Supporting Information:

SMILES Pair Encoding: A Data-Driven Substructure Tokenization Algorithm for Deep Learning

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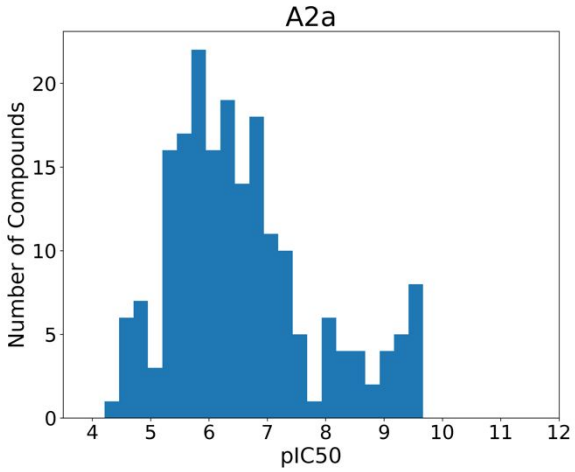
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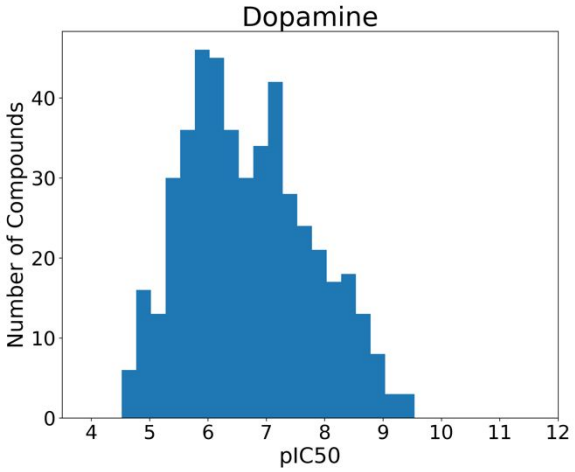
pIC50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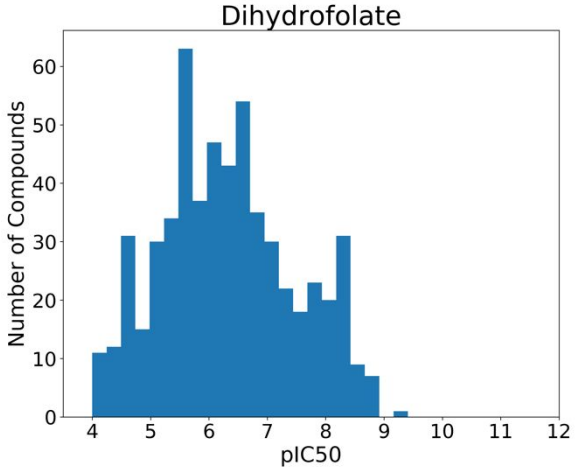
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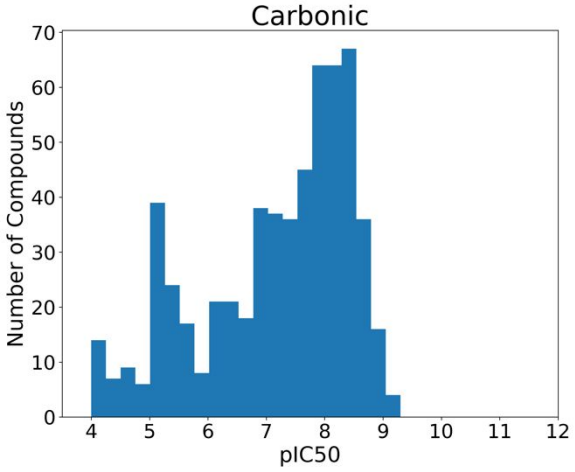
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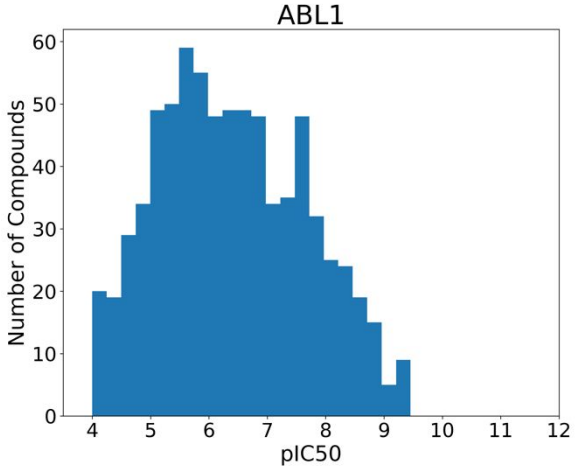
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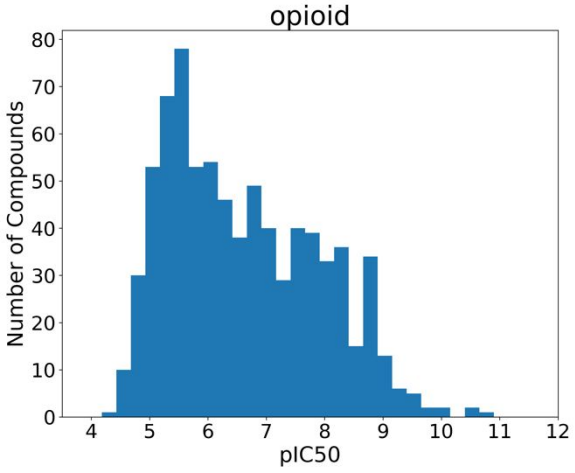
