Deconstructing Protein Binding of Sulfonamides and Sulfonamide Analogs

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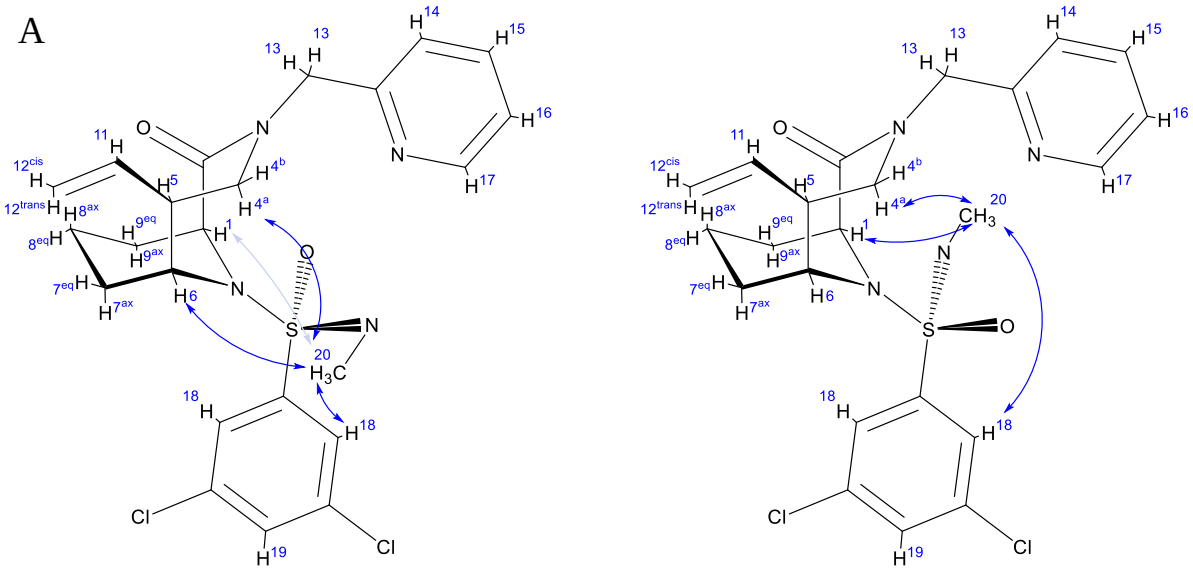
A



6a **6b**

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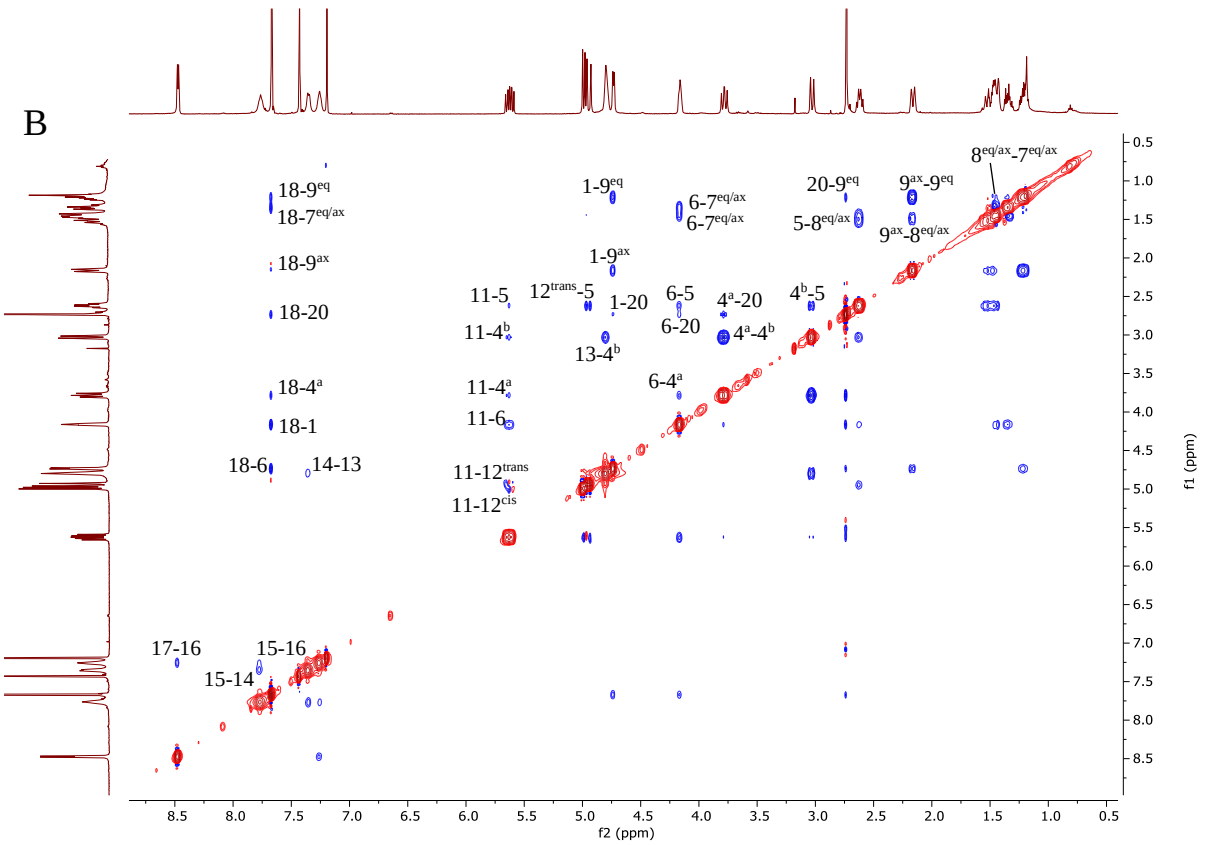
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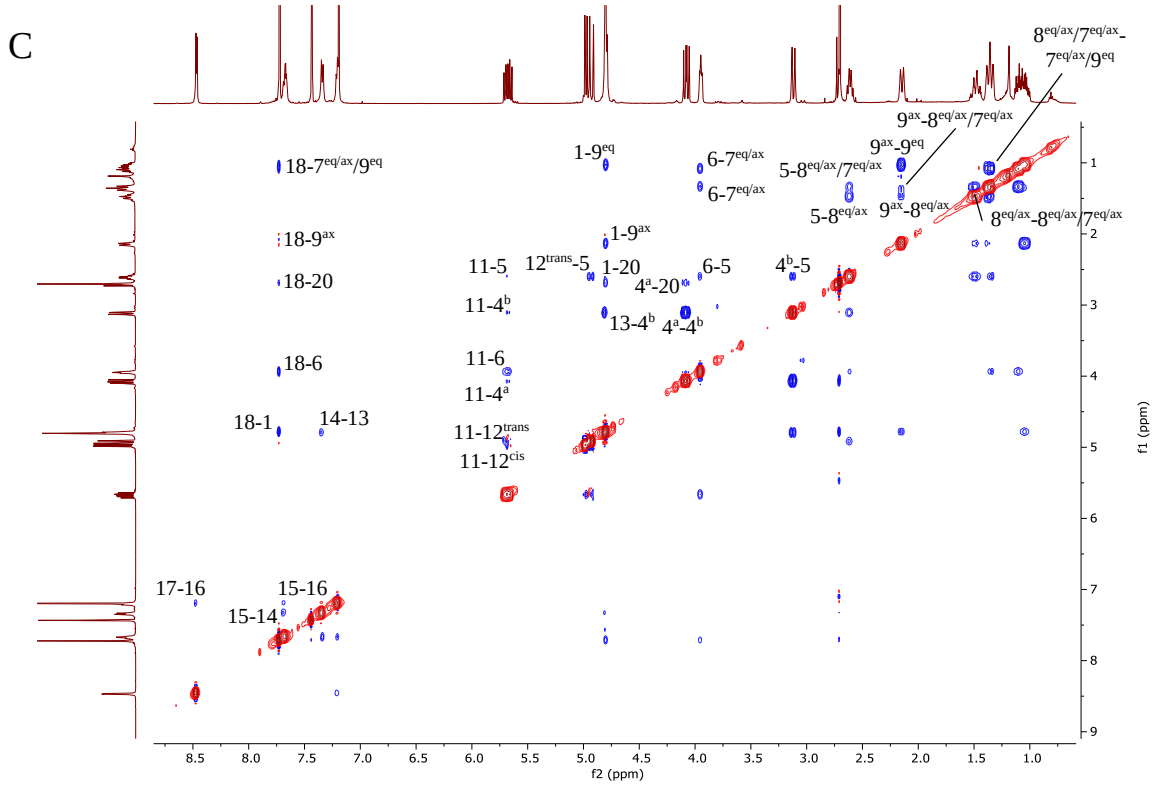
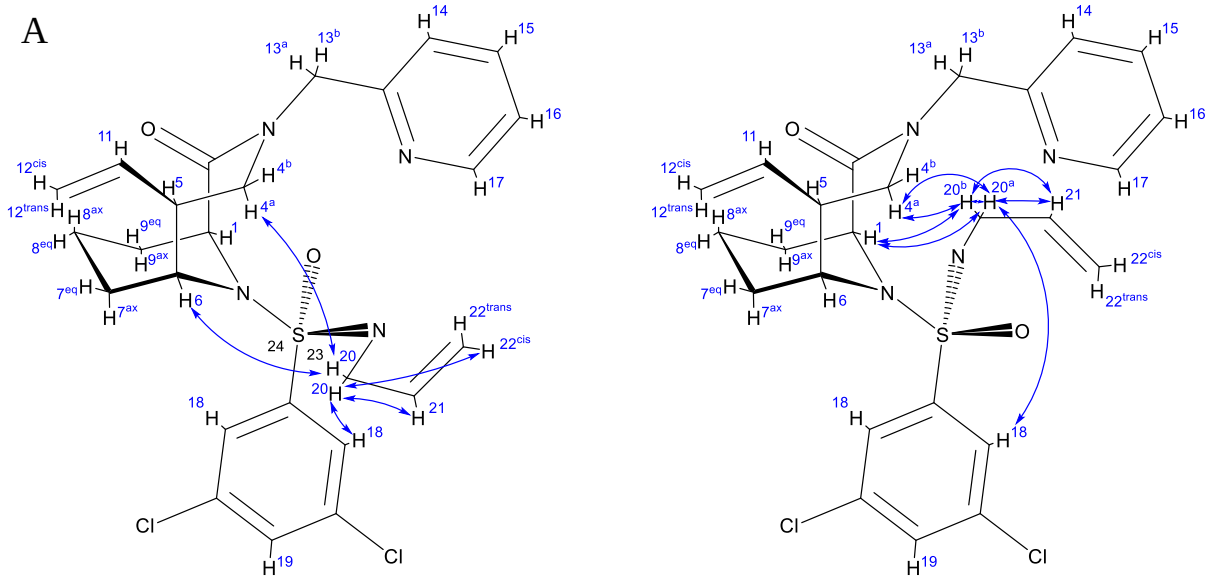


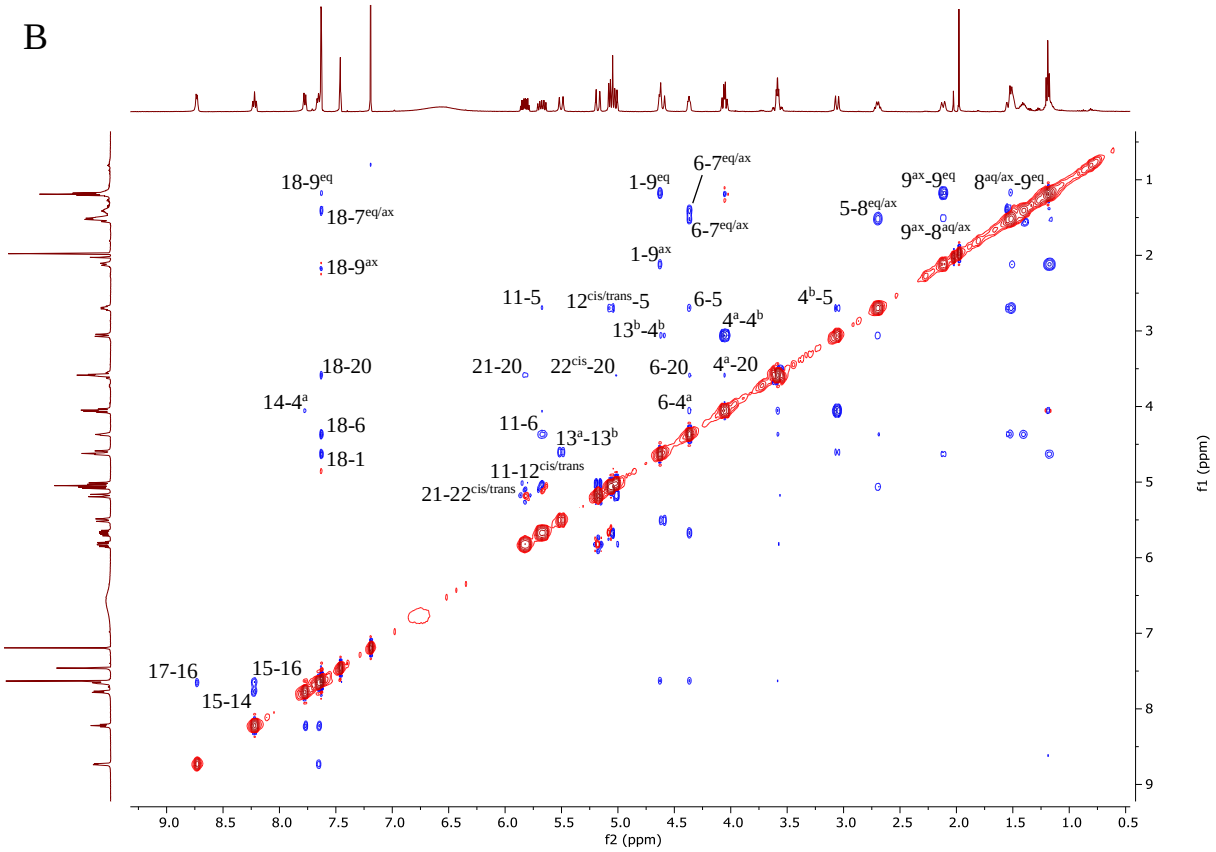
SI Figure 1. . A) Structures of **6a** and **6b** with numbered protons. ^{1}H-^{1}H NOESY interactions of H^{20} shown in blue arrows. B) ^{1}H-^{1}H NOESY spectrum of **6a**. C) ^{1}H-^{1}H NOESY spectrum of **6b**. In both compounds, H^{18} couples with H^{1}, H^{6}, H^{7} and H^{9}, suggesting that the dichlorophenyl group is positioned underneath the pipecolate. In **6a**, a weak coupling between H^{18} and H^{4a} can be observed, showing a small population of the conformation where the dichlorophenyl ring is positioned away from the pipecolate. H^{20} couples with H^{6} and weakly with H^{1}. The coupling to H^{1} likely corresponds to the conformation in which the dichlorophenyl ring is positioned away from the pipecolate. In **6b**, H^{20} couples with H^{1}, but not with H^{6}. These couplings are only possible if **6a** has a *S*-configured and **6b** a *R*-configured sulfur atom.

A



7a **7b**

B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1-9ax
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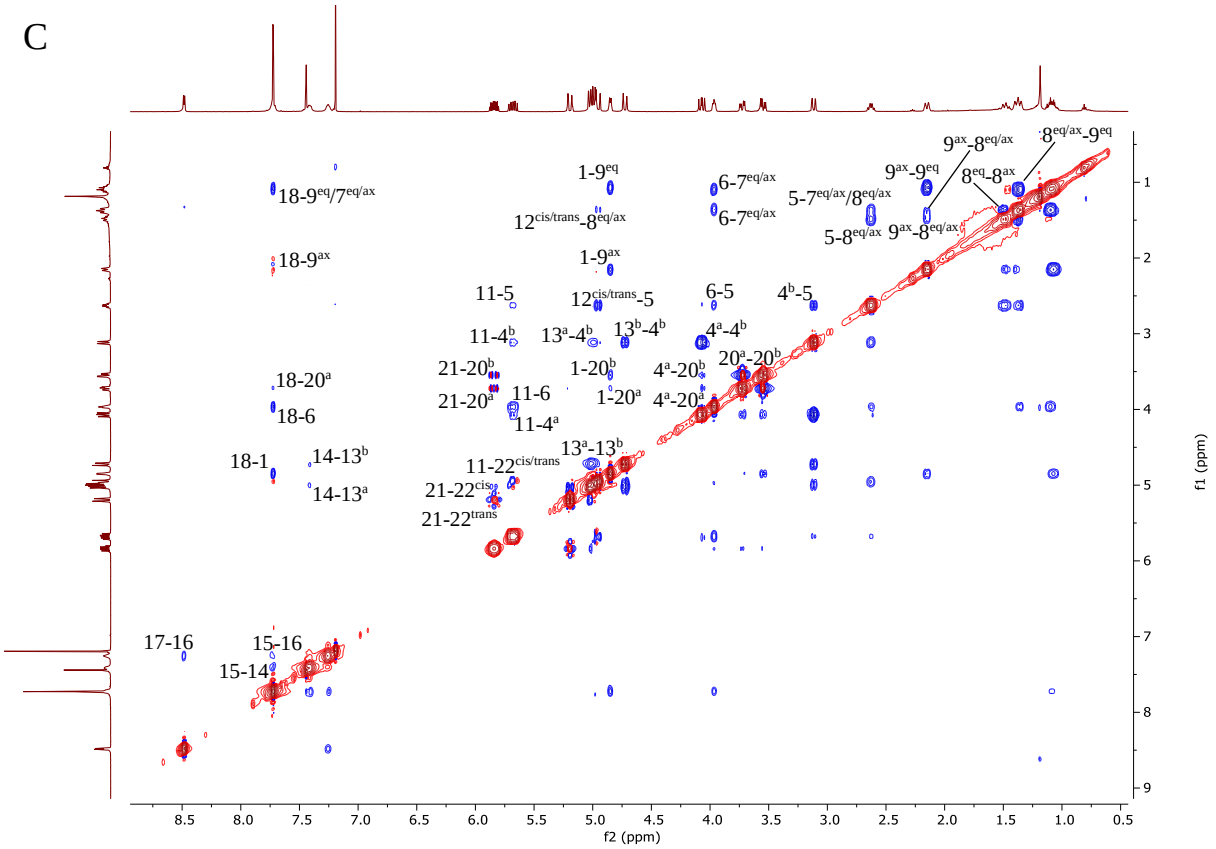
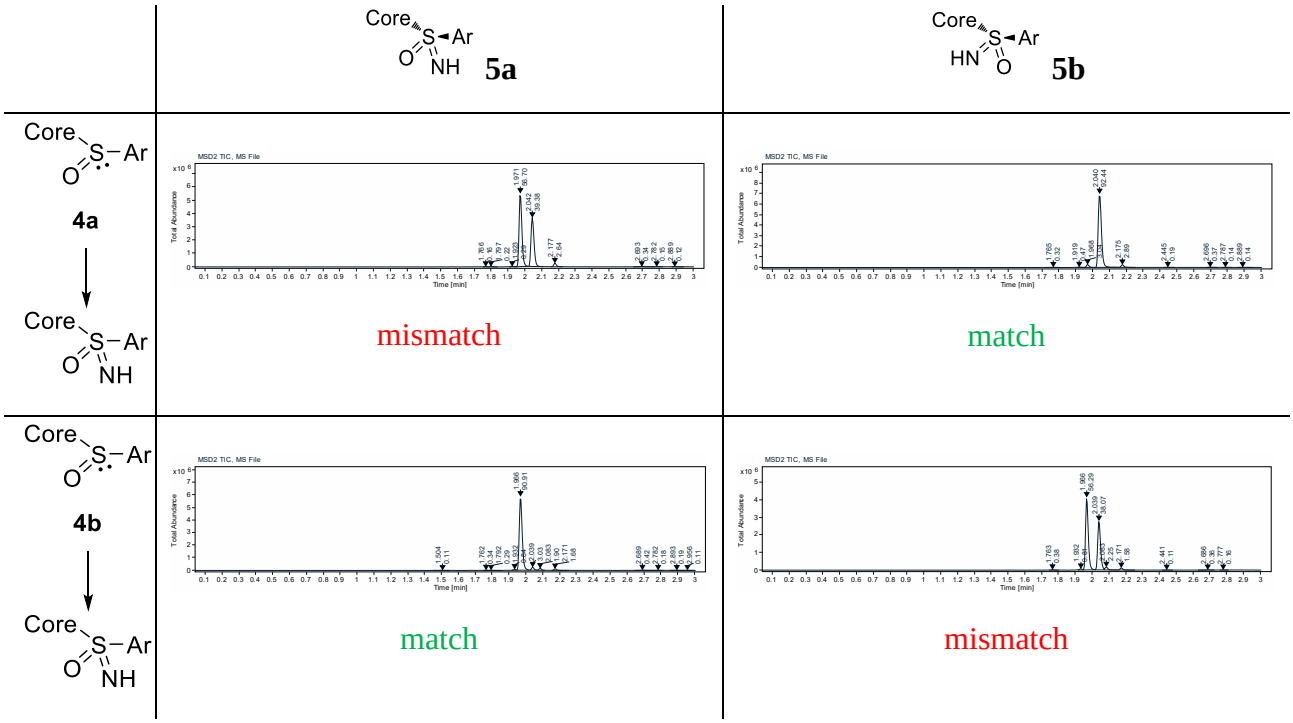
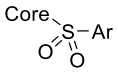
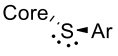
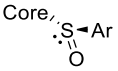
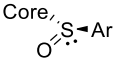
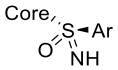
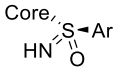
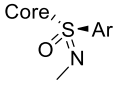
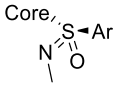
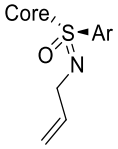
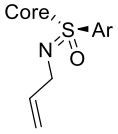


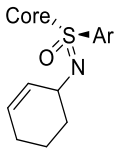
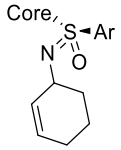
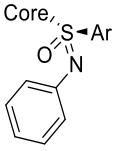
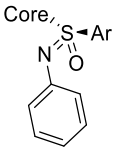
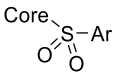
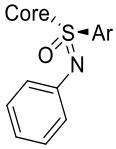
SI Figure 2. A) Structures of **7a** and **7b** with numbered protons. ^{1}H-^{1}H NOESY interactions of H^{20} shown in blue arrows. B) ^{1}H-^{1}H NOESY spectrum of **7a**. C) ^{1}H-^{1}H NOESY spectrum of **7b**. In both compounds, H^{18} couples with H^{1}, H^{6}, H^{7} and H^{9}, suggesting that the dichlorophenyl group is positioned underneath the pipecolate. In **7a** H^{20} couples with H^{6} but not with H^{1}. In **7b**, H^{20} couples with H^{1}, but not with H^{6}. These couplings are only possible if **7a** has a *S*-configured and **7b** a *R*-configured sulfur atom.

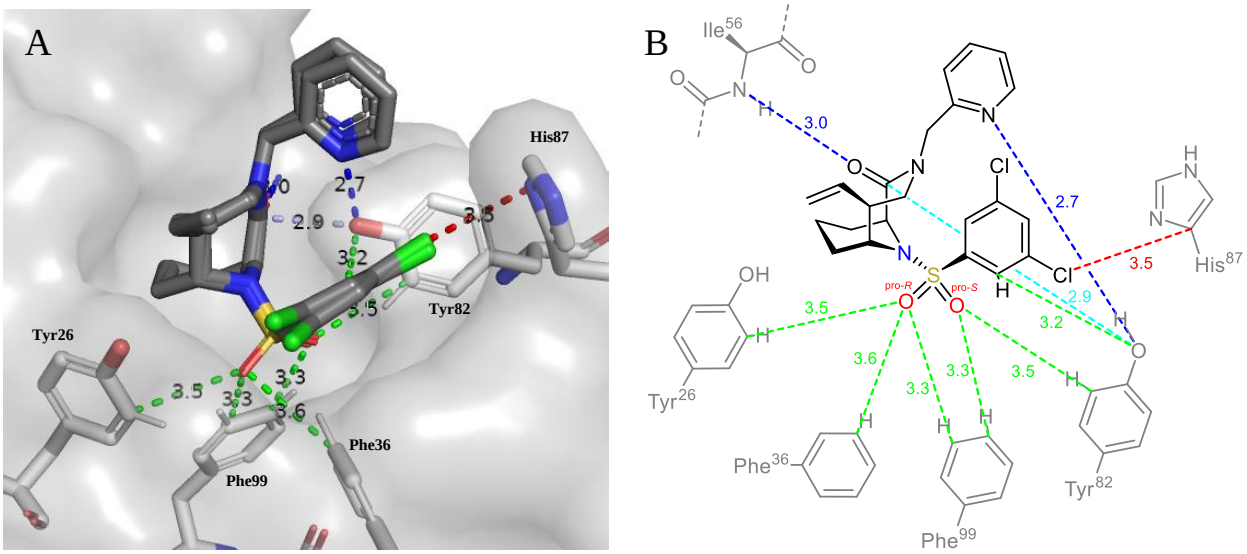


SI Figure 3. Isolated sulfinamides **4a** and **b** were iminated via a nitrene under literature known conditions. This imination reaction is known to procede under retention of the stereocenter at the sulfur atom. The imination reactions of the isolated sulfinamides **4a** and **b** were co-injected in a LC-MS analysis with the diastereomerically pure and assigned **5a** and **b**. To allow an easier evaluation of the experiment, single ion monitoring (SIM) mass spectrometry was performed, analyzing only the mass of the sulfonimidamide product. The sulfonimidamide formed from sulfinamide **4a** matches with the reference sulfonimidamide **5b**, and the sulfonimidamide of **4b** matches with **5a**. Under retention of the configuration of the sulfur atom, the sulfinamide **4a** must be in *S*-configuration and **4b** in *R*-configuration.

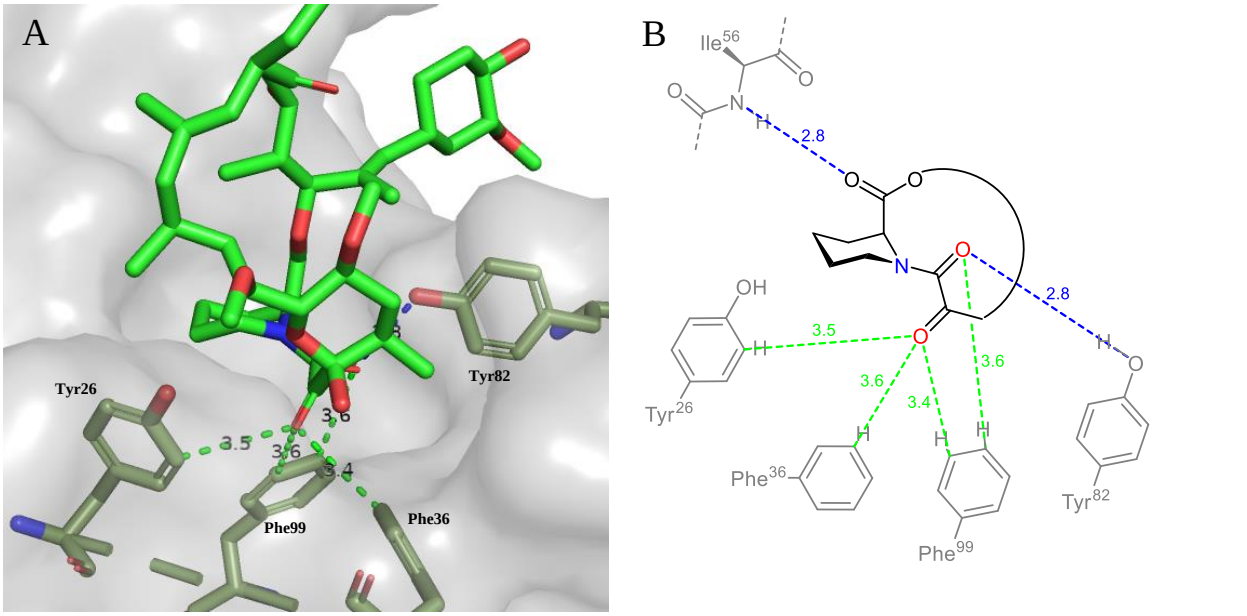
SI Table 1. Binding affinities of all sulfonamide analogs for FKBP12, FKBP12.6, FKBP51FK1, FKBP52FK1, AbFBP (1-113) and paFKPA (23-253), measured in a competitive fluorescence polarization assay. Core = (1*S*,5*S*,6*R*)-2-oxo-3-(pyirin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-10-yl, Ar = 3,5-dichlorophenyl (corresponds to 2, see Scheme 1). *Cocrystal structure with FKBP12 solved. †Cocrystal structure with FKBP51FK1 solved. n.a. = not available, data was not measured.

Compound	Structure C5 substituent	Sulfur motif	K_D for **FKBP 12** in nM	K_D for **FKBP 12.6** in nM	K_D for **FKBP 51** in nM	K_D for **FKBP 52** in nM	K_D for **Ab-FBP(1-113)** in nM	K_D for **paF-KPA (23-253)** in nM
1*	Vinyl		2.6 ±0.2	6.9 ±0.6	97 ±6	92 ±2	2.2 ±0.4	38 ±6
3	Vinyl		509 ±152	1,360 ±520	> 40,000	> 40,000	5,340 ±2300	7,370 ±890
4a	Vinyl		129 ±19	394 ±68	4,780 ±900	5,210 ±1,200	104 ±9	851 ±98
4b*†	Vinyl		67 ±5	211 ±32	2,240 ±330	3,980 ±1,260	265 ±29	3,690 ±350
5a*†	Vinyl		360 ±27	857 ±188	12,600 ±3,700	20,000 ±3000	828 ±95	8,460 ±840
5b*†	Vinyl		283 ±24	608 ±128	11,800 ±3,000	12,000 ±2,400	803 ±85	8,800 ±840
6a*†	Vinyl		1,390 ±190	3,650 ±230	> 40,000	> 40,000	5,720 ±370	> 40,000
6b	Vinyl		1,160 ±120	4,380 ±260	> 40,000	> 40,000	4,350 ±260	> 40,000
7a	Vinyl		1,570 ±180	7,700 ±830	> 40,000	> 40,000	3,600 ±260	> 40,000
7b	Vinyl		912 ±108	4,580 ±260	> 40,000	> 40,000	4,700 ±260	> 40,000

8a	Vinyl		490 ±57	3,990 ±870	> 40,000	> 40,000	2,090 ±150	> 40,000
8b	Vinyl		577 ±85	4,030 ±950	> 40,000	> 40,000	n.A.	n.A.
9a	Vinyl		658 ±160	4,380 ±900	> 40,000	> 40,000	3,390 ±330	> 40,000
9b	Vinyl		> 40,000	> 40,000	> 40,000	> 40,000	2,680 ±440	> 40,000
11	1,2-Dihydroxy-ethyl		0.6 ±0.1	3.2 ±0.3	30 ±3	25 ±3	n.a.	n.a.
10	1,2-Dihydroxy-ethyl		8,770 ±610	23,600 ±2600	> 40,000	> 40,000	6,270 ±1,290	> 40,000



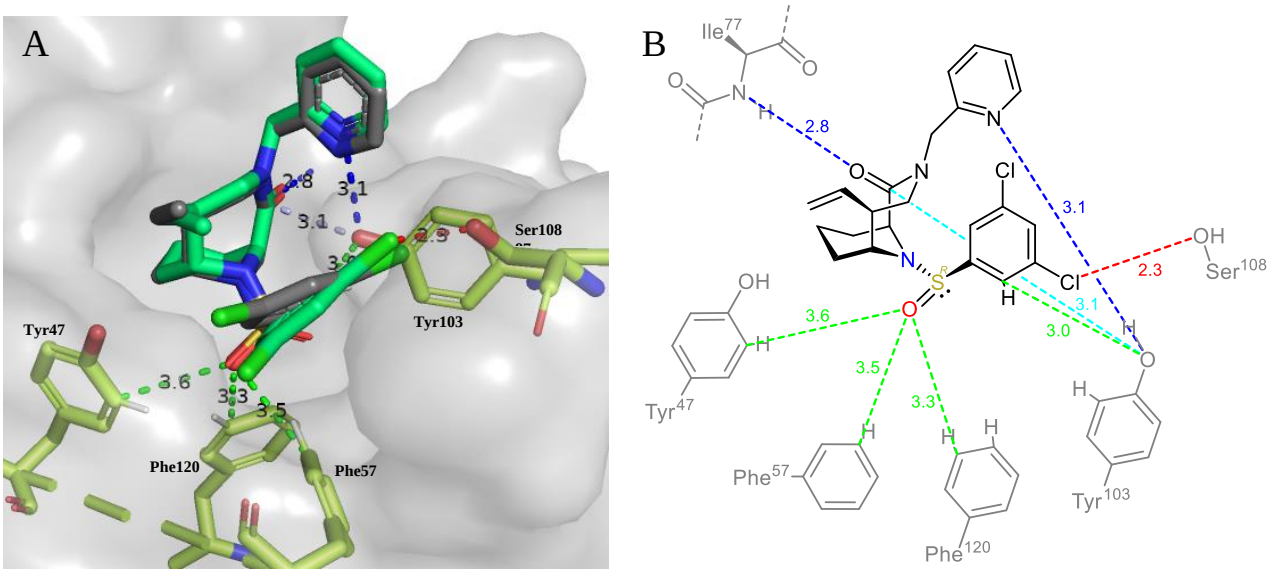
SI Figure 4. Compound **1** cocrystallized in complex with FKBP12 with two complexes per unit cell (PDB: 8CHL). Here shown is the complex of chain B overlayed with the ligand **1** from chain A. 3D- and 2D-Interaction network shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.



