Article

Isatin bis-imidathiazole hybrids identified as FtsZ inhibitors with on-target activity against *Staphylococcus aureus*

Rita Morigi [1], Daniele Esposito [1], Matteo Calvaresi [2,3], Tainah Dorina Marforio [2,3], Giovanna Angela Gentilomi [4,5], Francesca Bonvicini [4,*] and Alessandra Locatelli [1]

[1] Department of Pharmacy and Biotechnology, Alma Mater Studiorum-University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy; rita.morigi@unibo.it (R.M.); daniele.esposito6@unibo.it (D.E.); alessandra.locatelli@unibo.it (A.L.)

[2] Department of Chemistry "Giacomo Ciamician", Alma Mater Studiorum-University of Bologna, Via Selmi 2, Bologna, 40126, Italy; matteo.calvaresi3@unibo.it (M.C.); tainah.marforio2@unibo.it (T.M.)

[3] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy,matteo.calvaresi3@unibo.it (M.C.); tainah.marforio2@unibo.it (T.M.)

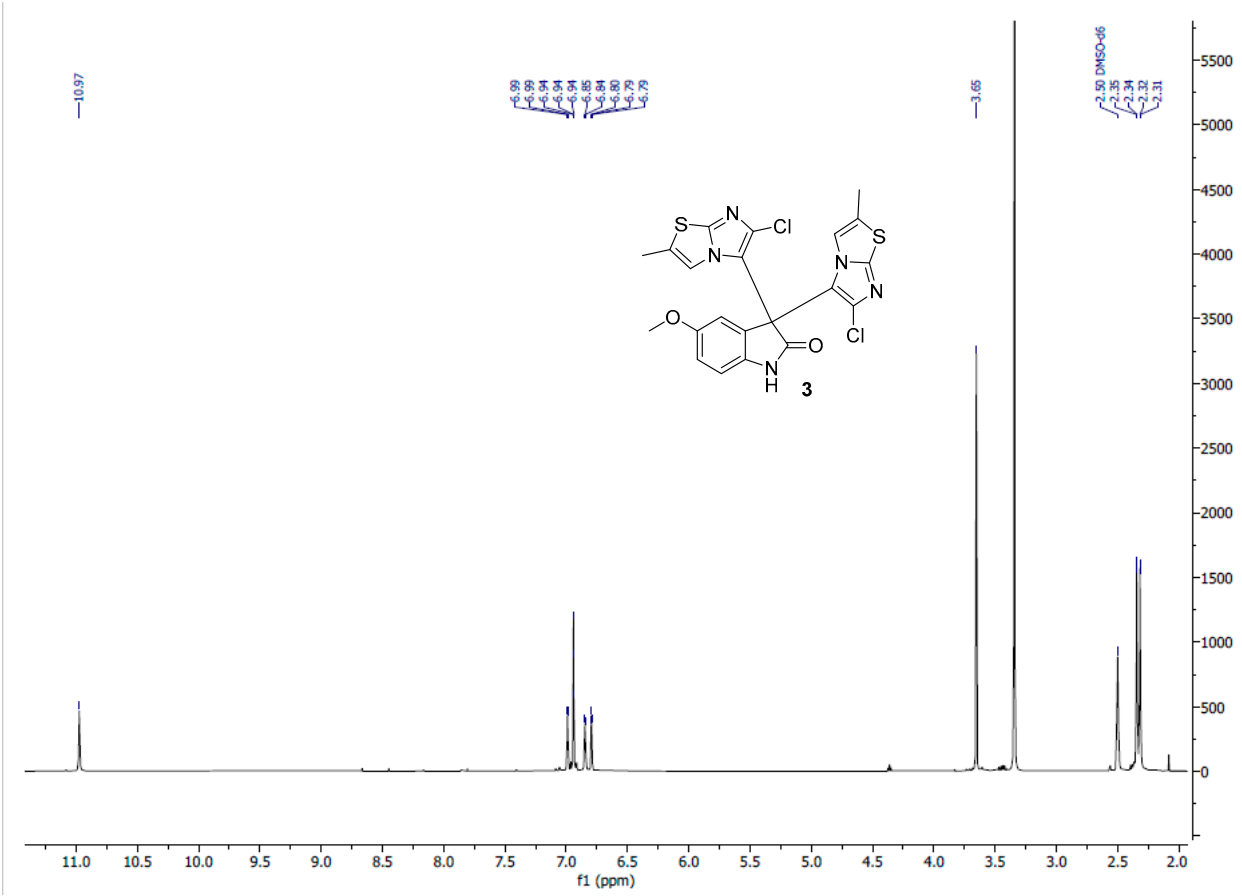
[4] Department of Pharmacy and Biotechnology, Alma Mater Studiorum-University of Bologna, Via Massarenti 9, 40138 Bologna, Italy; giovanna.gentilomi@unibo.it (G.G.)

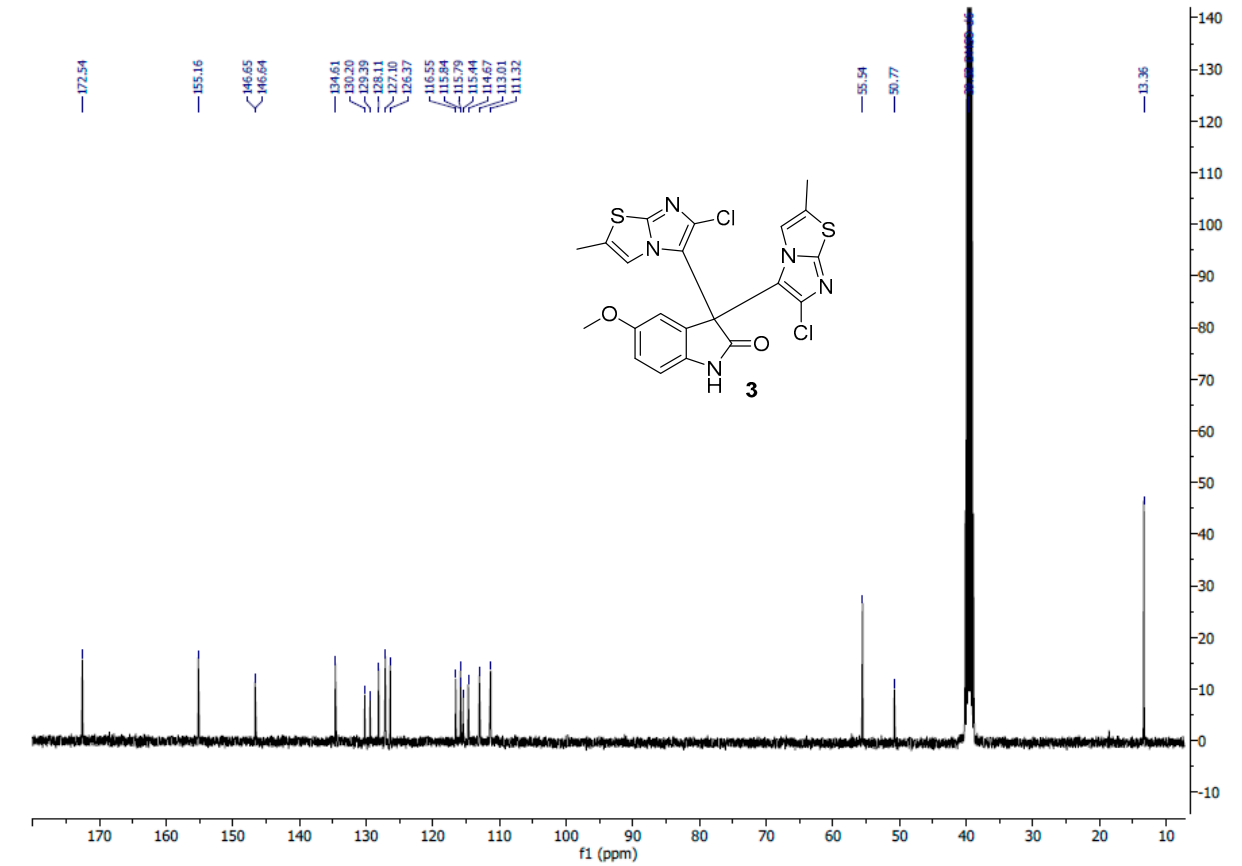
[5] Division of Microbiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Massarenti 9, 40138 Bologna, Italy; giovanna.gentilomi@unibo.it (G.G.)

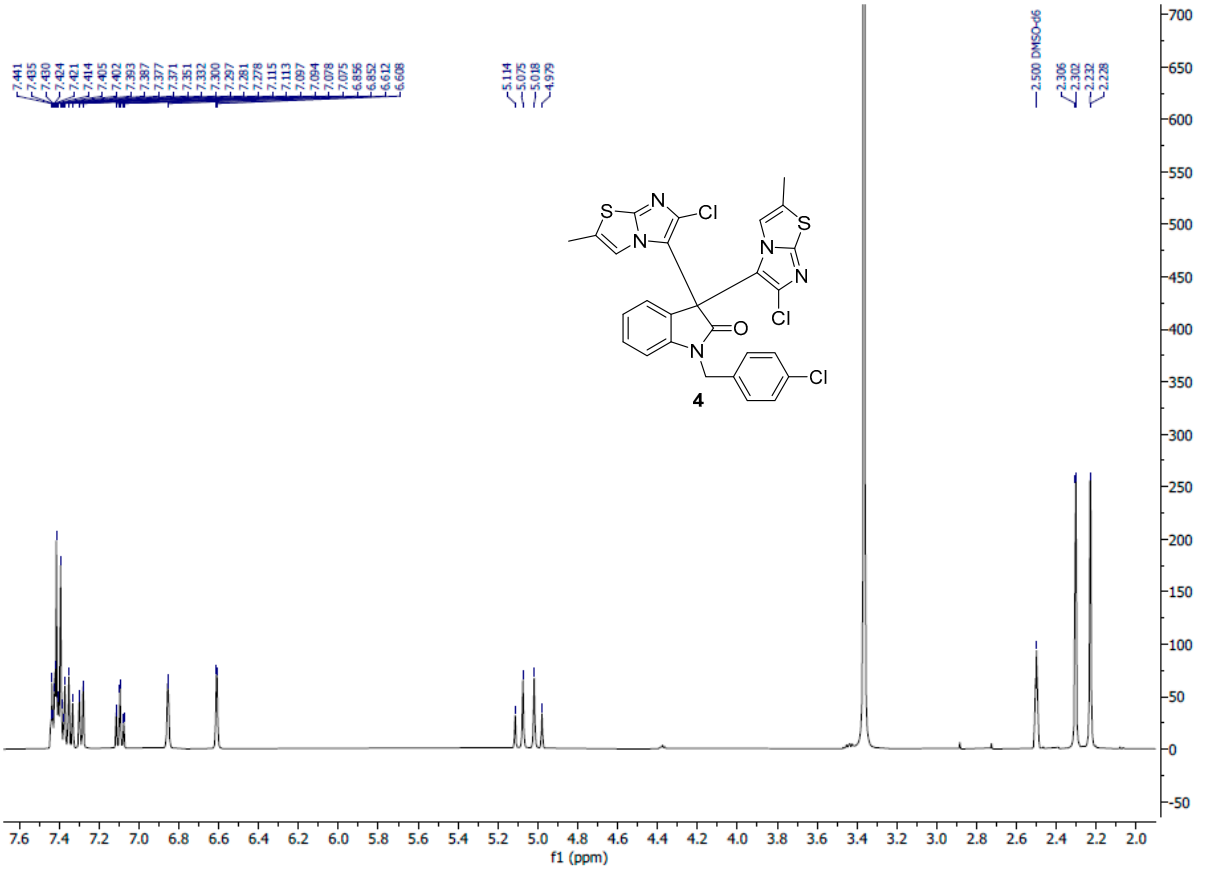
* Correspondence: francesca.bonvicini4@unibo.it (F.B.)

Contents:

Figure S1: ^{1}H and ^{13}C NMR spectra of the new compounds.