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Number of Compounds
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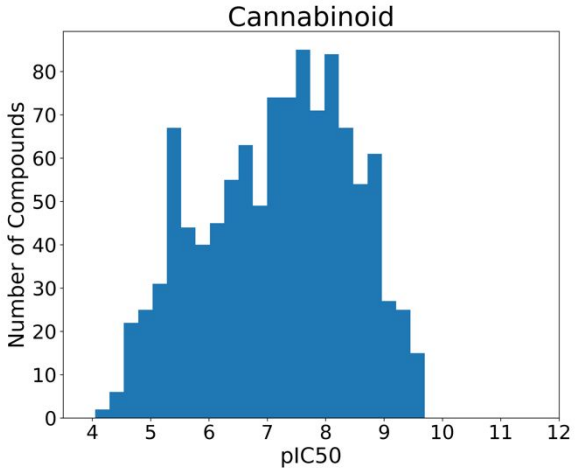
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Number of Compounds
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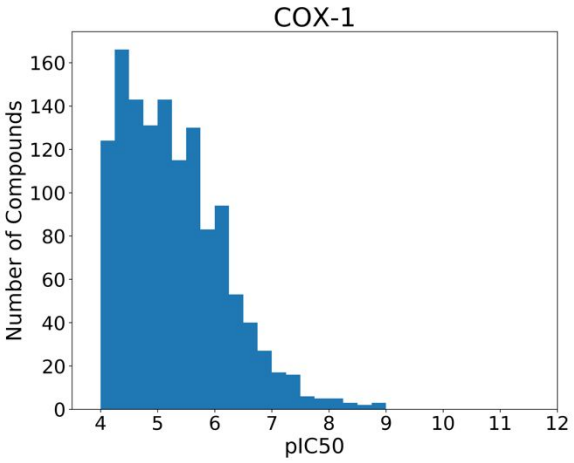
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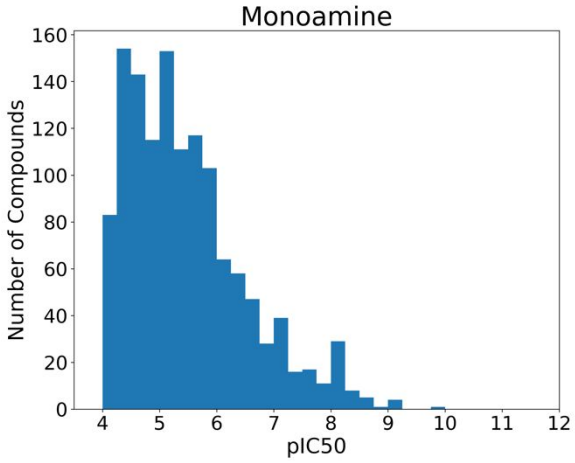
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Number of Compounds
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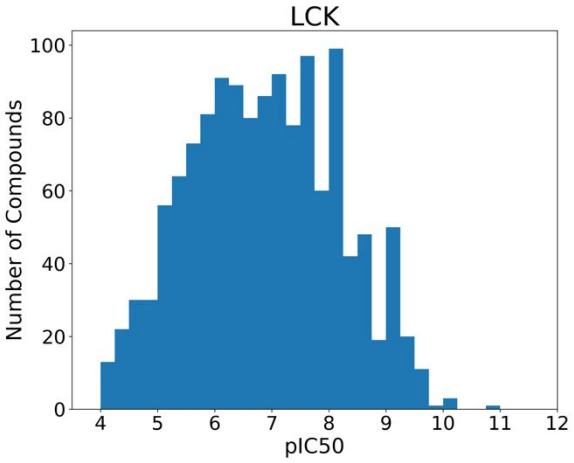
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Number of Compounds
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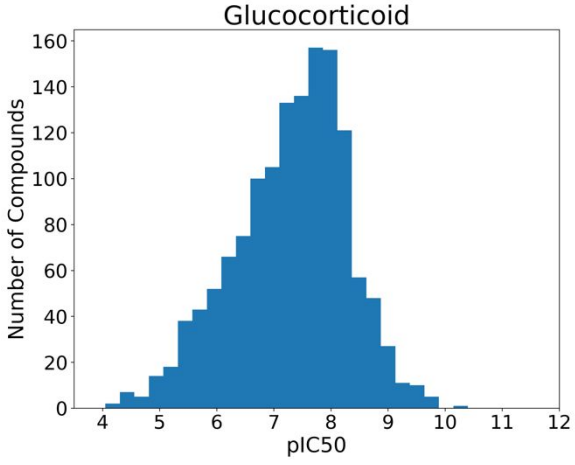