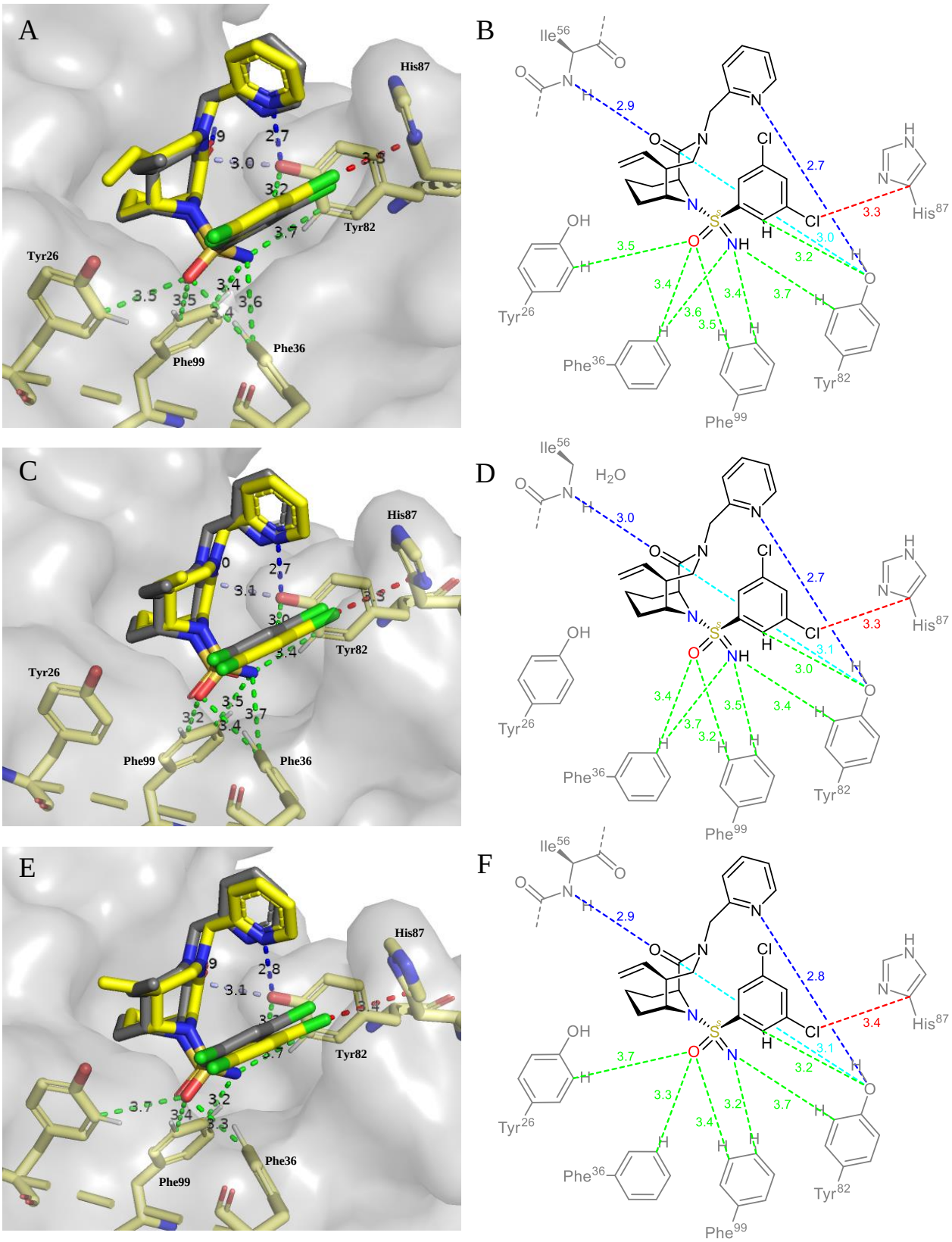
SI Figure 5. Cocrystal structure of FKBP12 with FK506 (PDB: 1FKJ). 3D- and 2D-Interaction network shown. Interactions of the Ketoamide group highlighted. Hydrogen bonds are shown in blue, CH…O interactions are shown in green. Distances of dashed lines are given in Å.

$$\Delta\Delta G = \Delta G_2 - \Delta G_1 = -RT \ln\left(\frac{c^\circ}{K_{D2}}\right) + RT \ln\left(\frac{c^\circ}{K_{D1}}\right) = RT \ln\left(\frac{K_{D2}}{K_{D1}}\right)$$

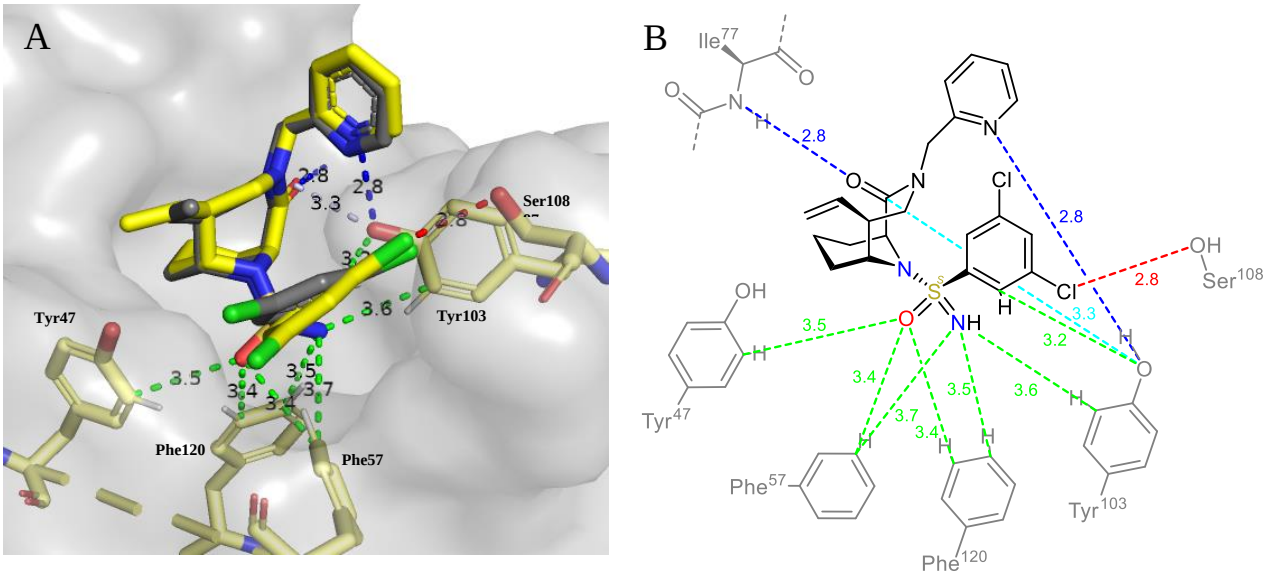
SI Equation 1. Calculating the difference in free binding ΔΔG for two different ligands from their respective binding affinities K_{D2} and K_{D1}. c° is the standard concentration of 1 mol/L.



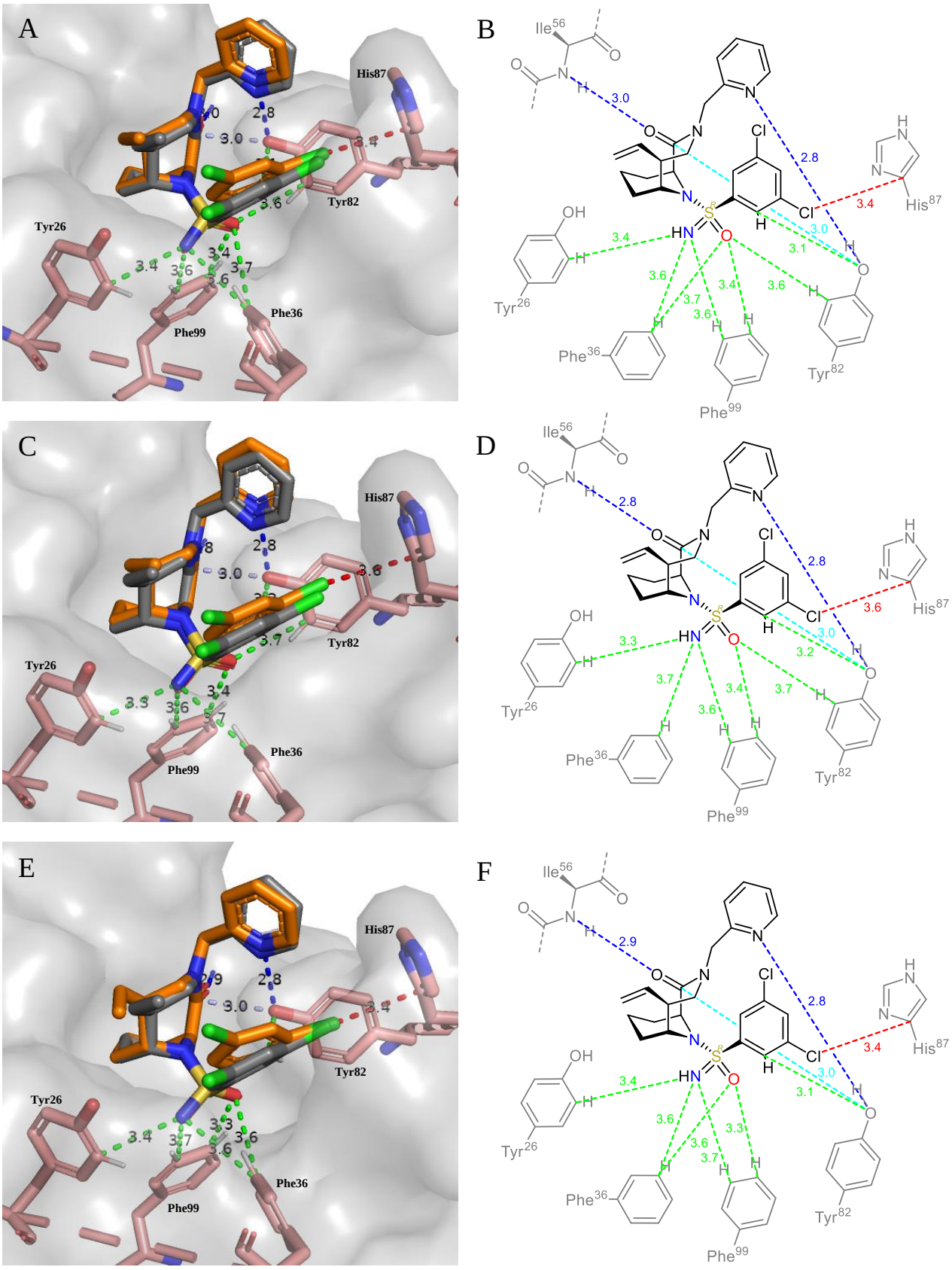
SI Figure 6. Cocrystal structure of **4b** and FK1 domain of FKBP51 (PDB: 8CHP) overlayed with **1** (grey, from cocrystal structure with FKBP12). 3D- and 2D-Interaction network shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.



SI Figure 7. Cocrystal structure of **5a** and FKBP12 (PDB: 8CHK). **5a**-FKBP12 crystallized with three complexes per unit cell (A+B: Chain A; C+D: Chain B; E+F: Chain C). Each complex is overlayed with **1** (grey). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.



SI Figure 8. Cocrystal structure of **5a** and FK1 domain of FKBP51 (PDB: 8CHN) overlayed with **1** (grey, from cocrystal structure with FKBP12). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.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Phe99
B
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Tyr82
Tyr26
Phe36
Phe99
D
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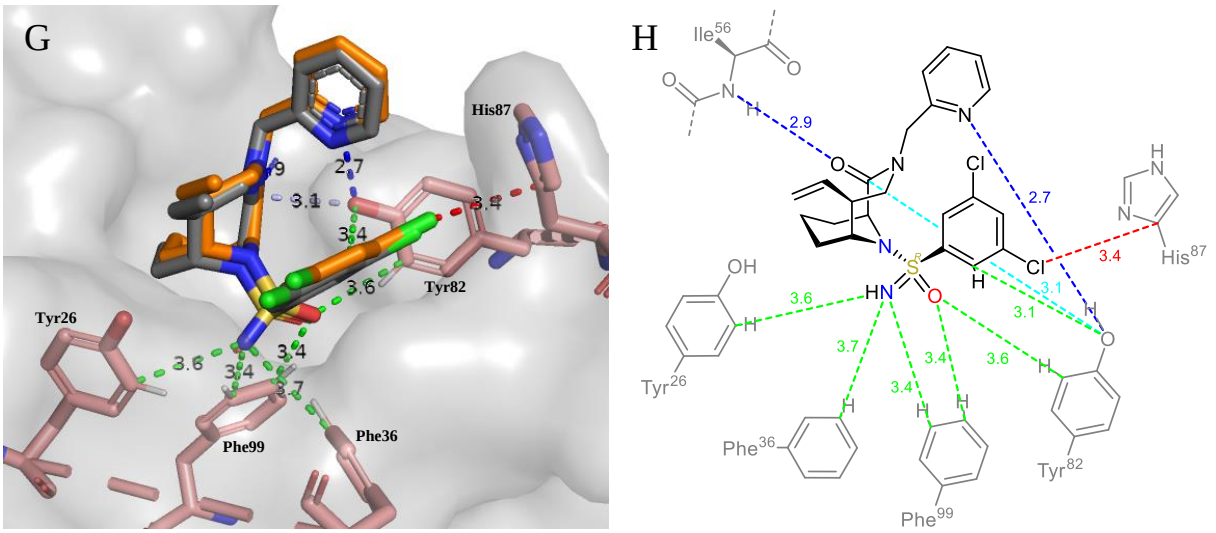
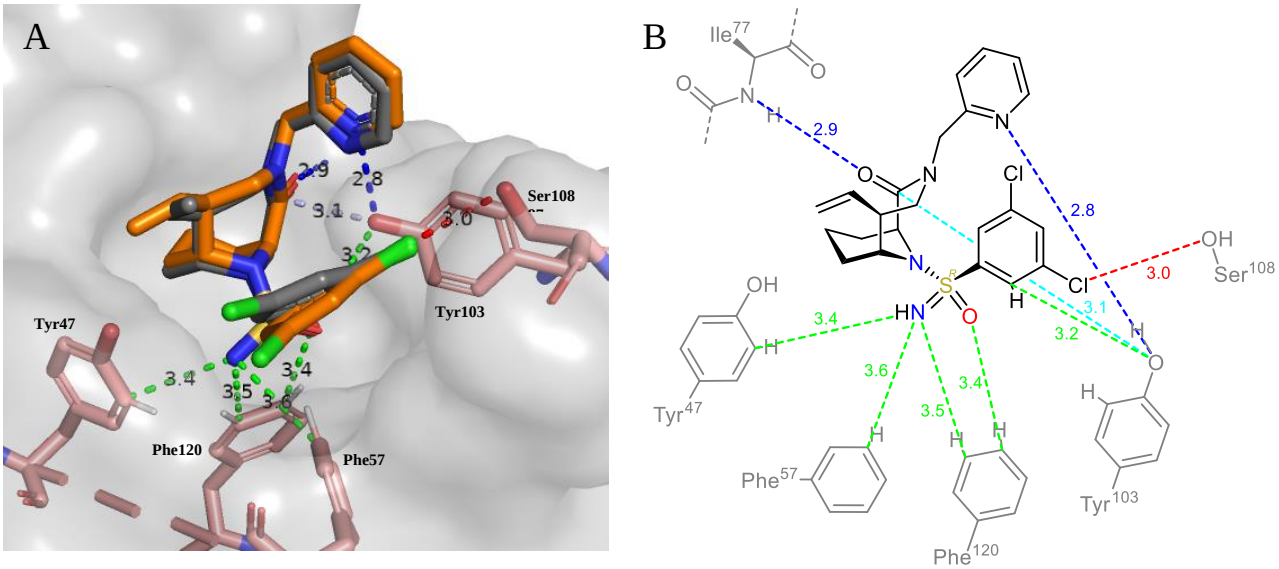
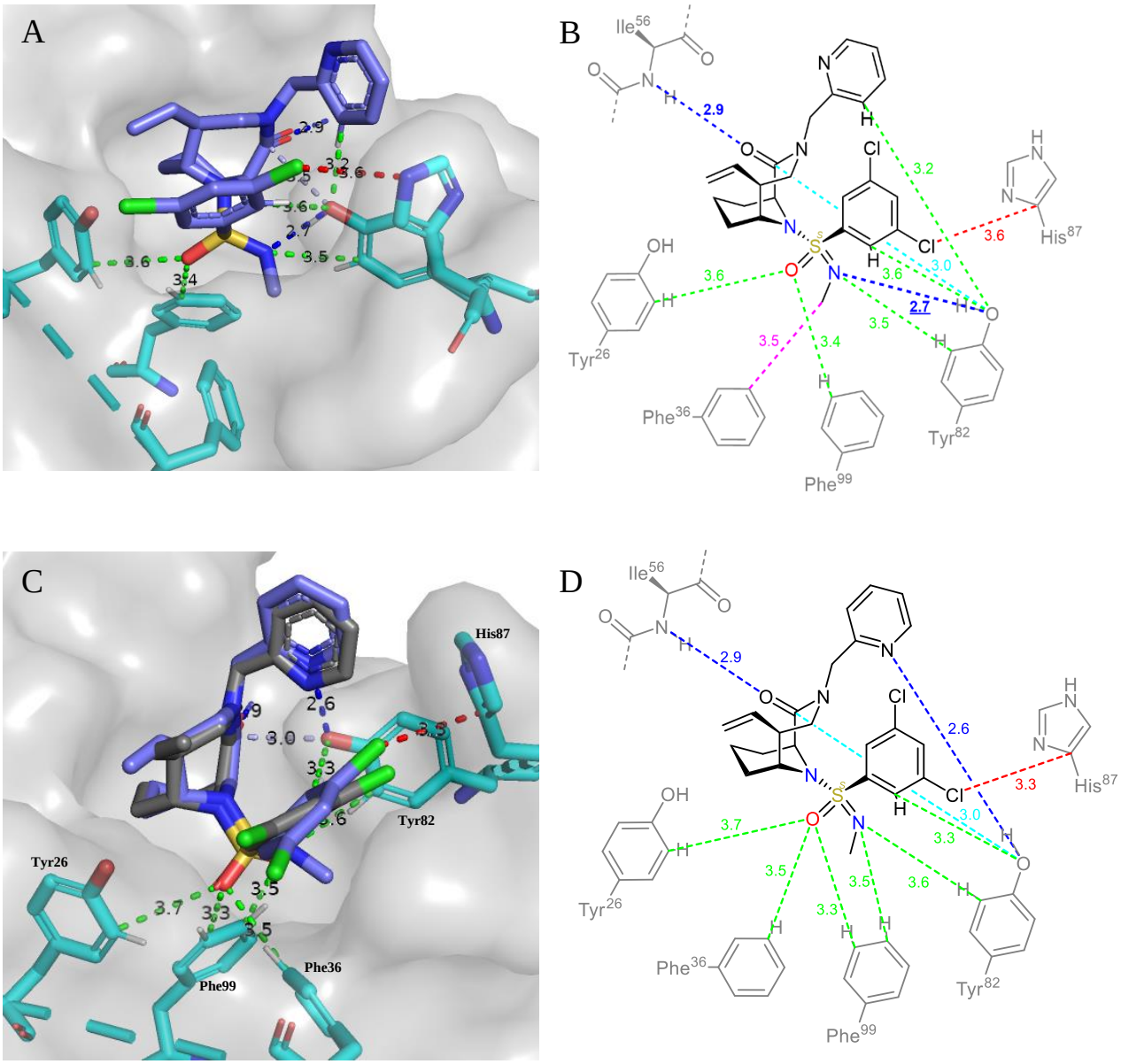


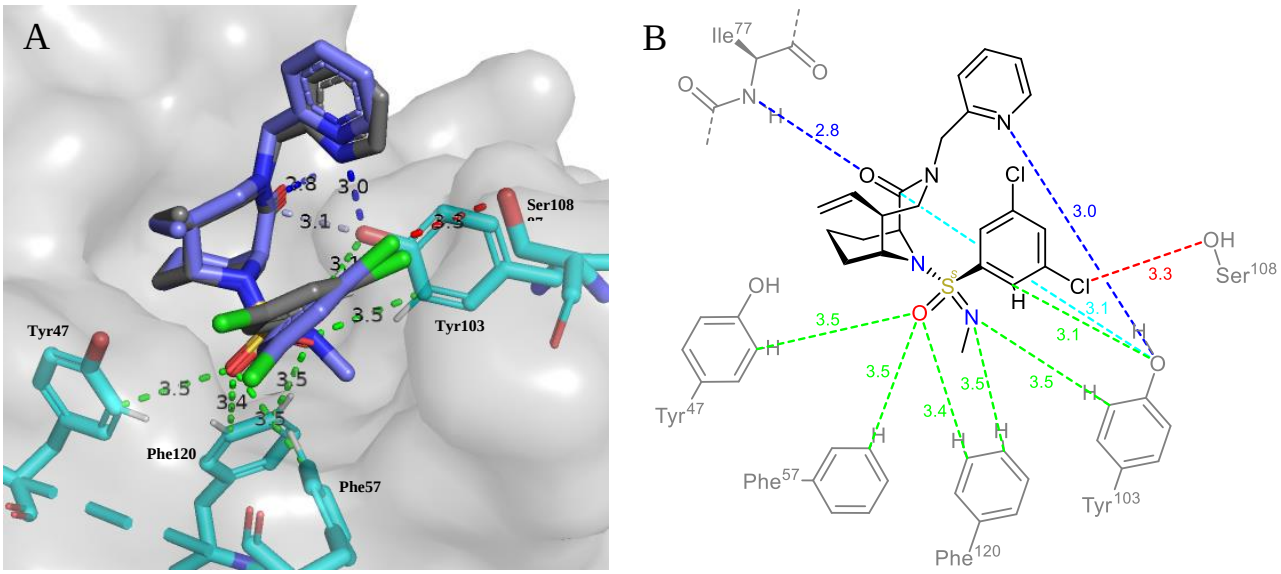
SI Figure 9. Cocrystal structure of **5b** and FKBP12 (PDB: 8CHJ). **5b**-FKBP12 crystallized with four complexes per unit cell (A+B: Chain A; C+D: Chain B; E+F: Chain C; G+H: Chain D). Each complex is overlayed with **1** (grey). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.



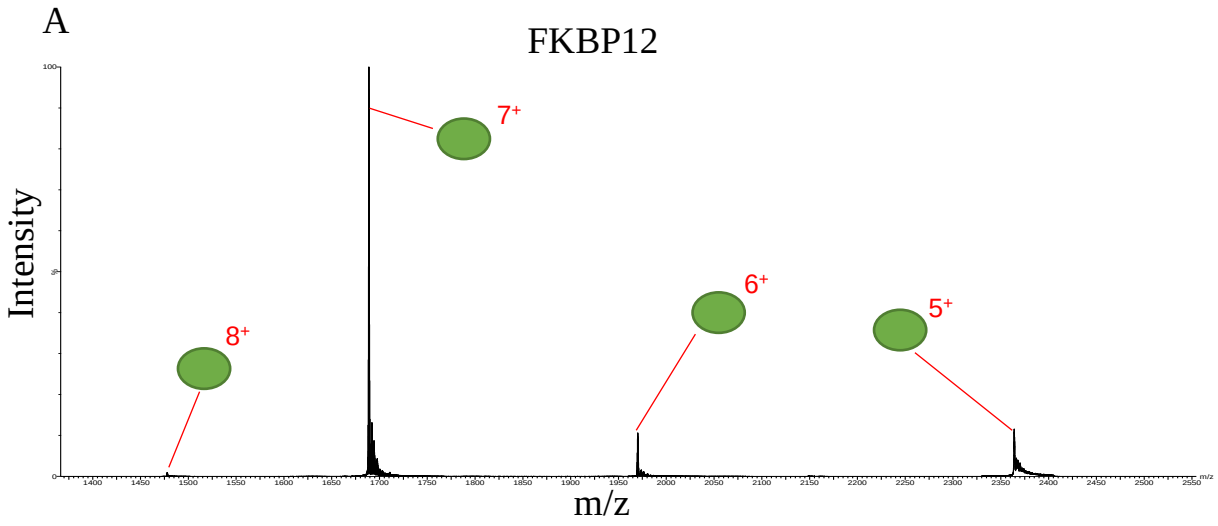
SI Figure 10. Cocrystal structure of **5b** and FK1 domain of FKBP51 (PDB: 8CHR) overlayed with **1** (grey, from cocrystal structure with FKBP12). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.

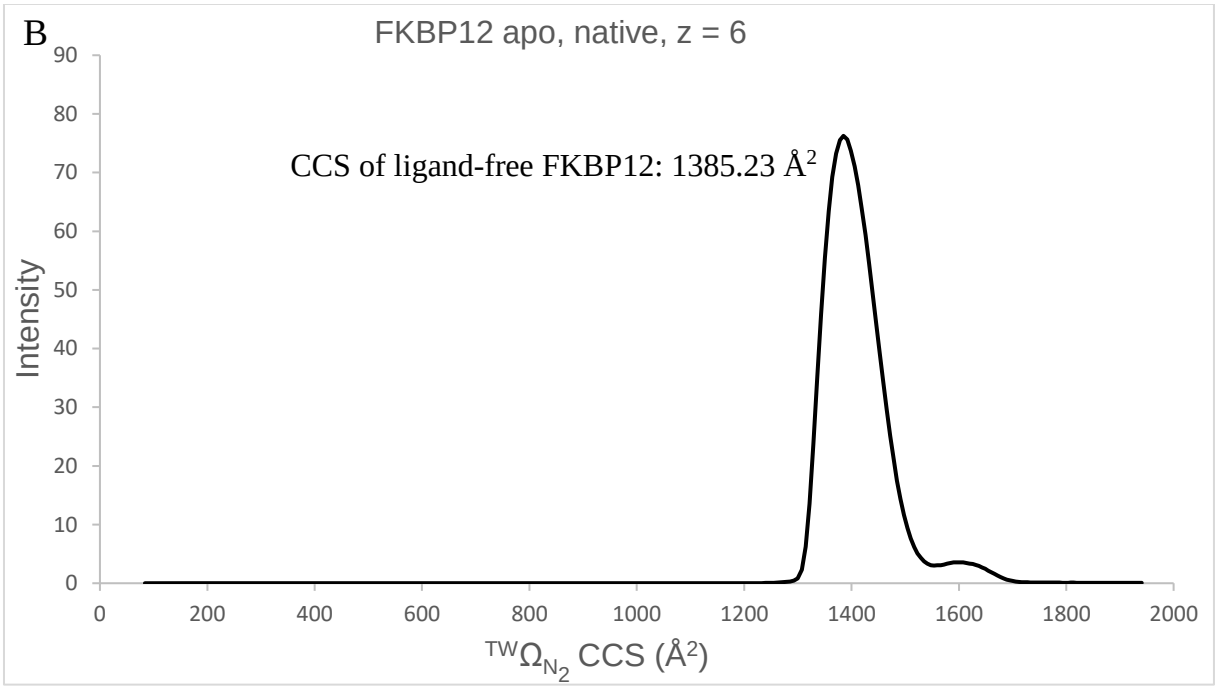


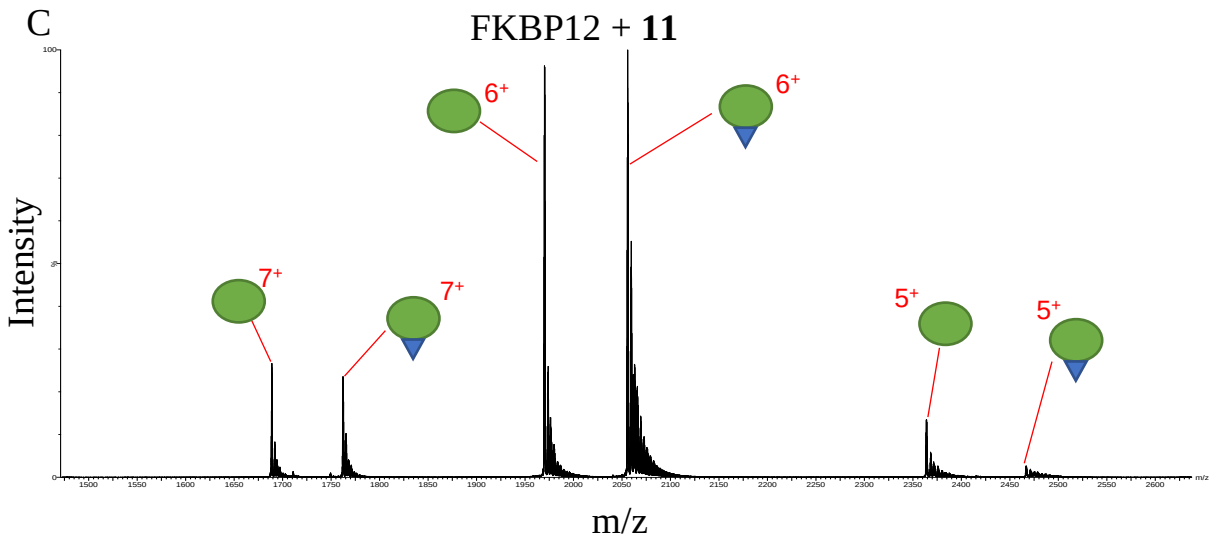
SI Figure 11. Cocrystal structure of **6a** and FKBP12 (PDB: 8CHI). **6a**-FKBP12 crystallized with two complexes per unit cell (A+B: Chain A; C+D: Chain B). Chain A was shown in the main manuscript (Fig. 2 E) and is shown here again in a different perspective to highlight the novel hydrogen bond of the sulfonimidamide. Complex C is overlayed with **1** (grey). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.

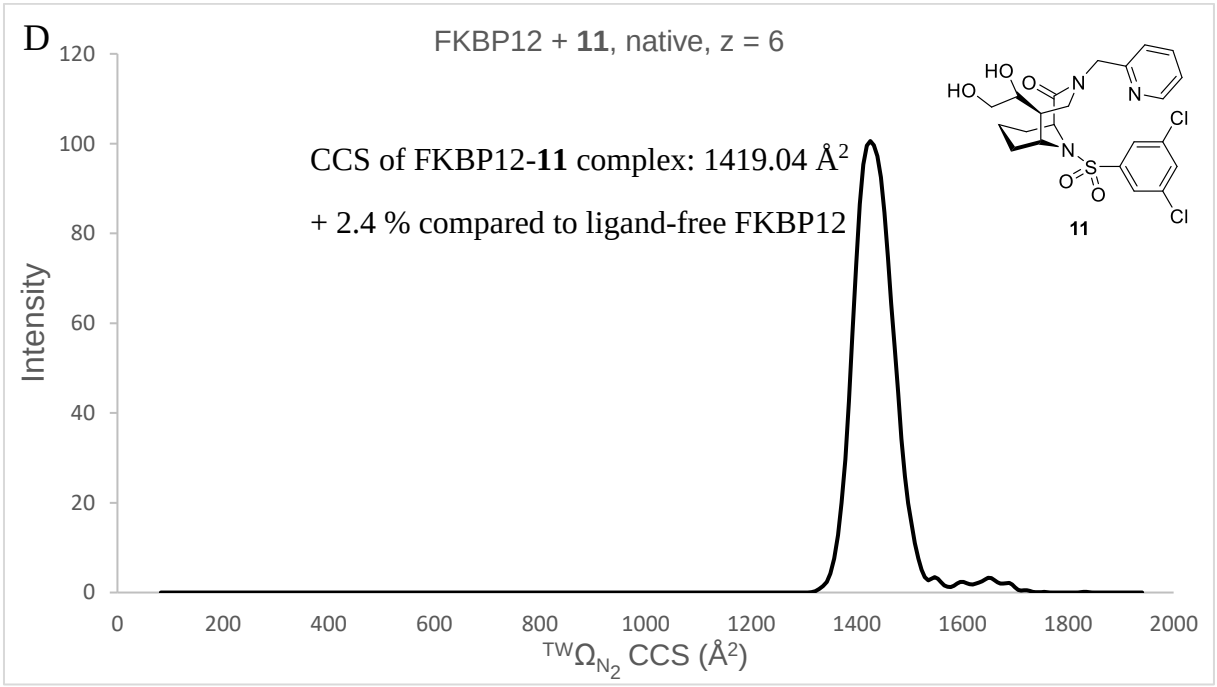


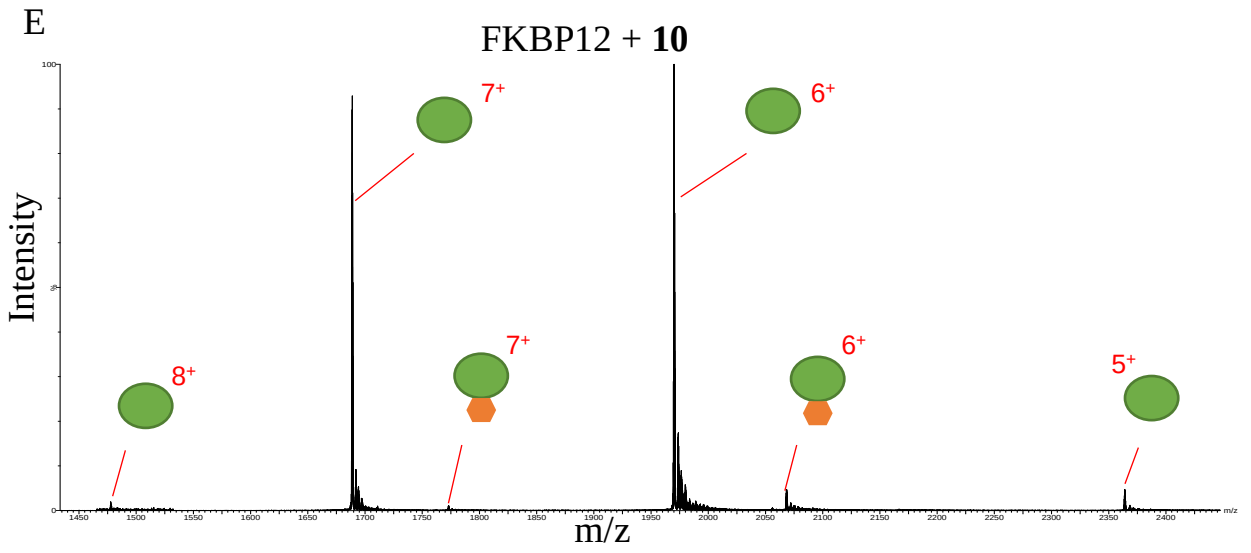
SI Figure 12. Cocrystal structure of **6a** and FK1 domain of FKBP51 (PDB: 8CHQ) overlayed with **1** (grey, from cocrystal structure with FKBP12). 3D- and 2D-Interaction network of each complex in the unit cell shown. Hydrogen bonds are shown in blue, haloge-π-interactions are shown in red, CH…O interactions are shown in green, other polar contacts are shown in light blue. Distances of dashed lines are given in Å.

