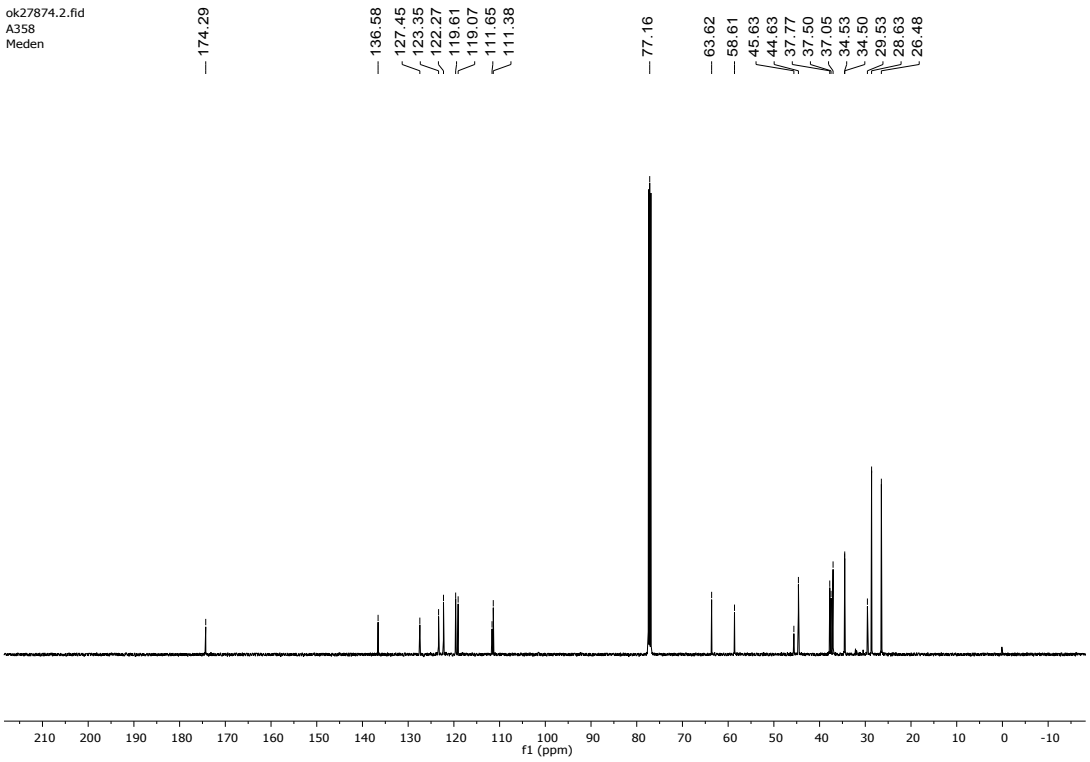
S40



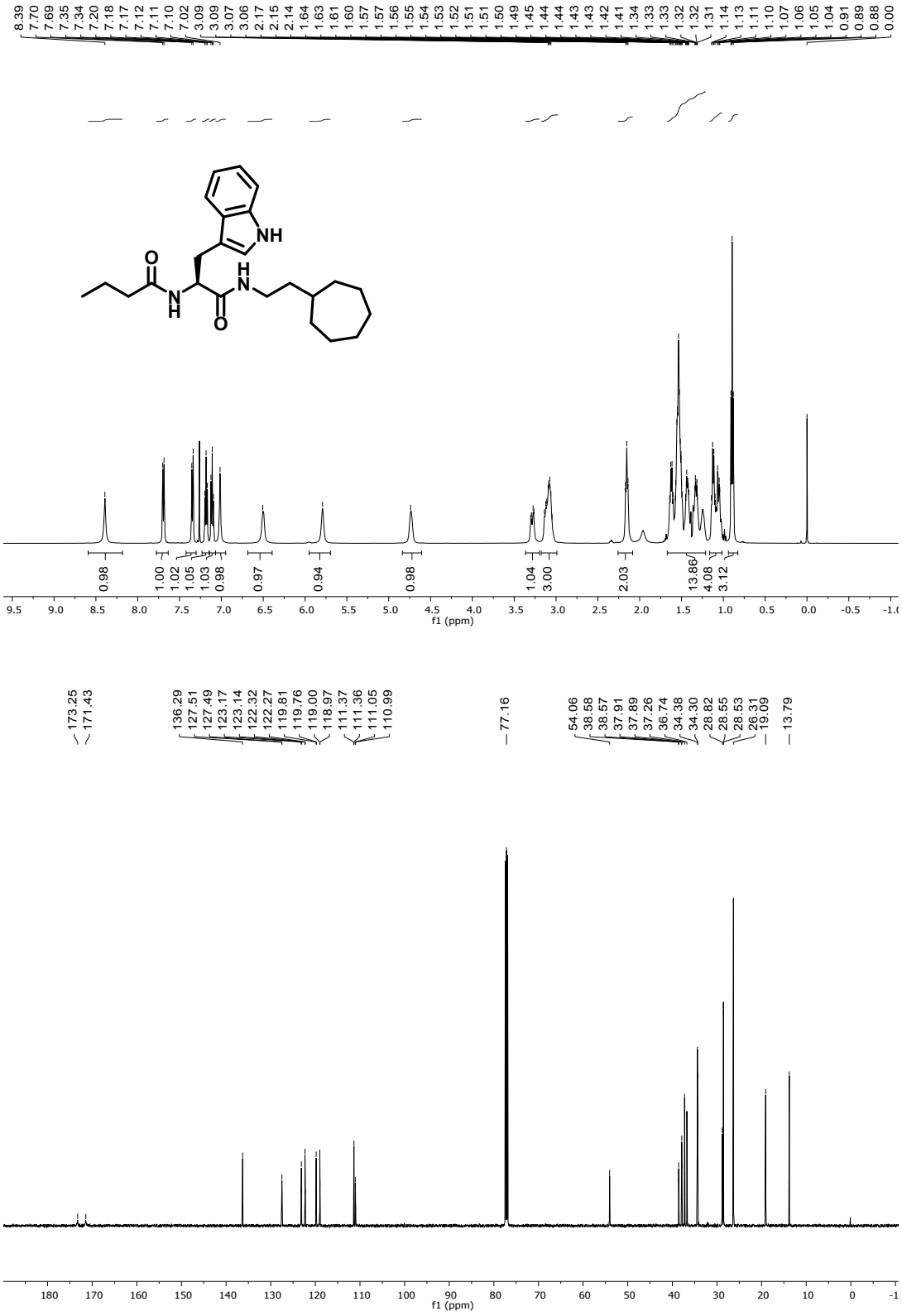
S41



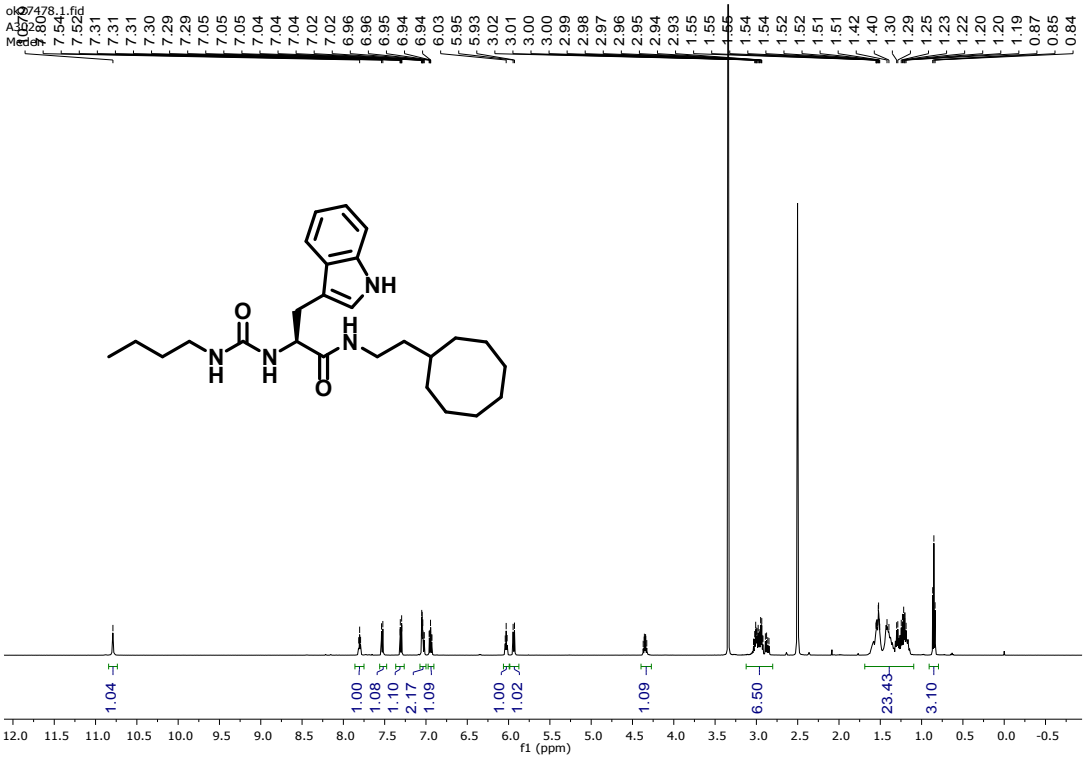

HN
N
N
H
H
N
O
0.94
1.00
1.09
1.05
1.07
2.13
2.23
2.06
1.61
1.20
1.07
2.47
5.81
16.31
2.29
f1 (ppm)

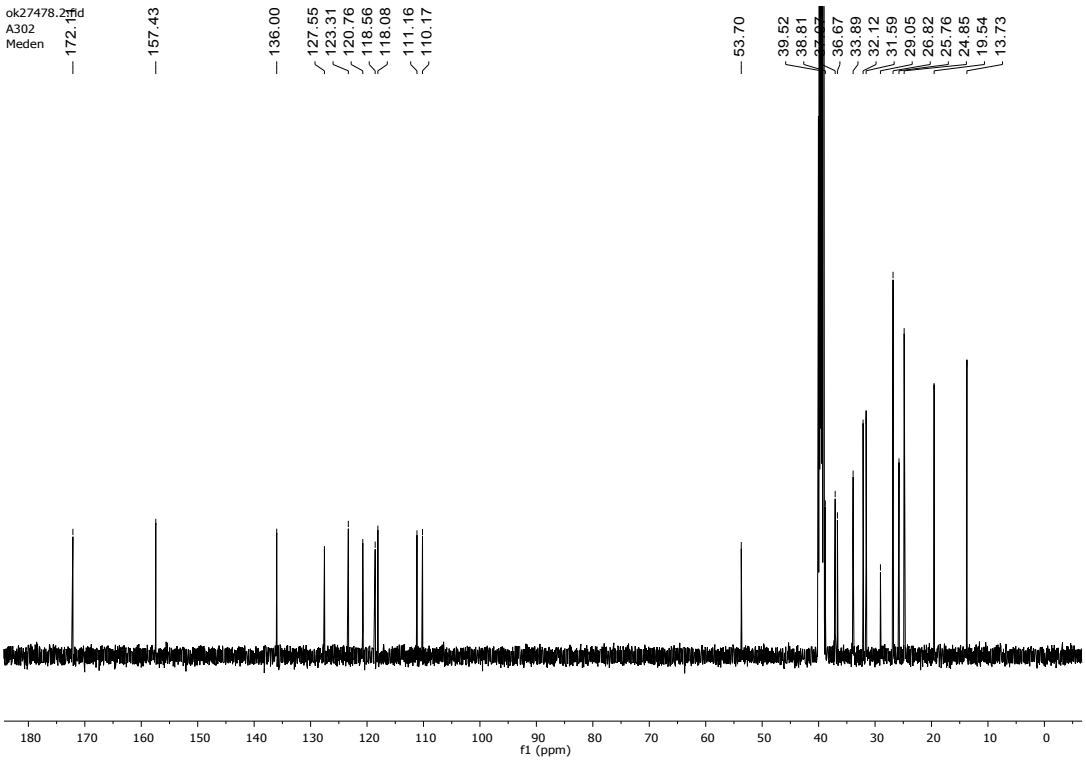

ok27874.2.fid
A358
Meden
174.29
136.58
127.45
123.35
122.27
119.61
119.07
111.65
111.38
77.16
63.62
58.61
45.63
44.63
37.77
37.50
37.05
34.53
34.50
29.53
28.63
26.48
f1 (ppm)