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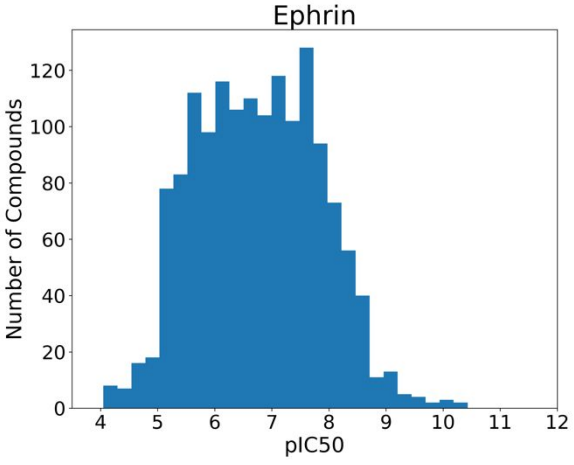
Number of Compounds
pIC50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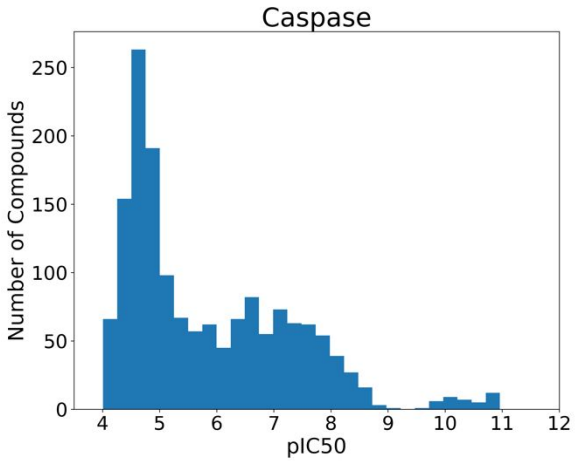
Number of Compounds
pIC50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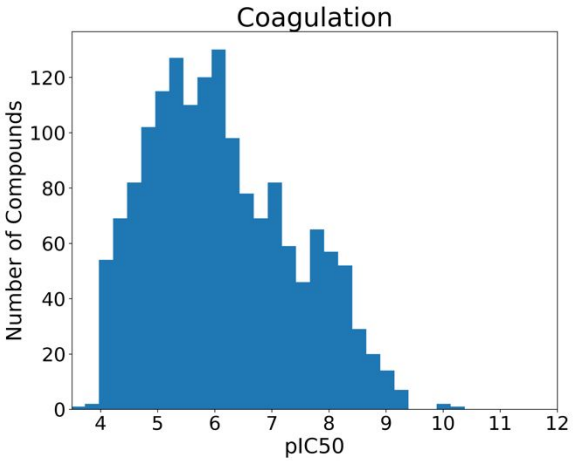
Number of Compounds
pIC50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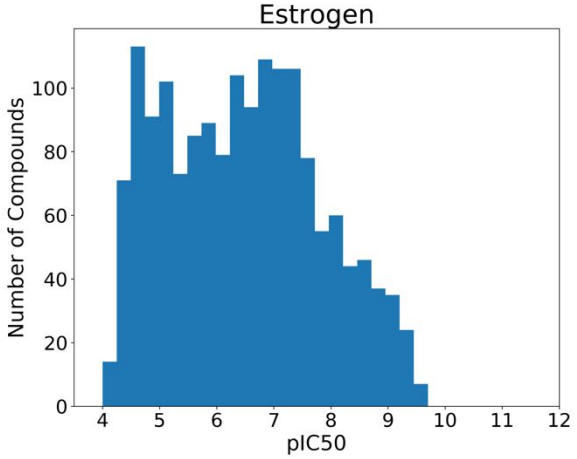
Number of Compounds
pIC50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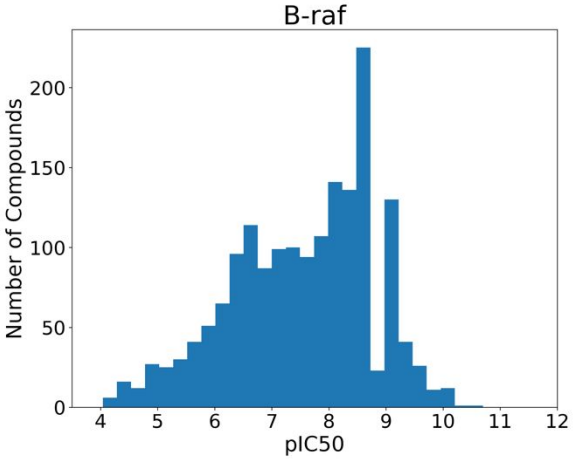
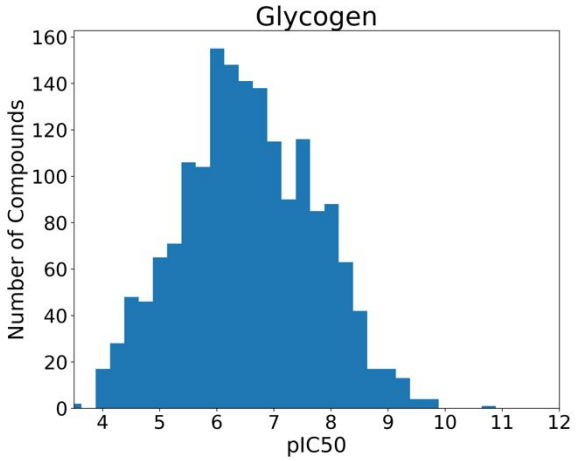
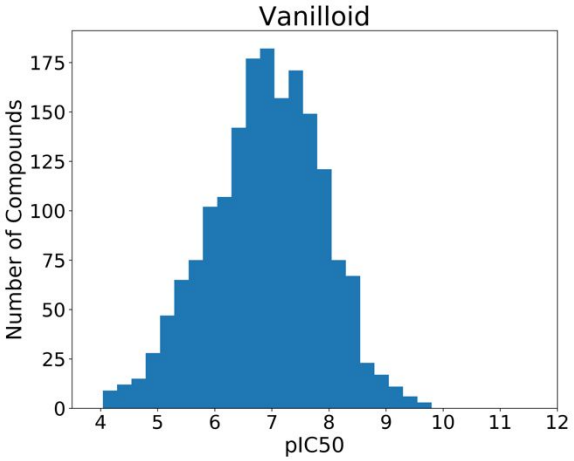
Number of Compounds
pIC50


