Supplementary Information

Picomolar FKBP inhibitors enabled by a single water-displacing methyl group in bicyclic [4.3.1] aza-amides

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1. Water network

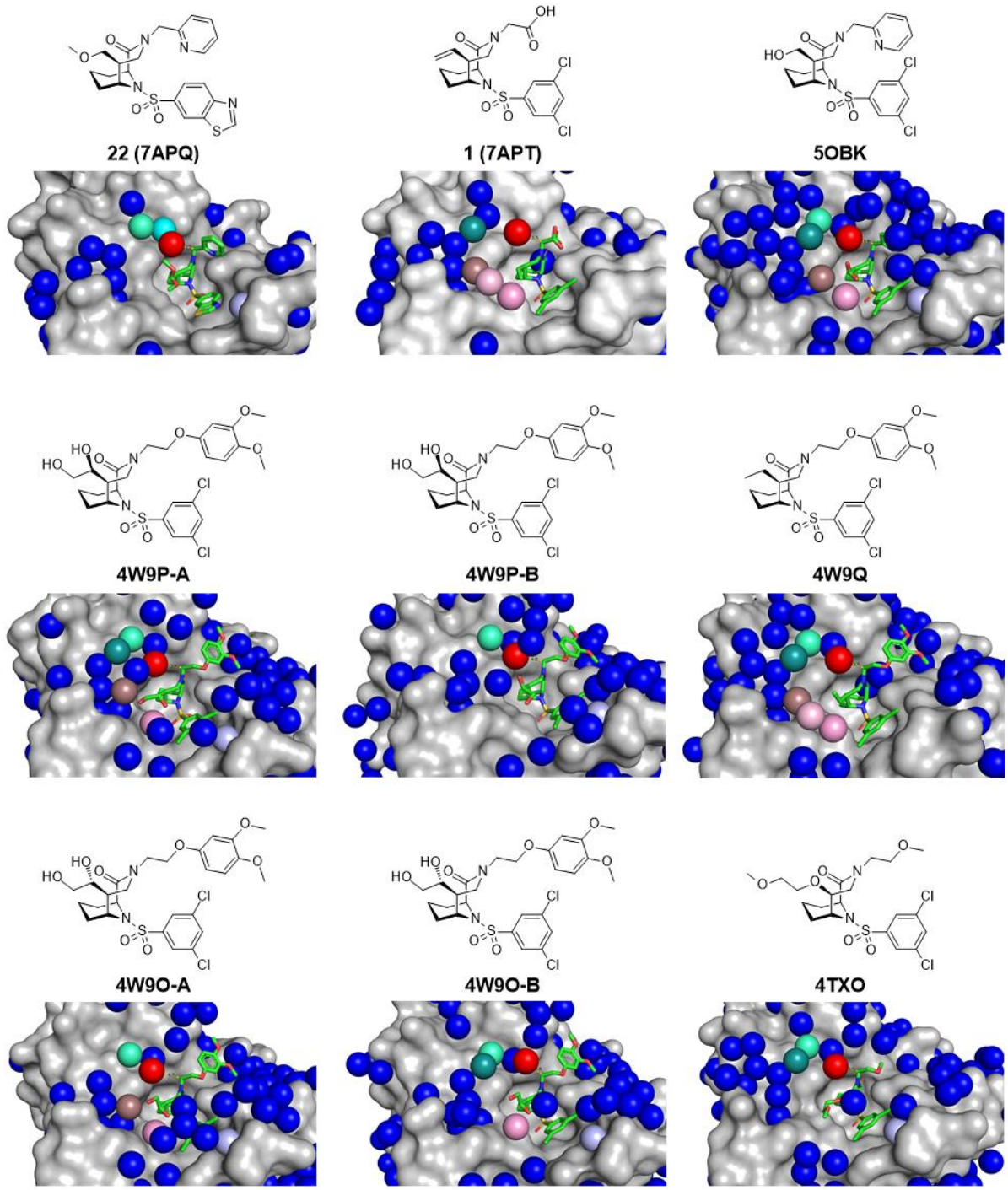


Figure S1: Analysis of all available crystal structures (PDB-ID indicated) of FKBP51 (grey surface) containing bicyclic [4.3.1.] sulfonamide ligands (green sticks; chemical structures are given above the crystal structures). Crystallographically resolved water molecules are shown as blue spheres, the conserved water displaced by a methyl group in the α-position is highlighted in red, the distance to the α-position is indicated as yellow dotted lines in Å. Further waters consistently conserved throughout the available crystal structures are highlighted in cyan, green, brown, pink and light pink.

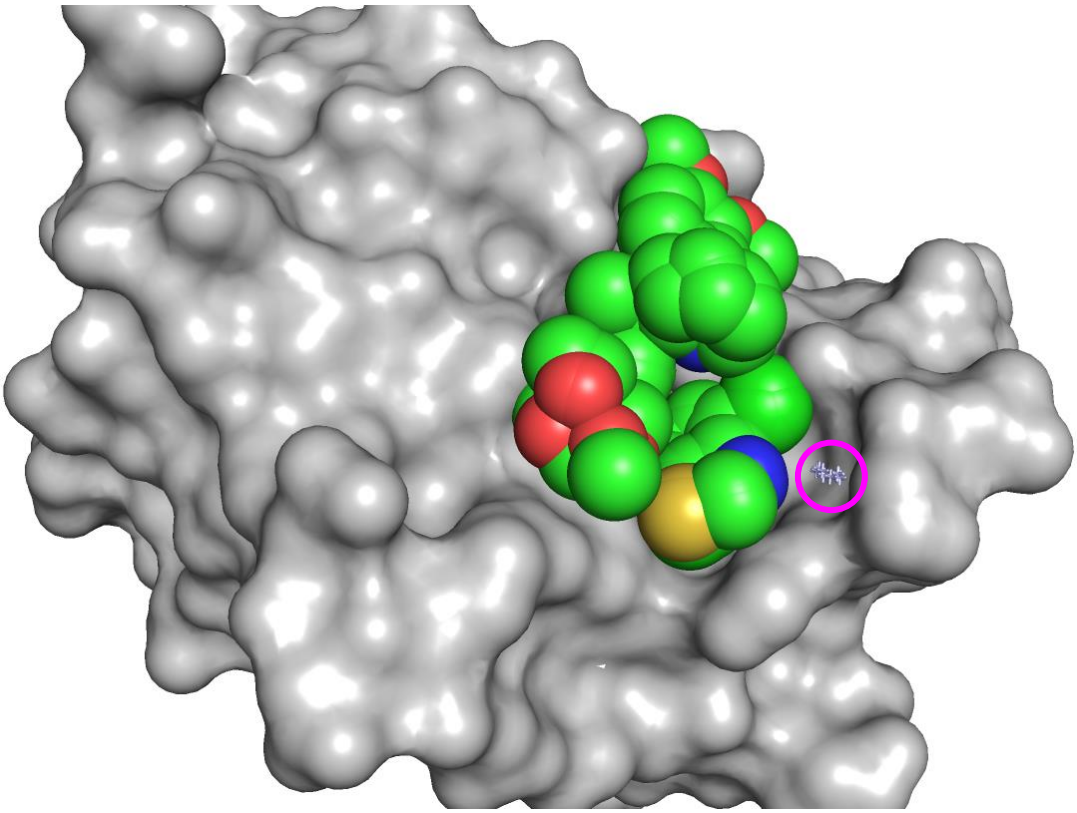


Figure S2. Overlay of the cocrystal structures of **22** (7APQ), **22**$^{(S)\text{-}Me}$, 5OBK, 4W9P_A, 4W9P_B, 4W9O_A, 4W9O_B und 4TXO in complex with FKBP51 (5OBK), with the conserved energetically favorable water molecule (HOH324 in **22**) highlighted in a pink circle.

2. 3D-RISM calculations

3D-RISM calculations with MOE were performed for the crystal structures of **22**/**22**$^{(S)\text{-}Me}$ and **1**/**1**$^{(S)\text{-}Me}$.[1-2] For compounds **22** and **1**, in both cases indeed a water site was predicted in close proximity (**22**: 0.83 Å, **1**: 1.00 Å) to the conserved water (red in **Fig. S2**) found in the crystal structure (**Fig. S2, Fig. S3**). This computationally supports the findings that a water at this place is highly conserved for this type of compounds. For compounds **22**$^{(S)\text{-}Me}$ and **1**$^{(S)\text{-}Me}$, no water site is predicted near the additional methyl group in accordance with the respective crystal structure (**Fig. S4**). The local free energy (ΔG_{local}) of the conserved water site is predicted to be considerably positive for both **22** (ΔG_{local} = + 26.03 kJ/mol, **Fig. S2 A** and **1** (ΔG_{local} = + 28.18 kJ/mol, **Fig. S2 B**) which means that the respective water can be displaced with low/no desolvation cost. For **22**, the predicted interaction energy ($\Delta G_{interact}$) of the water site with the receptor is +3.22 kJ/mol, for **1**, $\Delta G_{interact}$ is predicted to be + 2.77 kJ/mol (**Table S1**). Therefore, displacement of the water through the additional methyl group of **22**$^{(S)\text{-}Me}$ and **1**$^{(S)\text{-}Me}$ could stabilize the respective complex accordingly (**Fig. S5**). ΔG_{local} is an estimate of the total cost of desolvation, whereas $\Delta G_{interact}$ only describes the interaction energy between the respective water and the receptor.

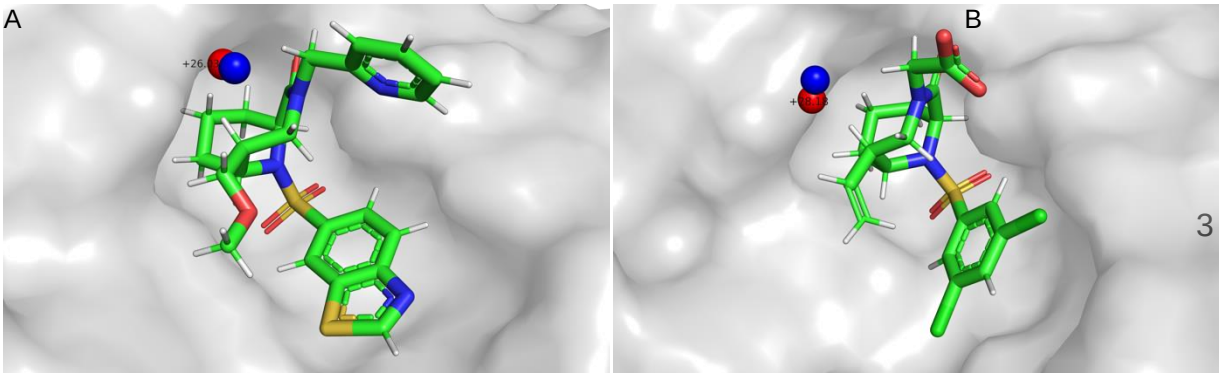


Figure S3. Predicted water site via 3D-RISM calculations. **A: 22** (ΔG_{local} = + 26.03 kJ/mol, distance to crystal water 0.83 Å). **B: 1** (ΔG_{local} = + 28.18 kJ/mol, distance to crystal water 1.00 Å). Red sphere = predicted water site, blue sphere = water found in crystal structure.

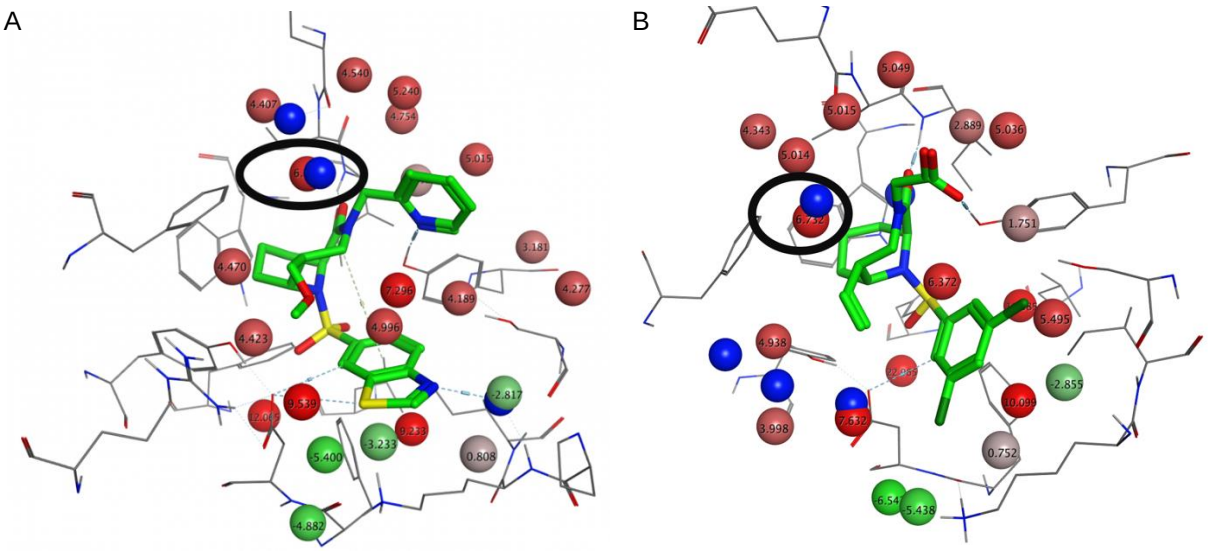


Figure S4. **A:** Predicted water sites (spheres) for **22** in 5 Å around the binding site. **B:** Predicted water sites (spheres) for **1** in 5 Å around the binding site. The sites are colored according to their predicted local free energy. Red = positive ΔG_{local}, green = negative ΔG_{local}, grey = ΔG_{local} near zero, blue spheres = crystal structure water. The displaced water is highlighted with a black circle. ΔG_{local} is in kcal/mol.

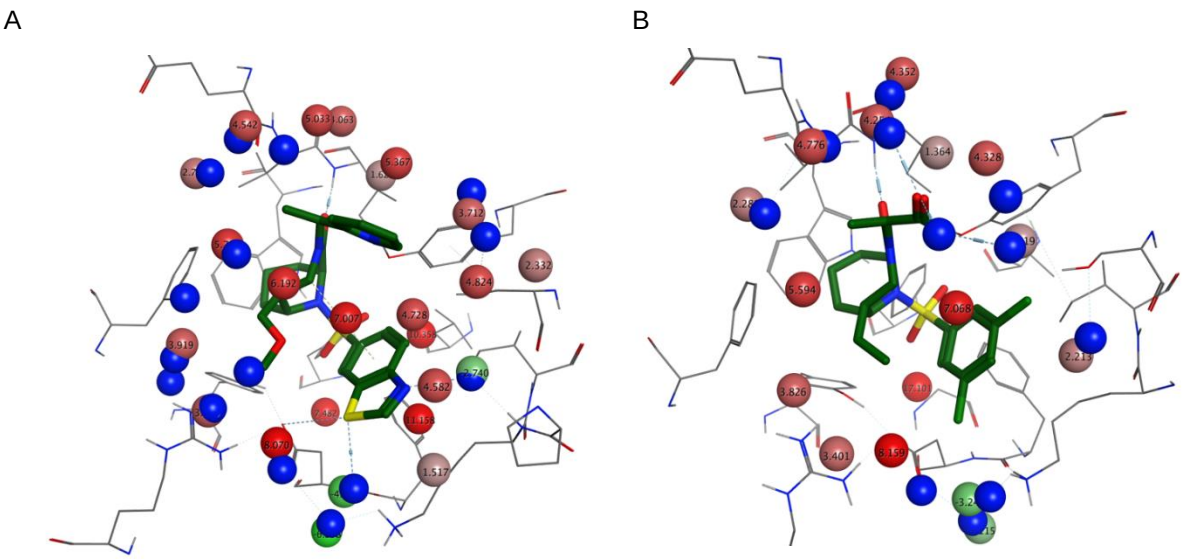


Figure S5. A: Predicted water sites (spheres) for **22**$^{(S)\text{-Me}}$ in 5 Å around the binding site. B: Predicted water sites (spheres) for **1** $^{(S)\text{-Me}}$ in 5 Å around the binding site. The sites are colored according to their

predicted local free energy. Red = positive ΔG_{local}, green = negative ΔG_{local}, grey = ΔG_{local} near zero, blue spheres = crystal structure water. ΔG_{local} in kcal/mol.

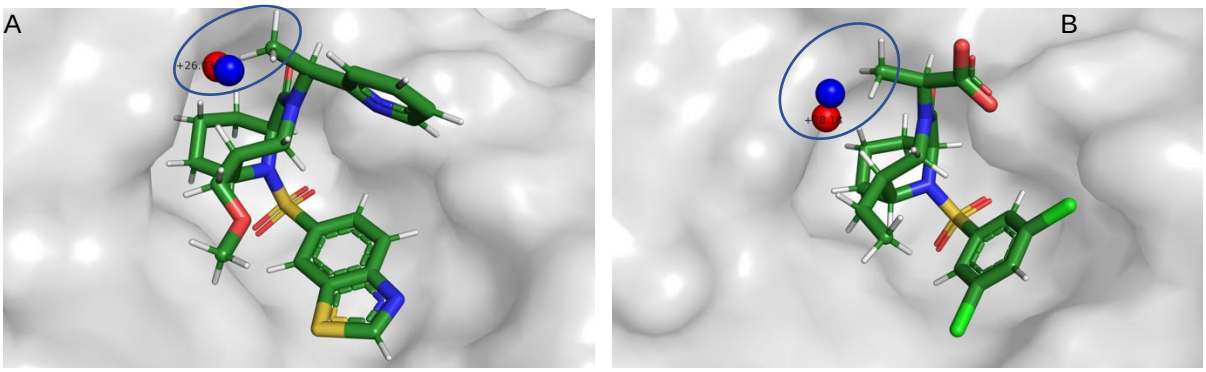


Fig. S6. **A:** Overlay of the crystal structure of **22**$^{(S)\text{-}Me}$-complex with the predicted water site of **22**-complex. **B:** Overlay of the crystal structure of **1**$^{(S)\text{-}Me}$-complex with the predicted water site of **1**-complex. The methyl group can displace the water in both cases with no desolvation cost.

Table S1: Parameters for water sites near conserved waters in the crystal structures of compounds **22**/**1** as predicted via 3D-RISM calculations. See also **Fig. S6A** for **22** and **Fig. S6B** for **1**.

Complex	Conserved crystal water	Distance of predicted water site to crystal water (Å)	ΔG_{local} (kJ/mol)	$\Delta G_{interact}$ (kJ/mol)
22	HOH372 (red)	0.83	+ 26.03	+ 3.22
	HOH364 (cyan)	1.34	+ 18.45	+ 1.51
	HOH364 (cyan)	2.88	+ 19.01	– 10.38
	HOH348 (green)	2.39	+ 18.45	+ 1.51
	HOH324 (light blue)	0.37	– 11.79	– 23.28
1	HOH440 (red)	1.00	+ 28.18	+ 2.76
	HOH396 (green light)	2.35	+ 18.17	+ 3.01
	HOH411 (bright pink)	0.53	+ 31.95	– 17.21
	HOH430 (light pink)	1.53	+ 16.75	– 0.42
	HOH435 (brown)	2.23	+ 20.68	– 2.47

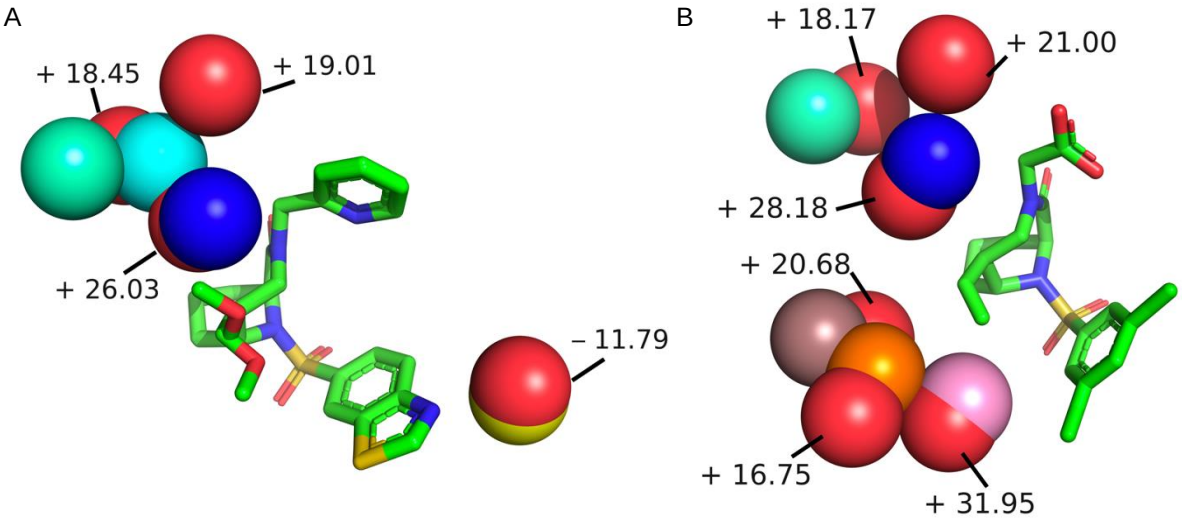


Fig. S7. Local free energy ΔG_{local} (in kJ/mol) for predicted water sites (red spheres) near conserved waters found in the crystal structure of **22** (A) and **1** (B) in close proximity to the respective ligand.

Procedure

3D-RISM

To predict water sites and their respective energies, 3D-RISM (Reference Interaction Site Model) calculations[1-3] with MOE[4] were performed. RISM belongs to the class of implicit solvent methods developed on the basis of density functional theory of liquids. RISM uses statistical mechanics description of the solvent structure. In the 3-dimensional version, a solute molecule is treated as a single object, but the solvent molecules are modelled as a set of atoms or sites, respectively.[5] 3D-RISM is theoretically equivalent to infinite long MD simulations. From the RISM equations, H and O density maps as well as free energy maps can be computed. To solve the equations, approximations are necessary. Within MOE, the KH closure is used.[6]

Structure pre-processing.

The respective crystal structures (**22**/**22**$^{(S)\text{-}Me}$ and **1**/**1**$^{(S)\text{-}Me}$) were prepared for the calculations using the QuickPrep utility of MOE with default settings except the deletion of water molecules and the refinement step (**Fig. S8**).

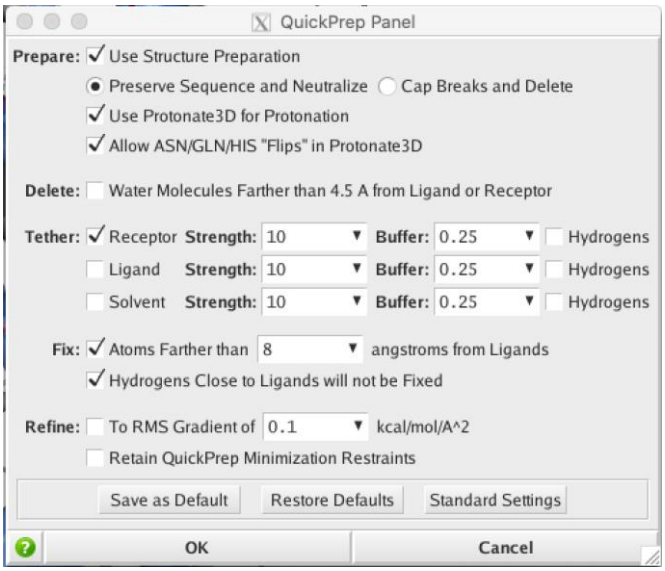


Figure S8. Settings for preparation of the crystal structures.

3D-RISM calculations

3D-RISM calculations were performed using the Solvent Analysis utility in MOE. All atoms with a maximal distance of 15 Å around the receptor were included in the calculation. The grid around the solute was generated such that the minimum distance between any solute atom and the edge of solvent box (Buffer in MOE notation) was equal to 15 Å. The linear grid spacing in each of the three directions was 0.3 Å. Tight convergence was set for quantitative reproducibility (**Fig. S9**).

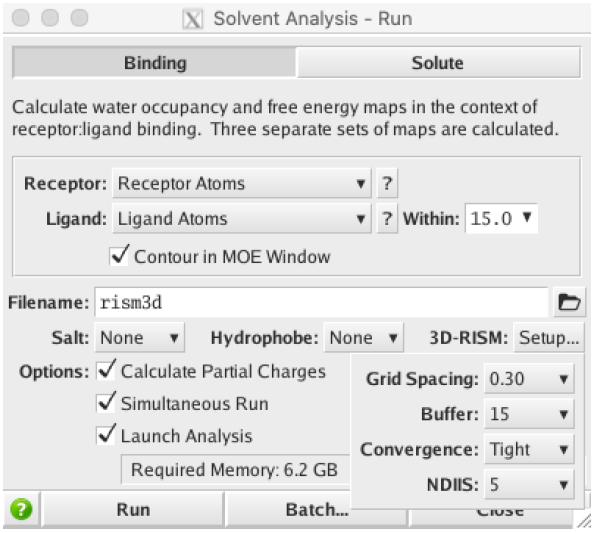


Figure S9. Settings used for RISM calculations.

The predicted radial distributions functions for the oxygen density and the free energy maps were analyzed using the Solvent-Analysis-Grids panel. The predicted water sites were monitored using the Solvent-Analysis-Sites panel (**Fig. S10**). Only water sites within 5 A around the ligand and with a maximal distance of 3.5 A to a crystal water were considered for further analysis.

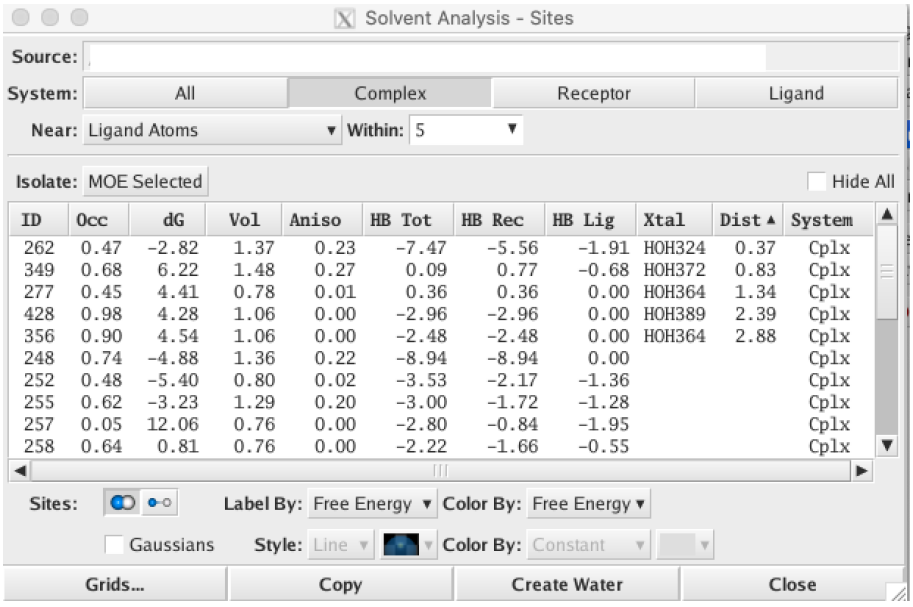


Figure S10. Water sites results panel.

3. Compound 2 & Synthesis of $22^{(R)\text{-}Me}$ and $22^{(S)\text{-}Me}$

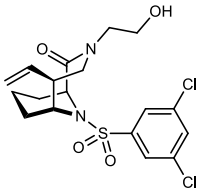
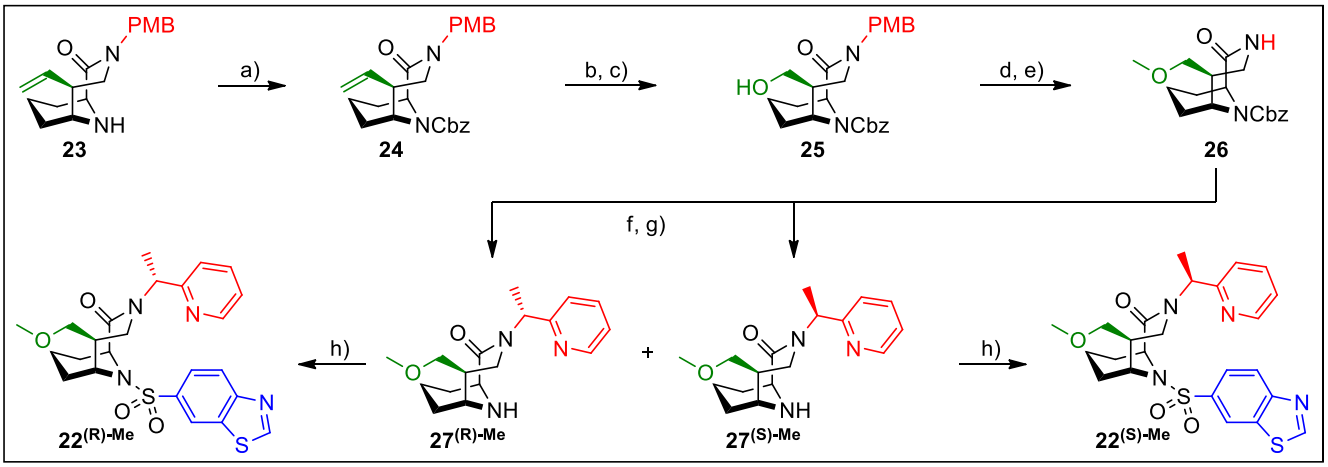


Fig. S11. Structure of **2**.



Scheme S1. Synthesis of $\mathbf{22^{(R)\text{-}Me}}$ and $\mathbf{22^{(S)\text{-}Me}}$. Reagents and conditions: (a) CbzCl, DIPEA, DCM, rt, 1 h; (b) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O, rt, 20 h; (c) $NaBH_4$, EtOH, 1 h, rt, 66% (over 3 steps); (d) MeI, NaH, rt, 1 h; (e) CAN, MecN/H_2O, rt, 4 h, 55% (over 2 steps); (f) 2-(1-bromoethyl)pyridine, NaH, DMF, rt, 1 h; (g) BCl_3*SMe_2, DCM, rt, 1 h, separation of diastereomers: $\mathbf{27^{(R)\text{-}Me}}$: 23%, $\mathbf{27^{(S)\text{-}Me}}$: 12% (over 2 steps); (h) benzo[d]thiazole-6-sulfonyl chloride, DIPEA, DMAP, DCM, rt, 20 h, $\mathbf{22^{(R)\text{-}Me}}$: 40%, $\mathbf{22^{(S)\text{-}Me}}$: 46%.

4. FP-Assay data

All proteins (FKBP12, -12.6, -51FK1, -52FK1) were recombinantly expressed in E. coli BL21DE2Gold and had a final purity of >95% as visually judged by Coomassie gel. The proteins were stored in HEPES buffer (20 mM HEPES, 20 mM NaCl (150 mM NaCl for FKBP12.6), +/- 5% (v/v) Glycerol, pH 8.0). The fluorescent ligand FT was developed by Pomplun et al[7] (**Fig. S12**).

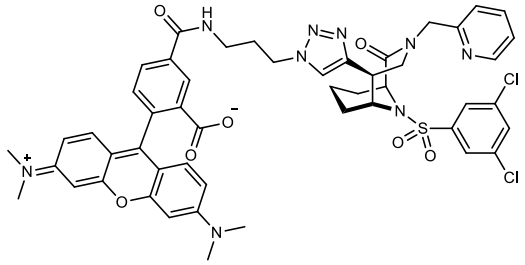


Figure S12. Chemical structure of the fluorescent ligand **FT**.

Fluorescent ligand dissociation constants as well as final concentrations of the fluorescent ligand **FT** and proteins FKBP12, 12.6, 51FK1 and 52FK1 are summarized in **Tab. S2**. The competition curves were analyzed using Prism 6.0 (GraphPad Software).

Table S2. Concentrations of proteins and fluorescent ligand FT and dissociation constants of FT.

FKBP	**12**	**12.6**	**51FK1**	**52FK1**
[FKBP]/nM	1	10	15	10
[FT]/nM	0.5	1	1	1
Kd (FT)/nM	0.30 ± 0.06	1.7 ± 0.1	5.7 ± 0.2	4.1 ± 0.2

For the analysis of K_d values, data were fitted to the following equation (provided in Kozany et al.; Supporting Information, Appendix 3).[8]

$$A = (A_{max} - A_{min}) / [L]_t \times (([L]_t \times ((2\times((K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^2 - 3\times(K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}))^{0.5} \times COS(ARCCOS((-2\times(K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^3 + 9\times(K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t) \times (K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}) - 27\times(-1\times K_{lig} \times K_{comp} \times [R]_t)) / (2\times ((((K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^2 - 3\times (K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}))^3)^{0.5}))) / 3)) - (K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t))) / ((3\times K_{lig}) + ((2\times((K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^2 - 3\times(K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}))^{0.5} \times COS(ARCCOS((-2\times(K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^3 + 9\times(K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t) \times (K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}) - 27\times(-1\times K_{lig} \times K_{comp} \times [R]_t)) / (2\times(((K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)^2 - 3\times(K_{comp} \times ([L]_t - [R]_t) + K_{lig} \times ([I]_t - [R]_t) + K_{lig} \times K_{comp}))^3)^{0.5})))/3)) - (K_{lig} + K_{comp} + [L]_t + [I]_t - [R]_t)))) + A_{min}$$

In this equation K_{lig} and K_{comp} stand for the K_d values of the used tracer or competing ligand, $[L]_t$ and $[R]_t$ are referring to the total concentrations of the used tracer or the protein and $[I]_t$ is referring to the total concentration of the titrated ligand. A stands for the fluorescence anisotropy (A_{min} = minimal measured anisotropy, A_{max} = maximal measured anisotropy).

Table S3. FP-Assay data of all tested compounds for all tested FKBPs.

#	FKBP12 [nM]	FKBP51 [nM]	FKBP52 [nM]	R^1	R^2	R^3
FK506	0.70 +- 0.04	129 +- 7	49.14 +- 2.98	X	X	X
Rapamycin	0.43 +- 0.04	31 +- 1	34.40 +- 1.74	X	X	X
$1^{(R)\text{-}Me}$	48	123	296	CH((R)-CH_3)COOH	DCB[a]	Vinyl
1	33	172	320	CH_2COOH		
$1^{(S)\text{-}Me}$	13	22	80	CH((S)-CH_3)COOH		
$8^{(R)\text{-}Me}$	>5000	>5000	>5000	CH((R)-CH_3)CH_2OBn	BTZ[b]	Vinyl
$8^{(S)\text{-}Me}$	28	263	316	CH((S)-CH_3)CH_2OBn		
$9^{(R)\text{-}Me}$	>5000	>5000	>5000	CH((R)-CH_3)CH_2OH	BTZ[b]	Vinyl
$9^{(S)\text{-}Me}$	21	110	102	CH((S)-CH_3)CH_2OH		
$10^{(R)\text{-}Me}$	>5000	>5000	>5000	CH((R)-CH_3)CH_2OBn	DCB[a]	Vinyl
$10^{(S)\text{-}Me}$	58	1076	1028	CH((S)-CH_3)CH_2OBn		
$11^{(R)\text{-}Me}$	>5000	>5000	>5000	CH((R)-CH_3)CH_2OH	DCB[a]	Vinyl
$11^{(S)\text{-}Me}$	3.5	107	116	CH((S)-CH_3)CH_2OH		
$16^{(R)\text{-}Me}$	130	>1000	>1000	CH((R)-CH_3)Py	DCB[a]	Vinyl
16	1.3	119	54	CH_2Py		
$16^{(S)\text{-}Me}$	0.72	2.6	2.2	CH((S)-CH_3)Py		
$17^{(R)\text{-}Me}$	240	4546	3451	CH((R)-CH_3)Py	BTZ[b]	Vinyl
17	7.5	294	276	CH_2Py		
$17^{(S)\text{-}Me}$	2.2	33	29	CH((S)-CH_3)Py		
18	0.52	33	19	CH_2Py	DCB[a]	CH_2OH
$18^{(S)\text{-}Me}$	0.29	2.6	3.6	CH((S)-CH_3)Py		
19	0.65	12	11	CH_2Py	DCB[a]	CH_2OMe
$19^{(S)\text{-}Me}$	0.33	2.9	3.2	CH((S)-CH_3)Py		
20	6.5	410	285	CH_2Py	BTZ[b]	Ethyl
$20^{(S)\text{-}Me}$	1.9	27	22	CH((S)-CH_3)Py		
21	5.5	283	190	CH_2Py	BTZ[b]	CH_2OH
$21^{(S)\text{-}Me}$	1.5	27.2	18.2	CH((S)-CH_3)Py		
$22^{(R)\text{-}Me}$	52	696	735	CH((R)-CH_3)Py	BTZ[b]	CH_2OMe
22	2.5	104	60	CH_2Py		
$22^{(S)\text{-}Me}$	2.2	32	17	CH((S)-CH_3)Py		

[a] DCB = 3,5-Dichlorobenzene. [b] BTZ = 6-Benzothiazole. n.d. = not determined.

5. ITC data

The binding thermodynamics of selected compounds to FKBP51FK1 were determined by isothermal titration calorimetry at 25 °C. In brief, a 10-20 µM solution of FKBP51FK1 formulated in 20 mM HEPES pH 8.0, 20 mM NaCl and 0.5-1% DMSO was placed in the sample cell of a PEAK-ITC instrument. The syringe was filled with a 100-200 µM solution of the respective compound formulated in the same buffer. After equilibration the compound was titrated into the sample cell by 18 injections of 2 µl each. The obtained data was then analyzed using the MicroCal analysis software, fitted to a one-site binding model yielding the thermodynamic parameters of the interaction.

Table S4: ITC data of selected compounds for FKBP51.

#	Ki nM	dH kJ/mol	TdS kJ/mol	dG kJ/mol	R^1	R^2	R^3
1	210±60	-45±1	7±2	-38±1	CH_2COOH	DCB[a]	Vinyl
$1^{(S)\text{-}Me}$	26±7	-47±1	4±1	-43±1	CH((S)-CH_3)COOH		
$9^{(R)\text{-}Me}$	4500±1000	-47±4	17±5	-31±1	CH((R)-CH_3)CH_2OH	BTZ[b]	Vinyl
$9^{(S)\text{-}Me}$	170±25	-53±2	14±2	-39±1	CH((S)-CH_3)CH_2OH		
$17^{(R)\text{-}Me}$	2700±450	-40±2	8±2	-32±1	CH((R)-CH_3)Py	BTZ[b]	Vinyl
17	280±58	-52±2	15±3	-37±1	CH2Py		
$17^{(S)\text{-}Me}$	13±6	-54±2	9±2	-45±1	CH((S)-CH_3)Py		
18	44±7	-71±1	29±1	-42±1	CH_2Py	DCB[a]	CH_2OH
$18^{(S)\text{-}Me}$	4±2	-71±1	22±2	-48±1	CH((S)-CH_3)Py		
19	16±8	-56±2	12±2	-45±1	CH_2Py	DCB[a]	CH_2OMe
$19^{(S)\text{-}Me}$	1.6±0.8	-55±1	5±1	-50±1	CH((S)-CH_3)Py		
20	250±70	-53±3	15±3	-38±1	CH_2Py	BTZ[b]	Ethyl
$20^{(S)\text{-}Me}$	33±6	-50±1	7±1	-43±1	CH((S)-CH_3)Py		
21	200±66	-64±2	26±3	-39±1	CH_2Py	BTZ[b]	CH_2OH
$21^{(S)\text{-}Me}$	20±4	-63±1	19±1	-44±1	CH((S)-CH_3)Py		
22	237±80	-50±2	12±2	-38±1	CH_2Py	BTZ[b]	CH_2OMe
$22^{(S)\text{-}Me}$	14±5	-50±2	5±2	-45±1	CH((S)-CH_3)Py		

[a] DCB = 3,5-Dichlorobenzene. [b] BTZ = 6-Benzothiazole.

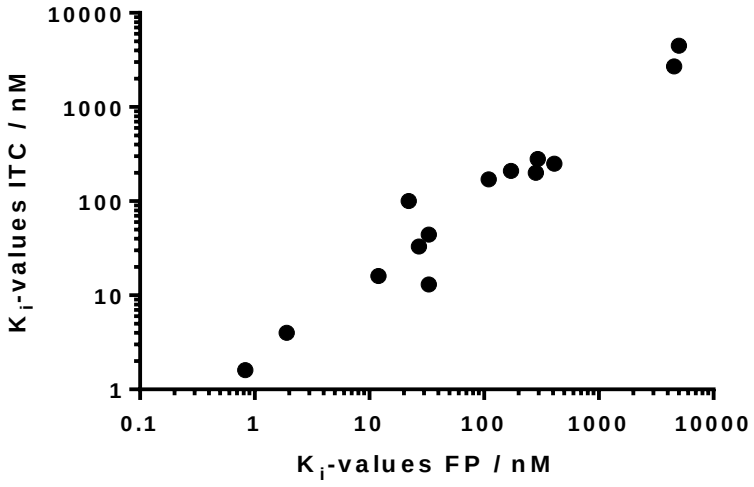


Figure S13. Correlation of FP-assay and ITC data.

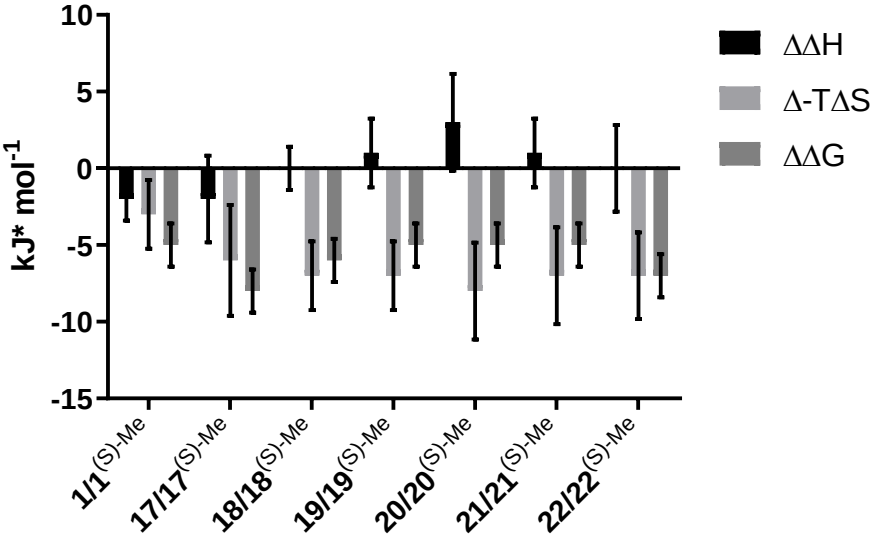


Figure S14. Thermodynamic signature of the affinity increases of selected compound pairs with and without α-methyl group.

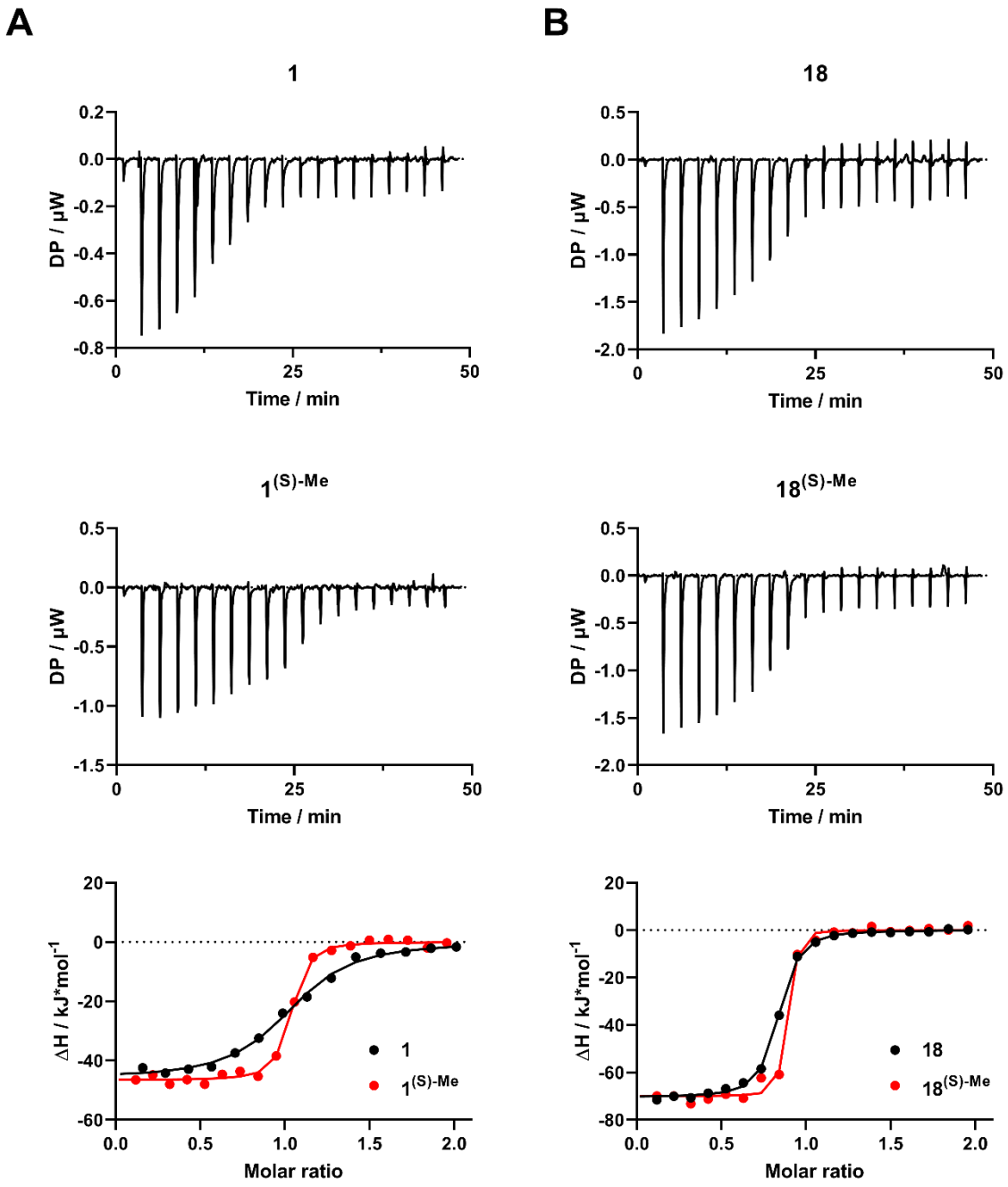


Figure S15. Example ITC traces of compounds **1**, **1**$^{(S)\text{-Me}}$ (A), **18** and **18**$^{(S)\text{-Me}}$ (B) binding to FKBP51FK1 at 25 °C. In general, a 10 µM solution of FKBP51FK1 formulated in 20 mM HEPES pH 8.0, 20 mM NaCl and 1% DMSO was placed in the sample cell of a PEAK-ITC instrument. The syringe was filled with a 100 µM solution of the respective compound formulated in the very same buffer. After equilibration the compound was titrated to the FKBP51FK1 solution by 18 injections of 2 µl each. The obtained data was analyzed using the provided software package and fitted to a one-site binding model yielding the thermodynamic parameters (mean ± SD from 3 independent experiments) summarized in table **S4**.

