SUPPORTING INFORMATION

Synthesis and biological evaluation of 5-methylpyrimidine derivatives as dual inhibitors of EGFR and Src for cancer treatment

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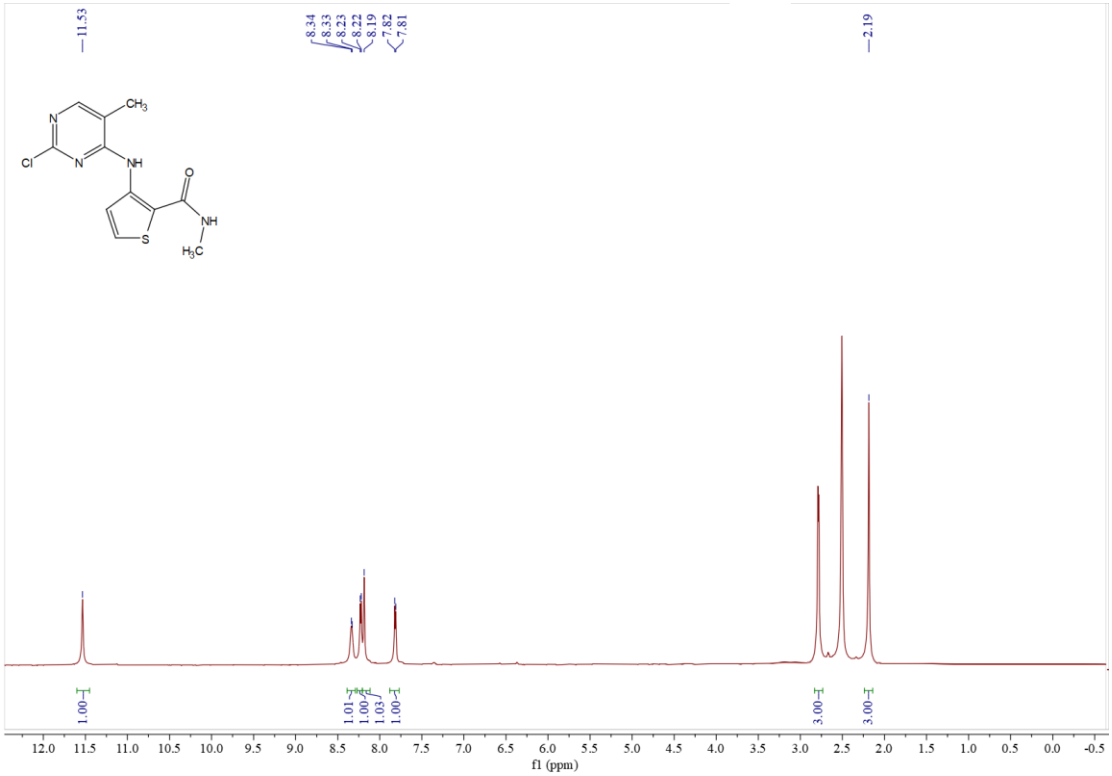


