SUPPLEMENTARY FILE

Unveiling Multifunctional Inhibitors: Holistic Spectral, Electronic and Molecular Characterization Coupled with Biological Profiling of Substituted Pyridine Derivatives Against LD Transpeptidase, Heme Oxygenase and PPAR Gamma

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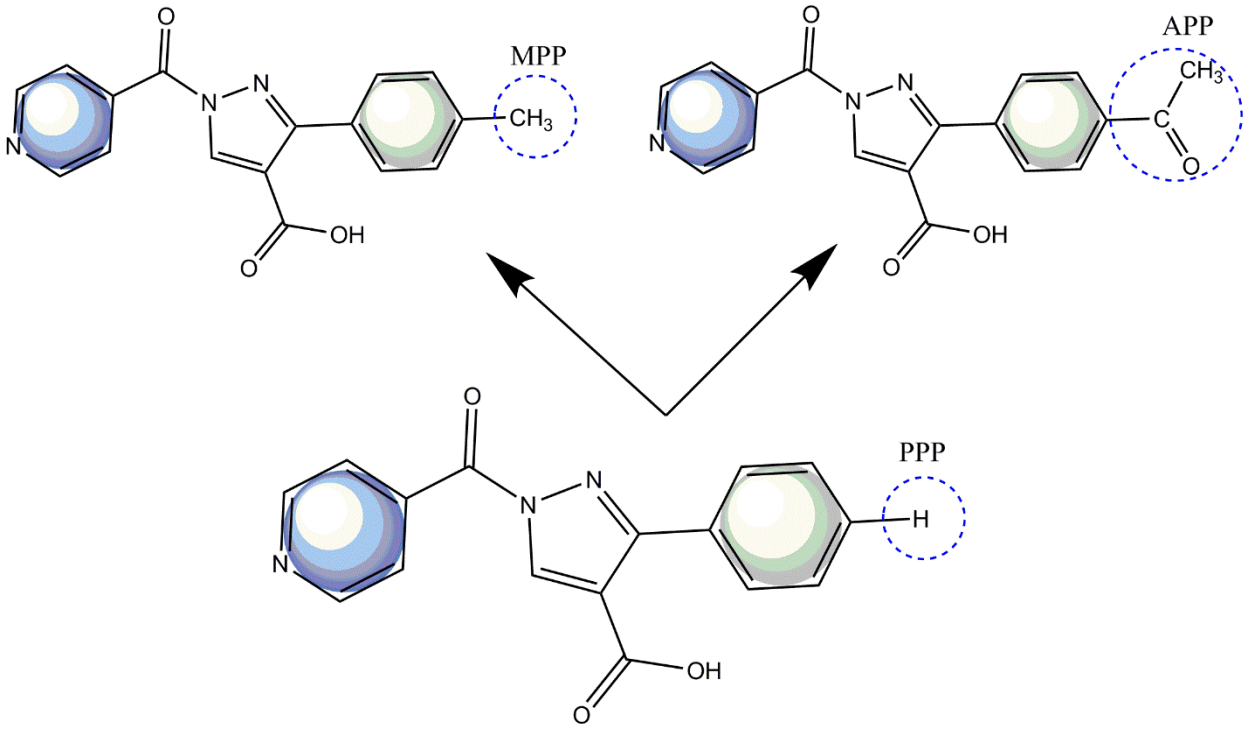
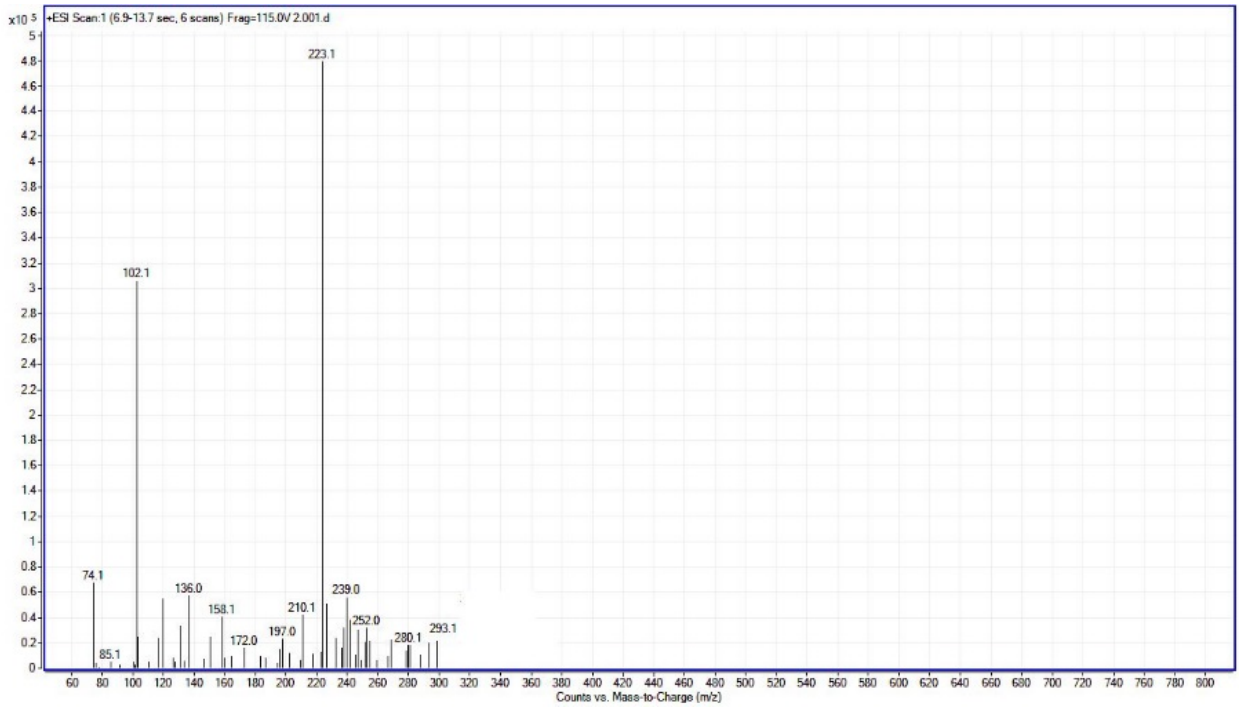
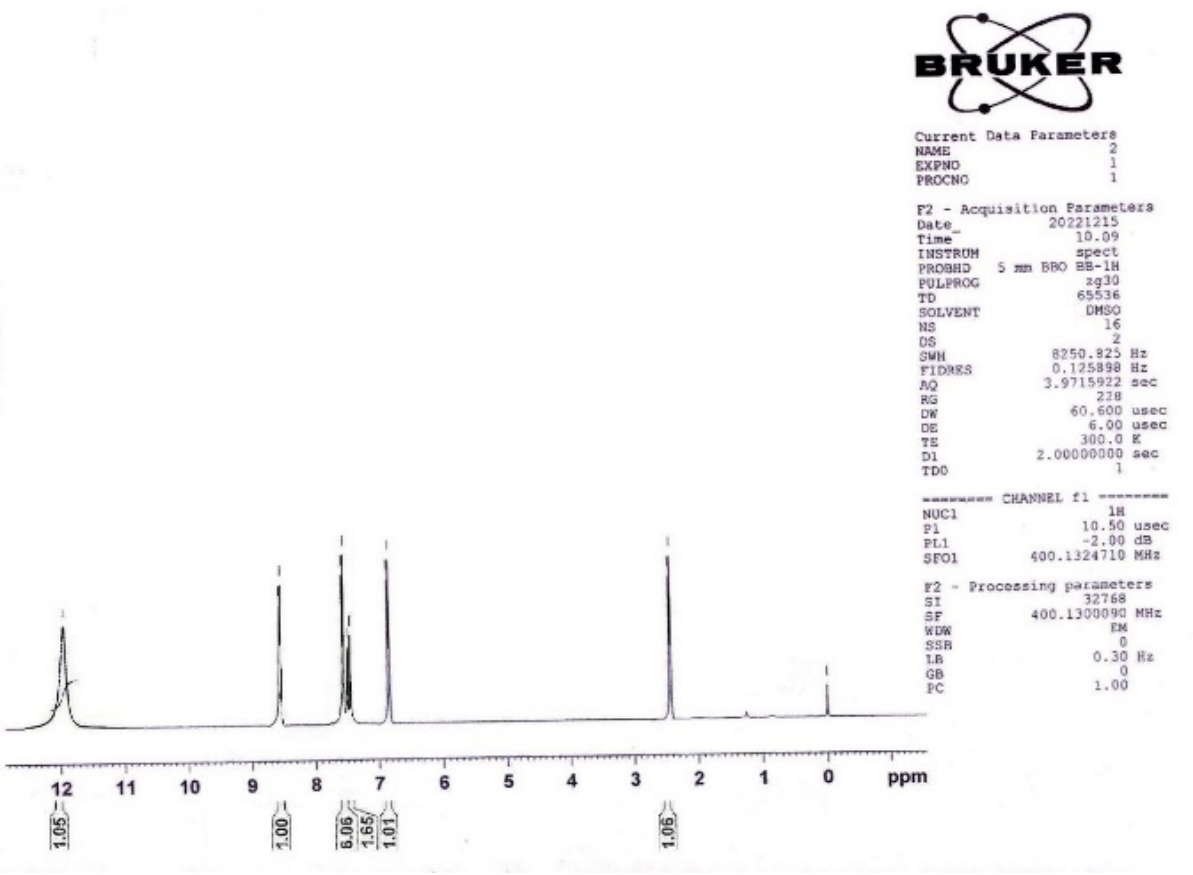