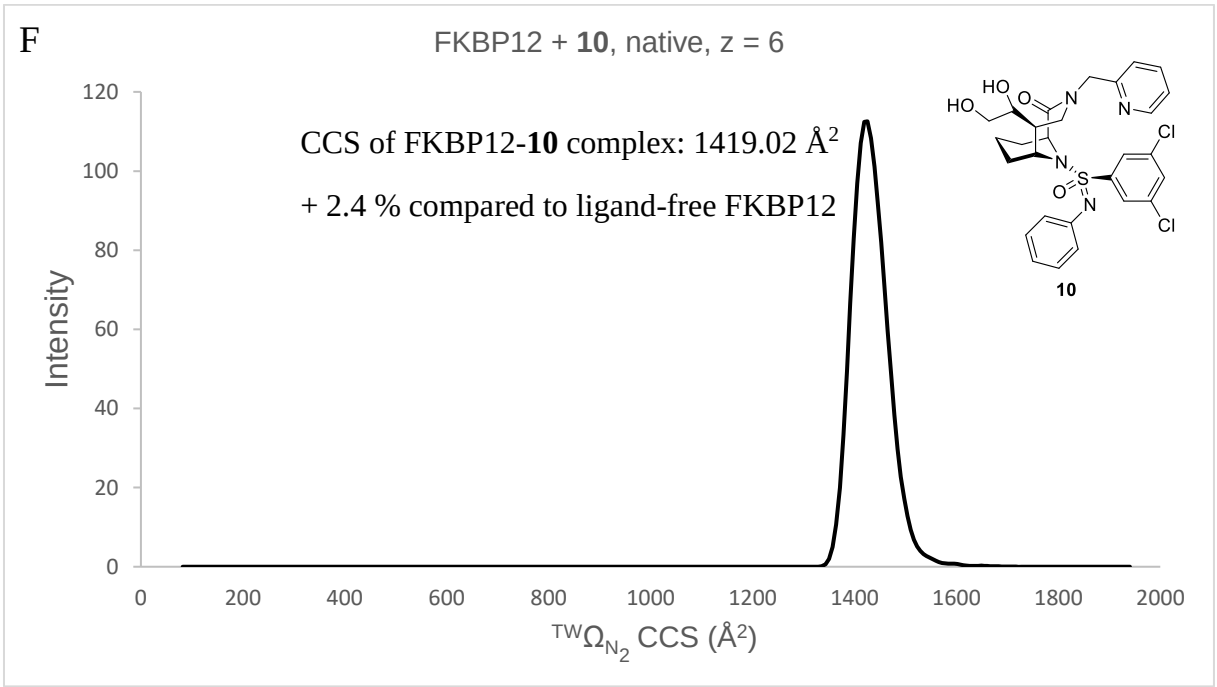

A
FKBP12
Intensity
m/z
8+
7+
6+
5+


B
FKBP12 apo, native, z = 6
CCS of ligand-free FKBP12: 1385.23 Å2
Intensity
TWΩN2 CCS (Å2)


C
FKBP12 + 11
Intensity
6+
6+
7+
7+
5+
5+
m/z

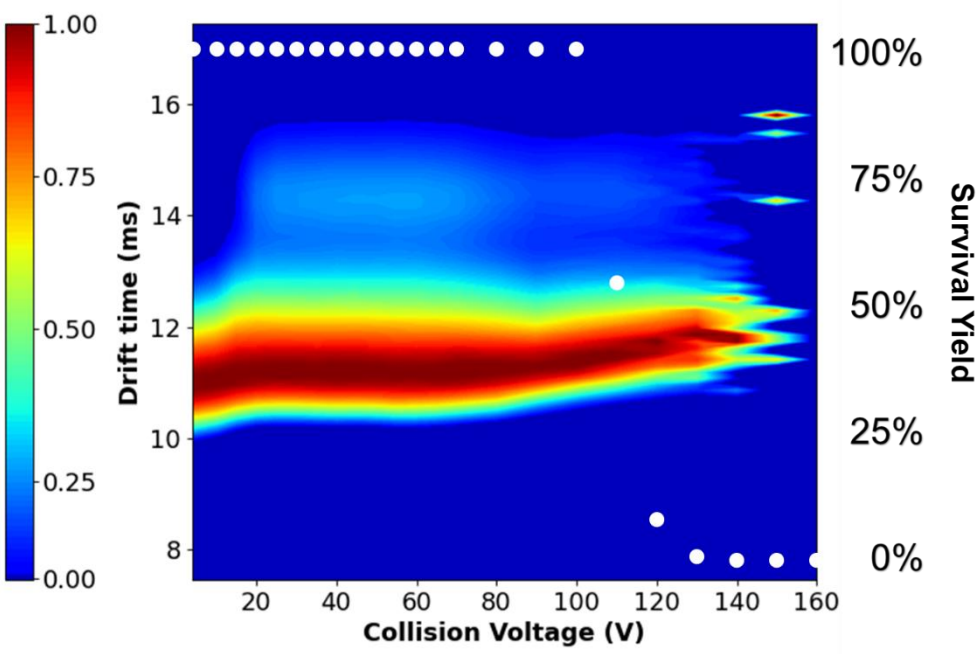

D
FKBP12 + 11, native, z = 6
CCS of FKBP12-11 complex: 1419.04 Å2
+ 2.4 % compared to ligand-free FKBP12
11
Intensity
TWΩN2 CCS (Å2)



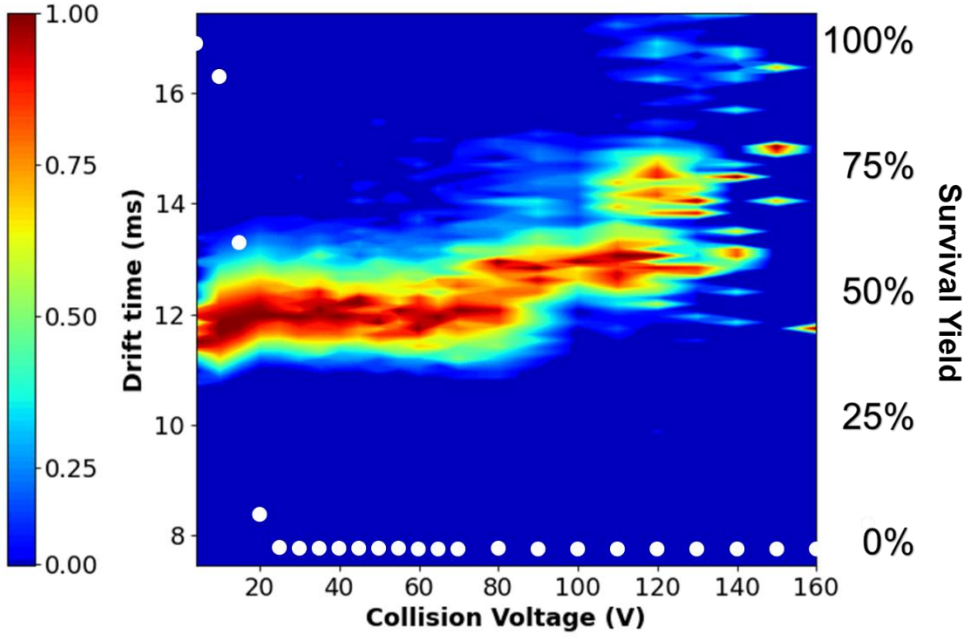


SI Figure 13. Ion mobility mass spectra of FKBP12-ligand complexes. Mass spectra of native FKBP12 (represented by green oval) (A), native FKBP12 with **11** (blue triangle) (C) and native FKBP12 with **10** (orange hexagon) (E). Ion mobility data (B, D, F) show that there is only a small increase in collision cross section of the bound complexes compared to the ligand-free state (data for the 6+ charge state shown in all three cases), indicating that no major conformational change occurs upon binding.

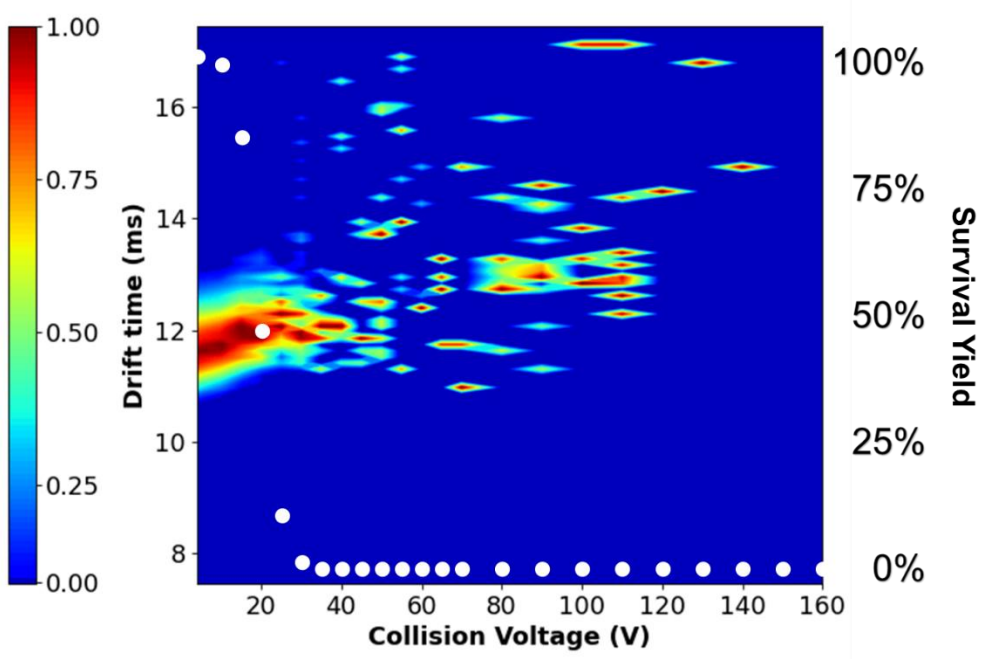
A) FKBP12 without ligand



B) FKBP12 in complex with **11**

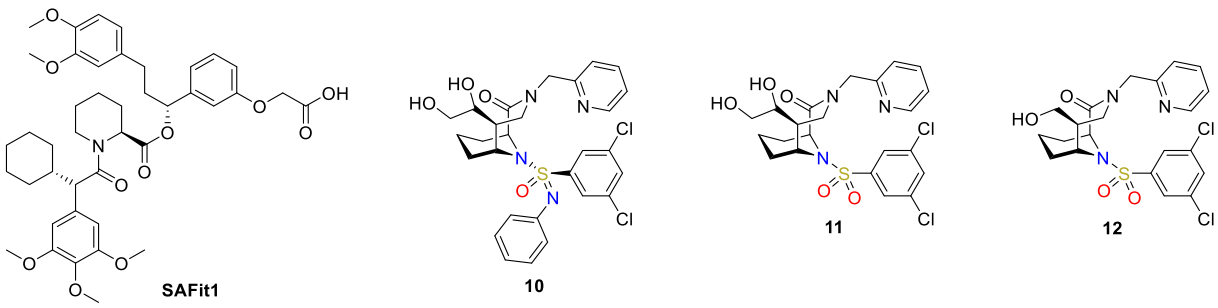


C) FKBP12 in complex with **10**

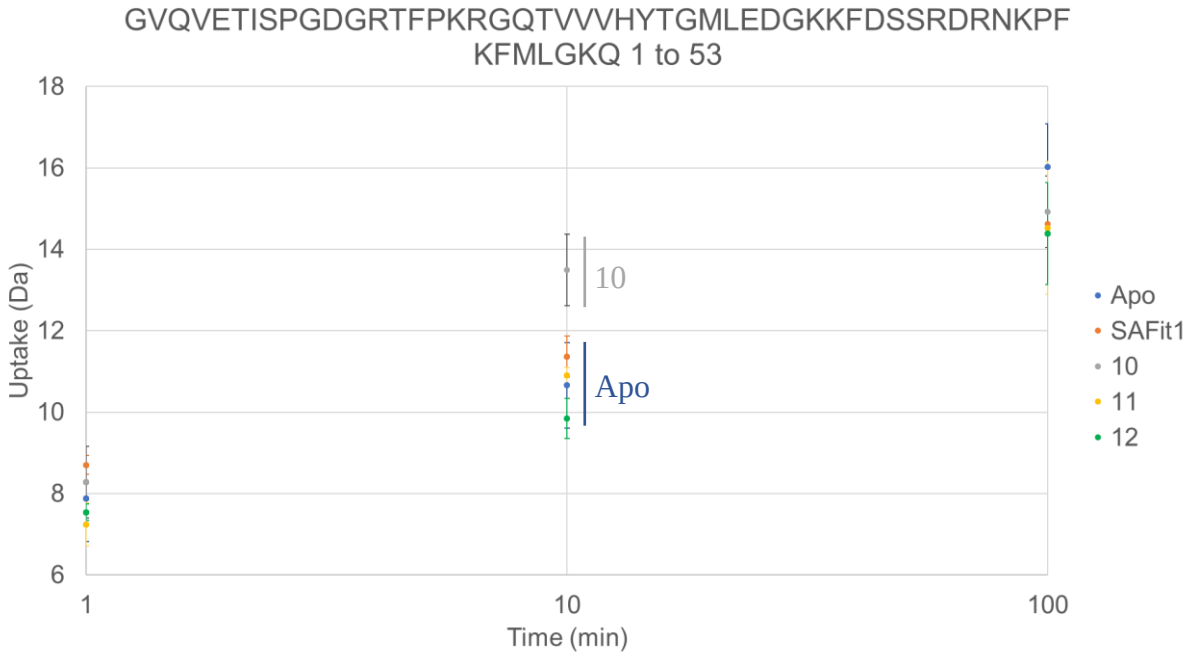


SI Figure 14. Collision-induced unfolding and dissociation of native FKBP12 (A), the FKBP12-**11** (B) and the FKBP12-**10** (C) complex. The survival yield of each analyzed species (*i.e.*, the fraction of the population of the complex ions that remains intact) is shown in white dots as a functionof the collision energy. Although the survival yield of both FKBP12-**11** and -**10** complexes is small beyond 20-40 V collision energy, traces of the FKBP12-**11** complex (B) are clearly detectable up to 110 V collision energy, whereas the FKBP12-**10** complex (C) is not detectable anymore. This indicates a greater stability of the FKBP12-**11** complex compared to the FKBP12-**10** complex under these experimental conditions. Note that when the survival yield drops to zero, no meaningful data were acquired beyond that collision energy, and therefore the apparent signals in panel C beyond 40 V only represent detector noise plotted by the CIU visualization software.[1]

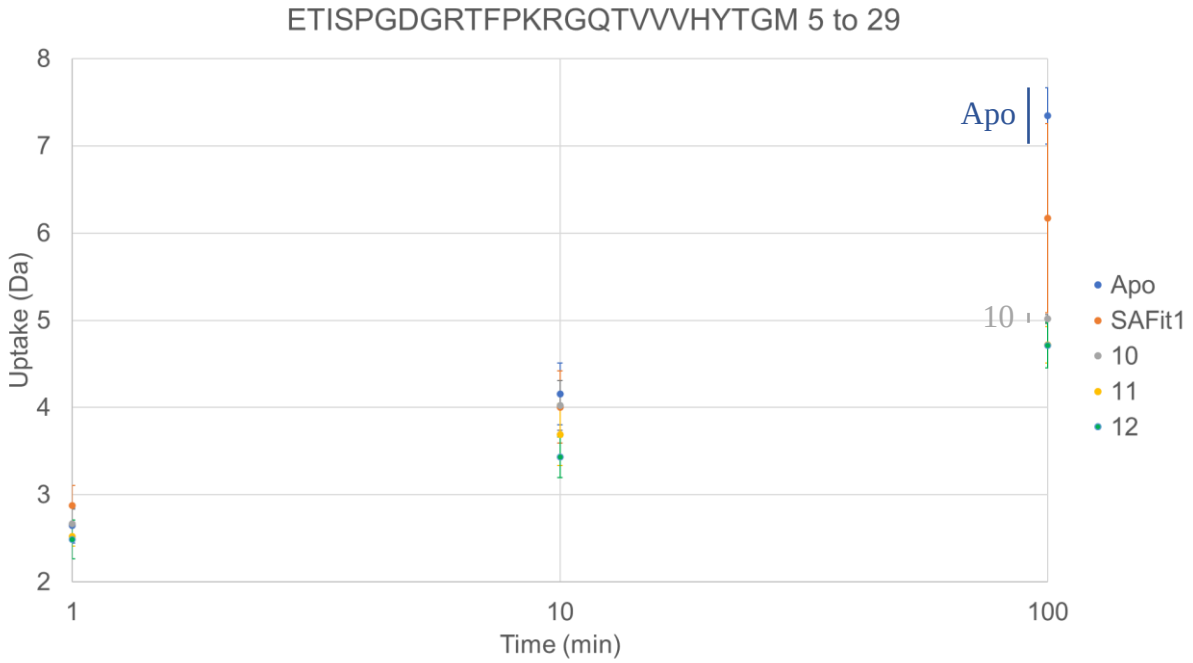
A)


SAFit1
10
11
12

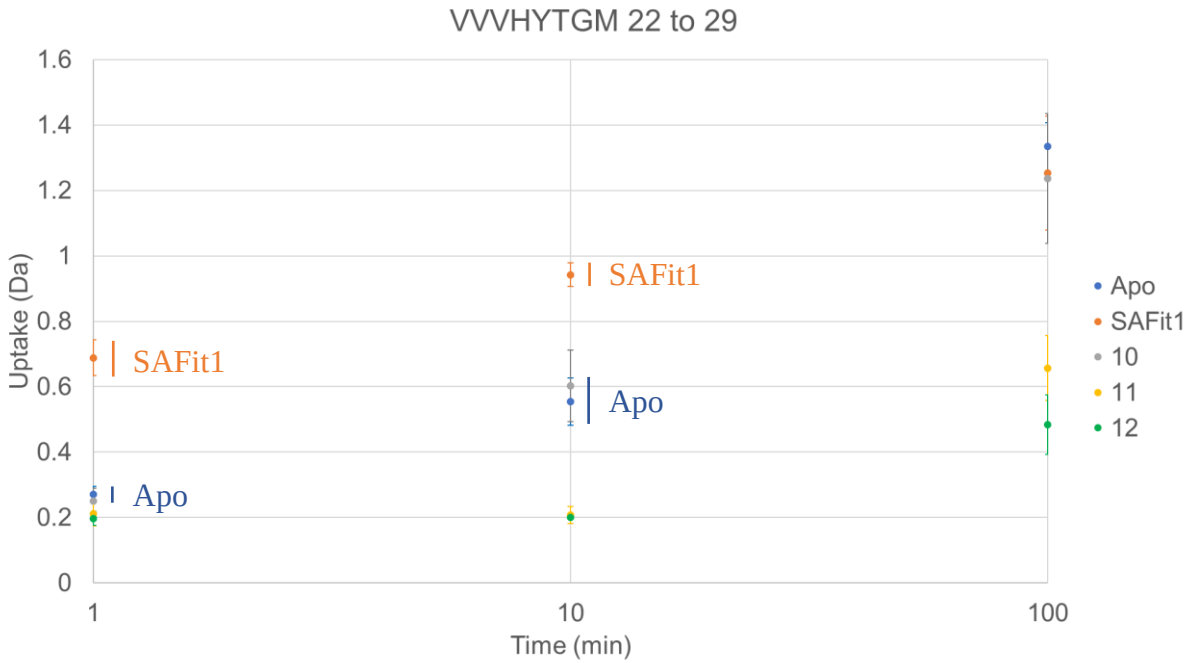
B)


GVQVETISPGDGRTFPKRGQTVVVHYTGMLEDGKKFDSSRDRNKPF
KFMLGKQ 1 to 53
Uptake (Da)
Time (min)
10
Apo
Apo
SAFit1
10
11
12

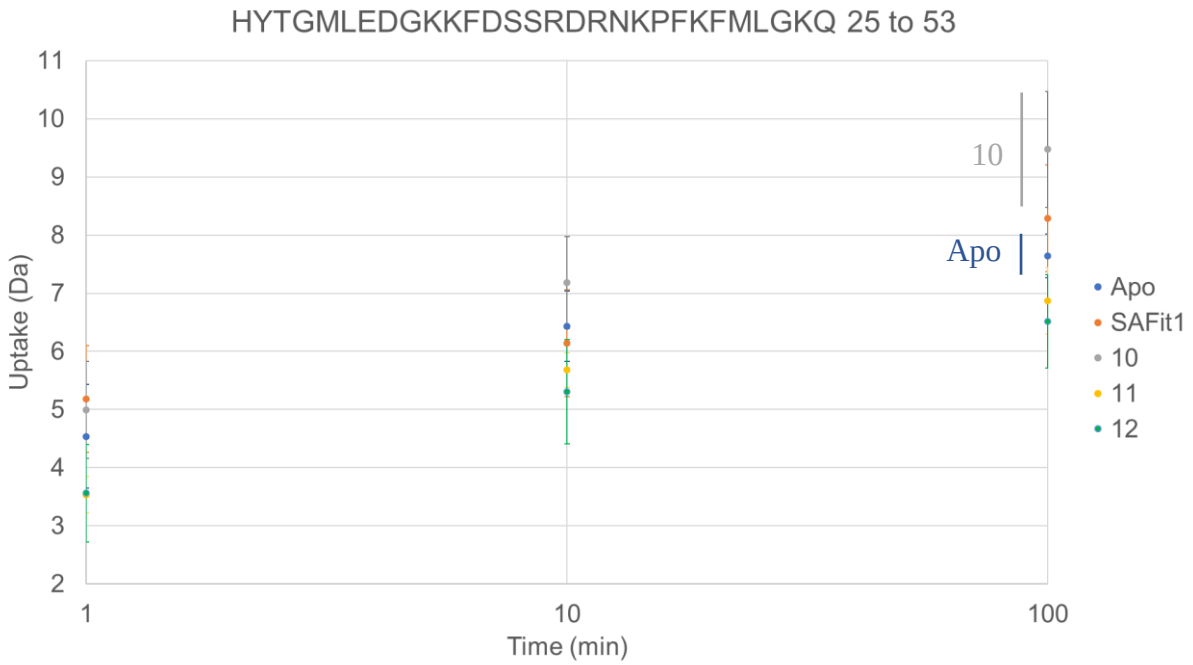
C)


ETISPGDGRTFPKRGQTVVVHYTGM 5 to 29
Uptake (Da)
Time (min)
Apo
10
Apo
SAFit1
10
11
12

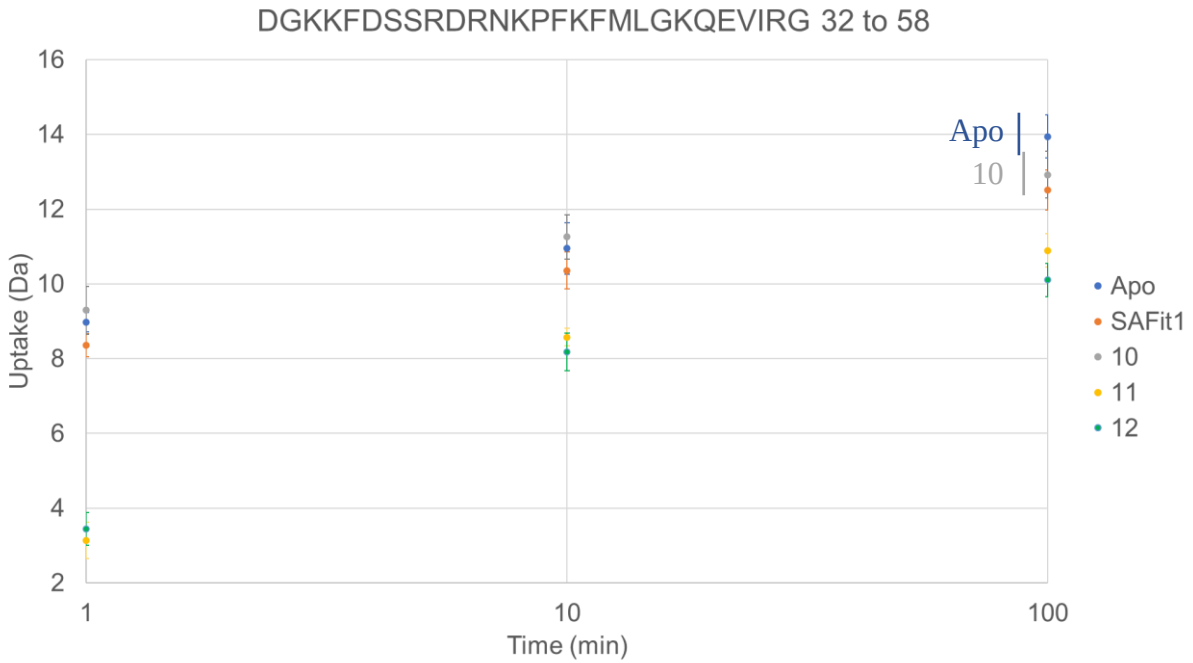
D)


VVVHYTGM 22 to 29
Uptake (Da)
Time (min)
SAFit1
SAFit1
Apo
Apo
Apo
SAFit1
10
11
12

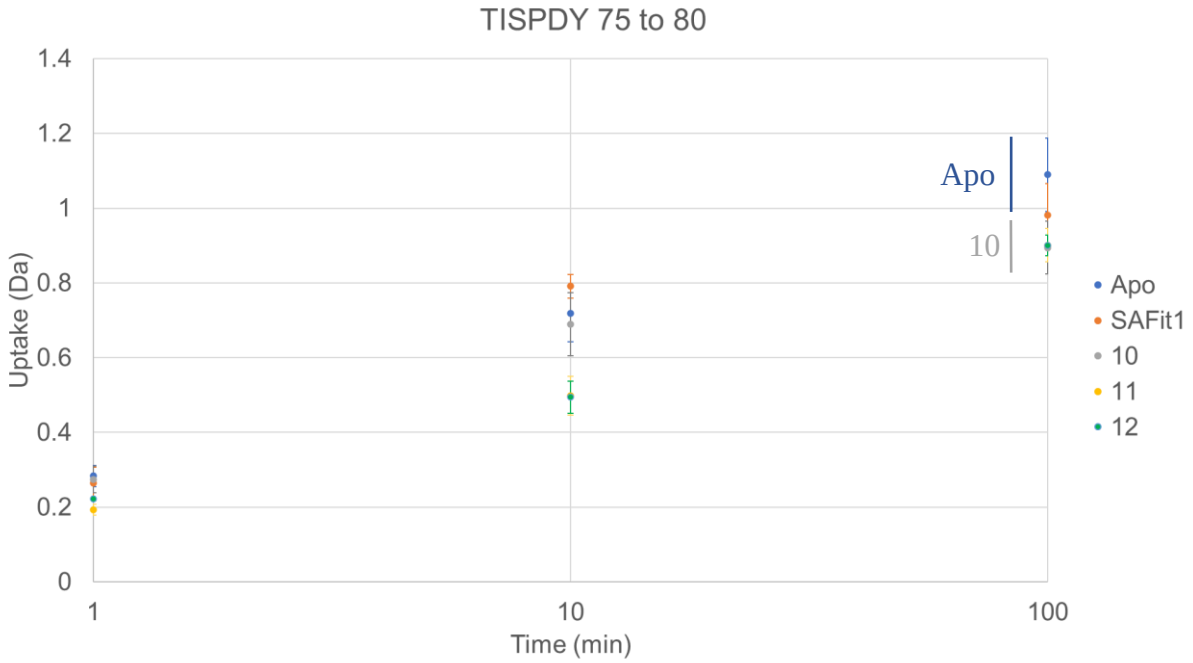
E)


HYTGMLEDGKKFDSSRDRNKPFKFMLGKQ 25 to 53
Uptake (Da)
Time (min)
10
Apo
Apo
SAFit1
10
11
12

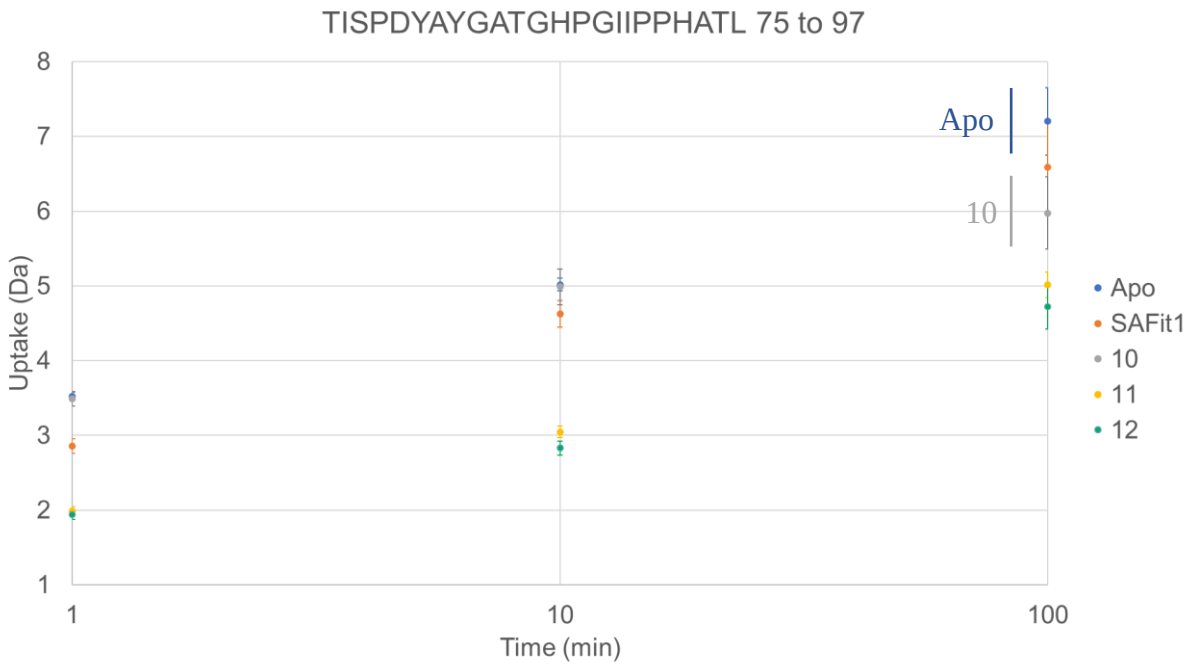
F)


DGKKFDSSRDRNKPFKFMLGKQEVIRG 32 to 58
Uptake (Da)
Time (min)
Apo
10
Apo
SAFit1
10
11
12

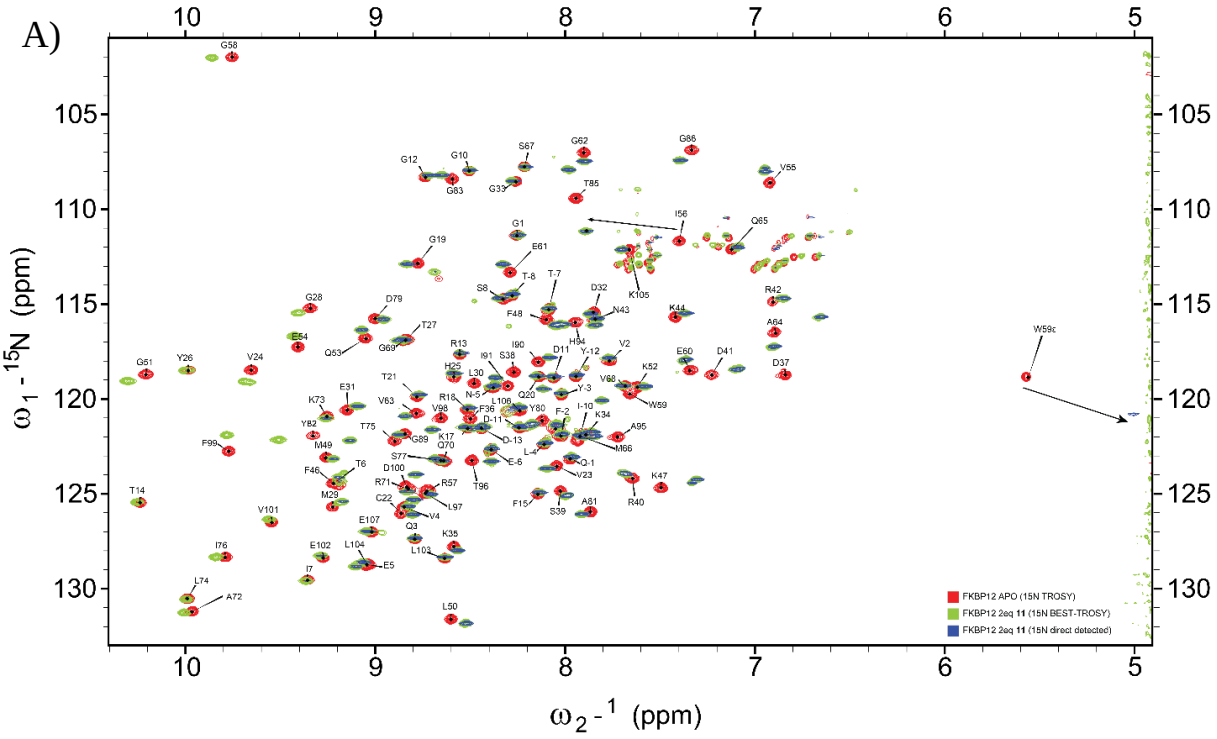
G)

