*Supporting Information*

*for*

# Co-Localization Strategy Unveils an Underside Binding Site in the Transmembrane Domain of Smoothened Receptor

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## Supporting Information

## Table of Contents

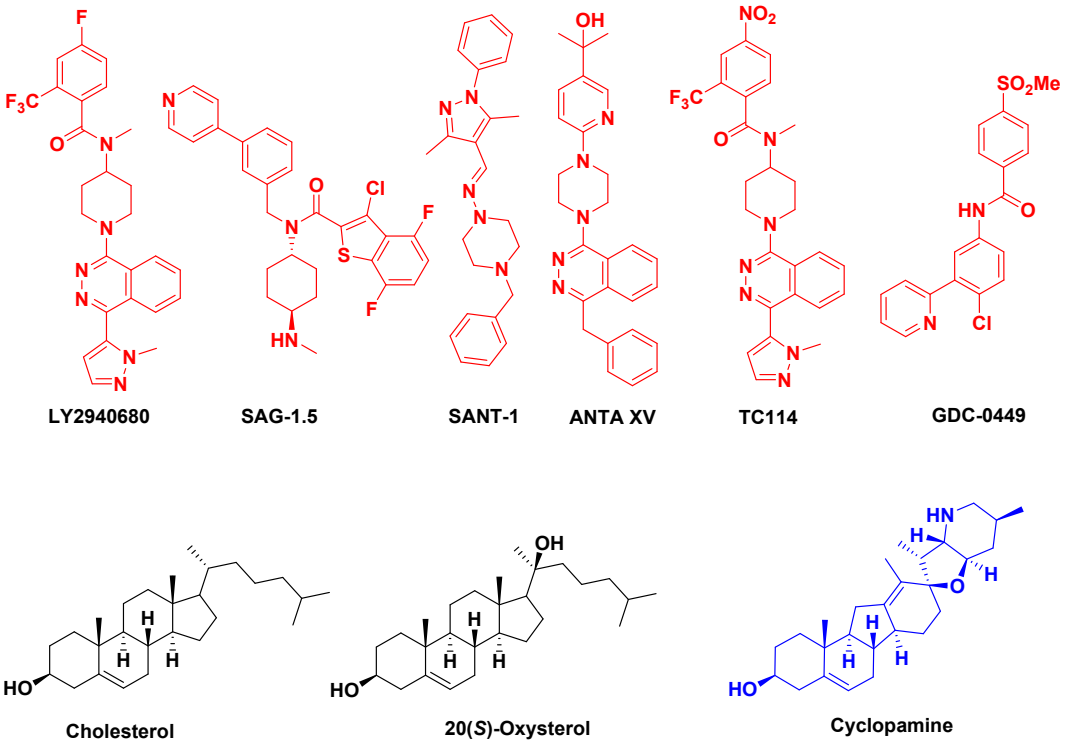



**Figure S1.** Ligands co-crystallized with smoothened receptor. Compounds, including LY2940680, SAG-1.5, SANT-1, ANTA XV, TC114 and GDC-0449, bound in transmembrane domain are colored in red, while compounds, including cholesterol and its metabolite 20(*S*)-oxysterol, in extracellular domain in black. Cyclopamine (CP) in blue can be bound in both domains.

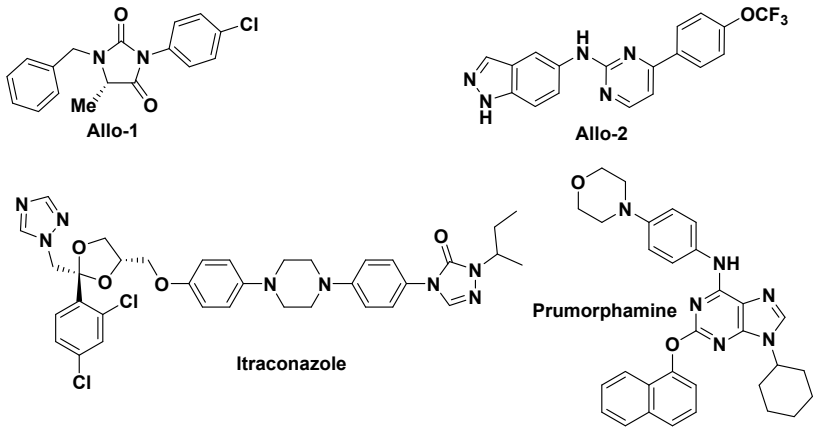



**Figure S2.** Ligands not co-crystallized with smoothened receptor also maintain inhibitory activity against drug-resistant mutant SMO.

**Table S1.** Known interactions of Allo-1 with CP, SAG and their derivatives[1].

| | [$H^3$]CP | BODIPY-CP | [$H^3$]SAG | SAG1.5 |
|---|---|---|---|---|
| Allo-1 | Non-competition | Competition | Non-competition | Non-competitive inhibition |
| Allo-2 | Competition | Competition | Non-competition | Non-competitive inhibition |

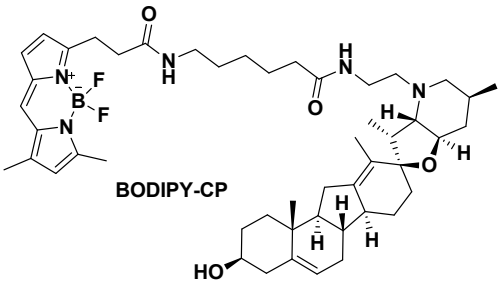



**Figure S3.** Structure of BODIPY-CP, a classic fluorescent probe for smoothened receptor[2].

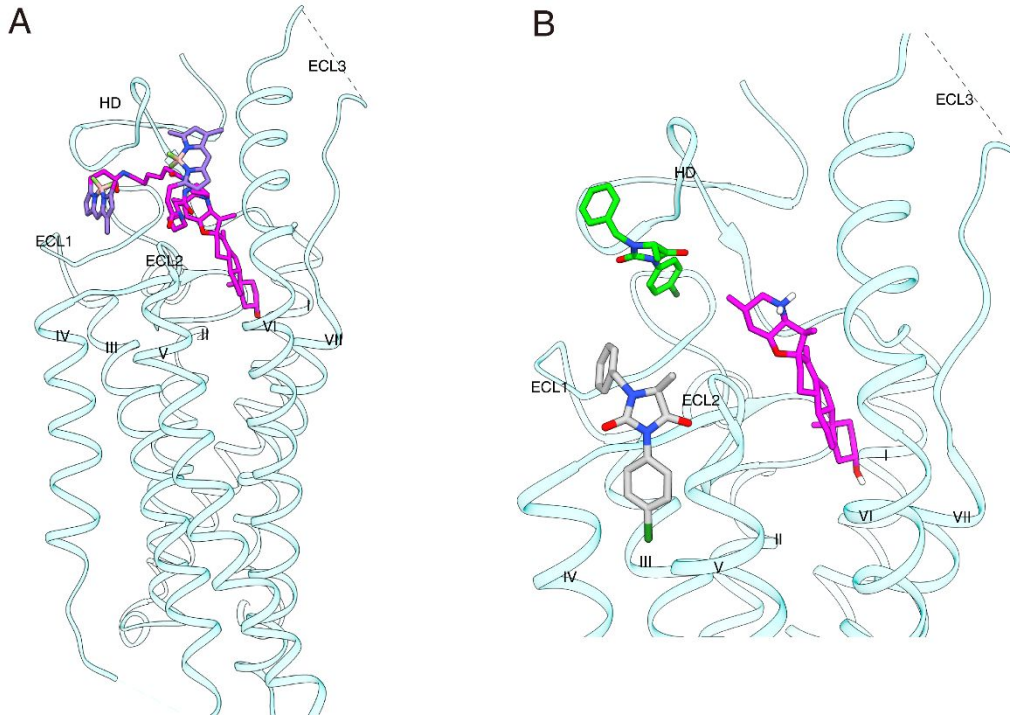



**Figure S4.** Allo-1 does not bind where BODIPY binds (PDB codes: 4O9R). (**A**) Docking of BODIPY-CP in the co-crystal structure of SMO with CP. BODIPY in probe BODIPY-CP was found floating in the outward vicinity of CP binding in SMO with a moderate score. Two possible binding poses of BODIPY were generated, as shown in violet. (**B**) When BODIPY was replaced with Allo-1, the docking pose (green) showed non-stable binding in a short molecular dynamics simulation (grey).

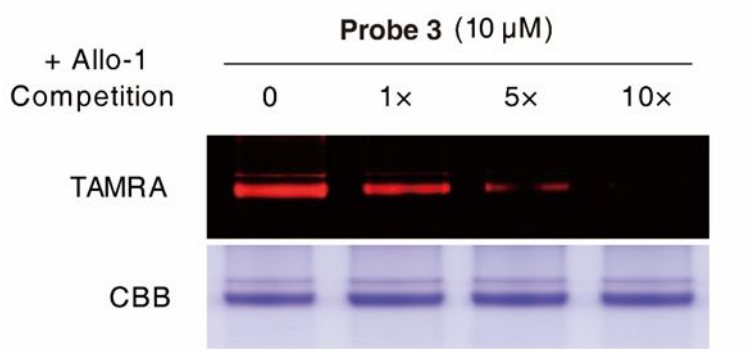
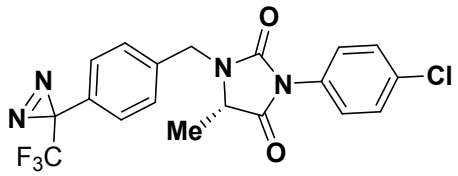



**Figure S5.** Specific binding to SMO of probe **3** was proved by competition test in the presence of various concentrations of Allo-1.




**Probe 4**

$IC_{50}$ = 872± 582 nM

*K*i = 197±38 nM

**Figure S6.** Diazirine equipped photoaffinity probe **4** exhibited losses of activity and binding affinity.

**Table S2.** Distances between residues labeled by Probe **1** and Probe **2**.

| Probe 2 \ Probe 1 | E135 | K186 | L498 | K510 | E518 |
|---|---|---|---|---|---|
| H103 | 20.7Å | 19.8 Å | 15.6 Å | 36.0 Å | 49.3 Å |
| E158 | 23.6 Å | 27.5 Å | 18.0 Å | 22.5 Å | 37.1 Å |
| A345 | 101.9 Å | 85.4 Å | 78.5 Å | 58.0 Å | 41.9 Å |
| T349 | 106.1 Å | 90.5 Å | 81.8 Å | 61.0 Å | 46.1 Å |
| G527 | 80.1 Å | 63.2 Å | 53.9 Å | 33.4 Å | 14.4 Å |
| T528 | 79.1 Å | 63.3 Å | 53.8 Å | 34.4 Å | 14.8 Å |
| G529 | 81.1 Å | 63.8 Å | 56.6 Å | 36.9 Å | 18.9 Å |

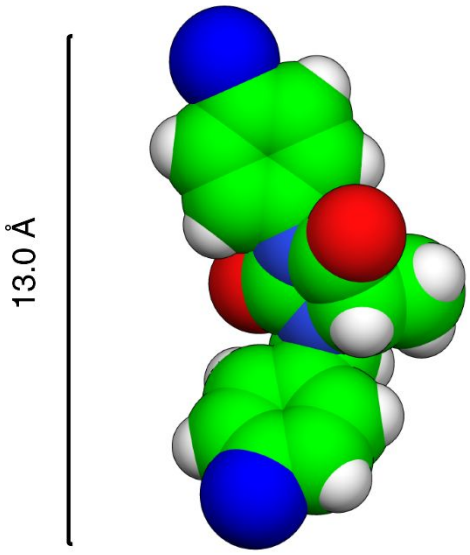



**Figure S7.** Distance between two nitrogens of probe **1** and probe **2** is 13.0 Å.

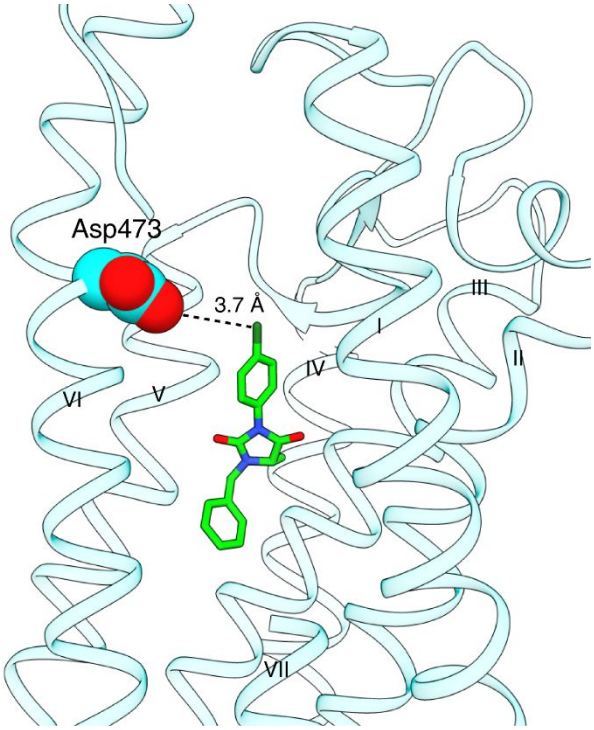
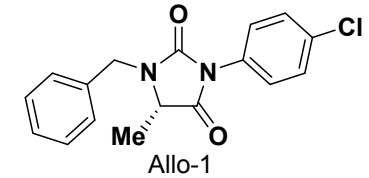



**Figure S8.** Allo-1 is about 3.7 Å away from Asp473 (PDB code: 4N4W).

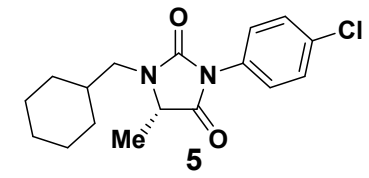
**Table S3.** Computational calculation of binding free energy and docking scores for the Allo-1 analogs.

| Compds. | XP gScore | MM-GBSA dG bind (kcal/mol) | $IC_{50}$ (nM) |
|---|---|---|---|
| Allo-1 | -11.405 | -88.45 | 59±9 |
| 5 | -10.945 | -76.77 | 383±109 |
| 6 | -11.371 | -79.88 | 7382±2618 |
| 7 | -10.635 | -80.30 | 547±453 |
| 8 | -11.737 | -85.26 | 92±38 |
| 9 | -10.557 | -69.95 | 8006±1994 |
| 10 | -11.213 | -73. 49 | 1533±262 |
| 11 | -10.581 | -82.12 | 8097±1921 |
| 12 | -11.014 | -75.18 | 3791±673 |
| 13 | -11.246 | -85.19 | 4552±2245 |

Corresponding Structures:




Allo-1

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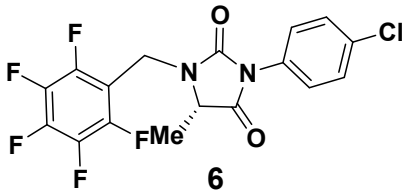


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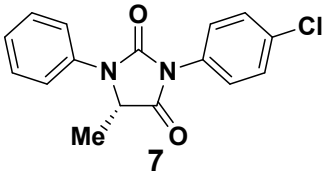


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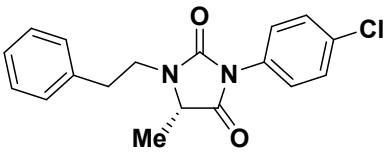


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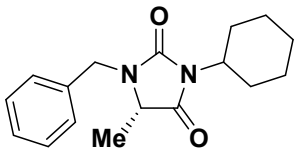


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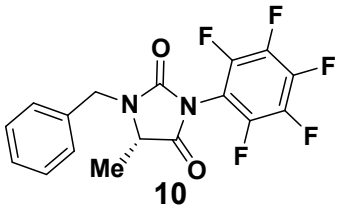


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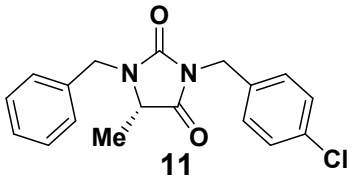


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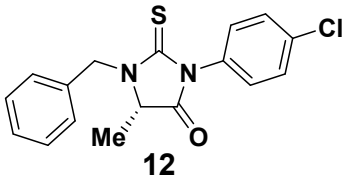


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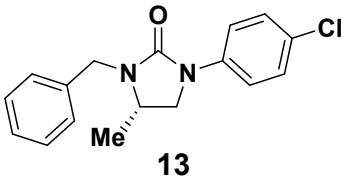


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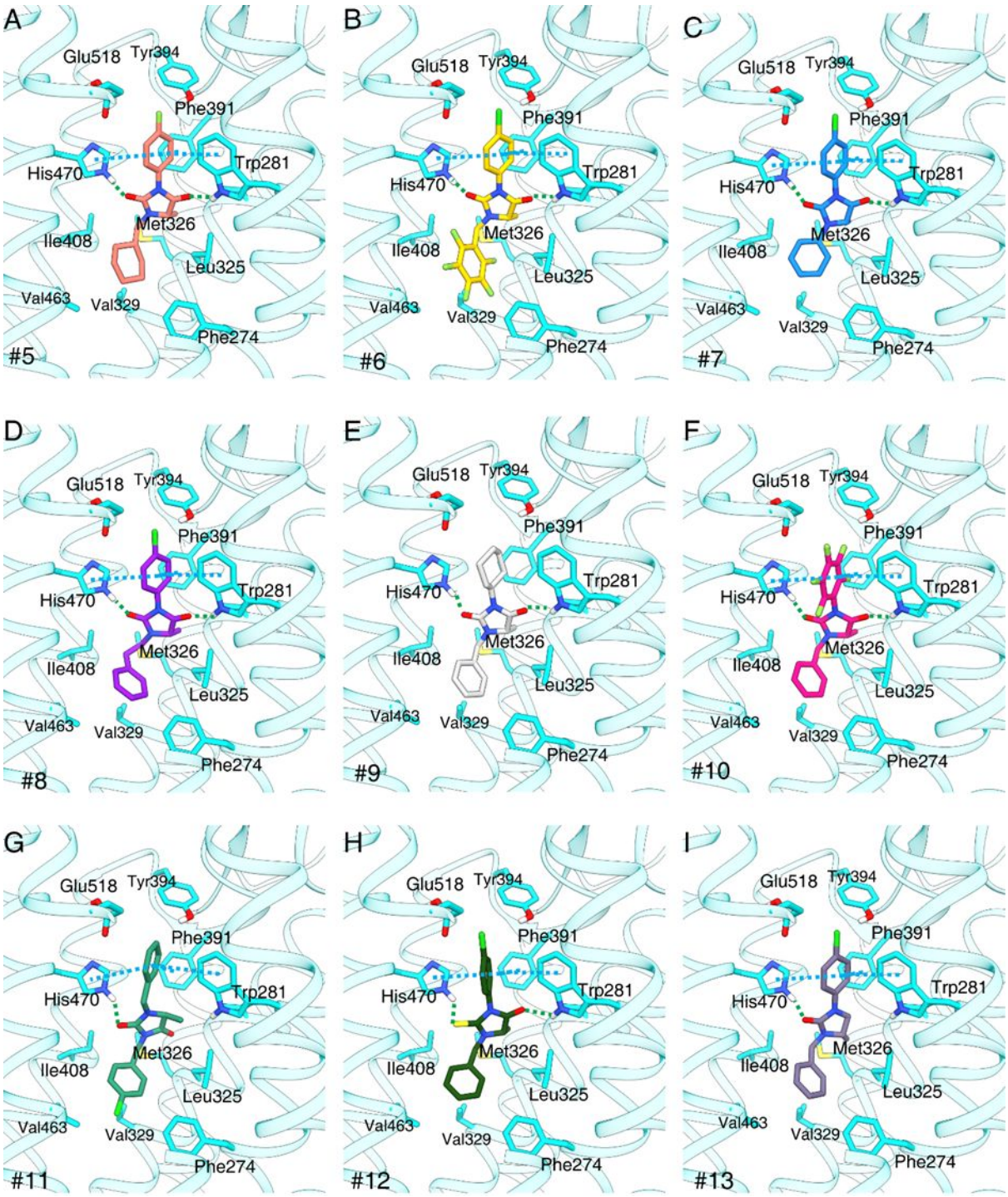



**Figure S9.** Docking study of Allo-1 analogs (PDB code: 4N4W).

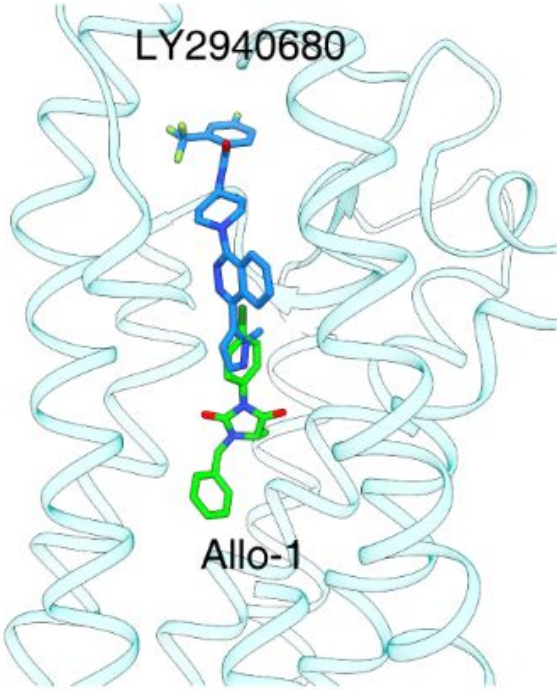



**Figure S10.** LY2940680 is partially overlapped with Allo-1 (PDB code: 4N4W).

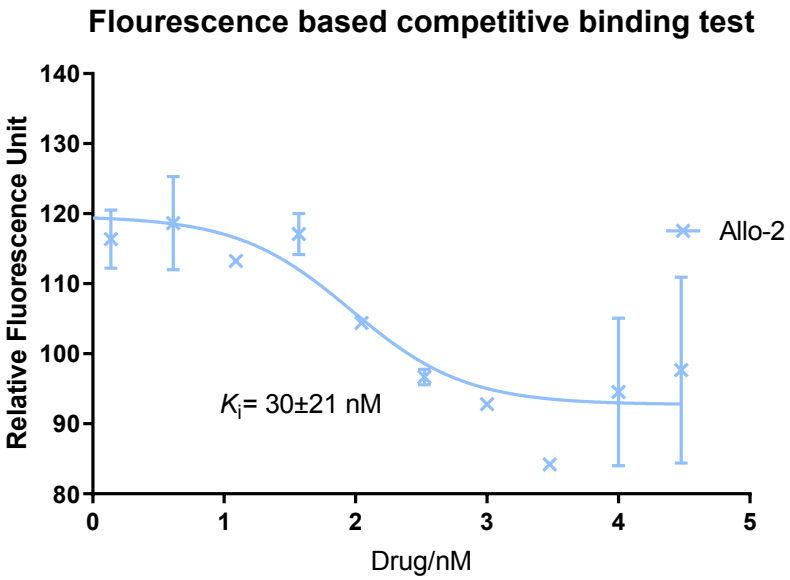



**Figure S11.** The competitive binding of Allo-2 with LY2940680 derived probe BODIPY-LY.

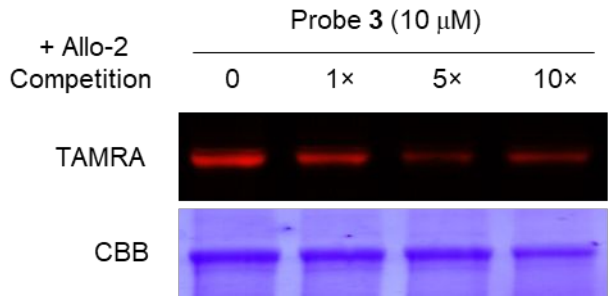



**Figure S12.** Probe **3** used for Allo-1 specific labeling was competed by the addition of Allo-2.

**Procedures for molecular docking**

Structures of SMO receptor (PDB code: 4O9R[3], 4N4W[3]) were obtained from RCSB PDB server, and fusion partners and non-ligand molecules were removed. Protein structures were processed by Prepwizard[4] of Schrödinger 2015-4 suite[5] with default parameters. Glu518 was neutralized by Propka of Schrödinger 2015-4 suite. Structures of Allo-1, BODIPY-CP and other small molecules were prepared by LigPrep of Schrödinger 2015-4 suite with default parameters. BODIPY-CP was docked into SMO (4O9R) by Glide XP[6], with a core of heavy atoms of CP with RMSD less than 0.3 Å. Allo-1 was docked into SMO (4O9R) by Glide XP. Docking of allosteric site: Induced-Fit Docking[7] workflow was used for initial docking of Allo-1 into SMO (4N4W) with default parameters and Leu325 was restrained. Other Allo-1 analogs and Allo-2 were docked into the Induced-Fit docking trained conformation of SMO by Glide XP, followed by Prime/MM-GBSA[8] for free-energy scoring.

**Procedures for molecular dynamic simulation**

Molecular dynamic simulation of two complexes, Allo-1/CP-SMO (4O9R), Allo-1-SMO (4N4W) were processed by GROMACS 5.1.2[9] in a local HPC cluster. Protein of these three complexes were parametrized by Amber99-SB-ILDN[10] force field, and the N-terminal and C-terminal were capped by ACE and CT3 respectively, and Glu518 was neutralized. Ligands were parameterized by antechamber of AMBER14[11] with GAFF[12] and AM1-BCC charge model, and then converted to GROMACS format by ACPYPE[13]. Protein-membrane system was built by CHARMM-GUI[14] server with ~128 POPC lipids in a rectangular box, and all POPC lipids were converted to Stockholm lipids force field[15] format, which is an AMBER consistent force field for lipids. Model of water and ions are TIP3P, $Na^+$ and $Cl^-$ at a concentration of 0.15 M. The equilibration of molecular system included a 5000-step minimization, a short NVT equilibration, and 5 NPT equilibration with a decreasing restraint described as CHARMM-GUI. After equilibration, a 200 ns production molecular dynamics was launched. Long distance cut-off was 10 Å and the covalent bond of H was constrained by LINCS[16] algorithm. The energy and RMSD analysis were analyzed by GROMACS 5.1.2, the interaction finger prints were calculated by ODDT[17] library of Python for every 10 ns per frame from simulation trajectory.