Figure S1. Chemical structure of 3-Phenyl-1-(Pyridine-4-Carbonyl)-1H-Pyrazole-4-Carboxylic Acid (PPP), 3-(4-Acetophenyl-)1-(Pyridine-4-Carbonyl)-1H-Pyrazole-4-Carboxylic Acid (APP) and 3-(4-Methylphenyl)-1-(Pyridine-4-Carbonyl)-1H-Pyrazole-4-Carboxylic Acid (MPP) derivatives

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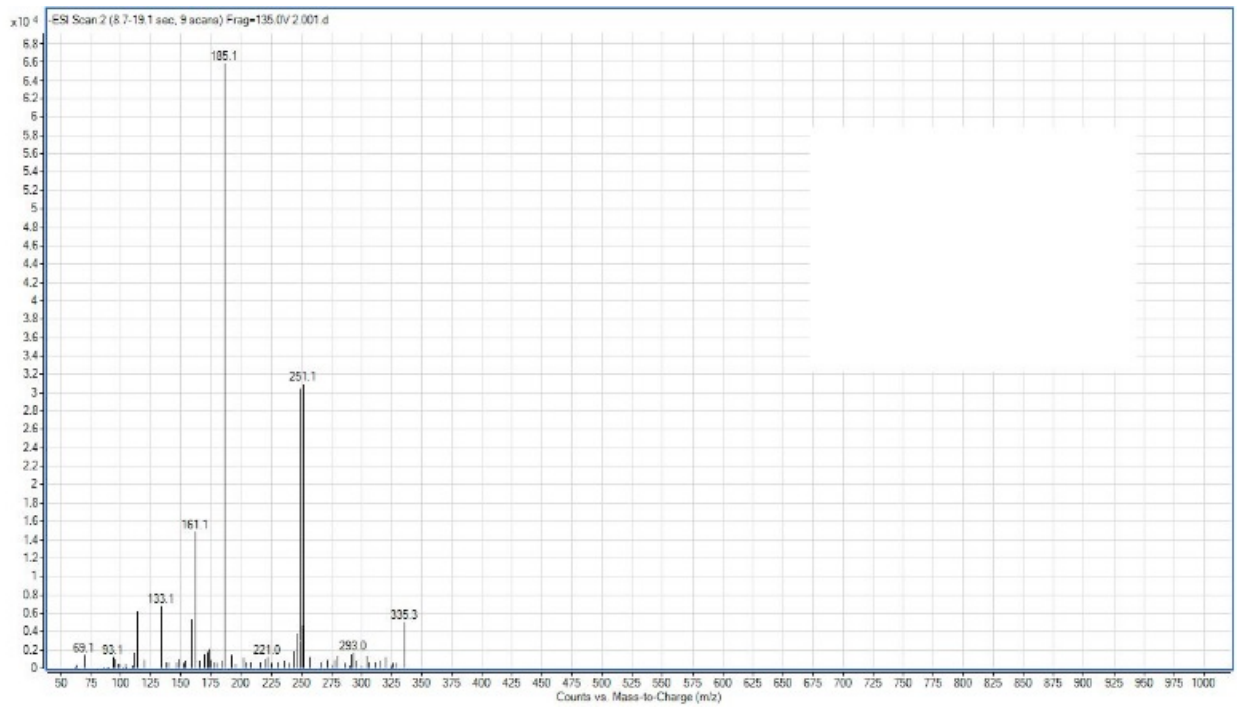