6. Crystallographic data

6.1 Crystallization of the complex of FKBP51fk1 with $1^{(S)\text{-}Me}$

Complexes were prepared by mixing FKBP51fk1 at 2.19 mM with **$1^{(S)\text{-}Me}$** at 6.25 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution. Crystals were obtained after seeding with reservoir solutions containing 38% PEG-3350, 0.2 M NH_4-acetate and HEPES-NaOH pH 7.5.

6.2 Structure solution and refinement of the complex of FKBP51fk1 with $1^{(S)\text{-}Me}$

Diffraction data were collected at beamline ID30B of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. Diffraction data were integrated with XDS[9] and further processed with the implemented programs of the CCP4i interface (Collaborative Computational Project).[10-11] The data reduction was conducted with Aimless[11-13]. Crystal structures were solved by molecular replacement employing the program Molrep.[14-15] Iterative model improvement and refinement were performed with Coot[16] and Refmac5.[17-21] The dictionary for the compound was generated with PRODRG implemented in CCP4i.[22] Residues facing solvent channels without detectable side chain density were truncated at Cβ.

6.3 Crystallization of the complex of FKBP51fk1 with 1

Complexes were prepared by mixing FKBP51fk1 at 2.19 mM with **1** at 2.5 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution. Crystals were obtained after seeding with reservoir solutions containing 38% PEG-3350, 0.2 M NH_4-acetate and HEPES-NaOH pH 7.5.

6.4 Structure solution and refinement of the complex of FKBP51fk1 with 1

Diffraction data were collected at beamline ID29 of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. The GrenADeS/EDNA (Ref. PMID: 23682196) pipeline was used for data processing. Crystal structures were solved by molecular replacement employing the program Molrep.[14-15] Iterative model improvement and refinement were performed with Coot[16] and Refmac5. [17-20] The dictionary for the compound was generated with PRODRG implemented in CCP4i.[22] Residues facing solvent channels without detectable side chain density were truncated at Cβ.

6.5 Crystallization of the complex of FKBP51fk1 with 22

Complexes were prepared by mixing FKBP51fk1 at 2.19 mM with 22 at 2.5 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution. Crystals were obtained after seeding with reservoir solutions containing 36% or 40% PEG-3350, 0.2 M NH_4-acetate and HEPES-NaOH pH 7.5.

6.6 Structure solution and refinement of the complex of FKBP51fk1 with 22

Diffraction data were collected at beamline ID29 of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. The GrenADeS/EDNA (Ref. PMID: 23682196) pipeline was used for data processing. Crystal structures were solved by molecular replacement employing the program Molrep.[14-15] Iterative model improvement and refinement were performed with Coot[16] and Refmac5.[17-21] The dictionary for the compound was generated with PRODRG implemented in CCP4i.[22] Residues facing solvent channels without detectable side chain density were truncated at Cβ.

6.7 Crystallization of the complex of FKBP51fk1 with 22(S)-Me

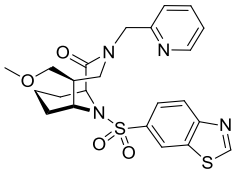
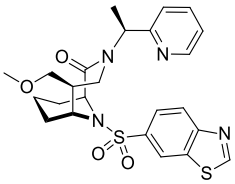
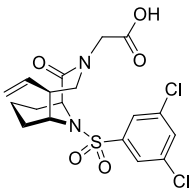
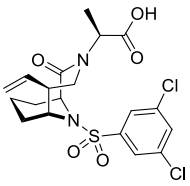
Complexes were prepared by mixing FKBP51fk1 at 2.08 mM with **22$^{(S)\text{-}Me}$** at 4.17 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution. Crystals were obtained after seeding with reservoir solutions containing 36% PEG-3350, 0.2 M NH4-acetate and HEPES-NaOH pH 7.5.

6.8 Structure solution and refinement of the complex of FKBP51fk1 with 22(S)-Me

Diffraction data were collected by Jerome Basquin (MPI of Biochemistry, Martinsried, Germany) at beamline X10SA of the Swiss Light Source (SLS) in Villigen, Switzerland. Diffraction data were integrated with XDS[6] and further processed with the implemented programs of the CCP4i interface (Collaborative Computational Project).[7] The data reduction was conducted with Aimless.[7b, 8] Crystal structures were solved by molecular replacement employing the program Molrep.[14-15] Iterative model improvement and refinement were performed with Coot[10] and Refmac5.[11] The dictionary for the compound was generated with PRODRG implemented in CCP4i.[12] Residues facing solvent channels without detectable side chain density were truncated at Cβ.

6.3 Refinement data

Table S5. Data collection and refinement statistics of the complexes with compounds **22**, **22$^{(S)\text{-}Me}$**, **1** and **1$^{(S)\text{-}Me}$**.

Lig. Name	**22**	**22$^{(S)\text{-}Me}$**	**1**	**1$^{(S)\text{-}Me}$**
Lig. Structure				
PDB-ID	7APQ	7APW	7APT	7APS
Protein residues	13-140	13-140	13-140	13-140
Synchrotron	ESRF	SLS	ESRF	ESRF
Beamline	ID29	X10SA	ID29	ID30B
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P1$
***a* (Å)**	41.82	41.91	41.92	34.81
***b* (Å)**	54.61	54.93	54.55	39.92
***c* (Å)**	56.46	56.82	56.28	43.55
α (°)	90	90	90	74.06
β (°)	90	90	90	76.11
γ (°)	90	90	90	74.05
Integration software	*GrenADeS/EDNA/XDS*	*XDS*	*GrenADeS/EDNA/XDS*	*XDS*
Resolution limits (Å)	39.28-1.09 (1.11-1.09)	41.91-0.89 (0.90-0.89)	39.17-1.13 (1.15-1.13)	37.42-0.94 (0.95-0.94)
⟨*I*/σ(*I*)⟩	5.9 (2.0)	13.7 (2.4)	9.5 (2.0)	16.3 (1.2)
Multiplicity	3.5 (3.2)	7.2 (2.3)	3.2 (2.6)	3.7 (3.1)
Completeness (%)	100 (99.8)	89.5 (23.1)	100 (99.9)	85.9 (76.0)
Refinement program	*REFMAC*	*REFMAC*	*REFMAC*	*REFMAC*
Resolution range (Å)	30.00-1.09	30.00-0.89	28.62-1.13	30.00-0.94
Reflections$_{all}$	54712	86740	48910	119854
Reflections$_{free}$	2760	4542	2536	6102
R_{work}	0.181	0.124	0.167	0.141
R_{free}	0.215	0.144	0.216	0.165
No. of atoms (B-Factor)				
Protein	2077 (15.3)	2242 (11.0)	2096 (19.5)	2211 (15.5), 2244 (12.7)

Ligand	122 (22.4)	62 (10.4)	47 (19.8)	50 (9.5), 50 (12.5)
Water	118 (16.7)	289 (27.9)	155 (30.7)	141 (23.9), 131 (21.9)
R.m.s.d. bonds (Å)	0.015	0.026	0.021	0.014
R.m.s.d. angles (°)	1.888	2.335	2.200	1.950

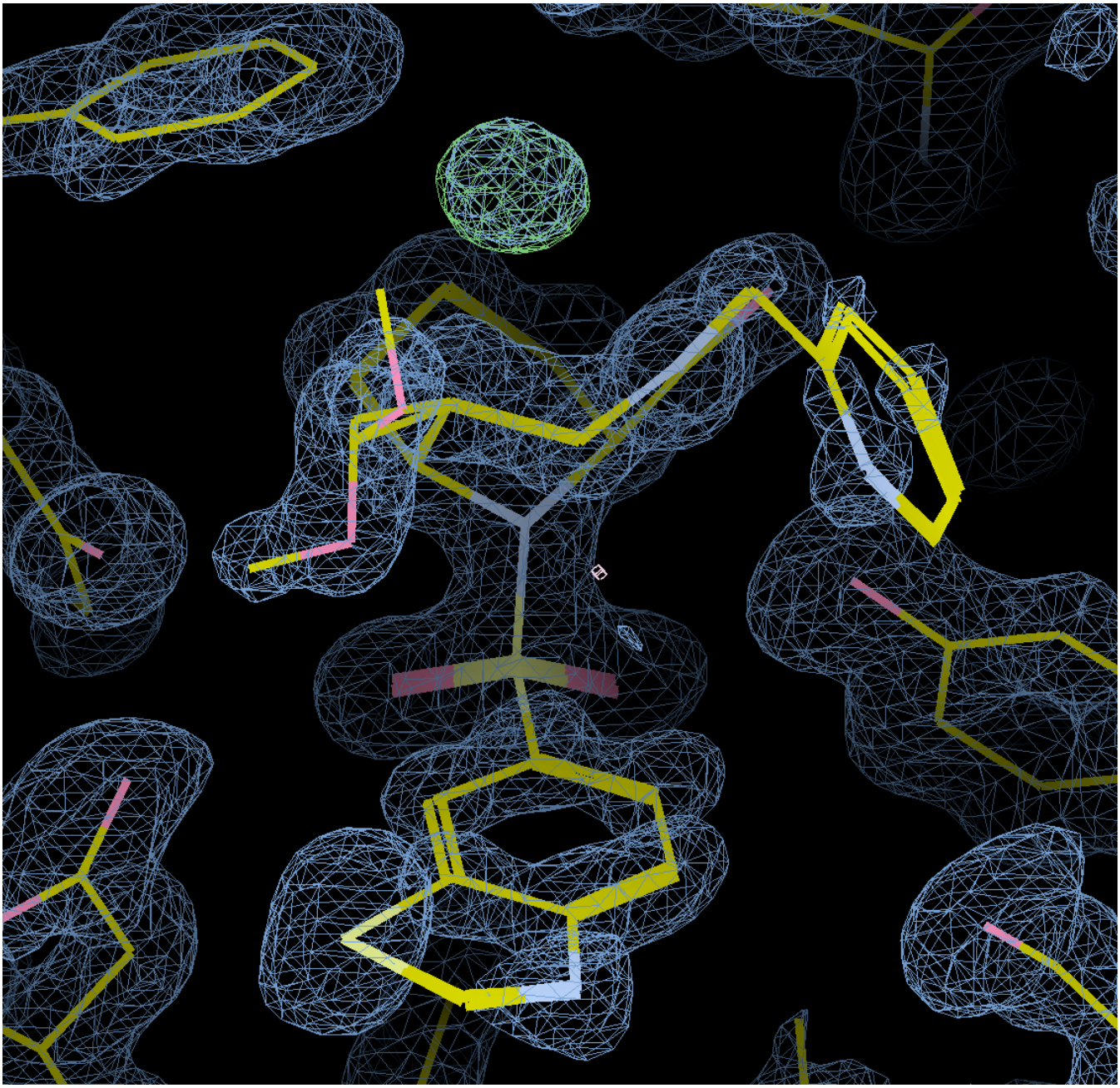


Figure S16. Omitmap of **22**.

7 DFT calculations

All quantum chemical calculations were run with the ORCA suite of programs, version 4.1.2 or higher[23]. All structures were taken from crystallographic data published herein. Geometries were optimized with the density functional BP86 under the resolution of the identity approximation using Ahlrich's def2-TZVP basis set with a def2/J auxiliary basis[24-28]. Environmental effects were considered using the CPCM model with water as the solvent modeled[29]. Dispersion corrections were introduced with Grimme's D3zero scheme[30]. The integration grid was increased to 6 in ORCA nomenclature and no final grid was set. The SCF convergence criteria were set to tight in ORCA nomenclature.

For the potential energy surface scan used to estimate rotational degrees of freedom, the CNCC and NCCN dihedral angles (see **Fig. 6**) were kept fixed at values between -180° and +180° in increments of 20°, while relaxing the positions of all other atoms. This results in a grid of 18x18 calculations that covers the complete rotation about the central NC and CC bonds, respectively. For energetic minima identified under these constraints, full geometry relaxations were performed. The resulting geometric parameters and energies are shown in **Tab. S6**.

For all fully relaxed geometries, thermodynamic corrections at the same level of theory as the geometry optimization were calculated, except omitting the solvent model. To gauge the influence of the density functional, additional single point energies with the B2PLYP density functional were performed[31]. For these B2PLYP calculations, the RIJONX approximation with an automatically selected auxiliary basis was used, keeping all other settings identical to those above. No significant differences are seen (**Tab. S6).**

In order to estimate the stabilization energies upon introduction of the ligand into the binding pocket, computational models of the binding pocket with the most relevant amino acids and some crystallographically resolved water molecules were constructed. The resulting models contained at least 299 atoms. Only the positions of the hydrogen atoms of the binding pocket were optimized. The amino acids included are: Tyr57, Phe67, Asp68, Arg73, Phe77, Val86, Ile87, Trp90, Tyr113, Ser118, Lys121, Ile122, Leu128, (Phe130), strongly bound H_2O; Cartesian coordinates are supplied below.

The stabilization energies ΔE_{stab}^{all} shown in **Tab. S7** were calculated as the energy difference between a model in which the ligand is bound in the pocket and models for the individual components, i.e. the empty binding pocket and the free ligand. Similarly, to evaluate individual interactions between amino acids that form the pocket and the ligand, smaller models that contain only individual amino acids or

chains of amino acids that are covalently bound were constructed. Analogously to the total stabilization energy described above, individual stabilization energies were computed as energy differences between the complete model (ligand with amino acid(s)) and individual components (separate ligand and amino acid(s)). No geometry relaxation effects were considered for these energies. The differences between the methylated and unmethylated ligand are approximately the same in both cases, see ΔΔ*E*-values in **Tab. S7**.

Table S6. Final single point energies (Eh) calculated with the BP and B2PLYP density functionals, relative final single point energies within each set of ligand conformations (kcal/mol) and thermodynamic data (kcal/mol) calculated with the BP density functional for the ligands in different conformations as denoted by the CNCC and NCCN dihedral angles. XRD corresponds to the conformation found in the crystal structure.

Ligand	θ(CNCC)	δ(NCCN)	FSPE(BP) [Eh]	ΔFSPE(BP) [kcal/mol]	FSPE(B2PLYP) [Eh]	ΔFSPE(B2PLYP) [kcal/mol]	ΔH [kcal/mol]	ΔS [kcal/mol]	ΔG [kcal/mol]
22	106.3	142.3	-2209.1672	1.4	-2207.5972	1.2	2.3	0.7	1.6
	109.8	-55.4	-2209.1661	2.1	-2207.5964	1.7	3.5	0.8	2.7
	-112.4	64.8	-2209.1681	0.9	-2207.5982	0.6	3.1	0.0	3.1
	-108.3	-115.2	-2209.1695	0.0	-2207.5992	0.0	0.0	0.0	0.0
22$_{XRD}$	-119.5	39.0	-2209.1666	1.8	-2207.5971	1.3	2.5	-1.0	3.5
22$^{(S)\text{-}Me}$	54.7	48.9	-2248.4936	4.5	-2246.8832	4.2	4.6	0.1	4.5
	56.2	-140.1	-2248.4939	4.3	-2246.8832	4.2	6.5	0.1	6.4
	-121.4	66.0	-2248.4994	0.9	-2246.8887	0.7	3.1	-0.2	3.2
	-121.2	-111.1	-2248.5008	0.0	-2246.8898	0.0	0.0	0.0	0.0
22$^{(S)\text{-}Me}_{XRD}$	-123.5	48.2	-2248.4985	1.5	-2246.8879	1.2	3.2	0.1	3.1
22$^{(R)\text{-}Me}$	119.3	118.9	-2248.4970	0.0	-2246.8858	0.0	0.0	0.0	0.0
	-97.7	65.0	-2248.4891	4.9	-2246.8791	4.2	7.3	0.9	6.4
	-83.6	-97.7	-2248.4925	2.8	-2246.8813	2.9	2.3	0.5	1.8
	-55.5	142.2	-2248.4940	1.8	-2246.8839	1.2	3.5	1.0	2.5

Table S7. Stabilization energies (kcal/mol) calculated for the complete binding pocket (ΔE_{stab}^{all}) or individual amino acids (ΔE_{stab}^{AA}), and differences between the stabilisation energies between the (S)-methylated ligand and the unmethylated ligand denotes as ΔΔ*E*.

	ΔE(22$^{(H)}$)	**ΔE(22$^{(S)\text{-}Me}$)**	**ΔΔE(22$^{(S)\text{-}Me}$ – 22$^{(H)}$)**	**ΔE(1$^{(H)}$)**	**ΔE(1$^{(S)\text{-}Me}$)**	**ΔΔE(1$^{(S)\text{-}Me}$ – 1)**
ΔE_{stab}^{all}	-42.6	-49.0	-6.4	-29.5	-37.7	-8.2
$\Delta E_{stab}^{Val86/Ile87}$	-6.8	-7.6	-0.8	-5.8	-7.0	-1.2
ΔE_{stab}^{Tyr113}	-11.4	-11.7	-0.3	-9.5	-9.9	-0.4
ΔE_{stab}^{Ser118}	-3.7 [a]	-3.9 [a]	-0.2 [a]	+0.2	-1.0	-1.2
$\Delta E_{stab}^{Phe67/Asp68/Tyr57/Arg73}$	-9.9	-13.2	-3.3	-4.6	-8.9	-4.3
$\Delta E_{stab}^{W\bullet\bullet\bullet Lys121/Ile122}$	-0.3	-3.2	-2.9	-1.5	-3.8	-2.3
ΔE_{stab}^{Trp90}	-5.3	-5.4	-0.1	-4.3	-5.1	-0.8
ΔE_{stab}^{Phe77}	-5.0	-5.5	-0.5	-3.6	-3.6	0

[a] model incl. W86.

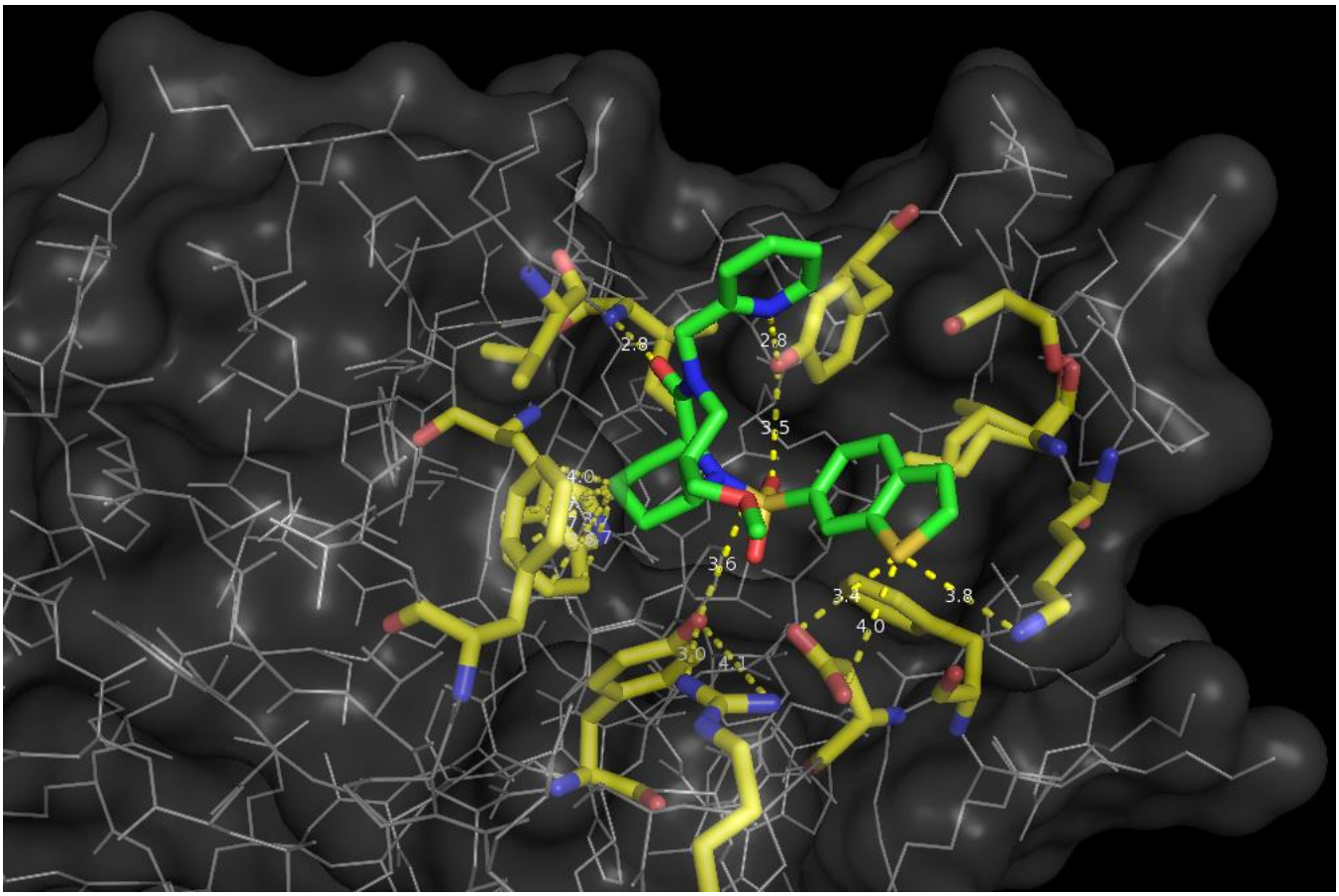


Figure S17. Structures/Models of the binding pocket of FKBP51 (grey surface) in complex with **22** (green sticks) highlighting the interactions (yellow dotted lines) to the amino acids (yellow sticks) calculated in **Table S7**.

8 Cellular assays

8.1 Competitve NanoBRET assay

The fluorescent ligands 2b or 2c [from M. Gnatzy and T. Geiger et.al[32]] were dissolved in Opti-MEM at eightfold concentration required for the final sample. For the target engagement matrix different final tracer concentrations were chosen. HEK293T cells expressing the FKBP-NanoLuc fusion protein (FKBP12-NLuc or FKBP51-NLuc) were detached from the culture dish and resuspended in Opti-MEM I Reduced Serum Media. The cell number was adjusted to 1.81 x 106 cells/mL using the stable FKBP-NanoLuc cell line. A cell-tracer mixture was prepared mixing one part of the tracer stock solution with three parts of the cell suspension (e.g., 500 µL tracer stock solution + 1500 µL cell suspension). Test ligands were dissolved in DMSO at thousand-fold the concentration required for the final sample. This ligand stock was used to prepare a 1:2 serial dilution in DMSO. Each dilution was then diluted with Opti-MEM I Reduced Serum Media to generate a ligand dilution series with double the concentration required for the final sample. To a white non-binding 384-well assay plate (No.: 3574; Corning Life Sciences B.V., Schiphol-Rijk, Netherlands) 20 µL of cell-tracer mixture and 20 µL of test compound solution were added and the plate was incubated at 37 °C for two hours. Afterwards the plate was equilibrated at room temperature for 15 minutes. For BRET detection the Intracellular TE NanoGlo® (No.:N2160; Promega) was used diluting the NanoBRETTM NanoGlo® Substrate 1: 664 and the extracellular NanoLuc® inhibitor 1:2000 in Opti-MEM I Reduced Serum Media. 20 µL of the detection solution was added per well and the plate was incubated for three minutes at room temperature. The donor emission was measured at 450 nm and the acceptor emission at 660 nm using a ClarioStar plate reader (BMG Labtech, Ortenberg, Germany) or a Tecan Spark (Cailsheim, Germany). The BRET ratio was calculated as shown in the supplementary information. IC50 values were determined by a four-parameter fitting. Ki,app values were determined according a linear Cheng-Prusoff analysis[33] using the following formula.

$$IC_{50} = K_{i,app}(1 + \frac{c(tracer)}{K_{D,app}})$$

8.2 INA-6 BRE-luc reporter assay

INA-6 cells, a kind gift from Dr Martin Gramatzki (University of Erlangen-Nurnberg, Erlangen, Germany), were cultured in RPMI-1640 with 2 mM L-glutamine, hereafter called RPMI (Sigma-Aldrich Norway, Oslo, Norway), supplemented with 10% fetal calf serum (FCS) and 1 ng/mL interleukin (IL)-6 (Gibco, Thermo Fisher Scientific, Waltham, MA, USA). The cells were maintained in 37 °C in a humidified atmosphere containing 5% CO_2 and tested regularly for mycoplasma.

In order to generate a bi-directional luciferase reporter plasmid that reports on SMAD1/5/8 transcriptional activity and baseline expression of renilla luciferase as internal control, the promoter sequence and firefly luciferase gene of pGL3 BRE Luciferase (Addgene plasmid # 45126) was subcloned into pMuLE ENTR MCS L1-R5 (Addgene plasmid # 62084)[34]. Using Gateway recombination cloning pMuLE ENTR BRE Luciferase L1-R5 was recombined with pMuLE ENTR CMV Renilla Luciferase L5-L2 (Addgene plasmid #62186) and pLenti X1 Puro DEST (694-6) (Addgene plasmid #17297) to generate a bi-directional BRE dual luciferase construct «pLenti X1 Puro BRE Luciferase rev Renilla Luciferase», in short pLentiX1-pBREFLrRL, following the protocol described by Albers et al.[35] pGL3 BRE Luciferase was a gift from Martine Roussel (Memphis, United States of America) & Peter ten Dijke (Amsterdam, The Netherlands), pLenti X1 Puro DEST (694-6) from Eric Campeau & Paul Kaufman (Worcester, United States of America) and pMuLE ENTR CMV Renilla Luciferase L5-L2 and pMuLE ENTR MCS L1-R5 from Ian Frew (Zurich, Switzerland). Used primers are listed in S8 table.

The resulting plasmid pLentiX1-pBREFLrRL was cotransfected with 3rd generation lentiviral packaging plasmids using Genejuice (Novagen, Merck Life Science AS, Oslo, Norway) to transfect 293T packaging cells (Open Biosystems, Thermo Fisher Scientific). Supernatants containing lentivirus were used to transduce the INA-6 myeloma cell line. Positively transduced cells were selected in medium containing puromycin (0,5 µg/mL) and single-cell cloned. One clone was selected for use in reporter assays which were performed as follows: Cells were washed once in Hanks' balanced salt solution and resuspended

in RPMI with 0,1% bovine serum albumin (BSA) and IL-6 (1 ng/mL). 50 000 cells were seeded per well in 96-well optical plates and treated as indicated. Recombinant human BMP-6 was from R&D Systems (Cat. # 507-BP-020, Bio-Techne, Abingdon, UK) and FK506 was from Selleckchem (Munich, Germany). After 18 hours Britelite™ plus luciferase detection reagent (PerkinElmer Inc., Waltham, MA, USA) was added according to the manufacturer's protocol and luminescence was determined using Victor 1420 multilabel counter (PerkinElmer Inc.).

Table S8

pMuLE ENTR BRE Luciferase L1-R5 cloning	
BRE Luc BamHI for	GCAGCAGGATCCTGCAATTGTTGTTGTTAACTTGTTTATTG
BRE Luc Poly A EcoRI rev	TGCTGCGAATTCGGTACGGGAGGTACTTGGAGCG

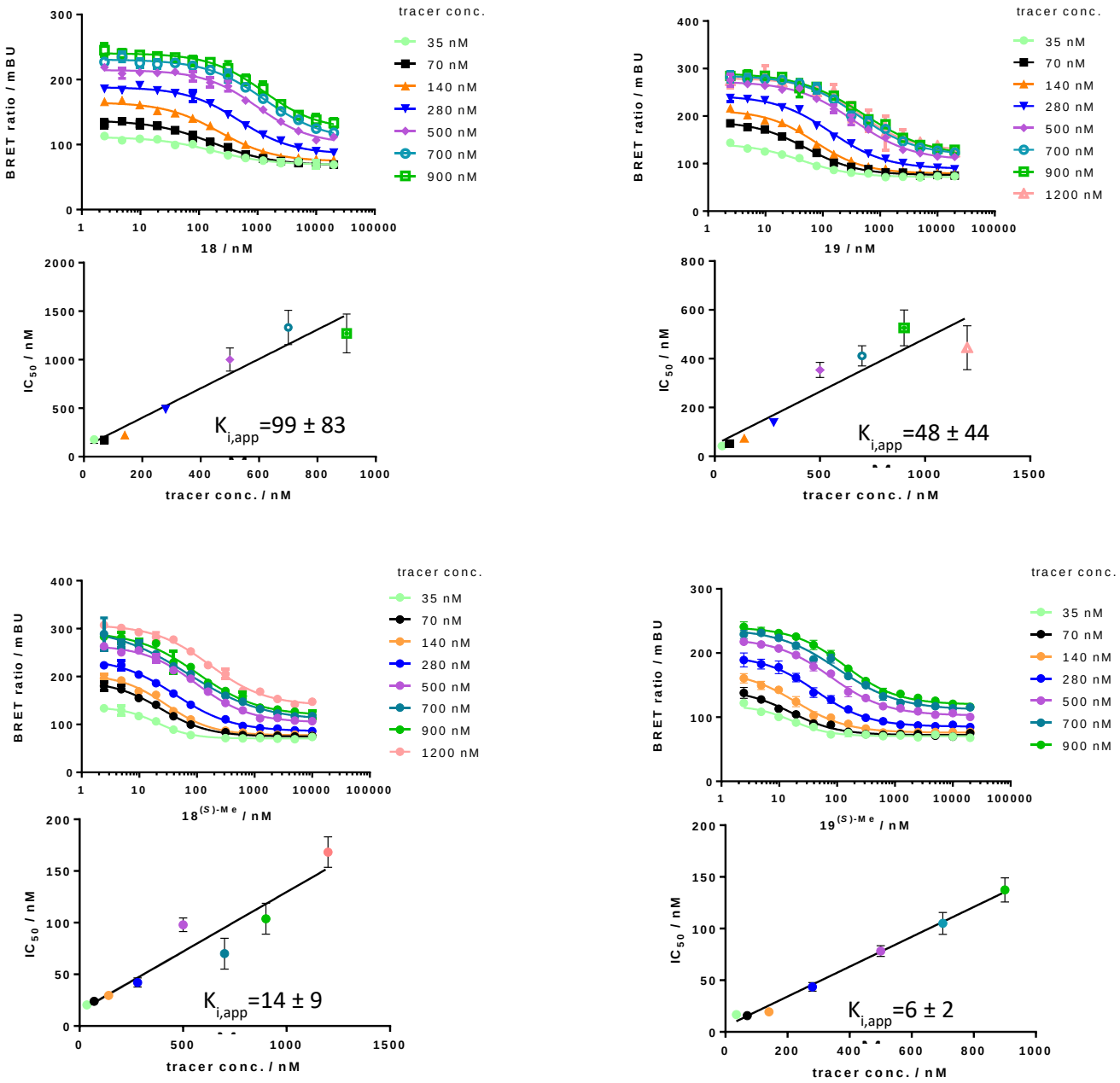


Fig. S18. Intracellular FKBP51-NLuc engagement of compounds **18**, **18$^{(S)-Me}$**, **19** and **19$^{(S)-Me}$** determined by competitive NanoBRET assay. HEK293T cells stably expressing a full length FKBP51-NLuc constructs were treated with increasing concentrations of **18**, **18$^{(S)-Me}$**, **19**, or **19$^{(S)-Me}$** in the presence of varying concentrations of NanoBRET tracer as shown in the upper panels. Each curve was fitted to determine an IC50, which was plotted in the lower panels in dependence of the tracer concentration to determine the Ki,app by Cheng-Prusoff analysis.

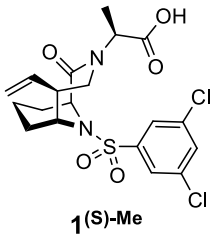
9 Compound Synthesis

9.1 General Methods

All purchased chemicals were used without further purification. Reaction monitoring was performed on Merck silica gel sheets with fluorescence indicator UV254 using cyclohexane/ethyl acetate or dichloromethane/methanol as solvent systems. Column chromatography was performed with Machery-Nagel silica 60 M (0.04 – 0.063 mm). Spots were visualized by irradiation with ultraviolet light and/or typical staining reagents (Hanessian and ninhydrin stain). All compounds were subjected to freeze drying by dissolving in acetonitrile/water mixtures (2:1), cooling to -78 °C and placing in a Heto FD 1.0 under reduced pressure. Purities were greater than 95% for all final compounds and were determined by high performance liquid chromatography utilizing a Dionex P580 pump, Dionex ASI-100 automated sample injector and Dionex UCD 340U Photodiode Array Detector. The column was a Phemomenex Kinetex 5 µm C18 100 Å, 250 x 4.6 mm. Eluents were 0.1% TFA (Eluent A) in water and 0.1% TFA in acetonitrile (Eluent B). The measurement time was 20 minutes with a gradient from 0 – 100% Eluent B and a flowrate of 1.5 ml min-1. ^{1}H and ^{13}C NMR spectra were recorded at the Technical University Darmstadt on a Bruker Avance 500 (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C) or at the Department of Chemistry and Pharmacy at LMU Munich on a Bruker AC300, Bruker XL400 oder Bruker AMX600 using $CDCl_3$ as a solvent. Chemical shifts are given in ppm relative to the residual solvent peak. High-resolution mass spectrometry analysis was performed for all new compounds using a quadrupole time-of-flight spectrometer from Bruker Daltonics. For previously synthesized intermediates mass spectrometry analysis was conducted on an LC-MS system with a Beckman Coulter System Gold 126 solvent module, Beckman Coulter System Gold 508 autosampler and Beckman Coulter System Gold 166 detector; a YMC-Pack Pro C18 3 µm 120 Å, 100 x 4.6 mm column and a Thermo Finnigan LCQ Deca XP Plus.

9.2 Synthesis

1$^{(S)\text{-}Me}$: (2S)-2-((1S,5R,6R)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)propanoic acid



1$^{(S)\text{-}Me}$

11$^{(S)\text{-}Me}$ (103 mg, 0.23 mmol, 1 eq.) was dissolved in acetone (10 ml) and cooled to 0 °C with an ice bath. Jones' reagent (230 µl, 0.46 mmol, 2 eq., 2 M in aq. H_2SO_4) was added and the mixture was stirred for 2 h at rt. The mixture was quenched with i-PrOH (10 ml) and stirred for 30 min. The mixture was diluted with DCM (50 ml) and washed with brine (30 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; cycH/EA = 1:1 + 1% HCOOC) afforded the title compound as white solids.

Yield: 90% (95 mg, 0.21 mmol)

Appearance: white solids

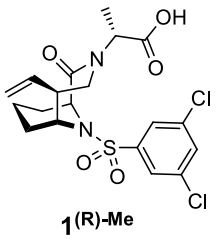
TLC: R_f = 0.11 (EA)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.24 – 1.32 (m, 3H), 1.46 (dd, *J* = 8.6, 7.2 Hz, 3H), 1.53 – 1.59 (m, 2H), 1.60 – 1.71 (m, 1H), 2.24 – 2.32 (m, 1H), 2.90 (ddd, *J* = 19.9, 14.3, 1.9 Hz, 1H), 2.98 (q, *J* = 8.9 Hz, 1H), 3.80 (dd, *J* = 14.0, 10.5 Hz, 1H), 3.95 – 4.03 (m, 1H), 4.95 (q, *J* = 7.1 Hz, 1H), 5.10 – 5.18 (m, 2H), 5.44 (q, *J* = 7.3 Hz, 1H), 5.78 (dddd, *J* = 17.0, 10.1, 8.9, 2.1 Hz, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.70 (dd, *J* = 1.8, 0.8 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.5, 15.6, 26.6, 27.9, 49.7, 50.1, 54.7, 55.1, 56.9, 57.5, 117.2, 125.1, 132.9, 136.5, 137.1, 144.0, 170.5, 175.3.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}Cl_2N_2O_5S$ 461.0605; Found 461.0718

1$^{(R)\text{-}Me}$: (2R)-2-((1S,5R,6R)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)propanoic acid



1$^{(R)\text{-}Me}$

11$^{(R)\text{-}Me}$ (51 mg, 0.11 mmol, 1 eq.) was dissolved in acetone (10 ml) and cooled to 0 °C with an ice bath. Jones' reagent (115 µl, 0.23 mmol, 2 eq., 2 M in aq. H_2SO_4) was added and the mixture was stirred for 2 h at rt. The mixture was quenched with i-PrOH (10 ml) and stirred for 30 min. The mixture was diluted with DCM (50 ml) and washed with brine (30 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; cycH/EA = 1:1 + 1% HCOOC) afforded the title compound as white solids.

Yield: 65% (32 mg, 0.07 mmol)

Appearance: white solids

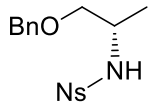
TLC: R_f = 0.11 (EA)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 3.6 Hz, 3H), 1.29 – 1.38 (m, 2H), 1.50 – 1.60 (m, 3H), 1.65 (dtd, *J* = 18.1, 9.1, 8.0, 5.3 Hz, 1H), 2.25 – 2.31 (m, 1H), 2.88 – 2.94 (m, 1H), 2.94 – 3.01 (m, 1H), 3.80 (dd, *J* = 14.0, 10.5 Hz, 1H), 3.99 (tt, *J* = 8.1, 6.4 Hz, 1H), 4.96 (q, *J* = 7.0 Hz, 1H), 5.10 – 5.17 (m, 2H), 5.43 (q, *J* = 7.4 Hz, 1H), 5.74 – 5.83 (m, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.70 (dd, *J* = 1.9, 0.8 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.9, 15.6, 26.2, 27.6, 48.2, 48.4, 54.7, 55.0, 57.0, 117.4, 125.0, 132.9, 136.5, 137.3, 144.1, 171.4, 175.7.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}Cl_2N_2O_5S$ 461.0605; Found 461.0701

(S)-4: (S)-N-(1-(benzyloxy)propan-2-yl)-2-nitrobenzenesulfonamide



(S)-4

L-Alaninol **(S)-3** (2.00 g, 26.6 mmol, 1 eq.) was dissolved in THF (0.9 molar) and treated with NaH (1.07 g, 26.6 mmol, 1.0 eq., 60% dispersion in mineral oil) and heated to reflux (66 °C) for 30 min. Benzyl chloride (3.47 g, 27.4 mmol, 1.03 eq.) was added and the mixture was refluxed for additional 2 h. After allowing the mixture to cool to rt, water was added (0.05 molar) and solvents were removed under reduced pressure. NaOH (1M) was added and the mixture was extracted with DCM (3 x). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. The residue was dissolved in DCM (0.1 molar) and Ns-Cl (5.9 g, 26.6 mmol, 1.0 eq.) and DIPEA (3.4 g, 26.6 mmol, 1.0 eq.) were added. The mixture was stirred for 2 h at rt, treated with NaOH and extracted with DCM (3 x). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (300 g silica; cycH/EA = 7:3) afforded the product as yellow oil, which solidified upon standing.

Yield: 64 % (5.9 g, 16.8 mmol, over 2 steps)

Appearance: yellow solid

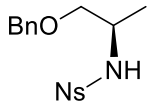
TLC: R_f = 0.21 (cycH/EA 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, 1H, J = 6.7 Hz), 3.20–3.33 (m, 2H), 3.55–3.70 (m, 1H), 4.24 (s, 1H), 5.60 (d, 1H, J = 7.2 Hz), 7.03–7.11 (m, 2H), 7.14–7.25 (m, 3H), 7.49–7.61 (m, 2H), 7.66 (dd, 1H, J = 7.2/2.1 Hz), 8.03 (dd, 1H, J = 7.2/2.0 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.8, 50.8, 73.2, 73.2, 125.4, 127.7, 127.8, 128.5, 130.7, 132.8, 133.3, 134.9, 137.6, 147.7.

Mass (ESI): $[M + H]^+$ = 351.10

(R)-4: (R)-N-(1-(benzyloxy)propan-2-yl)-2-nitrobenzenesulfonamide



(R)-4

D-Alaninol **(R)-3** (2.00 g, 26.6 mmol, 1 eq.) was dissolved in THF (0.9 molar) and treated with NaH (1.07 g, 26.6 mmol, 1.0 eq., 60% dispersion in mineral oil) and heated to reflux (66 °C) for 30 min. Benzyl chloride (3.47 g, 27.4 mmol, 1.03 eq.) was added and the mixture was refluxed for additional 2 h. After allowing the mixture to cool to rt, water was added (0.05 molar) and solvents were removed under reduced pressure. NaOH (1M) was added and the mixture was extracted with DCM (3 x). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. The residue was dissolved in DCM (0.1 molar) and Ns-Cl (5.9 g, 26.6 mmol, 1.0 eq.) and DIPEA (3.4 g, 26.6 mmol, 1.0 eq.) were added. The mixture was stirred for 2 h at rt, treated with NaOH and extracted with DCM (3 x). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (300 g silica; cycH/EA = 7:3) afforded the product as yellow oil, which solidified upon standing.

Yield: 65 % (6.1 g, 17.4 mmol, over 2 steps)

Appearance: yellow oil

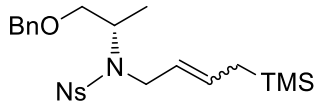
TLC: R_f = 0.44 (cycH/EA 7:3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.22 (d, J = 6.8 Hz, 3H), 3.30 – 3.38 (m, 2H), 3.63 – 3.76 (m, 1H), 4.28 – 4.37 (m, 2H), 5.67 (d, J = 7.2 Hz, 1H), 7.13 – 7.17 (m, 2H), 7.23 – 7.32 (m, 3H), 7.59 – 7.69 (m, 2H), 7.76 (dd, J = 7.8, 1.4 Hz, 1H), 8.12 (dd, J = 7.7, 1.6 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 18.9, 50.8, 73.2, 73.3, 125.5, 127.7, 128.5, 130.7, 132.8, 133.2, 135.0, 137.5, 147.8.

Mass (ESI): $[M + H]^+$ = 350.95

(S)-5: (S)-N-(1-(benzyloxy)propan-2-yl)-2-nitro-N-(4-(trimethylsilyl)but-2-en-1-yl)benzenesulfonamide



(S)-5

(S)-4 (48.76 g, 139.2 mmol, 1.0 eq.) was dissolved in DMF (400 ml). K_2CO_3 (38.74 g, 280.3 mmol, 2.0 eq.) and allyl bromide (16 ml, 184.9 mmol, 1.3 eq.) were added and the mixture was stirred at 60 °C under argon atmosphere for 4.5 h. After cooling to room temperature, Et_2O was added and it was washed with brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (Cy/EA 5:1) and a part (8.0 g, 20.5 mmol, 1 eq.), p-benzoquinone (0.33 g, 3.07 nmol, 0.15 eq.), Grubbs Catalyst 2nd gen. (0.96 g,1.54 mmol, 0.08 eq.) and allyltrimethylsilane (23.4 g, 205 mmol, 10 eq.) were dissolved in DCM under argon atmosphere and refluxed for 6 h. Tris(hydroxymethyl)phosphine (1M aqueous solution, 0.04 molar of catalyst) was added and refluxed overnight. The reaction mixture was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (300 g silica, Cy/EA 4:1) to afford the desired product as yellow oil.

Yield: 44% (4.3 g, 9.02 mmol, based on 8.0 g intermediate)

Appearance: yellow oil

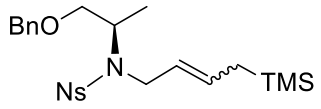
TLC: R_f = 0.41 (cycH/EA 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.02–0.04 (m, 9H), 1.26 (d, 3H, J = 7.0 Hz), 1.40 (d, 1H, J = 8.1 Hz), 1.48 (d, 1H, J = 8.8 Hz), 3.40–3.50 (m, 1H), 3.53–3.65 (m, 1H), 3.80–4.09 (m, 2H), 4.19–4.36 (m, 1H), 4.37–4.51 (m, 2H), 5.23–5.37 (m, 1H), 5.39–5.63 (m, 1H), 7.22–7.29 (m, 2H), 7.30–7.39 (m, 3H), 7.41–7.52 (m, 1H), 7.52–7.62 (m, 2H), 8.05–8.14 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -1.6, 17.1, 22.8, 46.8, 53.7, 72.1, 73.2, 124.0, 125.5, 127.9, 128.5, 131.1, 131.2, 131.4, 132.9, 137.9, 148.2.

Mass (ESI): $[M + Na]^+$ = 499.27

(R)-5: (R)-N-(1-(benzyloxy)propan-2-yl)-2-nitro-N-(4-(trimethylsilyl)but-2-en-1-yl)benzenesulfonamide



(R)-5

(R)-4 (6.1 g, 17.4 mmol, 1.0 eq.) was dissolved in DMF (100 ml). K_2CO_3 (4.8 g, 34.8 mmol, 2.0 eq.) and allyl bromide (2.7 g, 22.6 mmol, 1.3 eq.) were added and the mixture was stirred at 60 °C under argon atmosphere for 4.5 h. After cooling to room temperature, Et_2O was added and it was washed with brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (Cy/EA 5:1) and a part (4.0 g, 10.3 mmol, 1 eq.), p-benzoquinone (0.17 g, 1.54 nmol, 0.15 eq.), Grubbs Catalyst 2nd gen. (0.48 g,0.72 mmol, 0.08 eq.) and allyltrimethylsilane (11.7 g, 103 mmol, 10 eq.) were dissolved in DCM under argon atmosphere and refluxed for 6 h. Tris(hydroxymethyl)phosphine (1M aqueous solution, 0.04 molar of catalyst) was added and refluxed overnight. The reaction mixture was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (100 g silica, Cy/EA 4:1) to afford the desired product as yellow oil.