**Procedures for cell-based luciferase reporter assay**

The activities of newly synthesized Allo-1 analogs were measured with cell-based luciferase reporter assay. NIH3T3 cells expressed firefly luciferase gene with the regulation of Gli responsive. The cells were then cultured to confluency with DMEM consisting of 175 μg/mL hygromycin and 10% (v/v) newborn calf serum in 96-well plates. After that, various concentrations of Allo-1 compounds in DMEM containing 0.5% NCS was added. After 2 hours' incubation at 37 °C, SAG (commercial source) was added to the final concentration of 100 mM. After another 24 hours' incubation at 37 °C, the intensity of the firefly luciferase was tested with Bright-Glo® Luciferase Assay System (Promega) on the Envision (PerkinElmer) under the guidance of description. The inhibition curve and $IC_{50}$ of these antagonists were obtained with GraphPad Prism. Each point of data was the mean of the duplicated results.

**Procedure for fluorescence-based competition assay**

The engineered SMO construct was expressed in HEK293F cells (Invitrogen) in the presence of 5 μM vismodegib. HEK293F cells at a cell density of 1.0-1.3*$10^6$ cells $mL^{-1}$ were transiently transfected with PEI:DNA at a ratio of 2:1, and cultured at 37 °C. The cells were seeded into 96-well plates and subjected to BODIPY-LY in a 2 μM final concentration. After incubation for 10 minutes at 4 °C, the cells were subjected to various concentrations of tested ligand and incubated for another 15 minutes at 4 °C. Unbound compounds were removed by centrifugation and wash. The cells were resuspended and analyzed by a flow cytometry. Data were plotted, and $K_i$ values were determined using GraphPad Prism. Each data point represents the mean±s.d. repeated in triplicates.

**Procedures for photoaffinity labeling**

Recombinant SMO protein (10 μg, 0.5 μg/μL) was incubated with probe **1** or probe **2** (both 20 μM) at room temperature for 3 h, followed by UV irradiation (365 nm, 8 watt) for 15 min on ice. 4 μL of ProteaseMax solution (Promega, 1% in 50 mM $NH_4HCO_3$) was added and incubated at room temperature for another 30 min. 75 μL of 50 mM $NH_4HCO_3$ was added and the samples were reduced with 20 mM DTT at 56 °C for 15 min and alkylated with 50 mM iodoacetamide at room temperature for 30 min in dark. 1 μL of ProteaseMax solution (Promega) was added and the samples were subjected to in solution digestion with 1 μg of trypsin/LysC mixture (Promega) at 37 °C overnight. The digests were desalted by Ziptip desalting column (Pierce) and evaporated to dryness on a SpeedVac. The dried peptides were suspended in 8 μL $ddH_2O$ containing 0.1% formic acid with sonication.

A volume of 3.0 μL of each sample was desalted by loading on a Thermo C18 PepMap100 precolumn (300 mm × 5 mm) and eluted on a Thermo Acclaim PepMap RSLC analytical column (75 mm × 15 cm). Mobile phase A (0.1% formic acid in $H_2O$) and mobile phase B (0.1% formic acid in acetonitrile) were used to establish the 120 min gradient comprised of 85 min of 4–30% B, 15 min of 30–50% B, and 5 min of 90% B, followed by re-equilibrating at 4% B for 15 min. The flow rate was 0.3 mL/min. Peptides were then analyzed on a Thermo Orbitrap Fusion Lumos proteomic mass spectrometer (Thermo Scientific) in a data-dependent manner, with automatic switching between MS and MS/MS scans using a top 10 method. MS spectra were acquired at a resolution of 70000 with a target value of $3\times10^6$ ions or a maximum integration time of 50 ms. The scan range was limited from 375 to 1400 *m/z*. Peptide fragmentation was performed via higher-energy collision dissociation (HCD) with the energy set at 32 NCE. The MS/MS spectra were acquired at a resolution of 35000 with a target value of $1\times10^5$ ions or a maximum integration time of 100 ms. The fixed first *m/z* was 100, and the isolation window was 1.2 *m/z*.

Data processing was performed using Proteome Discoverer 2.1 software (Thermo Scientific) and peptide sequences were determined by matching protein database with the acquired fragmentation pattern by SEQUEST HT algorithm. The precursor mass tolerance was set to 10 ppm and fragment ion mass tolerance to 0.02 Da. Two missed cleavage site of trypsin was

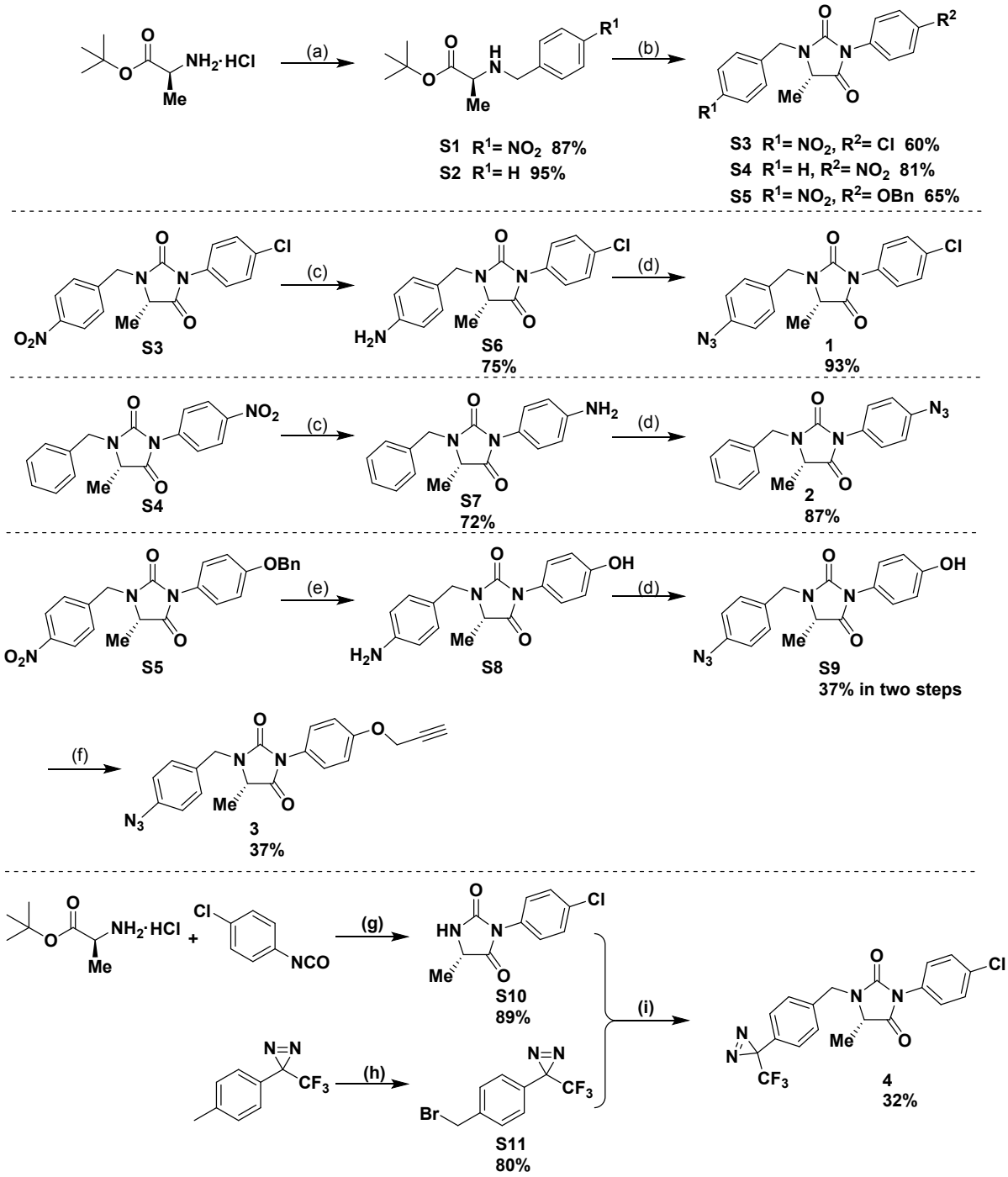
allowed. Probe **1** or probe **2** (any amino acids), Carbamidomethyl (C), and Oxidation (M) were used as variable modifications. All spectra were searched against protein sequence of SMO protein using a target false discovery rate (FDR) of 1%. Manual verification was performed to ensure confident peptide identification.

**Procedures of photoaffinity labeling and fluorescent gel-based analysis**

Recombinant human SMO protein was diluted to a final concentration of 0.1 μg/μL in buffer (25 mM HEPES, 100 mM NaCl, 0.01% n-Dodecyl-β-D-Maltoside (DDM), 0.002% Cholesteryl Hemisuccinate (CHS), 5% glycerol) and incubated with probe **3** as indicated for 1 h at room temperature. Samples were transferred to 96-well plate and irradiated with UV (365 nm, 8 Watt) on ice for 20 minutes. Each of 20 μL protein samples were transferred to 0.6 mL tube and added with freshly prepared 0.25 μL each of TAMRA-$N_3$ (10 mM stock in DMSO, Lumiprobe), $CuSO_4$ (100 mM stock in $H_2O$), THPTA (Tris(3-hydroxypropyltriazolylmethyl) amine, 10 mM stock in $H_2O$, Sigma) and sodium ascorbate (100 mM stock in $H_2O$). The samples were incubated at room temperature for 1 h and the reaction was quenched by addition of 5 μL of SDS-PAGE loading buffer. 20 μL of each sample was applied to SDS-PAGE and detected by FUJIFILM FLA 9000 plus DAGE fluorescence scanner. Finally, the gel was visualized by coomassie blue staining.

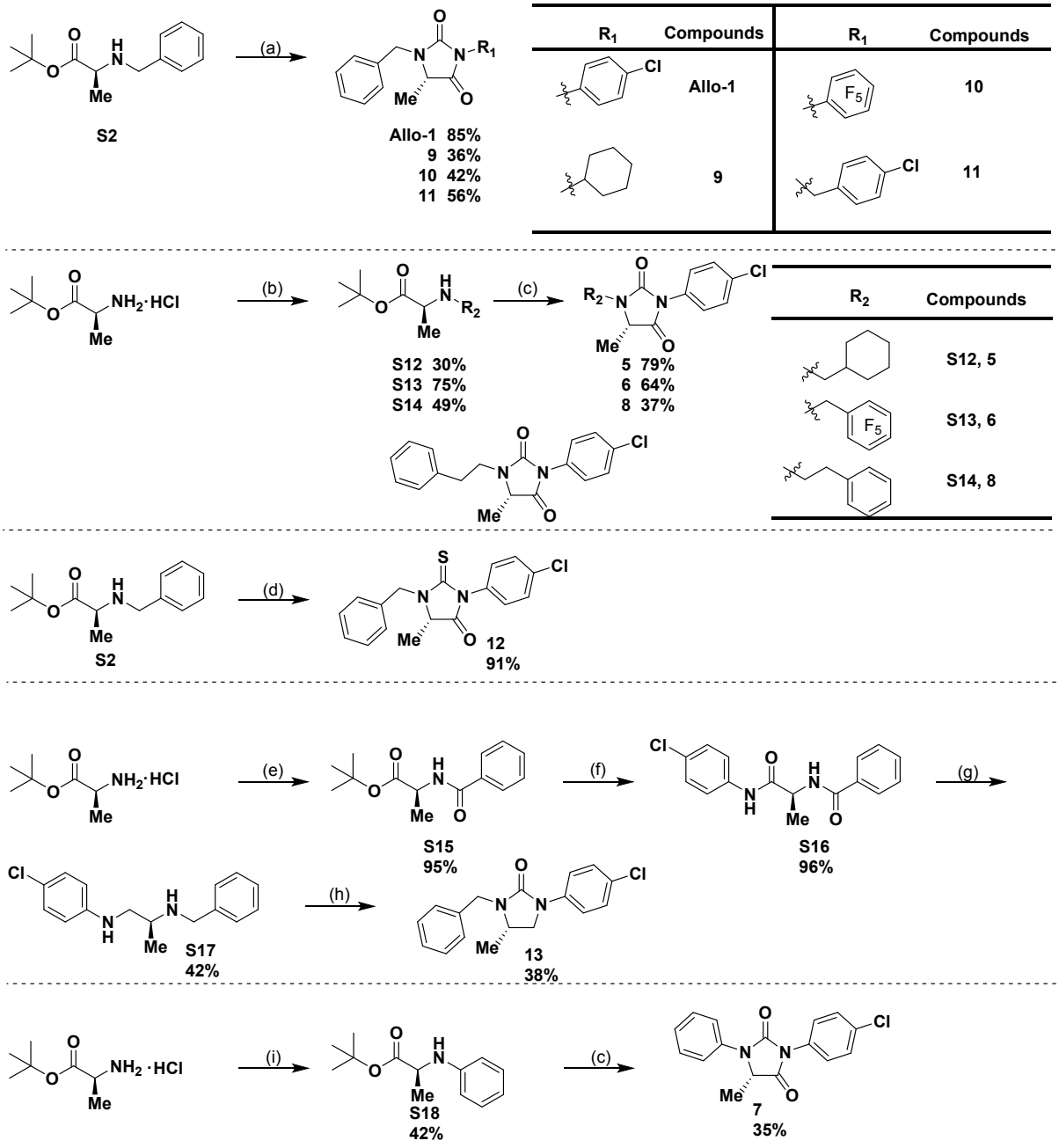
## Chemical synthesis

**Scheme S1.** Synthesis of photoaffinity probe **1**-**4**



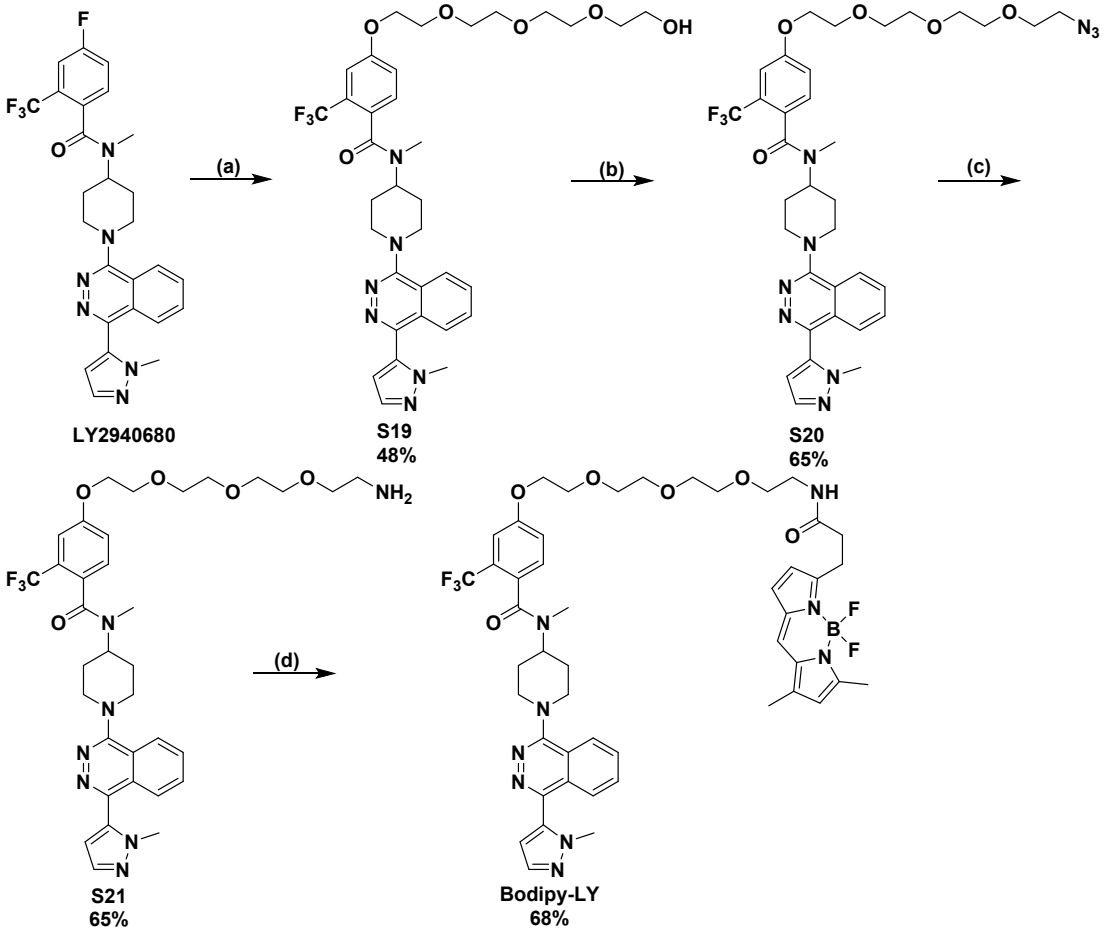

*Reagents and Conditions:* (a) benzyl bromide, DIPEA, $CH_3CN$; (b) i. phenyl isocyanate, $CH_3CN$, r.t., overnight; ii. 12 N HCl, r.t., 10 h; (c) Fe, $NH_4Cl$, MeOH, $H_2O$; (d) $NaNO_2$, $NaN_3$, 6 N HCl, 0 °C to r.t., 1.5 h; (e) $H_2$, Pd/C, MeOH, overnight; (f) 3-bromopropyne, $K_2CO_3$, acetone, r.t., overnight; (g) i. 4-chlorophenyl isocyanate, $CH_3CN$, r.t., overnight; ii. 12 N HCl, r.t., 10 h; (h) NBS, AIBN, $CCl_4$, reflux, 2h; (i) $Cs_2CO_3$, $CH_3CN$, r.t., overnight.

**Scheme S2.** Synthesis of Allo-1 analogs




*Reagents and Conditions:* (a) i. isocyanate, $CH_3CN$, r.t., overnight; ii. 12 N HCl, r.t., 10 h; (b) $K_2CO_3$, alkyl bromides, $CH_3CN$, 70 °C, overnight; (c) i. 4-chlorophenyl isocyanate, $CH_3CN$, r.t., overnight; ii. 12 N HCl, r.t., 10 h; (d) i. 1-chloro-4-isothiocyanatobenzene, $CH_3CN$, r.t., overnight; ii.12 N HCl, r.t., 10 h; (e) benzoyl chloride, $Et_3N$, $CH_2Cl_2$, r.t., 2h; (f) i. TFA, $CH_2Cl_2$, r.t., 2h; ii. 4-chloroaniline, DIPEA, HATU, DMF, 70 °C, 4 h; (g) $LiAlH_4$, THF, 0 °C to reflux, overnight; (h) triphosgene, THF, r.t., 2 h; (i) phenylboronic acid, $O_2$, $Cu(OAc)_2$, $Et_3N$, 4 Å molecular sieve, $CH_2Cl_2$ r.t., overnight.

**Scheme S3**. Synthesis of BODIPY-LY for the competition assay with Allo-1




*Reagents and Conditions:* (a) tetraethylene glycol, NaH, DMF, 120 °C, overnight; (b) DPPA, DBU, THF, r.t. to reflux, 18-24 h; (c) $H_2$, Pd/C, MeOH, r.t. 4 h; (d) Bodipy NHS ester, DIPEA, $CH_3CN$, 1.5 h.

## Procedures for the synthesis of photoaffinity probe 1-4

### General procedure for the synthesis of *tert*-butyl benzylalaninate (S1, S2)

To a solution of *tert*-butyl *L*-alaninate hydrochloride (27.6 mmol, 5.0 g) in 30 mL $CH_3CN$ was added DIPEA (55.2 mmol, 7.1 g) and benzyl bromide (24.8 mmol). After the mixture was stirred overnight at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc for three times. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $Na_2SO_4$. The reaction was concentrated and purified by flash column chromatography (EtOAc/PE from 1:5 to 1:1) on silica gel to obtain **S1** and **S2** respectively.

### General procedure for the synthesis of hydatoin compounds (S3, S4 and S5)

To a solution of *tert*-butyl benzylalaninate (1.0 mmol) in $CH_3CN$ was added corresponding phenyl isocyanate. The reaction mixture was stirred at room temperature overnight, then 0.5 mL concentrated hydrochloric acid was added followed by another 10 h stirring. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc for three times. The combined organic layer was washed with brine and dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE from 1:10 to 1:3) to obtain the **S3**, **S4** and **S5**.

### General procedure for the synthesis of amine compounds (S6, S7)

A solution of nitro containing Allo-1 analogs (**S3**, **S4**) (0.76 mmol) in 3 mL MeOH and 1 mL $H_2O$ was added Fe (3.8 mmol, 213mg) and $NH_4Cl$ (7.6 mmol, 420 mg). The reaction was stirred at 60 °C overnight. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc for three times. The combined organic layer was washed with brine and dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:3) to obtain the **S6** and **S7**.

### General procedure for the synthesis of S8

A solution of nitro containing Allo-1 analogs **S5** (1.0 mmol) in 5 mL MeOH was treated with Pd/C (10 wt%) respectively. The reaction was degased under vacuum and filled with $H_2$ atmosphere. The reaction was stirred at r.t. overnight before being filtered and concentrated for further use without purification.

### Synthesis of Compound S9

**S9** were obtained with the same procedure as the synthesis of compound **1** and **2**.

### Synthesis of S10

To a solution of *L*-alaninate hydrochloride (1.6 mmol, 300 mg) in 10 mL $CH_3CN$ was added 4-chlorophenyl isocyanate (1.8 mmol, 280 mg) and $Et_3N$ (2.5 mmol, 250 mg). The reaction mixture was stirred at room temperature overnight before being treated with 0.5 mL 12 N hydrochloric acid, followed by another 10 h stirring. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc for three times. The combined organic layer was washed with brine and dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:3) to obtain **S10**.

**Synthesis of S11**

**S11** was synthesized according to literature procedure with slight modification[18].

**Synthesis of Compound 4**

To a solution of **S10** (0.67 mmol, 150 mg) and **S11** (1.0 mmol, 280 mg) in 5 mL $CH_3CN$ was added $Cs_2CO_3$ (0.89 mmol, 200 mg). The mixture was stirred at room temperature overnight. The reaction was quenched with saturated $NH_4Cl$ solution and extracted with EtOAc for three times. The combined organic layer was washed with saturated $NH_4Cl$ solution and brine, dried over $Na_2SO_4$. Finally, the reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:5) to obtain compound **4**.

## Procedures for the synthesis of Allo-1 analogs to study the interaction between Allo-1 and SMO

### General procedure for the synthesis of Allo-1, compound 9, compound 10 and compound 11

Allo-1, compound **9**, compound **10**, and compound **11** were obtained with the same procedure as the synthesis of hydatoin compounds.

### Synthesis of compound 12

To a solution of **S2** (0.85 mmol, 200 mg) in 2 mL $CH_3CN$ was added 1-chloro-4-isothiocyanatobenzene (0.71 mmol, 120 mg). The reaction mixture was stirred at room temperature overnight. After adding 0.5 mL concentrated hydrochloric acid, the reaction was stirred for another 10 h. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc for three times. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:5) to obtain compound **12**.

### General procedure for the synthesis of S12, S13, S14

To a solution of *tert*-butyl *L*-analinate hydrochloride (2.8 mmol, 509 mg) in $CH_3CN$, $K_2CO_3$ (2.8 mmol, 390 mg), and corresponding bromide (2.2 mmol) was added. The reaction mixture was stirred at 70 °C overnight before being quenched with saturated $NH_4Cl$ solution. The reaction mixture was extracted with EtOAc for three times. The combined organic layer was washed with saturated $NH_4Cl$ solution and brine, dried over $Na_2SO_4$. Finally, the reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:1) to obtain **S12**, **S13** and **S14**.

### General procedure for the synthesis of compound 5, compound 6 and compound 8

Compound **5**, compound **6** and compound **8** were obtained with the same procedure as the synthesis of hydatoin compounds.

### Synthesis of S15

To a solution of *tert*-butyl *L*-analinate hydrochloride (5.5 mmol, 1.0 g), $NEt_3$ (11 mmol, 1.1 g) in 8 mL anhydrous $CH_2Cl_2$, benzoyl chloride (6.0 mmol, 856 mg) in 8 mL $CH_2Cl_2$ was added. The reaction mixture was stirred for 6 h at room temperature before being quenched with saturated $NH_4Cl$ solution. The reaction was extracted with EtOAc for three times and washed with saturated $NH_4Cl$ solution and brine sequentially, dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:3) to obtain **S15**.

**Synthesis of S16**

To a solution of **S15** (2.6 mmol, 655 mg) in 5 mL $CH_2Cl_2$ was added 2 mL TFA. The mixture was stirred at room temperature for 4 h and then concentrated for further use. The reaction was added a solution of 4-chloroaniline (2.9 mmol, 365 mg), 2-(7-aza-*1H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (3.1 mmol, 1.2 g), DIPEA (5.2 mmol, 860 uL) in 5 mL DMF. The reaction was stirred at 70 °C for 4 h before being quenched with saturated $NH_4Cl$ solution. The reaction was extracted with EtOAc for three times and washed with saturated $NH_4Cl$ solution and brine sequentially, dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:5) to obtain **S16**.

**Synthesis of S17**

To a solution of **S16** (2.0 mmol, 604 mg) in anhydrous THF was slowly added $LiAlH_4$ (4.0 mmol, 152 mg). The reaction was refluxed overnight before being quenched with $NaHCO_3$ solution. The mixture was extracted with EtOAc for three times and washed with saturated $NaHCO_3$ solution and brine, dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (MeOH/DCM 1:20) to obtain **S17**.

**Synthesis of compound 13**

To a solution of **S17** (0.07mmol, 20 mg) in anhydrous THF was added triphosgene (0.05 mmol, 15 mg). The mixture was stirred at r.t. for 1 h before the reaction was concentrated and then purified with column chromatography (EtOAc/PE 1:5) to obtain compound **13**.

**Synthesis of S18**

To a mixture of *tert*-butyl *L*-analinate hydrochloride (5 mmol, 905 mg), phenylboronic acid (10.0 mmol, 1.2 g), $Cu(OAc)_2$ (5.5 mmol, 990 mg) and 4 Å molecular sieve in $CH_2Cl_2$ under $O_2$, was added a solution of $Et_3N$ (10.0 mmol, 1.0 g) in $CH_2Cl_2$. The mixture was stirred at room temperature overnight before being quenched with saturated $NH_4Cl$ solution. The reaction was extracted with EtOAc for three times and washed with saturated $NH_4Cl$ solution and brine, dried over $Na_2SO_4$. The reaction was filtered, concentrated and purified with column chromatography (EtOAc/PE 1:5) to obtain **S18**.

**Synthesis of compound 7**

Compound **7** was obtained with the same procedure as the synthesis of hydatoin compounds.