(a)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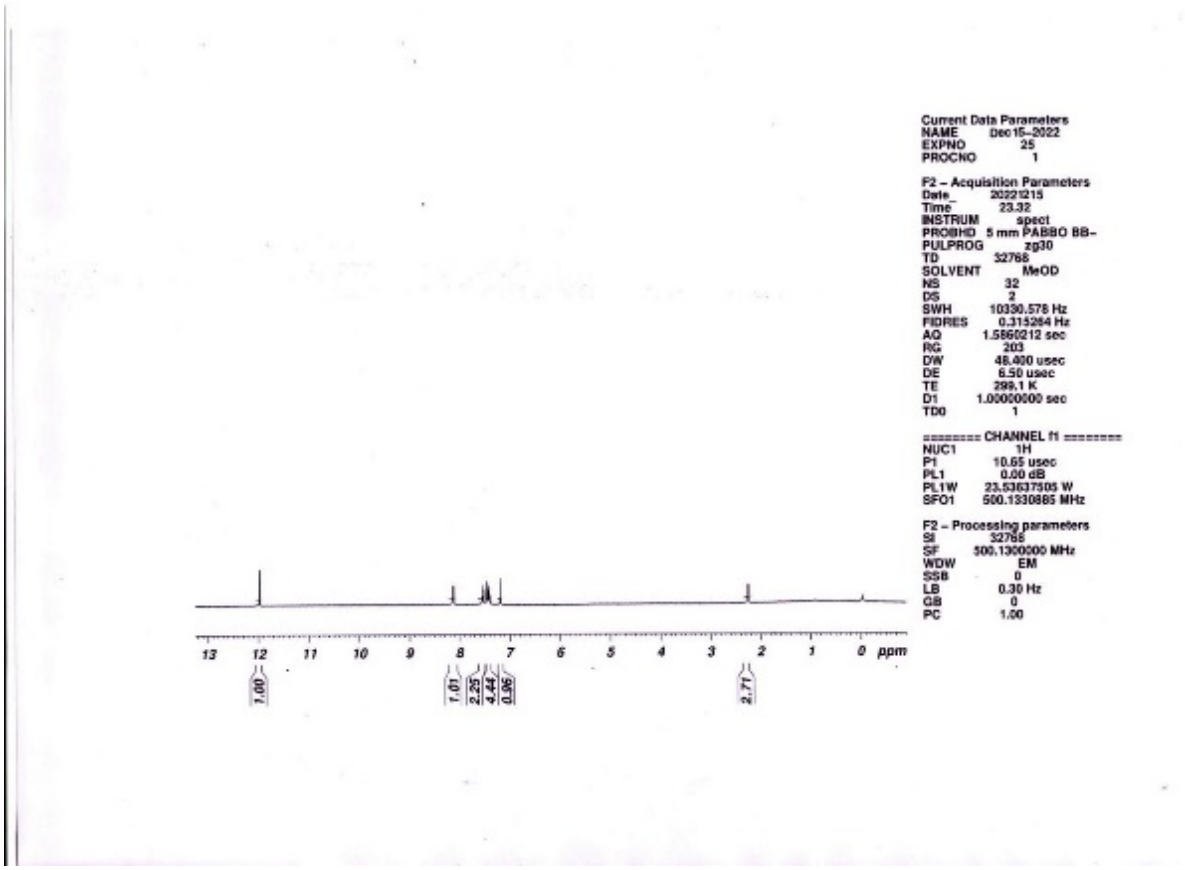
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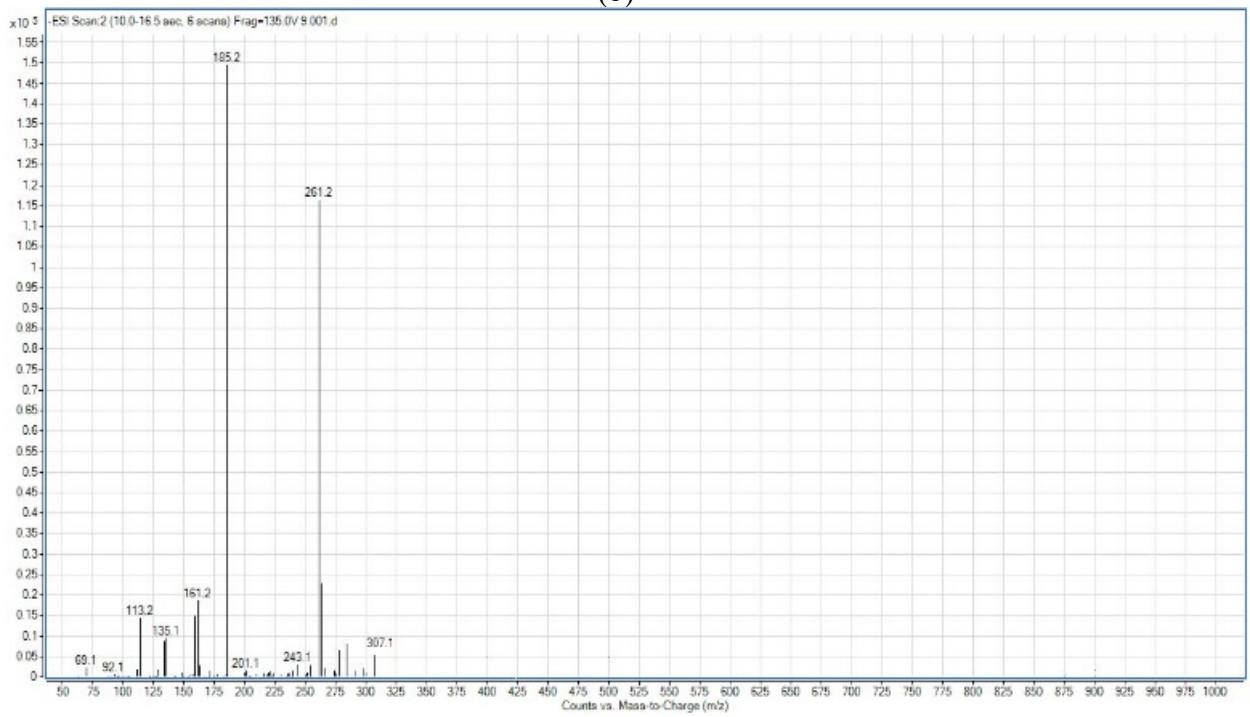
(b)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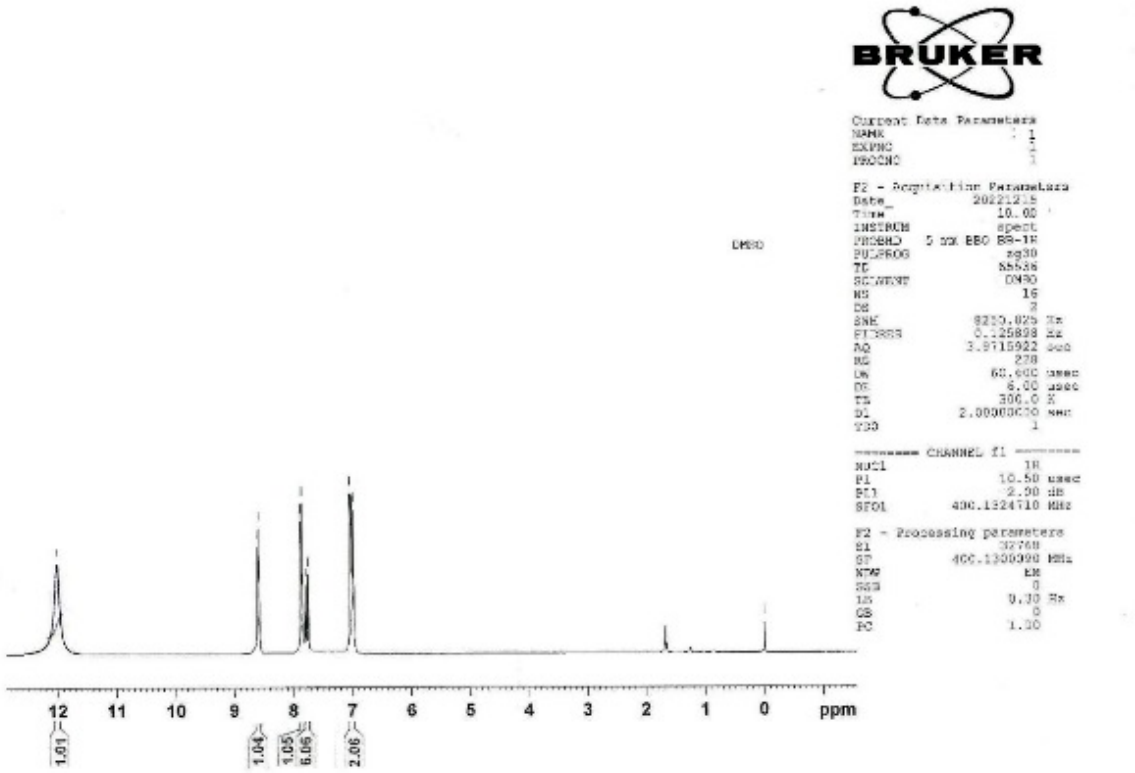
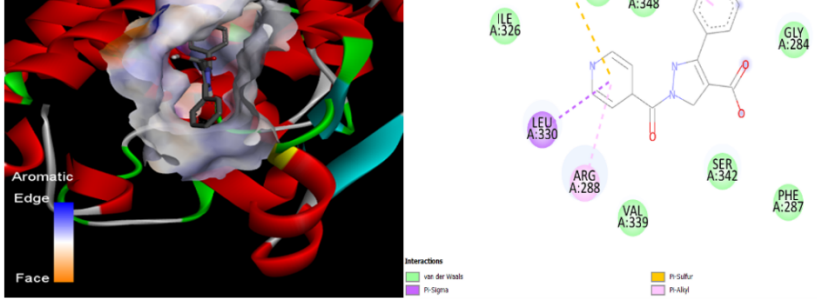