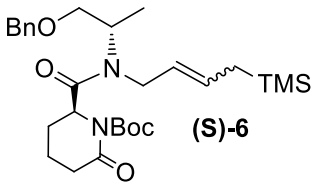
Yield: 63% (3.05 g, 6.4 mmol, based on 4.0 g intermediate)

Appearance: yellow oil

TLC: R_f = 0.38 (cycH/EA 4:1)

Mass (ESI): $[M + Na]^+$ = 499.10

(S)-6: (S)-tert-butyl 2-(((S)-1-(benzyloxy)propan-2-yl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)-6-oxopiperidine-1-carboxylate



(S)-6

(S)-5 (4.3 g, 9.0 mmol, 1.0 eq.) and K_2CO_3 (3.7 g, 27.1 mmol, 3.0 eq.) were dissolved in DMF (0.1 molar) under argon atmosphere. Thiophenol (1.2 g, 10.8 mmol, 1.2 eq.) was added and the reaction mixture was stirred at room temperature over night. Et_2O was added and washed with 1M NaOH, the organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (EA + 3 % TEA) dissolved in DMF (0.1 molar) under argon atmosphere and cooled to 0 °C. (S)-6-Oxo-2-piperidinecarbocylic acid (1.3 g, 9.1 mmol, 1.2 eq.), HATU (3.4 g, 9.1 mmol, 1.2 eq.) and DIPEA (2.3 g, 18.1 mmol, 2.4 eq.) were added. The reaction mixture was slowly heated to rt and stirred over night. Et_2O was added and washed with brine, the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude intermediate was dissolved in DCM (50 ml) under argon atmosphere, DIPEA (1.7 g, 13.4 mmol, 2.0 eq.) and Boc_2O (5.9 g, 27.0 mmol, 4.0 eq.) were added. DMAP was added in small portions until a continuous gas formation was visible. The reaction mixture was stirred at room temperature over night. It was washed with brine and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (Cy/EA 5:1 + 3 % TEA).

Yield: 43% (4.3 g, 9.02 mmol, over 3 steps)

Appearance: yellow oil

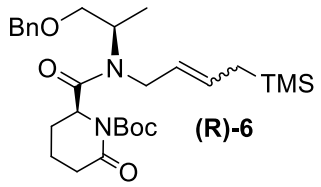
TLC: R_f = 0.51 (cycH/EA 1:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.06–0.06 (m, 9H), 1.19 (d, 3H, J = 7.0 Hz), 1.23–1.28 (m, 2H), 1.47–1.51 (m, 9H), 1.58–1.98 (m, 4H), 2.33–2.49 (m, 1H), 2.50–2.64 (m, 1H), 3.36–3.77 (m, 3H), 3.78–4.19 (m, 2H), 4.45–4.57 (m, 2H), 4.77–5.07 (m, 1H), 5.22–5.46 (m, 1H), 5.46–5.71 (m, 1H), 7.21–7.39 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -1.7, 15.2, 18.3, 22.9, 26.1, 28.1, 34.6, 47.4, 51.2, 56.4, 72.0, 73.0, 83.0, 125.0, 127.6, 127.7, 127.8, 128.4, 128.5, 130.4, 138.4, 153.6, 171.7, 171.8.

Mass (ESI): $[M + Na]^+$ = 539.29

(R)-6: (R)-tert-butyl 2-(((S)-1-(benzyloxy)propan-2-yl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)-6-oxopiperidine-1-carboxylate



(R)-5 (6.1 g, 12.8 mmol, 1.0 eq.) and K_2CO_3 (5.3 g, 38.6 mmol, 3.0 eq.) were dissolved in DMF (0.1 molar) under argon atmosphere. Thiophenol (1.7 g, 15.4 mmol, 1.2 eq.) was added and the reaction mixture was stirred at room temperature over night. Et_2O was added and washed with 1M NaOH, the organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (EA + 3 % TEA) and a part (3.4 g, 11.7 mmol, 1.0 eq.) dissolved in DMF (0.1 molar) under argon atmosphere and cooled to 0 °C. (S)-6-Oxo-2-piperidinecarbocylic acid (2.0 g, 14.0 mmol, 1.2 eq.), HATU (5.3 g, 14.0 mmol, 1.2 eq.) and DIPEA (3.6 g, 28.0 mmol, 2.4 eq.) were added. The reaction mixture was slowly heated to rt and stirred over night. Et_2O was added and washed with brine, the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude intermediate was dissolved in DCM (50 ml) under argon atmosphere, DIPEA (2.9 g, 22.6 mmol, 2.0 eq.) and Boc_2O (1.4 g, 11.3 mmol, 1.0 eq.) were added. DMAP was added in small portions until a continuous gas formation was visible. The reaction mixture was stirred at room temperature over night. It was washed with brine and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography (300 g silica, cycH/EA 7:3).

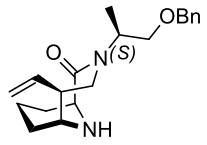
Yield: 59% (4.0 g, 7.7 mmol, over 3 steps)

Appearance: yellow oil

TLC: R_f = 0.52 (cycH/EA 3:2)

Mass (ESI): $[M + Na]^+$ = 539.08

7$^{(S)\text{-}Me}$: (1S,5R,6R)-3-((S)-1-(benzyloxy)propan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



7$^{(S)\text{-}Me}$

(S)-6 (11.48 g, 22.22 mmol, 1.0 eq.) was dissolved in THF (200 ml) under argon atmosphere. The solution was cooled to -98 °C and DIBAL-H (22 ml, 22.0 mmol, 1.0 eq., 1M in DCM) was added dropwise. Glauber's salt was added excessively and the solution was allowed to warm to room temperature, then additional Glauber's salt was added. The mixture was diluted with Et_2O, filtered over celite and the solvent was evaporated. The crude intermediate was dissolved in DCM (500 ml) and cooled to -84 °C. Then HF (60 mL, 2.31 mol, 104 eq., 70% in pyridine) was added and the reaction mixture was warmed to 0 °C. It was stirred at 0 °C for 4 h, then 500 ml sat. $CaCO_3$ solution and 800 ml 10 M NaOH was added carefully. The slurry was filtered over celite and extracted with DCM, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (cycH/EA 1:1 + 3 % TEA → EA + 5 % MeOH + 3 % TEA) to afford the desired compound as yellow oil.

Yield: 76% (5.51 g, over 2 steps)

Appearance: yellow oil

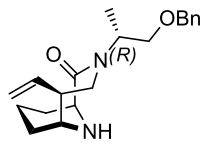
TLC: R_f = 0.33 (EA + 5 % MeOH + 3 % TEA)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, 3H, J = 6.9 Hz), 2.25–2.32 (m, 1H), 2.50 (q, 1H, J = 8.9 Hz), 2.78–2.83 (m, 1H), 3.00 (d, 1H, J = 14.1 Hz), 3.42 (dd, 1H, J = 10.5/5.1 Hz), 3.50 (dd, 1H, J = 10.5/8.1 Hz), 3.68 (dd, 1H, J = 14.2/10.7 Hz), 3.76–3.80 (m, 1H), 4.45 (d, 1H, J = 12.0 Hz), 4.55 (d, 1H, J = 12.1 Hz), 4.98 (s, 1H), 5.01 (d, 1H, J = 7.4 Hz), 5.07–5.15 (m, 1H), 5.62–5.71 (m, 1H), 7.27–7.37 (m, 5H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.5, 17.0, 28.1, 29.7, 44.4, 49.6, 50.5, 53.1, 58.2, 71.7, 72.8, 115.0, 127.8, 127.8, 128.5, 138.4, 139.4, 174.9.

Mass (ESI): $[M + H]^+$ = 329.30

7$^{(R)-Me}$: (1S,5R,6R)-3-((R)-1-(benzyloxy)propan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



7$^{(R)-Me}$

(R)-6 (4.0 g, 7.5 mmol, 1.0 eq.) was dissolved in THF (100 ml) under argon atmosphere. The solution was cooled to -98 °C and DIBAL-H (9.1 ml, 9.1 mmol, 1.0 eq., 1M in toluene) was added dropwise. Glauber's salt was added excessively and the solution was allowed to warm to room temperature, then additional Glauber's salt was added. The mixture was diluted with Et_2O, filtered over celite and the solvent was evaporated. The crude intermediate was dissolved in DCM (400 ml) and cooled to -84 °C. Then HF (20 ml, 0.77 mol, 104 eq., 70% in pyridine) was added and the reaction mixture was warmed to 0 °C. It was stirred at 0 °C for 4 h, then 300 ml sat. $CaCO_3$ solution and 500 ml 10 M NaOH was added carefully. The slurry was filtered over celite and extracted with DCM, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (400 g silica, cycH/EA 1:1 + 3 % TEA → EA + 3 % MeOH + 3 % TEA) to afford the desired compound as yellow oil.

Yield: 69% (1.7 g, 5.2 mmol, over 2 steps)

Appearance: yellow oil

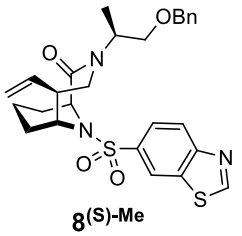
TLC: R_f = 0.41 (EA + 3 % MeOH + 3 % TEA)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.12 (d, 3H, J = 6.9 Hz), 1.20 (ddt, J = 10.0, 6.6, 3.5 Hz, 1H), 1.24 – 1.33 (m, 1H), 1.42 – 1.52 (m, 2H), 1.52 – 1.60 (m, 2H), 1.61 – 1.68 (m, 1H), 2.26 (dt, J = 8.9, 2.8 Hz, 1H), 2.56 – 2.66 (m, 1H), 2.81 (td, J = 5.3, 4.4, 1.5 Hz, 1H), 3.04 (dd, J = 14.0, 1.8 Hz, 1H), 3.73 (dd, J = 14.0, 10.6 Hz, 1H), 3.78 (q, J = 2.2 Hz, 1H), 4.42 – 4.55 (m, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.87 – 4.98 (m, 2H), 5.14 (m, 1H), 5.64 (ddd, J = 17.0, 10.3, 8.4 Hz, 1H), 7.24 – 7.36 (m, 5H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.8, 16.8, 28.4, 30.0, 44.2, 49.2, 49.5, 52.9, 58.2, 71.7, 73.2, 114.8, 127.6, 128.3, 138.3, 139.6, 174.5.

Mass (ESI): $[M + H]^+$ = 329.10

8$^{(S)\text{-}Me}$: (1S,5R,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((S)-1-(benzyloxy)propan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



8$^{(S)\text{-}Me}$

7$^{(S)\text{-}Me}$ (400 mg, 1.22 mmol, 1.0 eq.), benzothiazole-6-sulfonyl chloride (370 mg, 1.58 mmol, 1.3 eq.) and DMAP (15 mg, 0.12 mmol, 0.1 eq.) were dissolved in DCM under argon atmosphere and DIPEA (205 mg, 1.58 mmol, 1.3 eq.) was added. The reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (25 g silica, Cy/EA 7:3) to afford the desired compound as white solids.

Yield: 33% (213 mg, 0.41 mmol)

Appearance: white solids

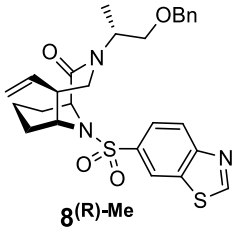
TLC: R_f = 0.27 (cycH/EA 3:2)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.9 Hz, 3H), 1.16 – 1.22 (m, 1H), 1.24 – 1.32 (m, 2H), 1.41– 1.51 (m, 2H), 2.24 (ddt, *J* = 14.2, 4.5, 2.7 Hz, 1H), 2.42 – 2.49 (m, 1H), 3.01 (dd, *J* = 14.5, 1.8 Hz, 1H), 3.38 – 3.50 (m, 2H), 3.77 (dd, *J* = 14.5, 10.6 Hz, 1H), 4.02 – 4.08 (m, 1H), 4.43 – 4.56 (m, 2H), 4.83 (dt, *J* = 6.0, 1.9 Hz, 1H), 5.00 (td, *J* = 7.2, 5.2 Hz, 1H), 5.04 – 5.10 (m, 2H), 5.78 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 7.93 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.6, 0.6 Hz, 1H), 8.51 (dd, *J* = 1.8, 0.6 Hz, 1H), 9.20 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.5, 15.7, 26.3, 27.8, 45.6, 50.2, 50.9, 54.9, 57.1, 71.5, 73.0, 116.5, 121.7, 124.3, 124.7, 127.7, 128.5, 134.4, 137.8, 138.2, 138.7, 155.5, 158.0, 170.4,

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{32}N_3O_4S_2$ 526.1834; Found 526.1887

8$^{(R)\text{-}Me}$: (1S,5R,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((R)-1-(benzyloxy)propan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



8$^{(R)\text{-}Me}$

7$^{(R)\text{-}Me}$ (500 mg, 1.52 mmol, 1.0 eq.), benzothiazole-6-sulfonyl chloride (462 mg, 1.98 mmol, 1.3 eq.) and DMAP (19 mg, 0.15 mmol, 0.1 eq.) were dissolved in DCM under argon atmosphere and DIPEA (256 mg, 1.98 mmol, 1.3 eq.) was added. The reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (25 g silica, Cy/EA 7:3) to afford the desired compound as white solids.

Yield: 42% (340 mg, 0.65 mmol)

Appearance: white solids

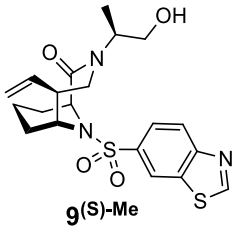
TLC: R_f = 0.27 (cycH/EA 3:2)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 7.0 Hz, 3H), 1.14 (dt, *J* = 16.5, 4.1 Hz, 1H), 1.19 – 1.30 (m, 2H), 1.29 – 1.39 (m, 1H), 1.44 (dt, *J* = 13.4, 3.6 Hz, 1H), 2.11 – 2.21 (m, 1H), 2.49 – 2.61 (m, 1H), 2.94 (dd, *J* = 14.4, 1.8 Hz, 1H), 3.36 – 3.44 (m, 2H), 3.70 (dd, *J* = 14.4, 10.5 Hz, 1H), 4.00 (ddd, *J* = 7.0, 4.2, 1.5 Hz, 1H), 4.34 – 4.58 (m, 2H), 4.75 (dt, *J* = 5.9, 1.9 Hz, 1H), 4.88 – 5.02 (m, 2H), 5.15 (pd, *J* = 7.0, 5.5 Hz, 1H), 5.75 (ddd, *J* = 17.0, 10.1, 8.9 Hz, 1H), 7.21 – 7.30 (m, 5H), 7.89 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.6, 0.6 Hz, 1H), 8.47 (dd, *J* = 1.9, 0.6 Hz, 1H), 9.17 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.6, 15.4, 26.6, 28.1, 44.5, 49.1, 49.5, 55.0, 57.3, 71.2, 73.2, 116.3, 121.6, 124.2, 124.7, 127.8, 127.0, 128.4, 134.4, 138.0, 138.7, 155.4, 158.0, 170.3.

Mass (ESI): $[M + H]^+$ = 526.08

9$^{(S)\text{-}Me}$: (1S,5R,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((S)-1-hydroxypropan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



9$^{(S)\text{-}Me}$

Compound **8$^{(S)\text{-}Me}$** (212 mg, 0.4 mmol, 1 eq.) was dissolved in DCM (50 ml). BCl_3*SMe_2 (1.0 ml, 2.0 mmol, 5 eq., 2 M in DCM) was added and the mixture was stirred for 16 h at rt. The reaction was washed with sat. aq. $NaHCO_3$ solution (20 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (25 g SiO_2, cycH/EA = 1:4).

Yield: 58% (102 mg, 0.37 mmol)

Appearance: white solids

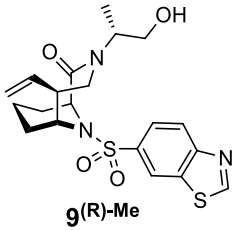
TLC: R_f = 0.16 (cycH/EA 1:9)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.9 Hz, 3H), 1.19 (td, *J* = 6.6, 6.1, 4.4 Hz, 1H), 1.36 – 1.44 (m, 1H), 1.35 – 1.53 (m, 2H), 1.54 – 1.60 (m, 1H), 1.98 (s, 1H), 2.18 – 2.26 (m, 1H), 2.53 (qd, *J* = 8.0, 3.8 Hz, 1H), 2.98 (dd, *J* = 14.5, 1.8 Hz, 1H), 3.53 – 3.63 (m, 2H), 3.81 (dd, *J* = 14.4, 10.6 Hz, 1H), 4.07 – 4.19 (m, 1H), 4.68 (dt, *J* = 6.2, 2.0 Hz, 1H), 4.78 – 4.89 (m, 1H), 5.07 – 5.17 (m, 2H), 5.84 (ddd, *J* = 17.2, 9.9, 8.9 Hz, 1H), 7.93 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.26 (dd, *J* = 8.7, 0.6 Hz, 1H), 8.53 (dd, *J* = 1.8, 0.6 Hz, 1H), 9.22 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 13.9, 15.6, 26.4, 27.5, 45.5, 49.8, 54.1, 55.0, 57.0, 64.5, 116.9, 121.9, 124.2, 124.7, 134.5, 137.5, 138.2, 155.6, 158.1, 171.7.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}N_3O_4S_2$ 436.1365; Found 436.1416

9$^{(R)\text{-}Me}$: (1S,5R,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((R)-1-hydroxypropan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



9$^{(R)\text{-}Me}$

Compound **8$^{(R)\text{-}Me}$** (289 mg, 0.55 mmol, 1 eq.) was dissolved in DCM (50 ml). BCl_3*SMe_2 (1.4 ml, 2.7 mmol, 5 eq., 2 M in DCM) was added and the mixture was stirred for 16 h at rt. The reaction was washed with sat. aq. $NaHCO_3$ solution (20 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (25 g SiO_2, cycH/EA = 1:9).

Yield: 70% (163 mg, 0.37 mmol)

Appearance: white solids

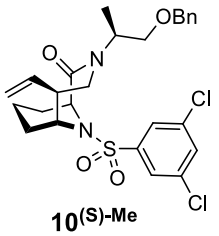
TLC: R_f = 0.16 (cycH/EA = 1:9)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 7.0 Hz, 3H), 1.15 (tdd, *J* = 13.6, 6.0, 4.0 Hz, 1H), 1.20 – 1.27 (m, 2H), 1.37 – 1.49 (m, 1H), 1.63 (qt, *J* = 14.0, 3.8 Hz, 1H), 2.00 – 2.07 (m, 1H), 2.16 – 2.26 (m, 1H), 2.66 – 2.76 (m, 1H), 2.90 (dd, *J* = 14.3, 1.8 Hz, 1H), 3.40 – 3.70 (m, 2H), 3.81 (dd, *J* = 14.3, 10.6 Hz, 1H), 4.05 (ddd, *J* = 7.0, 4.5, 2.1 Hz, 1H), 4.80 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.94 (dqd, *J* = 9.8, 7.0, 4.1 Hz, 1H), 5.09 – 5.18 (m, 2H), 5.82 (ddd, *J* = 17.0, 10.1, 8.9 Hz, 1H), 7.94 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.26 (dd, *J* = 8.6, 0.6 Hz, 1H), 8.52 (dd, *J* = 1.9, 0.6 Hz, 1H), 9.21 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.2, 15.6, 26.0, 27.6, 45.1, 48.8, 53.3, 55.1, 57.3, 64.6, 117.0, 121.6, 124.2, 124.7, 134.5, 137.7, 138.6, 155.5, 158.1, 172.7.

Mass (ESI): $[M + H]^+$ = 436.06

10$^{(S)\text{-}Me}$: (1S,5R,6R)-3-((S)-1-(benzyloxy)propan-2-yl)-10-((3,5-dichlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



10$^{(S)\text{-}Me}$

7$^{(S)\text{-}Me}$ (410 mg, 1.3 mmol, 1.0 eq.) and 3,5-dichlorobenzenesulfonyl chloride (613 g, 2.5 mmol, 2.0 eq.) were dissolved in DCM under argon atmosphere and DIPEA (484 mg, 3.7 mmol, 3.0 eq.) and DMAP (152 mg, 1.3 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (25 g silica, Cy/EA 5:1).

Yield: 46% (290 mg, 0.54 mmol)

Appearance: white solids

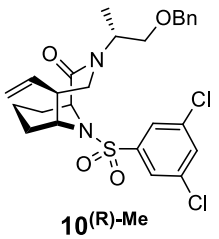
TLC: R_f = 0.32 (cycH/EA = 3:1)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, 3H, J = 6.9 Hz), 1.10–1.29 (m, 3H), 1.38–1.51 (m, 2H), 2.22(d, 1H, J = 13.7 Hz), 2.39 (q, 1H, J = 9.2 Hz), 2.97 (dd, 1H, J = 14.7/1.8 Hz), 3.34 (dd, 1H, J = 10.2/5.1 Hz), 3.43 (dd, 1H, J = 10.2/7.3 Hz), 3.66 (dd, 1H, J = 14.6/10.6 Hz), 3.88–3.94 (m, 1H), 4.39 (d, 1H, J = 12.0 Hz), 4.48 (d, 1H, J = 12.1 Hz), 4.63–4.69 (m, 1H), 4.86–4.95 (m, 1H), 4.96–5.05 (m, 2H), 5.65–5.75 (m, 1H), 7.18–7.22 (m, 1H), 7.24–7.30 (m, 4H), 7.46 (t, 1H, J = 1.9 Hz), 7.63 (d, 2H, J = 1.8 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.5, 15.6, 26.4, 27.9, 45.7, 50.2, 51.2, 55.2, 57.2, 71.6, 73.0, 116.7, 125.1, 127.7, 127.7, 128.5, 132.7, 136.4, 137.6, 138.2, 144.4, 170.0.

Mass (ESI): $[M + H]^+$ = 537.62

10$^{(R)\text{-}Me}$: (1S,5R,6R)-3-((R)-1-(benzyloxy)propan-2-yl)-10-((3,5-dichlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



10$^{(R)\text{-}Me}$

9$^{(R)\text{-}Me}$ (800 mg, 2.4 mmol, 1.0 eq.) and 3,5-dichlorobenzenesulfonyl chloride (1.2 g, 4.9 mmol, 2.0 eq.) were dissolved in DCM under argon atmosphere and DIPEA (944 mg, 7.3 mmol, 3.0 eq.) and DMAP (297 mg, 2.4 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (40 g silica, cycH/EA = 5:1).

Yield: 47% (614 mg, 1.14 mmol)

Appearance: white solids

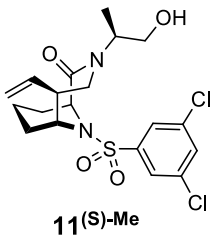
TLC: R_f = 0.43 (cycH/EA = 4:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 7.0 Hz, 3H), 1.16 (tdd, *J* = 13.6, 6.0, 3.9 Hz, 1H), 1.21 – 1.27 (m, 2H, H), 1.30 – 1.36 (m, 1H), 1.40 (dtt, *J* = 13.6, 3.4, 1.4 Hz, 1H), 1.49 (tdd, *J* = 13.7, 8.5, 4.8 Hz, 1H), 2.25 (ddt, *J* = 13.7, 3.6, 1.8 Hz, 1H), 2.54 – 2.65 (m, 1H), 2.98 (dd, *J* = 14.5, 1.8 Hz, 1H), 3.38 – 3.48 (m, 2H), 3.66 (dd, *J* = 14.5, 10.5 Hz, 1H), 3.94 (ddd, *J* = 6.6, 3.9, 1.8 Hz, 1H), 4.49 (dd, *J* = 87.3, 11.6 Hz, 2H), 4.71 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.93 – 5.07 (m, 2H), 5.14 – 5.23 (m, 1H), 5.75 (ddd, *J* = 17.0, 10.1, 8.9 Hz, 1H), 7.27 – 7.33 (m, 5H), 7.55 (t, *J* = 1.8 Hz, 1H), 7.68 (d, *J* = 1.9 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.6, 15.4, 26.7, 28.2, 44.5, 49.0, 49.5, 55.3, 57.4, 71.1, 73.2, 116.5, 125.0, 127.8, 128.0, 128.4, 132.7, 136.4, 137.8, 144.3, 170.0.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_4S$ 537.1382; Found 537.1404

11$^{(S)\text{-}Me}$: (1S,5R,6R)-10-((3,5-dichlorophenyl)sulfonyl)-3-((S)-1-hydroxypropan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



11$^{(S)\text{-}Me}$

10$^{(S)\text{-}Me}$ (290 mg, 0.5 mmol, 1 eq.) was dissolved in DCM (50 ml). BCl_3*SMe_2 (1.4 ml, 2.7 mmol, 5 eq., 2 M in DCM) was added and the mixture was stirred for 16 h at rt. The reaction was washed with sat. aq. $NaHCO_3$ solution (20 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (25 g SiO_2, cycH/EA = 1:4).

Yield: 47% (110 mg, 0.25 mmol)

Appearance: white solids

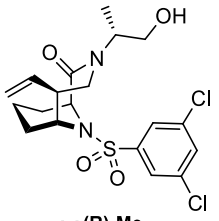
TLC: R_f = 0.38 (cycH/EA = 2:3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.9 Hz, 3H), 1.19 – 1.28 (m, 1H), 1.38 (dtdd, *J* = 10.6, 7.3, 5.1, 2.2 Hz, 1H), 1.56 (ddt, *J* = 13.9, 10.5, 3.5 Hz, 3H), 1.86 (s, 1H), 2.28 (ddt, *J* = 12.1, 3.5, 1.9 Hz, 1H), 2.53 (dddd, *J* = 10.9, 8.8, 6.8, 2.0 Hz, 1H), 2.99 (dd, *J* = 14.5, 1.9 Hz, 1H), 3.55 – 3.63 (m, 1H), 3.75 (dd, *J* = 14.5, 10.7 Hz, 1H), 4.04 (ddd, *J* = 6.8, 4.4, 2.2 Hz, 1H), 4.63 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.82 (dqd, *J* = 8.3, 6.9, 5.0 Hz, 1H), 5.13 (dd, *J* = 6.2, 1.1 Hz, 1H), 5.77 – 5.85 (m, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 13.9, 15.6, 26.5, 27.6, 45.4, 49.9, 54.1, 55.2, 57.1, 64.5, 117.1, 125.1, 132.9, 137.2, 143.9, 171.2.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}Cl_2N_2O_4S$ 447.0812; Found 447.0961

11$^{(R)\text{-}Me}$: (1S,5R,6R)-10-((3,5-dichlorophenyl)sulfonyl)-3-((R)-1-hydroxypropan-2-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



11$^{(R)\text{-}Me}$

10$^{(R)\text{-}Me}$ (604 mg, 1.1 mmol, 1.0 eq.) was dissolved in DCM (50 ml). BCl_3*SMe_2 (2.8 ml, 5.6 mmol, 5 eq., 2 M in DCM) was added and the mixture was stirred for 16 h at rt. The reaction was washed with sat. aq. $NaHCO_3$ solution (20 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (25 g SiO_2, cycH/EA = 1:4).

Yield: 76% (379 mg, 0.85 mmol)

Appearance: white solids

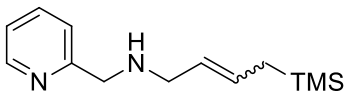
TLC: R_f = 0.40 (cycH/EA = 1:4)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 7.0 Hz, 3H), 1.16 – 1.35 (m, 2H), 1.51 (tdd, *J* = 10.0, 6.6, 3.6 Hz, 1H), 1.59 – 1.72 (m, 1H), 1.91 (s, 1H), 2.28 (dt, *J* = 14.8, 2.9 Hz, 1H), 2.67 – 2.79 (m, 1H), 2.91 (dd, *J* = 14.5, 1.8 Hz, 1H), 3.43 (dd, *J* = 11.6, 10.1 Hz, 1H), 3.64 – 3.78 (m, 2H), 3.93 – 4.01 (m, 1H), 4.72 (dt, *J* = 5.9, 2.0 Hz, 1H), 4.94 (dqd, *J* = 10.0, 7.0, 4.1 Hz, 1H), 5.09 – 5.20 (m, 2H), 5.80 (ddd, *J* = 17.0, 10.1, 8.9 Hz, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.1, 15.6, 26.1, 27.7, 45.0, 48.8, 53.3, 55.4, 57.4, 64.5, 117.2, 125.0, 132.8, 136.5, 137.5, 144.2, 172.3.

Mass (ESI/MicrOTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}Cl_2N_2O_4S$ 447.0812; Found 447.0910

13a: N-(Pyridin-2-ylmethyl)-4-(trimethylsilyl)but-2-en-1-amine



13a

2-(4-(trimethylsilyl)but-2-en-1-yl)isoindoline-1,3-dione **12** (33.7 g, 123.26 mmol, 1 eq.) was dissolved in MeOH (500 ml) and Hydrazin (8 ml, 255 mmol, 2 eq.) was added. The mixture was refluxed for 20 h. 1 M NaOH (300 ml) and DCM (500 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (1 x 100 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar). The residue was diluted with EtOH (150 ml) and picolinaldehyde (11.8 ml, 123 mmol, 1 eq.) was added. The mixture was stirred at rt for 3 h. After adding $NaBH_4$ (7 g, 185 mmol, 1.5 eq.) stirring was continued until no more gas formation was observed (4 h). Sat. aq. $NaHCO_3$ (200 ml) was added carefully and the mixture was extracted with DCM (3 x 300 ml). The combined organic phases were dried over $MgSO_4$ and solvents were reduced under reduced pressure. Column chromatography (1000 g SiO_2, EA + 3% TEA) afforded the title compound as yellow oil.

Yield: 69% (31.20 g, 84.05 mmol, over 2 steps)

Appearance: yellow oil

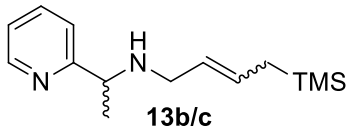
TLC: R_f = 0.30 (EA + 3% TEA; UV, ninhydrin)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.04 – 0.00 (m, 9H), 1.42 – 1.48 (m, 2H), 2.32 (s, 1H), 3.20 – 3.30 (m, 2H), 3.87 – 3.91 (m, 2H), 5.34 – 5.46 (m, 1H), 5.49 – 5.62 (m, 1H), 7.11 – 7.16 (m, 1H), 7.27 – 7.32 (m, 1H), 7.58 – 7.65 (m, 1H), 8.52 – 8.55 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -2.0, 1.0, 19.0, 22.7, 51.6, 54.2, 54.6, 121.8, 122.3, 125.2, 126.3, 128.3, 129.6, 136.4, 149.3, 159.7.

Mass (ESI): $[M + H]^+$ = 235.02

13b/c: N-(1-(pyridin-2-yl)ethyl)-4-(trimethylsilyl)but-2-en-1-amine



13b/c

2-(4-(trimethylsilyl)but-2-en-1-yl)isoindoline-1,3-dione **12** (5.0 g, 18.29 mmol, 1 eq.) was dissolved in MeOH (70 ml) and Hydrazin (1.2 ml, 36.6 mmol, 2 eq.) was added. The mixture was refluxed for 24 h. 1 M NaOH (15 ml) and DCM (50 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (1 x 50 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar). The residue was diluted with MeOH (10 ml). 1-(pyridine-2-yl)ethanone (2.2 ml, 18.3 mmol, 1 eq.) and titanium(IV)isopropoxide (5.4 ml, 18.3 mmol, 1 eq.) were added and The mixture was stirred at rt for 4 h. After adding $NaBH_4$ (1.0 g, 27.4 mmol, 1.5 eq.) stirring was continued until no more gas formation was observed (2 h). Sat. aq. $NaHCO_3$ (100 ml) was added carefully and the mixture was extracted with DCM (3 x 100 ml). The combined organic phases were dried over $MgSO_4$ and solvents were reduced under reduced pressure. Column chromatography (150 g SiO_2, EA + 3% TEA) afforded the title compound as yellow oil.

Yield: 62% (2.85 g, 11.47 mmol, over 2 steps)

Appearance: yellow oil

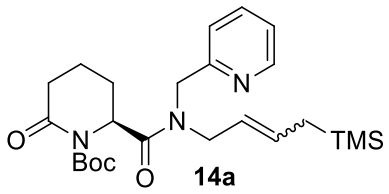
TLC: R_f = 0.30 (EA + 3% TEA; UV, ninhydrin)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.05 (d, *J* = 12.4 Hz, 9H), 1.28 – 1.51 (m, 5H), 1.76 (s, 2H), 2.91 – 3.14 (m, 2H), 3.88 (q, *J* = 6.7 Hz, 1H), 5.19 – 5.60 (m, 2H), 6.98 – 7.20 (m, 1H), 7.20 – 7.39 (m, 1H), 7.63 (tt, *J* = 7.7, 2.1 Hz, 1H), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -0.0, 0.1, 20.8, 24.6, 46.2, 51.9, 60.4, 61.0, 123.2, 123.7, 127.6, 128.9, 129.9, 130.9, 138.3, 151.3, 166.7.

Mass (ESI): $[M + H]^+$ = 248.99

14a: (S)-tert-butyl-2-[(pyridine-2-ylmethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbomyl]piperidine-1-carboxylate



14a

Compound **13a** (5.0 g, 21.3 mmol, 1 eq.) and (S)-6-oxopiperidine-2-carboxylic acid (3.05 g, 21.3 mmol, 1 eq.) were dissolved in DMF (50 ml). After stirring for 30 min at rt a mixture of EDC-HCl (4.91 g, 25.6 mmol, 1.2 eq) and HOBt (3.92 g, 25.6 mmol, 1.2 eq.) was added and the reaction mixture was stirred at rt for 3 h. Et_2O (400 ml) was added and the mixture was washed with brine (1 x 100 ml, 3 x 20 ml) dried over $MgSO_4$ and concentrated in vacuo. The resulting brown oil (10.9 g) was dissolved in DCM (5 ml) and DIPEA (20 ml, 6 eq.) was added. The mixture was stirred for 15 min before Boc_2O (23.3 g, 107.0 mmol, 5 eq.) and DMAP (0.25 g, 2.0 mmol, 0.1 eq.) were added. Stirring was continued at rt for 2 h. The reaction mixture was washed with brine (2 x 100 ml), dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (400 g SiO_2, cycH/EA = 2:3 → EA) afforded the desired product as yellow oil.

Yield: 61% (6.01 g, 13.0 mmol, over 2 steps)

Appearance: yellow oil

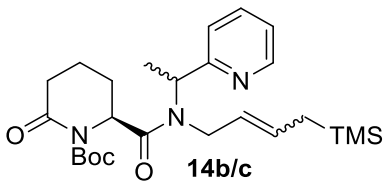
TLC: R_f = 0.47 (EA; UV)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.04 – 0.00 (m, 9H), 1.47 – 1.51 (m, 11H), 1.65 – 1.75 (m, 1H), 1.80 – 1.95 (m, 2H), 2.00 – 2.08 (m, 1H), 2.40 – 2.50 (m, 1H), 2.57 – 2.62 (m, 1H), 3.90 – 4.30 (m, 2H), 4.45 – 4.85 (m, 1H), 4.90 – 5.10 (m, 2H), 5.20 – 5.40 (m, 1H), 5.50 – 6.00 (m, 1H), 7.18 – 7.25 (m, 1H), 7.36 – 7.42 (m, 1H), 7.64 – 7.74 (m, 1H), 8.48 – 8.58 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -1.9, -1.5, 18.2, 22.8, 23.0, 25.7, 25.9, 34.4, 34.5, 48.6, 50.2, 50.4, 51.5, 55.7, 55.9, 83.1, 121.6, 122.0, 122.4, 122.7, 132.0, 132.4, 137.1, 139.5, 149.5, 153.7, 156.8, 157.0, 171.3, 171.4.

Mass (ESI): $[M + H]^+$ = 460.01

14b/c: (6S)-tert-butyl 2-oxo-6-((1-(pyridin-2-yl)ethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)piperidine-1-carboxylate



14b/c

(S)-6-oxopiperidine-2-carboxylic acid (1.32 g, 9.2 mmol, 1.1 eq.) was dissolved in DMF (15 ml) and HATU (3.8 g, 10.0 mmol, 1.2 eq.) was added. After adding DIPEA (3.0 ml, 16.8 mmol, 2 eq.) the mixture was stirred for 15 min. Compound **13b/c** (2.1 g, 8.4 mmol, 1 eq.) was added and the reaction was stirred for 3 h at rt. The reaction was diluted with Et_2O (70 ml) and washed with brine (50 ml). Solvents were evaporated and the residue was dissolved in DCM (20 ml). Boc_2O (7.33 g, 33.6 mmol, 4 eq.), DIPEA (4.0 ml, 42.0 mmol, 5 eq.) and DMAP (210 mg, 1.7 mmol, 0.2 eq.) were added and the mixture was stirred for 14 h at rt. DCM (100 ml) was added and the mixture was washed with brine. Solvents were removed under reduced pressure and the crude material was purified by column chromatography (250 g silica, cycH/EA = 1:1).

Yield: 37% (1.45 g, 3.4 mmol, over 2 steps)

Appearance: yellow oil

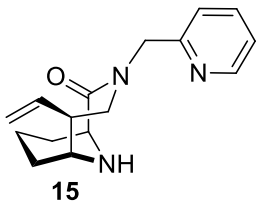
TLC: R_f = 0.56 (EA; UV)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.17 – 0.07 (m, 9H), 1.19 – 1.78 (m, 18H), 1.86 – 2.05 (m, 2H), 2.37 – 2.51 (m, 1H), 2.51 – 2.68 (m, 1H), 3.48 – 4.29 (m, 3H), 4.74 – 4.96 (m, *J* = 48.4, 4.5 Hz, 1H), 5.03 – 5.42 (m, 1H), 5.43 – 5.64 (m, 1H), 5.75 – 5.93 (m, 1H), 7.06 – 7.23 (m, 1H), 7.32 – 7.42 (m, 1H), 7.49 – 7.75 (m, 1H), 8.46 – 8.64 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -0.0, 0.1, 16.1, 18.1, 18.3, 20.1, 20.2, 20.3, 21.1, 22.9, 24.5, 24.7, 27.8, 28.2, 29.9, 29.9, 30.0, 36.3, 36.6, 43.5, 47.3, 48.9, 55.8, 56.1, 57.8, 59.6, 62.3, 84.9, 123.0, 124.0, 124.1, 124.5, 124.9, 125.1, 126.3, 127.0, 127.4, 130.1, 131.0, 132.2, 138.2, 138.3, 138.5, 150.4, 151.5, 155.8, 162.0, 173.4, 174.2, 174.4.

Mass (APCI): $[M + H]^+$ = 474.28

15: (1S,5S,6R)-3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazobicyclo[4.3.1] decan-2-one



15

Compound **14a** (15.0 g, 32.6 mmol, 1 eq.) was dissolved in THF (200 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (42.4 ml, 42.4 mmol, 1.3 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and the solvent was removed under reduced pressure. The resulting yellow oil (13.6 g) was dissolved in 1800 ml DCM in a fluorinated HDPE bottle and cooled to -78 °C. HF (74 ml, 4061 mmol, 125 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (500 ml) and 10 M NaOH (600 ml). The phases were separated and the aqueous phase was extracted with DCM (5 x 300 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (500 g SiO_2, EA + 3% TEA + 5% MeOH) afforded the desired product as an orange resin.

Yield: 37% (3.31 g, 12.1 mmol, over 2 steps)

Appearance: orange resin

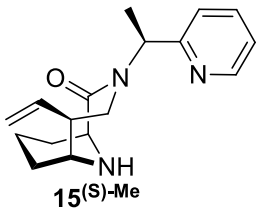
TLC: R_f = 0.11 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.44 – 1.74 (m, 5H), 2.07 (s, 1H), 2.20 – 2.40 (m, 1H), 2.55 – 2.70 (m, 1H), 2.75 – 2.90 (m, 1H), 3.05 – 3.15 (m, 1H), 3.80 – 3.88 (m, 1H), 3.96 – 4.10 (m, 1H), 4.67 – 4.96 (m, 1H), 4.81 – 4.95 (m, 3H), 5.50 – 5.66 (m, 1H), 7.10 – 7.23 (m, 1H), 7.29 – 7.38 (m, 1H), 7.60 – 7.70 (m, 1H), 8.46 – 8.58 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.9, 28.1, 29.4, 49.5, 51.2, 52.6, 55.9, 57.8, 115.0, 122.3 (2C), 136.7, 139.0, 149.1, 157.8, 174.9.

Mass (ESI): $[M + H]^+$ = 272.11

15$^{(S)\text{-}Me}$: (1S,5S,6R)-3-((S)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



15$^{(S)\text{-}Me}$

Compound **14b/c** (1.45 g, 3.07 mmol, 1 eq.) was dissolved in THF (35 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (3.4 ml, 3.37 mmol, 1.1 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and solvents were removed under reduced pressure. The resulting yellow oil was dissolved in 150 ml DCM in a HDPE bottle and cooled to -78 °C. HF (6.5 ml, 306 mmol, 100 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (50 ml) and 10 M NaOH (60 ml). The phases were separated and the aqueous phase was extracted with DCM (5 x 100 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, EA + 3% TEA + 5% MeOH) afforded the desired product as a yellow resin.

Yield: 19% (166 mg, 0.58 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.15 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

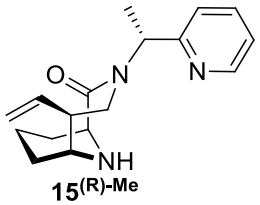
HPLC: R_t **=** 8.27 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.45 – 1.73 (m, 8H), 2.13 – 2.41 (m, 2H), 2.42 – 2.61 (m, 1H), 2.79 (dd, *J* = 7.0, 4.0 Hz, 1H), 2.90 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.46 (dd, *J* = 14.3, 10.7 Hz, 1H), 3.87 (q, *J* = 2.1 Hz, 1H), 4.84 – 5.08 (m, 2H), 5.58 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 6.18 (q, *J* = 6.9 Hz, 1H), 7.15 (ddt, *J* = 7.6, 4.8, 0.8 Hz, 1H), 7.23 – 7.34 (m, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 8.55 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2, 16.9, 28.1, 29.8, 45.3, 50.6, 52.8, 54.3, 58.0, 115.0, 122.1, 122.9, 136.4, 139.0, 148.9, 160.0, 174.3.

Mass (ESI): $[M + H]^+$ = 286.19

15$^{(R)\text{-}Me}$: (1S,5S,6R)-3-((R)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



15$^{(R)\text{-}Me}$

Compound **15$^{(R)\text{-}Me}$** was obtained in the previous reaction and was isolated by column chromatography.

Yield: 16% (140 mg, 0.49 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.29 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

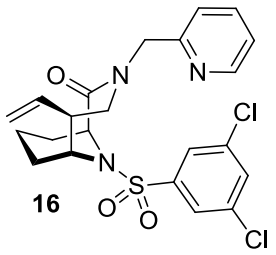
HPLC: R_t **=** 8.33 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30 – 1.73 (m, 8H), 2.09 (m, *J* = 18.3, 9.3 Hz, 2H), 2.29 – 2.40 (m, 1H), 2.74 (t, *J* = 4.7 Hz, 1H), 3.02 (dd, *J* = 13.9, 1.9 Hz, 1H), 3.72 (dd, *J* = 13.8, 10.5 Hz, 1H), 3.78 – 3.90 (m, 1H), 4.52 (d, *J* = 17.1 Hz, 1H), 4.76 (d, *J* = 10.2 Hz, 1H), 5.43 (ddd, *J* = 17.9, 10.1, 8.3 Hz, 1H), 6.19 (q, *J* = 7.0 Hz, 1H), 7.16 (dd, *J* = 7.4, 5.0 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 8.53 (d, *J* = 4.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 16.9, 28.0, 29.7, 44.9, 49.7, 52.6, 54.0, 58.0, 114.8, 122.3, 122.9, 136.4, 139.1, 148.7, 160.2, 174.4.

