Supplementary Information

Rational design strategies for innovative small-molecule scaffolds inspired by three pivotal protein secondary structures

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1. General Information

Chemical Synthesis

All commercially available sources were used without further purification unless otherwise specified and purchased from Sigma-Aldrich, Alfa-Aesar/Acros, Tokyo Chemical Industry, and Combi-blocks. Solvents were used from commercial vendors and without further purification. Dried solvents were passed through solvent purification systems. The progression of each reaction was monitored using analytical thin-layer chromatography (TLC) (silica-gel 60, F_{254}, 0.25 mm, Merck, Germany) or low-resolution mass spectrometry (LRMS) (LCMS-2020, Shimadzu, Japan). The components on the TLC plate were observed under UV light (254 nm, 365 nm) or by treating the plates with staining solution (Ninhydrin, $KMnO_4$, PMA followed by thermal visualization). Flash column chromatography was performed using Merck Kiesel gel 60 (230–400 mesh). Normal-phase high-performance liquid chromatography (nHPLC) was carried out on 1200 Quaternary Pump (Agilent Technologies, G1311A) at a flow rate of 5.0 mL/min of eluent solutions. All compounds used for biological assays were HPLC-purified and lyophilized compounds.

Computational methods

All quantum mechanical calculations were performed in Gaussian09W. The ground state structures were optimized using density functional theory (DFT) at the B3LYP/6-31G(d) level. All protein crystal structures were obtained from a protein data bank (PDB). The visualization of molecules and superimposition with protein crystal structures were performed using Discovery Studio. The scaffold and protein C-alpha were overlapped, and the distance between them was obtained and used to calculate the RMSD value. Principal component analysis (PCA) was performed using R.Studio, iPPi database was used for 2246 PPI modulators (2023 February updated), and eDrug 3D database was used for 1596 FDA approved drugs (~2023 June accepted). The chemical properties used in the PCA are molecular weight, cLogP value, number of hydrogen bonding donor/acceptors, topological polar surface area, and number of rotatable bonds.

Characterization of Chemical Compounds

NMR analyses were carried out using Agilent 400-MR DD2 Magnetic Resonance System (400 MHz, Agilent, USA), Bruker Ascend 500 (500 MHz, Bruker, Germany) spectrometer. Chemical shifts were recorded as parts per million (δ) from the internal reference, tetramethylsilane (TMS), or to the solvent residual peak. Multiplicities of proton (^{1}H) NMR peaks were indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); quin (quintet); m (multiplet); dd (doublet of doublet); dt (doublet of triplet); br. s (broad singlet), br. d (broad doublet). Coupling constants were reported in hertz (Hz). Low-resolution mass spectrometry (LRMS) was conducted by LCMS-2020 (Shimadzu), and gas chromatography high-resolution mass spectrometry (GC-HRMS) of final compounds was confirmed BC-HRTOFMS (JMS-T2000GC) EI mode. The ground state structures of virtual compounds were optimized using density functional theory (DFT) calculations at the B3LYP/6-31G level. Single-crystal X-ray diffraction (SC-XRD) studies were carried out using Cu Kα radiation on an XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer or Mo Kα radiation on a Bruker D8 Quest diffractometer.

X-ray Crystallographic Studies on 1s. Single crystals of **1s** were prepared by slow diffusion of hexane into a chloroform solution of this material. A colorless crystal (approximate dimensions 0.130 × 0.120 × 0.080 mm^3) was placed onto a nylon loop with NVH immersion oil and mounted on a Bruker D8 Quest diffractometer. The data was collected using Mo Kα radiation, and the crystal was kept at T = 100 K. A total of 43575 reflections were measured ($4.536° \leq 2\theta \leq 56.626°$). The structure was solved with SHELXT[3] using direct methods and refined with SHELXL[4] refinement package of OLEX2.[5] A total of 4629 unique reflections were used in all calculations. The final $R1$ was 0.0722 ($I \geq 2\sigma(I)$), and $wR2$ was 0.1412 (all data). CCDC 2353935 contains the supplementary crystallographic data for this structure.

X-ray Crystallographic Studies on 2s. Single crystals of **2s** were prepared by slow diffusion of EtOAc into a pentane solution of this material. A colorless crystal (approximate dimensions 0.381 × 0.133 × 0.101 mm^3) was placed onto a nylon loop with paratone-N oil and mounted on an XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer. The data collection was carried out using Cu Kα radiation, and the crystal was kept at T = 93 K. A total of 68194 reflections were measured (7.026° ≤ 2θ ≤ 158.892°). The structure was solved with SHELXT[3] using direct methods and refined with SHELXL[4] refinement package of OLEX2.[5] A total of 14962 unique reflections were used in all calculations. The final $R1$ was 0.0958 ($I \geq 2\sigma(I)$), and $wR2$ was 0.2911 (all data). CCDC 2353937 contains the supplementary crystallographic data for this structure.

X-ray Crystallographic Studies on 3s. Single crystals of **3s** were prepared by slow diffusion of hexane into a chloroform solution of this material. A colorless crystal (approximate dimensions 0.300 × 0.120 × 0.080 mm^3) was placed onto a nylon loop with NVH immersion oil and mounted on a Bruker D8 Quest diffractometer. The data was collected using Mo Kα radiation, and the crystal was kept at T = 100 K. A total of 47655 reflections were measured (4.654° ≤ 2θ ≤ 56.928°). The structure was solved with SHELXT[3] using direct methods and refined with SHELXL[4] refinement package of OLEX2.[5] A total of 13071 unique reflections were used in all calculations. The final $R1$ was 0.0900 ($I \geq 2\sigma(I)$), and $wR2$ was 0.1548 (all data). CCDC 2353936 contains the supplementary crystallographic data for this structure.

X-ray Crystallographic Studies on S10. Single crystals of **S10** were prepared by slow diffusion of hexane into a Chloroform and MeOH (9:1) solution of this material. A colorless crystal (approximate dimensions 0.450 × 0.300 × 0.150 mm^3) was placed onto a nylon loop with NVH immersion oil and mounted on a Bruker D8 Quest diffractometer. The data was collected using Mo Kα radiation, and the crystal was kept at T = 100 K. A total of 66933 reflections were measured (4.690° ≤ 2θ ≤ 56.592°). The structure was solved with SHELXT[3] using direct methods and refined with SHELXL[4] refinement package of OLEX2.[5] A total of 3315 unique reflections were used in all calculations. The final $R1$ was 0.0342 ($I \geq 2\sigma(I)$), and $wR2$ was 0.0812 (all data). CCDC 2353938 contains the supplementary crystallographic data for this structure.

Reagents and Materials for Bioassay

Dulbecco's modified eagle medium (DMEM), RPMI 1640 medium (RPMI), and phosphate-buffered saline (PBS) buffer were purchased WELGENE (Gyeongsan, Korea). Fetal bovine serum (FBS), antibiotic-antimycotic (AA) solution, TrypLE™ Express solution, and geneticin were purchased from Gibco, Invitrogen (Carlsbad, CA, USA). Raw264.7 murine macrophage cell, HeLa human cervical cancer cell, and C2C12 murine myoblast cell lines were obtained from the American Type Culture Collection [ATCC, Manassas, VA, USA]. BiFC-tau stable HEK293 human embryonic kidney cells were kindly provided by Dr. Yun Kyung Kim, Korea Institute of Science and Technology (KIST). Compounds were prepared in dimethylsulfoxide (DMSO) solution for biological applications. Ez-Cytox WST assay reagent was purchased from Daeil Bio Co. Ltd [Seoul, Korea]. Hoechst 33342 was purchased from Thermo Fisher Scientific [Waltham, MA]. Thapsigargin (TG) was purchased from Sigma-Aldrich [St. Louis, MO]. Seoul-Fluor 44 (SF44) for lipid droplet staining was synthesized within our laboratory or purchased from SPARK Biopharma [Seoul, Korea]. 100-mm cell culture dishes and transparent 96-well plates were purchased from SPL Life Sciences [Pocheon, Korea]. A black 96-well plate and a black 384-well plate were purchased from CORNING [Glendale, AZ].

Instruments and programs

The absorbance measurement in 96-well plates for the WST assay was performed with a BioTek Synergy HT microplate reader [Winooski, VT]. Lipid droplet (LD) and BiFC-tau screening were performed with InCell Analyzer 2500HS from GE Healthcare [Chicago, IL, USA]. Data were analyzed using InCell Developer software from GE Healthcare [Chicago, IL, USA]. The provided graphs were analyzed with GraphPad Prism 8 [La Jolla, CA].

Cell culture

HeLa human cervical cancer cells were cultured in RPMI with 10% (v/v) FBS and 1% AA solution. BiFC-tau stable HEK293 human embryonic kidney cells were cultured in DMEM with 10% FBS, 1% (v/v) AA solution, and geneticin (100 μg/mL). Raw264.7 murine macrophage cells and C2C12 murine myoblast cells were cultured in DMEM with 10% (v/v) FBS and 1% (v/v) AA solution. Cells were maintained in a 100-mm cell culture dish in an incubator at 37℃ under a humidified atmosphere with 5% CO_2.

Tau aggregation screening using BiFC-tau Venus HEK293 cell

BiFC-tau HEK293 cells were seeded into black 384-well plates at a density of 7×10^4 cells/well in 40 μL media for 24 h. Compounds were treated with 80 nM thapsigargin in 10 μL media. After 24 h, nuclei were stained by Hoechst 33342 for 10 min. Plates were scanned in an InCell Analyzer 2500 at $\lambda_{ex}/\lambda_{em}$ =490/525 nm (for FITC channel) for Venus fluorescence and at $\lambda_{ex}/\lambda_{em}$=350/455 nm (for DAPI channel) for nuclei. Obtained images were analyzed to quantify Venus fluorescence intensity per cell using InCell Developer software.

Lipid droplet screening with SF44

HeLa cells were seeded into black 96-well plates at a density of 4×10^4 cells/well in 100 μL media. After 24 h, the compounds were treated. Oleic acid (10 μM) and serum-free RPMI were used as a positive and negative control, respectively. Due to the cytotoxicity, serum-free RPMI was treated for 20 h. After incubation, SF44 was treated to each well in a final concentration of 5 μM for 20 min, followed by Hoechst 33342 staining for an additional 10 min. Plates were scanned in an InCell Analyzer 2500 at $\lambda_{ex}/\lambda_{em}$=430/605 nm (for FITC channel) for SF44 fluorescence on lipid droplets and at $\lambda_{ex}/\lambda_{em}$=350/455 nm (for DAPI channel) for nuclei. The images obtained were analyzed using InCell Developer software. The fluorescence intensity of LDs was interpreted as a cellular granule, and the area of individual cells was recognized by nuclei staining with collar segmentation.

Cell Viability assay

HeLa human cervical cancer cells, Raw264.7 murine macrophage cells, and C2C12 murine myoblast cells were seeded in transparent 96-well plates. After 24 h, compounds were treated at a concentration of 10 μM for 24 h. Then, a cell viability assay was performed with a WST assay following the manufacturer's protocol.

2. Supporting Table & Figures

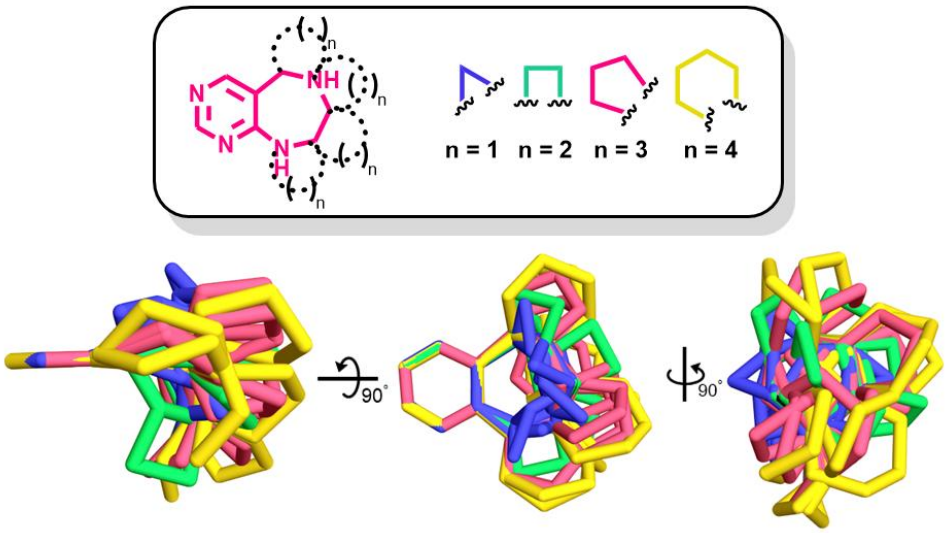
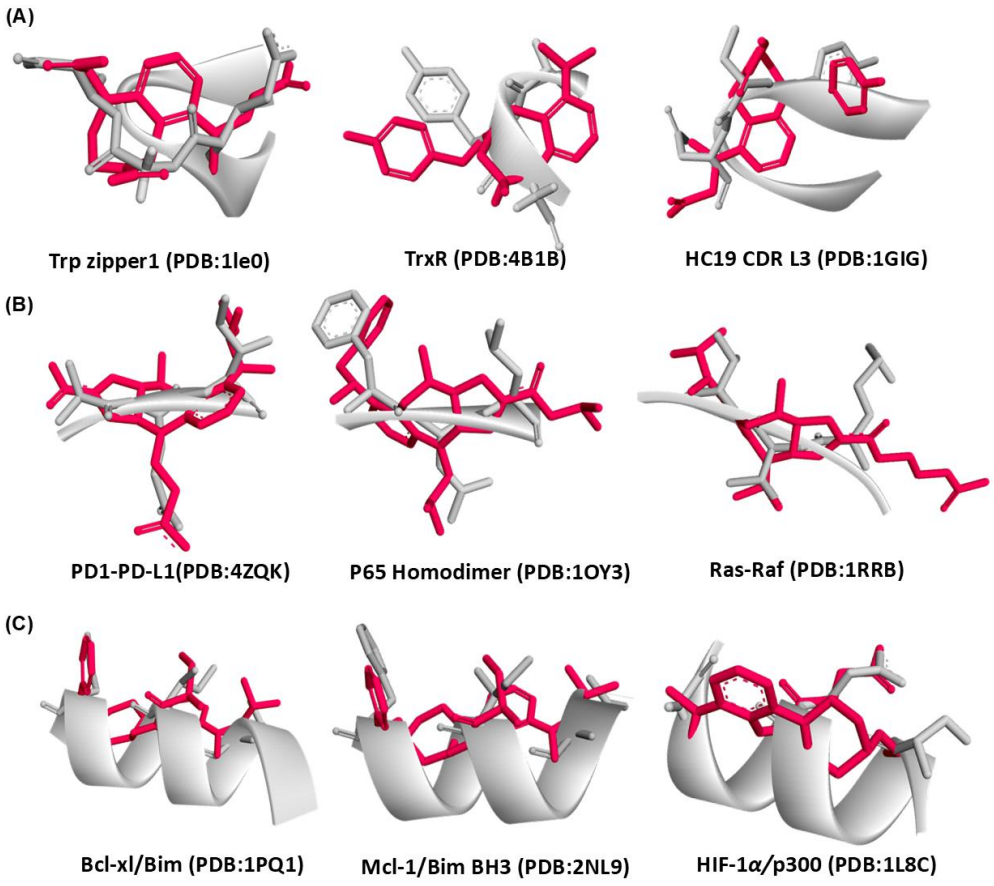


Figure S1. Possible scaffolds based on pyrimidodiazepine. Virtual construction of pyrimidodiazepine-embedded scaffold candidates for mimicking protein secondary structures. We constructed tricyclic scaffolds by combining pyrimidodiazepine with additional rings of varying sizes (3, 4, 5, and 6 members) and exploring all possible stereoisomers at each Csp3-carbon junction. This resulted in 41 geometrically distinct tricycles as potential core skeletons. The resulting 41 skeletons were aligned with pyrimidine and displayed above. Subsequently, we analyzed the structural characteristics of three pivotal protein secondary structures (β-turn, β-strand, and α-helix), focusing on the geometric positioning of key Cα centers where amino acid residues attach. This analysis allowed us to identify scaffold candidates capable of accommodating side-chain residues in spatial arrangements compatible with these secondary structures.

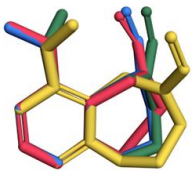


(D)

	Distance between Cα equivalents (Å)			RMSD (Å)
	Cα	Cα+1	Cα+2	
Tryptophan zipper 1 (PDB: 1le0)	0.801	0.526	0.328	0.585
Thioredoxin reductase (PDB:4B1B)	0.534	0.743	0.727	0.675
HC19 CDR L3 (PDB:1GIG)	0.493	0.625	0.625	0.584
PD-1/PD-L1 (PDB:4ZQK)	0.796	0.830	0.803	0.810
P65 Homodimer (PDB:1OY3)	0.889	0.505	0.917	0.793
Ras-Raf (PDB:1RRB)	0.764	0.654	0.809	0.745
Bcl-xl/Bim (PDB:1PQ1)	1.117	0.205	1.255	0.977
Mcl-1/Bim BH3 (PDB:2NL9)	1.349	0.374	1.175	1.055
HIF-1α/p300 (PDB:1L8C)	1.307	0.360	1.097	1.007

Figure S2. *In-silico* design strategy. (A) Alignment of β-turn mimetic scaffold with experimental secondary structures of peptides (Tryptophan zipper 1; Thioredoxin reductase; HC19 CDR L3) from the PDB. (B) Alignment of β-strand mimetic scaffold with experimental secondary structures of peptides (PD-1/PD-L1; p65 Homodimer; Ras-Raf) from PDB. (C) Alignment of α-helix mimetic scaffold with experimental secondary structures of peptides (Bcl-xl/Bim; Mcl-1/Bim BH3; HIF-1α/p300) from PDB. (D) RMSD values and distances between Cα equivalents on the mimetic scaffolds and Cα of reported peptide structures.

(A)



1
β-Turn mimetic

RMSD between each conformation

	1st	2nd	3rd	4th
1st		0.071	0.226	0.226
2nd			0.216	0.189
3rd				0.084

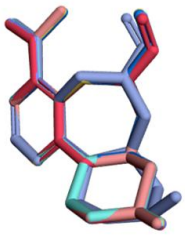
(B)

2
β-Strand mimetic

RMSD between each conformation

	1st	2nd	3rd
1st		0.018	0.010
2nd			0.150

(C)



3
α-Helix mimetic

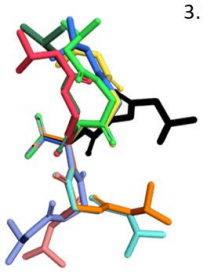
RMSD between each conformation

	1st	2nd	3rd	4th	5th
1st		0.049	0.058	0.720	0.039
2nd			0.012	0.687	0.109
3rd				0.663	0.118
4th					0.689

(D)

RMSD between each conformation

	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
1st		3.002	3.325	0.333	7.043	7.174	6.919	1.860	6.954	5.158
2nd			0.651	2.803	7.494	7.297	6.851	1.571	6.876	3.436
3rd				3.122	7.568	7.193	6.653	2.104	6.674	3.298
4th					7.075	7.147	6.958	1.728	6.987	5.117
5th						2.221	3.778	7.210	3.736	6.928
6th							2.927	7.371	2.820	6.840
7th								7.049	0.135	5.366
8th									7.083	4.097
9th										5.427



Peptide Backbone

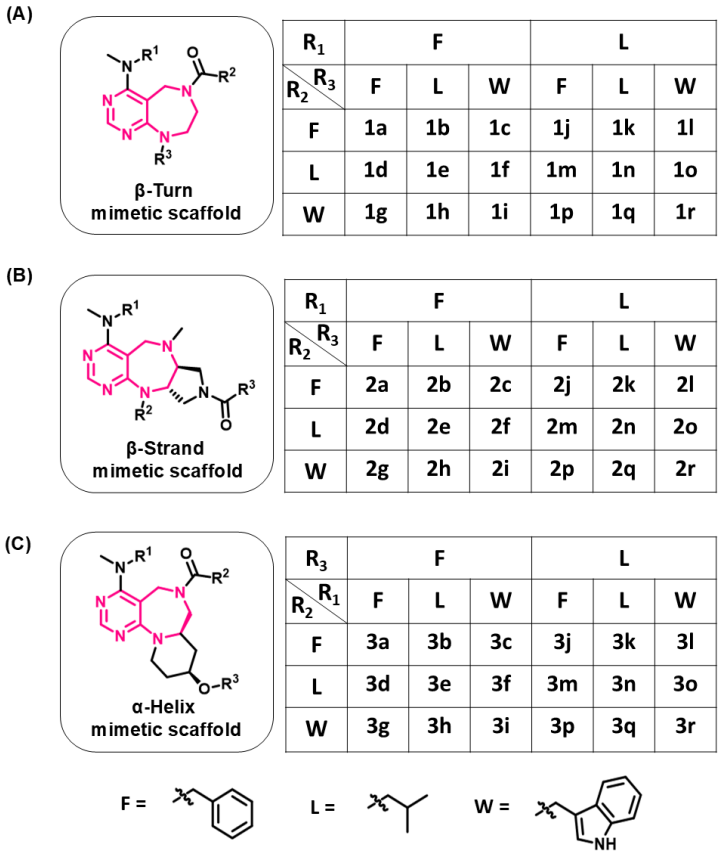
Figure S3. Possible conformations for each mimetic scaffold. (A) Overlaid structures of possible conformers of β-turn mimetic scaffold **1** under ambient temperature (<2.8 kcal/mol of Gibbs free energy) and root-mean-square deviation (RMSD) values between each conformer; (B) Overlaid structures of possible conformers of β-strand mimetic scaffold **2** under ambient temperature and RMSD values between each conformer; (C) Overlaid structures of possible conformers of α-helix mimetic scaffold **3** under ambient temperature and RMSD values between each conformer. (D) Overlaid structures of possible conformers of linear peptide under ambient temperature and RMSD values between each conformer.

Table S1. Conformational analysis search method.

Force Field	MMF94s
Solvent Effect	None
Electrostatic Calculation Method	Bond Charge Increment
Optimization Method	Full-Matrix Newton-Raphson
Optimize by	Energy
Search Limit	2.5 %
	Corner Flap (O)
	Edge Flip (O)
	Stepwise Rotation (O)

Table S2. Conformational analysis result.

Scaffold	Potential energy (kcal/mol)	Relative energy (kcal/mol)	Boltzmann population (%)
1 (β-Turn mimetic scaffold)	-86.3224	0	71.5
	-85.4986	0.8238	17.8
	-84.9524	1.3700	7.1
	-84.546	1.7764	3.6
2 (β-Strand mimetic scaffold)	-26.6099	0	53.9
	-26.0771	0.5328	21.9
	-26.0757	0.5342	21.9
3 (α-Helix mimetic scaffold)	-73.9580	0	22.6
	-73.9512	0.0068	22.3
	-73.6617	0.2963	13.7
	-73.6562	0.3018	13.6
	-73.6385	0.3195	13.2
	-72.9735	0.9845	4.3
	-72.9698	0.9882	4.3
Peptide backbone	43.8666	0	47.3
	44.7820	0.9154	10.1
	44.8991	1.0325	8.3
	44.9415	1.0749	7.7
	45.0466	1.1800	6.5
	45.2132	1.3466	4.8
	45.2312	1.3646	4.7
	45.2501	1.3835	4.6
	45.3364	1.4698	4.0
	45.8119	1.9453	1.8



(A) R_1	F			L		
R_2 \ R_3	F	L	W	F	L	W
F	1a	1b	1c	1j	1k	1l
L	1d	1e	1f	1m	1n	1o
W	1g	1h	1i	1p	1q	1r

(B) R_1	F			L		
R_2 \ R_3	F	L	W	F	L	W
F	2a	2b	2c	2j	2k	2l
L	2d	2e	2f	2m	2n	2o
W	2g	2h	2i	2p	2q	2r

(C) R_3	F			L		
R_2 \ R_1	F	L	W	F	L	W
F	3a	3b	3c	3j	3k	3l
L	3d	3e	3f	3m	3n	3o
W	3g	3h	3i	3p	3q	3r

Figure S4. Synthetic results of pryimidodiazepine based peptide inspired scaffold library compounds that has diverse character. (A) β-turn mimetic compounds. (B) β-strand mimetic compounds. (C) α-helix mimetic compounds.

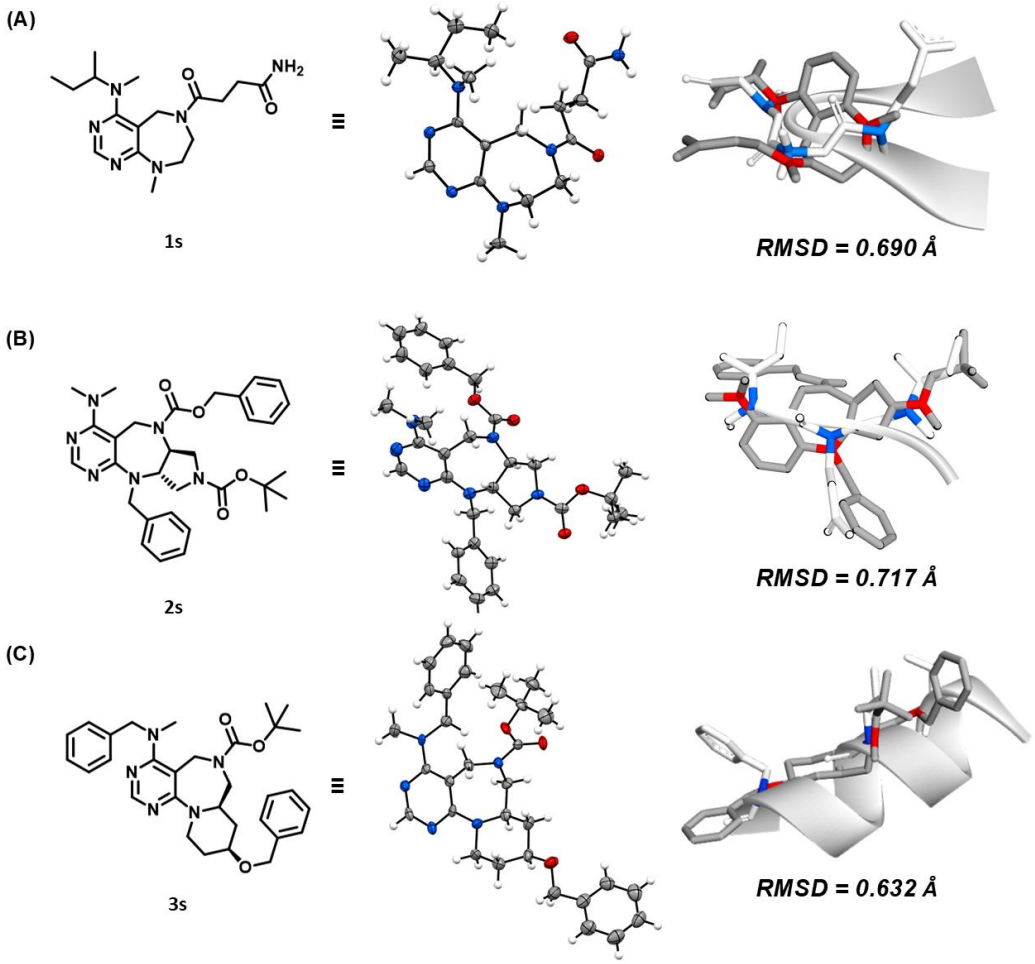


Figure S5. X-ray crystallography data for designed scaffolds. (A) X-ray crystallography of β-turn mimetic scaffold **1s**. (B) X-ray crystallography of β-strand mimetic scaffold **2s**. (C) X-ray crystallography of α-helix mimetic scaffold **3s**.

Table S3. Summary of X-ray crystallographic data.

	1s	**2s**	**3s**	**S10**
Chemical formula	$C_{17}H_{28}N_6O_2$, H_2O	$C_{31}H_{38}N_6O_4$	$C_{31}H_{39}N_5O_3$	$C_{14}H_{20}N_2O_2$
Formula weight	366.47	558.67	529.67	248.32
Crystal system	triclinic	orthorhombic	triclinic	orthorhombic
Space group	$P\bar{1}$	$P2_12_12_1$	$P1$	$P2_12_12_1$
Color of crystal	colorless	colorless	colorless	colorless
a (Å)	9.4842(6)	10.14310(10)	6.2988(6)	6.5324(2)
b (Å)	10.3978(7)	25.1649(4)	12.7745(11)	9.4931(4)
c (Å)	11.3997(8)	28.1114(4)	18.4302(14)	21.5113(8)
α (°)	114.680(2)	-	103.810(3)	-
β (°)	111.139(2)	-	97.871(3)	-
γ (°)	91.753(2)	-	104.236(3)	-
Volume (Å^3)	930.73(11)	7175.44(17)	1365.4(2)	1333.97(9)
Z	2	8	2	4
R_{int}	0.1102	0.0956	0.1144	0.0475
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0722 $wR2$ = 0.1412	$R1$ = 0.0958 $wR2$ = 0.2794	$R1$ = 0.0900 $wR2$ = 0.1347	$R1$ = 0.0342 $wR2$ = 0.0784
Final R indices [all data]	$R1$ = 0.1228 $wR2$ = 0.1668	$R1$ = 0.1044 $wR2$ = 0.2911	$R1$ = 0.1418 $wR2$ = 0.1548	$R1$ = 0.0372 $wR2$ = 0.0812
Goodness-of-fit on F^2	1.068	1.113	1.092	1.099

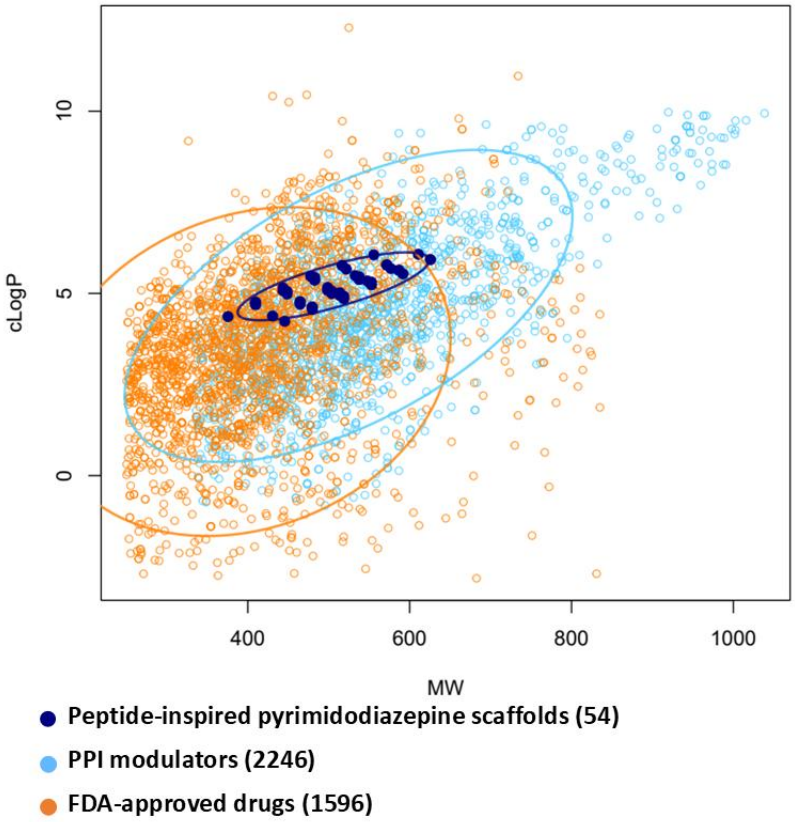
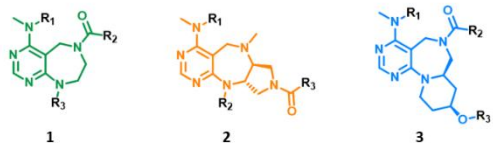


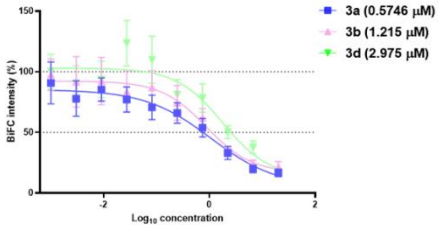
Figure S6. A plot of representative physical properties. A plot of molecular weight vs. cLogP highlights that our peptide-inspired pyrimidodiazepine compounds (navy) occupy a central space between FDA-approved drugs (orange) and PPI modulators (blue). This indicates that our innovative library has unique chemical features with high drug-likeness and the possibility of PPI modulators. The ellipses represent 90% confidence intervals.

(A)



		R_1	R_2	R_3	Tau BiFC % inhibition at 10 μM (IC_{50})	Lipid droplet % inhibition at 10 μM (IC_{50})
β-Turn mimetic scaffolds	1a	Bn (F)	Bn (F)	Bn (F)	43.8	-0.3
	1b	Bn (F)	Bn (F)	*i*-Bu (L)	40.6	4.1
	1d	Bn (F)	*i*-Bu (L)	Bn (F)	-11.8	-11.6
β-Strand mimetic scaffolds	2a	Bn (F)	Bn (F)	Bn (F)	50.0	**81.8 (2.26 μM)**
	2b	Bn (F)	Bn (F)	*i*-Bu (L)	8.6	**85.1 (2.47 μM)**
	2d	Bn (F)	*i*-Bu (L)	Bn (F)	-11.8	**71.2 (2.71 μM)**
α-Helix mimetic scaffolds	3a	Bn (F)	Bn (F)	Bn (F)	**81.3 (0.58 μM)**	14.6
	3b	Bn (F)	Bn (F)	*i*-Bu (L)	**75.1 (2.98 μM)**	13.0
	3d	Bn (F)	*i*-Bu (L)	Bn (F)	**77.3 (1.21 μM)**	14.7

(B)



(C)

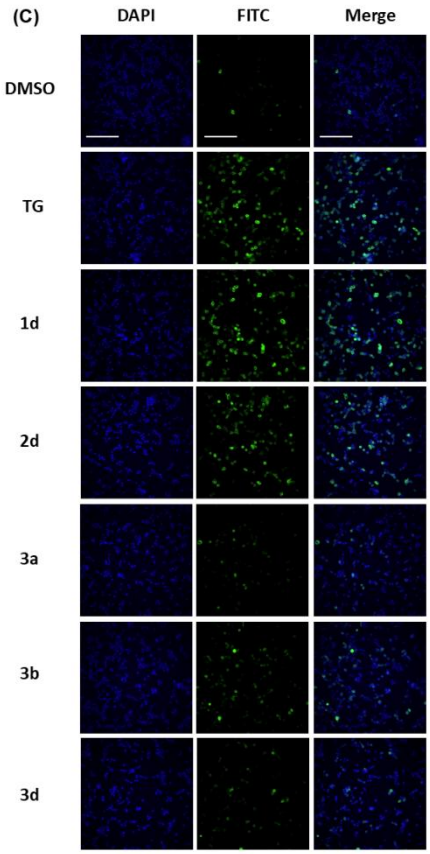
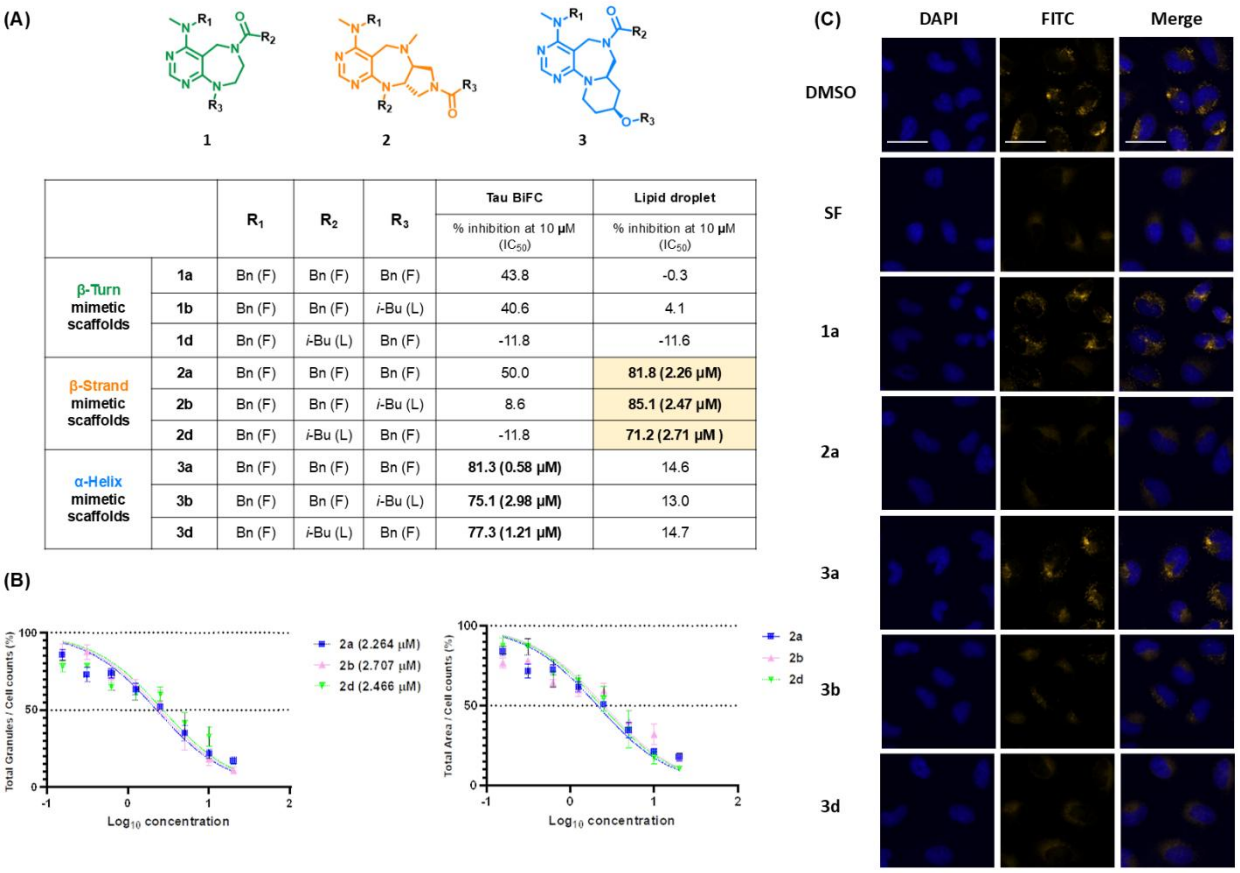


Figure S7. Biological activities of peptide-inspired compounds that show distinct features depending on their scaffolds. (A) The results of two kinds of disease-mimicking phenotypic assays for BiFC-tau and lipid droplets. (B) IC_{50} graph of the α-helix mimetic compounds, **3a**, **3b**, and **3d** in BiFC-tau screening (n = 6) Data are shown as means ± SEMs. ; (C) Fluorescence images of BiFC-tau screening upon treatment of the designated compounds at 10 μM. Scale bar = 200 μm.



		R_1	R_2	R_3	Tau BiFC	Lipid droplet
					% inhibition at 10 μM (IC_{50})	% inhibition at 10 μM (IC_{50})
β-Turn mimetic scaffolds	1a	Bn (F)	Bn (F)	Bn (F)	43.8	-0.3
	1b	Bn (F)	Bn (F)	*i*-Bu (L)	40.6	4.1
	1d	Bn (F)	*i*-Bu (L)	Bn (F)	-11.8	-11.6
β-Strand mimetic scaffolds	2a	Bn (F)	Bn (F)	Bn (F)	50.0	**81.8 (2.26 μM)**
	2b	Bn (F)	Bn (F)	*i*-Bu (L)	8.6	**85.1 (2.47 μM)**
	2d	Bn (F)	*i*-Bu (L)	Bn (F)	-11.8	**71.2 (2.71 μM)**
α-Helix mimetic scaffolds	3a	Bn (F)	Bn (F)	Bn (F)	**81.3 (0.58 μM)**	14.6
	3b	Bn (F)	Bn (F)	*i*-Bu (L)	**75.1 (2.98 μM)**	13.0
	3d	Bn (F)	*i*-Bu (L)	Bn (F)	**77.3 (1.21 μM)**	14.7

Figure S8. Biological activities of peptide-inspired compounds that show distinct features depending on their scaffolds. (A) The results of two kinds of disease-mimicking phenotypic assays for BiFC-tau and lipid droplets. (B) IC_{50} graph of the β-strand mimetic compounds, **2a**, **2b**, and **2d** in lipid droplet (LD) screening analyzed by either total granule/cell or total area/cell (n=3) Data are shown as means ± SEMs. ; (C) Fluorescence images of LD screening upon treatment of the designated compounds at 10 μM. Scale bar = 30 μm.

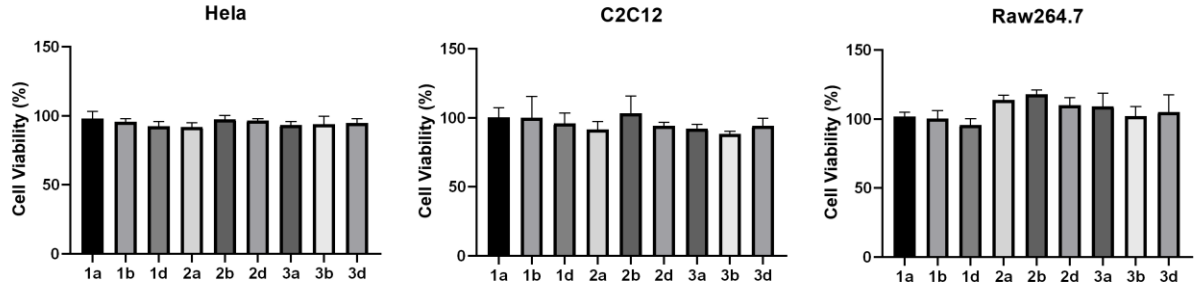
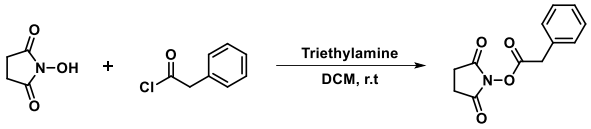


Figure S9. Cell viability of library compounds. The WST data in HeLa, C2C12, and Raw264.7 cells upon treatment of the designated compounds at 10 μM ($n \geq 2$). Data are shown as means ± SEMs.

3. Experimental Section

3.1. Reagent Preparation and Compound Characterization

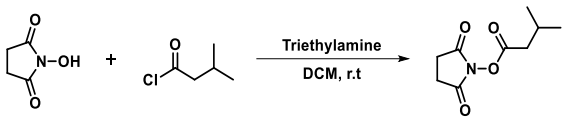


S1

(2,5-Dioxopyrrolidin-1-yl) 2-phenylacetate (S1)

To a solution of *N*-hydroxysuccinimide (100 mg, 0.868 mmol) in 8.2 mL of dichloromethane (DCM, 0.1 M) was added 2-phenylacetyl chloride (174.6 mg, 1.13 mmol, 1.3 equiv.) at 0 ℃. The mixture was stirred at room temperature (r.t) for 2.5 h. After the completion of the reaction, as indicated by thin-layer chromatography (TLC), saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S1** (153 mg, 75% yield) as a white powder.

^{1}H NMR (400 MHz, DMSO): δ 7.36 (m, 3H), 7.32–7.28 (m, 2H), 4.11 (s, 2H), 2.80 (s, 4H); ^{13}C NMR (100 MHz, DMSO): δ 170.18, 167.44, 132.38, 129.38, 128.63, 127.44, 36.64, 25.47.

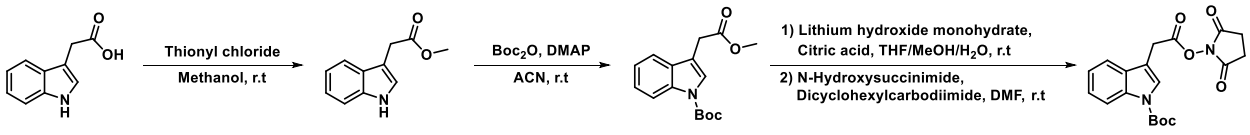


S2

(2,5-Dioxopyrrolidin-1-yl) 3-methylbutanoate (S2)

To a solution of *N*-hydroxy succinimide (1 g, 8.69 mmol) in 50 mL of DCM (0.2 M) was added 3-methylbutanoyl chloride (1.36 g, 11.3 mmol, 1.3 equiv.) at 0 ℃. The mixture was stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S2** (1.7 g, 98% yield) as a beige powder.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.84 (4 H, d, *J* = 7.4 Hz), 2.48 (2 H, d, *J* = 7.1 Hz), 2.22 (1 H, dt, *J* = 13.6, 6.7 Hz), 1.06 (6 H, d, *J* = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.34, 168.00, 39.91, 26.08, 25.73, 22.33.



S3 S4 S5

Methyl 2-(1*H*-indol-3-yl)acetate (S3)

To a solution of 2-(1*H*-indol-3-yl)acetic acid (2 g, 11.4 mmol) in 110 mL of MeOH (0.1 M) was added Thionyl chloride (6.79 g, 57.1 mmol, 5.0 equiv.) at 0 ℃. The mixture was stirred at 0 ℃ for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with ethyl acetate (EtOAc) three times. The combined organic layer was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, and brine each once. The organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the

filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S3** (2.01 g, 93% yield) as a white powder.

The synthesis of compound **S3** was previously reported.[1]

***tert*-Butyl 3-(2-methoxy-2-oxo-ethyl)indole-1-carboxylate (S4)**

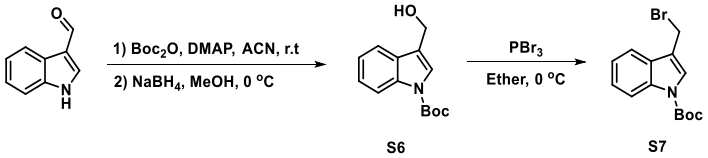
To a solution of **S3** (2 g, 10.6 mmol) in 103 mL of ACN (0.1 M) were added Boc_2O (3.48 g, 15.9 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (DMAP) (130 mg, 1.1 mmol, 0.1 equiv.) at r.t. The mixture was stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The resultant was dissolved in DCM and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S4** (3.04 g, 98% yield) as a white powder.

The synthesis of compound **S4** was previously reported. [1]

***tert*-Butyl 3-[2-(2,5-dioxopyrrolidin-1-yl)oxy-2-oxo-ethyl]indole-1-carboxylate (S5)**

To a solution of **S4** (3.04 g, 10.5 mmol) in 105 mL of THF, 42 mL of MeOH and 63 mL of H_2O (0.05 M, THF:MeOH:H_2O=5:2:3) were added citric acid (6.06 g, 31.52 mmol, 3.0 equiv.) and lithium hydroxide monohydrate (1.32 g, 31.52 mmol, 3.0 equiv.) at r.t. The mixture was stirred at r.t for 20 h. After the completion of the reaction, as indicated by TLC, 60 mL of 10% citric acid solution was added. The resulting aqueous solution was extracted with EtOAc three times. The combined organic layer was washed with water and brine each once. This organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure. The crude product, 2-(1-*tert*-butoxycarbonylindol-3-yl)acetic acid, was dissolved in 21.0 mL of dimethylformamide (DMF) and *N*-hydroxy succinimide (2.42 g, 21.0 mmol, 2 equiv.), dicyclohexylcarbodiimide (DCC) (3.25 g, 15.8 mmol, 1.5 equiv.) were added. The mixture was stirred at r.t for 6 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with diethyl ether. The filtrate was diluted with EtOAc, and washed with saturated $NaHCO_3$ solution and brine each once. The organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S5** (2.76 g, 70% overall yield) as a beige powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (1 H, d, *J* = 8.3 Hz), 7.70 (1 H, s), 7.55 (1 H, d, *J* = 7.7 Hz), 7.34 (1 H, ddd, *J* = 8.4, 7.2, 1.4 Hz), 7.30–7.25 (1 H, m), 4.03 (2 H, d, *J* = 1.2 Hz), 2.82 (4 H, s), 1.67 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.03, 166.33, 149.56, 135.51, 129.60, 125.15, 124.93, 122.95, 118.93, 115.44, 110.67, 83.99, 28.29, 28.01, 25.70.



***tert*-Butyl 3-(hydroxymethyl)indole-1-carboxylate (S6)**

To a solution of 1*H*-indole-3-carbaldehyde (3 g, 20.7 mmol) in 64 mL of acetonitrile (ACN, 0.3 M) was added Boc_2O (4.96 g, 22.7 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (DMAP) (252 mg, 2.07 mmol, 0.1 equiv.) at r.t. The mixture was stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated $NaHCO_3$ solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure. The crude product, *tert*-

butyl 3-formylindole-1-carboxylate, was dissolved in 206 mL of MeOH, and $NaBH_4$ (1.17 g, 31.0 mmol, 1.5 equiv.) was added at 0 ℃. The mixture was stirred at 0 ℃ for 30 min. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S6** (5.06 g, 98% overall yield) as a colorless oil.

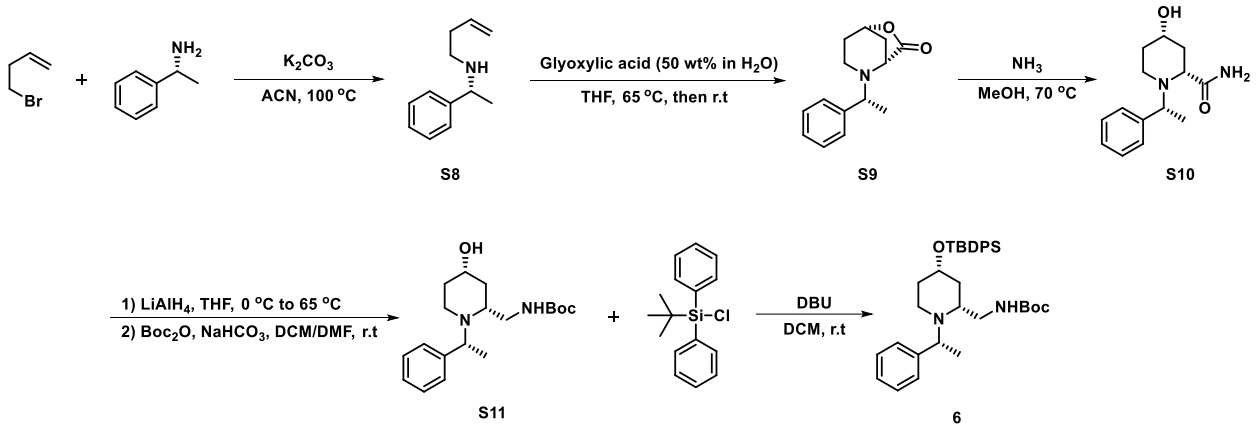
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1 H, d, *J* = 8.3 Hz), 7.65–7.61 (1 H, m), 7.56 (1 H, s), 7.33 (1 H, ddd, *J* = 8.4, 7.2, 1.3 Hz), 7.28–7.22 (1 H, m), 4.82 (2 H, d, *J* = 4.9 Hz), 1.66 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.03, 166.33, 149.56, 135.51, 129.60, 125.15, 124.93, 122.95, 118.93, 115.44, 110.67, 83.99, 28.29, 28.01, 25.70.

***tert*-Butyl 3-(bromomethyl)indole-1-carboxylate (S7)**

To a solution of **S6** (100 mg, 0.404 mmol) in 2.0 mL of diethyl ether (0.2 M), phosphorous tribromide was added (38.3 mg, 0.142 mmol, 0.35 equiv.) at 0 ℃. The mixture was stirred at 0 ℃ for 2 h. After the completion of the reaction, as indicated by TLC, saturated $NaHCO_3$ solution was poured into the reaction mixture and extracted with diethyl ether three times. The combined organic layer was dried over anhydrous $MgSO_4$(s) and filtered, and the filtrate was condensed under reduced pressure to afford **S7** (92 mg, 73% yield) as a pink powder.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (1 H, d, *J* = 8.4 Hz), 7.71–7.64 (2 H, m), 7.36 (1 H, ddd), 7.31 (1 H, td), 4.69 (2 H, s), 1.67 (9 H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.47, 135.88, 128.85, 125.17, 125.12, 123.03, 119.45, 117.29, 115.58, 84.28, 28.30, 24.66.

3.2. Synthetic Procedure of Building Block and Compound Characterization



***N*-[(1*R*)-1-Phenylethyl]but-3-en-1-amine (S8)**

To a mixture of (1*R*)-1-phenylethanamine (32.31 g, 266.7 mmol, 1.2 equiv.), K_2CO_3 (46.07 g, 333.3 mmol, 1.5 equiv.) in 388 mL of dry ACN (0.5 M) was added 4-bromobut-1-ene (30 g, 222.2 mmol) in dropwise (5 mL/h) at 100 ℃. The mixture was stirred at 100 ℃ for 24 h. After the completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The resultant was dissolved in EtOAc and extracted with 1N NaOH three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S8** (36.7 g, 94% yield) as yellow oil.

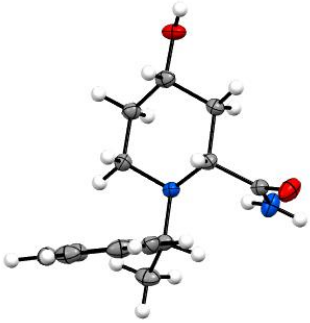
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (4 H, m), 7.24–7.18 (1 H, m), 5.73 (1 H, dddd, *J* = 17.1, 10.2, 6.9, 5.8 Hz), 5.11–4.95 (2 H, m), 3.75 (1 H, q, *J* = 6.6 Hz), 2.60–2.45 (2 H, m), 2.26–2.17 (2 H, m), 1.39–1.27 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.79, 136.60, 136.56, 128.44, 126.87, 126.59, 116.31, 58.31, 58.23, 46.75, 34.40, 24.40, 24.37.

(1*R*,5*S*)-2-[(1*R*)-1-Phenylethyl]-6-oxa-2-azabicyclo[3.2.1]octan-7-one (S9)

To a solution of **S8** (37 g, 221.1 mmol) in 493 mL of dry tetrahydrofuran (THF, 0.4 M) was added glyoxylic acid (50 wt% in H_2O) (46.89 g, 316.7 mmol, 1.5 equiv.) in dropwise over 1 h at r.t. The mixture was stirred at 65 ℃ for 8 h, then cooled to r.t, and left stirred for 16 h. After the completion of the reaction, as indicated by TLC, the resultant was diluted with water, 1N NaOH solution was added until pH 8~9, and the resulting solution was extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S9** (15.07 g, 31% yield) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.36 (2 H, m), 7.35–7.29 (2 H, m), 7.28–7.22 (1 H, m), 4.77 (1 H, t), 3.69 (1 H, q, *J* = 6.6 Hz), 3.34 (1 H, dd), 3.19 (1 H, d), 2.47 (1 H, td), 2.12–2.01 (2 H, m), 1.91 (1 H, td), 1.82 (1 H, d), 1.32 (3 H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.29, 144.76, 128.70, 127.69, 127.34, 76.65, 62.52, 57.35, 44.26, 37.49, 29.48, 21.57; $[\alpha]_D^{25}$ +87.315 (c=1.0, $CHCl_3$).

(2*R*,4*S*)-4-Hydroxy-1-[(1*R*)-1-phenylethyl]piperidine-2-carboxamide (S10)



S9 (15.07 g, 65.2 mmol) was added to 7 N NH_3 solution (in MeOH, 74.46 mL, 521.3 mmol, 8.0 equiv.) and stirred at 70 ℃ for 3 days. After the completion of the reaction, as indicated by TLC, the solvent and remaining NH_3 were removed under reduced pressure, followed by silica-gel flash column chromatography to afford S10 (14.2 g, 88% yield) as a pale-yellow oil. We obtained the X-ray crystal structure of S10 and deposited at The Cambridge Crystallographic Data Centre, under deposition number CCDC 2353938.

^{1}H NMR (400 MHz, $CDCl_3$/MeOD-*d4* (9:1)): δ 7.33 (2 H, dd), 7.29–7.24 (1 H, m), 7.21–7.16 (2 H, m), 3.98 (1 H, q), 3.60 (2 H, s), 3.38 (1 H, td), 3.08–3.00 (1 H, m), 2.93 (1 H, dd), 2.10–2.02 (1 H, m), 1.90–1.81 (2 H, m), 1.57 (1 H, dd), 1.47 (4 H, d); ^{13}C NMR (100 MHz, $CDCl_3$/MeOD-*d4* (9:1)): δ 177.96, 137.70, 128.83, 127.94, 127.43, 66.68, 62.97, 59.32, 41.60, 38.19, 33.06, 18.98.

***tert*-Butyl *N*-[[(2*R*,4*S*)-4-hydroxy-1-[(1*R*)-1-phenylethyl]-2-piperidyl]methyl]carbamate (S11)**

To a solution of **S10** (14.15 g, 57 mmol) in 522 mL of dry THF (0.1 M) was added $LiAlH_4$ (2.4 M in THF) (47.5 mL, 113.9 mmol, 2.0 equiv.) in dropwise over 5 h at 0 ℃. The mixture was stirred at 65 ℃ for 16 h. After the completion of the reaction, as indicated by TLC & LC-MS, water was slowly added to quench the remaining $LiAlH_4$, and the resultant was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. The crude product, (*2R,4S*)-2-(aminomethyl)-1-[(*1R*)-1-phenylethyl]piperidin-4-ol, was dissolved in DCM/DMF co-solvent (188 mL(70%)/80 mL(30%), 0.2 M) and $NaHCO_3$ (20.34 g, 113.9 mmol, 2 equiv.), Boc_2O (14.3 g, 65.5 mmol, 1.15 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 1.5 h; after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **S11** (12.6 g, 66% overall yield) as a colorless oil.

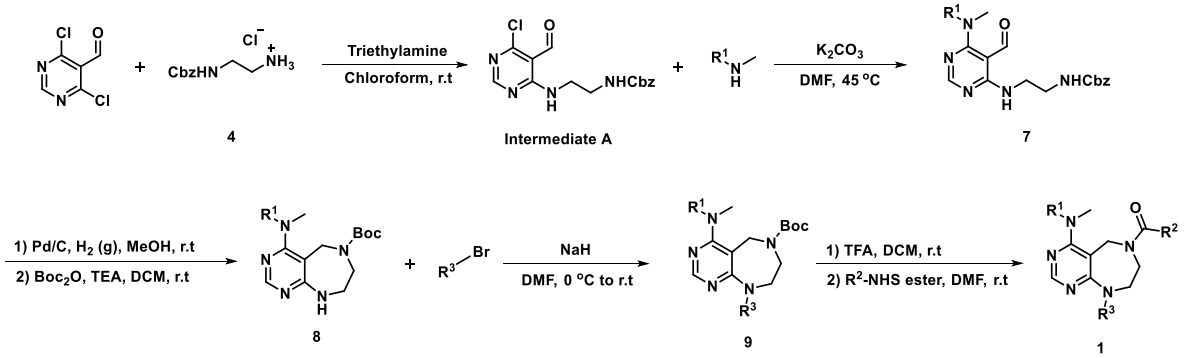
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.29 (2 H, m), 7.27–7.21 (3 H, m), 4.93 (1 H, t), 4.10 (1 H, q), 3.60 (2 H, ddt), 3.14 (2 H, dddd), 2.45 (1 H, ddt), 2.28 (1 H, s), 2.03–1.95 (1 H, m), 1.91–1.76 (2 H, m), 1.51 (2 H, dt), 1.44 (12 H, d); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.65, 140.14, 128.29, 128.13, 127.18, 79.39, 67.82, 56.13, 54.33, 42.51, 42.00, 37.89, 34.19, 28.56, 19.55.

***tert*-Butyl *N*-[[(2R,4S)-4-[*tert*-butyl(diphenyl)silyl]oxy-1-[(1*R*)-1-phenylethyl]-2-piperidyl]methyl]carbamate (6)**

To a solution of **S11** (12.6 g, 37.6 mmol) in 162 mL of DCM (0.2 M) were sequentially added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 11.46 g, 75.3 mmol, 2.0 equiv.), *tert*-butyl-chloro-diphenyl-silane (TBDPS-Cl, 15.52 g, 56.5 mmol, 1.5 equiv.) and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **6** (21.24 g, 98% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (4 H, ddd), 7.45–7.40 (2 H, m), 7.40–7.35 (4 H, m), 7.30 (2 H, dd), 7.26–7.19 (3 H, m), 5.01 (1 H, t), 4.09 (1 H, q), 3.67–3.45 (2 H, m), 3.39–3.22 (1 H, m), 2.99 (1 H, dt), 2.50–2.34 (1 H, m), 1.88–1.56 (5 H, m), 1.53 (9 H, s), 1.42 (3 H, d), 1.06 (9 H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.54, 140.10, 135.85, 135.82, 134.60, 134.37, 129.70, 129.65, 128.33, 128.07, 127.68, 127.61, 127.10, 69.60, 55.68, 54.06, 42.60, 42.54, 38.35, 34.24, 28.62, 27.07, 19.50, 19.19.

3.3. General Synthetic Procedure 1 for β-Turn Mimetic Compounds(1a–1r) and Compound Characterization



General procedure 1:

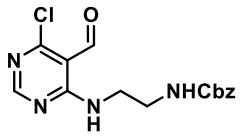
To a solution of **4** (2.20 g, 9.55 mmol, 1.3 equiv.) in 70 mL of chloroform (0.1 M) were sequentially added triethylamine (TEA; 2.23 g, 22.04 mmol, 3 equiv.) and 4,6-dichloropyrimidine-5-carbaldehyde (1.3 g, 7.35 mmol, 1.0 equiv.) at 0 °C, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **Intermediate A** (1.86 g, 75% yield) as a white solid. A mixture of **Intermediate A** and K_2CO_3 (3 equiv.) were dissolved in dry DMF (0.1 M), and *N*-methyl-R^1 amine (1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **7a, 7b**.

To a solution of **7a** (or **7b**) in MeOH (0.1 M) was added Pd/C (30 wt%) at r.t, and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for the indicated time. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in DCM (0.1 M). Dry TEA (2 equiv.) and Boc_2O (1.15 equiv.) were sequentially added at 0 °C, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the resultant was quenched with saturated NH_4Cl solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **8a** (or **8b**).

A mixture of **8a** (or **8b**) and sodium hydride (NaH; 60% dispersion in mineral oil, 3 equiv.) was cooled to 0 °C and dissolved in dry DMF (0.1 M) under argon atmospheric conditions. After stirring at 0 °C for 0.5 h, R^3-bromide (1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9a**–**9f**.

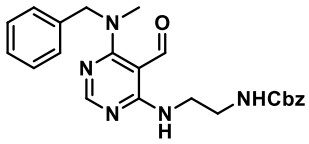
To a solution of **9a–9f** in DCM (0.05 M) was added trifluoroacetic acid (TFA; 10v/v% dissolved in DCM) at r.t and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of remained TFA, and the crude resultant was dissolved in DMF (0.1 M). Dry TEA (5 equiv.) and R^2-NHS ester (1.5 equiv.) were sequentially added and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1a**–**1r**.

Benzyl *N*-[2-[(6-chloro-5-formyl-pyrimidin-4-yl)amino]ethyl]carbamate (Intermediate A)



Following the general synthetic procedure 1, **Intermediate A** was obtained in 75% yield.

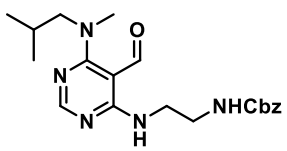
Benzyl *N*-[2-[[6-[benzyl(methyl)amino]-5-formyl-pyrimidin-4-yl]amino]ethyl]carbamate (7a)



To a solution of **Intermediate A** (1.86 g, 5.56 mmol) in 55 mL of dry DMF (0.1 M) were added K_2CO_3 (2.31 g, 16.7 mmol, 3 equiv.) and *N*-methyl-benzylamine (1.01 g, 8.34 mmol, 1.5 equiv.), stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **7a** (2.14 g, 92% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 9.34 (t, *J* = 6.1 Hz, 1H), 8.19 (s, 1H), 7.38–7.23 (m, 10H), 5.48 (t, *J* = 5.7 Hz, 1H), 5.10 (s, 2H), 4.86 (s, 2H), 3.70 (q, *J* = 5.9 Hz, 2H), 3.45 (q, *J* = 5.8 Hz, 2H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.22, 167.10, 162.89, 159.79, 157.95, 156.62, 136.66, 128.97, 128.61, 128.21, 128.18, 127.82, 127.59, 96.45, 66.79, 56.54, 41.74, 40.83, 40.66; LRMS (ESI): *m/z* calcd for $C_{23}H_{26}N_5O_3^+$ $[M+H]^+$: 420.20; Found: 420.1.

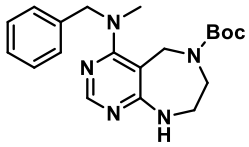
Benzyl *N*-[2-[[5-formyl-6-[isobutyl(methyl)amino]pyrimidin-4-yl]amino]ethyl]carbamate (7b)



To a solution of **Intermediate A** (1.20 g, 3.58 mmol) in 35 mL of dry DMF (0.1 M) were added K_2CO_3 (1.49 g, 10.8 mmol, 3 equiv.) and *N*-methyl-isobutylamine (469 mg, 5.38 mmol, 1.5 equiv.), stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **7b** (1.25 g, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 9.23 (d, *J* = 6.4 Hz, 1H), 8.13 (s, 1H), 7.37–7.26 (m, 5H), 5.53 (t, *J* = 5.5 Hz, 1H), 5.09 (s, 2H), 3.68 (q, *J* = 6.0 Hz, 2H), 3.51 (d, *J* = 7.6 Hz, 2H), 3.44 (q, *J* = 5.8 Hz, 2H), 3.22 (s, 3H), 2.15–2.05 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.14, 167.52, 162.79, 159.54, 156.62, 136.65, 128.58, 128.17, 128.14, 96.38, 66.75, 60.27, 42.16, 41.70, 40.58, 27.24, 20.04; LRMS (ESI): *m/z* calcd for $C_{20}H_{28}N_5O_3^+$ $[M+H]^+$: 386.22; Found: 386.1.

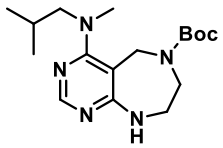
***tert*-Butyl 4-[benzyl(methyl)amino]-5,7,8,9-tetrahydropyrimido[4,5-e][1,4]diazepine-6-carboxylate (8a)**



To a solution of **7a** (2.14 g, 5.10 mmol) in 50 mL of MeOH (0.1 M) was added Pd/C (30 wt%) at r.t, and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 48 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in 200 mL of DCM (0.1 M). Dry TEA (1.03 g, 10.2 mmol, 2 equiv.) and Boc_2O (1.28 g, 5.85 mmol, 1.15 equiv.) were sequentially added at 0 °C, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the resultant was quenched with saturated NH_4Cl solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **8a** (1.03 g, 55% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.40–7.29 (m, 5H), 5.45 (s, 1H), 4.44 (m, 4H), 3.81 (t, *J* = 6.1 Hz, 2H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.87 (s, 3H), 1.47–1.28 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.94, 164.52, 155.12, 137.98, 128.70, 127.63, 127.36, 97.15, 80.10, 57.13, 47.86, 43.93, 41.86, 38.63, 29.81, 28.39; LRMS (ESI): *m/z* calcd for $C_{20}H_{28}N_5O_2^+$ $[M+H]^+$: 370.22; Found: 370.1.

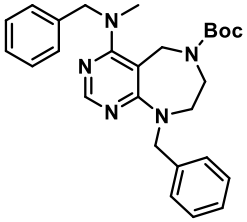
***tert*-Butyl 4-[isobutyl(methyl)amino]-5,7,8,9-tetrahydropyrimido[4,5-e][1,4]diazepine-6-carboxylate (8b)**



To a solution of **7b** (1.25 g, 3.24 mmol, 1.0 equiv.) in 30 mL of MeOH (0.1 M) was added Pd/C (30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 24 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in 128 mL of DCM (0.1 M). Dry TEA (656 mg, 6.49 mmol, 2 equiv.) and Boc_2O (814 mg, 3.73 mmol, 1.15 equiv.) were sequentially added at 0 °C, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the resultant was quenched with saturated NH_4Cl solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **8b** (565 mg, 52% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 5.44 (m, 1H), 4.37 (m, 2H), 3.86–3.71 (m, 2H), 3.58 (m, 2H), 3.23–3.07 (m, 2H), 2.95 (d, *J* = 16.4 Hz, 3H), 2.04 (p, *J* = 6.8 Hz, 1H), 1.36 (m, 9H), 0.88 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.06, 164.52, 156.34, 154.96, 96.40, 80.06, 60.67, 47.71, 44.41, 42.06, 39.31, 28.37, 26.91, 20.39; LRMS (ESI): *m/z* calcd for $C_{17}H_{30}N_5O_2^+$ $[M+H]^+$: 336.24; Found: 336.1.

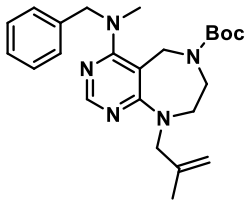
***tert*-Butyl 9-benzyl-4-[benzyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9a)**



A mixture of **8a** (200 mg, 0.54 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 65 mg, 1.62 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 5.3 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (138.8 mg, 0.812 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9a** (213.6 mg, 85% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.40–7.28 (m, 10H), 4.88 (m, 2H), 4.56 (s, 2H), 4.44 (m, 2H), 3.80–3.60 (m, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 2.88 (s, 3H), 1.39 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.14, 164.17, 156.16, 155.02, 138.66, 138.25, 128.70, 128.67, 127.91, 127.72, 127.31, 97.72, 80.07, 57.00, 52.41, 47.16, 45.60, 44.94, 39.04, 28.34; LRMS (ESI): *m/z* calcd for $C_{27}H_{34}N_5O_2^+$ $[M+H]^+$: 460.27; Found: 460.2.

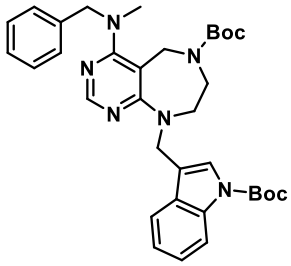
***tert*-Butyl 4-[benzyl(methyl)amino]-9-(2-methylallyl)-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9b)**



A mixture of **8a** (200 mg, 0.54 mmol) and NaH (60% dispersion in mineral oil, 65 mg, 1.62 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 5.3 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (109.6 mg, 0.812 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9b** (181.7 mg, 80% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.38–7.27 (m, 5H), 4.89 (s, 1H), 4.80 (s, 1H), 4.42 (m, 4H), 4.20 (m, 2H), 3.80–3.68 (m, 2H), 3.57 (t, *J* = 5.9 Hz, 2H), 2.83 (s, 3H), 1.74 (s, 3H), 1.36 (d, *J* = 79.7 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.08, 163.99, 156.10, 154.88, 142.10, 138.25, 128.67, 127.69, 127.29, 111.66, 97.67, 80.02, 57.06, 54.59, 47.04, 45.76, 44.81, 39.00, 28.31, 20.22; LRMS (ESI): *m/z* calcd for $C_{24}H_{34}N_5O_2^+$ $[M+H]^+$: 424.27; Found: 424.2.

***tert-B*utyl 4-[benzyl(methyl)amino]-9-[(1-*tert*-butoxycarbonylindol-3-yl)methyl]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9c)**

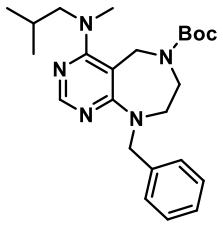


A mixture of **8a** (200 mg, 0.54 mmol) and NaH (60% dispersion in mineral oil, 65 mg, 1.62 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 5.3 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (251.8 mg, 0.812 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9c** (276.5 mg, 85% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.15–8.02 (s, 1H), 7.71–7.61 (m, 1H), 7.55 (s, 1H), 7.39–7.26 (m, 6H), 7.20 (t, *J* = 7.5 Hz, 1H), 4.97 (s, 2H), 4.56 (s, 2H), 4.30 (s, 2H), 3.76 (s, 1.5H), 3.55 (s, 2.5H), 2.86 (s, 3H), 1.67 (s,

9H), 1.29 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.16, 164.04, 156.06, 154.91, 149.88, 138.22, 135.84, 129.98, 128.68, 127.71, 127.29, 124.82, 124.71, 122.82, 119.97, 117.88, 115.30, 97.95, 83.87, 80.02, 60.48, 56.91, 46.27, 45.28, 44.93, 43.51, 39.00, 29.81, 28.34, 14.31, 14.23; LRMS (ESI): *m/z* calcd for $C_{34}H_{43}N_6O_4^+$ $[M+H]^+$: 599.33; Found: 599.2.

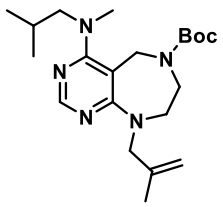
tert-Butyl 9-benzyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9d)



A mixture of **8b** (100 mg, 0.298 mmol) and NaH (60% dispersion in mineral oil, 35.8 mg, 0.89 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 2.93 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, benzyl bromide (76.5 mg, 0.447 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9d** (125 mg, 98% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.17 (s, 1H), 7.34–7.23 (m, 5H), 4.81 (s, 2H), 4.42 (s, 0.5H), 4.27 (s, 1.5H), 3.77 (s, 1.5H), 3.62 (s, 0.5H), 3.51 (t, *J* = 5.7 Hz, 2H), 3.17 (d, *J* = 7.6 Hz, 2H), 2.93 (m, 3H), 2.04 (hept, *J* = 6.9 Hz, 1H), 1.42 (s, 2H), 1.28 (s, 7H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.25, 164.18, 156.16, 154.78, 138.73, 128.64, 127.92, 127.25, 96.88, 80.04, 60.37, 52.26, 47.27, 45.42, 40.00, 28.54, 28.35, 26.91, 20.46; LRMS (ESI): *m/z* calcd for $C_{24}H_{36}N_5O_2^+$ $[M+H]^+$: 426.28; Found: 426.1.

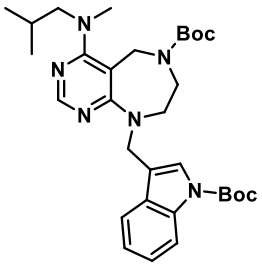
tert-Butyl 9-isobutyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9e)



A mixture of **8b** (100 mg, 0.298 mmol) and NaH (60% dispersion in mineral oil, 35.8 mg, 0.89 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 2.93 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (60.4 mg, 0.447 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9e** (113 mg, 98% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.14 (s, 1H), 4.88 (s, 1H), 4.77 (s, 1H), 4.41 (s, 0.5H), 4.26 (s, 1.5H), 4.20 (s, 0.5H), 4.15 (s, 1.5H), 3.83–3.68 (m, 2H), 3.56 (t, *J* = 5.9 Hz, 2H), 3.15 (m, 2H), 2.93 (m, 3H), 2.02 (dq, *J* = 13.7, 6.8 Hz, 1H), 1.73 (s, 3H), 1.43 (s, 2H), 1.25 (s, 7H), 0.90 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.08, 163.88, 156.00, 154.54, 142.03, 111.51, 96.70, 79.89, 60.30, 54.34, 47.07, 45.49, 45.12, 39.84, 28.42, 28.21, 26.76, 20.33, 20.10; LRMS (ESI): *m/z* calcd for $C_{21}H_{36}N_5O_2^+$ $[M+H]^+$: 390.28; Found: 390.2.

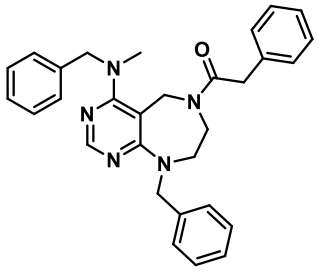
tert-Butyl 9-[(1-_tert_-butoxycarbonylindol-3-yl)methyl]-4-[isobutyl(methyl)amino]-7,8-dihydro-5_H_-pyrimido[4,5-e][1,4]diazepine-6-carboxylate (9f)



A mixture of **8b** (200 mg, 0.596 mmol) and NaH (60% dispersion in mineral oil, 71.6 mg, 1.79 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 5.96 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (277.4 mg, 0.894 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **9f** (327.8 mg, 97% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (s, 1H), 8.10 (s, 1H), 7.70–7.57 (m, 1H), 7.54 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.95 (s, 2H), 4.31 (d, *J* = 69.3 Hz, 2H), 3.78 (s, 1.5H), 3.54 (d, *J* = 5.5 Hz, 2.5H), 3.19 (d, *J* = 7.5 Hz, 2H), 2.93 (s, 3H), 2.04 (dt, *J* = 13.6, 6.9 Hz, 1H), 1.67 (s, 9H), 1.29 (d, *J* = 14.9 Hz, 9H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.26, 164.02, 156.03, 154.65, 149.82, 135.81, 129.95, 124.77, 124.64, 122.76, 119.92, 117.89, 115.24, 97.10, 96.68, 83.78, 79.97, 60.29, 46.41, 45.31, 45.10, 43.72, 43.35, 39.92, 28.32, 28.29, 26.87, 20.41; LRMS (ESI): *m/z* calcd for $C_{31}H_{45}N_6O_4^+$ $[M+H]^+$: 565.35; Found: 565.2.

1-[9-Benzyl-4-[benzyl(methyl)amino]-7,8-dihydro-5_H_-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1a)

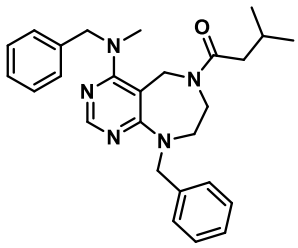


To a solution of **9a** (40.8 mg, 0.088 mmol) in 1.8 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 271.7 mg, 2.38 mmol, 26.8 equiv.) at r.t, stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.83 mL of DMF (0.1 M). Dry TEA (44.9 mg, 0.44 mmol, 5 equiv.) and **S1** (31.0 mg, 0.13 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1a** (38.7 mg, 91% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (d, *J* = 11.7 Hz, 1H), 7.42–7.18 (m, 13H), 7.14–7.09 (m, 0.7H), 7.09–7.04 (m, 1.3H), 4.82 (s, 1.3H), 4.60 (s, 0.7H), 4.58 (s, 0.7H), 4.50 (s, 0.7H), 4.47 (s, 1.3H), 4.41 (s, 1.3H), 3.88 (t, *J* = 5.7 Hz, 1H), 3.58–3.52 (m, 2.5H), 3.52 (s, 0.7H), 3.44 (s, 1.3H), 2.85 (s, 1H), 2.83 (s, 2H), 1.94 (m, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.78, 170.39, 167.10, 166.46, 164.06, 163.71, 155.39, 155.03, 138.77, 138.27, 138.16, 137.82, 134.83, 134.56, 128.92, 128.78, 128.74, 128.69, 128.67, 128.65, 128.48, 127.91, 127.89, 127.83, 127.81, 127.50, 127.43, 127.38, 127.16, 126.92, 126.87, 96.84, 96.30, 77.41, 77.16, 76.91, 57.28, 56.63, 52.23, 51.89, 48.07, 47.38, 46.53, 45.56, 44.72, 42.40, 41.34, 41.17, 39.26; LRMS (ESI): *m/z* calcd for $C_{30}H_{32}N_5O^+$ $[M+H]^+$: 478.26; Found: 478.1.

1-[9-Benzyl-4-[benzyl(methyl)amino]-7,8-dihydro-5_H_-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1b)

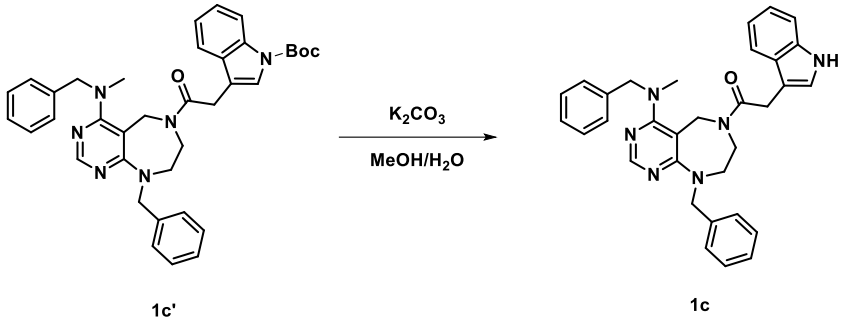
To a solution of **9a** (40.8 mg, 0.088 mmol, 1.0 equiv.) in 1.8 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 271.7 mg, 2.38 mmol, 26.8 equiv.) at r.t, stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant



was dissolved in 0.83 mL of DMF (0.1 M). Dry TEA (44.9 mg, 0.44 mmol, 5 equiv.) and **S2** (26.5 mg, 0.13 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1b** (17.6 mg, 45% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 16.2 Hz, 1H), 7.41–7.23 (m, 10H), 4.89 (s, 0.6H), 4.84 (s, 1.4H), 4.61 (s, 0.5H), 4.58 (s, 0.5H), 4.54 (s, 1.5H), 4.43 (s, 1.5H), 3.89 (t, *J* = 5.7 Hz, 1H), 3.66 (t, *J* = 5.4 Hz, 0.5H), 3.63–3.53 (m, 2H), 2.87 (d, *J* = 5.2 Hz, 3H), 2.09–1.99 (m, 1H), 1.97 (d, *J* = 6.9 Hz, 0.6H), 1.94 (d, *J* = 7.0 Hz, 1.4H), 1.79 (s, 0.5H), 0.90 (d, *J* = 6.6 Hz, 1.5H), 0.80 (d, *J* = 6.5 Hz, 4.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.44, 171.95, 167.13, 166.66, 164.33, 163.87, 155.41, 155.04, 138.80, 138.30, 138.24, 138.11, 128.83, 128.70, 128.67, 128.03, 127.93, 127.88, 127.71, 127.53, 127.41, 127.18, 97.52, 96.62, 57.22, 56.75, 52.53, 52.26, 48.18, 47.98, 46.55, 45.36, 44.54, 42.28, 42.25, 39.69, 39.15, 25.68, 25.48, 22.84, 22.61; LRMS (ESI): *m/z* calcd for $C_{27}H_{34}N_5O^+$ $[M+H]^+$: 444.27; Found: 444.2.

1-[9-Benzyl-4-[benzyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-(1*H*-indol-3-yl)ethanone (1c)



1c' 1c

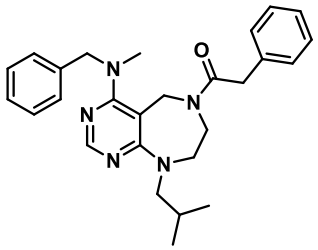
To a solution of **9a** (40.8 mg, 0.088 mmol) in 1.8 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 271.7 mg, 2.38 mmol, 26.8 equiv.) at r.t, stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.83 mL of DMF (0.1 M). Dry TEA (44.9 mg, 0.44 mmol, 5 equiv.) and **S5** (49.6 mg, 0.13 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1c′** (22 mg, 41% overall yield) as a white solid. To a solution of **1c′** (22 mg, 0.035 mmol) in MeOH/H2O co-solvent (1.0 mL/0.35 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 24.6 mg, 0.178 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1c** (16.1 mg, 87% yield) as a white solid.

1c′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.16 (m, 2H), 7.45–7.14 (m, 14H), 4.72 (m, 2H), 4.60–4.35 (m, 4H), 4.03–3.75 (m, 1.5H), 3.63–3.56 (m, 1.5H), 3.56–3.49 (m, 3H), 2.86 (s, 1H), 2.76 (s, 2H), 1.65 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.31, 169.89, 167.15, 166.61, 163.95, 163.73, 155.27, 155.05, 149.63, 138.80, 138.31, 138.22, 137.77, 135.55, 130.00, 128.82, 128.75, 128.70, 128.68, 127.94, 127.91, 127.49, 127.47, 127.42, 127.19, 124.86, 124.78, 123.75, 123.60, 122.85, 122.73, 119.03, 115.43, 115.41, 113.99,

113.78, 96.73, 96.39, 83.98, 83.72, 57.60, 56.69, 52.11, 51.96, 48.32, 47.50, 46.27, 45.81, 44.83, 42.53, 39.33, 38.83, 31.56, 31.45, 28.34, 28.32; LRMS (ESI): *m/z* calcd for $C_{37}H_{41}N_6O_3^+$ $[M+H]^+$: 617.32; Found: 617.2.

1c ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.52–8.48 (m, 0.3H), 8.40–8.24 (m, 0.7H), 8.22 (s, 0.35H), 8.17 (s, 0.65H), 7.52 (dd, *J* = 7.8, 5.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.35 (dt, *J* = 25.7, 7.5 Hz, 3H), 7.28–7.18 (m, 7H), 7.17–7.06 (m, 2H), 6.92 (d, *J* = 2.4 Hz, 0.35H), 6.82 (d, *J* = 2.3 Hz, 0.65H), 4.83 (s, 1.3H), 4.64 (s, 0.7H), 4.62 (s, 0.8H), 4.47 (s, 1.2H), 4.39 (s, 1.3H), 4.29 (s, 0.7H), 3.93 (t, *J* = 5.9 Hz, 1H), 3.73–3.60 (m, 3H), 3.57 (t, *J* = 5.8 Hz, 1.3H), 3.47 (t, *J* = 5.6 Hz, 0.7H), 2.89 (s, 1H), 2.76 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.47, 171.28, 167.10, 166.50, 163.97, 163.76, 155.13, 154.99, 138.60, 138.32, 138.22, 137.75, 136.27, 136.25, 128.74, 128.69, 127.90, 127.86, 127.81, 127.62, 127.41, 127.40, 127.38, 127.21, 127.08, 127.00, 122.73, 122.43, 122.35, 119.80, 119.70, 118.78, 118.38, 111.52, 111.29, 108.83, 108.73, 96.84, 96.36, 57.45, 56.65, 52.19, 51.59, 47.98, 47.10, 46.44, 45.77, 44.72, 42.40, 39.34, 38.87, 31.75, 31.48; LRMS (ESI): *m/z* calcd for $C_{37}H_{41}N_6O_3^+$ $[M+H]^+$: 517.27; Found: 517.2.

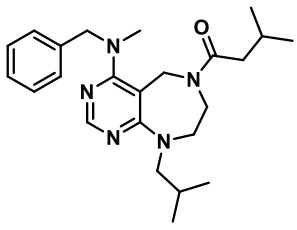
1-[4-[Benzyl(methyl)amino]-9-isobutyl-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1d)



To a solution of **9b** (162 mg, 0.38 mmol) in EtOAc/MeOH co-solvent (3.82 mL/3.82 mL; 1:1, 0.05 M) was added Pd/C (30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 35.7 mg of crude resultant was dissolved in 1.6 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 255.8 mg, 2.24 mmol, 26.7 equiv.) was added. The reaction mixture was stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.78 mL of DMF (0.1 M). Dry TEA (42.5 mg, 0.42 mmol, 5 equiv.) and **S1** (29.4 mg, 0.125 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1d** (23.9 mg, 64% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.14 (s, 1H), 7.40–7.02 (m, 10H), 4.58 (d, *J* = 32.0 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 3H), 3.94 (t, *J* = 5.7 Hz, 1H), 3.73 (d, *J* = 5.3 Hz, 1H), 3.63 (m, 2H), 3.43 (d, *J* = 6.6 Hz, 3H), 3.12 (d, *J* = 7.6 Hz, 0.5H), 2.81 (d, *J* = 10.2 Hz, 3H), 2.02 (m, 1H), 1.88 (s, 0.5H), 0.87 (dd, *J* = 9.5, 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.66, 170.31, 166.98, 166.44, 164.24, 164.16, 155.06, 154.85, 138.38, 137.92, 134.73, 134.58, 128.93, 128.77, 128.72, 128.63, 128.56, 127.92, 127.85, 127.47, 127.13, 126.96, 126.85, 96.92, 96.21, 57.47, 57.25, 56.78, 56.70, 49.14, 48.70, 48.21, 45.60, 45.54, 42.44, 41.45, 41.15, 39.26, 39.24, 27.88, 27.83, 20.24, 20.21; LRMS (ESI): *m/z* calcd for $C_{27}H_{34}N_5O^+$ $[M+H]^+$: 444.27; Found: 444.2.

1-[4-[Benzyl(methyl)amino]-9-isobutyl-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1e)

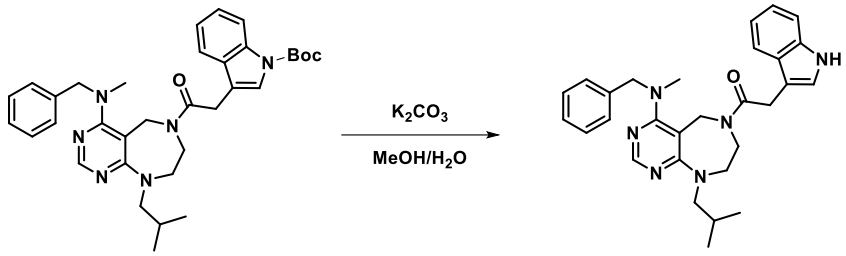


To a solution of **9b** (162 mg, 0.38 mmol) in EtOAc/MeOH co-solvent (3.82 mL/3.82 mL; 1:1, 0.05 M) was added Pd/C (30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 35.7 mg of crude resultant was dissolved in 1.6 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 255.8 mg, 2.24 mmol, 26.7 equiv.) was added. The reaction mixture was stirred at r.t for 5 h. After the

completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.78 mL of DMF (0.1 M). Dry TEA (42.5 mg, 0.42 mmol, 5 equiv.) and **S2** (25.1 mg, 0.125 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1e** (14.1 mg, 41% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.17 (d, *J* = 20.3 Hz, 1H), 7.38–7.24 (m, 5H), 4.61 (s, 0.4H), 4.52 (d, *J* = 29.5 Hz, 2H), 4.42 (s, 1.6H), 3.94 (t, *J* = 5.7 Hz, 1.5H), 3.79 (d, *J* = 5.4 Hz, 0.3H), 3.70 (t, *J* = 5.8 Hz, 1.7H), 3.44 (dd, *J* = 9.9, 7.5 Hz, 2H), 2.84 (s, 3H), 2.20 (d, *J* = 6.8 Hz, 0.5H), 2.03 (m, 2H), 1.93 (d, *J* = 6.9 Hz, 1.5H), 1.78 (s, 0.5H), 0.92 (dd, *J* = 14.1, 6.6 Hz, 7H), 0.79 (d, *J* = 6.5 Hz, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.26, 171.84, 166.99, 166.60, 164.43, 164.29, 155.08, 154.86, 138.40, 138.20, 128.80, 128.65, 127.94, 127.73, 127.48, 127.14, 97.56, 96.52, 57.37, 57.33, 56.75, 49.86, 48.72, 48.14, 45.40, 45.26, 42.40, 42.31, 39.69, 39.14, 28.02, 27.88, 25.67, 25.63, 22.88, 22.62, 20.31, 20.29; LRMS (ESI): *m/z* calcd for $C_{24}H_{35}N_5O^+$ $[M+H]^+$: 410.29; Found: 410.2.

1-[4-[Benzyl(methyl)amino]-9-isobutyl-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-(1*H*-indol-3-yl)ethanone (1f)



1f' 1f

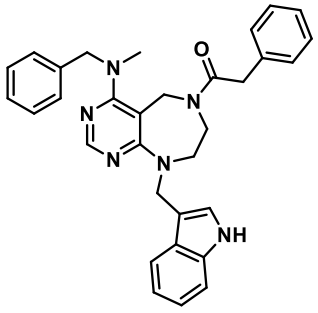
To a solution of **9b** (162 mg, 0.38 mmol) in EtOAc/MeOH co-solvent (3.82 mL/3.82 mL; 1:1, 0.05 M) was added Pd/C (30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 35.7 mg of crude resultant was dissolved in 1.6 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 255.8 mg, 2.24 mmol, 26.7 equiv.) was added. The reaction mixture was stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.78 mL of DMF (0.1 M). Dry TEA (42.5 mg, 0.42 mmol, 5 equiv.) and **S5** (46.9 mg, 0.125 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1f′** (22.4 mg, 46% overall yield) as a white solid. To a solution of **1f′** (22 mg, 0.037 mmol) in MeOH/H2O co-solvent (1.1 mL/0.38 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 26.1 mg, 0.189 mmol, 5.0 equiv.), stirred at 70 °C for 5 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1f** (14.1 mg, 77% yield) as a white solid.

1f′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.13 (d, *J* = 4.6 Hz, 2H), 7.50–7.27 (m, 4H), 7.25–7.13 (m, 5H), 4.62 (s, 0.4H), 4.50 (d, *J* = 50.8 Hz, 2H), 4.34 (s, 1.6H), 3.97 (t, *J* = 5.6 Hz, 1.5H), 3.77 (d, *J* = 8.4 Hz, 1H), 3.69 (t, *J* = 5.8 Hz, 1.5H), 3.62 (d, *J* = 5.5 Hz, 0.5H), 3.48–3.41 (m, 3H), 3.10 (d, *J* = 7.5 Hz, 0.5H), 2.82 (s, 0.7H), 2.74 (s, 2.3H), 2.10–1.95 (m, 1H), 1.66 (d, *J* = 2.7 Hz, 9H), 0.89 (d, *J* = 6.7 Hz, 5H), 0.84 (d, *J* = 6.7 Hz, 1H); ^{13}C

NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.04, 169.78, 166.98, 166.59, 164.14, 164.12, 155.06, 154.83, 149.65, 138.39, 137.79, 135.55, 130.07, 128.70, 128.64, 127.91, 127.49, 127.37, 127.14, 124.83, 124.71, 123.80, 123.67, 122.84, 122.72, 119.08, 118.93, 115.44, 115.35, 113.88, 96.84, 96.22, 83.93, 83.68, 57.77, 57.19, 56.70, 48.96, 48.50, 48.30, 45.63, 45.61, 42.49, 39.30, 38.83, 31.53, 31.32, 28.34, 28.32, 27.89, 27.84, 20.29, 20.23; LRMS (ESI): *m/z* calcd for $C_{34}H_{43}N_6O_3^+$ $[M+H]^+$: 583.33; Found: 583.2.

1f ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (m, 2H), 7.51 (dd, *J* = 28.8, 7.9 Hz, 1H), 7.40–7.30 (m, 2H), 7.26–7.07 (m, 6H), 6.93–6.76 (m, 1H), 4.61 (s, 0.5H), 4.55 (s, 0.5H), 4.42 (s, 1.5H), 4.31 (s, 1.5H), 3.95 (t, *J* = 5.7 Hz, 1.5H), 3.82 (s, 0.5H), 3.76 (t, *J* = 5.4 Hz, 0.5H), 3.66 (t, *J* = 5.8 Hz, 1.5H), 3.56 (s, 2H), 3.42 (d, *J* = 7.5 Hz, 1.5H), 2.94 (d, *J* = 7.6 Hz, 0.5H), 2.82 (s, 0.7H), 2.68 (s, 2.3H), 2.05 (dt, *J* = 13.8, 6.9 Hz, 0.75H), 1.91 (dt, *J* = 13.8, 6.9 Hz, 0.25H), 0.88 (d, *J* = 6.7 Hz, 4.5H), 0.79 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.27, 171.14, 166.96, 166.50, 164.15, 164.09, 154.88, 154.79, 138.42, 137.82, 136.27, 128.71, 128.67, 127.93, 127.66, 127.37, 127.17, 127.14, 127.05, 122.73, 122.48, 122.31, 119.76, 119.69, 118.83, 118.35, 111.48, 111.26, 108.81, 108.78, 96.93, 96.19, 57.63, 57.22, 56.69, 56.54, 48.94, 48.61, 48.14, 45.71, 45.55, 42.39, 39.32, 38.84, 31.64, 31.53, 27.89, 27.72, 20.28, 20.18; LRMS (ESI): *m/z* calcd for $C_{29}H_{35}N_6O^+$ $[M+H]^+$: 483.28 Found: 483.1.

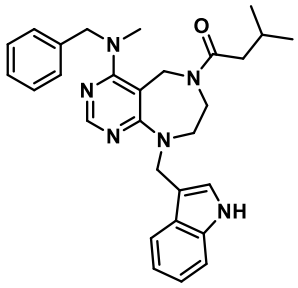
1-[4-[Benzyl(methyl)amino]-9-(1*H*-indol-3-ylmethyl)-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1g)



To a solution of **9c** (40 mg, 0.067 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;205 mg, 1.80 mmol, 26.9 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 27.7 mg, 0.200 mmol, 3.0 equiv.), stirred at 70 °C for 2.5 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 0.63 mL of DMF (0.1 M) and TEA (20.3 mg, 0.200 mmol, 3.0 equiv.), **S1** (23.35 mg, 0.100 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1g** (21.9 mg, 63% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.39 (d, *J* = 31.7 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 52.9, 7.9 Hz, 1H), 7.40–7.29 (m, 4H), 7.27–7.05 (m, 9H), 6.89 (dd, *J* = 7.0, 1.8 Hz, 1H), 5.01 (s, 1.2H), 4.87 (s, 0.8H), 4.58–4.37 (m, 4H), 3.82 (t, *J* = 5.6 Hz, 1H), 3.59 (m, 2H), 3.42 (s, 1H), 3.24 (t, *J* = 5.5 Hz, 1H), 2.90 (s, 1H), 2.82 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.83, 170.67, 167.18, 166.56, 164.04, 163.60, 155.38, 154.93, 138.35, 137.90, 136.53, 135.00, 134.69, 128.81, 128.77, 128.72, 128.70, 128.68, 128.61, 127.96, 127.87, 127.52, 127.21, 127.18, 127.11, 126.92, 126.70, 124.07, 123.73, 122.72, 122.34, 120.32, 119.83, 119.40, 119.34, 113.34, 112.50, 111.48, 111.36, 97.14, 96.79, 57.42, 56.79, 48.87, 47.22, 45.82, 45.65, 45.10, 43.53, 43.31, 42.40, 41.15, 40.69, 39.30; LRMS (ESI): *m/z* calcd for $C_{32}H_{33}N_6O^+$ $[M+H]^+$: 517.27; Found: 517.2.

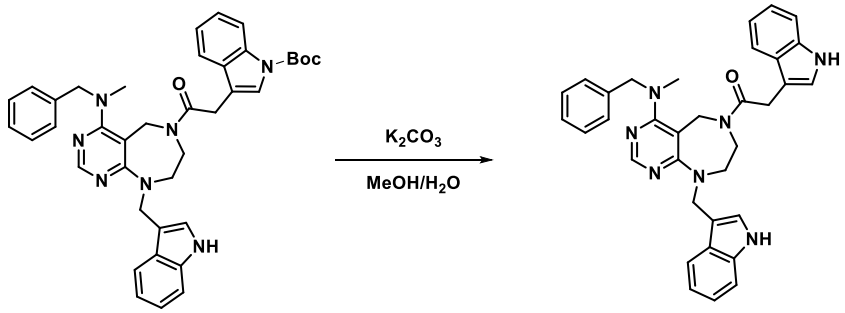
1-[4-[Benzyl(methyl)amino]-9-(1*H*-indol-3-ylmethyl)-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1h)



To a solution of **9c** (40 mg, 0.067 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;205 mg, 1.80 mmol, 26.9 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 27.7 mg, 0.200 mmol, 3.0 equiv.), stirred at 70 °C for 2.5 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 0.63 mL of DMF (0.1 M) and TEA (20.3 mg, 0.200 mmol, 3.0 equiv.), **S2** (20.0 mg, 0.100 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1h** (13.4 mg, 42% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.36–8.25 (m, 2H), 7.7–7.54 (m, 1H), 7.41–7.26 (m, 6H), 7.24–7.17 (m, 2H), 7.12–7.07 (m, 1H), 5.04 (d, *J* = 27.7 Hz, 2H), 4.58–4.38 (m, 4H), 3.88–3.79 (m, 1.3H), 3.70 (t, *J* = 5.5 Hz, 0.7H), 3.59 (t, *J* = 5.8 Hz, 1.3H), 3.35 (t, *J* = 5.5 Hz, 0.7H), 2.85 (d, *J* = 8.2 Hz, 3H), 2.04–1.98 (m, 0.75H), 1.94 (d, *J* = 6.9 Hz, 1.5H), 1.88–1.82 (m, 0.25H), 1.44 (d, *J* = 7.0 Hz, 0.5H), 0.81 (d, *J* = 6.5 Hz, 4H), 0.74 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.47, 172.10, 167.15, 166.68, 164.25, 163.75, 155.35, 154.92, 138.37, 138.18, 136.52, 128.84, 128.66, 127.97, 127.73, 127.52, 127.27, 127.16, 127.13, 124.08, 123.71, 122.70, 122.38, 120.31, 119.87, 119.41, 113.41, 112.62, 111.37, 111.33, 97.74, 97.08, 57.29, 56.87, 48.41, 47.73, 45.79, 45.45, 44.84, 43.68, 43.48, 42.29, 42.16, 41.70, 39.69, 39.16, 25.70, 25.18, 22.71, 22.65; LRMS (ESI): *m/z* calcd for $C_{29}H_{35}N_6O^+$ $[M+H]^+$: 483.28; Found: 483.2.

1-[4-[Benzyl(methyl)amino]-9-(1*H*-indol-3-ylmethyl)-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-(1*H*-indol-3-yl)ethanone (1i)



1i' 1i

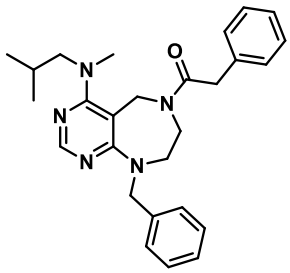
To a solution of **9c** (40 mg, 0.067 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;205 mg, 1.80 mmol, 26.9 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 27.7 mg, 0.200 mmol, 3.0 equiv.), stirred at 70 °C for 2.5 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 0.63 mL of DMF (0.1 M) and TEA

(20.3 mg, 0.200 mmol, 3.0 equiv.), **S5** (37.3 mg, 0.100 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1i′** (14.2 mg, 32% overall yield) as a white solid. To a solution of **1i′** (14.2 mg, 0.022 mmol) in MeOH/H2O co-solvent (0.65 mL/0.22 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 15.0 mg, 0.108 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1i** (3.2 mg, 27% yield) as a white solid.

1i′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.31–8.22 (m, 2H), 8.11 (d, *J* = 33.4 Hz, 1H), 7.70–7.54 (m, 1H), 7.40–7.28 (m, 5H), 7.23–7.07 (m, 8H), 4.96 (m, 2H), 4.56 (s, 1.6H), 4.42 (s, 1.4H), 4.35 (s, 1H), 3.85 (s, 1H), 3.60 (dt, *J* = 30.2, 5.7 Hz, 2.3H), 3.49 (d, *J* = 1.2 Hz, 1H), 3.27 (t, *J* = 5.5 Hz, 0.7H), 2.87 (m, 1H), 2.79 (d, *J* = 42.6 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.26, 170.05, 167.19, 166.66, 163.89, 163.58, 155.23, 154.92, 138.35, 137.81, 136.54, 136.50, 130.07, 128.75, 128.67, 127.95, 127.48, 127.41, 127.25, 127.17, 127.10, 124.78, 124.64, 124.08, 123.79, 123.68, 122.82, 122.75, 122.66, 122.37, 120.41, 119.85, 119.50, 119.35, 119.07, 115.42, 115.30, 114.10, 113.89, 113.43, 112.54, 111.48, 111.34, 97.06, 96.86, 83.88, 83.75, 57.69, 56.82, 49.12, 47.22, 45.84, 45.63, 45.21, 43.39, 43.30, 42.46, 39.31, 38.86, 31.41, 30.55, 28.34, 0.13; LRMS (ESI): *m/z* calcd for $C_{39}H_{42}N_7O_3^+$ $[M+H]^+$: 656.33; Found: 656.2.

1i ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.26 (d, *J* = 29.8 Hz, 1H), 8.15–7.97 (m, 2H), 7.69–7.48 (m, 2H), 7.42–7.30 (m, 4H), 7.25–7.07 (m, 7H), 7.04 (d, *J* = 2.4 Hz, 0.6H), 6.87 (d, *J* = 2.4 Hz, 0.4H), 6.79 (d, *J* = 2.4 Hz, 0.4H), 6.74 (d, *J* = 2.3 Hz, 0.6H), 5.00 (s, 1H), 4.64 (m, 2.5H), 4.39 (m, 2.5H), 3.84 (s, 1.2H), 3.59 (d, *J* = 7.4 Hz, 2H), 3.53 (t, *J* = 5.5 Hz, 1H), 3.37 (t, *J* = 5.6 Hz, 1H), 3.22 (s, 0.8H), 2.85 (s, 1.2H), 2.73 (s, 1.8H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.33, 155.12, 138.42, 136.46, 136.26, 128.77, 128.70, 127.98, 127.66, 127.43, 127.18, 123.97, 123.70, 122.67, 122.47, 122.41, 122.33, 119.82, 119.77, 119.33, 119.01, 118.55, 112.62, 111.40, 111.34, 111.29, 108.96, 97.19, 96.91, 57.57, 48.76, 46.87, 46.21, 45.91, 45.18, 43.69, 42.38, 39.37, 38.94, 31.64; LRMS (ESI): *m/z* calcd for $C_{34}H_{34}N_7O^+$ $[M+H]^+$: 556.28; Found: 556.0.

1-[9-Benzyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1j)

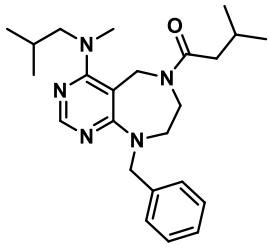


To a solution of **9d** (32.7 mg, 0.077 mmol) in 1.4 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;215 mg, 1.90 mmol, 24.6 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.71 mL of DMF (0.1 M). Dry TEA (38.8 mg, 0.38 mmol, 5 equiv.) and **S1** (26.8 mg, 0.115 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1j** (29.7 mg, 87% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.16 (d, *J* = 4.8 Hz, 1H), 7.30 (q, *J* = 7.4 Hz, 3H), 7.27–7.17 (m, 5H), 7.09 (dd, *J* = 27.3, 7.4 Hz, 2H), 4.83–4.40 (m, 4H), 3.91 (t, *J* = 5.8 Hz, 1.3H), 3.63–3.52 (m, 2.7H), 3.51 (s, 0.8H), 3.42 (s, 1.2H), 3.25 (d, *J* = 7.4 Hz, 0.7H), 3.07 (d, *J* = 7.4 Hz, 1.3H), 2.94 (d, *J* = 9.3 Hz, 3H), 2.03 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 2H), 0.88 (d, *J* = 6.7 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.83, 170.37, 167.25, 166.79, 164.10, 163.75, 155.32, 154.87, 138.87, 138.26, 134.88, 134.68, 128.93, 128.77, 128.68, 128.66, 128.61, 127.98, 127.86, 127.43, 127.36, 126.91, 126.85, 96.67, 95.84, 60.96, 60.03, 52.17,

51.95, 48.13, 47.60, 46.54, 45.87, 44.79, 42.71, 41.42, 40.90, 40.81, 39.89, 29.80, 26.99, 26.87, 20.42, 20.34; LRMS (ESI): *m/z* calcd for $C_{27}H_{34}N_5O^+$ $[M+H]^+$: 444.27; Found: 444.2.

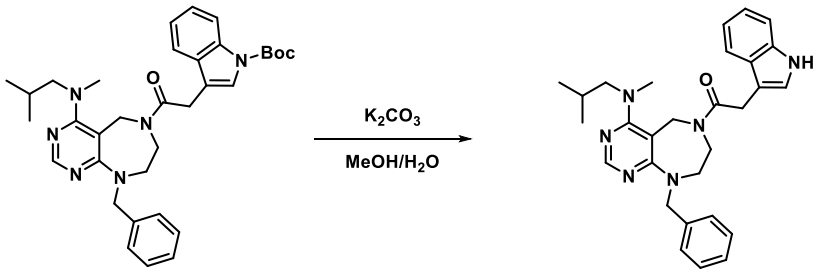
1-[9-Benzyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1k)



To a solution of **9d** (32.7 mg, 0.077 mmol) in 1.4 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;215 mg, 1.90 mmol, 24.6 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.71 mL of DMF (0.1 M). Dry TEA (38.8 mg, 0.38 mmol, 5.0 equiv.) and **S2** (22.9 mg, 0.115 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1k** (17.8 mg, 57% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.17 (d, *J* = 10.6 Hz, 1H), 7.35–7.22 (m, 5H), 4.84 (d, *J* = 29.1 Hz, 2H), 4.48 (d, *J* = 70.1 Hz, 2H), 3.92 (t, *J* = 5.9 Hz, 1.5H), 3.64 (t, *J* = 5.4 Hz, 0.5H), 3.59 (q, *J* = 5.9, 5.2 Hz, 2H), 3.23 (t, *J* = 7.4 Hz, 2H), 2.95 (d, *J* = 17.3 Hz, 3H), 2.03 (dt, *J* = 13.4, 6.8 Hz, 2H), 1.98 (d, *J* = 7.0 Hz, 0.5H), 1.89 (d, *J* = 7.1 Hz, 1.5H), 0.96–0.72 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.51, 171.91, 167.22, 166.96, 164.36, 163.90, 155.16, 154.90, 138.84, 138.33, 128.81, 128.67, 128.05, 127.89, 127.48, 127.36, 97.22, 96.03, 60.20, 60.18, 52.52, 52.06, 48.41, 47.86, 46.43, 45.68, 44.52, 42.51, 42.30, 42.06, 41.20, 40.53, 29.81, 26.99, 26.84, 25.61, 25.51, 22.86, 22.49, 20.53, 20.37; LRMS (ESI): *m/z* calcd for $C_{24}H_{36}N_5O^+$ $[M+H]^+$: 410.29; Found: 410.2.

1-[9-Benzyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-(1*H*-indol-3-yl)ethanone (1l)



1l' 1l

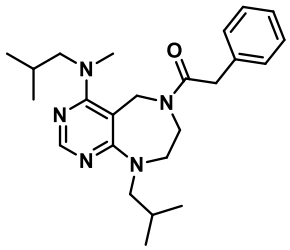
To a solution of **9d** (32.7 mg, 0.077 mmol) in 1.4 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;215 mg, 1.90 mmol, 24.6 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.71 mL of DMF (0.1 M). Dry TEA (38.8 mg, 0.38 mmol, 5.0 equiv.) and **S5** (42.8 mg, 0.115 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1l′** (11.2 mg, 25% overall yield) as a white solid. To a solution of **1i′** (11.2 mg, 0.019 mmol) in MeOH/H2O co-solvent (0.58 mL/0.19 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 13.3 mg, 0.096 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the

reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1l** (8.3 mg, 89% yield) as a white solid.

1l′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.14 (d, *J* = 10.3 Hz, 2H), 7.44–7.27 (m, 5H), 7.26–7.17 (m, 4H), 4.81 (s, 1.3H), 4.59 (s, 0.7H), 4.56 (s, 0.7H), 4.47 (s, 1.3H), 3.93 (d, *J* = 5.9 Hz, 1.4H), 3.58 (dd, *J* = 7.9, 4.2 Hz, 2.6H), 3.50 (d, *J* = 36.0 Hz, 2H), 3.25 (d, *J* = 7.4 Hz, 0.65H), 3.03 (d, *J* = 7.4 Hz, 1.35H), 2.92 (d, *J* = 30.4 Hz, 3H), 2.03 (m, 1H), 1.66 (d, *J* = 3.4 Hz, 9H), 0.93 (d, *J* = 6.6 Hz, 2H), 0.83 (d, *J* = 6.6 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.17, 169.86, 167.29, 166.84, 164.05, 163.75, 155.29, 154.90, 149.70, 138.89, 138.29, 135.53, 130.12, 128.83, 128.70, 127.96, 127.48, 127.41, 124.85, 124.66, 123.85, 123.77, 122.83, 122.67, 119.21, 115.43, 115.32, 113.99, 113.93, 96.61, 95.86, 84.00, 83.68, 61.09, 60.08, 52.12, 52.01, 48.33, 47.72, 46.31, 45.96, 44.91, 42.82, 40.85, 39.59, 31.48, 31.24, 28.37, 28.34, 27.04, 26.84, 20.36, 20.34; LRMS (ESI): *m/z* calcd for $C_{34}H_{43}N_6O_3^+$ $[M+H]^+$: 583.33; Found: 583.2.

1l ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.37 (d, *J* = 91.3 Hz, 1H), 8.16 (d, *J* = 18.0 Hz, 1H), 7.49 (dd, *J* = 34.7, 7.9 Hz, 1H), 7.37–7.21 (m, 6H), 7.19–7.13 (m, 1H), 7.10–7.06 (m, 1H), 6.91 (dd, *J* = 17.3, 2.3 Hz, 1H), 4.81 (s, 1.2H), 4.58 (s, 0.8H), 4.48 (s, 1.2H), 4.33 (s, 0.8H), 3.96 (t, *J* = 5.8 Hz, 1H), 3.69 (s, 0.8H), 3.64 (t, *J* = 5.5 Hz, 1H), 3.59 (t, *J* = 6.7 Hz, 2.2H), 3.47 (t, *J* = 5.5 Hz, 1H), 3.28 (d, *J* = 7.5 Hz, 0.8H), 3.02 (d, *J* = 7.4 Hz, 1.2H), 2.94 (d, *J* = 41.5 Hz, 3H), 2.07 (dt, *J* = 13.7, 6.9 Hz, 0.5H), 1.99 (dt, *J* = 13.6, 6.9 Hz, 0.5H), 0.96 (d, *J* = 6.7 Hz, 2.5H), 0.83 (d, *J* = 6.6 Hz, 3.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.42, 171.21, 167.26, 166.69, 164.04, 163.77, 155.09, 154.83, 138.70, 138.29, 136.25, 128.71, 128.68, 127.89, 127.88, 127.37, 127.18, 127.03, 122.75, 122.57, 122.36, 122.24, 119.79, 119.61, 118.89, 118.43, 111.50, 111.23, 108.91, 96.64, 95.90, 61.07, 60.04, 52.15, 51.66, 47.98, 47.33, 46.48, 46.06, 44.79, 42.70, 40.88, 39.58, 31.50, 31.31, 27.04, 26.86, 20.35; LRMS (ESI): *m/z* calcd for $C_{29}H_{35}N_6O^+$ $[M+H]^+$: 483.28; Found: 483.1.

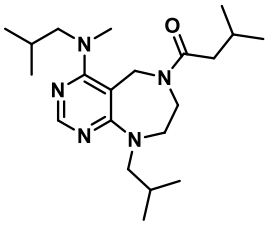
1-[9-Isobutyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1m)



To a solution of **9e** (33.5 mg, 0.086 mmol) in 1.7 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;262 mg, 2.30 mmol, 26.9 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.80 mL of DMF (0.1 M). Dry TEA (43.3 mg, 0.43 mmol, 5.0 equiv.) and **S1** (30.0 mg, 0.128 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1m** (20.9 mg, 60% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.33–7.02 (m, 5H), 4.54 (s, 0.5H), 4.41 (s, 1.5H), 3.96 (t, *J* = 5.7 Hz, 1H), 3.74 (d, *J* = 5.4 Hz, 1H), 3.69 (t, *J* = 5.8 Hz, 1.5H), 3.58 (t, *J* = 5.3 Hz, 0.5H), 3.40 (d, *J* = 7.2 Hz, 3H), 3.21 (d, *J* = 7.5 Hz, 0.5H), 3.15 (d, *J* = 7.6 Hz, 0.5H), 3.03 (d, *J* = 7.5 Hz, 1.5H), 2.91 (d, *J* = 6.2 Hz, 3H), 2.01 (dq, *J* = 13.7, 6.9 Hz, 2H), 1.86 (s, 0.5H), 0.91 (d, *J* = 6.6 Hz, 1.5H), 0.86 (dd, *J* = 6.7, 3.3 Hz, 11.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.67, 170.27, 167.11, 166.73, 164.23, 164.20, 154.95, 154.71, 134.78, 134.67, 128.93, 128.73, 128.71, 128.55, 126.96, 126.81, 96.67, 95.71, 61.09, 60.02, 57.17, 56.82, 49.42, 48.75, 48.17, 45.81, 45.72, 42.76, 41.50, 40.87, 40.67, 39.83, 27.95, 27.79, 26.94, 26.83, 20.43, 20.34, 20.23; LRMS (ESI): *m/z* calcd for $C_{24}H_{36}N_5O^+$ $[M+H]^+$: 410.29; Found: 410.2.

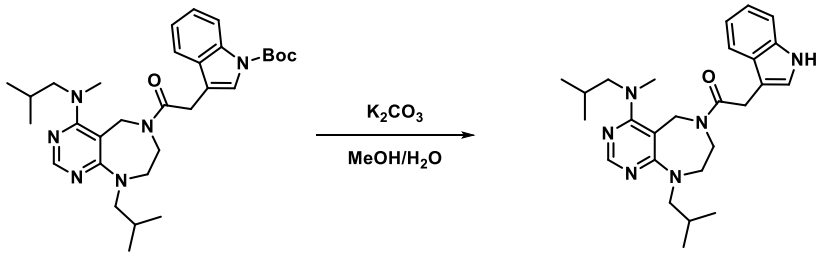
1-[9-Isobutyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1n)



To a solution of **9e** (33.5 mg, 0.086 mmol) in 1.7 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;262 mg, 2.30 mmol, 26.9 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.80 mL of DMF (0.1 M). Dry TEA (43.3 mg, 0.43 mmol, 5.0 equiv.) and **S2** (25.6 mg, 0.128 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1n** (18.4 mg, 58% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.11 (d, *J* = 12.3 Hz, 1H), 4.55 (s, 0.3H), 4.39 (s, 1.7H), 3.96 (t, *J* = 5.9 Hz, 1.6H), 3.81 (t, *J* = 5.4 Hz, 0.4H), 3.70 (q, *J* = 5.8 Hz, 2H), 3.42 (dd, *J* = 14.4, 7.6 Hz, 2H), 3.18 (dd, *J* = 13.3, 7.5 Hz, 2H), 2.92 (d, *J* = 19.5 Hz, 3H), 2.02 (m, 3H), 1.87 (d, *J* = 7.0 Hz, 2H), 0.95–0.91 (m, 6.5H), 0.90 (d, *J* = 6.7 Hz, 6.5H), 0.73 (d, *J* = 6.6 Hz, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.29, 171.79, 167.10, 166.88, 164.43, 164.33, 154.81, 154.74, 97.19, 95.94, 60.32, 60.15, 57.32, 57.15, 50.19, 48.62, 47.94, 45.54, 45.41, 42.59, 42.42, 42.08, 41.13, 40.40, 27.90, 26.94, 26.80, 25.68, 25.55, 22.91, 22.50, 20.54, 20.37, 20.29; LRMS (ESI): *m/z* calcd for $C_{21}H_{38}N_5O^+$ $[M+H]^+$: 376.30; Found: 376.2.

2-(1*H*-indol-3-yl)-1-[9-isobutyl-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]ethanone (1o)



1o' 1o

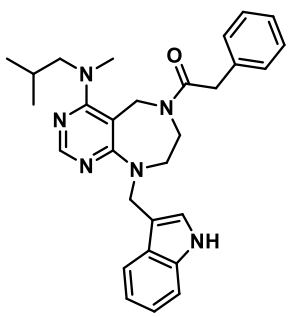
To a solution of **9e** (33.5 mg, 0.086 mmol) in 1.7 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;262 mg, 2.30 mmol, 26.9 equiv.), and stirred at r.t for 5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.80 mL of DMF (0.1 M). Dry TEA (43.3 mg, 0.43 mmol, 5.0 equiv.) and **S5** (47.8 mg, 0.128 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1o′** (36.7 mg, 78% overall yield) as a white solid. To a solution of **1o′** (35.0 mg, 0.064 mmol) in MeOH/H2O co-solvent (1.9 mL/0.64 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 44.1 mg, 0.319 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1o** (14.7 mg, 52% yield) as a white solid.