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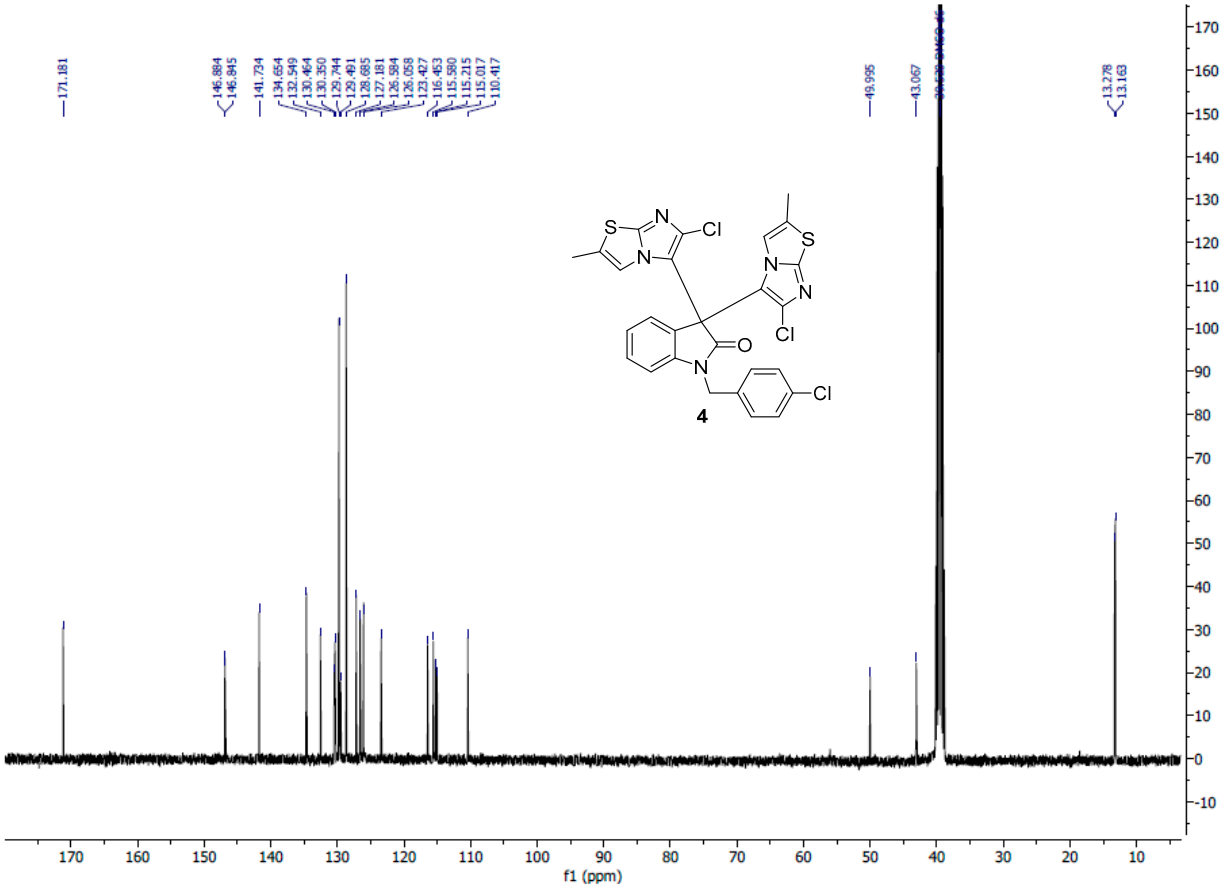
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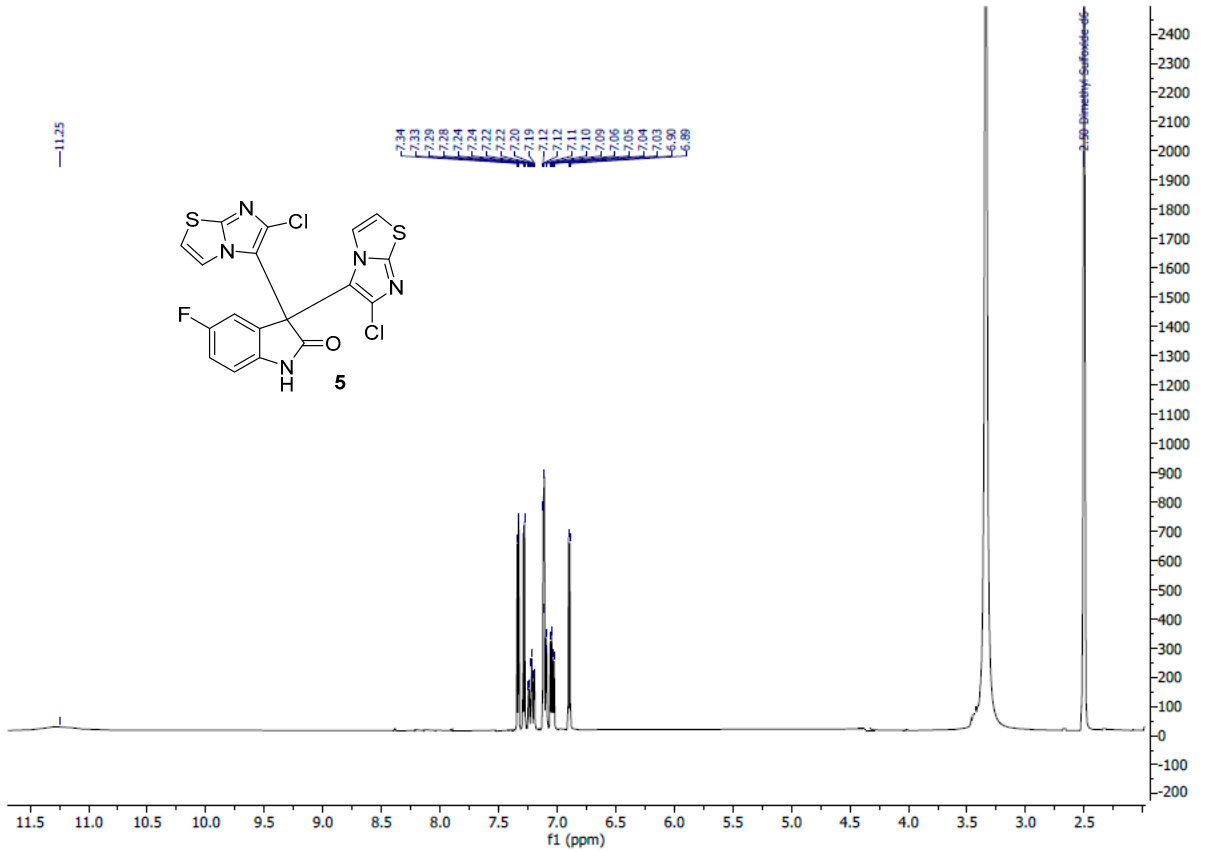
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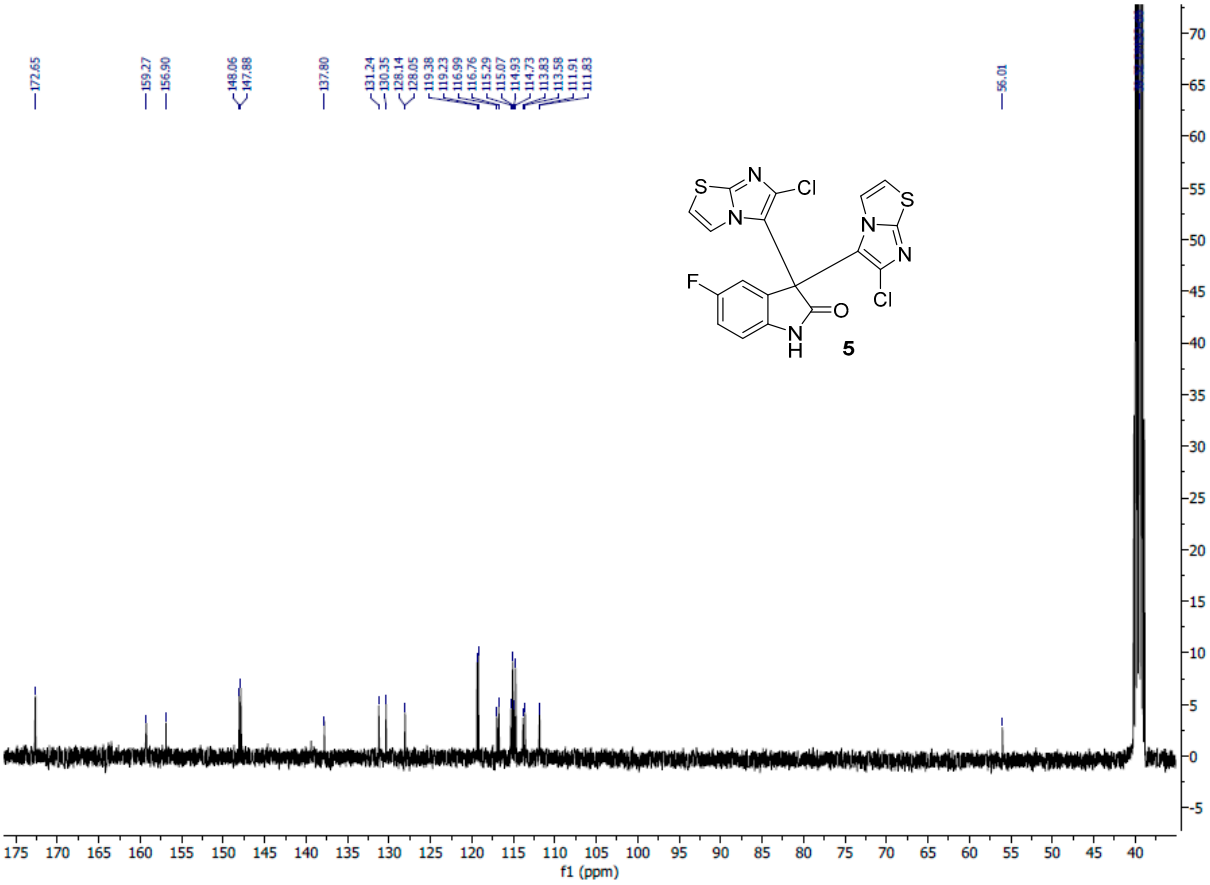
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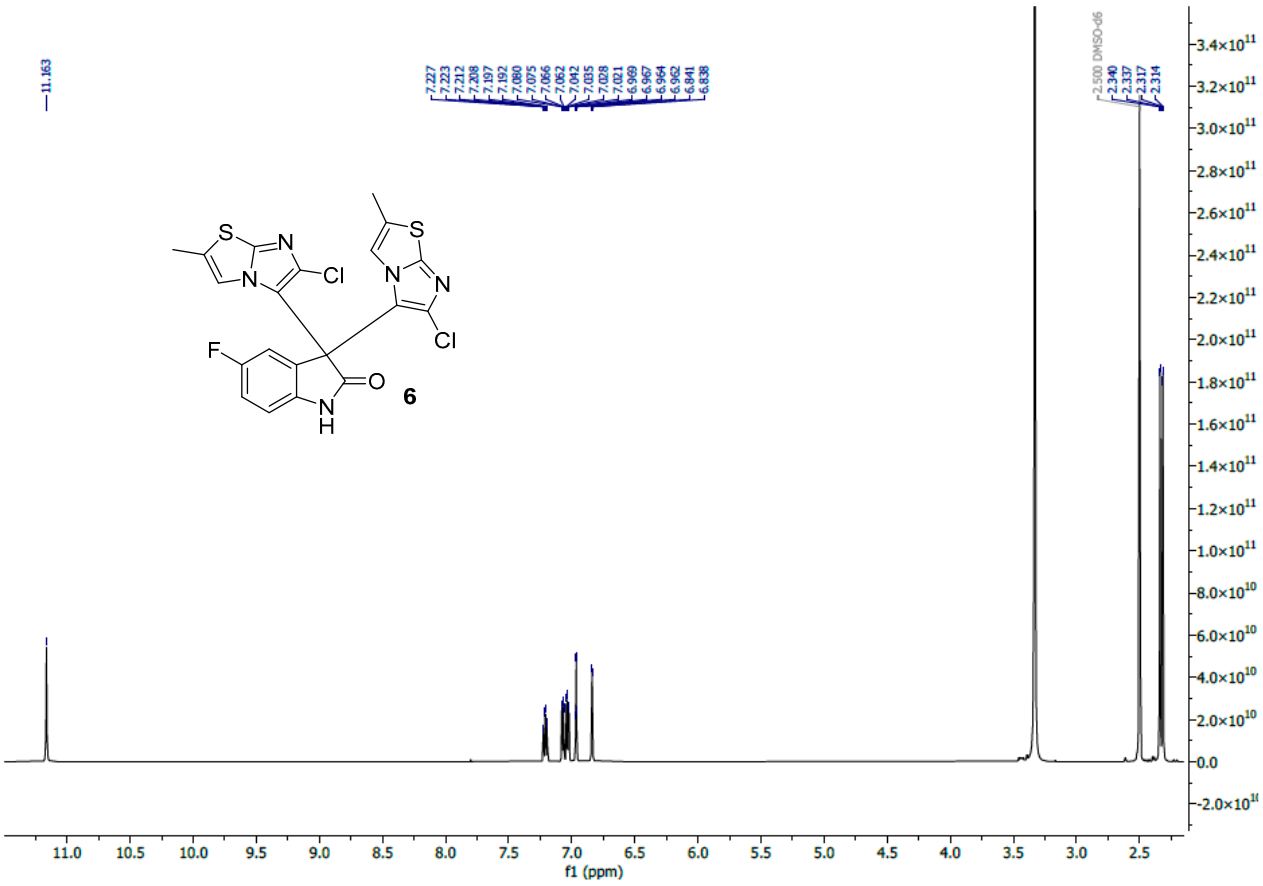
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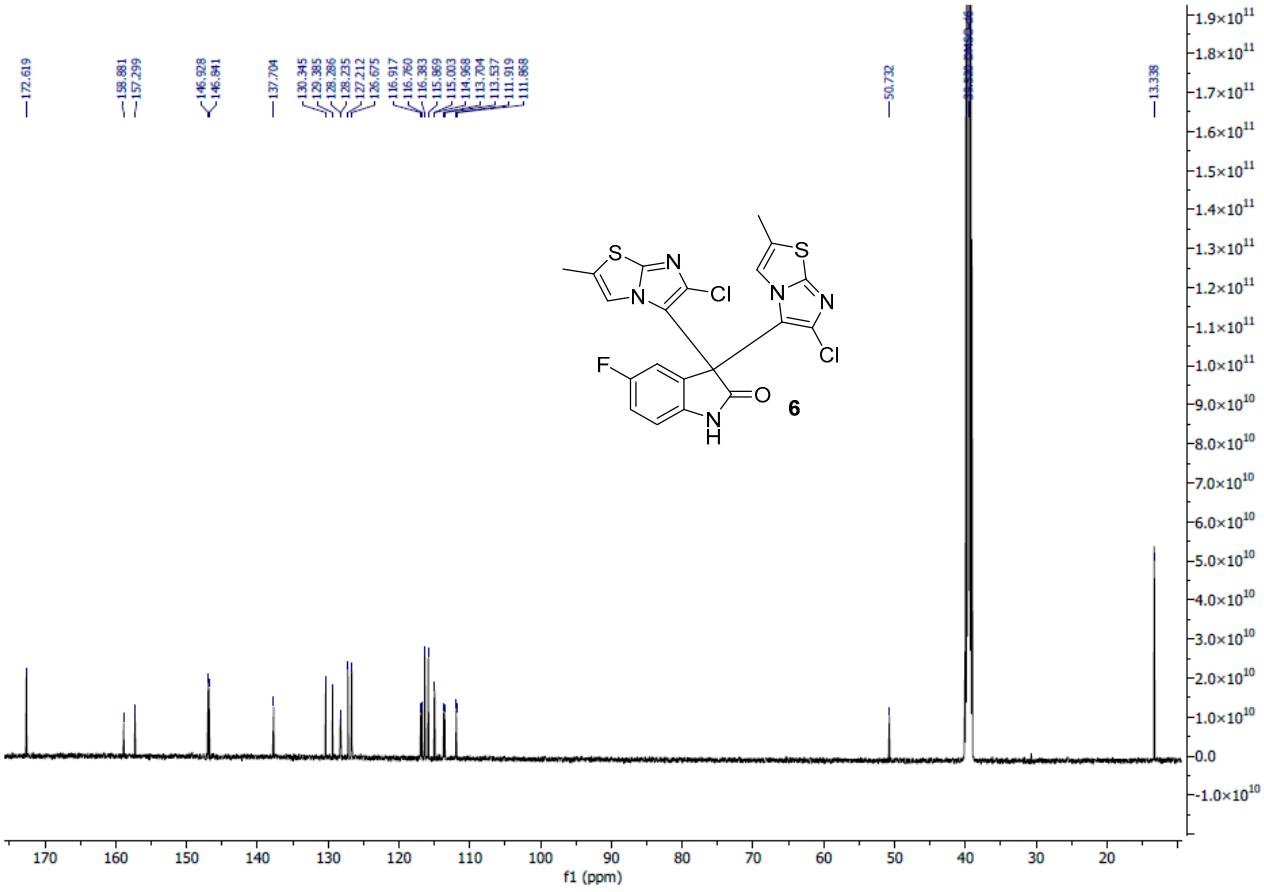
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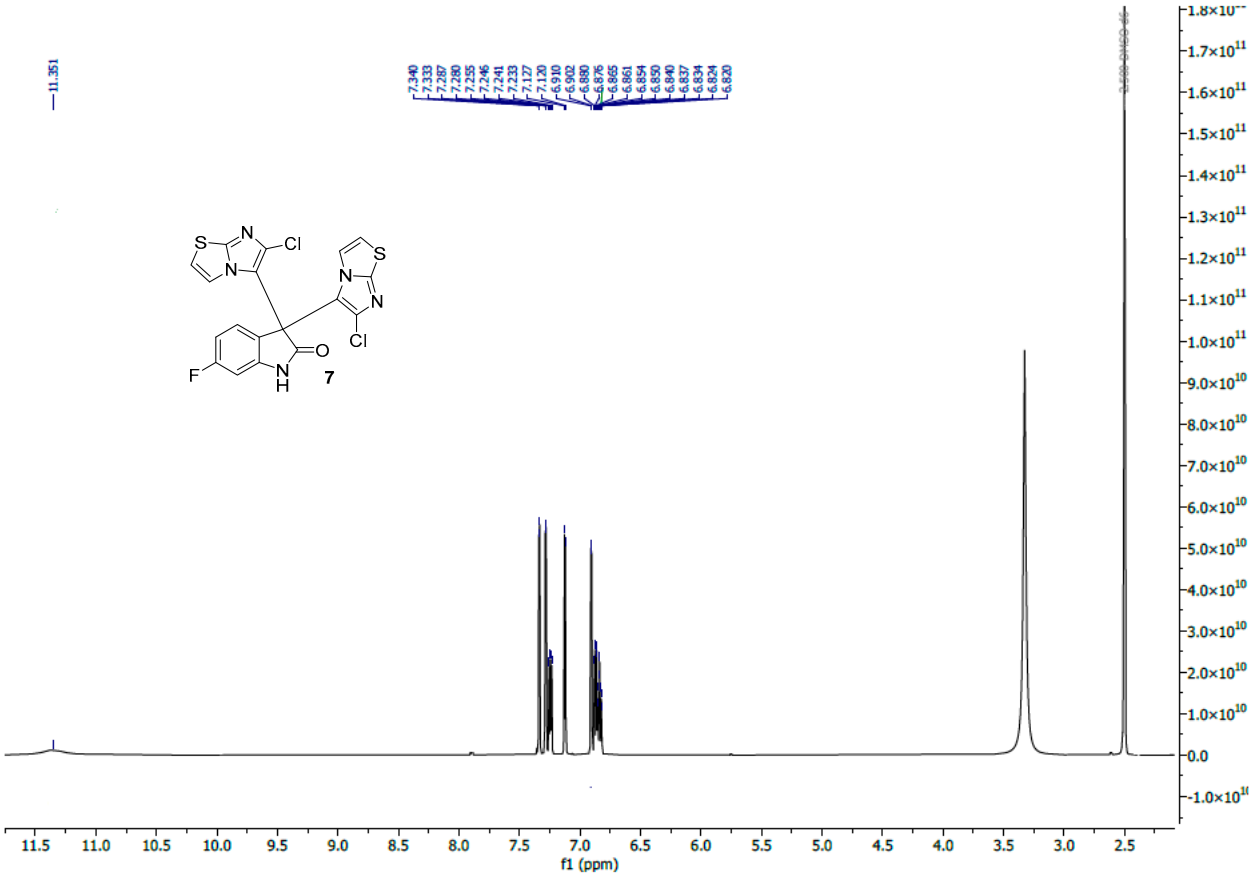
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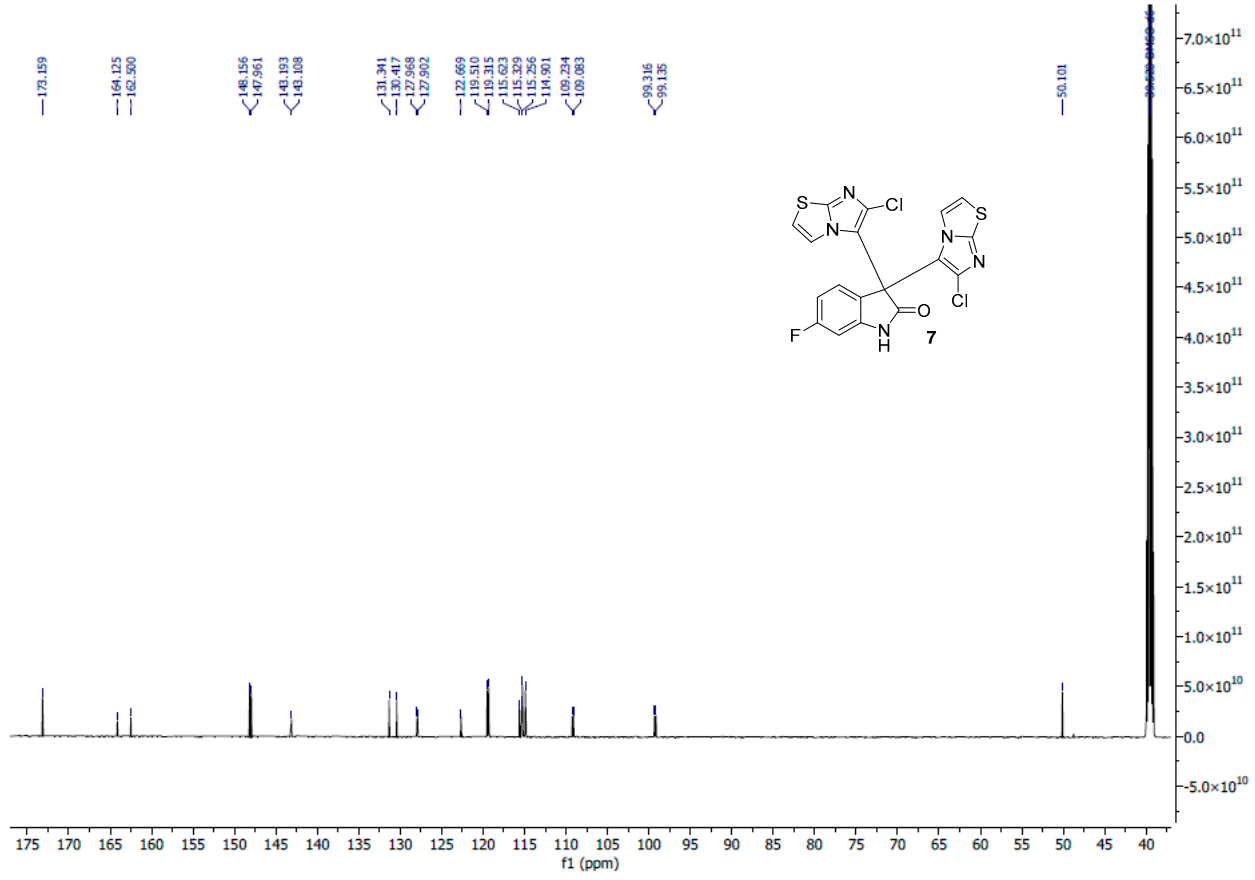
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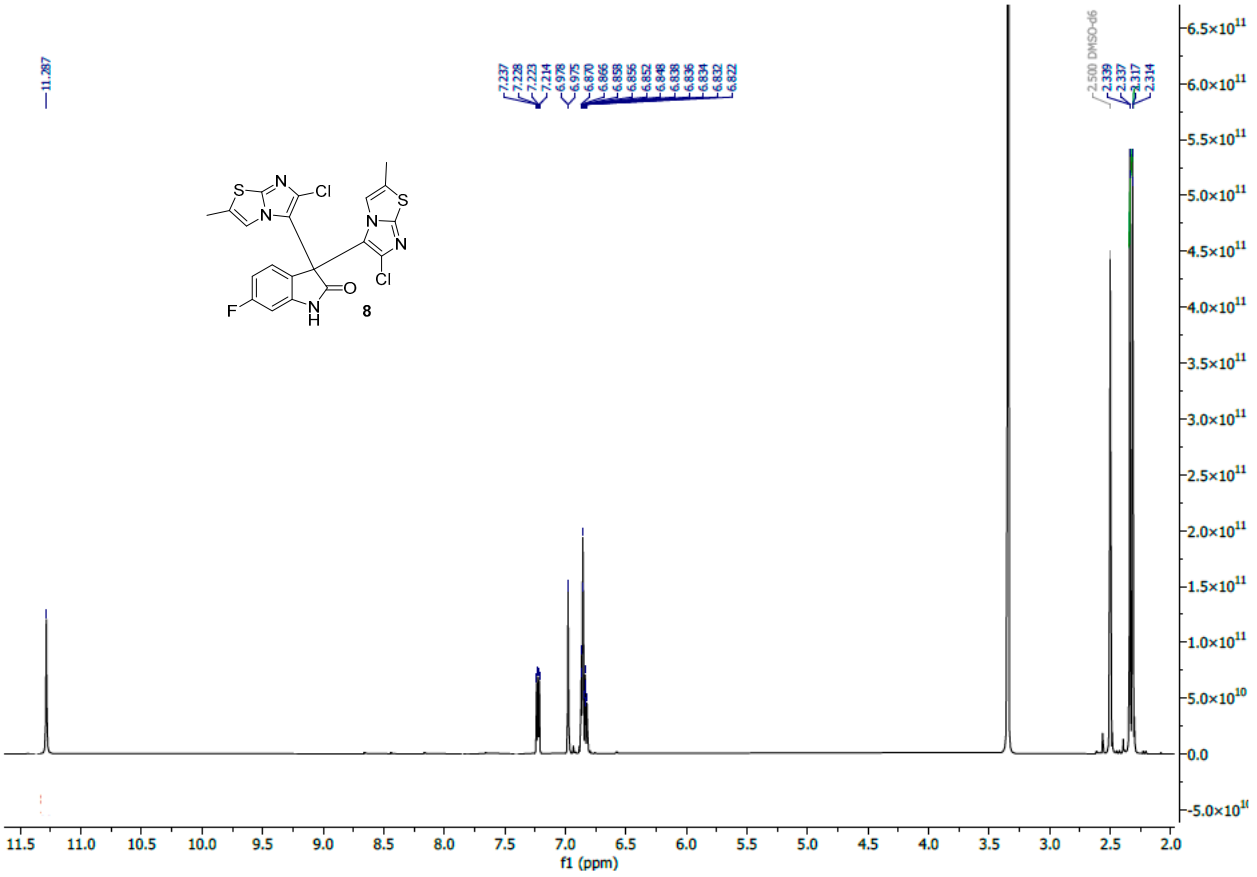
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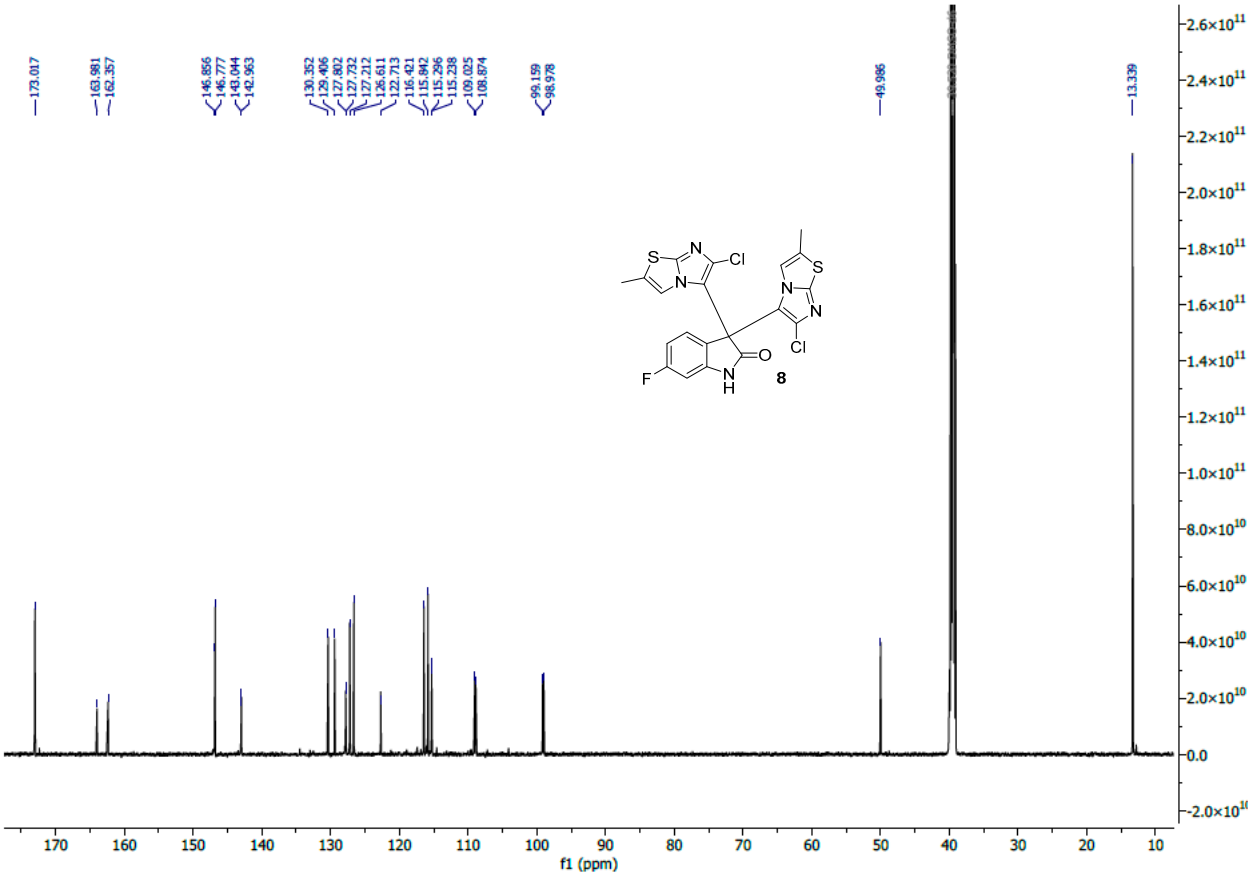
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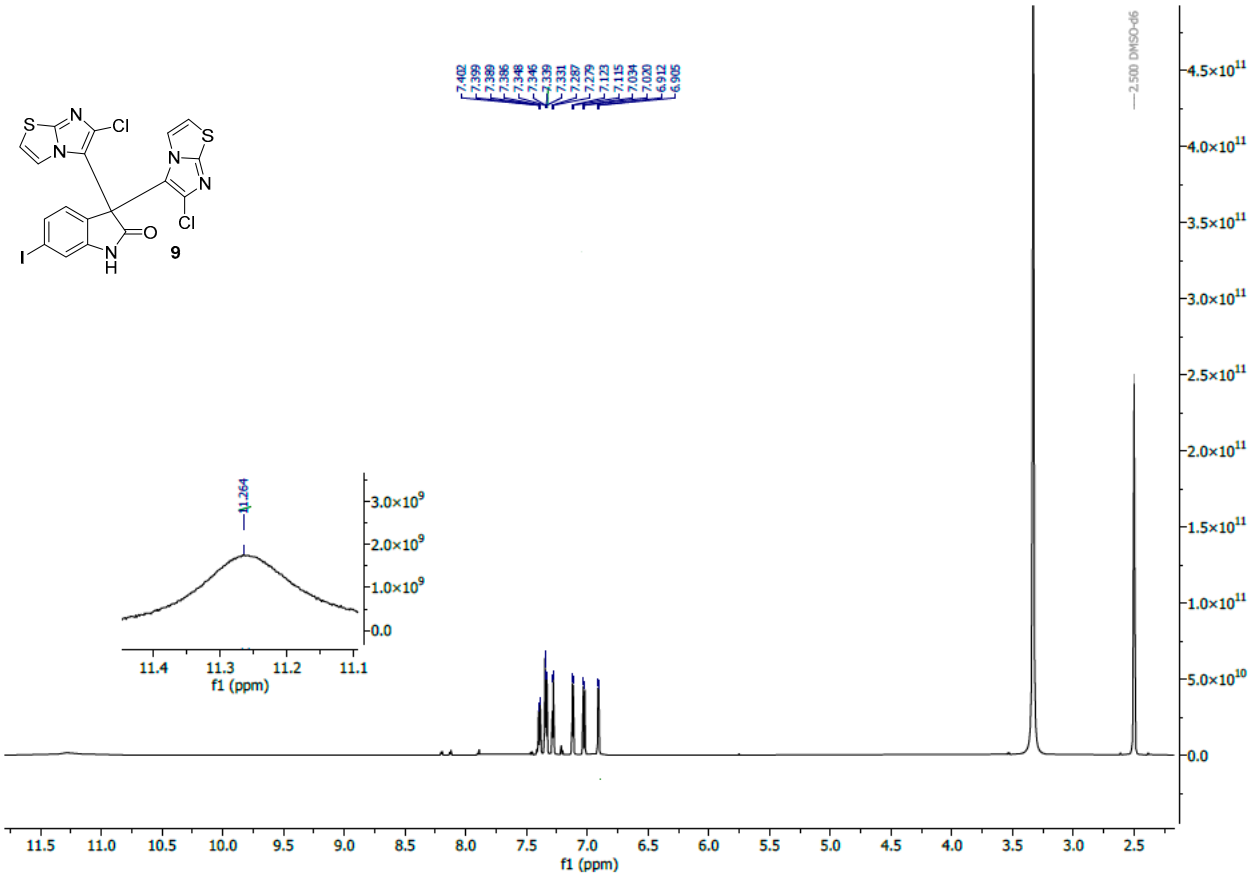
