Supporting Information

Looking Back To The Future: Predicting *In vivo* Efficacy of Small Molecules Versus *Mycobacterium tuberculosis*

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Running title: Predicting in vivo efficacy

Table S1. Curated mouse in vivo TB data and molecule structures. ND = no data. (see excel file)

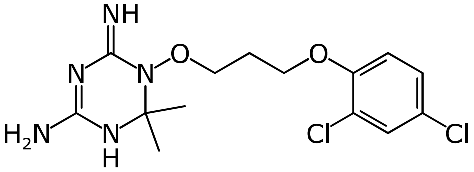
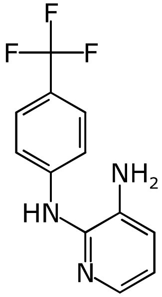
Table S2. Descriptors for training set molecules. (see excel file)

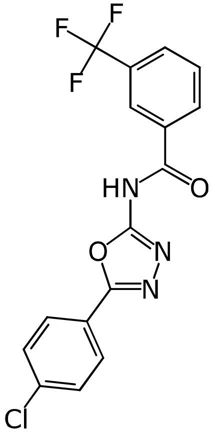
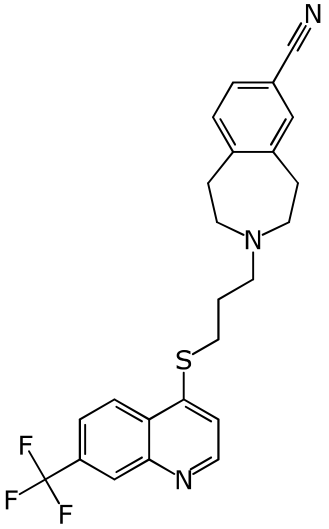
Table S3. Predictions for GSK 177 compounds (see excel file)

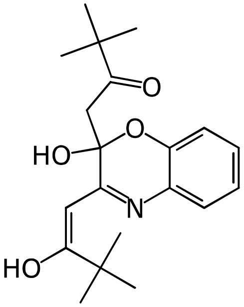
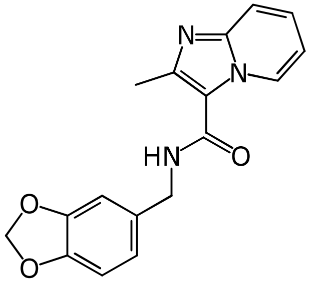
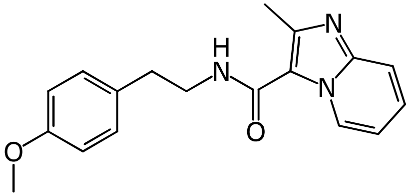
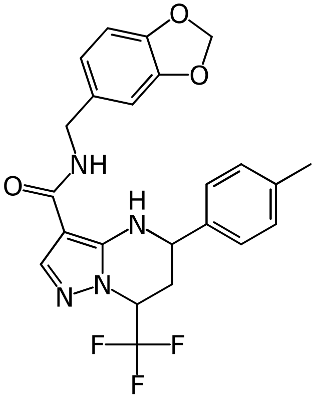
Table S4. Mean (Standard Deviation) of molecular descriptors for *in vivo* N= 177 *in vitro* actives from GSK. We compared predicted consensus in vivo actives and inactives for statistical differences. MWT = molecular weight, HBD = hydrogen bond donor, HBA = Hydrogen bond acceptor, FPSA = Fractional polar surface area, RBN = rotatable bond number. * $p < 0.05$. ** $p < 0.0001$ (Fractional polar surface area = Total partially positively charged molecular surface area divided by the total molecular surface area).