1o′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.12 (d, *J* = 23.2 Hz, 2H), 7.54–7.33 (m, 2H), 7.32–7.19 (m, 2H), 4.58 (s, 0.5H), 4.49 (s, 1.5H), 4.00 (t, *J* = 5.8 Hz, 1.5H), 3.81 (t, *J* = 5.4 Hz, 0.5H), 3.79 (s, 0.5H), 3.73 (t, *J* = 5.8 Hz, 1.5H), 3.62 (t, *J* = 5.3 Hz, 0.5H), 3.45 (t, *J* = 3.7 Hz, 3H), 3.22 (d, *J* = 7.6 Hz, 0.5H), 3.15 (d, *J* = 7.5

Hz, 0.5H), 3.02 (d, *J* = 7.4 Hz, 1.5H), 2.91 (d, *J* = 16.8 Hz, 3H), 2.07 (dt, *J* = 13.6, 6.9 Hz, 1H), 2.00 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.68 (s, 9H), 0.93 (d, *J* = 6.5 Hz, 1.5H), 0.90 (d, *J* = 6.6 Hz, 4.5H), 0.86 (d, *J* = 6.6 Hz, 1.5H), 0.82 (d, *J* = 6.6 Hz, 4.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.90, 169.73, 167.13, 166.81, 164.23, 164.20, 155.04, 154.74, 149.71, 135.52, 130.18, 124.84, 124.60, 123.91, 122.84, 122.66, 119.29, 115.46, 115.26, 114.01, 113.90, 96.66, 95.69, 83.64, 61.24, 60.03, 57.21, 56.77, 49.33, 48.59, 48.23, 45.81, 45.79, 42.82, 40.75, 39.61, 31.09, 28.37, 28.35, 27.98, 27.80, 26.99, 26.81, 20.35, 20.30, 20.25; LRMS (ESI): *m/z* calcd for $C_{31}H_{45}N_6O_3^+$ $[M+H]^+$: 549.35; Found: 549.2.

1o ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.54 (s, 0.3H), 8.35 (s, 0.7H), 8.13 (s, 0.7H), 8.11 (s, 0.3H), 7.51 (m, 1H), 7.33 (m, 1H), 7.23–7.05 (m, 2H), 6.91 (m, 1H), 4.57 (s, 0.6H), 4.47 (s, 1.4H), 4.00 (t, *J* = 5.7 Hz, 1.3H), 3.84 (s, 0.7H), 3.80 (t, *J* = 5.4 Hz, 0.6H), 3.71 (t, *J* = 5.8 Hz, 1.4H), 3.55 (s, 2H), 3.42 (d, *J* = 7.6 Hz, 1.4H), 3.23 (d, *J* = 7.4 Hz, 0.6H), 2.99 (dd, *J* = 13.4, 7.5 Hz, 2H), 2.93 (s, 1H), 2.85 (s, 2H), 2.04 (m, 1H), 1.95 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 2H), 0.88 (d, *J* = 6.7 Hz, 4H), 0.81 (dd, *J* = 8.3, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.21, 171.06, 167.09, 166.66, 164.20, 164.11, 154.82, 154.63, 136.28, 136.22, 127.22, 127.05, 122.77, 122.62, 122.28, 122.14, 119.70, 119.54, 118.89, 118.37, 111.49, 111.19, 108.88, 108.78, 96.65, 95.69, 61.18, 60.01, 57.16, 56.56, 49.20, 48.69, 48.05, 45.95, 45.66, 42.70, 40.76, 39.53, 31.56, 31.18, 27.94, 27.68, 26.98, 26.81, 20.33, 20.26, 20.18; LRMS (ESI): *m/z* calcd for $C_{26}H_{37}N_6O_3^+$ $[M+H]^+$: 449.30; Found: 449.2.

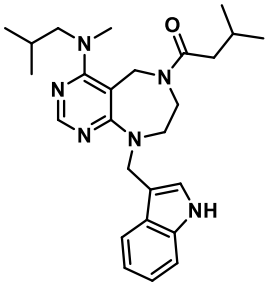
1-[9-(1*H*-indol-3-ylmethyl)-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-2-phenyl-ethanone (1p)



To a solution of **9f** (50 mg, 0.088 mmol) in 1.6 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;255 mg, 2.24 mmol, 25.3 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 36.7 mg, 0.265 mmol, 3.0 equiv.), stirred at 70 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 0.85 mL of DMF (0.1 M) and TEA (26.8 mg, 0.265 mmol, 3.0 equiv.), **S1** (30.9 mg, 0.133 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1p** (22.3 mg, 52% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.19 (d, *J* = 4.4 Hz, 1H), 7.58 (m, 1H), 7.39 (m, 1H), 7.35–6.95 (m, 8H), 6.83 (m, 1H), 4.99 (d, *J* = 4.5 Hz, 1H), 4.88 (d, *J* = 4.4 Hz, 1H), 4.45 (d, *J* = 4.1 Hz, 1H), 4.38 (d, *J* = 4.5 Hz, 1H), 3.78 (t, *J* = 5.4 Hz, 1H), 3.62 (dq, *J* = 10.5, 5.3 Hz, 2H), 3.27 (d, *J* = 4.1 Hz, 2H), 3.19 (dd, *J* = 9.1, 4.0 Hz, 2H), 3.01 (dd, *J* = 7.5, 4.5 Hz, 1H), 2.93 (dd, *J* = 10.6, 4.5 Hz, 3H), 2.80 (d, *J* = 4.5 Hz, 1H), 0.91 (dd, *J* = 6.6, 4.5 Hz, 3H), 0.85 (dd, *J* = 6.6, 4.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.23, 171.24, 166.93, 166.49, 163.81, 163.38, 155.01, 154.43, 136.45, 134.63, 134.32, 128.59, 128.58, 128.48, 128.44, 127.06, 126.93, 126.87, 126.61, 124.25, 123.93, 122.33, 121.91, 119.95, 119.41, 118.92, 112.45, 111.53, 111.48, 111.37, 96.68, 96.19, 61.09, 60.29, 49.72, 49.55, 49.38, 49.21, 49.04, 48.97, 48.86, 48.69, 47.21, 45.87, 45.66, 45.33, 43.33, 43.22, 42.68, 40.79, 40.46, 40.31, 39.44, 26.84, 26.73, 20.19, 20.12; LRMS (ESI): *m/z* calcd for $C_{29}H_{35}N_6O_3^+$ $[M+H]^+$: 483.28; Found: 483.2.

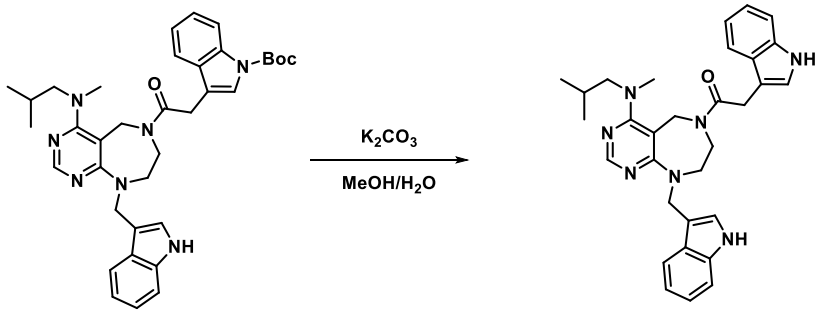
1-[9-(1*H*-indol-3-ylmethyl)-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]-3-methyl-butan-1-one (1q)



To a solution of **9f** (50 mg, 0.088 mmol) in 1.6 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;255 mg, 2.24 mmol, 25.3 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H_2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 36.7 mg, 0.265 mmol, 3.0 equiv.), stirred at 70 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 0.85 mL of DMF (0.1 M) and TEA (26.8 mg, 0.265 mmol, 3.0 equiv.), **S2** (26.4 mg, 0.133 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1q** (17.1 mg, 43% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.38 (s, 1H), 8.26 (d, *J* = 9.7 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 0.7H), 7.56 (d, *J* = 7.9 Hz, 0.3H), 7.35 (dd, *J* = 8.1, 4.1 Hz, 1H), 7.18 (ddd, *J* = 12.1, 6.2, 1.9 Hz, 2H), 7.12–7.06 (m, 1H), 5.04 (s, 0.5H), 4.99 (s, 1.5H), 4.49 (s, 0.5H), 4.37 (s, 1.5H), 3.87 (t, *J* = 5.8 Hz, 1.5H), 3.68 (t, *J* = 5.4 Hz, 0.5H), 3.58 (t, *J* = 5.8 Hz, 1.5H), 3.38 (t, *J* = 5.5 Hz, 0.5H), 3.21 (d, *J* = 7.5 Hz, 2H), 2.95 (s, 0.8H), 2.91 (s, 2.2H), 2.02 (hept, *J* = 6.7 Hz, 2H), 1.89 (d, *J* = 7.0 Hz, 1.5H), 1.48 (d, *J* = 7.0 Hz, 0.5H), 0.94 (d, *J* = 6.6 Hz, 4.5H), 0.90 (d, *J* = 6.6 Hz, 1.5H), 0.75 (dd, *J* = 6.7, 5.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 173.56, 172.09, 167.20, 166.97, 164.27, 163.79, 155.08, 154.76, 136.52, 136.49, 127.28, 127.14, 124.11, 123.77, 122.60, 122.31, 120.24, 119.81, 119.40, 119.33, 113.35, 112.61, 111.37, 111.31, 97.42, 96.47, 60.35, 60.25, 48.29, 47.91, 45.76, 45.65, 44.90, 43.65, 43.27, 42.46, 42.09, 41.77, 41.19, 40.42, 28.32, 27.00, 26.86, 25.64, 25.25, 22.72, 22.54, 20.55, 20.40; LRMS (ESI): *m/z* calcd for $C_{26}H_{37}N_6O_3^+$ $[M+H]^+$: 449.30; Found: 449.2.

2-(1*H*-indol-3-yl)-1-[9-(1*H*-indol-3-ylmethyl)-4-[isobutyl(methyl)amino]-7,8-dihydro-5*H*-pyrimido[4,5-e][1,4]diazepin-6-yl]ethanone (1r)



1r' 1r

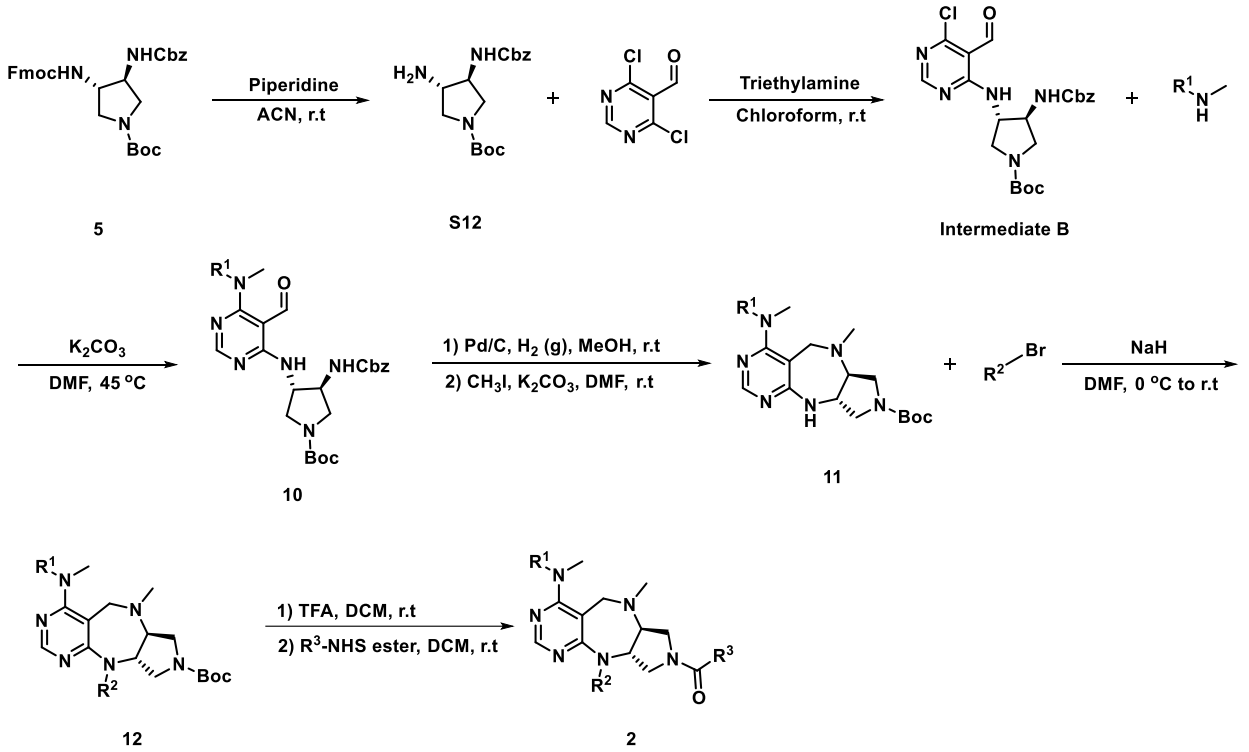
To a solution of **9f** (50 mg, 0.088 mmol) in 1.6 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;255 mg, 2.24 mmol, 25.3 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H_2O co-solvent (1.0 mL/0.33 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 36.7 mg, 0.265 mmol, 3.0 equiv.), stirred at 70 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent

was removed under reduced pressure. This crude mixture was dissolved in 0.85 mL of DMF (0.1 M) and TEA (26.8 mg, 0.265 mmol, 3.0 equiv.), **S5** (49.3 mg, 0.133 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 16 h. After the completion of the reaction, as indicated by TLC, LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **1r′** (16.2 mg, 26% overall yield) as a white solid. To a solution of **1r′** (16.2 mg, 0.026 mmol) in MeOH/H2O co-solvent (0.78 mL/0.26 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 18.0 mg, 0.130 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **1r** (6.7 mg, 50% yield) as a white solid.

1r′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.35–8.18 (m, 2H), 8.09 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 0.6H), 7.55 (d, *J* = 7.9 Hz, 0.4H), 7.40–7.26 (m, 3H), 7.26–7.01 (m, 5H), 5.01 (d, *J* = 7.6 Hz, 1.3H), 4.92 (s, 0.7H), 4.50 (s, 0.7H), 4.44 (s, 1.3H), 3.86 (t, *J* = 5.5 Hz, 1H), 3.64–3.56 (m, 2H), 3.45 (s, 1H), 3.28 (t, *J* = 5.5 Hz, 0.8H), 3.22 (d, *J* = 7.4 Hz, 1H), 3.02 (d, *J* = 7.4 Hz, 1H), 2.93 (m, 1.7H), 2.88 (s, 1.5H), 2.01 (m, 1H), 1.65 (d, *J* = 5.0 Hz, 9H), 0.92 (dd, *J* = 6.6, 3.0 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.12, 170.01, 167.25, 166.84, 163.96, 163.59, 155.21, 154.72, 136.52, 136.48, 130.09, 127.26, 127.12, 124.65, 124.63, 124.08, 123.91, 123.74, 123.72, 122.76, 122.68, 122.64, 122.32, 120.38, 119.81, 119.46, 119.32, 119.25, 119.07, 115.33, 115.29, 114.11, 114.02, 113.42, 112.54, 111.47, 111.33, 96.83, 96.33, 83.89, 83.70, 61.08, 60.28, 49.09, 47.33, 46.02, 45.72, 45.34, 43.37, 43.25, 42.74, 40.68, 39.64, 31.10, 30.65, 28.36, 28.34, 27.01, 26.82, 20.38, 20.34; LRMS (ESI): *m/z* calcd for $C_{36}H_{44}N_7O_3^+$ $[M+H]^+$: 622.35; Found: 622.2.

1r ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.24 (d, *J* = 15.7 Hz, 1H), 8.15 (d, *J* = 22.1 Hz, 1H), 8.10–8.02 (m, 1H), 7.64 (d, *J* = 7.9 Hz, 0.5H), 7.48 (dd, *J* = 13.8, 7.9 Hz, 1H), 7.33 (dd, *J* = 13.9, 8.4 Hz, 1H), 7.30–7.26 (m, 1.5H), 7.21–7.14 (m, 2H), 7.12–7.05 (m, 2H), 6.95 (d, *J* = 2.4 Hz, 0.5H), 6.84 (d, *J* = 2.4 Hz, 0.5H), 6.79 (d, *J* = 2.4 Hz, 0.5H), 6.75 (d, *J* = 2.3 Hz, 0.5H), 4.97 (s, 1H), 4.70 (s, 1H), 4.51 (s, 0.8H), 4.45 (s, 1.2H), 3.85 (m, 1H), 3.60 (t, *J* = 5.8 Hz, 1H), 3.55 (s, 1H), 3.51 (t, *J* = 5.5 Hz, 1H), 3.37 (t, *J* = 5.5 Hz, 1H), 3.25–3.20 (m, 1.75H), 3.01 (d, *J* = 7.4 Hz, 1H), 2.94 (s, 1.5H), 2.87 (s, 1.5H), 2.01 (ddq, *J* = 34.1, 13.6, 6.8 Hz, 1.15H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.34, 171.36, 167.25, 166.76, 163.95, 163.67, 155.07, 154.71, 136.44, 136.24, 136.12, 127.26, 127.21, 127.16, 127.05, 124.02, 123.81, 122.76, 122.71, 122.55, 122.24, 122.20, 120.16, 119.71, 119.61, 119.30, 119.20, 119.04, 118.52, 113.09, 112.42, 111.45, 111.42, 111.36, 111.28, 109.02, 109.00, 96.91, 96.41, 61.04, 60.21, 48.72, 47.03, 46.29, 46.17, 45.43, 43.63, 43.03, 42.70, 40.79, 39.73, 31.11, 30.95, 27.04, 26.86, 20.38, 20.36; LRMS (ESI): *m/z* calcd for $C_{31}H_{36}N_7O^+$ $[M+H]^+$: 522.29; Found: 522.1.

3.4. General Synthetic Procedure 2 for β-Strand mimetic Compounds(2a–2r) and Compound Characterization



General procedure 2:

To a solution of **5** (5.5 g. 9.86 mmol) in 90 mL of ACN (0.1 M) was added piperidine (8.40 g, 98.6 mmol, 10.0 equiv.) at r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, solvent was removed under reduced pressure, followed by short silica-gel flash column chromatography to afford **S12**.

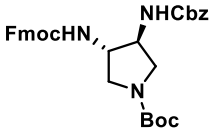
To a solution of **S12** (3.31 g, 9.87 mmol) in 92 mL of Chloroform (0.1 M) were added triethylamine (TEA; 3.99 g, 39.48 mmol, 4.0 equiv.) and 4,6-dichloropyrimidine-5-carbaldehyde (3.49 g, 19.74 mmol, 2.0 equiv.) at r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, the resultant was quenched with saturated NH_4Cl solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **Intermediate B** (3.28 g, 70% overall yield) as a white solid. A mixture of **Intermediate B** and K_2CO_3 (3 equiv.) were dissolved in dry DMF (0.1 M) and *N*-methyl-R^1 amine (1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **10a, 10b**.

To a solution of **10a**/**10b** in MeOH (0.1 M) was added Pd/C (30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for the indicated time. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in DMF (0.05 M). K_2CO_3 (5 equiv.) and methyl iodide (CH_3I; 3 equiv.) were sequentially added at r.t, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **11a, 11b**.

A mixture of **11a**/**11b** and sodium hydride (NaH; 60% dispersion in mineral oil, 3.0 equiv.) was cooled to 0 °C and dissolved in dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, R^2-Bromide (1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12a–12f**.

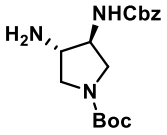
To a solution of **12a–12f** in DCM (0.05 M) was added trifluoroacetic acid (TFA; 10v/v% dissolved in DCM) at r.t, and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in DCM (0.05 M). Dry TEA (5.0 equiv.) and R^3-NHS ester (1.5 equiv.) were sequentially added and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2a–2r**.

***tert*-Butyl (3*S*,4*S*)-3-(benzyloxycarbonylamino)-4-(9*H*-fluoren-9-yl methoxy carbonylamino) pyrrolidine-1-carboxylate (5)**



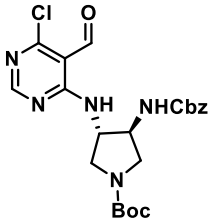
The synthesis of compound **5** was previously reported.[2]

***tert*-Butyl (3S,4S)-3-amino-4-(benzyloxycarbonylamino)pyrrolidine-1-carboxylate (S12)**



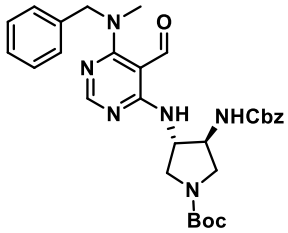
Following the general synthetic procedure 2, **S12** was obtained in crude product.

***tert*-Butyl (3*S*,4*S*)-3-(benzyloxycarbonylamino)-4-[(6-chloro-5-formyl-pyrimidin-4-yl)amino]pyrrolidine-1-carboxylate (Intermediate B)**



Following the general synthetic procedure 2, **Intermediate B** was obtained in 70% yield.

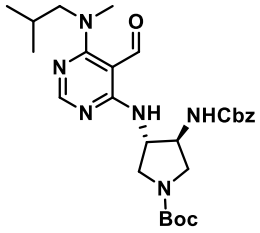
***tert*-Butyl (3*S*,4*S*)-3-[[6-[benzyl(methyl)amino]-5-formyl-pyrimidin-4-yl]amino]-4-(benzyloxycarbonylamino) pyrrolidine-1-carboxylate (10a)**



To a solution of **Intermediate B** (1.65 g, 3.47 mmol) in 16.7 mL of dry DMF (0.2 M) were added K_2CO_3 (1.44 g, 10.4 mmol, 3.0 equiv.) and *N*-methyl-benzylamine (630 mg, 5.20 mmol, 1.5 equiv.), stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **10a** (1.45 g, 75% overall yield) as a white solid.

The synthesis of compound **10a** was previously reported.[2]

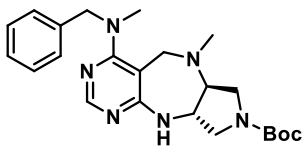
***tert*-Butyl (3*S*,4*S*)-3-(benzyloxycarbonylamino)-4-[[5-formyl-6-[isobutyl(methyl)amino]pyrimidin-4-yl]amino] pyrrolidine-1-carboxylate (10b)**



To a solution of **Intermediate B** (1.63 g, 3.42 mmol) in 16.5 mL of dry DMF (0.2 M) were added K_2CO_3 (1.42 g, 10.3 mmol, 3.0 equiv.) and *N*-methyl-isobutyl amine (448 mg, 5.14 mmol, 1.5 equiv.), stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **10b** (1.43 g, 79% overall yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) (as a mixture of rotamers): δ 9.81 (s, 1H), 9.28 (d, *J* = 7.3 Hz, 1H), 8.11 (d, *J* = 2.5 Hz, 1H), 7.32 (m, 5H), 6.51 (s, 0.5H), 6.09 (s, 0.5H), 5.07 (q, *J* = 12.6, 11.9 Hz, 2H), 4.72 (p, *J* = 8.0 Hz, 1H), 4.14–3.92 (m, 2H), 3.85 (m, 1H), 3.68–3.54 (m, 1H), 3.45 (m, 1H), 3.36–3.26 (m, 1H), 3.24 (s, 3H), 3.13 (m, 1H), 2.12 (hept, *J* = 6.8 Hz, 1H), 1.46 (s, 9H), 0.92 (dd, *J* = 6.7, 5.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (as a mixture of rotamers): δ 188.22, 167.15, 162.70, 159.30, 156.46, 156.26, 154.11, 136.45, 128.61, 128.33, 128.22, 128.17, 96.32, 80.06, 66.86, 60.17, 57.39, 56.23, 54.01, 53.12, 50.93, 49.98, 49.31, 48.54, 42.27, 28.54, 27.25, 20.10, 20.02; LRMS (ESI): *m/z* calcd for $C_{27}H_{39}N_6O_5^+$ $[M+H]^+$: 527.29; Found: 527.2.

***tert*-Butyl (6a*S*,9a*S*)-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (11a)**

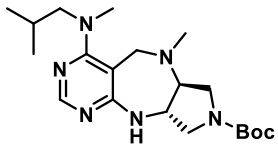


To a solution of **10a** (1.45 g, 2.59 mmol) in 26 mL of MeOH (0.1 M) was added Pd/C (435 mg, 30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 16 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in 51 mL of DMF (0.05 M). K_2CO_3 (1.78 g, 12.9 mmol, 5.0 equiv.) and methyl iodide (CH_3I; 1.10 g, 7.75 mmol, 3.0 equiv.) were sequentially added at r.t, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **11a** (530 mg, 48% overall yield).

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.14 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.33–7.28 (m, 3H), 5.16 (d, *J* = 9.7 Hz, 1H), 4.81–4.69 (m, 2H), 3.89 (dd, *J* = 10.0, 7.8 Hz, 0.5H), 3.80 (ddd, *J* = 10.9, 7.7, 4.2 Hz, 1H), 3.68 (dd, *J* = 10.2, 7.3 Hz, 0.5H), 3.59 (d, *J* = 13.8 Hz, 1H), 3.33 (t, *J* = 10.3 Hz, 1H), 3.14 (m, 2H), 3.03 (d, *J* = 2.3

Hz, 3H), 2.80 (d, *J* = 13.8 Hz, 1H), 2.39–2.29 (m, 1H), 2.02 (s, 3H), 1.46 (d, *J* = 7.1 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.52, 167.49, 166.85, 166.80, 154.76, 154.70, 154.28, 154.26, 138.36, 138.31, 128.77, 127.26, 127.12, 100.01, 99.89, 80.00, 79.91, 77.36, 71.71, 71.19, 59.98, 59.48, 57.38, 57.33, 57.27, 50.47, 50.01, 49.37, 48.85, 44.80, 38.10, 38.06, 28.55; LRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_6O_2^+$ $[M+H]^+$: 425.26; Found: 425.1.

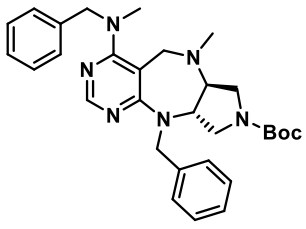
tert-Butyl (6a*S*,9a*S*)-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (11b)



To a solution of **10b** (1.43 g, 2.71 mmol) in 27 mL of MeOH (0.1 M) was added Pd/C (427 mg, 30 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 16 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in 53 mL of DMF (0.05 M). K_2CO_3 (1.87 g, 13.6 mmol, 5.0 equiv.) and methyl iodide (CH_3I; 1.15 g, 8.13 mmol, 3.0 equiv.) were sequentially added at r.t, and the resulting mixture was left to stir for 1 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, followed by silica-gel flash column chromatography to afford **11b** (543 mg, 52% overall yield).

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.07 (s, 1H), 5.12 (d, *J* = 21.9 Hz, 1H), 3.88 (tdd, *J* = 10.7, 7.1, 3.9 Hz, 2H), 3.80 (dd, *J* = 9.9, 7.8 Hz, 0.5H), 3.74 (dd, *J* = 10.3, 7.2 Hz, 0.5H), 3.59 (dd, *J* = 13.8, 1.9 Hz, 1H), 3.33 (t, *J* = 10.3 Hz, 1H), 3.16 (t, *J* = 10.1 Hz, 2H), 3.12 (d, *J* = 2.7 Hz, 3H), 2.92–2.81 (m, 2H), 2.44–2.38 (m, 1H), 2.37 (d, *J* = 4.4 Hz, 3H), 2.09–2.01 (m, 1H), 1.47 (s, 9H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.52, 166.91, 166.89, 154.59, 154.50, 154.31, 154.25, 99.60, 99.53, 79.97, 79.90, 77.36, 71.59, 71.03, 60.07, 59.53, 59.31, 59.25, 58.15, 58.12, 50.58, 50.16, 49.36, 48.88, 45.36, 40.07, 39.97, 28.57, 28.55, 26.90, 20.44, 19.85; LRMS (ESI): *m/z* calcd for $C_{20}H_{35}N_6O_2^+$ $[M+H]^+$: 391.282; Found: 391.1.

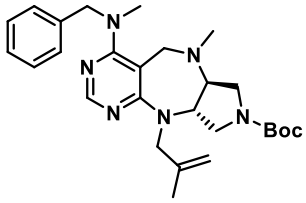
tert-Butyl (6a*S*,9a*S*)-10-benzyl-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e] pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (12a)



A mixture of **11a** (150 mg, 0.35 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 42.4 mg, 1.06 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.5 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (90.7 mg, 0.530 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12a** (141.3 mg, 78% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (s, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32–7.20 (m, 8H), 5.04 (m, 1H), 4.85–4.75 (m, 3H), 3.84 (dd, *J* = 10.0, 7.3 Hz, 0.5H), 3.70–3.61 (m, 1H), 3.59–3.49 (m, 2.5H), 3.44 (t, *J* = 10.2 Hz, 1H), 3.14–3.01 (m, 5H), 2.76 (m, 1H), 2.04 (s, 3H), 1.40 (d, *J* = 5.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.72, 166.86, 166.81, 154.73, 154.68, 154.19, 154.11, 140.12, 139.89, 138.75, 138.71, 128.72, 128.69, 128.65, 127.21, 127.16, 127.12, 127.08, 127.05, 99.53, 99.34, 79.81, 79.80, 77.36, 67.27, 66.82, 62.11, 61.41, 57.17, 57.08, 56.70, 50.23, 50.08, 49.27, 48.85, 48.53, 48.00, 43.07, 38.15, 38.10, 28.53, 28.47; LRMS (ESI): *m/z* calcd for $C_{30}H_{39}N_6O_2^+$ $[M+H]^+$: 515.31; Found: 515.2.

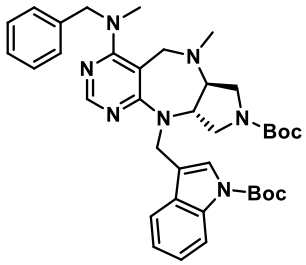
***tert*-Butyl (6a*S*,9a*S*)-4-(benzyl(methyl)amino)-6-methyl-10-(2-methylallyl)-5,6a,7,9,9a,10-hexahydropyrimido [4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (12b)**



A mixture of **11a** (170 mg, 0.40 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 48 mg, 1.20 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 4 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (81.1 mg, 0.600 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12b** (147.2 mg, 77% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.23 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31–7.25 (m, 3H), 4.94 (s, 1H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.79 (d, *J* = 2.9 Hz, 2H), 4.52 (d, *J* = 16.8 Hz, 1H), 4.03–3.95 (m, 1.5H), 3.89–3.84 (m, 0.5H), 3.71 (dd, *J* = 10.6, 7.7 Hz, 0.4H), 3.63 (dd, *J* = 10.5, 7.8 Hz, 0.6H), 3.50 (m, 3H), 3.15 (td, *J* = 10.1, 3.4 Hz, 1H), 3.06–2.96 (m, 4H), 2.77 (q, *J* = 8.9 Hz, 1H), 2.07 (s, 3H), 1.74 (d, *J* = 8.0 Hz, 3H), 1.45 (d, *J* = 5.3 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.65, 167.55, 166.89, 166.80, 154.53, 154.29, 154.25, 143.44, 143.27, 138.76, 138.73, 128.70, 127.16, 127.14, 111.40, 111.24, 99.46, 99.33, 79.88, 79.84, 77.36, 67.59, 66.77, 61.92, 57.21, 57.10, 56.79, 56.71, 51.61, 49.50, 48.98, 48.06, 47.63, 43.28, 43.08, 38.14, 38.07, 28.57, 20.53; LRMS (ESI): *m/z* calcd for $C_{27}H_{39}N_6O_2^+$ $[M+H]^+$: 479.31; Found: 479.2.

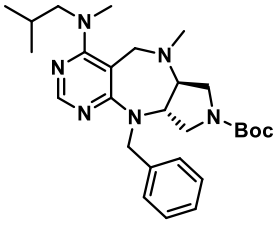
***tert*-Butyl (6a*S*,9a*S*)-4-(benzyl(methyl)amino)-10-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (12c)**



A mixture of **11a** (180 mg, 0.424 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 51 mg, 1.27 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 4.2 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (197.3 mg, 0.636 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12c** (219.2 mg, 80% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.32 (d, *J* = 3.4 Hz, 1H), 8.17–8.03 (m, 1H), 7.56 (d, *J* = 23.1 Hz, 1H), 7.33 (dq, *J* = 17.2, 9.5, 8.2 Hz, 7H), 7.19 (dd, *J* = 11.6, 7.2 Hz, 1H), 5.13 (s, 1H), 4.81 (s, 3H), 4.01 (q, *J* = 6.9, 6.5 Hz, 0.5H), 3.84 (s, 0.5H), 3.69–3.62 (m, 0.6H), 3.61–3.52 (m, 2.4H), 3.46–3.38 (m, 1H), 3.14 (t, *J* = 9.0 Hz, 1H), 3.07 (d, *J* = 2.8 Hz, 3H), 3.03 (d, *J* = 14.3 Hz, 1H), 2.95–2.75 (m, 1H), 1.97 (s, 3H), 1.68 (s, 9H), 1.40 (d, *J* = 11.4 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.22, 166.75, 154.86, 154.77, 154.18, 154.12, 149.79, 138.70, 138.66, 135.85, 135.71, 129.56, 129.44, 128.67, 127.14, 127.11, 124.67, 124.10, 123.77, 122.74, 122.70, 119.35, 119.17, 115.41, 99.59, 99.36, 83.83, 79.85, 79.82, 77.36, 57.10, 57.03, 56.37, 48.93, 48.53, 48.14, 42.40, 41.93, 41.66, 38.11, 38.05, 29.77, 28.51, 28.48, 28.32; LRMS (ESI): *m/z* calcd for $C_{37}H_{48}N_7O_4^+$ $[M+H]^+$: 654.37; Found: 654.2.

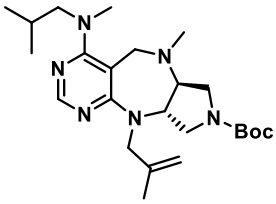
***tert*-Butyl (6a*S*,9a*S*)-10-benzyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e] pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylatecarboxylate (12d)**



A mixture of **11b** (150 mg, 0.38 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 46.1 mg, 1.15 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.8 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (98.5 mg, 0.576 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12c** (137.5 mg, 75% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (s, 1H), 7.34–7.28 (m, 3H), 7.27–7.20 (m, 2H), 5.05 (dd, *J* = 29.5, 16.3 Hz, 1H), 4.82–4.69 (m, 1H), 3.83 (dd, *J* = 10.1, 7.5 Hz, 0.5H), 3.74–3.64 (m, 2H), 3.60 (dd, *J* = 10.4, 7.8 Hz, 0.5H), 3.57–3.48 (m, 2H), 3.48–3.40 (m, 1H), 3.18–3.07 (m, 6H), 2.77 (dq, *J* = 27.6, 8.4 Hz, 1H), 2.33 (d, *J* = 2.5 Hz, 3H), 2.06 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.41 (d, *J* = 10.2 Hz, 9H), 0.91 (t, *J* = 6.2 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.67, 167.00, 166.95, 154.57, 154.52, 154.24, 154.12, 140.21, 139.98, 128.67, 128.64, 127.21, 127.12, 127.04, 127.01, 99.30, 99.13, 79.80, 77.36, 67.19, 66.69, 62.11, 61.43, 59.37, 57.45, 57.39, 50.07, 49.94, 49.35, 48.95, 48.47, 47.96, 43.46, 39.87, 39.75, 28.55, 28.48, 26.96, 20.43, 20.41, 20.09, 20.06; LRMS (ESI): *m/z* calcd for $C_{27}H_{41}N_6O_2^+$ $[M+H]^+$: 481.32; Found: 481.2.

***tert*-Butyl (6a*S*,9a*S*)-4-(isobutyl(methyl)amino)-6-methyl-10-(2-methylallyl)-5,6a,7,9,9a,10-hexahydropyrimido [4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (12e)**

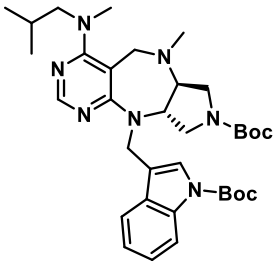


A mixture of **11b** (150 mg, 0.38 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 46.1 mg, 1.15 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.8 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (77.8 mg, 0.576 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12d** (142 mg, 83% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.17 (s, 1H), 4.95 (d, *J* = 3.8 Hz, 1H), 4.89 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 17.0 Hz, 1H), 4.00–3.84 (m, 2H), 3.78–3.64 (m, 2H), 3.56–3.46 (m, 3H), 3.19 (q, *J* = 9.8 Hz, 1H), 3.13 (m, 5H), 2.81 (d, *J* = 9.0 Hz, 1H), 2.37 (d, *J* = 3.3 Hz, 3H), 2.05 (dq, *J* = 8.4, 6.3 Hz, 1H), 1.74 (d, *J* = 9.0 Hz, 3H), 1.46 (s, 9H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.59, 167.49, 167.03, 166.94, 154.39, 154.35, 154.26, 143.53, 143.36, 111.33, 111.17, 99.24, 99.12, 79.88, 79.85, 77.36, 67.50, 66.64, 59.42, 59.37, 57.47, 57.43, 51.47, 49.58, 49.08, 48.00, 47.60, 43.69, 43.44, 39.84, 39.69, 28.59, 28.56, 26.95, 20.53, 20.43, 20.40, 20.05; LRMS (ESI): *m/z* calcd for $C_{24}H_{41}N_6O_2^+$ $[M+H]^+$: 445.32; Found: 445.2.

***tert*-Butyl (6a*S*,9a*S*)-10-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepine-8(6*H*)-carboxylate (12f)**

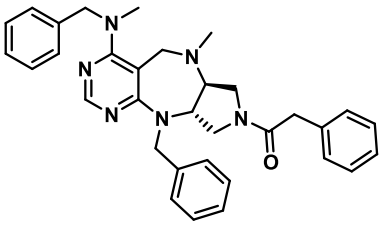
A mixture of **11b** (213 mg, 0.545 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 65.5 mg, 1.64 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 5.5 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (253.8 mg, 0.818 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to



r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **12f** (302 mg, 89% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 3.3 Hz, 1H), 8.16–8.06 (m, 1H), 7.56 (d, *J* = 23.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 0.5H), 7.31 (dd, *J* = 10.9, 7.7 Hz, 1.5H), 7.17 (dt, *J* = 14.7, 7.4 Hz, 1H), 5.12 (s, 1H), 4.83 (d, *J* = 16.4 Hz, 1H), 4.00 (dt, *J* = 9.8, 5.8 Hz, 0.5H), 3.84 (dd, *J* = 8.7, 3.7 Hz, 0.5H), 3.70 (dd, *J* = 10.5, 7.7 Hz, 0.5H), 3.64–3.53 (m, 3.5H), 3.44 (dd, *J* = 13.0, 6.8 Hz, 1H), 3.29–3.22 (m, 1H), 3.17 (d, *J* = 10.1 Hz, 1H), 3.14 (s, 3H), 3.10 (d, *J* = 13.1 Hz, 1H), 2.90 (d, *J* = 42.4 Hz, 1H), 2.26 (s, 3H), 2.06 (dq, *J* = 14.0, 7.0 Hz, 1H), 1.67 (s, 9H), 1.41 (d, *J* = 17.7 Hz, 9H), 0.90 (t, *J* = 6.3 Hz, 3H), 0.88–0.84 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 167.20, 166.91, 154.75, 154.66, 154.26, 154.16, 149.81, 135.76, 129.57, 129.46, 124.68, 124.09, 123.76, 122.72, 122.68, 119.40, 119.21, 115.41, 99.46, 99.29, 90.91, 83.81, 79.89, 79.85, 77.36, 70.30, 66.20, 62.61, 59.49, 57.15, 57.06, 49.04, 48.67, 48.54, 48.18, 42.76, 41.89, 41.59, 39.66, 39.57, 29.80, 28.54, 28.50, 28.34, 26.97, 20.39, 20.14, 20.10; LRMS (ESI): *m/z* calcd for $C_{27}H_{39}N_6O_5^+$ $[M+H]^+$: 527.29; Found: 527.2.

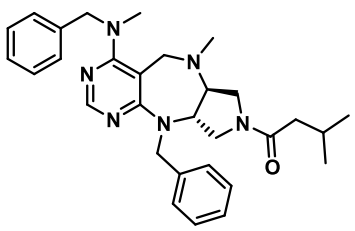
1-((6a*S*,9a*S*)-10-Benzyl-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2a)



To a solution of **12a** (37 mg, 0.088 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 204.7 mg, 1.80 mmol, 25.0 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (36.4 mg, 0.36 mmol, 5.0 equiv.) and **S1** (25.2 mg, 0.11 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 3 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2a** (26.1 mg, 68% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.24 (d, *J* = 5.5 Hz, 1H), 7.39–7.18 (m, 14H), 7.05–7.02 (m, 1H), 5.13 (d, *J* = 16.0 Hz, 0.5H), 4.93–4.70 (m, 3.5H), 4.14–4.06 (m, 0.5H), 3.83 (dd, *J* = 11.9, 7.9 Hz, 0.5H), 3.73–3.65 (m, 1H), 3.56–3.43 (m, 5H), 3.25 (q, *J* = 9.4 Hz, 0.5H), 3.18–3.09 (m, 1H), 3.06 (d, *J* = 7.9 Hz, 3H), 2.96 (d, *J* = 13.3 Hz, 0.5H), 2.87–2.73 (m, 0.5H), 2.59 (d, *J* = 9.0 Hz, 0.5H), 2.02 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.48, 169.44, 167.78, 167.61, 166.76, 166.72, 154.71, 154.61, 139.83, 139.69, 138.56, 138.47, 134.22, 134.01, 129.08, 128.97, 128.79, 128.76, 128.68, 128.65, 128.64, 127.21, 127.12, 127.06, 127.04, 127.03, 126.96, 126.92, 126.78, 99.23, 99.12, 67.35, 66.34, 62.56, 57.05, 56.93, 56.76, 56.45, 50.52, 50.05, 49.94, 49.13, 47.97, 43.32, 43.00, 41.96, 41.12, 38.05, 38.01; LRMS (ESI): *m/z* calcd for $C_{33}H_{37}N_6O^+$ $[M+H]^+$: 533.30; Found: 533.1.

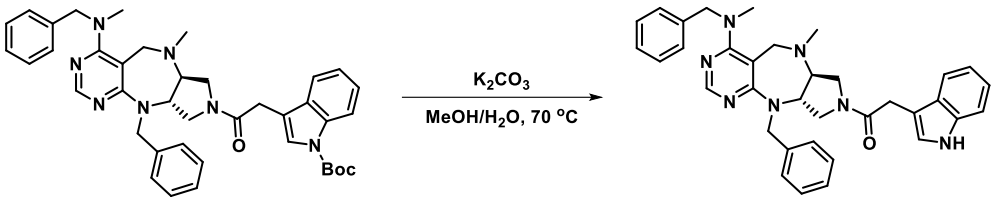
1-((6a*S*,9a*S*)-10-Benzyl-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2b)



To a solution of **12a** (37 mg, 0.088 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 204.7 mg, 1.80 mmol, 25.0 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with Toluene to get rid of remained TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (36.4 mg, 0.36 mmol, 5.0 equiv.) and **S2** (21.5 mg, 0.11 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 3 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2b** (20.6 mg, 57% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.26 (d, *J* = 3.3 Hz, 1H), 7.41–7.33 (m, 3H), 7.33–7.27 (m, 6H), 7.23 (q, *J* = 7.4, 7.0 Hz, 1H), 5.19 (d, *J* = 16.4 Hz, 0.5H), 4.97 (d, *J* = 16.5 Hz, 0.5H), 4.92–4.82 (m, 1H), 4.82–4.80 (m, 1H), 4.80–4.63 (m, 1H), 4.13–4.06 (m, 0.5H), 3.82 (dd, *J* = 11.8, 7.8 Hz, 0.5H), 3.70 (ddd, *J* = 22.2, 9.1, 7.0 Hz, 1H), 3.60–3.47 (m, 3H), 3.25 (t, *J* = 9.7 Hz, 0.5H), 3.15 (dd, *J* = 11.8, 9.9 Hz, 0.5H), 3.07 (d, *J* = 9.8 Hz, 4H), 2.82–2.67 (m, 1H), 2.11 (dq, *J* = 13.1, 6.6 Hz, 1H), 2.05–2.02 (m, 4H), 1.95 (dd, *J* = 7.0, 4.4 Hz, 1H), 0.93–0.90 (m, 3H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.26, 167.79, 167.70, 166.90, 166.80, 154.75, 154.73, 139.94, 139.90, 138.67, 138.60, 129.03, 128.92, 128.83, 128.74, 128.70, 127.31, 127.20, 127.14, 127.12, 127.09, 127.07, 99.52, 99.34, 67.58, 66.32, 57.20, 57.04, 56.72, 56.61, 50.52, 50.16, 49.91, 49.25, 48.70, 47.66, 43.13, 42.99, 42.68, 38.17, 38.07, 25.64, 25.33, 25.19, 22.82, 22.78, 22.73, 22.68; LRMS (ESI): *m/z* calcd for $C_{30}H_{39}N_6O^+$ $[M+H]^+$: 499.31; Found: 499.2.

1-((6a*S*,9a*S*)-10-Benzyl-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-(1H-indol-3-yl)ethan-1-one (2c)



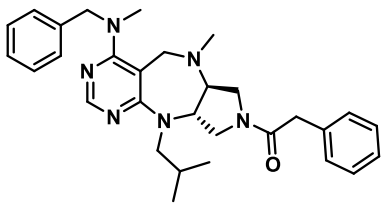
2c' 2c

To a solution of **12a** (37 mg, 0.088 mmol) in 1.3 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 204.7 mg, 1.80 mmol, 25.0 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (36.4 mg, 0.36 mmol, 5.0 equiv.) and **S5** (40.2 mg, 0.11 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4.5 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2c′** (13.0 mg, 27% overall yield). To a solution of **2c′** (9 mg, 0.013 mmol) in MeOH/H2O co-solvent (0.4 mL/0.13 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 9.26 mg, 0.067 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2c** (5.7 mg, 75% yield) as a white solid.

2c′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 4.6 Hz, 1H), 8.19–8.03 (m, 1H), 7.53–7.26 (m, 10H), 7.25–7.17 (m, 3H), 7.11 (d, *J* = 7.2 Hz, 1H), 5.15 (d, *J* = 16.4 Hz, 0.5H), 4.89 (d, *J* = 16.3 Hz, 0.5H), 4.85–4.68 (m, 3H), 4.15–4.08 (m, 0.5H), 3.83 (dd, *J* = 11.9, 7.8 Hz, 0.5H), 3.77 (ddd, *J* = 8.8, 7.2, 3.8 Hz, 1H), 3.64–3.44 (m, 5H), 3.34 (t, *J* = 9.7 Hz, 0.5H), 3.18 (dd, *J* = 11.9, 9.9 Hz, 0.5H), 3.14–2.95 (m, 4H), 2.83 (d, *J* = 9.4 Hz, 0.5H), 2.65 (d, *J* = 9.0 Hz, 0.5H), 2.02 (d, *J* = 3.8 Hz, 3H), 1.66 (d, *J* = 19.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 176.49, 168.84, 167.68, 166.84, 166.77, 154.79, 154.70, 149.66, 139.73, 139.69, 138.61, 138.54, 135.46, 130.29, 130.10, 129.06, 128.89, 128.78, 128.73, 127.30, 127.19, 127.11, 126.97, 124.78, 124.66, 124.14, 123.97, 122.83, 122.73, 119.10, 115.42, 115.33, 115.27, 113.37, 113.24, 99.37, 99.20, 83.88, 83.78, 67.46, 66.17, 57.14, 57.02, 56.69, 56.50, 50.51, 50.24, 50.02, 49.26, 49.13, 48.08, 43.14, 38.14, 38.09, 36.32, 31.78, 31.05, 28.33, 28.29, 18.56, 13.86; LRMS (ESI): *m/z* calcd for $C_{40}H_{46}N_7O_3^+$ $[M+H]^+$: 672.36; Found: 672.2.

2c ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.26 (d, *J* = 10.1 Hz, 1H), 8.18–8.08 (m, 1H), 7.60 (dd, *J* = 7.9, 3.7 Hz, 1H), 7.40–7.29 (m, 8H), 7.28–7.11 (m, 5H), 7.10 (dd, *J* = 3.4, 1.7 Hz, 0.5H), 6.80 (d, *J* = 2.4 Hz, 0.5H), 5.16 (d, *J* = 16.2 Hz, 0.5H), 4.89–4.69 (m, 3.5H), 4.19–4.08 (m, 0.4H), 3.89–3.76 (m, 1.6H), 3.70 (s, 1H), 3.62 (s, 1H), 3.59–3.45 (m, 3H), 3.37–3.15 (m, 1H), 3.14–2.95 (m, 4H), 2.82 (s, 0.5H), 2.61 (d, *J* = 8.7 Hz, 0.5H), 2.02 (d, *J* = 14.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.05, 169.95, 166.84, 154.83, 154.71, 140.02, 138.69, 138.61, 136.25, 136.21, 128.79, 128.77, 128.75, 127.39, 127.22, 127.18, 127.16, 127.13, 127.04, 122.77, 122.51, 122.38, 119.98, 119.81, 119.02, 118.82, 111.30, 108.68, 108.45, 99.39, 57.18, 57.06, 56.83, 56.56, 50.50, 50.03, 49.27, 48.09, 43.35, 38.17, 38.12, 32.33, 31.42; LRMS (ESI): *m/z* calcd for $C_{35}H_{38}N_7O^+$ $[M+H]^+$: 572.31; Found: 572.1.

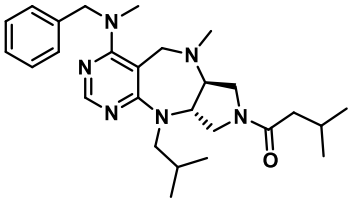
1-((6a*S*,9a*S*)-4-(Benzyl(methyl)amino)-10-isobutyl-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2d)



To a solution of **12b** (122.2 mg, 0.255 mmol) in EtOAc/MeOH co-solvent (2.55 mL/2.55 mL; 1:1, 0.05 M) was added Pd/C (12.2 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 33.1 mg (0.068 mmol) of crude resultant was dissolved in 1.37 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 210.3 mg, 1.84 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.33 mL of DCM (0.05 M). Dry TEA (34.8 mg, 0.34 mmol, 5.0 equiv.) and **S1** (24.1 mg, 0.103 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4.5 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2d** (30.5 mg, 88% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.23 (d, *J* = 9.0 Hz, 1H), 7.37–7.23 (m, 10H), 4.82–4.72 (m, 2H), 4.18 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 3.91 (m, 1.5H), 3.78 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.67 (d, *J* = 4.5 Hz, 1H), 3.63–3.61 (m, 1H), 3.55 (t, *J* = 9.9 Hz, 1H), 3.49 (m, 2H), 3.32 (t, *J* = 9.7 Hz, 0.5H), 3.25 (dd, *J* = 11.9, 9.8 Hz, 0.5H), 3.03 (m, 5H), 2.69 (bd, 1H), 2.05 (d, *J* = 13.9 Hz, 3H), 1.81 (dd, *J* = 17.5, 11.0 Hz, 0.5H), 1.69 (p, *J* = 6.9, 6.4 Hz, 0.5H), 0.91–0.83 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.78, 169.59, 166.84, 166.75, 154.56, 154.49, 138.70, 138.63, 134.34, 134.32, 129.03, 128.93, 128.87, 128.82, 128.70, 127.16, 127.13, 127.08, 127.04, 99.78, 99.61, 57.16, 57.02, 56.63, 53.25, 53.12, 50.51, 49.37, 48.98, 47.87, 43.08, 42.04, 41.30, 38.02, 37.96, 29.29, 20.28, 20.27, 20.02; LRMS (ESI): *m/z* calcd for $C_{30}H_{39}N_6O^+$ $[M+H]^+$: 499.31; Found: 499.1.

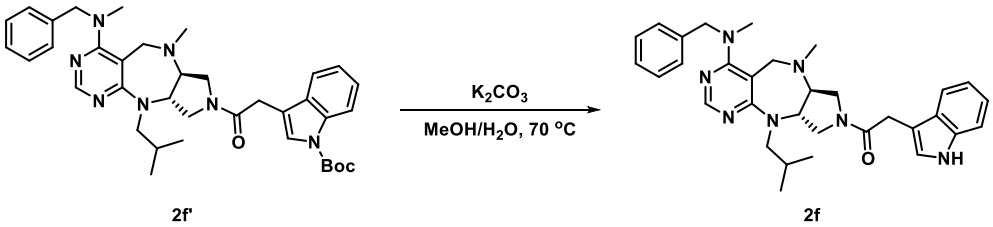
1-((6a*S*,9a*S*)-4-(Benzyl(methyl)amino)-10-isobutyl-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2e)



To a solution of **12b** (122.2 mg, 0.255 mmol) in EtOAc/MeOH co-solvent (2.55 mL/2.55 mL; 1:1, 0.05 M) was added Pd/C (12.2 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 33.1 mg (0.068 mmol) of crude resultant was dissolved in 1.37 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 210.3 mg, 1.84 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.33 mL of DCM (0.05 M). Dry TEA (34.8 mg, 0.34 mmol, 5.0 equiv.) and **S2** (20.5 mg, 0.103 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 3 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2e** (19.2 mg, 60% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.24 (s, 1H), 7.36 (td, *J* = 7.5, 2.4 Hz, 2H), 7.32–7.27 (m, 3H), 4.83–4.72 (m, 2H), 4.17 (dd, *J* = 11.3, 7.8 Hz, 0.5H), 4.00 (bs, 0.5H), 3.96–3.91 (m, 0.5H), 3.89 (dd, *J* = 11.8, 7.9 Hz, 0.5H), 3.76 (dd, *J* = 9.8, 7.7 Hz, 0.5H), 3.60 (dd, *J* = 23.3, 14.1 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 3.49 (d, *J* = 12.9 Hz, 0.5H), 3.41 (bs, 0.5H), 3.31 (t, *J* = 9.7 Hz, 0.6H), 3.24 (dd, *J* = 11.8, 9.8 Hz, 0.4H), 3.04 (d, *J* = 10.1 Hz, 4.5H), 2.81 (bs, 1H), 2.19–2.15 (m, 1H), 2.13 (m, 1H), 2.09 (dd, *J* = 11.2, 3.1 Hz, 3H), 1.83 (dt, *J* = 20.7, 6.9 Hz, 1H), 0.98–0.86 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.52, 171.30, 166.94, 166.76, 154.61, 154.55, 138.77, 138.71, 128.74, 127.19, 127.16, 127.13, 99.76, 77.42, 77.16, 76.91, 57.26, 57.06, 56.73, 56.61, 53.41, 53.06, 50.59, 47.51, 43.06, 42.76, 38.08, 37.97, 29.39, 25.65, 25.48, 22.87, 22.84, 22.83, 20.41, 20.32, 20.17, 20.05, 0.14; LRMS (ESI): *m/z* calcd for $C_{27}H_{41}N_6O^+$ $[M+H]^+$: 465.33; Found: 465.2.

1-((6a*S*,9a*S*)-4-(Benzyl(methyl)amino)-10-isobutyl-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (2f)



2f' 2f

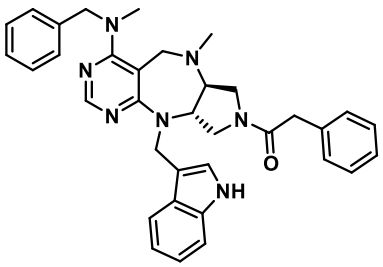
To a solution of **12b** (122.2 mg, 0.255 mmol) in EtOAc/MeOH co-solvent (2.55 mL/2.55 mL; 1:1, 0.05 M) was added Pd/C (12.2 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 33.1 mg (0.068 mmol, 1.0 equiv.) of crude resultant was dissolved in 1.37 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 210.3 mg, 1.84 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.33 mL of DCM (0.05 M). Dry TEA (34.8 mg, 0.34 mmol, 5.0 equiv.) and **S5** (38.4 mg, 0.103 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 3 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure,

followed by silica-gel flash column chromatography to afford **2f′** (9.2 mg, 21% overall yield) as a white solid. To a solution of **2f′** (9.2 mg, 0.013 mmol) in MeOH/H2O co-solvent (0.43 mL/0.14 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 9.97 mg, 0.072 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2f** (6.8 mg, 87% yield) as a white solid.

2f′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.23 (d, *J* = 10.3 Hz, 1H), 8.13 (s, 1H), 7.62–7.49 (m, 2H), 7.32 (, 6H), 7.26–7.21 (m, 1H), 4.84–4.71 (m, 2H), 4.21 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 4.00 (dd, *J* = 9.6, 7.7 Hz, 0.5H), 3.92 (dd, *J* = 11.9, 7.8 Hz, 0.5H), 3.86 (dd, *J* = 9.8, 7.7 Hz, 0.5H), 3.70 (m, 2H), 3.59 (m, 1H), 3.45 (m, 2.5H), 3.28 (dd, *J* = 11.9, 9.8 Hz, 0.5H), 3.03 (m, 5H), 2.72 (m, 1H), 2.05 (d, *J* = 10.6 Hz, 3H), 1.85–1.67 (m, 2H), 1.66 (s, 9H), 0.88 (dd, *J* = 14.5, 6.6 Hz, 3H), 0.82 (dd, *J* = 10.4, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.08, 168.90, 166.89, 166.78, 154.58, 149.68, 138.72, 138.67, 135.54, 130.34, 130.20, 128.74, 127.19, 127.17, 127.14, 127.12, 124.85, 124.74, 124.18, 124.06, 122.88, 122.79, 119.17, 115.48, 115.41, 113.45, 113.43, 99.66, 83.88, 57.21, 57.06, 56.65, 53.16, 47.93, 38.06, 38.00, 32.00, 31.20, 29.31, 28.34, 20.30, 20.24, 20.04; LRMS (ESI): *m/z* calcd for $C_{37}H_{48}N_7O_3^+$ $[M+H]^+$: 638.38; Found: 638.1.

2f ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.36–8.24 (m, 1H), 8.22 (d, *J* = 13.0 Hz, 1H), 7.63 (dd, *J* = 10.8, 7.9 Hz, 1H), 7.38–7.26 (m, 6H), 7.22–7.09 (m, 3H), 4.76 (t, *J* = 6.2 Hz, 2H), 4.21 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 3.99 (dd, *J* = 9.6, 7.6 Hz, 0.5H), 3.91 (dd, *J* = 11.8, 7.8 Hz, 0.5H), 3.84 (dd, *J* = 9.9, 7.7 Hz, 0.5H), 3.76 (d, *J* = 20.1 Hz, 2H), 3.56 (q, *J* = 7.5, 4.1 Hz, 1H), 3.48 (m, 2H), 3.37 (t, *J* = 9.7 Hz, 0.5H), 3.26 (t, *J* = 9.8 Hz, 0.5H), 3.02 (m, 5H), 2.72 (bs, 1H), 2.03 (d, *J* = 22.2 Hz, 3H), 1.79 (p, *J* = 6.6 Hz, 0.5H), 1.67 (s, 1H), 1.64 (m, 1H), 0.87 (dd, *J* = 13.8, 6.6 Hz, 3H), 0.79 (dd, *J* = 17.1, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.30, 170.16, 166.87, 166.77, 154.58, 138.74, 138.68, 136.28, 128.73, 127.40, 127.29, 127.18, 127.17, 127.12, 122.83, 122.70, 122.51, 122.38, 119.98, 119.81, 118.85, 118.79, 111.43, 111.35, 108.64, 99.72, 57.21, 57.06, 56.65, 53.17, 49.32, 48.55, 47.89, 38.06, 37.99, 32.24, 31.51, 29.28, 20.31, 20.21, 20.04; LRMS (ESI): *m/z* calcd for $C_{32}H_{40}N_7O^+$ $[M+H]^+$: 538.32; Found: 538.1.

1-((6a*S*,9a*S*)-10-((1*H*-indol-3-yl)methyl)-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2g)

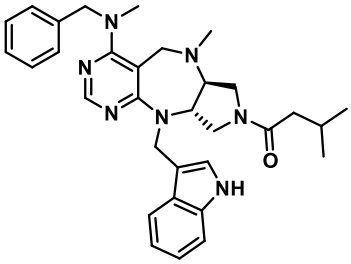


To a solution of **12c** (50 mg, 0.076 mmol) in 1.52 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;230 mg, 2.02 mmol, 26.4 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.14 mL/0.38 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 52.8 mg, 0.383 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.5 mL of DCM (0.05 M) and TEA (23.22 mg, 0.230 mmol, 3.0 equiv.), **S1** (26.76 mg, 0.114 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2g** (5.6 mg, 13% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.33 (d, *J* = 11.9 Hz, 1H), 8.05 (d, *J* = 10.1 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 0.5H), 7.41 (d, *J* = 8.2 Hz, 0.5H), 7.38–7.26 (m, 7H), 7.25–7.12 (m, 5H), 7.06–6.98 (m, 1H), 6.93–6.89 (m, 1H), 5.11 (s, 0.5H), 5.01 (d, *J* = 15.9 Hz, 0.5H), 4.92 (d, *J* = 16.0 Hz, 0.5H), 4.79 (d, *J* = 8.6 Hz, 2H), 4.21 (dd, *J* = 11.5, 7.7 Hz, 0.5H), 3.82 (dd, *J* = 11.9, 7.9 Hz, 0.5H), 3.77 (dd, *J* = 9.9, 7.9 Hz, 0.5H), 3.71 (d, *J* = 10.5 Hz, 0.5H), 3.69–3.58 (m, 1H), 3.56 (s, 1H), 3.51–3.31 (m, 3H), 3.25 (t, *J* = 9.9 Hz, 0.5H), 3.15–3.05 (m, 3.5H), 2.95 (d, *J* = 13.1

Hz, 1H), 2.67 (s, 0.5H), 1.95 (s, 1.7H), 1.88 (s, 1.3H); LRMS (ESI): *m/z* calcd for $C_{35}H_{38}N_7O^+$ $[M+H]^+$: 572.31; Found: 572.1.

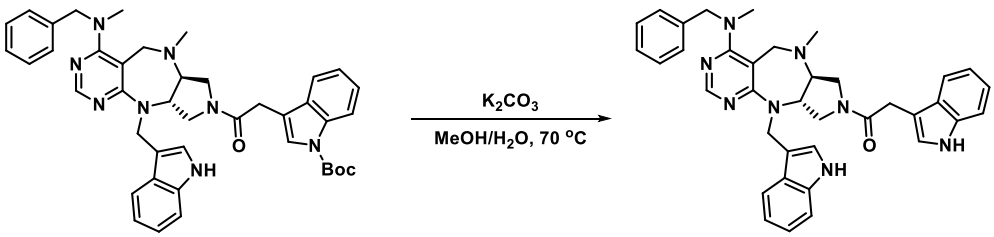
1-((6a*S*,9a*S*)-10-((1*H*-indol-3-yl)methyl)-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2h)



To a solution of **12c** (50 mg, 0.076 mmol) in 1.52 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;230 mg, 2.02 mmol, 26.4 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.14 mL/0.38 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 52.8 mg, 0.383 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.5 mL of DCM (0.05 M) and TEA (23.22 mg, 0.230 mmol, 3.0 equiv.), **S2** (22.8 mg, 0.114 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2h** (6.7 mg, 16% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.35 (d, *J* = 1.7 Hz, 1H), 8.12 (d, *J* = 28.0 Hz, 1H), 7.50–7.27 (m, 7H), 7.26–7.16 (m, 2H), 7.08 (dt, *J* = 35.4, 7.5 Hz, 1H), 5.22–5.06 (m, 1H), 4.96 (m, 1H), 4.85–4.77 (m, 2H), 4.21 (dd, *J* = 11.4, 7.7 Hz, 0.5H), 3.80 (ddd, *J* = 10.5, 7.8, 4.1 Hz, 1H), 3.75–3.61 (m, 1.5H), 3.54 (dq, *J* = 18.7, 9.2 Hz, 1H), 3.42 (dd, *J* = 20.2, 12.8 Hz, 1H), 3.24 (t, *J* = 9.9 Hz, 0.5H), 3.14–3.01 (m, 4.5H), 2.85 (m, 1H), 2.13 (dt, *J* = 13.2, 6.7 Hz, 0.5H), 2.08–1.99 (m, 1.5H), 1.95 (d, *J* = 23.5 Hz, 3H), 1.87 (d, *J* = 7.1 Hz, 1H), 0.92 (dd, *J* = 6.5, 4.8 Hz, 3H), 0.80 (dd, *J* = 21.4, 6.6 Hz, 3H); LRMS (ESI): *m/z* calcd for $C_{32}H_{40}N_7O^+$ $[M+H]^+$: 538.32; Found: 538.1.

1-((6a*S*,9a*S*)-10-((1*H*-indol-3-yl)methyl)-4-(benzyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (2i)



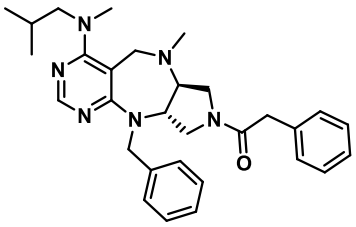
To a solution of **12c** (50 mg, 0.076 mmol) in 1.52 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA;230 mg, 2.02 mmol, 26.4 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.14 mL/0.38 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 52.8 mg, 0.383 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.5 mL of DCM (0.05 M) and TEA (23.22 mg, 0.230 mmol, 3.0 equiv.), **S5** (42.7 mg, 0.114 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was

quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2i′** (9.6 mg, 18% overall yield) as a white solid. To a solution of **2i′** (9.6 mg, 0.013 mmol) in MeOH/H2O co-solvent (0.40 mL/0.14 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 9.33 mg, 0.067 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2i** (4.8 mg, 58% yield) as a white solid.

2i′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.34 (d, *J* = 8.5 Hz, 1H), 8.25–7.97 (m, 2H), 7.56–7.39 (m, 2H), 7.38–7.26 (m, 7H), 7.26–7.14 (m, 2.5H), 7.05 (dt, *J* = 19.5, 7.6 Hz, 1H), 6.78 (s, 0.5H), 5.04–4.89 (m, 1H), 4.84–4.67 (m, 2H), 3.85 (dd, *J* = 9.8, 7.7 Hz, 0.5H), 3.81–3.77 (m, 0.5H), 3.73–3.66 (m, 1H), 3.63 (d, *J* = 18.5 Hz, 1H), 3.59–3.48 (m, 1H), 3.48–3.34 (m, 2H), 3.31 (t, *J* = 9.9 Hz, 0.3H), 3.16 (q, *J* = 10.9, 10.0 Hz, 0.7H), 3.08–3.02 (m, 3H), 2.81 (dd, *J* = 13.9, 9.5 Hz, 1H), 2.02 (d, *J* = 17.5 Hz, 0.5H), 1.89 (d, *J* = 36.1 Hz, 2.5H), 1.70–1.63 (m, 9H), 1.34–1.26 (m, 1.5H), 0.91–0.79 (m, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 168.78, 168.66, 166.52, 154.91, 138.58, 136.55, 136.36, 130.17, 128.73, 128.61, 127.04, 127.02, 126.68, 126.49, 124.77, 124.63, 123.93, 123.77, 123.13, 122.88, 122.67, 122.38, 122.30, 119.82, 119.70, 119.25, 119.10, 118.66, 115.27, 115.18, 113.58, 111.53, 111.24, 84.10, 56.93, 56.25, 50.06, 43.40, 38.08, 38.00, 31.88, 29.72, 28.28, 28.23; LRMS (ESI): *m/z* calcd for $C_{42}H_{47}N_8O_3^+$ $[M+H]^+$: 711.37; Found: 711.1.

2i ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.33 (d, *J* = 17.9 Hz, 1H), 8.15–7.78 (m, 2H), 7.59 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.45–7.26 (m, 7.5H), 7.25–6.97 (m, 5H), 6.69–6.36 (m, 1.5H), 5.14–4.75 (m, 4H), 4.21 (dd, *J* = 11.6, 7.9 Hz, 0.5H), 3.81 (ddd, *J* = 16.8, 11.0, 7.9 Hz, 1.5H), 3.75–3.64 (m, 1.4H), 3.58 (d, *J* = 19.9 Hz, 2H), 3.46–3.35 (m, 1.6H), 3.30 (t, *J* = 10.0 Hz, 0.3H), 3.14 (dd, *J* = 11.9, 9.9 Hz, 0.7H), 3.06 (d, *J* = 11.5 Hz, 3H), 2.94 (d, *J* = 12.9 Hz, 1H), 2.62 (s, 1H), 1.89 (d, *J* = 42.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.95, 166.76, 154.86, 138.66, 136.52, 136.19, 128.75, 128.73, 127.20, 127.16, 126.60, 123.15, 123.07, 122.77, 122.43, 122.38, 119.88, 119.83, 119.36, 119.26, 118.98, 111.48, 111.36, 111.16, 108.18, 98.52, 61.26, 57.09, 56.89, 50.54, 49.28, 49.10, 42.52, 38.19, 38.13, 32.75, 31.58; LRMS (ESI): *m/z* calcd for $C_{37}H_{39}N_8O^+$ $[M+H]^+$: 611.32; Found: 611.1.

1-((6a*S*,9a*S*)-10-Benzyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2j)

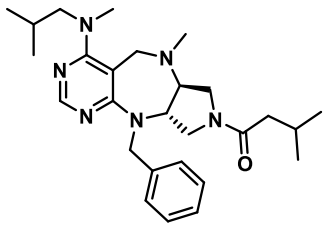


To a solution of **12d** (35.8 mg, 0.075 mmol) in 1.34 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 228.2 mg, 2.0 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (37.7 mg, 0.37 mmol, 5.0 equiv.) and **S1** (26.1 mg, 0.112 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2j** (14.1 mg, 38% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.18 (d, *J* = 3.5 Hz, 1H), 7.41–7.14 (m, 9H), 7.06–7.01 (m, 1H), 5.13 (d, *J* = 16.4 Hz, 0.5H), 4.83 (d, *J* = 2.8 Hz, 1H), 4.72 (d, *J* = 16.1 Hz, 0.5H), 4.14–4.02 (m, 0.4H), 3.88 (dd, *J* = 11.9, 7.8 Hz, 0.6H), 3.75 (td, *J* = 10.0, 2.4 Hz, 1H), 3.67 (p, *J* = 5.5 Hz, 1H), 3.57 (d, *J* = 8.8 Hz, 1H), 3.53–3.49 (m, 2H), 3.45 (s, 1H), 3.29 (t, *J* = 9.7 Hz, 0.4H), 3.22–3.04 (m, 5H), 3.02 (d, *J* = 13.1 Hz, 0.6H), 2.84 (s, 0.4H), 2.68–2.59 (m, 0.6H), 2.32 (d, *J* = 12.9 Hz, 3H), 2.06 (ddq, *J* = 13.1, 8.7, 6.7 Hz, 1H), 1.78 (s, 1H), 0.95–0.80 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.59, 169.58, 167.85, 167.67, 167.03, 166.95, 154.64, 154.57, 140.03, 139.87, 134.35, 134.13, 129.08, 128.89, 128.84, 128.78, 128.73, 127.27, 127.15, 127.10, 127.07, 127.02,

99.12, 98.98, 67.39, 66.30, 62.66, 59.28, 57.61, 57.25, 50.48, 50.26, 49.89, 49.32, 49.22, 48.01, 43.84, 43.53, 42.06, 41.25, 40.01, 39.81, 26.96, 26.93, 20.44, 20.41, 20.10, 20.03; LRMS (ESI): *m/z* calcd for $C_{30}H_{39}N_6O^+$ $[M+H]^+$: 499.31; Found: 499.2.

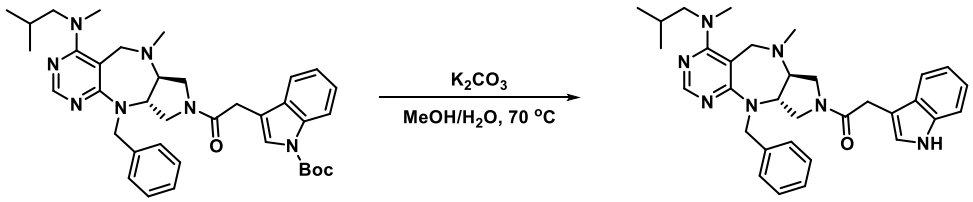
1-((6a*S*,9a*S*)-10-Benzyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2k)



To a solution of **12d** (35.8 mg, 0.075 mmol) in 1.34 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 228.2 mg, 2.0 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (37.7 mg, 0.37 mmol, 5.0 equiv.) and **S2** (22.3 mg, 0.112 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2k** (12.9 mg, 37% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (d, *J* = 4.1 Hz, 1H), 7.37–7.27 (m, 4H), 7.27–7.20 (m, 1H), 5.18 (d, *J* = 16.4 Hz, 0.5H), 4.98 (d, *J* = 16.5 Hz, 0.5H), 4.84 (d, *J* = 16.3 Hz, 0.5H), 4.69 (d, *J* = 16.2 Hz, 0.5H), 4.09 (q, *J* = 5.8 Hz, 0.5H), 3.86 (dd, *J* = 11.8, 7.8 Hz, 0.5H), 3.78–3.67 (m, 2H), 3.61–3.52 (m, 2H), 3.52–3.44 (m, 1H), 3.28 (t, *J* = 9.7 Hz, 0.5H), 3.22–3.09 (m, 5.5H), 2.83 (d, *J* = 8.8 Hz, 0.5H), 2.74 (d, *J* = 8.7 Hz, 0.5H), 2.35 (s, 3H), 2.17–1.99 (m, 3H), 1.96 (dd, *J* = 7.0, 4.9 Hz, 1H), 0.95–0.83 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): 171.33, 171.27, 167.68, 167.06, 166.94, 154.62, 154.60, 140.05, 140.00, 128.83, 128.71, 127.30, 127.14, 127.12, 127.05, 99.33, 99.11, 67.50, 66.21, 59.35, 57.50, 57.33, 50.39, 50.27, 49.80, 49.22, 48.82, 47.64, 43.54, 43.02, 42.71, 39.95, 39.77, 26.97, 26.95, 25.64, 25.35, 22.85, 22.80, 22.76, 22.72, 20.46, 20.41, 20.10, 20.06; LRMS (ESI): *m/z* calcd for $C_{27}H_{41}N_6O^+$ $[M+H]^+$: 465.33; Found: 465.2.

1-((6a*S*,9a*S*)-10-Benzyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (2l)



2l' 2l

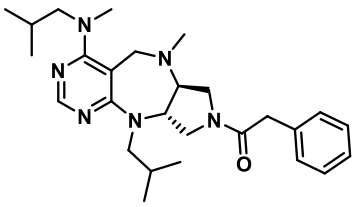
To a solution of **12d** (35.8 mg, 0.075 mmol) in 1.34 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 228.2 mg, 2.0 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (37.7 mg, 0.37 mmol, 5.0 equiv.) and **S5** (41.6 mg, 0.112 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2l′** (22.3 mg, 47% overall yield) as a white solid. To a solution of **2l′** (22.3 mg, 0.035 mmol) in MeOH/H2O co-solvent (1.0 mL/0.35 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 24.2 mg, 0.175 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as

indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2l** (11.8 mg, 63% yield) as a white solid.

2l′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.18 (d, *J* = 3.1 Hz, 2H), 7.58–7.39 (m, 2H), 7.37–7.26 (m, 3.5H), 7.25–7.18 (m, 2.5H), 7.12–7.09 (m, 1H), 5.15 (d, *J* = 16.2 Hz, 0.4H), 4.90 (d, *J* = 16.4 Hz, 0.6H), 4.76–4.65 (m, 1H), 4.15–4.08 (m, 0.4H), 3.85 (ddd, *J* = 24.9, 10.8, 7.7 Hz, 1H), 3.77 (dd, *J* = 8.7, 6.7 Hz, 0.6H), 3.70 (ddd, *J* = 17.4, 13.6, 6.7 Hz, 1H), 3.64–3.48 (m, 5H), 3.37 (t, *J* = 9.8 Hz, 0.5H), 3.25–3.17 (m, 1H), 3.16–3.06 (m, 4.5H), 2.87 (s, 0.4H), 2.68 (s, 0.6H), 2.33 (d, *J* = 3.2 Hz, 3H), 2.06 (dt, *J* = 14.8, 6.6 Hz, 1H), 1.66 (d, *J* = 17.6 Hz, 9H), 0.91 (t, *J* = 6.0 Hz, 3H), 0.84 (dd, *J* = 8.4, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 168.89, 168.83, 167.68, 167.03, 166.93, 154.64, 154.57, 149.69, 139.82, 135.49, 130.33, 130.14, 129.11, 128.78, 128.73, 127.29, 127.24, 127.13, 127.10, 127.00, 124.79, 124.68, 124.16, 124.02, 122.85, 122.74, 119.12, 115.44, 115.36, 113.42, 113.26, 99.18, 98.99, 83.89, 83.78, 66.08, 59.33, 59.28, 57.48, 57.23, 50.38, 49.89, 49.26, 48.04, 43.58, 40.03, 39.76, 31.80, 31.08, 28.35, 28.31, 26.95, 26.93, 20.44, 20.40, 20.09, 20.04; LRMS (ESI): *m/z* calcd for $C_{37}H_{48}N_7O_3^+$ $[M+H]^+$: 638.38; Found: 638.1.

2l ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.32 (d, *J* = 34.0 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.36–7.08 (m, 8H), 6.90 (dd, *J* = 151.4, 2.3 Hz, 1H), 5.13 (d, *J* = 16.4 Hz, 0.4H), 4.86–4.67 (m, 1.6H), 4.17–4.05 (m, 0.4H), 3.87 (dd, *J* = 11.8, 7.8 Hz, 0.6H), 3.82–3.71 (m, 1.6H), 3.69 (s, 0.8H), 3.67–3.62 (m, 0.4H), 3.59 (s, 1.2H), 3.56–3.44 (m, 3H), 3.34 (t, *J* = 9.8 Hz, 0.4H), 3.22–3.08 (m, 5H), 3.02 (d, *J* = 13.1 Hz, 0.6H), 2.85–2.79 (m, 0.4H), 2.68–2.57 (m, 0.6H), 2.30 (d, *J* = 16.2 Hz, 3H), 2.05 (ddt, *J* = 12.9, 8.3, 6.4 Hz, 1H), 0.90 (dd, *J* = 6.6, 3.8 Hz, 3H), 0.84 (dd, *J* = 9.2, 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.13, 170.07, 167.77, 167.65, 167.03, 166.94, 154.63, 154.55, 140.06, 139.87, 136.26, 136.24, 128.77, 128.72, 127.38, 127.23, 127.14, 127.09, 127.04, 122.89, 122.87, 122.41, 122.28, 119.89, 119.73, 118.97, 118.75, 111.35, 111.34, 108.52, 108.26, 99.15, 99.01, 66.17, 59.33, 59.29, 57.55, 57.22, 50.35, 49.89, 49.30, 49.23, 48.03, 43.72, 43.50, 40.05, 39.78, 32.30, 31.39, 26.97, 26.93, 20.44, 20.41, 20.10, 20.04; LRMS (ESI): *m/z* calcd for $C_{32}H_{40}N_7O^+$ $[M+H]^+$: 538.32; Found: 538.1.

1-((6a*S*,9a*S*)-10-Isobutyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2m)

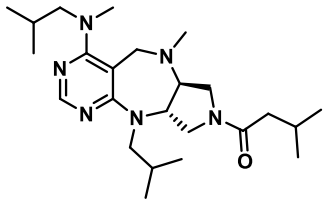


To a solution of **12e** (116.7 mg, 0.262 mmol) in EtOAc/MeOH co-solvent (2.62 mL/2.62 mL; 1:1, 0.05 M) was added Pd/C (11.6 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 32.4 mg (0.073 mmol) of crude resultant was dissolved in 1.45 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 222 mg, 1.94 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.40 mL of DCM (0.05 M). Dry TEA (36.7 mg, 0.36 mmol, 5.0 equiv.) and **S1** (25.4 mg, 0.109 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2m** (18.5 mg, 55% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.16 (d, *J* = 7.3 Hz, 1H), 7.33 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.29–7.24 (m, 3H), 4.18 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 4.04–3.78 (m, 2.5H), 3.72–3.62 (m, 3H), 3.56 (t, *J* = 9.8 Hz, 1H), 3.49 (dd, *J* = 13.0, 10.3 Hz, 2H), 3.38–3.27 (m, 1H), 3.11 (s, 5.5H), 2.94–2.64 (m, 1.5H), 2.35 (d, *J* = 13.9 Hz, 3H), 2.04 (dddd, *J* = 13.2, 8.2, 6.5, 1.7 Hz, 1H), 1.83–1.77 (m, 0.5H), 1.68 (dt, *J* = 14.7, 6.6 Hz, 0.5H), 0.90–0.80 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.81, 169.69, 166.98, 166.88, 154.40, 154.35, 134.38, 134.33, 129.06, 128.93, 128.84, 127.14, 127.06, 99.54, 99.35, 59.40, 59.33, 57.43, 57.34, 53.16, 53.02, 50.62,

49.51, 48.99, 47.87, 42.03, 41.34, 39.77, 39.48, 29.30, 26.92, 26.89, 20.44, 20.39, 20.30, 20.28, 20.05, 20.02; LRMS (ESI): *m/z* calcd for $C_{27}H_{41}N_6O^+$ $[M+H]^+$: 465.33; Found: 465.2.

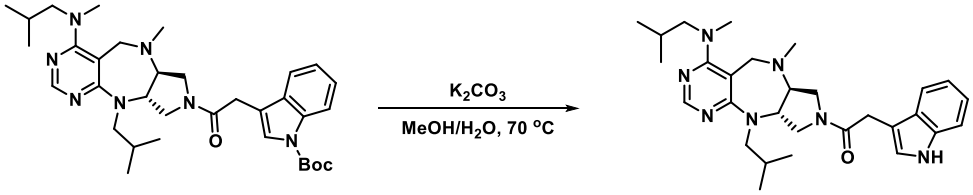
1-((6a*S*,9a*S*)-10-Isobutyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo [3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2n)



To a solution of **12e** (116.7 mg, 0.262 mmol) in EtOAc/MeOH co-solvent (2.62 mL/2.62 mL; 1:1, 0.05 M) was added Pd/C (11.6 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 32.4 mg (0.073 mmol) of crude resultant was dissolved in 1.45 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 222 mg, 1.94 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.40 mL of DCM (0.05 M). Dry TEA (36.7 mg, 0.36 mmol, 5.0 equiv.) and **S2** (21.7 mg, 0.109 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2n** (12.7 mg, 41% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.18 (s, 1H), 4.16 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 3.93 (dd, *J* = 12.0, 7.8 Hz, 1.5H), 3.81 (dd, *J* = 9.8, 7.7 Hz, 0.5H), 3.65 (dt, *J* = 20.0, 11.9 Hz, 1.5H), 3.58–3.47 (m, 2H), 3.42 (s, 0.5H), 3.36–3.26 (m, 1H), 3.18 (s, 0.5H), 3.12 (s, 5.5H), 2.77 (s, 0.5H), 2.38 (d, *J* = 2.9 Hz, 3H), 2.22–2.12 (m, 3H), 2.05 (dtd, *J* = 13.0, 6.5, 3.3 Hz, 1H), 1.90–1.76 (m, 2H), 1.00–0.96 (m, 6H), 0.94–0.86 (m, 9H), 0.82 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.52, 171.38, 167.04, 166.87, 154.44, 154.39, 99.65, 99.48, 59.47, 59.39, 57.43, 53.29, 52.97, 50.68, 49.04, 47.52, 43.06, 42.77, 39.74, 39.44, 29.37, 26.94, 26.92, 25.62, 25.48, 22.88, 22.85, 22.84, 22.82, 20.47, 20.42, 20.39, 20.32, 20.18, 20.06; LRMS (ESI): *m/z* calcd for $C_{24}H_{43}N_6O^+$ $[M+H]^+$: 431.34; Found: 431.2.

2-(1*H*-Indol-3-yl)-1-((6a*S*,9a*S*)-10-isobutyl-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydro pyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)ethan-1-one (2o)



2o' 2o

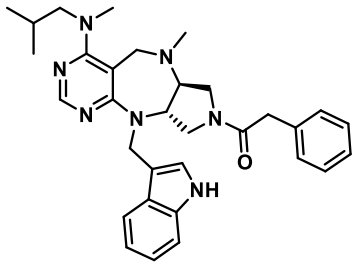
To a solution of **12e** (116.7 mg, 0.262 mmol) in EtOAc/MeOH co-solvent (2.62 mL/2.62 mL; 1:1, 0.05 M) was added Pd/C (11.6 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 32.4 mg (0.073 mmol) of crude resultant was dissolved in 1.45 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 222 mg, 1.94 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.40 mL of DCM (0.05 M). Dry TEA (36.7 mg, 0.36 mmol, 5.0 equiv.) and **S5** (40.5 mg, 0.109 mmol, 1.5 equiv.) were

sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2o′** (18.8 mg, 43% overall yield) as a white solid. To a solution of **2o′** (18.8 mg, 0.031 mmol) in MeOH/H2O co-solvent (0.93 mL/0.31 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 21.5 mg, 0.156 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2o** (11.4 mg, 72% yield) as a white solid.

2o′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.17 (d, *J* = 8.6 Hz, 2H), 7.62–7.50 (m, 2H), 7.33 (tdd, *J* = 8.2, 2.5, 1.2 Hz, 1H), 7.27–7.23 (m, 1H), 4.20 (dd, *J* = 11.4, 7.9 Hz, 0.5H), 4.03–3.89 (m, 2H), 3.79–3.54 (m, 4.5H), 3.55–3.40 (m, 2.5H), 3.31 (dd, *J* = 11.9, 9.8 Hz, 0.5H), 3.11 (d, *J* = 1.8 Hz, 4H), 3.04 (d, *J* = 14.6 Hz, 1.5H), 2.94–2.66 (m, 1.5H), 2.36 (d, *J* = 6.9 Hz, 3H), 2.04 (dtq, *J* = 13.1, 6.4, 3.9, 3.2 Hz, 1H), 1.81 (dd, *J* = 14.5, 7.4 Hz, 1H), 1.66 (s, 9H), 0.91–0.80 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.07, 168.96, 167.01, 166.89, 154.39, 149.77, 149.66, 135.54, 130.35, 130.20, 124.83, 124.74, 124.18, 124.07, 122.87, 122.78, 119.17, 115.46, 115.40, 113.47, 113.41, 99.53, 99.38, 83.84, 59.44, 59.33, 57.40, 53.21, 53.03, 50.77, 49.10, 47.91, 39.80, 39.46, 31.97, 31.20, 29.31, 28.33, 28.31, 26.93, 26.90, 20.46, 20.39, 20.30, 20.28, 20.24, 20.06, 20.04; LRMS (ESI): *m/z* calcd for $C_{34}H_{50}N_7O_3^+$ $[M+H]^+$: 604.39; Found: 604.1.

2o ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.38 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 10.8 Hz, 1H), 7.64 (dd, *J* = 7.9, 5.1 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22–7.08 (m, 3H), 4.20 (dd, *J* = 11.4, 7.8 Hz, 0.5H), 4.02–3.87 (m, 2H), 3.78 (d, *J* = 11.3 Hz, 2.5H), 3.65 (d, *J* = 11.5 Hz, 1H), 3.57 (t, *J* = 10.7 Hz, 1H), 3.52–3.38 (m, 2.5H), 3.30 (dd, *J* = 11.8, 9.7 Hz, 0.5), 3.10 (s, 4H), 3.05–2.59 (m, 3H), 2.33 (d, *J* = 19.7 Hz, 3H), 2.04 (dtd, *J* = 13.2, 6.6, 3.2 Hz, 1H), 1.82–1.78 (m, 0.5H), 1.65 (p, *J* = 6.8 Hz, 0.5H), 0.91–0.84 (m, 6H), 0.83–0.76 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.35, 170.26, 167.00, 166.88, 154.40, 154.36, 136.29, 127.41, 127.30, 122.88, 122.77, 122.45, 122.34, 119.93, 119.78, 118.81, 118.77, 111.44, 111.38, 108.59, 108.54, 99.55, 99.40, 59.44, 59.34, 57.42, 53.16, 53.05, 50.71, 49.52, 49.11, 47.90, 39.83, 39.49, 32.21, 31.49, 29.25, 26.94, 26.90, 20.46, 20.40, 20.31, 20.21, 20.07, 20.05; LRMS (ESI): *m/z* calcd for $C_{29}H_{42}N_7O^+$ $[M+H]^+$: 504.34; Found: 504.1.

1-((6a*S*,9a*S*)-10-((1*H*-Indol-3-yl)methyl)-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-2-phenylethan-1-one (2p)

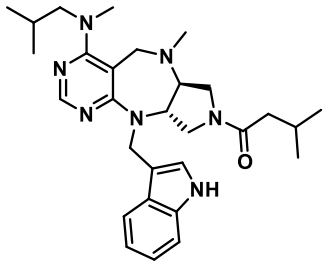


To a solution of **12f** (50 mg, 0.081 mmol) in 1.60 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 230 mg, 2.02 mmol, 25.0 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.21 mL/0.40 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 55.7 mg, 0.40 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.58 mL of DCM (0.05 M) and TEA (24.5 mg, 0.242 mmol, 3.0 equiv.), **S1** (28.2 mg, 0.121 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2p** (7.2 mg, 17% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.27 (d, *J* = 11.2 Hz, 1H), 8.08 (d, *J* = 13.6 Hz, 1H), 7.48–7.34 (m, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.26–7.17 (m, 4H), 7.16–7.11 (m, 1H), 7.05–6.98 (m, 1H), 6.93–6.90 (m, 1H), 5.13–4.88 (m, 2H), 4.20 (dd, *J* = 11.4, 7.6 Hz, 0.4H), 3.86 (dd, *J* = 11.9, 7.8 Hz, 0.6H), 3.82–3.59 (m, 3H), 3.58 (s, 1H), 3.52–3.41 (m, 2.4H), 3.39 (d, *J* = 5.5 Hz, 0.6H), 3.37–3.25 (m, 1H), 3.22–3.10 (m, 4.5H), 3.02 (d, *J* = 13.0 Hz,

1H), 2.71 (s, 0.5H), 2.25 (s, 2H), 2.15 (s, 1H), 2.06 (h, *J* = 6.5 Hz, 1H), 0.91–0.83 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.65, 166.90, 154.73, 136.68, 136.45, 134.32, 129.09, 128.83, 128.82, 127.04, 126.89, 126.61, 123.22, 122.57, 122.43, 120.01, 119.82, 119.41, 118.74, 111.50, 111.34, 99.32, 89.34, 59.40, 57.39, 56.65, 49.00, 42.24, 41.96, 41.37, 39.85, 39.75, 26.99, 26.97, 20.42, 20.24, 20.11; LRMS (ESI): *m/z* calcd for $C_{32}H_{40}N_7O^+$ $[M+H]^+$: 538.32; Found: 538.1.

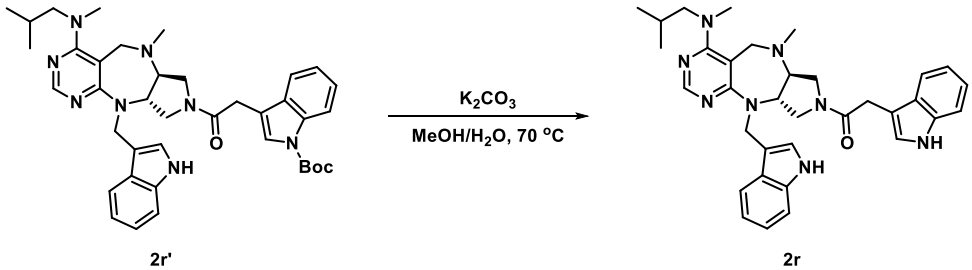
1-((6a*S*,9a*S*)-10-((1*H*-Indol-3-yl)methyl)-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-3-methylbutan-1-one (2q)



To a solution of **12f** (50 mg, 0.081 mmol) in 1.60 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 230 mg, 2.02 mmol, 25.0 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in MeOH/H2O co-solvent (1.21 mL/0.40 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 55.7 mg, 0.40 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.58 mL of DCM (0.05 M) and TEA (24.5 mg, 0.242 mmol, 3.0 equiv.), **S2** (24.1 mg, 0.121 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2q** (7.7 mg, 19% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (d, *J* = 2.0 Hz, 1H), 8.20–8.10 (m, 1H), 7.50–7.34 (m, 2H), 7.26–7.16 (m, 2H), 7.13–7.02 (m, 1H), 5.19–4.92 (m, 2H), 4.20 (dd, *J* = 11.2, 7.5 Hz, 0.4H), 3.84 (dd, *J* = 11.8, 7.8 Hz, 0.6H), 3.81–3.71 (m, 1H), 3.70–3.48 (m, 3H), 3.45 (t, *J* = 12.6 Hz, 1H), 3.35–3.28 (m, 0.4H), 3.29–3.20 (m, 1H), 3.20–3.03 (m, 4.6H), 3.00 (d, *J* = 7.5 Hz, 0.5H), 2.81 (s, 0.5H), 2.27 (s, 1.6H), 2.20 (s, 1.4H), 2.14 (dt, *J* = 13.2, 6.7 Hz, 0.5H), 2.10–2.03 (m, 2H), 1.98 (dt, *J* = 13.4, 6.7 Hz, 0.5H), 1.88 (d, *J* = 7.1 Hz, 1H), 0.95–0.76 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.43, 166.96, 166.90, 155.01, 154.77, 136.69, 136.40, 126.86, 126.71, 123.28, 123.20, 122.53, 122.41, 120.03, 119.80, 119.46, 118.71, 111.51, 111.32, 99.45, 59.54, 59.45, 57.33, 50.54, 48.58, 42.93, 42.82, 42.16, 39.78, 39.73, 27.00, 26.98, 25.63, 25.44, 22.86, 22.83, 22.71, 22.60, 20.43, 20.41, 20.24, 20.13; LRMS (ESI): *m/z* calcd for $C_{29}H_{42}N_7O^+$ $[M+H]^+$: 504.34; Found: 504.2.

1-((6a*S*,9a*S*)-10-((1*H*-Indol-3-yl)methyl)-4-(isobutyl(methyl)amino)-6-methyl-5,6a,7,9,9a,10-hexahydropyrimido[4,5-e]pyrrolo[3,4-b][1,4]diazepin-8(6*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (2r)



To a solution of **12f** (50 mg, 0.081 mmol) in 1.60 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 230 mg, 2.02 mmol, 25.0 equiv.), and stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved

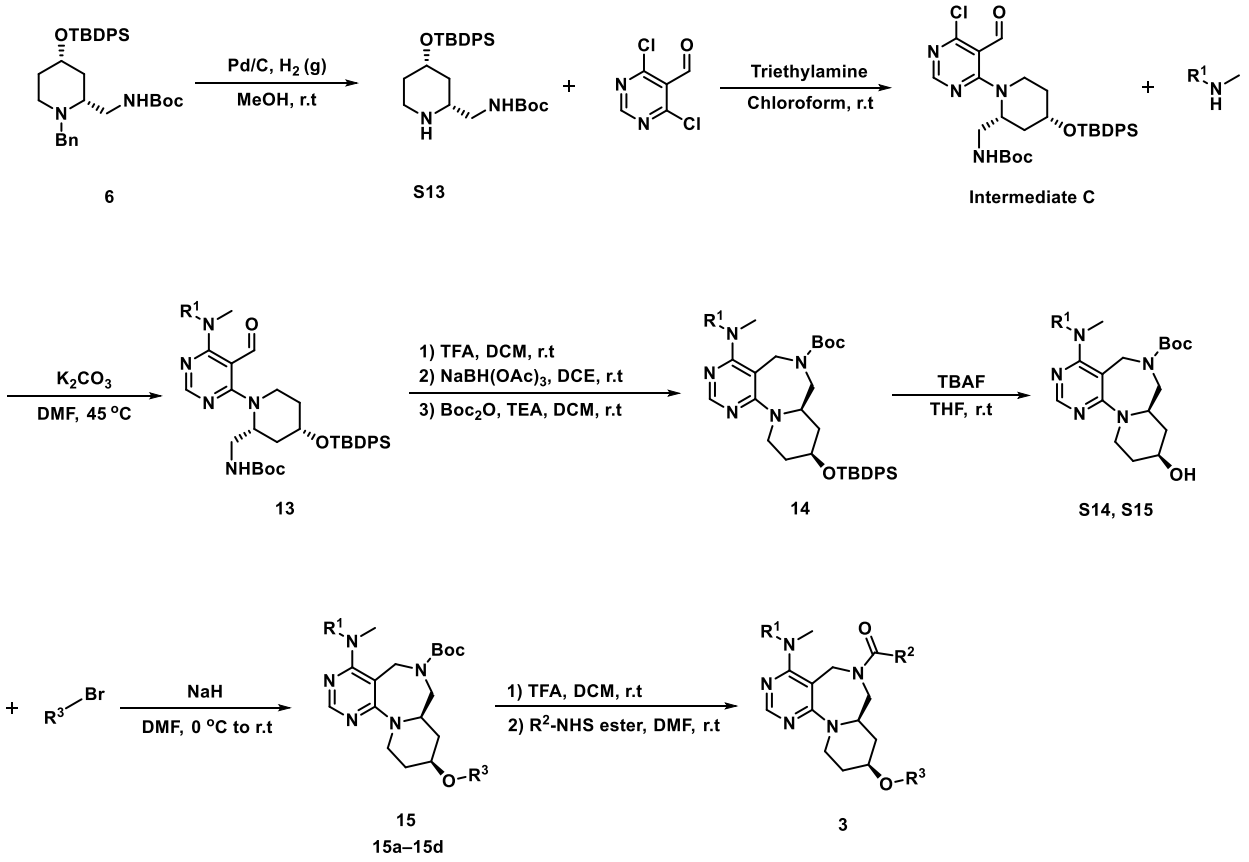
in MeOH/H2O co-solvent (1.21 mL/0.40 mL;3:1, 0.05 M) was added potassium carbonate (K_2CO_3; 55.7 mg, 0.40 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure. This crude mixture was dissolved in 1.58 mL of DCM (0.05 M) and TEA (24.5 mg, 0.242 mmol, 3.0 equiv.), **S5** (45.0 mg, 0.121 mmol, 1.5 equiv.) were sequentially added. The reaction mixture was stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **2r′** (10.1 mg, 19% overall yield) as a white solid. To a solution of **2r′** (4.0 mg, 0.006 mmol) in MeOH/H2O co-solvent (0.18 mL/0.06 mL;3:1, 0.025 M) was added potassium carbonate (K_2CO_3; 4.1 mg, 0.030 mmol, 5.0 equiv.), stirred at 70 °C for 4 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **2r** (2.9 mg, 85% yield) as a white solid.

2r′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29–8.04 (m, 2.5H), 7.57–7.26 (m, 5H), 7.25–6.98 (m, 3H), 6.78 (s, 0.5H), 5.16–4.69 (m, 2H), 4.25–3.95 (m, 0.8H), 3.88–3.79 (m, 1.2H), 3.78–3.62 (m, 2H), 3.60–3.52 (m, 1H), 3.48 (d, *J* = 15.1 Hz, 1H), 3.42 (dd, *J* = 14.2, 6.8 Hz, 1H), 3.37–3.15 (m, 2H), 3.13 (d, *J* = 3.8 Hz, 3H), 2.93–2.77 (m, 1H), 2.37 (d, *J* = 9.9 Hz, 0.4H), 2.18 (d, *J* = 38.7 Hz, 2.6H), 2.06 (dt, *J* = 14.0, 6.9 Hz, 1H), 1.67 (d, *J* = 15.4 Hz, 11H), 0.91–0.78 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 168.85, 166.80, 154.92, 136.68, 136.50, 126.82, 126.64, 124.89, 124.75, 124.07, 123.93, 123.27, 123.00, 122.79, 122.49, 122.41, 119.92, 119.79, 119.42, 119.24, 118.83, 115.41, 115.32, 113.70, 111.65, 111.34, 99.18, 82.73, 59.45, 57.14, 49.58, 42.89, 39.86, 39.70, 31.85, 29.85, 28.40, 28.36, 26.99, 20.43, 20.38, 20.23, 20.17; LRMS (ESI): *m/z* calcd for $C_{39}H_{49}N_8O_3^+$ $[M+H]^+$: 677.39; Found: 677.1.

2r ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.26 (d, *J* = 17.1 Hz, 1H), 8.20–7.72 (m, 2.5H), 7.60 (t, *J* = 7.1 Hz, 1H), 7.48–7.29 (m, 3H), 7.19 (td, *J* = 7.7, 4.0 Hz, 1H), 7.13 (dt, *J* = 14.6, 7.5 Hz, 2H), 7.09–6.99 (m, 1H), 6.70–6.33 (m, 1.5H), 4.89 (s, 2H), 4.20 (dd, *J* = 11.5, 7.8 Hz, 0.5H), 3.83 (td, *J* = 10.7, 9.7, 7.8 Hz, 1.5H), 3.76 (dd, *J* = 9.9, 7.8 Hz, 0.5H), 3.69 (d, *J* = 21.9 Hz, 1.5H), 3.59 (t, *J* = 10.4 Hz, 1H), 3.56 (s, 1H), 3.49–3.38 (m, 2H), 3.33 (t, *J* = 10.0 Hz, 0.6H), 3.21–3.15 (m, 1.4H), 3.12 (d, *J* = 11.0 Hz, 3H), 3.00 (d, *J* = 12.9 Hz, 1.2H), 2.65 (s, 0.8H), 2.23 (s, 2H), 2.12 (s, 1H), 2.06 (ddd, *J* = 13.5, 8.2, 6.3 Hz, 1H), 0.92–0.80 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 169.99, 166.90, 154.73, 136.54, 136.19, 126.61, 123.16, 123.12, 122.41, 122.37, 119.86, 119.80, 119.29, 119.01, 111.47, 111.35, 111.15, 109.33, 108.15, 83.36, 59.44, 58.31, 50.77, 50.32, 43.07, 39.73, 32.77, 31.94, 27.00, 20.42, 20.10; LRMS (ESI): *m/z* calcd for $C_{34}H_{41}N_8O^+$ $[M+H]^+$: 577.34; Found: 577.1.

3.5. General Synthetic Procedure 3, 4 for α-Helix mimetic Compounds(3a–3r) and Compound Characterization

3.5.1. General Synthetic Procedure 3 (Route 1)



General procedure 3:

To a solution of **6** (6.38 g. 11.14 mmol) in 222 mL of MeOH (0.05 M) was added Pd/C (1.28 g, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 18 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure to afford **S13**.

To a solution of **S13** (5.22 g, 11.14 mmol) in 218 mL of chloroform (0.05 M) were added triethylamine (TEA; 3.38 g, 33.41 mmol, 3.0 equiv.) and 4,6-dichloropyrimidine-5-carbaldehyde (1.58 g, 8.91 mmol, 0.8 equiv.) at r.t, and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, the resultant was quenched with saturated NH_4Cl solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, the filtrate was condensed under reduced pressure to afford **Intermediate C**.

A crude mixture of **Intermediate C** and K_2CO_3 (3.0 equiv.) was dissolved in dry DMF (0.1 M) and *N*-methyl-R^1 amine (1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **13a, 13b**.

To a solution of **13a/13b** in DCM (0.05 M) was added trifluoroacetic acid (TFA; 10v/v% dissolved in DCM) at r.t and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in DCE (0.05 M). Sodium triacetoxy borohydride ($NABH(OAc)_3$; 2 equiv.) was added and stirred at r.t for the indicated time. After

the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, and the crude resultant was dissolved in DCM (0.05 M). Dry TEA (3.0 equiv.) and Boc_2O (1.3 equiv.) were sequentially added and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **14a, 14b**.

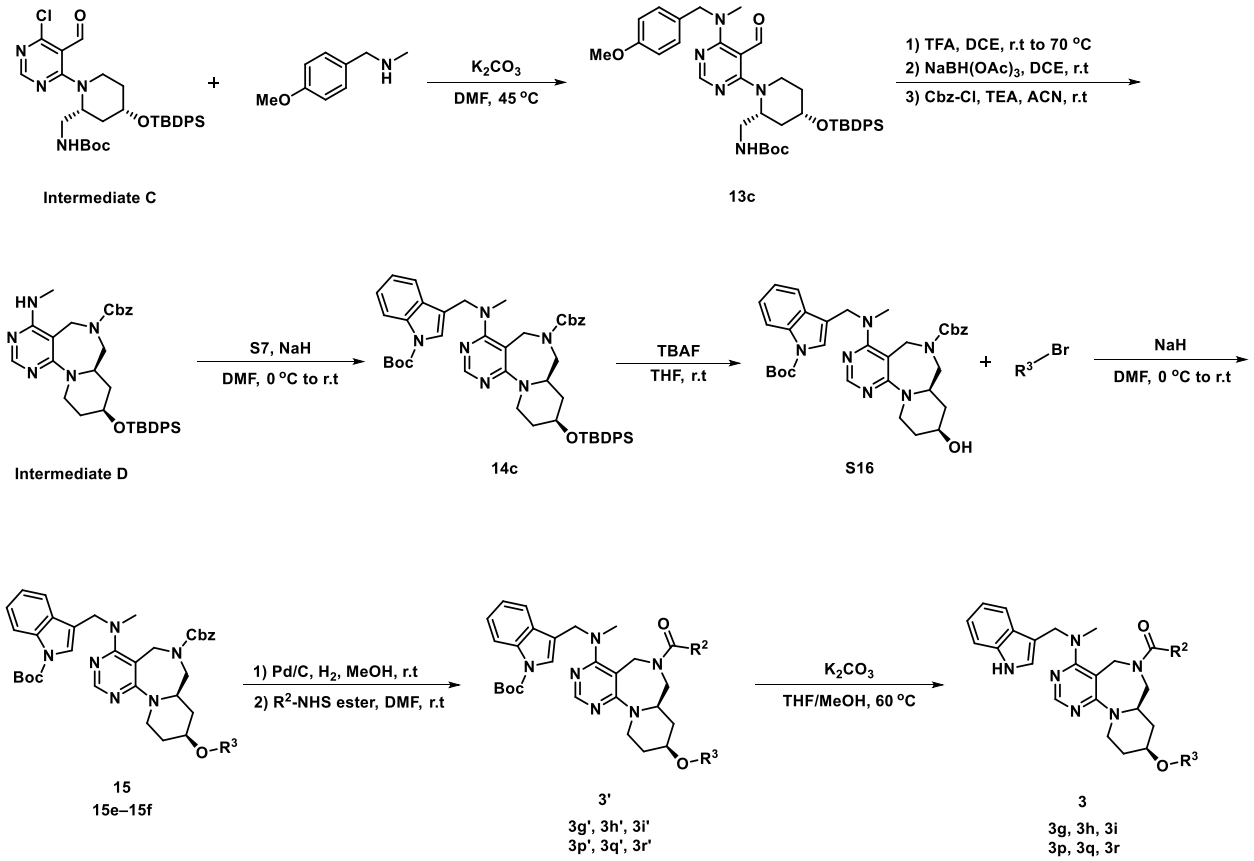
To a solution of **14a**/**14b** in tetrahydrofuran (THF; 0.05 M) was added tetrabutylammonium fluoride (TBAF; 1 M THF solution, 2.0 equiv.) at r.t, stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **S14**/**S15**.

A mixture of **S14**/**S15** and sodium hydride (NaH; 60% dispersion in mineral oil, 3.0 equiv.) was cooled to 0 °C and dissolved in dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, R^3-Bromide (1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15a–15d**.

To a solution of **15a–15d** in DCM (0.05 M) was added trifluoroacetic acid (TFA; 10v/v% dissolved in DCM) at r.t, and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in DMF (0.1 M). Dry TEA (5.0 equiv.) and R^2-NHS ester (1.5 equiv.) were sequentially added and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3** (**3a–3f**, **3j–3o**).

3.5.2. General Synthetic Procedure 4 (Route 2)

General procedure 4:



Following the general synthetic procedure 3, **Intermediate C** was obtained in crude mixture. A crude mixture of **Intermediate C** and K_2CO_3 (3.0 equiv.) were dissolved in dry DMF (0.1 M) and 4-methoxy-*N*-methylbenzylamine (1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **13c**.

To a solution of **13c** in DCE (0.05 M) was added trifluoroacetic acid (TFA; 10v/v% dissolved in DCM) at r.t, and stirred at r.t for 12 h, and warmed to 70 °C, and stirred them for 24 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in DCE (0.05 M). Sodium tri acetoxy borohydride ($NABH(OAc)_3$; 2.0 equiv.) was added and stirred at r.t for 2 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, and the crude resultant was dissolved in ACN (0.05 M). Dry TEA (3.0 equiv.) and Cbz-Cl (1.1 equiv.) were sequentially added at 0 °C and stirred at r.t for indicated 1 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **Intermediate D**.

A mixture of **Intermediate D** and sodium hydride (NaH; 60% dispersion in mineral oil, 3.0 equiv.) was cooled to 0 °C and dissolved in dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (1.5

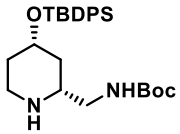
equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 1.5 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **14c**.

To a solution of **14c** in THF (0.1 M) was added tetrabutylammonium fluoride (TBAF; 2.5 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **S16**. A mixture of **S16** and sodium hydride (NaH; 60% dispersion in mineral oil, 3.0 equiv.) was cooled to 0 °C and dissolved in dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, R^3-Bromide (1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 1.5 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15e**, **15f**.

To a solution of **15e/15f** in MeOH (0.05 M) was added Pd/C (20 wt%) at r.t, and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure, and the crude resultant was dissolved in DMF (0.05 M). Dry TEA (3.0 equiv.) and R^2-NHS ester (1.5 equiv.) were sequentially added and stirred at r.t for the indicated time. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3′** (**3g′**, **3h′**, **3i′**, **3p′**, **3q′**, **3r′**).

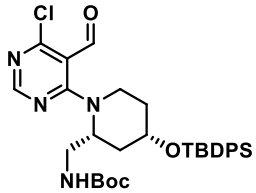
To a solution of **3′** in THF/MeOH co-solvent (1:1, 0.025 M) was added potassium carbonate (K_2CO_3) at r.t, and stirred at 60 °C for the indicated time. After the completion of the reaction, as indicated by TLC, solvent was removed under reduced pressure, followed by column chromatography to afford **3** (**3g**, **3h**, **3i**, **3p**, **3q**, **3r**).

***tert*-Butyl *N*-[[(2*R*,4*S*)-4-[*tert*-butyl(diphenyl)silyl]oxy-2-piperidyl]methyl]carbamate (S13)**



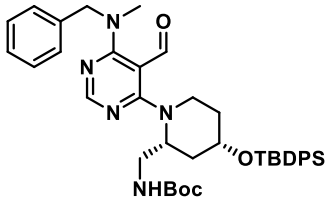
To a solution of **6** (6.38 g, 11.14 mmol) in 223 mL of MeOH (0.05 M) was added Pd/C (1.28 g, 20 wt%) at r.t, and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was condensed under reduced pressure to obtain **S13**. This was used in the next step without any further purification.

***tert*-Butyl *N*-[[(2*R*,4*S*)-4-[*tert*-butyl(diphenyl)silyl]oxy-2-piperidyl]methyl]carbamate (Intermediate C)**



To a solution of **S13** (5.22 g, 11.14 mmol) in 218 mL of chloroform (0.05 M) was added triethylamine (TEA; 3.38 g, 33.41 mmol, 3.0 equiv.), 4,6-dichloropyrimidine-5-carbaldehyde (1.58 g, 8.91 mmol, 0.8 equiv.) at r.t and stirred at r.t for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure to afford **Intermediate C**. This was used in the next steps without any further purification.

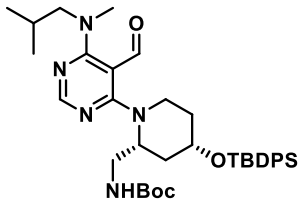
***tert*-Butyl *N*-[[(2*R*,4*S*)-1-[6-[benzyl(methyl)amino]-5-formyl-pyrimidin-4-yl]-4-[*tert*-butyl(diphenyl)silyl]oxy-2-piperidyl]methyl]carbamate (13a)**



A crude mixture of **Intermediate C** (2.72 g, 4.46 mmol) and K_2CO_3 (1.85 g, 13.4 mmol, 3.0 equiv.) was dissolved in 44 mL of dry DMF (0.1 M) and *N*-methylbenzylamine (812 mg, 6.70 mmol, 1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **13a** (1.31 g, 43% overall yield) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 9.42 (s, 1H), 8.07 (s, 1H), 7.67 (d, *J* = 6.6 Hz, 4H), 7.47–7.26 (m, 11H), 5.19 (s, 2H), 5.01 (d, *J* = 15.1 Hz, 1H), 4.87 (d, *J* = 15.1 Hz, 1H), 4.19 (t, *J* = 3.1 Hz, 1H), 4.11 (ddd, *J* = 15.6, 11.0, 5.6 Hz, 1H), 4.00 (t, *J* = 11.6 Hz, 1H), 3.48–3.28 (m, 2H), 3.15 (s, 3H), 1.95–1.82 (m, 2H), 1.54 (d, *J* = 12.4 Hz, 2H), 1.32 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 182.03, 166.89, 166.01, 158.87, 156.04, 136.81, 135.96, 135.92, 133.80, 133.58, 130.02, 129.99, 128.84, 127.93, 127.92, 127.87, 127.71, 96.45, 78.82, 77.36, 65.87, 55.30, 42.77, 40.20, 33.78, 33.44, 29.82, 28.49, 27.23, 19.21; LRMS (ESI): *m/z* calcd for $C_{40}H_{52}N_5O_4Si^+$ $[M+H]^+$: 694.37; Found: 694.1.

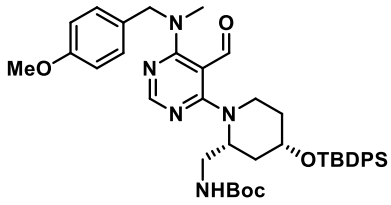
***tert*-Butyl *N*-[[(2*R*,4*S*)-4-[*tert*-butyl(diphenyl)silyl]oxy-1-[5-formyl-6-[isobutyl(methyl)amino]pyrimidin-4-yl]-2-piperidyl]methyl]carbamate (13b)**



A crude mixture of **Intermediate C** (2.72 g, 4.46 mmol) and K_2CO_3 (1.85 g, 13.4 mmol, 3.0 equiv.) was dissolved in 44 mL of dry DMF (0.1 M), and *N*-methyl-isobutyl amine (584 mg, 6.70 mmol, 1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **13b** (1.99 g, 68% overall yield) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 9.38 (s, 1H), 8.02 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 4H), 7.48–7.35 (m, 6H), 5.16 (m, 2H), 4.19 (t, *J* = 3.0 Hz, 1H), 4.10 (td, *J* = 10.8, 10.2, 5.6 Hz, 1H), 3.99 (s, 1H), 3.92 (d, *J* = 12.3 Hz, 1H), 3.52–3.34 (m, 2H), 3.21 (s, 4H), 2.11 (dq, *J* = 8.4, 6.3 Hz, 1H), 1.87 (d, *J* = 16.7 Hz, 2H), 1.54 (s, 2H), 1.30 (s, 9H), 1.12 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 181.99, 166.99, 166.21, 158.64, 156.03, 135.97, 135.92, 133.82, 133.60, 130.02, 129.99, 127.92, 127.87, 96.55, 78.76, 77.41, 77.36, 77.16, 76.91, 65.92, 59.25, 42.68, 41.28, 33.73, 33.45, 29.83, 28.46, 27.23, 27.21, 20.26, 19.89, 19.22, 0.13; LRMS (ESI): *m/z* calcd for $C_{37}H_{54}N_5O_4Si^+$ $[M+H]^+$: 660.39; Found: 660.2.