(c)

Figure S2. NMR and mass spectrometry data for all derivatives (a) PPP, (b) APP, (c) MPP, obtained through experimental



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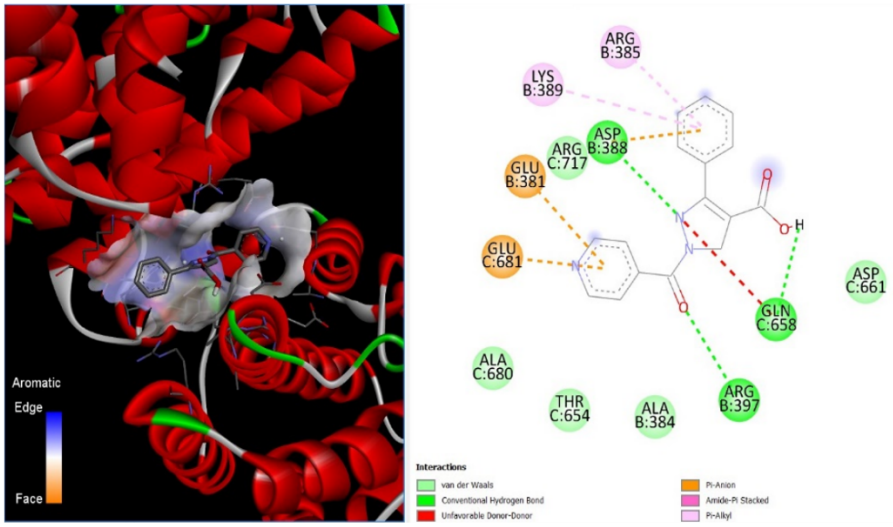


PDB ID : 4JMN

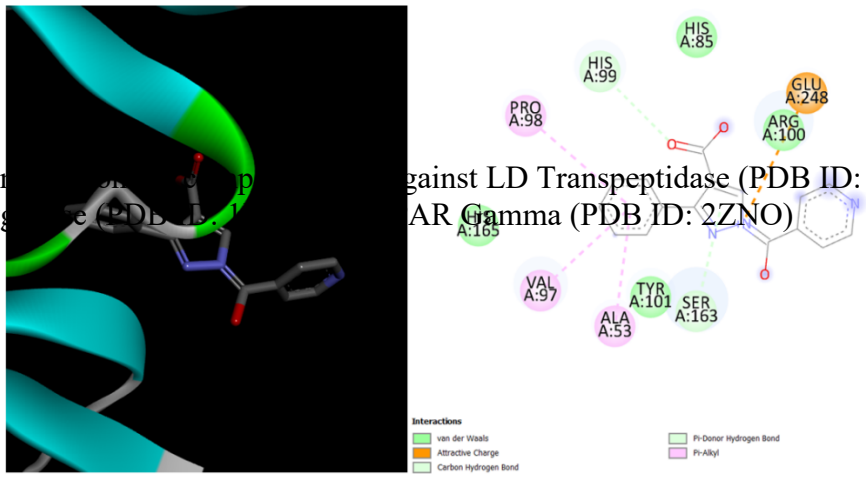
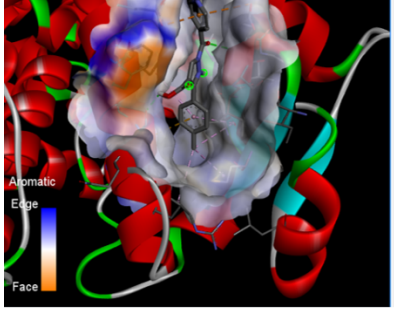


Figure S3. The binding in[illegible]gainst LD Transpeptidase (PDB ID: 4JMN), Heme Oxyg[illegible]AR Gamma (PDB ID: 2ZNO)



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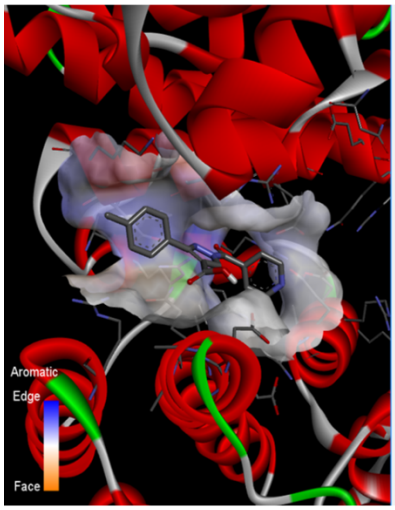

