Supporting Information for

Original article

Discovery of a small molecule inhibitor of cullin neddylation that triggers ER stress to induce autophagy

Yanan Li[a,b], Chaorong Wang[c], Tiantian Xu[a,b], Peichen Pan[c], Qing Yu[a,b], Lei Xu[d], Xiufang Xiong[a,b], Tingjun Hou[c], Sunliang Cui[c,*], Yi Sun[a.b,*]

[a]*Cancer Institute of the 2nd affiliated hospital and Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310029, China*

[b]*Cancer Center, Zhejiang University, Hangzhou, Zhejiang 310012, China*

[c]*College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang 310058, China*

[d]*Institute of Bioinformatics and Medical Engineering, School of Electrical and Information Engineering, Jiangsu University of Technology, Changzhou 212013, China*

*Corresponding authors. Tel./fax: +86 571 86971683 (Yi Sun), +86 571 88981456 (Sunliang Cui).

E-mail addresses: yisun@zju.edu.cn (Yi Sun), slcui@zju.edu.cn (Sunliang Cui).

Received 16 March 2021; received in revised form 17 June 2021; accepted 1 July 2021

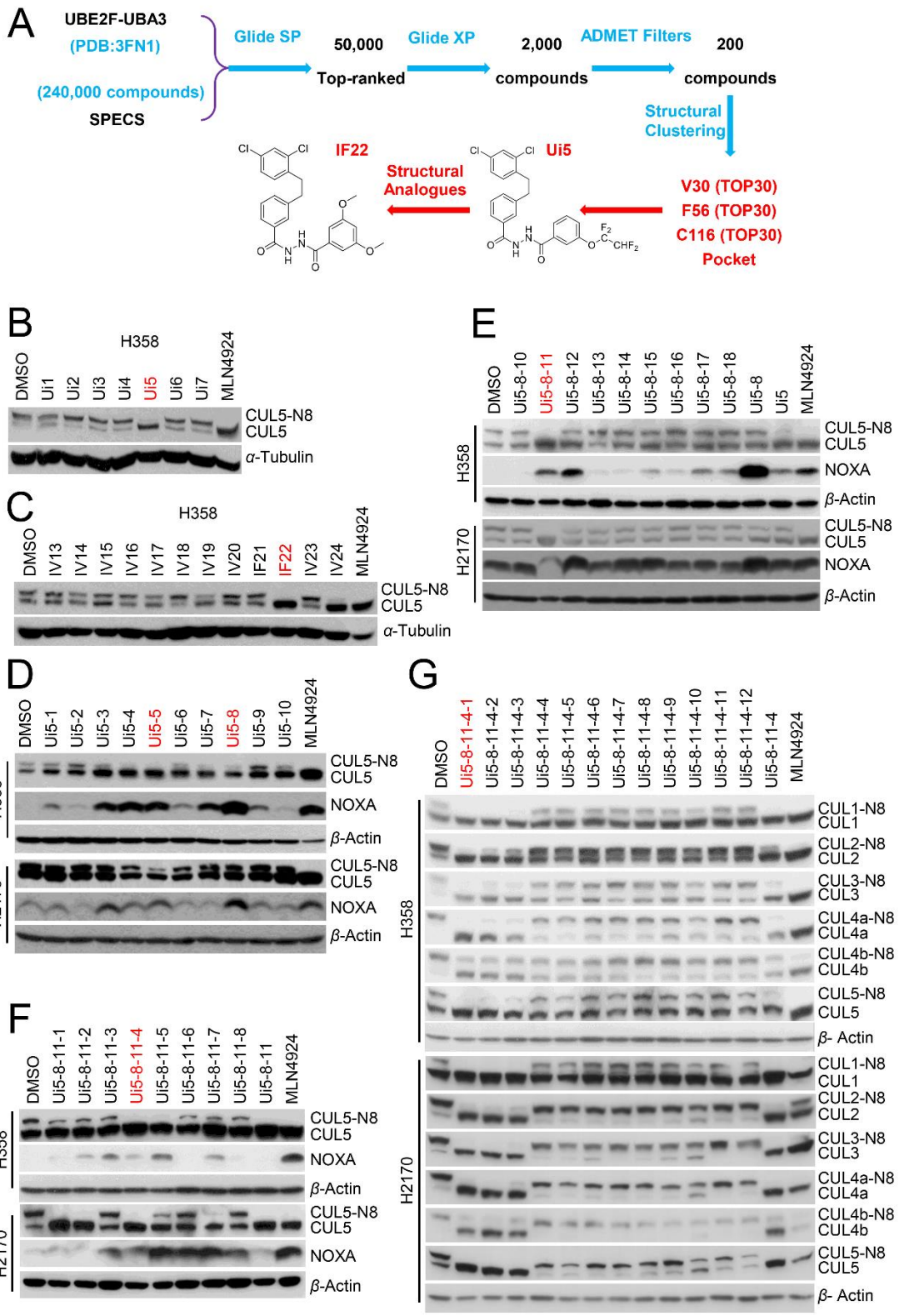


Figure S1 Western blotting verification of candidates. (A) Flow chart of virtual screening (Section 3). (B–G) Representative Western blotting results. Cells were treated with indicated small molecules (20 μmol/L) for 24 h, followed by Western blotting analysis. N8, NEDD8.

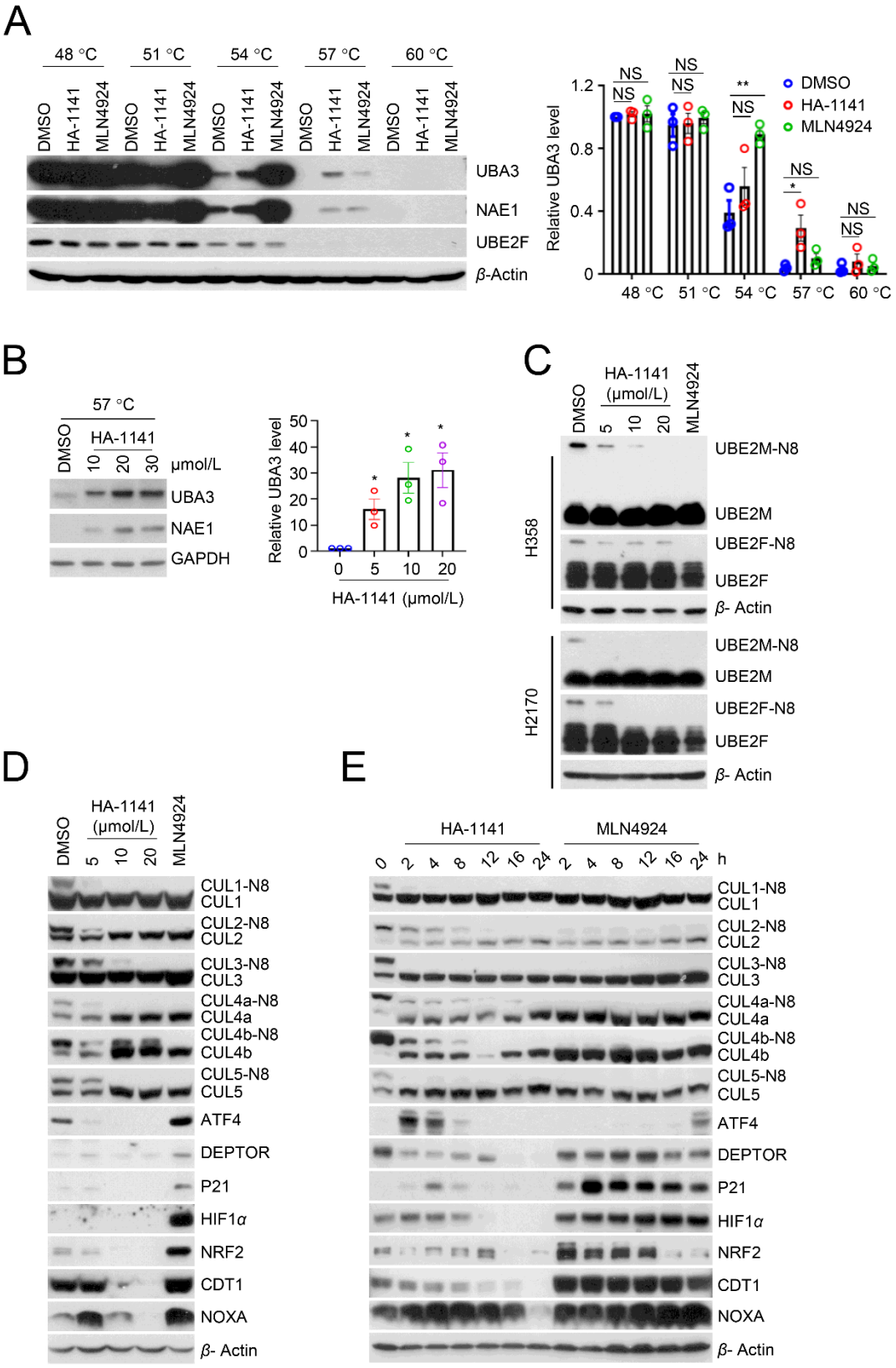


Figure S2 HA-1141 binds with UBA3, inhibits cullin neddylation but reduces substrates of CRLs. (A) Enhanced thermal stability of UBA3/NAE1 proteins in cells. H2170 cells were treated with HA-1141 (20 μmol/L), MLN4924 (1 μmol/L) or DMSO

for 24 h, followed by heating at indicated temperatures for 3 min. Protein levels were analyzed by Western blotting analysis. Shown were mean ± SEM (*n*=3). ***P*<0.01, **P* < 0.05, NS, no significance *vs.* control. (B) Dose-dependent enhancement of thermal stability of UBA3/NAE1 in cells. H2170 were treated with HA-1141 at different concentrations for 24 h and then heated at 57 °C for 3 min. Protein levels of UBA3/NAE1 were analyzed by Western blotting. Shown were mean ± SEM (*n*=3). **P* < 0.05 *vs.* control. (C) Inhibition of E2-NEDD8 thioester. H358 and H2170 were treated by HA-1141, DMSO or MLN4924 (0.3 μmol/L) for 24 h. Cell lysates were prepared and subjected to Western blotting using antibodies against UBE2M or UBE2F. (D, E) Inhibition of cullin neddylation but reduction of CRL substrates. H2170 were treated with HA-1141, MLN4924 (0.3 μmol/L) for 24 h, or with 20μmol/L of HA-1141 for indicated time followed by western blotting. N8, NEDD8.

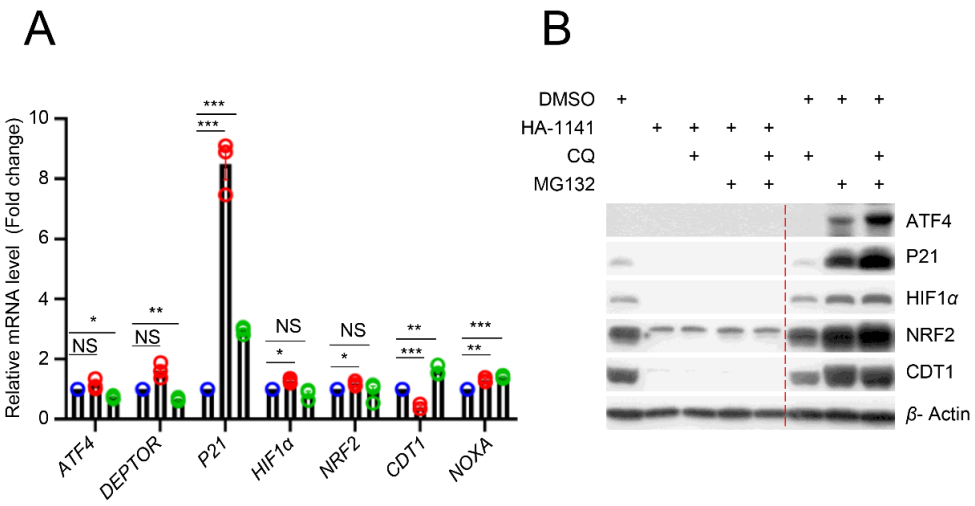


Figure S3 HA-1141 does not reduce CRLs' substrates on transcriptional or post-translation level. (A) HA-1141 does not reduce mRNA level of most CRLs' substrates. H2170 cells were treated with HA-1141 (20 μmol/L) or MLN4924 (0.3 μmol/L) for 24 h, followed by RT-PCR analysis. Shown were mean ± SEM (*n*=3). ****P*<0.001, ***P*<0.01, **P* < 0.05. NS, no significance *vs.* DMSO control. (B) CQ and MG132 cannot rescue protein reduction caused by HA-1141. H2170 cells were treated by HA-1141 (20 μmol/L) or DMSO for 24 h, CQ (50 μmol/L) or MG132 (10 μmol/L) was added to the medium 5 h before harvested, followed by Western blotting.

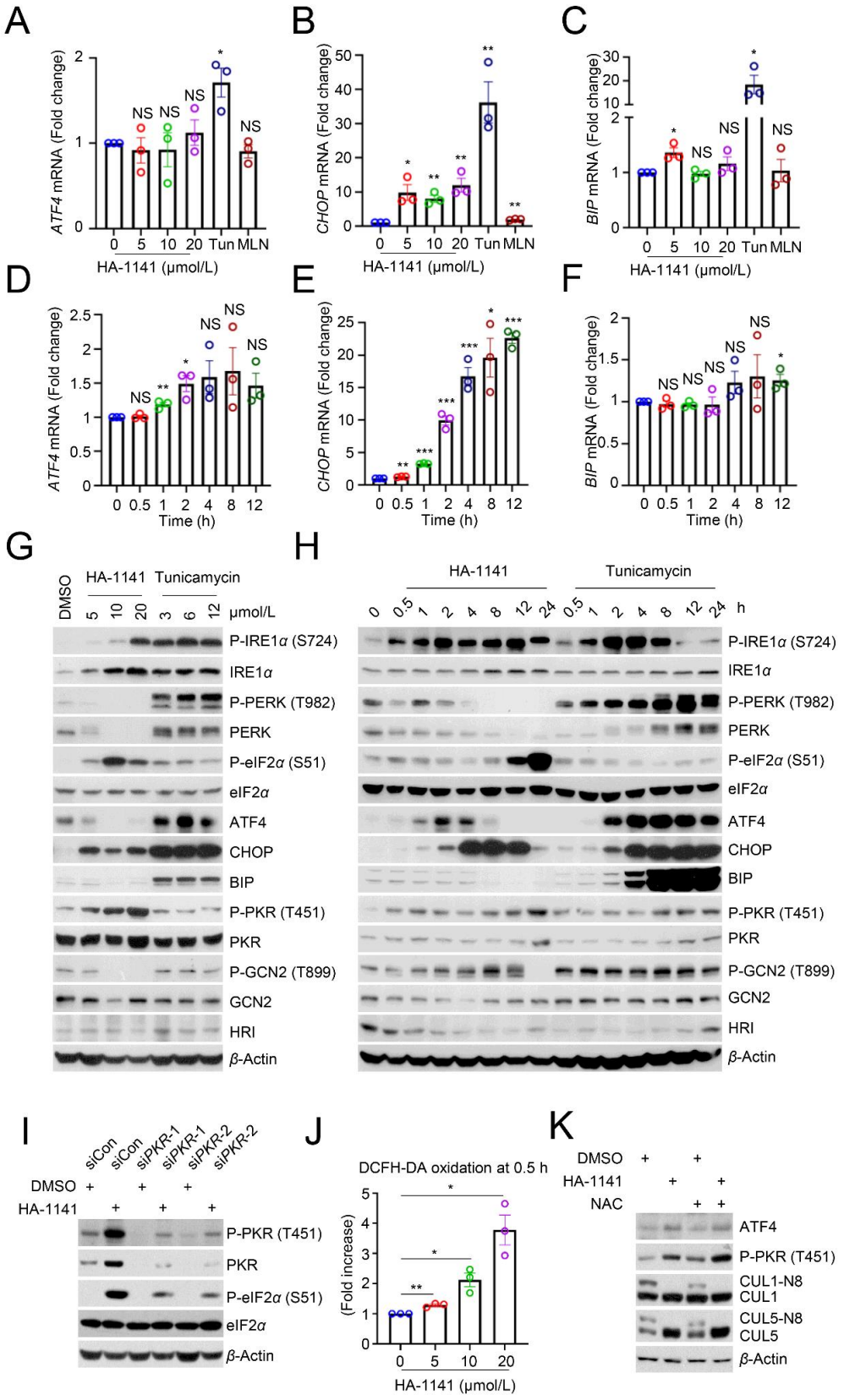


Figure S4 HA-1141 triggers non-canonical ER stress, integrated stress response (ISR) and ROS production. (A–F) HA-1141 triggers ER stress in a dose and time-dependent manner. H2170 cells were exposed to indicated concentration of HA-1141, Tun (12

μmol/L) or MLN (0.3 μmol/L) for 24 h, or treated with HA-1141 (20 μmol/L) for indicated periods of time. Relative mRNA level was analyzed by RT-PCR analysis. Shown were mean ± SEM (n=3). ***P<0.001, **P<0.01, *P<0.05, NS, no significance *vs.* control. Tun, tunicamycin, MLN, MLN4924. (G, H) HA-1141 induces non canonical ER stress and ISR. H2170 cells were treated with HA-1141 or tunicamycin at indicated concentrations for 24 h, or with 20 μmol/L of HA-1141 or 3 μmol/L of tunicamycin for indicated periods of time, followed by Western blotting. (I) PKR knockdown rescues P-eIF2α induced by HA-1141. H2170 cells were transfected with indicated siRNAs for 72 h, then treated with DMSO or HA-1141 (20 μmol/L) for 24 h, followed by Western blotting. (J) HA-1141 induces ROS production. H2170 cells were treated with HA-1141 for 0.5 h, then labeled with DCFH-DA (2 μmol/L) for 15min at 37 ℃, followed by FACS analysis (n=3). Shown were mean ± SEM. **P<0.01, *P<0.05 *vs.* control. (K) NAC rescues upregulation of ATF4 by HA-1141. H2170 cells were pre-treated with NAC (10 mmol/L) for 2 h, then co-incubated with HA-1141 (20 μmol/L) or DMSO for 12 h, followed by Western blotting.

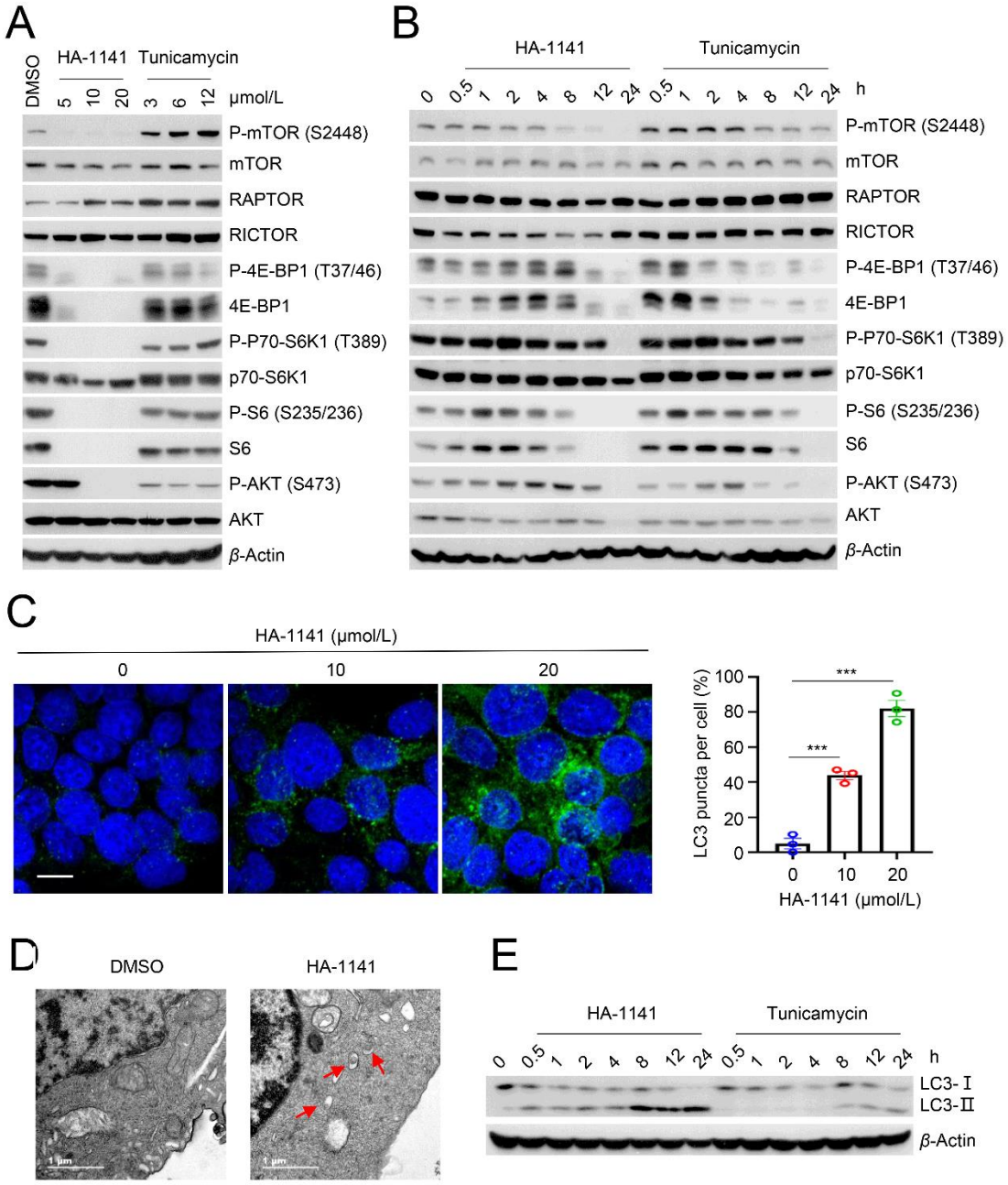


Figure S5 HA-1141 inactivates mTORC1 to induce autophagy. (A, B) HA-1141 inactivates mTORC1. H2170 cells were treated with HA-1141 or tunicamycin at indicated concentrations for 24 h, or with 20 μmol/L of HA-1141 or 3 μmol/L of tunicamycin for indicated periods of time, followed by Western blotting. (C) Autophagy measured by appearance of punctate vesicle structure: H2170 were treated with HA-1141 at indicated concentration for 24 h before photography under a fluorescent microscope (left panels). Cells with LC3 puncta were counted in 5 independent areas and data were plotted in a bar graph (right panel). Shown were mean ± SEM (n=3), size bar, 10 μm. ***P<0.001*vs.* control. (D) Detection of autophagosomes by TEM: H2170

cells were treated with HA-1141 (20 μmol/L) for 24 h, along with DMSO vehicle control, followed by the TEM analysis. Autohpagosomes were indicated by arrows. Direct magnification: ×30000, size bar, 1 μm. (E) Time dependent LC3-II conversion: H2170 cells were treated with HA-1141 (20 μmol/L) or tunicamycin (3 μmol/L) for indicated time followed by Western blotting.

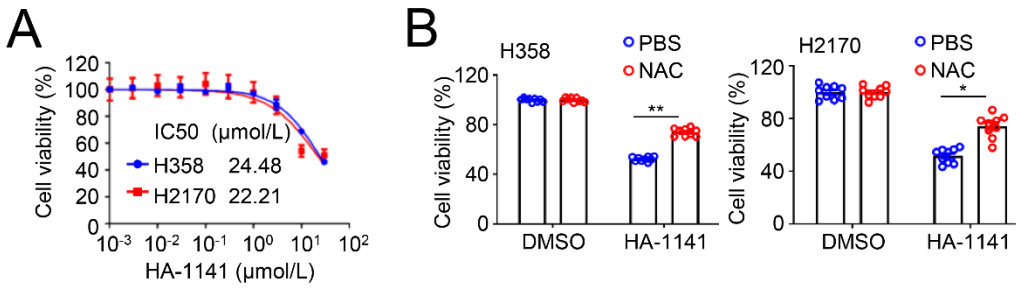


Figure S6 NAC rescues antitumor effect of HA-1141. (A) The IC50 determination. H358 or H2170 cells were seeded in triplicates in 96-well plate and treated with HA-1141 at indicated concentrations for 24 h, followed by CCK8 proliferation analysis. Shown was mean ± SEM (*n*=3). (B) NAC rescues antitumor effect of HA-1141. Cells were pretreated with NAC (10 mmol/L) for 3 h, then co-incubated with HA-1141 (20 μmol/L) for 24 h, followed by CCK8 proliferation analysis.