Figure S5. ^{1}H NMR spectrum of compound **5**

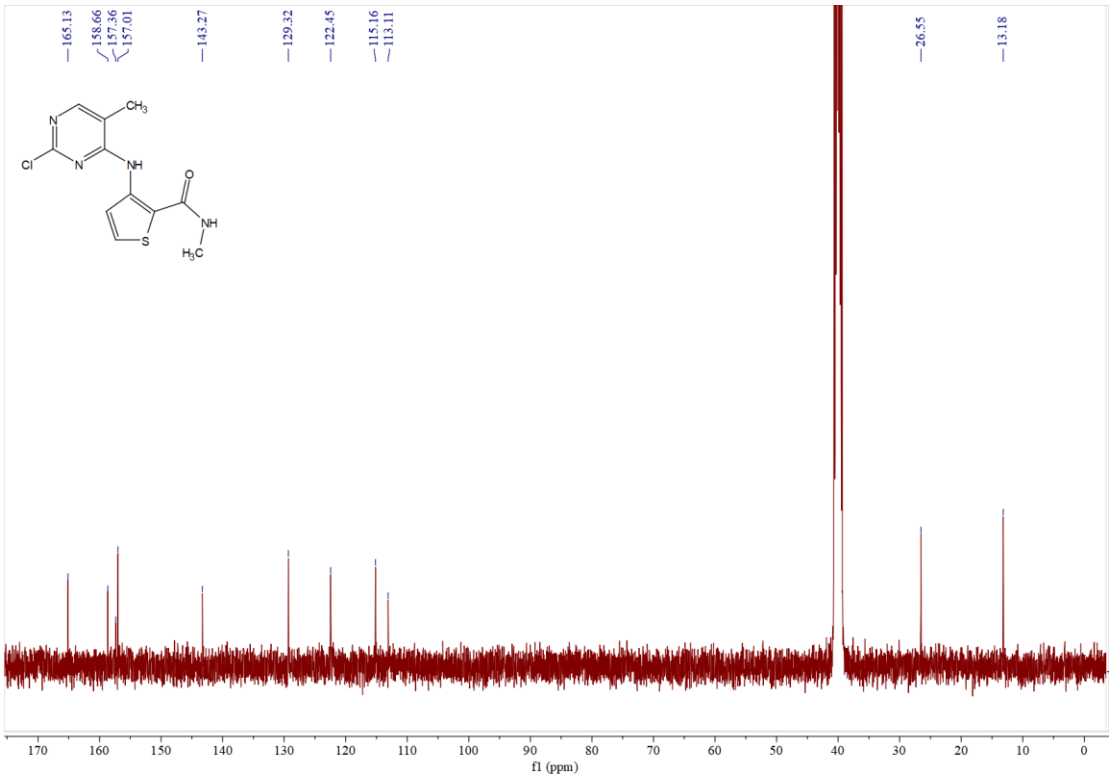


Figure S5. ^{13}C NMR spectrum of compound **5**

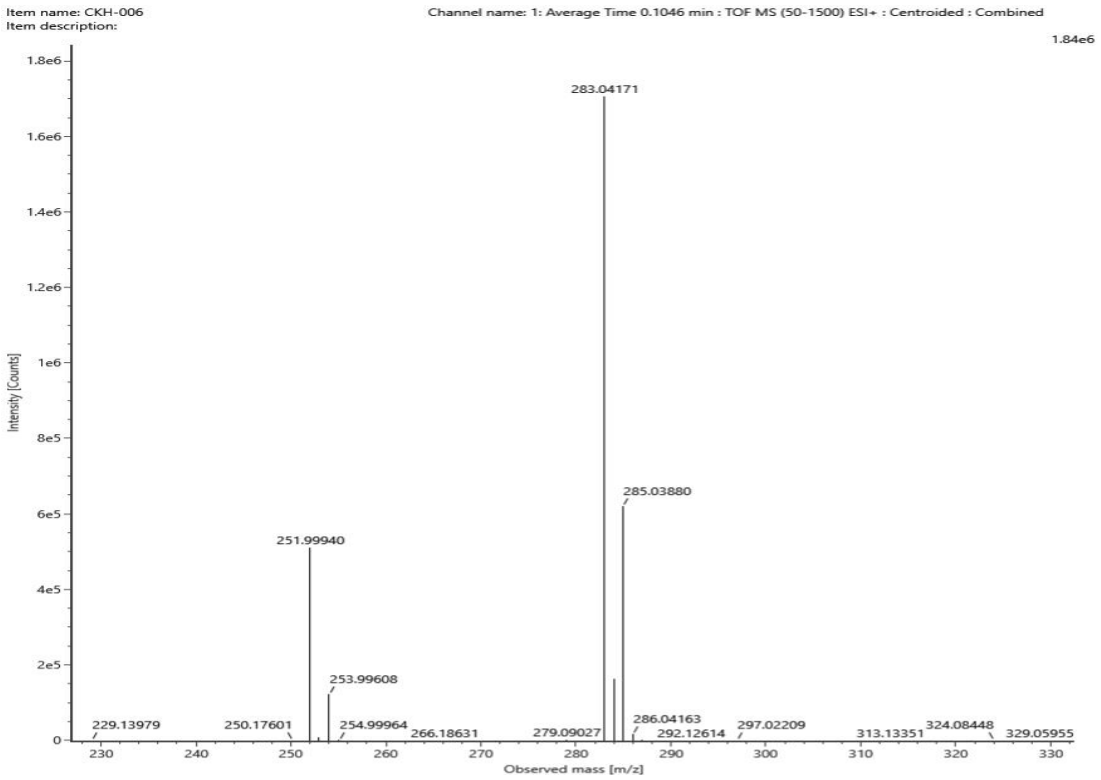


Figure S5. HR-MS (ESI) spectrogram of compound **5**

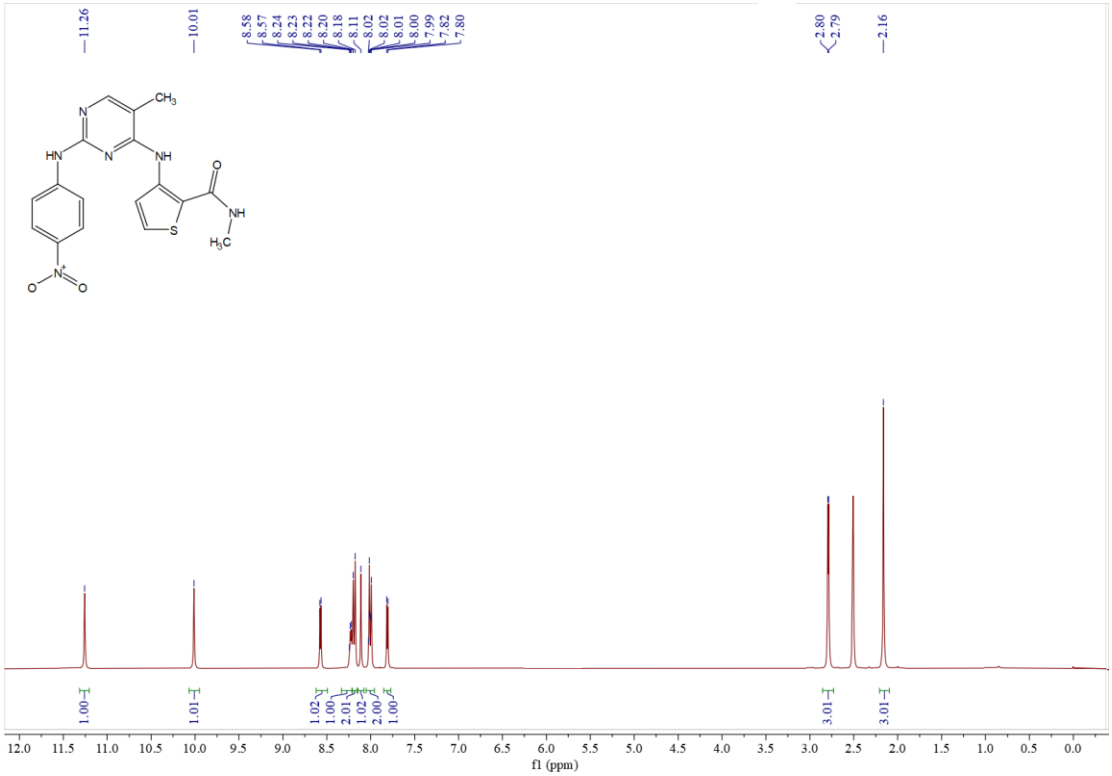


Figure S6. ^{1}H NMR spectrum of compound **6**

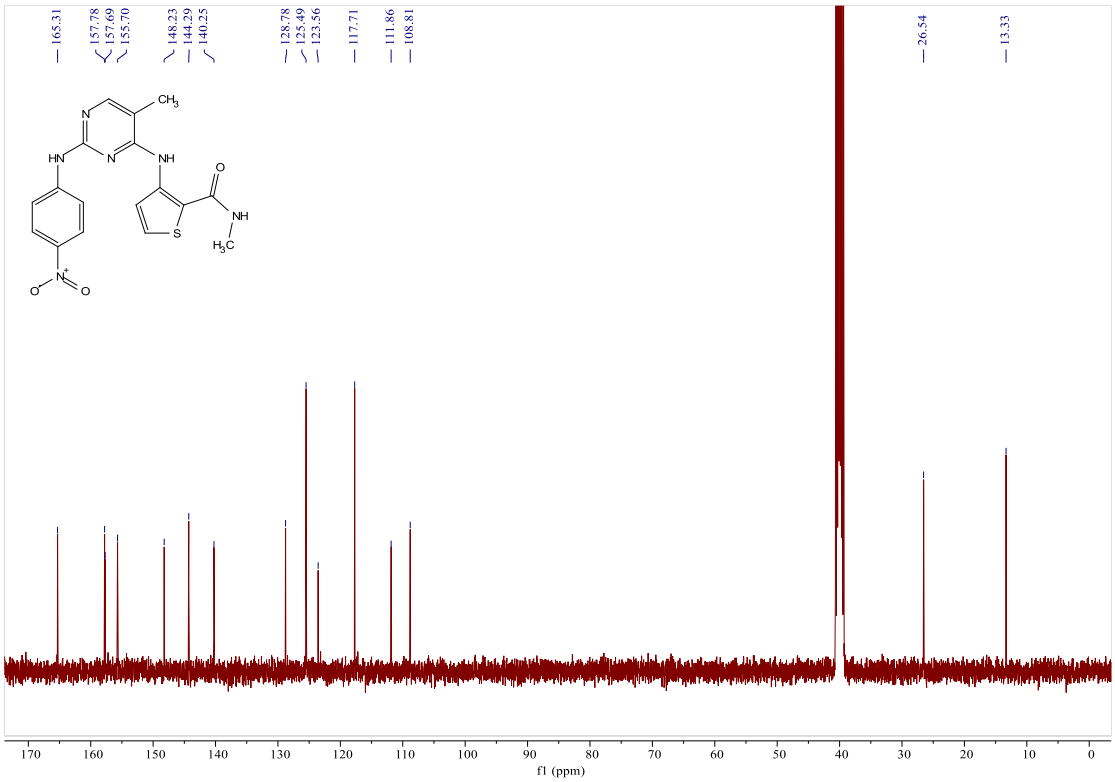


Figure S6. ^{13}C NMR spectrum of compound **6**

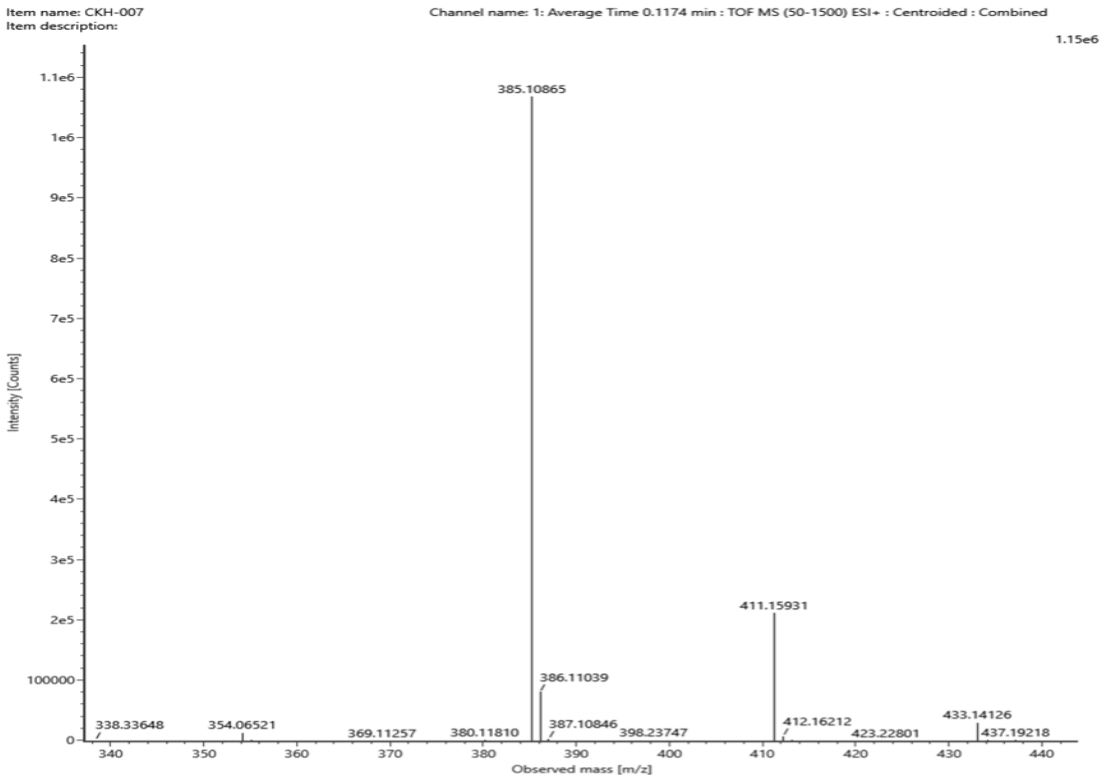


Figure S6. HR-MS (ESI) spectrogram of compound **6**

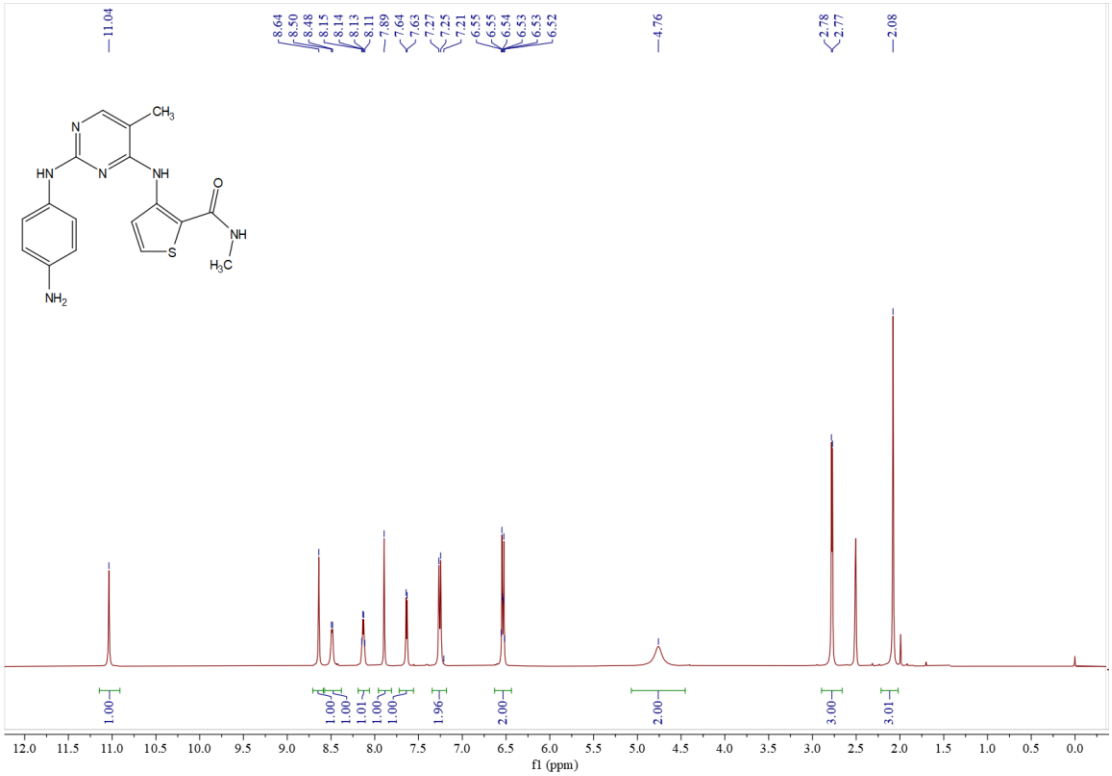


Figure S7. [1]H NMR spectrum of compound **7**

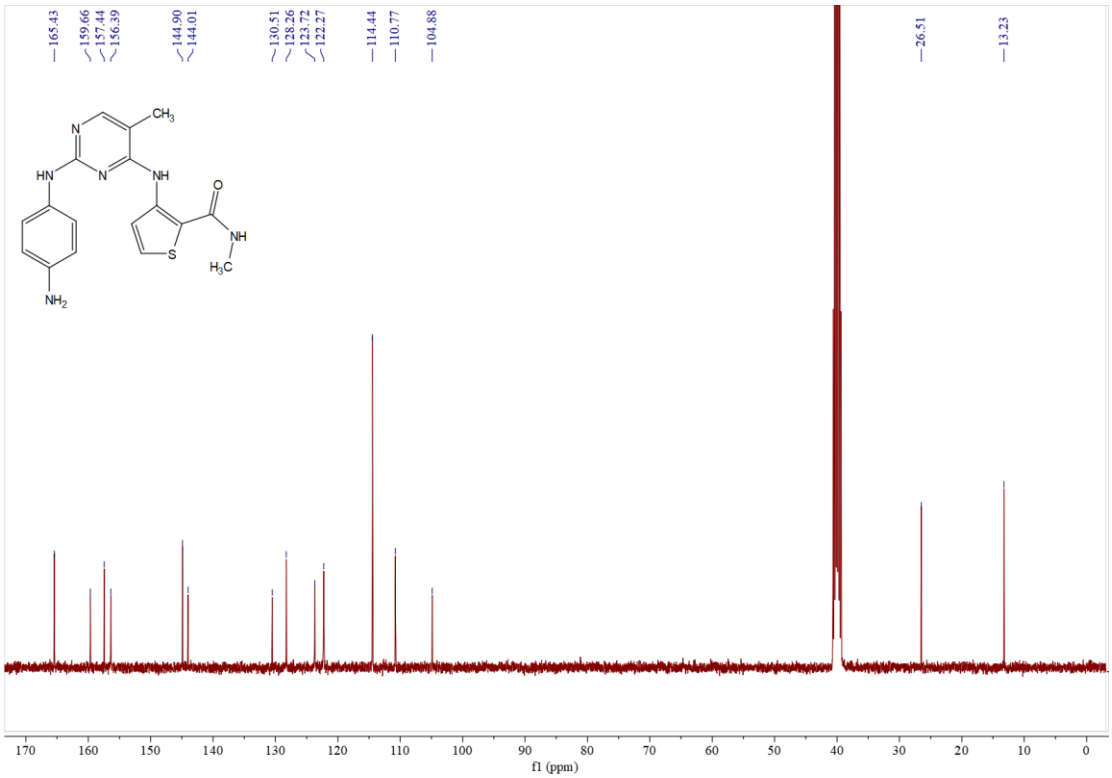


Figure S7. [13]C NMR spectrum of compound 7

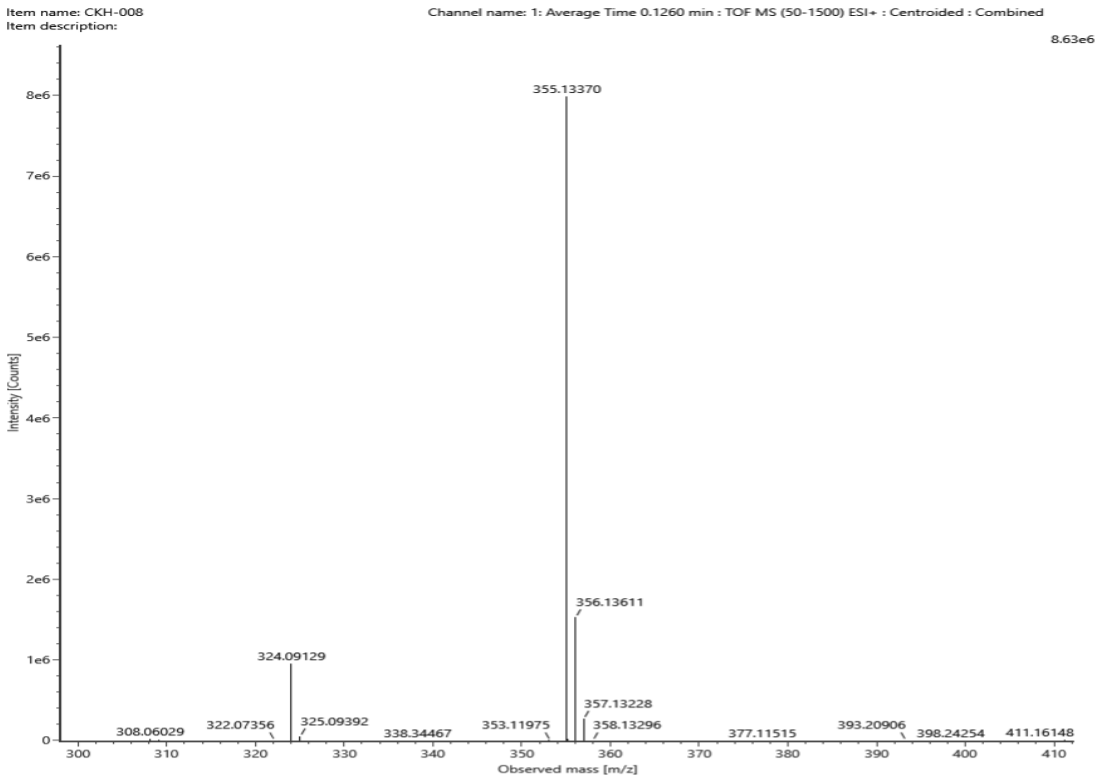


Figure S7. HR-MS (ESI) spectrogram of compound **7**

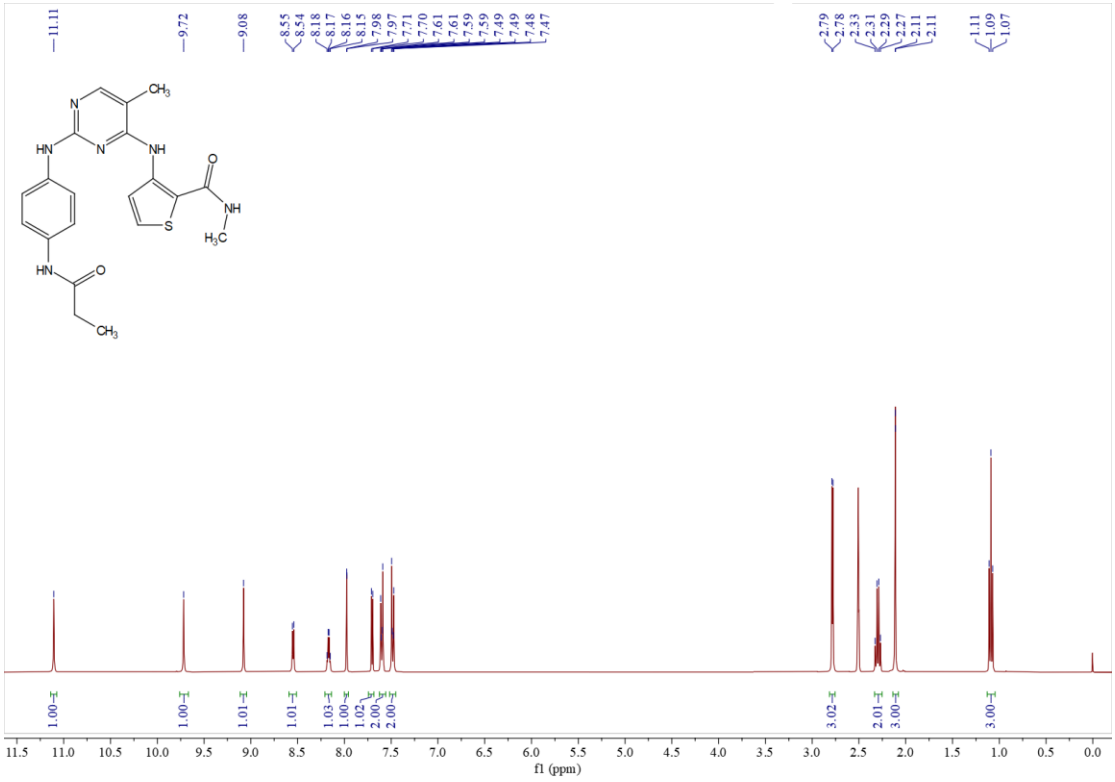
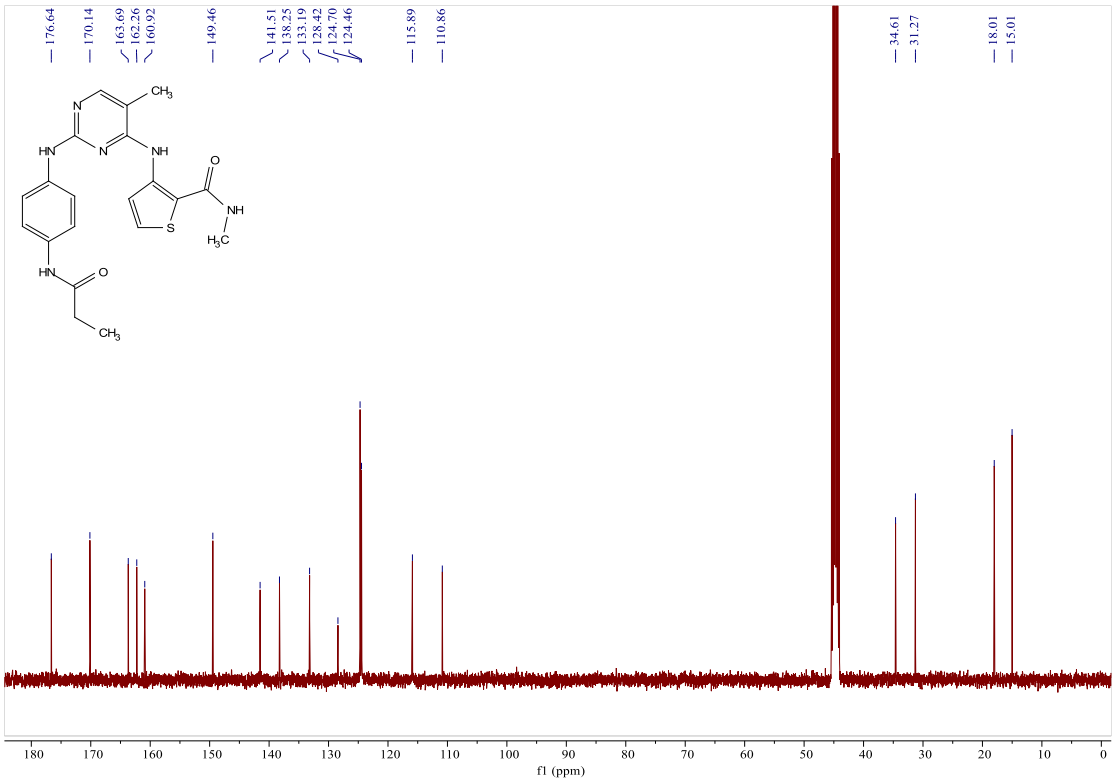


Figure S8. ^{1}H NMR spectrum of compound **8a**



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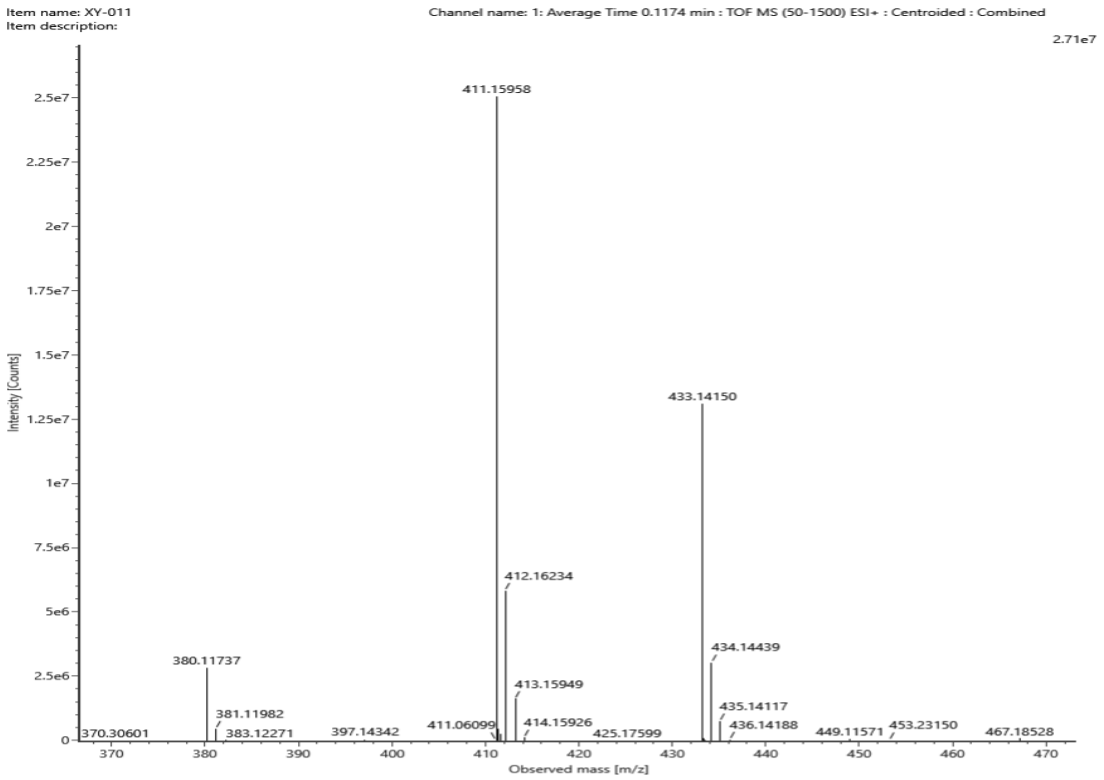


Figure S8. HR-MS (ESI) spectrogram of compound **8a**

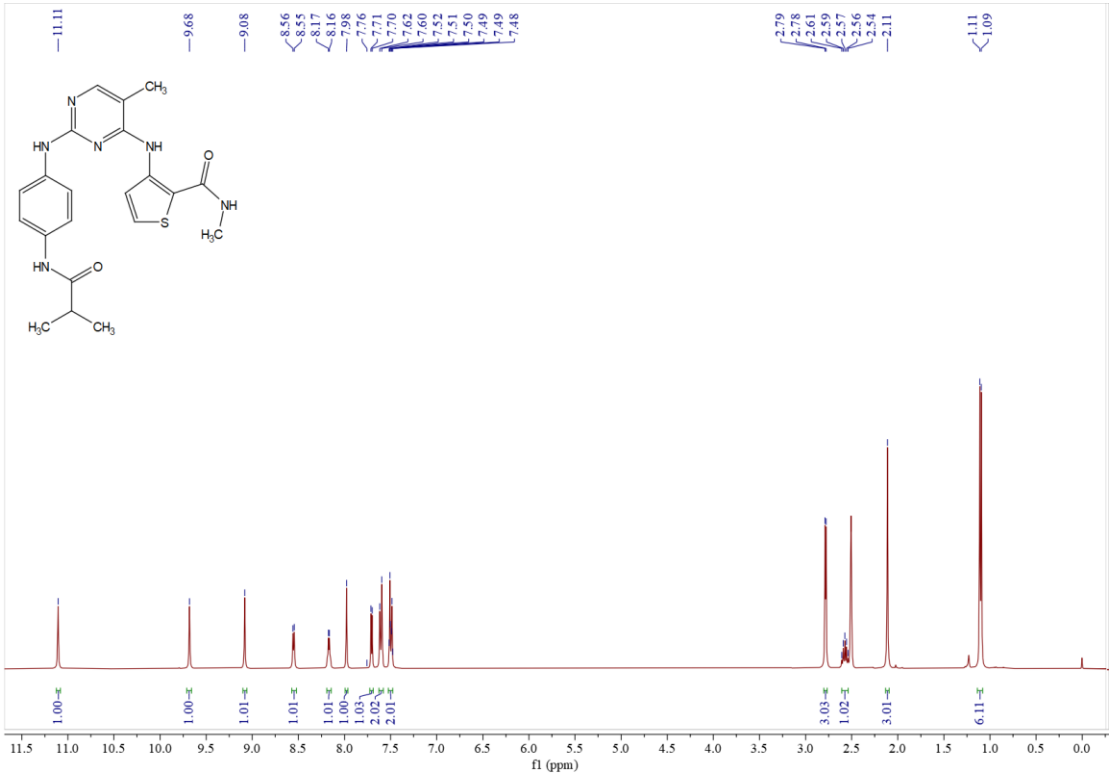


Figure S9. [1]H NMR spectrum of compound **8b**

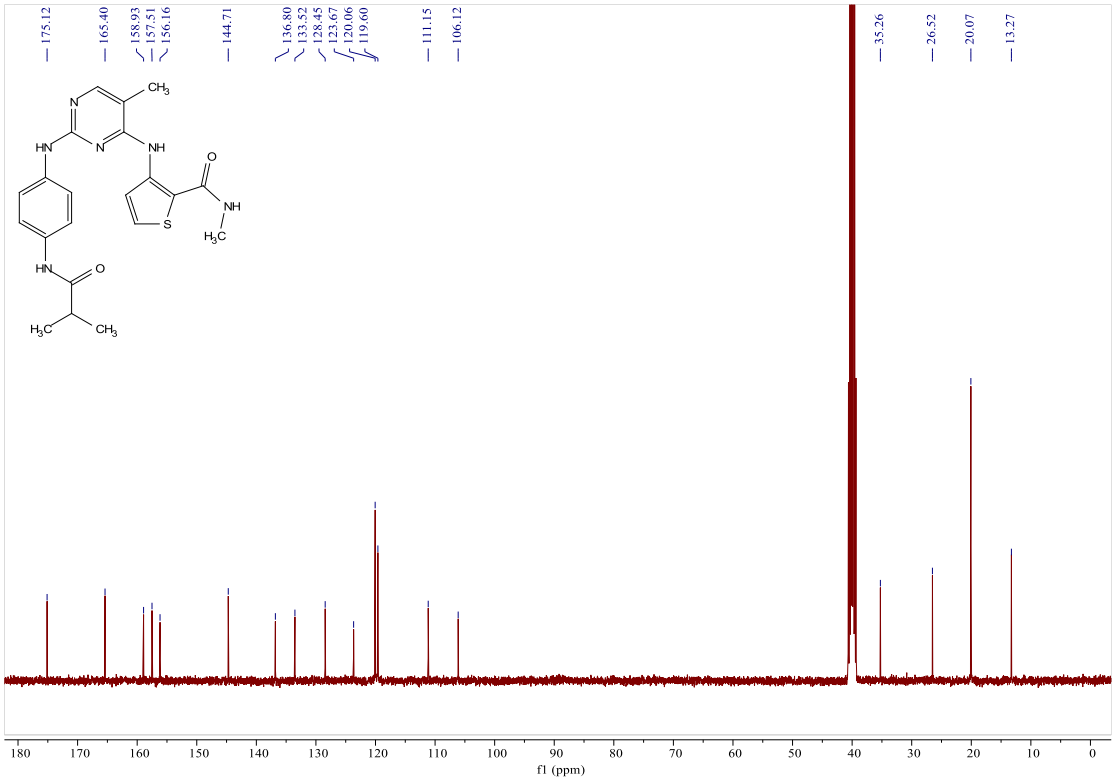


Figure S9. [13]C NMR spectrum of compound **8b**

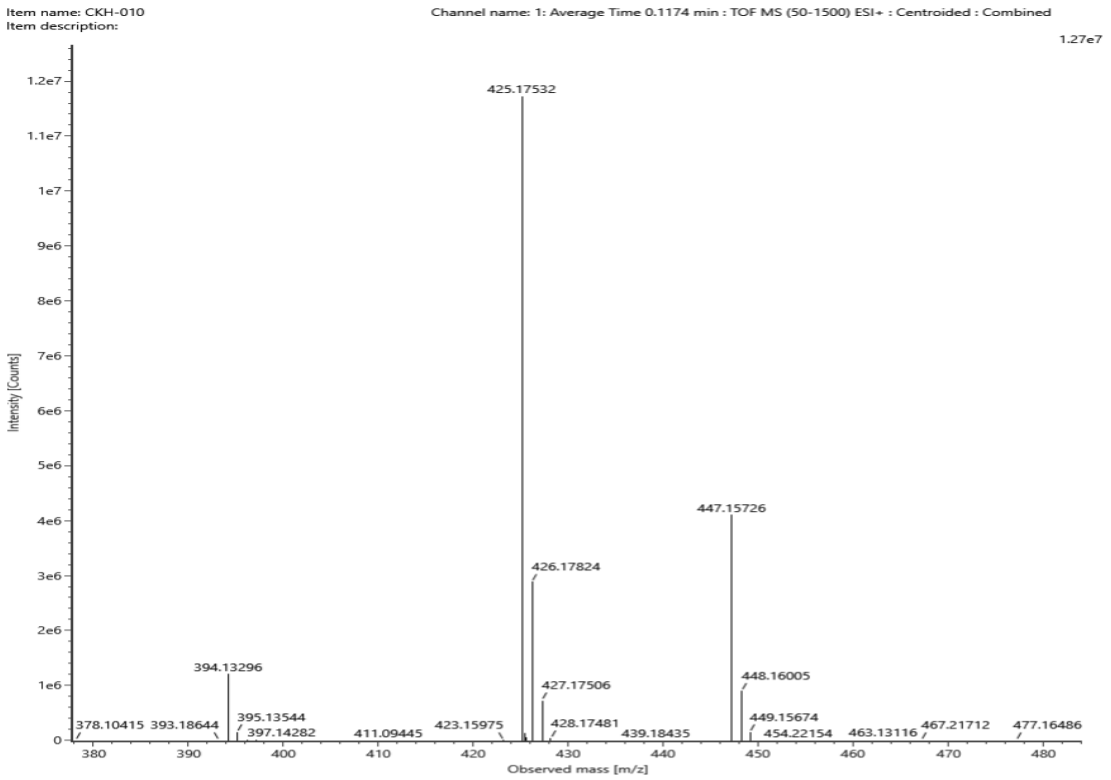
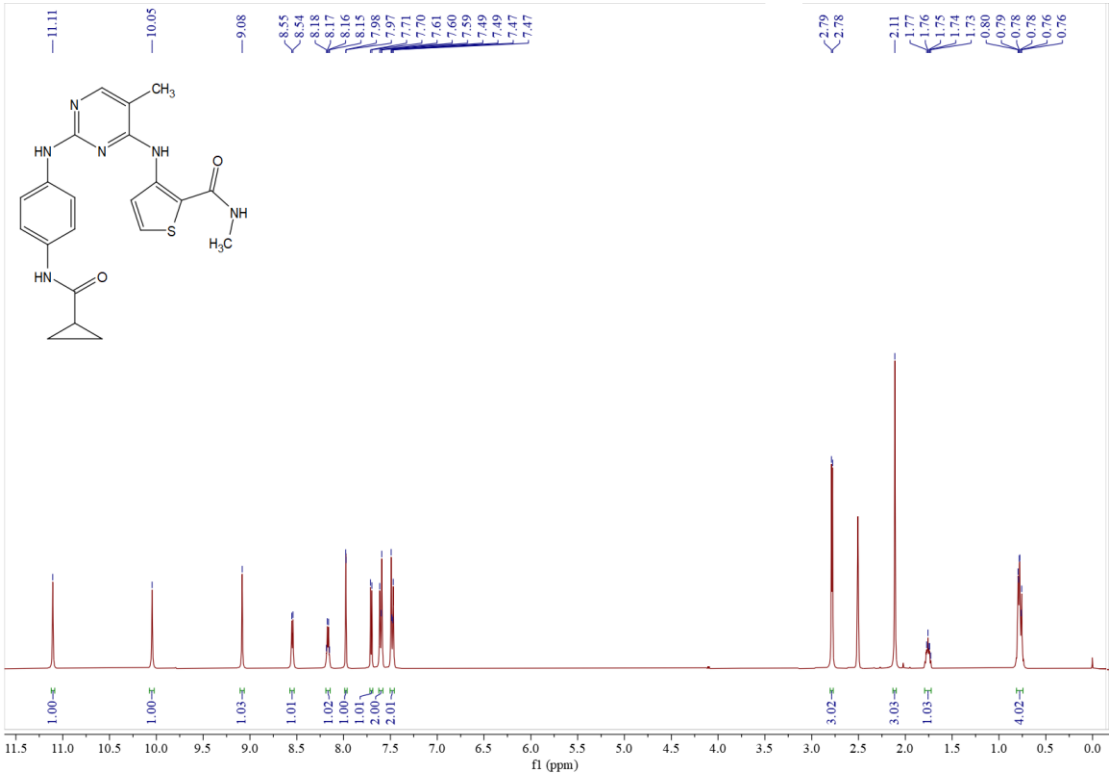


Figure S9. HR-MS (ESI) spectrogram of compound **8b**



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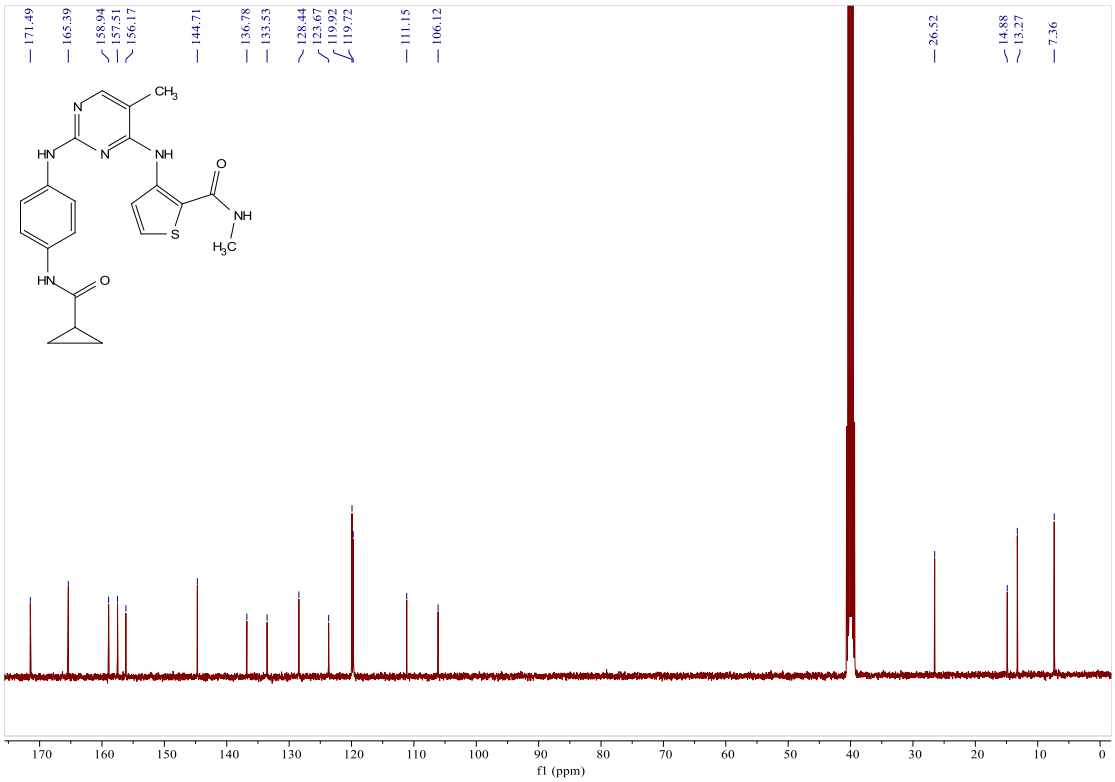