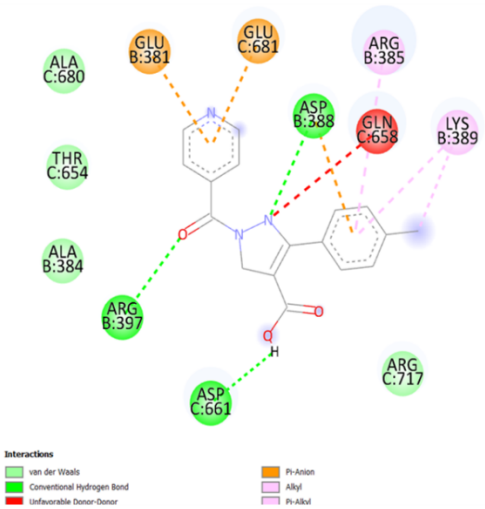

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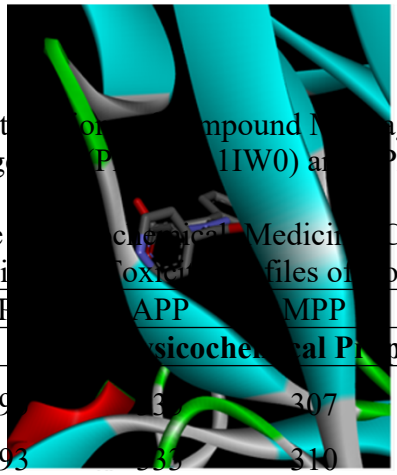

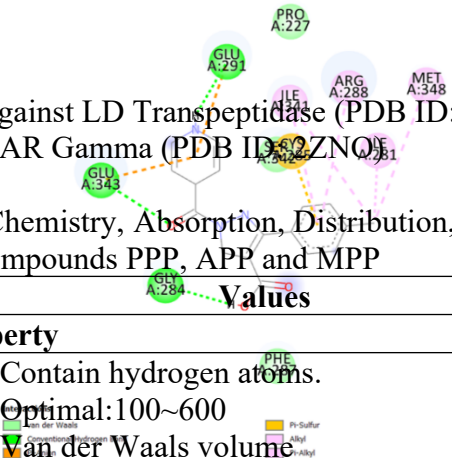

Figure S4. The binding int[illegible] of [illegible]mpound [illegible] against LD Transpeptidase (PDB ID: 4JMN), Heme Oxyg[illegible] P[illegible] 1IW0) a[illegible] PAR Gamma (PDB ID: 2ZNO).

Table S5. Comprehensive [illegible]ch[illegible]ical Medici[illegible] Chemistry, Absorption, Distribution, Metabolism, Excreti[illegible] Toxic[illegible] files o[illegible]mpounds PPP, APP and MPP

Property	PP[illegible]	APP	MPP	Values
		[illegible]ysicoche[illegible]cal P[illegible]perty		
Molecular Weight	29[illegible]	[illegible]	307	Contain hydrogen atoms. Optimal:100~600
Volume	293	335	310	Van der Waals volume
Density	1	1	1	Density = MW / Volume
nHA	6	7	6	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	1	1	Number of hydrogen bond donors. Optimal:0~7
nRot	4	5	4	Number of rotatable bonds. Optimal:0~11
nRing	1	1	1	Number of rings. Optimal:0~6
MaxRing	6	6	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	6	7	6	Number of heteroatoms. Optimal:1~15

fChar	0.0	0.0	0.0	Formal charge. Optimal:-4 ~4
nRig	19	20	19	Number of rigid bonds. Optimal:0~30
Flexibility	0.0	0.30	0.20	Flexibility = nRot /nRig
Stereo Centers	0.0	0.0	0.0	Stereo Centers. Optimal: 2
TPSA	85.00	102.15	85.08	Topological Polar Surface Area. Optimal:0~140
logS	-3.00	-3.70	-4.41	The logarithm of aqueous solubility value.
logP	1.27	1.32	1.98	The logarithm of the n-octanol/water distribution coefficients at pH=7.4.
logD	1.49	1.55	1.86	The logarithm of the n-octanol/water distribution coefficient.
pka (Acid)	3.55	4.09	4.04	Acid-base dissociation constant (pKa) value represents the strength of a drug molecule's acidity or basicity.
pka (Base)	1.26	1.53	1.65	Acid-base dissociation constant (pKa) value represents the strength of a drug molecule's acidity or basicity.
Melting point	230.94	250.84	247.79	The predicted melting point of a compound is expressed in degrees Celsius (°C). Melting points below 25°C are classified as liquids, while melting points above 25°C are classified as solids.
Boiling point	323.65	305.95	293.70	The predicted melting point of a compound is expressed in degrees Celsius (°C). A normal boiling point below 25°C is categorized as a gas.
2. Medicinal Chemistry				
QED	0.80	0.74	0.80	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; ■ unattractive: 0.49~0.67; ■ too complex: < 0.34
GASA	0.0	0.0	0.0	■ ES: Easy to synthesize; HS: Hard to synthesize; ■ The output value represents the probability of being difficult to synthesize, ranging from 0 to 1.
Synth	2.0	2.0	2.0	■ 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	0.0	0.056	0.059	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp3 0.42 is considered a suitable value.
MCE-18	16.0	18.0	17.0	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18 45 is considered a suitable value.
NPscore	-1.01	-0.91	-1.07	■ 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	0.0	0.0	0.0	■ 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	0.0	0.0	0.0	■ logP > 3; TPSA < 75 ■ Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	0.0	0.0	0.0	■ MW 400; logP 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	0.0	0.0	0.0	■ 200 MW 500; -2 logD 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	0 alerts	0 alerts	frequent hitters, Alpha-screen artifacts and reactive compound 480 substructures (J Med Chem 201053:2719-40)
ALARM NMR	0 alerts	0 alerts	0 alerts	Thiol reactive compounds.
BMS	0 alerts	0 alerts	0 alerts	undesirable, reactive compounds 176 substructures (J Chem Inf Model 200646:1060-8)
Chelator Rule	0 alerts	0 alerts	0 alerts	Chelating compounds.
Colloidal aggregators	0.01	0.04	0.05	■ Category 0: non-colloidal aggregators; ■ Category 1: colloidal aggregators. ■ The output value is the probability of being colloidal aggregators, within the range of 0 to 1.
FLuc inhibitors	0.17	0.27	0.34	■ Category 0: non-fLuc inhibitors;