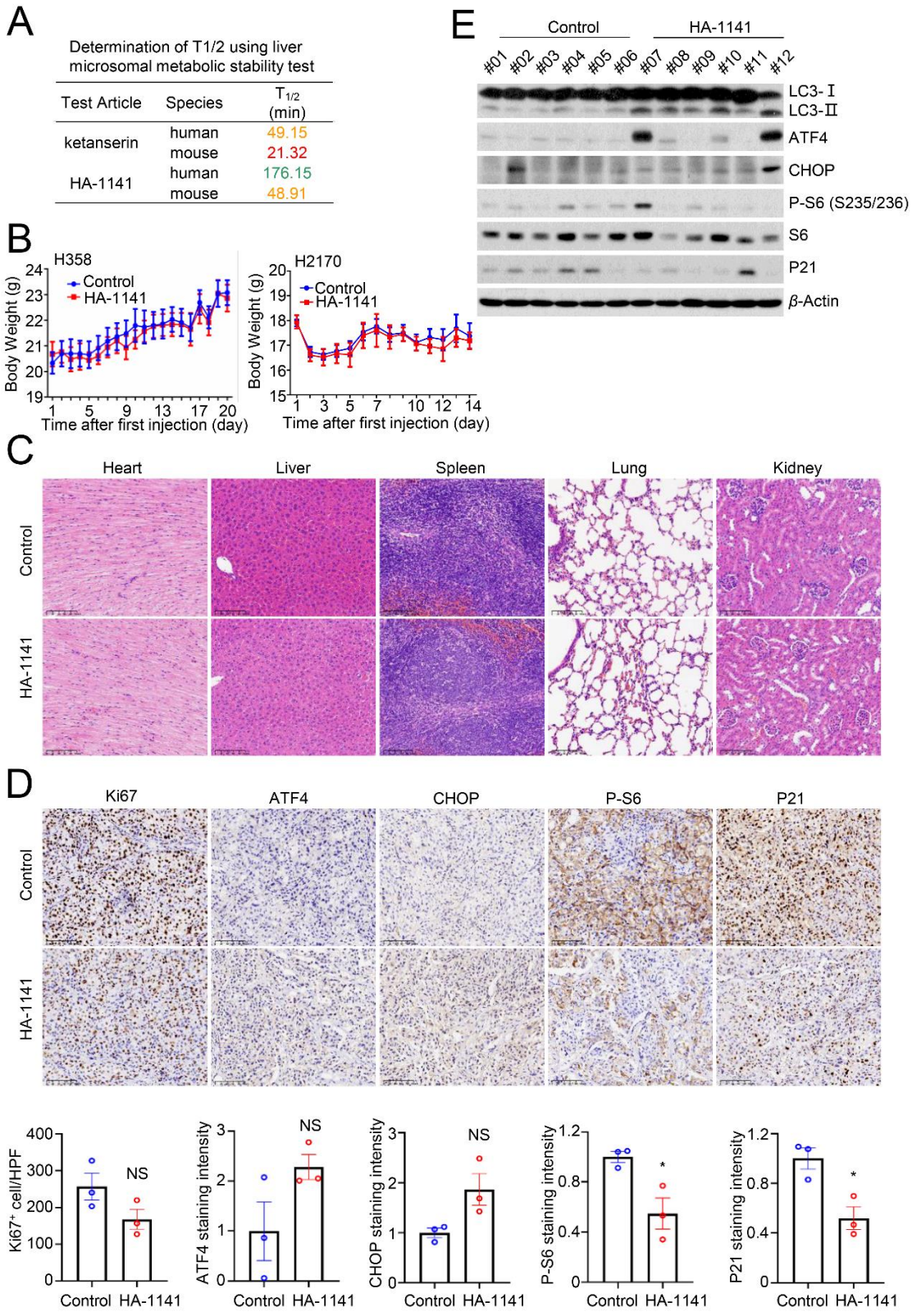


Figure S7 Evaluation of HA-1141 *in vivo*. (A) Liver microsomal metabolic stability. HA-1141 was subjected to this test, and the result was shown. Ketanserin served as quality control. (B) Body weights of nude mice. H358 cells or H2170 cells were injected 5×10^6 per flank in both flanks of nude mice. Solvent control (n=5 for H358,

n=6 for H2170) or 25mg/kg of HA-1141 (*n*=6) were injected i.p. once a day when tumor volume reached ~100 mm^3, 5 days per week for 3 or 2 weeks. Body weights were measured every day and plotted. (C) Typical H&E staining images of the vital organs. Vital organs from the mice bearing H2170 xenograft tumors were examined (*n*=3), size bar: 100 μm. (D) IHC Stainning. Three tumor tissues derived from H2170 xenograft mice for each group were collected for immunohistochemical staining. Five random areas of each tumor were photographed and then quantified. Shown was mean ± SEM (*n*=3). **P*<0.05, NS, no significance, size bar: 100 μm. (E) HA-1141 induces autophagy *in vivo.* Tumor tissues from H2170 xenograft mice models were subjected to Western blotting analysis.

Table S1 Antibodies used in Western blot and IHC analysis.

Antibody	Source	Identifier
4E-BP1	Cell Signaling Technology, MA, USA	Cat# 9644S
AKT	Cell Signaling Technology, MA, USA	Cat# 4691P
ATF4	Cell Signaling Technology, MA, USA	Cat# 11815S
BIP	Cell Signaling Technology, MA, USA	Cat# 3177S
CDT1	Santa Cruz Biotechnology, USA	Cat# sc-28262
CHOP	Cell Signaling Technology, MA, USA	Cat# 2895S
CUL1	Santa Cruz Biotechnology, USA	Cat# sc-11384
$CUL1^{CTD}$	Proteintech, USA	Cat# 12895-1-AP
CUL2	Abcam, England	Cat# ab166917
CUL3	Cell Signaling Technology, MA, USA	Cat# 2759S
CUL4A	Cell Signaling Technology, MA, USA	Cat# 2699S
CUL4B	Proteintech, USA	Cat# 12916-1-AP
CUL5	Santa Cruz Biotechnology, USA	Cat# sc-373822
$CUL5^{CTD}$	Sigma–Aldrich, MO, USA	Cat# AV35127
DEPTOR	Cell Signaling Technology, MA, USA	Cat# 11816S
GAPDH	Sigma-Aldrich, MO, USA	Cat# G9545
GCN2 (F-7)	Santa Cruz Biotechnology, USA	Cat# sc-374609
HIF1α	Novus, USA	Cat# nb100479
HRI (D-12)	Santa Cruz Biotechnology, USA	Cat# sc-365239
IRE1α	Cell Signaling Technology, MA, USA	Cat# 3294S

Ki67	Abcam, England	Cat# ab16667
LC3B	Sigma–Aldrich, MO, USA	Cat# L7543
mTOR	Cell Signaling Technology, USA	Cat# 2983P
NAE1	Cell Signaling Technology, MA, USA	Cat# 14321S
NEDD8	Abcam, England	Cat# ab81264
NOXA	EMD Millipore, USA	Cat# OP180
NRF2	Santa Cruz Biotechnology, USA	Cat# sc-722
P21	Cell Signaling Technology, MA, USA	Cat# 2947S
P-4E-BP1 (T37/46)	Cell Signaling Technology, MA, USA	Cat# 2855S
P-AKT (Ser 473)	Cell Signaling Technology, MA, USA	Cat# 4060S
PERK	Cell Signaling Technology, MA, USA	Cat# 5683S
P-GCN2 (T899)	Abcam, England	Cat# ab75836
P-IRE1α (S724)	Abcam, England	Cat# ab48187
PKR (B-10)	Santa Cruz Biotechnology, USA	Cat# sc-6282
P-mTOR (Ser2448)	Cell Signaling Technology, MA, USA	Cat# 5536P
P-PERK (T982)	Affinity Biosciences, USA	Cat# DF7576
P-PKR (T451)	Abcam, England	Cat# ab81303
P-S6 (S235/236)	Cell Signaling Technology, MA, USA	Cat# 4858S
P-S6K1 (T389)	Cell Signaling Technology, MA, USA	Cat# 9234S
RAPTOR	Cell Signaling Technology, MA, USA	Cat# 2280P
RICTOR	Cell Signaling Technology, MA, USA	Cat# 2114P
S6	Cell Signaling Technology, MA, USA	Cat# 2217S
S6K1	Cell Signaling Technology, USA	Cat# 2708S
UBA3	Abcam, England	Cat# ab124728
UBE2F	Santa Cruz Biotechnology, USA	Cat# sc-398668
UBE2M	Santa Cruz Biotechnology, USA	Cat# sc-390064
α-Tubulin	Sigma–Aldrich, MO, USA	Cat# T8203
β-Actin	Sigma–Aldrich, MO, USA	Cat# A5441

Table S2 Primers used in RT-PCR.

Primer	Sequence	
ATF4	Forward	5′-TTCTCCAGCGACAAGGCTAAGG-3′
	Reverse	5′-CTCCAACATCCAATCTGTCCCG-3′
BIP	Forward	5′-AAGAACCAGCTCACCTCCAACCC-3′
	Reverse	5′-TTCAACCACCTTGAACGGCAA-3′
CDT1	Forward	5′-GGAGGTCAGATTACCAGCTCAC-3′
	Reverse	5′-TTGACGTGCTCCACCAGCTTCT-3′
CHOP	Forward	5′-GGAAACAGAGTGGTCATTCCC-3′
	Reverse	5′-CTGCTTGAGCCGTTCATTCTC-3′
DEPTOR	Forward	5′-GCAGCAGGAATGAAGGTCTG-3′
	Reverse	5′-GTATGTGCGGAGAAGACTCGTAT-3′
GAPDH	Forward	5′-GGAGTCAACGGATTTGGT-3′
	Reverse	5′-GTGATGGGATTTCCATTGAT-3′
HIF1α	Forward	5′-TATGAGCCAGAAGAACTTTTAGGC-3′
	Reverse	5′-CACCTCTTTTGGCAAGCATCCTG-3′
NOXA	Forward	5′-GACTGTTCGTGTTCAGCTCG-3′
	Reverse	5′-CACTCGACTTCCAGCTCTGCT-3′
NRF2	Forward	5′-TATTATCCATTCCTGAGTTACAGTGTCT-3′
	Reverse	5′-GGTCTTCTGTGGAGAGGATGCT-3′
P21	Forward	5′-CTGTCACTGTCTTGTACCCTTGT-3′
	Reverse	5′-GGTAGAAATCTGTCATGCTGGT-3′

Chemical synthesis and characterization

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-600, a Bruker AV-500 or a WNMR-I-400 spectrometer. chloroform-d, acetone-d_6 and dimethyl sulfoxide-d_6 was used as solvent, chemical shifts were referenced relative to residual solvent. The following abbreviations are used to describe peak patterns where appropriate: br = broad, s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are reported in Hertz (Hz). HRMS were performed on Agilent Technologies 6546-LC/Q-TOF LC/MS apparatus (ESI-TOF). Flash column chromatography was carried out on silica gel (200−300 mesh).

Solvents, such as dichloromethane (DCM), ethyl acetate (EA), petroleum ether

(PE), tetrahydrofuran (THF), acetonitrile (MeCN), *N*,*N*-dimethylformamide(DMF), acetone, ethanol, toluene (PhMe) and methanol (MeOH) were commercially available. As necessary, solvents were dried *via* corresponding chemical technologies. All reagents were purchased and used as received from commercial sources without further purification. All compounds were confirmed to ≥95% purity by NMR. Structure of all compounds was showed in Figs. S1–S5.

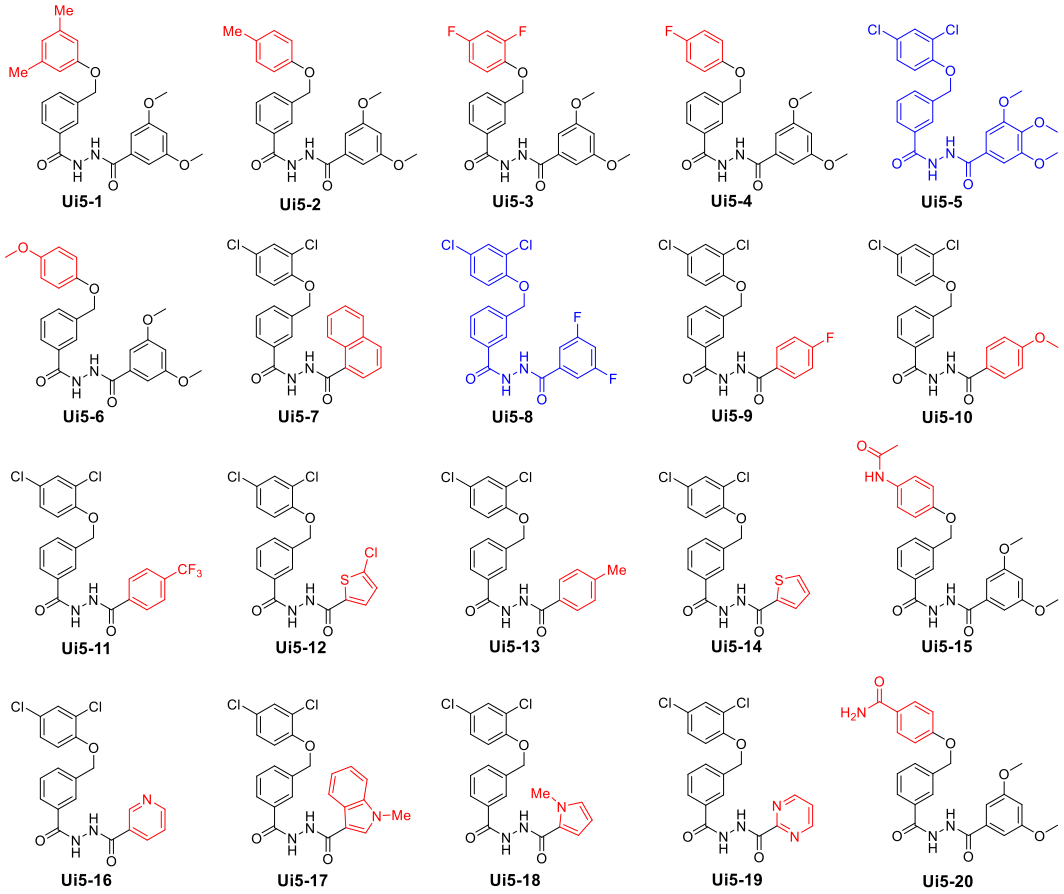


Figure S1 Chemical Structures of **Ui5** series.

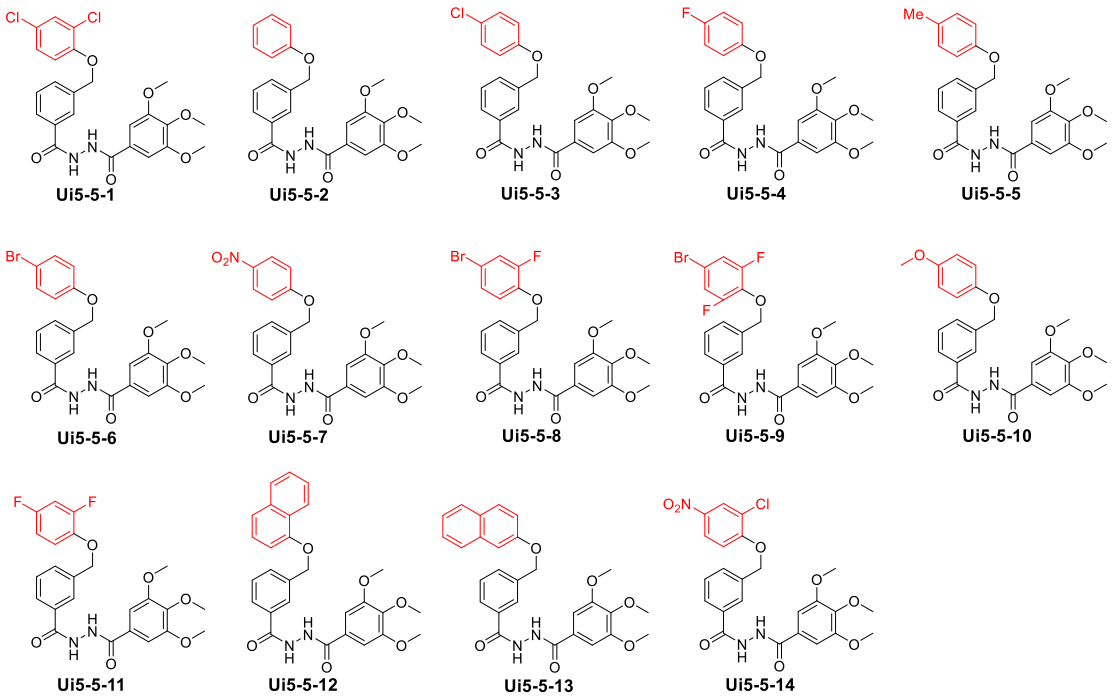


Figure S2 Chemical Structures of **Ui5-5** series.

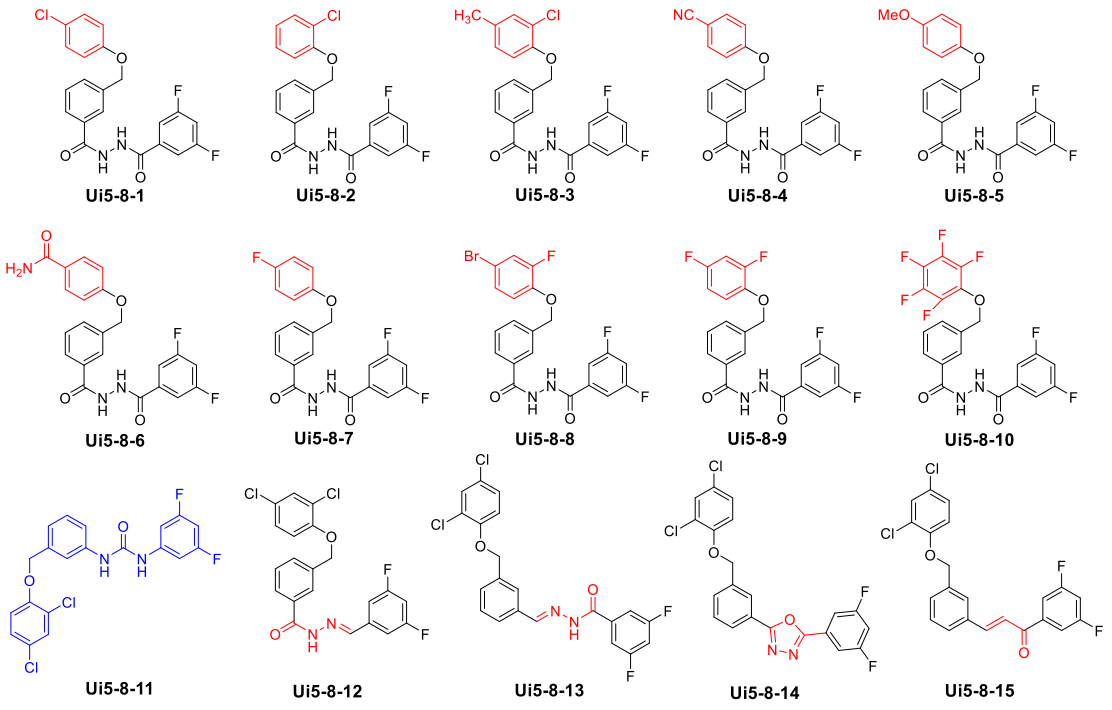


Figure S3 Chemical Structures of **Ui5-8** series.

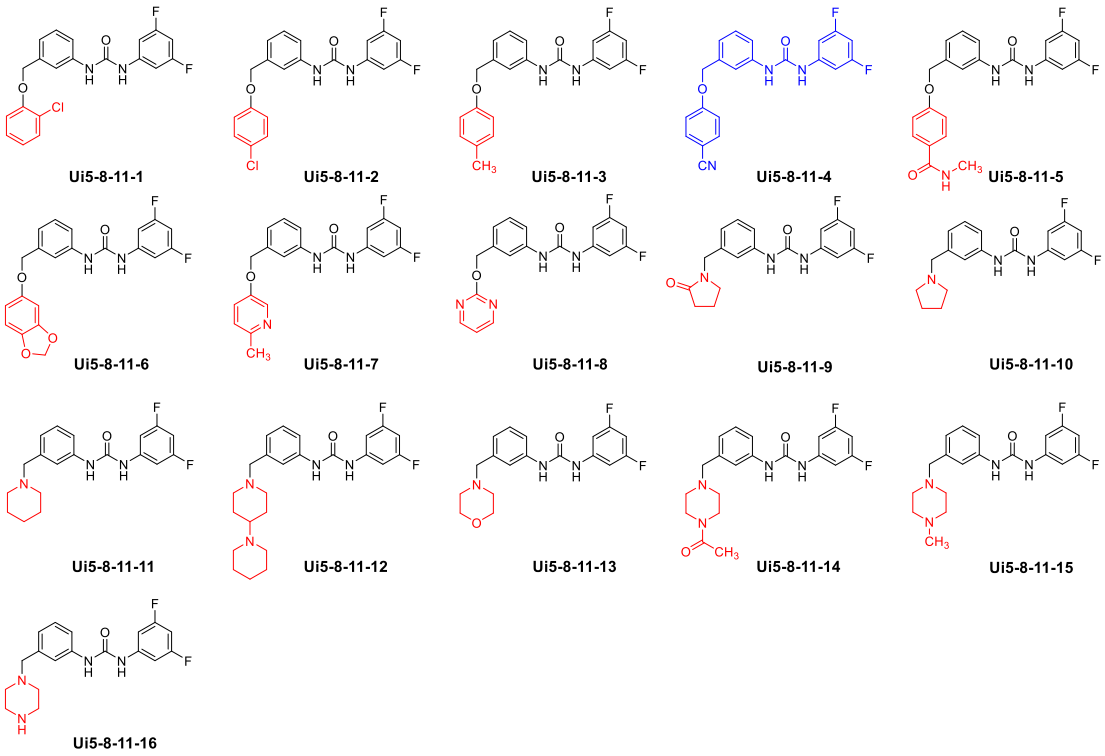


Figure S4 Chemical Structures of **Ui5-8-11** series.

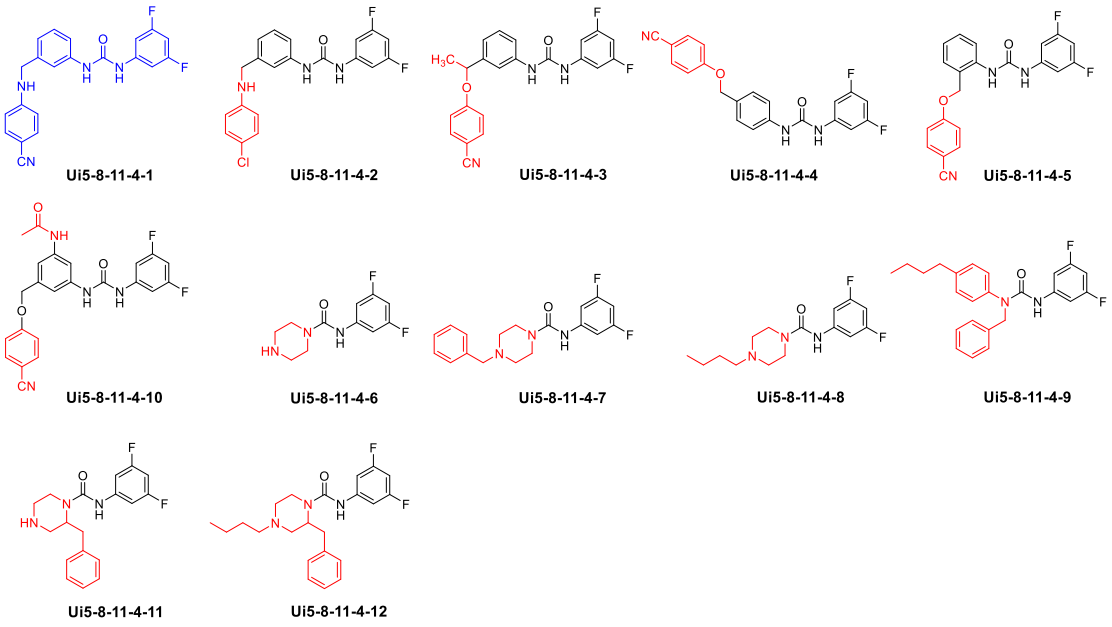


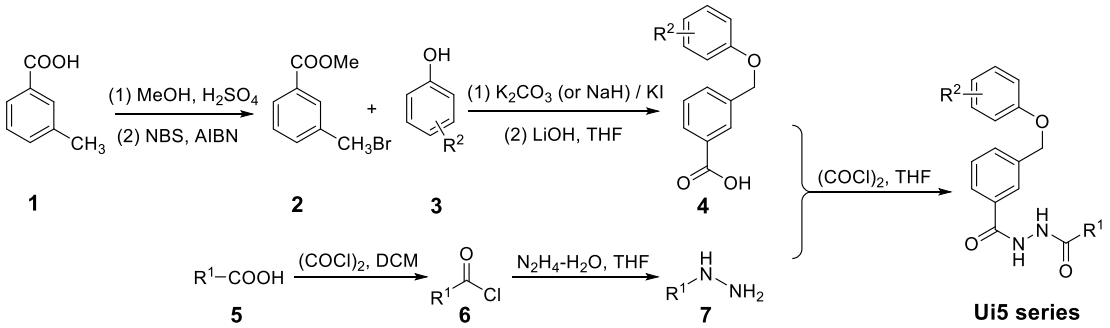
Figure S5 Chemical Structures of **Ui5-8-11-4** series.