11

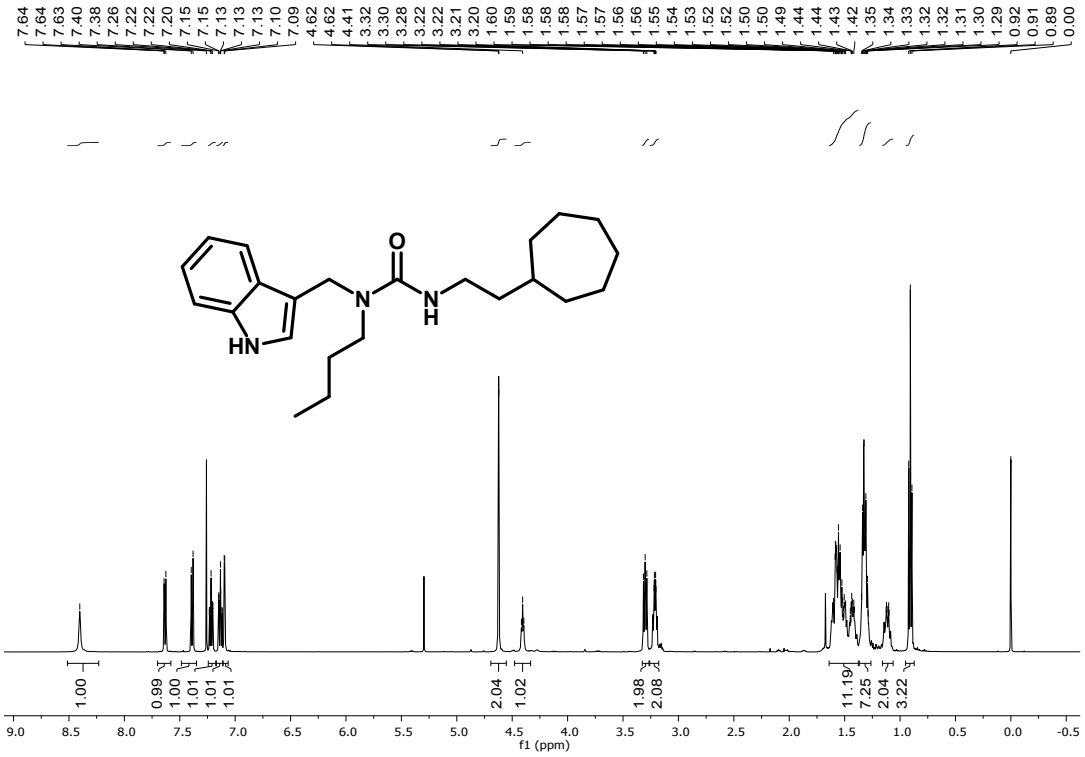

8.39 7.70 7.69 7.35 7.34 7.20 7.18 7.17 7.12 7.11 7.10 7.02 3.09 3.09 3.07 3.06 2.17 2.15 2.14 1.64 1.63 1.61 1.60 1.57 1.57 1.56 1.55 1.54 1.53 1.52 1.51 1.51 1.50 1.49 1.45 1.44 1.44 1.43 1.43 1.42 1.41 1.34 1.33 1.33 1.32 1.32 1.31 1.14 1.13 1.11 1.10 1.07 1.06 1.05 1.04 0.91 0.89 0.88 0.00
NH
O
N
H
H
N
O
0.98 1.00 1.02 1.05 1.03 0.98 0.97 0.94 0.98 1.04 3.00 2.03 13.86 4.08 3.12
f1 (ppm)
173.25 171.43 136.29 127.51 127.49 123.17 123.14 122.32 122.27 119.81 119.76 119.00 118.97 111.37 111.36 111.05 110.99 77.16 54.06 38.58 38.57 37.91 37.89 37.26 36.74 34.38 34.30 28.82 28.55 28.53 26.31 19.09 13.79
f1 (ppm)

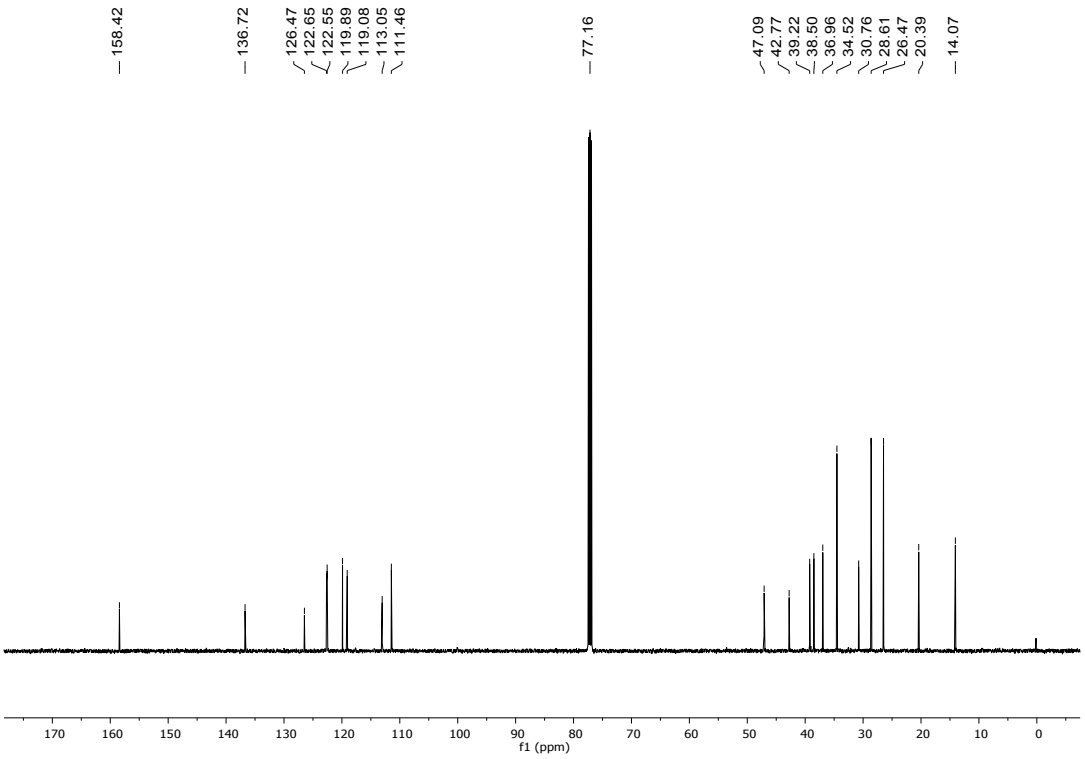
S42


ok27478.1.fid
A302
Meden
NH
O
N
H
N
H
H
N
O
1.04
1.00
1.08
1.10
2.17
1.09
1.00
1.02
1.09
6.50
23.43
3.10
f1 (ppm)

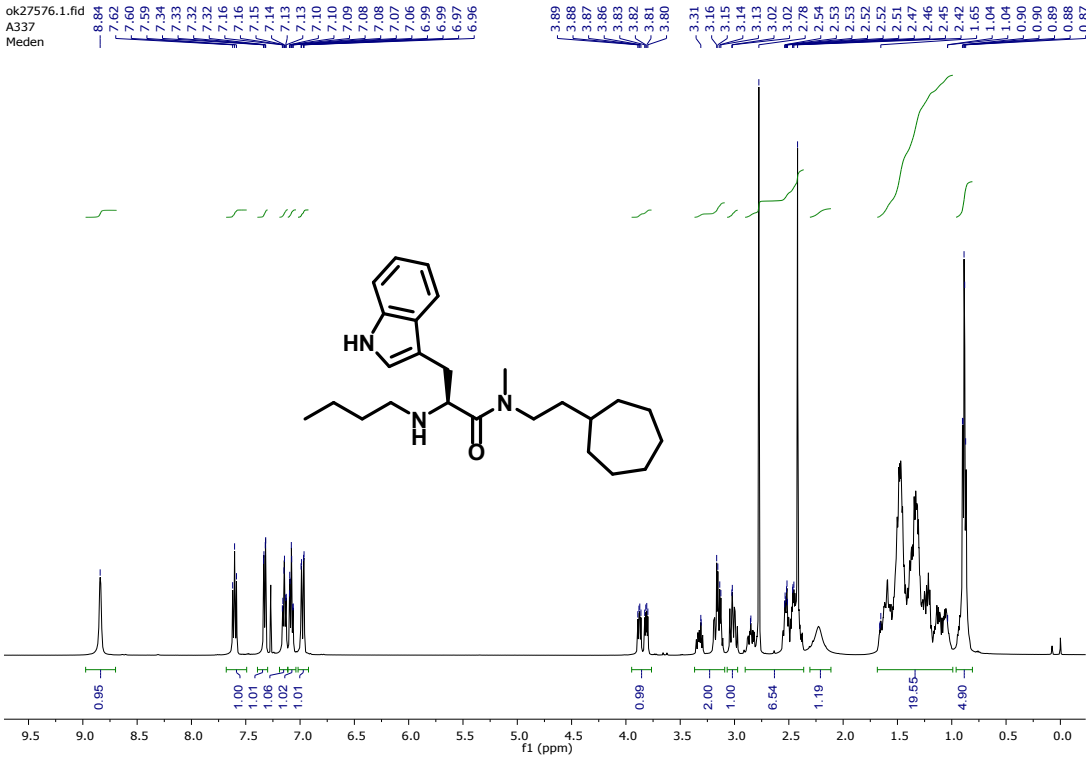

ok27478.2.fid
A302
Meden
172.14
157.43
136.00
127.55
123.31
120.76
118.56
118.08
111.16
110.17
53.70
39.52
38.81
36.67
33.89
32.12
31.59
29.05
26.82
25.76
24.85
19.54
13.73
f1 (ppm)

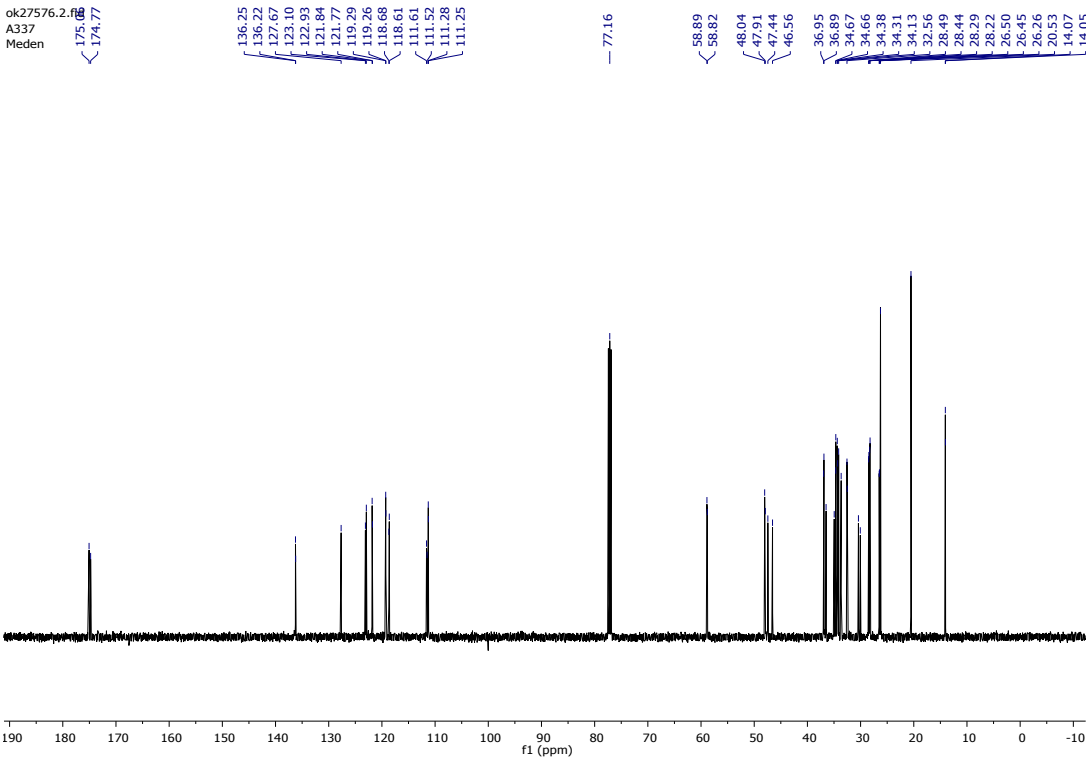
S43


7.64 7.64 7.63 7.40 7.38 7.26 7.22 7.22 7.20 7.15 7.15 7.13 7.13 7.13 7.10 7.09
4.62 4.62 4.41 3.32 3.30 3.28 3.22 3.22 3.21 3.20 1.60 1.59 1.58 1.58 1.58 1.57 1.57 1.56 1.56 1.55 1.54 1.53 1.52 1.52 1.50 1.50 1.49 1.44 1.44 1.43 1.42 1.35 1.34 1.33 1.32 1.32 1.31 1.30 1.29 0.92 0.91 0.89 0.00
O
N
N
H
HN
1.00 0.99 1.00 1.01 1.01 1.01 2.04 1.02 1.98 2.08 11.19 7.25 2.04 3.22
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)