***tert*-Butyl (((2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-1-(5-formyl-6-((4-methoxybenzyl) (methyl)amino) pyrimidin-4-yl)piperidin-2-yl)methyl)carbamate (13c)**

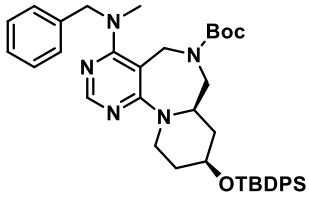


A crude mixture of **Intermediate C** (7.15 g, 11.74 mmol) and K_2CO_3 (4.87 g, 35.21 mmol, 3.0 equiv.) was dissolved in 57 mL of dry DMF (0.2 M), and 4-methoxy-*N*-methylbenzylamine (2.66 g, 17.6 mmol, 1.5 equiv.) was added at r.t. The reaction mixture was stirred at 45 °C for 1 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate

was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **13c** (3.62 g, 43% overall yield) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 9.40 (s, 1H), 8.07 (s, 1H), 7.67 (d, *J* = 6.4 Hz, 4H), 7.41 (ddt, *J* = 27.2, 12.5, 7.3 Hz, 6H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 2H), 4.95–4.79 (m, 2H), 4.19 (s, 1H), 4.11 (ddd, *J* = 15.7, 11.1, 5.3 Hz, 1H), 4.01 (d, *J* = 13.6 Hz, 1H), 3.78 (s, 3H), 3.51–3.27 (m, 2H), 3.13 (s, 3H), 1.87 (q, *J* = 14.3, 9.8 Hz, 2H), 1.54 (d, *J* = 13.5 Hz, 2H), 1.32 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 182.03, 166.74, 165.99, 159.24, 158.85, 156.05, 135.96, 135.92, 133.80, 133.58, 130.02, 129.98, 129.38, 128.79, 127.92, 127.86, 114.20, 96.43, 78.80, 77.36, 65.87, 55.40, 54.72, 42.75, 39.91, 33.78, 33.44, 28.49, 27.22, 19.21; LRMS (ESI): *m/z* calcd for $C_{41}H_{54}N_5O_5Si^+$ $[M+H]^+$: 724.38; Found: 724.4.

tert-Butyl (7a*R*,9*S*)-4-(benzyl(methyl)amino)-9-((_tert_-butyldiphenylsilyl)oxy)-7,7a,8,9,10,11-hexahydropyrido [1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (14a)

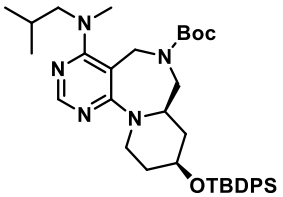


To a solution of **13a** (1.31 g, 1.89 mmol) in 34 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 5.22 g, 45.8 mmol, 24.2 equiv.) at r.t, stirred at r.t for 12 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 38 mL of DCE (0.05 M). Sodium tri acetoxy borohydride ($NABH(OAc)_3$; 802 mg, 3.8 mmol, 2.0 equiv.) was added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, and the crude resultant was dissolved in DCM (36.4 mL, 0.05 M). Dry TEA (572.6 mg, 5.66 mmol, 3.0 equiv.) and Boc_2O (535.2 mg, 2.45 mmol,1.3 equiv.) were sequentially added and stirred at r.t for 30 min. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **14a** (759 mg, 59% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 6.8 Hz, 1H), 7.72–7.62 (m, 4H), 7.42 (dd, *J* = 7.0, 3.4 Hz, 2H), 7.40–7.35 (m, 4H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.32–7.20 (m, 4H), 4.78 (d, *J* = 15.3 Hz, 0.5H), 4.60–4.41 (m, 2H), 4.26 (q, *J* = 13.7, 12.3 Hz, 1H), 4.21–4.08 (m, 1.5H), 3.84 (m, 1.5H), 3.71 (dd, *J* = 14.8, 4.7 Hz, 0.5H), 3.58–3.43 (m, 1H), 3.25 (s, 0.5H), 3.17–2.94 (s, 0.5H), 2.89 (s, 3H), 2.78 (dt, *J* = 24.0, 11.6 Hz, 1H), 1.89 (d, *J* = 12.6 Hz, 1H), 1.85–1.78 (m, 1H), 1.78–1.70 (m, 0.4H), 1.66 (d, *J* = 9.4 Hz, 1H), 1.58–1.50 (m, 0.6H), 1.43 (s, 3.5H), 1.30 (s, 5.5H), 1.06 (d, *J* = 4.8 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.83, 165.68, 165.34, 165.03, 156.26, 155.45, 155.21, 138.12, 135.88, 135.85, 134.39, 134.30, 134.07, 129.83, 129.78, 128.77, 128.64, 127.77, 127.73, 127.30, 96.74, 96.52, 80.24, 80.04, 70.45, 70.16, 57.99, 57.76, 56.63, 55.56, 46.89, 46.32, 45.79, 45.50, 45.05, 44.78, 39.98, 39.86, 38.69, 37.89, 35.60, 35.35, 28.49, 28.22, 27.05, 19.48, 19.20; LRMS (ESI): *m/z* calcd for $C_{40}H_{52}N_5O_3Si^+$ $[M+H]^+$: 678.38; Found: 678.1.

tert-Butyl (7a*R*,9*S*)-9-((_tert_-butyldiphenylsilyl)oxy)-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (14b)

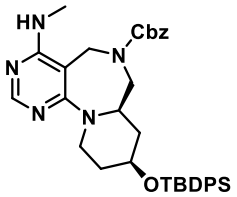
To a solution of **13b** (1.99 g, 3.02 mmol) in 60 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 9.21 g, 80.8 mmol, 26.7 equiv.) at r.t and stirred at r.t for 12 h. After the completion of the reaction, as indicated by TLC, LC-MS, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 61 mL of DCE (0.05 M). Sodium tri acetoxy borohydride ($NABH(OAc)_3$; 1.60 g, 7.57 mmol, 2.5 equiv.) was added and stirred at r.t for 6 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, and the crude resultant



was dissolved in DCM (58.5 mL, 0.05 M). Dry TEA (921.1 mg, 9.10 mmol, 3.0 equiv.) and Boc_2O (861 mg, 3.94 mmol,1.3 equiv.) were sequentially added and stirred at r.t for 30 min. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **14b** (1.19 g, 62% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.20 (s, 1H), 7.71–7.65 (m, 4H), 7.45–7.41 (m, 2H), 7.38 (m, 4H), 4.45 (d, *J* = 13.6 Hz, 0.5H), 4.25 (q, *J* = 13.6 Hz, 1H), 4.14 (dt, *J* = 13.4, 4.0 Hz, 1.5H), 3.84 (tt, *J* = 9.6, 5.0 Hz, 1.5H), 3.70 (m, 0.5H), 3.57 (d, *J* = 14.6 Hz, 0.5H), 3.52–3.45 (m, 1H), 3.31 (s, 1H), 3.15–3.07 (m, 0.5H), 3.00 (t, *J* = 8.4 Hz, 1H), 2.96 (s, 3H), 2.82–2.65 (m, 1H), 2.05–1.97 (m, 1H), 1.93–1.86 (m, 1H), 1.79 (d, *J* = 8.8 Hz, 1H), 1.76–1.70 (m, 0.5H), 1.64 (q, *J* = 12.9, 12.1 Hz, 1.5H), 1.48 (d, *J* = 8.9 Hz, 9H), 1.06 (d, *J* = 1.8 Hz, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 1.5H), 0.78 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 166.19, 165.97, 165.24, 164.96, 156.27, 156.16, 155.31, 155.25, 135.90, 135.87, 134.41, 134.32, 134.13, 129.83, 129.79, 127.78, 127.73, 96.53, 96.42, 80.22, 80.12, 70.66, 70.22, 59.84, 59.56, 58.11, 57.59, 46.79, 46.37, 46.10, 45.65, 45.26, 44.67, 40.23, 39.97, 39.16, 39.07, 35.72, 35.36, 28.54, 27.07, 27.05, 26.92, 26.89, 20.30, 20.27, 20.14, 20.09, 19.22; LRMS (ESI): *m/z* calcd for $C_{37}H_{54}N_5O_3Si^+$ $[M+H]^+$: 644.39; Found: 644.2.

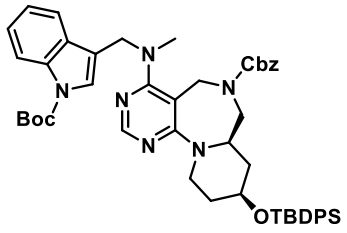
Benzyl (7a*R*,9*S*)-9-((*tert*-butyldiphenylsilyl)oxy)-4-(methylamino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (Intermediate D)



To a solution of **13c** (3.62 g, 5.00 mmol) in 200 mL of DCE (0.025 M) was added trifluoroacetic acid (TFA; 15.35 g, 134.6 mmol, 26.7 equiv.) at r.t, stirred at r.t for 12 h. After the cyclization, the reaction mixture was warmed to 70 °C and stirred for 24 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 100 mL of DCE (0.05 M). Sodium tri acetoxy borohydride ($NABH(OAc)_3$; 4.24 g, 20.0 mmol, 4.0 equiv.) was added and stirred at r.t for 12 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted three times with DCM. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, and the crude resultant was dissolved in ACN (98 mL, 0.05 M). Dry TEA (1.52 g, 15.0 mmol, 3.0 equiv.) and benzyl carbonochloridate (Cbz-Cl; 938.8 mg, 5.50 mmol, 1.1 equiv.) were sequentially added at 0 °C and stirred at 0 °C for 1.5 h. After the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with DCM three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **Intermediate D** (1.63 g, 52% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 5.2 Hz, 1H), 7.66 (d, *J* = 6.9 Hz, 4H), 7.42 (d, *J* = 6.9 Hz, 2H), 7.40–7.27 (m, 9H), 5.23–5.09 (m, 2H), 5.01 (q, *J* = 4.8 Hz, 0.6H), 4.37 (dd, *J* = 33.9, 14.9 Hz, 1H), 4.27 (dd, *J* = 17.9, 14.8 Hz, 1H), 4.04–3.95 (m, 1H), 3.84 (tq, *J* = 17.0, 7.5, 5.9 Hz, 1.4H), 3.74 (dd, *J* = 14.4, 7.0 Hz, 0.6H), 3.47 (ddd, *J* = 24.2, 14.3, 2.9 Hz, 1H), 3.34 (d, *J* = 9.2 Hz, 0.4H), 3.26 (tt, *J* = 7.2, 3.1 Hz, 0.6H), 3.01–2.87 (m, 3H), 2.82 (d, *J* = 4.7 Hz, 1H), 1.85–1.73 (m, 2H), 1.71–1.56 (m, 2H), 1.06 (d, *J* = 9.3 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 163.46, 161.56, 161.29, 157.08, 156.99, 156.56, 155.60, 136.52, 135.90, 135.87, 134.33, 134.27, 134.21, 134.14, 129.84, 128.85, 128.70, 128.49, 128.34, 128.22, 128.12, 127.79, 127.77, 127.75, 95.68, 95.40, 77.36, 69.92, 69.68, 67.69, 56.65, 56.57, 48.58, 44.67, 44.34, 41.89, 39.63, 39.30, 35.02, 34.92, 28.56, 27.08, 27.05, 19.21; LRMS (ESI): *m/z* calcd for $C_{36}H_{44}N_5O_3Si^+$ $[M+H]^+$: 622.32; Found: 622.4.

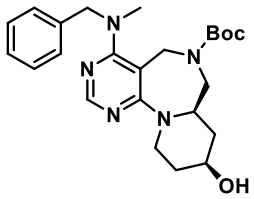
Benzyl (7a*R*,9*S*)-4-(((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)(methyl)amino)-9-((*tert*-butyldiphenylsilyl) oxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (14c)



A mixture of **Intermediate D** (1.63 g, 2.62 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 209.3 mg, 5.23 mmol, 2.0 equiv.) was cooled to 0 °C and dissolved in 26.2 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, **S7** (1.22 g, 3.92 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **14c** (1.64 g, 74% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (s, 1H), 8.10 (s, 1H), 7.67 (dt, *J* = 12.7, 6.4 Hz, 4H), 7.51 (d, *J* = 16.2 Hz, 1H), 7.44–7.34 (m, 7H), 7.29 (td, *J* = 14.1, 12.4, 5.7 Hz, 3H), 7.23–7.14 (m, 3H), 7.09 (dd, *J* = 6.5, 3.0 Hz, 1H), 5.15–5.00 (m, 1H), 4.93 (t, *J* = 15.6 Hz, 1H), 4.76 (dd, *J* = 22.5, 14.0 Hz, 1H), 4.55 (t, *J* = 16.4 Hz, 1H), 4.48–4.30 (m, 2H), 4.09 (tt, *J* = 13.4, 4.2 Hz, 1H), 3.98 (td, *J* = 13.7, 13.1, 6.0 Hz, 1H), 3.87 (tq, *J* = 9.8, 4.8 Hz, 1H), 3.57 (ddd, *J* = 36.4, 14.5, 2.8 Hz, 1H), 3.34 (s, 0.6H), 3.22 (s, 0.4H), 2.86 (m, 4H), 1.91–1.75 (m, 2H), 1.67 (s, 9H), 1.65 (m, 2H), 1.06 (d, *J* = 6.7 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.81, 165.74, 165.36, 165.15, 156.31, 155.83, 155.67, 149.80, 136.61, 135.92, 135.88, 135.86, 134.34, 134.23, 134.15, 134.06, 129.98, 129.86, 129.82, 128.63, 128.51, 128.23, 128.08, 128.00, 127.79, 127.76, 127.74, 127.59, 124.73, 124.66, 124.61, 124.17, 122.87, 119.71, 119.42, 119.23, 117.66, 117.41, 115.47, 115.39, 96.60, 96.49, 83.90, 77.36, 69.89, 67.47, 67.07, 57.17, 56.99, 47.70, 47.22, 47.02, 46.89, 45.73, 45.48, 44.21, 39.40, 38.66, 35.15, 29.82, 28.35, 28.31, 27.08, 27.05, 19.21, 19.20; LRMS (ESI): *m/z* calcd for $C_{50}H_{59}N_6O_5Si^+$ $[M+H]^+$: 851.43; Found: 851.4.

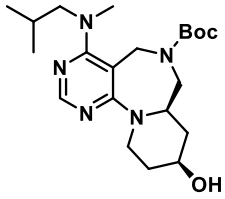
***tert*-Butyl (7a*R*,9*S*)-4-(benzyl(methyl)amino)-9-hydroxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (S14)**



To a solution of **14a** (758 mg, 1.12 mmol) in 8.4 mL of tetrahydrofuran (THF; 0.1 M) was added tetrabutylammonium fluoride (TBAF; 731 mg, 2.80 mmol, 2.5 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **S14** (470 mg, 96% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (d, *J* = 4.1 Hz, 1H), 7.30 (m, 5H), 4.81 (d, *J* = 15.3 Hz, 0.4H), 4.65–4.46 (m, 2H), 4.38 (d, *J* = 13.7 Hz, 0.6H), 4.33–4.26 (m, 1H), 4.20 (dd, *J* = 18.6, 13.5 Hz, 1H), 4.00–3.79 (m, 2H), 3.61 (dt, *J* = 15.6, 5.1 Hz, 1H), 3.45–3.25 (m, 1H), 3.08–2.95 (m, 1H), 2.92 (s, 3H), 2.12–1.94 (m, 3H), 1.79 (s, 0.5H), 1.63–1.51 (m, 1.5H), 1.46 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.85, 165.73, 165.39, 165.15, 156.33, 155.49, 155.10, 138.05, 128.82, 128.69, 127.77, 127.36, 127.31, 96.90, 96.58, 80.42, 80.24, 69.31, 68.86, 58.27, 57.92, 56.63, 55.55, 46.84, 46.13, 45.78, 45.42, 44.98, 39.98, 39.55, 38.70, 37.91, 35.60, 35.09, 28.51, 28.24; LRMS (ESI): *m/z* calcd for $C_{24}H_{34}N_5O^+$ $[M+H]^+$: 440.26; Found: 440.1.

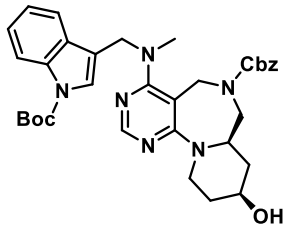
***tert*-Butyl (7a*R*,9*S*)-9-hydroxy-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (S15)**



To a solution of **14b** (736 mg, 1.14 mmol) in 8.0 mL of tetrahydrofuran (THF; 0.1 M) was added tetrabutylammonium fluoride (TBAF; 747 mg, 2.86 mmol, 2.5 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **S15** (445 mg, 96% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 3.5 Hz, 1H), 4.50 (d, *J* = 13.6 Hz, 0.5H), 4.36 (d, *J* = 13.7 Hz, 0.5H), 4.27 (m, 1H), 4.18 (d, *J* = 13.7 Hz, 0.5H), 4.15–4.09 (m, 0.5H), 3.90 (m, 2H), 3.61 (ddd, *J* = 13.4, 10.6, 2.7 Hz, 1H), 3.51–3.21 (m, 2H), 3.05 (m, 1.5H), 2.98 (d, *J* = 3.4 Hz, 3H), 2.94–2.82 (m, 0.5H), 2.25–1.98 (m, 4H), 1.64–1.50 (m, 2H), 1.48 (d, *J* = 6.3 Hz, 9H), 0.87 (dd, *J* = 6.6, 2.8 Hz, 3H), 0.81 (dd, *J* = 11.4, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 166.15, 165.98, 165.23, 165.03, 156.30, 156.18, 155.33, 155.13, 96.59, 96.44, 80.39, 80.28, 69.38, 68.80, 59.82, 59.58, 58.29, 57.68, 46.74, 46.07, 45.55, 45.49, 44.80, 40.12, 39.60, 39.07, 39.05, 35.66, 35.11, 29.81, 28.54, 26.90, 26.87, 20.29, 20.08; LRMS (ESI): *m/z* calcd for $C_{21}H_{36}N_5O_3^+$ $[M+H]^+$: 406.28; Found: 406.1.

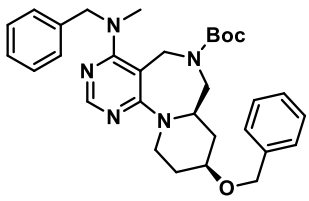
Benzyl (7a*R*,9*S*)-4-(((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)(methyl)amino)-9-hydroxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (S16)



To a solution of **14c** (1.64 g, 1.93 mmol) in 15.4 mL of tetrahydrofuran (THF; 0.1 M) was added tetrabutylammonium fluoride (TBAF; 1M THF solution, 1.01 g, 3.85 mmol, 2.5 equiv.) at r.t, stirred at r.t for 3 h. After the completion of the reaction, as indicated by TLC, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **S16** (1.17 g, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.31 (d, *J* = 4.2 Hz, 1H), 8.10 (s, 1H), 7.52 (d, *J* = 11.0 Hz, 1H), 7.38 (t, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 6.2 Hz, 3H), 7.25–7.13 (m, 3H), 7.10–7.07 (m, 1H), 5.41–5.00 (m, 1H), 4.91 (dd, *J* = 18.2, 13.7 Hz, 1H), 4.80–4.75 (m, 1H), 4.60 (d, *J* = 14.9 Hz, 0.5H), 4.56–4.48 (m, 1H), 4.45 (d, *J* = 13.7 Hz, 0.5H), 4.32–4.20 (m, 2H), 3.92 (dtd, *J* = 36.6, 22.0, 18.4, 8.2 Hz, 2H), 3.69 (d, *J* = 14.7 Hz, 1H), 3.45–3.25 (m, 1H), 3.04–2.94 (m, 1H), 2.88 (d, *J* = 32.5 Hz, 3H), 2.07–2.02 (m, 1H), 2.01–1.90 (m, 1H), 1.73 (d, *J* = 7.8 Hz, 1H), 1.67 (s, 9H), 1.59–1.41 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.72, 165.58, 165.46, 165.25, 156.54, 156.47, 155.92, 155.59, 149.80, 136.49, 135.81, 129.98, 129.74, 128.66, 128.51, 128.28, 128.15, 128.03, 127.64, 124.75, 124.67, 124.17, 122.88, 119.33, 119.19, 117.60, 117.34, 115.51, 115.44, 96.48, 96.28, 83.93, 77.36, 69.08, 68.83, 67.54, 67.20, 57.88, 57.76, 47.73, 46.83, 46.67, 45.95, 45.63, 45.28, 45.04, 39.85, 39.72, 38.62, 35.41, 35.14, 28.36; LRMS (ESI): *m/z* calcd for $C_{34}H_{41}N_6O_5^+$ $[M+H]^+$: 613.31; Found: 613.4.

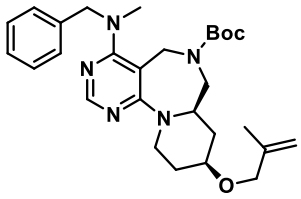
***tert*-Butyl (7a*R*,9*S*)-4-(benzyl(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido [5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15a** or **3s)**



A mixture of **S14** (120 mg, 0.273 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 32.8 mg, 0.82 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 2.7 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (70.0 mg, 0.410 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15a (**or **3s)** (120 mg, 83% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (s, 1H), 7.35 (d, *J* = 4.1 Hz, 5H), 7.31–7.22 (m, 5H), 4.80–4.36 (m, 5H), 4.34–4.15 (m, 2H), 3.98 (dd, *J* = 14.7, 5.5 Hz, 0.65H), 3.89 (dd, *J* = 15.0, 5.3 Hz, 0.35H), 3.64 (tq, *J* = 9.9, 6.2, 4.5 Hz, 1H), 3.56 (dd, *J* = 14.8, 2.8 Hz, 1H), 3.39–3.28 (m, 1H), 3.00 (q, *J* = 12.7, 12.1 Hz, 1H), 2.90 (s, 3H), 2.16–2.11 (m, 1.5H), 2.06–2.00 (m, 0.5H), 1.66–1.50 (m, 2H), 1.43 (s, 2.5H), 1.29 (s, 6.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.83, 165.34, 165.11, 156.28, 155.50, 155.03, 138.60, 138.08, 128.78, 128.65, 128.56, 127.78, 127.71, 127.66, 127.63, 127.32, 96.80, 80.25, 80.16, 77.36, 75.45, 75.25, 70.04, 58.01, 57.82, 56.59, 55.59, 47.11, 46.15, 45.76, 45.30, 44.99, 44.78, 38.70, 37.91, 36.57, 32.21, 29.81, 29.47, 28.51, 28.24; LRMS (ESI): *m/z* calcd for $C_{31}H_{40}N_5O_3^+$ $[M+H]^+$: 530.31; Found: 530.2.

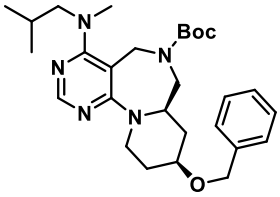
***tert*-Butyl (7a*R*,9*S*)-4-(benzyl(methyl)amino)-9-((2-methylallyl)oxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a] pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15b)**



A mixture of **S14** (150 mg, 0.341 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 41 mg, 1.02 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.4 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (69.1 mg, 0.512 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15b** (160 mg, 94% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.27 (d, *J* = 6.3 Hz, 1H), 7.37–7.22 (m, 5H), 4.98 (s, 1H), 4.89 (s, 1H), 4.82–4.53 (m, 2H), 4.53–4.44 (m, 0.5H), 4.38 (d, *J* = 13.7 Hz, 0.5H), 4.30–4.14 (m, 2H), 3.96 (m, 3H), 3.60–3.51 (m, 2H), 3.36 (d, *J* = 10.1 Hz, 1H), 3.02 (d, *J* = 13.7 Hz, 1H), 2.90 (s, 3H), 2.12–1.96 (m, 2H), 1.75 (d, *J* = 5.4 Hz, 3H), 1.64–1.48 (m, 2 H), 1.44 (s, 2.5H), 1.28 (s, 6.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.84, 165.35, 165.11, 156.26, 155.51, 155.06, 142.54, 138.08, 128.78, 128.65, 127.78, 127.31, 112.21, 112.06, 96.81, 80.24, 80.14, 77.36, 75.28, 75.11, 72.10, 57.97, 57.82, 56.61, 55.60, 47.11, 46.16, 45.75, 45.31, 44.95, 44.76, 38.70, 37.90, 36.51, 32.20, 32.07, 28.51, 28.22, 19.65; LRMS (ESI): *m/z* calcd for $C_{28}H_{40}N_5O_3^+$ $[M+H]^+$: 494.31; Found: 494.1.

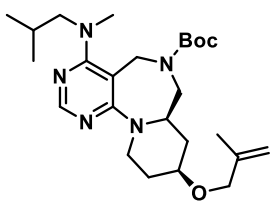
***tert*-Butyl (7a*R*,9*S*)-9-(benzyloxy)-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido [5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15c)**



A mixture of **S15** (120 mg, 0.295 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 35.5 mg, 0.89 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.2 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (75.9 mg, 0.443 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15c** (130 mg, 88% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 2.1 Hz, 1H), 7.37–7.27 (m, 5H), 4.65–4.55 (m, 2H), 4.48 (d, *J* = 13.8 Hz, 0.5H), 4.39 (d, *J* = 13.8 Hz, 0.5H), 4.32–4.25 (m, 1H), 4.15 (dd, *J* = 13.7, 8.3 Hz, 1H), 4.00 (dd, *J* = 15.1, 5.3 Hz, 0.6H), 3.86 (dd, *J* = 14.9, 4.9 Hz, 0.4H), 3.68–3.54 (m, 2H), 3.52–3.39 (m, 1H), 3.38–3.22 (m, 1H), 3.08–3.00 (m, 1H), 2.97 (s, 4H), 2.16–2.12 (m, 1.3H), 2.07–2.00 (m, 1.7H), 1.66–1.54 (m, 2H), 1.48 (s, 9H), 0.87 (t, *J* = 5.8 Hz, 3H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 166.16, 166.06, 165.22, 165.02, 156.18, 155.36, 155.07, 138.70, 138.62, 128.56, 127.72, 127.67, 127.64, 96.53, 80.25, 80.21, 75.75, 75.32, 70.07, 70.05, 59.83, 59.61, 58.04, 57.83, 46.95, 46.05, 45.45, 45.12, 44.87, 39.15, 39.07, 36.97, 36.70, 32.25, 28.56, 26.92, 26.89, 20.32, 20.10, 20.07; LRMS (ESI): *m/z* calcd for $C_{28}H_{42}N_5O_3^+$ $[M+H]^+$: 496.32; Found: 496.2.

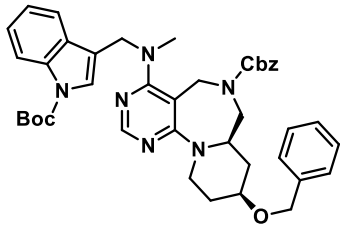
***tert*-Butyl (7a*R*,9*S*)-4-(isobutyl(methyl)amino)-9-((2-methylallyl)oxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a] pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15d)**



A mixture of **S15** (120 mg, 0.295 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 35.5 mg, 0.89 mmol, 3.0 equiv.) was cooled to 0 °C and dissolved in 3.2 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (59.9 mg, 0.443 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15d** (116 mg, 85% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 2.5 Hz, 1H), 4.99 (s, 1H), 4.90 (s, 1H), 4.47 (d, *J* = 13.7 Hz, 0.4H), 4.38 (d, *J* = 13.7 Hz, 0.6H), 4.33–4.23 (m, 1H), 4.15 (dd, *J* = 13.7, 9.7 Hz, 1H), 4.04–3.85 (m, 3H), 3.57 (ddt, *J* = 15.3, 10.2, 4.2 Hz, 2H), 3.51–3.24 (m, 2H), 3.07–2.90 (m, 5H), 2.09 (tt, *J* = 8.9, 4.2 Hz, 1.7H), 2.01 (q, *J* = 8.1, 7.4 Hz, 1.3H), 1.75 (s, 3H), 1.64–1.51 (m, 2H), 1.48 (d, *J* = 5.6 Hz, 9H), 0.88 (t, *J* = 5.5 Hz, 3H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 166.17, 166.06, 165.24, 165.03, 156.17, 155.37, 155.11, 142.67, 142.56, 112.21, 112.06, 96.56, 80.25, 80.19, 75.58, 75.16, 72.10, 72.08, 59.83, 59.60, 58.06, 57.81, 46.96, 46.15, 46.05, 45.48, 45.11, 44.84, 39.17, 39.07, 36.92, 36.63, 32.23, 28.56, 28.54, 26.91, 26.89, 20.31, 20.09, 20.07, 19.68, 19.66; LRMS (ESI): *m/z* calcd for $C_{25}H_{42}N_5O_3^+$ $[M+H]^+$: 460.32; Found: 460.2.

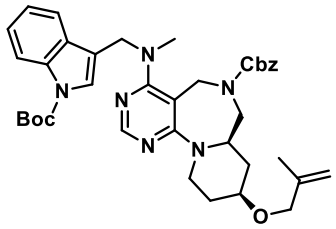
Benzyl (7a*R*,9*S*)-9-(benzyloxy)-4-(((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)(methyl)amino)-7, 7a,8,9 ,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15e)



A mixture of **S16** (566.8 mg, 0.925 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 92.5 mg, 2.31 mmol, 2.5 equiv.) was cooled to 0 °C and dissolved in 9.1 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, Benzyl bromide (237.3 mg, 1.39 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t, and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15e** (424 mg, 66% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): 8.31 (d, *J* = 3.5 Hz, 1H), 8.10 (s, 1H), 7.52 (d, *J* = 15.3 Hz, 1H), 7.43–7.26 (m, 9H), 7.24–7.15 (m, 3H), 7.09–7.06 (m, 1H), 5.15 (d, *J* = 12.3 Hz, 0.5H), 5.03 (d, *J* = 12.3 Hz, 0.5H), 4.96–4.87 (m, 1H), 4.79 (dd, *J* = 13.9, 9.5 Hz, 1H), 4.61–4.41 (m, 4H), 4.28 (dd, *J* = 18.5, 13.8 Hz, 2H), 4.02 (ddd, *J* = 29.7, 14.8, 5.4 Hz, 1H), 3.65 (ddd, *J* = 15.3, 9.5, 4.9 Hz, 2H), 3.40 (s, 0.6H), 3.32 (s, 0.4H), 2.99 (m, 1H), 2.88 (d, *J* = 32.5 Hz, 3H), 2.17–2.08 (m, 1.6H), 1.98 (d, *J* = 13.0 Hz, 0.4H), 1.67 (s, 9H), 1.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.75, 165.23, 156.44, 155.96, 155.57, 138.58, 136.66, 136.50, 135.83, 129.75, 128.66, 128.59, 128.51, 128.26, 128.11, 128.02, 127.75, 127.69, 127.61, 124.76, 124.69, 124.18, 122.90, 119.40, 119.21, 117.62, 117.39, 115.51, 115.43, 96.41, 83.94, 75.21, 70.07, 70.00, 67.46, 67.19, 57.78, 57.56, 47.73, 46.86, 45.85, 45.61, 44.97, 38.63, 36.66, 36.47, 32.19, 28.37; LRMS (ESI): *m/z* calcd for $C_{41}H_{47}N_6O_5^+$ $[M+H]^+$: 703.36; Found: 703.4.

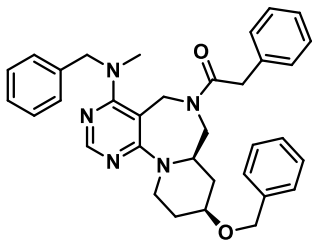
Benzyl (7a*R*,9*S*)-4-(((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)(methyl)amino)-9-((2-methylallyl)oxy)-7, 7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepine-6(5*H*)-carboxylate (15f)



A mixture of **S16** (588.2 mg, 0.960 mmol) and sodium hydride (NaH; 60% dispersion in mineral oil, 96 mg, 2.4 mmol, 2.5 equiv.) was cooled to 0 °C and dissolved in 9.5 mL of dry DMF (0.1 M) under argon atmospheric condition. After stirring at 0 °C for 0.5 h, 3-bromo-2-methyl-prop-1-ene (194.4 mg, 1.44 mmol, 1.5 equiv.) was added to the reaction mixture, warmed to r.t and stirred at r.t for 2 h. After the completion of the reaction, as indicated by TLC, saturated NH_4Cl solution was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **15f** (555 mg, 86% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.31 (d, *J* = 2.6 Hz, 1H), 8.10 (s, 1H), 7.55–7.48 (m, 1H), 7.43–7.30 (m, 4H), 7.23–7.15 (m, 3H), 7.09–7.06 (m, 1H), 5.15 (d, *J* = 12.2 Hz, 0.5H), 5.04 (d, *J* = 12.3 Hz, 0.5H), 4.99–4.90 (m, 2H), 4.88 (d, *J* = 8.9 Hz, 1H), 4.80 (d, *J* = 13.2 Hz, 1.5H), 4.58 (d, *J* = 15.0 Hz, 0.5H), 4.49 (dd, *J* = 26.4, 14.7 Hz, 2H), 4.28 (d, *J* = 14.0 Hz, 2H), 4.03 (m, 1H), 3.92 (d, *J* = 20.4 Hz, 2H), 3.65 (d, *J* = 14.3 Hz, 1H), 3.59–3.53 (m, 1H), 3.50–3.48 (m, 1H), 3.41 (s, 0.6H), 3.35 (s, 0.4H), 3.09–2.99 (m, 1H), 2.91 (s, 1H), 2.84 (s, 2H), 2.08 (d, *J* = 12.5 Hz, 1.6H), 1.94 (d, *J* = 12.9 Hz, 0.4H), 1.74 (d, *J* = 6.5 Hz, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 165.85, 156.44, 156.00, 142.62, 136.61, 128.66, 128.54, 128.13, 128.04, 127.66, 124.77, 124.27, 122.92, 119.26, 117.69, 115.53, 112.18, 96.64, 83.94, 77.36, 75.07, 72.16, 67.50, 67.24, 57.74, 51.00, 47.74, 47.05, 45.64, 38.69, 36.57, 32.15, 28.40, 19.67; LRMS (ESI): *m/z* calcd for $C_{38}H_{47}N_6O_5^+$ $[M+H]^+$: 667.36; Found: 667.4.

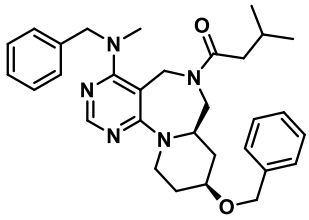
1-((7a*R*,9*S*)-4-(Benzyl(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3a)



To a solution of **15a** (25.7 mg, 0.048 mmol) in 1.0 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 149 mg, 1.31 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.94 mL of DMF (0.05 M). Dry TEA (24.6 mg, 0.24 mmol, 5.0 equiv.) and **S1** (17.0 mg, 0.073 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3a** (15.8 mg, 60% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (d, *J* = 14.2 Hz, 1H), 7.45–7.16 (m, 14H), 7.12–7.08 (m, 1H), 4.80–4.60 (m, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.57–4.45 (m, 2H), 4.44–4.31 (m, 2H), 4.25–4.18 (m, 1H), 4.10 (d, *J* = 13.4 Hz, 0.5H), 3.80 (dd, *J* = 14.6, 6.0 Hz, 0.5H), 3.77–3.70 (m, 0.8H), 3.68–3.50 (m, 2H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.27–3.19 (m, 1.2H), 3.09 (d, *J* = 13.9 Hz, 0.5H), 3.00 (t, *J* = 12.5 Hz, 0.5H), 2.82 (d, *J* = 38.1 Hz, 3H), 2.16–2.04 (m, 1.6H), 1.76 (s, 1H), 1.59 (dt, *J* = 13.1, 7.3 Hz, 1.4H), 1.49 (dt, *J* = 12.6, 9.6 Hz, 0.4H), 1.38 (dt, *J* = 12.7, 10.5 Hz, 0.6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.24, 170.11, 165.89, 165.21, 164.92, 156.48, 156.28, 138.57, 138.53, 137.97, 137.93, 134.90, 134.24, 129.06, 129.04, 128.96, 128.76, 128.69, 128.63, 128.60, 128.57, 127.83, 127.72, 127.65, 127.63, 127.32, 127.11, 127.08, 127.05, 96.19, 74.93, 74.71, 70.00, 69.94, 57.87, 56.86, 55.59, 47.19, 44.80, 44.23, 41.88, 40.62, 38.63, 37.85, 36.41, 35.77, 32.10, 31.61; LRMS (ESI): *m/z* calcd for $C_{34}H_{38}N_5O_2^+$ $[M+H]^+$: 548.30; Found: 548.1.

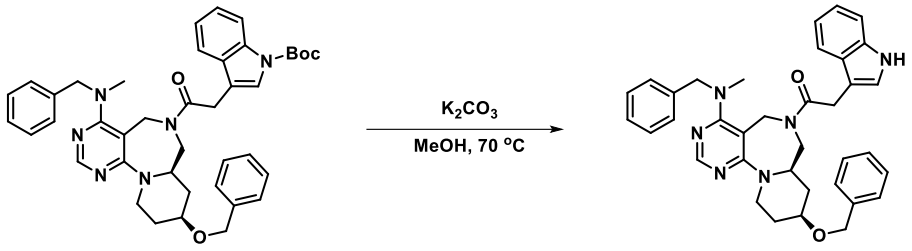
1-((7a*R*,9*S*)-4-(benzyl(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3b)



To a solution of **15a** (25.7 mg, 0.048 mmol) in 1.0 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 149 mg, 1.31 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (36.4 mg, 0.36 mmol, 5.0 equiv.) and **S2** (14.5 mg, 0.073 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3b** (9.7 mg, 39% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (d, *J* = 22.6 Hz, 1H), 7.40–7.27 (m, 9H), 7.26–7.22 (m, 1H), 4.73 (d, *J* = 15.3 Hz, 0.4H), 4.63 (d, *J* = 11.8 Hz, 0.6H), 4.57 (t, *J* = 3.5 Hz, 2H), 4.55–4.51 (m, 1H), 4.46 (d, *J* = 16.5 Hz, 0.8H), 4.40 (s, 0.5H), 4.36 (d, *J* = 13.1 Hz, 1.2H), 4.26 (t, *J* = 4.0 Hz, 0.5H), 4.22 (d, *J* = 13.0 Hz, 1H), 4.16 (d, *J* = 12.7 Hz, 0.5H), 3.85 (m, 0.5H), 3.74–3.59 (m, 1.5H), 3.52 (d, *J* = 14.9 Hz, 1H), 3.39–3.28 (m, 0.7H), 3.17 (s, 0.3H), 3.00 (t, *J* = 12.4 Hz, 0.5H), 2.90 (d, *J* = 50.9 Hz, 3H), 2.17–2.09 (m, 2H), 1.99 (m, 1H), 1.74–1.70 (m, 1H), 1.66–1.62 (m, 0.4H), 1.60 (m, 0.3H), 1.53 (m, 0.6H), 1.43 (m, 0.7H), 0.89 (dd, *J* = 16.0, 6.5 Hz, 2H), 0.78 (dd, *J* = 6.7, 3.5 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.74, 171.63, 165.88, 165.32, 165.02, 156.50, 156.24, 138.53, 138.51, 138.01, 137.85, 129.08, 128.68, 128.63, 128.59, 127.84, 127.75, 127.68, 127.65, 127.30, 126.90, 96.61, 96.54, 75.06, 70.28, 70.07, 57.90, 57.28, 55.47, 46.72, 44.88, 44.42, 44.17, 42.54, 41.30, 38.60, 37.79, 36.57, 36.03, 32.19, 31.62, 25.83, 24.80, 22.77, 22.72, 22.57; LRMS (ESI): *m/z* calcd for $C_{31}H_{40}N_5O_2^+$ $[M+H]^+$: 514.31; Found: 514.1.

1-((7a*R*,9*S*)-4-(Benzyl(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (3c)



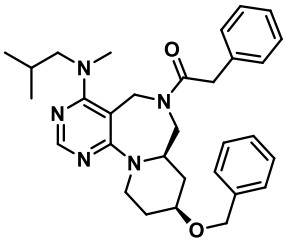
3c' 3c

To a solution of **15a** (38.6 mg, 0.072 mmol) in 1.5 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 224 mg, 1.97 mmol, 26.9 equiv.) at r.t, stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.4 mL of DCM (0.05 M). Dry TEA (36.4 mg, 0.36 mmol, 5.0 equiv.) and **S5** (40.7 mg, 0.11 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 3 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3c′** (37.6 mg, 75% overall yield) as a white solid. To a solution of **3c′** (25 mg, 0.036 mmol) in 1.46 mL of MeOH (0.025 M) was added potassium carbonate (K_2CO_3; 25.2 mg, 0.182 mmol, 5.0 equiv.), stirred at 70 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3c** (10.8 mg, 50% yield) as a white solid.

3c′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 13.6 Hz, 1H), 8.10 (s, 1H), 7.54–7.16 (m, 14H), 4.72 (d, *J* = 15.3 Hz, 0.5H), 4.57 (d, *J* = 19.0 Hz, 0.5H), 4.52 (d, *J* = 5.7 Hz, 1H), 4.49 (d, *J* = 7.7 Hz, 0.5H), 4.46 (d, *J* = 2.6 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.41–4.37 (m, 1H), 4.31 (d, *J* = 13.4 Hz, 0.5H), 4.19–4.10 (m, 1H), 3.87 (dd, *J* = 14.5, 5.9 Hz, 0.5H), 3.83–3.71 (m, 1H), 3.71–3.65 (m, 0.5H), 3.64–3.44 (m, 2H), 3.39 (s, 1H), 3.26 (d, *J* = 16.1 Hz, 0.5H), 3.14 (d, *J* = 16.1 Hz, 0.5H), 3.07 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.84 (d, *J* = 60.5 Hz, 3H), 2.07 (dq, *J* = 14.9, 6.5, 4.9 Hz, 1.5H), 1.87 (s, 1H), 1.77 (dt, *J* = 12.2, 3.6 Hz, 0.5H), 1.63 (d, *J* = 16.4 Hz, 9H), 1.39 (q, *J* = 10.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.41, 169.49, 165.99, 165.71, 165.22, 164.82, 156.34, 156.25, 149.64, 138.51, 138.43, 137.91, 137.81, 135.45, 130.11, 129.89, 129.09, 128.61, 128.55, 128.50, 127.77, 127.66, 127.59, 127.23, 127.13, 126.81, 124.85, 124.64, 124.18, 123.85, 122.84, 122.65, 119.25, 119.10, 115.39, 115.34, 113.99, 113.48, 96.28, 96.07, 83.92, 83.68, 74.46, 69.95, 69.90, 57.32f, 56.77, 55.25, 47.08, 45.24, 44.37, 44.12, 38.79, 37.73, 35.90, 31.77, 31.64, 30.32, 28.28, 28.25; LRMS (ESI): *m/z* calcd for $C_{41}H_{47}N_6O_4^+$ $[M+H]^+$: 687.36; Found: 687.1.

3c ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.24 (d, *J* = 6.2 Hz, 1H), 8.06 (d, *J* = 42.9 Hz, 1H), 7.53 (dd, *J* = 26.0, 7.9 Hz, 1H), 7.40–7.26 (m, 8H), 7.26–7.18 (m, 2H), 7.18–7.13 (m, 1H), 7.08 (td, *J* = 7.5, 2.7 Hz, 1H), 6.92 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.74–4.47 (m, 3H), 4.44–4.34 (m, 2H), 4.27 (dd, *J* = 20.3, 14.7 Hz, 1H), 4.22–4.08 (m, 1H), 3.83–3.76 (m, 1H), 3.64 (dd, *J* = 14.5, 2.8 Hz, 0.5H), 3.60–3.51 (m, 1H), 3.45 (tt, *J* = 9.5, 4.6 Hz, 0.5H), 3.40 (s, 1H), 3.32 (s, 0.6H), 3.17 (s, 0.4H), 2.96 (t, *J* = 12.1 Hz, 1H), 2.75 (d, *J* = 58.9 Hz, 3H), 2.11–2.00 (m, 1.5H), 1.71 (s, 1H), 1.56–1.47 (m, 1H), 1.45–1.25 (m, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.56, 170.80, 166.00, 165.75, 165.23, 164.85, 156.38, 156.30, 138.66, 138.60, 138.14, 138.03, 136.19, 136.15, 129.01, 128.68, 128.60, 128.58, 127.84, 127.81, 127.74, 127.65, 127.63, 127.60, 127.32, 127.30, 127.21, 126.89, 122.91, 122.70, 122.52, 122.40, 119.97, 119.78, 119.00, 118.64, 111.37, 111.29, 109.15, 108.46, 96.39, 96.16, 74.89, 69.89, 69.86, 57.79, 57.00, 56.70, 55.49, 47.25, 44.86, 44.62, 44.38, 38.66, 38.04, 36.33, 35.97, 32.08, 31.90, 30.99; LRMS (ESI): *m/z* calcd for $C_{36}H_{39}N_6O_2^+$ $[M+H]^+$: 587.31; Found: 587.1.

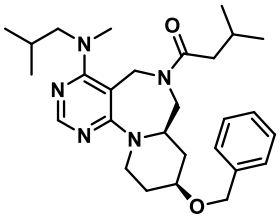
1-((7a*R*,9*S*)-9-(Benzyloxy)-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3d)



To a solution of **15c** (27.3 mg, 0.055 mmol) in 1.0 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 168 mg, 1.48 mmol, 26.8 equiv.) at r.t, stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.51 mL of DMF (0.1 M). Dry TEA (27.8 mg, 0.275 mmol, 5.0 equiv.) and **S1** (19.2 mg, 0.082 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3d** (21.6 mg, 77% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (s, 1H), 7.40–7.22 (m, 10H), 4.59 (d, *J* = 2.1 Hz, 1H), 4.51–4.36 (m, 2H), 4.28 (d, *J* = 13.0 Hz, 1H), 4.19 (dt, *J* = 13.4, 4.1 Hz, 0.5H), 4.11 (d, *J* = 13.4 Hz, 0.5H), 3.81–3.71 (m, 2.5H), 3.65 (ddd, *J* = 15.0, 10.6, 4.0 Hz, 1H), 3.59–3.45 (m, 1.5H), 3.36 (d, *J* = 9.7 Hz, 0.5H), 3.28–3.17 (m, 1H), 2.98 (d, *J* = 11.0 Hz, 1.5H), 2.90 (s, 1.5H), 2.74 (dd, *J* = 13.5, 6.1 Hz, 0.5H), 2.57 (s, 1.5H), 2.18–2.07 (m, 1H), 2.07–1.96 (m, 1H), 1.91–1.79 (m, 1H), 1.64–1.52 (m, 1.5H), 1.46 (tt, *J* = 12.8, 10.1 Hz, 1H), 0.86 (d, *J* = 6.6 Hz, 1.5H), 0.80 (t, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.05, 170.07, 166.11, 166.05, 165.13, 164.91, 156.33, 156.18, 138.55, 134.96, 134.36, 129.04, 129.01, 128.99, 128.71, 128.57, 127.79, 127.73, 127.66, 127.62, 127.18, 127.16, 96.14, 95.98, 74.94, 70.04, 69.94, 59.45, 59.35, 57.72, 56.94, 48.99, 47.72, 44.98, 44.55, 44.46, 41.84, 41.49, 39.57, 39.13, 36.44, 36.00, 32.02, 31.78, 26.89, 26.62, 20.39, 20.34, 20.11; LRMS (ESI): *m/z* calcd for $C_{31}H_{40}N_5O_2^+$ $[M+H]^+$: 514.31; Found: 514.1.

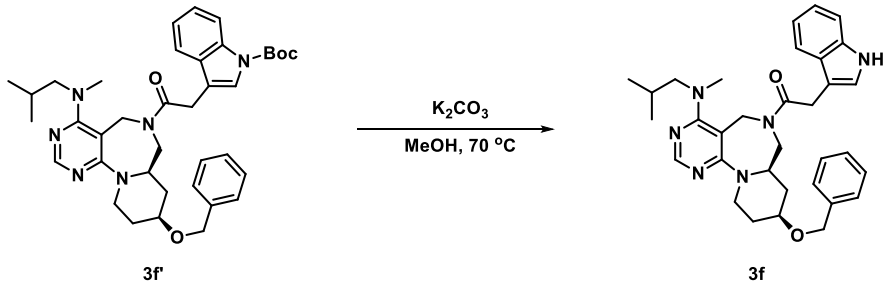
1-((7a*R*,9*S*)-9-(Benzyloxy)-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3e)



To a solution of **15c** (27.3 mg, 0.055 mmol) in 1.0 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 168 mg, 1.48 mmol, 26.8 equiv.) at r.t, stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.51 mL of DMF (0.1 M). Dry TEA (27.8 mg, 0.275 mmol, 5.0 equiv.) and **S2** (16.4 mg, 0.082 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3e** (15.1 mg, 57% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 3.3 Hz, 1H), 7.39–7.32 (m, 4H), 7.32–7.28 (m, 1H), 4.67–4.52 (m, 3H), 4.41 (d, *J* = 13.6 Hz, 0.5H), 4.28 (d, *J* = 13.6 Hz, 1H), 4.17 (ddt, *J* = 22.4, 13.1, 4.1 Hz, 1H), 3.85–3.72 (m, 1H), 3.67 (qt, *J* = 9.3, 4.4 Hz, 1H), 3.45 (m, 2.5H), 3.19–3.11 (m, 0.5H), 3.08 (dd, *J* = 12.2, 3.8 Hz, 0.5H), 3.00 (dt, *J* = 13.3, 5.1 Hz, 1H), 2.94 (d, *J* = 12.0 Hz, 3H), 2.28–2.10 (m, 4.5H), 2.01 (m, 1.5H), 1.70–1.61 (m, 1.5H), 1.54 (dt, *J* = 12.7, 9.6 Hz, 0.5H), 0.97 (t, *J* = 6.5 Hz, 3H), 0.93 (dd, *J* = 6.3, 3.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.80 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.47, 171.61, 166.14, 166.12, 165.20, 165.03, 156.24, 156.19, 138.55, 128.60, 128.57, 127.81, 127.72, 127.66, 96.51, 96.48, 75.27, 74.57, 70.22, 70.10, 60.01, 59.52, 57.32, 57.05, 48.74, 47.30, 44.96, 44.47, 43.83, 42.58, 42.05, 39.41, 39.27, 36.46, 35.89, 31.80, 26.89, 26.84, 25.85, 25.32, 22.89, 22.86, 22.83, 20.42, 20.36, 20.13; LRMS (ESI): *m/z* calcd for $C_{28}H_{42}N_5O_2^+$ $[M+H]^+$: 480.33; Found: 480.2.

1-((7a*R*,9*S*)-9-(Benzyloxy)-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (3f)

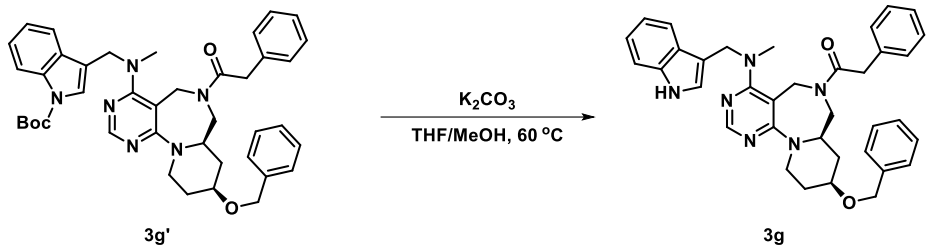


To a solution of **15c** (41 mg, 0.083 mmol) in 1.0 mL of DCM (0.05 M) was added trifluoroacetic acid (TFA; 252 mg, 2.22 mmol, 26.8 equiv.) at r.t, stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.77 mL of DMF (0.1 M). Dry TEA (41.7 mg, 0.412 mmol, 5.0 equiv.) and **S5** (46.0 mg, 0.124 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3f′** (33.6 mg, 63% overall yield) as a white solid. To a solution of **3f′** (9 mg, 0.014 mmol) in 0.56 mL of MeOH (0.025 M) was added potassium carbonate (K_2CO_3; 9.53 mg, 0.069 mmol, 5.0 equiv.), stirred at 70 °C for 3 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3f** (4.16 mg, 55% yield) as a white solid.

3f′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (m, 2H), 7.57 (dd, *J* = 12.6, 7.8 Hz, 1H), 7.51 (d, *J* = 15.5 Hz, 1H), 7.36–7.27 (m, 6H), 7.25–7.21 (m, 1H), 4.68 (d, *J* = 21.1 Hz, 0.5H), 4.57 (s, 1H), 4.48 (d, *J* = 6.7 Hz, 0.5H), 4.46 (d, *J* = 7.8 Hz, 1H), 4.38 (d, *J* = 13.3 Hz, 0.5H), 4.32–4.23 (m, 0.5H), 4.14 (ddd, *J* = 17.9, 10.1, 4.0 Hz, 1H), 3.88–3.72 (m, 3H), 3.69–3.56 (m, 1H), 3.56–3.49 (m, 1H), 3.45 (s, 0.5H), 3.31 (s, 0.5H), 3.21–3.05 (m, 1H), 3.05–2.89 (m, 1.3H), 2.79 (d, *J* = 36.5 Hz, 3.7H), 2.15–2.06 (m, 1.4H), 1.97 (dtd, *J* = 13.1, 6.5, 2.0 Hz, 0.6H), 1.86 (ddt, *J* = 13.0, 8.7, 4.4 Hz, 1H), 1.77 (ddd, *J* = 11.3, 5.4, 2.6 Hz, 0.5H), 1.65 (d, *J* = 7.2 Hz, 9H), 1.59–1.48 (m, 1.5H), 0.83 (d, *J* = 6.6 Hz, 1.5H), 0.79 (d, *J* = 6.6 Hz, 1.5H), 0.72 (d, *J* = 6.6 Hz, 1.5H), 0.67 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.33, 169.46, 166.04, 166.00, 165.16, 164.88, 156.25, 156.18, 149.64, 138.53, 138.46, 135.49, 130.13, 129.95, 128.55, 128.53, 127.75, 127.68, 127.66, 127.63, 124.89, 124.82, 124.25, 123.92, 122.86, 119.19, 115.41, 114.03, 113.52, 96.22, 95.88, 83.98, 83.83, 74.94, 74.50, 70.02, 69.92, 59.92, 59.10, 57.09, 49.10, 47.69, 45.38, 44.61, 44.42, 39.79, 38.92, 36.25, 35.93, 31.72, 31.23, 28.29, 28.28, 26.85, 26.65, 20.27, 20.18, 20.07, 20.01; LRMS (ESI): *m/z* calcd for $C_{38}H_{49}N_6O_4^+$ $[M+H]^+$: 653.38; Found: 653.2.

3f ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.31 (d, *J* = 35.7 Hz, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.62 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.38–7.27 (m, 6H), 7.19 (td, *J* = 7.3, 4.3 Hz, 1H), 7.15–7.02 (m, 2H), 4.55 (d, *J* = 3.3 Hz, 1H), 4.48–4.41 (m, 1H), 4.40–4.29 (m, 1.5H), 4.22–4.10 (m, 1H), 3.92–3.77 (m, 2.5H), 3.70 (dd, *J* = 14.5, 2.8 Hz, 0.5H), 3.66–3.52 (m, 1H), 3.43 (tt, *J* = 9.7, 4.6 Hz, 1H), 3.36 (s, 0.5H), 3.16 (d, *J* = 23.4 Hz, 1H), 2.98 (t, *J* = 11.7 Hz, 1H), 2.75 (d, *J* = 99.0 Hz, 4H), 2.17–2.05 (m, 1H), 2.05–1.94 (m, 1H), 1.83–1.73 (m, 1H), 1.62–1.50 (m, 1H), 1.49–1.24 (m, 2H), 0.81 (dd, *J* = 18.8, 6.6 Hz, 3H), 0.67 (dd, *J* = 22.1, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.55, 170.73, 166.03, 165.96, 165.14, 164.90, 156.26, 156.19, 138.68, 138.58, 136.23, 128.58, 127.77, 127.74, 127.67, 127.60, 127.26, 126.95, 122.92, 122.75, 122.54, 122.49, 119.97, 118.78, 118.75, 111.39, 111.37, 109.19, 108.56, 96.16, 95.96, 75.15, 74.95, 69.99, 69.78, 59.58, 59.24, 57.69, 57.20, 49.00, 47.78, 44.96, 44.57, 39.64, 39.05, 36.39, 36.20, 32.04, 31.94, 31.44, 26.89, 26.65, 20.30, 20.20, 20.12, 20.03; LRMS (ESI): *m/z* calcd for $C_{33}H_{41}N_6O_2^+$ $[M+H]^+$: 553.32; Found: 553.1.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3g)



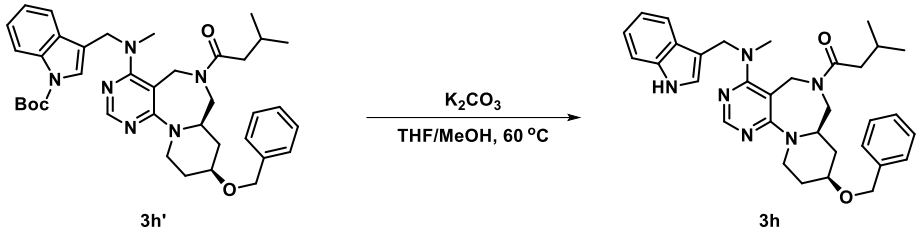
3g' 3g

To a solution of **15e** (53 mg, 0.075 mmol) in EtOAc/MeOH co-solvent (0.15 mL/1.36 mL, 1:9, 0.05 M)) was added Pd/C (10.6 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 9 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.2 mg of crude mixture was dissolved in 0.24 mL of DMF (0.1 M), and dry TEA (7.58 mg, 0.075 mmol, 3.0 equiv.), **S1** (8.73 mg, 0.038 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3g′** (3.8 mg, 22% overall yield) as a white solid. To a solution of **3g′** (1.8 mg, 0.0026 mmol) in THF/MeOH co-solvent (0.05 mL/0.05 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.1 mg, 0.0078 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3g** (1.21 mg, 79% yield) as a white solid.

3g′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (d, *J* = 4.1 Hz, 1H), 8.13 (d, *J* = 24.0 Hz, 1H), 7.52 (s, 1H), 7.43–7.27 (m, 7H), 7.24–7.14 (m, 3H), 7.07 (dq, *J* = 14.2, 6.6 Hz, 2H), 6.94 (d, *J* = 7.2 Hz, 1H), 4.83 (dd, *J* = 28.7, 15.1 Hz, 1H), 4.69–4.52 (m, 2H), 4.48 (q, *J* = 11.9 Hz, 1H), 4.35 (t, *J* = 12.5 Hz, 2H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.14 (d, *J* = 15.4 Hz, 0.6H), 3.77 (d, *J* = 14.2 Hz, 0.4H), 3.73–3.66 (m, 1H), 3.65–3.50 (m, 2H), 3.41 (d, *J* = 3.5 Hz, 1H), 3.28 (s, 1H), 3.00 (t, *J* = 12.8 Hz, 1H), 2.84 (s, 1.3H), 2.54 (s, 1.7H), 2.16–1.99 (m, 2H), 1.69 (d, *J* = 10.9 Hz, 9H), 1.51–1.33 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.08, 170.05, 165.73, 165.32, 165.08, 156.56, 156.35, 138.61, 134.96, 134.11, 128.96, 128.87, 128.74, 128.66, 128.62, 128.61, 127.85, 127.76, 127.68, 127.11, 126.93, 125.01, 124.71, 124.32, 122.98, 119.29, 117.56, 117.32, 115.66, 115.41, 96.56, 84.15, 74.51, 70.04, 58.18, 47.50, 47.42, 44.87, 44.26, 41.88, 41.16, 38.57, 38.41, 36.55, 32.13, 28.38; LRMS (ESI): *m/z* calcd for $C_{41}H_{47}N_6O_4^+$ $[M+H]^+$: 687.36; Found: 687.4.

3g ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.30 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 18.3 Hz, 1H), 7.50–7.43 (m, 1H), 7.42–7.26 (m, 7H), 7.25–7.12 (m, 4H), 7.12–7.02 (m, 2H), 6.87 (d, *J* = 7.1 Hz, 1H), 4.92–4.76 (m, 1.5H), 4.64 (d, *J* = 14.9 Hz, 0.5H), 4.62–4.53 (m, 1.5H), 4.52–4.46 (m, 1H), 4.43 (d, *J* = 14.3 Hz, 2H), 4.25 (d, *J* = 12.3 Hz, 1H), 4.21 (s, 0.5H), 4.07 (s, 0.5H), 3.76 (s, 0.5H), 3.73–3.53 (m, 3H), 3.30 (m, 2H), 3.05–2.98 (m, 1H), 2.86 (s, 1.3H), 2.68 (s, 1.7H), 2.13–1.98 (m, 2H), 1.42 (td, *J* = 22.5, 21.8, 11.4 Hz, 2H); HRMS (EI+): *m/z* calcd for $C_{36}H_{38}N_6O_2$ [M]: 586.30; Found: 586.3057.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3h)



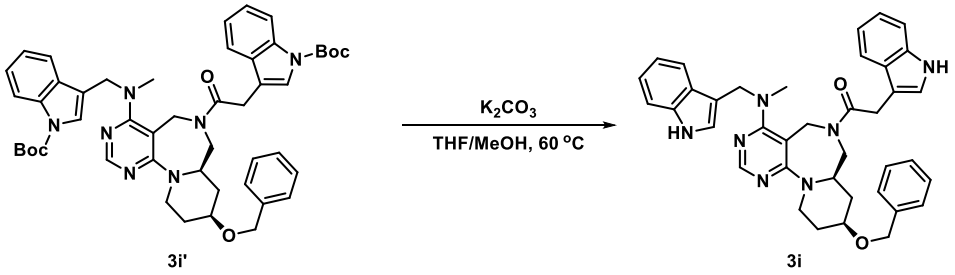
3h' 3h

To a solution of **15e** (53 mg, 0.075 mmol) in EtOAc/MeOH co-solvent (0.15 mL/1.36 mL, 1:9, 0.05 M)) was added Pd/C (10.6 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 9 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.2 mg of crude mixture was dissolved in 0.24 mL of DMF (0.1 M), and dry TEA (7.58 mg, 0.075 mmol, 3.0 equiv.), **S2** (7.46 mg, 0.038 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3h′** (4.1 mg, 25% overall yield) as a white solid. To a solution of **3h′** (2.0 mg, 0.003 mmol) in THF/MeOH co-solvent (0.06 mL/0.06 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.27 mg, 0.009 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3h** (1.55 mg, 91% yield) as a white solid.

3h′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.32 (d, *J* = 12.2 Hz, 1H), 8.12 (s, 1H), 7.56 (d, *J* = 30.2 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.37–7.32 (m, 4H), 7.32–7.26 (m, 2H), 7.20 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.83 (dd, *J* = 47.3, 15.6 Hz, 1.2H), 4.67–4.36 (m, 4.8H), 4.35–4.15 (m, 2H), 3.87–3.60 (m, 2H), 3.58–3.35 (m, 2H), 3.07 (d, *J* = 14.1 Hz, 1H), 2.96 (s, 1.8H), 2.86 (s, 1.2H), 2.20–1.95 (m, 4H), 1.85 (dd, *J* = 15.5, 6.7 Hz, 1H), 1.68 (d, *J* = 5.1 Hz, 10H), 0.87 (dd, *J* = 18.0, 6.6 Hz, 3H), 0.71 (dd, *J* = 21.6, 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.57, 171.56, 165.87, 165.12, 156.53, 156.29, 138.56, 128.64, 128.61, 127.85, 127.77, 127.70, 125.06, 124.00, 123.02, 119.19, 117.67, 115.63, 115.39, 70.28, 70.10, 48.75, 46.96, 42.54, 41.67, 38.57, 38.38, 28.37, 25.81, 24.91, 22.79, 22.74, 22.70, 22.46; LRMS (ESI): *m/z* calcd for $C_{38}H_{49}N_6O_4^+$ $[M+H]^+$: 653.38; Found: 653.4.

3h ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.32 (d, *J* = 10.9 Hz, 1H), 8.08 (d, *J* = 29.5 Hz, 1H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.41–7.27 (m, 5H), 7.26–7.15 (m, 3H), 7.09 (q, *J* = 8.1 Hz, 1H), 4.84 (dd, *J* = 27.3, 15.3 Hz, 1.5H), 4.68–4.55 (m, 3H), 4.53 (d, *J* = 10.8 Hz, 0.5H), 4.45 (d, *J* = 37.4 Hz, 1.5H), 4.27 (dd, *J* = 23.2, 13.4 Hz, 1.5H), 4.16 (d, *J* = 12.9 Hz, 0.5H), 3.98 (s, 0.3H), 3.84 (s, 0.5H), 3.74–3.47 (m, 3H), 3.37 (s, 1H), 3.20 (s, 0.7H), 3.05 (t, *J* = 12.4 Hz, 1H), 2.96 (s, 2H), 2.87 (s, 1H), 2.17–2.10 (m, 2H), 1.72–1.63 (m, 2H), 0.86 (dd, *J* = 19.5, 6.5 Hz, 3H), 0.69 (dd, *J* = 22.1, 6.6 Hz, 3H); HRMS (EI+): *m/z* calcd for $C_{33}H_{40}N_6O_2$ [M]: 552.32; Found: 552.3213.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-(benzyloxy)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-(1*H*-indol-3-yl)ethan-1-one (3i)

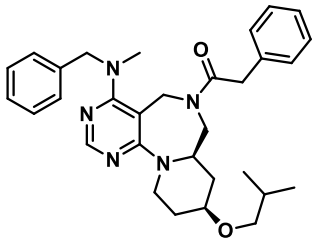


To a solution of **15e** (53 mg, 0.075 mmol) in EtOAc/MeOH co-solvent (0.15 mL/1.36 mL, 1:9, 0.05 M)) was added Pd/C (10.6 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 9 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.2 mg of crude mixture was dissolved in 0.24 mL of DMF (0.1 M), and dry TEA (7.58 mg, 0.075 mmol, 3.0 equiv.), **S5** (14.0 mg, 0.038 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3i′** (4.8 mg, 24% overall yield) as a white solid. To a solution of **3i′** (2.4 mg, 0.0029 mmol) in THF/MeOH co-solvent (0.06 mL/0.06 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.20 mg, 0.0087 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3i** (1.61 mg, 88% yield) as a white solid.

3i′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (d, *J* = 2.4 Hz, 1H), 8.09 (s, 2H), 7.58–7.26 (m, 11H), 7.20–7.11 (m, 2H), 4.77 (dd, *J* = 77.9, 15.3 Hz, 2H), 4.61–4.38 (m, 5H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.92–3.68 (m, 2H), 3.68–3.50 (m, 2H), 3.42 (q, *J* = 15.9 Hz, 2H), 3.15 (s, 1H), 2.92–2.84 (m, 1.8H), 2.78 (s, 1.2H), 2.09 (d, *J* = 12.9 Hz, 1H), 1.82–1.70 (m, 1H), 1.67 (d, *J* = 6.0 Hz, 9H), 1.62 (d, *J* = 17.9 Hz, 9H), 1.47 (t, *J* = 10.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.35, 169.46, 165.84, 165.36, 165.03, 156.40, 149.67, 138.60, 138.53, 136.58, 135.72, 130.14, 129.98, 129.54, 128.61, 128.57, 127.82, 127.72, 127.67, 125.03, 124.86, 124.74, 124.65, 124.29, 124.20, 123.93, 123.04, 122.92, 122.87, 122.76, 119.44, 119.16, 119.07, 118.98, 117.46, 117.23, 115.65, 115.40, 114.03, 113.36, 96.63, 84.15, 83.95, 83.71, 70.02, 57.98, 49.20, 48.37, 47.36, 46.54, 44.43, 38.54, 38.48, 35.97, 35.31, 31.72, 30.44, 28.37, 28.34, 28.30; LRMS (ESI): *m/z* calcd for $C_{48}H_{56}N_7O_6^+$ $[M+H]^+$: 826.42; Found: 826.6.

3i ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (s, 1H), 8.10–7.69 (m, 2H), 7.53–7.44 (m, 2H), 7.39–7.33 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 3H), 7.25–7.00 (m, 5H), 6.90–6.48 (m, 2H), 4.92–4.79 (m, 1H), 4.66–4.51 (m, 2H), 4.47–4.32 (m, 2.5H), 4.24 (d, *J* = 13.5 Hz, 0.6H), 4.14 (d, *J* = 13.5 Hz, 0.4H), 3.89–3.70 (m, 1.5H), 3.67–3.44 (m, 3H), 3.35 (s, 0.6H), 3.18 (s, 0.4H), 3.03–2.94 (m, 1H), 2.84 (s, 1H), 2.38 (s, 2H), 2.11 (d, *J* = 11.4 Hz, 1.5H), 1.47–1.34 (m, 1.5H), 1.29 (d, *J* = 8.0 Hz, 1H), 0.90–0.80 (m, 1H); HRMS (EI+): *m/z* calcd for $C_{38}H_{39}N_7O_2$ [M]: 625.31; Found: 625.3155.

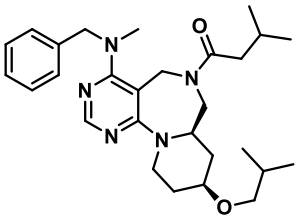
1-((7a*R*,9*S*)-4-(Benzyl(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3j)



To a solution of **15b** (120 mg, 0.243 mmol) in EtOAc/MeOH co-solvent (2.43 mL/2.43 mL; 1:1, 0.05 M) was added Pd/C (12.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 29.7 mg (0.060 mmol) of crude resultant was dissolved in 1.20 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 184.2 mg, 1.61 mmol, 27.0 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.16 mL of DMF (0.05 M). Dry TEA (30.3 mg, 0.30 mmol, 5.0 equiv.) and **S1** (21.0 mg, 0.090 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3j** (16.8 mg, 55% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.25 (d, *J* = 11.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.34–7.25 (m, 4H), 7.24–7.17 (m, 4H), 7.08–7.05 (m, 1H), 4.72 (d, *J* = 15.3 Hz, 0.6H), 4.51 (dd, *J* = 15.8, 9.2 Hz, 1H), 4.41 (dd, *J* = 14.5, 5.7 Hz, 0.7H), 4.33 (d, *J* = 14.8 Hz, 1.3H), 4.19–4.13 (m, 1H), 4.09 (s, 0.4H), 3.79–3.70 (m, 1H), 3.56 (ddd, *J* = 61.0, 14.8, 3.0 Hz, 1H), 3.42 (ddt, *J* = 34.9, 9.8, 5.1 Hz, 1.24H), 3.31 (d, *J* = 27.2 Hz, 0.8H), 3.21 (td, *J* = 7.6, 6.7, 2.4 Hz, 2H), 3.14 (ddd, *J* = 27.4, 8.8, 6.5 Hz, 1H), 3.04 (d, *J* = 12.7 Hz, 1H), 2.82 (s, 1H), 2.76 (s, 2H), 2.06–1.99 (m, 1.5H), 1.81 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.77 (s, 0.5H), 1.56–1.46 (m, 1H), 1.41 (dt, *J* = 12.5, 9.8 Hz, 0.4H), 1.30 (dt, *J* = 12.8, 10.2 Hz, 0.6H), 0.91 (dd, *J* = 6.6, 1.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.20, 170.09, 165.91, 165.85, 165.25, 164.97, 156.43, 156.30, 137.98, 137.94, 134.90, 134.28, 129.04, 129.00, 128.95, 128.75, 128.68, 128.64, 127.84, 127.65, 127.31, 127.13, 127.10, 127.02, 96.27, 96.13, 75.68, 75.30, 75.25, 57.72, 56.88, 55.58, 47.14, 44.90, 44.57, 44.26, 41.81, 40.66, 38.61, 37.87, 36.29, 35.93, 32.03, 31.73, 28.86, 19.56; LRMS (ESI): *m/z* calcd for $C_{31}H_{40}N_5O_2^+$ $[M+H]^+$: 514.31; Found: 514.1.

1-((7a*R*,9*S*)-4-(Benzyl(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3k)

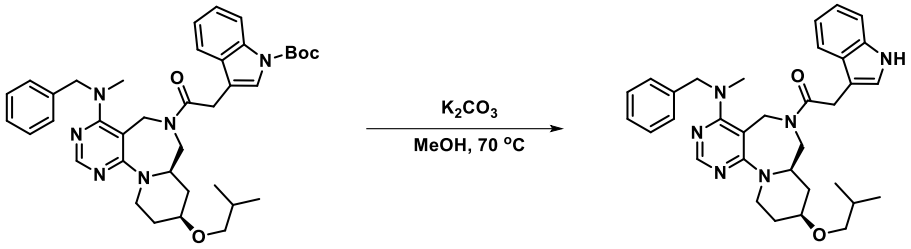


To a solution of **15b** (120 mg, 0.243 mmol) in EtOAc/MeOH co-solvent (2.43 mL/2.43 mL; 1:1, 0.05 M) was added Pd/C (12.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 29.7 mg (0.060 mmol, 1.0 equiv.) of crude resultant was dissolved in 1.20 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 184.2 mg, 1.61 mmol, 27.0 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.16 mL of DMF (0.05 M). Dry TEA (30.3 mg, 0.30 mmol, 5.0 equiv.) and **S2** (17.9 mg, 0.090 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3k** (15.8 mg, 56% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28 (d, *J* = 24.1 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.33–7.23 (m, 4H), 4.73 (d, *J* = 15.3 Hz, 0.3H), 4.50 (ddd, *J* = 48.8, 15.7, 11.2 Hz, 2.7H), 4.38–4.17 (m, 2H), 4.11–3.88 (m,

0.7H), 3.67 (dd, *J* = 13.9, 3.0 Hz, 0.3H), 3.51 (ddt, *J* = 34.3, 10.0, 4.8 Hz, 2H), 3.36 (d, *J* = 9.2 Hz, 0.5H), 3.30–3.19 (m, 2.3H), 3.05 (t, *J* = 12.3 Hz, 0.7H), 2.90 (d, *J* = 48.7 Hz, 3H), 2.29–2.10 (m, 1H), 2.06 (dt, *J* = 12.7, 3.4 Hz, 1.5H), 1.97 (ddd, *J* = 24.7, 13.0, 5.4 Hz, 1H), 1.83 (ddd, *J* = 14.6, 13.3, 6.8 Hz, 1H), 1.79–1.58 (m, 2H), 1.57–1.28 (m, 2H), 0.95–0.74 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.70, 171.61, 165.95, 165.89, 165.33, 165.07, 156.45, 156.13, 138.04, 137.87, 129.06, 128.67, 127.83, 127.62, 127.28, 126.91, 96.75, 96.60, 75.84, 75.43, 75.39, 57.75, 57.26, 55.53, 49.04, 46.68, 44.70, 44.50, 44.05, 42.58, 41.32, 38.61, 37.82, 36.45, 32.17, 31.41, 28.96, 28.83, 25.79, 24.80, 22.77, 22.73, 22.55, 19.61, 19.52; LRMS (ESI): *m/z* calcd for $C_{28}H_{42}N_5O_2^+$ $[M+H]^+$: 480.33; Found: 480.2.

1-((7a*R*,9*S*)-4-(Benzyl(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4] diazepin-6(5*H*)-yl)-2-(1H-indol-3-yl)ethan-1-one (3l)



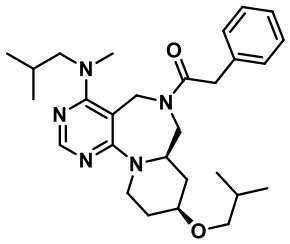
3l' 3l

To a solution of **15b** (120 mg, 0.243 mmol) in EtOAc/MeOH co-solvent (2.43 mL/2.43 mL; 1:1, 0.05 M) was added Pd/C (12.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 44.6 mg (0.090 mmol, 1.0 equiv.) of crude resultant was dissolved in 1.80 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 276.3 mg, 2.42 mmol, 27.0 equiv.) was added. The reaction mixture was stirred at r.t for 4 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 1.73 mL of DMF (0.05 M). Dry TEA (45.5 mg, 0.45 mmol, 5.0 equiv.) and **S5** (50.2 mg, 0.134 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 16 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3l′** (36.9 mg, 63% overall yield) as a white solid. To a solution of **3i′** (2.4 mg, 0.0029 mmol) in 1.2 mL of MeOH (0.025 M) was added potassium carbonate (K_2CO_3; 1.20 mg, 0.0087 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3i** (1.61 mg, 88% yield) as a white solid.

3l′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.26 (d, *J* = 8.9 Hz, 1H), 8.19–8.03 (m, 1H), 7.56–7.29 (m, 5.5H), 7.28–7.19 (m, 3.5H), 4.73 (d, *J* = 15.3 Hz, 0.5H), 4.50 (dd, *J* = 11.9, 3.7 Hz, 1H), 4.45 (d, *J* = 24.1 Hz, 1H), 4.42–4.32 (m, 1.5H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.94–3.76 (m, 1H), 3.74–3.53 (m, 1H), 3.47 (dp, *J* = 13.5, 4.3 Hz, 2H), 3.30 (d, *J* = 16.1 Hz, 0.5H), 3.23–3.11 (m, 3.5H), 2.85 (d, *J* = 56.9 Hz, 3H), 2.03 (ddd, *J* = 17.2, 8.3, 4.2 Hz, 2H), 1.92–1.75 (m, 2H), 1.66 (d, *J* = 13.7 Hz, 9H), 1.61–1.50 (m, 1.5H), 1.37 (dd, *J* = 12.8, 9.4 Hz, 0.5H), 0.94–0.89 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.38, 169.47, 166.03, 165.75, 165.26, 164.89, 156.26, 156.23, 149.65, 137.94, 137.82, 135.46, 130.13, 129.92, 129.07, 128.69, 128.61, 127.78, 127.63, 127.23, 126.85, 124.83, 124.61, 124.17, 123.83, 122.80, 122.63, 119.25, 119.08, 115.39, 115.33, 113.99, 113.55, 96.42, 96.15, 83.87, 83.64, 75.40, 75.33, 75.23, 57.33, 57.01, 55.28, 49.35, 47.01, 45.40, 44.37, 43.84, 38.80, 37.76, 35.75, 31.62, 30.35, 28.83, 28.80, 28.30, 28.28, 19.55, 19.54, 19.51; LRMS (ESI): *m/z* calcd for $C_{38}H_{49}N_6O_4^+$ $[M+H]^+$: 653.38; Found: 653.2.

3l ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.28–8.08 (m, 2H), 7.53 (dd, *J* = 34.3, 7.9 Hz, 1H), 7.40–7.27 (m, 3.5H), 7.26–7.14 (m, 3.5H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 42.7, 2.3 Hz, 1H), 4.69 (d, *J* = 15.3 Hz, 0.5H), 4.50 (dd, *J* = 15.7, 6.5 Hz, 1H), 4.47–4.34 (m, 1.5H), 4.30–4.25 (m, 1H), 4.14 (dt, *J* = 14.9, 4.9 Hz, 1H), 3.90–3.78 (m, 1H), 3.68–3.49 (m, 1H), 3.43 (dd, *J* = 21.7, 5.8 Hz, 2H), 3.34 (ddd, *J* = 19.7, 10.1, 5.8 Hz, 1H), 3.21 (s, 0.4H), 3.20–3.15 (m, 1H), 3.08 (ddd, *J* = 29.9, 9.0, 6.7 Hz, 1H), 2.99 (d, *J* = 15.8 Hz, 0.6H), 2.79 (s, 1.2H), 2.68 (s, 1.8H), 2.02 (ddt, *J* = 17.5, 13.2, 5.6 Hz, 1.5H), 1.79 (tp, *J* = 13.3, 6.7 Hz, 2H), 1.56–1.41 (m, 1.5H), 1.40–1.26 (m, 1H), 0.90 (ddd, *J* = 8.1, 6.6, 2.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.54, 170.79, 166.00, 165.74, 165.25, 164.90, 156.30, 138.11, 138.03, 136.19, 136.18, 128.97, 128.66, 127.84, 127.57, 127.34, 127.28, 127.21, 126.91, 122.89, 122.65, 122.48, 122.36, 119.89, 119.74, 118.97, 118.58, 111.39, 111.27, 109.13, 108.48, 96.51, 96.15, 75.66, 75.34, 75.14, 57.59, 57.10, 56.69, 55.48, 47.19, 45.03, 44.39, 38.64, 38.03, 36.21, 31.96, 31.79, 31.01, 28.83, 28.82, 19.57, 19.54; LRMS (ESI): *m/z* calcd for $C_{33}H_{41}N_6O_2^+$ $[M+H]^+$: 553.32; Found: 553.1.

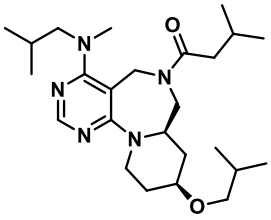
1-((7a*R*,9*S*)-9-Isobutoxy-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3m)



To a solution of **15d** (90 mg, 0.196 mmol) in EtOAc/MeOH co-solvent (1.96 mL/1.96 mL; 1:1, 0.05 M) was added Pd/C (9.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 26.1 mg (0.057 mmol, 1.0 equiv.) of crude resultant was dissolved in 1.02 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 173.0 mg, 1.52 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.53 mL of DMF (0.1 M). Dry TEA (28.7 mg, 0.284 mmol, 5.0 equiv.) and **S1** (19.9 mg, 0.085 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3m** (13.5 mg, 50% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (d, *J* = 1.9 Hz, 1H), 7.34–7.24 (m, 5H), 4.66 (s, 0.3H), 4.45 (dd, *J* = 14.0, 5.7 Hz, 0.5H), 4.37 (d, *J* = 13.2 Hz, 0.5H), 4.27 (d, *J* = 13.1 Hz, 0.7H), 4.13 (dt, *J* = 13.6, 4.0 Hz, 1H), 3.84–3.64 (m, 3H), 3.49 (tt, *J* = 9.6, 4.2 Hz, 1.5H), 3.37 (ddd, *J* = 14.8, 10.6, 6.2 Hz, 1H), 3.24 (tt, *J* = 8.5, 4.2 Hz, 2H), 3.18–3.09 (m, 1H), 3.01 (dt, *J* = 35.1, 9.6 Hz, 1.5H), 2.90 (s, 1.5H), 2.79–2.68 (m, 0.4H), 2.59 (s, 1H), 2.11–1.96 (m, 2H), 1.88–1.76 (m, 2H), 1.57–1.35 (m, 2.5H), 0.94–0.89 (m, 6H), 0.85 (d, *J* = 6.6 Hz, 1.5H), 0.80 (dd, *J* = 6.6, 3.4 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.04, 170.09, 166.08, 165.17, 164.98, 156.30, 156.22, 134.96, 134.40, 129.02, 129.01, 128.73, 127.21, 127.17, 96.24, 95.93, 75.70, 75.42, 75.20, 59.53, 59.36, 57.59, 57.14, 48.98, 47.68, 45.09, 44.51, 41.80, 41.52, 39.56, 39.13, 36.31, 36.17, 31.95, 28.88, 28.86, 26.90, 26.64, 20.41, 20.35, 20.12, 19.57; LRMS (ESI): *m/z* calcd for $C_{28}H_{42}N_5O_2^+$ $[M+H]^+$: 480.33; Found: 480.2.

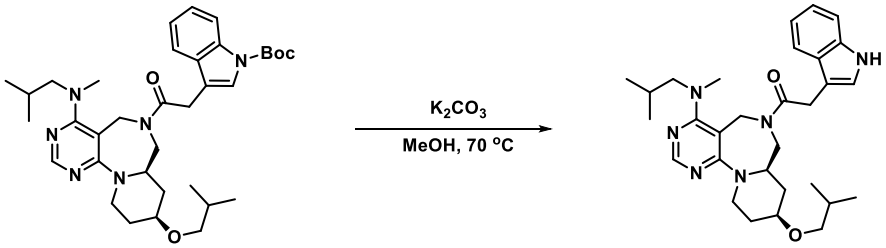
1-((7a*R*,9*S*)-9-Isobutoxy-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3n)



To a solution of **15d** (90 mg, 0.196 mmol) in EtOAc/MeOH co-solvent (1.96 mL/1.96 mL; 1:1, 0.05 M) was added Pd/C (9.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 26.1 mg (0.057 mmol) of crude resultant was dissolved in 1.02 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 173.0 mg, 1.52 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with toluene to get rid of the remaining TFA, and the crude resultant was dissolved in 0.53 mL of DMF (0.1 M). Dry TEA (28.7 mg, 0.284 mmol, 5.0 equiv.) and **S2** (17.0 mg, 0.085 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3n** (20.0 mg, 79% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.22 (d, *J* = 3.6 Hz, 1H), 4.63–4.55 (m, 0.7H), 4.41–4.26 (m, 1.3H), 4.15–4.03 (m, 1H), 3.87 (dd, *J* = 14.6, 5.8 Hz, 0.5H), 3.73 (dd, *J* = 14.3, 3.0 Hz, 0.5H), 3.57–3.39 (m, 3.5H), 3.28 (dd, *J* = 8.8, 6.7 Hz, 0.5H), 3.25–3.17 (m, 2H), 3.15–3.07 (m, 0.5H), 2.99 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.94 (d, *J* = 9.1 Hz, 3H), 2.32–2.12 (m, 3H), 2.09–1.99 (m, 2.5H), 1.95 (dq, *J* = 12.5, 2.6 Hz, 0.5H), 1.83 (dp, *J* = 13.3, 6.6 Hz, 1.5H), 1.55 (dddd, *J* = 44.7, 22.1, 11.0, 3.4 Hz, 2H), 0.99–0.86 (m, 15H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.47, 171.62, 166.18, 166.15, 165.22, 165.09, 156.16, 156.11, 96.63, 96.57, 75.64, 75.48, 75.33, 60.00, 59.55, 57.11, 56.79, 48.86, 47.24, 45.09, 44.39, 42.61, 42.06, 39.47, 39.31, 36.15, 35.63, 31.68, 28.94, 28.86, 26.90, 26.84, 25.83, 25.32, 22.86, 22.84, 22.81, 20.44, 20.36, 20.13, 19.59, 19.55; LRMS (ESI): *m/z* calcd for $C_{25}H_{44}N_5O_2^+$ $[M+H]^+$: 446.34; Found: 446.2.

2-(1*H*-Indol-3-yl)-1-((7a*R*,9*S*)-9-isobutoxy-4-(isobutyl(methyl)amino)-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)ethan-1-one (3o)



3o' 3o

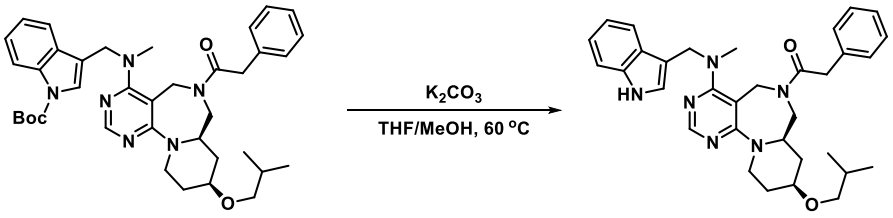
To a solution of **15d** (90 mg, 0.196 mmol) in EtOAc/MeOH co-solvent (1.96 mL/1.96 mL; 1:1, 0.05 M) was added Pd/C (9.0 mg, 10 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure, and the 39.1 mg (0.086 mmol) of crude resultant was dissolved in 1.5 mL of DCM (0.05 M) and trifluoroacetic acid (TFA; 260 mg, 2.28 mmol, 26.8 equiv.) was added. The reaction mixture was stirred at r.t for 3.5 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was co-evaporated with Toluene to get rid of remained TFA, and the crude resultant was dissolved in 0.80 mL of DMF (0.1 M). Dry TEA (43.0 mg, 0.425 mmol, 5.0 equiv.) and **S5** (47.7 mg, 0.127 mmol, 1.5 equiv.) were sequentially added and stirred at r.t for 4 h. After the completion of the reaction, as indicated by LC-MS, the reaction mixture was quenched with 5% Na_2CO_3 solution and extracted with EtOAc three times. The combined organic layer

was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3o′** (42.1 mg, 80% overall yield) as a white solid. To a solution of **3o′** (28 mg, 0.045 mmol) in 1.8 mL of MeOH (0.025 M) was added potassium carbonate (K_2CO_3; 31.3 mg, 0.226 mmol, 5.0 equiv.), stirred at 70 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3o** (14.3 mg, 60% yield) as a white solid.

3o′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.19 (d, *J* = 3.8 Hz, 1H), 8.12 (d, *J* = 12.7 Hz, 1H), 7.56 (dd, *J* = 27.3, 7.8 Hz, 1H), 7.50 (d, *J* = 5.8 Hz, 1H), 7.35–7.29 (m, 1H), 7.23 (td, *J* = 7.5, 4.8 Hz, 1H), 4.75–4.51 (m, 1H), 4.47–4.36 (m, 1H), 4.17–4.02 (m, 1H), 3.90–3.78 (m, 1.5H), 3.77–3.70 (m, 1.5H), 3.49 (dqd, *J* = 10.6, 7.8, 7.3, 4.0 Hz, 2H), 3.45–3.32 (m, 1H), 3.27–3.08 (m, 3H), 3.05–2.91 (m, 1H), 2.79 (d, *J* = 32.0 Hz, 3.3H), 2.08–1.99 (m, 1.7H), 1.98–1.90 (m, 1H), 1.90–1.81 (m, 1H), 1.78 (ddt, *J* = 13.3, 9.8, 4.7 Hz, 1H), 1.66 (d, *J* = 1.7 Hz, 9H), 1.59–1.43 (m, 2H), 0.92 (dd, *J* = 6.6, 2.9 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.85–0.77 (m, 3H), 0.70 (dd, *J* = 24.6, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 170.31, 169.45, 166.06, 166.01, 165.18, 164.92, 156.17, 156.15, 149.64, 135.49, 130.13, 129.97, 124.85, 124.78, 124.22, 123.89, 122.83, 122.81, 119.19, 115.40, 115.37, 114.01, 113.56, 96.34, 95.92, 83.92, 83.79, 75.69, 75.41, 75.17, 59.98, 59.10, 57.06, 49.21, 47.59, 45.55, 44.60, 44.35, 39.79, 38.89, 36.23, 35.69, 31.68, 31.20, 28.82, 28.30, 26.84, 26.65, 20.27, 20.18, 20.06, 20.00, 19.56, 19.53; LRMS (ESI): *m/z* calcd for $C_{35}H_{51}N_6O_4^+$ $[M+H]^+$: 619.39; Found: 619.2.

3o ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.43 (s, 1H), 8.18 (d, *J* = 6.7 Hz, 1H), 7.61 (t, *J* = 8.3 Hz, 1H), 7.34 (dd, *J* = 8.2, 5.0 Hz, 1H), 7.19 (tdd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 7.14–7.07 (m, 2H), 4.64 (s, 0.3H), 4.53–4.41 (m, 1H), 4.32 (d, *J* = 13.3 Hz, 0.7H), 4.13 (t, *J* = 12.3 Hz, 1H), 3.94–3.83 (m, 2H), 3.83–3.69 (m, 1H), 3.55–3.27 (m, 2.5H), 3.25–3.19 (m, 1H), 3.16 (d, *J* = 12.3 Hz, 0.5H), 3.08 (ddd, *J* = 29.8, 8.9, 6.7 Hz, 1.5H), 3.01–2.87 (m, 1H), 2.74 (d, *J* = 90.1 Hz, 3.5H), 2.11–1.93 (m, 2H), 1.85–1.73 (m, 2H), 1.51 (dqd, *J* = 12.4, 4.6, 3.0, 2.2 Hz, 1H), 1.47–1.24 (m, 2H), 0.90 (ddd, *J* = 14.7, 6.7, 1.8 Hz, 6H), 0.80 (dd, *J* = 16.5, 6.6 Hz, 3H), 0.67 (dd, *J* = 22.8, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.56, 170.74, 166.01, 165.96, 165.16, 164.94, 156.18, 136.26, 136.24, 127.26, 126.98, 122.92, 122.72, 122.51, 122.45, 119.93, 119.90, 118.75, 118.73, 111.41, 111.36, 109.17, 108.55, 96.27, 95.96, 75.88, 75.41, 75.08, 59.64, 59.22, 57.52, 57.32, 49.06, 47.71, 45.10, 44.59, 39.65, 39.00, 36.35, 31.86, 31.42, 28.84, 28.82, 26.87, 26.64, 20.29, 20.20, 20.11, 20.02, 19.57, 19.55; LRMS (ESI): *m/z* calcd for $C_{30}H_{43}N_6O_2^+$ $[M+H]^+$: 519.34; Found: 519.1.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a]pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-phenylethan-1-one (3p)



3p' 3p

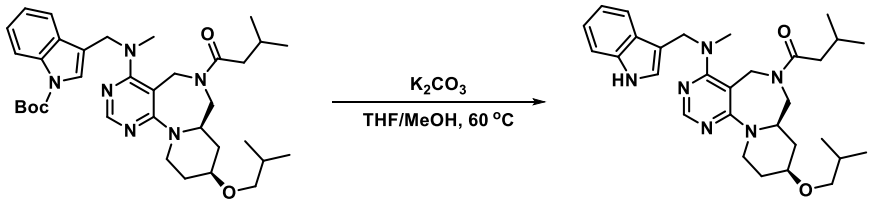
To a solution of **15f** (55 mg, 0.081 mmol) in EtOAc/MeOH co-solvent (0.16 mL/1.46 mL, 1:9, 0.05 M) was added Pd/C (10.8 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 7 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.4 mg (0.027 mmol) of crude mixture was dissolved in 0.26 mL of DMF (0.1 M), and dry TEA (8.18 mg, 0.081 mmol, 3.0 equiv.), **S1** (9.42 mg, 0.040 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure,

followed by silica-gel flash column chromatography to afford **3p′** (4.6 mg, 26% overall yield) as a white solid. To a solution of **3p′** (2.3 mg, 0.0035 mmol) in THF/MeOH co-solvent (0.07 mL/0.07 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.46 mg, 0.011 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3p** (1.7 mg, 87% yield) as a white solid.

3p′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 22.0 Hz, 1H), 7.52 (s, 1H), 7.41–7.29 (m, 2H), 7.25–7.15 (m, 3H), 7.07 (dt, *J* = 14.0, 6.8 Hz, 2H), 6.94 (d, *J* = 7.2 Hz, 1H), 4.83 (dd, *J* = 21.9, 15.2 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 0.5H), 4.35 (td, *J* = 28.5, 13.7 Hz, 2H), 4.24–4.14 (m, 1.5H), 3.74 (dd, *J* = 25.4, 10.6 Hz, 1H), 3.68–3.53 (m, 1H), 3.48 (td, *J* = 9.7, 4.6 Hz, 1H), 3.40 (d, *J* = 4.6 Hz, 1H), 3.33 (d, *J* = 38.0 Hz, 1H), 3.22 (td, *J* = 8.6, 7.7, 5.1 Hz, 1H), 3.18–3.09 (m, 1H), 3.05 (t, *J* = 12.8 Hz, 1H), 2.70 (d, *J* = 139.7 Hz, 3H), 2.11–1.93 (m, 2H), 1.82 (tq, *J* = 13.0, 6.6 Hz, 1H), 1.69 (d, *J* = 10.4 Hz, 9H), 1.53–1.30 (m, 3H), 0.91 (d, *J* = 6.7 Hz, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 171.06, 170.05, 165.74, 165.35, 165.13, 156.51, 156.37, 134.95, 134.15, 129.74, 128.95, 128.85, 128.76, 128.73, 128.67, 127.13, 126.91, 125.01, 124.70, 124.32, 122.98, 122.95, 119.45, 119.29, 117.57, 117.33, 115.66, 115.41, 96.63, 84.15, 75.76, 75.39, 75.26, 47.52, 47.38, 46.80, 44.98, 44.28, 41.81, 41.18, 38.60, 38.38, 36.41, 32.08, 29.85, 28.90, 28.38, 19.58; LRMS (ESI): *m/z* calcd for $C_{38}H_{49}N_6O_4^+$ $[M+H]^+$: 653.38; Found: 653.4.

3p ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.30 (d, *J* = 4.6 Hz, 1H), 8.09 (d, *J* = 17.3 Hz, 1H), 7.46 (dd, *J* = 12.2, 8.0 Hz, 1H), 7.39 (dd, *J* = 16.9, 8.2 Hz, 1H), 7.22 (d, *J* = 13.5 Hz, 2H), 7.17 (dd, *J* = 11.7, 4.8 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.11–7.08 (m, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 4.82 (dd, *J* = 32.2, 15.2 Hz, 1H), 4.64 (d, *J* = 15.0 Hz, 1H), 4.42 (d, *J* = 14.0 Hz, 2H), 4.26–4.08 (m, 2H), 3.79–3.60 (m, 2H), 3.54–3.43 (m, 1.5H), 3.38 (s, 1H), 3.30 (t, *J* = 13.4 Hz, 1.5H), 3.24–3.20 (m, 1H), 3.20–3.03 (m, 2H), 2.77 (d, *J* = 82.2 Hz, 3H), 2.02 (s, 2H), 1.86–1.78 (m, 1H), 1.51 (s, 1H), 0.91 (d, *J* = 6.7 Hz, 6H); HRMS (EI+): *m/z* calcd for $C_{33}H_{40}N_6O_2$ [M]: 552.32; Found: 552.3203.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a] pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-3-methylbutan-1-one (3q)



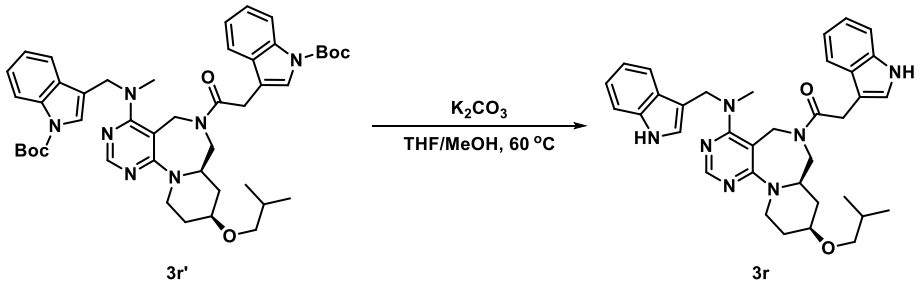
3q' 3q

To a solution of **15f** (55 mg, 0.081 mmol) in EtOAc/MeOH co-solvent (0.16 mL/1.46 mL, 1:9, 0.05 M) was added Pd/C (10.8 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 7 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.4 mg (0.027 mmol) of crude mixture was dissolved in 0.26 mL of DMF (0.1 M), and dry TEA (8.18 mg, 0.081 mmol, 3.0 equiv.), **S2** (8.05 mg, 0.040 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3q′** (3.6 mg, 22% overall yield) as a white solid. To a solution of **3q′** (1.8 mg, 0.0035 mmol) in THF/MeOH co-solvent (0.06 mL/0.06 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.21 mg, 0.0087 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3q** (1.5 mg, 99% yield) as a white solid.

3q′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.32 (d, *J* = 13.4 Hz, 1H), 8.12 (s, 1H), 7.56 (d, *J* = 26.5 Hz, 1H), 7.44 (dd, *J* = 13.2, 7.9 Hz, 1H), 7.32 (dt, *J* = 19.9, 7.7 Hz, 1H), 7.20 (dd, *J* = 12.0, 5.3 Hz, 1H), 4.84 (dd, *J* = 40.3, 15.5 Hz, 1H), 4.61 (d, *J* = 15.1 Hz, 0.5H), 4.47 (dd, *J* = 19.8, 14.4 Hz, 2H), 4.28 (d, *J* = 13.4 Hz, 0.5H), 4.20 (d, *J* = 14.0 Hz, 0.6H), 4.12 (s, 0.5H), 3.88 (s, 0.5H), 3.70 (d, *J* = 14.2 Hz, 0.4H), 3.61–3.35 (m, 3H), 3.29–3.07 (m, 3H), 2.91 (d, *J* = 45.4 Hz, 3H), 2.26–2.15 (m, 1H), 2.08 (dd, *J* = 22.2, 9.8 Hz, 2H), 1.95 (td, *J* = 12.5, 11.5, 5.6 Hz, 1H), 1.88–1.72 (m, 2H), 1.68 (d, *J* = 4.8 Hz, 10H), 1.39 (q, *J* = 10.6 Hz, 1H), 0.96–0.79 (m, 9H), 0.71 (dd, *J* = 15.7, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture of rotamers): δ 172.55, 171.56, 165.88, 165.17, 156.47, 156.20, 129.57, 125.04, 124.70, 124.02, 123.01, 122.94, 119.54, 119.19, 117.68, 117.38, 115.62, 115.38, 97.08, 83.69, 75.48, 75.40, 48.71, 46.93, 46.77, 44.09, 42.59, 41.70, 38.60, 38.41, 32.10, 28.99, 28.87, 28.36, 25.78, 24.93, 22.79, 22.76, 22.67, 22.47, 19.63, 19.55; LRMS (ESI): *m/z* calcd for $C_{35}H_{51}N_6O_4^+$ $[M+H]^+$: 619.39; Found: 619.5.

3q ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.36–8.26 (m, 1H), 8.09 (d, *J* = 27.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 16.6, 8.2 Hz, 1H), 7.25–7.16 (m, 2H), 7.09 (q, *J* = 7.6 Hz, 1H), 4.84 (dd, *J* = 23.1, 15.2 Hz, 1H), 4.62 (dd, *J* = 31.4, 15.3 Hz, 1.5H), 4.48 (t, *J* = 13.8 Hz, 1.5H), 4.29 (d, *J* = 13.4 Hz, 0.5H), 4.19 (d, *J* = 13.4 Hz, 0.6H), 4.07 (s, 0.5H), 3.90 (s, 0.5H), 3.66 (d, *J* = 14.4 Hz, 0.4H), 3.58–3.45 (m, 2H), 3.39 (s, 0.5H), 3.30–3.18 (m, 2.2H), 3.09 (t, *J* = 12.2 Hz, 0.8H), 2.95 (s, 1.5H), 2.88 (s, 1.5H), 2.23–2.13 (m, 1H), 2.07 (dd, *J* = 17.1, 12.3 Hz, 2H), 1.95 (td, *J* = 13.4, 6.9 Hz, 1H), 1.85–1.78 (m, 1.4H), 1.71–1.60 (m, 1.6H), 1.45–1.35 (m, 1H), 0.97–0.60 (m, 12H); HRMS (EI+): *m/z* calcd for $C_{30}H_{42}N_6O_2$ [M]: 518.33; Found: 518.3359.

1-((7a*R*,9*S*)-4-(((1*H*-Indol-3-yl)methyl)(methyl)amino)-9-isobutoxy-7,7a,8,9,10,11-hexahydropyrido[1,2-a] pyrimido[5,4-f][1,4]diazepin-6(5*H*)-yl)-2-(1H-indol-3-yl)ethan-1-one (3r)



3r' 3r

To a solution of **15f** (55 mg, 0.081 mmol) in EtOAc/MeOH co-solvent (0.16 mL/1.46 mL, 1:9, 0.05 M)) was added Pd/C (10.8 mg, 20 wt%) at r.t and the mixture was vigorously stirred under H_2 (g, 1 atm) atmosphere for 7 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was condensed under reduced pressure. 14.4 mg (0.027 mmol) of crude mixture was dissolved in 0.26 mL of DMF (0.1 M), and dry TEA (8.18 mg, 0.081 mmol, 3.0 equiv.), **S5** (15.1 mg, 0.040 mmol, 1.5 equiv.) were sequentially added. Stirred at r.t for 18 h, after the completion of the reaction, as indicated by LC-MS, saturated NH_4Cl solution was poured into the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4(s) and filtered, and the filtrate was condensed under reduced pressure, followed by silica-gel flash column chromatography to afford **3r′** (6.2 mg, 30% overall yield) as a white solid. To a solution of **3r′** (3.1 mg, 0.0039 mmol) in THF/MeOH co-solvent (0.08 mL/0.08 mL, 1:1, 0.025 M) was added potassium carbonate (K_2CO_3; 1.6 mg, 0.012 mmol, 3.0 equiv.), stirred at 60 °C for 2 h. After the completion of the reaction, as indicated by TLC & LC-MS, solvent was removed under reduced pressure, followed by silica-gel flash column chromatography to afford **3r** (1.9 mg, 89% yield) as a white solid.

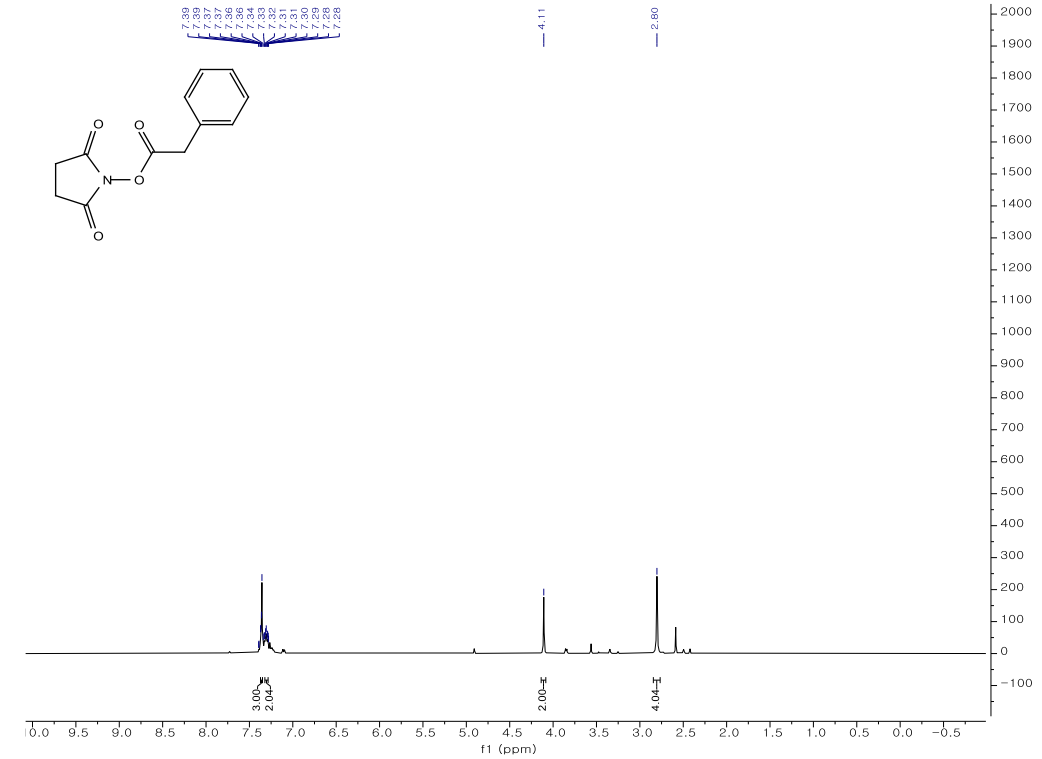
3r′ ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.27 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 2H), 7.57–7.26 (m, 6H), 7.20–7.11 (m, 2H), 4.84 (d, *J* = 15.1 Hz, 0.5H), 4.69 (d, *J* = 15.6 Hz, 0.5H), 4.54 (d, *J* = 15.1 Hz, 1H), 4.51–4.36 (m, 2H), 4.17 (s, 0.5H), 4.06 (s, 0.5H), 3.92–3.78 (m, 1H), 3.77–3.69 (m, 1H), 3.52–3.37 (m, 3H), 3.27–3.05 (m, 3H), 2.87 (s, 1.7H), 2.77 (s, 1.3H), 2.07–1.96 (m, 1.6H), 1.79 (ddt, *J* = 20.3, 13.3, 6.9 Hz, 1.4H), 1.67 (d, *J* = 6.4 Hz, 9H), 1.63 (d, *J* = 15.1 Hz, 9H), 1.57 (d, *J* = 31.2 Hz, 3H), 0.92–0.83 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) (as a mixture

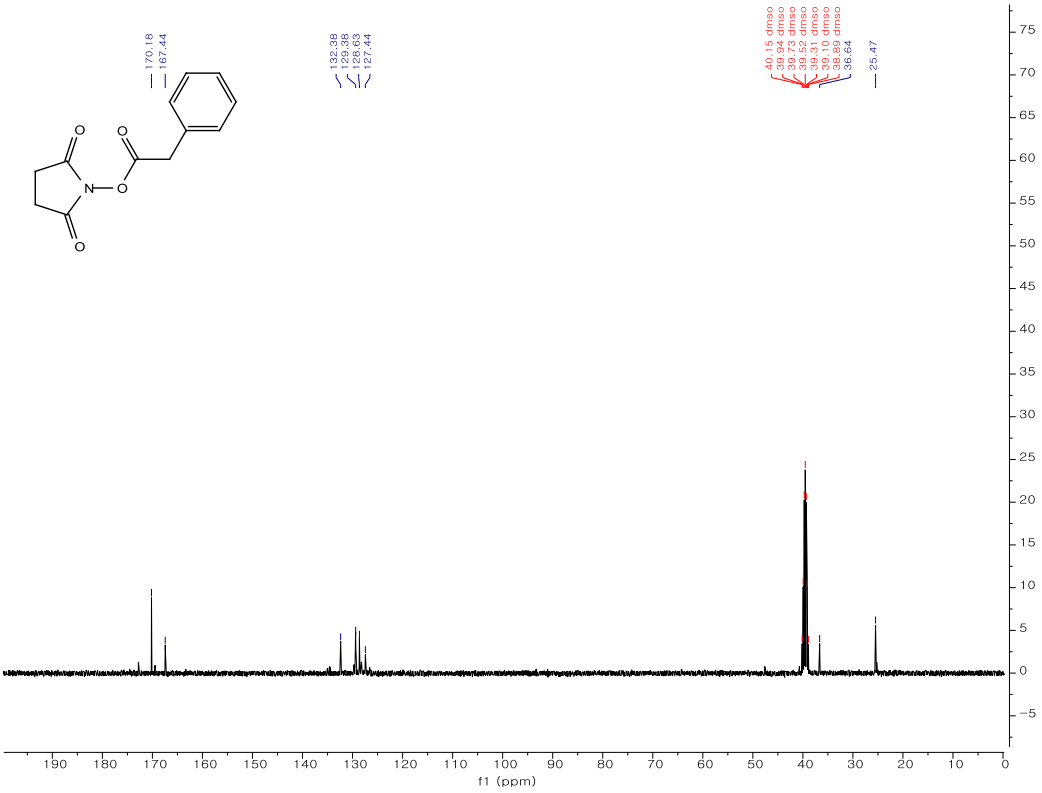
of rotamers): δ 170.33, 169.45, 165.87, 165.67, 165.38, 165.08, 156.31, 130.15, 129.98, 129.57, 125.00, 124.83, 124.74, 124.67, 124.62, 124.28, 124.22, 123.91, 123.02, 122.92, 122.81, 122.73, 119.44, 119.08, 118.99, 117.47, 117.25, 115.64, 115.39, 114.03, 113.41, 96.76, 84.12, 83.84, 83.67, 75.44, 75.28, 48.34, 47.28, 46.57, 44.42, 38.54, 38.49, 31.66, 30.46, 28.91, 28.87, 28.37, 28.34, 28.32, 19.60, 19.58; LRMS (ESI): *m/z* calcd for $C_{45}H_{58}N_7O_6^+$ $[M+H]^+$: 792.44; Found: 792.5.

3r ; ^{1}H NMR (500 MHz, $CDCl_3$) (as a mixture of rotamers): δ 8.29 (d, *J* = 2.2 Hz, 1H), 8.08 (s, 1H), 7.75 (s, 0.4H), 7.55–7.42 (m, 2.6H), 7.40–7.27 (m, 2H), 7.23–7.00 (m, 5H), 6.90 (s, 0.4H), 6.56 (d, *J* = 2.4 Hz, 0.6H), 4.86–4.76 (m, 1H), 4.65 (t, *J* = 19.9 Hz, 1H), 4.55–4.32 (m, 3H), 4.17 (t, *J* = 15.4 Hz, 1H), 3.87–3.63 (m, 2H), 3.57–3.45 (m, 2.5H), 3.41–3.31 (m, 1H), 3.22 (q, *J* = 7.7, 6.6 Hz, 1.5H), 3.16–2.95 (m, 2H), 2.83 (s, 1H), 2.38 (s, 2H), 2.04 (s, 2H), 1.85–1.74 (m, 1H), 1.39 (dd, *J* = 22.2, 11.6 Hz, 1H), 0.90 (ddd, *J* = 10.1, 6.6, 2.0 Hz, 6H); HRMS (EI+): *m/z* calcd for $C_{35}H_{41}N_7O_2$ [M]: 591.33; Found: 591.3313.