Mass (ESI): $[M + H]^+$ = 286.20

16: (1S,5S,6R)-10-[(3,5-dichlorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazobicyclo[4.3.1]decan-2-one



16

Compound **15** (280 mg, 1.03 mmol, 1 eq.), 3,5-dichlorobenzenesulfonyl chloride (330 mg, 1.34 mmol, 1.3 eq.) and ZnO (168 mg, 2.07 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (30 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (80 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 63% (301 mg, 0.65 mmol)

Appearance: colorless solids

TLC: R_f = 0.27 (cycH/EA = 1:1; UV, PMA)

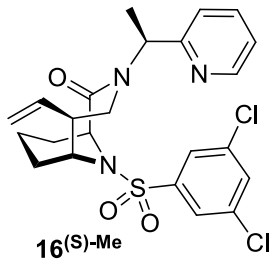
HPLC: R_t **=** 13.46 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.01 – 1.44 (m, 2H), 1.44 – 1.73 (m, 3H), 2.31 (dt, *J* = 15.2, 2.7 Hz, 1H), 2.62 – 2.83 (m, 1H), 3.12 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.90 – 4.12 (m, 2H), 4.62 – 5.19 (m, 5H), 5.71 (ddd, *J* = 16.9, 10.2, 8.8 Hz, 1H), 7.20 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.63 – 7.81 (m, 3H), 8.43 – 8.59 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.4, 27.6, 49.1, 52.1, 54.9, 56.1, 56.9, 116.9, 122.1, 122.5, 124.9, 132.7, 136.3, 137.2, 144.1, 149.0, 156.8, 170.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}Cl_2N_3O_3S$ 480.0910; Found 480.0916

16$^{(S)\text{-}Me}$: (1S,5S,6R)-10-((3,5-dichlorophenyl)sulfonyl)-3-((S)-1-(pyridin-2-yl) ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



16$^{(S)\text{-}Me}$

Compound **15$^{(S)\text{-}Me}$** (150 mg, 0.55 mmol, 1 eq.), 3,5-dichlorobenzene-1-sulfonyl chloride (203 mg, 0.83 mmol, 1.5 eq.) and DIPEA (290 µl, 1.66 mmol, 3 eq.) were placed in a flask under argon atmosphere. MeCN (50 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (150 ml) and washed with brine (50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 42% (110 mg, 0.23 mmol)

Appearance: white solids

TLC: R_f = 0.50 (cycH/EA = 1:1; UV, Hanessian)

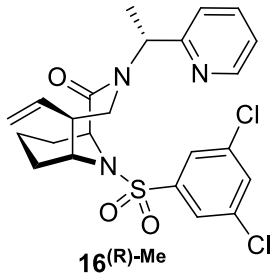
HPLC: R_t **=** 14.10 min (0 – 100% B in 20 min)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.25 (m, 2H), 1.31 (tt, *J* = 13.1, 5.3 Hz, 1H), 1.42 – 1.58 (m, 6H), 2.23 – 2.35 (m, 1H), 2.40 – 2.53 (m, 1H), 2.82 (dd, *J* = 14.8, 1.9 Hz, 1H), 3.32 (dd, *J* = 14.8, 10.7 Hz, 1H), 3.93 (ddd, *J* = 7.0, 4.4, 1.7 Hz, 1H), 4.69 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.94 – 5.09 (m, 2H), 5.63 (ddd, *J* = 16.9, 10.1, 8.8 Hz, 1H), 6.08 (q, *J* = 6.9 Hz, 1H), 7.10 – 7.14 (m, 1H), 7.21 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.48 (t, *J* = 1.9 Hz, 1H), 7.56 – 7.66 (m, 3H), 8.49 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.0, 15.6, 26.5, 27.9, 46.0, 50.2, 55.0, 55.1, 57.1, 116.8, 122.4, 122.9, 124.9, 132.7, 136.3, 136.8, 137.1, 144.1, 148.9, 159.0, 169.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}Cl_2N_3O_3S$ 494.1066; Found 494.1069

16$^{(R)\text{-}Me}$: (1S,5S,6R)-10-((3,5-dichlorophenyl)sulfonyl)-3-((R)-1-(pyridin-2-yl) ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



16$^{(R)\text{-}Me}$

Compound **15$^{(R)\text{-}Me}$** (90 mg, 0.32 mmol, 1 eq.), 3,5-dichlorobenzene-1-sulfonyl chloride (116 mg, 0.47 mmol, 1.5 eq.) and DIPEA (165 µl, 0.95 mmol, 3 eq.) were placed in a flask under argon atmosphere. MeCN (30 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (150 ml) and washed with brine (50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 42% (65 mg, 0.13 mmol)

Appearance: white solids

TLC: R_f = 0.48 (cycH/EA = 1:1; UV, Hanessian)

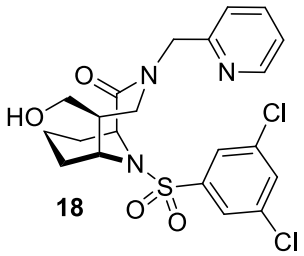
HPLC: R_t **=** 14.38 min (0 – 100% B in 20 min)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 – 1.35 (m, 2H), 1.39 – 1.47 (m, 1H), 1.52 (tdd, *J* = 8.4, 5.4, 2.6 Hz, 2H), 1.59 (d, *J* = 7.0 Hz, 3H), 2.20 (q, *J* = 8.6 Hz, 1H), 2.29 – 2.45 (m, 1H), 3.12 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.70 (dd, *J* = 14.3, 10.5 Hz, 1H), 3.95 (ddd, *J* = 7.0, 4.6, 2.3 Hz, 1H), 4.69 (dt, *J* = 16.9, 1.1 Hz, 1H), 4.79 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.94 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.61 (ddd, *J* = 16.9, 10.1, 8.8 Hz, 1H), 6.15 (q, *J* = 7.1 Hz, 1H), 7.16 – 7.28 (m, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 1.8 Hz, 1H), 7.67 – 7.80 (m, 3H), 8.50 – 8.69 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 15.8, 26.3, 27.8, 45.8, 49.2, 54.8, 54.9, 57.1, 116.5, 122.6, 122.8, 124.9, 132.6, 136.3, 137.0, 137.3, 144.2, 148.6, 159.6, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C2_3H_{25}Cl_2N_3O_3S$ 494.1066; Found 494.1068

18: (1S,5S,6R))-10-((3,5-dichlorophenyl)sulfonyl)-5-(hydroxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



18

Compound **16** (230 mg, 0.48 mmol, 1 eq.) was dissolved in Aceton (9 ml) and water (1 ml), 2,6-lutidine (110 µl, 0.96 mmol, 2 eq.), NMO (84 mg, 0.96 mmol, 2 eq.) and OsO_4 (120 µL, 0.0096 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (308 mg, 0.96 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (0 ml), extracted with EA (50 ml), washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in EtOH (15 ml). After cooling to 0 °C $NaBH_4$ (15 mg, 0.40 mmol, 1.5 eq.) was added, the mixture stirred for 15 min at 0 °C and 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (EA) afforded the title compound as white solids.

Yield: 56% (130 mg, 0.27 mmolover 2 steps)

Appearance: white solids

TLC: R_f = 0.14 (EA; UV)

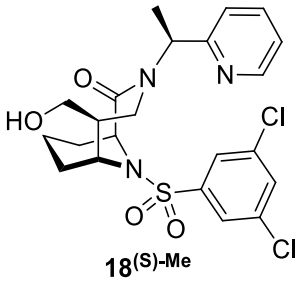
HPLC: R_t **=** 10.72 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.11 – 1.58 (m, 5H), 2.10 – 2.34 (m, 2H), 2.55 (bs, 1H), 3.32 (dd, *J* = 14.4, 1.9 Hz, 1H), 3.47 (d, *J* = 6.4 Hz, 2H), 3.78 (dd, *J* = 14.4, 10.6 Hz, 1H), 3.88 (td, *J* = 5.2, 2.6 Hz, 1H), 4.61 – 4.81 (m, 3H), 7.14 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 4.6, 1.8 Hz, 3H), 8.43 (d, *J* = 4.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 27.9, 27.9, 46.8, 49.5, 52.4, 56.0, 57.1, 63.3, 122.6, 124.9, 132.7, 136.3, 137.2, 144.0, 149.0, 156.9, 170.4.

Mass (ESI): $[M + H]^+$ = 484.54

18$^{(S)\text{-}Me}$: (1S,5S,6R)-10-((3,5-dichlorophenyl)sulfonyl)-5-(hydroxymethyl)-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



18$^{(S)\text{-}Me}$

Compound **16$^{(S)\text{-}Me}$** (100 mg, 0.20 mmol, 1 eq.) was dissolved in Aceton (5.5ml) and water (0.5 ml), 2,6-lutidine (47 µl, 0.40 mmol, 2 eq.), NMO (48 mg, 0.40 mmol, 2 eq.) and OsO_4 (50 µL, 0.0040 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (130 mg, 0.40 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in EtOH (10 ml). After cooling to 0 °C $NaBH_4$ (7.5 mg, 0.20 mmol, 1.0 eq.) was added, the mixture stirred for 15 min at 0 °C and 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (EA) afforded the title compound as white solids.

Yield: 54% (54 mg, 0.11 mmol, over 2 steps)

Appearance: white solids

TLC: R_f = 0.38 (EA; UV, Hanessian)

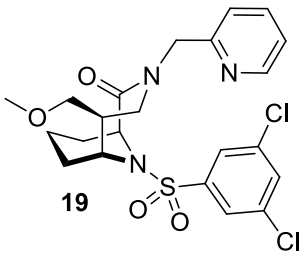
HPLC: R_t **=** 11.45 min (0 – 100% B in 20 min)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.26 (m, 2H), 1.33 – 1.45 (m, 1H), 1.45 – 1.58 (m, 6H), 2.12 (tq, *J* = 12.9, 10.0, 8.5 Hz, 1H), 2.29 (dq, *J* = 14.8, 2.8, 2.4 Hz, 1H), 3.10 – 3.21 (m, 2H), 3.44 – 3.57 (m, 2H), 3.89 (ddd, *J* = 6.7, 4.9, 1.9 Hz, 1H), 4.70 (dt, *J* = 6.0, 2.0 Hz, 1H), 6.07 (q, *J* = 6.9 Hz, 1H), 7.15 (ddd, *J* = 7.8, 4.9, 1.1 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 7.4, 1.9 Hz, 3H), 8.49 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 28.2, 28.3, 43.5, 47.7, 52.5, 55.1, 57.2, 63.6, 122.5, 123.0, 124.9, 132.7, 136.3, 137.1, 144.0, 148.6, 158.9, 169.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}Cl_2N_3O_4S$ 498.1016; Found 498.1016

19: (1S,5S,6R))-10-((3,5-dichlorophenyl)sulfonyl)-5-(methoxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



19

Compound **18** (85 mg, 0.18 mmol, 1 eq.) was dissolved in DMF (8 ml) and cooled to 0 °C. NaH (21 mg, 0.53 mmol, 3 eq.) and MeI (44 µL, 0.70 mmol, 4 eq.) were added successively. After 90 min the reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents followed by column chromatography (EA) afforded the title compound as colorless oil.

Yield: 89% (77 mg, 0.16 mmol)

Appearance: colorless oil

TLC: R_f = 0.32 (EA; UV)

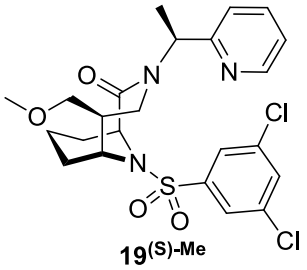
HPLC: R_t **=** 14.88 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.19 – 1.38 (m, 1H), 1.45 (ddd, *J* = 18.3, 8.9, 4.9 Hz, 1H), 1.50 – 1.73 (m, 3H), 2.25 – 2.41 (m, 2H), 3.14 – 3.30 (m, 6H), 3.73 (dd, *J* = 14.3, 10.7 Hz, 1H), 3.97 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.68 – 4.81 (m, 2H), 4.87 (d, *J* = 15.3 Hz, 1H), 7.18 – 7.25 (m, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 1.9 Hz, 1H), 7.71 (t, *J* = 2.3 Hz, 3H), 8.54 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.6, 28.1, 28.1, 44.5, 49.6, 52.7, 56.1, 57.0, 59.0, 73.3, 122.0, 122.5, 125.0, 132.6, 136.3, 137.2, 144.0, 149.0, 156.8, 170.4.

Mass (ESI): $[M + H]^+$ = 498.28

19$^{(S)\text{-}Me}$: (1S,5S,6R)-10-((3,5-dichlorophenyl)sulfonyl)-5-(methoxymethyl)-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



19$^{(S)\text{-}Me}$

Compound **18$^{(S)\text{-}Me}$** (50 mg, 0.10 mmol, 1 eq.) was dissolved in DMF (5 ml). NaH (12 mg, 0.30 mmol, 3 eq.) and MeI (25 µL, 0.40 mmol, 4 eq.) were added successively and the mixture was stirred for 4 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution (20 ml), extracted with EA (80 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (10 g SiO_2, cycH/EA = 1:1)

Yield: 92% (47 mg, 0.09 mmol)

Appearance: white solids

TLC: R_f = 0.23 (cycH/EA = 1:1; UV, Hanessian)

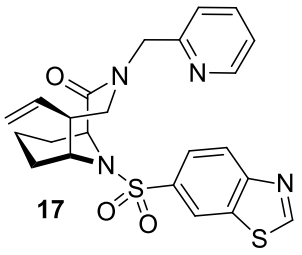
HPLC: R_t **=** 13.31 min (0 – 100% B in 20 min)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.25 (ddt, *J* = 13.5, 11.6, 5.8 Hz, 1H), 1.37 – 1.46 (m, 1H), 1.46 – 1.58 (m, 6H), 2.09 – 2.20 (m, 1H), 2.29 (dq, *J* = 13.7, 2.4 Hz, 1H), 2.99 (dd, *J* = 14.7, 2.1 Hz, 1H), 3.08 (dd, *J* = 14.7, 10.3 Hz, 1H), 3.15 – 3.22 (m, 2H), 3.24 (s, 3H), 3.88 (td, *J* = 5.8, 4.9, 2.0 Hz, 1H), 4.72 (dt, *J* = 6.0, 2.0 Hz, 1H), 6.07 (q, *J* = 6.9 Hz, 1H), 7.14 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 1.8 Hz, 1H), 7.58 – 7.65 (m, 3H), 8.50 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 28.2, 28.4, 43.6, 45.6, 52.9, 55.0, 57.2, 59.1, 73.4, 122.4, 122.8, 125.0 (2C), 132.6, 136.2 (2C), 137.0, 144.0, 148.6, 159.0, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}Cl_2N_3O_4S$ 512.1172; Found 512.1173

17: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



17

Compound **15** (30 mg, 0.11 mmol, 1 eq.), 1,3-benzothiazole-6-sulfonyl chloride (39 mg, 0.17 mmol, 1.5 eq.) and DIPEA (40 µl, 0.2 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (20 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (50 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (12 g SiO_2, EA) afforded the title compound as colorless resin.

Yield: 29% (15 mg, 0.032 mmol)

Appearance: colorless resin

TLC: R_f = 0.17 (EA; UV)

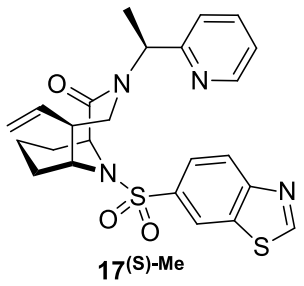
HPLC: R_t **=** 10.21 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.13 (tdd, *J* = 13.2, 6.1, 3.9 Hz, 1H), 1.25 (ddt, *J* = 13.8, 9.1, 4.8 Hz, 1H), 1.34 – 1.63 (m, 3H), 2.06 – 2.26 (m, 1H), 2.53 – 2.71 (m, 1H), 3.07 (dd, *J* = 14.1, 2.1 Hz, 1H), 3.87 – 4.19 (m, 2H), 4.68 – 4.85 (m, 2H), 4.89 – 5.12 (m, 3H), 5.68 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 7.27 (t, *J* = 6.4 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.87 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 8.41 – 8.54 (m, 2H), 9.15 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.3, 27.4, 49.1, 52.4, 54.7, 55.2, 56.8, 116.9, 121.6, 122.9, 123.0, 124.0, 124.7, 134.4, 137.1, 138.4, 139.0, 147.1, 155.5, 156.2, 158.0, 171.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_4O_3S_2$ 469.1363; Found 469.1362

17$^{(S)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((S)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



17$^{(S)\text{-}Me}$

Compound **15$^{(S)\text{-}Me}$** (15 mg, 0.053 mmol, 1 eq.), 1,3-benzothiazole-6-sulfonyl chloride (24.6 mg, 0.105 mmol, 1.5 eq.) and DIPEA (18 µl, 0.105 mmol, 1.5 eq.) were placed in a flask under argon atmosphere. DCM (0.5 ml) was added and the mixture was stirred for 20 h at rt. The reaction mixture was loaded on silica and purified by column chromatography (10 g SiO_2, cycH/EA = 1:4) afforded the title compound as colorless resin.

Yield: 43% (11 mg, 0.020 mmol)

Appearance: colorless resin

TLC: R_f = 0.50 (cycH/EA = 1:4; UV)

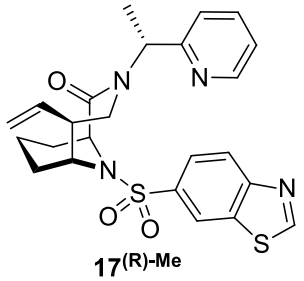
HPLC: R_t **=** 13.50 min (0 – 100% B in 20 min)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.19 – 1.24 (m, 1H), 1.30 – 1.37 (m, 1H), 1.47 – 1.57 (m, 3H), 1.59 (d, J = 6.9 Hz, 3H), 2.25 – 2.31 (m, 1H), 2.49 – 2.58 (m, 1H), 2.83 – 2.90 (m, 1H), 3.47 (dd, J = 14.6, 10.7 Hz, 1H), 4.07 – 4.10 (m, 1H), 4.83 (dt, J = 6.0, 1.9 Hz, 1H), 5.04 – 5.13 (m, 2H), 5.72 (ddd, J = 17.0, 10.1, 8.9 Hz, 1H), 6.15 (q, J = 6.8 Hz, 1H), 7.17 – 7.21 (m, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.65 (td, J = 7.8, 2.3 Hz, 1H), 7.92 (dd, J = 8.6, 1.9 Hz, 1H), 8.24 (dd, J = 8.6, 0.6 Hz, 1H), 8.51 (dd, J = 1.9, 0.6 Hz, 1H), 8.55 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 9.22 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 15.0, 15.5, 26.3, 27.7, 46.1, 50.1, 54.8, 54.9, 56.9, 116.6, 121.5, 122.3, 122.9, 124.0, 124.6, 134.3, 136.8, 137.2, 138.3, 148.6, 155.4, 157.8, 158.9, 170.3.

Mass (ESI): $[M + H]^+$ = 483.11

17$^{(R)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-3-((R)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



17$^{(R)\text{-}Me}$

Compound **15$^{(R)\text{-}Me}$** (15 mg, 0.053 mmol, 1 eq.), 1,3-benzothiazole-6-sulfonyl chloride (24.6 mg, 0.105 mmol, 1.5 eq.) and DIPEA (18 µl, 0.105 mmol, 1.5 eq.) were placed in a flask under argon atmosphere. DCM (0.5 ml) was added and the mixture was stirred for 20 h at rt. The reaction mixture was loaded on silica and purified by column chromatography (10 g SiO_2, cycH/EA = 1:4) afforded the title compound as colorless resin.

Yield: 43% (11 mg, 0.020 mmol)

Appearance: colorless resin

TLC: R_f = 0.50 (cycH/EA = 1:4; UV)

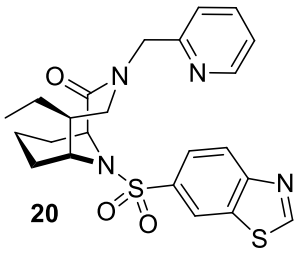
HPLC: R_t **=** 14.00 min (0 – 100% B in 20 min)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.24 – 1.26 (m, 2H), 1.38 – 1.51 (m, 3H), 1.53 (d, J = 7.1 Hz, 3H), 2.09 – 2.15 (m, 1H), 2.25 – 2.32 (m, 1H), 3.07 (dd, J = 14.2, 1.8 Hz, 1H), 3.74 (dd, J = 14.2, 10.5 Hz, 1H), 3.97 – 4.03 (m, 1H), 4.63 (dt, J = 17.0, 1.1 Hz, 1H), 4.85 (dt, J = 6.0, 1.9 Hz, 1H), 4.87 – 4.91 (m, 1H), 5.61 (ddd, J = 17.0, 10.1, 8.8 Hz, 1H), 6.15 (q, J = 7.1 Hz, 1H), 7.16 – 7.21 (m, 1H), 7.36 (dd, J = 7.9, 1.1 Hz, 1H), 7.66 (td, J = 7.7, 1.9 Hz, 1H), 7.94 (dd, J = 8.6, 1.9 Hz, 1H), 8.26 (dd, J = 8.7, 0.6 Hz, 1H), 8.52 (dd, J = 1.8, 0.6 Hz, 1H), 8.55 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H), 9.21 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 15.7, 26.1, 27.7, 29.7, 45.6, 49.2, 54.5, 54.6, 57.0, 116.3, 121.5, 122.4, 122.7, 124.1, 124.6, 134.3, 136.6, 137.5, 138.5, 148.8, 155.4, 157.8, 159.7, 170.2.

Mass (ESI): $[M + H]^+$ = 483.13

20: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-ethyl-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



20

To a solution of **17** (10.0 mg, 0.021 mmol) in MeOH (0.5 mL) was added Pd/C (10 %, 2.27 mg, 0.0021 mmol) and the solution was saturated with H_2 . After 1 h the mixture was filtered through SiO_2 and washed with EA. The solvent was removed under reduced pressure affording the title compound as colorless solids.

Yield: quant. (10 mg, 0.021 mmol)

Appearance: colorless solids

TLC: R_f = 0.17 (EA = 1:4; UV)

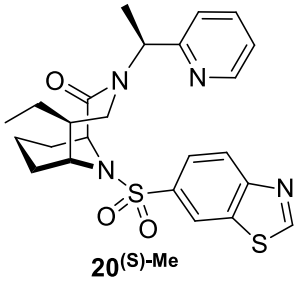
HPLC: R_t **=** 7.30 min (0 – 100% B in 20 min)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.30 – 1.36 (m, 5H), 1.47 – 1.73 (m, 5H), 1.82 – 1.88 (m, 1H), 2.24 (d, J = 14.4 Hz, 1H), 3.10 (dd, J = 14.4, 1.8 Hz, 1H), 3.86 (dd, J = 14.2, 10.6 Hz, 1H), 3.90 – 3.95 (m, 1H), 4.71 (d, J = 15.1 Hz, 1H), 4.83 (dt, J = 6.1, 1.9 Hz, 1H), 4.91 (d, J = 15.1 Hz, 1H), 7.20 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.31 – 7.35 (m, 1H), 7.67 (td, J = 7.7, 1.8 Hz, 1H), 7.94 (dd, J = 8.6, 1.9 Hz, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.50 – 8.55 (m, 2H), 9.22 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 11.51, 15.68, 26.22, 27.32, 27.49, 29.67, 45.60, 51.04, 55.26, 55.95, 56.81, 121.57, 122.18, 122.47, 124.09, 124.59, 134.32, 136.99, 138.54, 148.99, 155.37, 157.12, 157.87, 170.84.

Mass (ESI): $[M + H]^+$ = 471.16

20$^{(S)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-ethyl-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



20$^{(S)\text{-}Me}$

To a solution of **17$^{(S)\text{-}Me}$** (9.0 mg, 0.019 mmol) in MeOH (0.5 mL) was added Pd/C (10 %, 2.0 mg, 0.00187 mmol) and the solution was saturated with H_2. After 16 h the mixture was filtered through SiO_2 and washed with EA, affording the title compound as a colorless solid.

Yield: quant. (9 mg, 0.019 mmol)

Appearance: colorless solid

TLC: R_f = 0.50 (cycH/EA = 1:4; UV)

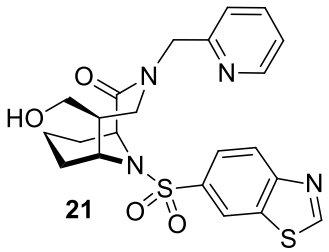
HPLC: R_t **=** 13.65 min (0 – 100% B in 20 min)

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 1.21 – 1.26 (m, 2H), 1.39 – 1.45 (m, 4H), 1.48 – 1.52 (m, 2H), 1.54 – 1.60 (m, 2H), 1.60 – 1.62 (m, 3H), 1.83 – 1.89 (m, 1H), 2.27 – 2.32 (m, 1H), 2.95 (dd, J = 14.6, 1.7 Hz, 1H), 3.27 (dd, J = 14.7, 10.5 Hz, 1H), 3.96 (dt, J = 6.7, 3.1 Hz, 1H), 4.85 (dt, J = 5.8, 1.9 Hz, 1H), 6.18 (q, J = 6.9 Hz, 1H), 7.20 – 7.24 (m, 1H), 7.27 – 7.28 (m, 1H), 7.65 – 7.69 (m, 1H), 7.94 (dd, J = 8.6, 1.8 Hz, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H), 8.57 – 8.58 (m, 1H), 9.24 (s, 1H).

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 10.88, 14.13, 14.71, 25.58, 26.59, 26.92, 28.68, 44.30, 45.58, 53.98, 54.53, 55.95, 120.57, 121.37, 121.96, 123.09, 123.61, 133.33, 137.52, 147.71, 154.39, 156.84, 158.15, 169.38.

Mass (ESI): $[M + H]^+$ = 485.19

21: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-(hydroxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



21

To a solution **17** (60 mg, 0.128 mmol) in dioxane/H_2O (0.8 mL, 3:1) was added $NaIO_4$ (110 mg, 0.512 mmol), OsO_4 (2.5 % Solution in tert-Butanol, 0.00178 mmol, 0.022 mL) and 2,6-Lutidine (59 µL mL, 0.512 mmol). The solution was stirred for 20 h at room temperature, then Et_2O (90 mL) was added to the reaction and washed with sat. aq. NaCl solution (3 × 10 mL). The solvent was removed under reduced pressure, the obtained crude product was dissolved in EtOH (1 mL) and $NaBH_4$ (7.27 mg, 0.192 mmol) was added and stirred for 1 h at room temperature. Et_2O (90 mL) was added to the reaction and washed with sat. aq. NaCl solution (3 x 10 mL). Column chromatography over SiO_2 (EA) afforded the title compound as a colorless solid.

Yield: 27% (16 mg, 0.034 mmol)

Appearance: colorless solid

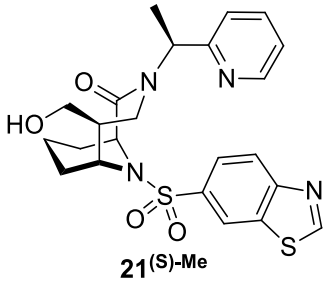
HPLC: R_t **=** 10.88 min (0 – 100% B in 20 min)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.34 – 1.41 (m, 2H), 1.45 – 1.49 (m, 3H), 2.22 – 2.27 (m, 2H), 3.38 – 3.42 (m, 1H), 3.50 (d, J = 8.6 Hz, 1H), 3.54 – 3.57 (m, 1H), 3.95 (dd, J = 14.3, 10.6 Hz, 1H), 4.01 – 4.06 (m, 1H), 4.75 – 4.86 (m, 4H), 7.19 – 7.21 (m, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.65 – 7.68 (m, 1H), 7.94 (dd, J = 8.6, 1.9 Hz, 1H), 8.26 (dd, J = 8.7, 0.7 Hz, 1H), 8.49 – 8.54 (m, 2H), 9.22 (s, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 15.58, 27.71, 29.67, 46.86, 49.57, 56.02, 56.95, 61.85, 63.59, 72.25, 121.60, 122.36, 124.03, 124.64, 134.35, 137.09, 138.35, 149.01, 155.43, 156.96, 157.92, 170.66.

Mass (ESI): $[M + H]^+$ = 475.12

21$^{(S)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-(hydroxymethyl)-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



21$^{(S)\text{-}Me}$

To a solution of **17$^{(S)\text{-}Me}$** (200mg, 0.414 mmol) in dioxane/H_2O (4 mL, 3:1) was added $NaIO_4$ (355 mg, 1.66 mmol), OsO_4 (2.5 % Solution in *tert*-Butanol, 0.009 mmol, 0.104 mL) and 2,6-Lutidine (0.096 mL, 0.829 mmol). The solution was stirred for 3 h at room temperature, then sat. aq. NaCl solution (30 mL) was added to the reaction and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The obtained crude product was dissolved in EtOH (12 mL) and $NaBH_4$ (23.5 mg, 0.622 mmol) was added and stirred for 1 h at room temperature. Et_2O (90 mL) was added to the reaction and washed with sat. aq. NaCl solution (3 × 10 mL). Column chromatography over SiO_2 (Cyclohexane/EtOAc = 3:7) afforded the title compound as a colorless solid.

Yield: 70% (140 mg, 0.28 mmol)

Appearance: colorless solid

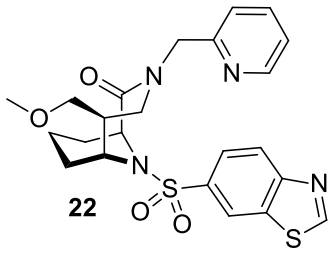
HPLC: R_t **=** 10.96 min (0 – 100% B in 20 min)

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 1.40 – 1.46 (m, 1H), 1.48 – 1.60 (m, 4H), 1.61 (d, J = 6.9 Hz, 3H), 2.16 – 2.23 (m, 1H), 2.25 – 2.31 (m, 1H), 3.16 – 3.24 (m, 1H), 3.32 (dd, J = 14.6, 10.6 Hz, 1H), 3.55 – 3.61 (m, 2H), 4.00 – 4.04 (m, 1H), 4.84 (dt, J = 6.0, 1.9 Hz, 1H), 6.14 (q, J = 6.9 Hz, 1H), 7.19 – 7.24 (m, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.65 (td, J = 7.6, 1.8 Hz, 1H), 7.91 (dd, J = 8.5, 1.8 Hz, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.51 (d, J = 1.8 Hz, 1H), 8.54 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H), 9.22 (s, 1H).

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 15.10, 15.66, 28.06, 28.17, 43.62, 47.76, 52.24, 55.08, 57.12, 60.41, 63.68, 121.63, 122.52, 123.07, 124.06, 124.67, 134.37, 138.35, 148.53, 155.46, 157.96, 158.97, 170.29.

Mass (ESI): $[M + H]^+$ = 487.21

22: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-(methoxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



22

Compound **21** (7.6 mg, 0.016 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (1.2 mg, 0.048 mmol, 3 eq.) and MeI (4 µL, 0.064 mmol, 4 eq.) were added successively and the mixture was stirred for 2 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution (10 ml), extracted with EA (2 x 40 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (5 g SiO_2, cycH/EA = 1:1)

Yield: 89% (7 mg, 0.014 mmol)

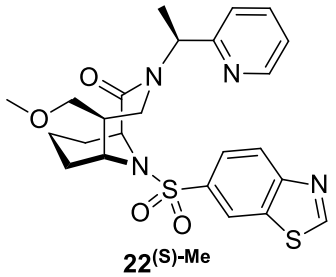
Appearance: white solids

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 – 1.68 (m, 5H), 2.17 – 2.29 (m, 1H), 2.34 (m, 1H), 3.18 – 3.28 (m, 6H), 3.83 (dd, J = 14.2, 10.7 Hz, 1H), 4.01 (d, J = 5.3 Hz, 1H), 4.56 (m, 1H), 4.73 (d, J = 15.3 Hz, 1H), 4.84 (d, J = 5.9 Hz, 1H), 4.90 (d, J = 15.3 Hz, 1H), 7.20 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.30 (s, 3H), 7.67 (td, J = 7.7, 1.8 Hz, 1H), 7.95 (ddd, J = 12.8, 8.6, 1.8 Hz, 1H), 8.27 (ddd, J = 13.9, 8.7, 0.6 Hz, 1H), 8.38 – 8.59 (m, 2H), 9.23 (d, J = 7.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 15.6, 20.6, 22.7, 27.8, 28.0, 29.7, 31.9, 44.5, 49.7, 52.4, 56.1, 56.9, 58.9, 60.4, 73.4, 76.7, 77.0, 77.2, 77.3, 121.7, 122.0, 122.5, 123.2, 124.1, 124.5, 124.6, 134.3, 137.2, 138.4, 148.9, 155.4, 156.9, 158.0, 170.8, 174.5.

Mass (ESI): $[M + H]^+$ = 487.18

22$^{(S)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-(methoxymethyl)-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



22$^{(S)\text{-}Me}$

To a solution of **27$^{(S)\text{-}Me}$** (8.00 mg, 0.026 mmol) in CH_2Cl_2 (0.5 mL) were added DIPEA (9.21 µL, 0.053 mmol), DMAP (0.322 mg, 2.64 µmol) and benzo[d]thiazole-6-sulfonyl chloride (12.3 mg, 0.053 mmol). The mixture was stirred for 20 h at room temperature and then loaded on SiO_2 and purified by column chromatography (100% EtOAc) affording the title compound (6 mg, 0.0120 mmol, 46%) as a colorless solid.

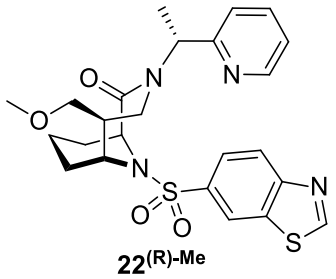
R_f: 0.27 (EtOAc)

^{1}H NMR (800 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.8 Hz, 2H), 1.48 – 1.54 (m, 3H), 1.59 (d, *J* = 6.9 Hz, 3H), 2.21 – 2.24 (m, 1H), 2.27 – 2.31 (m, 1H), 3.05 (dd, *J* = 14.7, 1.8 Hz, 1H), 3.21 – 3.26 (m, 2H), 3.27 – 3.32 (m, 4H), 3.97 – 4.02 (m, 1H), 4.85 (dt, *J* = 6.1, 2.0 Hz, 1H), 6.15 (q, *J* = 6.9 Hz, 1H), 7.15 – 7.20 (m, 1H), 7.20 – 7.23 (m, 1H), 7.62 (td, *J* = 7.7, 1.9 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 8.53 – 8.56 (m, 1H), 9.22 (s, 1H).

^{13}C NMR (200 MHz, $CDCl_3$) δ 13.11, 14.01, 19.46, 26.99, 27.15, 28.34, 28.64, 28.67, 42.49, 44.54, 53.91, 58.05, 72.44, 98.73, 120.61, 123.05, 123.57, 133.27, 137.32, 147.80, 154.34, 156.92, 158.08, 169.30.

HPLC (0-100% B in A in 20 min): R_t = 12.73 min

22$^{(R)\text{-}Me}$: (1S,5S,6R)-10-(benzo[d]thiazol-6-ylsulfonyl)-5-(methoxymethyl)-3-((R)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



22$^{(R)\text{-}Me}$

To a solution of **22$^{(R)\text{-}Me}$** (15 mg, 0.049 mmol) in CH_2Cl_2 (1 mL) were added DIPEA (17.0 µL, 0.099 mmol), DMAP (0.904 mg, 4.94 µmol) and benzo[d]thiazole-6-sulfonyl chloride (23.1 mg, 0.099 mmol). The mixture was stirred for 20 h at room temperature and then loaded on SiO_2 and purified by column chromatography (100% EtOAc) affording the title compound (10 mg, 0.0200 mmol, 40%) as a colorless solid.

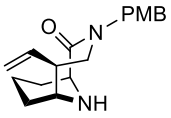
R_f: 0.27 (EtOAc)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.33 – 1.37 (m, 2H), 1.41 – 1.45 (m, 3H), 1.50 (d, *J* = 7.1 Hz, 3H), 1.73 – 1.79 (m, 1H), 2.25 – 2.34 (m, 1H), 3.01 – 3.18 (m, 6H), 3.45 (dd, *J* = 14.2, 10.4 Hz, 1H), 3.90 – 3.97 (m, 1H), 4.88 (dt, *J* = 6.0, 1.9 Hz, 1H), 6.14 (q, *J* = 7.1 Hz, 1H), 7.14 – 7.20 (m, 1H), 7.31 – 7.36 (m, 1H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 7.93 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.26 (dd, *J* = 8.7, 0.6 Hz, 1H), 8.51 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 9.21 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 17.46, 27.88, 28.13, 29.70, 42.85, 44.28, 52.48, 54.60, 57.17, 58.76, 73.45, 76.70, 77.02, 77.22, 77.34, 121.63, 122.45, 122.83, 124.18, 124.55, 134.31, 136.59, 138.55, 148.87, 155.38, 157.90, 159.62, 170.32.

HPLC (0-100% B in A in 20 min): R_t = 12.84 min

23: (1S,5R,6R)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



25

23 was synthesized in 8 steps from **12**, as previously published within our group[7].

Appearance: yellow resin

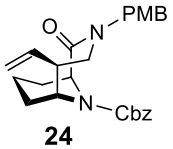
TLC: R_f = 0.19 (EA + 3% TEA + 2% MeOH; UV, ninhydrin)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 – 1.82 (m, 5H), 2.11 – 2.40 (m, 2H), 2.41 – 2.58 (m, 1H), 2.83 (dd, *J* = 7.4, 3.8 Hz, 1H), 2.95 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.83 (s, 4H), 3.85 – 4.01 (m, 2H), 4.47 (d, *J* = 14.3 Hz, 1H), 4.71 – 4.98 (m, 3H), 5.58 (m, 1H), 6.84 – 6.93 (m, 2H), 7.21 – 7.29 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 28.1, 29.4, 49.5, 50.2, 52.5, 53.0, 55.3, 57.8, 113.9, 115.1, 129.4, 129.9, 139.1, 158.9, 174.5.

Mass (ESI): $[M + H]^+$ = 301.01

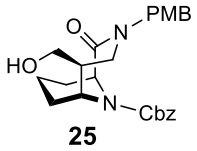
24: (1S,5R,6R)-benzyl 3-(4-methoxybenzyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decane-10-carboxylate



24

To a solution of **23** (600 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) were added CbzCl (375 mg. 2.20 mmol) and DIPEA (698 mL, 3.99 mmol) and the reaction was stirred for 1 h at room temperature. Sat. aq. $NaHCO_3$ solution (25 mL) was added to the mixture and extracted with CH_2Cl_2 (250 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure affording the crude product which was used for the next step without further purification.

25: (1S,5R,6R)-benzyl 5-(hydroxymethyl)-3-(4-methoxybenzyl)-2-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate



25

To a solution of **24** (445 mg, 1.024 mmol) in Dioxane/H_2O (12 mL, 3:1) was added $NaIO_4$ (876 mg, 4.10 mmol), OsO_4 (2.5 % Solution in *tert*-Butanol, 0.020 mmol, 0.257 mL) and 2,6-Lutidine (0.474 mL, 4.10 mmol). The solution was stirred for 3 h at room temperature, then sat. aq. NaCl solution (30 mL) was added to the reaction and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The obtained crude product was dissolved in EtOH (12 mL) and $NaBH_4$ (58.1 mg, 1.54 mmol) was added and stirred for 1 h at room temperature. Et_2O (90 mL) was added to the reaction and washed with sat. aq. NaCl solution (3 × 10 mL). Column chromatography over SiO_2 (Cyclohexane/EtOAc = 3/7) afforded the title compound (295 mg, 0.672 mmol, 66%) as a colorless solid.

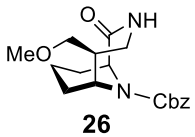
Yield: 66% (295 mg, 0.672 mmol)

Appearance: colorless solids

^{1}H NMR (400 MHz $CDCl_3$) δ = 1.51 – 1.75 (m, 5H), 1.89 – 2.00 (m, 1H), 2.40 – 2.50 (m, 1H), 2.54 (s, 2H), 3.06 – 3.28 (m, 2H), 3.43 – 3.49 (m, 1H), 3.77 – 3.85 (m, 3H), 4.02 – 4.18 (m, 1H), 4.31 – 4.43 (m, 1H), 4.72 – 4.85 (m, 1H), 5.05 – 5.28 (m, 3H), 6.79 – 6.89 (m, 2H), 7.15 – 7.26 (m, 2H), 7.30 – 7.43 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.93, 28.49, 28.97, 47.23, 47.32, 47.53, 49.17, 49.45, 53.02, 53.15, 55.26, 56.03, 56.37, 63.81, 64.09, 67.80, 67.86, 113.99, 114.02, 120.24, 127.92, 128.15, 128.27, 128.61, 129.25, 129.45, 129.53, 156.31, 159.05, 171.59.

26: (1S,5R,6R)benzyl 5-(methoxymethyl)-2-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate



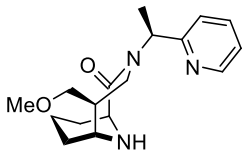
26

A solution of **25** (295 mg, 0.673 mmol) in DMF (5 mL) was cooled to 0 °C. NaH (60 % dispersion in mineral oil, 19.4 mg, 0.807 mmol) was added and the solution was stirred for 30 minutes. CH_3I (477 mg, 209 µL, 3.36 mmol) was added. After 3 h Et_2O (90 mL) was added to the mixture and washed with sat. aq. NaCl sol. (3 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product obtained was used for the next step without further purification.

To a solution of (1S,5R,6R)-benzyl 3-(4-methoxybenzyl)-5-(methoxymethyl)-2-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate (304 mg, 0.672 mmol) in MeCN/H_2O (7.50 mL, 2:1) was added CAN (1.11 g, 2.02 mmol). After 4h stirring at room temperature sat. aq. NaCl solution (50 mL) was added to the mixture and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography over SiO_2 (Cyclohexane/EtOAc = 1:4) afforded the title compound (120 mg, 0.361 mmol, 55%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 – 1.78 (m, 5H), 2.25 – 2.37 (m, 2H), 2.97 – 3.20 (m, 3H), 3.23 – 3.28 (m, 2H), 3.28 – 3.34 (m, 2H), 4.09 – 4.19 (m, 1H), 4.91 – 5.30 (m, 3H), 6.30 – 6.42 (m, 1H), 7.27 – 7.40 (m, 5H).

27$^{(S)\text{-}Me}$: (1S,5R,6R)-5-(methoxymethyl)-3-((S)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



27$^{(S)\text{-}Me}$

A solution of **26** (100 mg, 0.301 mmol) in dry DMF (3 mL) was cooled to 0 °C and NaH (15.6 mg, 0.391 mmol) was added. After 20 minutes 2-(1-bromoethyl)pyridine (72.8 mg, 0.391 mmol) was added and the reaction was allowed to reach room temperature. After 1 h the mixture was diluted with Et_2O (50 mL) and washed with sat. aq. NaCl sol. (3 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was then dissolved in CH_2Cl_2 (3 mL) and BCl_3 dimethylsulfide complex (2 M solution in CH_2Cl_2, 0.743 mL, 1.486 mmol) was added to the solution. After 1 h NaOH (1 M in H_2O, 25 mL) was added to the mixture and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and he solvent was removed under reduced pressure. Column chromatography over SiO_2 (EtOAc + 5% MeOH + 5% TEA) afforded the title compounds (11 mg, 0.0363 mmol, 12%).

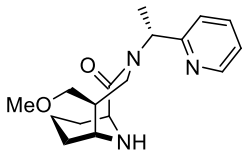
R_f: (EtOAc + 5 % MeOH + 5 % TEA): 0.15

^{1}H NMR (800 MHz, Chloroform-*d*) δ 1.50 (dtd, *J* = 12.6, 2.8, 1.3 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.62 – 1.67 (m, 3H), 1.73 (dddd, *J* = 12.8, 8.4, 4.6, 2.4 Hz, 1H), 2.15 – 2.22 (m, 1H), 2.32 – 2.36 (m, 1H), 2.68 (ddd, *J* = 7.1, 4.7, 1.9 Hz, 1H), 3.09 – 3.13 (m, 2H), 3.18 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.25 – 3.31 (m, 4H), 3.33 – 3.39 (m, 1H), 3.88 – 3.92 (m, 1H), 6.21 (q, *J* = 6.9 Hz, 1H), 7.16 – 7.20 (m, 1H), 7.30 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.64 (td, *J* = 7.6, 1.8 Hz, 1H), 8.56 – 8.60 (m, 1H).

^{13}C NMR (200 MHz, $CDCl_3$) δ 15.17, 29.45, 30.18, 34.50, 43.05, 46.23, 49.63, 54.35, 58.10, 58.94, 74.33, 122.14, 122.81, 136.51, 148.94, 160.09, 174.26.

MS (ESI): *m/z* (%) = 304.05 $[M + H]^+$

27$^{(R)\text{-}Me}$: (1S,5R,6R)-5-(methoxymethyl)-3-((R)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



27$^{(R)\text{-}Me}$

27$^{(R)\text{-}Me}$ was isolated from the same reaction as **27$^{(S)\text{-}Me}$**.

R_f: (EtOAc + 5 % MeOH + 5 % TEA): 0.29

^{1}H NMR (800 MHz, $CDCl_3$) δ 1.55 – 1.59 (m, 5H), 1.65 – 1.74 (m, 3H), 2.05 – 2.09 (m, 1H), 2.33 – 2.37 (m, 1H), 2.65 – 2.71 (m, 1H), 2.88 – 3.00 (m, 2H), 3.06 (s, 3H), 3.16 – 3.23 (m, 1H), 3.24 – 3.31 (m, 1H), 3.64 (dd, *J* = 14.1, 10.6 Hz, 1H), 3.88 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.21 (q, *J* = 7.1 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.36 – 7.42 (m, 1H), 7.65 (td, *J* = 7.7, 1.9 Hz, 1H), 8.55 – 8.59 (m, 1H).

^{13}C NMR (200 MHz, $CDCl_3$) δ 21.09, 29.24, 29.90, 42.62, 44.86, 49.50, 54.11, 58.08, 58.59, 60.43, 74.13, 122.27, 123.05, 136.48, 148.66, 160.13, 171.20.

MS (ESI): *m/z* (%) = 304.05 $[M + H]^+$

10 Analytical data

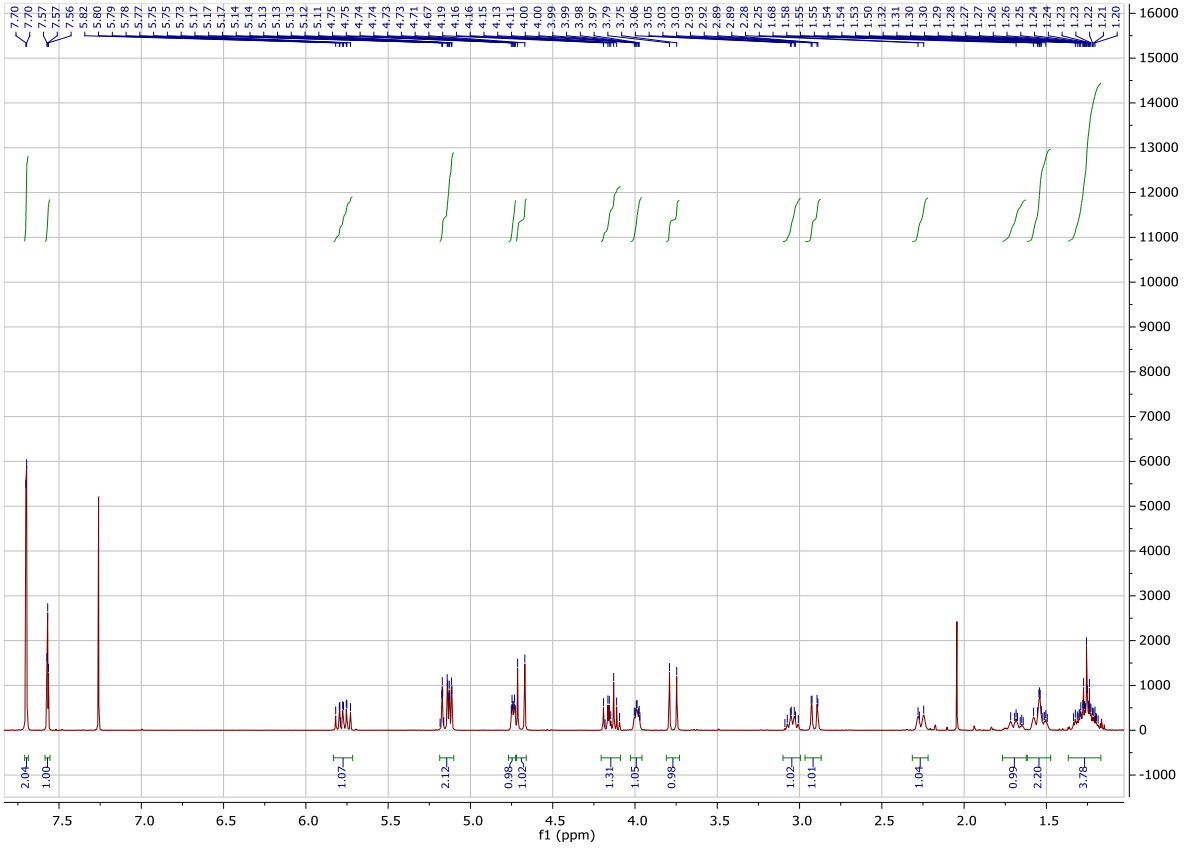


Figure S17. ^{1}H-NMR of compound **1**.

