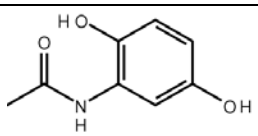
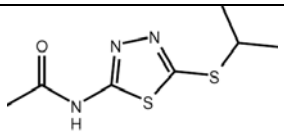
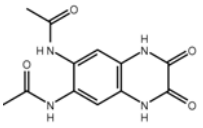
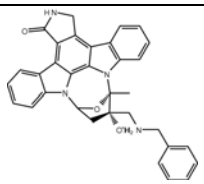
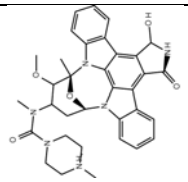
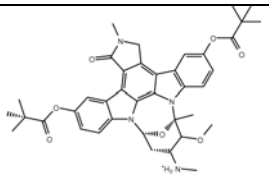
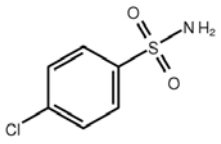
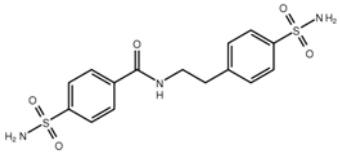
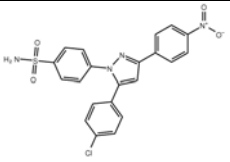
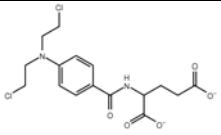
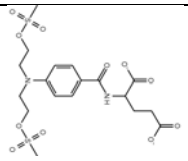
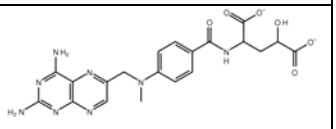
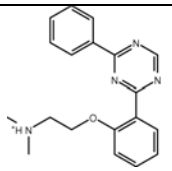
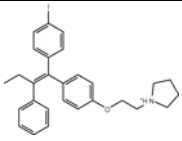
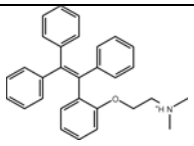
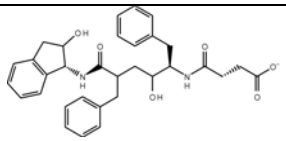
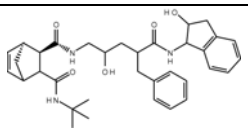
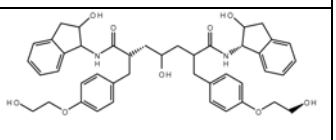
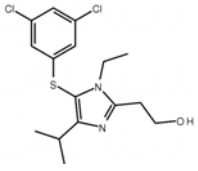
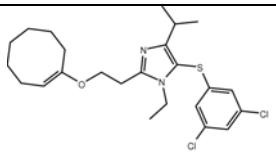
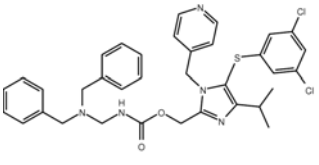
Table S1. Best settings for a target and comparison with default Linear and Radial fingerprints.

Target	Fingerprint	Atom types	Scalings	Metrics	Best EF(1%)	Linear	Radial
CA	Molprint2D	Estate,Carhart, Daylight	Most Scalings	Most Metrics	80.0	52.5	45.0
CDK2	Dendritic, Linear	Hybrid	F, F^2,$F^{1/2}$	Distance metrics, Tanimoto,Buser, Dice, Petke	27.3	11.7	9.1
COX2	Radial	TXHB	F^2M, None	Petke, Dice, Tanimoto, Soergel, Kulczynski, Pearson	26.1	18.7	16.7
DHFR	Torsion	Carhart, Daylight	None	Dixon, Kulczynski, Yule	61.5	38.4	34.6
ER	Triplet	Daylight	None	Kulczynski	24.3	10.8	12.2
HIVpr	Radial	Carhart, Mol2	F, F^2, $F^{1/2}$, None	Petke, Pearson	40.4	28.7	28.7
HIVrt	Molprint2D	Carhart	FM	Euclidean, Hamann, Variance	10.7	3.4	2.7
NA	Triplet, Molprint2D	Estate, ElemRC	None	Dixon has highest bedroc, most metrics	66.6	41.6	33.3
PTP1B	Molprint2D	ElemR, ElemRC	$F^{1/2}$I, $F^{1/2}$F	Yule, Dixon, Hamann	75.0	50.0	50.0
Throm.	Torsion Carhart	Carhart	None	Petke	32.0	30.5	26.0
TS	Torsion, Dendritic	Estate	None	Soergel, Dice, Tanimoto	77.4	71.0	58.0

Figure S1: Highest ranking inactive compounds for each target using MOLPRINT2D fingerprints, Daylight atom typing, no bit scaling, and Buser similarity.