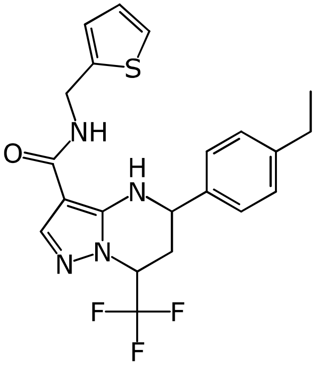
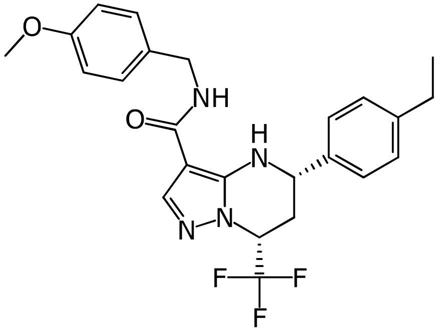
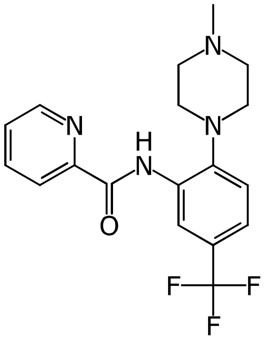
	MWT	**AlogP**	**HBD**	**HBA**	**Num Rings**	**Num Arom Rings**	**FPSA**	**RBN**
All (N =177)	357.65 ± 64.52	3.37 ± 1.06	1.14 ± 1.05	4.21 ± 1.68	3.52 ± 0.89	2.89 ± 0.78	0.24 ± 0.09	4.90 ± 2.15
Active (N = 24)	362.90 ± 55.73	3.43 ± 1.11	1.20 ± 0.66	3.29 ± 1.16	3.29 ± 0.75	2.67 ± 0.70	0.19 ± 0.05	4.50 ± 1.14
Inactive (N = 153)	356.83 ± 65.92	3.36 ± 1.06	1.14 ± 1.10	4.36 ± 1.70*	3.55 ± 0.90	2.92 ± 0.78	0.24 ± 0.09**	4.96 ± 2.27

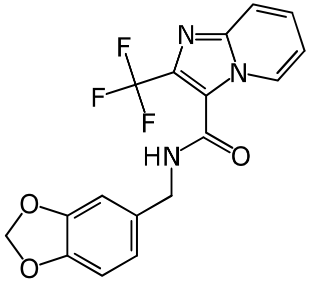
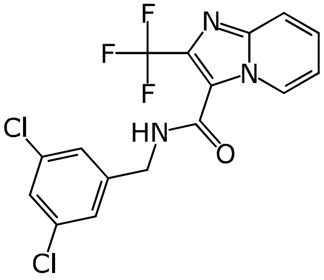
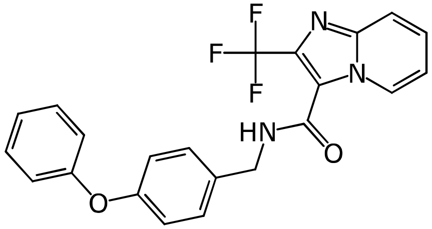
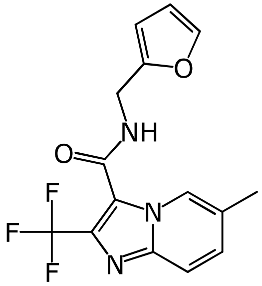
Table S5 GSK 24 consensus predicted compounds with maximum Tanimoto similarity to the training set, TB Mobile predictions and clustering with the TB Mobile dataset in Discovery Studio to infer the target/s.