## Procedures for the synthesis of BODIPY-LY

### Synthesis of S19

To a solution of tetraethylene glycol (3.0 mmol, 582 mg) in 10 mL DMF was added 60% sodium hydride (1.5 mmol, 60 mg). The reaction mixture was stirred at room temperature for 30 min before LY2940680 (1.0 mmol, 512 mg) was added. The reaction mixture was heated at 120 °C and stirred overnight. The reaction was cooled and quenched by the addition of saturated $NH_4Cl$ solution. The reaction mixture was extracted 3 times with $CH_2Cl_2$. The combined organic layer was washed with saturated $NH_4Cl$ solution and brine sequentially, dried over $Na_2SO_4$. After filtration, the solution was concentrated in vacuum and the crude product was purified by flash column chromatography (MeOH/DCM 1:7) on silica gel to obtain **S19**.

### Synthesis of S20

To a solution of **S19** (0.5 mmol, 343 mg) in 5 mL THF was added Diphenylphosphoryl azide (DPPA, 2.0 mmol, 550 mg) and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU, 1.5 mmol, 228 mg). The reaction mixture was stirred at room temperature overnight and then heat at reflux for 6 hours. The reaction was quenched by the addition of brine. The reaction mixture was extracted 3 times with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over $Na_2SO_4$. After filtration, the solution was concentrated in vacuum and the crude product was purified by flash column chromatography (MeOH/DCM 1:10) on silica gel to obtain **S20**.

### Synthesis of S21

A solution of **S20** (0.035 mmol, 25mg) in 5 mL MeOH was treated with Pd/C (10 wt%). The reaction was degased under vacuum and filled with $H_2$ atmosphere. The reaction was stirred at r.t. overnight. After that, the reaction was filtered and concentrated for further use.

### Synthesis of BODIPY-LY

To a solution of **S21** (0.014 mmol, 10 mg) and Bodipy NHS ester (0.015 mmol, 6 mg) in 1 mL $CH_3CN$ was added DIPEA (0.014 mmol, 2.5 ul). The reaction was stirred at room temperature for 1.5 h before being quenched with saturated $NH_4Cl$ solution. The reaction was extracted with EtOAc for three times and washed with saturated $NH_4Cl$ solution and brine sequentially, dried over $Na_2SO_4$. The organic layer was combined and filtered, concentrated and purified by HPLC ($CH_3CN/H_2O$, gradient elution) to obtain BODIPY-LY.

**(S)-3-(4-chlorophenyl)-5-methyl-1-(4-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzyl)imidazolidine-2,4-dione (Compound 4)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.45-7.42 (m, 4H), 7.38 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 5.00 (d, $J$ = 15.4 Hz, 1H), 4.30 (d, $J$ = 15.4 Hz, 1H), 3.94 (q, $J$ = 6.9 Hz, 1H), 1.47 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 171.9, 155.0, 137.5, 133.9, 130.3, 129.4, 129.3, 128.7, 127.3, 127.1, 55.0, 44.5, 15.6. HRMS calcd for $C_{19}H_{14}ClF_3N_4O_2$ $[M+H]^+$: 423.0836; found: 423.0832. HPLC: $t_R$ 11.9 min, purity >95%.

**(S)-3-(4-chlorophenyl)-1-(cyclohexylmethyl)-5-methylimidazolidine-2,4-dione (Compound 5)**, white solid. $^1$H NMR (800 MHz, Chloroform-*d*), $\delta$ (ppm) 7.41 (m, 4H), 4.09 (q, $J$ = 7.0 Hz, 1H), 3.54 (m, 1H), 3.01 (m, 1H), 1.80-1.58 (m, 6H), 1.52 (d, $J$ = 7.0 Hz, 3H), 1.29-1.17 (m, 3H), 1.08-0.94 (m, 2H). $^{13}$C NMR (201 MHz, Chloroform-*d*), $\delta$ (ppm) 172.4, 154.8, 133.5, 130.4, 129.1, 127.0, 55.5, 47.0, 36.4, 30.9, 30.6, 26.2, 25.7, 25.6, 15.5. HRMS calcd for $C_{17}H_{21}ClN_2O_2$ $[M+H]^+$: 321.1370; found: 321.1368. HPLC: $t_R$ 11.4 min, purity >95%.

**(S)-3-(4-chlorophenyl)-5-methyl-1-((perfluorophenyl)methyl)imidazolidine-2,4-dione (Compound 6)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.42-7.26 (m, 4H), 5.14 (d, $J$ = 15.3, 1H), 4.40 (d, $J$ = 15.3, 1H), 4.00 (q, $J$ = 6.9 Hz, 1H), 1.59 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 171.5, 154.3, 134.0, 130.1, 129.3, 129.1, 127.1, 55.3, 32.5, 15.5. HRMS calcd for $C_{17}H_{10}ClF_5N_2O_2$ $[M+H]^+$: 405.0429; found: 405.0428. HPLC: $t_R$ 11.5 min, purity >95%.

**(S)-3-(4-chlorophenyl)-5-methyl-1-phenylimidazolidine-2,4-dione (Compound 7)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.50-7.40 (m, 8H), 7.30-7.22 (m, 1H), 4.73 (q, $J$ = 6.9 Hz, 1H), 1.57 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 171.5, 152.8, 135.4, 134.1, 130.1, 129.6, 129.4, 127.5, 126.0, 122.3, 56.2, 16.0. HRMS calcd for $C_{16}H_{13}ClN_2O_2$ $[M+H]^+$: 301.0744; found: 301.0741. HPLC: $t_R$ 11.3 min, purity >95%.

**(S)-3-(4-chlorophenyl)-5-methyl-1-phenethylimidazolidine-2,4-dione (Compound 8)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.36-7.28 (m, 4H), 7.26-7.24 (m, 2H), 7.20-7.15 (m, 3H), 3.92-3.86 (m, 1H), 3.79 (q, $J$ = 7.0 Hz, 1H), 3.38-3.31 (m, 1H), 2.95-2.83 (m, 2H), 1.34 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 172.3, 154.6, 138.1, 133.7, 130.4, 129.3, 128.9, 128.8, 127.2, 127.1, 55.7, 42.6, 34.5, 15.5. HRMS calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1057; found: 329.1055. HPLC: $t_R$ 11.4 min, purity >95%.

**(S)-1-benzyl-3-cyclohexyl-5-methylimidazolidine-2,4-dione (Compound 9)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.37-7.28 (m, 3H), 7.27-7.21 (m, 2H), 4.94 (d, $J$ = 15.3 Hz, 1H), 4.14 (d, $J$ = 15.3 Hz, 1H), 3.96-3.89 (m, 1H), 3.69 (q, $J$ = 7.0 Hz, 1H), 2.19-2.10 (m, 2H), 1.84-1.82 (m, 2H), 1.70-1.64 (m, 3H), 1.33-1.21 (m, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 173.8, 156.4, 136.1, 129.0, 128.2, 128.1, 54.3, 51.8, 44.7, 29.56, 29.53, 26.0, 25.98, 25.2, 15.4. HRMS calcd for $C_{17}H_{22}N_2O_2$ $[M+H]^+$: 287.1760; found: 287.1757. HPLC: $t_R$ 11.6 min, purity >95%.

**(S)-1-benzyl-5-methyl-3-(perfluorophenyl)imidazolidine-2,4-dione (Compound 10)**, white

solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.42-7.33 (m, 3H), 7.32-7.28 (m, 2H), 5.07 (d, $J$ = 15.3 Hz, 1H), 4.24 (d, $J$ = 15.3 Hz, 1H), 4.05 (d, $J$ = 7.0 Hz, 1H), 1.50 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 170.9, 152.9, 135.0, 129.3, 128.6, 128.2, 55.6, 45.2, 15.5. HRMS calcd for $C_{17}H_{11}F_5N_2O_2$ $[M+H]^+$: 371.0819; found: 371.0819. HPLC: $t_R$ 11.5 min, purity >95%.

**(S)-1-benzyl-3-(4-chlorobenzyl)-5-methylimidazolidine-2,4-dione (Compound 11)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.36-7.29 (m, 7H), 7.24-7.22 (m, 2H), 4.96 (d, $J$ = 15.2 Hz, 1H), 4.64 (q, $J$ = 14.5 Hz, 2H), 4.14 (d, $J$ = 15.2 Hz, 1H), 3.78 (q, $J$ = 7.0 Hz, 1H), 1.34 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 173.3, 156.0, 135.7, 134.8, 134.0, 130.2, 129.1, 129.0, 128.3, 128.2, 55.0, 44.8, 42.0, 15.2. HRMS calcd for $C_{18}H_{17}ClN_2O_2$, $[M+H]^+$: 329.1057; found: 329.1055. HPLC: $t_R$ 11.5 min, purity >95%.

**(S)-1-benzyl-3-(4-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (Compound 12)**, white solid. $^1$H NMR (800 MHz, Chloroform-*d*), $\delta$ (ppm) 7.62 (d, $J$ = 8.2 Hz, 2H), 7.40-7.35 (m, 5H), 7.30 (d, $J$ = 8.2 Hz, 2H), 5.77 (d, $J$ = 15.1 Hz, 1H), 4.64 (d, $J$ = 15.1 Hz, 1H), 4.06 (q, $J$ = 7.0 Hz, 1H), 1.53 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (201 MHz, Chloroform-*d*), $\delta$ (ppm) 182.1, 173.3, 135.2, 134.8, 131.9, 129.9, 129.4, 129.2, 128.6, 128.4, 57.3, 48.7, 15.4. HRMS calcd for $C_{17}H_{15}ClN_2OS$ $[M+H]^+$: 331.0666; found: 331.0666. HPLC: $t_R$ 11.7 min, purity >95%.

**(S)-3-benzyl-1-(4-chlorophenyl)-4-methylimidazolidin-2-one (Compound 13)**, white solid. $^1$H NMR (800 MHz, Chloroform-*d*), $\delta$ (ppm) 7.53-7.52 (m, 2H), 7.34-7.31 (m, 4H), 7.29-7.28 (m, 3H), 4.85 (d, $J$ = 15.3 Hz, 1H), 4.15 (d, $J$ = 15.3 Hz, 1H), 3.86 (t, $J$ = 8.7 Hz, 1H), 3.65-3.62 (m, 1H), 3.34-3.32 (m, 1H), 1.27 (d, $J$ = 6.2 Hz, 3H). $^{13}$C NMR (201 MHz, Chloroform-*d*), $\delta$ (ppm) 157.4, 139.3, 137.1, 128.9, 128.8, 128.3, 127.7, 127.4, 118.6, 50.3, 47.4, 45.4, 18.9. HRMS calcd for $C_{17}H_{17}ClN_2O$, $[M+H]^+$: 301.1108; found: 301.1108. HPLC: $t_R$ 12.0 min, purity >95%.

**(S)-3-(4-chlorophenyl)-5-methyl-1-(4-nitrobenzyl)imidazolidine-2,4-dione (S3)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 8.26 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.7 Hz, 2H), 7.46-7.42 (m, 4H), 5.00 (d, $J$ = 15.8 Hz, 1H), 4.49 (d, $J$ = 15.8 Hz, 1H), 4.01 (q, $J$ = 7.0 Hz, 1H), 1.49 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 171.6, 155.0, 147.9, 143.0, 134.0, 130.0, 129.3, 128.9, 127.0, 124.3, 55.3, 44.5, 15.6. HRMS calcd for $C_{17}H_{14}ClN_3O_4$, $[M+H]^+$: 360.0751; found: 360.0751.

**(S)-3-(4-(benzyloxy)phenyl)-5-methyl-1-(4-nitrobenzyl)imidazolidine-2,4-dione (S5)**，yellow solid. $^1$H NMR (800 MHz, Chloroform-*d*), $\delta$ (ppm) 8.25 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.7 Hz, 2H), 7.43-7.42 (m, 2H), 7.38-7.40 (m, 2H), 7.34-7.33 (m, 3H), 7.06 (d, $J$ = 8.9 Hz, 2H), 5.09 (s, 2H)，4.98 (d, $J$ = 15.8 Hz, 1H), 4.48 (d, $J$ = 15.8 Hz, 1H), 3.99 (q, $J$ = 6.9 Hz, 1H), 1.48 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 172.2, 158.6, 155.8, 148.0, 143.4, 136.7, 129.0, 128.8, 128.2, 127.6, 127.5, 124.5, 124.4, 115.5, 70.4, 55.5, 44.6, 15.8. HRMS calcd for $C_{24}H_{21}N_3O_5$ $[M+H]^+$: 432.1559; found: 432.1553.

**(S)-1-(4-aminobenzyl)-3-(4-chlorophenyl)-5-methylimidazolidine-2,4-dione (S6)**, yellow solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.44-7.40 (m, 4H), 7.10 (d, $J$ = 8.2 Hz, 2H), 6.67 (d, $J$ = 8.2 Hz, 2H), 4.98 (d, $J$ = 15.0 Hz, 1H), 4.06 (d, $J$ = 15.0 Hz, 1H), 3.93 (q, $J$ = 7.0 Hz, 1H), 3.73 (s, 2H), 1.47 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 172.5, 154.8, 146.6, 133.7, 130.5, 129.8, 129.3, 127.2, 125.1, 115.5, 54.4, 44.5, 15.4. HRMS calcd for $C_{17}H_{16}ClN_3O_2$ $[M+H]^+$: 330.1004; found: 330.1012.

**(S)-3-(4-chlorophenyl)-5-methylimidazolidine-2,4-dione (S10)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.46-7.43 (m, 2H), 7.40-7.389 (m, 2H), 6.39 (s, 1H), 4.26 (q, $J$ = 7.0 Hz, 1H), 1.55 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 173.3, 156.1, 134.1, 130.1, 129.4, 127.4, 53.0, 28.7, 17.9. HRMS calcd for $C_{10}H_9ClN_2O_2$ $[M+H]^+$: 225.0425; found: 225.0422.

**tert-butyl (cyclohexylmethyl)-L-alaninate (S12)**, white solid. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 3.14 (q, $J$ = 6.9 Hz, 1H), 2.41-2.28 (m, 2H), 1.80-1.59 (m, 6H), 1.45 (s, 9H), 1.46-1.32 (m, 1H), 1.29-1.08 (m, 5H), 0.98-0.81 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 175.3, 80.6, 57.5, 54.7, 38.2, 31.5, 31.2, 28.0, 26.5, 26.0, 25.9, 19.0. HRMS calcd for $C_{14}H_{27}NO_2$ $[M+H]^+$: 242.2120; found: 242.2119.

**tert-butyl phenethyl-L-alaninate (S14)**, colorless oil.$^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) 7.29 (td, $J$ = 7.2, 1.6 Hz, 2H), 7.23-7.17 (m, 3H), 3.23 (q, $J$ = 7.0 Hz, 1H), 2.90-2.81 (m, 2H), 2.79-2.72 (m, 2H), 1.43 (s, 9H), 1.24 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) 174.8, 139.7, 128.5, 128.3, 126.0, 80.7, 57.2, 49.1, 36.5, 27.9, 18.9. HRMS calcd for $C_{15}H_{23}NO_2$ $[M+H]^+$: 250.1807; found: 250.1808.

**(S)-N2-benzyl-N1-(4-chlorophenyl)propane-1,2-diamine (S17)**, yellow solid. $^1$H NMR (800 MHz, Chloroform-*d*), $\delta$ (ppm) 7.35-7.29 (m, 4H), 7.26-7.24 (m, 1H), 7.11-7.08 (m, 2H), 6.53-6.49 (m, 2H), 3.87 (d, $J$ = 13.1 Hz, 1H), 3.74 (d, $J$ = 13.1 Hz, 1H), 3.14-3.08 (m, 1H), 3.01-2.96 (m, 1H), 2.92 (ddd, $J$ = 12.1, 7.0, 5.2 Hz, 1H), 1.18 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (201 MHz, Chloroform-*d*), $\delta$ (ppm) 147.2, 140.4, 129.0, 128.5, 128.0, 127.0, 121.7, 114.0, 51.4, 51.1, 49.3, 18.9. HRMS calcd for $C_{16}H_{19}ClN_2$ $[M+H]^+$: 275.1315; found: 275.1319.

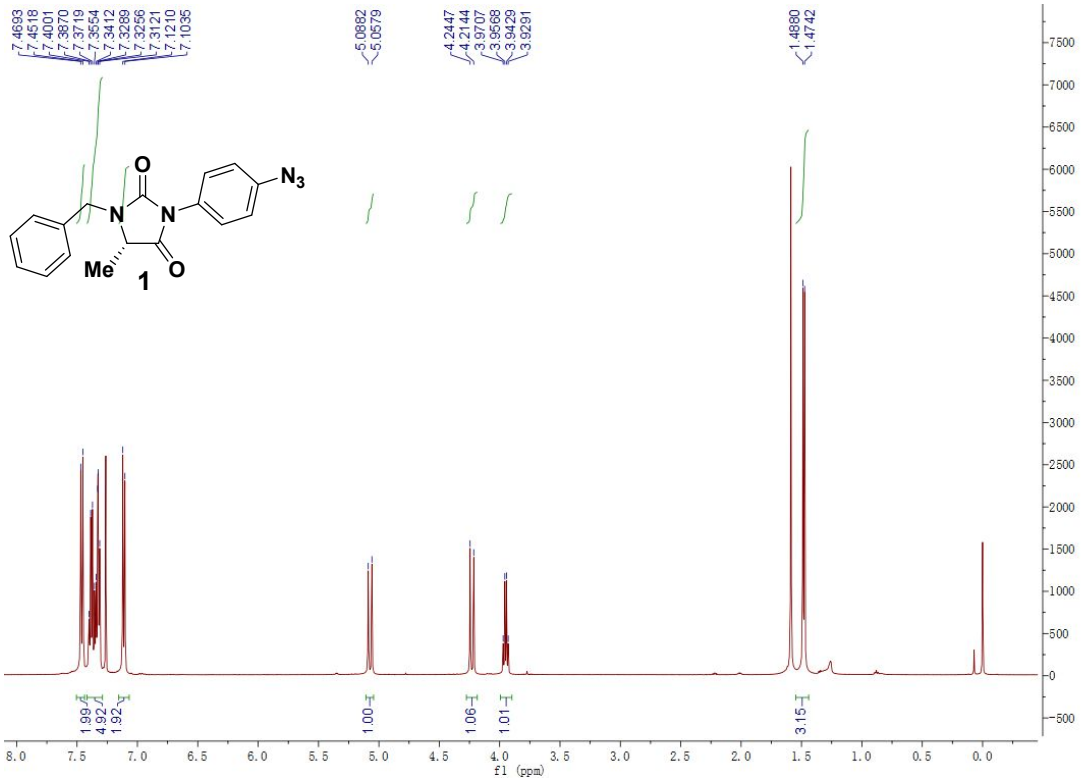
**4-(2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethoxy)-N-methyl-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)phthalazin-1-yl)piperidin-4-yl)-2-(trifluoromethyl)benzamide (S19)**, colorless oil. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) major rotamer, $\delta$ (ppm) 8.14-8.03 (m, 2H), 7.91-7.82 (m, 2H), 7.66 (d, $J$ = 2.0 Hz, 1H), 7.39-7.25 (m, 2H), 7.17 (d, $J$ = 1.5 Hz, 1H), 6.60 (d, $J$ = 2.0 Hz, 1H), 4.94-4.90 (m, 1H), 4.24-4.20 (m, 4H), 4.06 (s, 3H), 3.91-3.88 (m, 2H), 3.75-3.67 (m, 12H), 3.61 (d, $J$ = 4.0 Hz, 2H), 3.39-3.37 (m, 2H,), 2.77 (s, 3H), 2.26-1.76 (m, 4H); minor rotamer, $\delta$ (ppm) 8.14-8.03 (m, 2H), 7.91-7.82 (m, 2H), 7.64 (d, $J$ = 2.0 Hz, 1H), 7.39-7.25 (m, 2H), 7.15 (d, $J$ = 1.5 Hz, 1H), 6.58 (d, $J$ = 2.0 Hz, 1H), 4.18-4.11 (m, 4H), 4.02 (s, 3H), 3.91-3.88 (m, 2H), 3.75-3.67 (m, 12H), 3.61 (d, $J$ = 4.0 Hz, 2H), 3.52-3.49 (m, 1H), 3.10 (s, 3H), 2.99-2.93 (m, 2H), 2.24-1.76 (m, 4H); $^{13}$C NMR (126 MHz, Chloroform-

*d*), $\delta$ (ppm) major rotamer, $\delta$ 171.0, 168.8, 159.4, 158.7, 147.2, 138.0, 136.6, 131.9, 131.4, 128.4, 127.7, 127.4 (q, $J$ = 31.4 Hz), 126.0, 124.8 (q, $J$ = 2.5 Hz), 124.5, 123.6(q, $J$ = 272.2 Hz), 121.2, 118.0, 112.8 (q, $J$ = 4.5 Hz), 108.9, 72.4, 70.6, 70.4, 70.3, 70.0, 69.2, 67.7, 61.4, 56.7, 51.0, 50.7, 38.0, 31.6, 28.5, 27.9, 27.4, 20.9; minor rotamer, $\delta$ (ppm) 171.0, 168.7, 159.3, 158.8, 147.5, 138.0, 136.5, 132.0, 131.5, 128.0, 127.4, 127.4 (q, $J$ = 31.4 Hz), 126.0, 124.3, 124.0 (q, $J$ = 2.1 Hz), 123.6 (q, $J$ = 272.2 Hz), 121.2, 117.9, 113.0 (q, $J$ = 4.5 Hz), 109.0, 72.4, 70.6, 70.4, 70.3, 70.0, 69.2, 67.7, 60.2, 53.3, 50.9, 50.2, 49.9, 38.0, 29.5, 29.0, 14.0; HRMS calcd for $C_{34}H_{41}F_3N_6O_6$ $[M+H]^+$: 687.3112; found: 687.3135.

**4-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-N-methyl-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)phthalazin-1-yl)piperidin-4-yl)-2-(trifluoromethyl)benzamide (S20)**, colorless oil. $^1$H NMR (500 MHz, Chloroform-*d*), $\delta$ (ppm) major rotamer, $\delta$ (ppm) 8.12-8.04 (m, 2H), 7.89-7.80 (m, 2H), 7.66 (d, $J$ = 2.0 Hz, 1H), 7.27-7.24 (m, 2H), 7.14 (d, $J$ = 1.5 Hz, 1H), 6.59 (d, $J$ = 2.0 Hz, 1H), 4.96-4.90 (m, 1H), 4.22-4.19 (m, 4H), 4.06 (s, 3H), 3.91-3.88 (m, 2H), 3.74-3.66 (m, 10H), 3.40-3.38 (m, 4H), 2.75 (s, 3H), 2.27-1.74 (m, 4H), 1.66-1.63 (m, 2H); minor rotamer, $\delta$ (ppm) 8.12-8.04 (m, 2H), 7.89-7.88 (m, 2H), 7.65 (d, $J$ = 2.0 Hz, 1H), 7.27-7.24 (m, 2H), 7.13 (d, $J$ = 1.5 Hz, 1H), 6.58 (d, $J$ = 2.0 Hz, 1H), 4.22-4.19 (m, 4H), 4.02 (s, 3H), 3.91-3.88 (m, 2H), 3.74-3.66 (m, 10H), 3.54-3.47 (m, 1H), 3.10 (s, 3H), 2.98-2.91 (m, 2H), 2.24-1.76 (m, 4H), 1.66-1.63 (m, 2H); $^{13}$C NMR (126 MHz, Chloroform-*d*), $\delta$ (ppm) major rotamer, $\delta$ 168.6, 159.2, 158.5, 147.0, 137.7, 136.4, 131.7, 131.2, 129.4, 128.3, 127.7, 127.4 (q, $J$ = 31.4 Hz), 126.4, 125.0 (q, $J$ = 2.5 Hz), 124.9, 123.1 (q, $J$ = 272.2 Hz), 121.0, 117.7, 112.7 (q, $J$ = 4.5 Hz), 108.7, 70.9, 70.4, 70.24, 70.21 70.20, 69.6, 69.0, 67.6, 56.4, 50.8, 50.6, 50.4, 50.2, 49.8, 42.4, 37.8, 31.4, 29.2, 28.8, 28.4, 27.7, 27.2; minor rotamer, $\delta$ (ppm) 168.4, 159.0, 158.7, 147.2, 137.7, 136.3, 131.8, 131.3, 129.2, 128.3, 127.4, 127.4 (q, $J$ = 31.4 Hz), 126.3, 124.3, 124.0 (q, $J$ = 2.1 Hz), 123.1 (q, $J$ = 272.2 Hz), 120.9, 117.6, 112.9 (q, $J$ = 4.5 Hz), 109.0, 72.4, 70.6, 70.4, 70.3, 70.0, 69.2, 67.7, 60.2, 53.3, 50.9, 50.2, 49.9, 37.8, 29.5, 29.0, 14.0; HRMS calcd for $C_{34}H_{40}F_3N_9O_5$ $[M+H]^+$: 712.3177; found: 712.3178.

**4-((15-(5,5-difluoro-7,9-dimethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-3-yl)-13-oxo-3,6,9-trioxa-12-azapentadecyl)oxy)-N-methyl-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)phthalazin-1-yl)piperidin-4-yl)-2-(trifluoromethyl)benzamide (BODIPY-LY)**, yellow solid. $^1$H NMR (600 MHz, Chloroform-*d*), $\delta$ (ppm) 8.14-8.13 (m, 1H)， 8.09-8.06 (m, 2H), 7.90-7.83 (m, 3H), 7.68-7.67 (m, 1H), 7.24 (br, 1H), 7.21 (d, $J$ = 4 Hz, 1H), 7.12-7.10(m, 1H), 6.88-6.87 (m, 1H), 6.60-6.58 (m, 1H), 6.33-6.29 (m, 2H), 6.10 (s, 1H), 4.96-4.90 (m, 1H), 4.17-4.15 (m, 4H), 4.06-4.02 (m, 3H), 3.86-3.85 (m, 2H), 3.73-3.71 (m, 2H), 3.67-3.58 (m, 6H), 3.54-3.47 (m, 2H), 3.43-3.38 (m, 3H), 3.29-3.27 (m, 2H), 3.10(s, 1H), 2.74 (s, 1H), 2.64-2.62 (m, 2H), 2.56-2.55 (m, 2H), 2..25-2.20 (m, 4H), 2.01(s, 3H). HRMS calcd for $C_{44}H_{53}BF_5N_9O_6$ $[M+H]^+$: 960.4367; found: 960.4368.

