

Discovery of Palazestrant (OP-1250), a Potent and Orally Bioavailable Complete Estrogen Receptor Antagonist (CERAN) and Selective Estrogen Receptor Degradar (SERD)

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Assay Data

Table S1. In vitro (Lanthascreen competitive binding assay) potency geometric mean values of **10-11, 21-42**

Number	ER α LBD Binding pIC ₅₀	n
10	9.3 [9.0, 9.6]	4
11	9.7 [9.4, 10.1]	4
21	8.7 [8.6, 8.9]	6
22	8.8 [8.4, 9.3]	5
23	8.8 [8.1, 9.5]	4
24	8.4 [7.5, 9.3]	4
25	8.4 [6.5, 10.4]	3
26	8.6 [7.8, 9.3]	4
27	8.7 [8.3, 9.2]	4
28	8.4 [8.4, 8.5]	4
29	8.6 [8.1, 9.1]	4
30	8.6 [8.3, 9.0]	4
31	8.3 [7.9, 8.8]	6
32	8.7 [8.6, 8.8]	4
33	9.3 [9.0, 9.6]	3
34	9.3 [8.9, 9.7]	3
35	8.8 [8.1, 9.5]	3
36	8.6 [7.8, 9.5]	3
37	9.3 [8.7, 9.9]	4
38	9.0 [8.7, 9.4]	5
39	8.9 [7.2, 10.5]	4
40	8.9 [8.5, 9.2]	4
41	9.0 [8.7, 9.3]	4
42	7.8 [7.5, 8.1]	5

95% confidence intervals of geometric mean [lower 95%, upper 95%] when the number of runs (n) are higher than or equal to 3.

Table S2. In vitro (alkaline phosphatase assay) potency geometric mean values of **10-11, 21-42**.

	Antagonism	Agonism		
Number	ECC-1 AP pIC ₅₀	ECC-1 AP E _{max} (%)	Classification	n
10	9.8 [9.0, 10.5]	5.2	Non-Agonist	10
11	10.0	0	Non-Agonist	2
21	8.5 [8.4, 8.5]	0.3	Non-Agonist	36
22	<7	52 [42, 63]	Full Agonist	14
23	8.9 [8.9, 9.0]	0.3	Non-Agonist	12
24	8.5 [8.4, 8.6]	8.5	Non-Agonist	14
25	8.1 [8.1, 8.2]	22 [19, 25]	Partial Agonist	6
26	8.7 [8.6, 8.7]	2.1	Non-Agonist	14
27	8.3 [8.2, 8.4]	7.4	Non-Agonist	12
28	8.0 [7.9, 8.1]	3.1	Non-Agonist	12
29	< 7	79 [69, 89]	Full Agonist	16
30	9.1 [9.0, 9.2]	0	Non-Agonist	12

31	8.8 [8.6, 8.9]	5.4	Non-Agonist	14
32	8.8 [8.8, 8.9]	0.3	Non-Agonist	16
33	8.1	10	Non-Agonist	2
34	8.3	4.6	Non-Agonist	2
35	< 7	27	Partial Agonist	2
36	< 7	93	Full Agonist	2
37	8.0 [8.0, 8.1]	0.7	Non-Agonist	12
38	9.8 [9.7, 9.9]	0	Non-Agonist	12
39	6.4 [5.2, 7.6]	2.0	Non-Agonist	12
40	8.5 [8.5, 8.5]	0.4	Non-Agonist	12
41	8.3 [8.3, 8.4]	0.9	Non-Agonist	12
42	7.3 [7.3, 7.4]	0	Non-Agonist	2

95% confidence intervals of geometric mean [lower 95%, upper 95%] when the number of runs (n) are higher than or equal to 3.

Table S3. In vitro (CAMA-1 cell proliferation assay) inhibition arithmetic mean values of 11, 21-32, 37-42.

Number	CAMA-1 Cell Proliferation	N
11	7.5 [6.8, 8.3]	6
21	6.9 [6.7, 7.1]	20
22	6.7	2
23	7.4	2
24	7.1	2
25	6.7	2
26	7.3	2
27	7.1	2
28	6.6	2
29	7.1	2
30	7.5	2
31	7.2 [6.9, 7.5]	4
32	7.2	2
37	6.5	2
38	7.1	2
39	< 6	2
40	6.5	2
41	6.5	2
42	6.8	2

95% confidence intervals of geometric mean [lower 95%, upper 95%] when the number of runs (n) are higher than or equal to 3.

Table S4. In vitro (MCF7 cell proliferation assay) inhibition arithmetic mean values of 21, 23, 30, and 32.

Number	MCF7 Cell Proliferation	N
21	8.1 [8.0, 8.2]	39
23	7.9 [7.9, 8.0]	14
30	8.1 [7.9, 8.0]	7
32	8.1 [8.0, 8.3]	16

95% confidence intervals of geometric mean [lower 95%, upper 95%] when the number of runs (n) are higher than or equal to 3.

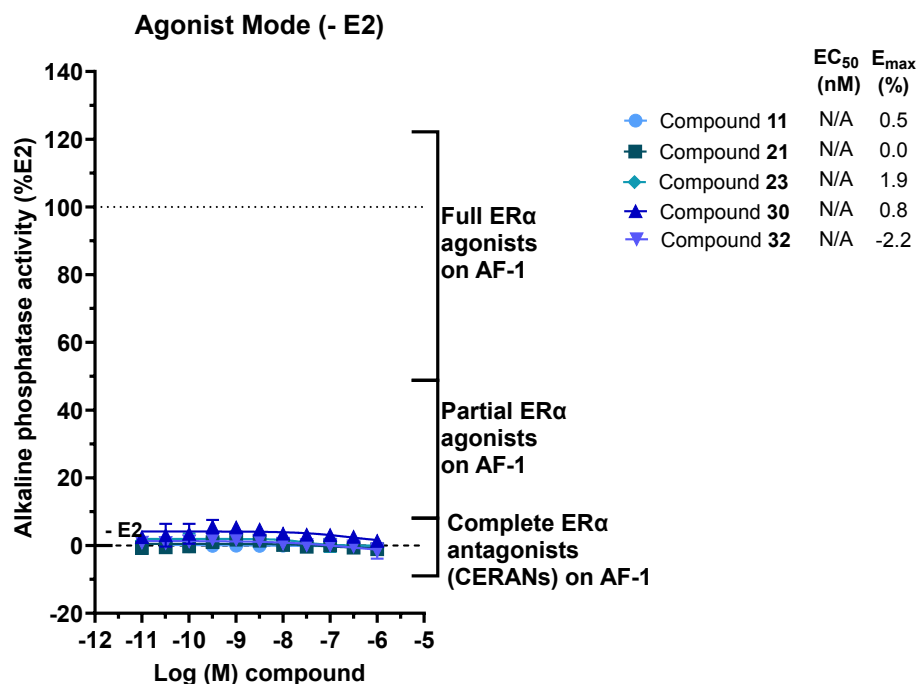


Figure S1. AP activity of Ishikawa cells in estrogen-depleted media following incubation for 72 h with compounds 11, 21, 23, 30 and 32 in the absence of 500 pM E2

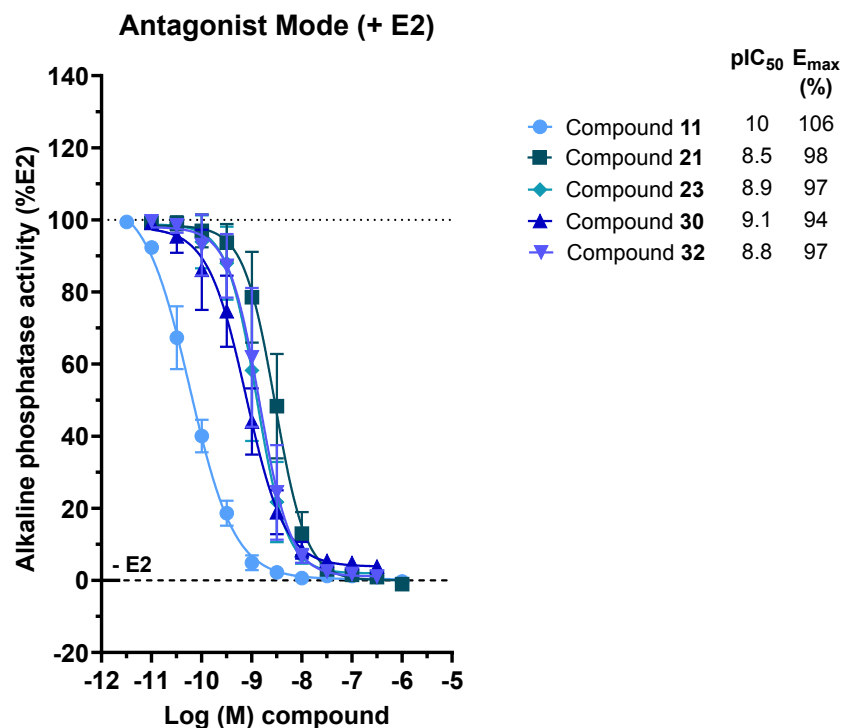


Figure S2. AP activity of Ishikawa cells in estrogen-depleted media following incubation for 72 h with compounds 11, 21, 23, 30 and 32 in the presence of 500 pM E2

HDX-MS and X-ray Crystallography

HDX-MS

WT ERα LBD was used for HDX-MS studies and was recombinantly expressed and purified as previously described¹. HDX-MS experiments were performed by the Mass Spectrometry Research Center at Vanderbilt University following earlier studies with ERα LBD complexes. A file termed "HDX MS Raw Values" shows the sequences, peptide masses, HDX time, Uptake \pm std.dev., retention time \pm std.dev. ^{1,2}

Sequence	Start	End	Compound 3	Compound 21
			% D incorporation vs apo (±SD)	
ALSLTADQ	307	314	2.5 ± 9.3	6.4 ± 9
LSLTADQ	308	314	-1.8 ± 6.5	3.7 ± 7.2
LSLTADQM	308	315	0.8 ± 7.4	4.9 ± 7.6
TADQMVSAL	311	319	-12.9 ± 2.9	-10.2 ± 2.6
MVSALL	315	320	-26.1 ± 0.8	-22.4 ± 0.9
LDAEPPI	320	327	-2.7 ± 4.7	5.1 ± 4.6
DAEPPIL	321	327	-2.1 ± 8.9	3.9 ± 10.2
DAEPPILYSEYDPTPF	321	338	5.9 ± 3.5	3.4 ± 2.7
AEPPIYSEYD	322	332	-0.2 ± 1.2	-0.3 ± 1.4
YSEYDPTPFSE	328	339	-8.5 ± 3.6	1.7 ± 1.6
YSEYDPTPFSEASM	328	342	-11.4 ± 3.5	2 ± 2.3
EYDPTPFSEASM	330	342	-13.5 ± 2.4	0.6 ± 2.7
MGLLTNL	343	349	-29.6 ± 4.5	-22.7 ± 4.3
LTNLADRE	346	353	-43.3 ± 2.3	-40.1 ± 3
ADRELVHM	350	357	-30.4 ± 2.4	-31.5 ± 1
ADRELVHMINW	350	360	-31 ± 2.8	-28.3 ± 1.6
ADRELVHMINWAKRVP	350	367	-23.6 ± 2.6	-23 ± 1.6
ADRELVHMINWAKRVPFVD	350	369	-26.1 ± 2.1	-22.6 ± 1.5
LVHMINW	354	360	-22.1 ± 5.1	-18.8 ± 1.5
LVHMINWAKRVP	354	367	-15.2 ± 1.9	-14.3 ± 1.7
LVHMINWAKRVPFVDL	354	370	-18.4 ± 2.1	-15 ± 1.8
INWAKRVP	358	367	-15.8 ± 2.6	-13.5 ± 2.4
INWAKRVPFVD	358	369	-16.2 ± 2.2	-11.9 ± 1.8
TLHDQVHL	371	378	-8.7 ± 1.6	-8.5 ± 0.8
TLHDQVHLE	371	380	-6.9 ± 1	-6.7 ± 0.8
HDQVHLE	373	380	-5.8 ± 2	-7.1 ± 2.3
QVHLE	375	380	-4.3 ± 0.8	-5.2 ± 0.9
LEILMIGLVWRSME	384	397	-16.3 ± 3.2	-14.7 ± 2.1
IGLVWRSMEHPGKL	389	402	-11.9 ± 1.1	-8.1 ± 1.1
LVWRSMEHPGKL	391	402	-13.3 ± 0.9	-9.8 ± 0.9
VWRSMEHPGKL	392	402	-13.2 ± 1.8	-9.1 ± 1.6
VWRSMEHPGKLLF	392	404	-22.1 ± 1.6	-17.3 ± 1.4
VWRSMEHPGKLLFAPNLL	392	409	-26.5 ± 2	-19.4 ± 1.5
VWRSMEHPGKLLFAPNLLL	392	410	-31.3 ± 3.5	-21.5 ± 2.2
LFAPNL	403	408	-30 ± 4.5	-25.7 ± 3.9
LFAPNLL	403	409	-24.6 ± 6.4	-17.4 ± 6.4
LFAPNLLL	403	410	-29.6 ± 5.8	-22 ± 5.8
DRNQKQKVEGM	411	421	-10.7 ± 8.1	2.1 ± 3.2
RNQKQKVEGMVE	412	423	-9.3 ± 9.5	1.2 ± 7
VEGMVE	418	423	4.6 ± 1.5	4 ± 1.7
VEGMVEI	418	424	-1.3 ± 1.7	1.7 ± 1.8
VEIFDML	422	428	-12.4 ± 7	-8 ± 1.9
IFDMLL	424	429	-9.7 ± 0.7	-4.5 ± 1.1
LATSSRF	429	435	-10.1 ± 1.9	-9.8 ± 1.7
LATSSRFMMNL	429	440	-12.2 ± 6.6	-7.8 ± 6.9
LATSSRFMMNLQ	429	441	4.1 ± 3.2	4.1 ± 2
RMMNLQGE	436	444	-8.5 ± 2.5	-4 ± 1.6
RMMNLQGEF	436	445	-6.9 ± 3.3	-2.9 ± 1
IILLNSGV	451	458	-8.1 ± 3.4	-1.4 ± 3.2
LNSGVY	454	459	-13.7 ± 1.8	-2 ± 2.3
LNSGVYT	454	460	-15.9 ± 2.3	-1.3 ± 3.1
VYTLFSLTKSLEEK	458	472	2.3 ± 2.3	2.1 ± 3.1
TFLSSTL	460	466	-13.6 ± 5.3	0.7 ± 5.4
KSLEEKDHIHRVLDKITDTL	467	486	-8.6 ± 1.3	-2.9 ± 1.5
MAKAGLTQQQHQL	490	504	-9.9 ± 1.5	-2 ± 3
MAKAGLTQQQHQLAQ	490	506	-15.1 ± 6.5	-2.4 ± 3.2
MAKAGLTQQQHQLAQL	490	507	-8.2 ± 0.9	-1.9 ± 2.9
MAKAGLTQQQHQLAQLL	490	508	-9.8 ± 4.9	-1.7 ± 2.6
TLQQQHQLAQL	496	507	-2.9 ± 0.7	-1.3 ± 1
TLQQQHQLAQLL	496	508	-3.5 ± 0.7	-1.1 ± 0.8
LLILSHIRHMSNKGMEHL	508	525	-10.9 ± 0.8	-10.4 ± 0.9
LILSHIRHMSNKGMEHL	509	525	-11.4 ± 1	-10.7 ± 0.9
ILSHIRHMSNKGMEHL	510	525	-13.4 ± 1.1	-12.1 ± 0.9
LSHIRHMSNKGMEHL	511	525	-13.9 ± 2.3	-12 ± 1.9
YSMKCKNVVPLYDLL	526	540	-11.7 ± 2.2	-15.8 ± 1.9
KCKNVVPLYDLL	529	540	-14.5 ± 2.8	-20.3 ± 2.5
LEMLDA	541	546	-6.4 ± 2.6	-7.9 ± 1.4
LEMLDAHRLHAPTS	541	554	-10 ± 3.3	-3.4 ± 2
LAHRLHAPTS	544	554	-4.2 ± 3.2	2.2 ± 1.9
DAHRLHAPTS	545	554	-3.1 ± 2	1.9 ± 1.8
SLTADQMVSALLDAEP	309	324	-16.7 ± 2	-11.6 ± 1.6
LSLTADQMVSALLDAEP	308	324	-19 ± 2	-12.1 ± 1.3

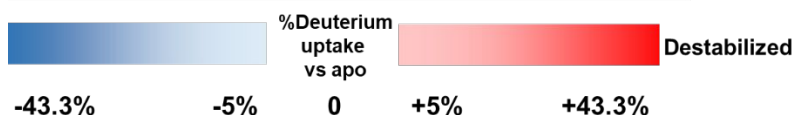


Figure S3. Percent deuterium uptake difference between drug-bound and apo states at the 1-hour time point shown as a heat map (blues for protection and reds for deprotection). Data are colored only if they show a >5% or <-5% difference between the two states.

X-ray Crystallography

Small molecule crystal of **21** acetonitrile solvate

Data collection was collected at 173 K for greater accuracy of thermal ellipsoids.

The **21**-acetonitrile solvate crystallized in the chiral trigonal space group $P3_221$ (Flack 0.3(3)) – retaining its chirality with moderate confidence -- with an R_1 value of 0.0474 ($I > 2\sigma(I)$). This form is anhydrous with minimal void spaces (0.2%, 8.01 Å³) and no solvent channels, and an API:acetonitrile solvent ratio of 1:1.

Materials

Data collection strategies were created and optimized using the Bruker Apex3 v2018-7.2 software. Frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm, except where necessary for short-exposure fast scan data points to replace overexposed reflections. All data was corrected for absorption effects and anomalous dispersion using the Multi-Scan method (SADABS-2016/2). Structures were solved and refined using Olex2 incorporating the SHELXTL Software Package¹, or with the direct method using the SHELX software suite². The PLATON software suite³ was used to evaluate solvent disorder, Bijvoet pair statistics, initial symmetry assignment, and generate graphics and XRPD simulations. The Mercury (v2020.2.0) software was used in parallel for void space evaluation and graphics generation.

Compound 21 - acetonitrile solvate

The proposed structure of the acetonitrile solvate of compound **21** was verified by x-ray analysis. A Thermal Ellipsoid plot of the compound in the crystal is shown in Figure S4. A plate-like single crystal with high diffraction quality, selected out from the batch, was immersed in MiTeGen LV5 (an oil based cryoprotectant) and mounted on a MiTeGen cryoloop in a random orientation and immersed in a stream of liquid nitrogen at 173K. The X-ray intensity data were measured on a Bruker D8 VENTURE (I μ S microfocus X-ray source, Cu K α , λ = 1.54178Å, PHOTON CMOS detector) diffractometer. The frames were integrated with the Bruker SAINT software package. The integration of the data using a trigonal unit cell in the space group $P3_221$ yielded a total of 50168 reflections to a maximum θ angle of 66.631° (0.83 Å resolution), of which 5089 were independent (R_{int} = 9.38%) and were greater than $2\sigma(F^2)$. The final cell constants of $a = b = 10.0115(2)$ Å, $c = 49.8608(16)$ Å, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, cell volume = 4328.0(2) Å³, are based upon the refinement of the XYZ-centroids of 4341 reflections above 10 $\sigma(I)$ with $2.658^\circ < \theta < 66.631^\circ$. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The absorption coefficient μ of this material is 0.585 mm⁻¹ at this wavelength (1.54178 Å). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.929 and 0.984. The agreement factor for the structure (R_1) was 4.74% based on intensity.

¹ Fanning, S.W. et al., *eLife* **2016**, 5, e12792; Fanning, S.W. et al. *eLife* **2018**, 7:e37161

² Sheldrick, G.M. *Acta Cryst.* **2008**, A64, 112-122.

³ A.L.Spek, *Inorg. Chim. Acta* **2018**, 470, 232-237

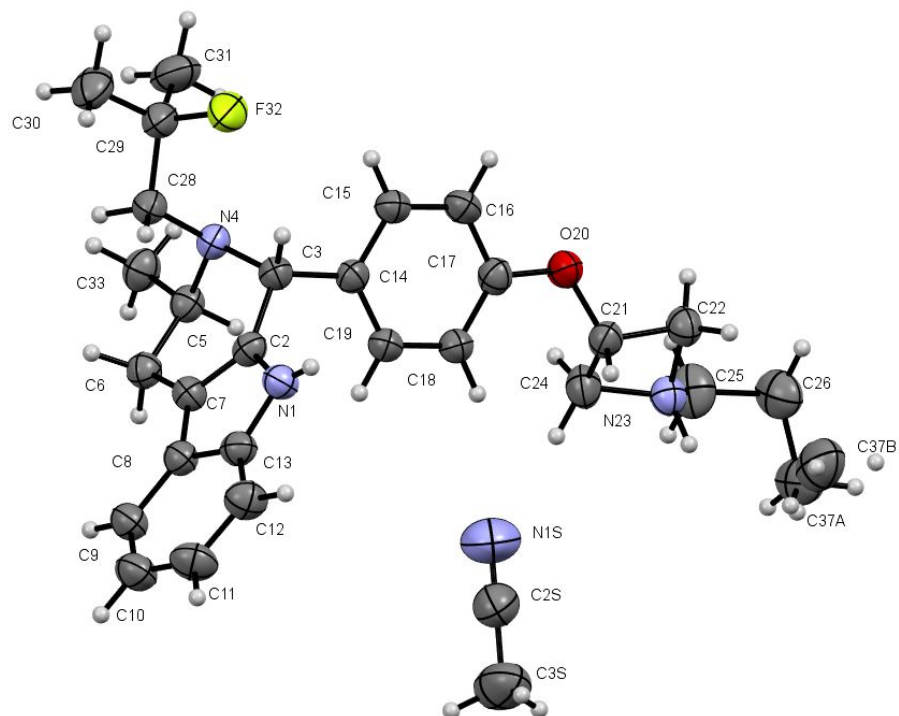


Figure S4. Ortep diagram of an asymmetric unit of the compound 21 acetonitrile solvate crystal, displaying thermal ellipsoids at 50% confidence interval.

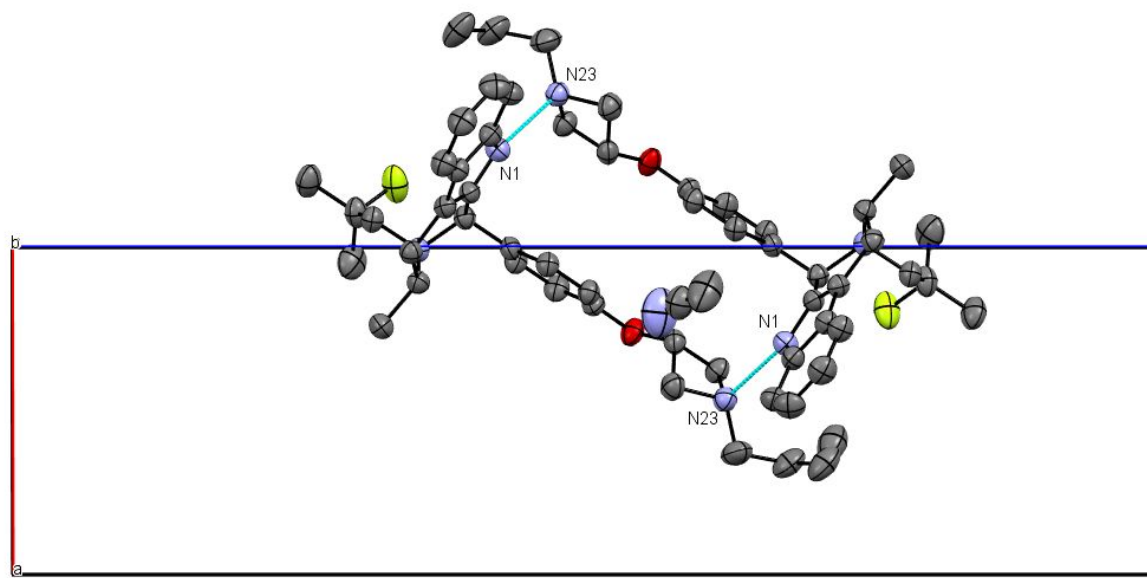


Figure S5. Hydrogen bonding packing influence displayed in the acetonitrile solvate of compound 21, view along the *b*-axis. Thermal ellipsoids shown at 50% confidence interval. Hydrogen atoms omitted for clarity.

The solvated API forms a pseudo-dimer via paired hydrogen bonds between the terminal amine N23 and the secondary cyclic amine, N1 (Figure S6). The distance of this contact, as defined by the gap between the donor and acceptor, is 2.983(4) Å, placing it within the realm of a strong electrostatic interaction. The unit cell contains several other short contacts of interest (Table S5). In particular, the nitrogen of the acetonitrile solvent N1S forms three minor Van der Waals interactions with C24 (3.544(7) Å), C18 (3.453(6)Å), and C25 (3.643(7)Å). While each of these is long as such interactions are considered, a single donor atom would not be expected to begin with the electron density to be able to form three strong donation interactions. Finally, there is a notable interaction between the fluorine (F32) and the adjacent aromatic hydrogen atoms, primarily the hydrogen bound to C3 (3.048(4)Å). The hydrogen bond pairs well with this particular interaction in support of the pseudo-dimeric conformation.

Table S5. Crystallographic details and parameters of the C₂₈H₃₆FN₃O·CH₃CN crystal

Empirical formula	C30 H40 F N4 O	
Formula weight	491.66	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Trigonal	
Space group	P3 ₂ 21	
Unit cell dimensions	a = 10.0115(2) Å	α = 90°.
	b = 10.0115(2) Å	β = 90°.
	c = 49.8608(16) Å	γ = 120°.
Volume	4328.0(2) Å ³	
Z	6	
Density (calculated)	1.132 Mg/m ³	
Absorption coefficient	0.585 mm ⁻¹	
F(000)	1590	
Crystal size	0.128 x 0.111 x 0.028 mm ³	
Theta range for data collection	2.658 to 66.631°.	
Index ranges	-11<=h<=11, -11<=k<=11, -59<=l<=59	
Reflections collected	50168	
Independent reflections	5089 [R(int) = 0.0938]	
Completeness to theta = 66.631°	100.0 %	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	5089 / 0 / 347	
Goodness-of-fit on F ²	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0474, wR2 = 0.1177	
R indices (all data)	R1 = 0.0574, wR2 = 0.1263	
Absolute structure parameter	0.3(3)	
Extinction coefficient	0.0021(3)	

ER α LBD Co-crystallization with **21**

For x-ray co-crystal structural analysis, a C381S, C417S, C530S, and L536S ER α LBD mutant construct was used to obtain diffraction-quality co-crystals with **21**. Protein was recombinantly expressed and purified as previously described⁴. Hanging drop vapor diffusion was used to obtain diffraction-quality co-crystals of the LBD-**21** complex. Briefly, 500 μ M LBD was incubated for 16 hours at 4 °C with 1 mM **21**. Precipitated protein/ligand was removed by centrifugation at 20,000 g for 30 minutes at 4 °C. Clear cubic crystals emerged in 15% PEG 8,000, 100 mM MgCl₂, 100 mM HEPES pH 7.0 after 2 weeks at room temperature. Crystals were cryo-protected in mother liquor with the addition of 25% glycerol then flash frozen in liquid N₂. This data set was collected at beamline 19-BM at the Structural Biology Center, Advanced Photon Source, Argonne National Laboratories (0.97 Å). Data were indexed, integrated, scaled and merged using HKL 3,000⁵. Phaser was used to perform molecular replacement with the PDB: 5UFX used for the starting model with all ligands and solvent atoms removed⁴. The model was refined using iterative rounds of Phenix Refine and manual inspection/editing in Coot⁶. Clear density was observed for the **21** ligand after one refinement. Elbow in Phenix was used to generate the ligand model and constraints. Atoms were only included where they were observed in the map. No Ramachandran outliers were present in the final model. The structure factors and models are available under the PDB accession code 8VV1. All images were generated using Pymol.

Table S6.

ER α LBD - 21	
PDB ID	8VV1
Data Collection	
Space Group	C2
a, b, c (Å)	102.13, 57.27, 87.15
α , β , γ (°)	90.00, 103.01, 90.00
Resolution Range (Å)	50 – 2.20
Number of Reflections (all/unique)	24,981, 6,751
Completeness (Highest Resolution)	98.8
Redundancy	3.7
CC ^{1/2} (Highest Resolution)	0.51
Refinement	
R _{work} /R _{free}	21.17/25.66
No. Atoms	3,720
Water Molecules	138
Ligand Molecules	2
Bond Lengths (Å)	0.003
Bond Angles (°)	0.715
Ramachandran Plot Statistics	

Preferred (%)	Number	98.39
Additional (%)	Allowed	0.77
Outliers (%)		0

4. Hancock, G. R.; Young, K. S.; Hosfield, D. J.; Joiner, C.; Sullivan, E. A.; Yildiz, Y.; Lainé, M.; Greene, G. L.; Fanning, S. W. Unconventional isoquinoline-based SERMs elicit fulvestrant-like transcriptional programs in ER+ breast cancer cells. *npj Breast Cancer* 2022, 8 (1),130.

5. Minor, W.; Cymborowski, M.; Otwinowski, Z.; Chruszcz, M. HKL-3000: the integration of data reduction and structure solution--from diffraction images to an initial model in minutes. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* 2006, 62 (Pt 8), 859-866.

6. Liebschner, D.; Afonine, P. V.; Baker, M. L.; Bunkóczi, G.; Chen, V. B.; Croll, T. I.; Hintze, B.; Hung, L. W.; Jain, S.; McCoy, A. J.; Moriarty, N. W.; Oeffner, R. D.; Poon, B. K.; Prisant, M. G.; Read, R. J.; Richardson, J. S.; Richardson, D. C.; Sammito, M. D.; Sobolev, O. V.; Stockwell, D. H.; Terwilliger, T. C.; Urzhumtsev, A. G.; Videau, L. L.; Williams, C. J.; Adams, P. D. Macromolecular structure determination using X-rays, neutrons and electrons: recent developments in Phenix. *Acta Crystallogr., Sect. D: Struct. Biol.* 2019, 75 (Pt 10), 861–877.

Molecular Dynamics Simulations

Protein refinement:

The PDB structure of estrogen receptor alpha (PDB: 7MSA) was taken for docking studies of the compounds to conduct the MD simulation. The structure was prepared initially by modeling the loops in the ligand binding domain-as it was missing in the X-ray structure.

Prior to the docking process protein and ligand was prepared using the Protein preparation, Lig-Prep, module of the Schrodinger Discovery suite.

Protein preparation: The protein structure (PDB: 7MSA) was downloaded from the Protein Data bank (PDB) and prepared through the protein preparation wizard of Schrodinger suite keeping the default parameters. The method adds the required hydrogens to the amino acids and corrected the bond length and angles including removing of all the water molecules. The restrained minimization was carried out using an OPLS4 force field.

Ligand preparation:

The structures of the compounds were initially prepared using the Lig-Prep modules keeping the required stereochemistry in place.

Ligand docking:

The prepared ligands were subjected to molecular docking using the Induced fit module of Schrodinger suite with default parameters. This module was chosen to provide flexibility to the ligand as well the side chains of the protein.

MD simulation:

Molecular dynamics (MD) simulation for each of the protein-ligand complex was carried out using the Desmond GPU version from Schrodinger. The system was setup using the predefined TIP3 solvent model. Within an orthorhombic box of 10Å³. The system was then neutralized by adding an appropriate amount of Na⁺ ions. Additional 0.15 M of Na⁺ as Positive salt ion and Cl⁻ as negative ions was added to the system. OPLS4 forcefield was used to generate the system.

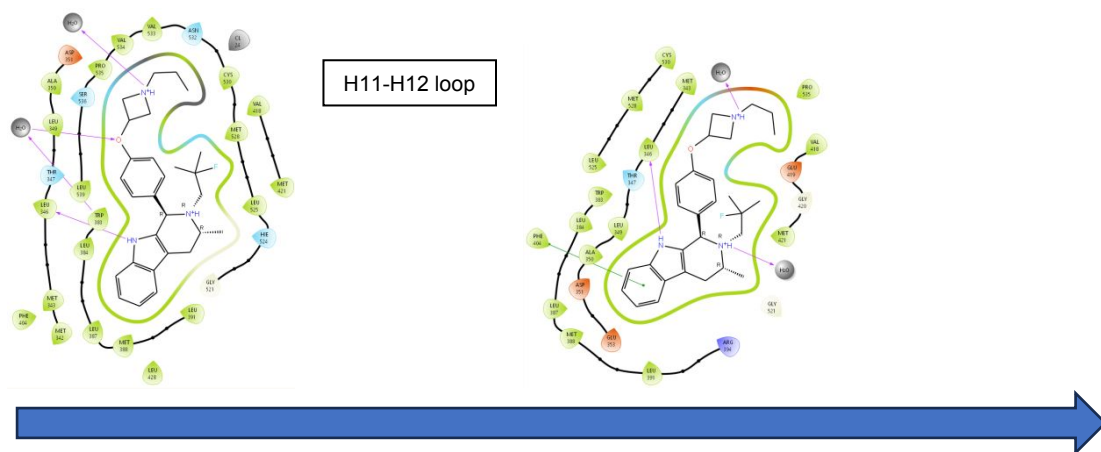
Each system was then subjected to a simulation run of 500ns. Under normal pressure and temperature (NPT) at 1.01 pressure (bar). 1000 frames were recorded at 500ps each time interval to analyze the trajectory of the simulation.

Automated simulation interaction diagram (SID) was generated within the Desmond run to analyze the simulation results. These interaction maps were used to understand the movement of the complexes during simulation.

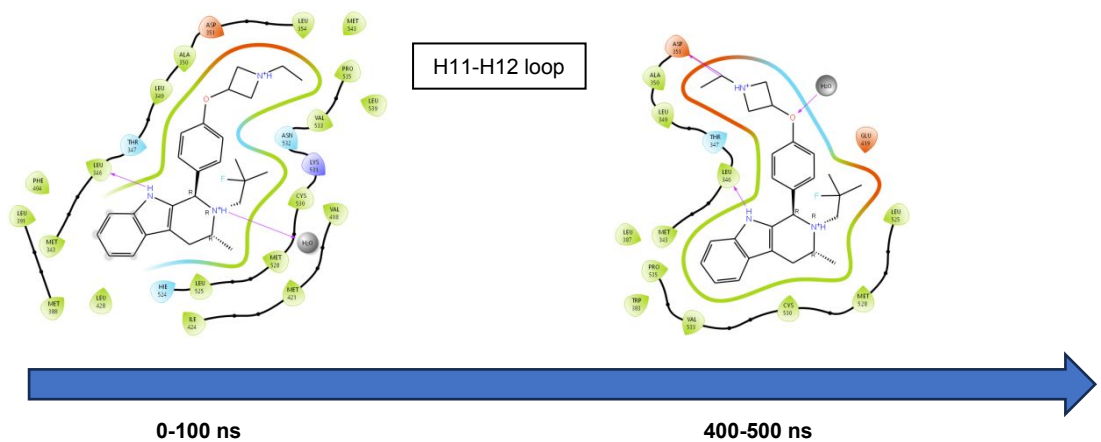
RMSF calculation:

The RMSF calculation were carried out through the automated script in Schrodinger tool.

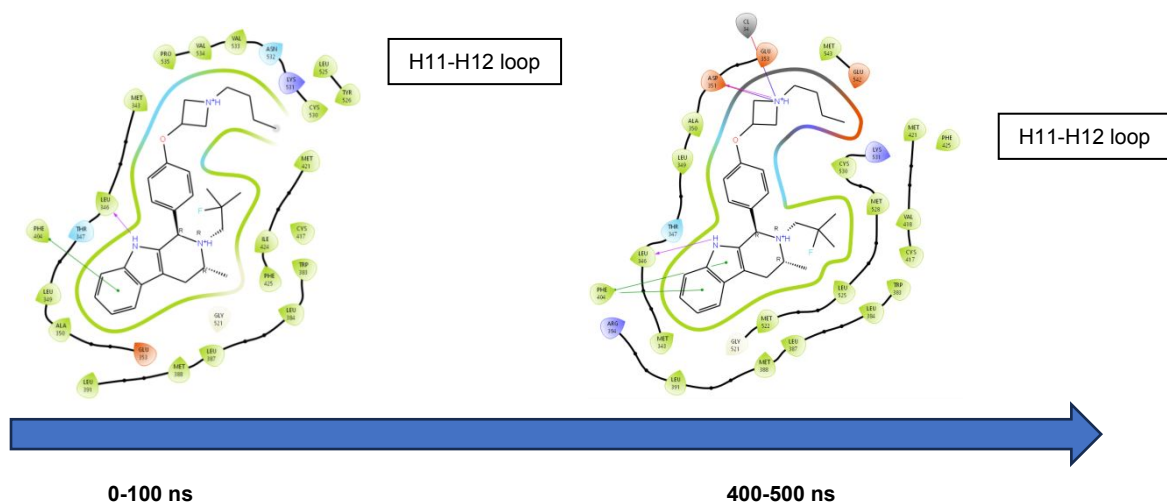
(A) Compound 21 (0-100 ns) to (400-500 ns)



(B) Compound 34 (0-100 ns) to (400-500 ns)



(C) Compound 35 (0-100 ns) to (400-500 ns)



(D) Compound 36 (0-100 ns) to (400-500 ns)

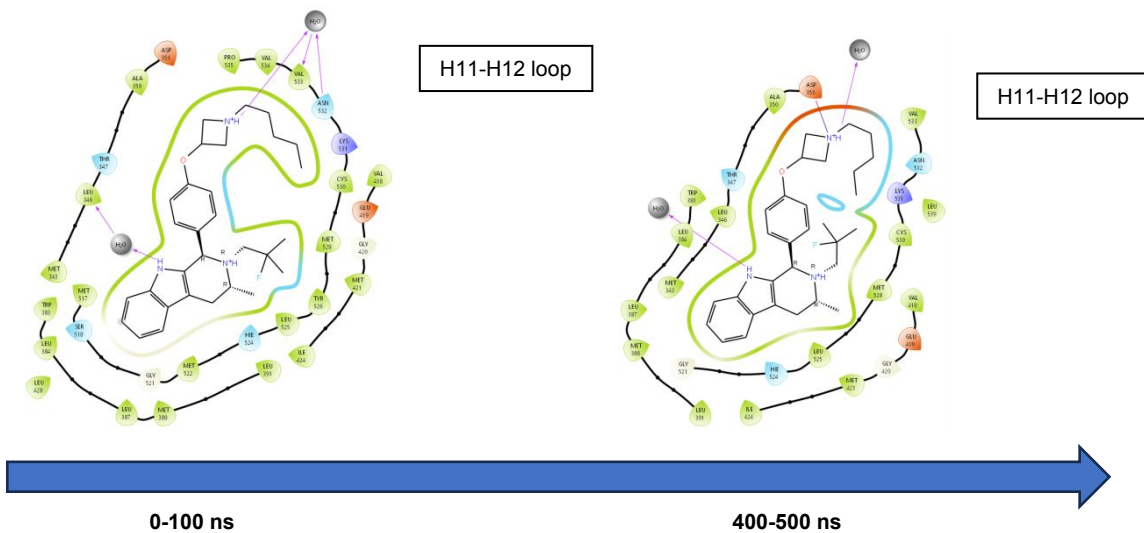
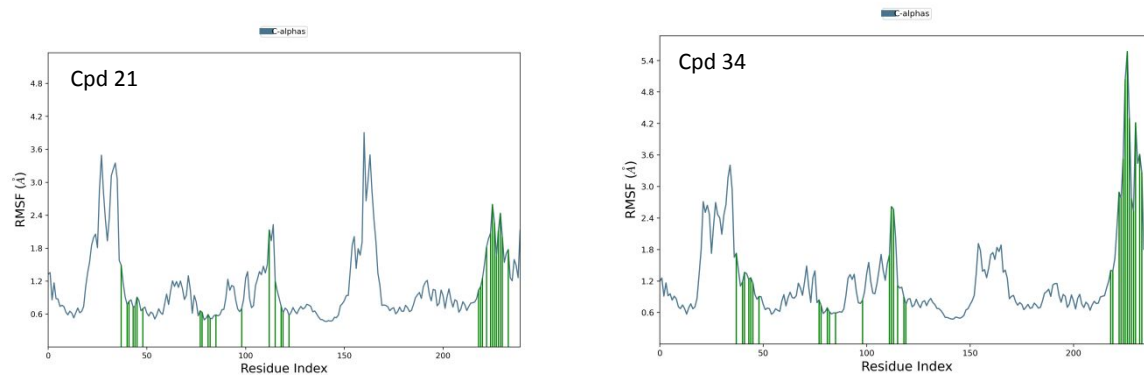


Figure S6. Molecular dynamics simulations of ER LBD in complex with 21 (A), alkyl analogs, 34 (B), 35 (C), and 36 (D) comparing the predicted structures between 0 and 100 ns then 400-500 ns and highlighting differences of nearby amino acids and solvent accessibility.



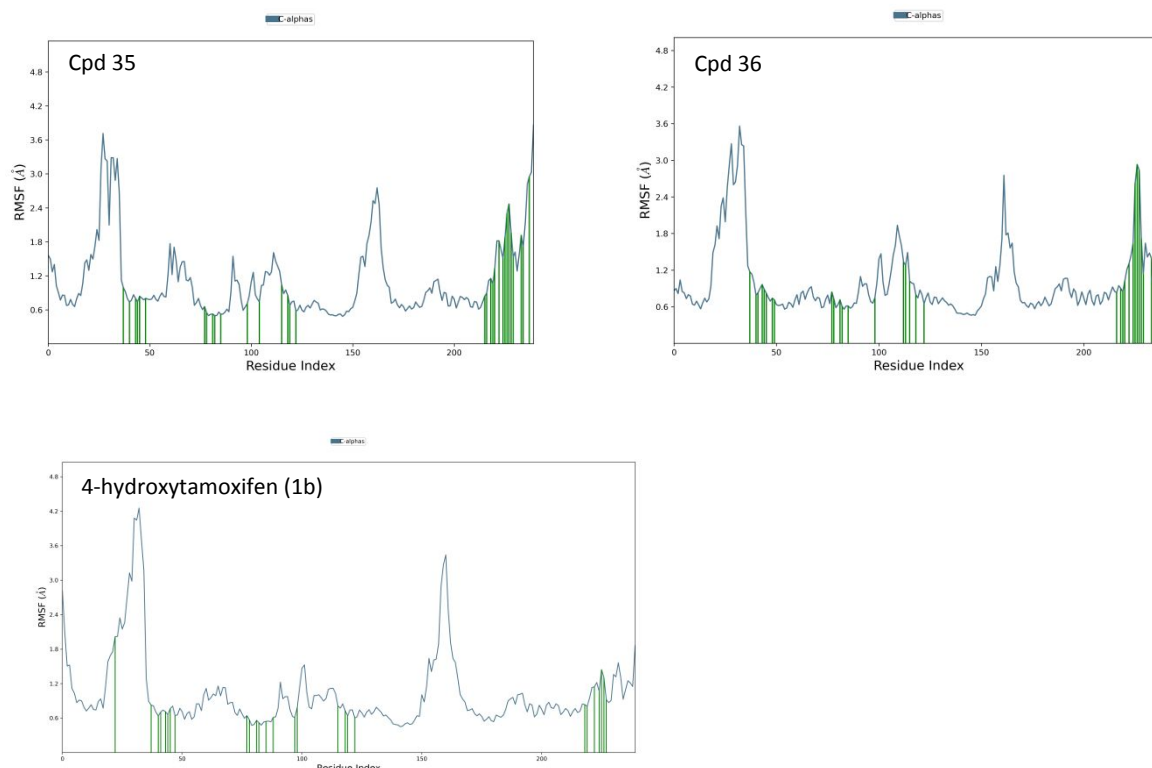


Figure S7. RMSF analysis shows greater movement of the C-terminal regions (H11-12 loop and H12) of ER LBD in the presence of CERANs/SERDs compared to the SERM 4-hydroxytamoxifen 1b (4OHT). Green bars are points of contact between the ligand and given residue. The major differences are green bars after 200 residue index.

As CERAN/SERDs are known to destabilize the H11-12 loop and H12 region, root mean squared fluctuations were calculated to measure differences in residue dynamics based on C α position. Each CERAN/SERD showed increased RMSF and interactions with the H11-12 loop and H12 compared to the SERM, 4-hydroxytamoxifen **1b** in these analyses. Together, these MD simulation studies show that the *n*-propyl side-arm of tetrahydro- β -carboline **21** is the most energetically favored.

Table S7. Calculated binding energy and ligand strain differences at the beginning and the end of the MD simulations. Δ energy = energy_{500ns} – energy_{100ns}.

Cpd	Complex energy (ligand strain) energy at 100 ns (Kcal/mol)	Complex energy and ligand strain at 500 ns (Kcal/mol)	Δ Complex energy (ligand strain) (Kcal/mol)
21	-7061 (5.7)	-7119 (3.2)	-58 (-2.5)
34	-7003 (4.5)	-7025 (5.4)	-21 (0.9)
35	-6980 (6.9)	-7012 (4.9)	-32 (-2)
36	-6962 (3.2)	-6908 (7.2)	54 (4)

Trends emerged in the calculated ligand binding and ligand strain energies that point to key activity differences. Compound **21** significantly improved ligand binding and strain energies over the course of the simulation while the analogs with different alkyl chain lengths **34-36** either show no change (and are less favored) or an energetic penalty over the course of the simulation.

Experimental Procedures and LC-MS / NMR Spectra

Abbreviations

AcOH: Acetic acid

ACN: Acetonitrile

Anhyd.: Anhydrous

Aq.: Aqueous

Bn: Benzyl

Boc: tert-butoxy carbonyl

Boc₂O: Di-tert-butyl dicarbonate

n-BuOH: n-butanol

DCE: 1,2-dichloroethane

DCM: Dichloromethane

de: diastereomeric excess

DEA: Diethylamine

DHP: Dihydropyran

DIBAL-H: Diisobutylaluminum hydride

DIPA: Diisopropylamine

DIPEA or DIEA: N,N-Diisopropylethylamine

DMA: N,N-Dimethylacetamide

DME: 1,2-Dimethoxyethane

DMAP: 4-Dimethylaminopyridine

DMF: N,N-Dimethylformamide

DMP: Dess-Martin periodinane

DMSO: Dimethyl sulfoxide

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

ee: Enantiomeric excess

EA: Ethyl acetate

EtOAc: Ethyl acetate

EtOH: Ethanol

FA: Formic acid

h or hrs: Hours

HCl: Hydrochloric acid

HPLC: High performance liquid chromatography

IBX: 2-Iodoxybenzoic acid
IPA: Isopropyl alcohol
 K_2CO_3 : Potassium carbonate
LAH: Lithium aluminium hydride
LDA: Lithium diisopropylamide
M: molar
MeCN: Acetonitrile
MeOH: Methanol
MeONa: Sodium methoxide
MeI: Iodomethane
min: Minutes
mL: Milliliters
mM: Millimolar
mmol: Millimoles
MsCl: Methanesulfonyl chloride
MTBE: Methyl *tert*-butyl ether
n-BuLi: *n*-Butyllithium
 $NaNO_2$: Sodium nitrite
NaOH: Sodium hydroxide
NBS: N-Bromo succinimide
NMP: N-Methyl pyrrolidine
NMR: Nuclear Magnetic Resonance
OTf: Trifluoromethanesulfonate
°C: Degrees Celsius
Pd/C: Palladium on Carbon
 $Pd(OAc)_2$: Palladium Acetate
PE: Petroleum ether
 PPh_3 : Triphenylphosphine
R.T. or rt: Room temperature
Sat.: Saturated
SFC: Supercritical fluid chromatography
t-BuOK: Potassium *tert*-butoxide
TEA: Triethylamine
 Tf_2O : Trifluoromethanesulfonic anhydride
TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TLC: Thin layer chromatography

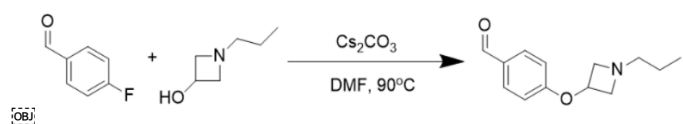
TMEDA: Tetramethylethylenediamine

wt: Weight

STAB: Sodium triacetoxyborohydride

Synthesis of common intermediates

Scheme S1. Synthesis of 4-((1-propylazetidin-3-yl)oxy)benzaldehyde

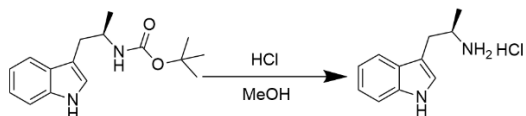


To a stirred solution of 1-propylazetidin-3-ol (5.0 g, 43.41 mmol, 1.0 eq.) in DMF (100 mL) was added 4-fluorobenzaldehyde (4.85 g, 39.07 mmol, 0.9 eq.), cesium carbonate (29.70 g, 91.20 mmol, 2.1 eq.) and the reaction mixture was refluxed at 90°C for 16 h. The reaction mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were separated, dried over anhydrous sodium sulfate, filtered and dried *in-vacuo* to obtain the 4-((1-propylazetidin-3-yl)oxy)benzaldehyde (7.2 g, 75.63%) as an orange liquid compound.

^1H NMR (500 MHz, CDCl_3): δ 9.88 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 6.87 (d, J = 6.8 Hz, 2H), 4.89-4.84 (m, 1H), 3.85-3.82 (m, 2H), 3.13-3.09 (m, 2H), 2.47 (t, J = 7.5 Hz, 2H), 1.44-1.37 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

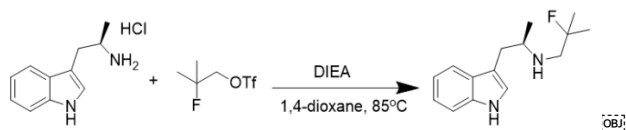
LCMS: m/z (ESI): 220.08 $[\text{M}+\text{H}]^+$.

Scheme S2. Preparation of (*R*)-1-(1H-indol-3-yl)propan-2-amine hydrochloride



To tert-butyl (*R*)-1-(1H-indol-3-yl)propan-2-ylcarbamate (10.0 g, 36.4 mmol) was added HCl (100 mL, 3 M in methanol) and stirred for 16 h at room temperature. The solution was concentrated and azeotroped with toluene 3 times to give (*R*)-1-(1H-indol-3-yl)propan-2-amine hydrochloride as a tan solid (7.1 g, 99% yield). LCMS: m/z = 175.1 $[\text{M}+\text{H}-\text{HCl}]^+$

Scheme S3. Synthesis of (*R*)-*N*-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine



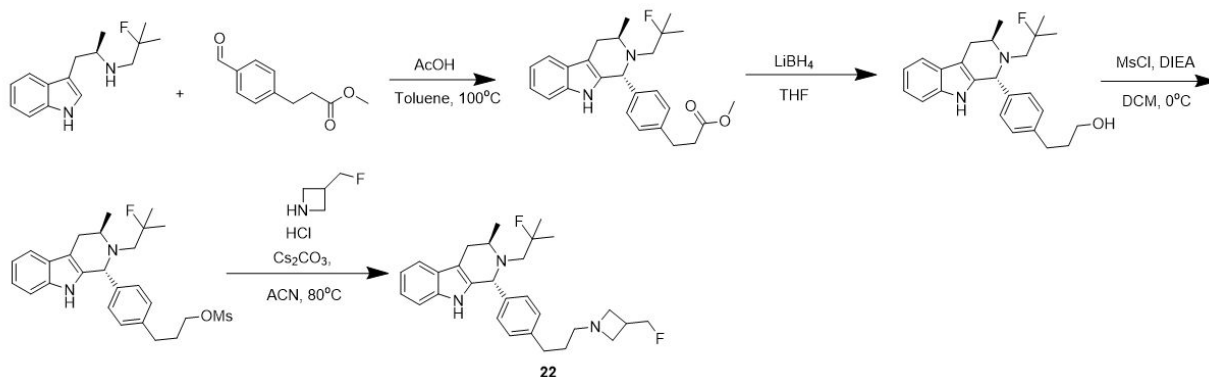
To a stirred solution of (*R*)-1-(1*H*-indol-3-yl)propan-2-amine hydrochloride (8.0 g, 37.97 mmol, 1.0 eq.) in 1,4-dioxane (14.0 mL) was added 2-fluoro-2-methylpropyl trifluoromethanesulfonate (18.72 g, 83.53 mmol, 2.2 eq.), *N,N'*-diisopropylethylamine (19.9 mL, 113.9 mmol, 3.0 eq.) and stirred at 85 °C for 5 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and dried in *vacuo*. The crude material was purified by silica gel flash column chromatography (30% ethyl acetate in *n*-hexane) to afford (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (6 g, 63.63%) as a pale brown solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.79 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.07-7.03 (m, 1H), 6.98-6.94 (m, 1H), 2.90-2.78 (m, 2H), 2.70-2.59 (m, 3H), 1.28 (d, *J* = 21.6 Hz, 3H), 1.27 (d, *J* = 22.0 Hz, 3H), 0.97 (d, *J* = 8.0 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -140.79.

LCMS: *m/z* (ESI): 249.05 [M+H]⁺

Scheme S4. Preparation of 22



Synthesis of methyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate:

To a stirred solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (800 mg, 3.22 mmol, 1 eq.) and methyl 3-(4-formylphenyl)propanoate (743 mg, 3.86 mmol, 1.2 eq.) in toluene (10 mL) was added acetic acid (0.78 mL, 13.69 mmol, 4.25 eq.), molecular sieves (4Å, 500 mg) and stirred at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and quenched with sodium bicarbonate solution (100 mL). The mixture was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were dried over sodium sulphate, filtered, and dried in-*vacuo*. The crude material was purified by silica-gel flash column chromatography (0-30% ethyl acetate in *n*-hexane) to afford methyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (900 mg, 66% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.61 (brs, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.36-7.29 (m, 1H), 7.27-7.22 (m, 2H), 7.19-7.17 (m, 1H), 7.16-7.10 (m, 3H), 5.04 (s, 1H), 3.67 (s, 3H), 3.35 (s, 1H), 2.94 (t, *J* = 8.0 Hz, 2H), 2.77-2.52 (m, 6H), 1.45 (d, *J* = 21.6 Hz, 3H), 1.35 (d, *J* = 20.5 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H).

LCMS: *m/z* (ESI): 423.48 [M+H]⁺.

Synthesis of 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol:

To a stirred solution of methyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (1g, 2.36 mmol, 1eq.) in dry THF (10 mL) was added lithium borohydride (206.18 mg, 9.46 mmol, 4 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried in-*vacuo*. The crude material was further purified by silica gel flash column chromatography (0-30 % ethyl acetate in *n*-hexane) to afford 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol (850 mg, 91% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.60 (brs, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14-7.09 (m, 4H), 5.04 (s, 1H), 3.67 (q, *J* = 6 Hz, 2H), 2.80-2.50 (m, 8H), 1.91-1.80 (m, 2H), 1.44 (d, *J* = 21.6 Hz, 3H), 1.29 (d, *J* = 24.0 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H).

LCMS: *m/z* (ESI): 395.07 [M+H]⁺

Synthesis of 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate:

Methanesulfonyl chloride (0.131 mL, 1.69 mmol, 1.34 eq.) was added drop wise to a solution of 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol (500 mg, 1.26 mmol, 1 eq.), *N,N*-diisopropylethylamine (0.34 mL, 1.97 mmol, 1.56 eq.) in DCM (10 mL) at 0 °C for 1 h. The reaction mixture was quenched with a saturated sodium bicarbonate solution (20 mL), stirred at 0 °C for 30 min and diluted with ethyl acetate (50 mL). After layers separation, the organic layer was washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo* to afford 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate (735 mg, 98% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.62 (brs, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.26-7.22 (m, 2H), 7.18-7.08 (m, 4H), 5.04 (s, 1H), 4.22 (t, *J* = 6.4 Hz, 2H), 3.67 (s, 1H), 3.13-2.98 (m, 3H), 2.74-2.70 (m, 4H), 2.68-2.52 (m, 2H), 2.10-2.03 (m, 2H), 1.52-1.46 (m, 2H), 1.44 (d, *J* = 22.0 Hz, 3H), 1.30 (d, *J* = 21.2 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H)

LCMS: *m/z* (ESI): 473.50 [M+H]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (22):

To a stirred solution of 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate (730 mg, 1.54 mmol, 1 eq.), 3-(fluoromethyl)azetidine hydrochloride (290.9 mg, 2.31 mmol, 1.5 eq.) in acetonitrile (14 mL) was added cesium carbonate (1 g, 3.08 mmol, 2 eq.) and stirred at 90 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate (20 mL) and washed with saturated sodium bicarbonate solution (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was further purified by prep-HPLC (24 mL/min, X-SELECT-CSH-C18 (150*30) using 0.1% formic acid in H₂O: acetonitrile gradient (5-45% over 12.5 mins). The pure fractions were lyophilized to afford (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (200 mg, 28% yield) as a yellow gum.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.79 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.20-7.13 (m, 4H), 7.07-7.02 (m, 1H), 7.00-6.95 (m, 1H), 5.05 (s, 1H), 4.54 (dd, *J* = 5.2, 47.2 Hz, 2H), 3.92-3.68 (m, 4H), 3.12-2.91 (m, 5H), 2.72 (t, *J* = 16.0 Hz, 1H), 2.58-2.54 (m, 4H), 1.70-1.63 (m, 2H), 1.47 (d, *J* = 21.60 Hz, 3H), 1.29 (d, *J* = 21.60 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 163.7 (formic acid), 158.4, 141.0, 144.1, 139.8, 136.8, 133.6, 128.9, 127.1, 121.1, 118.7, 118.1, 111.4, 109.0, 98.3 (d, *J* = 165 Hz), 83.2 (d, *J* = 163 Hz), 62.8, 55.1, 55.0, 53.9, 50.8, 47.7, 32.0, 29.8, 29.6 (d, *J* = 20 Hz), 26.61, 26.17.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -138.33, -227.02.

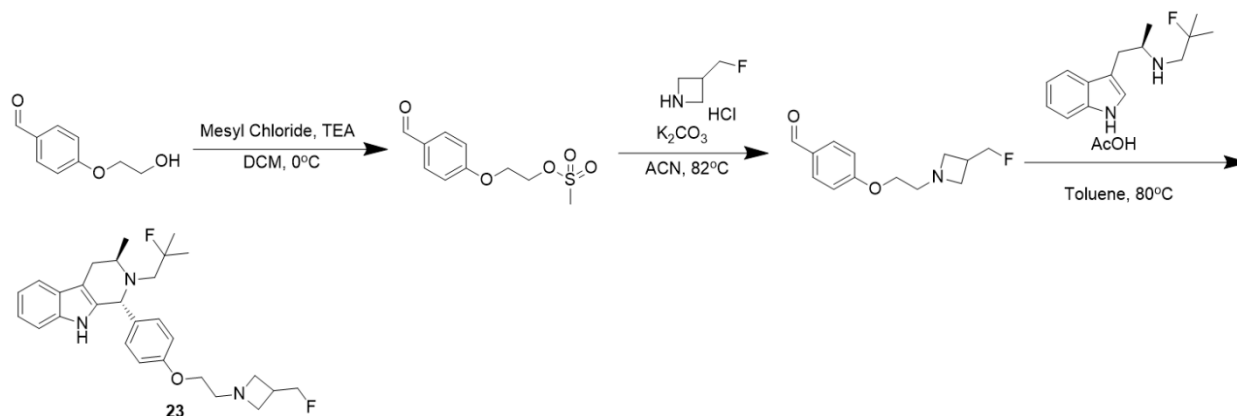
LCMS: *m/z* (ESI): 466.50 [M+H]⁺

HRMS (ESI): C₂₉H₃₈F₂N₃ [M+H]⁺ calc. 466.3028, found: 466.3023.

HPLC: 95.08%

[α]_D²⁰ -5 (c 0.1, acetonitrile).

Scheme S5. Preparation of 23



Synthesis of 2-(4-formylphenoxy)ethyl methanesulfonate:

Mesyl chloride (0.500 ml, 6.5 mmol) was added to a solution of 4-(2-hydroxyethoxy)benzaldehyde (1.01 g, 6.1 mmol) and TEA (1.1 ml, 7.9 mmol) in DCM (20 mL) at 0 °C. After stirring for 30 min, saturated aqueous sodium bicarbonate solution was added and stirred at 0 °C for 30 min. After separation, the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford 2-(4-formylphenoxy)ethyl methanesulfonate (1.46 g, 98% yield).

¹H NMR (300 MHz, CDCl₃): δ 9.91 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 4.60 (t, *J* = 4.5 Hz, 2H), 4.34 (t, *J* = 4.5 Hz, 2H), 3.10 (s, 3H).

LCMS: *m/z* (ESI): 245.30 [M+H]⁺

Synthesis of 4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde:

A suspension of 2-(4-formylphenoxy)ethyl methanesulfonate (1.46 g, 6.0 mmol), potassium carbonate (1.9 g, 13.7 mmol) and 3-(fluoromethyl)azetidine hydrochloride (734 mg, 5.8 mmol) in CH₃CN was heated to 82 °C with vigorous stirring overnight. The reaction was cooled to ambient temperature and concentrated in vacuo. The residue was diluted with EtOAc (100 mL) and water (50 mL). After separation, the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude was purified via flash chromatography in 0-5% MeOH in DCM to give 4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde (450 mg, 32% yield).

¹H NMR (300 MHz, CDCl₃): δ 9.88 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.51 (dd, *J* = 47.4, 5.7 Hz, 2H), 4.05 (t, *J* = 5.4 Hz, 2H), 3.50 (t, *J* = 7.4 Hz, 2H), 3.17 (t, *J* = 7.4 Hz, 2H), 2.89 - 2.85 (m, 3H).

LCMS: *m/z* (ESI): 238.32 [M+H]⁺

Synthesis of (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (23).

4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde (87 mg, 0.4 mmol) was added to a solution of (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (70 mg, 0.3 mmol) in anhydrous toluene (1.5 mL) and glacial acetic acid (0.100 ml, 1.7 mmol). The solution was stirred under nitrogen in the dark at 80 °C for 8 hours. The reaction was allowed to cool to room temperature, diluted with DCM and washed with a saturated aqueous sodium bicarbonate solution. The aqueous layer was washed with DCM and the organic layer was dried over sodium sulfate. The solution was filtered, dried in-vacuo, dissolved in ACN (2 mL), and purified via HPLC in 40-90% ACN in water to give (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white powder (32 mg, 23% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.70 (brs, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.26-7.25 (m, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.16-7.08 (m, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 4.97 (brs, 1H), 4.50 (dd, *J* = 6.0 Hz, *J* = 47.6 Hz, 1H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.49-3.45 (m, 2H), 3.37 (brs, 1H), 3.13 (t, *J* = 7.0 Hz, 2H), 2.87-2.51 (m, 7H), 1.41 (d, *J* = 21.6 Hz, 3H), 1.27 (d, *J* = 21.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 158.1, 136.3, 134.6, 133.6, 130.2, 127.4, 121.5, 119.2, 118.1, 114.0, 110.8, 97.9 (d, *J* = 165.0 Hz), 84.3 (d, *J* = 167.1 Hz), 66.4, 61.8, 58.0, 56.6, 56.5, 54.6, 47.8, 31.4 (d, *J* = 20.2 Hz), 25.6 (d, *J* = 24.9), 25.1 (d, *J* = 24.8 Hz).

¹⁹F NMR (376 MHz, CDCl₃): -140.01 - -139.78 (m), -222.05 - -222.36 (m).

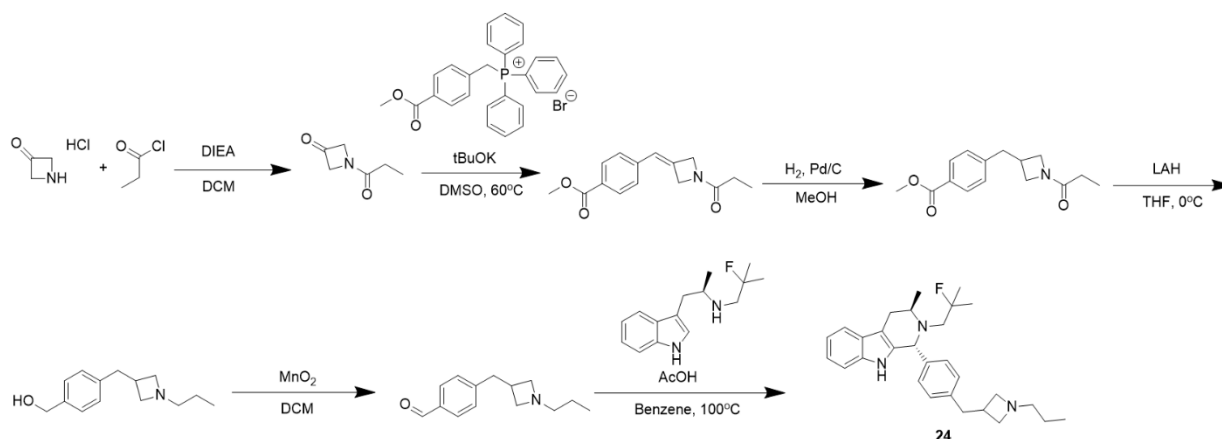
LCMS: *m/z* (ESI): 468.40 [M+H]⁺.

HRMS (ESI): C₂₈H₃₆ON₃F₂ [M+H]⁺ calc. 468.2821, found: 468.2820.

HPLC: 98.29%

[α]D²⁰ -1 (c 0.1, acetonitrile).

Scheme S6. Preparation of 24



Synthesis of 1-propionylazetidin-3-one:

To a solution of 3-azetidinone hydrochloride (5.00 g, 46.73 mmol, 1 eq.) in anhydrous dichloromethane (50 mL) was added *N,N*-diisopropylethylamine, (19.49 mL, 112.15 mmol, 2.4 eq.) and cooled to 0 °C. Propionyl chloride (4.86 mL, 56.07 mmol, 1.2 eq.) dissolved in DCM (5 mL) was added dropwise to the cooled suspension to give a yellow solution. The reaction was allowed to stir at room temperature for 16 h. The solvent was removed under reduced pressure to afford the crude material, which was suspended in ethyl acetate (100 mL) and stirred for 30 minutes at room temperature. The suspension was filtered and the solid washed with ethyl acetate (2 x 100 mL). The filtrate was evaporated under reduced pressure and purified by silica-gel flash chromatography (0-5% methanol in dichloromethane) to afford 1-propionylazetidin-3-one (2.2 g, 37% yield) as a brown liquid.

¹H NMR (400 MHz, CDCl₃): δ 4.82 (d, J = 5.6 Hz, 4H), 2.31 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H).

Synthesis of methyl 4-((1-propionylazetidin-3-ylidene)methyl)benzoate:

To a solution of (4-(methoxycarbonyl)benzyl)triphenylphosphonium bromide (2.2 g, 17.30 mmol, 1 eq.) in anhydrous dimethyl sulfoxide (22 mL) was added potassium *tert*-butoxide (2.136 g, 19.03 mmol, 1.1 eq.). The resultant mixture was stirred at room temperature for 10 min followed by the addition of a solution of 1-propionylazetidin-3-one (9.35 g, 19.034 mmol, 1.1 eq.) in anhydrous DMSO (35 mL). The reaction mixture was heated at 60 °C for 4 h. The mixture was cooled to room temperature, poured into ice water (300 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulphate, filtered, and dried *in vacuo*. The crude material was purified by silica-gel flash chromatography (0-30% ethyl acetate in *n*-hexane) to afford methyl 4-((1-propionylazetidin-3-ylidene)methyl)benzoate (4.4 g, 16.97 mmol, 98% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, J = 8.40 Hz, 2H), 7.65-7.60 (m, 2H), 6.41 (d, J = 10.5 Hz, 1H), 5.05-4.73 (m, 4H), 3.92 (s, 3H), 2.26-2.17 (q, J = 7.20 Hz, 2H), 1.17 (t, J = 7.60 Hz, 3H).

LCMS: m/z (ESI): 260.05 [M+H]⁺

Synthesis of methyl 4-((1-propionylazetidin-3-yl)methyl)benzoate:

To a solution of methyl 4-((1-propionylazetidin-3-ylidene)methyl)benzoate (4.4 g, 16.97 mmol, 1 eq.) in methanol (45 mL) was added 10% Pd/C (902.98 mg, 8.45 mmol, 0.5 eq.). The reaction mixture was vacuum degassed and backfilled with nitrogen (3 times) then stirred under hydrogen atmosphere at room temperature for 16 h. The mixture was filtered through celite bed and washed with methanol (100 mL). The filtrate was concentrated under reduced pressure to afford the crude material, which was purified by silica gel flash chromatography (0-40% ethyl acetate in *n*-hexane). The pure fraction was collected and evaporated under reduced pressure to afford methyl 4-((1-propionylazetidin-3-yl)methyl)benzoate (730 mg, 16% yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 4.12 (td, J = 8.0, 21.0 Hz, 2H), 3.91 (s, 3H), 3.81-3.72 (m, 2H), 3.02-2.89 (m, 3H), 2.09 (q, J = 8.0 Hz, 2H), 1.12 (t, J = 7.20 Hz, 3H).

LCMS: m/z (ESI): 262.09 [M+H]⁺

Synthesis of (4-((1-propylazetidin-3-yl)methyl)phenyl)methanol:

Lithium aluminium hydride (4.92 mL, 11.98 mmol, 11 eq., 2 M in tetrahydrofuran) was suspended into tetrahydrofuran (15 mL) and cooled to 0 °C. A solution of methyl 4-((1-propionylazetidin-3-yl)methyl)benzoate (700 mg, 1.09 mmol, 1 eq.) in tetrahydrofuran (50 mL) was added dropwise via a syringe over 15 minutes. The reaction mixture was heated at 60 °C for 16 h. The reaction mixture was cooled in an ice bath and quenched by the addition of a sodium sulphate solution (50 mL). The solvent mixture was filtered through celite bed and the solid was washed with ethyl acetate (4 x 50 mL). The separated organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 4-((1-propylazetidin-3-yl)methyl)phenyl)methanol (500 mg, 84% yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 7.26 (d, *J* = 8.00 Hz, 2H), 7.11 (d, *J* = 8.00 Hz, 2H), 4.65 (s, 2H), 3.39 (t, *J* = 7.20 Hz, 2H), 2.85-2.72 (m, 6H), 2.38-2.37 (m, 2H), 1.38-1.32 (m, 2H), 0.88 (t, *J* = 7.60 Hz, 3H).

LCMS: *m/z* (ESI): 220.09 [M+H]⁺

Synthesis of 4-((1-propylazetidin-3-yl)methyl)benzaldehyde:

To a solution of 4-((1-propylazetidin-3-yl)methyl)phenyl)methanol (500 mg, 2.80 mmol, 1 eq.) in dichloromethane (20 mL) was added manganese dioxide (1.981 g, 22.797 mmol, 10 eq.) and stirred at RT for 16 h. The mixture was filtered through celite bed, eluting with dichloromethane (15 mL). The filtrate was concentrated under reduced pressure to afford 4-((1-propylazetidin-3-yl)methyl)benzaldehyde (490 mg, 2.25 mmol, 98% yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 9.97 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.71-3.66 (m, 2H), 2.95-2.93 (m, 2H), 2.87-2.77 (m, 3H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.32 (q, *J* = 7.6 Hz, 2H), 0.86 (t, *J* = 7.2 Hz, 3H).

LCMS: *m/z* (ESI): 218.31 [M+H]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)methyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (24):

To a stirred solution of 4-((1-propylazetidin-3-yl)methyl)benzaldehyde (490 mg, 2.2 mmol, 1 eq.) in anhydrous benzene (15 mL) was added (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (839 mg, 3.38 mmol, 1.5 eq.), glacial acetic acid (2.7 mL, 47.35 mmol, 21 eq.) and 4Å molecular sieves. This mixture was stirred under argon atmosphere in the dark at 100 °C for 16 h. The reaction mixture was diluted with dichloromethane (35 mL) and washed with saturated aqueous sodium bicarbonate solution (25 mL). The organic layers were separated, dried over anhydrous sodium sulphate, filtered and dried *in vacuo*. The crude material was purified using preparative HPLC (7 mL/min, X-BRIDGE-OB D C18, 250×10 mm), using 0.1% formic acid in water: acetonitrile gradient (5-35%, over 11 mins) to afford (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)methyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (25 mg, 2.4% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.68 (brs, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18-7.12 (m, 2H), 7.01 (d, *J* = 10.8 Hz, 2H), 5.04 (brs, 1H), 3.69 (brs, 2H), 3.40-3.10 (m, 3H), 2.98-2.93 (m, 1H), 2.90-2.83 (m, 2H), 2.71-2.64 (m, 2H), 2.61-2.52 (m, 4H), 1.49-1.45 (m, 2H), 1.44 (d, *J* = 22.0, 3H), 1.29 (d, *J* = 21.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 168.9 (formic acid), 140.6, 137.9, 136.3, 133.2, 129.4, 128.1, 127.8, 127.3, 125.6, 121.5, 119.2, 118.1, 110.8, 110.2, 97.8 (d, *J* = 165 Hz), 62.3, 59.8, 58.9, 54.4, 47.8, 39.4, 31.2, 26.9, 25.7 (d, *J* = 24 Hz), 24.9 (d, *J* = 25 Hz), 19.40, 11.4.

¹⁹F NMR (376 MHz, CDCl₃): δ -139.59 - -140.37 (m).

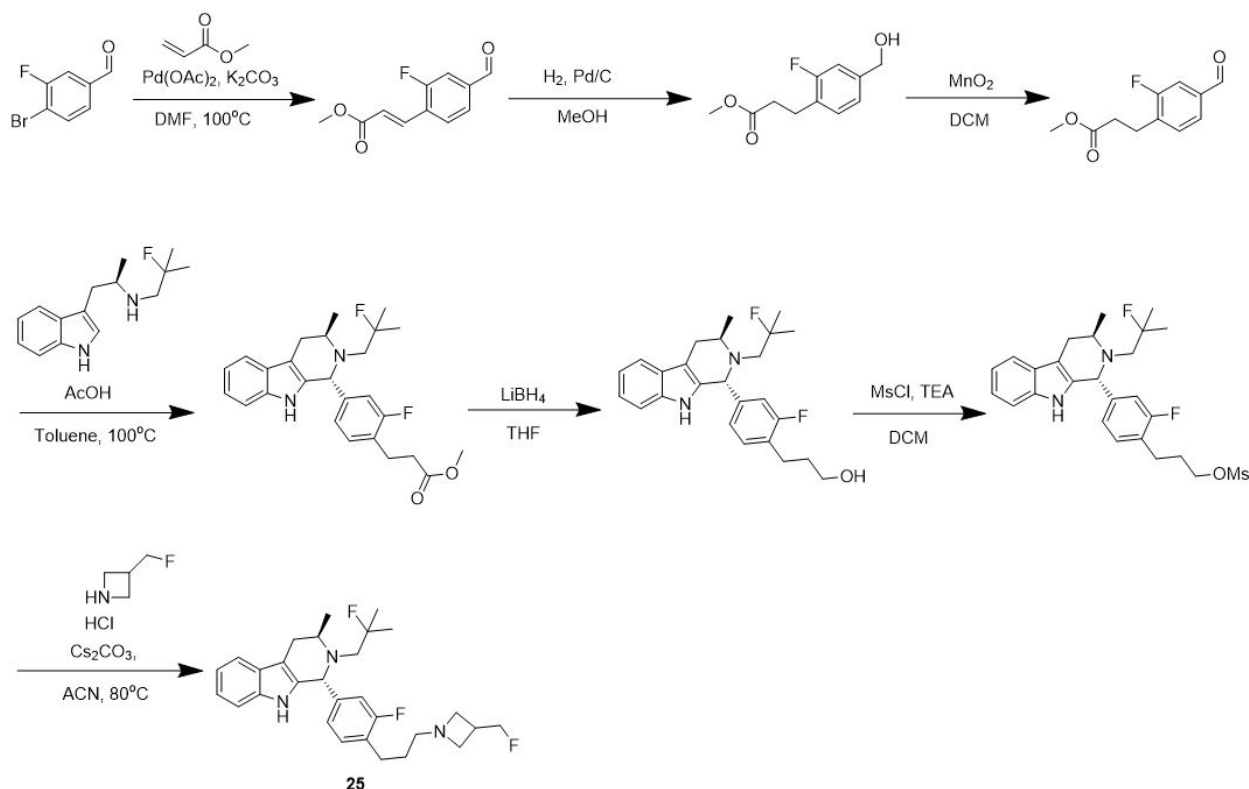
LCMS: *m/z* (ESI): 448.53 [M+H]⁺

HRMS (ESI): C₂₉H₃₉FN₃[M+H]⁺ calc. 448.3122, found: 448.3101.