General synthetic procedures

Reactions were performed in round-bottom flasks and moisture- and air-sensitive reactions were performed under argon atmosphere. The reaction progress was monitored by thin-layer chromatography (TLC) under UV lamp (254 nm). The

following synthesis procedure refer to the key procedure.

Procedure A:



To a stirred solution of 3-methylbenzoic acid **1** (10 mmol) in MeOH (20 mL), concentrated sulfuric acid (2−3 drops) was added. The reaction mixture was stirred at 70 °C for 3h. The excess methanol is removed under vacuum and saturated $NaHCO_3$ (20 mL) was added, the resulting aqueous layer was extracted with EtOAc (×3), the combined organic layers were concentrated under reduced pressure. The crude 3-methyl-benzoicacimethylester was used directly in the next step without further purification. A two-necked flask was charged with *N*-bromosuccinimide (NBS, 10 mmol), 2,2′-azobis(2-methylpropionitrile; AIBN, 0.05 mol %) and the flask was purged with argon for three times, 3-methyl-benzoicacimethylester (10 mmol) in CCl_4 (30 mL) was added, the reaction mixture was stirred under refluxing overnight. the solvent was evaporated under vacuum and the water was added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using ethyl acetate/petroleum ether (*v*/*v*, 1:30) as eluent to give **2**.

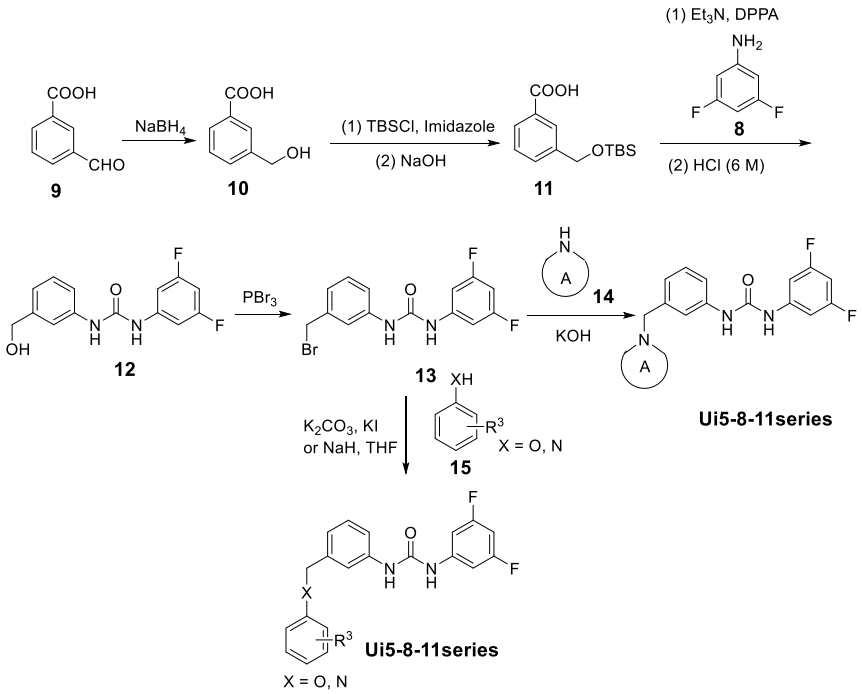
An oven-dried 50 mL round-bottom flask was charged with methyl 3-(bromomethyl)-benzoate **2** (0.2 mmol), corresponding phenols **3** (0.24 mmol), K_2CO_3 (0.3 mmol), KI (0.3 mmol), acetone was added as solvent. The solution was stirred under refluxing until **2** was fully consumed. the solvent was evaporated under vacuum, saturated $NaHCO_3$ were added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using ethyl acetate/petroleum ether (*v*/*v*, 1:10 to 1:5) as eluent to give the desired products. The above product was added into an oven-dried 50 mL round-bottom flask, THF was utilized as solvent, aqueous solution of LiOH (40%) was added. The resulting mixture was stirred at rt until the esters were fully consumed, the solvent was evaporated under vacuum, water was added, then HCl

(3N, aq.) were added until pH was ~2.0. The resulting aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum to give acids **4** without further purification.

A two-necked flask was charged with corresponding acids **5** (0.2 mmol), DMF (2−3 drops) were added as catalysis and the flask was purged with argon for three times. Anhydrous DCM (15 mL) was added as solvent and the solution was cooled to 0 ℃, oxalyl chloride (0.4 mmol) was added dropwise *via* syringe. Afterwards, the reaction mixture was slowly warmed to room temperature, stirred at room temperature overnight. The next day, the solvent was evaporated under vacuum to produce **6**. A two-necked flask was purged with argon for three times and hydrazine hydrate (80%, 0.5 mmol) was added. Anhydrous THF (20 mL) was added as solvent, the solution was cooled to 0 ℃, acyl chloride **6** was added dropwise via dropping funnel, stirred at room temperature until the reaction was completed to produce **7**.

A two-necked flask was charged with corresponding acids **4** (0.2 mmol), DMF (2−3 drops) were added as catalysis and the flask was purged with argon for three times. Anhydrous DCM (20 mL) was added as solvent and the solution was cooled to 0 ℃, oxalyl chloride (0.4 mmol) was added dropwise via syringe. Afterwards, the reaction mixture was slowly warmed to room temperature, stirred at room temperature overnight. The next day, the solvent was evaporated under vacuum to produce the crude product. A two-necked flask was purged with argon for three times and compound **7** (0.2 mmol) was added. Anhydrous THF (20 mL) was added as solvent, the solution was cooled to 0 ℃, corresponding acyl chloride of **4** (0.2 mmol) was added dropwise via dropping funnel, stirred at room temperature until the reaction was completed. The products were recrystallized with ethyl acetate/petroleum ether (*v*/*v*) to afford **Ui5** series compounds.

Procedure B:



To a stirred solution of 3-carboxybenzaldehyde **9** (10 mmol) in MeOH (20 mL), the solution was cooled to 0 ℃ before $NaBH_4$ (15 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, quenched with a saturated aqueous solution of NH_4Cl. The excess methanol is removed under vacuum and then HCl (3N, aq.) were added until pH was ~2.0, the resulting aqueous layer was extracted with EtOAc (×3), the combined organic layers were concentrated under reduced pressure. The desired product **10** was obtained. An oven-dried 50 mL round-bottom flask was charged with **10** (5.0 mmol), DMF (15 mL) was added as solvent, the solution was cooled to 0 ℃. TBSCl (6.0 mmol) and imidazole (6.0 mmol) were added. The reaction mixture was slowly warmed to room temperature, stirred at room temperature until **10** was fully consumed, diluted with water. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude product was added into an oven-dried 50 mL round-bottom flask, THF was utilized as solvent, aqueous solution of NaOH (5%, 1.2 mmol) was added. The resulting mixture was stirred at rt for 1 h, acidified with HCl (1 M), extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum to produce crude product **11**.

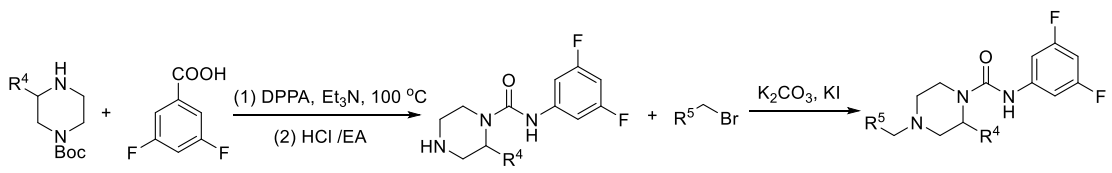
A two-necked flask was charged with corresponding acids **11** (2.0 mmol), amines **8** (2.0 mmol) and the flask was purged with argon for three times. Anhydrous toluene (20 mL) was used as solvent, DPPA (2.4 mmol), Et_3N (6.0 mmol) were added, the

resulting solution was stirred at 100 ℃ until the reaction was fully consumed. Afterwards, the solvent was evaporated under vacuum, water was added. The aqueous phase was extracted with EtOAc (×2) and the combined organic layers were washed with HCl (6 M, ×2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The purification was performed by flash column chromatography on silica gel using DCM/MeOH (*v*/*v*, 10:1) as eluent to 1**2**. To a stirred solution of **12** (1.0 mmol) in THF (20 mL), the solution was cooled to 0 ℃, PBr_3 (2.0 mmol) was added dropwise via syringe. The reaction mixture was stirred at room temperature until the reaction was fully consumed. Afterwards, the solvent was evaporated under vacuum, water was added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were washed with brine (×1), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The purification was performed by flash column chromatography on silica gel using PE/EA as eluent to give pure product **13**.

An oven-dried 50 mL round-bottom flask was charged with benzyl bromide **13** (0.2 mmol), corresponding amines **14** (0.48 mmol), ethanol was added as solvent. KOH (0.22 mmol) was added. The solution was stirred at room temperature until the reaction was fully consumed. the solvent was evaporated under vacuum, water was added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using DCM/EtOAc as eluent to give the desired product.

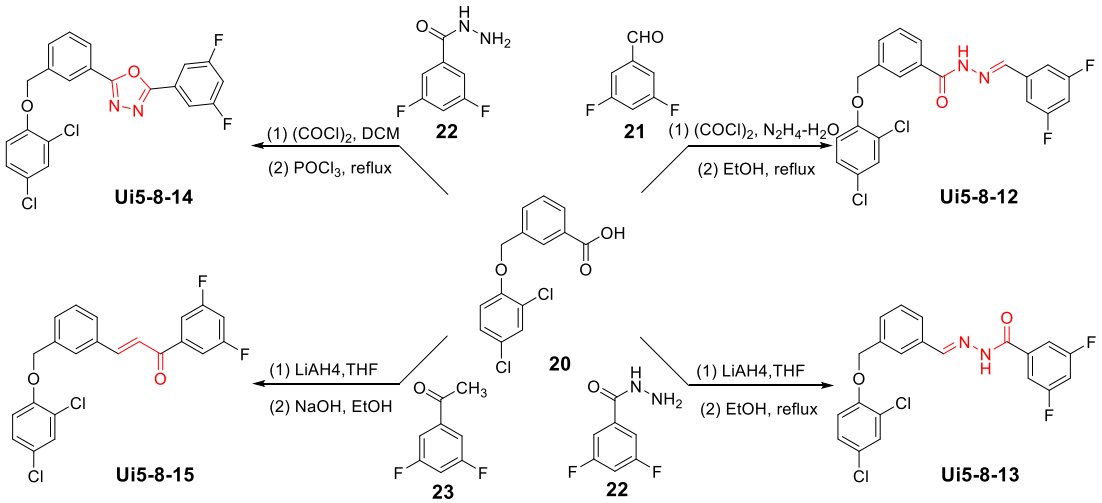
An oven-dried 50 mL round-bottom flask was charged with benzyl bromide **13** (0.2 mmol), corresponding phenols and anilines **15** (0.24 mmol), K_2CO_3 (or NaH, 0.3 mmol), KI (0.3 mmol), acetone (or THF) was added as solvent. The solution was stirred under refluxing until **13** was fully consumed. the solvent was evaporated under vacuum, saturated $NaHCO_3$ were added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using ethyl acetate/petroleum ether (*v*/*v*, 10:1 to 5:1) as eluent to give **Ui5-8-11** series.

Procedure C：



A two-necked flask was charged with corresponding acids **17** (0.1 mmol), amines **16** (0.1 mmol) and the flask was purged with argon for three times. Anhydrous toluene (10 mL) was used as solvent, DPPA (0.12 mmol), Et_3N (0.3 mmol) were added, the resulting solution was stirred at 100 ℃ until the reaction was fully consumed. Afterwards, the solvent was evaporated under vacuum, water was added. The aqueous phase was extracted with EtOAc (×2) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using ethyl acetate/petroleum ether (*v*/*v*, 1:5) as eluent to give the desired product. The above product was added into an oven-dried 50 mL round-bottom flask, a HCl solution in EtOAc was added and the resulting solution was stirred at rt until the reaction was fully consumed. The resulting hydrochloride of **18** was obtained. An oven-dried 50 mL round-bottom flask was charged with **19** (0.2 mmol), corresponding hydrochloride of **18** (0.24 mmol), K_2CO_3 (0.5 mmol), KI (0.3 mmol), acetone was added as solvent. The solution was stirred under refluxing until **19** was fully consumed. the solvent was evaporated under vacuum, water was added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were concentrated under vacuum. The crude mixture was purified by chromatography on silica gel using ethyl acetate/petroleum ether (*v*/*v*, 10:1 to 5:1) as eluent to give **Ui5-8-11-4** series.

Procedure D:



20 and **22** were synthesized from corresponding starting materials via **Procedure A.** A two-necked flask was charged with acids **20** (0.2 mmol), DMF (2−3 drops) were added as catalysis and the flask was purged with argon for three times. Anhydrous DCM (15 mL) was added as solvent and the solution was cooled to 0 ℃, oxalyl chloride (0.4 mmol) was added dropwise via syringe. Afterwards, the reaction mixture was slowly

warmed to room temperature, stirred at room temperature overnight. The next day, the solvent was evaporated under vacuum to produce the acyl chloride. A two-necked flask was purged with argon for three times and hydrazine hydrate (80%, 0.5 mmol) was added. Anhydrous THF (20 mL) was added as solvent, the solution was cooled to 0 ℃, acyl chloride was added dropwise via dropping funnel, stirred at room temperature until the reaction was completed to produce the desired product. To a stirred solution of the above product (0.2 mmol) and 3,5-difluorobenzaldehyde **21** (0.2 mmol) in EtOH (20 mL), the solution was stirred under refluxing until the reaction was completed. The excess EtOH is removed under vacuum. The products were recrystallized with ethyl acetate/petroleum ether to afford **Ui5-8-12**.

An oven-dried 50 mL round-bottom flask was charged with acids **20** (0.2 mmol), Anhydrous THF (15 mL) was used as solvent, the solution was cooled to 0 ℃ before $LiAH_4$ (0.3 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with a saturated aqueous solution of NH_4Cl. The excess THF is removed under vacuum and the resulting aqueous layer was extracted with EtOAc (×3), concentrated under reduced pressure. The desired product was obtained. To a stirred solution of the above product (0.2 mmol) in DCM (15 mL), MnO_2 was added, the solution was performed under refluxing until completed. The reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the crude product. To a stirred solution of the crude product (0.2 mmol) and 3,5-difluorobenzoicacidhydrazide **22** (0.2 mmol) in EtOH (20 mL), the solution was stirred under refluxing until the reaction was completed. The excess EtOH is removed under vacuum. The products were recrystallized with ethyl acetate/petroleum ether to afford **Ui5-8-13**.

A two-necked flask was charged with acids **20** (0.2 mmol), DMF (2−3 drops) were added as catalysis and the flask was purged with argon for three times. Anhydrous DCM (15 mL) was added as solvent and the solution was cooled to 0 ℃, oxalyl chloride (0.4 mmol) was added dropwise via syringe. Afterwards, the reaction mixture was slowly warmed to room temperature, stirred at room temperature overnight. The next day, the solvent was evaporated under vacuum to produce the acyl chloride. A two-necked flask was charged with 3,5-difluorobenzoicacidhydrazide **22** (0.2 mmol) and purged with argon for three times. Anhydrous THF (20 mL) was added as solvent, the solution was cooled to 0 ℃, corresponding acyl chloride was added dropwise via dropping funnel, stirred at room temperature until the reaction was completed. The products were

recrystallized with ethyl acetate / petroleum ether to afford the desired compounds. The above product (0.2 mmol) was added into an oven-dried 50 mL round-bottom flask, $POCl_3$ (5 mL) was added. The reaction mixture was stirred under refluxing for 2 h, quenched with a saturated aqueous solution of H_2O slowly. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were washed with brine (×1), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The products were recrystallized with ethyl acetate / petroleum ether to afford **Ui5-8-14**.

An oven-dried 50 mL round-bottom flask was charged with acids **20** (0.2 mmol), Anhydrous THF (15 mL) was used as solvent, the solution was cooled to 0 ℃ before $LiAH_4$ (0.3 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with a saturated aqueous solution of NH_4Cl. The excess THF is removed under vacuum and the resulting aqueous layer was extracted with EtOAc (×3), concentrated under reduced pressure. The desired product was obtained. To a stirred solution of the above product (0.2 mmol) in DCM (15 mL), MnO_2 was added, the solution was performed under refluxing until completed. The reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the crude product. To a stirred solution of the crude product (0.2 mmol) and 3,5-difluoroacetophenone **23** (0.2 mmol) in EtOH (20 mL), aqueous solution of NaOH (10%) was added, the solution was stirred under room temperature until the reaction was completed. The excess EtOH is removed under vacuum and water was added. The aqueous phase was extracted with EtOAc (×3) and the combined organic layers were washed with brine (×1), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The products were recrystallized with ethyl acetate / petroleum ether to afford **Ui5-8-15**.

Characterization of all compounds

***N′*-(3-((3,5-dimethylphenoxy)methyl)benzoyl)-3,5-dimethoxybenzohydrazide (Ui5-1).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.29 (s, 2H), 7.94 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 2.2 Hz, 2H), 6.63 (d, J = 5.7 Hz, 4H), 5.08 (s, 2H), 3.83 (s, 6H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.72, 165.34, 160.43, 158.29, 138.68, 137.89, 134.50, 132.76, 130.91, 128.66, 126.67, 122.50, 112.51, 105.34, 103.80, 98.96, 68.55, 55.49, 21.11. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{26}N_2O_5Na$ $[M+Na]^+$: 457.1734; Found: 457.1734.

3,5-dimethoxy-*N*′-(3-((p-tolyloxy)methyl)benzoyl)benzohydrazide (Ui5-2). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.51 (d, J = 13.8 Hz, 2H), 7.92 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 2.2 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.61 (t, J = 2.2 Hz, 1H), 5.05 (s, 2H), 3.80 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 165.50, 160.91, 156.48, 138.22, 133.23, 131.59, 131.24, 130.49, 130.08, 129.00, 126.80, 126.44, 114.78, 105.16, 69.39, 55.61, 20.60. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{24}N_2O_5Na$ $[M+Na]^+$: 443.1577; Found: 443.1579.

***N*′-(3-((2,4-difluorophenoxy)methyl)benzoyl)-3,5-dimethoxybenzohydrazide (Ui5-3).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.53 (d, J = 18.7 Hz, 2H), 7.92 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 2.2 Hz, 2H), 6.97–6.83 (m, 2H), 6.79–6.72 (m, 1H), 6.61 (t, J = 2.2 Hz, 1H), 5.10 (s, 2H), 3.81 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 165.33, 165.17, 160.83, 158.14, 158.03, 155.73, 154.11, 153.99, 151.52, 142.97, 142.83, 137.21, 133.07, 131.53, 131.22, 129.00, 127.03, 126.44, 116.78, 116.71, 110.56, 110.37, 105.25, 105.06, 104.99, 104.76, 71.54, 55.49. HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{20}F_2N_2O_5Na$ $[M+Na]^+$: 465.1232; Found: 465.1233.

***N*′-(3-((4-fluorophenoxy)methyl)benzoyl)-3,5-dimethoxybenzohydrazide (Ui5-4).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.03 (d, J = 7.0 Hz, 2H), 7.88 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.01–6.90 (m, 4H), 6.88–6.81 (m, 2H), 6.54 (t, J = 2.2 Hz, 1H), 4.95 (s, 2H), 3.73 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 165.50, 165.44, 160.74, 158.58, 156.21, 154.51, 137.60, 132.99, 131.45, 131.04, 128.88, 126.82, 126.35, 115.97, 115.82, 115.74, 105.02, 69.76, 55.45. HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{21}FN_2O_5Na$ $[M+Na]^+$: 447.1327; Found: 447.1330.

***N*′-(3-((2,4-dichlorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.43 (s, 1H), 10.22 (s, 1H), 7.84 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.36–7.28 (m, 2H), 7.13–7.04 (m, 3H), 6.80 (d, J = 8.8 Hz, 1H), 4.99 (s, 2H), 3.83 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 165.98, 165.70, 153.00, 152.62, 141.47, 136.99, 131.40, 130.87, 130.07, 129.01, 127.61, 126.81, 126.37,

126.03, 125.93, 123.99, 114.65, 104.65, 70.24, 60.83, 56.08. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{22}Cl_2N_2O_6Na$ $[M+Na]^+$: 527.0747; Found: 527.0744.

3,5-dimethoxy-*N*′-(3-((4-methoxyphenoxy)methyl)benzoyl)benzohydrazide (Ui5-6). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.07 (d, *J* = 19.7 Hz, 2H), 7.87 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 2H), 6.89–6.76 (m, 4H), 6.53 (t, *J* = 2.2 Hz, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 3.72 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 165.42, 165.35, 160.75, 154.04, 152.57, 138.08, 133.07, 131.43, 131.10, 128.84, 126.68, 126.32, 115.76, 114.63, 105.01, 69.85, 55.65, 55.46. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{24}N_2O_6Na$ $[M+Na]^+$: 459.1527; Found: 459.1530.

***N*′-(3-((2,4-dichlorophenoxy)methyl)benzoyl)-1-naphthohydrazide (Ui5-7).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 10.53 (s, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.16–7.92 (m, 4H), 7.76–7.54 (m, 7H), 7.46–7.24 (m, 2H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.09, 165.66, 152.66, 136.84, 133.14, 132.83, 132.76, 130.96, 130.37, 129.98, 129.43, 128.84, 128.24, 128.15, 127.04, 127.00, 126.91, 126.45, 125.63, 125.50, 125.02, 124.87, 122.69, 115.64, 70.06. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{18}Cl_2N_2O_3$ $[M+Na]^+$: 487.0587; Found: 487.0585.

***N*′-(3-((2,4-dichlorophenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (d, *J* = 20.1 Hz, 2H), 8.02 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.68–7.50 (m, 5H), 7.40 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.66, 163.64, 163.52, 163.34, 161.18, 161.06, 152.64, 136.89, 135.83, 132.69, 131.02, 129.42, 128.86, 128.15, 127.00, 126.91, 124.88, 122.68, 115.63, 111.06, 110.79, 107.84, 107.58, 107.32, 69.99. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{15}Cl_2F_2N_2O_3$ $[M+H]^+$: 451.0422; Found: 451.0422.

3-((2,4-dichlorophenoxy)methyl)-*N*′-(4-fluorobenzoyl)benzohydrazide (Ui5-9). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 2H), 8.09–7.98 (m, 3H), 7.92 (d, *J* = 6.3 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.64–7.54 (m, 2H), 7.38 (t, *J* = 8.8 Hz, 3H), 7.29 (d, *J* = 8.9 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (101

MHz, DMSO-d_6) δ 165.71, 165.50, 164.82, 163.02, 152.64, 136.84, 132.87, 130.91, 130.26, 130.17, 129.42, 129.01, 128.82, 128.14, 126.96, 126.90, 124.86, 122.67, 115.69, 115.62, 115.48, 70.00. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{15}Cl_2FN_2O_3Na$ $[M+Na]^+$: 455.0336; Found: 455.0332.

3-((2,4-dichlorophenoxy)methyl)-*N*′-(4-methoxybenzoyl)benzohydrazide (Ui5-10). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 10.39 (s, 1H), 8.02 (s, 1H), 7.92 (t, *J* = 6.8 Hz, 3H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.65–7.51 (m, 2H), 7.39 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 5.31 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.75, 165.34, 162.07, 152.64, 136.82, 133.00, 130.87, 129.43, 129.41, 128.81, 128.16, 126.94, 126.91, 124.85, 124.67, 122.66, 115.63, 113.77, 70.01, 55.44. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{18}Cl_2N_2O_4Na$ $[M+Na]^+$: 467.0536; Found: 467.0536.

3-((2,4-dichlorophenoxy)methyl)-*N*′-(4-(trifluoromethyl)benzoyl)benzohydrazide (Ui5-11). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.69 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.03 (s, 1H), 7.93 (t, *J* = 7.2 Hz, 3H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.64–7.55 (m, 2H), 7.43–7.35 (m, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.65, 164.77, 152.64, 136.89, 136.32, 132.75, 131.92, 131.60, 131.01, 129.44, 128.87, 128.45, 128.17, 126.98, 126.92, 125.70, 125.66, 125.26, 124.86, 122.66, 122.55, 115.63, 69.98. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{16}Cl_2F_3N_2O_3$ $[M+H]^+$: 483.0485; Found: 483.0471.

5-chloro-*N*′-(3-((2,4-dichlorophenoxy)methyl)benzoyl)thiophene-2-carbohydrazide (Ui5-12). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 10.62 (s, 1H), 7.99 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.65–7.53 (m, 2H), 7.40 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.33–7.24 (m, 2H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.92, 165.01, 157.81, 142.08, 141.68, 139.11, 137.83, 136.20, 134.61, 134.29, 134.04, 133.65, 133.34, 132.13, 132.05, 130.04, 127.84, 120.82, 75.14. HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{13}Cl_3N_2O_3SNa$ $[M+Na]^+$: 476.9605; Found: 476.9599.