## NMR Spectra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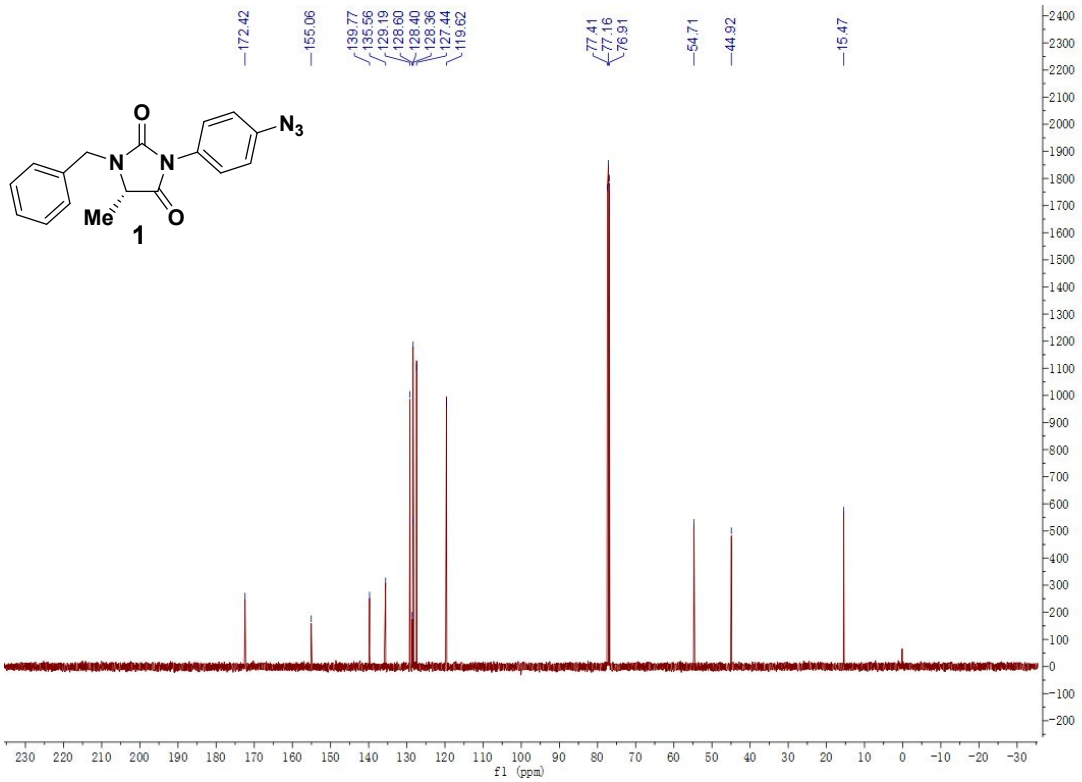
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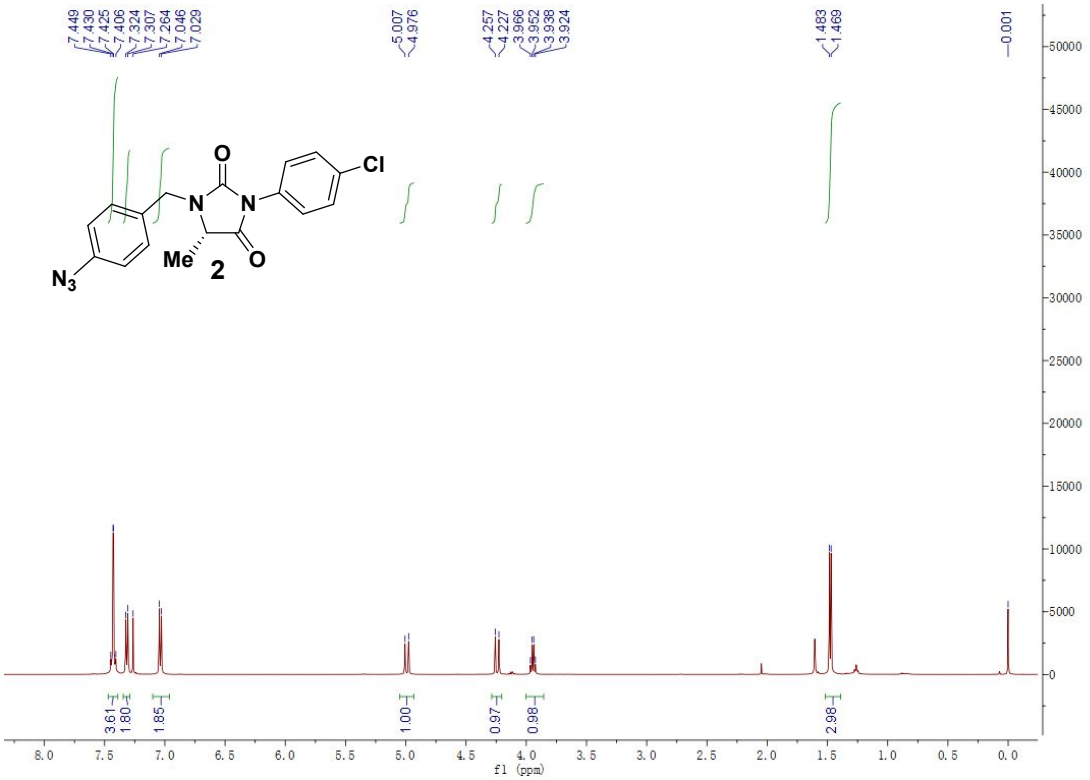
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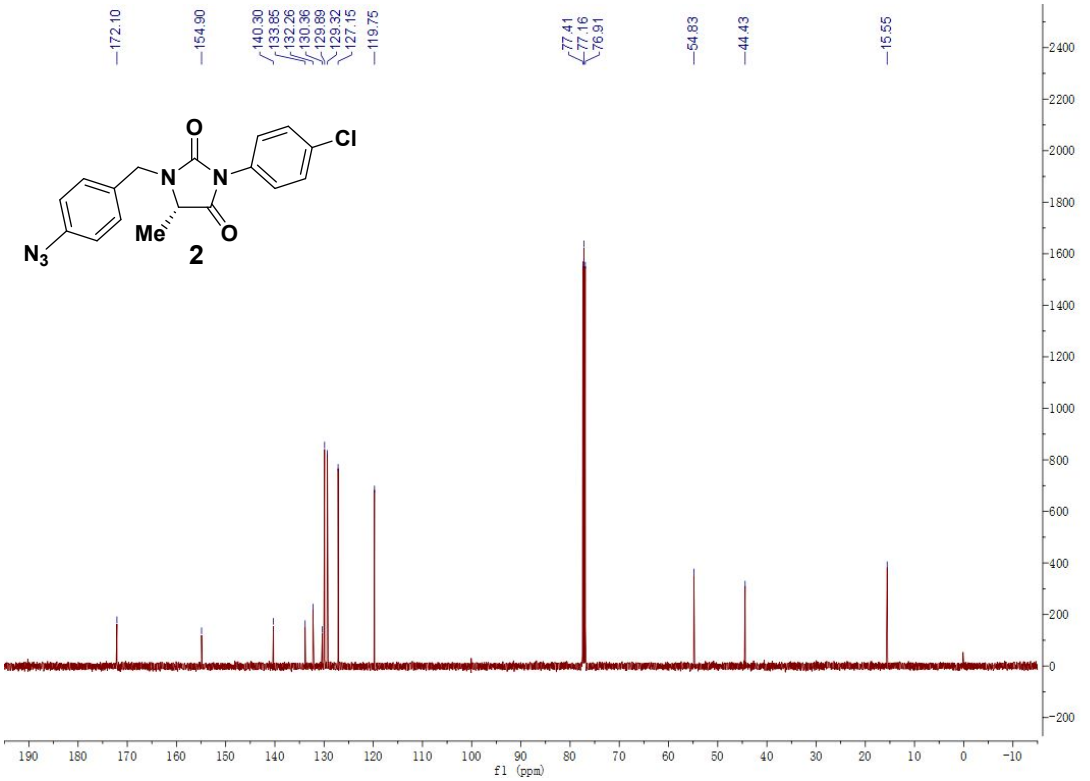
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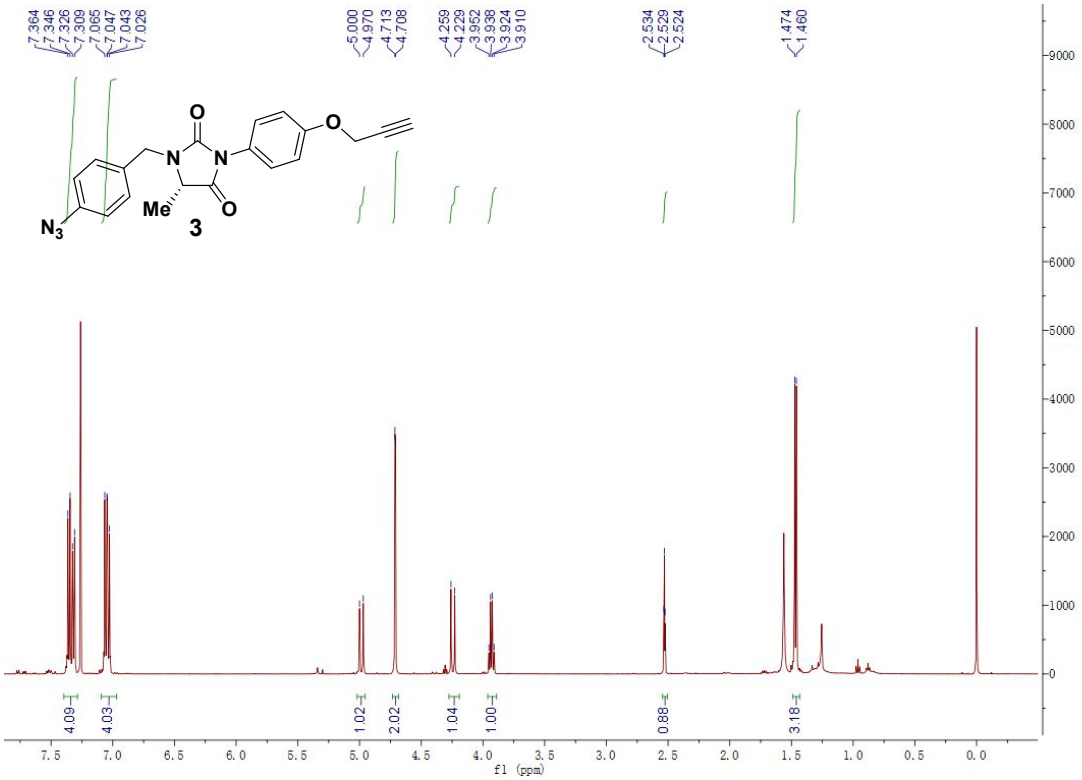
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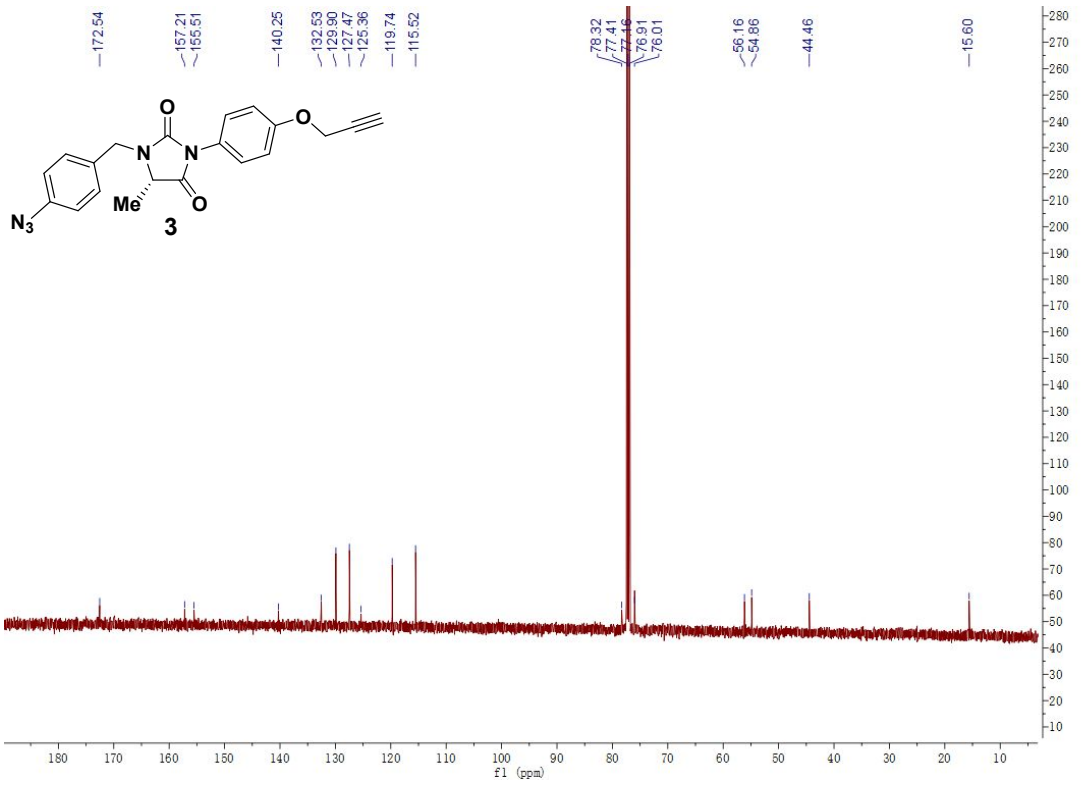
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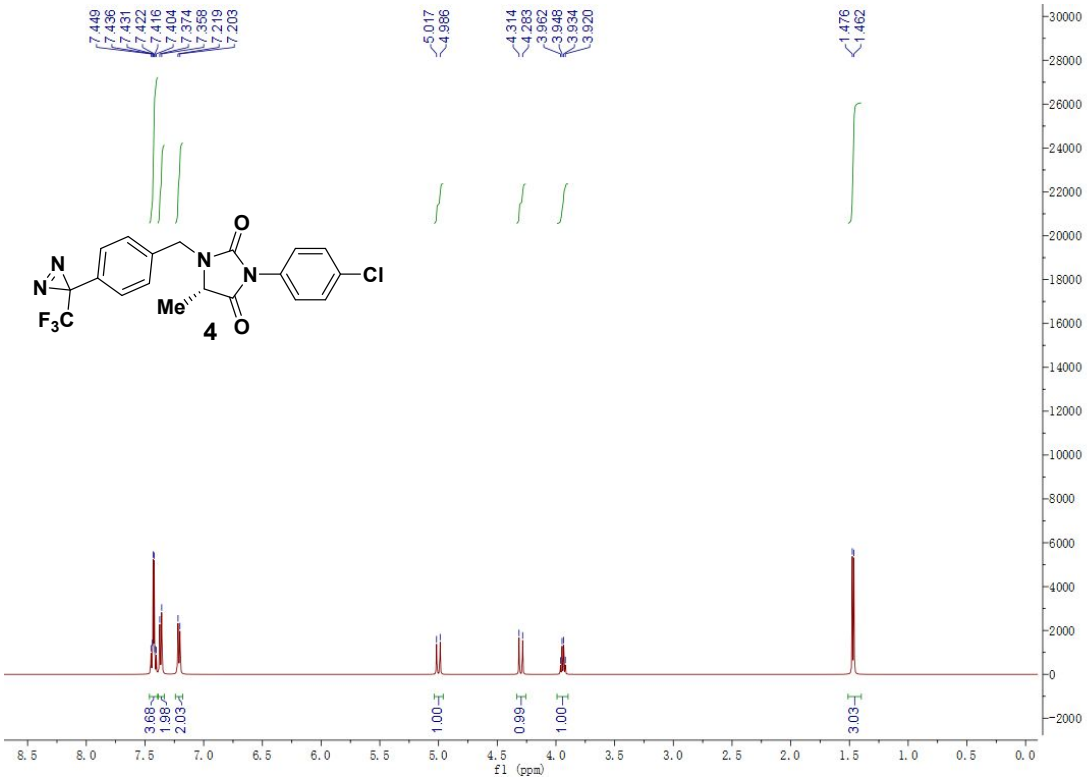
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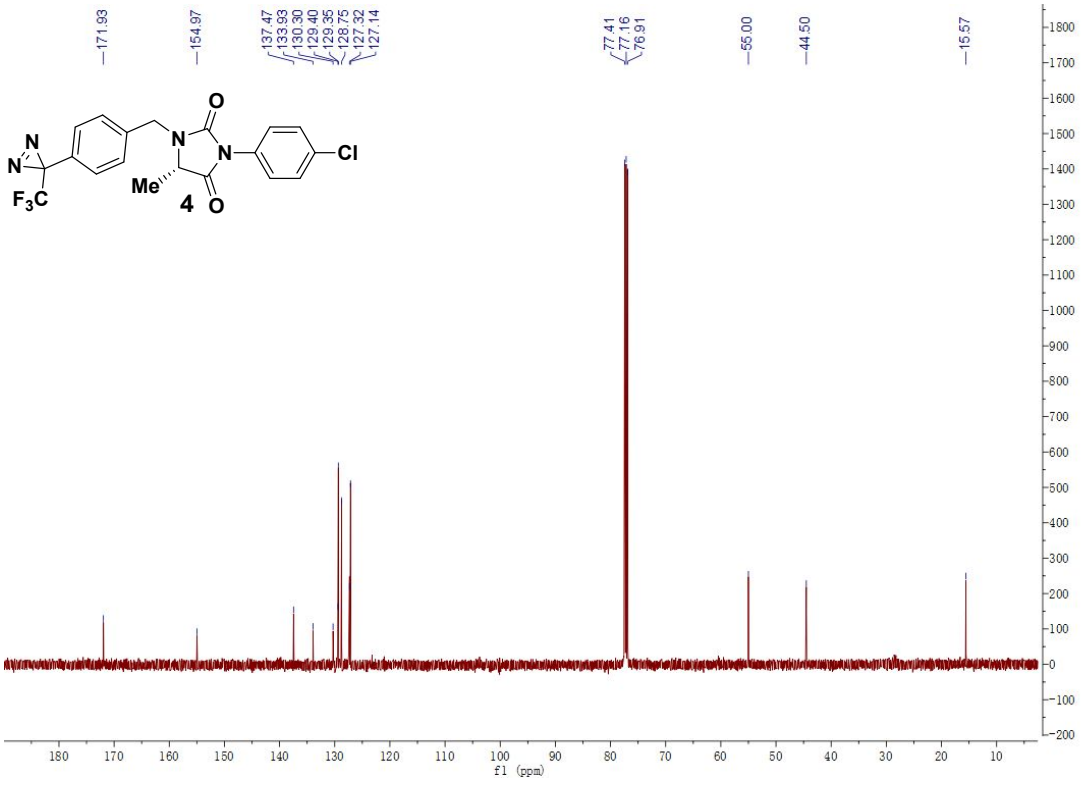
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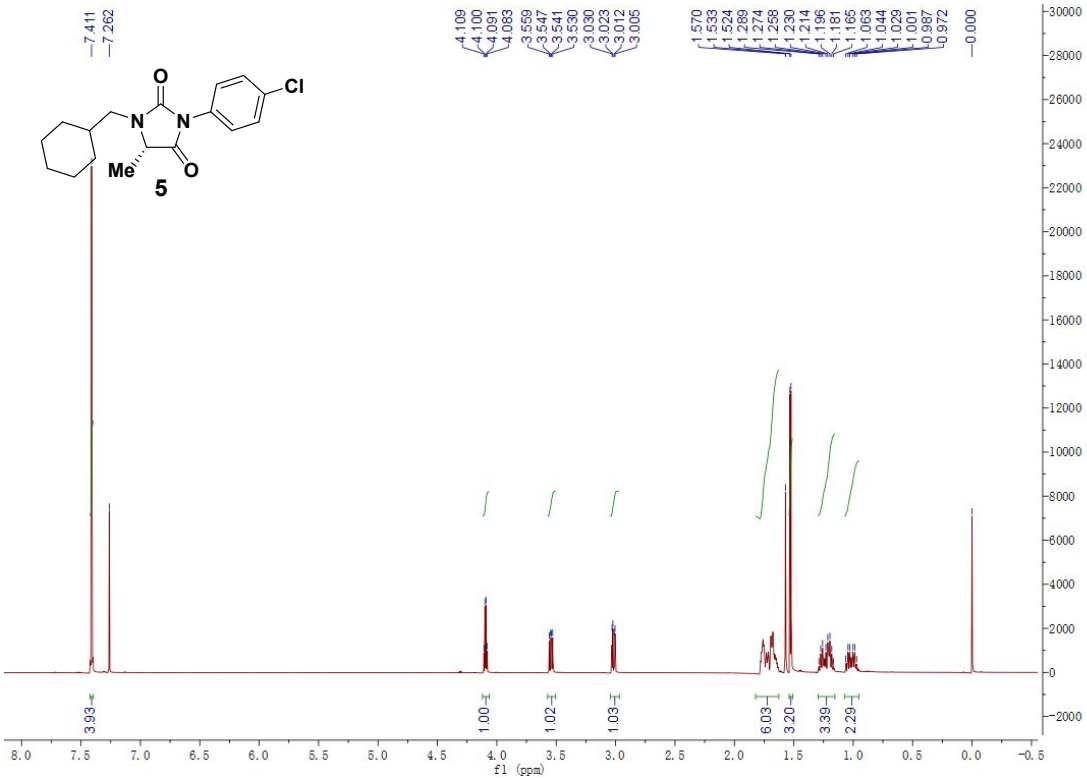
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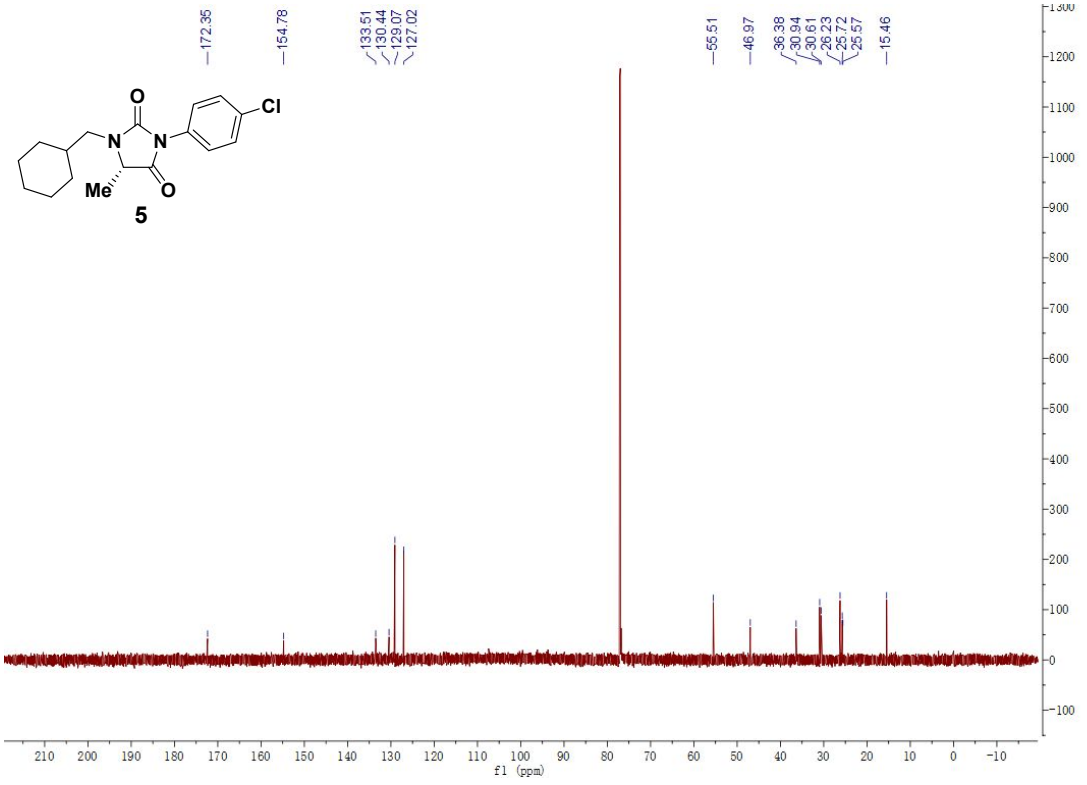
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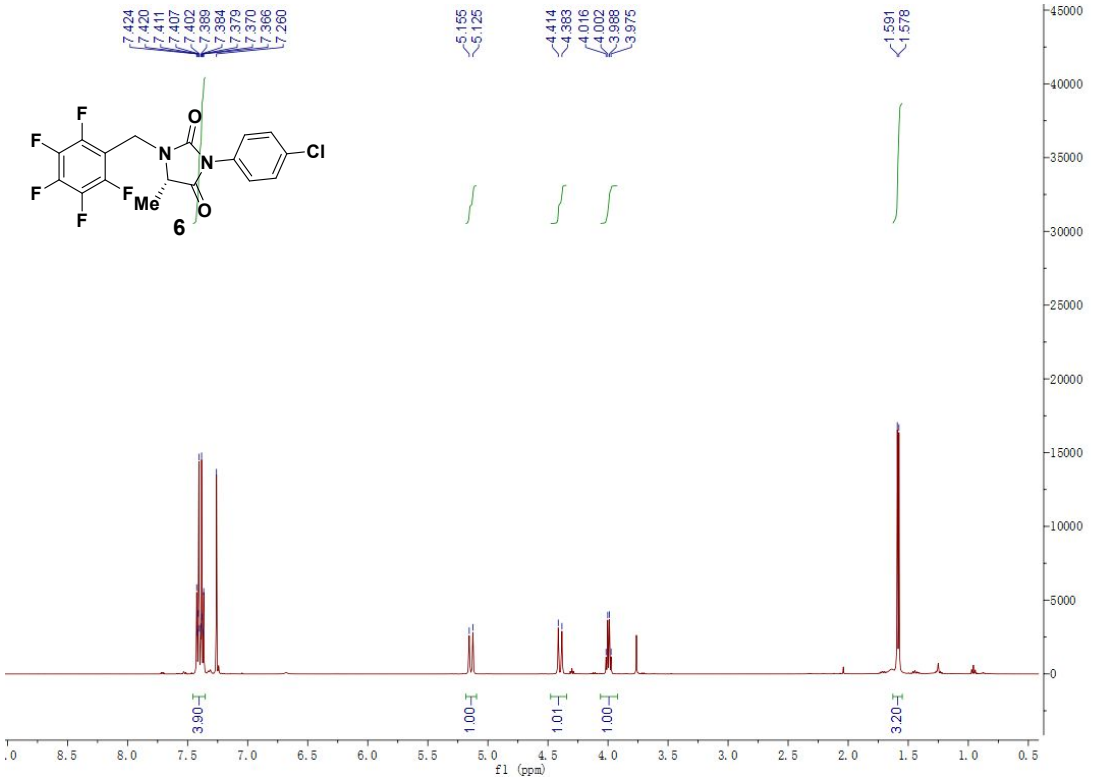
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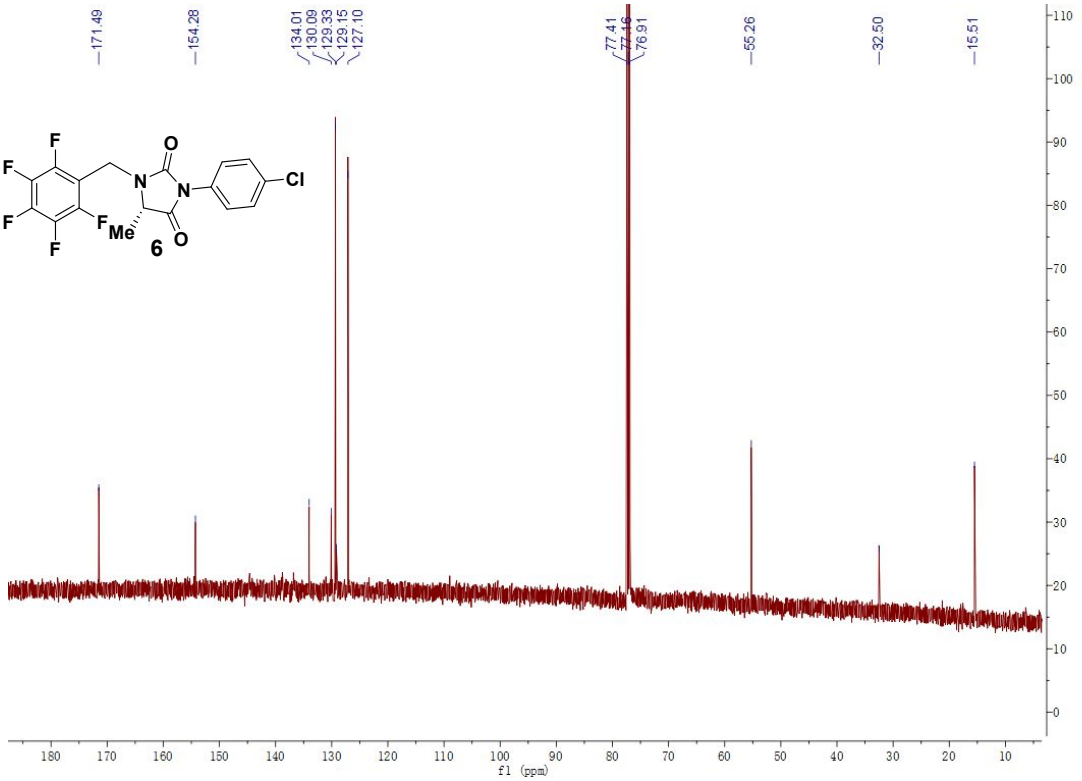
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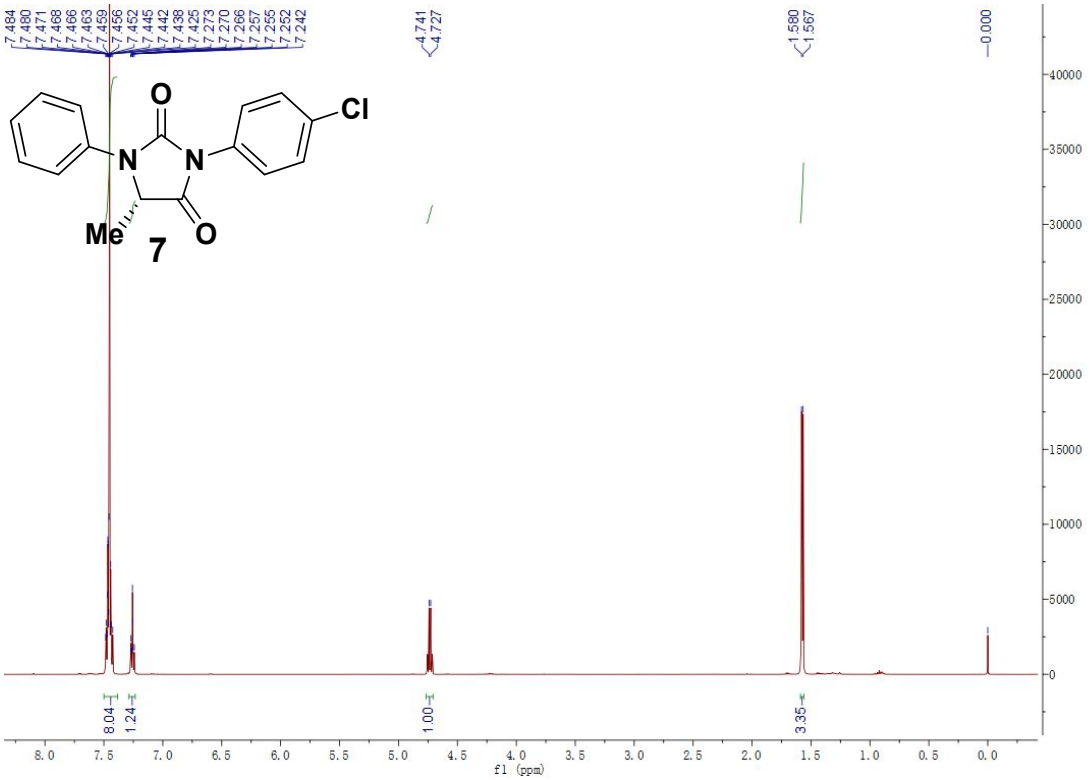
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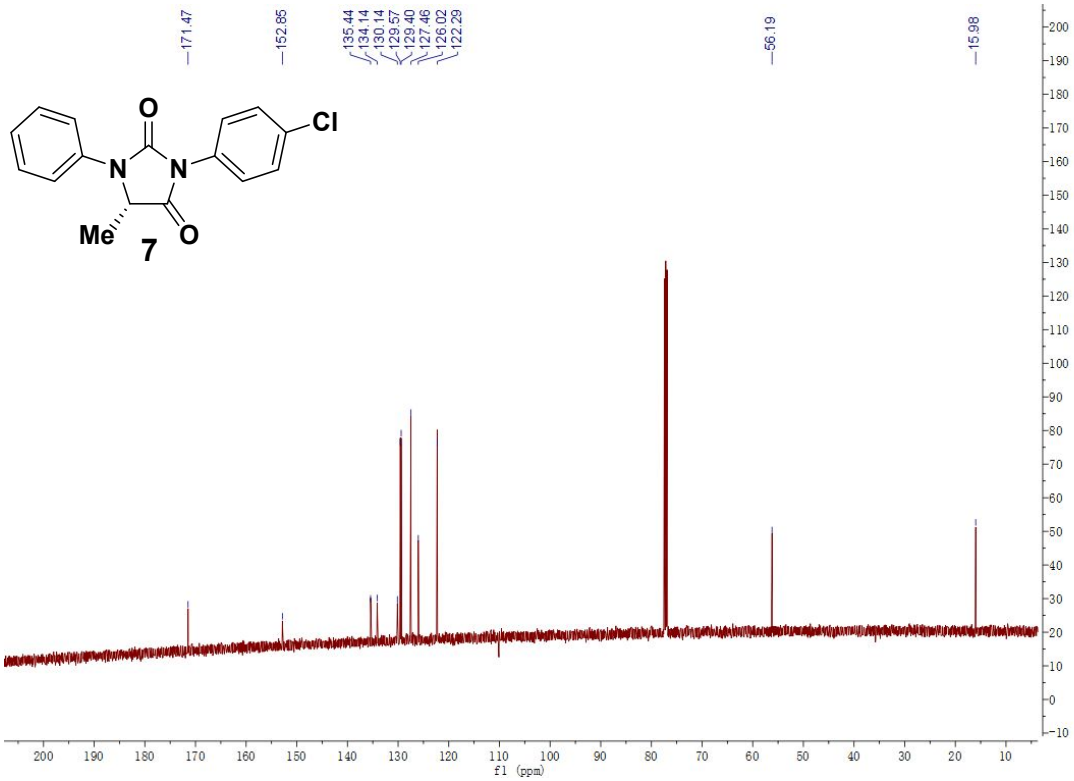
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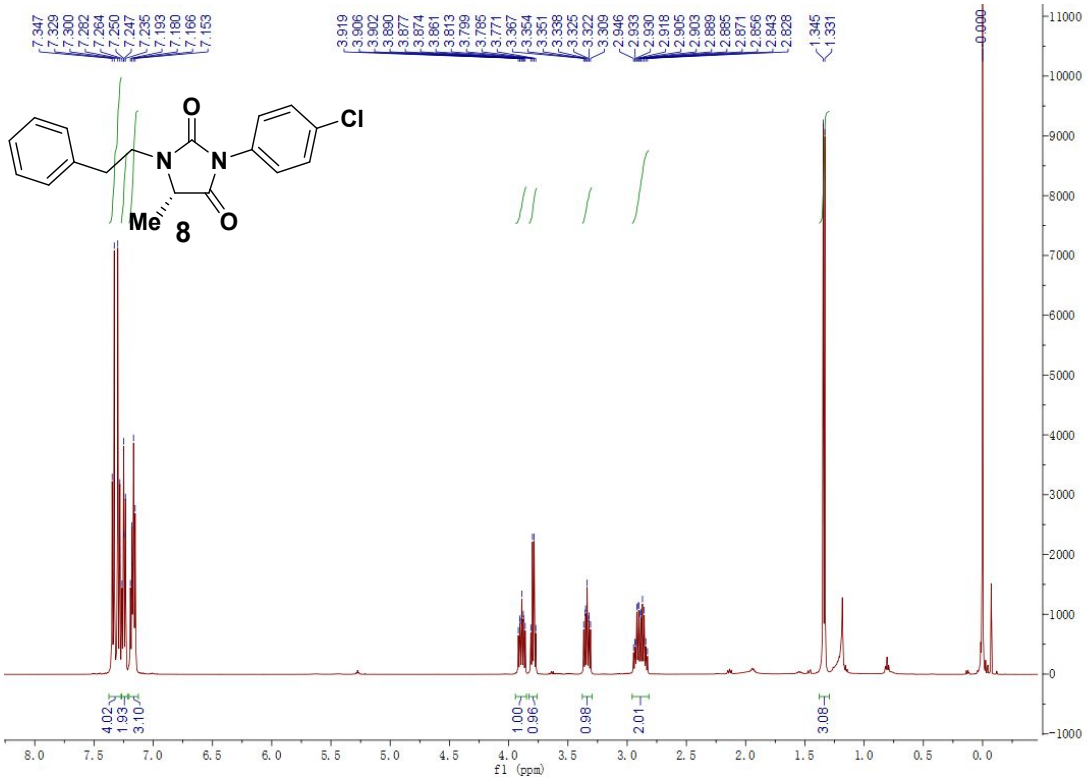
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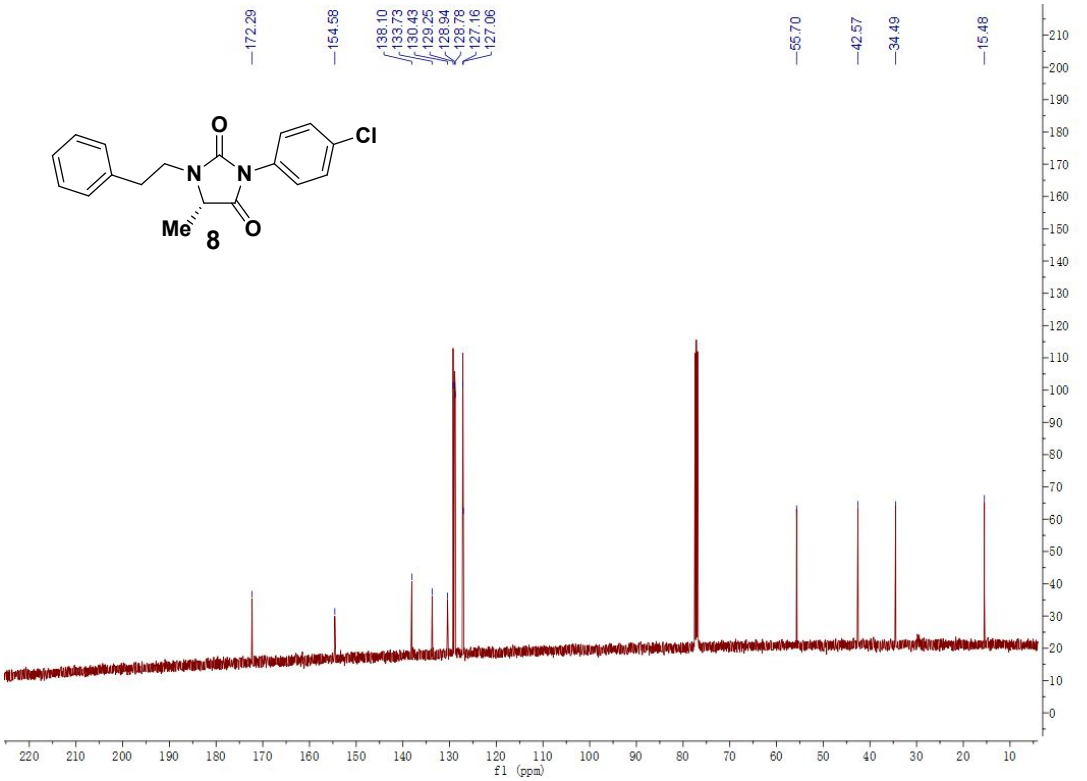
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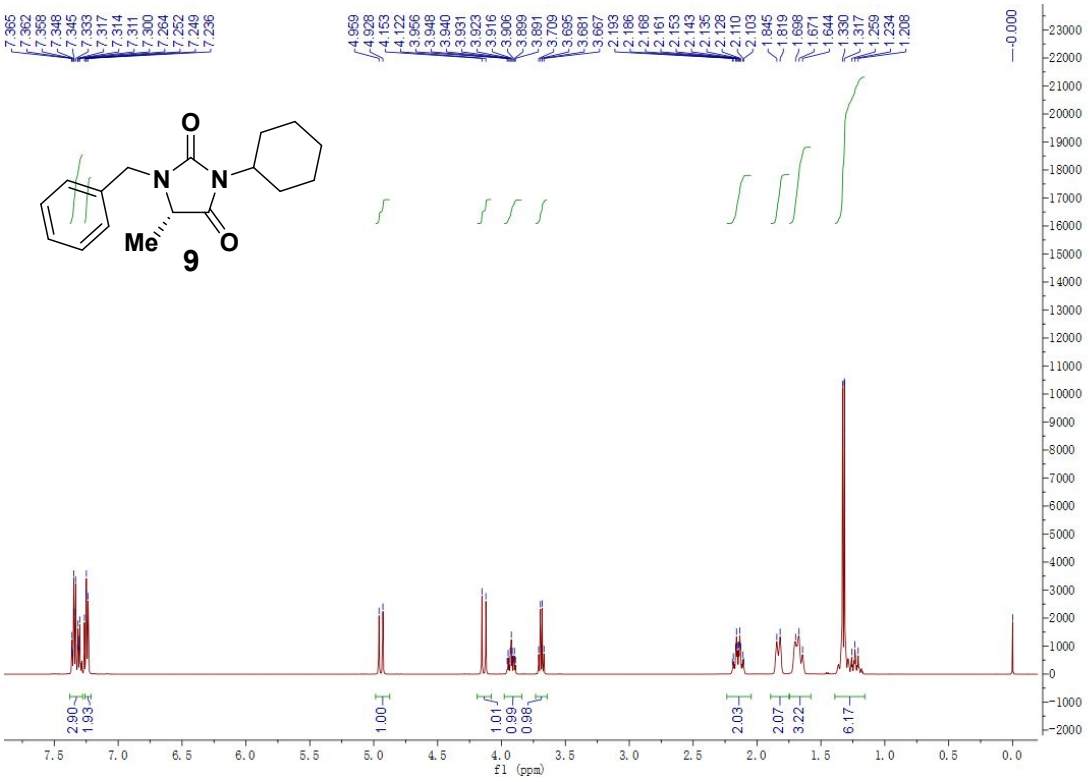
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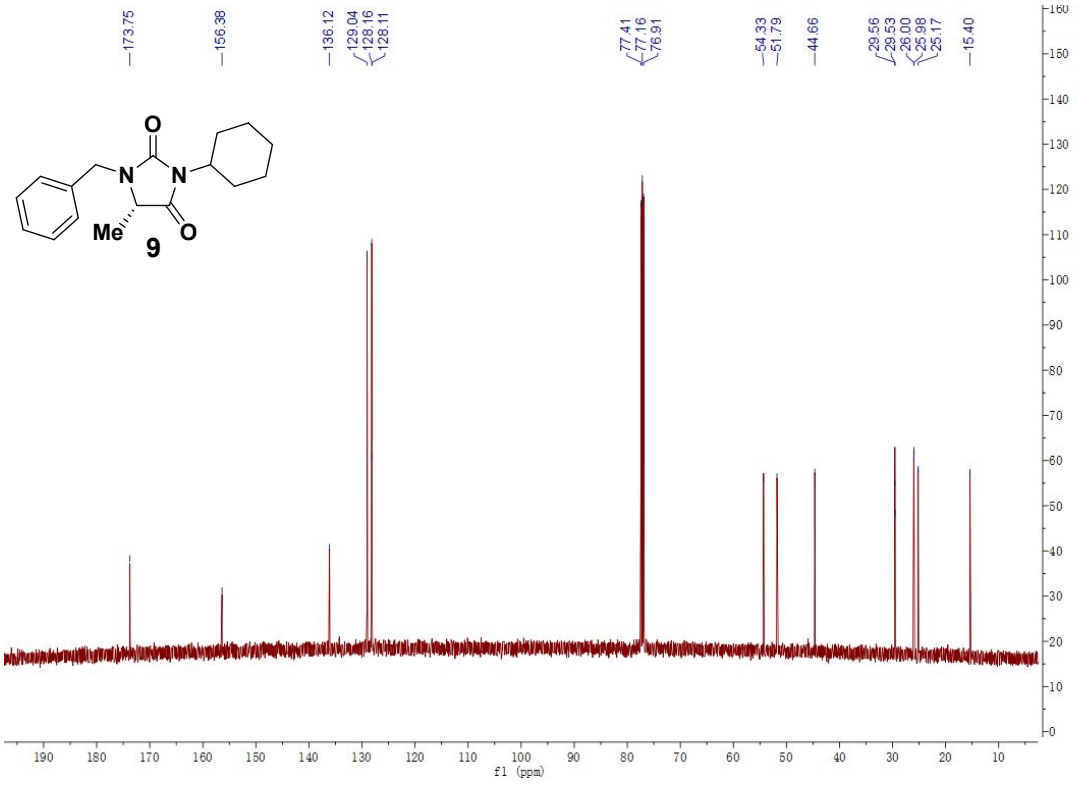
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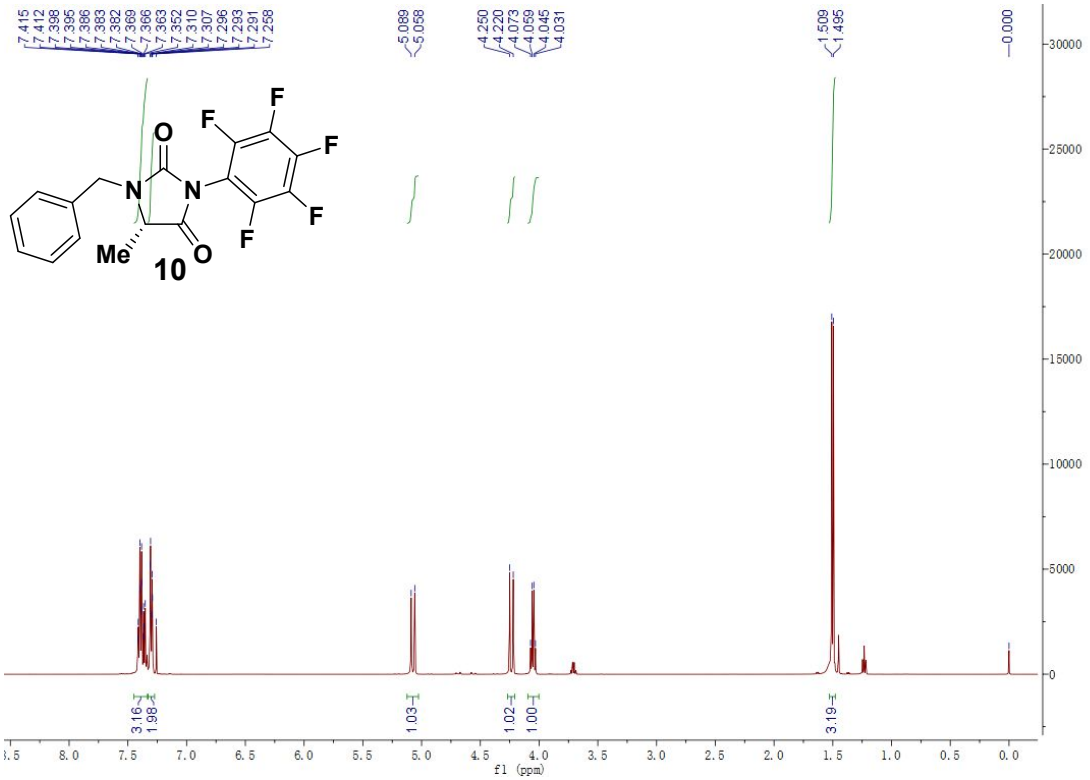
N
O
Me
9
f1 (ppm)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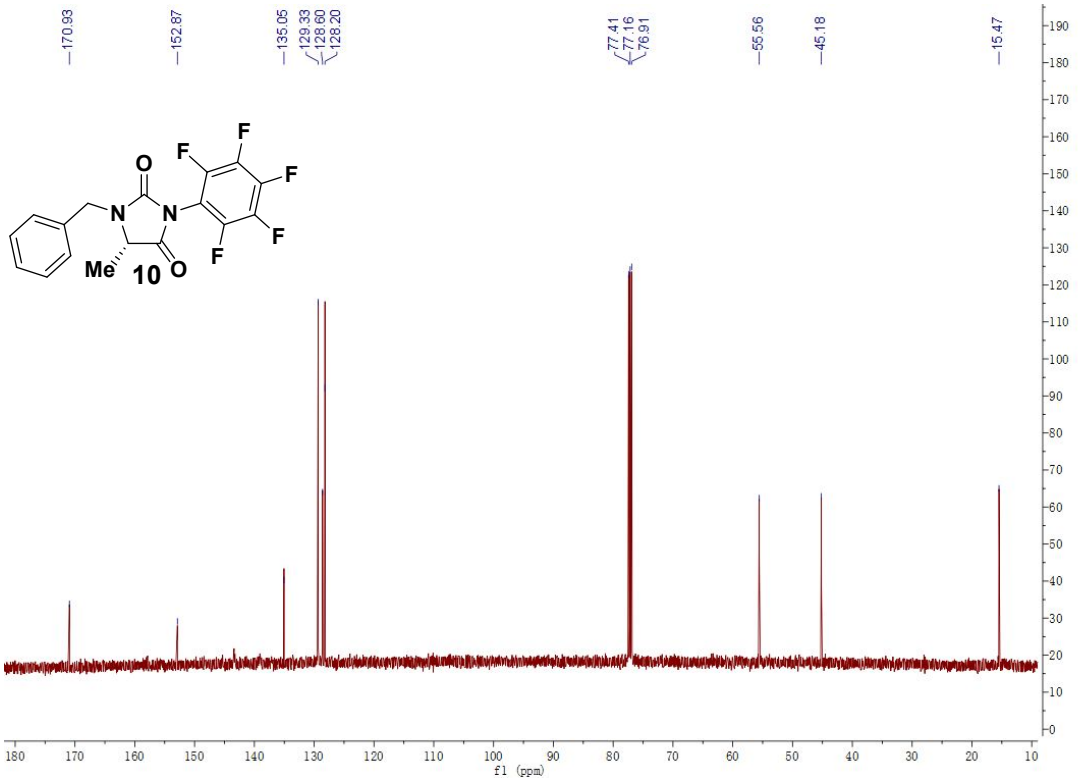
7.369
7.366
7.363
7.352
7.310
7.307
7.296
7.293
7.291
7.258
5.089
5.058
4.250
4.220
4.073
4.059
4.045
4.031
1.509
1.495
0.000
O
F
F
F
N
N
F
F
Me
O
10
3.16
1.98
1.03
1.02
1.00
3.19
f1 (ppm)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77.16
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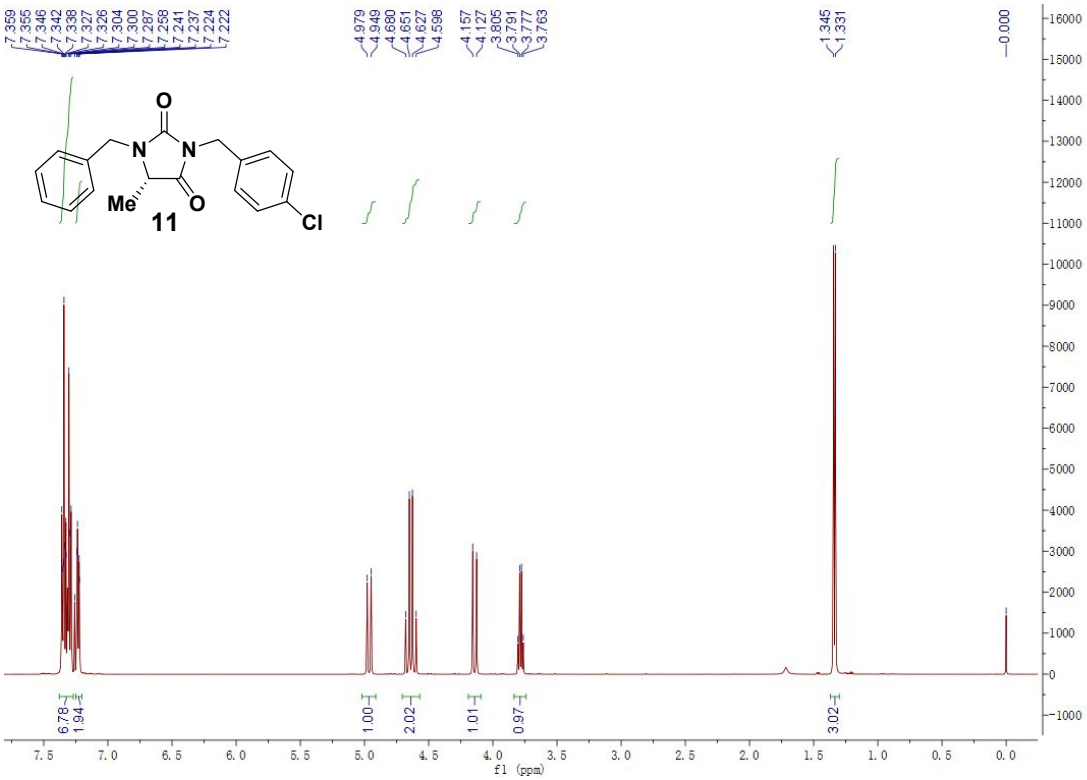
15.47
O
F
F