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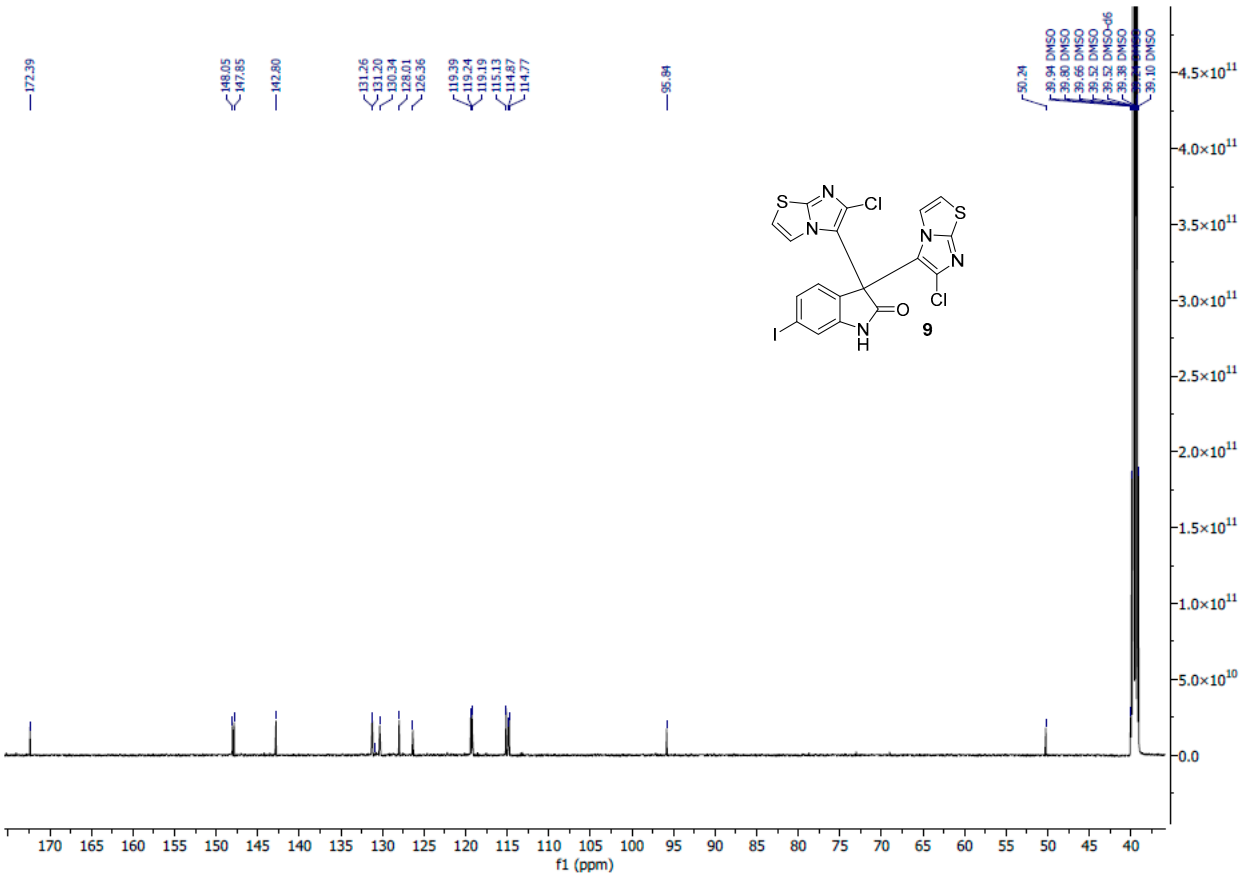
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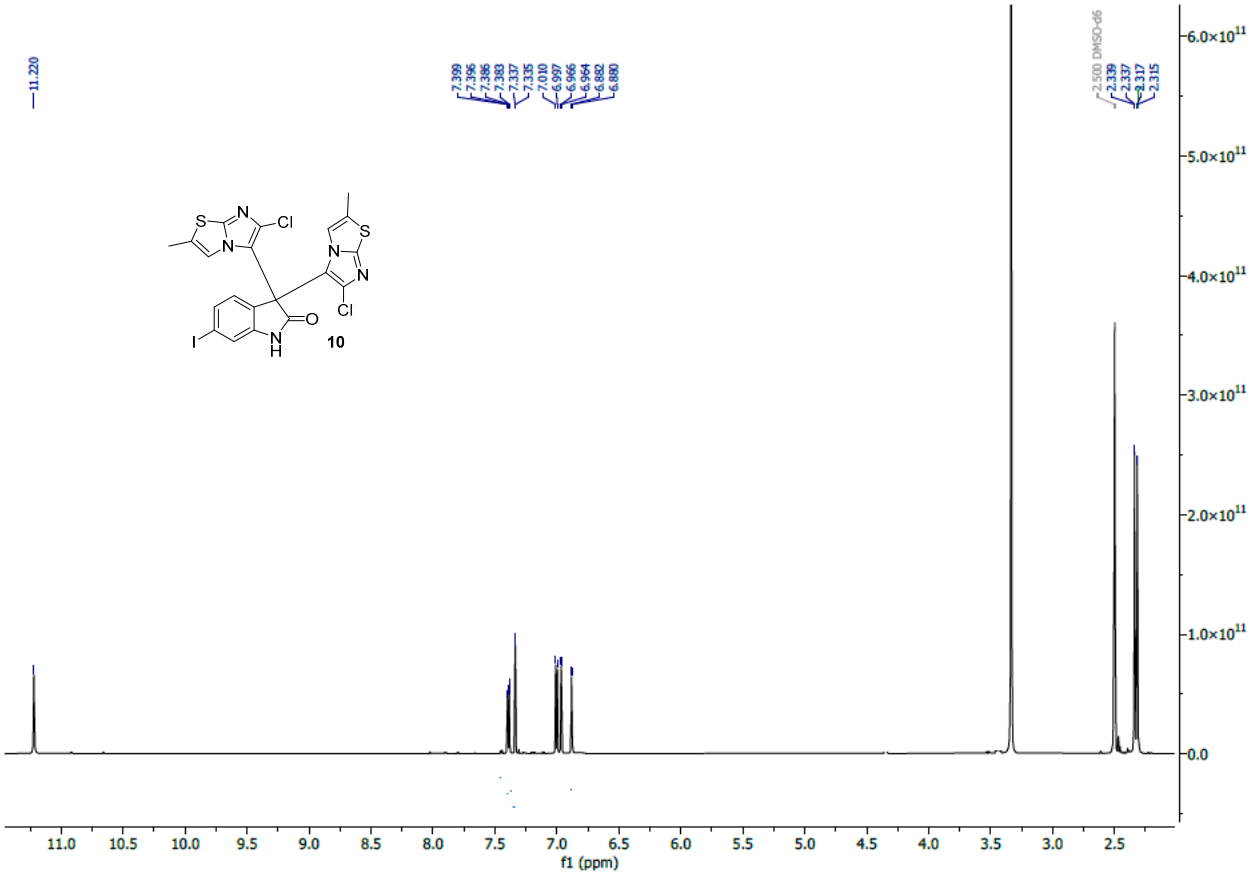
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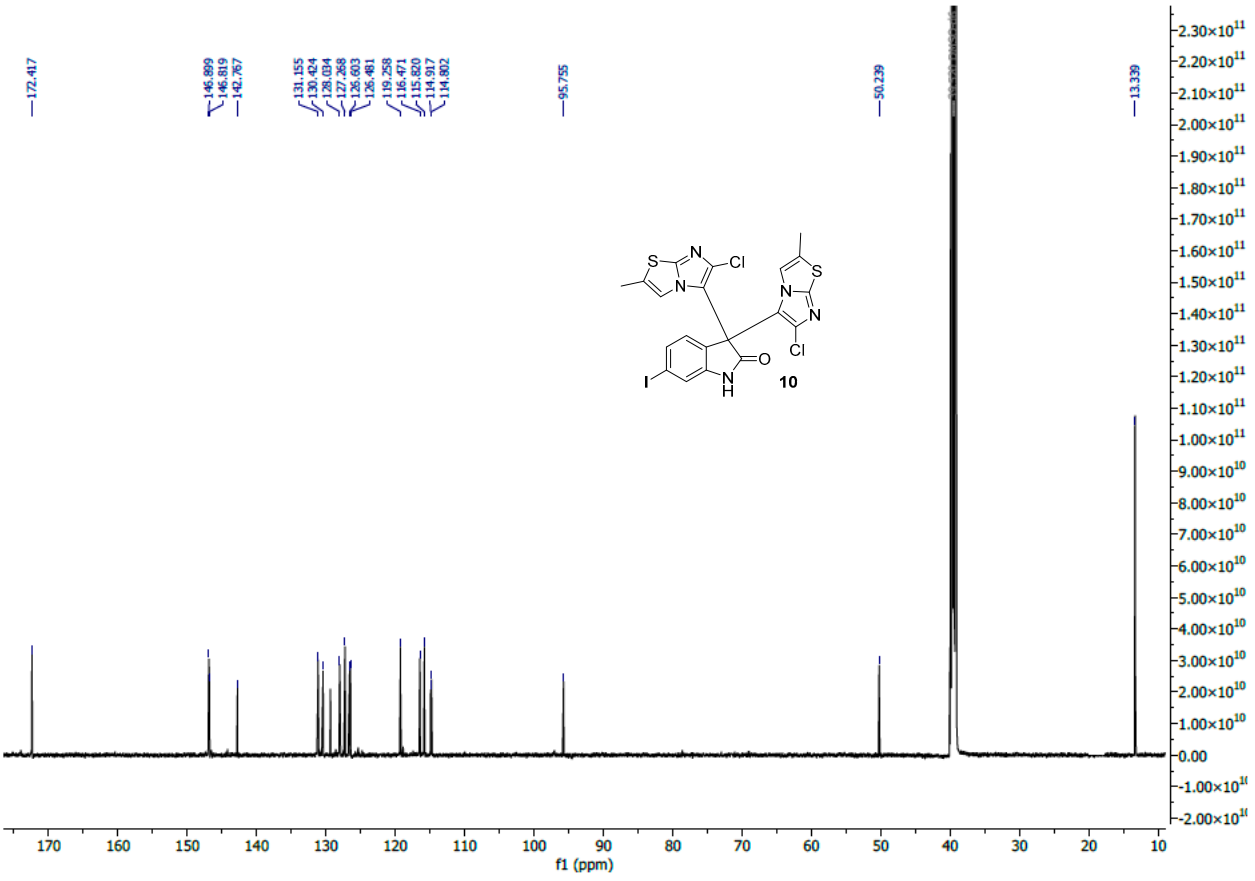
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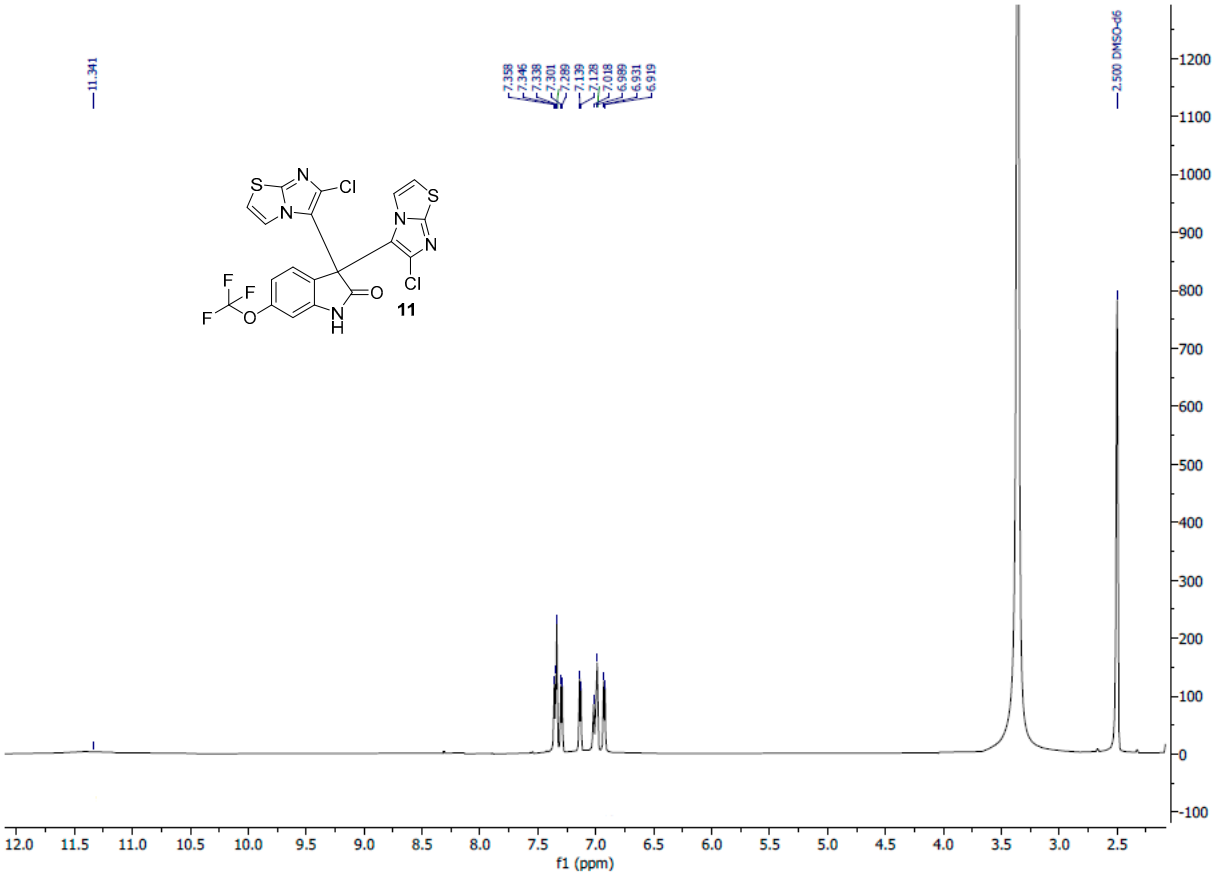
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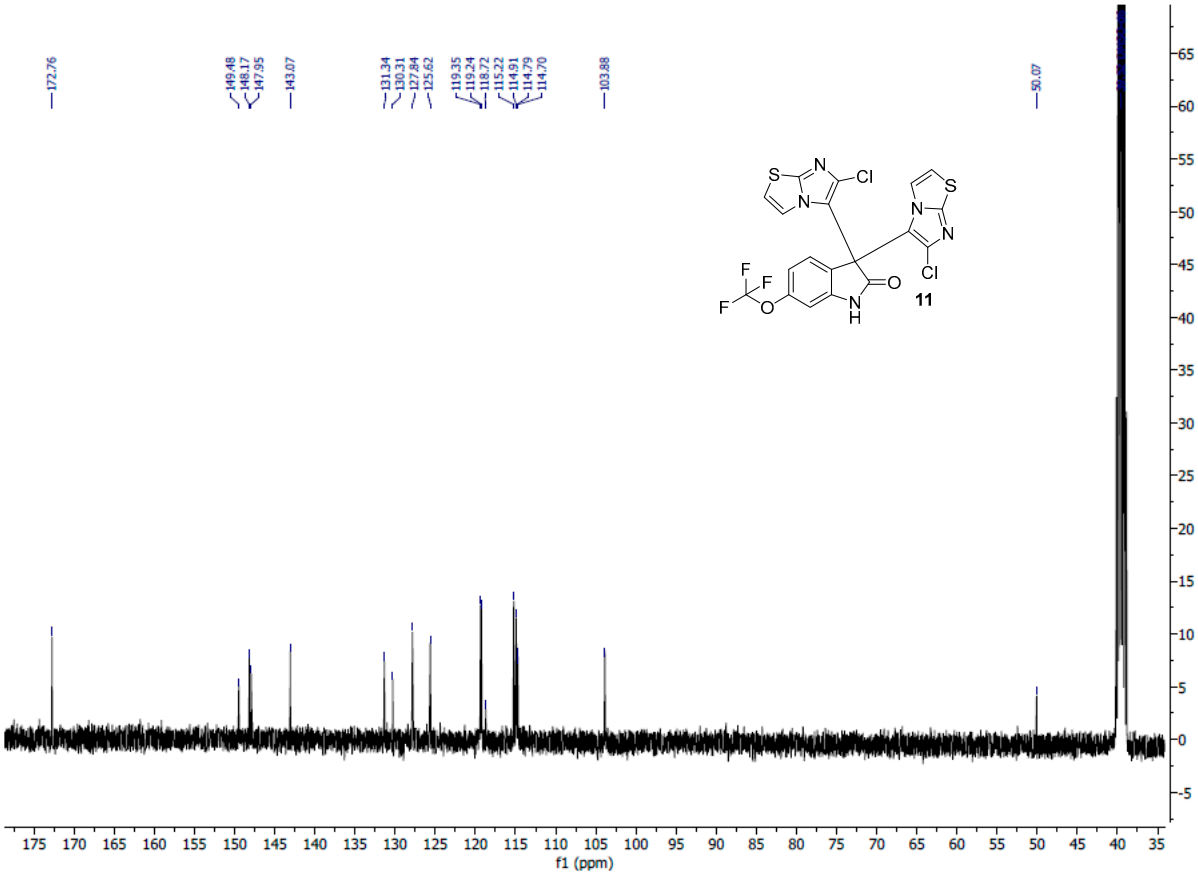
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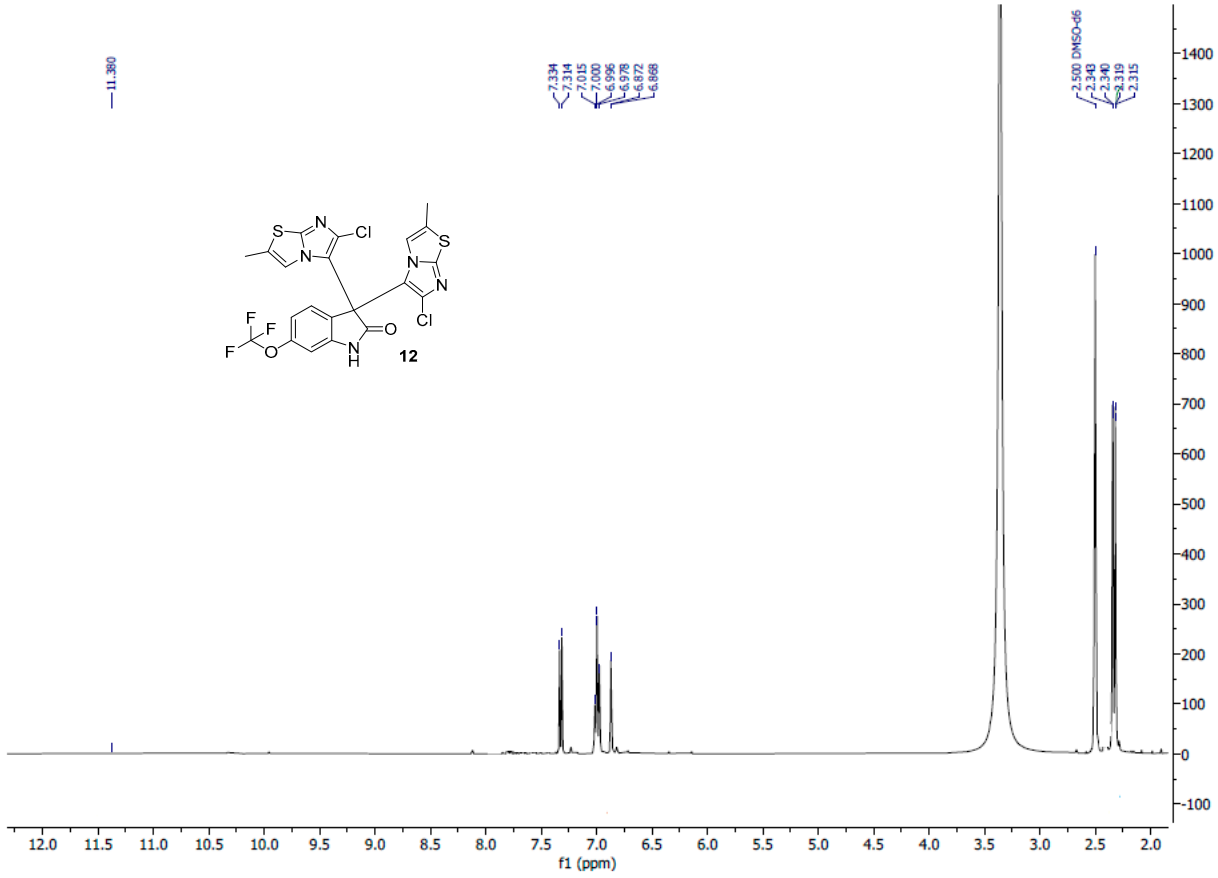
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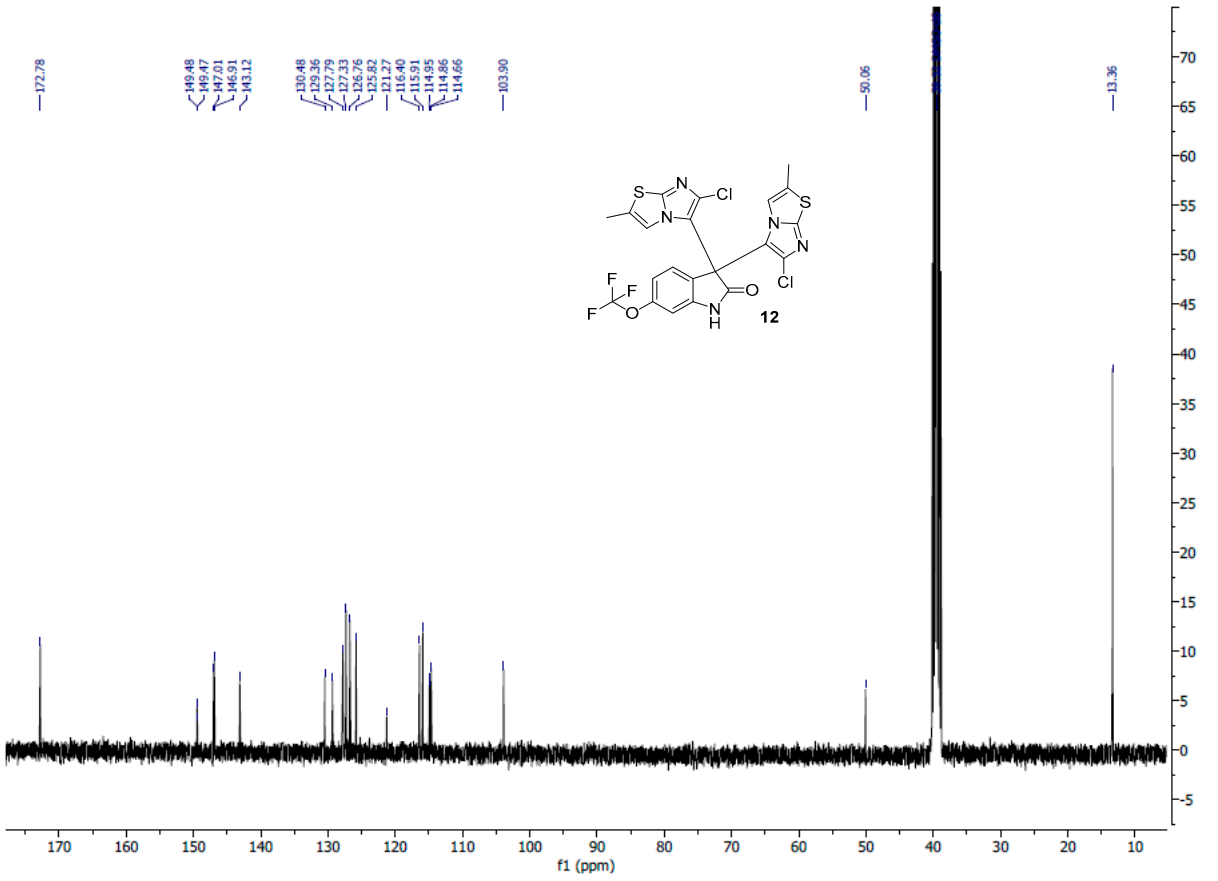
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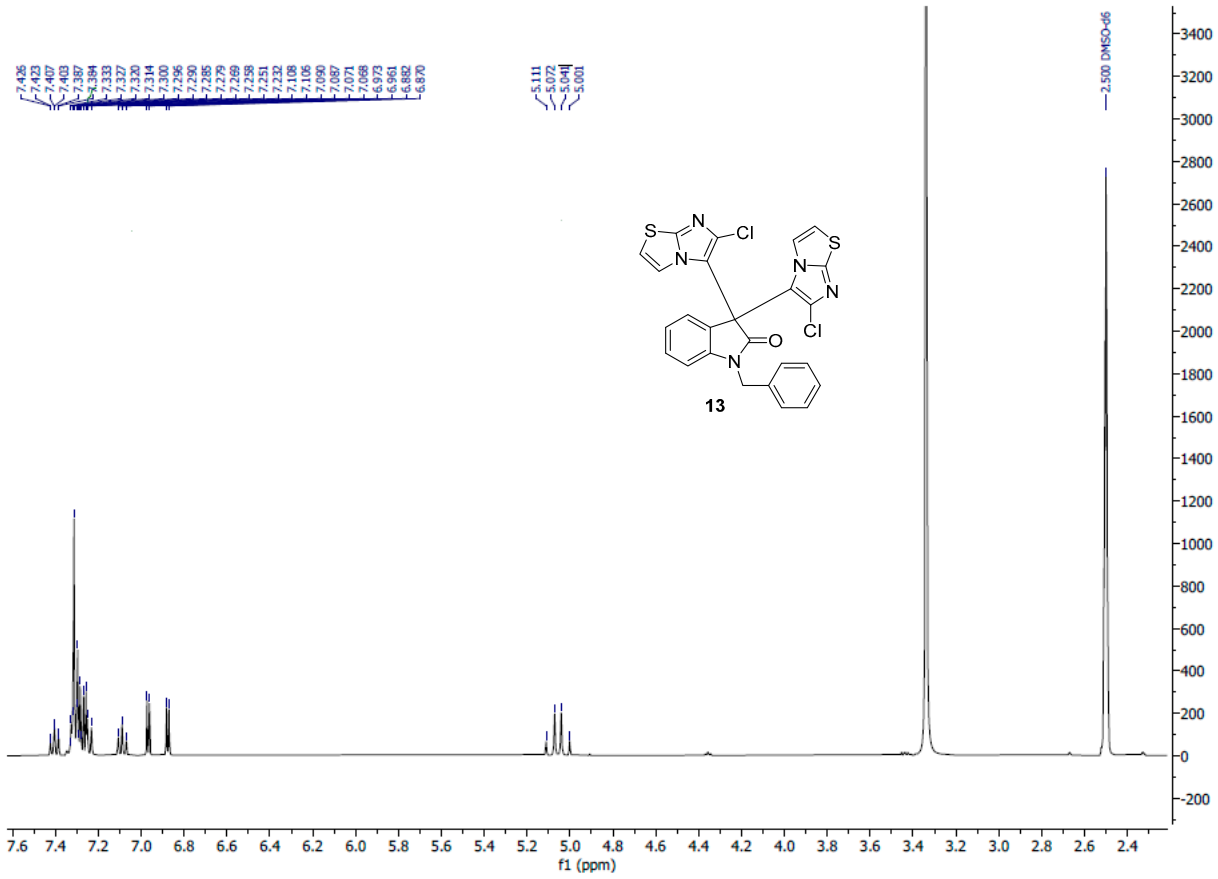
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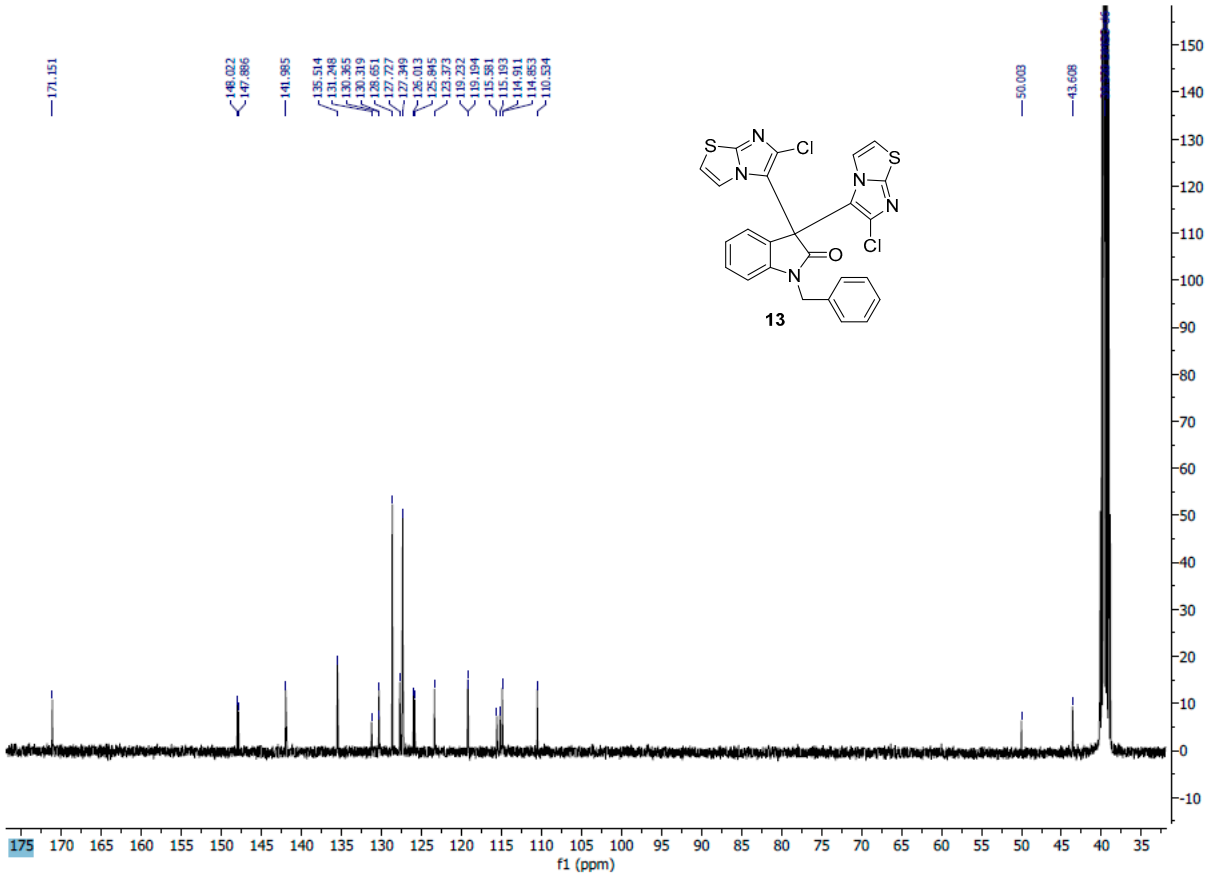