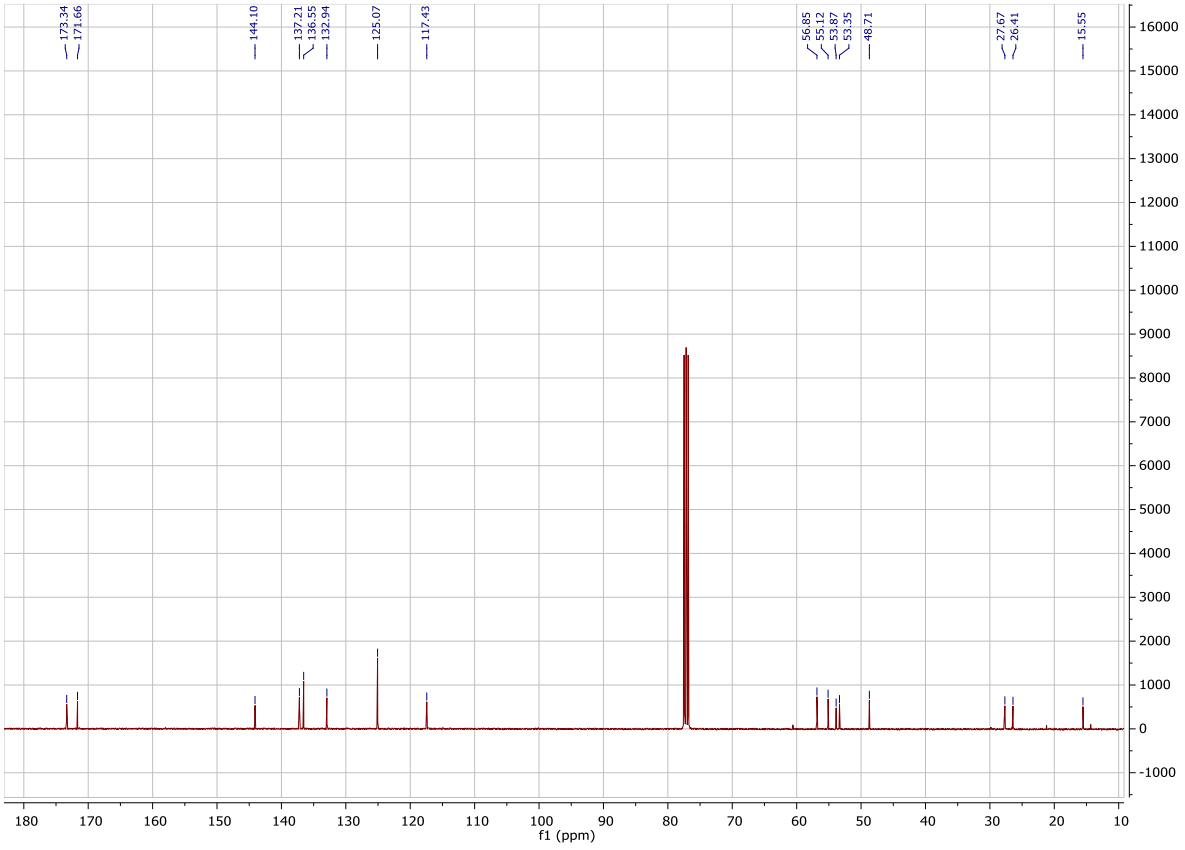


Figure S18. ^{13}C-NMR of compound **1**.

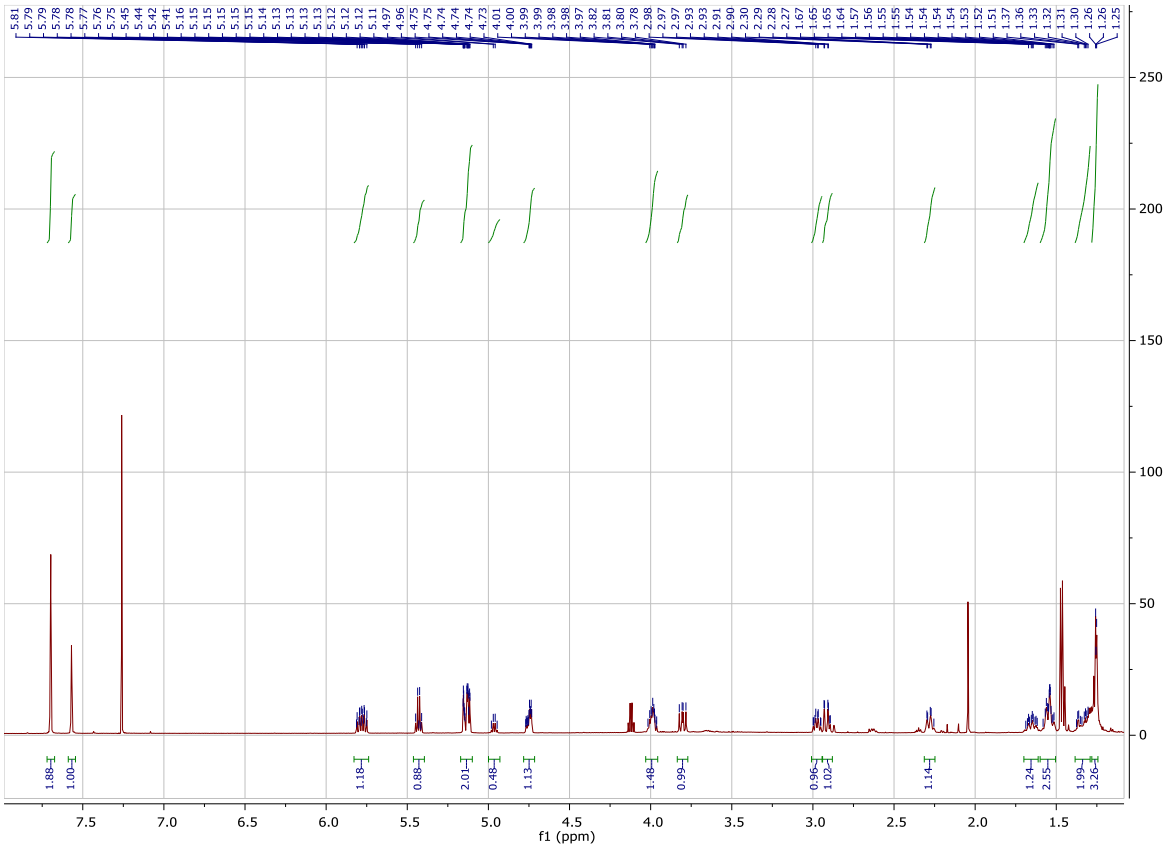


Figure S19. ^{1}H-NMR of compound **1$^{(R)\text{-}Me}$**.

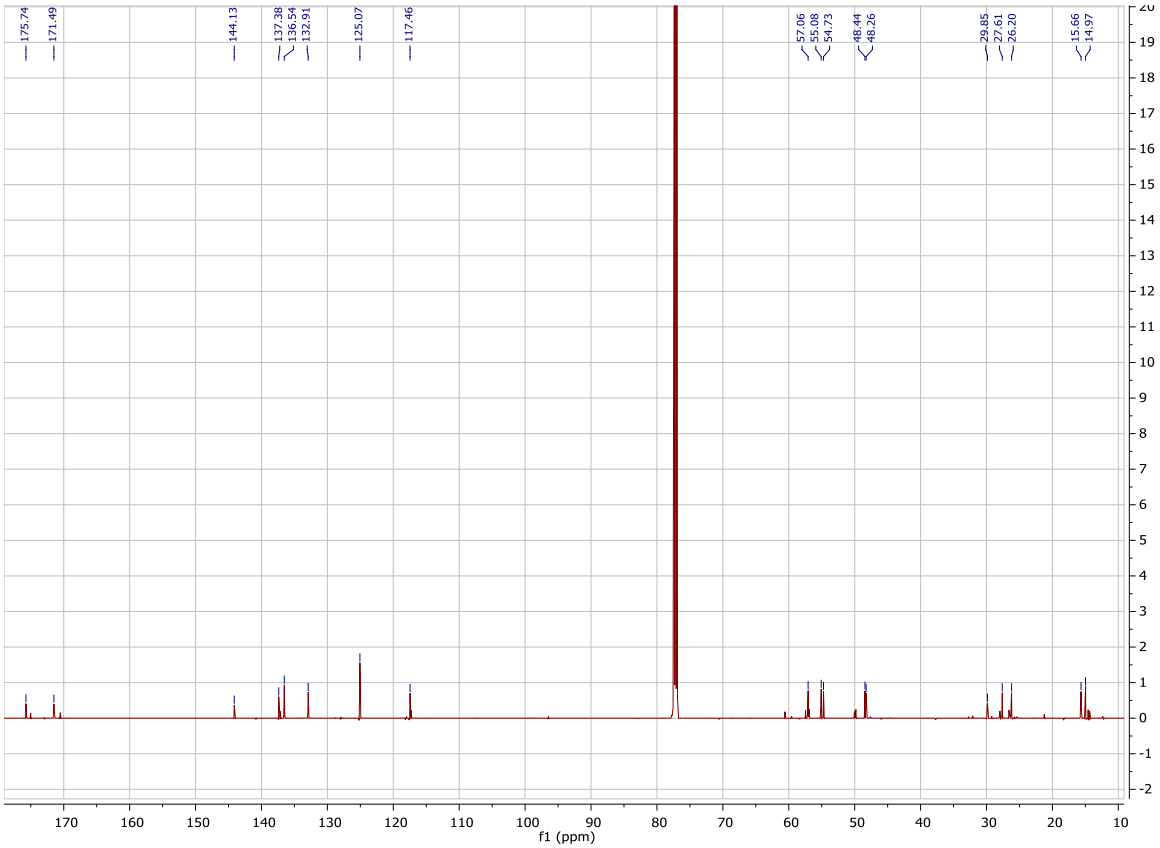


Figure S20. ^{13}C-NMR of compound **1$^{(R)\text{-}Me}$**.

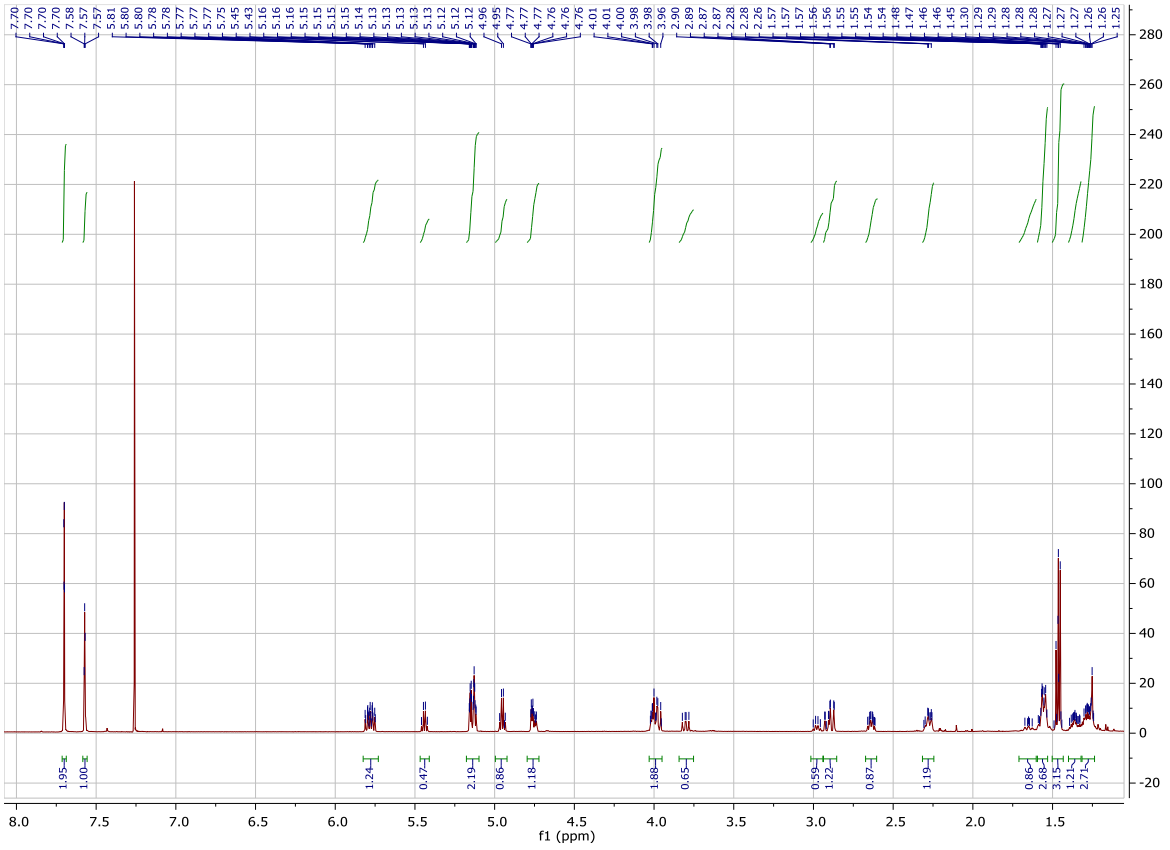


Figure S21. ^{1}H-NMR of compound **1$^{(S)\text{-}Me}$**.

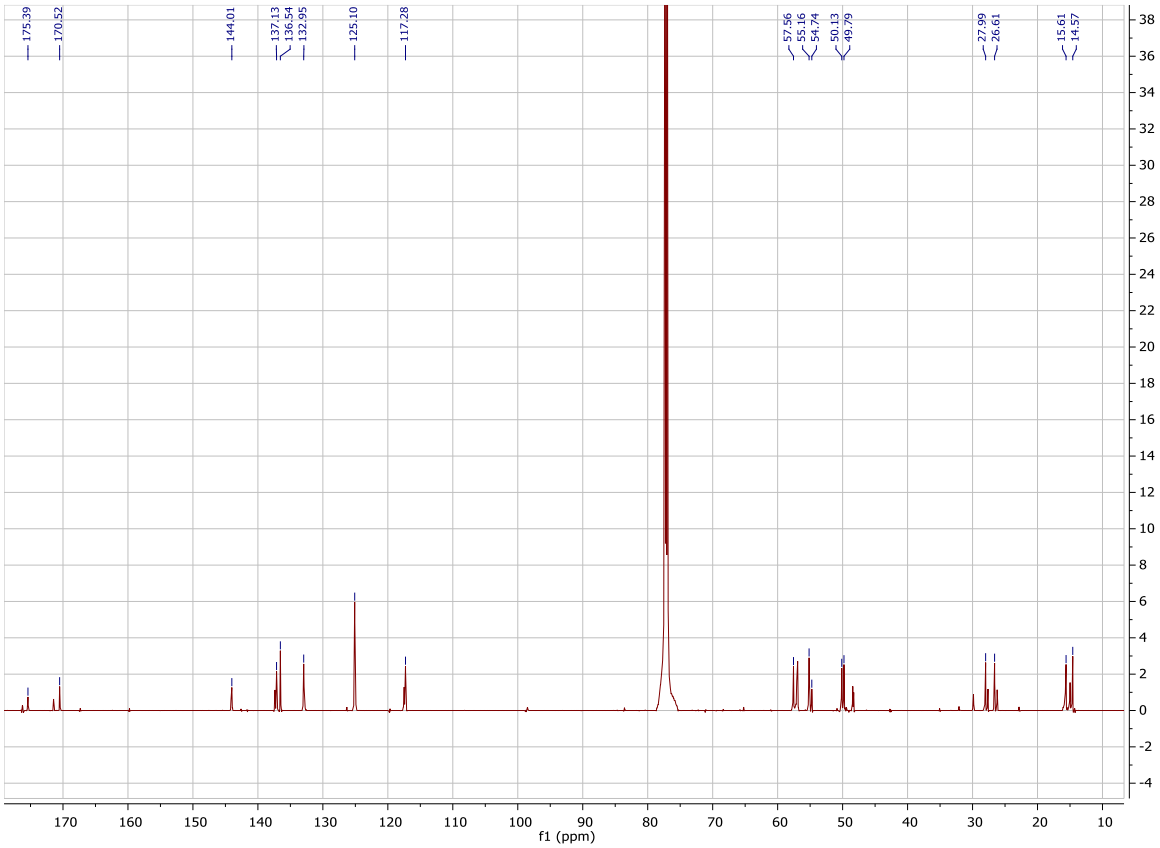


Figure S22. ^{13}C-NMR of compound **1$^{(S)\text{-}Me}$**.

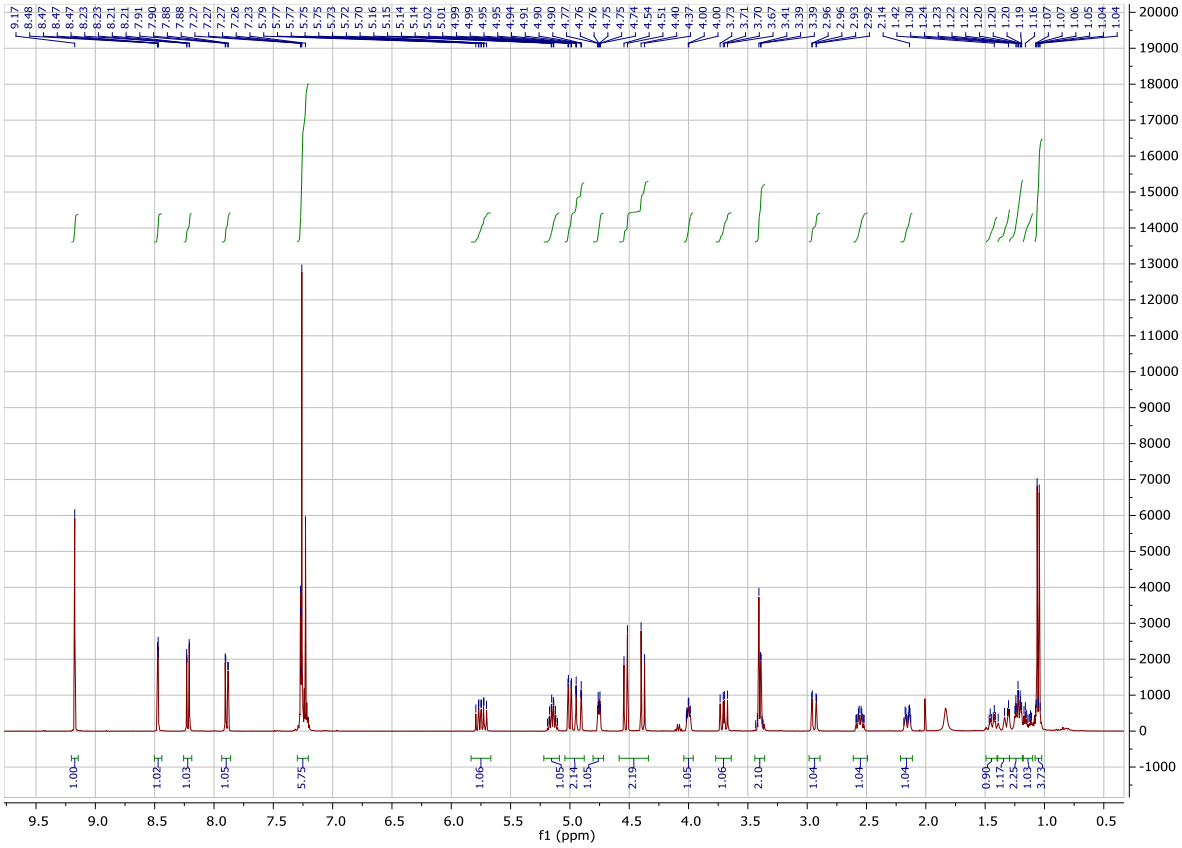


Figure S23. ^{1}H-NMR of compound **8$^{(R)\text{-}Me}$**.

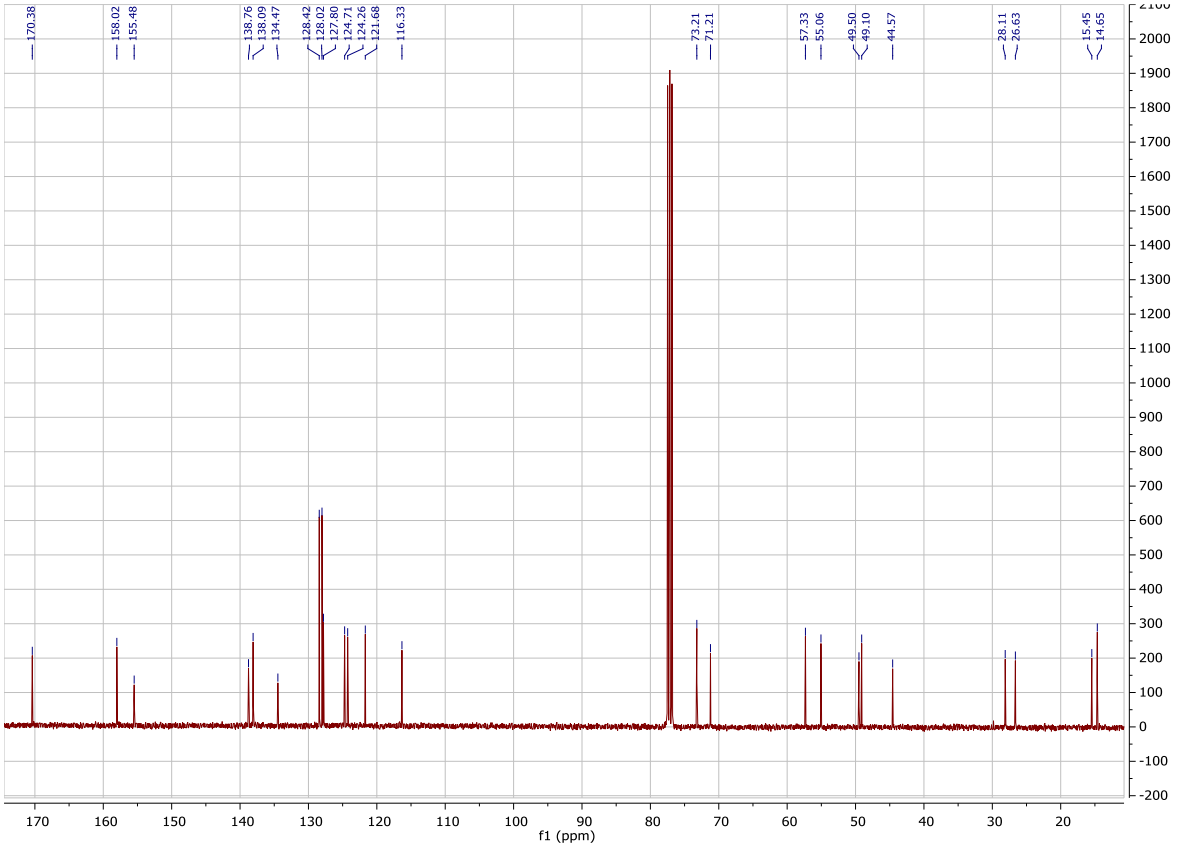


Figure S24. ^{13}C-NMR of compound **8$^{(R)\text{-}Me}$**.

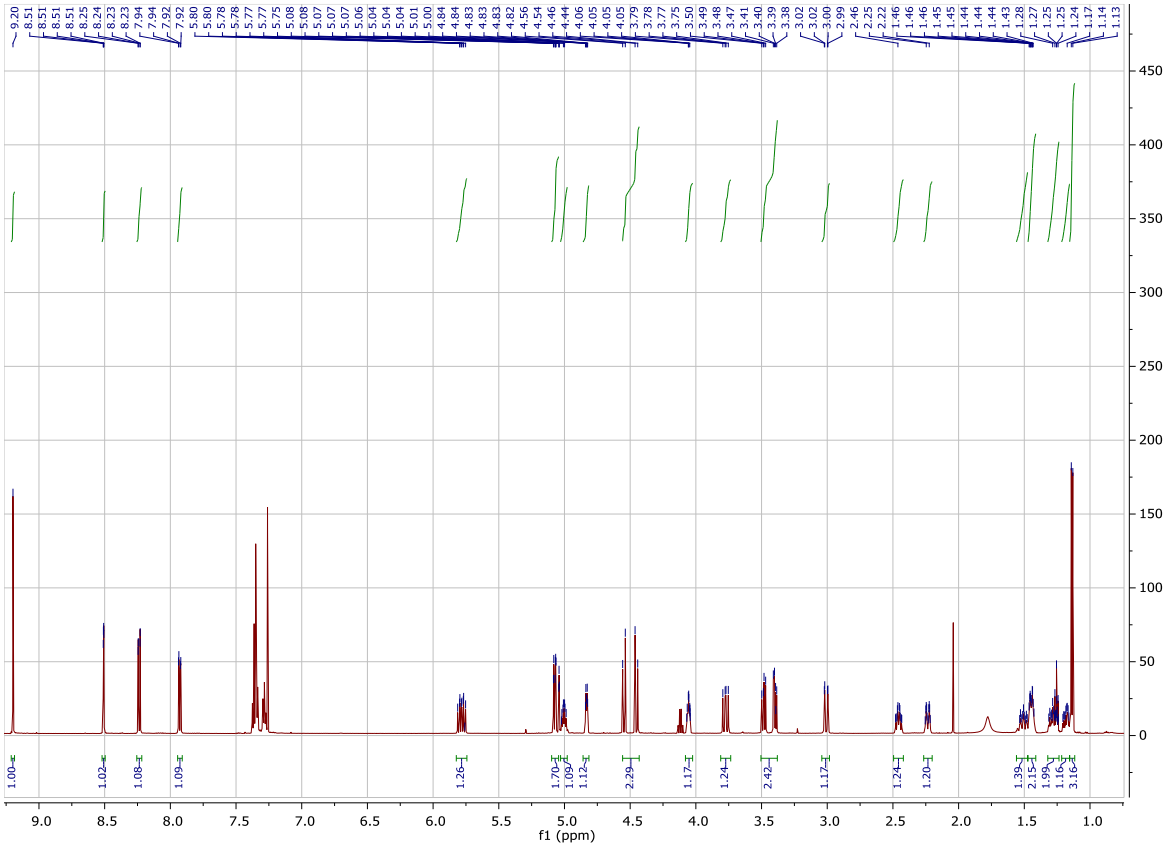


Figure S25. ^{1}H-NMR of compound **8$^{(S)\text{-}Me}$**.

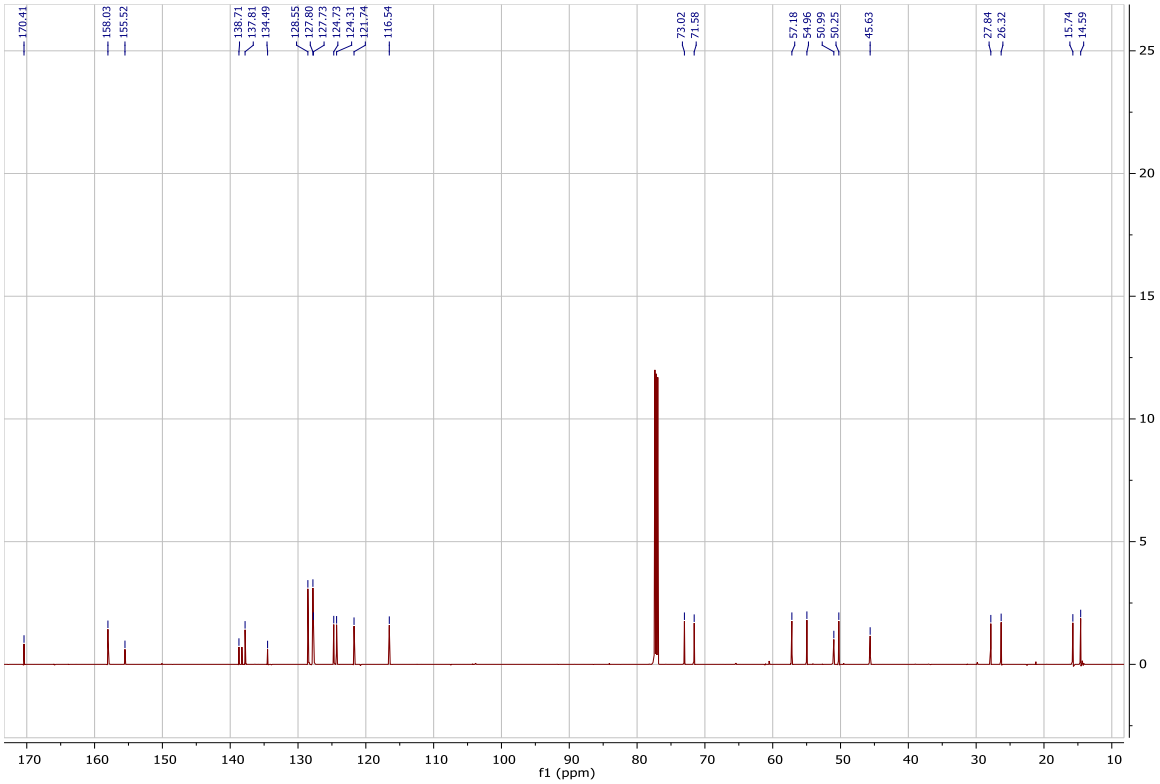


Figure S26. ^{13}C-NMR of compound **8$^{(S)\text{-}Me}$**.

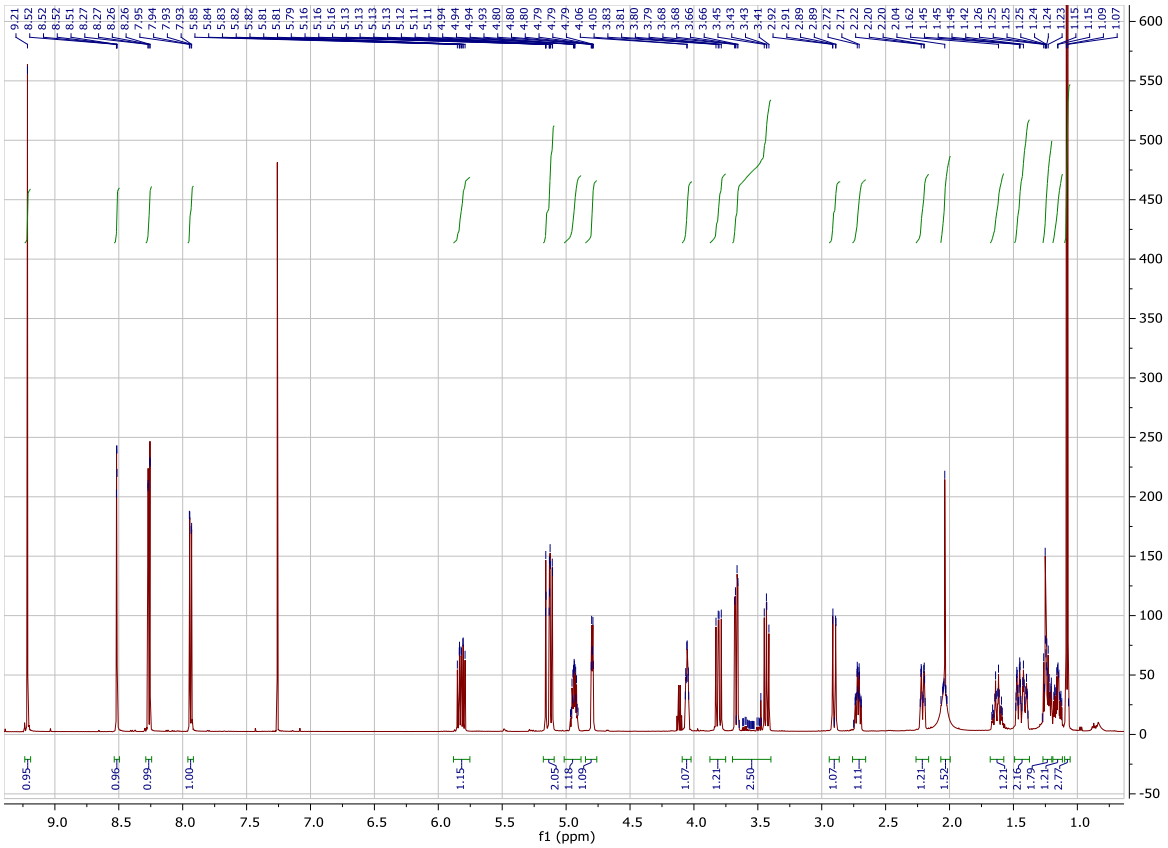


Figure S27. ^{1}H-NMR of compound **9$^{(R)\text{-}Me}$**.

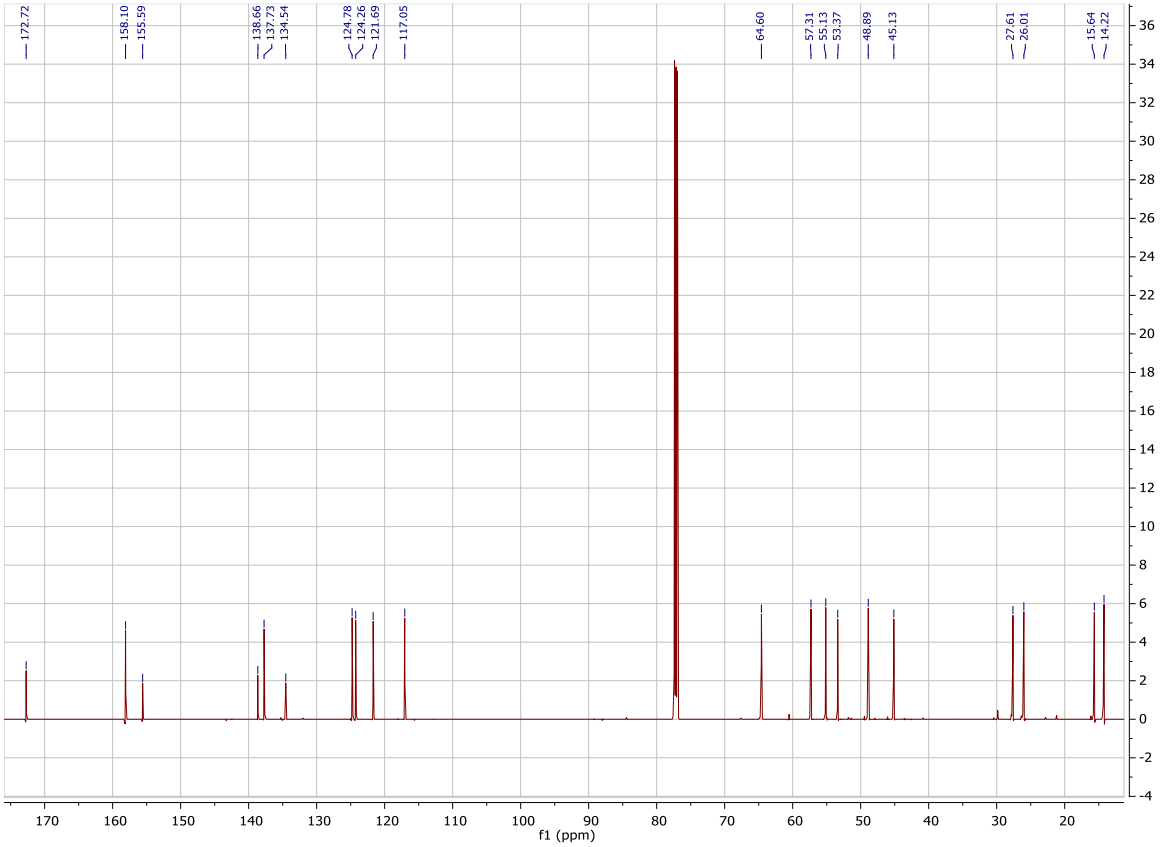


Figure S28. ^{13}C-NMR of compound **9$^{(R)\text{-}Me}$**.

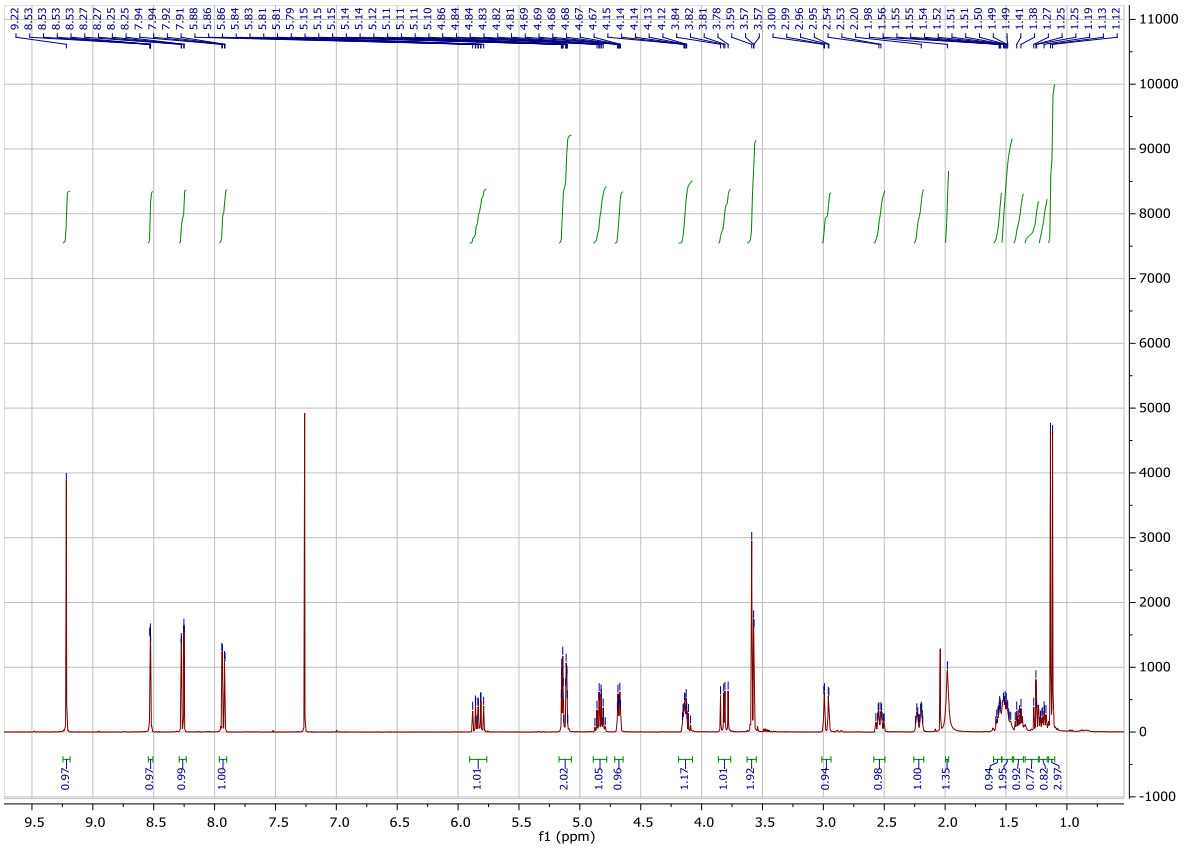


Figure S29. ^{1}H-NMR of compound **9$^{(S)\text{-}Me}$**.

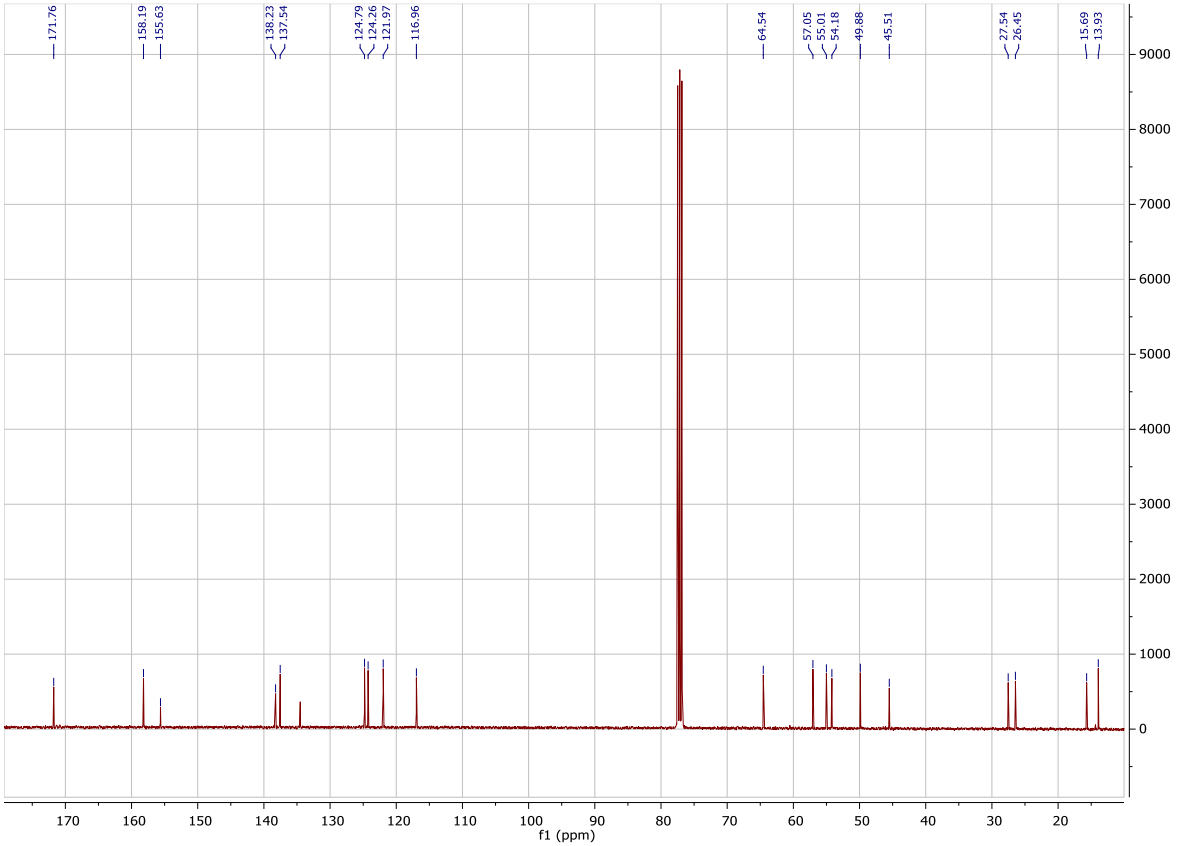


Figure S30. ^{13}C-NMR of compound **9$^{(S)\text{-}Me}$**.

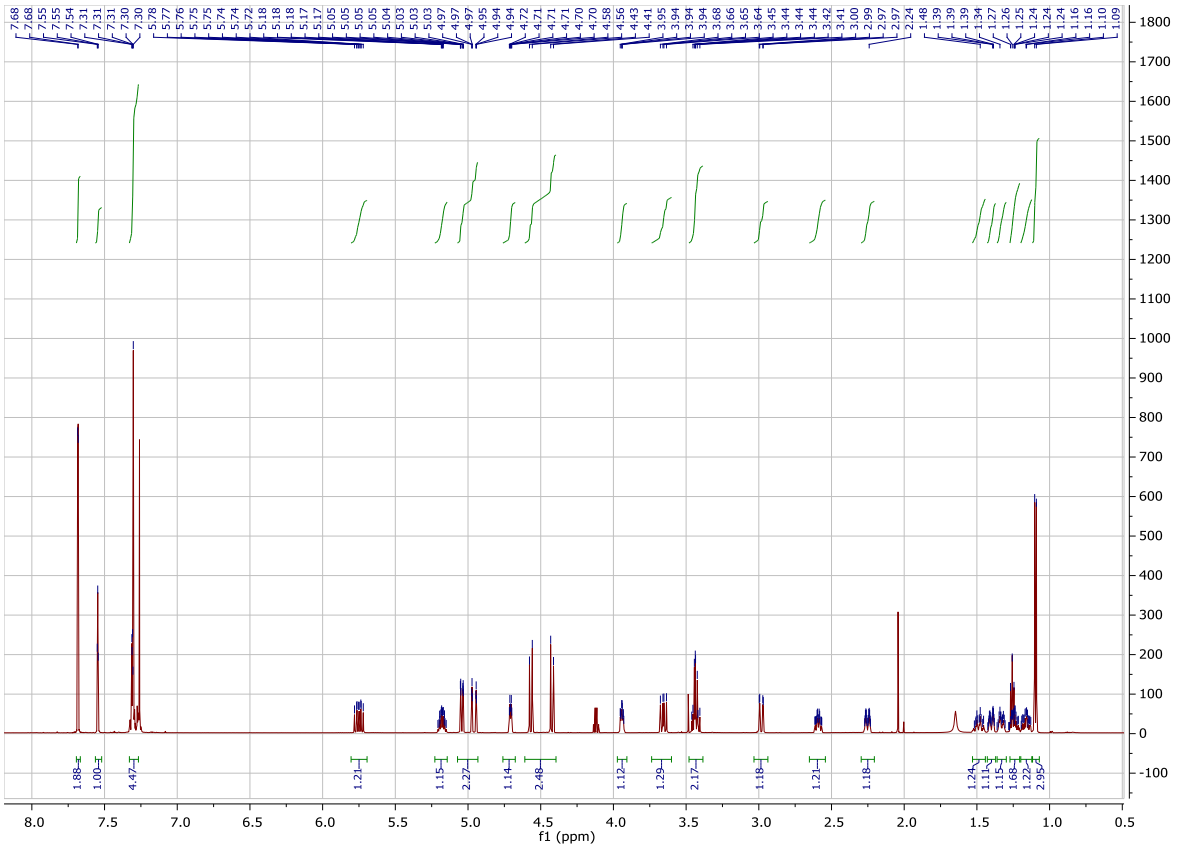


Figure S31. ^{1}H-NMR of compound **10$^{(R)\text{-}Me}$**.