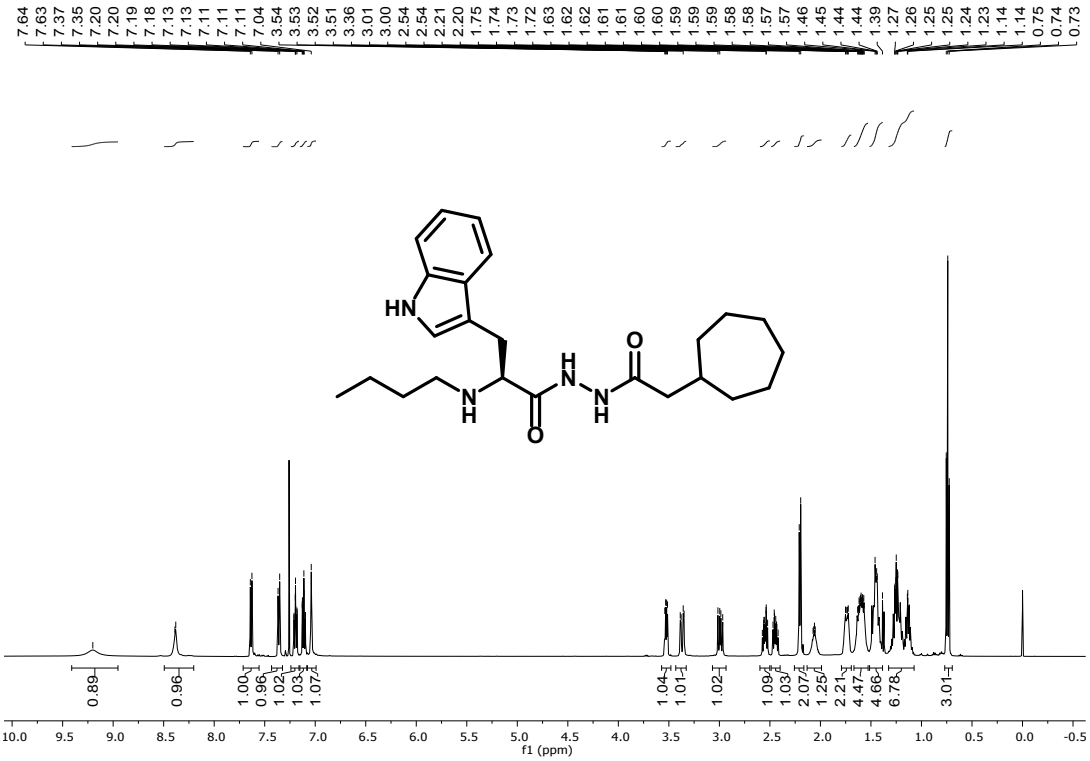

158.42 136.72 126.47 122.65 122.55 119.89 119.08 113.05 111.46 77.16 47.09 42.77 39.22 38.50 36.96 34.52 30.76 28.61 26.47 20.39 14.07
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

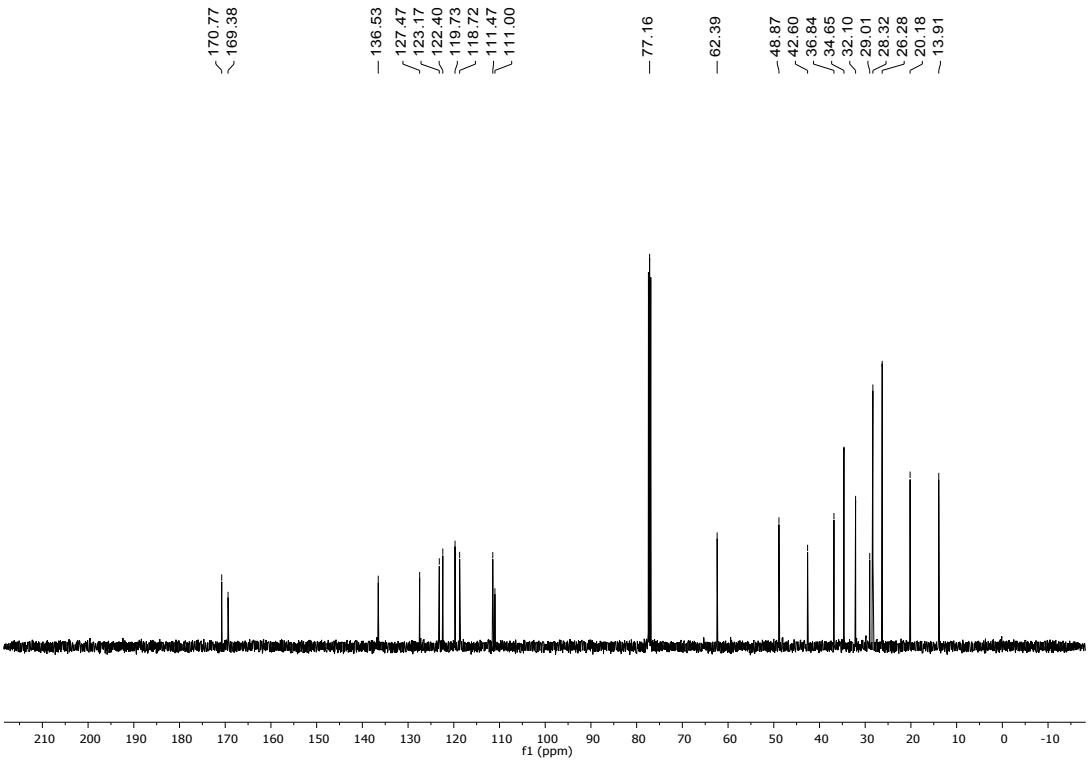
S44


ok27576.1.fid
A337
Meden
HN
N
H
N
O
f1 (ppm)

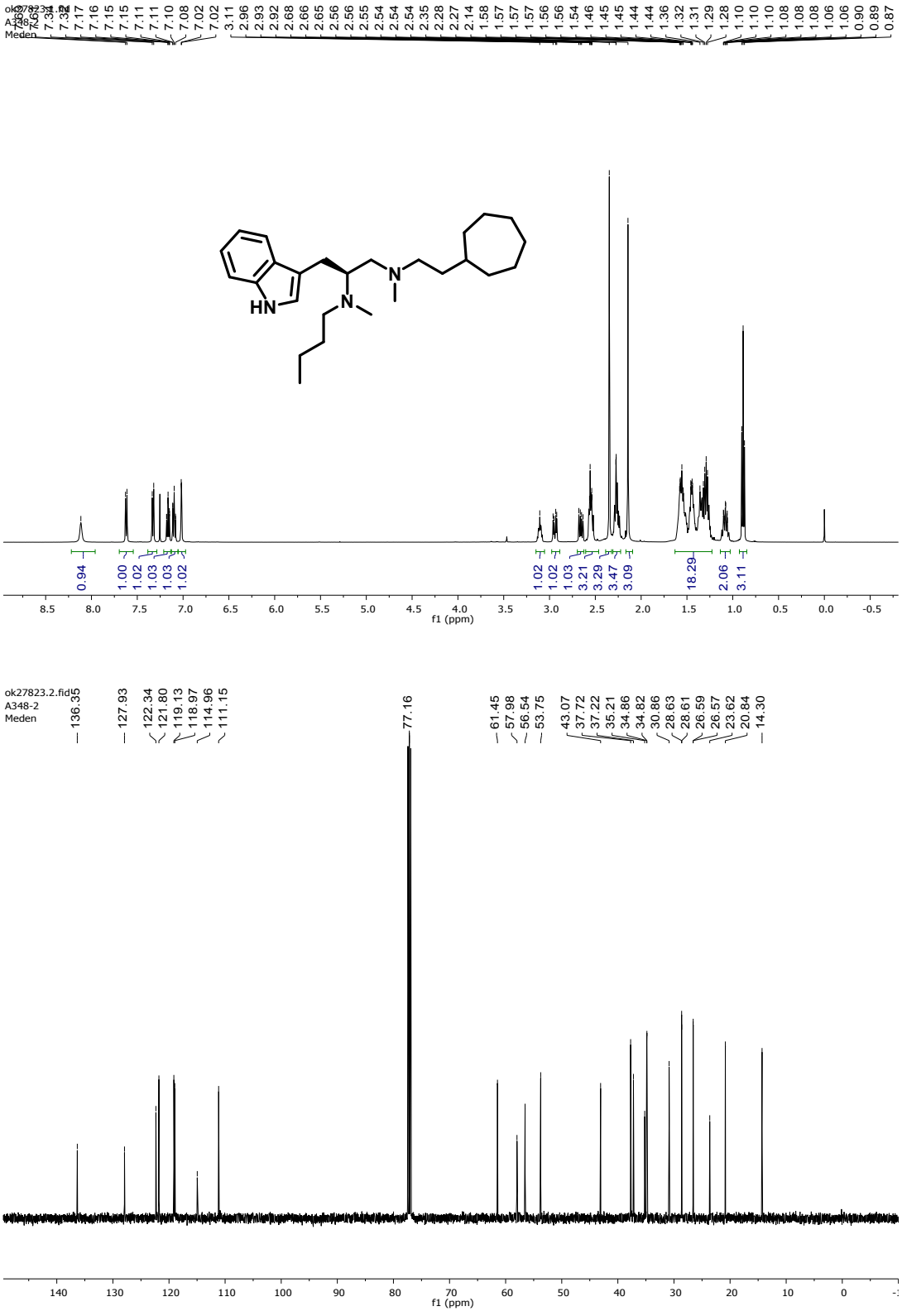

ok27576.2.fid
A337
Meden
f1 (ppm)

