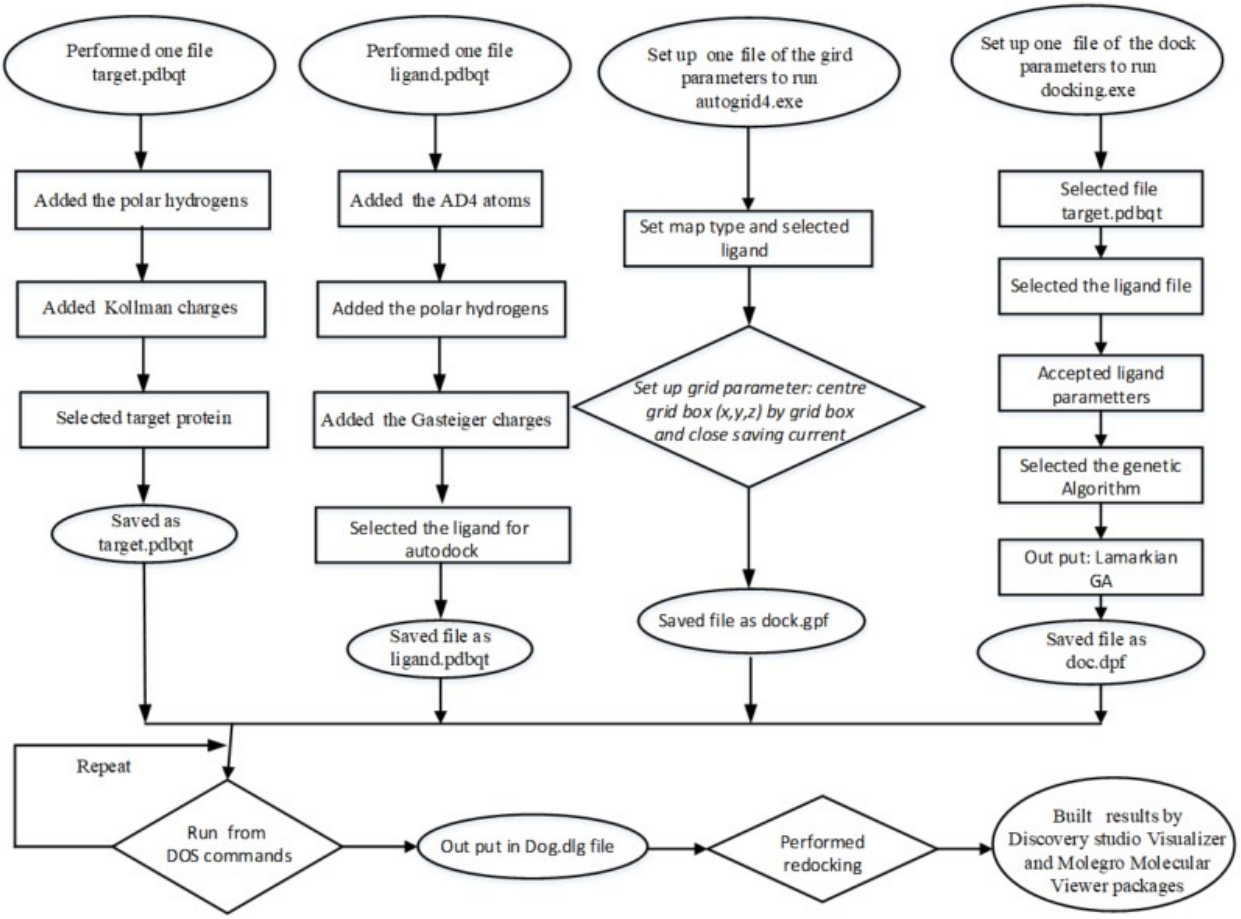
Appendix A. Supplementary data



Scheme S1. The general procedure for docking of ligand to enzyme or macro protein performed by Autodock tools (ADT) and built model by DSC and Molegro Molecular Viewer (MMV).