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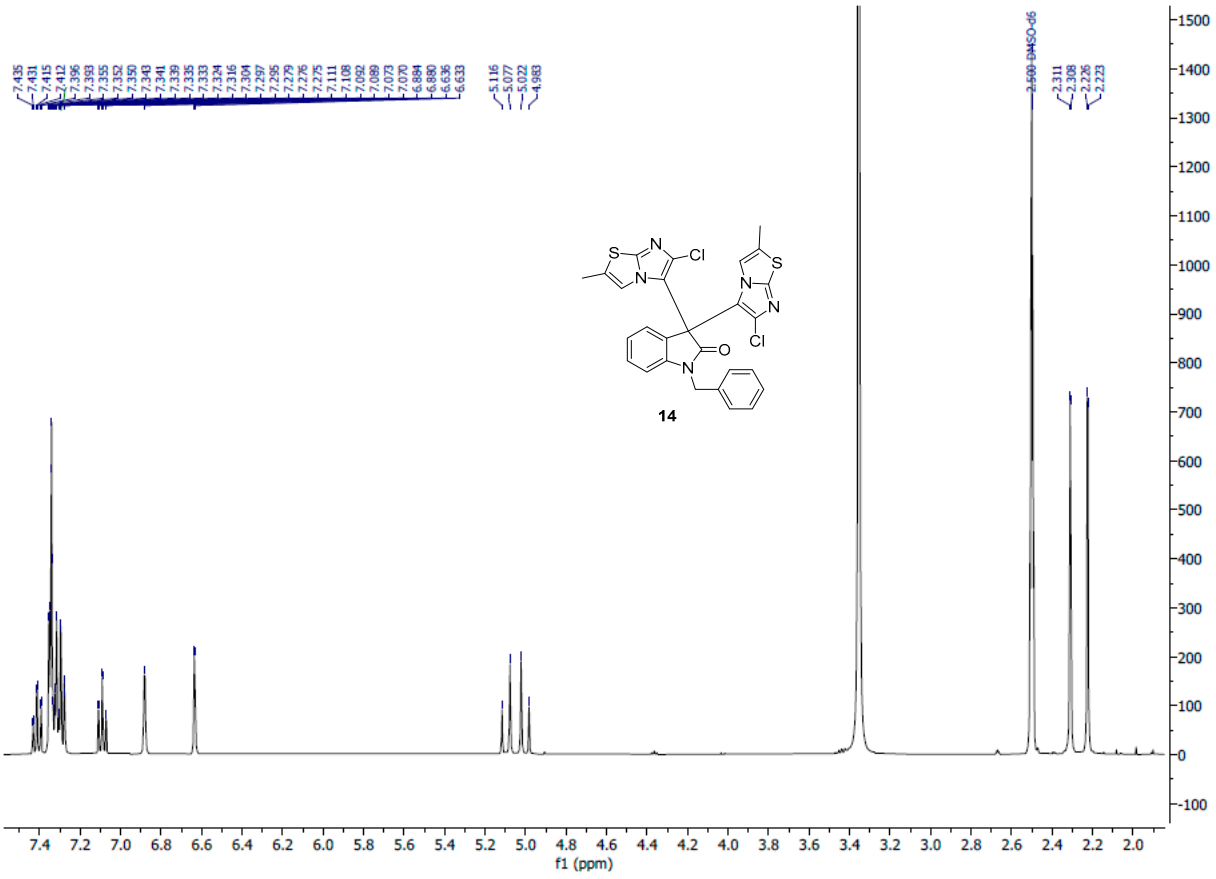
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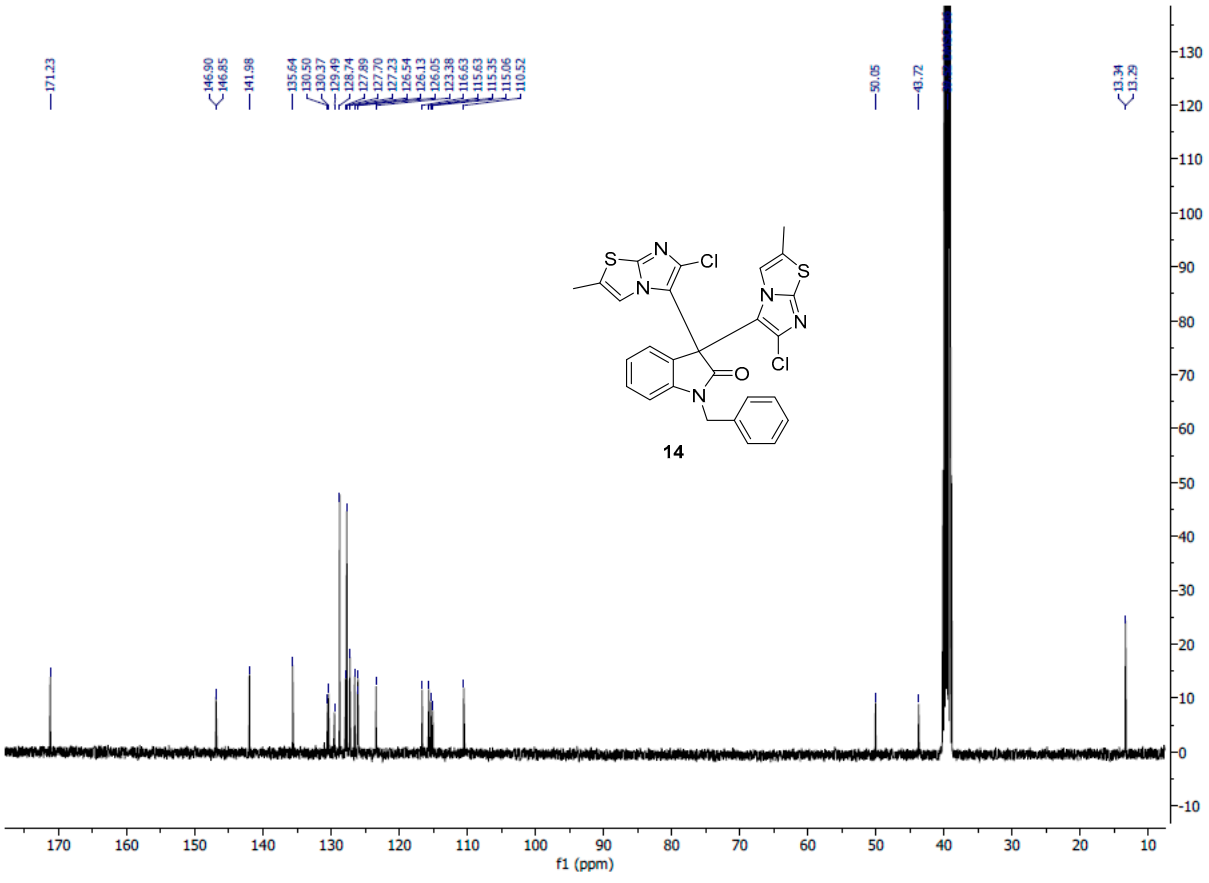
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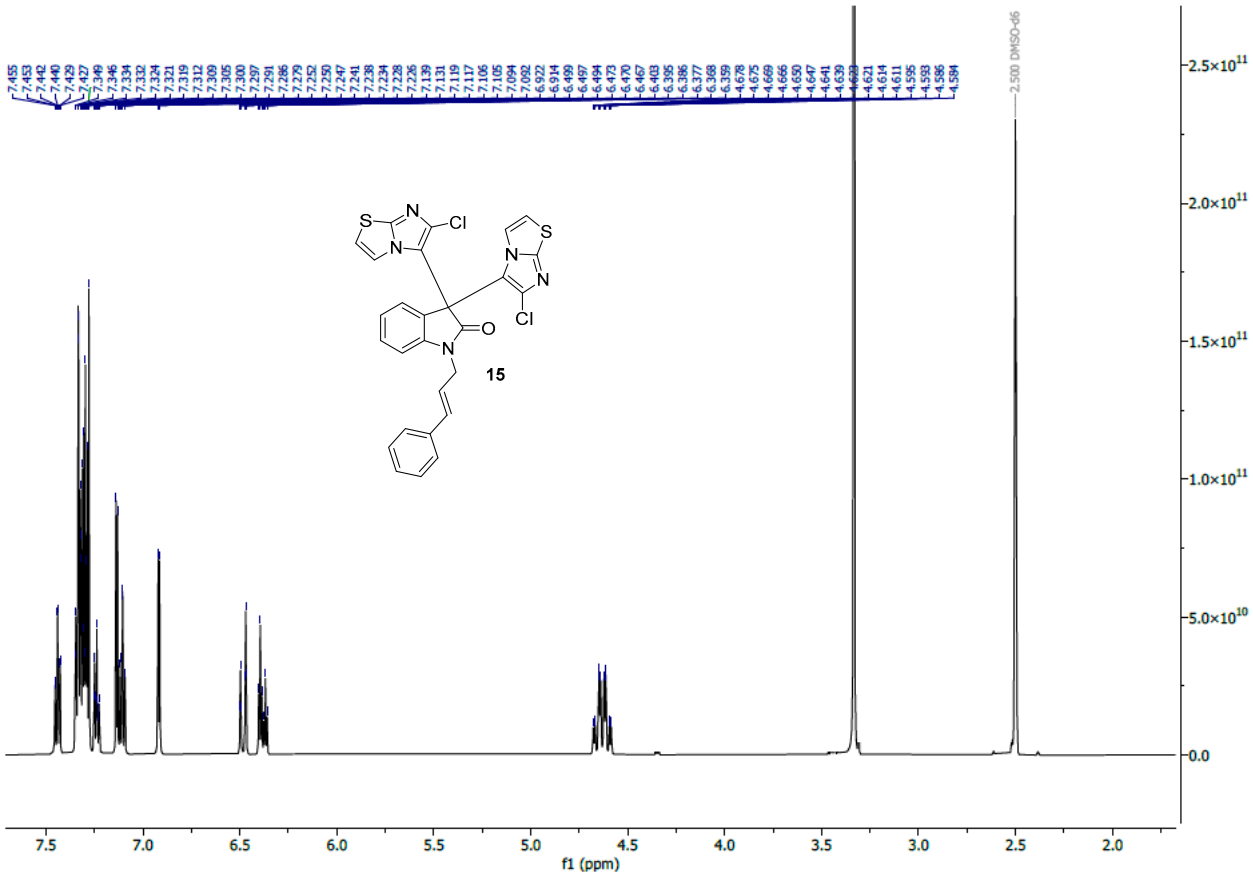
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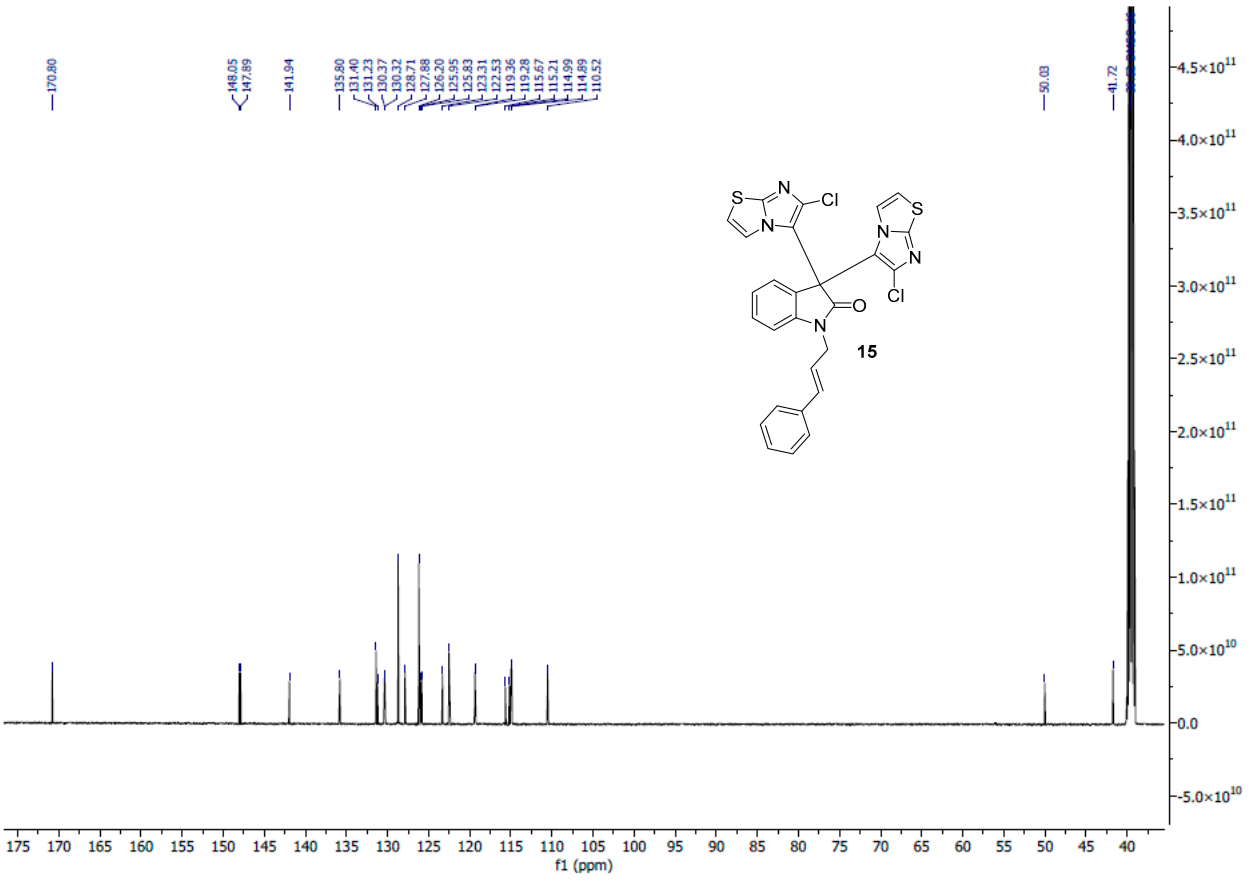
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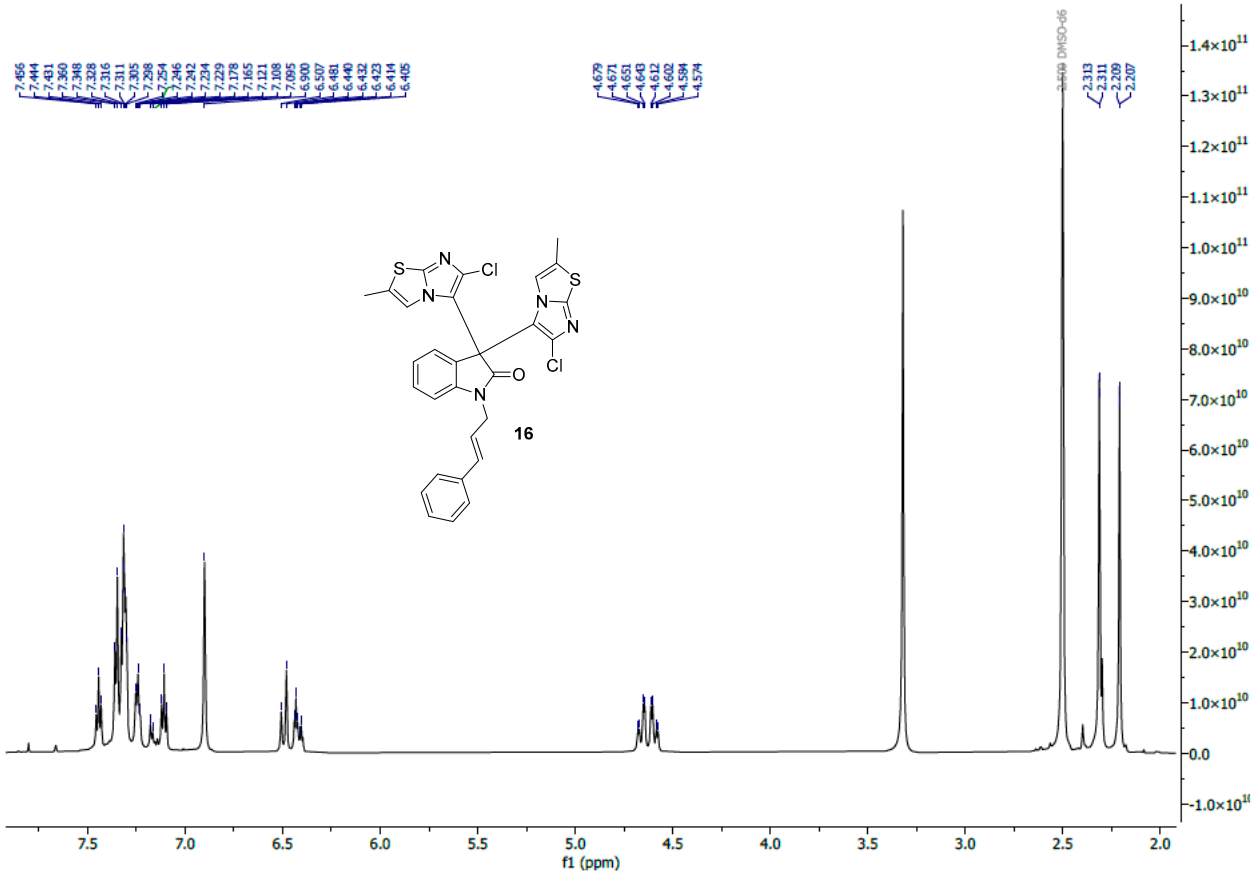
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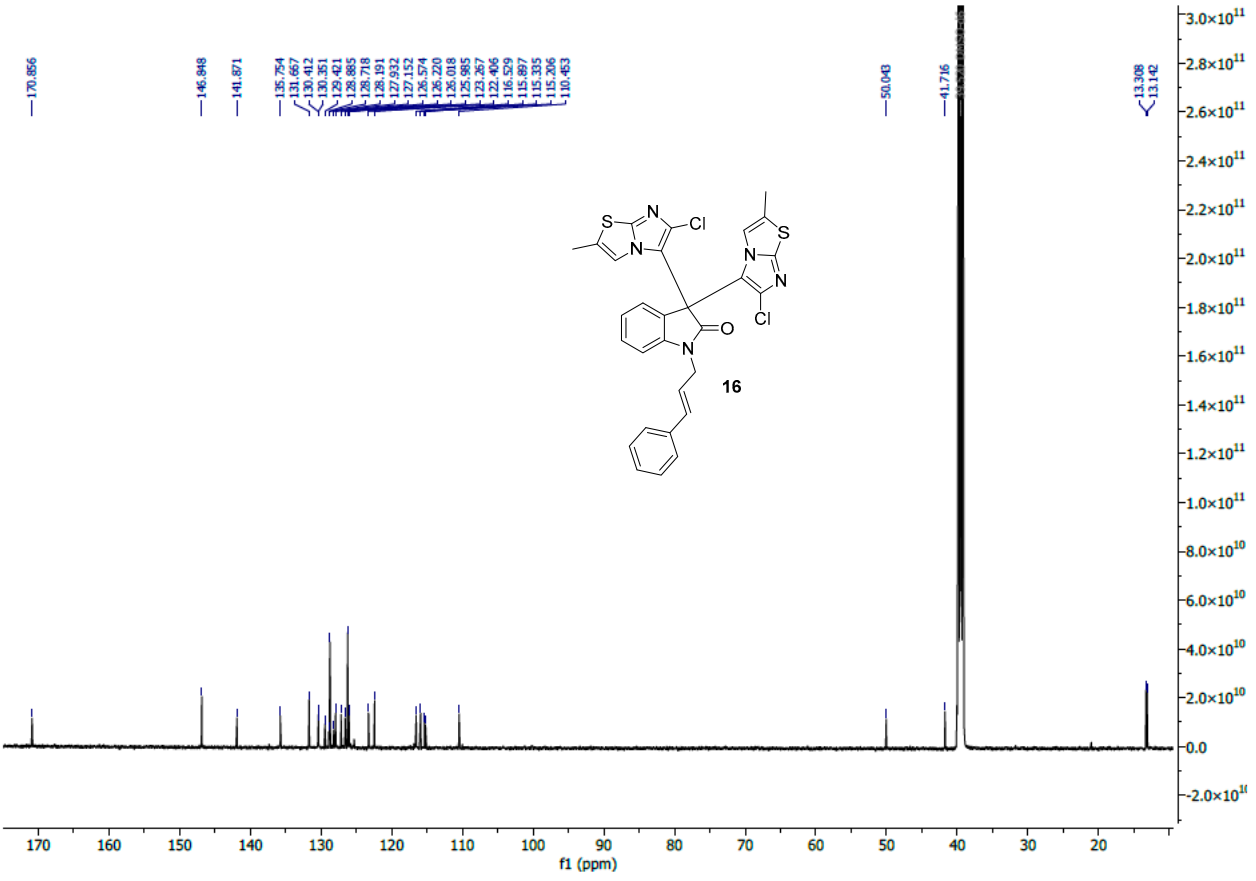
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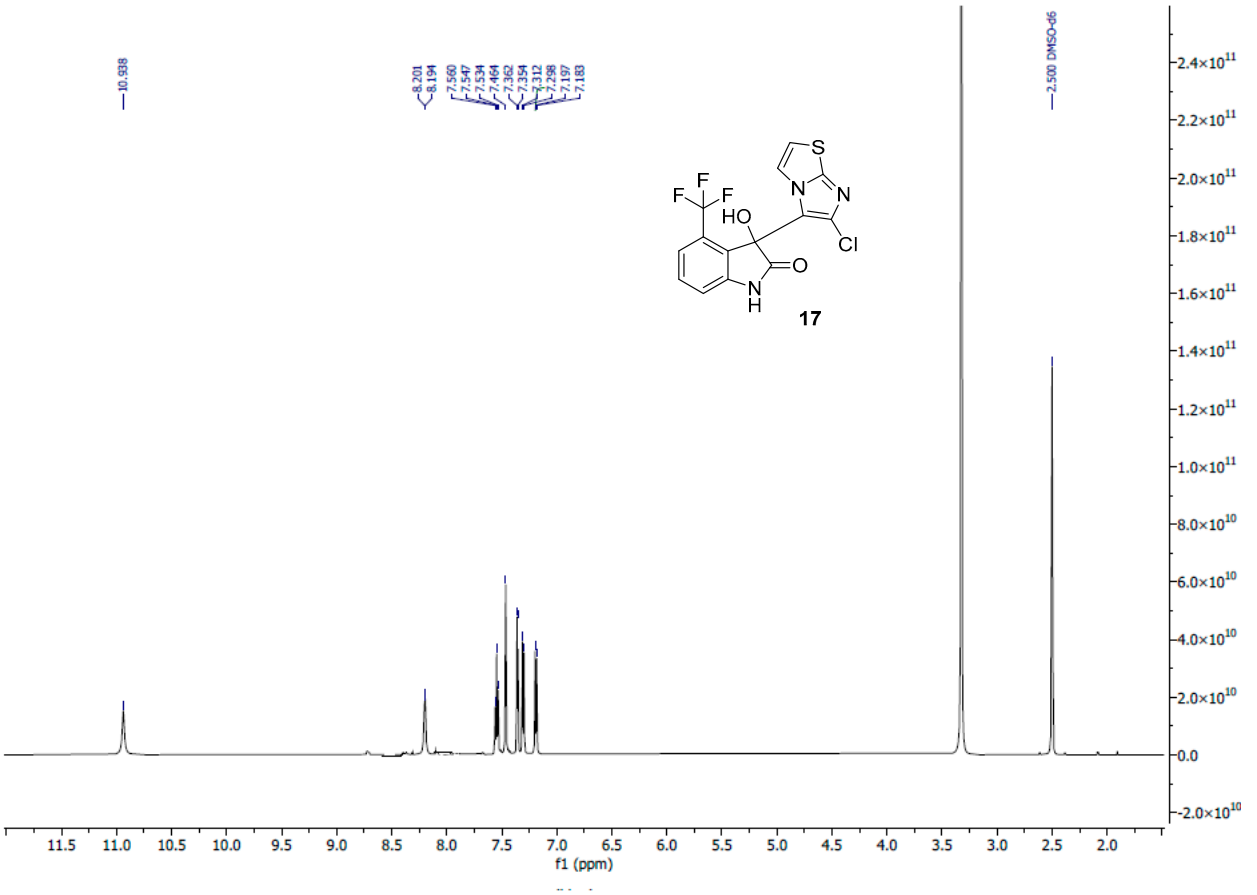
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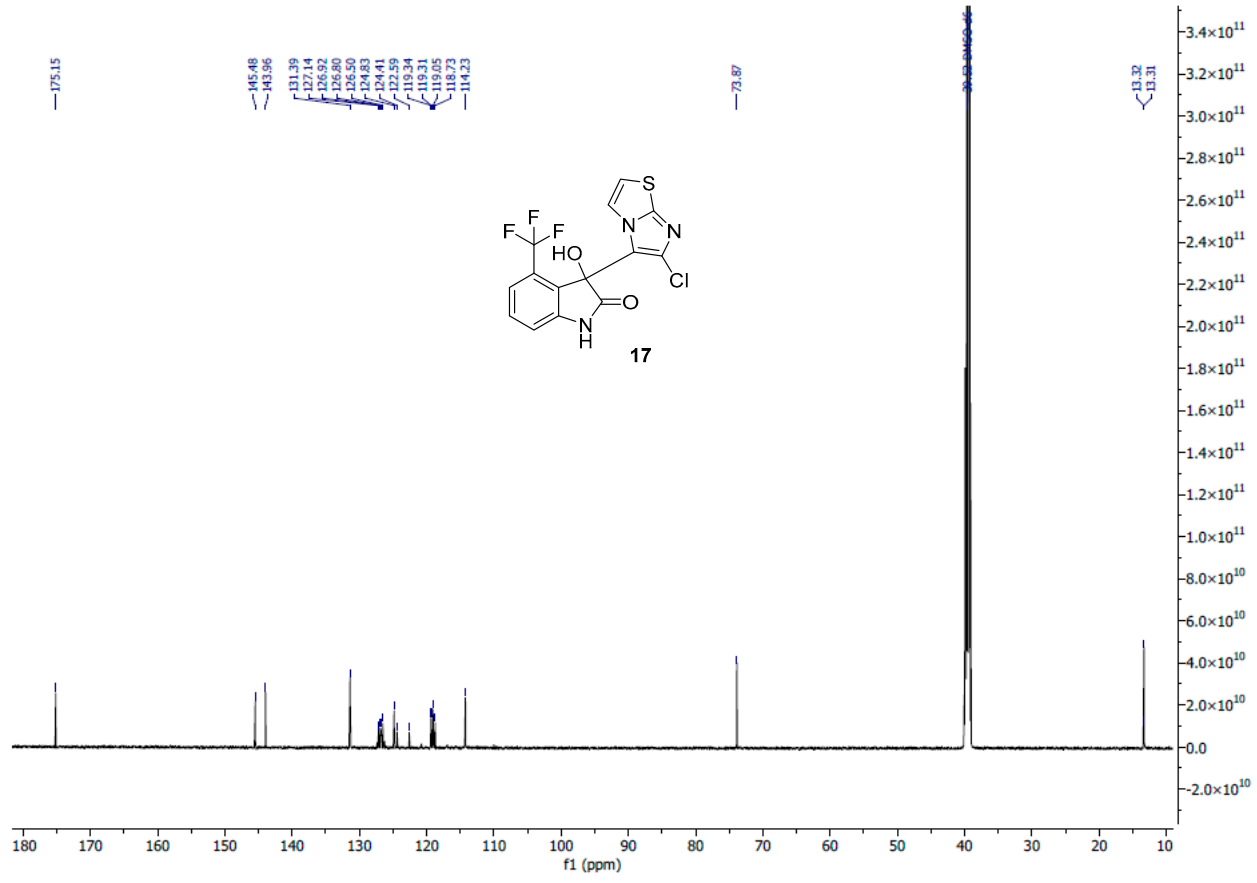
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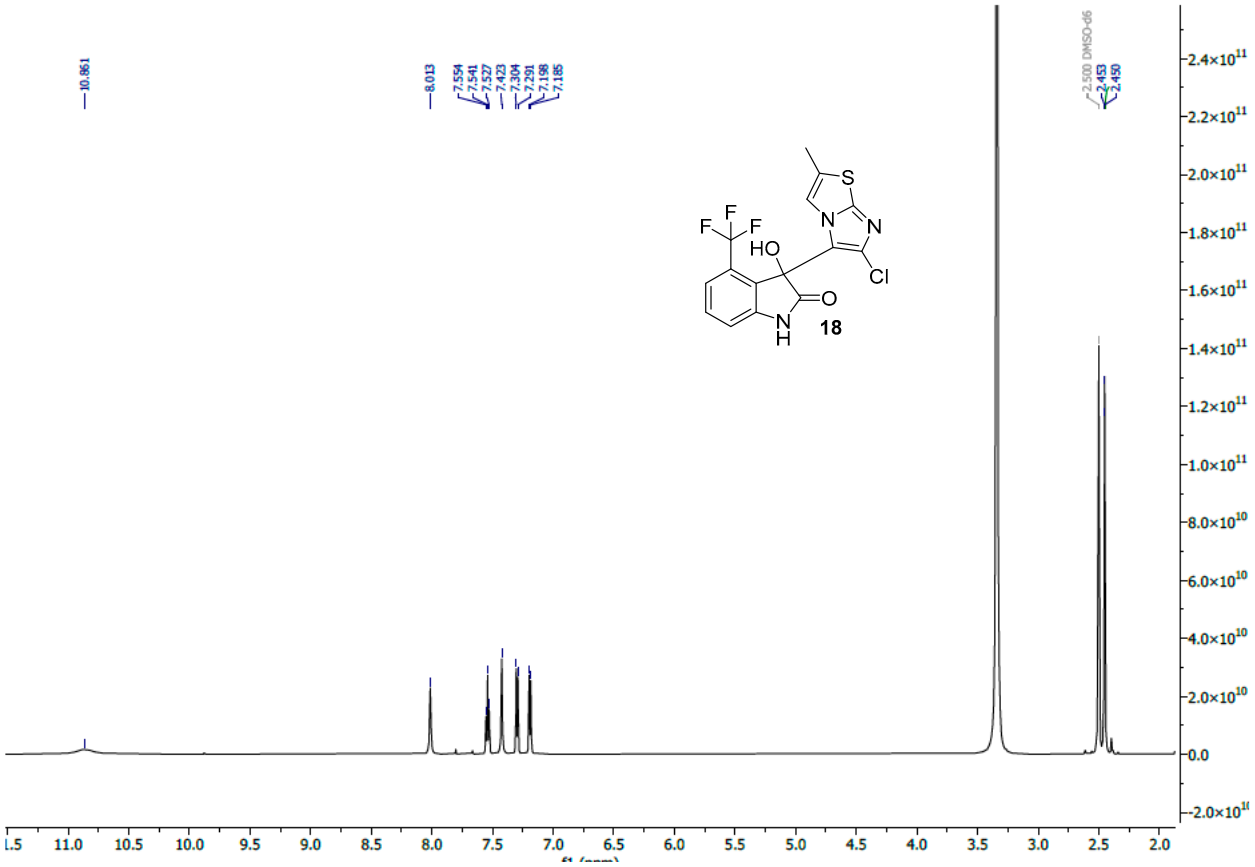
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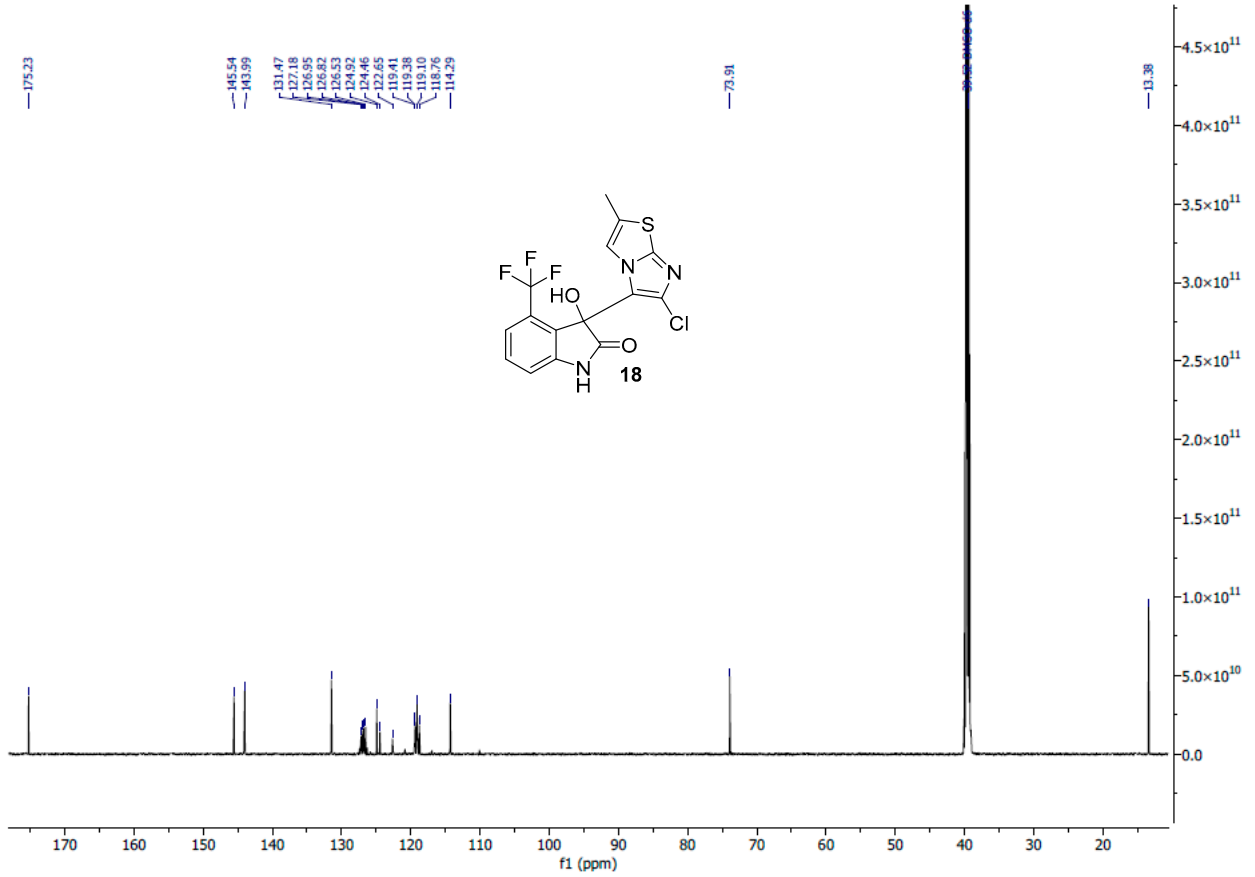