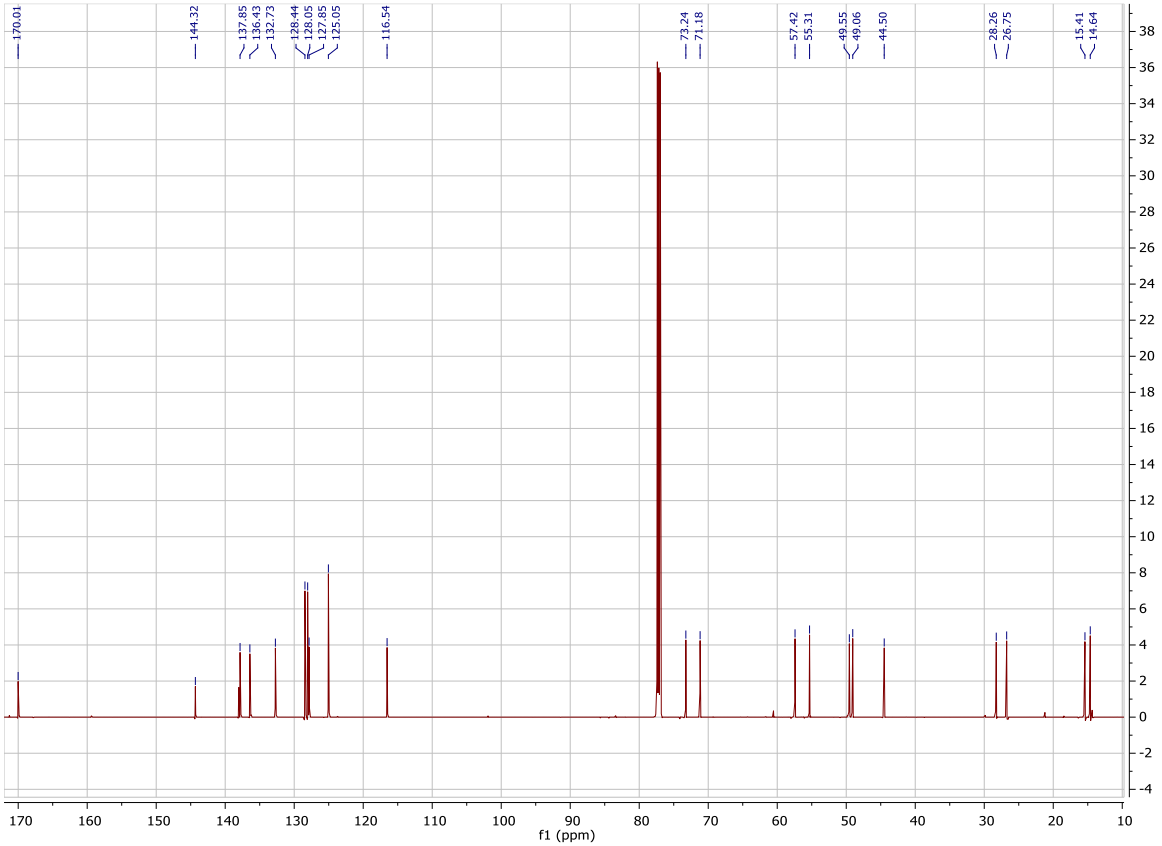


Figure S32. ^{13}C-NMR of compound **10$^{(R)\text{-}Me}$**.

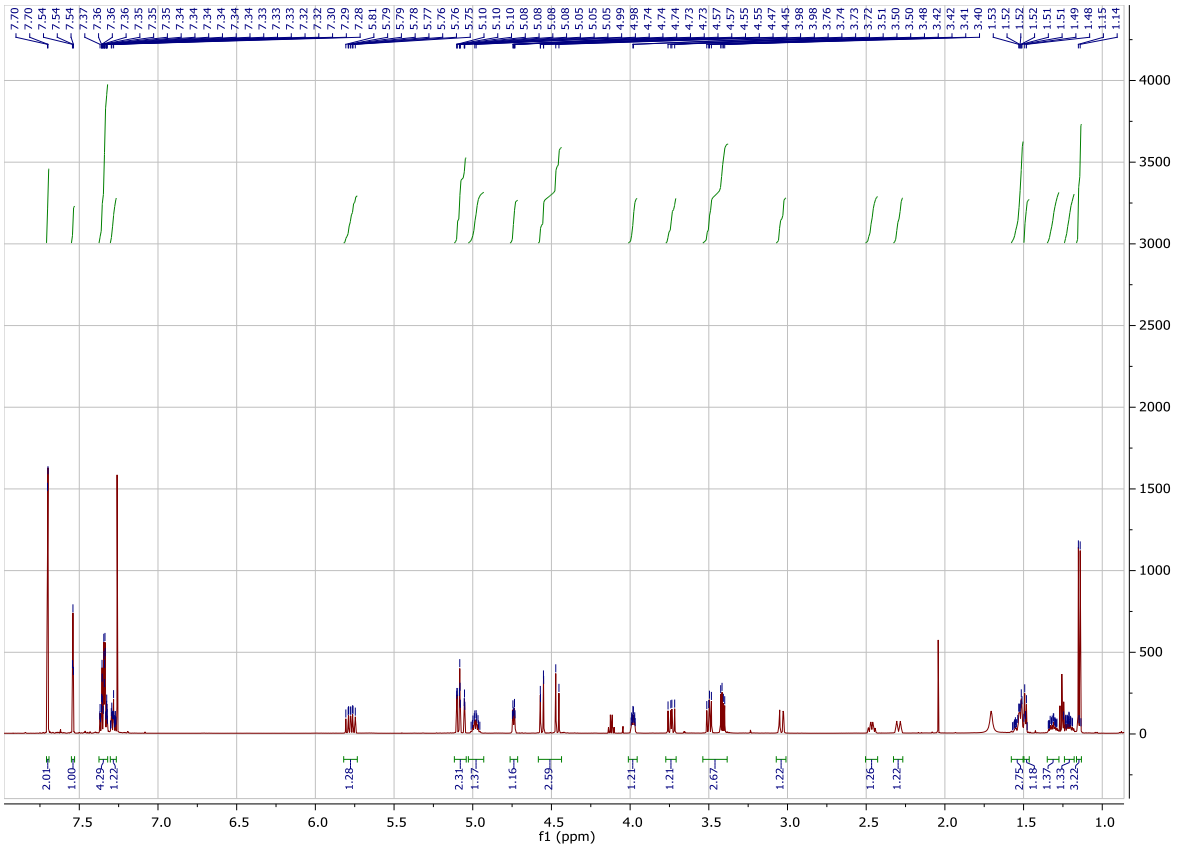


Figure S33. ^{1}H-NMR of compound **10$^{(S)\text{-}Me}$**.

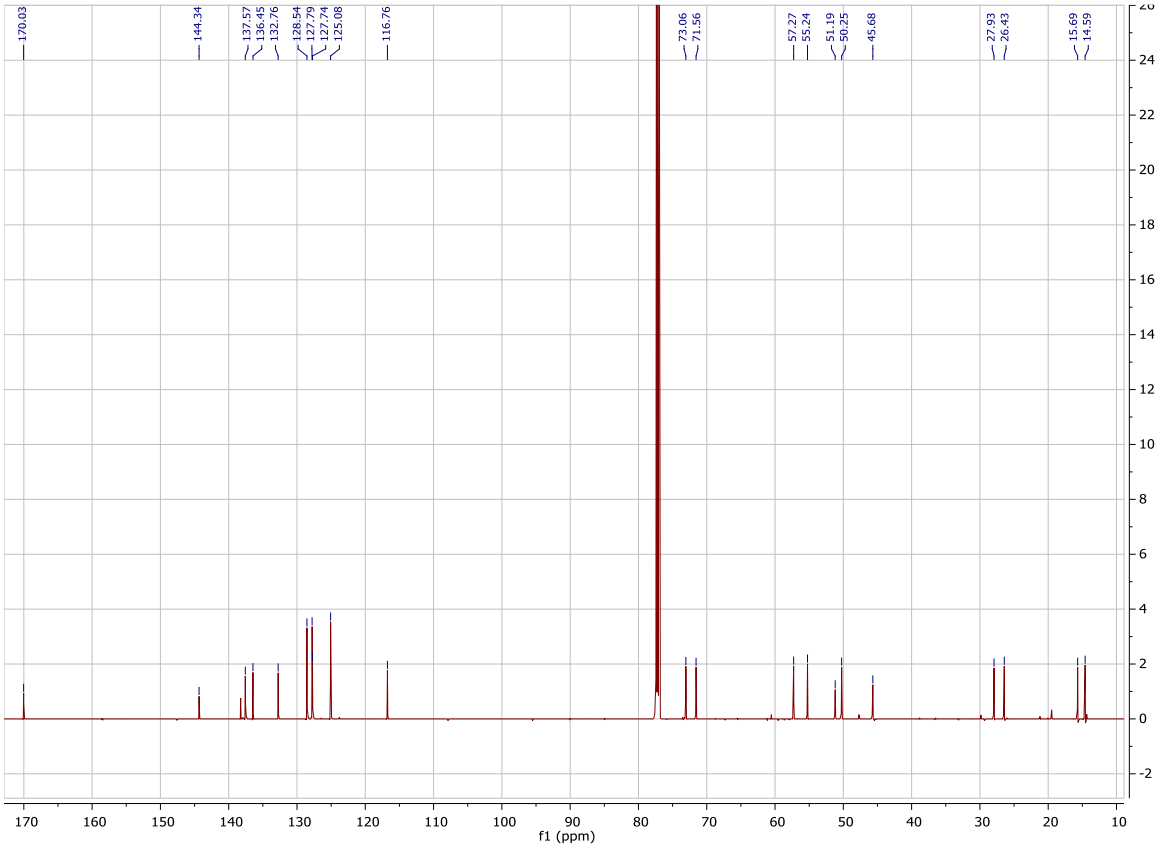


Figure S34. ^{13}C-NMR of compound **10$^{(S)\text{-}Me}$**.

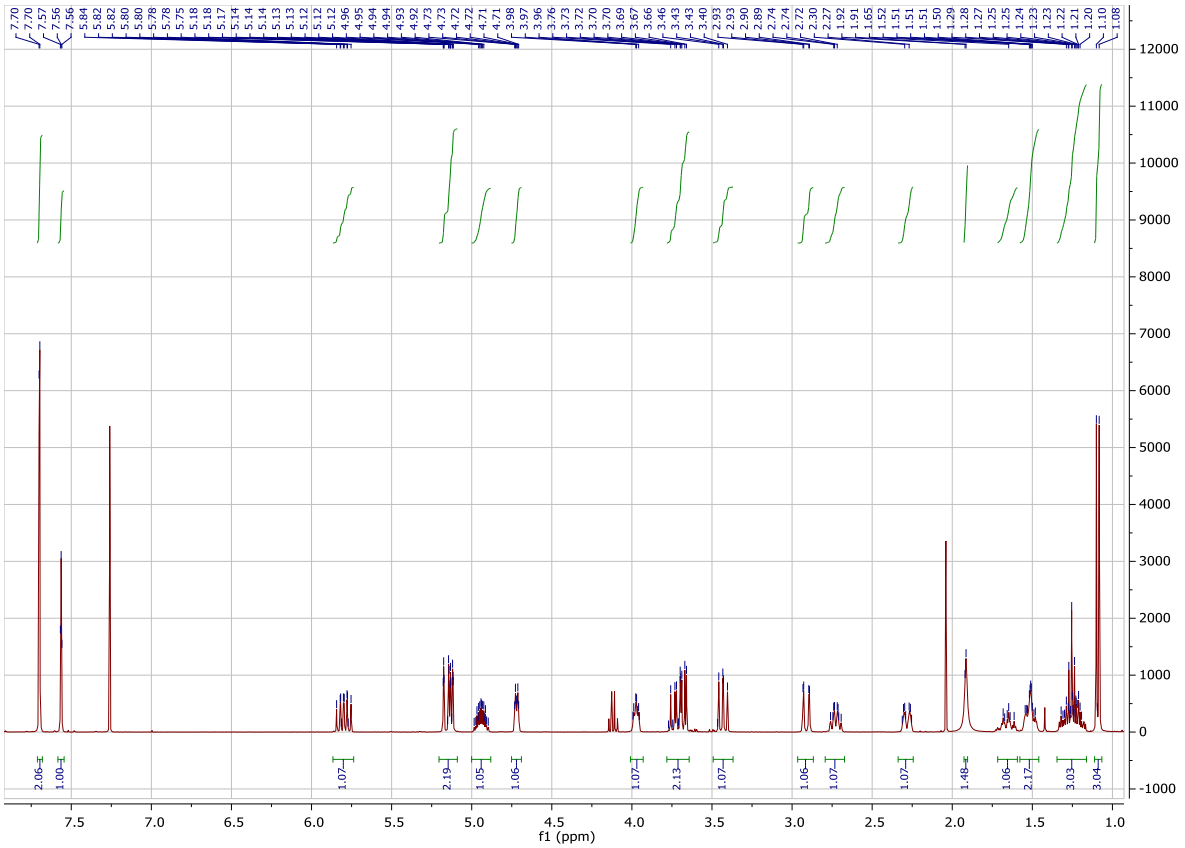


Figure S35. ^{1}H-NMR of compound **11$^{(R)\text{-Me}}$**.

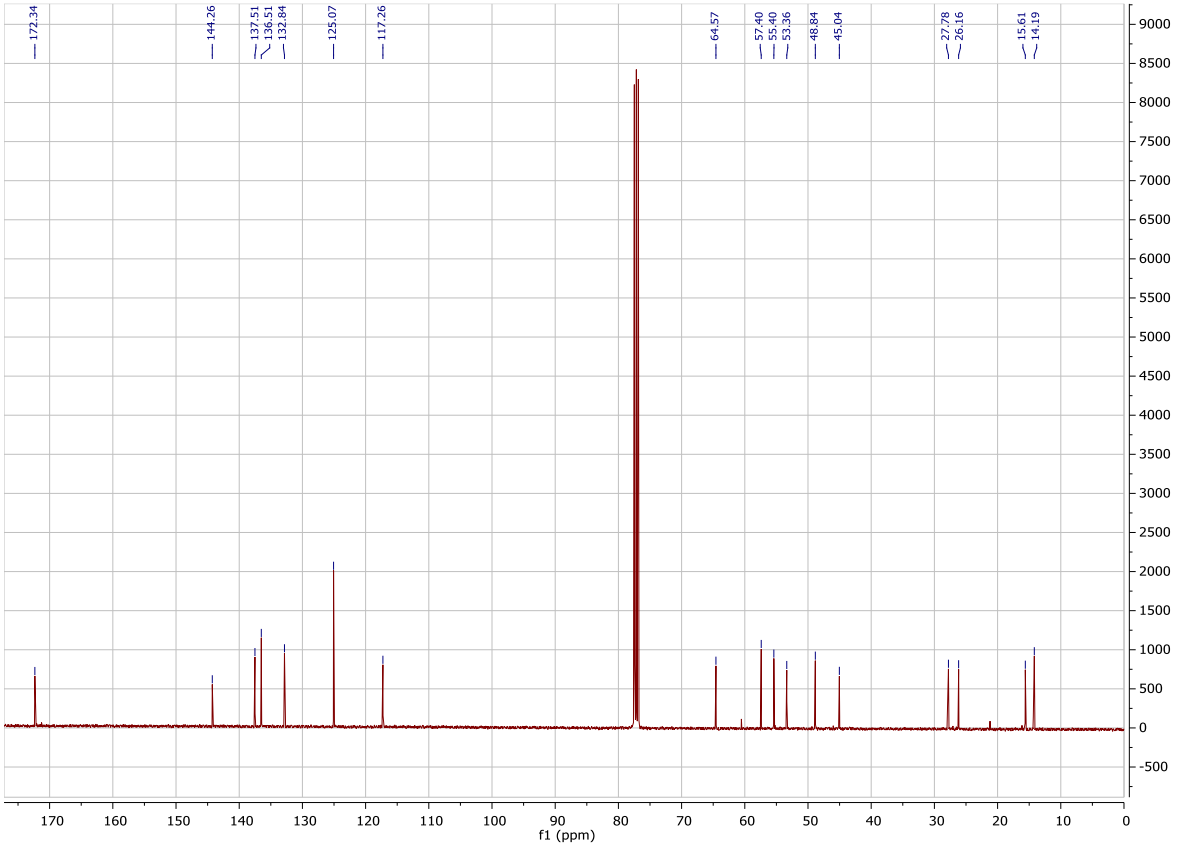


Figure S36. ^{13}C-NMR of compound **11$^{(R)\text{-Me}}$**.

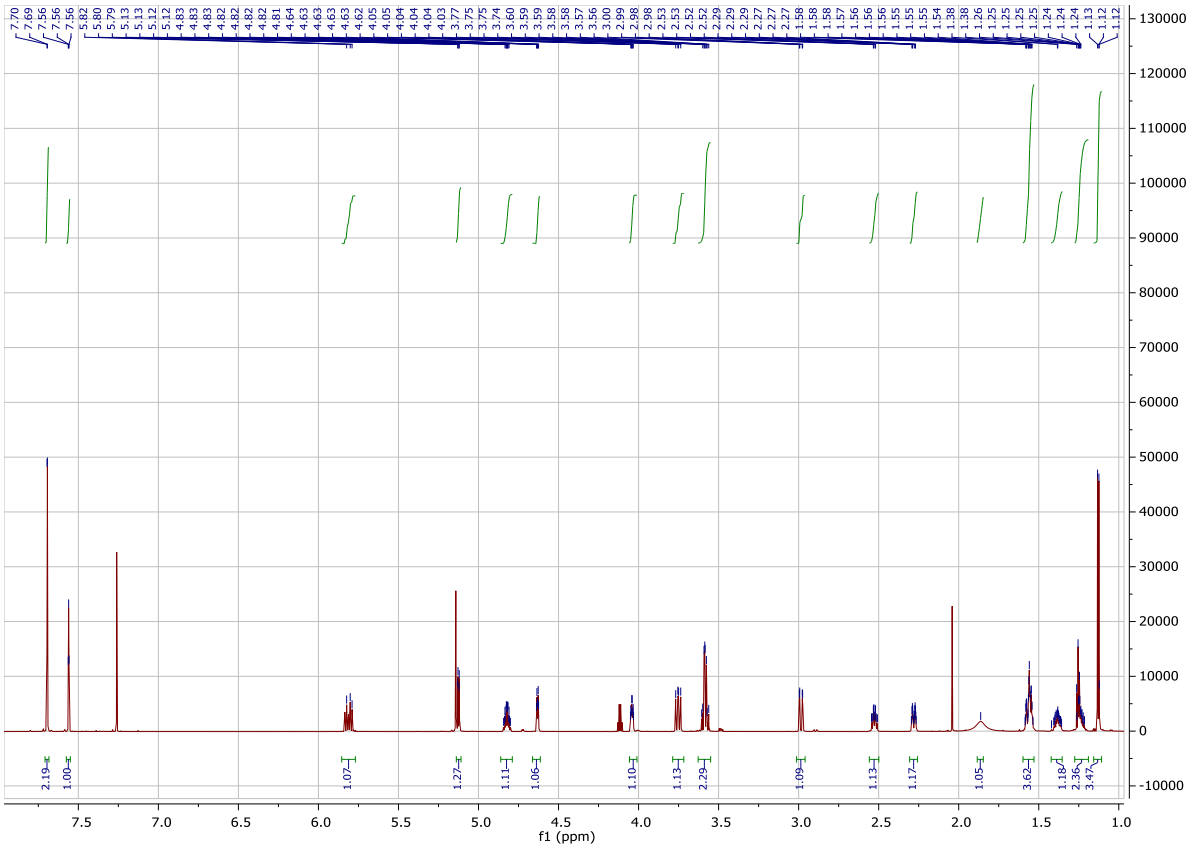


Figure S37. ^{1}H-NMR of compound **11$^{(S)\text{-}Me}$**.

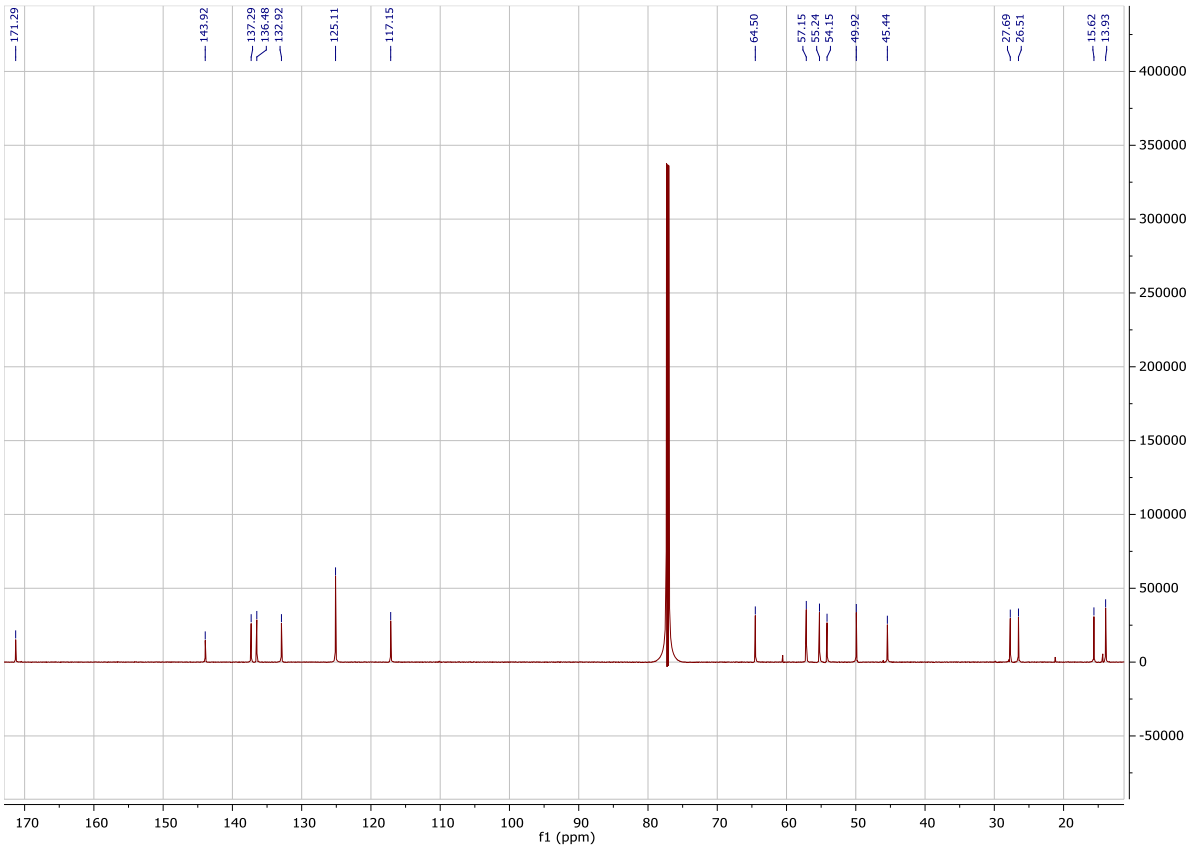


Figure S38. ^{13}C-NMR of compound **11$^{(S)\text{-}Me}$**.

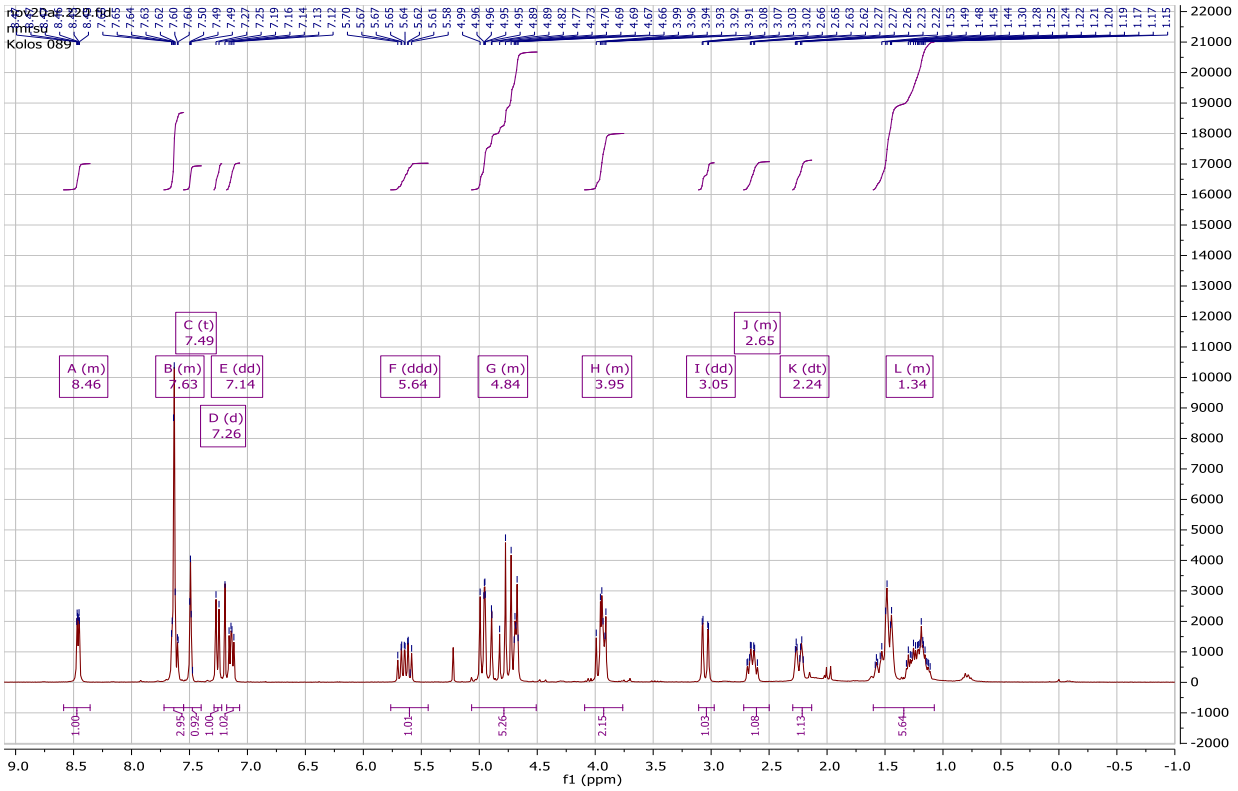


Figure S39. ^{1}H-NMR of compound **16**.

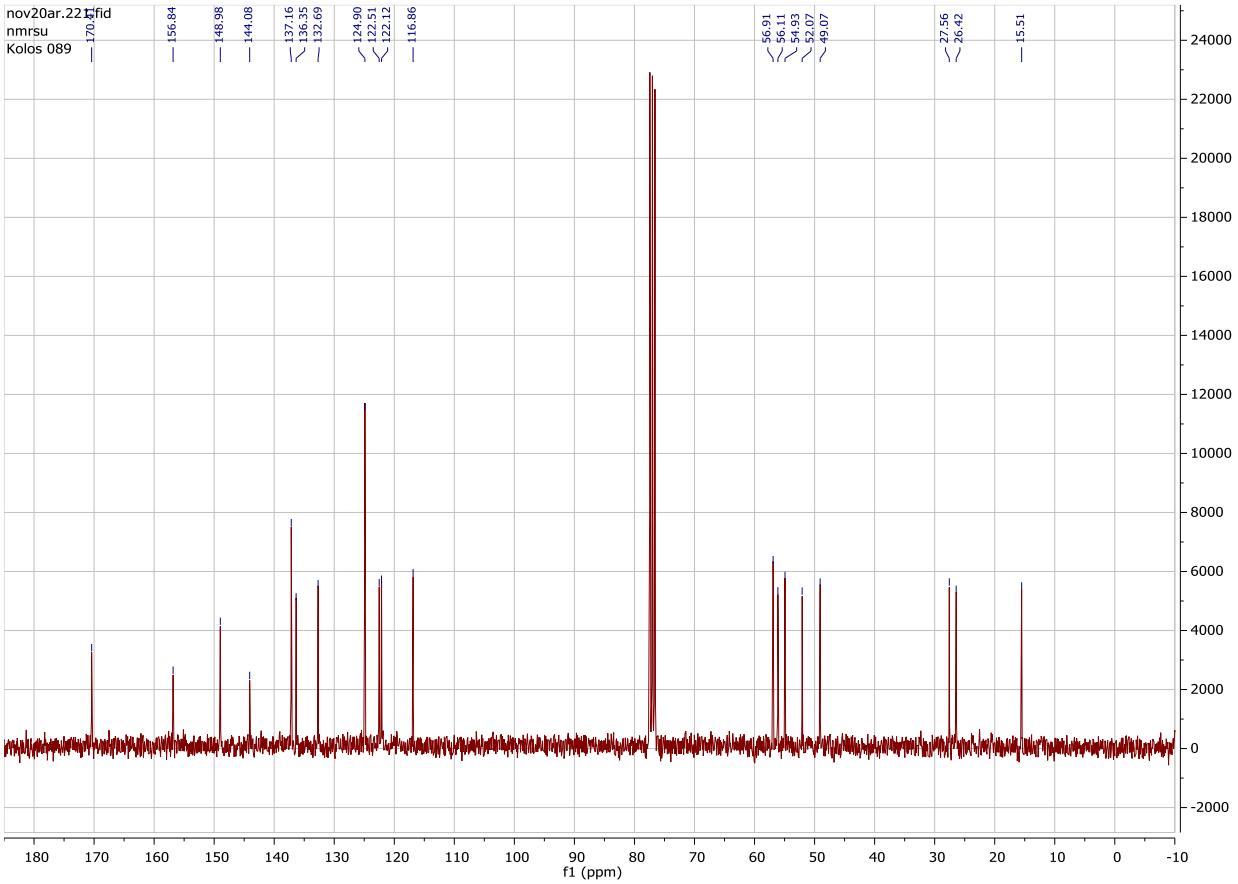


Figure S40. ^{13}C-NMR of compound **16**.

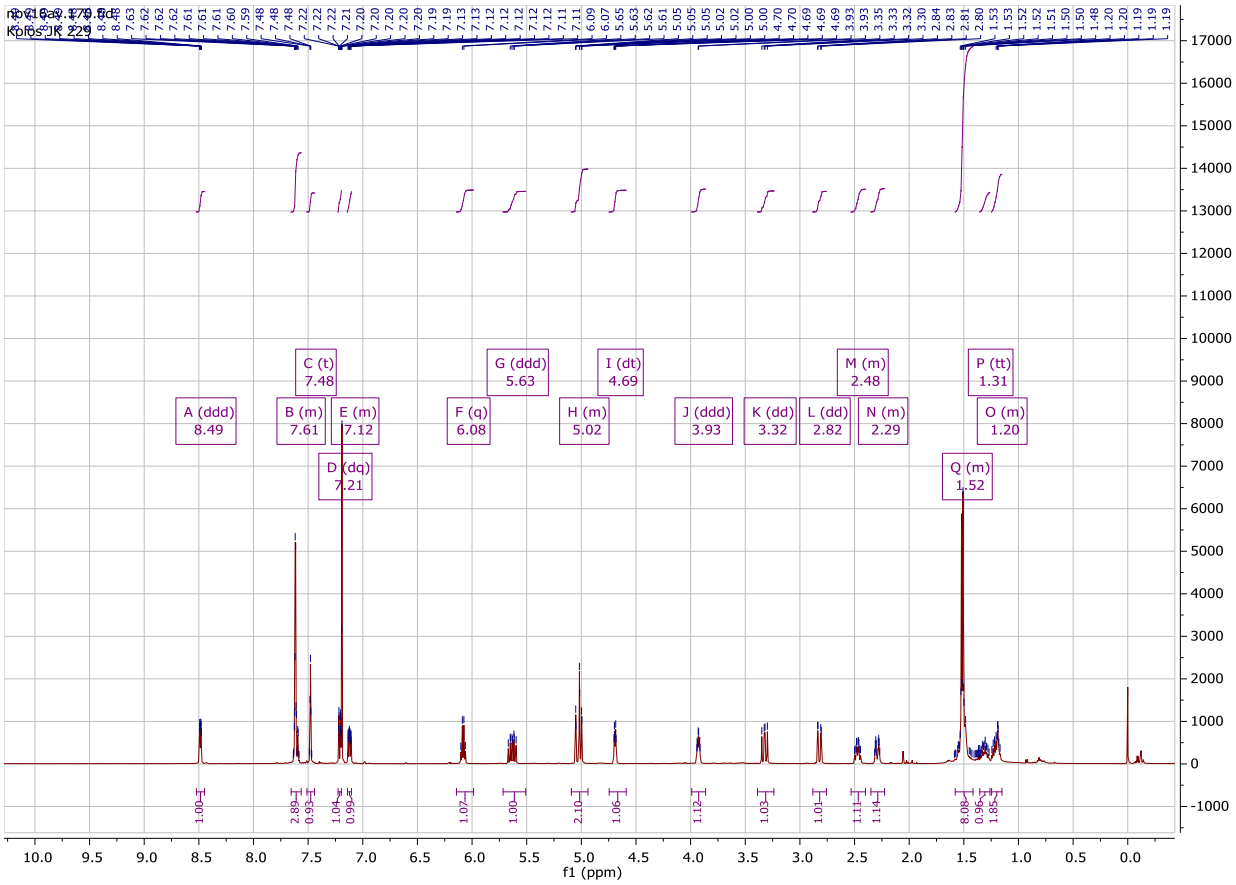


Figure S41. ^{1}H-NMR of compound **16$^{(S)\text{-}Me}$**.

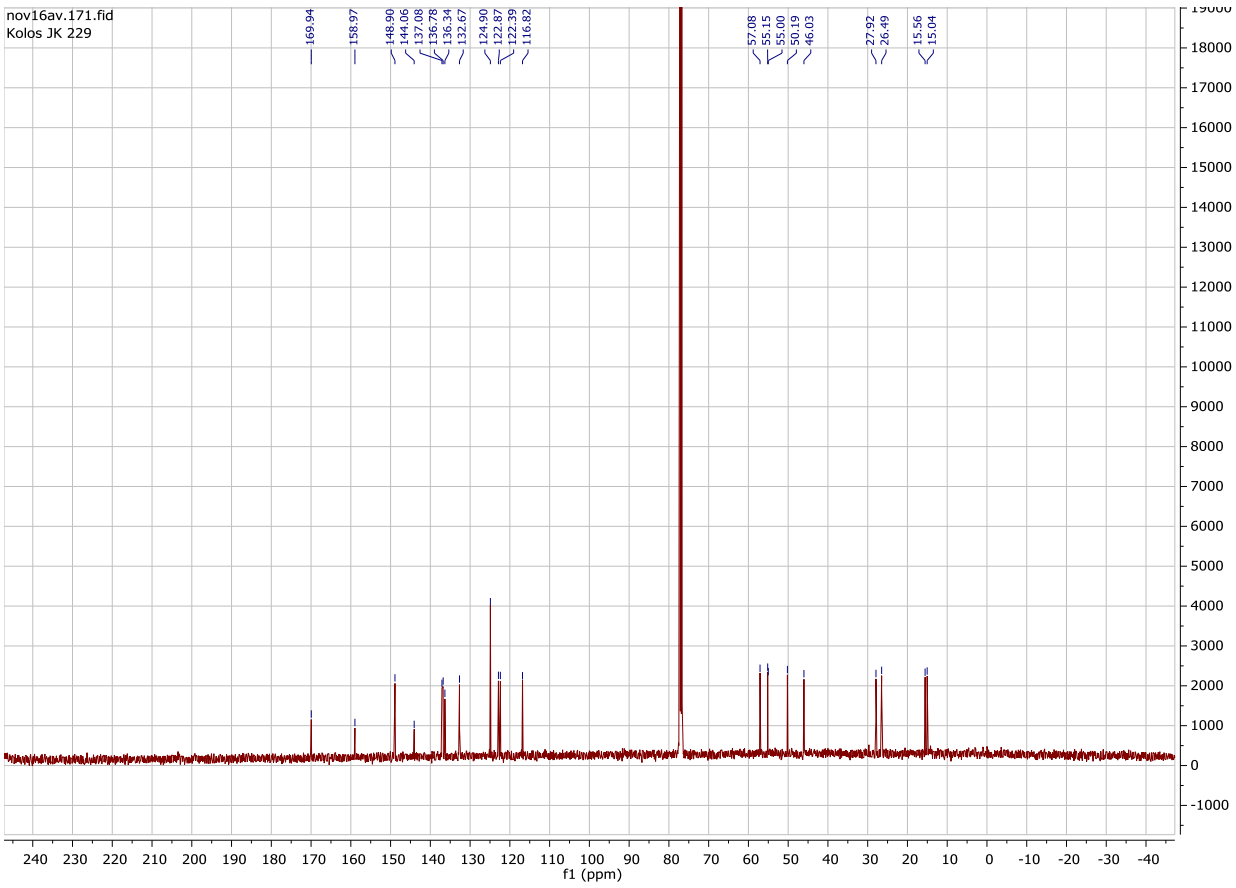


Figure S42. ^{13}C-NMR of compound **16$^{(S)\text{-}Me}$**.

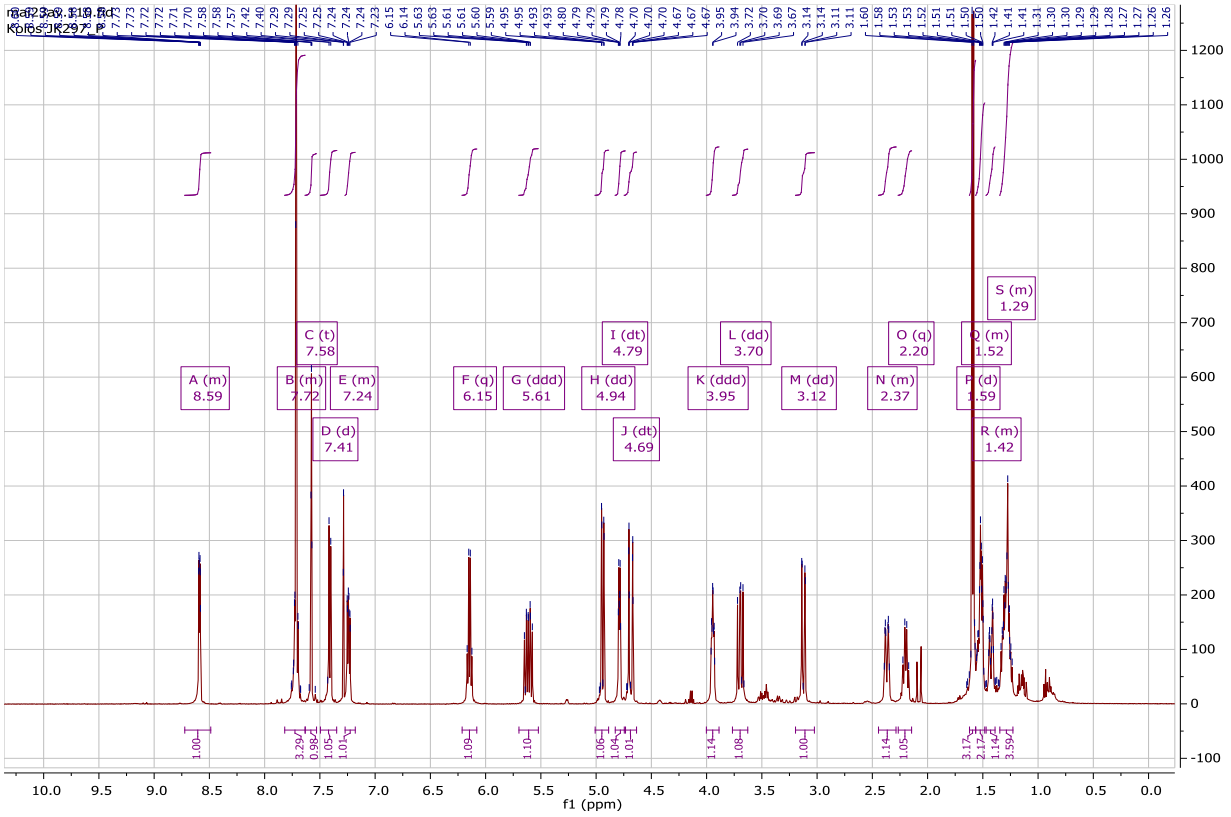


Figure S43. ^{1}H-NMR of compound **16$^{(R)\text{-}Me}$**.

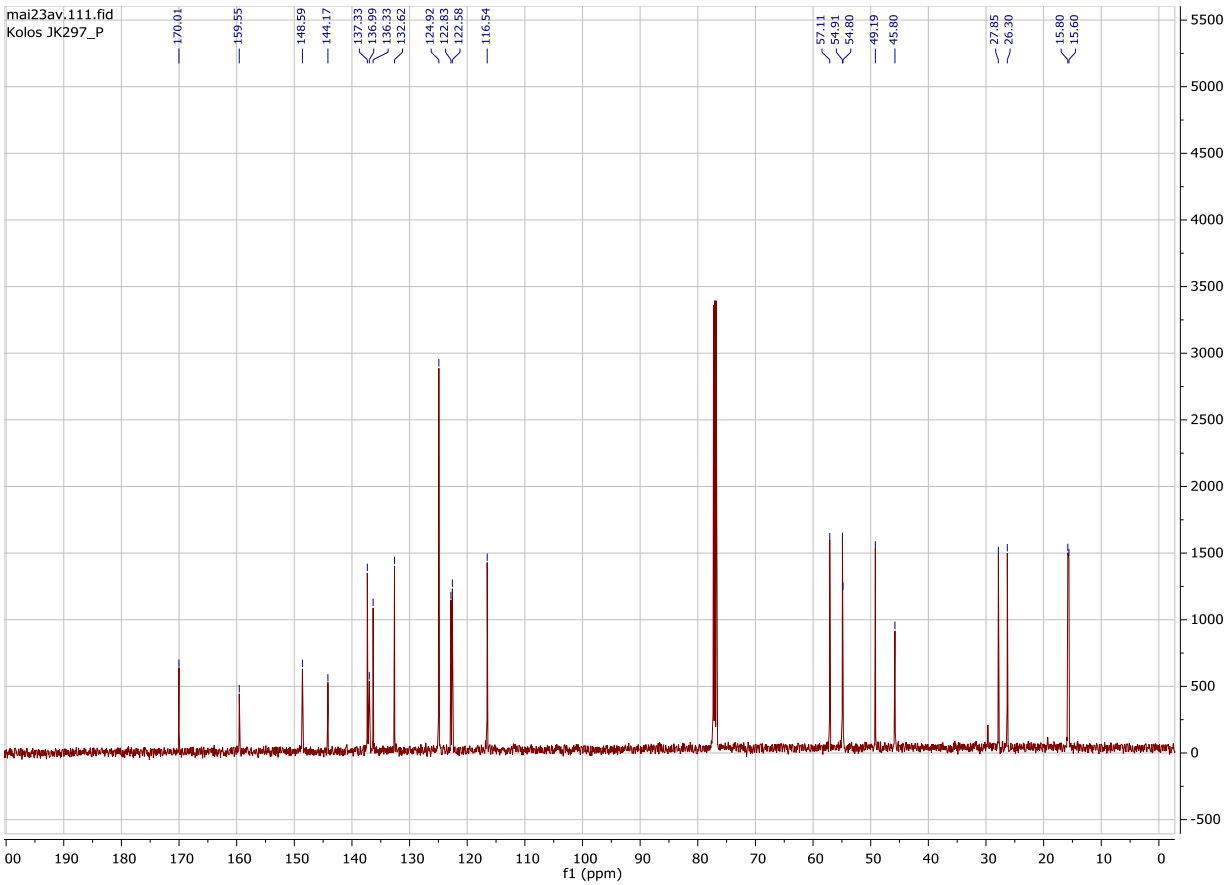


Figure S44. ^{13}C-NMR of compound **16$^{(R)\text{-}Me}$**.