3-((2,4-dichlorophenoxy)methyl)-*N*′-(4-methylbenzoyl)benzohydrazide (Ui5-13). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s,

1H), 10.46 (s, 1H), 8.02 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.65–7.52 (m, 2H), 7.39 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.31 (dd, *J* = 17.8, 8.5 Hz, 3H), 5.31 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.90, 170.89, 157.83, 147.09, 142.00, 138.15, 136.05, 134.94, 134.61, 134.25, 133.99, 133.33, 132.70, 132.12, 132.08, 130.03, 127.85, 120.82, 75.20, 26.25. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{18}Cl_2N_2O_3Na$ $[M+Na]^+$: 451.0587; Found: 451.0585.

***N′*-(3-((2,4-dichlorophenoxy)methyl)benzoyl)thiophene-2-carbohydrazide (Ui5-14).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (d, *J* = 6.6 Hz, 2H), 8.01 (s, 1H), 7.96–7.82 (m, 3H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.65–7.53 (m, 2H), 7.40 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.25–7.17 (m, 1H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.94, 166.01, 157.81, 142.55, 142.04, 137.97, 136.91, 136.13, 134.60, 134.23, 134.01, 133.41, 133.33, 132.12, 132.06, 130.03, 127.84, 120.82, 75.16. HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{14}Cl_2N_2O_3SNa$ $[M+Na]^+$: 442.9994; Found: 442.9992.

***N*-(4-((3-(2-(3,5-dimethoxybenzoyl)hydrazine-1-carbonyl)benzyl)oxy)phenyl)acetamide (Ui5-15).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 10.50 (s, 1H), 9.80 (s, 1H), 8.00 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 25.4, 8.3 Hz, 3H), 7.09 (d, *J* = 2.1 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.72 (t, *J* = 2.0 Hz, 1H), 5.14 (s, 2H), 3.81 (s, 6H), 3.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.78, 165.72, 165.33, 160.43, 153.93, 137.77, 134.50, 132.90, 132.77, 131.02, 128.68, 126.78, 120.50, 114.85, 105.34, 103.81, 68.99, 55.49, 23.83. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{25}N_3O_6Na$ $[M+Na]^+$: 486.1636; Found: 486.1641.

***N′*-(3-((2,4-dichlorophenoxy)methyl)benzoyl)nicotinohydrazide (Ui5-16).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.69 (s, 1H), 9.12 (s, 1H), 8.82 (d, *J* = 3.8 Hz, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 8.05 (s, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.62 (dd, *J* = 11.7, 3.5 Hz, 3H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.11, 164.93, 153.07, 153.02, 148.90, 137.31, 135.70, 133.20, 131.41, 129.86, 129.28, 128.64, 128.59, 127.41, 127.32, 125.30, 124.19, 123.12, 116.10, 70.44. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{16}Cl_2N_3O_3$ $[M+H]^+$: 416.0563; Found: 416.0561.

***N′*-(3-((2,4-dichlorophenoxy)methyl)benzoyl)-1-methyl-1H-indole-3-carbohydrazide (Ui5-17).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.97 (s, 1H), 8.19–8.08 (m, 2H), 8.02 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.64–7.49 (m, 3H), 7.39 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 17.4, 9.0 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 5.31 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.93, 163.89, 152.66, 136.77, 136.70, 133.18, 132.23, 130.78, 129.43, 128.78, 128.17, 126.95, 126.64, 124.84, 122.67, 122.25, 121.07, 120.99, 115.65, 110.44, 107.22, 70.05, 33.16. HRMS (ESI) m/z calcd. for $C_{24}H_{19}Cl_2N_3O_3Na$ $[M+Na]^+$: 490.0696; Found: 490.0692.

***N′*-(3-((2,4-dichlorophenoxy)methyl)benzoyl)-1-methyl-1H-pyrrole-2-carbohydrazide (Ui5-18).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.99 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 2.5 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.39 (dd, J = 8.9, 2.5 Hz, 1H), 7.28 (d, J = 8.9 Hz, 1H), 6.98 (d, J = 15.3 Hz, 2H), 6.18–5.99 (m, 1H), 5.30 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.89, 160.84, 152.63, 136.77, 133.06, 130.80, 129.42, 128.76, 128.60, 128.15, 126.90, 124.83, 123.26, 122.64, 115.62, 113.31, 107.00, 70.00, 36.27. HRMS (ESI) m/z calcd. for $C_{20}H_{17}Cl_2N_3O_3Na$ $[M+Na]^+$: 440.0539; Found: 440.0538.

***N′*-(3-((2,4-dichlorophenoxy)methyl)benzoyl)pyrimidine-2-carbohydrazide (Ui5-19).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.80 (s, 1H), 8.14 (d, J = 4.6 Hz, 2H), 7.14 (s, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.87 (t, J = 4.6 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.75–6.64 (m, 2H), 6.51 (d, J = 8.7 Hz, 1H), 6.40 (d, J = 8.9 Hz, 1H), 4.43 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.67, 162.27, 158.31, 157.99, 153.13, 137.25, 133.29, 131.33, 129.86, 129.23, 128.59, 127.48, 127.39, 125.34, 123.92, 123.18, 116.18, 70.55. HRMS (ESI) m/z calcd. for $C_{19}H_{14}Cl_2N_4O_3Na$ $[M+Na]^+$: 439.0335; Found: 439.0335.

4-((3-(2-(3,5-dimethoxybenzoyl)hydrazine-1-carbonyl)benzyl)oxy)benzamide (Ui5-20). Prepared according to general procedure A. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 10.51 (s, 1H), 8.02 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 7.13–7.05 (m, 2H), 6.72 (s, 1H), 5.30 (s, 2H), 3.81 (s, 6H). ^{13}C NMR (101 MHz,

DMSO-d_6) δ 165.66, 165.40, 161.70, 160.47, 136.78, 134.50, 134.31, 132.89, 131.24, 128.87, 127.11, 127.02, 119.15, 115.97, 105.37, 103.83, 103.21, 69.29, 55.51. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{24}N_3O_6$ $[M+H]^+$: 450.1660; Found: 450.1663.

3,4,5-trimethoxy-*N*′-(3-(phenoxymethyl)benzoyl)benzohydrazide (Ui5-5-2). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.20 (d, *J* = 4.0 Hz, 1H), 9.76 (d, *J* = 4.2 Hz, 1H), 7.97 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.39–7.26 (m, 2H), 7.16 (s, 2H), 7.03-6.98 (m, 3H), 5.09 (s, 2H), 3.91 (s, 3H), 3.85 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.24, 165.64, 158.66, 153.16, 140.85, 138.16, 133.28, 131.46, 130.01, 129.16, 128.01, 127.24, 121.33, 115.26, 105.41, 69.15, 60.59, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{24}N_2O_6Na$ $[M+Na]^+$: 459.1527; Found: 459.1527.

***N*′-(3-((4-chlorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-3).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.16 (d, *J* = 4.5 Hz, 1H), 9.84 (d, *J* = 4.6 Hz, 1H), 7.97 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.28–7.24 (m, 2H), 7.17(s, 2H), 6.97–6.85 (m, 2H), 5.05 (s, 2H), 3.92 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.18, 165.64, 157.51, 153.15, 140.84, 137.75, 133.29, 131.50, 129.76, 129.20, 128.00, 127.35, 127.28, 125.03, 117.08, 105.41, 69.58, 60.58, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{23}ClN_2O_6Na$ $[M+Na]^+$: 493.1137; Found: 493.1134.

***N*′-(3-((4-fluorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-4).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.21 (s, 1H), 9.84 (s, 1H), 8.01 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.56–7.48 (m, 1H), 7.21 (s, 2H), 7.07–7.05 (m, 2H), 6.98–6.94 (m, 2H), 5.09 (s, 2H), 3.96 (s, 3H), 3.90 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.20, 165.64, 158.04, 156.16, 154.98, 153.15, 140.84, 137.98, 133.28, 131.49, 129.17, 128.00, 127.30, 127.26, 116.61, 116.55, 116.45, 116.27, 105.41, 69.82, 60.59, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{23}FN_2O_6Na$ $[M+Na]^+$: 477.1432; Found: 477.1432.

3,4,5-trimethoxy-*N*′-(3-((p-tolyloxy)methyl)benzoyl)benzohydrazide (Ui5-5-5). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.19 (s, 1H), 9.77 (s, 1H), 7.99 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H),

7.53–7.45 (m, 1H), 7.18 (s, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.92–6.88 (m, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.25, 165.64, 156.54, 153.16, 140.85, 138.31, 133.25, 132.27, 131.39, 130.33, 129.99, 129.12, 128.02, 127.18, 115.13, 105.42, 69.22, 60.58, 56.47, 20.55. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{26}N_2O_6Na$ $[M+Na]^+$: 473.1683; Found: 473.1681.

***N*′-(3-((4-bromophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-6).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.14 (d, *J* = 4.5 Hz, 1H), 9.84 (d, *J* = 4.6 Hz, 1H), 7.98 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.44–7.38 (m, 2H), 7.17 (s, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.06 (s, 2H), 3.93 (s, 3H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.18, 165.64, 157.95, 153.15, 140.85, 137.72, 133.30, 132.65, 131.50, 129.20, 128.00, 127.27, 117.62, 117.59, 112.76, 105.41, 69.52, 60.59, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{23}BrN_2O_6Na$ $[M+Na]^+$: 537.0632; Found: 537.0625.

3,4,5-trimethoxy-*N*′-(3-((4-nitrophenoxy)methyl)benzoyl)benzohydrazide (Ui5-5-7). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.02 (d, *J* = 4.6 Hz, 1H), 9.80 (d, *J* = 4.6 Hz, 1H), 8.25–8.20 (m, 2H), 7.99 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.16 (s, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 5.19 (s, 2H), 3.92 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.13, 165.65, 163.94, 153.15, 141.52, 140.86, 137.02, 133.38, 131.68, 129.31, 127.98, 127.59, 127.45, 126.39, 115.88, 105.41, 70.18, 60.58, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{23}N_3O_8Na$ $[M+Na]^+$: 504.1377; Found: 504.1376.

***N*′-(3-((4-bromo-2-fluorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-8).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.13 (s, 1H), 9.87 (s, 1H), 7.98 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.33–7.24 (m, 2H), 7.17 (s, 2H), 6.89 (t, *J* = 8.5 Hz, 1H), 5.13 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.16, 165.63, 153.15, 151.28, 146.15, 146.07, 140.85, 137.24, 137.21, 133.36, 131.64, 129.47, 129.34, 129.28, 128.94, 128.10, 128.07, 127.99, 127.54, 127.47, 119.92, 119.75, 117.60, 112.01, 111.94, 105.41, 70.48, 60.59, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{22}BrFN_2O_6Na$ $[M+H]^+$: 555.0537; Found: 555.0533.

***N′*-(3-((4-bromo-2,6-difluorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-9).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.12 (d, *J* = 4.5 Hz, 1H), 9.67 (d, *J* = 4.6 Hz, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.17 (s, 2H), 7.10 (d, *J* = 7.3 Hz, 2H), 5.18 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.04, 165.61, 157.02, 156.97, 155.03, 154.98, 153.15, 140.84, 137.05, 134.64, 134.52, 133.25, 132.19, 129.18, 128.08, 127.99, 127.91, 116.92, 116.87, 116.77, 116.71, 114.70, 114.61, 105.41, 75.76, 60.58, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{21}BrF_2N_2O_6Na$ $[M+Na]^+$: 573.0443; Found: 573.0439.

3,4,5-trimethoxy-*N′*-(3-((4-methoxyphenoxy)methyl)benzoyl)benzohydrazide (Ui5-5-10). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.19 (d, *J* = 4.4 Hz, 1H), 9.74 (d, *J* = 4.5 Hz, 1H), 7.96 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.17 (s, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 5.04 (s, 2H), 3.91 (s, 3H), 3.86 (s, 6H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.25, 165.64, 154.01, 153.16, 152.64, 140.85, 138.39, 133.24, 131.39, 129.11, 128.01, 127.17, 116.22, 115.08, 105.42, 69.75, 60.59, 56.47, 55.79. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{26}N_2O_7Na$ $[M+Na]^+$: 489.1632; Found: 489.1633.

***N′*-(3-((2,4-difluorophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-11).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.15 (d, *J* = 4.4 Hz, 1H), 9.82 (d, *J* = 4.5 Hz, 1H), 7.97 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.16 (s, 2H), 7.01–6.85 (m, 2H), 6.81–6.77 (m, 1H), 5.11 (s, 2H), 3.91 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.18, 165.64, 157.19, 157.10, 155.28, 155.20, 153.15, 153.10, 153.00, 151.13, 151.03, 143.30, 143.27, 143.21, 143.19, 140.85, 137.45, 133.34, 131.64, 129.24, 128.00, 127.49, 116.85, 116.83, 116.77, 116.75, 111.42, 111.39, 111.24, 111.21, 105.57, 105.41, 105.35, 105.17, 70.91, 60.58, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{22}F_2N_2O_6Na$ $[M+Na]^+$: 495.1338; Found: 495.1338.

3,4,5-trimethoxy-*N′*-(3-((naphthalen-1-yloxy)methyl)benzoyl)benzohydrazide (Ui5-5-12). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.15 (s, 1H), 9.84 (s, 1H), 8.38–8.31 (m, 1H), 8.05 (s, 1H), 7.91–7.80 (m, 2H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.58–7.42 (m, 4H),

7.37 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.24 (s, 2H), 3.91 (s, 3H), 3.85 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.29, 165.66, 154.05, 153.16, 140.85, 138.16, 134.55, 133.39, 131.31, 129.28, 128.02, 127.99, 127.30, 127.08, 126.99, 126.64, 125.93, 125.45, 122.02, 120.78, 106.31, 105.42, 69.54, 60.59, 56.48. HRMS (ESI) *m*/*z* calcd. for $C_{28}H_{26}N_2O_6Na$ $[M+Na]^+$: 509.1683; Found: 509.1681.

3,4,5-trimethoxy-*N*′-(3-((naphthalen-2-yloxy)methyl)benzoyl)benzohydrazide (Ui5-5-13). Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.22 (d, *J* = 4.7 Hz, 1H), 9.88 (d, *J* = 4.7 Hz, 1H), 8.05 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.85–7.71 (m, 4H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.51–7.45 (m, 2H), 7.43–7.36 (m, 1H), 7.24–7.21 (m, 1H), 7.18 (s, 2H), 5.18 (s, 2H), 3.92 (s, 3H), 3.86 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.24, 165.65, 156.59, 153.16, 140.85, 137.97, 134.66, 133.32, 131.61, 129.89, 129.20, 129.08, 128.02, 127.37, 127.35, 127.18, 126.94, 124.20, 119.23, 107.80, 105.42, 69.38, 60.59, 56.48. HRMS (ESI) *m*/*z* calcd. for $C_{28}H_{26}N_2O_6Na$ $[M+Na]^+$: 509.1683; Found: 509.1681.

***N*′-(3-((2-chloro-4-nitrophenoxy)methyl)benzoyl)-3,4,5-trimethoxybenzohydrazide (Ui5-5-14).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.01 (d, *J* = 4.5 Hz, 1H), 9.85 (d, *J* = 4.6 Hz, 1H), 8.33 (d, *J* = 2.7 Hz, 1H), 8.16 (dd, *J* = 9.1, 2.7 Hz, 1H), 8.00 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.16 (s, 2H), 7.06 (d, *J* = 9.0 Hz, 1H), 5.28 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.14, 165.63, 159.24, 153.15, 141.37, 140.85, 136.60, 133.47, 131.52, 129.38, 127.97, 127.62, 127.47, 125.95, 125.07, 122.52, 114.37, 105.41, 71.08, 60.59, 56.47. HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{22}ClN_3O_8Na$ $[M+Na]^+$: 538.0988; Found: 538.0985.

***N*′-(3-((4-chlorophenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8-1).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.99 (d, *J* = 19.3 Hz, 2H), 8.12 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.67–7.54 (m, 3H), 7.40–7.27 (m, 3H), 7.10 (d, *J* = 8.5 Hz, 2H), 5.25 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.89, 163.79, 163.71, 162.15, 162.07, 157.56, 137.81, 133.00, 130.98, 129.28, 128.77, 126.93, 126.67, 125.29, 116.48, 110.82, 110.78, 110.68, 110.64, 107.22, 107.05, 106.88, 69.44. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{15}ClF_2N_2O_3Na$ $[M+Na]^+$: 439.0631; Found: 439.0628.

***N′*-(3-((2-chlorophenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8-2).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.98 (d, J = 19.1 Hz, 2H), 8.16 (s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.68–7.57 (m, 3H), 7.46 (d, J = 7.8 Hz, 1H), 7.37–7.24 (m, 3H), 7.01 (t, J = 7.6 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.95, 163.79, 163.71, 163.69, 163.67, 162.15, 162.06, 154.11, 137.68, 133.03, 130.83, 130.13, 128.78, 128.09, 126.90, 126.66, 122.52, 121.82, 114.32, 110.82, 110.79, 110.68, 110.64, 107.21, 107.04, 106.87, 69.95. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{15}ClF_2N_2O_3Na$ $[M+Na]^+$: 439.0631; Found: 439.0630.

***N′*-(3-((2-chloro-4-methylphenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8-3).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.98 (d, J = 20.7 Hz, 2H), 8.16 (s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.69–7.54 (m, 3H), 7.40–7.29 (m, 2H), 7.12 (s, 1H), 6.84 (dd, J = 8.0, 1.8 Hz, 1H), 5.32 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.98, 163.79, 163.71, 163.69, 163.67, 162.15, 162.06, 153.81, 138.28, 137.78, 133.00, 130.83, 129.66, 128.75, 126.85, 126.66, 122.42, 119.45, 115.10, 110.82, 110.78, 110.68, 110.64, 107.21, 107.04, 106.87, 69.90, 20.37. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{17}ClF_2N_2O_3Na$ $[M+Na]^+$: 453.0788; Found: 453.0784.

***N′*-(3-((4-cyanophenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8-4).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.03 (d, J = 14.1 Hz, 2H), 8.18 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 8.1 Hz, 3H), 7.65 (t, J = 7.6 Hz, 3H), 7.33 (dd, J = 23.9, 8.7 Hz, 3H), 5.40 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.87, 163.79, 163.74, 163.71, 162.14, 162.06, 162.02, 137.18, 136.29, 134.02, 133.04, 131.13, 128.87, 127.13, 126.84, 118.62, 115.84, 110.82, 110.78, 110.68, 110.64, 107.24, 107.07, 106.90, 104.19, 69.51. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{15}F_2N_3O_3Na$ $[M+Na]^+$: 430.0974; Found: 430.0971.

3,5-difluoro-*N′*-(3-((4-methoxyphenoxy)methyl)benzoyl)benzohydrazide (Ui5-8-5). Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.00 (d, J = 16.2 Hz, 2H), 8.19 (d, J = 24.9 Hz, 1H), 8.04 (dd, J = 25.6, 7.7 Hz, 1H), 7.86–7.56 (m, 4H), 7.38 (t, J = 8.9 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.3 Hz, 2H), 5.23 (d, J = 4.4 Hz, 2H), 3.81 (d, J = 5.0 Hz, 3H). ^{13}C NMR (151 MHz, acetone-d_6) δ

165.94, 163.80, 163.72, 163.68, 162.15, 162.07, 154.24, 152.77, 152.76, 138.53, 138.46, 132.95, 131.82, 130.88, 130.80, 128.85, 128.66, 128.60, 128.48, 126.74, 126.55, 115.80, 115.78, 114.55, 110.82, 110.78, 110.68, 110.64, 107.20, 107.03, 106.86, 69.69, 69.58, 54.93. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{18}F_2N_2O_4Na$ $[M+Na]^+$: 435.1127; Found: 435.1127.

4-((3-(2-(3,5-difluorobenzoyl)hydrazine-1-carbonyl)benzyl)oxy)benzamide (Ui5-8-6). Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.03 (s, 2H), 8.13 (s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 8.1 Hz, 3H), 7.68–7.54 (m, 3H), 7.28 (dd, J = 23.1, 8.8 Hz, 3H), 5.35 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 167.61, 165.23, 163.88, 163.80, 162.23, 162.15, 162.12, 137.17, 135.89, 135.84, 133.82, 132.58, 132.52, 131.07, 128.66, 127.02, 126.50, 118.58, 115.56, 110.64, 110.60, 110.50, 110.46, 106.95, 106.78, 103.79, 69.34. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{18}F_2N_3O_4$ $[M+H]^+$: 426.1260; Found: 426.1261.

3,5-difluoro-*N*′-(3-((4-fluorophenoxy)methyl)benzoyl)benzohydrazide (Ui5-8-7). Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.99 (d, J = 18.8 Hz, 1H), 8.13 (s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.70–7.50 (m, 3H), 7.34 (tt, J = 8.9, 2.4 Hz, 1H), 7.16–7.02 (m, 4H), 5.23 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.94, 163.79, 163.71, 162.14, 162.06, 158.08, 156.52, 155.03, 138.05, 132.95, 131.90, 130.97, 129.00, 128.74, 128.67, 128.56, 126.88, 126.65, 116.13, 116.08, 115.76, 115.61, 110.82, 110.78, 110.68, 110.64, 107.22, 107.05, 106.88, 69.71. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{15}F_3N_2O_3Na$ $[M+Na]^+$: 423.0927; Found: 423.0926.

***N*′-(3-((4-bromo-2-fluorophenoxy)methyl)benzoyl)-3,5-difluorobenzohydrazide (Ui5-8-8).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.99 (d, J = 13.6 Hz, 2H), 8.13 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.70–7.56 (m, 3H), 7.44 (dd, J = 10.8, 2.4 Hz, 1H), 7.39–7.23 (m, 3H), 5.34 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.84, 163.79, 163.71, 163.68, 162.15, 162.06, 153.38, 151.73, 146.26, 146.19, 137.23, 136.35, 133.08, 131.13, 128.84, 127.54, 127.51, 127.15, 126.88, 119.49, 119.35, 117.13, 117.11, 111.89, 111.83, 110.82, 110.78, 110.68, 110.64, 107.22, 107.05, 106.88, 70.50. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{14}BrF_3N_2O_3Na$ $[M+Na]^+$: 501.0032; Found: 501.0022.

***N′*-(3-((2,4-difluorophenoxy)methyl)benzoyl)-3, 5-difluorobenzohydrazide (Ui5-8-9).** Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.00 (d, J = 13.4 Hz, 2H), 8.13 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.72–7.56 (m, 3H), 7.32 (ddq, J = 18.4, 9.3, 5.3, 4.0 Hz, 2H), 7.13 (ddd, J = 11.6, 8.6, 3.0 Hz, 1H), 7.04–6.92 (m, 1H), 5.31 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.91, 163.79, 163.70, 162.14, 162.06, 157.37, 157.30, 155.78, 155.71, 153.37, 153.28, 151.72, 151.64, 143.32, 143.28, 137.50, 136.33, 133.01, 131.15, 128.80, 127.10, 126.89, 116.68, 116.66, 116.61, 116.60, 110.82, 110.78, 110.68, 110.64, 110.61, 110.59, 110.46, 110.44, 107.22, 107.05, 106.88, 104.76, 104.61, 104.58, 104.43, 71.04. HRMS (ESI) m/z calcd. for $C_{21}H_{15}F_4N_2O_3$ $[M+H]^+$: 419.1013; Found: 419.1009.

3,5-difluoro-*N′*-(3-((perfluorophenoxy)methyl)benzoyl)benzohydrazide (Ui5-8-10). Prepared according to general procedure A. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.99 (d, J = 13.6 Hz, 2H), 8.13 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.69–7.57 (m, 3H), 7.34 (tt, J = 9.0, 2.5 Hz, 1H), 5.40 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 165.66, 163.80, 163.72, 163.69, 163.67, 163.65, 163.62, 162.16, 162.07, 142.93, 138.26, 136.51, 136.36, 133.10, 131.97, 128.90, 128.40, 128.04, 127.79, 127.70, 124.54, 110.82, 110.78, 110.68, 110.64, 107.22, 107.05, 106.88, 98.99, 76.46. HRMS (ESI) m/z calcd. for $C_{21}H_{11}F_7N_2O_4Na$ $[M+Na]^+$: 495.0550; Found: 495.0547.

1-(3-((2,4-dichlorophenoxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone-d_6) δ 8.49 (s, 1H), 8.30 (s, 1H), 7.66 (t, J = 1.9 Hz, 1H), 7.51 (dd, J = 8.3, 2.2 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.37–7.28 (m, 2H), 7.27–7.18 (m, 3H), 7.16 (d, J = 7.6 Hz, 1H), 6.59 (tt, J = 9.2, 2.4 Hz, 1H), 5.21 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 164.09, 163.99, 162.48, 162.38, 153.25, 152.07, 142.82, 142.72, 142.63, 139.69, 137.33, 129.51, 129.00, 127.86, 125.31, 123.39, 121.52, 118.49, 117.66, 115.30, 101.21, 101.17, 101.06, 101.01, 98.99, 96.85, 96.67, 96.50, 70.65. HRMS (ESI) m/z calcd. for $C_{20}H_{14}Cl_2F_2N_2O_2Na$ $[M+Na]^+$: 445.0293; Found: 445.0291.