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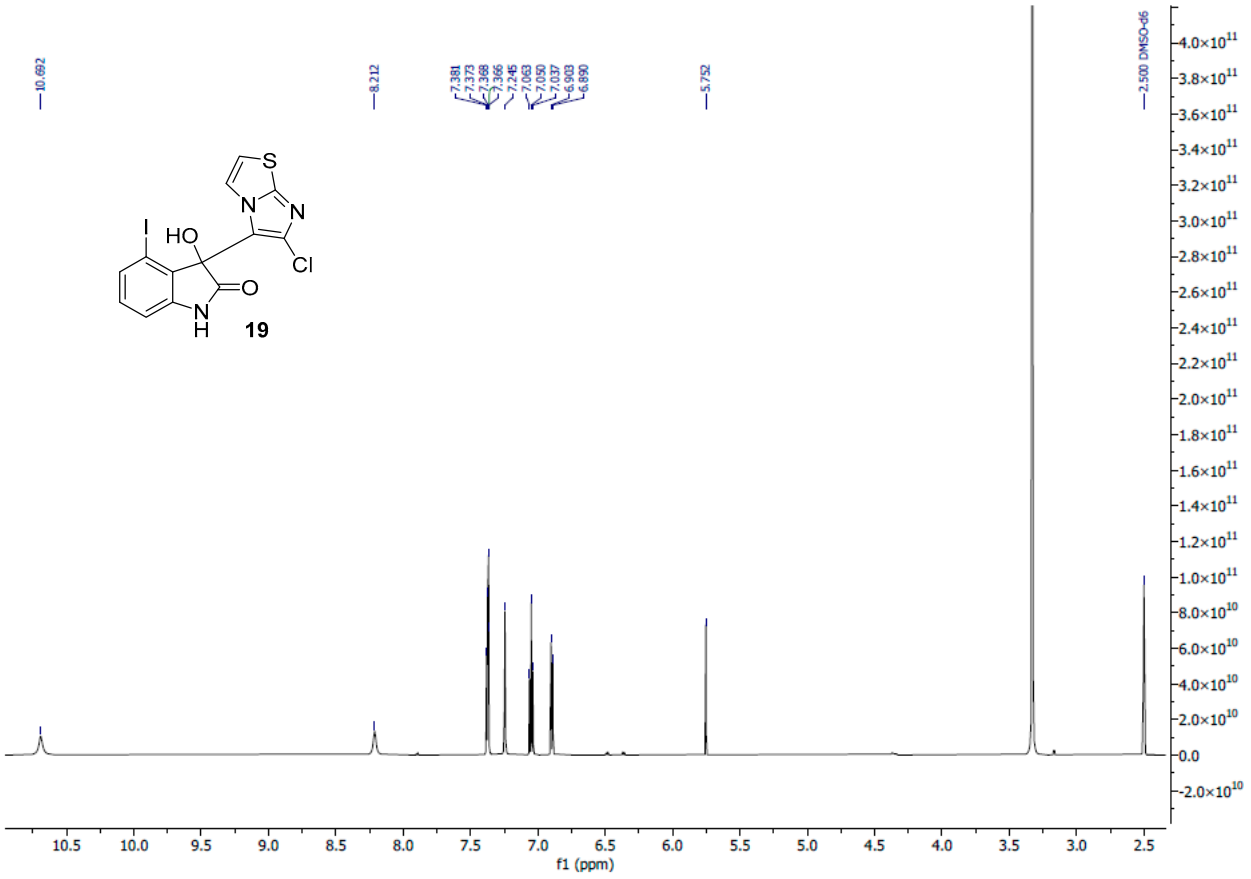
119.41
119.38
119.10
118.76
114.29
73.91
39.52
13.38
F
F
F
HO
S
N
N
Cl
O
N
H
18
f1 (ppm)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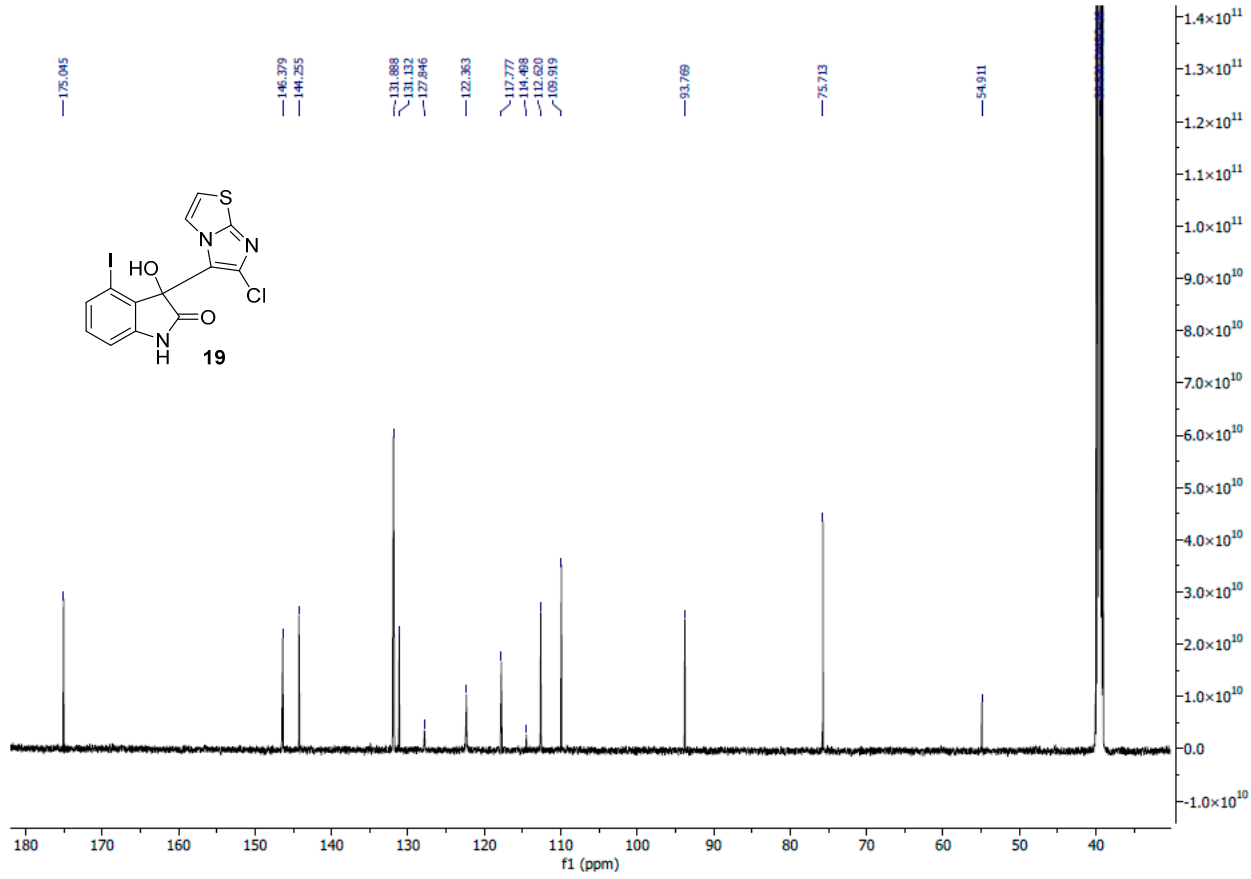
7.381
7.373
7.368
7.366
7.245
7.063
7.050
7.037
6.903
6.890
5.752
2.500 DMSO-d6
S
N
N
HO
Cl
I
O
N
H
19
f1 (ppm)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146.379
144.255
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131.132
127.846
122.363
117.777
114.488
112.620
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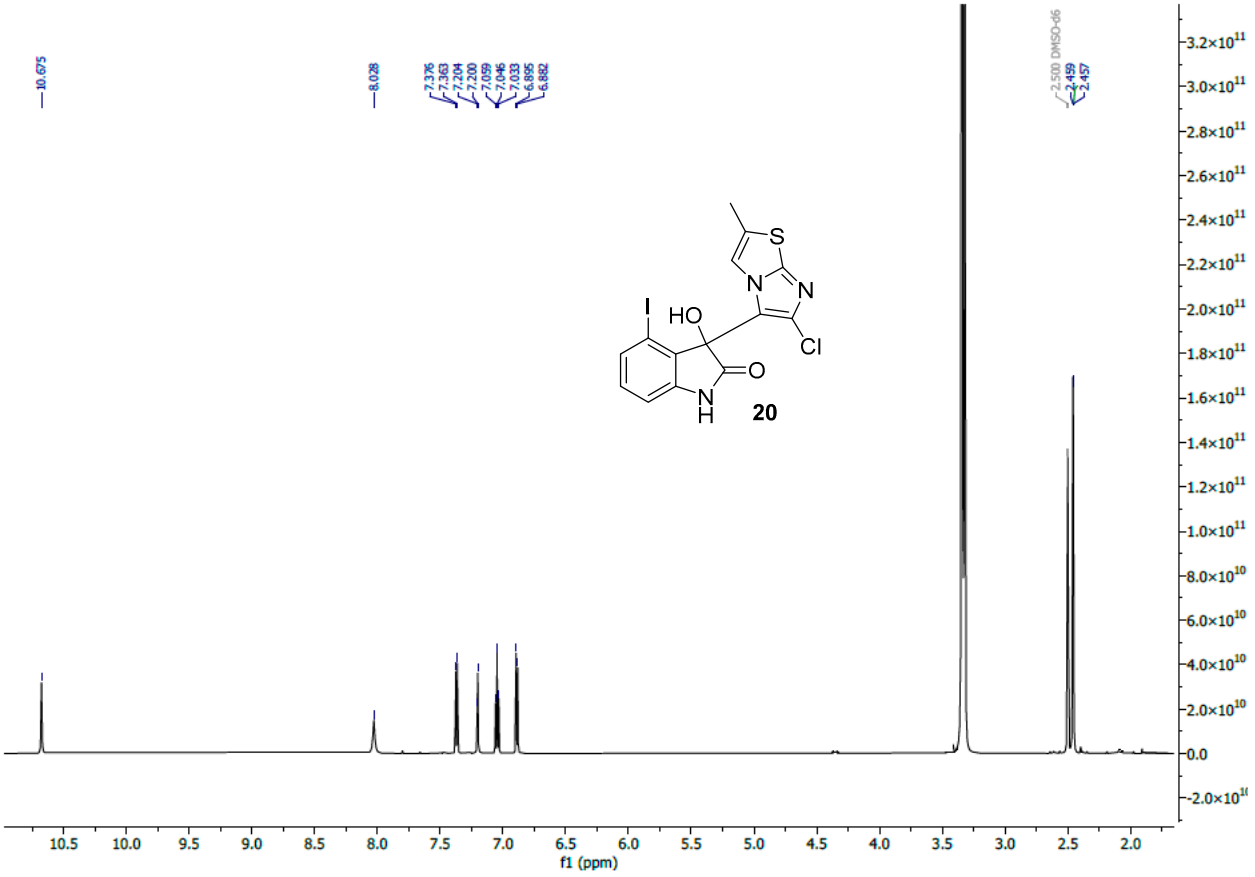
75.713
54.911
S
N
N
HO
Cl
I
O
N
H
19
f1 (ppm)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7.363
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7.200
7.059
7.046
7.033
6.895
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2.459
2.457
HO
I
S
N
N
Cl
O
N
H
20
f1 (ppm)