F
N
N
F
F
Me
10
O
f1 (ppm)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7.237
7.224
7.222
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4.949
4.680
4.651
4.627
4.598
4.157
4.127
3.805
3.791
3.777
3.763
1.345
1.331
0.000
O
N
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Cl
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1.94
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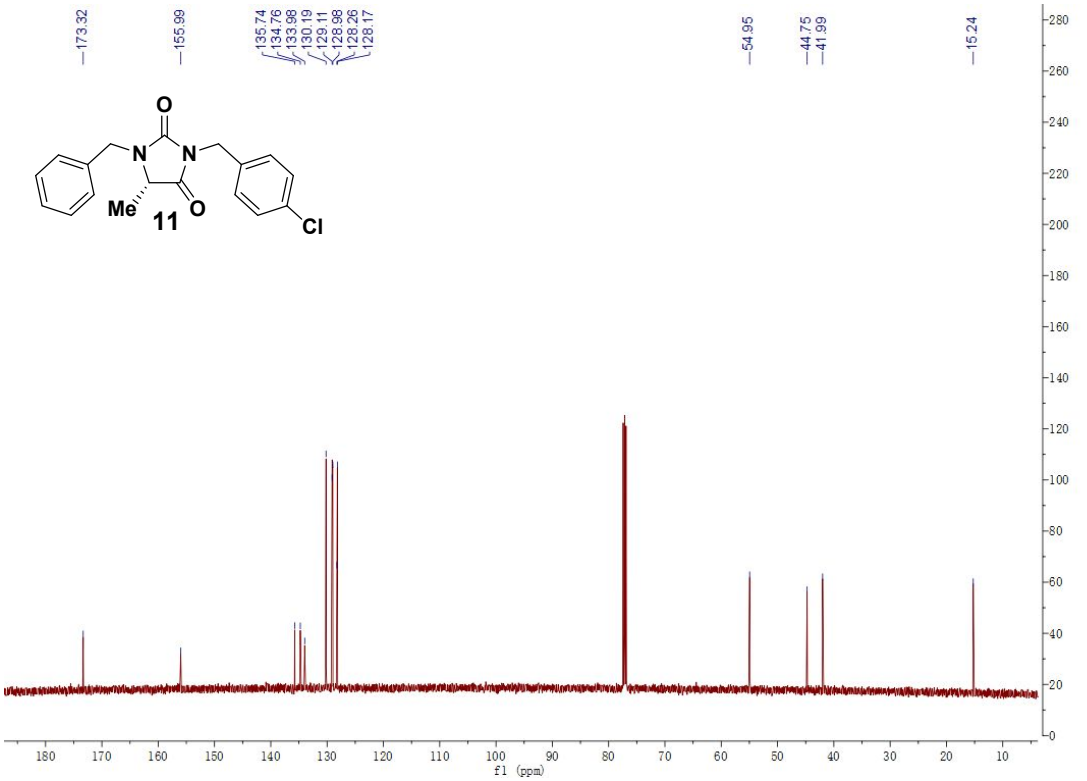
2.02
1.01
0.97
3.02
f1 (ppm)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130.19
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128.98
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128.17
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41.99
15.24
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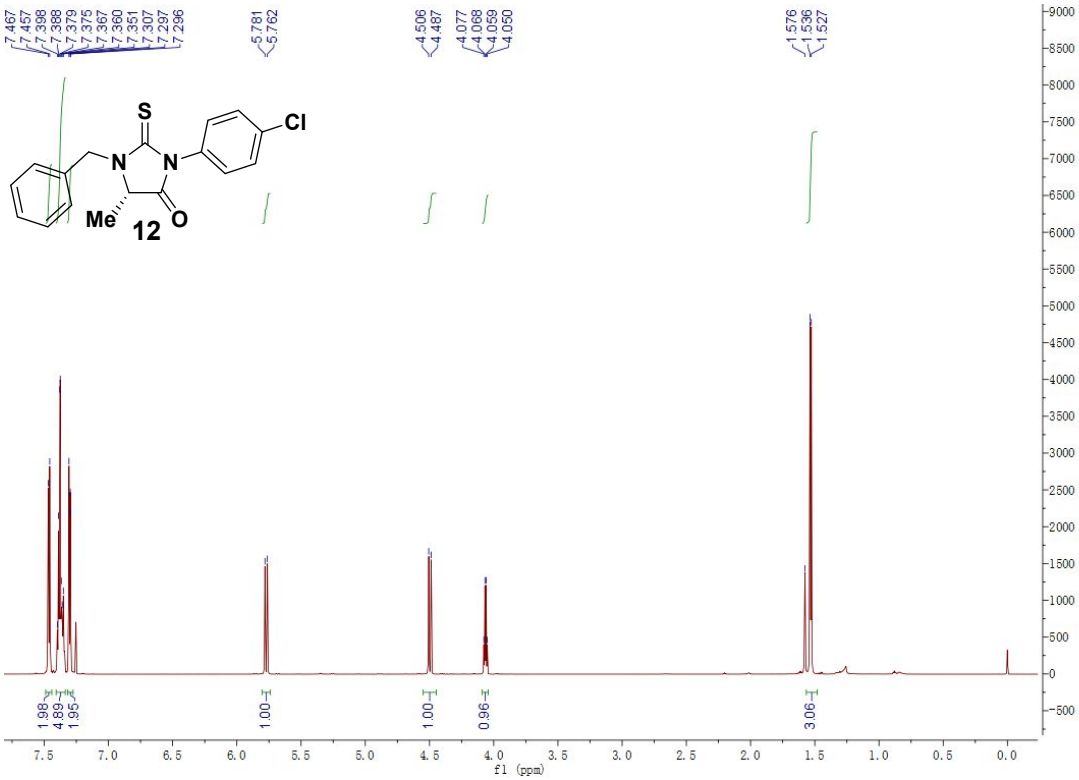
N
N
O
Me
O
11
Cl
f1 (ppm)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7.367
7.360
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7.307
7.297
7.296
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5.762
4.506
4.487
4.077
4.068
4.059
4.050
1.576
1.536
1.527
S
Cl
N
N
Me
12
O
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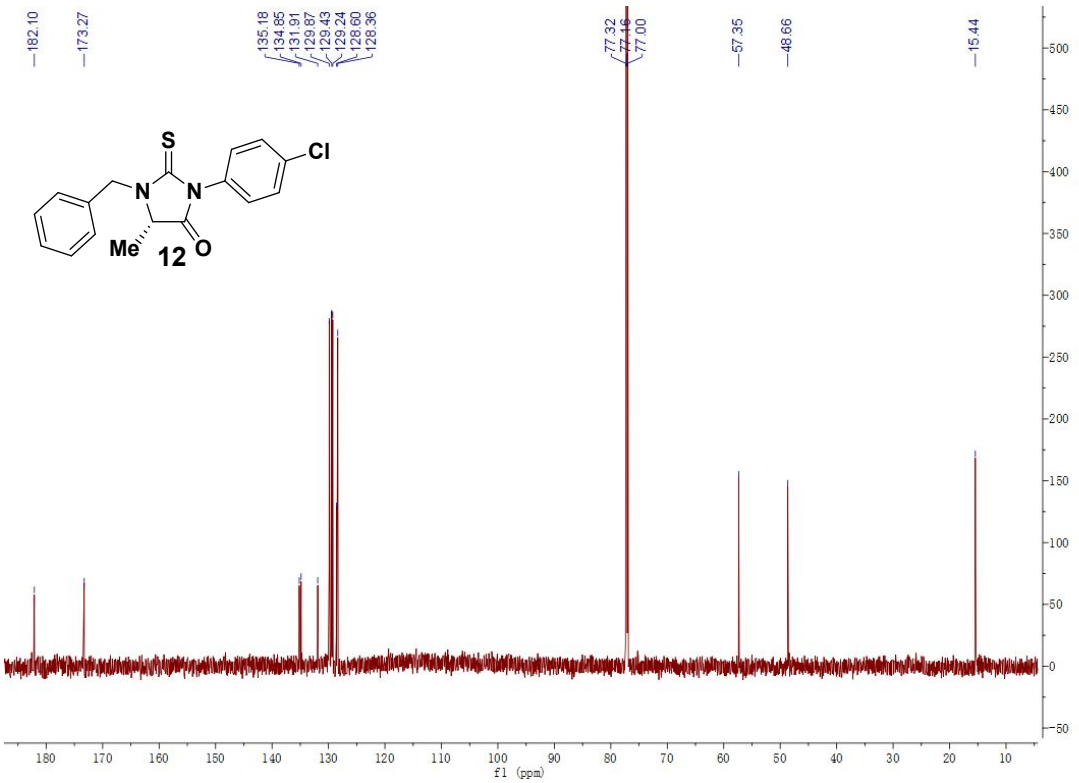
4.89
1.95
1.00
1.00
0.96
3.06
f1 (ppm)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77.00
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48.66
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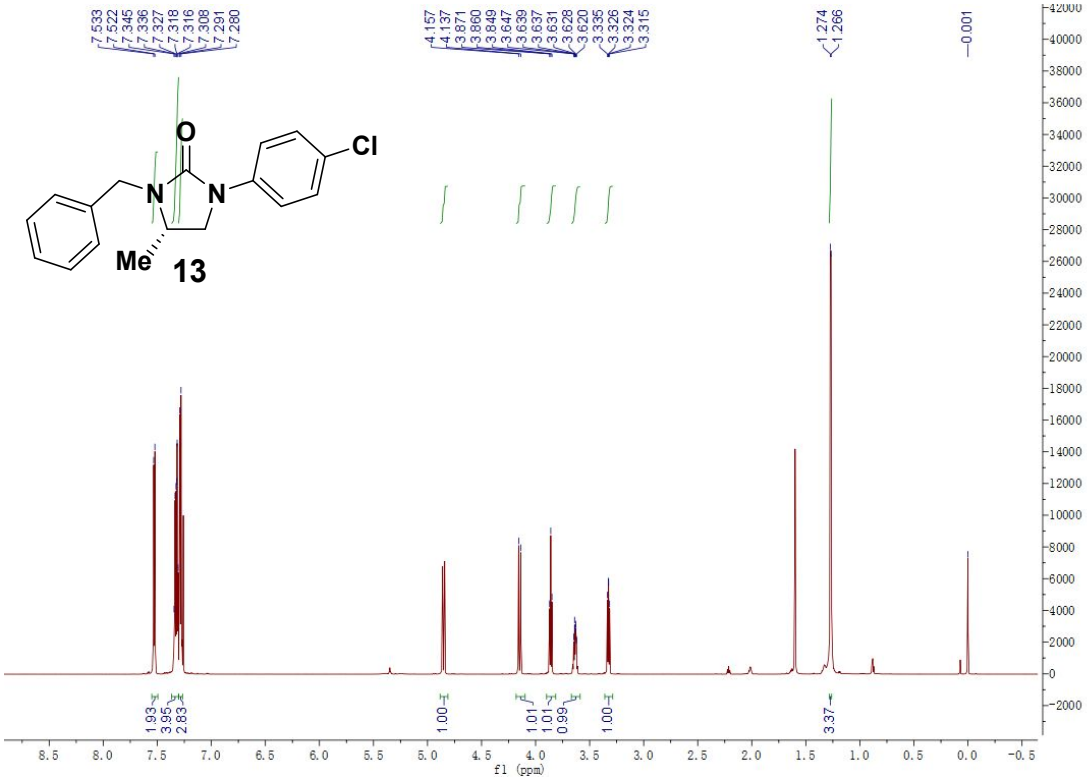
Cl
N
N
Me
12
O
f1 (ppm)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7.316
7.308
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7.280
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4.137
3.871
3.860
3.849
3.647
3.639
3.637
3.631
3.628
3.620
3.335
3.326
3.324
3.315
1.274
1.266
0.001
O
N
N
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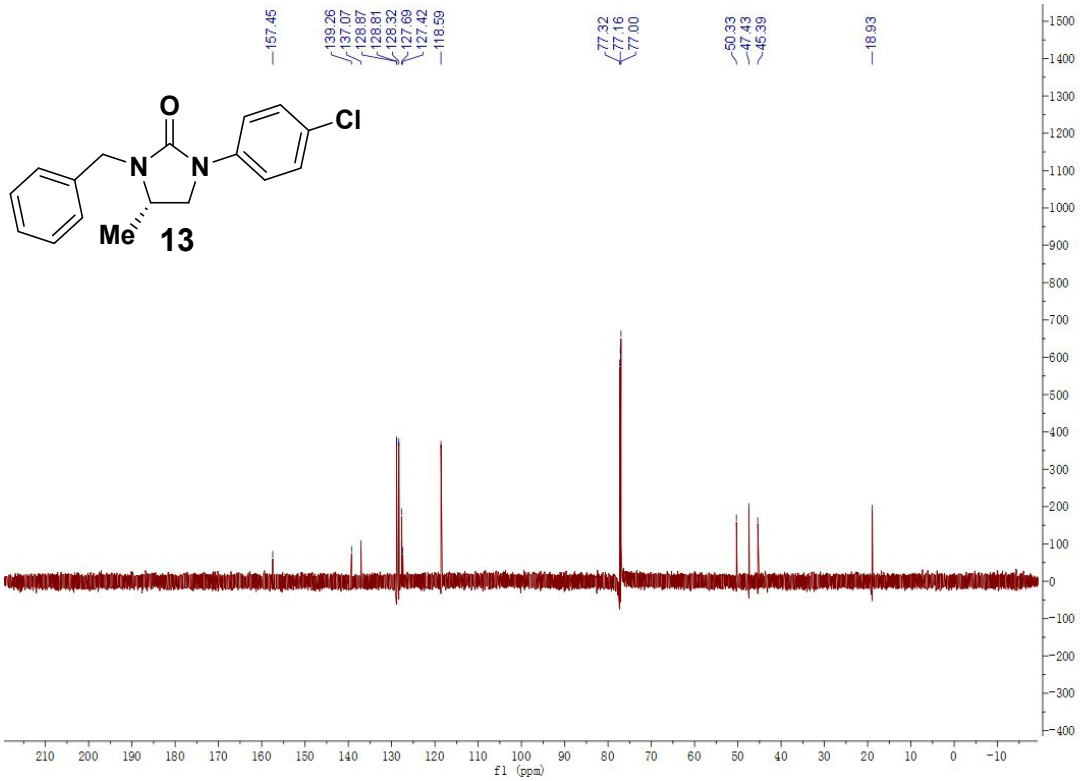
3.37
f1 (ppm)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127.42
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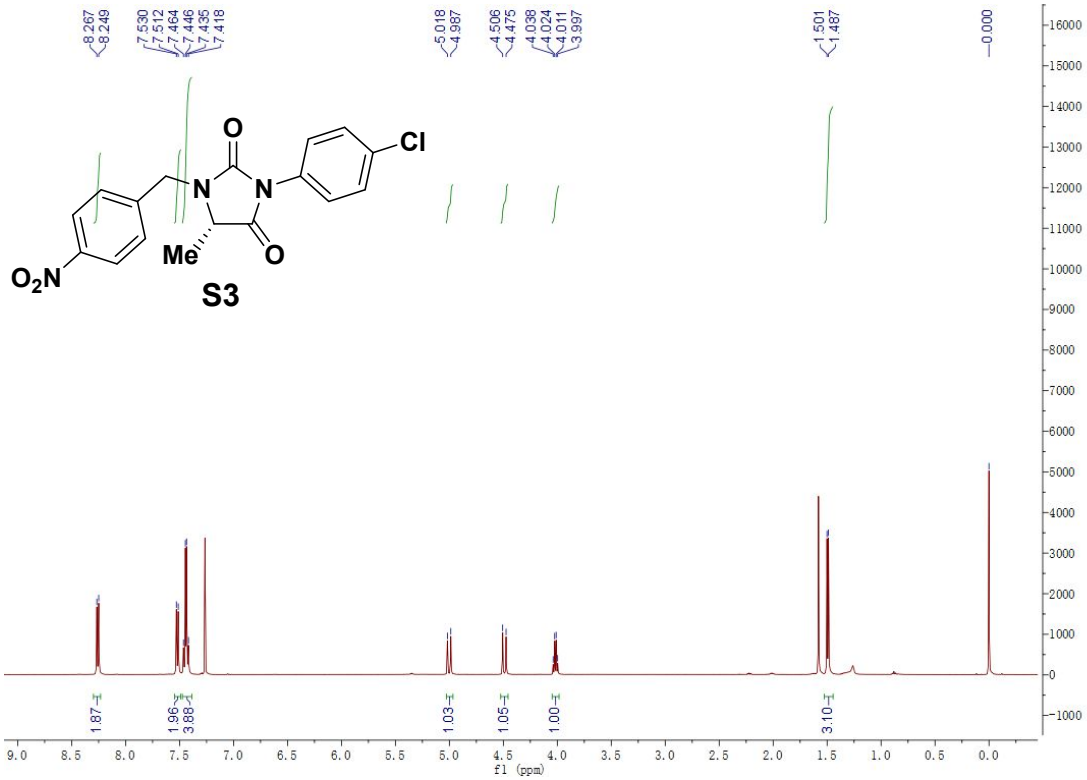
77.16
77.00
50.33
47.43
45.39
18.93
O
N
N
Cl
Me
13
f1 (ppm)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7.418