B-raf
Number of Compounds
pIC50


Glycogen
Number of Compounds
pIC50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Number of Compounds
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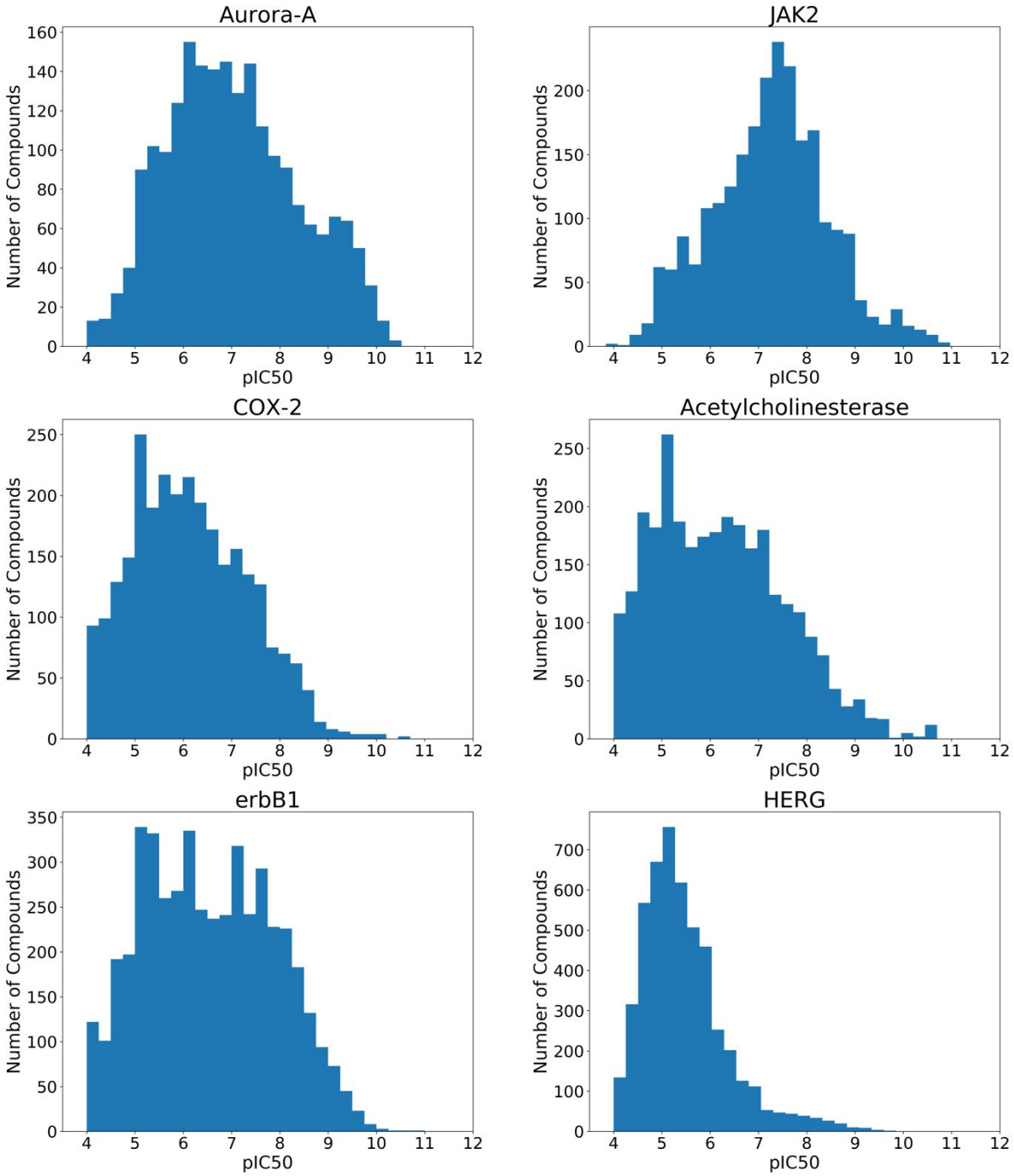

Figure S1. Distributions of QSAR Benchmark Datasets.