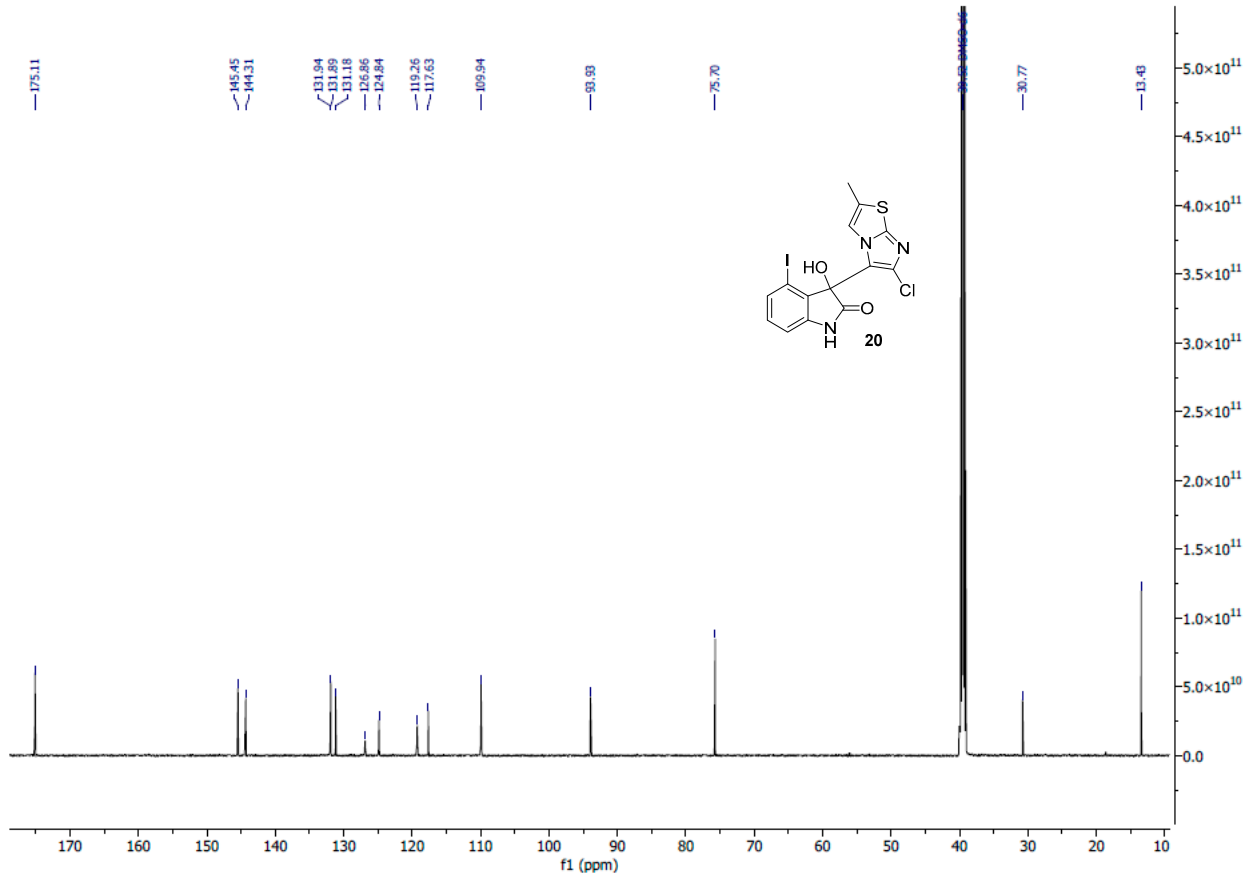

175.11
145.45
144.31
131.94
131.89
131.18
126.86
124.84
119.26
117.63
109.94
93.93
75.70
39.52 DMSO-d6
30.77
13.43
HO
I
S
N
N
Cl
O
N
H
20
f1 (ppm)

Figure S2. A) Multiple sequence alignment (obtained with Chimera, using the Match-Align tool) of the primary sequences of PDBs 6LL6 (from *E. coli*), 3VOB (from *S. aureus*), 8GZV (from *K. pneumoniae),* 2VAW (from *P. aeruginosa*), AF-B0VNZ4-F1 (predicted for *A. baumannii*) and AF-A0A0A5PLG7-F1 (predicted for *E. hormaechei).* B) Superimposition of 3D structures of PDBs 6LL6, 3VOB, 8GZV, 2VAW, AF-B0VNZ4-F1 and AF-A0A0A5PLG7-F1 in blue, red, yellow, green, magenta and cyan, respectively.

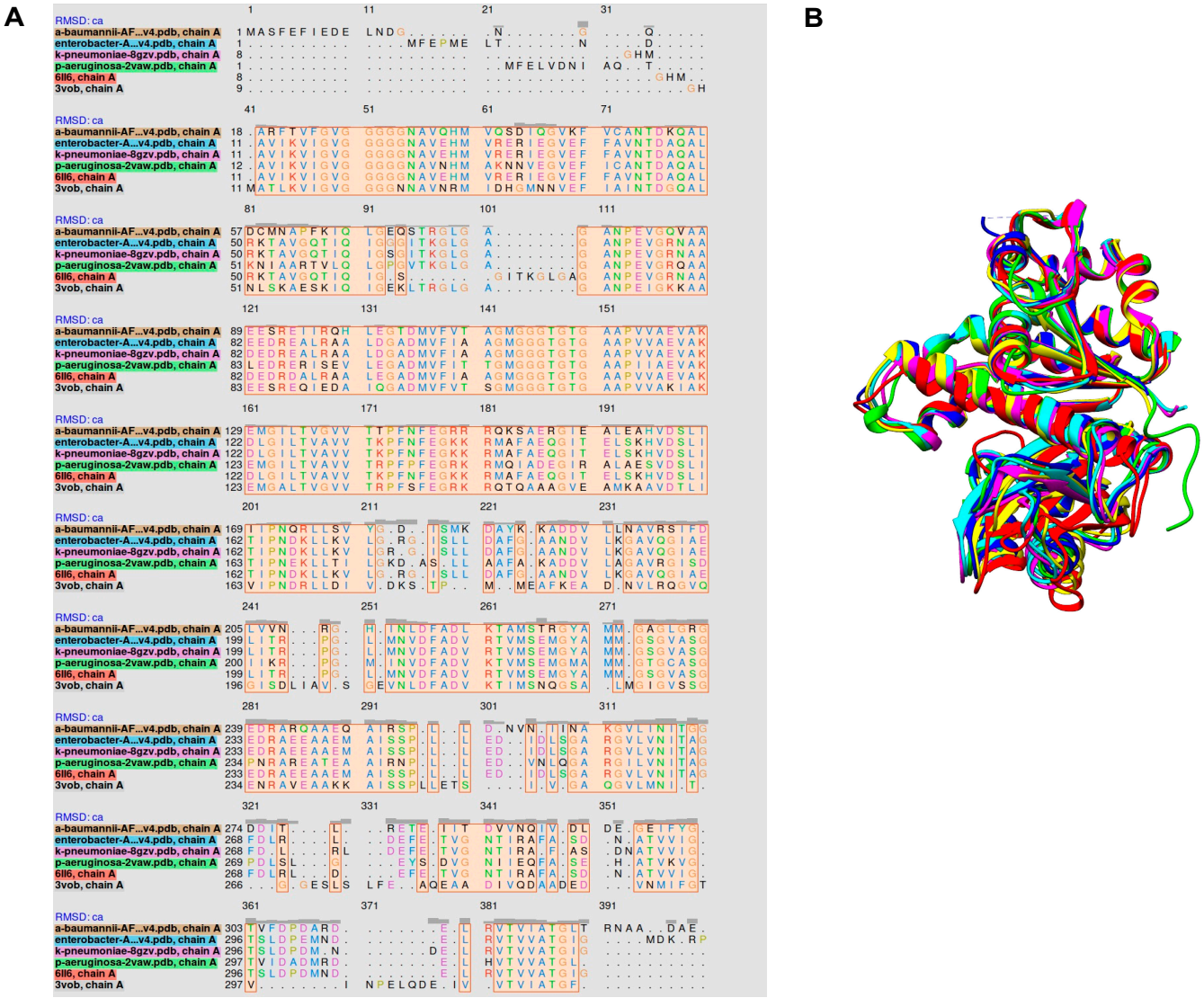


Table S1. Hemolytic activity of derivative **11** on hRBCs (range concentration: 100 -1.56 μM)**.** Data are the mean percentage values and standard deviations of the hemoglobin content measured at 405 nm in the supernatants of the treated cells.

Compound 11	Percentage values[§]
100 μM	1.1 ± 0.4
50 μM	0.7 ± 1.5
25 μM	1.8 ± 1.5
12.5 μM	2.2 ± 0.5
6.25 μM	2.3 ± 0.2
3.125 μM	1.1 ± 1.2
1.56 μM	0.9 ± 1.8

§ data are relative to untreated hRBCs (incubated with PBS) and hRBCs incubated with 1% Triton X-100.

Table S2. Antibiotic-resistance profile of the clinical isolates of S. *aureus*

Clinical isolate	Antibiotic-resistance profile
MRSA 1[§]	GEN^{S}, LVX^{R}, **OX^{R}**, **P^{R}**, TE^{S}, TEC^{S}, SXT^{S}, VA^{S}
MRSA 2[§]	GEN^{S}, LVX^{R}, **OX^{R}**, **P^{R}**, TE^{S}, TEC^{S}, SXT^{S}, VA^{S}
MRSA 3[§]	**CM^{R}, E^{R},** GEN^{S}, **LVX^{R}**, **OX^{R}**, **P^{R}**, TEC^{S}, TE^{S}, SXT^{S}, VA^{S}
MRSA 4[§]	CM^{S}, E^{S}, GEN^{S}, **LVX^{R}**, **OX^{R}**, **P^{R}**, TE^{S}, TEC^{S}, SXT^{S}, VA^{S}
MRSA 5[§]	CM^{S}, E^{S}, GEN^{S}, **LVX^{R}**, **OX^{R}**, **P^{R}**, TE^{S}, TEC^{S}, SXT^{S}, VA^{S}

CM = Clindamicyn; E = Erythromycin; GEN = Gentamicin; P = Penicillin; LVX = Levofloxacin; OX = Oxacillin; TE = Tetracycline; TEC = Teicoplanin; SXT = Trimethoprim/Sulfamethoxazole; VA = Vancomycin
R = Resistant; S = Susceptible; I = Intermediate, as defined following the EUCAST guidelines
[§]*Staphylococcus* species resistant to oxacillin were declared, by convention, methicillin-resistant.

Figure S3. A) Root of mean squared deviation (RMSD), B) Root of mean squared fluctuation RMSF, C) Gyration Radius (RG) and D) Solvent Accessible Surface Area (SASA) and ΔSASA ([$SASA_{protein}$+$SASA_{compound11}$]-$SASA_{complex}$) obtained by CPPTRAJ post-processing analysis of 100ns MD simulation of compound **11** in the interdomain cleft. All the analysis are carried out on 5000 snapshots obtained from the simulation.

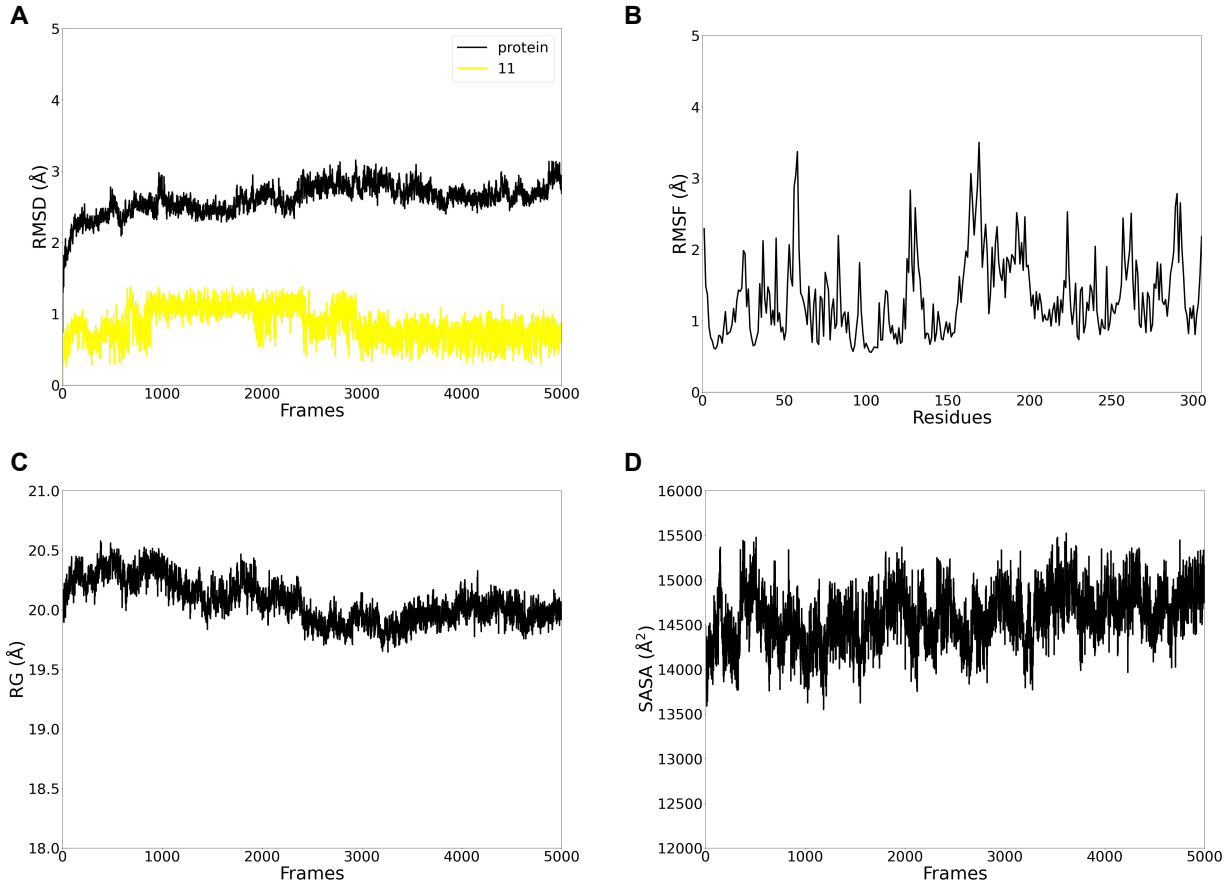
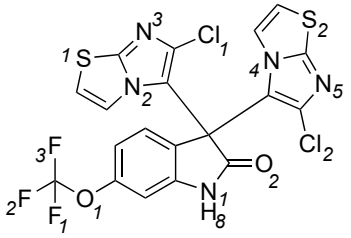


Table S3. Inter-molecular hydrogen bond analysis carried out on the MD simulation of compound **11** in the interdomain cleft.



Acceptor	DonorH	Donor	%	Avg Distance	Avg Angle
GLN_181@O	C11_305@H8	C11_305@N1	36,2	2,8	156,1
GLY_185@O	C11_305@H8	C11_305@N1	30,2	2,8	150,8
GLN_181@OE1	C11_305@H8	C11_305@N1	13,1	2,8	156,1
C11_305@N3	SER_193@HG	SER_193@OG	1,3	2,9	161,9
C11_305@O2	GLN_184@HE22	GLN_184@NE2	1,0	2,9	160,7
C11_305@N5	THR_298@HG1	THR_298@OG1	0,5	2,9	154,9
ASP_188@OD2	C11_305@H8	C11_305@N1	0,3	2,8	163,7
C11_305@O2	GLN_184@HE21	GLN_184@NE2	0,2	2,9	155,4
C11_305@N3	ASN_252@HD22	ASN_252@ND2	0,2	2,9	148,9
C11_305@O2	GLN_181@HE21	GLN_181@NE2	0,1	2,9	161,1
C11_305@O2	GLN_181@HE22	GLN_181@NE2	0,1	2,8	155,7
ASP_188@OD1	C11_305@H8	C11_305@N1	0,1	2,8	154,3

Figure S4. A) Root of mean squared deviation (RMSD), B) Root of mean squared fluctuation RMSF, C) Gyration Radius (RG) and D) Solvent Accessible Surface Area (SASA) obtained by CPPTRAJ post-processing analysis of 100ns MD simulation of compound **11** in the GPT-binding pocket. All the analysis are carried out on 5000 snapshots obtained from the simulation.

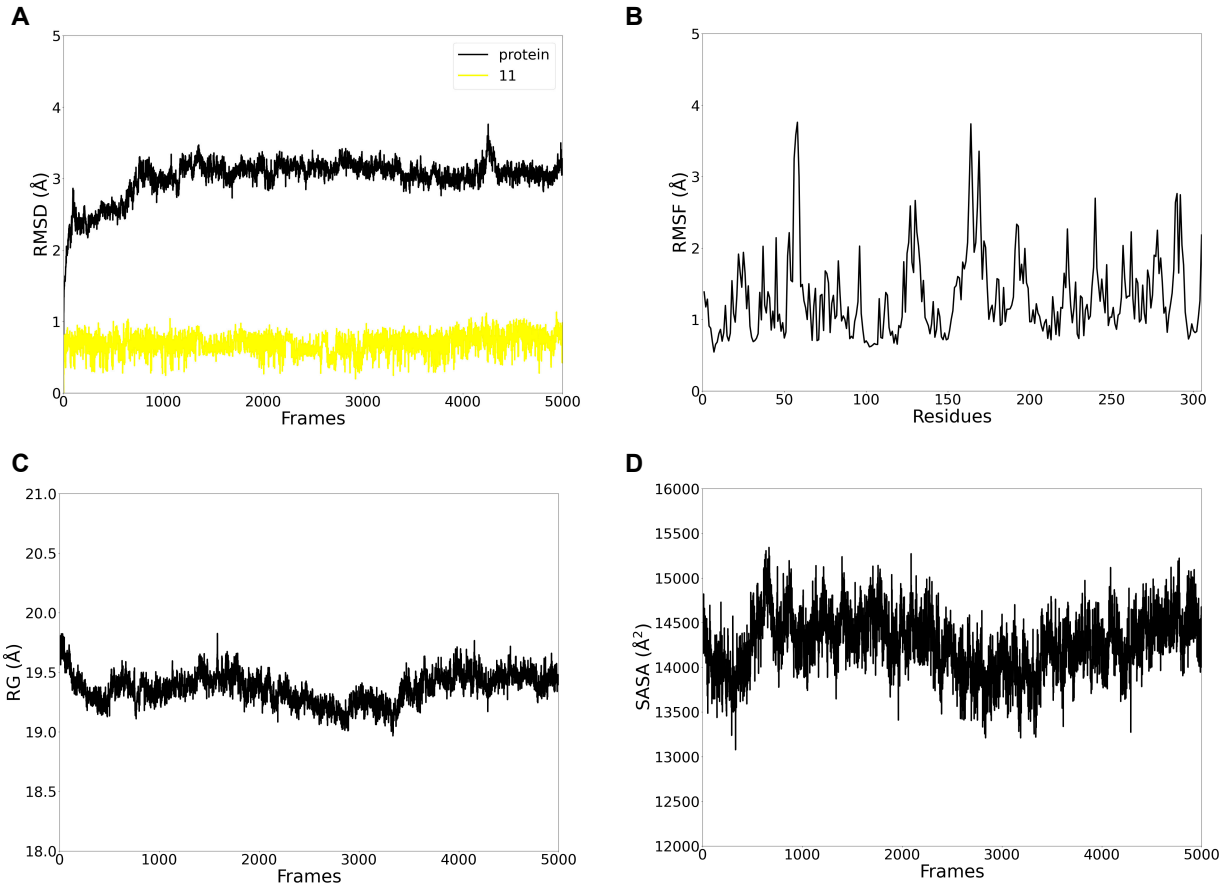
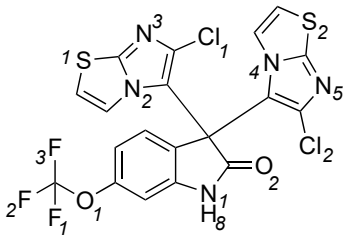


Table S4. Inter-molecular hydrogen bond analysis carried out on the MD simulation of compound **11** in the GTP-binding pocket.



Acceptor	DonorH	Donor	%	Avg Distance	Avg Angle
C11_305@N5	ASN_14@HD22	ASN_14@ND2	14,2	2,9	159,1
C11_305@N5	GLY_11@H	GLY_11@N	6,2	2,9	159,9
ASP_176@OD1	C11_305@H8	C11_305@N1	5,2	2,8	164,3
ASP_176@OD2	C11_305@H8	C11_305@N1	2,4	2,8	164,0
C11_305@N3	ASN_155@HD21	ASN_155@ND2	2,2	2,9	152,3
ASN_14@OD1	C11_305@H8	C11_305@N1	0,7	2,8	147,7
C11_305@O2	ARG_18@HH12	ARG_18@NH1	0,3	2,8	147,8
C11_305@N3	THR_122@HG1	THR_122@OG1	0,3	2,9	147,3
PHE_172@O	C11_305@H8	C11_305@N1	0,1	2,9	141,4

Figure S5. A) Root of mean squared deviation (RMSD), B) Root of mean squared fluctuation RMSF, C) Gyration Radius (RG) and D) Solvent Accessible Surface Area (SASA) obtained by CPPTRAJ post-processing analysis of 100ns MD simulation of apo-FtsZ. All the analysis are carried out on 5000 snapshots obtained from the simulation.