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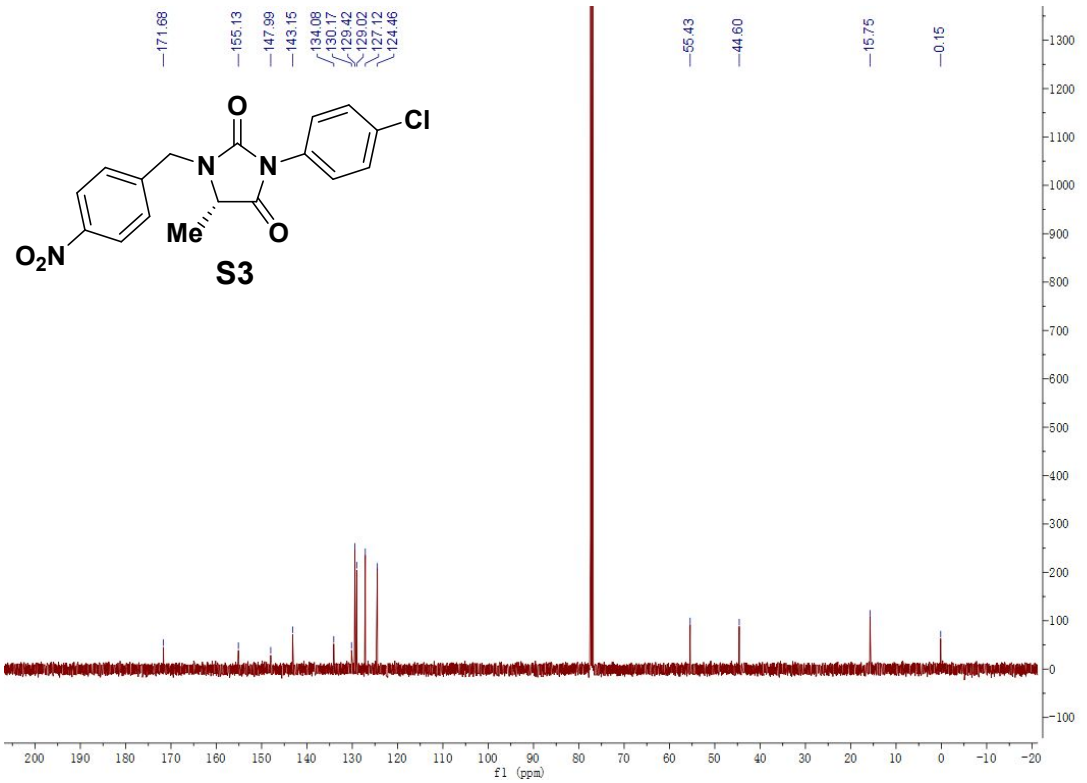
4.506
4.475
4.038
4.024
4.011
3.997
1.501
1.487
0.000
O
N
N
Cl
Me
O
O2N
S3
1.87
1.96
3.88
1.03
1.05
1.00
3.10
f1 (ppm)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130.17
129.42
129.02
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15.75
0.15
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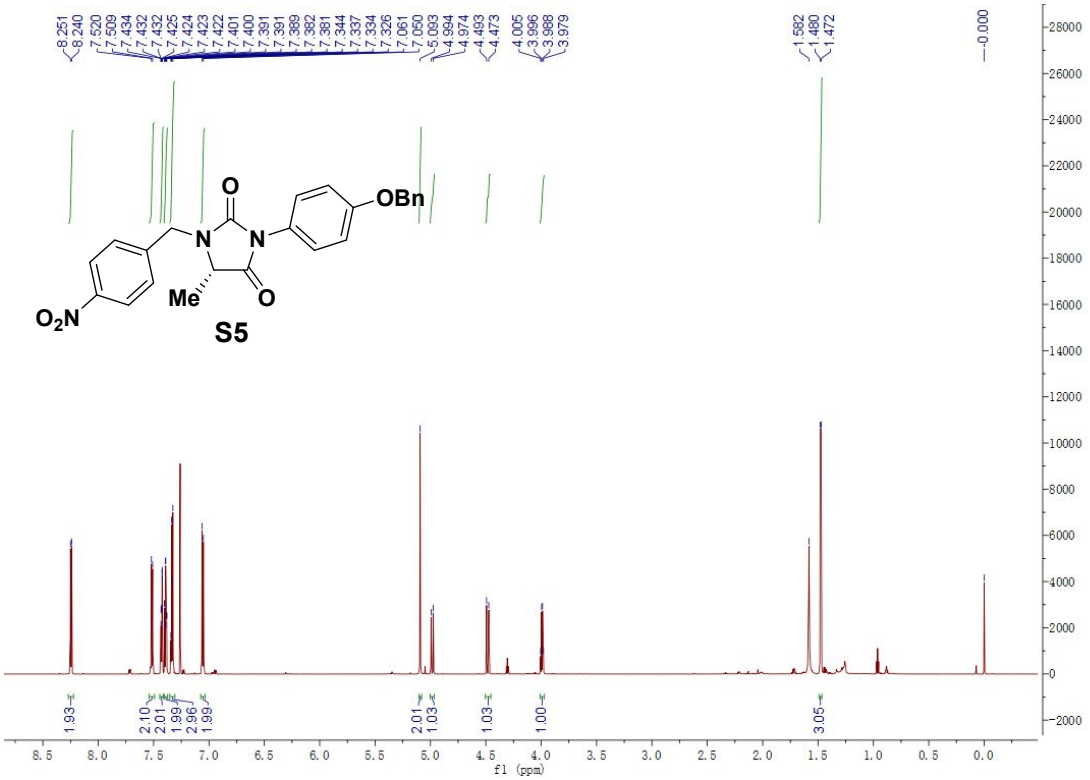
N
N
Cl
Me
O
O2N
S3
f1 (ppm)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7.382
7.381
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7.337
7.334
7.326
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7.050
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4.994
4.974
4.493
4.473
4.005
3.996
3.988
3.979
1.582
1.480
1.472
0.000
OBn
N
N
O
O
Me
O2N
S5
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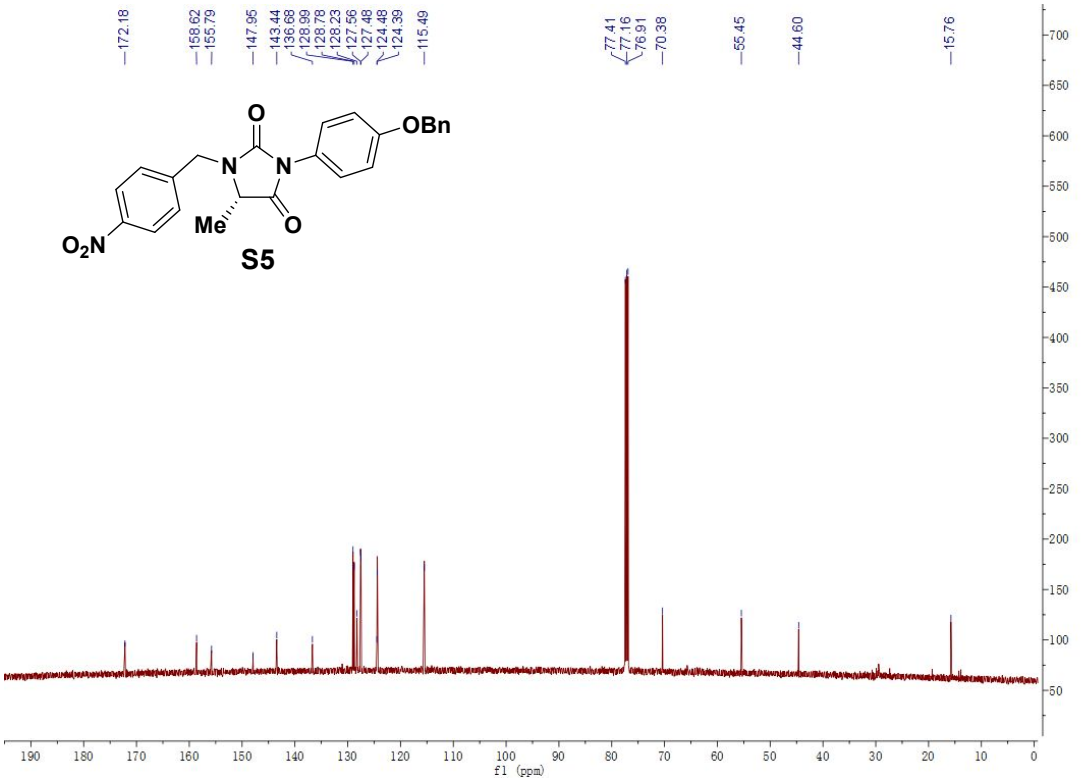
2.01
1.03
1.03
1.00
3.05
f1 (ppm)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127.48
124.48
124.39
115.49
77.41
77.16
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70.38
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44.60
15.76
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N
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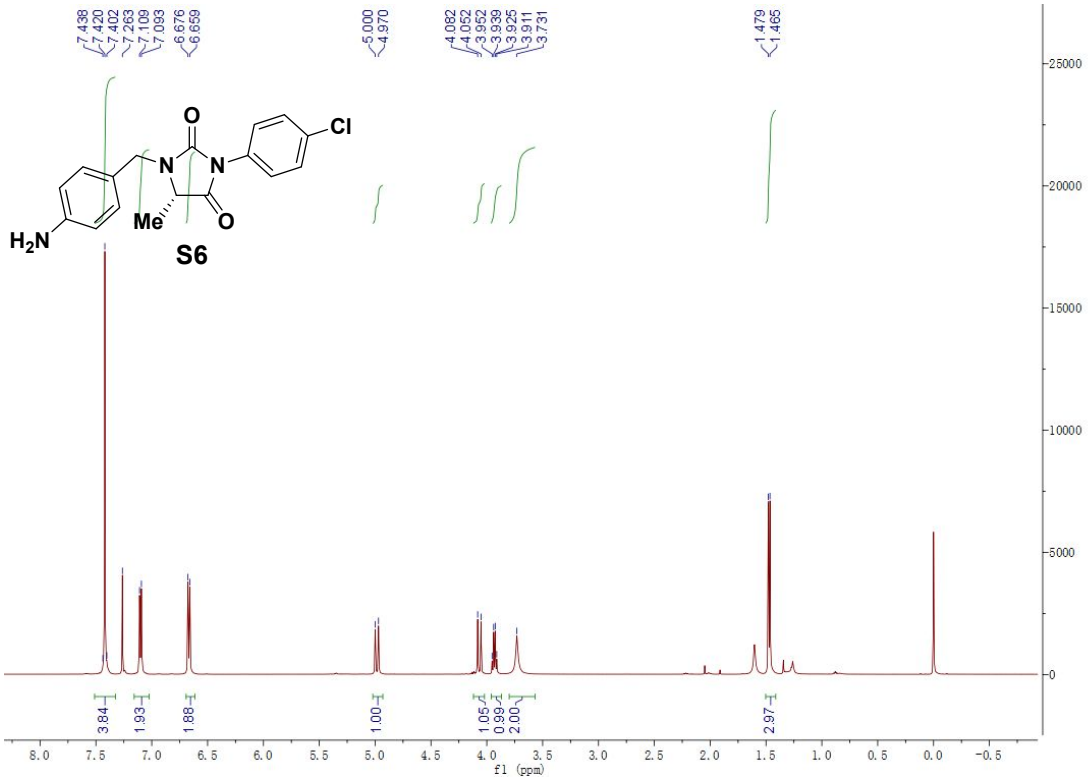
O
O
Me
O2N
S5
f1 (ppm)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1.465
O
N
N
Cl
O
Me
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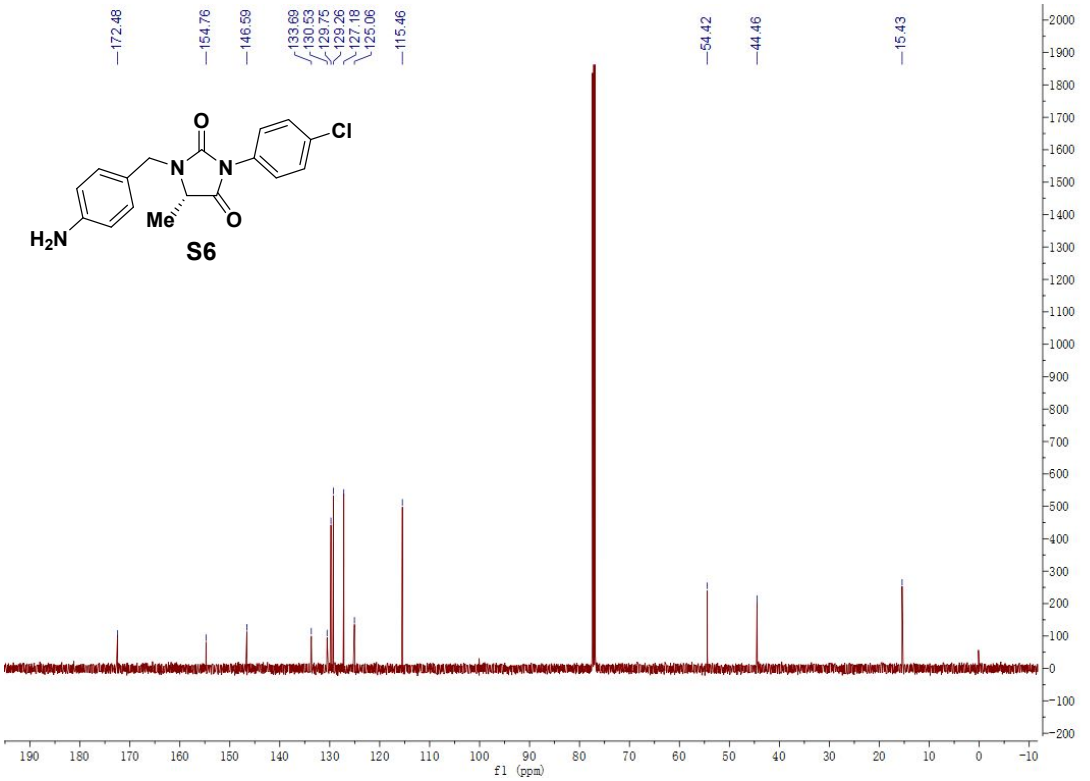
2.97
f1 (ppm)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127.18
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O
Me
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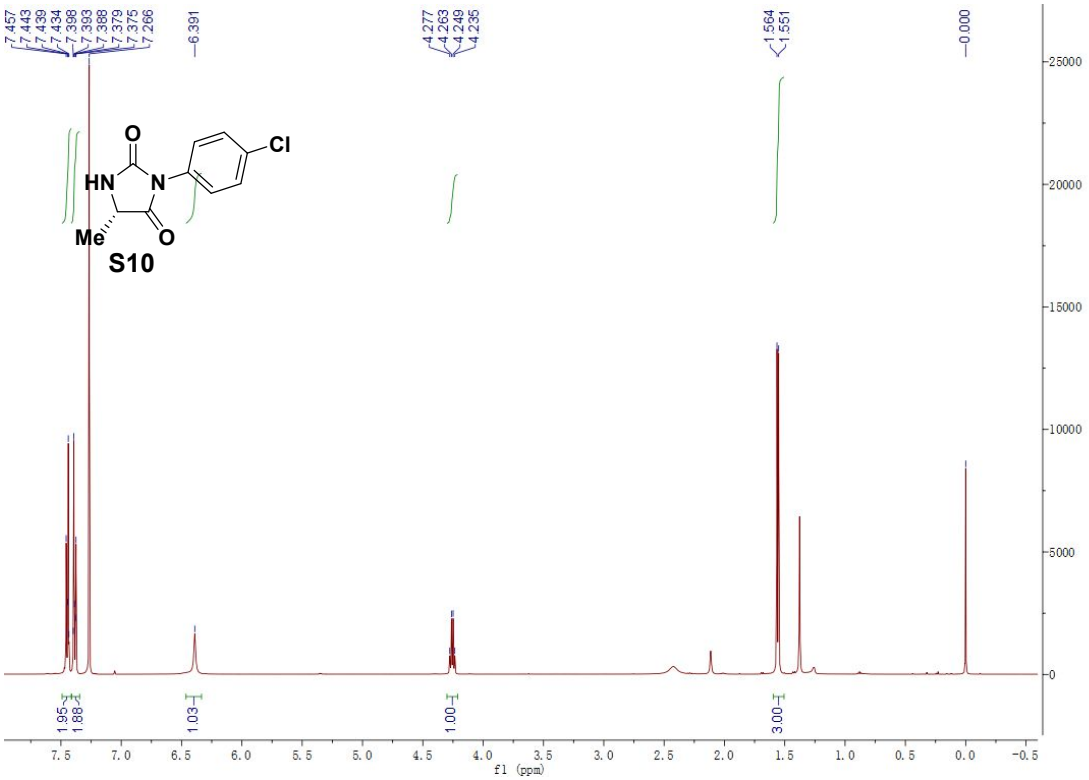
H2N
S6
f1 (ppm)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4.235
1.564
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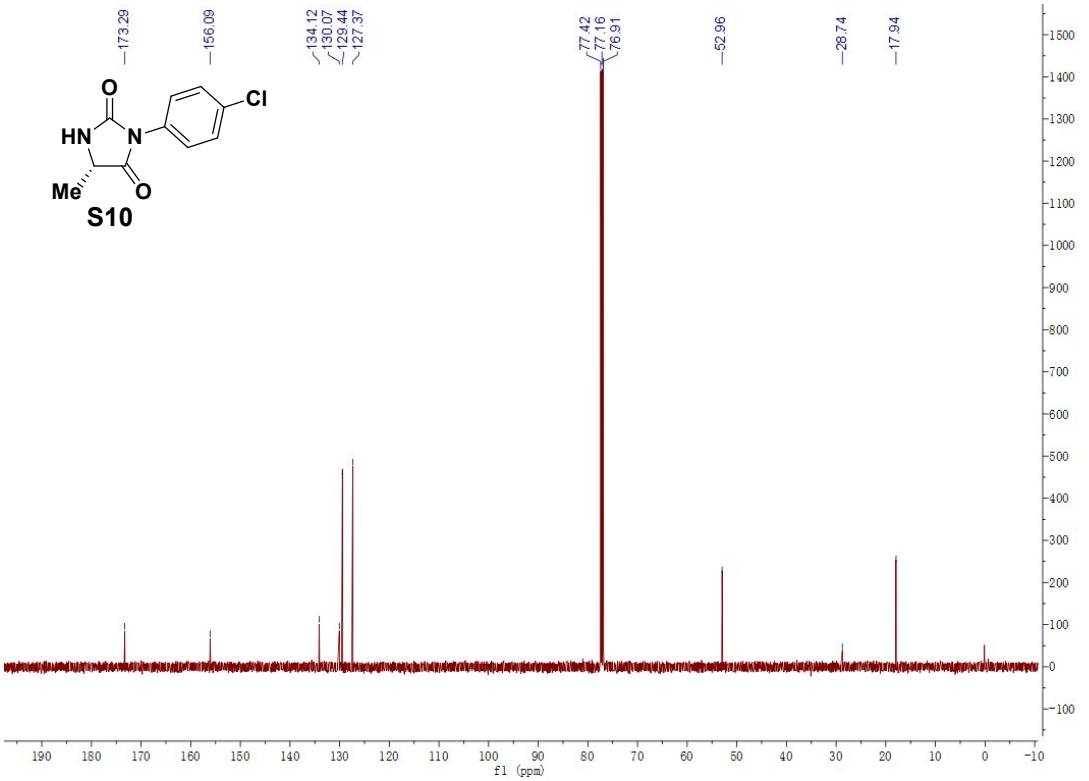
1.88
1.03
1.00
3.00
f1 (ppm)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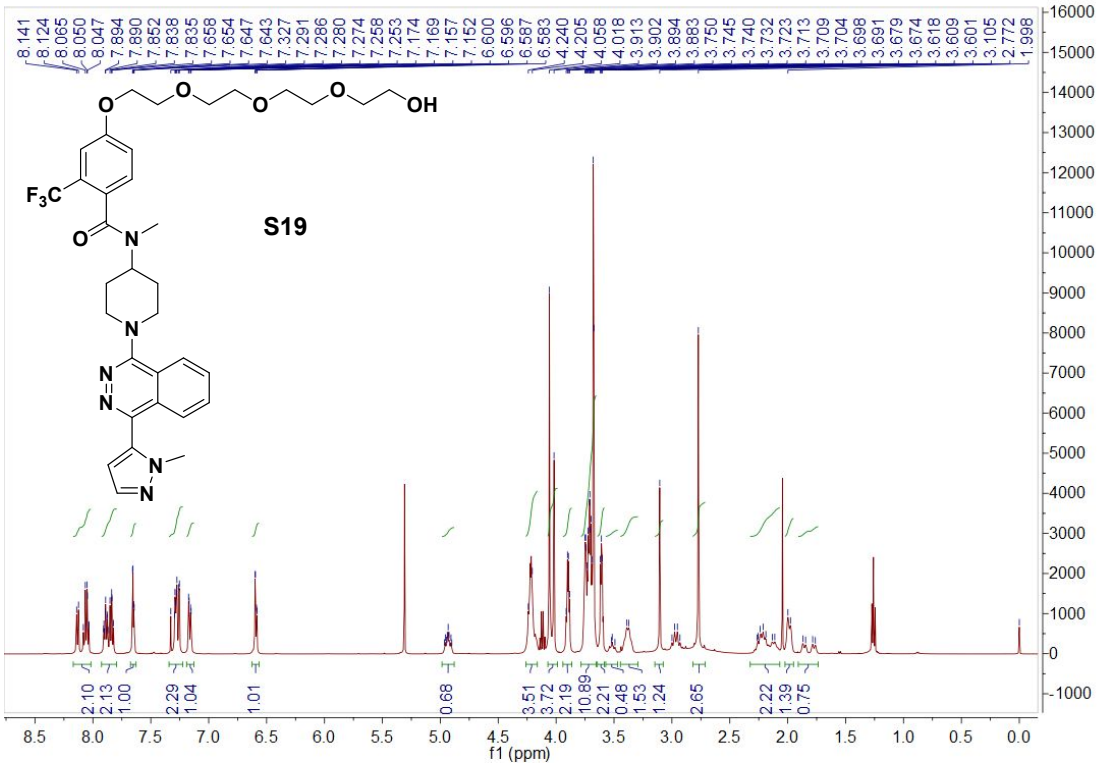
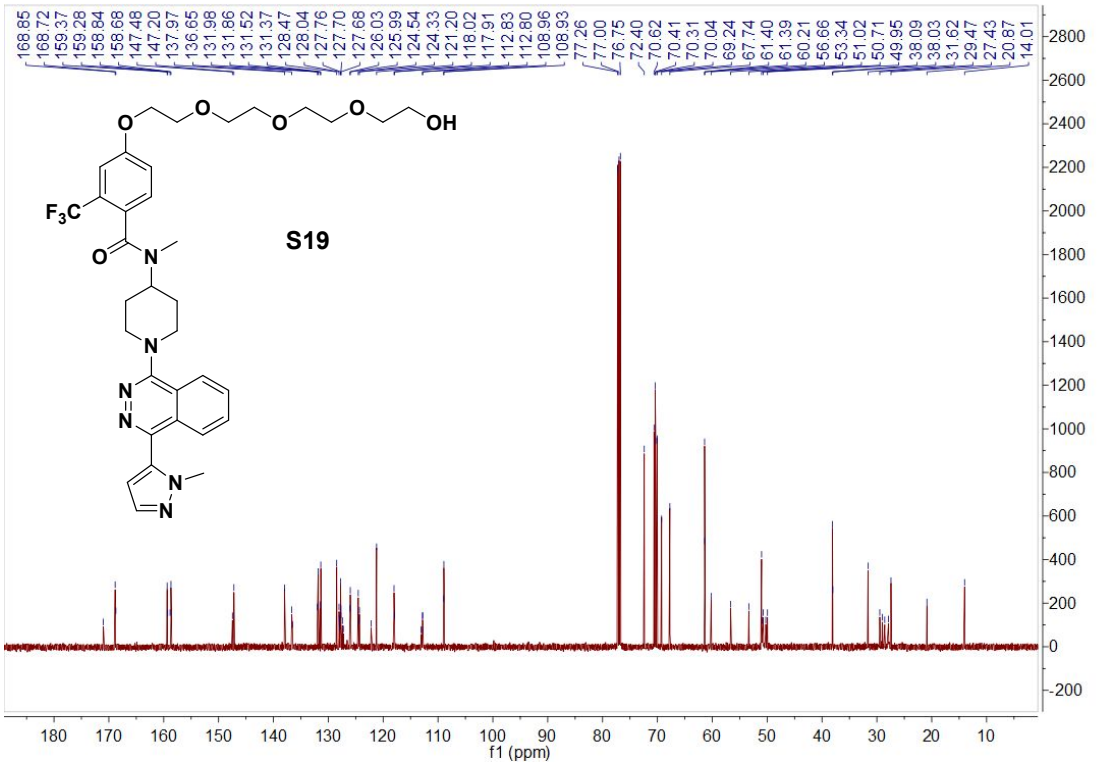
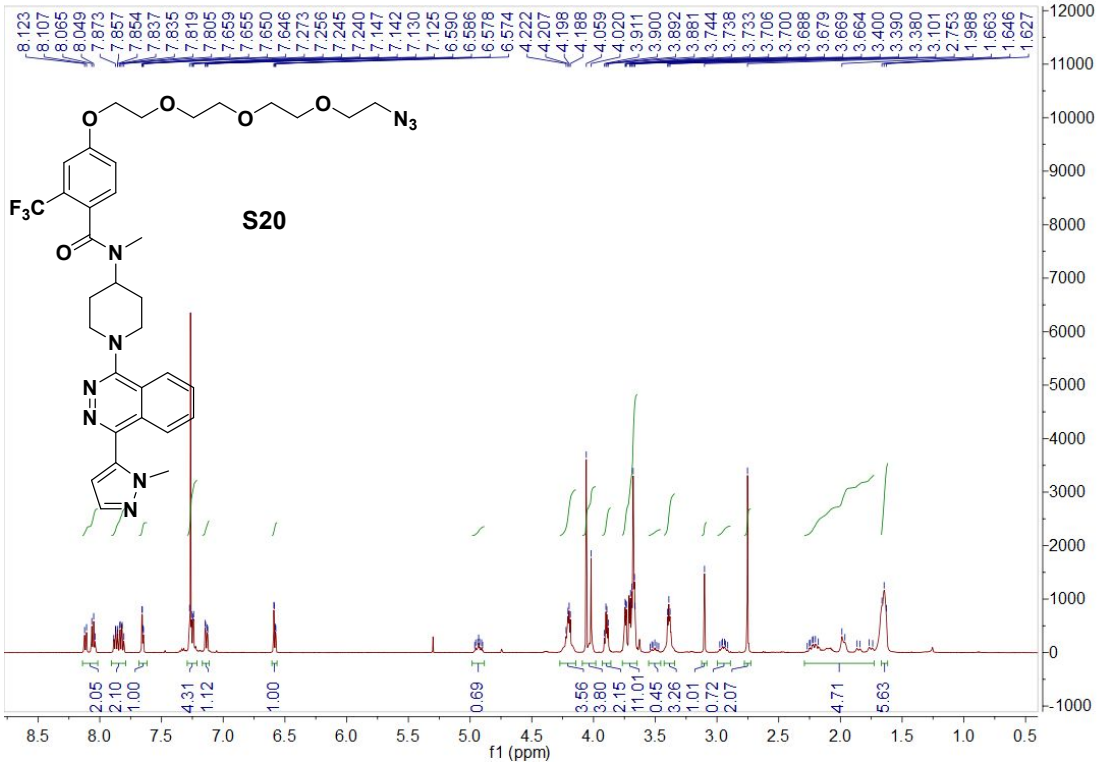
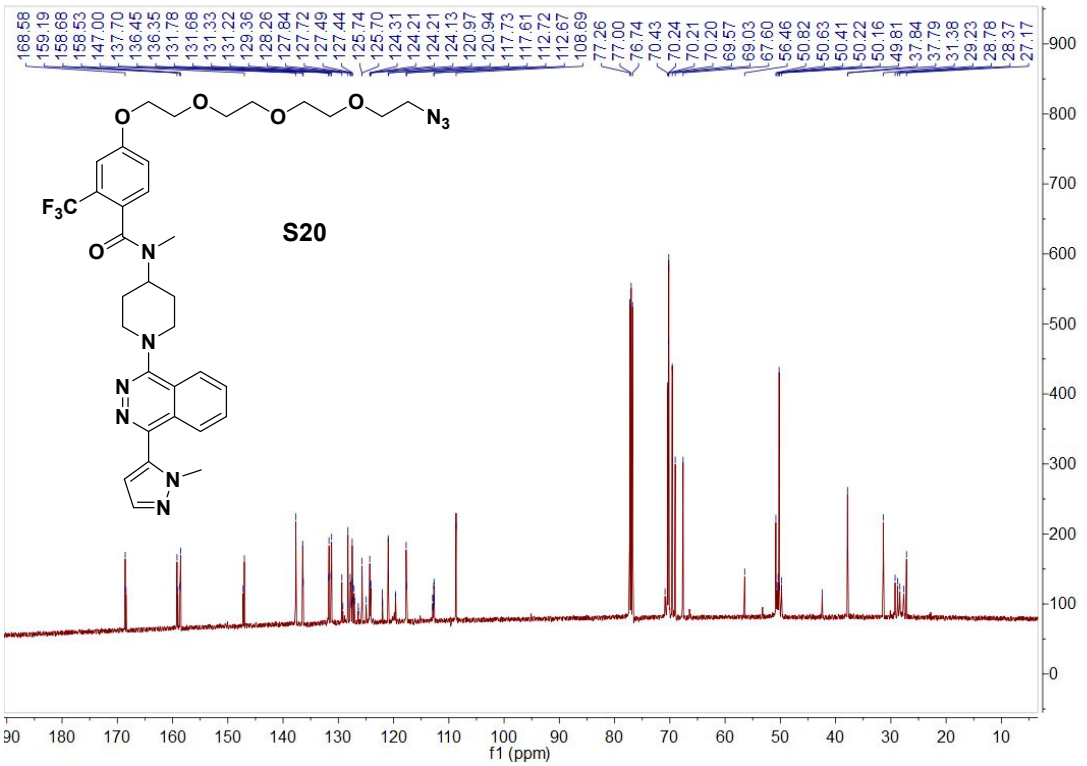
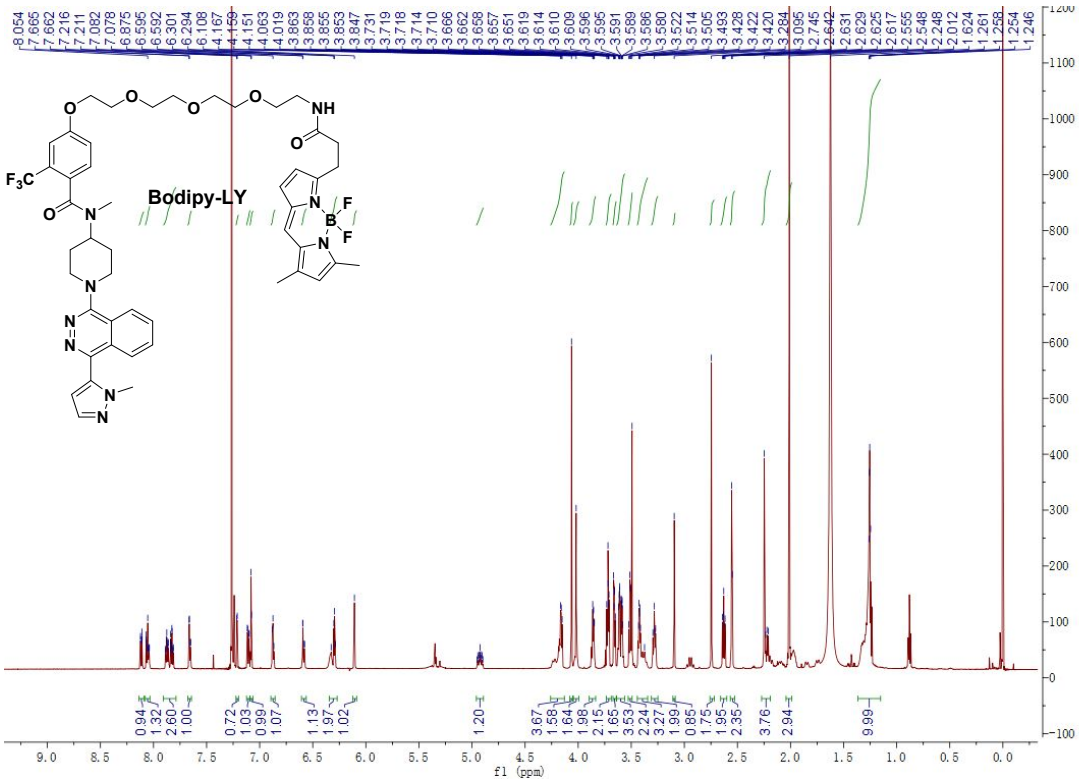
Cl
Me
O
S10
f1 (ppm)