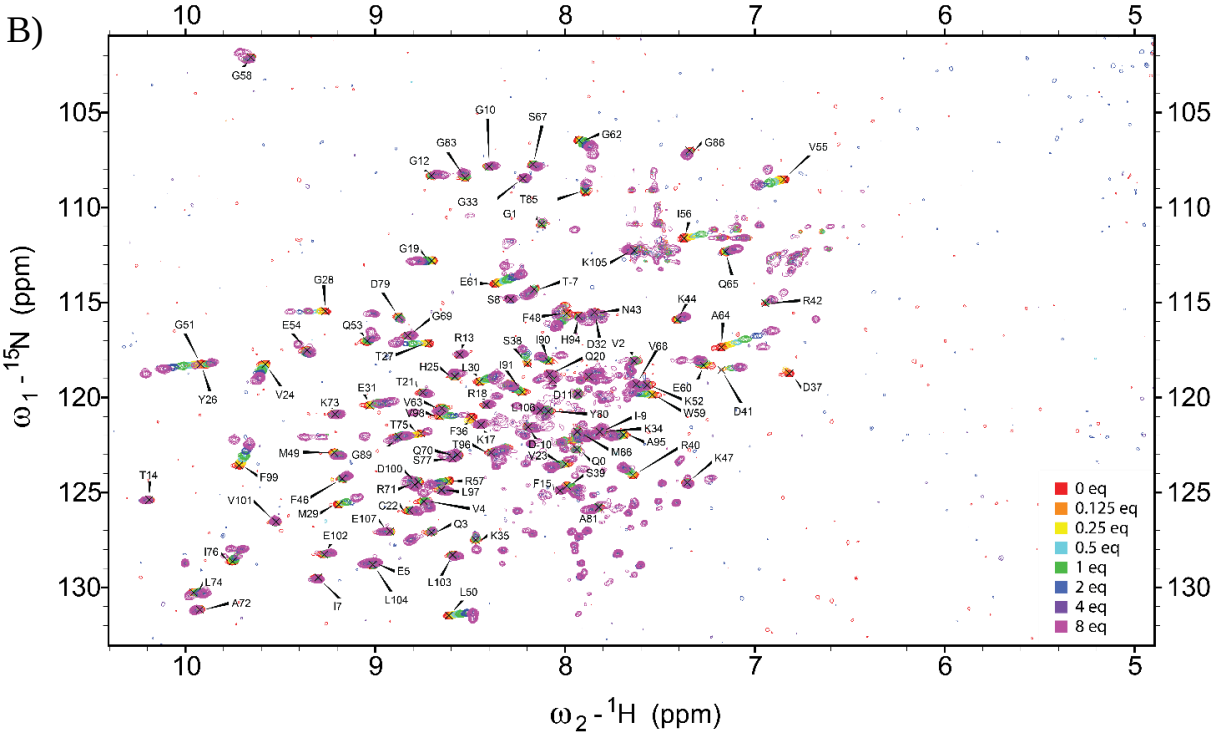


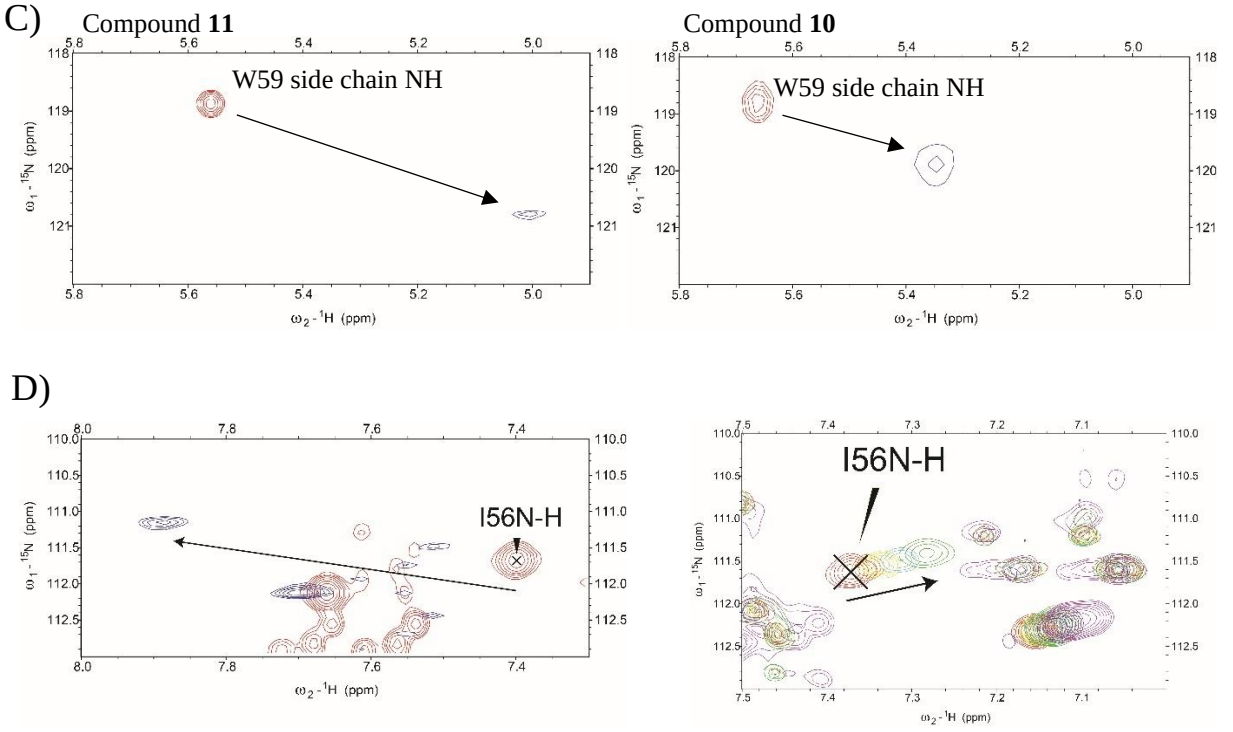
H)



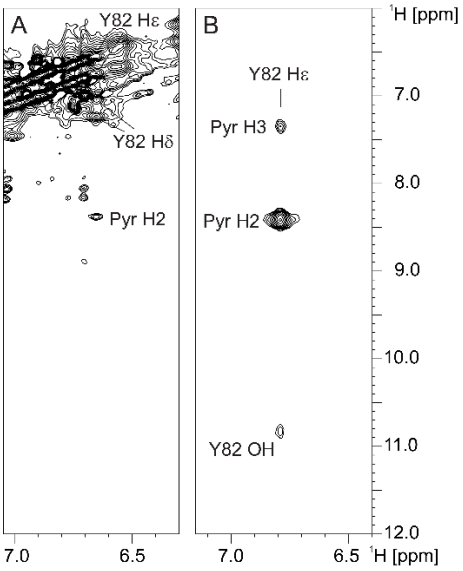
SI Figure 15. HDX measurements of FKBP12 without a ligand present (Apo, blue), with 11 (yellow), 10 (grey), SAFit1 (orange) or 12[2,3] (green, see A for chemical structures)). The deuterium uptake was measured at 1, 10 and 100 minutes exchange time. The sulfonamide ligands 11 and 12 induce a more closed conformation in multiple regions of FKBP12 (reflected by reduced deuterium uptake compared to the *apo* state, B-H). The sulfonimidamide 10 also shields parts of FKBP12 such as the 80s loop overhanging the FK506 binding site compared to the *apo* state (indicated by peptides in C and F-H). At the same time, 10 increases the susceptibility to HDX around the 30s loop indicated by a facilitated deuterium uptake of peptides in B (10-minute time point) and E (10- and 100-minute time points). An induction of solvent accessibility was observed for peptide V^{22}-M^{29} by the ligand SAFit1 (D; effect most visible at 1- and 10-minute time points), which is known to induce a more flexible conformation in FKBPs.[4,5]


A)
ω1 - 15N (ppm)
ω2 - 1 (ppm)
FKBP12 APO (15N TROSY)
FKBP12 2eq 11 (15N BEST-TROSY)
FKBP12 2eq 11 (15N direct detected)


B)
ω1 - 15N (ppm)
ω2 - 1H (ppm)
0 eq
0.125 eq
0.25 eq
0.5 eq
1 eq
2 eq
4 eq
8 eq



SI Figure 16. A) ^{1}H, ^{15}N HSQC of FKBP12 with 2 eq. **11** (green and blue) overlayed with the FKBP12 apo spectrum (red). B) ^{1}H, ^{15}N HSQC of FKBP12 titrated with 0-8 eq. **10** (red to purple). C) Zoom in on the signal of the Trp59 side chain NH. D) Zoom in on the signal of the Ile56 backbone NH. E) Bar diagram of the chemical shift pertubations of each backbone NH signal of FKBP12 with either 2 eq. **11** (orange) or 8 eq. **10** (blue). Grey bars indicate a missing signal.

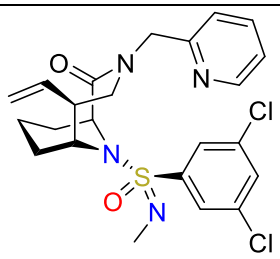
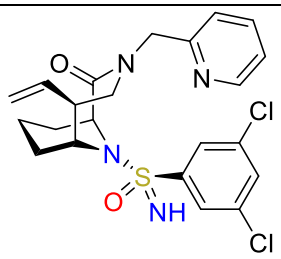
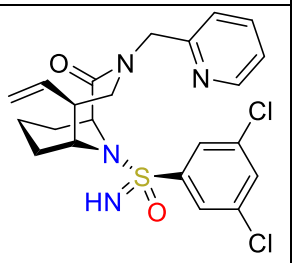


SI Figure 17. Expansions from NOESY spectra of FKBP12 complexes with **11** (A) and **10** (B), recorded at a temperature of 298 K using 0.5 mM samples of [u-^{13}C/^{15}N]-labeled FKBP12 with a two-fold excess of inhibitors in 25 mM phosphate buffer, pH7, containing 5% D_2O. Panel A shows a 2D F_2-^{13}C-edited NOESY (800 MHz), recorded without ^{13}C-decoupling in the indirect (vertical) dimension to allow a distinction between intra- and intermolecular NOEs. The spectrum shown in panel B is a F_1-F_3 plane from a 3D F_1-^{13}C/^{15}N-filtered NOESY-[^{13}C,^{1}H]-HMQC (950 MHz), taken at the ^{13}C chemical shift of Tyr82 C^{ε}. This experiment exclusively detects intermolecular NOEs. Exceptions are hydroxyl protons which escape the ^{13}C/^{15}N filter due to the lack of a coupling. Note that in the **11** complex the Tyr82 OH is observable even at 298 K, indicating a strong hydrogen bond.

SI Table 2. Parameters of the performed FP Assays.

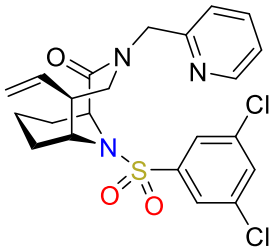
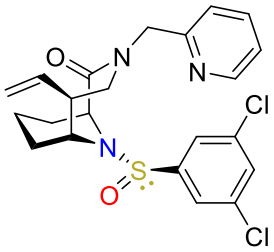
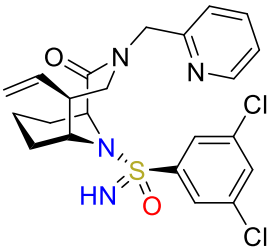
	FKBP12	FKBP12.6	FKBP51FK1	FKBP52FK1	Ab-FBP (1-113)	paFKPA (23-253)
Protein concentration in nM	1	10	15	10	8	40
Tracer concentration in nM	0.5	1	1	1	1	1
Tracer affinity in nM	0.3	1.7	5.7	4.1	3.3	18

SI Table 3. Refinement data of the cocrystal structures of FKBP12 with compounds **6a**, **5b** and **5a**.

PDB entry	**8CHI**	**8CHJ**	**8CHK**
Protein	**FKBP12**	**FKBP12**	**FKBP12**
Ligand name	**6a**	**5b**	**5a**
Ligand structure			
Data collection			
Beamline	BESSY II (BL14.2)	BESSY II (BL14.2)	BESSY II (BL14.1)
Wavelength	λ = 0.9184 Å	λ = 0.9184 Å	λ = 0.9184 Å
Space group	P 4_1 2_1 2	P 1 2_1 1	P 2_1 2_1 2_1
Cell dimensions			
a, *b*, *c* (Å)	69.36, 69.36, 129.85	48.72, 80.12, 66.87	44.87, 53.42, 124.97
α, β, γ (°)	90, 90, 90	90, 91.07, 90	90, 90, 90
Resolution (Å)	47.40-1.70 (1.73-1.70)	48.71-1.70 (1.73-1.70)	49.12-1.55 (1.58-1.55)
R_{merge}	0.114 (1.776)	0.071 (1.007)	0.104 (1.501)
R_{pim}	0.032 (0.488)	0.045 (0.634)	0.066 (0.978)
$I/\sigma(I)$	22.2 (2.2)	13.2 (1.7)	10.8 (1.1)

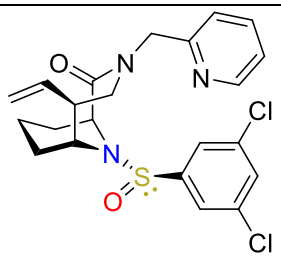
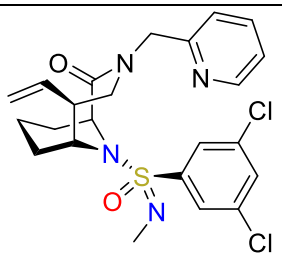
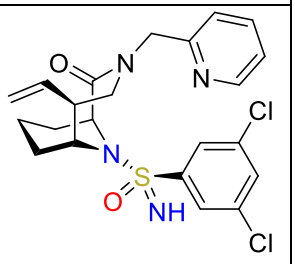
CC1/2	1.000 (0.732)	0.999 (0.711)	0.998 (0.345)
Completeness (%)	100.0 (100.0)	99.7 (96.3)	98.9 (91.6)
Redundancy	25.7 (27.2)	6.7 (6.5)	6.1 (5.2)
Refinement			
Resolution (Å)	47.40-1.70	48.71-1.70	49.12-1.55
No. of reflections	35656	56687	44070
R_{work}/R_{free} (%)	18.8/22.2	19.2/21.2	20.8/24.0
No. of atoms	3713	7049	5459
Average *B* ($Å^2$)	25.0	29.0	20.0
R.m.s. deviations			
Bond lengths (Å)	0.0144	0.0119	0.0135
Bond angles (°)	1.799	1.664	1.731
Ramachandran plot			
Favoured (%)	97.0	97.0	97.0
Allowed (%)	3.0	3.0	3.0
Outlier (%)	0.0	0.0	0.0

SI Table 4. Refinement data of the cocrystal structures of FKBP12 with compounds **1**, **4b** and FKBP51FK1 with compound **5a**.

PDB entry	**8CHL**	**8CHM**	**8CHN**
Protein	**FKBP12**	**FKBP12**	**FKBP51FK1**
Ligand name	**1**	**4b**	**5a**
Ligand structure			
Data collection			
Beamline	BESSY II (BL14.1)	BESSY II (BL14.1)	BESSY II (BL14.1)
Wavelength	λ = 0.9184 Å	λ = 0.9184 Å	λ = 0.9184 Å
Space group	P 6_1	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions			
a, *b*, *c* (Å)	70.58, 70.58, 84.26	35.59, 40.08, 91.21	42.22, 54.05, 56.09
α, β, γ (°)	90, 90, 120	90, 90, 90	90, 90, 90
Resolution (Å)	35.29-1.40 (1.42-1.40)	45.61-1.12 (1.14-1.12)	38.92-0.99 (1.01-0.99)
R_{merge}	0.073 (1.518)	0.032 (0.106)	0.037 (0.852)
R_{pim}	0.039 (1.052)	0.015 (0.056)	0.022 (0.524)
$I/\sigma(I)$	13.6 (0.8)	30.7 (14.8)	18.0 (1.9)
CC1/2	0.999 (0.313)	0.999 (0.996)	0.999 (0.683)
Completeness (%)	99.8 (97.9)	99.7 (99.6)	99.8 (99.5)
Redundancy	3.2 (1.8)	7.0 (7.2)	6.9 (6.6)
Refinement			
Resolution (Å)	35.29-1.40	45.61-1.12	38.92-0.99
No. of reflections	46741	50866	71869
R_{work}/R_{free} (%)	19.5/22.3	14.2/15.2	19.7/20.3
No. of atoms	3686	1949	2213

Average *B* (Å^2)	17.0	13.0	14.0
R.m.s. deviations			
Bond lengths (Å)	0.0134	0.0168	0.0139
Bond angles (°)	1.743	1.878	1.884
Ramachandran plot			
Favoured (%)	97.0	97.0	99.0
Allowed (%)	3.0	3.0	1.0
Outlier (%)	0.0	0.0	0.0

SI Table 5. Refinement data of the cocrystal structures of FKBP51FK1 with compounds **4b**, **6a** and **5b**.

PDB entry	**8CHP**	**8CHQ**	**8CHR**
Protein	**FKBP51FK1**	**FKBP51FK1**	**FKBP51FK1**
Ligand name	**4b**	**6a**	**5b**
Ligand structure			
Data collection			
Beamline	BESSY II (BL14.1)	BESSY II (BL14.1)	BESSY II (BL14.1)
Wavelength	λ = 0.9184 Å	λ = 0.9184 Å	λ = 0.9184 Å
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions			
a, *b*, *c* (Å)	42.31, 54.45, 56.41	42.35, 54.65, 56.65	42.13, 54.22, 56.01
α, *β*, *γ* (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	28.74-1.00 (1.02-1.00)	39.33-1.01 (1.03-1.01)	38.96-1.10 (1.12-1.10)

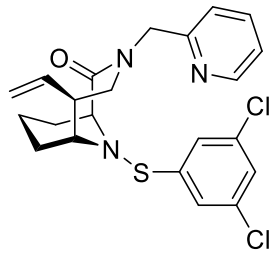
R_{merge}	0.031 (0.363)	0.029 (0.620)	0.047 (1.104)
R_{pim}	0.013 (0.162)	0.017 (0.368)	0.028 (0.656)
I/σ(I)	26.3 (4.9)	25.4 (2.9)	16.0 (1.6)
CC1/2	1.000 (0.923)	1.000 (0.836)	1.000 (0.632)
Completeness (%)	100.0 (100.0)	98.4 (96.3)	100.0 (100.0)
Redundancy	7.0 (6.8)	7.1 (7.0)	7.1 (7.2)
Refinement			
Resolution (Å)	28.74-1.00	39.33-1.01	38.96-1.10
No. of reflections	71000	68326	52743
R_{work}/R_{free} (%)	18.3/19.9	15.7/17.2	17.2/20.1
No. of atoms	2227	2216	2155
Average *B* ($Å^2$)	11.0	15.0	16.0
R.m.s. deviations			
Bond lengths (Å)	0.0145	0.0101	0.0139
Bond angles (°)	1.903	1.683	1.893
Ramachandran plot			
Favoured (%)	99.0	99.0	98.0
Allowed (%)	1.0	1.0	2.0
Outlier (%)	0.0	0.0	0.0

Synthetic procedures

General information

Air- and water-sensitive reactions were performed under argon atmosphere with commercially available dry solvents. All commercially available chemicals and solvents were used as received. Silica gel column chromatography was performed on silica (SiO_2) from Macherey-Nagel (particle size 0.04-0.063 mm) with a mixture of cyclohexane and ethyl acetate (Cy/EA) as mobile phase. Thin-layer chromatography (TLC) was performed on precoated aluminium plates with a fluorescence indicator from Merck (silica gel 60 F_{254}). ^{1}H-NMR and ^{13}C-NMR spectra were measured by the NMR Department of the Technical University Darmstadt, either on a 300 MHz Avance II spectrometer or a 500 MHz spectrometer DRX 500 from Bruker BioSpin GmbH. Chemical shifts are given in parts per million (ppm) and are referenced to residual solvents (^{1}H-NMR: $CDCl_3$, δ = 7.26 ppm; ^{13}C-NMR: $CDCl_3$, δ = 77.16 ppm.). Coupling constants (*J*) are given in hertz (Hz). LC-MS (liquid chromatography – mass spectrometry) was performed on an Agilent 1260 Infinity II system with a Poroshell 120 EC-C18 1.9 µm, 2.1 x 50 mm column from Agilent. Eluents were 0.1 % formic acid in water (Eluent A) and 0.1 % formic acid in acetonitrile (Eluent B), the used method was 5 % B to 100 % B in 2 min. MS was recorded with an Agilent InfinityLab G6125B LC/MSD. High-resolution mass spectrometry (HRMS) was measured by the MS Department of the Technical University Darmstadt on a Bruker Daltonics Impact II mass spectrometer (quadrupole time-of-flight).

Compound **3**: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)thio)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



3,5-Dichlorobenzenethiol (105 mg, 586 µmol, 1.0 eq.) was wetted with acetic acid (32 µL, 560 µmol, 1.0 eq.) and cooled to -40 °C. Sulfuryl chloride (100 µL, 1237 µmol, 2.1 eq.) was added and the reaction mixture was allowed to warm to room temperature without stirring. At room temperature, the reaction mixture was completely liquid. Coproducts were removed *in vacuo* to give the crude sulfenyl chloride. (1*S*,5*R*,6*R*)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one **2** (95 mg, 350 µmol, 0.6 eq.) was dissolved in MeCN (20 mL) under argon atmosphere. DIPEA (300 µL, 1764 µmol, 3.0 eq.) was added and the reaction mixture was cooled to 0 °C. The crude sulfenyl chloride was dissolved in a small amount of MeCN and added to the reaction mixture. The solution was allowed to warm to room temperature and stirred for 19 h under argon atmosphere. The reaction was quenched with water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1) to afford **3**.

Yield: 87 mg, 55 %

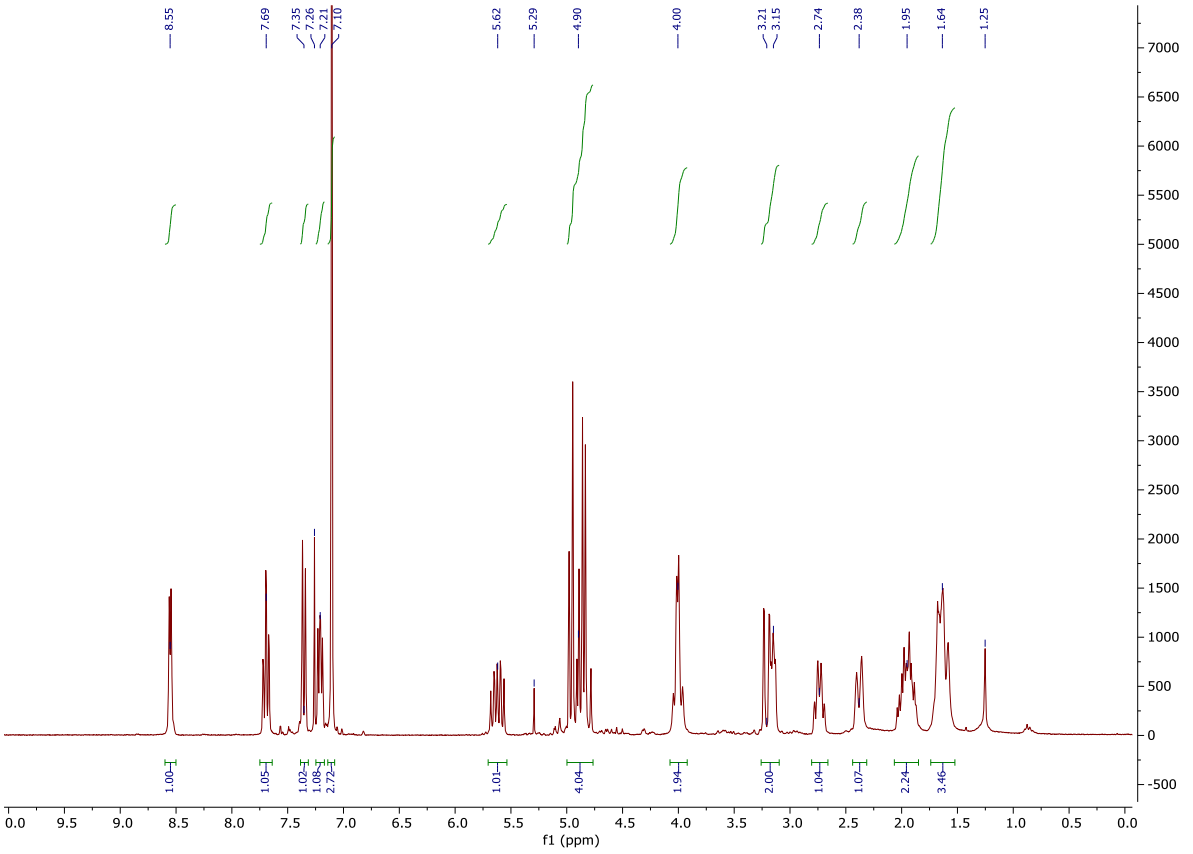
Purity: 88 % (HPLC, UV-absorption 220 nm)

TLC: R_f = 0.42 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{22}H_{23}Cl_2N_3OS$: $[M+H]^+$ = 448.10117, found: $[M+H]^+$ = 448.10139, error: 0.22 mDa or 0.50 ppm

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.52–1.74 (m, 3H), 1.85–2.07 (m, 2H,), 2.38 (d, 1H, *J* = 13.5 Hz), 2.66–2.81 (m, 1H), 3.09–3.17 (m, 1H), 3.21 (dd, 1H, *J* = 14.4/1.8 Hz), 3.92–4.07 (m, 2H), 4.76–5.00 (m, 4H), 5.54–5.70 (m, 1H), 7.10 (s, 3H), 7.21 (dd, 1H, *J* = 7.4/5.3 Hz), 7.35 (d, 1H, *J* = 7.9 Hz), 7.69 (ddd, 1H, *J* = 7.7/7.7/1.7 Hz), 8.55 (d, 1H, *J* = 4.7 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.4, 28.6, 29.7, 50.1, 51.8, 56.3, 65.7, 69.0, 116.2, 120.4, 122.3, 122.6, 125.6, 135.8, 137.1, 138.5, 146.3, 149.3, 157.5, 173.4 ppm.


8.55
7.69
7.35
7.26
7.21
7.10
5.62
5.29
4.90
4.00
3.21
3.15
2.74
2.38
1.95
1.64
1.25
1.00
1.05
1.02
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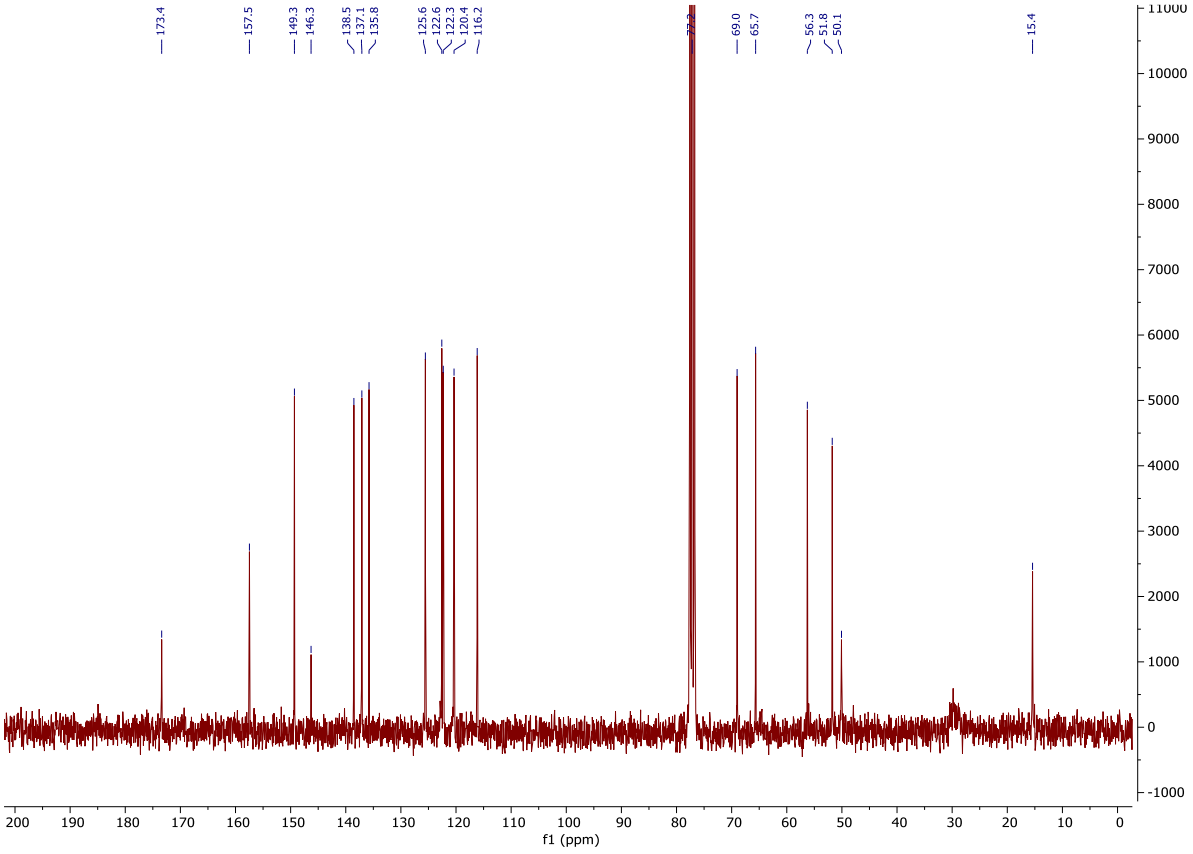
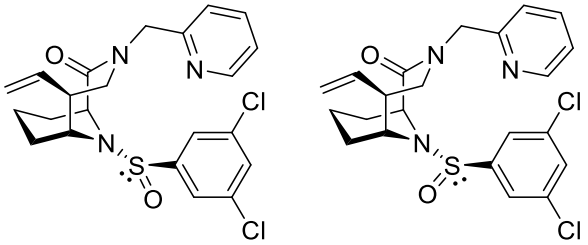
1.94
2.00
1.04
1.07
2.24
3.46
f1 (ppm)


173.4
157.5
149.3
146.3
138.5
137.1
135.8
125.6
122.6
122.3
120.4
116.2
77.2
69.0
65.7
56.3
51.8
50.1
15.4
f1 (ppm)

Compound **4a** and **4b**: (1*S*,5*S*,6*R*)-10-((*R*)-(3,5-dichlorophenyl)sulfinyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one and (1*S*,5*S*,6*R*)-10-((*S*)-(3,5-dichlorophenyl)sulfinyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



KF (12.1 mg, 210 µmol, 1.9 eq.) and mCPBA (70 %, wet with water, 44.6 mg, 181 µmol, 1.7 eq.) were dissolved in MeCN/H_2O 5:1 (5 mL) and cooled to 0 °C. After stirring for 30 min at 0 °C, sulfenamide **3** (49 mg, 109 µmol, 1.0 eq.) was added to the reaction. The mixture was stirred at 0 °C for 4.5 h, then sat. aq. $NaHCO_3$ was added and it was extracted with EA. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 1:2) to afford both diastereomers **4a** and **4b**.

4b:

Yield: 2.4 mg, 5 %

Purity: 93 % (HPLC, UV-absorption 220 nm)

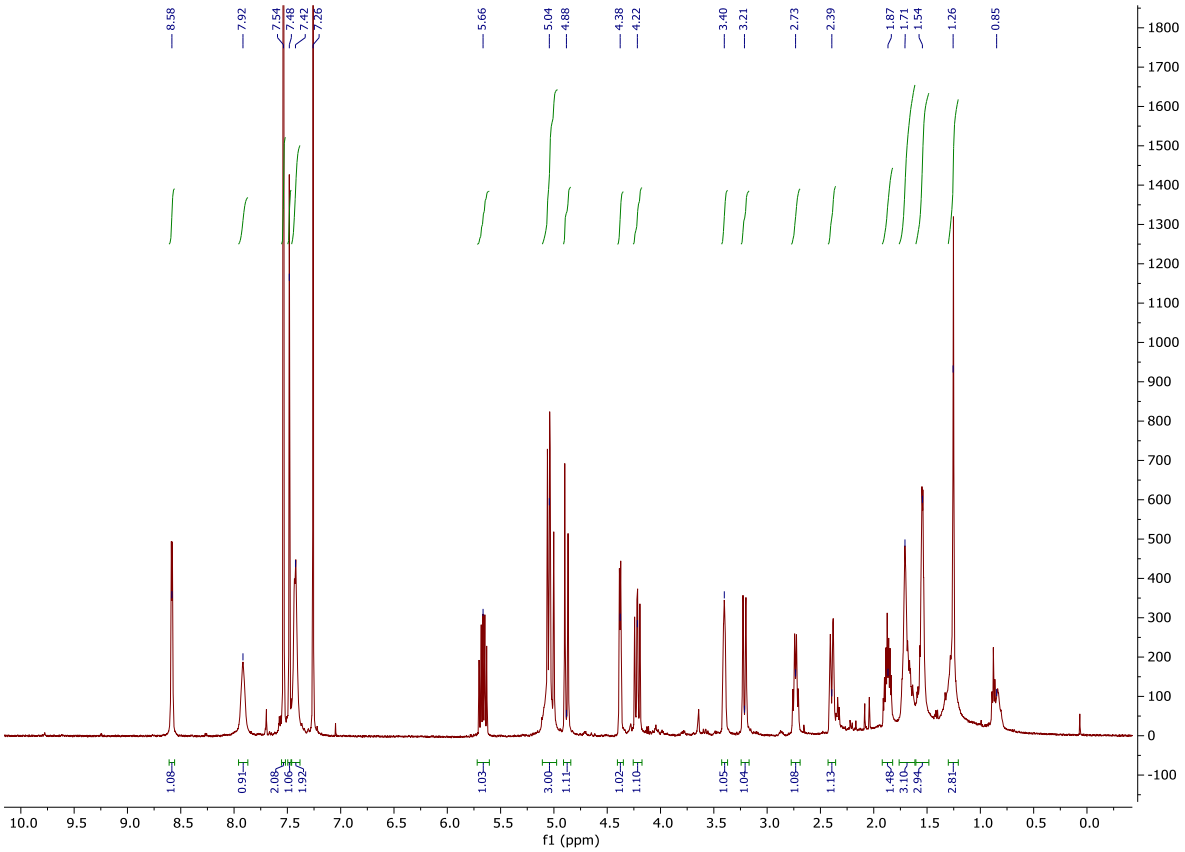
Appearance: colourless solid

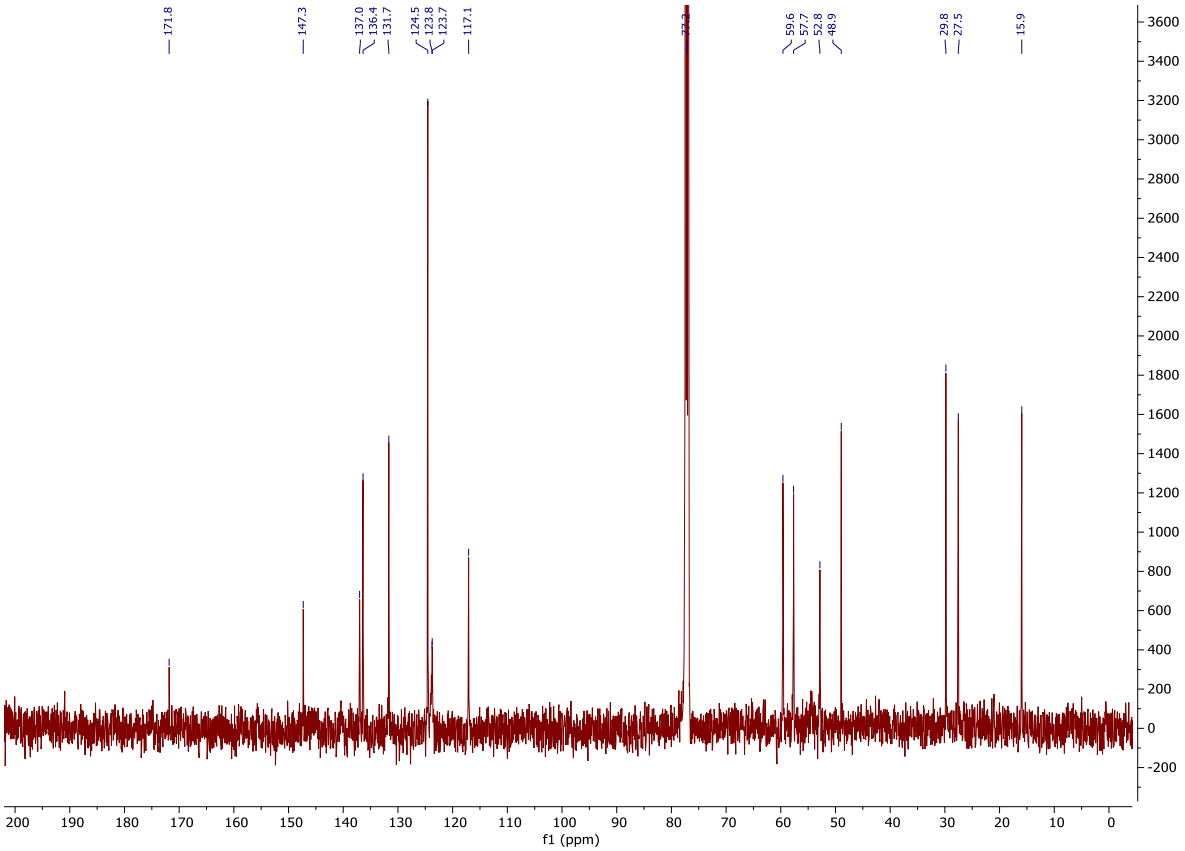
TLC: R_f = 0.44 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{22}H_{23}Cl_2N_3O_2S$: $[M+H]^+$ = 464.09608, found: $[M+H]^+$ = 464.09640, error: 0.32 mDa or 0.69 ppm

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.48–1.61 (m, 2H), 1.61–1.78 (m, 2H), 1.82–1.92 (m, 1H), 2.39 (d, 1H, *J* = 13.5 Hz), 2.69–2.77 (m, 1H), 3.21 (d, 1H, *J* = 13.8 Hz), 3.37–3.43 (m, 1H), 4.22 (dd, 1H, *J* = 13.9/10.8 Hz), 4.38 (d, 1H, *J* = 6.0 Hz), 4.88 (d, 1H, *J* = 15.5 Hz), 4.97–5.11 (m, 3H), 5.61–5.71 (m, 1H), 7.38–7.46 (m, 2H), 7.48 (t, 1H, *J* = 1.8 Hz), 7.54 (d, 2H, *J* = 1.9 Hz), 7.87–7.96 (m, 1H), 8.58 (d, 1H, *J* = 5.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.9, 27.5, 29.8, 48.9, 52.9 , 57.7, 59.6, 117.1, 123.7, 123.8, 124.5, 131.7, 136.4, 137.0, 147.3, 171.8 ppm.