S45

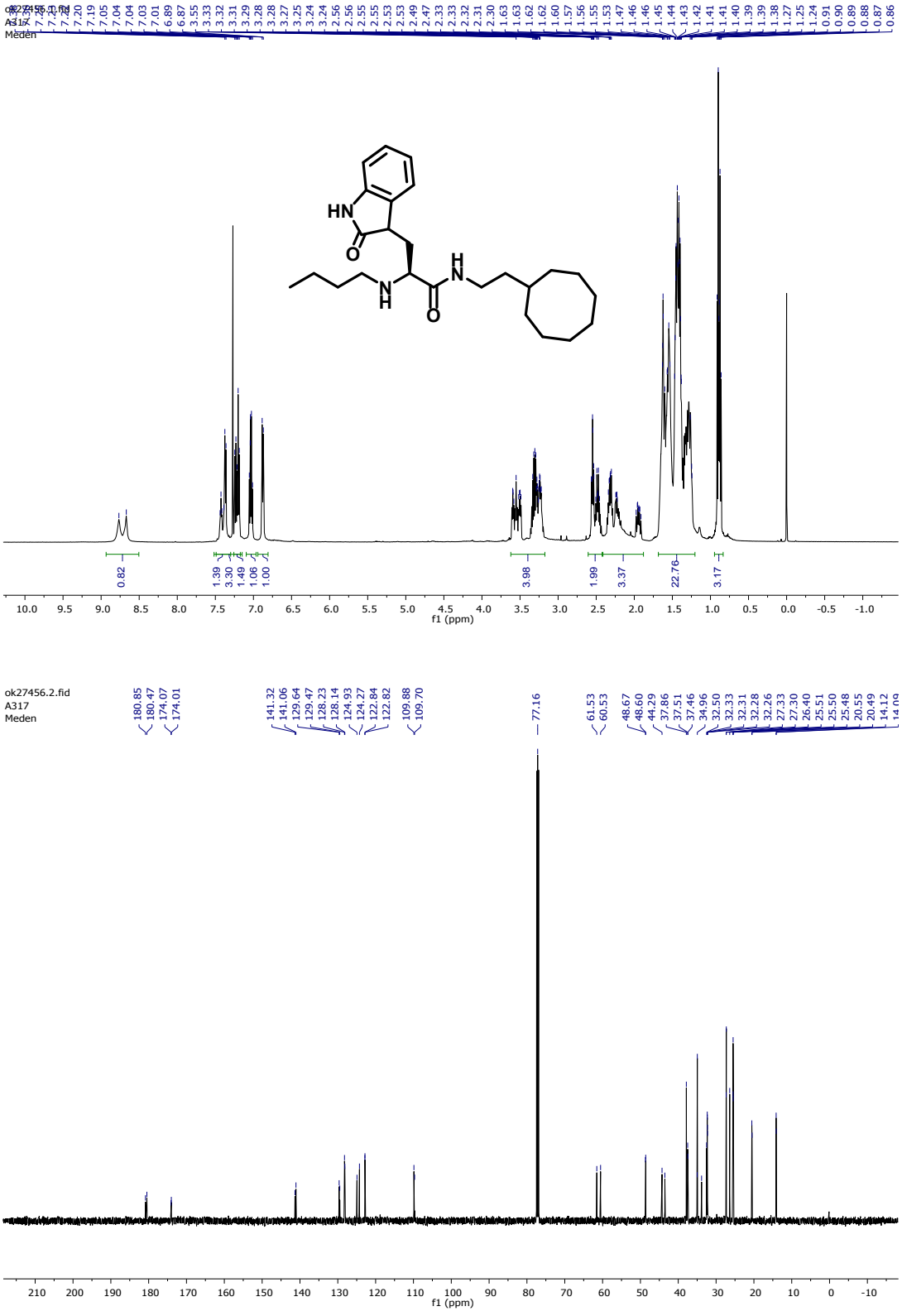

7.64 7.63 7.37 7.35 7.20 7.20 7.19 7.18 7.13 7.13 7.11 7.11 7.11 7.04 3.54 3.53 3.52 3.51 3.36 3.01 3.00 2.54 2.54 2.21 2.20 1.75 1.74 1.73 1.72 1.63 1.62 1.62 1.61 1.61 1.60 1.60 1.59 1.59 1.59 1.58 1.58 1.57 1.57 1.46 1.45 1.44 1.44 1.39 1.27 1.26 1.25 1.25 1.24 1.23 1.14 1.14 0.75 0.74 0.73
HN
O
H
N
N
H
N
H
O
0.89 0.96 1.00 0.96 1.02 1.03 1.07 1.04 1.01 1.02 1.09 1.03 2.07 1.25 2.21 4.47 4.66 6.78 3.01
f1 (ppm)


170.77 169.38 136.53 127.47 123.17 122.40 119.73 118.72 111.47 111.00 77.16 62.39 48.87 42.60 36.84 34.65 32.10 29.01 28.32 26.28 20.18 13.91
f1 (ppm)

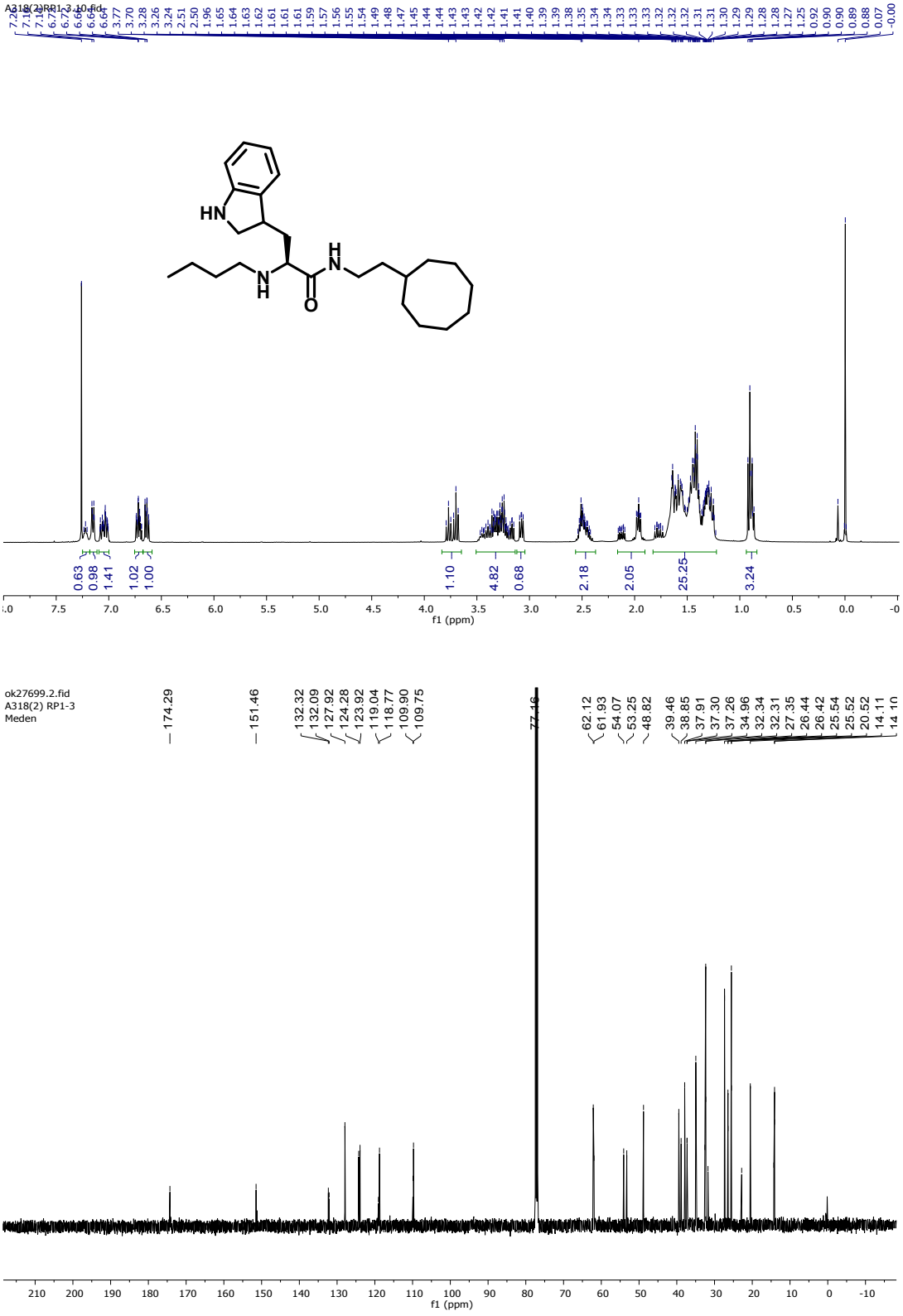
12


ok27823.2.fid
A348-2
Meden
HN
N
N
0.94
1.00
1.02
1.03
1.03
1.02
1.02
1.02
1.03
3.21
3.29
3.47
3.09
18.29
2.06
3.11
f1 (ppm)
136.35
127.93
122.34
121.80
119.13
118.97
114.96
111.15
77.16
61.45
57.98
56.54
53.75
43.07
37.72
37.22
35.21
34.86
34.82
30.86
28.63
28.61
26.59
26.57
23.62
20.84
14.30
f1 (ppm)

S46

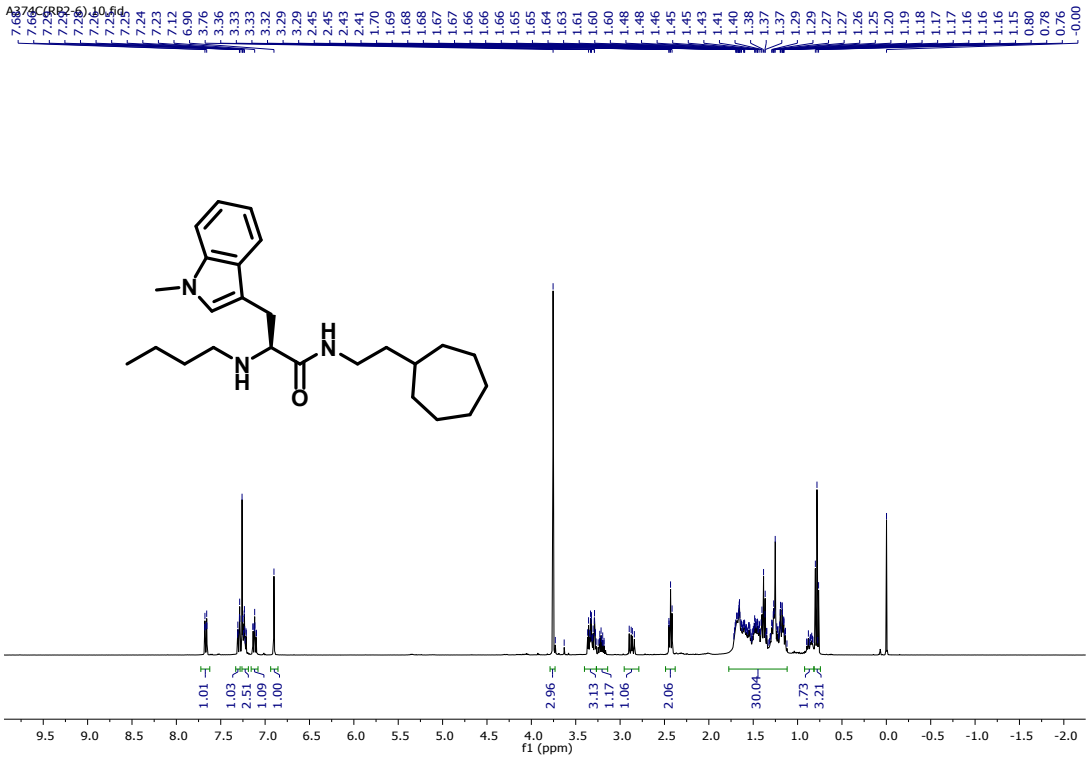


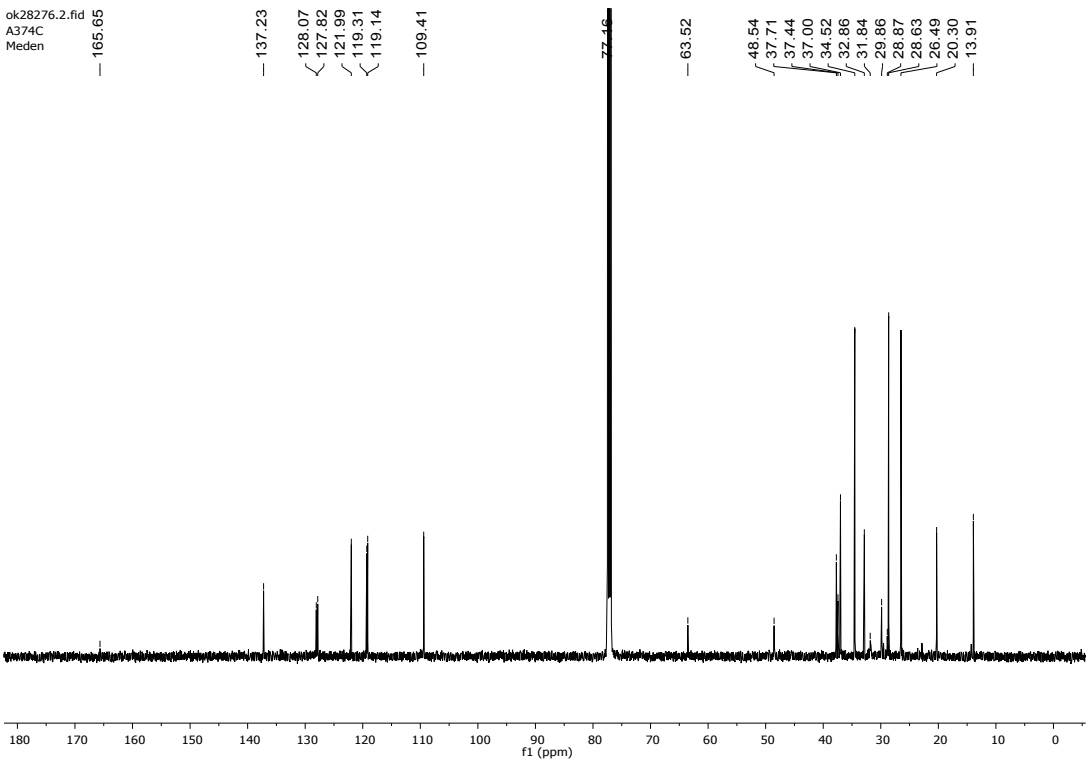
A mixture of two diastereomers.