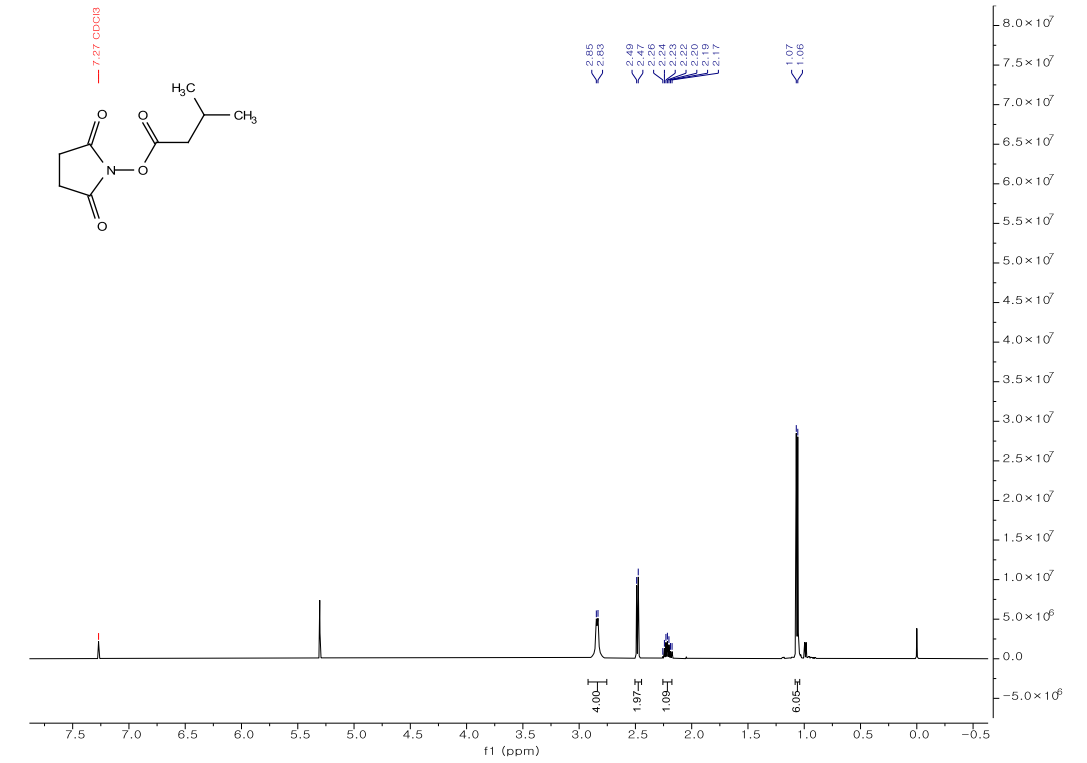
4. ^{1}H and ^{13}C NMR Spectra of New Compounds

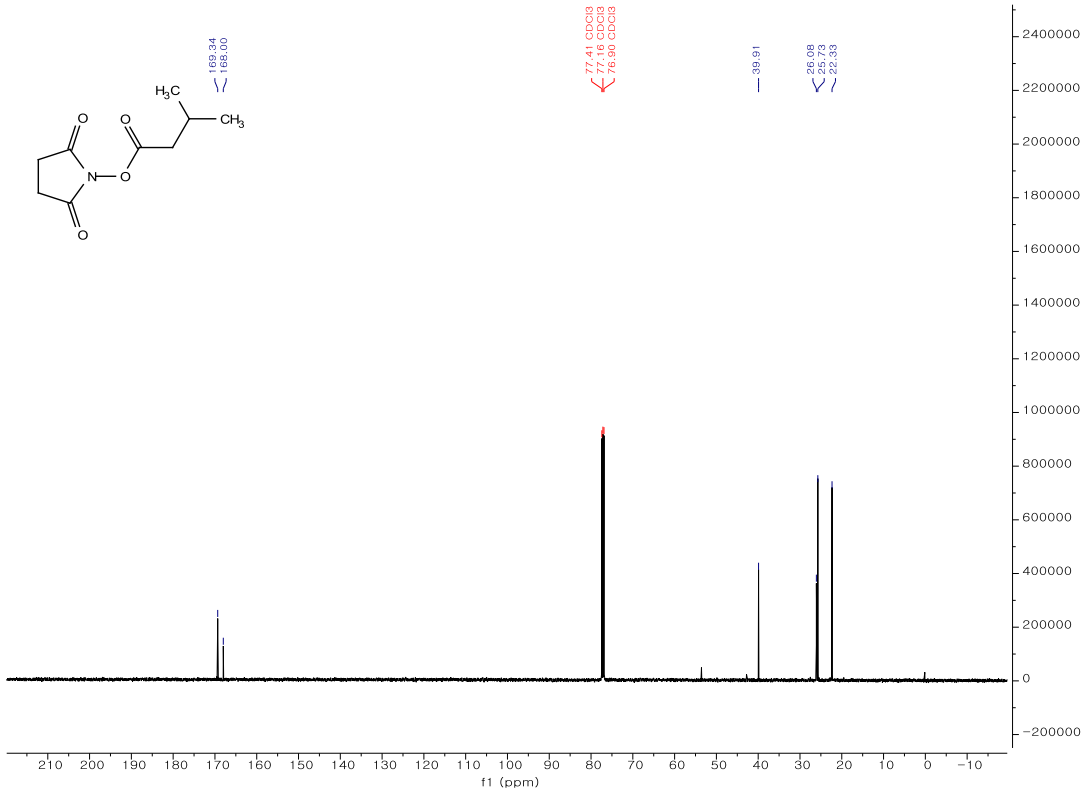
S1



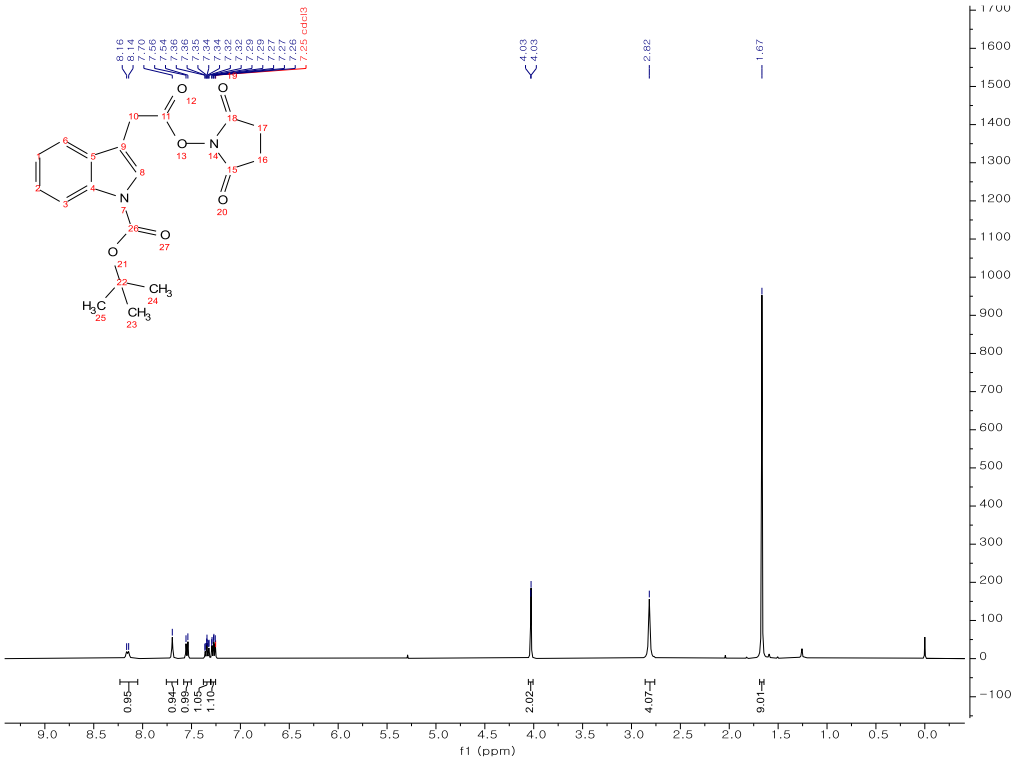


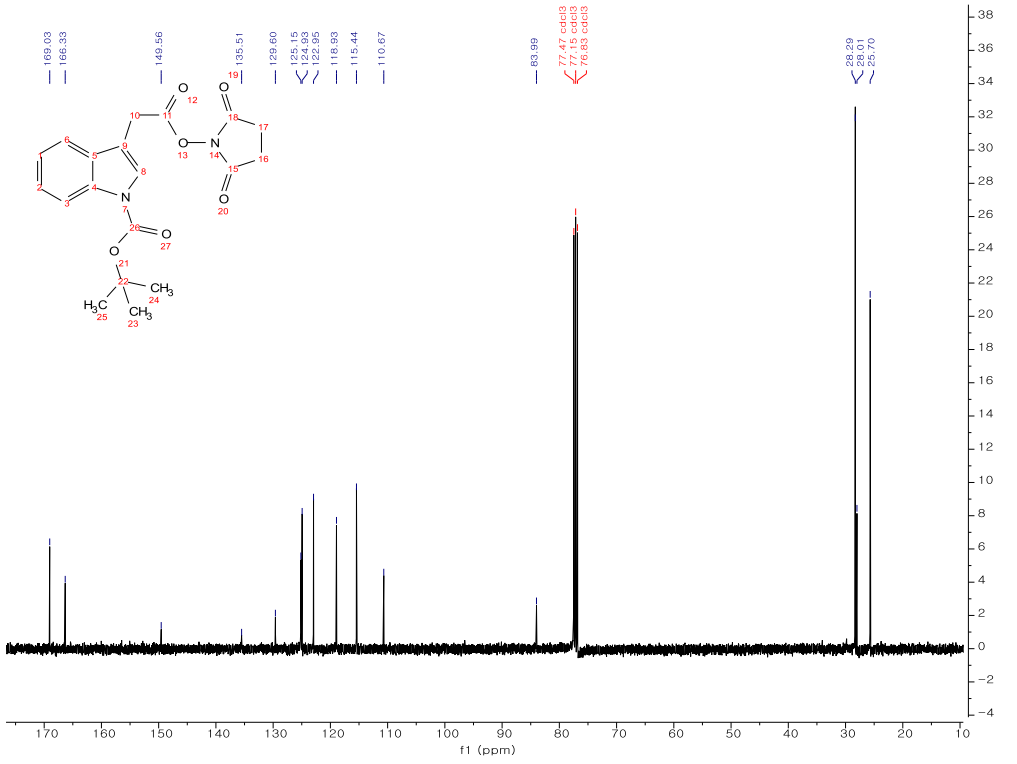
S2


7.27 CDCl3
2.85
2.83
2.49
2.47
2.26
2.24
2.23
2.22
2.20
2.19
2.17
1.07
1.06
4.00
1.97
1.09
6.05
f1 (ppm)

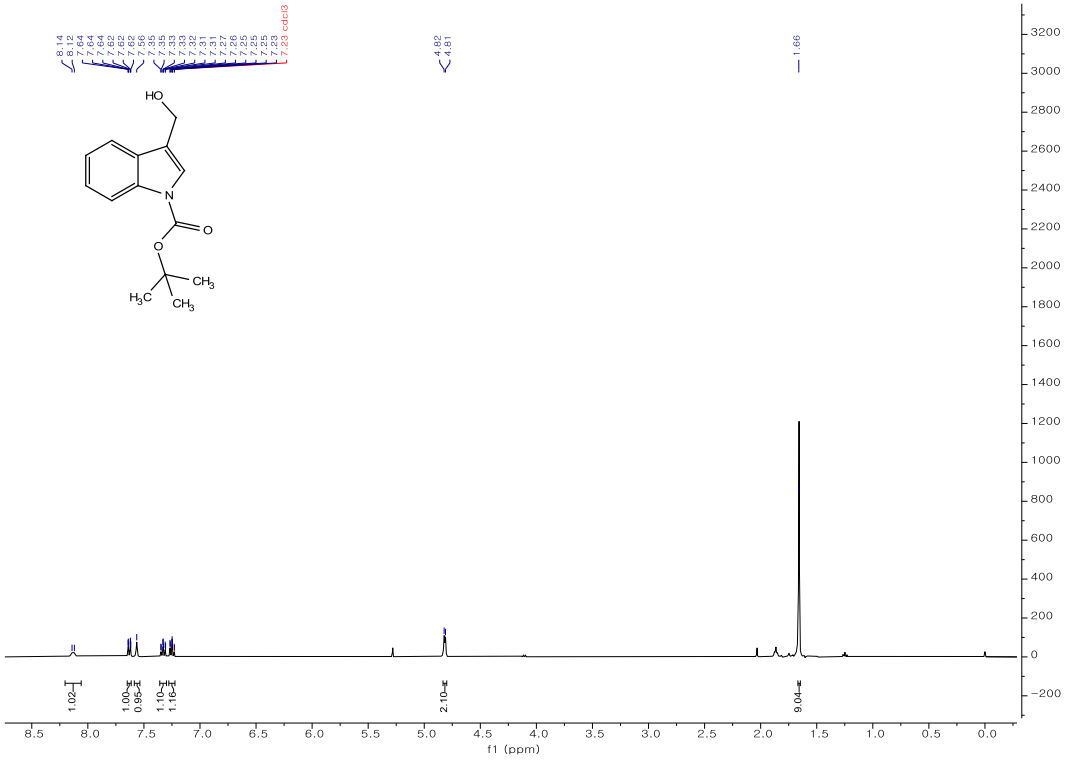

169.34
168.00
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
39.91
26.08
25.73
22.33
f1 (ppm)

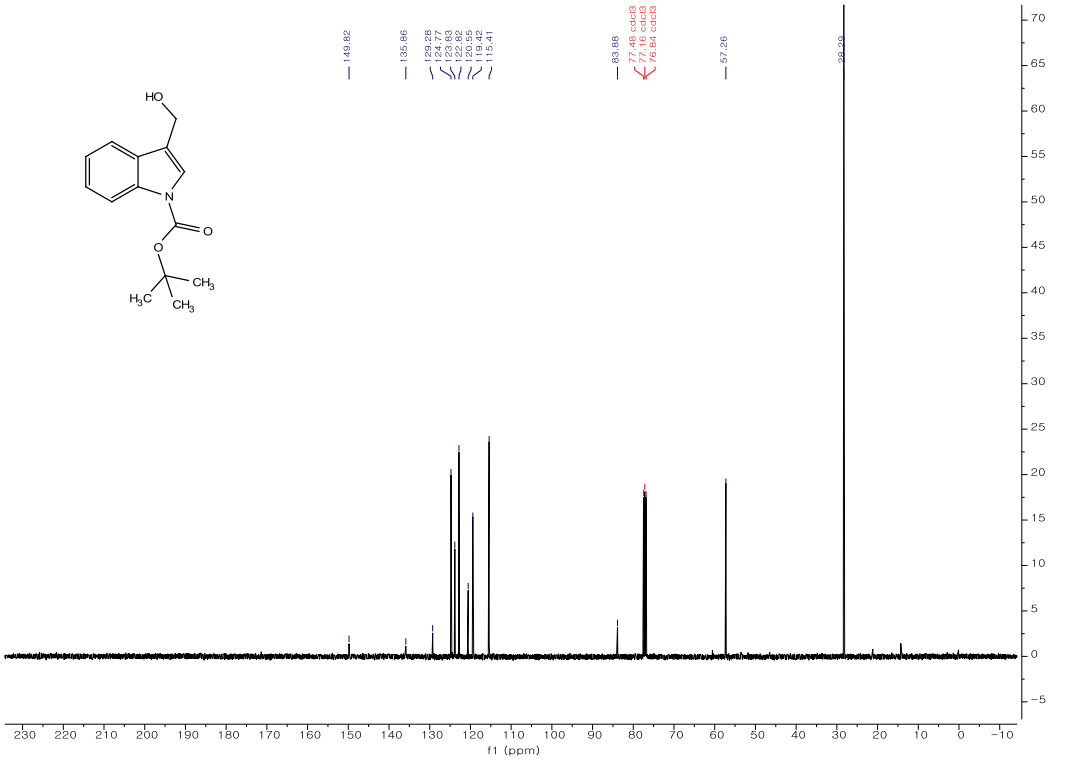
S5


8.16
8.14
7.70
7.56
7.54
7.36
7.35
7.34
7.32
7.32
7.29
7.29
7.27
7.27
7.26
7.25 cdcl3
4.03
4.03
2.82
1.67
0.95
0.94
0.99
1.05
1.10
2.02
4.07
9.01
f1 (ppm)

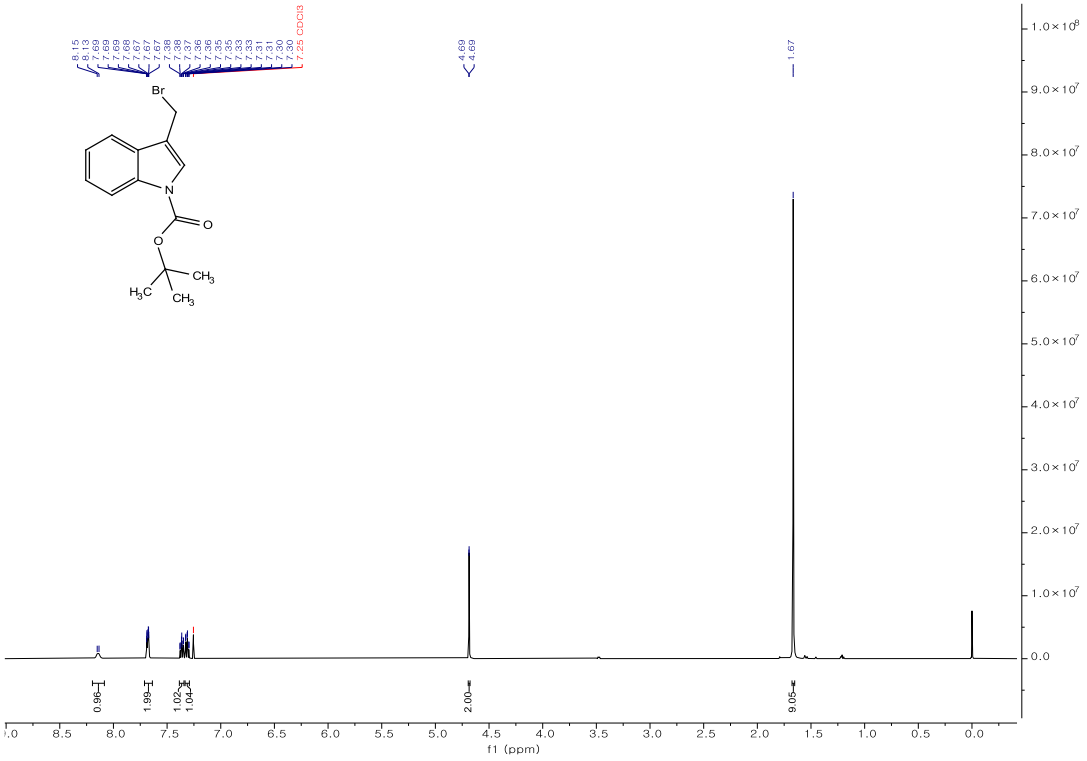

169.03
166.33
149.56
135.51
129.60
125.15
124.93
122.95
118.93
115.44
110.67
83.99
77.47 cdcl3
77.15 cdcl3
76.83 cdcl3
28.29
28.01
25.70
f1 (ppm)

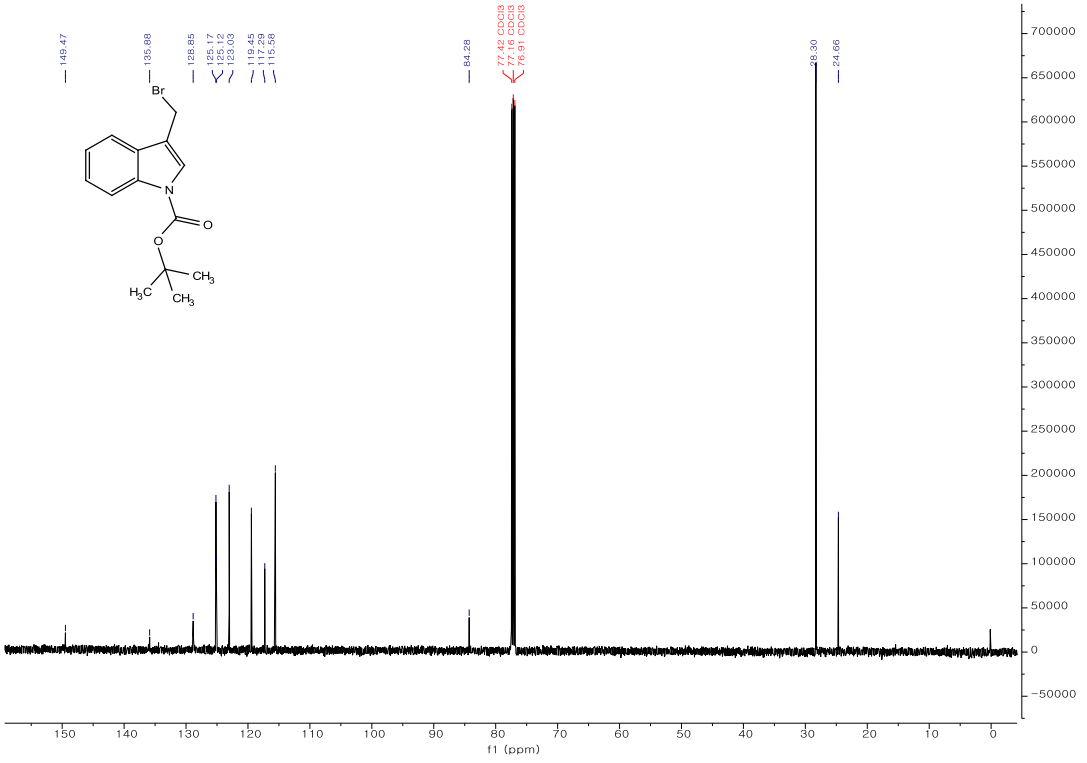
S6


8.14
8.12
7.64
7.64
7.62
7.62
7.62
7.62
7.56
7.35
7.33
7.32
7.31
7.27
7.26
7.25
7.25
7.23
7.23 cdcl3
4.82
4.81
1.66
HO
N
O
O
CH3
H3C
CH3
1.02
1.00
0.95
1.10
1.16
2.10
9.04
f1 (ppm)

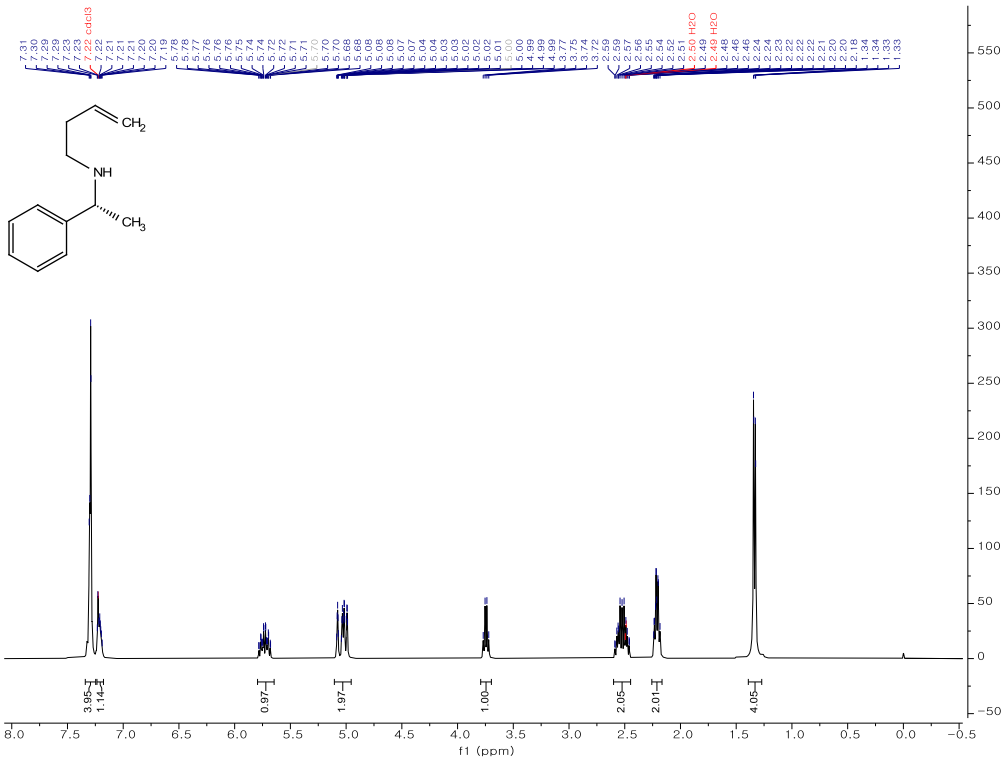

149.82
135.86
129.28
124.77
123.83
122.82
120.55
119.42
115.41
83.88
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
57.26
28.29
HO
N
O
O
CH3
H3C
CH3
f1 (ppm)

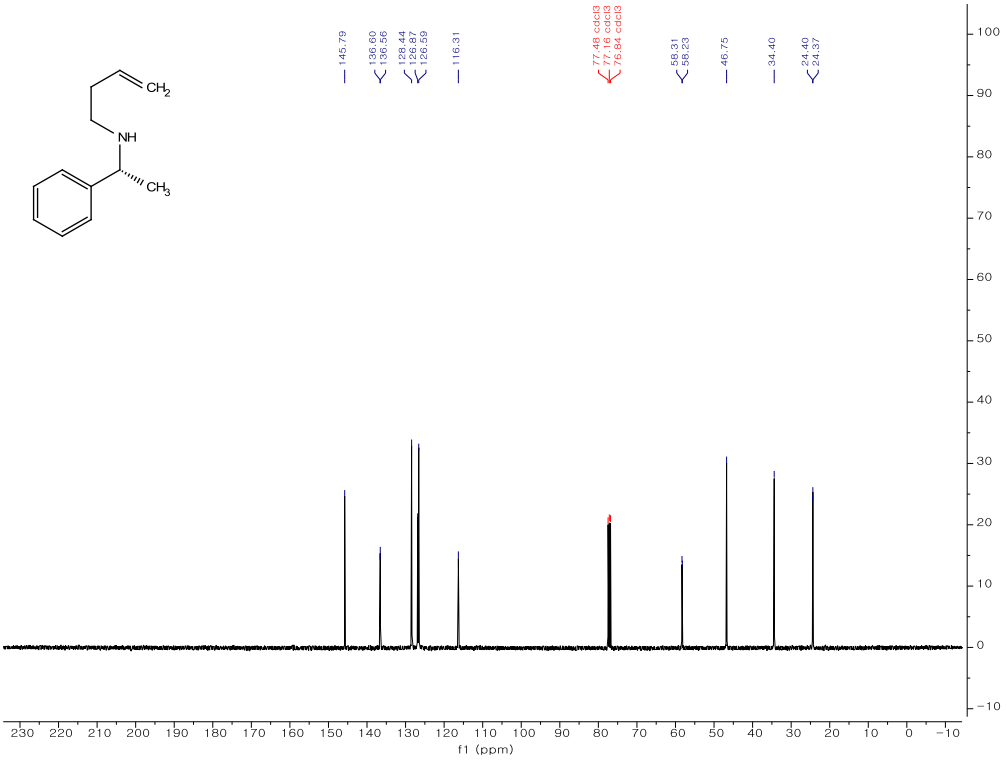
S7


8.15
8.13
7.69
7.69
7.69
7.68
7.67
7.67
7.67
7.38
7.38
7.37
7.36
7.35
7.35
7.33
7.33
7.31
7.30
7.30
7.25 CDCl3
4.69
4.69
1.67
Br
N
O
O
CH3
H3C
CH3
0.96
1.99
1.02
1.04
2.00
9.05
f1 (ppm)

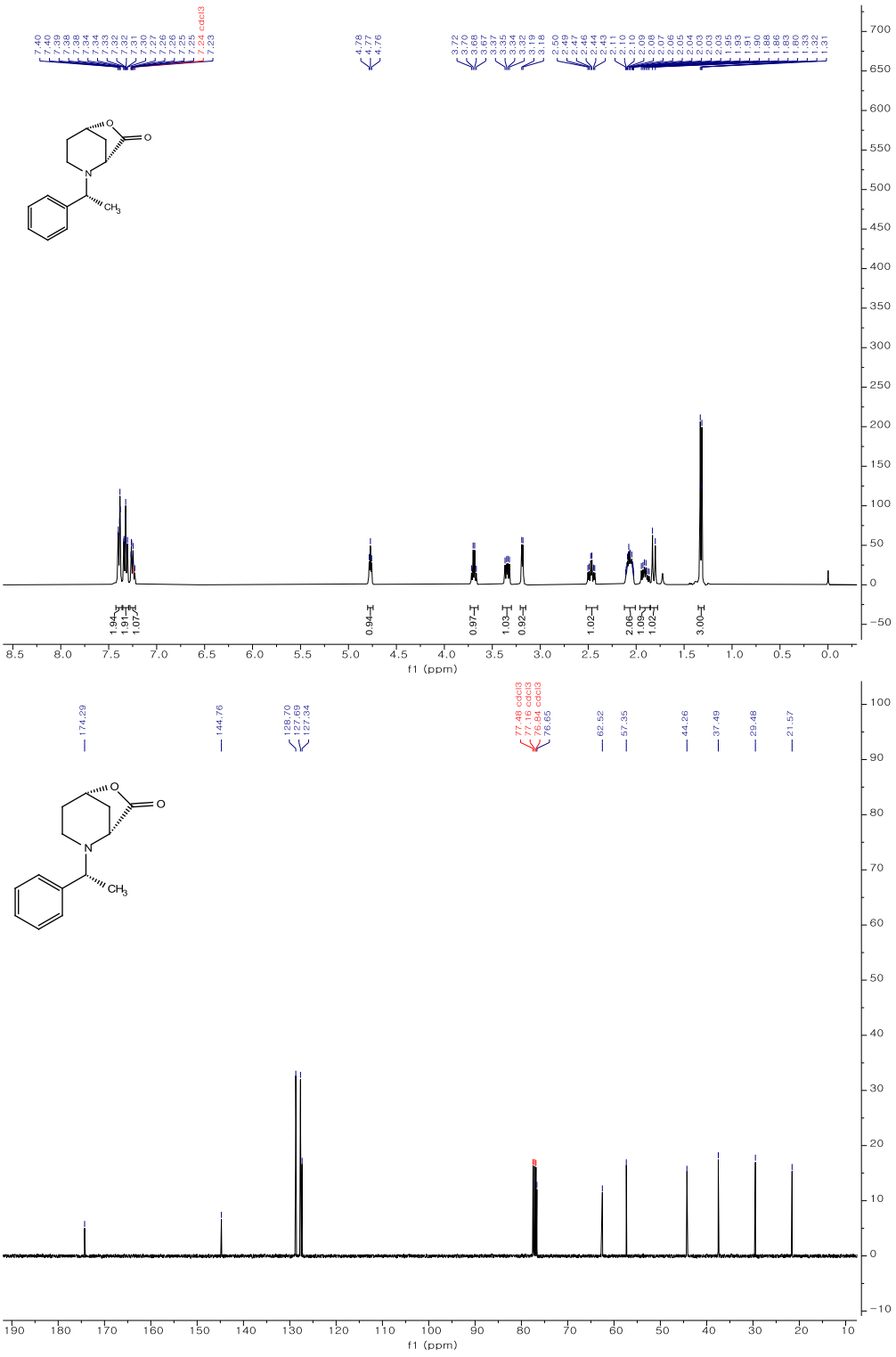

149.47
135.89
128.85
125.17
125.12
123.03
119.45
117.29
115.58
84.28
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
28.30
24.66
Br
N
O
O
CH3
H3C
CH3
f1 (ppm)

S8

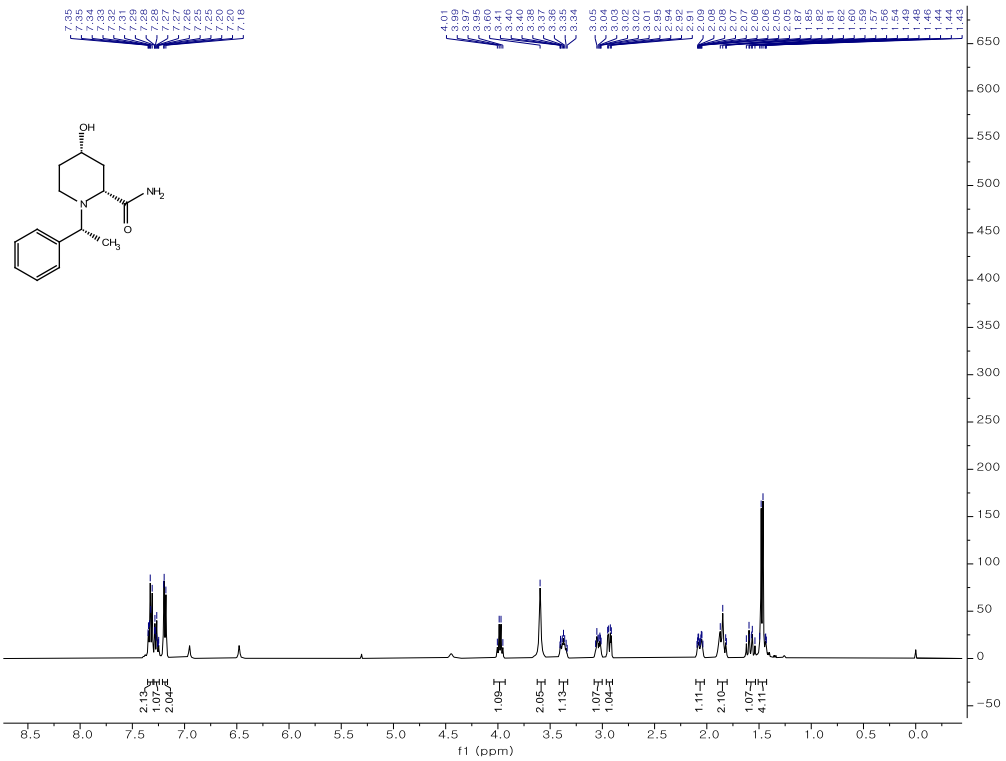

CH2
NH
CH3
3.95
1.14
0.97
1.97
1.00
2.05
2.01
4.05
f1 (ppm)

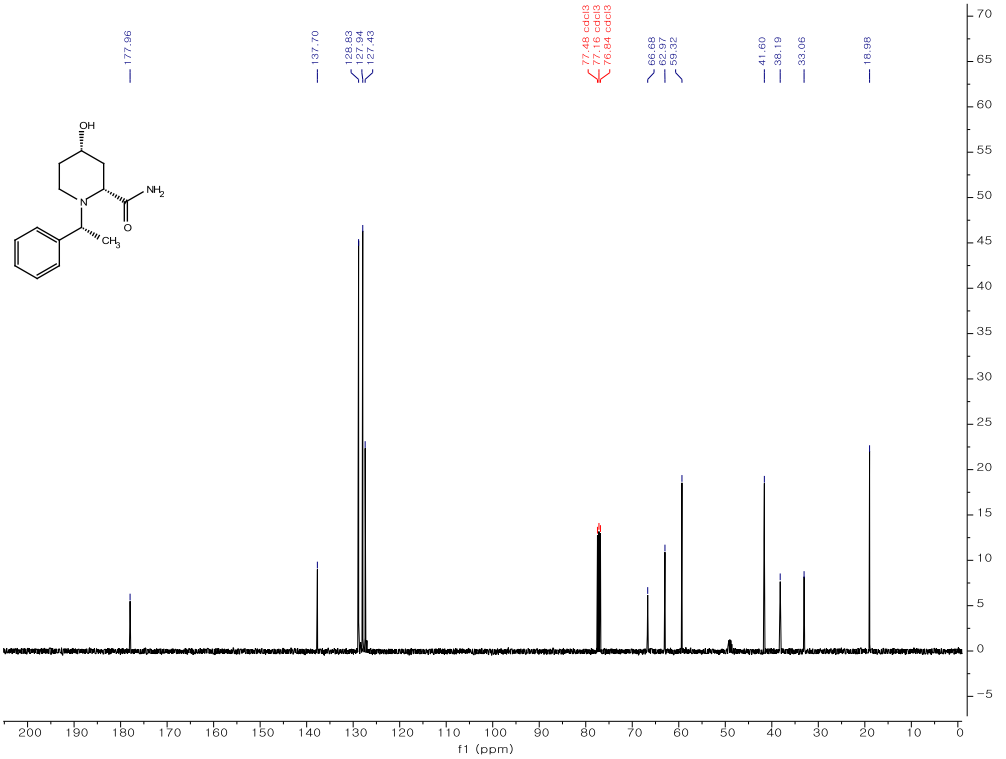

CH2
NH
CH3
145.79
136.60
136.56
128.44
126.87
126.59
116.31
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
58.31
58.23
46.75
34.40
24.40
24.37
f1 (ppm)

S9

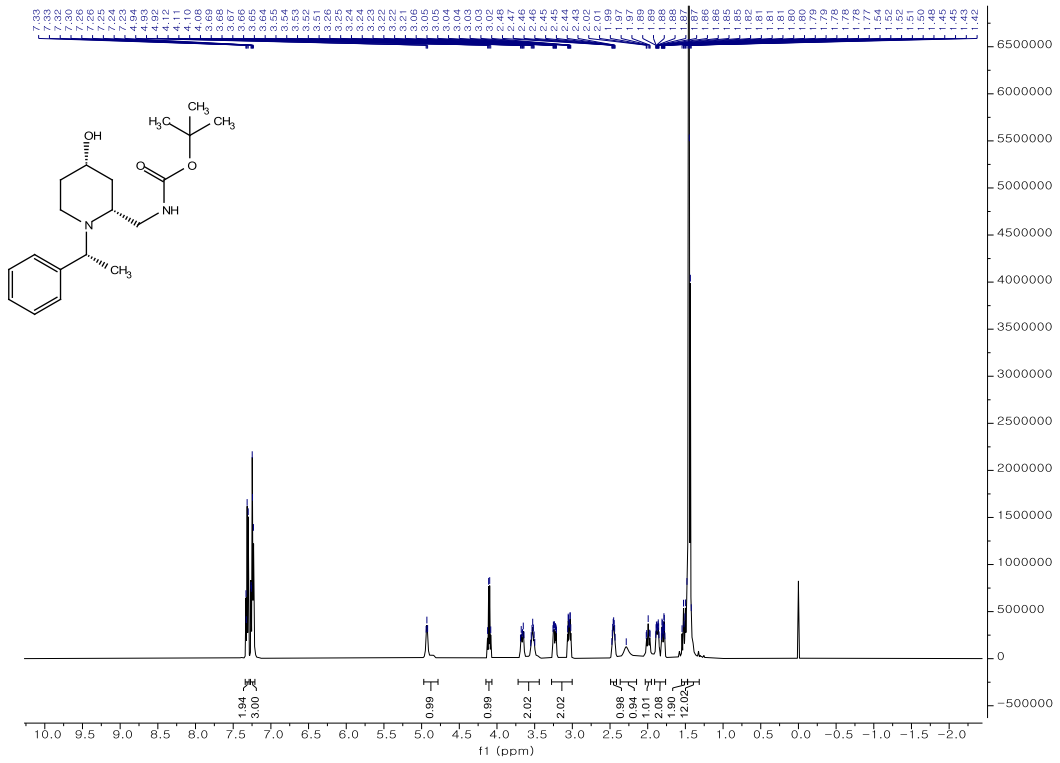

7.40 7.40 7.39 7.38 7.38 7.34 7.34 7.33 7.32 7.31 7.30 7.27 7.26 7.26 7.25 7.24 cdcl3 7.23
4.78 4.77 4.76
3.72 3.70 3.68 3.67 3.37 3.35 3.34 3.32 3.19 3.18
2.50 2.49 2.47 2.46 2.44 2.43 2.11 2.10 2.09 2.08 2.07 2.06 2.05 2.04 2.03 2.03 2.03 1.95 1.93 1.91 1.90 1.88 1.86 1.83 1.80 1.33 1.32 1.31
O
O
N
CH3
1.94 1.91 1.07 0.94 0.97 1.03 0.92 1.02 2.06 1.09 1.02 3.00
f1 (ppm)
174.29 144.76 128.70 127.69 127.34 77.48 cdcl3 77.16 cdcl3 76.84 cdcl3 76.65 62.52 57.35 44.26 37.49 29.48 21.57
O
O
N
CH3
f1 (ppm)

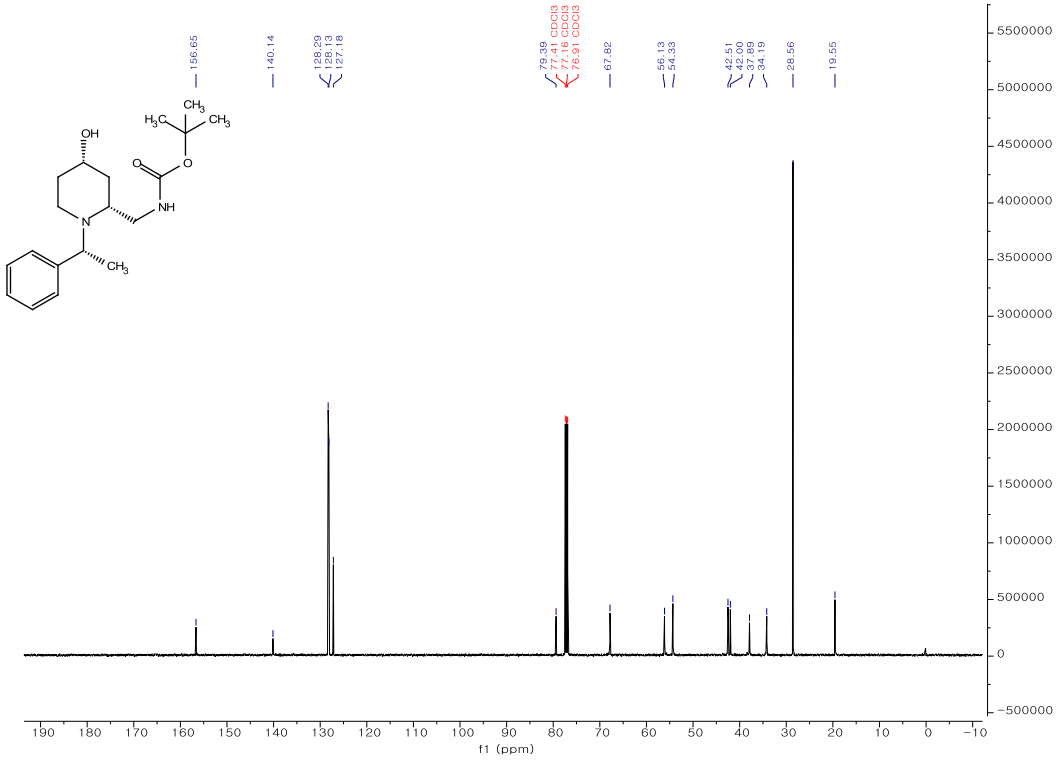
S10


OH
NH2
O
N
CH3
f1 (ppm)

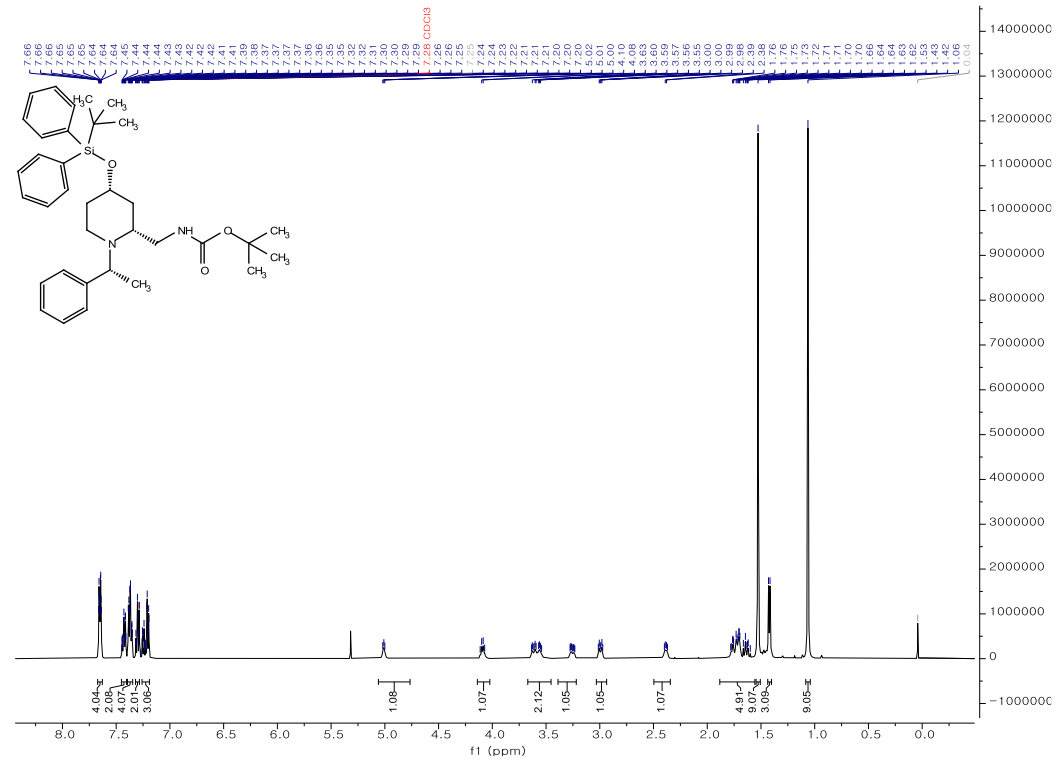

OH
NH2
O
N
CH3
177.96
137.70
128.83
127.94
127.43
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
66.68
62.97
59.32
41.60
38.19
33.06
18.98
f1 (ppm)

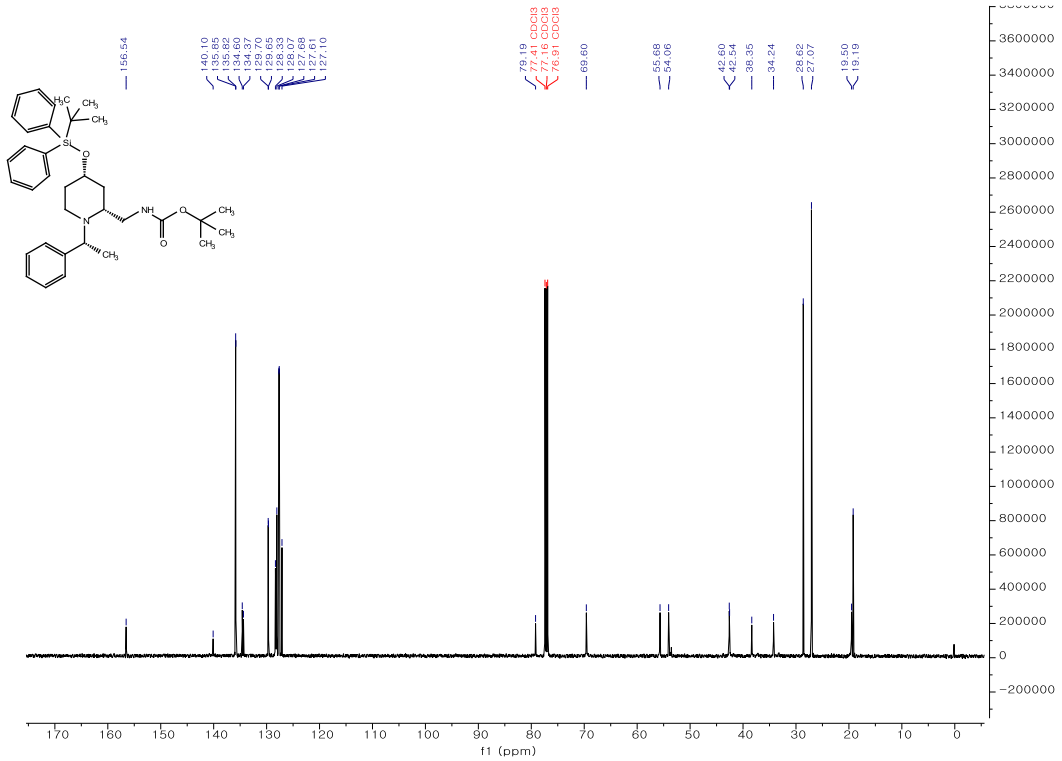
S11


OH
CH3
H3C
CH3
O
O
NH
N
CH3
1.94
3.00
0.99
0.99
2.02
2.02
0.98
0.94
1.01
2.08
1.90
12.02
f1 (ppm)

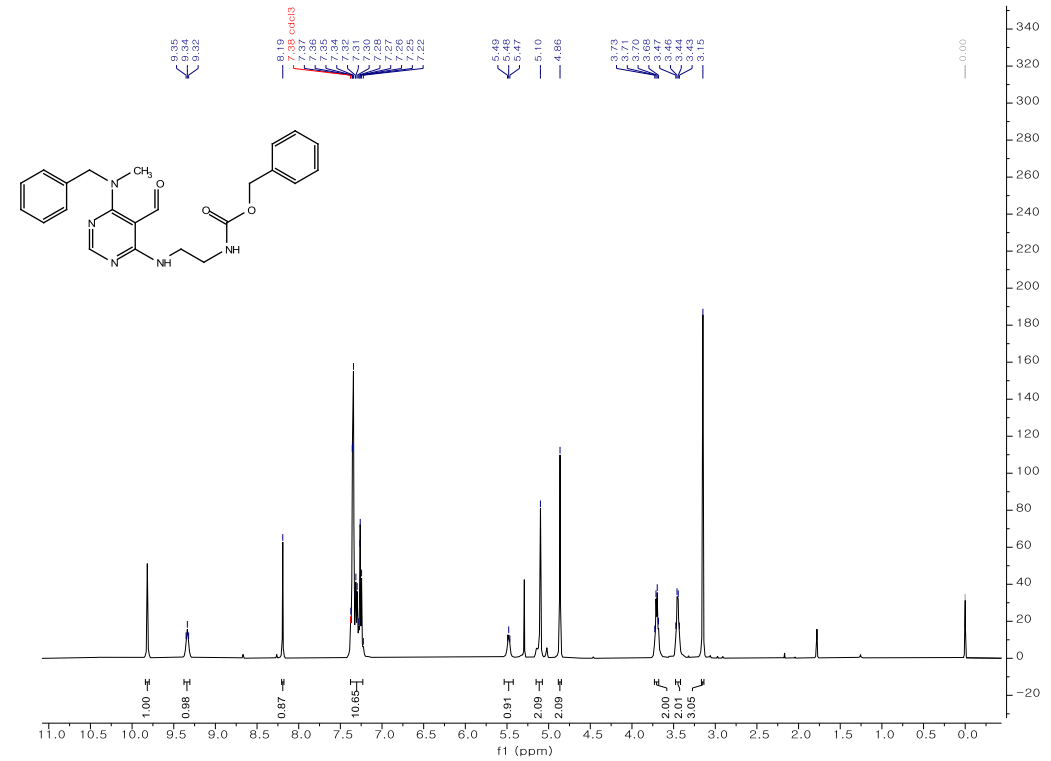

OH
CH3
H3C
CH3
O
O
NH
N
CH3
156.65
140.14
128.99
128.13
127.18
79.39
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
67.82
56.13
54.33
42.51
42.00
32.89
34.19
28.56
19.55
f1 (ppm)

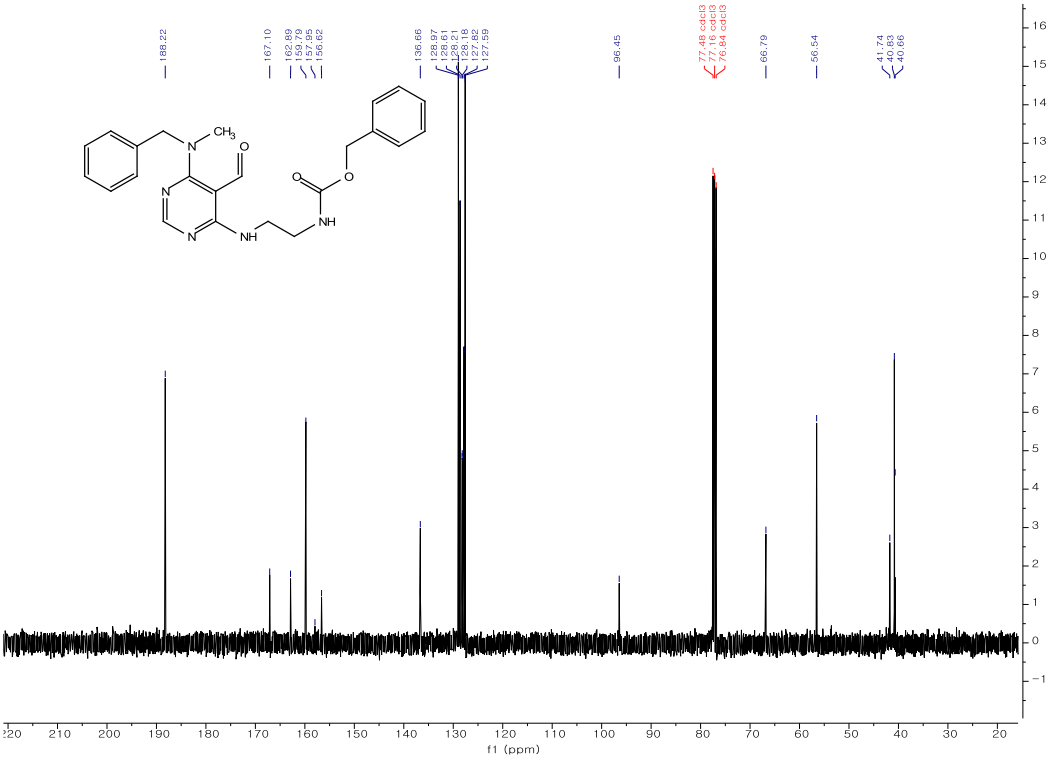
6



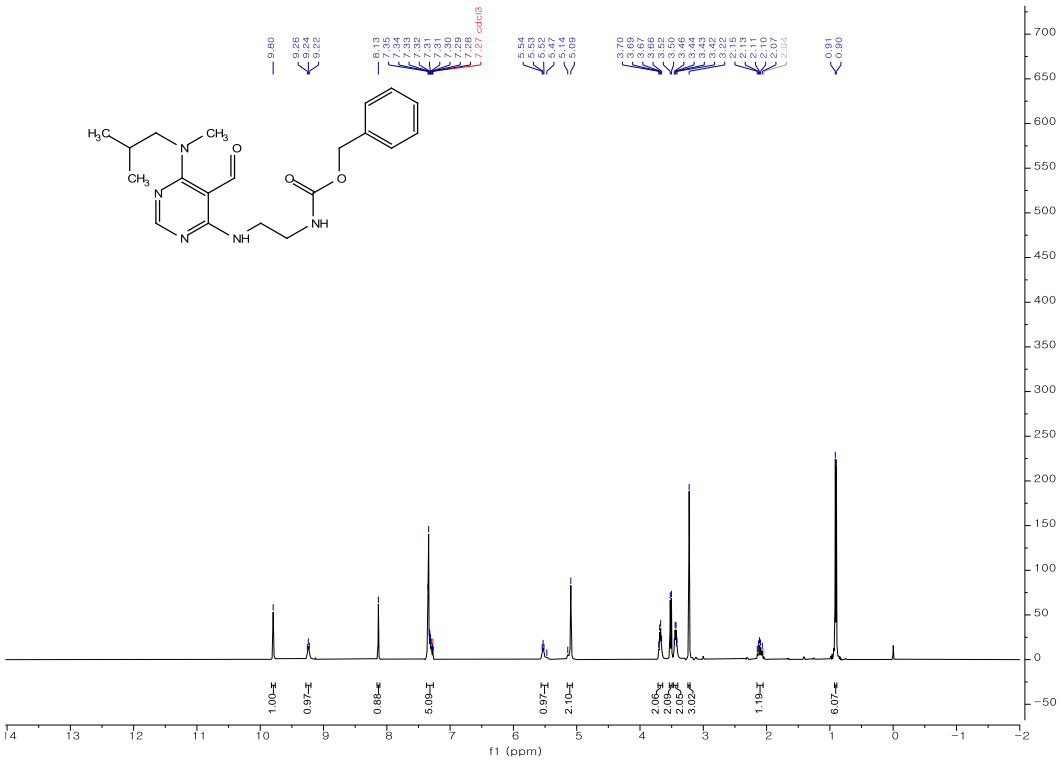


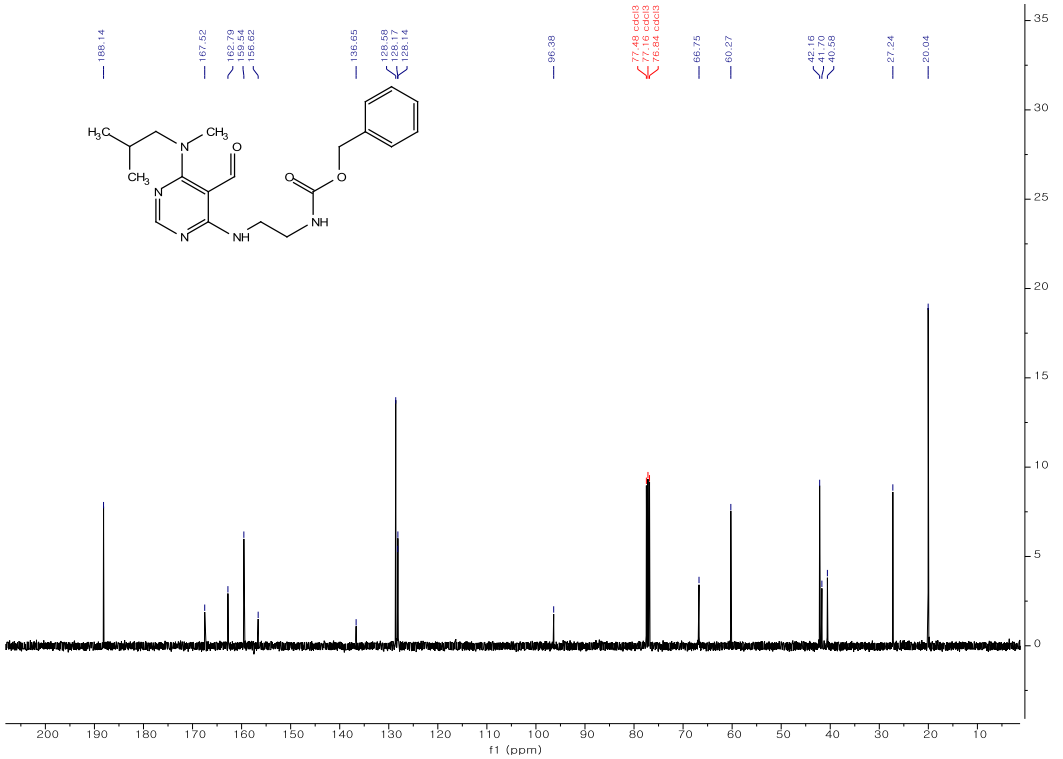
7a


9.35
9.34
9.32
8.19
7.39 cdcl3
7.37
7.36
7.35
7.34
7.32
7.31
7.30
7.28
7.27
7.26
7.25
7.22
5.49
5.48
5.47
5.10
4.86
3.73
3.71
3.70
3.68
3.47
3.46
3.44
3.43
3.15
0.00
1.00
0.98
0.87
10.65
0.91
2.09
2.09
2.00
2.01
3.05
f1 (ppm)

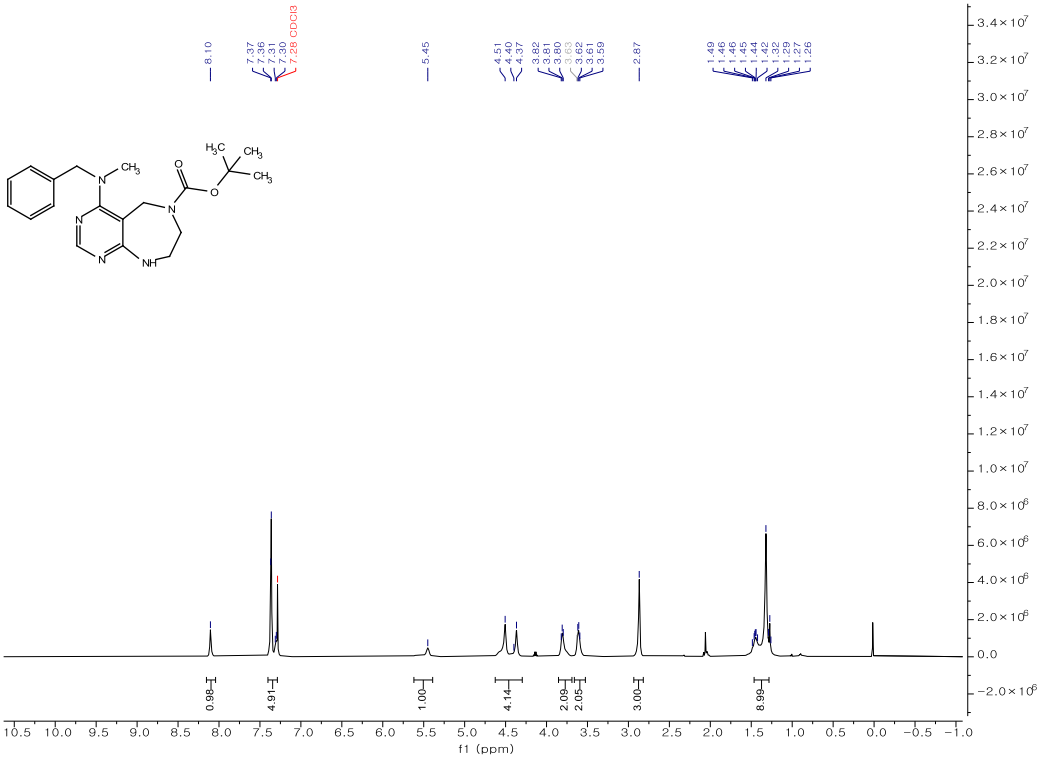

188.22
167.10
162.89
159.79
157.95
156.62
136.66
128.97
128.61
128.21
128.18
127.82
127.59
96.45
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
66.79
56.54
41.74
40.83
40.66
f1 (ppm)

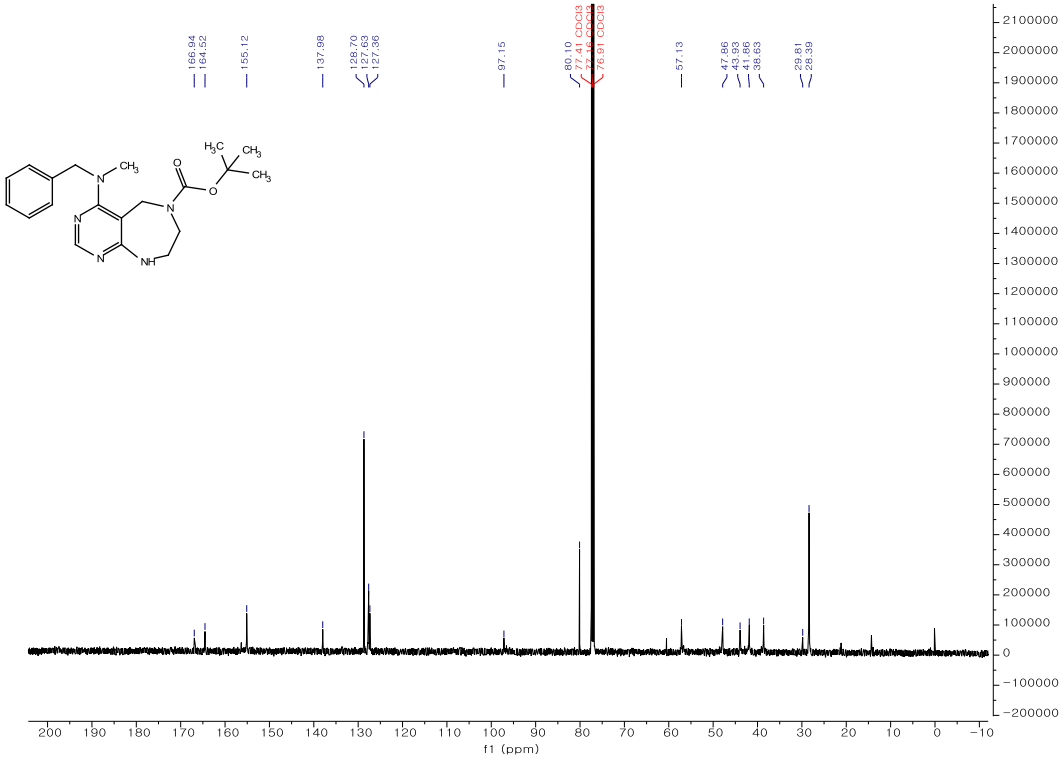
7b


9.80
9.26
9.24
9.22
8.13
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.27 cdcl3
5.54
5.53
5.52
5.47
5.14
5.09
3.70
3.69
3.67
3.66
3.52
3.50
3.46
3.44
3.43
3.42
3.22
2.15
2.13
2.11
2.10
2.07
2.04
0.91
0.90
1.00
0.97
0.88
5.09
0.97
2.10
2.06
2.09
2.05
3.02
1.19
6.07
f1 (ppm)

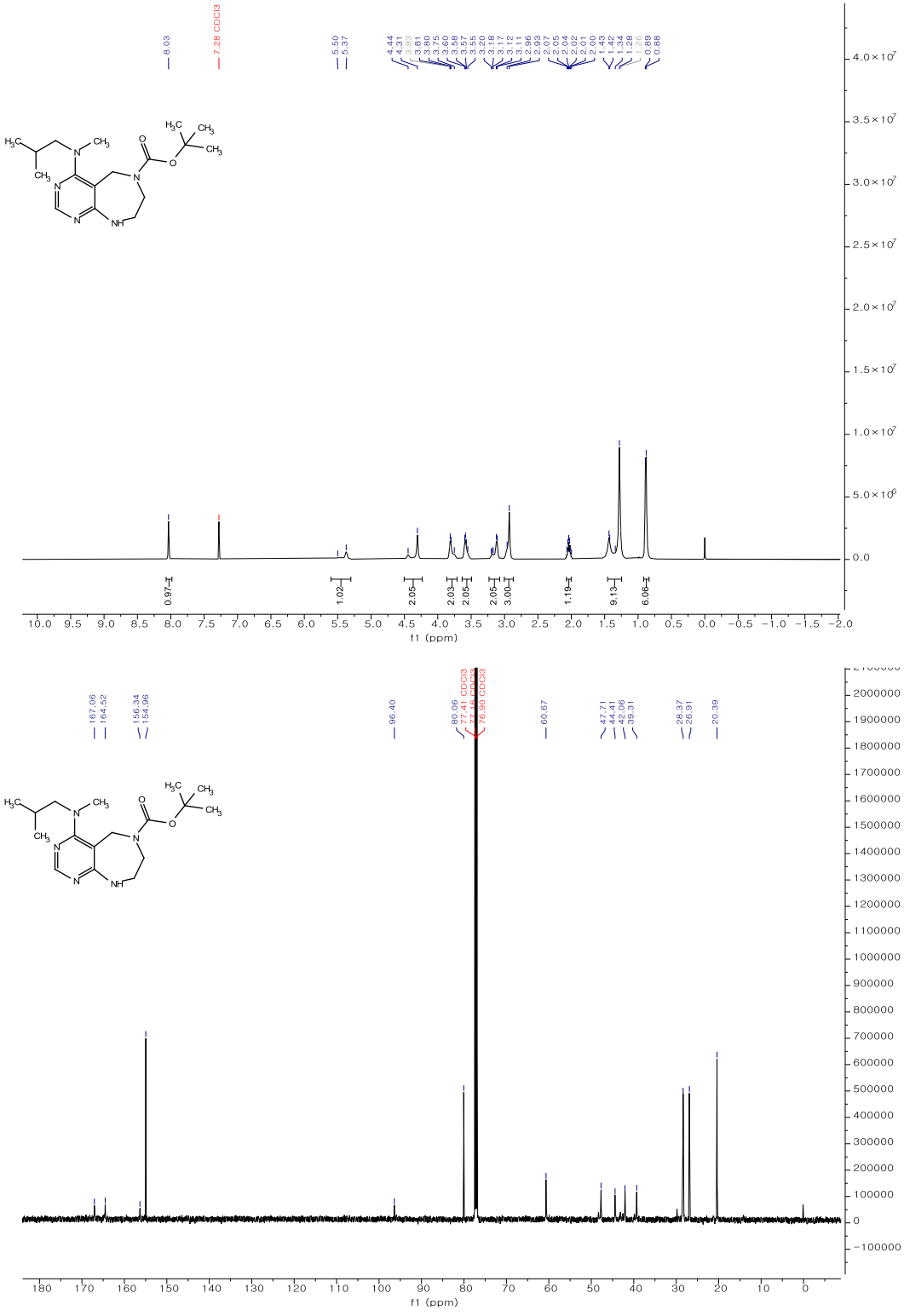

188.14
167.52
162.79
159.54
156.62
136.65
128.58
128.17
128.14
96.38
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
66.75
60.27
42.16
41.70
40.58
27.24
20.04
f1 (ppm)

8a

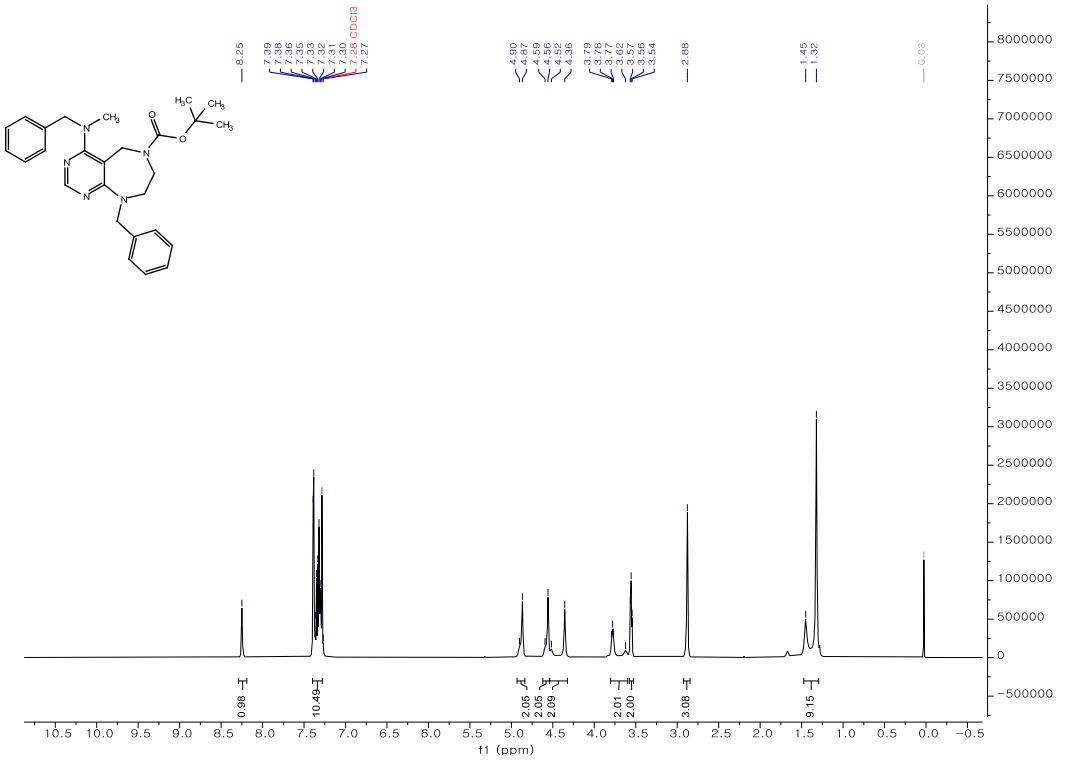

8.10
7.37
7.36
7.31
7.30
7.28 CDCl3
5.45
4.51
4.40
4.37
3.82
3.81
3.80
3.63
3.62
3.61
3.59
2.87
1.49
1.46
1.46
1.45
1.44
1.42
1.32
1.29
1.27
1.26
0.98
4.91
1.00
4.14
2.09
2.05
3.00
8.99
f1 (ppm)

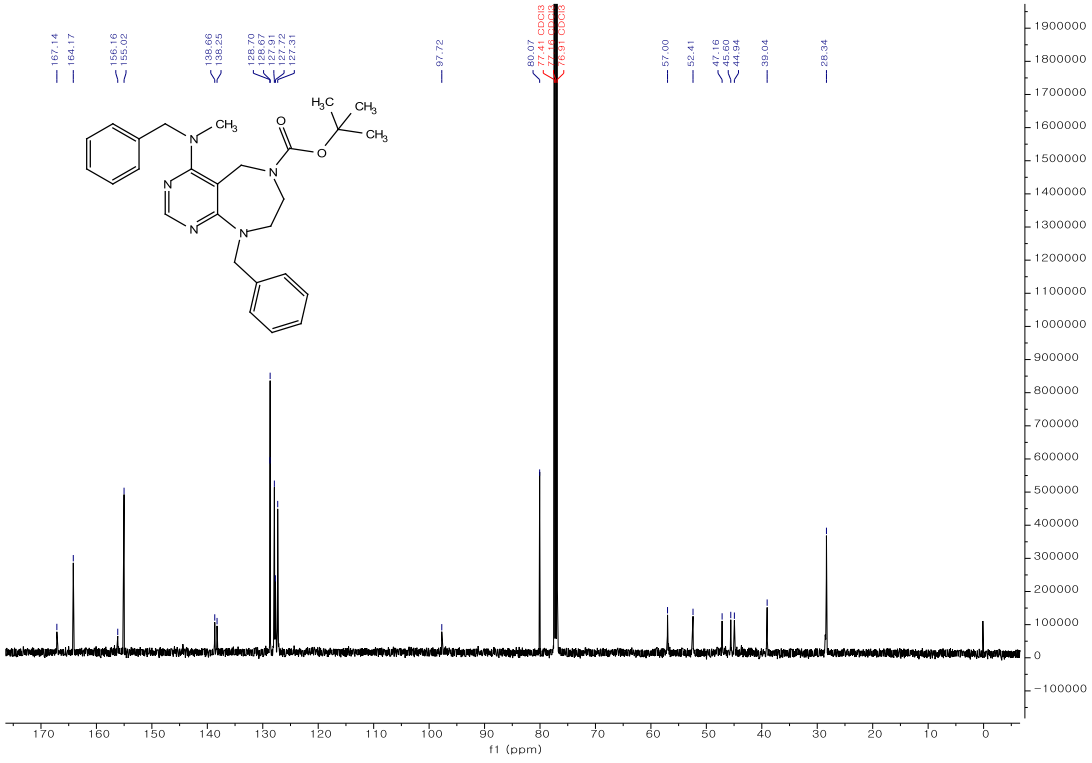

166.94
164.52
155.12
137.98
128.70
127.63
127.36
97.15
80.10
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
57.13
47.86
43.93
41.86
38.63
29.81
28.39
f1 (ppm)

8b

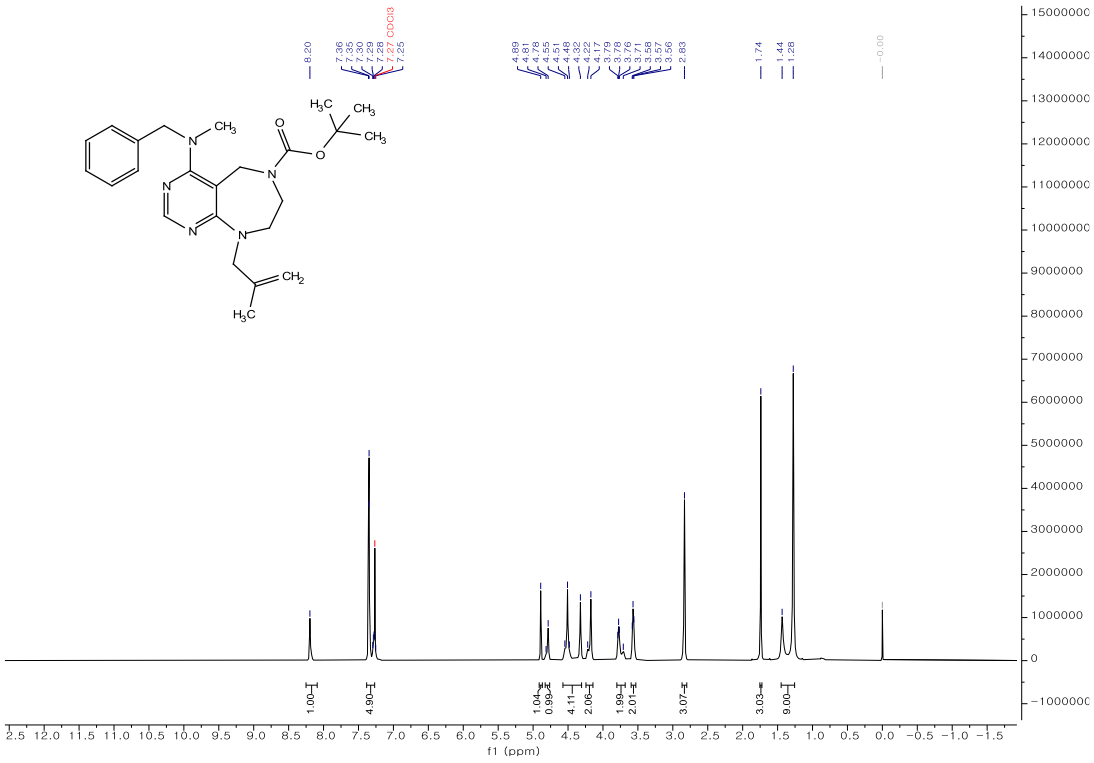

8.03
7.28 CDCl3
5.50
5.37
4.44
4.31
3.83
3.81
3.80
3.75
3.60
3.58
3.57
3.55
3.20
3.18
3.17
3.12
3.11
2.96
2.93
2.07
2.05
2.04
2.02
2.01
2.00
1.49
1.42
1.34
1.28
1.26
0.89
0.88
0.97
1.02
2.05
2.03
2.05
2.05
3.00
1.19
9.13
6.06
f1 (ppm)
167.06
164.52
156.34
154.96
96.40
80.06
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
60.67
47.71
44.41
42.06
39.31
28.37
26.91
20.39
f1 (ppm)

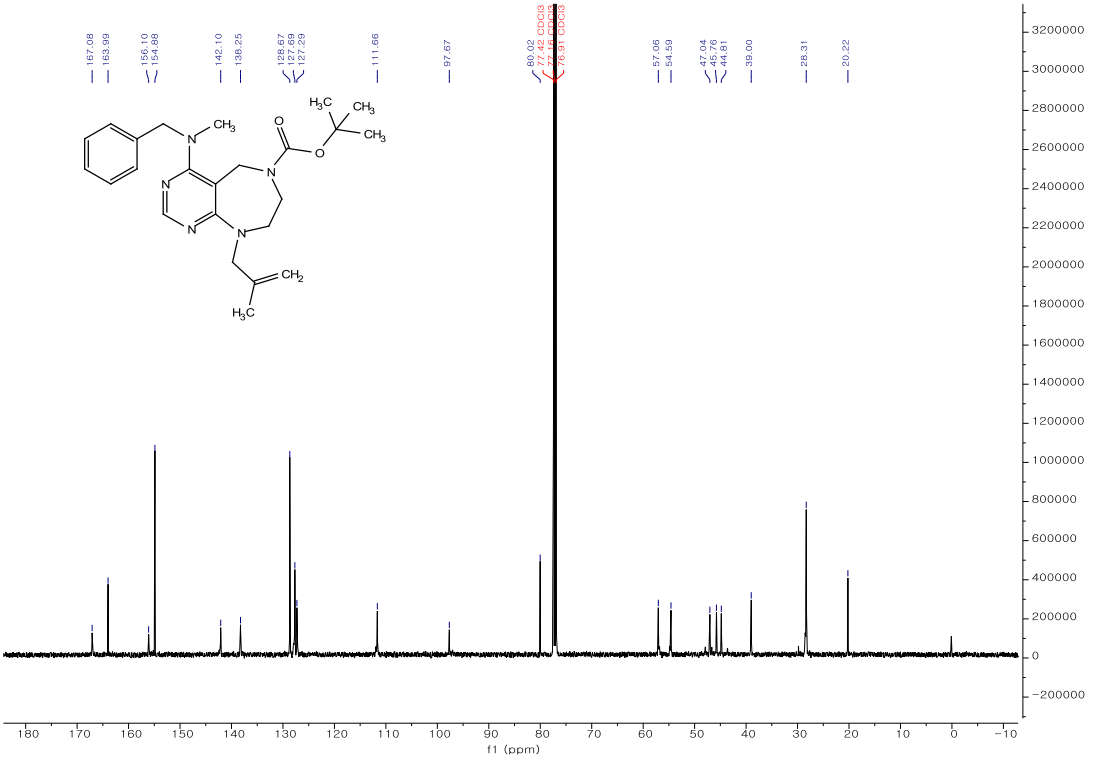
9a


8.25
7.39
7.38
7.36
7.35
7.33
7.32
7.31
7.30
7.28 CDCl3
7.27
4.90
4.87
4.59
4.56
4.52
4.36
3.79
3.78
3.77
3.62
3.57
3.56
3.54
2.88
1.45
1.32
0.03
0.98
10.49
2.05
2.05
2.09
2.01
2.00
3.08
9.15
f1 (ppm)

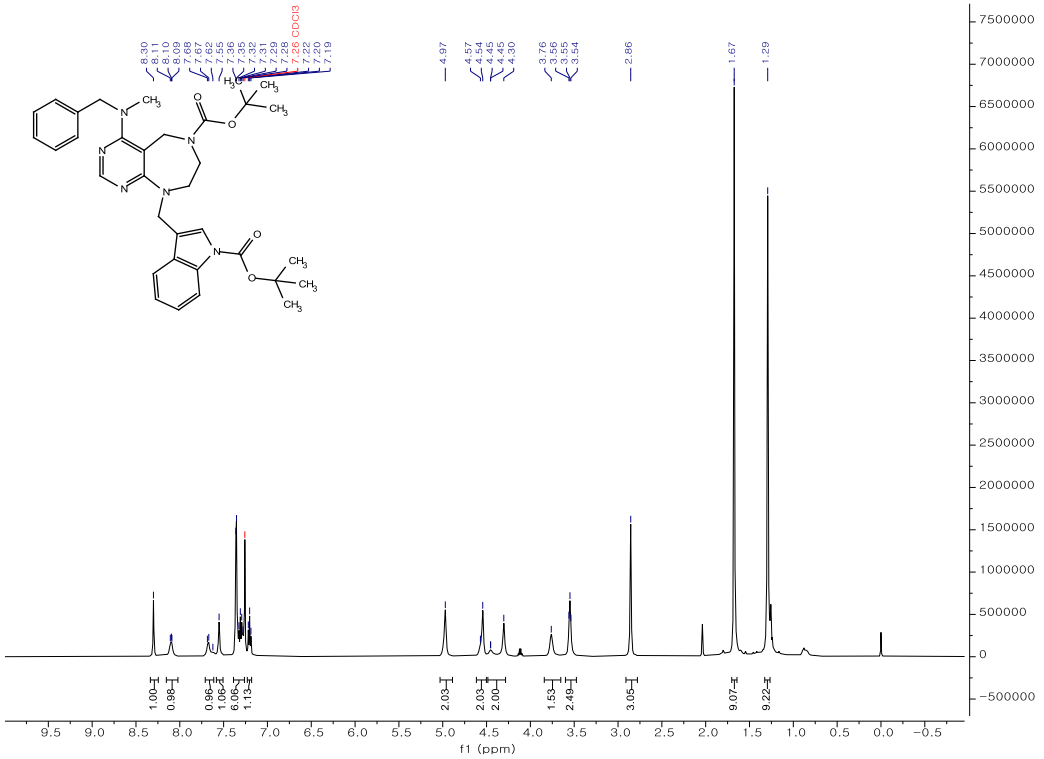

167.14
164.17
156.16
155.02
138.66
138.25
128.70
128.67
127.91
127.72
127.31
97.72
80.07
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
57.00
52.41
47.16
45.60
44.94
39.04
28.34
f1 (ppm)

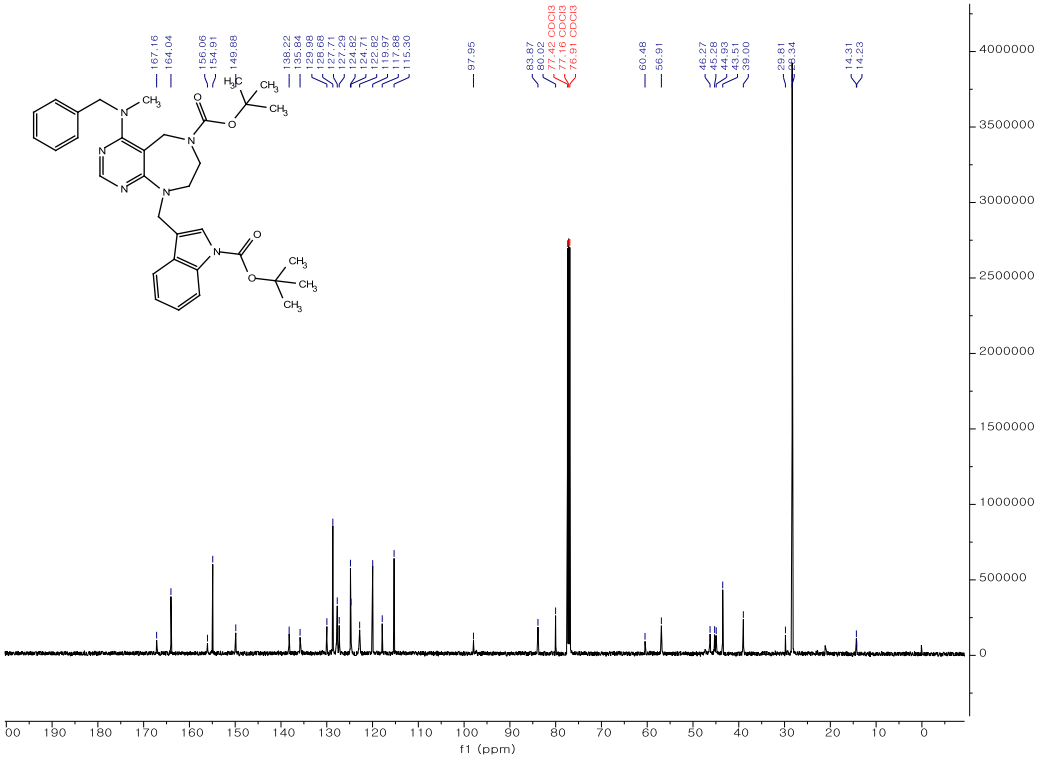
9b


8.20
7.36
7.35
7.30
7.29
7.28
7.27 CDCl3
7.25
4.89
4.81
4.78
4.55
4.51
4.48
4.32
4.22
4.17
3.79
3.78
3.76
3.71
3.58
3.57
3.56
2.83
1.74
1.44
1.28
0.00
1.00
4.90
1.04
0.99
4.11
2.06
1.99
2.01
3.07
3.03
9.00
f1 (ppm)

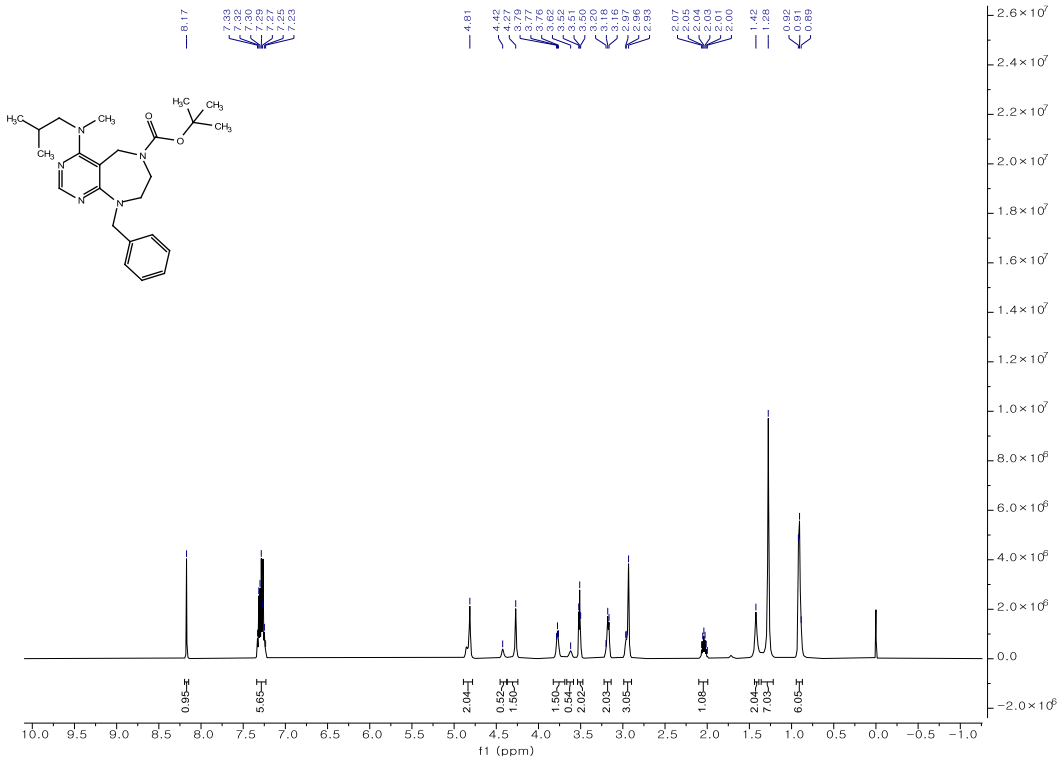

167.08
163.99
156.10
154.88
142.10
138.25
128.67
127.68
127.29
111.66
97.67
80.02
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
57.06
54.59
47.04
45.76
44.81
39.00
28.31
20.22
f1 (ppm)

9c


8.30
8.11
8.10
8.09
7.68
7.67
7.62
7.55
7.36
7.35
7.32
7.31
7.29
7.28
7.26 CDCl3
7.22
7.20
7.19
4.97
4.57
4.54
4.46
4.45
4.30
3.76
3.56
3.55
3.54
2.86
1.67
1.29
1.00
0.98
0.96
1.06
6.06
1.13
2.03
2.03
2.00
1.53
2.49
3.05
9.07
9.22
f1 (ppm)


167.16
164.04
156.06
154.91
149.88
138.22
135.84
128.88
128.66
127.71
127.29
124.82
124.71
122.82
119.97
117.88
115.30
97.95
83.87
80.02
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
60.48
56.91
46.27
44.28
44.93
43.51
39.00
29.81
28.34
14.31
14.23
f1 (ppm)

9d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3.51
3.50
3.20
3.18
3.16
3.07
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2.93
2.07
2.05
2.04
2.03
2.01
2.00
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1.28
0.92
0.91
0.89
0.95
5.65
2.04
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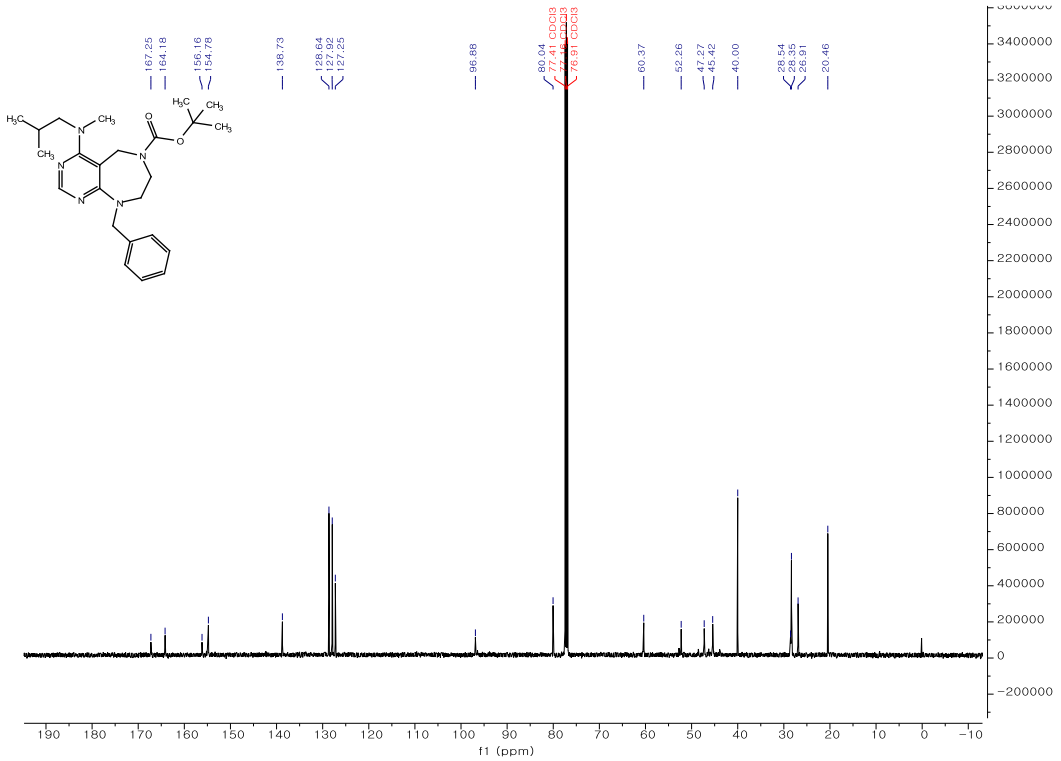
2.03
3.05
1.08
2.04
7.03
6.05
f1 (ppm)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80.04
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77.16 CDCl3
76.91 CDCl3
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25.91
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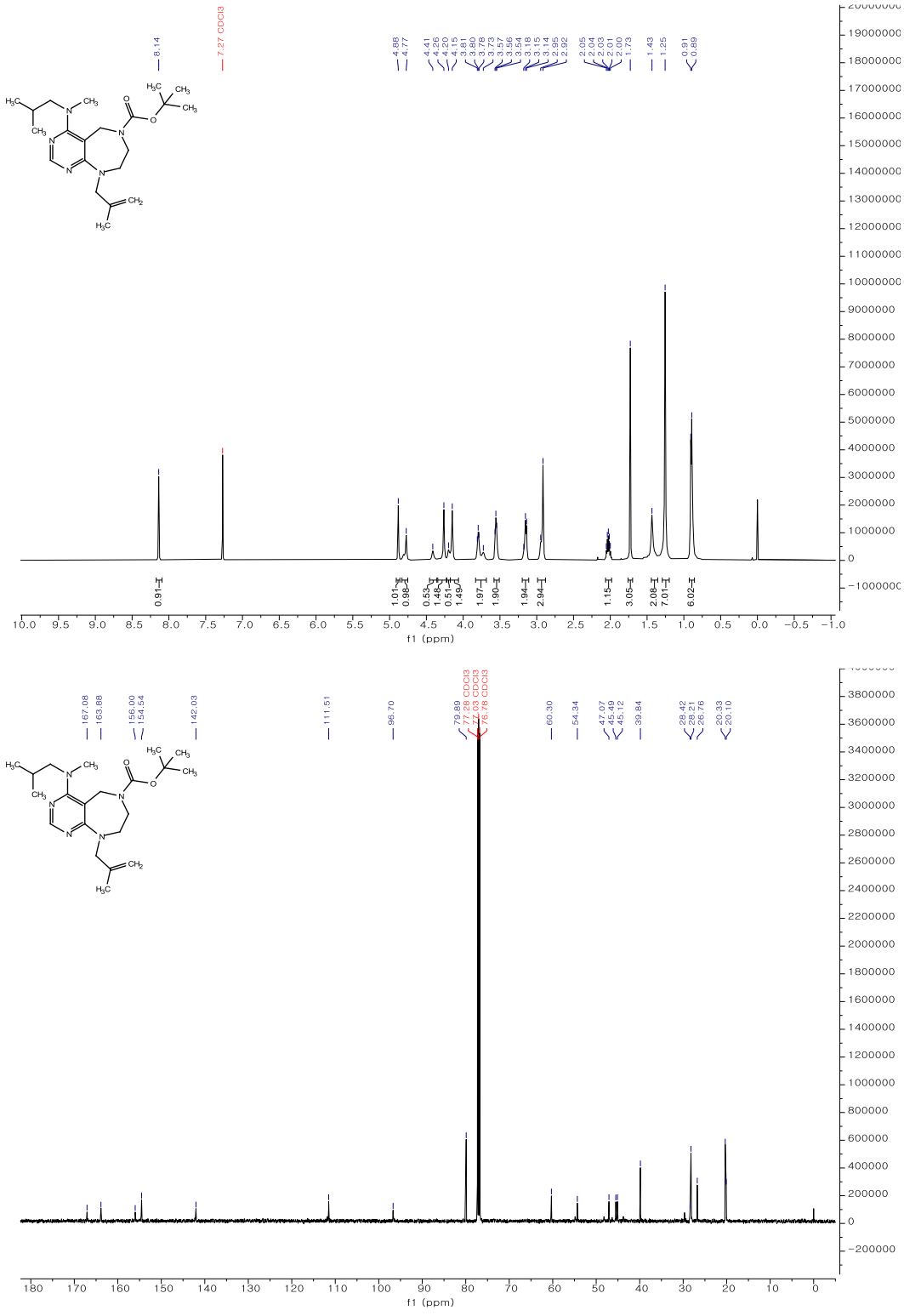
f1 (ppm)

9e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0.51
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1.97
1.90
1.94
2.94
1.15
3.05
2.08
7.01
6.02
f1 (ppm)
167.08
163.88
156.00
154.54
142.03
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96.70
79.89
77.28 CDCl3
77.03 CDCl3
76.78 CDCl3
60.30
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28.42
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26.76
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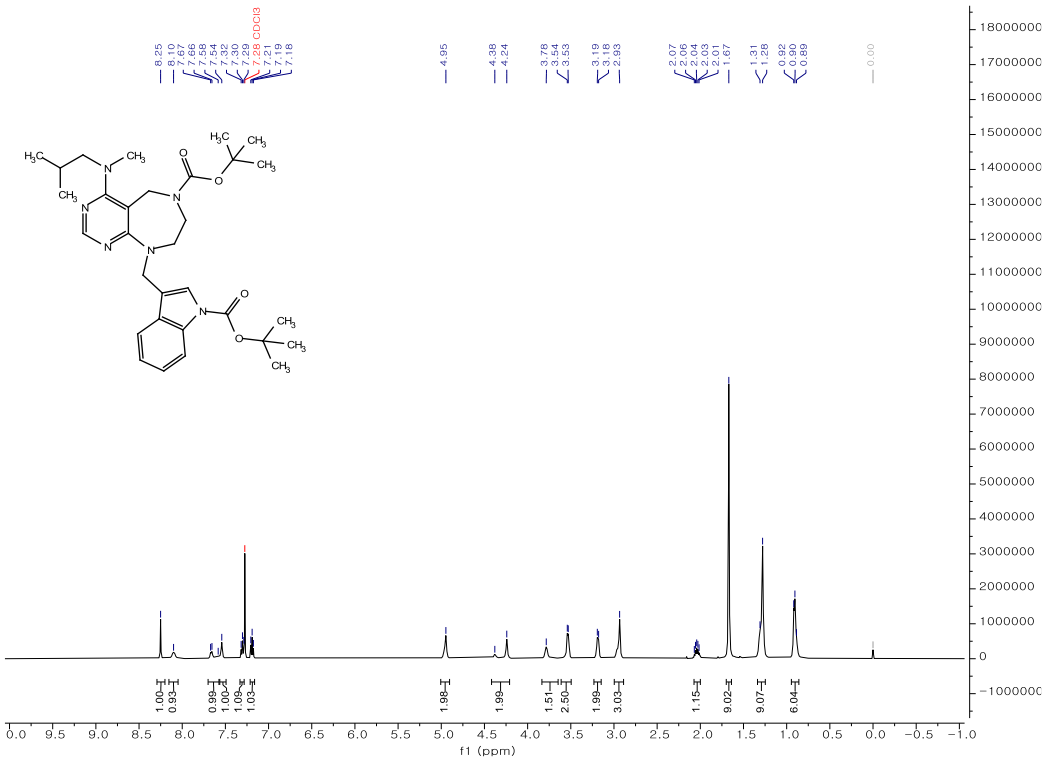
20.10
f1 (ppm)

9f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2.01
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1.31
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1.09
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1.99
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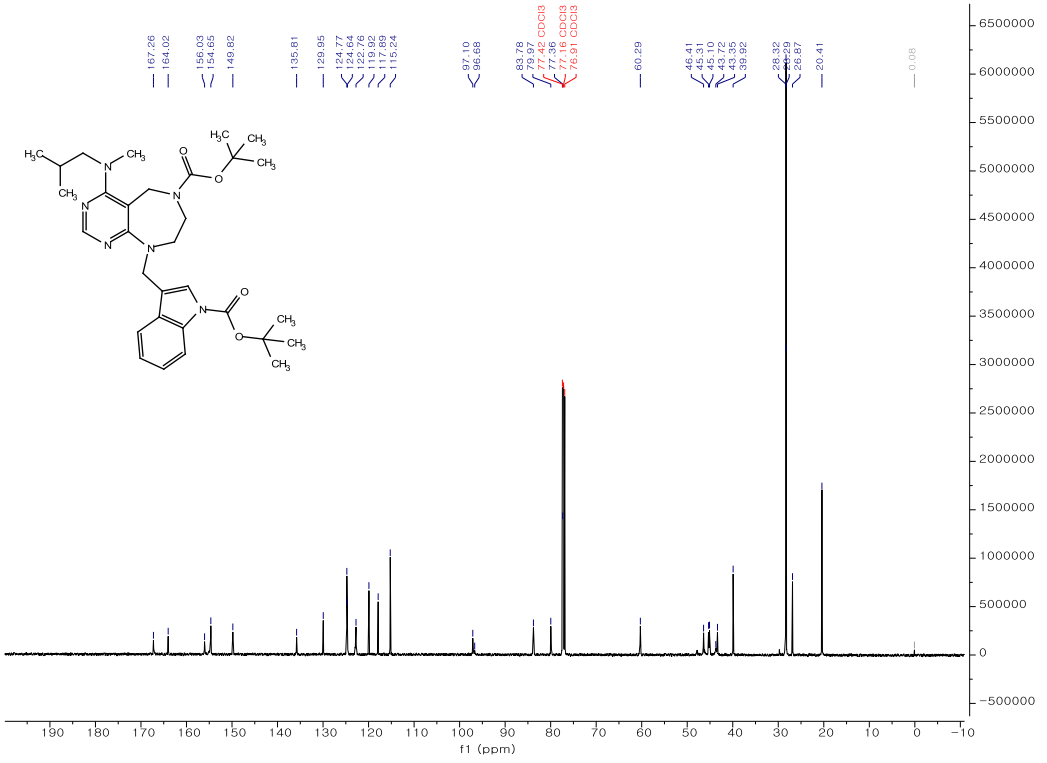
1.15
9.02
9.07
6.04
f1 (ppm)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124.64
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119.92
117.89
115.24
97.10
96.88
83.78
79.97
77.42 CDCl3
77.36
77.16 CDCl3
76.91 CDCl3
60.29
46.41
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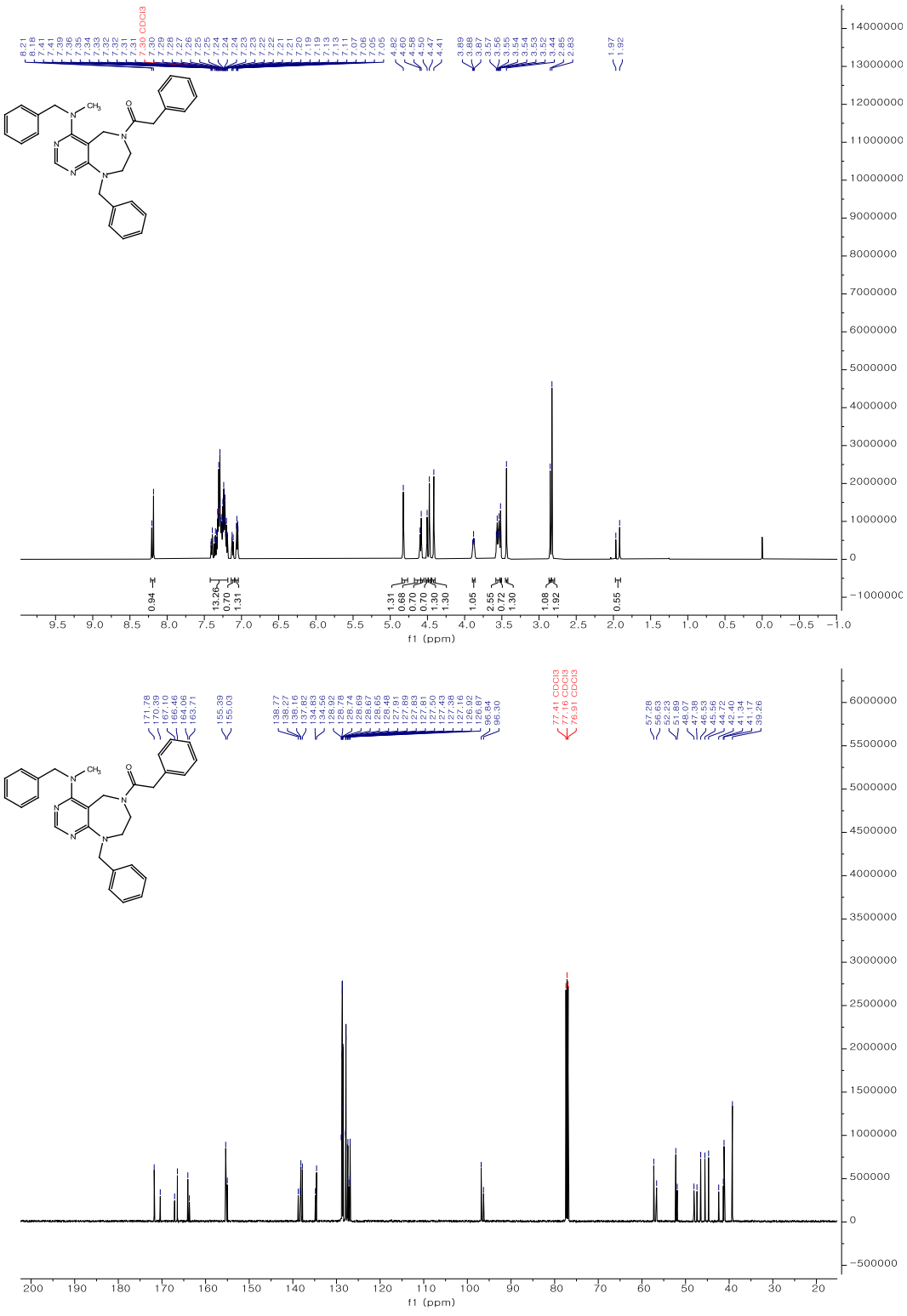
28.32
28.29
28.07
20.41
0.08
f1 (ppm)

1a



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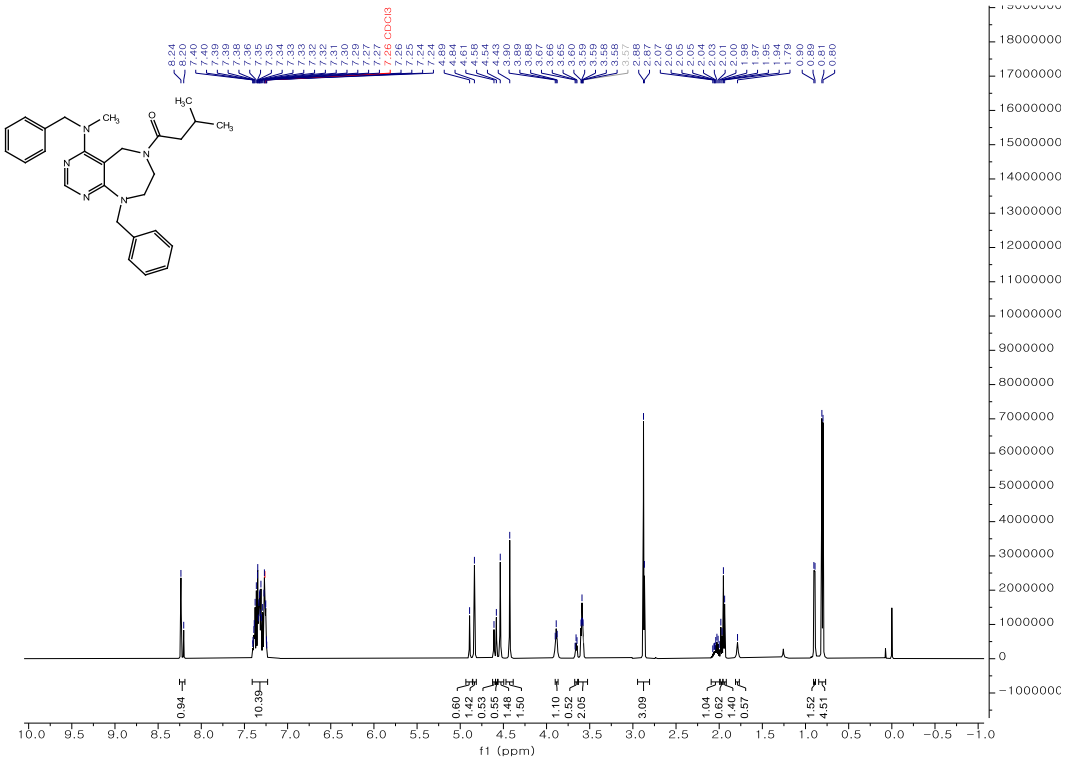

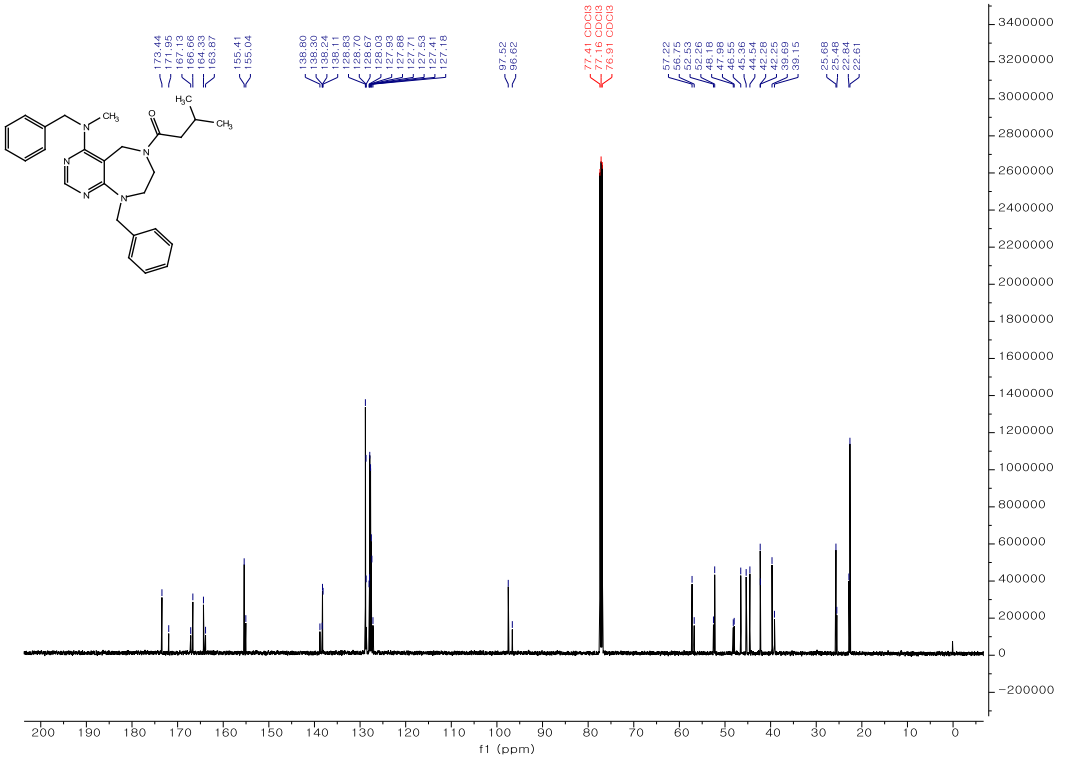

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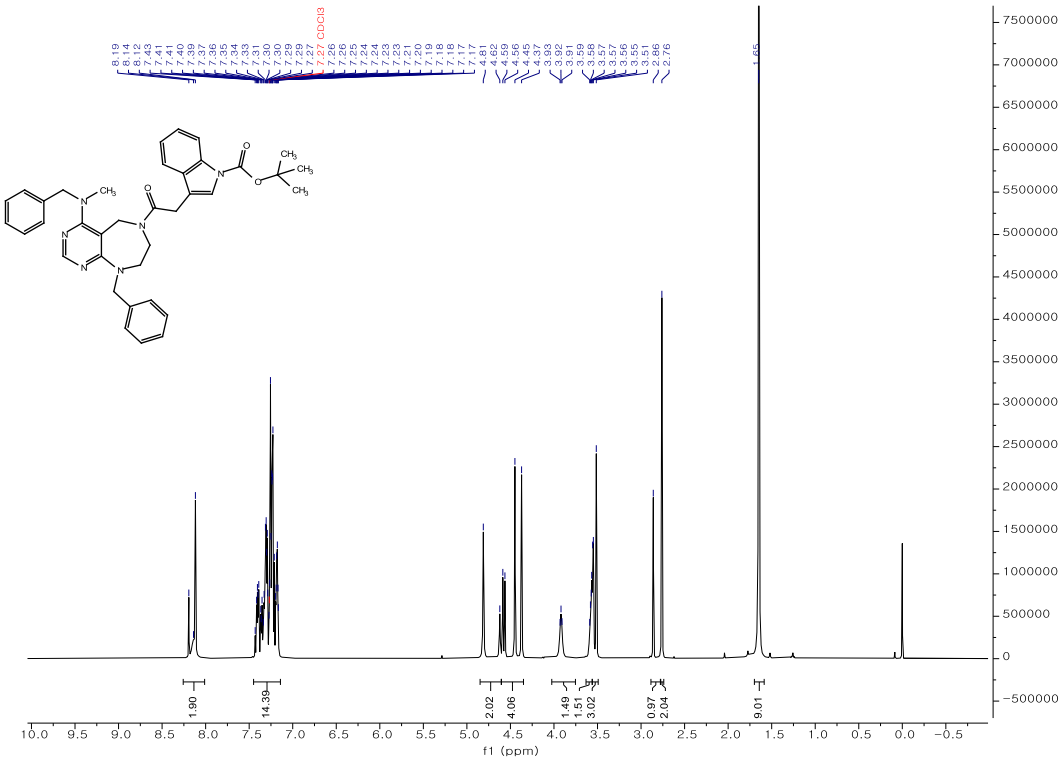
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7.29
7.29
7.27 CDCl3
7.26
7.25
7.24
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7.20
7.19
7.18
7.17
7.17
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4.62
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4.56
4.45
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3.93
3.92
3.91
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3.55
3.51
2.96
2.76
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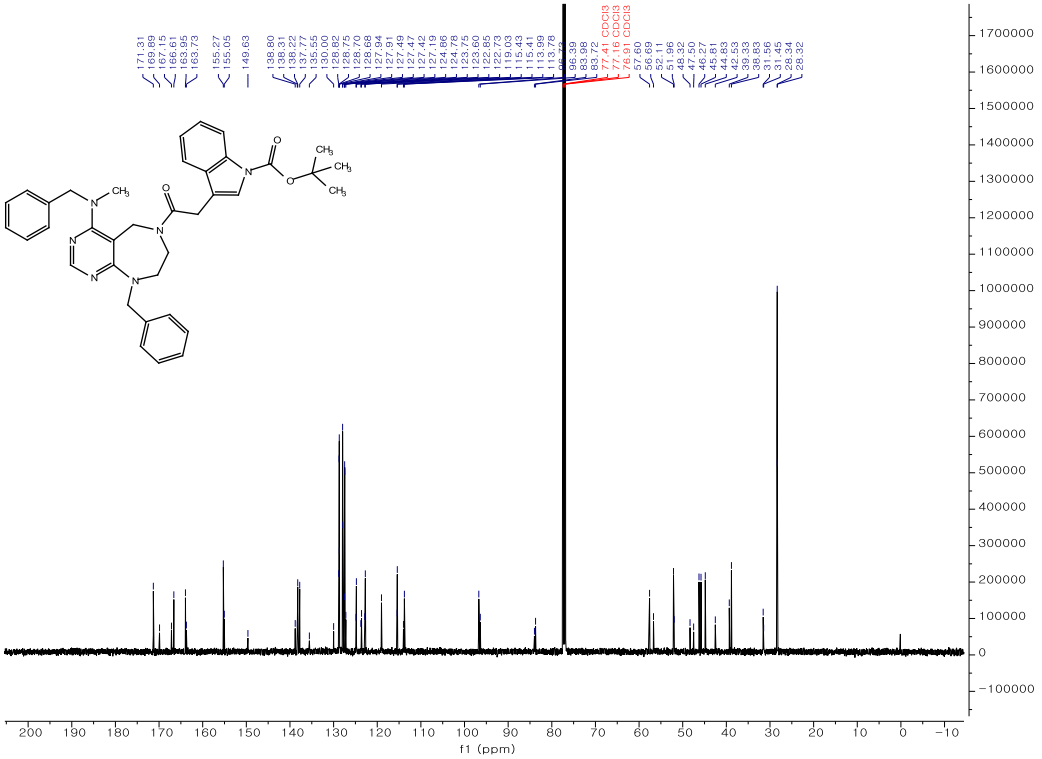
1.49
1.51
3.02
0.97
2.04
9.01
f1 (ppm)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127.91
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127.42
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119.03
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113.99
113.78
98.39
83.98
83.72
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
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56.69
52.11
51.96
48.32
47.50
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42.53
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38.83
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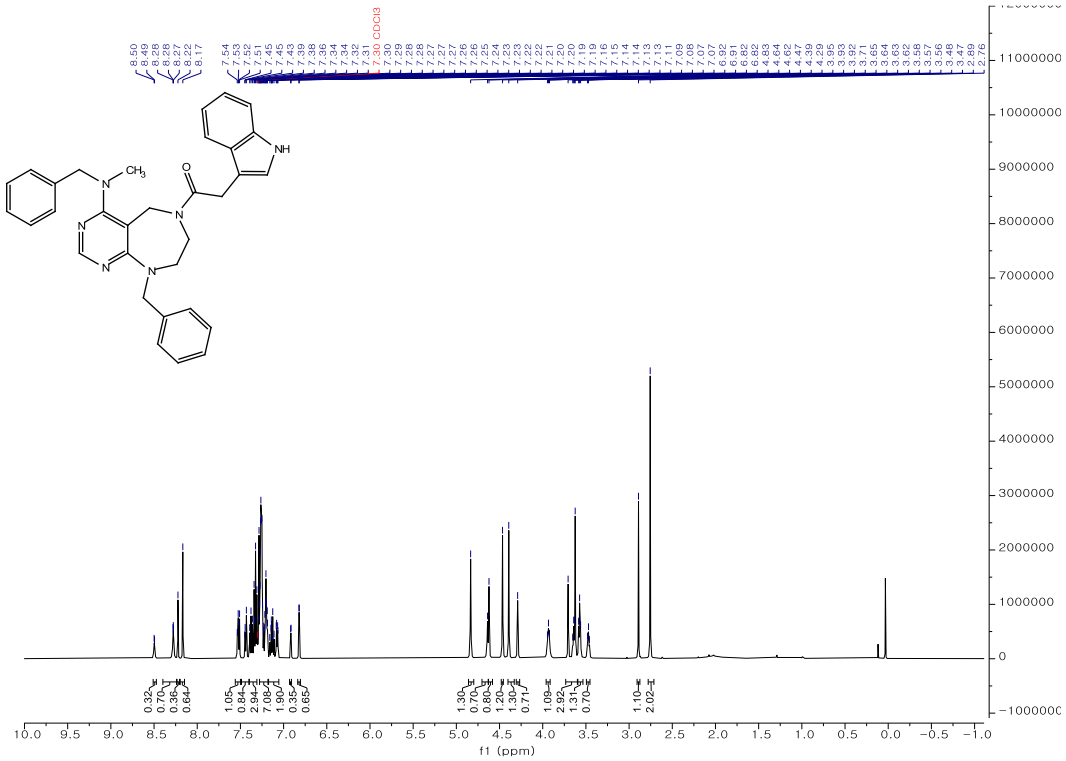
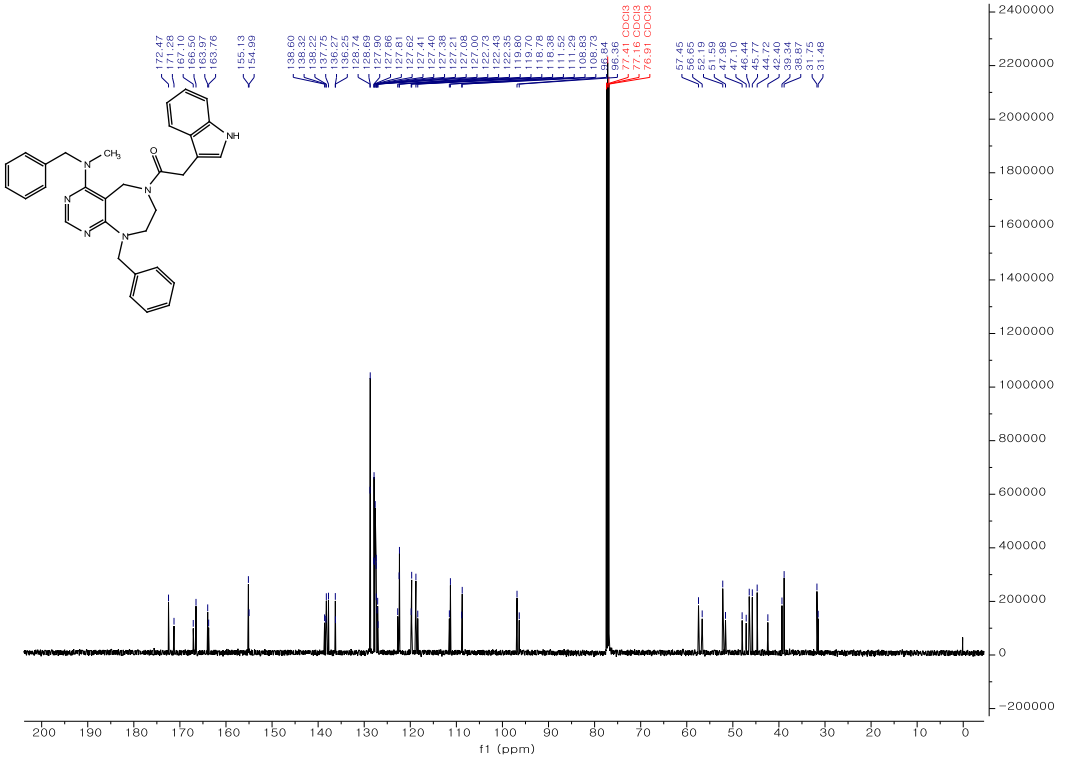
31.45
28.34
28.32
f1 (ppm)

1c





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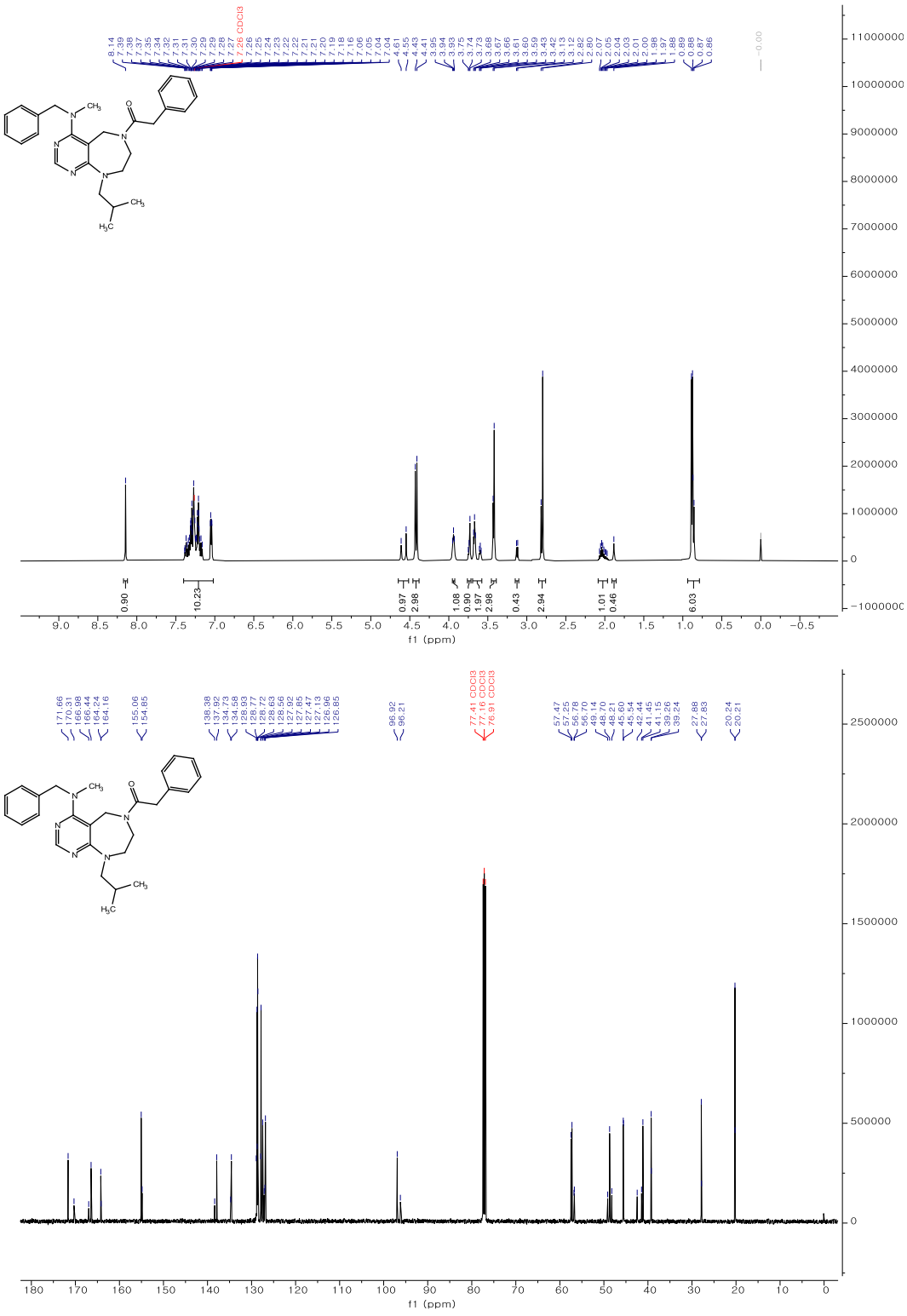

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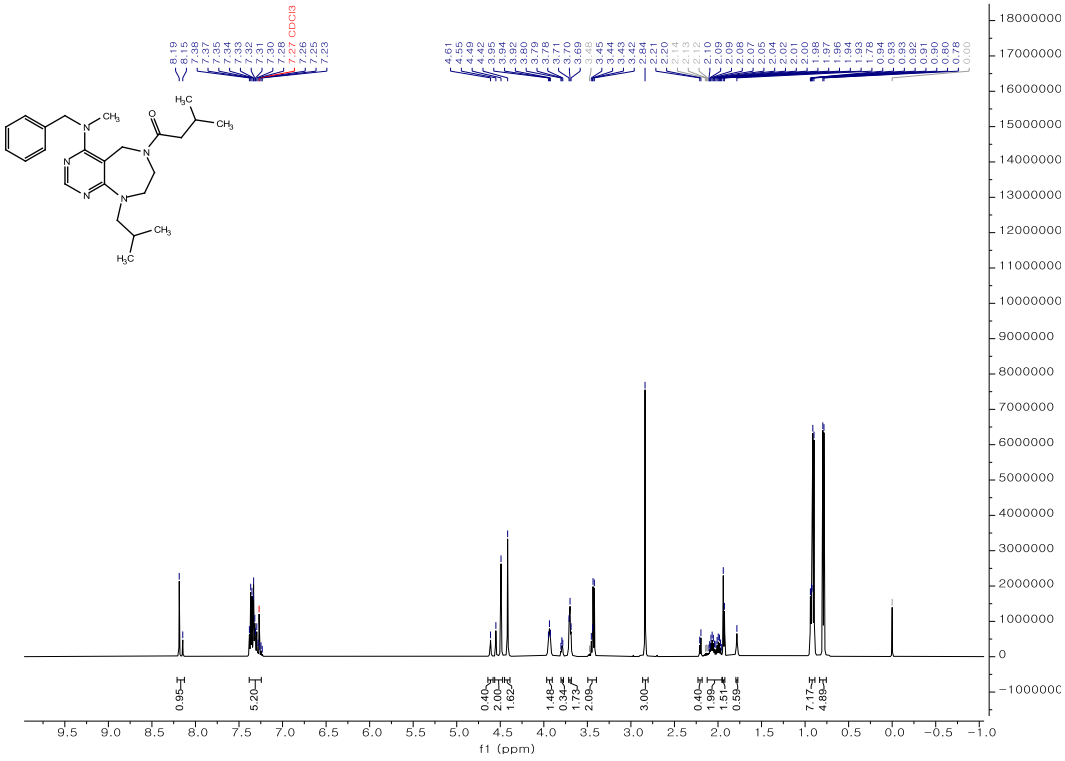