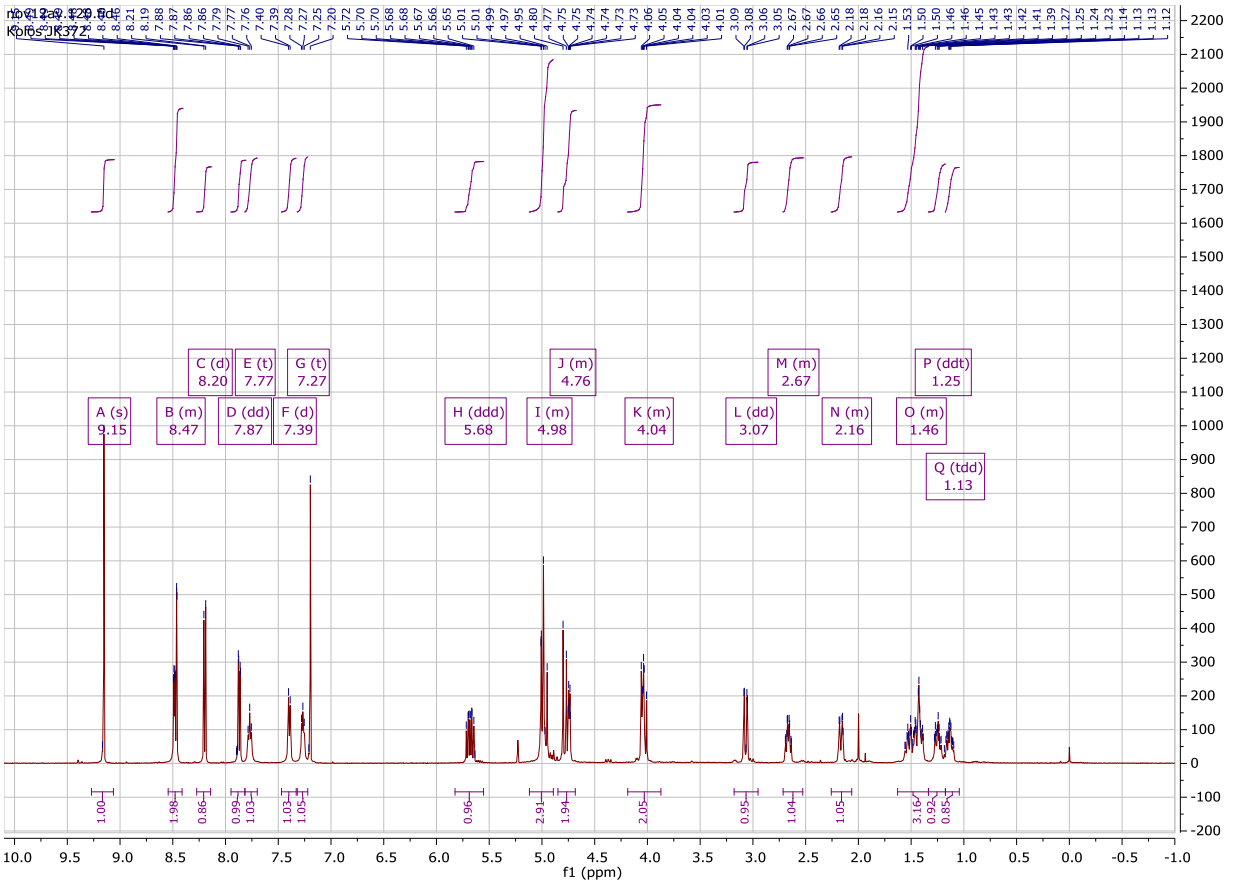


Figure S45. ^{1}H-NMR of compound **17**.

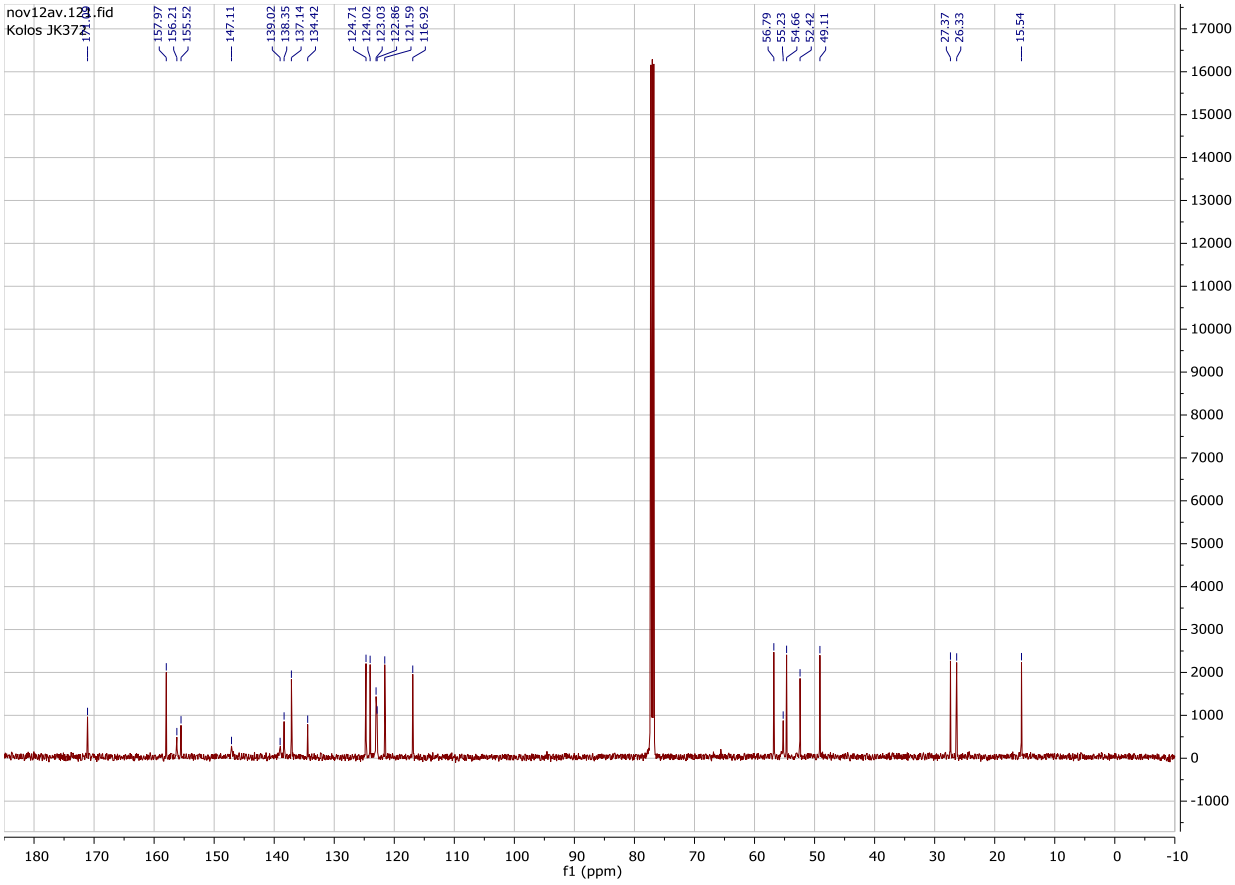


Figure S46. ^{13}C-NMR of compound **17**.

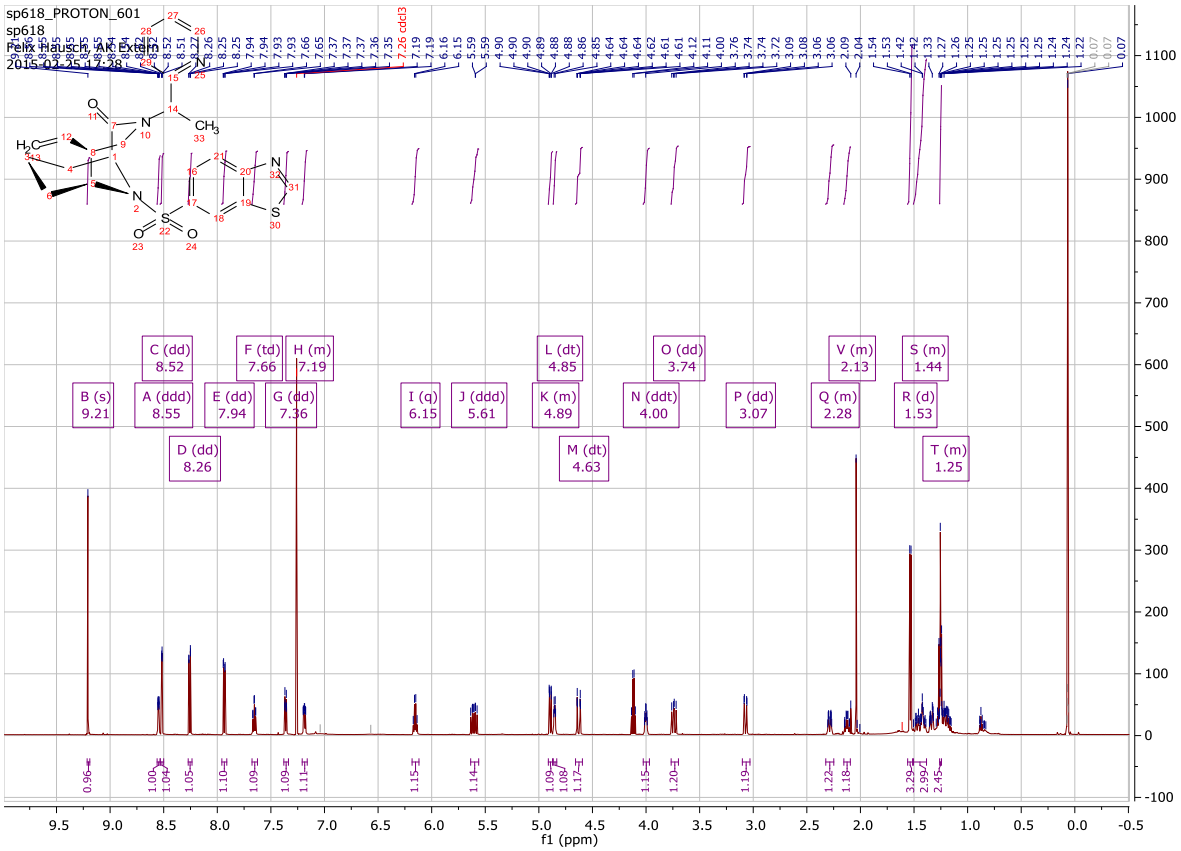


Figure S47. ^{1}H-NMR of compound **17$^{(R)\text{-}Me}$**.

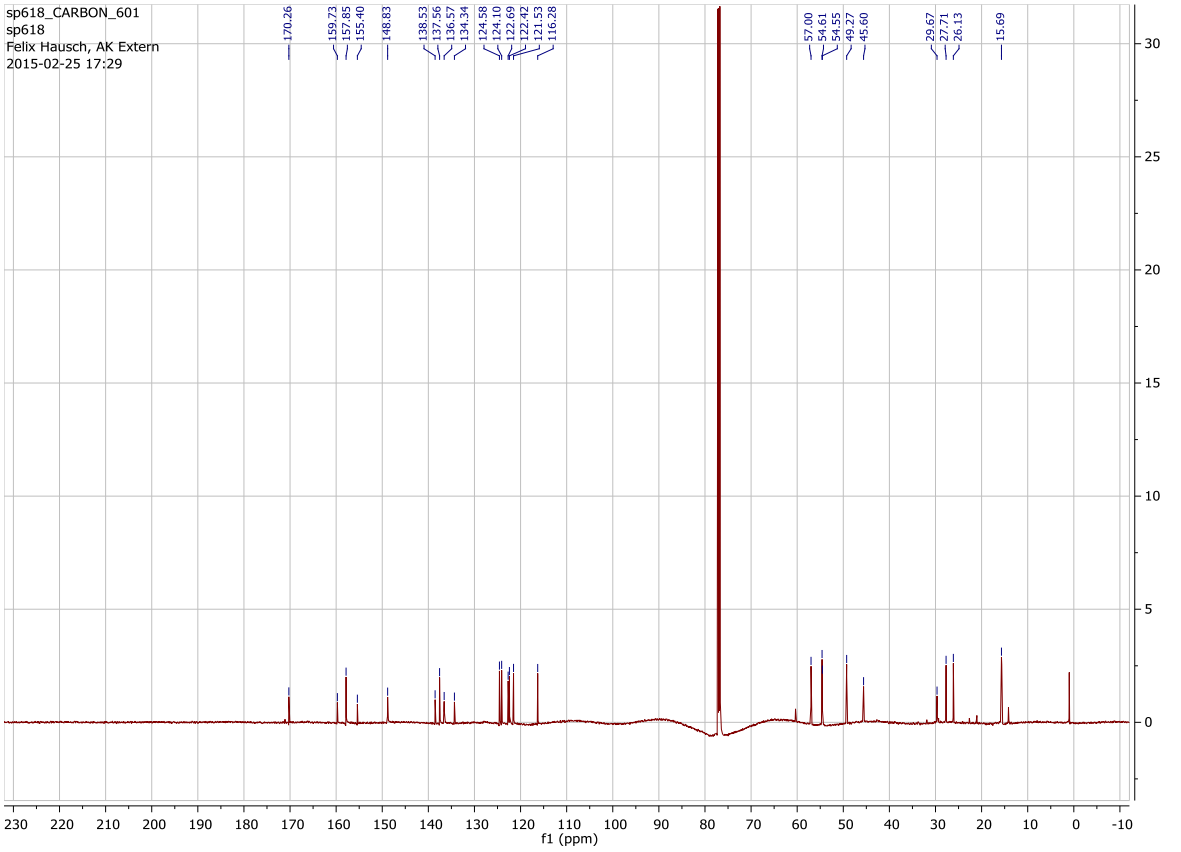


Figure S48. ^{13}C-NMR of compound **17$^{(R)\text{-}Me}$**.

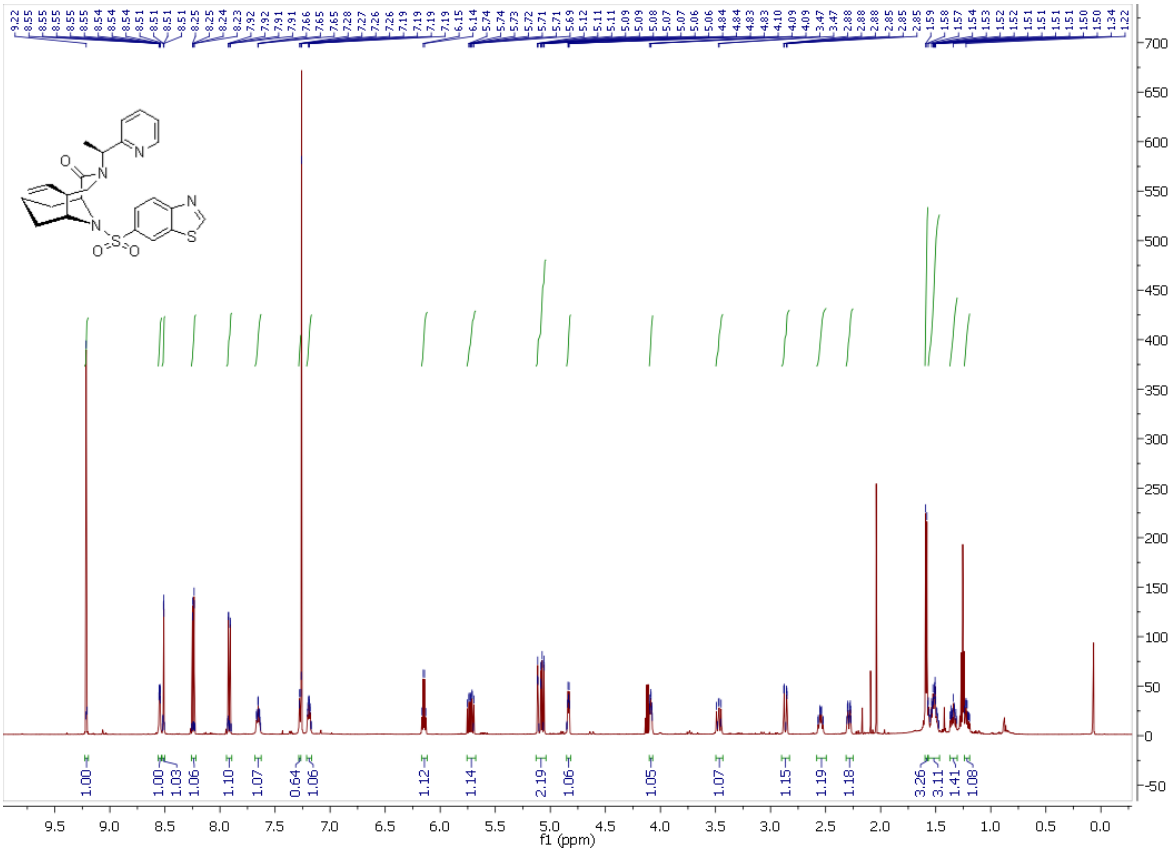


Figure S49. ^{1}H-NMR of compound **17$^{(S)\text{-}Me}$**.

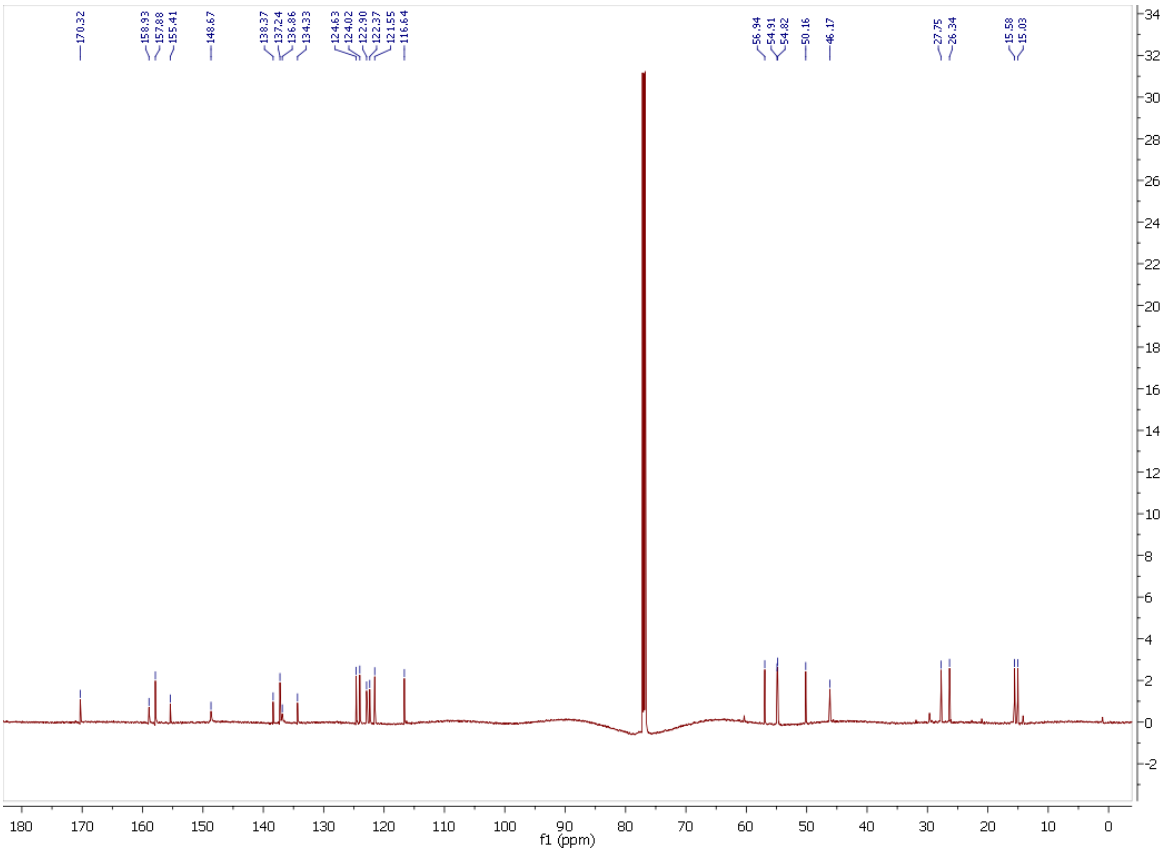


Figure S50. ^{13}C-NMR of compound **17$^{(S)\text{-}Me}$**.

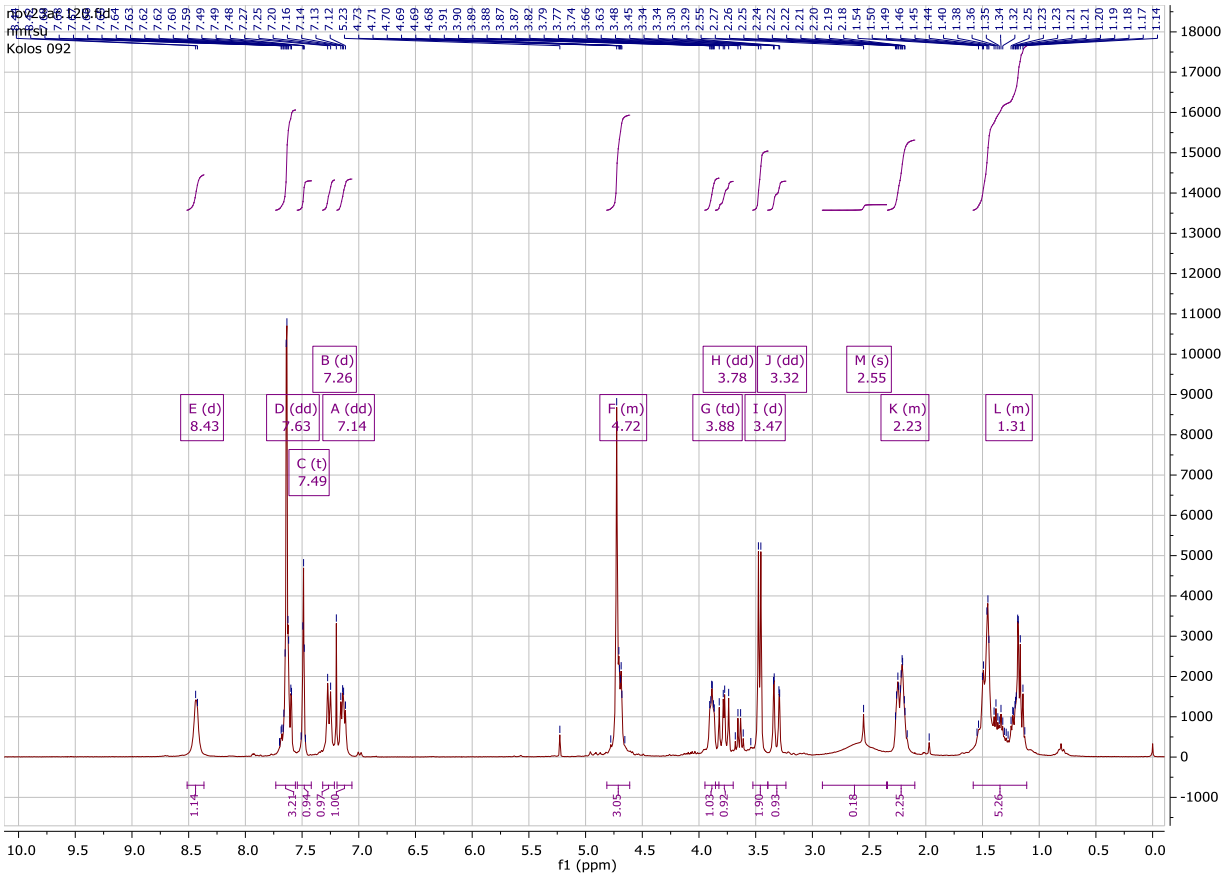


Figure S51. ^{1}H-NMR of compound **18**.

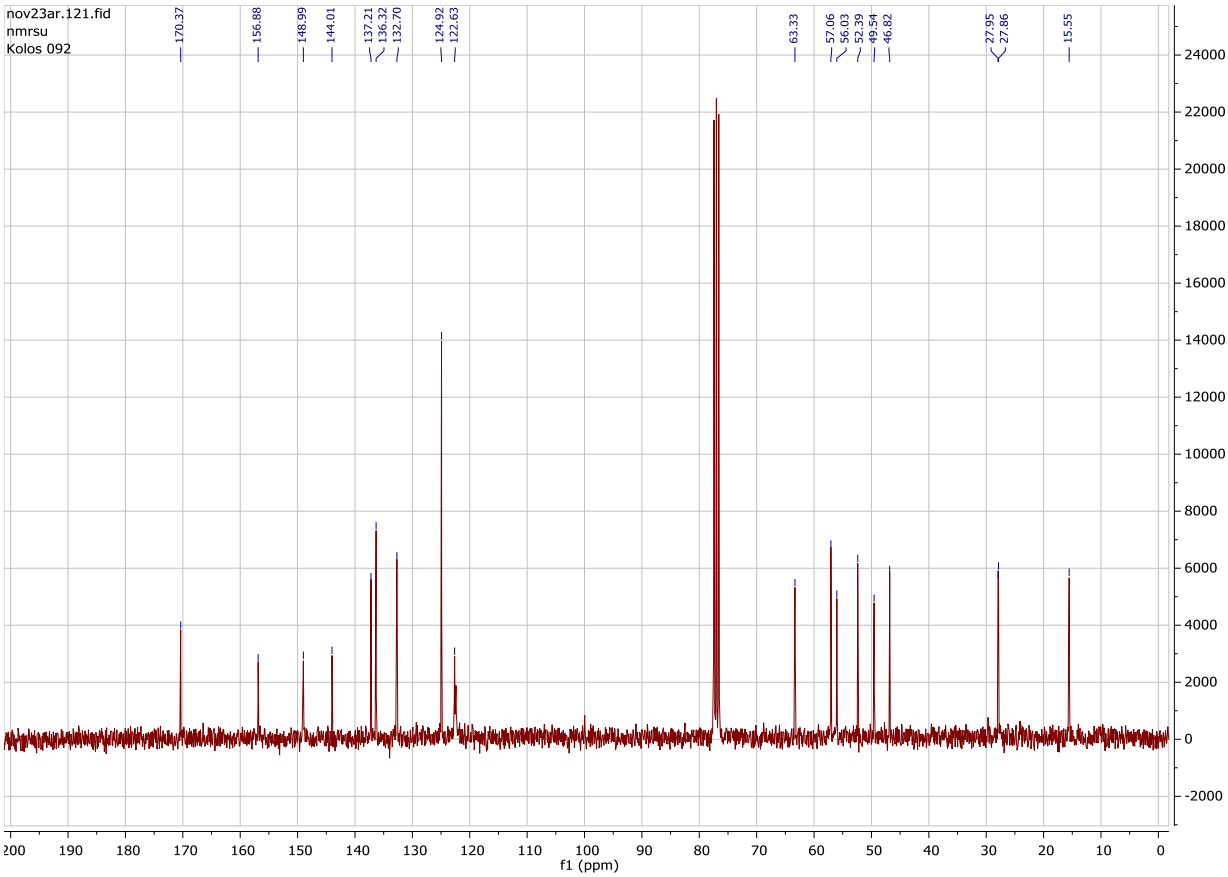


Figure S52. ^{13}C-NMR of compound **18**.

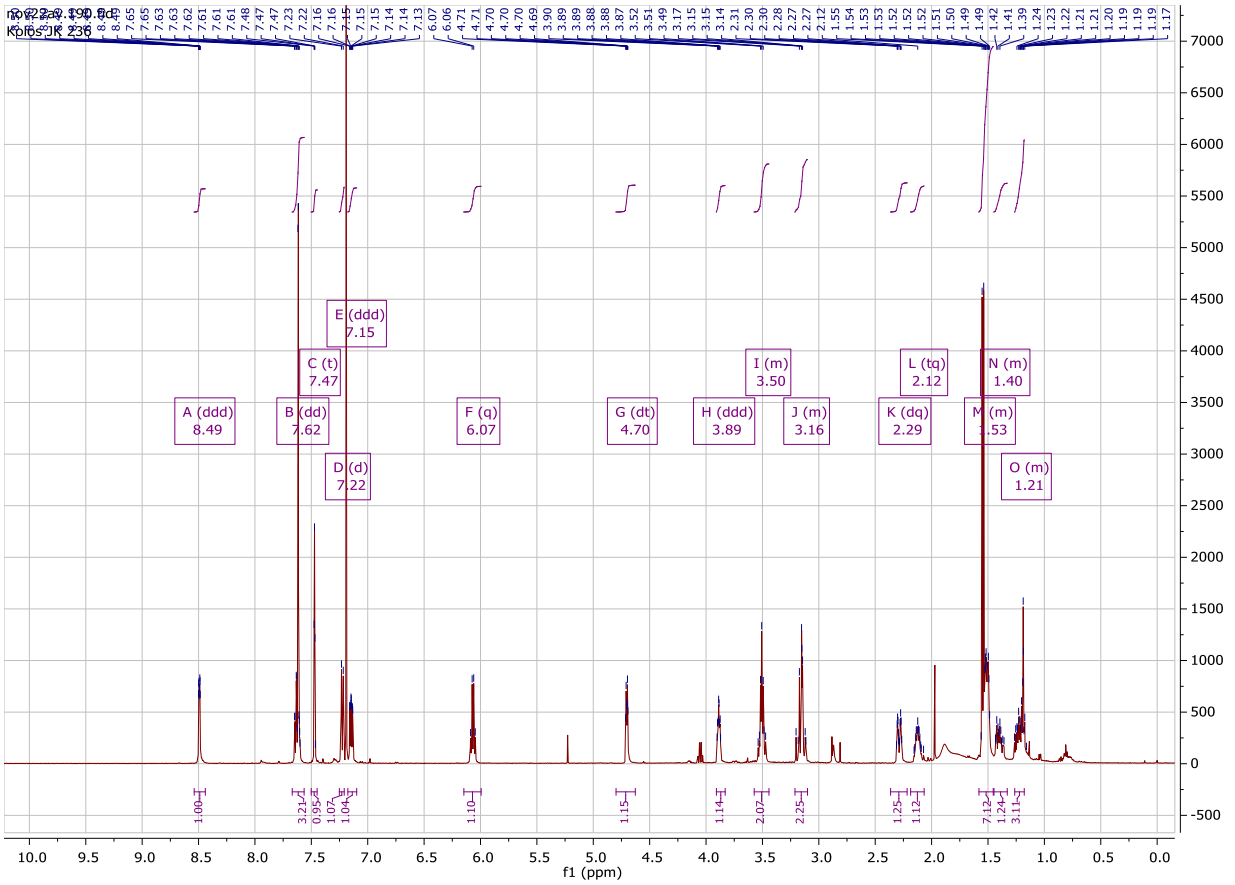


Figure S53. ^{1}H-NMR of compound **18$^{(S)\text{-}Me}$**.

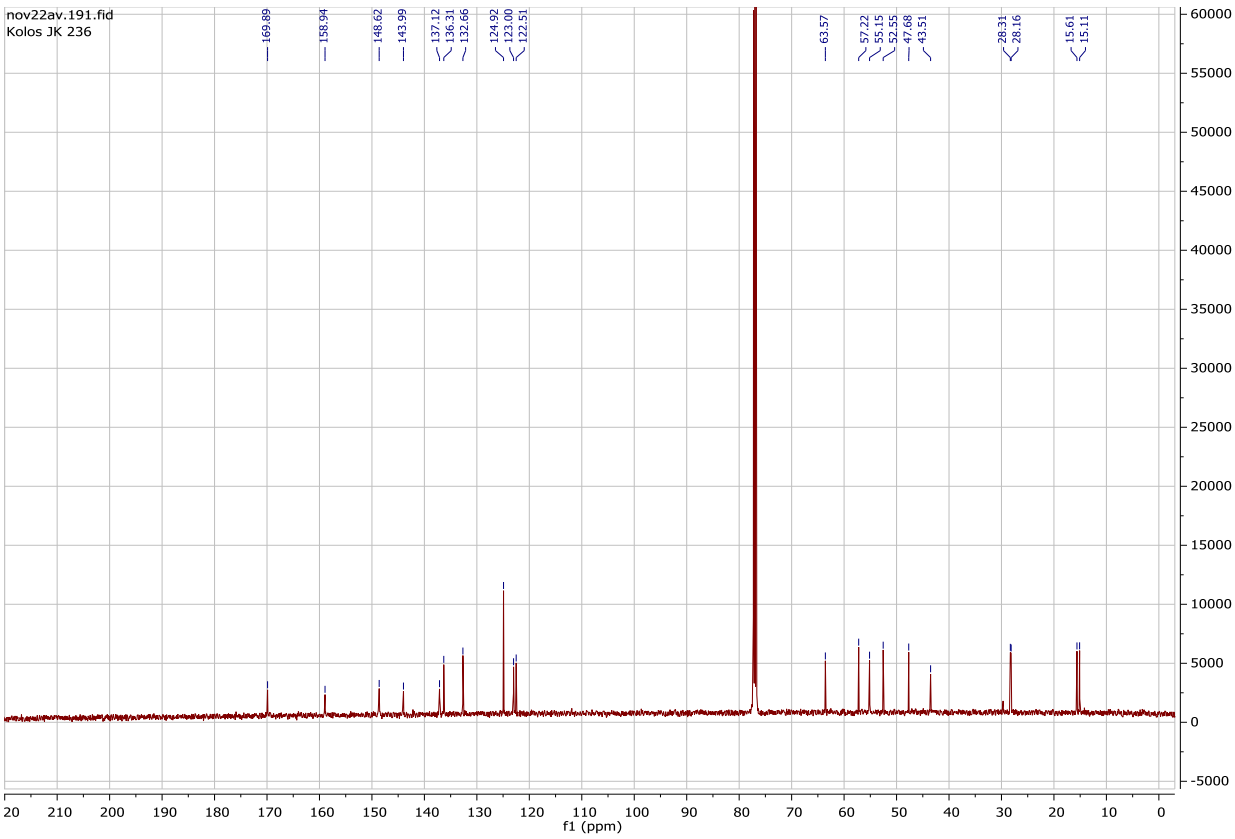


Figure S54. ^{13}C-NMR of compound **18$^{(S)\text{-}Me}$**.

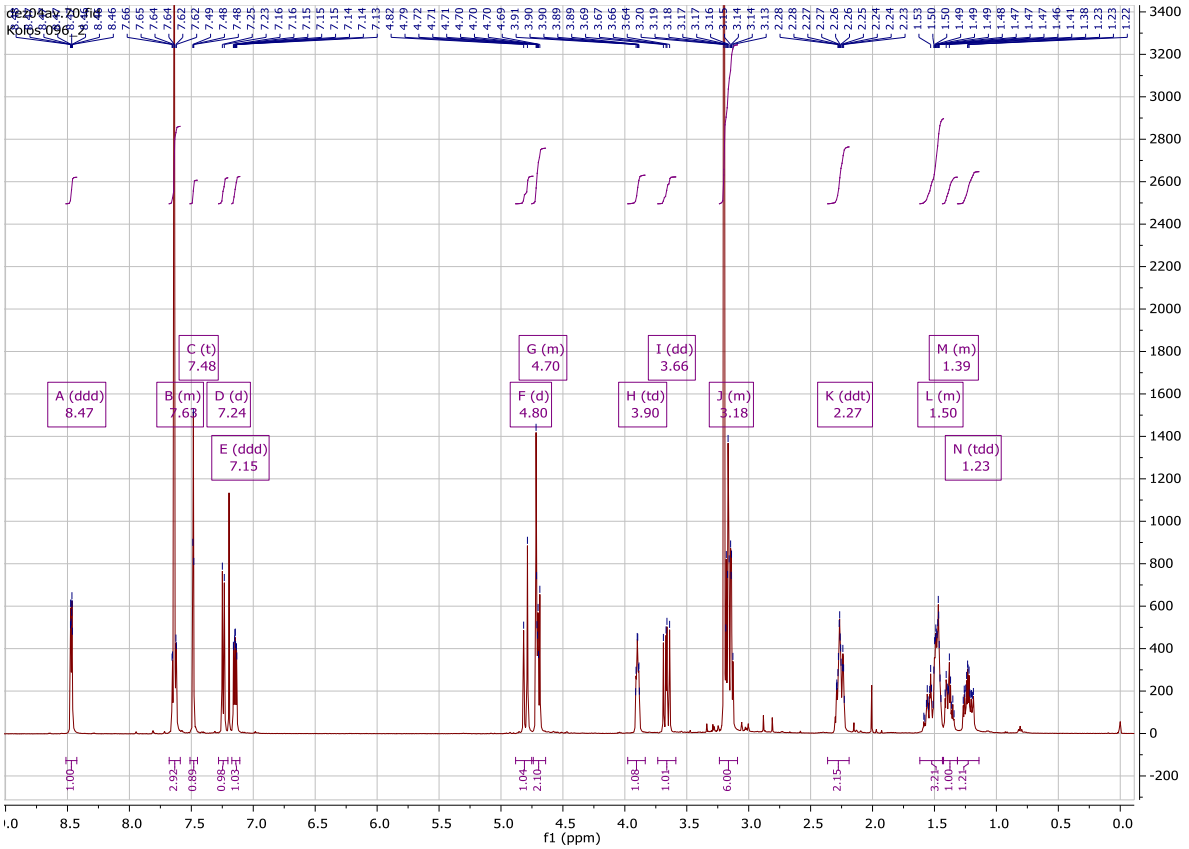


Figure S55. ^{1}H-NMR of compound **19**.

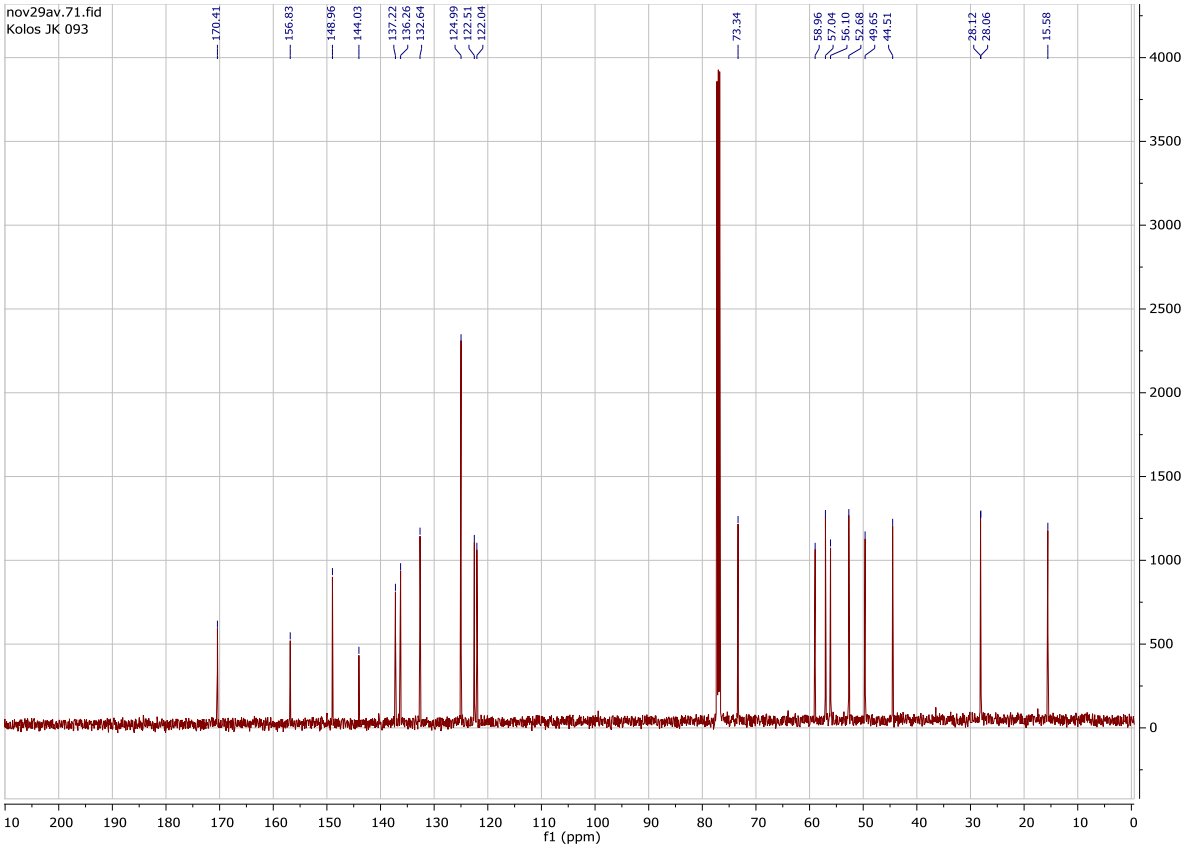


Figure S56. ^{13}C-NMR of compound **19**.

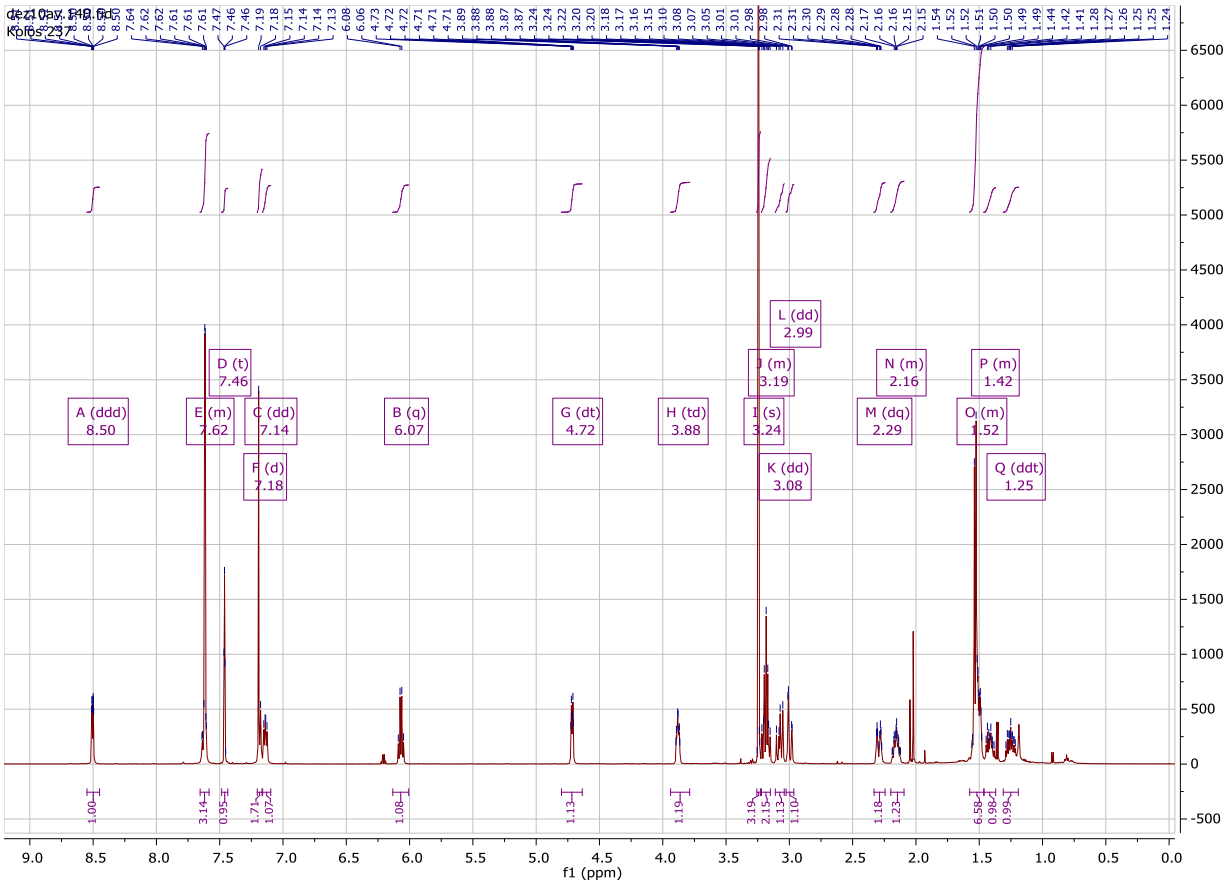


Figure S57. ^{1}H-NMR of compound **19$^{(S)\text{-}Me}$**.

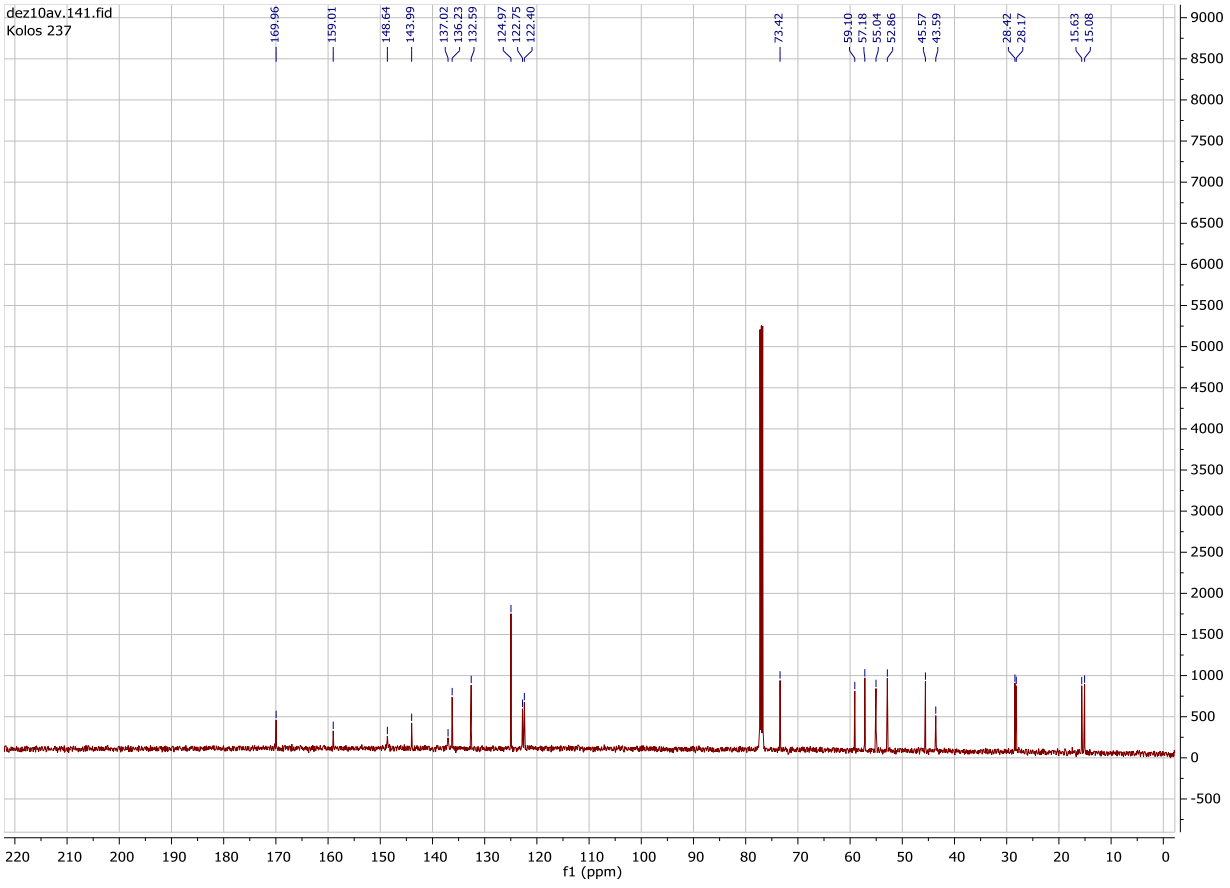


Figure S58. ^{13}C-NMR of compound **19$^{(S)\text{-}Me}$**.