HPLC: 99.20%

[α]_D²⁰ -12 (c 0.1, acetonitrile).

Scheme S7. Preparation of 25



Synthesis of methyl (E)-3-(2-fluoro-4-formylphenyl)acrylate:

To a stirred solution of 4-bromo-3-fluorobenzaldehyde (5 g, 24.63 mmol, 1 eq.), methyl acrylate (3.18 g, 36.94 mmol, 1.5 eq.) in DMF (30 mL) was added potassium carbonate (8.51 g, 61.57 mmol, 2.5 eq.), purged with argon for 10 min, then added palladium (II) acetate (1.106 g, 4.93 mmol, 0.2 eq.). The reaction mixture was stirred at 100°C for 16 h. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (10% EtOAc in *n*-hexane) to afford methyl (E)-3-(2-fluoro-4-formylphenyl)acrylate (1.8 g, 35% yield) as an off white solid.

^1H NMR (500 MHz, CDCl_3): δ 10.00 (s, 1H), 7.83 (d, $J = 16$ Hz, 1H), 7.73-7.68 (m, 2H), 7.62 (d, $J = 1.5$ Hz, 1H), 6.66 (d, $J = 16$ Hz, 1H), 3.84 (s, 3H)

^{19}F NMR (470 MHz, CDCl_3): -112.70

LCMS: m/z (ESI): 209.24 $[\text{M}+\text{H}]^+$

Synthesis of methyl 3-(2-fluoro-4-(hydroxymethyl)phenyl)propanoate:

To a stirred solution of methyl (E)-3-(2-fluoro-4-formylphenyl)acrylate (0.9 g, 4.32 mmol, 1 eq.) in methanol (50 mL) was added 10% palladium on carbon (0.3 g) and stirred at room temperature under hydrogen atmosphere for 16h. Then the reaction mixture was diluted with 10% MeOH in DCM and filtered through celite bed. The filtrate was evaporated under reduced pressure to yield the crude material, which was purified by silica-gel flash column chromatography (20% EtOAc in *n*-hexane) to afford methyl 3-(2-fluoro-4-(hydroxymethyl)phenyl)propanoate (310 mg, 9% yield) as a colourless liquid.

^1H NMR (400 MHz, CDCl_3): δ 7.19 (t, $J = 7.6$ Hz, 1H), 7.05 (d, $J = 9.2$ Hz, 2H), 4.66 (d, $J = 5.2$ Hz, 2H), 3.66 (s, 3H), 2.96 (t, $J = 7.6$ Hz, 2H), 2.63 (t, $J = 7.6$ Hz, 2H), 1.74 (t, $J = 6.0$ Hz, 1H)

^{19}F NMR (376 MHz, CDCl_3): δ -118.33

Synthesis of methyl 3-(2-fluoro-4-formylphenyl)propanoate:

To a stirred solution of methyl 3-(2-fluoro-4-(hydroxymethyl)phenyl)propanoate (310 mg, 1.46 mmol, 1 eq.) in DCM (7 mL) was added manganese dioxide (1.27 g, 14.61 mmol, 10 eq.) at 0°C and stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (2 x 30 mL) and filtered through celite bed. The filtrate was dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by neutral alumina flash column chromatography (20-100% EtOAc in *n*-hexane) to afford methyl 3-(2-fluoro-4-formylphenyl)propanoate (220 mg, 72 % yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 9.95 (s, 1H), 7.60 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.54 (dd, *J* = 1.2 Hz, 9.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 3.67 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃): δ -116.53

LCMS: *m/z* (ESI): 211.32 [M+H]⁺

Synthesis of methyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate:

To a stirred solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (210 mg, 0.85 mmol, 1 eq.) and methyl 3-(2-fluoro-4-formylphenyl)propanoate (213 mg, 1.01 mmol, 1.2 eq.) in toluene (4 mL) was added acetic acid (215.81 mg, 3.59 mmol, 4.25 eq.), molecular sieves (4Å, 400 mg) and stirred at 100 °C for 16 h. The reaction mixture was quenched with a saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (10% EtOAc in *n*-hexane) to afford methyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (160 mg, 43% yield) as a brown gum.

¹H NMR (400 MHz, CDCl₃): δ 7.64 (brs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.07 (m, 3H), 7.03-6.99 (m, 2H), 5.04 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 3.29 (s, 1H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.73-2.51 (m, 6H), 1.47 (d, *J* = 21.6 Hz, 3H), 1.30 (d, *J* = 21.2 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H)

LCMS: *m/z* (ESI): 441.26[M+H]⁺

Synthesis of 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol:

To a stirred solution of methyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (160 mg, 0.36 mmol, 1 eq.) in dry THF (4 mL) was added lithium borohydride (63.283 mg, 2.906 mmol, 8 eq.) at 0 °C and stirred at room temperature for 6 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (2 x 30 mL). The separated organic layers were washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo* to afford 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol (120 mg, 80% yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 7.64 (brs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.09 (m, 3H), 7.04-6.97 (m, 2H), 5.05 (brs, 1H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.30 (brs, 1H), 2.77-2.51 (m, 6H), 1.90-1.83 (m, 2H), 1.55-1.50 (m, 3H), 1.48 (d, *J* = 22.0 Hz, 3H), 1.28 (d, *J* = 21.2 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H)

¹⁹F NMR (376 MHz, CDCl₃): -119.13, -140.82

LCMS: *m/z* (ESI): 413.26 [M+H]⁺

Synthesis of 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate:

To a stirred solution of 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol (120 mg, 0.29 mmol, 1 eq.) and *N,N*-diisopropylethylamine (0.102 mL, 0.58 mmol, 2 eq.) in DCM (3 mL) at 0 °C was added methanesulfonyl chloride (0.034 mL, 0.44 mmol, 1.5 eq.) and stirred at 0 °C for 1 h. The reaction mixture was quenched with a saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 30 mL). The separated organic layers were washed with brine (20 mL), dried over sodium sulphate, filtered and dried *in-vacuo* to afford 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate (165 mg, 98% yield) as a pale yellow gum.

¹⁹F NMR (470 MHz, CDCl₃): δ -118.49, -141.64

LCMS: *m/z* (ESI): 491.15[M+H]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (25):

To a stirred solution of 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methane sulfonate (160 mg, 0.33 mmol, 1 eq.) and 3-(fluoromethyl)azetidine hydrochloride (49.14 mg, 0.39 mmol, 1.2 eq.) in ACN (3 mL) was added cesium carbonate (212.52 mg, 0.65 mmol, 2 eq.) and stirred at 80 °C for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (40 mL) and extracted with ethyl acetate (2 x 100 mL). The separated organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by preparative-HPLC (17 mL/min, X-BRIDGE-OBDB C18, 150-19 mm) using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (40-75%, for 13 mins). Pure fractions were lyophilized to afford (1*R*,3*R*)-2-

(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (30 mg, 19% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.76 (bs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.18-7.10 (m, 2H), 7.04 (t, *J* = 4.0 Hz, 1H), 6.98-6.97 (m, 2H), 5.03 (s, 1H), 4.47 (dd, *J* = 5.6 Hz, 7.2 Hz, 2H), 4.42 (d, *J* = 6.0 Hz, 1H), 3.37-3.23 (m, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.83-2.50 (m, 7H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.65-1.58 (m, 2H), 1.67-1.58 (m, 3H), 1.26 (d, *J* = 5.2 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃): δ 161.0 (d, *J* = 244 Hz), 159.7, 142.6, 136.3, 132.6, 130.0, 127.7, (d, *J* = 17 Hz), 127.2, 124.4, 121.7, 119.3, 118.2, 115.6 (d, *J* = 23 Hz), 110.5, 97.8 (d, *J* = 165 Hz), 84.4 (d, *J* = 166 Hz), 62.1, 58.9, 55.7, 55.7, 54.3, 47.9, 47.9, 30.7, 27.8, 26.5, 25.7 (d, *J* = 24 Hz), 25.7 (d, *J* = 28 Hz), 24.9 (d, *J* = 26 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ -119.10, -140.68- -141.23

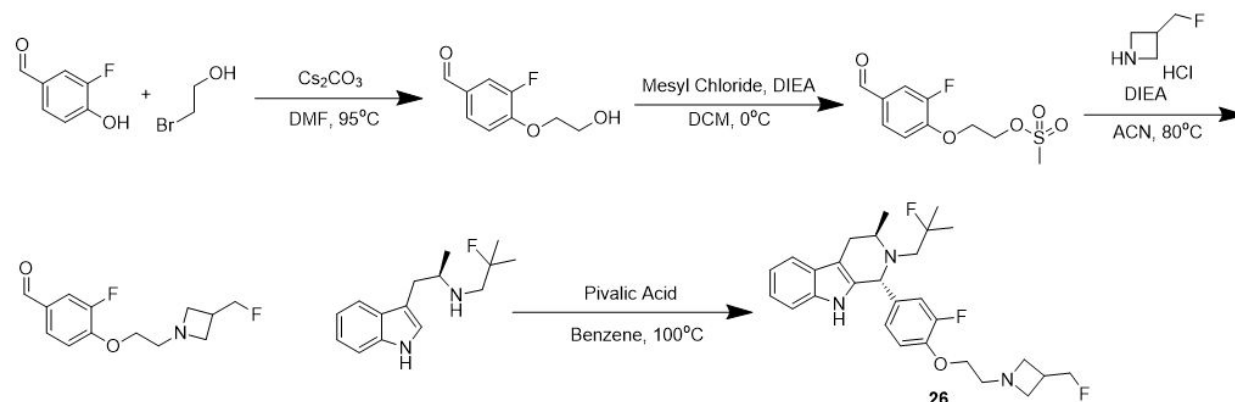
LCMS: *m/z* (ESI): 484.40 [M+H]⁺

HRMS (ESI): C₂₉H₃₇F₃N₃ [M+H]⁺ calc.484.2934, found: 484.2930.

HPLC: 99.70%

[α]_D²⁰ +12 (c 0.1, acetonitrile).

Scheme S8. Preparation of 26



Synthesis of 3-Fluoro-4-(2-hydroxyethoxy)benzaldehyde:

A suspension of 3-fluoro-4-hydroxybenzaldehyde (2 g, 14.28 mmol, 1 eq), 2-bromoethanol (3.568 g, 28.549 mmol, 2 eq) and cesium carbonate (9.302 g, 28.549 mmol, 2 equiv.) in DMF (20 mL) was stirred at 90 °C for 16 h. The reaction was cooled to ambient temperature and partitioned with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed twice with water, once with brine, dried over sodium sulphate, filtered, and dried in vacuo. The crude was purified by flash chromatography using 0-30% ethyl acetate in n-hexanes to afford 3-fluoro-4-(2-hydroxyethoxy)benzaldehyde (1.4 g, 53% yield) as a pale brown solid.

¹H NMR (500 MHz, CDCl₃): δ 9.88 (d, *J* = 2.0 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.10 (t, *J* = 8.20 Hz, 1H), 4.24 (t, *J* = 4.50 Hz, 2H), 4.05-4.03 (m, 2H), 2.18 (t, *J* = 6.0 Hz, 1H).

LCMS: *m/z* (ESI): 184.93 [M+H]⁺

Synthesis of 2-(2-Fluoro-4-formylphenoxy)ethyl methanesulfonate:

A suspension of 3-fluoro-4-(2-hydroxyethoxy)benzaldehyde (1.4 g, 7.60 mmol, 1 eq), freshly distilled DIEA (2.07 mL, 11.85 mmol, 1.5 eq) in DCM (15 mL) in a 500 mL RB flask was cooled in an ice bath for 15 minutes. Mesyl chloride (0.78 mL, 10.19 mmol, 1.34 eq.) was added to the vial via syringe dropwise over 2 minutes. After stirring at 0 °C for 1 h, saturated aqueous sodium bicarbonate solution was added and the mixture was stirred at 0 °C to room temperature for 20 min vigorously. The organic and aqueous layers were then separated, and the organic layer was washed with brine, dried over sodium sulphate, filtered, and concentrated to afford 2-(2-fluoro-4-formylphenoxy)ethyl methanesulfonate as an orange oil (1.9 g, 95% yield).

¹H NMR (400 MHz, CDCl₃): δ 9.88 (d, *J* = 2.40 Hz, 1H), 7.66 - 7.62 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 4.66-4.64 (m, 2H), 4.41-4.39 (m, 2H), 3.13 (s, 3H).

LCMS: *m/z* (ESI): 262.92 [M+H]⁺

Synthesis of 3-Fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde:

A suspension of DIEA (266.138 mg, 1.01 mmol, 1.8 eq) and 3-(fluoromethyl)azetidine hydrochloride (172.38 mg, 1.22 mmol, 1.2 eq) in acetonitrile (2 mL) was stirred at room temperature for 30 min under argon, then 2-(2-fluoro-4-formylphenoxy)ethyl methanesulfonate (300 mg, 1.144 mmol, 1.0 eq) was added and the mixture was stirred at 80 °C for 16 h. The reaction was cooled to ambient temperature and evaporated under reduced pressure. The crude was purified by flash chromatography in 0-5% MeOH in DCM to afford 3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde (220 mg, 75% yield) as a pale-yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 9.86 (s, 1H), 7.63-7.59 (m, 2H), 7.05 (t, *J* = 8.00 Hz, 1H), 4.52 (dd, *J* = 6.00, 47.40 Hz, 2H), 4.13 (t, *J* = 5.60 Hz, 2H), 3.54 (t, *J* = 6.40 Hz, 2H), 3.20 (t, *J* = 6.40 Hz, 2H), 2.91 (t, *J* = 5.60 Hz, 2H), 2.38-2.31 (m, 1H).

LCMS: *m/z* (ESI): 256.02 [M+H]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (26):

3-Fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)benzaldehyde (250 mg, 0.98 mmol, 1 eq) was added to a solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (194.578 mg, 0.783 mmol, 0.8 eq) in anhydrous benzene (5.0 mL), pivalic acid (1.56 g, 15.28 mmol, 15.6 eq) and molecular sieves (4Å, 500 mg). The reaction was stirred under argon in the dark at 100 °C. After 16 h. The reaction mixture was filtered through celite, eluting with ethyl acetate. The filtrate was washed with saturated aqueous sodium bicarbonate solution. The aqueous layer was washed with ethyl acetate and the combined organic layers were dried over sodium sulphate. The resulting solution was concentrated, dissolved into 2 mL ACN and purified by Prep HPLC (16 mL/min, 25 °C, YMC-ACTUS-TRIART C18 (150*20mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: 75-98% over 15 mins). Pure fractions were lyophilised to afford (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (15.1 mg, 0.031 mmol, 3.1% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.62 (bs, 1H), 7.53 (d, *J* = 8.00 Hz, 1H), 7.29 (d, *J* = 8.00 Hz, 1H), 7.19-7.07 (m, 3H), 6.92 (d, *J* = 8.40 Hz, 1H), 6.81 (t, *J* = 8.40 Hz, 1H), 4.99 (brs, 1H), 4.50 (dd, *J* = 6.00, 47.0 Hz, 2H), 4.01 (t, *J* = 5.60 Hz, 2H), 3.52-3.49 (m, 2H), 3.32 (bs, 1H), 3.18 (t, *J* = 10.8 Hz, 2H), 2.90-2.80 (m, 3H), 2.78-2.49 (m, 4H), 1.45 (d, *J* = 21.60 Hz, 3H), 1.29 (d, *J* = 21.60 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 152.5 (d, *J* = 245 Hz), 146.0 (d, *J* = 14 Hz), 136.3, 136.0, 132.7, 127.2, 124.4, 121.7, 119.3, 118.2, 116.8, (d, *J* = 19 Hz), 114.0, 110.8, 97.8 (d, *J* = 165 Hz), 84.3 (d, *J* = 166 Hz), 68.2, 61.8 (d, *J* = 10 Hz), 57.7, 56.7, 54.3, 47.8, 31.5, 25.5, 24.95 (d, *J* = 24 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ -134.28 (s, 1F), -140.25 -141.05 (m, 1F), -222.25, -222.43 (m, 1H).

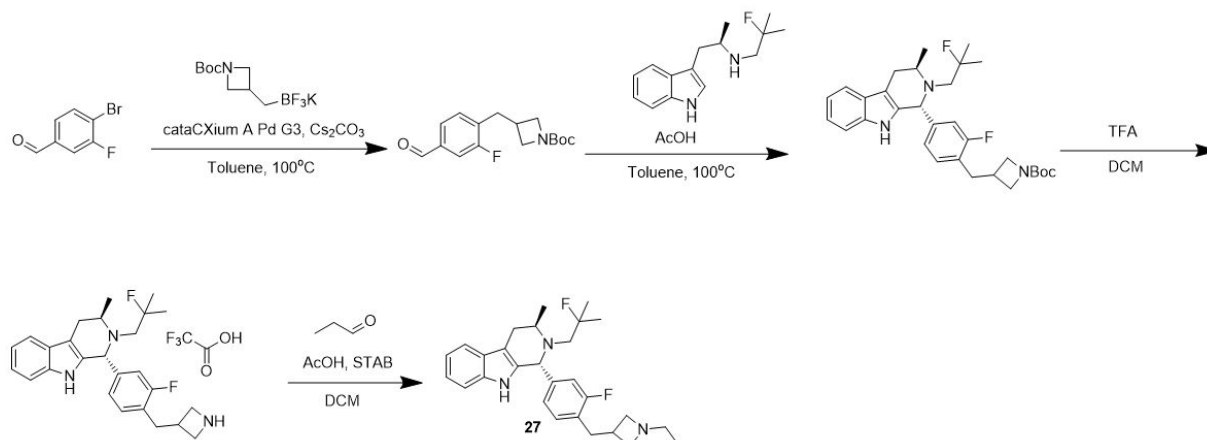
LCMS: *m/z* (ESI): 486.45 [M+H]⁺

HRMS: C₂₈H₃₅F₃N₃O [M+H]⁺ calc.486.2726, found: 486.2660.

HPLC: 97.22%

[α]_D²⁰ +3 (c 0.1, acetonitrile)

Scheme S9. Preparation of 27



Synthesis of *tert*-butyl 3-(2-fluoro-4-formylbenzyl)azetidine-1-carboxylate:

To a stirred solution of 4-bromo-3-fluorobenzaldehyde (0.50 g, 2.46 mmol, 1 eq.), *tert*-butyl 3-((trifluoro-*l*-boraneyl)methyl)azetidine-1-carboxylate, potassium salt (1.024 g, 3.69 mmol, 1.5 eq.) and cesium carbonate (2.00 g, 6.16 mmol, 2.5 eq.) in toluene (10 mL) and water (1 mL) was purged with argon for 3 min. CataCXium® A Pd G3 (0.536 g, 0.74 mmol, 0.3 eq.) was added and the mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through celite and washed with ethyl acetate (50 mL) and water (30 mL). The separated organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-40% ethyl acetate in *n*-hexane) to afford *tert*-butyl 3-(2-fluoro-4-formylbenzyl)azetidine-1-carboxylate (450 mg, 62% yield) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 9.95 (s, 1H), 7.61 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.54 (dd, *J* = 1.6 Hz, 9.6 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.66 (dd, *J* = 5.2 Hz, 8.4 Hz, 2H), 3.01 (d, *J* = 8.0 Hz, 2H), 2.88-2.86 (m, 1H), 1.44 (s, 9H).

LCMS: *m/z* (ESI): 237.99 [M+H-tBu]⁺

Synthesis of *tert*-butyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate:

To a stirred solution of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-fluoro-2-methylpropan-1-amine (0.42 g, 1.79 mmol, 1.5 eq.) and *tert*-butyl 3-(2-fluoro-4-formylbenzyl)azetidine-1-carboxylate (0.35 g, 1.19 mmol, 1 eq.) in benzene (10 mL) was added acetic acid (1.45 mL, 25.06 mmol, 21 eq.), molecular sieves (4Å, 300 mg). The mixture was stirred at 100 °C for 16 h, cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by silica gel flash column chromatography (0-40% ethyl acetate in *n*-hexane) to afford *tert*-butyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate (350 mg, 56% yield) as an off white solid.

¹H NMR (500 MHz, CDCl₃): δ 7.68 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.33-7.30 (m, 1H), 7.19-7.16 (m, 1H), 7.14-7.11 (m, 1H), 7.04-6.99 (m, 3H), 5.06 (s, 1H), 3.97 (t, *J* = 8.5 Hz, 2H), 3.63 (dd, *J* = 5.5 Hz, 8.5 Hz, 2H), 3.27 (s, 1H), 2.89-2.79 (m, 2H), 2.78-2.51 (m, 4H), 1.48 (d, *J* = 21.5 Hz, 3H), 1.43 (s, 9H), 1.30 (d, *J* = 21.5 Hz, 3H), 1.27-1.24 (m, 3H).

LCMS: *m/z* (ESI): 523.97 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-3-fluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole trifluoroacetate:

To a stirred solution of *tert*-butyl 3-(2-fluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate (0.350 g, 0.668 mmol, 1 eq.) in DCM (10 mL) was added trifluoroacetic acid (3.51 mL) at room temperature. The mixture was stirred for 3 h at the same temperature. The solvent was removed under reduced pressure to afford (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-3-fluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole trifluoroacetate (250 mg, 88% yield) as a light green gum.

LCMS: *m/z* (ESI): 424.27 [M+H]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-((1-propylazetidin-3-yl)methyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (27):

To a stirred solution of (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-3-fluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (250 mg, 0.59 mmol, 1 eq.) and triethyl amine (0.41 mL, 2.95 mmol, 5 eq.) in DCM (5 mL) were sequentially added propionaldehyde (34.282 mg, 0.590 mmol, 1 eq.) and acetic acid (0.170 mL, 2.951 mmol, 5 eq.). The reaction mixture was stirred at room temperature for 1 h. STAB (375.29 mg, 1.77 mmol, 3 eq.) was added and the reaction mixture was stirred at room temperature for another 1 h. The reaction mixture was poured into a mixture of saturated sodium bicarbonate solution (10 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by preparative HPLC (0.60 mL/min, ACQUITY UPLC BEH C18, 20.1'50), using 0.1% FA in H₂O: acetonitrile gradient (0-50% over 10 mins). The pure fractions were lyophilised to afford ((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-((1-propylazetidin-3-yl)methyl)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (50 mg, 18% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.57 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.19-7.16 (m, 2H), 7.13-7.10 (m, 3H), 5.05 (s, 1H), 3.93 (brs, 2H), 3.47-3.25 (m, 3H), 3.12-3.06 (m, 1H), 2.88-2.78 (m, 2H), 2.77-2.51 (m, 6H), 1.56-1.54 (m, 2H), 1.48 (d, *J* = 21.0 Hz, 3H), 1.30 (d, *J* = 21.0 Hz, 3H), 1.10 (d, *J* = 8.0 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 168.7 (formic acid), (d, *J* = 195 Hz), 159.9, 144.1, 136.42, 132.3, 130.0, 127.1, 124.8, 123.6 (d, *J* = 13 Hz), 123.55, 119.3, 118.1, 115.9 (d, *J* = 18 Hz), 110.9, 110.5, 97.8 (d, *J* = 132 Hz), 62.1, 58.1 (d, *J* = 12 Hz), 54.2, 47.9, 32.4, 29.9, 25.8 (d, *J* = 19 Hz), 25.4, 24.8 (d, *J* = 21 Hz), 18.4, 11.1.

¹⁹F NMR (470 MHz, CDCl₃): δ -140.95, -118.47

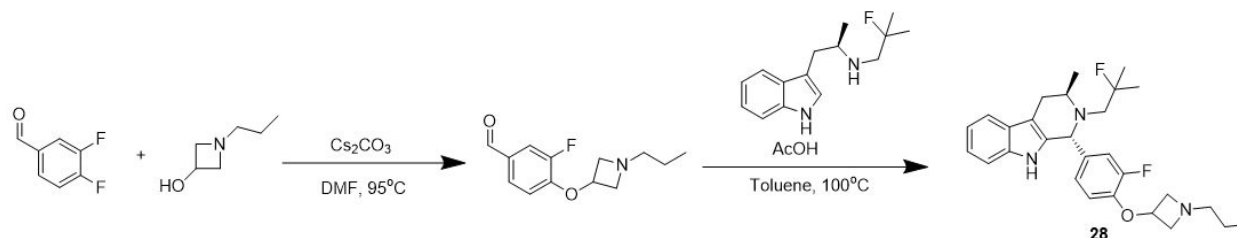
LCMS: m/z (ESI): 466.36 [M+H]⁺

HRMS (ESI): C₂₉H₃₈F₂N₃ [M+H]⁺ calc.466.3028, found: 466.3011.

HPLC: 95.05%

[α]_D²⁰ +13 (c 0.1, acetonitrile).

Scheme S10. Preparation of 28



Synthesis of 3-Fluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde:

To a stirred solution of 3,4-difluorobenzaldehyde (500 mg, 3.52 mmol, 1 eq.) in DMF (10 mL) was added propylazetidin-3-ol (405.25 mg, 3.52 mmol, 1 eq.) and cesium carbonate (2.29 g, 7.04 mmol, 2 eq.). The resulting mixture was stirred at 95 °C for 12 h. The mixture was filtered and the filtrate was diluted with ethyl acetate (20 mL)/water (20 mL). The organic layer was washed with water (2 x 20 mL), brine (2 x 20 mL), dried over sodium sulphate, filtered, and dried in vacuo to give the 3-fluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde (650 mg, 82% yield) as a pale brown liquid.

¹H NMR (400 MHz, CDCl₃): δ 9.85 (d, *J* = 2.4 Hz, 1H), 7.63 - 7.58 (m, 2H), 6.84 (t, *J* = 8.4 Hz, 1H), 4.92 - 4.76 (m, 1H), 3.90 - 3.86 (m, 2H), 3.18 - 3.13 (m, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.44 - 1.36 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

LCMS: m/z (ESI): 238.13 [M+H]⁺.

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-((1-propylazetidin-3-yl)oxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (28):

To a stirred solution of 3-fluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde (458.6 mg, 1.93 mmol, 1.2 eq.) in anhydrous toluene (1.5 mL) and glacial acetic acid (411 μL, 6.845 mmol, 4.25 eq.) was added (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (400 mg, 1.611 mmol, 1 eq.) along with 4Å molecular sieves. The solution was stirred under argon atmosphere in the dark at 80 °C for 8 h. The solution was allowed to cool to room temperature and dried in-vacuo. DCM (20 mL) was added, and the solution was passed through a syringe filter. The solution was concentrated and diluted in ACN (20 mL) and purified by Prep HPLC (16 mL/min, 25 °C, X-SELECT-CSH-Phenyl Hexyl (250*19), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: 65-75% over 15 mins). The pure fractions were lyophilised to afford (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-((1-propylazetidin-3-yl)oxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (161 mg, 21% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.66 (bs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.09 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.62 (t, *J* = 8.4 Hz, 1H), 5.00 (bs, 1H), 4.79-4.74 (m, 1H), 3.83-3.80 (m, 2H), 3.29 (bs, 1H), 3.10-3.07 (m, 2H), 2.73-2.49 (m, 4H), 2.47 (t, *J* = 7.6 Hz, 2H), 1.46 (d, *J* = 22.4 Hz, 3H), 1.42-1.33 (m, 2H), 1.29 (d, *J* = 24.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 152.2 (d, *J* = 245 Hz), 144.3 (d, *J* = 13 Hz), 136.5 (d, *J* = 5 Hz), 136.40, 132.6, 127.2, 124.5, 121.7, 119.3, 118.2, 117.1, 116.6 (d, *J* = 57 Hz), 114.1, 110.9, 110.5, 97.7 (d, *J* = 165 Hz), 67.8, 61.9, 61.6, 61.5, 54.2, 54.0, 47.7, 25.8 (d, *J* = 24 Hz), 25.5, 24.9 (d, *J* = 25 Hz), 21.0, 11.8.

¹⁹F NMR (376 MHz, CDCl₃): δ -134.38, -139.98 -140.30 (m).

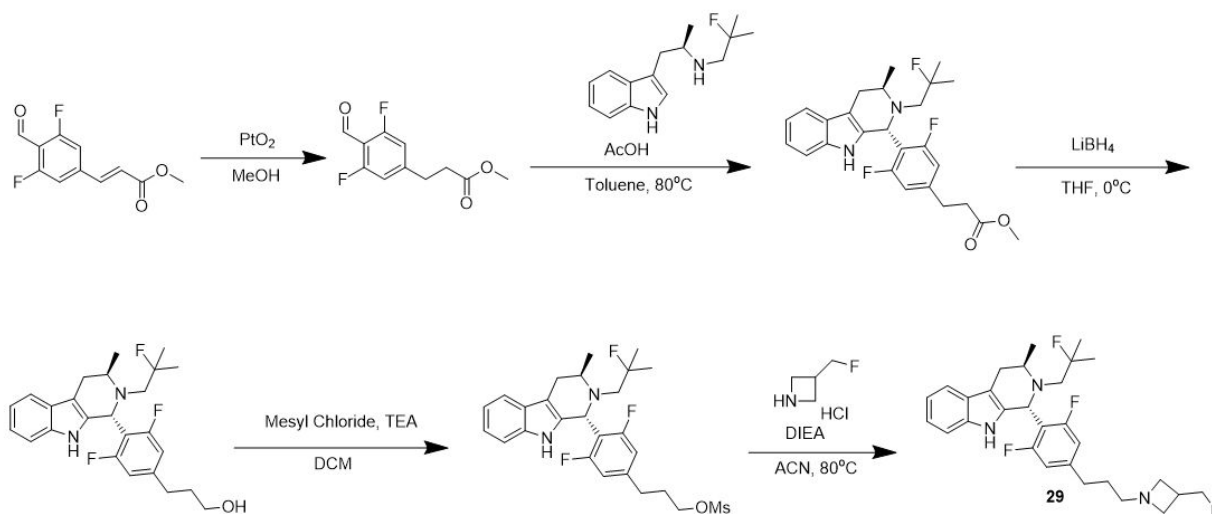
LCMS: m/z (ESI): 468.52 [M+H]⁺.

HRMS (ESI): C₂₈H₃₆F₂N₃O [M+H]⁺ calc.468.2748, found: 468.2768.

HPLC: 97.12%

[α]_D²⁰ +2 (c 0.1, acetonitrile).

Scheme S11. Preparation of 29



Synthesis of methyl 3-(3,5-difluoro-4-formylphenyl)propanoate: To a stirred solution of methyl (*E*)-3-(3,5-difluoro-4-formylphenyl)acrylate (5 g, 22.02 mmol, 1 eq.) in methanol (100 mL) and ethyl acetate (1.7 mL) was added 10 % PtO₂ (0.5 g, 2.20 mmol, 0.1 eq.) at room temperature under nitrogen atmosphere. The reaction mixture stirred under hydrogen atmosphere at room temperature for 16 h. The reaction mixture was filtered through celite and washed with methanol (170 mL). The filtrate was evaporated under reduced pressure to afford the crude material, which was purified by neutral alumina flash column chromatography (0-30% ethyl acetate in *n*-hexane) to afford methyl 3-(3,5-difluoro-4-formylphenyl)propanoate (2 g, 36% yield) as a colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 10.29 (s, 1H), 6.86 (d, *J* = 9.6 Hz, 2H), 3.68 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H).

LCMS: *m/z* (ESI): 229.27 [M+H]⁺

Synthesis of methyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate:

To a stirred solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (650 mg, 2.62 mmol, 1 eq.), methyl 3-(3,5-difluoro-4-formylphenyl)propanoate (717 mg, 3.14 mmol, 1.2 eq.) in toluene (15 mL) was added acetic acid (668.80 mg, 0.64 mL, 11.14 mmol, 4.25 eq.) along with molecular sieves (4Å, 300 mg) and stirred at 100 °C for 16 h. Then the reaction mixture was cooled to room temperature and quenched with saturated sodium bicarbonate solution (25 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was further purified by silica-gel flash chromatography (0-10 % ethyl acetate in *n*-hexane) to afford methyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (790 mg, 66% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.52-7.50 (m, 1H), 7.43 (s, 1H), 7.23-7.21 (m, 1H), 7.12-7.08 (m, 2H), 6.69 (d, *J* = 7.6 Hz, 2H), 5.25 (s, 1H), 3.69 (s, 3H), 3.68-3.64 (m, 1H), 3.09-3.06 (m, 1H), 2.91 (d, *J* = 6.0 Hz, 2H), 2.86-2.82 (m, 1H), 2.63-2.60 (m, 3H), 2.42-2.34 (m, 1H), 1.20 (d, *J* = 21.5 Hz, 3H), 1.16 (d, *J* = 21.5 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

LCMS: *m/z* (ESI): 459.21 [M+H]⁺

Synthesis of 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol:

To a stirred solution of methyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propanoate (780 mg, 1.70 mmol, 1 eq.) in dry tetrahydrofuran (10 mL) at 0 °C added lithium borohydride (148.29 mg, 6.81 mmol, 4 eq.) and stirred at room temperature for 5 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo* to yield the crude 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol as a pale yellow solid. (730 mg, 73% yield), which was used for the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.53-7.50 (m, 1H), 7.43 (s, 1H), 7.23-7.21 (m, 1H), 7.13-7.06 (m, 2H), 6.75-6.68 (m, 2H), 5.25 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.68-3.65 (m, 3H), 3.10-3.06 (m, 1H), 2.91-2.82 (m, 1H), 2.68-2.62 (m, 3H), 2.59 (dd, *J* = 0.8 Hz, 4.0 Hz, 1H), 2.45-2.35 (m, 1H), 1.90-1.83 (m, 2H), 1.23 (d, *J* = 21.2 Hz, 3H), 1.21 (d, *J* = 22.0 Hz, 3H), 1.10 (d, *J* = 7.20 Hz, 3H).

LCMS: *m/z* (ESI): 431.25 [M+H]⁺

Synthesis of 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propyl methanesulfonate:

Methanesulfonyl chloride (260 mg, 1.7 mL, 2.27 mmol, 1.34 eq.) was added drop wise to the stirred solution of 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propan-1-ol (730 mg, 1.70 mmol, 1 eq.), *N,N*-diisopropylethylamine (0.475 mL, 2.65 mmol, 1.56 eq.) in DCM (10 mL) at 0 °C and stirred for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL), stirred at 0 °C for 30 min and diluted with EtOAc (50 mL). The organic layers were separated, washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo* to afford 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propylmethanesulfonate as a pale yellow solid (900 mg, 98% yield).

LCMS: *m/z* (ESI): 509.14 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(2,6-difluoro-4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (29):

To a stirred solution of 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)propylmethanesulfonate (600 mg, 1.18 mmol, 1 eq.), 3-(fluoromethyl)azetidine hydrochloride (221 mg, 1.77 mmol, 1.5 eq.) in acetonitrile (12 mL) was added cesium carbonate (767 mg, 2.36 mmol, 2 eq.) and stirred at 90 °C for 16 h. The reaction mixture was allowed to cool to room temperature, filtered through celite and washed with 10% MeOH in DCM, dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was further purified by preparative HPLC (22 mL/min, KROMASIL-C18, 150-25mm), using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: (50-98%, for 14 mins). The pure fractions were lyophilized to afford (1*R*,3*R*)-1-(2,6-difluoro-4-(3-(3-(fluoromethyl)azetidine-1-yl)propyl)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (75 mg, 13% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 7.52-7.49 (m, 2H), 7.26-7.21 (m, 1H), 7.12-7.007 (m, 2H), 6.66 (d, *J* = 10.0 Hz, 2H), 5.24 (s, 1H), 4.73 (bs, 1H), 4.49 (dd, *J* = 6.0 Hz, 47.5 Hz, 1H), 4.43 (d, *J* = 5.6 Hz, 1H), 3.70-3.66 (m, 1H), 3.33-3.31 (m, 2H), 3.11-3.05 (m, 1H), 2.98-2.90 (t, *J* = 6.5 Hz, 2H), 2.87-2.71 (m, 2H), 2.63-2.55 (m, 3H), 2.43-2.38 (m, 2H), 1.62 (q, *J* = 7.6 Hz, 2H), 1.21 (d, *J* = 21.0 Hz, 3H), 1.17 (d, *J* = 21.5 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 163.3 (d, *J* = 9 Hz), 161.0 (d, *J* = 7 Hz), 145.1, 136.1, 132.1, 127.7, 121.3, 119.2, 118.1, 114.4, 111.6 (d, *J* = 18 Hz), 110.6, 108.5, 97.3 (d, *J* = 166 Hz), 84.3 (d, *J* = 165 Hz), 56.9 (d, *J* = 17 Hz), 51.2, 33.0, 30.8 (d, *J* = 16 Hz), 28.4, 27.0, 25.2 (d, *J* = 24 Hz), 24.5 (d, *J* = 24 Hz), 12.3.

¹⁹F NMR (470 MHz, CDCl₃): δ -111.52, -115.29, -136.60--136.65, -139.16--139.43.

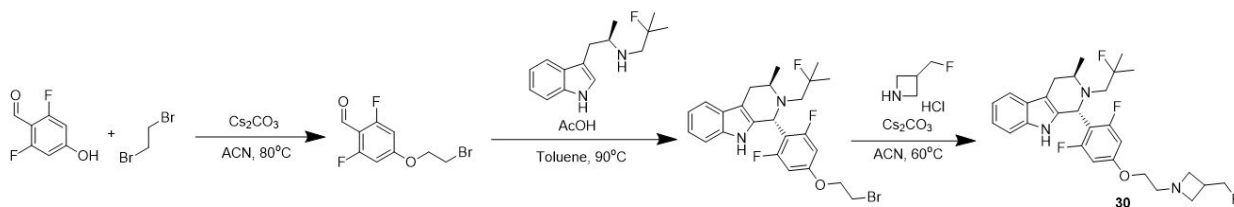
LCMS: *m/z*: 502.42 [M+H]⁺

HRMS (ESI): C₂₉H₃₆F₃N₄ [M+H]⁺ calc. 502.2840, found: 502.2837.

HPLC: 99.81%

[α]_D²⁰ -5 (c 0.1, acetonitrile).

Scheme S12. Preparation of 30



Synthesis of 4-(2-bromoethoxy)-2,6-difluorobenzaldehyde:

To a solution of 2,6-difluoro-4-hydroxybenzaldehyde (2 g, 12.65 mmol, 1.0 eq) in ACN (20 mL) was added Cs₂CO₃ (6.16 g, 18.98 mmol, 1.5 eq) followed by 1,2-dibromoethane (1.63 mL, 18.98 mmol, 1.5 eq). The reaction mixture was heated to 60 °C for 16 h, diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by combi-flash chromatography (using

100-200 silica gel and eluted with 30-100% in ethyl acetate and *n*-hexane) to afford 4-(2-bromoethoxy)-2,6-difluorobenzaldehyde (500 mg, 14% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 10.20 (s, 1H), 6.52 (dd, *J* = 5.00, 10.50 Hz, 2H), 4.34 (t, *J* = 6.00 Hz, 2H), 3.66 (t, *J* = 6.00 Hz, 2H).

LCMS: *m/z* (ESI): 264.83 [M+1]⁺, 266.83 [M+1]⁺.

Synthesis of (1*R*,3*R*)-1-(4-(2-bromoethoxy)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole:

To a stirred solution of 4-(2-bromoethoxy)-2,6-difluorobenzaldehyde (300 mg, 1.13 mmol, 0.8 eq) in anhydrous toluene (4 mL) was added (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (350 mg, 1.41 mmol, 1.0 eq), glacial acetic acid (0.150 mL, 3.52 mmol, 2.5 eq) and 4Å molecular sieves (300 mg). The resulting mixture was stirred at 90 °C for 16 h. The reaction was allowed to cool to room temperature and diluted in DCM (20 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic were dried over sodium sulphate. The solution was filtered and the filtrate was evaporated under reduced pressure to afford (1*R*,3*R*)-1-(4-(2-bromoethoxy)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (300 mg, 53% yield) as a semi solid.

LCMS: *m/z* (ESI): 495.84 [M+H]⁺, 497.84 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (30):

A solution of (1*R*,3*R*)-1-(4-(2-bromoethoxy)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (300 mg, 0.61 mmol, 1.0 eq), 3-(fluoromethyl)azetidine hydrochloride (152 mg, 1.21 mmol, 2 eq) and Cs₂CO₃ (434 mg, 1.34 mmol, 2.2 eq) in ACN (15 mL) was heated to 60 °C for 16 h. The reaction mixture was diluted with ethyl acetate and washed water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by Prep HPLC. (16 mL/min, 25 °C, YMC-ACTUS-TRIART C18 (150*20mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: 60-98% over 15 mins). The pure fractions were lyophilized to afford (1*R*,3*R*)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (25 mg, 0.050 mmol, 8.2% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.53-7.50 (m, 1H), 7.41 (s, 1H), 7.24-7.22 (m, 1H), 7.14-7.07 (m, 2H), 6.41-6.37 (m, 2H), 5.18 (s, 1H), 4.50 (dd, *J* = 5.20, 47.20 Hz, 2H), 3.92 (t, *J* = 5.60 Hz, 2H), 3.69-3.65 (m, 1H), 3.55 (t, *J* = 7.20 Hz, 2H), 3.20 (t, *J* = 7.20 Hz, 2H), 3.10 (d, *J* = 3.6, 15.2 Hz, 1H), 2.90-2.82 (m, 4H), 2.60 (dd, *J* = 2.4, 14.8 Hz, 1H), 2.43-2.32 (m, 1H), 1.23 (d, *J* = 21.60 Hz, 3H), 1.18 (d, *J* = 21.60 Hz, 3H), 1.10 (d, *J* = 6.40 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 162.7 (d, *J* = 259 Hz), 162.7 (d, *J* = 249 Hz), 159.6, 136.1, 132.3, 127.7, 121.2, 119.1, 118.1, 110.6, 109.5 (t, *J* = 15 Hz), 108.4, 98.5 (t, *J* = 27 Hz), 96.5, 83.7 (d, *J* = 167 Hz), 66.9, 57.1 (d, *J* = 12 Hz), 56.8, 56.4, 51.2, 50.4, 31.3 (d, *J* = 20 Hz), 27.1, 25.3 (d, *J* = 25 Hz), 24.5, 12.1.

¹⁹F NMR (376 MHz, CDCl₃): -109.23- -111.62 (m), -139.18- -139.41 (m), -222.63- -222.99 (m).

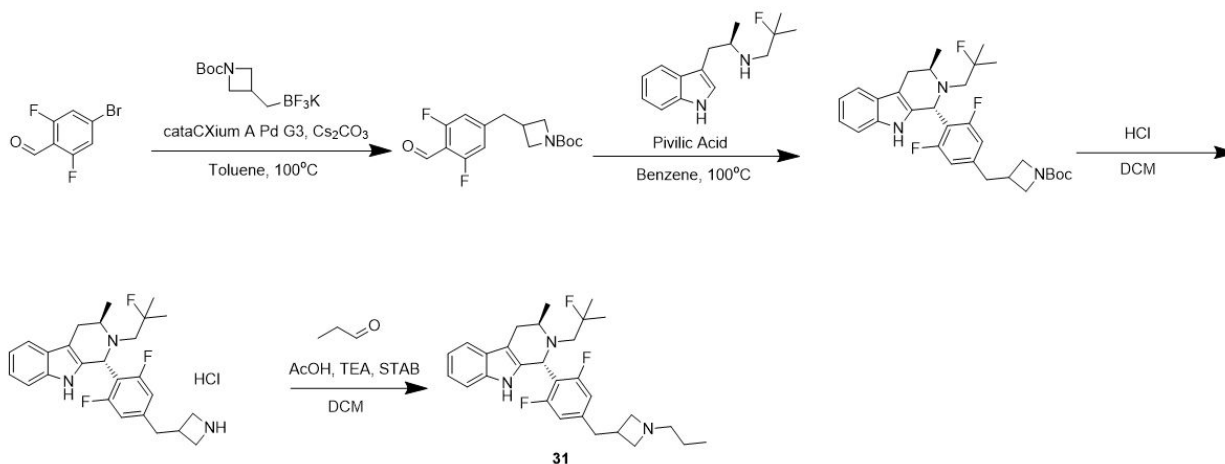
LCMS: *m/z* (ESI): 504.26 [M+H]⁺

HRMS: C₂₈H₃₄F₄N₃O [M+H]⁺ calc. 504.2632, found: 504.2617.

HPLC: 97.90%

[α]_D²⁰ -19 (c 0.1, acetonitrile)

Scheme S13. Preparation of 31



Synthesis of *tert*-butyl 3-(3,5-difluoro-4-formylbenzyl)azetidine-1-carboxylate:

To a stirred solution of 4-bromo-2,6-difluorobenzaldehyde (2 g, 9.05 mmol, 1 eq.) in toluene (16 mL) and water (4 mL) was added *tert*-butyl 3-(3,5-difluoro-4-formylbenzyl)azetidine-1-carboxylate (3.76 g, 13.67 mmol, 1.5 eq.), cesium carbonate (3.67 g, 22.62 mmol, 2.5 eq.) and the resulting mixture was degassed with argon for 3 min. CataCXium® A Pd G3 (1.7 g, 2.71 mmol, 0.3 eq.) was added and the mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature and filtered through celite and diluted with ethyl acetate (50 mL). The organic layer was washed with water (30 mL) and brine (10 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-40% ethyl acetate in *n*-hexane) to afford *tert*-butyl 3-(3,5-difluoro-4-formylbenzyl)azetidine-1-carboxylate (410 mg, 14% yield) as a yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.30 (s, 1H), 6.79 (d, *J* = 9.6 Hz, 2H), 4.04 (t, *J* = 8.4 Hz, 2H), 3.64-3.61 (m, 2H), 2.96 (d, *J* = 7.6 Hz, 2H), 2.85-2.78 (m, 1H), 1.44 (s, 9H).

LCMS: *m/z* (ESI): 256.02 [M+H-tBu]⁺.

Synthesis of *tert*-butyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate:

To a stirred solution of ((*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (306 mg, 1.12 mmol, 1.2 eq.) in toluene (3.5 mL) was added *tert*-butyl 3-(3,5-difluoro-4-formylbenzyl)azetidine-1-carboxylate (350 mg, 1.44 mmol, 1 eq.), acetic acid (0.32 mL, 5.62 mmol, 5 eq.) and molecular sieves (4Å, 300 mg). The mixture was stirred at 100 °C for 16 h, cooled to room temperature and was diluted with ethyl acetate (30 mL) and a saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-40 % ethyl acetate in *n*-hexane) to afford *tert*-butyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate (500 mg, 82% yield) as an off white solid.

¹H NMR (500 MHz, CDCl₃): δ 7.52 (d, *J* = 6.5 Hz, 1H), 7.43 (s, 1H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.13-7.08 (m, 2H), 6.64 (d, *J* = 10.0 Hz, 2H), 5.26 (s, 1H), 4.03-3.99 (m, 2H), 3.65-3.59 (m, 3H), 3.08-3.05 (m, 1H), 2.87-2.78 (m, 4H), 2.62 (dd, *J* = 3.5, 15.0 Hz, 1H), 2.42-2.35 (m, 1H), 1.44 (s, 9H), 1.22 (d, *J* = 21.5 Hz, 3H), 1.16 (d, *J* = 22.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

LCMS: *m/z* (ESI): 541.99 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride:

To a stirred solution of *tert*-butyl 3-(3,5-difluoro-4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)benzyl)azetidine-1-carboxylate (300 mg, 0.554 mmol, 1 eq.) in 1,4-dioxane (1 mL) was added conc. HCl (1 mL, 11.09 mmol, 20 eq.) at room temperature and stirred for 3 h. The solvent was evaporated under reduced pressure to afford (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (280 mg, 98% yield) as a white solid.

LCMS: *m/z* (ESI): 442.18 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(2,6-difluoro-4-((1-propylazetidin-3-yl)methyl)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (31):

To a stirred solution of (1*R*,3*R*)-1-(4-(azetidin-3-ylmethyl)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (280 mg, 0.71 mmol, 1.1 eq.) and TEA (195.13 mg, 0.27 mL, 1.93 mmol, 3 eq.) in DCM (10 mL) were sequentially added propionaldehyde (34 mg, 0.64 mmol, 1 eq.) and acetic acid (193 mg, 0.18 mL, 3.22

mmol, 5 eq.) and stirred at room temperature for 1 h. The resulting mixture was treated with STAB (345 mg, 1.64 mmol, 2.5 eq.) and stirred at room temperature for another 1 h. Then the reaction mixture was poured into a mixture of saturated sodium bicarbonate solution (10 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by preparative HPLC (16 mL/min, X-BRIDGE-OBDC18, 150-19 mm), using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (45-75%, for 12 mins). The pure fractions were lyophilised to afford (1*R*,3*R*)-1-(2,6-difluoro-4-((1-propylazetidin-3-yl)methyl)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (40 mg, 14% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): 7.73 (s, 1H), 7.53-7.51 (m, 1H), 7.23-7.21 (m, 1H), 7.12-7.07 (m, 2H), 6.61 (d, *J* = 10.00 Hz, 2H), 5.25 (s, 1H), 3.67-3.63 (m, 1H), 3.40 (q, *J* = 7.20 Hz, 2H), 3.07 (dd, *J* = 3.60 Hz, 15.00 Hz, 1H), 2.91-2.81 (m, 5H), 2.77-2.68 (m, 1H), 2.61 (dd, *J* = 3.60 Hz, 15.20 Hz, 1H), 2.43-2.34 (m, 3H), 1.38-1.31 (m, 2H), 1.27-1.18 (m, 6H), 1.18-1.09 (m, 3H), 0.87 (t, *J* = 7.60 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 163.3 (d, *J* = 8 Hz), 160.8 (d, *J* = 8 Hz), 143.1, 136.2, 132.0, 127.6, 121.3, 119.1, 118.1, 114.9 (t, *J* = 15 Hz), 111.6 (d, *J* = 23 Hz), 110.7, 108.6, 97.2 (d, *J* = 166 Hz), 61.6, 59.80, 59.76, 56.8 (d, *J* = 22 Hz), 50.8, 39.5, 31.3, 27.0, 25.2 (d, *J* = 25 Hz), 24.5 (d, *J* = 25 Hz), 20.6, 12.6, 11.7.

¹⁹F NMR (470 MHz, CDCl₃): δ -111.09--112.35, -139.02--139.53.

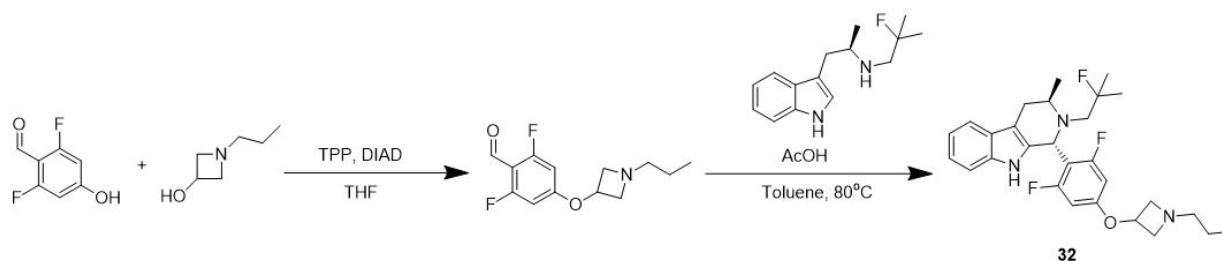
LCMS: *m/z*: 484.17 [M+H]⁺

HRMS (ESI): C₂₉H₃₇F₃N₃ [M+H]⁺ calc.484.2934, found: 484.2931.

HPLC: 99.58%

[α]_D²⁰ -15 (c 0.1, acetonitrile).

Scheme S14. Preparation of 32



Synthesis of 2,6-difluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde:

To a solution of 1-propylazetidin-3-ol (700 mg, 6.08 mmol, 1 eq), 2,6-difluoro-4-hydroxybenzaldehyde (1.05 g, 6.69 mmol, 1.1 eq) in THF (7 mL) was added triphenylphosphine (1.75 g, 6.69 mmol, 1.1 eq) and DIAD (1.32 mL, 6.69 mmol, 1.1 eq) sequentially at 0 °C. The resulting reaction mixture was stirred at room temperature for 3.5 h. The reaction was concentrated and purified via flash chromatography in 20-100% ethyl acetate in n-hexanes to afford 2,6-difluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde (160 mg, 14% yield) as a semi solid.

¹H NMR (400 MHz, CDCl₃): δ 10.20 (s, 1H), 6.41 (dd, *J* = 5.20, 15.20 Hz, 2H), 5.08 (q, *J* = 6.00 Hz, 1H), 4.40-4.36 (m, 2H), 3.54-3.49 (m, 2H), 2.85 (t, *J* = 8.00 Hz, 2H), 1.60-1.52 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H).

LCMS: *m/z* (ESI): 256.02 [M+H]⁺

Synthesis of (1*R*,3*R*)-1-(2,6-difluoro-4-((1-propylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (32):

2,6-Difluoro-4-((1-propylazetidin-3-yl)oxy)benzaldehyde (160 mg, 0.63 mmol, 1 eq) was added to a solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (171 mg, 0.69 mmol, 1.1 eq) in anhydrous toluene (2.0 mL), glacial acetic acid (0.150 mL, 3.15 mmol, 5 eq) and molecular sieves (4Å, 200 mg). The solution was stirred under argon in the dark at 80 °C for 16 h. The reaction was allowed to cool to room temperature and was diluted with DCM (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic layers were dried over sodium sulphate. The solution was filtered, the filtrate was evaporated under reduced pressure. The crude was purified by prep HPLC (15 mL/min, 25 °C, X-BRIDGE-OBDC18 (150*19mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: 60-98% over 16 mins). The pure fraction was lyophilised to afford (1*R*,3*R*)-1-(2,6-difluoro-4-((1-propylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (33 mg, 0.068 mmol, 10% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.52-7.50 (m, 1H), 7.40 (bs, 1H), 7.24-7.21 (m, 1H), 7.13-7.06 (m, 2H), 6.26 (d, *J* = 8.80 Hz, 2H), 5.18 (s, 1H), 4.76-4.71 (m, 1H), 3.83-3.79 (m, 2H), 3.68-3.64 (m, 1H), 3.11-3.05 (m, 3H), 2.89-2.80 (m, 1H), 2.60 (dd, *J* = 2.80, 14.80 Hz, 1H), 2.48 (t, *J* = 7.60 Hz, 2H), 2.42-2.32 (m, 1H), 1.45-1.35 (m, 2H), 1.23 (d, *J* = 21.60 Hz, 3H), 1.13 (d, *J* = 20.00 Hz, 3H), 1.09 (d, *J* = 6.40 Hz, 3H), 0.91 (t, *J* = 7.60 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 162.8 (d, *J* = 250 Hz), 162.7 (d, *J* = 249 Hz), 158.1, 136.1, 132.1, 127.7, 121.3, 119.2, 118.1, 110.6, 109.9 (t, *J* = 15 Hz), 108.6, 98.9 (d, *J* = 27 Hz), 97.2 (d, *J* = 165 Hz), 67.5, 61.6, 61.01, 60.99 56.8 (d, *J* = 21 Hz), 51.14, 51.11, 50.6, 27.0, 25.2 (d, *J* = 24 Hz), 24.5 (d, *J* = 25 Hz), 20.8, 12.3, 11.7.

¹⁹F NMR (376 MHz, CDCl₃): -109.06- -110.65 (m), -139.26- -139.49 (m).

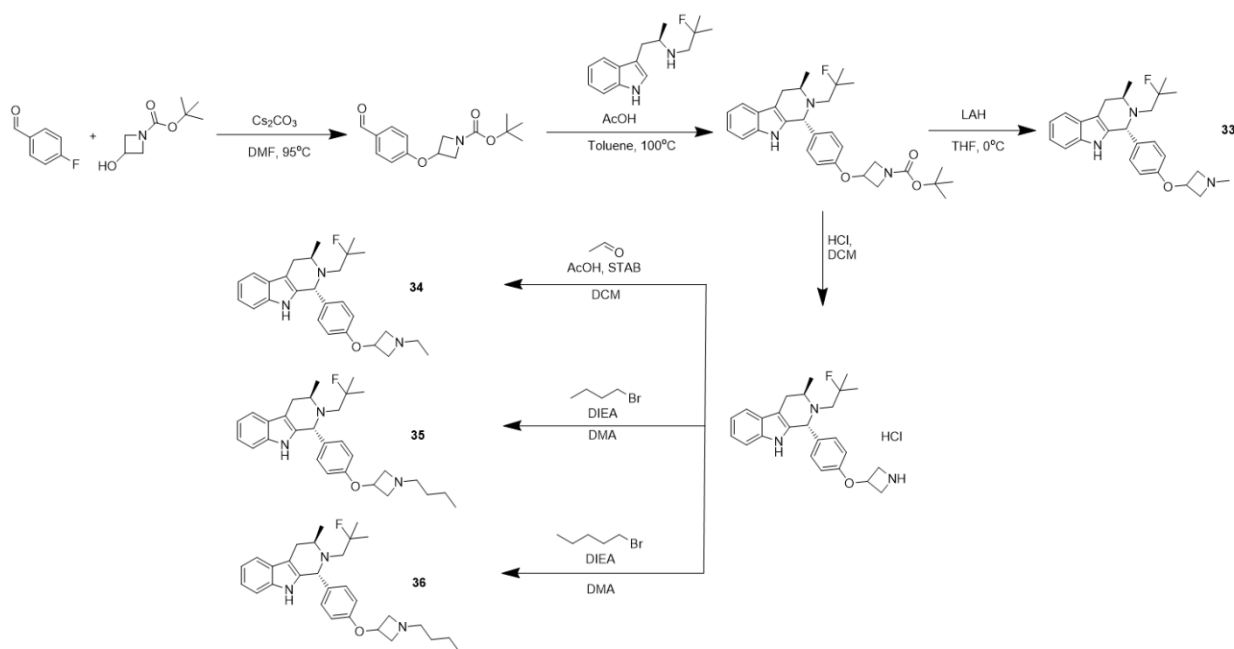
LCMS: *m/z* (ESI): 486.44 [M+H]⁺

HRMS (ESI): C₂₈H₃₅F₃N₃O[M+H]⁺ calc. 486.2726, found: 486.2705.

HPLC: 97.23%

[α]_D²⁰ -20 (c 0.1, acetonitrile).

Scheme S15. Preparation of 33, 34, 35, 36



Synthesis of *tert*-butyl 3-(4-formylphenoxy)azetidine-1-carboxylate:

To a stirred solution of cesium carbonate (20.48 g, 62.85 mmol, 2.6 eq.) and 4-fluorobenzaldehyde (3 g, 24.17 mmol, 1 eq.) were sequentially added to a solution of compound *tert*-butyl 3-hydroxyazetidine-1-carboxylate (5.44 g, 31.42 mmol, 1.30 eq.) in anhydrous DMF (30 mL) at room temperature. The yellowish suspension was stirred at 95 °C for 16 h and cooled to room temperature. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (2 x 100 mL) and brine (50 mL), dried over sodium sulphate, filtered, and dried in vacuo. The crude was purified by silica-gel flash chromatography using 0-10% ethyl acetate in *n*-hexanes to afford *tert*-butyl 3-(4-formylphenoxy)azetidine-1-carboxylate (5.5 g, 97% yield) as a pale yellow solid.

¹H-NMR (500 MHz, CDCl₃): δ 9.90 (s, 1H), 7.85 (td, *J* = 2.5, 9.0 Hz, 2H), 6.85 (td, *J* = 2.5, 9.0 Hz, 2H), 4.98-4.94 (m, 1H), 4.36-4.33 (m, 2H), 4.05-4.02 (m, 2H), 1.45 (s, 9H).

LCMS: *m/z* (ESI): 178.04 [M+H-Boc]⁺.

Synthesis of *tert*-butyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenoxy)azetidine-1-carboxylate:

A mixture of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (500 mg, 2.01 mmol, 1 eq.), *tert*-butyl 3-(4-formylphenoxy)azetidine-1-carboxylate (670 mg, 2.42 mmol, 1.20 eq) and acetic acid (242 mg, 4.03 mmol, 2 eq) in toluene (50 mL) was heated at 100 °C in a sealed bottle protected from light for 48 h. After cooling to room temperature, the mixture was

diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate solution (80 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulphate, filtered, and dried in vacuo. Collected organic layers, concentrated under reduced pressure to obtain crude. The crude was purified by flash chromatography in 0-25% ethyl acetate in *n*-hexanes to afford *tert*-butyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenoxy)azetidine-1-carboxylate (220 mg, 21% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.59-7.20 (bs, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18-7.09 (m, 2H), 6.64 (td, *J* = 2.8, 8.8 Hz, 2H), 5.00 (bs, 1H), 4.86-4.83 (m, 1H), 4.28-4.24 (m, 2H), 3.98 (dd, *J* = 4.0 Hz, 9.6 Hz, 2H), 3.33 (bs, 1H), 2.77-2.51 (m, 4H), 1.44 (s, 9H), 1.43 (d, *J* = 22.0 Hz, 3H), 1.28 (d, *J* = 21.6 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H).

LCMS: *m/z* (ESI): 508.51 [M+H]⁺.

Synthesis of (1*R*,3*R*)-1-(4-(azetidin-3-yloxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride:

Hydrogen chloride in 1,4-dioxane (4.0 M, 3.50 mL) was added to a solution of *tert*-butyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenoxy)azetidine-1-carboxylate (350 mg, 0.69 mmol, 1 eq.) in DCM (170 mL) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was evaporated under reduced pressure to afford (1*R*,3*R*)-1-(4-(azetidin-3-yloxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (270 mg, 96% yield) as a light brown solid.

¹H-NMR (500 MHz, CDCl₃): δ 7.62 (bs, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.31-7.26 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.18-7.09 (m, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 5.00-4.93 (m, 2H), 3.91-3.87 (m, 2H), 3.80-3.76 (m, 2H), 3.33 (bs, 1H), 2.78-2.50 (m, 4H), 1.45 (d, *J* = 21.6 Hz, 3H), 1.29 (d, *J* = 21.6 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H).

LCMS: *m/z* (ESI): 408.23 [M+H-HCl]⁺

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-methylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (33):

Lithium aluminium hydride (1M solution in THF, 2.95 mL, 2.95 mmol, 15 eq) was added to a solution of *tert*-butyl 3-(4-((1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenoxy)azetidine-1-carboxylate (100 mg, 0.20 mmol, 1 eq.) in tetrahydrofuran (dry, 1 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 4 h. The reaction was quenched with water (10 mL) and filtered through a pad of celite (10 g). The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by preparative HPLC (16 mL/min, 25 °C, X-BRIDGE-OBDC18 (150*19mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: 50-80% over 12 mins) to afford (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-methylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4.4 mg, 5.3% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.81 (s, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.05-7.02 (m, 1H), 6.98-6.94 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 1H), 4.71-4.65 (m, 1H), 3.72-3.69 (m, 2H), 3.10 (bs, 1H), 2.91-2.89 (t, *J* = 1.60 Hz, 2H), 2.78-2.72 (m, 1H), 2.60-2.53 (m, 2H), 2.49-2.43 (m, 1H), 2.26 (s, 3H), 1.45 (d, *J* = 21.6 Hz, 3H), 1.29 (d, *J* = 21.6 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ: 166.96 (formic acid), 154.8, 136.5, 136.3, 133.0, 130.6, 128.4, 128.2, 127.2, 121.6, 119.2, 118.1, 114.8, 114.1, 110.8, 110.2, 97.8 (d, *J* = 165 Hz), 64.4, 61.8, 54.3, 47.7, 42.9, 25.6 (d, *J* = 23 Hz), 25.0 (d, *J* = 25 Hz), 16.9.

LCMS: *m/z* (ESI): 420.34 [M-H]⁻

HRMS (ESI): C₂₆H₃₃FN₃O [M+H]⁺ calc. 422.2563, found: 422.2553.

¹⁹F NMR (376 MHz, CDCl₃): δ -138.63 (s, 1F).

HPLC: 99.08%

[α]_D²⁰ +2 (c 0.1, acetonitrile).

Synthesis of (1*R*,3*R*)-1-(4-((1-ethylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (34):

Acetaldehyde (113.5 mg, 2.58 mmol, 3 eq.) and acetic acid (361 mg, 6.01 mmol, 7 eq) were sequentially added to a solution of (1*R*,3*R*)-1-(4-(azetidin-3-yloxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (350 mg, 0.86 mmol, 1 eq.) as solution of DCM (5 mL). The resulting mixture was stirred at room temperature for 1 h. STAB (361 mg, 6.01 mmol, 7 eq.) was added and the reaction was stirred at room temperature for 30 min. The reaction mixture was poured into a mixture of saturated aqueous sodium bicarbonate solution (10 mL) and DCM (10 mL).

The layers were separated, and the aqueous layer was extracted with DCM (2 X 10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulphate, filtered, and dried in-vacuo. The crude was purified by Prep HPLC (16 mL/min, 25 °C, X-BRIDGE-OBDC18 (150*19mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient: (50-80% over 12 mins). Pure fractions were lyophilised to afford (1*R*,3*R*)-1-(4-((1-ethylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (23 mg, 6.1% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.62 (bs, 1H), 7.53 (d, *J* = 7.60 Hz, 1H), 7.28-7.26 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.18-7.09 (m, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.99 (s, 1H), 4.77-4.71 (m, 1H), 3.81-3.78 (m, 2H), 3.36 (s, 1H), 3.05-3.01 (m, 2H), 2.77-2.50 (m, 6H), 1.43 (d, *J* = 21.60 Hz, 3H), 1.28 (d, *J* = 21.20 Hz, 3H), 1.08 (d, *J* = 6.80 Hz, 3H), 0.99 (t, *J* = 7.20 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 156.4, 136.3, 135.0, 133.4, 130.3, 127.3, 121.5, 119.2, 118.9, 114.1, 110.7, 97.9 (d, *J* = 132 Hz), 66.5, 61.9 (d, *J* = 7 Hz), 61.1, 54.5, 53.8, 47.7, 25.7, 25.0 (d, *J* = 20 Hz), 12.5.

¹⁹F NMR (376 MHz, CDCl₃): δ -140.09 -140.86 (m).

LCMS: *m/z* (ESI): 436.51 [M+H]⁺,

HRMS (ESI): C₂₇H₃₅FN₃O, [M+H]⁺ calc. 436.2719, found: 436.2710.

HPLC: 99.15%

[α]_D²⁰ -3, (c 0.1, acetonitrile).

Synthesis of (1*R*,3*R*)-1-(4-((1-butylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (35):

A solution of 1-bromobutane (67 mg, 0.49 mmol) in DMA (1.5 mL) was added to a solution of (1*R*,3*R*)-1-(4-(azetidin-3-yloxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (400 mg, 0.98 mmol) and DIEA (0.84 mL, 4.9 mmol) in DMA (1.5 mL) at room temperature. The mixture was stirred for 24 hours at the same temperature. The reaction mixture was purified by prep-HPLC (T3 Atlantis waters column) in 70 to 100% acetonitrile in water to give (1*R*,3*R*)-1-(4-((1-butylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (40 mg, 18% yield).

LCMS: *m/z* (ESI): = 464.30 [M+H]⁺

¹H NMR (400 MHz, CDCl₃): δ = 7.88 (br s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.20 – 7.09 (m, 4H), 6.68 – 6.64 (m, 2H), 5.01 (br, s, 1H), 4.67 (quin, *J* = 5.8 Hz, 1H), 3.78 (q, *J* = 7.5 Hz, 2H), 3.35 (br s, 1H), 3.07 – 2.99 (m, 2H), 2.79 – 2.70 (m, 1H), 2.68 – 2.46 (m, 5H) 1.49 – 1.39 (m, 3H), 1.37 – 1.26 (m, 7H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.88 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): 156.4, 136.3, 135.0, 133.4, 130.3, 127.4, 121.5, 119.2, 118.1, 114.1, 110.8, 110.1, 98.7, 97.0, 66.6, 61.9, 61.6, 61.5, 59.8, 54.5, 54.3, 47.7, 29.9, 25.3 (br dd, *J* = 24 Hz, 62 Hz), 20.5, 14.0.

¹⁹F NMR (376 MHz, CDCl₃): -140.099 - -140.561 (m)

HRMS (ESI): C₂₉H₃₈FN₃O, [M+H]⁺ calc. 464.3034, found: 464.3031

Synthesis of (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-pentylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (36):

A solution of 1-bromopentane (91 mg, 0.6 mmol) in DMA (1.5 mL) was added to a solution of (1*R*,3*R*)-1-(4-(azetidin-3-yloxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole hydrochloride (203 mg, 0.5 mmol) and DIEA (0.43 mL, 2.5 mmol) in DMA (1.5 mL) at room temperature and the mixture was stirred for 18 hours. The reaction was diluted with water (10 mL) and EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with water (15 mL) and brine (15 mL), dried over sodium sulfate, filtered, and dried in vacuo. The crude was purified by flash chromatography on an Interchim MPLC (Biotage® Sfär KP-Amino D column, 28 g) in 0-100% DCM in heptanes to give (1*R*,3*R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-pentylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (95 mg, 40% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (brs, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.17-7.09 (m, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.00 (brs, 1H), 4.73-4.69 (m, 1H), 3.82-3.78 (m, 2H), 3.35 (brs, 1H), 3.04-3.00 (m, 2H), 2.60-2.55 (m, 4H), 2.48 (t, *J* = 7.25 Hz, 2H), 1.43 (d, *J* = 21.5 Hz, 3H), 1.42-1.27 (m, 6H), 1.28 (d, *J* = 21.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 5.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 156.4, 136.2, 134.9, 133.4, 130.3, 127.3, 121.5, 119.3, 118.1, 114.1, 110.8, 97.9 (d, *J* = 165.0 Hz), 66.6, 61.6, 60.1, 29.5, 27.5, 25.6 (d, *J* = 24.0 Hz), 25.0 (d, *J* = 25.2 Hz), 22.6, 14.0.

¹⁹F NMR (376 MHz, CDCl₃): -139.507 - -141.052 (m)

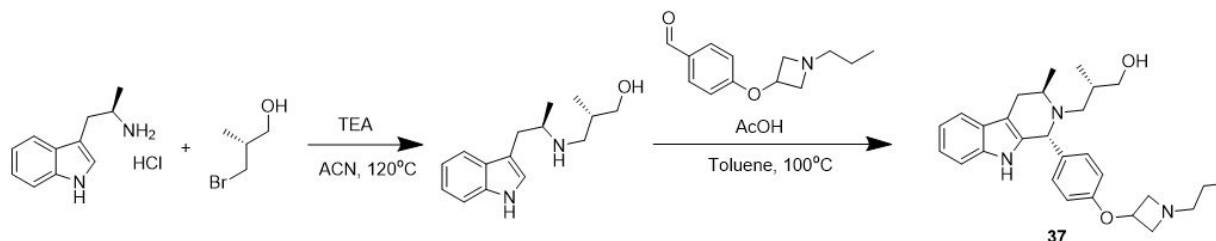
LCMS: m/z (ESI): 478.48 [M+H]⁺.

HRMS (ESI): C₃₀H₄₁ON₃F [M+H]⁺ calc. 478.3228, found: 478.3228.

HPLC: 97.31%

[α]_D²⁰ -4 (c 0.1, acetonitrile).

Scheme S16. Preparation of 37



Synthesis of (S)-3-(((R)-1-(1H-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol:

(2R)-1-(1H-Indol-3-yl)propan-2-amine hydrochloride (300 mg, 1.43 mmol, 1 eq.) and (R)-3-bromo-2-methylpropan-1-ol (876 mg, 5.71 mmol, 4 eq.) were dissolved in ACN (5 mL) and treated with TEA (0.827 mL, 5.72 mmol, 4 eq.). The resulting reaction mixture was heated at 120 °C under microwave irradiation for 3 h. The solvent was removed under reduced pressure and the residue was treated with water (20 mL) and DCM (30 mL). The organic layers were washed with brine (20 mL), dried over sodium sulphate, filtered, and dried in-vacuo. The crude material was purified by preparative HPLC (X-SELECT-CSH-C18 150-30, 10 mM ammonium bicarbonate). The pure fractions were lyophilised to afford (S)-3-(((R)-1-(1H-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol (150 mg, 42% yield) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.79 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.18-7.13 (m, 1H), 7.04 (t, *J* = 8.00 Hz, 1H), 6.96 (t, *J* = 7.00 Hz, 1H), 4.70 (brs, 1H), 3.32-3.24 (m, 2H), 2.83-2.81 (m, 2H), 2.59-2.56 (m, 4H), 1.65-1.61 (m, 1H), 0.95 (d, *J* = 4.80 Hz, 3H), 0.77 (d, *J* = 5.20 Hz, 3H).