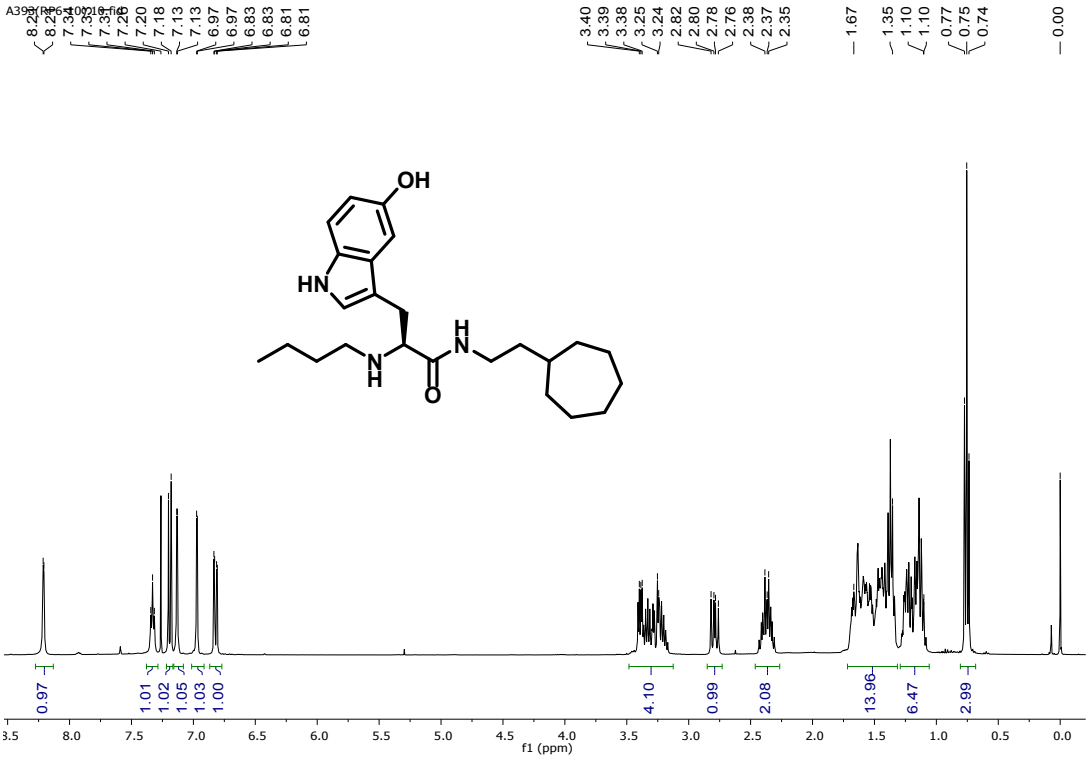
A mixture of two diastereomers.

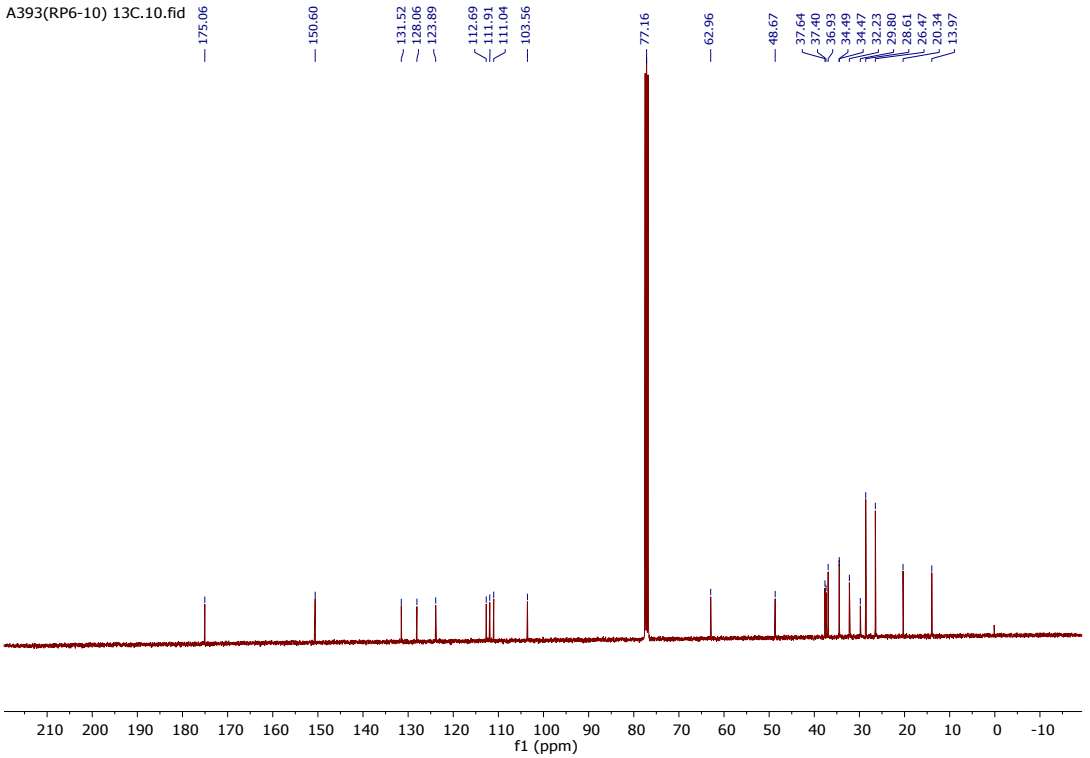
S48



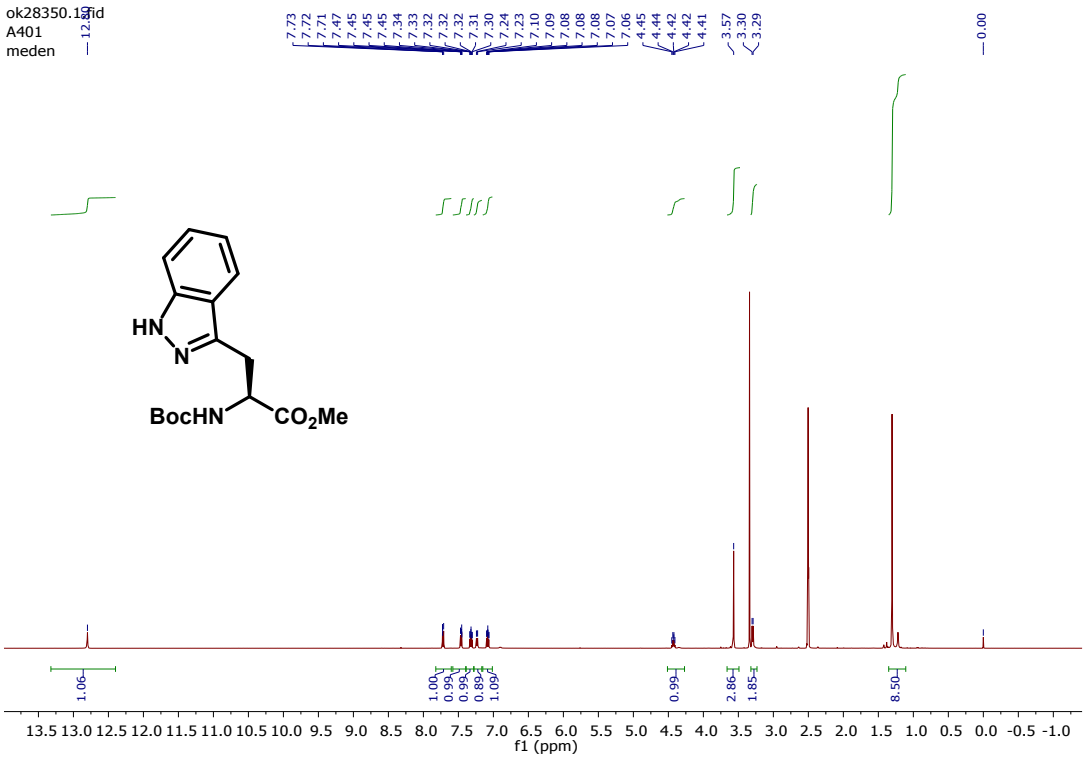


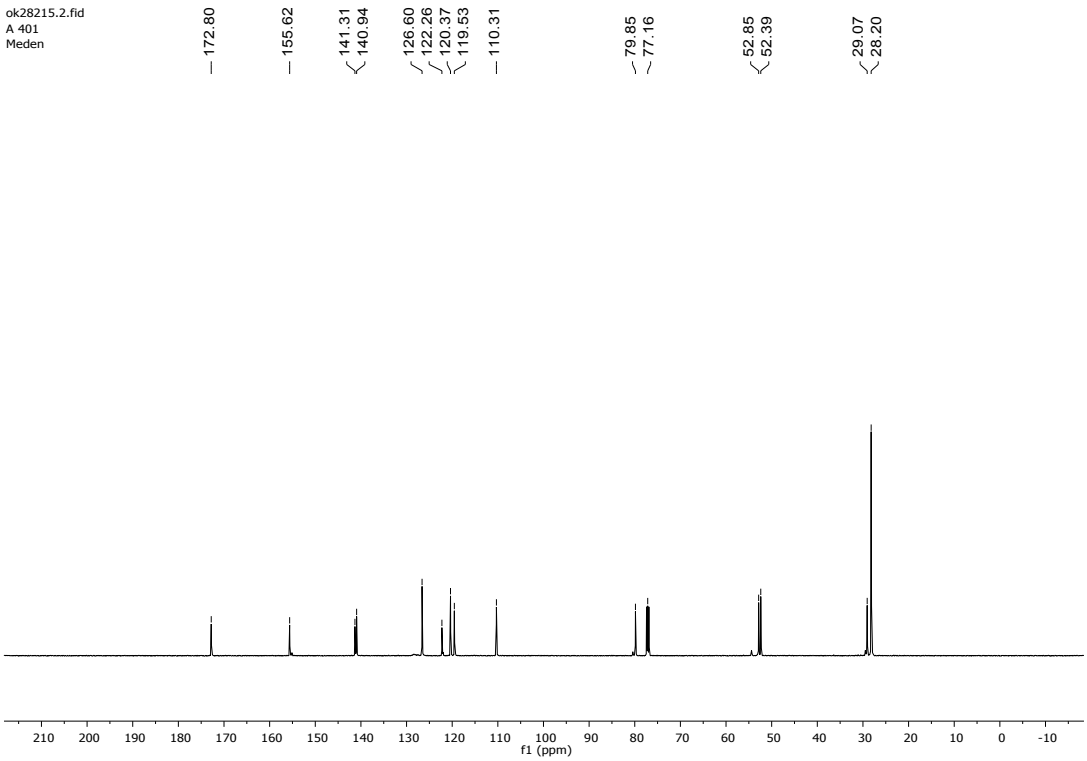
S49


8.23
7.36
7.35
7.34
7.28
7.20
7.18
7.13
7.13
6.97
6.97
6.83
6.83
6.81
6.81
3.40
3.39
3.38
3.25
3.24
2.82
2.80
2.78
2.76
2.38
2.37
2.35
1.67
1.35
1.10
1.10
0.77
0.75
0.74
0.00
OH
HN
H
N
N
H
O
0.97
1.01
1.02
1.05
1.03
1.00
4.10
0.99
2.08
13.96
6.47
2.99
f1 (ppm)