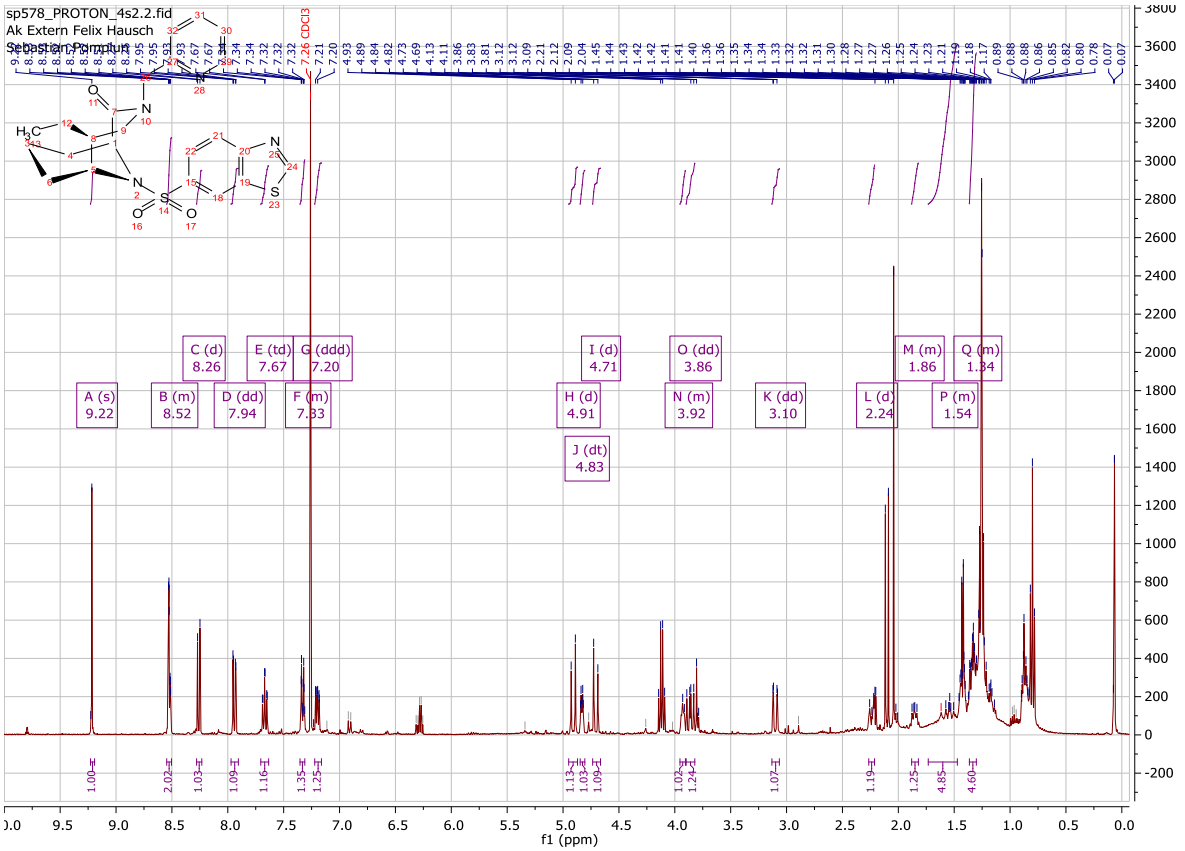


Figure S59. ^{1}H-NMR of compound **20**.

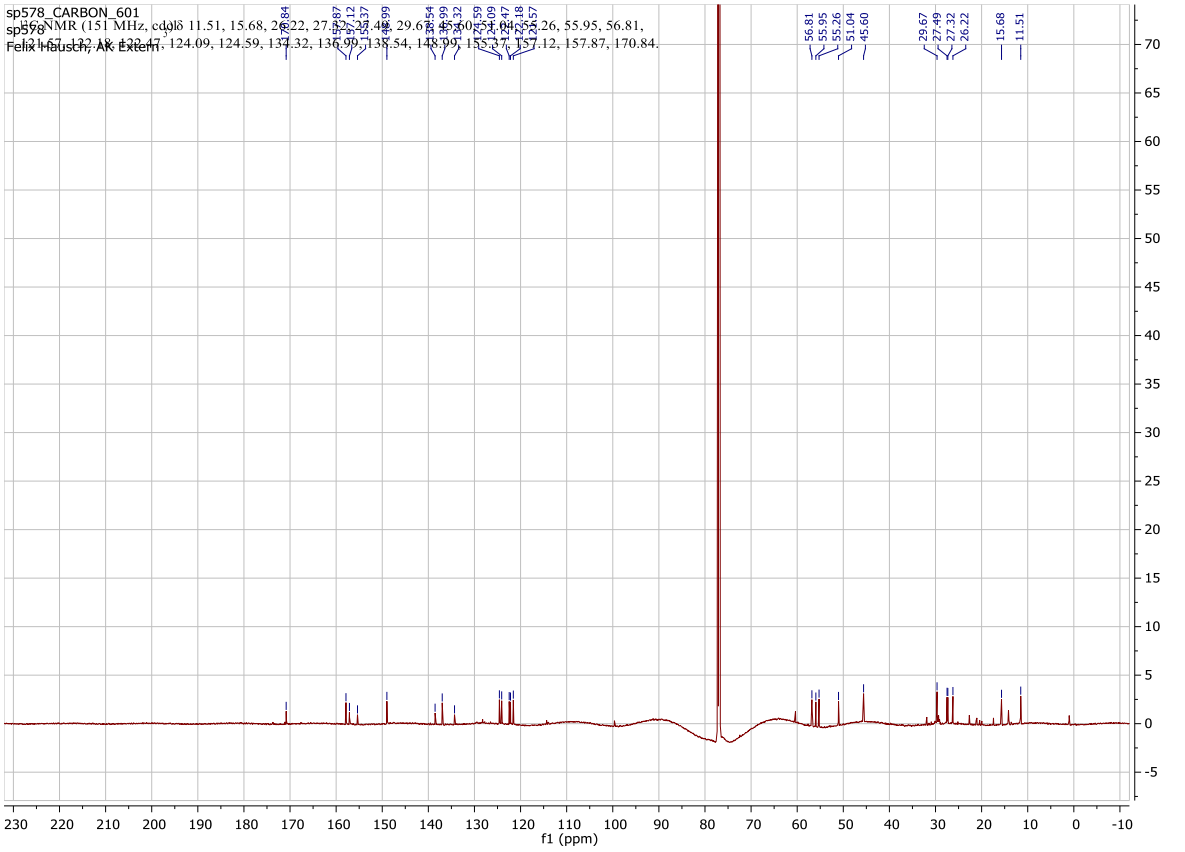


Figure S60. ^{13}C-NMR of compound **20**.

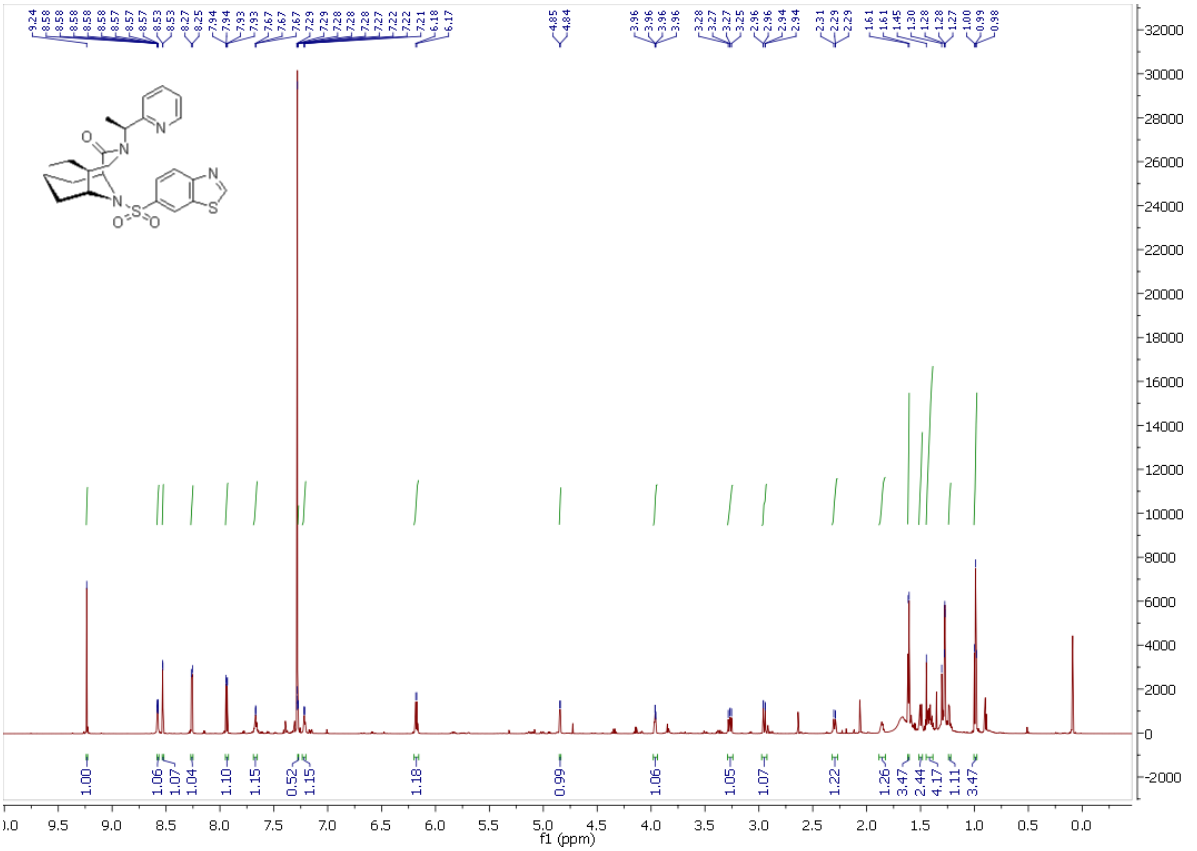


Figure S61. ^{1}H-NMR of compound **20$^{(S)\text{-}Me}$**.

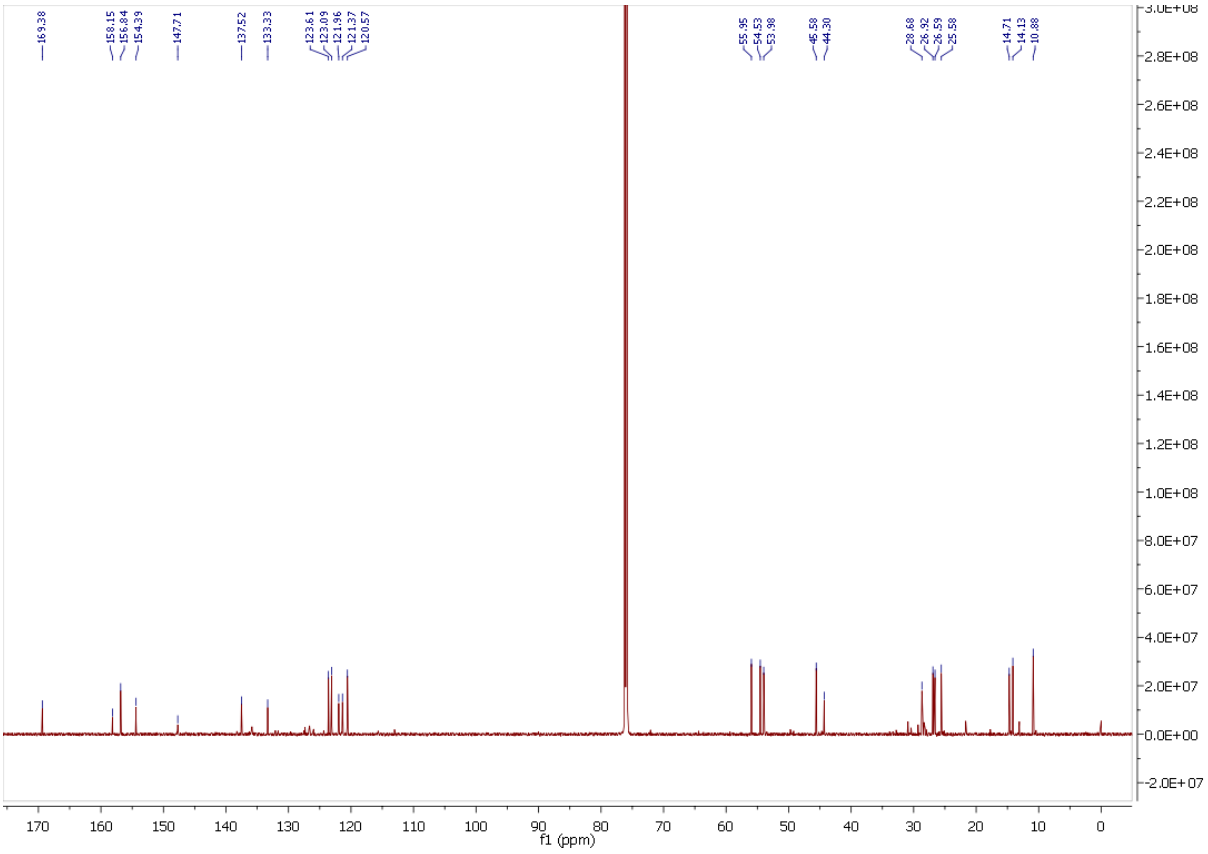


Figure S62. ^{13}C-NMR of compound **20$^{(S)\text{-}Me}$**.

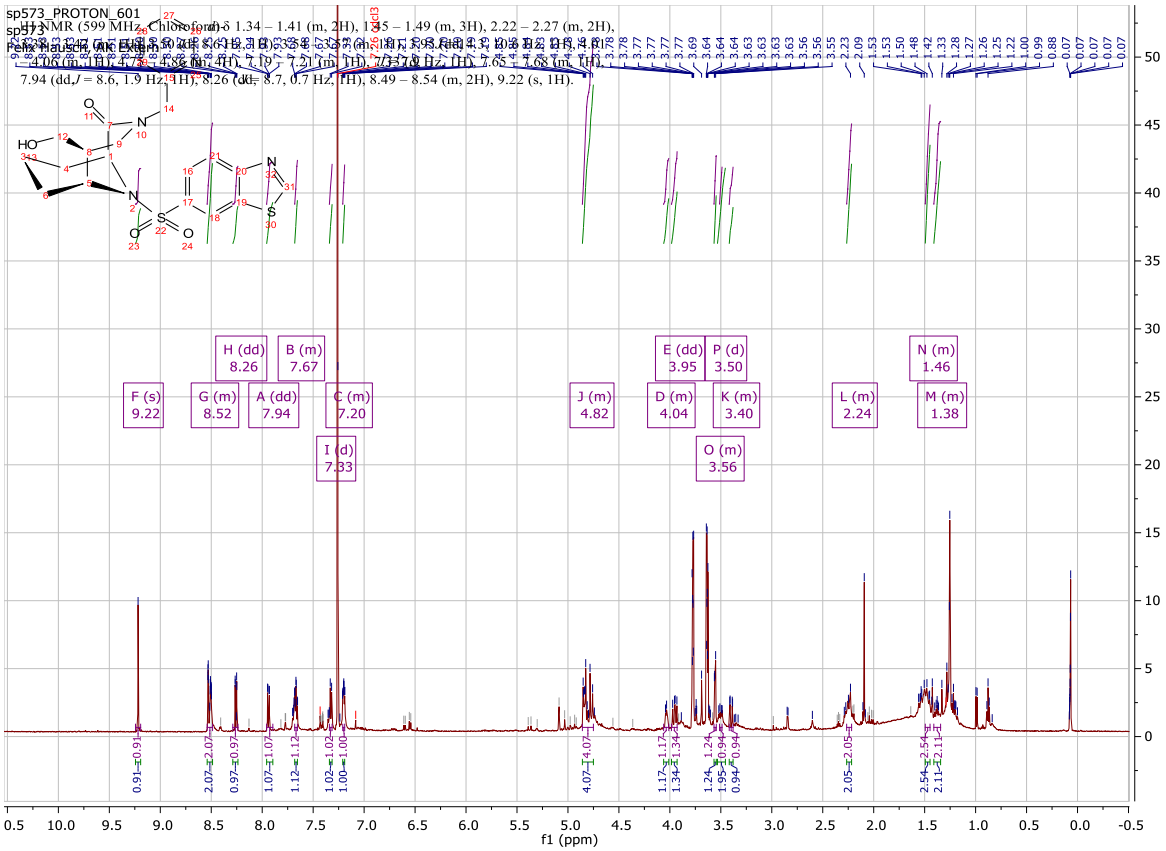


Figure S63. ^{1}H-NMR of compound **21**.

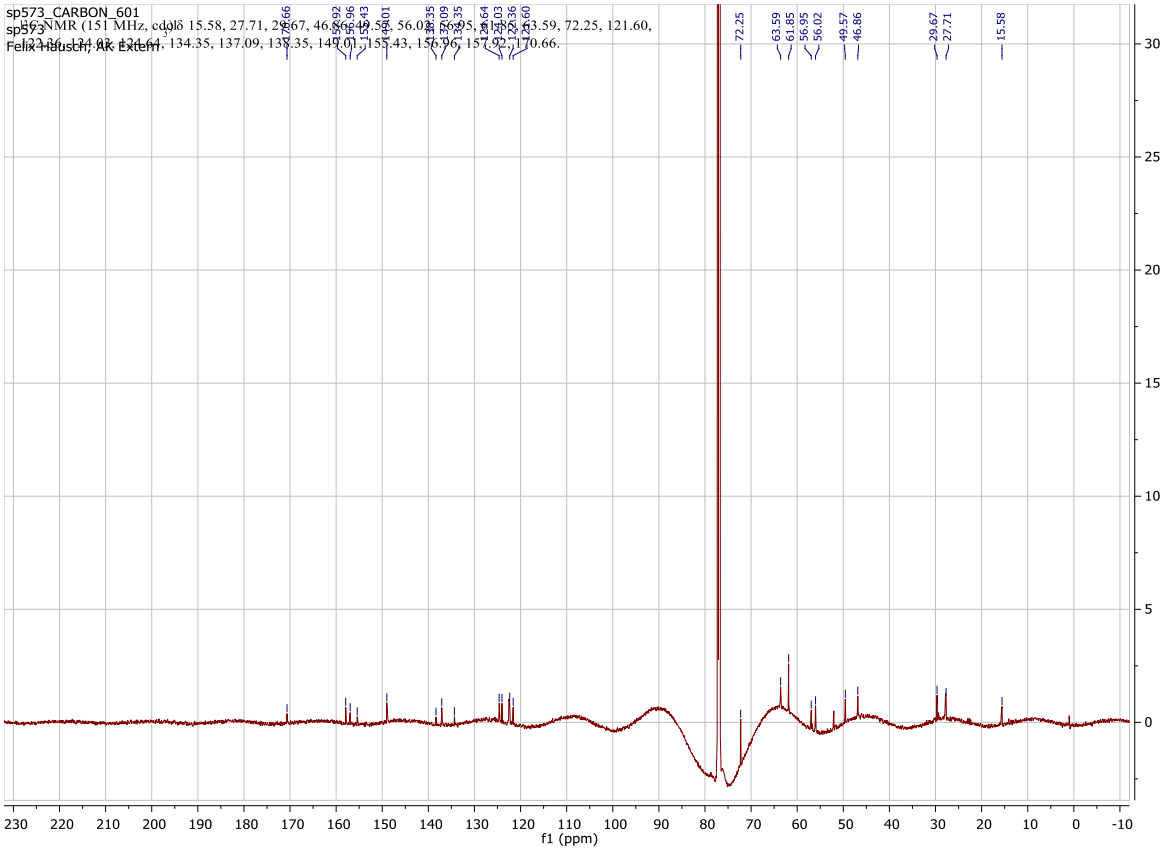


Figure S64. ^{13}C-NMR of compound **21**.

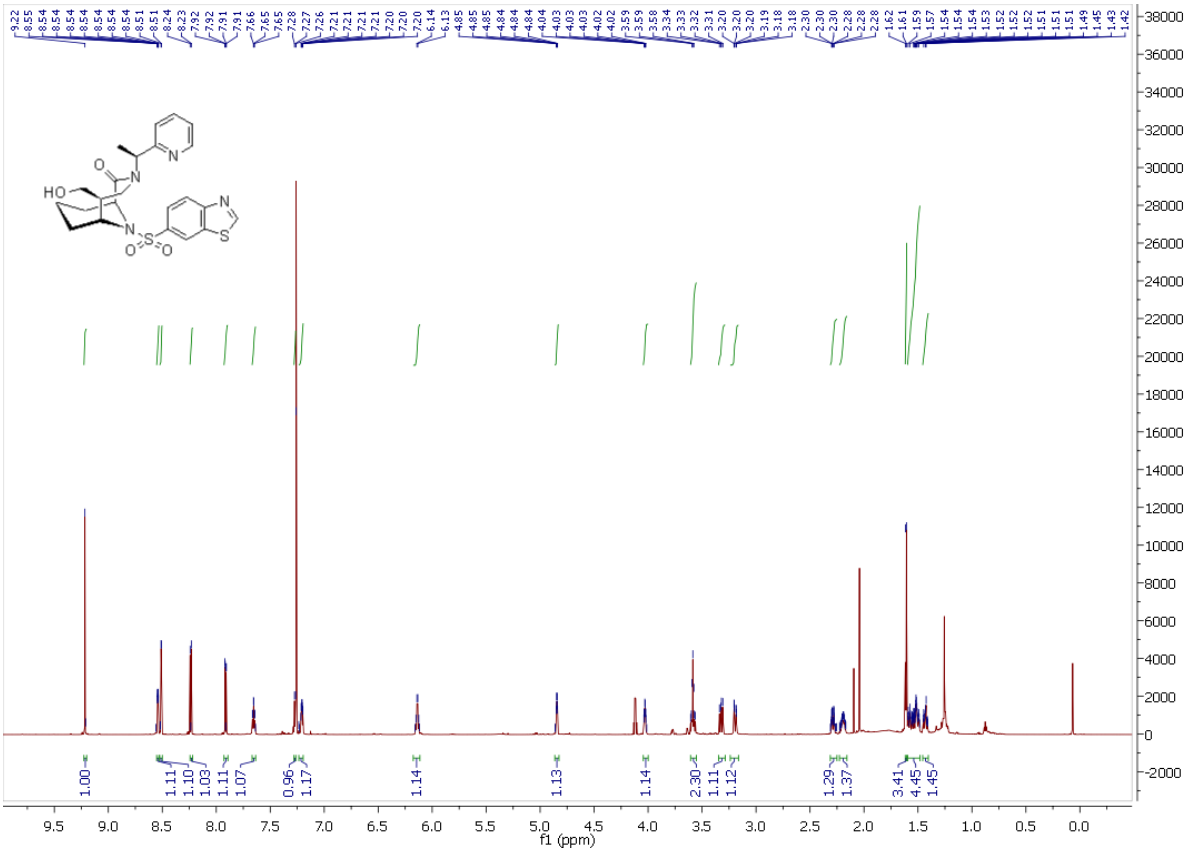


Figure S65. ^{1}H-NMR of compound **21$^{(S)-Me}$**.

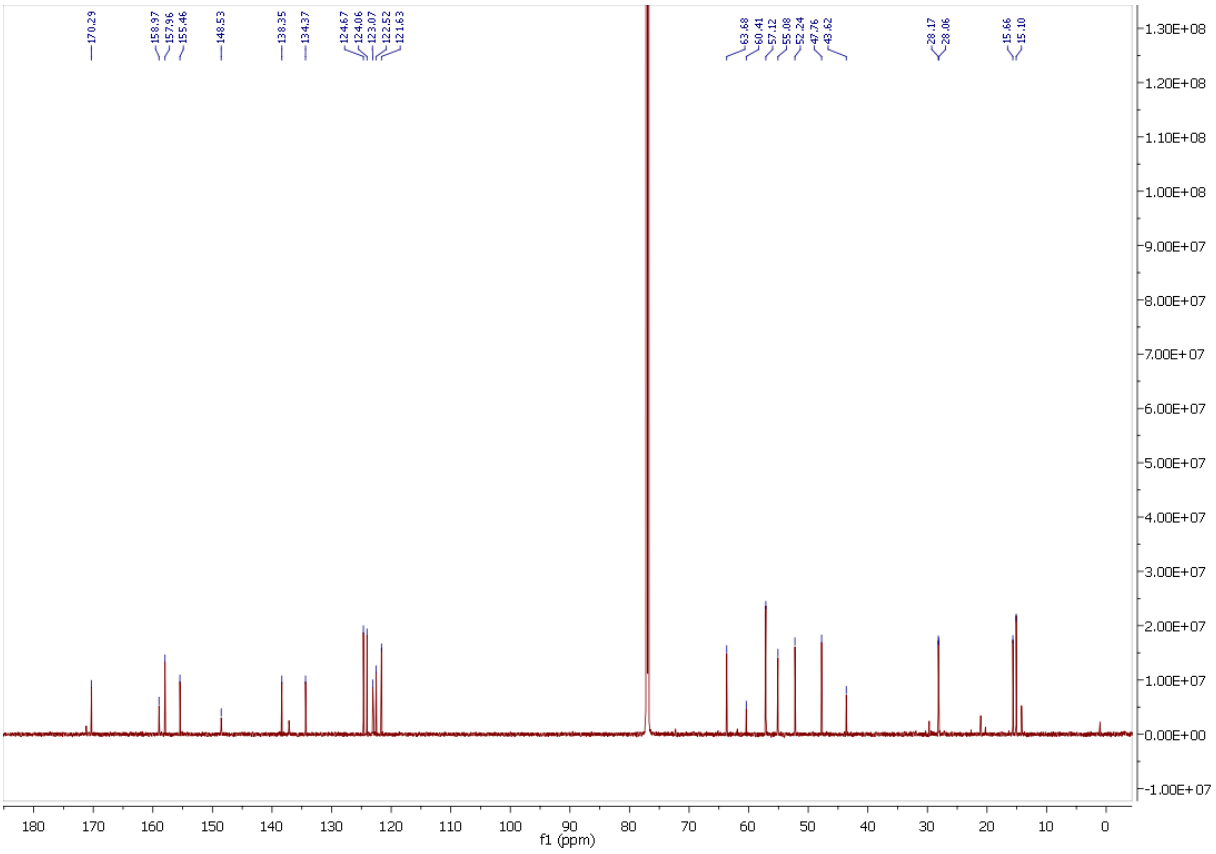


Figure S66. ^{13}C-NMR of compound **21$^{(S)-Me}$**.

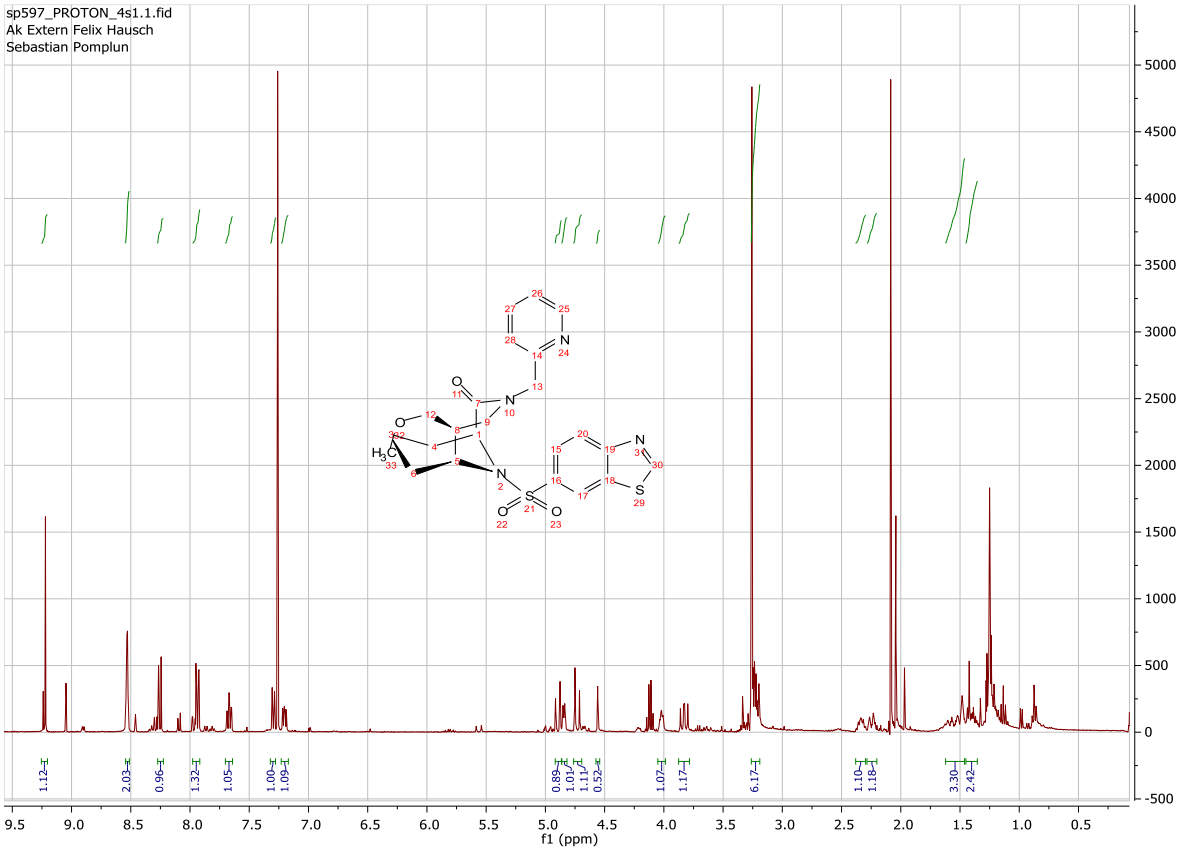


Figure S67. ^{1}H-NMR of compound **22**.

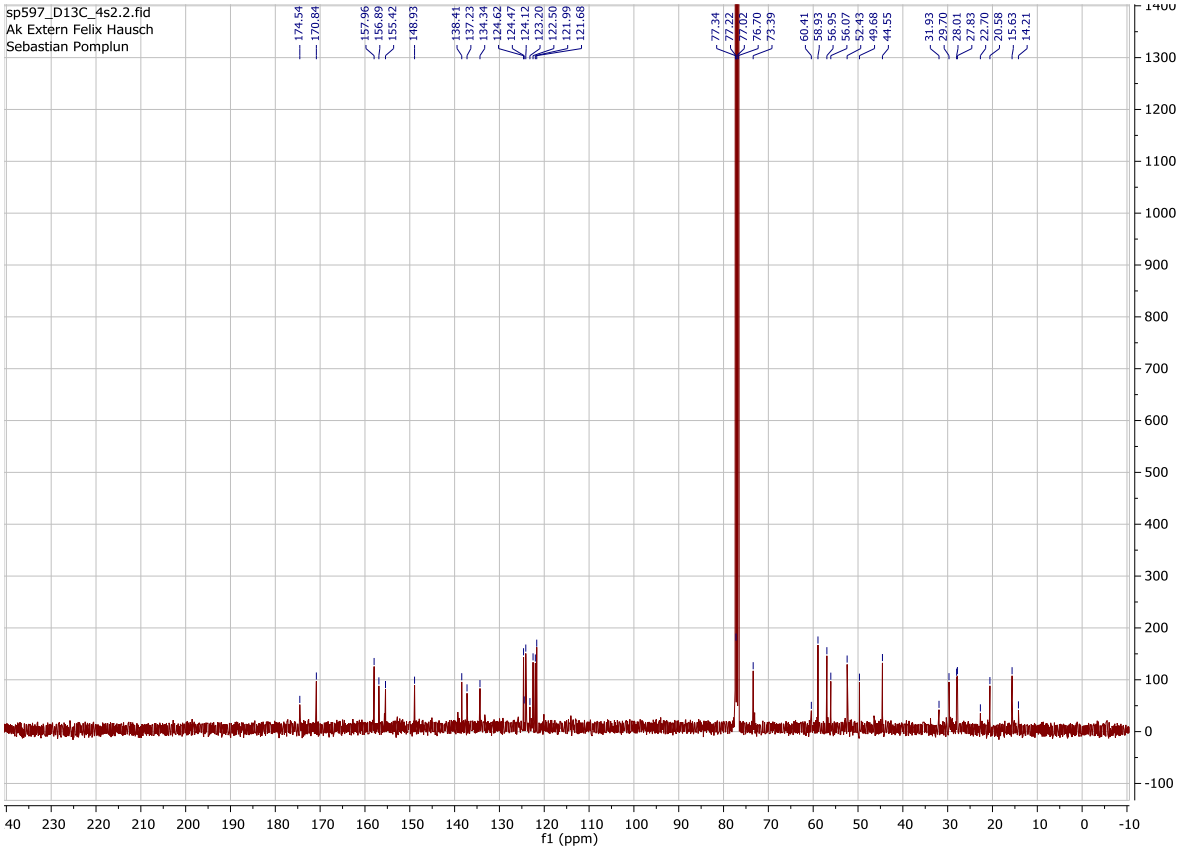


Figure S68. ^{13}C-NMR of compound **22**.

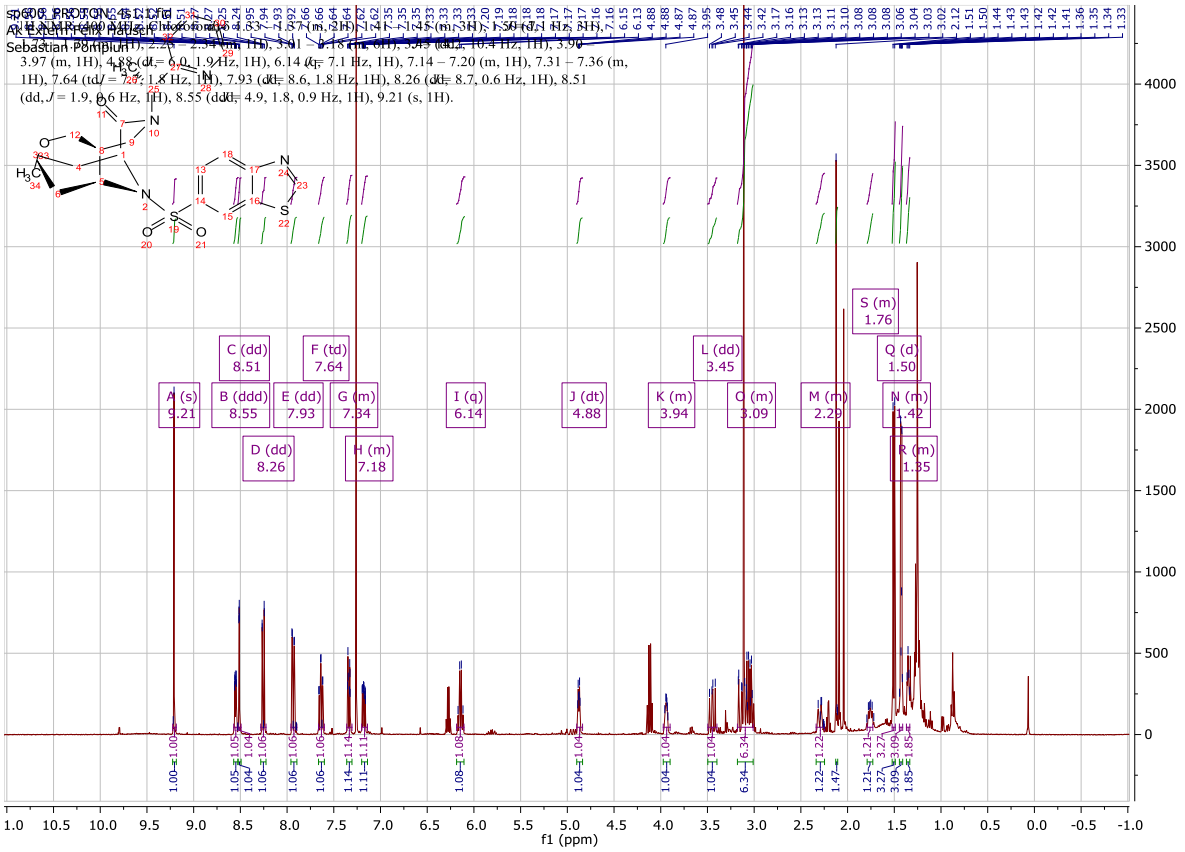


Figure S69. ^{1}H-NMR of compound **22$^{(R)\text{-}Me}$**.

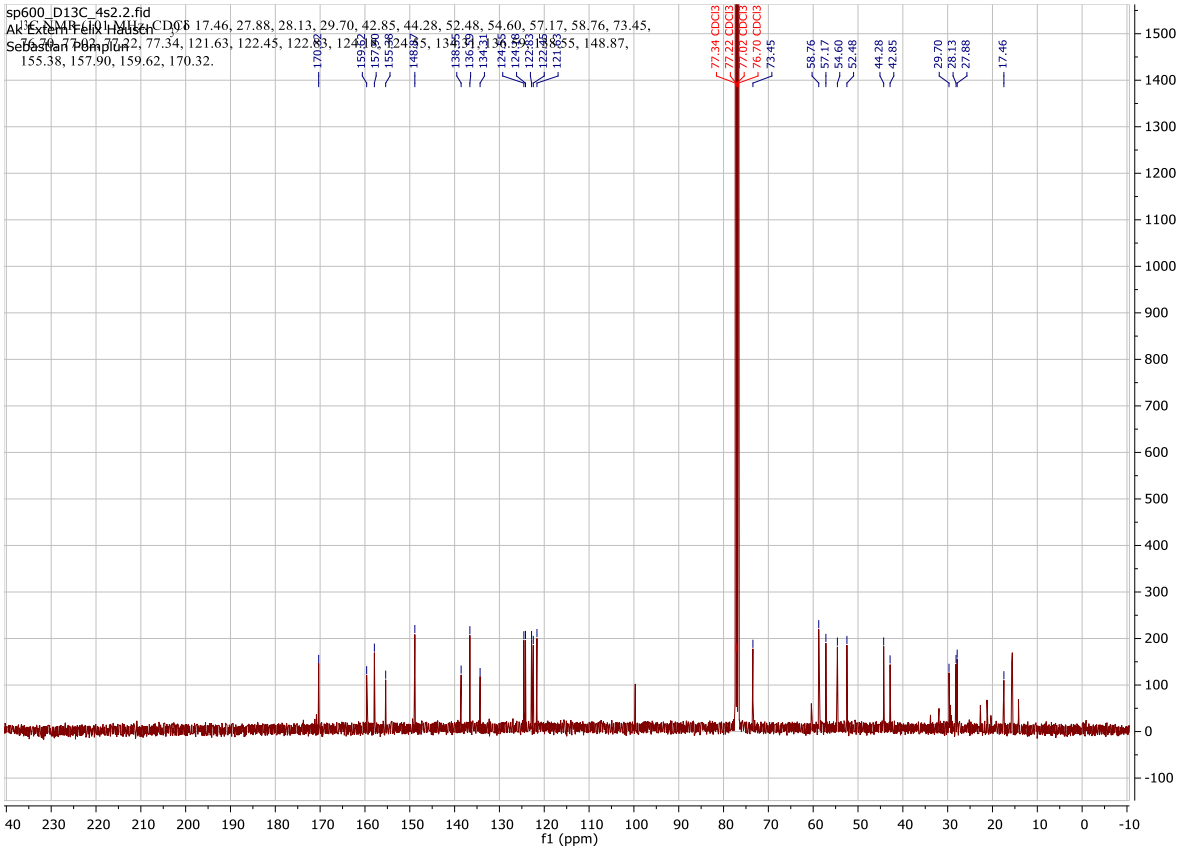


Figure S70. ^{13}C-NMR of compound **22$^{(R)\text{-}Me}$**.

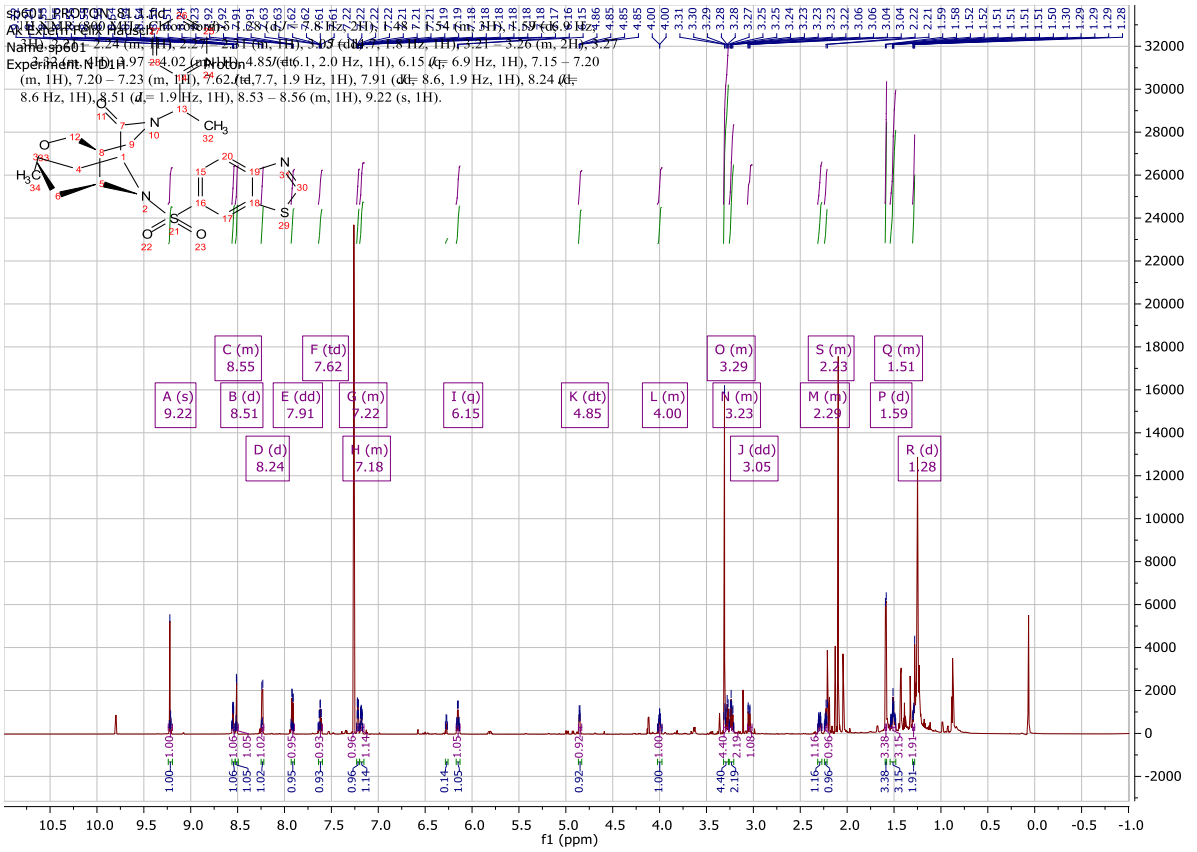


Figure S71. ^{1}H-NMR of compound **22$^{(S)\text{-}Me}$**.

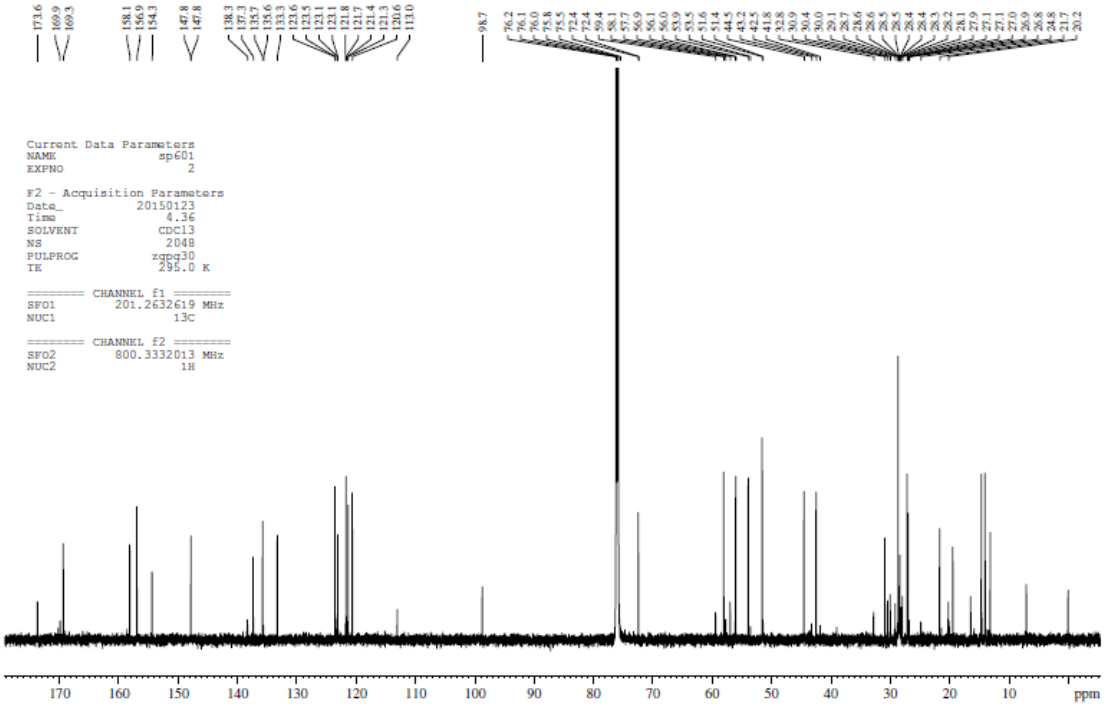


Figure S72. ^{13}C-NMR of compound **22$^{(S)\text{-}Me}$**.

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