S19
f1 (ppm)

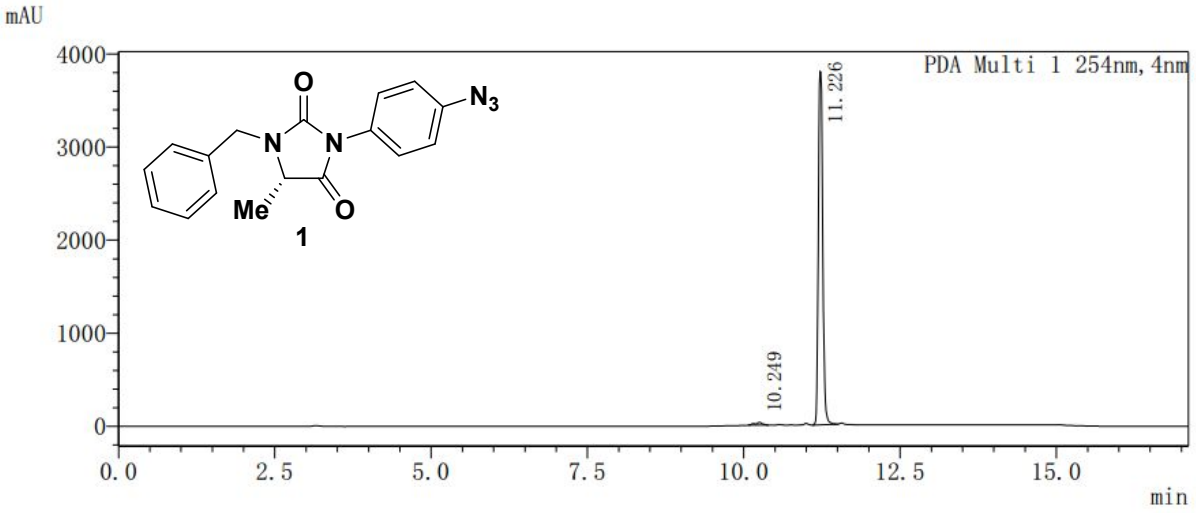

S19
f1 (ppm)