LCMS: m/z (ESI): 247.40 [M+H]⁺

Synthesis of (S)-2-methyl-3-(((1R,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propan-1-ol (37):

A solution of (S)-3-(((R)-1-(1H-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol (130 mg, 0.53 mmol, 1 eq.), 4-(1-propylazetidin-3-yl)oxybenzaldehyde (208 mg, 0.95 mmol, 1.8 eq.) in toluene (1.5 mL) was treated with molecular sieves (4Å, 200 mg) and acetic acid (0.15 mL, 2.65 mmol, 5 eq.). The mixture was heated for 16 h at 100 °C in a sealed tube. The solution was allowed to cool to room temperature and diluted with ethyl acetate (30 mL) and a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried over sodium sulphate, filtered, and dried in-vacuo. The crude material was purified by preparative HPLC (22 mL/min, 25 °C, X-SELECT-CSH-C18,150-30), using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (10-50%, over 12 mins). The pure fractions were lyophilized to afford (S)-2-methyl-3-(((1R,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propan-1-ol (15.2 mg, 41% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 10.60 (s, 1H), 7.41 (d, *J* = 7.60 Hz, 1H), 7.24 (d, *J* = 7.60 Hz, 1H), 7.09 (d, *J* = 8.40 Hz, 2H), 7.02 (t, *J* = 7.20 Hz, 1H), 6.95 (t, *J* = 6.80 Hz, 1H), 6.76 (d, *J* = 8.40 Hz, 2H), 4.82 (s, 1H), 4.79-4.69 (m, 2H), 3.70 (t, *J* = 1.60 Hz, 2H), 3.68-3.53 (m, 1H), 3.30-3.17 (m, 1H), 2.90-2.82 (m, 2H), 2.67-2.60 (m, 3H), 2.36 (t, *J* = 7.20 Hz, 2H), 2.16-2.12 (m, 1H), 1.97-1.82 (m, 1H), 1.31-1.28 (m, 3H), 1.04 (d, *J* = 6.80 Hz, 3H), 0.83 (t, *J* = 7.60 Hz, 3H), 0.76 (d, *J* = 6.80 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 156.7, 136.4, 133.0, 131.4, 130.7, 126.9, 121.9, 119.5, 118.2, 114.5, 110.9, 110.3, 71.5, 66.6, 61.9, 61.5, 60.5, 32.1, 24.7, 20.9, 15.0, 11.8.

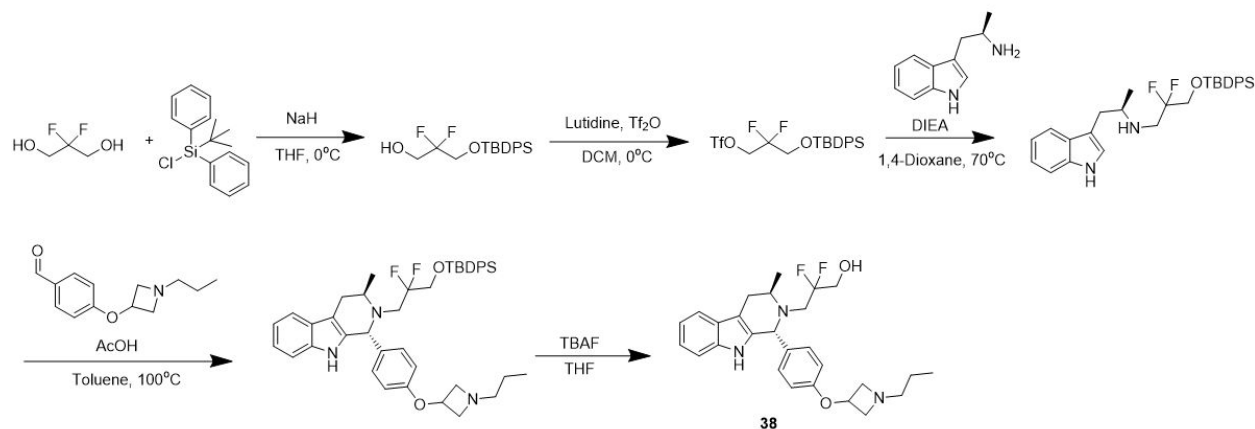
LCMS: m/z (ESI): 448.52 [M+H]⁺

HRMS (ESI): C₂₈H₃₈N₃O₂ [M+H]⁺ calc. 448.2958, found: 448.2944.

HPLC: 95.01%

[α]_D²⁰ -10 (c 0.1, acetonitrile).

Scheme S17. Preparation of 38



Synthesis of 3-((*tert*-Butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-ol:

A 60% dispersion of sodium hydride (3.6 g, 89.2 mmol) in mineral oil was added in portions over 30 minutes at 0 °C to a solution of 2,2-difluoropropane-1,3-diol (10.0 g, 89.2 mmol) in THF (430 mL) under nitrogen. After stirring for 30 min, *tert*-butyl(chloro)diphenylsilane (23.1 g, 89.2 mmol, 1.0) was added dropwise over 30 min. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and water (300 mL) was added while being stirred. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (400 mL), dried over sodium sulfate, filtered, and dried in vacuo. The crude was purified via flash chromatography in 0-20% EtOAc in hexanes to give 3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-ol (26.4 g, 84% yield).

LCMS: m/z (ESI) = 351.24 [M+H]⁺

Synthesis of 3-((*tert*-Butyldiphenylsilyl)oxy)-2,2-difluoropropyl trifluoromethanesulfonate:

Trifluoromethanesulfonic anhydride (10.5 mL, 62.2 mmol) was added at 0 °C to a solution of 3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-ol (10.9 g, 31.1 mmol) and 2,6-lutidine (10.9 mL, 93.3 mmol) in DCM (220 mL) under nitrogen. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was washed with 1 M HCl (2 x 150 mL), saturated sodium bicarbonate (150 mL) and brine (150 mL). The organic layer was dried over sodium sulfate, filtered, and dried in vacuo. The crude was purified via flash chromatography in 0-10% EtOAc in hexanes to give 3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl trifluoromethanesulfonate (11.1 g, 84% yield).

LCMS: m/z (ESI) = 483.1 [M+H]⁺

¹H NMR (400 MHz, CDCl₃): δ = 7.64 (d, J = 7.2 Hz, 4H), 7.52 - 7.33 (m, 6H), 4.74 (t, J = 11.4 Hz, 2H), 3.88 (t, J = 11.8 Hz, 2H), 1.11 - 1.01 (m, 9H).

Synthesis of (*R*)-*N*-(1-(1*H*-Indol-3-yl)propan-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-amine:

DIEA (3.5 mL, 20.3 mmol) was added to a mixture of (*R*)-1-(1*H*-indol-3-yl)propan-2-amine (2.44 g, 14.0 mmol) and 3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl trifluoromethanesulfonate (6.75 g, 14.0 mmol) in 1,4-dioxane (27 mL) and was stirred at 85 °C for 16 h. The reaction was cooled to room temperature and diluted with water (30 mL) and MTBE (30 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 x 30 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over magnesium sulfate, filtered, and dried in vacuo. The crude was purified via flash chromatography in 0-50% EtOAc (1% TEA) in heptanes to give (*R*)-*N*-(1-(1*H*-Indol-3-yl)propan-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-amine (3.9 g, 55% yield).

LCMS: m/z (ESI) = 507.3 [M+H]⁺

Synthesis of *tert*-butyl-[2,2-difluoro-3-[(1*R*,3*R*)-3-methyl-1-[4-(1-propylazetidin-3-yl)oxyphenyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-2-yl]propoxy]-diphenyl-silane:

4-(1-Propylazetidin-3-yl)oxybenzaldehyde (36 mg, 0.164 mmol) and (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropan-1-amine (96 mg, 0.184 mmol) were dissolved in dry toluene (0.5 mL) and acetic acid (46 μ L, 0.804 mmol) was added. The solution was heated at 100 °C for 4 h and allowed to cool to room temperature. The solution was diluted with EtOAc and neutralized with sodium bicarbonate solution. The organic layers were separated and washed with brine once. They were then dried over sodium sulfate, filtered, and dried in vacuo. The crude was purified with

flash chromatography in 0-20% EtOAc (2% TEA) in hexanes to give *tert*-butyl-[2,2-difluoro-3-[(1*R*,3*R*)-3-methyl-1-[4-(1-propylazetidin-3-yl)oxyphenyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-2-yl]propoxy]-diphenyl-silane (52.2 mg, 40% yield).

LCMS: m/z (ESI) = 709.0 1H [M+H]⁺

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.63 (s, 1H), 7.64 – 7.57 (m, 4H), 7.48 – 7.33 (m, 8H), 7.25 (d, J = 7.8 Hz, 1H), 7.06 – 6.92 (m, 4H), 6.63 (d, J = 8.3 Hz, 2H), 4.95 (s, 1H), 4.08 – 3.95 (m, 2H), 3.91 – 3.72 (m, 3H), 3.12 (s, 3H), 2.72 (d, J = 13.3 Hz, 3H), 1.33 (q, J = 7.5 Hz, 2H), 1.22 – 1.17 (m, 3H), 1.05 (dd, J = 6.4, 2.4 Hz, 3H), 1.01 (d, J = 1.8 Hz, 9H), 0.88 – 0.84 (m, 3H).

Synthesis of 2,2-difluoro-3-[(1*R*,3*R*)-3-methyl-1-[4-(1-propylazetidin-3-yl)oxyphenyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-2-yl]propan-1-ol (38):

Tert-butyl-[2,2-difluoro-3-[(1*R*,3*R*)-3-methyl-1-[4-(1-propylazetidin-3-yl)oxyphenyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-2-yl]propoxy]-diphenyl-silane (52.2 mg, 0.074 mmol) was dissolved in dry THF (1 mL) and TBAF (0.058 mL, 1M in THF) was added at room temperature. The reaction mixture was for 1 h at the same temperature. The solution was diluted with EtOAc, washed with a sodium bicarbonate solution, brine, dried over sodium sulfate, filtered, and dried in vacuo. The crude was purified by HPLC on a Kintetex 5 μ m C18 100Å column (size: 100 x 30.0 mm; gradient: 5-35% 0.1% formic acid in ACN in 0.1% formic acid in water) then lyophilized to give 2,2-difluoro-3-[(1*R*,3*R*)-3-methyl-1-[4-(1-propylazetidin-3-yl)oxyphenyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-2-yl]propan-1-ol as a white solid (formate salt) (8.4 mg, 24% yield).

¹H NMR (500 MHz, CDCl₃): δ 8.46 (s, 1H), 8.18 (brs, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.26-7.25 (m, 1H), 7.18-7.09 (m, 4H), 6.65 (d, J = 8.8 Hz, 2H), 5.01 (s, 1H), 4.81-4.78 (m, 1H), 4.17-4.11 (m, 2H), 3.87-3.79 (m, 2H), 3.40-3.12 (m, 4H), 2.95-2.80 (m, 2H), 2.72-2.68 (m, 2H), 2.58 (dd, J = 8.8 Hz, 16.0 Hz, 1H), 1.52-1.46 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 168.2 (formic acid), 156.1, 136.5, 133.7, 131.4, 130.8, 126.9, 121.9, 121.3 (t, J = 242 Hz), 119.4, 118.2, 114.6, 110.9, 109.6, 65.5 64.3 (t, J = 30.7 Hz), 61.8, 60.44, 60.41, 59.9, 50.1 (t, J = 28.8 Hz), 48.1, 25.4, 19.4, 11.3.

¹⁹F NMR (376 MHz, CDCl₃): -106.531- -108.681 (m)

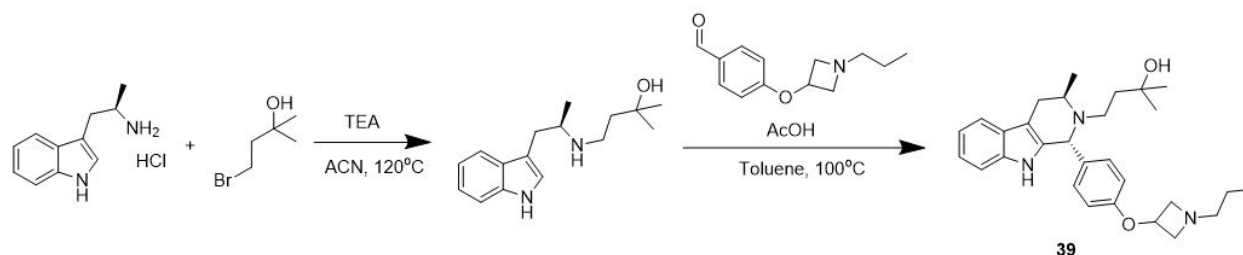
LCMS: m/z (ESI): 470.38 [M+H]⁺

HRMS (ESI): C₂₇H₃₄O₂N₃F₂ [M+H]⁺ calc. 470.2612, found: 470.2570.

HPLC: 96.04%

[α]_D²⁰ -5 (c 0.1, acetonitrile).

Scheme S18. Preparation of 39



Synthesis of ((*R*)-4-((1-(1*H*-indol-3-yl)propan-2-yl)amino))-2-methylbutan-2-ol:

To a stirred solution of (2*R*)-1-(1*H*-Indol-3-yl)propan-2-amine hydrochloride (300 mg, 1.42 mmol, 1 eq.) in acetonitrile (3 mL) was added 4-bromo-2-methylbutan-2-ol (190 mg, 1.14 mmol, 0.8 eq.) and TEA (0.39 mL, 2.85 mmol, 2 eq.). The reaction mixture was stirred at 120 °C under microwave irradiation for 3 h. The solvent was removed under reduced pressure, water (20 mL) was added, and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield the crude material, which was purified by silica-gel flash column chromatography (0-10% methanol in dichloromethane) to afford (*R*)-4-((1-(1*H*-indol-3-yl)propan-2-yl)amino)-2-methylbutan-2-ol (350 mg, 94% yield) as an off white solid.

LCMS: m/z (ESI): 261.47 [M+H]⁺

Synthesis of 2-methyl-4-((1*R*,3*R*)-3-methyl-1-[4-((1-propylazetidin-3-yl)oxy)phenyl]-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)butan-2-ol (39):

To a stirred solution of (*R*)-4-((1-(1*H*-indol-3-yl)propan-2-yl)amino)-2-methylbutan-2-ol (340 mg, 1.31 mmol, 1 eq.), 4-(1-propylazetidin-3-yl)oxybenzaldehyde (314 mg, 1.436 mmol, 1.1 eq.) in toluene (3.4 mL) was added acetic acid (0.37 mL, 6.53 mmol, 5 eq.) and molecular sieves (4Å, 200 mg). The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was

allowed to cool to room temperature and was diluted with ethyl acetate (30 mL) and a saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by preparative HPLC (14 mL/min, X-SELECT-CSH-Phenyl hexyl, 250-19, 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient, 30-65%, over 12 mins.). The pure fractions were lyophilised to afford 2-methyl-4-((1*R*,3*R*)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)butan-2-ol (46 mg, 7.6% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.54 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.03-7.01 (m, 1H), 7.00-6.95 (m, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.81 (s, 1H), 4.73-4.70 (m, 2H), 3.71-3.67 (m, 2H), 3.33-3.24 (m, 1H), 2.89-2.85 (m, 2H), 2.78-2.71 (m, 1H), 2.70-2.69 (m, 1H), 2.68-2.67 (m, 1H), 2.50-2.35 (m, 3H), 1.65-1.63 (m, 2H), 1.31-1.26 (m, 2H), 1.08-1.01 (m, 9H), 0.83 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.3 (formic acid), 155.8, 136.4, 134.7, 133.3, 130.0, 126.6, 120.5, 118.2, 117.6, 113.9, 110.9, 107.3, 69.0, 66.2, 61.1, 60.8, 59.2, 47.1, 41.8, 41.2, 29.8, 29.4, 25.5, 20.5, 16.2, 11.7.

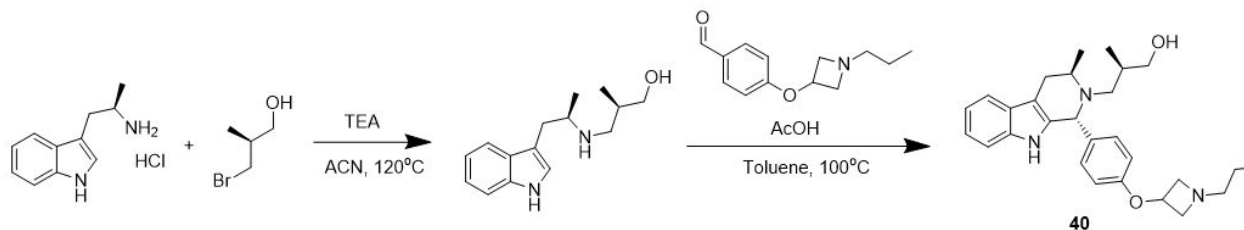
LCMS: *m/z*: 462.47 [M+H]⁺

HRMS(ESI): C₂₉H₄₀N₃O₂, [M+H]⁺calc. 462.3115, found: 462.3111.

HPLC: 97.76%

[α]_D²⁰ -29 (c 0.1, acetonitrile).

Scheme S19. Preparation of 40



Synthesis of (R)-3-(((R)-1-(1H-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol:

To a stirred solution of (2*R*)-1-(1*H*-Indol-3-yl)propan-2-amine hydrochloride (300 mg, 1.43 mmol, 1 eq.) and (S)-3-bromo-2-methylpropan-1-ol (240 mg, 1.57 mmol, 1.1 eq.) in acetonitrile (3 mL) was added triethylamine (1.39 mL, 10.01 mmol, 7 eq.) and the reaction mixture was heated at 120 °C under microwave irradiation for 3 h. The solvent was removed under reduced pressure. The residue was treated with water (20 mL) and extracted with DCM (2 x 30 mL). The organic layers were washed with brine (25 mL), dried over sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by preparative HPLC (16 mL/min, 25 °C, YMC-ACTUS-TRIART C18, 150-20 mm), using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (50-98% over 15 mins). The pure fractions were lyophilised to afford (R)-3-(((R)-1-(1*H*-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol (150 mg, 42% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): 8.45 (brs, 1H), 7.54 (d, *J* = 7.60 Hz, 1H), 7.40 (d, *J* = 8.00 Hz, 1H), 7.26-7.20 (m, 1H), 7.16-7.12 (m, 1H), 3.78-3.74 (m, 1H), 3.42 (q, *J* = 6.00 Hz, 1H), 3.28 (t, *J* = 10.80 Hz, 1H), 3.18-3.16 (m, 2H), 2.95-2.85 (m, 2H), 2.36-2.31 (m, 2H), 1.36 (d, *J* = 6.40 Hz, 3H), 0.79 (d, *J* = 6.80 Hz, 3H).

LCMS: *m/z* (ESI): 247.09 [M+H]⁺

Synthesis of (R)-2-methyl-3-((1*R*,3*R*)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)propan-1-ol (40):

To a stirred solution of (R)-3-(((R)-1-(1*H*-indol-3-yl)propan-2-yl)amino)-2-methylpropan-1-ol (150 mg, 0.61 mmol, 1 eq.) in toluene (1.5 mL) was added 4-((1-propylazetidin-3-yl)oxy)benzaldehyde (146 mg, 0.67 mmol, 1.1 eq.), acetic acid (0.17 mL, 3.05 mmol, 5 eq.) and molecular sieves (4Å, 200 mg). The resulting reaction mixture was heated at 100 °C for 16 h. The solution was allowed to cool to room temperature and diluted with ethyl acetate (30 mL) and a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL) and the combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by preparative HPLC (16 mL/min, 25 °C, YMC-ACTUS-TRIART C18, 150-20 mm), 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (50-98% over 15 mins). The pure fractions were lyophilised to afford (R)-2-methyl-3-((1*R*,3*R*)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)propan-1-ol (11 mg, 30% yield) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.63 (s, 1H), 7.40 (d, *J* = 7.60 Hz, 1H), 7.24 (d, *J* = 8.00 Hz, 1H), 7.08 (d, *J* = 8.40 Hz, 2H), 7.02 (t, *J* = 6.80 Hz, 1H), 6.98 (t, *J* = 6.80 Hz, 1H), 6.77 (d, *J* = 8.80 Hz, 2H), 4.75-4.70 (m, 2H), 4.43 (brs, 1H), 3.70 (t, *J* = 2.00

Hz, 2H), 3.32-3.20 (m, 2H), 2.87 (t, J = 6.80 Hz, 2H), 2.63-2.51 (m, 2H), 2.38-2.32 (m, 4H), 1.86-1.79 (m, 1H), 1.31-1.28 (m, 2H), 1.26-1.24 (m, 1H), 1.04 (d, J = 6.80 Hz, 3H), 0.92 (d, J = 6.80 Hz, 3H), 0.83 (t, J = 7.60 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 157.2, 136.4, 133.6, 132.7, 130.7, 127.6, 121.7, 119.4, 118.3, 114.9, 110.8, 107.5, 70.5, 66.7, 61.8, 61.5, 60.5, 56.1, 48.6, 31.5, 29.8, 27.4, 20.9, 15.0, 11.8.

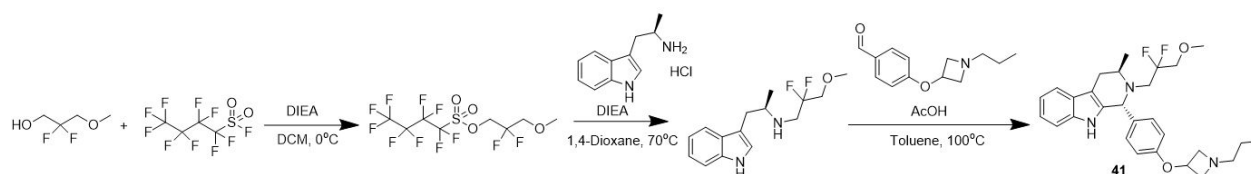
LCMS: m/z (ESI): 448.48 $[\text{M}+\text{H}]^+$

HRMS (ESI): $\text{C}_{28}\text{H}_{38}\text{N}_3\text{O}_2$, $[\text{M}+\text{H}]^+$: calc. 448.2958, found: 448.2939

HPLC: 98.15%

$[\alpha]_{\text{D}}^{20}$ -26 (c 0.1, acetonitrile).

Scheme S20. Preparation of 41



Synthesis of 2,2-difluoro-3-methoxypropyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate:

To a stirred solution of 2,2-difluoro-3-methoxypropan-1-ol (500 mg, 3.965 mmol, 1 eq.) in DCM (10 mL) added DIPEA (1.38 mL, 7.930 mmol, 2 eq.), cooled to 0 °C. To this solution perfluorobutanesulfonyl fluoride (1.317 g, 4.362 mmol, 1.1 eq.) was added dropwise and stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (30 mL) and washed with 1M HCl (3 x 10 mL), brine (10 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo* to afford 2,2-difluoro-3-methoxypropyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (1.2 g, 74% yield) as a colourless oil.

^1H NMR (400 MHz, CDCl_3): δ 4.68 (t, J = 11.6 Hz, 2H), 3.71 (t, J = 12.0 Hz, 2H), 3.46 (s, 3H).

Synthesis of (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2,2-difluoro-3-methoxypropan-1-amine:

To a stirred solution (2,2-difluoro-3-methoxy-propyl) 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (1.2 g, 2.94 mmol, 1 eq.) and (2R)-1-(1H-indol-3-yl)propan-2-amine hydrochloride (619 mg, 2.94 mmol, 1 eq.) in 1,4-dioxane (12 mL) was added DIPEA (2.05 mL, 11.76 mmol, 4 eq.). The mixture was stirred at 70 °C for 16 h, allowed to cool to room temperature and diluted with ethyl acetate (50 mL)/saturated sodium bicarbonate solution (30 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-5% methanol in DCM) to afford (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2,2-difluoro-3-methoxypropan-1-amine (290 mg, 35% yield) as a brown semi solid.

^1H NMR (400 MHz, CDCl_3): δ 8.01 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.21-7.17 (m, 2H), 7.13-7.09 (m, 1H), 7.09-7.04 (d, J = 2.4 Hz, 1H), 3.70-3.47 (m, 3H), 3.33 (s, 3H), 3.01-2.97 (m, 3H), 2.86-2.76 (m, 2H), 1.11 (d, J = 6.0 Hz, 3H).

LCMS: m/z (ESI): 283.32 $[\text{M}+\text{H}]^+$

Synthesis of (1R,3R)-2-(2,2-difluoro-3-methoxypropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (41):

To a stirred solution of (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2,2-difluoro-3-methoxypropan-1-amine (290 mg, 1.02 mmol, 1 eq.), 4-(1-propylazetidin-3-yl)oxybenzaldehyde (270 mg, 1.23 mmol, 1.2 eq.) in toluene (6 mL) was added acetic acid (262 mg, 4.365 mmol, 4.25 eq.) and molecular sieves (4Å, 200 mg). The mixture was stirred at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate (30 mL) and a saturated sodium bicarbonate solution (10 mL). The separated organic layer was washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered, and dried *in-vacuo*. The crude material was purified by prep-HPLC (22 mL/min, ACQUITY UPLC BEH C18, 150-30), using 0.1% FA in H_2O : acetonitrile gradient (0-50% over 19 mins). The pure fractions were lyophilised to afford (1R,3R)-2-(2,2-difluoro-3-methoxypropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (167 mg, 33% yield) as a pale-yellow solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.81 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.09-7.03 (m, 3H), 7.00-6.95 (m, 1H), 6.78 (d, J = 8.4 Hz, 2H), 4.95 (s, 1H), 4.79-4.75 (m, 1H), 3.83-3.65 (m, 4H), 3.52 (s, 3H), 3.35-3.10 (m, 2H), 2.70-2.49 (m, 5H), 1.314-1.27 (m, 2H), 1.06 (d, J = 6.8 Hz, 5H), 0.84 (t, J = 7.2 Hz, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 155.6, 136.3, 134.6, 132.4, 129.6, 126.5, 120.8, 118.3, 117.7, 114.1, 110.9, 108.5, 66.0, 62.2, 60.5 (d, *J* = 28 Hz), 59.1, 47.2, 40.1, 38.9, 24.7, 20.0, 18.8, 11.5.

¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -106.60 - -108.66 (m)

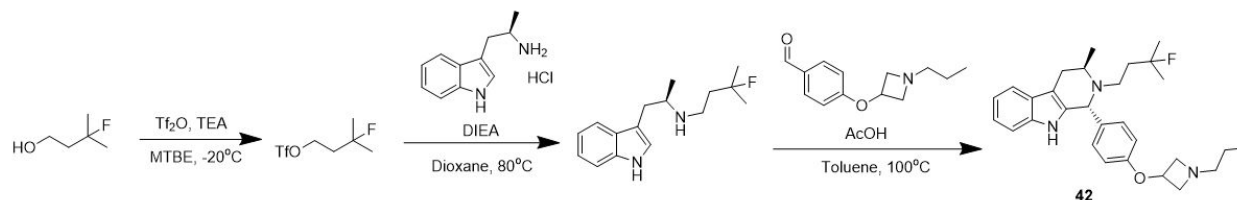
LCMS: *m/z*: 484.47 [M+H]⁺

HRMS (ESI): C₂₈H₃₆F₂N₃O₂ [M+H]⁺ calc.484.2731, found: 484.2769.

HPLC: 95.08%

[α]_D²⁰ -11 (c 0.1, acetonitrile).

Scheme S21. Preparation of 42



Synthesis of 3-fluoro-3-methylbutyl trifluoromethanesulfonate:

To a stirred solution of 3-fluoro-3-methylbutan-1-ol (700 mg, 6.59 mmol, 1 eq.) in methyl *tert*-butyl ether (2 mL) was added triethylamine (1.19 mL, 8.57 mmol, 1.3 eq.) at 0 °C followed by the addition of trifluoromethanesulfonic anhydride (2.2 g, 7.914 mmol, 1.2 eq.) at -20 °C. The mixture was stirred at the same temperature for 1 h and diluted with methyl *tert*-butyl ether (20 mL) and a saturated sodium bicarbonate solution (15 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-5% methanol in DCM) to afford 3-fluoro-3-methylbutyl trifluoromethanesulfonate (1.4 g, 89% yield) as pale pink oil.

¹H NMR (400 MHz, CDCl₃): δ 4.70 (t, *J* = 6.8 Hz, 2H), 2.17 (dt, *J* = 6.8 Hz, 13.4 Hz, 2H), 1.43 (d, *J* = 21.6 Hz, 3H), 1.37 (d, *J* = 20.0 Hz, 3H).

Synthesis of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-3-fluoro-3-methylbutan-1-amine:

To a stirred solution of 3-fluoro-3-methylbutyl trifluoromethanesulfonate (1.4 g, 5.88 mmol, 1 eq.) in 1,4-dioxane (10 mL) was added (*R*)-1-(1*H*-indol-3-yl)propan-2-amine hydrochloride (866.89 mg, 4.11 mmol, 0.7 eq.), *N,N*-diisopropylethylamine (4.11 mL, 23.510 mmol, 4 eq.), and stirred at 90 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 80 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by silica-gel flash column chromatography (0-5% methanol in DCM) to afford (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-3-fluoro-3-methylbutan-1-amine (310 mg, 20% yield) as a pale brown semi solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.82 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.05 (td *J* = 0.8 Hz, 8.0 Hz, 1H), 6.96 (td, *J* = 0.8 Hz, 8.0 Hz, 1H), 3.16 (s, 1H), 2.94-2.92 (m, 1H), 2.85 (dd, *J* = 5.6 Hz, 13.8 Hz, 1H), 2.74-2.50 (m, 3H), 1.76-1.68 (m, 2H), 1.29 (d, *J* = 21.6 Hz, 3H), 1.28 (d, *J* = 21.6 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H).

LCMS: *m/z* (ESI): 263.34 [M+H]⁺

Synthesis of (1*R*,3*R*)-2-(3-fluoro-3-methylbutyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (42):

To a stirred solution of (*R*)-*N*-(1-(1*H*-indol-3-yl)propan-2-yl)-3-fluoro-3-methylbutan-1-amine (310 mg, 1.18 mmol, 1 eq.), 4-((1-propylazetidin-3-yl)oxy)benzaldehyde (129.54 mg, 0.59 mmol, 0.5 eq.) in toluene was added acetic acid (301.55 mg, 5.02 mmol, 4.25 eq.) and molecular sieves (600 mg). The mixture was stirred at 100 °C for 16 h, cooled to room temperature and quenched with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and dried *in-vacuo*. The crude material was purified by preparative HPLC (22 mL/min, ACQUITY UPLC BEH C18,150-30), using 0.1% formic acid in H₂O: acetonitrile gradient (0-50% over 19 mins). The pure fractions were lyophilized to afford (1*R*,3*R*)-2-(3-fluoro-3-methylbutyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (92 mg, 17% yield) as a light brown solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.51 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.03-6.98 (m, 1H), 6.96-6.92 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.73-4.70 (m, 2H), 3.70-3.67 (m, 2H), 3.30-3.18 (m, 1H), 2.90-2.86

(m, 2H), 2.73-2.67 (m, 2H), 2.54-2.50 (m, 1H), 2.49-2.34 (m, 3H), 1.87-1.82 (m, 2H), 1.31-1.21 (m, 8H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.83 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (100 MHz, DMSO- d_6): δ 155.8, 136.3, 134.9, 133.6, 129.9, 126.7, 120.5, 118.1, 117.6, 114.1, 113.9, 110.9, 107.6, 95.2 (d, $J = 163$ Hz), 66.1, 61.1, 60.8, 59.4, 47.3, 41.3, 41.2, 40.6, 40.4, 40.1, 38.9, 26.64 (d, $J = 24$ Hz), 26.57 (d, $J = 24$ Hz), 25.6.

^{19}F NMR (376 MHz, DMSO- d_6): δ -133.94, -134.19.

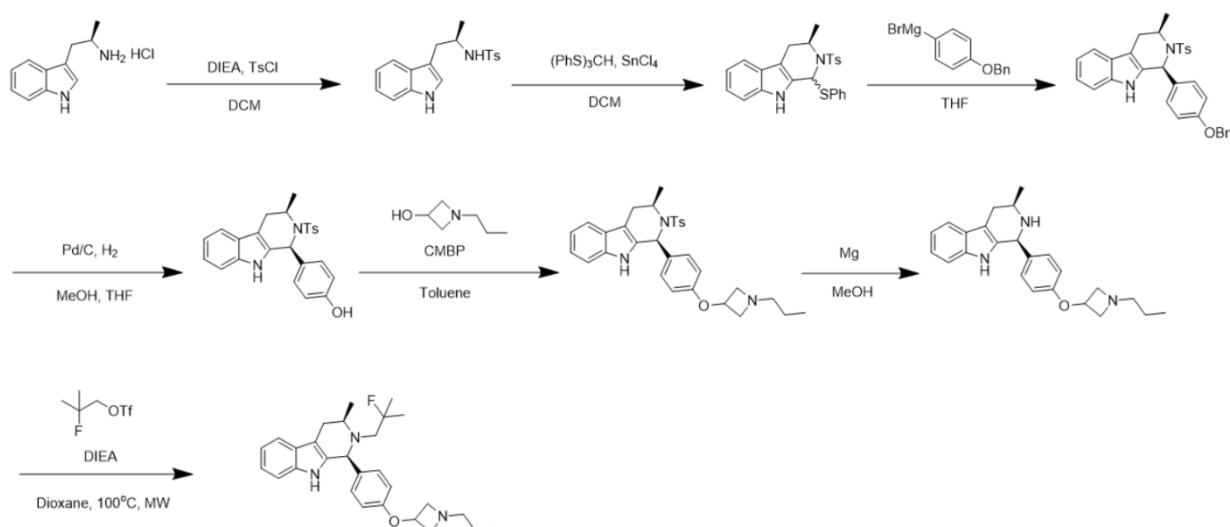
LCMS: m/z : 464.33 $[\text{M}+\text{H}]^+$

HRMS (ESI): $\text{C}_{29}\text{H}_{39}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$ calc.464.3032, found: 464.3069.

HPLC: 98.46%

$[\alpha]_{\text{D}}^{20}$ -26 (c 0.1, acetonitrile).

Scheme S22. Preparation of (1*S*, 3*R*) diastereomer of compound 21



Synthesis of (R)-N-(1-(1*H*-indol-3-yl)propan-2-yl)benzenesulfonamide:

To a stirred solution of (R)-1-(1*H*-indol-3-yl)propan-2-amine hydrochloride (15 g, 71.2 mmol, 1 eq.), 4-methylbenzenesulfonyl chloride (20.4 g, 106.8 mmol, 1.5 eq.) in DCM (225 mL) at 0 °C was added. DIEA (37.2 mL, 213.57 mmol, 3 eq.) was then added and stirred at room temperature for 16 h. The reaction was quenched with water (70 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and dried in vacuo. The crude was purified by silica-gel column chromatography (0-20% ethyl acetate in n-hexane) to afford (R)-N-(1-(1*H*-indol-3-yl)propan-2-yl)-4-methylbenzenesulfonamide (22 g, 94% yield) as a pale brown solid.

^1H NMR (500 MHz, DMSO- d_6): δ 10.77 (s, 1H), 7.65 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 7.0$ Hz, 1H), 7.32-7.29 (m, 3H), 7.23 (d, $J = 7.0$ Hz, 1H), 7.06 (d, $J = 2.5$ Hz, 1H), 7.06-7.01 (m, 1H), 6.93-6.90 (m, 1H), 3.34-3.31 (m, 1H), 2.80 (dd, $J = 5.0, 14.0$ Hz, 1H), 2.61-2.57 (m, 1H), 2.35 (s, 3H), 0.88 (d, $J = 6.5$ Hz, 3H).

LCMS: m/z (ESI): 329.02 $[\text{M}+\text{H}]^+$.

Synthesis of (3*R*)-3-methyl-1-(phenylthio)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole:

To a stirred solution of (R)-N-(1-(1*H*-indol-3-yl)propan-2-yl)-4-methylbenzenesulfonamide (10 g, 30.5 mmol, 1 eq.) and tris(phenylthio)methane (13.5 g, 39.6 mmol, 1.3 eq.) in DCM (150 mL) at -78 °C was added tin(IV) chloride (1M in DCM, 91.3 mL, 3 eq.). The reaction was stirred for 5 h while allowing it to warm to room temperature gradually. The reaction was quenched with a saturated sodium bicarbonate solution (50 mL) and extracted with DCM (2 x 200 mL). The combined organic

layers were dried over sodium sulphate, filtered, and dried in vacuo to afford the crude product. The crude product was purified by silica gel column chromatography (0-7% ethyl acetate in n-hexane) to afford (3*R*)-3-methyl-1-(phenylthio)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4.2 g, 31% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.22 (s, 1H), 7.73-7.71 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.48-7.42 (m, 2H), 7.41-7.39 (m, 2H), 7.37 (d, *J* = 15.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.13-7.10 (m, 1H), 6.98-6.94 (m, 1H), 6.86 (d, *J* = 1.2 Hz, 1H), 4.44-4.40 (m, 1H), 2.49-2.40 (m, 2H), 2.36 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 3H).

LCMS: *m/z* (ESI): 448.90[M+H]⁺.

Synthesis of (1*S*,3*R*)-3-methyl-1-(4-phenoxyphenyl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole:

To a mixture of (1*R*,3*R*)-3-methyl-1-(phenylthio)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (5 g, 11.15 mmol, 1 eq.) in THF (50 mL) at room temperature was added (4-(benzyloxy)phenyl)magnesium bromide (0.8 M in THF, 28 mL, 2 eq.). The reaction was stirred at room temperature for 12 h. The reaction quenched with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered, and dried in vacuo to obtain crude product. The crude product was purified by silica-gel column chromatography (0-20% ethyl acetate in pet. ether) to afford (1*S*,3*R*)-1-(4-(benzyloxy)phenyl)-3-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3 g, 52% yield) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.92 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.40-7.37 (m, 2H), 7.34-7.28 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.07-7.00 (m, 3H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.32 (s, 1H), 5.10 (s, 2H), 4.47-4.44 (m, 1H), 2.45-2.41 (m, 1H), 2.38-2.31 (m, 1H), 2.24 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

LCMS: *m/z* (ESI): 523.05 [M+H]⁺.

Synthesis of 4-((1*S*,3*R*)-3-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenol:

A solution of (1*S*,3*R*)-1-(4-(benzyloxy)phenyl)-3-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2.8 g, 5.36 mmol, 1 eq.) in methanol (58.8 mL) and THF (25.2 mL) was purged with argon for 5 minutes. The mixture was treated with 10% palladium on carbon (50% wet basis, 2.8 g) at room temperature and stirred under hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was filtered through a celite bed and washed with methanol (2 x 30 mL). The filtrate was evaporated under reduced pressure to afford crude product, which was purified by silica-gel column chromatography (0-10% methanol in dichloromethane) to afford 4-((1*S*,3*R*)-3-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenol (1.2 g, 52%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 10.91 (s, 1H), 9.44 (s, 1H), 7.65 (d, *J* = 10.0 Hz, 2H), 7.63-7.29 (m, 2H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.05 (t, *J* = 7.0 Hz, 1H), 6.94-6.91 (m, 1H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.29 (s, 1H), 4.46-4.41 (m, 1H), 2.49-2.33 (m, 2H), 2.25 (s, 3H), 0.90 (d, *J* = 7.0 Hz, 3H).

LCMS: *m/z* (ESI): 433.16 [M+H]⁺.

Synthesis of (1*S*,3*R*)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole:

To a stirred solution of 4-((1*S*,3*R*)-3-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenol (800 mg, 1.85 mmol, 1 eq.) in toluene (15 mL) at room temperature was added 1-propylazetidin-3-ol (320 mg, 2.80 mmol, 1.5 eq.) followed by CMBP (893 mg, 3.7 mmol, 2 eq.). The reaction mixture was stirred at 90 °C for 4 h. The reaction was allowed to cool to room temperature and quenched with water (100 mL). The mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and dried in-vacuo. The crude product was purified by silica-gel flash column chromatography (0-10% methanol in DCM) to afford (1*S*,3*R*)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (800 mg, 81% yield) as a brown oil.

LCMS: m/z (ESI): 530.16 [M+H]⁺.

Synthesis of (1S,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole:

To a stirred solution of magnesium turnings (792 mg, 33.01 mmol, 25 eq.) in anhydrous MeOH (3 mL) at room temperature was added dropwise a solution of (1S,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (700 mg, 1.32 mmol, 1 eq) in MeOH (12 mL). The reaction mixture was stirred under argon atmosphere for 12 h. The reaction was quenched with a saturated ammonium chloride solution (70 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and dried in-vacuo. The crude product was purified by silica-gel flash column chromatography (10-15% methanol in DCM) to afford (1S,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (70 mg, 14% yield) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-d₆): δ 10.19 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.99-6.90 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.13 (brs, 1H), 4.78-4.73 (m, 1H), 3.74-3.72 (m, 2H), 3.40-3.38 (m, 1H), 3.17-3.16 (m, 1H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.76-2.72 (m, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.32-1.29 (m, 2H), 1.27-1.23 (m, 3H), 0.85 (t, *J* = 7.2 Hz, 3H).

LCMS: m/z (ESI): 376.33 [M+H]⁺.

Synthesis of (1S,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ((1S, 3R) diastereomer of compound 21):

To a stirred solution of (1S,3R)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (300 mg, 0.8 mmol, 1 eq.) and 2-fluoro-2-methylpropyl trifluoromethanesulfonate (716 mg, 7.6 mmol, 4 eq.) in 1,4-dioxane (2 mL) was added DIEA (0.60 mL, 7.6 mmol, 4 eq.). The reaction mixture was stirred in microwave irradiation for 2 h at 110 °C. The solvent was evaporated under reduced pressure and purified by preparative HPLC (24 mL/min, X-SELECT-CSH-C18, 150*30) using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (60-98% over 17 mins) afforded (1S,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3.0 mg, 1% yield) as an off white solid.

¹H NMR (500 MHz, CDCl₃): δ 7.61 (brs, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.31-7.29 (m, 3H), 7.17 (td, *J* = 1.0 Hz, 7.0 Hz, 1H), 7.13-7.10 (m, 1H), 6.69-6.67 (m, 2H), 5.05 (s, 1H), 4.78-4.76 (m, 1H), 3.84-3.82 (m, 2H), 3.49-3.22 (m, 1H), 3.08-3.02 (m, 3H), 2.90-2.69 (m, 2H), 2.57 (dd, *J* = 3.0 Hz, 15.5 Hz, 1H), 2.48 (t, *J* = 7.5 Hz, 2H), 1.40 (d, *J* = 22.5 Hz, 3H), 1.39-1.24 (m, 2H), 1.25 (d, *J* = 21.5 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H).

LCMS: m/z (ESI): 450.23 [M+H]⁺.

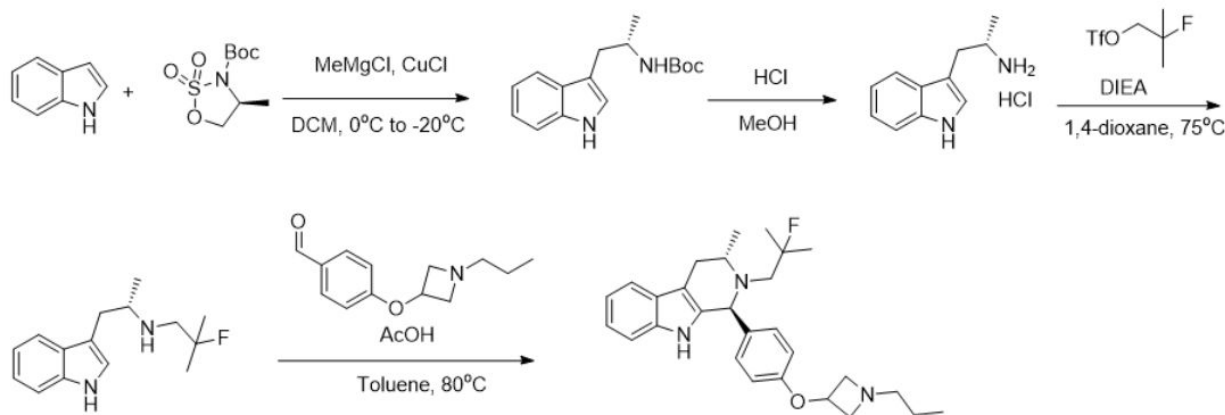
¹⁹F NMR (376 MHz, CDCl₃): -139.37 - -139.58 (m).

HRMS (ESI): C₂₈H₃₇ON₃F [M+H]⁺ calc. 450.2915, found: 450.2906.

HPLC: 98.23%

Chiral SFC: 94.98% de, (Column: (R,R) WHELK-01 (4.6 x 150 mm), 3.5 μm, co-solvent: 0.5% diethylamine in methanol, total flow: 3 mL/min, % of CO₂: 70, % co-solvent: 30, ABPR: 1500 psi, column temperature: 30 °C, diluent: acetonitrile).

Scheme S23. Preparation of (1S, 3S) enantiomer of compound 21



Synthesis of *tert*-butyl (S)-(1-(1H-indol-3-yl)propan-2-yl)carbamate:

To a stirred solution of 1H-indole (2.46 g, 21.07 mmol, 1 eq), copper(I) chloride (4.16 g, 23.2 mmol, 1.1 eq) in dichloromethane (63 mL) at 0 °C, added dropwise methylmagnesium chloride (3 M in THF, 9.13 mL, 1.3 eq), and stirred at 0 °C for 1 h. Reaction mixture temperature was brought to -20 °C and then added dropwise solution of *tert*-butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (5 g, 21.1 mmol, 0.9 eq) in DCM (19 mL) and additionally stirred at -20 °C for 18 h. Then the reaction mixture was quenched with water (50 mL) and extracted with DCM (2 x 50 mL). The organic phase was washed with brine (2 x 25 mL), dried over anhydrous sodium sulfate, filtered, and dried in-vacuo. The crude material was further purified by silica gel column chromatography (0-100% ethyl acetate in *n*-hexane) to afford *tert*-butyl (S)-(1-(1H-indol-3-yl)propan-2-yl)carbamate (4.0 g, 69% yield) as an off white solid.

¹H NMR (400MHz, DMSO-*d*₆): δ 10.77 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.73 (t, *J* = 6.8 Hz, 1H), 2.85 (dd, *J* = 5.6 Hz, 13.6 Hz, 1H), 2.61 (dd, *J* = 7.6 Hz, 14.0 Hz, 1H), 1.37 (s, 9H), 1.00 (d, *J* = 6.4 Hz, 3H).

LCMS: *m/z* (ESI): 275.38 [M+H]⁺.

Synthesis of (S)-1-(1H-indol-3-yl)propan-2-amine hydrochloride:

Hydrochloric acid in methanol (3 M, 40 mL) was added to *tert*-butyl (S)-(1-(1H-indol-3-yl)propan-2-yl)carbamate (4.0 g, 14.5 mmol, 1 eq) and stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was evaporated under reduced pressure and azeotroped with toluene to afford (S)-1-(1H-indol-3-yl)propan-2-amine (2.4 g, 94% yield) as a brown solid.

¹H NMR (400MHz, DMSO-*d*₆): δ 11.02 (s, 1H), 8.07 (s, 3H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.10 (td, *J* = 8.0 Hz, 1H), 7.02 (td, *J* = 7.6 Hz, 1H), 3.10 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H), 2.83 (dd, *J* = 4.8 Hz, 14 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H),

LCMS: *m/z* (ESI): 175.05 [M+H]⁺.

Synthesis of (S)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine:

To a stirred solution of DIEA (3.45 mL, 19.9 mmol, 1.45 eq.) and (S)-1-(1H-indol-3-yl)propan-2-amine hydrochloride (2.4 g, 13.7 mmol, 1.0 eq) in 1,4-dioxane (27 mL) was added 2-fluoro-2-methylpropyl trifluoromethanesulfonate (3.1 g, 13.7 mmol, 1.0 eq) and stirred at 75 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with water (30 mL) and MTBE (10 mL). The aqueous layer was extracted with MTBE (50 mL) and the combined organic layers were washed with water (30 mL), saturated brine solution (30 mL), dried over anhydrous magnesium sulfate, filtered, and dried in-vacuo. The crude was purified by silica gel flash chromatography (0-30% ethyl acetate in *n*-hexane) to afford (S)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (2.0 g, 60% yield) as a brown oil.

¹H NMR (500 MHz, DMSO-d₆): δ 10.02 (s, 1H), 8.02 (brs, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 8.02 (bs, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 (td, *J* = 1.0 Hz, 8.0 Hz, 1H), 7.11 (td, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 3.04-2.99 (m, 1H), 2.93 (dd, *J* = 6.5 Hz, 14.0 Hz, 1H), 2.80-2.67 (m, 3H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 21.5 Hz, 3H), 1.33 (d, *J* = 21.0 Hz, 3H).

LCMS: *m/z* (ESI): 249.09 [M+H]⁺.

Synthesis of (1S, 3S)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ((1S, 3S) enantiomer of compound 21):

To a stirred solution of 4-((1-propylazetidin-3-yl)oxy)benzaldehyde (0.75 g, 3.42 mmol, 1.0 eq), acetic acid (0.39 mL, 6.84 mmol, 2.0 eq) and molecular sieves (4 Å, 200 mg) in toluene (8 mL) was added (S)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (1.21 g, 4.86 mmol, 1.2 eq) at room temperature. The mixture was stirred at 80 °C for 48 h. The reaction was cooled to room temperature and diluted with saturated sodium bicarbonate solution (12 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated brine solution (20 mL), dried over sodium sulfate, filtered, and dried in-vacuo. The crude material was purified by preparative HPLC (24 mL/min, X-SELECT-CSH-C18, 150*30) using 10 mM ammonium bicarbonate in H₂O: acetonitrile gradient (60-98% over 17 mins). The pure fractions were lyophilized to afford the product (1S, 3S)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (545 mg, 37% yield) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.64 (brs, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.15-7.09 (m, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.99 (brs, 1H), 4.74 (q, *J* = 6.0 Hz, 1H), 3.81-3.78 (m, 2H), 3.35 (brs, 1H), 3.05 (q, *J* = 1.2 Hz, 2H), 2.76-2.50 (m, 4H), 2.46 (t, *J* = 7.6 Hz, 2H), 1.59 -1.39 (m, 5H), 1.28 (d, *J* = 21.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 156.3, 136.3, 135.02, 133.3, 130.3, 127.3, 121.4, 119.1, 118.0, 114.1, 110.7, 97.9 (d, *J* = 166 Hz), 66.5, 61.9, 61.6, 61.5, 54.3, 47.6, 25.6 (d, *J* = 20 Hz), 24.9 (d, *J* = 20 Hz), 20.9, 11.7.

¹⁹F NMR (376 MHz, CDCl₃): δ -139.08 - -141.229.

LCMS: *m/z* (ESI): 450.50 [M+H]⁺

HRMS (ESI): C₂₈H₃₇FN₃O [M+H]⁺ calc.450.2915, found: 450.2903.

HPLC: 95.54%.

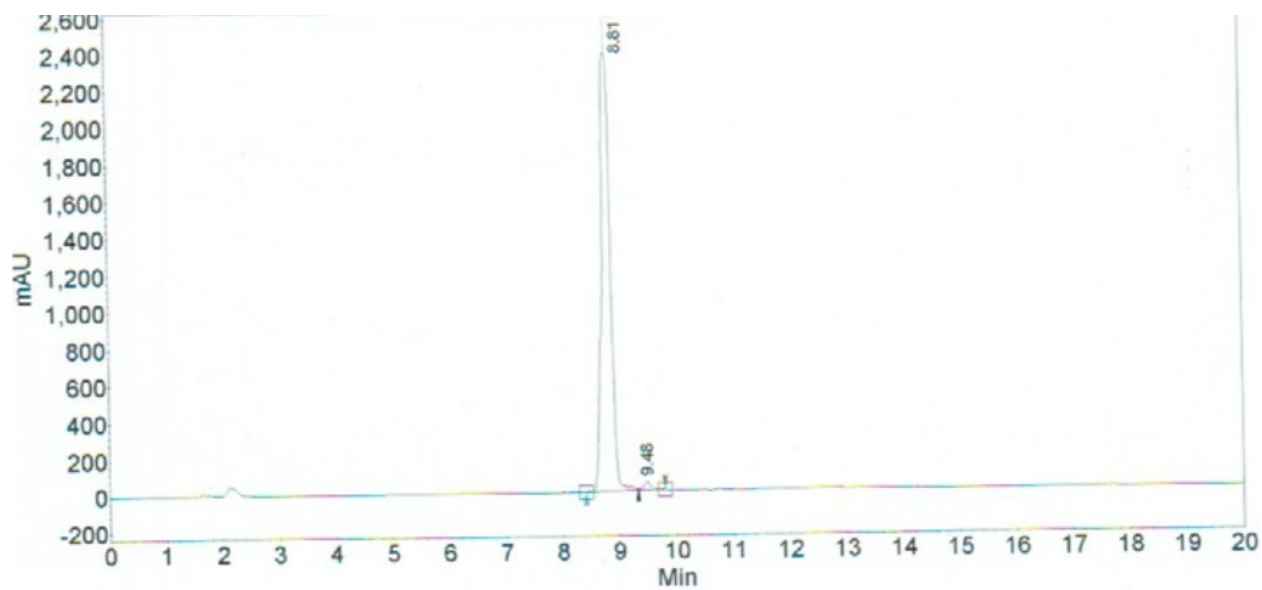
[α]_D²⁰ +5. (c 0.1, acetonitrile).

Chiral SFC: 99.92% ee (Column: (R,R) WHELK-01 (4.6 x 150 mm), 3.5 μm, co-solvent: 0.5% diethylamine in methanol, total flow: 3 mL/min, % of CO₂: 70, % co-solvent: 30, ABPR: 1500 psi, column temperature: 30°C, diluent: acetonitrile).

Analytical Spectra

Figure S8. HPLC chromatogram of Compound 11

LC



Peak	Index	Name	Time [Min]	Height [mAU]	Area [mAU.Sec]	Area [mAU.Min]	Area % [%]
	1	UNKNOWN	8.81	2378.9	28293.2	471.6	98.549
	2	UNKNOWN	9.48	41.8	416.6	6.9	1.451
	Total			2420.8	28709.9	478.5	100.000

Figure S9. ¹H-NMR spectrum of Compound 11

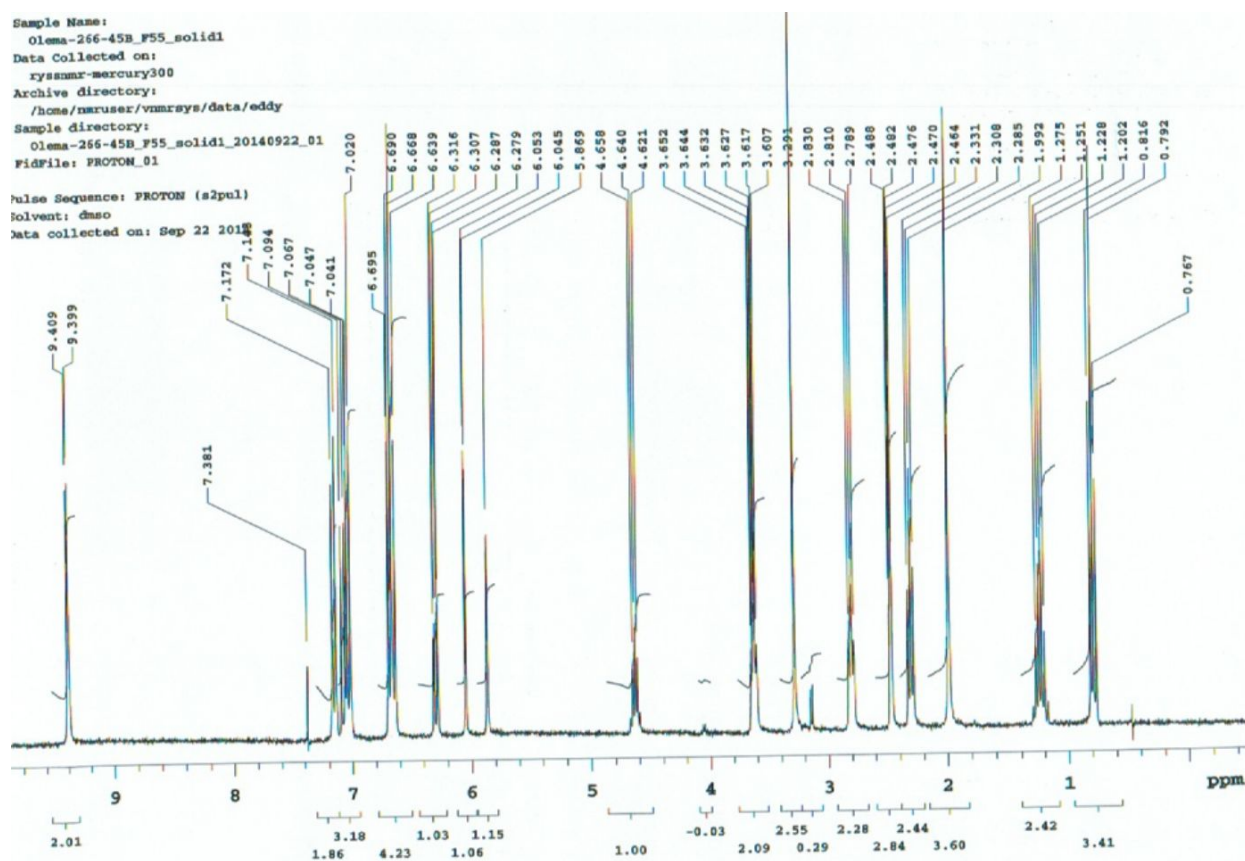
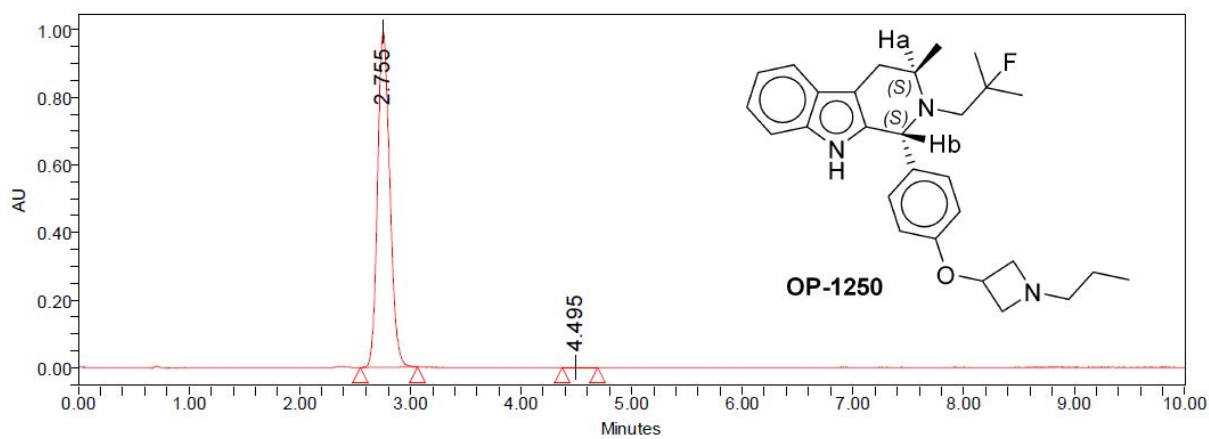


Figure S10. HPLC chromatogram of Compound 21

LC



Peak Results

	RT	Area	% Area
1	2.75	7597361	99.90
2	4.50	7834	0.10

Figure S11. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 21

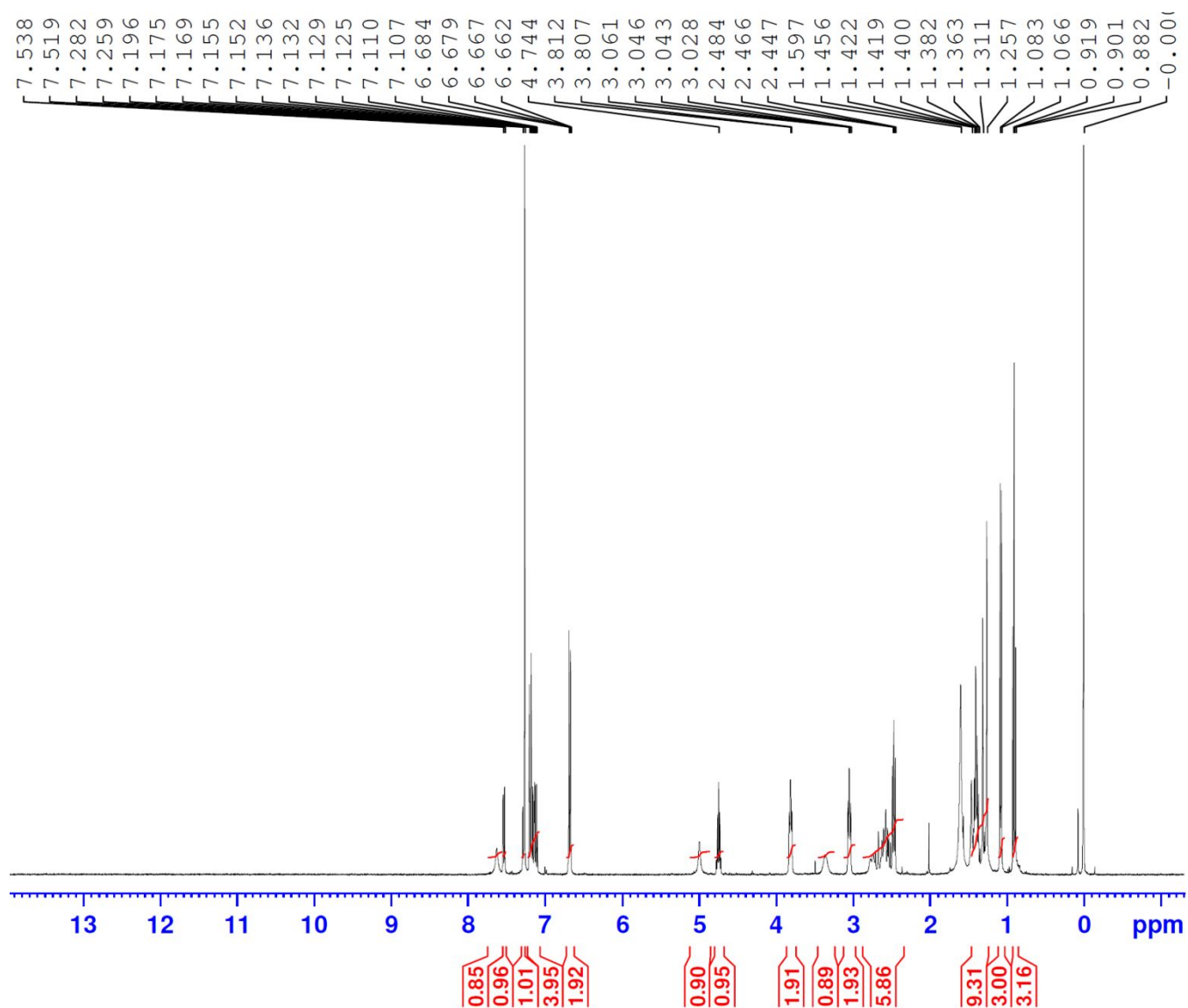


Figure S12. HRMS spectrum of Compound 21

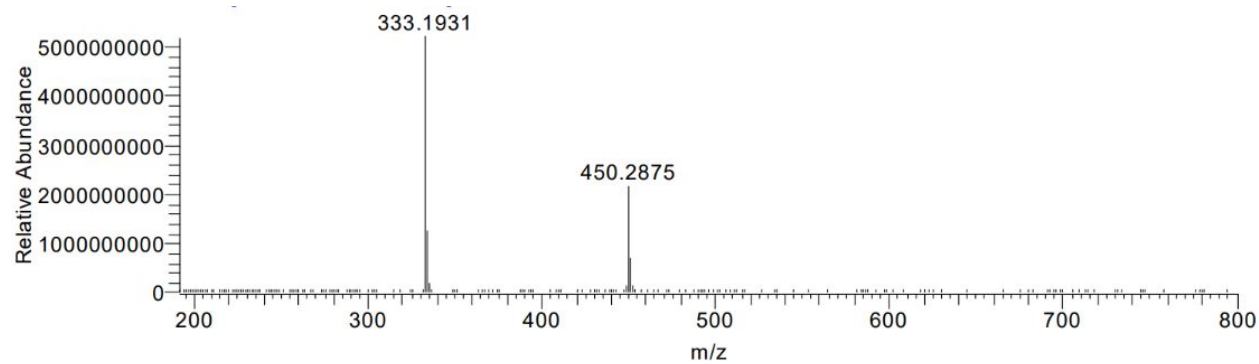


Figure S13. ^{19}F -NMR spectrum of Compound 21

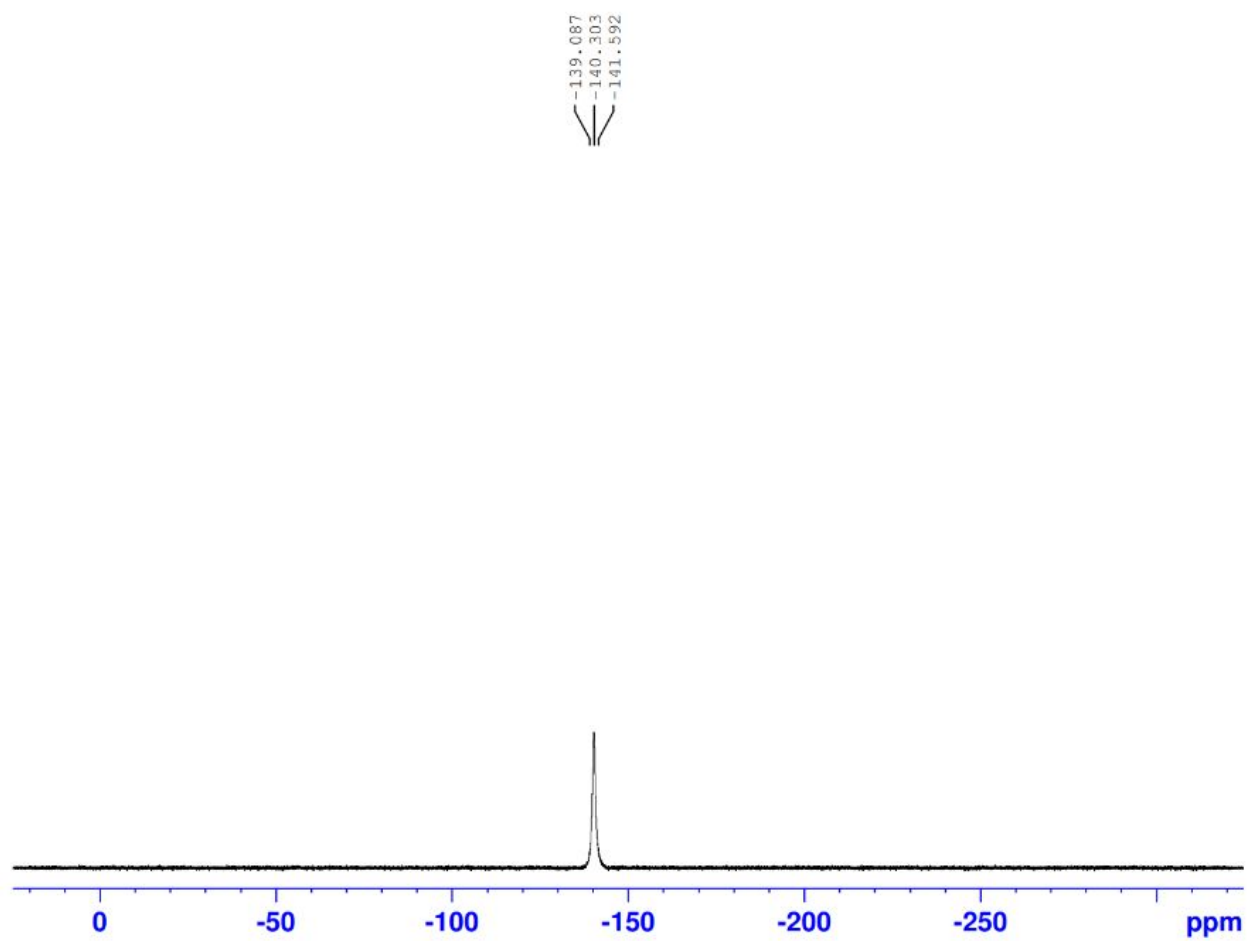


Figure S14. ^{13}C -NMR spectrum of Compound 21

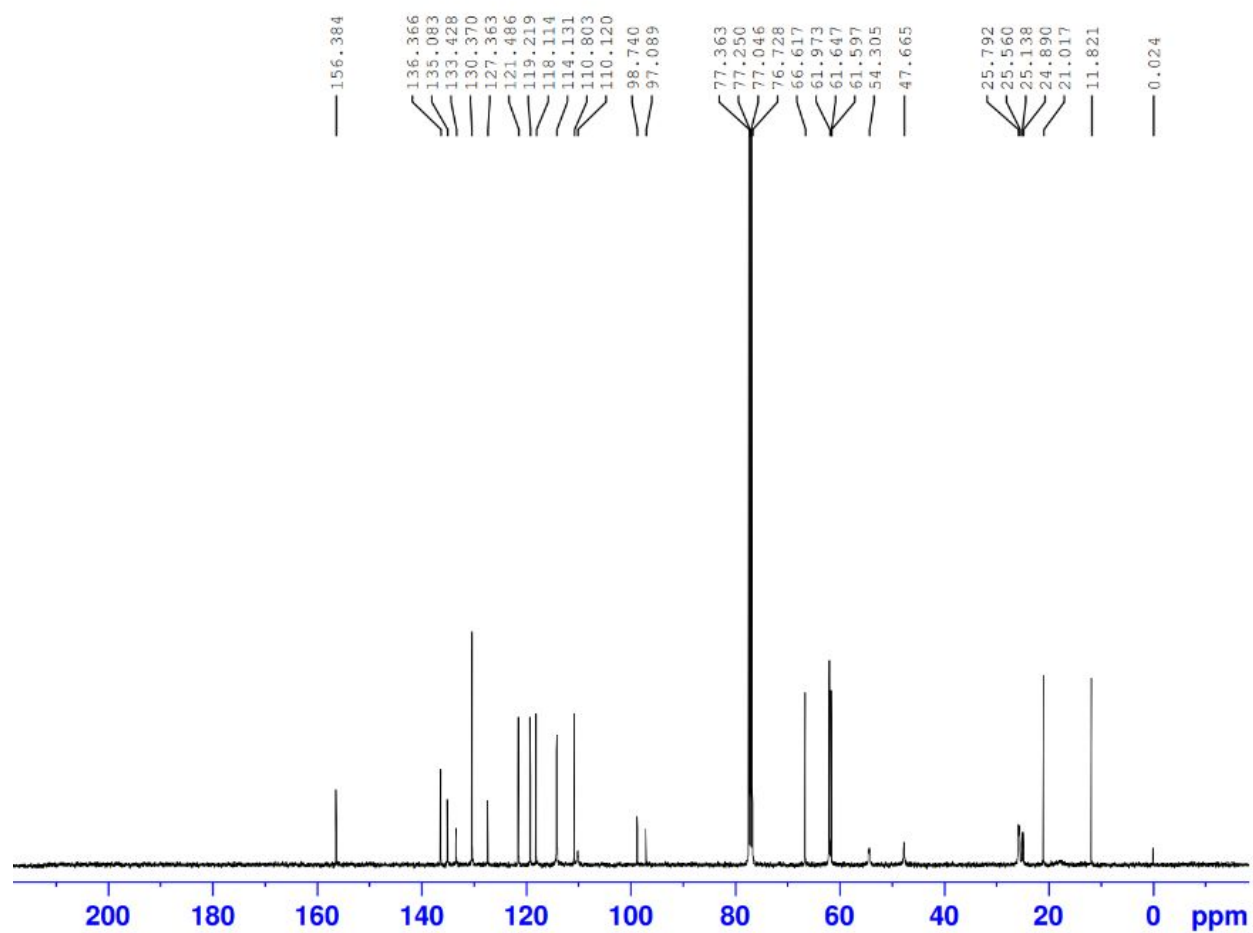
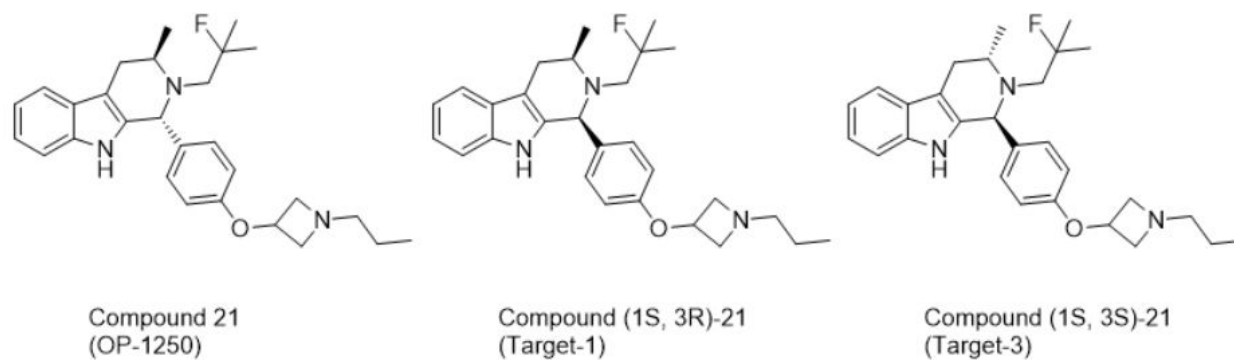
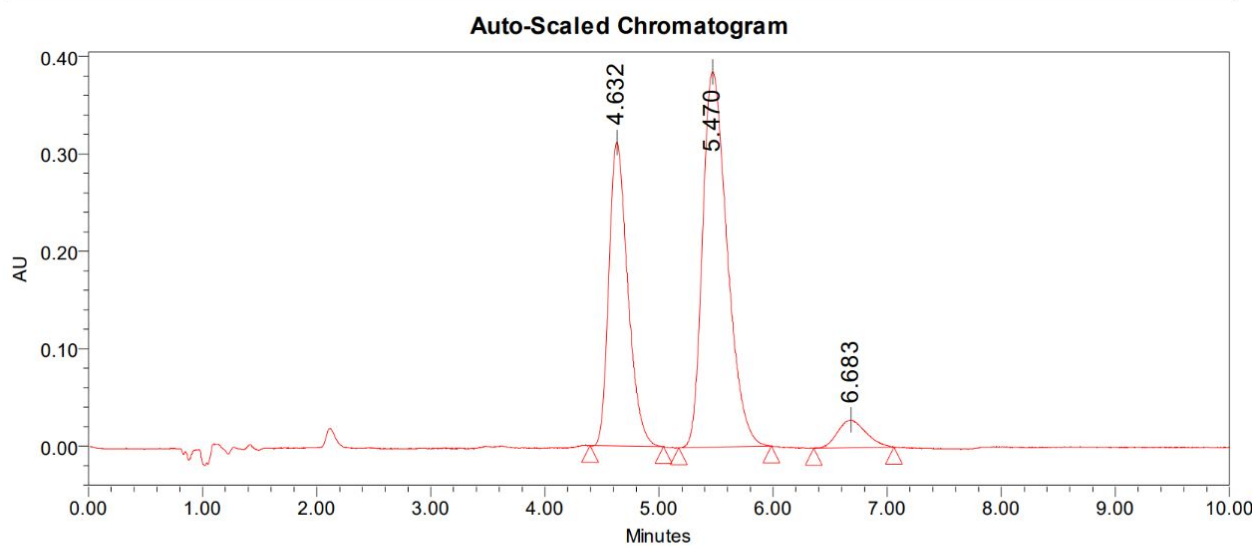


Figure S15. Chiral purity analysis of Compound 21 by HPLC



SFC Method Conditions :

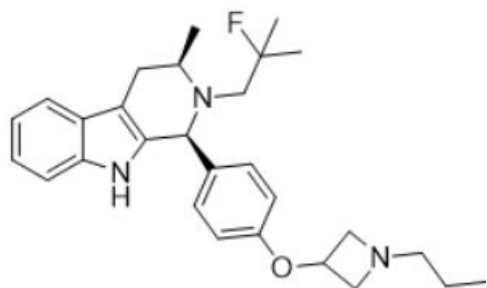
Column	: CHIRALCEL OX-H (4.6*250 mm) 5µm
Co-Solvent	: 0.5% DEA in Methanol
Total Flow	: 3 mL/min
% of CO ₂	: 70
% of Co Solvent	: 30
ABPR	: 1500psi
Column Temp	: 30°C
DILUENT	: ACN