(*E*)-3-((2,4-dichlorophenoxy)methyl)-*N′*-(3,5-difluorobenzylidene)benzohydrazide (Ui5-8-12). Prepared according to general procedure D. ^{1}H NMR (600 MHz, acetone-d_6) δ 11.34 (s, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.46 (d,

J = 2.5 Hz, 1H), 7.43–7.21 (m, 4H), 7.06 (t, *J* = 9.1 Hz, 1H), 5.31 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 164.07, 163.99, 162.44, 162.35, 153.17, 145.14, 138.75, 137.26, 133.96, 130.87, 129.58, 128.80, 127.92, 127.10, 126.91, 125.53, 123.48, 115.37, 109.80, 109.77, 109.66, 109.63, 104.92, 104.76, 104.58, 70.39. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{14}Cl_2F_2N_2O_2Na$ $[M+Na]^+$: 457.0293; Found: 457.0292.

(*E*)-*N*′-(3-((2,4-dichlorophenoxy)methyl)benzylidene)-3,5-difluorobenzohydrazide (Ui5-8-13). Prepared according to general procedure D. ^{1}H NMR (600 MHz, acetone-d_6) δ 11.19 (s, 1H), 8.53 (d, *J* = 6.3 Hz, 1H), 7.90 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.63–7.53 (m, 3H), 7.51–7.44 (m, 2H), 7.34–7.19 (m, 3H), 5.28 (s, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 163.78, 163.76, 163.69, 162.13, 162.12, 162.05, 160.74, 160.71, 153.18, 148.33, 137.39, 134.85, 129.54, 129.20, 129.04, 127.90, 127.17, 126.07, 125.43, 123.44, 115.35, 110.90, 110.86, 110.76, 110.72, 107.01, 106.84, 106.67, 70.35. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{14}Cl_2F_2N_2O_2Na$ $[M+Na]^+$: 457.0293; Found: 457.0291.

2-(3-((2,4-dichlorophenoxy)methyl)phenyl)-5-(3,5-difluorophenyl)-1,3,4-oxadiazole (Ui5-8-14). Prepared according to general procedure D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.93–7.82 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.66–7.60 (m, 2H), 7.42 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 5.37 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.81, 164.34, 164.26, 164.16, 162.89, 162.29, 162.19, 153.02, 138.24, 131.76, 130.24, 129.89, 128.64, 127.06, 126.36, 125.37, 123.74, 123.09, 116.05, 110.81, 110.75, 110.58, 108.30, 108.09, 107.89, 70.13. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{13}Cl_2F_2N_2O_2$ $[M+H]^+$: 433.0317; Found: 433.0306.

(*E*)-3-(3-((2,4-dichlorophenoxy)methyl)phenyl)-1-(3,5-difluorophenyl)prop-2-en-1-one (Ui5-8-15). Prepared according to general procedure D. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.85 (d, *J* = 15.7 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.61 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.56–7.50 (m, 3H), 7.49–7.39 (m, 3H), 7.17 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.04 (tt, *J* = 8.4, 2.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.10, 164.10, 164.00, 162.13, 162.03, 153.12, 145.45, 141.18, 141.12, 137.45, 135.13, 130.70, 129.84, 129.67, 129.35, 129.04, 128.57, 125.26, 123.09, 122.10, 115.92, 112.27, 112.22, 112.11, 112.06, 109.22, 109.01, 108.80, 70.61. HRMS

(ESI) *m*/*z* calcd. for $C_{22}H_{14}Cl_2F_2O_2Na$ $[M+Na]^+$: 441.0231; Found: 441.0217.

1-(3-((2-chlorophenoxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-1). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.50 (s, 1H), 8.32 (s, 1H), 7.65 (m, 1H), 7.53 (dd, J = 8.1, 1.2 Hz, 1H), 7.41 (dd, J = 7.9, 1.6 Hz, 1H), 7.33 (m, 1H), 7.29–7.25 (m, 1H), 7.23 (m, 2H), 7.18 (m, 2H), 6.95 (m, 1H), 6.60 (m, 1H), 5.20 (s, 2H). ^{13}C NMR (151 MHz, acetone) δ 164.90 (d, J = 243.1 Hz), 164.80 (d, J = 243.1 Hz), 155.78, 153.68, 144.35 (t, J = 14.0 Hz), 141.26, 139.38, 131.69, 130.60, 129.68, 123.96, 123.21, 123.10, 119.96, 119.18, 115.75, 102.73 (d, J = 24.2 Hz), 102.68 (d, J = 24.2 Hz), 98.29 (t, J = 26.2 Hz), 71.76. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{15}ClF_2N_2O_2Na$ $[M+Na]^+$: 411.0682; Found:411.0685.

1-(3-((4-chlorophenoxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-2). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.53 (s, 1H), 8.32 (s, 1H), 7.65 (m, 1H), 7.48 (dd, J = 8.1, 1.2 Hz, 1H), 7.33–7.27 (m, 3H), 7.26–7.20 (m, 2H), 7.12 (d, J = 7.8 Hz, 1H), 7.05–7.00 (m, 2H), 6.60 (m, 1H), 5.10 (s, 2H). ^{13}C NMR (151 MHz, acetone) δ 164.89 (d, J = 243.1Hz), 164.78 (d, J = 243.1 Hz), 159.27, 153.70, 144.34 (t, J = 14.1 Hz), 141.25, 139.50, 130.85, 130.56, 126.67, 123.29, 119.91, 119.39, 118.02, 102.72 (d, J = 24.2 Hz), 102.68 (d, J = 24.2 Hz), 98.29 (t, J = 26.2 Hz), 71.38. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{16}ClF_2N_2O_2$ $[M+H]^+$: 389.0863; Found: 389.0861.

1-(3,5-difluorophenyl)-3-(3-((*p*-tolyloxy)methyl)phenyl)urea (Ui5-8-11-3). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.53 (s, 1H), 8.31 (s, 1H), 7.62 (m, 1H), 7.49 (dd, J = 8.1, 1.3 Hz, 1H), 7.30 (m, 1H), 7.26–7.20 (m, 2H), 7.11 (m, 1H), 7.08 (m, 2H), 6.91–6.86 (m, 2H), 6.60 (m, , 1H), 5.05 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (151 MHz, acetone) δ 164.80 (dd, J = 241.6Hz), 164.70 (dd, J = 241.6Hz), 158.39, 153.70, 144.36 (t, J = 13.9 Hz), 141.18, 140.16, 131.41, 131.28, 130.48, 123.19, 119.72, 119.30, 116.21, 102.71(dd, J = 24.2Hz), 102.66(dd, J = 24.2Hz), 98.26 (t, J = 26.2 Hz), 70.99, 21.20. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{18}F_2N_2O_2Na$ $[M+Na]^+$: 391.1229; Found: 391.1233.

1-(3-((4-cyanophenoxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.54 (s,

1H), 8.34 (s, 1H), 7.71 (m, 3H), 7.47 (dd, J = 8.1, 1.3 Hz, 1H), 7.32 (m, 1H), 7.25–7.21 (m, 2H), 7.21–7.16 (m, 2H), 7.14 (m, 1H), 6.60 (m, 1H), 5.21 (s, 2H). ^{13}C NMR (151 MHz, acetone) δ 164.89 (d, J = 243.1 Hz), 164.79 (d, J = 243.1 Hz), 163.76, 153.70, 144.30 (t, J = 13.9 Hz), 141.33, 138.85, 135.62, 130.66, 123.43, 120.32, 120.12, 119.52, 117.42, 105.56, 102.73 (d, J = 24.2 Hz), 102.69 (d, J = 24.2 Hz), 98.32 (t, J = 26.2 Hz), 71.53. HRMS (ESI) m/z calcd. for $C_{21}H_{16}F_2N_3O_2$ $[M+H]^+$: 380.1205; Found: 380.1200.

4-((3-(3-(3,5-difluorophenyl)ureido)benzyl)oxy)-*N*-methylbenzamide (Ui5-8-11-5). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 9.05 (s, 1H), 8.90 (s, 1H), 8.26 (m, 1H), 7.81–7.73 (m, 2H), 7.53 (m, 1H), 7.38–7.33 (m, 1H), 7.27 (m, 1H), 7.15 (m, 2H), 7.04 (m, 1H), 7.02 (m, 2H), 6.75 (m, 1H), 5.10 (s, 2H), 2.71 (d, J = 4.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 167.06, 163.65 (d, J = 243.1 Hz), 163.54 (d, J = 243.1 Hz), 161.42, 153.19, 143.40 (t, J = 13.9 Hz), 140.37, 138.46, 129.98, 129.82, 127.96, 122.57, 119.02, 118.54, 115.27, 101.95 (d, J = 24.2 Hz), 101.91 (d, J = 24.2 Hz), 97.78 (t, J = 26.2 Hz), 70.27, 27.18. HRMS (ESI) m/z calcd. for $C_{22}H_{19}F_2N_3O_3Na$ $[M+Na]^+$: 434.1287; Found: 434.1291.

1-(3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-6). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.56 (s, 1H), 8.35 (s, 1H), 7.67 (m, 1H), 7.53 (dd, J = 8.1, 1.1 Hz, 1H), 7.35 (m, 1H), 7.31–7.25 (m, 2H), 7.15 (m, 1H), 6.78 (m, 1H), 6.69–6.59 (m, 2H), 6.49 (dd, J = 8.5, 2.5 Hz, 1H), 5.97 (s, 2H), 5.07 (s, 2H). ^{13}C NMR (151 MHz, acetone) δ 164.90 (d, J = 243.1 Hz), 164.80 (d, J = 243.1 Hz), 155.92, 153.69, 149.97, 144.36 (t, J = 14.0 Hz), 143.37, 141.19, 140.00, 130.50, 123.25, 119.78 (d, J = 16.4 Hz), 119.36 (d, J = 16.6 Hz), 109.46, 107.70, 102.73 (d, J = 24.2 Hz), 102.67 (d, J = 24.2 Hz), 99.63, 98.28 (t, J = 26.2 Hz), 71.86. HRMS (ESI) m/z calcd. for $C_{21}H_{16}F_2N_2O_4Na$ $[M+Na]^+$: 421.0970; Found: 421.0970.

1-(3,5-difluorophenyl)-3-(3-(((6-methylpyridin-3-yl)oxy)methyl)phenyl)urea (Ui5-8-11-7). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.26 (d, J = 3.0 Hz, 1H), 7.70 (s, 1H), 7.53 (dd, J = 8.1, 1.4 Hz, 1H), 7.39–7.32 (m, 2H), 7.31–7.25 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.65 (m, 1H), 5.19 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (151 MHz, acetone) δ 164.89 (d, J = 243.1 Hz), 164.79 (d, J = 243.1 Hz), 154.56, 153.70, 151.86, 144.34 (t, J = 14.0 Hz), 141.27,

139.50, 138.74, 130.59, 124.66, 123.47, 123.32, 119.94, 119.41, 102.73 (d, J = 24.2 Hz), 102.68(d, J = 24.2 Hz), 98.30 (t, J = 26.3 Hz), 71.40, 24.11. HRMS (ESI) m/z calcd. for $C_{20}H_{18}F_2N_3O_2$ $[M+H]^+$: 370.1362; Found: 370.1426.

1-(3,5-difluorophenyl)-3-(3-((pyrimidin-2-yloxy)methyl)phenyl)urea (Ui5-8-11-8). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 10.34 (s, 1H), 9.73 (s, 1H), 8.61 (dd, J = 3.9, 2.9 Hz, 1H), 8.40 (dd, J = 6.4, 2.7 Hz, 1H), 7.47 (m, 1H), 7.40 (m, 1H), 7.29 (m, 1H), 7.19 (m, 2H), 6.93 (m, 1H), 6.80 (m, 1H), 6.53 (m, 1H), 5.08 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 167.42, 164.70 (d, J = 243.1 Hz), 162.60 (d, J = 243.1 Hz), 156.64, 153.45, 150.96, 143.64 (t, J = 14.3 Hz), 140.66, 138.10, 130.17, 122.38, 118.52, 118.34, 105.16, 101.42 (d, J = 24.2 Hz), 101.37 (d, J = 6.3 Hz), 97.54 (t, J = 27.6 Hz), 54.14. HRMS (ESI) m/z calcd. for $C_{18}H_{14}F_2N_4O_2Na$ $[M+Na]^+$: 379.0977; Found: 379.0989.

1-(3,5-difluorophenyl)-3-(3-((2-oxopyrrolidin-1-yl)methyl)phenyl)urea (Ui5-8-11-9). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.74 (s, 1H), 8.50 (s, 1H), 7.49 (dd, J = 8.1, 1.3 Hz, 1H), 7.38 (m, 1H), 7.26–7.19 (m, 3H), 6.90 (m, 1H), 6.58 (m, 1H), 4.39 (s, 2H), 3.30 (t, J = 7.2 Hz, 2H), 2.33 (t, J = 7.8 Hz, 2H), 1.99 (m, 2H). ^{13}C NMR (151 MHz, acetone) δ 175.85, 164.89 (d, J = 243.1 Hz), 164.79 (d, J = 243.1 Hz), 153.79, 144.48 (t, J = 14.0 Hz), 141.45, 139.68, 130.60, 123.50, 119.60, 119.32, 102.65 (d, J = 24.2 Hz), 102.60 (d, J = 24.2 Hz), 98.15 (t, J = 26.3 Hz), 47.89, 47.45, 31.97, 19.22. HRMS (ESI) m/z calcd. for $C_{18}H_{17}F_2N_3O_2Na$ $[M+Na]^+$: 368.1181; Found: 368.1198.

1-(3,5-difluorophenyl)-3-(3-(pyrrolidin-1-ylmethyl)phenyl)urea (Ui5-8-11-10). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 9.72 (s, 1H), 9.33 (s, 1H), 7.78 (s, 1H), 7.54 (m, 1H), 7.32 (m, 1H), 7.26 (m, 3H), 6.55 (m, 1H), 4.44 (s, 2H), 2.15–2.05 (m, 8H). ^{13}C NMR (151 MHz, acetone) δ 164.83 (d, J = 243.1 Hz), 164.73 (d, J = 243.1 Hz), 153.98, 153.89, 144.35, 141.72, 133.65, 130.96, 125.73, 121.56, 120.72, 102.16 (d, J = 24.2 Hz), 102.11 (d, J = 24.2 Hz), 97.98 (t, J = 24.6 Hz), 55.05, 24.46. HRMS (ESI) m/z calcd. for $C_{18}H_{20}F_2N_3O$ $[M+H]^+$: 332.1569; Found: 332.1630.

1-(3,5-difluorophenyl)-3-(3-(piperidin-1-ylmethyl)phenyl)urea (Ui5-8-11-11).

Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 7.52 (s, 1H), 7.44 (dd, J = 8.1, 1.2 Hz, 1H), 7.24 (m, 2H), 7.20 (m, 1H), 6.98 (m, 1H), 6.60–6.50 (m, 1H), 3.48 (s, 2H), 2.44 (s, 4H), 1.63–1.52 (m, 4H), 1.42 (s, 2H). ^{13}C NMR (151 MHz, acetone) δ 164.81 (d, J = 243.1 Hz), 164.71 (d, J = 243.1 Hz), 153.76, 144.23 (t, J = 13.9 Hz), 140.80, 130.11, 124.92, 120.86, 119.14, 102.48 (d, J = 24.2 Hz), 102.44 (d, J = 24.2 Hz), 98.08 (t, J = 26.2 Hz), 64.58, 55.66, 27.05, 25.48. HRMS (ESI) m/z calcd. for $C_{19}H_{22}F_2N_3O$ $[M+H]^+$: 346.1725; Found: 346.1758.

1-(3-([1,4'-bipiperidin]-1'-ylmethyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-12). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 9.36 (s, 1H), 9.05 (s, 1H), 7.49 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.23 (m, 2H), 6.96 (m, 1H), 6.83 (m, 1H), 3.50 (s, 2H), 3.17–2.90 (m, 6H), 2.08–1.94 (m, 4H), 1.67 (m, 9H). ^{13}C NMR (151 MHz, DMSO) δ 163.67 (d, J = 243.1 Hz), 163.57 (d, J = 243.1 Hz), 153.24, 143.48 (t, J = 14.0 Hz), 140.18, 129.68, 124.00, 119.79, 118.29, 101.77 (d, J = 24.2 Hz), 101.73 (d, J = 24.2 Hz), 97.74 (t, J = 26.1 Hz), 63.61, 62.50, 52.37, 50.12, 26.83, 24.07, 22.74. HRMS (ESI) m/z calcd. for $C_{24}H_{31}F_2N_4O$ $[M+H]^+$: 429.2460; Found: 429.2486.

1-(3,5-difluorophenyl)-3-(3-(morpholinomethyl)phenyl)urea (Ui5-8-11-13). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone) δ 8.50 (s, 1H), 8.25 (s, 1H), 7.51 (m, 1H), 7.44 (dd, J = 8.0, 1.7 Hz, 1H), 7.23 (m, 3H), 6.99 (d, J = 7.5 Hz, 1H), 6.61 (m, 1H), 3.60 (t, J = 4.4 Hz, 4H), 3.45 (s, 2H), 2.39 (s, 4H). ^{13}C NMR (151 MHz, acetone) δ 164.90 (d, J = 243.1 Hz), 164.80 (d, J = 243.1 Hz), 153.71, 144.42 (t, J = 13.9 Hz), 140.96, 140.75, 130.18, 124.88, 120.90, 119.18, 102.68 (d, J = 24.2 Hz), 102.64 (d, J = 24.2 Hz), 98.22 (t, J = 26.2 Hz), 68.18, 64.57, 55.19. HRMS (ESI) m/z calcd. for $C_{18}H_{20}F_2N_3O$ $[M+H]^+$: 348.1518; Found: 348.1582.

1-(3-((4-acetylpiperazin-1-yl)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-14). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 9.05 (s, 1H), 8.87 (s, 1H), 7.43 (m, 1H), 7.33 (dd, J = 8.0, 1.7 Hz, 1H), 7.23 (m, 1H), 7.19 (m, 2H), 6.93 (d, J = 7.5 Hz, 1H), 6.79 (m, 1H), 3.44 (s, 2H), 3.43 (m, 4H), 2.35 (m, 2H), 2.29 (m, 2H), 1.97 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 168.61, 163.12 (d, J = 243.2 Hz), 162.02 (d, J = 243.2 Hz), 152.66, 142.92 (t, J = 13.9 Hz), 139.62, 139.08, 129.13, 123.39, 119.29, 117.74, 101.40 (d, J = 24.2 Hz), 101.36 (d, J = 24.2 Hz), 97.20 (t, J = 26.9 Hz), 62.41, 53.26, 52.75, 46.11, 41.28, 21.66. HRMS (ESI) m/z calcd. for

$C_{20}H_{23}F_2N_4O_2$ $[M+H]^+$: 389.1784; Found: 389.1820.

1-(3,5-difluorophenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)phenyl)urea (Ui5-8-11-15). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 9.33 (s, 1H), 9.06 (s, 1H), 7.44 (m, 1H), 7.37 (m, 1H), 7.24 (m, 3H), 6.94 (m, 1H), 6.82 (m, 1H), 3.44 (s, 2H), 2.39 (s, 8H), 2.19 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 163.69 (d, J = 243.1 Hz), 162.58 (d, J = 243.1 Hz), 153.28, 143.56 (t, J = 13.7 Hz), 140.19, 140.03, 129.61, 123.85, 119.73, 118.13, 101.86 (d, J =24.2 Hz), 101.81 (d, J = 24.2 Hz), 97.67 (t, J = 26.1 Hz), 63.16, 55.66, 53.47, 46.65. HRMS (ESI) m/z calcd. for $C_{19}H_{23}F_2N_4O$ $[M+H]^+$: 361.1834; Found: 361.1830.

1-(3,5-difluorophenyl)-3-(3-(piperazin-1-ylmethyl)phenyl)urea (Ui5-8-11-16). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO) δ 9.25 (s, 1H), 9.02 (s, 1H), 7.44 (m, 1H), 7.36 (m, 1H), 7.31–7.16 (m, 3H), 6.95 (m, 1H), 6.82 (m, 1H), 3.43 (s, 21H), 2.74 (s, 4H), 2.33 (s, 4H). ^{13}C NMR (151 MHz, DMSO) δ 163.68 (d, J = 243.1 Hz), 163.57 (d, J = 243.1 Hz), 153.26, 143.54 (t, J = 14.5 Hz), 140.13, 139.94, 129.57, 123.92, 119.81, 118.11, 101.88 (d, J = 24.2 Hz), 101.85 (d, J = 24.2 Hz), 97.69 (t, J = 25.9 Hz), 63.85, 54.64, 46.34. HRMS (ESI) m/z calcd. for $C_{18}H_{21}F_2N_4O$ $[M+H]^+$: 347.1678; Found: 347.1723.

1-(3-(((4-cyanophenyl)amino)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4-1). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone-d_6) δ 8.50 (s, 1H), 8.28 (s, 1H), 7.57 (m, 1H), 7.46 (m, 3H), 7.30 (m, 1H), 7.28–7.24 (m, 2H), 7.09 (m, 1H), 6.79 (m, 2H), 6.63 (m, 1H), 6.54 (t, J = 5.4 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 164.94 (d, J = 243.1 Hz), 164.84 (d, J = 243.1 Hz), 153.77, 153.73, 144.39 (t, J = 13.9 Hz), 141.54, 141.34, 134.93, 130.63, 123.09, 121.58, 119.30, 119.13, 114.07, 102.76 (d, J = 22.7 Hz), 102.71 (d, J = 22.7 Hz), 99.44, 98.30 (t, J = 26.2 Hz), 48.13. HRMS (ESI) m/z calcd. for $C_{21}H_{16}F_2N_4ONa$ $[M+Na]^+$: 401.1184; Found: 401.1184.

1-(3-(((4-chlorophenyl)amino)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4-2). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone-d_6) δ 8.53 (s, 1H), 8.29 (s, 1H), 7.54 (m, 1H), 7.48 (m, 1H), 7.30–7.23 (m, 3H), 7.12–7.05 (m, 3H), 6.70–6.66 (m, 2H), 6.63 (m, 1H), 5.74 (t, J = 6.3 Hz, 1H), 4.36 (d, J = 5.9 Hz,

2H). ^{13}C NMR (151 MHz, acetone-d_6) δ 164.92 (d, J = 243.1 Hz), 164.82 (d, J = 243.1 Hz), 153.74, 149.32, 144.42 (t, J = 13.6 Hz), 142.40, 141.21, 130.48, 130.25, 123.08, 121.90, 119.12, 119.06, 115.42, 102.71 (d, J = 24.2 Hz), 102.67 (d, J = 24.2 Hz), 98.23 (t, J = 25.7 Hz), 48.83. HRMS (ESI) m/z calcd. for $C_{20}H_{16}F_2N_3ONa$ $[M+Na]^+$: 410.0842; Found: 410.0844.

1-(3-(1-(4-cyanophenoxy)ethyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4-3). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.91 (s, 1H), 7.75-7.70 (m, 2H), 7.62-7.52 (m, 1H), 7.39 -7.34(m, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.27–7.17 (m, 2H), 7.13-7.06 (m, 3H), 6.85–6.77 (m, 1H), 5.71–5.58 (m, 1H), 1.61 (d, J = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.60 (d, J = 243.1 Hz), 163.49 (d, J = 243.1 Hz), 161.89, 153.09, 143.77, 144.32 (t, J = 13.6 Hz), 140.47, 135.02, 130.13, 120.57, 119.98, 118.81, 117.54, 116.35, 103.73, 101.93 (d, J = 24.2 Hz), 101.89 (d, J = 24.2 Hz), 97.72 (t, J = 25.7 Hz), 76.29, 24.90. HRMS (ESI) m/z calcd. for $C_{22}H_{18}F_2N_3O_2$ $[M+H]^+$: 394.1362; Found: 394.1363.

1-(4-((4-cyanophenoxy)methyl)phenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4-4). Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.97 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.22 (m, 4H), 6.82 (t, J = 9.2 Hz, 1H), 5.16 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.64 (d, J = 243.1 Hz), 163.54 (d, J = 243.1 Hz), 162.81, 153.17, 143.38 (t, J = 15.1 Hz), 140.15, 135.15, 130.75, 129.89, 120.13, 119.46, 116.86, 103.87, 101.95 (d, J = 24.2 Hz), 101.91 (d, J = 24.2 Hz), 97.75 (t, J = 27.2 Hz), 70.50. HRMS (ESI) m/z calcd. for $C_{21}H_{16}F_2N_3O_2$ $[M+H]^+$: 380.1205; Found: 380.1205.