Target	Best ranked decoy	Second best ranked decoy	Third best ranked decoy
CA			
CDK2			
COX2			
DHFR			
ER			
HIVpr			
HIVrt			

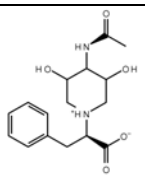
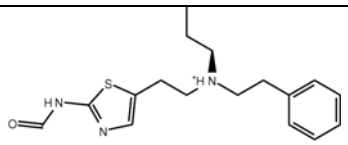
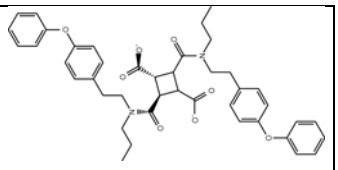
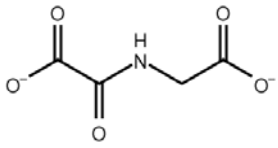
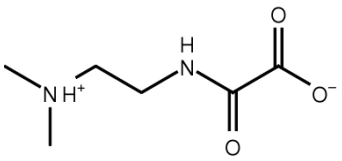
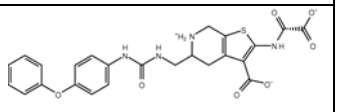
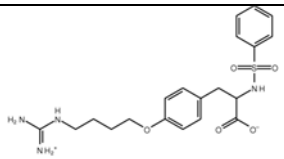
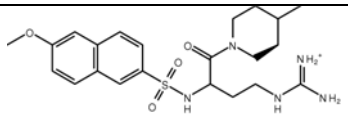
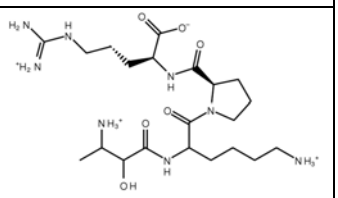
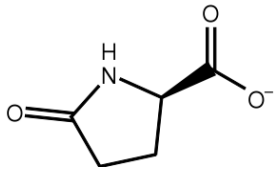
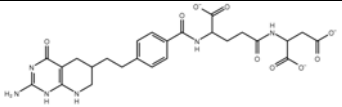
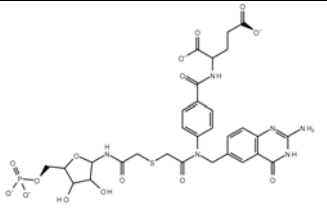
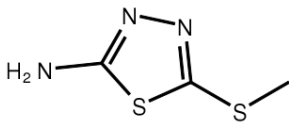
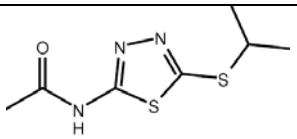
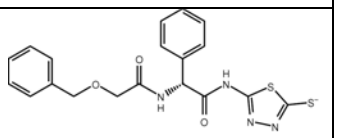
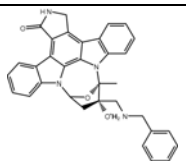
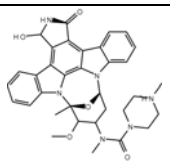
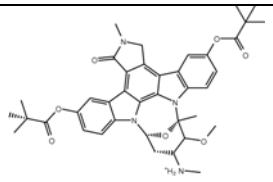
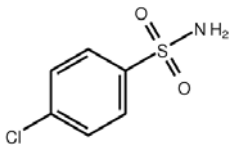
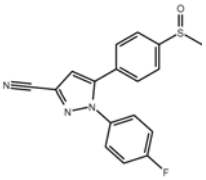
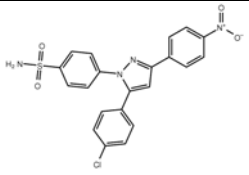
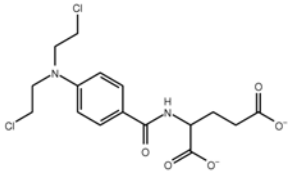
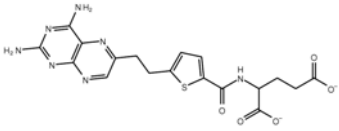
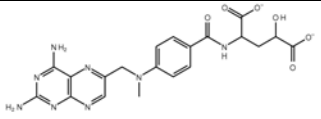
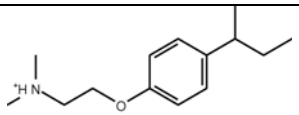
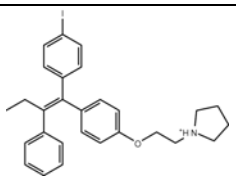
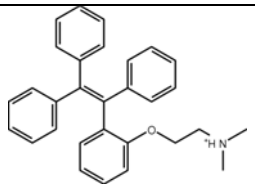
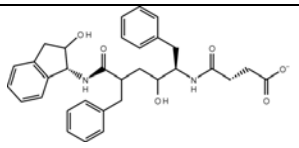
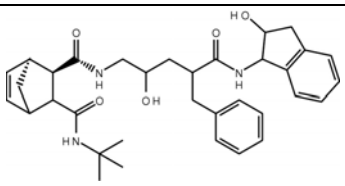
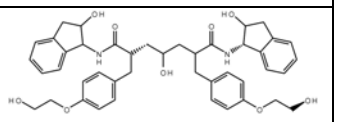
NA			
PTP1B			
Throm.			
TS			