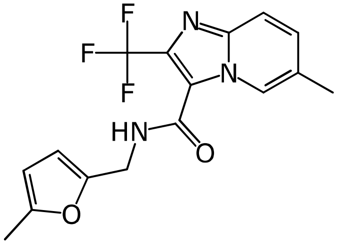
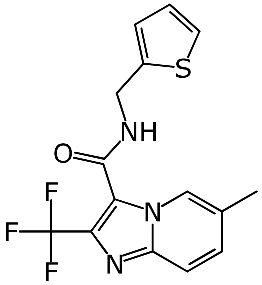
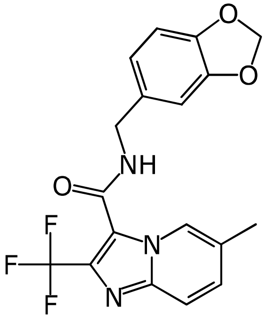
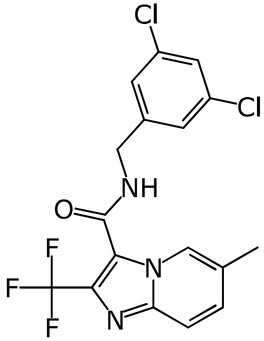
Molecule	**Molecule Name**	**Maximum Tanimoto Similarity to a training set molecule using MDL fingerprints (closest molecule)**	**TB Mobile predicted target/s (top 2 molecules)**	**Clustering with TB Mobile dataset - predicted target/s**
	BRL-51091AM	0.59 (ITR 103)	Emb A, Emb B, Emb C InhA, DnaE2	Cluster 19 DfrA
	GR135487X	0.56 (Hoggarth4compound4456)	Rv1885, SahH	Cluster 12 (no TB Mobile compounds) Close clusters are CysH and DapA

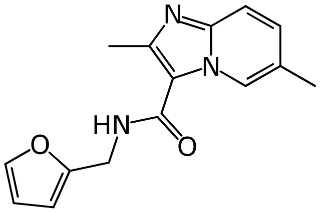
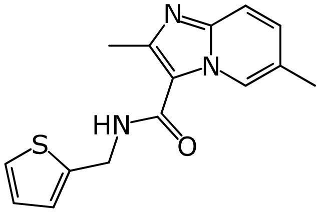
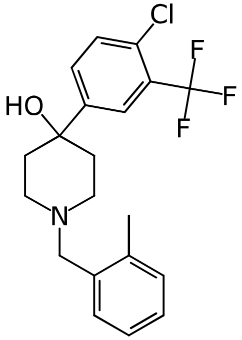
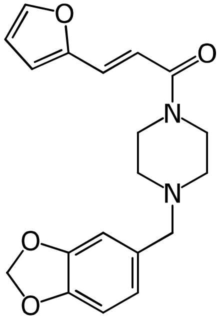
	GSK130506A	0.67 (6q Sriram JMC 2006)	InhA	Cluster 32 (no TB Mobile compounds) Close cluster are Mmpl3 and InhA
	GSK254610A	0.62 (Thioridazine)	InhA	Cluster 90 Rv3161c and Rv1211

	GSK262906A	0.54 (Clarithromycin)	AroD, KasA	Cluster 27 (no TB Mobile compounds) Close cluster Mca and CysH
	GSK498315A	0.72 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK762874A	0.74 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK937733A	0.98 (Remunian 3) Note if stereo chemistry was shown this would = 1	Mmpl3 (in software dataset)	Cluster 39 InhA, DprE and Mmpl3

	GSK1589671A	0.92 (yokokawa 9)	Mmpl3	Cluster 21 QcrB
	GSK1589673A	0.86 (Remunian 3)	Mmpl3 (in software dataset)	Cluster 59 Mmpl3
	GSK1750922A	0.82 (sudoterb)	InhA	Cluster 77 InhA, Mmpl3

	GSK1829671A	0.77 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829674A	0.88 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829676A	0.82 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829727A	0.88 (Abrahams IP3)	QcrB	Cluster 21 QcrB

	GSK1829728A	0.88 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829729A	0.90 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829732A	0.81 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829736A	0.93 (Abrahams IP3)	QcrB	Cluster 21 QcrB

	GSK1829819A	0.83 (Abrahams IP3)	QcrB	Cluster 21 QcrB
	GSK1829820A	0.84 (Abrahams IP3)	QcrB (in software dataset)	Cluster 21 QcrB
	GSK1985270A	0.63 (Remunian 4)	InhA	Cluster 8 AtpE
	GW713556X	0.68 (ketoconazole)	Glf	Cluster 89 InhA