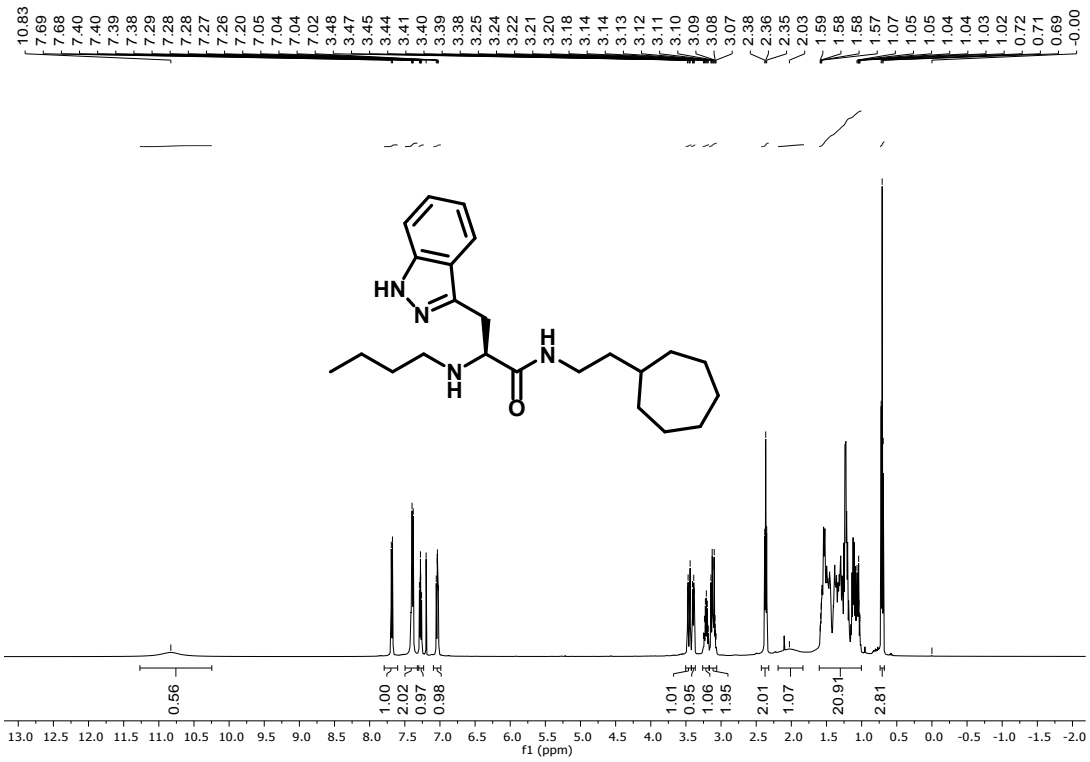

A393(RP6-10) 13C.10.fid
175.06
150.60
131.52
128.06
123.89
112.69
111.91
111.04
103.56
77.16
62.96
48.67
37.64
37.40
36.93
34.49
34.47
32.23
29.80
28.61
26.47
20.34
13.97
f1 (ppm)

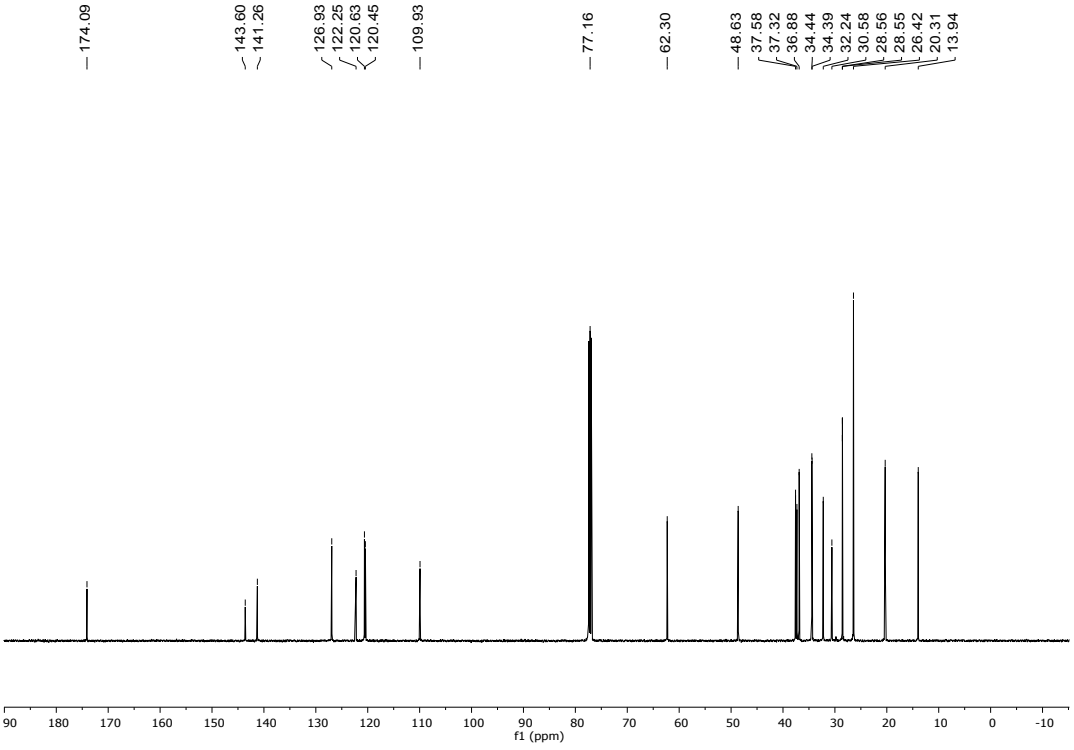
4


ok28350.1.fid
A401
meden
HN
N
BocHN
CO2Me
f1 (ppm)

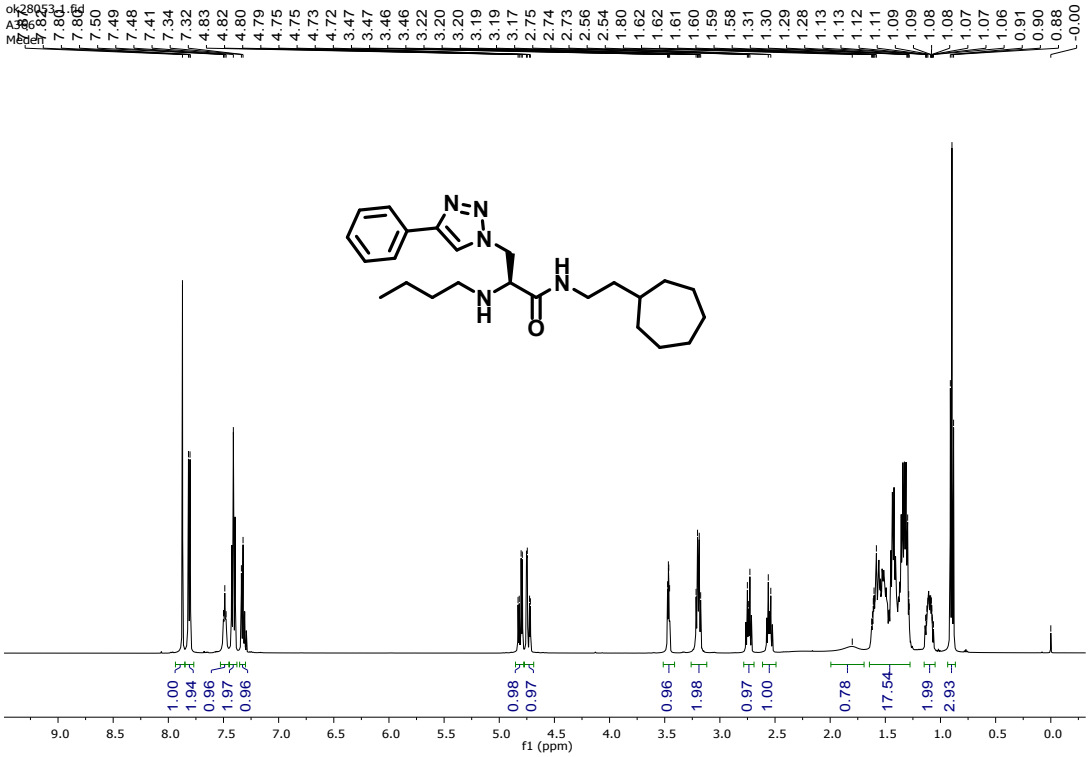

ok28215.2.fid
A 401
Meden
f1 (ppm)

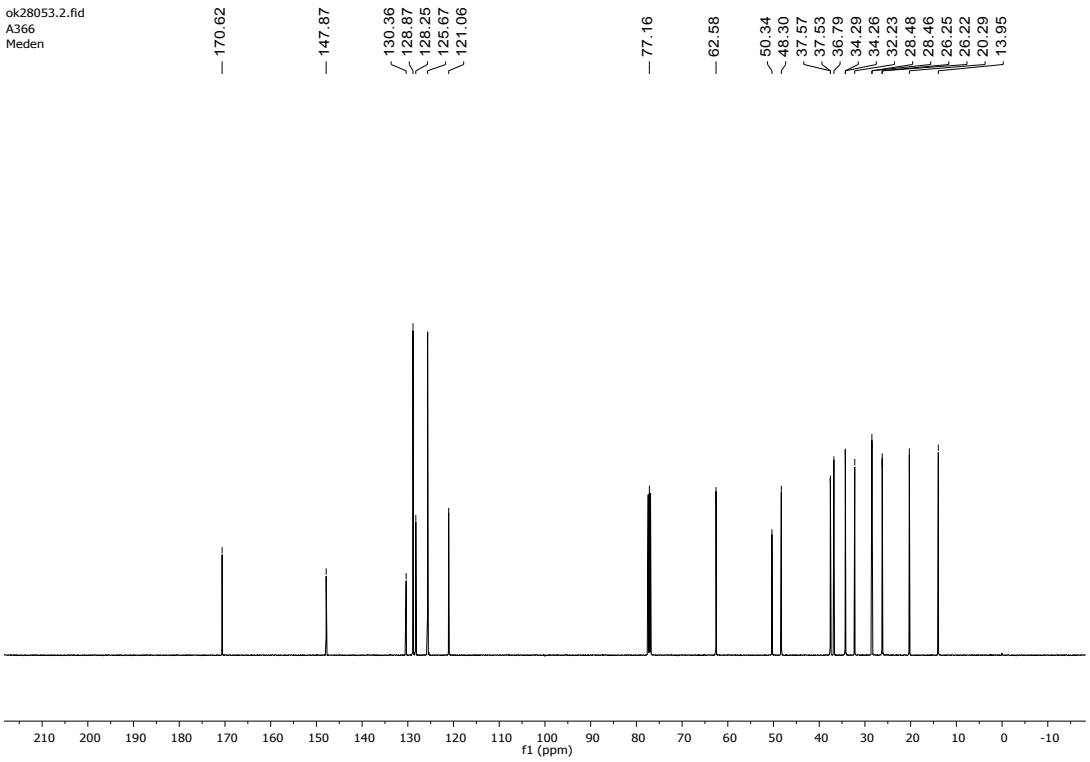
S50


10.83
7.69
7.68
7.40
7.40
7.39
7.38
7.29
7.28
7.28
7.27
7.26
7.20
7.05
7.04
7.04
7.02
3.48
3.47
3.45
3.44
3.41
3.40
3.39
3.38
3.25
3.24
3.22
3.21
3.20
3.18
3.14
3.14
3.13
3.12
3.11
3.10
3.09
3.08
3.07
2.38
2.36
2.35
2.03
1.59
1.58
1.58
1.57
1.07
1.05
1.05
1.04
1.04
1.03
1.02
0.72
0.71
0.69
-0.00
HN
N
N
H
H
N
O
0.56
1.00
2.02
0.97
0.98
1.01
0.95
1.06
1.95
2.01
1.07
20.91
2.81
f1 (ppm)