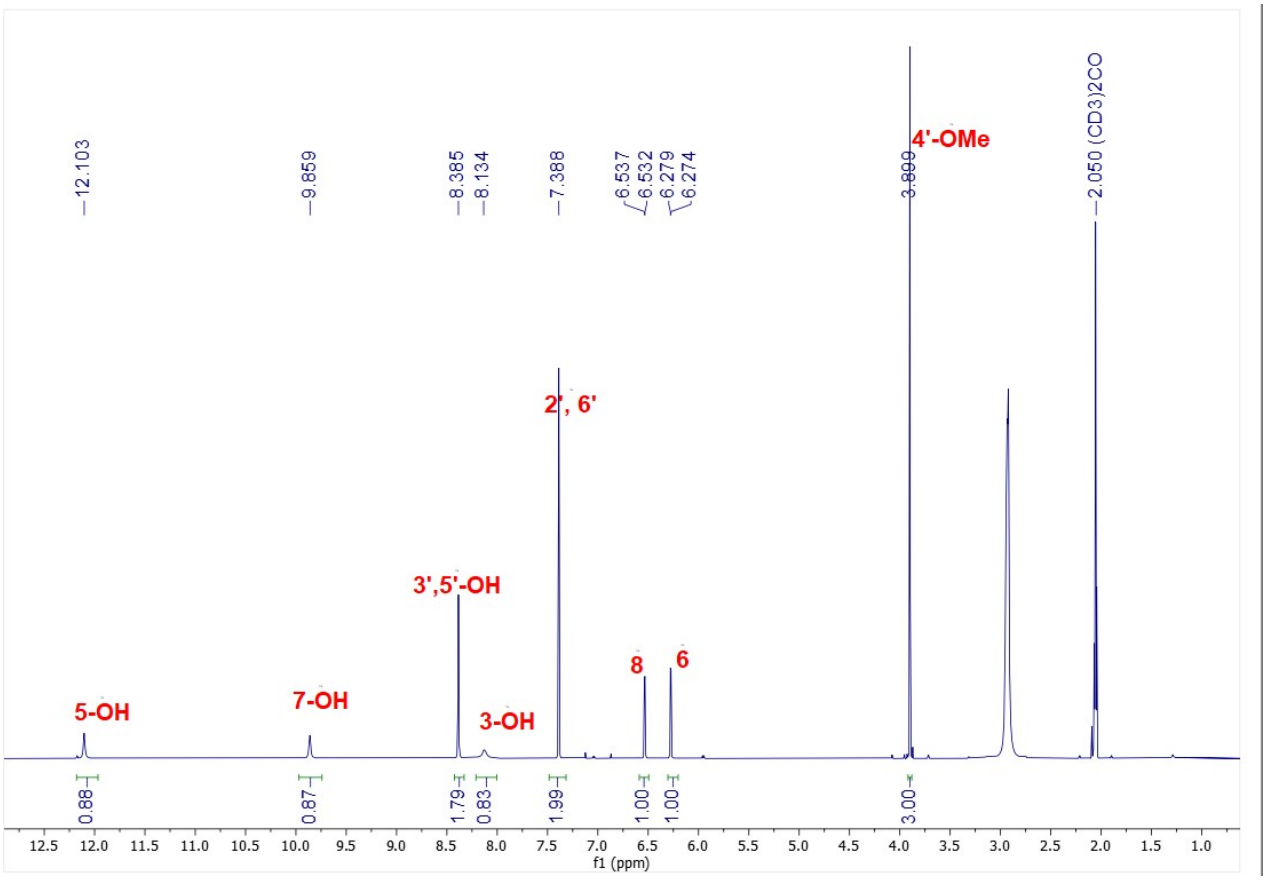


Figure S1. ^{1}H NMR spectrum (acetone-d_6) of **1**

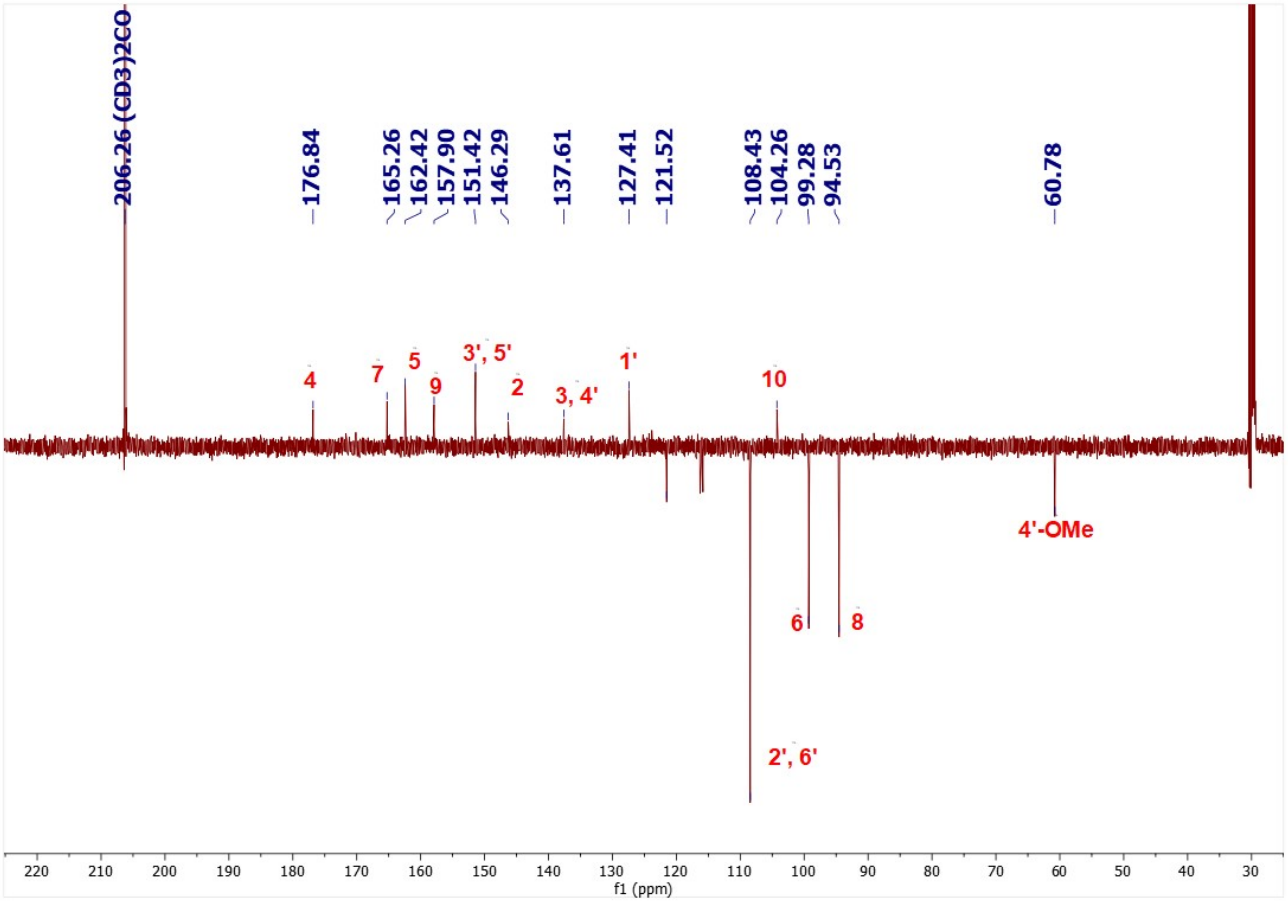


Figure S2. ^{13}C NMR spectrum (acetone-d_6) of **1**

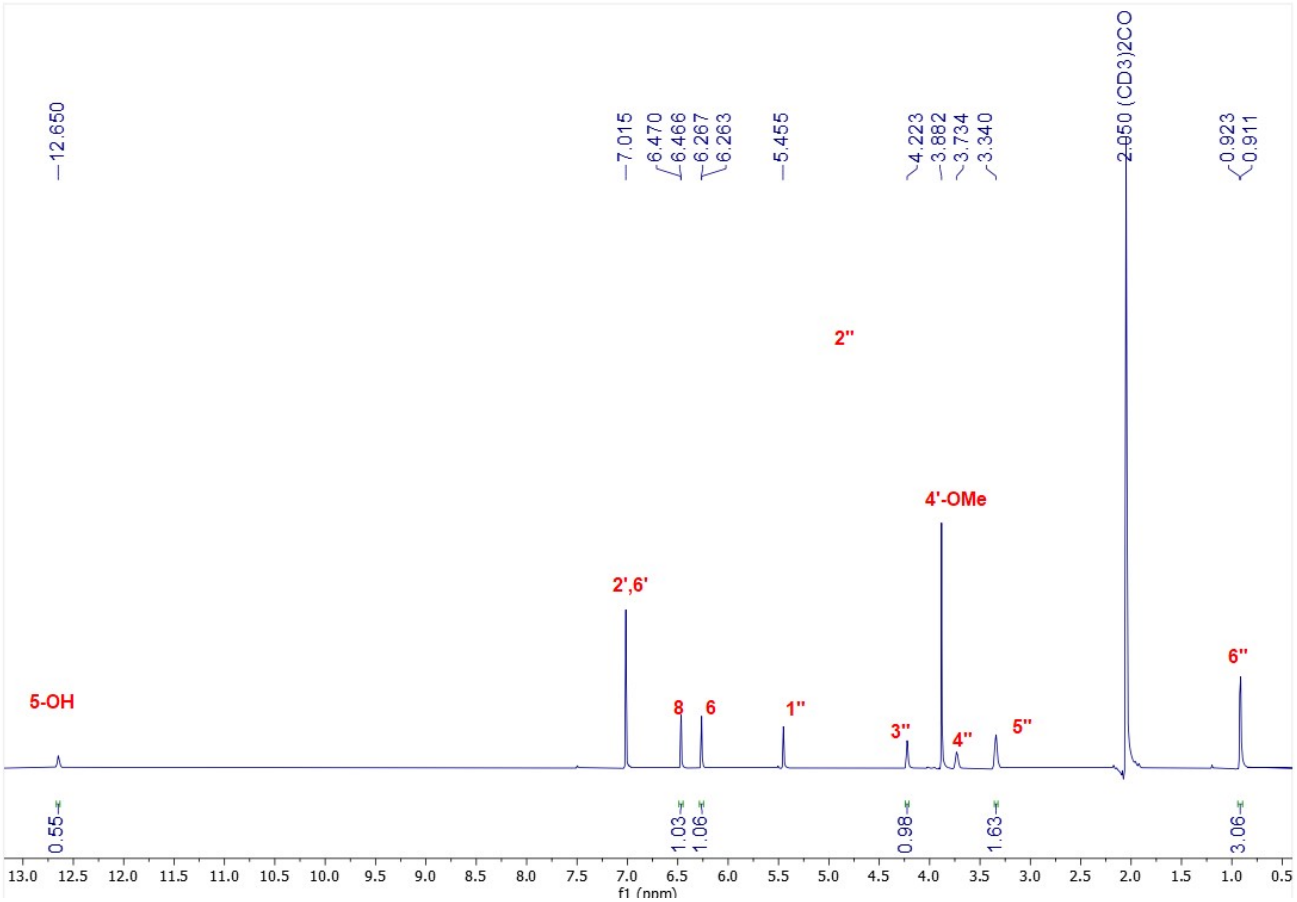


Figure S3. ^{1}H NMR spectrum (acetone-d_6) of **2**

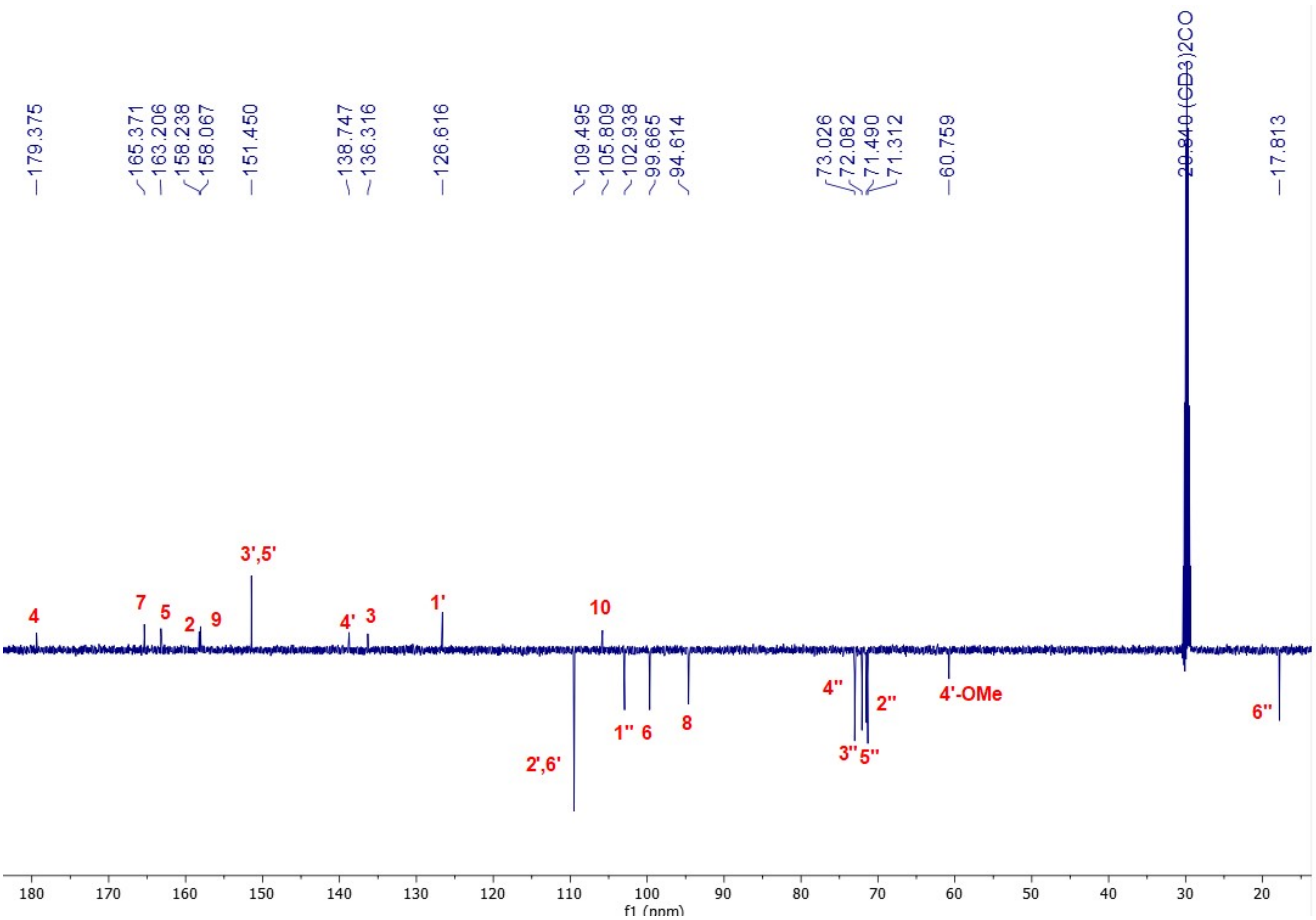


Figure S4. ^{13}C NMR spectrum (acetone-d_6) of **2**

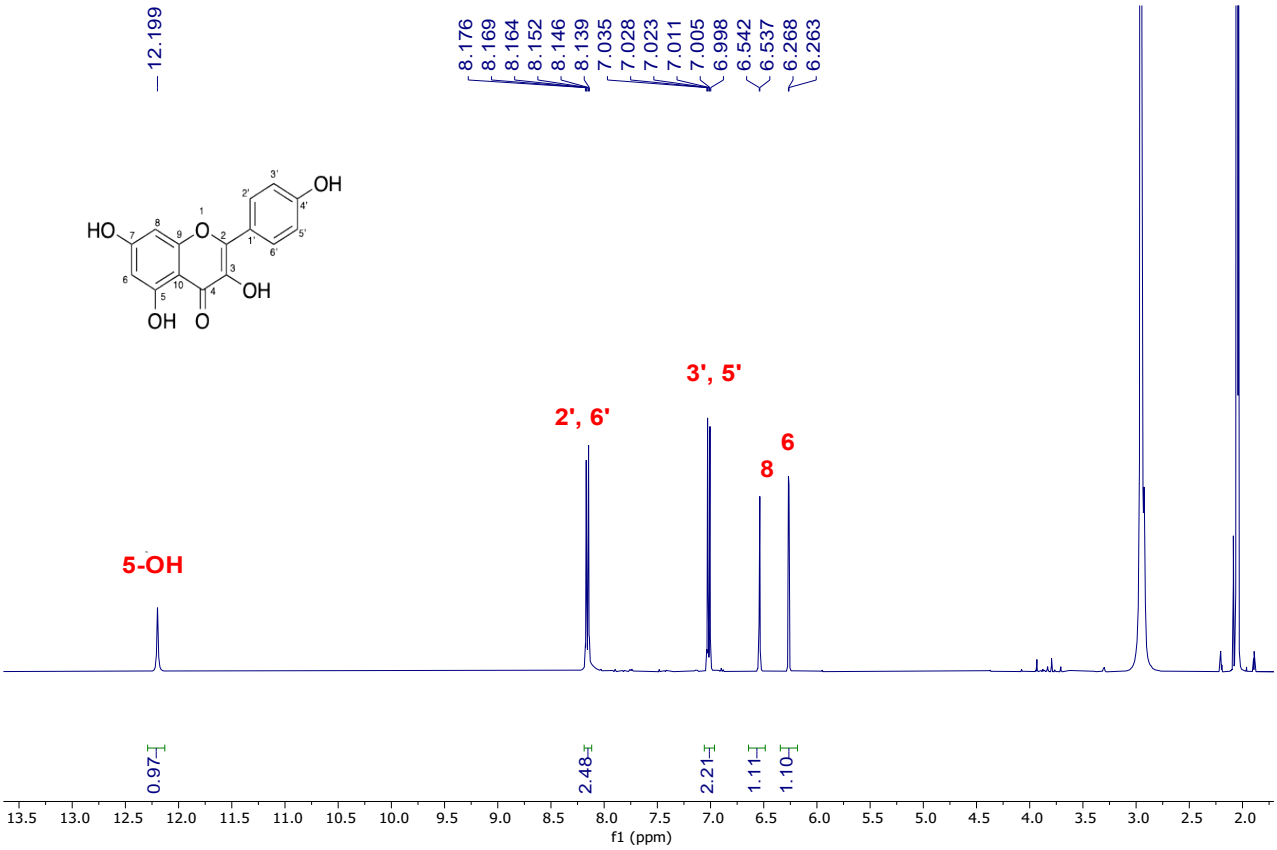


Figure S5. ^{1}H NMR spectrum (acetone-d_6) of **3**

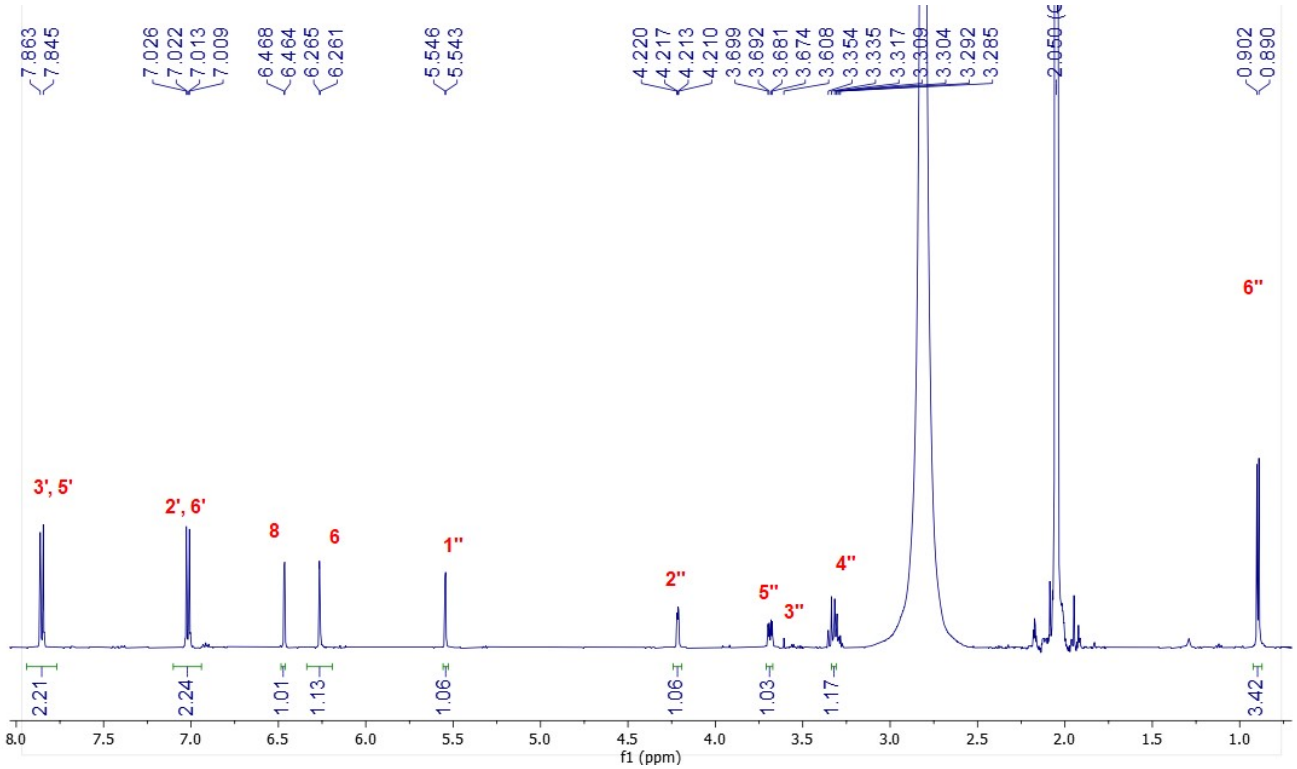


Figure S6. ^{1}H NMR spectrum (acetone-d_6) of **4**

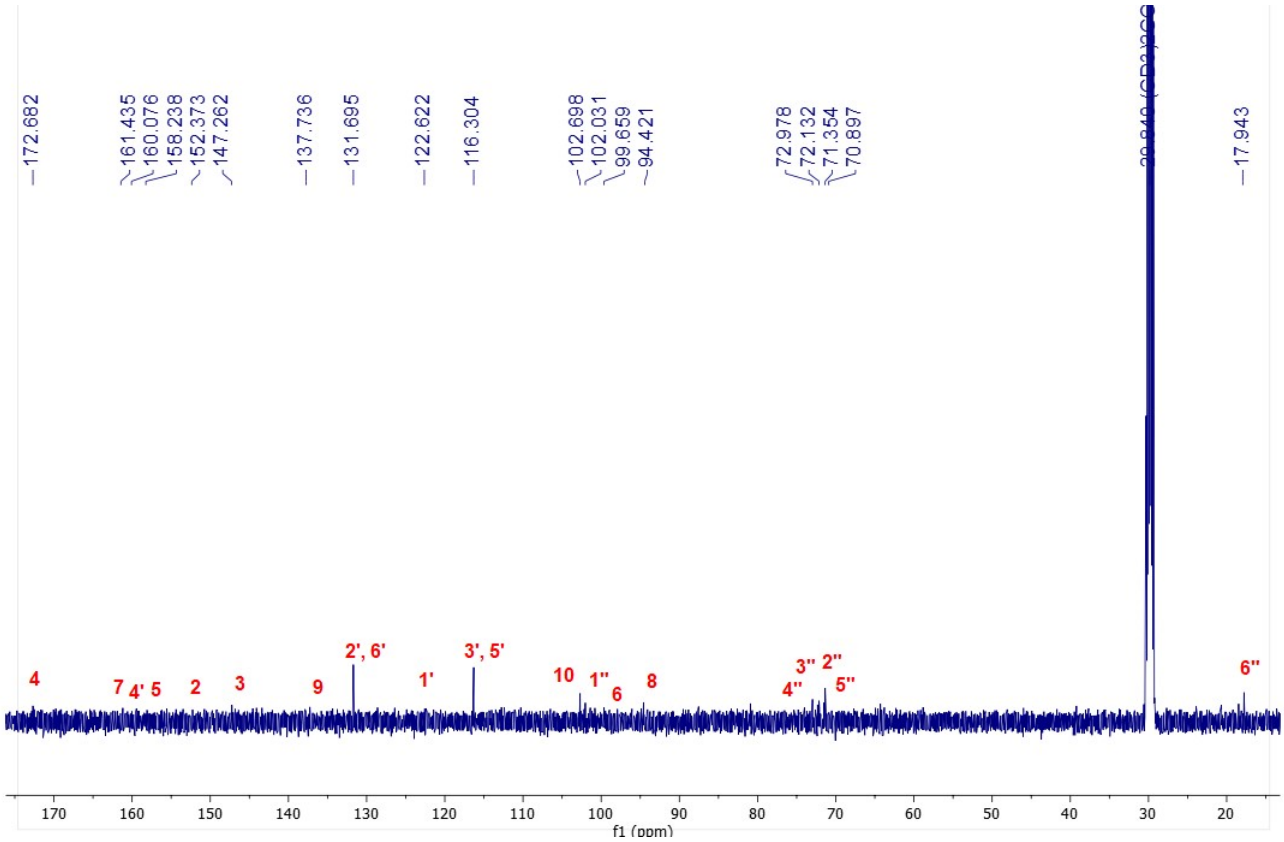


Figure S7. ^{13}C NMR spectrum (acetone-d_6) of **4**

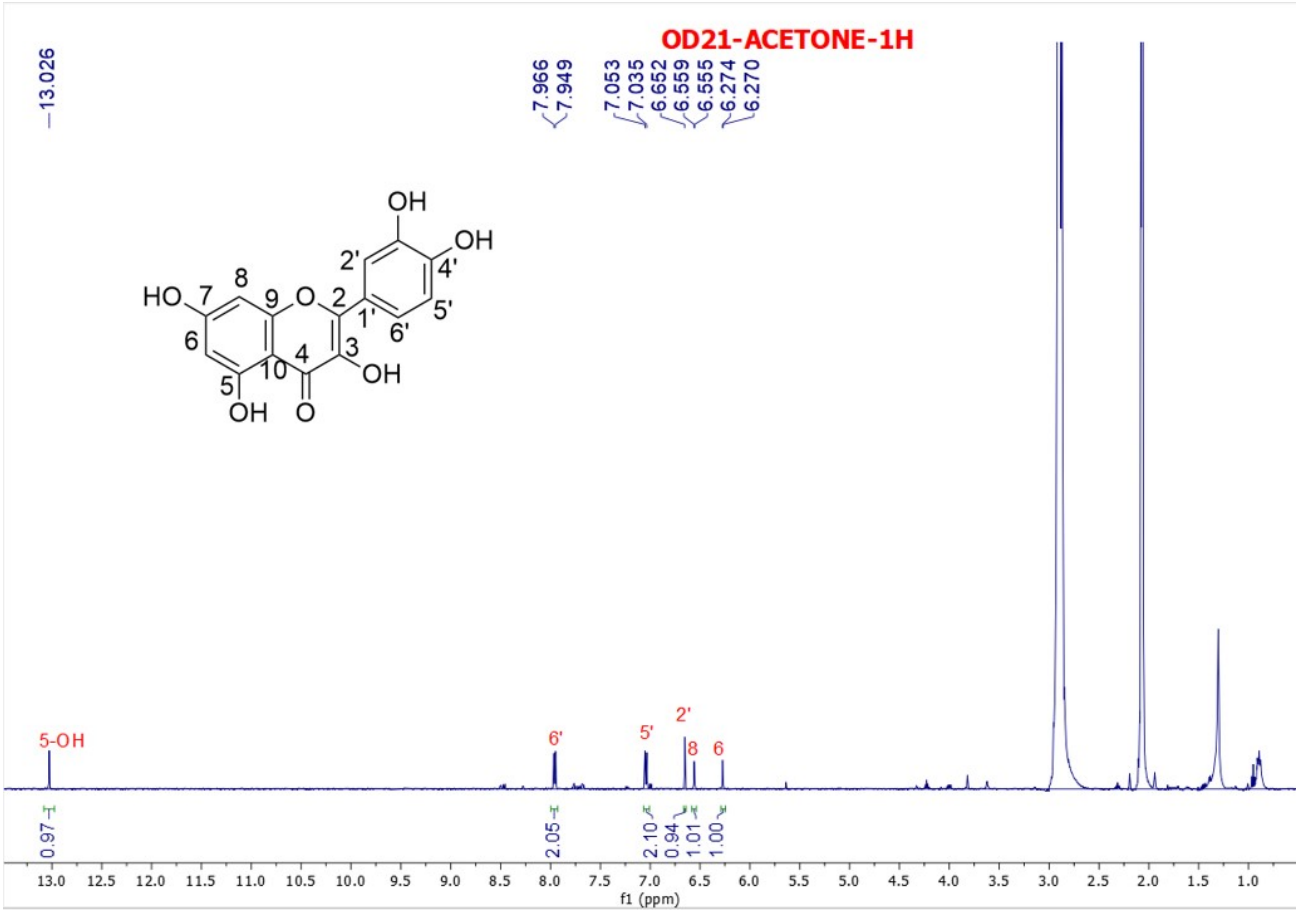


Figure S8. ^{1}H NMR spectrum (acetone-d_6) of **5**

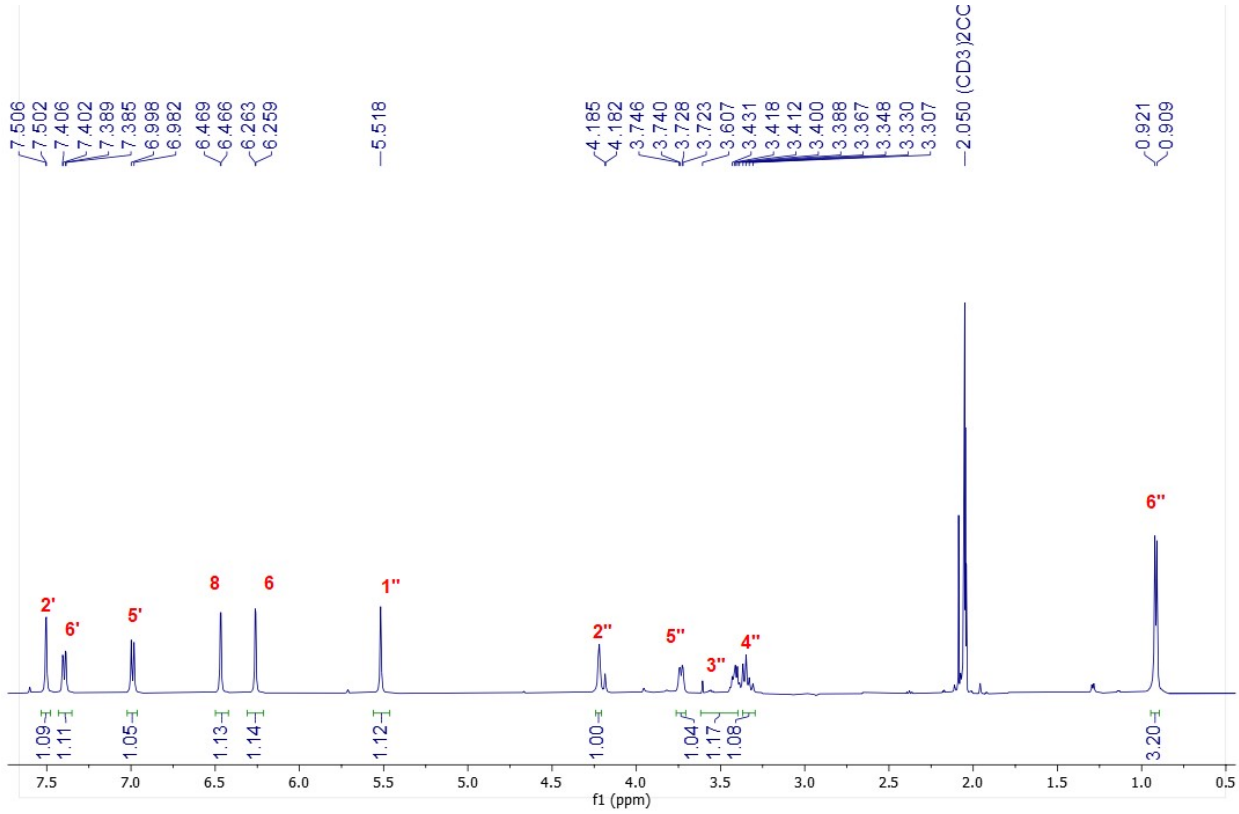


Figure S9. ^{1}H NMR spectrum (acetone-d_6) of **6**

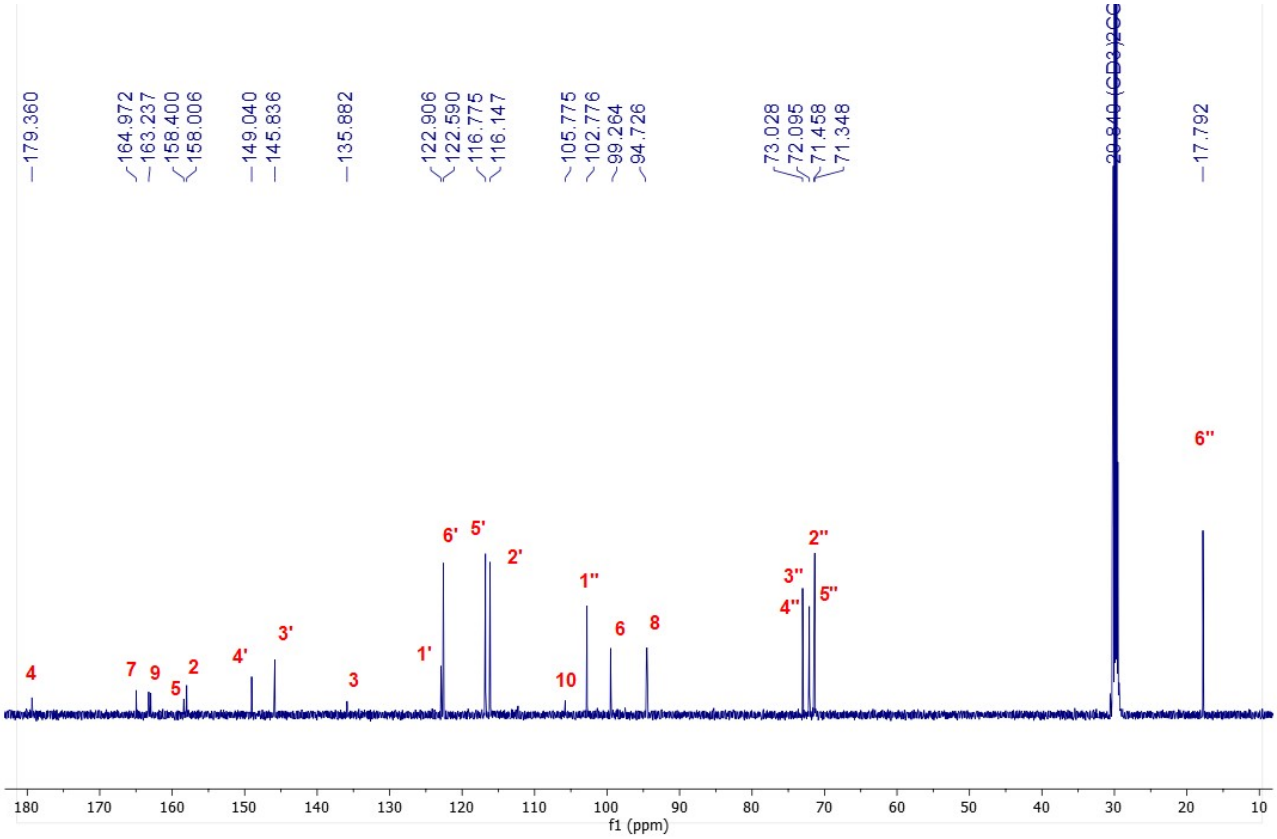


Figure S10. ^{13}C NMR spectrum (acetone-d_6) of **6**

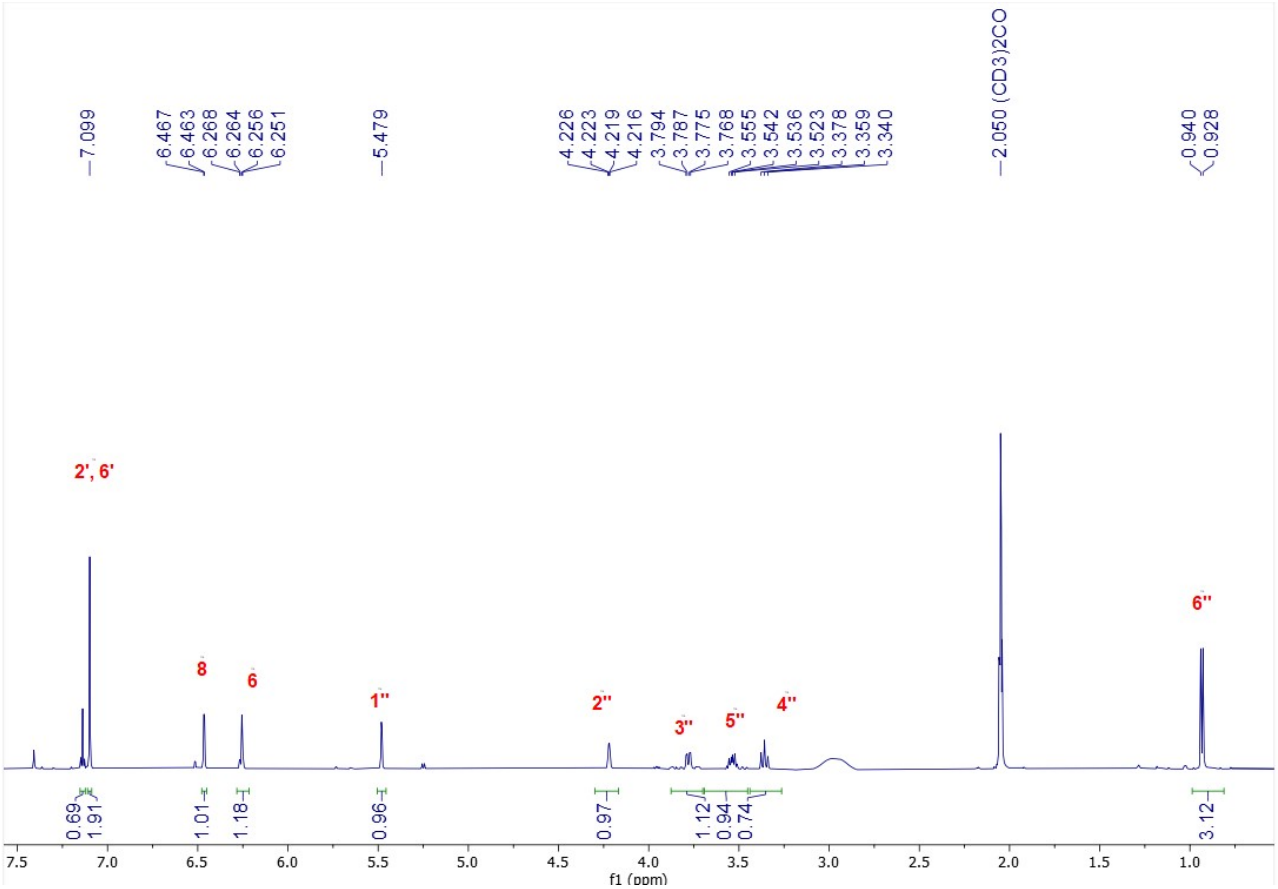


Figure S11. ^{1}H NMR spectrum (acetone-d_6) of **7**

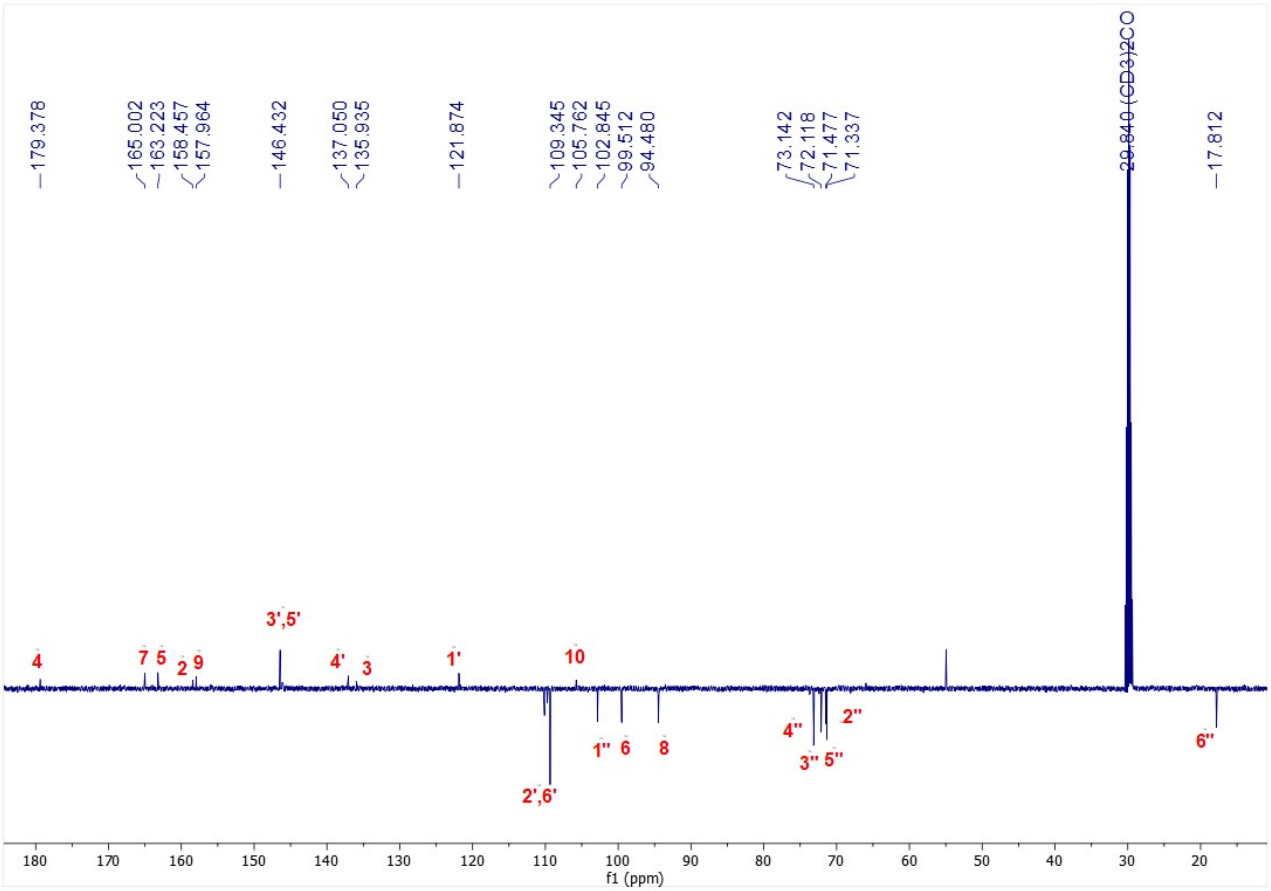


Figure S12. ^{13}C NMR spectrum (acetone-d_6) of **7**

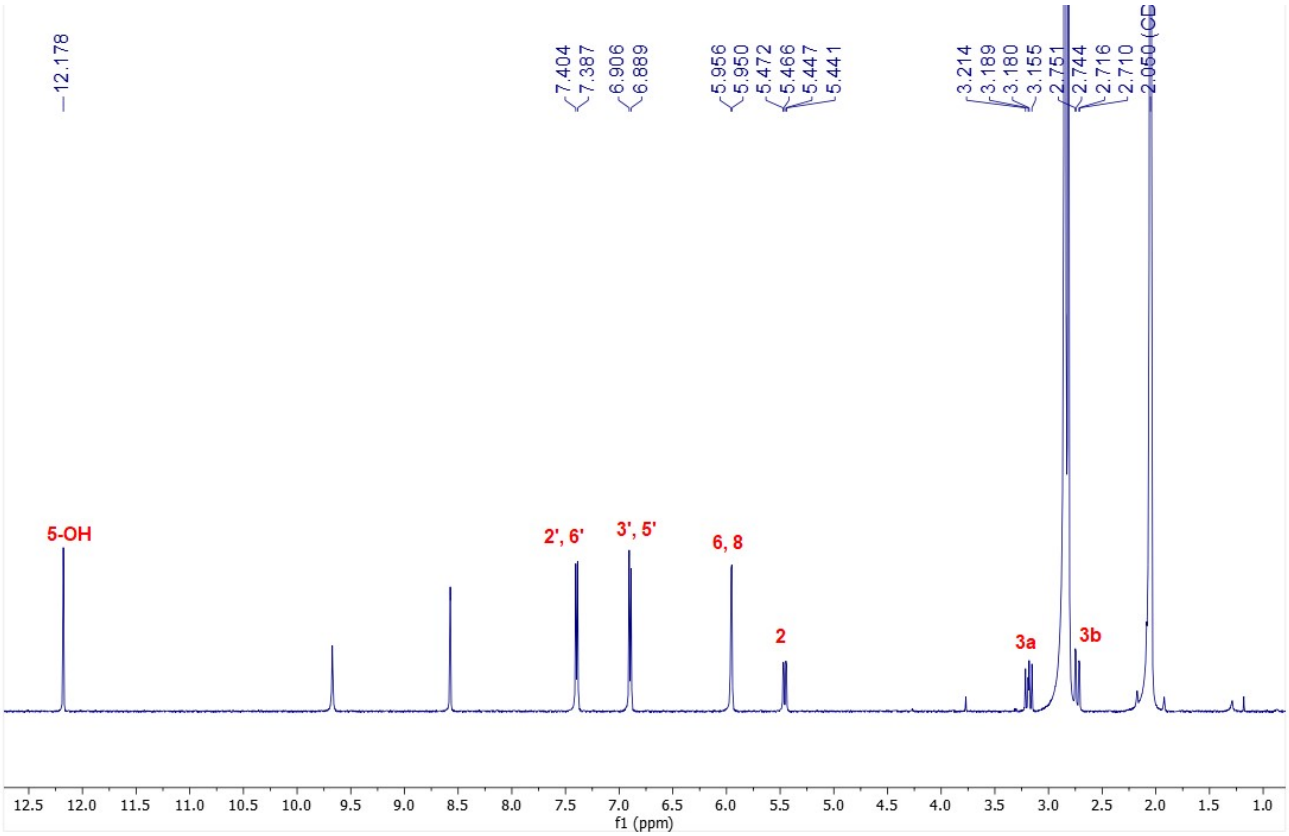


Figure S13. ^{1}H NMR spectrum (acetone-d_6) of **8**

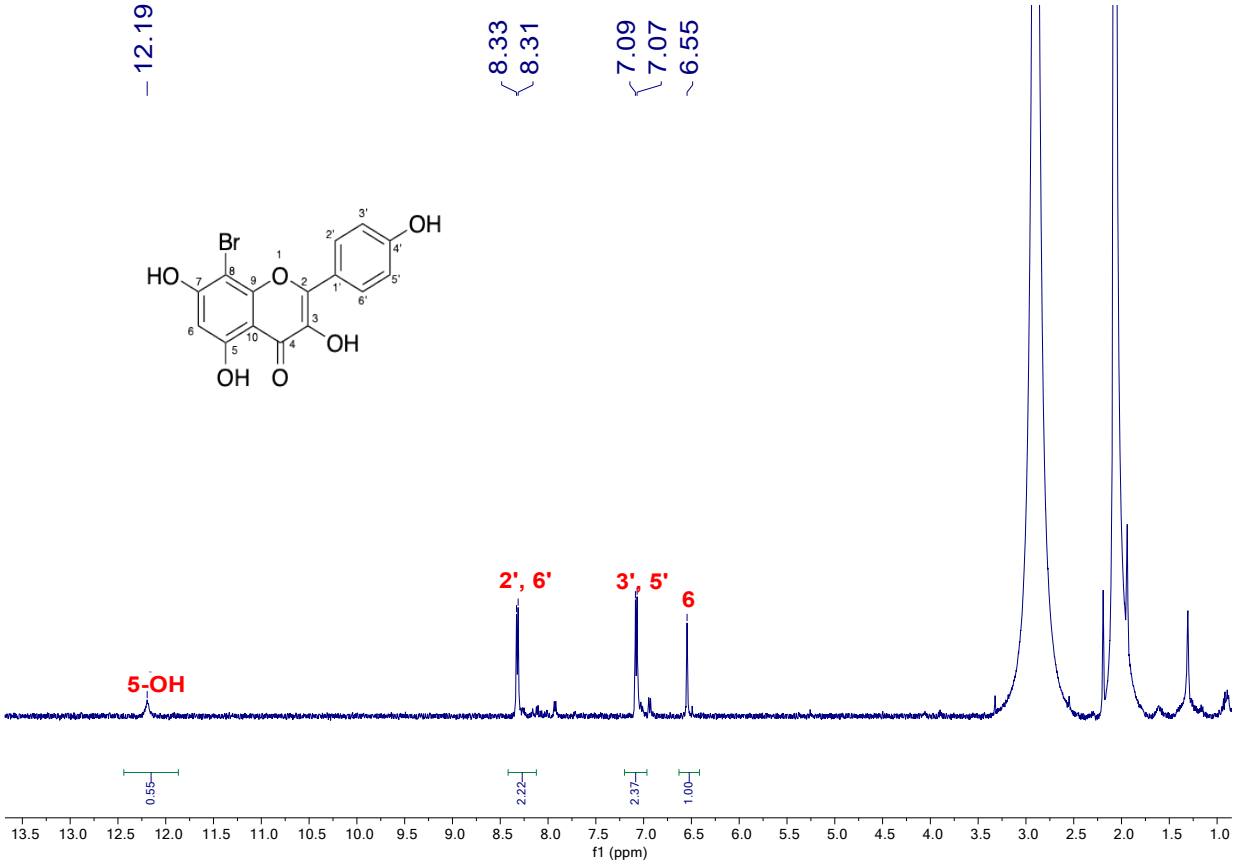


Figure S14. ^{1}H NMR spectrum (acetone-d_6) of **3a**

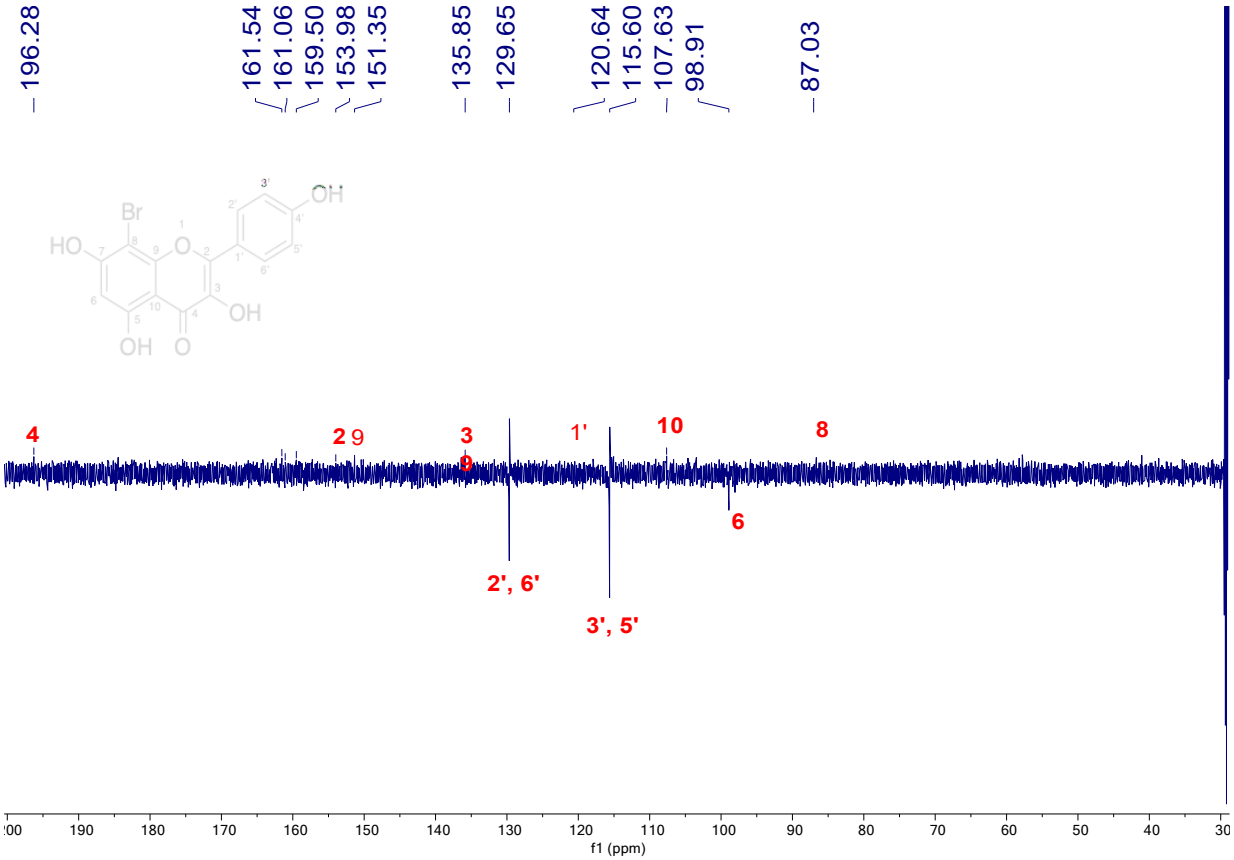