1-(2-((4-cyanophenoxy)methyl)phenyl)-3-(3, 5-difluorophenyl)urea (Ui5-8-11-4-5). Prepared according to general procedure B. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 9.49 (s, 1H), 8.28 (s, 1H), 7.85–7.81 (m, 2H), 7.80 (m, 1H), 7.50 (m, 1H), 7.42–7.37 (m, 1H), 7.27–7.23 (m, 2H), 7.23–7.16 (m, 3H), 6.82 (m, 1H), 5.24(s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.63 (d, J = 243.1 Hz), 163.52 (d, J = 243.1 Hz), 162.69, 153.57, 143.40(t, J = 13.6 Hz), 137.81, 135.15, 130.64, 129.87, 128.26, 124.87, 124.36, 120.08, 116.99, 104.11, 101.95 (d, J = 22.7 Hz), 101.91 (d, J = 22.7 Hz), 97.75 (t, J = 25.7 Hz), 67.94. HRMS (ESI) m/z calcd. for $C_{21}H_{16}F_2N_3O_2$ $[M+H]^+$: 380.1205; Found: 380.1205.

***N*-(3,5-difluorophenyl)piperazine-1-carboxamide (Ui5-8-11-4-6).** Prepared according to general procedure C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.31–7.24 (m, 2H), 6.75 (m, 1H), 3.44–3.36 (m, 4H), 2.74–2.69 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.34 (d, J = 241.6 Hz), 163.23 (d, J = 241.6 Hz), 155.29, 144.53 (t, J = 14.2 Hz), 102.57 (d, J = 22.7 Hz), 102.52 (d, J = 22.7 Hz), 97.23 (t, J = 26.2 Hz), 46.47, 45.87. HRMS (ESI) m/z calcd. for $C_{11}H_{14}F_2N_3O$ $[M+H]^+$: 242.1099; Found: 242.1111.

4-benzyl-*N*-(3,5-difluorophenyl)piperazine-1-carboxamide (Ui5-8-11-4-7). Prepared according to general procedure C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.36 (m, 4H), 7.29 (m, 3H), 6.75 (m, 1H), 3.54 (s, 2H), 3.48(t, J = 4.2 Hz, 4H), 2.41 (t, J = 4.2 Hz, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.35 (d, J = 241.6 Hz), 163.24 (d, J = 241.6 Hz), 155.18, 144.41 (t, J = 13.9 Hz), 138.78, 129.88, 129.18, 127.99, 102.62 (d, J = 6.5 Hz), 102.58 (d, J = 6.2 Hz), 97.36 (t, J = 26.5 Hz), 62.87, 53.34, 44.67. HRMS (ESI) m/z calcd. for $C_{18}H_{20}F_2N_3O$ $[M+H]^+$: 332.1569; Found: 332.1597.

4-butyl-*N*-(3,5-difluorophenyl)piperazine-1-carboxamide (Ui5-8-11-4-8). Prepared according to general procedure C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.31–7.23 (m, 2H), 6.74 (m, 1H), 3.47 (m, J = 4.8 Hz, 4H), 2.38 (t, J = 5.4 Hz, 4H), 2.31 (t, J = 7.2Hz, 2H), 1.45 (m, 2H), 1.33 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.32 (d, J = 241.6 Hz), 163.21 (d, J = 241.6 Hz), 155.15, 144.41 (t, J = 14.2 Hz), 102.57 (d, J = 24.2 Hz), 102.53 (d, J = 24.2 Hz), 97.28 (t, J = 26.2 Hz), 58.41, 53.57, 44.65, 29.31, 21.02, 14.83. HRMS (ESI) m/z calcd. for $C_{15}H_{22}F_2N_3O$ $[M+H]^+$: 298.1725; Found: 298.1781.

1-benzyl-1-(4-butylphenyl)-3-(3,5-difluorophenyl)urea (Ui5-8-11-4-9). Prepared according to general procedure B. ^{1}H NMR (600 MHz, acetone-d_6) δ 7.74 (s, 1H), 7.32 (m, 4H), 7.28–7.23 (m, 5H), 7.19 (m, 2H), 6.59 (m, 1H), 4.97 (s, 2H), 2.65(t, J = 7.8 Hz, 2H), 1.67–1.57 (m, 2H), 1.40 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, acetone-d_6) δ 164.66 (d, J = 243.11 Hz), 164.56 (d, J = 243.11 Hz), 155.73, 144.65 (t, J = 14.0 Hz), 143.89, 140.33, 140.20, 131.33, 129.83, 129.71, 129.61, 128.66, 103.42 (d, J = 24.2 Hz), 103.38 (d, J = 24.2 Hz), 98.16 (t, J = 26.2 Hz), 54.71, 36.48, 34.94, 23.76, 14.95. HRMS (ESI) m/z calcd. for $C_{24}H_{25}F_2N_2O$ $[M+H]^+$: 395.1929;

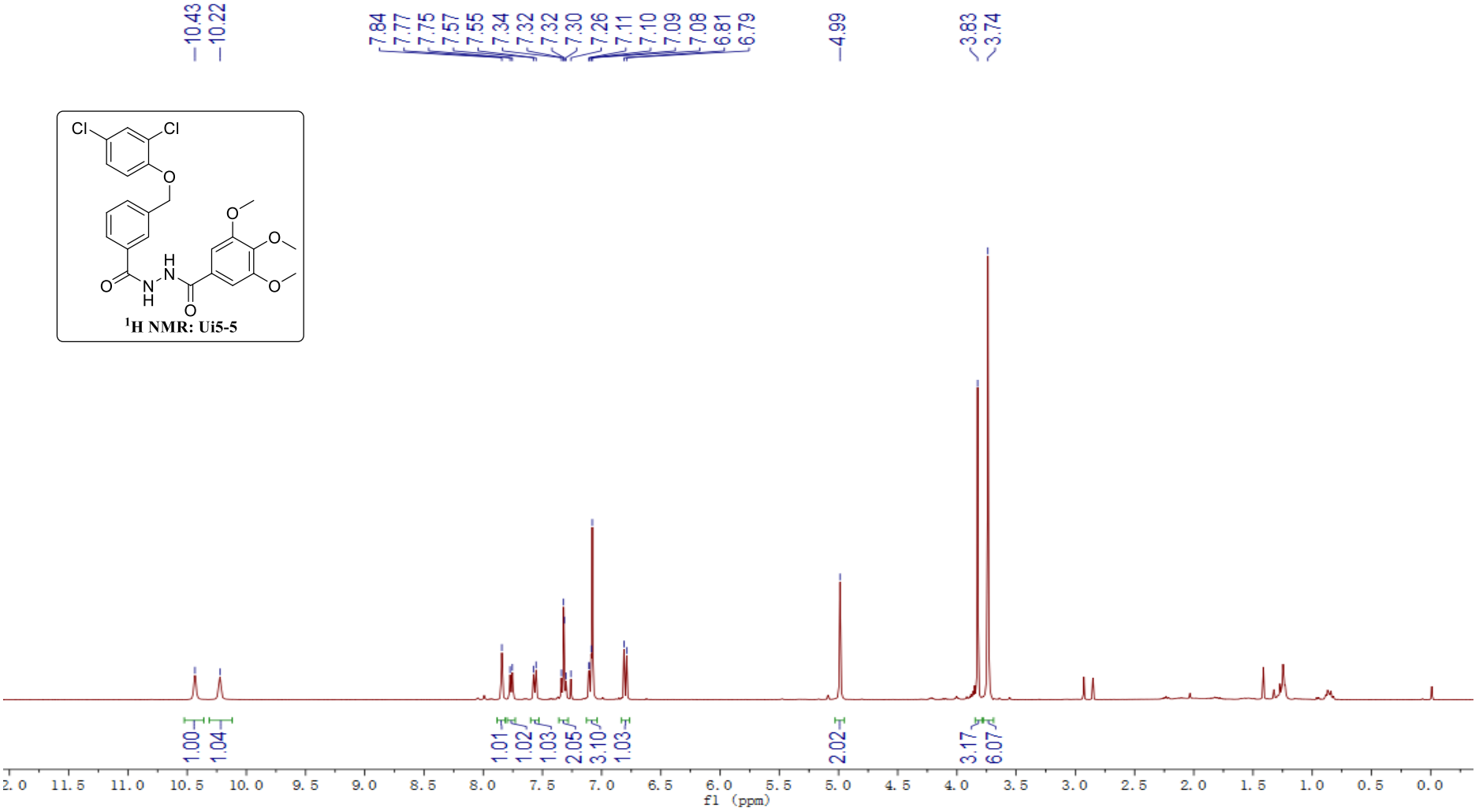
Found: 395.1956.

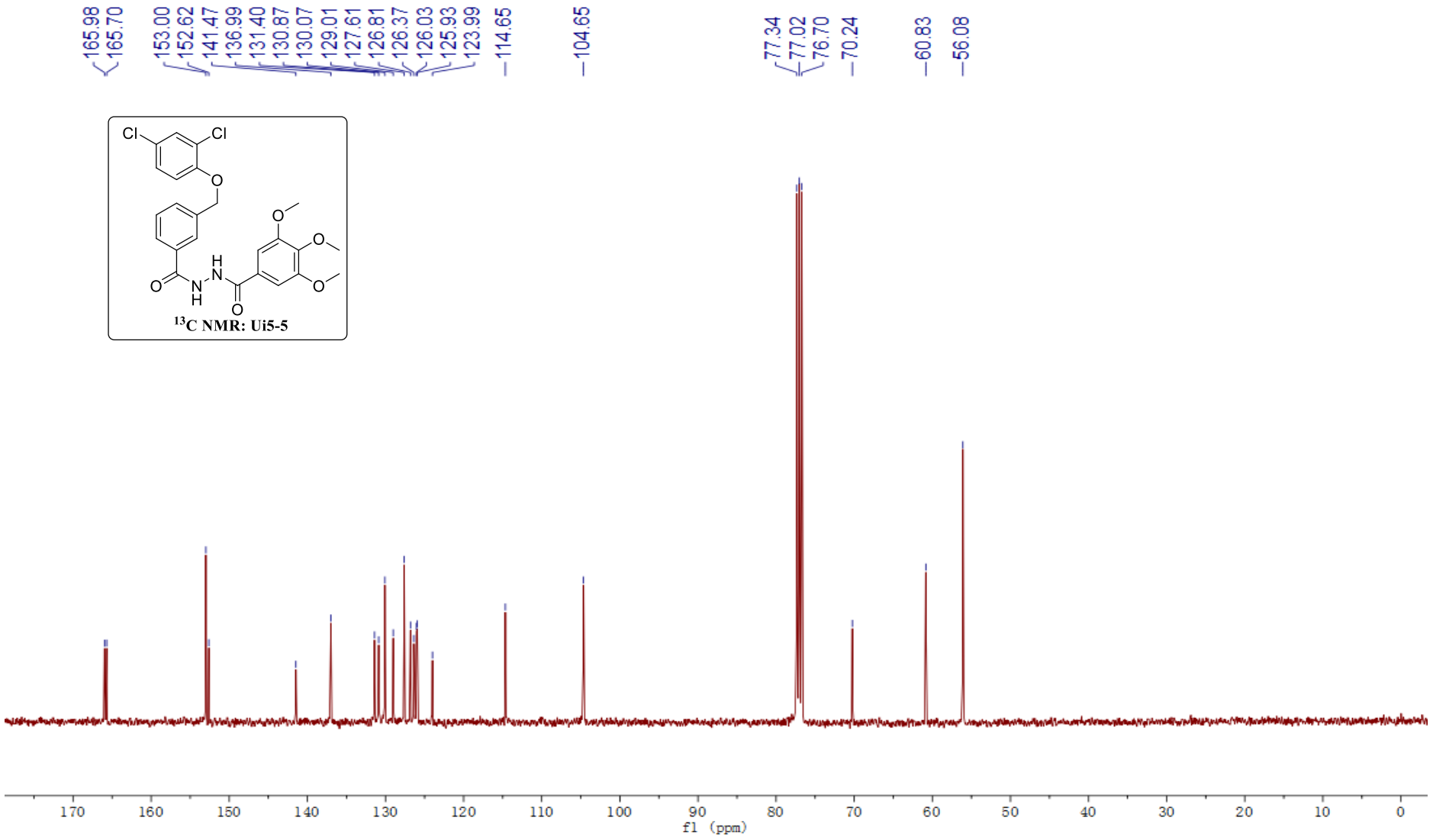
***N*-(3-((4-cyanophenoxy)methyl)-5-(3-(3,5-difluorophenyl)ureido)phenyl)acetamide (Ui5-8-11-4-10).** Prepared according to general procedure B. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.01 (s, 1H), 8.99 (s, 1H), 7.82 (m, 2H), 7.77 (s, 1H), 7.33 (m, 2H), 7.21 (m, 4H), 6.86–6.78 (m, 1H), 5.20 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.42, 163.61 (d, J = 243.11 Hz), 163.51 (d, J = 243.11 Hz), 162.68, 153.02, 143.29 (t, J = 14.1 Hz), 140.93, 140.62, 138.21, 135.16, 120.04, 116.85, 112.96, 112.88, 109.50, 103.99, 101.89 (d, J = 24.2 Hz), 101.85 (d, J = 24.2 Hz), 97.74 (t, J = 26.6 Hz), 70.68, 24.98. HRMS (ESI) m/z calcd. for $C_{23}H_{18}F_2N_4O_3Na$ $[M+Na]^+$: 459.1239; Found: 459.1246.

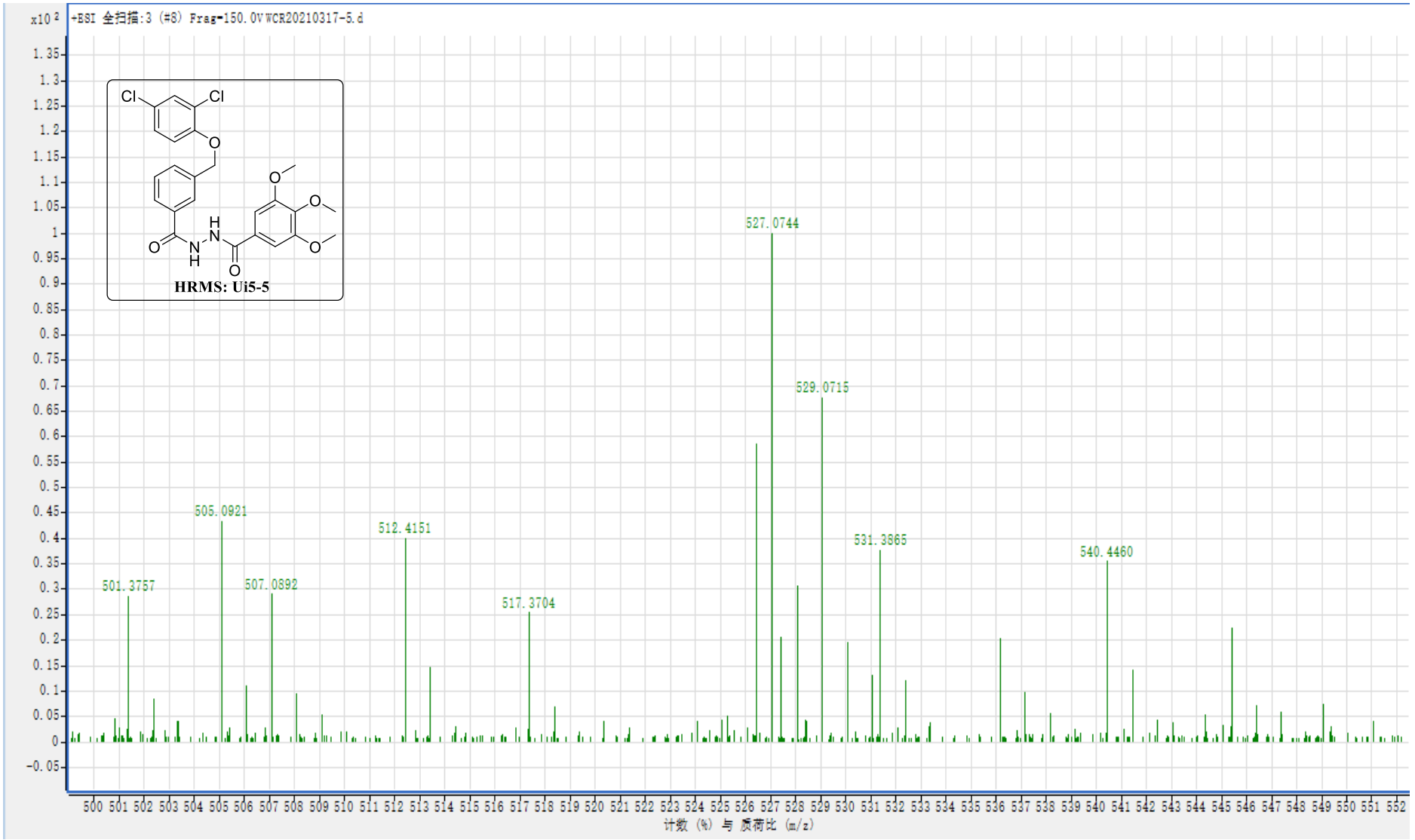
2-benzyl-*N*-(3,5-difluorophenyl)piperazine-1-carboxamide (Ui5-8-11-4-11). Prepared according to general procedure C. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.35 (m, 2H), 7.31–7.22 (m, 3H), 6.55 (m, 2H), 6.37 (m, 1H), 5.72 (s, 1H), 4.09–3.99 (m, 2H), 3.29–3.18 (m, 2H), 3.09–3.05 (m, 1H), 3.00 (d, J = 12.1 Hz, 1H), 2.92 (m, 2H), 2.79 m, 1H), 1.65 (s, 1H). ^{13}C NMR (151 MHz, chloroform-*d*) δ 163.14 (d, J = 244.6 Hz), 163.05 (d, J = 244.6 Hz), 154.50, 141.64 (t, J = 13.6 Hz), 139.18, 129.33, 127.27, 102.39 (d, J = 24.2 Hz), 102.35 (d, J = 24.2 Hz), 97.73 (t, J = 25.7 Hz), 55.66, 49.32, 46.30, 39.71, 35.76. HRMS (ESI) m/z calcd. for $C_{18}H_{20}F_2N_3O$ $[M+H]^+$: 332.1569; Found: 332.1584.

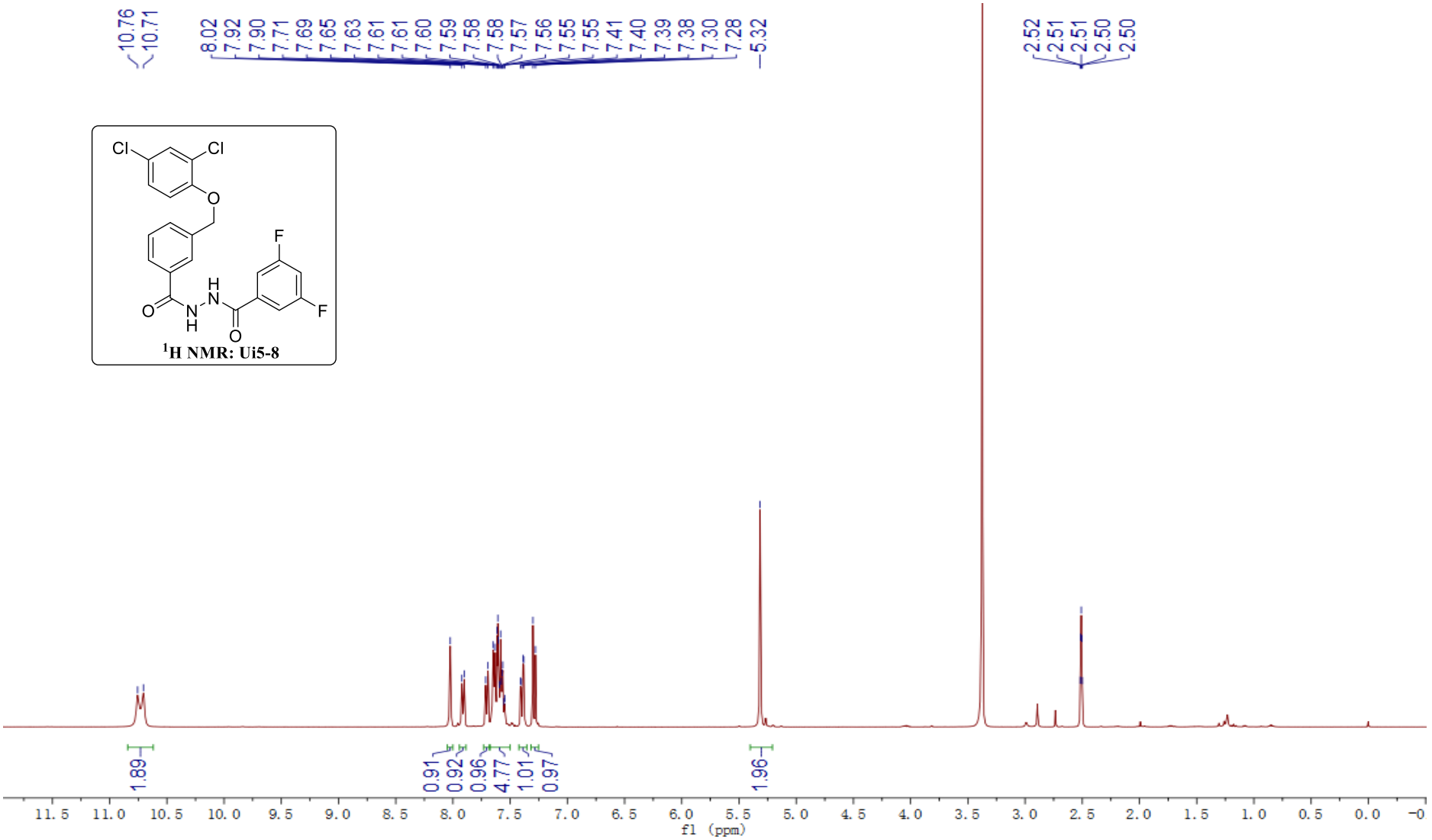
2-benzyl-4-butyl-*N*-(3,5-difluorophenyl)piperazine-1-carboxamide (Ui5-8-11-4-12). Prepared according to general procedure C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42–7.33 (m, 2H), 7.30 (m, 3H), 6.66 (m, 2H), 6.42 (m, 1H), 6.14 (s, 1H), 4.20–3.99 (m, 2H), 3.35 (td, J = 12.6, 3.1 Hz, 1H), 3.25–3.15 (m, 1H), 3.02 (dd, J = 13.2, 6.4 Hz, 1H), 2.89 (dd, J = 17.7, 11.5 Hz, 2H), 2.40 (m, 1H), 2.34–2.23 (m, 1H), 2.13–2.01 (m, 2H), 1.51 (m, 2H), 1.46–1.37 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 163.10 (d, J = 245.4 Hz), 162.96 (d, J = 245.4 Hz), 154.40, 141.69 (t, J = 13.5 Hz), 139.34, 129.35, 129.10, 127.01, 102.50 (d, J = 21.2 Hz), 102.42 (d, J = 21.2 Hz), 97.65 (t, J = 25.7 Hz), 58.18, 55.79, 55.48, 53.48, 39.51, 36.52, 29.00, 20.66, 14.12. HRMS (ESI) m/z calcd. for $C_{22}H_{28}F_2N_3O$ $[M+H]^+$: 388.2195; Found: 388.2256.