				■ Category 1: fLuc inhibitors. ■ The output value is the probability of being fLuc inhibitors, within the range of 0 to 1.
Blue fluorescence	0.16	0.24	0.22	■ Category 0: non-blue fluorescence; ■ Category 1: blue fluorescence. ■ The output value is the probability of being blue fluorescence, within the range of 0 to 1.
Green fluorescence	0.25	0.35	0.35	■ Category 0: non-green fluorescence; ■ Category 1: green fluorescence. ■ The output value is the probability of being green fluorescence, within the range of 0 to 1.
Reactive compounds	0.03	0.01	0.01	■ Category 0: non-reactive compound; ■ Category 1: reactive compound. ■ The output value is the probability of being reactive compound, within the range of 0 to 1.
Promiscuous compounds	0.01	0.05	0.03	■ Category 0: non-promiscuous compound; ■ Category 1: promiscuous compound. ■ The output value is the probability of being promiscuous compound, within the range of 0 to 1.
		3. Absorption		
Caco-2 Permeability	-5.12	-4.95	-4.60	Optimal: higher than -5.15 Log unit
MDCK Permeability	-4.60	-4.76	-4.70	■ low permeability: < 2 × 10-6 cm/s ■ medium permeability: 2-20 × 10-6 cm/s ■ high passive permeability: > 20 × 10-6 cm/s
PAMPA	0.98	0.98	0.99	■ The experimental data for Peff was logarithmically transformed (logPeff). ■ Molecules with log Peff values below 2.0 were classified as low-permeability (Category 0), while those with log Peff values exceeding 2.5 were classified as high-permeability (Category 1).
Pgp-inhibitor	0.02	0.02	0.04	■ Category 1: Inhibitor; ■ Category 0: Non-inhibitor; ■ The output value is the probability of being

Pgp-substrate	0.02	0.04	0.03	Pgp-inhibitor ■ Category 1: substrate; ■ Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.00	0.01	0.00	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); ■ Category 0: HIA-(HIA >= 30%); ■ The output value is the probability of being HIA+
F20%	0.01	0.01	0.02	■ 20% Bioavailability ■ Category 1: F 20% + (bioavailability < 20%); ■ Category 0: F 20% - (bioavailability 20%); ■ The output value is the probability of being F 20% +
F30%	0.05	0.03	0.02	■ 30% Bioavailability ■ Category 1: F 30% + (bioavailability < 30%); ■ Category 0: F 30% - (bioavailability 30%); ■ The output value is the probability of being F 30% +
F50%	0.11	0.08	0.06	■ 50% Bioavailability ■ Category 1: F 50% + (bioavailability < 50%); ■ Category 0: F 50% - (bioavailability 50%); ■ The output value is the probability of being F 50% +
4. Distribution				
PPB	99.04	95.68	98.71	■ Plasma Protein Binding Optimal: < 90%. ■ Drugs with high protein-bound may have a low therapeutic index.
VDss	-0.78	-0.64	-0.68	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB	0.07	0.01	0.03	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; ■ The output value is the probability of being BBB+

Fu	0.80	3.31	1.01	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%
OATP1B1 inhibitor	0.64	0.81	0.84	■ Category 0: Non-inhibitor; Category 1: inhibitor. ■ The output value is the probability of being inhibitor, within the range of 0 to 1.
OATP1B3 inhibitor	0.71	0.92	0.68	■ Category 0: Non-inhibitor; Category 1: inhibitor. ■ The output value is the probability of being inhibitor, within the range of 0 to 1.
BCRP inhibitor	0.04	0.02	0.01	■ Category 0: Non-inhibitor; Category 1: inhibitor. ■ The output value is the probability of being inhibitor, within the range of 0 to 1.
MRP1 inhibitor	0.92	0.94	0.96	■ Category 0: Non-inhibitor; Category 1: inhibitor. ■ The output value is the probability of being inhibitor, within the range of 0 to 1.
5. Metabolism				
CYP1A2 inhibitor	0.01	0.76	0.05	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.01	0.001	0.03	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.01	0.96	0.04	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.0	0.0	0.0	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.84	0.92	0.93	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.07	0.0	0.06	■ Category 1: Substrate; Category 0: Non-substrate;

CYP2D6 inhibitor	0.0	0.0	0.0	■ The output value is the probability of being substrate. ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.0	0.0	0.0	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.01	0.0	0.07	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.0	0.0	0.0	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2B6 inhibitor	0.16	0.0	0.10	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2B6 substrate	0.0	0.0	0.0	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C8 inhibitor	0.80	1.0	1.0	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
HLM Stability	0.26	0.90	0.34	■ human liver microsomal (HLM) stability ■ Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM 30 min). The output value is the probability of human liver microsomal instability, where a value closer to 1 indicates a higher likelihood of instability. The range is between 0 and 1.
6. Excretion				
CLplasma	1.63	1.88	1.70	■ The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance.
T1/2	1.42	1.32	1.31	■ The unit of predicted T1/2 is hours.