Figure S15. ^{13}C NMR spectrum (acetone-d_6) of **3a**

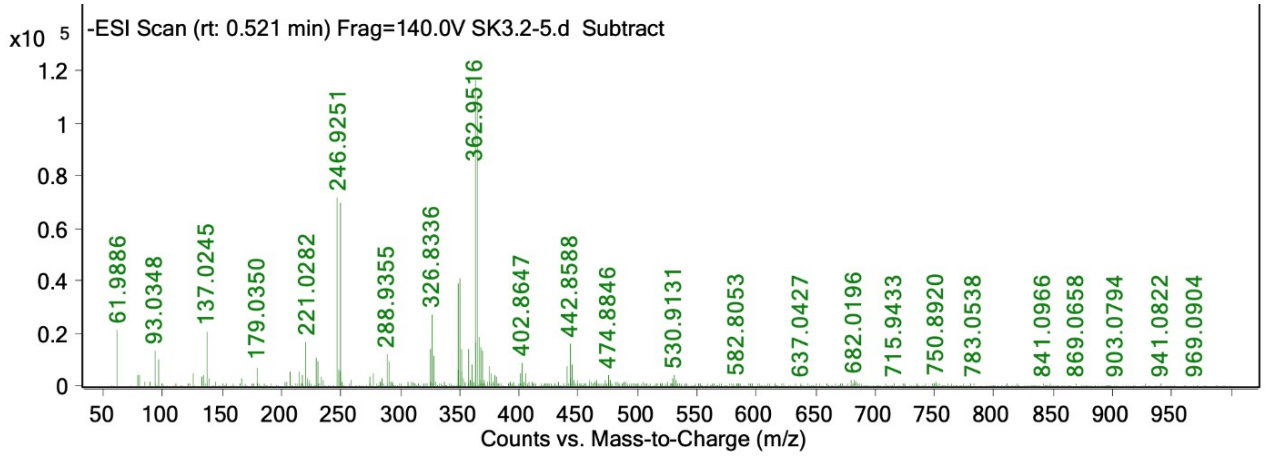


Figure S16. HRESIMS spectrum of **3a**

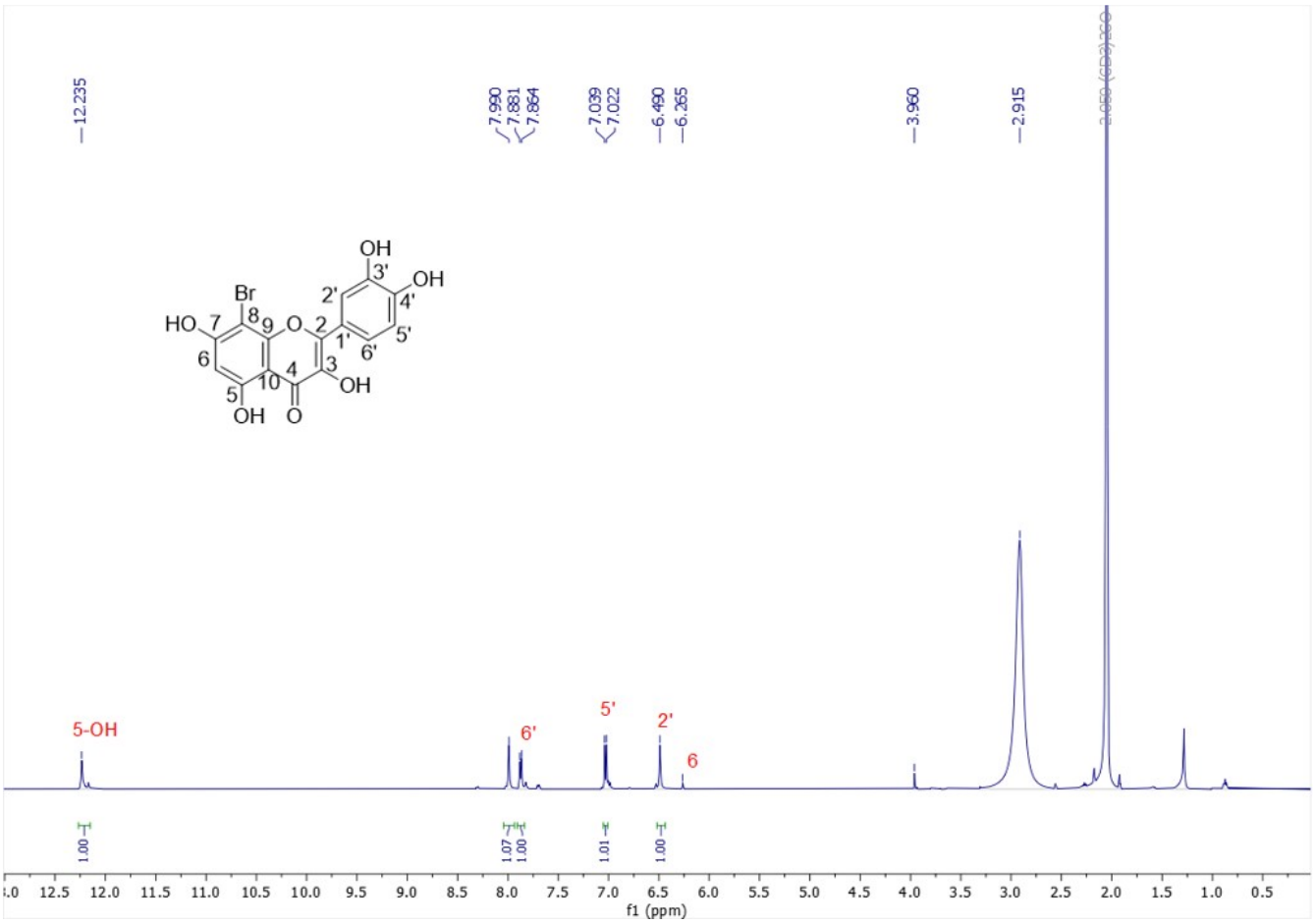


Figure S17. ^{1}H NMR spectrum (acetone-d_6) of **5a**

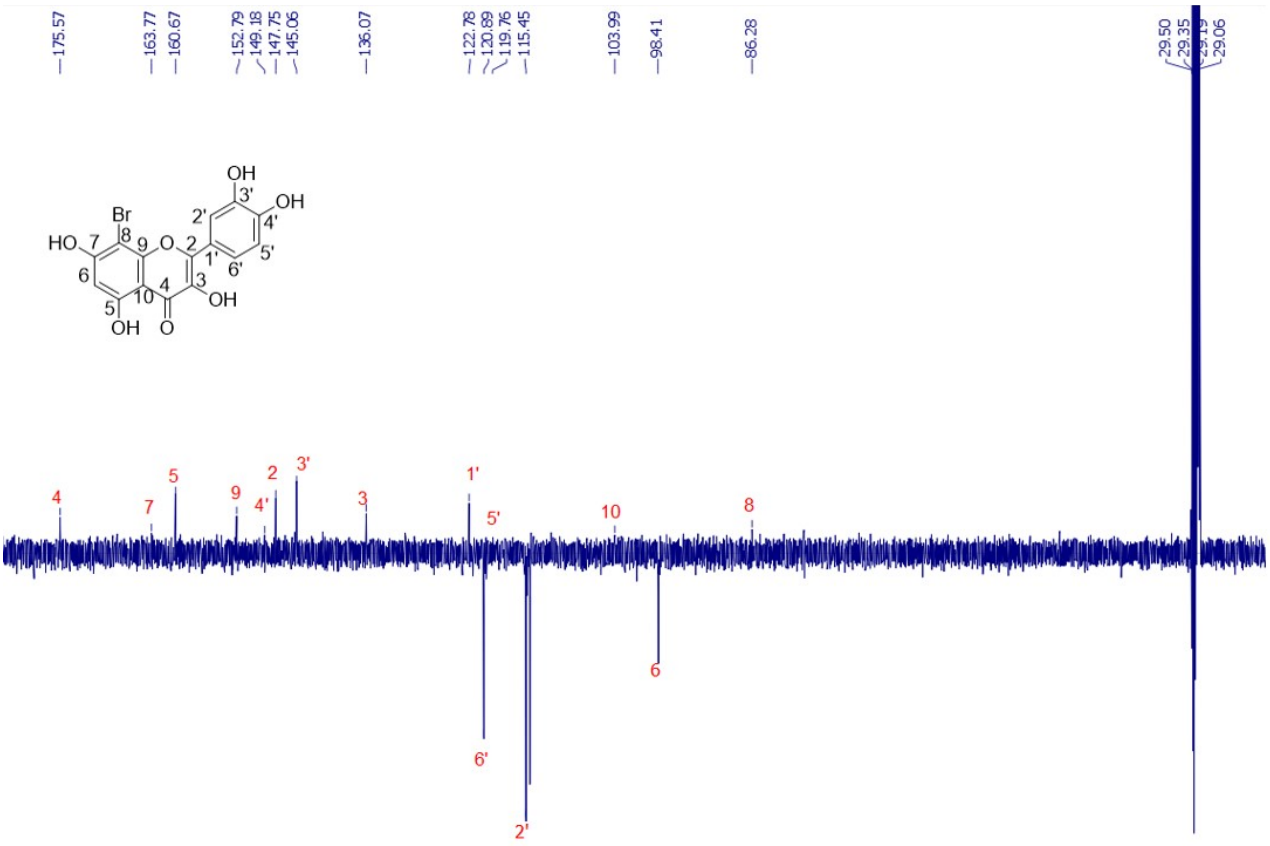


Figure S18. ^{13}C NMR spectrum (acetone-d_6) of **5a**

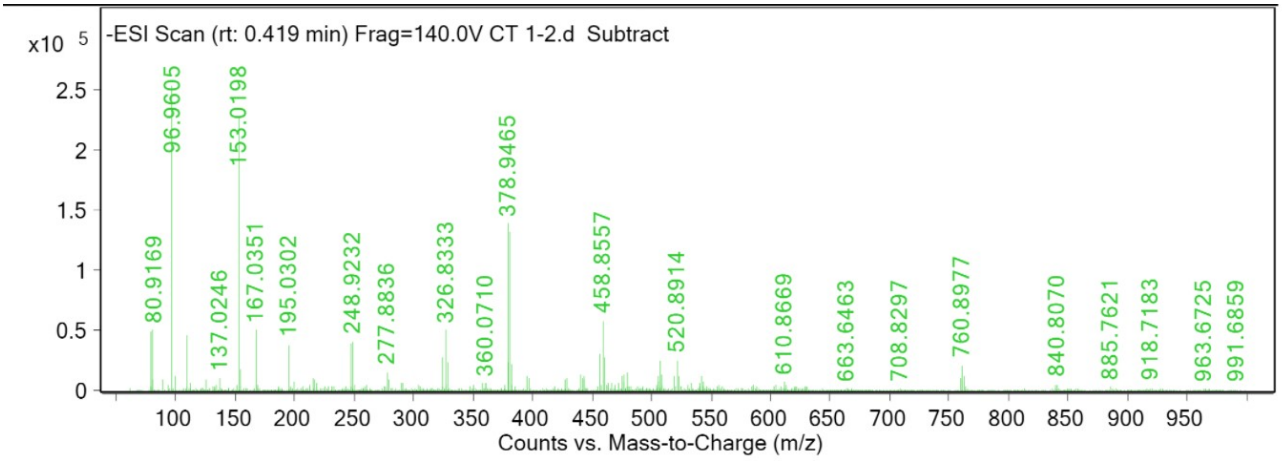


Figure S19. HRESIMS spectrum of **5a**

Table S1. Physicochemical properties of compound 5a

Property	Value	Comment
Molecular Weight	379.95	Contain hydrogen atoms. Optimal:100-600
Volume	302.05	Van der Waals volume
nHA	7	Number of hydrogen bond acceptors. Optimal:0-12
nHD	5	Number of hydrogen bond donors. Optimal:0-7
nRot	1	Number of rotatable bonds. Optimal:0-11
MaxRing	10	Number of atoms in the biggest ring. Optimal:0-18
nHet	8	Number of heteroatoms. Optimal:1-15
fChar	0	Formal charge. Optimal:-4-~4
nRig	18	Number of rigid bonds. Optimal:0-30
Flexibility	0.056	Flexibility =nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	131.36	Topological Polar Surface Area. Optimail: 0-140
logS	-4.064	Log of the aqueous solubility. Optimal: -4-0.5 log mol/L
logP	3.173	Log of the octanol/water partition coefficient. Optimal: 0-3
logD	1.851	logP at physiological pH 7.4. Optimal: 1-3

Table. S2. Medicinal Chemistry of compound 5a

Property	Value	Comment
QED	0.41	A measure of drug-likeness based on the concept of desirability; n Attractive: > 0.67; unattractive: 0.49~0.67; toocomplex: < 0.34