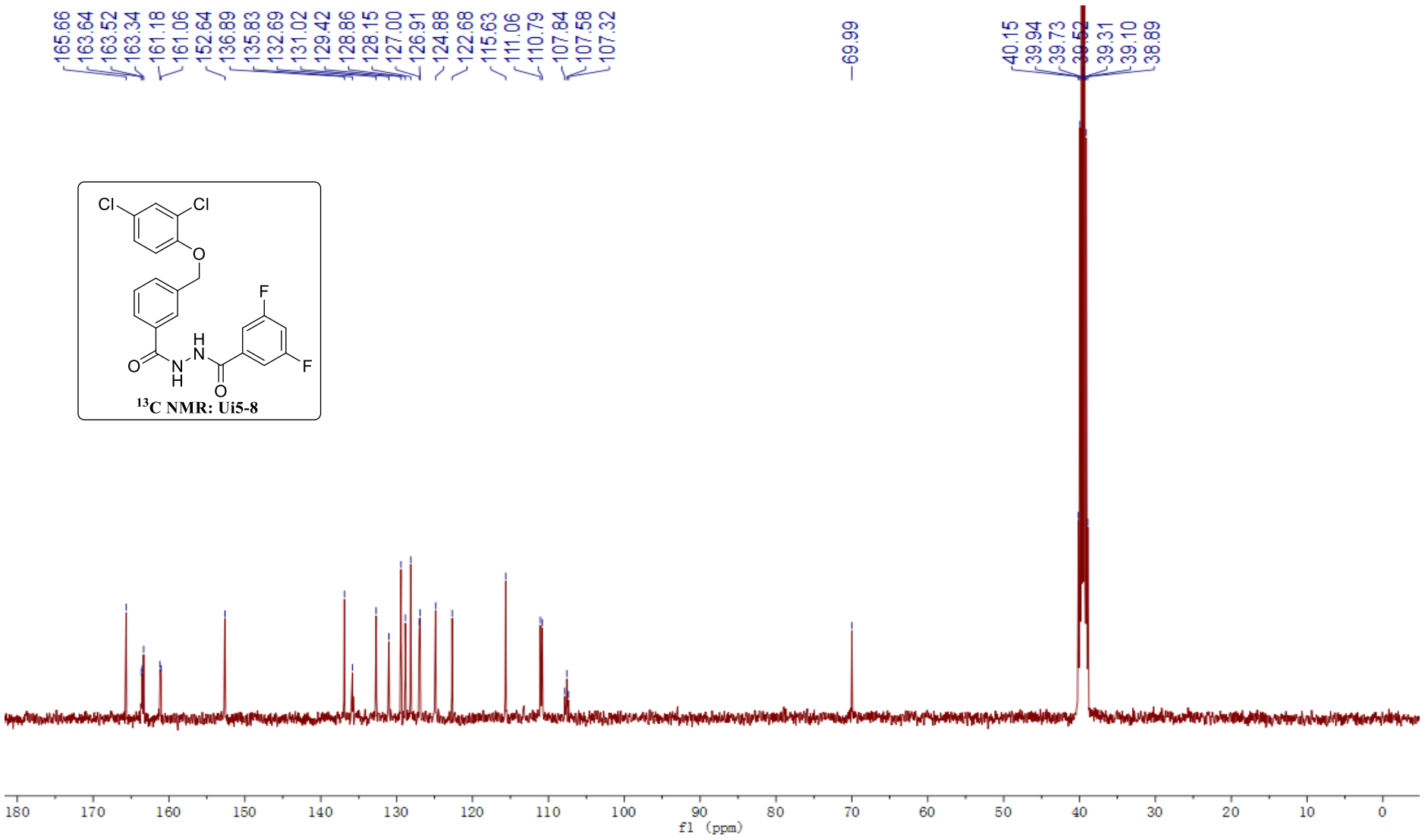
Spectra of key compounds

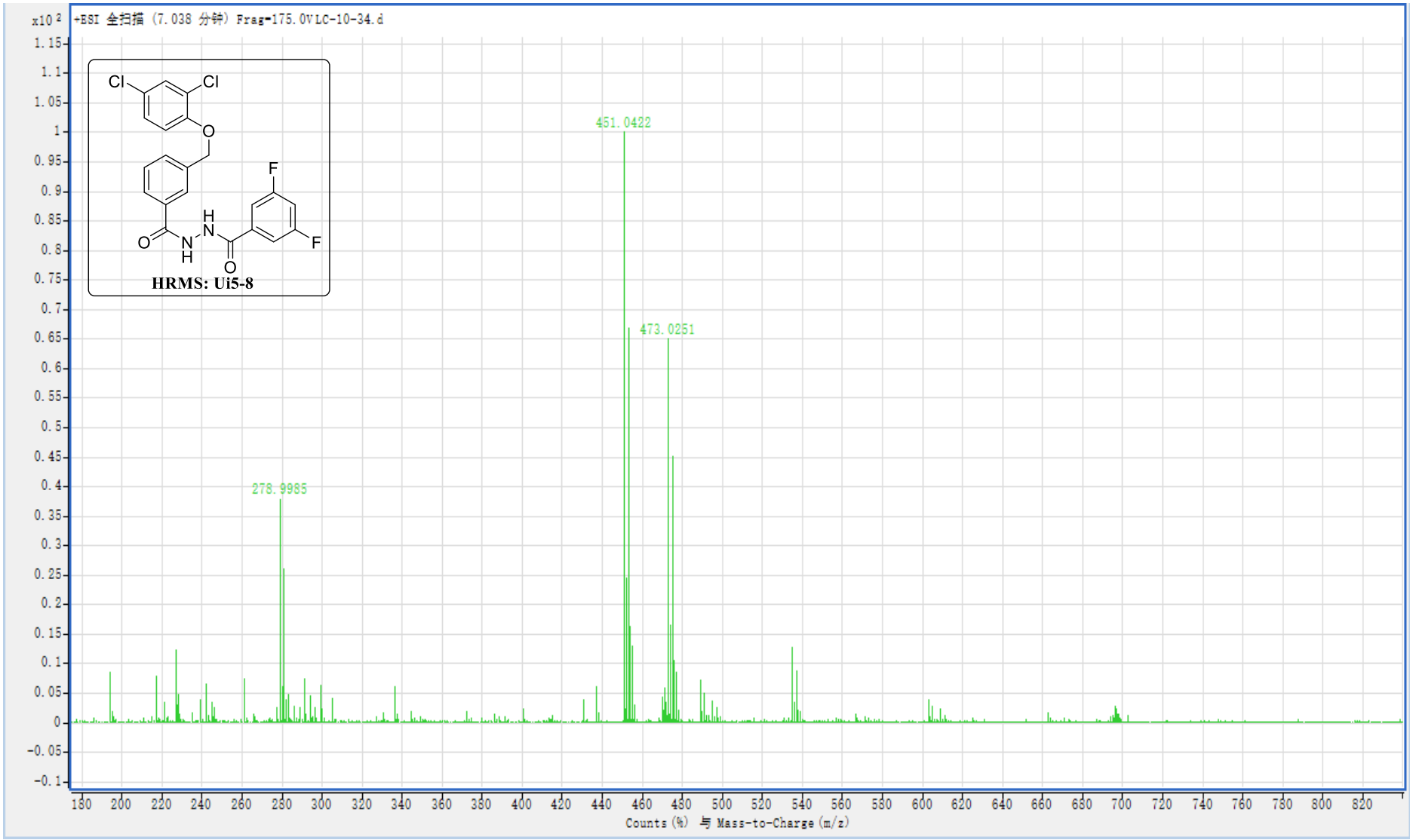


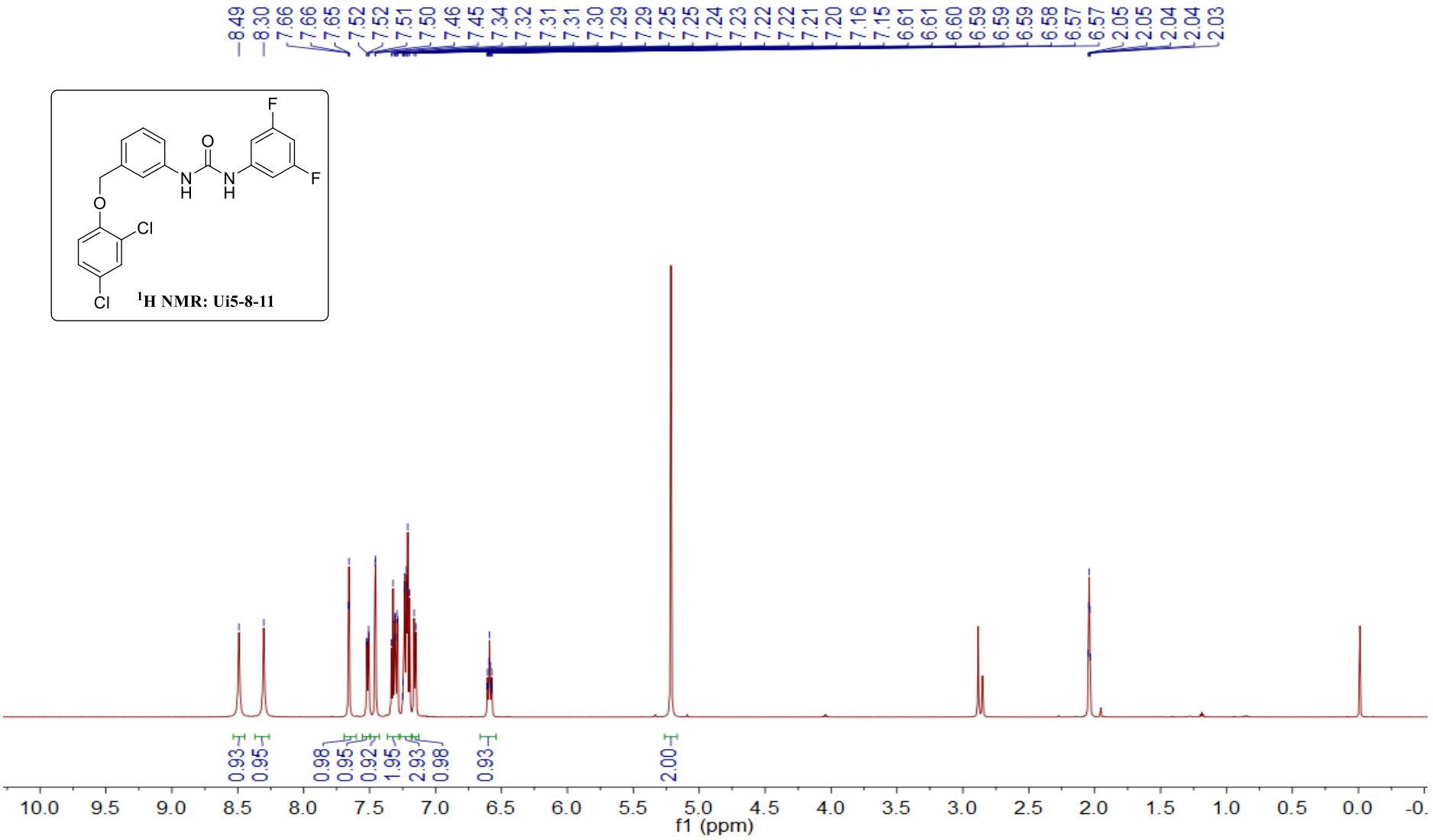

165.98
165.70
153.00
152.62
141.47
136.99
131.40
130.87
130.07
129.01
127.61
126.81
126.37
126.03
125.93
123.99
114.65
104.65
77.34
77.02
76.70
70.24
60.83
56.08
Cl
Cl
O
O
H
N
N
O
O
O
O
O
13C NMR: Ui5-5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

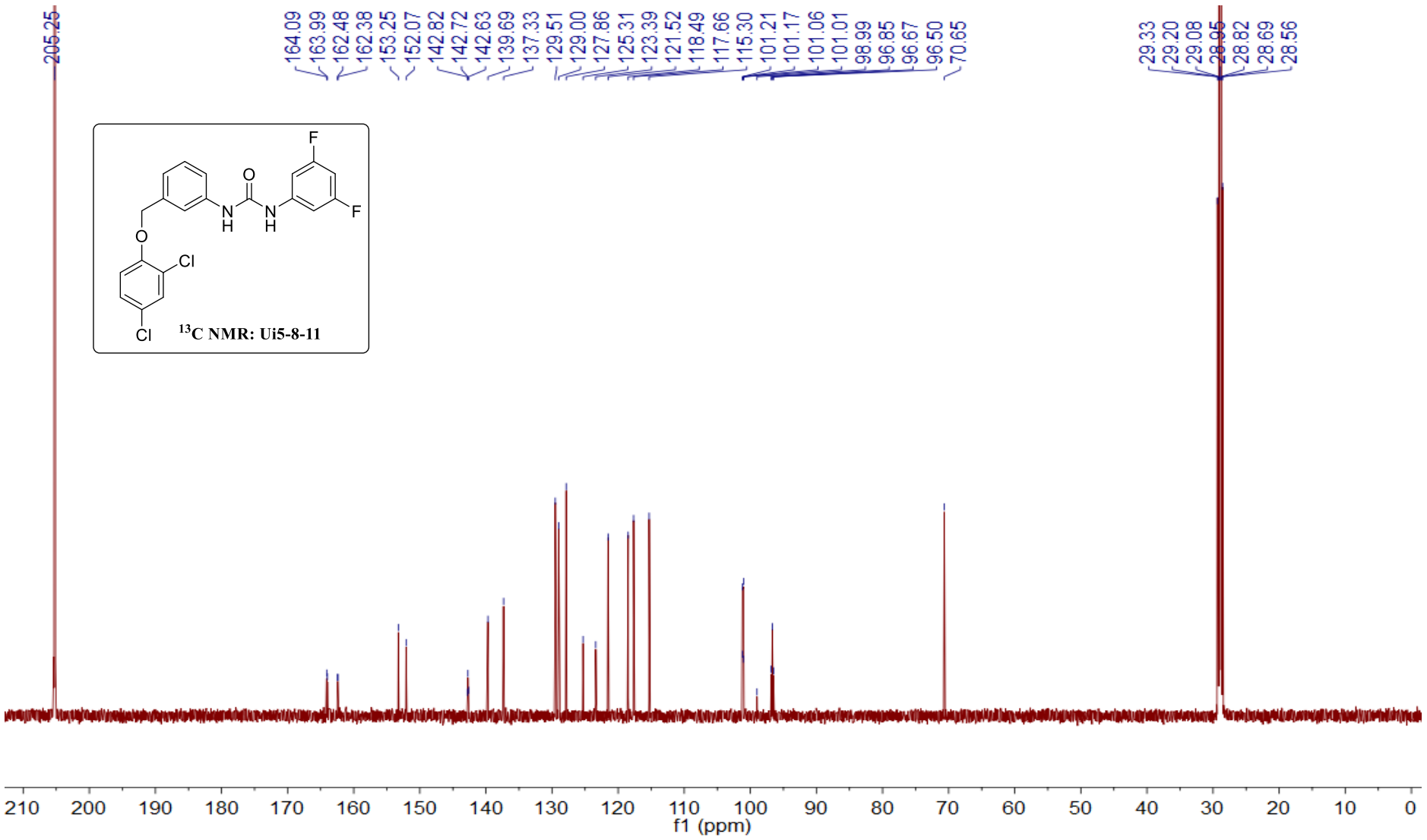

x10 2
+BSI 全扫描:3 (#8) Frag=150.0V WCR20210317-5.d
HRMS: Ui5-5
527.0744
529.0715
505.0921
512.4151
531.3865
540.4460
501.3757
507.0892
517.3704
计数 (%) 与 质荷比 (m/z)

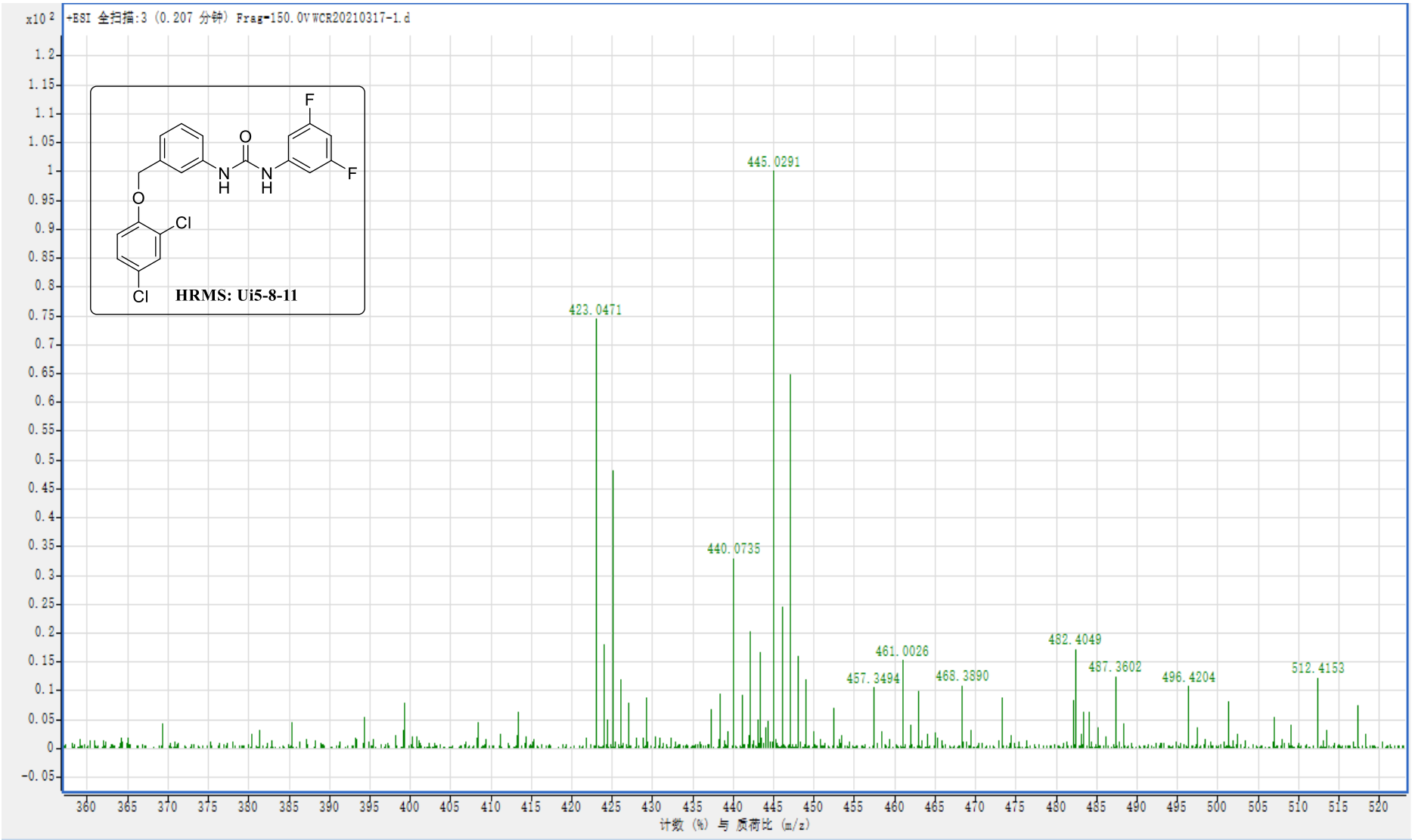

10.76
10.71
8.02
7.92
7.90
7.71
7.69
7.65
7.63
7.61
7.61
7.60
7.59
7.58
7.58
7.57
7.56
7.55
7.55
7.41
7.40
7.39
7.38
7.30
7.28
5.32
2.52
2.51
2.51
2.50
2.50
Cl
Cl
O
F
H
N
N
O
H
F
O
1H NMR: Ui5-8
1.89
0.91
0.92
0.96
4.77
1.01
0.97
1.96
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0
f1 (ppm)

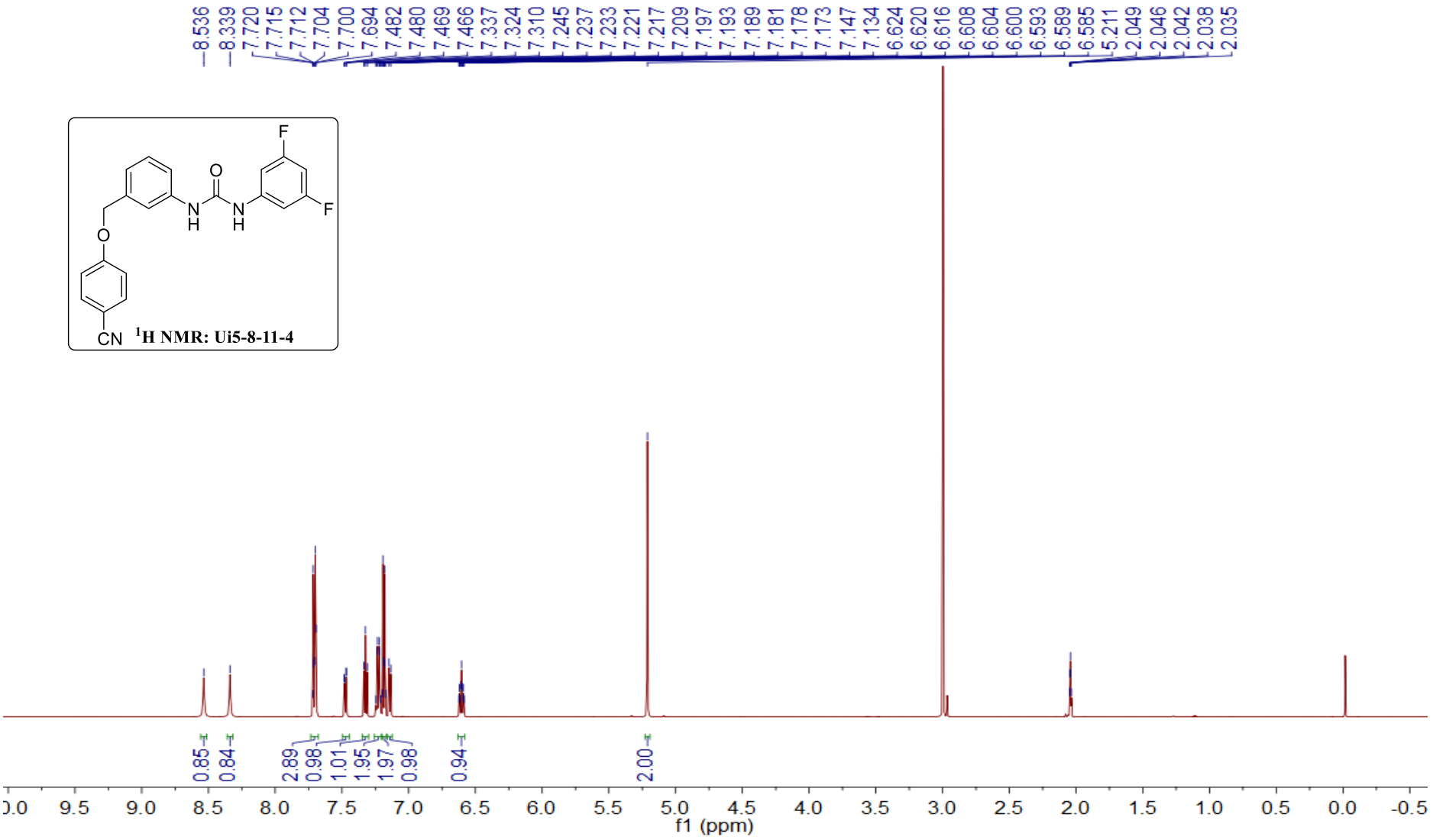

165.66
163.64
163.52
163.34
161.18
161.06
152.64
136.89
135.83
132.69
131.02
129.42
128.86
128.15
127.00
126.91
124.88
122.68
115.63
111.06
110.79
107.84
107.58
107.32
69.99
40.15
39.94
39.73
39.52
39.31
39.10
38.89
Cl
Cl
O
F
H
N
N
H
O
F
O
13C NMR: Ui5-8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

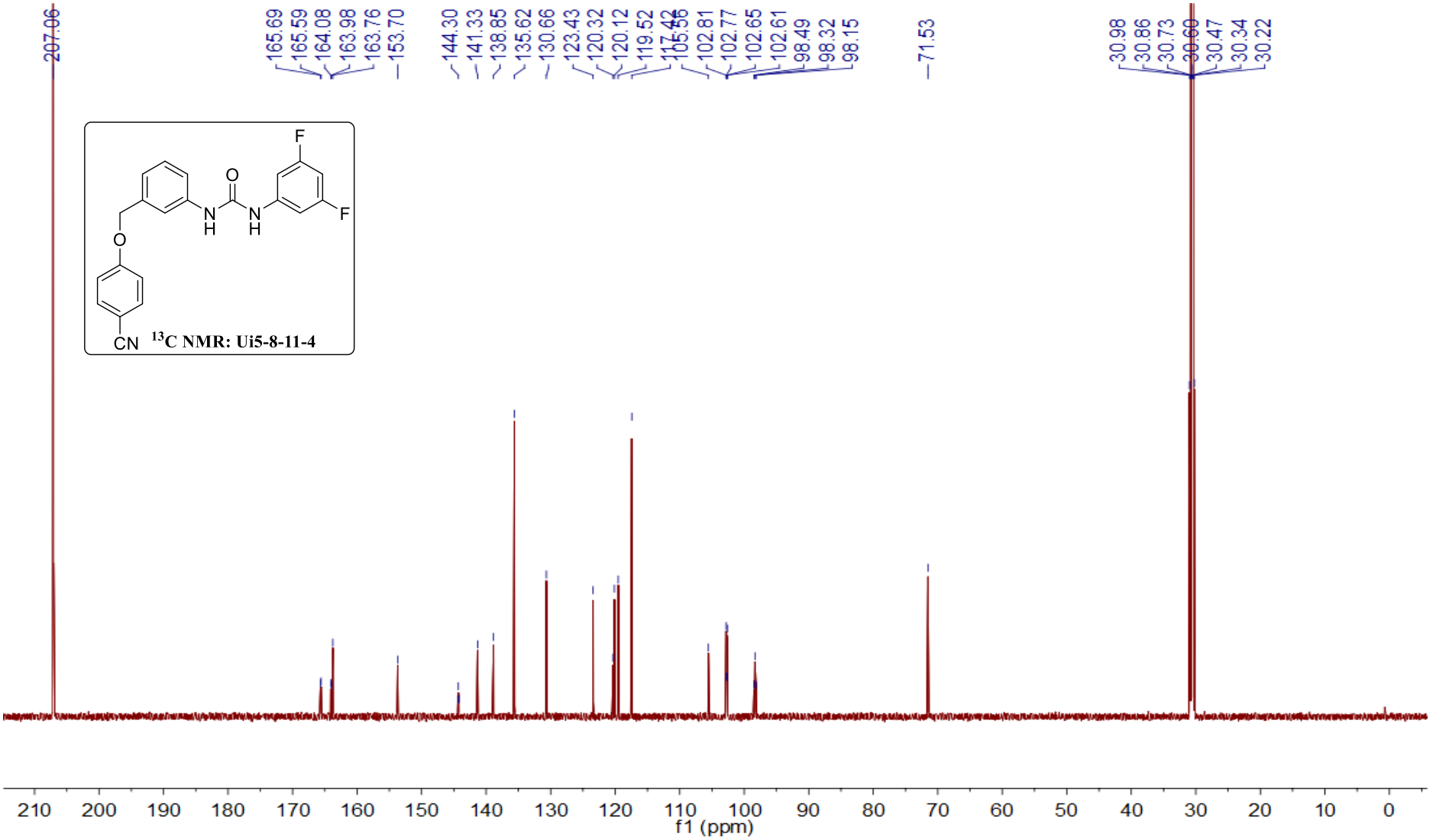

+BSI 全扫描 (7.038 分钟) Frag=175.0VLC-10-34.d
x10 2
HRMS: Ui5-8
451.0422
473.0251
278.9985
Counts (%) 与 Mass-to-Charge (m/z)