Figure S10. ^{13}C NMR spectrum of compound **8c**

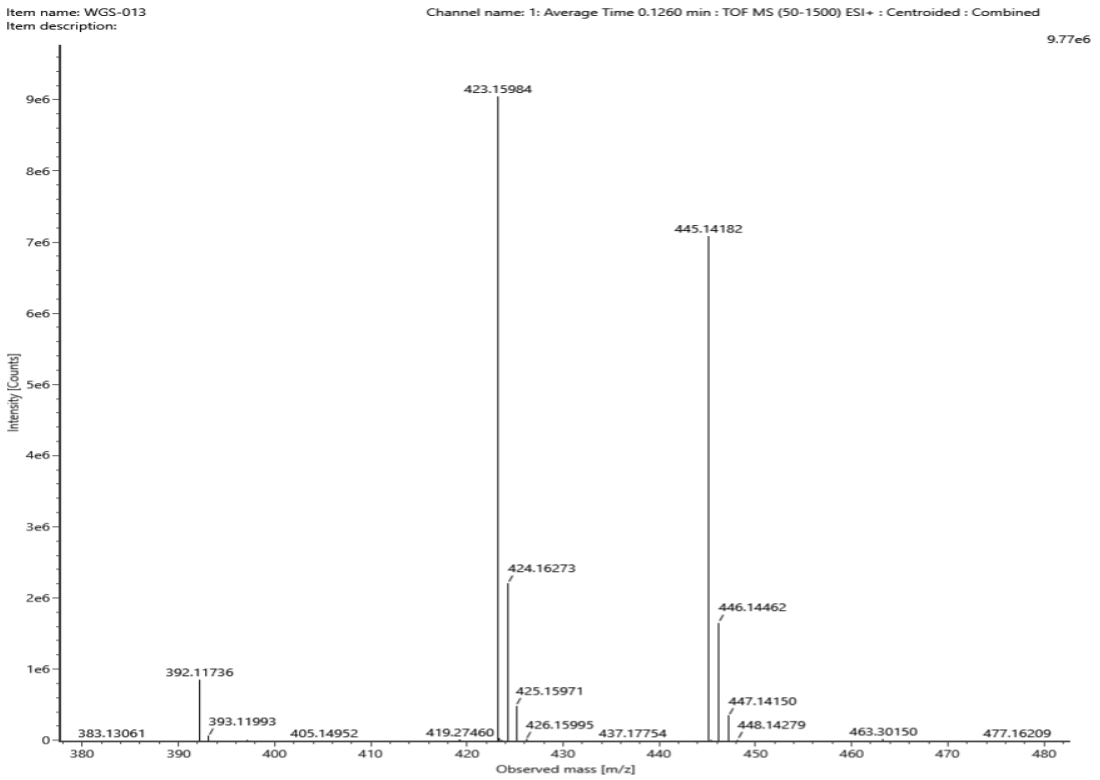


Figure S10. HR-MS (ESI) spectrogram of compound **8c**

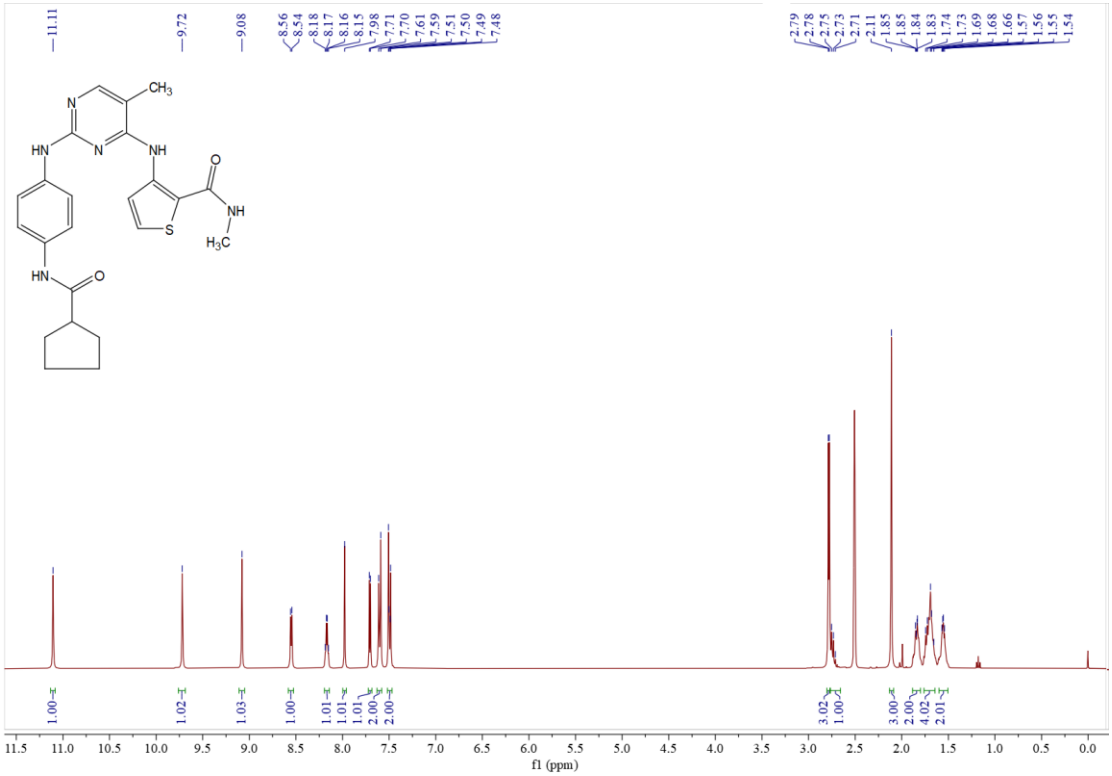


Figure S11. [1]H NMR spectrum of compound **8d**

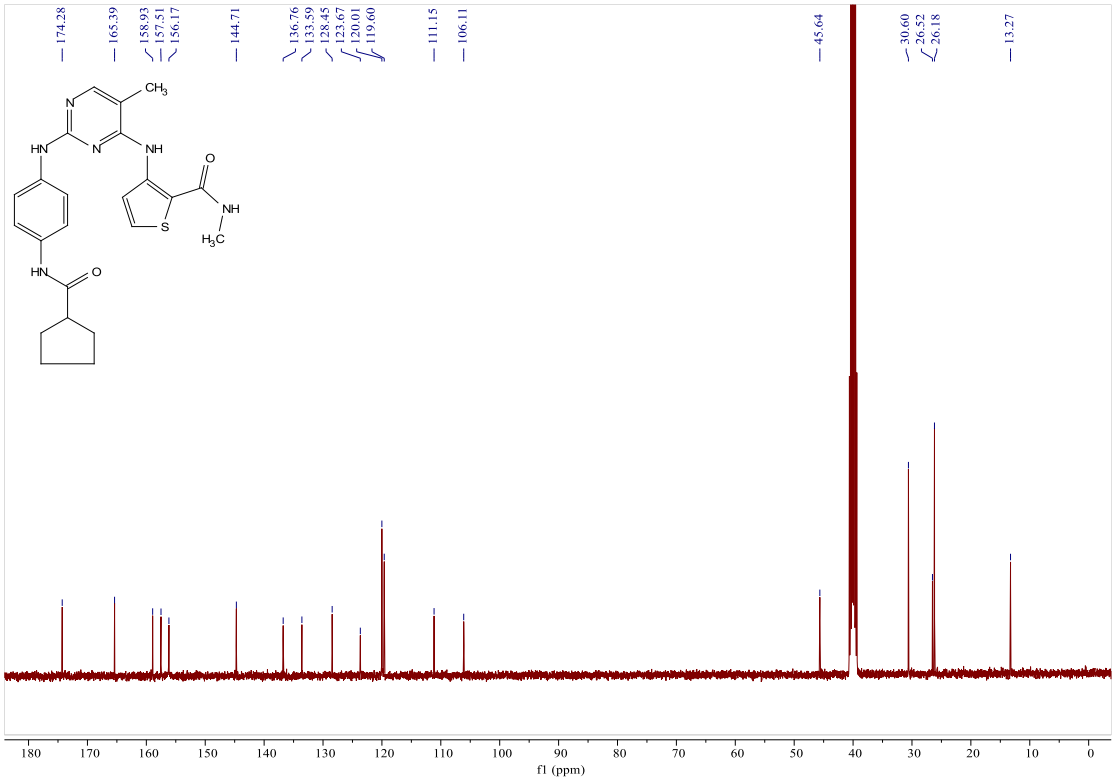


Figure S11. [13]C NMR spectrum of compound **8d**

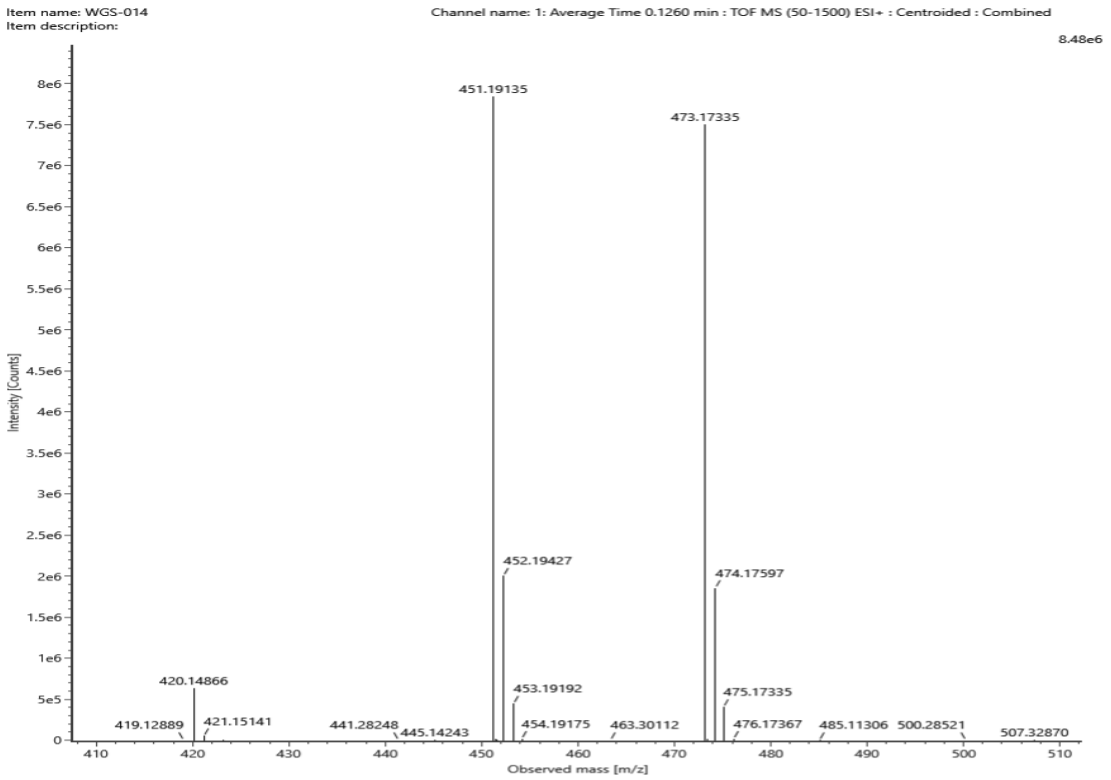


Figure S11. HR-MS (ESI) spectrogram of compound **8d**

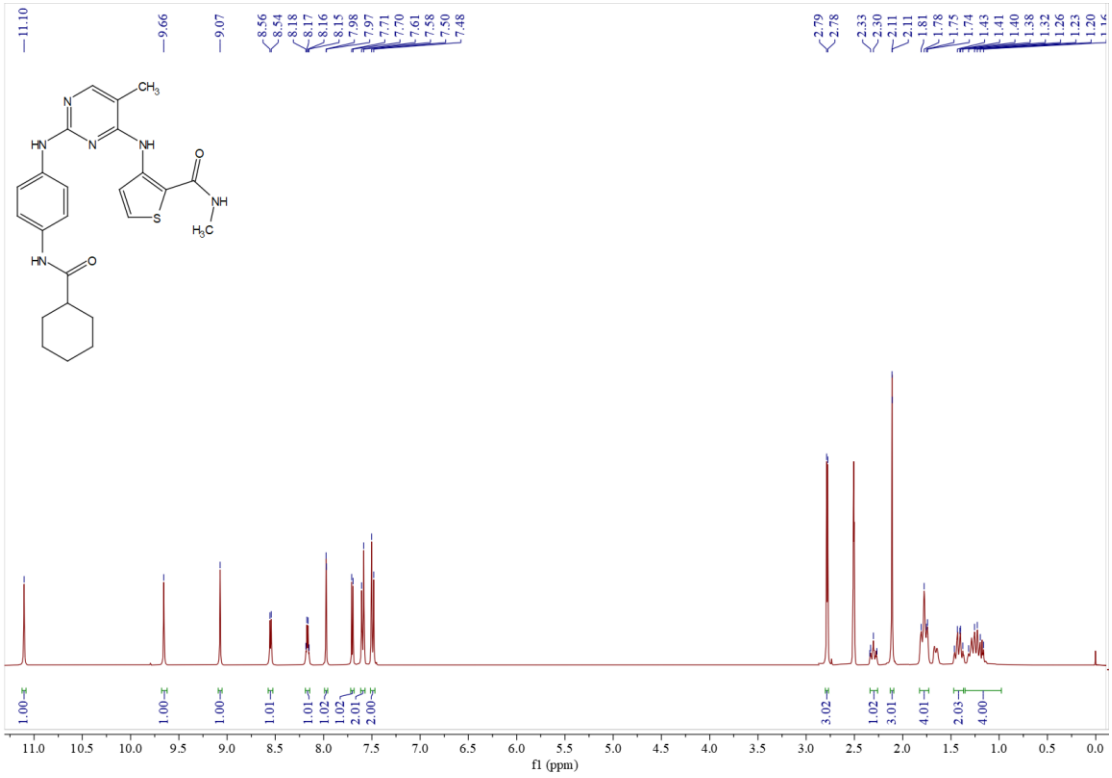


Figure S12. ^{1}H NMR spectrum of compound **8e**

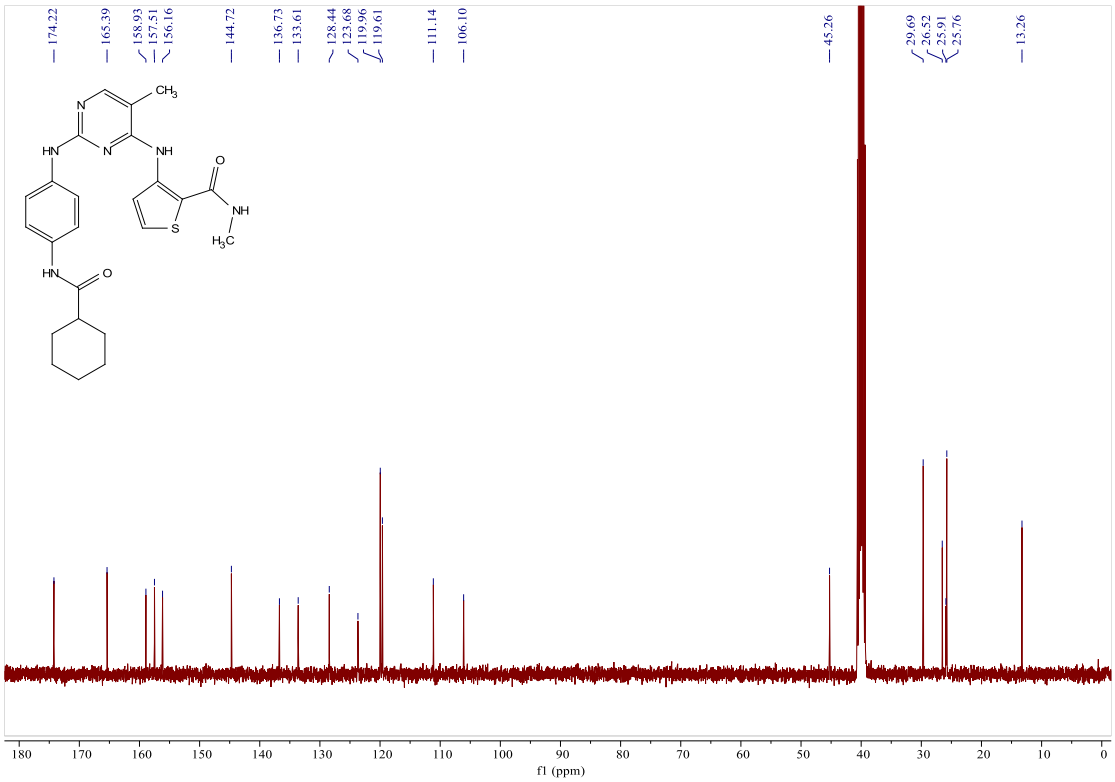


Figure S12. ^{13}C NMR spectrum of compound **8e**

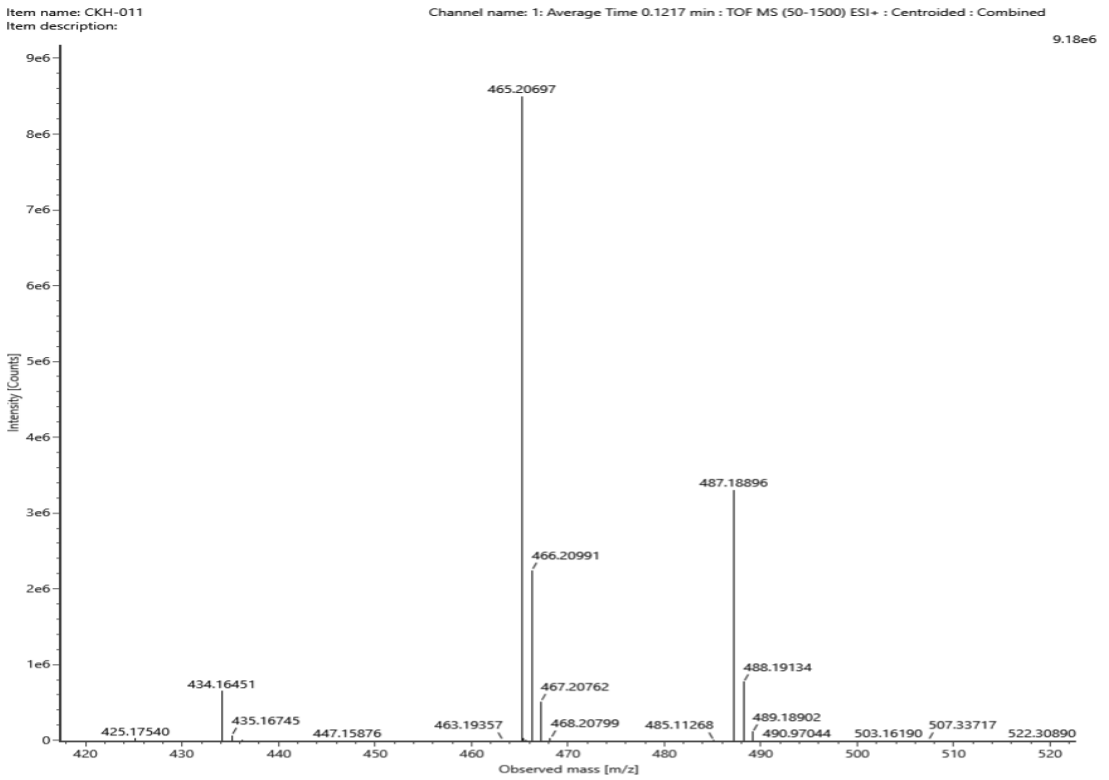
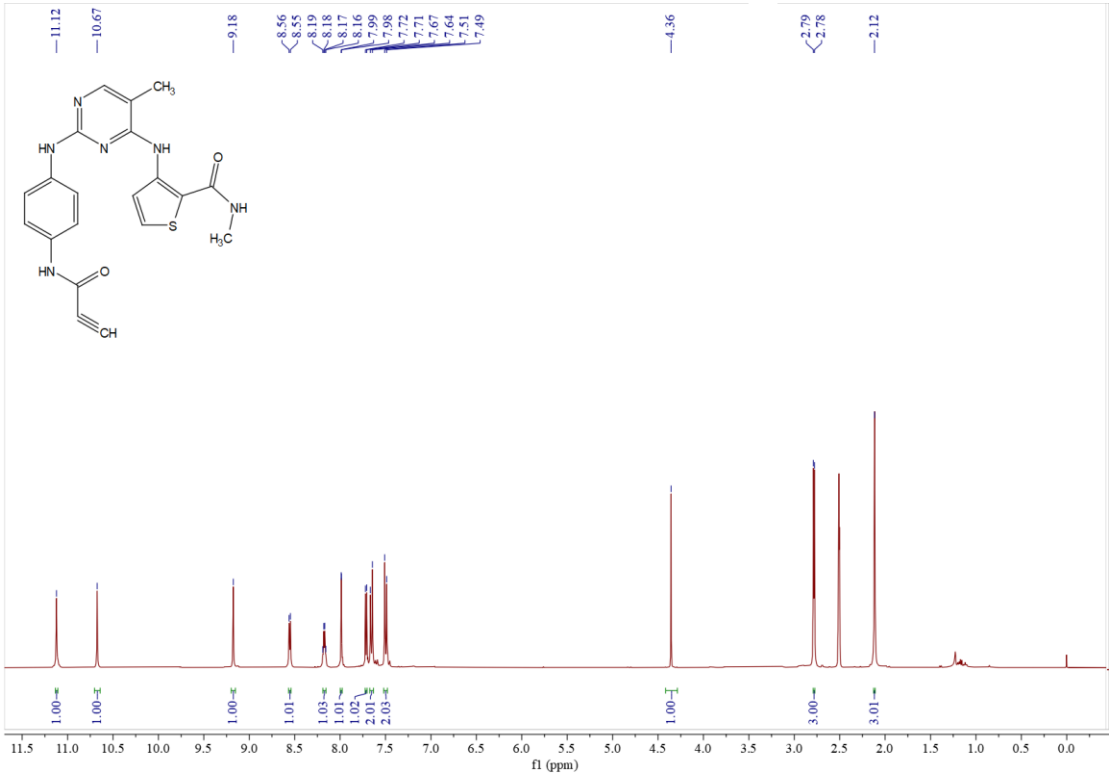


Figure S12. HR-MS (ESI) spectrogram of compound **8e**



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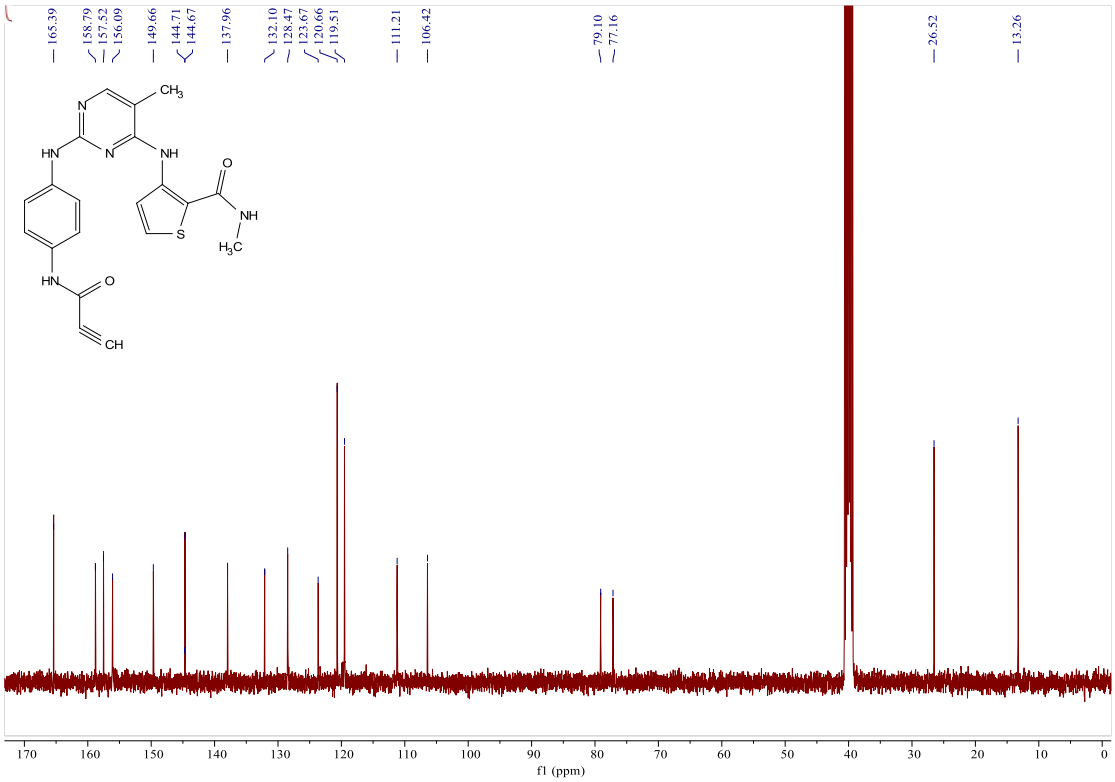