Peak Results

	RT	Area	% Area
1	4.63	3594155	36.33
2	5.47	5813657	58.76
3	6.68	486616	4.92

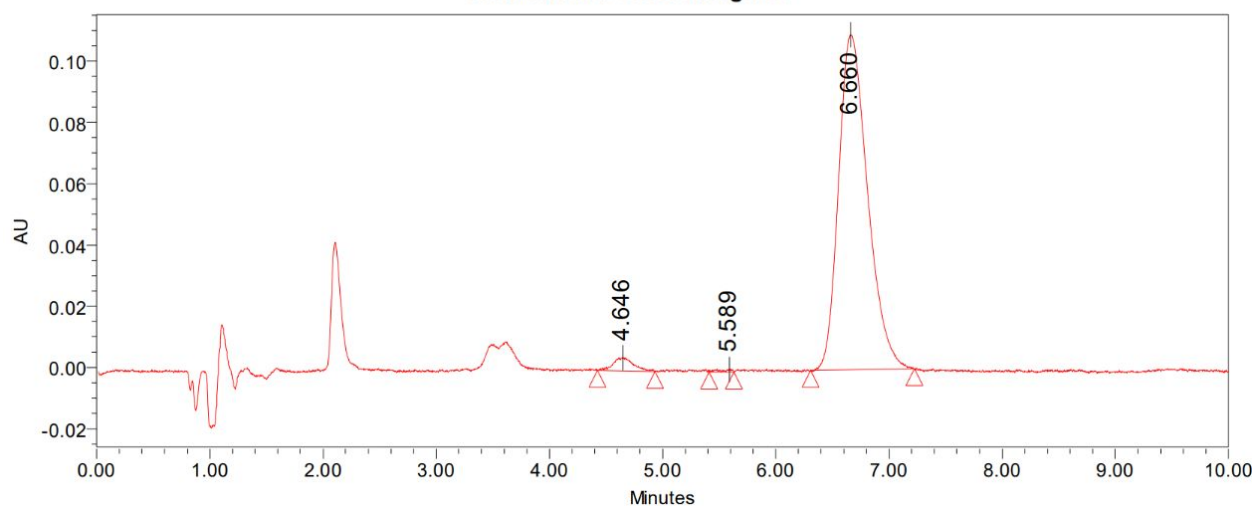
Figure S16. Chiral HPLC of (1*S*, 3*R*) diastereomer of compound 21



Compound (1*S*, 3*R*)-21
(Target-1)

SFC Method Conditions :
 Column : CHIRALCEL OX-H (4.6*250 mm) 5 μ m
 Co-Solvent : 0.5% DEA in Methanol
 Total Flow : 3 mL/min
 % of CO₂ : 70
 % of Co Solvent : 30
 ABPR : 1500psi
 Column Temp : 30°C
 DILUENT : ACN

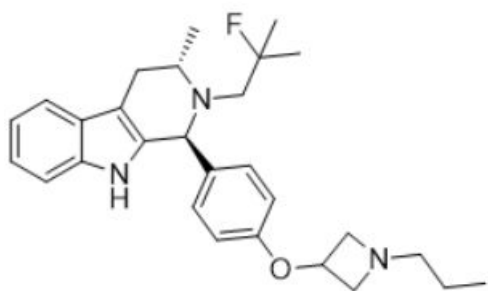
Auto-Scaled Chromatogram



Peak Results

	RT	Area	% Area
1	4.65	55857	2.76
2	5.59	6122	0.30
3	6.66	1958259	96.93

Figure S17. Chiral HPLC of (1*S*, 3*S*) diastereomer of compound 21

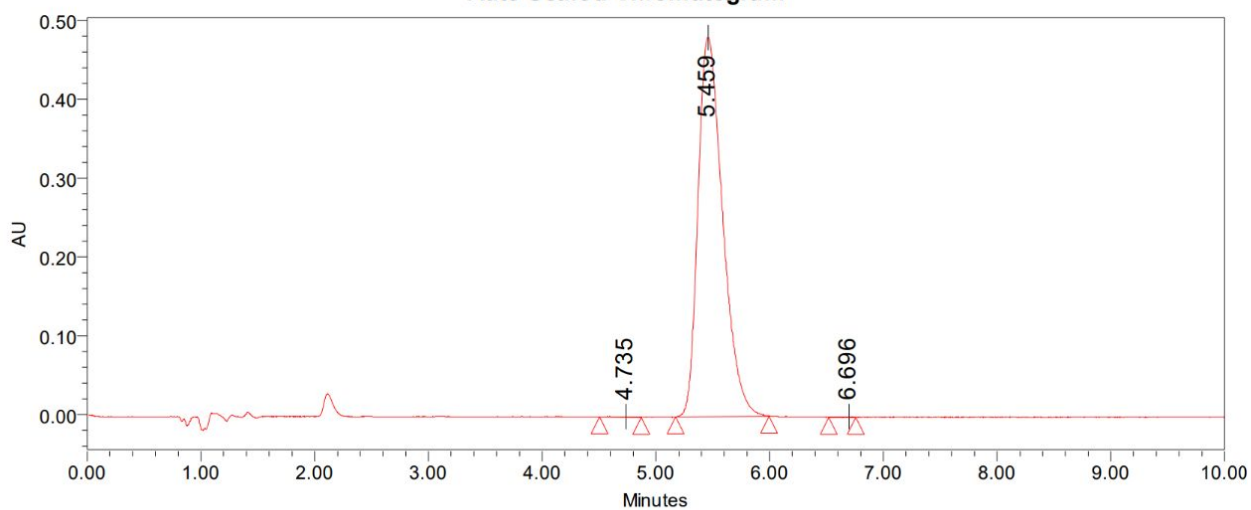


Compound (1*S*, 3*S*)-21
(Targer-3)

SFC Method Conditions :

Column : CHIRALCEL OX-H (4.6*250 mm) 5 μ m
 Co-Solvent : 0.5% DEA in Methanol
 Total Flow : 3 mL/min
 % of CO₂ : 70
 % of Co Solvent : 30
 ABPR : 1500psi
 Column Temp : 30°C
 DILUENT : ACN

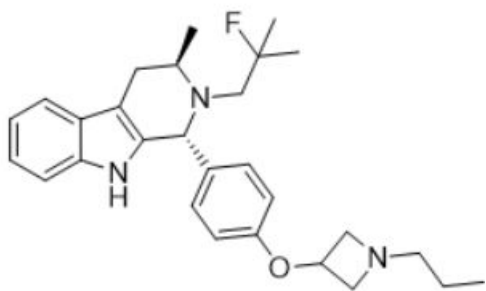
Auto-Scaled Chromatogram



Peak Results

	RT	Area	% Area
1	4.74	8853	0.12
2	5.46	7265632	99.77
3	6.70	7863	0.11

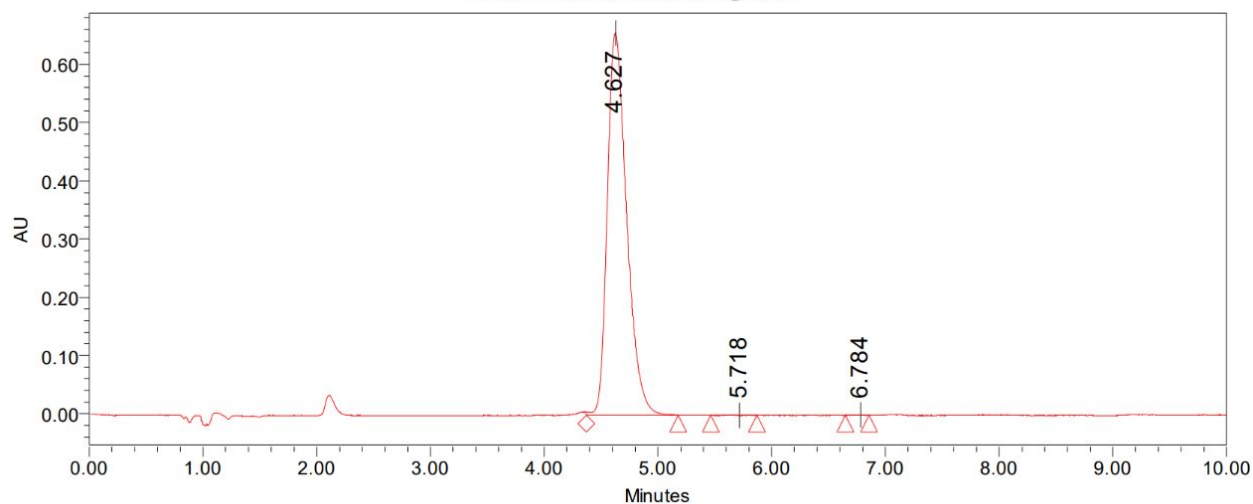
Figure S18. Chiral HPLC of Compound 21



Compound 21
(OP-1250)

SFC Method Conditions :
 Column : CHIRALCEL OX-H (4.6*250 mm) 5 μ m
 Co-Solvent : 0.5% DEA in Methanol
 Total Flow : 3 mL/min
 % of CO₂ : 70
 % of Co Solvent : 30
 ABPR : 1500psi
 Column Temp : 30°C
 DILUENT : ACN

Auto-Scaled Chromatogram



Peak Results

	RT	Area	% Area
1	4.63	7767999	99.89
2	5.72	6159	0.08
3	6.78	2111	0.03

Figure S19. NOE spectra of Compound 21

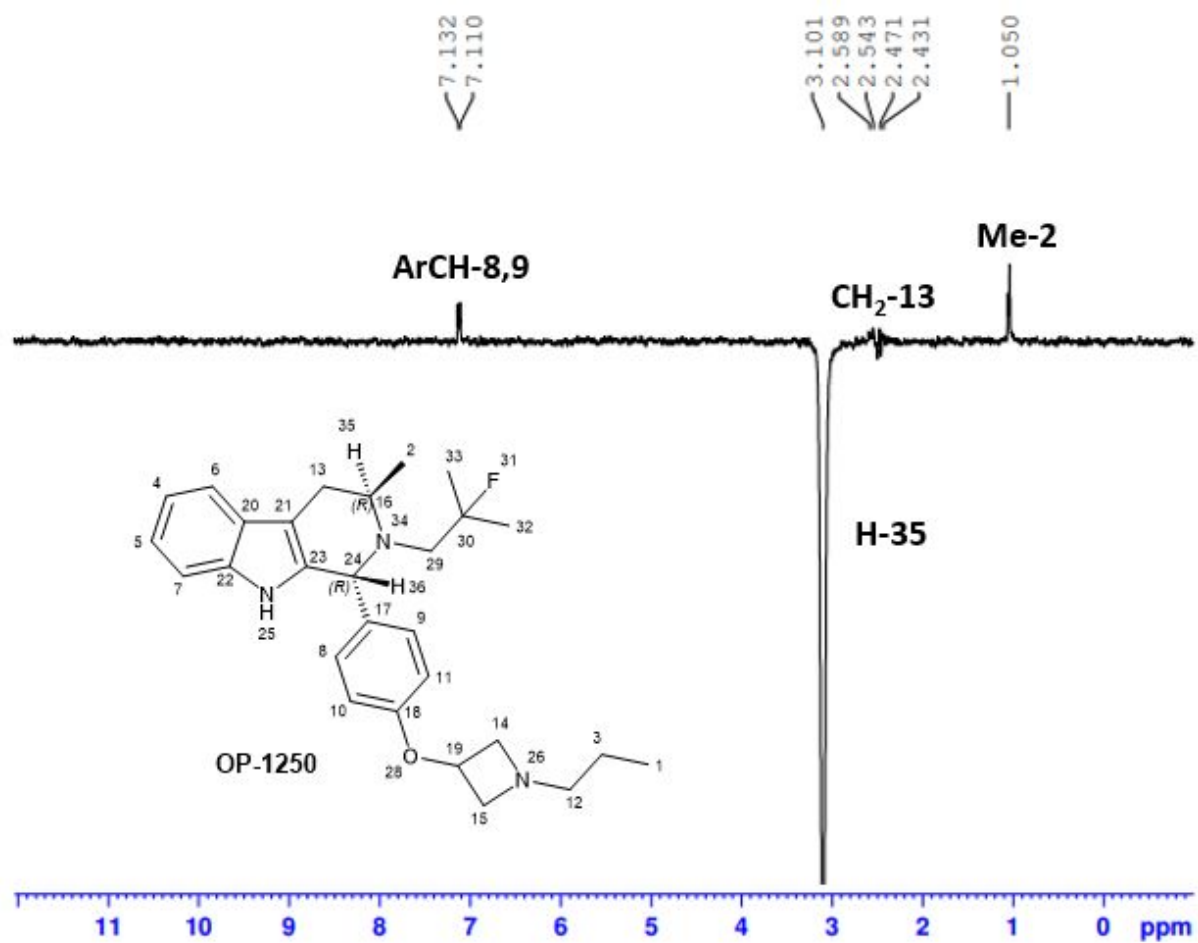


Figure S20. NOE spectra of Compound 21

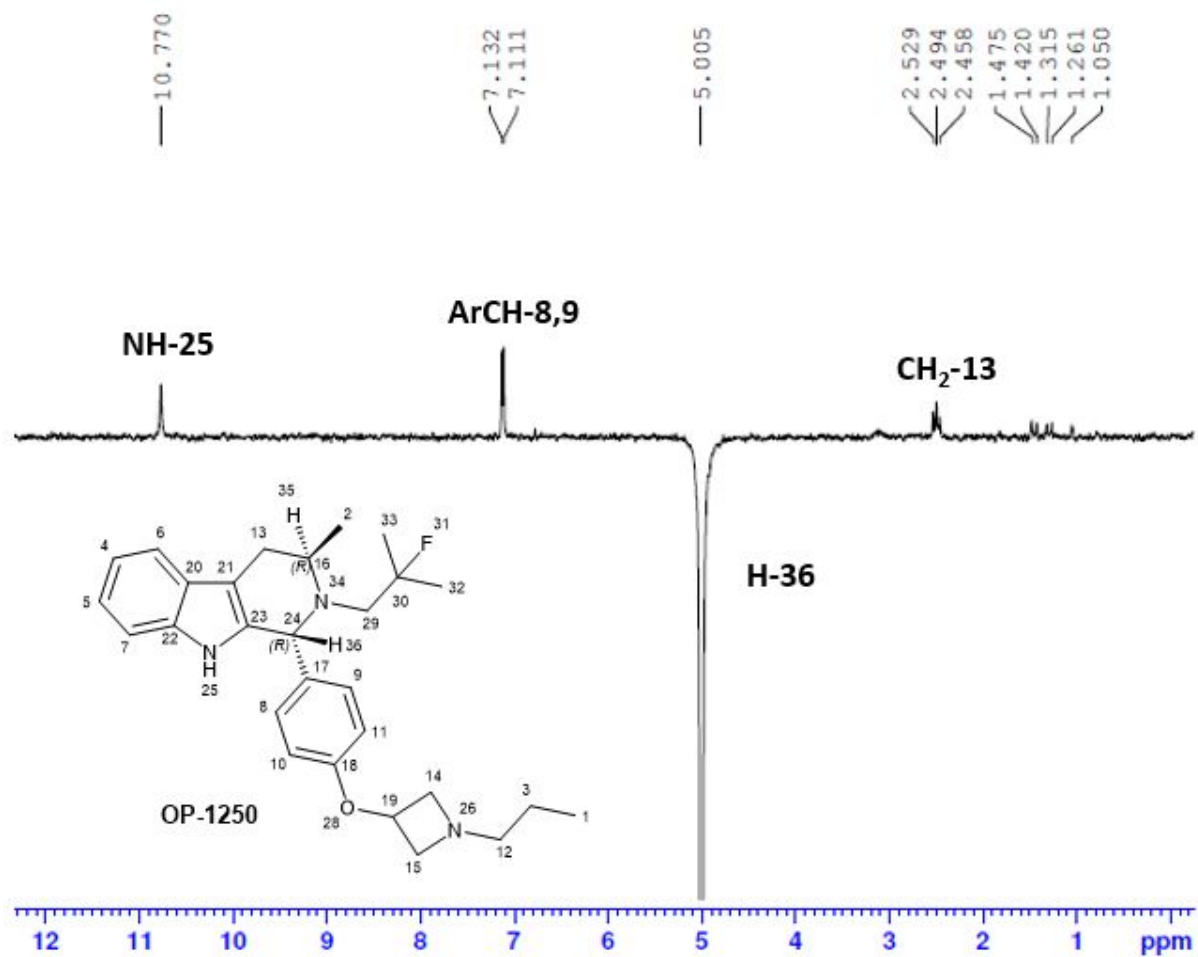


Figure S21. NOE spectra of (1*S*, 3*R*) diastereomer of compound 21

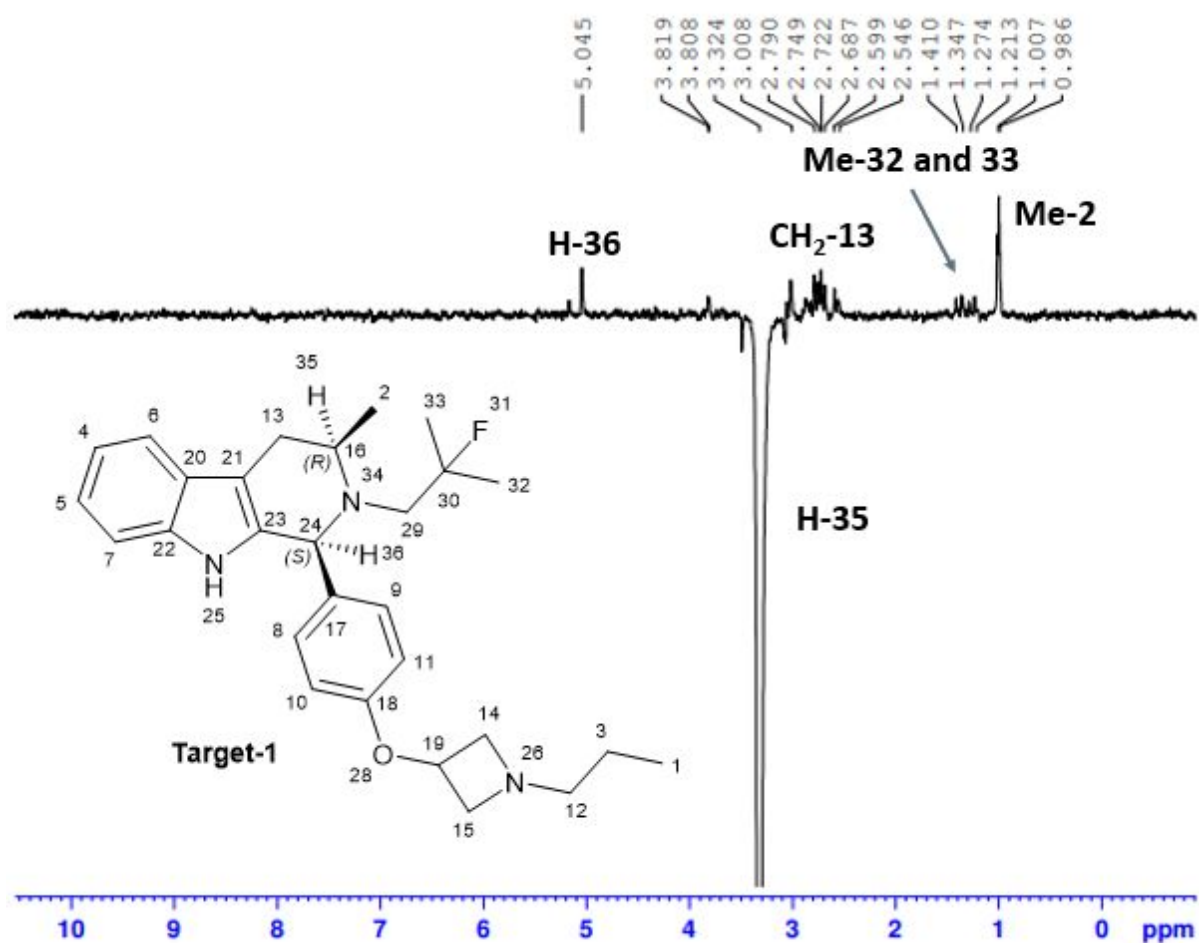


Figure S22. NOE spectra of (1*S*, 3*R*) diastereomer of compound 21

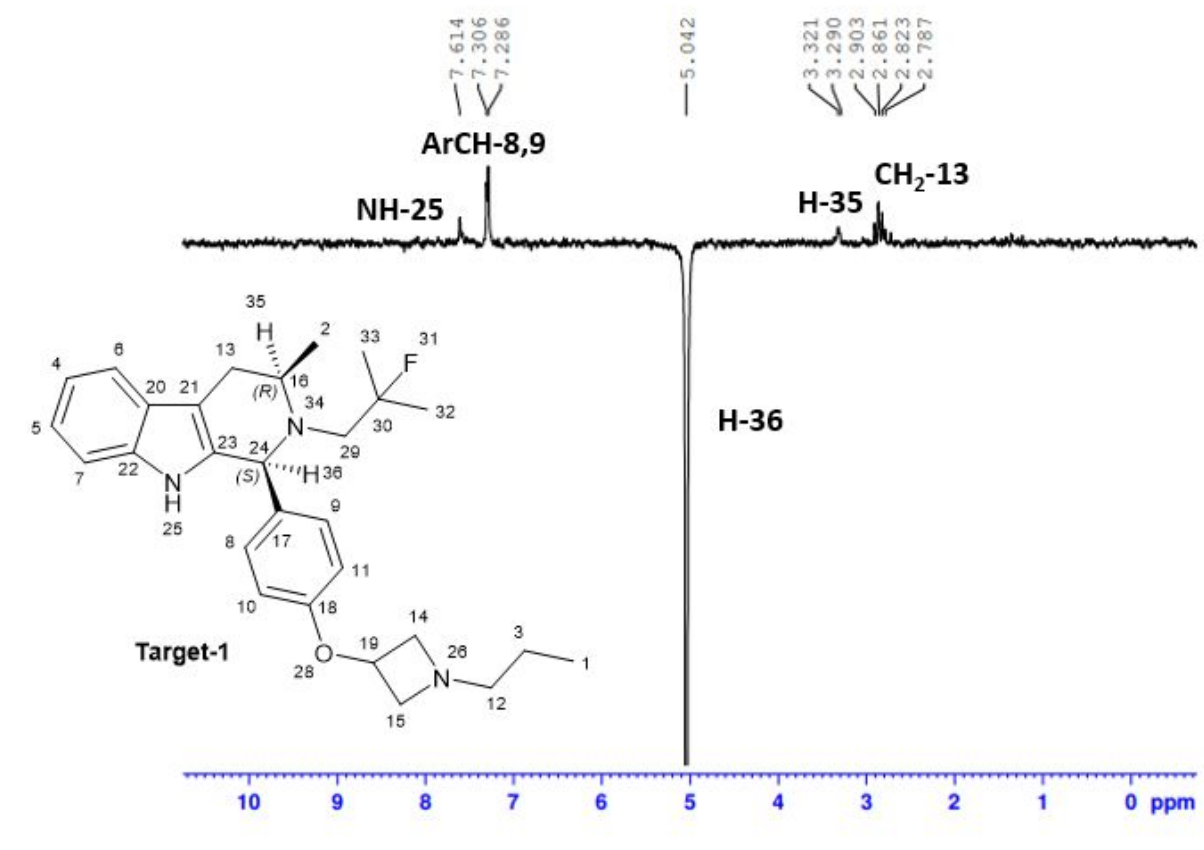
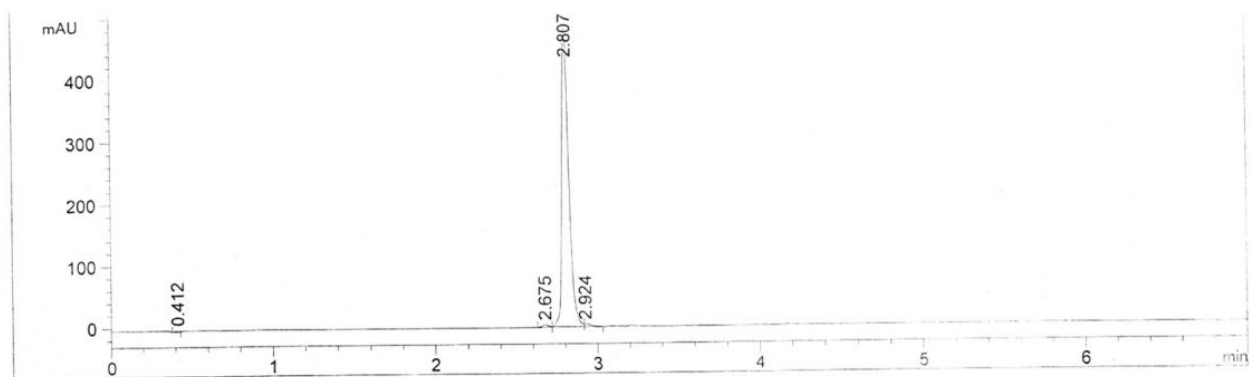


Figure S23. HPLC chromatogram of Compound 22



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	0.412	BV	0.0323	4.36399		2.03534	0.2981
2	2.675	BB	0.0377	8.48836		3.54785	0.5799
3	2.807	BV	0.0456	1439.63745		483.88589	98.3518
4	2.924	VB	0.0392	11.27317		4.21909	0.7702

Figure S24. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 22

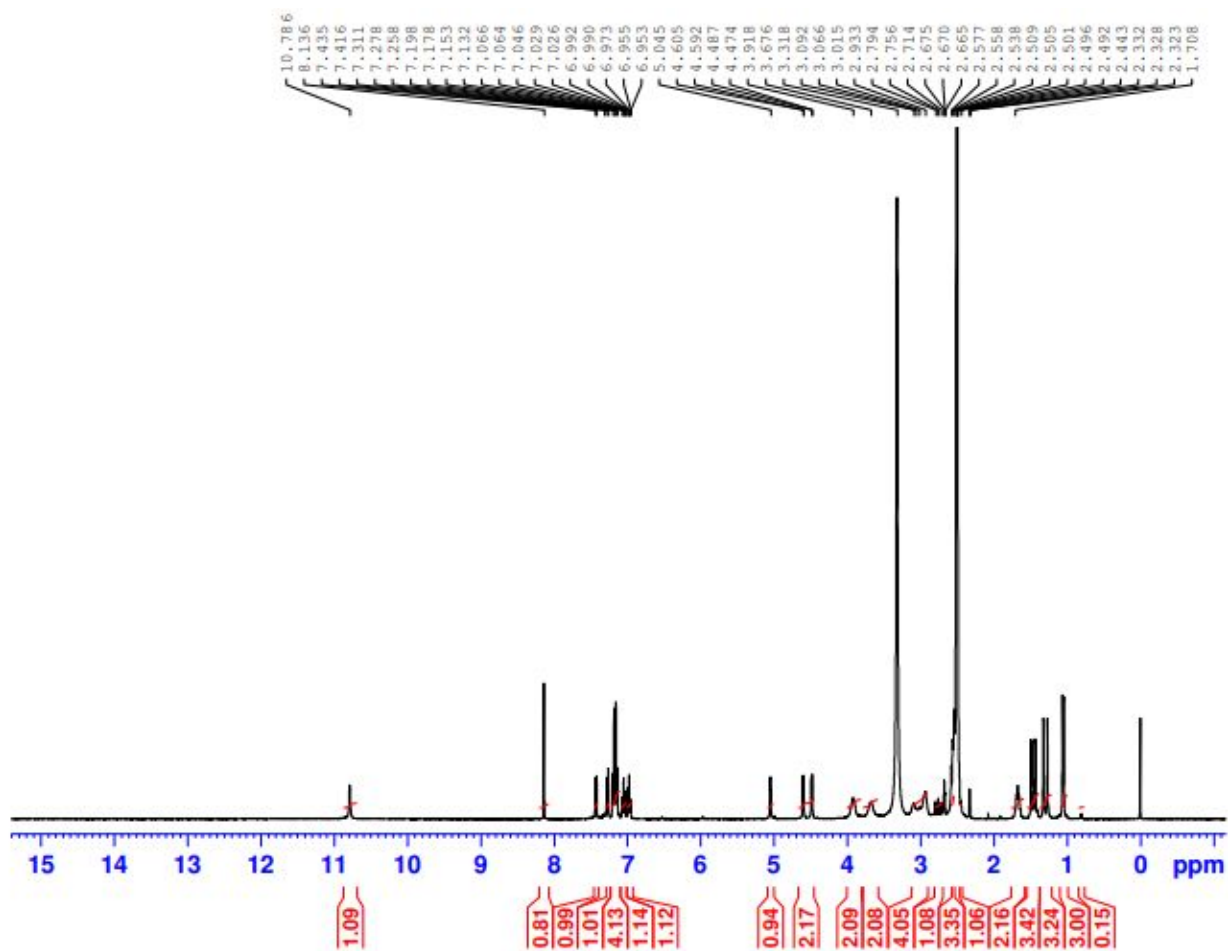


Figure S25. HRMS spectrum of Compound 22

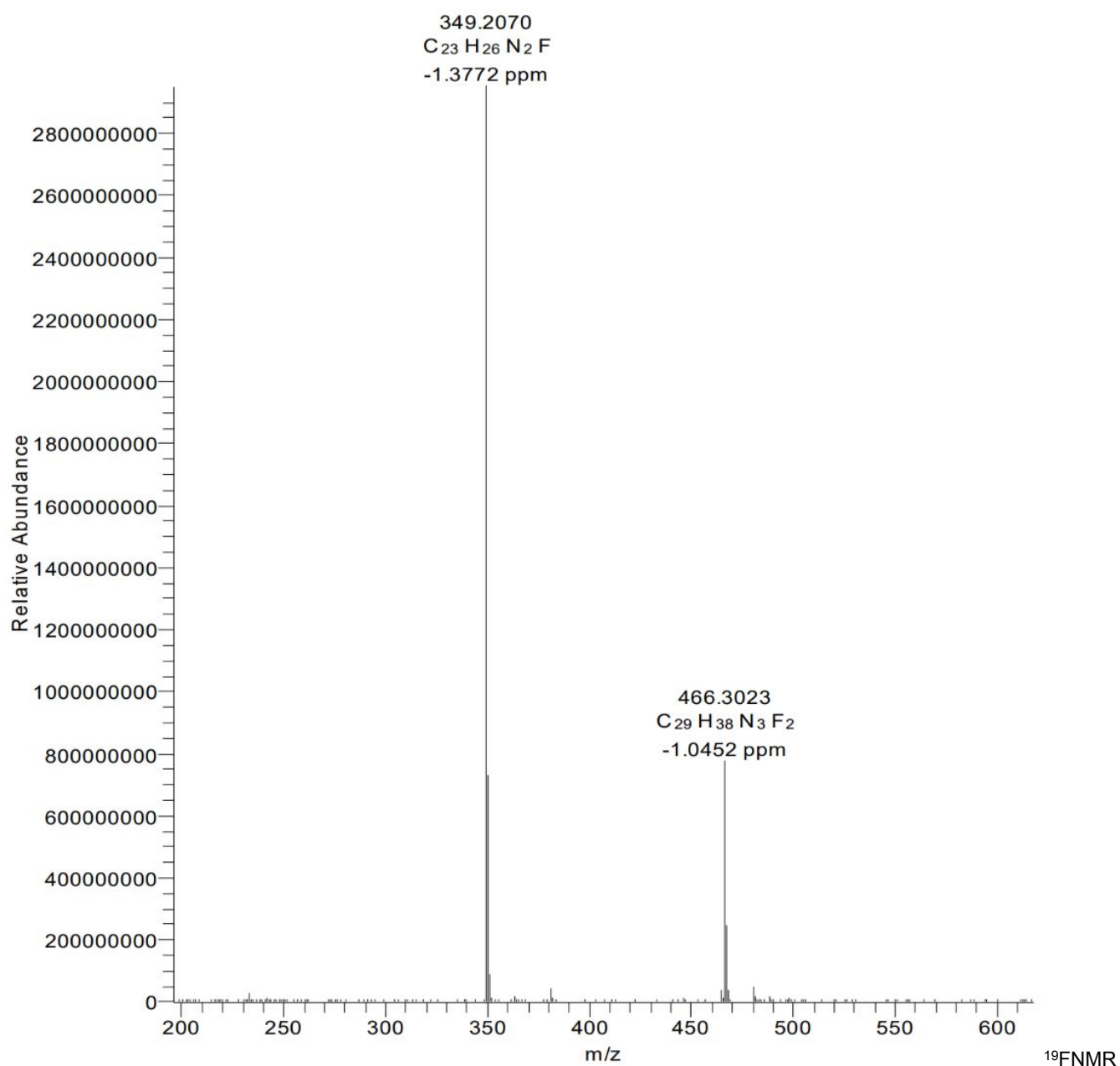


Figure S26. ^{19}F -NMR spectrum of Compound 22

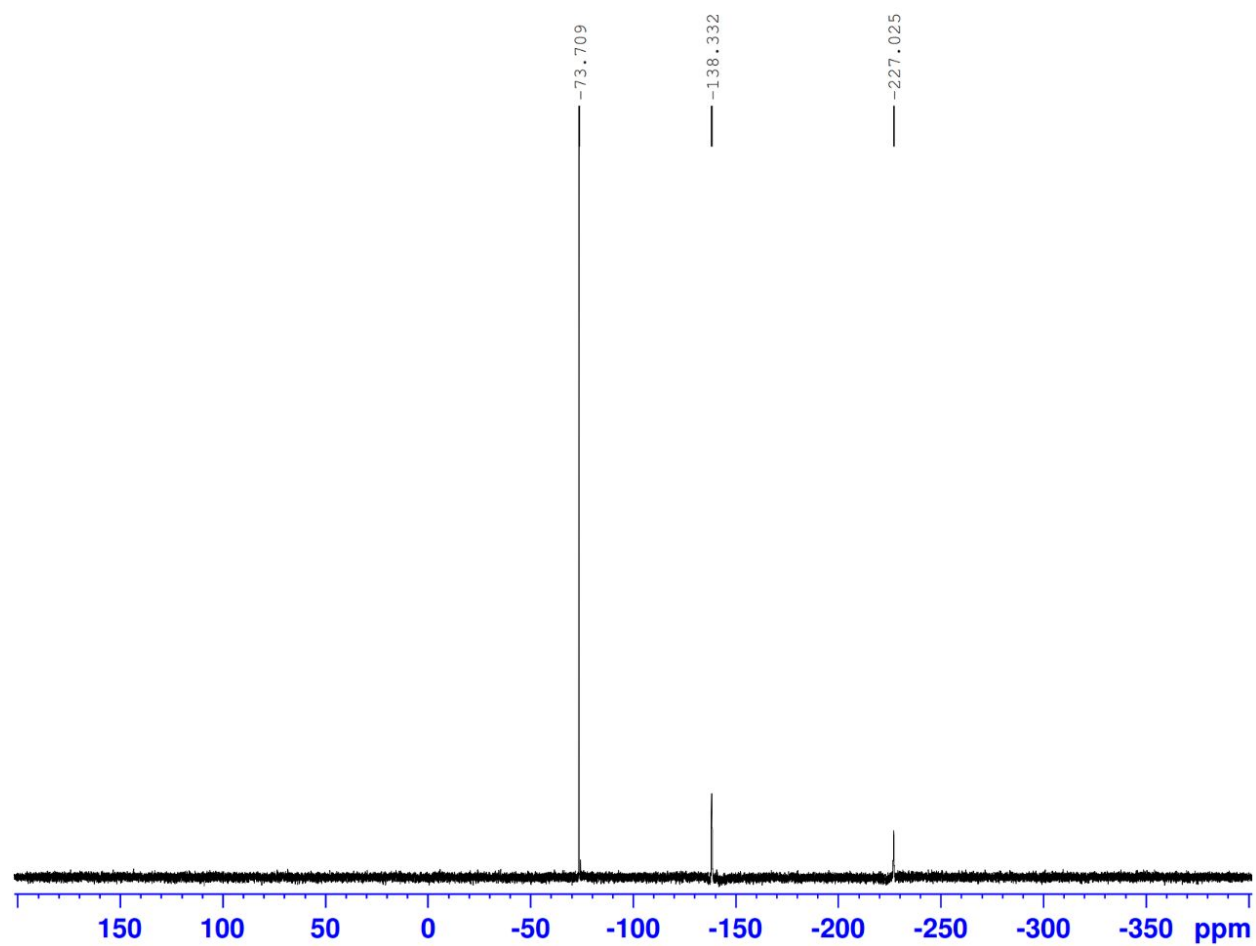


Figure S27. ^{13}C -NMR spectrum of Compound 22

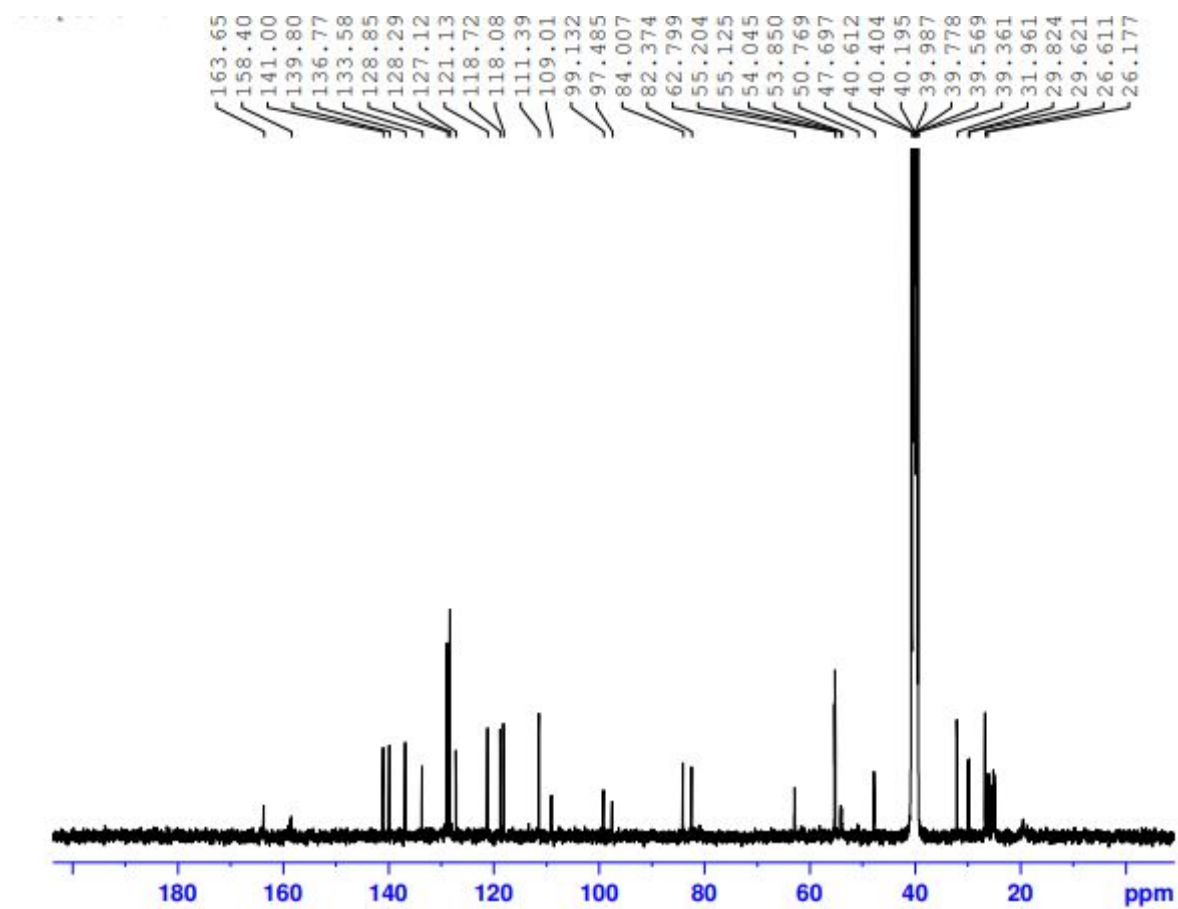
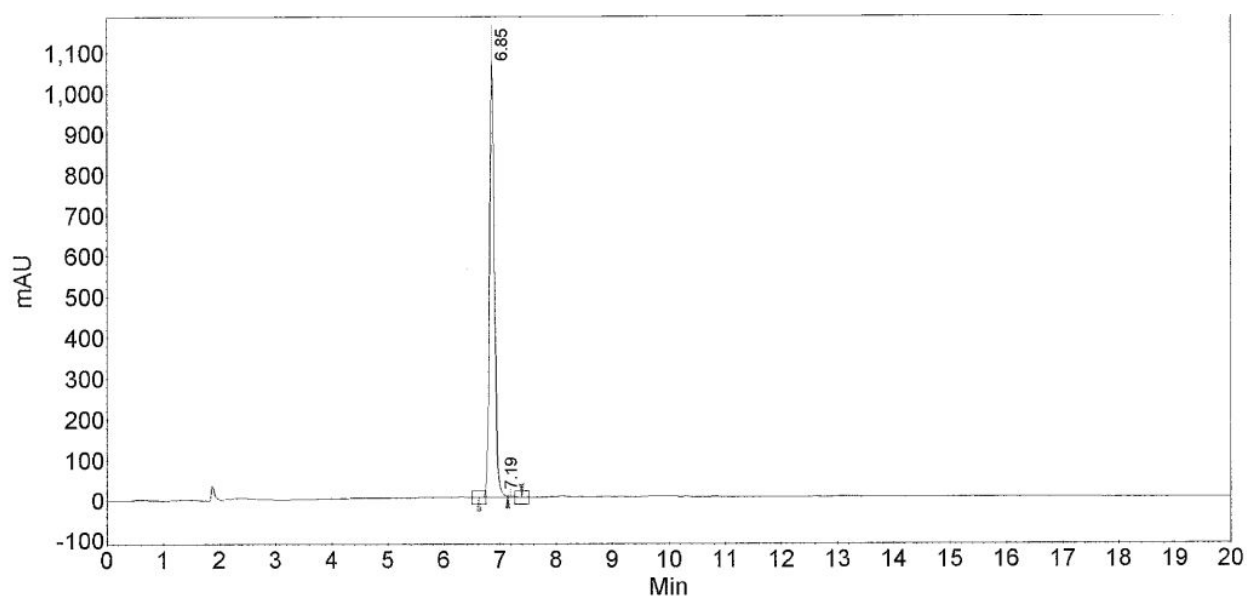


Figure S28. HPLC chromatogram of Compound 23



Peak	Index	Name	Time [Min]	Height [mAU]	Area [mAU.Sec]	Area [mAU.Min]	Area % [%]
	1	UNKNOWN	6.85	1072.5	6788.4	113.1	99.695
	2	UNKNOWN	7.19	2.9	20.8	0.3	0.305
	Total			1075.4	6809.2	113.5	100.000

Figure S29. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 23

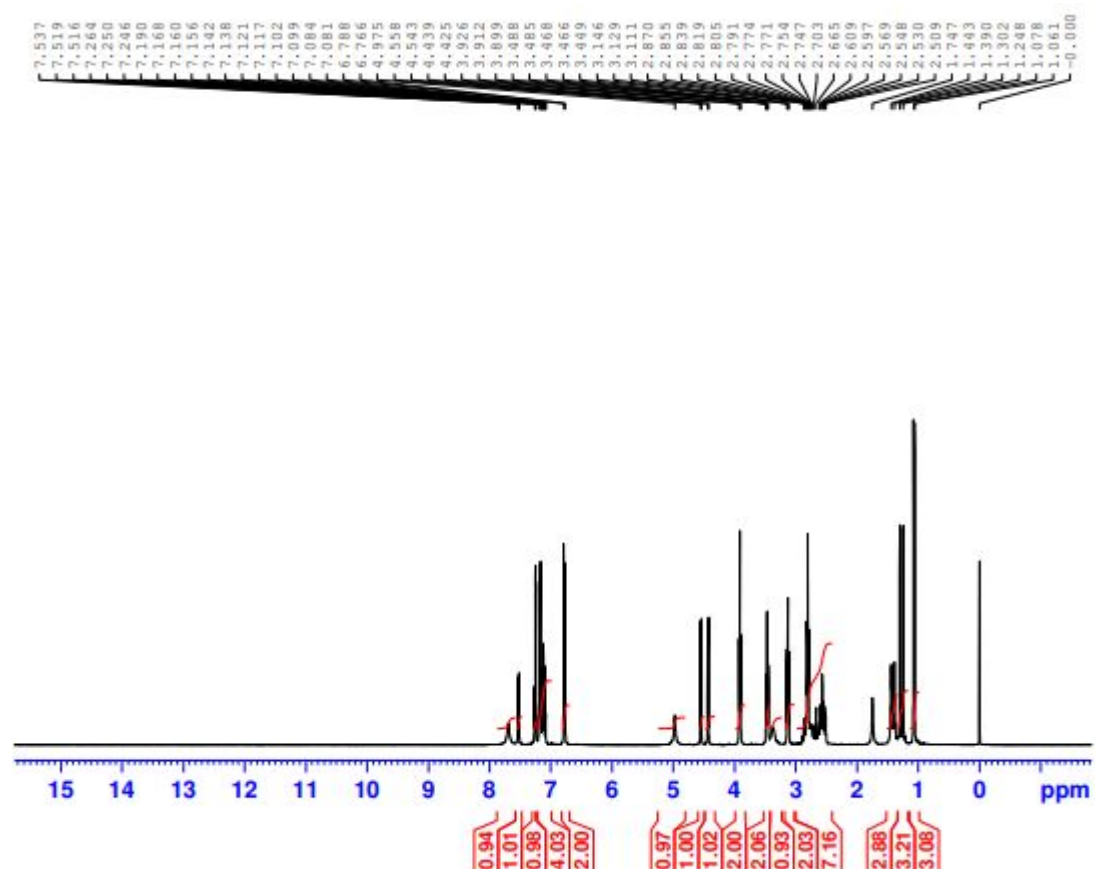


Figure S30. HRMS spectrum of Compound 23

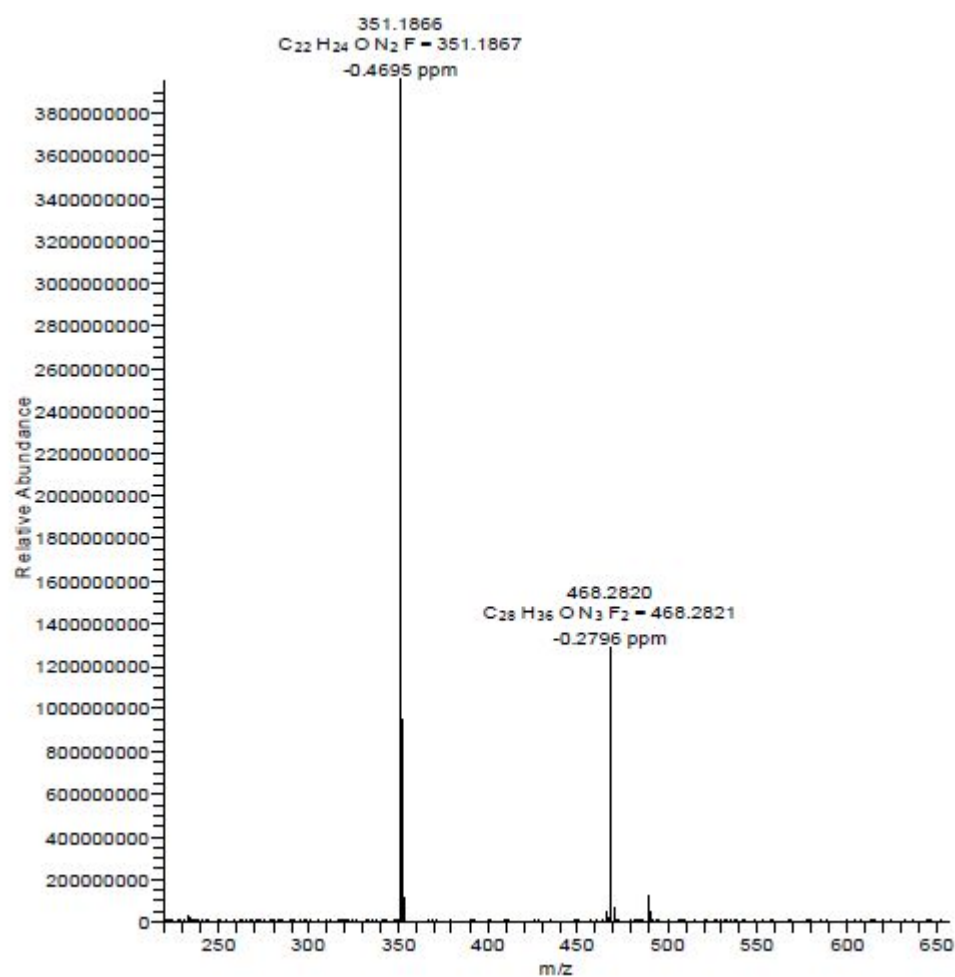


Figure S31. ^{19}F -NMR spectrum of Compound 23

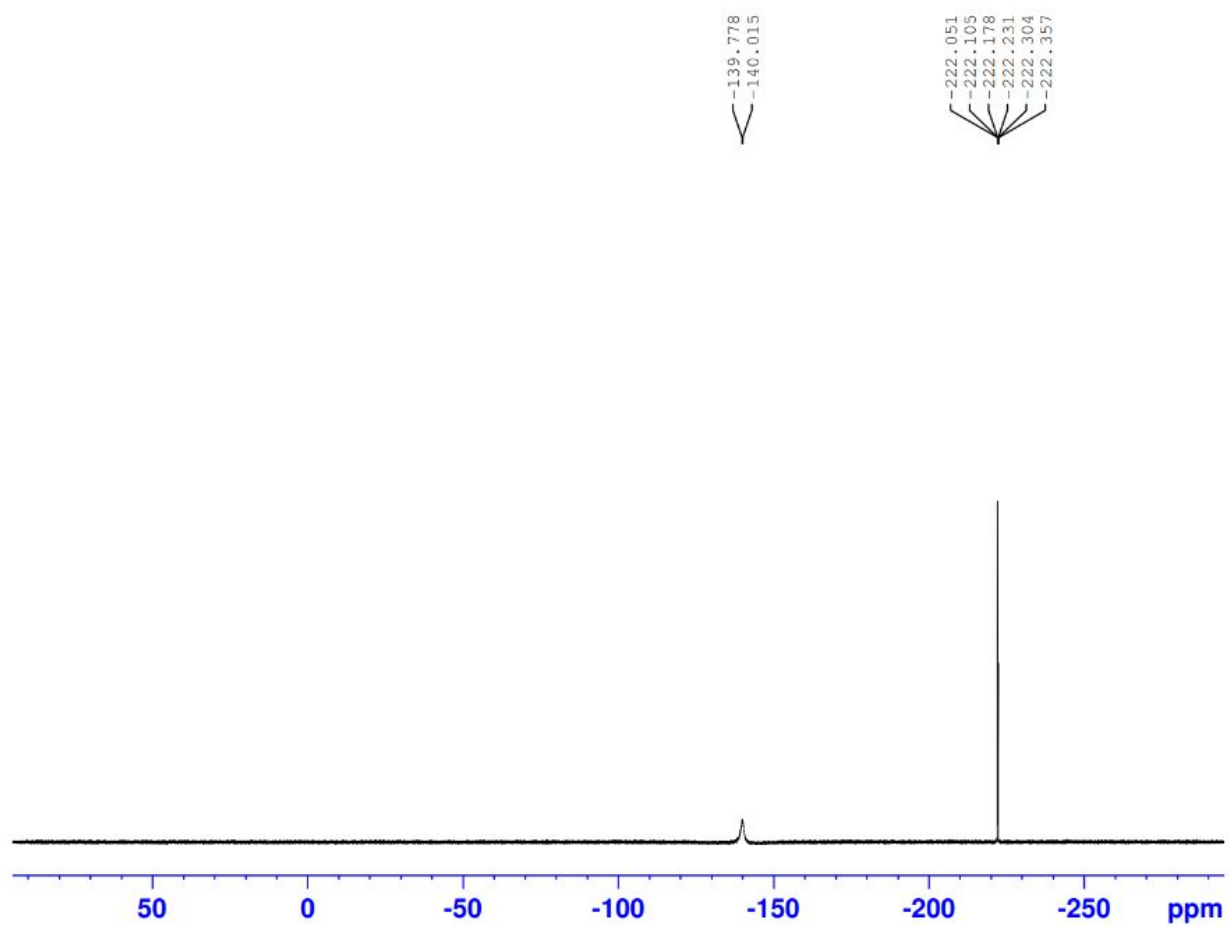


Figure S32. ^{13}C -NMR spectrum of Compound 23

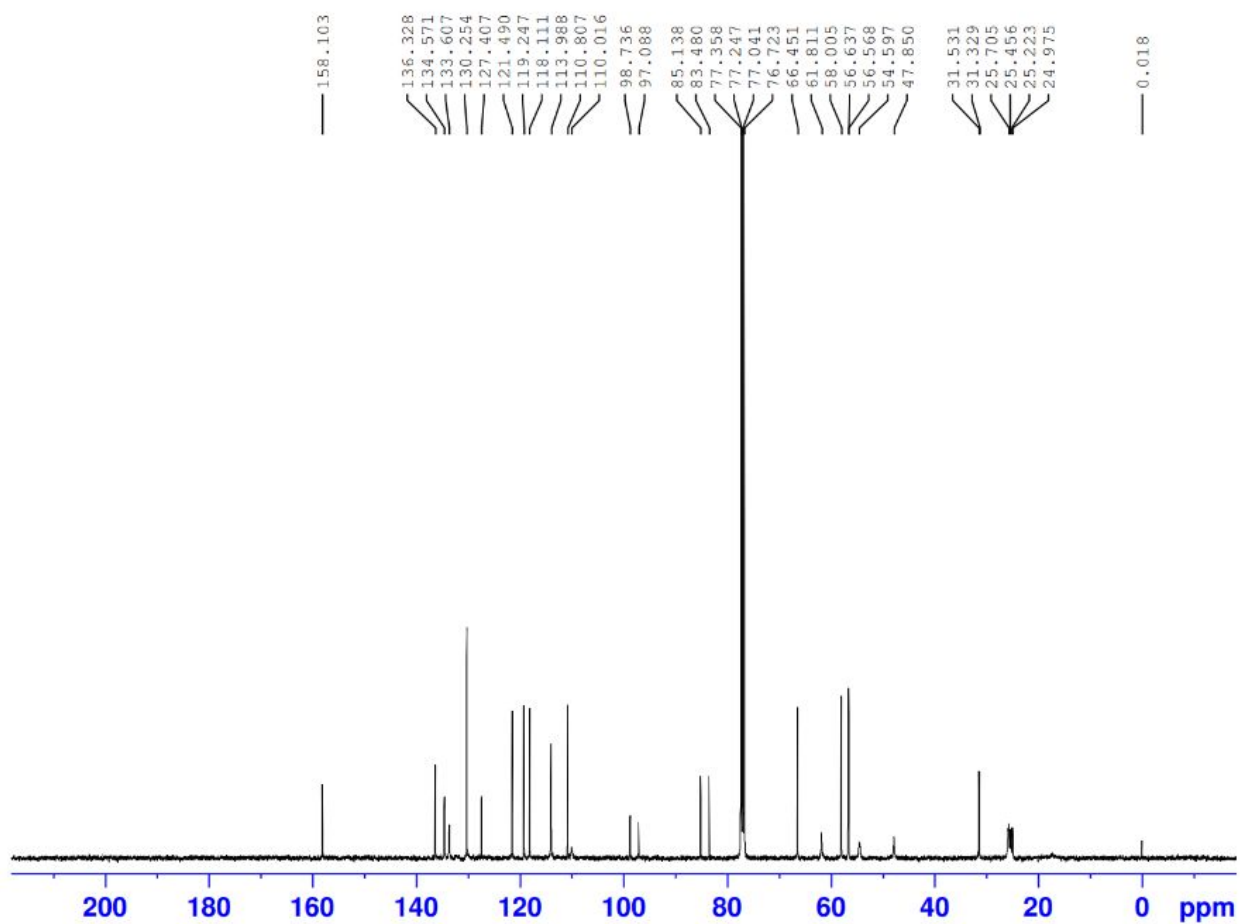
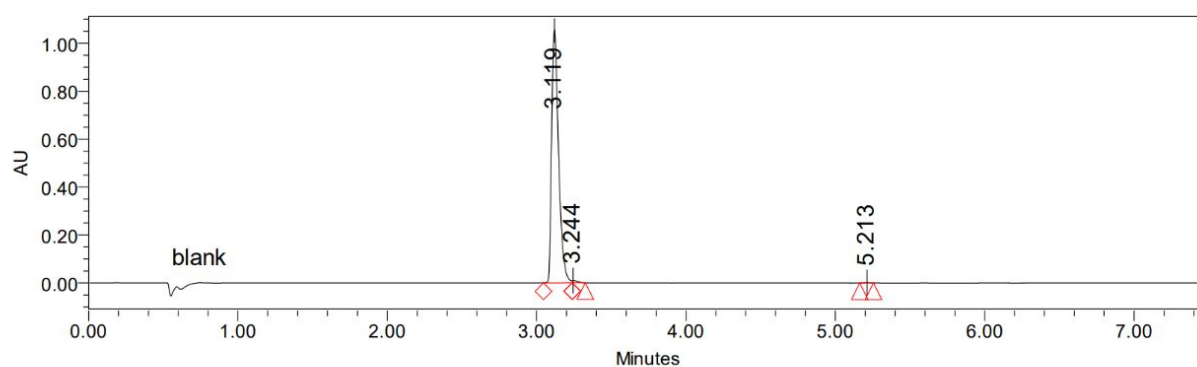


Figure S33. HPLC chromatogram of Compound 24



Peak Results

	RT	Area	% Area
1	3.119	3426060	99.20
2	3.244	24202	0.70
3	5.213	3377	0.10

Figure S34. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 24

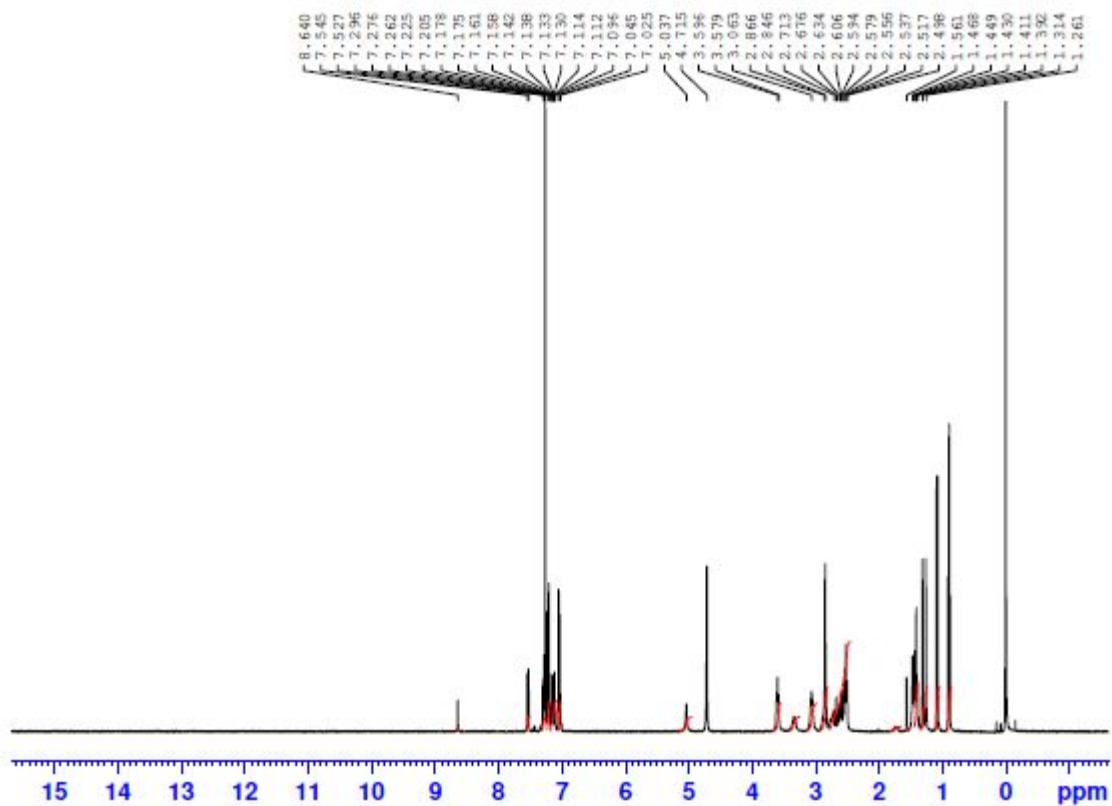


Figure S35. HRMS spectrum of Compound 24

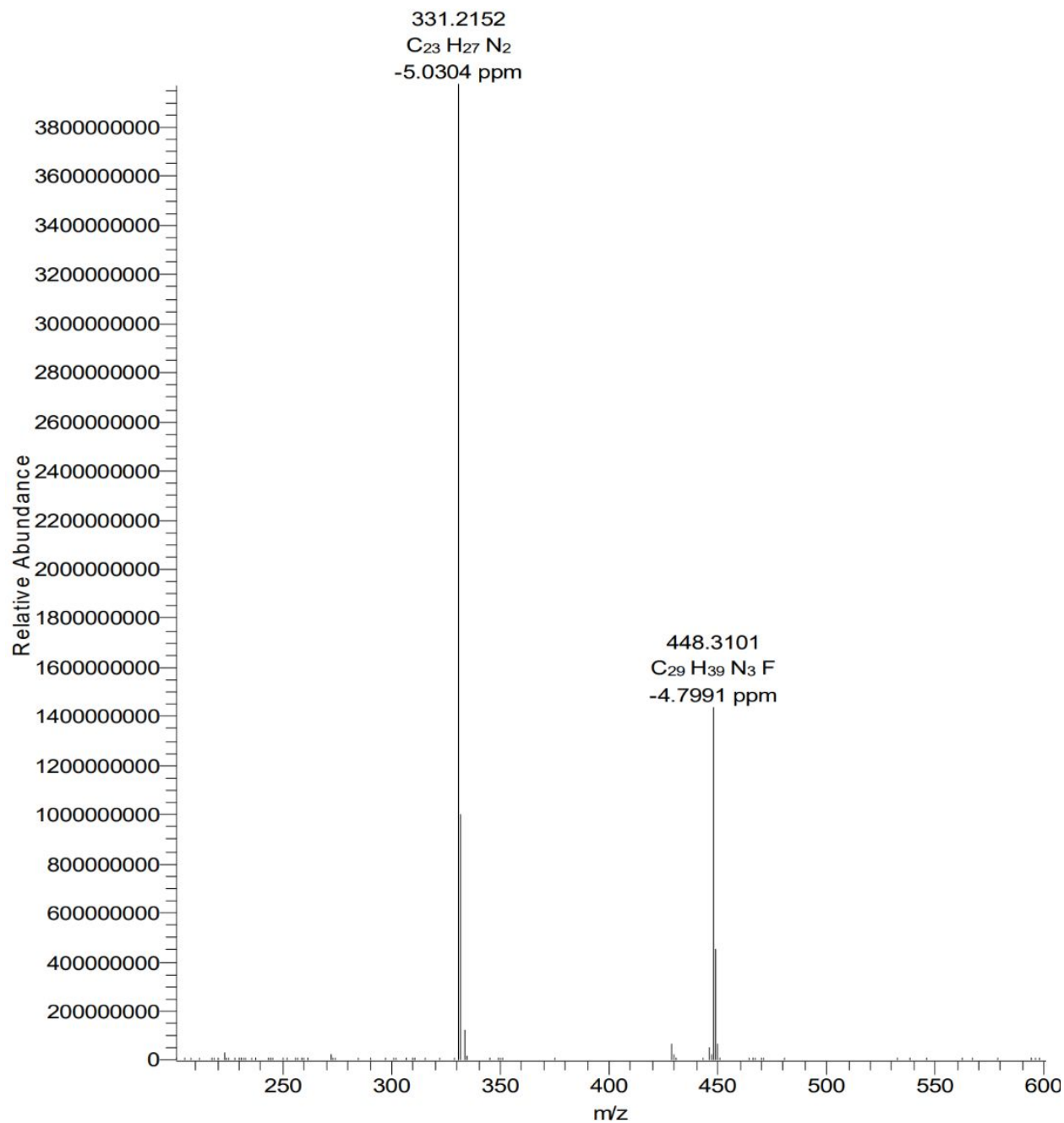


Figure S36. ^{19}F -NMR spectrum of Compound 24

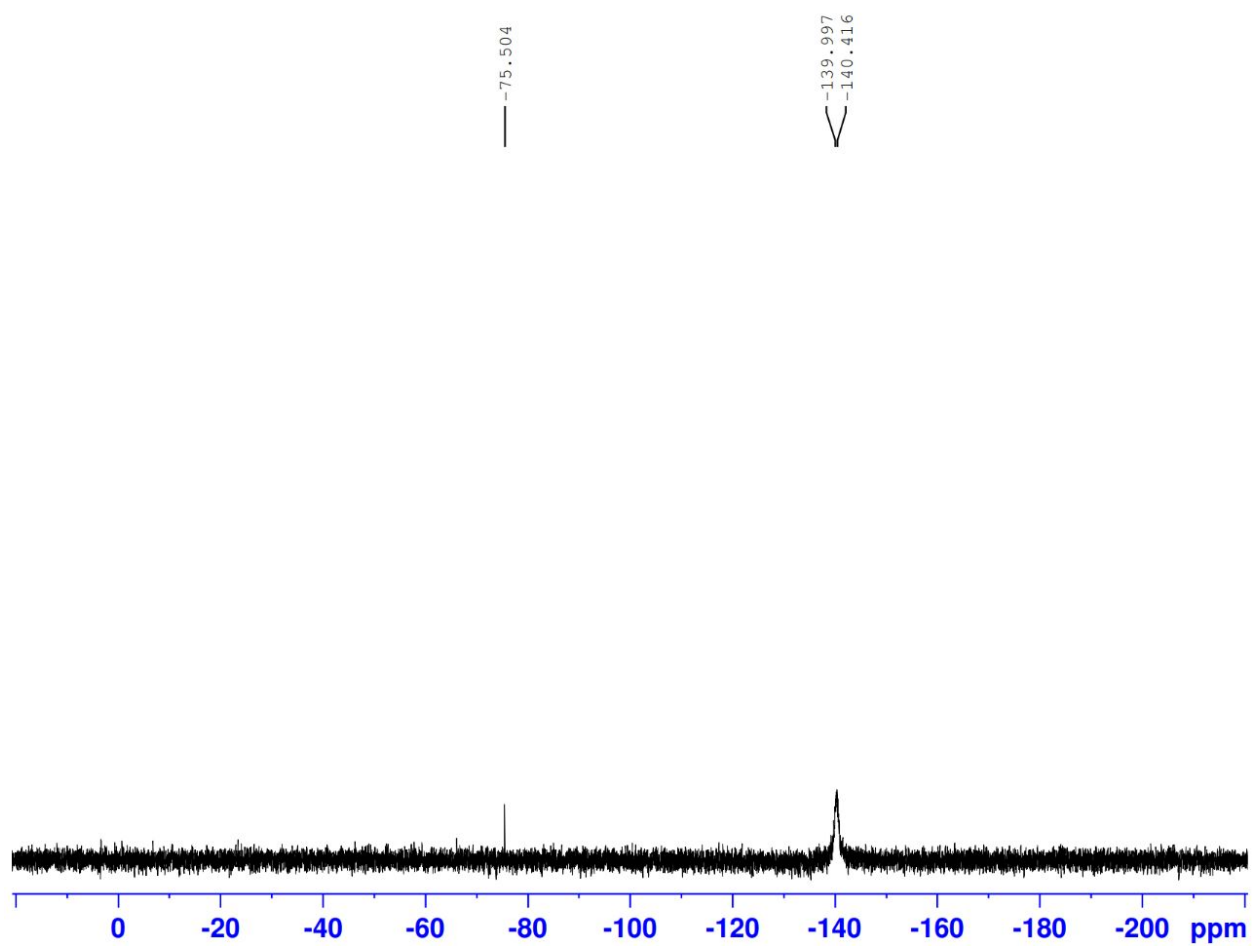


Figure S37. ^{13}C -NMR spectrum of Compound 24

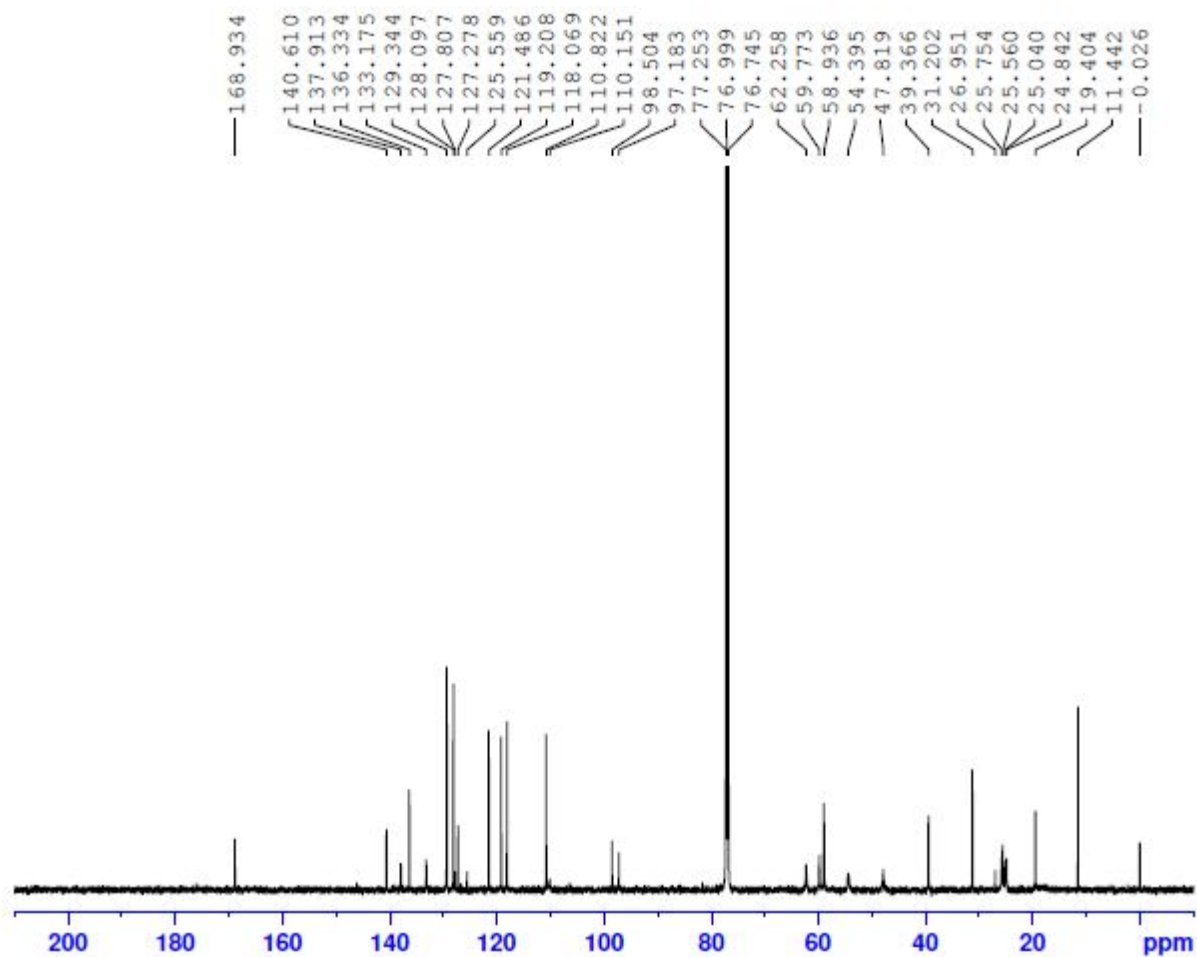
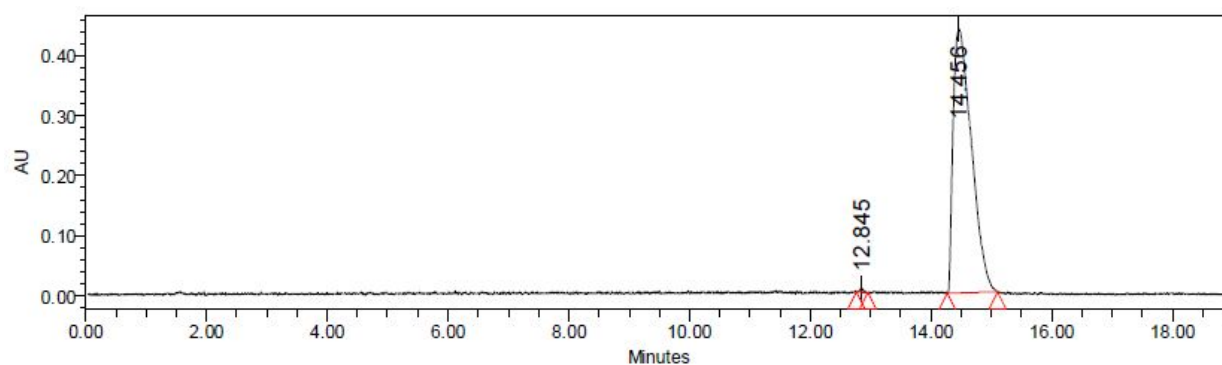


Figure S38. HPLC chromatogram of Compound 25



Peak Results

	RT	Area	Height	Purity1 Angle	Purity1 Threshold	% Area
1	12.845	27608	7336	20.444	24.051	0.30
2	14.456	9237255	438805	0.356	0.577	99.70