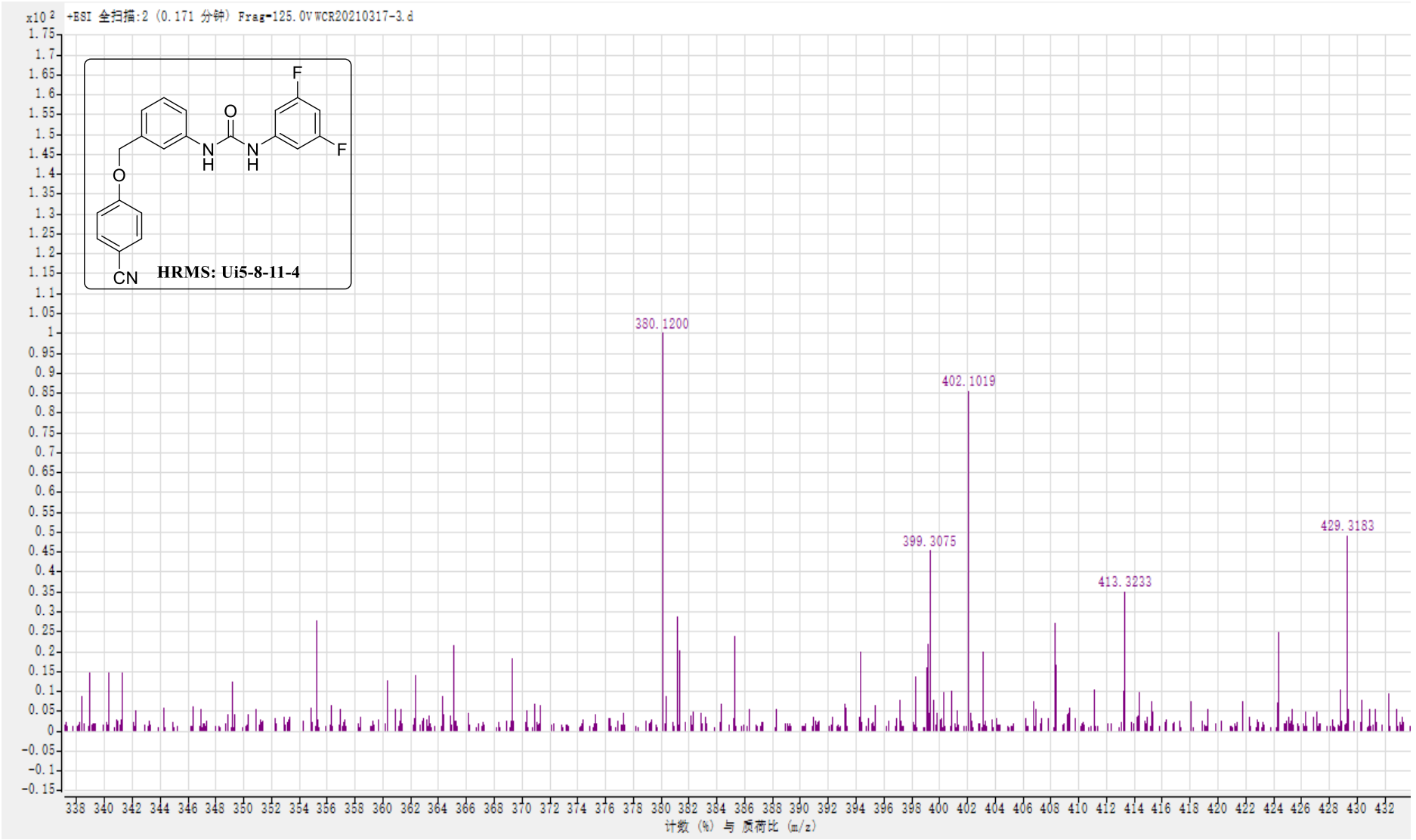

8.49
8.30
7.66
7.66
7.65
7.52
7.52
7.51
7.50
7.46
7.45
7.34
7.32
7.31
7.31
7.30
7.29
7.29
7.25
7.25
7.24
7.23
7.22
7.22
7.21
7.20
7.16
7.15
6.61
6.61
6.60
6.59
6.59
6.59
6.58
6.57
6.57
2.05
2.05
2.04
2.04
2.03
F
O
N
H
N
H
F
O
Cl
Cl
1H NMR: Ui5-8-11
0.93
0.95
0.98
0.95
0.92
1.95
2.93
0.98
0.93
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

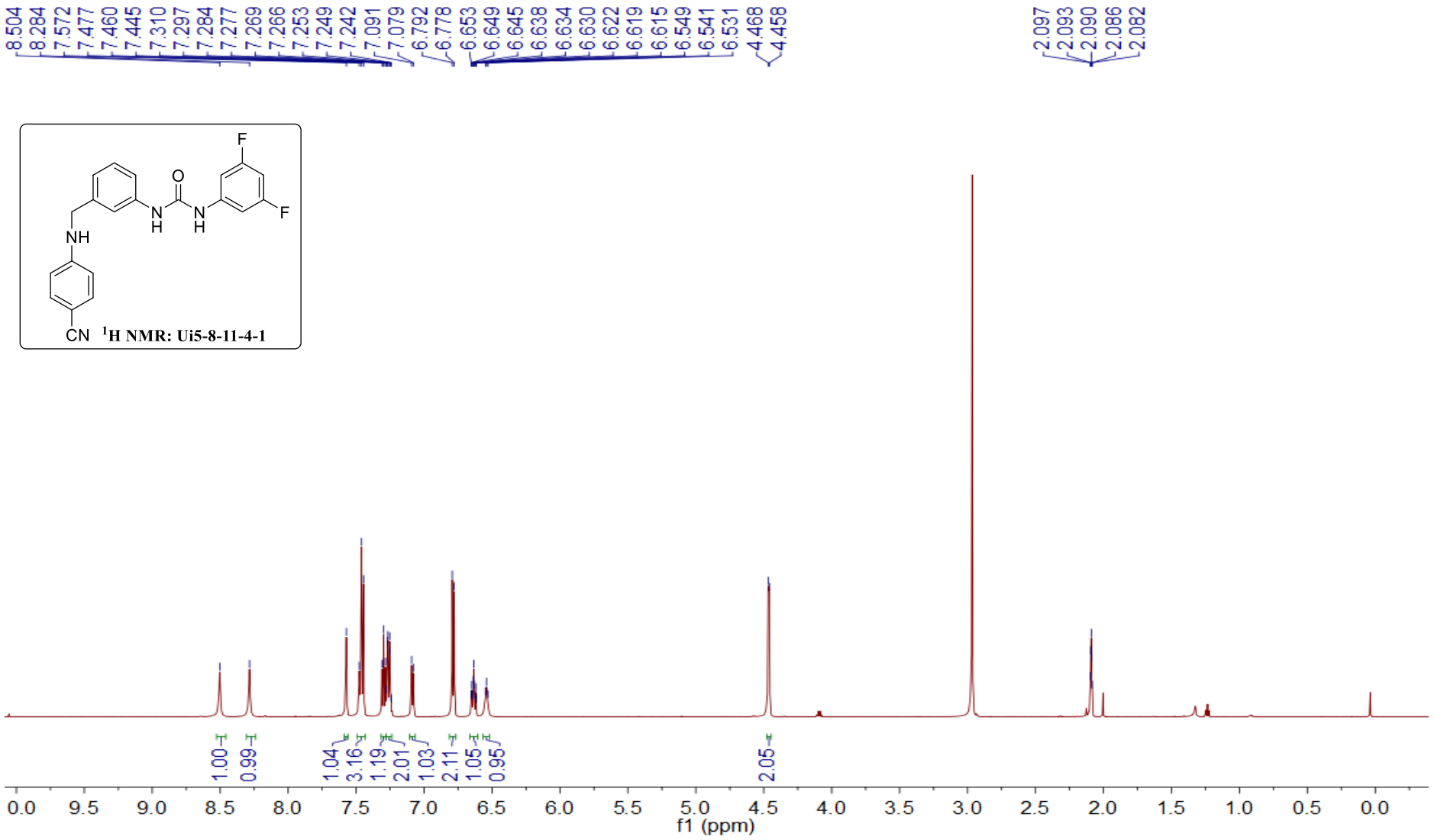

205.25
164.09
163.99
162.48
162.38
153.25
152.07
142.82
142.72
142.63
139.69
137.33
129.51
129.00
127.86
125.31
123.39
121.52
118.49
117.66
115.30
101.21
101.17
101.06
101.01
98.99
96.85
96.67
96.50
70.65
29.33
29.20
29.08
28.95
28.82
28.69
28.56
F
O
N
H
N
H
F
O
Cl
Cl
13C NMR: Ui5-8-11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

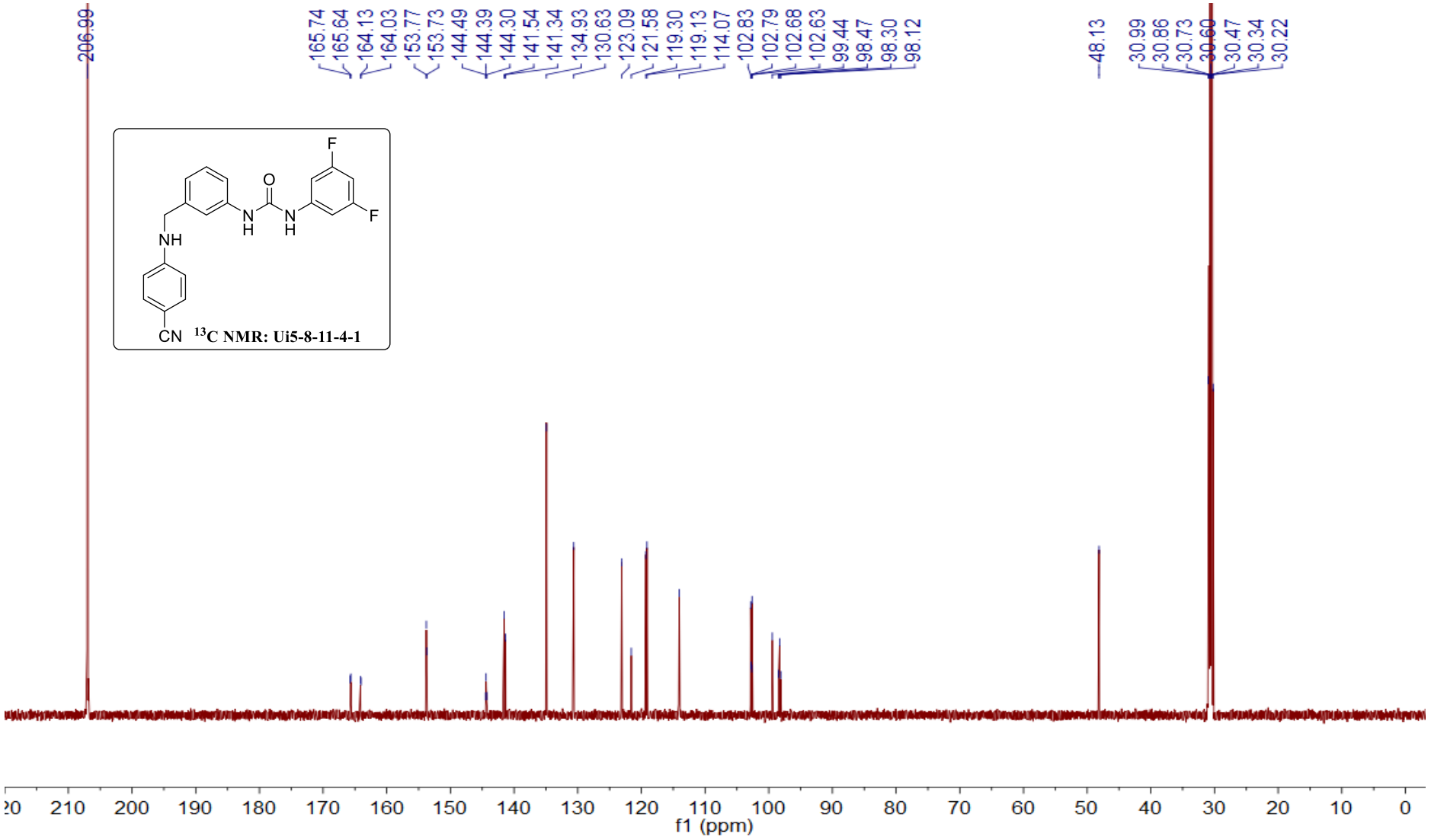

+ESI 全扫描:3 (0.207 分钟) Frag=150.0V WCR20210317-1.d
x10 2
HRMS: Ui5-8-11
445.0291
423.0471
440.0735
461.0026
457.3494
468.3890
482.4049
487.3602
496.4204
512.4153
计数 (%) 与 质荷比 (m/z)

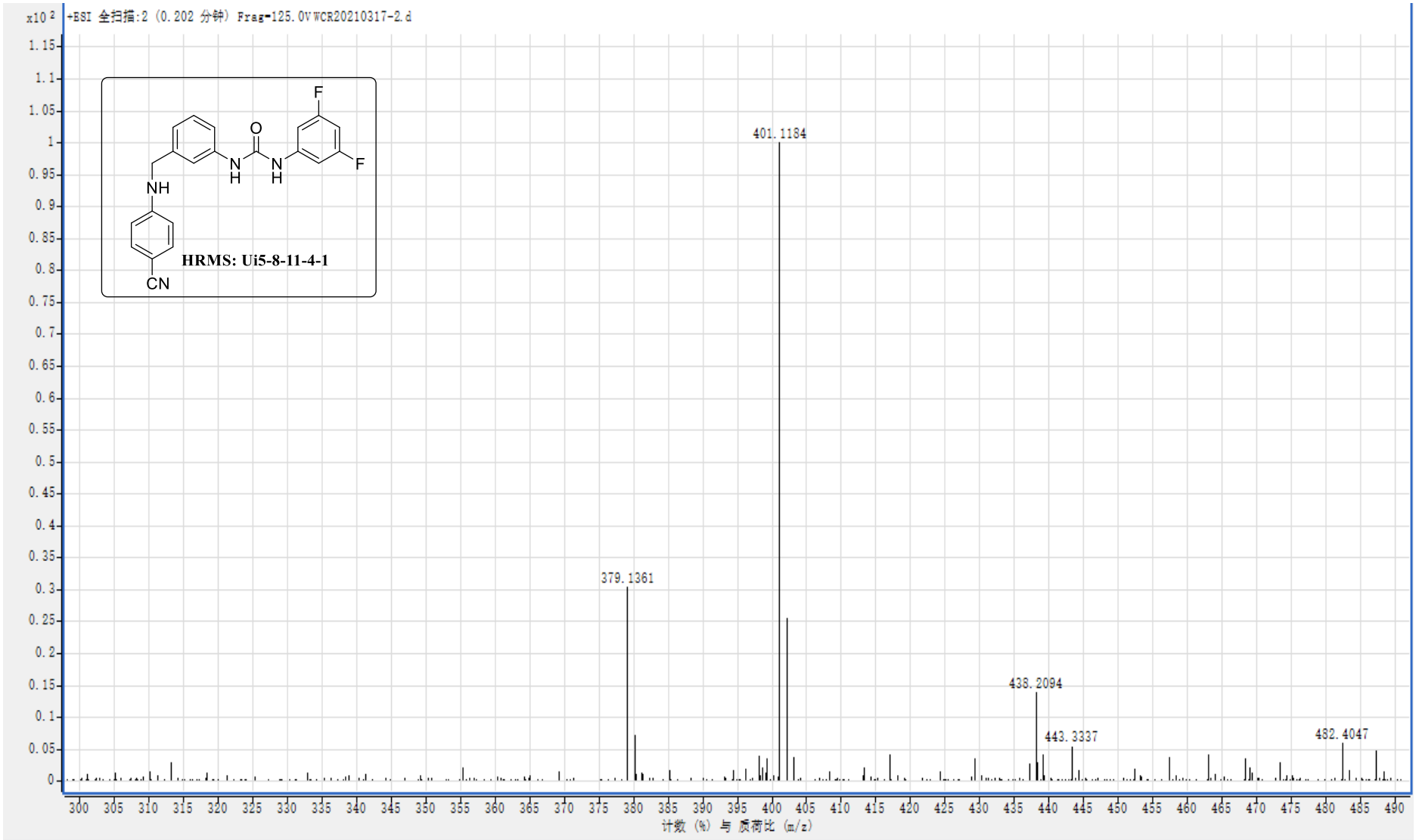

8.536
8.339
7.720
7.715
7.712
7.704
7.700
7.694
7.482
7.480
7.469
7.466
7.337
7.324
7.310
7.245
7.237
7.233
7.221
7.217
7.209
7.197
7.193
7.189
7.181
7.178
7.173
7.147
7.134
6.624
6.620
6.616
6.608
6.604
6.600
6.593
6.589
6.585
5.211
2.049
2.046
2.042
2.038
2.035
F
O
N
H
N
H
F
O
CN
1H NMR: Ui5-8-11-4
0.85
0.84
2.89
0.98
1.01
1.95
1.97
0.98
0.94
2.00
f1 (ppm)


207.06
165.69
165.59
164.08
163.98
163.76
153.70
144.30
141.33
138.85
135.62
130.66
123.43
120.32
120.12
119.52
117.42
115.56
102.81
102.77
102.65
102.61
98.49
98.32
98.15
71.53
30.98
30.86
30.73
30.60
30.47
30.34
30.22
F
O
N
H
N
H
F
O
CN
13C NMR: Ui5-8-11-4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


x10 2
+ESI 全扫描:2 (0.171 分钟) Frag=125.0V WCR20210317-3.d
HRMS: Ui5-8-11-4
380.1200
402.1019
399.3075
413.3233
429.3183
计数 (%) 与 质荷比 (m/z)


8.504
8.284
7.572
7.477
7.460
7.445
7.310
7.297
7.284
7.277
7.269
7.266
7.253
7.249
7.242
7.091
7.079
6.792
6.778
6.653
6.649
6.645
6.638
6.634
6.630
6.622
6.619
6.615
6.549
6.541
6.531
4.468
4.458
2.097
2.093
2.090
2.086
2.082
F
O
N
H
N
H
F
NH
CN
1H NMR: Ui5-8-11-4-1
1.00
0.99
1.04
3.16
1.19
2.01
1.03
2.11
1.05
0.95
2.05
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

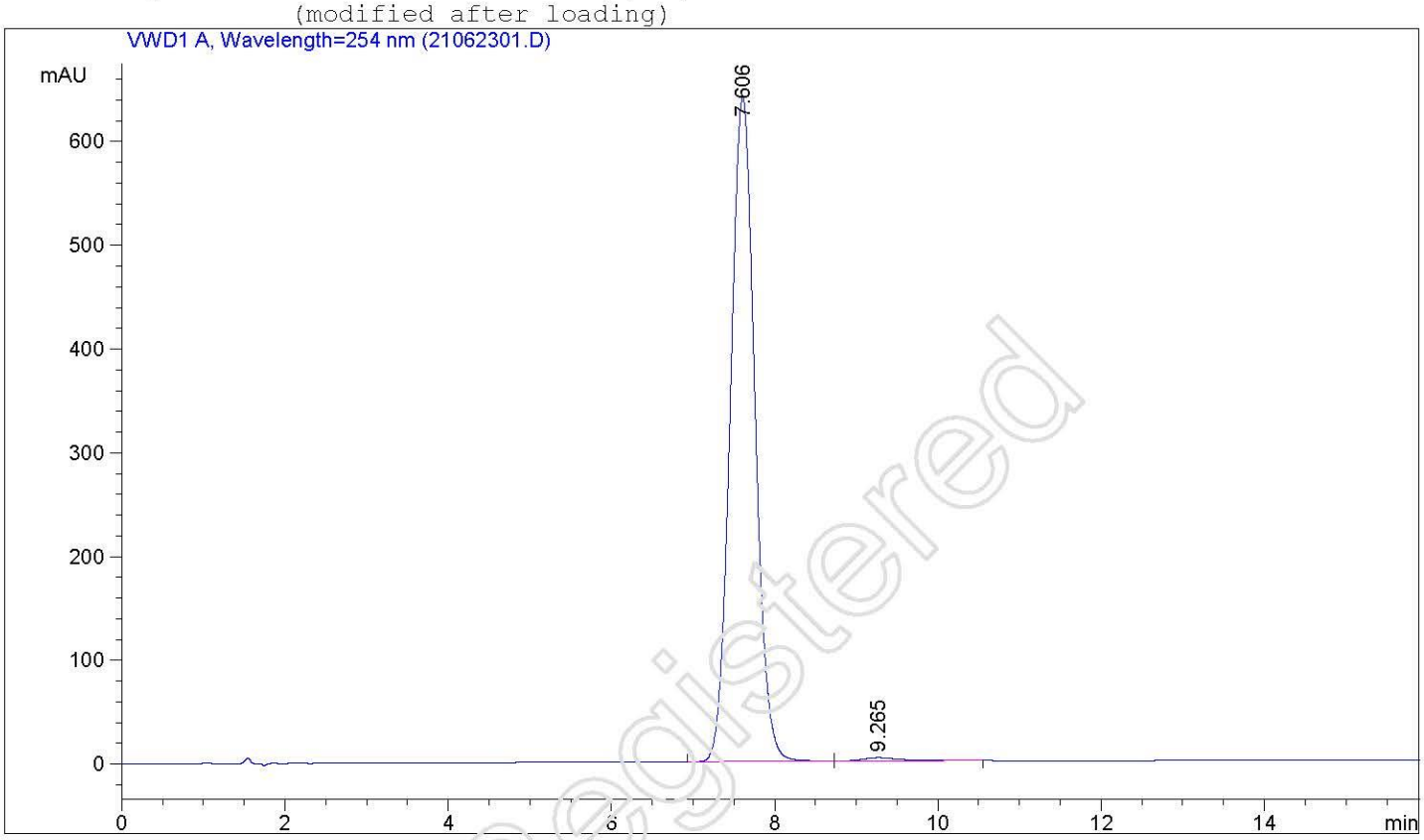

206.99
165.74
165.64
164.13
164.03
153.77
153.73
144.49
144.39
144.30
141.54
141.34
134.93
130.63
123.09
121.58
119.30
119.13
114.07
102.83
102.79
102.68
102.63
99.44
98.47
98.30
98.12
48.13
30.99
30.86
30.73
30.60
30.47
30.34
30.22
F
O
N
H
N
H
F
NH
CN
13C NMR: Ui5-8-11-4-1
f1 (ppm)


x10 2
+ESI 全扫描:2 (0.202 分钟) Frag=125.0V WCR20210317-2.d
HRMS: Ui5-8-11-4-1
401.1184
379.1361
438.2094
443.3337
482.4047
计数 (%) 与 质荷比 (m/z)

HPLC trace of HA-1141

MeOH:H2O=70:30

```
==========================================================================
Injection Date  : 2021-6-23 20:48:12 下午
Sample Name     : HA-1141                          Location : Vial 1
Acq. Operator   : WCR
Acq. Method     : F:\XUE\INT-1.M
Last changed    : 2021-6-23 20:23:32 下午 by WCR
                  (modified after loading)
Analysis Method : F:\XUE\INT-1.M
Last changed    : 2021-6-23 21:18:59 下午 by WCR
                  (modified after loading)
```




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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :     10.00000  [ng/ul]   (not used in calc.)


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   7.606 BV    0.3228 1.33367e4   640.29608  99.1328
   2   9.265 VB    0.5188  116.66977    3.23183   0.8672

Totals :                  1.34534e4   643.52791

 Results obtained with standard integrator!
==========================================================================
                        *** End of Report ***
```