Figure S13. [13]C NMR spectrum of compound **8f**

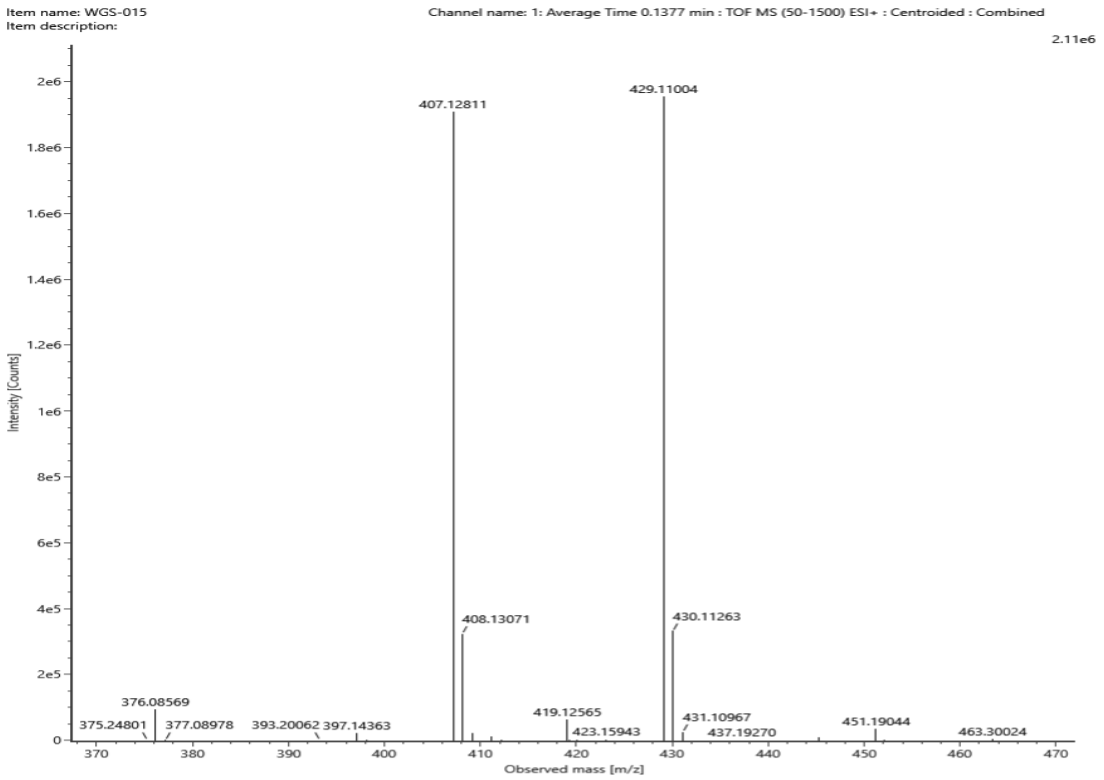

Figure S13. HR-MS (ESI) spectrogram of compound **8f**

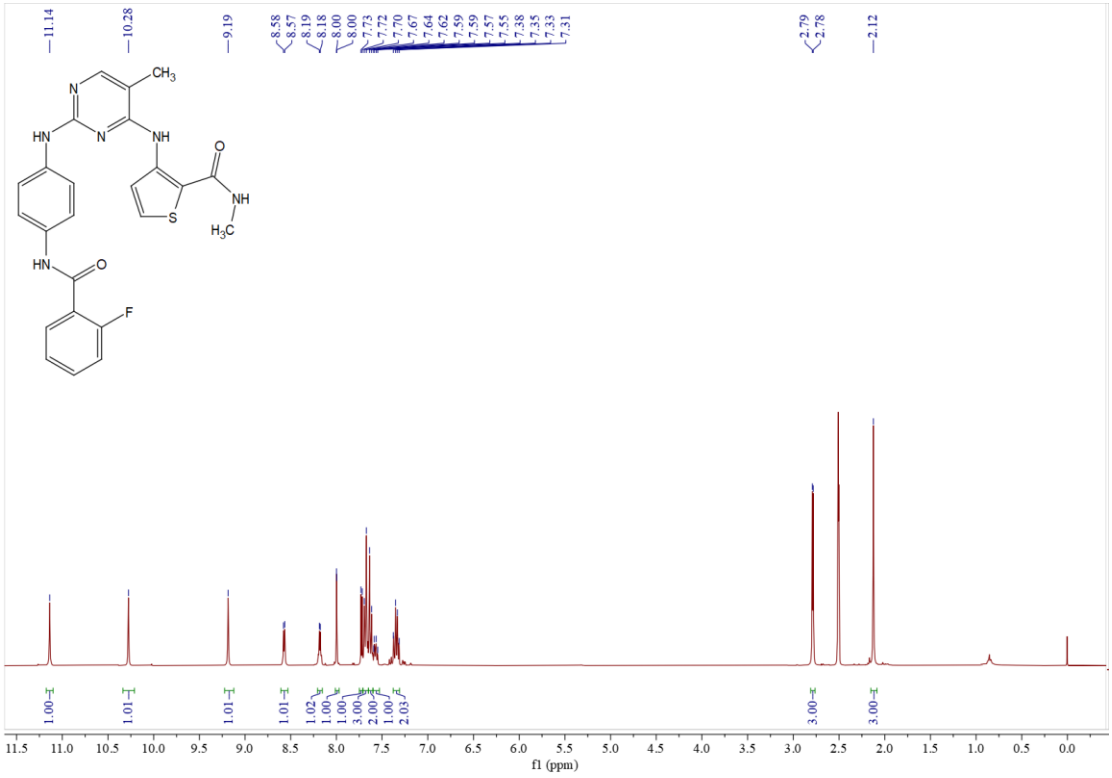

Figure S14. ^{1}H NMR spectrum of compound **8g**

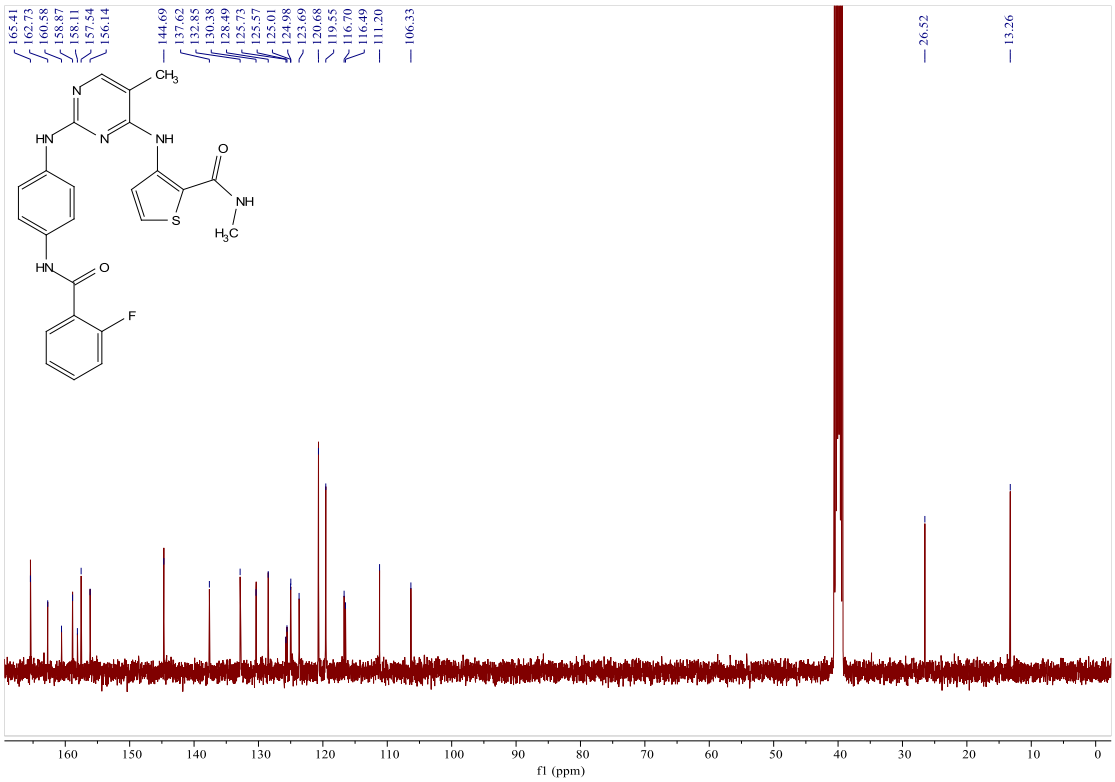

Figure S15. ^{13}C NMR spectrum of compound **8g**

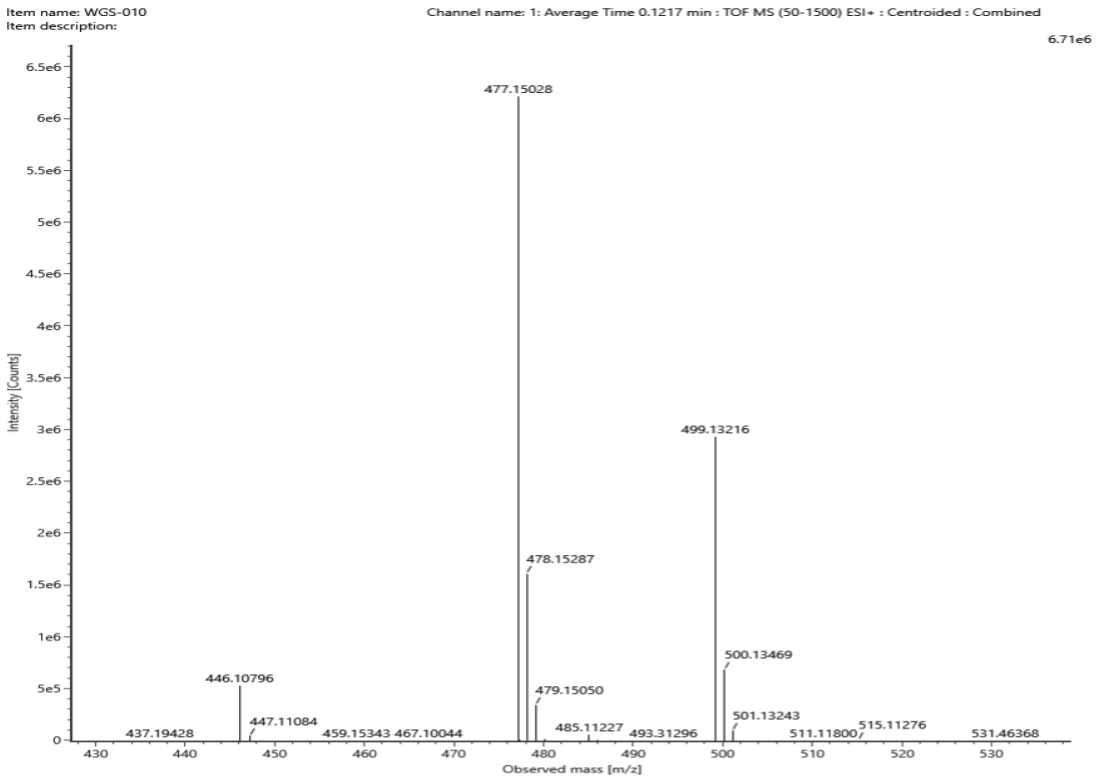

Figure S15. HR-MS (ESI) spectrogram of compound **8g**

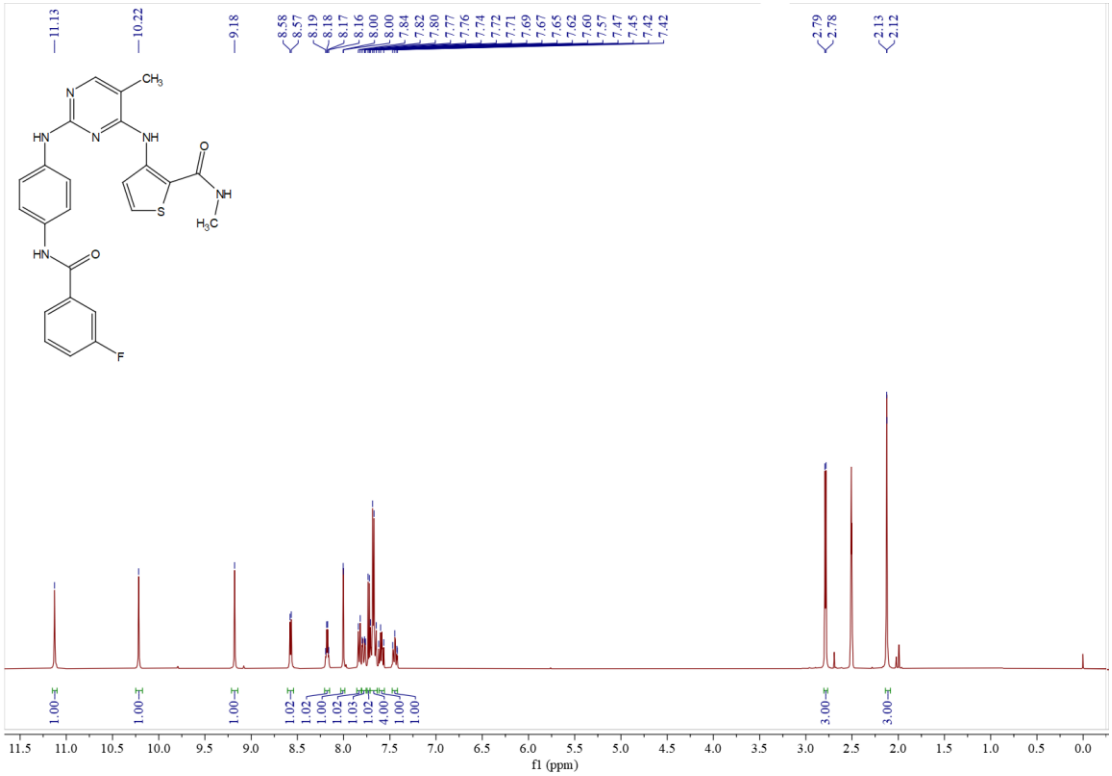

Figure S15. [1]H NMR spectrum of compound **8h**

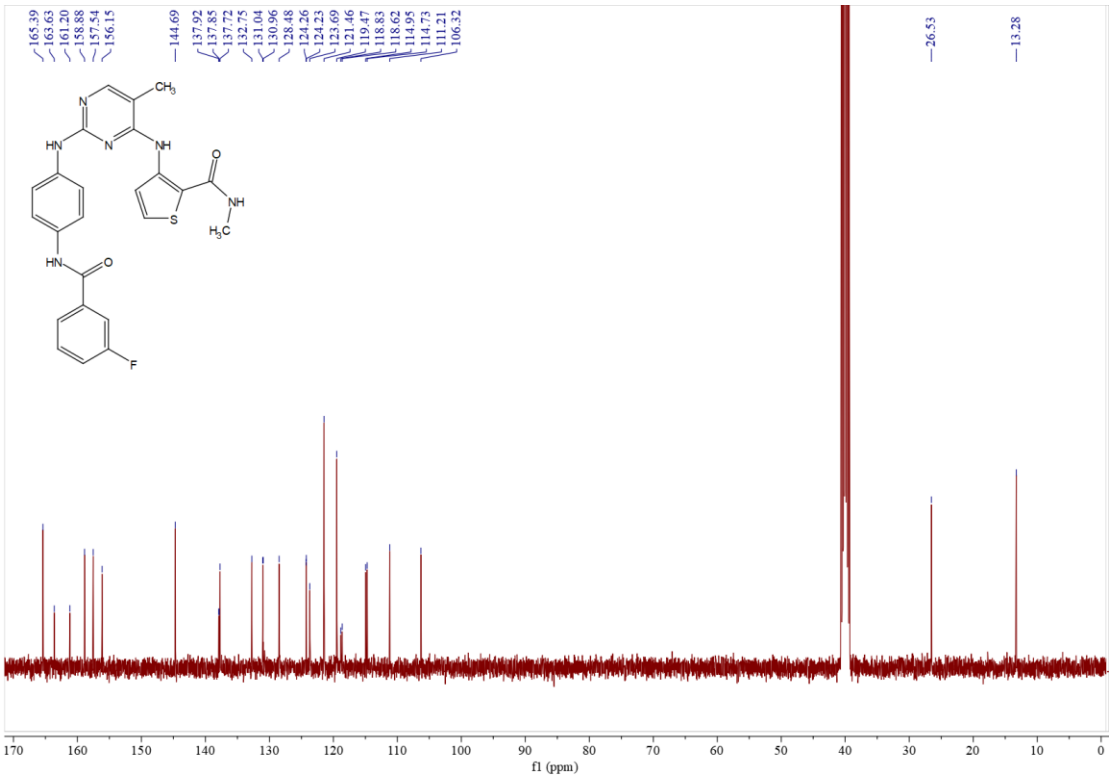

Figure S15. [13]C NMR spectrum of compound **8h**

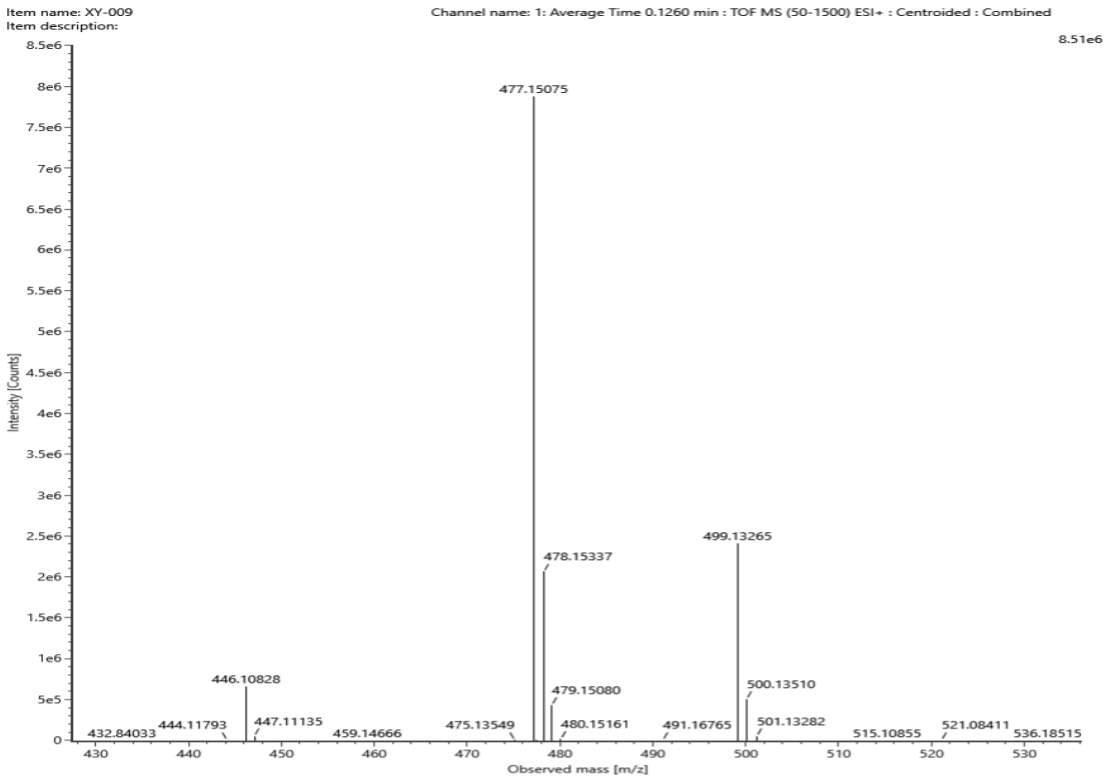

Figure S15. HR-MS (ESI) spectrogram of compound **8h**

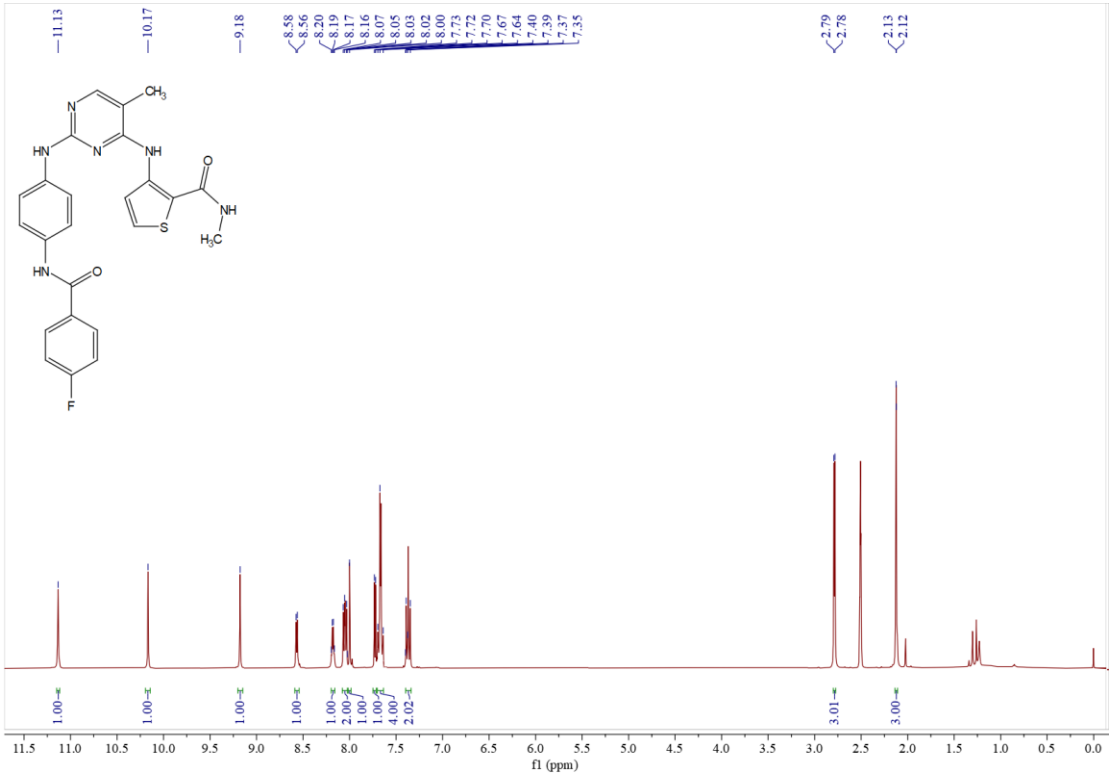

Figure S16. ^{1}H NMR spectrum of compound **8i**

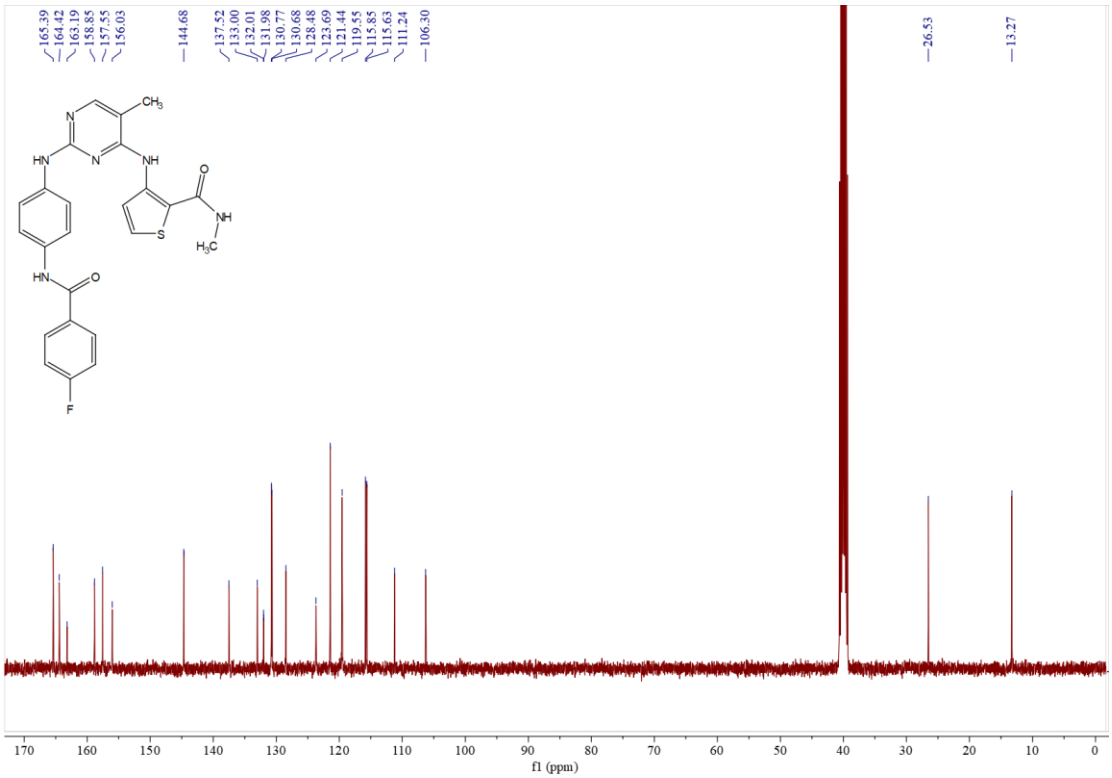

Figure S16. ^{13}C NMR spectrum of compound **8i**

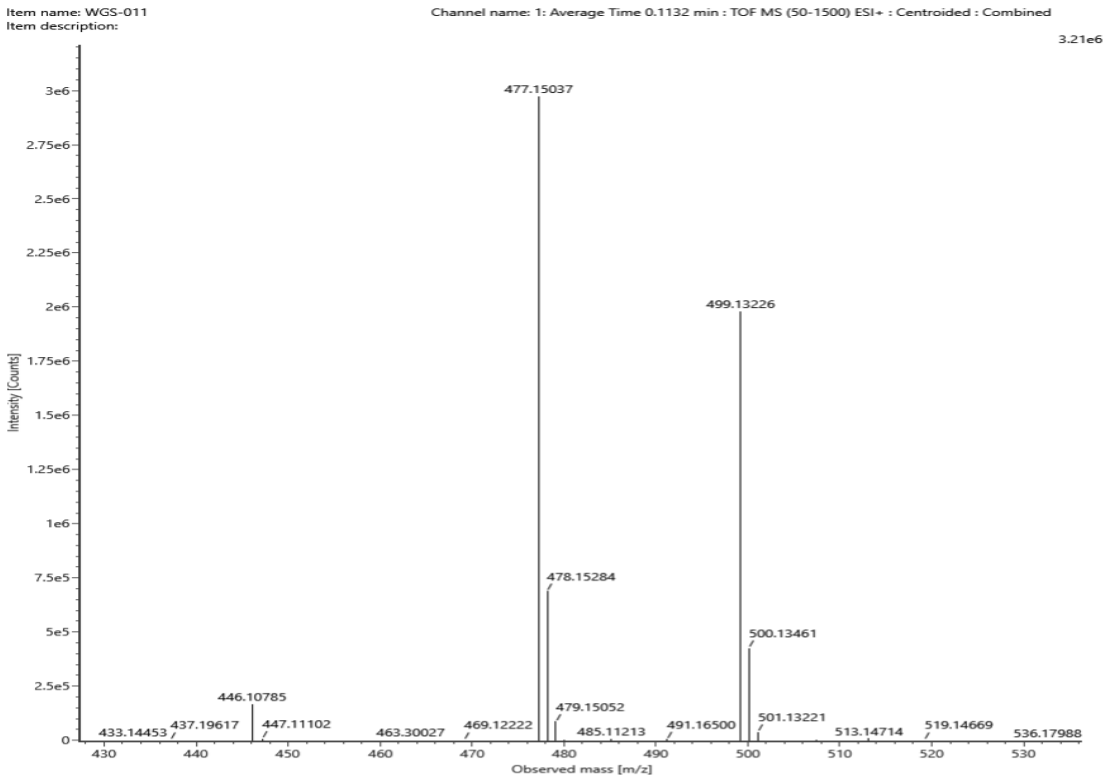

Figure S16. HR-MS (ESI) spectrogram of compound **8i**

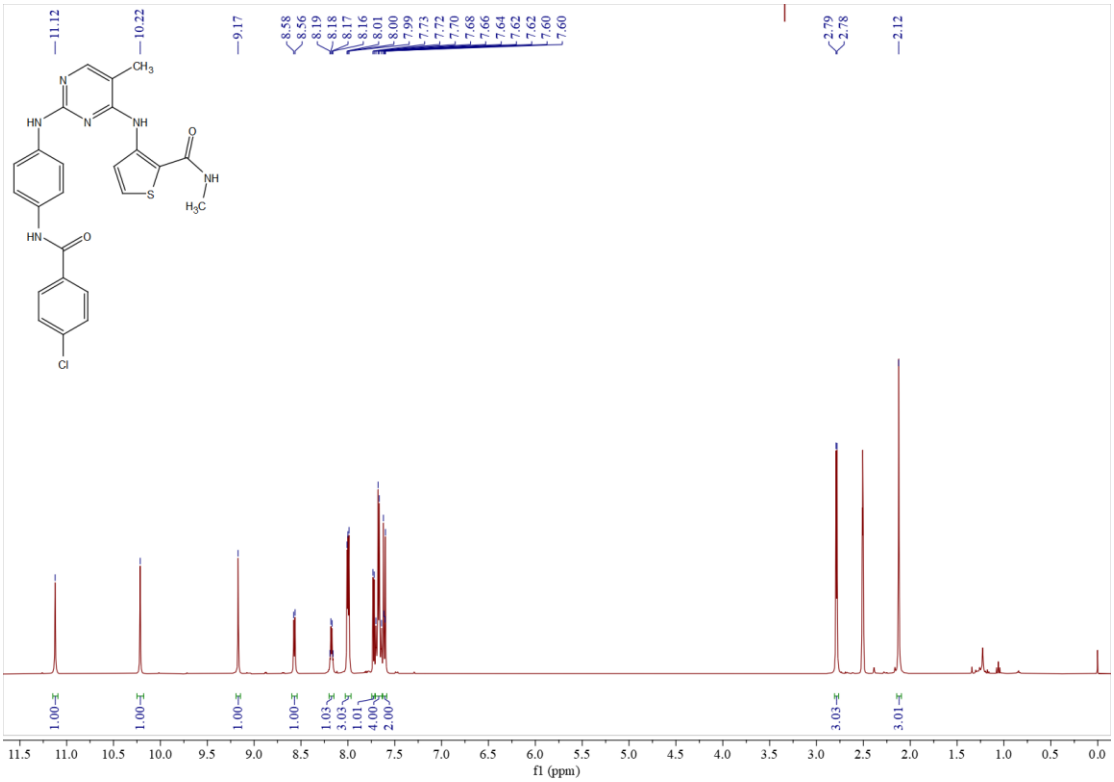

Figure S17. [1]H NMR spectrum of compound **8j**

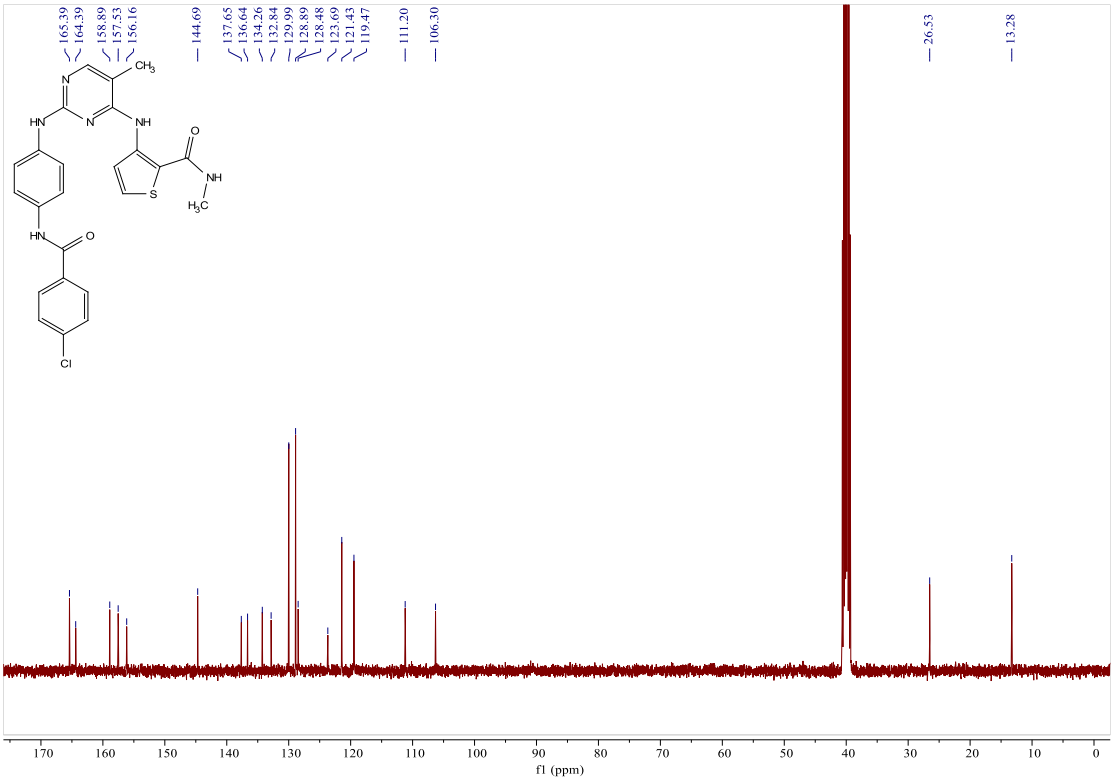

Figure S17. [13]C NMR spectrum of compound **8j**

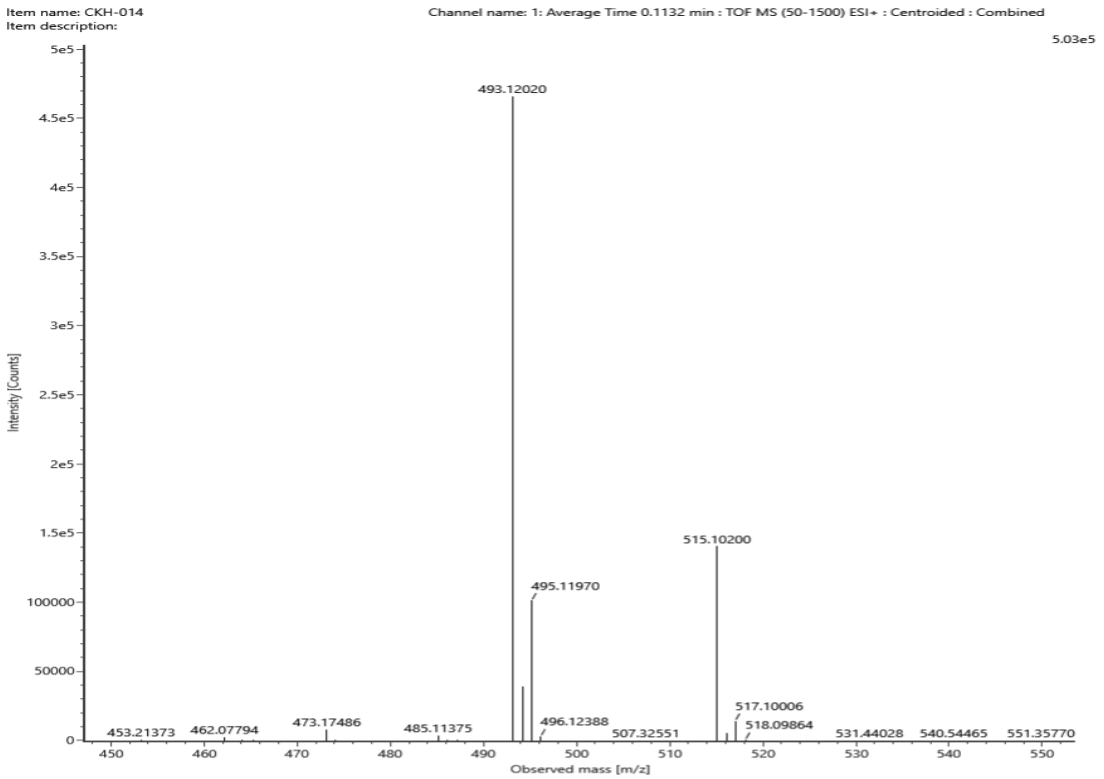

Figure S17. HR-MS (ESI) spectrogram of compound **8j**

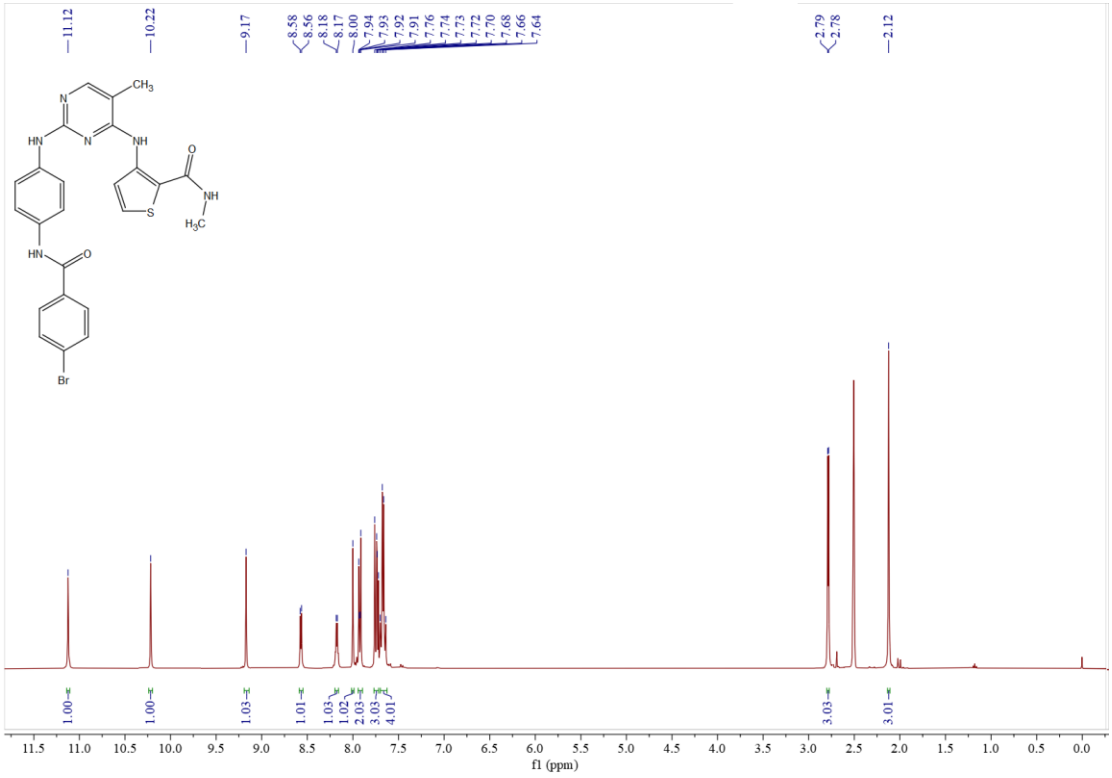

Figure S18. ^{1}H NMR spectrum of compound **8k**

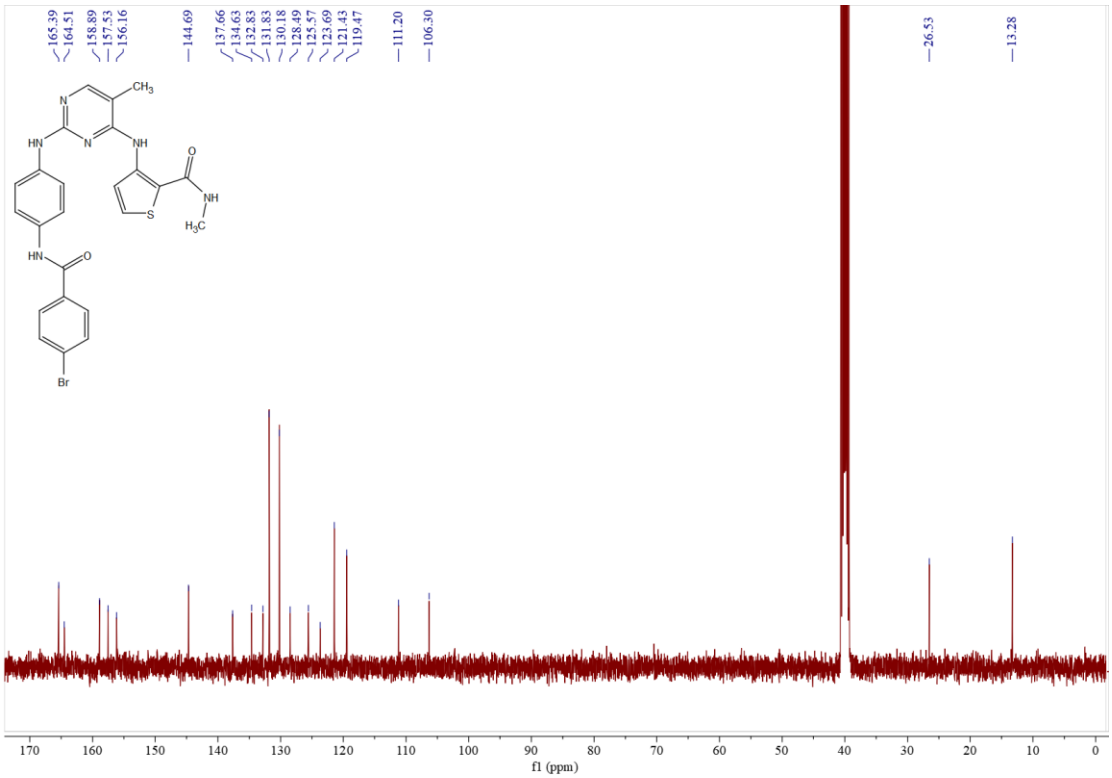

Figure S18. ^{13}C NMR spectrum of compound **8k**

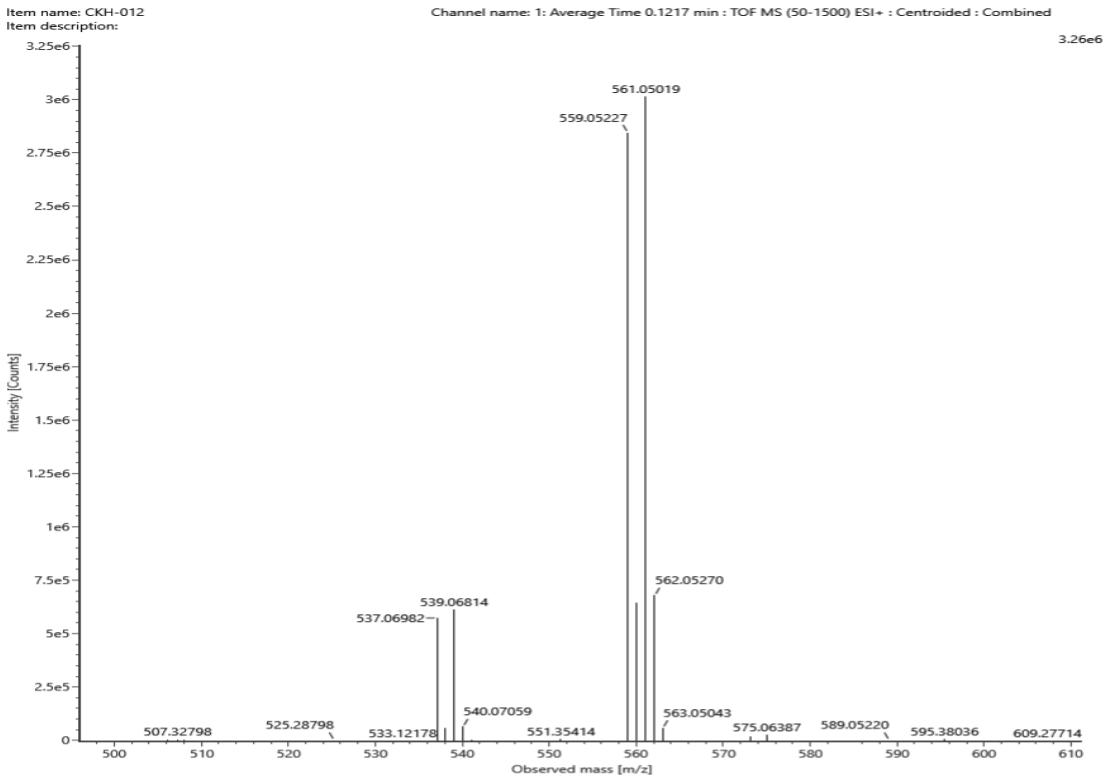

Figure S18. HR-MS (ESI) spectrogram of compound **8k**

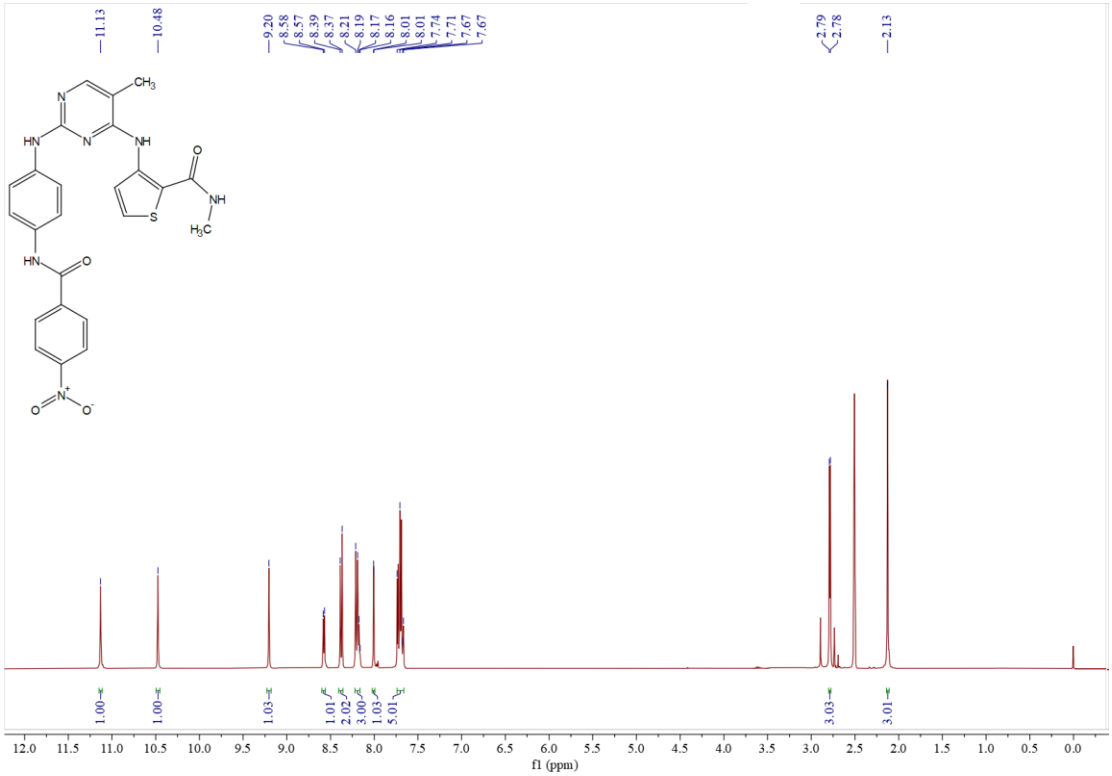

Figure S19. [1]H NMR spectrum of compound **8l**

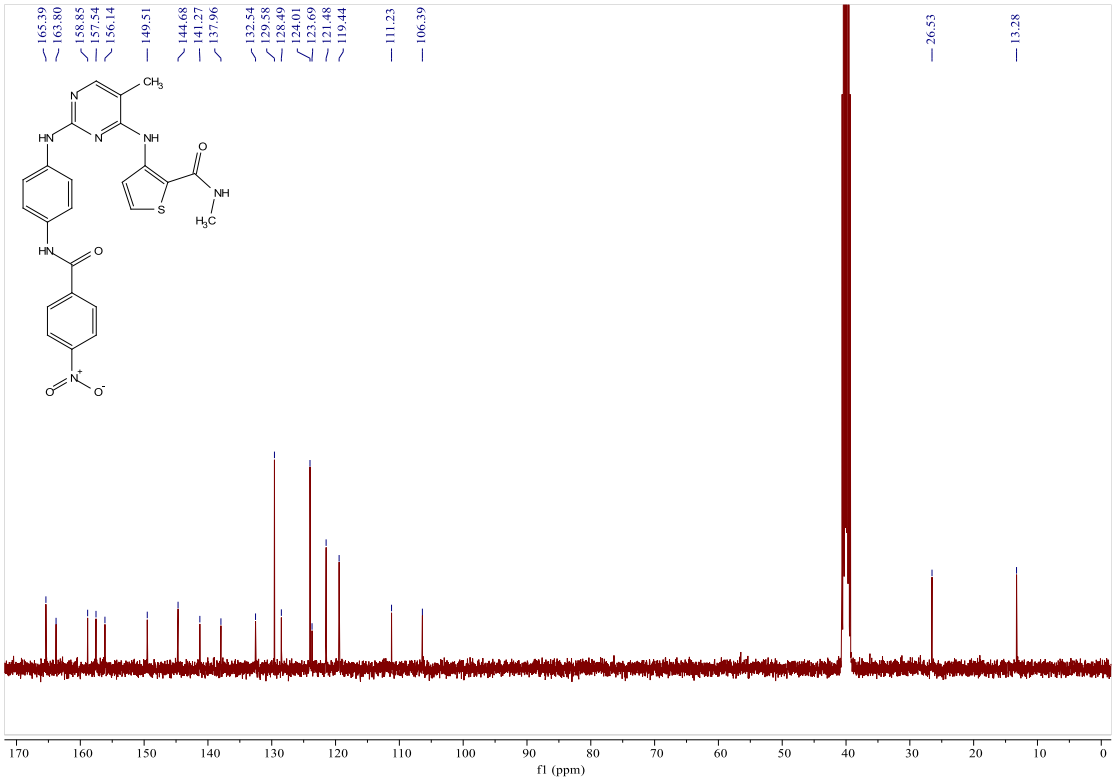

Figure S19 [13]C NMR spectrum of compound **8l**

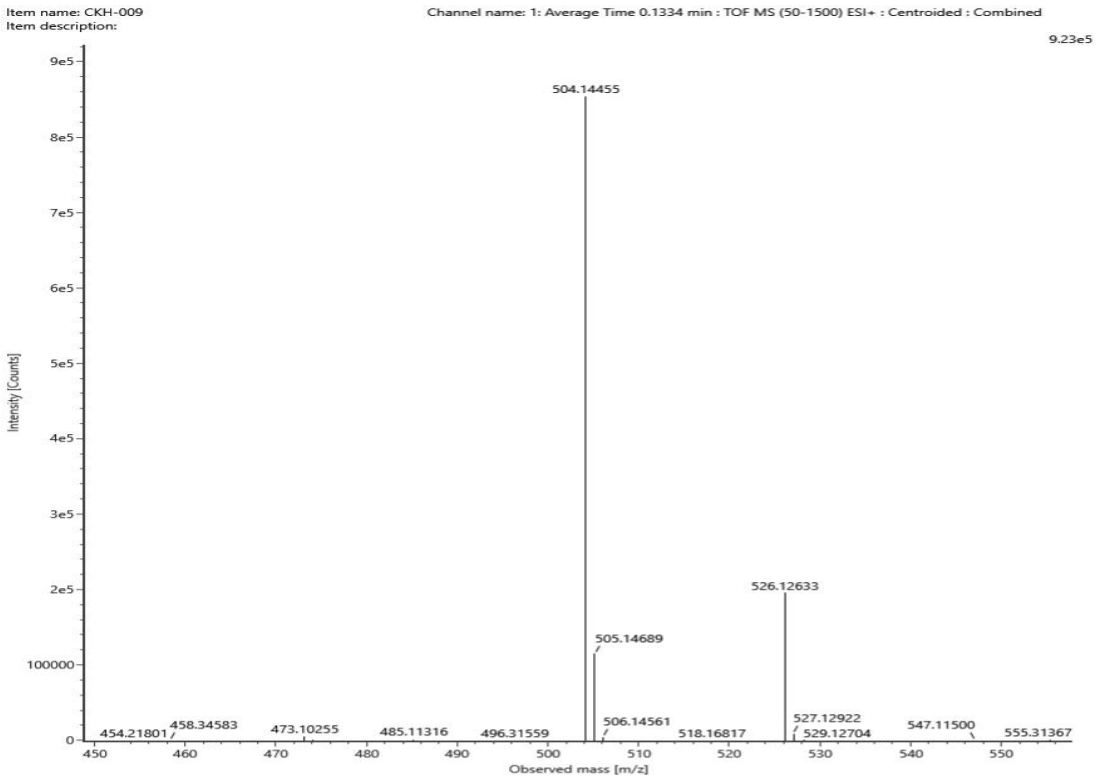

Figure S19. HR-MS (ESI) spectrogram of compound **8l**

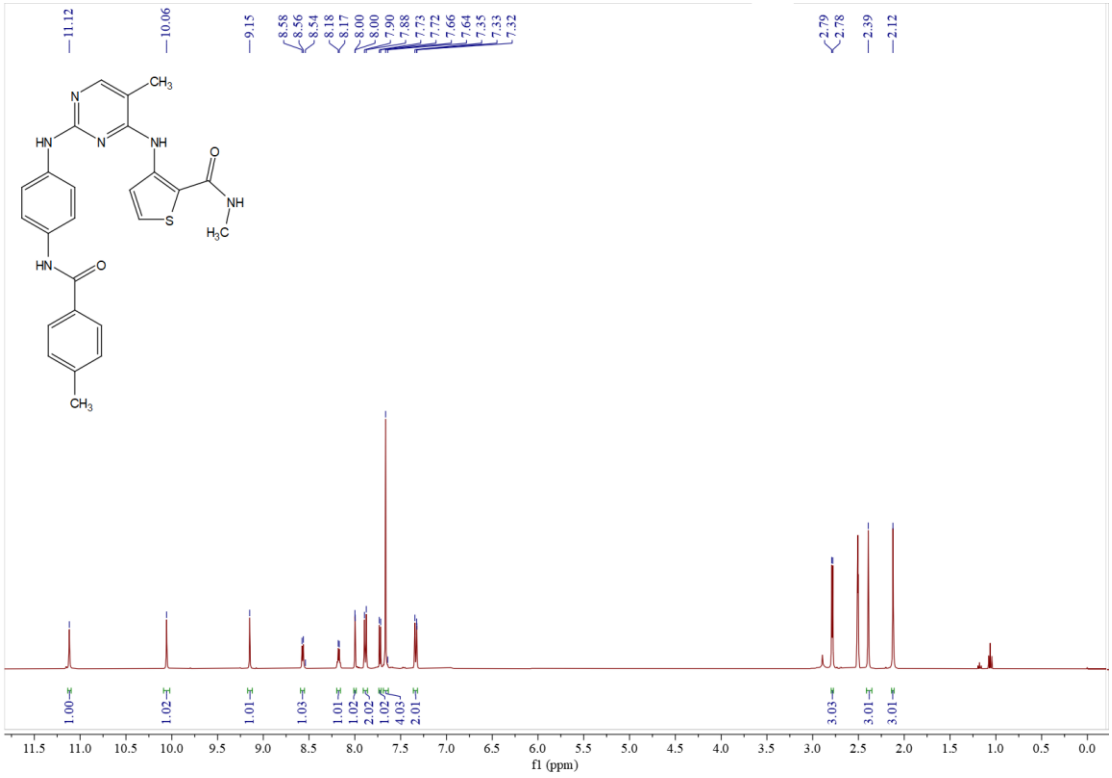

Figure S20. ^{1}H NMR spectrum of compound **8m**

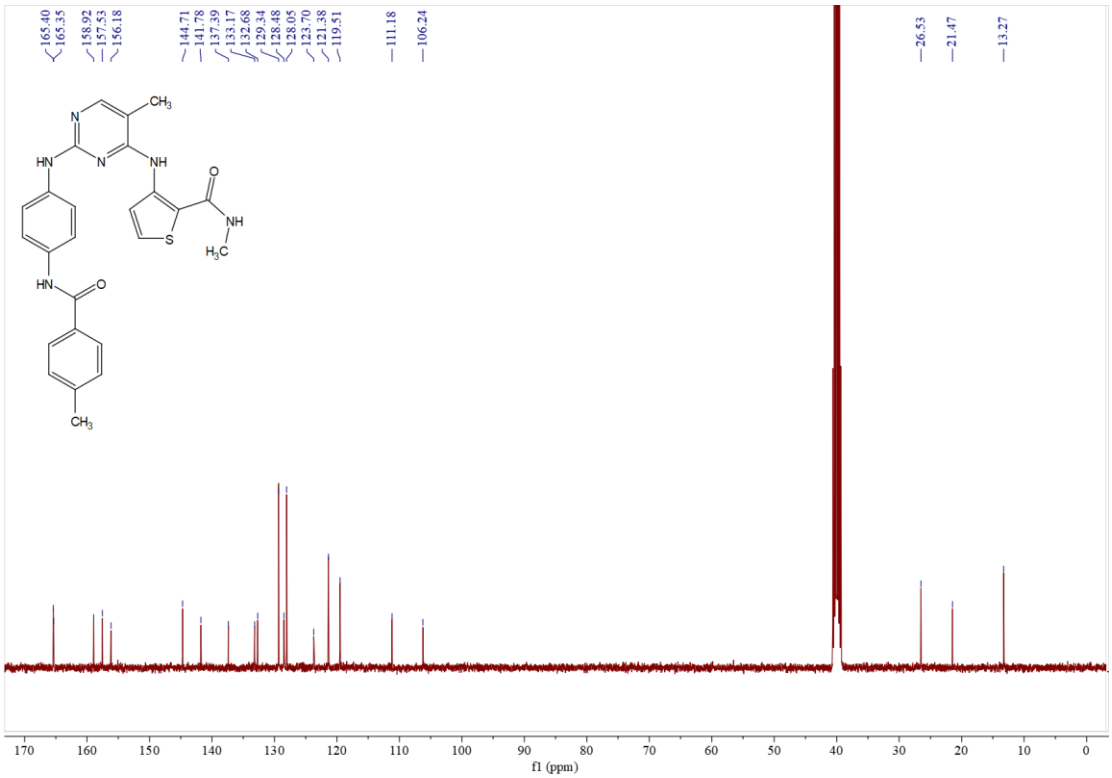

Figure S20. ^{13}C NMR spectrum of compound **8m**

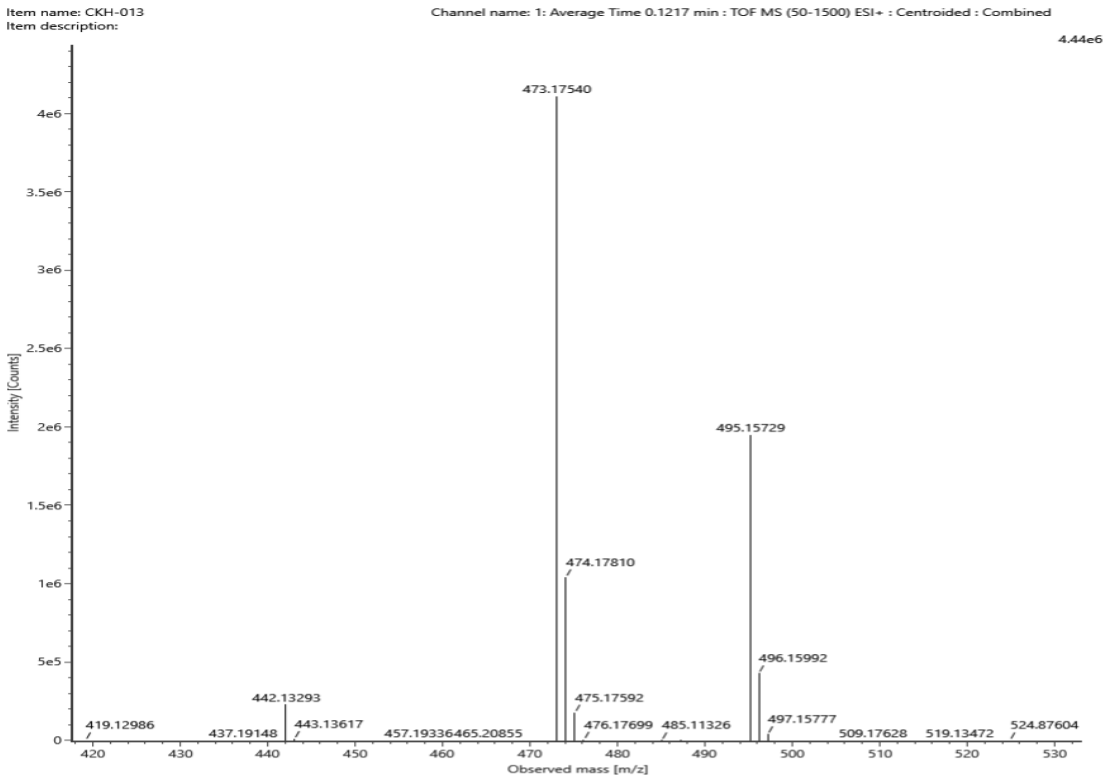

Figure S20. HR-MS (ESI) spectrogram of compound **8m**

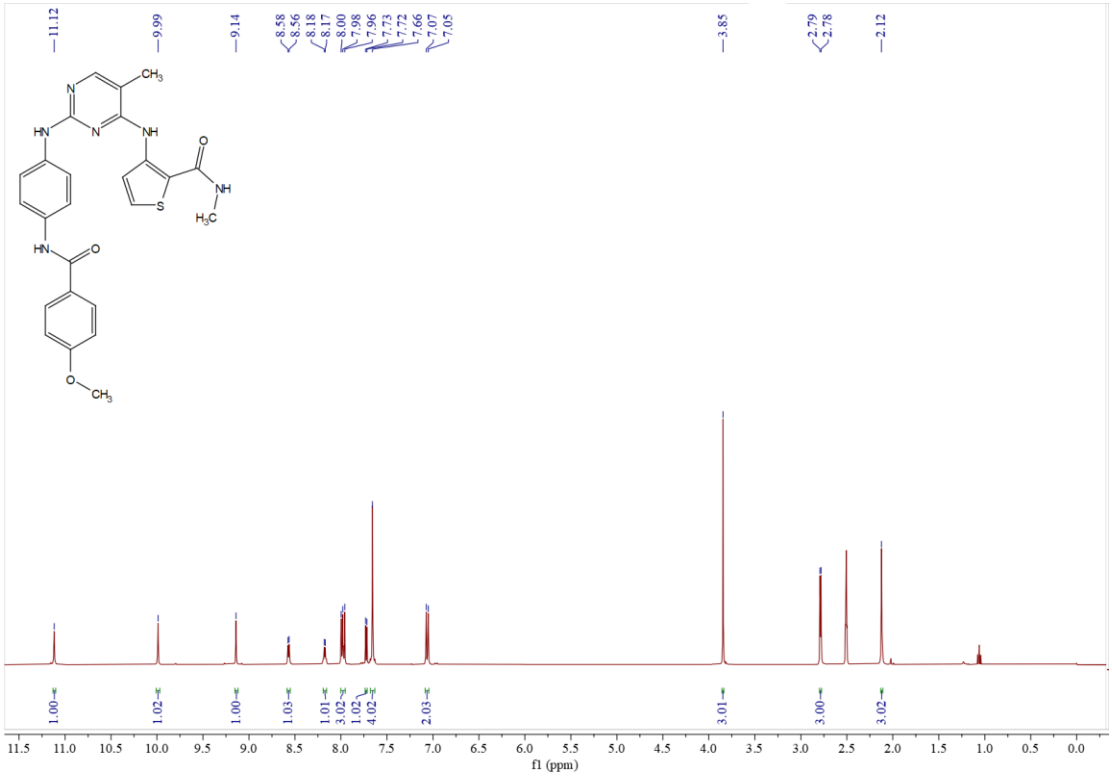

Figure S21. [1]H NMR spectrum of compound **8n**

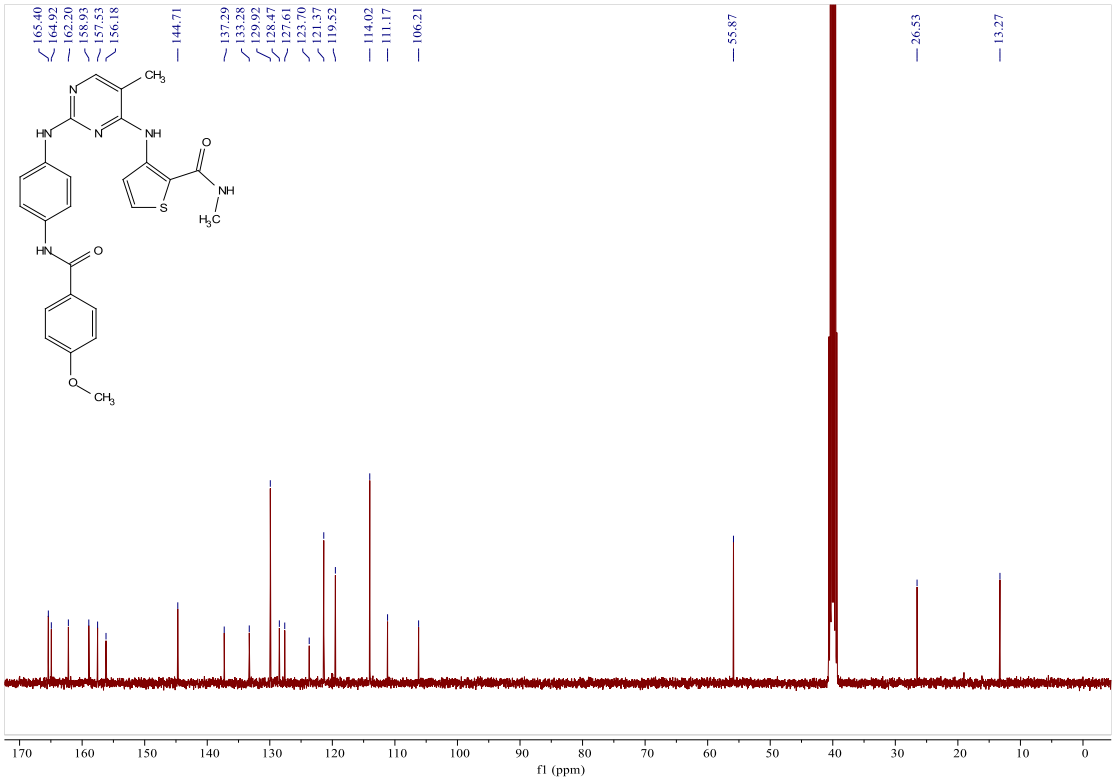

Figure S21. [13]C NMR spectrum of compound **8n**

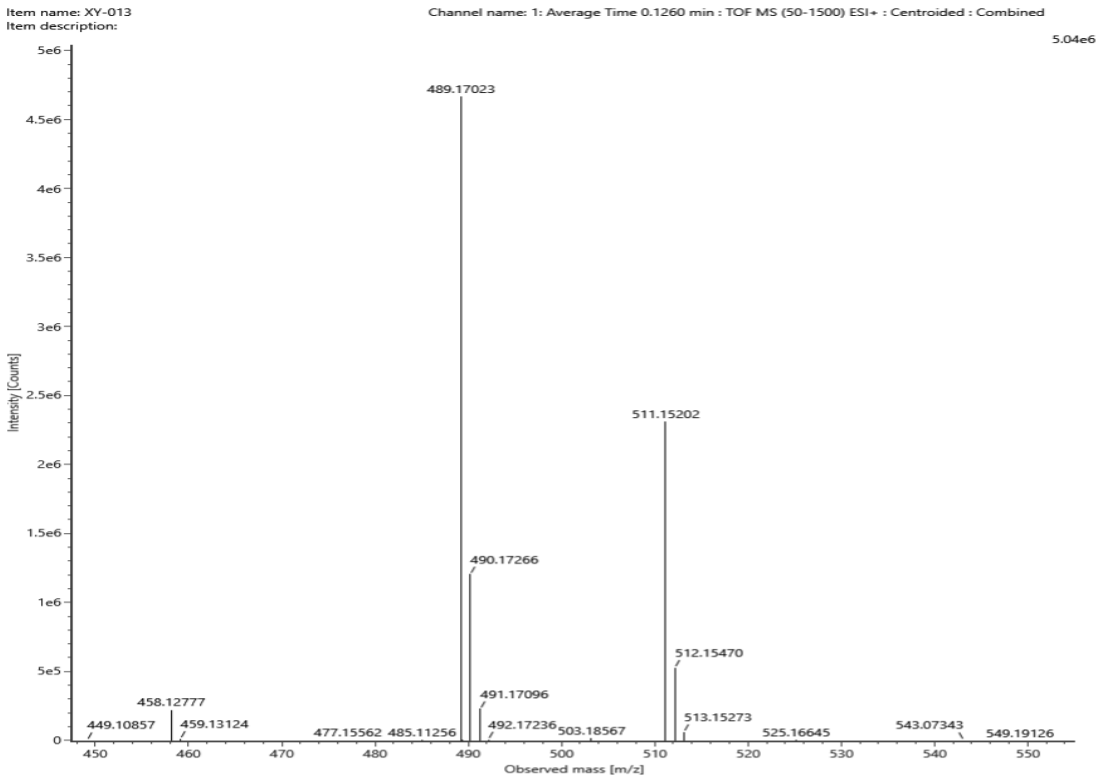

Figure S21. HR-MS (ESI) spectrogram of compound **8n**

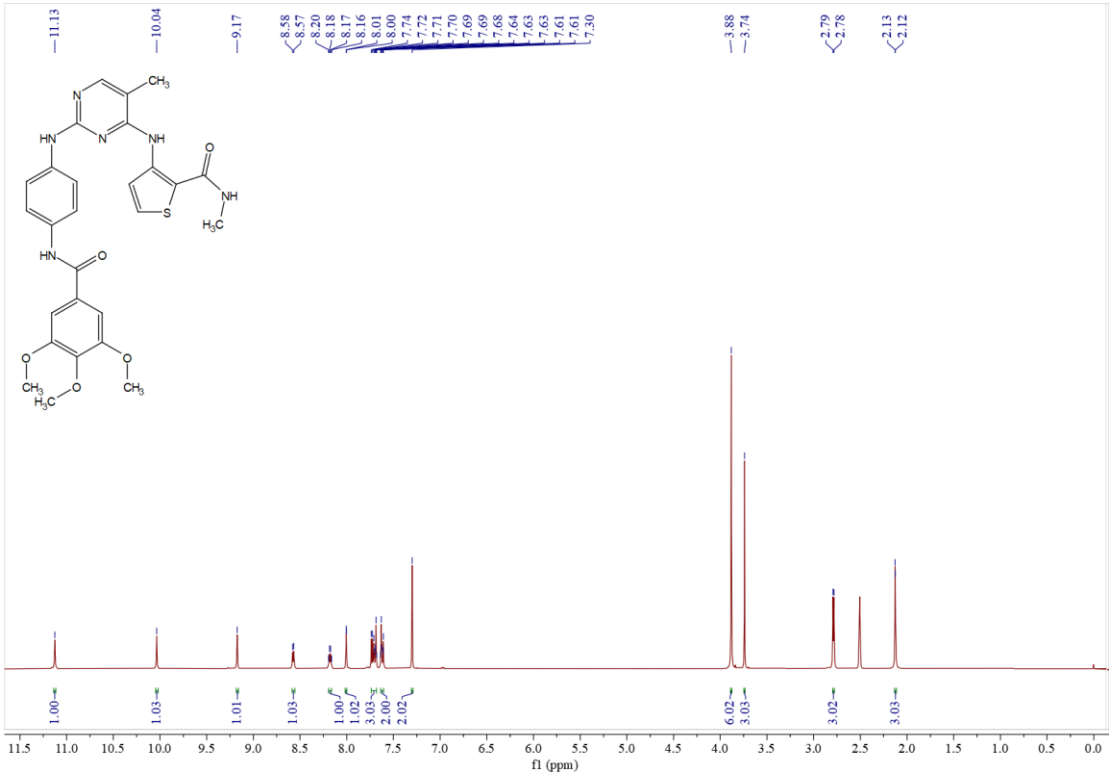

Figure S22. ^{1}H NMR spectrum of compound **8o**

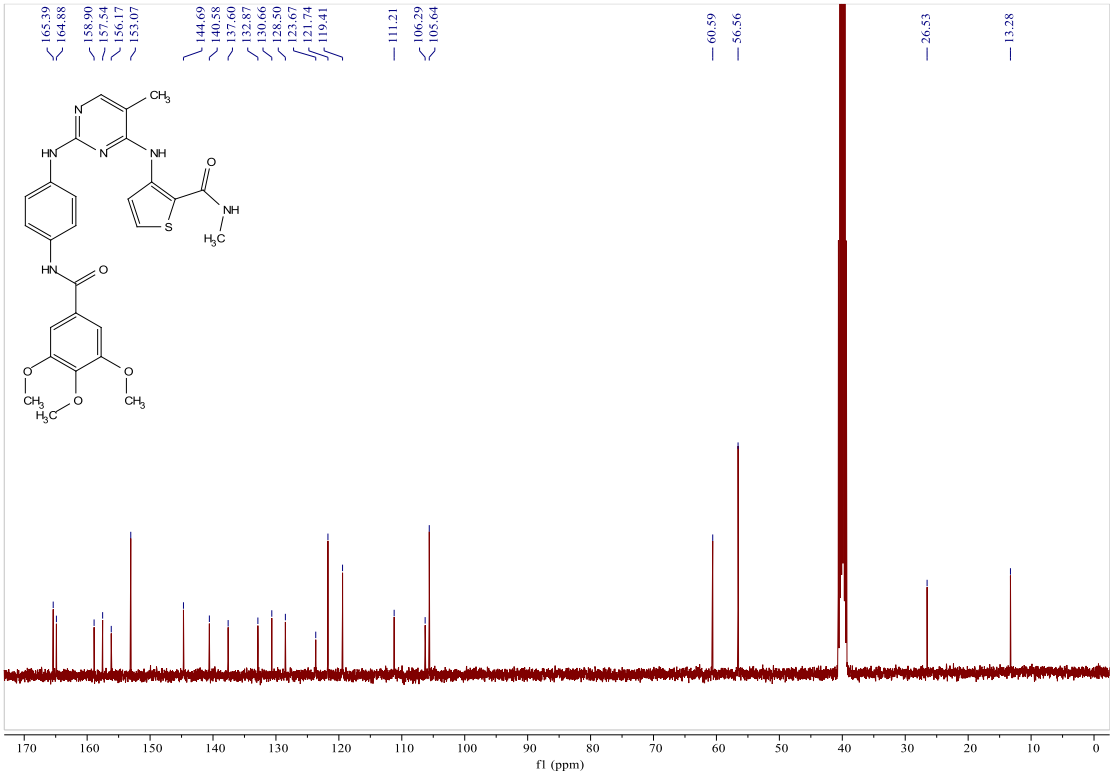

Figure S22. ^{13}C NMR spectrum of compound **8o**

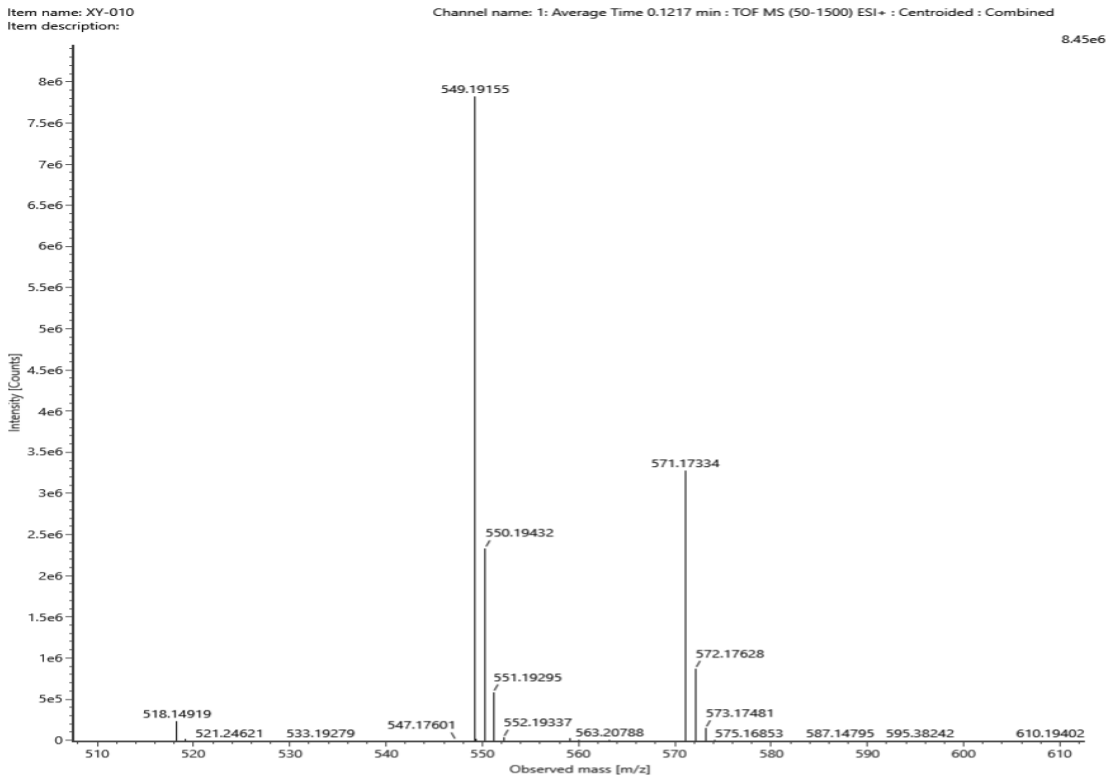

Figure S22. HR-MS (ESI) spectrogram of compound **8o**

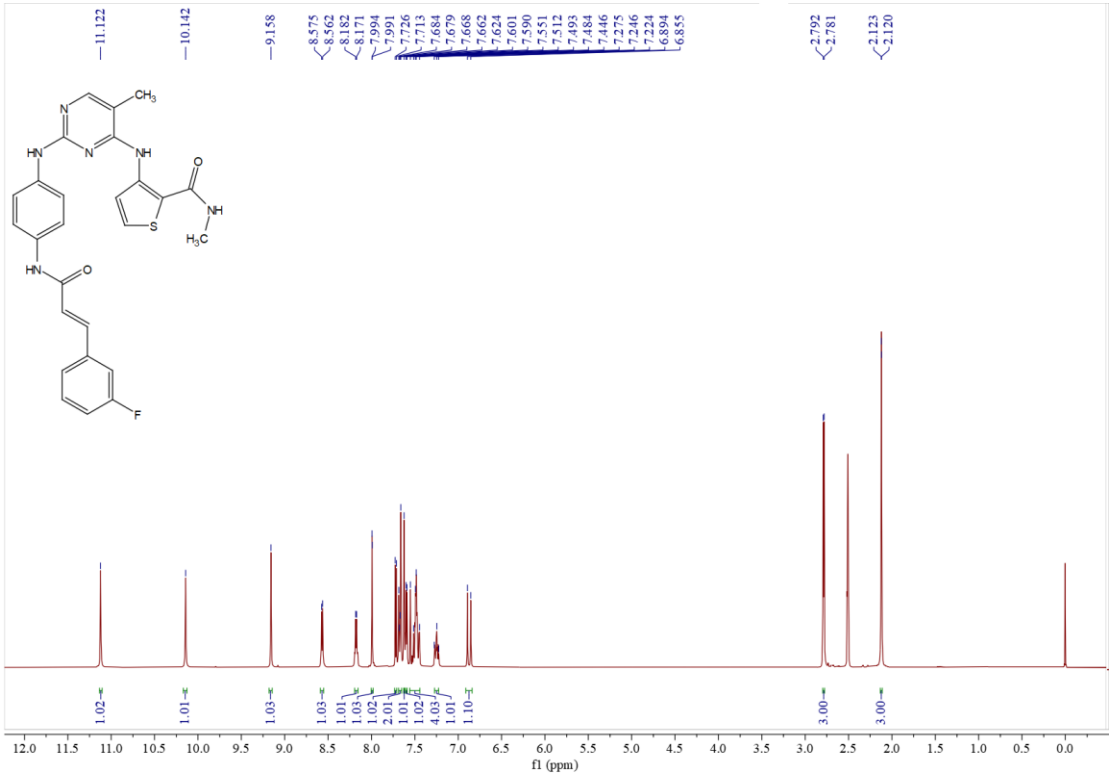

Figure S65. [1]H NMR spectrum of compound **8p**

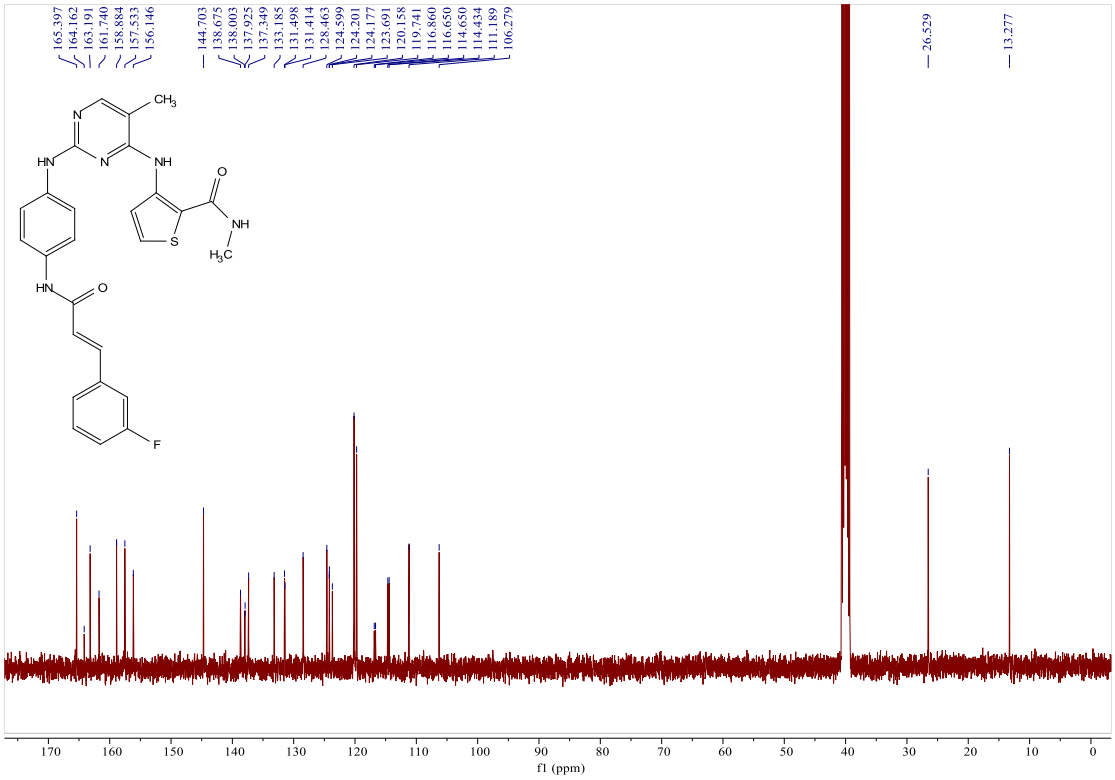

Figure S66. [13]C NMR spectrum of compound **8p**

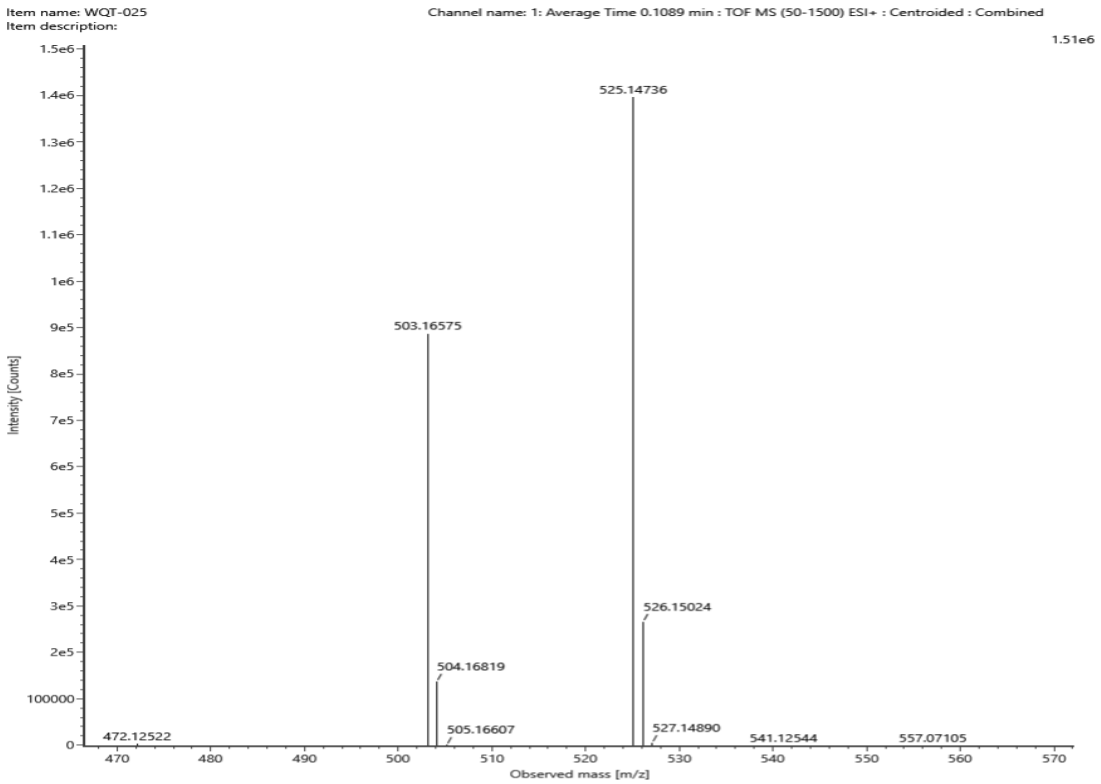

Figure S67. HR-MS (ESI) spectrogram of compound **8p**

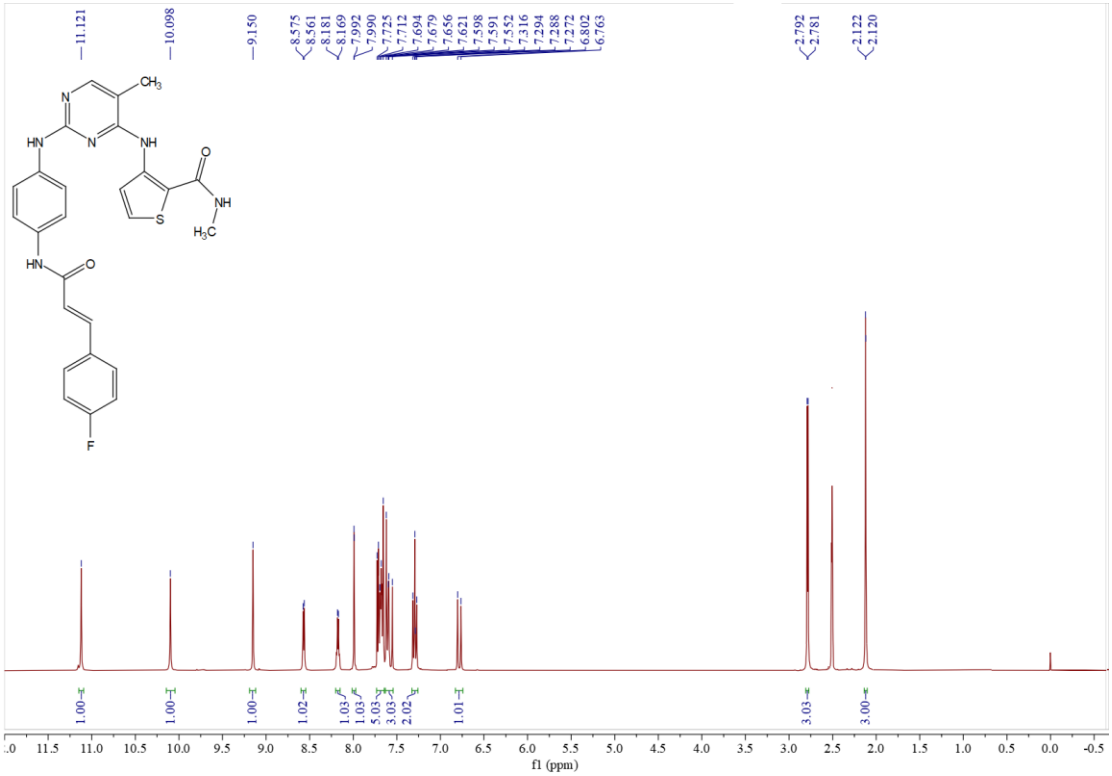

Figure S68. ^{1}H NMR spectrum of compound **8q**

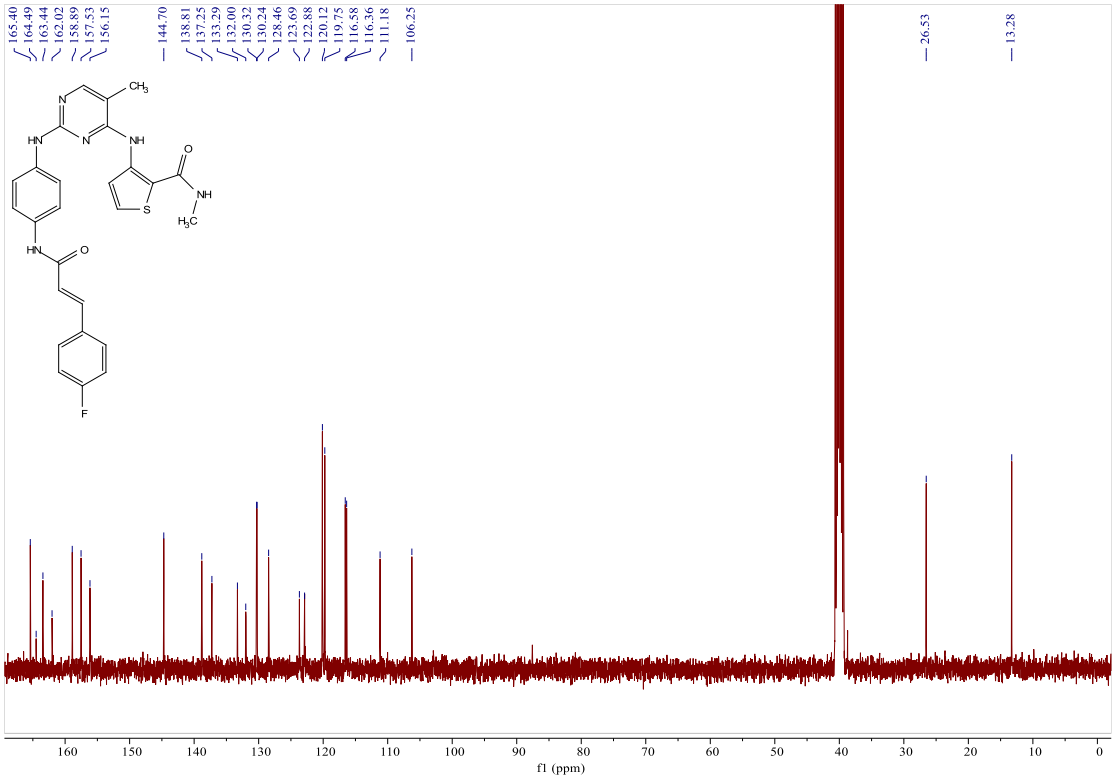

Figure S69. ^{13}C NMR spectrum of compound **8q**

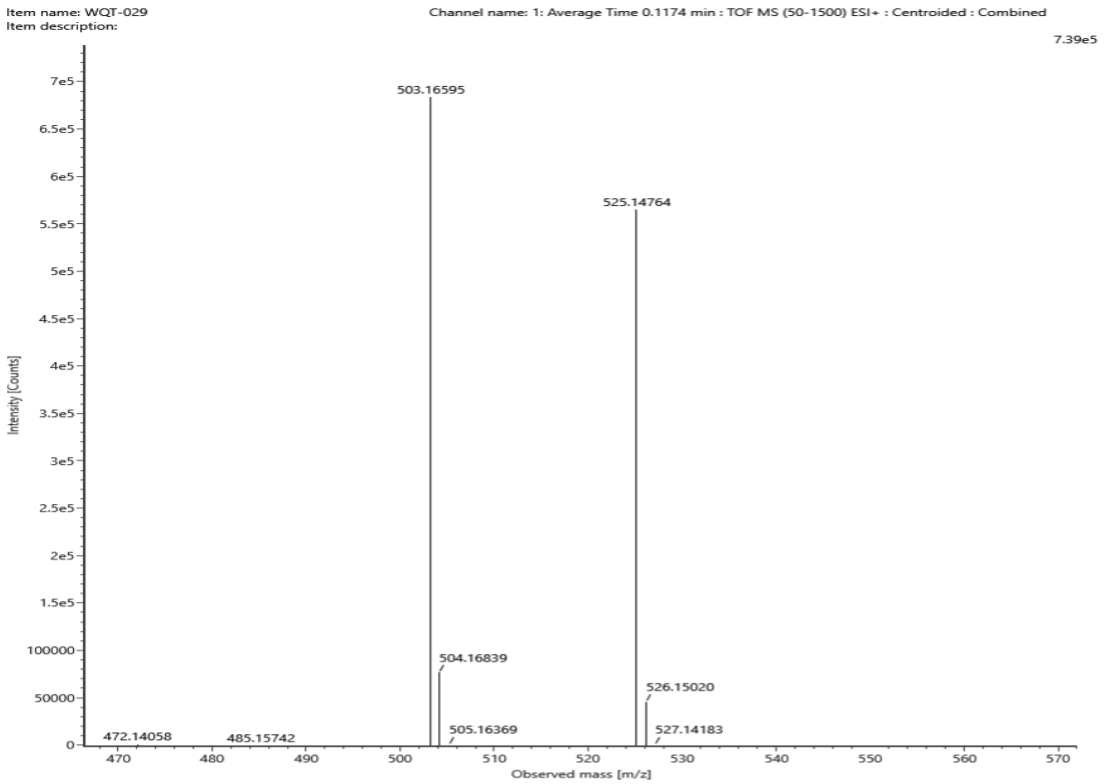

Figure S70. HR-MS (ESI) spectrogram of compound **8q**

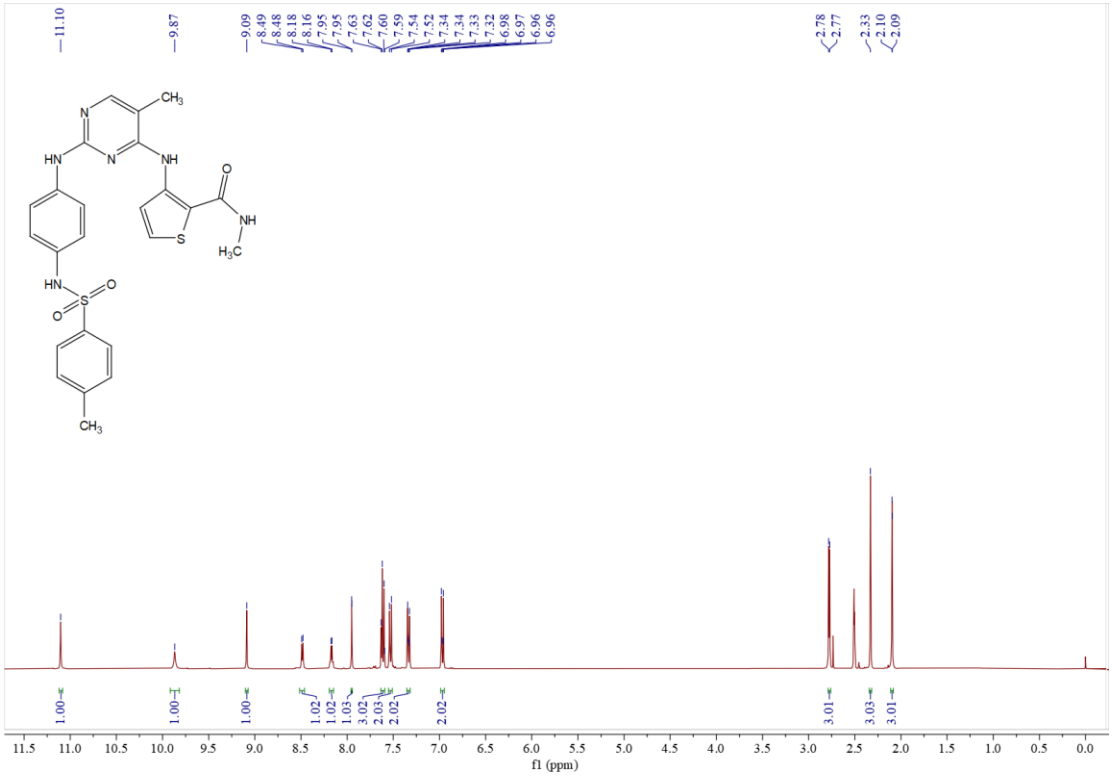

Figure S25. [1]H NMR spectrum of compound **8r**

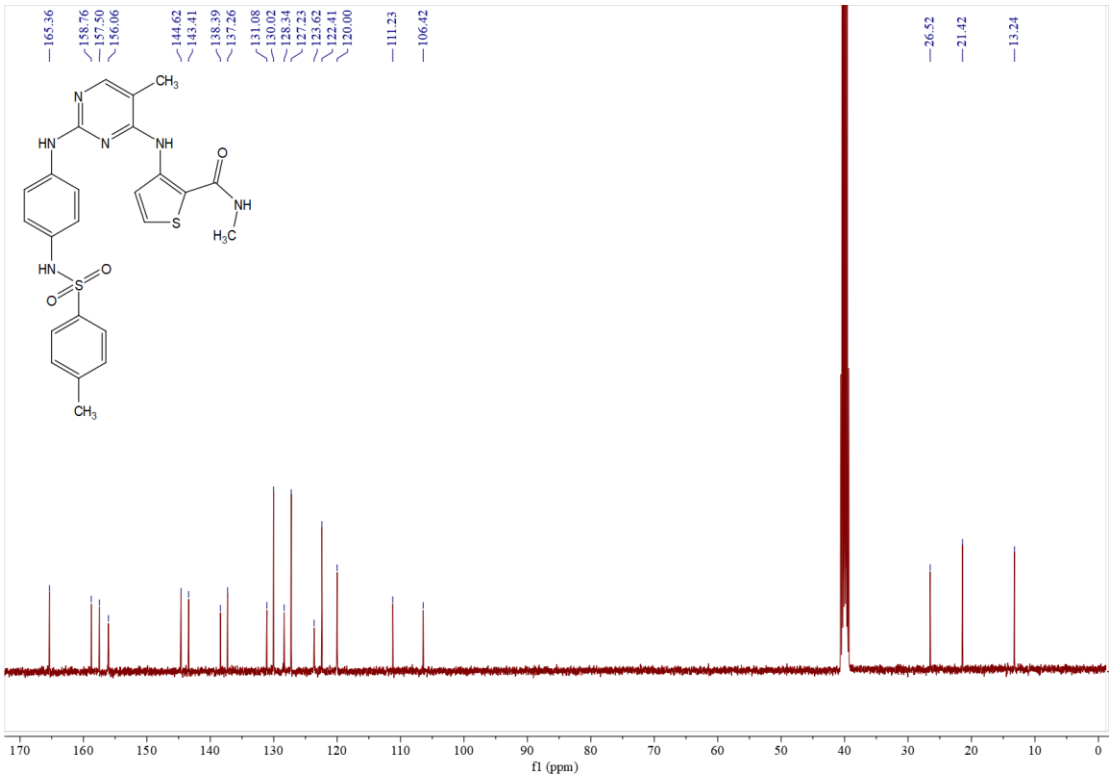

Figure S25. [13]C NMR spectrum of compound **8r**

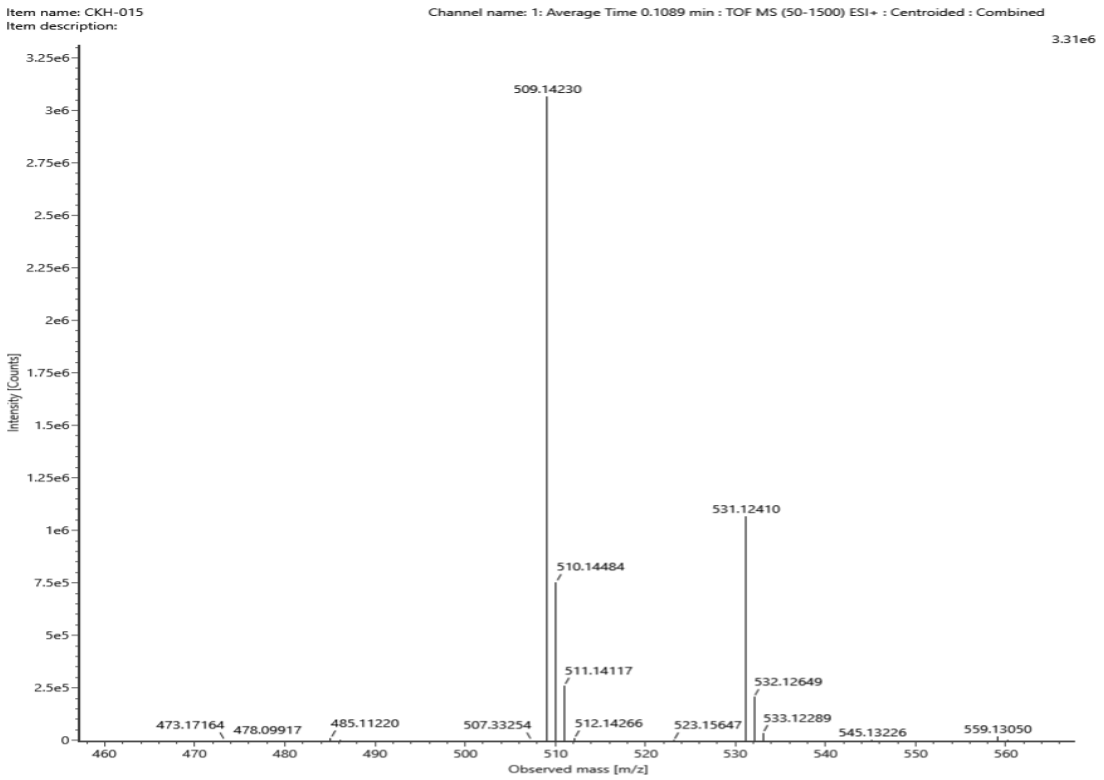

Figure S25. HR-MS (ESI) spectrogram of compound **8r**

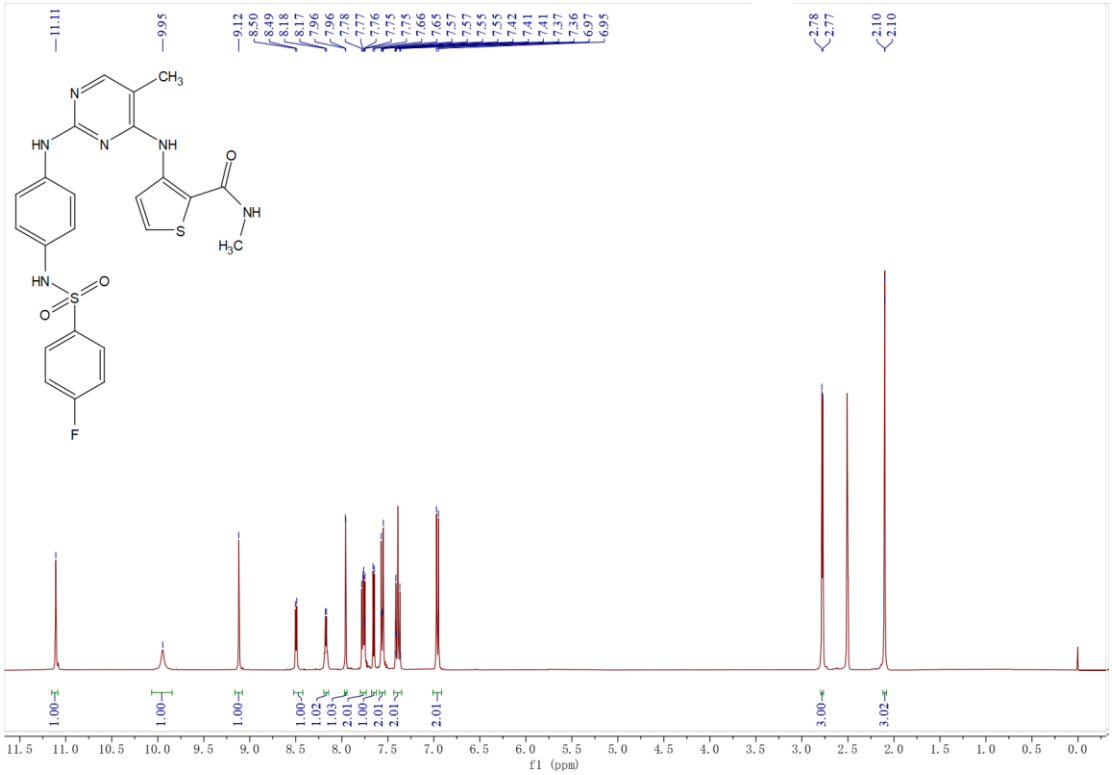

Figure S74. ^{1}H NMR spectrum of compound **8s**

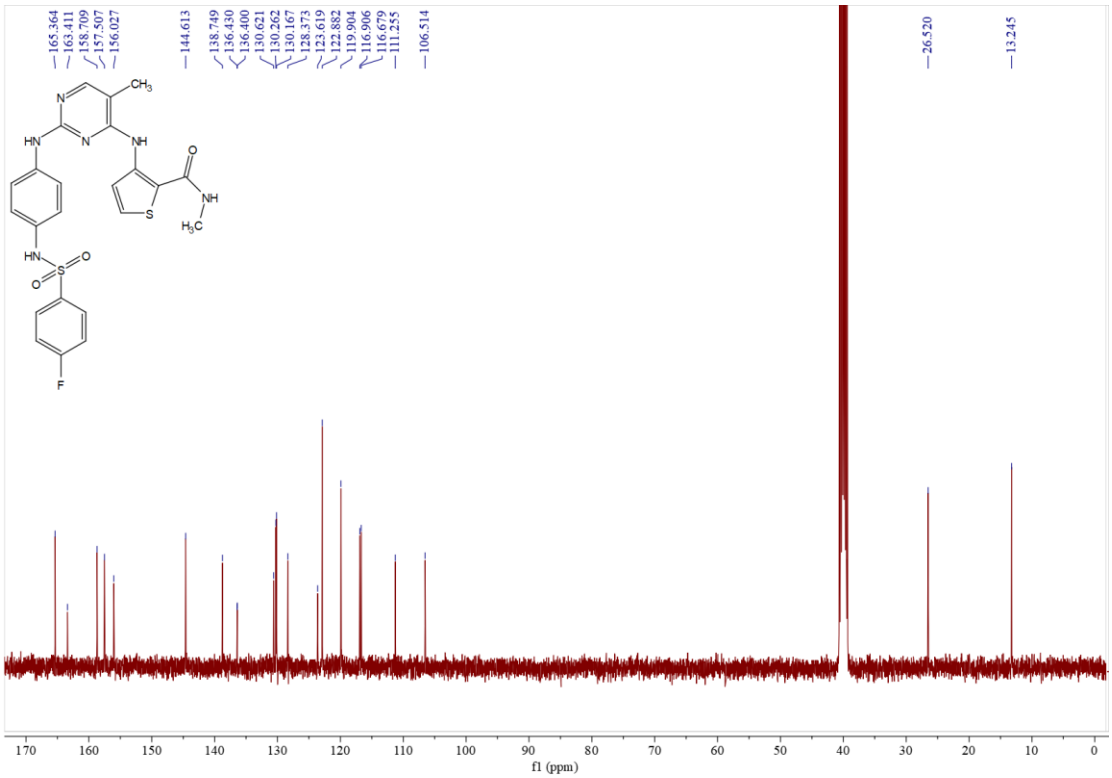

Figure S75. ^{13}C NMR spectrum of compound **8s**

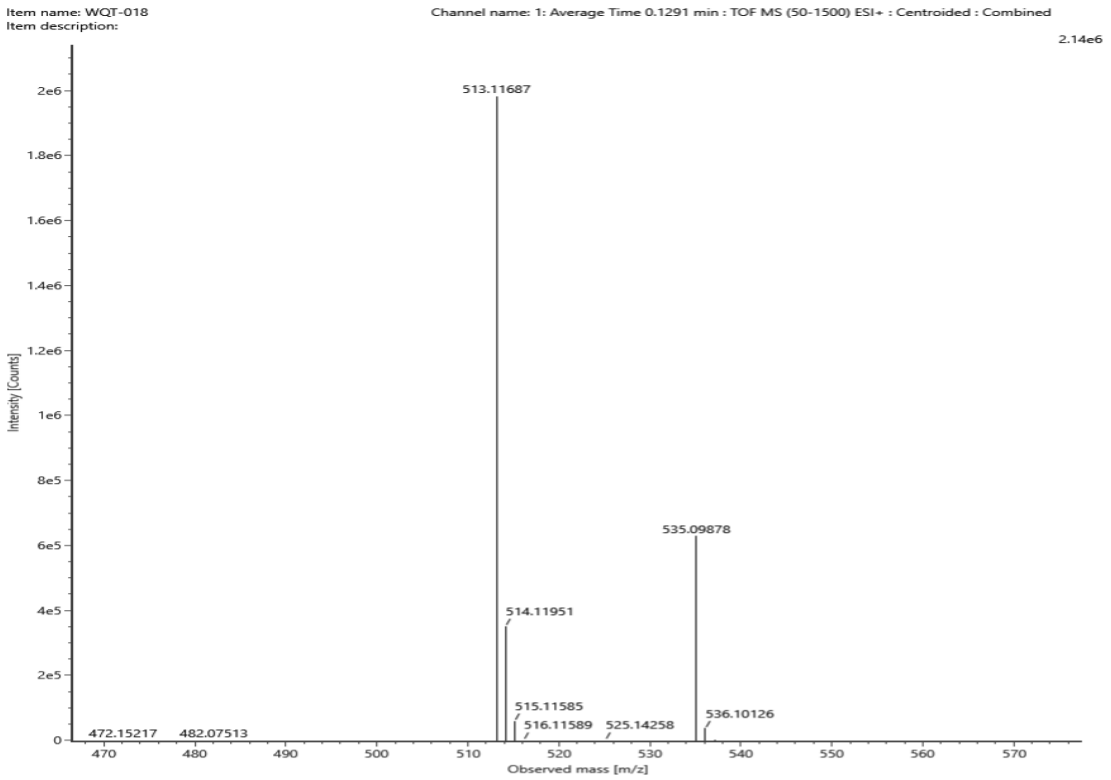

Figure S76. HR-MS (ESI) spectrogram of compound **8s**

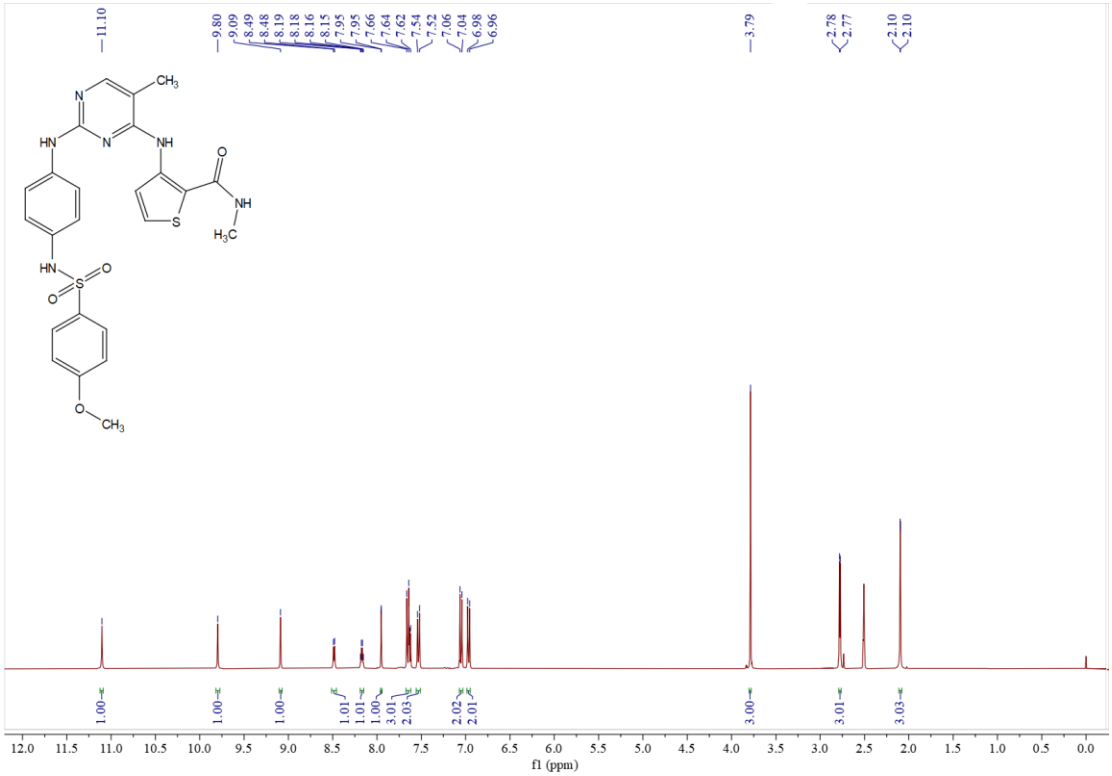

Figure S27. [1]H NMR spectrum of compound **8t**

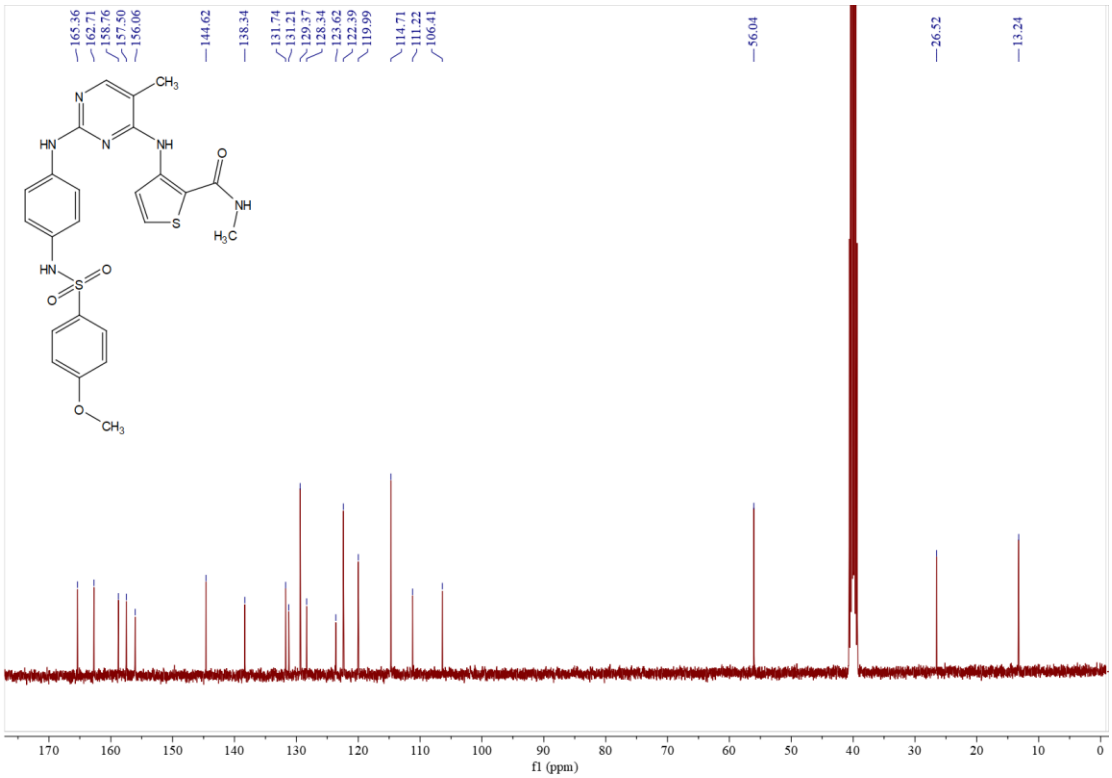

Figure S27. [13]C NMR spectrum of compound **8t**

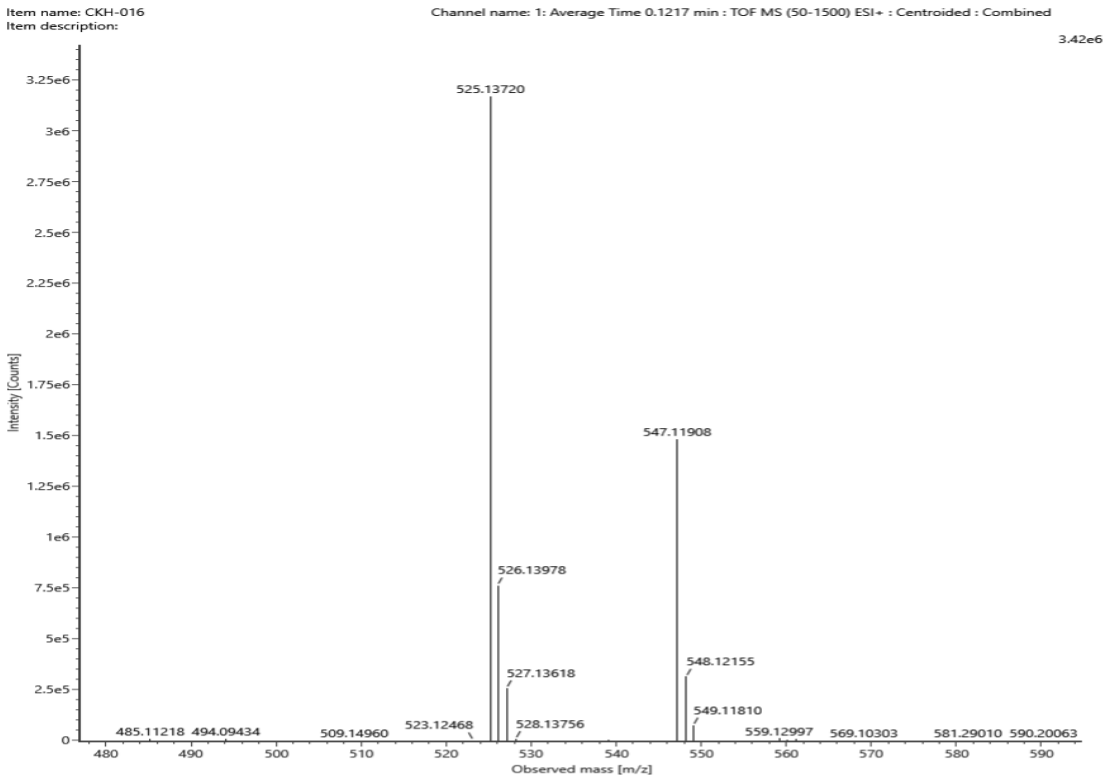

Figure S27. HR-MS (ESI) spectrogram of compound **8t**

ADMET Properties of compound 8f

ADMETlab 2.0

C#CC(=O)Nc1ccc(N=c2[nH]cc(C)c(=Nc3ccsc3C(=O)NC)[nH]2)cc1

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	406.12	Contain hydrogen atoms. Optimal:100~600