SAscore	2.845	Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize.
Fsp^3	0.0	The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. $Fsp^3 \geq 0.42$ is considered a suitable value
MCE-18	20.0	MCE-18 stands for medicinal chemistry evolution. MCE-18 ≥ 45 is considered a suitable value.
NPscore	1.589	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	Accepted	MW £ 400; logP £ 4; Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden	Accepted	200 £ MW £ 50; -2 £ logD £ 5; Compounds

Property	Value	Comment
Triangle		satisfying the Golden Triangle rule may have a more favorable ADMET profile
PAINS	1 alert	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	4 alerts	Thiol reactive compounds
BMS	1 alert	Undesirable, reactive compounds
Chelator Rule	2 alerts	Chelating compounds

Table S3. The Absorption of compound 5a

Property	Value	Comment
Caco-2 Permeability	-5.209	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.2e-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	0.113	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.0	Category 1: substrate; Category 0: Non-substrate; The output value is the probability of being Pgp-substrate
HIA	0.152	Human Intestinal Absorption; Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.012	20% Bioavailability; Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability≥ 20%); The output value is the probability of being F20%+
F30%	0.589	30% Bioavailability; Category 1: F30%+ (bioavailability < 30%); Category 0: F30%- (bioavailability ≥ 30%); The output value is the probability of being F30%+

Table S4. The properties of the drug distribution of compound 5a

Property	Value	Comment
PPB	99.32%	Plasma Protein Binding; Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.554	Volume Distribution; Optimal: 0.04-20 L/kg
BBB Penetration	0.006	Blood-Brain Barrier Penetration; Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	2.107%	The fraction unbound in plasms; Low: <5%; Middle: 5~20%; High: > 20%

Table S5. The properties of the drug metabolism of compound 5a

Property	Value	Comment
CYP1A2 inhibitor	0.937	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor
CYP1A2 substrate	0.11	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate
CYP2C19 inhibitor	0.105	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor
CYP2C19 Substrate	0.041	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate
CYP2C9 inhibitor	0.041	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C9 substrate	0.318	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2D6 inhibitor	0.138	Category 1: Inhibitor; Category 0: Non-inhibitor; the output value is the probability of being inhibitor.
CYP2D6 Substrate	0.167	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate
CYP3A4 inhibitor	0.143	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor