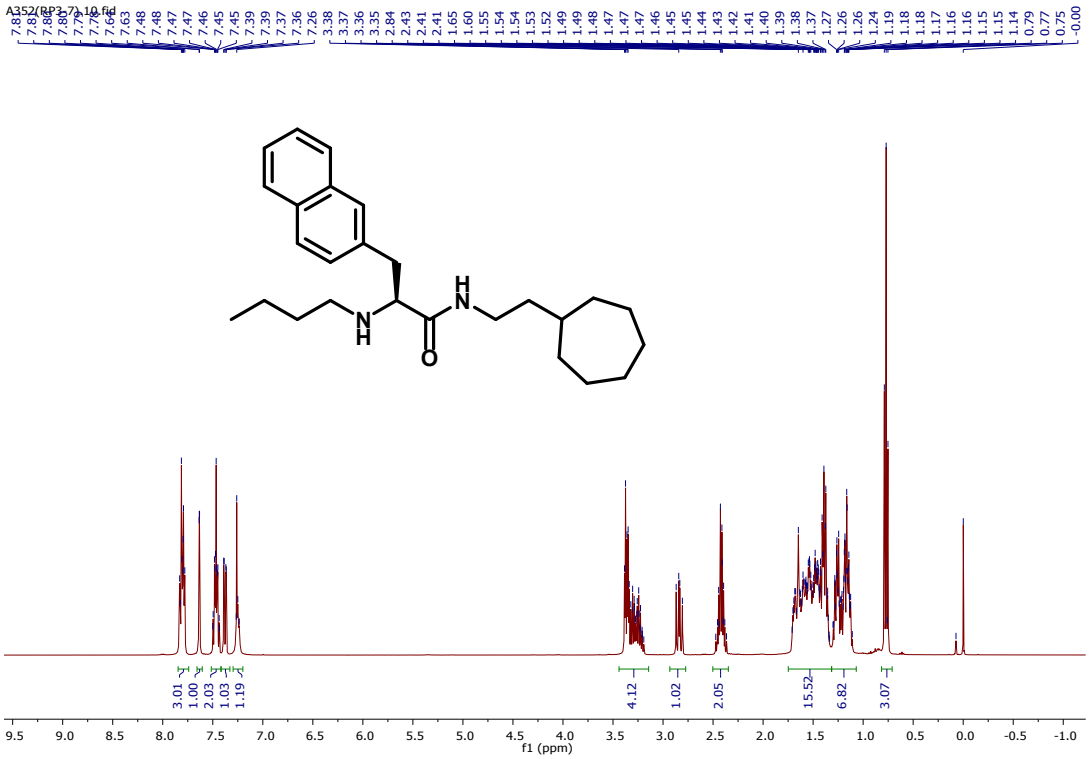

174.09
143.60
141.26
126.93
122.25
120.63
120.45
109.93
77.16
62.30
48.63
37.58
37.32
36.88
34.44
34.39
32.24
30.58
28.56
28.55
26.42
20.31
13.94
f1 (ppm)

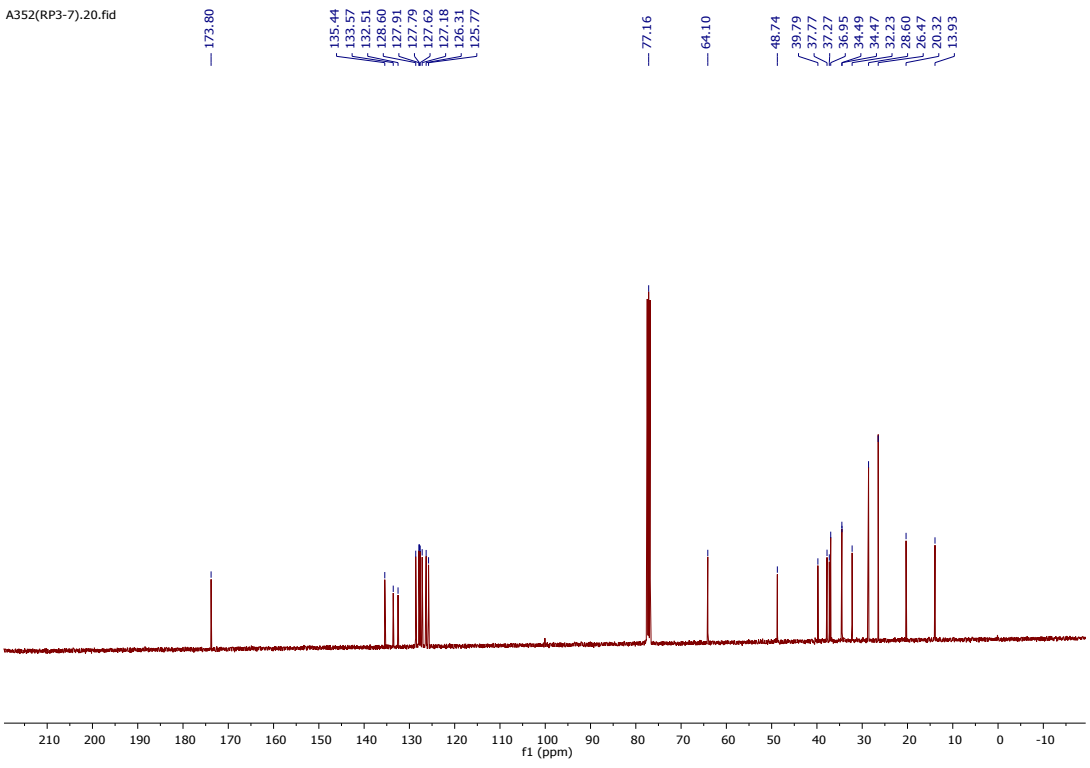
S51


ok28053.1.fid
A366
Meden
7.82
7.80
7.80
7.50
7.49
7.48
7.41
7.34
7.32
4.83
4.82
4.80
4.79
4.75
4.75
4.73
4.72
3.47
3.47
3.46
3.46
3.22
3.20
3.20
3.19
3.19
3.17
2.75
2.74
2.73
2.56
2.54
1.80
1.62
1.62
1.61
1.60
1.59
1.58
1.31
1.30
1.29
1.28
1.13
1.13
1.12
1.11
1.09
1.09
1.08
1.08
1.07
1.07
1.06
0.91
0.90
0.88
-0.00
N
N
N
H
N
H
O
1.00
1.94
0.96
1.97
0.96
0.98
0.97
0.96
1.98
0.97
1.00
0.78
17.54
1.99
2.93
f1 (ppm)


ok28053.2.fid
A366
Meden
170.62
147.87
130.36
128.87
128.25
125.67
121.06
77.16
62.58
50.34
48.30
37.57
37.53
36.79
34.29
34.26
32.23
28.48
28.46
26.25
26.22
20.29
13.95
f1 (ppm)