Volume	399.239	Van der Waals volume
Density	1.017	Density = MW / Volume
nHA	8	Number of hydrogen bond acceptors. Optimal:0~12
nHD	4	Number of hydrogen bond donors. Optimal:0~7
nRot	6	Number of rotatable bonds. Optimal:0~11
nRing	3	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	9	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	22	Number of rigid bonds. Optimal:0~30
Flexibility	0.273	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	114.5	Topological Polar Surface Area. Optimal:0~140
logS	-3.746	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	2.499	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	2.905	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.497	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.673	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.1	🔴	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	18.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	-0.969	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	3 alerts	-	Thiol reactive compounds.
BMS	1 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.987	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.8e-05	●	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.005	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.88	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.025	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.044	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	91.41%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.709	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.667	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	5.135%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.537	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.911	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.907	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.052	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.761	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.062	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.016	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.013	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.836	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.827	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	5.461	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.565	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.804	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.994	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.987	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.977	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.977	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.916	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.505	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.507	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.003	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.012	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.976	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.257	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	4.557	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.62	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	5.66	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.009	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.011	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.979	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.862	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.236	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.007	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.08	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.907	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.833	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.058	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.948	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.935	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	4 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	1 alerts	■ 164 substructures ■ MedChem unfriendly status

ADMET Properties of compound 8o

ADMETlab 2.0

CNC(=O)c1sccc1N=c1[nH]c(=Nc2ccc(NC(=O)c3cc(OC)c(OC)c(OC)c3)cc2)[nH]cc1C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	548.18	Contain hydrogen atoms. Optimal:100~600
Volume	535.489	Van der Waals volume
Density	1.024	Density = MW / Volume