Table S1. Number of Extracted Substructures.

	Training Set	**SPE**	**Atom-level**
# of BRICS Fragments	300,315	388,839	407,865
# of Functional Group	14,500	28,859	28,156
# of Scaffolds	474,646	601,502	649,974
# of Ring Systems	35,107	83,891	85,265

Table S2. Performance of QSAR models trained with SPE tokenization.

Targets	RMSE	R^2	MAE
A2a	0.669±0.111	0.724±0.116	0.523±0.078
DRD2	0.719±0.055	0.522±0.080	0.551±0.045
Dihydrofolate	0.771±0.053	0.545±0.049	0.586±0.042
Carbonic	0.582±0.035	0.781±0.046	0.427±0.032
ABL1	0.746±0.050	0.637±0.067	0.566±0.045
opioid	0.636±0.046	0.742±0.042	0.477±0.032
Cannabinoid	0.671±0.041	0.715±0.036	0.500±0.021
COX-1	0.655±0.064	0.486±0.064	0.489±0.046
Monoamine	0.604±0.054	0.645±0.046	0.454±0.037
LCK	0.758±0.035	0.673±0.048	0.589±0.028
Glucocorticoid	0.541±0.042	0.692±0.057	0.426±0.030
Ephrin	0.652±0.051	0.647±0.037	0.494±0.026
Caspase	0.586±0.098	0.835±0.079	0.440±0.093
Coagulation	0.771±0.037	0.622±0.039	0.580±0.031
Estrogen	0.630±0.037	0.780±0.024	0.459±0.032
B-raf	0.599±0.057	0.756±0.046	0.452±0.036
Glycogen	0.731±0.028	0.593±0.041	0.548±0.023
Vanilloid	0.669±0.055	0.543±0.080	0.522±0.032
Aurora-A	0.711±0.049	0.723±0.033	0.530±0.035
JAK2	0.623±0.046	0.725±0.041	0.467±0.026
COX-2	0.728±0.043	0.605±0.050	0.537±0.032
Acetylcholinesterase	0.675±0.0049	0.749±0.033	0.495±0.033
erbB1	0.658±0.023	0.757±0.011	0.492±0.019
HERG	0.536±0.019	0.625±0.033	0.395±0.019

Table S3. Performance of QSAR models trained with atom-level tokenization.

Targets	RMSE	R^2	MAE
A2a	0.776±0.224	0.612±0.215	0.550±0.151
DRD2	0.748±0.097	0.479±0.140	0.576±0.071
Dihydrofolate	0.794±0.101	0.525±0.101	0.592±0.072
Carbonic	0.578±0.069	0.792±0.046	0.421±0.052
ABL1	0.750 0.046	0.635±0.046	0.574±0.034
opioid	0.642±0.072	0.735±0.066	0.485±0.049
Cannabinoid	0.717±0.055	0.679±0.034	0.552±0.033
COX-1	0.665±0.094	0.484±0.089	0.478±0.058
Monoamine	0.624±0.061	0.633±0.053	0.467±0.048
LCK	0.835±0.165	0.591±0.181	0.617±0.047
Glucocorticoid	0.535±0.058	0.695±0.074	0.411±0.042
Ephrin	0.664±0.055	0.636±0.043	0.508±0.027
Caspase	0.587±0.061	0.837±0.050	0.444±0.046
Coagulation	0.770±0.037	0.622±0.045	0.582±0.023
Estrogen	0.655±0.044	0.761±0.028	0.474±0.031
B-raf	0.599±0.067	0.762±0.046	0.443±0.043
Glycogen	0.744±0.045	0.579±0.052	0.555±0.040
Vanilloid	0.670±0.065	0.542±0.082	0.515±0.040
Aurora-A	0.744±0.073	0.698±0.044	0.547±0.040
JAK2	0.642±0.035	0.708±0.042	0.481±0.023
COX-2	0.736±0.064	0.596±0.074	0.543±0.048
Acetylcholinesterase	0.679±0.060	0.745±0.044	0.485±0.037
erbB1	0.661±0.019	0.754±0.013	0.492±0.016
HERG	0.531±0.025	0.637±0.030	0.391±0.020

Table S4. Performance of QSAR models trained with k-mer tokenization.