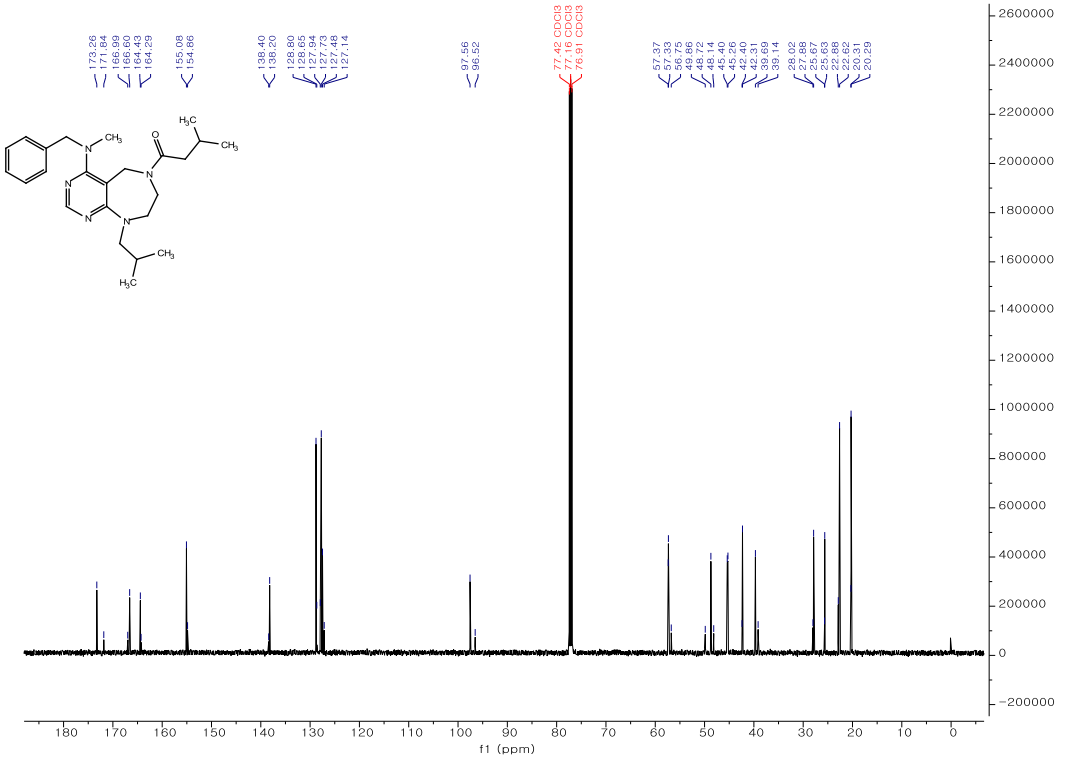

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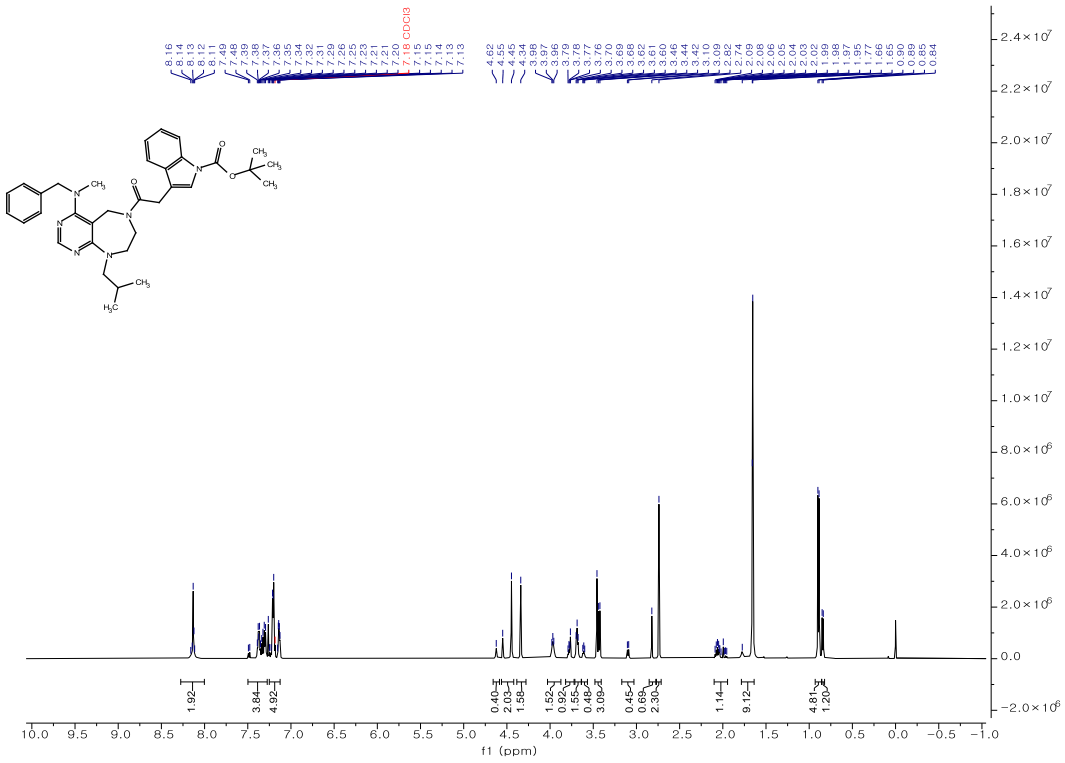

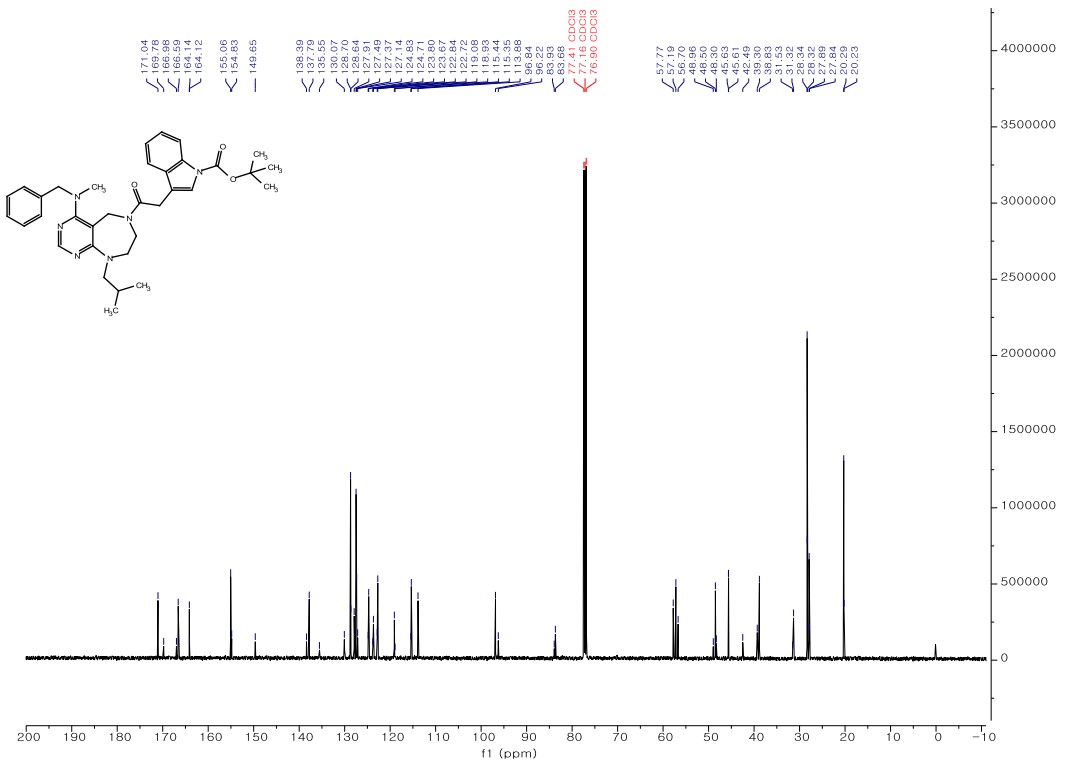

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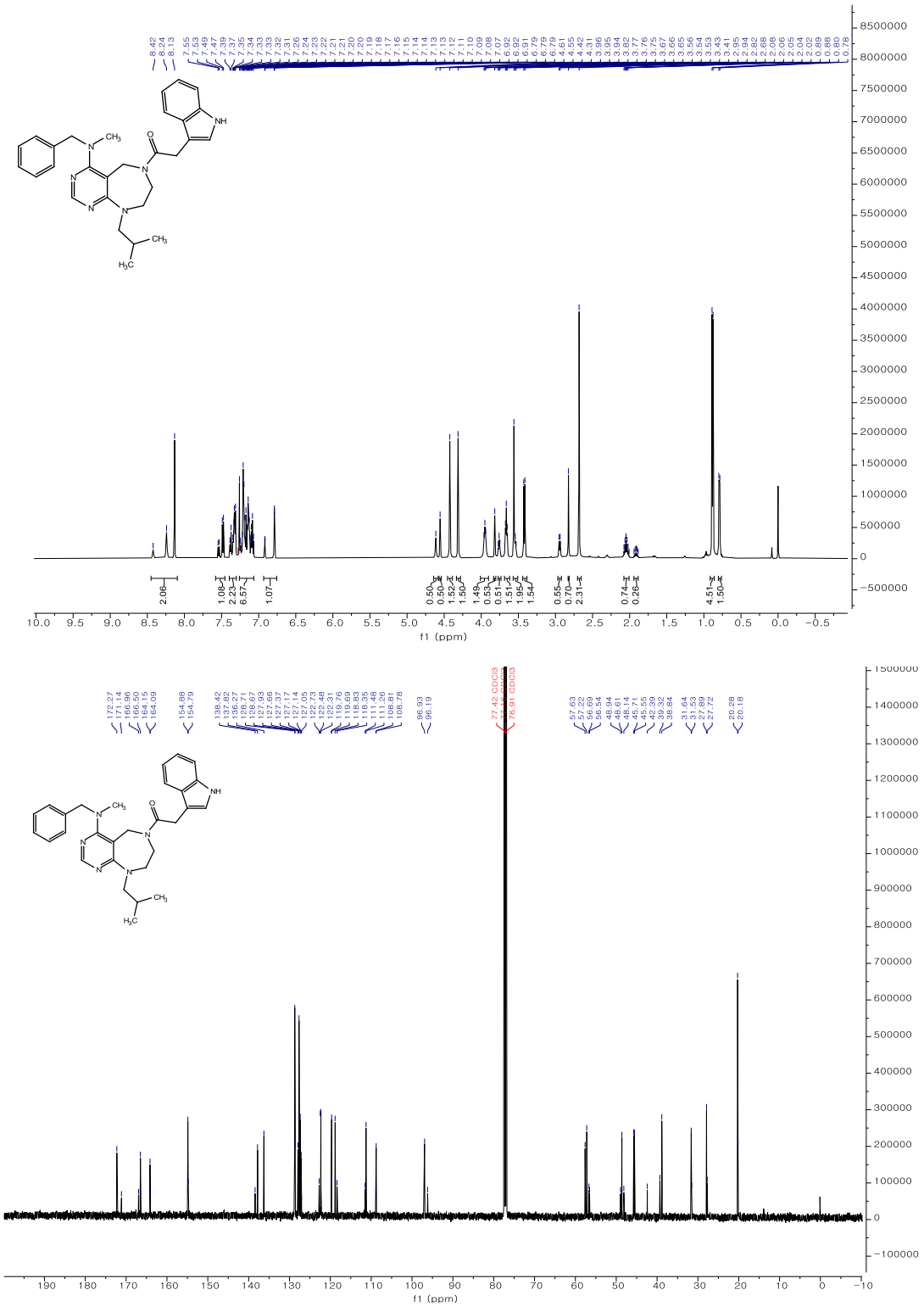

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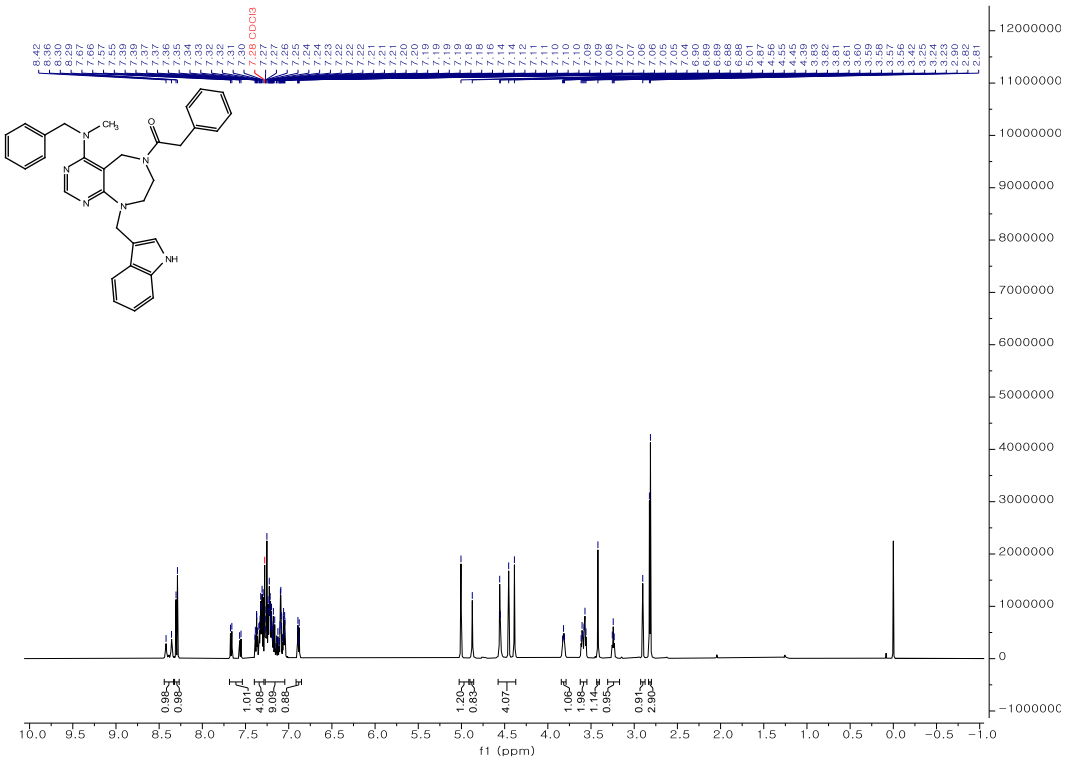
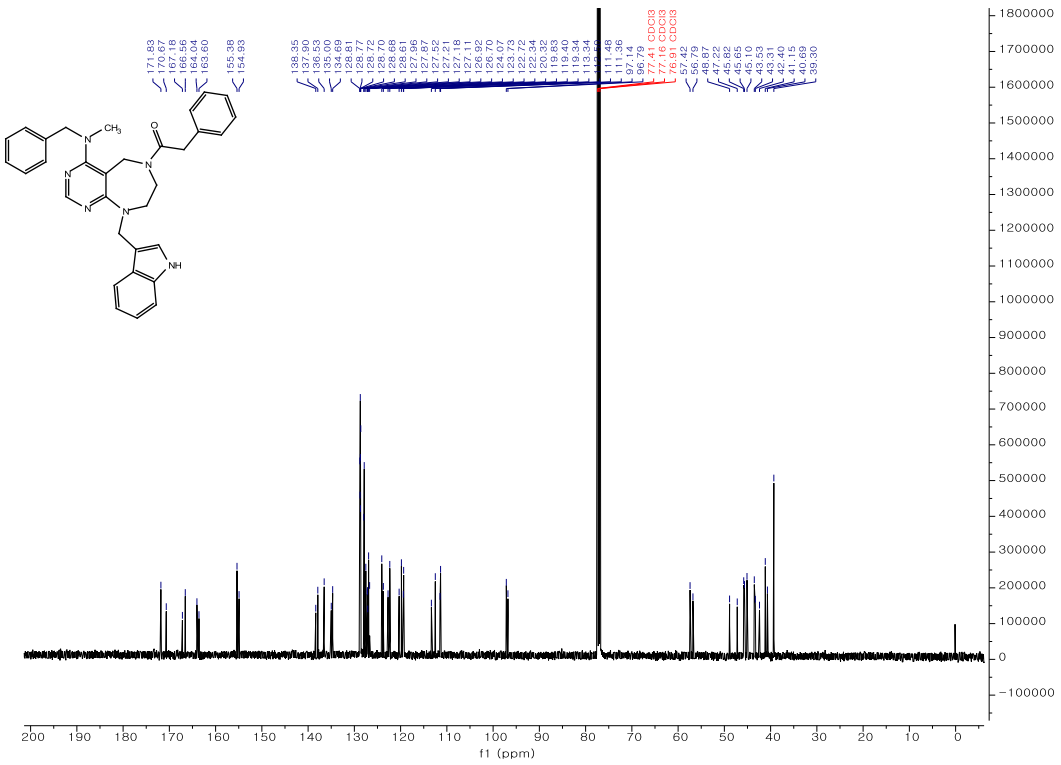
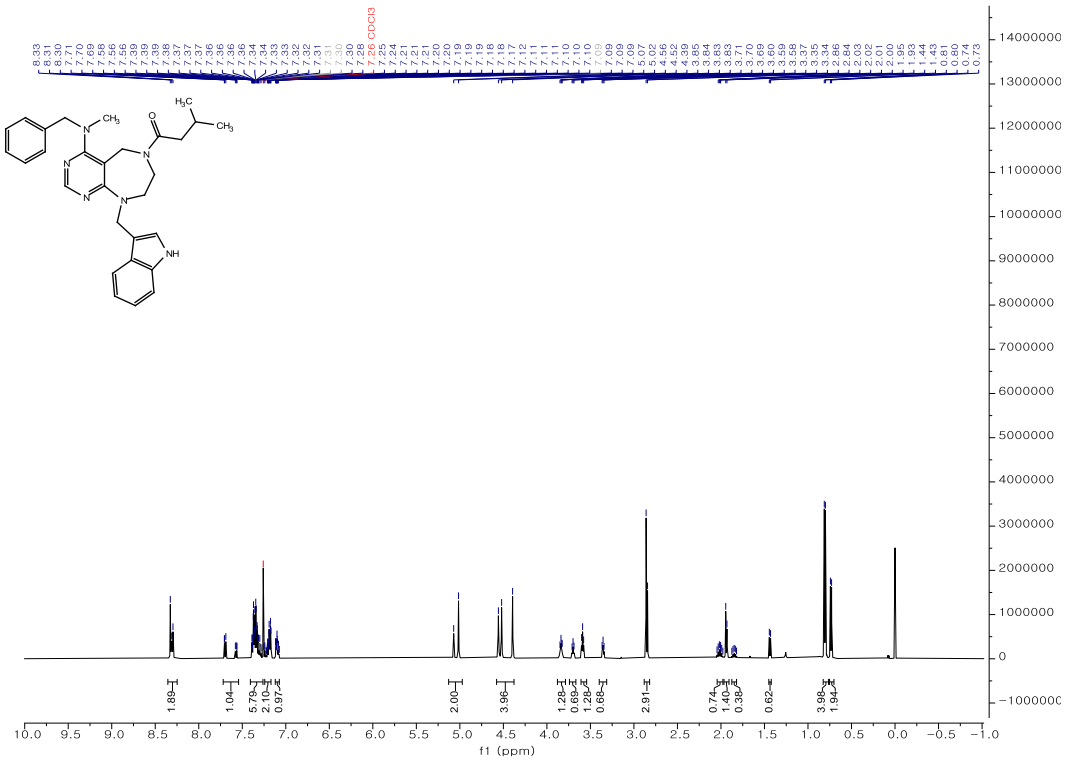




1h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7.31
7.30
7.30
7.28 CDCl3
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2.01
2.00
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1.93
1.44
1.43
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0.80
0.74
0.73
1.89
1.04
5.79
2.10
0.97
2.00
3.96
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0.62
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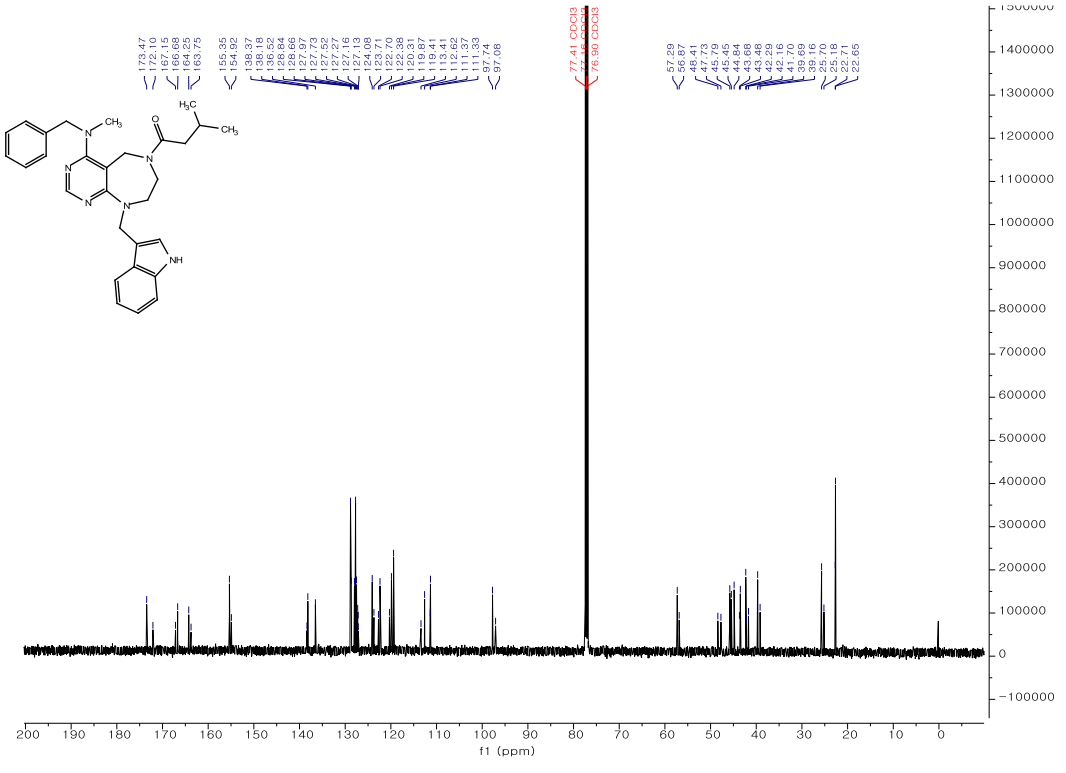
1.94
f1 (ppm)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127.16
127.13
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120.31
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119.41
119.41
112.62
111.37
111.33
97.74
97.08
77.41 CDCl3
77.00 CDCl3
76.90 CDCl3
57.29
55.87
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47.73
45.79
45.45
44.84
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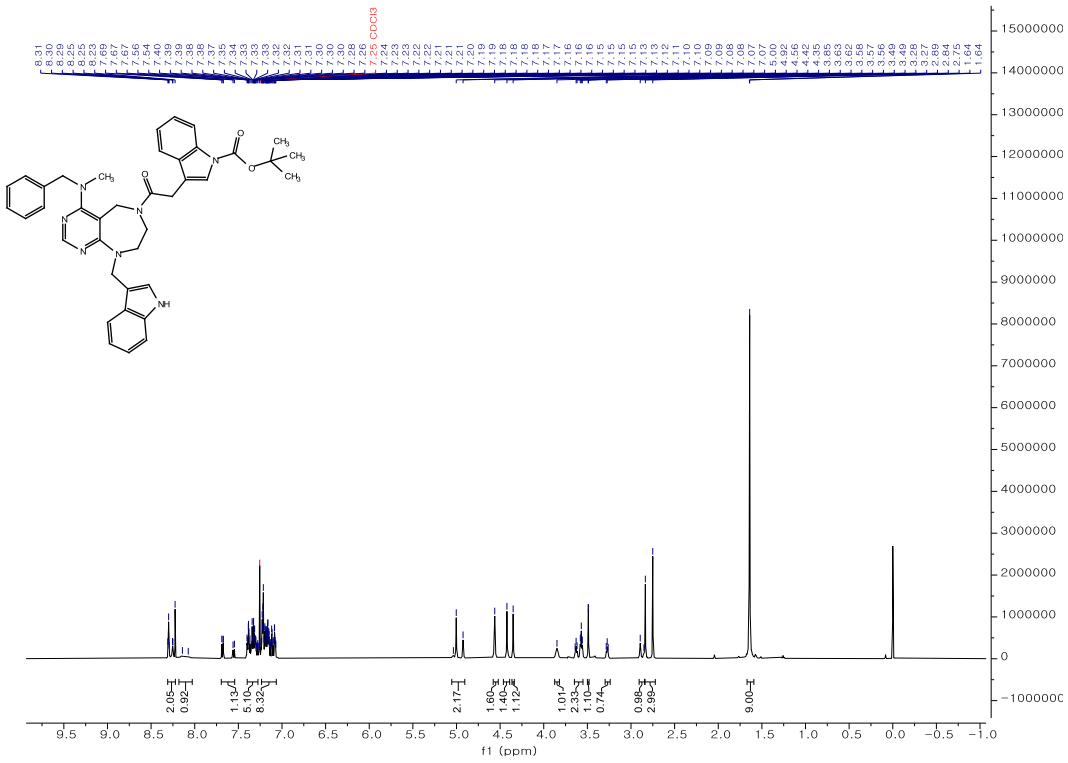
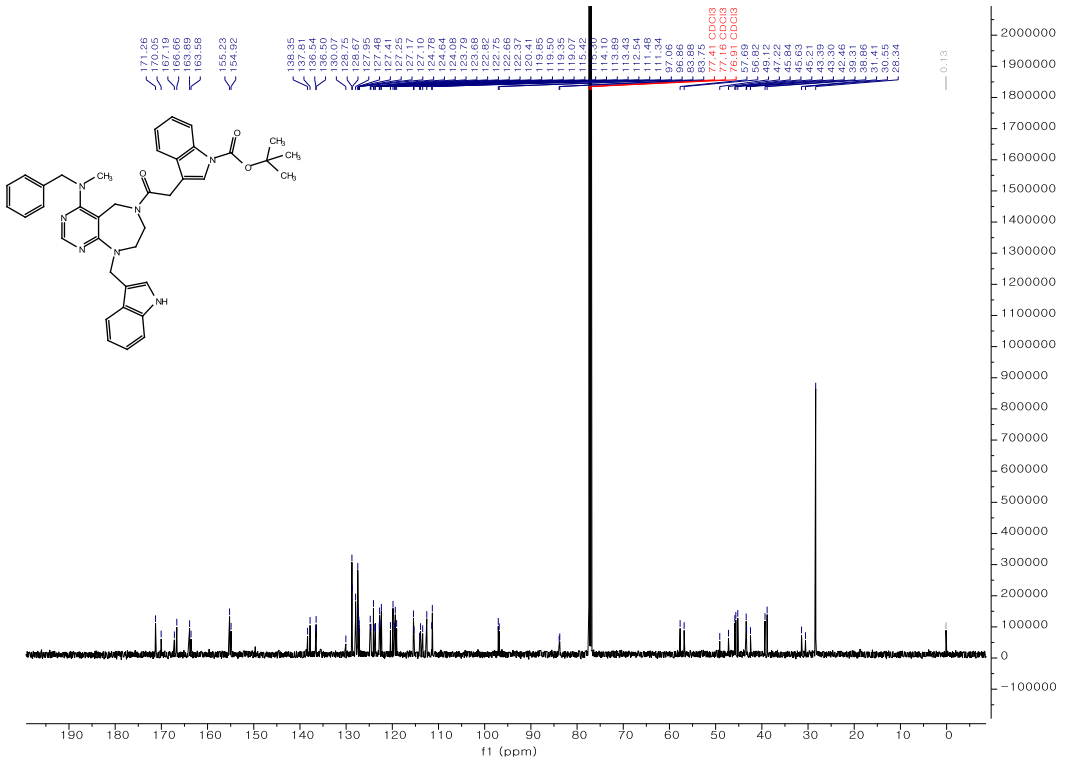
22.71
22.65
f1 (ppm)

1i’





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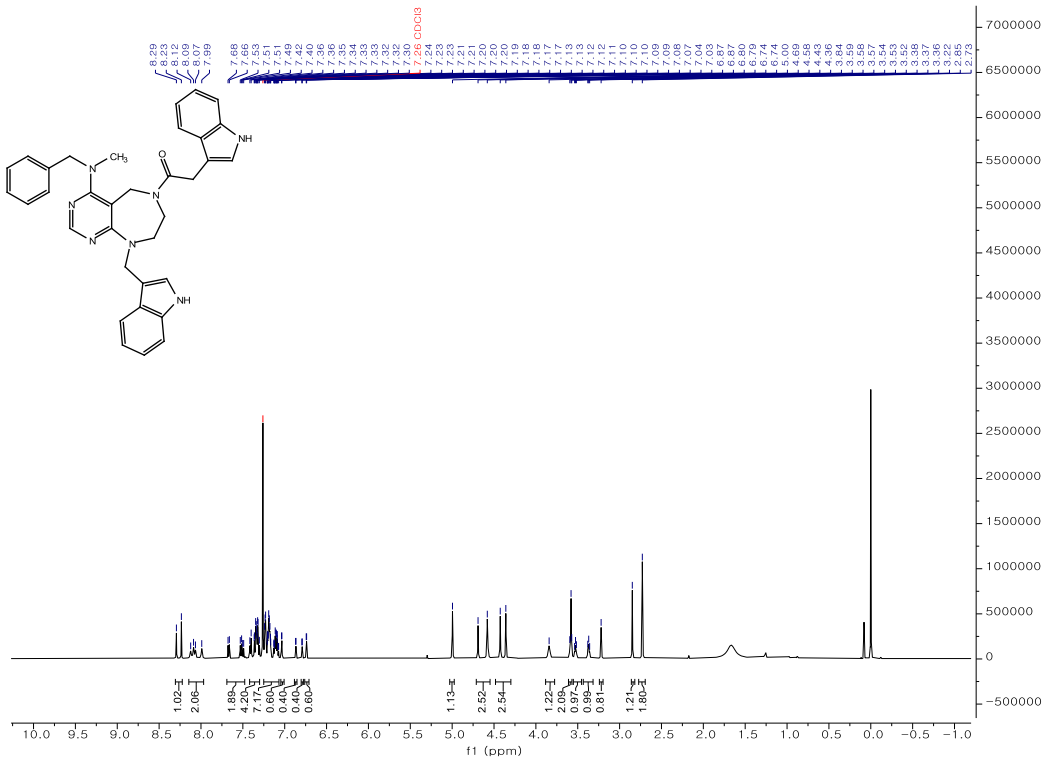

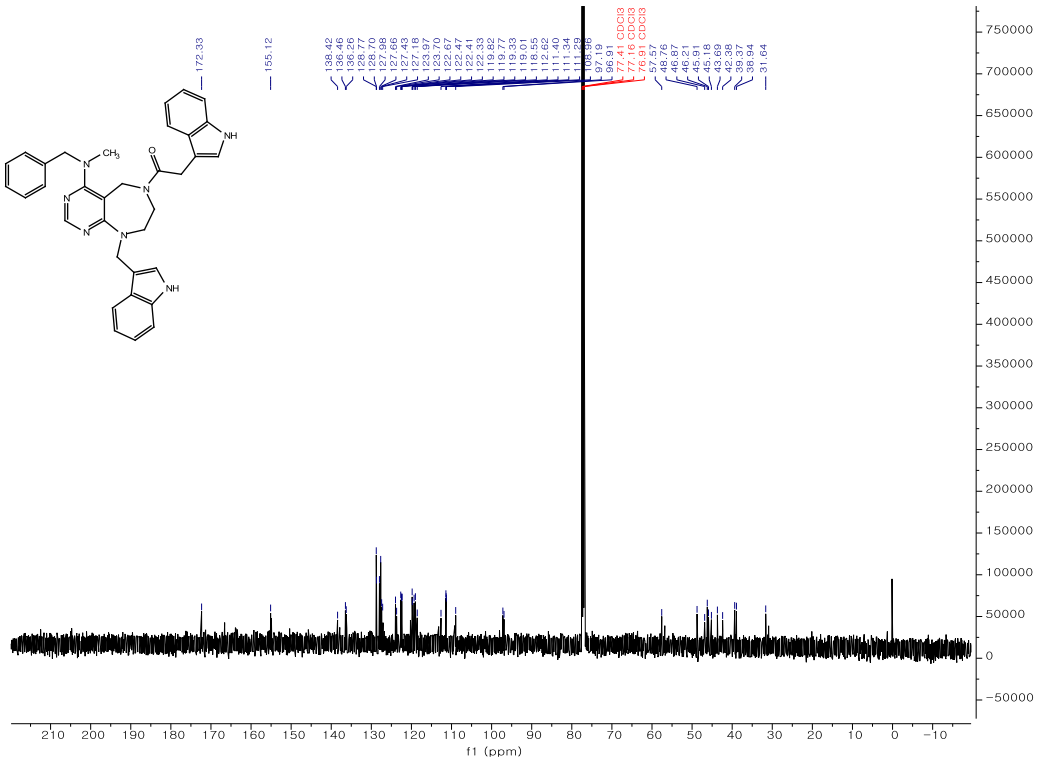

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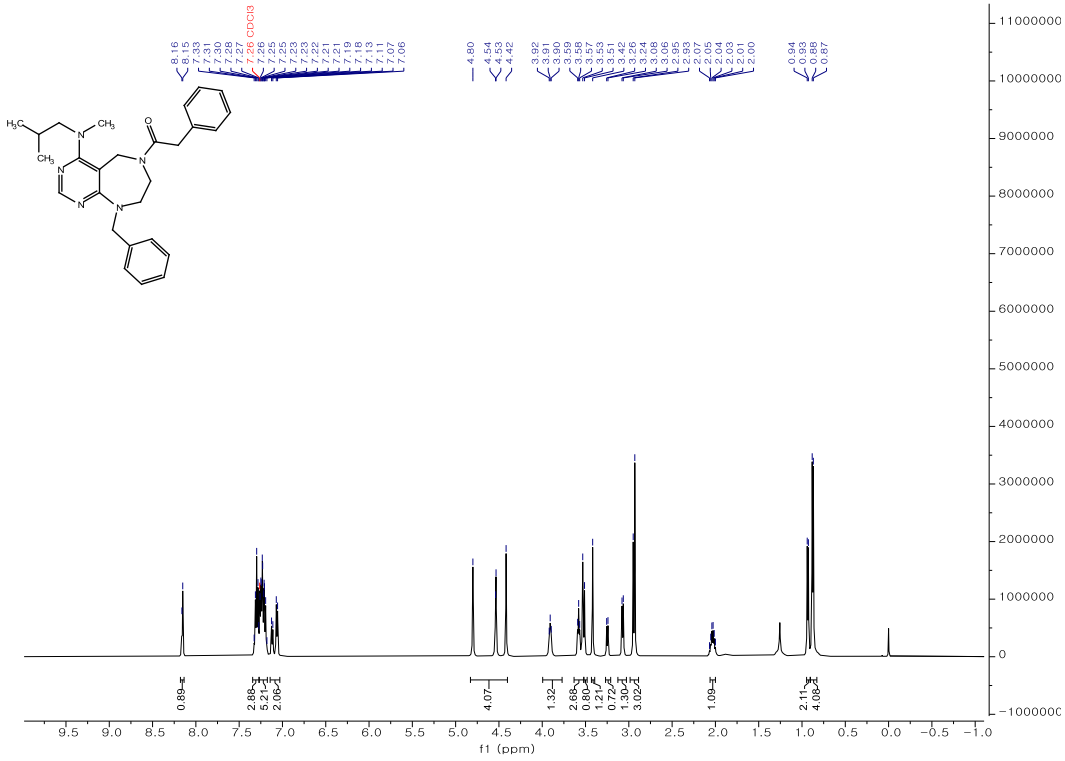

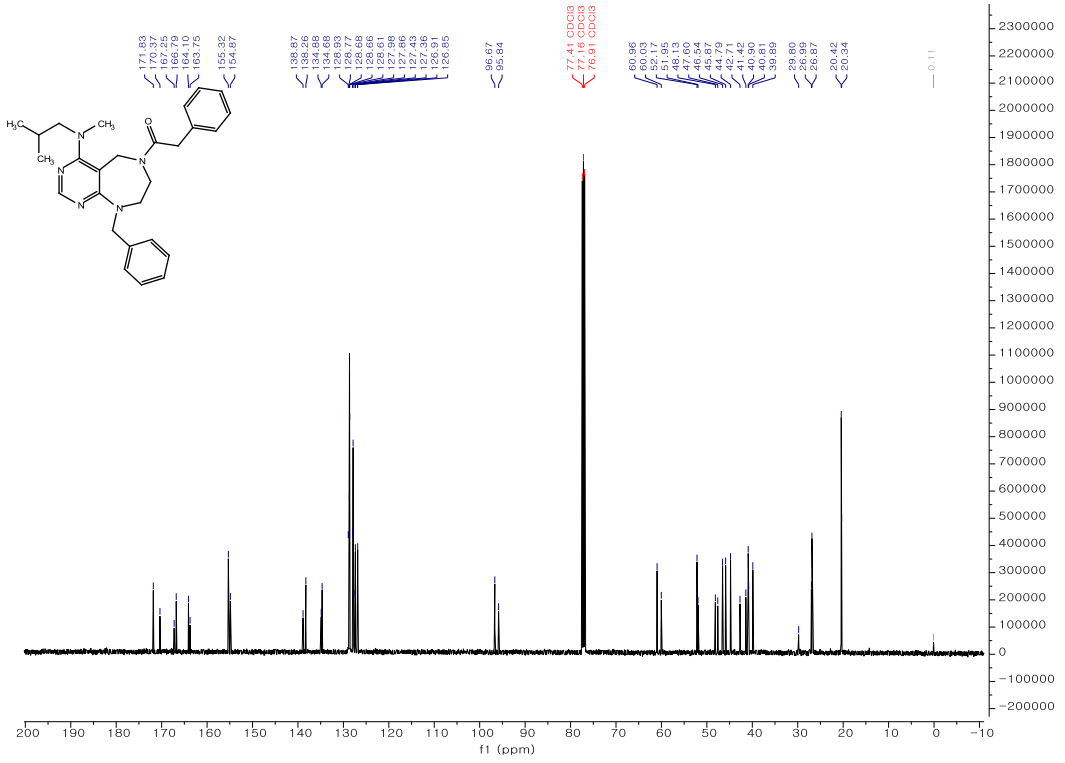

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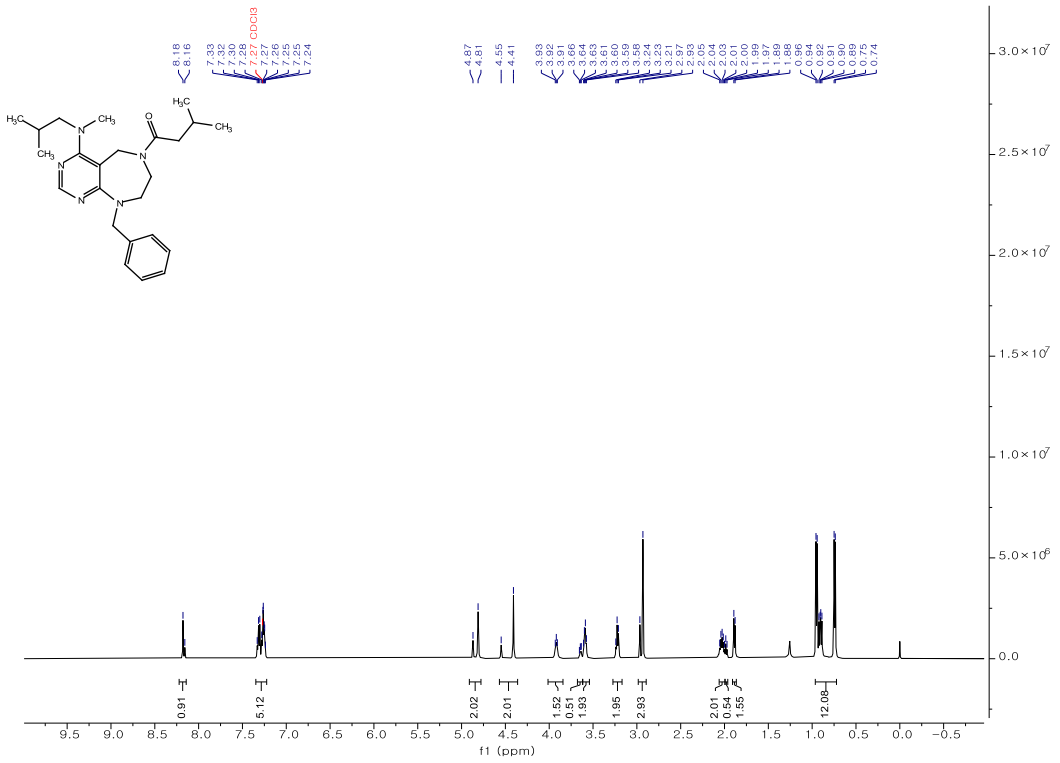

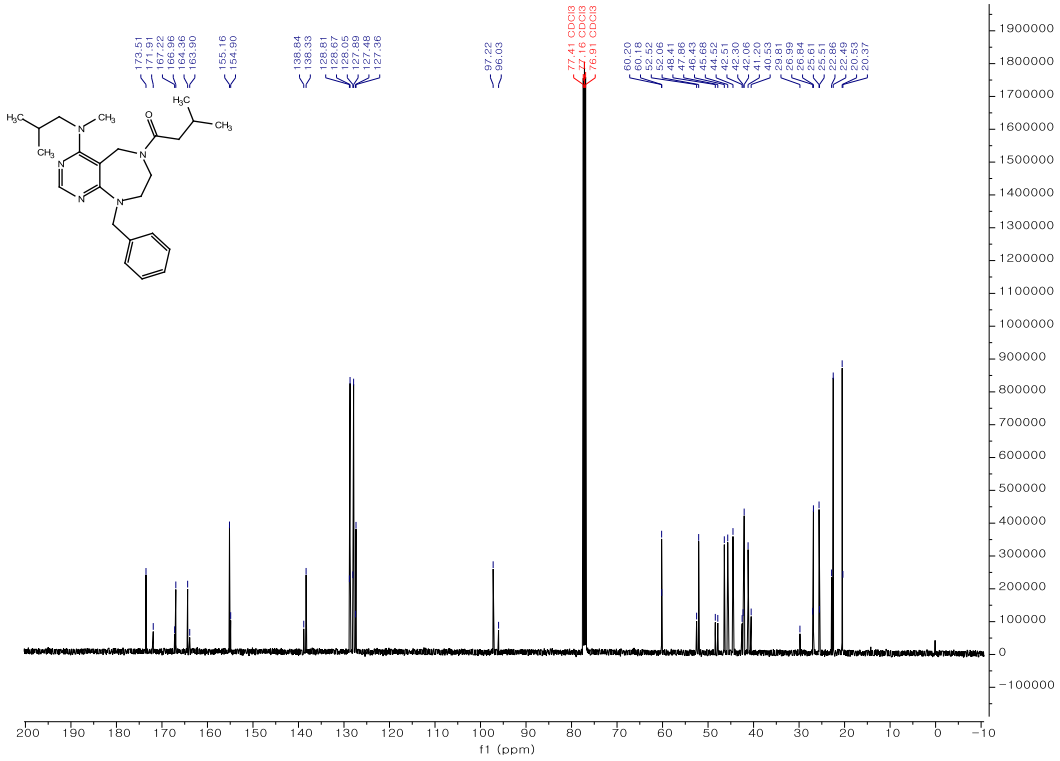

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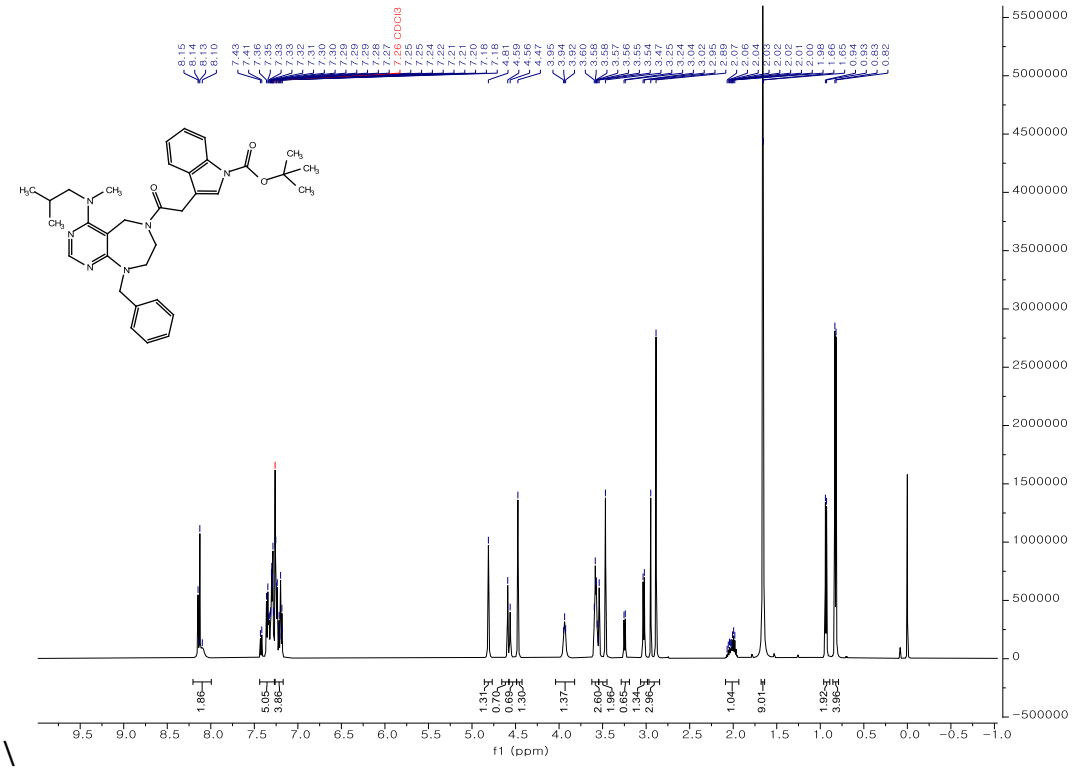

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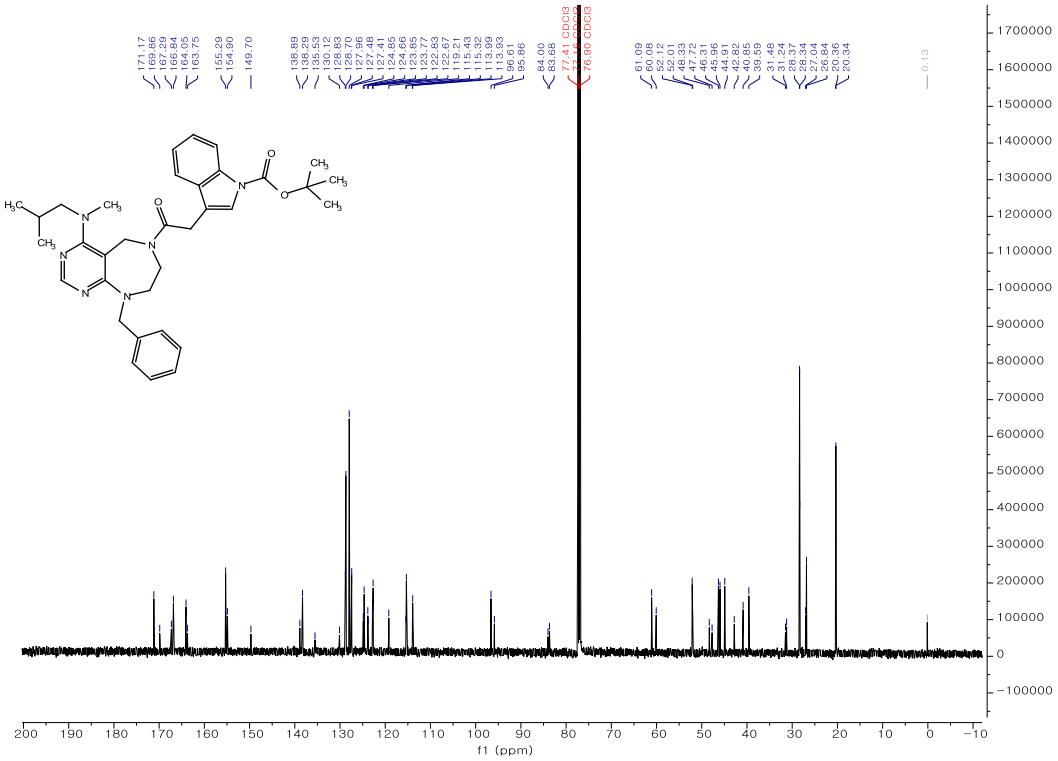

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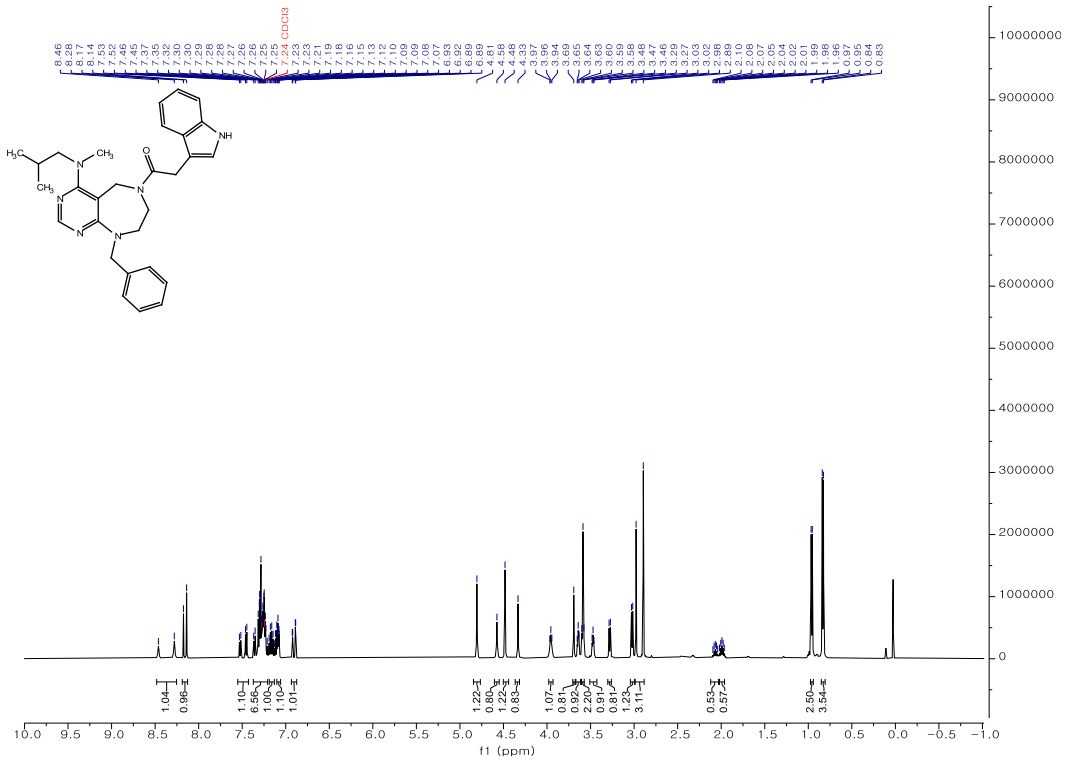
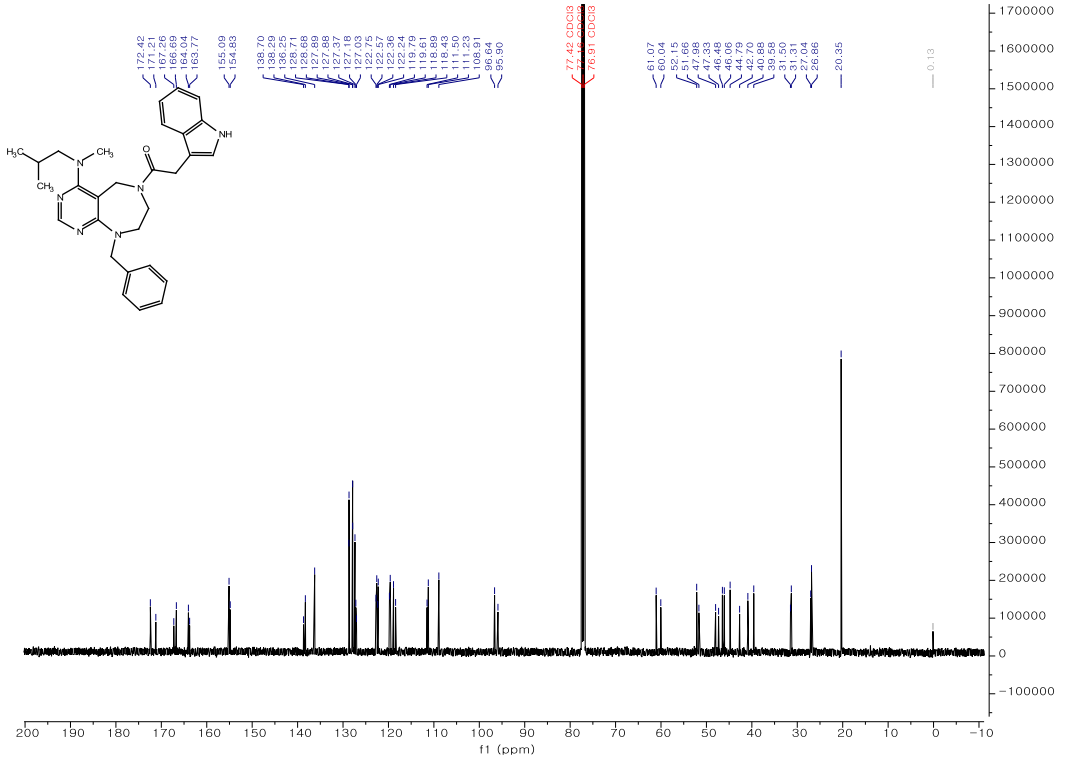
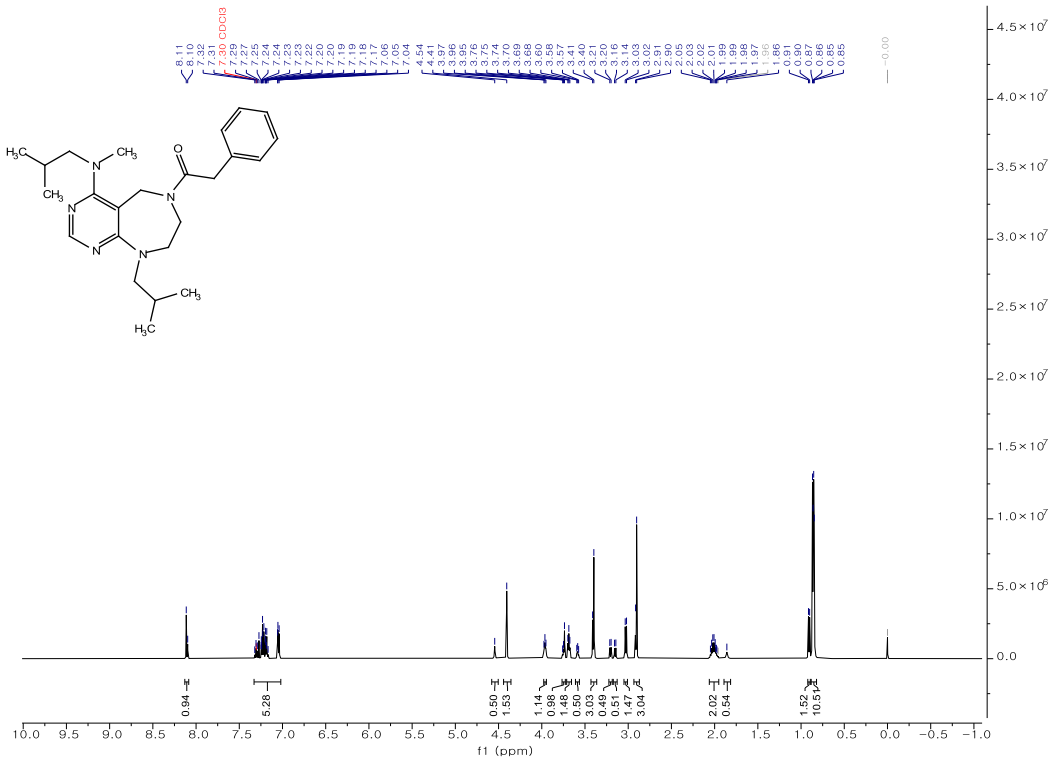
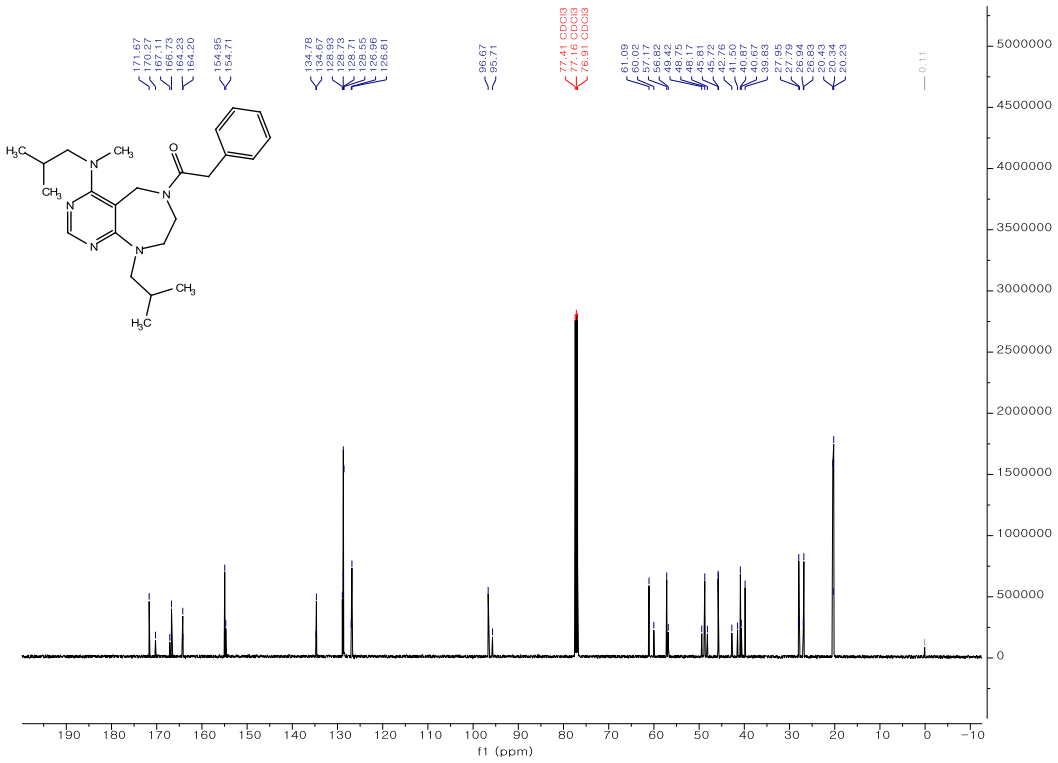




1m





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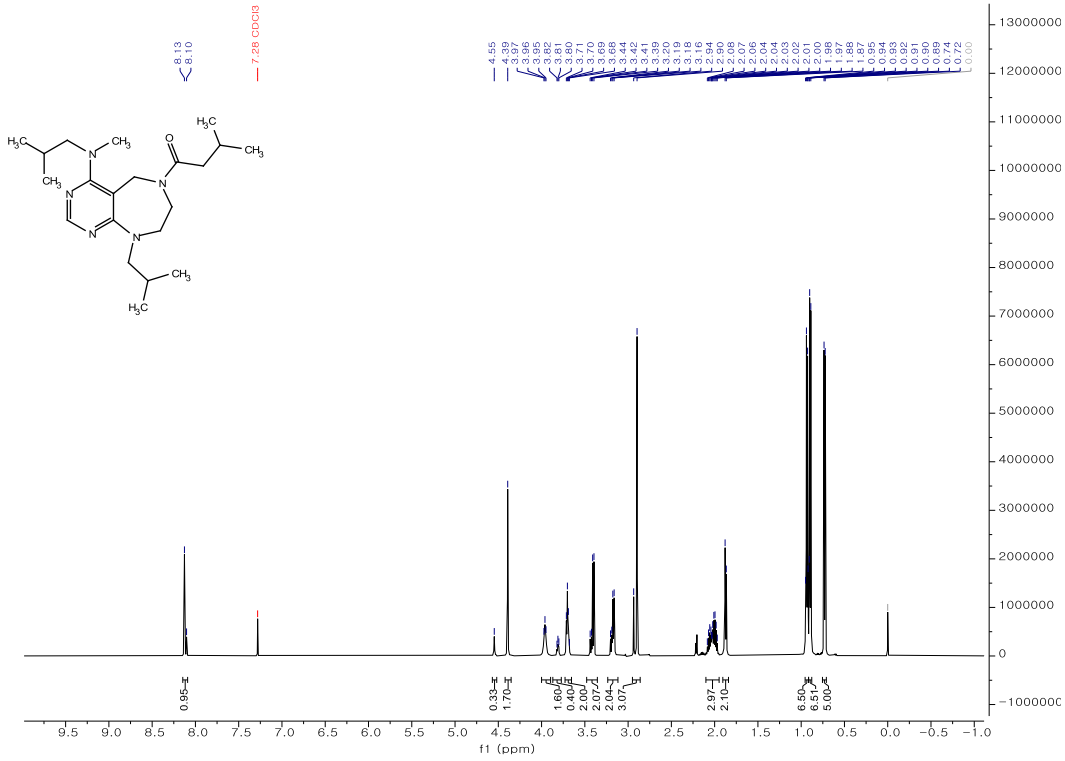
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4.39
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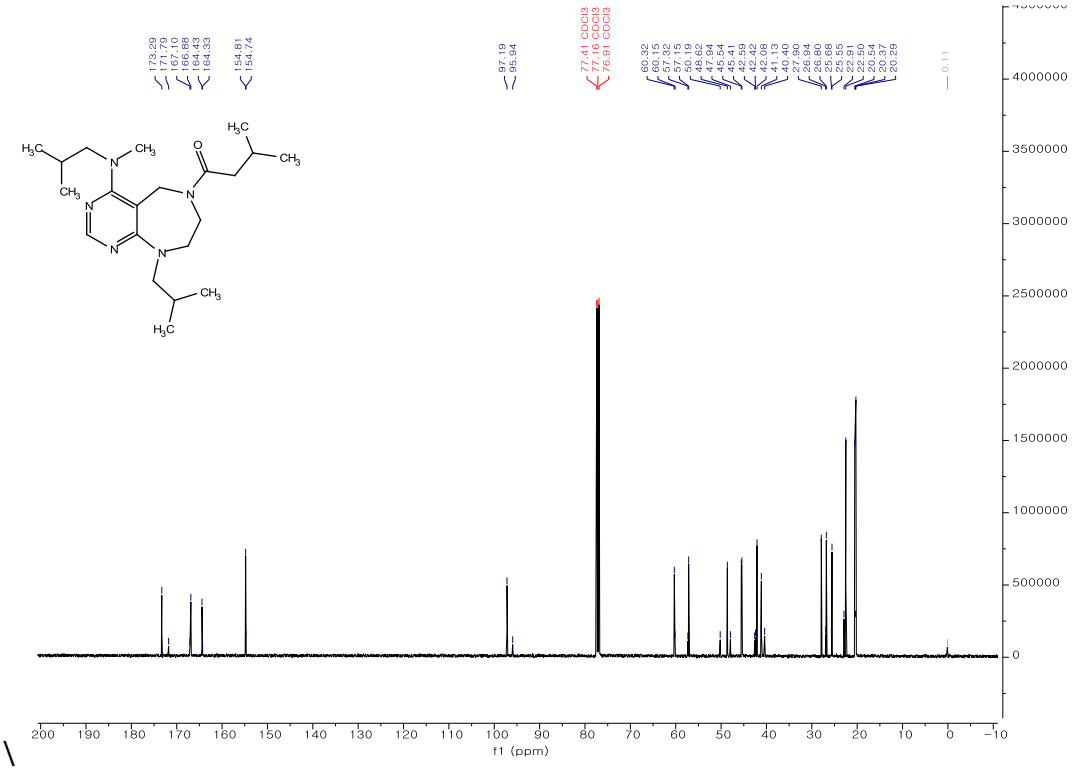
f1 (ppm)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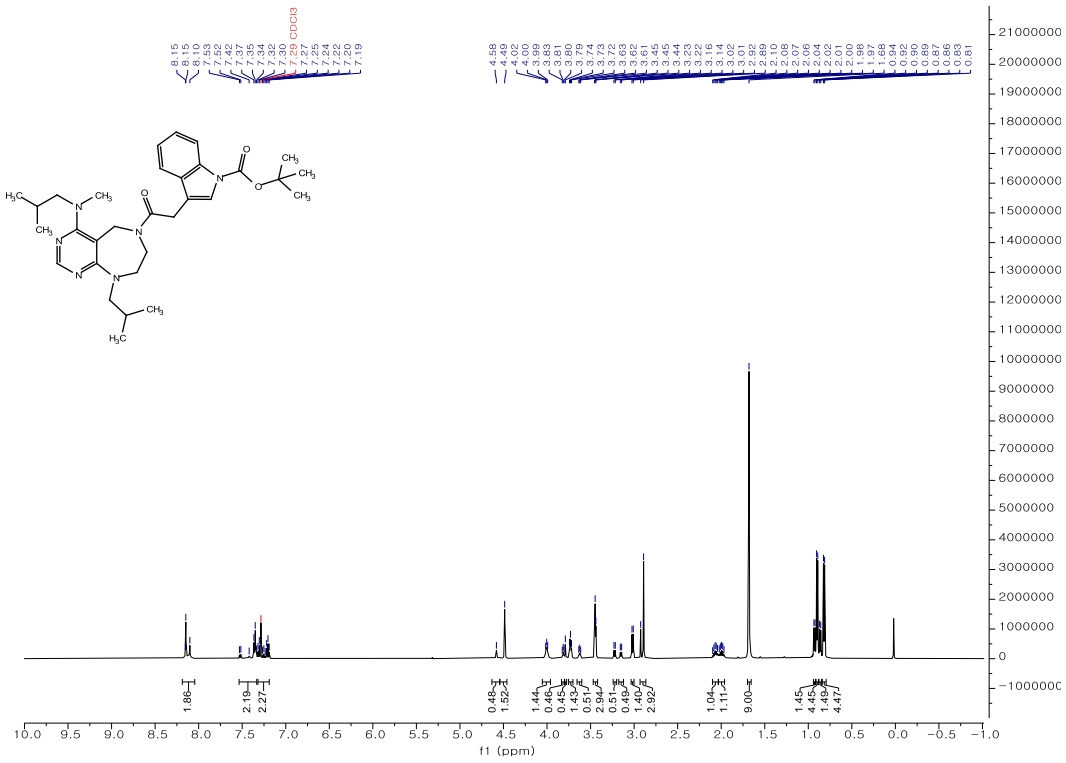
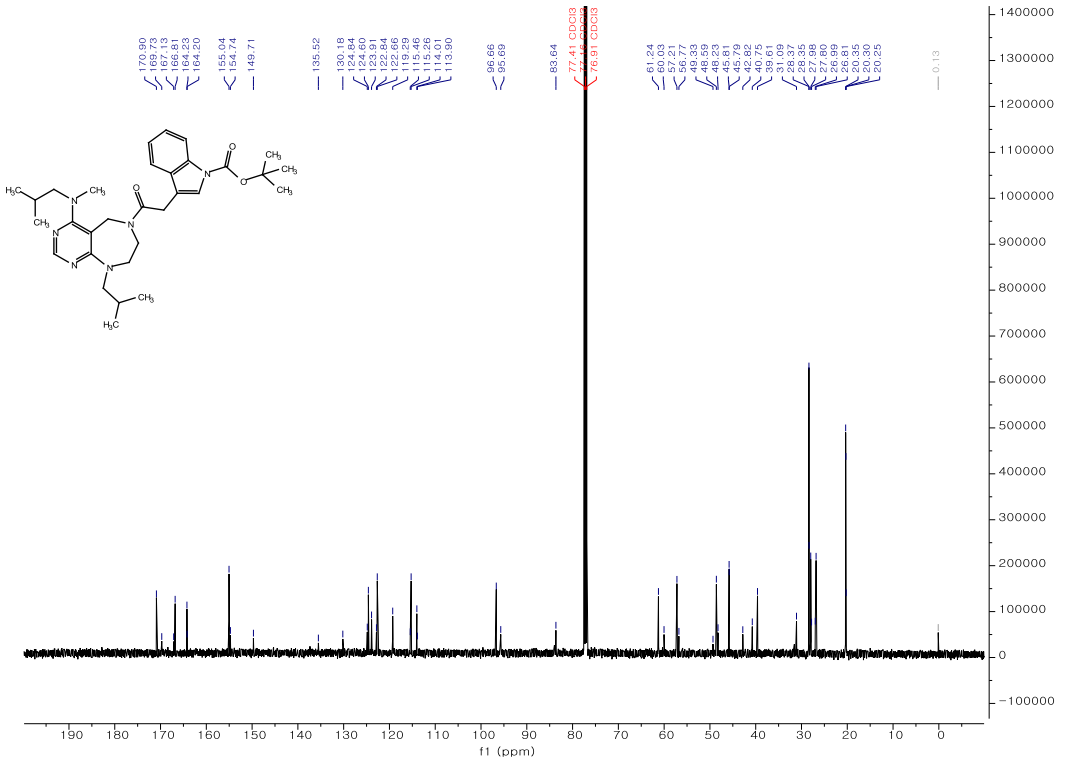
0.11
f1 (ppm)

\

1o’





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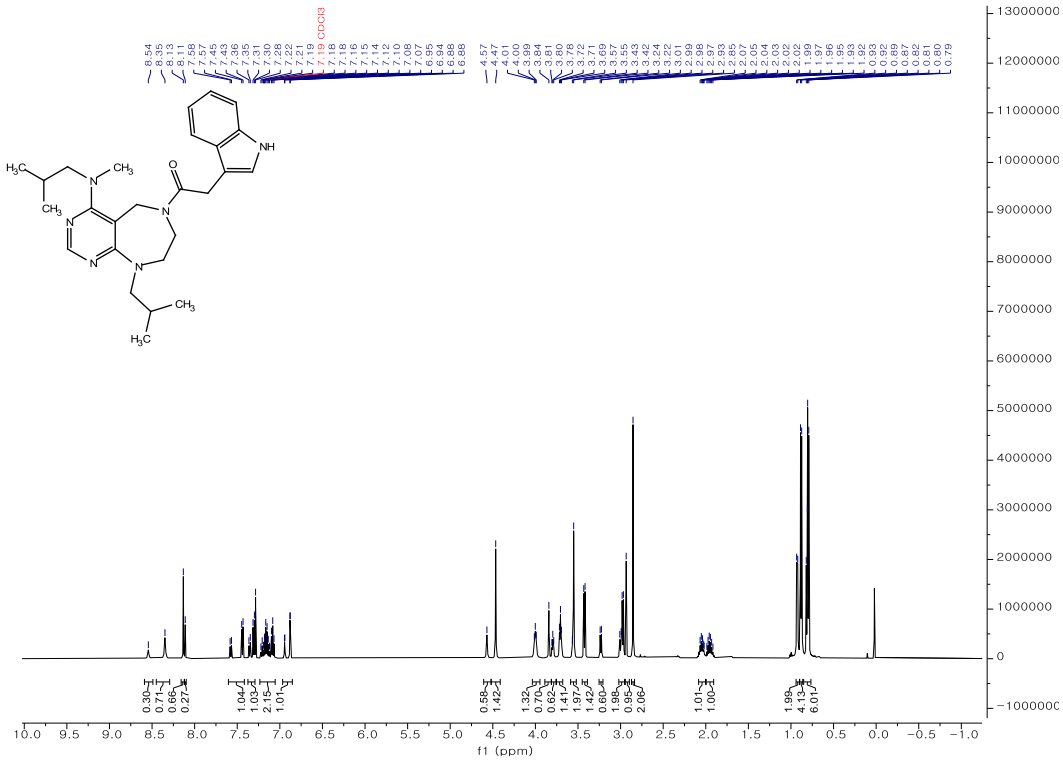

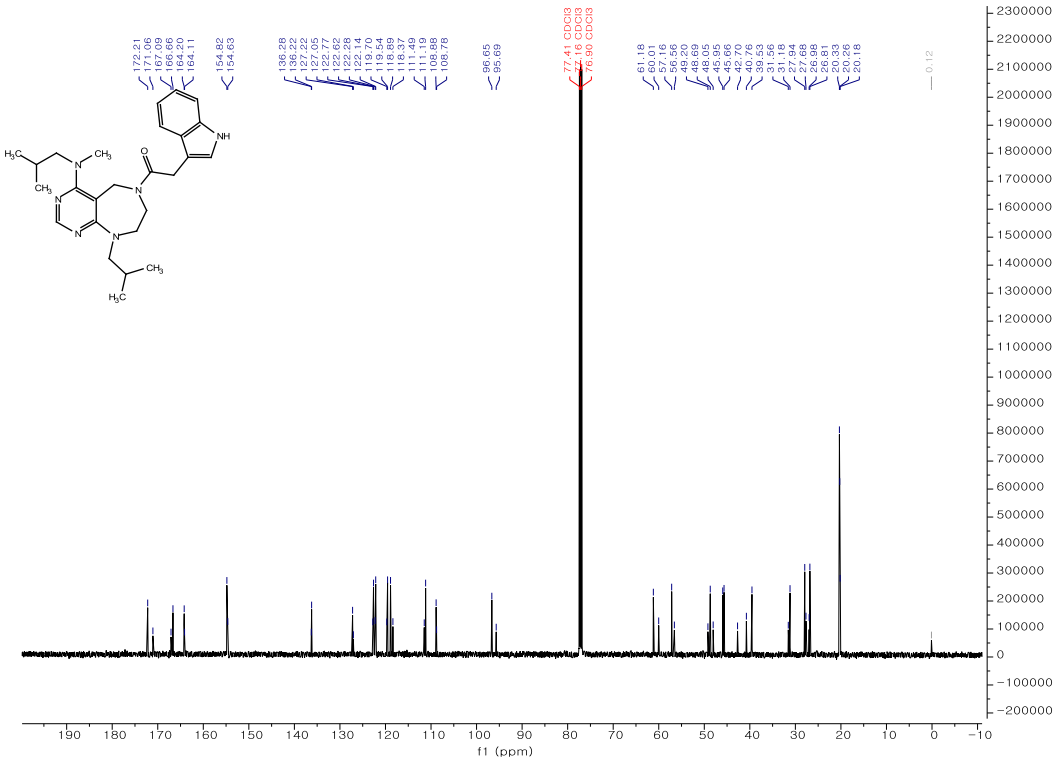

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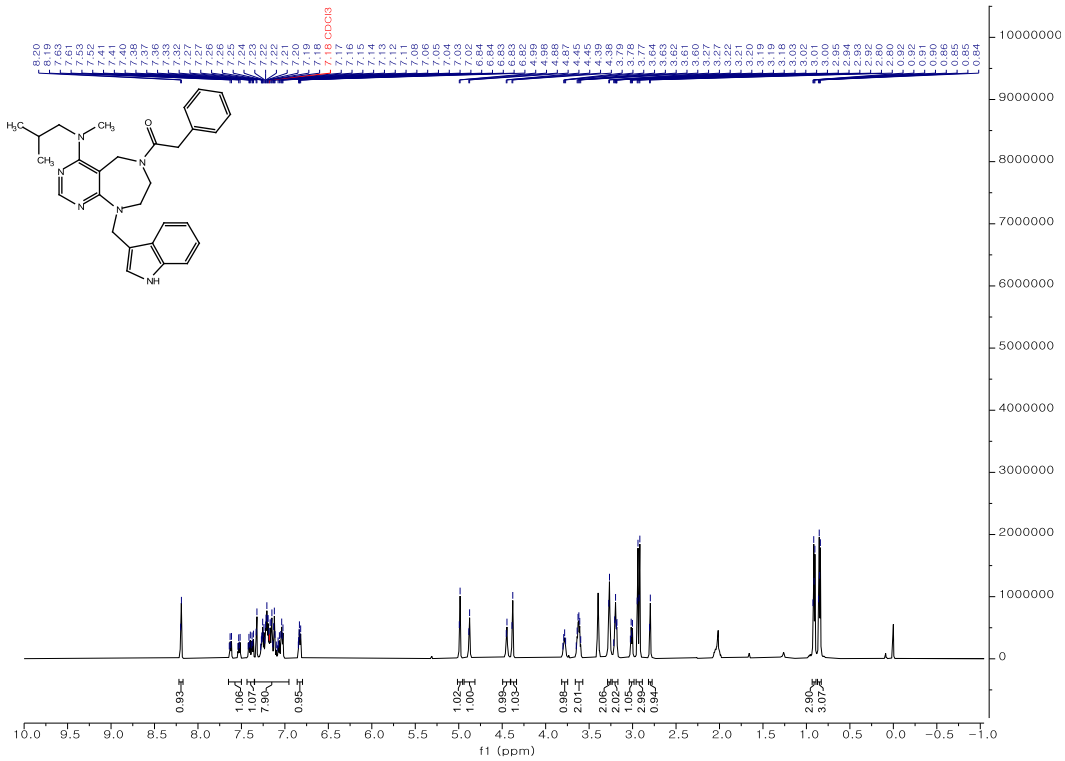

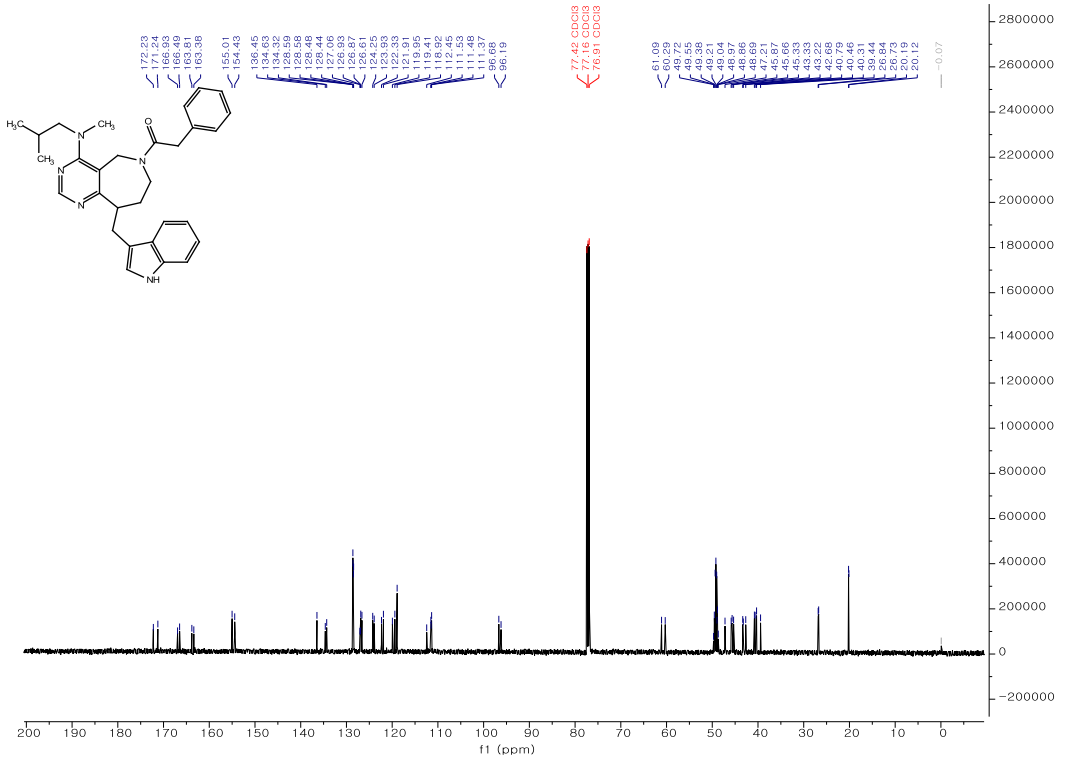

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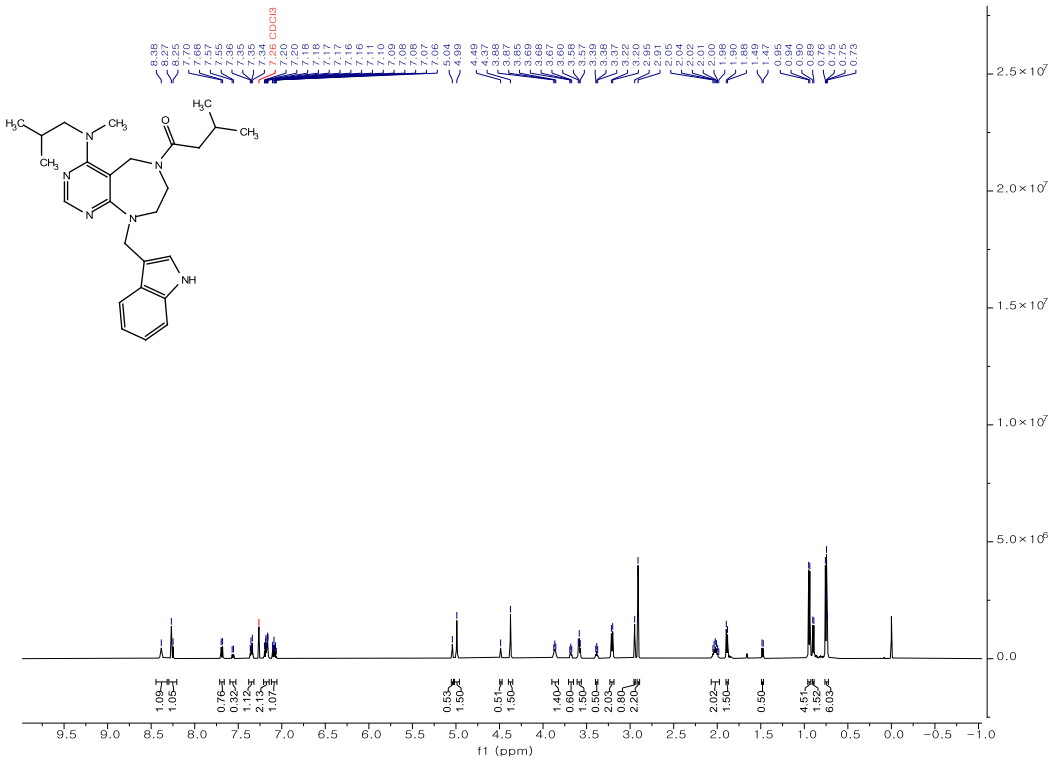

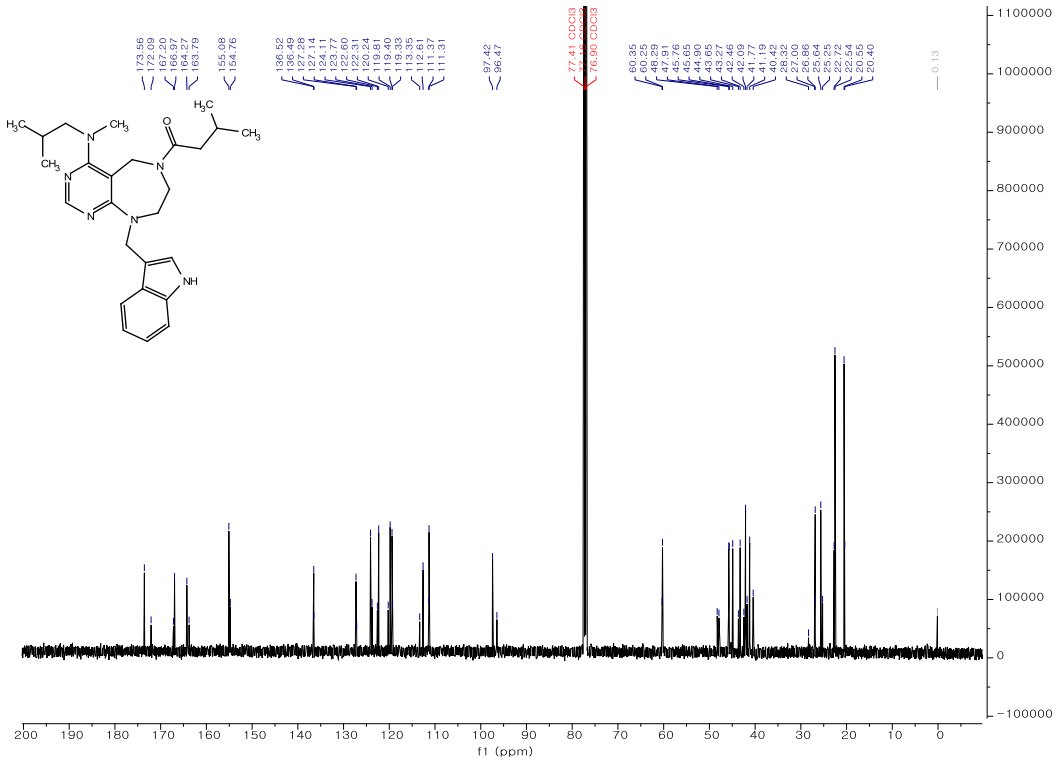

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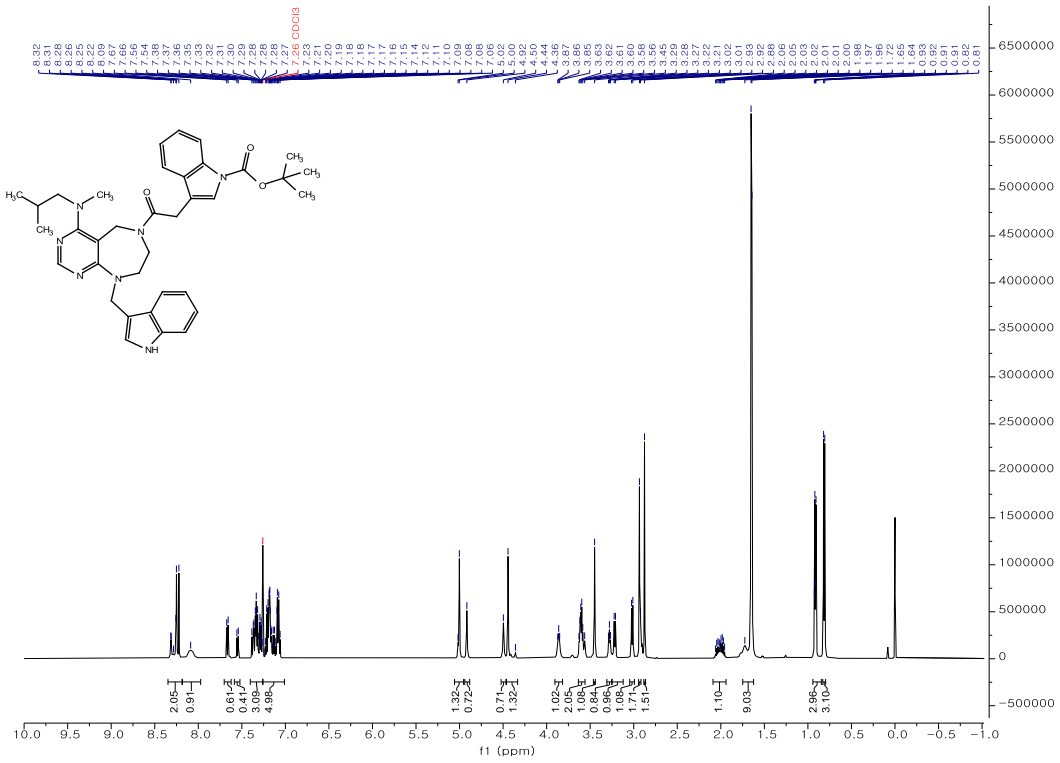

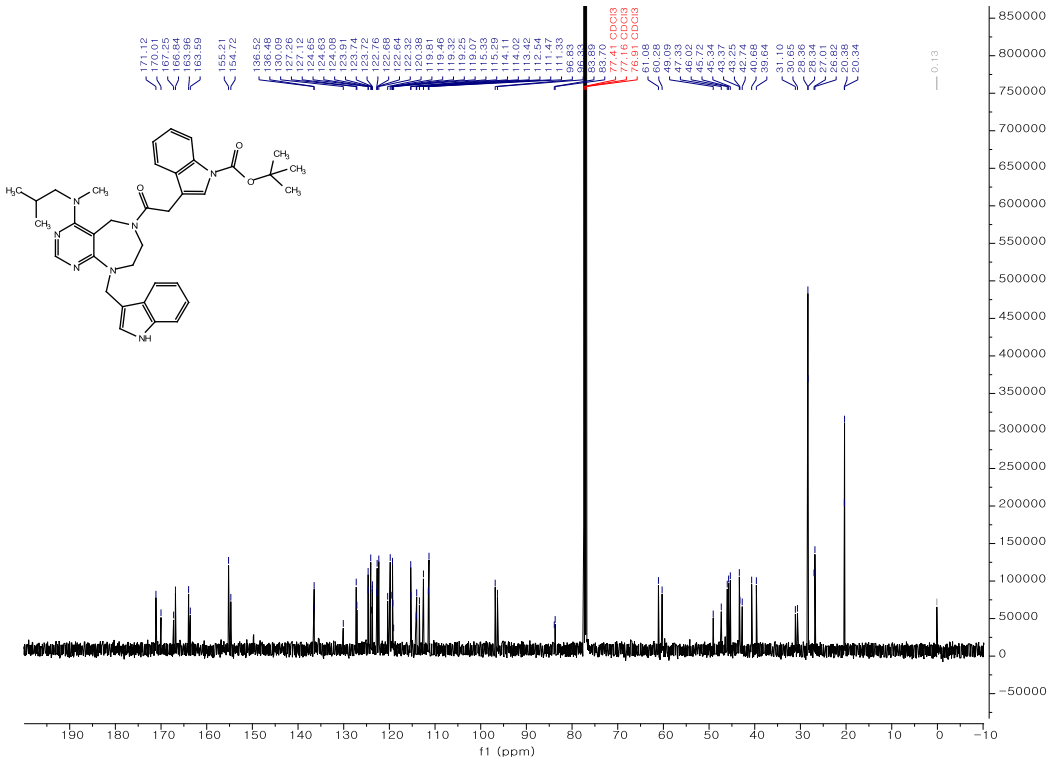

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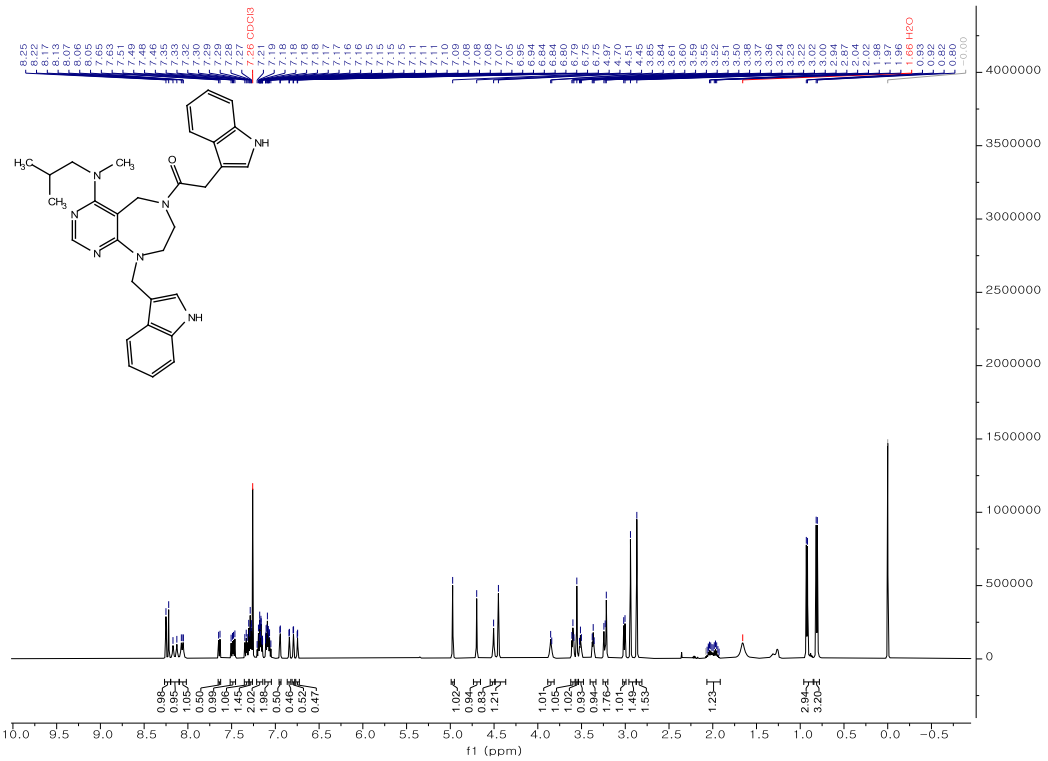
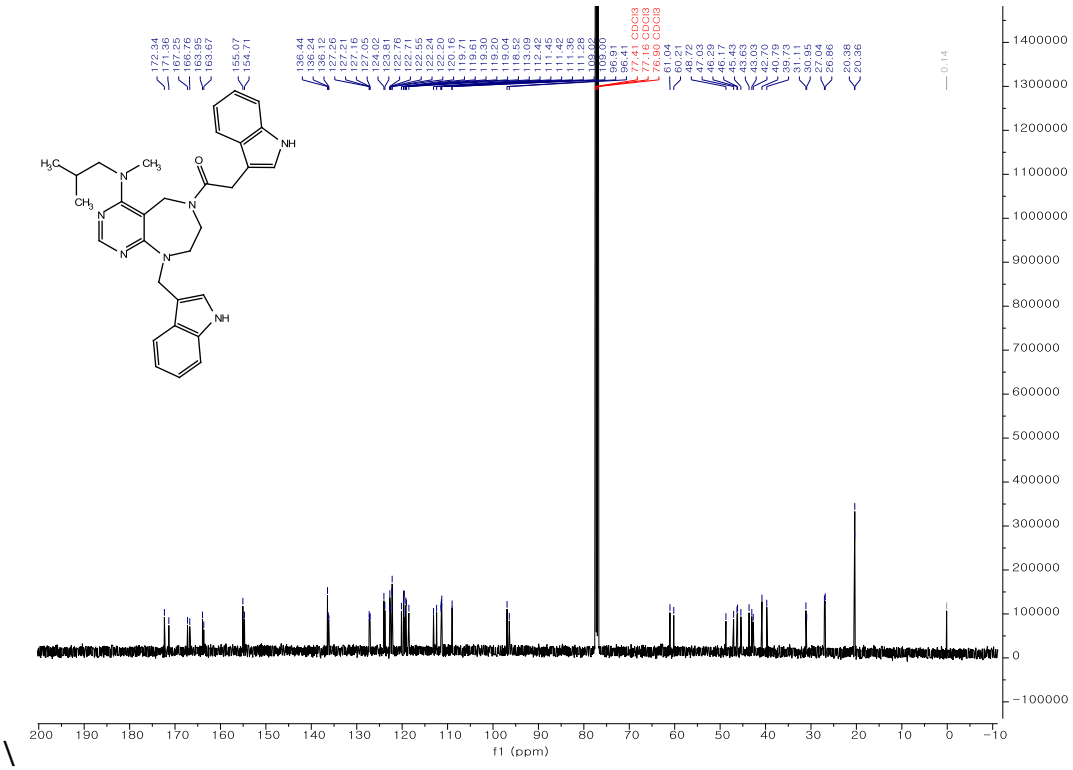
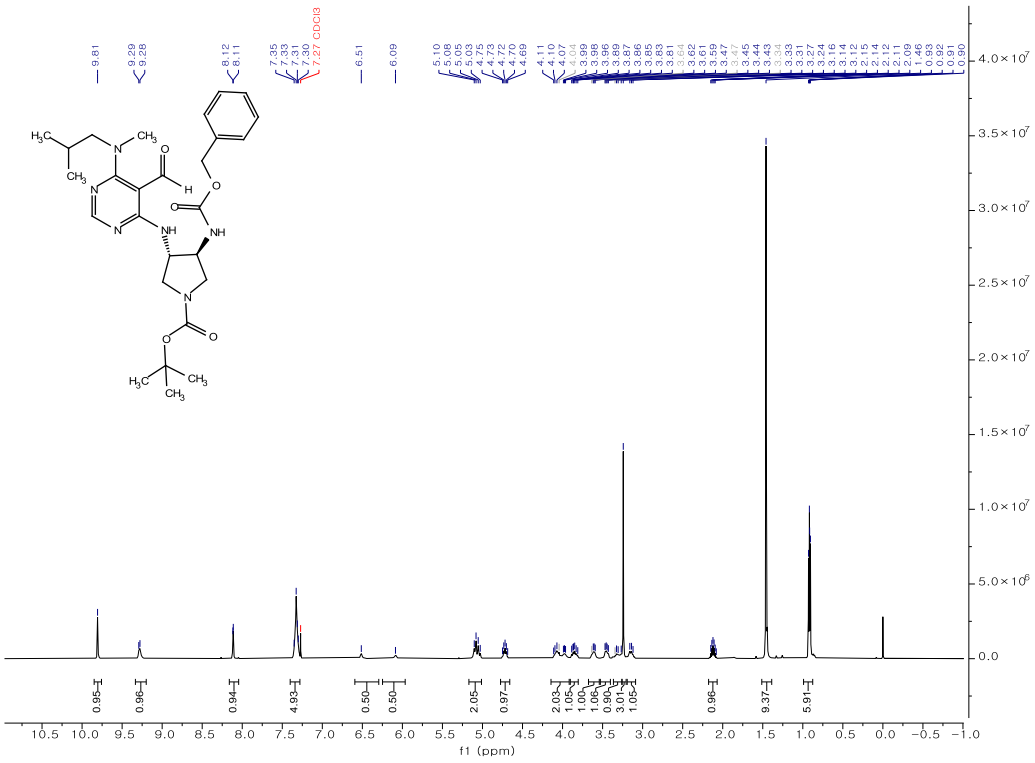
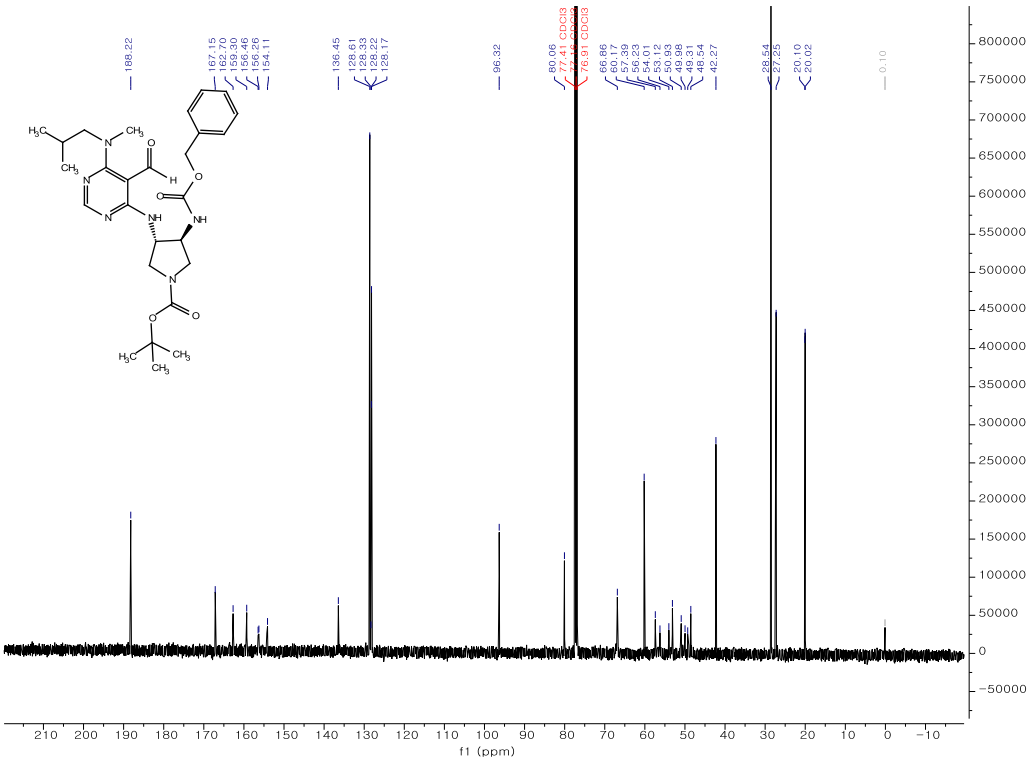


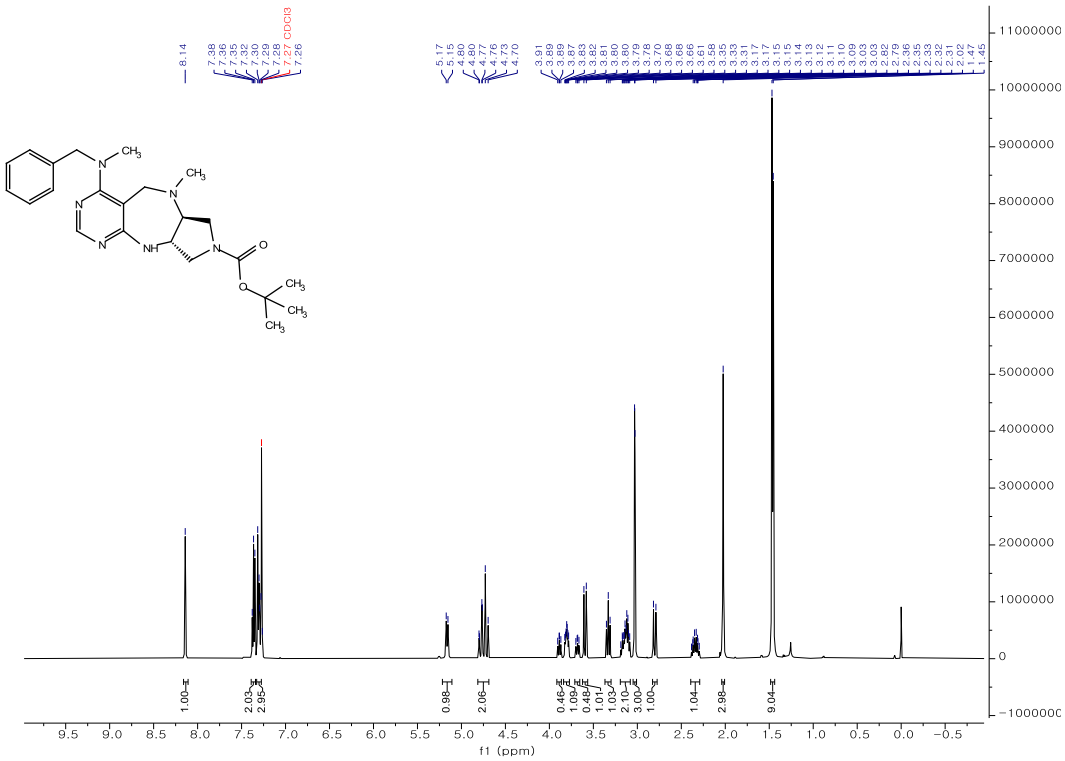


10b





11a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7.35
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7.30
7.29
7.28
7.27
CDCl3
7.26
5.17
5.15
4.80
4.77
4.76
4.73
4.70
3.91
3.89
3.89
3.87
3.83
3.82
3.81
3.80
3.80
3.79
3.78
3.70
3.68
3.66
3.61
3.58
3.35
3.33
3.31
3.17
3.17
3.15
3.15
3.14
3.13
3.12
3.11
3.10
3.09
3.03
3.03
2.82
2.79
2.36
2.35
2.33
2.32
2.31
2.07
1.47
1.45
1.00
2.03
2.95
0.98
2.06
0.46
1.09
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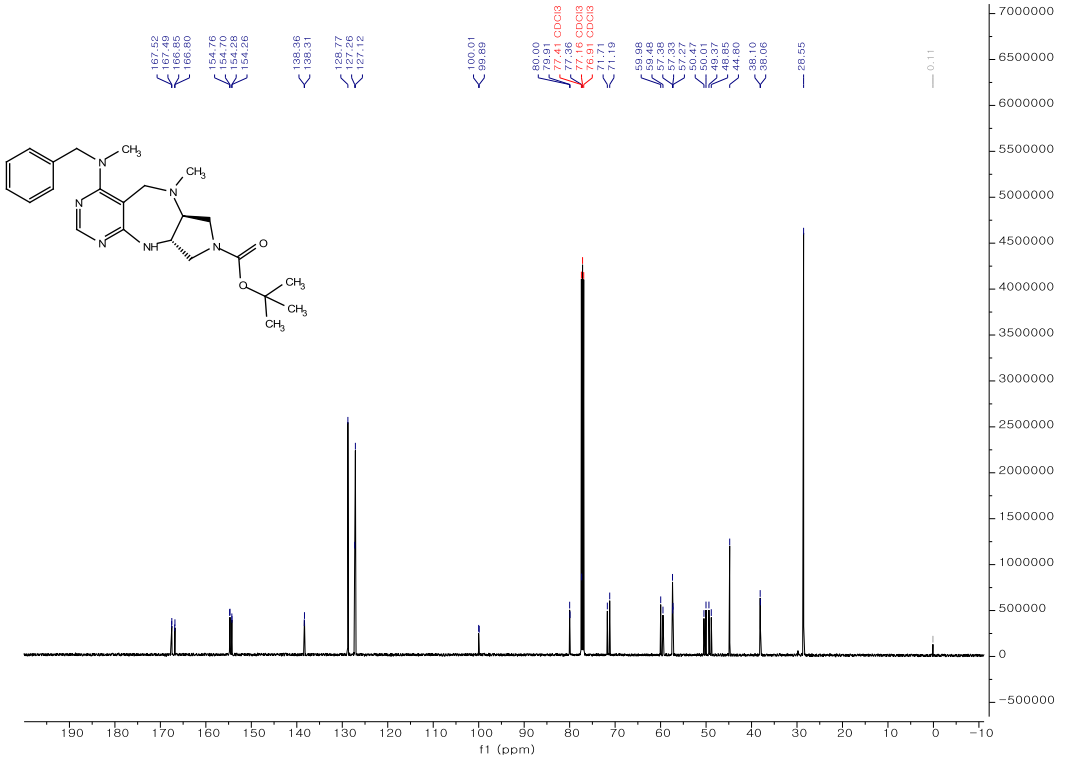
1.01
1.03
2.14
3.00
1.00
1.04
2.98
9.04
f1 (ppm)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167.49
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154.70
154.28
154.26
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138.31
128.77
127.26
127.12
100.01
99.89
80.00
79.91
77.41
CDCl3
77.16
CDCl3
76.91
CDCl3
71.71
71.19
59.98
58.48
57.38
57.33
57.27
50.47
50.01
49.37
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44.86
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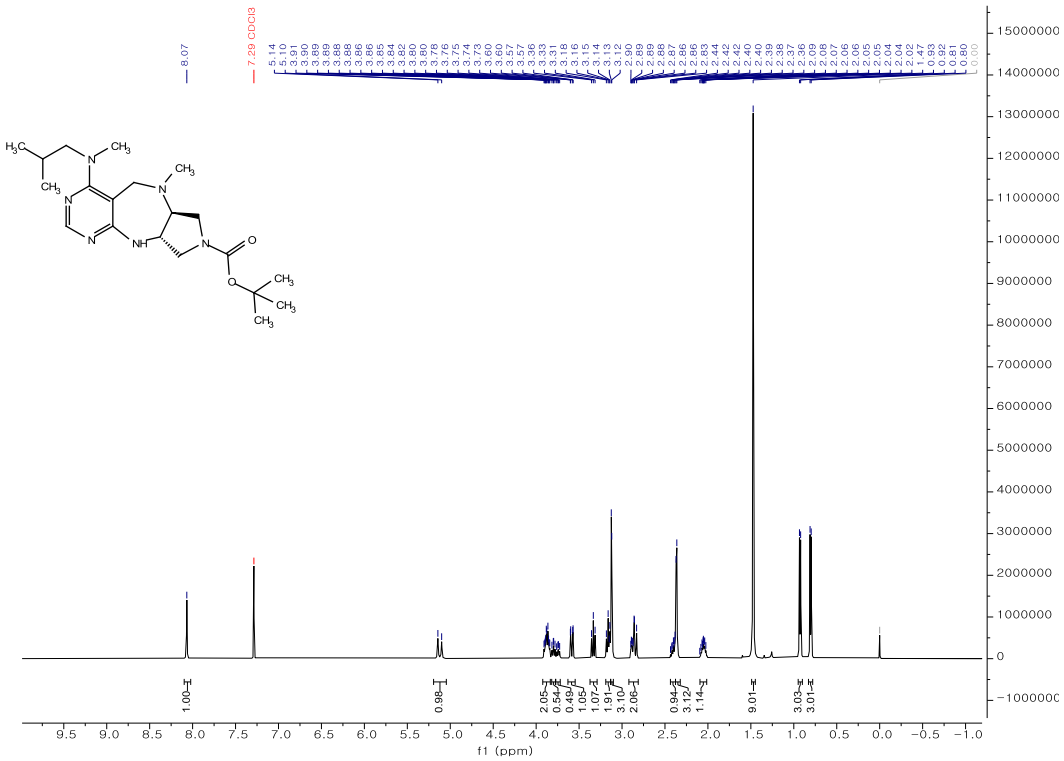
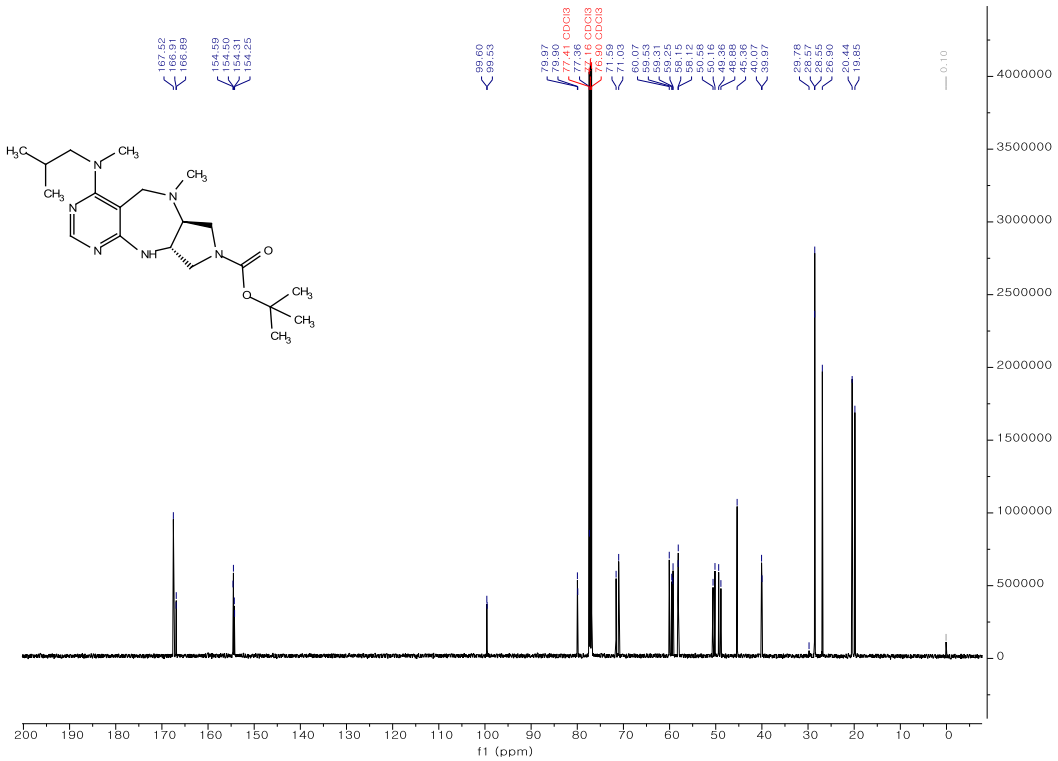
38.06
28.55
0.11
f1 (ppm)

11b


8.07
7.29 CDCl3
f1 (ppm)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166.89
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154.50
154.31
154.25
99.60
99.53
79.97
79.40
77.41 CDCl3
77.36
77.16 CDCl3
76.90 CDCl3
71.59
71.05
60.07
59.53
59.31
58.25
58.15
58.12
50.58
50.16
48.86
48.68
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26.90
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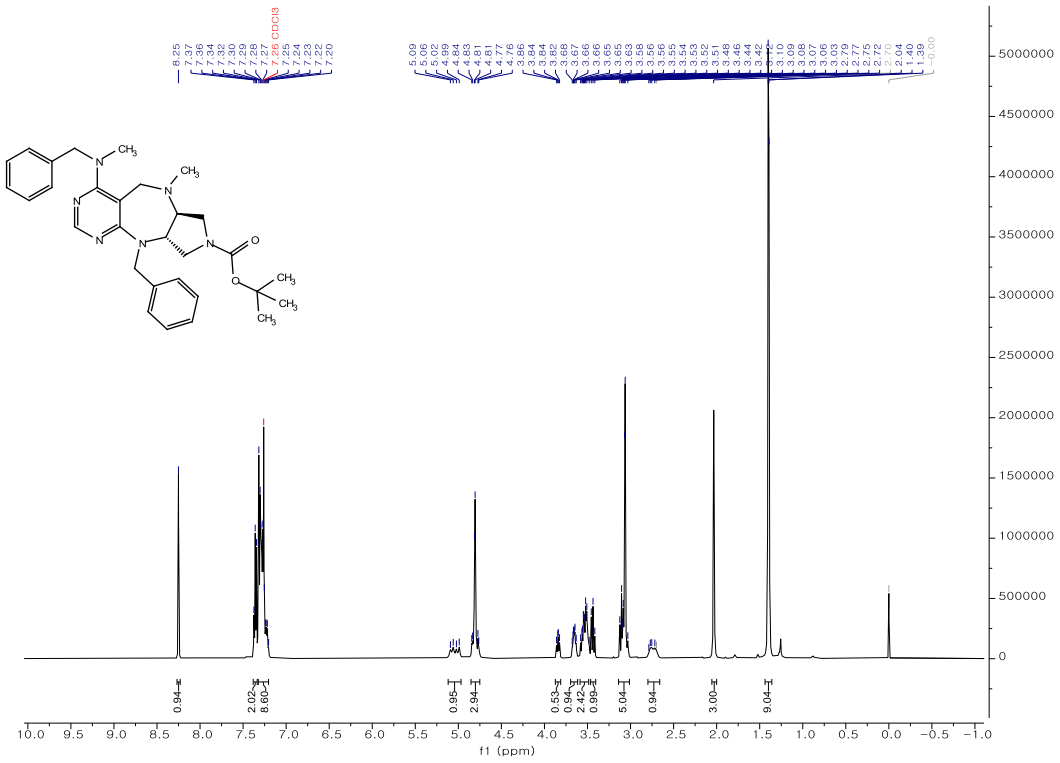
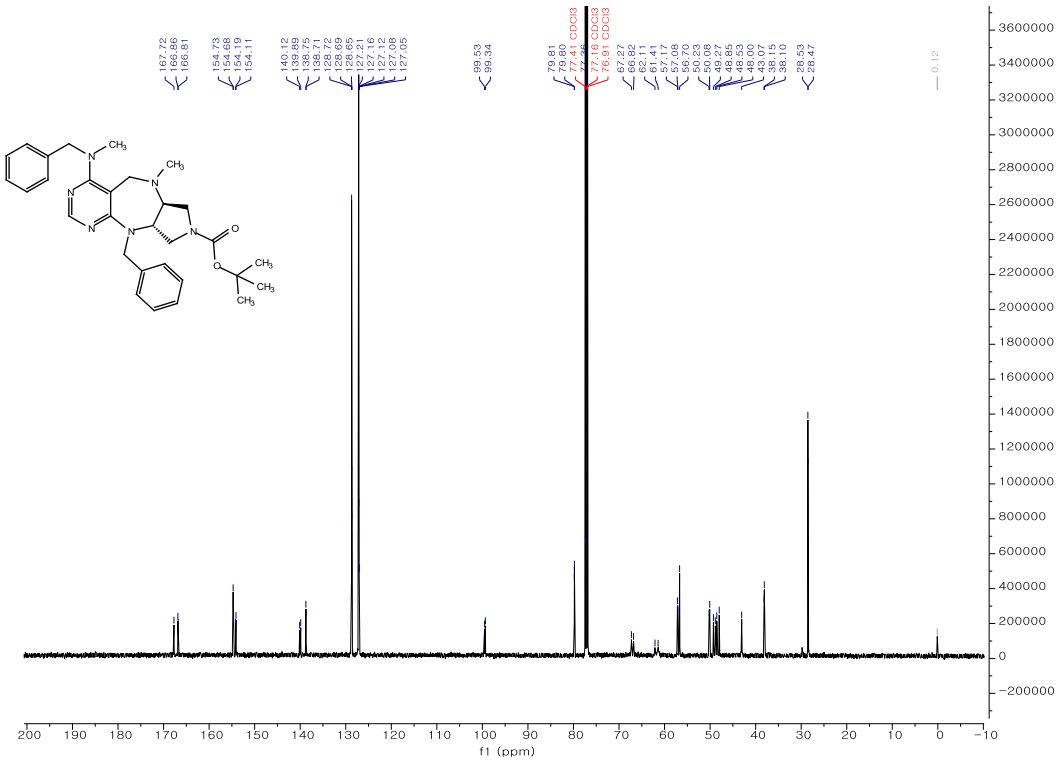
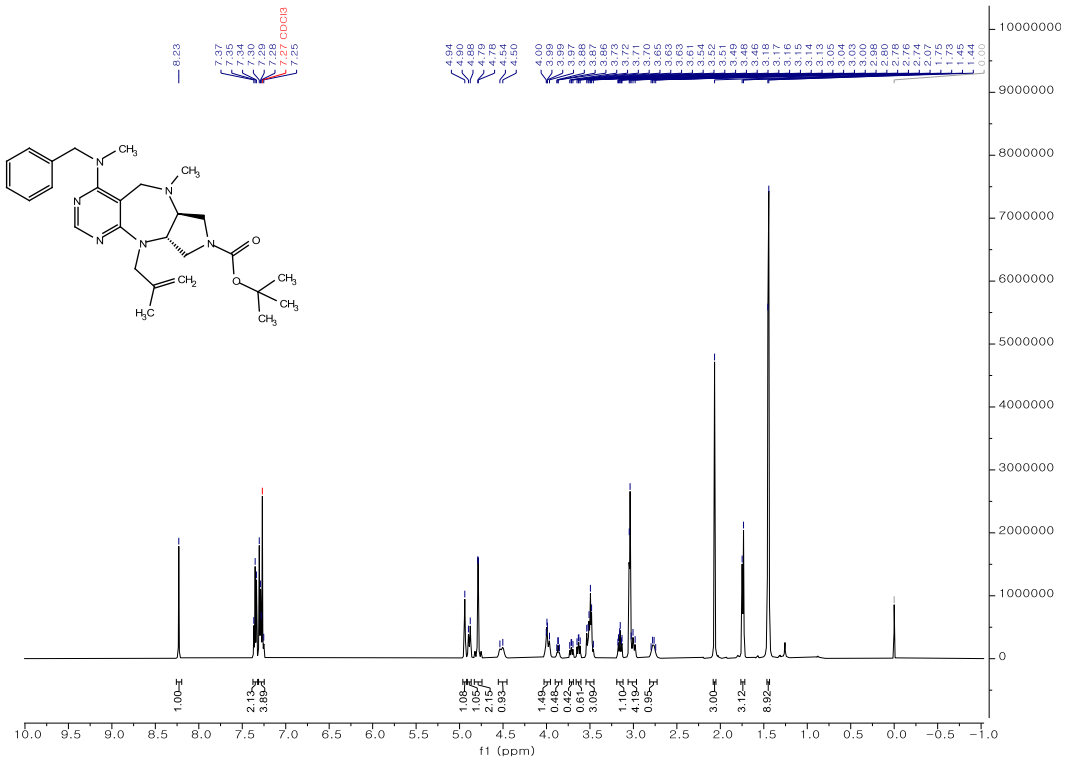
19.85
f1 (ppm)