Figure S39. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 25

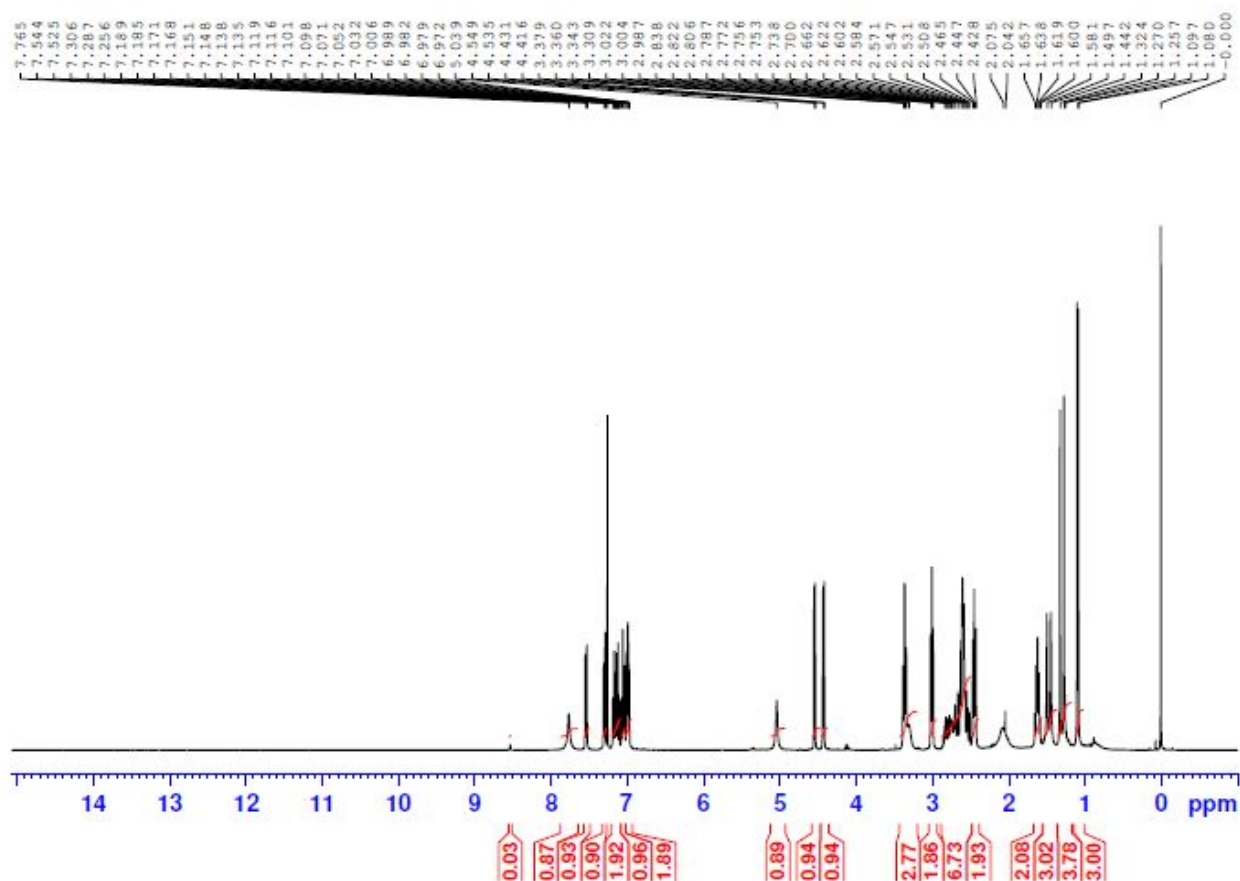


Figure S40. HRMS spectrum of Compound 25

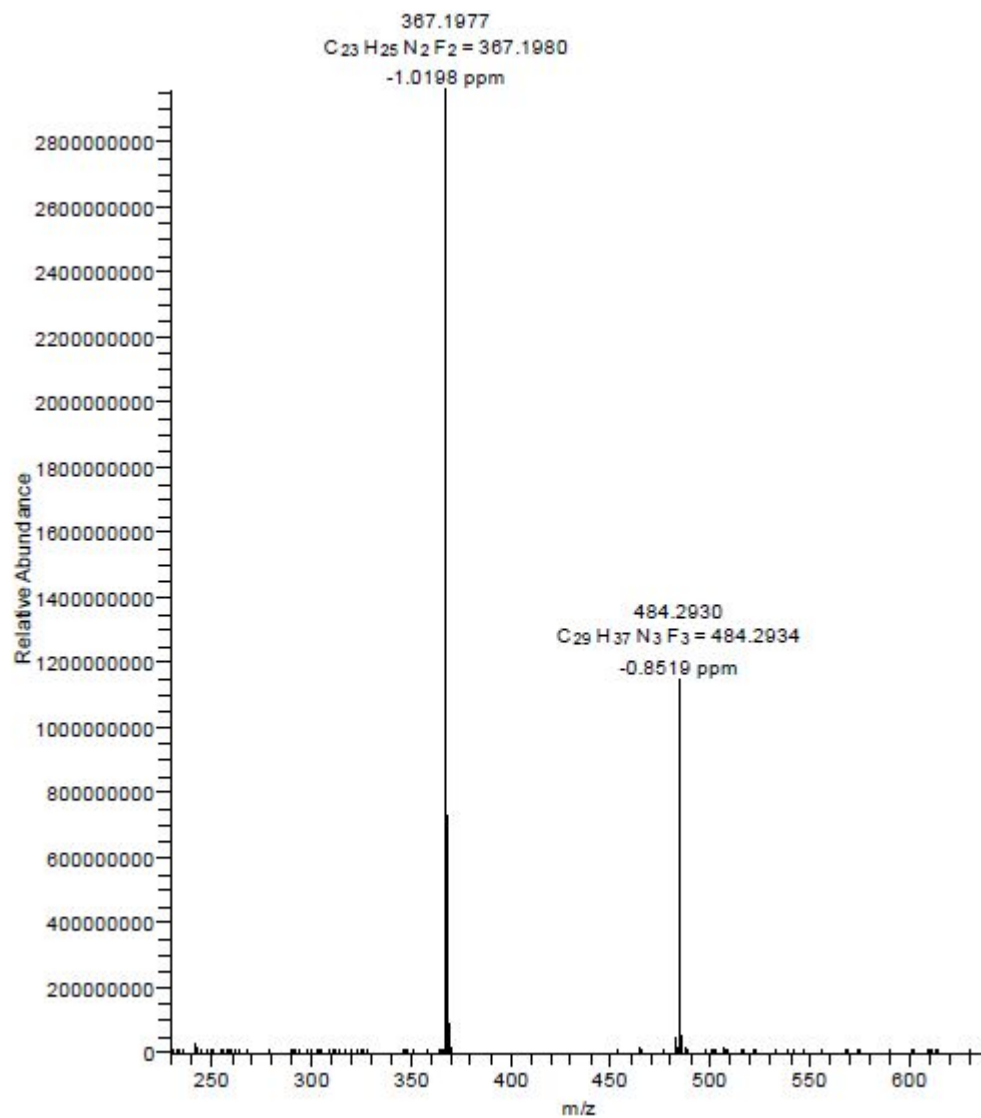


Figure S41. ^{19}F -NMR spectrum of Compound 25

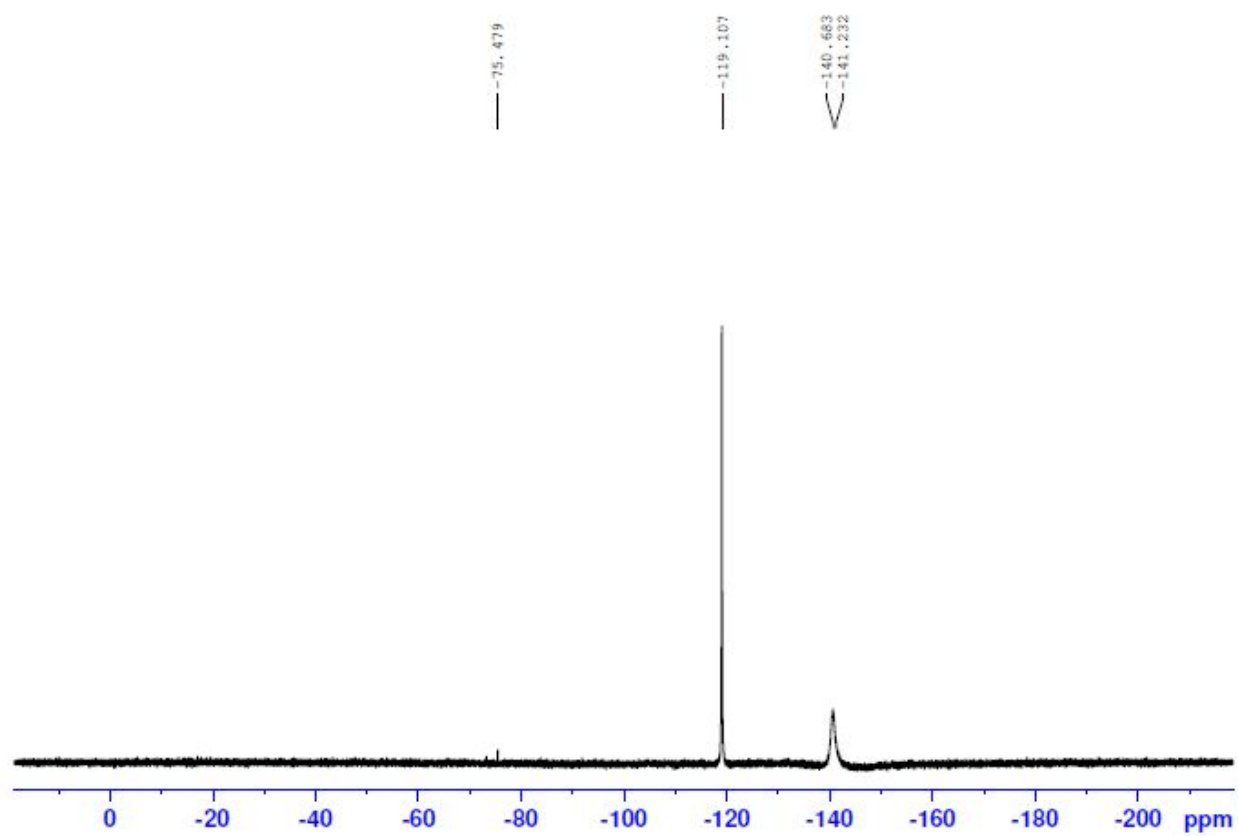


Figure S42. ^{13}C -NMR spectrum of Compound 25

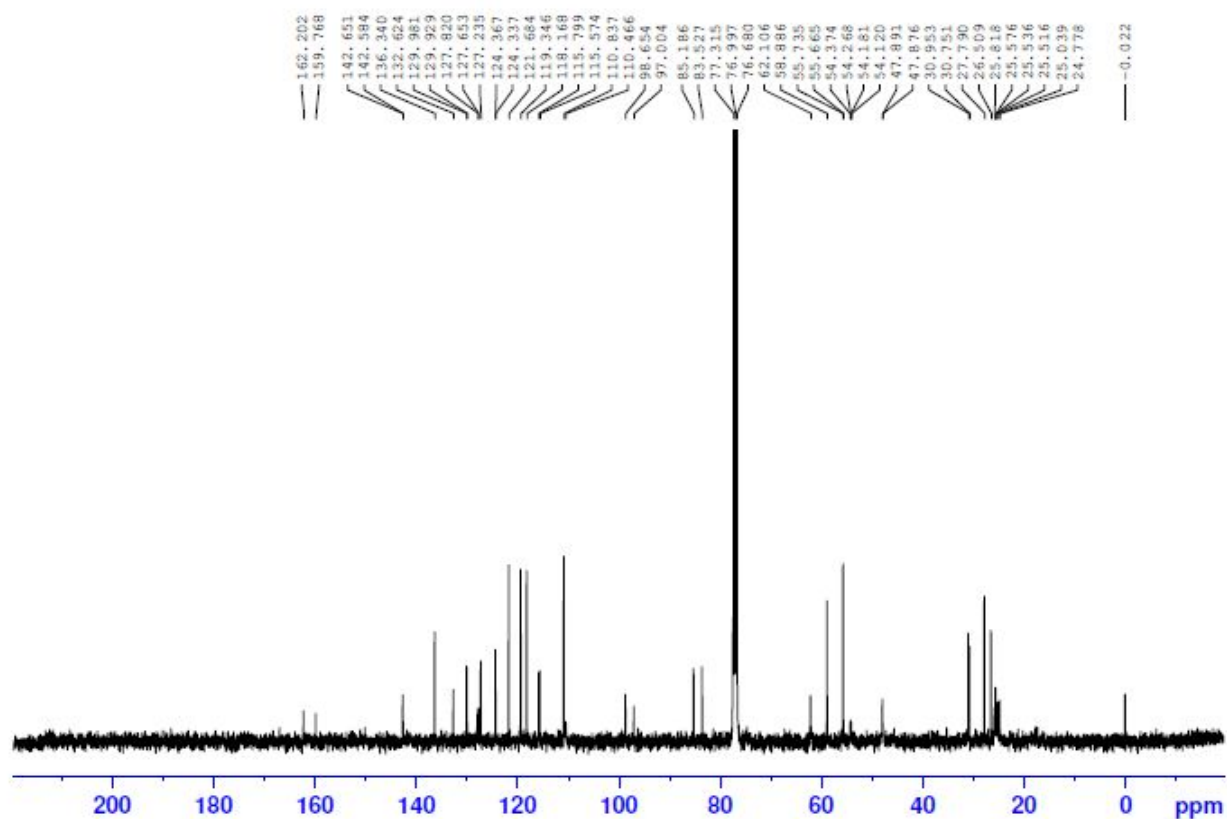


Figure S43. HPLC chromatogram of Compound 26

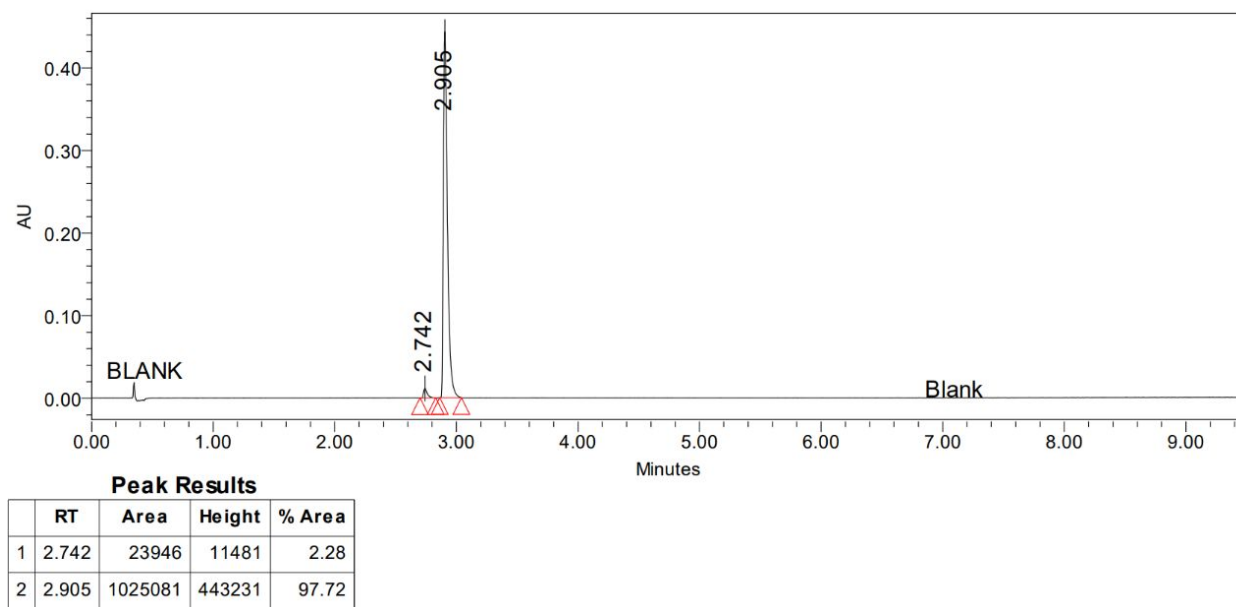


Figure S44. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 26

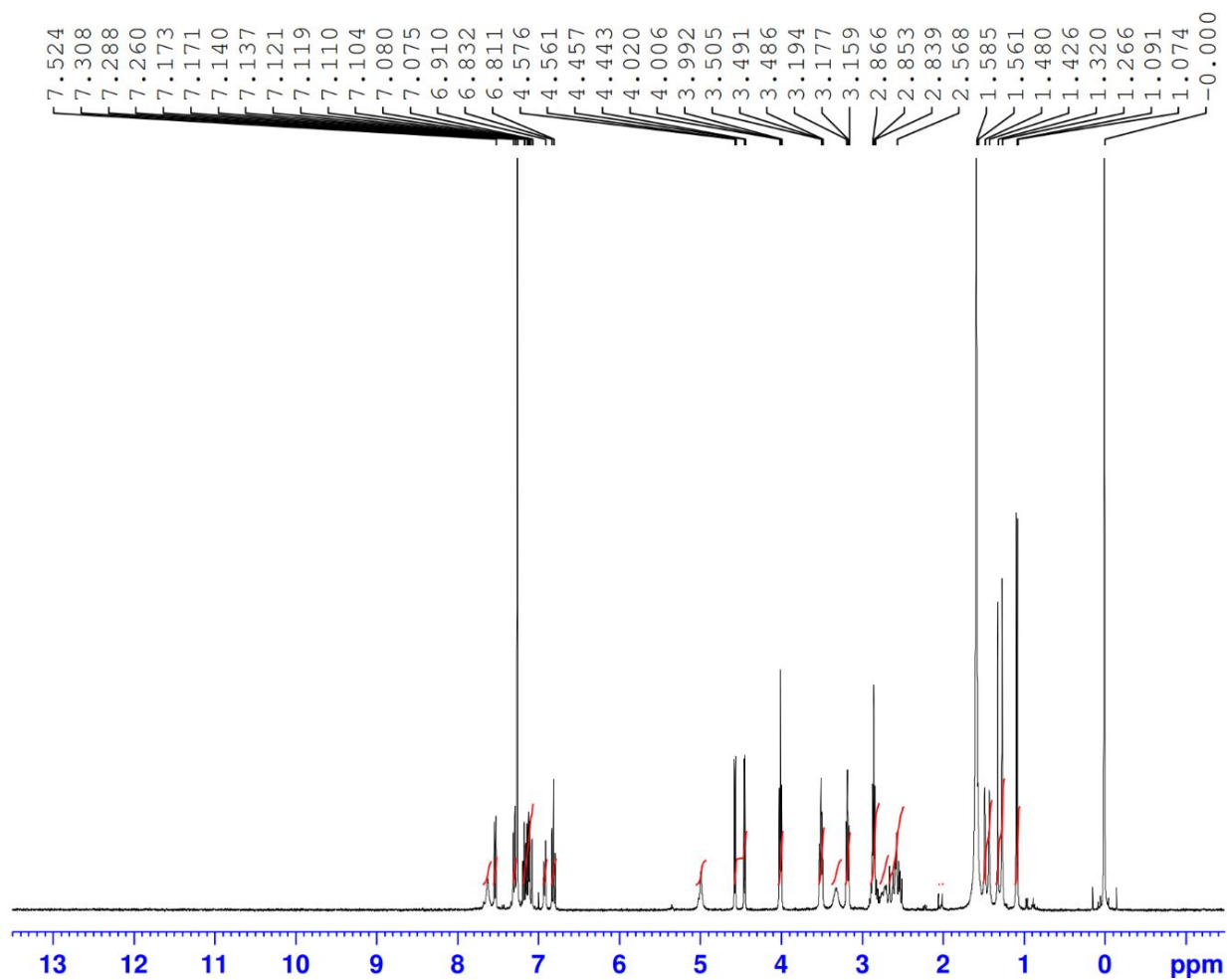


Figure S45. HRMS spectrum of Compound 26

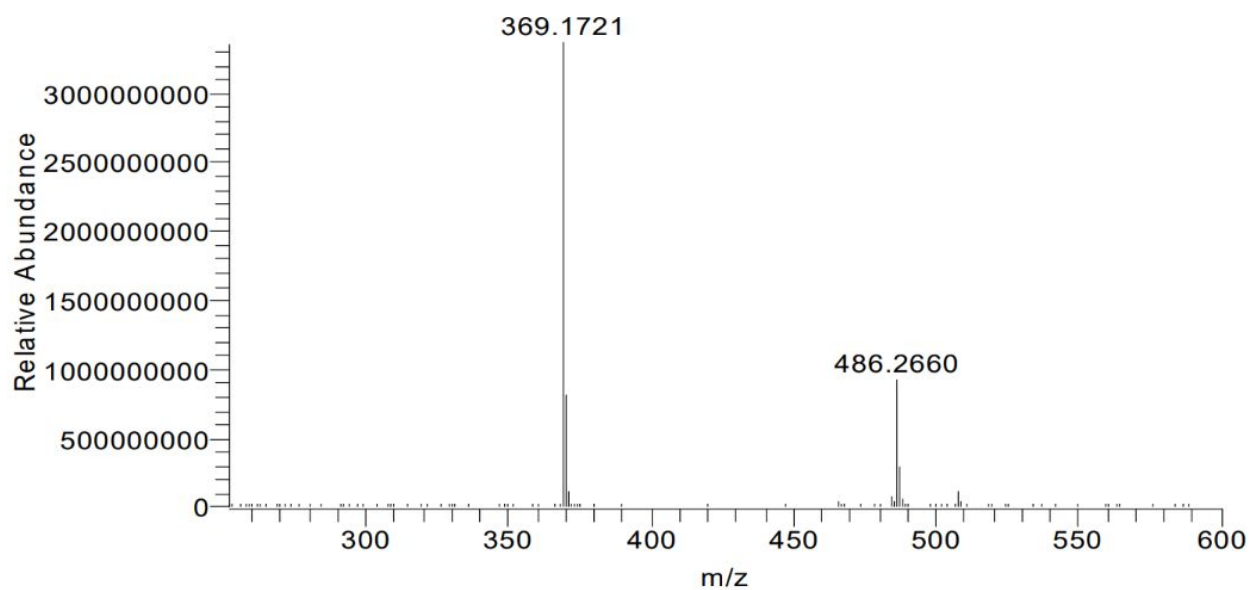


Figure S46. ^{19}F -NMR spectrum of Compound 26

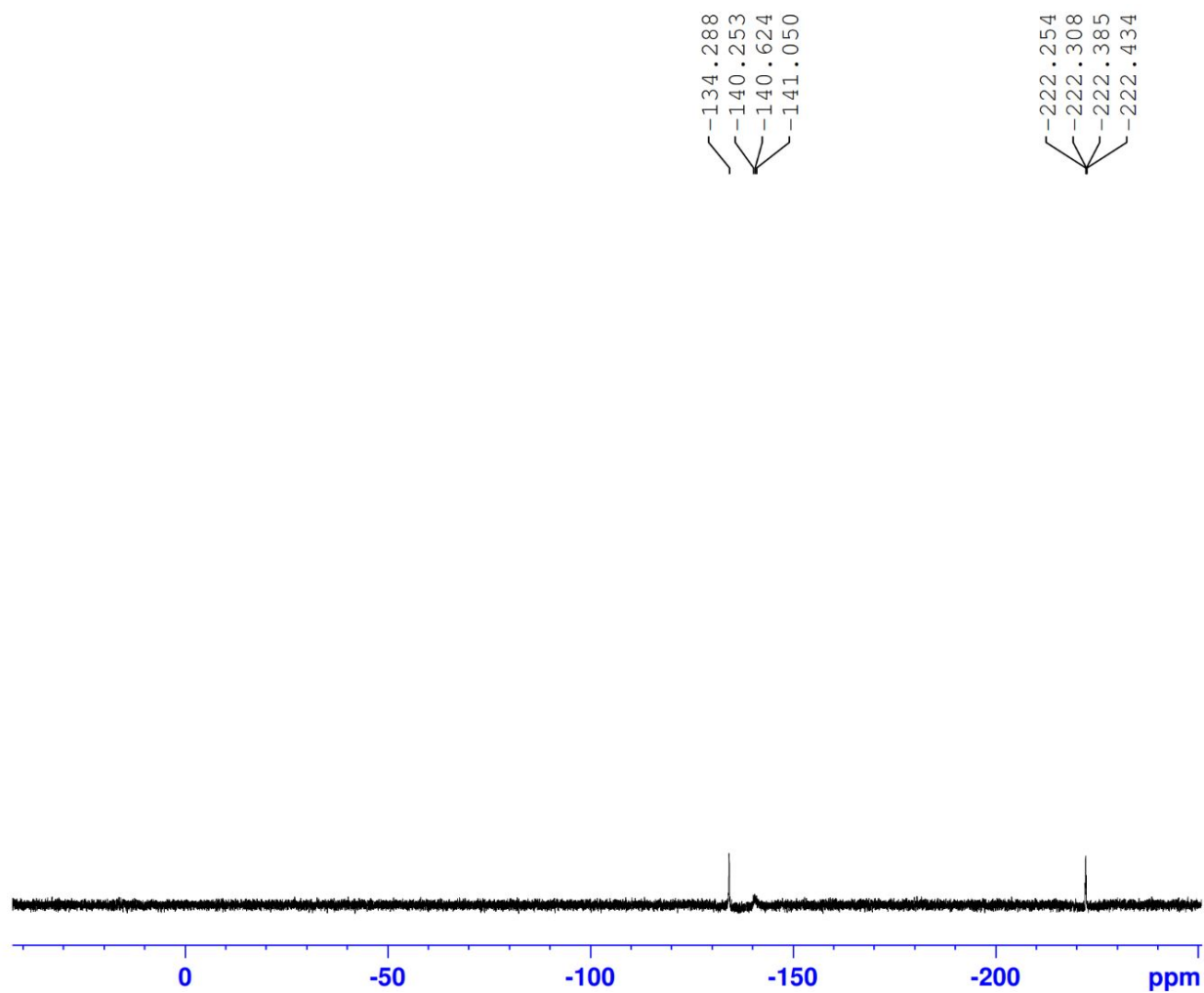


Figure S47. ^{13}C -NMR spectrum of Compound 26

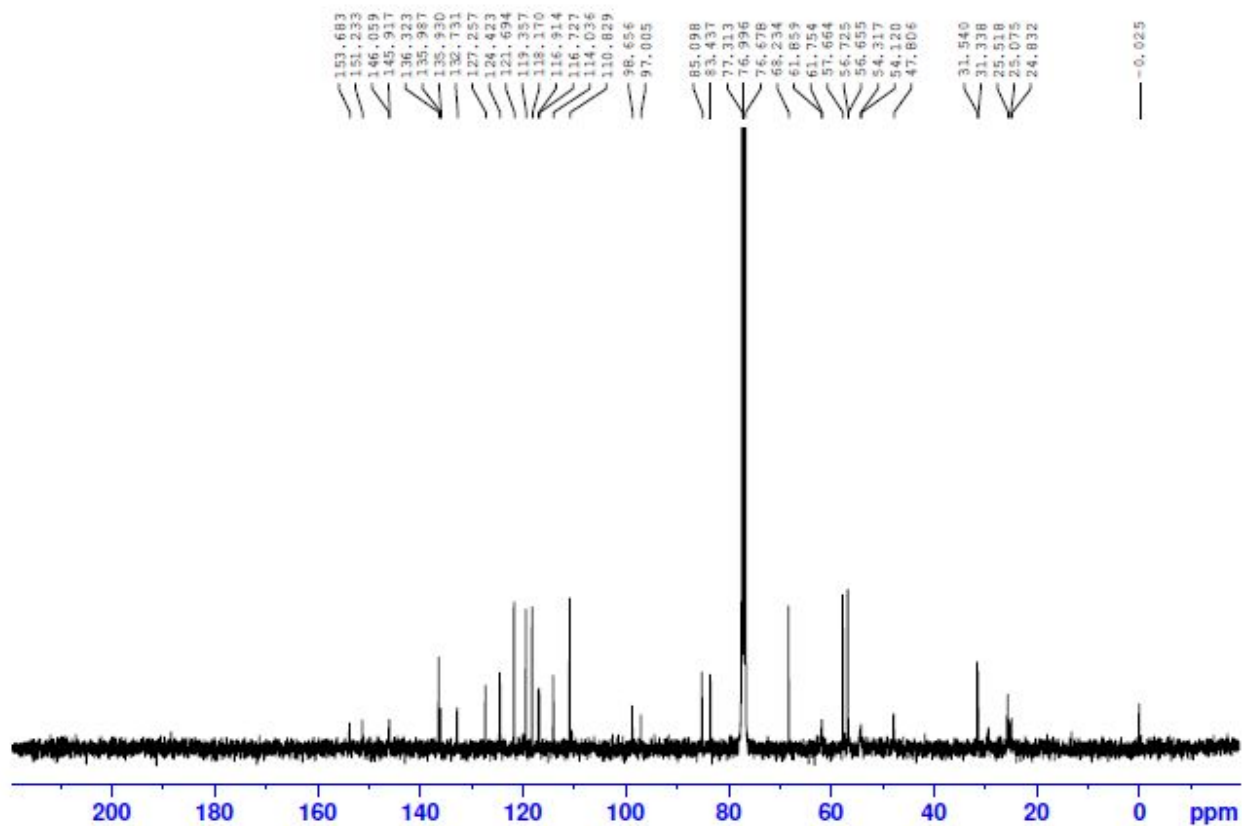
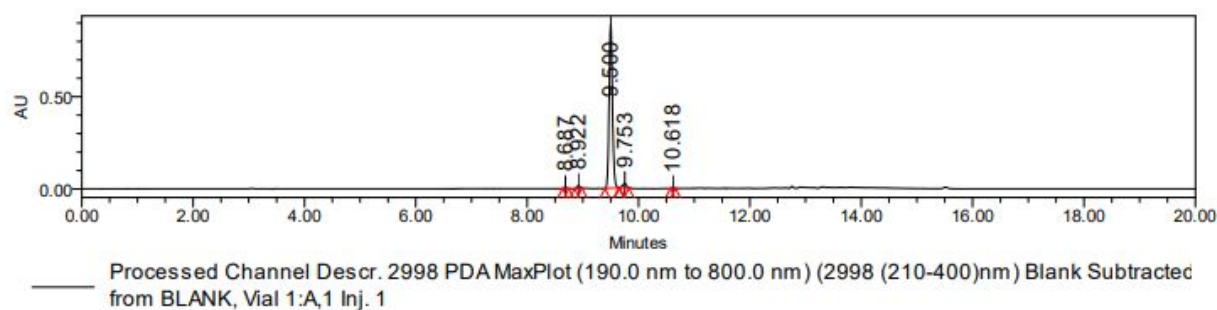


Figure S48. HPLC chromatogram of Compound 27



**Processed Channel: 2998 PDA
MaxPlot (190.0 nm to 800.0 nm)
(2998 (210-400)nm) Blank
Subtracted from BLANK, Vial 1:A,1
Inj. 1**

	Retention Time (min)	Area	Purity 1 Angle	Purity 1 Threshold	% Area
1	8.687	15978	4.396	5.575	0.41
2	8.922	53792	2.116	2.606	1.38
3	9.500	3697726	0.103	0.307	95.05
4	9.753	112326	1.352	1.751	2.89

Figure S49. $^1\text{H-NMR}$ (400 MHz, CDCl_3) spectrum of Compound 27

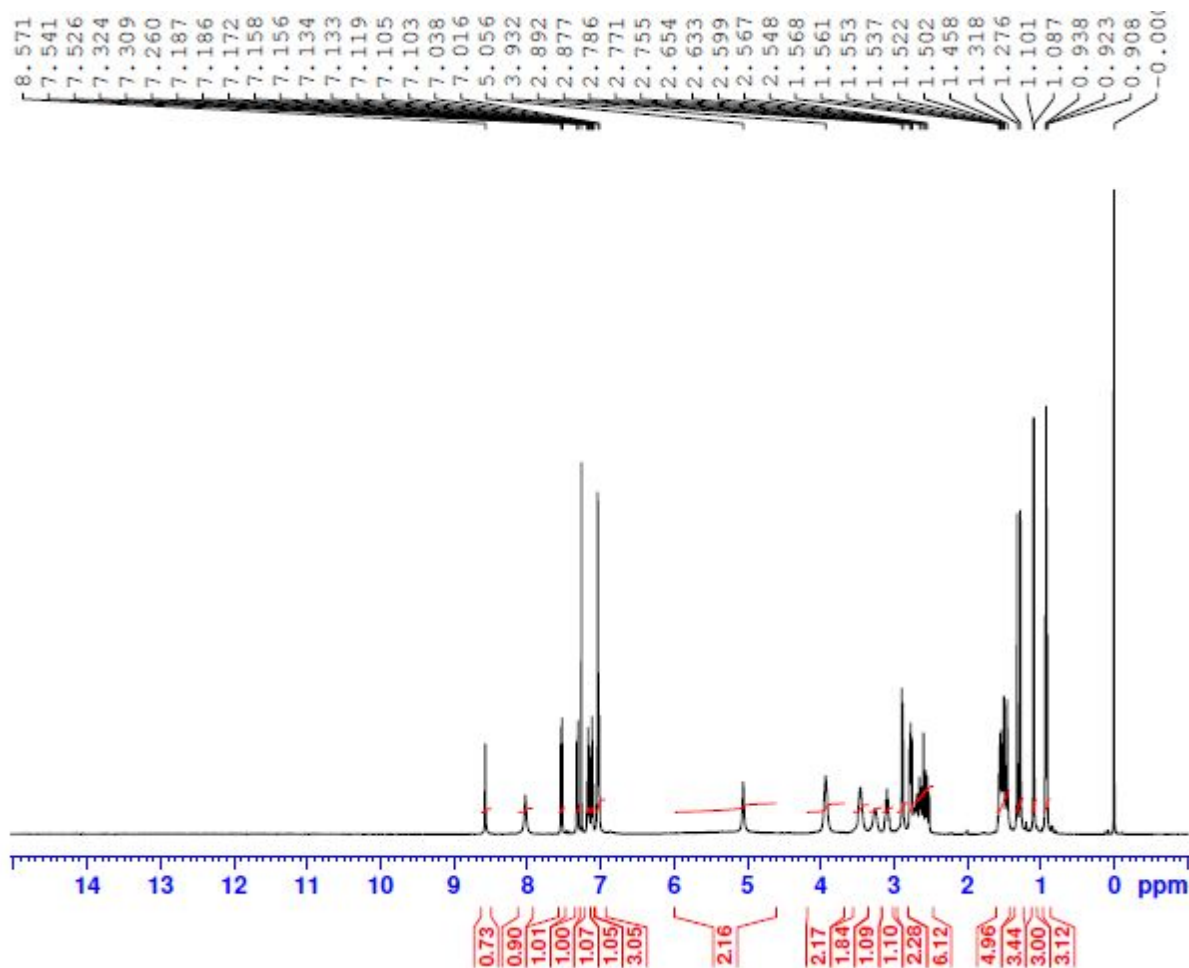


Figure S50. HRMS spectrum of Compound 27

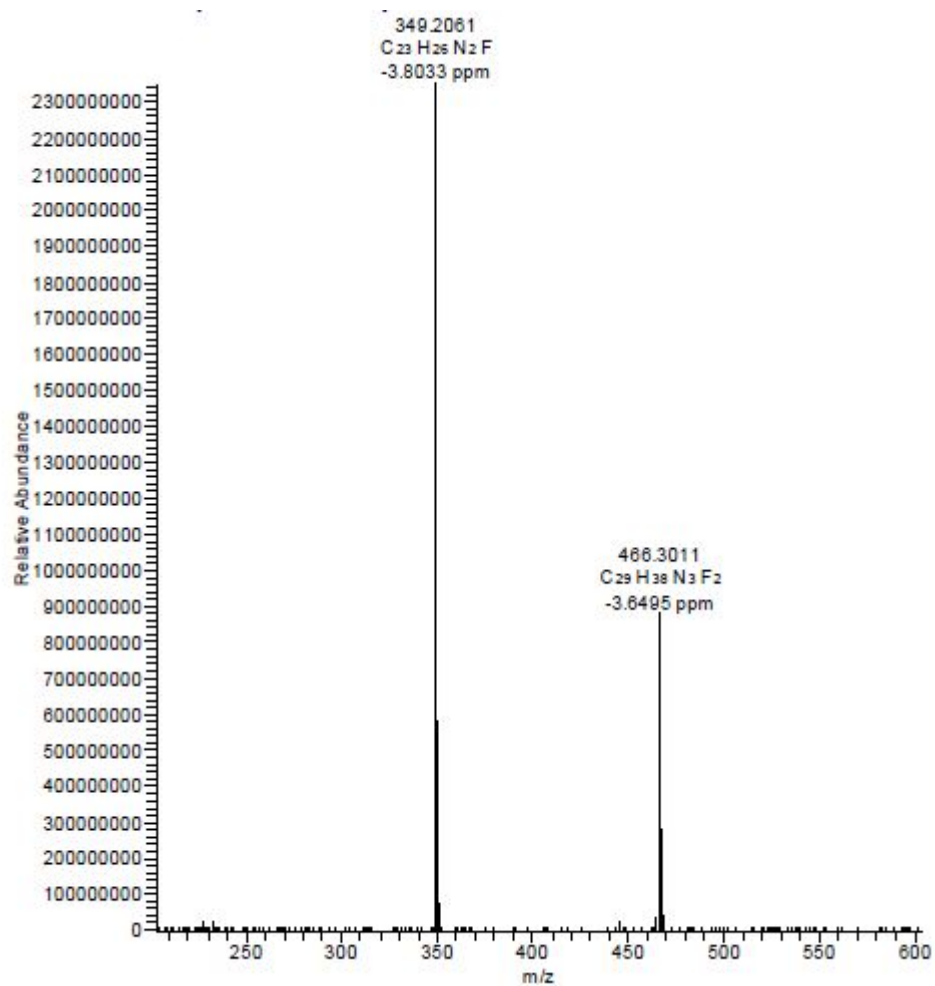


Figure S51. ^{19}F -NMR spectrum of Compound 27

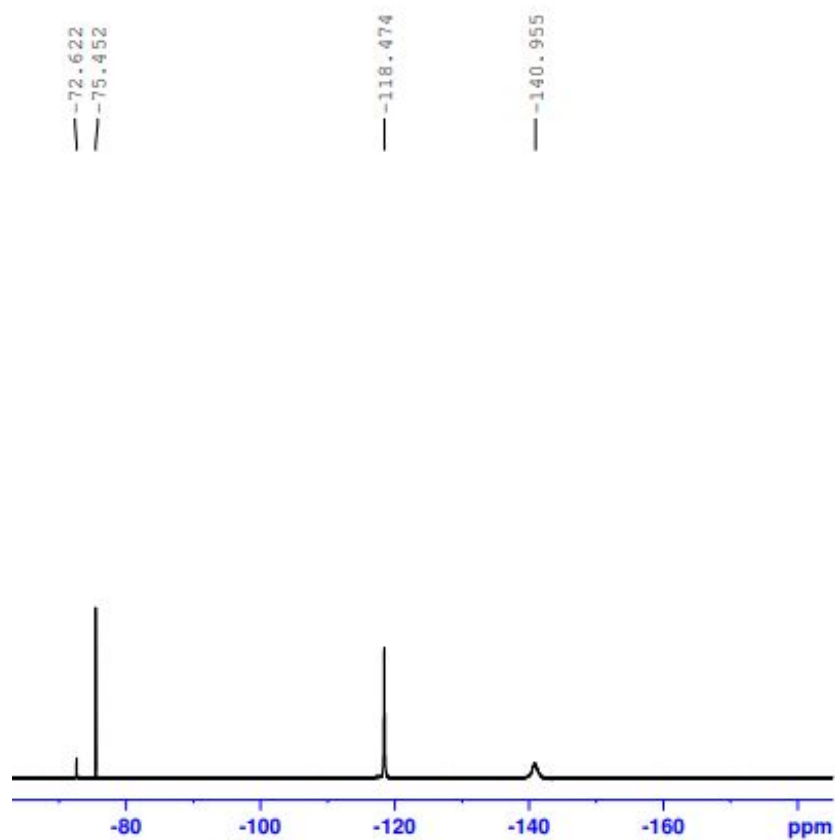


Figure S52. ^{13}C -NMR spectrum of Compound 27

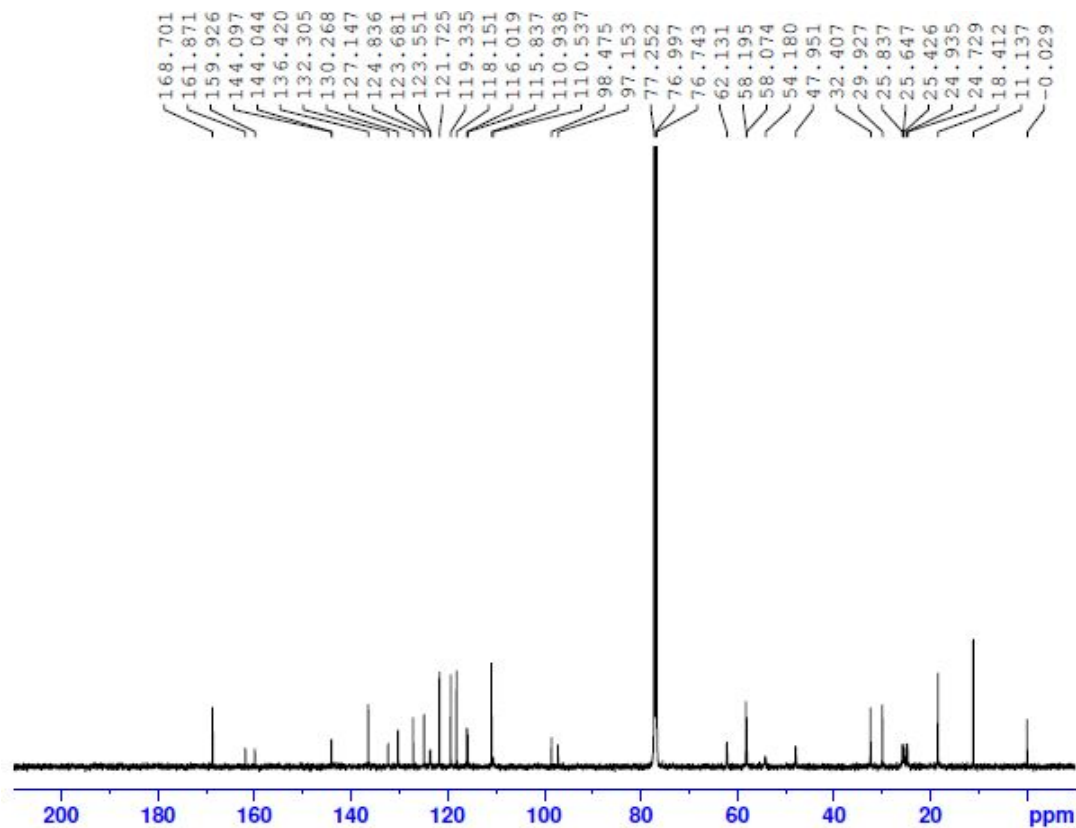
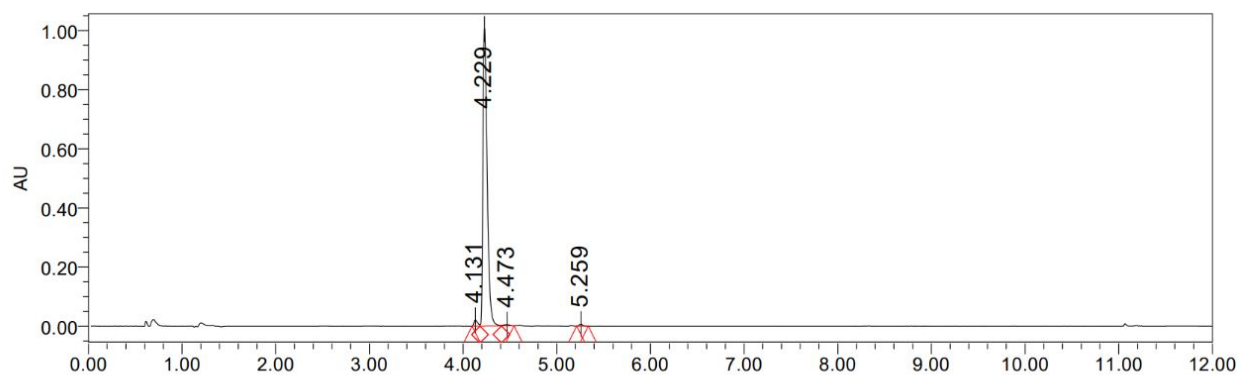


Figure S53. HPLC chromatogram of Compound 28



Peak Results

	RT	Area	% Area
1	4.131	56451	1.74
2	4.229	3156254	97.12
3	4.473	19152	0.59
4	5.259	17979	0.55

Figure S54. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 28

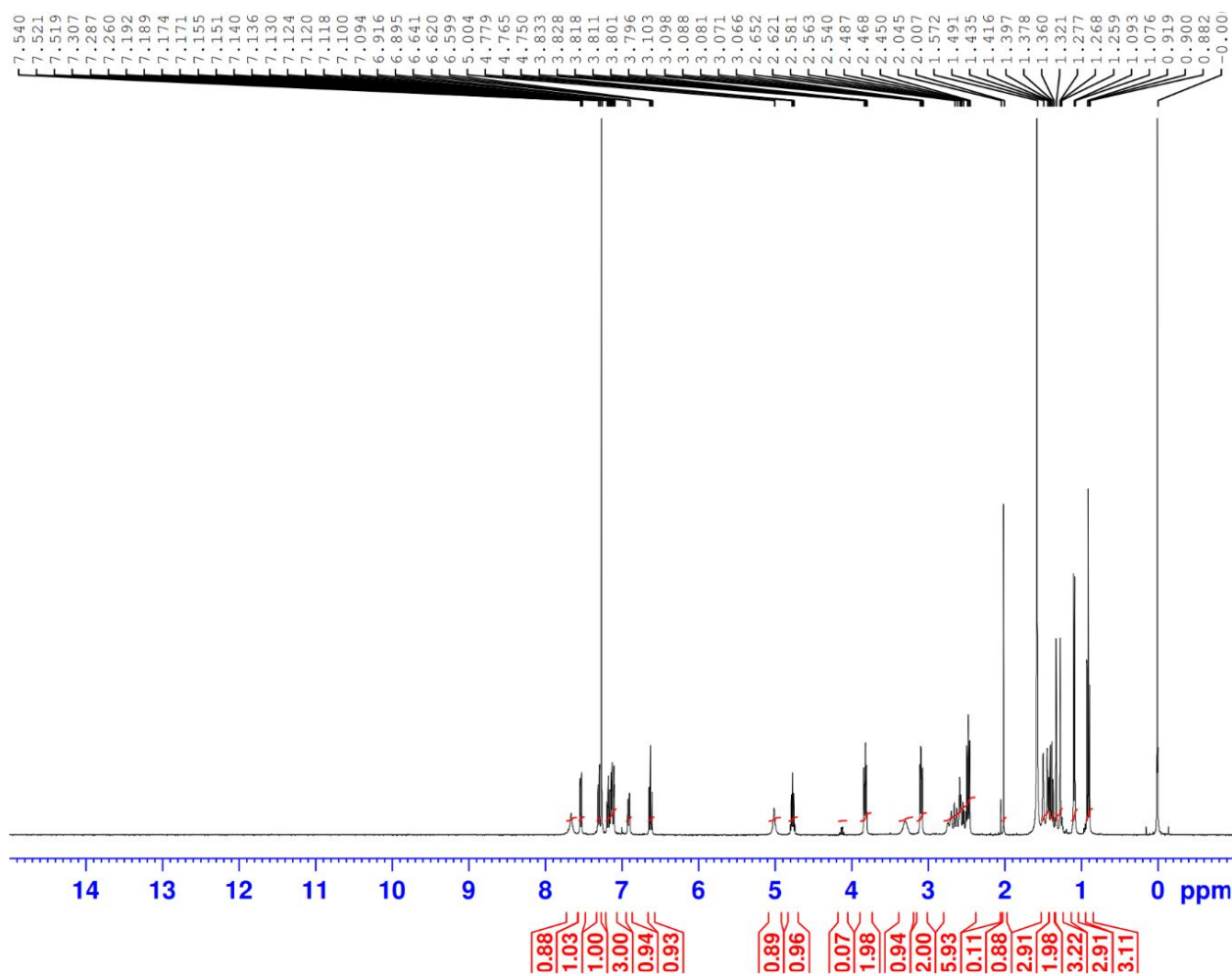


Figure S55. HRMS spectrum of Compound 28

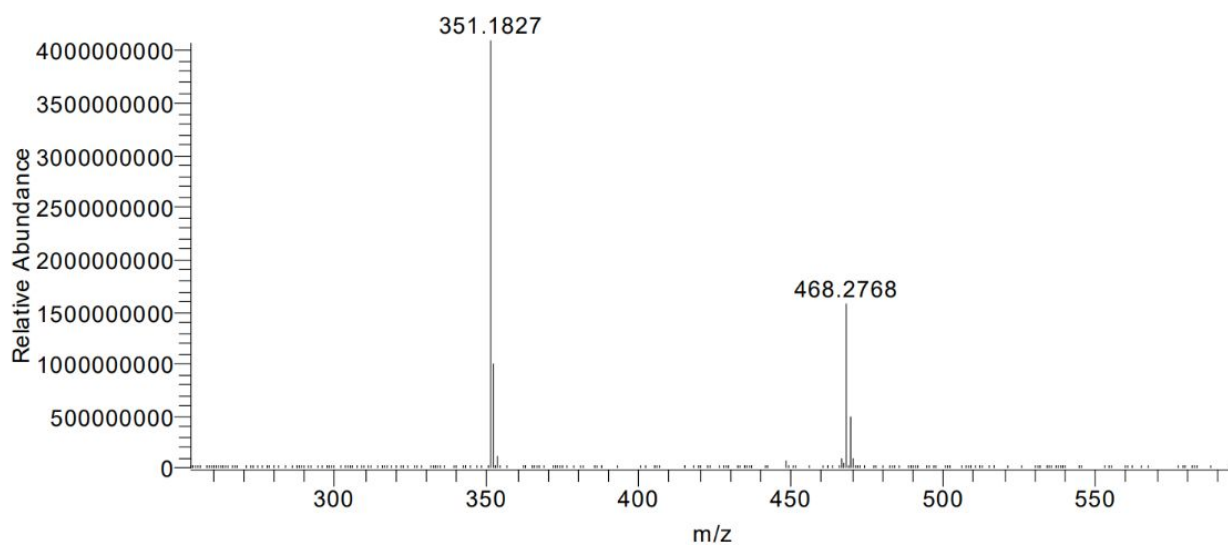


Figure S56. ^{19}F -NMR spectrum of Compound 28

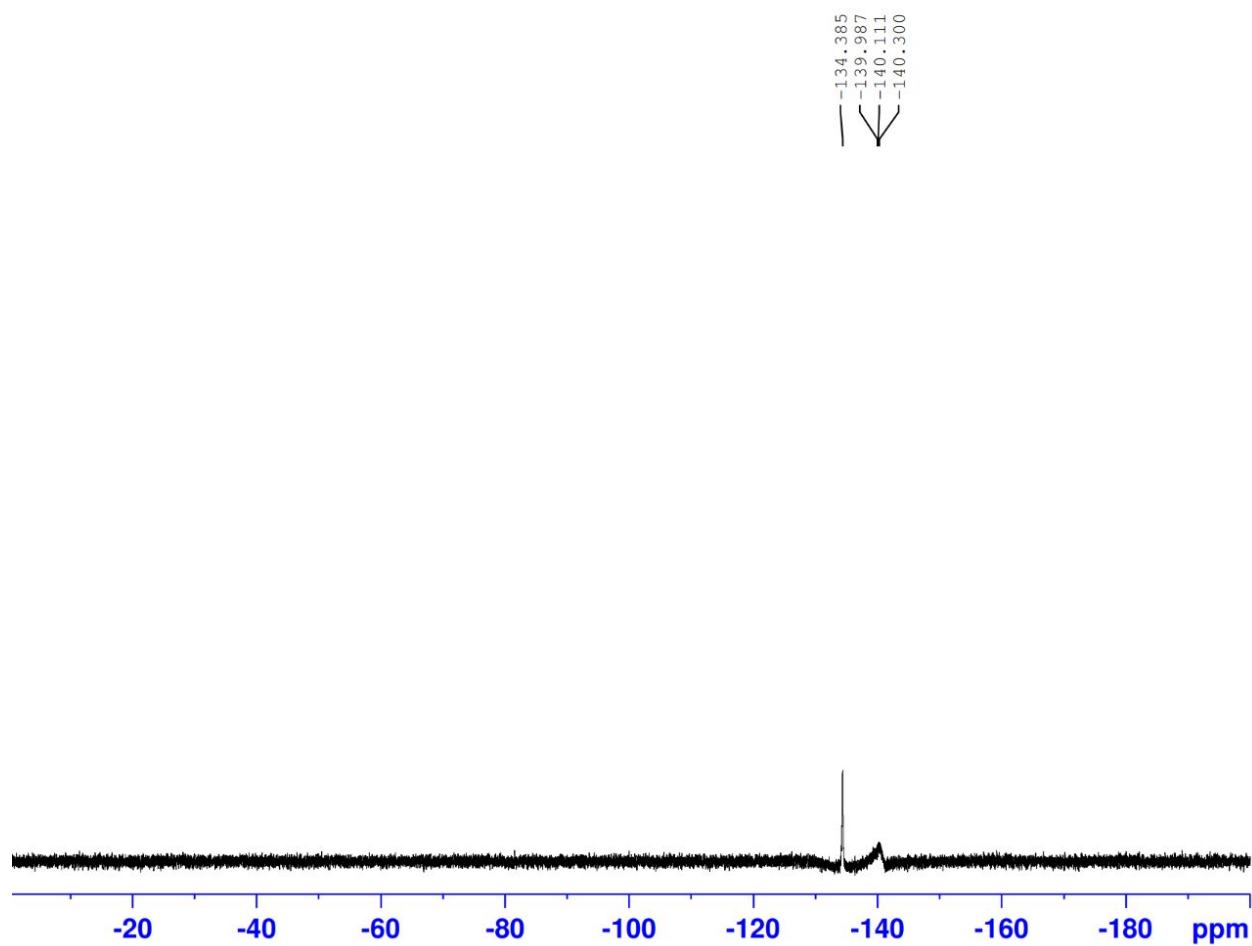


Figure S57. ^{13}C -NMR spectrum of Compound 28

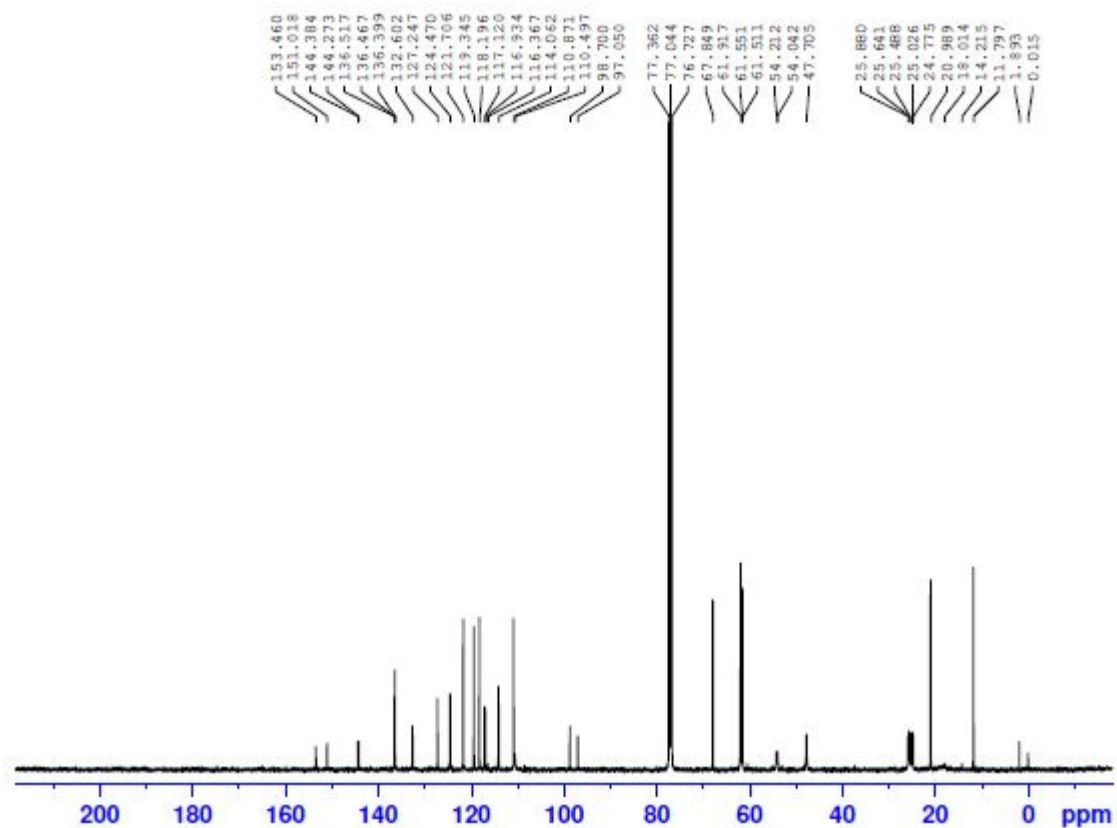
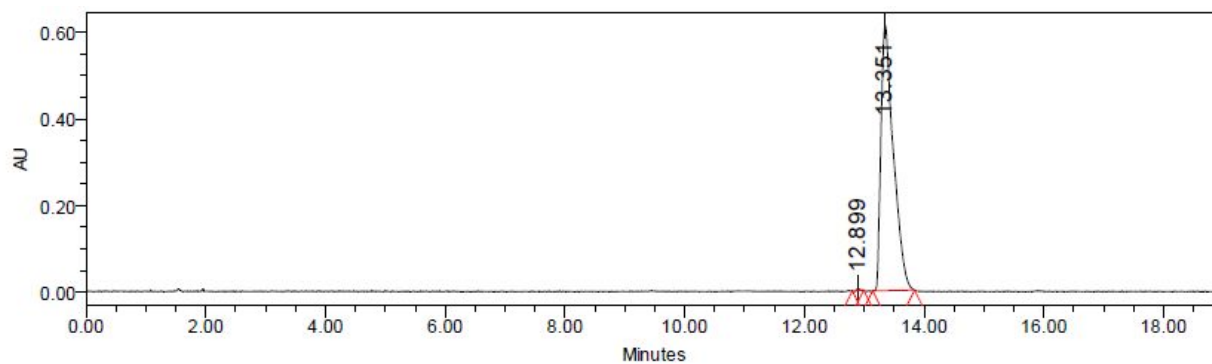


Figure S58. HPLC chromatogram of Compound 29



Peak Results

	RT	Area	Height	Purity1 Angle	Purity1 Threshold	% Area
1	12.899	18553	5351	26.624	32.651	0.21
2	13.351	8827236	611568	0.303	0.514	99.79