Targets	RMSE	R^2	MAE
A2a	0.746 ±0.197	0.648 ±0.177	0.532 ±0.125
DRD2	0.754 ±0.074	0.468 ±0.126	0.564 ±0.049
Dihydrofolate	0.783 ±0.078	0.540 ±0.065	0.571 ±0.054
Carbonic	0.588 ±0.062	0.783 ±0.050	0.431 ±0.054
ABL1	0.764 ±0.062	0.620 ±0.063	0.572 ±0.050
opioid	0.651 ±0.073	0.726 ±0.070	0.487 ±0.059
Cannabinoid	0.722 ±0.069	0.674 ±0.047	0.535 ±0.045
COX-1	0.667 ±0.100	0.47 ±0.010	0.480 ±0.062
Monoamine	0.630 ±0.067	0.625 ±0.059	0.464 ±0.046
LCK	0.768 ±0.045	0.663 ±0.053	0.590 ±0.026
Glucocorticoid	0.531 ±0.057	0.699 ±0.068	0.408 ±0.040
Ephrin	0.642 ±0.057	0.699 ±0.068	0.490 ±0.040
Caspase	0.604 ±0.066	0.828 ±0.050	0.458 ±0.067
Coagulation	0.771 ±0.044	0.621 ±0.033	0.581 ±0.026
Estrogen	0.647 ±0.052	0.766 ±0.029	0.470 ±0.046
B-raf	0.584 ±0.056	0.773 ±0.043	0.421 ±0.037
Glycogen	0.727 ±0.041	0.598 ±0.047	0.539 ±0.037
Vanilloid	0.671 ±0.070	0.538 ±0.105	0.510 ±0.042
Aurora-A	0.722 ±0.071	0.715 ±0.050	0.526 ±0.049
JAK2	0.620 ±0.043	0.726 ±0.044	0.459 ±0.023
COX-2	0.718 ±0.053	0.616 ±0.056	0.522 ±0.036
Acetylcholinesterase	0.686 ±0.047	0.740 ±0.035	0.492 ±0.032
erbB1	0.655 ±0.031	0.758 ±0.018	0.483 ±0.020
HERG	0.533 ±0.028	0.633 ±0.033	0.390 ±0.020

Table S5. Performance of random forest models trained ECFP6.

Targets	RMSE	R^2	MAE
A2a	0.738 ±0.238	0.647 ±0.224	0.541 ±0.120
DRD2	0.737 ±0.070	0.494 ±0.110	0.557 ±0.052
Dihydrofolate	0.790 ±0.098	0.527 ±0.111	0.584 ±0.068
Carbonic	0.619 ±0.062	0.763 ±0.036	0.435 ±0.043
ABL1	0.753 ±0.073	0.631 ±0.069	0.572 ±0.051
opioid	0.691 ±0.067	0.692 ±0.007	0.511 ±0.047
Cannabinoid	0.707 ±0.057	0.688 ±0.029	0.532 ±0.042
COX-1	0.719 ±0.092	0.397 ±0.084	0.522 ±0.058
Monoamine	0.663 ±0.037	0.583 ±0.058	0.487 ±0.022
LCK	0.785 ±0.040	0.649 ±0.047	0.609 ±0.035
Glucocorticoid	0.544 ±0.050	0.685 ±0.064	0.411 ±0.032
Ephrin	0.697 ±0.073	0.600 ±0.052	0.521 ±0.037
Caspase	0.540 ±0.056	0.863 ±0.040	0.395 ±0.032
Coagulation	0.811 ±0.049	0.580 ±0.049	0.608 ±0.035
Estrogen	0.702 ±0.037	0.725 ±0.029	0.507 ±0.024
B-raf	0.576 ±0.056	0.780 ±0.041	0.419 ±0.035
Glycogen	0.736 ±0.052	0.589 ±0.049	0.552 ±0.042
Vanilloid	0.708 ±0.044	0.489 ±0.073	0.552 ±0.032
Aurora-A	0.740 ±0.068	0.701 ±0.044	0.534 ±0.044
JAK2	0.624 ±0.033	0.724 ±0.035	0.459 ±0.022
COX-2	0.786 ±0.045	0.541 ±0.054	0.581 ±0.035
Acetylcholinesterase	0.738 ±0.052	0.699 ±0.037	0.539 ±0.043
erbB1	0.691 ±0.026	0.731 ±0.017	0.516 ±0.018
HERG	0.605 ±0.026	0.527 ±0.032	0.447 ±0.018