				■ ultra-short half-life drugs: 1/2 < 1 hour; short half-life drugs: T1/2 between 1-4 hours; intermediate short half-life drugs: T1/2 between 4-8 hours; long half-life drugs: T1/2 > 8 hours.
		7. Toxicity		
hERG Blockers	0.09	0.10	0.10	■ Molecules with IC50 10 M or 50% inhibition at 10 M were classified as hERG+ (Category 1), ■ while molecules with IC50 >10 M or < 50% inhibition at 10 M were classified as hERG - (Category 0). ■ The output value is the probability of being hERG+, within the range of 0 to 1.
hERG Blockers (10um)	0.10	0.07	0.10	■ Molecules with IC50 10 M are classified as hERG+ (Category 1), ■ and molecules with IC50 > 10 M are classified as hERG- (Category 0). ■ The output value is the probability of being hERG+, within the range of 0 to 1.
DILI	0.98	0.99	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 Muta genicity	0.25	0.42	0.24	■ AMES Toxicity ■ Category 1: Ames positive(+); ■ Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.48	0.43	0.43	■ Rat Oral Acute Toxicity. ■ Category 0: low-toxicity, > 500 mg/kg; ■ Category 1: high-toxicity; < 500 mg/kg. ■ The output value is the probability of being toxic, within the range of 0 to 1.
FDAMDD	0.32	0.30	0.30	■ FDA Maximum (Recommended) Daily Dose. ■ Category 1: FDAMDD (+); ■ Category 0: FDAMDD (-);

Skin Sensiti zation	0.30	0.13	0.34	The output value is the probability of being positive. ■ Category 1: Sensitizer; ■ Category 0: Non-sensitizer. ■ The output value is the probability of being toxic, within the range of 0 to 1.
Carcinogeni city	0.60	0.75	0.62	■ Category 1: carcinogens; ■ Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.0	0.0	0.0	■ Eye Corrosion ■ Category 1: corrosives; Category 0: noncorrosives; ■ The output value is the probability of being corrosives.
Eye Irritation	0.63	0.59	0.66	■ Eye Irritation ■ Category 1: irritants; Category 0: nonirritants; ■ The output value is the probability of being irritants.
Respiratory	0.71	0.78	0.70	■ Category 1: respiratory toxicants; ■ Category 0: non-respiratory toxicants. ■ The output value is the probability of being toxic, within the range of 0 to 1.
Human Hep atotoxicity	0.71	0.74	0.71	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); ■ Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
Drug-induce d Nephrotox icity	0.77	0.82	0.79	■ Category 0: non-nephrotoxic (-); ■ Category 1: nephrotoxic (+). ■ The output value is the probability of being nephrotoxic (+), within the range of 0 to 1.
Ototoxicity	0.59	0.73	0.64	■ Category 0: non-ototoxicity (-); ■ Category 1: ototoxicity (+). ■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.
Hematotoxic ity	0.43	0.60	0.47	■ Category 0: non-hematotoxicity (-); ■ Category 1: hematotoxicity (+). ■ The output value is the probability of being hematotoxicity (+), within the range of 0 to 1.
Genotoxicity	0.91	0.97	0.87	■ Category 0: non-Genotoxicity (-); ■ Category 1: Genotoxicity (+).

RPMI-8226 Immunitoxici ty	0.03	0.07	0.03	■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1. ■ Category 0: non-cytotoxicity (-); ■ Category 1: cytotoxicity (+). ■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.
A549 Cytotoxicity	0.01	0.01	0.01	■ Category 0: non-cytotoxicity (-); ■ Category 1: cytotoxicity (+). ■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.
Hek293 Cytotoxicity	0.06	0.07	0.05	■ Category 0: non-cytotoxicity (-); ■ Category 1: cytotoxicity (+). ■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.
Drug-induce d Neurotoxi city	0.75	0.72	0.78	■ Category 0: non-neurotoxic (-); ■ Category 1: neurotoxic (+). ■ The output value is the probability of being neurotoxic (+), within the range of 0 to 1.
8. Environmental toxicity				
Bioconcentration Factors	0.18	0.08	0.18	■ 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)]
IGC50	2.87	2.69	2.87	■ Tetrahymena pyriformis 50 percent growth inhibition concentration. ■ The unit is log10[(mg/L)/(1000*MW)]
LC50FM	3.36	3.27	3.36	■ 96-hour fathead minnow 50 percent lethal concentration. ■ The unit is log10[(mg/L)/(1000*MW)]
LC50DM	3.90	3.89	3.94	■ 48-hour daphnia magna 50 percent lethal concentration. ■ The unit is log10[(mg/L)/(1000*MW)]
9. Tox21 pathway				
NR-AhR	0.63	0.54	0.72	■ Aryl hydrocarbon receptor ■ Category 1: actives ; ■ Category 0: inactives;

NR-AR	0.09	0.09	0.11	■ The output value is the probability of being active. ■ Androgen receptor ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.01	0.0	0.0	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.16	0.02	0.04	■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.24	0.16	0.25	■ Estrogen receptor ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.0	0.0	0.00	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gam ma	0.23	0.03	0.08	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.64	0.21	0.38	■ Antioxidant response element ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.05	0.03	0.05	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active.
SR-HSE	0.15	0.02	0.11	■ Heat shock factor response element

SR-MMP	0.49	0.08	0.12	■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active. ■ Mitochondrial membrane potential
SR-p53	0.06	0.02	0.03	■ Category 1: actives ; ■ Category 0: inactives; ■ The output value is the probability of being active. ■ p53, a tumor suppressor protein
10. Toxicophore Rules				
Acute Toxicity Rule		0		■ 20 substructures; ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule		0		■ 117 substructures; ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule		0		■ 23 substructures; ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule		1 alerts		■ 155 substructures; ■ skin irritation
Aquatic Toxicity Rule		0		■ 99 substructures; ■ toxicity to liquid(water)
NonBiodegradable Rule		1 alerts		■ 19 substructures; ■ non-biodegradable
SureChEMBL Rule		0		■ 164 substructures; ■ MedChem unfriendly status
Toxicophores Rule		1 alerts		154 toxic substructures from FAF-Drug4