Figure S59. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 29

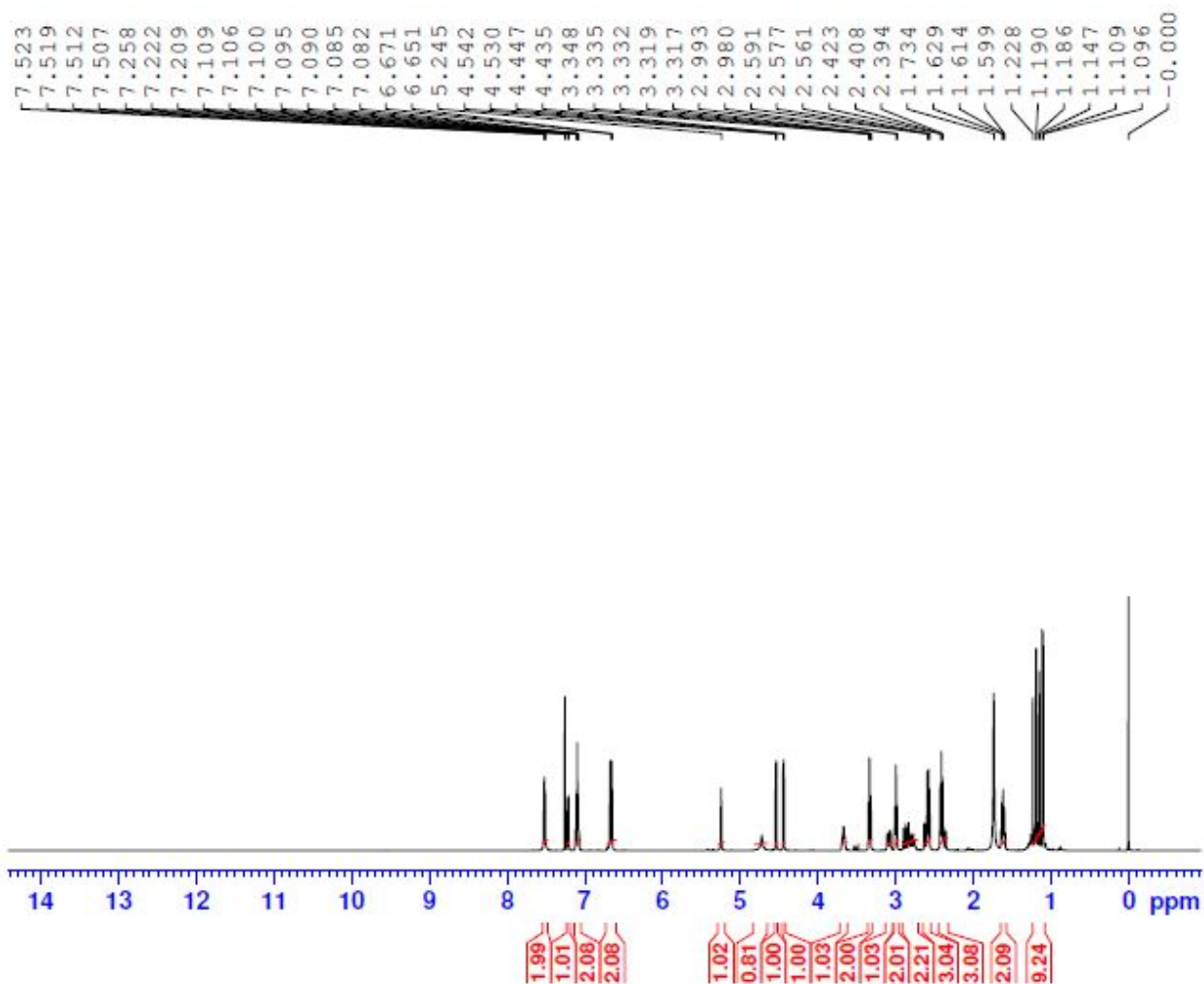


Figure S60. HRMS spectrum of Compound 29

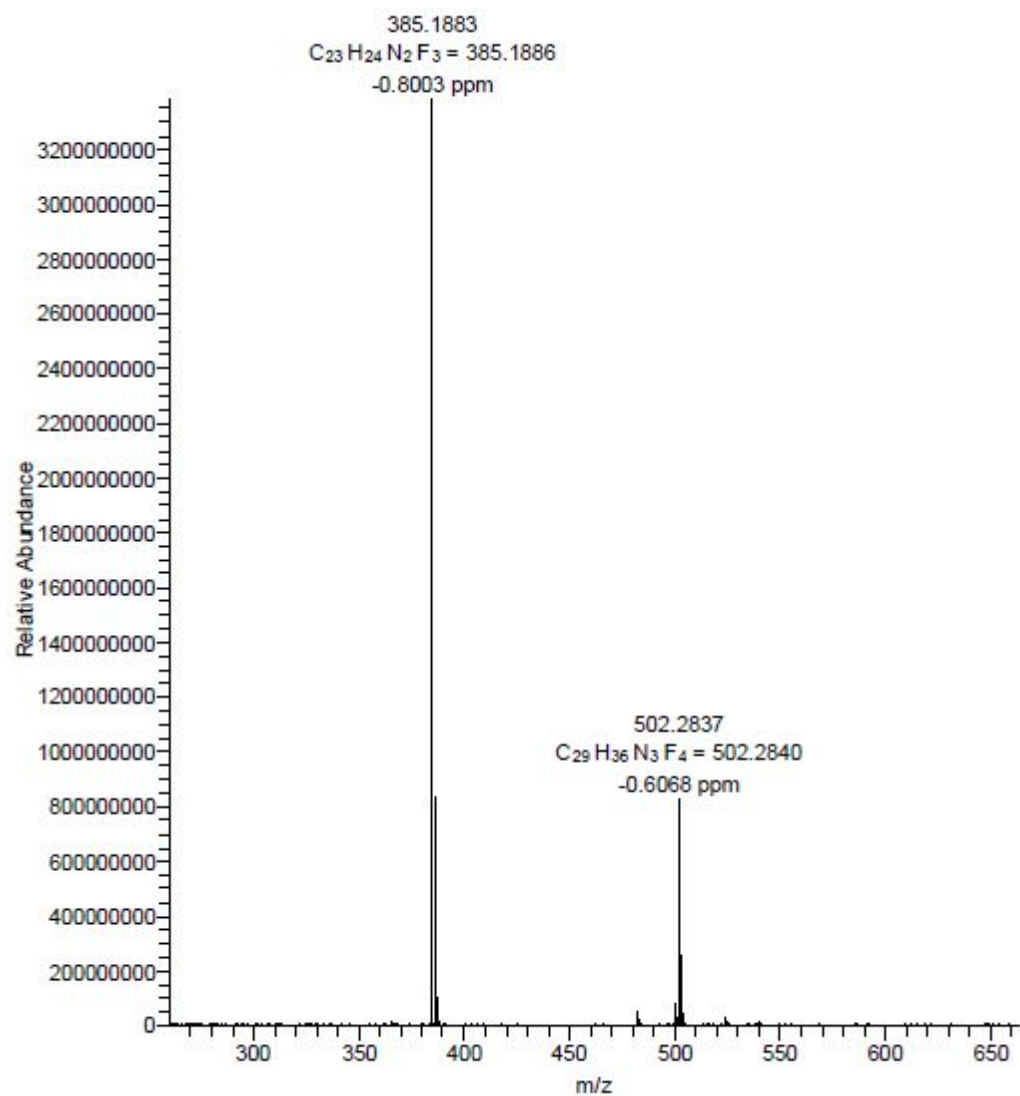


Figure S61. ^{19}F -NMR spectrum of Compound 29

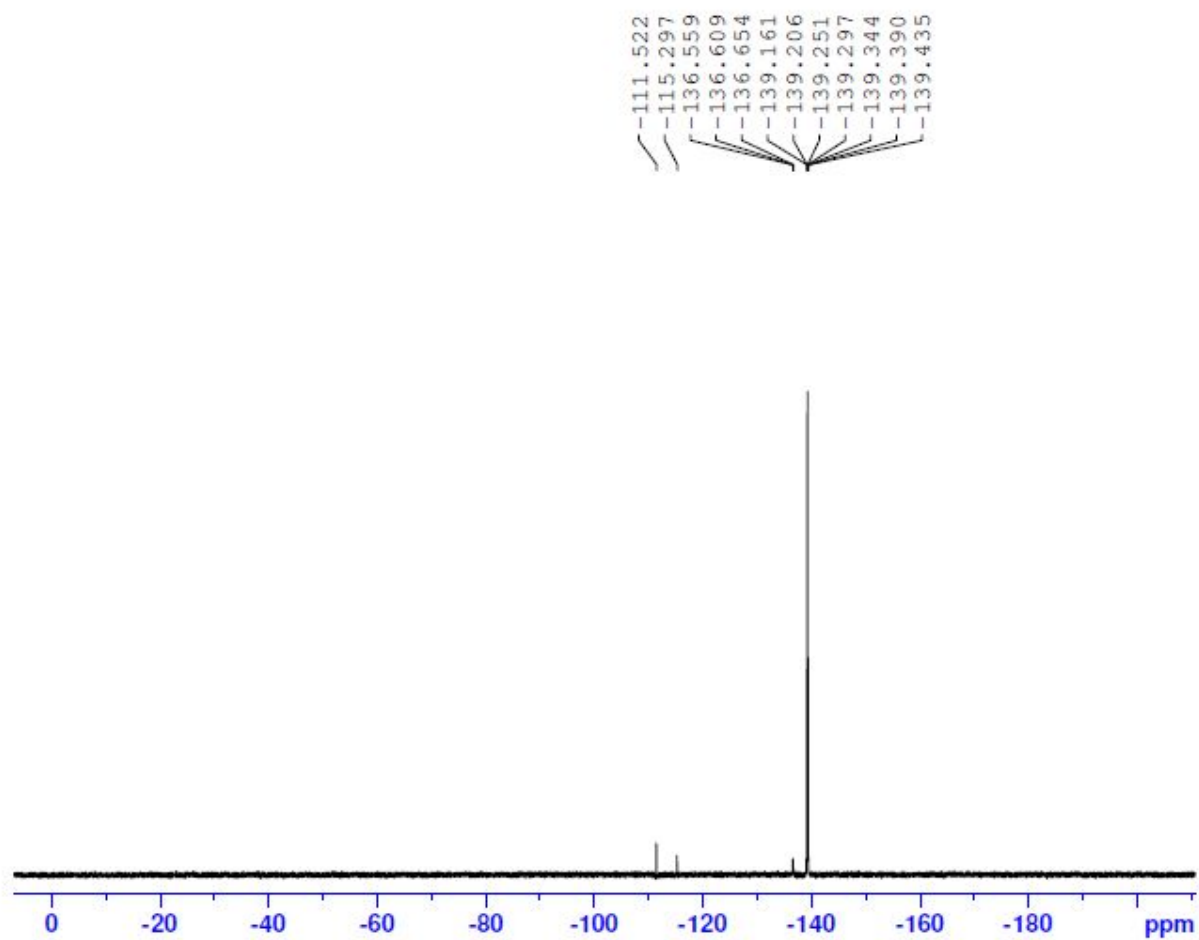


Figure S62. ^{13}C -NMR spectrum of Compound 29

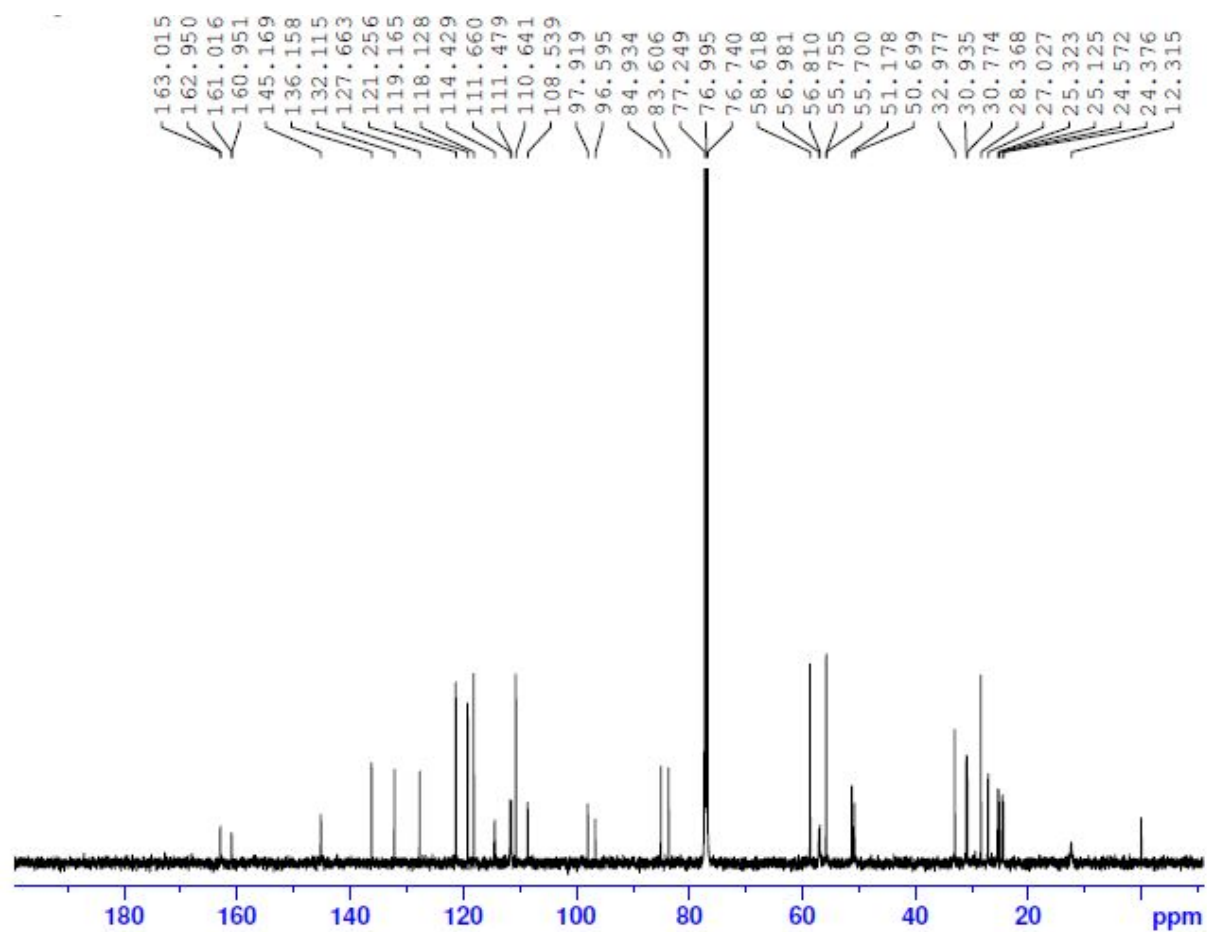


Figure S63. HPLC chromatogram of Compound 30

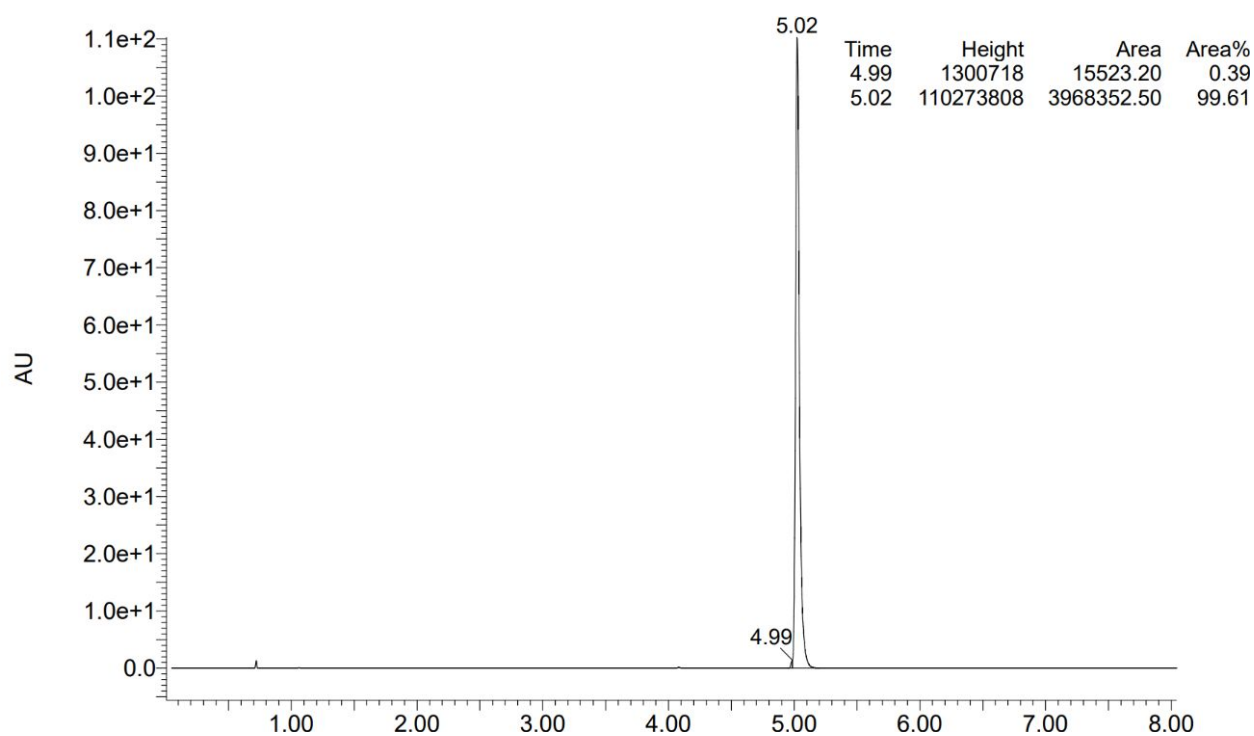


Figure S64. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 30

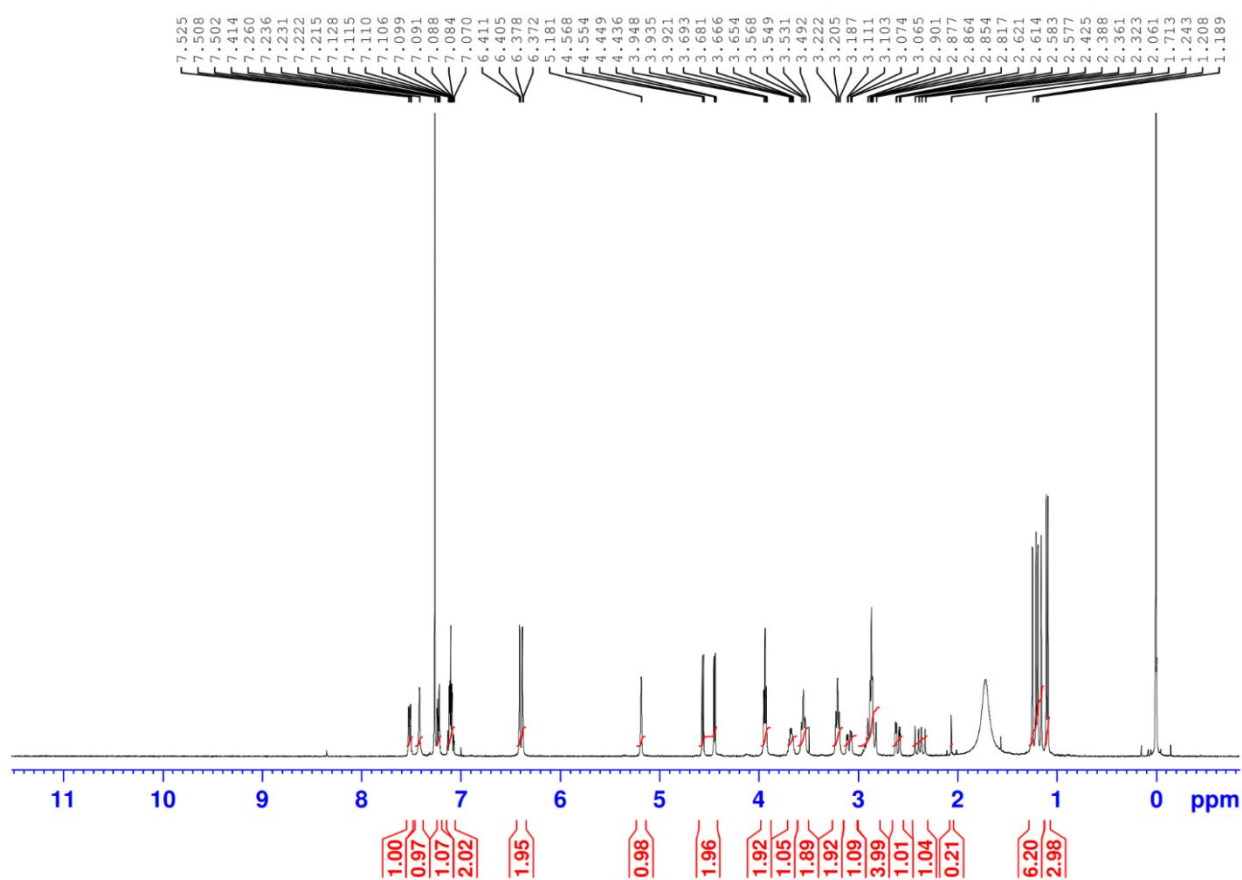


Figure S65. HRMS spectrum of Compound 30

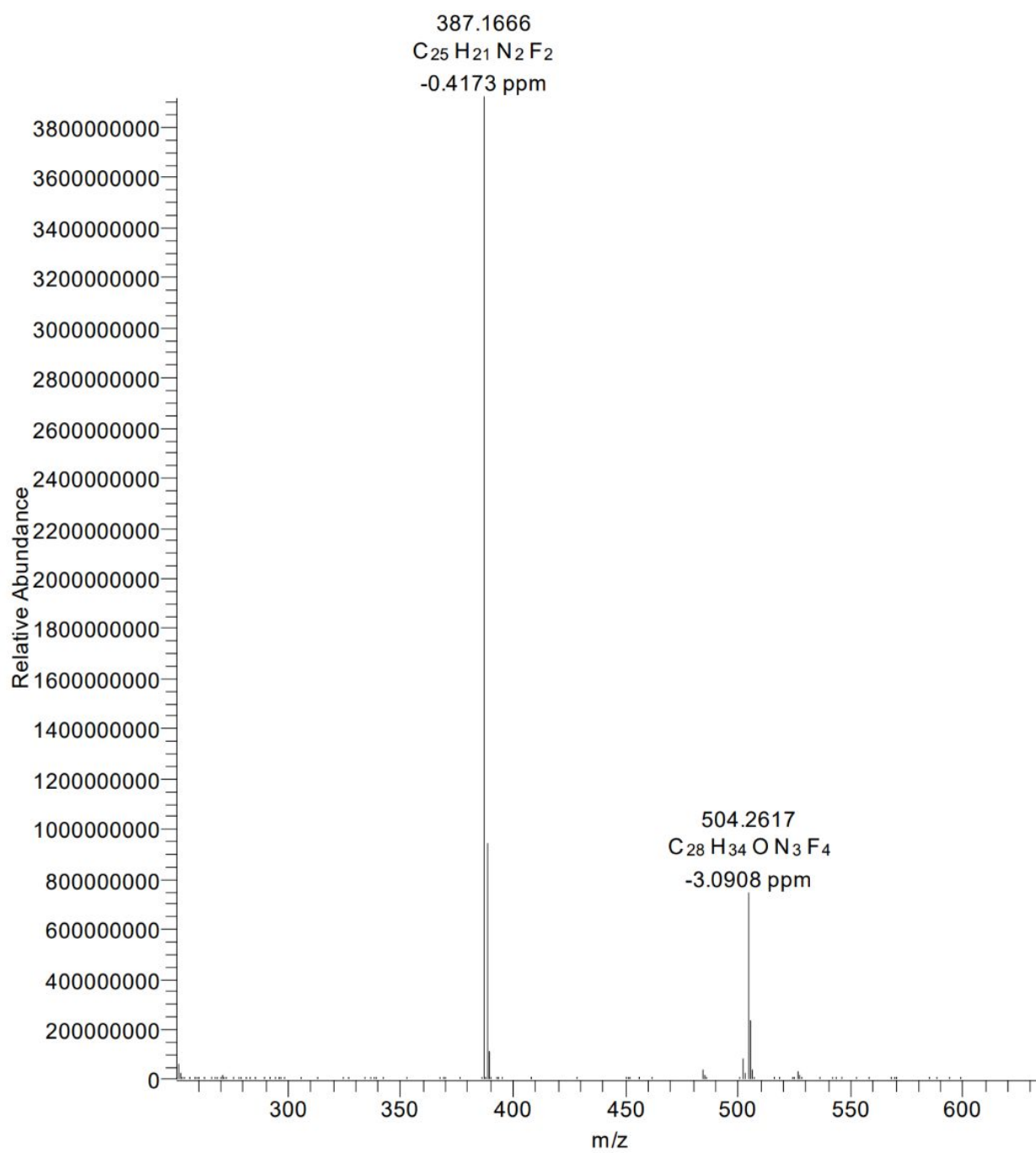


Figure S66. ^{19}F -NMR spectrum of Compound 30

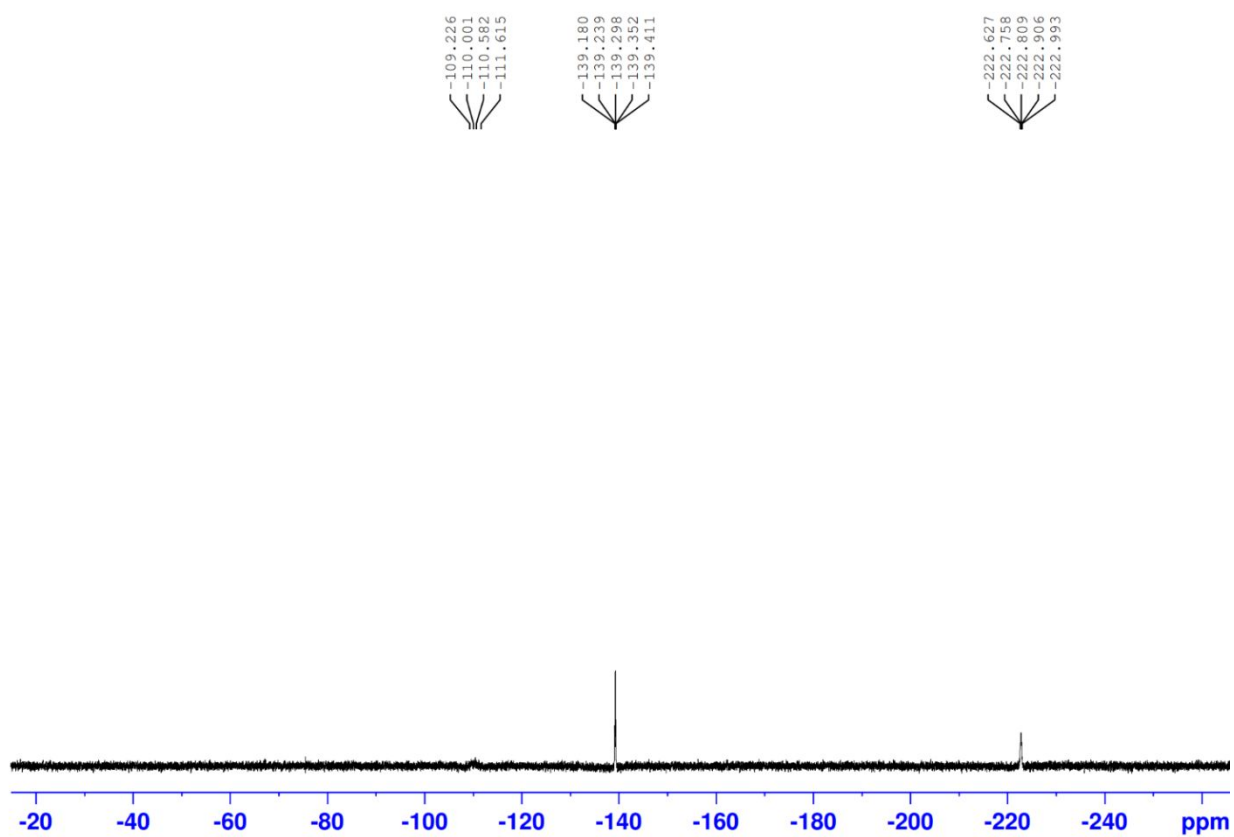


Figure S67. ^{13}C -NMR spectrum of Compound 30

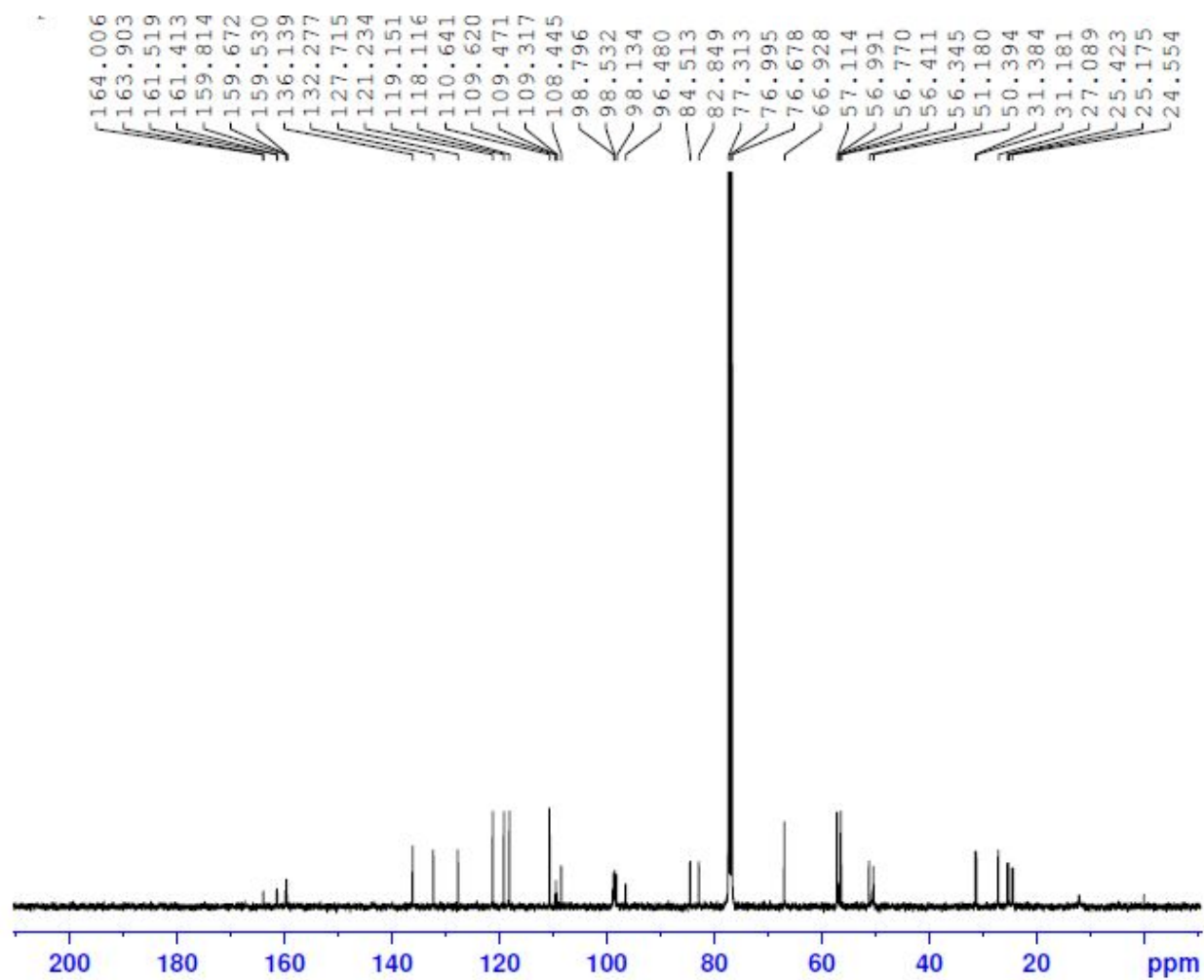
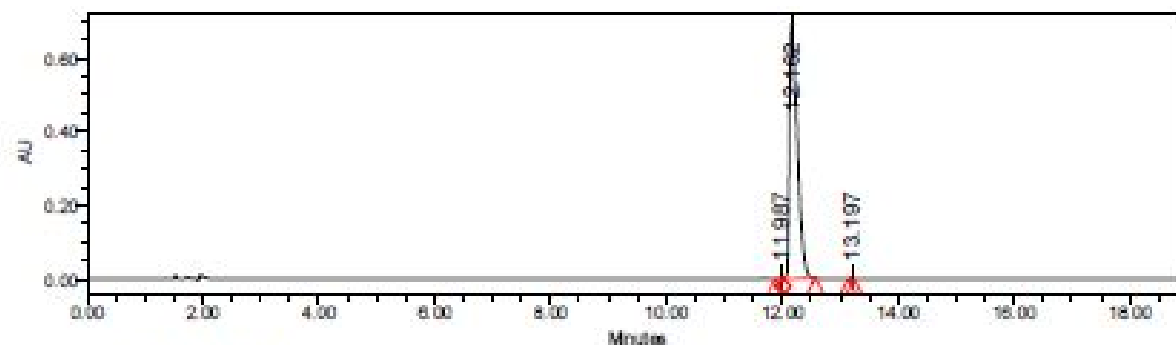


Figure S68. HPLC chromatogram of Compound 31



Peak Results

	RT	Area	Purity1 Angle	Purity1 Threshold	% Area
1	11.987	15040	7.735	10.581	0.23
2	12.182	6515258	0.232	0.327	99.58
3	13.187	12512	22.287	35.184	0.19

Figure S69. $^1\text{H-NMR}$ (400 MHz, CDCl_3) spectrum of Compound 31

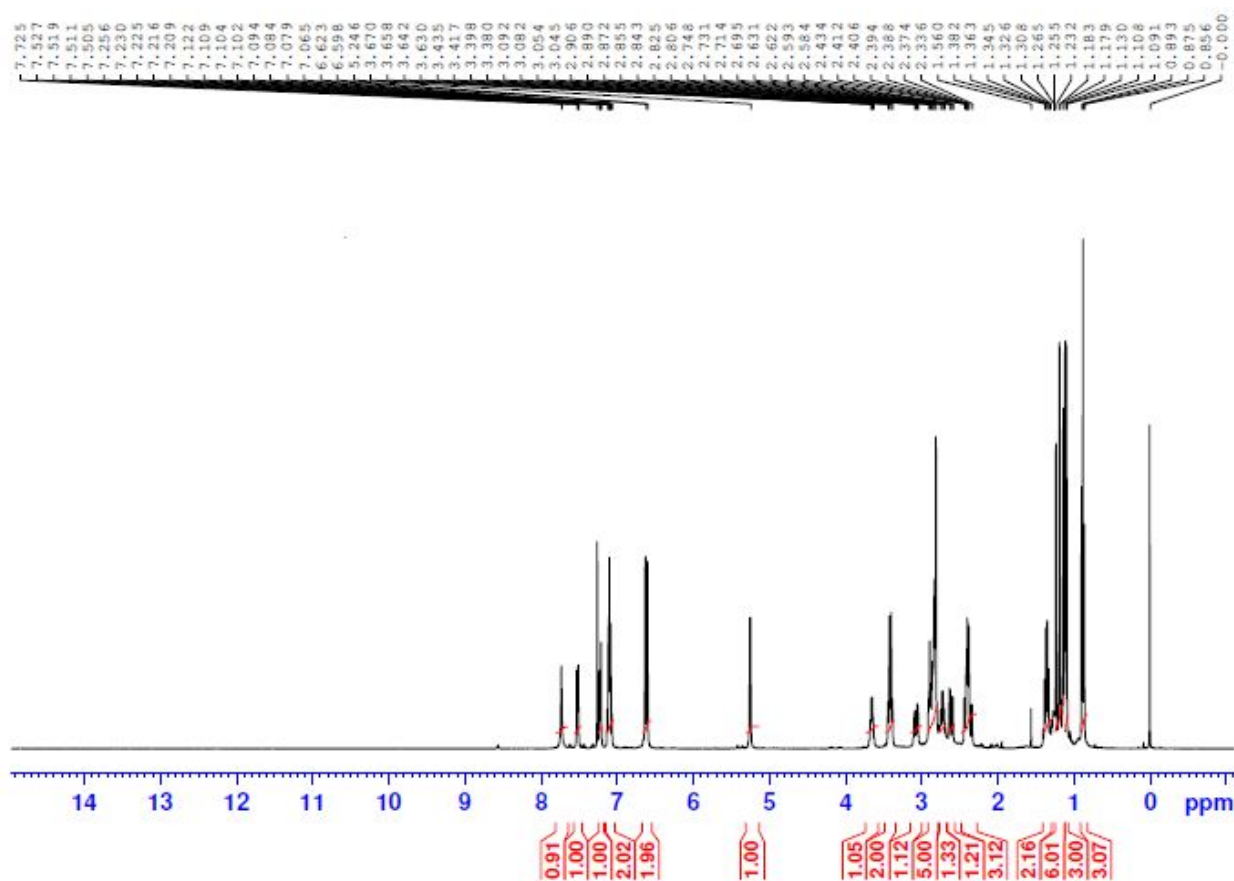


Figure S70. HRMS spectrum of Compound 31

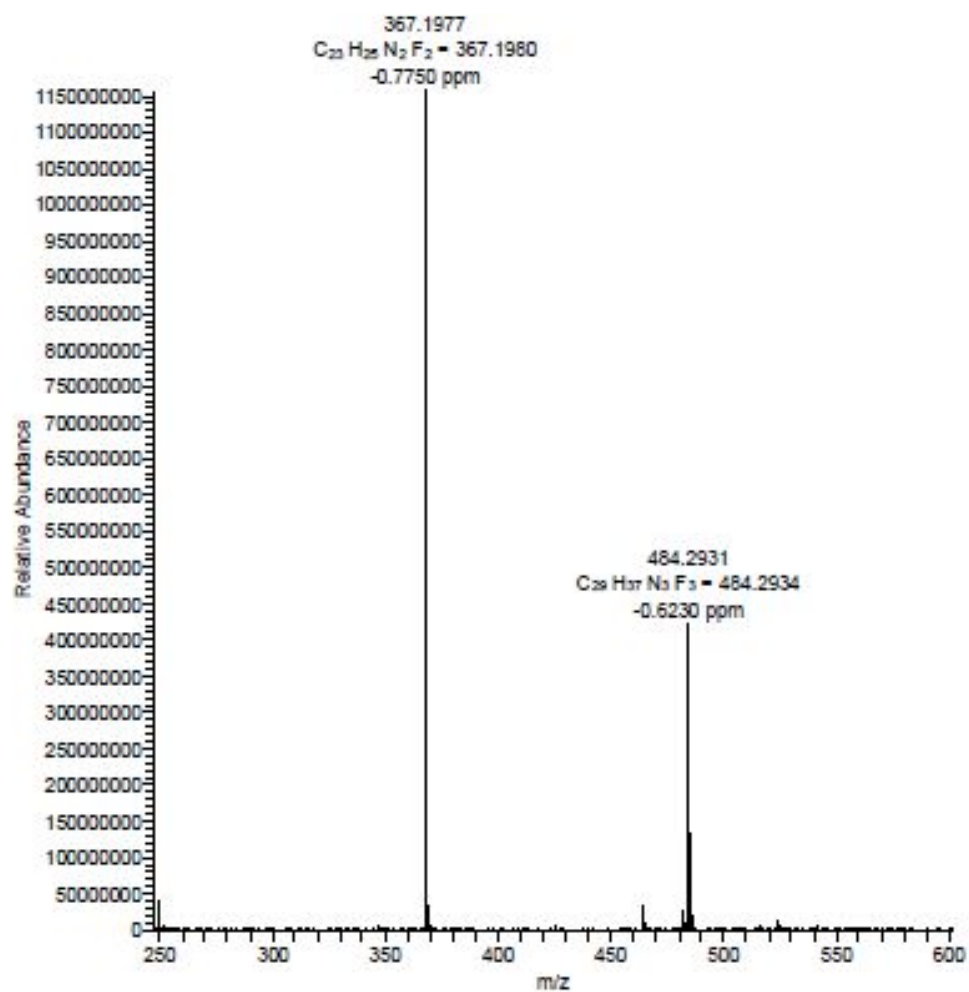


Figure S71. ^{19}F -NMR spectrum of Compound 31

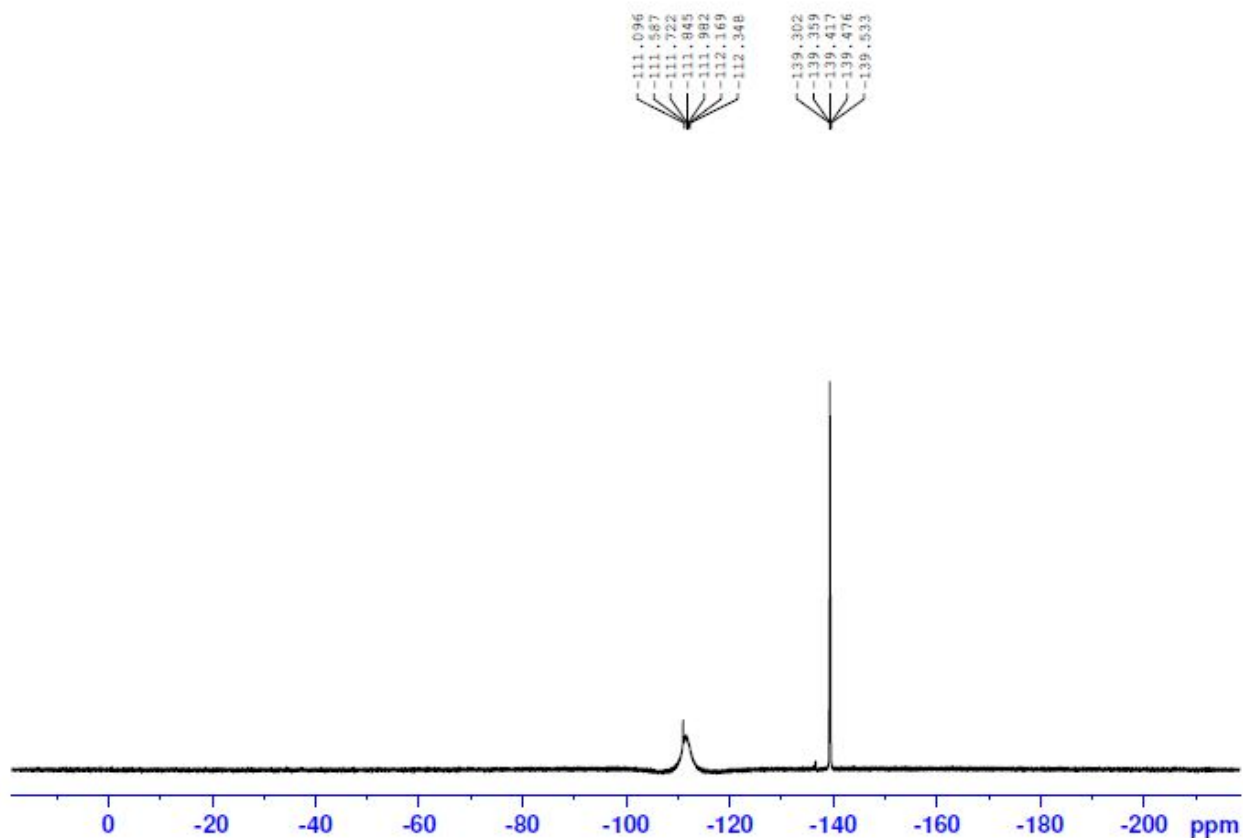


Figure S72. ^{13}C -NMR spectrum of Compound 31

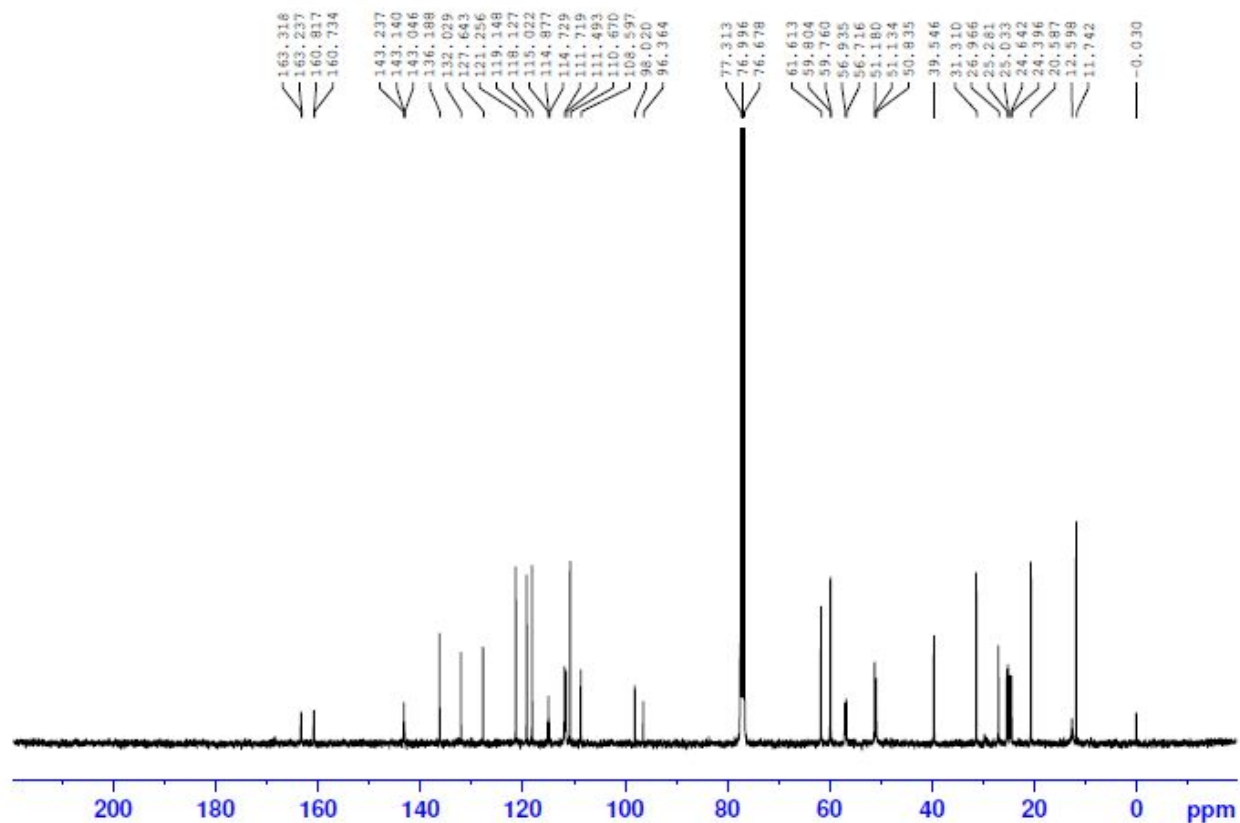
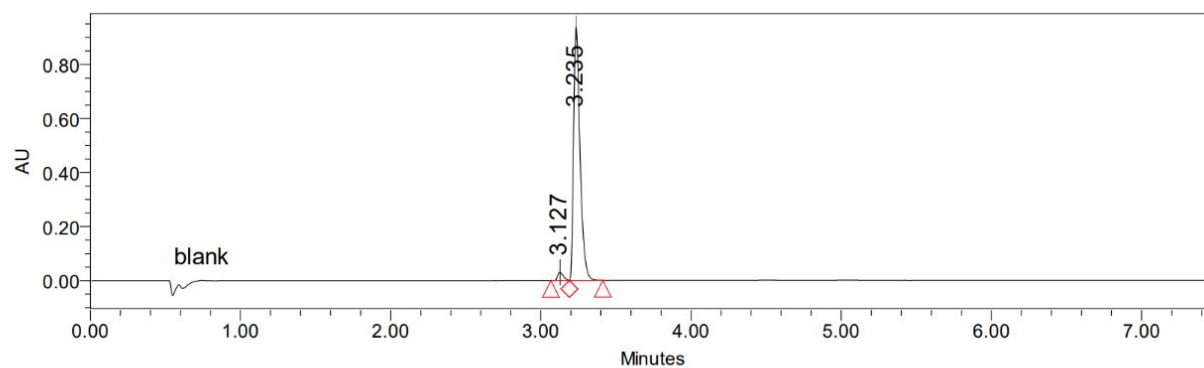


Figure S73. HPLC chromatogram of Compound 32



Peak Results

	RT	Area	% Area
1	3.127	79301	2.77
2	3.235	2783483	97.23

Figure S74. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 32

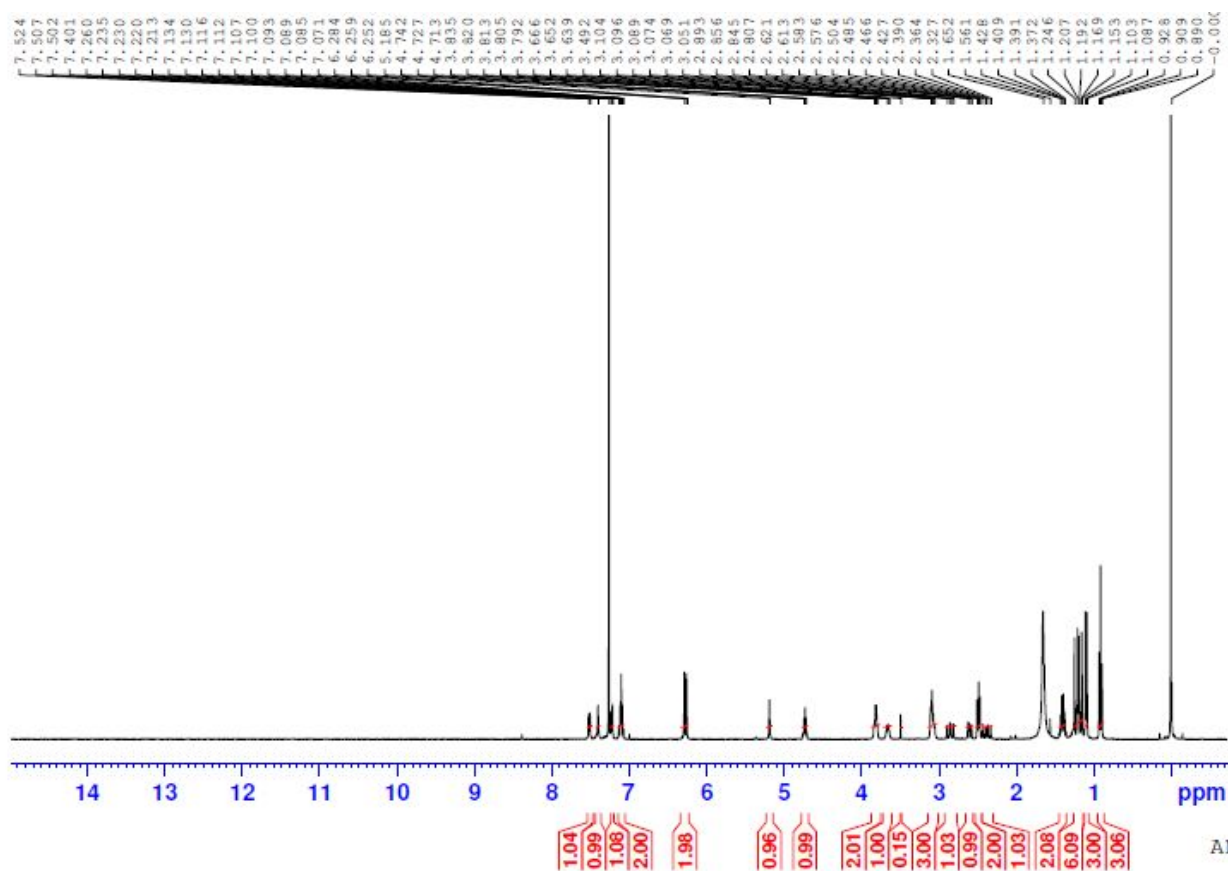


Figure S75. HRMS spectrum of Compound 32

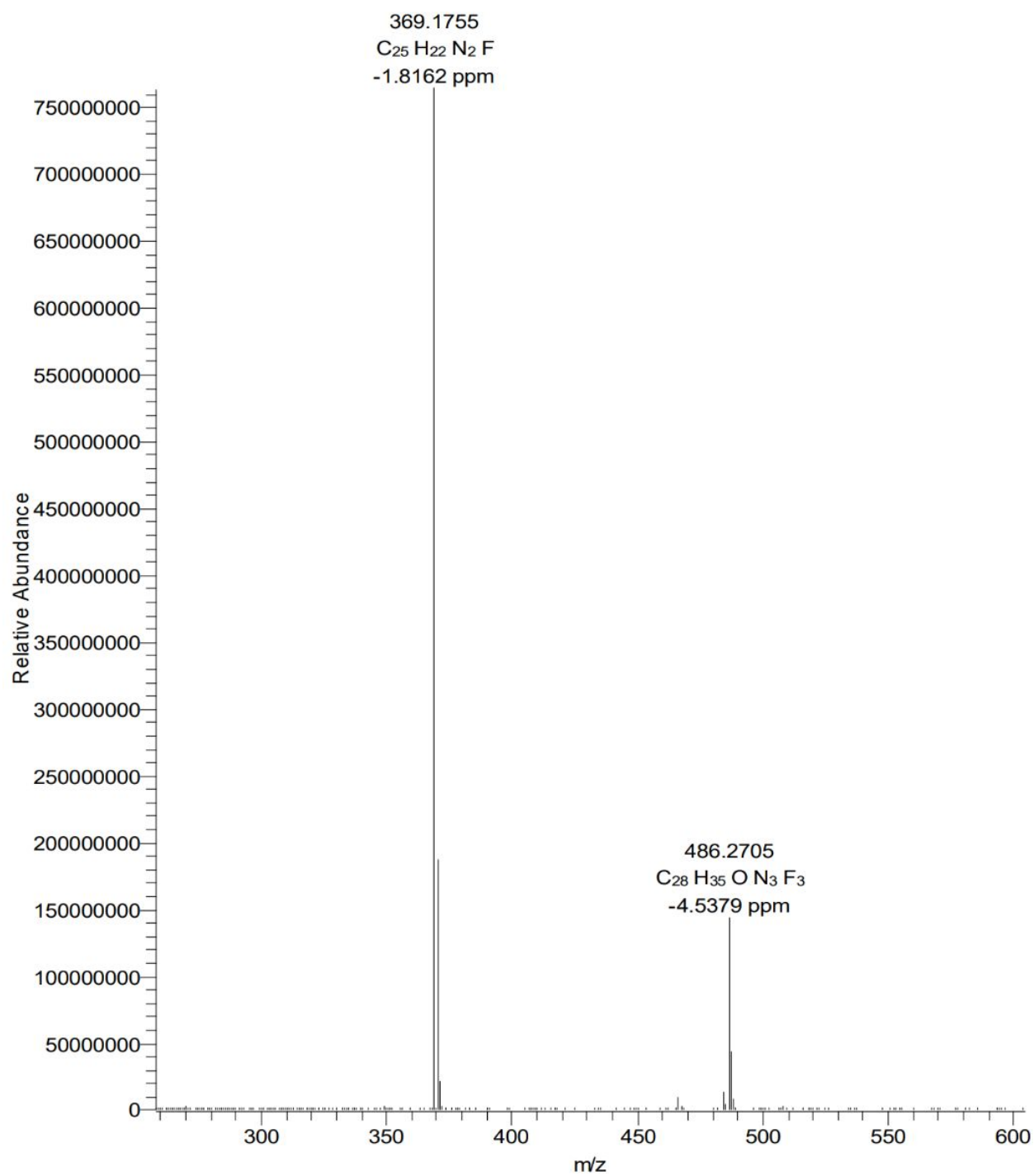


Figure S76. ^{19}F -NMR spectrum of Compound 32

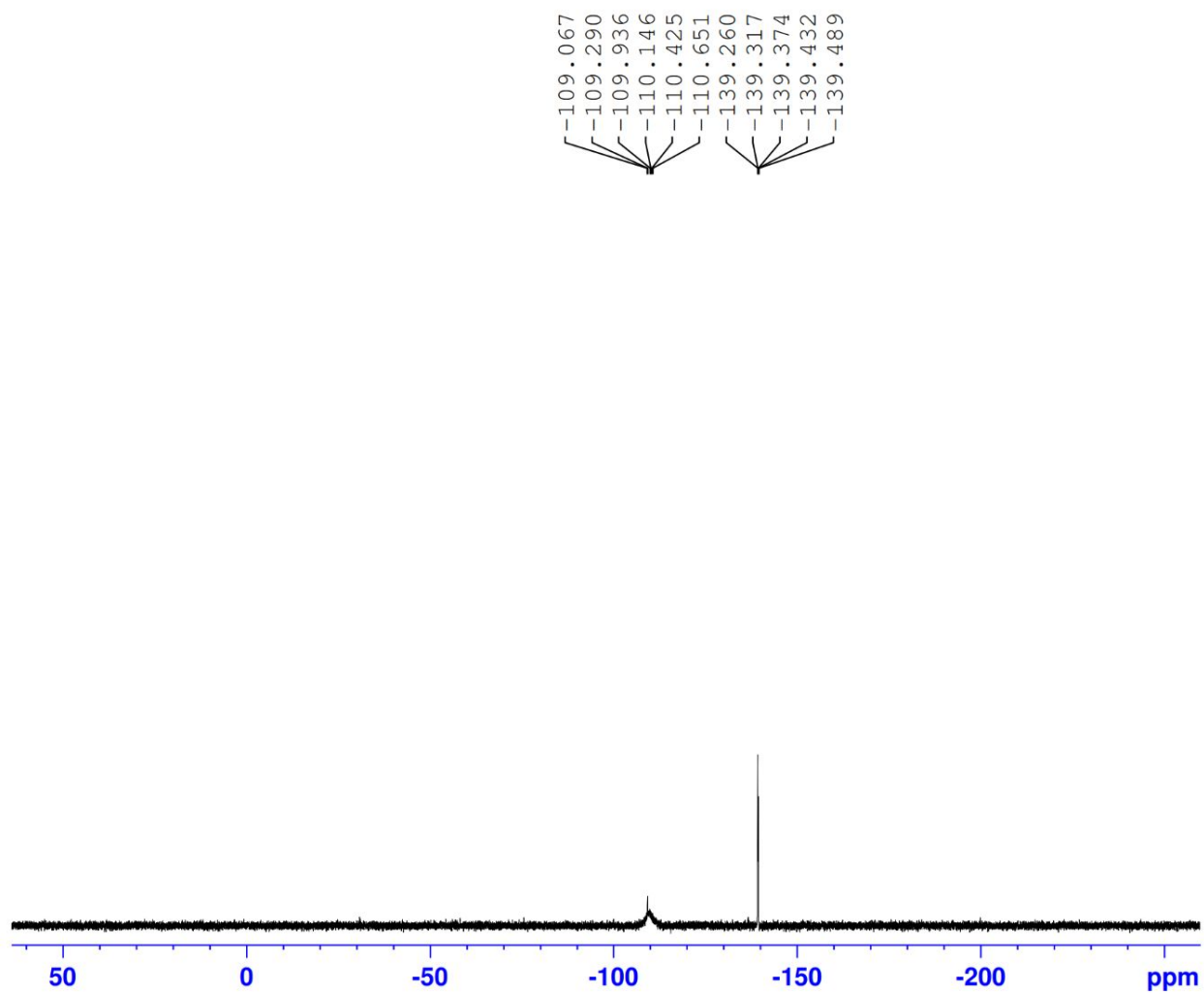


Figure S77. ^{13}C -NMR spectrum of Compound 32

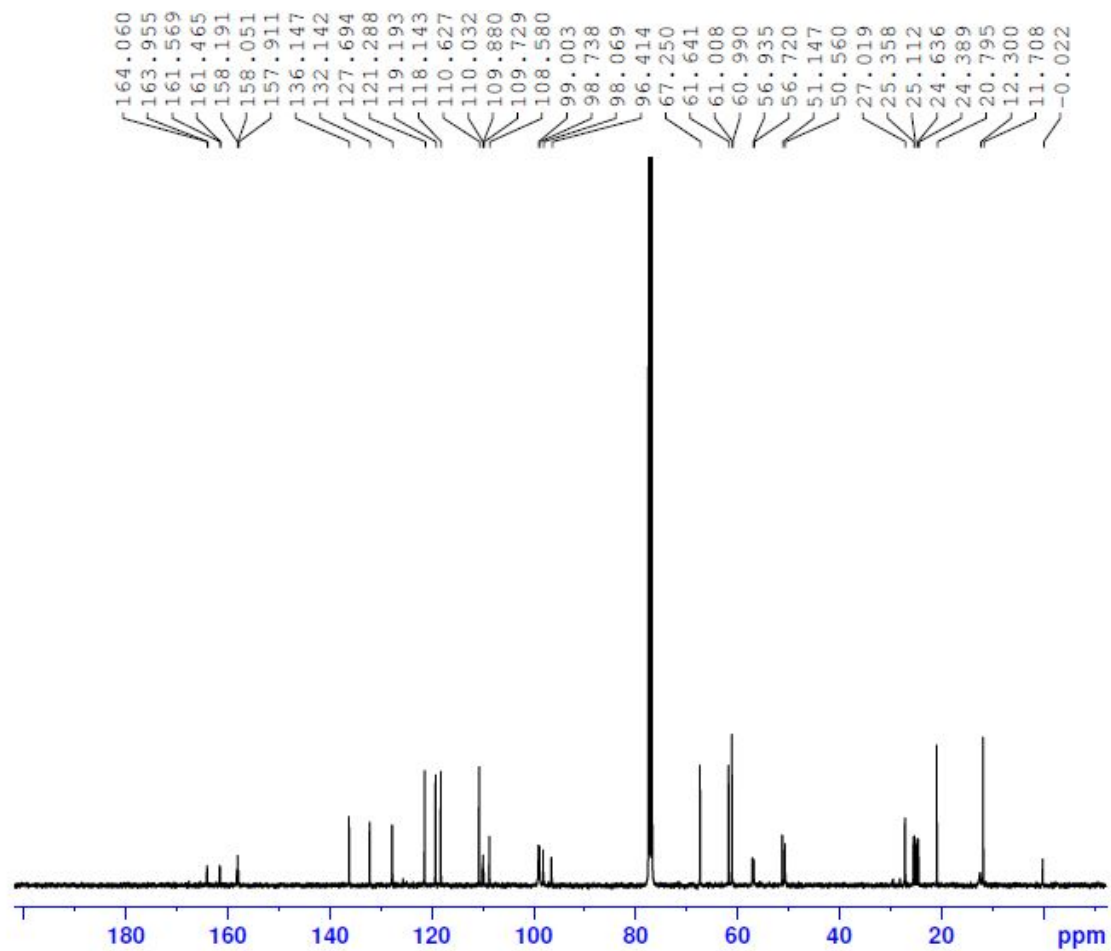
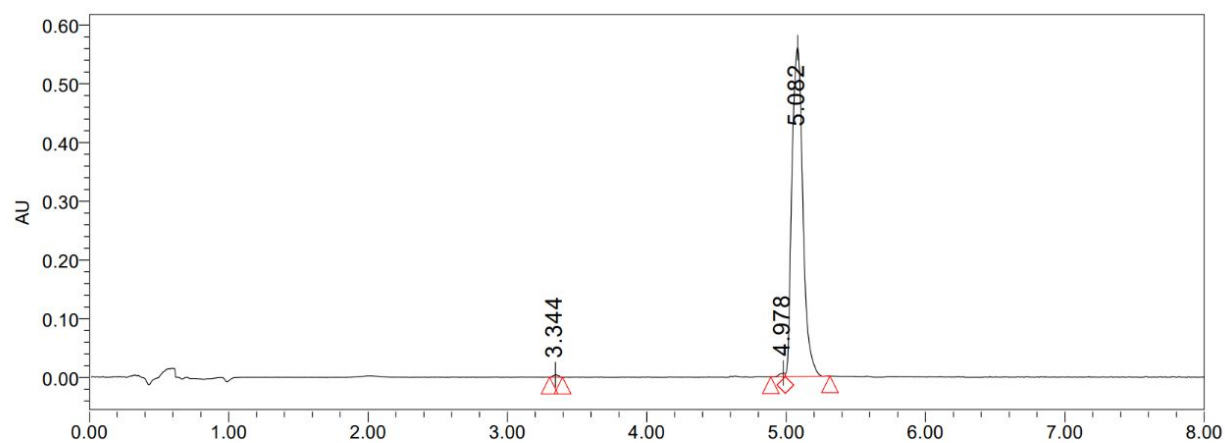


Figure S78. HPLC chromatogram of Compound 33



Peak Results

	RT	Area	% Area
1	3.344	10670	0.35
2	4.978	17598	0.57
3	5.082	3042130	99.08

Figure S79. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 33

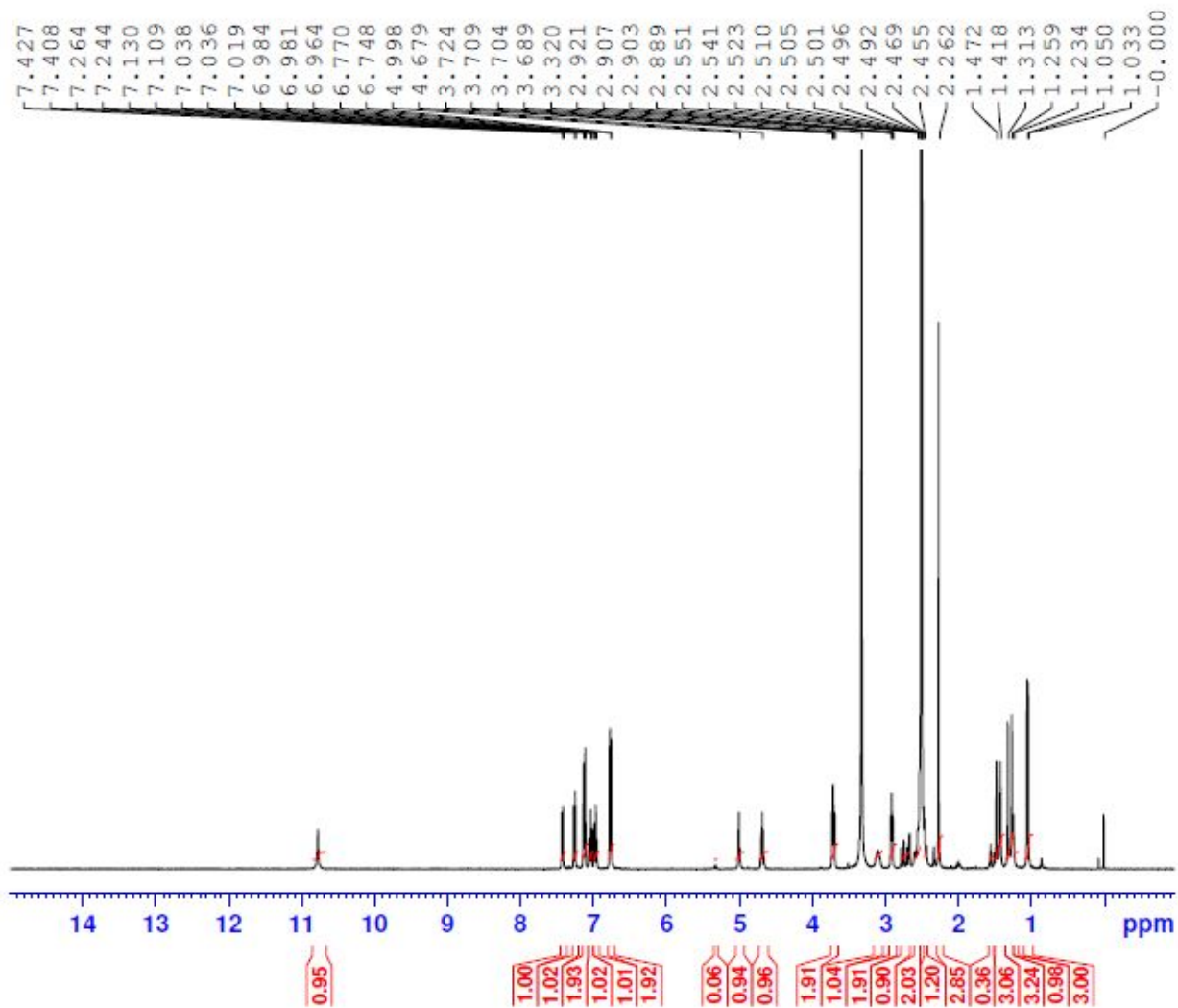


Figure S80. HRMS spectrum of Compound 33

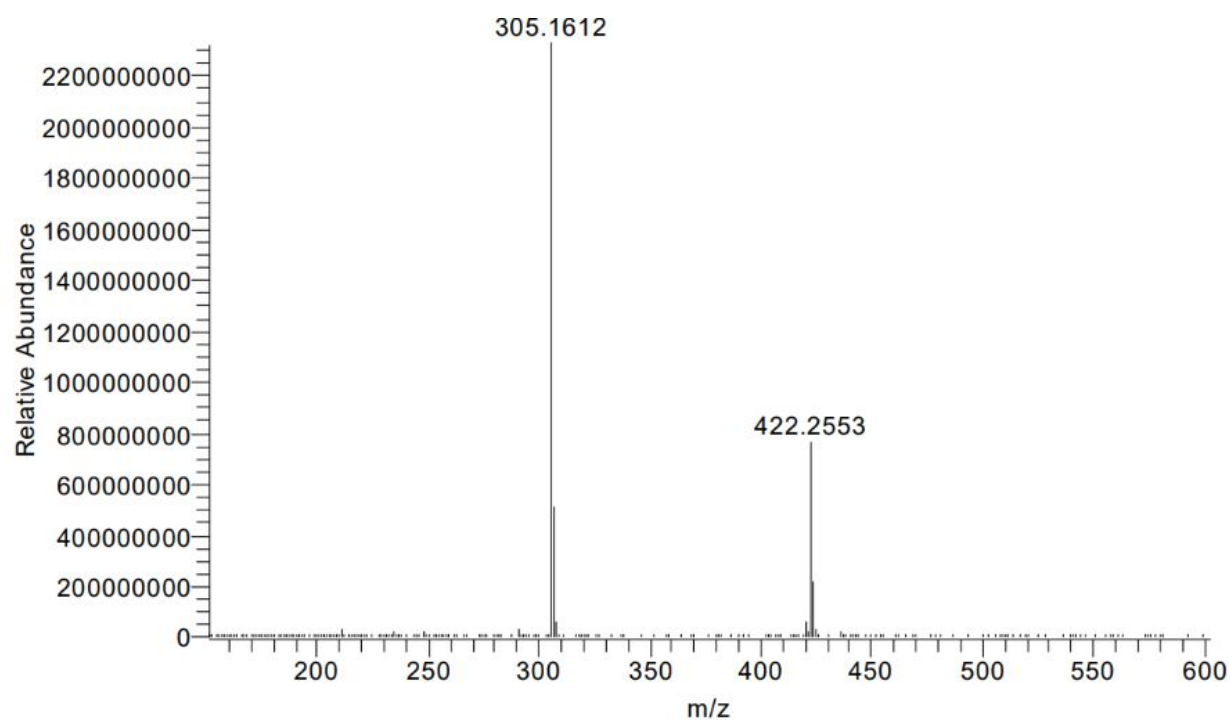


Figure S81. ^{19}F -NMR spectrum of Compound 33

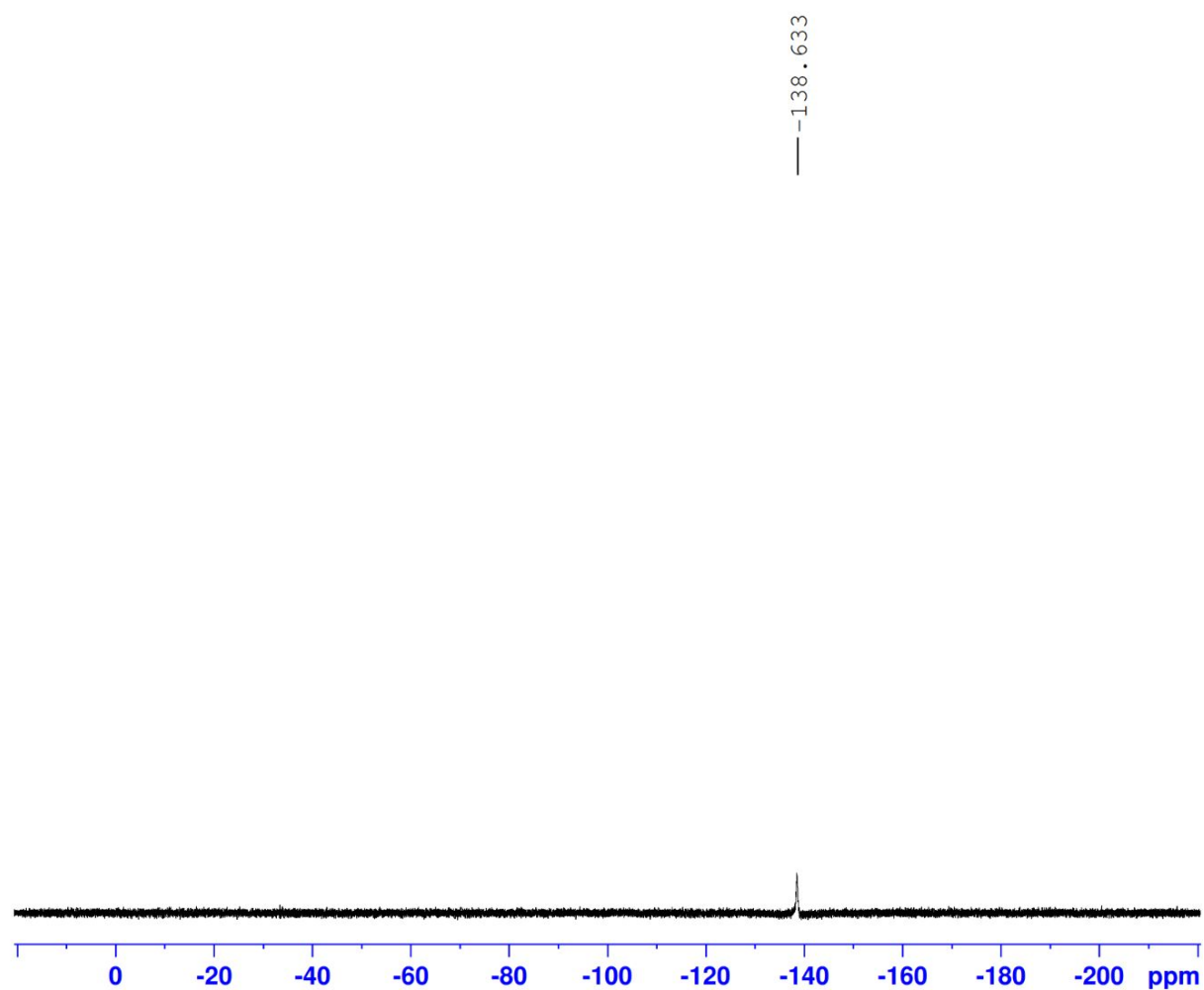


Figure S82. ^{13}C -NMR spectrum of Compound 33

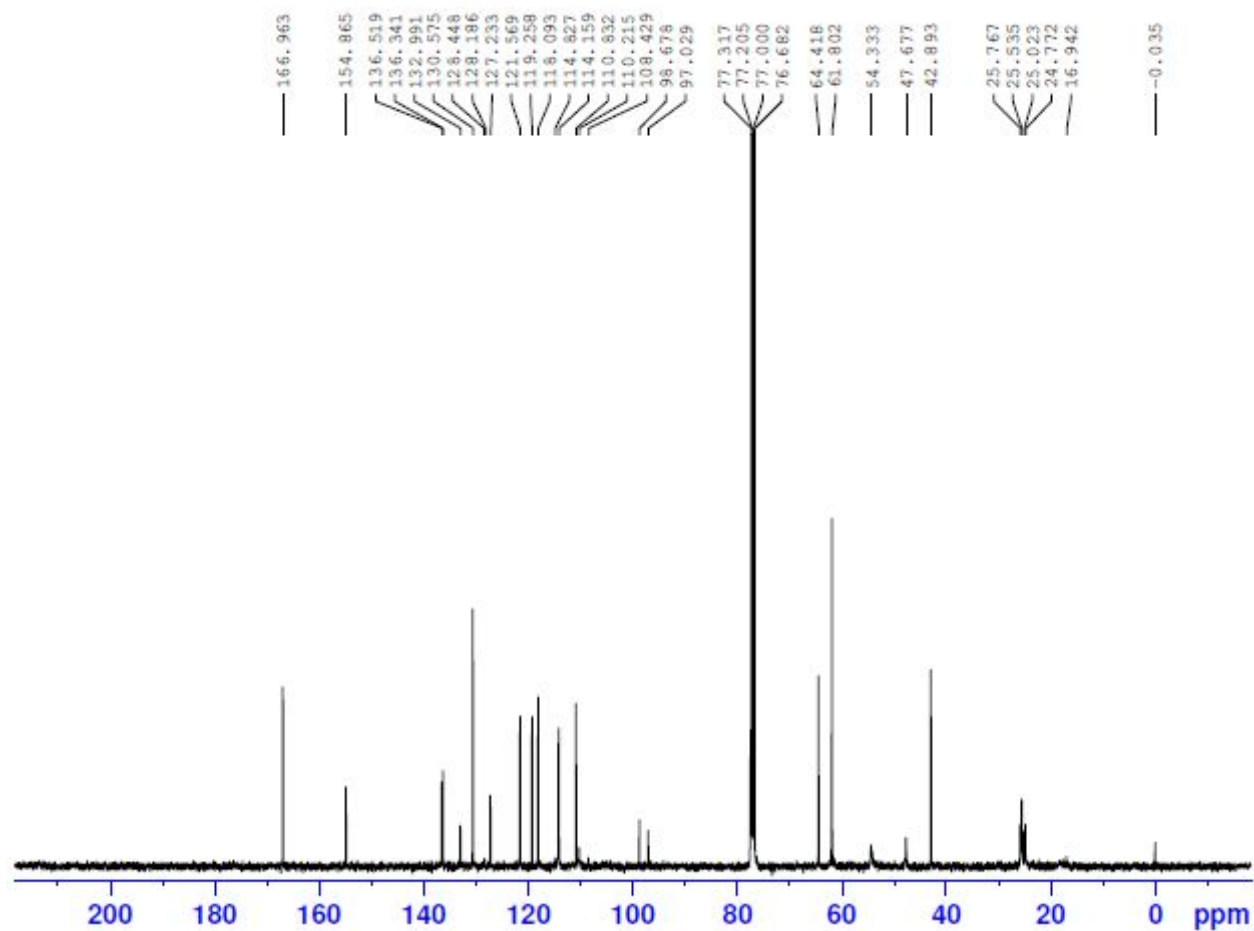
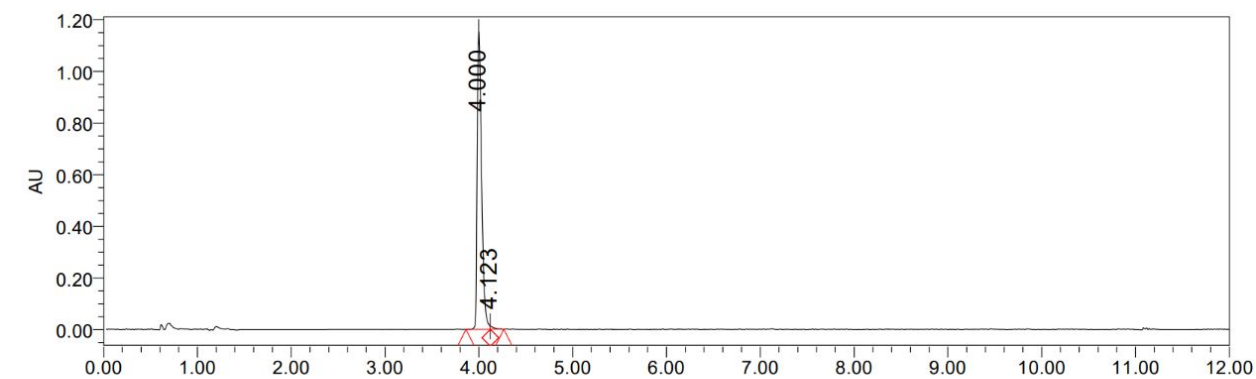


Figure S83. HPLC chromatogram of Compound 34



Peak Results

	RT	Area	% Area
1	4.000	3790585	99.15
2	4.123	32644	0.85

Figure S84. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 34

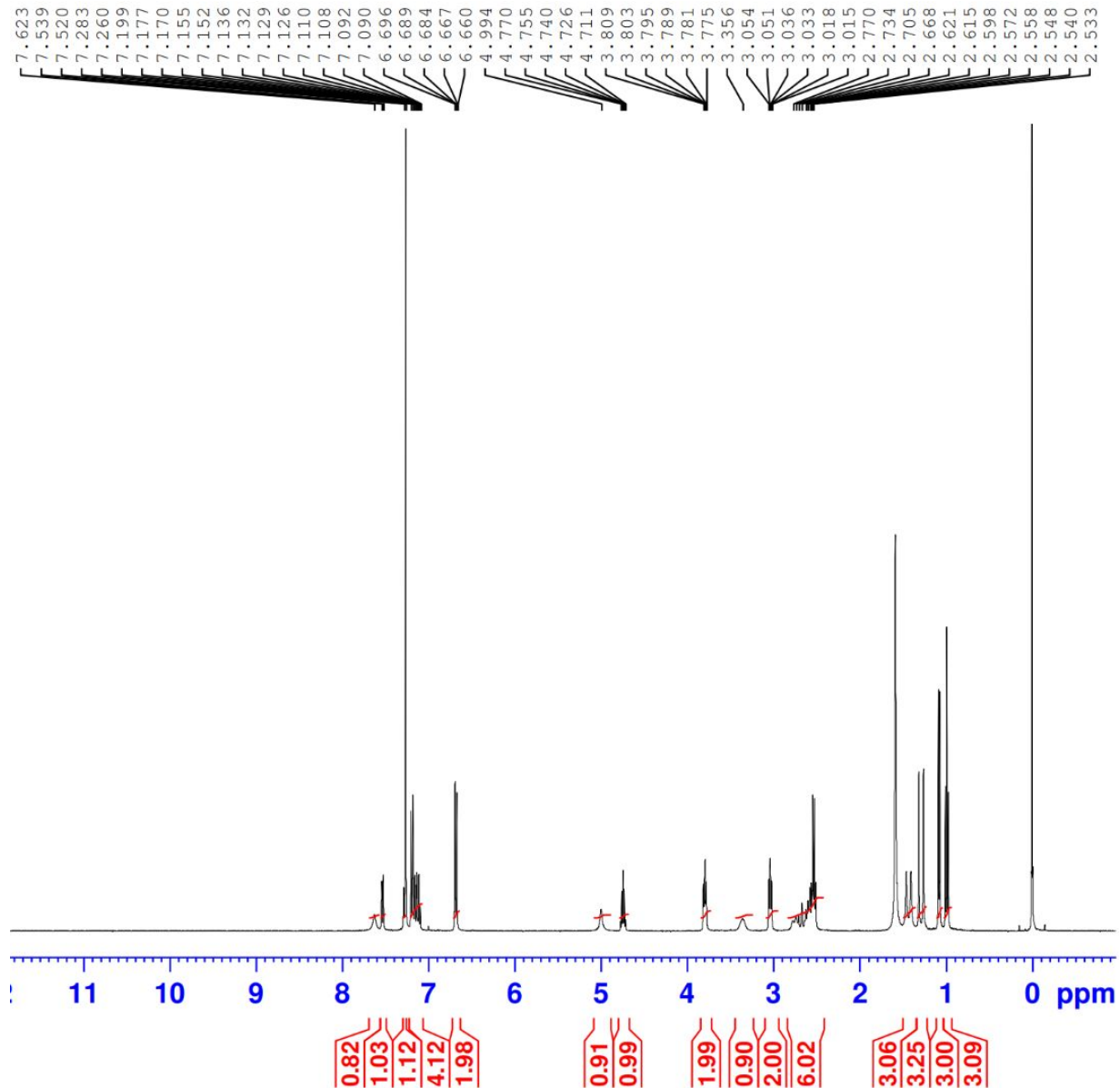


Figure S85. HRMS spectrum of Compound 34

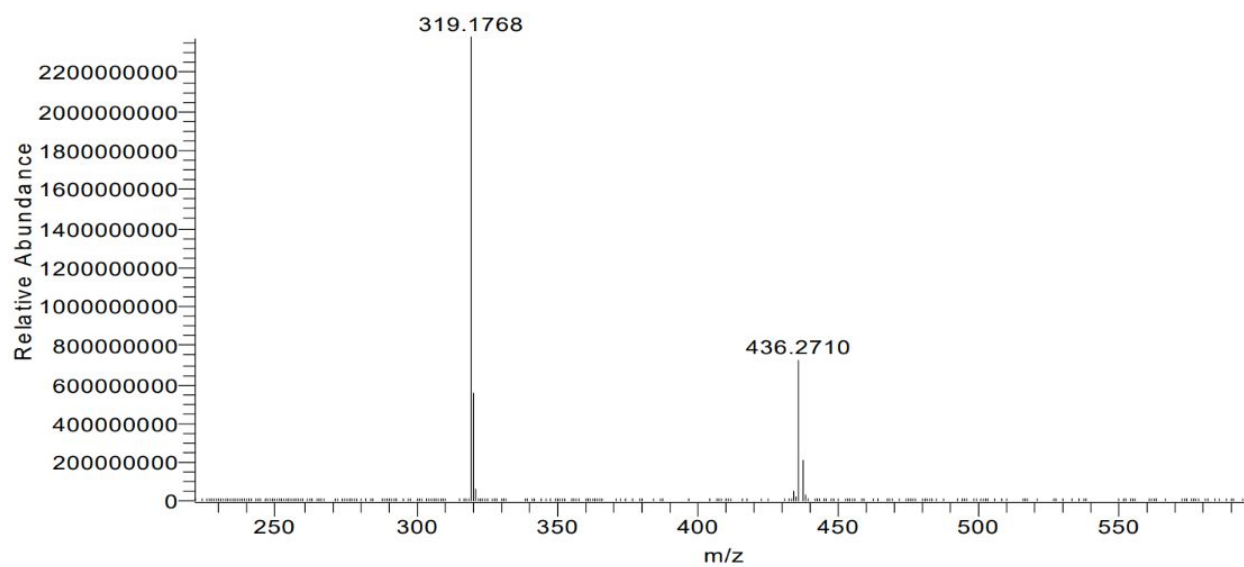


Figure S86. ^{19}F -NMR spectrum of Compound 34

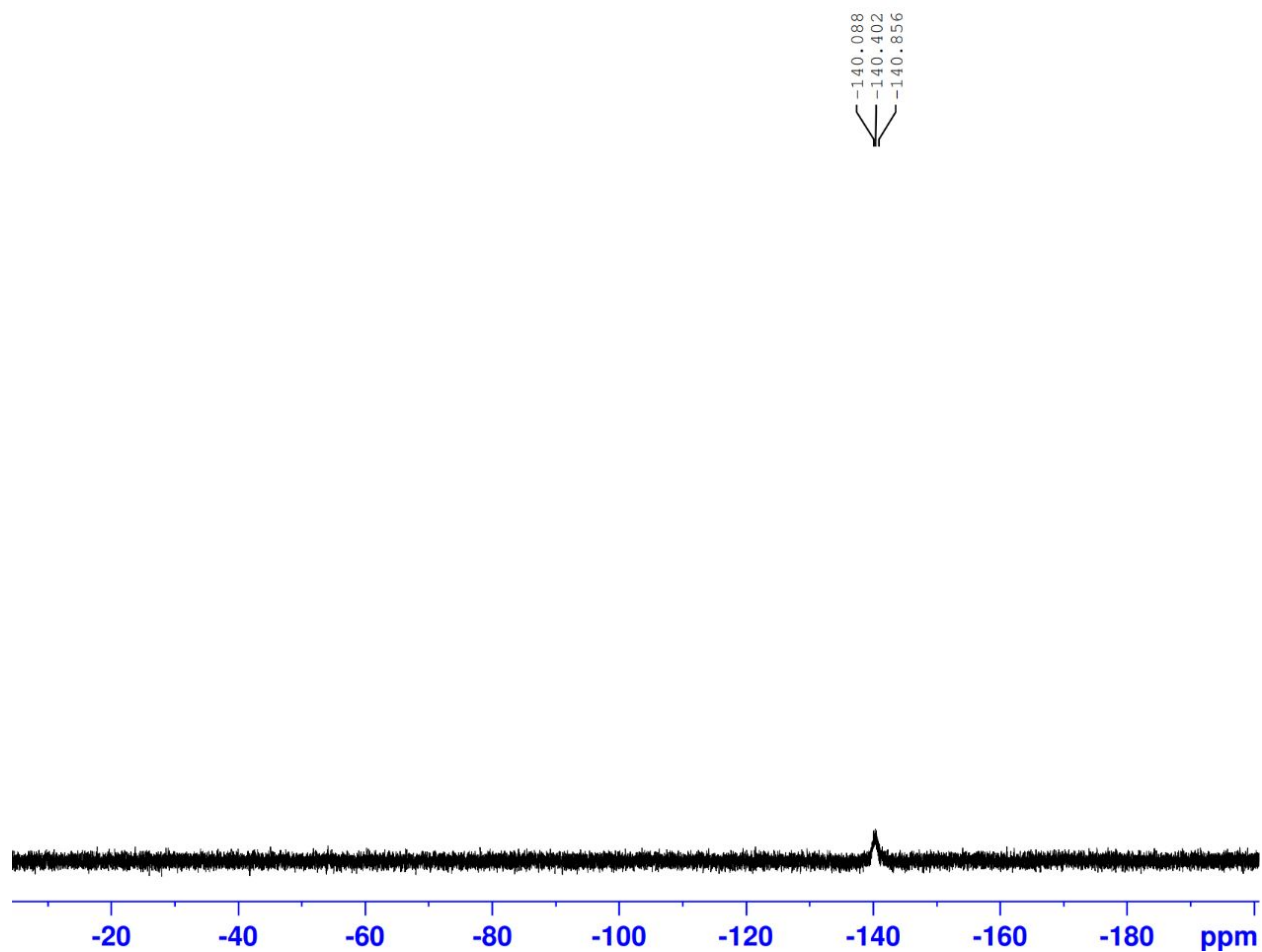


Figure S87. ^{13}C -NMR spectrum of Compound 34

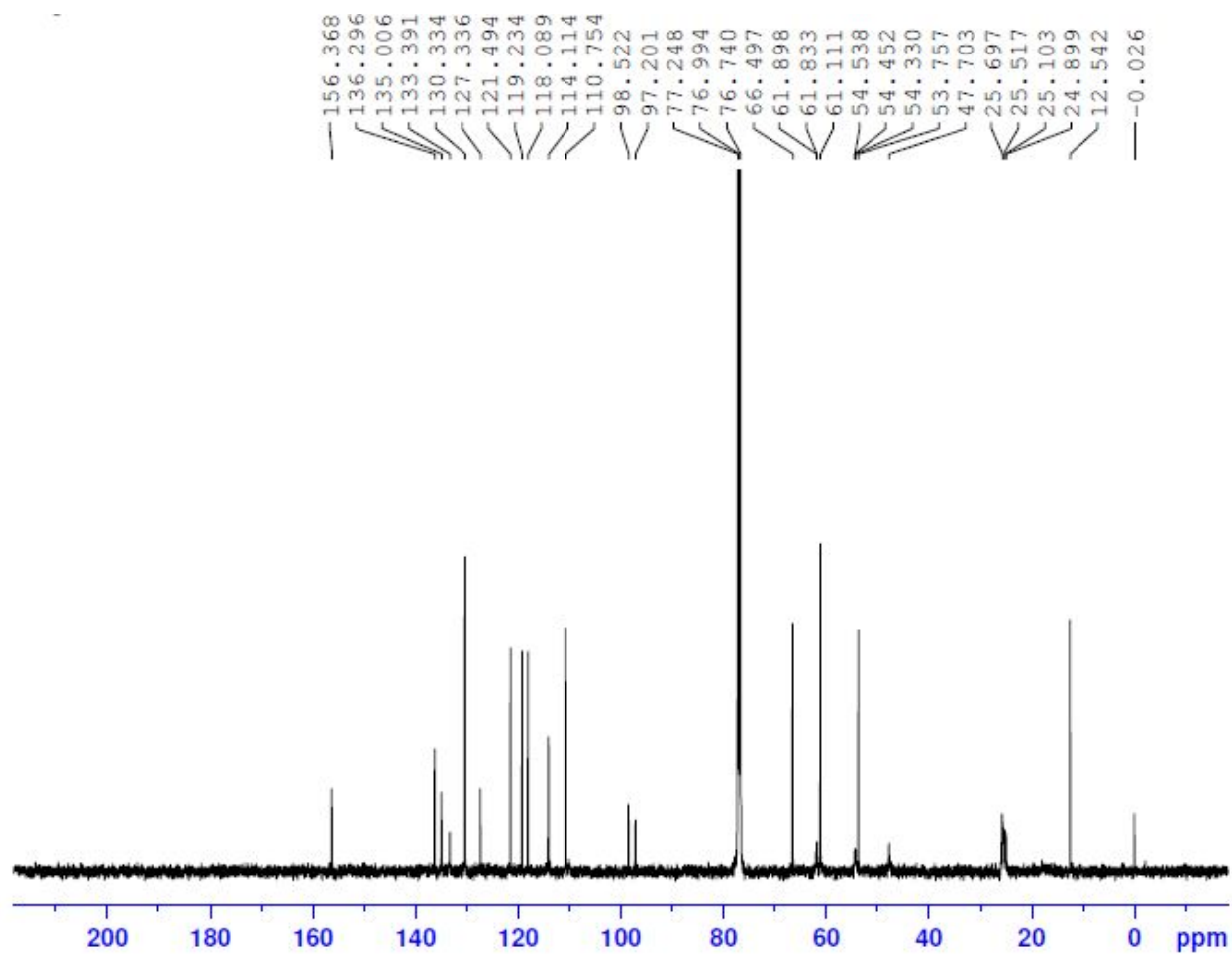
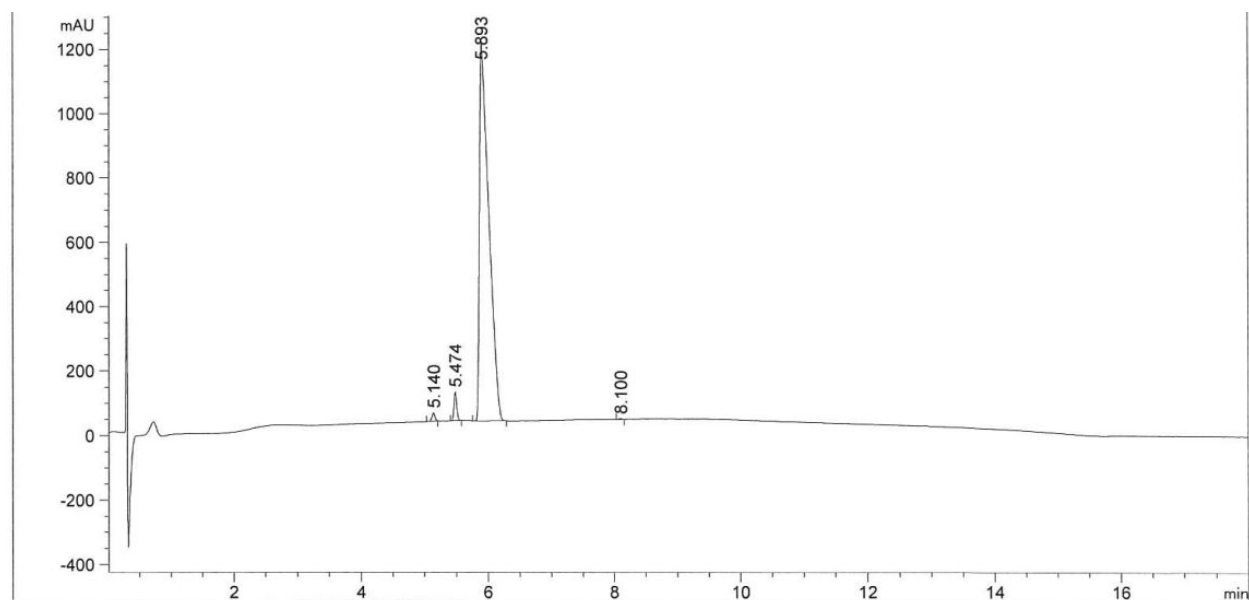