S52





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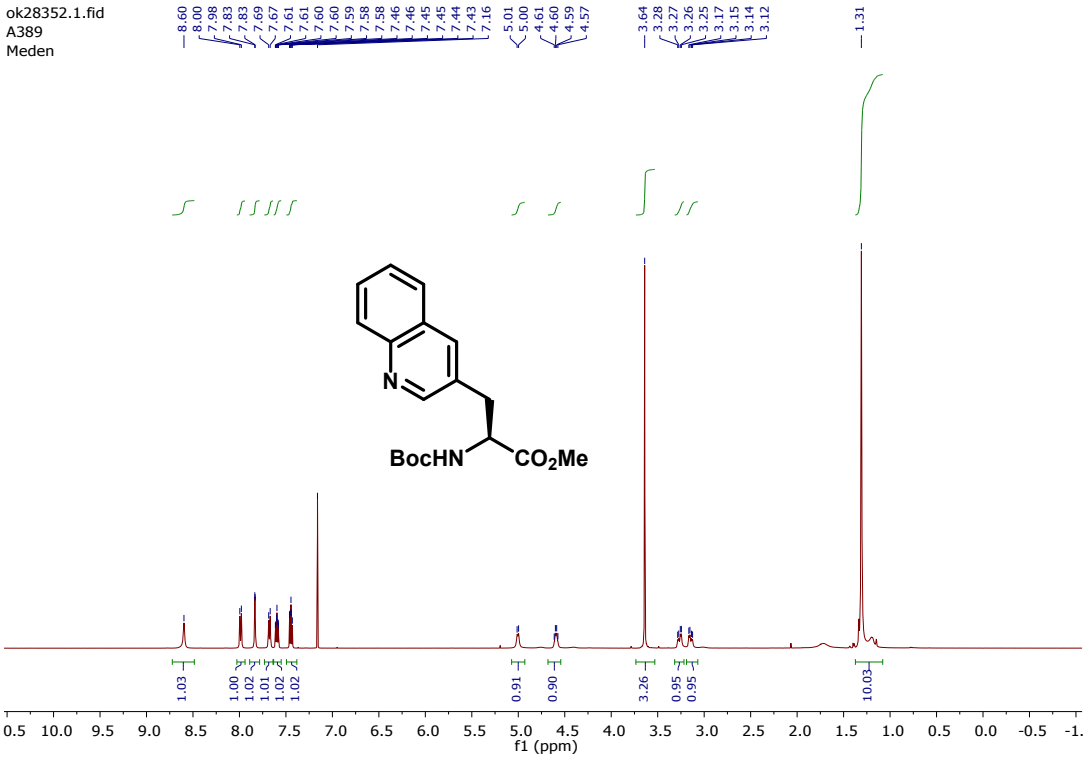
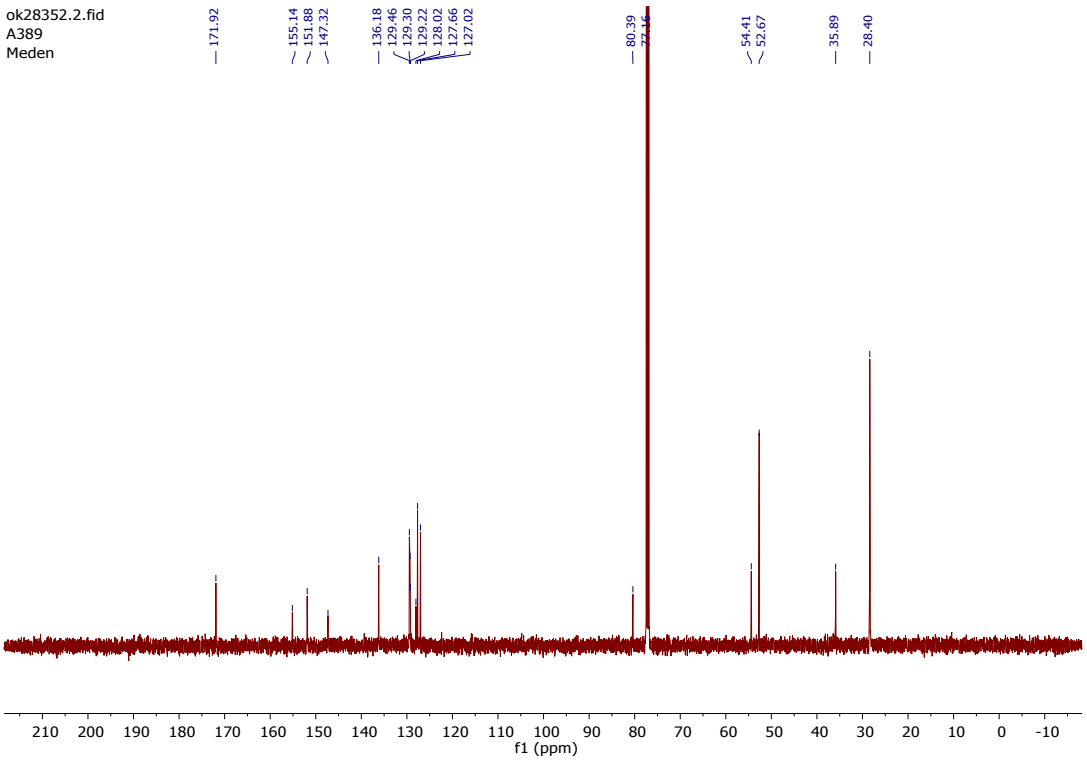
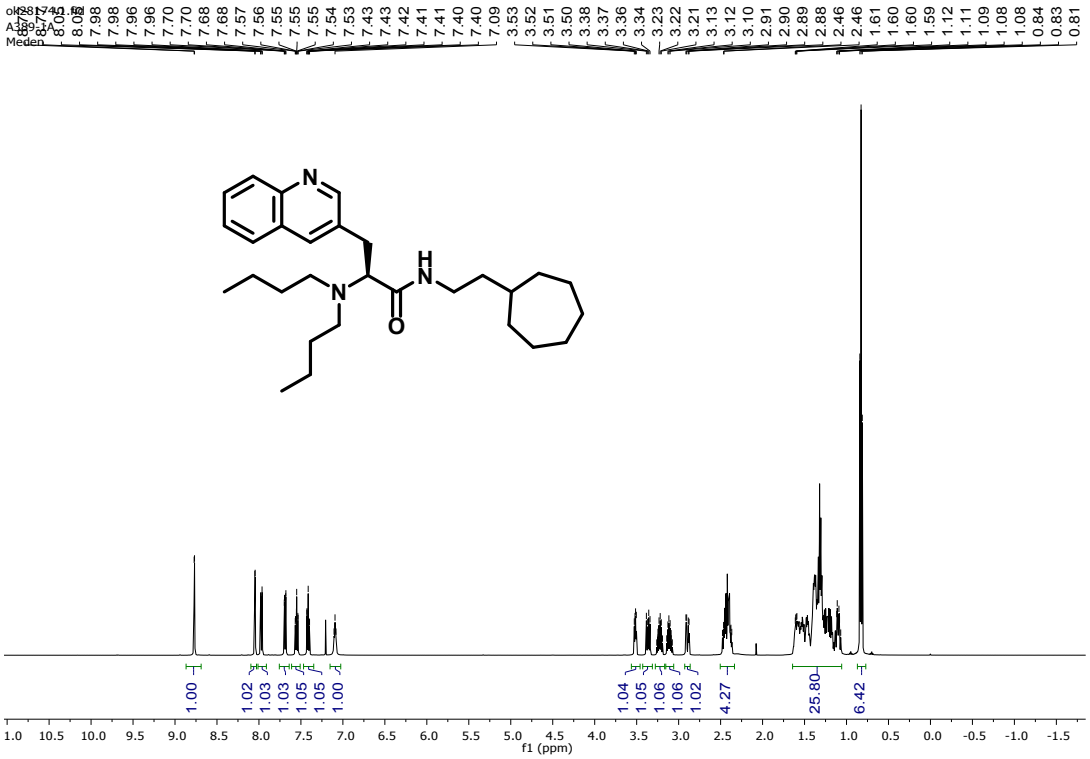
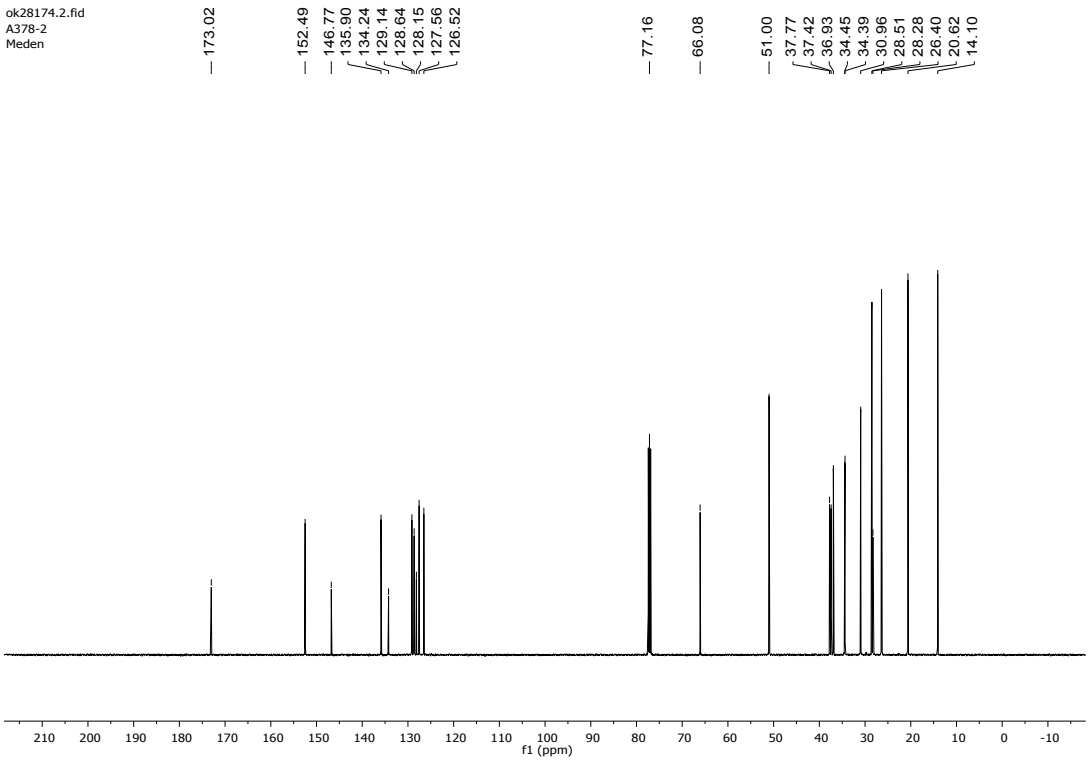
3

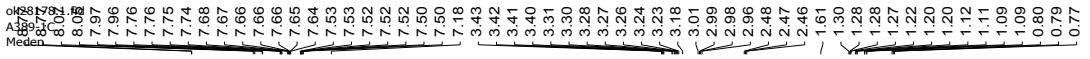

ok28352.1.fid
A389
Meden
8.60
8.00
7.98
7.83
7.83
7.69
7.67
7.61
7.61
7.60
7.60
7.59
7.58
7.58
7.46
7.46
7.45
7.45
7.44
7.43
7.16
5.01
5.00
4.61
4.60
4.59
4.57
3.64
3.28
3.27
3.26
3.25
3.17
3.15
3.14
3.12
1.31
N
BocHN
CO2Me
1.03
1.00
1.02
1.01
1.02
1.02
0.91
0.90
3.26
0.95
0.95
10.03
f1 (ppm)

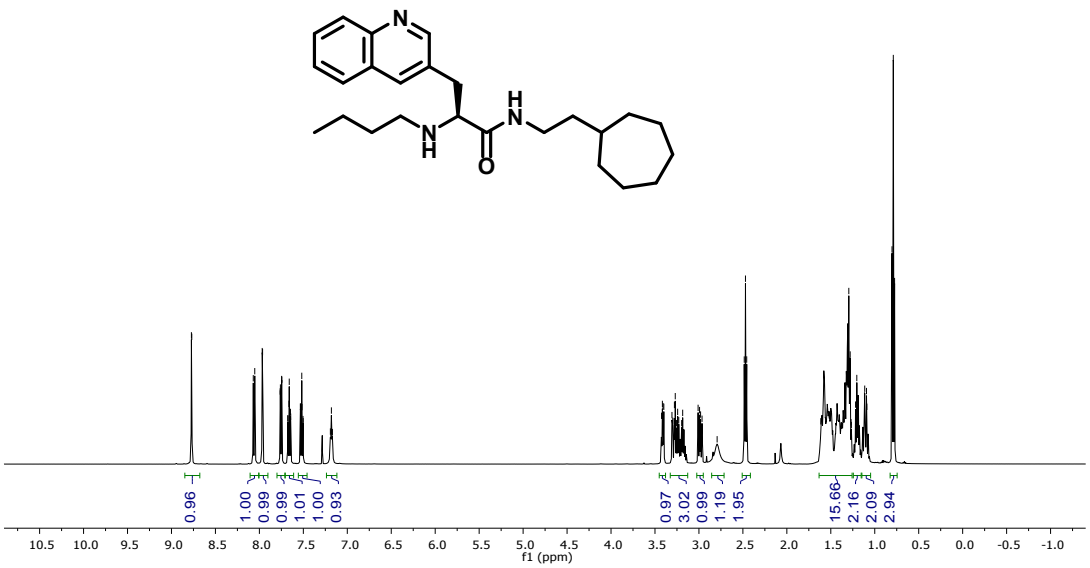

ok28352.2.fid
A389
Meden
171.92
155.14
151.88
147.32
136.18
129.46
129.30
129.22
128.02
127.66
127.02
80.39
77.16
54.41
52.67
35.89
28.40
f1 (ppm)

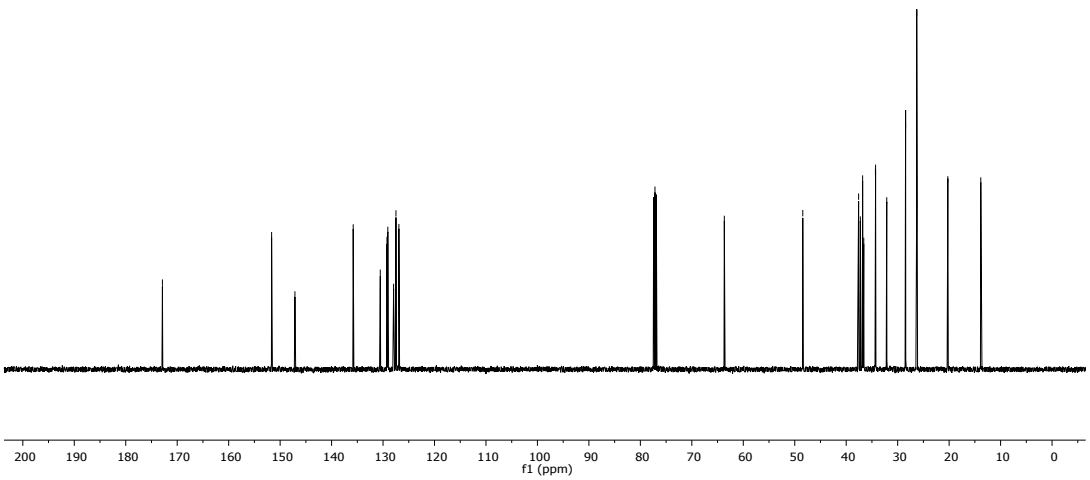

ok28174.2.fid
A378-2
Meden
8.02
8.00
7.98
7.98
7.96
7.96
7.70
7.70
7.68
7.68
7.57
7.56
7.55
7.55
7.55
7.54
7.53
7.43
7.43
7.42
7.41
7.41
7.40
7.40
7.09
3.53
3.52
3.51
3.50
3.38
3.37
3.36
3.34
3.23
3.22
3.21
3.13
3.12
3.10
2.91
2.90
2.89
2.88
2.46
1.61
1.60
1.60
1.59
1.12
1.11
1.09
1.08
1.08
0.84
0.83
0.81
N
H
N
N
O
1.00
1.02
1.03
1.03
1.05
1.05
1.00
1.04
1.05
1.06
1.06
1.02
4.27
25.80
6.42
f1 (ppm)


ok28174.2.fid
A378-2
Meden
173.02
152.49
146.77
135.90
134.24
129.14
128.64
128.15
127.56
126.52
77.16
66.08
51.00
37.77
37.42
36.93
34.45
34.39
30.96
28.51
28.28
26.40
20.62
14.10
f1 (ppm)

S54







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