S20
f1 (ppm)


S20
f1 (ppm)

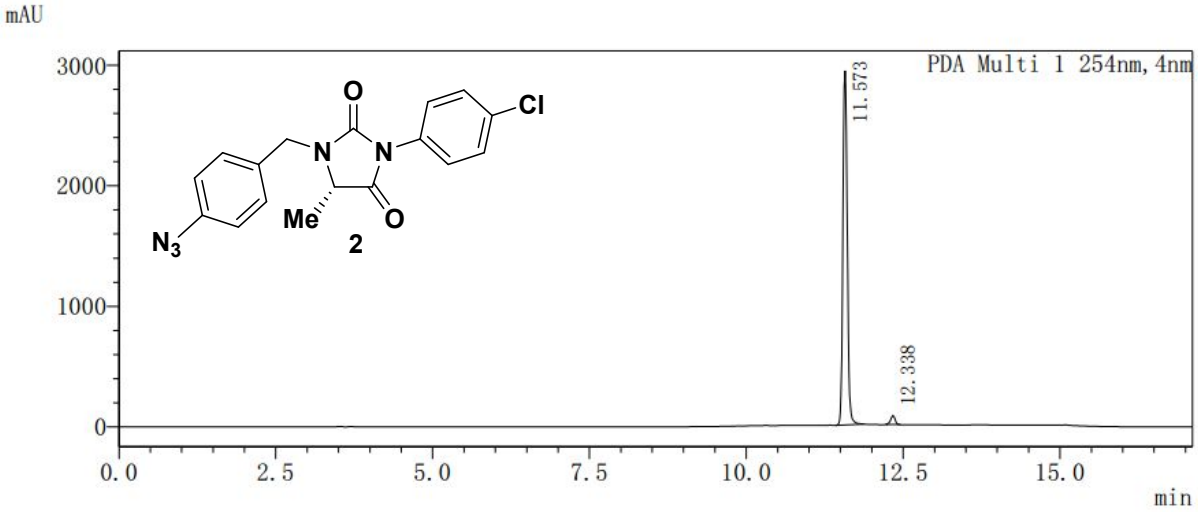

Bodipy-LY
f1 (ppm)

**Purity characterization**



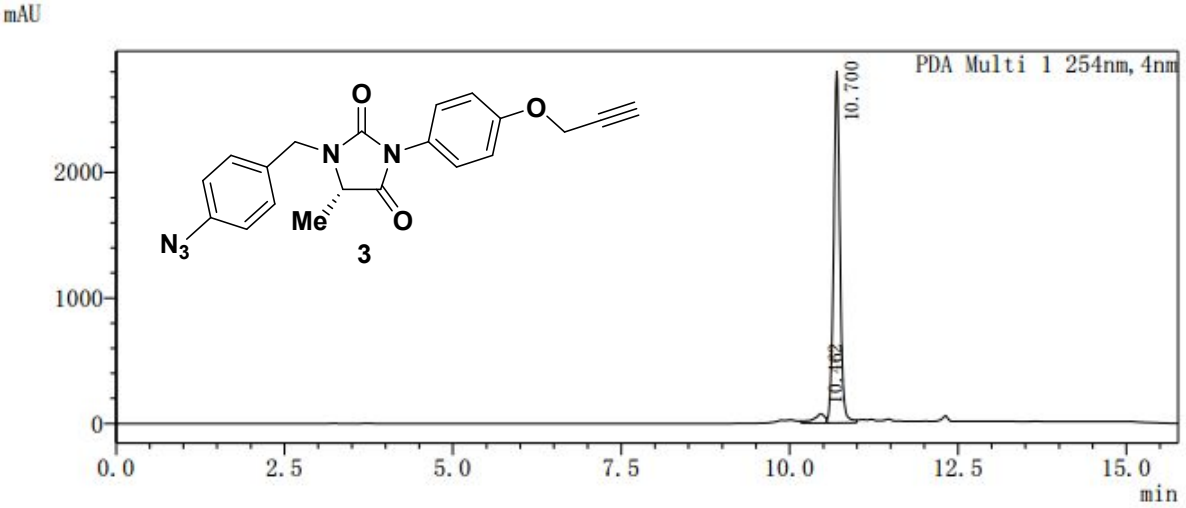

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 10.249 | 28484 | 0.745 | 230836 | 1.223 |
| 2 | 11.226 | 3793439 | 99.255 | 18648782 | 98.777 |
| 总计 | | 3821924 | 100.000 | 18879617 | 100.000 |



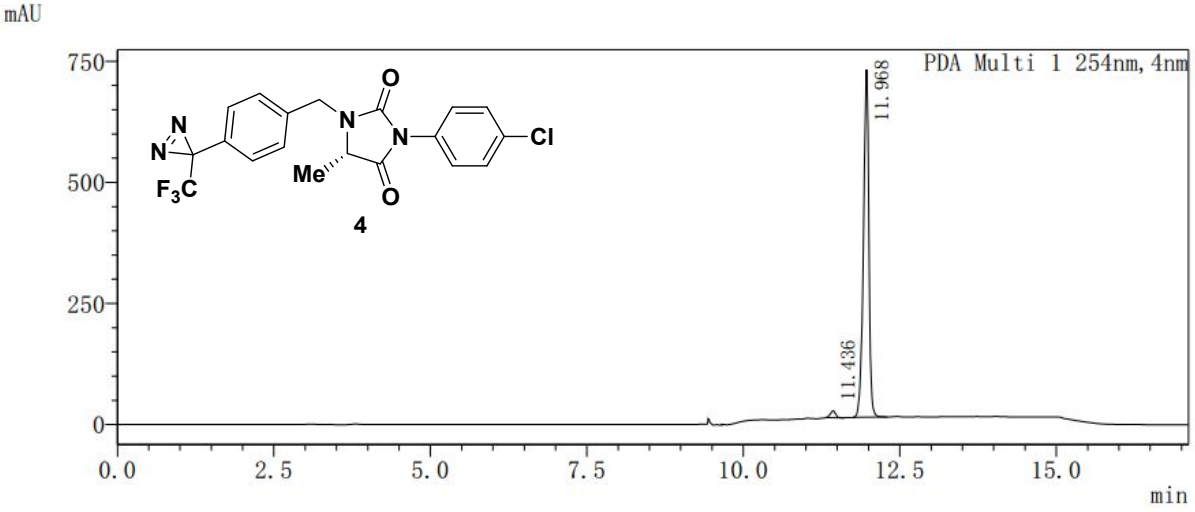

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.573 | 2938069 | 97.549 | 14381767 | 97.537 |
| 2 | 12.338 | 73813 | 2.451 | 363120 | 2.463 |
| 总计 | | 3011882 | 100.000 | 14744887 | 100.000 |




PDA Ch1 254nm

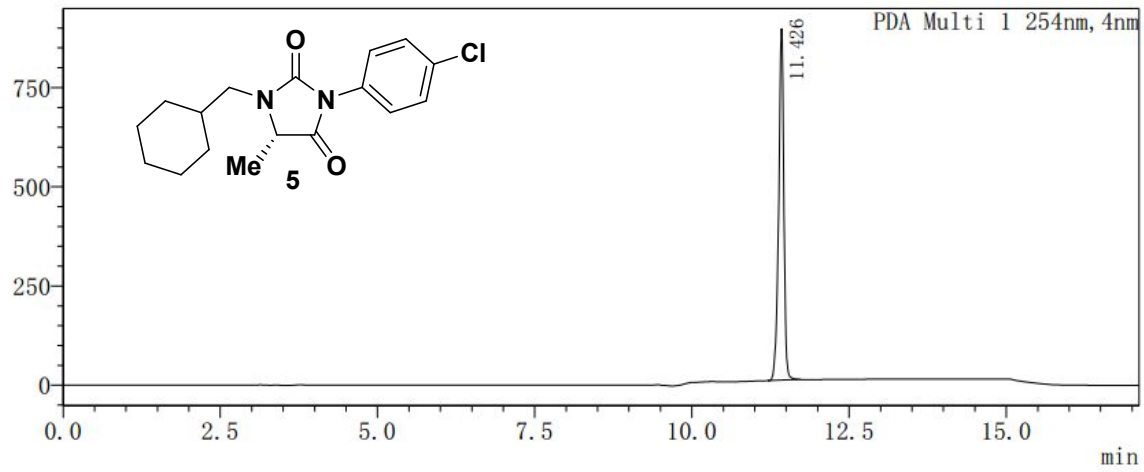
| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 10.462 | 72922 | 2.534 | 872271 | 4.590 |
| 2 | 10.700 | 2804875 | 97.466 | 18131772 | 95.410 |
| 总计 | | 2877797 | 100.000 | 19004043 | 100.000 |




PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.436 | 14334 | 1.958 | 81032 | 1.842 |
| 2 | 11.968 | 717828 | 98.042 | 4319056 | 98.158 |
| 总计 | | 732161 | 100.000 | 4400087 | 100.000 |

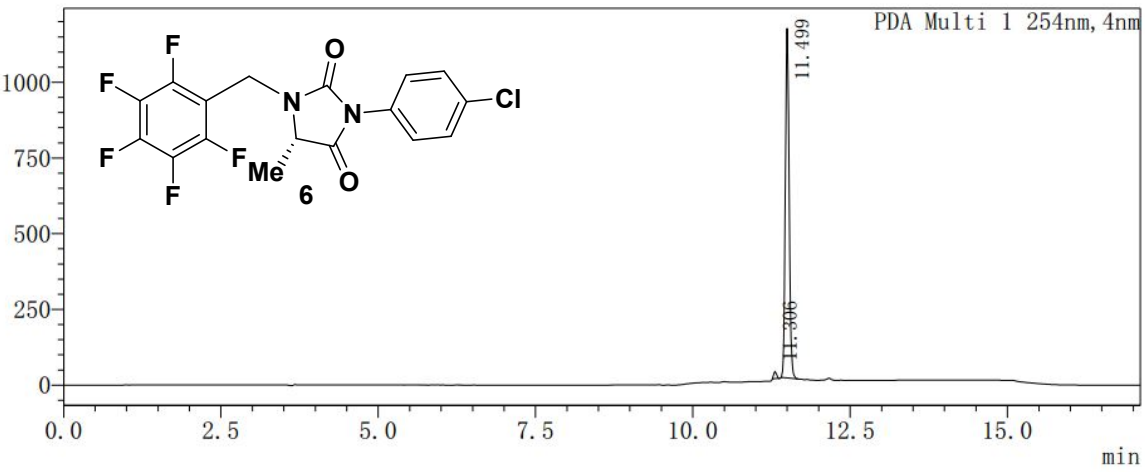
mAU




PDA Ch1 254nm

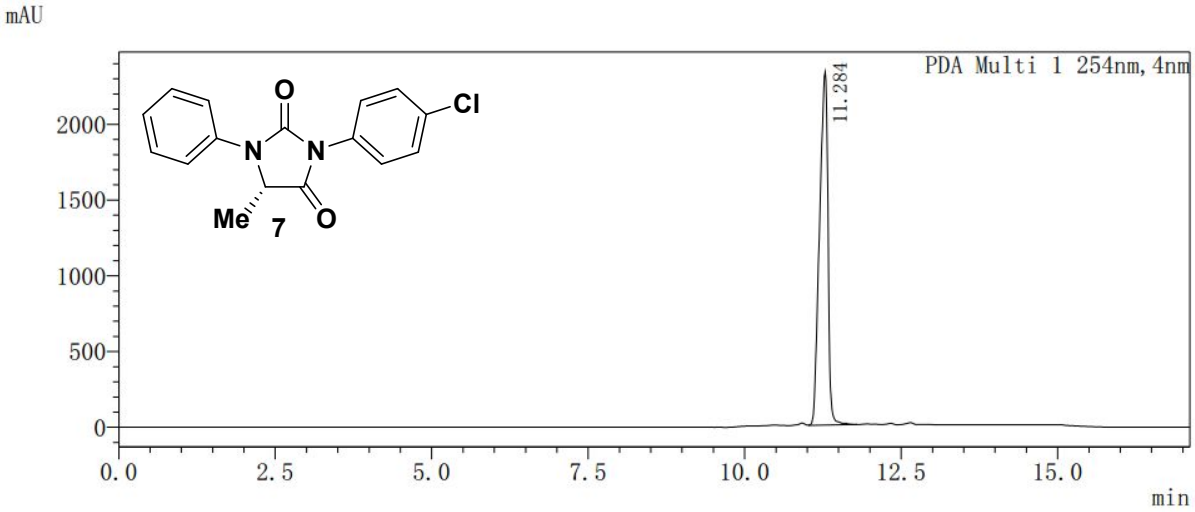
| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.426 | 886041 | 100.000 | 5085639 | 100.000 |
| 总计 | | 886041 | 100.000 | 5085639 | 100.000 |

mAU



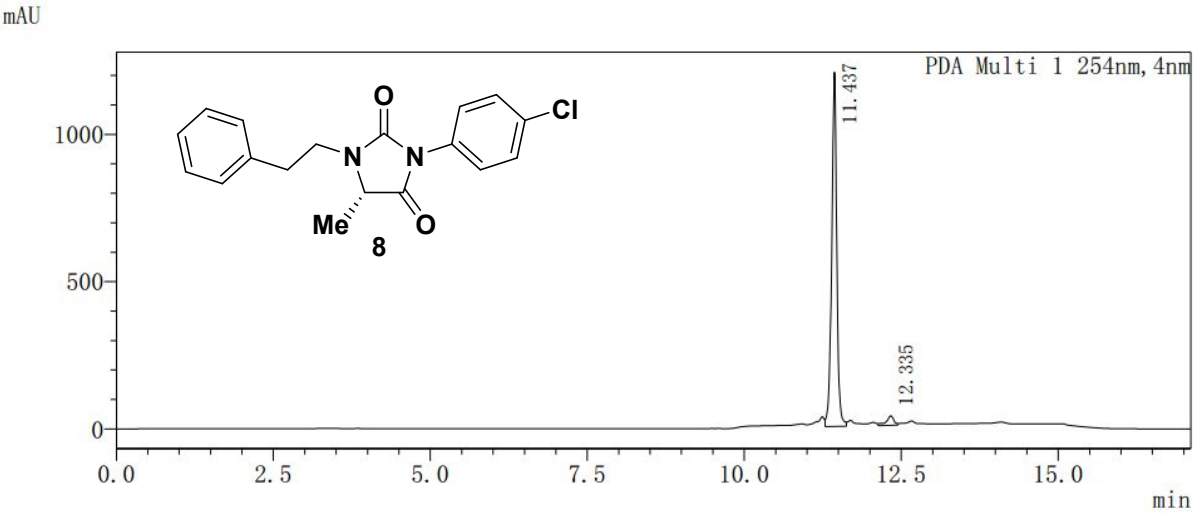

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.306 | 22947 | 1.949 | 72089 | 1.467 |
| 2 | 11.499 | 1154478 | 98.051 | 4841368 | 98.533 |
| 总计 | | 1177425 | 100.000 | 4913457 | 100.000 |



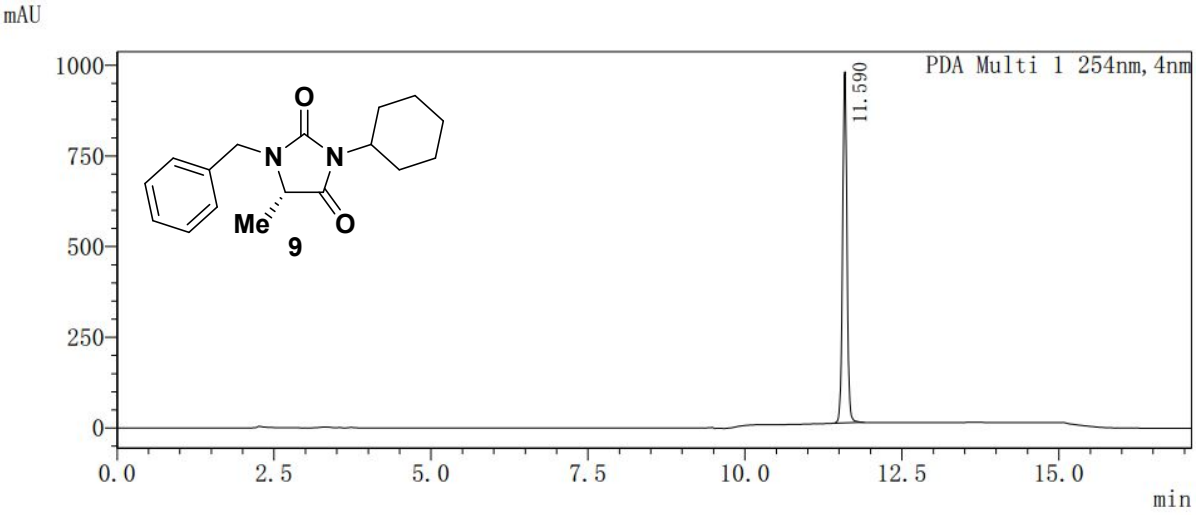

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.284 | 2330347 | 100.000 | 21757372 | 100.000 |
| 总计 | | 2330347 | 100.000 | 21757372 | 100.000 |



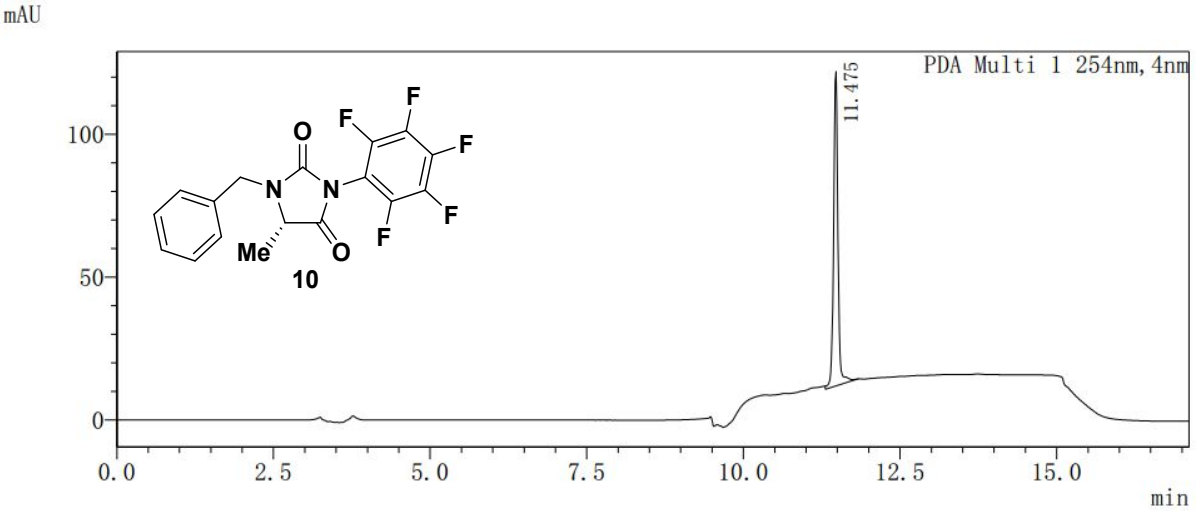

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.437 | 1203263 | 97.402 | 6733194 | 96.121 |
| 2 | 12.335 | 32094 | 2.598 | 271729 | 3.879 |
| 总计 | | 1235357 | 100.000 | 7004923 | 100.000 |



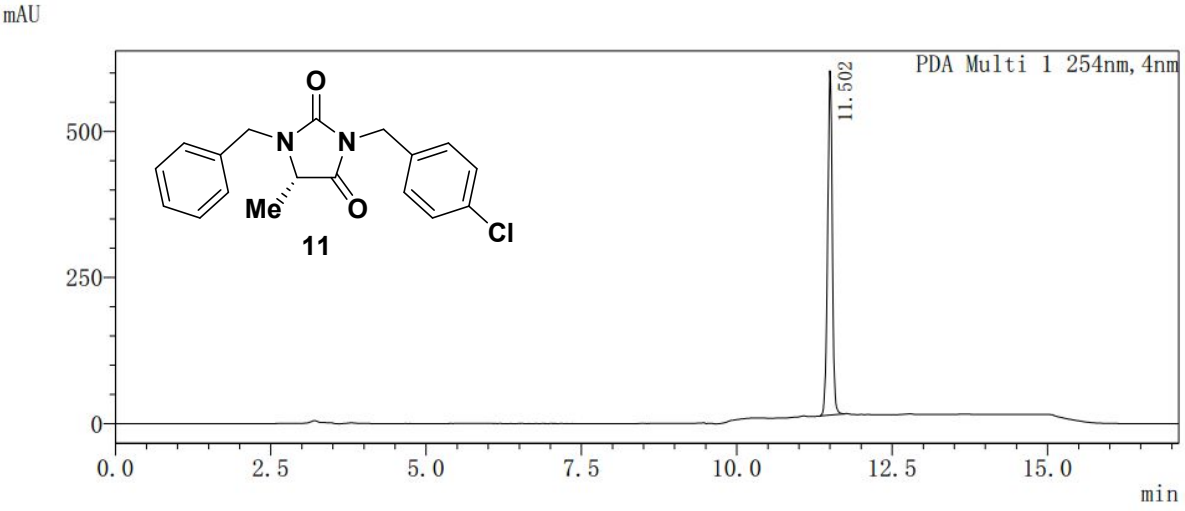

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.590 | 967987 | 100.000 | 4656821 | 100.000 |
| 总计 | | 967987 | 100.000 | 4656821 | 100.000 |



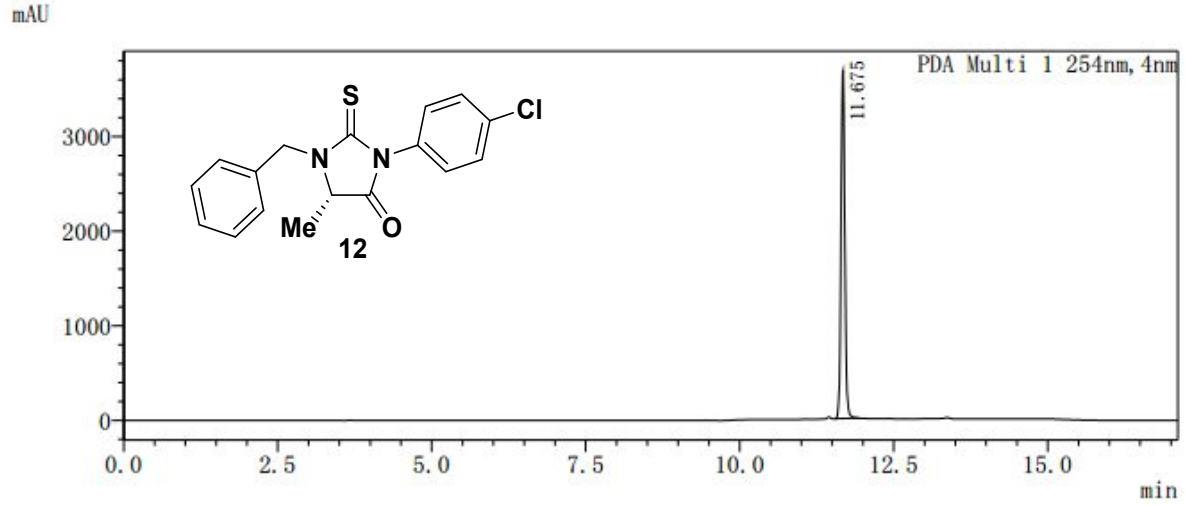

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.475 | 109978 | 100.000 | 522483 | 100.000 |
| 总计 | | 109978 | 100.000 | 522483 | 100.000 |



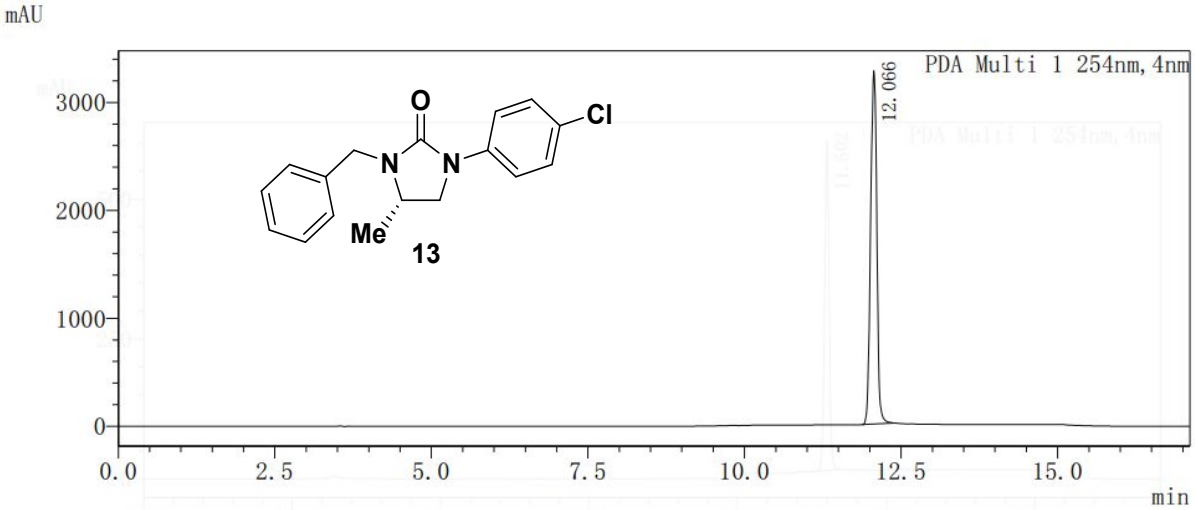

PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.502 | 589387 | 100.000 | 3050952 | 100.000 |
| 总计 | | 589387 | 100.000 | 3050952 | 100.000 |




PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 11.675 | 3677534 | 100.000 | 16072273 | 100.000 |
| 总计 | | 3677534 | 100.000 | 16072273 | 100.000 |




PDA Ch1 254nm

| Peak# | Ret. Time (min) | Height(mAU) | Height% | Area(mAU*s) | Area% |
|---|---|---|---|---|---|
| 1 | 12.066 | 3273420 | 100.000 | 22612991 | 100.000 |
| 总计 | | 3273420 | 100.000 | 22612991 | 100.000 |

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