Figure S2: Highest ranking inactive compounds for each target using MOLPRINT2D fingerprints, ElemRC atom typing, no bit scaling, and Buser similarity.

Target	Best ranked decoy	Second best ranked decoy	Third best ranked decoy
CA			
CDK2			
COX2			
DHFR			
ER			
HIVpr			

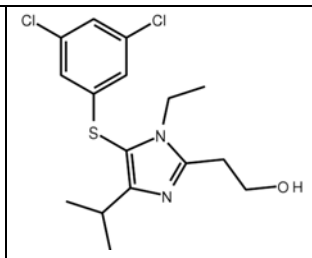
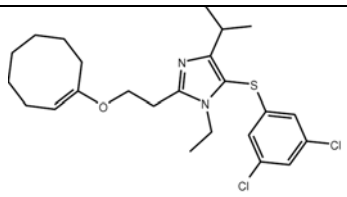
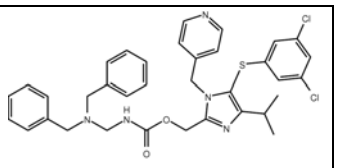
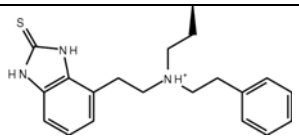
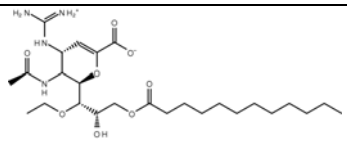
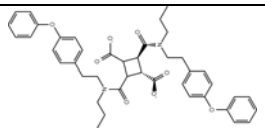
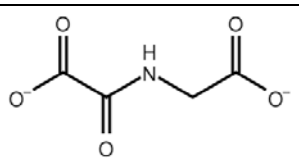
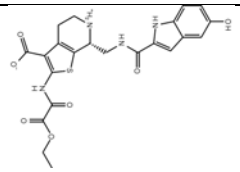
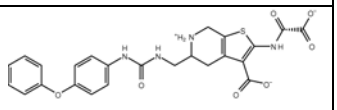
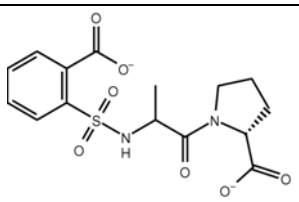
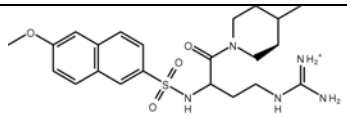
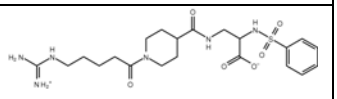
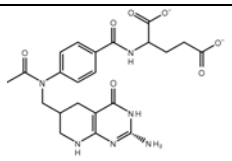
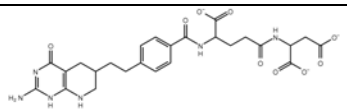
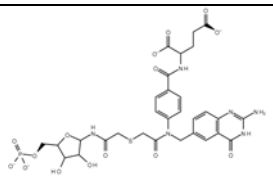
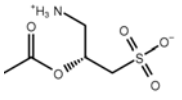
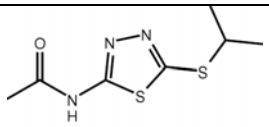
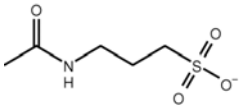
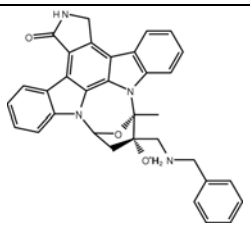
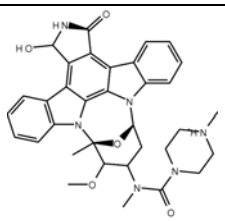
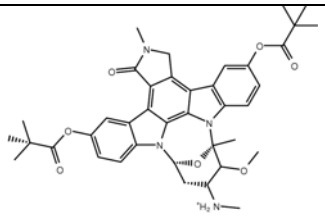
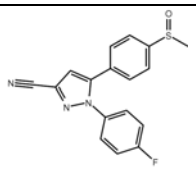
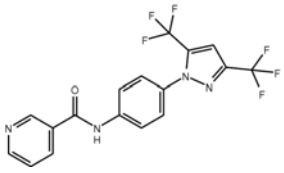