nHA	11	Number of hydrogen bond acceptors. Optimal:0~12
nHD	4	Number of hydrogen bond donors. Optimal:0~7
nRot	10	Number of rotatable bonds. Optimal:0~11
nRing	4	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	12	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	27	Number of rigid bonds. Optimal:0~30
Flexibility	0.37	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	142.19	Topological Polar Surface Area. Optimal:0~140
logS	-4.45	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.229	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.124	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.265	●	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.303	●	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.185	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	25.0	●	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	-0.886	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Rejected	🔴	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	🟢	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	🔴	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	🔴	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	5 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-5.721	🔴	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.4e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.987	🔴	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.966	🔴	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.45	🟡	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.006	🟢	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.094	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	98.09%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.597	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.018	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	3.506%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.432	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.966	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.692	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.058	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.721	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.074	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.006	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.028	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.829	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.924	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	5.021	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.618	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.925	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.993	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.98	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.954	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.736	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.934	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.111	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogenicity	0.113	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.003	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.008	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.85	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.712	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.981	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.681	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	6.002	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.024	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.02	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.98	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.846	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.51	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.028	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.112	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.89	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.9	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.048	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.938	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.931	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	6 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	0 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

ADMET Properties of compound 8p

ADMETlab 2.0

CNC(=O)c1sccc1N=c1[nH]c(=Nc2ccc(NC(=O)/C=C/c3cccc(F)c3)cc2)[nH]cc1C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	502.16	Contain hydrogen atoms. Optimal:100~600