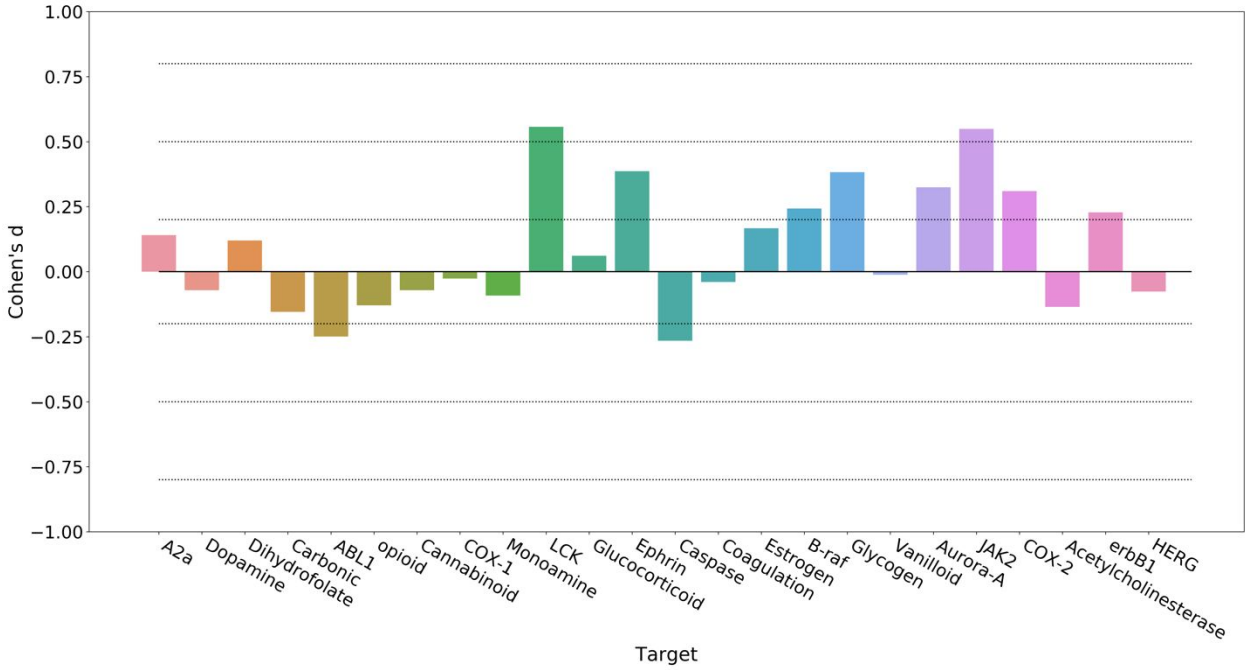

Figure S2. Cohen's d: Atom-level vs. k-mer

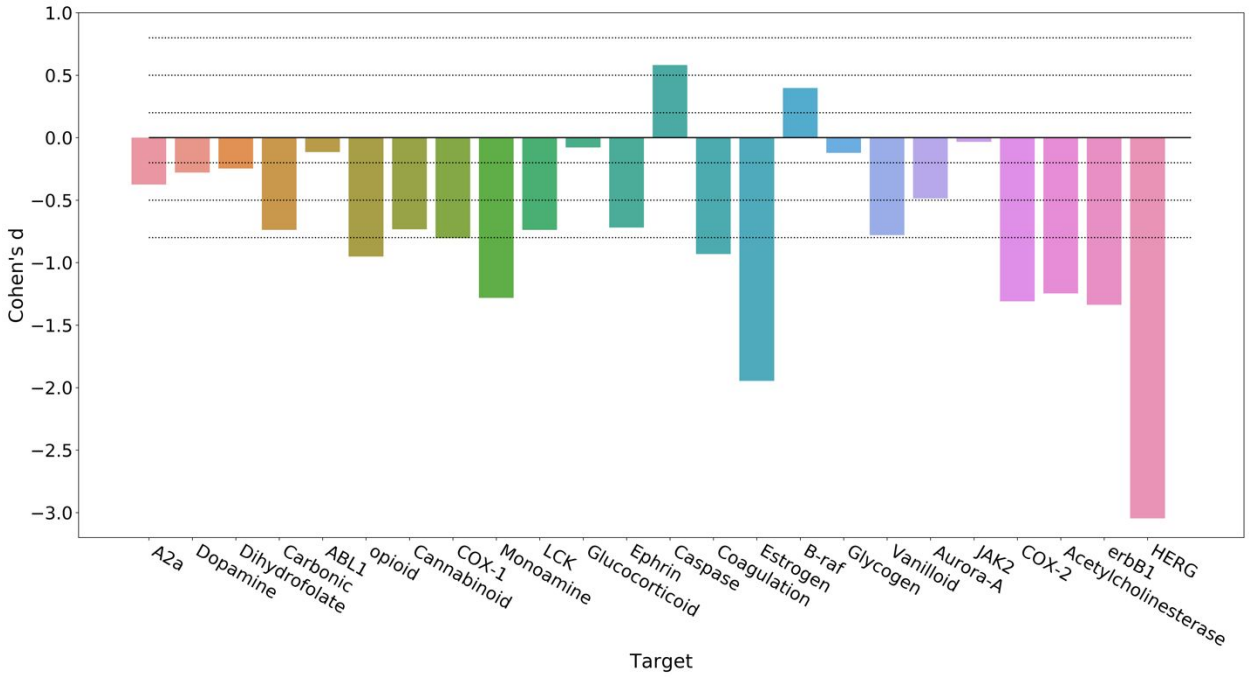

Figure S3. Cohen's d: SPE vs. ECFP6 (Random Forest Model)