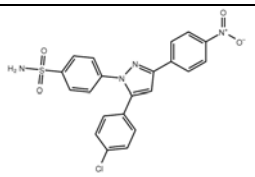
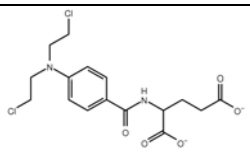
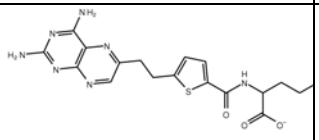
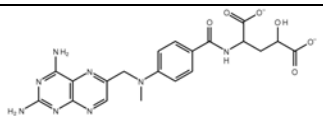
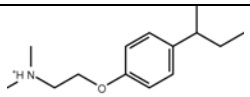
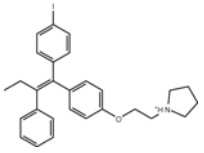
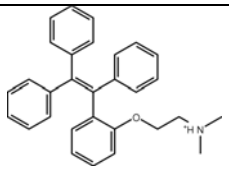
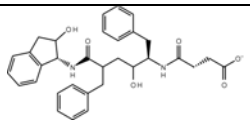
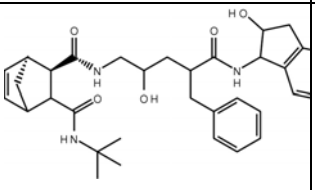
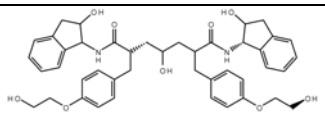
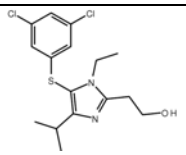
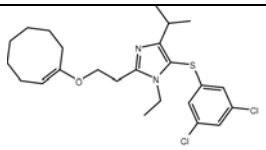
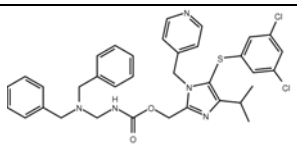
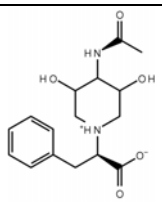
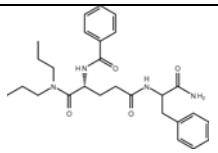
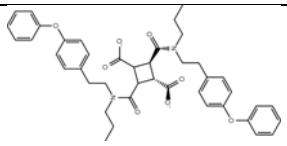
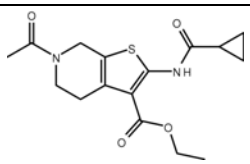
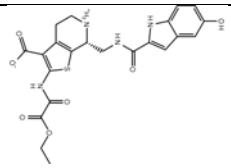
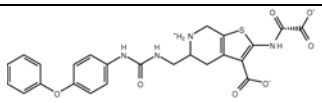
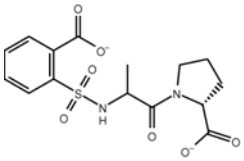
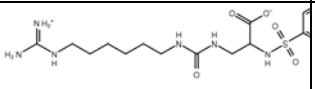
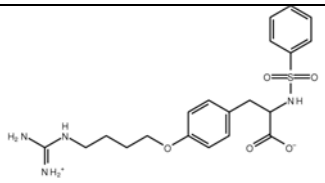
HIVrt			
NA			
PTP1B			
Throm.			
TS			

Figure S3: Highest ranking inactive compounds for each target using MOLPRINT2D fingerprints, Fn atom typing, no bit scaling, and Buser similarity.

Target	Best ranked decoy	Second best ranked decoy	Third best ranked decoy
CA			
CDK2			
COX2			
DHFR			
ER			
HIVpr			

HIVrt			
NA			
PTP1B			
Throm.			
TS