8.58
7.92
7.54
7.48
7.42
7.26
5.66
5.04
4.88
4.38
4.22
3.40
3.21
2.73
2.39
1.87
1.71
1.54
1.26
0.85
1.08
0.91
2.08
1.06
1.92
1.03
3.00
1.11
1.02
1.10
1.05
1.04
1.08
1.13
1.48
3.10
2.94
2.81
f1 (ppm)


171.8
147.3
137.0
136.4
131.7
124.5
123.8
123.7
117.1
77.2
59.6
57.7
52.8
48.9
29.8
27.5
15.9
f1 (ppm)

4a:

Yield: 3.6 mg, 7 %

Purity: 92 % (HPLC, UV-absorption 220 nm)

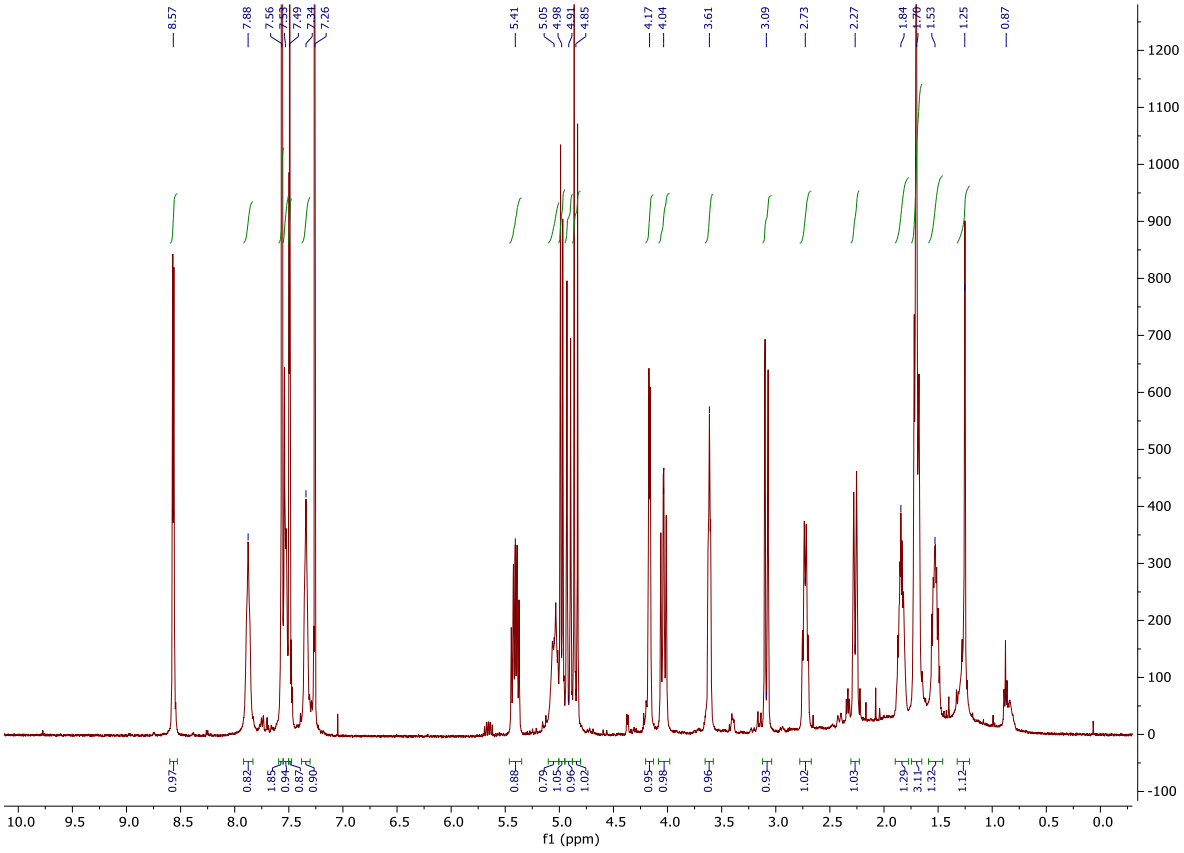
Appearance: colourless solid

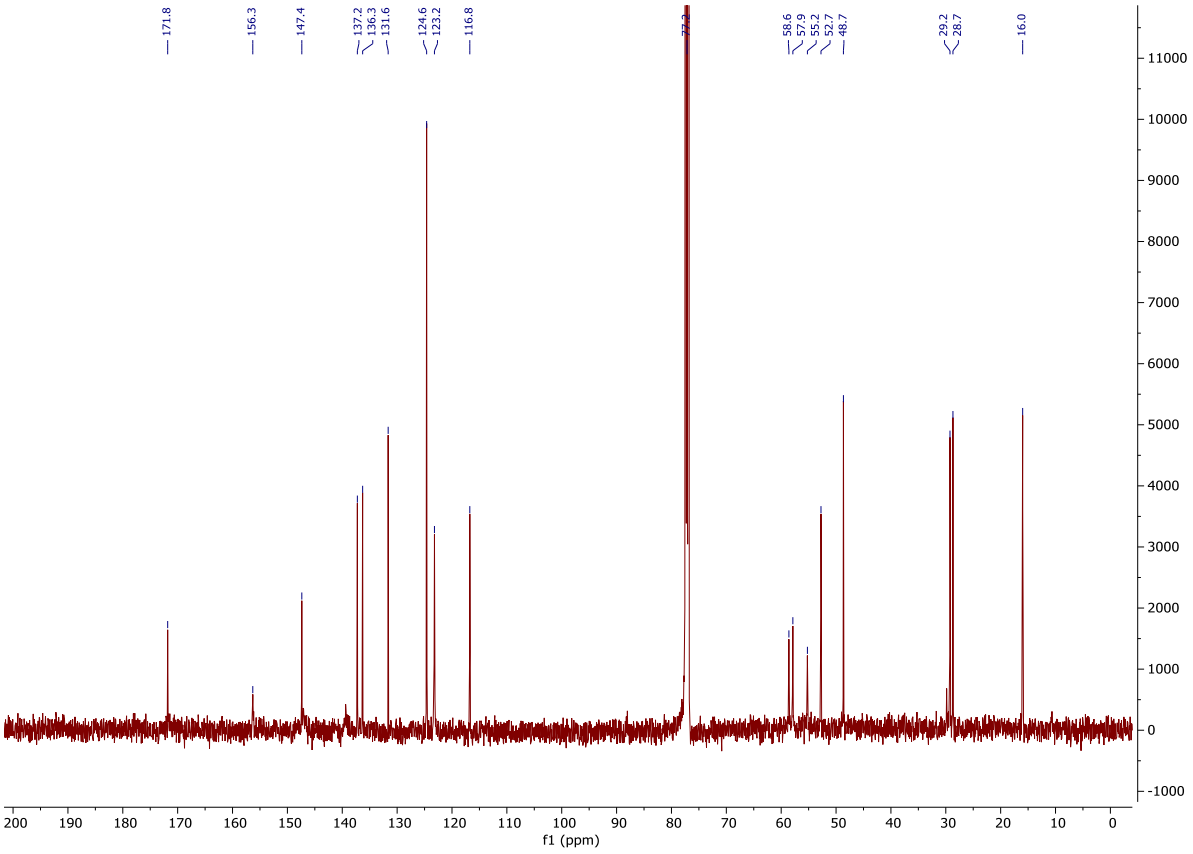
TLC: R_f = 0.41 (Cy/EA 1:2)

HR-MS (ESI): calculated for sum formula $C_{22}H_{23}Cl_2N_3O_2S$: $[M+H]^+$ = 464.09608, found: $[M+H]^+$ = 464.09663, error: 0.55 mDa or 1.18 ppm

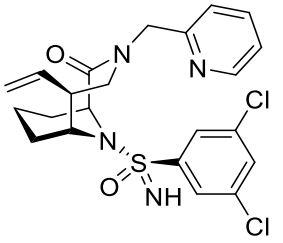
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.46–1.59 (m, 1H), 1.65–1.74 (m, 3H), 1.77–1.90 (m, 1H), 2.27 (d, 1H, *J* = 13.4 Hz), 2.67–2.78 (m, 1H), 3.09 (dd, 1H, *J* = 14.1/1.7 Hz), 3.58–3.65 (m, 1H), 4.04 (dd, 1H, *J* = 13.9/11.2 Hz), 4.17 (d, 1H, *J* = 5.9 Hz), 4.85 (d, 1H, *J* = 15.7 Hz), 4.91 (d, 1H, *J* = 17.0 Hz), 4.98 (d, 1H, *J* = 10.2 Hz), 5.01–5.10 (m, 1H), 5.35–5.46 (m, 1H), 7.30–7.38 (m, 1H), 7.49 (t, 1H, *J* = 1.9 Hz), 7.50–7.55 (m, 1H), 7.56 (d, 2H, *J* = 1.9 Hz), 7.83–7.92 (m, 1H), 8.57 (d, 1H, *J* = 4.8 Hz) ppm.

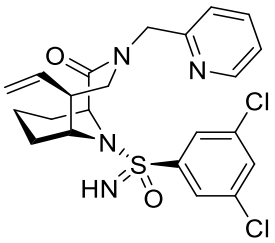
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 16.0, 28.7, 29.2, 48.7, 52.8, 55.2, 57.9, 58.6, 116.8, 123.2, 124.6, 131.6, 136.3, 137.3, 147.4, 156.3, 171.8 ppm.




171.8
156.3
147.4
137.2
136.3
131.6
124.6
123.2
116.8
77.2
58.6
57.9
55.2
52.7
48.7
29.2
28.7
16.0
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Compound **5a** and **5b**: (1*S*,5*S*,6*R*)-10-((*S*)-(3,5-dichlorophenyl)sulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one and (1*S*,5*S*,6*R*)-10-((*R*)-(3,5-dichlorophenyl)sulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one





Sulfenamide **3** (130 mg, 290 µmol, 1.0 eq.), (Diacetoxyiodo)benzene (305 mg, 947 µmol, 3.3 eq.) and ammonium acetate (104 mg, 1350 µmol, 4.7 eq.) were dissolved in MeOH (8 mL) and stirred at room temperature. After 19 h, water was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 1:2) to afford pure diastereomers **5a** and **5b**.

5a:

Yield: 36 mg, 26 %

Purity: 96 % (HPLC, UV-absorption 220 nm)

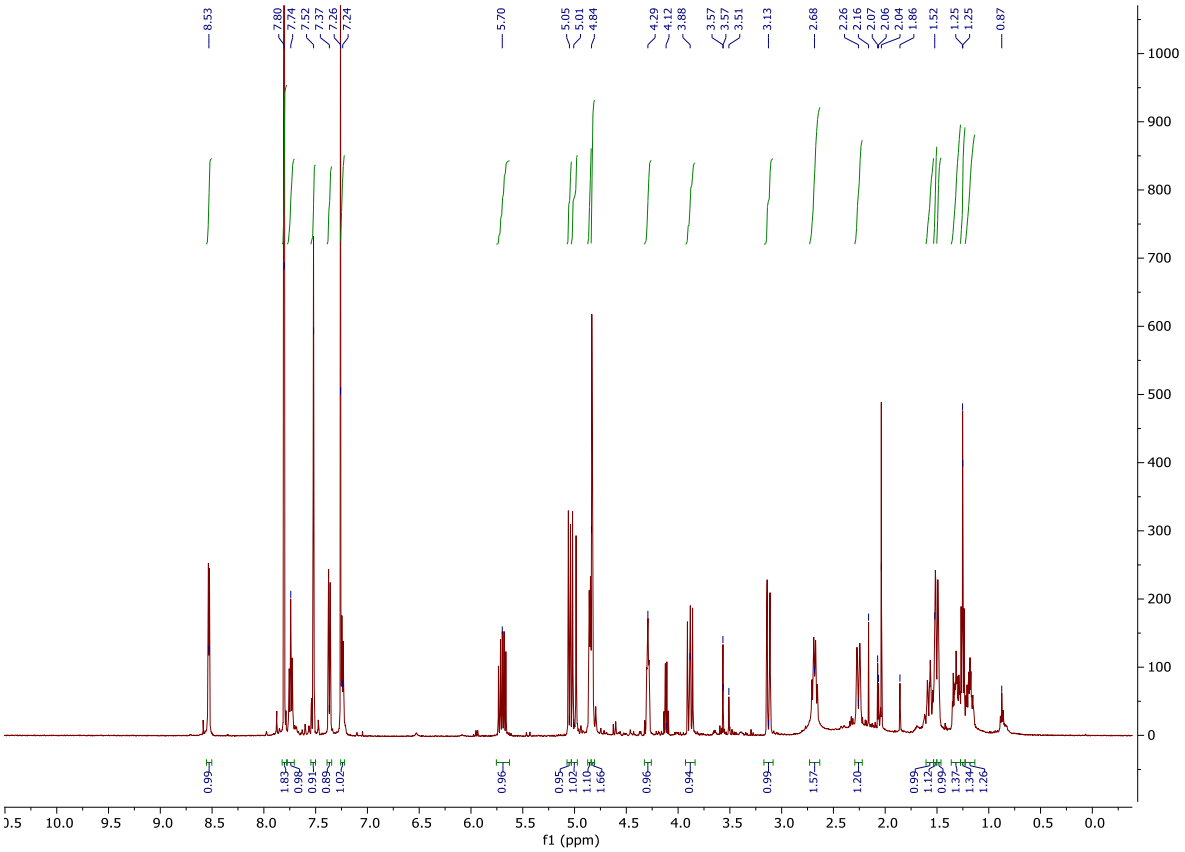
Appearance: colourless solid

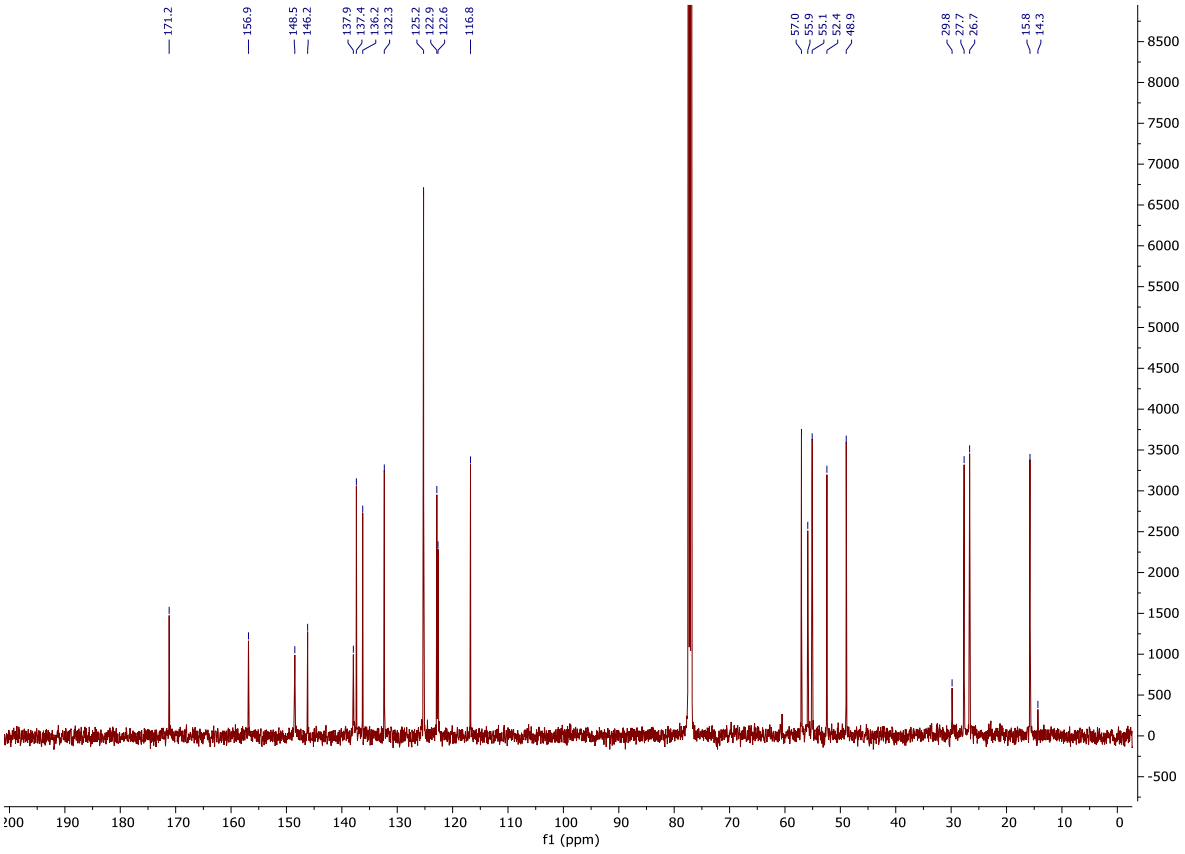
TLC: R_f = 0.26 (Cy/EA 1:2)

HR-MS (ESI): m/z calculated for sum formula $C_{22}H_{24}Cl_2N_4O_2S$: $[M+H]^+$ = 479.10698, found: $[M+H]^+$ = 479.10704, error: 0.06 mDa or 0.13 ppm

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13–1.23 (m, 1H), 1.27–1.36 (m, 1H), 1.50–1.53 (m, 1H), 1.53–1.61 (m, 1H), 2.22-2.29 (m, 1H), 2.63–2.73 (m, 1H), 3.13 (dd, 1H, *J* = 14.0/1.5 Hz), 3.38 (dd, 1H, *J* = 14.0/10.8 Hz), 4.26–5.33 (m, 1H), 4.81–4.84 (m, 2H), 4.84–4.87 (m, 1H), 5.00 (d, 1H, *J* = 17.1 Hz), 5.05 (d, 1H, *J* = 10.2 Hz), 5.64–5.75 (m, 1H), 7.22–7.26 (m, 1H), 7.37 (d, 1H, *J* = 7.9 Hz), 7.52 (t, 1H, *J* = 1.8 Hz), 7.74 (dd, 1H, *J* = 7.7/7.7 Hz), 7.80 (d, 1H, *J* = 1.8 Hz), 8.53 (d, 1H, *J* = 4.7 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.8, 26.7, 27.7, 48.9, 52.4, 55.1, 55.9, 57.0, 116.8, 122.6, 122.9, 125.3, 132.3, 136.2, 137.4, 137.9, 146.2, 148.5, 156.9, 171.2 ppm.


8.53
7.80
7.74
7.52
7.37
7.26
7.24
5.70
5.05
5.01
4.84
4.29
4.12
3.88
3.57
3.57
3.51
3.13
2.68
2.26
2.16
2.07
2.06
2.04
1.86
1.52
1.25
1.25
0.87
0.99
1.83
0.98
0.91
0.89
1.02
0.96
0.95
1.02
1.10
1.66
0.96
0.94
0.99
1.57
1.20
0.99
1.12
0.99
1.37
1.34
1.26
f1 (ppm)


171.2
156.9
148.5
146.2
137.9
137.4
136.2
132.3
125.2
122.9
122.6
116.8
57.0
55.9
55.1
52.4
48.9
29.8
27.7
26.7
15.8
14.3
f1 (ppm)

5b:

Yield: 53 mg, 35 %

Purity: 98 % (HPLC, UV-absorption 220 nm)

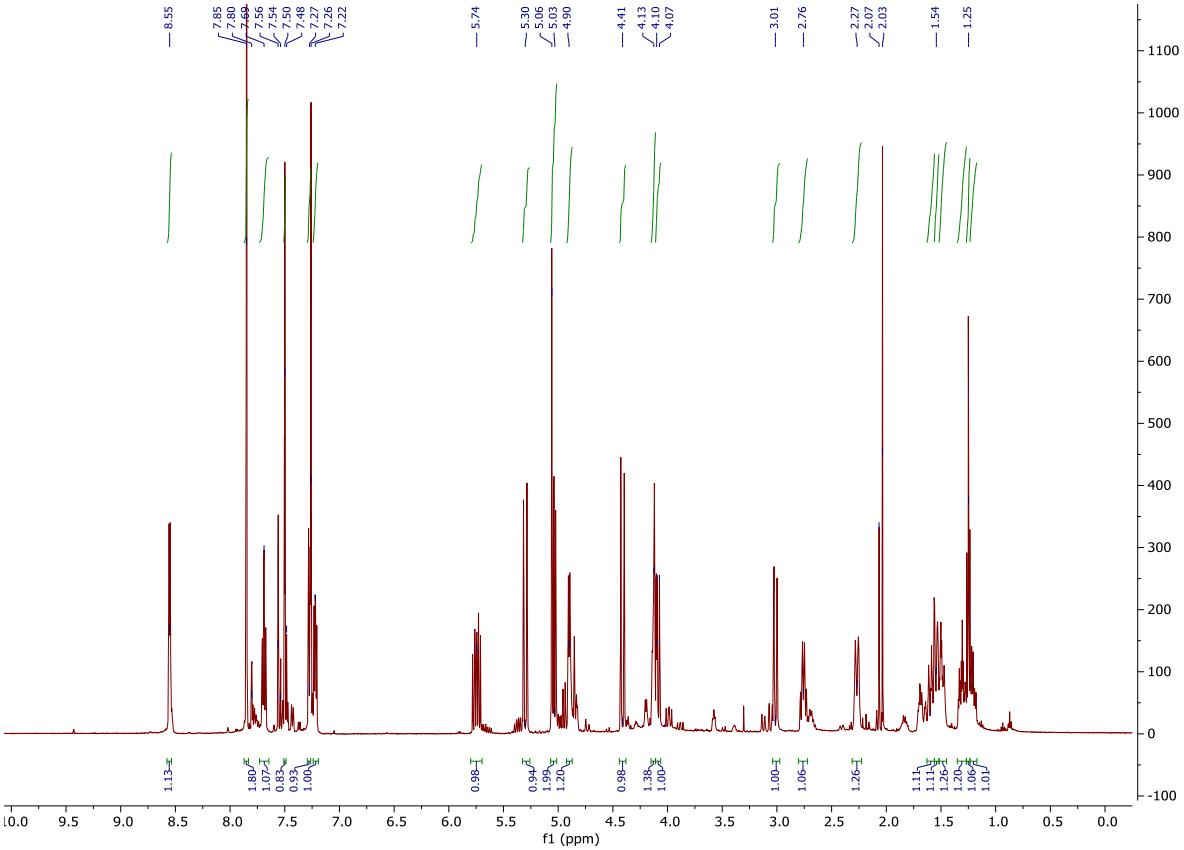
Appearance: colourless solid

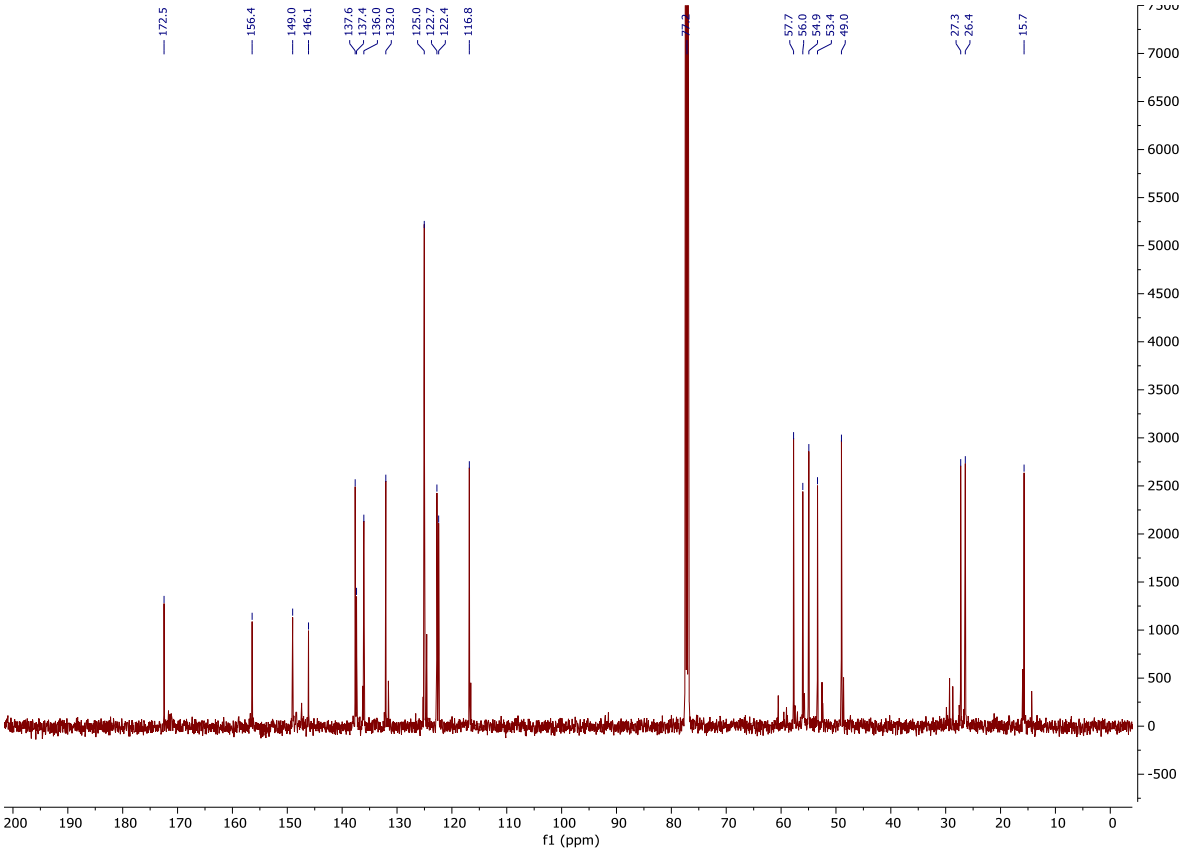
TLC: R_f = 0.17 (Cy/EA 1:2)

HR-MS (ESI): m/z calculated for sum formula $C_{22}H_{24}Cl_2N_4O_2S$: $[M+H]^+$ = 479.10698, found: $[M+H]^+$ = 479.10739, error: 0.38 mDa or 0.83 ppm

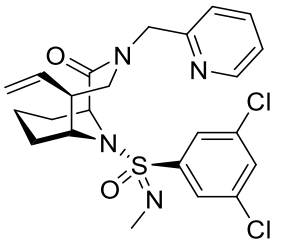
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15–1.23 (m, 1H), 1.27–1.35 (m, 1H), 1.45–1.52 (m, 1H), 1.52–1.56 (m, 1H), 1.56–1.63 (m, 1H), 2.23–2.31 (m, 1H), 2.72–2.80 (m, 1H), 3.01 (dd, 1H, *J* = 14.1/1.6 Hz), 4.06–4.11 (m, 1H), 4.11–4.15 (m, 1H), 4.41 (d, 1H, *J* = 15.7 Hz), 4.87–4.92 (m, 1H), 5.01–5.07 (m, 2H), 5.30 (d, 1H, *J* = 15.7 Hz), 5.70–5.80 (m, 1H), 7.72 (dd, 1H, *J* = 7.5/5.3 Hz), 7.27 (d, 1H, *J* = 8.0 Hz), 7.50 (t, 1H, *J* = 1.9 Hz), 7.69 (ddd, 1H, *J* = 7.8/7.7/1.7 Hz), 7.85 (d, 1H, *J* = 1.9 Hz), 8.55 (d, 1H, *J* = 5.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 26.4, 27.3, 49.0, 53.4, 54.9, 56.0, 57.7, 116.8, 122.4, 122.7, 125.0, 132.0, 136.1, 137.4, 137.6, 146.1, 149.0, 156.4, 172.5 ppm.




172.5
156.4
149.0
146.1
137.6
137.4
136.0
132.0
125.0
122.7
122.4
116.8
77.2
57.7
56.0
54.9
53.4
49.0
27.3
26.4
15.7
f1 (ppm)

Compound **6a**: (1*S*,5*S*,6*R*)-10-((*S*)-3,5-dichloro-*N*-methylphenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5a** (5.0 mg, 10.4 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 3.8 mg, 95.0 µmol, 9.1 eq.) was added and it was stirred for 30 min at 0 °C. MeI (7.0 µL, 112 µmol, 10.8 eq.) was added and the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with MeOH and water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 1:2) to afford **6a**.