Figure S88. HPLC chromatogram of Compound 35



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.140	BB	0.0491	80.46587	25.32180	0.6498
2	5.474	BB	0.0445	262.98920	88.90643	2.1239
3	5.893	BB	0.1339	1.20308e4	1180.88074	97.1594
4	8.100	BB	0.0491	8.28857	2.60355	0.0669

Figure S89. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 35

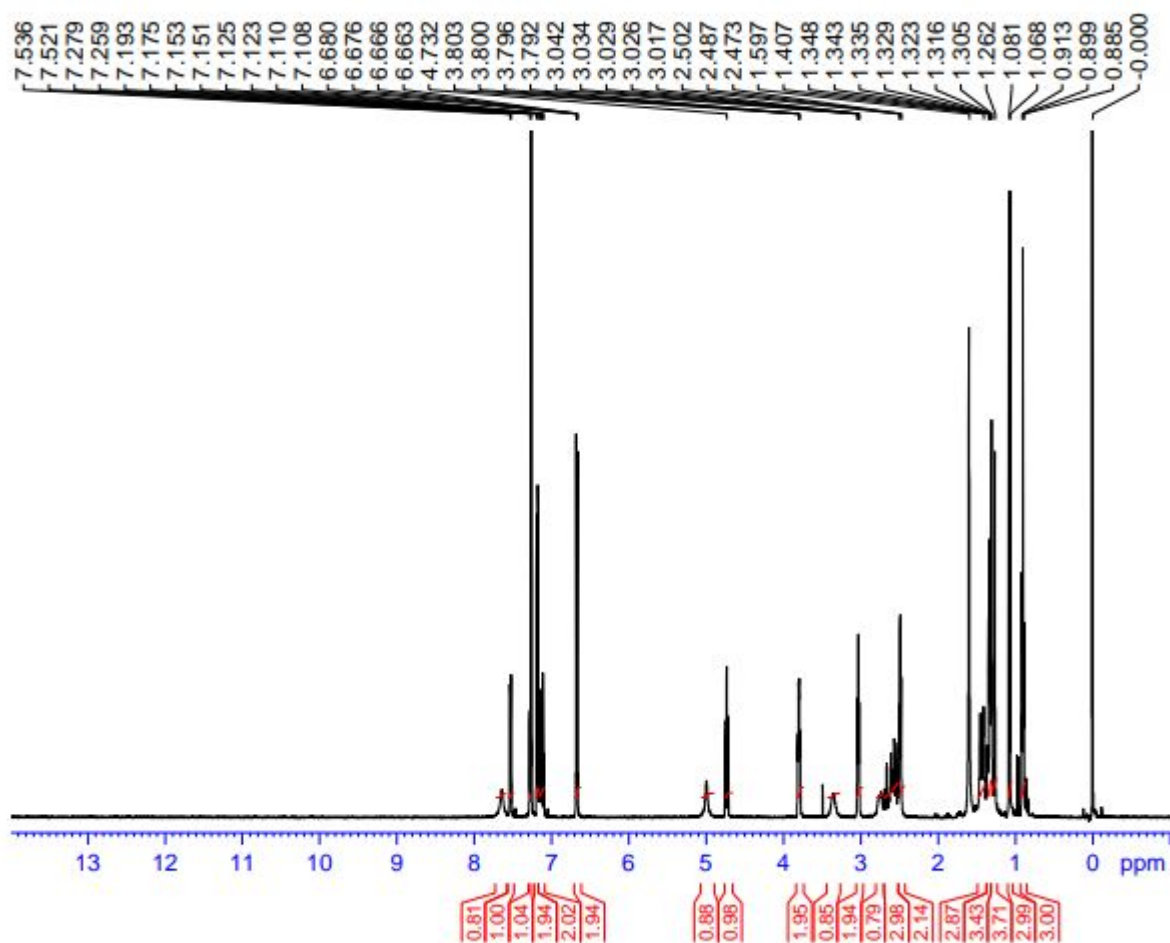


Figure S90. HRMS spectrum of Compound 35

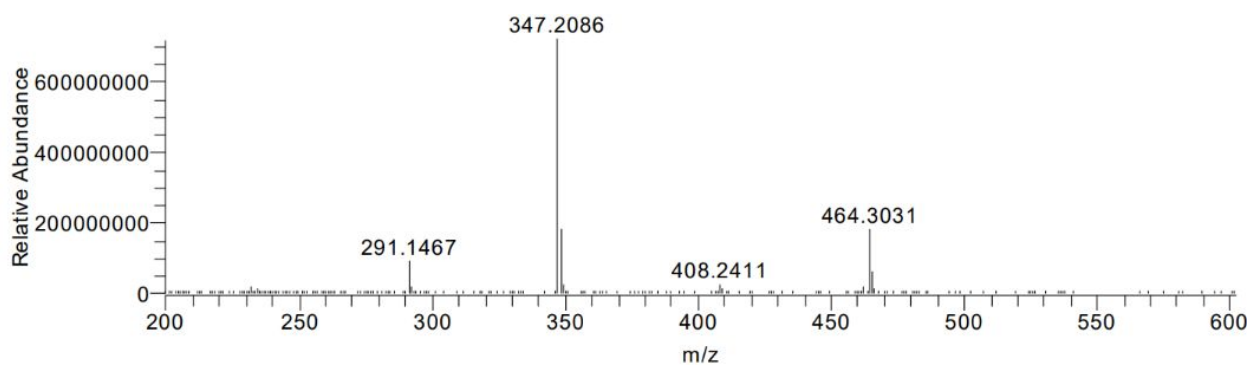


Figure S91. ^{19}F -NMR spectrum of Compound 35

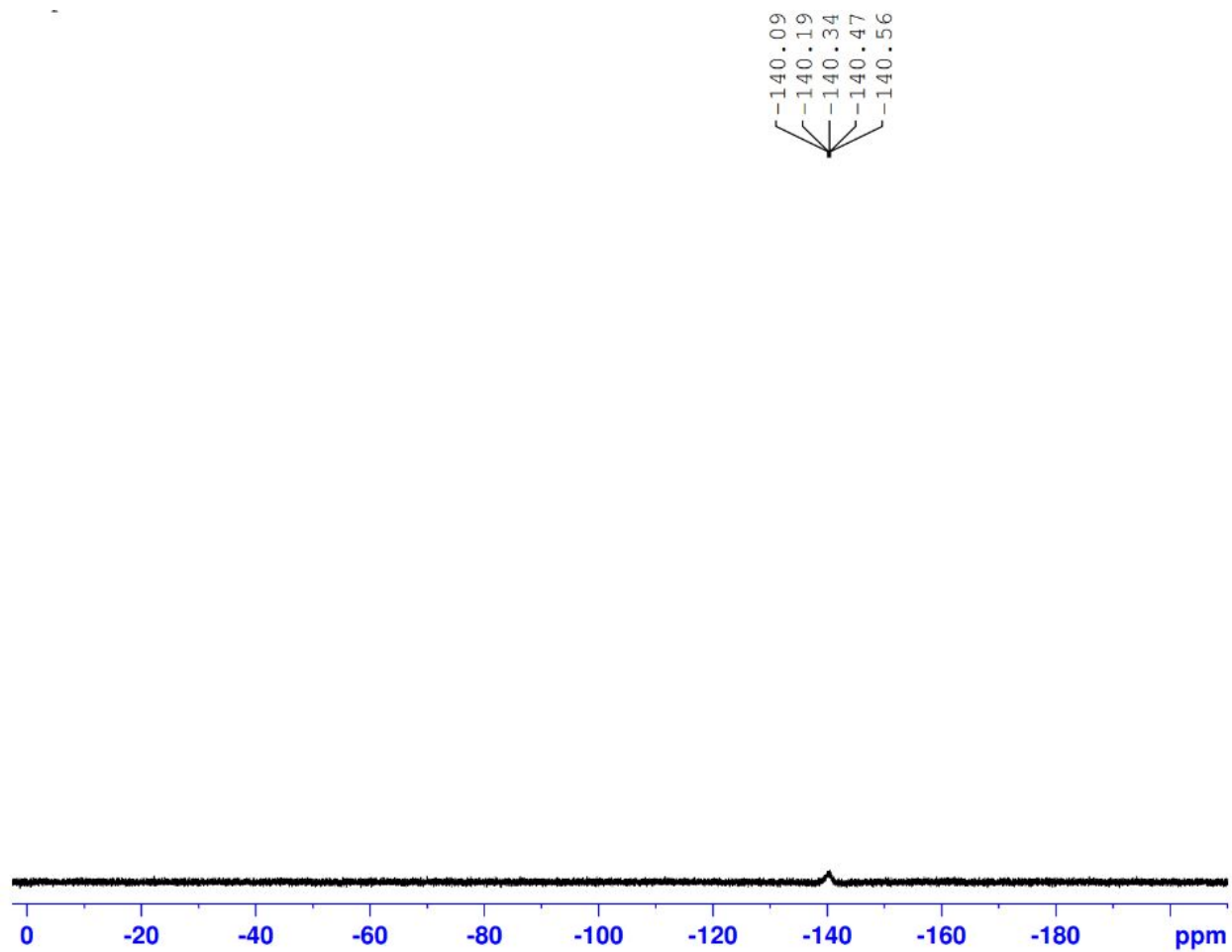


Figure S92. ^{13}C -NMR spectrum of Compound 35

^{13}C NMR (100 MHz, CDCl_3) δ = 156.39, 136.34, 135.02, 133.42, 130.34, 127.35, 121.48, 119.22, 118.09, 114.12, 110.77, 110.11, 98.67, 97.02, 66.61, 61.91, 61.62, 61.57, 59.77, 54.47, 54.31, 47.70, 29.88, 25.31 (br dd, J = 24.2, 61.6 Hz), 20.45, 14.00

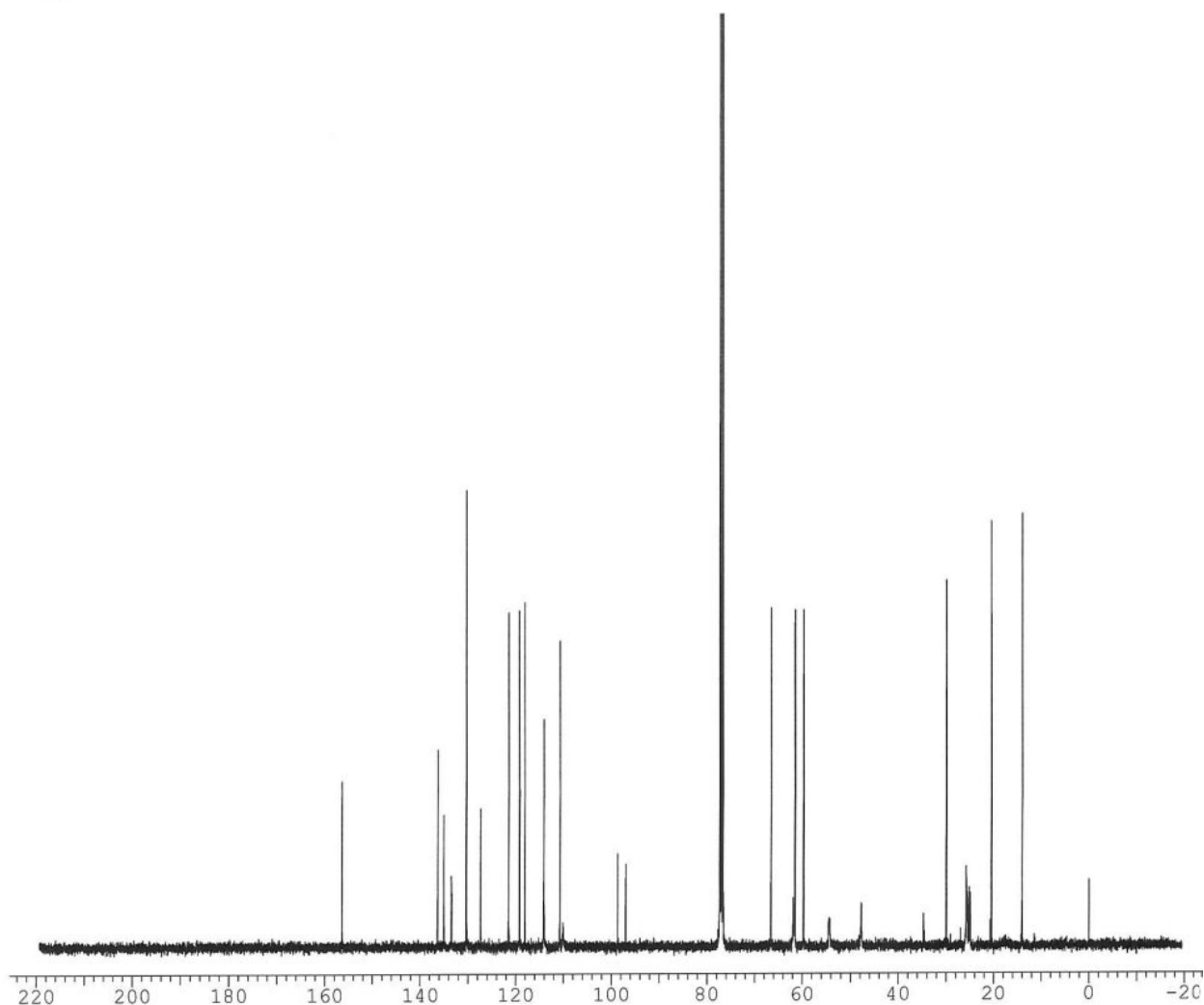
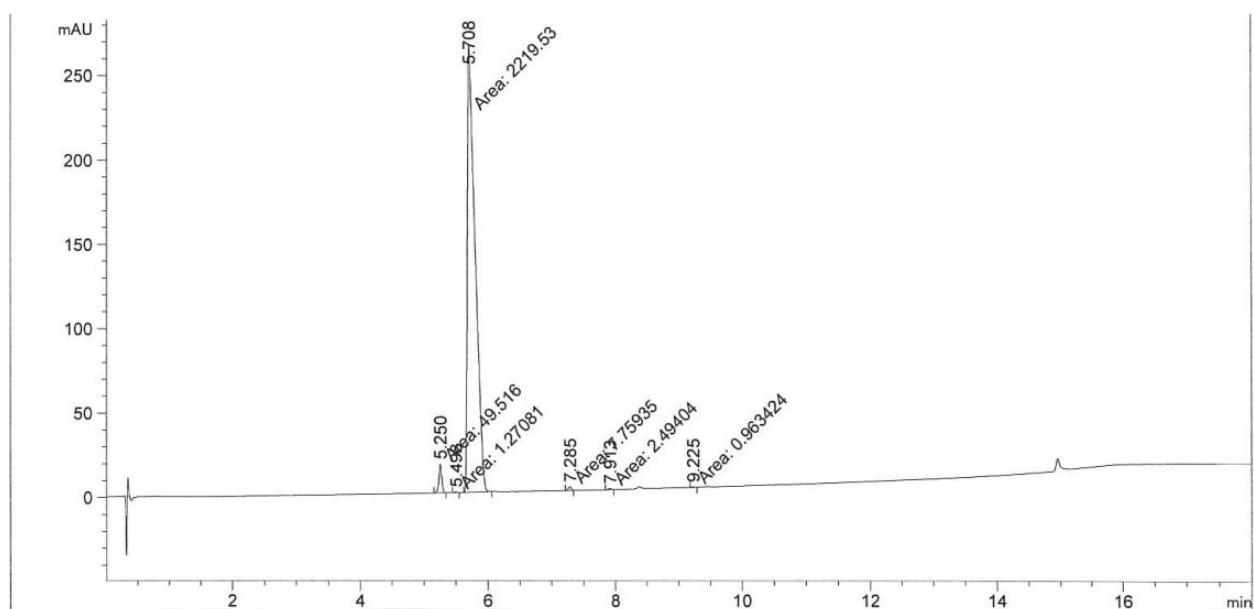


Figure S93. HPLC chromatogram of Compound 36



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.250	MM	0.0485	49.51603	17.00019	2.1703
2	5.498	MM	0.0481	1.27081	4.40232e-1	0.0557
3	5.708	MM	0.1395	2219.53394	265.20615	97.2824
4	7.285	MM	0.0577	7.75935	2.23962	0.3401
5	7.913	MM	0.0561	2.49404	7.41575e-1	0.1093
6	9.225	MM	0.0550	9.63424e-1	2.92002e-1	0.0422

Figure S94. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 36

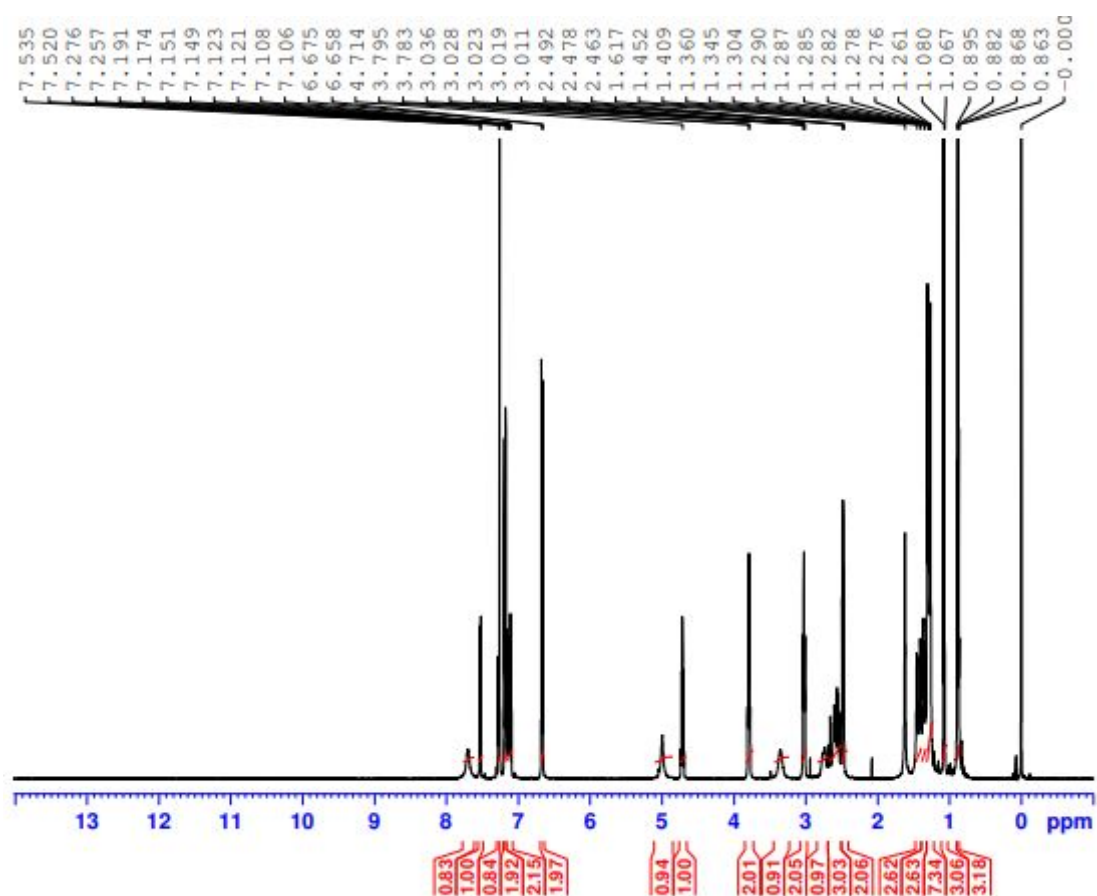


Figure S95. HRMS spectrum of Compound 36

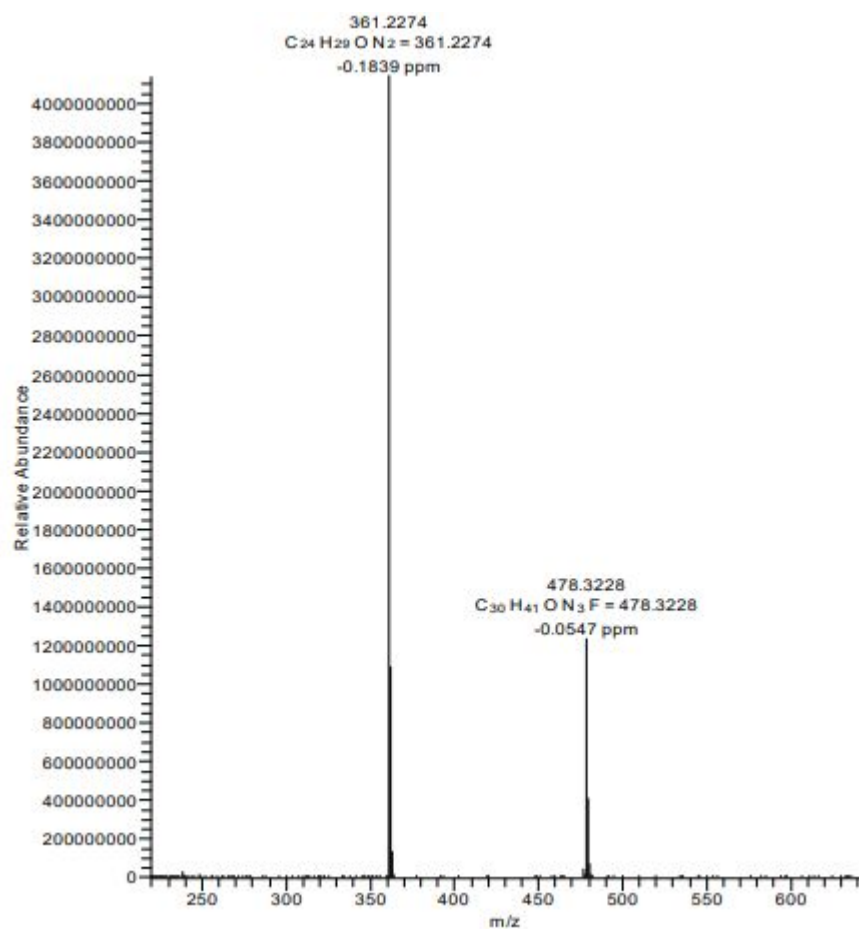


Figure S96. ^{19}F -NMR spectrum of Compound 36

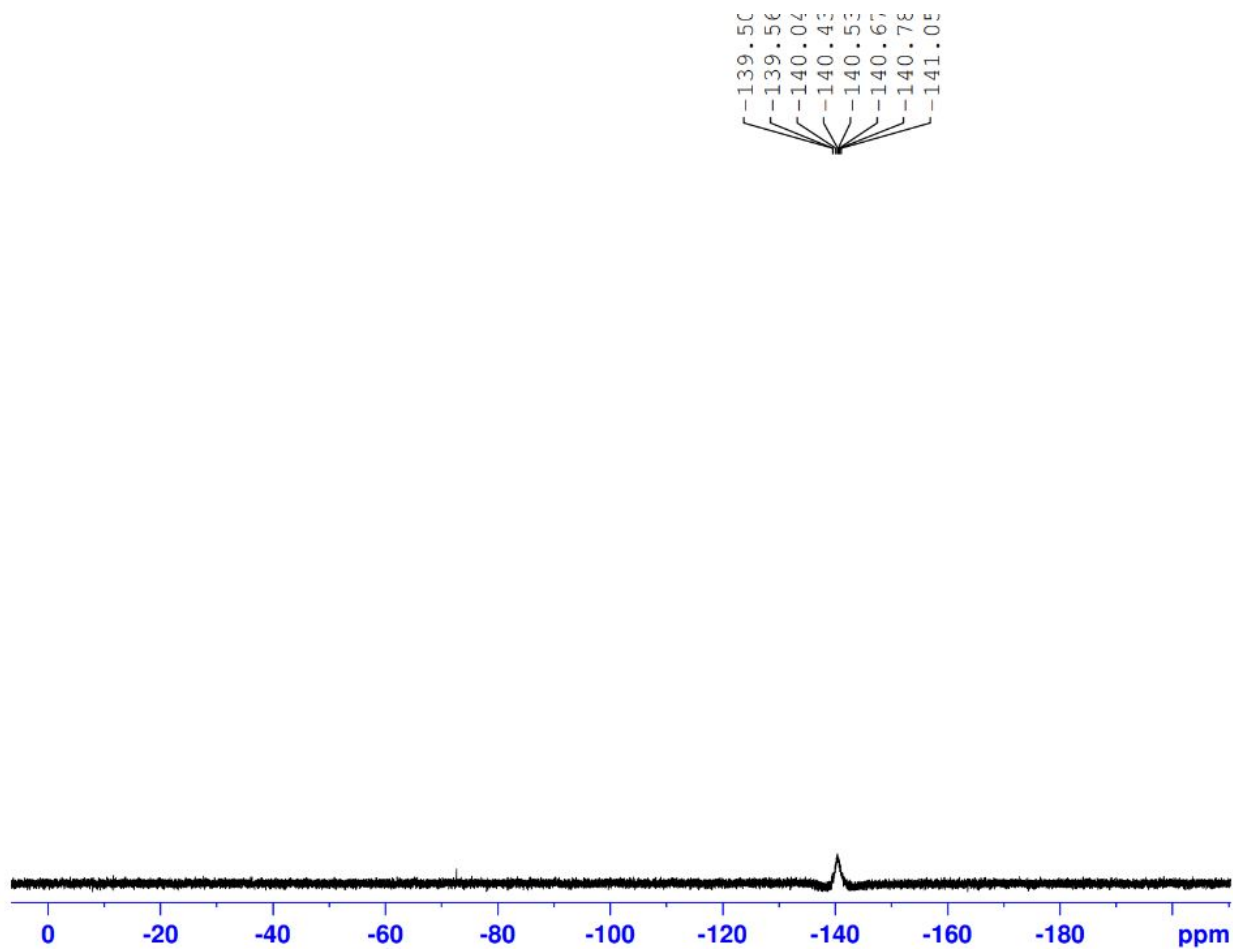


Figure S97. ^{13}C -NMR spectrum of Compound 36

^{13}C NMR (100 MHz, CDCl_3) δ = 156.42, 136.33, 134.98, 133.42, 130.34, 127.37, 121.51, 119.25, 118.10, 114.12, 110.76, 110.12, 98.66, 97.01, 66.65, 61.86, 61.63, 61.62, 60.09, 54.54, 54.33, 47.71, 29.51, 27.48, 25.72, 25.48, 25.15, 24.89, 22.59, 13.97

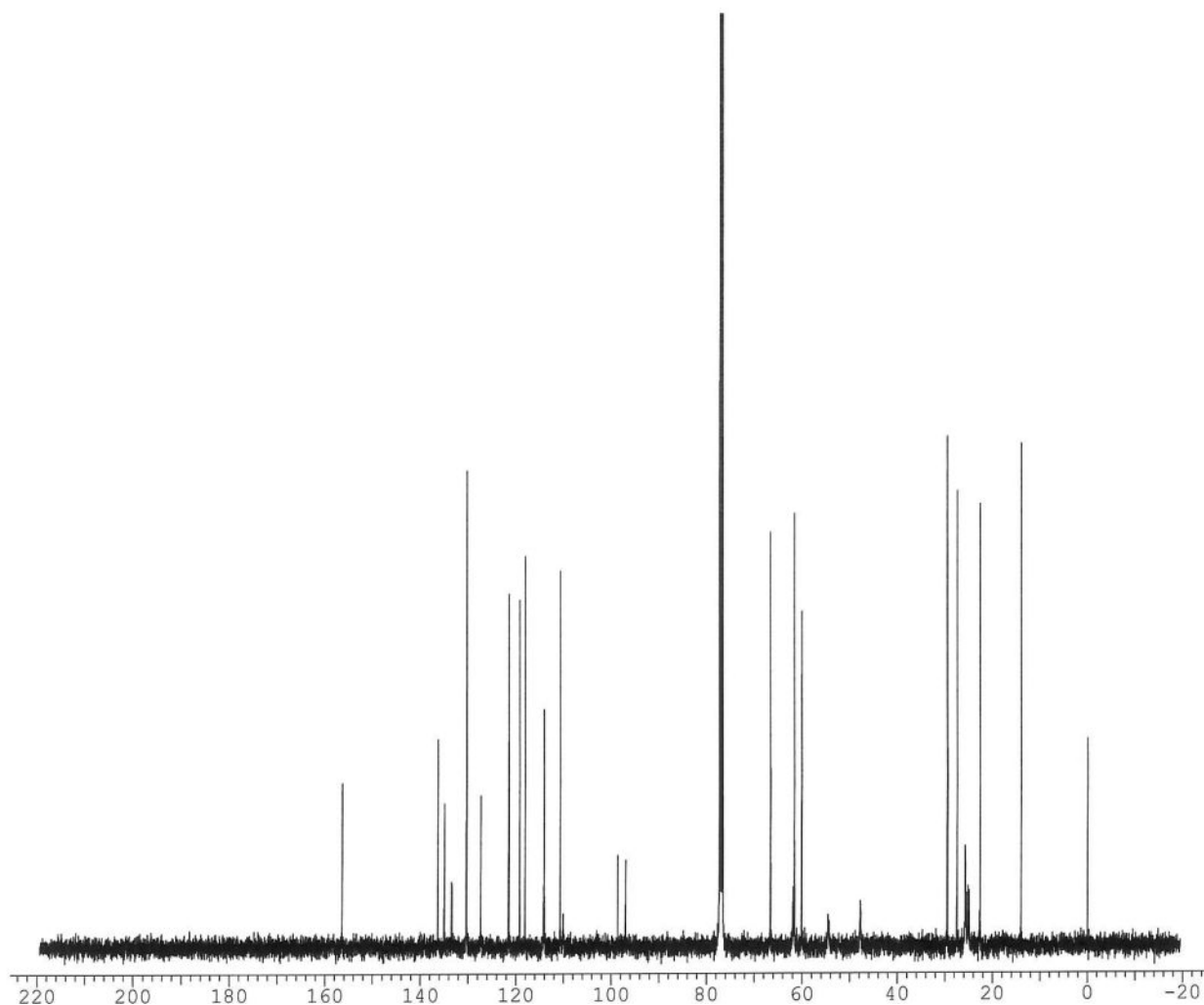
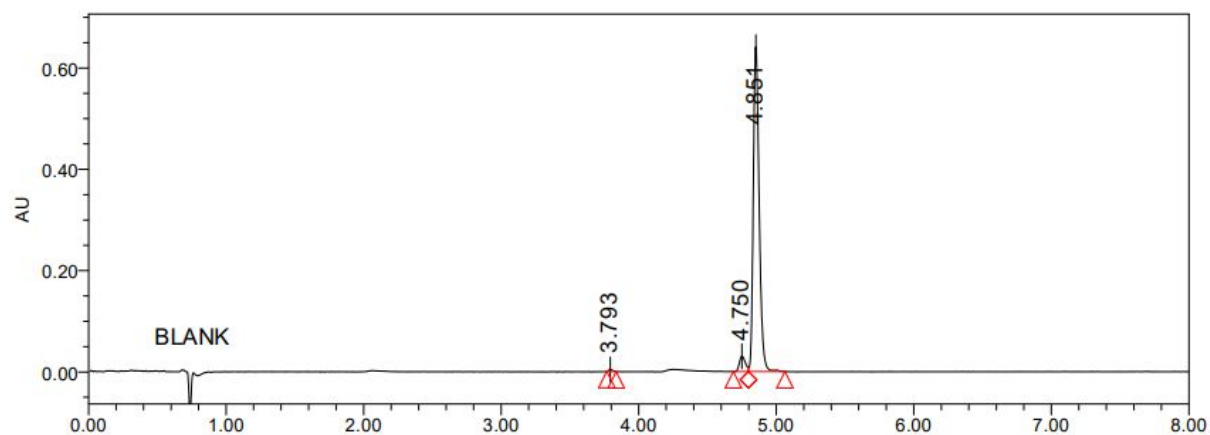


Figure S98. HPLC chromatogram of Compound 37



Peak Results

	RT	Area	% Area
1	3.793	7624	0.38
2	4.750	92245	4.61
3	4.851	1900903	95.01

Figure S99. $^1\text{H-NMR}$ (400 MHz, CDCl_3) spectrum of Compound 37

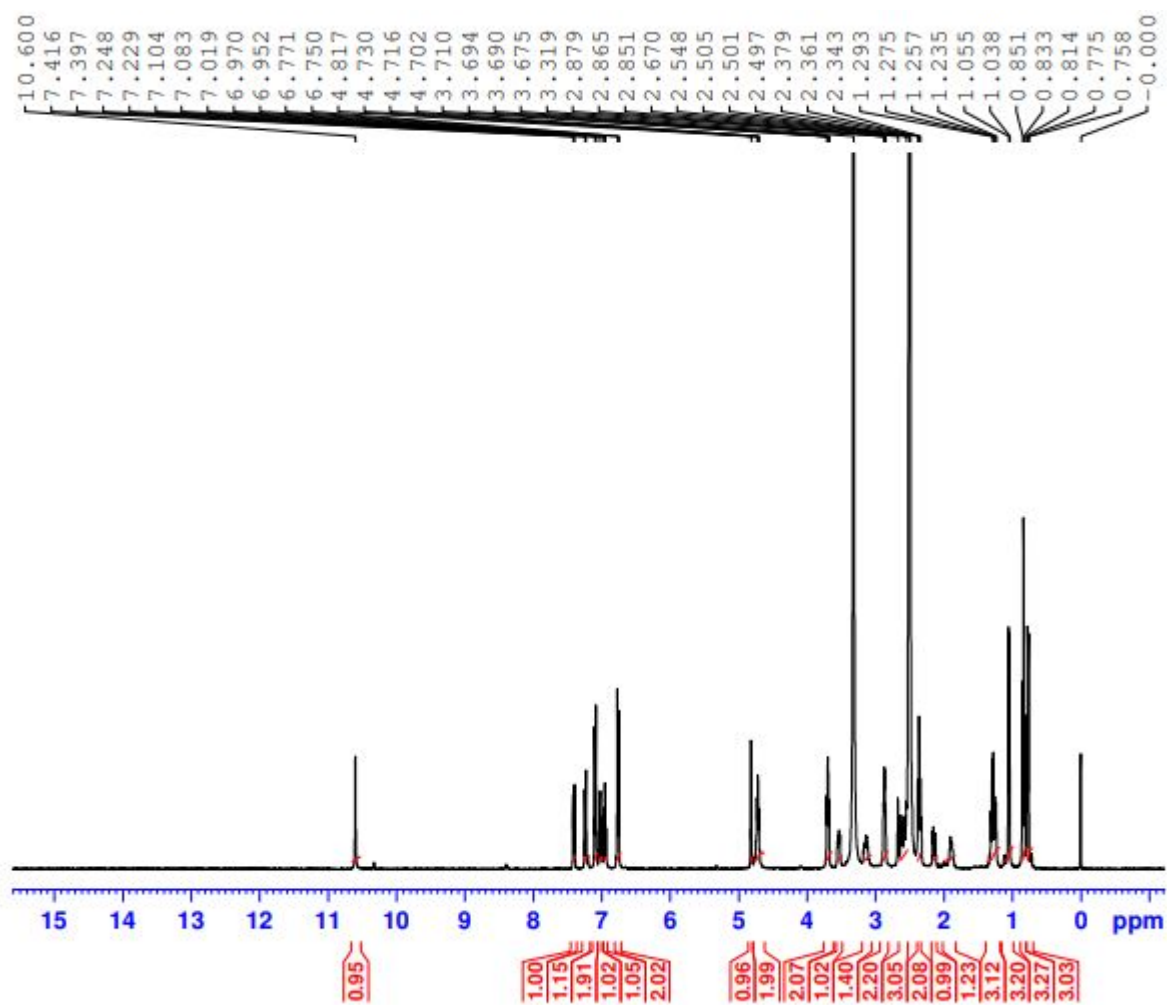


Figure S100. HRMS spectrum of Compound 37

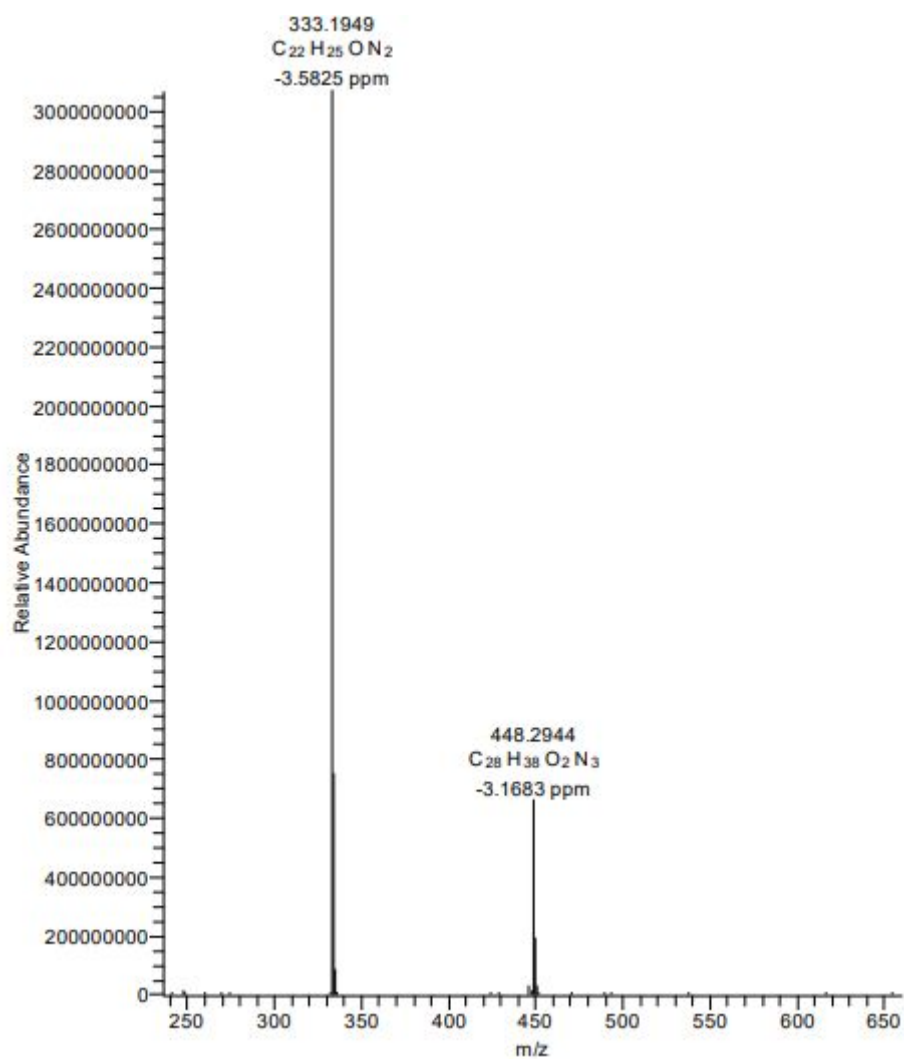


Figure S101. ^{13}C -NMR spectrum of Compound 37

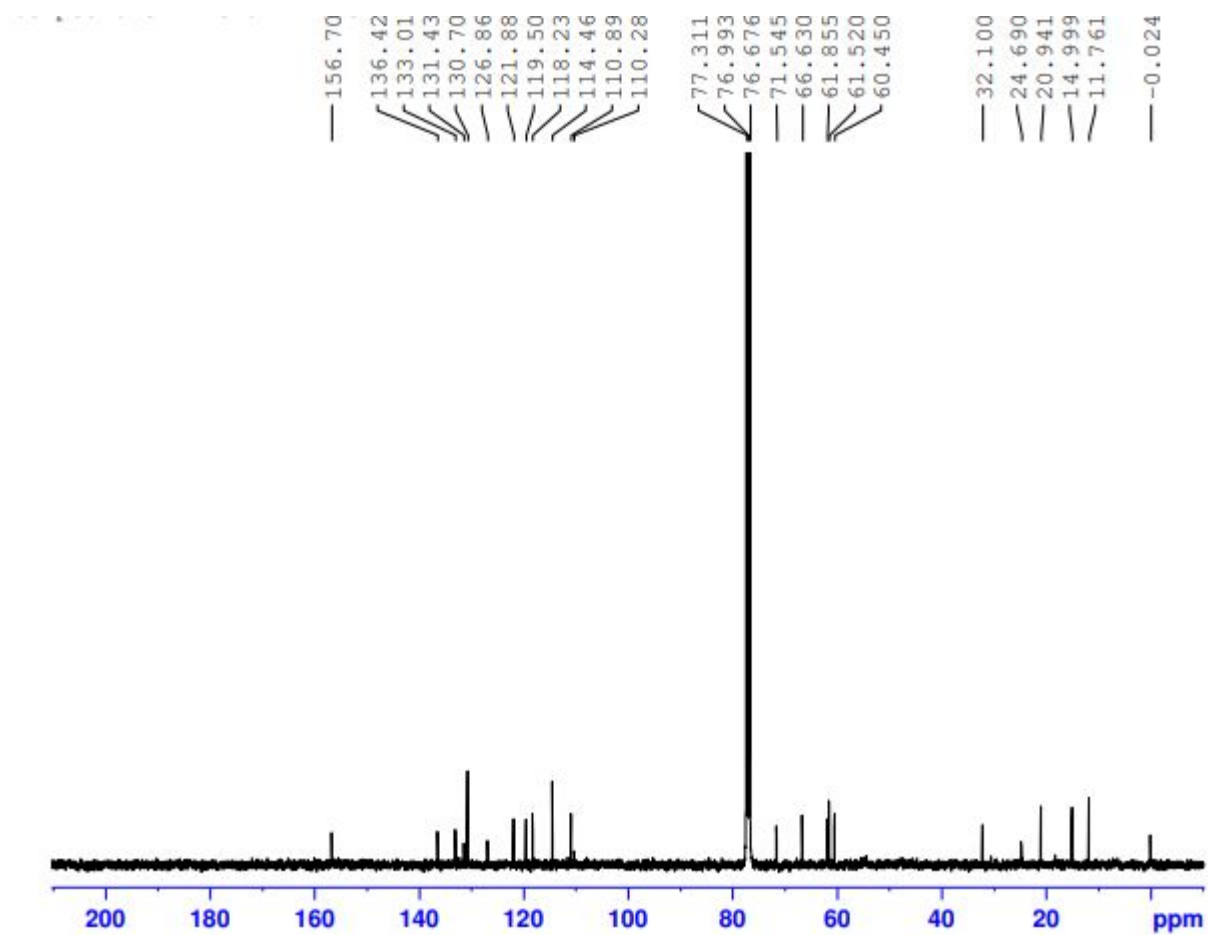
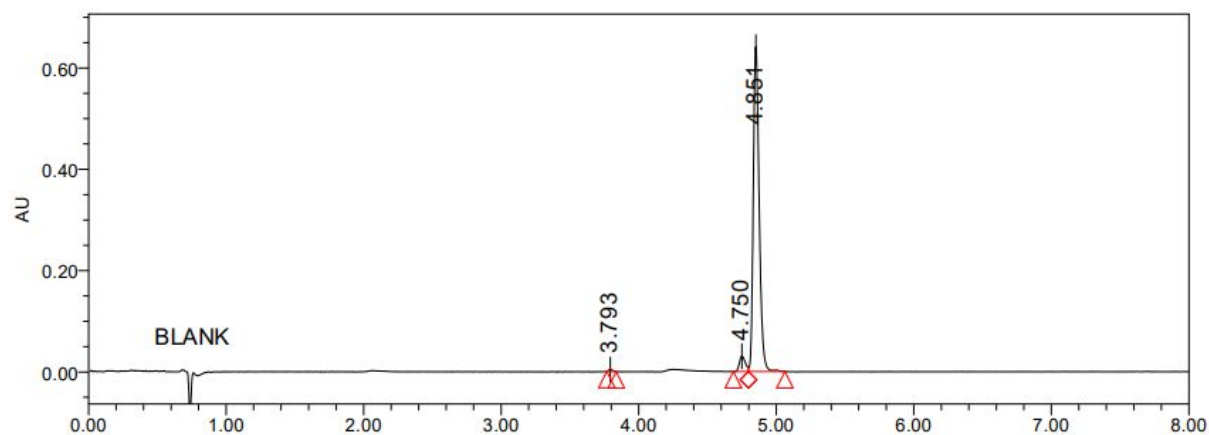


Figure S102. HPLC chromatogram of Compound 38



Peak Results

	RT	Area	% Area
1	3.793	7624	0.38
2	4.750	92245	4.61
3	4.851	1900903	95.01

Figure S103. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 38

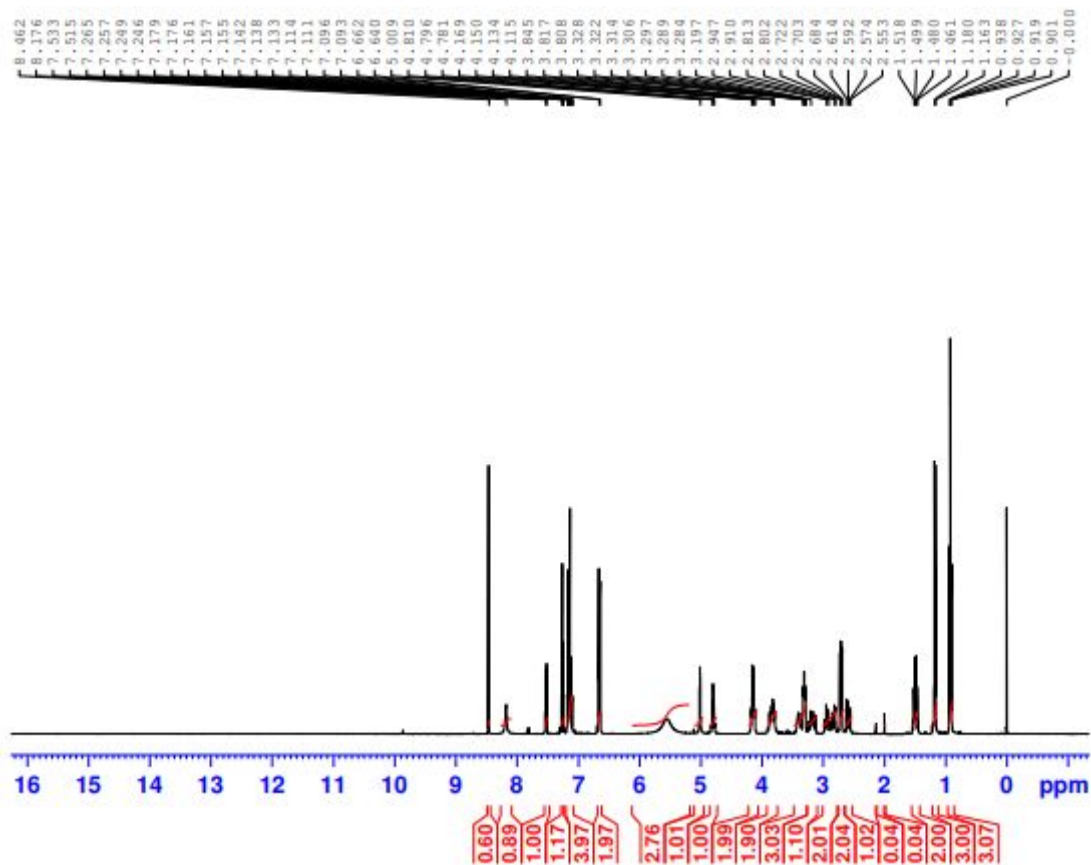


Figure S104. HRMS spectrum of Compound 38

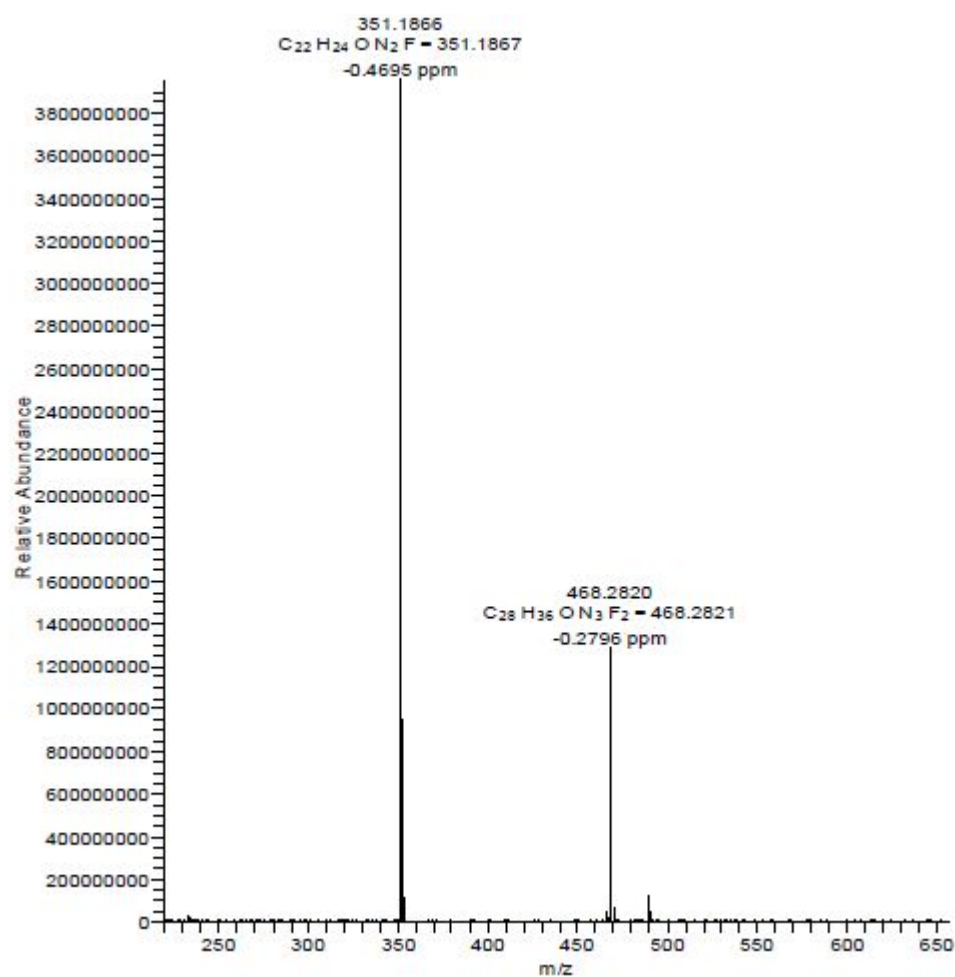


Figure S105. ^{19}F -NMR spectrum of Compound 38

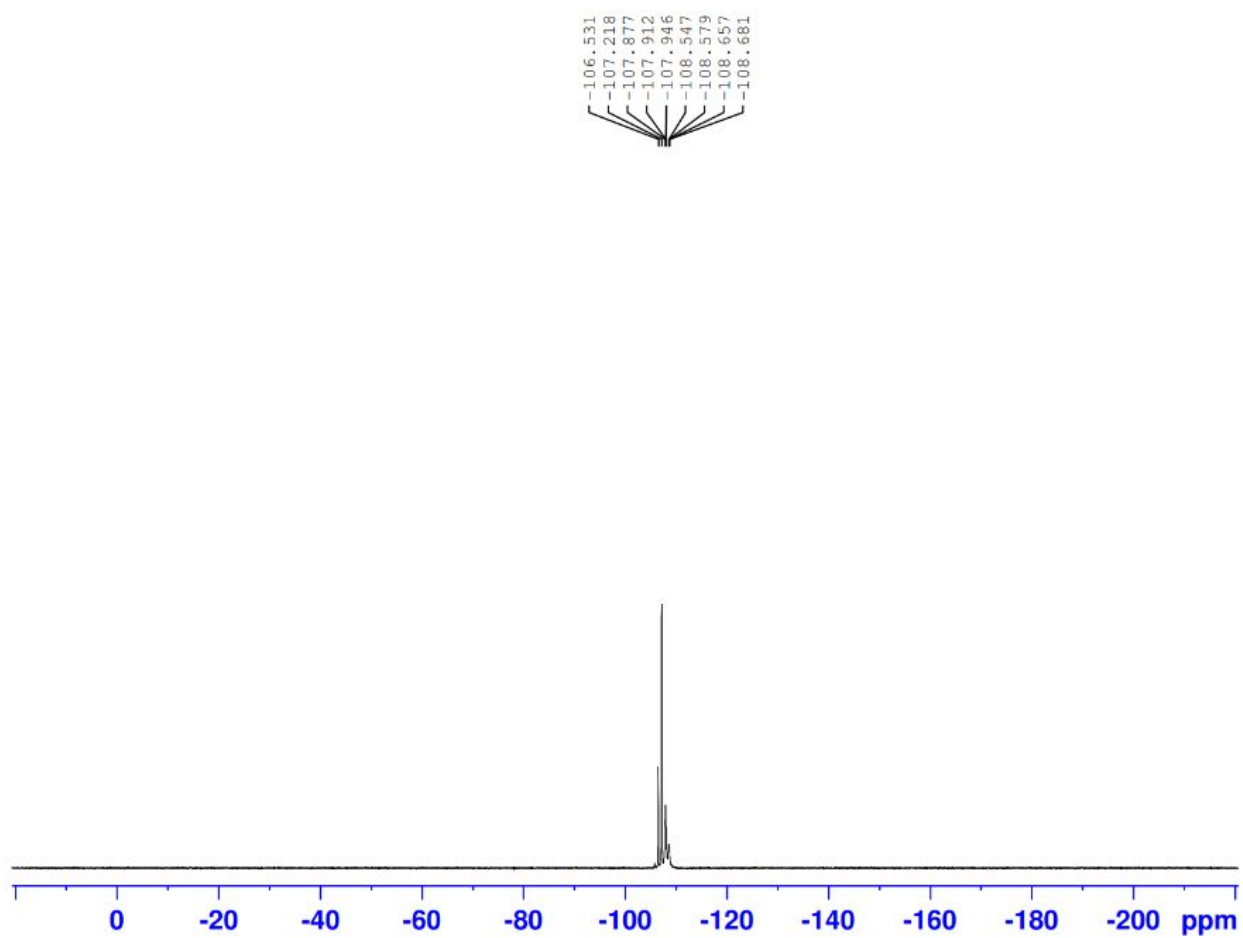


Figure S106. ^{13}C -NMR spectrum of Compound 38

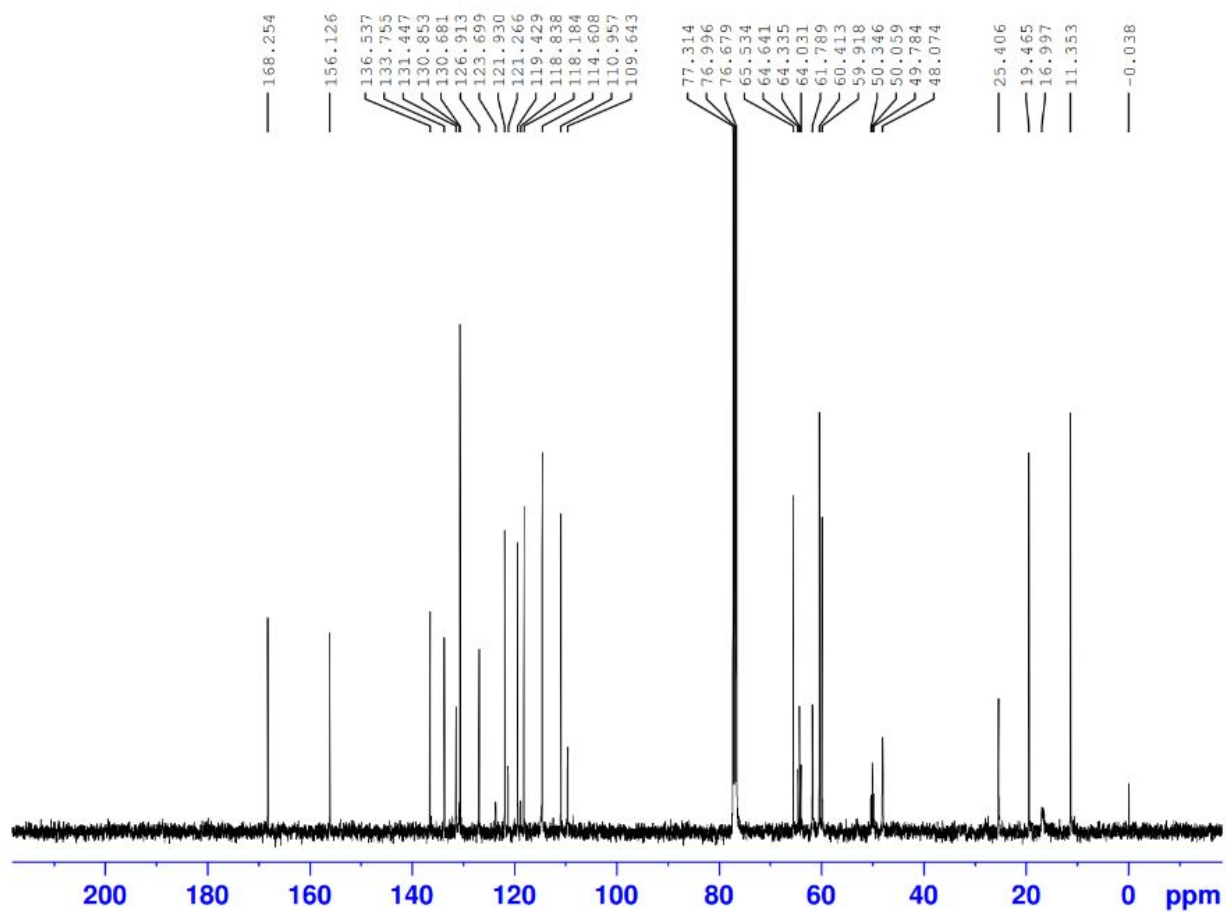


Figure S107. HPLC chromatogram of Compound 39

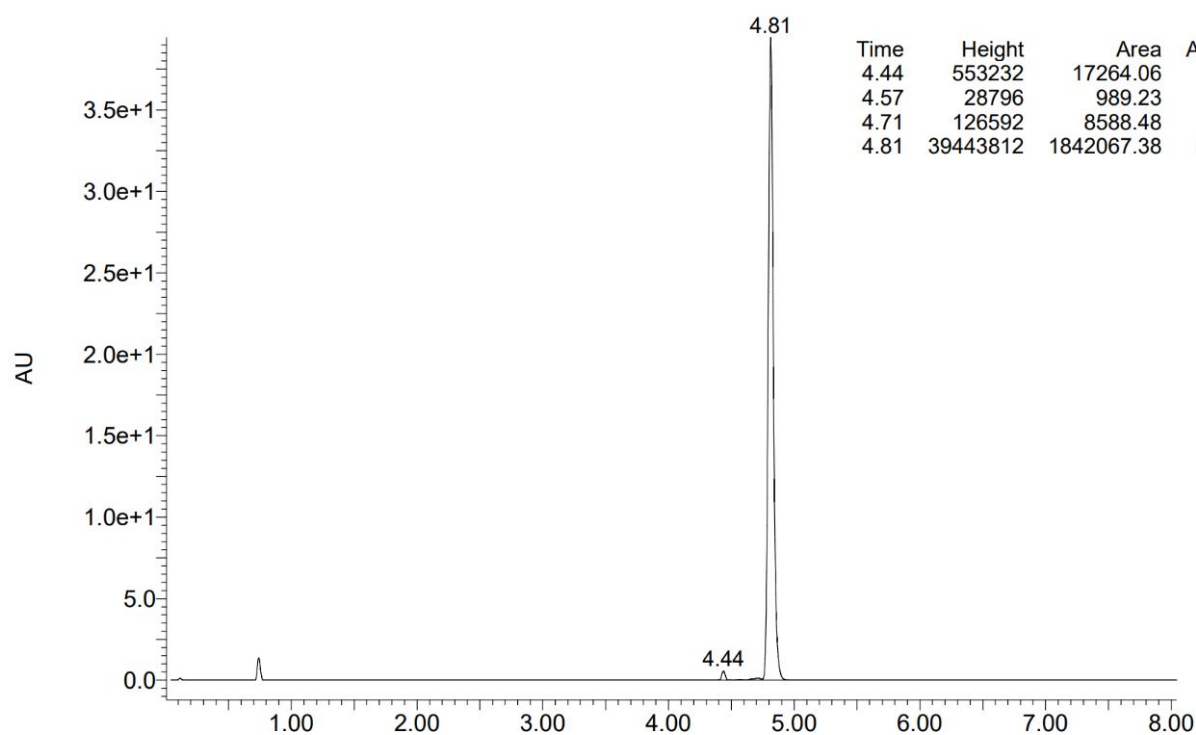


Figure S108. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 39

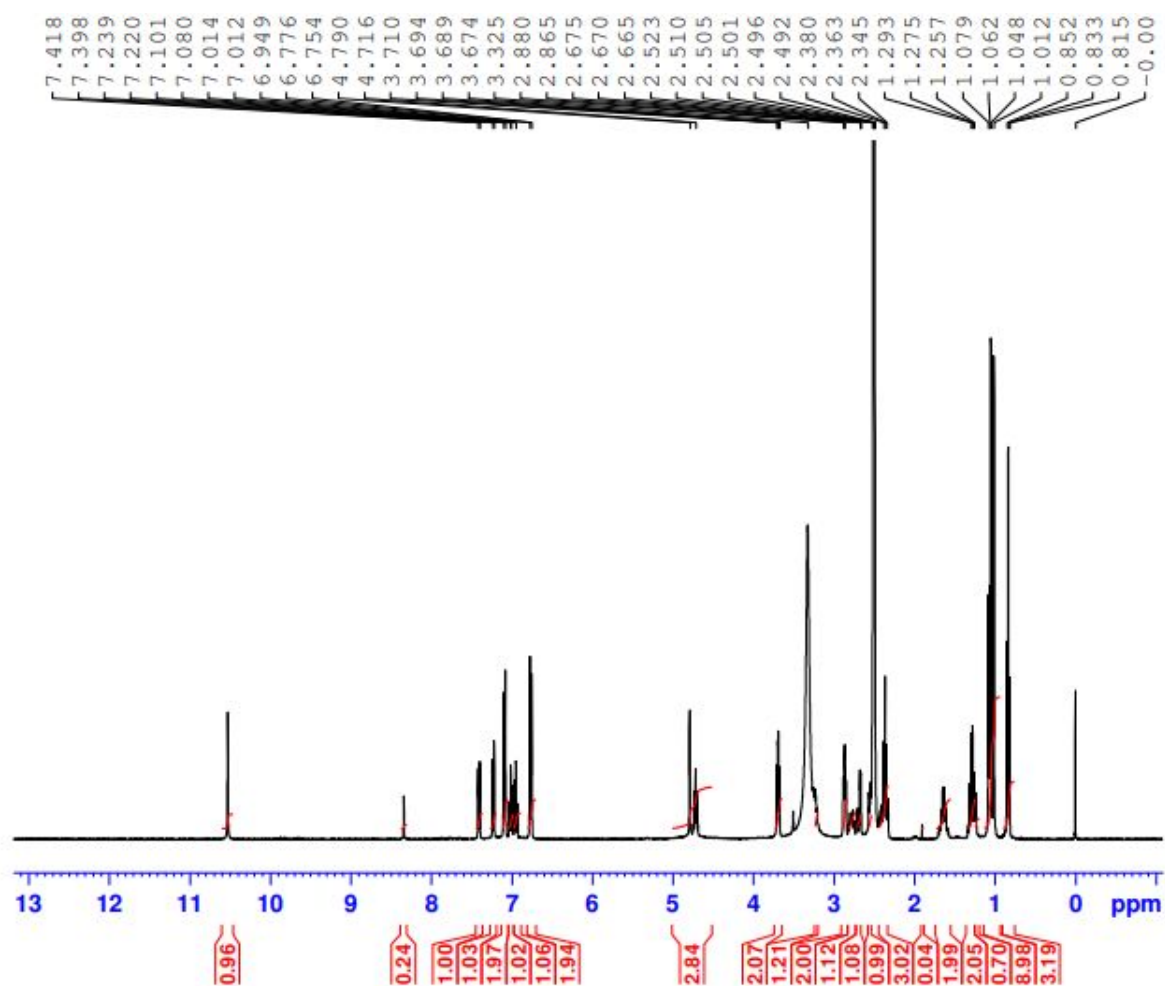


Figure S109. HRMS spectrum of Compound 39

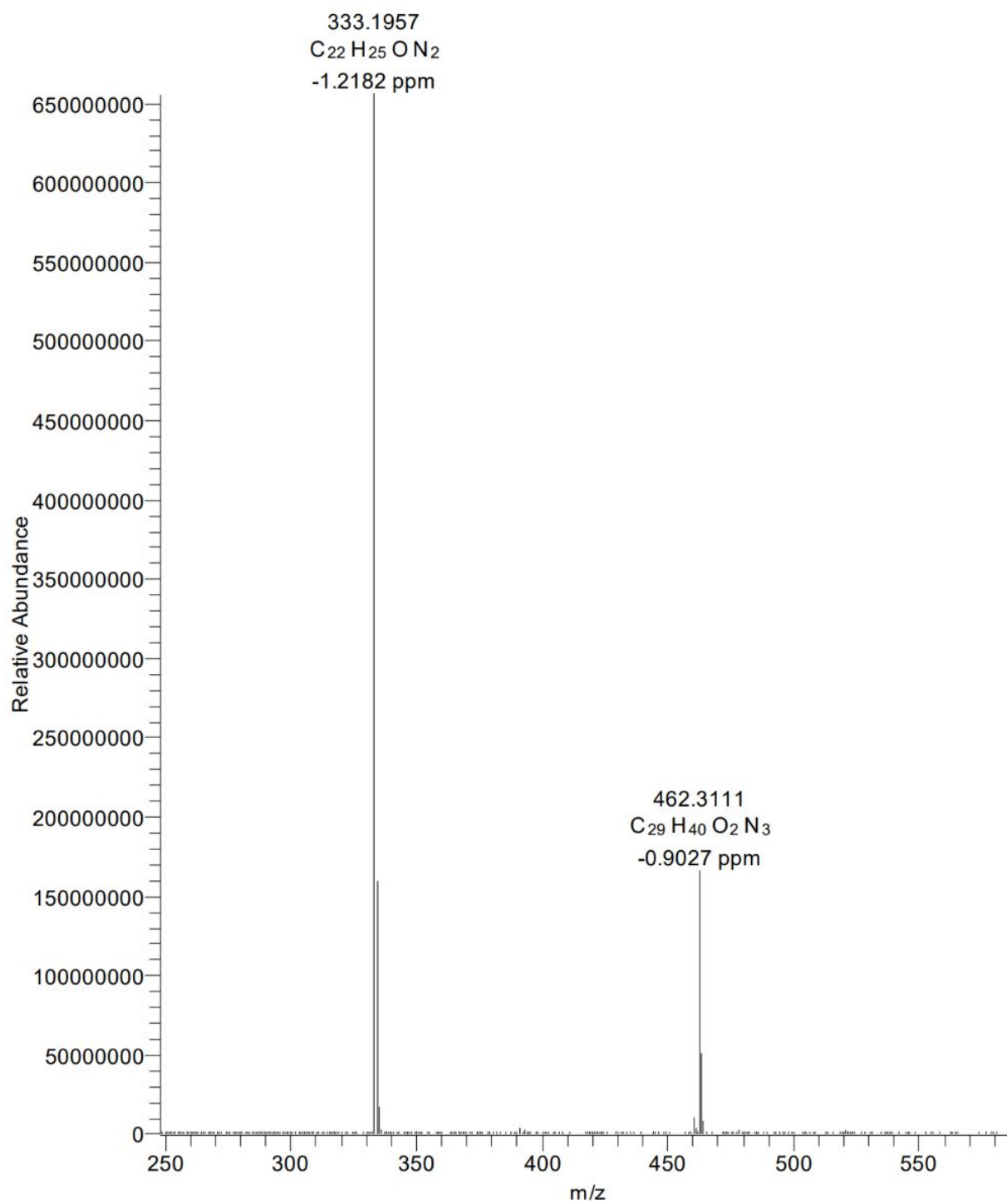


Figure S110. ^{13}C -NMR spectrum of Compound 39

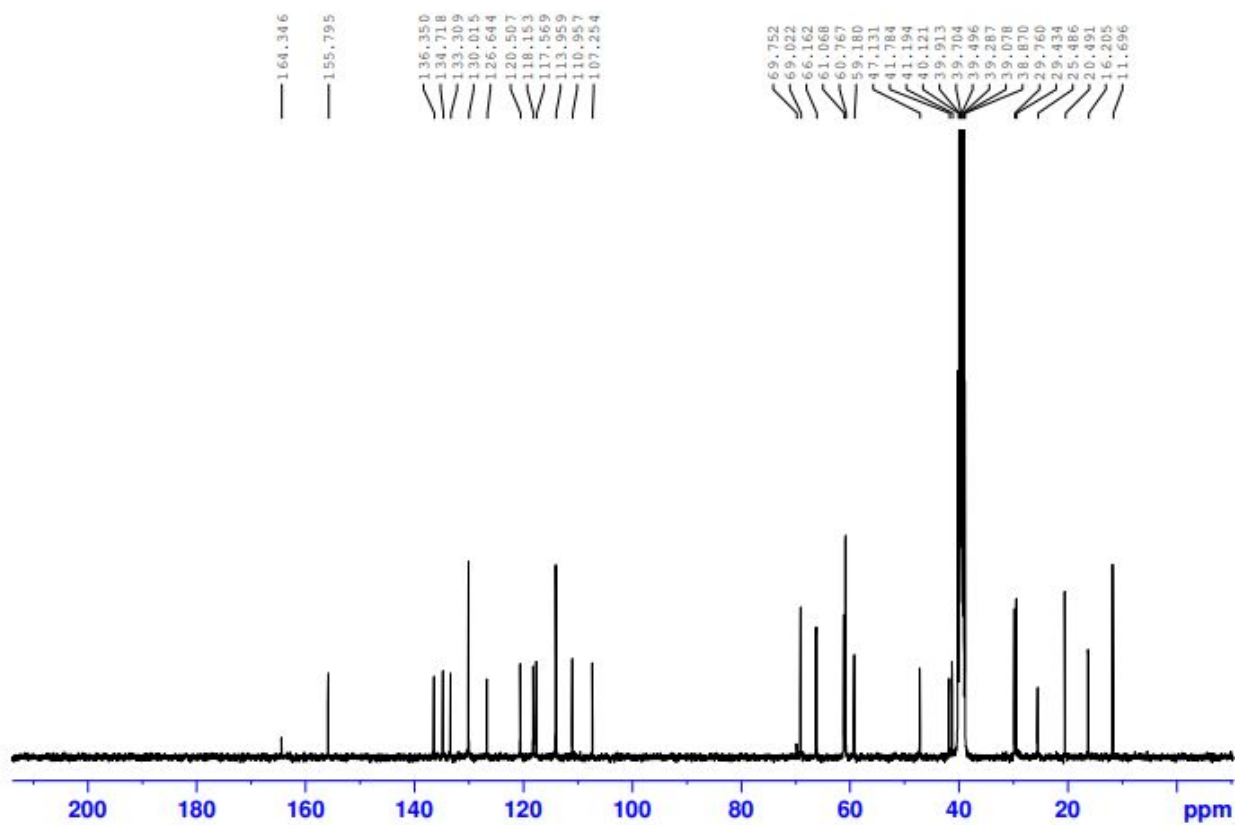
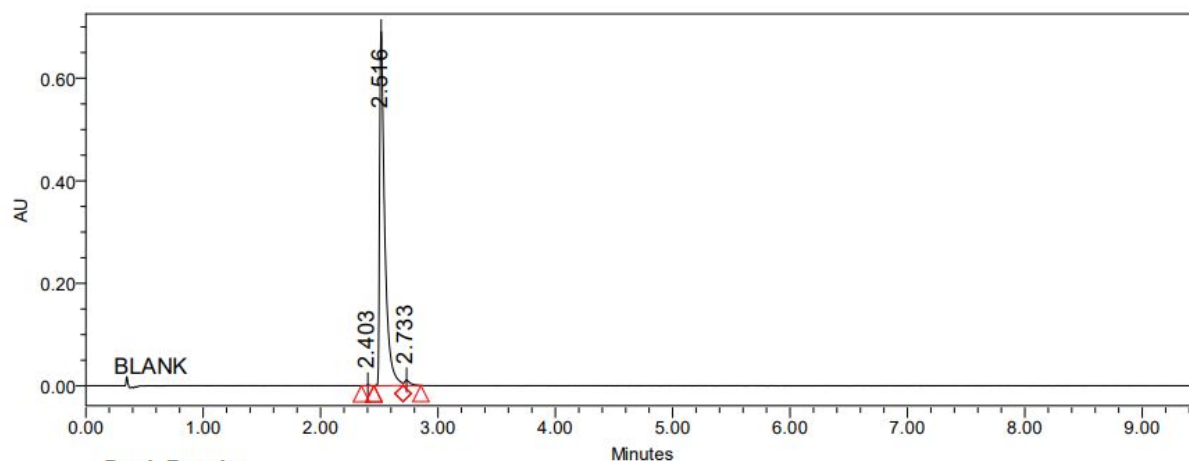