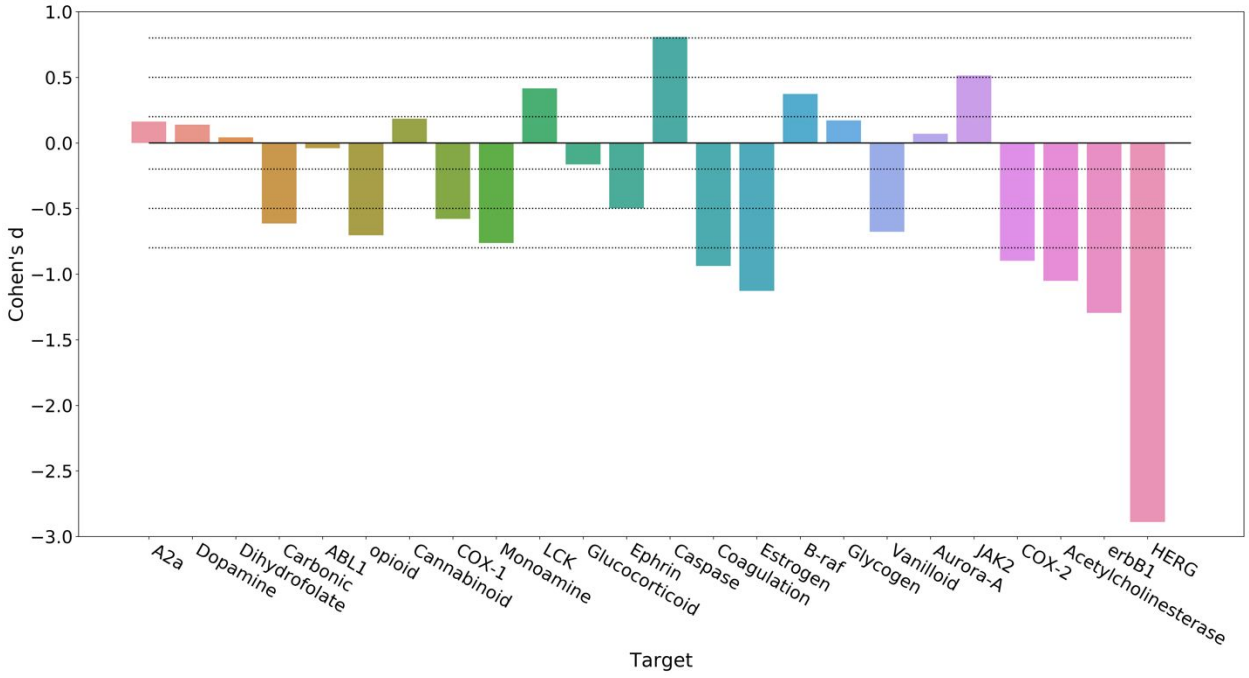

Figure S4. Cohen's d: Atom-level vs. ECFP6 (Random Forest Model)

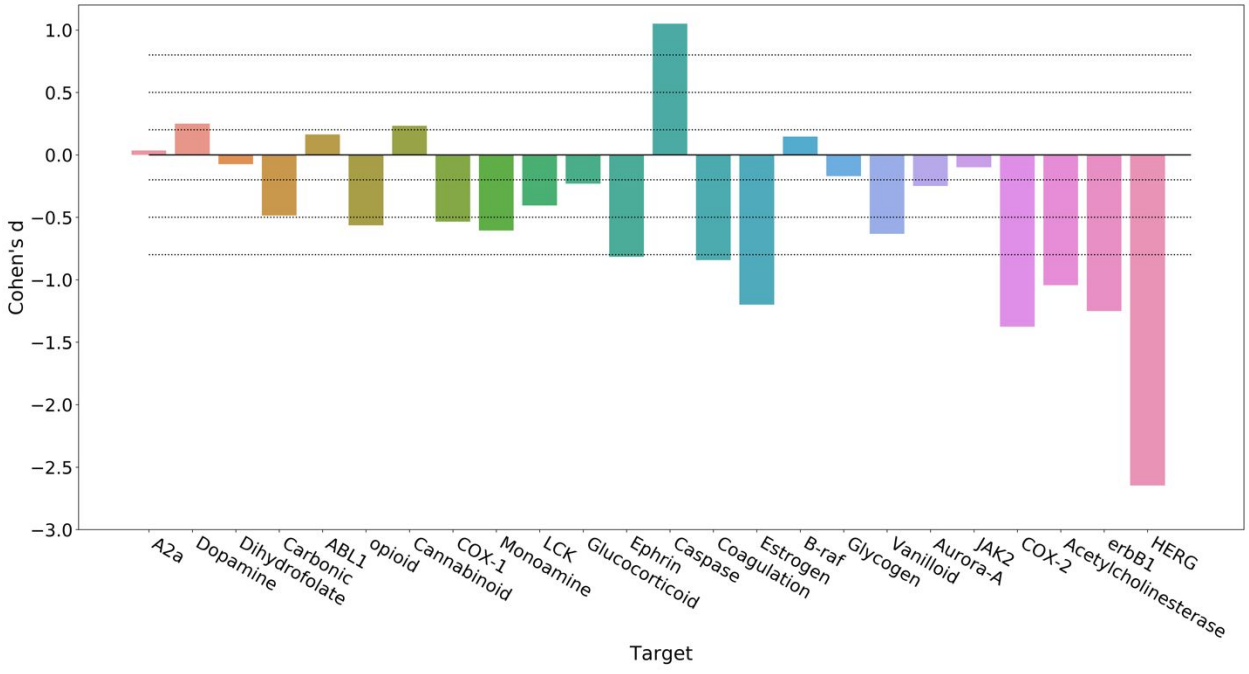

Figure S5. Cohen's d: k-mer vs. ECFP6 (Random Forest Model)