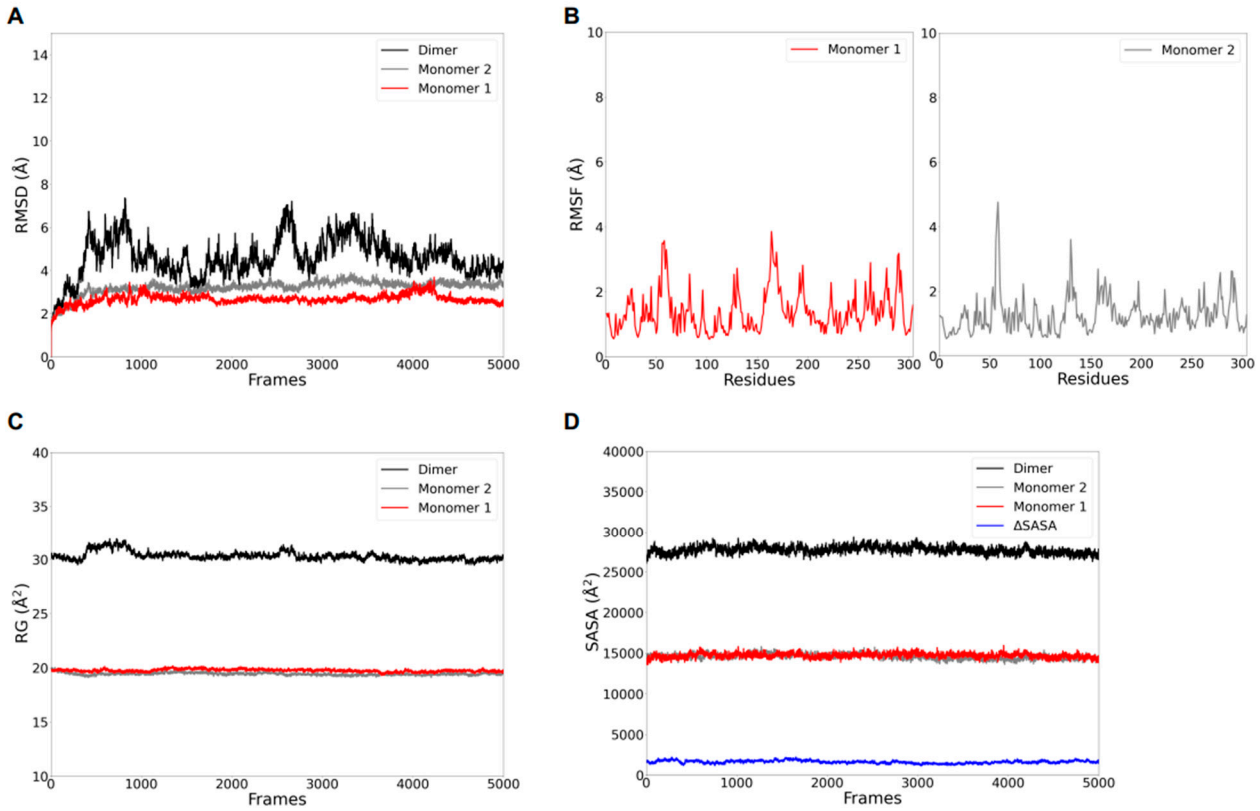


Table S5. Intra-molecular hydrogen bond analysis carried out on monomer 1 of the MD simulation of apo-FtsZ dimer. Only occurrences higher than 50% are reported.

Acceptor	DonorH	Donor	%
ALA_201@O	THR_205@HG1	THR_205@OG1	89,6
ILE_300@O	LEU_250@H	LEU_250@N	85,5
PHE_89@O	ILE_6@H	ILE_6@N	85,0
PHE_200@O	LYS_204@H	LYS_204@N	83,5
THR_117@O	ASP_148@H	ASP_148@N	82,8
VAL_120@O	THR_91@HG1	THR_91@OG1	82,1
ILE_253@O	THR_285@HG1	THR_285@OG1	81,7
GLY_119@O	ILE_151@H	ILE_151@N	81,4
VAL_8@O	SER_92@HG	SER_92@OG	79,0
VAL_118@O	VAL_90@H	VAL_90@N	76,3
LEU_116@O	VAL_88@H	VAL_88@N	73,9
ARG_130@O	THR_134@HG1	THR_134@OG1	73,7
ILE_66@O	ALA_70@H	ALA_70@N	72,8

VAL_88@O	VAL_118@H	VAL_118@N	72,8
ASP_163@O	THR_166@HG1	THR_166@OG1	72,6
GLY_218@O	VAL_297@H	VAL_297@N	72,4
ILE_32@O	GLY_9@H	GLY_9@N	71,6
ALA_115@O	THR_117@HG1	THR_117@OG1	70,8
LEU_250@O	ILE_300@H	ILE_300@N	70,4
ILE_30@O	GLY_7@H	GLY_7@N	70,2
ALA_70@O	SER_74@HG	SER_74@OG	69,6
GLU_28@O	VAL_5@H	VAL_5@N	69,6
ASN_17@OD1	LYS_43@H	LYS_43@N	69,5
VAL_286@O	THR_254@HG1	THR_254@OG1	69,0
ASN_177@O	GLN_181@H	GLN_181@N	68,3
GLY_211@O	LEU_150@H	LEU_150@N	68,0
VAL_121@O	ILE_153@H	ILE_153@N	67,8
ASP_176@OD1	ARG_18@HE	ARG_18@NE	67,4
ASP_293@O	ARG_225@HH11	ARG_225@NH1	67,4
GLY_9@O	ASN_13@H	ASN_13@N	67,2
THR_34@OG1	THR_98@HG1	THR_98@OG1	66,6
VAL_297@O	GLY_218@H	GLY_218@N	65,6
THR_149@O	GLY_119@H	GLY_119@N	64,9
ALA_136@O	VAL_140@H	VAL_140@N	64,5
ARG_130@O	THR_134@H	THR_134@N	64,4
GLY_139@O	MET_143@H	MET_143@N	64,0
VAL_140@O	LYS_144@H	LYS_144@N	63,2
VAL_296@O	THR_254@H	THR_254@N	62,7
ILE_6@O	THR_91@H	THR_91@N	62,6
GLY_248@O	THR_302@H	THR_302@N	61,6
THR_91@O	VAL_8@H	VAL_8@N	61,3
PRO_64@O	LYS_68@H	LYS_68@N	61,0
VAL_249@O	ILE_282@H	ILE_282@N	60,8
GLU_277@O	VAL_279@H	VAL_279@N	60,7
ASN_252@O	THR_298@H	THR_298@N	60,6
ALA_107@O	LYS_111@H	LYS_111@N	60,4
LYS_4@O	PHE_89@H	PHE_89@N	59,9
ARG_180@O	GLN_184@H	GLN_184@N	59,6
GLY_99@O	ALA_103@H	ALA_103@N	59,4
GLY_255@O	ASN_288@H	ASN_288@N	59,0
ASP_176@O	ARG_180@H	ARG_180@N	59,0
LYS_108@O	GLU_112@H	GLU_112@N	59,0
ILE_32@O	ASN_13@HD21	ASN_13@ND2	58,8
THR_302@O	GLN_247@H	GLN_247@N	58,1
GLN_181@O	GLY_185@H	GLY_185@N	57,8
ALA_301@O	LEU_214@H	LEU_214@N	57,5
VAL_90@O	VAL_120@H	VAL_120@N	56,6
THR_254@O	VAL_296@H	VAL_296@N	56,5
LYS_131@O	GLN_135@H	GLN_135@N	56,2
SER_220@O	ILE_295@H	ILE_295@N	56,1
GLY_216@O	VAL_299@H	VAL_299@N	55,5
GLY_51@O	THR_55@H	THR_55@N	55,4

VAL_5@O	ILE_30@H	ILE_30@N	55,0
VAL_203@O	MET_207@H	MET_207@N	54,8
MET_215@O	SER_235@HG	SER_235@OG	54,7
LYS_204@O	SER_208@HG	SER_208@OG	54,4
ILE_153@O	ARG_123@H	ARG_123@N	54,2
ILE_282@O	MET_251@H	MET_251@N	52,3
VAL_105@O	ILE_109@H	ILE_109@N	52,1
ASN_224@O	GLU_228@H	GLU_228@N	51,1
ASP_86@O	LEU_116@H	LEU_116@N	50,6
ARG_225@O	ALA_229@H	ALA_229@N	50,4
ARG_75@O	GLU_79@H	GLU_79@N	50,2
GLU_263@OE2	ARG_225@HH21	ARG_225@NH2	50,1

Table S6. Intra-molecular hydrogen bond analysis carried out on monomer 2 of the MD simulation of apo-FtsZ dimer. Only occurrences higher than 50% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163).

Acceptor	**DonorH**	**Doron**	**%**
ASP_467@O	THR_470@HG1	THR_470@OG1	94,5
VAL_424@O	THR_395@HG1	THR_395@OG1	88,1
THR_421@O	ASP_452@H	ASP_452@N	85,3
LEU_554@O	ILE_604@H	ILE_604@N	85,1
LYS_477@O	ARG_484@HH12	ARG_484@NH1	84,2
ILE_604@O	LEU_554@H	LEU_554@N	83,8
PHE_393@O	ILE_310@H	ILE_310@N	83,6
ILE_370@O	ALA_374@H	ALA_374@N	83,5
GLY_423@O	ILE_455@H	ILE_455@N	82,9
GLY_559@O	ASN_592@H	ASN_592@N	81,6
GLY_313@O	ASN_317@H	ASN_317@N	81,3
ALA_505@O	THR_509@HG1	THR_509@OG1	80,5
THR_558@O	VAL_600@H	VAL_600@N	79,4
PHE_504@O	LYS_508@H	LYS_508@N	78,6
GLY_522@O	VAL_601@H	VAL_601@N	78,6
LEU_420@O	VAL_392@H	VAL_392@N	78,4
GLY_588@O	THR_589@HG1	THR_589@OG1	75,6
ILE_336@O	GLY_313@H	GLY_313@N	75,6
VAL_590@O	THR_558@HG1	THR_558@OG1	75,5
VAL_425@O	ILE_457@H	ILE_457@N	74,2
GLU_332@O	VAL_309@H	VAL_309@N	74,0
VAL_603@O	GLY_520@H	GLY_520@N	73,9
GLY_520@O	VAL_603@H	VAL_603@N	73,5
GLN_488@O	ASP_492@H	ASP_492@N	73,1
ALA_374@O	SER_378@HG	SER_378@OG	72,8
ALA_419@O	THR_421@HG1	THR_421@OG1	71,6
VAL_312@O	SER_396@HG	SER_396@OG	70,8
LYS_308@O	PHE_393@H	PHE_393@N	70,6
ASN_321@OD1	LYS_347@H	LYS_347@N	69,9
VAL_422@O	VAL_394@H	VAL_394@N	69,4

THR_453@O	GLY_423@H	GLY_423@N	69,3
GLY_403@O	ALA_407@H	ALA_407@N	68,0
GLY_552@O	THR_606@H	THR_606@N	67,3
THR_589@O	GLU_499@H	GLU_499@N	67,1
VAL_392@O	VAL_422@H	VAL_422@N	67,1
ILE_334@O	GLY_311@H	GLY_311@N	66,8
ALA_605@O	LEU_518@H	LEU_518@N	66,7
PRO_368@O	LYS_372@H	LYS_372@N	66,5
PRO_471@O	ALA_475@H	ALA_475@N	66,1
LEU_518@O	ALA_605@H	ALA_605@N	65,4
THR_606@O	GLN_551@H	GLN_551@N	64,4
ALA_411@O	LYS_415@H	LYS_415@N	64,0
SER_491@O	ALA_495@H	ALA_495@N	63,7
LYS_535@O	SER_539@HG	SER_539@OG	62,8
ILE_457@O	ARG_427@H	ARG_427@N	62,2
VAL_531@O	LYS_535@H	LYS_535@N	62,1
ASN_317@O	ASN_321@H	ASN_321@N	61,7
ARG_379@O	GLU_383@H	GLU_383@N	61,2
THR_395@O	VAL_312@H	VAL_312@N	61,0
SER_524@O	ILE_599@H	ILE_599@N	60,7
THR_602@O	ASN_556@H	ASN_556@N	60,3
GLY_355@O	THR_359@HG1	THR_359@OG1	60,2
GLU_567@OE1	ARG_529@HH21	ARG_529@NH2	60,2
ASP_480@OD2	ARG_322@HH21	ARG_322@NH2	59,1
VAL_487@O	SER_491@H	SER_491@N	58,5
ARG_436@O	ALA_440@H	ALA_440@N	58,0
LEU_483@O	VAL_487@H	VAL_487@N	57,8
GLU_581@O	VAL_583@H	VAL_583@N	57,2
VAL_444@O	LYS_448@H	LYS_448@N	57,1
ILE_336@O	ASN_317@HD21	ASN_317@ND2	56,9
LEU_565@O	GLN_569@H	GLN_569@N	56,3
GLY_515@O	LEU_454@H	LEU_454@N	56,2
ALA_533@O	ALA_537@H	ALA_537@N	56,1
GLU_567@OE2	ARG_529@HE	ARG_529@NE	55,3
ARG_529@O	ALA_533@H	ALA_533@N	54,9
LEU_462@O	VAL_466@H	VAL_466@N	54,9
ILE_310@O	THR_395@H	THR_395@N	54,9
VAL_600@O	THR_558@H	THR_558@N	54,7
VAL_309@O	ILE_334@H	ILE_334@N	54,5
ILE_510@O	GLN_514@HE22	GLN_514@NE2	54,3
GLU_474@O	GLU_478@H	GLU_478@N	53,6
ASN_528@O	GLU_532@H	GLU_532@N	53,6
VAL_409@O	ILE_413@H	ILE_413@N	53,0
ASP_597@O	ARG_529@HH11	ARG_529@NH1	53,0
ARG_484@O	GLN_488@H	GLN_488@N	52,5
LYS_412@O	GLU_416@H	GLU_416@N	52,3
PRO_408@O	LYS_412@H	LYS_412@N	52,2
ASN_481@O	GLN_485@H	GLN_485@N	51,9
GLY_355@O	THR_359@H	THR_359@N	51,9

LYS_373@O	GLU_377@H	GLU_377@N	51,2
VAL_482@O	GLY_486@H	GLY_486@N	51,2
ASN_556@O	THR_602@H	THR_602@N	51,1
THR_338@O	GLN_353@HE22	GLN_353@NE2	50,8
PHE_429@O	GLU_432@H	GLU_432@N	50,1
GLU_432@O	ARG_436@H	ARG_436@N	50,1

Table S7. Inter-molecular hydrogen bond analysis carried out on monomer 1-2 of the MD simulation of apo-FtsZ dimer. Only occurrences higher than 20% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163).

Acceptor	**Donor**	**DonorH**	%
LEU_259@O	MET_472@H	MET_472@N	80,9
GLU_195@OE1	ARG_322@HH12	ARG_322@NH1	44,1
THR_470@O	LEU_261@H	LEU_261@N	28,7
GLU_195@OE2	ARG_322@HH22	ARG_322@NH2	22,0
GLU_195@OE2	ARG_322@HH12	ARG_322@NH1	20,2

Figure S6. A) Root of mean squared deviation (RMSD), B) Root of mean squared fluctuation RMSF, C) Gyration Radius (RG) and D) Solvent Accessible Surface Area (SASA) obtained by CPPTRAJ post-processing analysis of 100ns MD simulation of FtsZ dimer in presence of GTP and Ca^{2+}. All the analysis are carried out on 5000 snapshots obtained from the simulation.

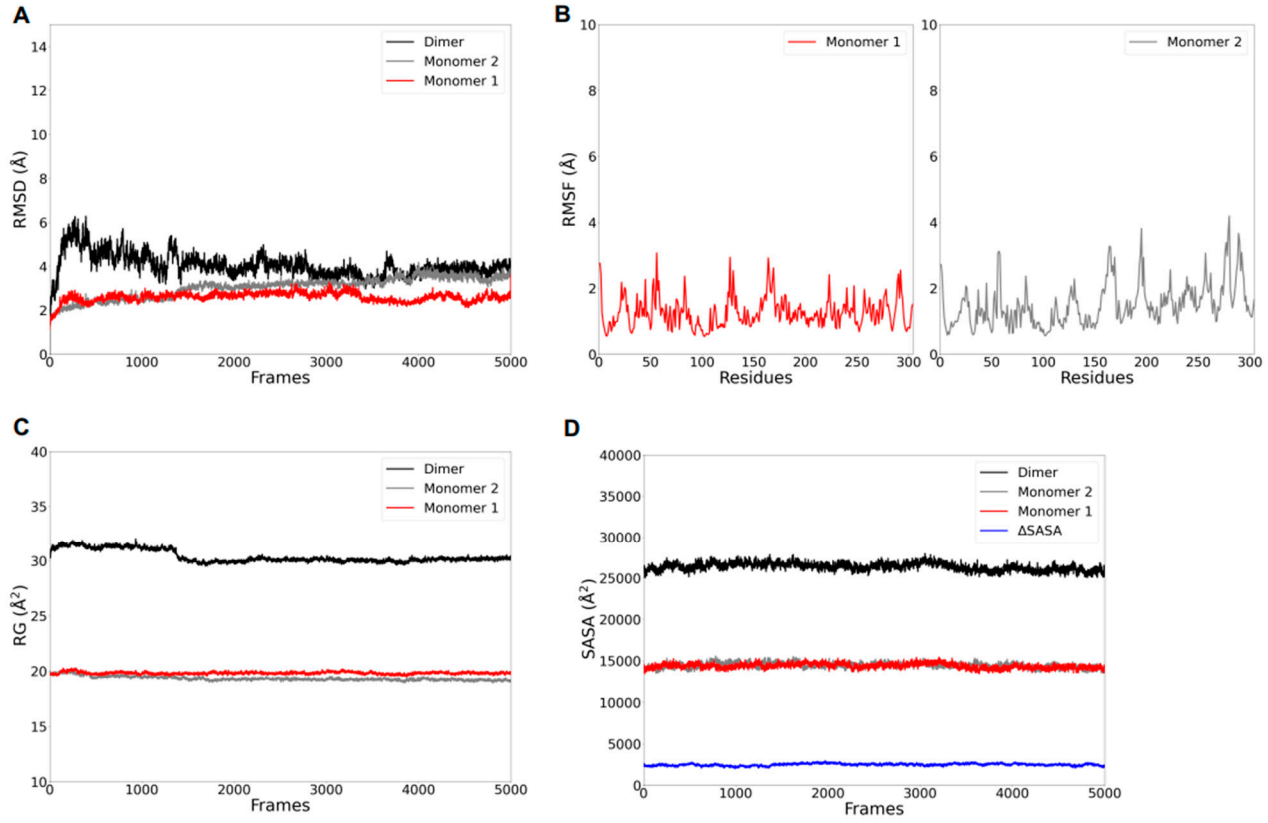


Table S8. Intra-molecular hydrogen bond analysis carried out on monomer 1 of the MD simulation of FtsZ dimer in presence of GTP and Ca^{2+}. Only occurrences higher than 50% are reported.

Acceptor	DonorH	Donor	%
ASP_176@OD2	ARG_18@HH21	ARG_18@NH2	91,4
VAL_120@O	THR_91@HG1	THR_91@OG1	89,8
ALA_201@O	THR_205@HG1	THR_205@OG1	89,6
PHE_89@O	ILE_6@H	ILE_6@N	85,1
GLY_9@O	ASN_13@H	ASN_13@N	85,0
ILE_300@O	LEU_250@H	LEU_250@N	84,9
GLU_28@O	VAL_5@H	VAL_5@N	84,5
GLY_284@O	THR_285@HG1	THR_285@OG1	84,4
VAL_296@O	THR_254@H	THR_254@N	81,5
GLY_255@O	ASN_288@H	ASN_288@N	80,6
PHE_200@O	LYS_204@H	LYS_204@N	80,1
GLU_263@OE2	ARG_225@HH21	ARG_225@NH2	78,7
THR_117@O	ASP_148@H	ASP_148@N	77,9
GLU_263@OE1	ARG_225@HE	ARG_225@NE	77,5
VAL_118@O	VAL_90@H	VAL_90@N	76,5

THR_254@O	VAL_296@H	VAL_296@N	76,3
GLY_218@O	VAL_297@H	VAL_297@N	75,0
ILE_253@O	VAL_286@H	VAL_286@N	73,6
LEU_116@O	VAL_88@H	VAL_88@N	72,4
ALA_301@O	LEU_214@H	LEU_214@N	72,4
ILE_66@O	ALA_70@H	ALA_70@N	72,2
LEU_250@O	ILE_300@H	ILE_300@N	71,6
VAL_121@O	ILE_153@H	ILE_153@N	70,6
LYS_4@O	PHE_89@H	PHE_89@N	70,1
ILE_30@O	GLY_7@H	GLY_7@N	70,0
ASP_293@O	ARG_225@HH11	ARG_225@NH1	69,6
ASN_13@OD1	ASN_33@HD22	ASN_33@ND2	69,5
ASP_163@O	THR_166@HG1	THR_166@OG1	69,0
ALA_70@O	SER_74@HG	SER_74@OG	68,0
VAL_140@O	LYS_144@H	LYS_144@N	67,6
ASN_17@OD1	LYS_43@H	LYS_43@N	67,1
PRO_64@O	LYS_68@H	LYS_68@N	67,0
VAL_8@O	SER_92@HG	SER_92@OG	66,2
ASN_252@O	THR_298@H	THR_298@N	65,2
GLY_139@O	MET_143@H	MET_143@N	64,9
ARG_180@O	GLN_184@H	GLN_184@N	64,4
VAL_5@O	ILE_30@H	ILE_30@N	64,0
ILE_6@O	THR_91@H	THR_91@N	63,2
SER_220@O	ILE_295@H	ILE_295@N	62,9
THR_98@O	ALA_102@H	ALA_102@N	62,8
THR_122@O	MET_94@H	MET_94@N	62,8
THR_91@O	VAL_8@H	VAL_8@N	62,4
ILE_32@O	GLY_9@H	GLY_9@N	62,3
VAL_297@O	GLY_218@H	GLY_218@N	61,9
VAL_227@O	LYS_231@H	LYS_231@N	61,8
VAL_88@O	VAL_118@H	VAL_118@N	61,1
ARG_130@O	THR_134@H	THR_134@N	60,9
GLU_277@O	VAL_279@H	VAL_279@N	60,0
GLY_10@O	ASN_14@H	ASN_14@N	59,5
ASP_188@OD1	THR_298@HG1	THR_298@OG1	59,5
GLY_248@O	THR_302@H	THR_302@N	59,4
LEU_214@O	ALA_301@H	ALA_301@N	59,4
GLY_119@O	ILE_151@H	ILE_151@N	59,1
ALA_115@O	THR_117@HG1	THR_117@OG1	58,6
THR_149@O	GLY_119@H	GLY_119@N	58,6
ALA_107@O	LYS_111@H	LYS_111@N	58,6
GLN_181@O	GLY_185@H	GLY_185@N	58,1
ASP_176@OD2	ARG_18@HE	ARG_18@NE	56,8
GLY_216@O	VAL_299@H	VAL_299@N	56,7
ALA_136@O	VAL_140@H	VAL_140@N	56,7
ARG_130@O	THR_134@HG1	THR_134@OG1	56,6
VAL_105@O	ILE_109@H	ILE_109@N	56,3
VAL_249@O	ILE_282@H	ILE_282@N	55,9
ALA_102@O	VAL_106@H	VAL_106@N	55,6

ARG_225@O	ALA_229@H	ALA_229@N	55,5
ASN_280@O	VAL_249@H	VAL_249@N	55,4
GLY_7@O	ILE_32@H	ILE_32@N	55,2
GLY_51@O	THR_55@H	THR_55@N	55,1
ILE_153@O	ARG_123@H	ARG_123@N	54,8
LYS_69@O	GLU_73@H	GLU_73@N	54,7
GLU_65@O	LYS_69@H	LYS_69@N	54,5
VAL_183@O	SER_187@HG	SER_187@OG	54,3
THR_302@O	GLN_247@H	GLN_247@N	53,8
VAL_178@O	GLY_182@H	GLY_182@N	53,1
PRO_104@O	LYS_108@H	LYS_108@N	52,5
GLY_211@O	LEU_150@H	LEU_150@N	52,4
VAL_90@O	VAL_120@H	VAL_120@N	52,2
LYS_68@O	GLU_72@H	GLU_72@N	52,2
ASP_148@OD2	THR_117@H	THR_117@N	52,1
LYS_204@O	SER_208@HG	SER_208@OG	51,7
LYS_108@O	GLU_112@H	GLU_112@N	51,4
ASP_176@OD1	ARG_18@HE	ARG_18@NE	51,2
ASN_224@O	GLU_228@H	GLU_228@N	51,0
ASP_176@O	ARG_180@H	ARG_180@N	50,7
ALA_275@O	GLY_245@H	GLY_245@N	50,7
ASN_33@O	ILE_50@H	ILE_50@N	50,0

Table S9. Intra-molecular hydrogen bond analysis carried out on monomer 2 of the MD simulation of FtsZ dimer in presence of GTP and Ca^{2+}. Only occurrences higher than 50% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163).