Yield: 4.2 mg, 82 %

Purity: 98 % (HPLC, UV-absorption 220 nm)

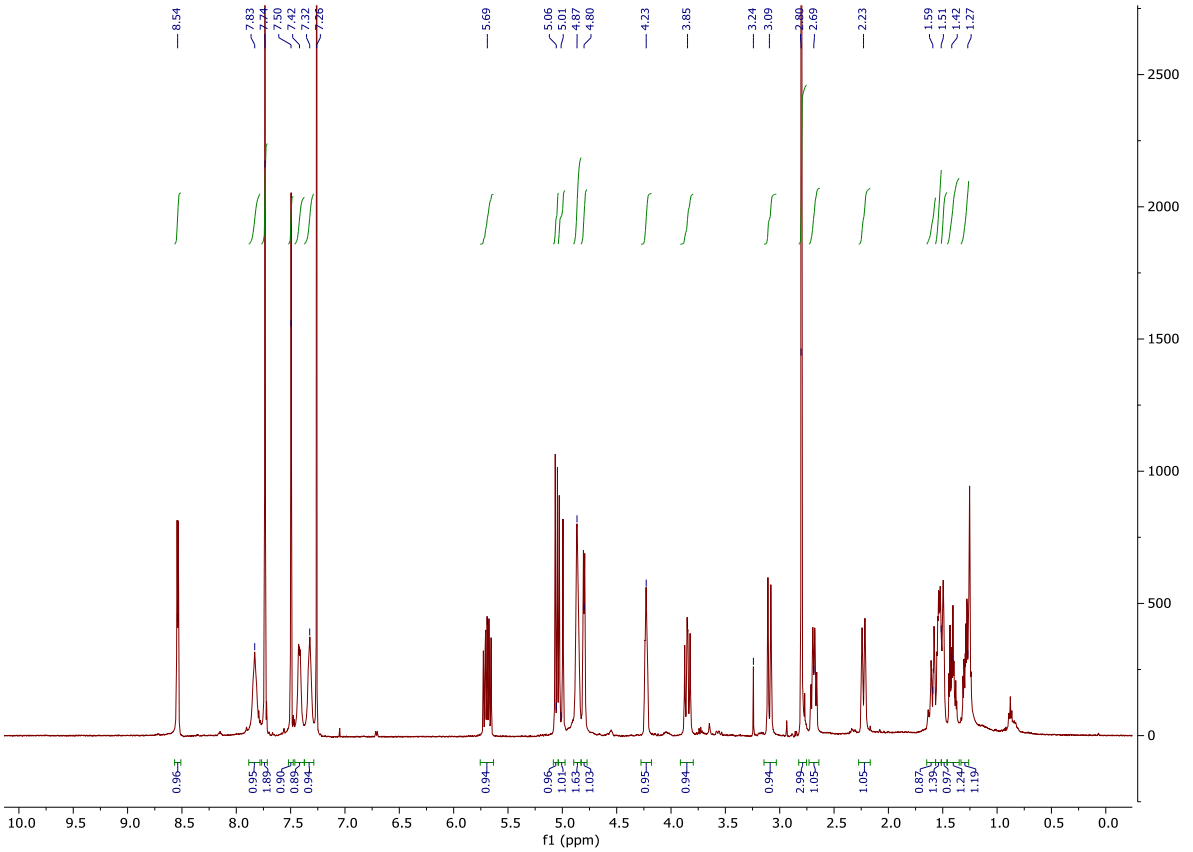
Appearance: colourless solid

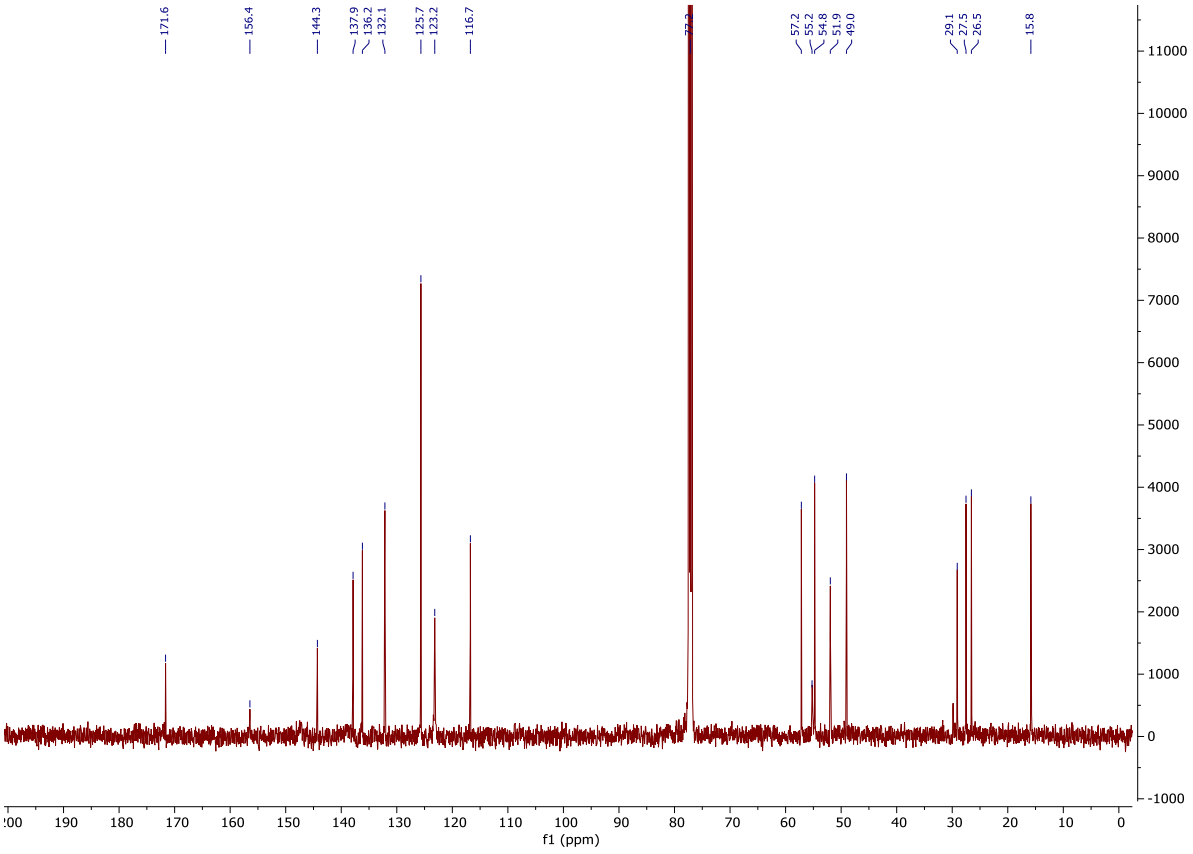
TLC: R_f = 0.43 (Cy/EA 1:2)

HR-MS (ESI): m/z calculated for sum formula $C_{23}H_{26}Cl_2N_4O_2S$: $[M+H]^+$ = 493.12263, found: $[M+H]^+$ = 493.12305, error: 0.42 mDa or 0.86 ppm

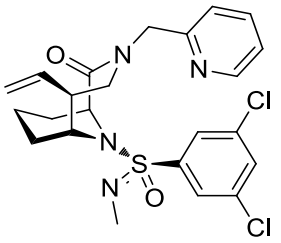
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.26–1.33 (m, 1H), 1.35–1.46 (m, 1H), 1.46–1.51 (m, 1H), 1.51–1.57 (m, 1H), 1.57–1.65 (m, 1H), 2.23 (d, 1H, *J* = 13.5 Hz), 2.64–2.73 (m, 1H), 2.80 (s, 3H), 3.09 (d, 1H, *J* = 14.1 Hz), 3.85 (dd, 1H, *J* = 13.8/11.0 Hz), 4.18–4.28 (m, 1H), 4.80 (d, 1H, *J* = 6.0 Hz), 4.83–4.90 (m, 2H), 5.01 (d, 1H, *J* = 17.0 Hz), 5.06 (d, 1H, *J* = 10.1 Hz), 5.64–5.75 (m, 1H), 7.29–7.37 (m, 1H), 7.37–7.47 (m, 1H), 7.50 (t, 1H, *J* = 1.9 Hz), 7.74 (d, 2H, *J* = 1.9 Hz), 7.78–7.88 (m, 1H), 8.54 (d, 1H, *J* = 4.8 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.8, 26.6, 27.5, 29.1, 49.0, 52.0, 54.7, 55.2, 57.2, 116.8, 123.2, 125.7, 132.1, 136.2, 137.9, 144.3, 156.5, 171.6 ppm.


8.54
7.83
7.81
7.50
7.42
7.32
7.26
5.69
5.06
5.01
4.87
4.80
4.23
3.85
3.24
3.09
2.80
2.69
2.23
1.59
1.51
1.42
1.27
0.96
0.95
1.89
0.90
0.89
0.94
0.94
0.96
1.01
1.63
1.03
0.95
0.94
0.94
2.99
1.05
1.05
0.87
1.39
0.97
1.24
1.19
f1 (ppm)


171.6
156.4
144.3
137.9
136.2
132.1
125.7
123.2
116.7
77.3
57.2
55.2
54.8
51.9
49.0
29.1
27.5
26.5
15.8
f1 (ppm)

Compound **6b**: (1*S*,5*S*,6*R*)-10-((*R*)-3,5-dichloro-*N*-methylphenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5**b (8.3 mg, 17.3 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 4.2 mg, 105 µmol, 8.7 eq.) was added and it was stirred for 30 min at 0 °C. MeI (11 µL, 177 µmol, 10.2 eq.) was added and the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with MeOH and water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 1:2) to afford **6b**.

Yield: 5.4 mg, 64 %

Purity: 96 % (HPLC, UV-absorption 220 nm)

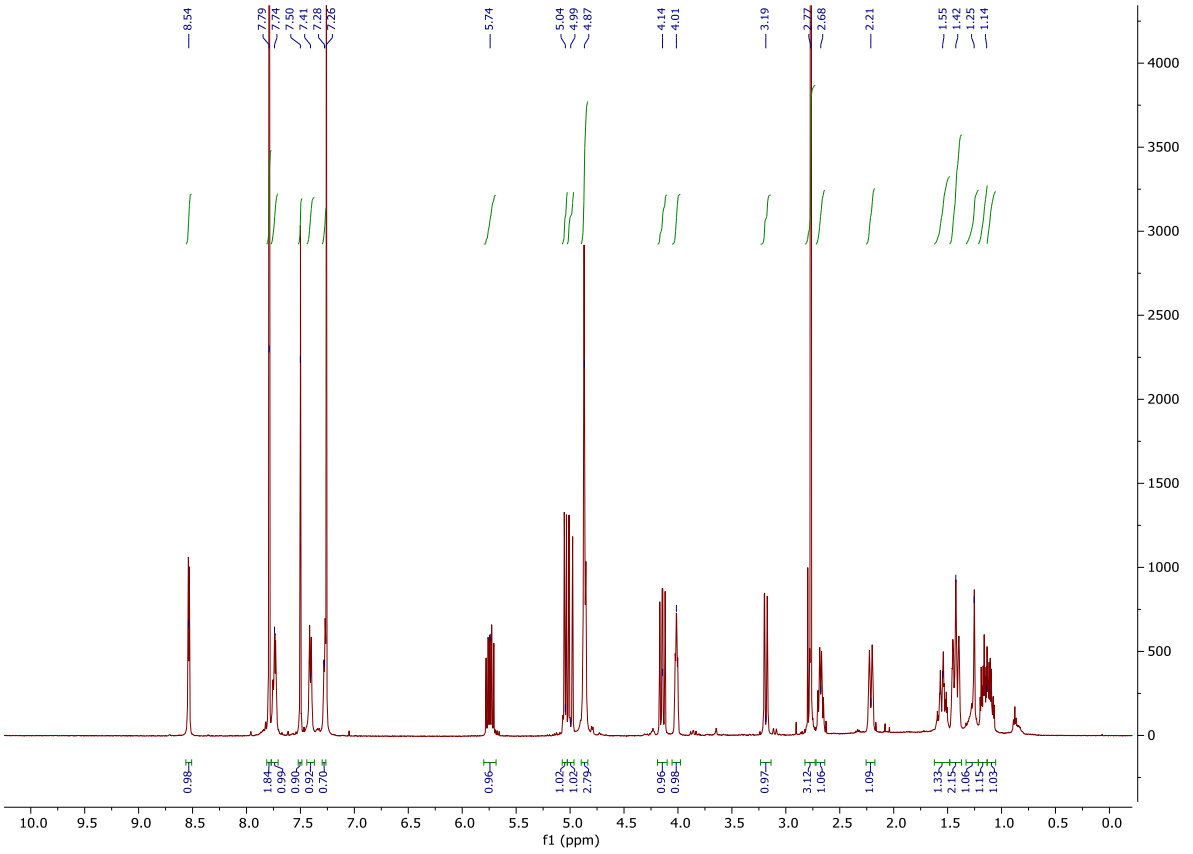
Appearance: colourless solid

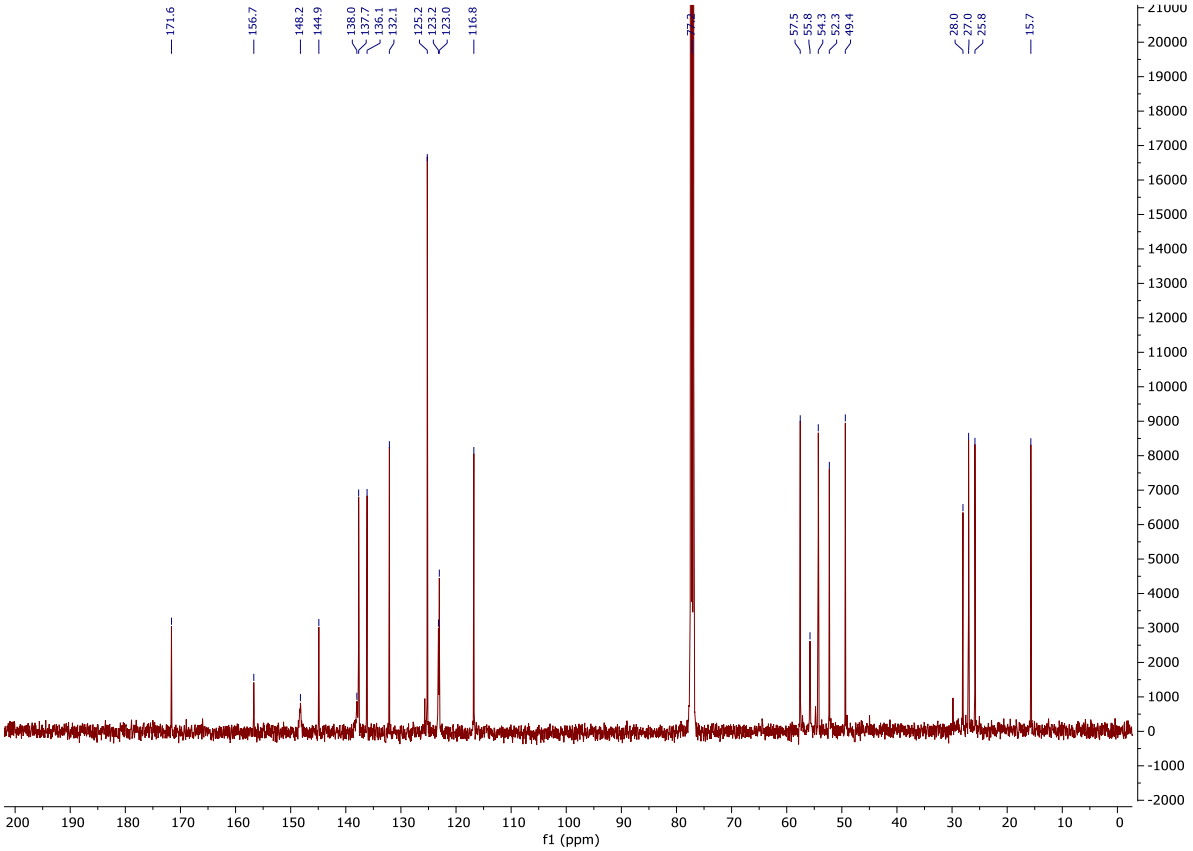
TLC: R_f = 0.40 (Cy/EA 1:2)

HR-MS (ESI): m/z calculated for sum formula $C_{23}H_{26}Cl_2N_4O_2S$: $[M+H]^+$ = 493.12263, found: $[M+H]^+$ = 493.12303, error: 0.40 mDa or 0.82 ppm

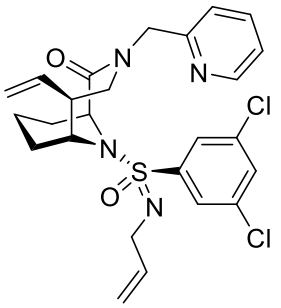
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.06–1.13 (m, 1H), 1.13–1.21 (m, 1H), 1.37–1.48 (m, 2H), 1.48–1.62 (m, 1H), 2.21 (d, 1H, *J* = 13.7 Hz), 2.64–2.72 (m, 1H), 2.77 (s, 3H), 3.19 (dd, 1H, *J* = 14.0/1.6 Hz), 3.98–4.05 (m, 1H), 4.14 (dd, 1H, *J* = 14.0/10.8 Hz), 4.84–4.90 (m, 3H), 4.99 (d, 1H, *J* = 17.0 Hz), 5.04 (d, 1H, *J* = 10.2 Hz), 5.69–5.79 (m, 1H), 7.26–7.30 (m, 1H), 7.41 (d, 1H, *J* = 7.7 Hz), 7.50 (t, 1H, *J* = 1.9 Hz), 7.71–7.77 (m, 1H), 7.79 (d, 2H, *J* = 1.9 Hz), 5.84 (d, 1H, *J* = 4.8 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 25.9, 27.0, 28.0, 49.4, 52.3, 54.3, 55.8, 57.6, 116.8, 123.0, 123.2, 125.2, 132.1, 136.1, 137.7, 138.0, 144.9, 148.2, 156.7, 171.6 ppm.


8.54
7.79
7.74
7.50
7.41
7.28
7.26
5.74
5.04
4.99
4.87
4.14
4.01
3.19
2.77
2.68
2.21
1.55
1.42
1.25
1.14
0.98
1.84
0.99
0.90
0.92
0.70
0.96
1.02
1.02
2.79
0.96
0.98
0.97
3.12
1.06
1.09
1.33
2.15
1.06
1.15
1.03
f1 (ppm)


171.6
156.7
148.2
144.9
138.0
137.7
136.1
132.1
125.2
123.2
123.0
116.8
77.3
57.5
55.8
54.3
52.3
49.4
28.0
27.0
25.8
15.7
f1 (ppm)

Compound **7a**: (1*S*,5*S*,6*R*)-10-((*S*)-*N*-allyl-3,5-dichlorophenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5a** (5.8 mg, 12.1 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 3.7 mg, 55.3 µmol, 4.6 eq.) was added and it was stirred for 30 min at 0 °C. Allylbromide (20 µL, 231 µmol, 19.1 eq.) was added and the reaction mixture was allowed to reach room temperature. After 17 h the solution was again cooled to 0 °C, NaH (60 % in mineral oil, 7.2 mg, 108 µmol, 8,9 eq.) and allylbromide (20 µL, 231 µmol, 19.1 eq.) were added and the reaction mixture was allowed to reach room temperature. After another 25 h water was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1–1:1) to afford **7a**.

Yield: 6.3 mg, 100 %

Purity: 95 % (HPLC, UV-absorption 220 nm)

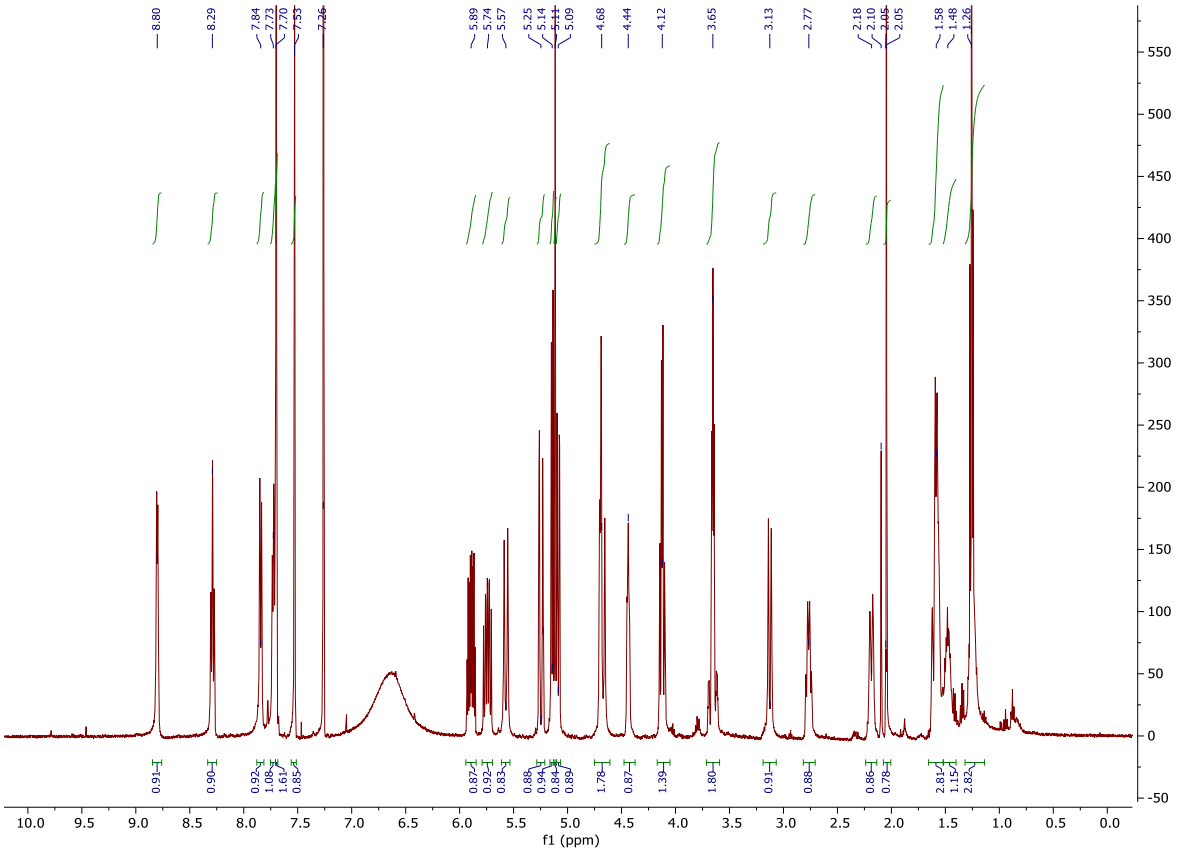
Appearance: colourless solid

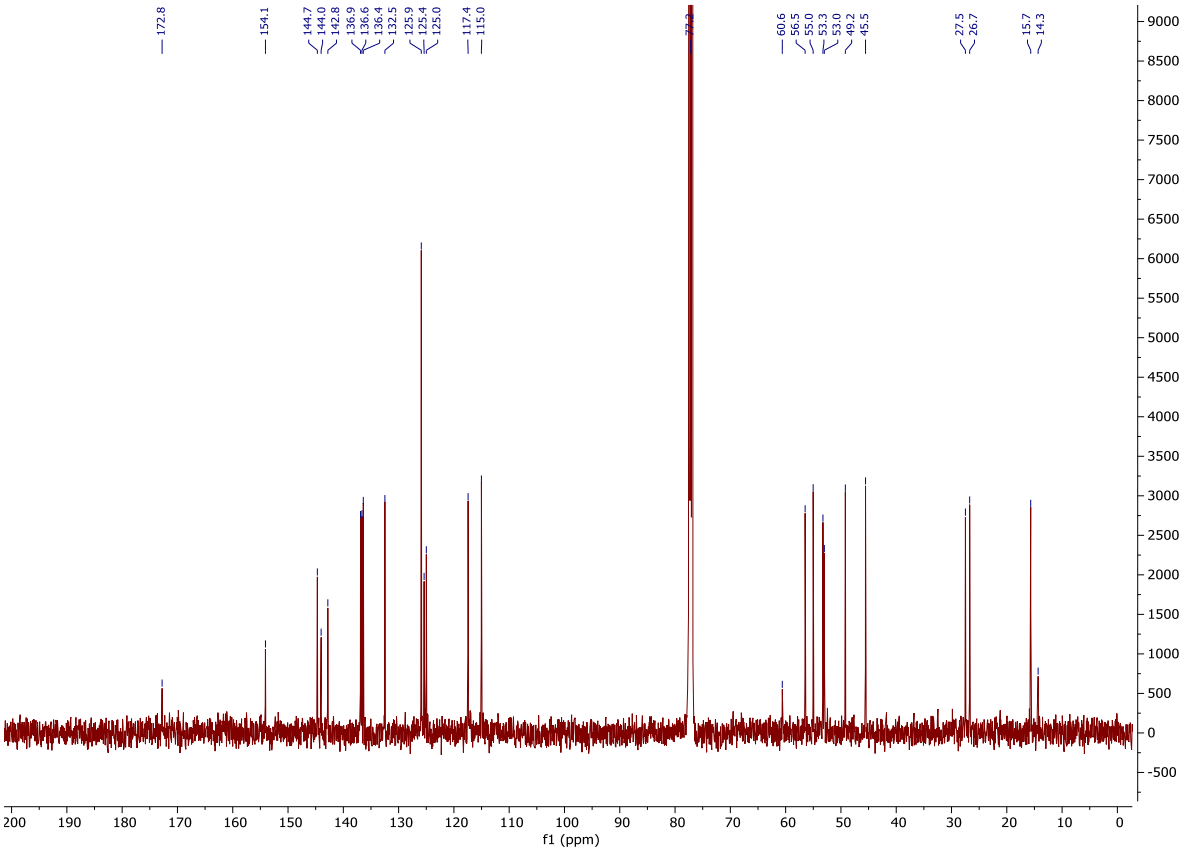
TLC: R_f = 0.38 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{25}H_{28}Cl_2N_4O_2S$: $[M+H]^+$ = 519.13828, found: $[M+H]^+$ = 519.13826, error: 0.01 mDa or 0.03 ppm

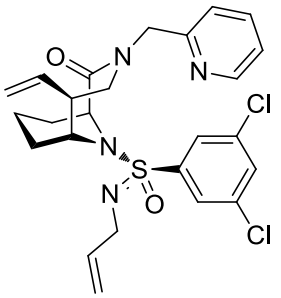
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19–1.30 (m, 1H), 1.43–1.52 (m, 1H), 1.52–1.66 (m, 3H), 2.18 (d, 1H, *J* = 13.0 Hz), 2.71–2.81 (m, 1H), 3.13 (d, 1H, *J* = 13.9 Hz), 3.59–3.71 (m, 2H), 4.08–4.16 (m, 1H), 4.40–4.47 (m, 1H), 4.62–4.73 (m, 2H), 5.06–5.10 (m, 1H), 5.11 (s, 1H), 5.14 (d, 1H, *J* = 7.7 Hz), 5.21–5.28 (m, 1H), 5.57 (d, 1H, *J* = 16.5 Hz), 5.69–6.79 (m, 1H), 5.85–5.94 (m, 1H), 7.53 (t, 1H, *J* = 1.8 Hz), 7.70 (d, 2H, *J* = 1.8 Hz), 7.71–7.75 (m, 1H), 7.84 (d, 1H, *J* = 8.0 Hz), 8.26–8.33 (m, 1H), 8.80 (d, 1H, *J* = 5.2 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.3, 15.7, 26.7, 27.5, 45.6, 49.2, 53.0, 53.3, 55.0, 56.5, 115.0, 117.4, 125.0, 125.4, 125.9, 132.5, 136.4, 136.6, 136.9, 142.8, 144.0, 144.7, 154.1, 172.8 ppm.


8.80
8.29
7.84
7.73
7.70
7.53
7.26
5.89
5.74
5.57
5.25
5.14
5.11
5.09
4.68
4.44
4.12
3.65
3.13
2.77
2.18
2.10
2.05
2.05
1.58
1.48
1.26
0.91
0.90
0.92
1.08
1.61
0.85
0.87
0.92
0.83
0.88
0.94
0.84
0.89
1.78
0.87
1.39
1.80
0.91
0.88
0.86
0.78
2.81
1.15
2.82
f1 (ppm)


172.8
154.1
144.7
144.0
142.8
136.9
136.6
136.4
132.5
125.9
125.4
125.0
117.4
115.0
77.3
60.6
56.5
55.0
53.3
53.0
49.2
45.5
27.5
26.7
15.7
14.3
f1 (ppm)

Compound **7b**: (1*S*,5*S*,6*R*)-10-((*R*)-*N*-allyl-3,5-dichlorophenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5b** (5.3 mg, 11.1 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 3.9 mg, 58.3 µmol, 5.3 eq.) was added and it was stirred for 30 min at 0 °C. Allylbromide (20 µL, 231 µmol, 20.8 eq.) was added and the reaction mixture was allowed to reach room temperature. After 17 h the solution was again cooled to 0 °C, NaH (60 % in mineral oil, 7.5 mg, 112 µmol, 10.1 eq.) and allylbromide (20 µL, 231 µmol, 20.8 eq.) were added and the reaction mixture was allowed to reach room temperature. After another 25 h water was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 1:1–1:2) to afford **7b**.

Yield: 4.6 mg, 81 %

Purity: 96 % (HPLC, UV-absorption 220 nm)

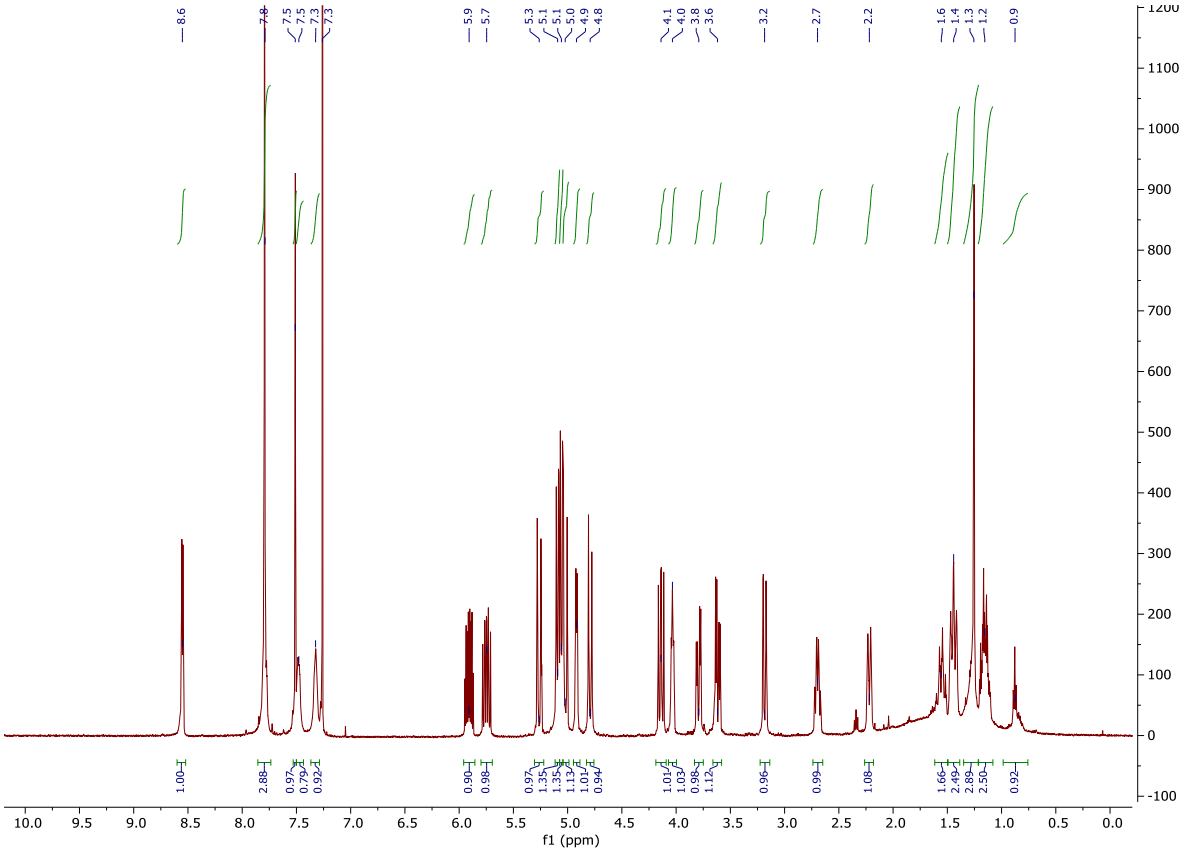
Appearance: colourless solid

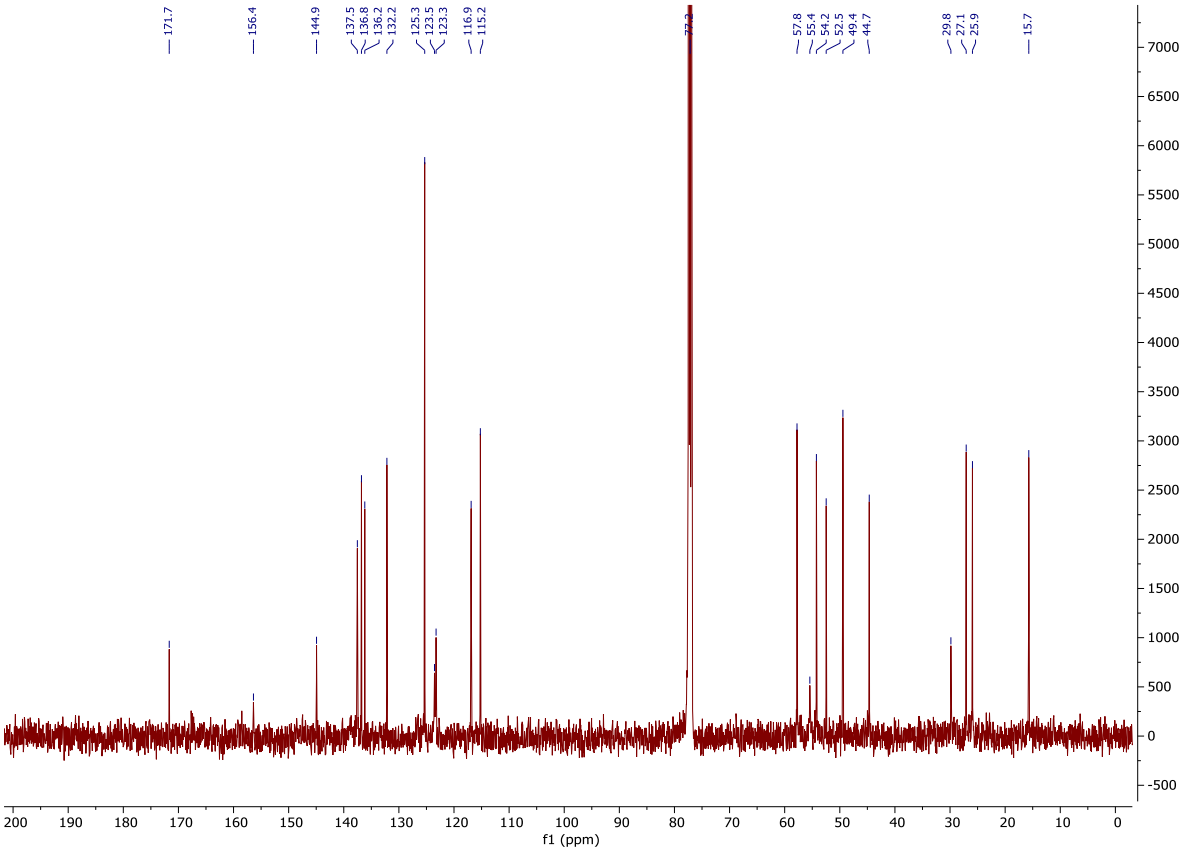
TLC: R_f = 0.45 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{25}H_{28}Cl_2N_4O_2S$: $[M+H]^+$ = 519.13828, found: $[M+H]^+$ = 519.13865, error: 0.37 mDa or 0.71 ppm

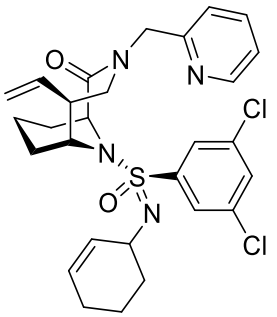
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.08–1.21 (m, 2H), 1.38–1.50 (m, 2H), 1.50–1.62 (m, 1H), 2.22 (d, 1H, *J* = 13.1 Hz), 2.65–2.74 (m, 1H), 3.18 (dd, 1H, *J* = 13.9/1.5 Hz), 3.58–3.66 (m, 1H), 3.76–3.83 (m, 1H), 4.00–4.07 (m, 1H), 4.14 (dd, 1H, *J* = 13.9/10.7 Hz), 4.79 (d, 1H, *J* = 15.3 Hz), 4.92 (d, 1H, *J* = 6.1 Hz), 5.02 (d, 1H, *J* = 17.0 Hz), 5.06 (d, 1H, *J* = 10.2 Hz), 5.07–5.11 (m, 1H), 5.23–5.29 (m, 1H), 4.70–4.80 (m, 1H), 4.86–4.95 (m, 1H), 7.29–7.37 (m, 1H), 7.44–7.50 (m, 1H), 7.51 (t, 1H, *J* = 1.9 Hz), 7.75–7.85 (m, 3H), 8.55 (d, 1H, *J* = 5.1 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 25.9, 27.1, 44.7, 49.4, 52.5, 54.2, 55.4, 57.8, 115.2, 116.9, 123.3, 123.5, 125.3, 132.2, 136.2, 136.8, 137.5, 144.9, 156.4, 171.7 ppm.


8.6
7.8
7.5
7.5
7.3
7.3
5.9
5.7
5.3
5.1
5.1
5.0
4.9
4.8
4.1
4.0
3.8
3.6
3.2
2.7
2.2
1.6
1.4
1.3
1.2
0.9
f1 (ppm)


171.7
156.4
144.9
137.5
136.8
136.2
132.2
125.3
123.5
123.3
116.9
115.2
77.3
57.8
55.4
54.2
52.5
49.4
44.7
29.8
27.1
25.9
15.7
f1 (ppm)

Compound **8a**: (1*S*,5*S*,6*R*)-10-((*S*)-3,5-dichloro-*N*-(cyclohex-2-en-1-yl)phenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5a** (15.5 mg, 32.3 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 11 mg, 165 µmol, 5.1 eq.) was added and it was stirred for 30 min at 0 °C. 3-Bromocyclohexene (73 µL, 626 µmol, 19.4 eq.) was added and the reaction mixture was allowed to reach room temperature. After 45 h the solution was again cooled to 0 °C, NaH (60 % in mineral oil, 10 mg, 150 µmol, 4.6 eq.) and 3-bromocyclohexene (73 µL, 626 µmol, 19.4 eq.) were added and the reaction mixture was allowed to reach room temperature. After another 3 d water was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1–1:1) to afford **8a** as a mixture of (*R*)- and (*S*)-cyclohex-2-en-1-yl epimers. Analytical HPLC showed no separation of these diastereomers.