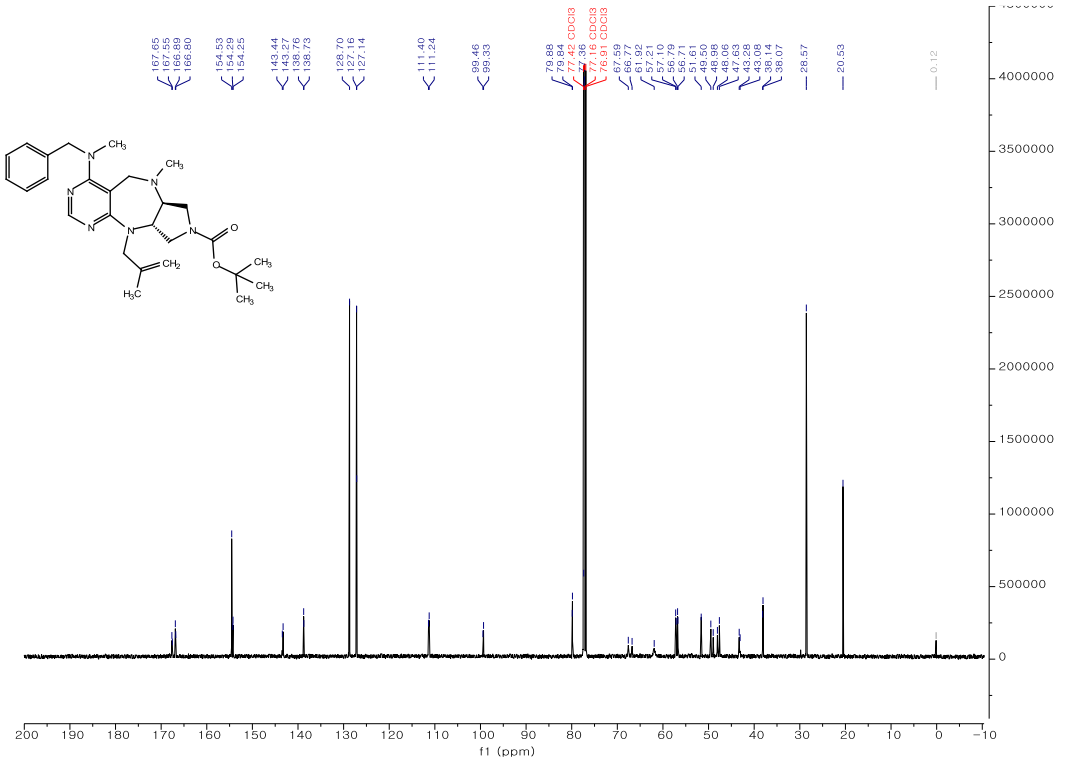
12a





12b





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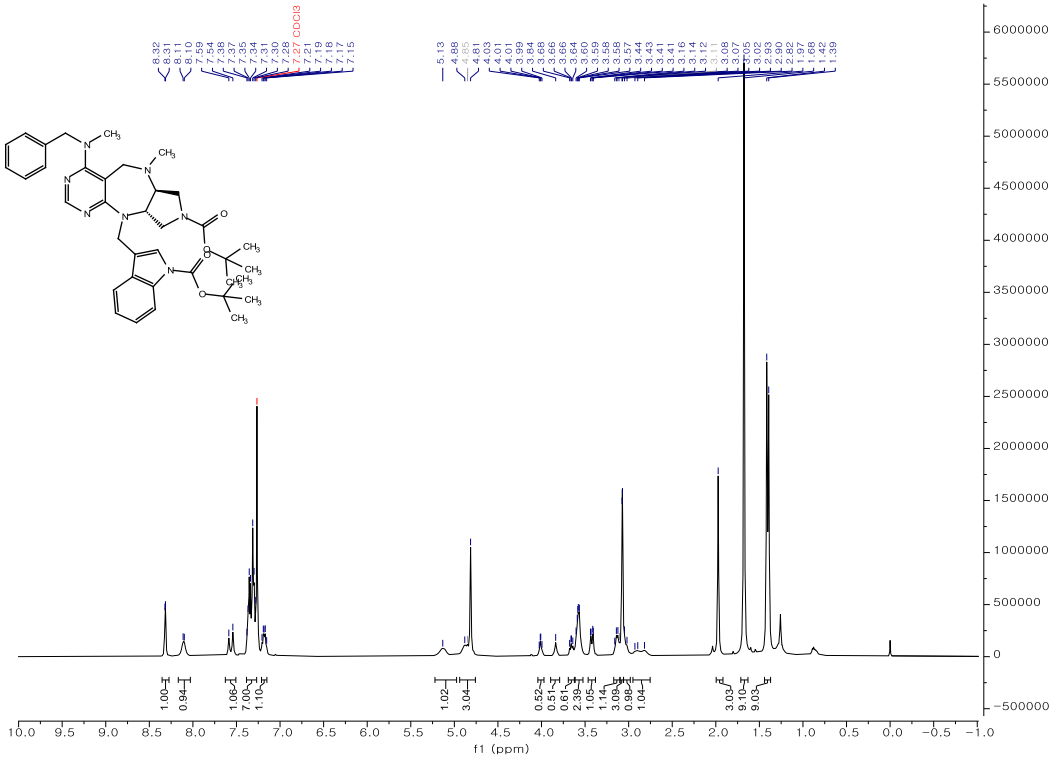
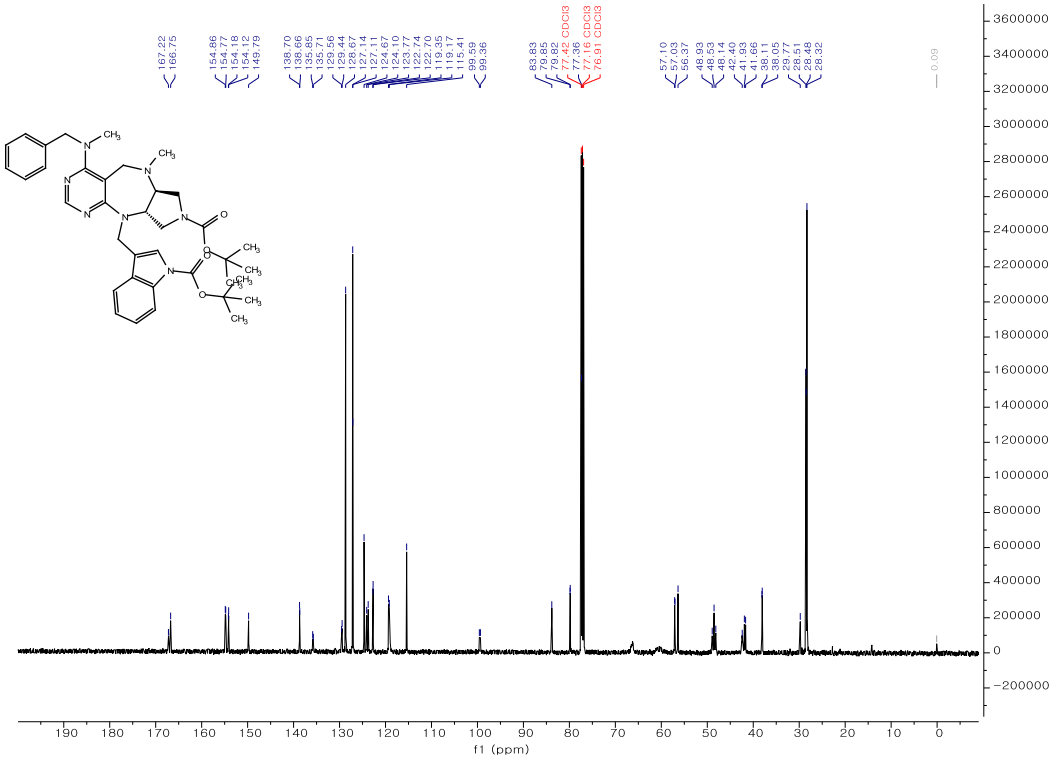
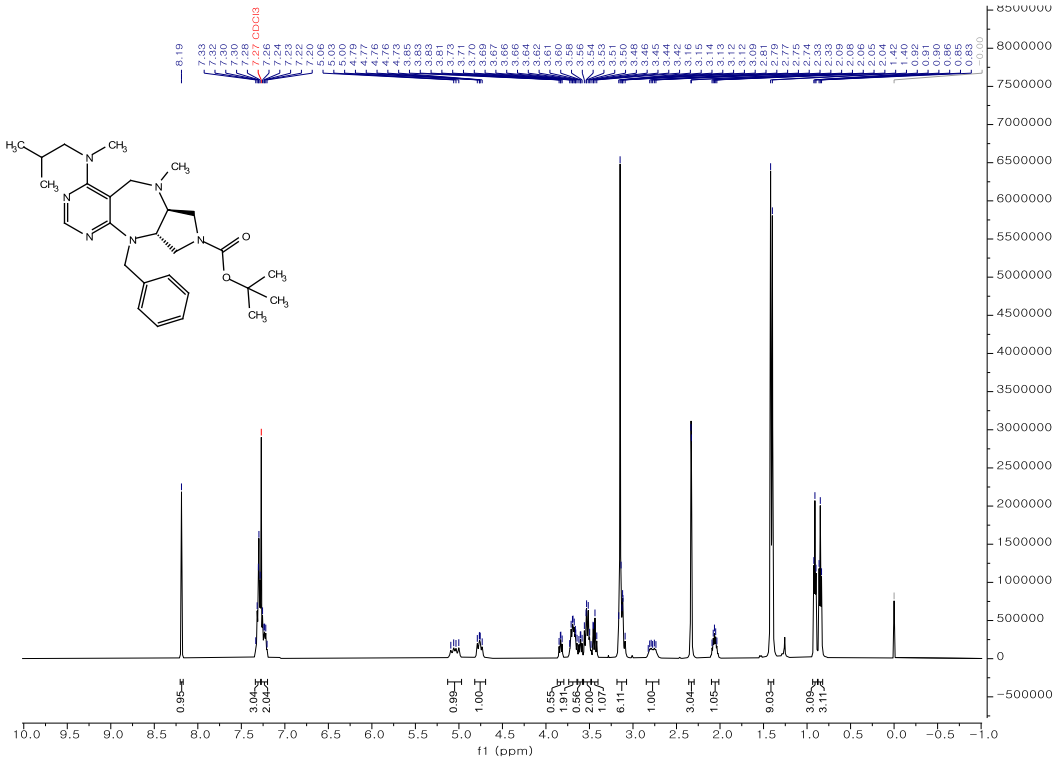
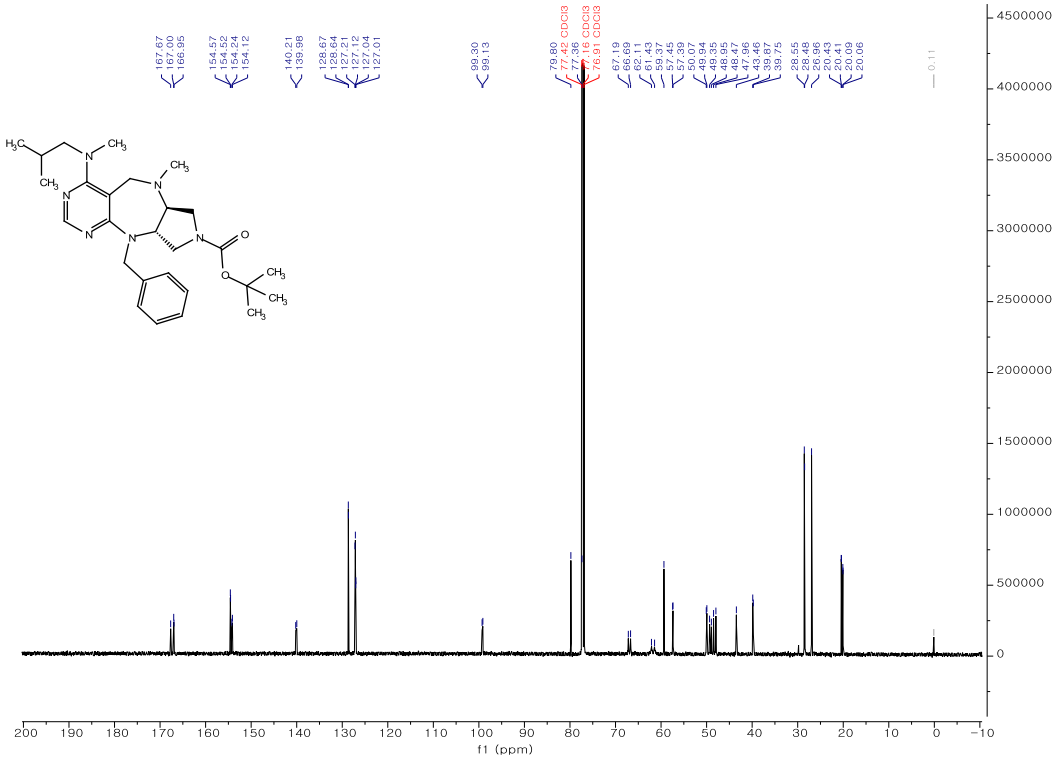


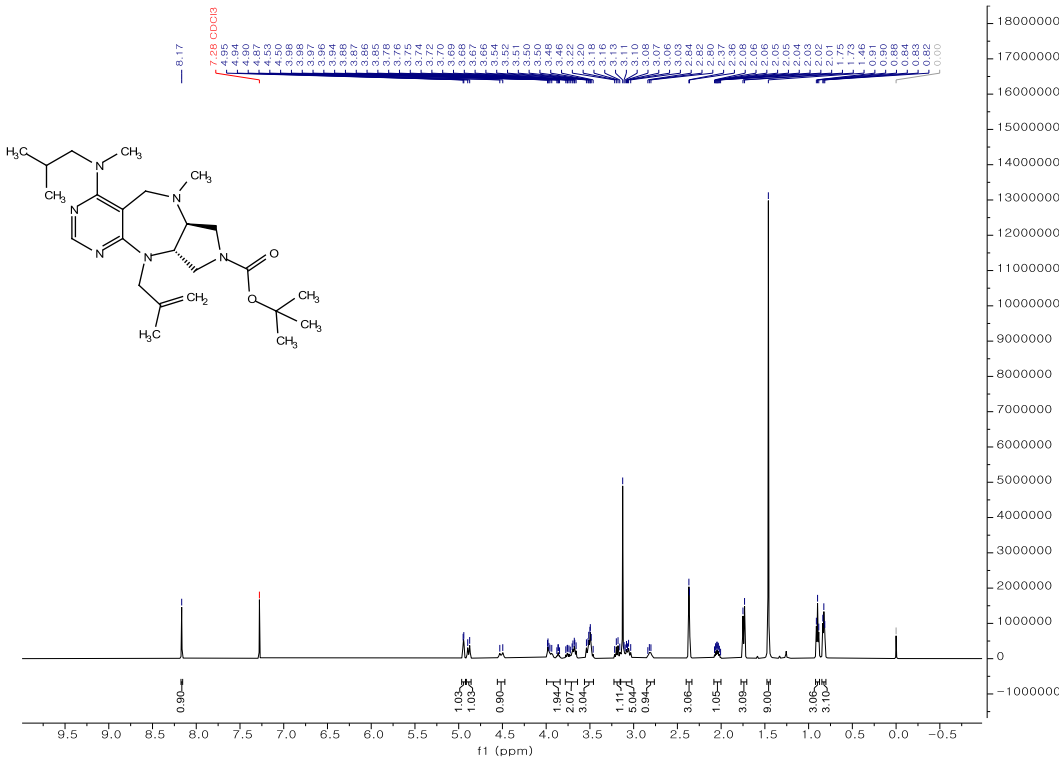


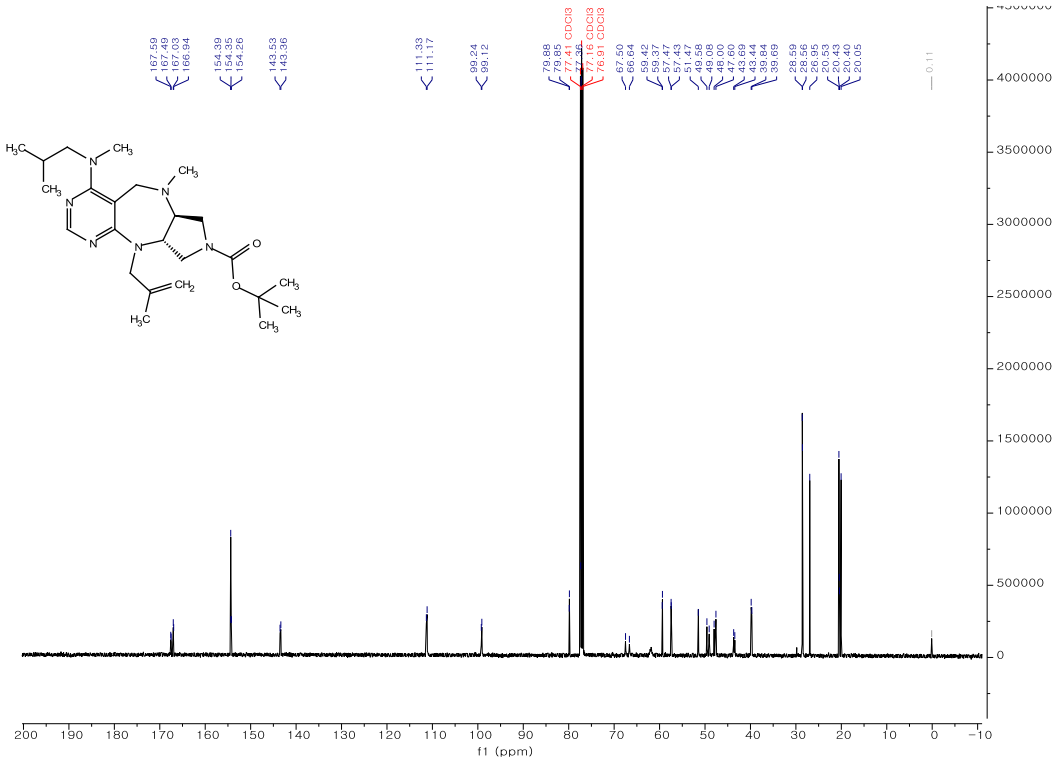
12d





12e





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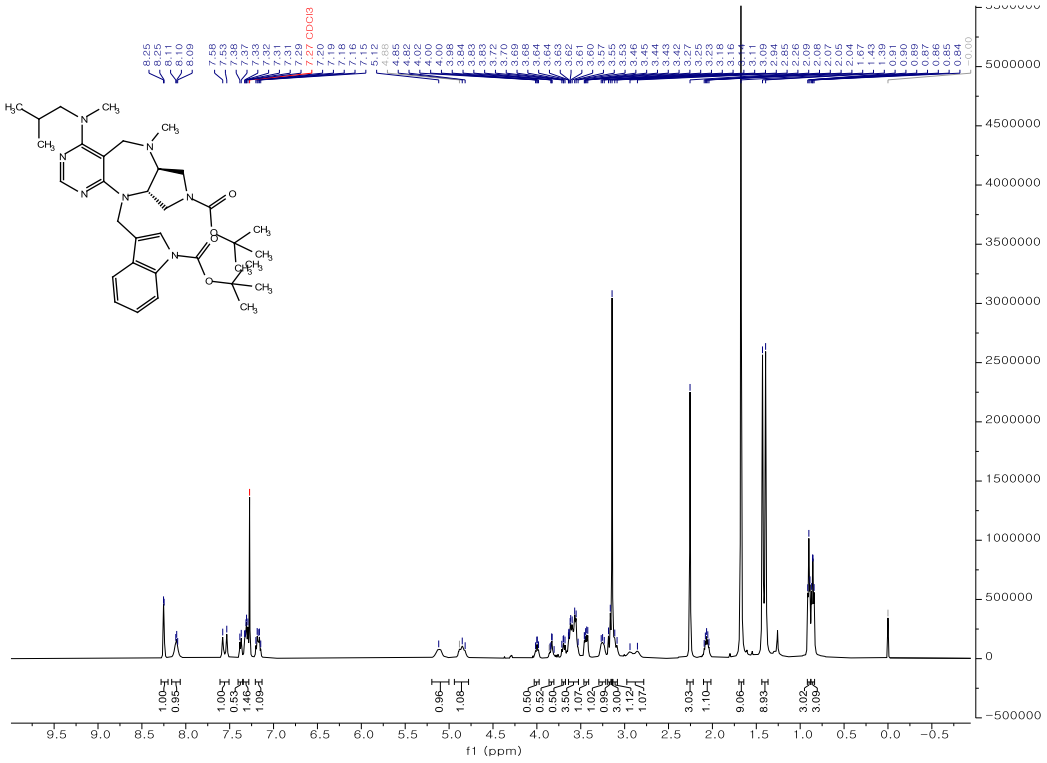
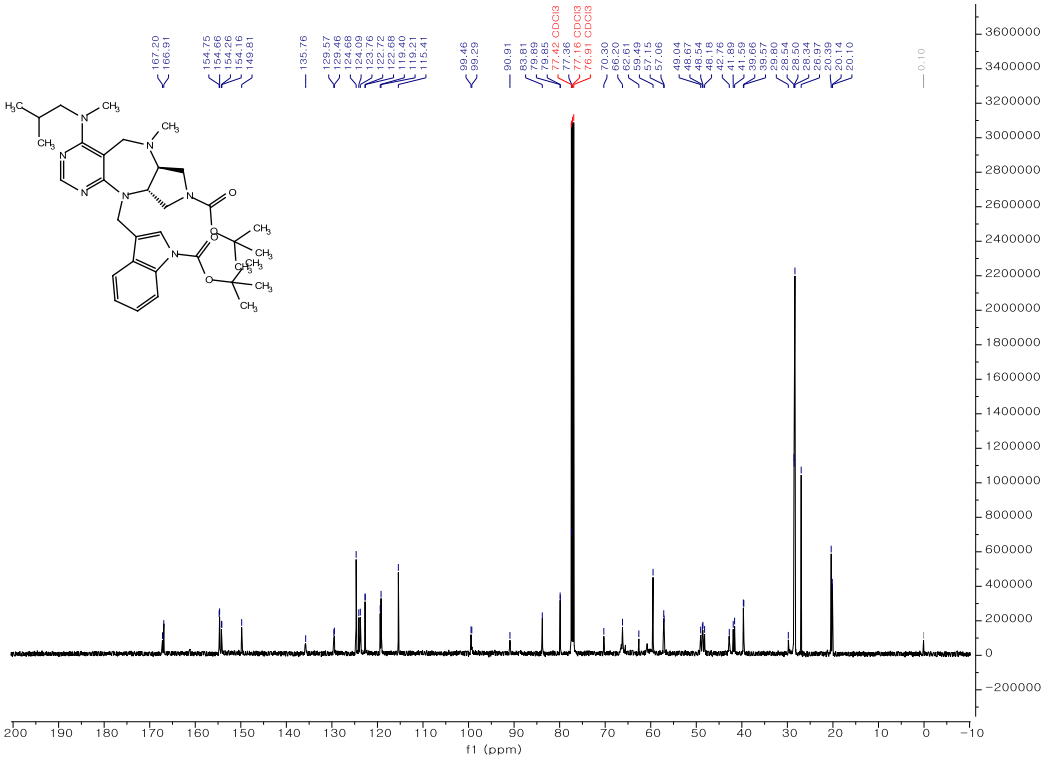
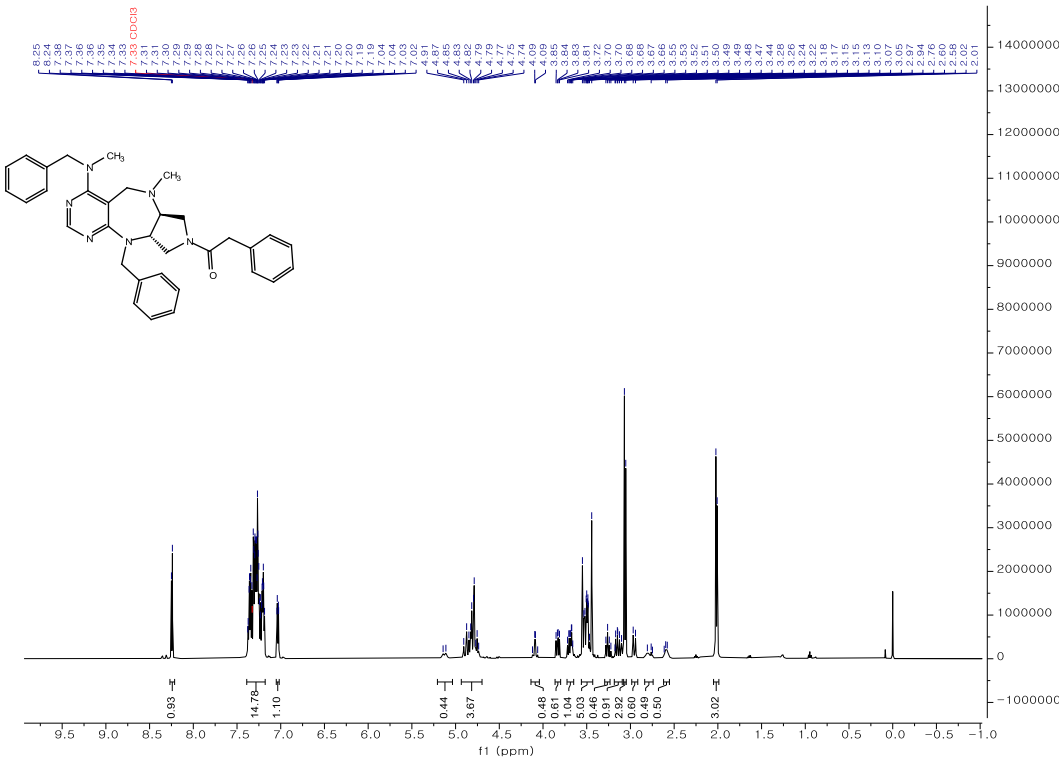
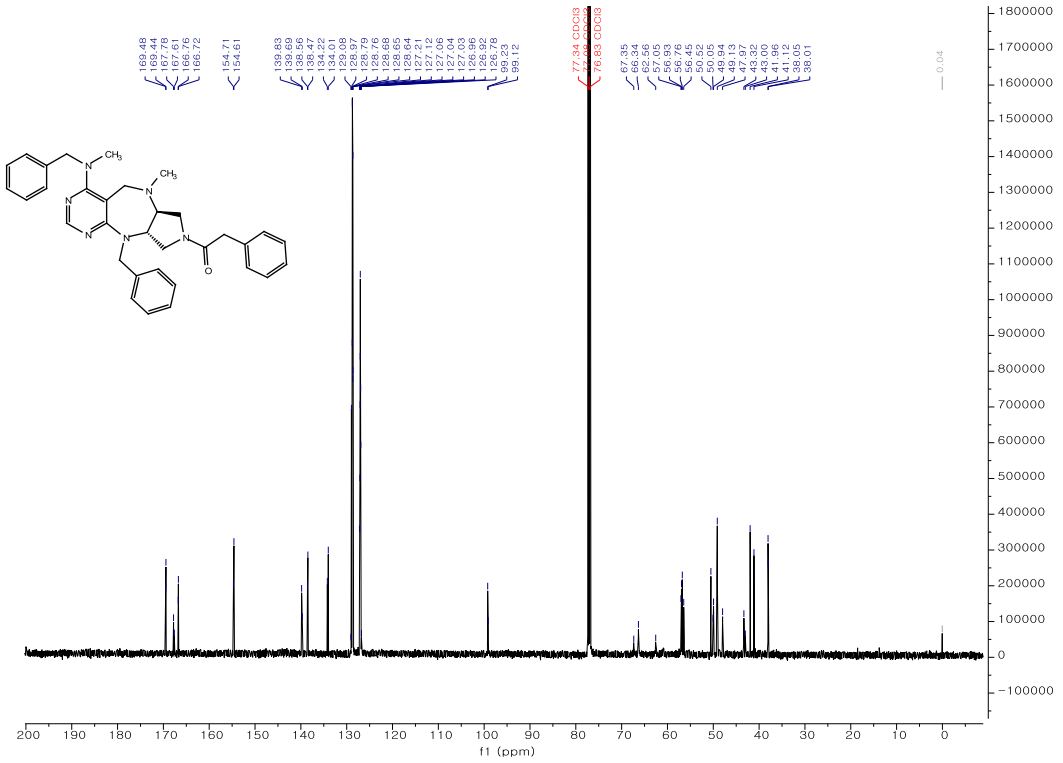




2a





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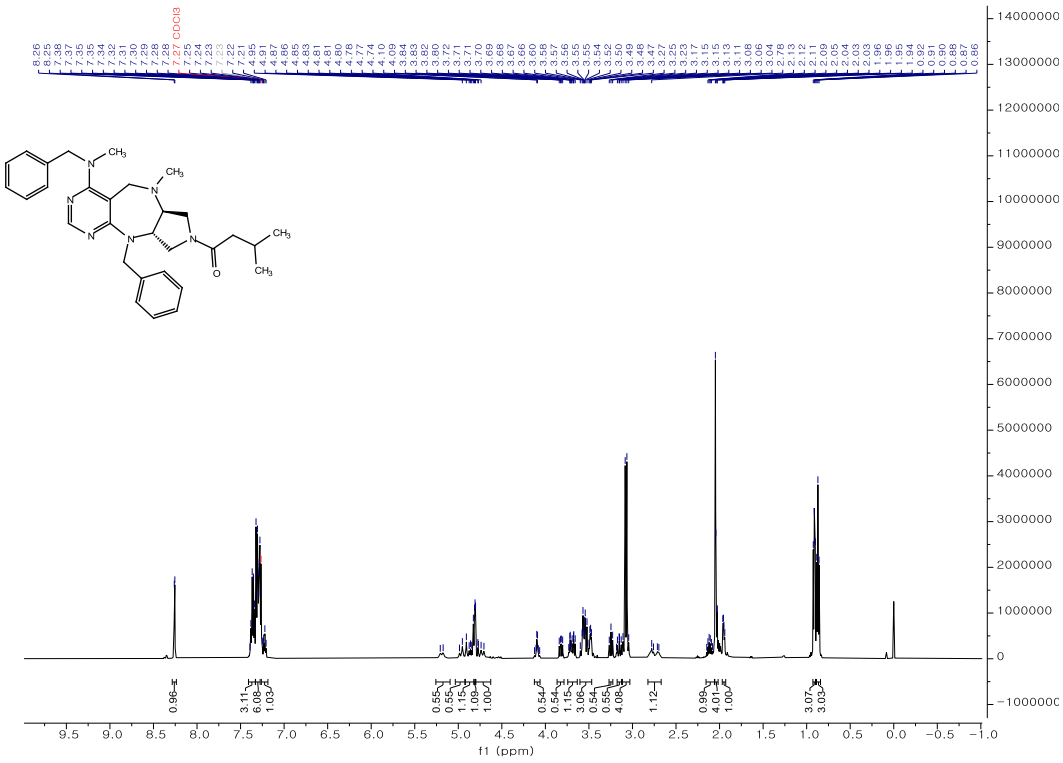

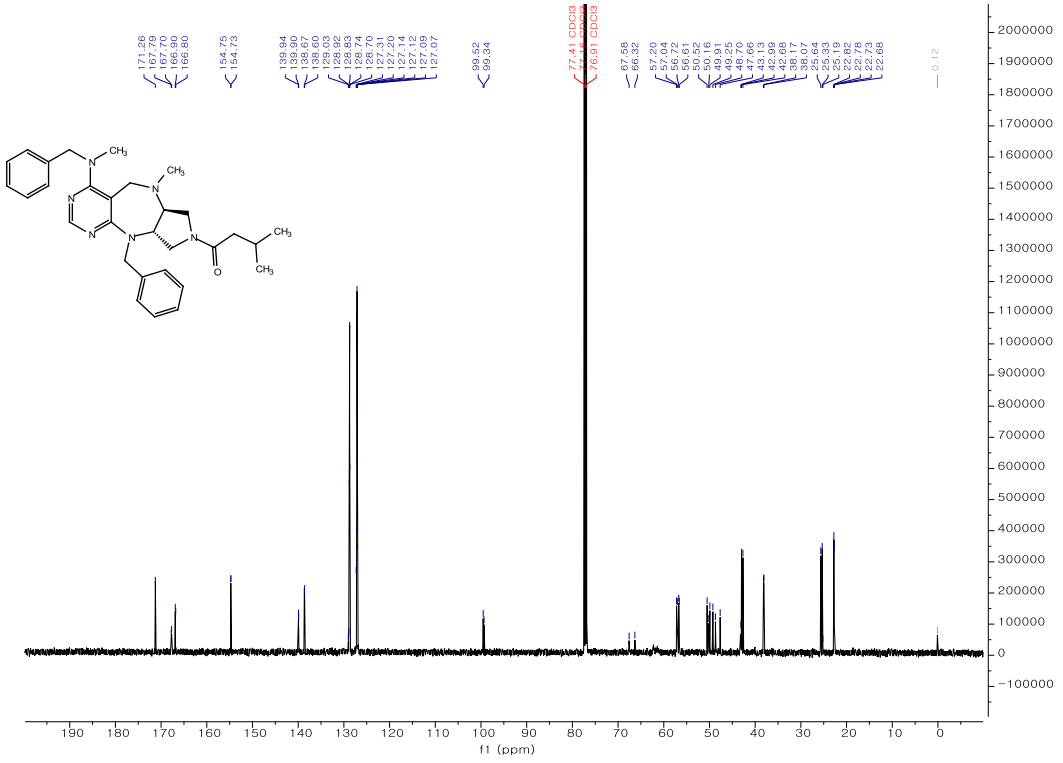

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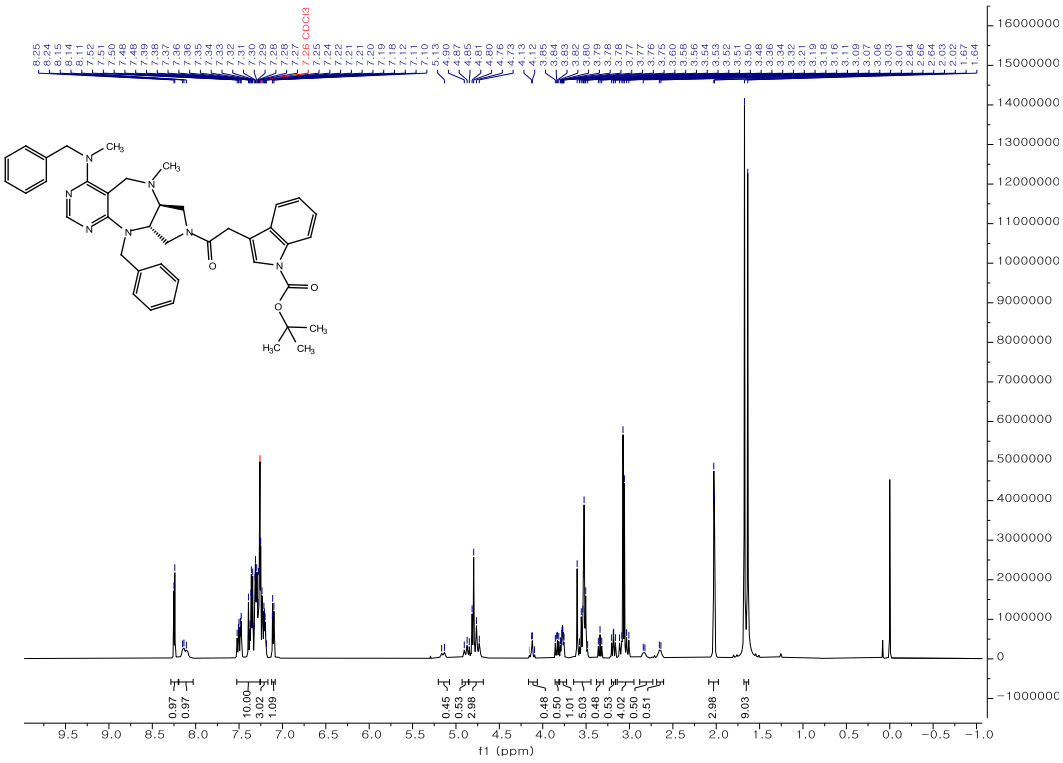

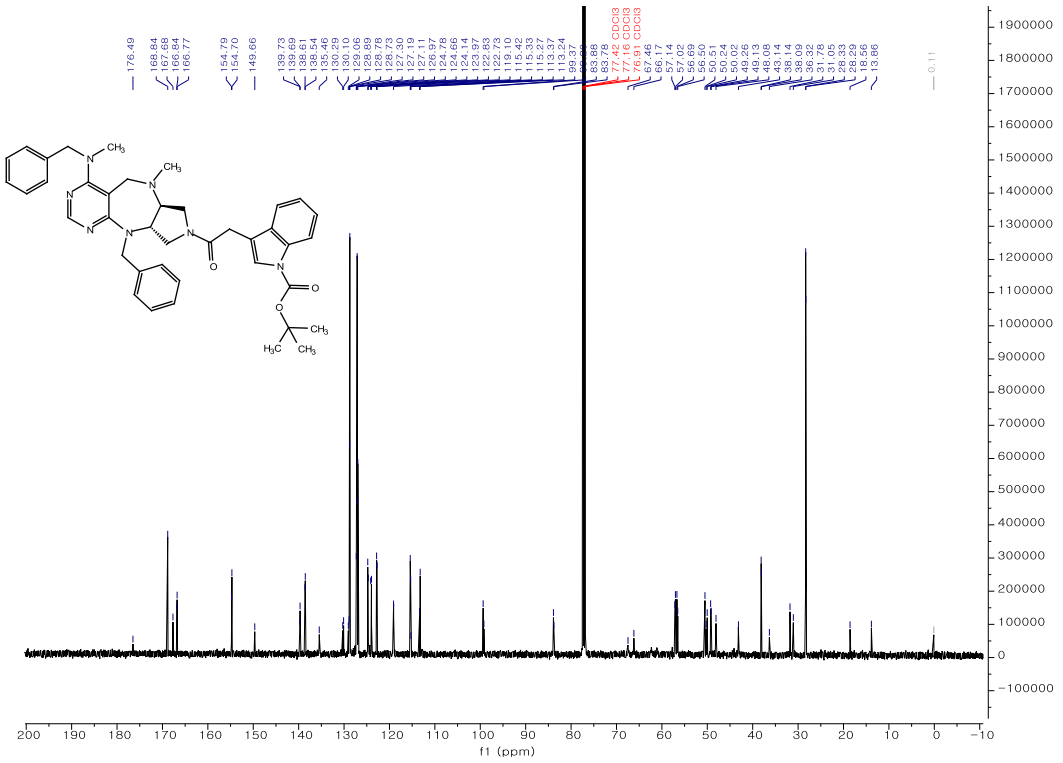

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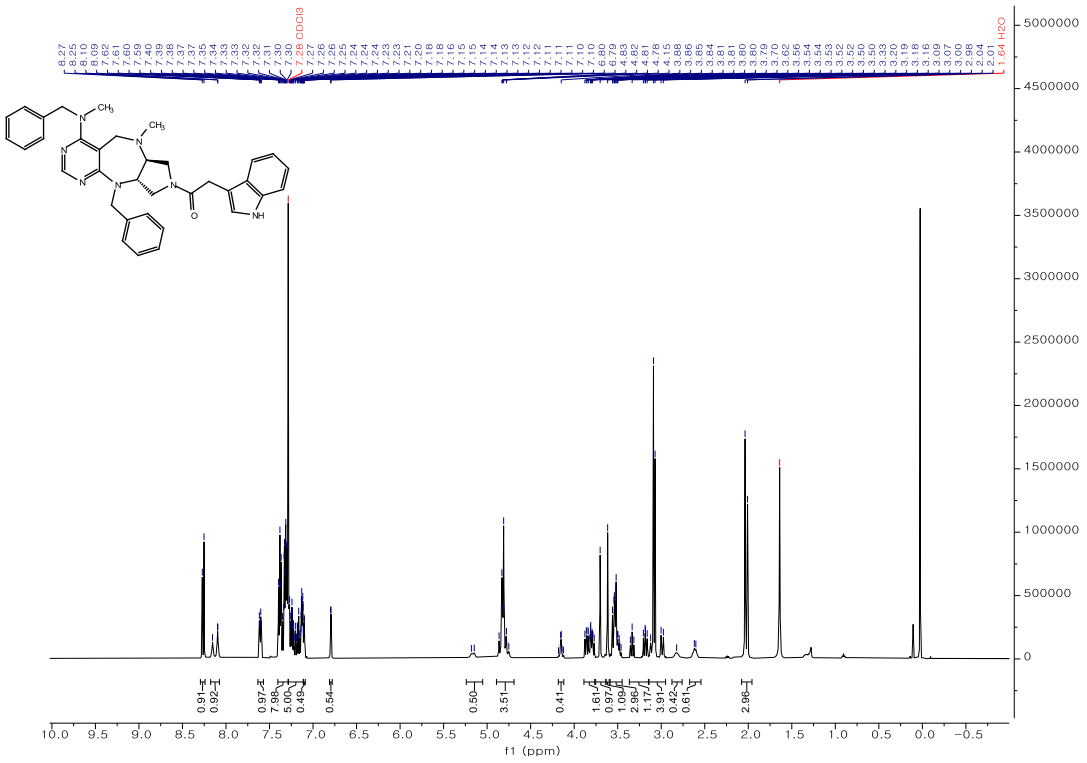
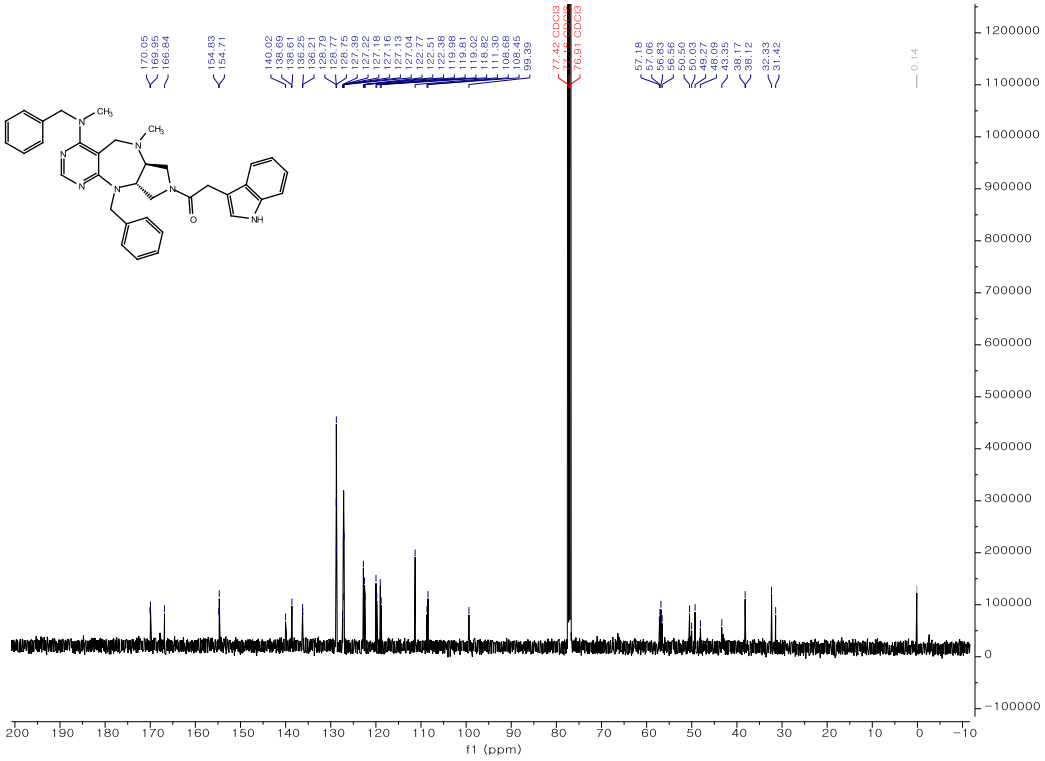
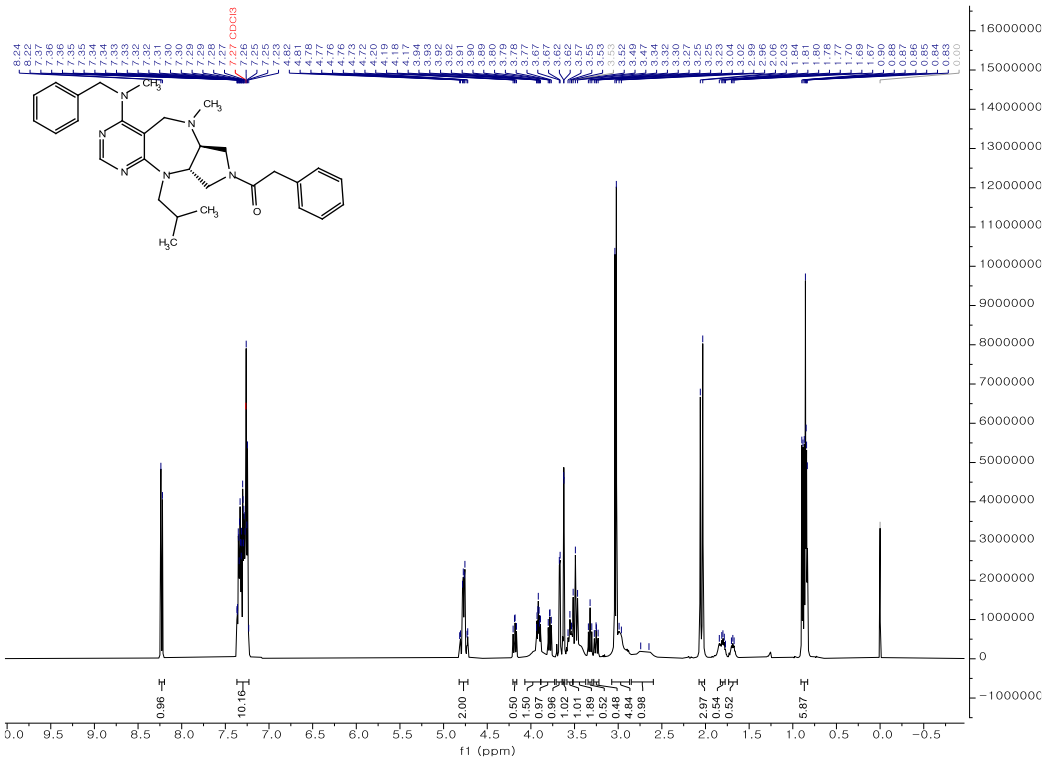
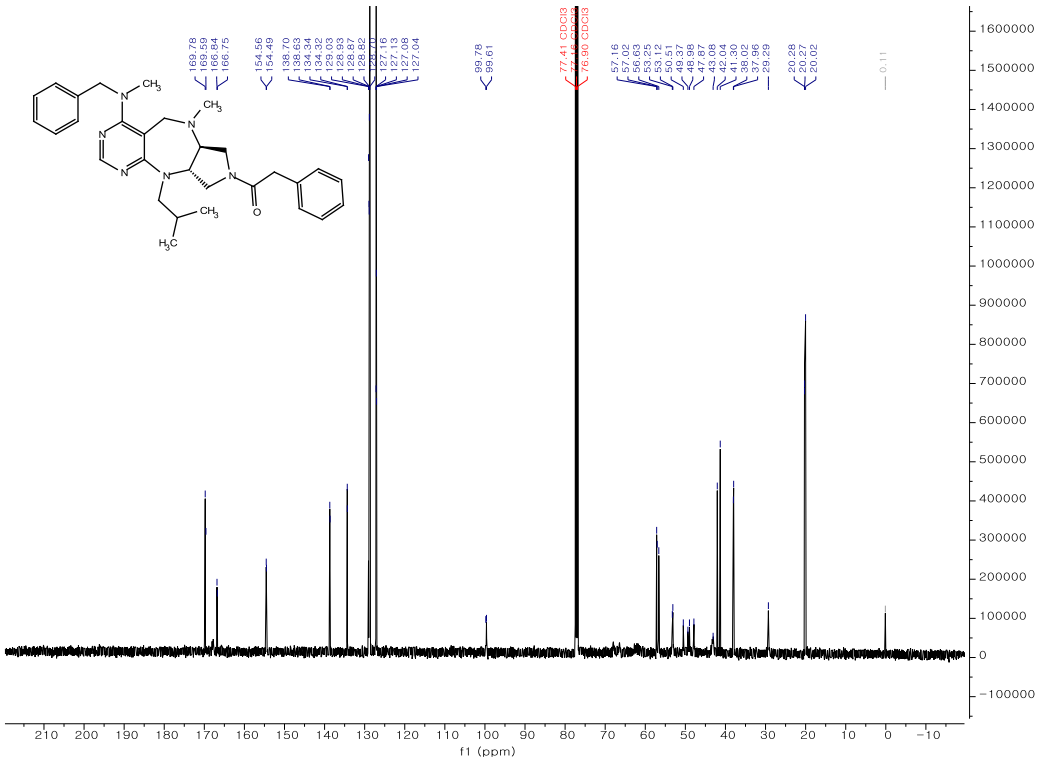


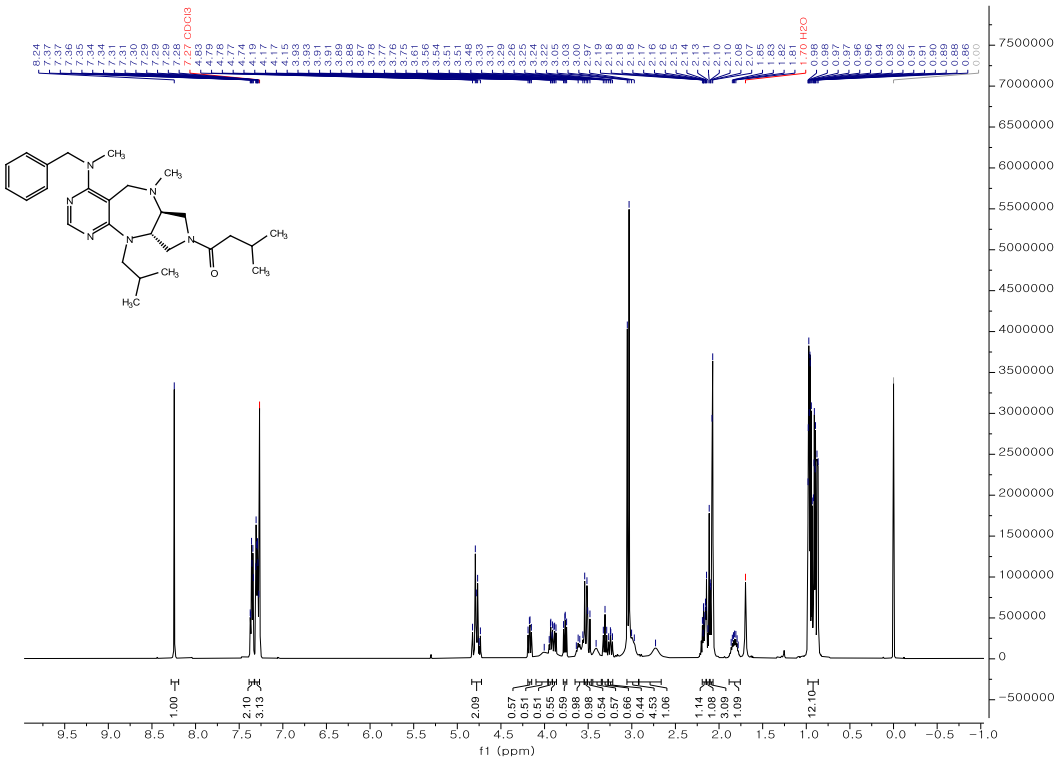


2d





2e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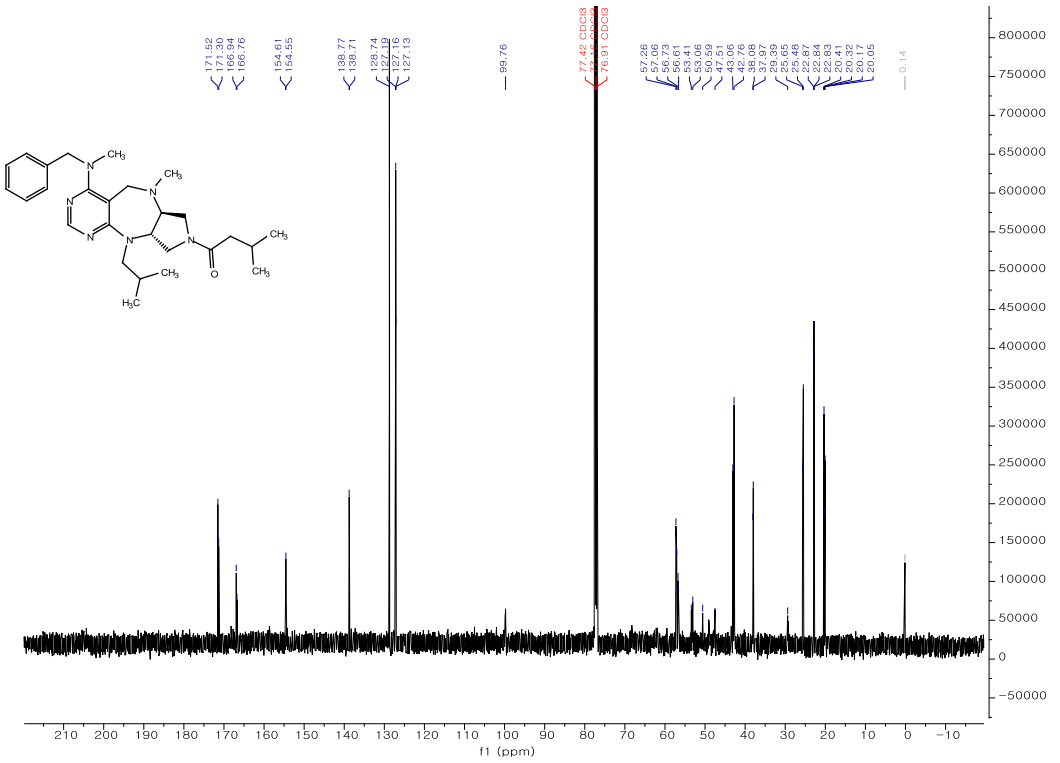
1.70 H2O
f1 (ppm)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127.13
99.76
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
57.26
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56.73
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53.41
53.06
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43.06
42.76
39.99
37.97
29.39
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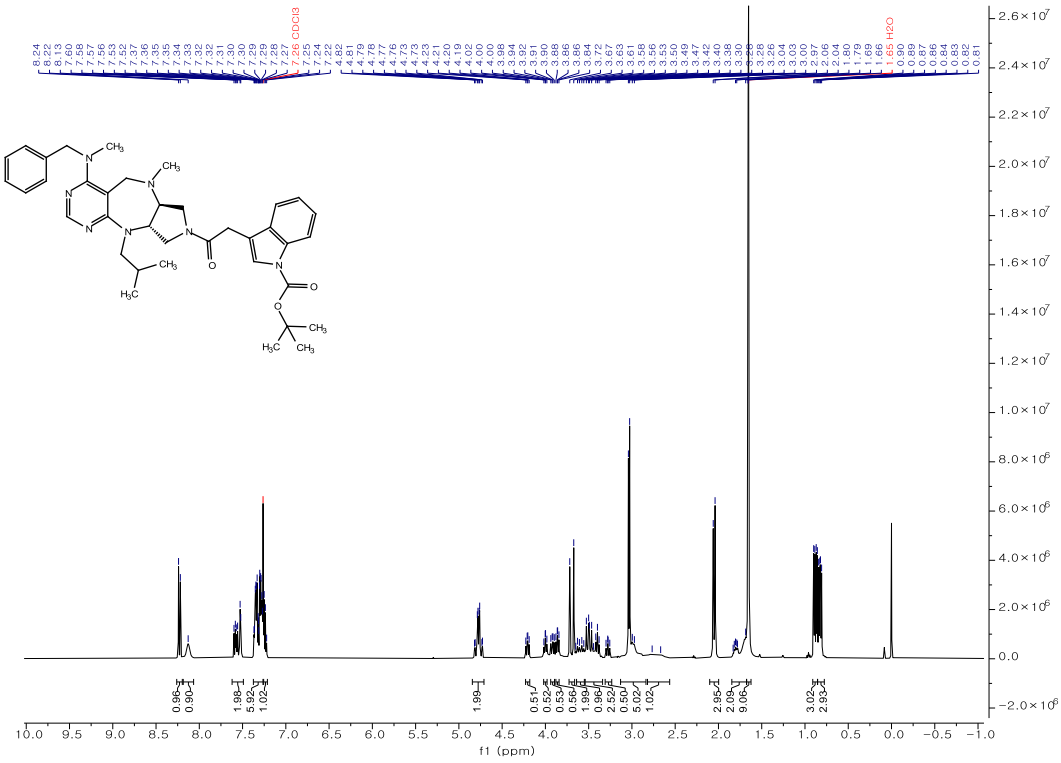
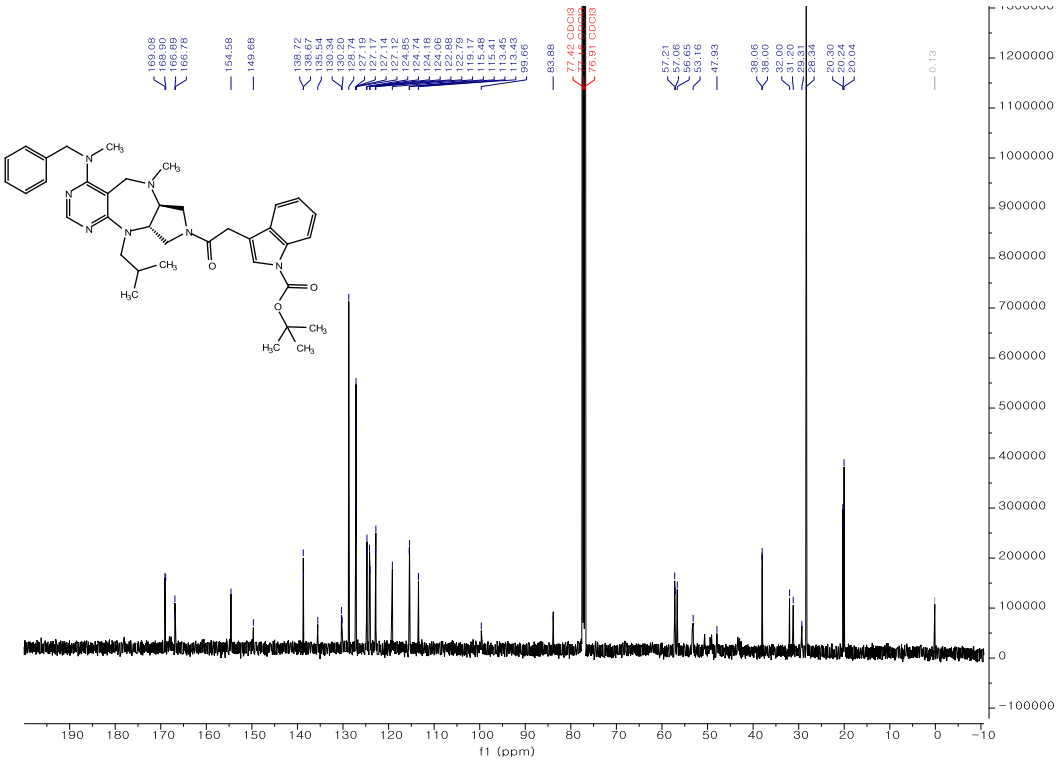
22.84
22.83
20.41
20.22
20.17
20.05
0.14
f1 (ppm)

2f'





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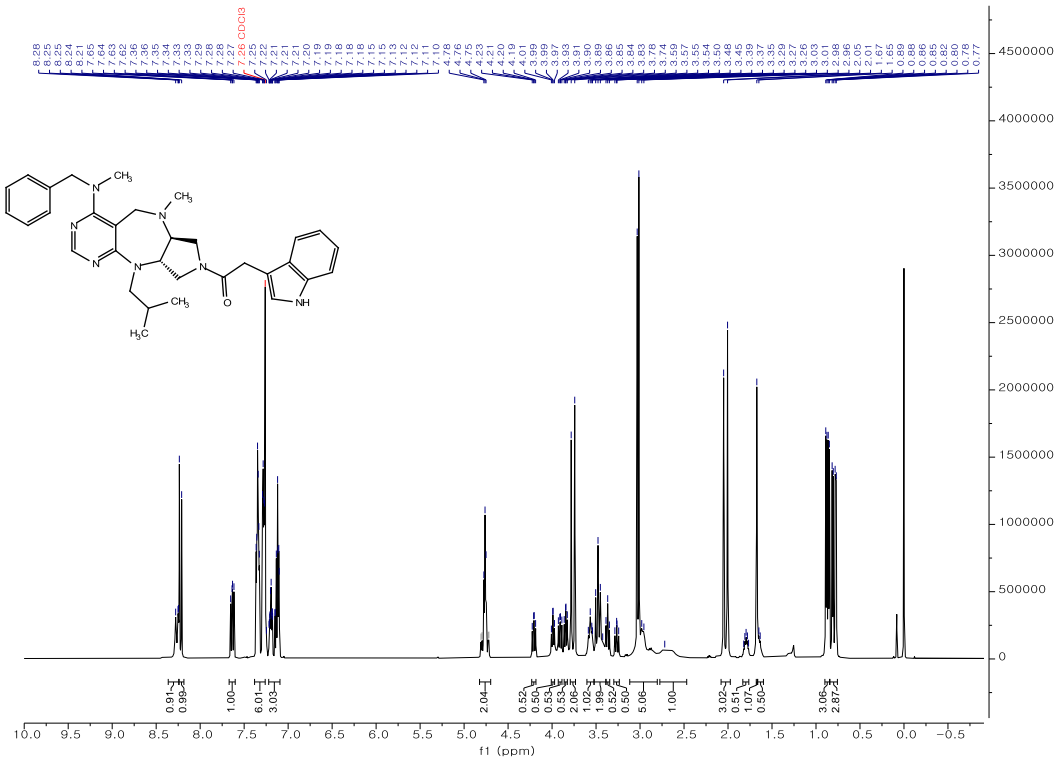
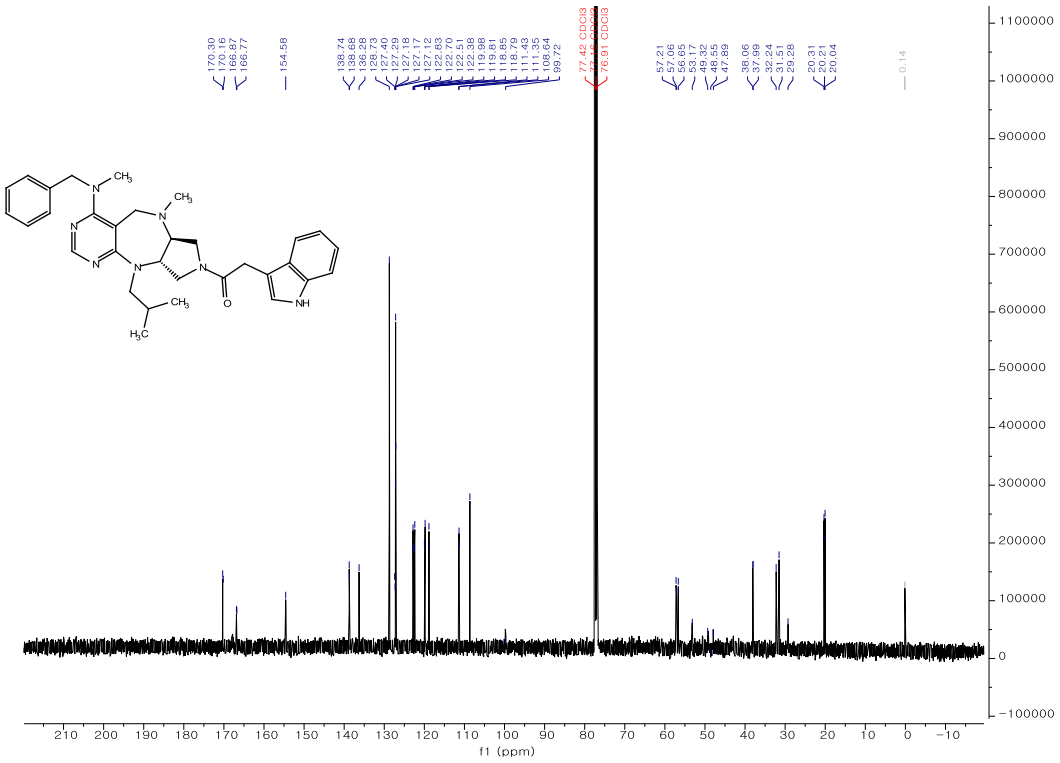
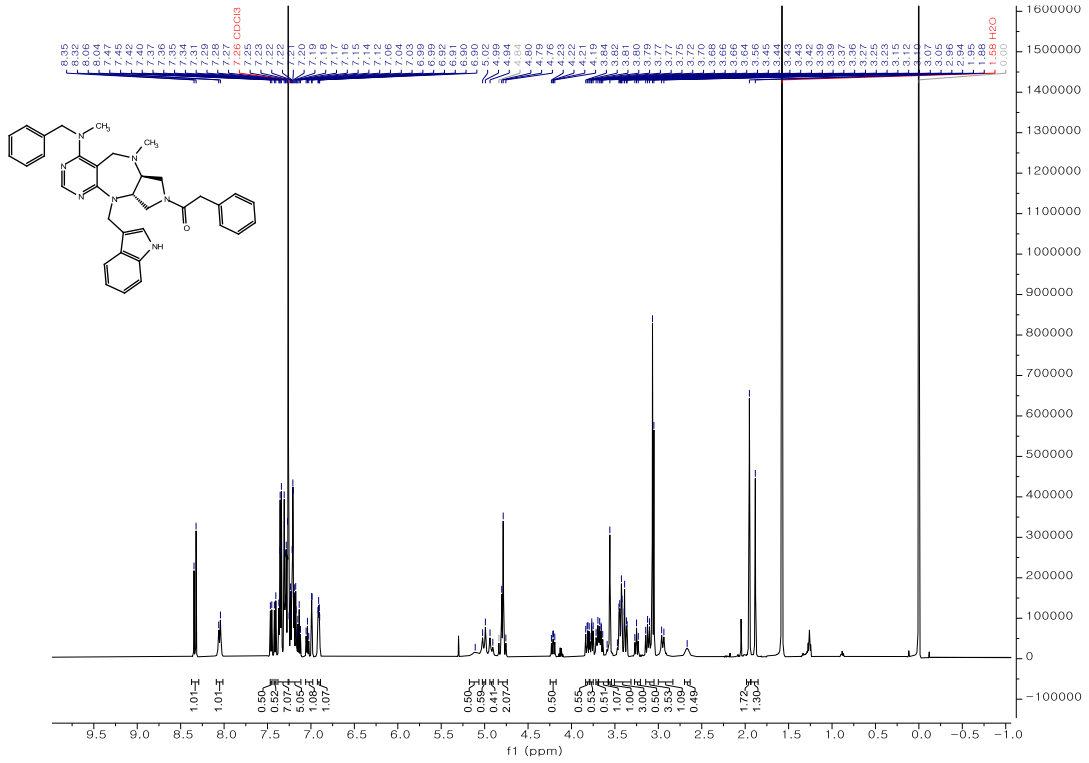
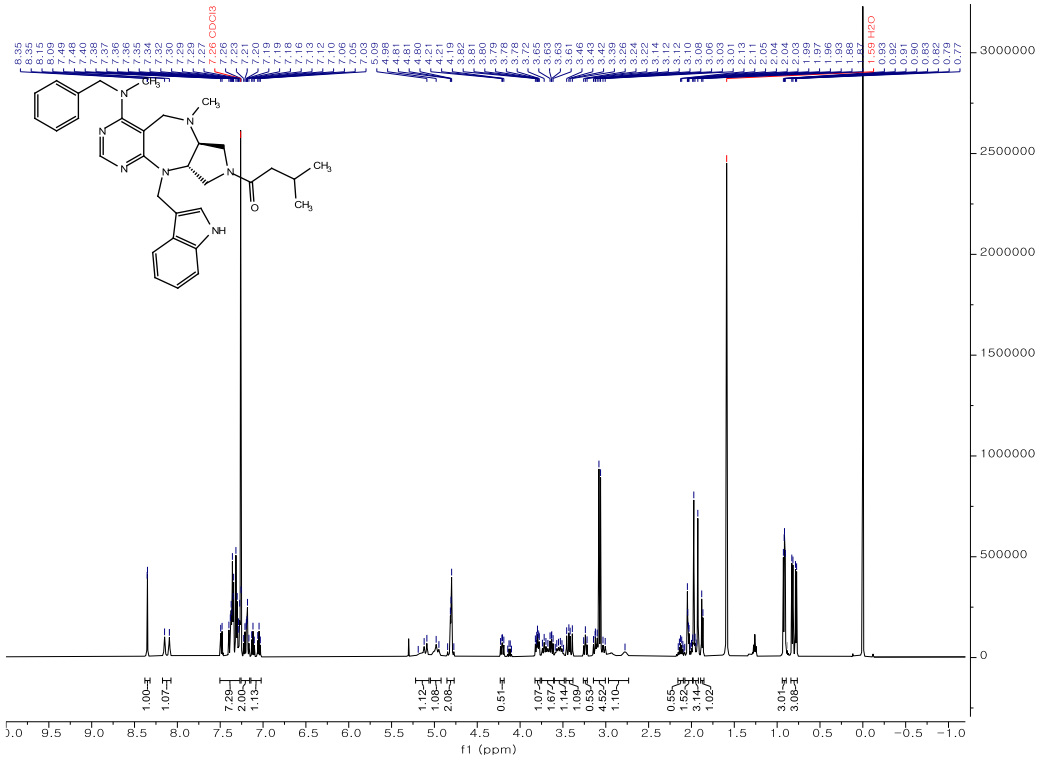




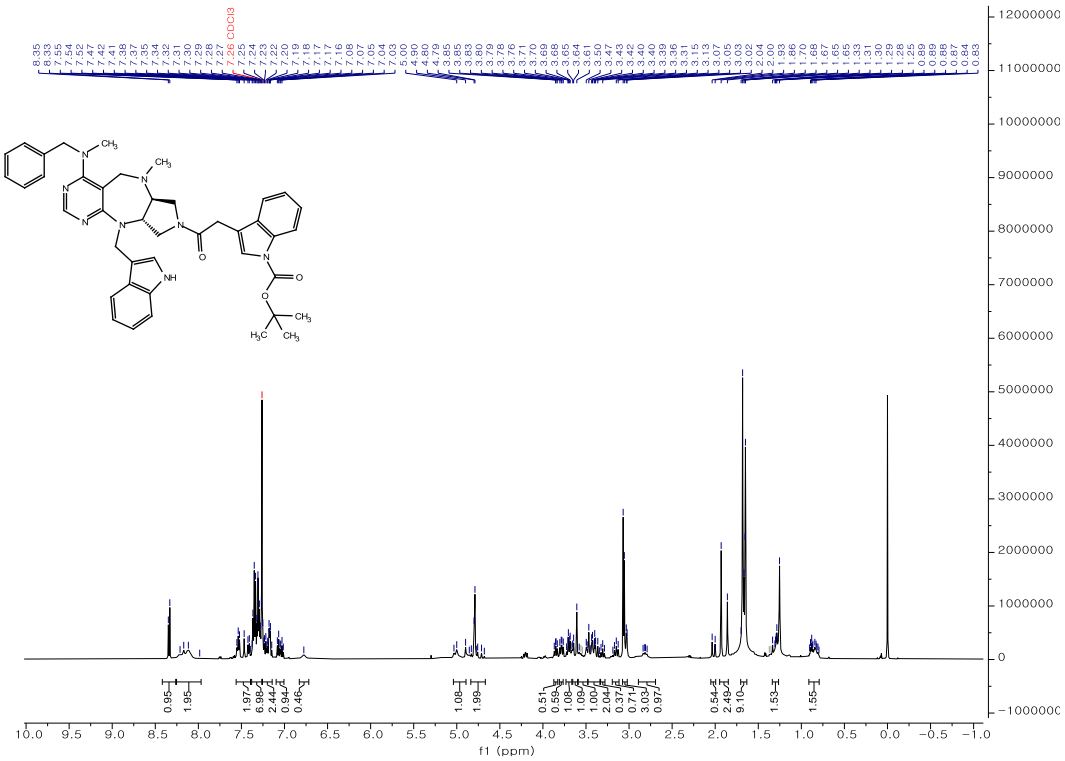
2g

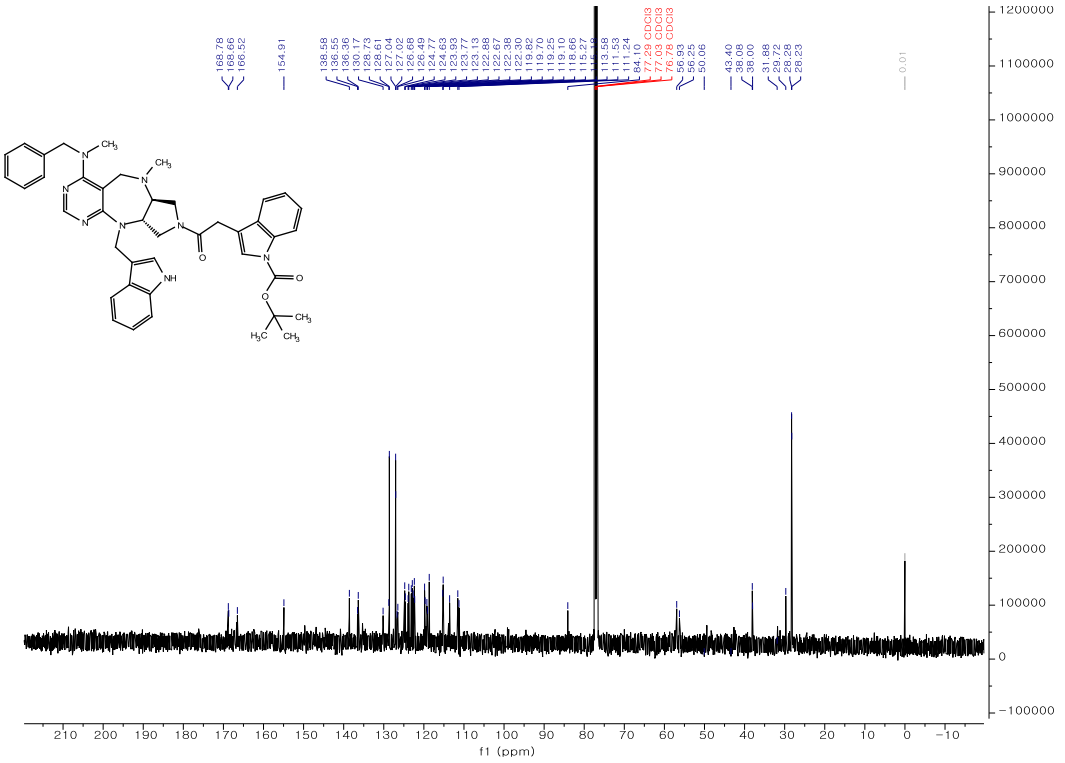


2h

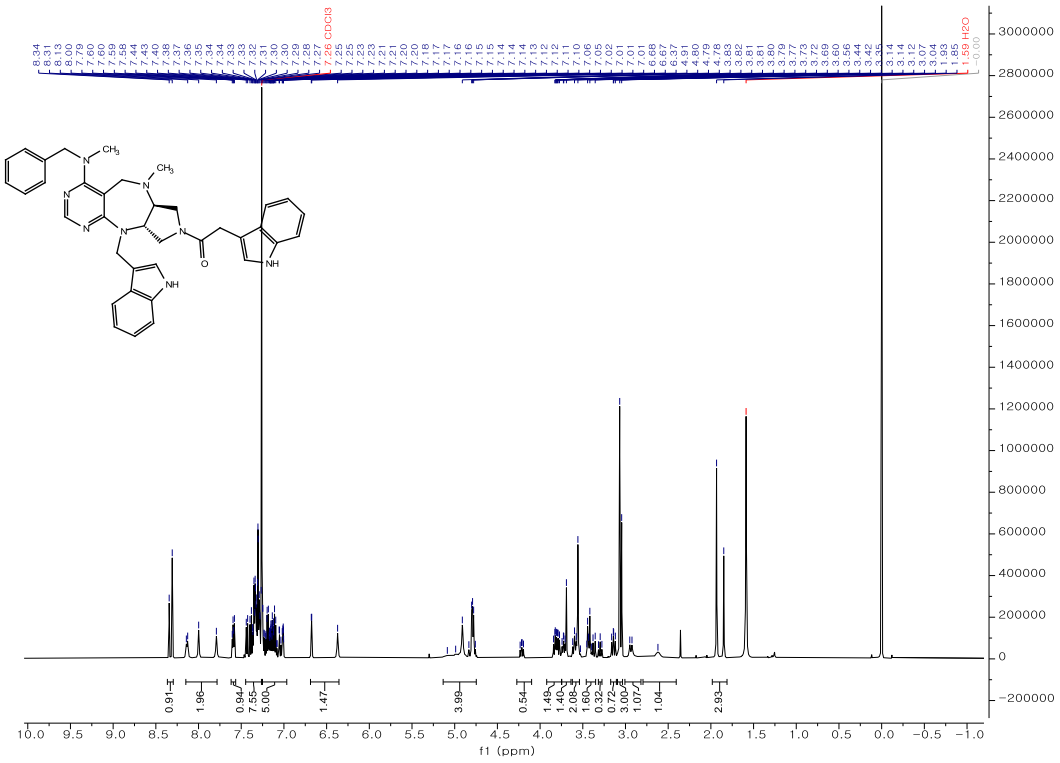


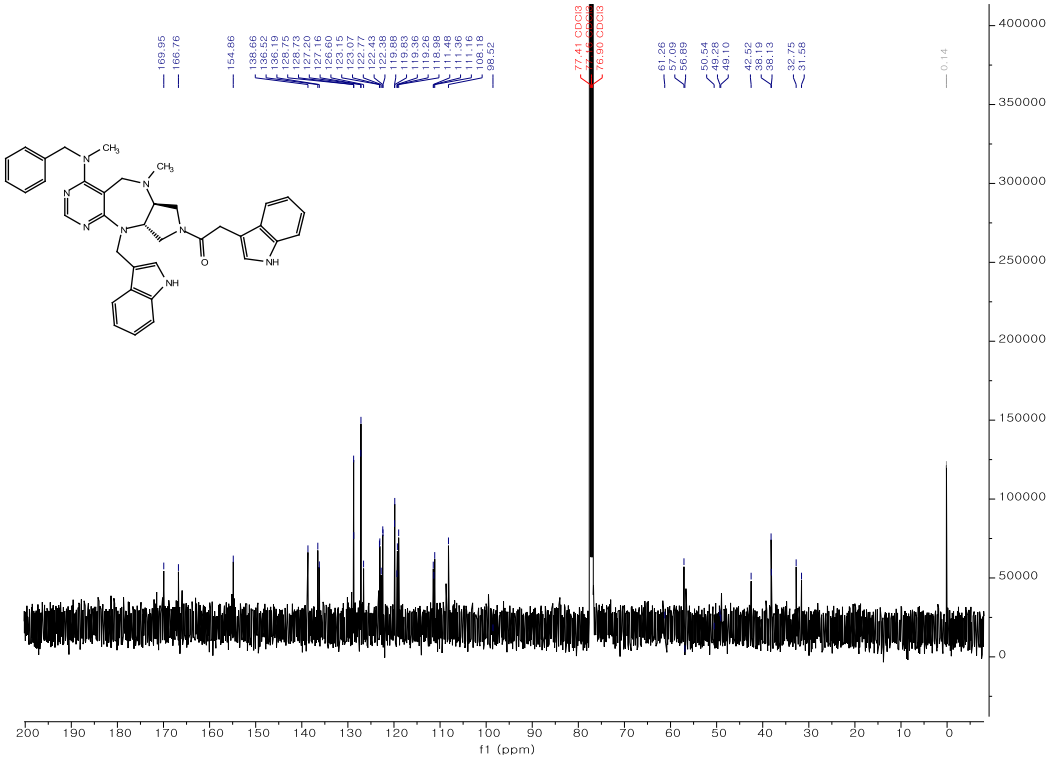
2i’





2i





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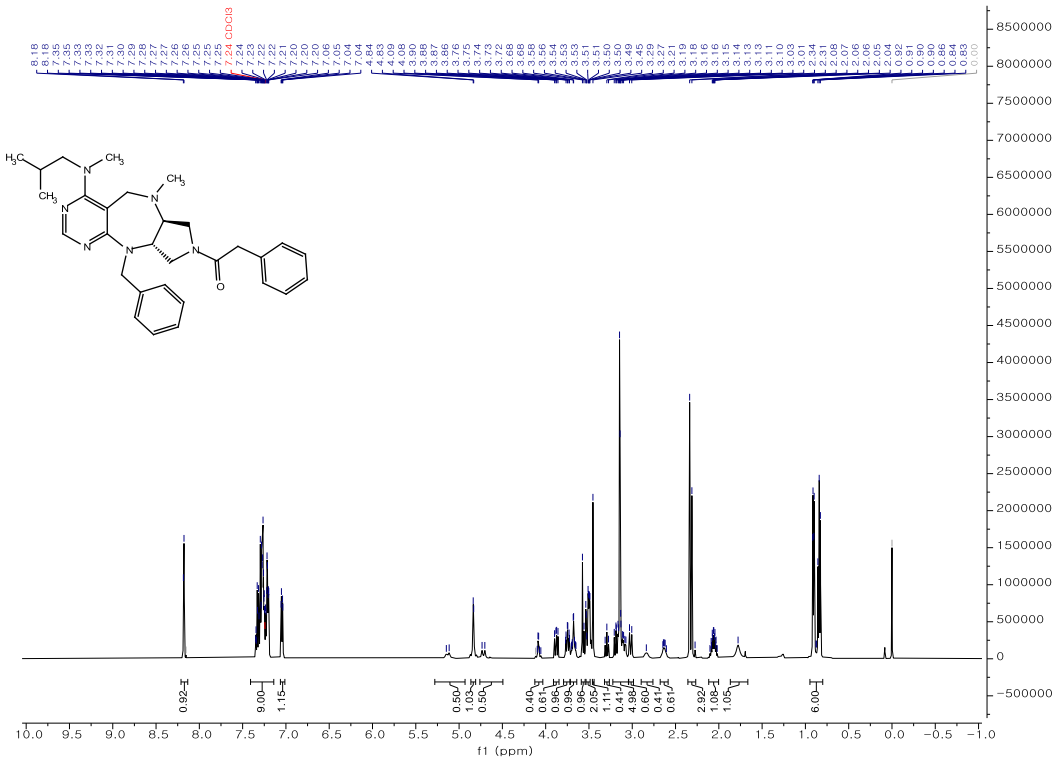

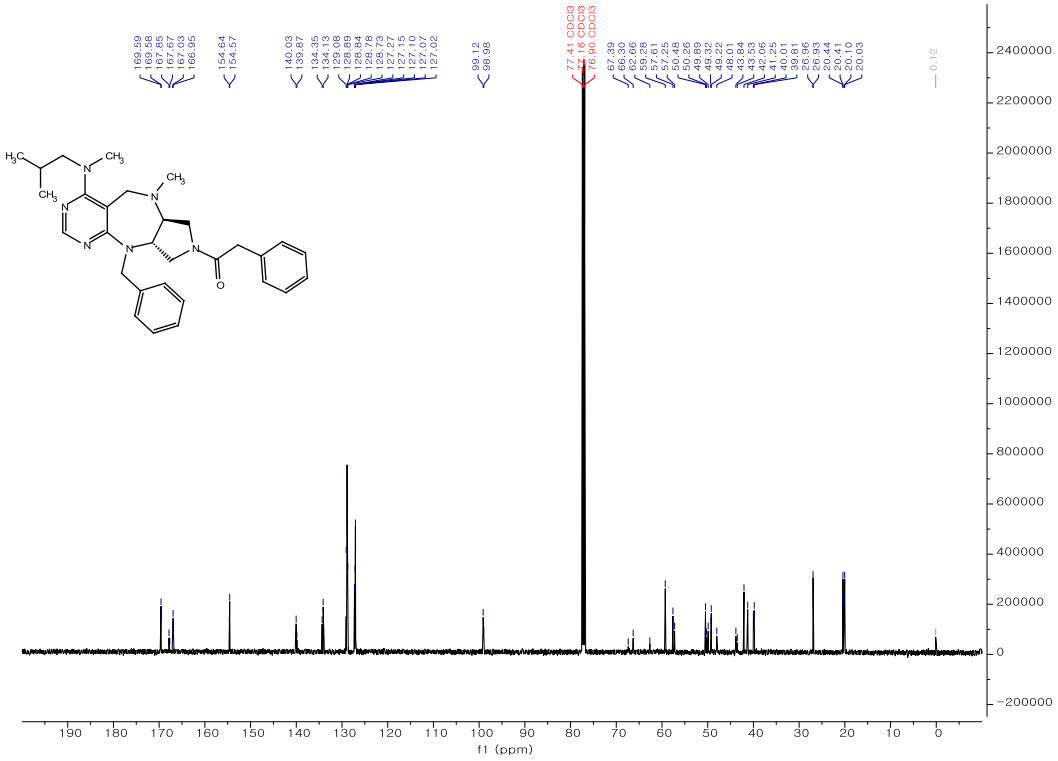

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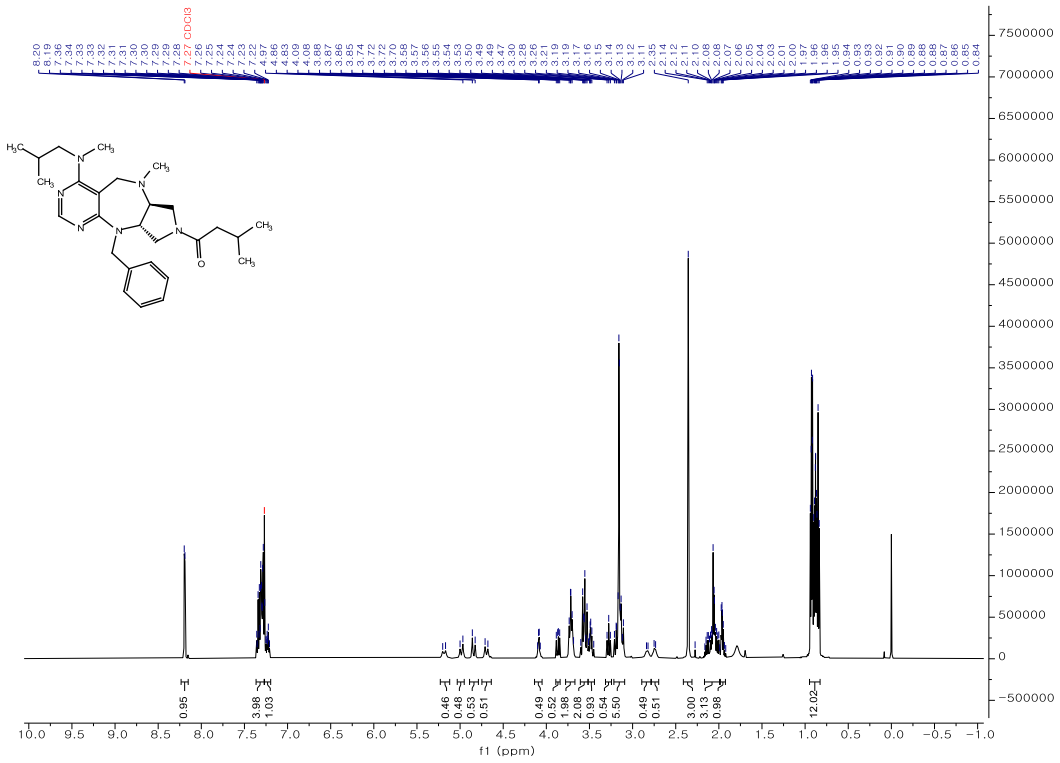

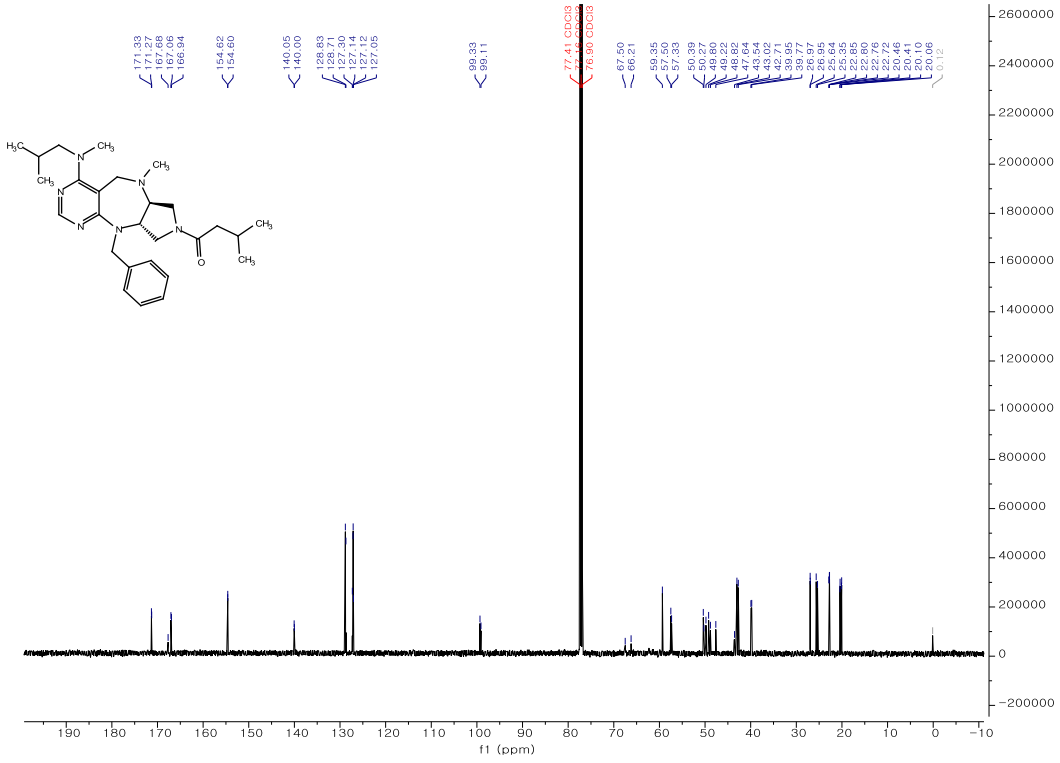

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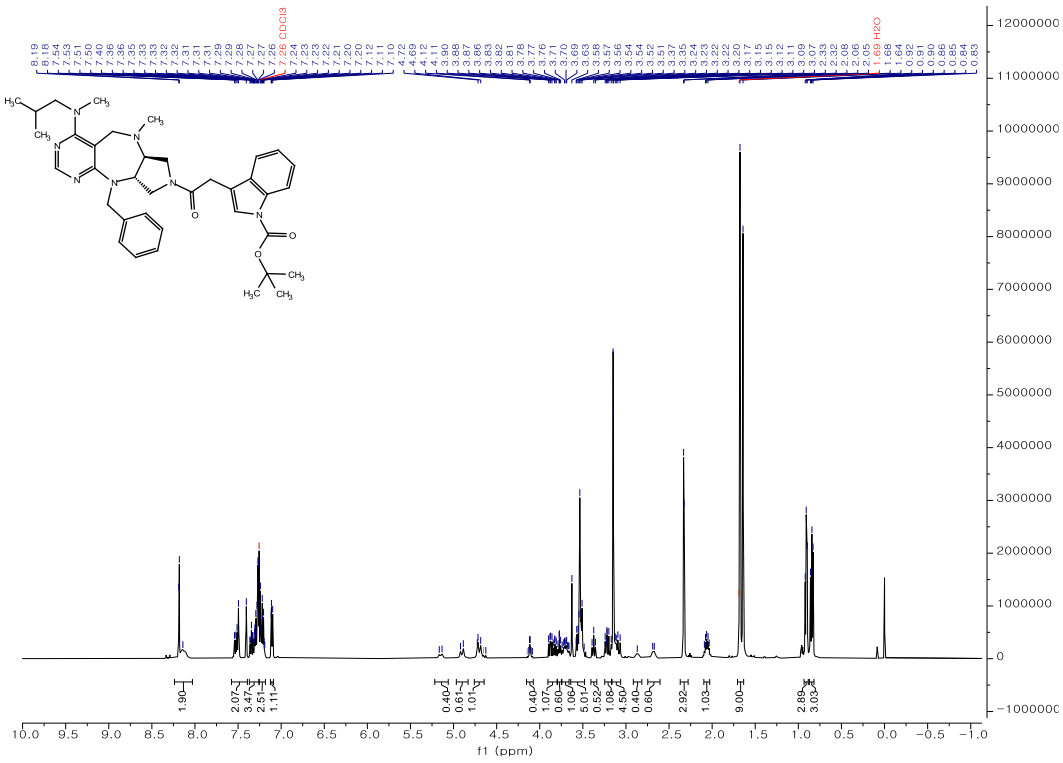

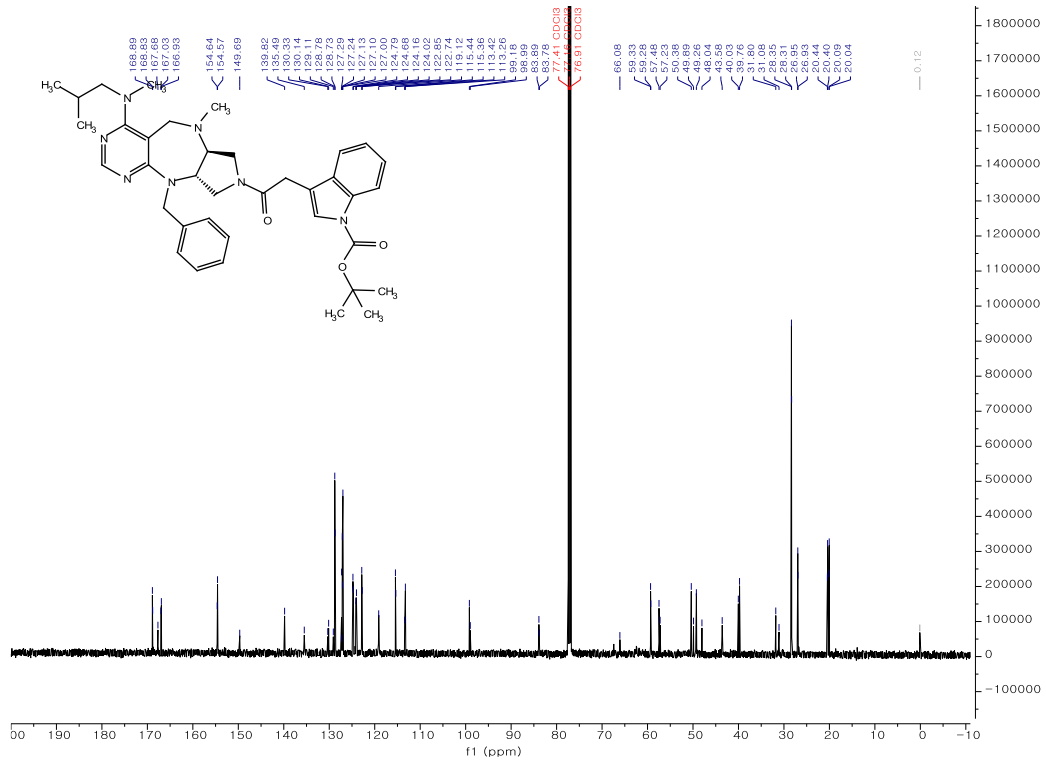

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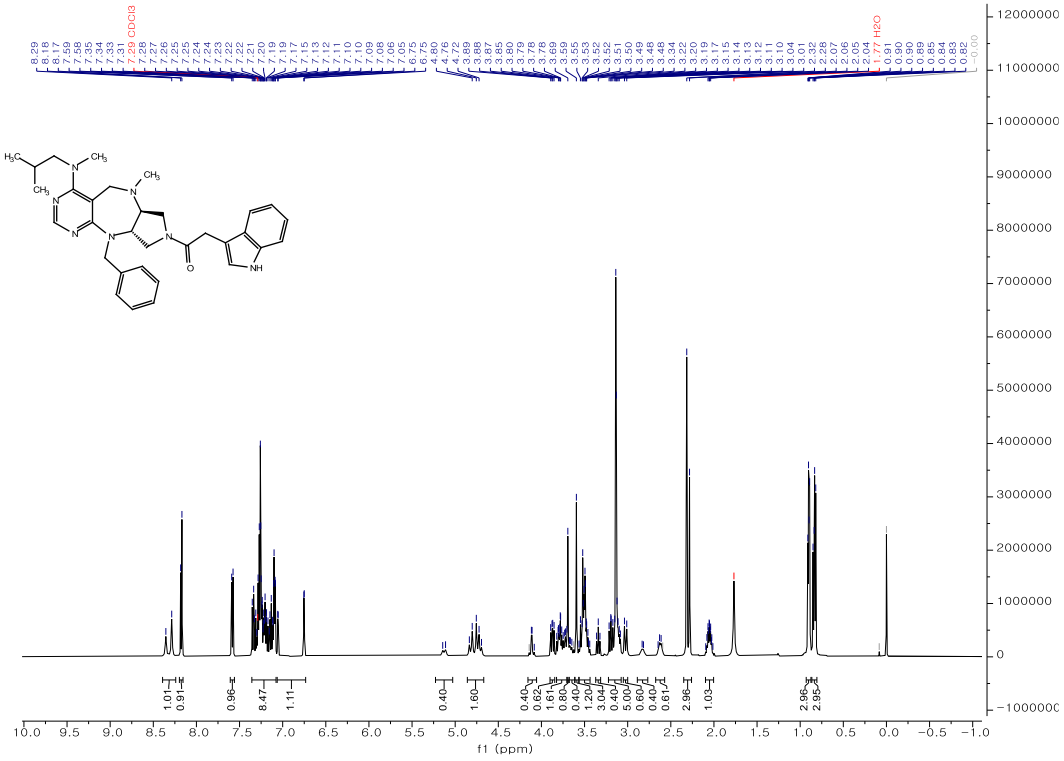

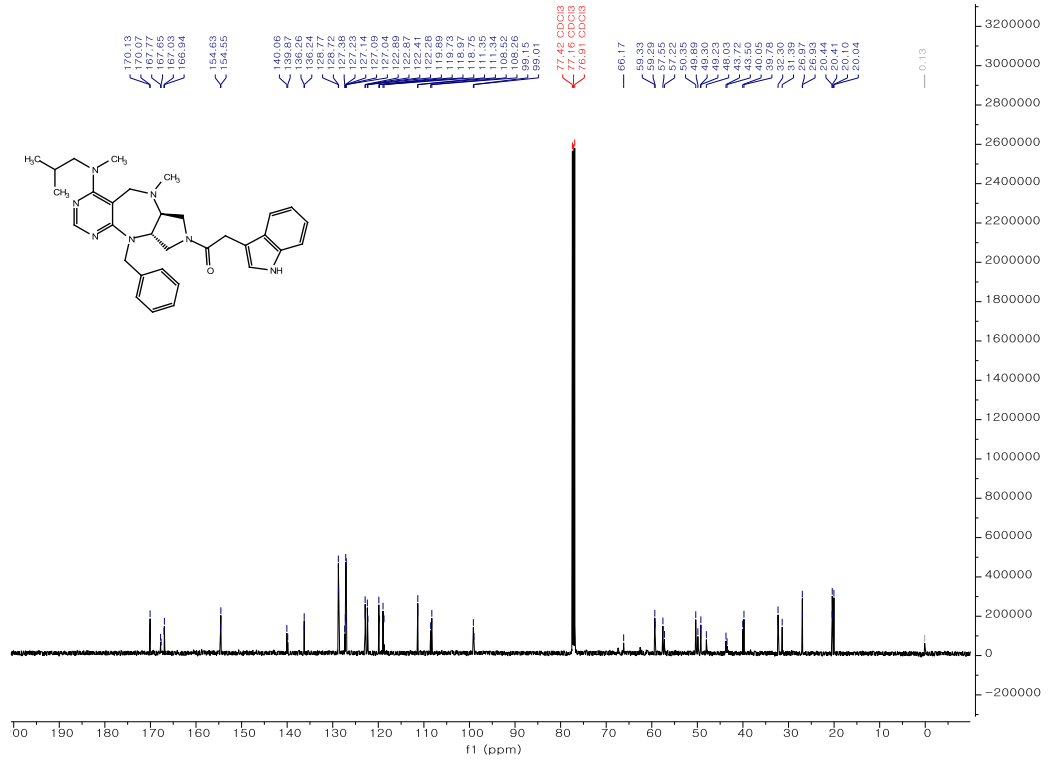

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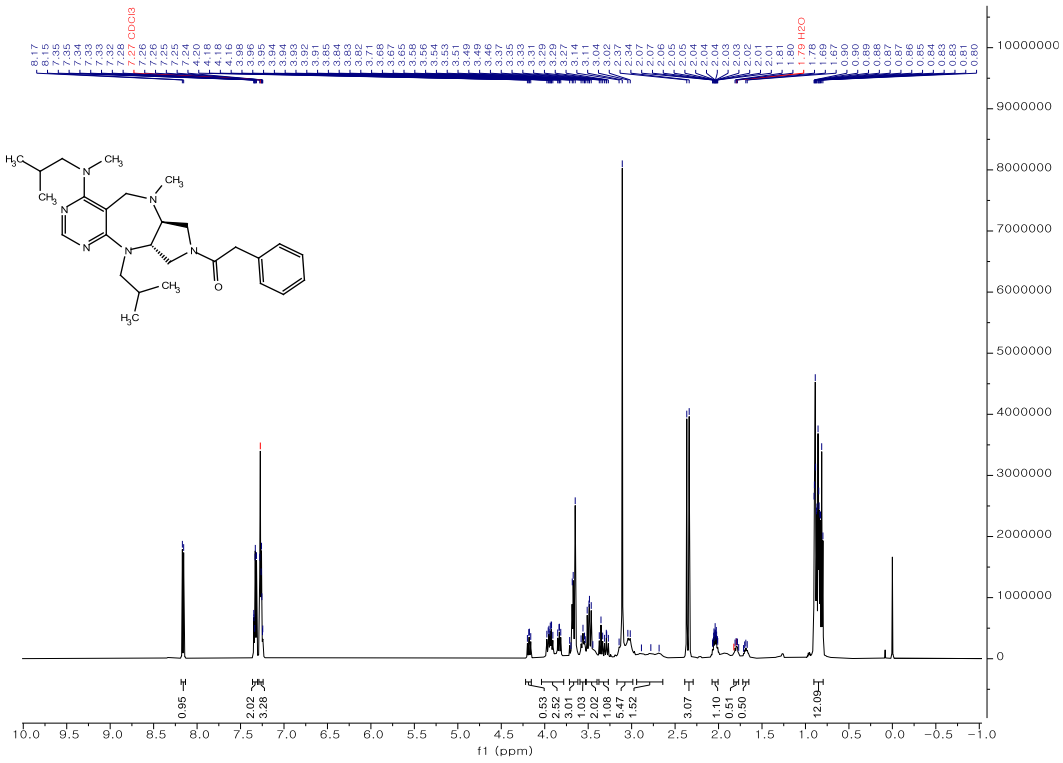

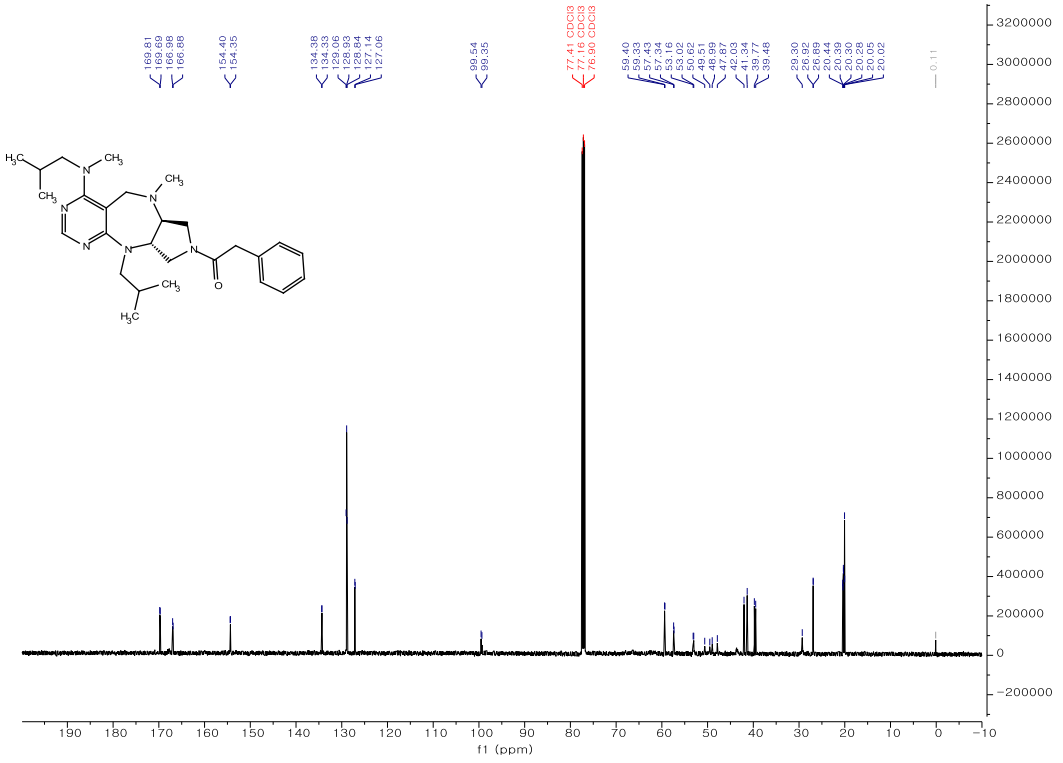

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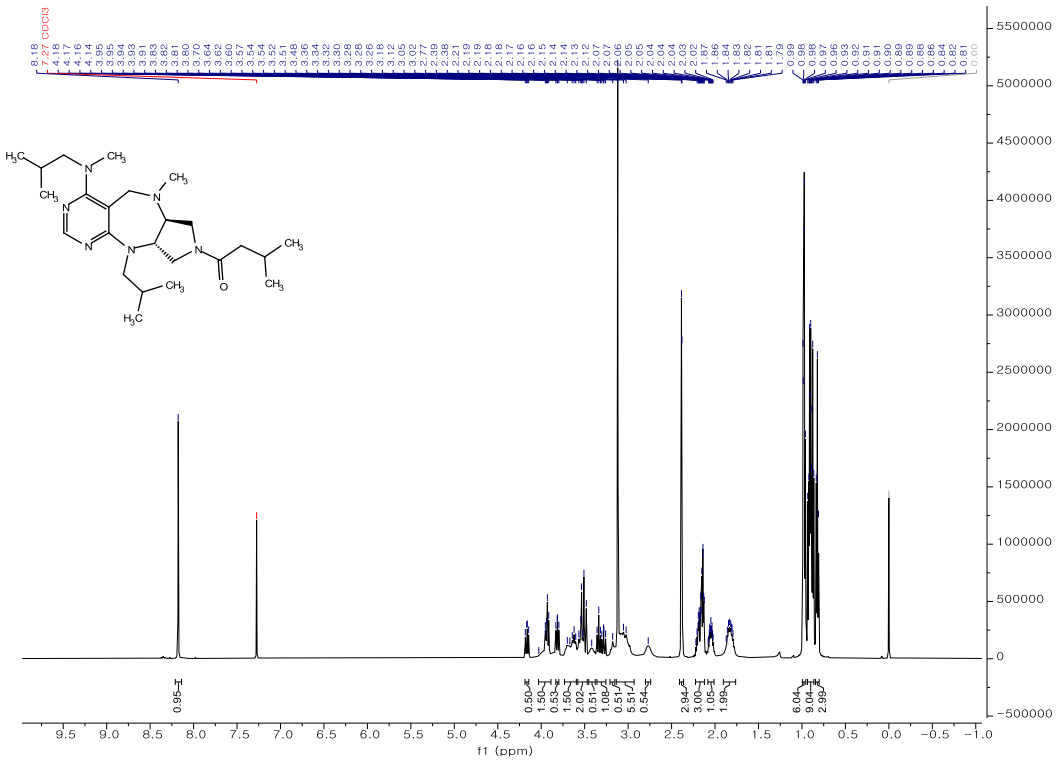

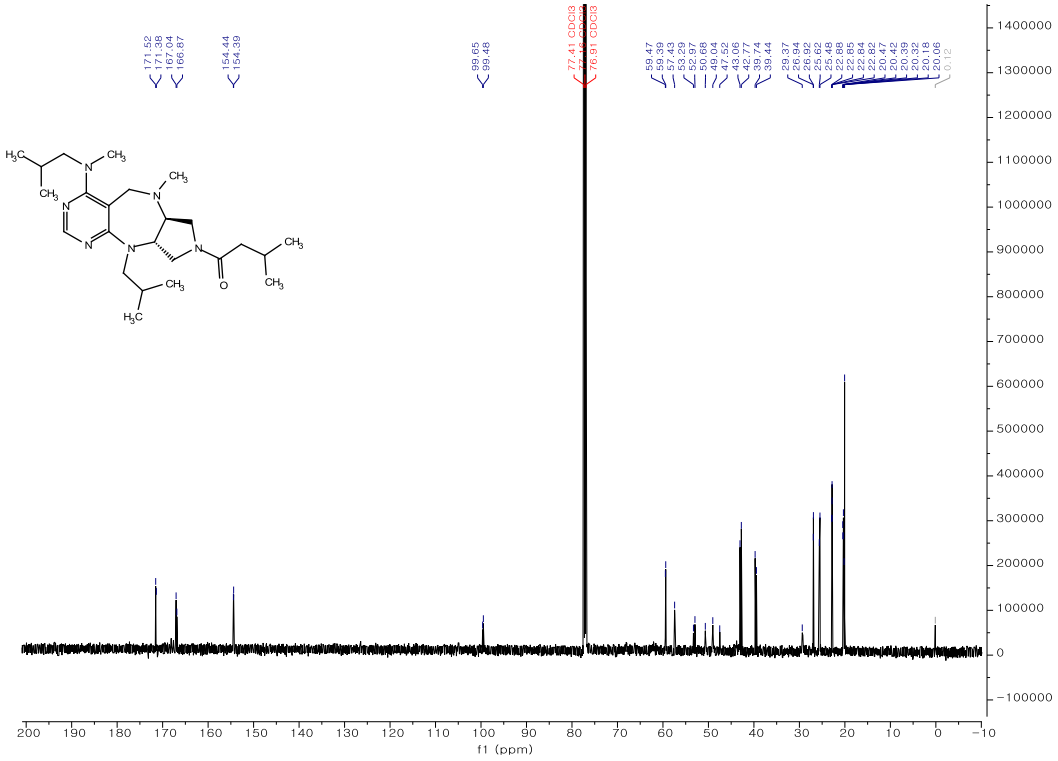

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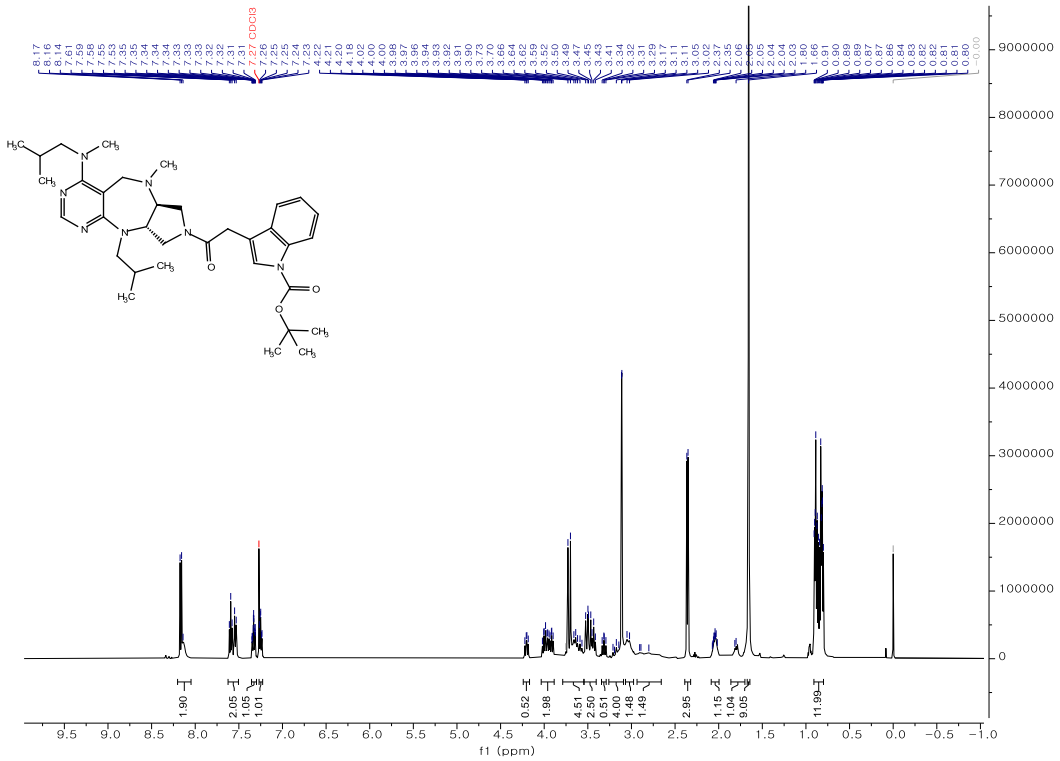

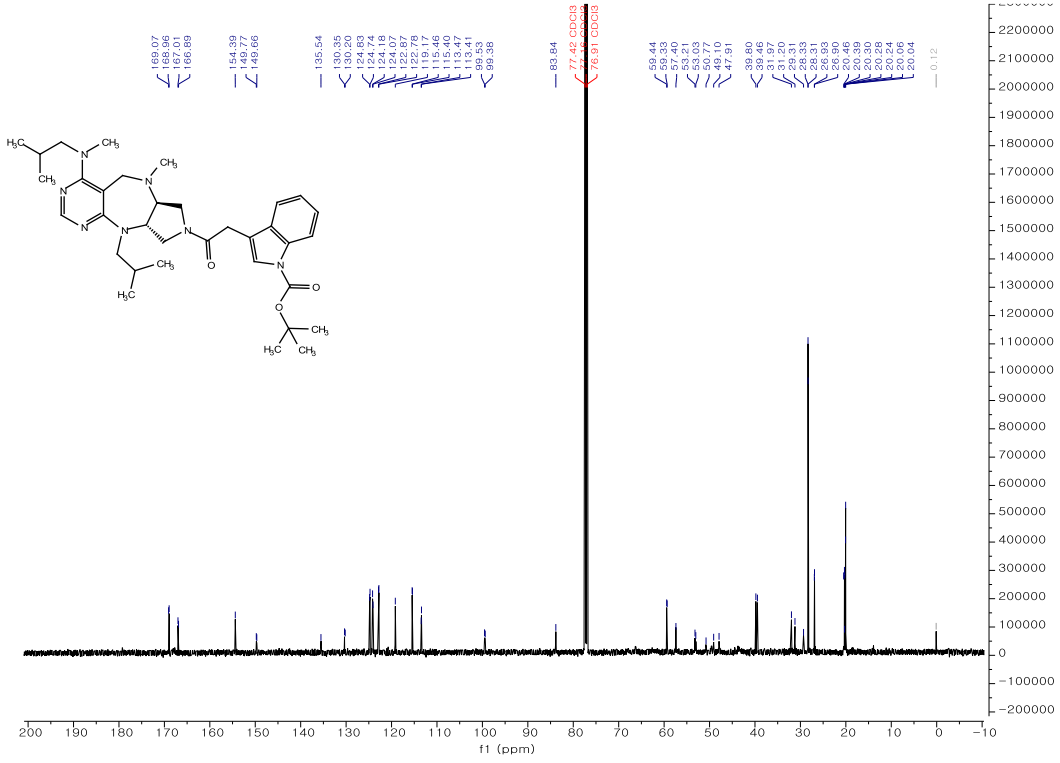

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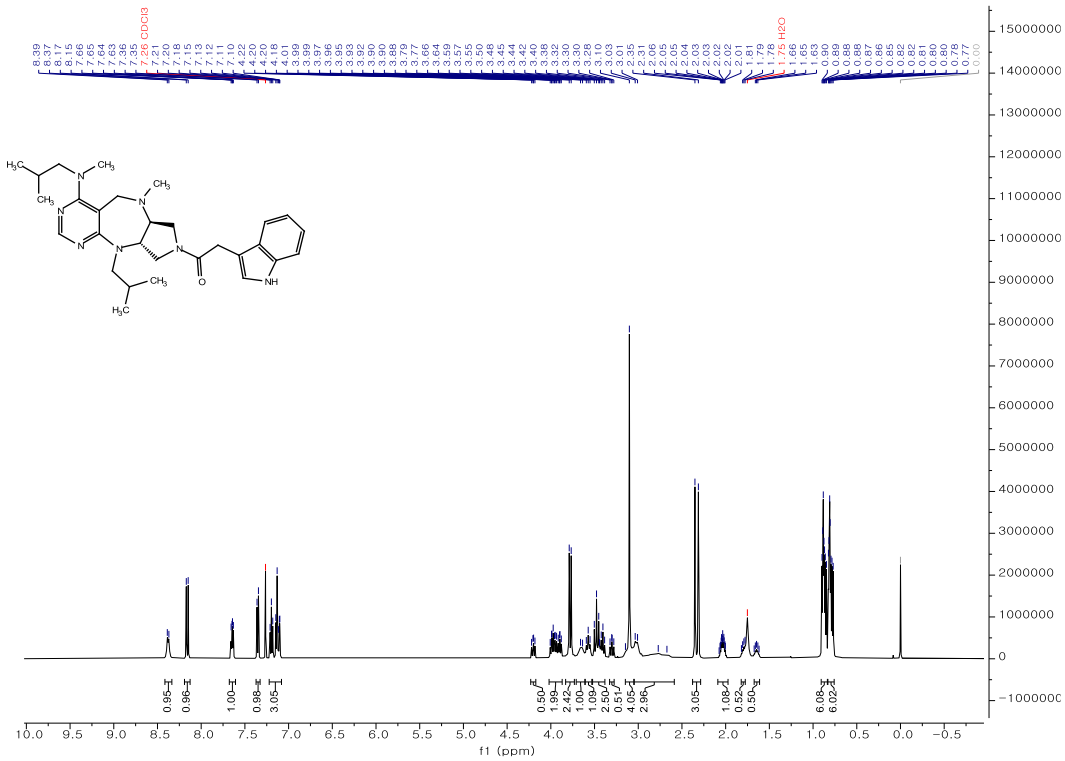