Acceptor	**DonorH**	**Donor**	**%**
ASP_469@O	THR_472@HG1	THR_472@OG1	95,2
VAL_592@O	THR_560@HG1	THR_560@OG1	93,8
ALA_507@O	THR_511@HG1	THR_511@OG1	85,5
GLY_561@O	ASN_594@H	ASN_594@N	81,6
ASP_482@O	ARG_486@H	ARG_486@N	81,2
GLU_334@O	VAL_311@H	VAL_311@N	81,0
VAL_427@O	ILE_459@H	ILE_459@N	79,6
ILE_606@O	LEU_556@H	LEU_556@N	79,5
ARG_436@O	THR_440@HG1	THR_440@OG1	78,3
LEU_556@O	ILE_606@H	ILE_606@N	78,3
VAL_314@O	SER_398@HG	SER_398@OG	78,3
GLY_524@O	VAL_603@H	VAL_603@N	78,0
PHE_395@O	ILE_312@H	ILE_312@N	77,7
ILE_312@O	THR_397@H	THR_397@N	77,3
THR_423@O	ASP_454@H	ASP_454@N	76,9
GLY_522@O	VAL_605@H	VAL_605@N	76,9
LEU_422@O	VAL_394@H	VAL_394@N	75,9
ILE_372@O	ALA_376@H	ALA_376@N	75,3
GLY_425@O	ILE_457@H	ILE_457@N	75,3
GLY_315@O	ASN_319@H	ASN_319@N	74,5

VAL_424@O	VAL_396@H	VAL_396@N	74,1
PHE_506@O	LYS_510@H	LYS_510@N	73,7
LYS_310@O	PHE_395@H	PHE_395@N	70,9
THR_604@O	ASN_558@H	ASN_558@N	70,7
ILE_336@O	GLY_313@H	GLY_313@N	70,5
THR_455@O	GLY_425@H	GLY_425@N	70,2
GLY_316@O	ASN_320@H	ASN_320@N	69,0
ASP_482@OD1	ARG_324@HH21	ARG_324@NH2	68,6
GLY_554@O	THR_608@H	THR_608@N	68,3
LYS_437@O	GLN_441@H	GLN_441@N	68,2
ASN_323@OD1	LYS_349@H	LYS_349@N	67,5
PRO_370@O	LYS_374@H	LYS_374@N	66,4
VAL_533@O	LYS_537@H	LYS_537@N	65,9
ARG_436@O	THR_440@H	THR_440@N	65,7
GLY_445@O	MET_449@H	MET_449@N	64,6
LYS_537@O	SER_541@HG	SER_541@OG	64,5
GLY_357@O	THR_361@HG1	THR_361@OG1	64,3
THR_560@O	VAL_602@H	VAL_602@N	64,1
VAL_394@O	VAL_424@H	VAL_424@N	63,9
ALA_376@O	SER_380@HG	SER_380@OG	63,3
GLY_517@O	LEU_456@H	LEU_456@N	63,1
ASP_482@OD2	ARG_324@HE	ARG_324@NE	63,0
VAL_489@O	SER_493@H	SER_493@N	63,0
ILE_338@O	GLY_315@H	GLY_315@N	62,9
SER_526@O	ILE_601@H	ILE_601@N	62,6
MET_557@O	GLY_590@H	GLY_590@N	62,6
LEU_520@O	ALA_607@H	ALA_607@N	61,4
ALA_413@O	LYS_417@H	LYS_417@N	61,3
ALA_421@O	THR_423@HG1	THR_423@OG1	60,4
VAL_605@O	GLY_522@H	GLY_522@N	60,3
VAL_311@O	ILE_336@H	ILE_336@N	59,3
GLY_357@O	THR_361@H	THR_361@N	59,2
THR_406@OG1	GLY_401@H	GLY_401@N	58,6
ASP_482@OD2	ARG_486@HH11	ARG_486@NH1	58,4
THR_397@O	VAL_314@H	VAL_314@N	57,8
ALA_607@O	LEU_520@H	LEU_520@N	57,2
LEU_485@O	VAL_489@H	VAL_489@N	56,8
ASP_508@O	ILE_512@H	ILE_512@N	56,3
THR_340@O	GLN_355@HE22	GLN_355@NE2	55,0
VAL_603@O	GLY_524@H	GLY_524@N	54,9
THR_404@O	ALA_408@H	ALA_408@N	54,6
LEU_567@O	GLN_571@H	GLN_571@N	54,5
LYS_374@O	GLU_378@H	GLU_378@N	54,5
GLN_487@O	GLY_491@H	GLY_491@N	54,4
ARG_438@O	ALA_442@H	ALA_442@N	53,7
VAL_322@O	ILE_326@H	ILE_326@N	53,5
ALA_408@O	VAL_412@H	VAL_412@N	53,3
ARG_381@O	GLU_385@H	GLU_385@N	53,1
LYS_414@O	GLU_418@H	GLU_418@N	52,6

ILE_338@O	ASN_319@HD21	ASN_319@ND2	52,6
GLY_405@O	ALA_409@H	ALA_409@N	52,5
ASN_530@O	GLU_534@H	GLU_534@N	52,2
GLU_569@OE1	ARG_531@HH21	ARG_531@NH2	52,1
GLN_490@O	ASP_494@H	ASP_494@N	52,1
ALA_442@O	VAL_446@H	VAL_446@N	52,0
ASP_392@O	LEU_422@H	LEU_422@N	51,4
THR_608@O	GLN_553@H	GLN_553@N	51,4
ALA_535@O	ALA_539@H	ALA_539@N	51,2
ALA_337@O	ILE_354@H	ILE_354@N	51,0
VAL_396@O	VAL_426@H	VAL_426@N	50,9
VAL_484@O	GLY_488@H	GLY_488@N	50,8
LEU_456@O	ALA_519@H	ALA_519@N	50,6
ASN_558@O	THR_604@H	THR_604@N	50,3
ASN_319@O	ASN_323@H	ASN_323@N	50,2
ILE_459@O	ARG_429@H	ARG_429@N	50,1
VAL_446@O	LYS_450@H	LYS_450@N	50,1

Table S10. Inter-molecular hydrogen bond analysis carried out on monomers 1-2 of the MD simulation of FtsZ dimer in presence of GTP and Ca^{2+}. Only occurrences higher than 20% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163).

Acceptor	**DonorH**	**Donor**	**%**
LEU_259@O	MET_474@H	MET_474@N	68,5
MET_281@O	ARG_436@H	ARG_436@N	39,3
ASN_197@O	ARG_438@HH21	ARG_438@NH2	23,8
ASP_202@OD2	LYS_437@HZ2	LYS_437@NZ	20,2
THR_472@O	LEU_261@H	LEU_261@N	49,2
LYS_470@O	SER_260@HG	SER_260@OG	47,6
MET_281@O	ARG_436@H	ARG_436@N	39,3
ASN_197@O	ARG_438@HH21	ARG_438@NH2	23,8
ASP_202@OD2	LYS_437@HZ2	LYS_437@NZ	20,2

Figure S7. A) Root of mean squared deviation (RMSD), B) Root of mean squared fluctuation RMSF, C) Gyration Radius (RG) and D) Solvent Accessible Surface Area (SASA) obtained by CPPTRAJ post-processing analysis of 100ns MD simulation of FtsZ dimer in presence of GTP, $Ca^{2+}$and compound **11**. All the analysis are carried out on 5000 snapshots obtained from the simulation.

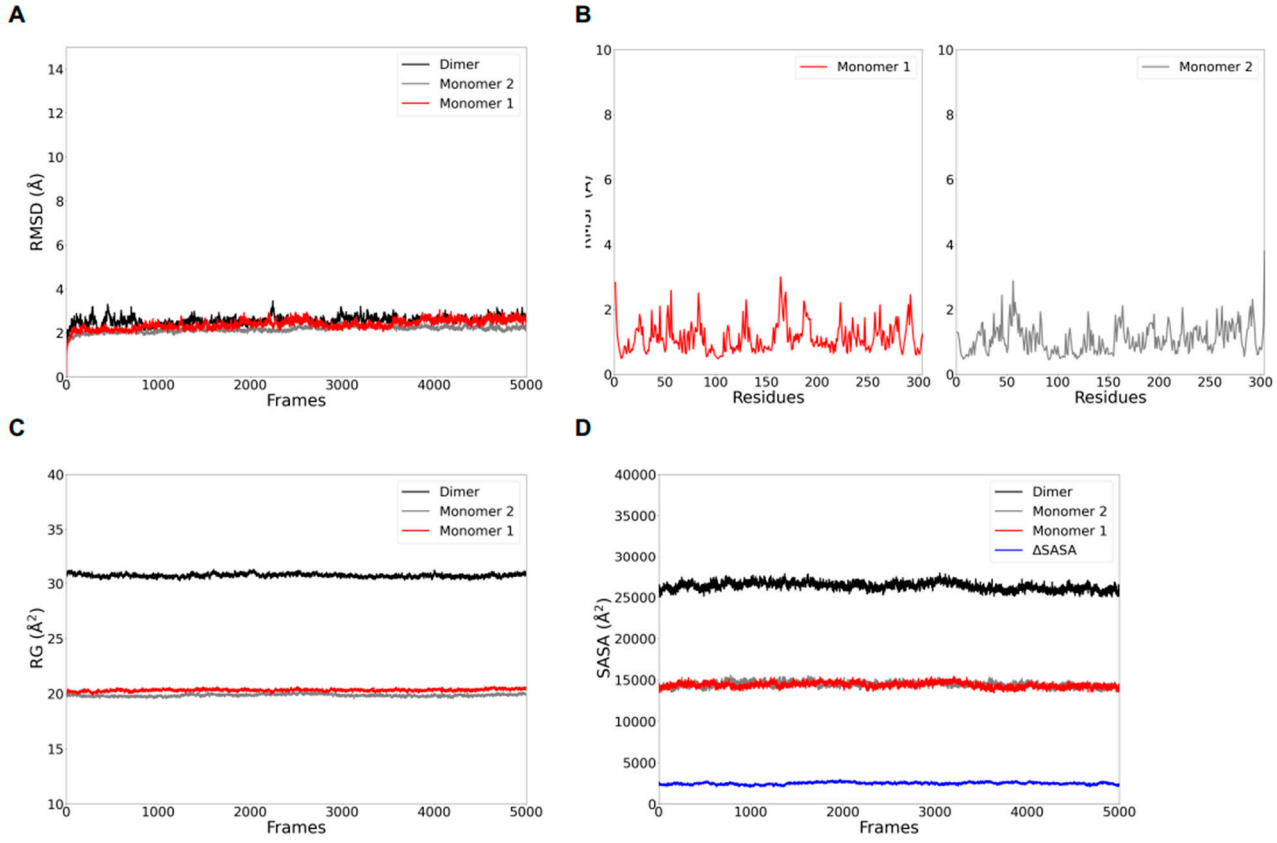


Table S11. Intra-molecular hydrogen bond analysis carried out on monomer 1 of the MD simulation of FtsZ dimer in presence of GTP, $Ca^{2+}$and compound **11**. Only occurrences higher than 50% are reported.

Acceptor	DonorH	Donor	%
ASP_176@OD2	ARG_18@HH21	ARG_18@NH2	96,4
ALA_201@O	THR_205@HG1	THR_205@OG1	91,9
VAL_120@O	THR_91@HG1	THR_91@OG1	90,8
LEU_58@O	THR_34@HG1	THR_34@OG1	89,4
LEU_250@O	ILE_300@H	ILE_300@N	87,3
ILE_300@O	LEU_250@H	LEU_250@N	83,5
VAL_296@O	THR_254@H	THR_254@N	83,3
PHE_89@O	ILE_6@H	ILE_6@N	83,2
GLY_255@O	ASN_288@H	ASN_288@N	79,9
THR_117@O	ASP_148@H	ASP_148@N	78,8
GLU_28@O	VAL_5@H	VAL_5@N	76,0
ALA_301@O	LEU_214@H	LEU_214@N	76,0
THR_254@O	VAL_296@H	VAL_296@N	75,1

LEU_116@O	VAL_88@H	VAL_88@N	74,8
ILE_66@O	ALA_70@H	ALA_70@N	73,1
ALA_175@O	LEU_179@H	LEU_179@N	71,6
ASP_163@O	THR_166@HG1	THR_166@OG1	71,4
ASP_293@O	ARG_225@HH11	ARG_225@NH1	70,7
GLY_218@O	VAL_297@H	VAL_297@N	70,2
GLY_9@O	ASN_13@H	ASN_13@N	69,5
ILE_6@O	THR_91@H	THR_91@N	69,5
ILE_253@O	VAL_286@H	VAL_286@N	68,9
VAL_118@O	VAL_90@H	VAL_90@N	68,4
ILE_30@O	GLY_7@H	GLY_7@N	68,2
GLY_119@O	ILE_151@H	ILE_151@N	68,0
VAL_140@O	LYS_144@H	LYS_144@N	67,4
PRO_64@O	LYS_68@H	LYS_68@N	67,4
ASN_17@OD1	LYS_43@H	LYS_43@N	66,8
ILE_32@O	GLY_9@H	GLY_9@N	66,5
ASP_148@O	GLY_211@H	GLY_211@N	66,3
ILE_153@O	ARG_123@H	ARG_123@N	66,1
GLY_139@O	MET_143@H	MET_143@N	66,0
VAL_105@O	ILE_109@H	ILE_109@N	65,9
ALA_70@O	SER_74@HG	SER_74@OG	65,6
THR_149@O	GLY_119@H	GLY_119@N	65,0
THR_100@OG1	GLY_95@H	GLY_95@N	64,0
GLY_284@O	THR_285@HG1	THR_285@OG1	63,8
PHE_200@O	LYS_204@H	LYS_204@N	63,7
ARG_130@O	THR_134@H	THR_134@N	63,2
VAL_227@O	LYS_231@H	LYS_231@N	62,3
GLY_10@O	ASN_14@H	ASN_14@N	62,2
ILE_282@O	MET_251@H	MET_251@N	61,9
ALA_115@O	THR_117@HG1	THR_117@OG1	61,5
THR_302@O	GLN_247@H	GLN_247@N	61,3
ASP_176@OD1	ARG_18@HE	ARG_18@NE	61,2
ARG_75@O	GLU_79@H	GLU_79@N	60,9
VAL_5@O	ILE_30@H	ILE_30@N	60,6
VAL_121@O	ILE_153@H	ILE_153@N	60,2
LYS_4@O	PHE_89@H	PHE_89@N	60,0
ASN_224@O	GLU_228@H	GLU_228@N	59,7
ALA_136@O	VAL_140@H	VAL_140@N	59,7
VAL_8@O	SER_92@HG	SER_92@OG	59,3
VAL_88@O	VAL_118@H	VAL_118@N	59,0
ALA_107@O	LYS_111@H	LYS_111@N	58,5
VAL_90@O	VAL_120@H	VAL_120@N	57,7
ALA_31@O	ILE_48@H	ILE_48@N	57,3
ARG_180@O	GLN_184@H	GLN_184@N	56,7
GLY_96@O	GLN_135@HE22	GLN_135@NE2	56,3
ALA_102@O	VAL_106@H	VAL_106@N	55,5
THR_34@O	GLN_49@HE22	GLN_49@NE2	55,2
SER_220@O	ILE_295@H	ILE_295@N	54,8
ASN_13@O	ASN_17@H	ASN_17@N	54,7

VAL_297@O	GLY_218@H	GLY_218@N	54,7
GLY_248@O	THR_302@H	THR_302@N	54,7
GLU_277@O	VAL_279@H	VAL_279@N	54,5
THR_91@O	VAL_8@H	VAL_8@N	53,9
LYS_69@O	GLU_73@H	GLU_73@N	53,3
VAL_249@O	ILE_282@H	ILE_282@N	53,2
GLY_99@O	ALA_103@H	ALA_103@N	53,0
LYS_108@O	GLU_112@H	GLU_112@N	52,8
GLU_65@O	LYS_69@H	LYS_69@N	51,9
GLN_184@OE1	ARG_180@HE	ARG_180@NE	51,3
GLN_133@O	ALA_137@H	ALA_137@N	51,1
THR_298@O	ASN_252@H	ASN_252@N	51,1
LEU_3@O	GLU_28@H	GLU_28@N	50,8

Table S12. Intra-molecular hydrogen bond analysis carried out on monomer 2 of the MD simulation of FtsZ dimer in presence of GTP, $Ca^{2+}$and compound **11**. Only occurrences higher than 50% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163).

Acceptor	**DonorH**	**Donor**	**%**
ASP_482@OD2	ARG_324@HH21	ARG_324@NH2	99,2
VAL_314@O	SER_398@HG	SER_398@OG	95,8
VAL_426@O	THR_397@HG1	THR_397@OG1	92,8
GLU_434@OE1	ARG_438@HH11	ARG_438@NH1	92,2
ALA_507@O	THR_511@HG1	THR_511@OG1	89,4
ILE_606@O	LEU_556@H	LEU_556@N	87,9
GLY_425@O	ILE_457@H	ILE_457@N	87,4
ILE_336@O	GLY_313@H	GLY_313@N	86,4
THR_397@O	VAL_314@H	VAL_314@N	86,2
ASP_482@O	ARG_486@H	ARG_486@N	85,7
THR_423@O	ASP_454@H	ASP_454@N	84,3
GLY_561@O	ASN_594@H	ASN_594@N	84,1
ILE_372@O	ALA_376@H	ALA_376@N	83,4
VAL_427@O	ILE_459@H	ILE_459@N	82,8
VAL_602@O	THR_560@H	THR_560@N	81,0
LEU_422@O	VAL_394@H	VAL_394@N	80,1
ARG_486@O	GLN_490@H	GLN_490@N	80,1
PHE_395@O	ILE_312@H	ILE_312@N	79,5
ILE_459@O	ARG_429@H	ARG_429@N	79,5
VAL_424@O	VAL_396@H	VAL_396@N	79,3
ALA_607@O	LEU_520@H	LEU_520@N	79,1
GLY_524@O	VAL_603@H	VAL_603@N	78,6
ALA_376@O	SER_380@HG	SER_380@OG	75,3
ALA_442@O	VAL_446@H	VAL_446@N	74,6
ASP_482@OD1	ARG_324@HE	ARG_324@NE	73,4
ARG_436@O	THR_440@HG1	THR_440@OG1	73,3
GLY_445@O	MET_449@H	MET_449@N	73,1

ILE_312@O	THR_397@H	THR_397@N	71,5
THR_560@O	VAL_602@H	VAL_602@N	71,0
GLU_334@O	VAL_311@H	VAL_311@N	70,9
SER_398@O	THR_428@H	THR_428@N	70,6
ASP_469@O	THR_472@HG1	THR_472@OG1	69,3
PHE_506@O	LYS_510@H	LYS_510@N	69,1
ALA_421@O	THR_423@HG1	THR_423@OG1	68,8
ILE_559@O	VAL_592@H	VAL_592@N	68,8
ALA_321@O	MET_325@H	MET_325@N	67,7
ARG_381@O	GLU_385@H	GLU_385@N	67,5
ARG_436@O	THR_440@H	THR_440@N	67,1
LEU_556@O	ILE_606@H	ILE_606@N	66,6
GLY_357@O	THR_361@H	THR_361@N	66,3
GLY_317@O	ALA_321@H	ALA_321@N	65,8
THR_404@O	ALA_408@H	ALA_408@N	64,7
THR_404@OG1	THR_340@HG1	THR_340@OG1	64,6
ILE_338@O	ASN_319@HD21	ASN_319@ND2	64,2
THR_608@O	GLN_553@H	GLN_553@N	64,2
ASN_323@OD1	LYS_349@H	LYS_349@N	63,7
SER_526@O	ILE_601@H	ILE_601@N	62,9
MET_400@O	THR_406@HG1	THR_406@OG1	62,8
VAL_502@O	THR_591@H	THR_591@N	62,6
ASP_508@OD2	ASP_505@H	ASP_505@N	62,3
GLY_590@O	THR_591@HG1	THR_591@OG1	62,2
ILE_588@O	MET_557@H	MET_557@N	62,2
VAL_555@O	ILE_588@H	ILE_588@N	61,6
ASN_558@O	THR_604@H	THR_604@N	60,9
THR_455@O	GLY_425@H	GLY_425@N	60,6
VAL_603@O	GLY_524@H	GLY_524@N	60,6
VAL_396@O	VAL_426@H	VAL_426@N	60,3
GLY_522@O	VAL_605@H	VAL_605@N	60,1
VAL_446@O	LYS_450@H	LYS_450@N	60,1
VAL_489@O	SER_493@HG	SER_493@OG	59,9
ASP_392@O	LEU_422@H	LEU_422@N	58,7
VAL_411@O	ILE_415@H	ILE_415@N	58,3
GLU_583@O	VAL_585@H	VAL_585@N	57,4
LEU_485@O	VAL_489@H	VAL_489@N	57,0
ASN_530@O	GLU_534@H	GLU_534@N	56,9
ARG_438@O	ALA_442@H	ALA_442@N	56,6
LEU_520@O	ALA_607@H	ALA_607@N	56,0
ASP_469@O	THR_472@H	THR_472@N	55,3
VAL_509@O	MET_513@H	MET_513@N	55,3
ALA_408@O	VAL_412@H	VAL_412@N	55,1
VAL_533@O	LYS_537@H	LYS_537@N	54,9
ALA_413@O	LYS_417@H	LYS_417@N	54,8
VAL_394@O	VAL_424@H	VAL_424@N	54,8
LYS_375@O	GLU_379@H	GLU_379@N	54,8
ASP_599@O	ARG_531@HH11	ARG_531@NH1	54,3
LYS_310@O	PHE_395@H	PHE_395@N	53,9

GLU_569@OE1	ARG_531@HH21	ARG_531@NH2	53,7
LYS_437@O	GLN_441@H	GLN_441@N	52,9
LEU_567@O	GLN_571@H	GLN_571@N	51,9
VAL_311@O	ILE_336@H	ILE_336@N	51,9
ILE_415@O	MET_419@H	MET_419@N	51,1
ASN_319@O	ASN_323@H	ASN_323@N	50,7
ALA_581@O	GLY_551@H	GLY_551@N	50,6
GLY_313@O	ILE_338@H	ILE_338@N	50,3
THR_428@O	MET_400@H	MET_400@N	50,0

Table S13. Inter-molecular hydrogen bond analysis carried out on monomer 1-2 of the MD simulation of FtsZ dimer in presence of GTP, Ca^{2+} and compound **11**. Only occurrences higher than 20% are reported. To the residue number in monomer 2, 304 units needs to be subtracted to obtain the original residue number (ASP_467 = ASP_163)

Acceptor	**DonorH**	**Donor**	%
LEU_259@O	MET_474@H	MET_474@N	86,3
LYS_470@O	SER_260@HG	SER_260@OG	41,0
GTP_612@O5	ASN_197@H	ASN_197@N	30,3
GTP_612@O6	ASN_197@H	ASN_197@N	28,9
GLN_265@OE1	SER_432@HG	SER_432@OG	27,3
GTP_612@O3	ASN_197@HD22	ASN_197@ND2	27,0