Yield: 11.9 mg, 66 %

Purity: 97 % (HPLC, UV-absorption 220 nm)

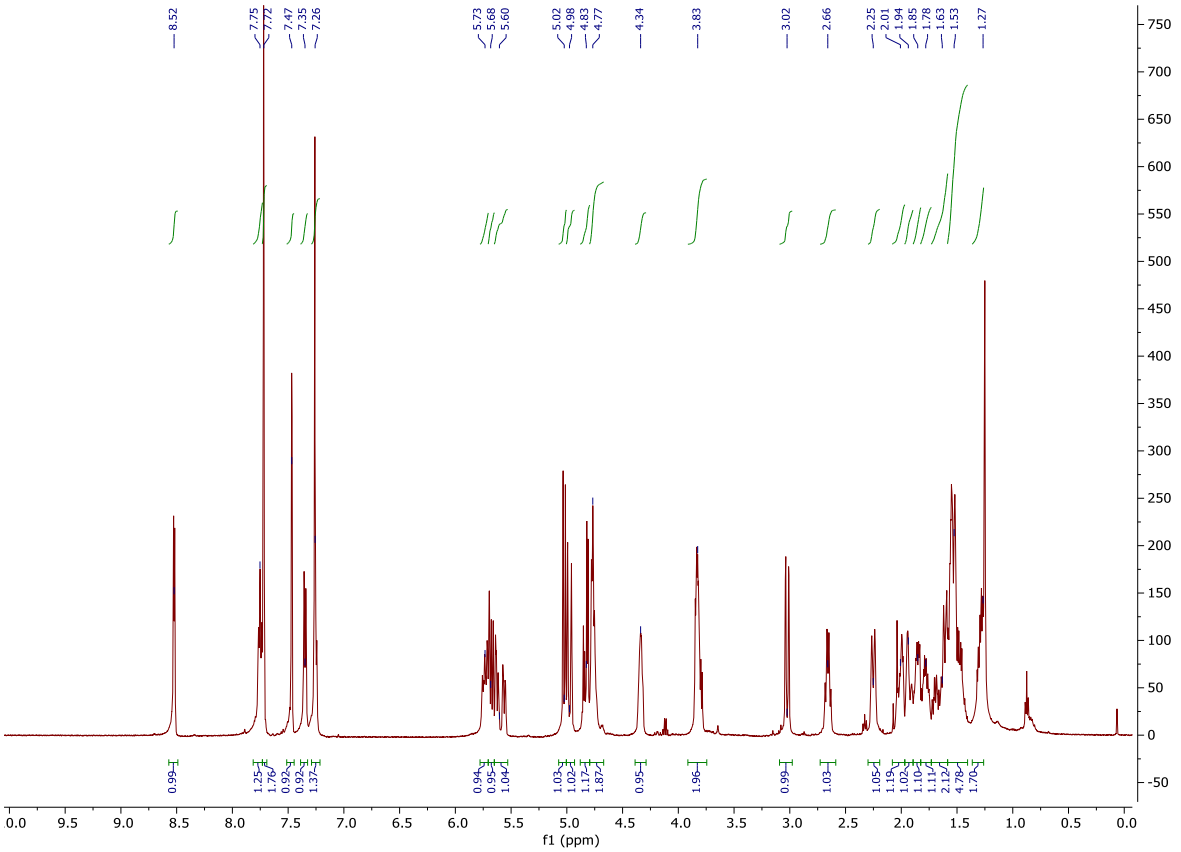
Appearance: colourless solid

TLC: R_f = 0.38 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{28}H_{32}Cl_2N_4O_2S$: $[M+H]^+$ = 559.16958, found: $[M+H]^+$ = 559.16916, error: 0.42 mDa or 0.75 ppm

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.26–1.35 (m, 1H), 1.40–1.58 (m, 4H), 1.58–1.73 (m, 2H), 1.73–1.83 (m, 1H), 1.83–1.89 (m, 1H), 1.89–1.97 (m, 1H), 1.97–2.06 (m, 1H), 2.25 (d, 1H, *J* = 13.5 Hz), 2.59–2.73 (m, 1H), 3.02 (dd, 1H, *J* = 14.0/1.3 Hz), 3.75–3.91 (m, 2H), 4.29–4.39 (m, 1H), 4.67–4.80 (m, 2H), 4.79–4.88 (m, 1H), 4.98 (d, 1H, *J* = 16.9 Hz), 5.02 (d, 1H, *J* = 10.1 Hz), 5.53–5.65 (m, 1H), 5.65–5.71 (m, 1H), 5.70–5.78 (m, 1H), 7.22–7.29 (m, 1H), 7.35 (d, 1H, *J* = 7.9 Hz), 7.45–7.49 (m, 1H), 7.69–7.73 (m, 2H), 7.73–7.79 (m, 1H), 8.52 (m, 1H, *J* = 4.9 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.9, 20.2, 20.4, 24.9, 24.9, 26.8, 26.9, 27.8, 27.9, 29.8, 33.0, 33.0, 49.1, 49.1, 49.4, 49.9, 52.0, 54.9, 55.7, 56.6, 56.7, 116.6, 122.7, 122.8, 125.8, 125.8, 128.7, 128.9, 131.0, 131.4, 132.0, 136.0, 136.0, 137.8, 138.1, 145.3, 145.4, 148.2, 156.9, 171.7 ppm.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7.75
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5.60
5.02
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4.34
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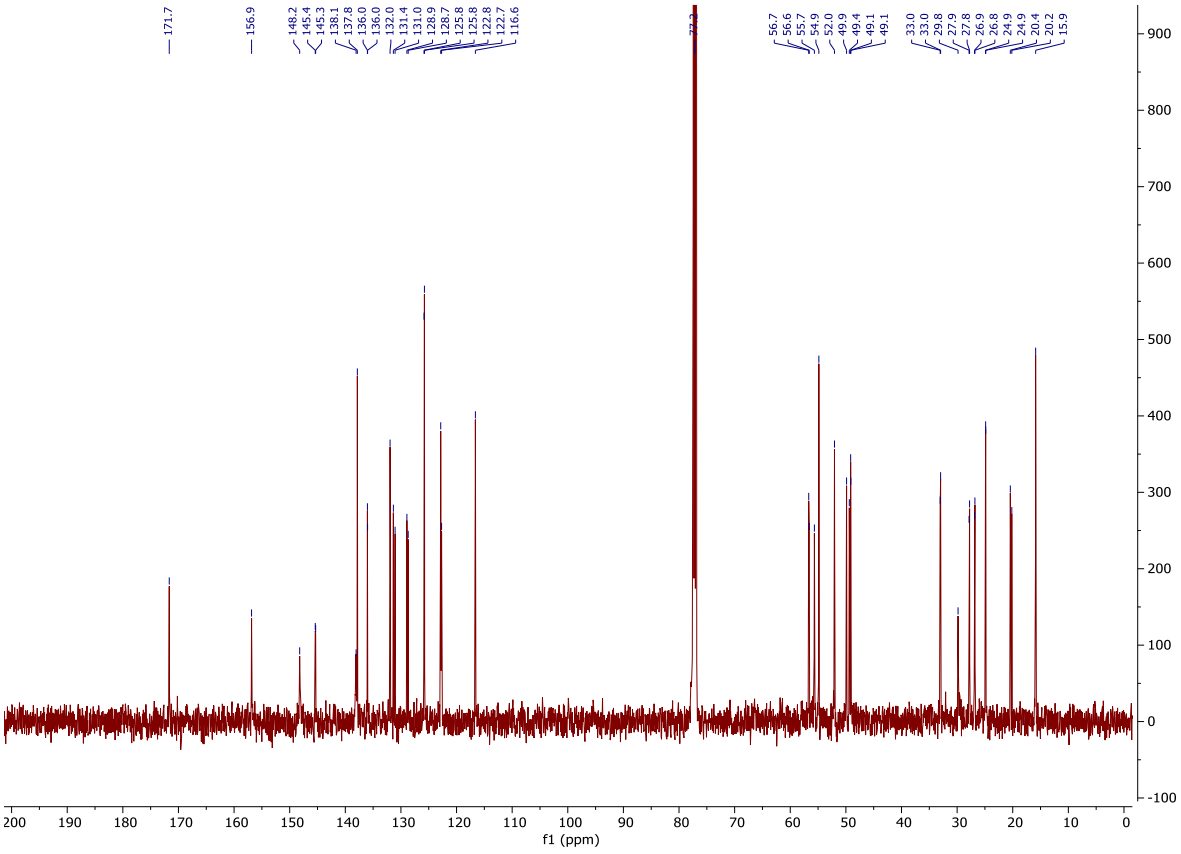
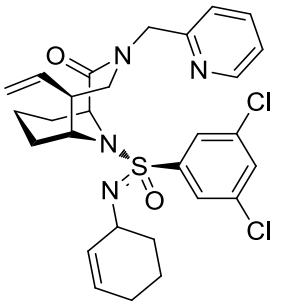
1.85
1.78
1.63
1.53
1.27
f1 (ppm)


171.7
156.9
148.2
145.4
145.3
138.1
137.8
136.0
136.0
132.0
131.4
131.0
128.9
128.7
125.8
125.8
122.8
122.7
116.6
77.2
56.7
56.6
55.7
54.9
52.0
49.9
49.4
49.1
33.0
33.0
29.8
27.9
27.8
26.9
26.8
24.9
24.9
20.4
20.2
15.9
f1 (ppm)

Compound **8b**: (1*S*,5*S*,6*R*)-10-((*R*)-3,5-dichloro-*N*-(cyclohex-2-en-1-yl)phenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5b** (15.9 mg, 33.2 µmol, 1.0 eq.) was dissolved in THF (1.0 mL) under argon atmosphere and cooled to 0 °C. NaH (60 % in mineral oil, 9.0 mg, 135 µmol, 4.1 eq.) was added and it was stirred for 30 min at 0 °C. 3-Bromocyclohexene (73 µL, 626 µmol, 18.9 eq.) was added and the reaction mixture was allowed to reach room temperature. After 42 h water was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1–1:1) to afford **8b** as a mixture of (*R*)- and (*S*)-cyclohex-2-en-1-yl epimers. Analytical HPLC showed a ratio of 56/44 for these diastereomers.

Yield: 15.8 mg, 85 %

Purity: >99 % (HPLC, UV-absorption 220 nm)

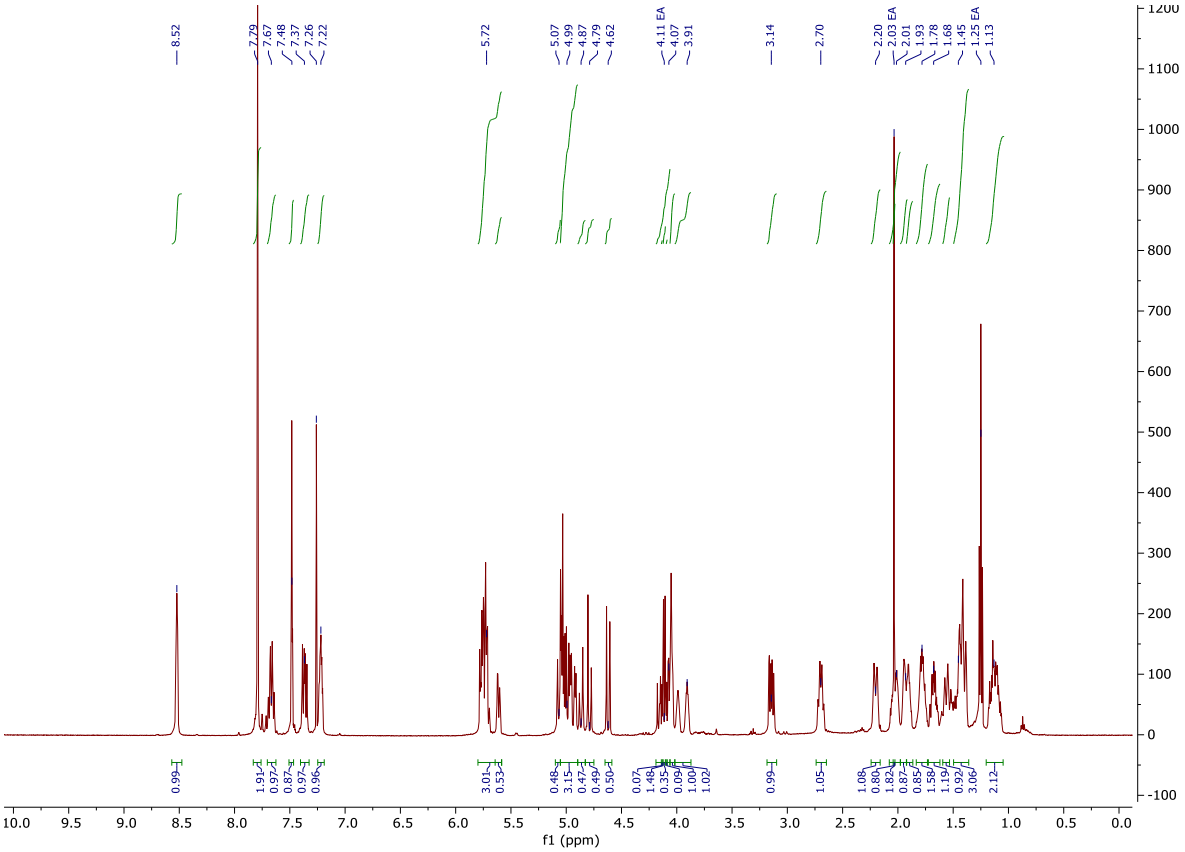
Appearance: colourless oil

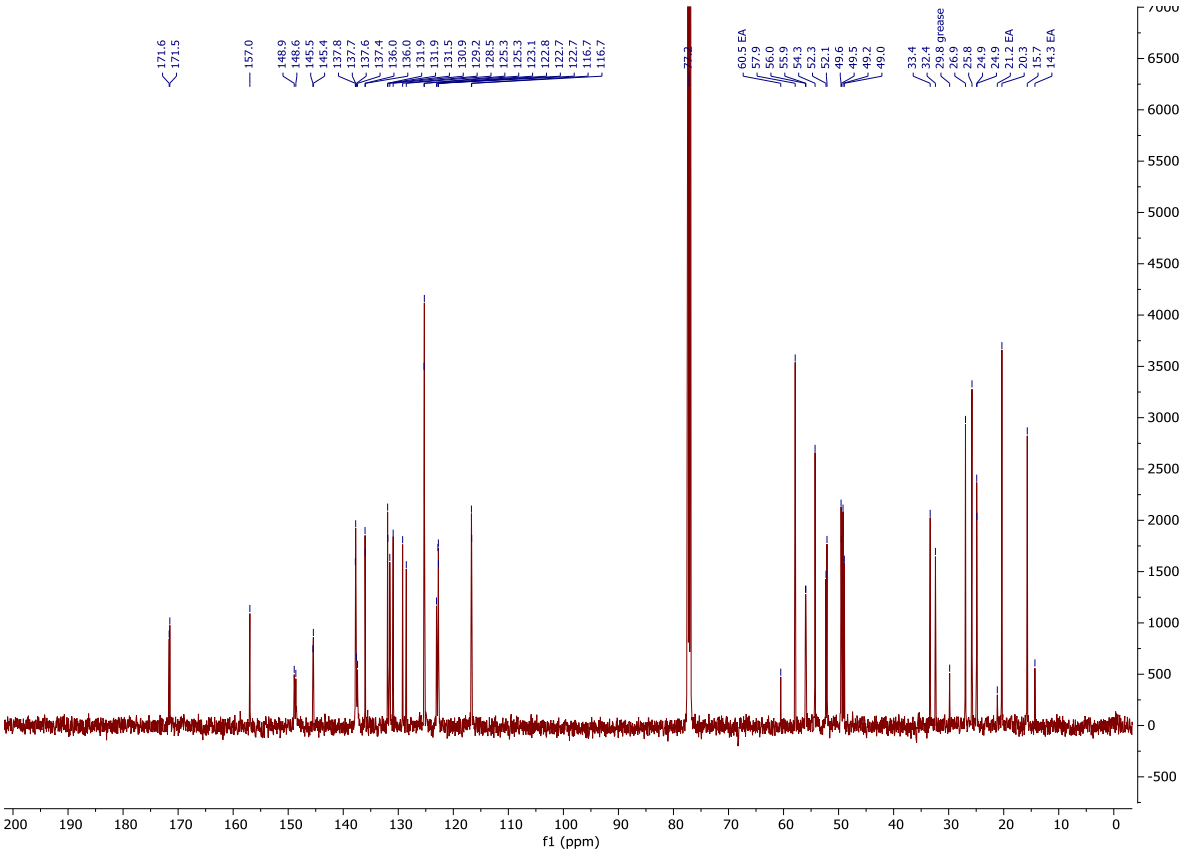
TLC: R_f = 0.41 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{28}H_{32}Cl_2N_4O_2S$: $[M+H]^+$ = 559.16958, found: $[M+H]^+$ = 559.16995, error: 0.37 mDa or 0.67 ppm

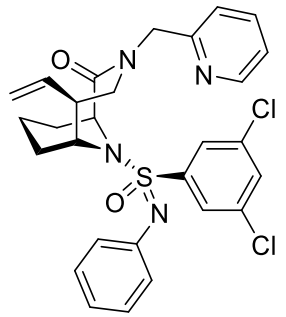
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.05–1.20 (m, 2H), 1.35–1.47 (m, 3H), 1.53–1.59 (m, 1H), 1.62–1.72 (m, 1H), 1.73–1.83 (m, 1H), 1.86–1.92 (m, 1H), 1.92–1.98 (m, 1H), 1.98–2.08 (m, 1H), 2.20 (d, 1H, *J* = 13.5 Hz), 2.65–2.74 (m, 1H), 3.14 (ddd, 1H, *J* = 13.9/7.2/1.6 Hz), 3.87–4.02 (m, 1H), 4.02–4.06 (m, 1H), 4.06–4.19 (m, 1H), 4.62 and 5.07 (d, 1H, *J* = 15.1 Hz, each 50 %), 4.79 and 4.87 (d, 1H, *J* = 15.1 Hz, each 50 %), 4.90–5.05 (m, 3H), 5.58–5.80 (m, 3H), 7.19–7.25 (m, 1H), 7.37 (dd, 1H, *J* = 12.2/7.9 Hz), 7.47–7.50 (m, 1H), 7.63–7.70 (m, 1H), 7.79 (t, 1H, *J* = 1.6 Hz), 8.49–8.56 (m, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 20.3, 24.9, 24.9, 25.8, 26.9, 32.4, 33.4, 49.0, 49.2, 49.5, 49.6, 52.1, 52.3, 54.3, 55.9, 56.0, 57.9, 116.7, 116.7, 122.7, 122.7, 122.8, 123.1, 125.3, 125.3, 128.5, 129.2, 130.9, 131.5, 131.9, 131.9, 136.0, 136.0, 137.4, 137.6, 137.7, 137.8, 145.4, 145.5, 148.6, 148.9, 157.0, 171.5, 171.6 ppm.


8.52
7.79
7.67
7.48
7.37
7.26
7.22
5.72
5.07
4.99
4.87
4.79
4.62
4.11 EA
4.07
3.91
3.14
2.70
2.20
2.03 EA
2.01
1.93
1.78
1.68
1.45
1.25 EA
1.13
f1 (ppm)


171.6
171.5
157.0
148.9
148.6
145.5
145.4
137.8
137.7
137.6
137.4
136.0
136.0
131.9
131.9
131.5
130.9
129.2
128.5
125.3
125.3
123.1
122.8
122.7
122.7
116.7
116.7
77.3
60.5 EA
57.9
56.0
55.9
54.3
52.3
52.1
49.6
49.5
49.2
49.0
33.4
32.4
29.8 grease
26.9
25.8
24.9
24.9
21.2 EA
20.3
15.7
14.3 EA
f1 (ppm)

Compound **9a**: (1*S*,5*S*,6*R*)-10-((*S*)-3,5-dichloro-*N*-phenylphenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5a** (8.6 mg, 17.9 µmol, 1.0 eq.), phenylboronic acid (18.3 mg, 150 µmol, 8.4 eq.) and $Cu(OAc)_2$ (7.3 mg, 40.2 µmol, 2.2 eq.) were dissolved in MeCN (1 mL) under argon atmosphere, then TEA (5 µL, 36.1 µmol, 2.0 eq.) was added. The reaction mixture was stirred at room temperature for 42 h, then water was added and it was extracted with EA. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1–1:1) to afford **9a**.

Yield: 10.0 mg, 100 %

Purity: 96 % (HPLC, UV-absorption 220 nm)

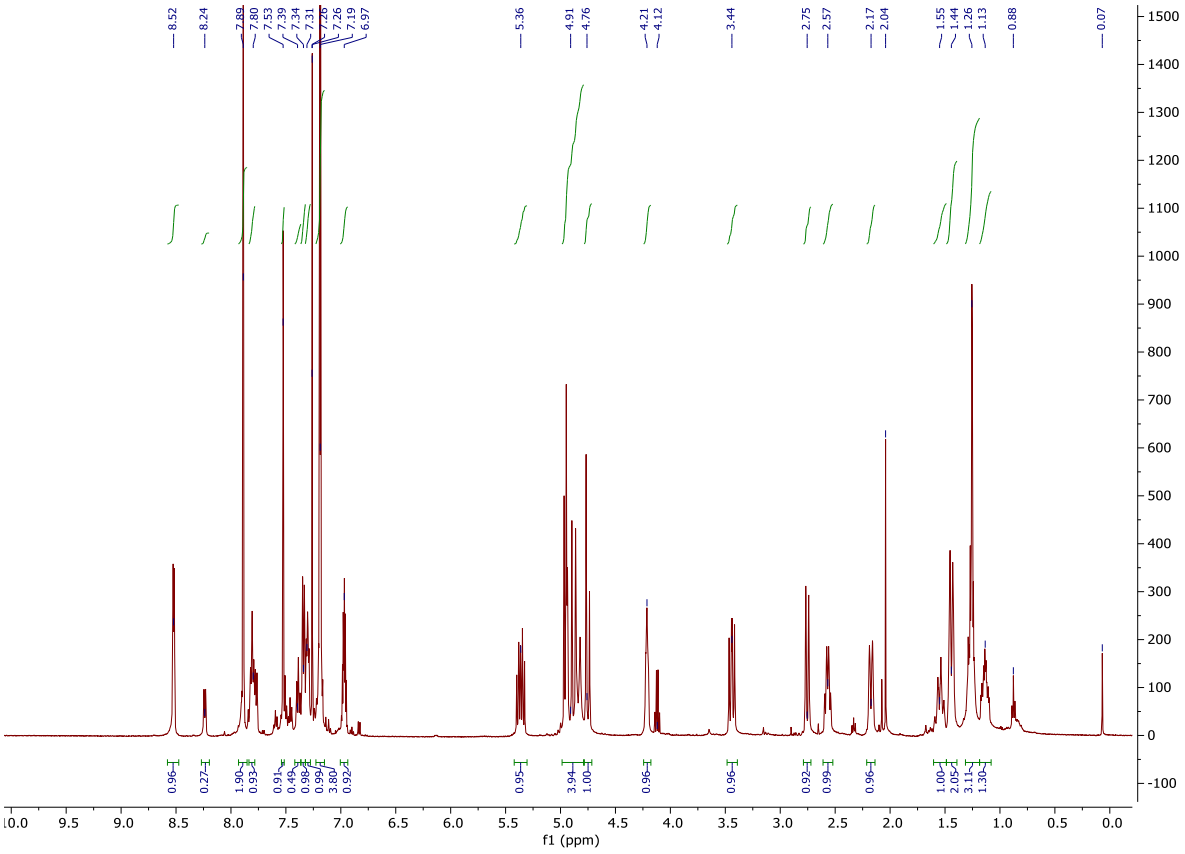
Appearance: colourless solid

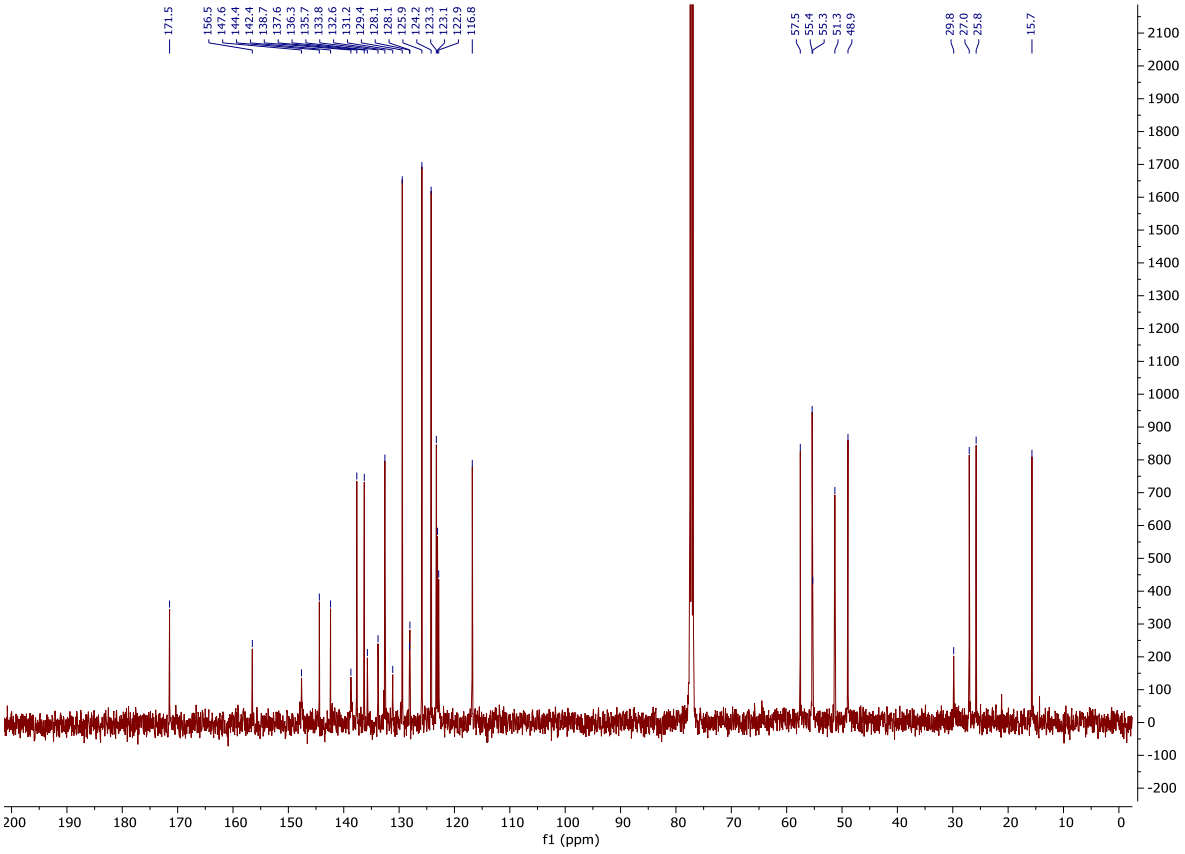
TLC: R_f = 0.34 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{28}H_{28}Cl_2N_4O_2S$: $[M+H]^+$ = 555.13828, found: $[M+H]^+$ = 555.13832, error: 0.04 mDa or 0.08 ppm

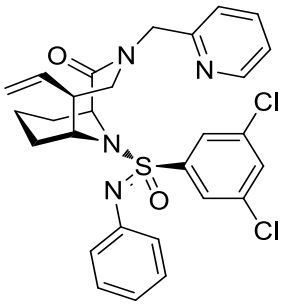
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.08–1.18 (m, 1H), 1.18–1.31 (m, 1H), 1.39–1.48 (m, 2H), 1.41–1.61 (m, 1H), 2.17 (d, 1H, *J* = 13.6 Hz), 2.52–2.61 (m, 1H), 2.75 (d, 1H, *J* = 14.1 Hz), 3.44 (dd, 1H, *J* = 14.0/10.9 Hz), 4.18–4.24 (m, 1H), 4.76 (d, 1H, *J* = 15.4 Hz), 4.79–4.99 (m, 4H), 5.30–5.42 (m, 1H), 6.94–7.00 (m, 1H), 7.15–7.23 (m, 4H), 7.28–7.32 (m, 1H), 7.32–7.36 (m, 1H), 7.53 (t, 1H, *J* = 1.9 Hz), 7.78–7.84 (m, 1H), 7.89 (d, 1H, *J* = 1.9 Hz), 8.52 (d, 1H, *J* = 4.8 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 25.8, 27.0, 48.9, 51.3, 55.3, 55.4, 57.5, 116.8, 122.9, 123.1, 123.3, 124.2, 125.9, 129.4, 132.6, 136.3, 137.6, 138.7, 142.4, 144.4, 147.6, 156.5, 171.5 ppm.


8.52
8.24
7.89
7.80
7.53
7.39
7.34
7.31
7.26
7.19
6.97
5.36
4.91
4.76
4.21
4.12
3.44
2.75
2.57
2.17
2.04
1.55
1.44
1.26
1.13
0.88
0.07
f1 (ppm)


171.5
156.5
147.6
144.4
142.4
138.7
137.6
136.3
135.7
133.8
132.6
131.2
129.4
128.1
125.9
124.2
123.3
123.1
122.9
116.8
57.5
55.4
55.3
51.3
48.9
29.8
27.0
25.8
15.7
f1 (ppm)

Compound **9b**: (1*S*,5*S*,6*R*)-10-((*R*)-3,5-dichloro-N-phenylphenylsulfonimidoyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



Sulfonimidamide **5b** (7.4 mg, 15.4 µmol, 1.0 eq.), phenylboronic acid (14.9 mg, 122 µmol, 7.9 eq.) and $Cu(OAc)_2$ (9.9 mg, 54.5 µmol, 3.5 eq.) were dissolved id MeCN (1 mL) under argon atmosphere, then TEA (5 µL, 36.1 µmol, 2.3 eq.) was added. The reaction mixture was stirred at room temperature for 18 h, then water was added and it was extracted with EA. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Cy/EA 2:1–1:2) to afford **9b**.

Yield: 7.5 mg, 87 %

Purity: 98 % (HPLC, UV-absorption 220 nm)

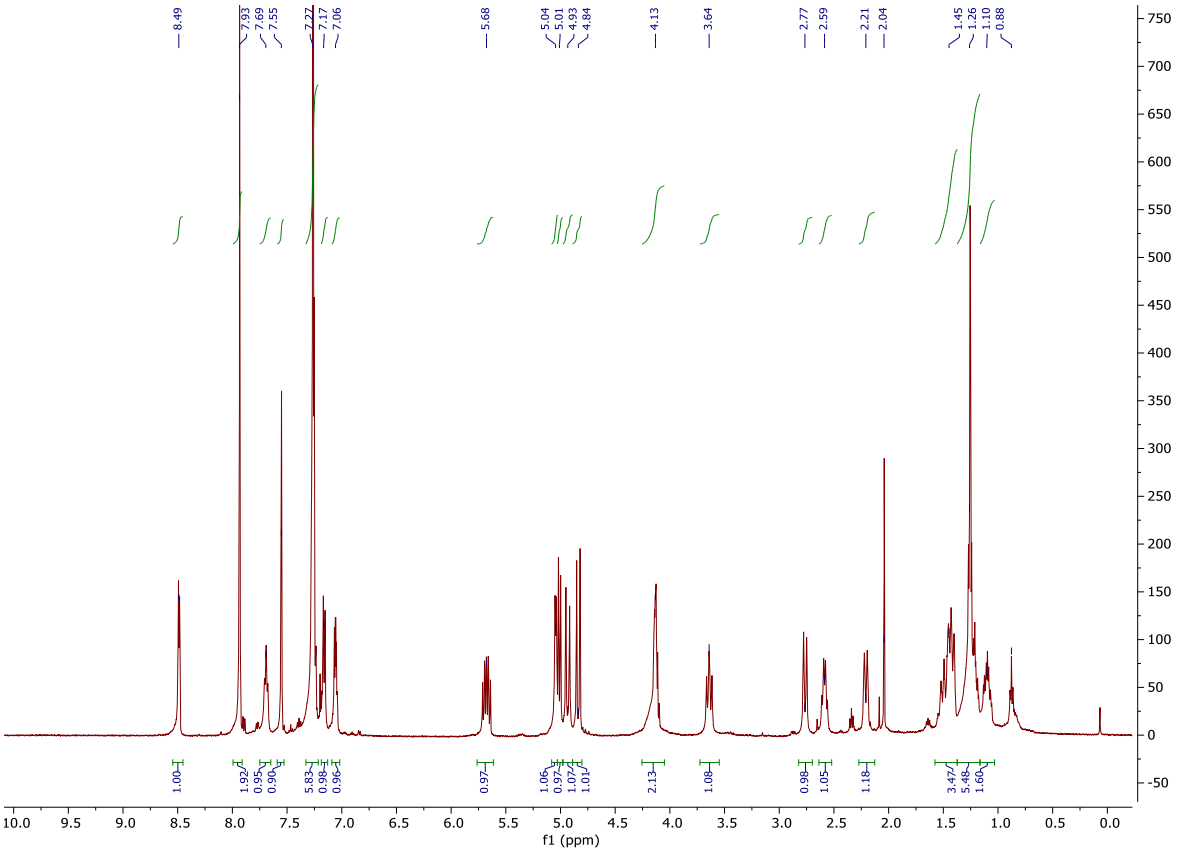
Appearance: colourless solid

TLC: R_f = 0.33 (Cy/EA 1:1)

HR-MS (ESI): m/z calculated for sum formula $C_{28}H_{28}Cl_2N_4O_2S$: $[M+H]^+$ = 555.13828, found: $[M+H]^+$ = 555.13811, error: 0.17 mDa or 0.30 ppm

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.03–1.16 (m, 1H), 1.16–1.29 (m, 1H), 1.37–1.58 (m, 3H), 2.21 (d, 1H, *J* = 13.3 Hz), 2.52–2.64 (m, 1H), 2.27 (d, 1H, *J* = 13.8 Hz), 3.64 (dd, 1H, *J* = 13.3/11.2 Hz), 4.05–4.25 (m, 2H), 4.84 (d, 1H, *J* = 15.7 Hz), 4.93 (d, 1H, *J* = 17.0 Hz), 5.01 (d, 1H, *J* = 10.2 Hz), 5.04 (d, 1H, *J* = 6.0 Hz), 5.62–5.74 (m, 1H), 7.02–7.09 (m, 1H), 7.16 (d, 1H, *J* = 7.8 Hz), 7.24–7.30 (m, 4H), 7.55 (t, 1H, *J* = 1.9 Hz), 7.65–7.75 (m, 1H), 7.93 (d, 2H, *J* = 1.9 Hz), 8.49 (d, 1H, *J* = 4.9 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.7, 26.1, 27.1, 49.5, 51.2, 54.4, 54.8, 58.1, 116.8, 122.9, 123.0, 123.7, 124.9, 125.5, 129.4, 132.5, 136.3, 137.5, 139.3, 142.0, 144.7, 147.3, 156.4, 171.0 ppm.