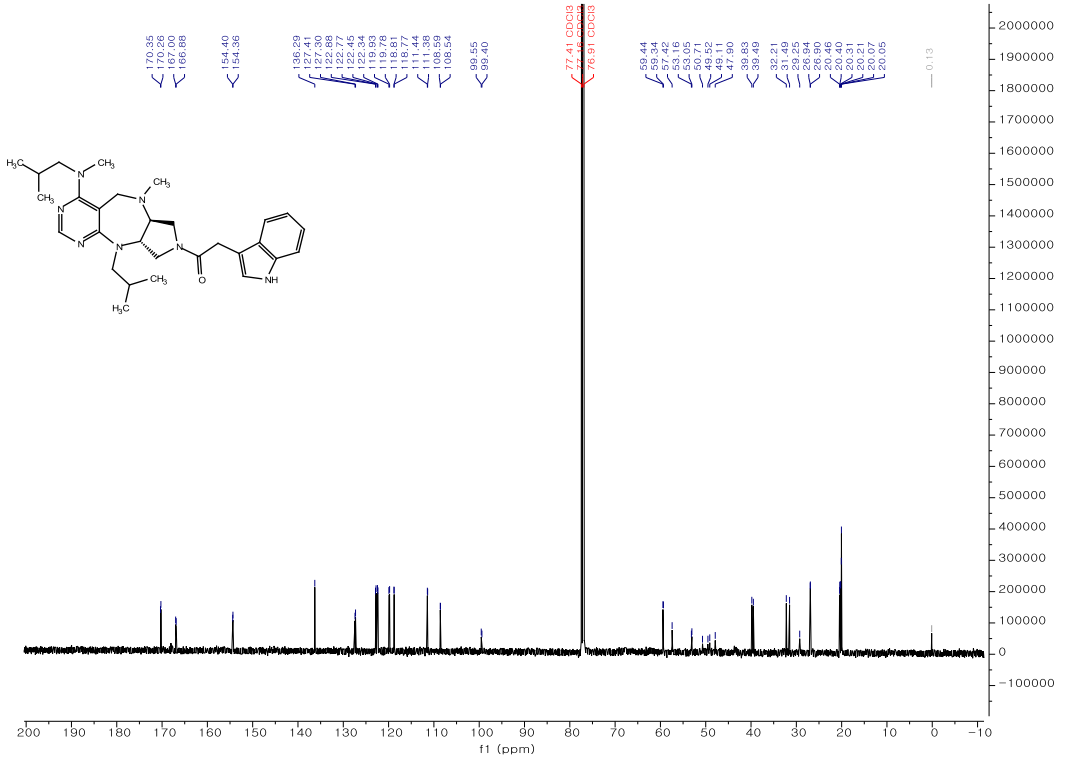

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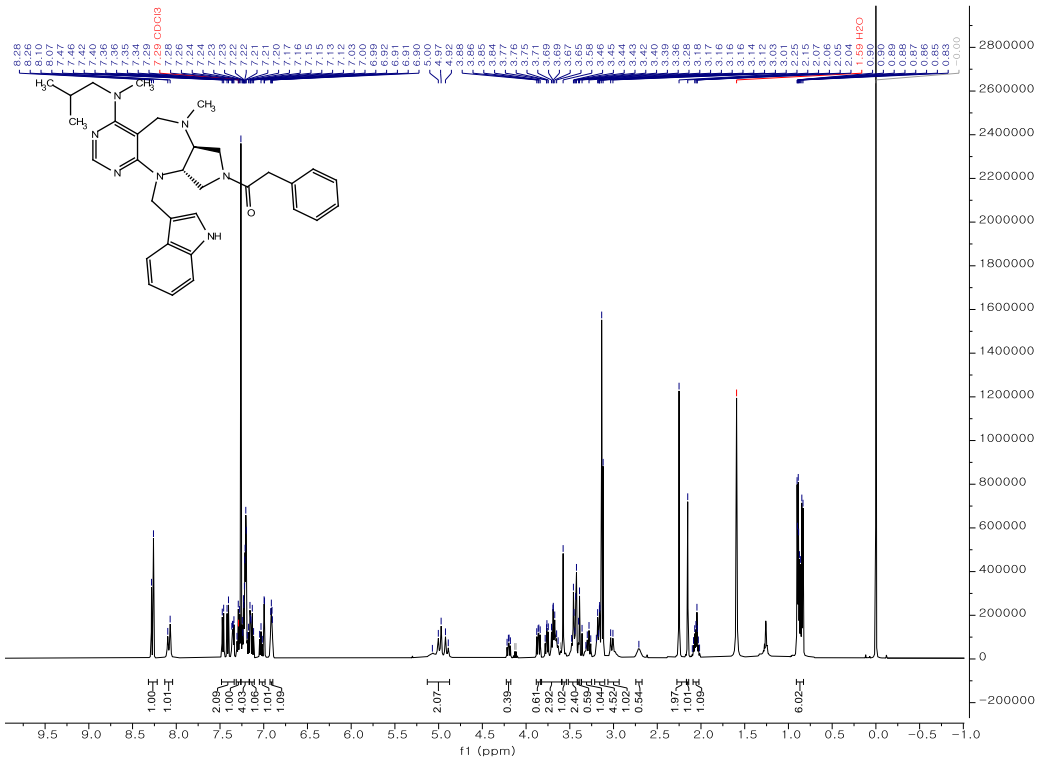

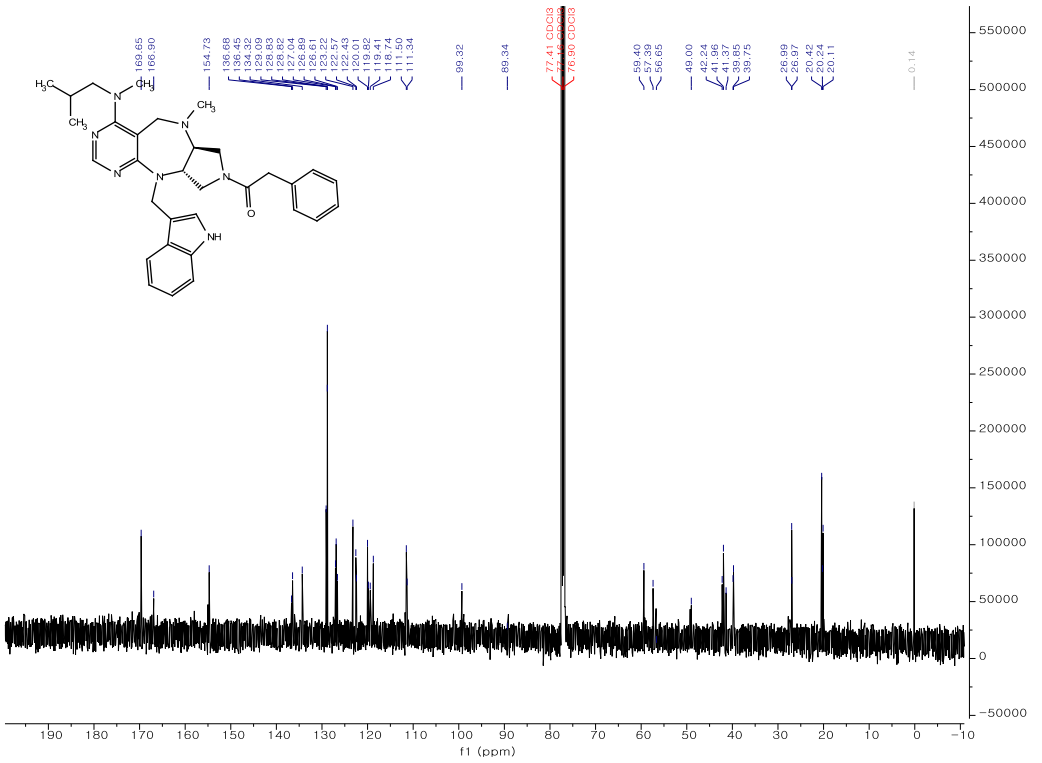

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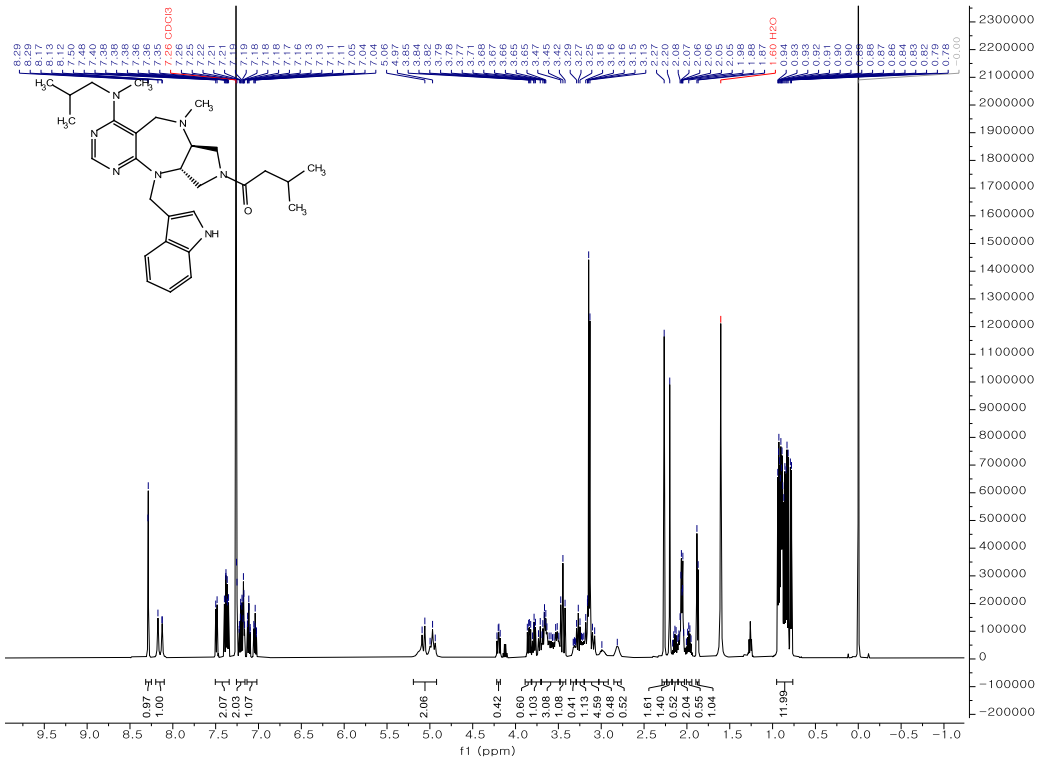

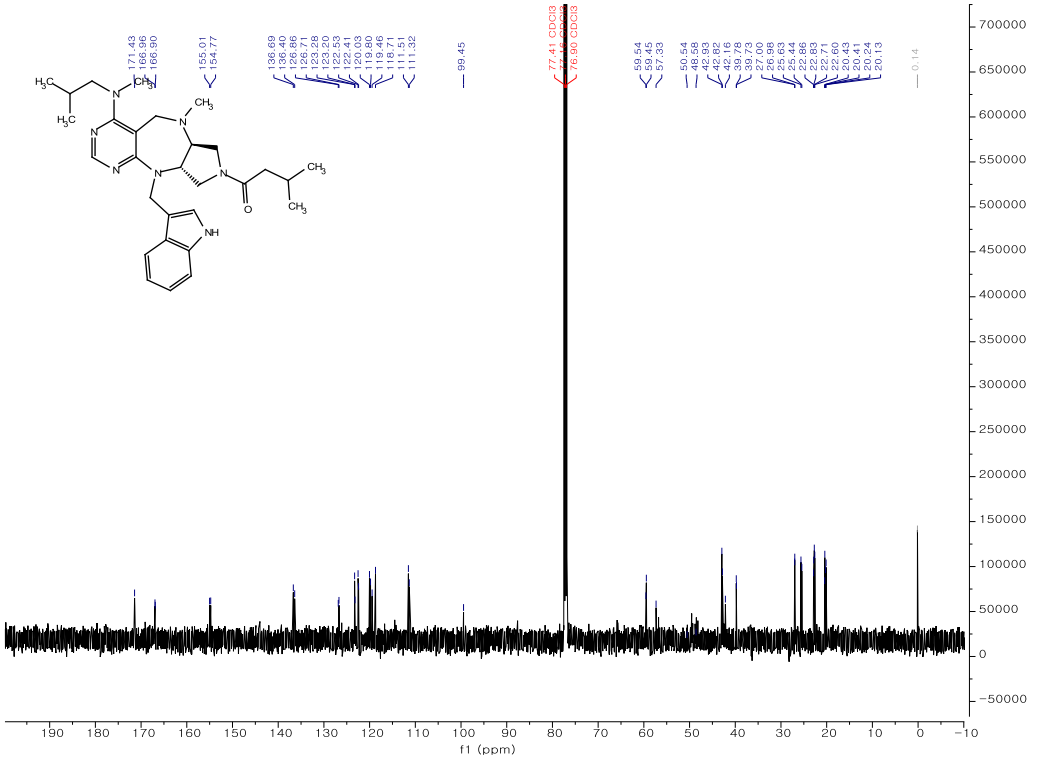

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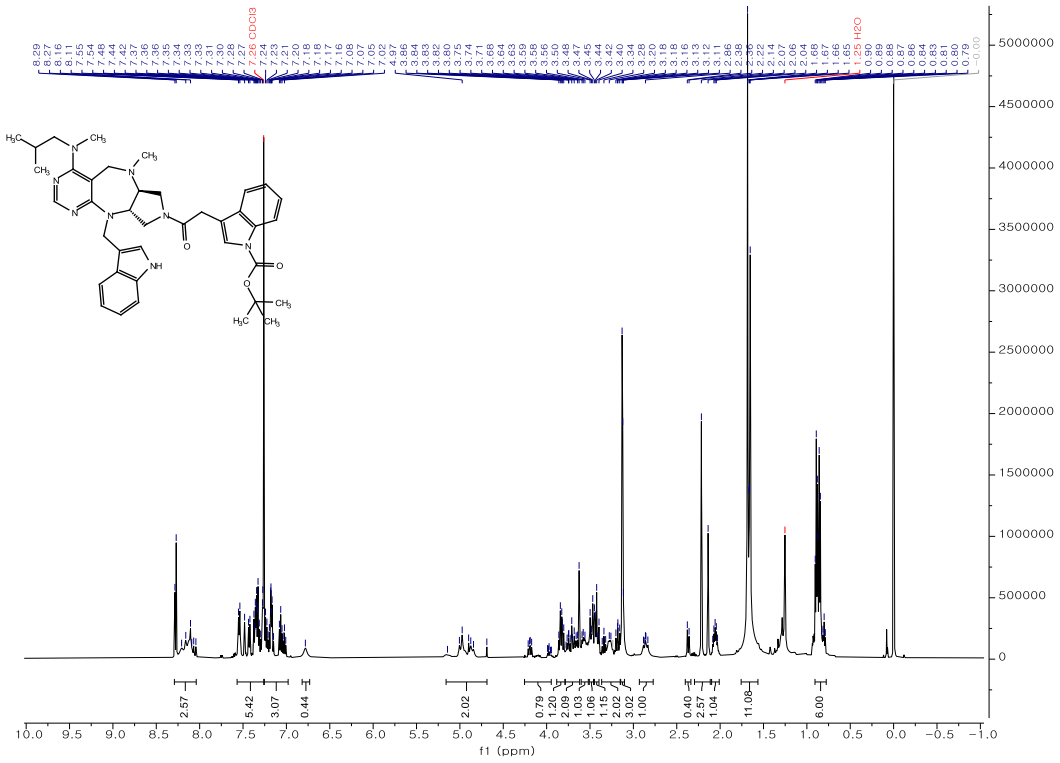

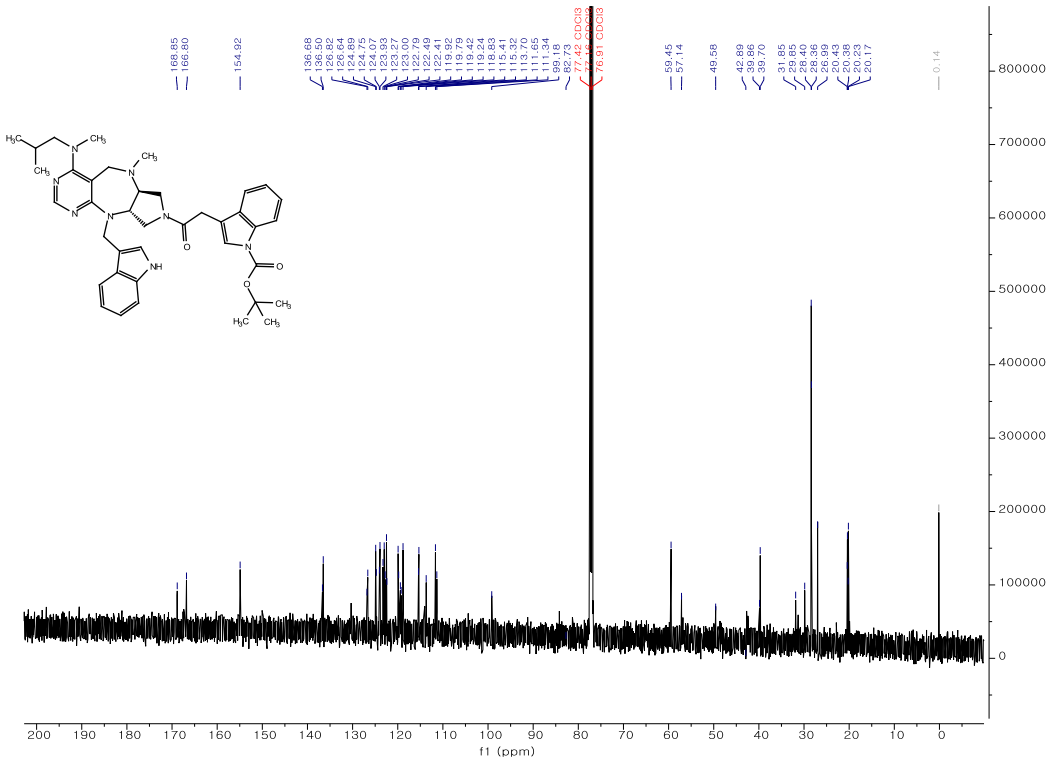

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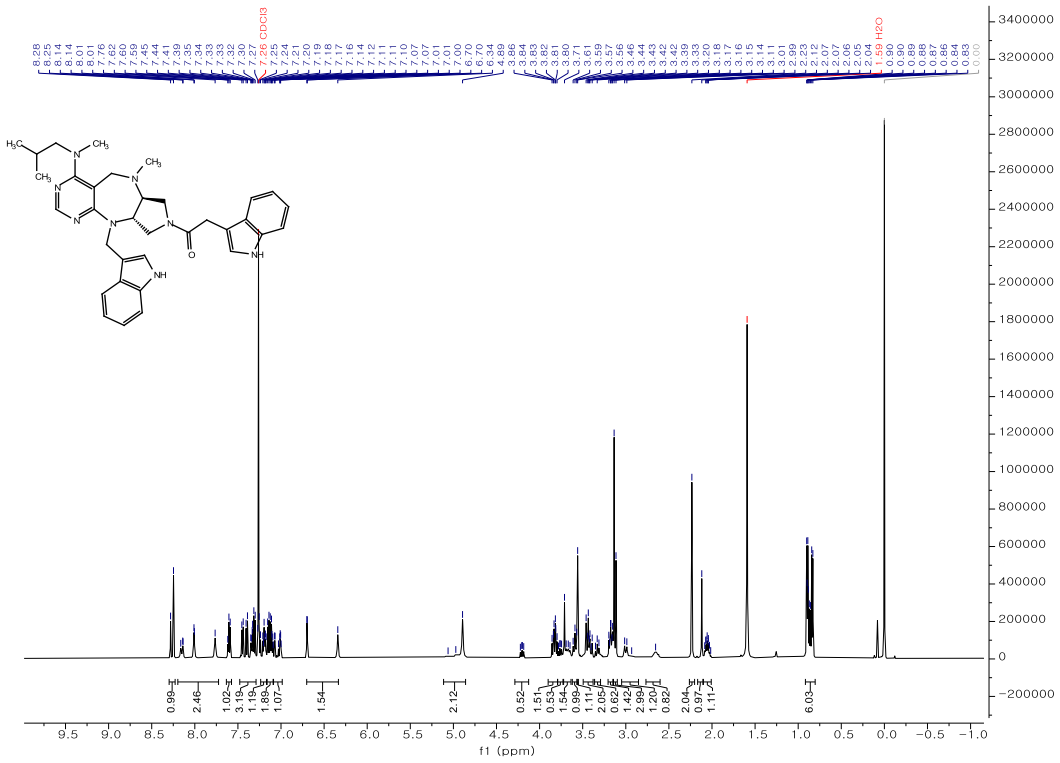

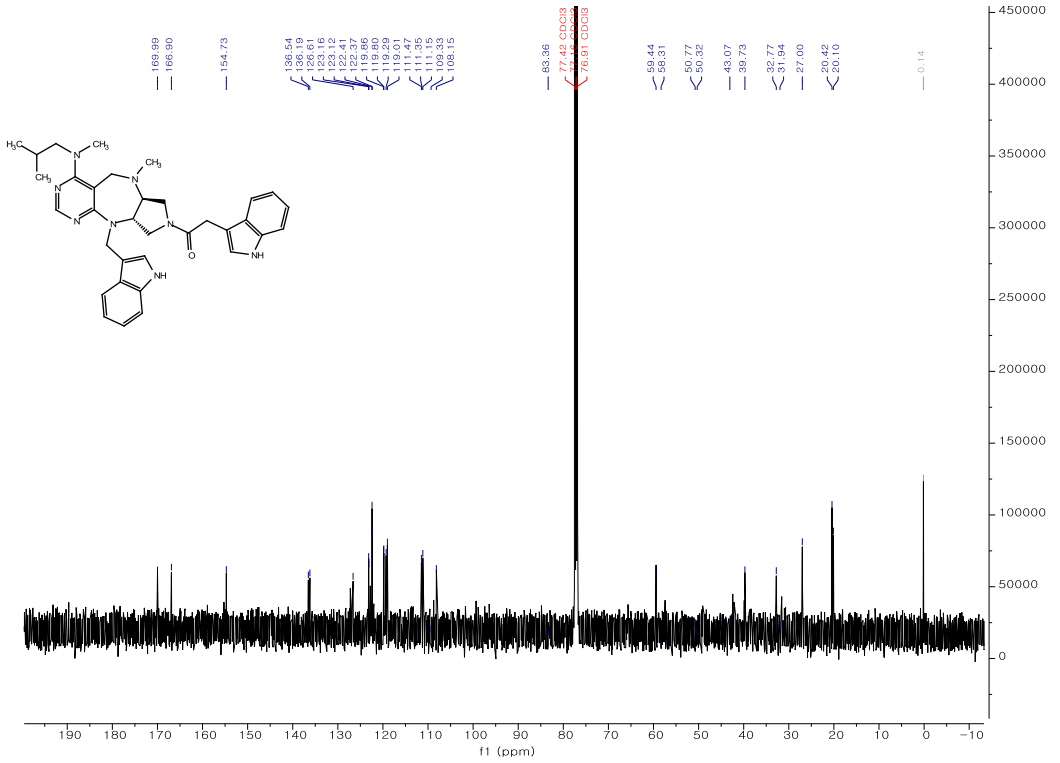

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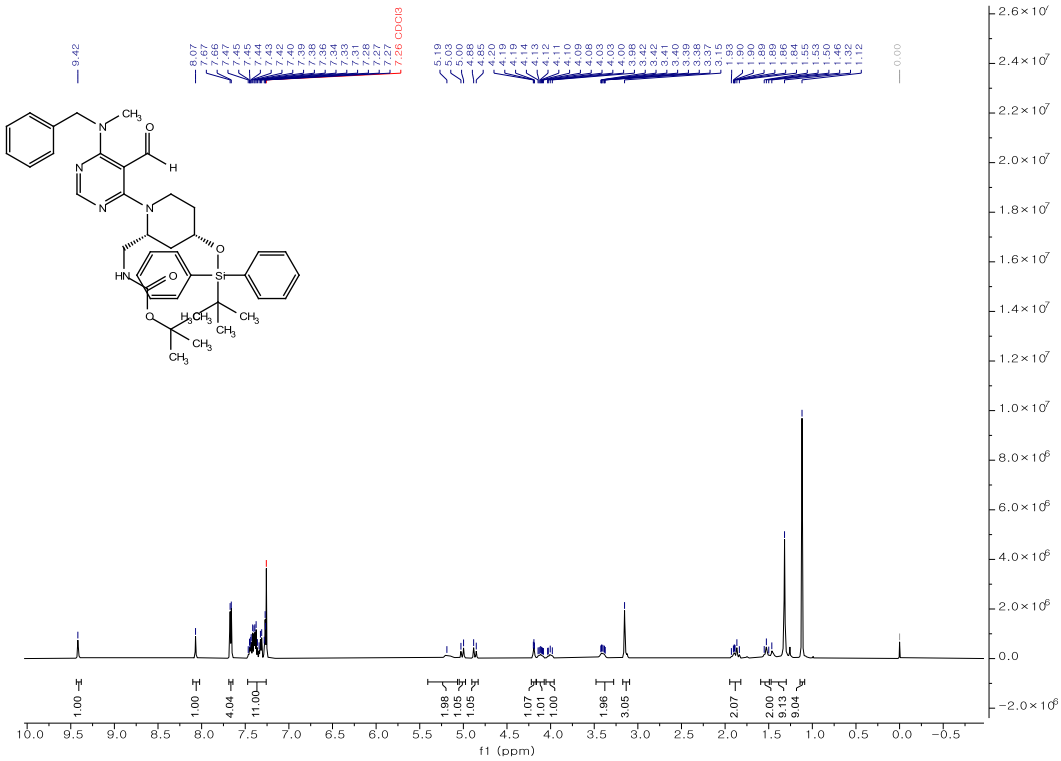

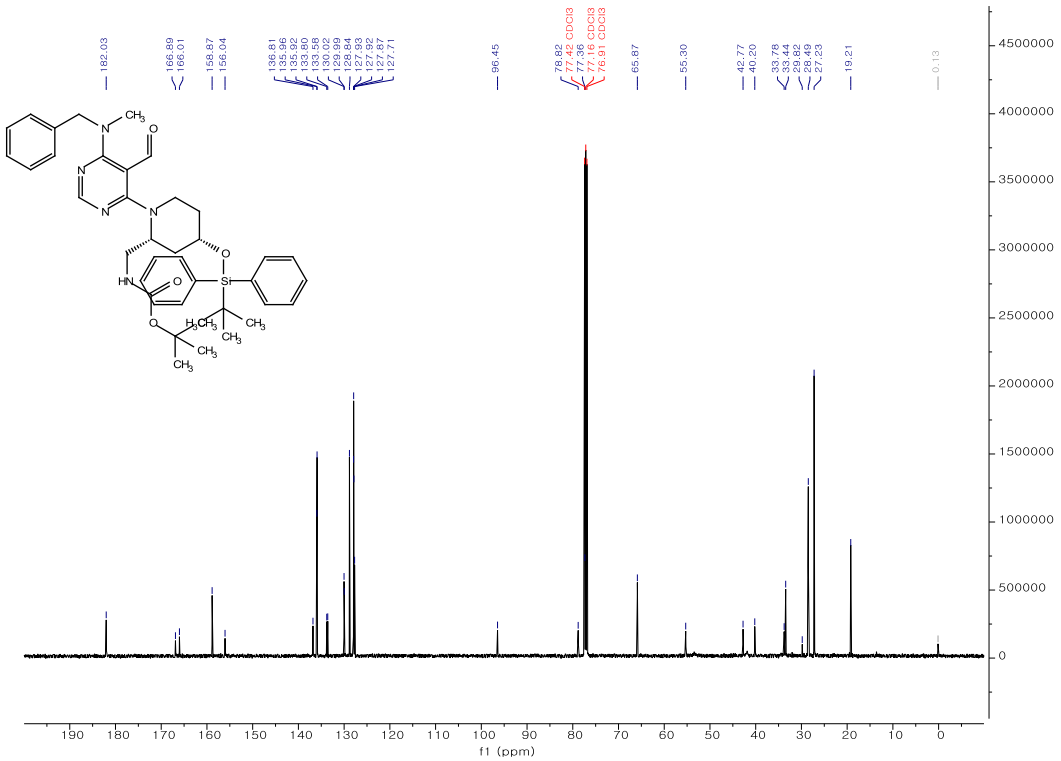

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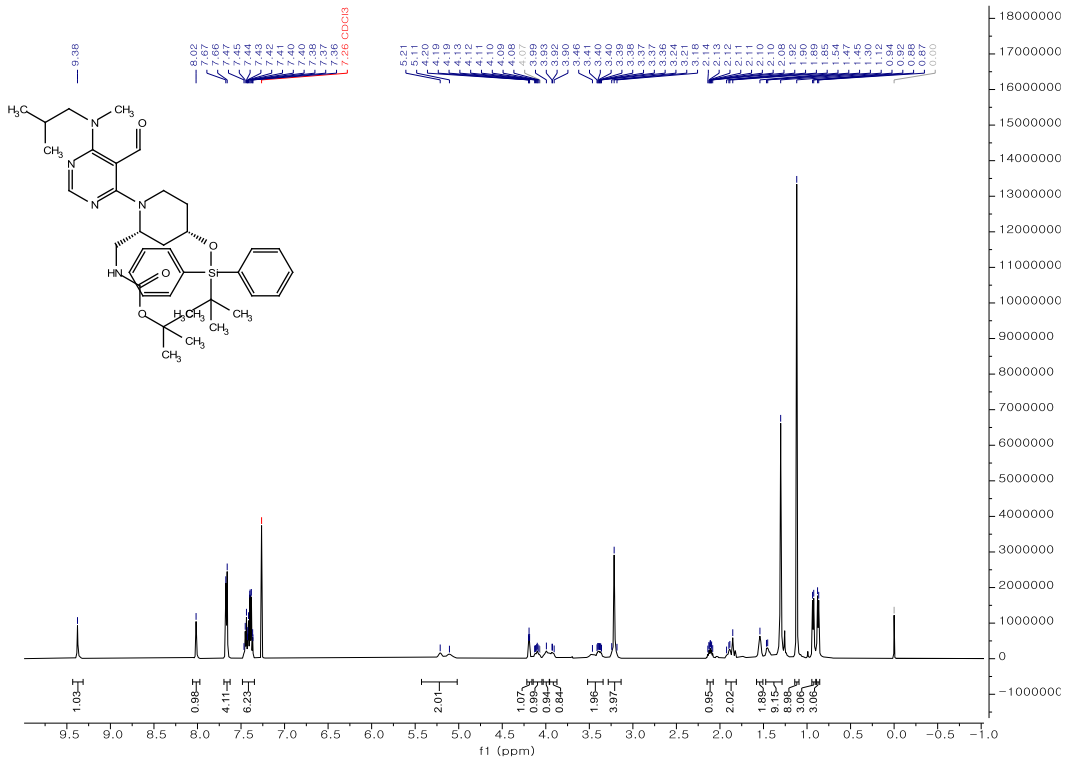

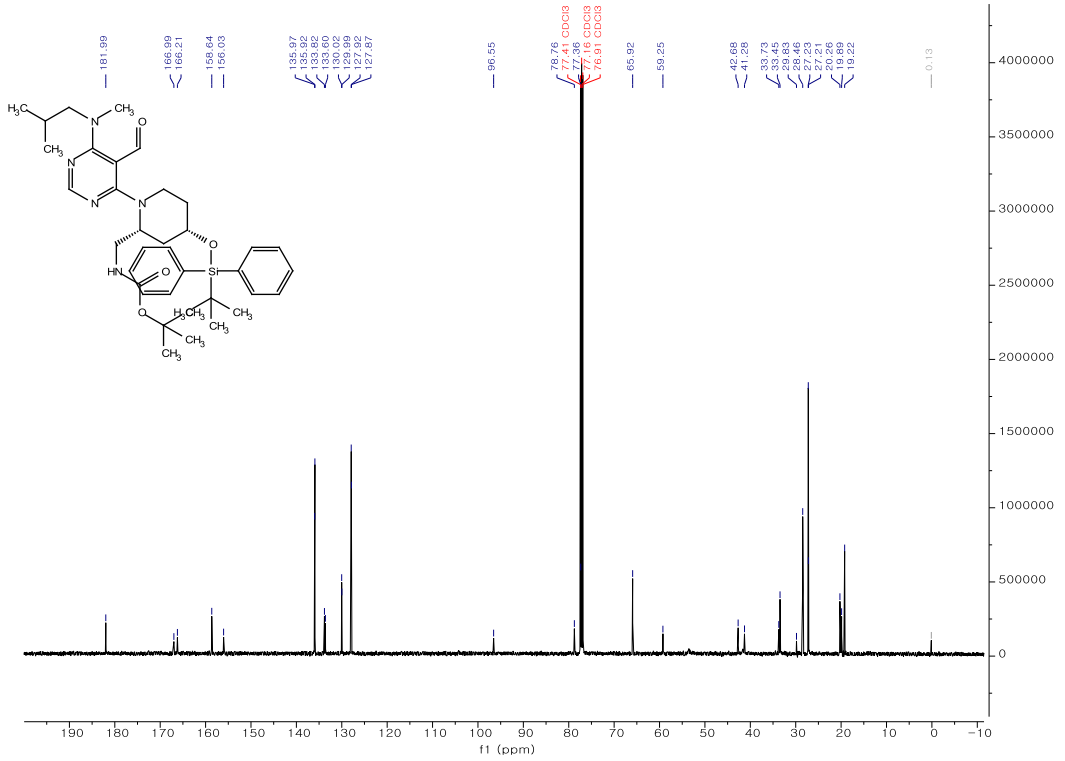

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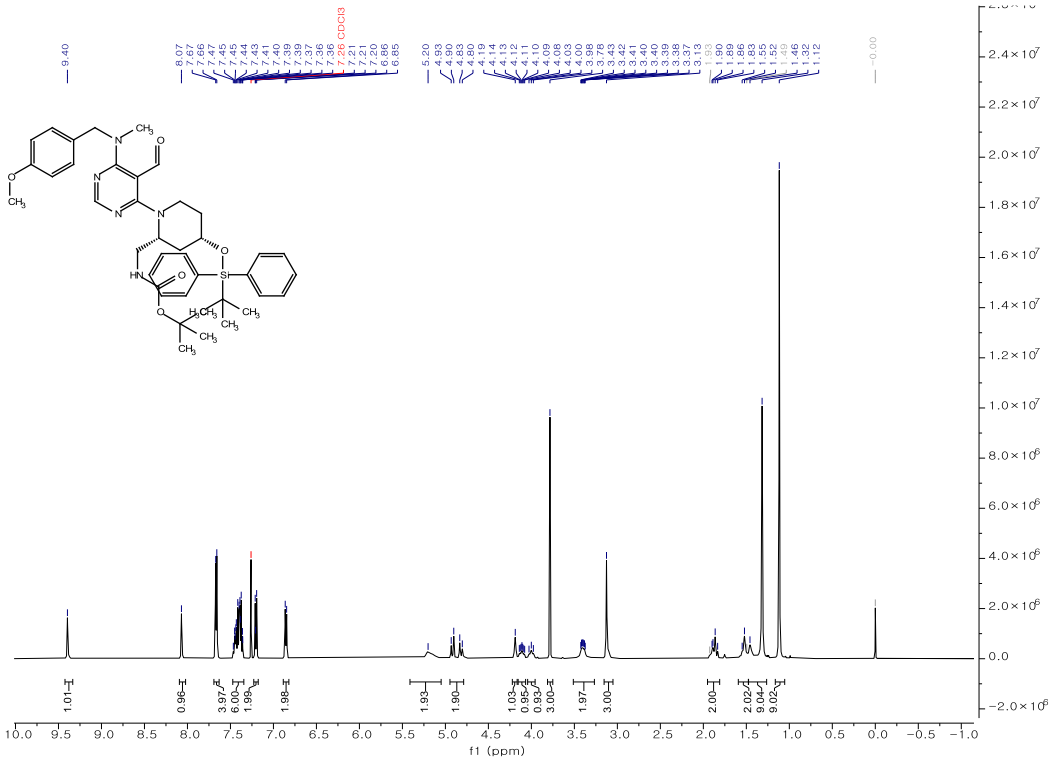

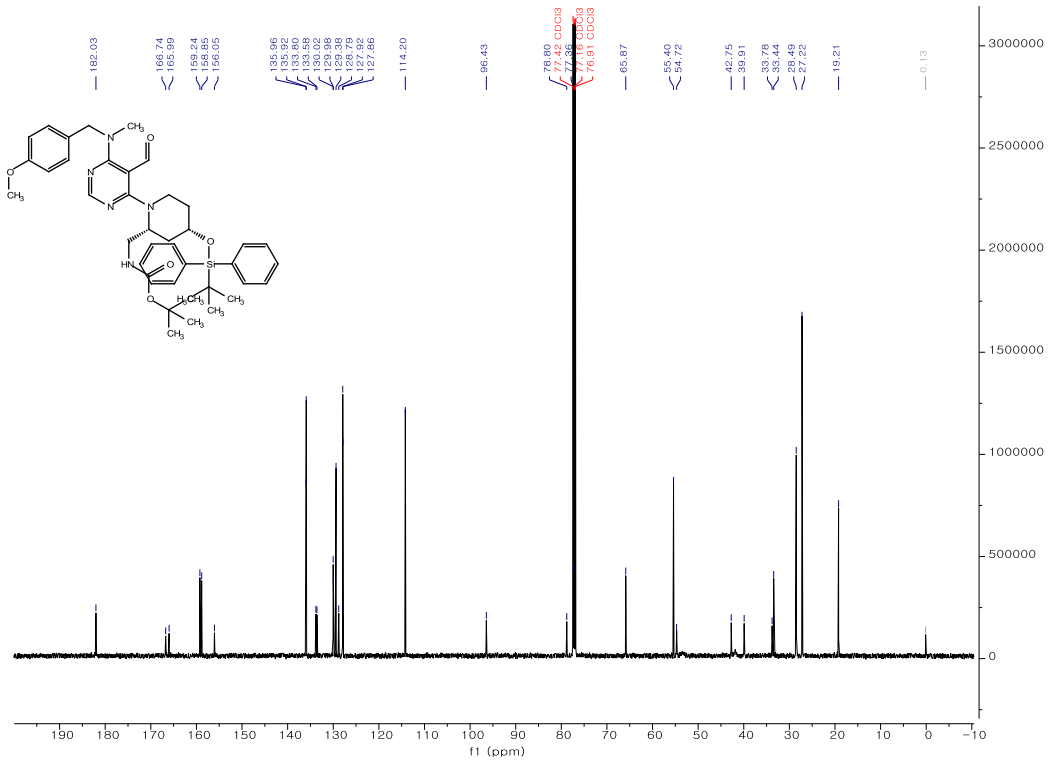

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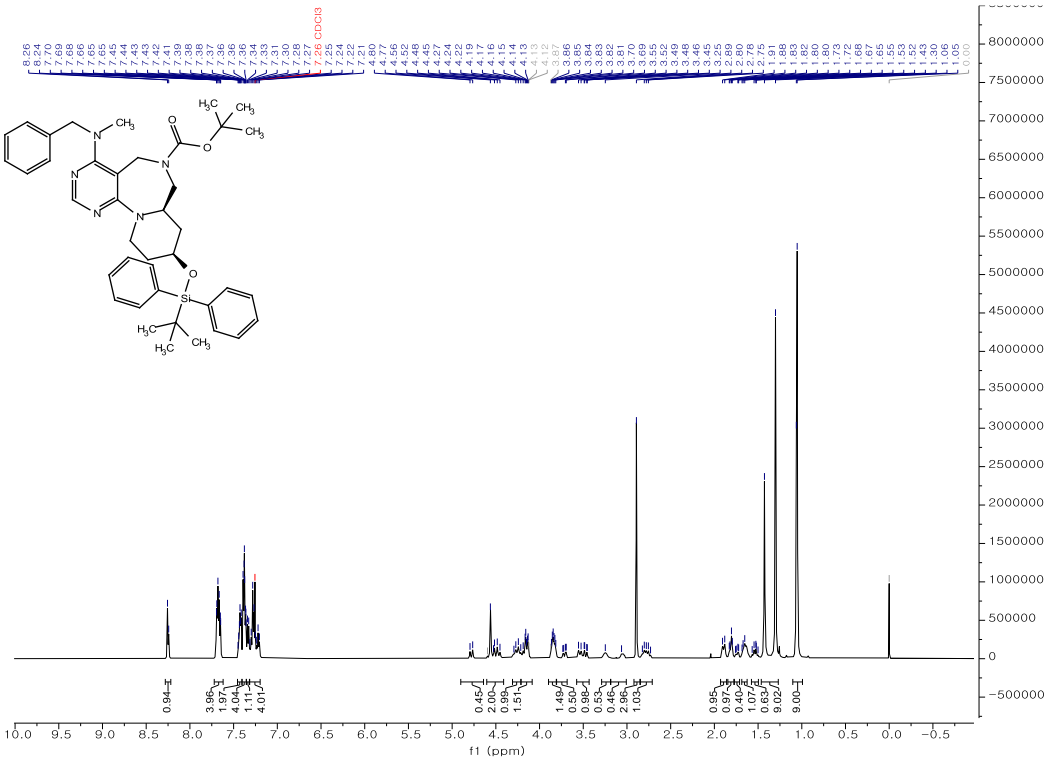

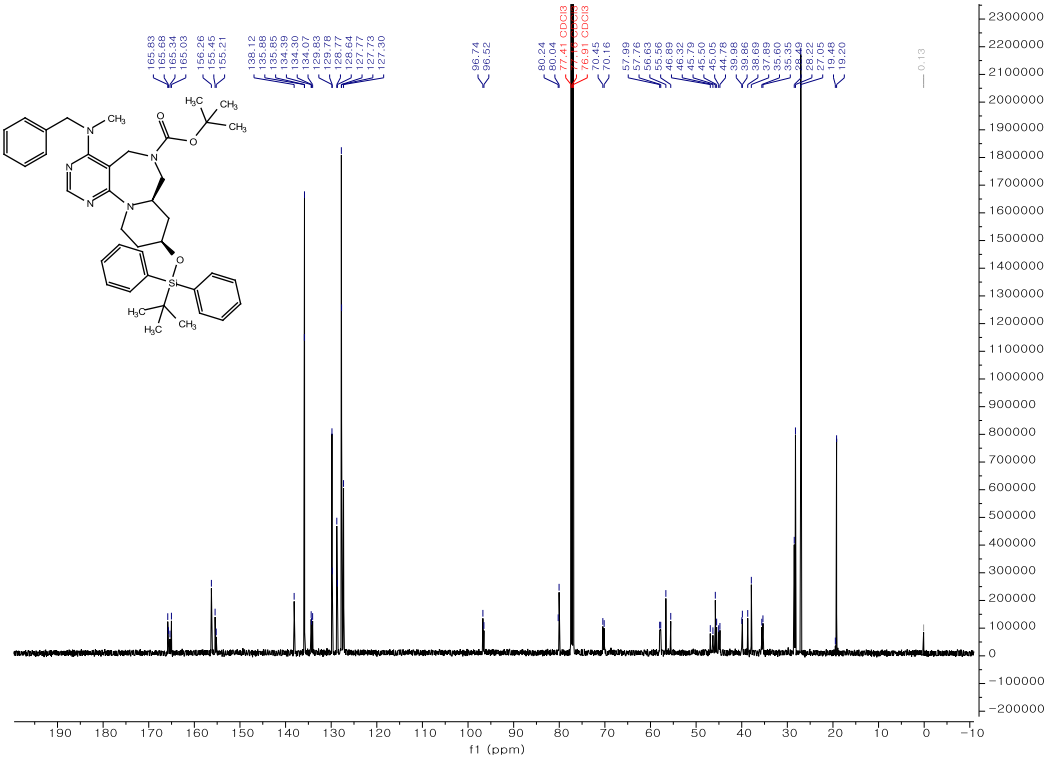

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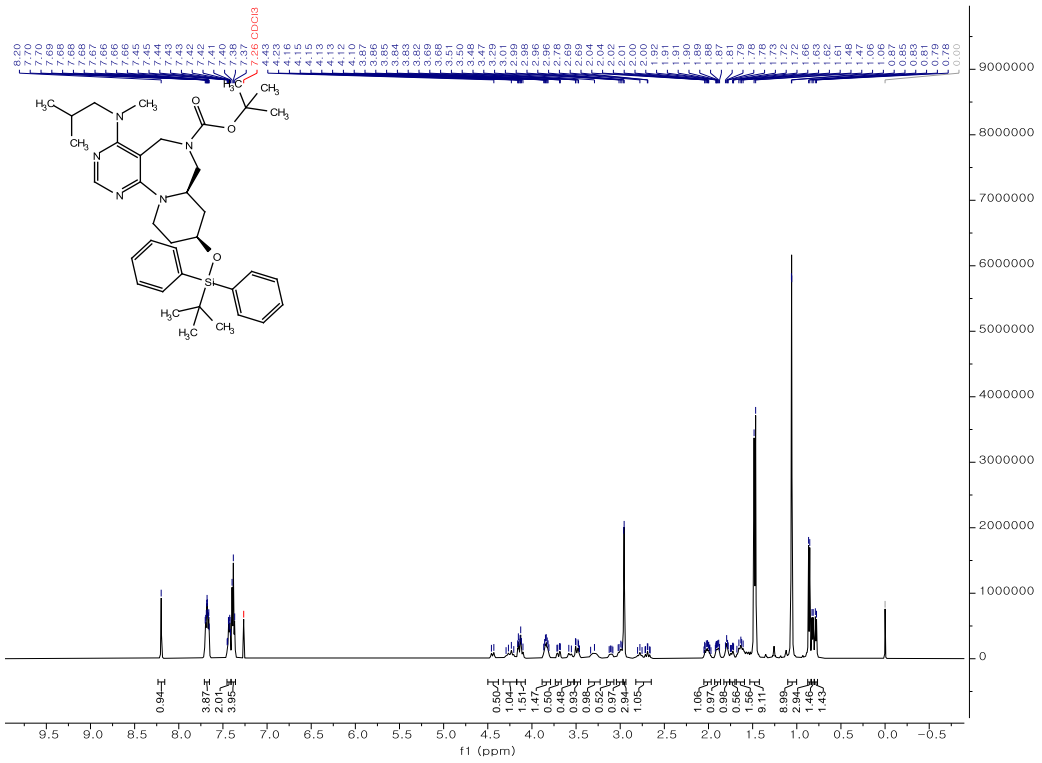
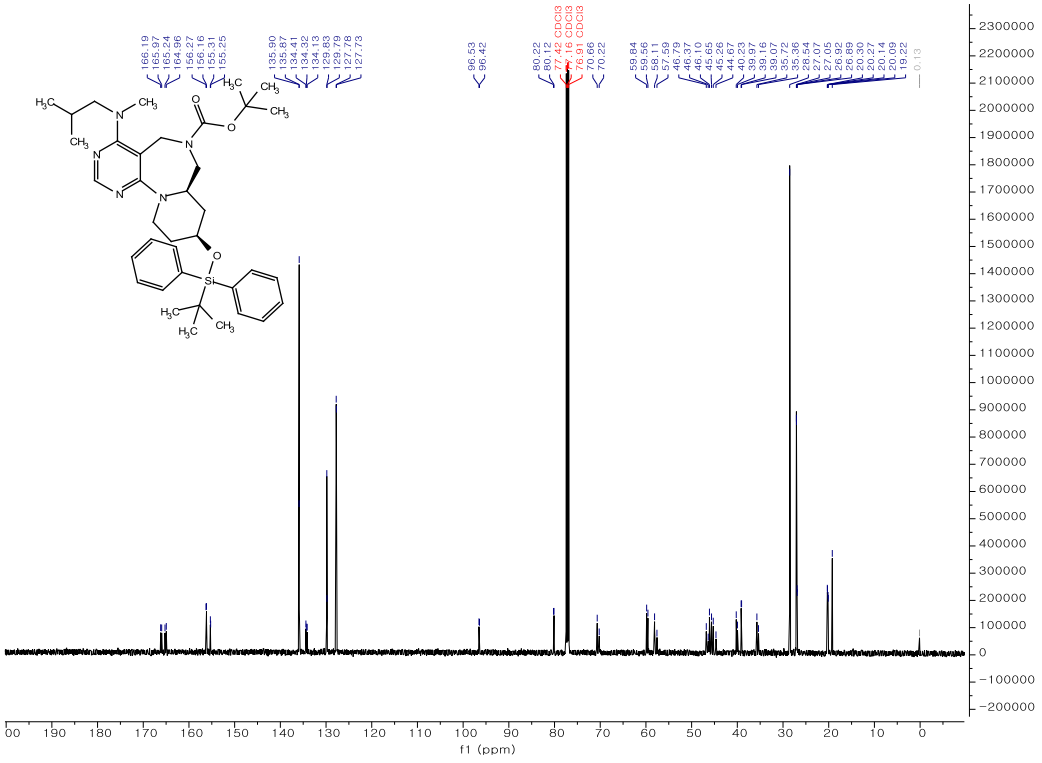
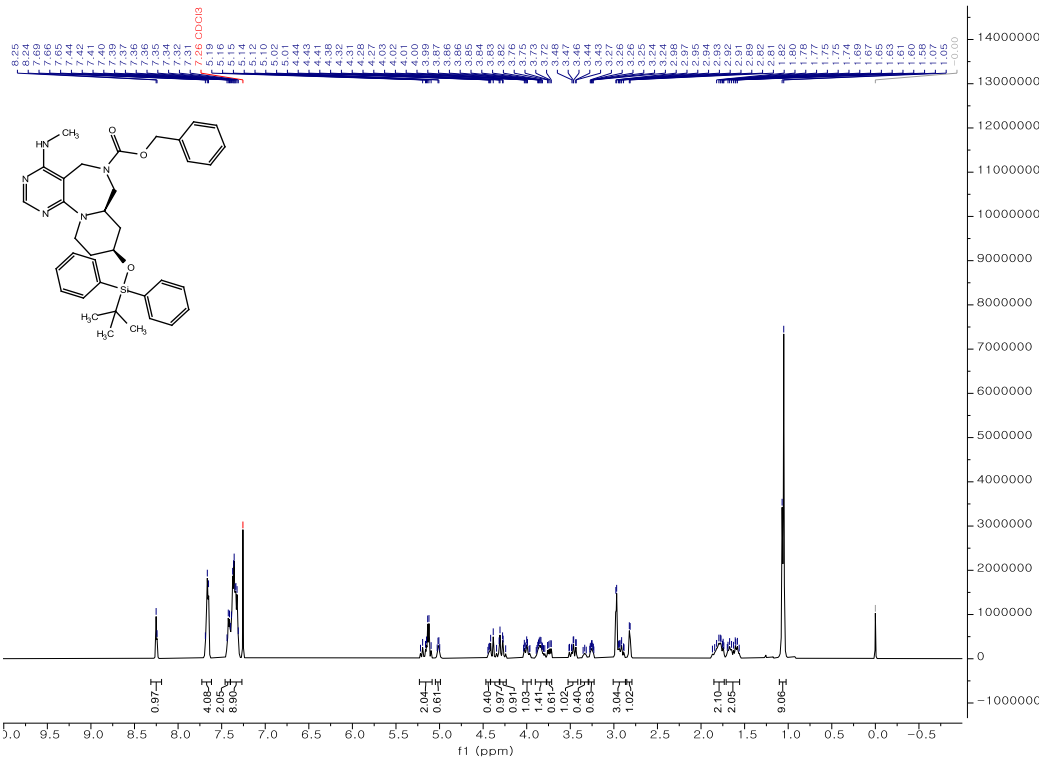
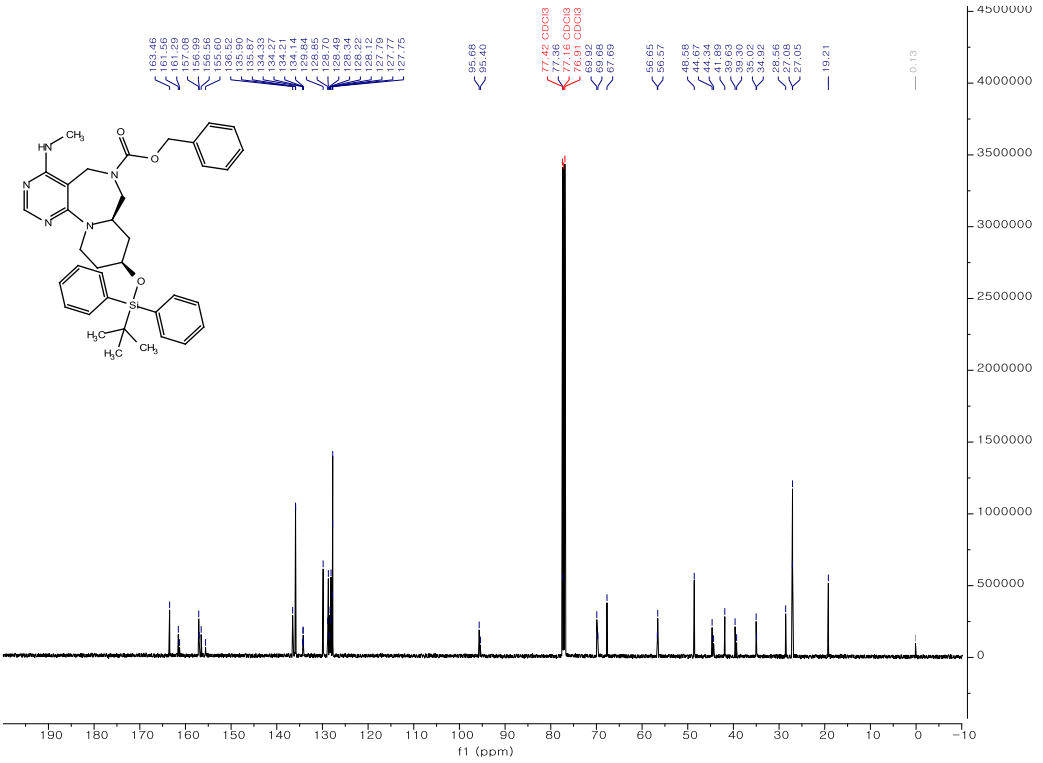




Intermediate D





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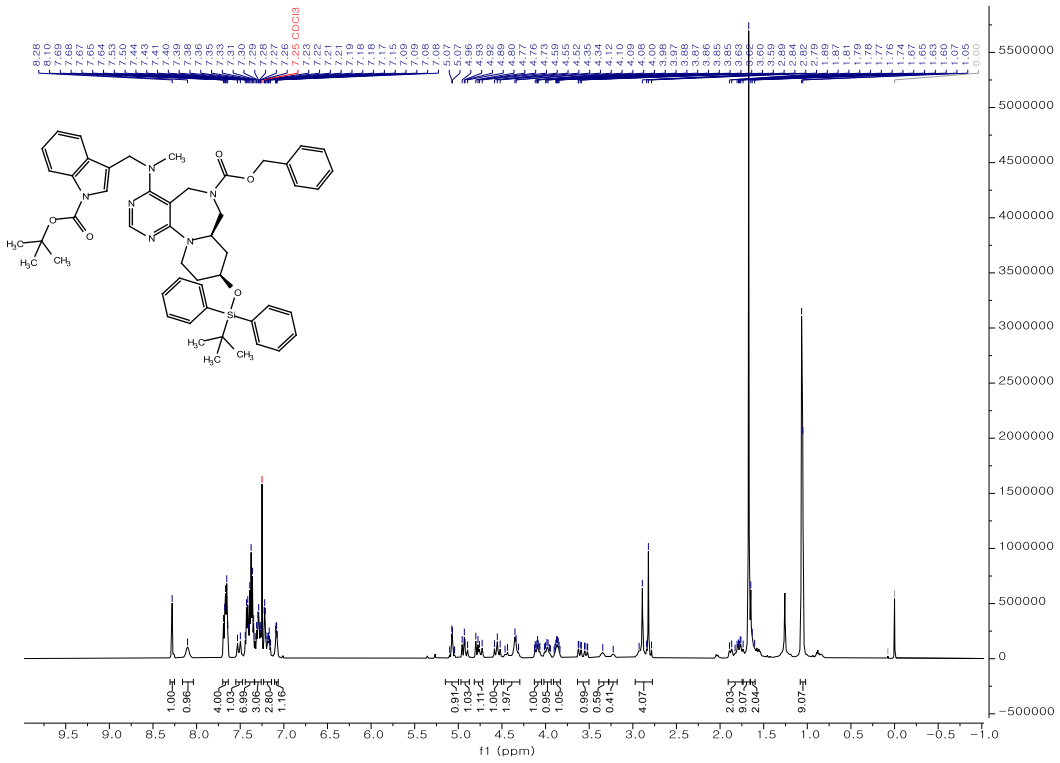

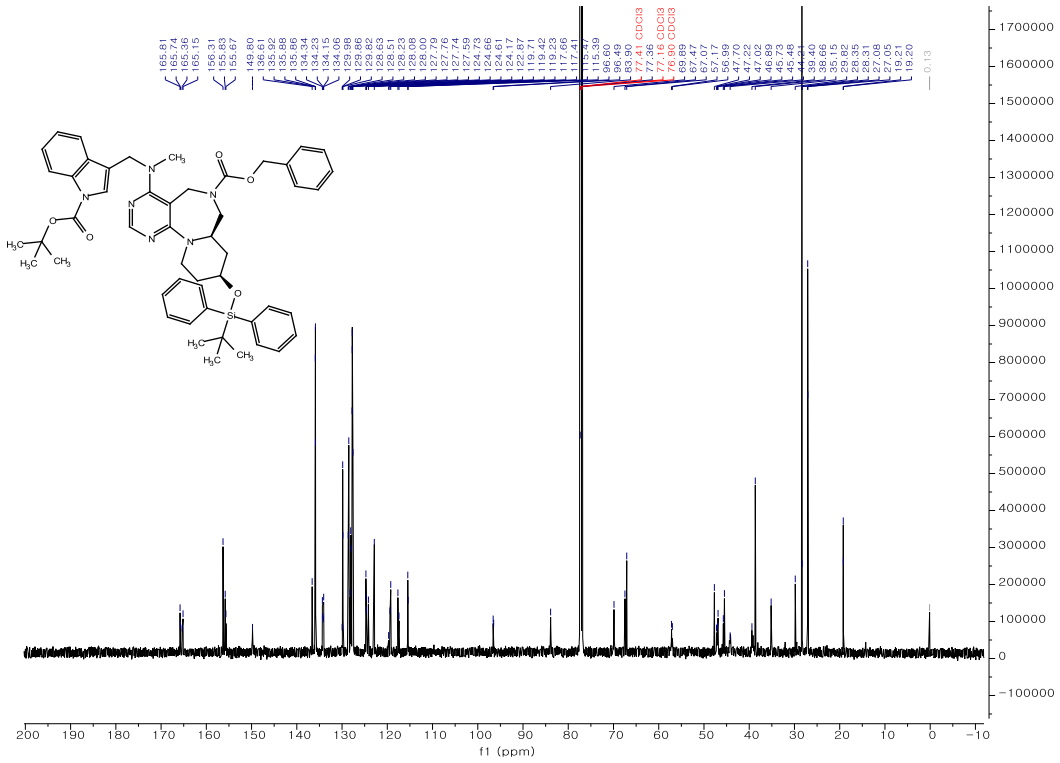

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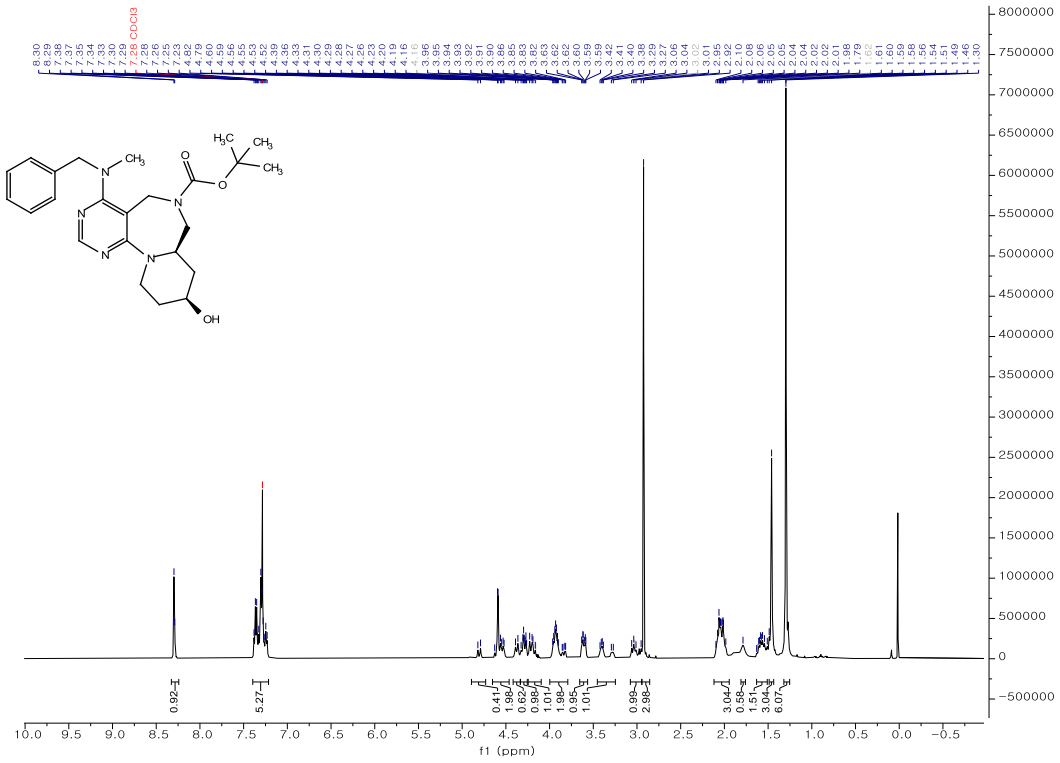

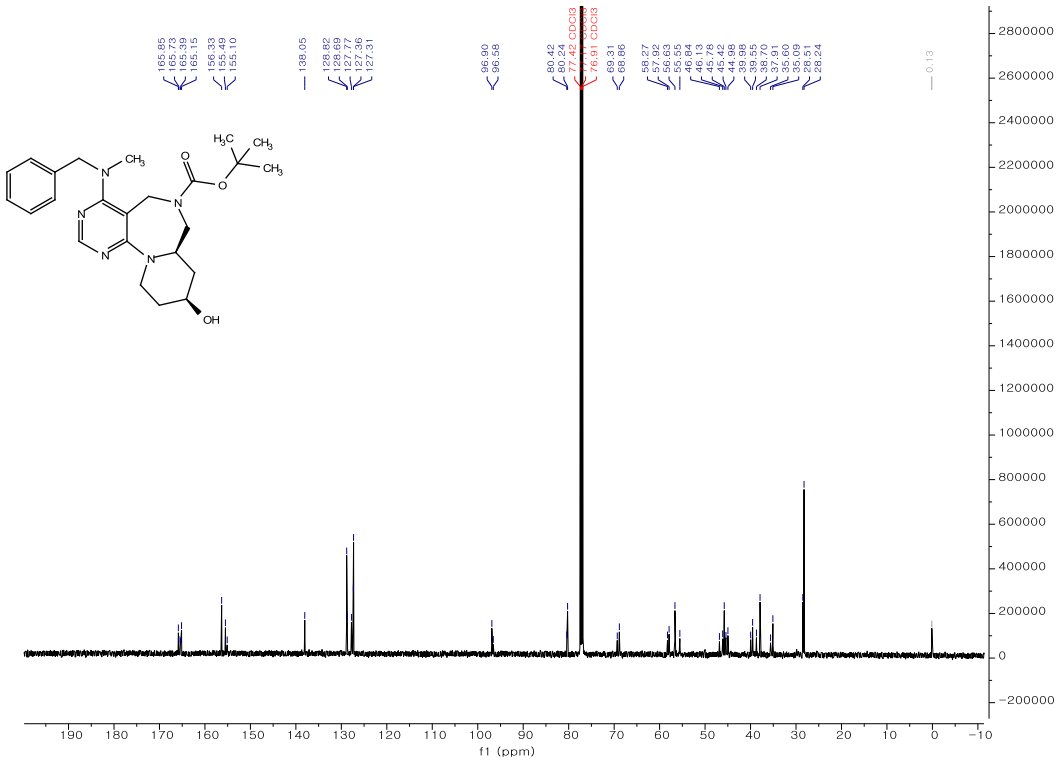

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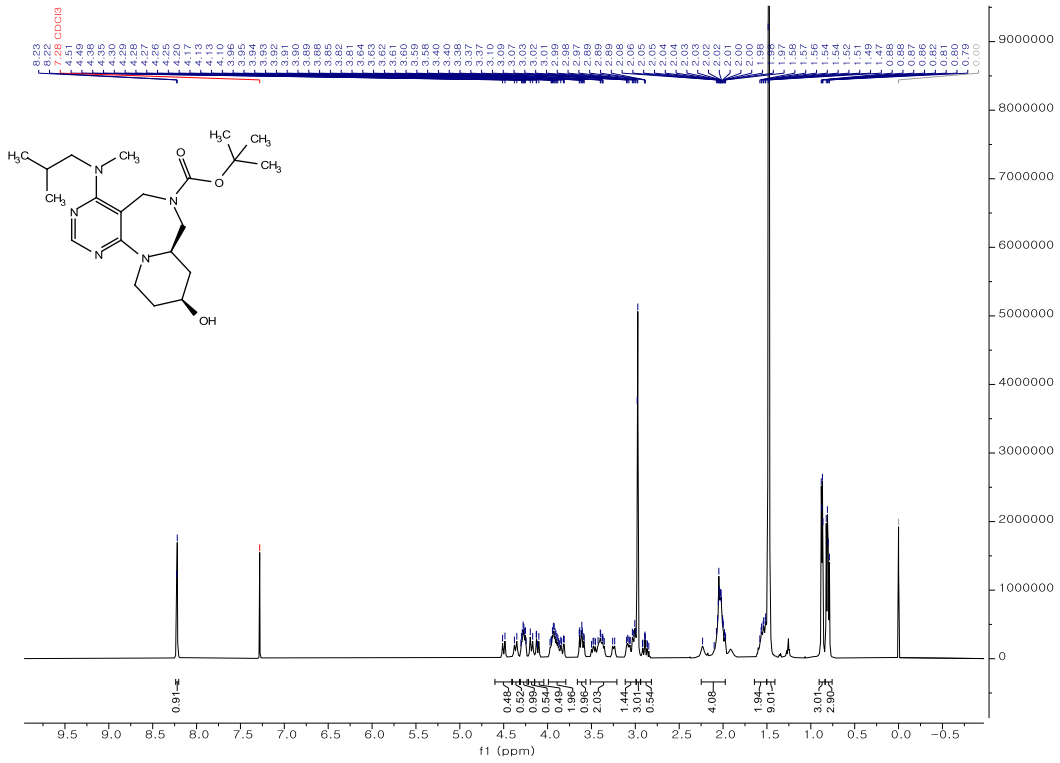

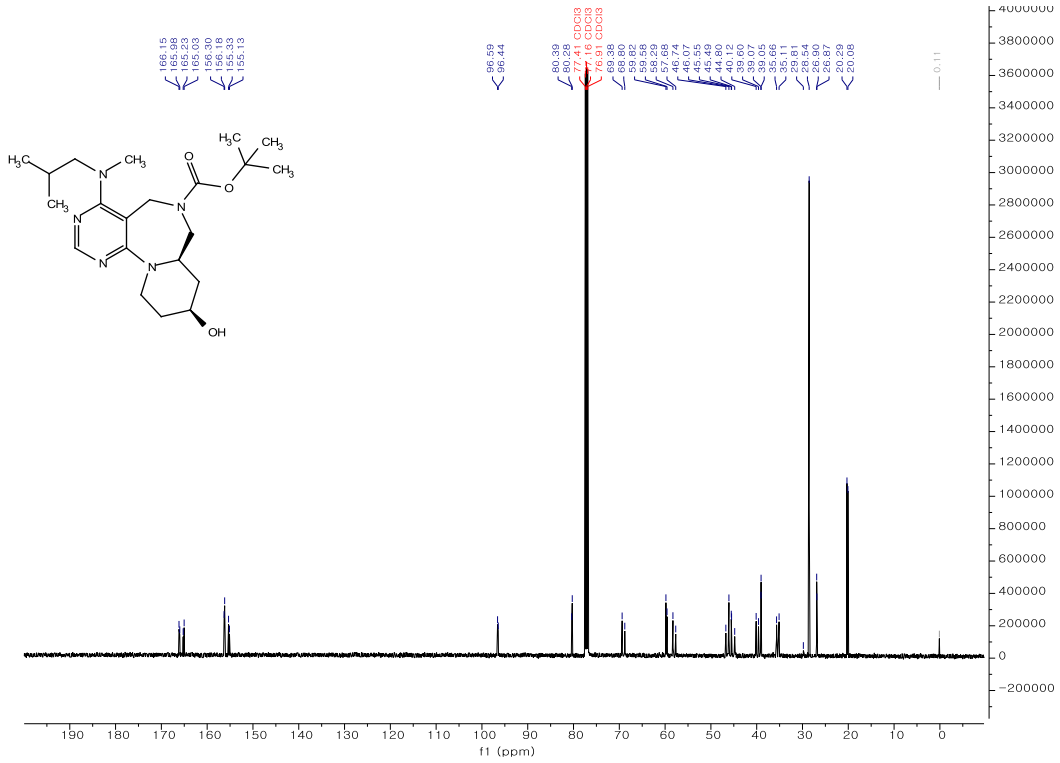

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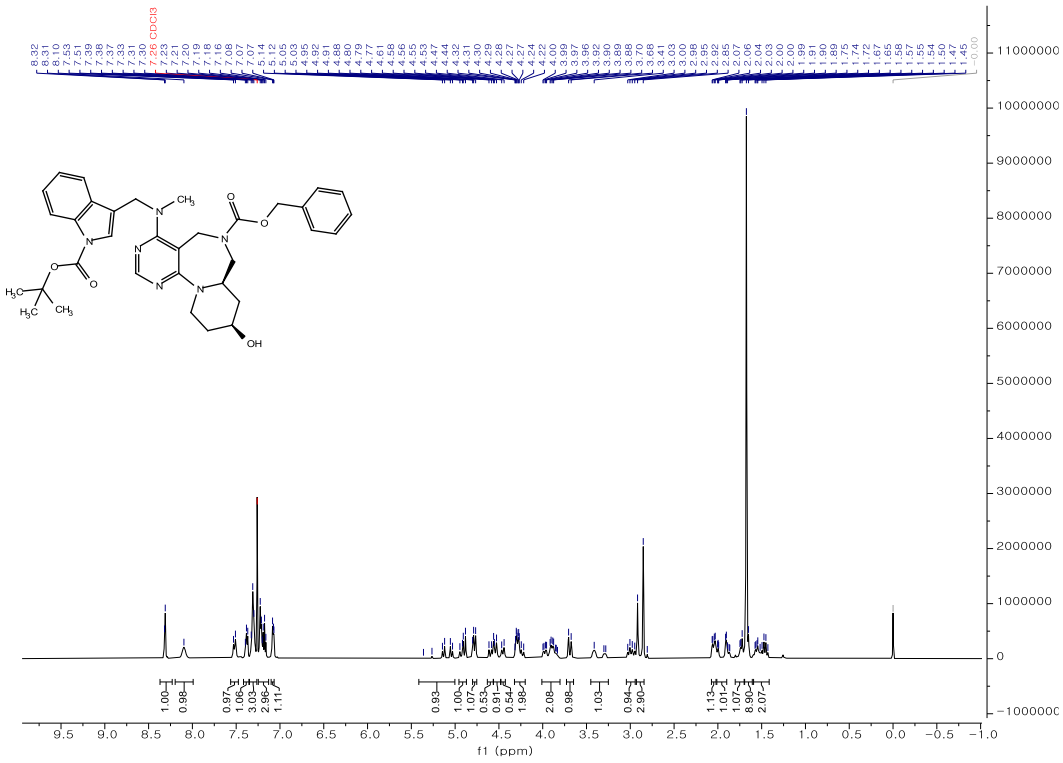

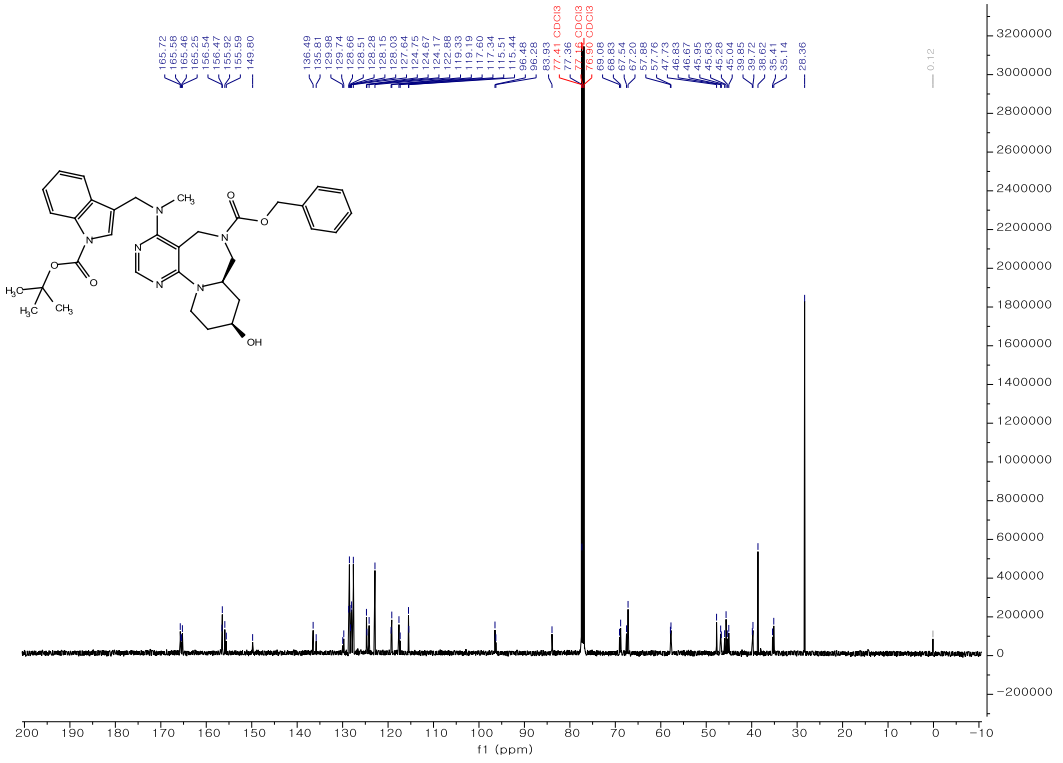

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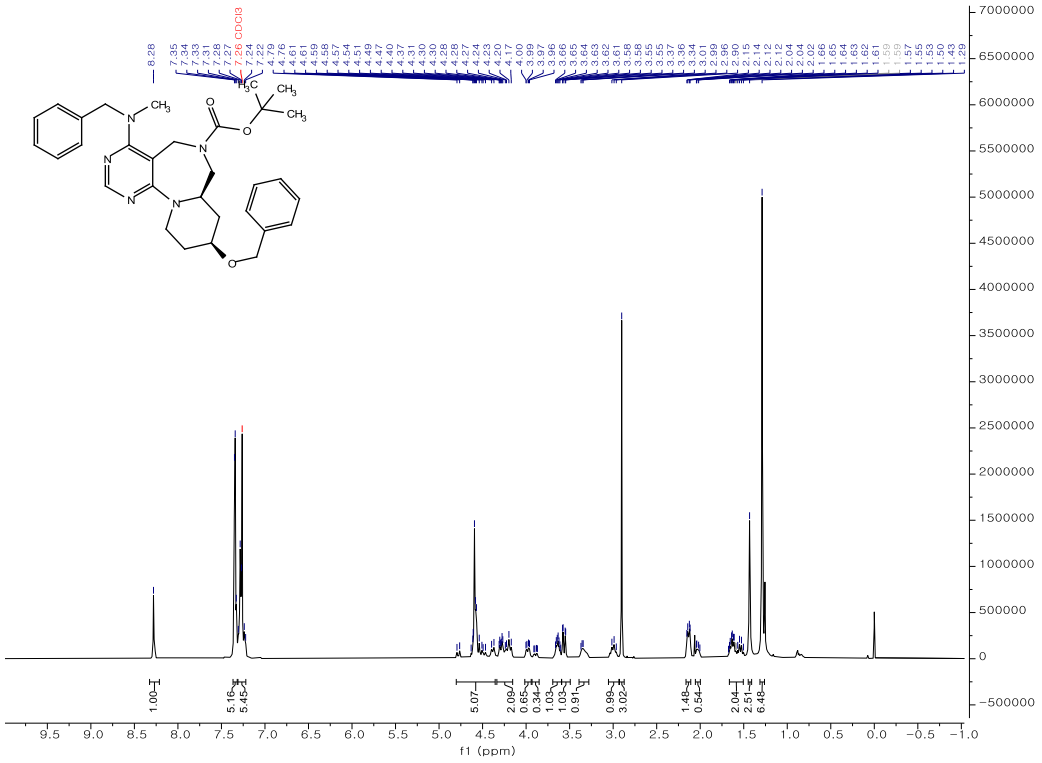

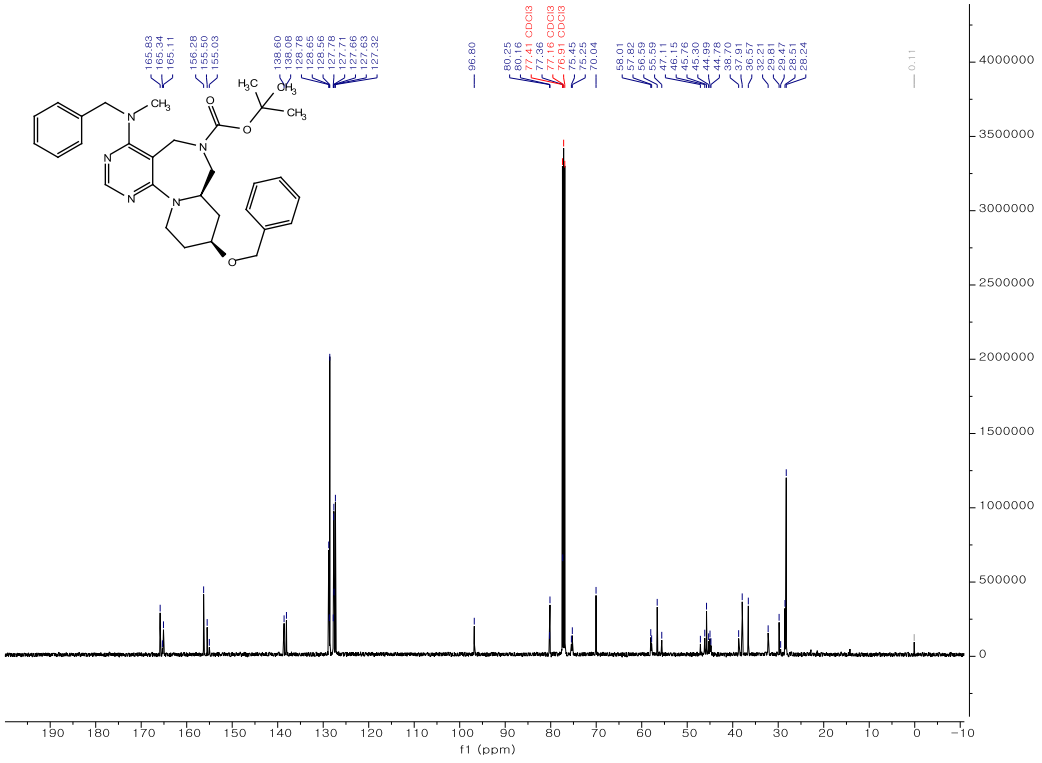

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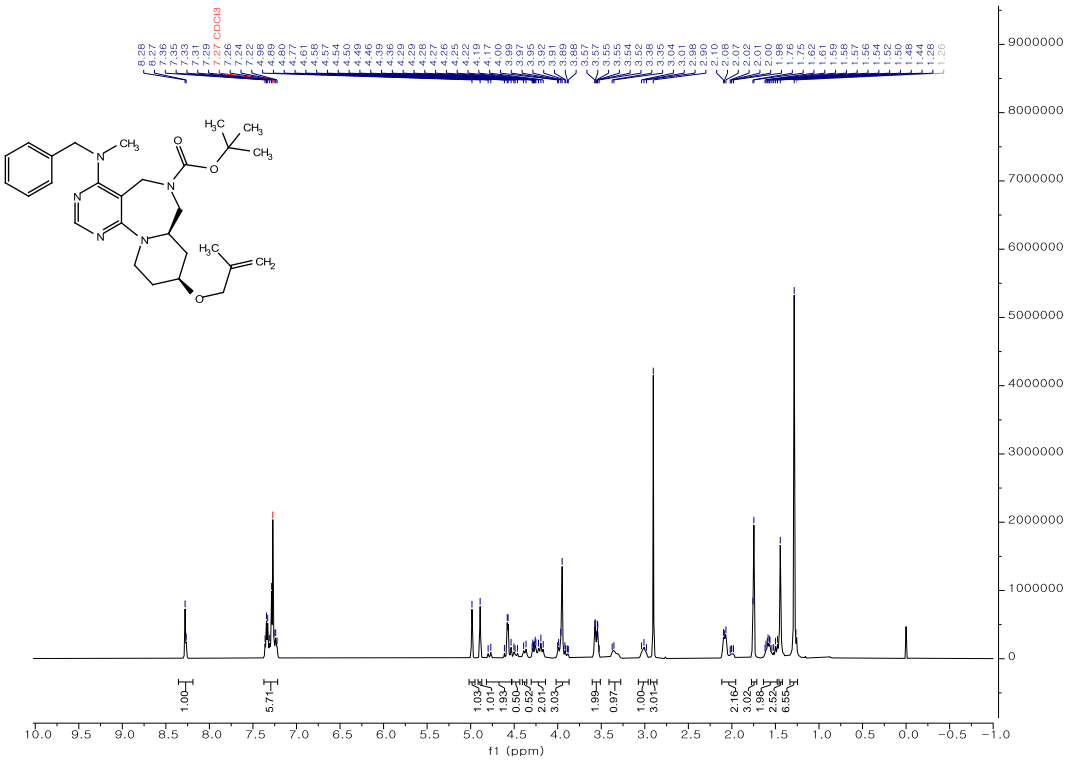

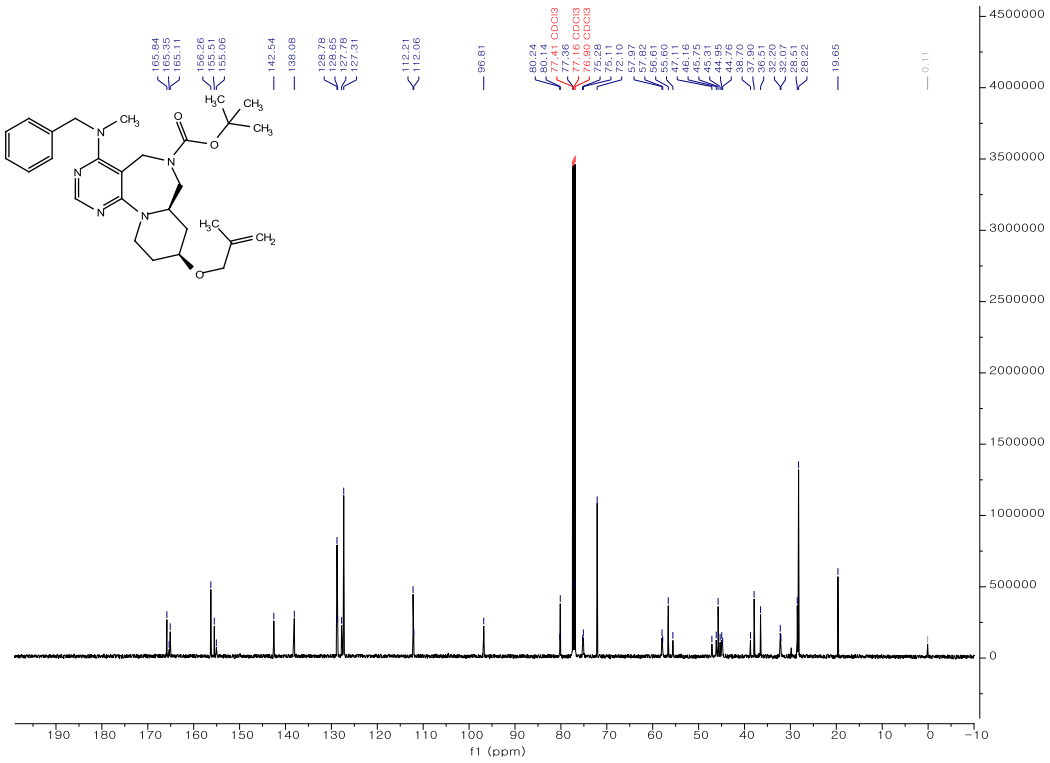

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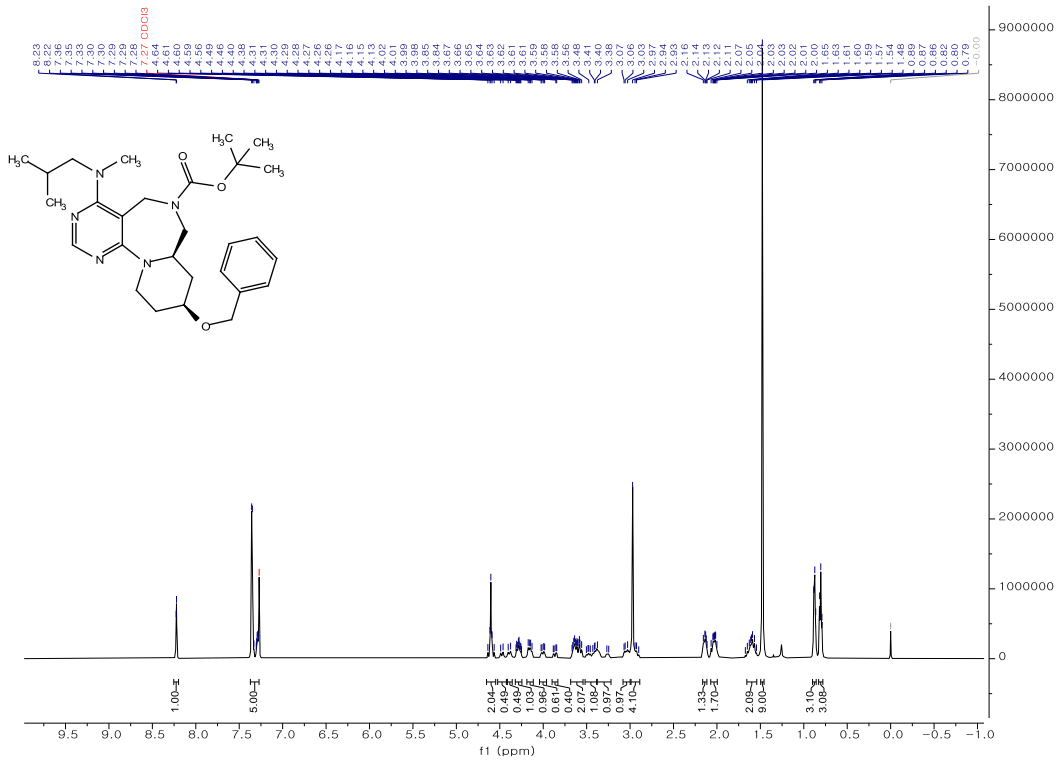

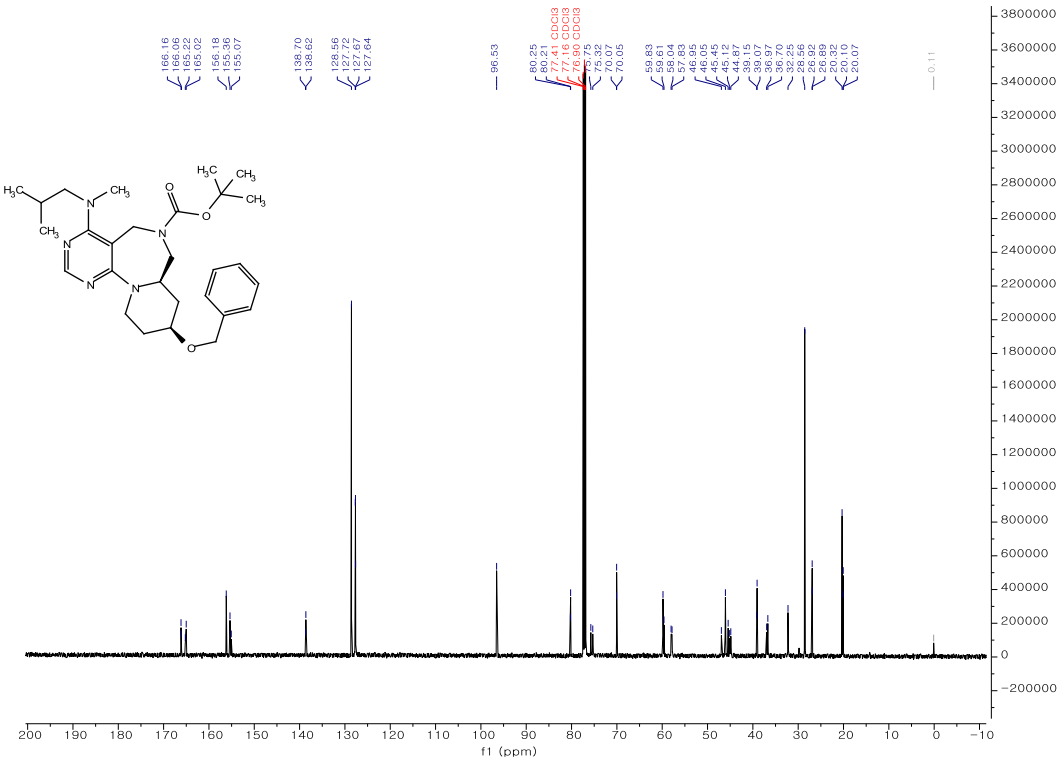

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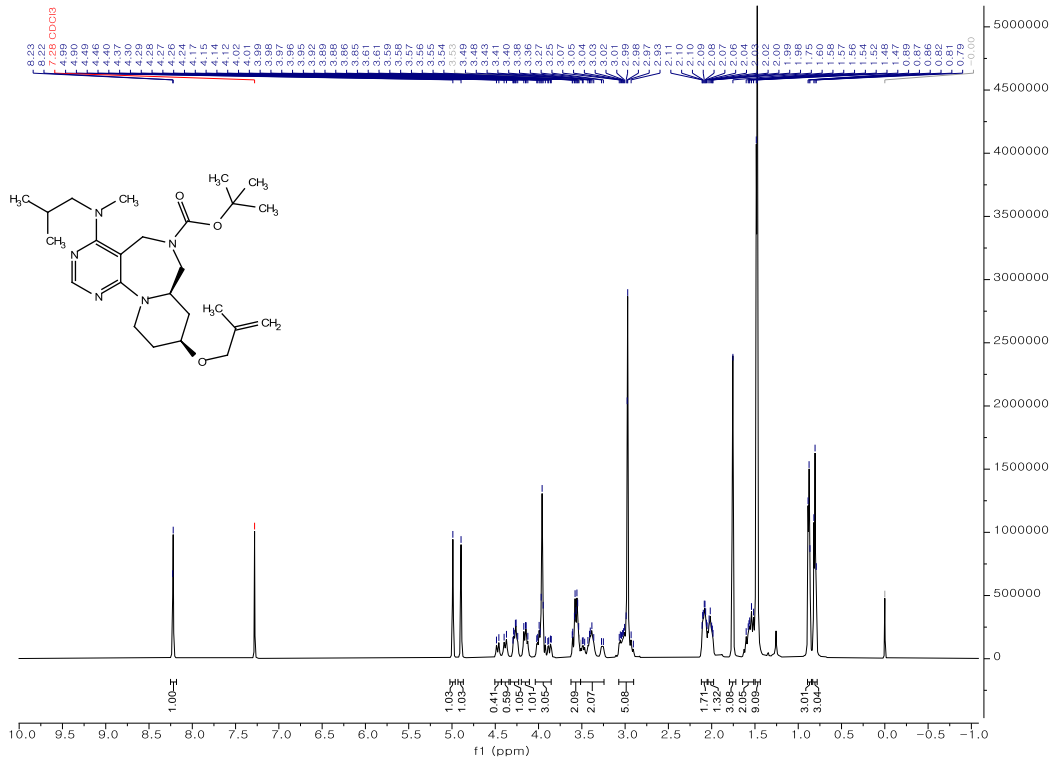

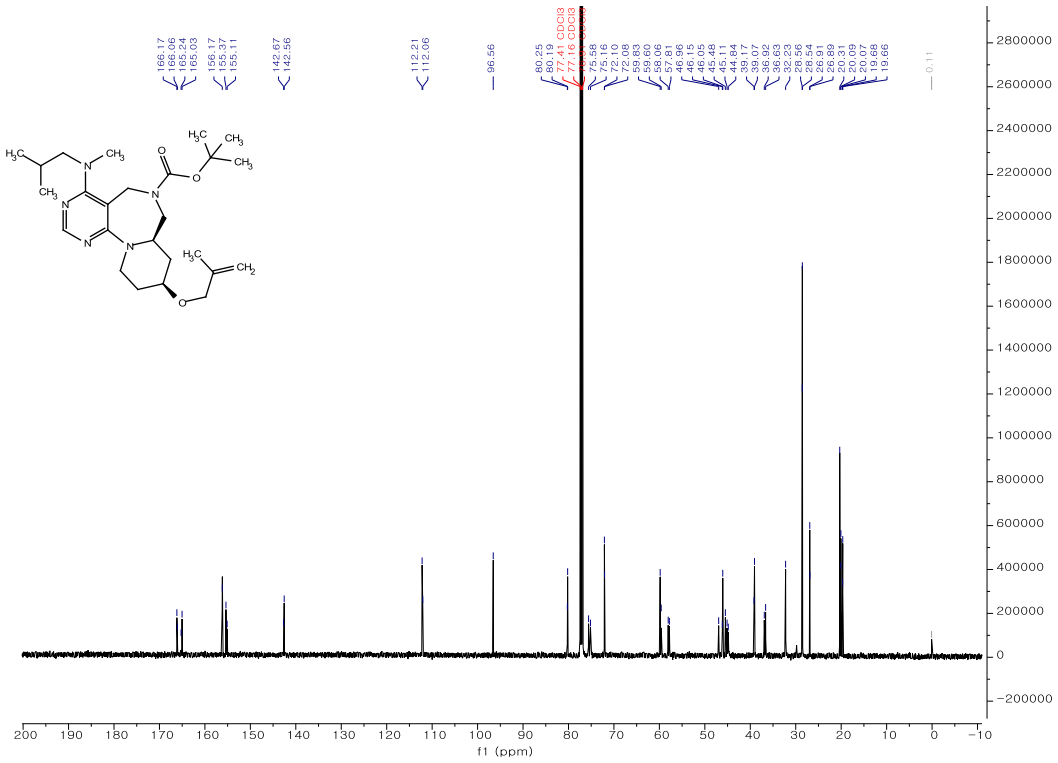

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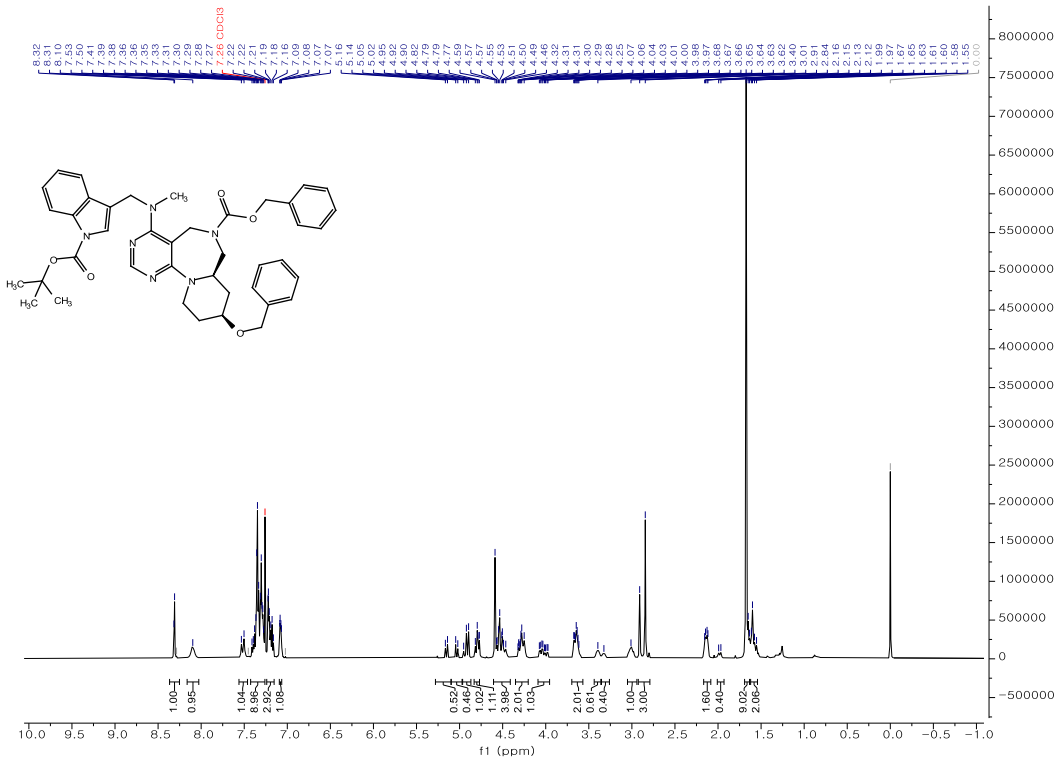

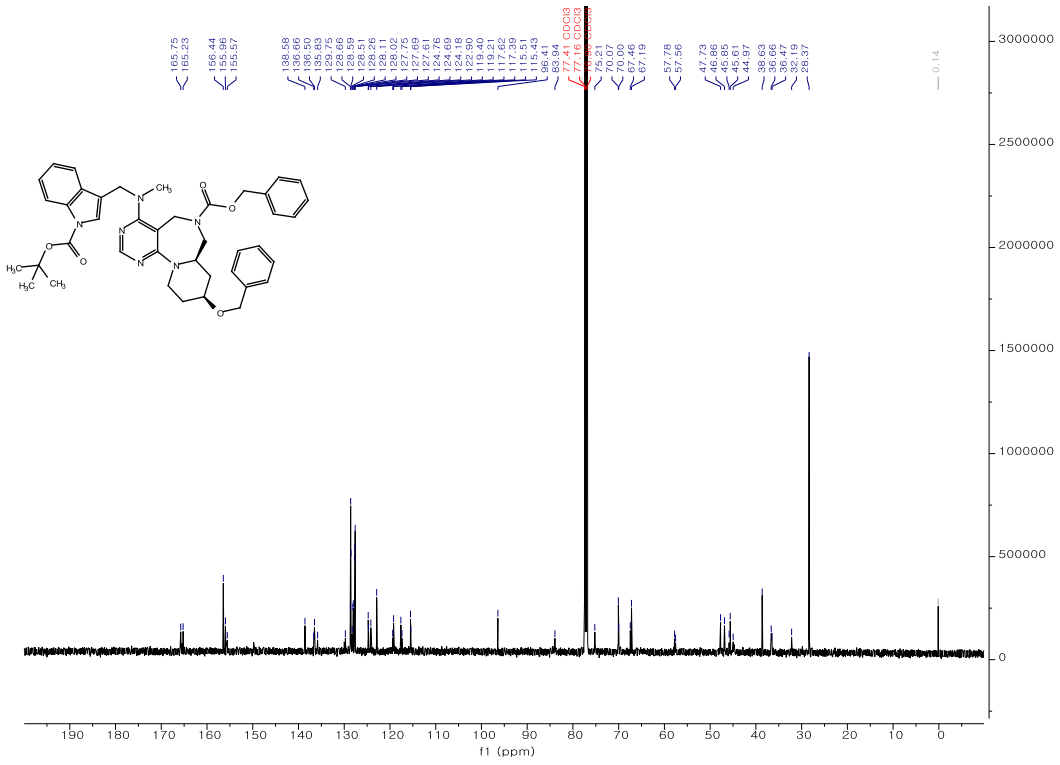

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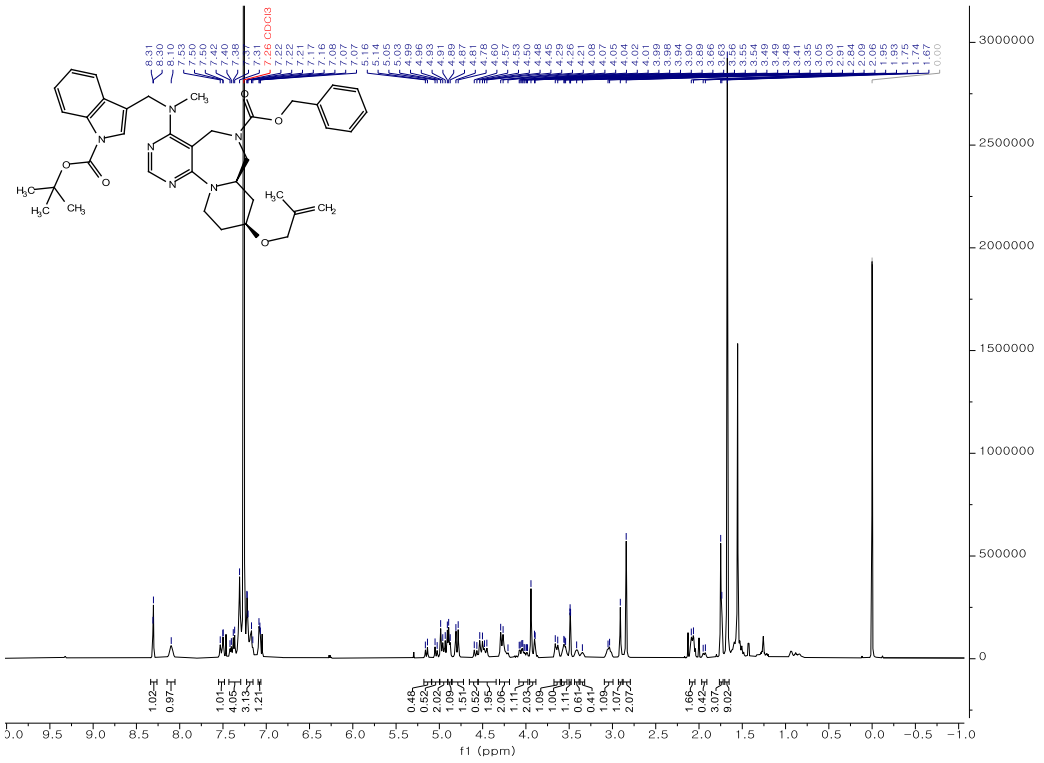

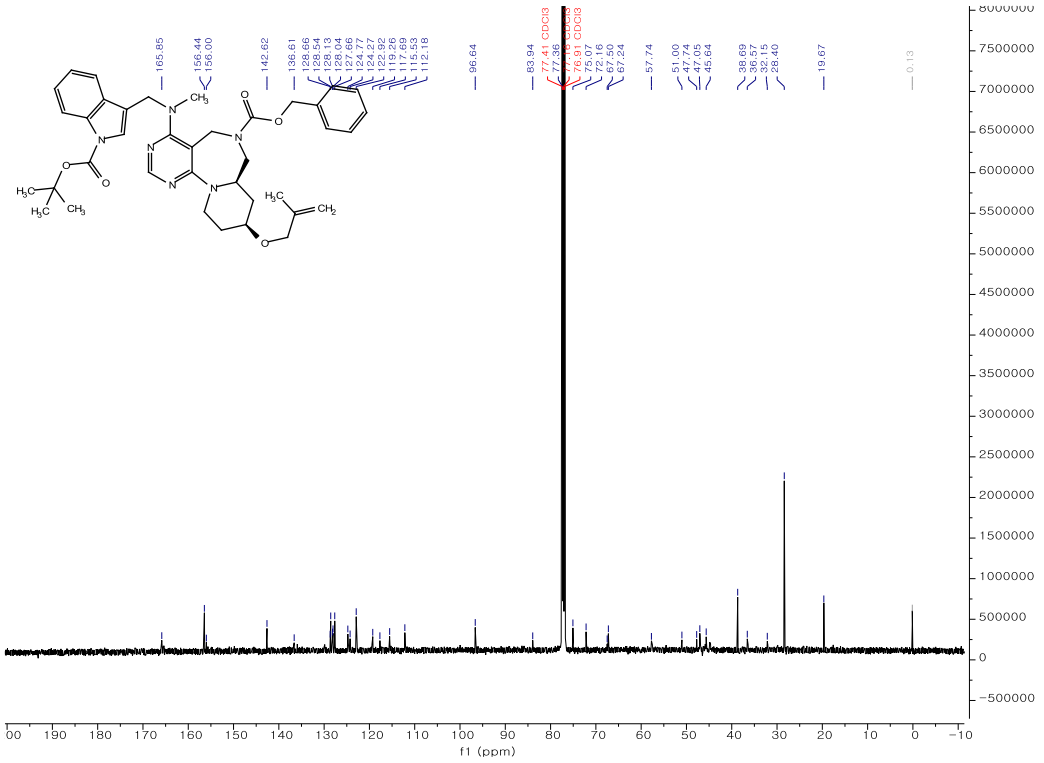

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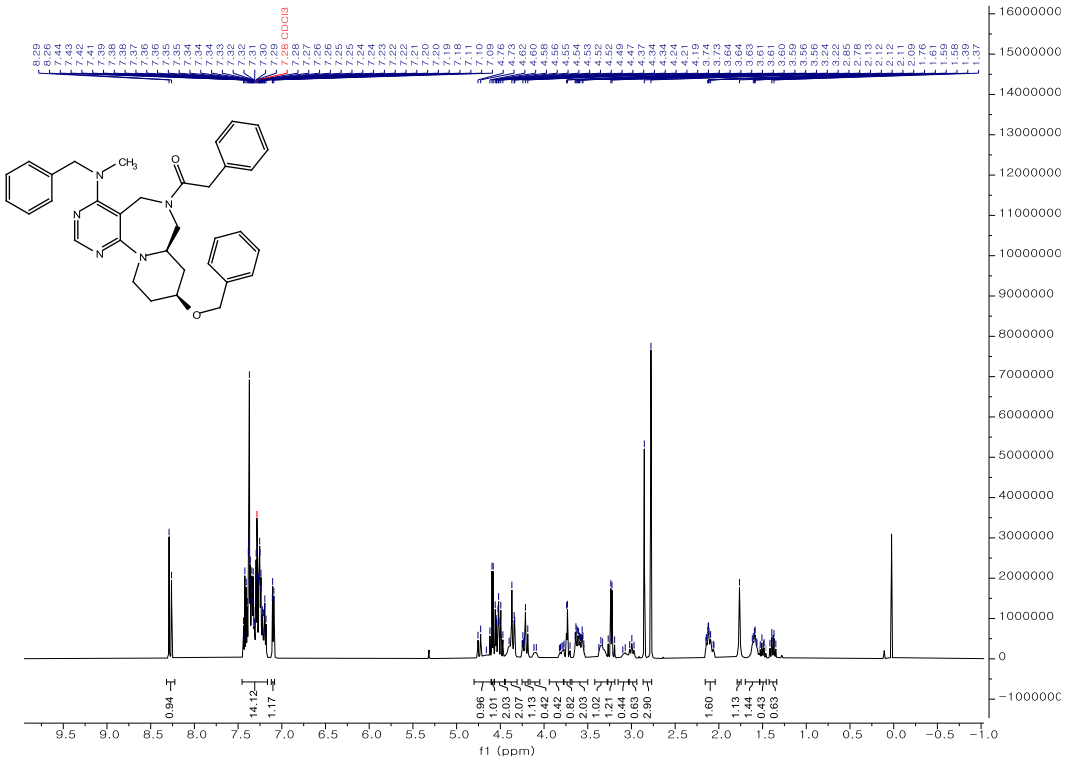

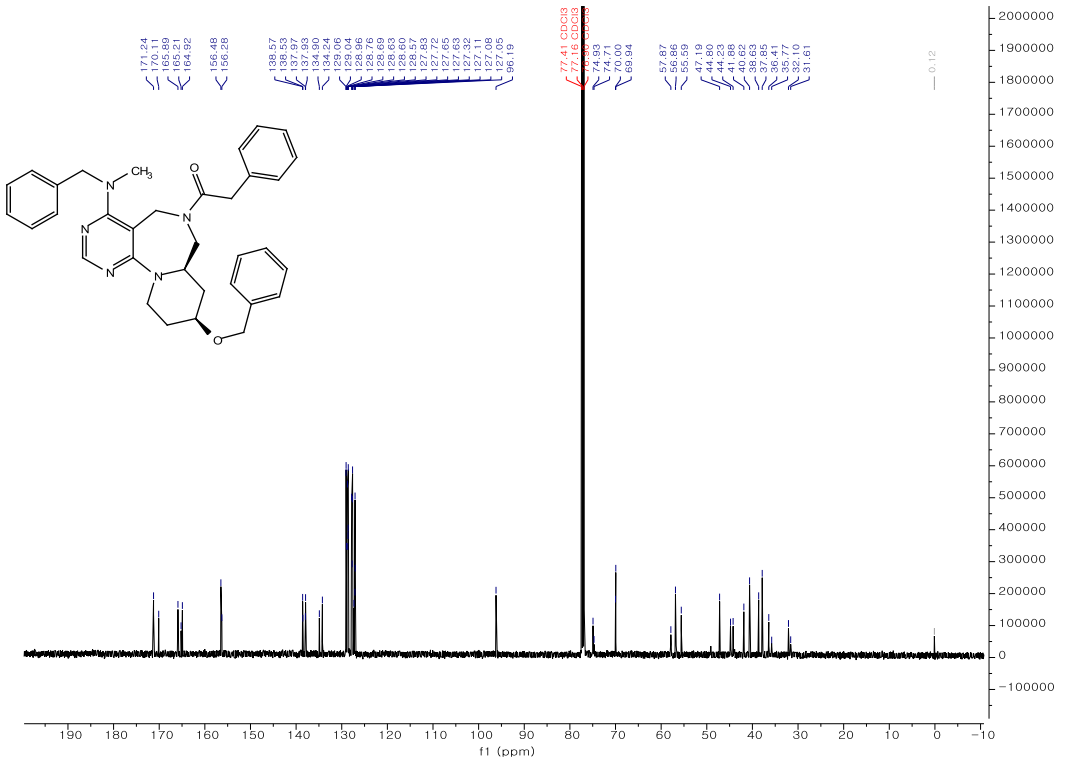

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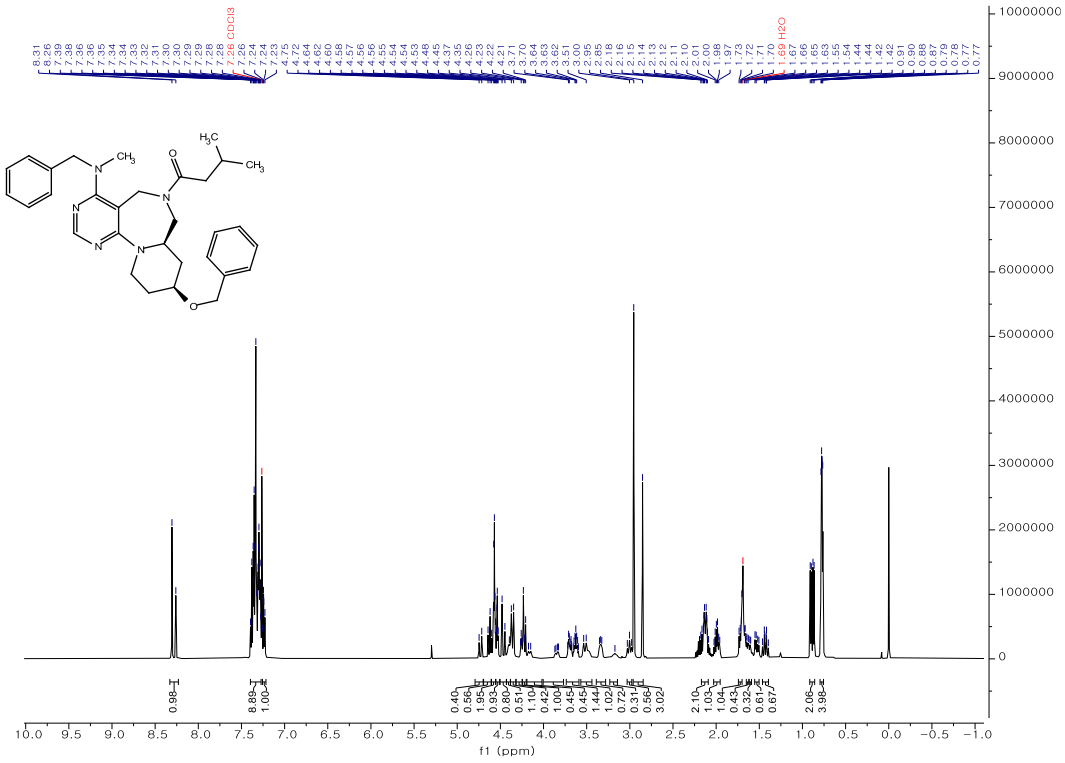

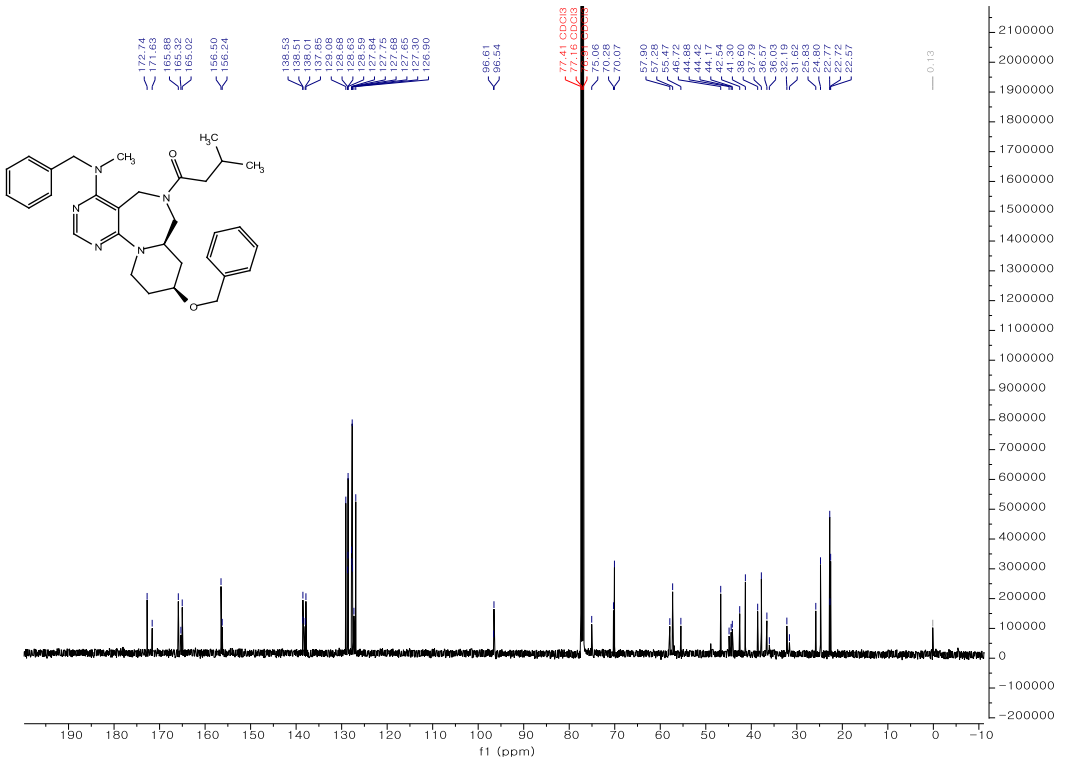

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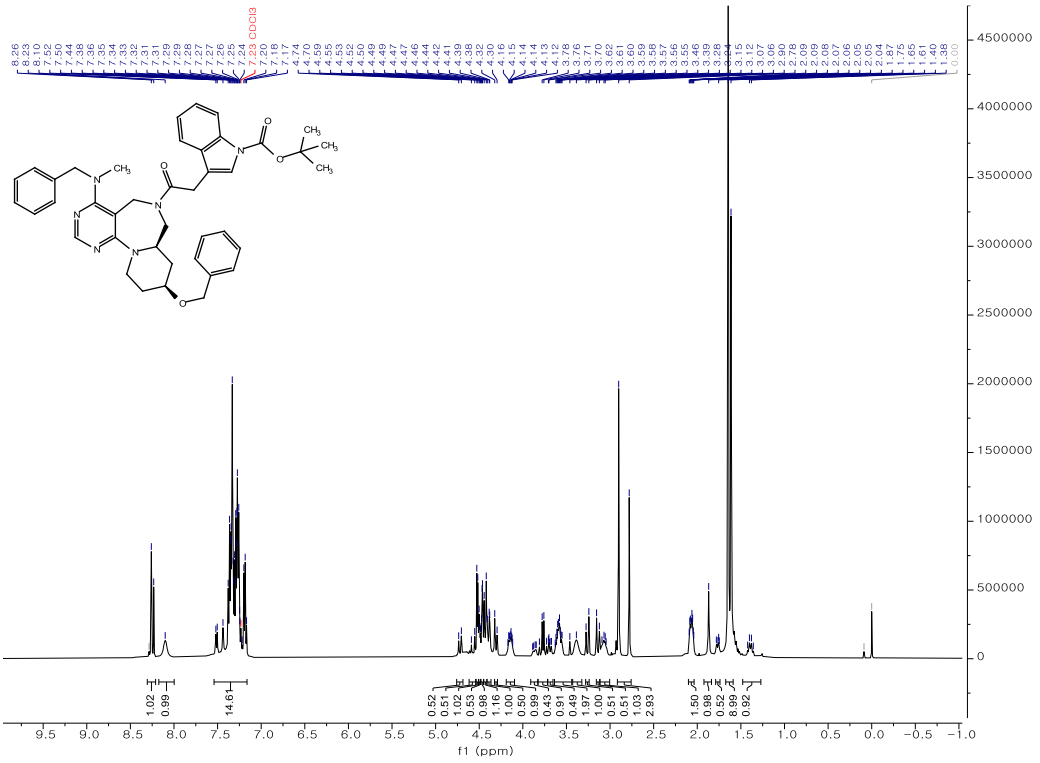