CYP3A4 Substrate	0.042	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate

Table S6. The properties of the drug excretion of compound 5a

Property	Value	Comment
CL	5.759	Clearance; High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
T1/2	0.915	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.

Table S7. The properties of the drug toxicity of compound 5a

Property	Value	Comment
hERG Blockers	0.022	Category 1: active; Category 0: inactive; The output value is the probability
H-HT	0.153	Human Hepatotoxicity; Category 1: H-HT positive(+); Category 0: H-HT negative(-); The output value is the probability of
DILI	0.988	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	0.814	Category 1: Ames positive(+); Category 0: Ames negative(-); The output value is the probability of being toxic
Rat Oral Acute Toxicity	0.123	Category 0: low-toxicity; Category 1: high-toxicity; The output value is the probability of being highly toxic
FDAMDD	0.089	Maximum Recommended Daily Dose; Category 1: FDAMDD (+); Category 0: FDAMDD (-); The output value is the probability of being positive.
Skin Sensitization	0.903	Category 1: Sensitizer; Category 0: Non-sensitizer; The output value is the probability of being sensitizer.
Carcinogenicity	0.106	Category 1: carcinogens; Category 0: non-carcinogens; The output value is the probability of being toxic.

Eye corrosion	0.004	Category 1: corrosives ; Category 0: noncorrosives; The output value is the probability of being corrosives