8.49
7.93
7.69
7.55
7.27
7.17
7.06
5.68
5.04
5.01
4.93
4.84
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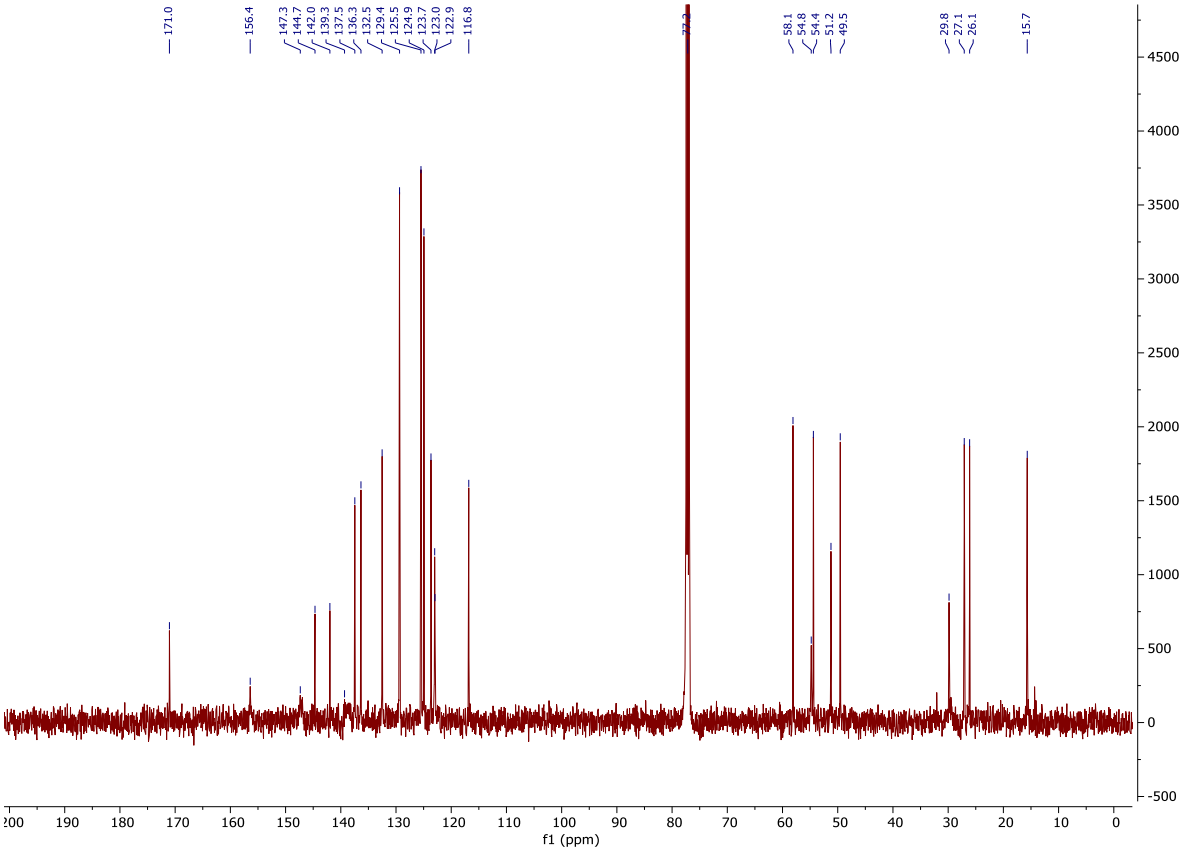
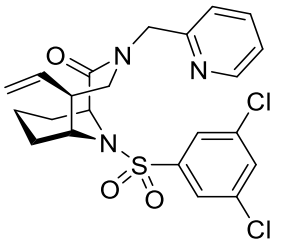
3.64
2.77
2.59
2.21
2.04
1.45
1.26
1.10
0.88
1.00
1.92
0.95
0.90
5.83
0.98
0.96
0.97
1.06
0.97
1.07
1.01
2.13
1.08
0.98
1.05
1.18
3.47
5.48
1.60
f1 (ppm)


171.0
156.4
147.3
144.7
142.0
139.3
137.5
136.3
132.5
129.4
125.5
124.9
123.7
123.0
122.9
116.8
77.3
58.1
54.8
54.4
51.2
49.5
29.8
27.1
26.1
15.7
f1 (ppm)

Compound **1**: (1*S*,5*S*,6*R*)-10-(3,5-dichlorophenylsulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



(1*S*,5*S*,6*R*)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one **2** (83 mg, 306 µmol, 1.0 eq.) was dissolved in dry MeCN (5 mL) under argon atmosphere. DIPEA (100 µL, 588 µmol, 1.9 eq.) and 3,5-dichlorobenzenesulfonyl chloride (130 mg, 530 µmol, 1.7 eq.) were added and the reaction mixture was stirred at room temperature. After 19 h water was added and it was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by semi-preparative HPLC (40-80 % MeCN in water) to afford **1**.

Yield: 70.4 mg, 48 %

Purity: >99 % (HPLC, UV-absorption 220 nm)

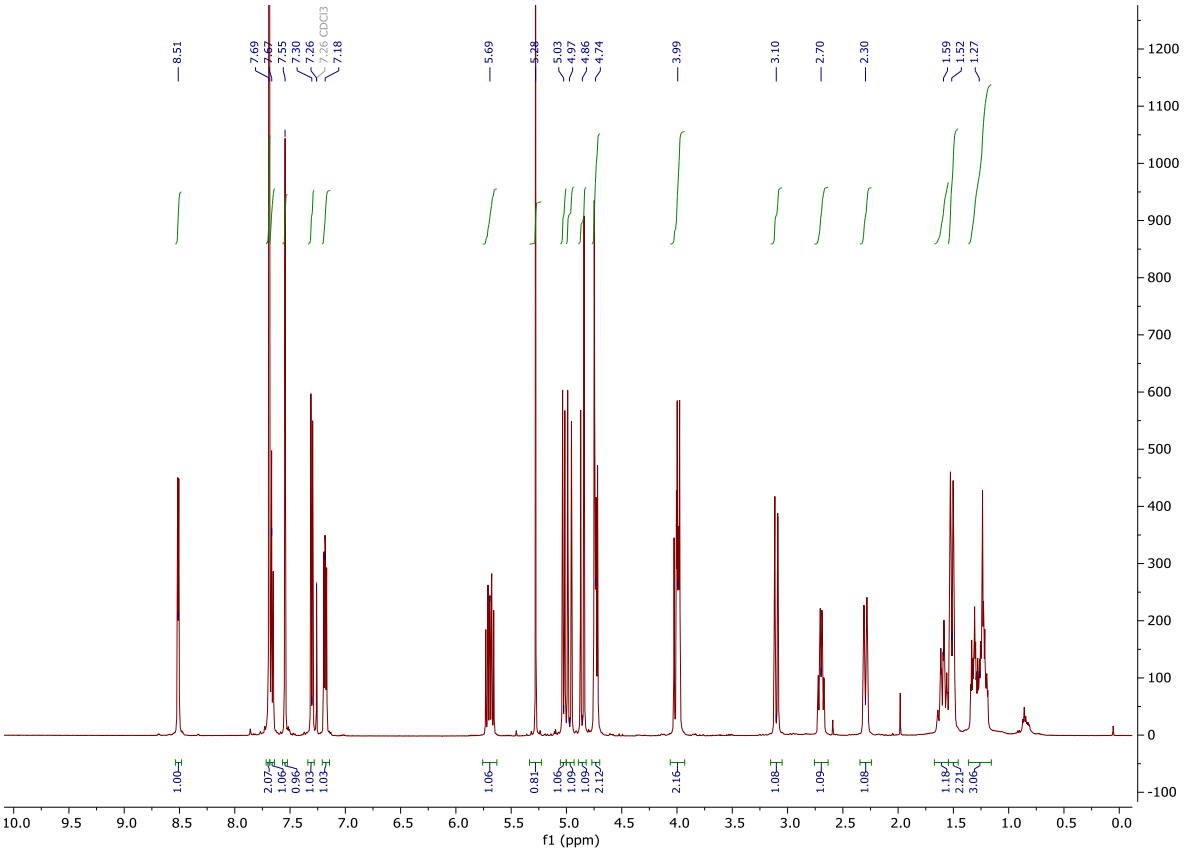
Appearance: colourless solid

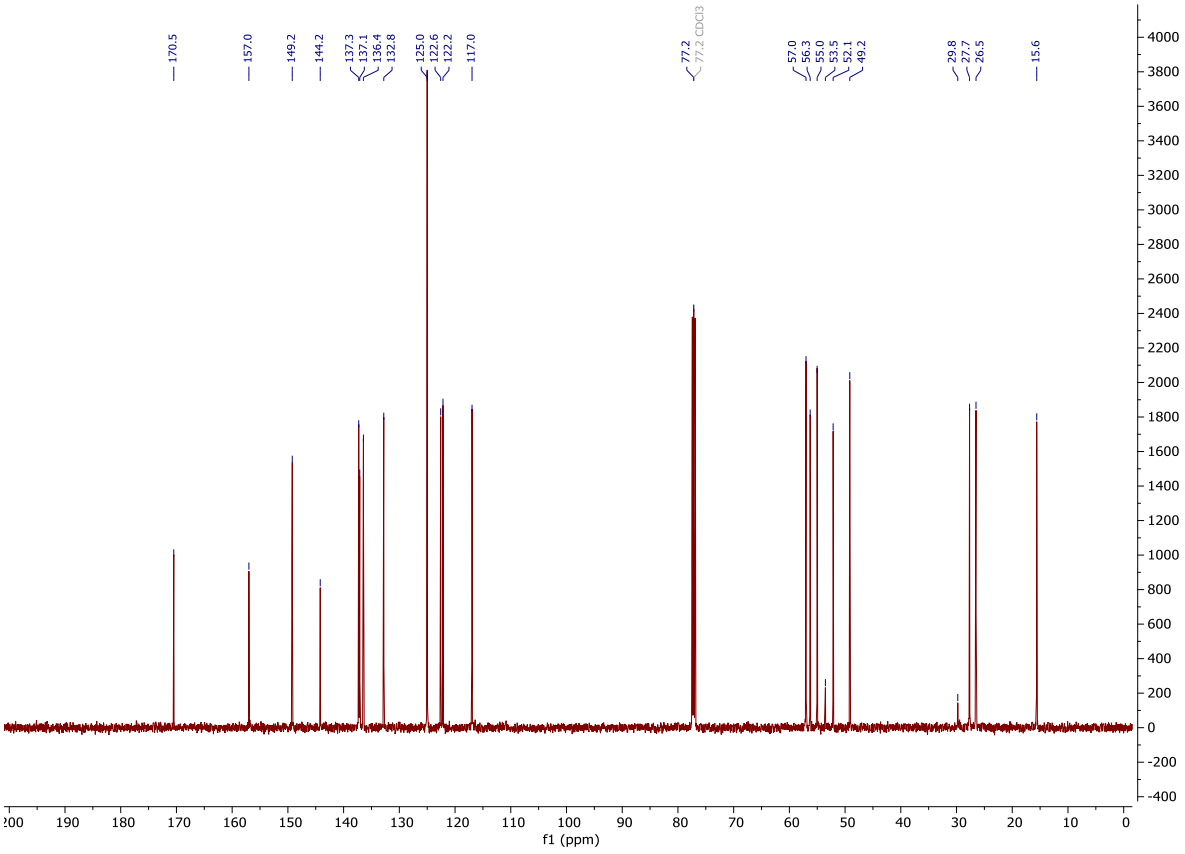
TLC: R_f = 0.30 (Cy/EA 1:2)

MS (ESI): m/z calculated for sum formula $C_{22}H_{23}Cl_2N_3O_3S$: $[M+H]^+$ = 480.1, found: $[M+H]^+$ = 480.0, error: 0.1 Da or 0.2 ‰

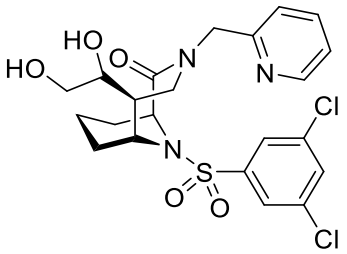
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16–1.36 (m, 2H), 1.46–1.55 (m, 2H), 1.55–1.67 (m, 1H), 2.30 (d, 1H, *J* = 13.5 Hz), 2.64–2.75 (m, 1H), 3.10 (dd, 1H, *J* = 14.2/1.7 Hz), 3.95–4.05 (m, 2H), 4.70–4.77 (m, 2H), 4.86 (d, 1H, *J* = 15.2 Hz), 4.97 (d, 1H, *J* = 17.0 Hz), 5.03 (d, 1H, *J* = 10.1 Hz), 5.63–5.76 (m, 1H), 7.18 (dd, 1H, *J* = 7.4/4.8 Hz), 7.30 (d, 1H, *J* = 7.8 Hz), 7.55 (t, 1H, *J* = 1.8 Hz), 7.64–7.68 (m, 1H), 7.69 (d, 2H, *J* = 1.8 Hz), 8.51 (d, 1H, *J* = 4.8 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.6, 26.5, 27.7, 49.2, 52.1, 55.0, 56.3, 57.0, 117.0, 122.2, 122.6, 125.0, 132.8, 136.4, 137.1, 137.3, 144.2, 149.2, 157.0, 170.5 ppm.


8.51
7.69
7.67
7.55
7.30
7.26
7.26 CDCl3
7.18
5.69
5.28
5.03
4.97
4.86
4.74
3.99
3.10
2.70
2.30
1.59
1.52
1.27
1.00
2.07
1.06
0.96
1.03
1.03
1.06
0.81
1.06
1.09
1.09
2.12
2.16
1.08
1.09
1.08
1.18
2.21
3.06
f1 (ppm)


170.5
157.0
149.2
144.2
137.3
137.1
136.4
132.8
125.0
122.6
122.2
117.0
77.2
77.2 CDCl3
57.0
56.3
55.0
53.5
52.1
49.2
29.8
27.7
26.5
15.6
f1 (ppm)

Compound **11**: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-(1,2-dihydroxyethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



1 (24 mg, 50 µmol, 1.0 eq.) was dissolved in acetone (7 mL) and water (1 mL). 2,6-Lutidine (11.6 µL, 100 µmol, 2.0 eq.), NMO (11.7 mg, 100 µmol, 2.0 eq.) and OsO_4 (2.5 wt.-% in ^{t}BuOH, 12.5 µL, 0.1 µmol, 2 mol-%) were added and the mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and extracted with EA. The crude product was purified by silica gel column chromatography (Cy/EA 1:1 – EA + 10% MeOH) to affort **11**.

Yield: 14 mg, 54 %

Purity: >99 % (HPLC, UV-absorption 220 nm), diastereomeric ratio 51:49

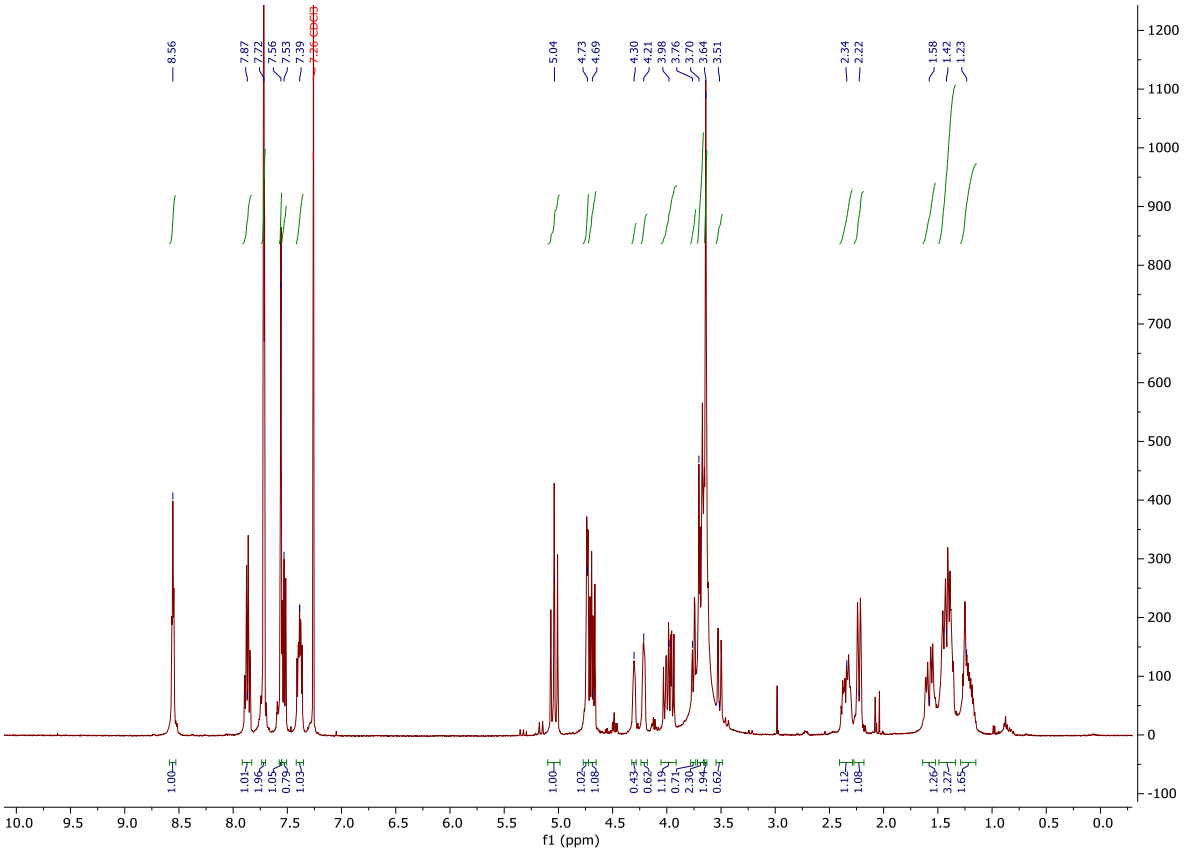
Appearance: colourless solid

TLC: R_f = 0.30 (Cy/EA 1:2)

MS (ESI): m/z calculated for sum formula $C_{22}H_{25}Cl_2N_3O_5S$: $[M+H]^+$ = 514.1, found: $[M+H]^+$ = 514.7, error: 0.6 Da or 1.2 ‰

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15-1.28 (m, 1H), 1.33-1.49 (m, 3H), 1.53-1.64 (m, 1H), 2.23 (d, 1H, J = 13.0 Hz), 2.28-2.40 (m, 1H), 3.61-3.60 (m, 2H), 3.65-3.69 (m, 1H), 3.69-3.72 (m, 1H), 3.98 (ddd, 1H, J = 22.7/14.5/10.5 Hz), 4.18-4.33 (m, 1H), 4.69 (dd, 1H, J = 14.9/7.6 Hz), 4.73 (d, 1H, J = 5.8 Hz), 5.04 (t, 1H, J = 15.4 Hz), 7.35-7.43 (m, 1H), 7.50-7.55 (m, 1H), 7.55-7.57 (m, 1H), 7.70-7.73 (m, 2H), 7.83-7.91 (m, 1H), 8.53-8.59 (m, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.5, 27.6, 28.0, 28.3, 28.9, 46.6, 47.2, 49.0, 49.7, 52.7, 52.8, 55.2, 55.4, 57.1, 57.2, 64.1, 64.3, 72.5, 73.2, 123.7, 123.8, 124.4, 124.6, 125.1, 125.1, 132.9, 136.5, 139.6, 139.8, 144.0, 144.1, 147.1, 147.3, 156.1, 156.2, 170.6, 170.7 ppm.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7.87
7.72
7.56
7.53
7.39
7.26 CDCl3
5.04
4.73
4.69
4.30
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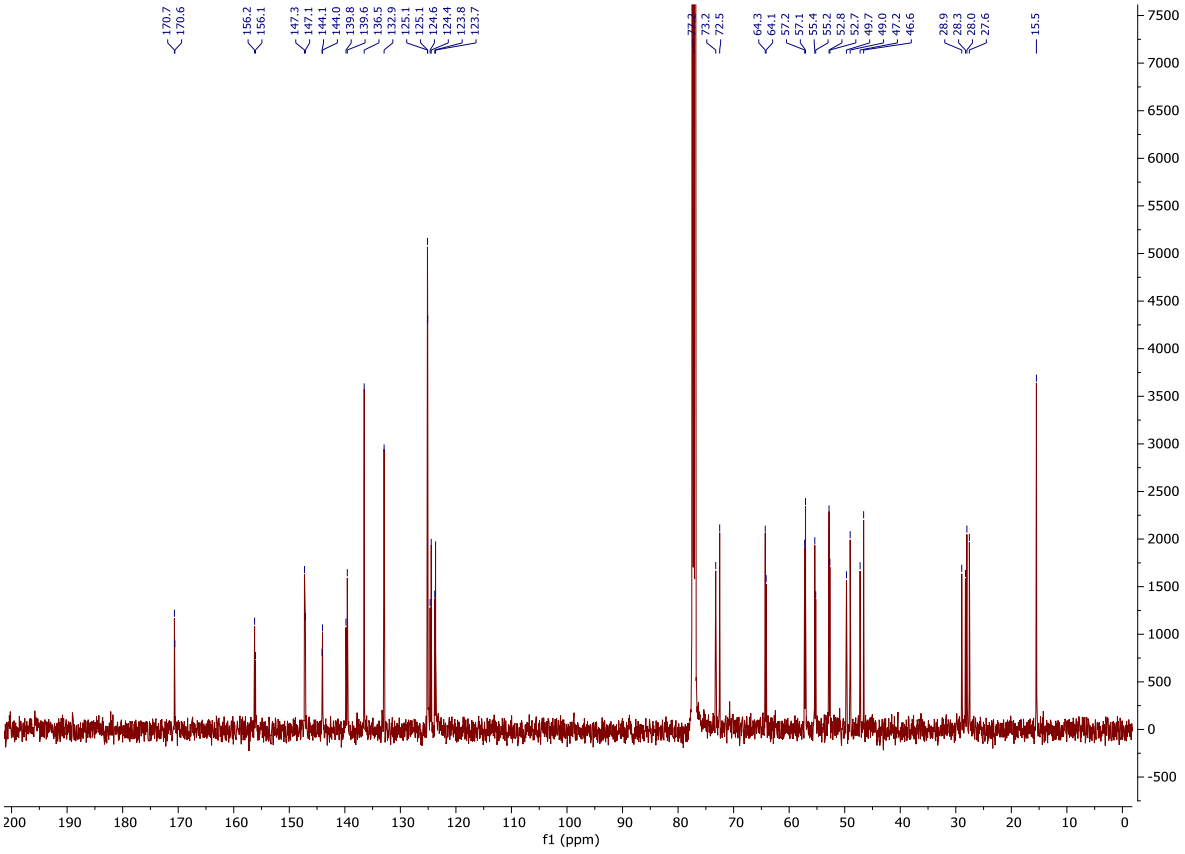
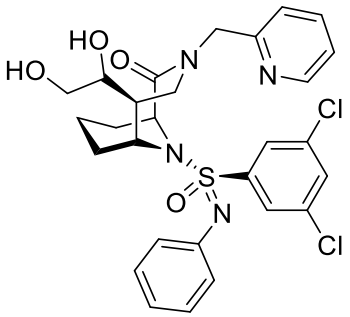
3.98
3.76
3.70
3.64
3.51
2.34
2.22
1.58
1.42
1.23
1.00
1.01
1.96
1.05
0.79
1.03
1.00
1.02
1.08
0.43
0.62
1.19
0.71
2.30
1.94
0.62
1.12
1.08
1.26
3.27
1.65
f1 (ppm)


170.7
170.6
156.2
156.1
147.3
147.1
144.1
144.0
139.8
139.6
136.5
132.9
125.1
125.1
124.6
124.4
123.8
123.7
77.2
73.2
72.5
64.3
64.1
57.2
57.1
55.4
55.2
52.8
52.7
49.7
49.0
47.2
46.6
28.9
28.3
28.0
27.6
15.5
f1 (ppm)

Compound **10**: (1*S*,5*S*,6*R*)-10-((*S*)-3,5-dichloro-*N*-phenylphenylsulfonimidoyl)-5-(1,2-dihydroxyethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



9a (5.0 mg, 9.0 µmol, 1.0 eq.) was dissolved in acetone (1.0 mL) and water (0.1 mL). NMO (4.2 mg, 36 µmol, 4.0 eq.), 2,6-lutidine (2.1 µL, 18 µmol, 2.0 eq.) and OsO_4 (2.5 wt-% in ^{t}BuOH, 5.8 µL, 450 nmol, 0.05 eq.) were added and the reaction stirred at room temperature. After 17 h, additional NMO (4.0 mg, 34 µmol, 3.8 eq.) and OsO_4 (2.5 wt-% in ^{t}BuOH, 5.8 µL, 450 nmol, 0.05 eq.) were added. After 3 d, sat. aq. $Na_2S_2O_3$ was added and stirred for 30 min. Water was added and it was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by semi-prep. HPLC (25-65 % MeCN in H_2O) to afford **10**.

Yield: 3.3 mg, 62 %

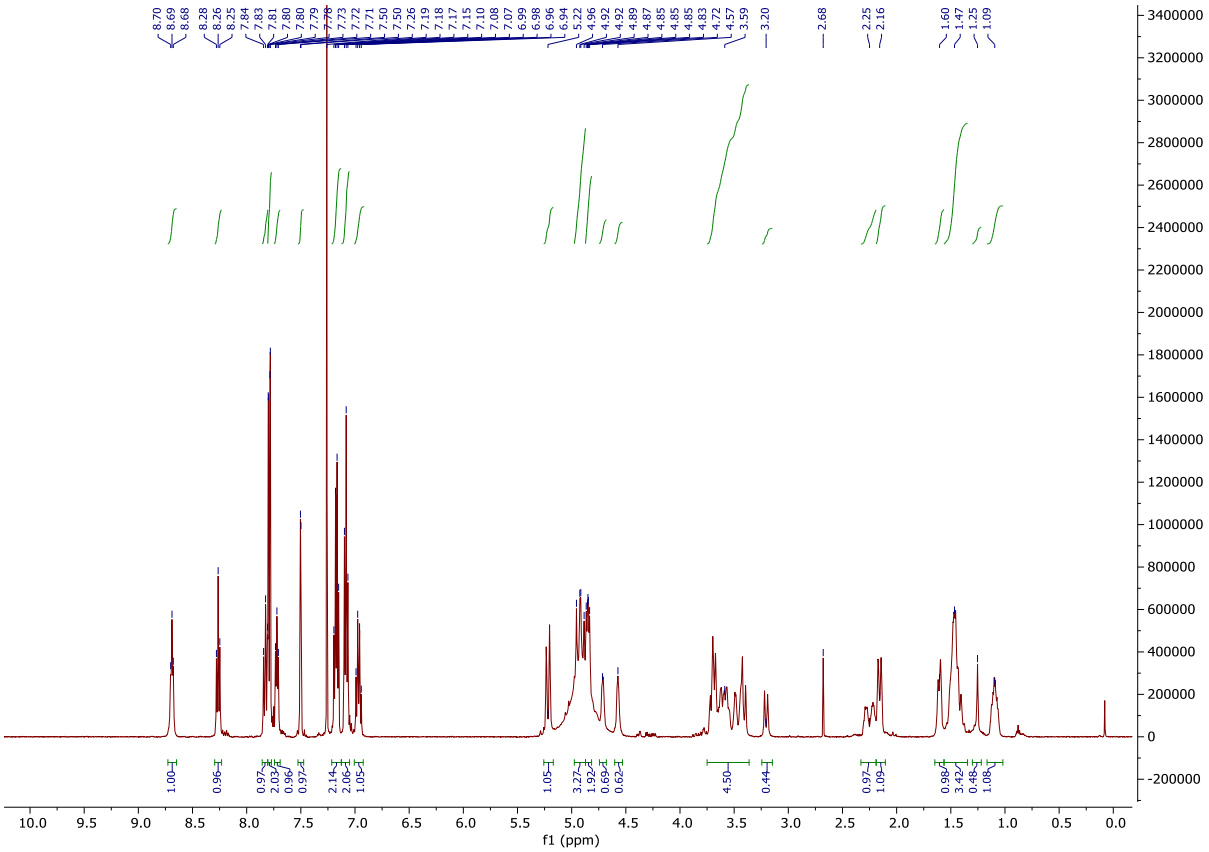
Purity: 98 % (HPLC, UV-absorption 220 nm)

Appearance: colourless solid

TLC: R_f = 0.49 (DCM/MeOH 10:1)

HR-MS (ESI): m/z calculated for sum formula $C_{28}H_{30}Cl_2N_4O_4S$: $[M+H]^+$ = 589.14376, found: $[M+H]^+$ = 589.14340, error: 0.36 mDa or 0.61 ppm

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.05-1.18 (m, 1H), 1.38-1.57 (m, 3H), 1.59-1.67 (m, 1H), 2.18 (d, 1H, J = 14.0 Hz), 2.21-2.35 (m, 1H), 3.23 (d, 0.5H, J = 14.2 Hz), 3.39-3.77 (m, 4.5H), 4.55-4.62 (m, 0.5H), 4.70-4.77 (m, 0.5H), 4.85-4.90 (m, 1H), 4.95 (dd, 1H, J = 19.9/15.4 Hz), 5.24 (d, 1H, J = 15.5 Hz), 6.99 (q, 1H, J = 7.7 Hz), 7.11 (t, 2H, J = 8.0 Hz), 7.20 (q, 2H, J = 7.3 Hz), 7.53 (d, 1H, J = 2.5 Hz), 7.75 (t, 1H, J = 6.6 Hz), 7.82 (dd, 2H, J = 7.9/1.9 Hz), 7.85 (t, 1H, J = 9.2 Hz), 8.29 (t, 1H, J = 7.8 Hz), 8.71 (t, 1H, J = 6.0 Hz) ppm.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8.69
8.68
8.28
8.26
8.25
7.84
7.83
7.81
7.80
7.80
7.79
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7.73
7.72
7.71
7.50
7.50
7.26
7.19
7.18
7.17
7.15
7.10
7.08
7.07
6.99
6.98
6.96
6.94
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4.96
4.92
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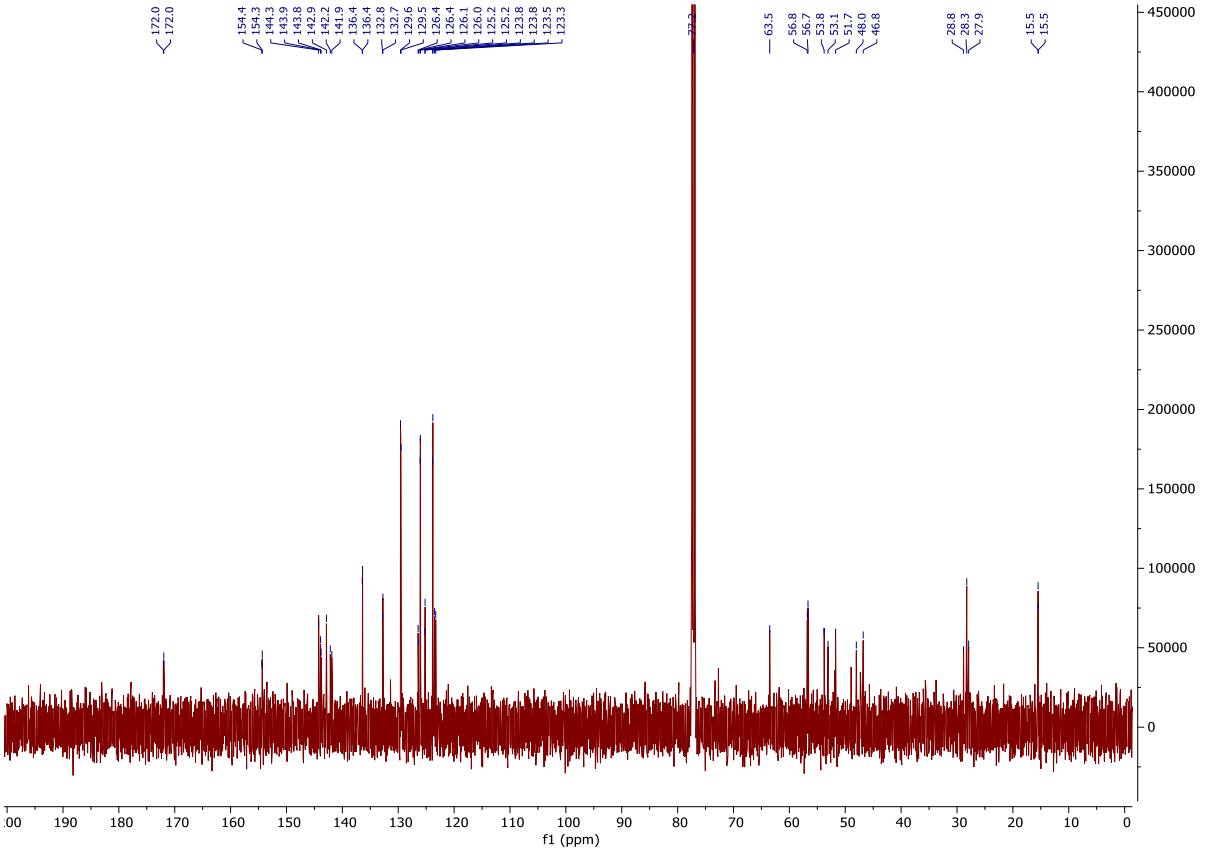
4.83
4.72
4.57
3.59
3.20
2.68
2.25
2.16
1.60
1.47
1.25
1.09
1.00
0.96
0.97
2.03
0.96
0.97
2.14
2.06
1.05
1.05
3.27
1.92
0.69
0.62
4.50
0.44
0.97
1.09
0.98
3.42
0.48
1.08
f1 (ppm)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154.4
154.3
144.3
143.9
143.8
142.9
142.2
141.9
136.4
136.4
132.8
132.7
129.6
129.5
126.4
126.4
126.1
126.0
125.2
125.2
123.8
123.5
123.3
77.2
63.5
56.8
56.7
53.8
53.1
51.7
48.0
46.8
28.8
28.3
27.9
15.5
15.5
f1 (ppm)

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