Volume	495.253	Van der Waals volume
Density	1.014	Density = MW / Volume
nHA	8	Number of hydrogen bond acceptors. Optimal:0~12
nHD	4	Number of hydrogen bond donors. Optimal:0~7
nRot	8	Number of rotatable bonds. Optimal:0~11
nRing	4	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	10	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	28	Number of rigid bonds. Optimal:0~30
Flexibility	0.286	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	114.5	Topological Polar Surface Area. Optimal:0~140
logS	-4.761	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	4.12	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.507	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.294	●	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.373	●	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.077	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	23.0	●	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	-1.22	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	4 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-5.282	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.5e-05	●	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.983	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.017	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.857	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.002	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.006	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	98.68%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.501	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.054	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	1.377%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.603	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.86	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.94	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.05	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.904	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.096	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.025	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.019	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.874	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.785	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	3.753	🔴	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.19	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.952	🔴	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.996	🔴	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.982	🔴	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.976	🔴	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.881	🔴	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.961	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.238	🟢	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogenicity	0.4	🟡	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.003	🟢	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.01	🟢	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.93	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.887	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	4.402	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.766	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	6.044	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.011	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.428	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.983	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.923	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.742	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.006	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.579	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.908	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.947	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.066	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.939	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.96	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	2 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	6 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	4 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	1 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

ADMET Properties of compound 8q

ADMETlab 2.0