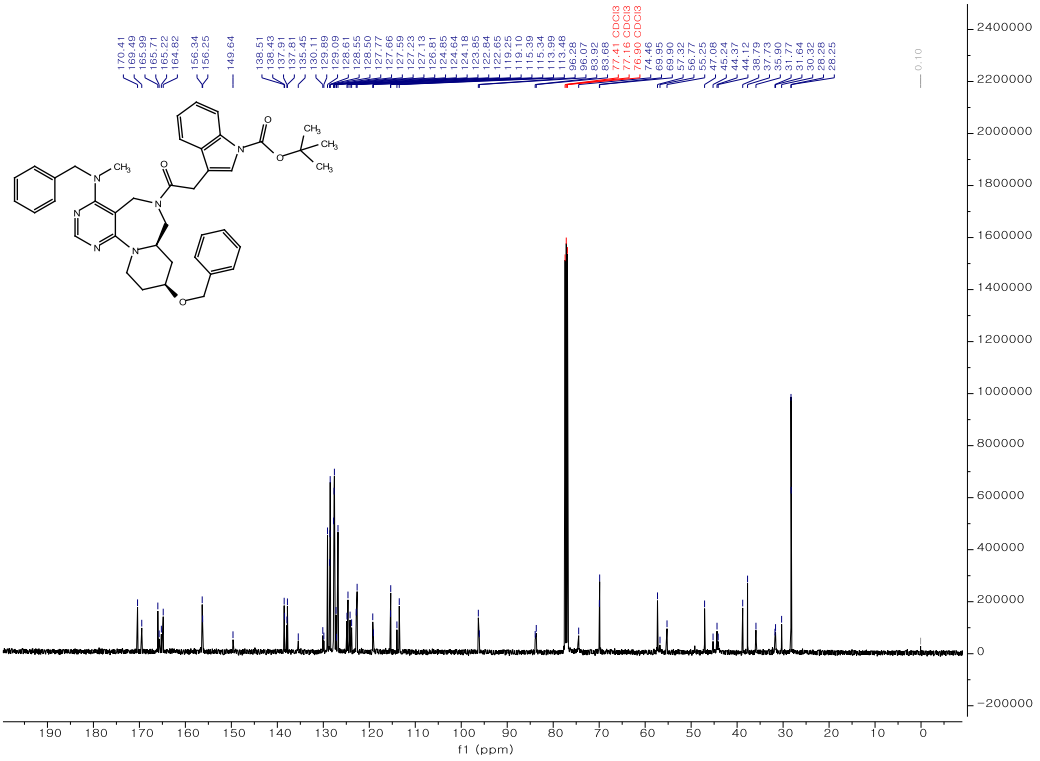

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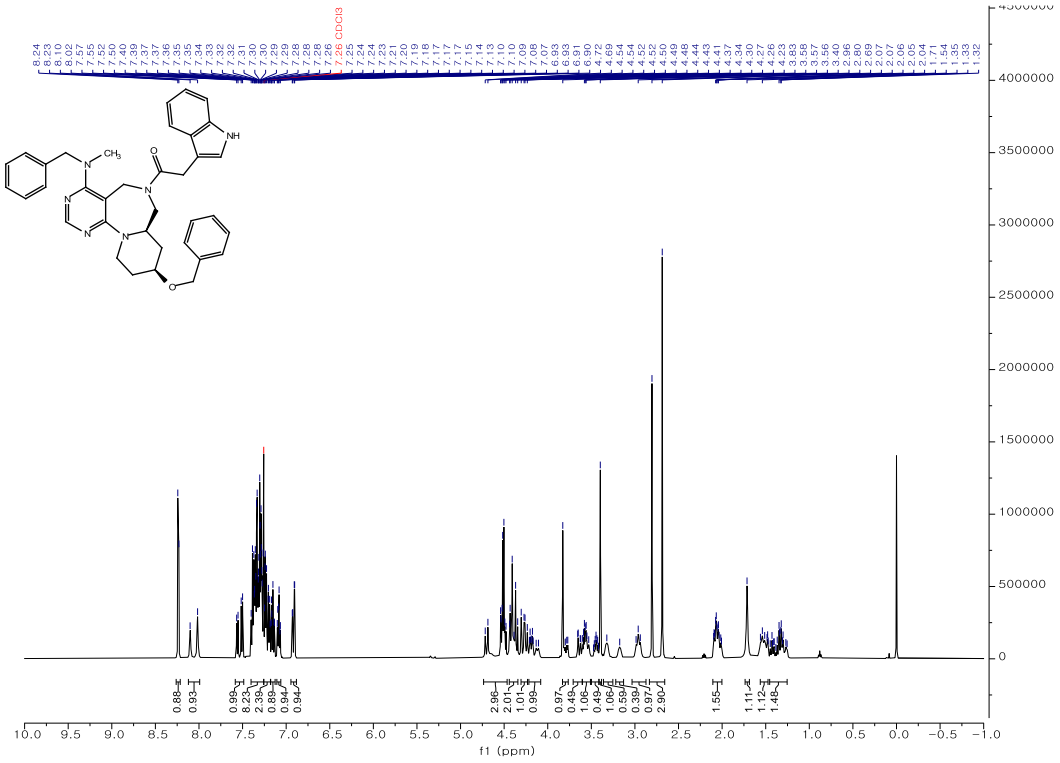

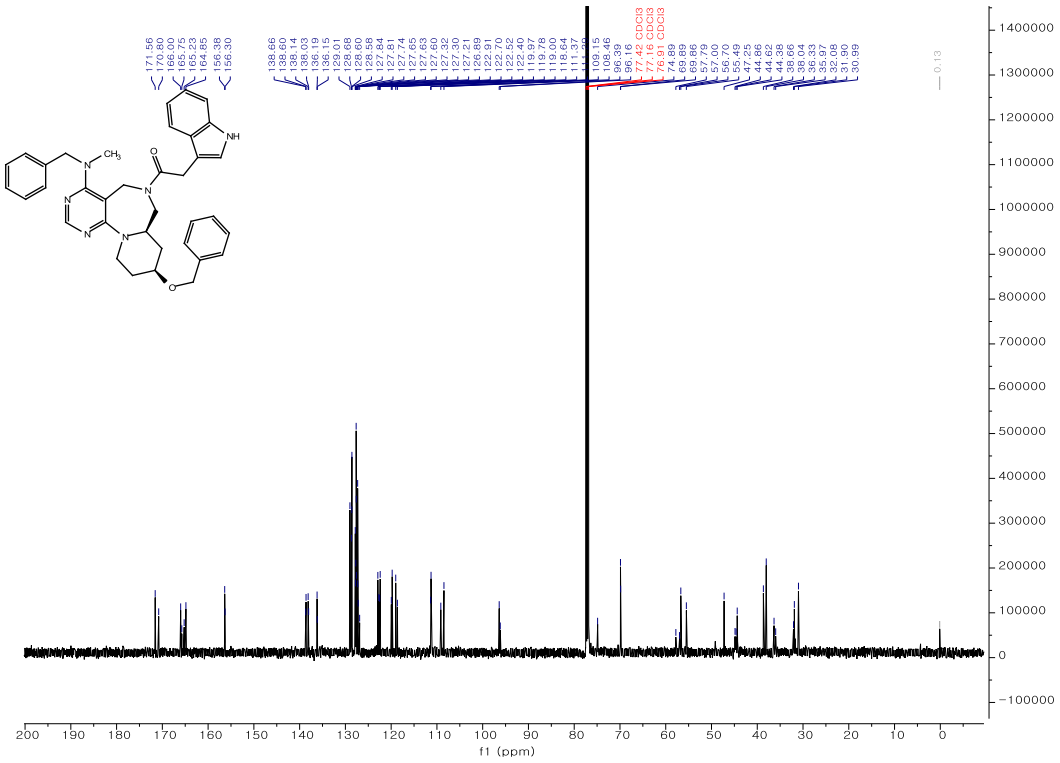

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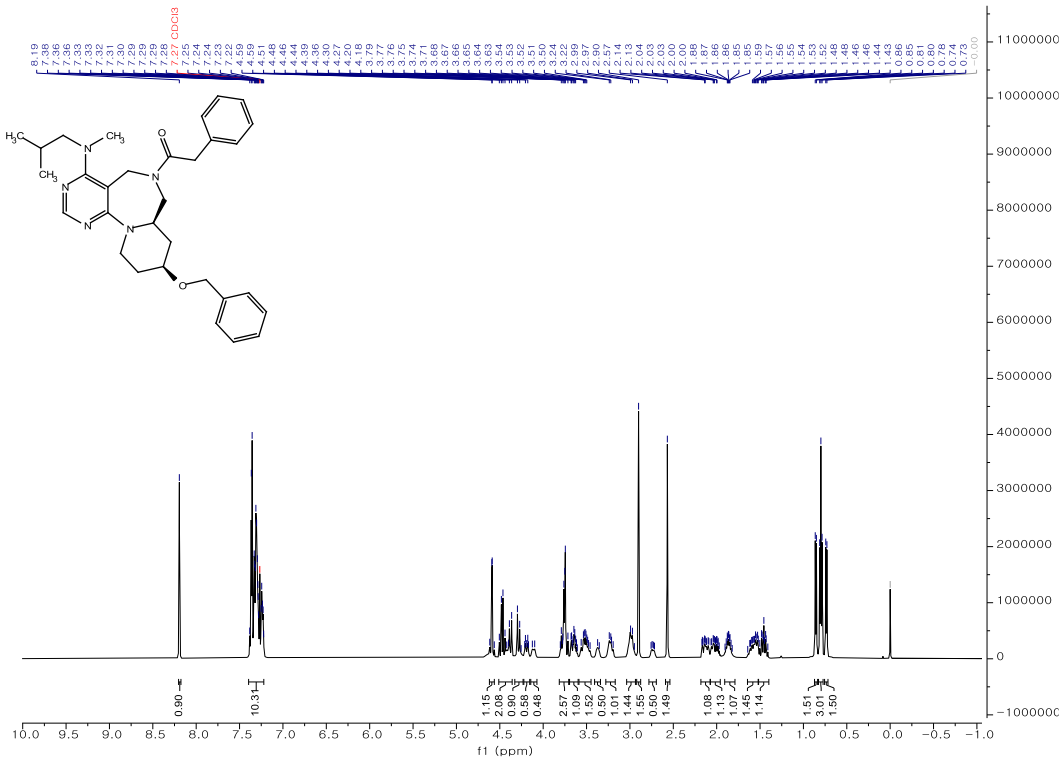

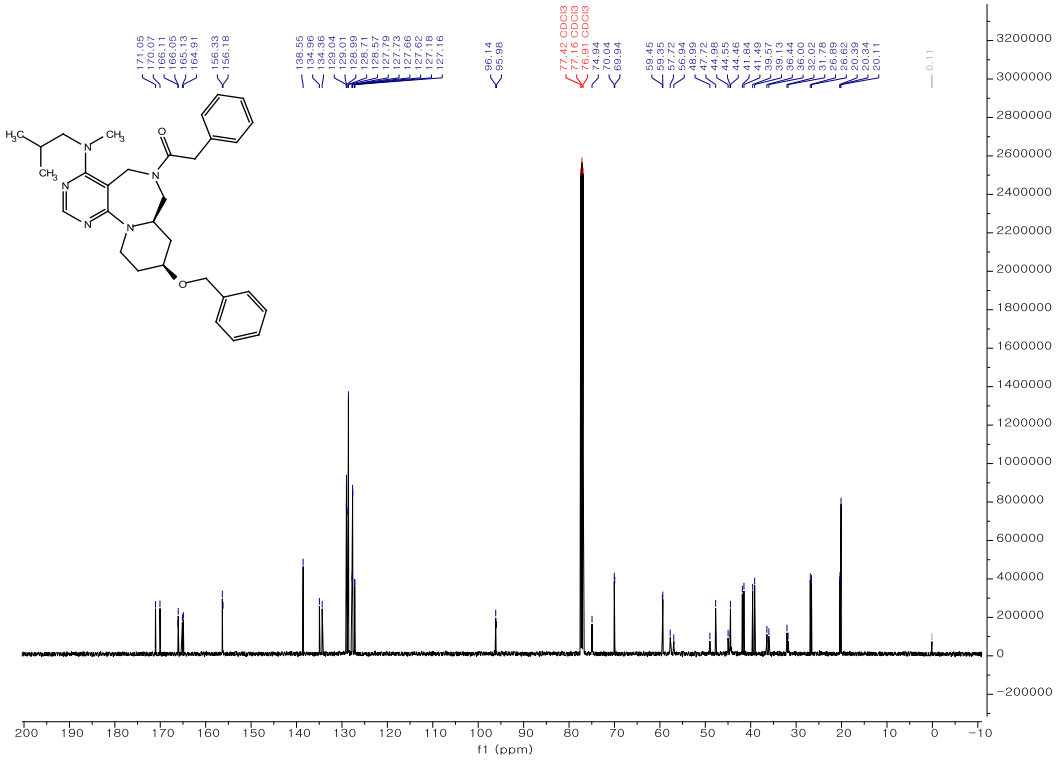

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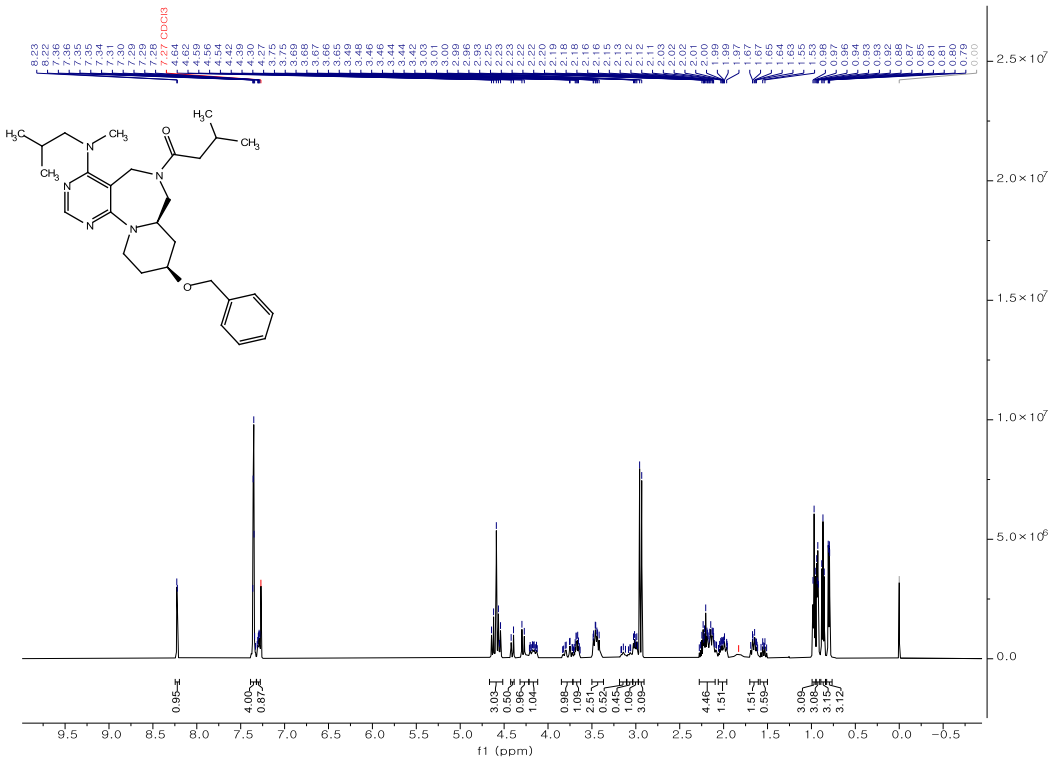

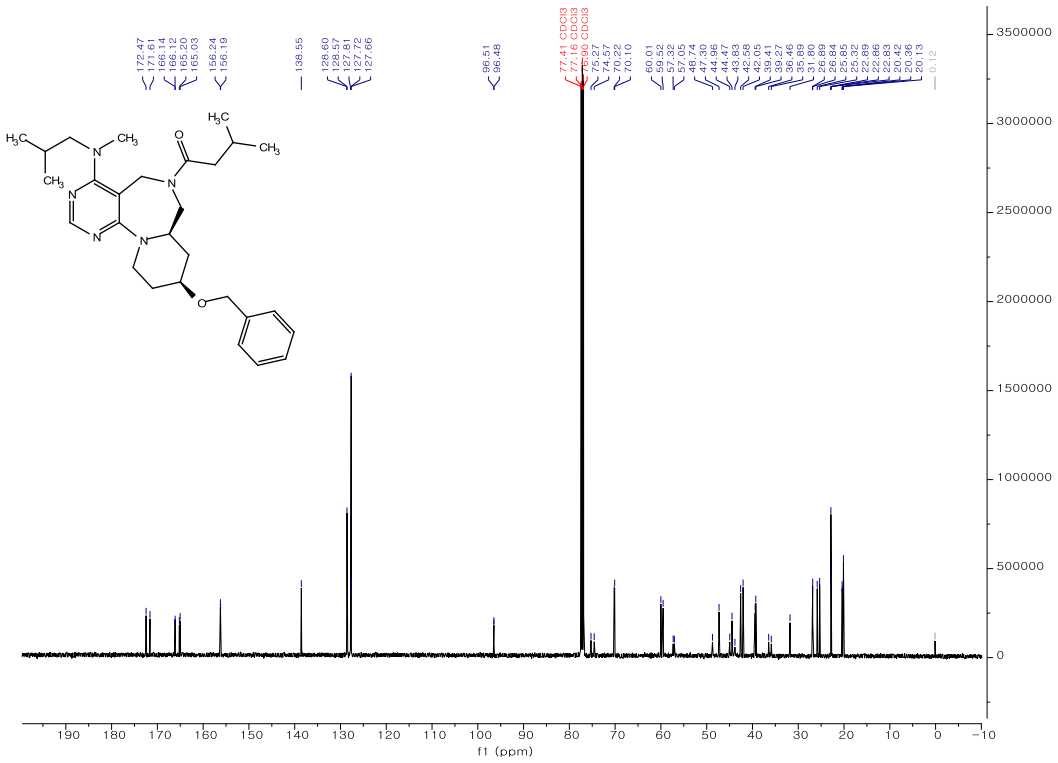

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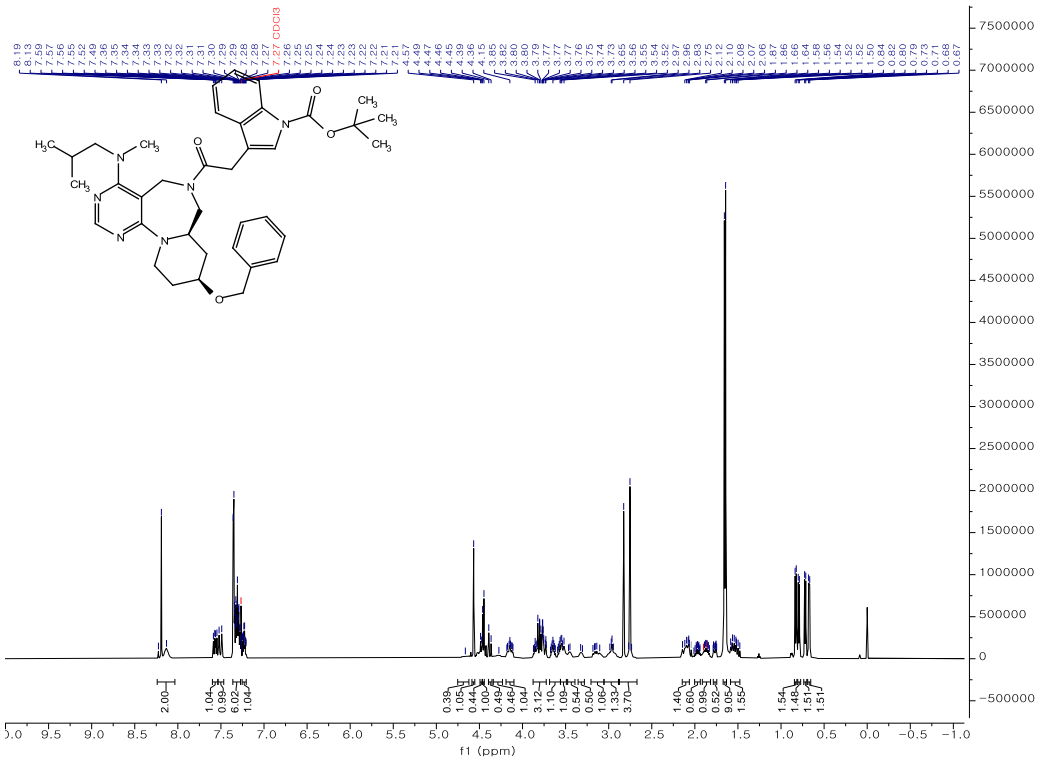

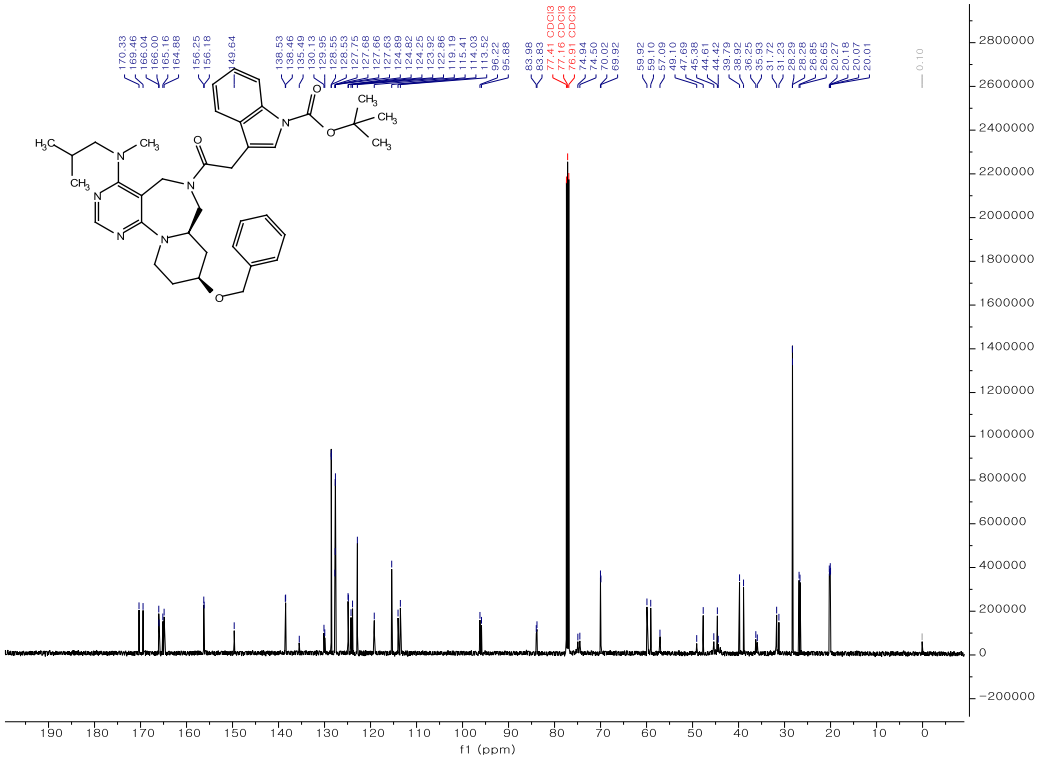

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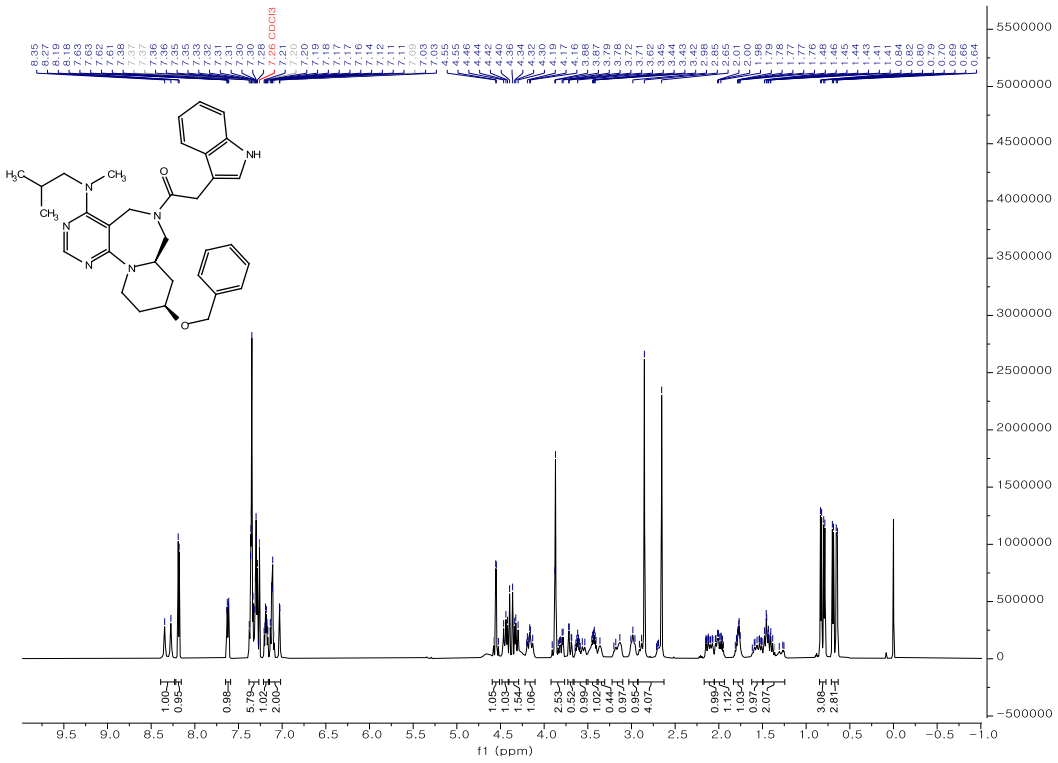

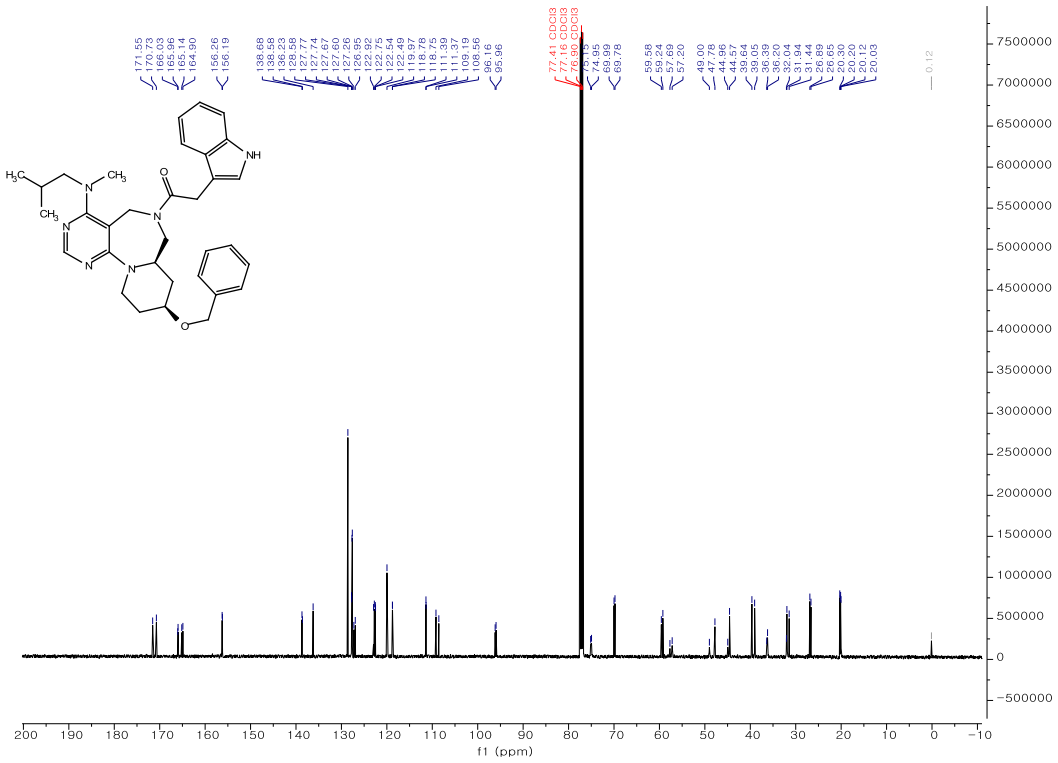

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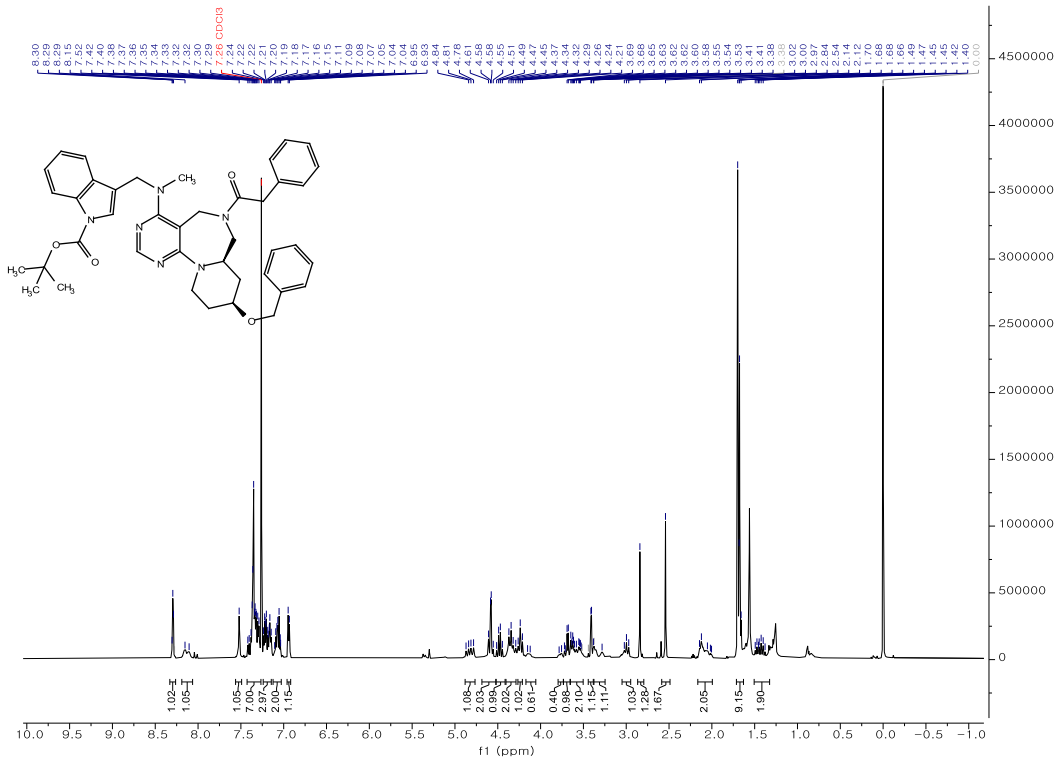

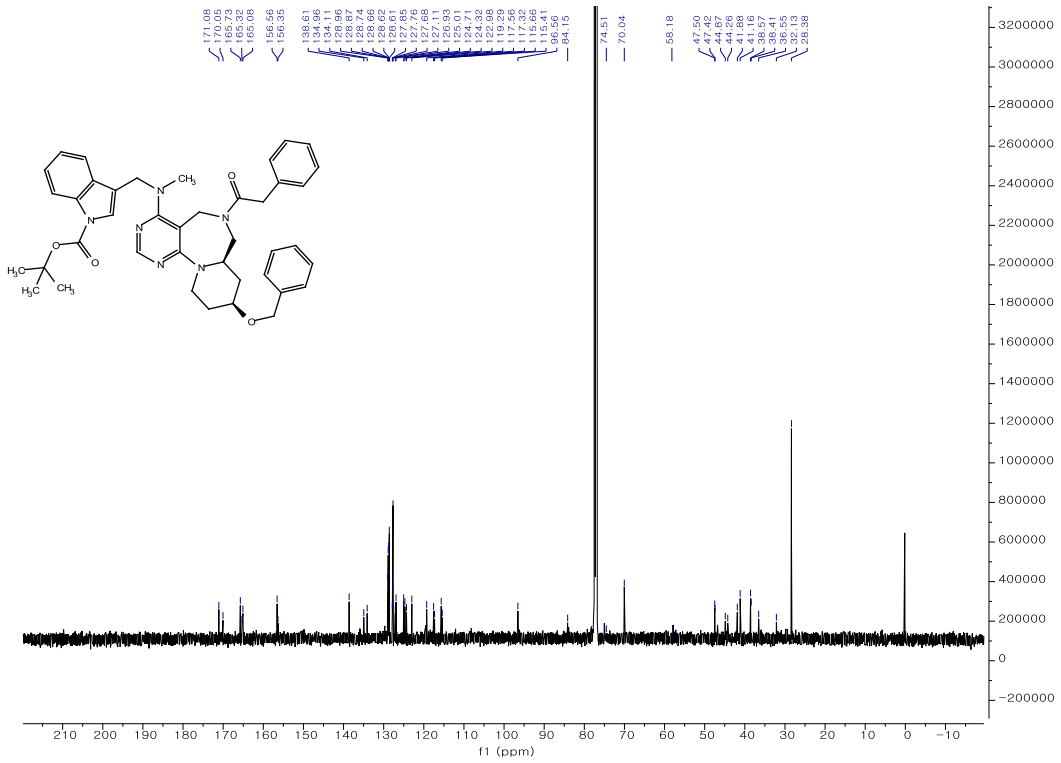

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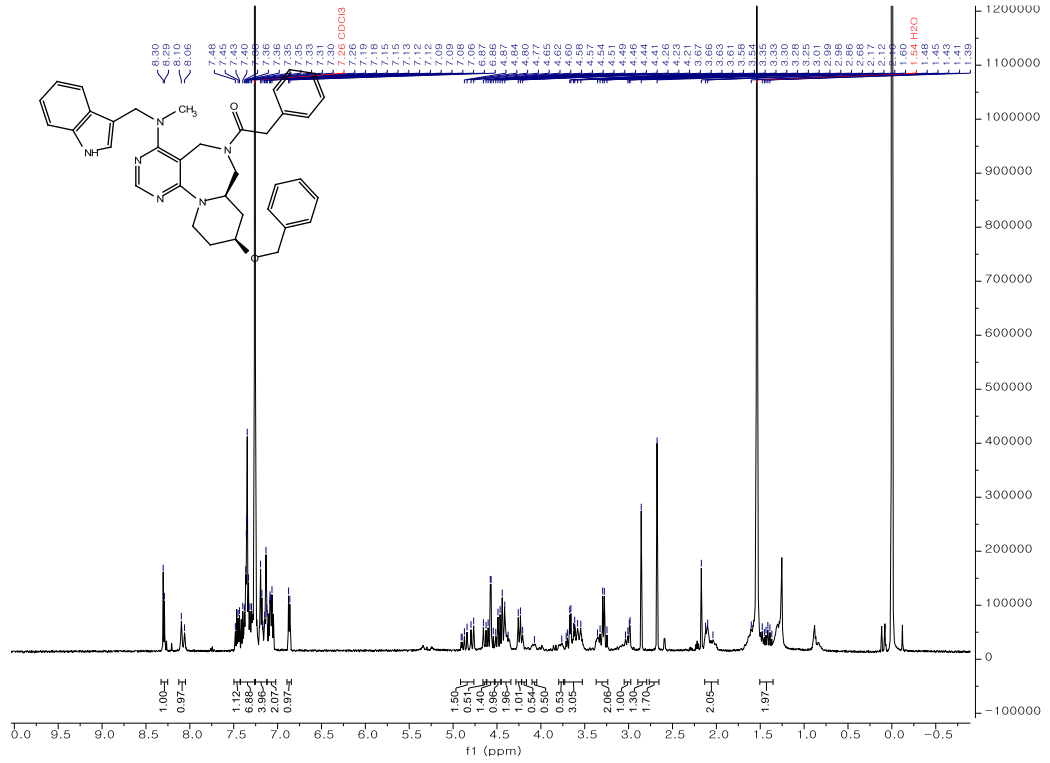

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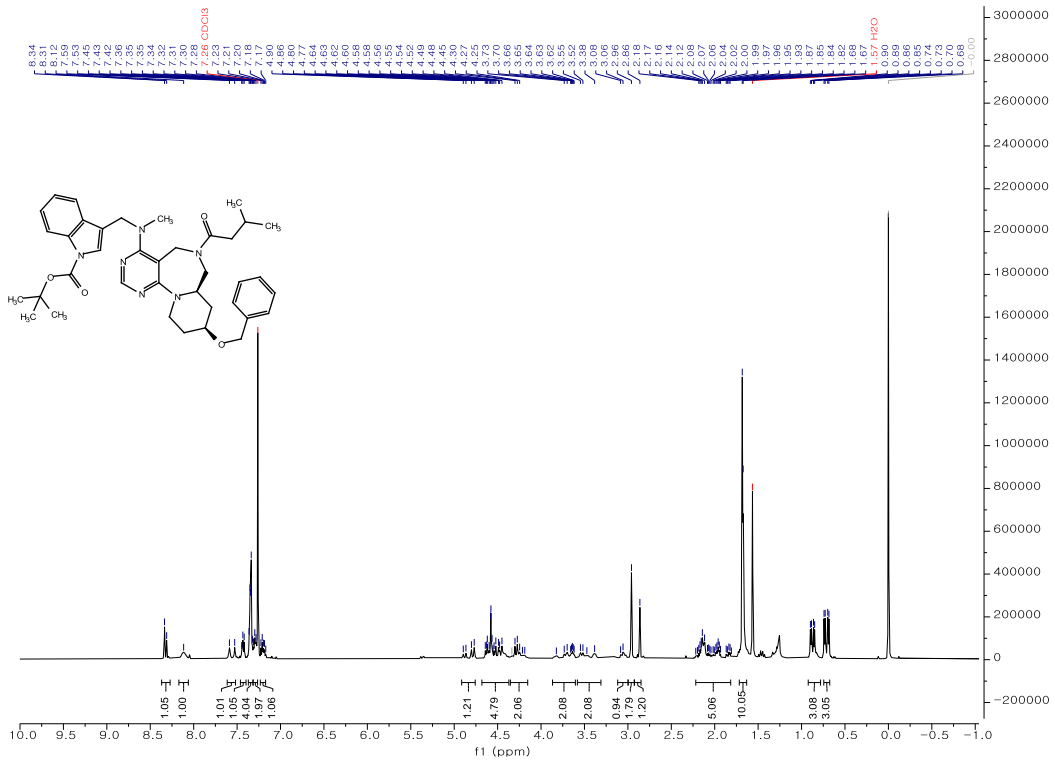

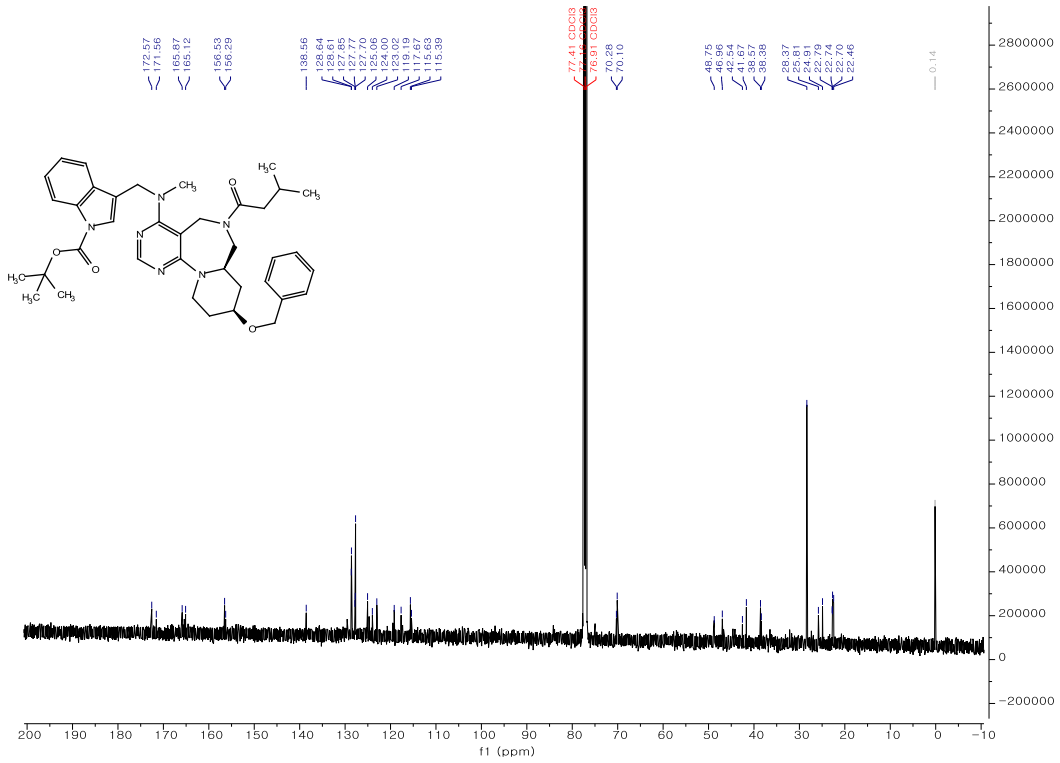

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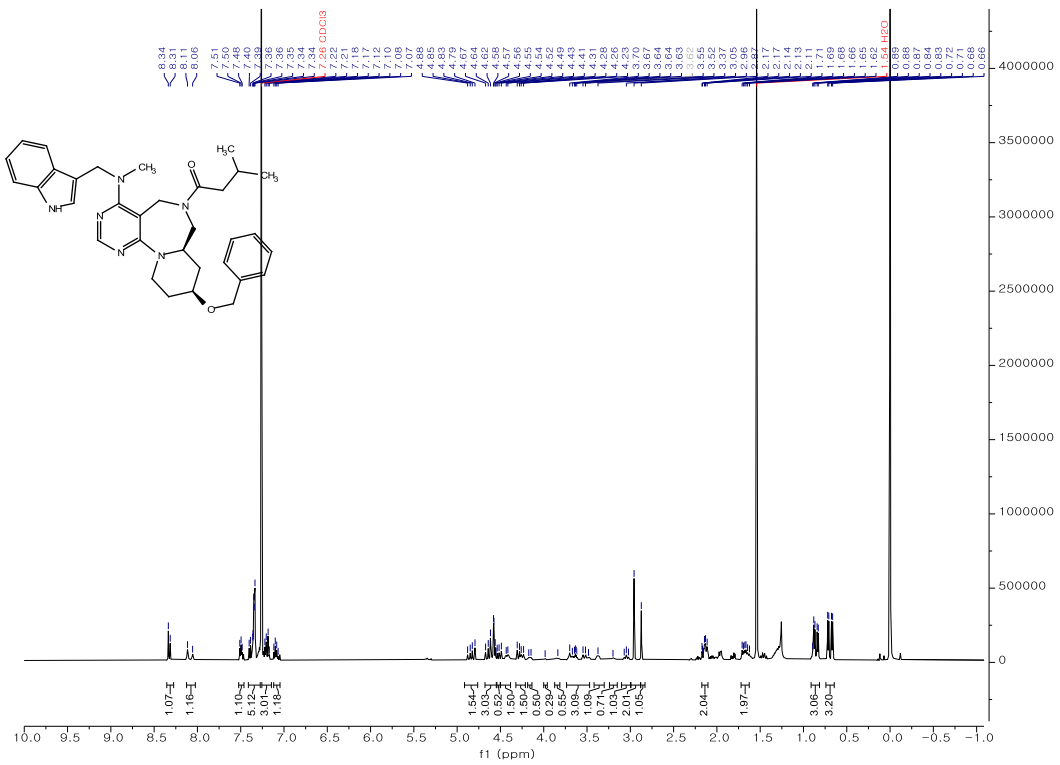
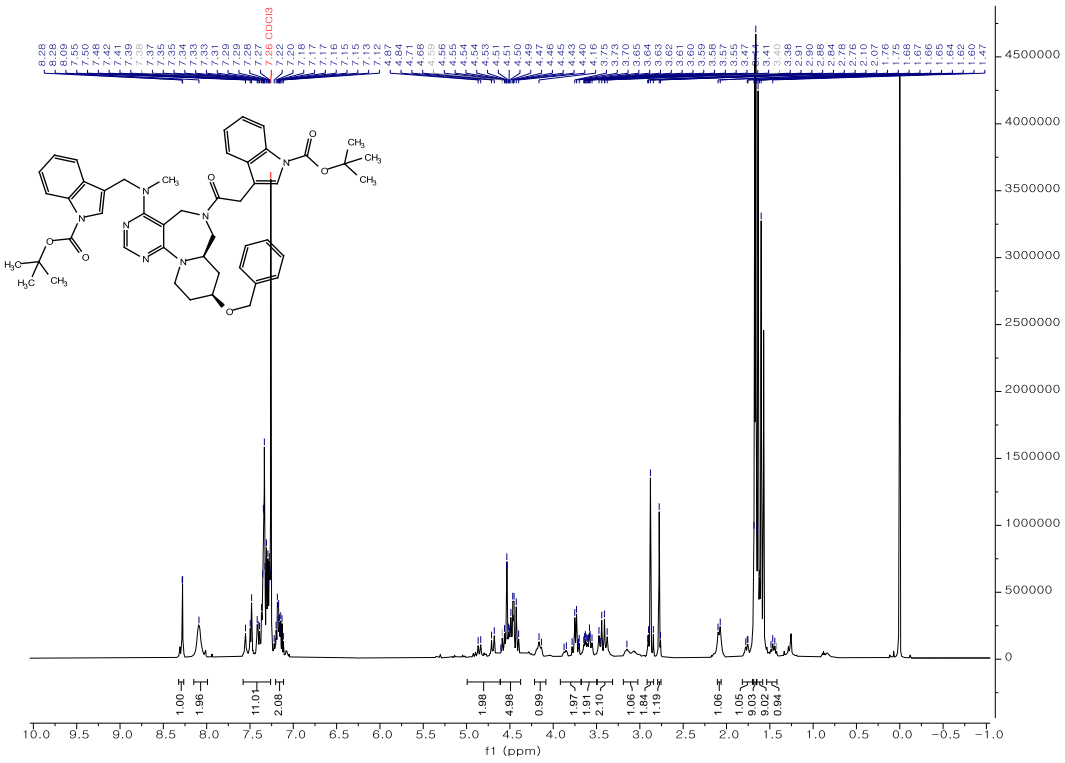
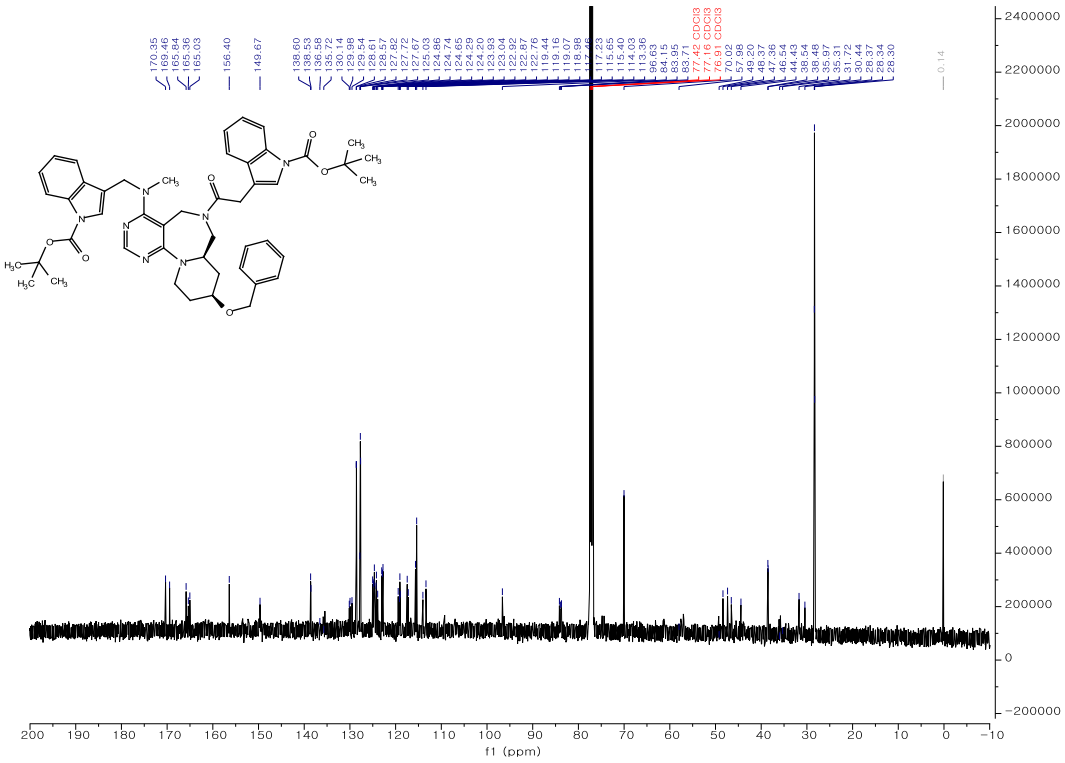
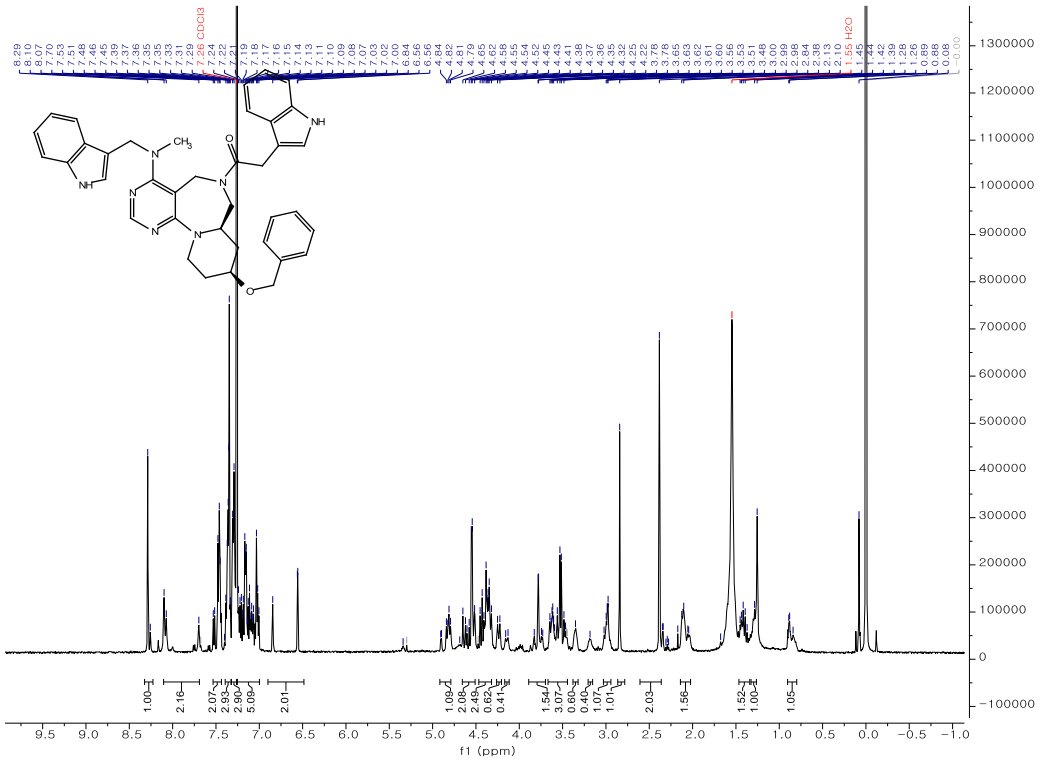


3i’


7.26 CDCl3
1.00
1.96
11.01
2.08
1.98
4.98
0.99
1.97
1.91
2.10
1.06
1.84
1.19
1.06
1.05
9.03
9.02
0.94
f1 (ppm)


77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
f1 (ppm)

3i



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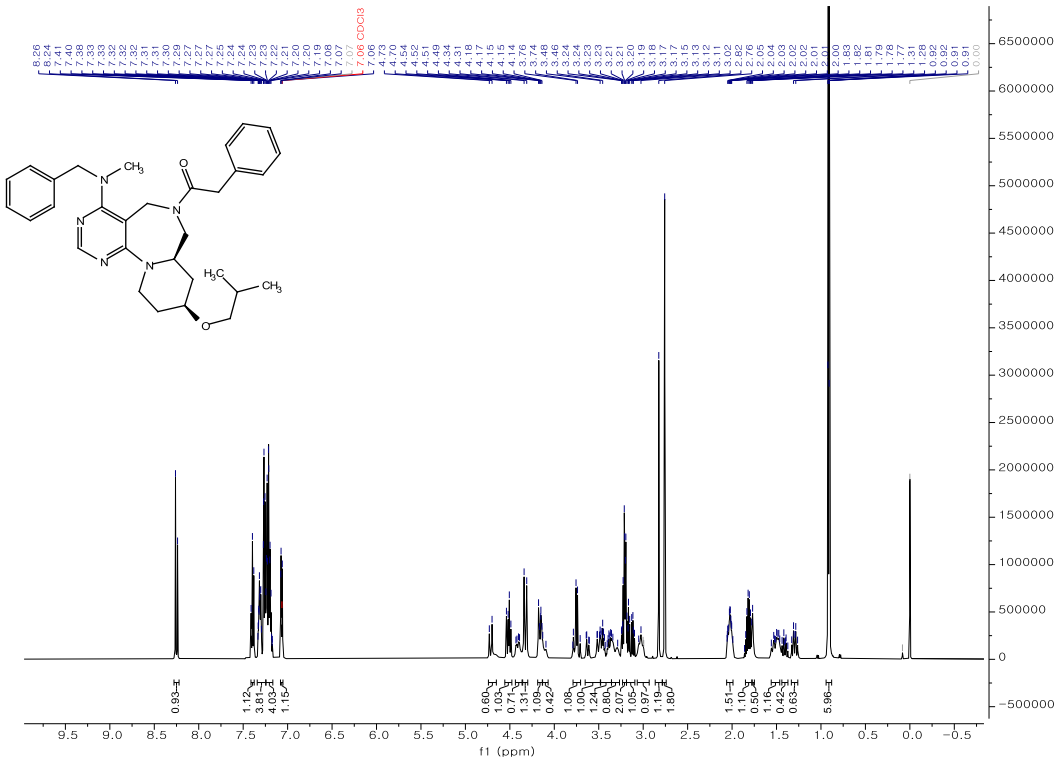
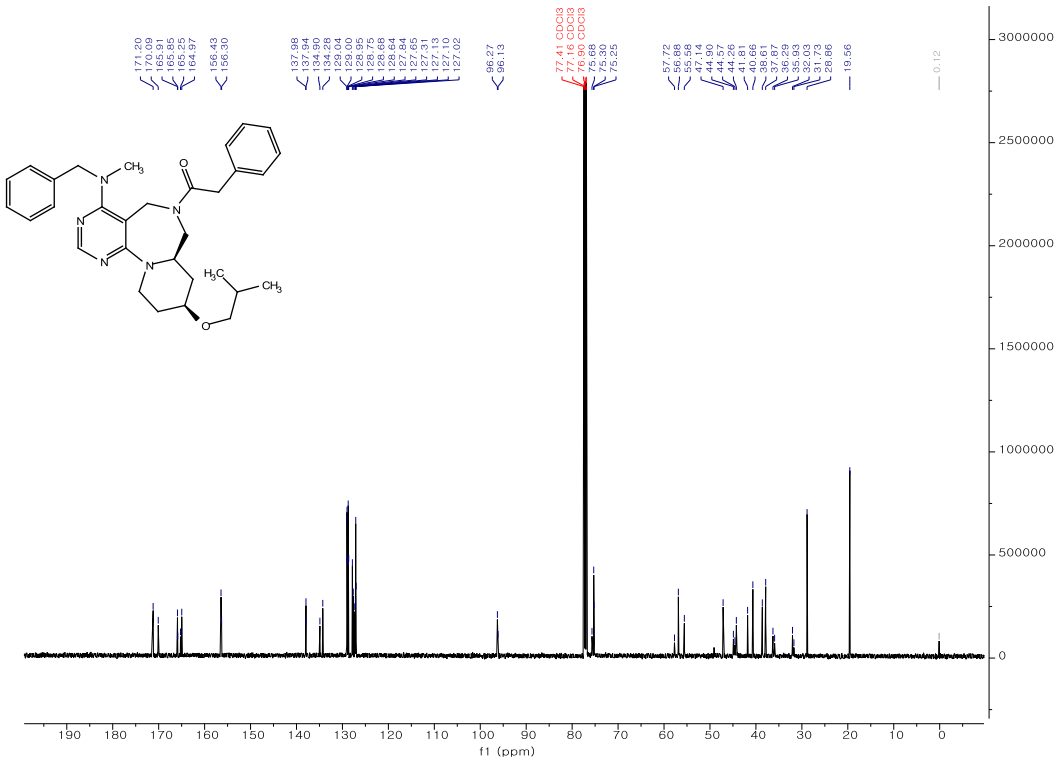
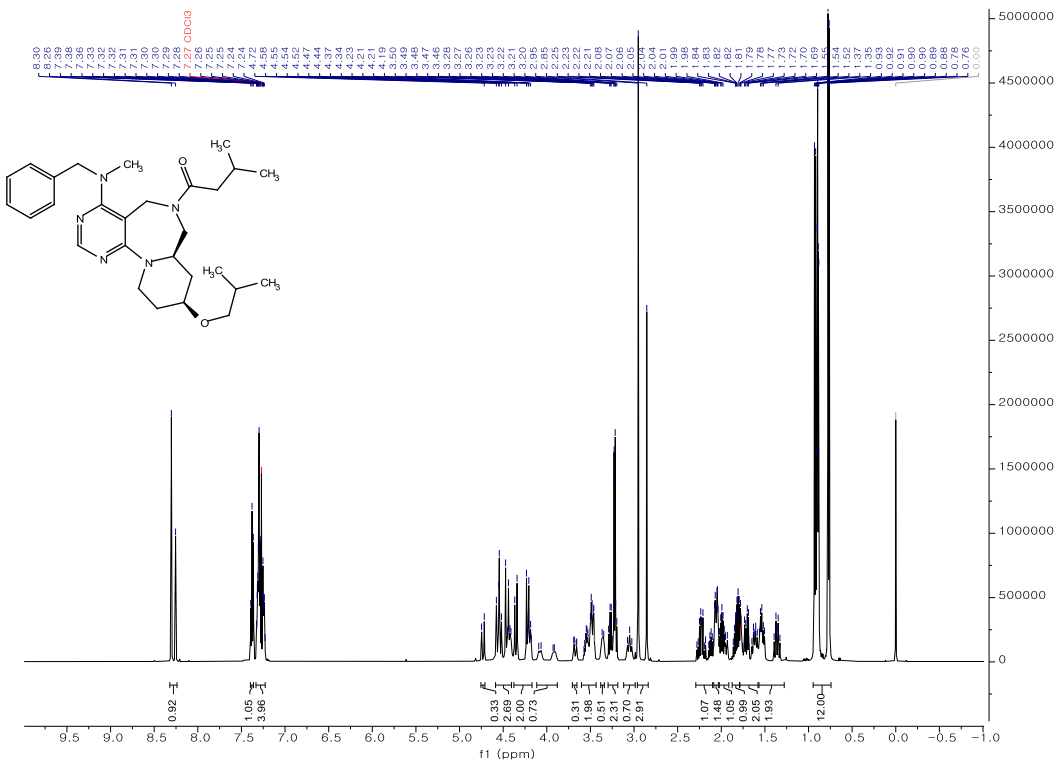
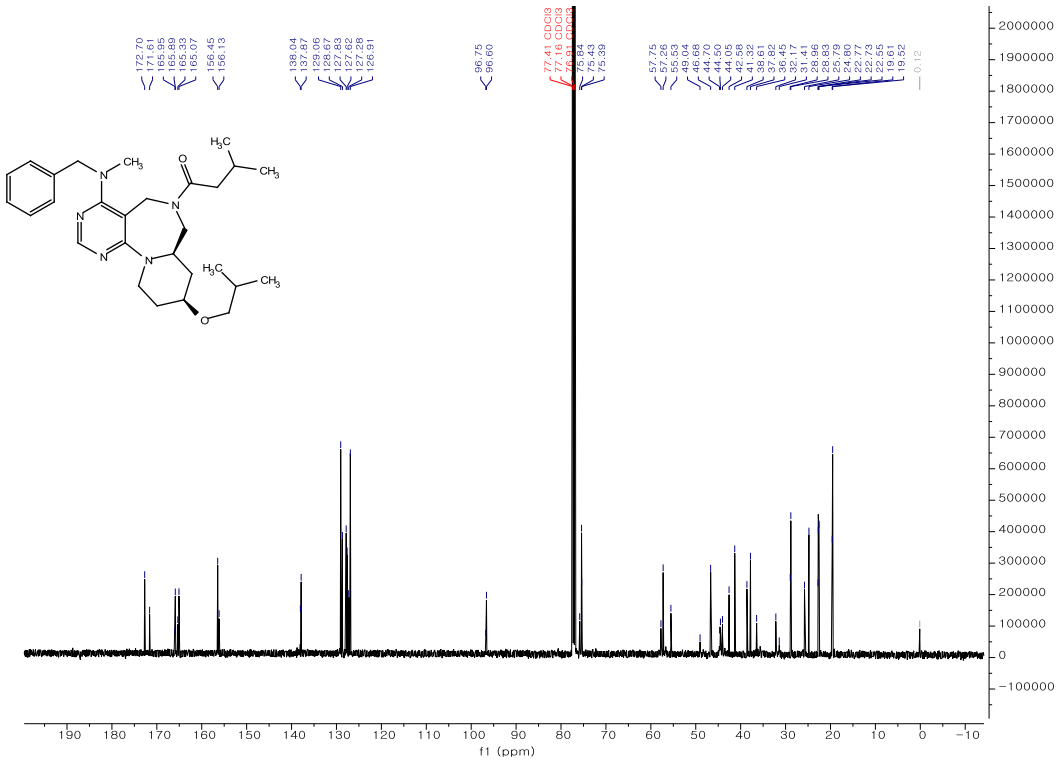


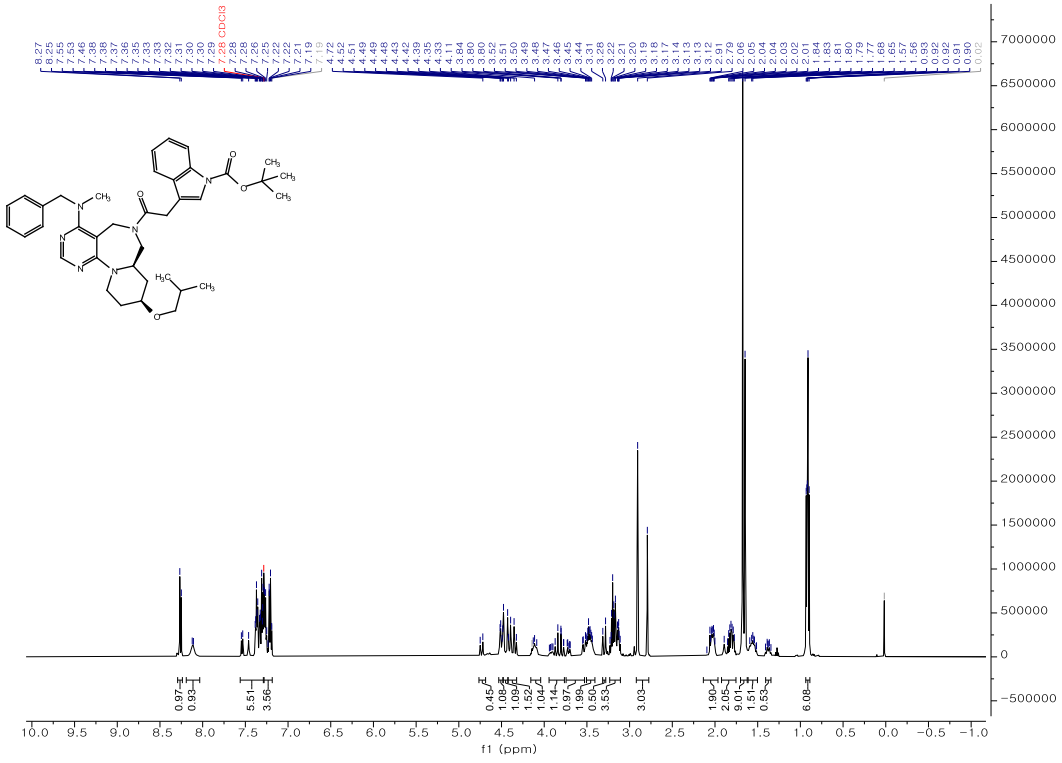


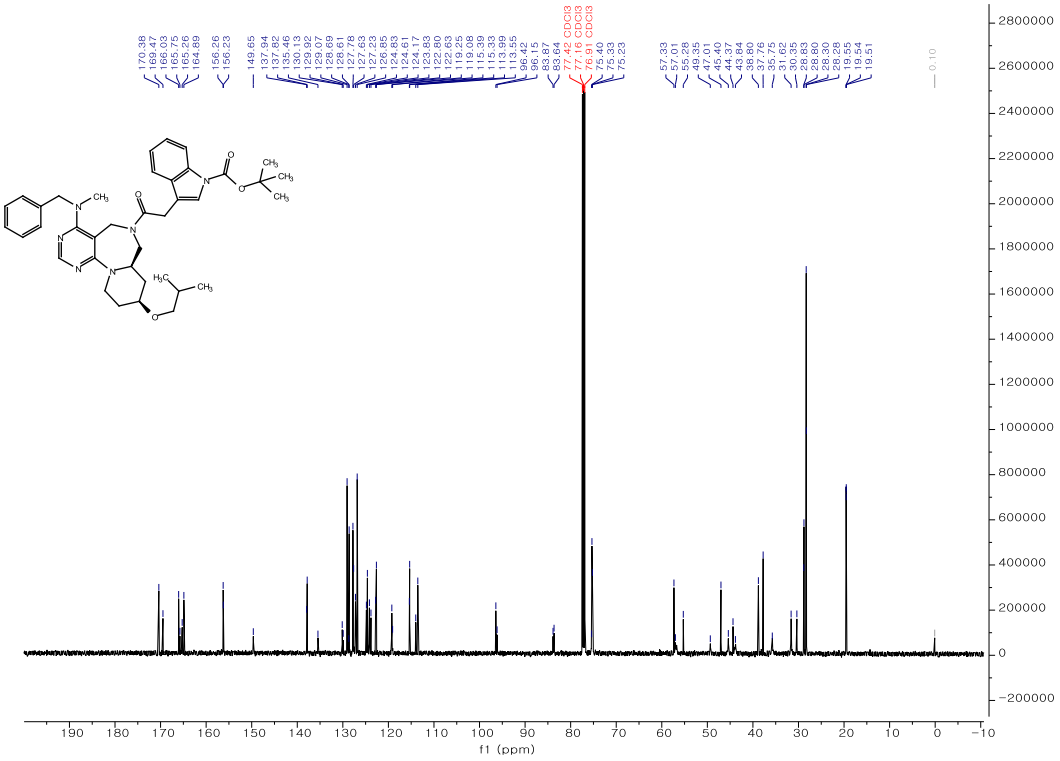
3k





3l’





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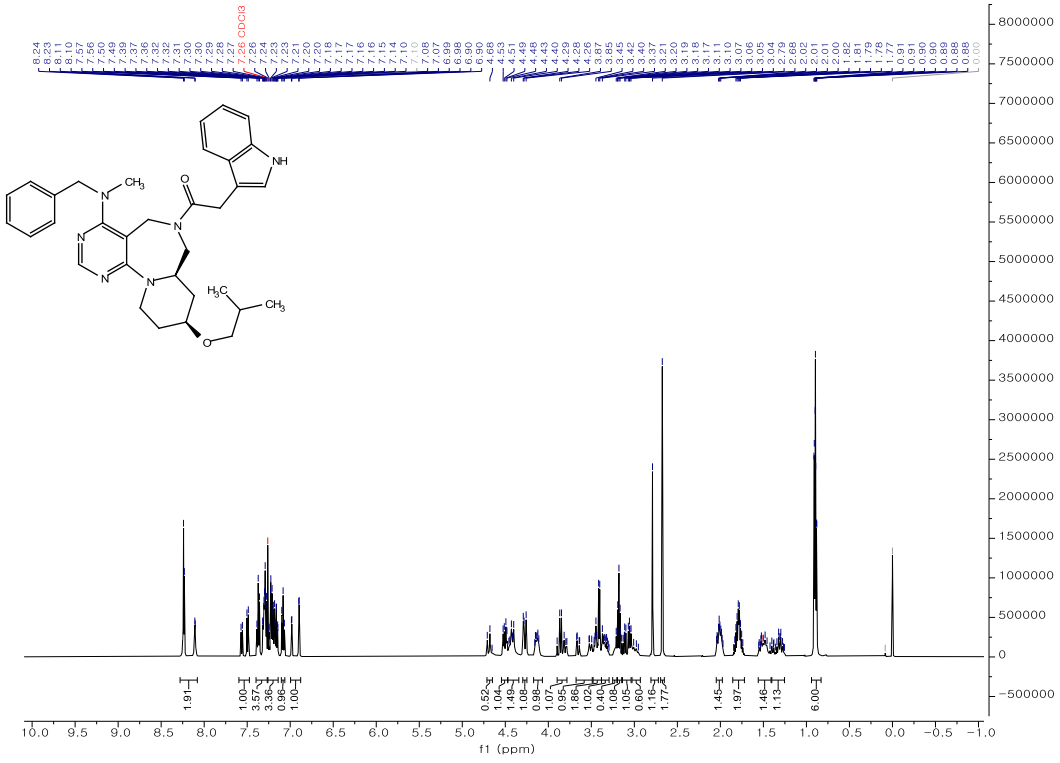
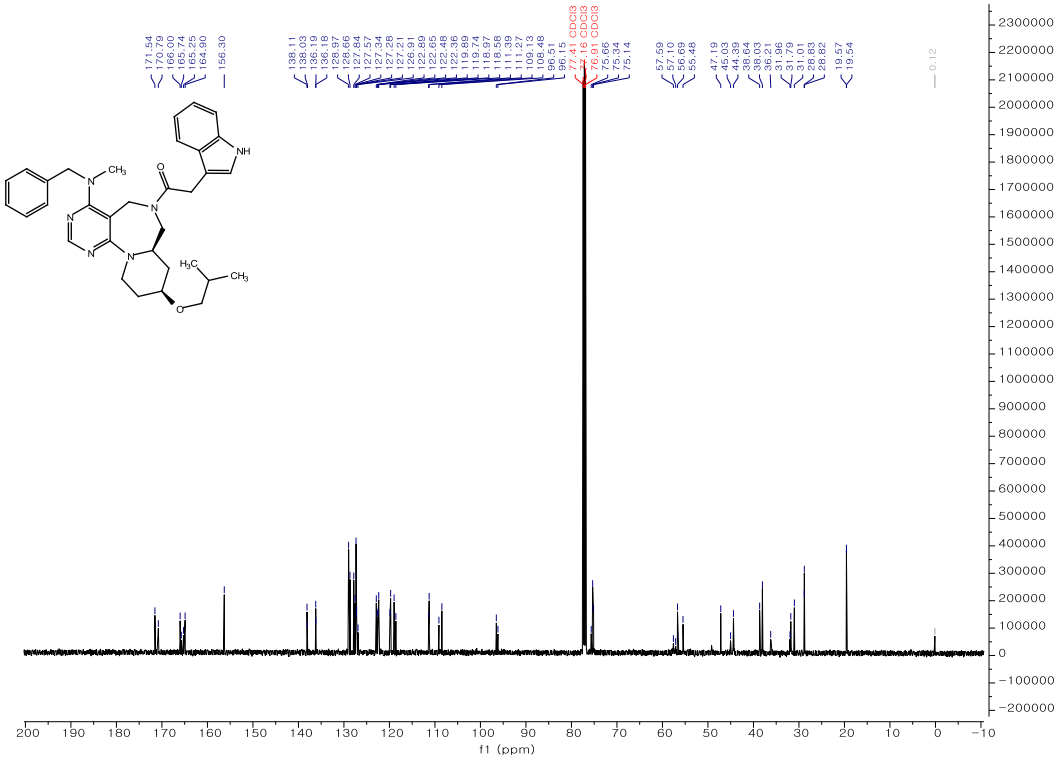
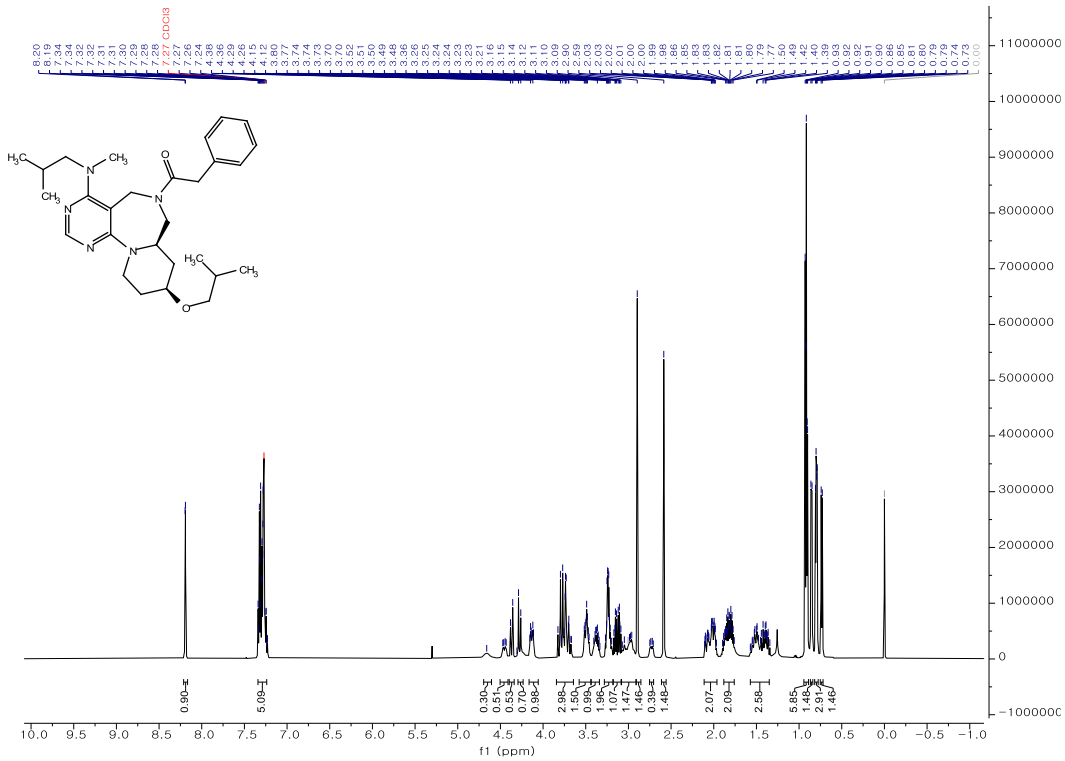
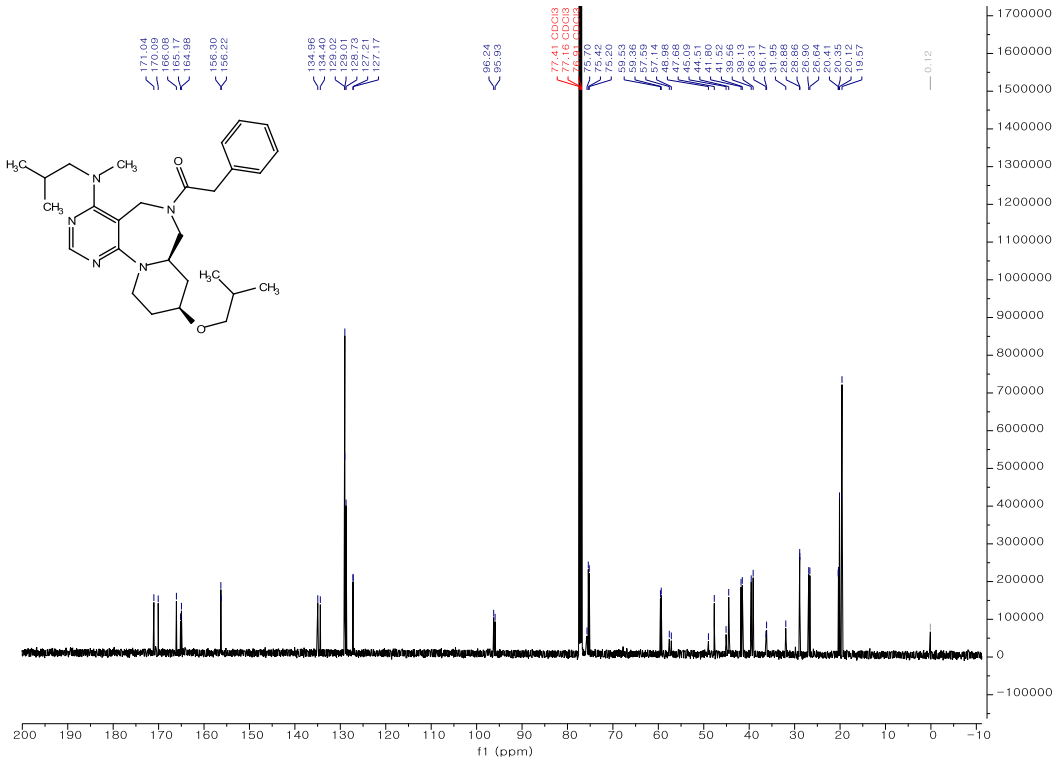


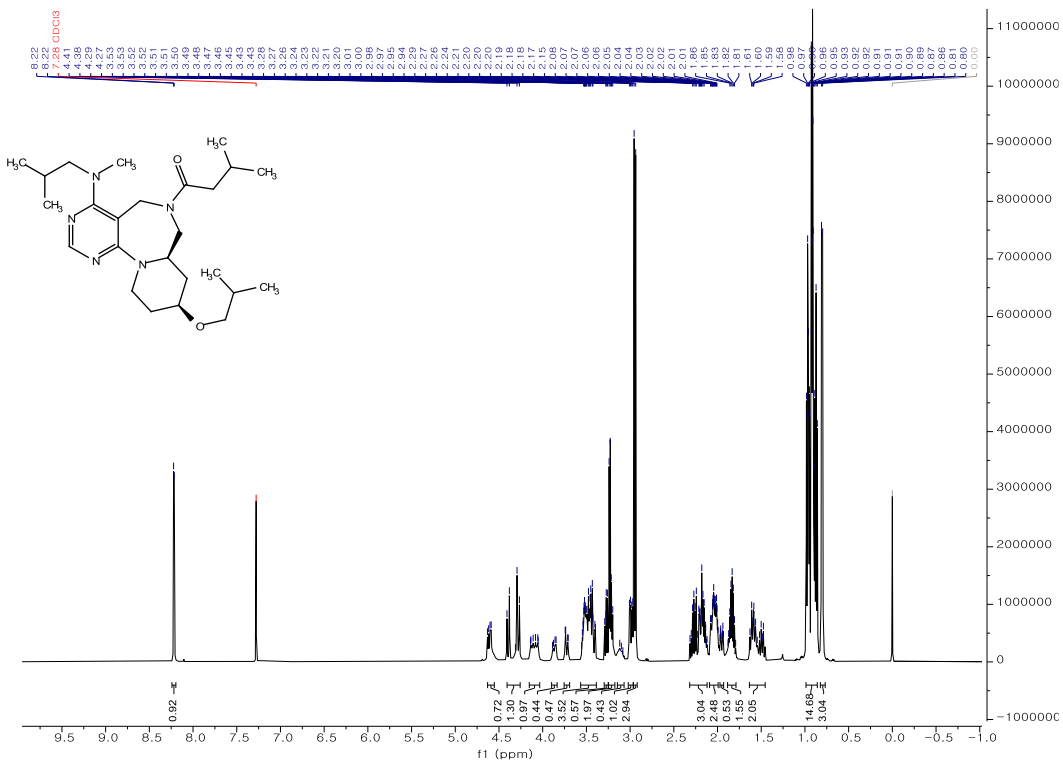


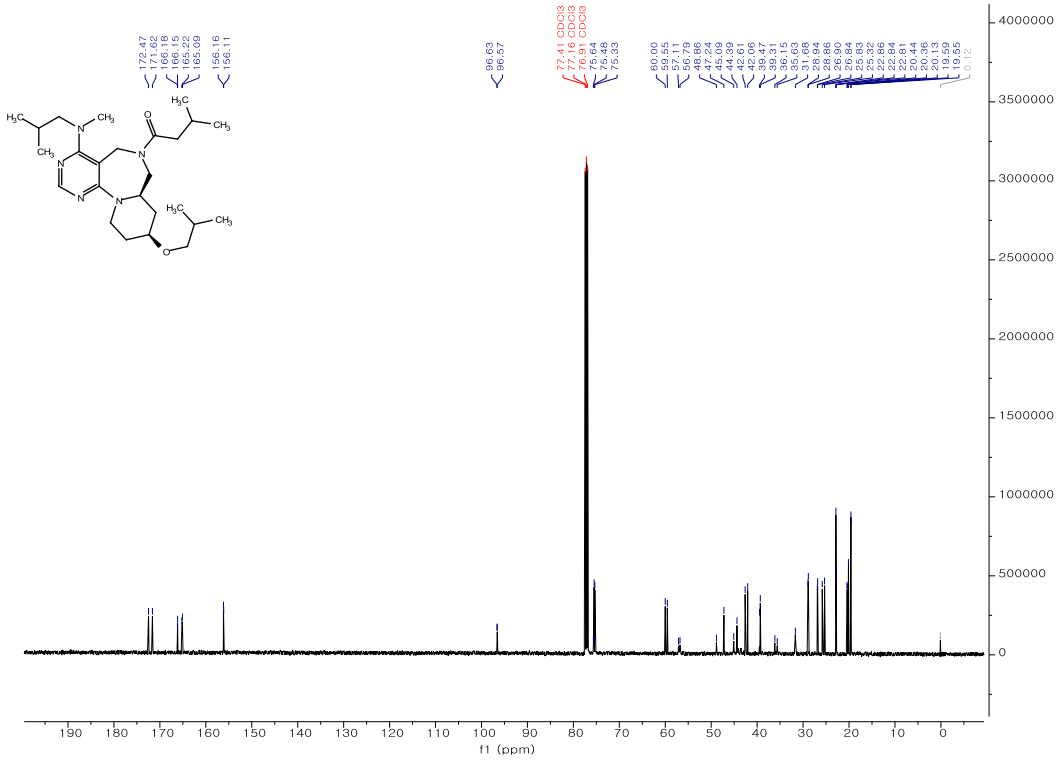
3m



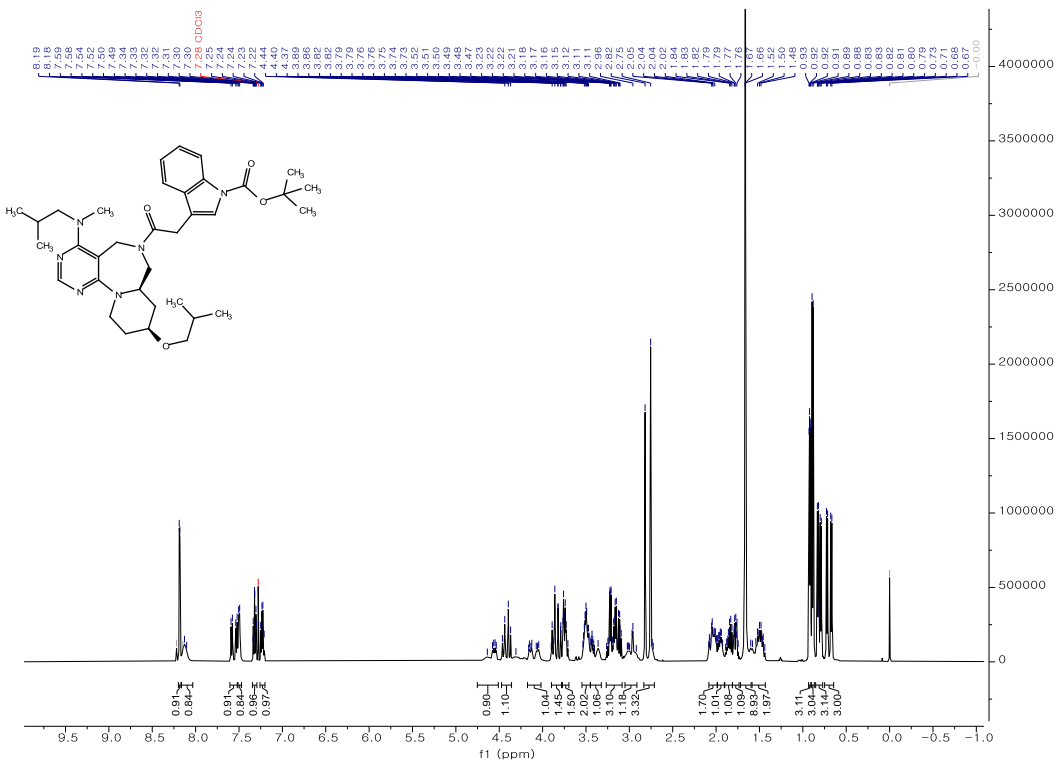

171.04
170.09
166.08
165.17
163.98
156.30
156.22
134.96
134.40
129.02
128.01
127.73
127.21
127.17
96.24
95.93
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
75.70
75.42
75.20
69.53
59.36
57.59
57.14
48.88
47.68
45.09
44.51
41.80
41.52
39.56
39.13
36.31
35.77
31.95
28.88
28.86
28.60
26.64
20.41
20.35
20.12
19.57
0.12
f1 (ppm)

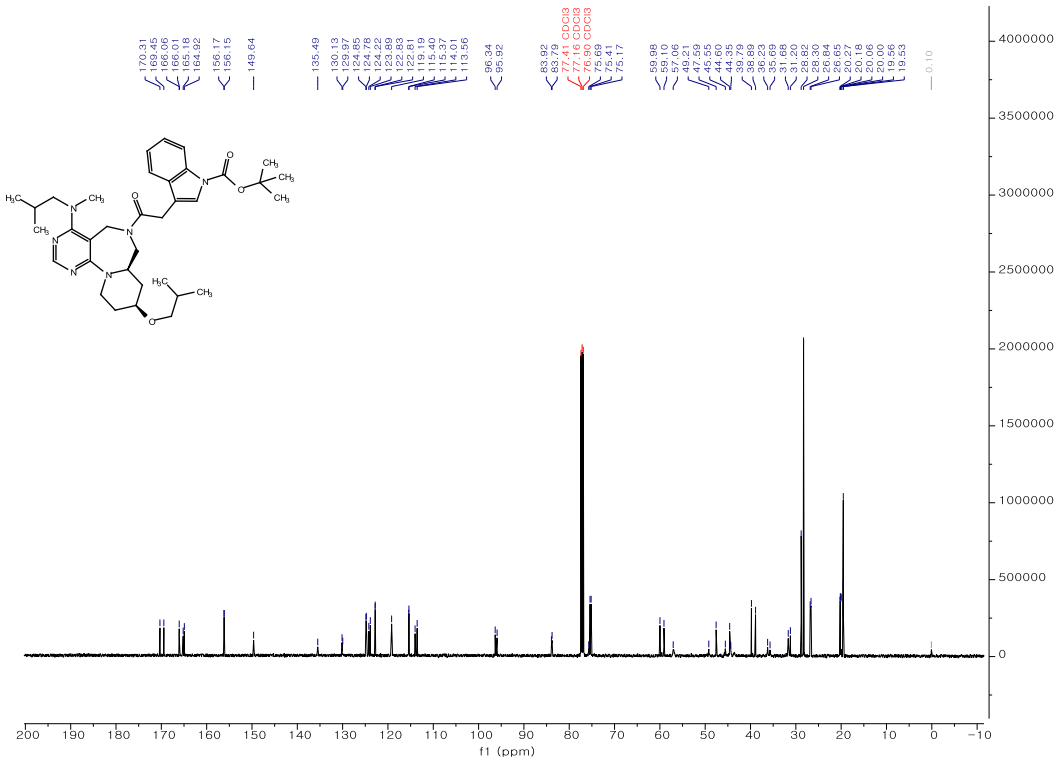
3n


8.22
8.22
7.28 CDCl3
4.41
4.38
4.28
4.27
3.53
3.53
3.52
3.52
3.51
3.51
3.50
3.49
3.48
3.47
3.46
3.45
3.43
3.28
3.27
3.26
3.24
3.23
3.22
3.21
3.20
3.01
3.00
2.98
2.97
2.95
2.94
2.29
2.27
2.26
2.24
2.21
2.20
2.20
2.19
2.18
2.18
2.17
2.15
2.09
2.07
2.07
2.06
2.05
2.04
2.04
2.03
2.02
2.02
2.01
2.01
1.86
1.85
1.83
1.82
1.81
1.61
1.60
1.59
1.58
0.98
0.97
0.96
0.96
0.95
0.95
0.92
0.92
0.91
0.91
0.91
0.90
0.89
0.87
0.86
0.81
0.80
0.00
0.92
0.72
1.99
1.97
0.44
0.47
3.52
0.57
1.97
0.43
1.02
2.94
3.04
2.48
0.53
1.55
2.05
14.68
3.04
f1 (ppm)



3o’





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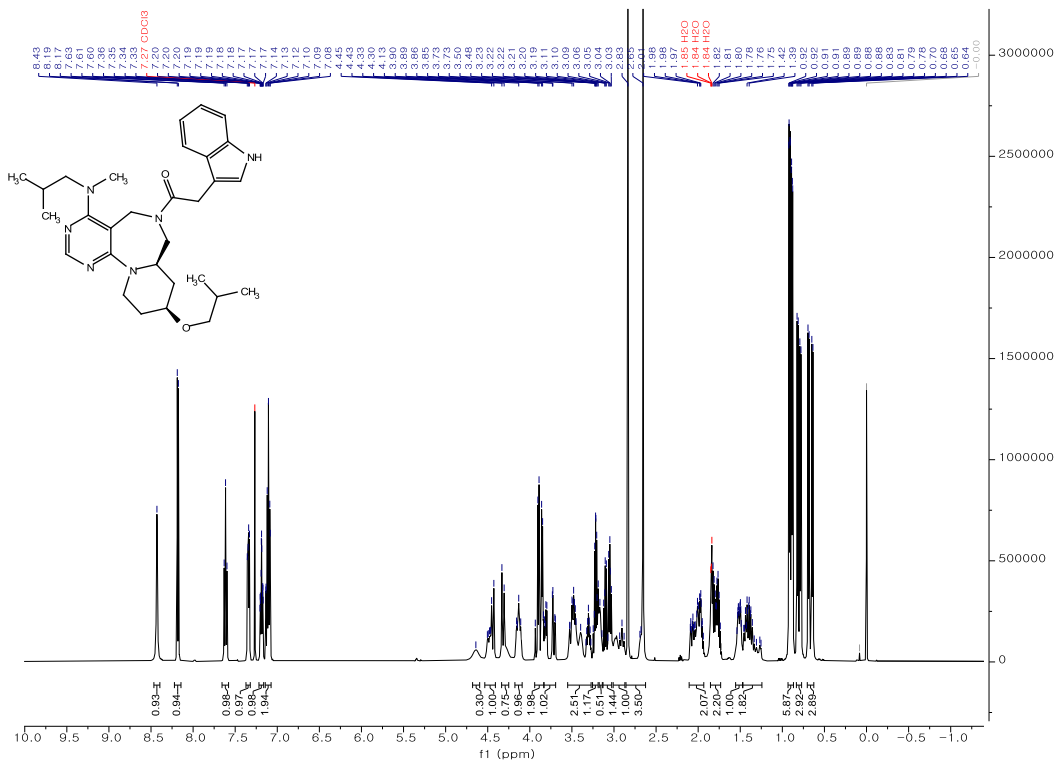

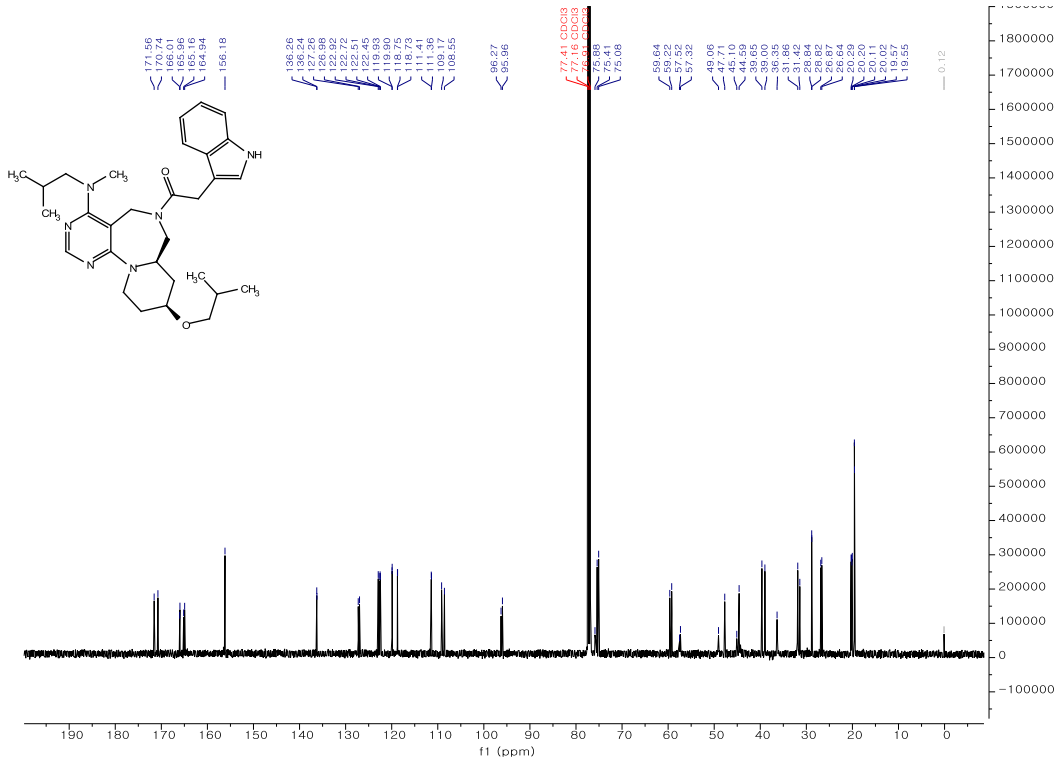

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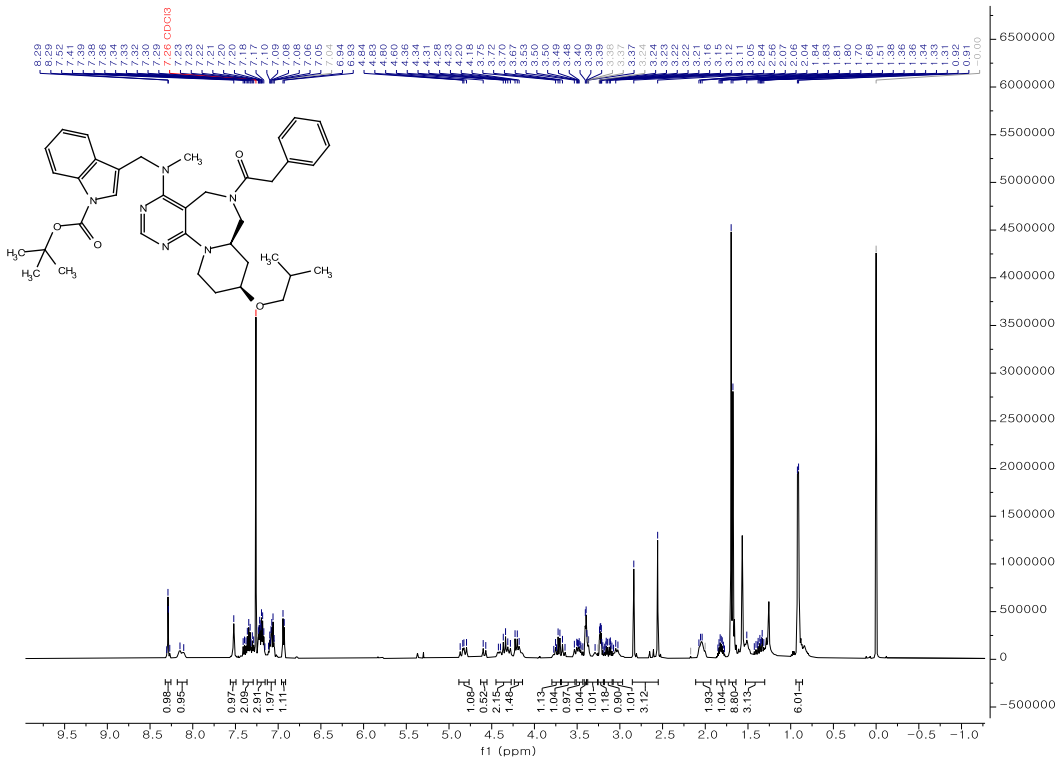

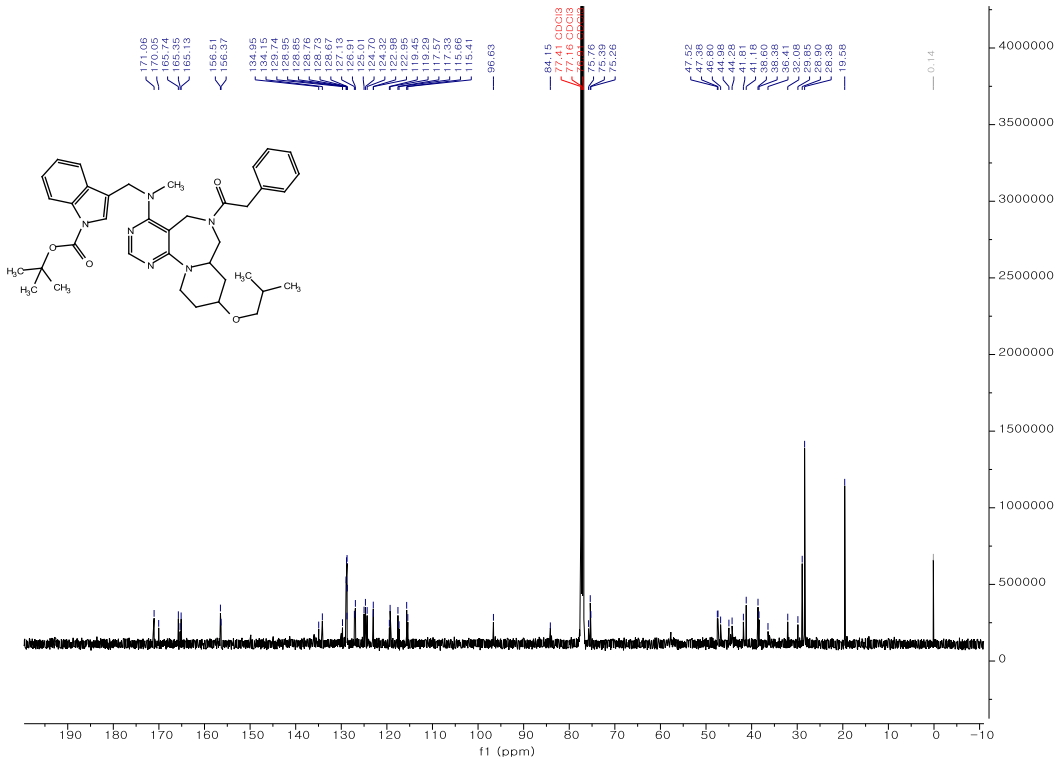

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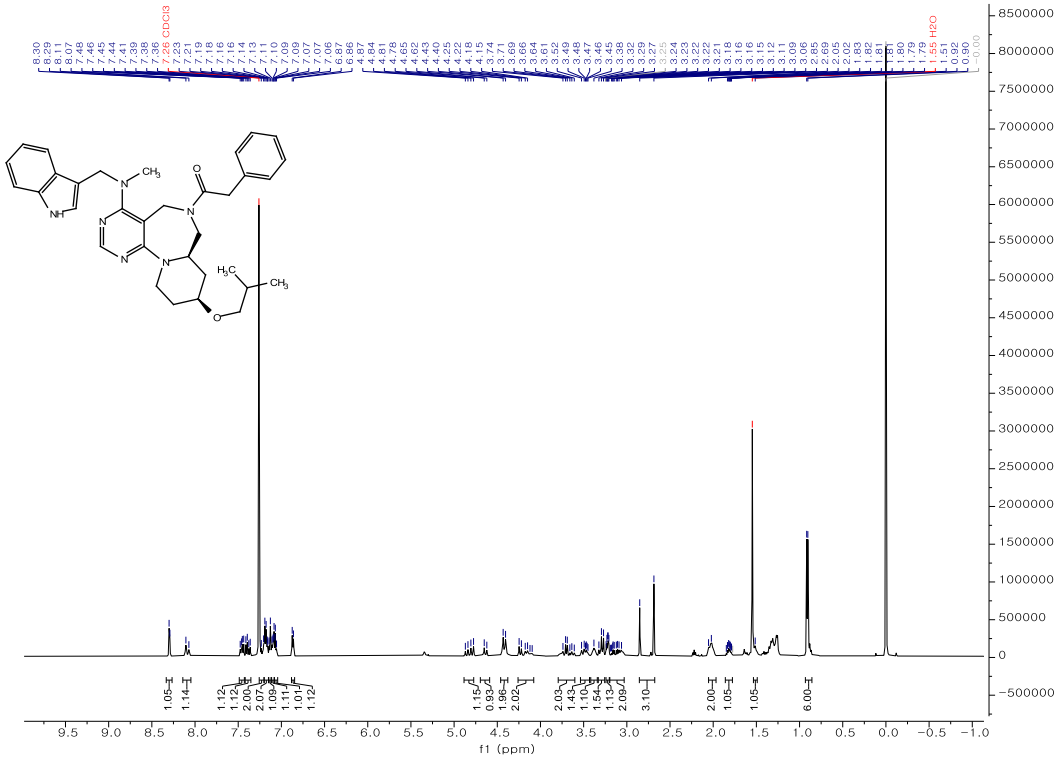

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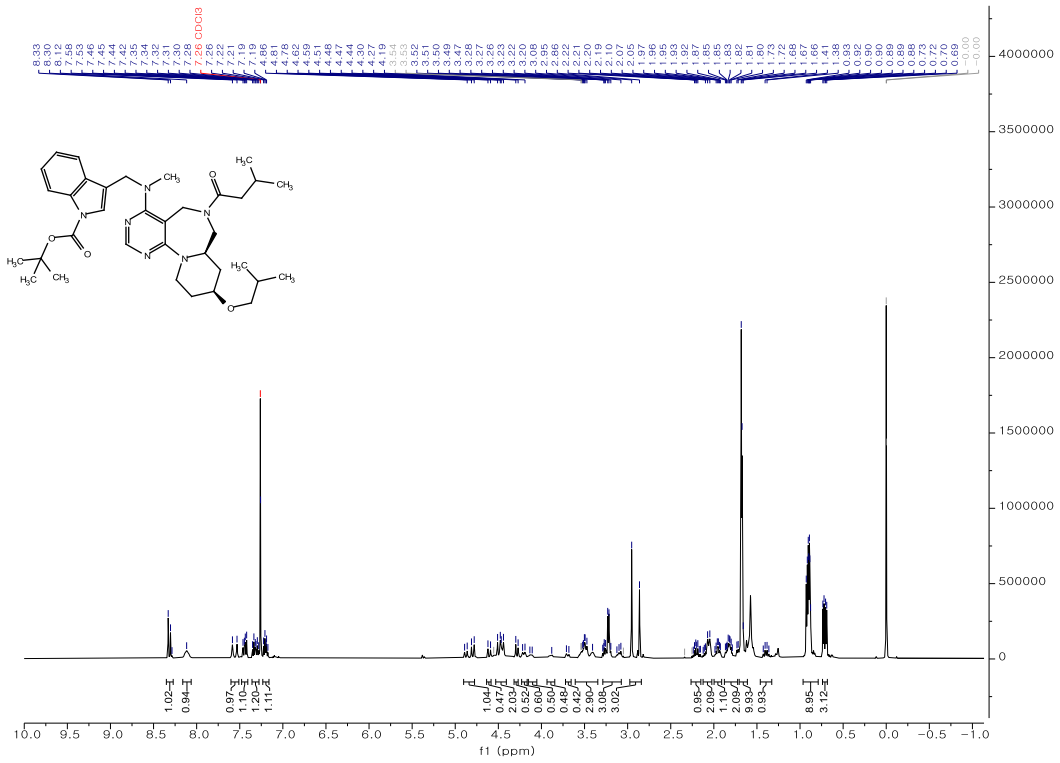

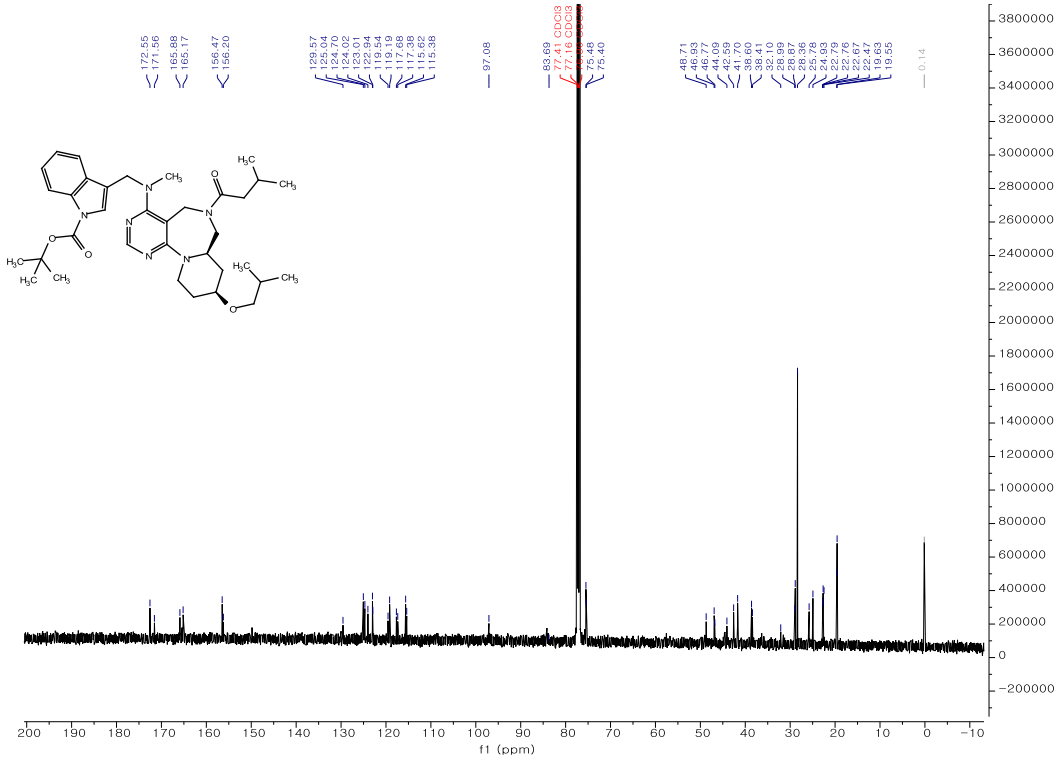

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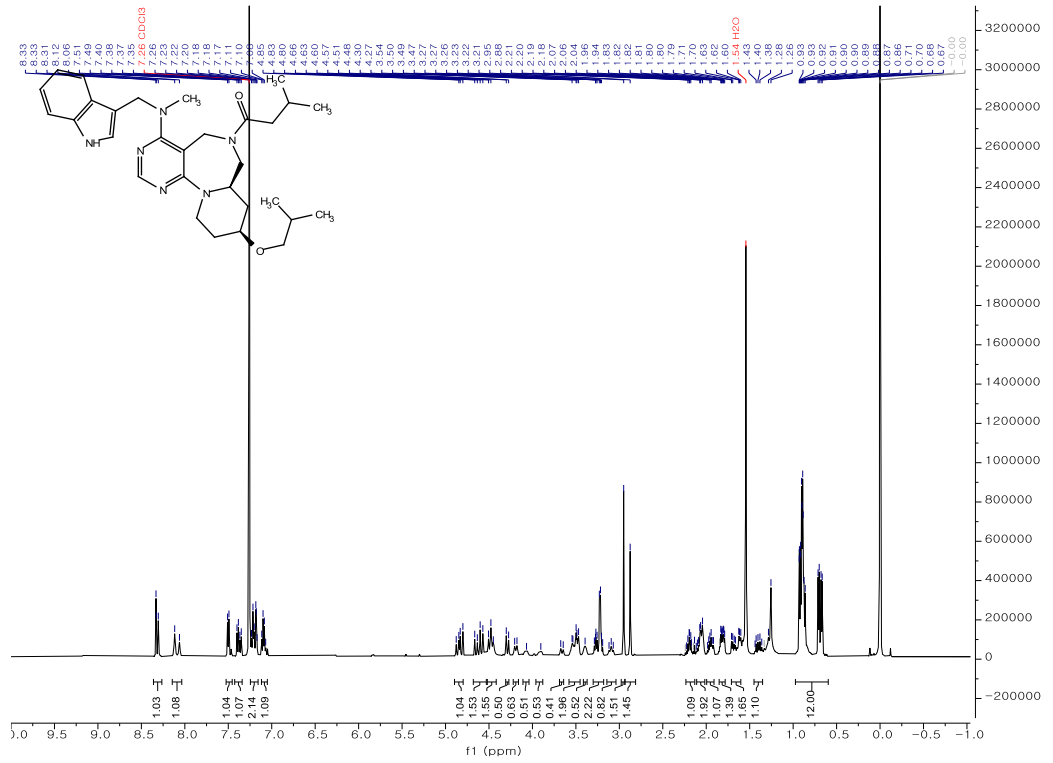
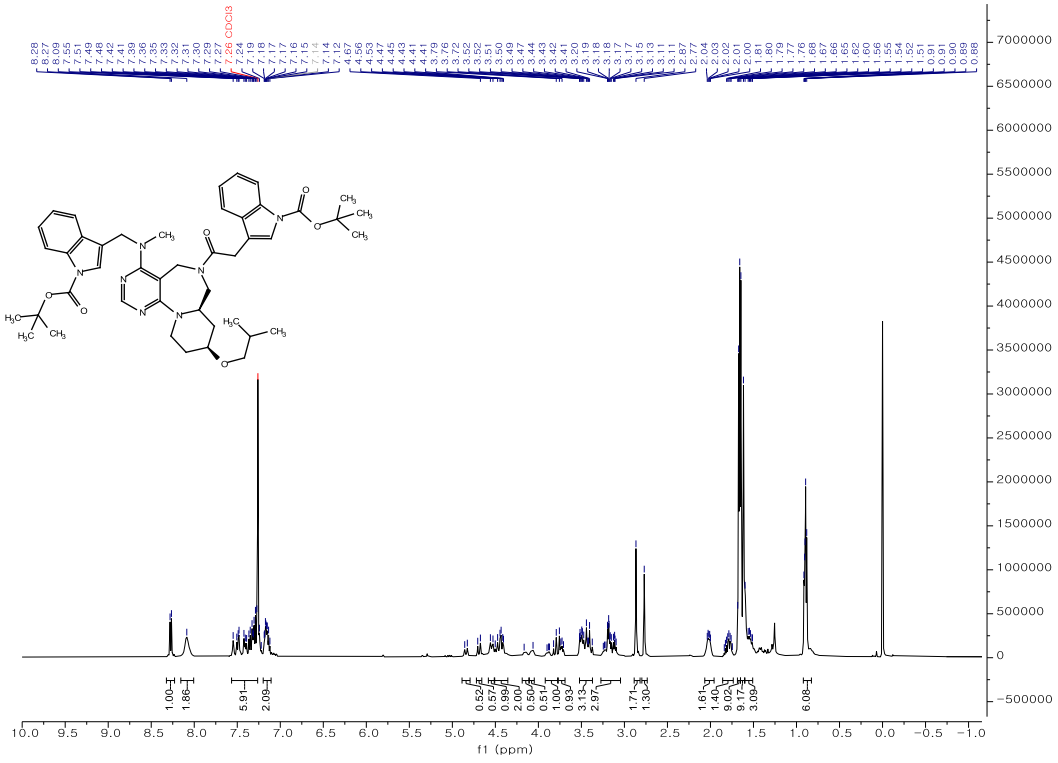
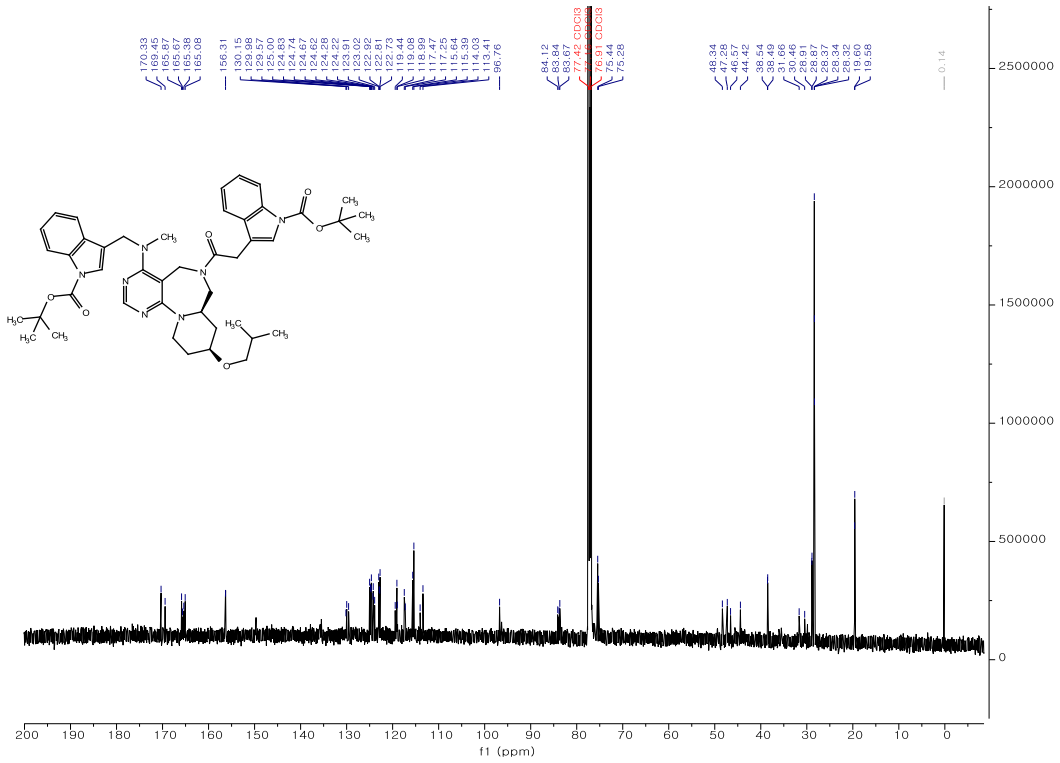


3r’





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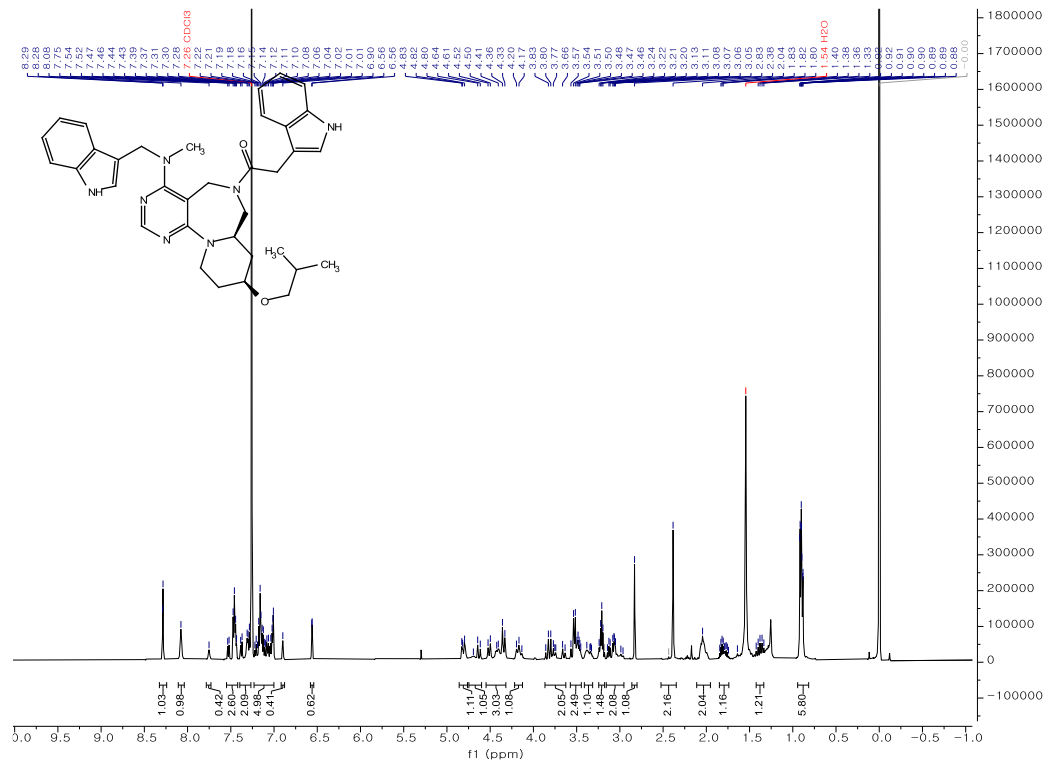

5. References

(1) *J. Med. Chem.* **2007**, 50, 18, 4329–4339

(2) *Angew. Chem. Int. Ed.* ***2022,*** *61, e202115695*.