Eye irritation	0.923	Category 1: irritants; Category 0: nonirritants; The output value is the probability of being irritants.
Respiratory Toxicity	0.079	Category 1: respiratory toxicants; Category 0: respiratory nontoxicants; The output value is the probability of being toxic.

Table S8. The properties of the Environmental toxicity of compound 5a

Property	Value	Comment
Bioconcentration Factors	1.09	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}	4.206	Tetrahymena pyriformis 50 percent growth inhibition concentration; The unit is -log10[(mg/L)/(1000*MW)].
$LC_{50}FM$	5.575	96-hour fathead minnow 50 percent lethal concentration; The unit is -log10[(mg/L)/(1000*MW)].
$LC^{50}DM$	5.463	48-hour daphnia magna 50 percent lethal concentration; The unit is -log10[(mg/L)/(1000*MW)].

Table S9. The properties of the Tox21 pathway of compound 5a

Property	Value	Comment
NR-AR	0.012	Androgen receptor; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
NR-AR-LBD	0.094	Androgen receptor ligand-binding domain; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
NR-AhR	0.956	Aryl hydrocarbon receptor; Category 1: actives ; Category 0: inactives The output value is the probability of being active.
NR-Aromatase	0.875	Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-ER	0.818	Estrogen receptor; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
NR-ER-LBD	0.886	Estrogen receptor ligand-binding domain; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
NR-PPARgamma	0.937	Peroxisome proliferator-activated receptor gamma; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
SR-ARE	0.637	Antioxidant response element; Category 1: actives ; Category 0: inactives; The output value is the probability of being

		active.
SR-ATAD5	0.209	ATPase family AAA domain-containing protein 5; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
SR-HSE	0.291	Heat shock factor response element; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
SR-MMP	0.917	Mitochondrial membrane potential; Category 1: actives ; Category 0: inactives; The output value is the probability of being active.
SR-p53	0.784	Category 1: actives ; Category 0: inactives; The output value is the probability of being active.

Table S10. Toxicophore rules of compound 5a

Property	Value	Comment
Acute Toxicity Rule	0 alert	20 substructures; Acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alert	117 substructures; Carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	8 alerts	23 substructures; Carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	8 alerts	155 substructures; Skin irritation
Aquatic Toxicity Rule	1 alert	99 substructures; Toxicity to liquid(water)
NonBiodegradable Rule	1 alert	19 substructures; Non-biodegradable;
SureChEMBL Rule	0 alert	164 substructures; MedChem unfriendly status