CNC(=O)c1sccc1N=c1[nH]c(=Nc2ccc(NC(=O)/C=C/c3ccc(F)cc3)cc2)[nH]cc1C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	502.16	Contain hydrogen atoms. Optimal:100~600
Volume	495.253	Van der Waals volume
Density	1.014	Density = MW / Volume
nHA	8	Number of hydrogen bond acceptors. Optimal:0~12
nHD	4	Number of hydrogen bond donors. Optimal:0~7
nRot	8	Number of rotatable bonds. Optimal:0~11
nRing	4	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	10	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	28	Number of rigid bonds. Optimal:0~30
Flexibility	0.286	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	114.5	Topological Polar Surface Area. Optimal:0~140
logS	-4.662	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	4.137	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.47	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.294	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.33	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.077	🔴	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	23.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	-1.139	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	4 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-5.223	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.5e-05	●	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.987	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.023	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.839	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.002	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.006	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	98.60%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.531	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.053	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	1.384%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.585	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.856	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.931	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.05	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.87	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.105	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.026	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.019	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.846	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.812	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	3.67	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.155	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.948	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.996	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.983	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.981	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.931	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.948	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.205	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogenicity	0.395	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.003	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.01	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.923	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.971	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	4.413	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.793	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	6.069	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.008	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.541	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.984	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.951	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.747	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.008	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.558	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.917	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.951	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.073	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.94	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.962	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	2 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	6 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	4 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	1 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status