Figure S111. HPLC chromatogram of Compound 40



Peak Results

	RT	Area	Height	% Area
1	2.403	2633	1430	0.12
2	2.516	2104311	691505	98.15
3	2.733	36927	10714	1.72

Figure S112. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 40

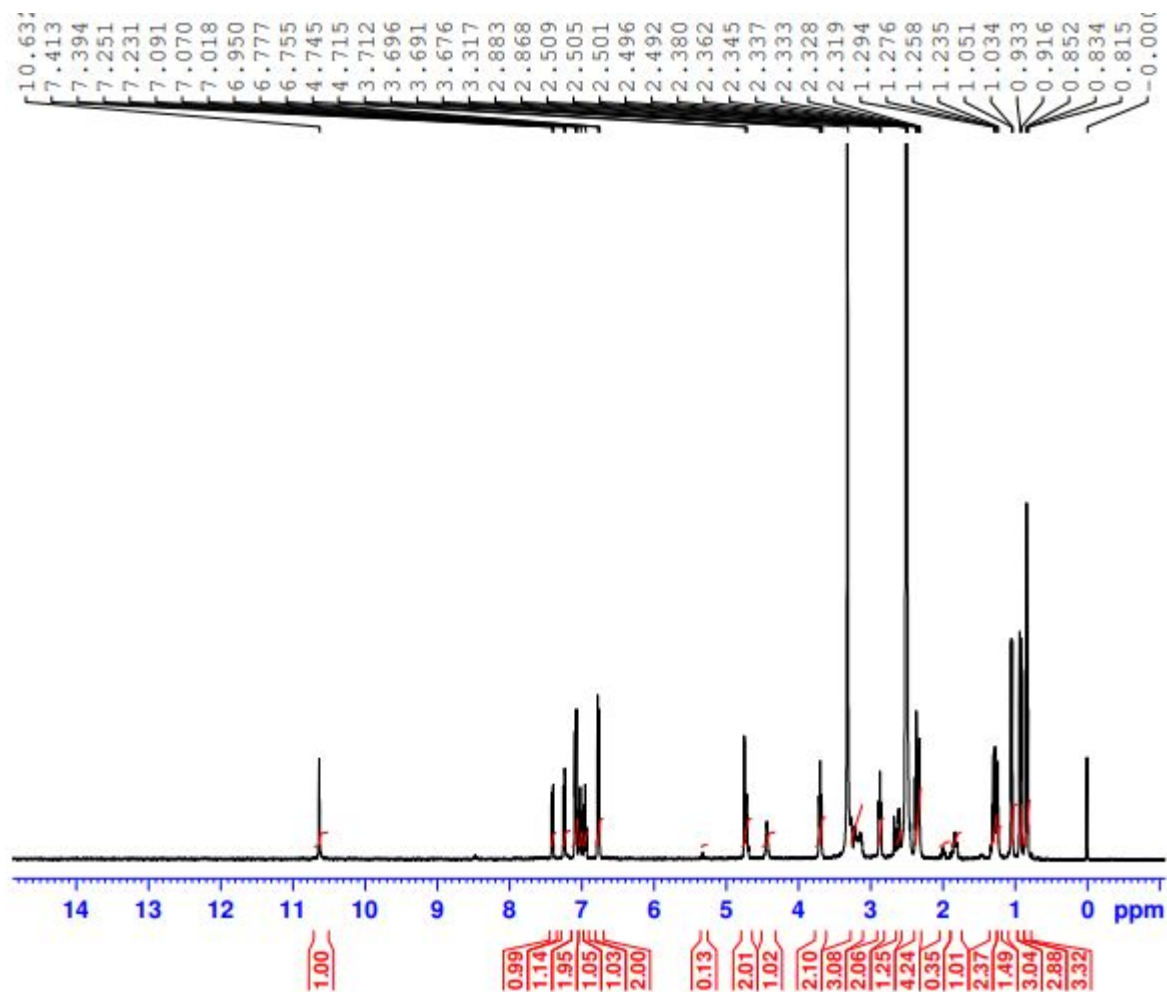


Figure S113. HRMS spectrum of Compound 40

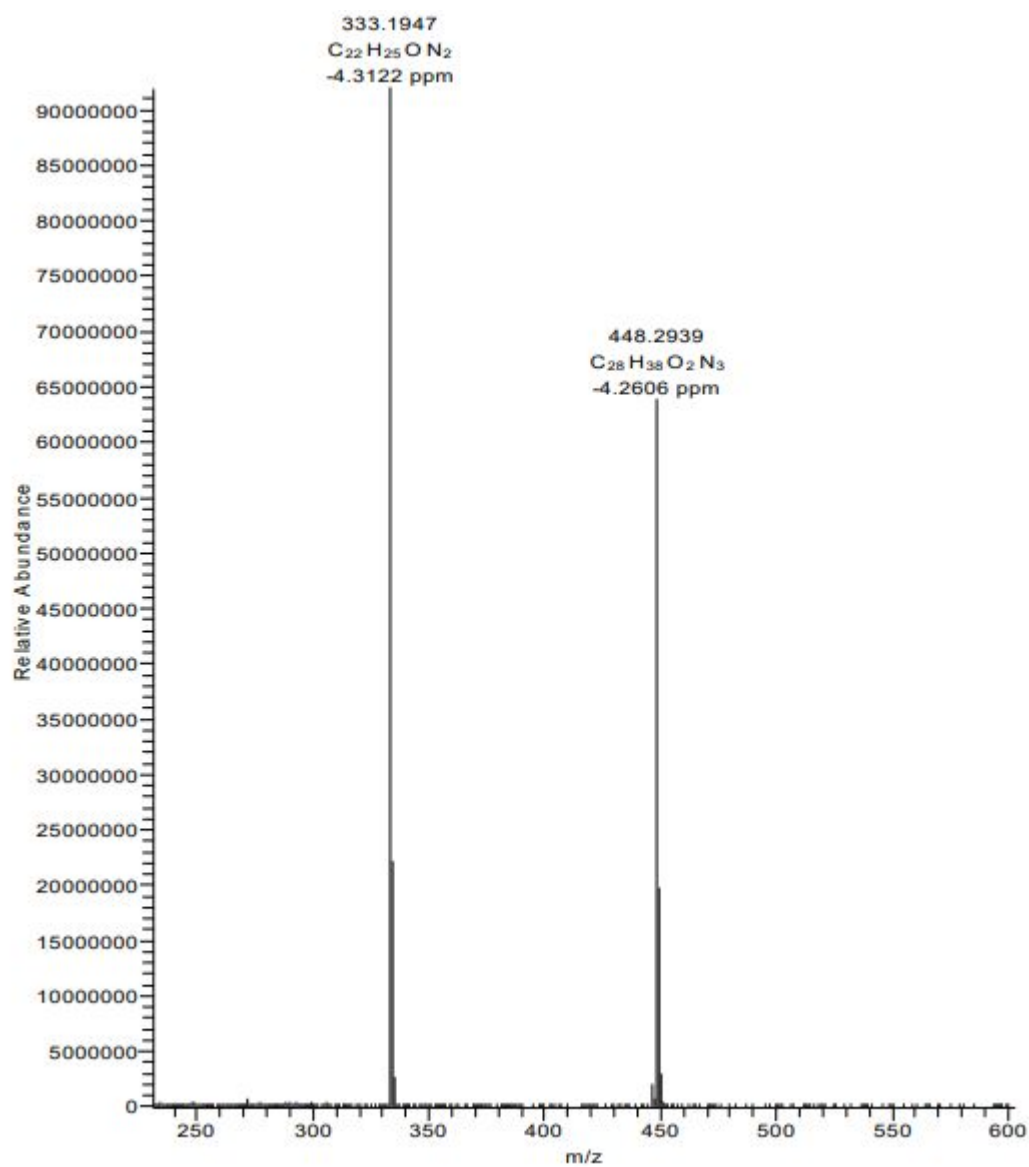


Figure S114. ^{13}C -NMR spectrum of Compound 40

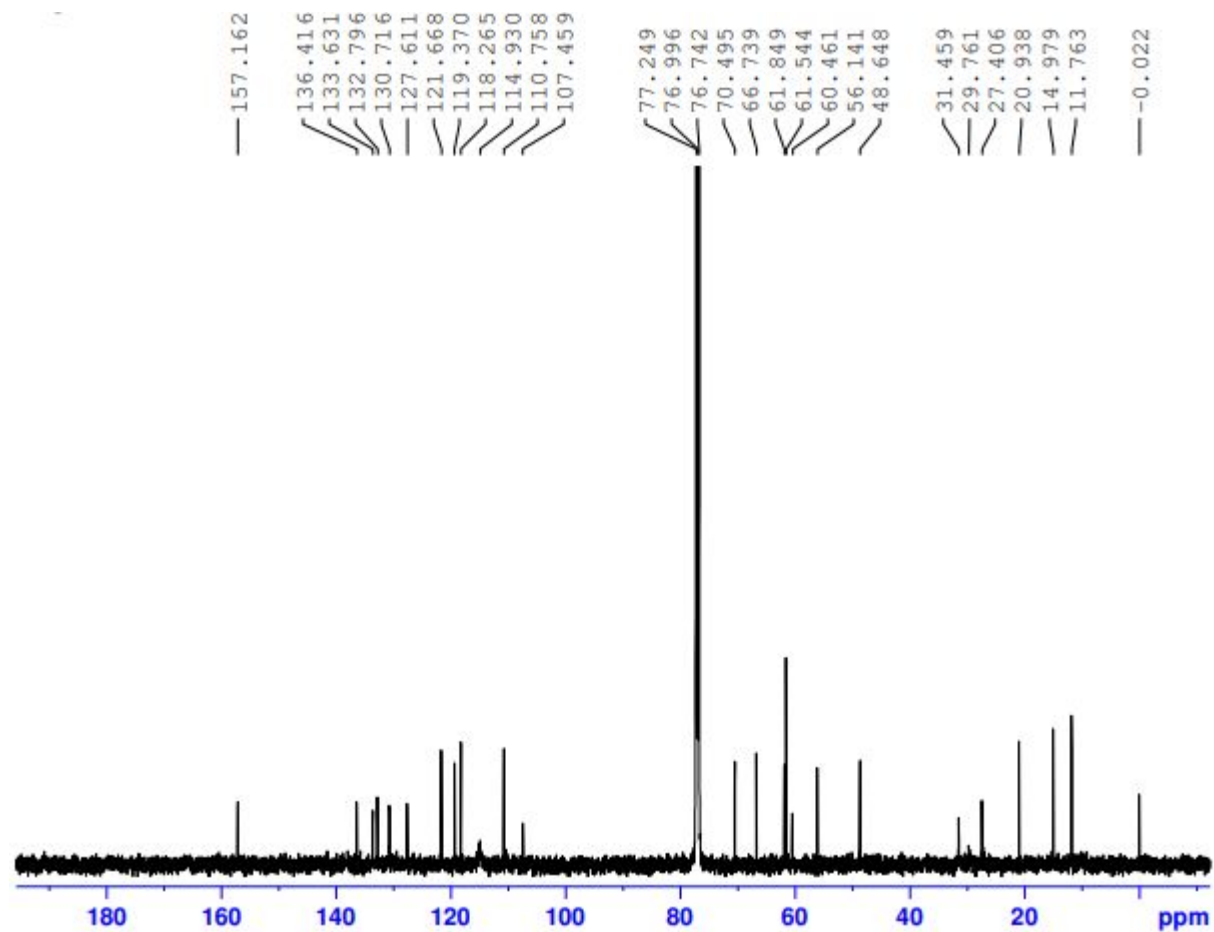
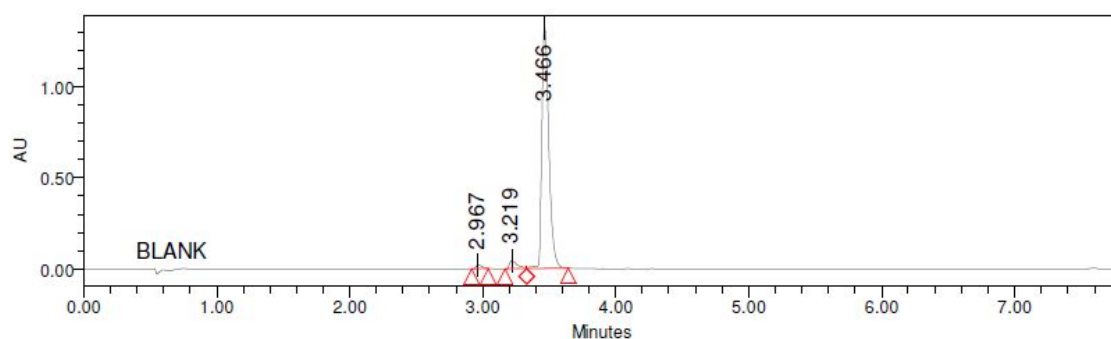


Figure S115. HPLC chromatogram of Compound 41



Peak Results

	RT	Area	% Area
1	2.967	64236	1.26
2	3.219	186659	3.66
3	3.466	4849123	95.08

Figure S116. ^1H -NMR (400 MHz, CDCl_3) spectrum of Compound 41

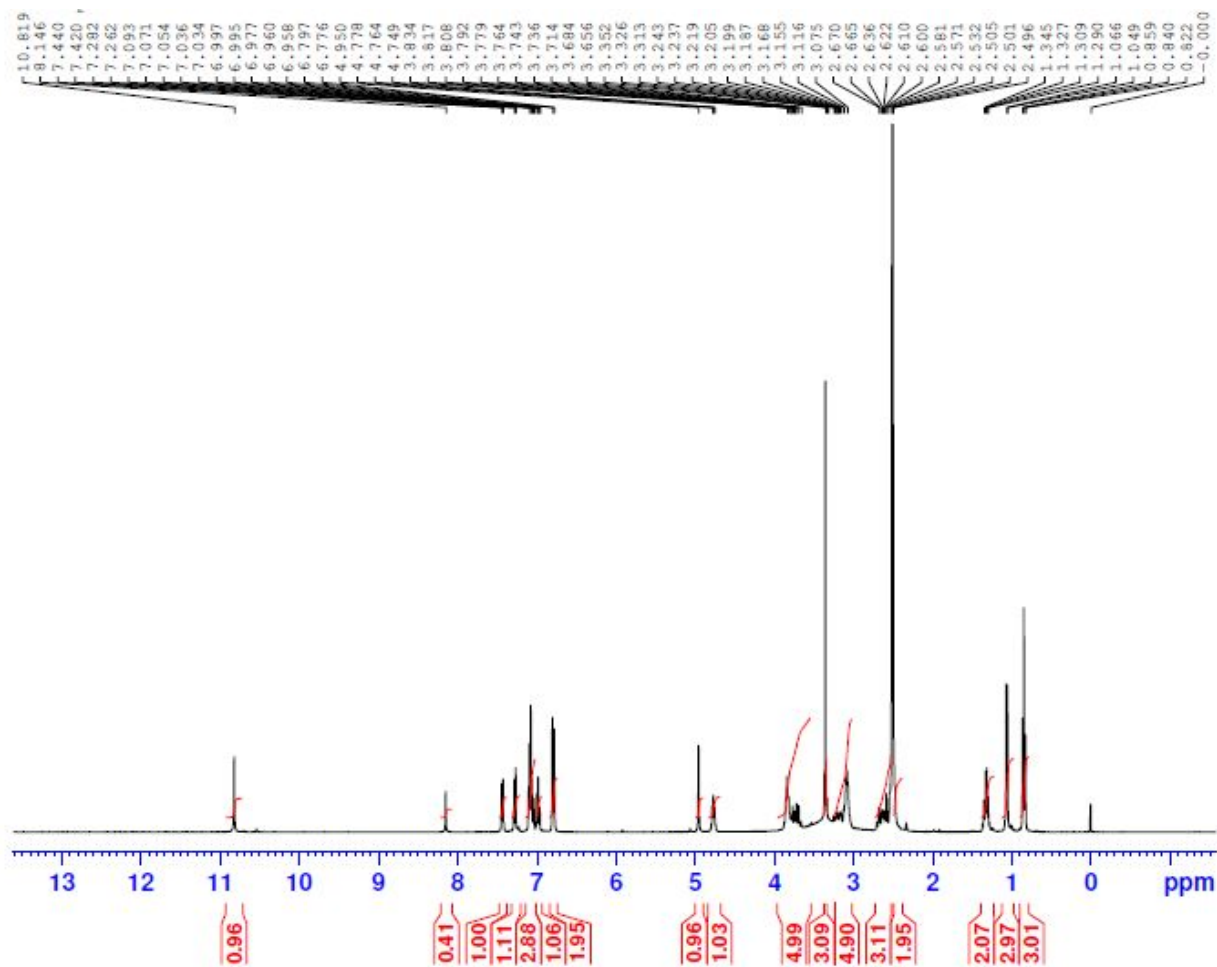


Figure S117. HRMS spectrum of Compound 41

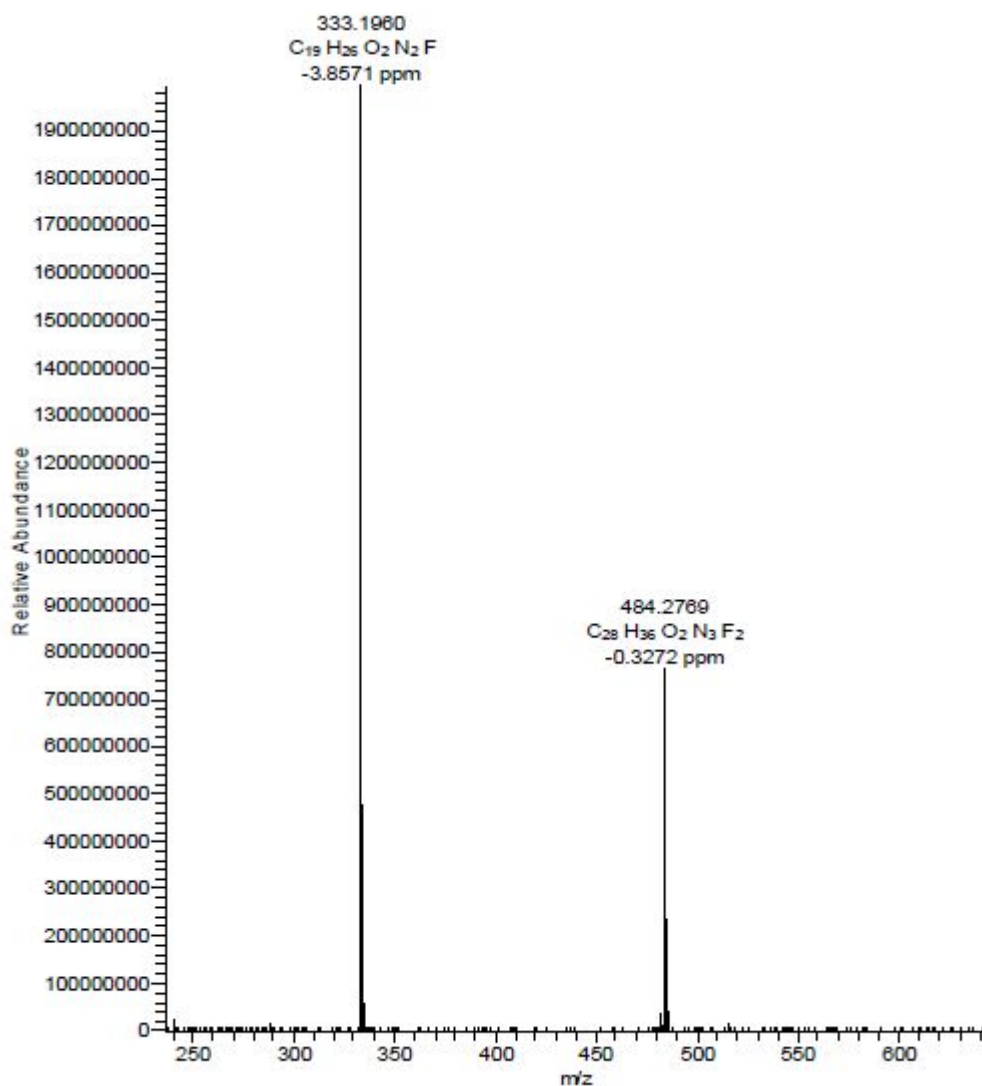


Figure S118. ^{19}F -NMR spectrum of Compound 41

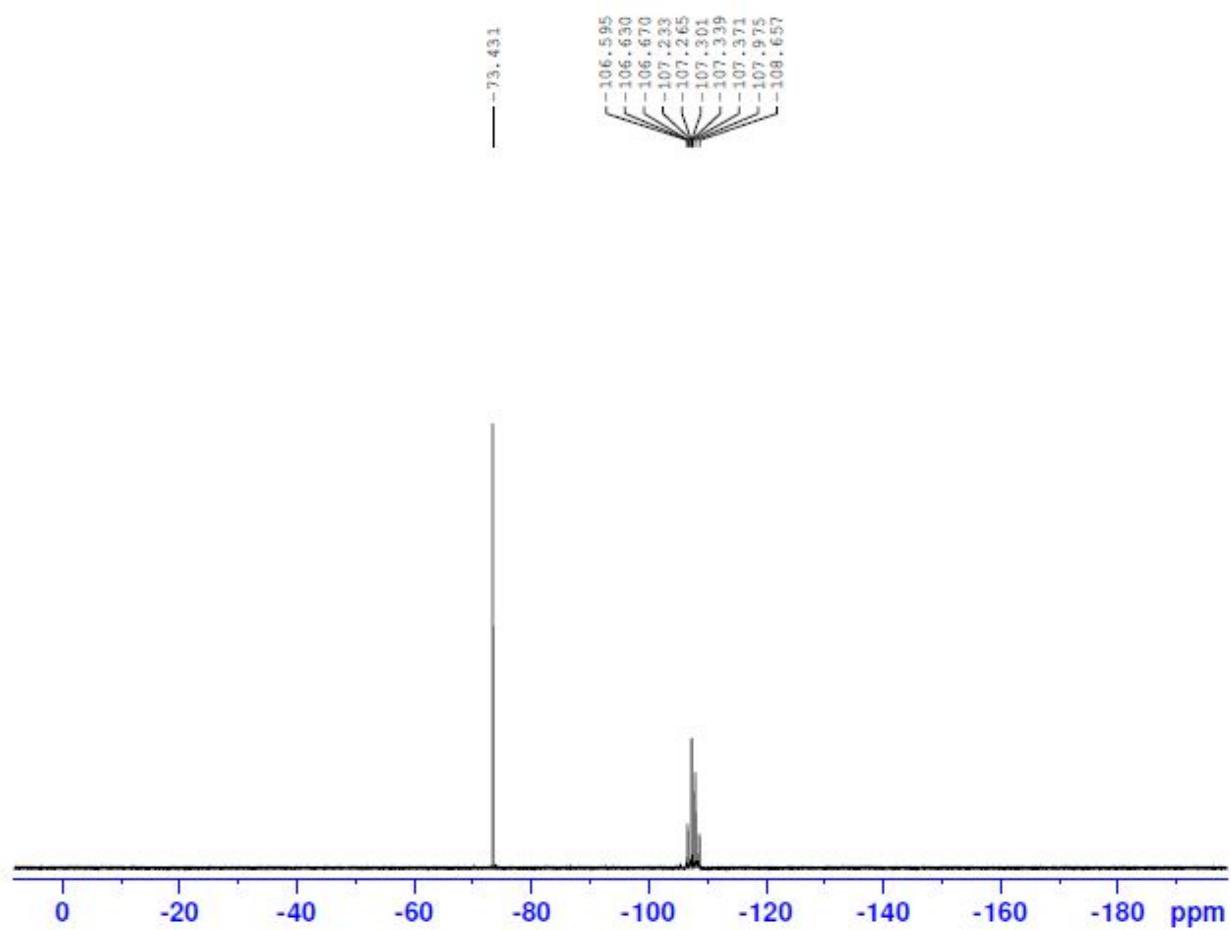


Figure S119. ^{13}C -NMR spectrum of Compound 41

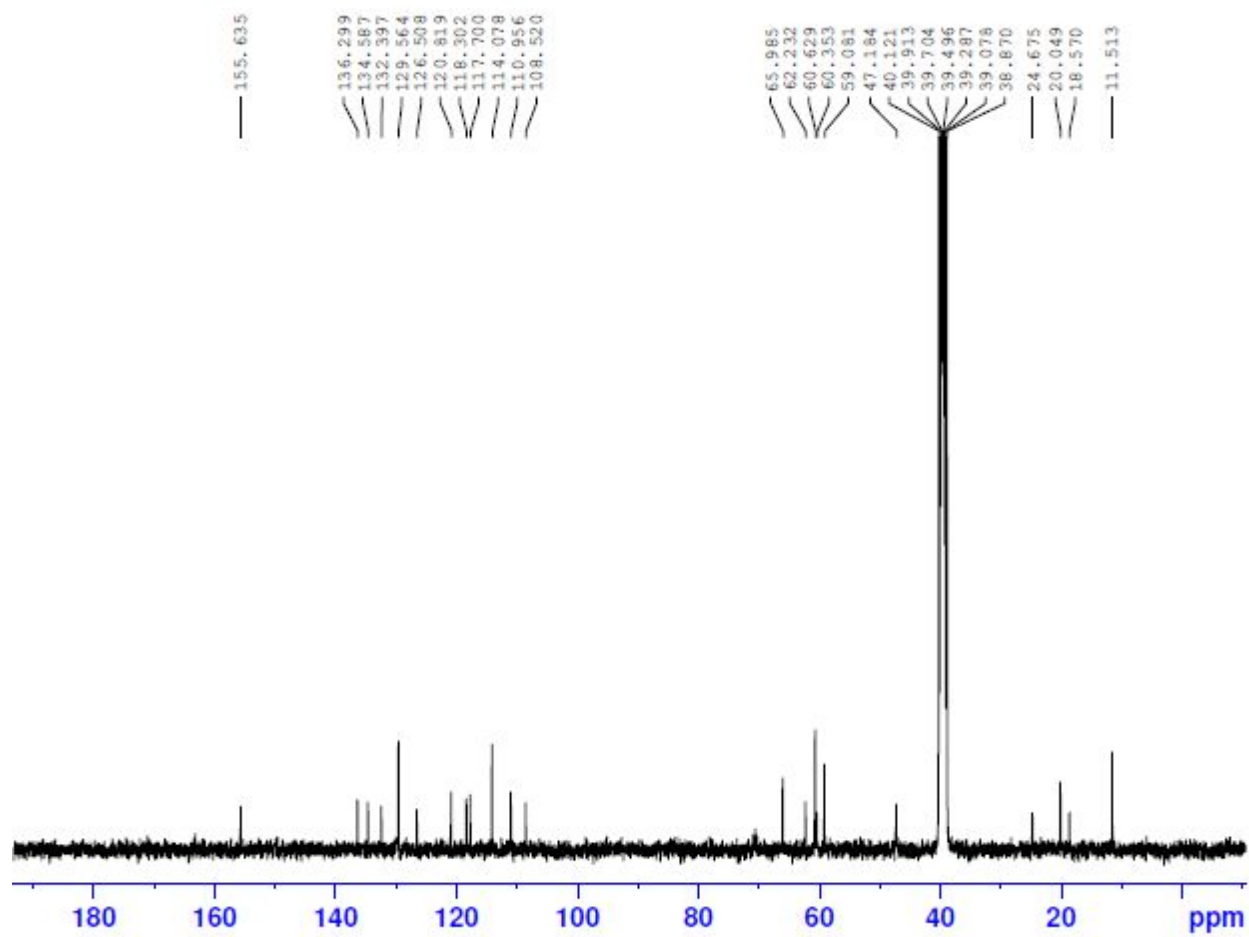
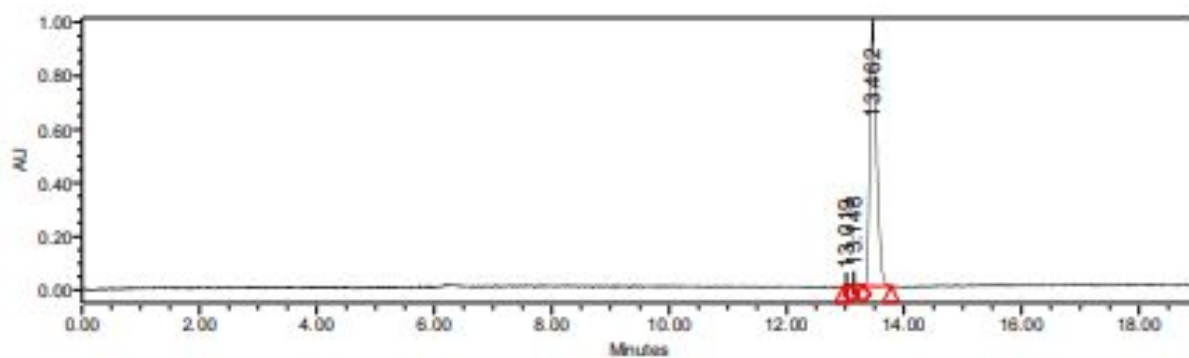


Figure S120. HPLC chromatogram of Compound 42



	RT	Area	Height	Purity1 Angle	Purity1 Threshold	% Area
1	13.019	29322	7916	17.658	19.034	0.37
2	13.148	91325	11931	10.101	10.543	1.18
3	13.462	7733516	954348	0.235	0.432	98.46

Figure S121. ¹H-NMR (400 MHz, CDCl₃) spectrum of Compound 42

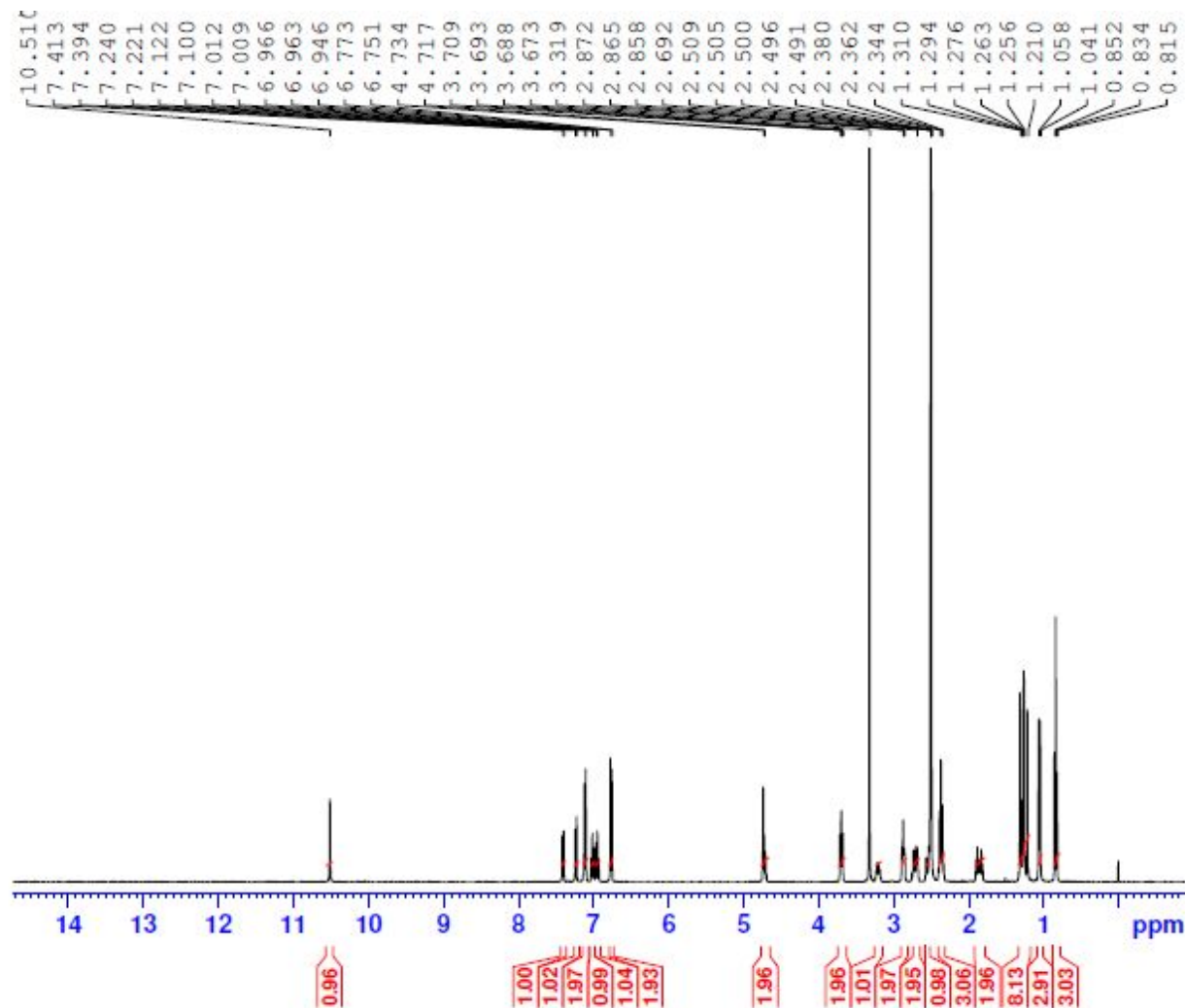


Figure S122. HRMS spectrum of Compound 42

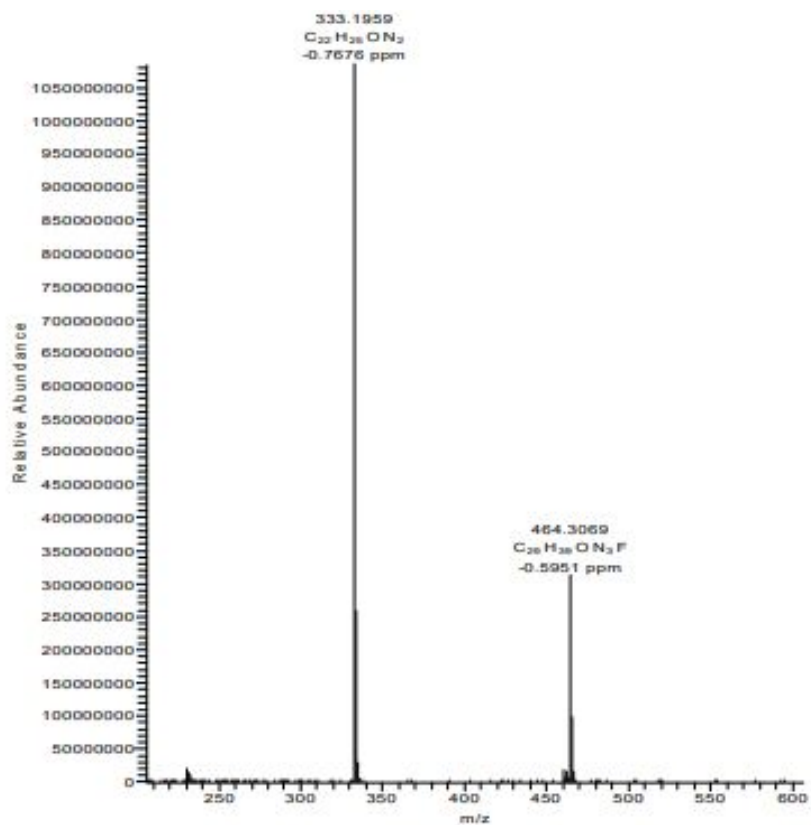


Figure S123. ^{19}F -NMR spectrum of Compound 42

^{19}F NMR

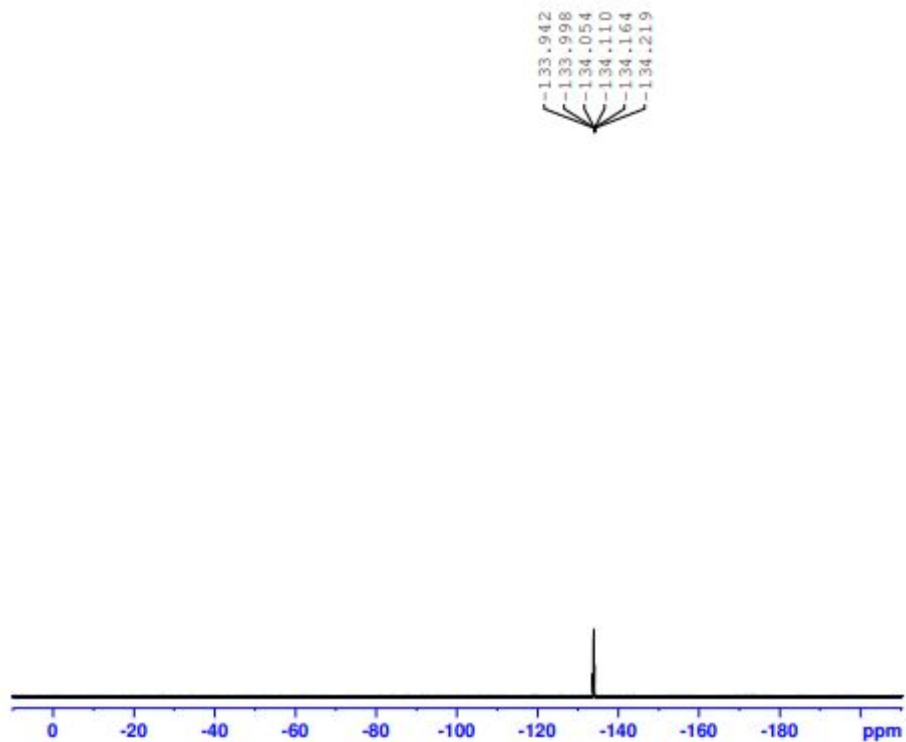


Figure S124. ^{13}C -NMR spectrum of Compound 42

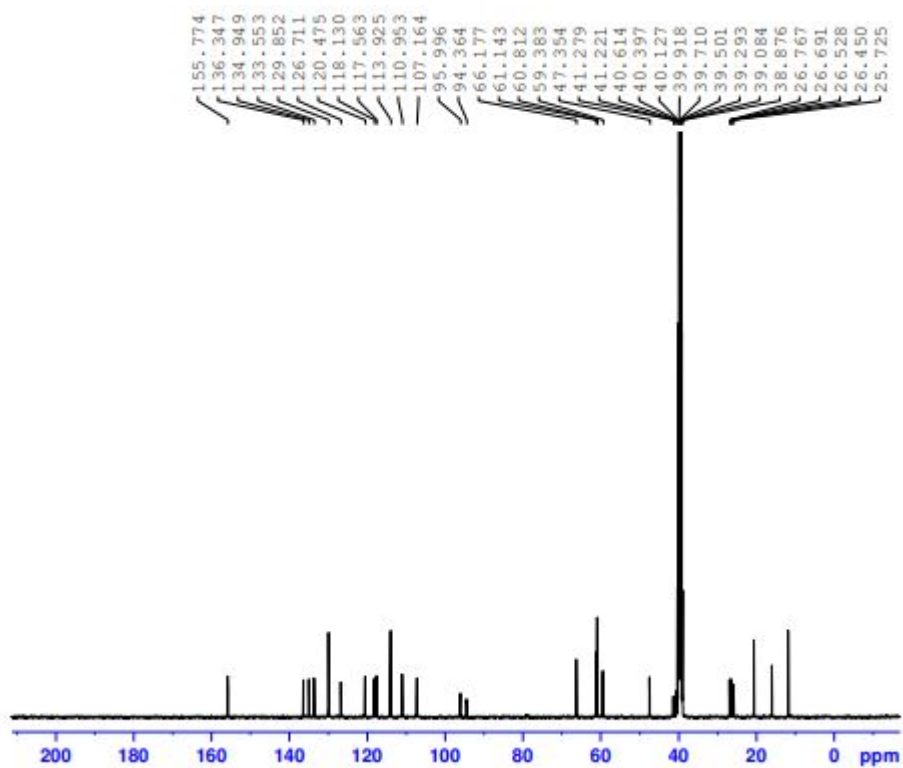
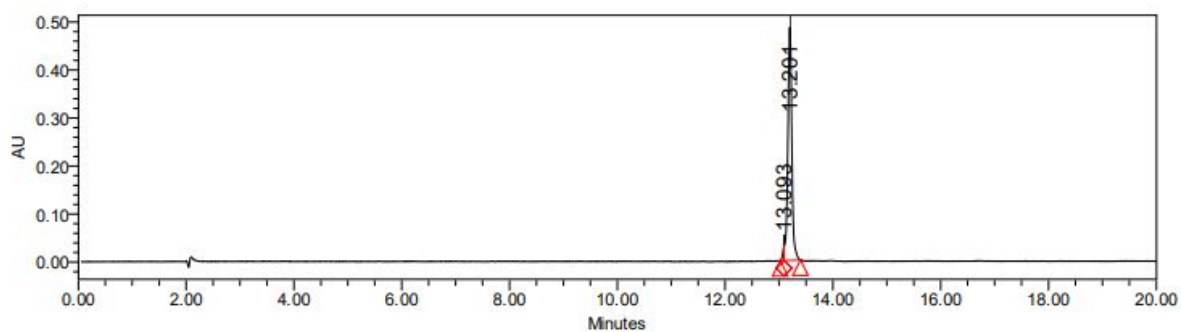


Figure S125. HPLC chromatogram of (1*S*, 3*R*) diastereomer of compound 21



Peak Results

	RT	Area	Height	% Area
1	13.093	44976	29130	1.77
2	13.201	2499289	485372	98.23

Figure S126. ¹H-NMR (400 MHz, CDCl₃) spectrum of (1*S*, 3*R*) diastereomer of compound 21

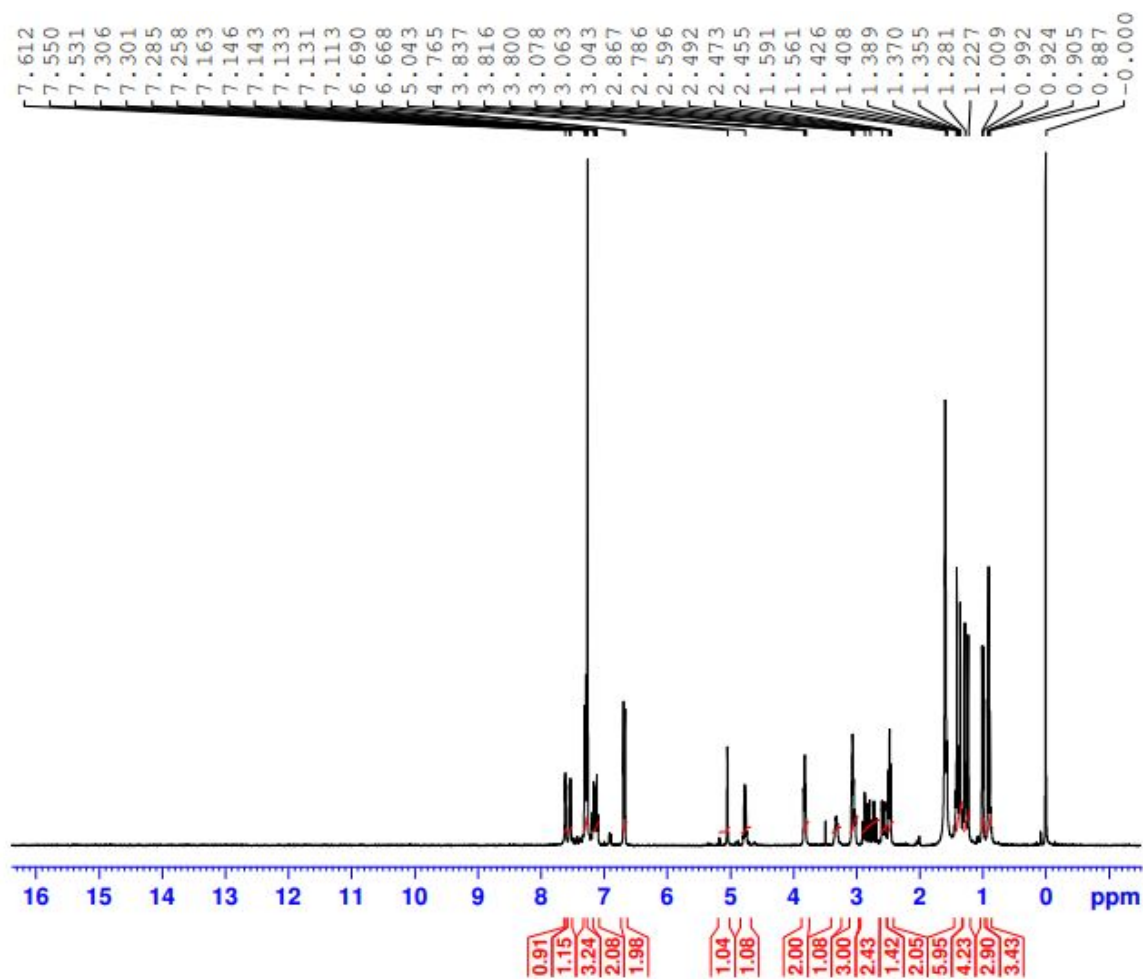


Figure S127. HRMS spectrum of (1*S*, 3*R*) diastereomer of compound 21

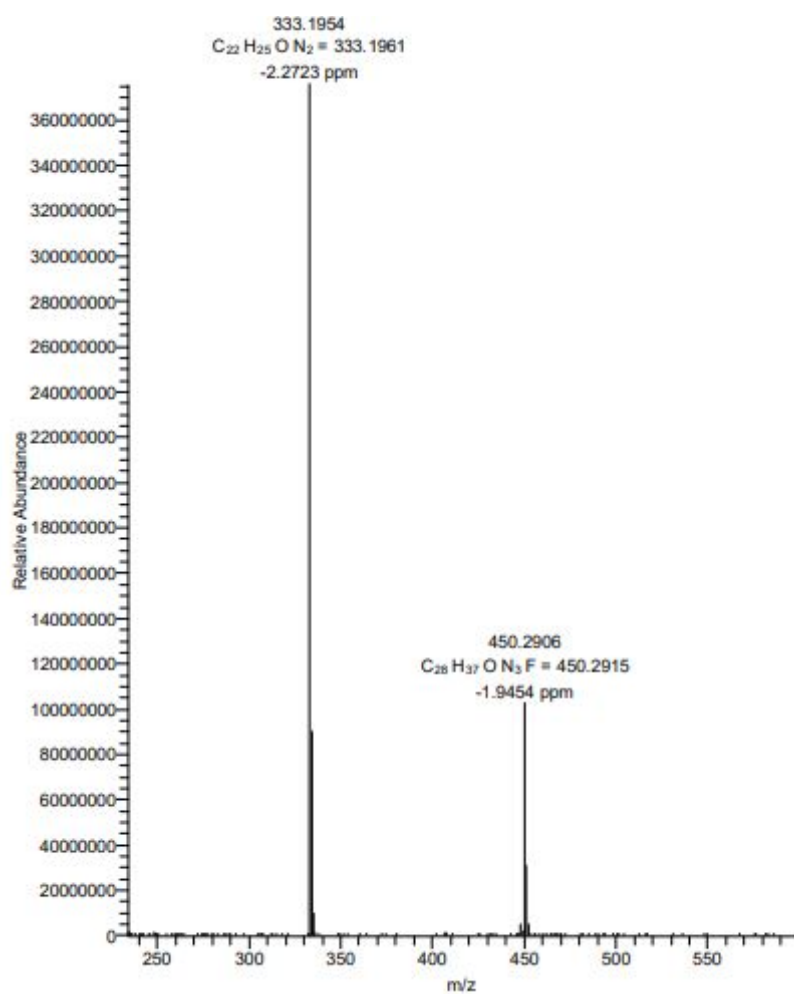


Figure S128. ^{19}F -NMR spectrum of (1*S*, 3*R*) diastereomer of compound 21

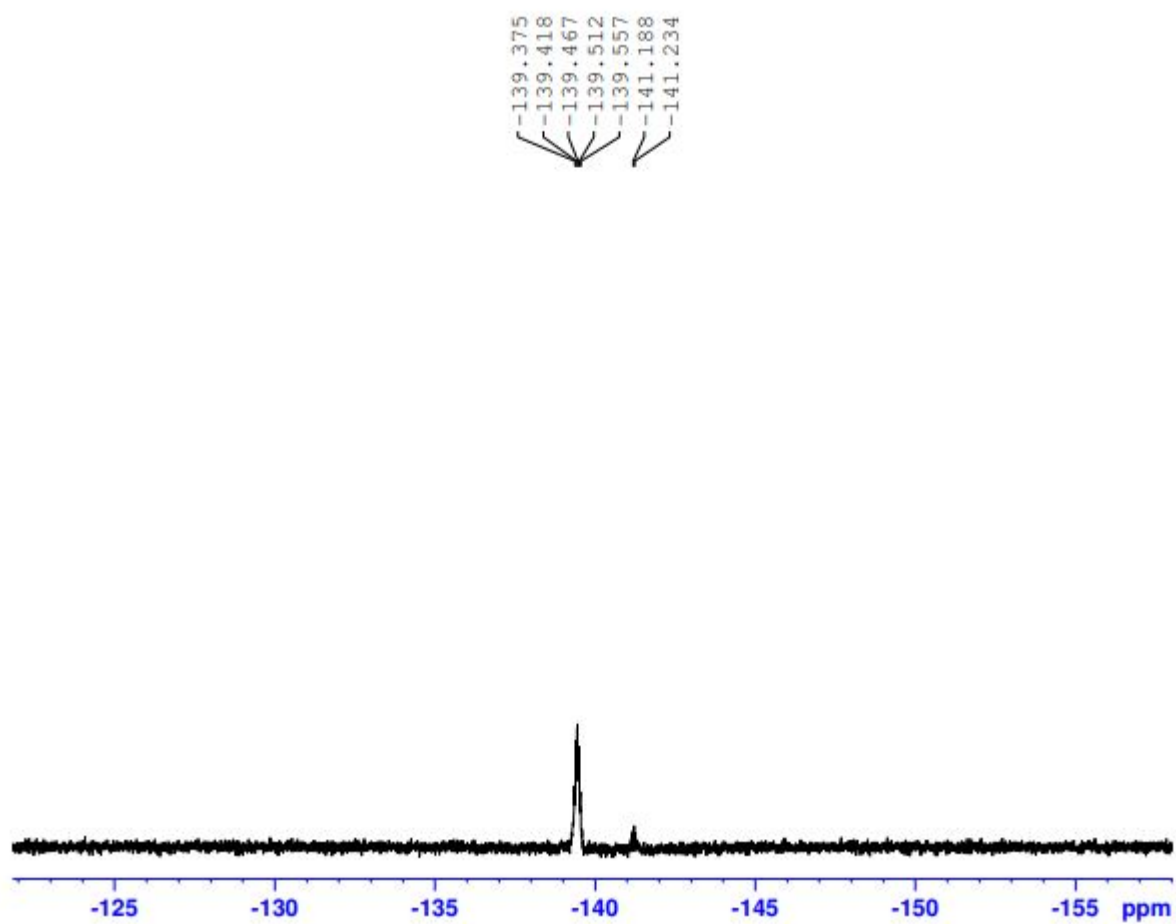
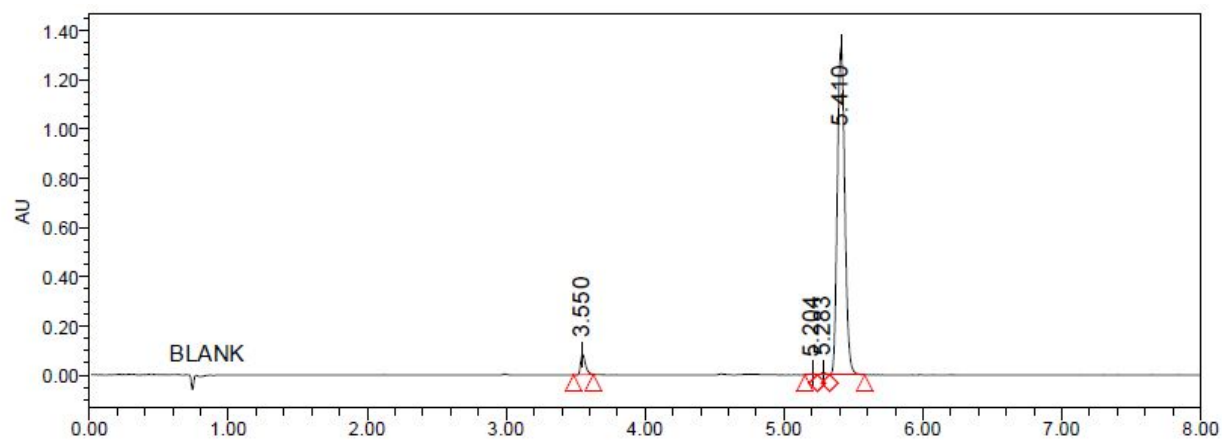


Figure S129. HPLC chromatogram of (1S, 3S) enantiomer of compound 21



Peak Results

	RT	Area	% Area
1	3.550	198249	3.81
2	5.204	11423	0.22
3	5.283	22181	0.43
4	5.410	4965734	95.54

Figure S130. ¹H-NMR (400 MHz, CDCl₃) spectrum of (1S, 3S) enantiomer of compound 21

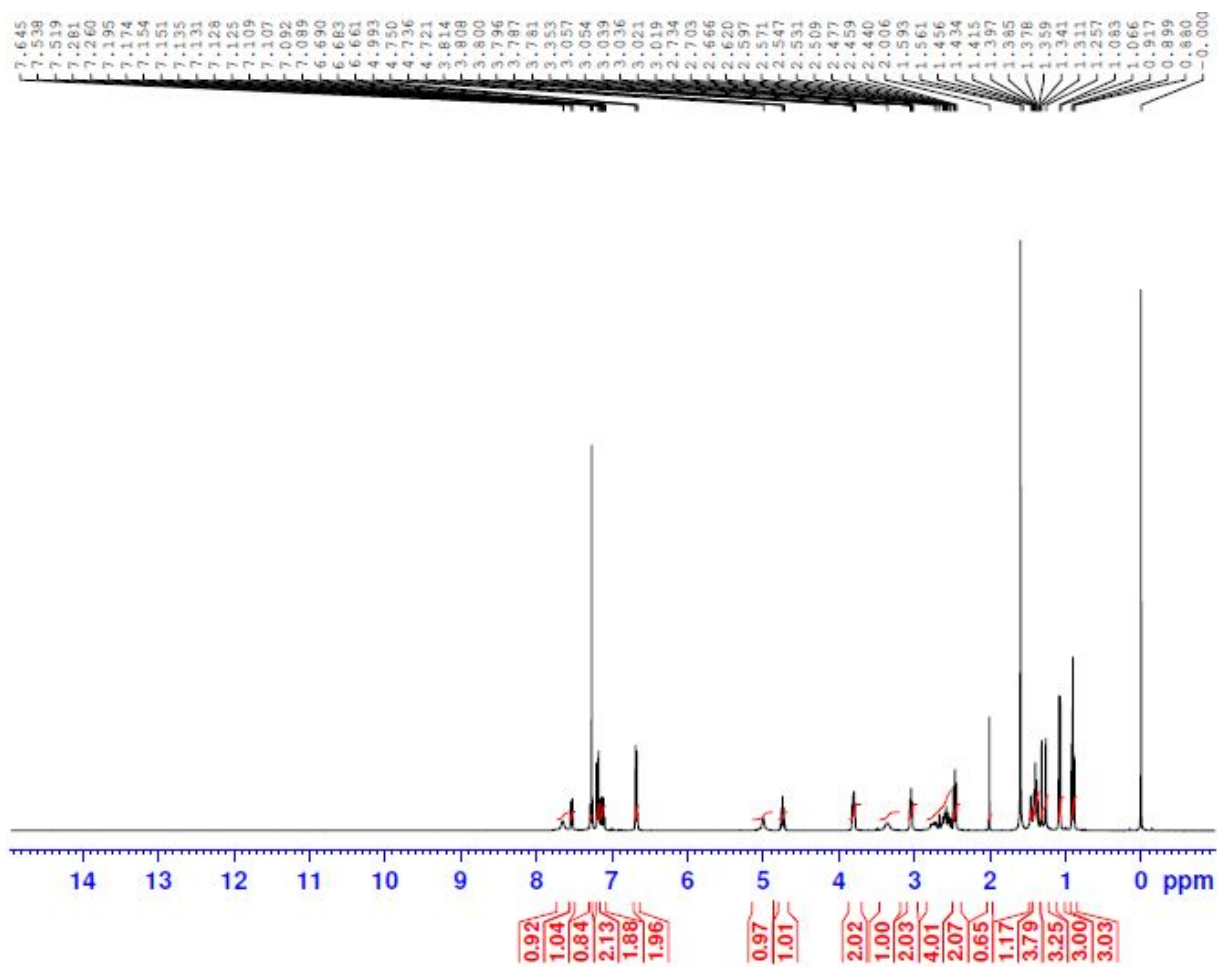


Figure S131. HRMS spectrum of (1S, 3S) enantiomer of compound 21

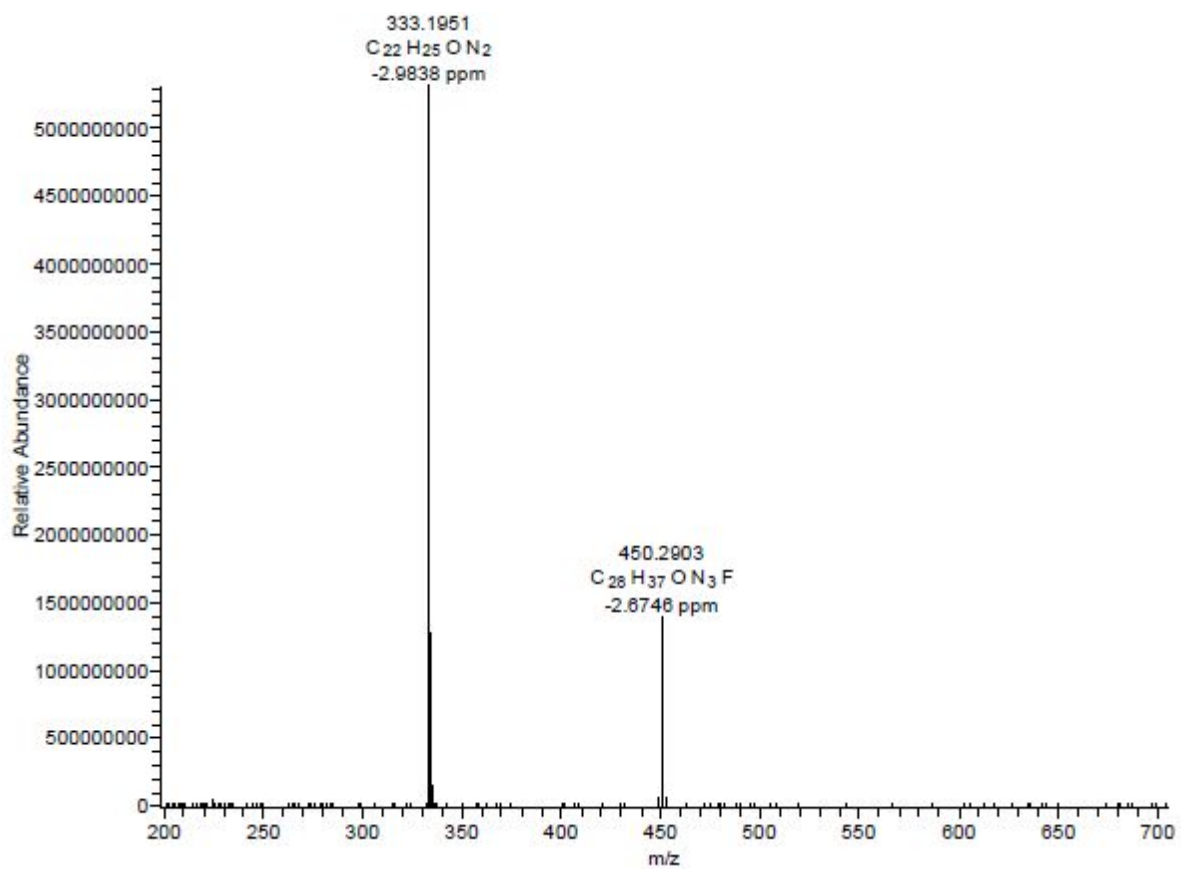


Figure S132. ^{19}F -NMR spectrum of (1S, 3S) enantiomer of compound 21

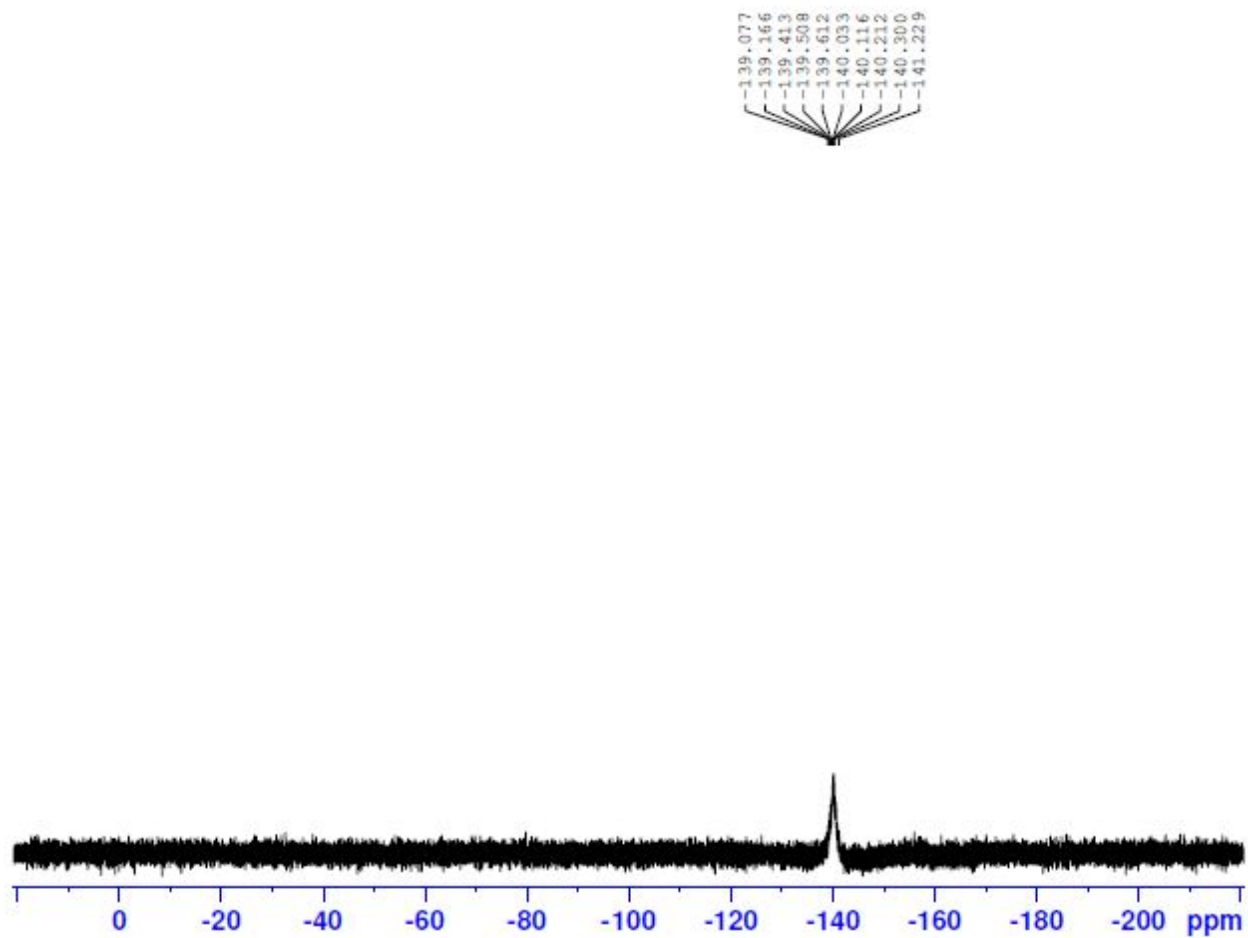


Figure S133. ^{13}C -NMR spectrum of (1S, 3S) enantiomer of compound 21

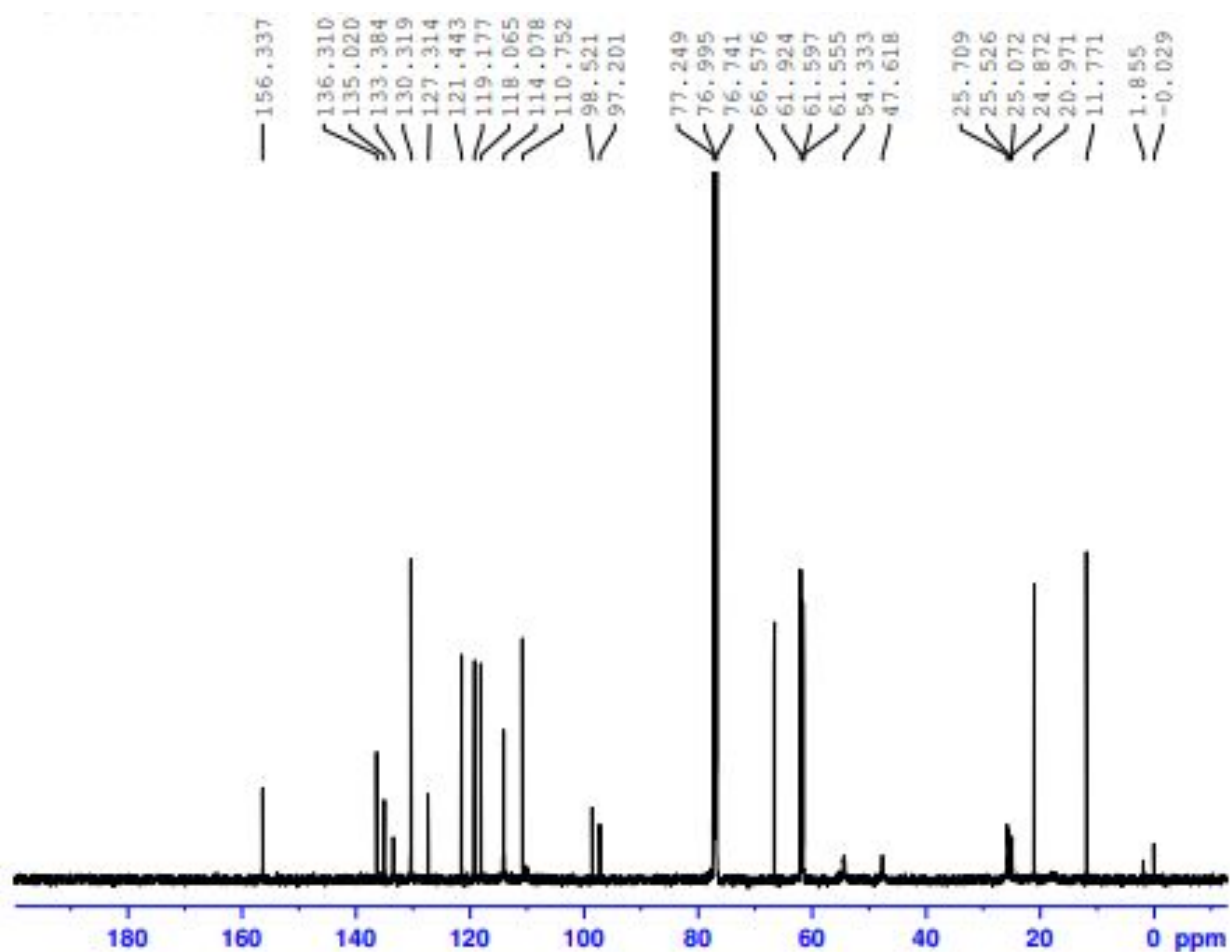


Figure S134. Chiral HPLC Chromatogram assessment of *tert*-butyl (*R*)-(1-(1H-indol-3-yl)propan-2-yl)carbamate

Chiral purity by HPLC (area normalization)

Principle NP HPLC with UV detection

Assessment in area %

Reagents:

2- Propanol HPLC grade, MREDA

Hex HPLC grade, MREDA

Solvent: 2- Propanol

Equipment

apparatus Agilent 1260 HPLC

Column CHIRALPAK, IC-3,3 μm , 4.6mm * 250mm

Chromatographic conditions

Mobile phase B: Hexane: 2- Propanol =85:15

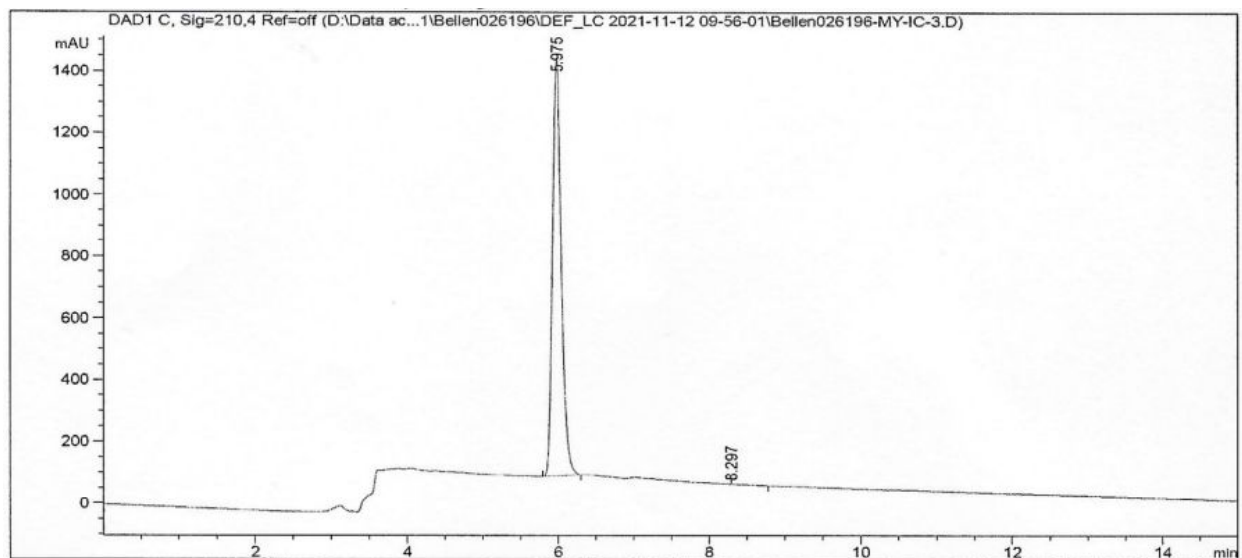
	Time [min.]	Phase B[%]	
isocratic	0.0	100	
	15.0	100	End of acquisition

Flow rate: 1.0ml/min

Detection UV 210nm

Column temperature 40°C

Injection volume: 1.0ul



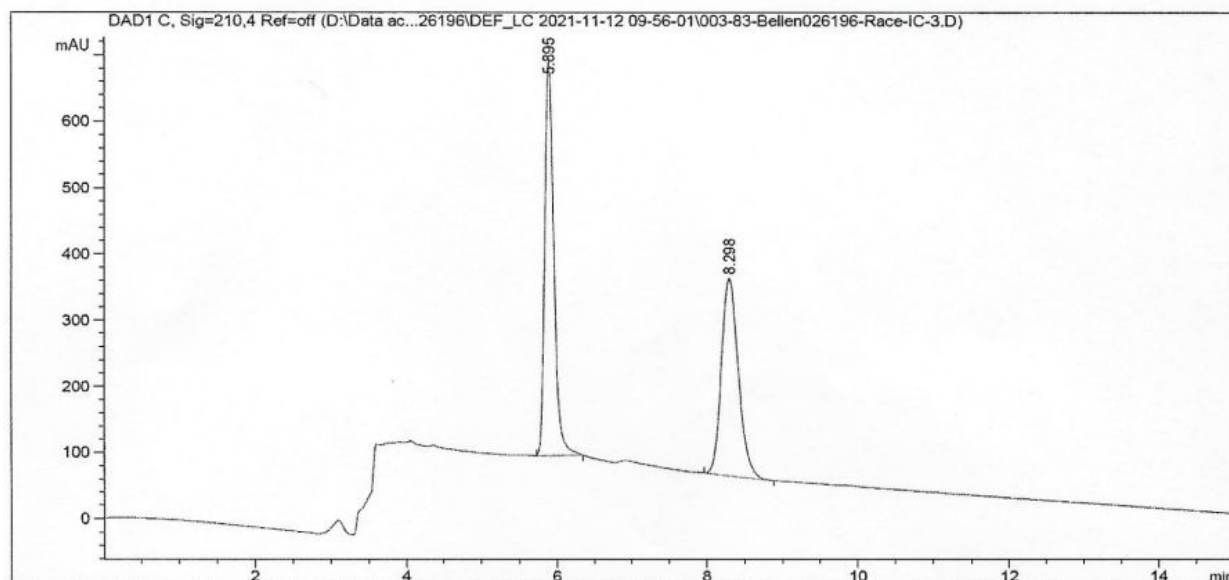
=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.975	BB	0.1266	1.11654e4	1348.27185	99.9809
2	8.297	MM R	0.1371	2.12797	1.95257e-1	0.0191

Figure S135. Chiral HPLC Chromatogram of Racemic mixture as Reference



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.895	BBA	0.1275	4983.72852	596.04736	51.3784
2	8.298	BBA	0.2425	4716.31689	298.22845	48.6216

Totals : 9700.04541 894.27582