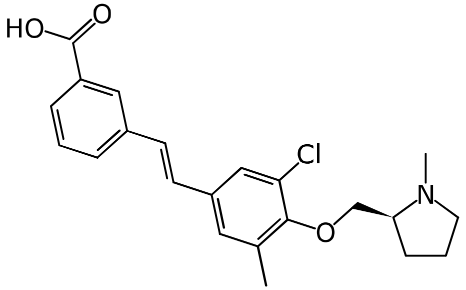
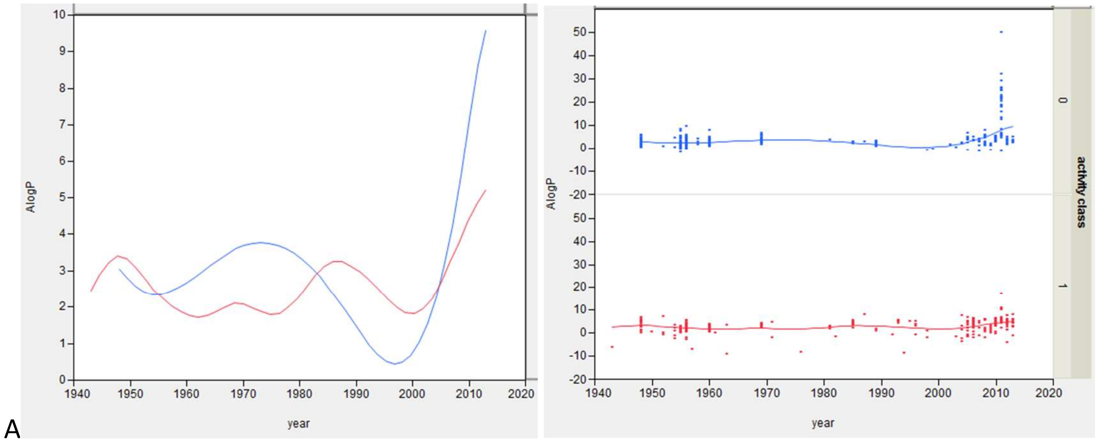
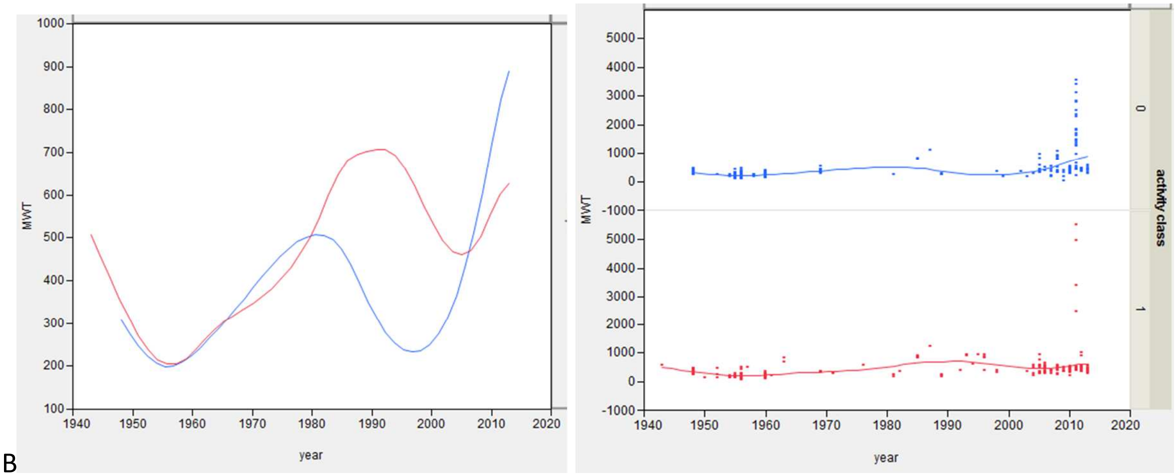
	SB-829405	0.69 (ketoconazole)	InhA	Cluster 75 GyrA, RpoB, MurD

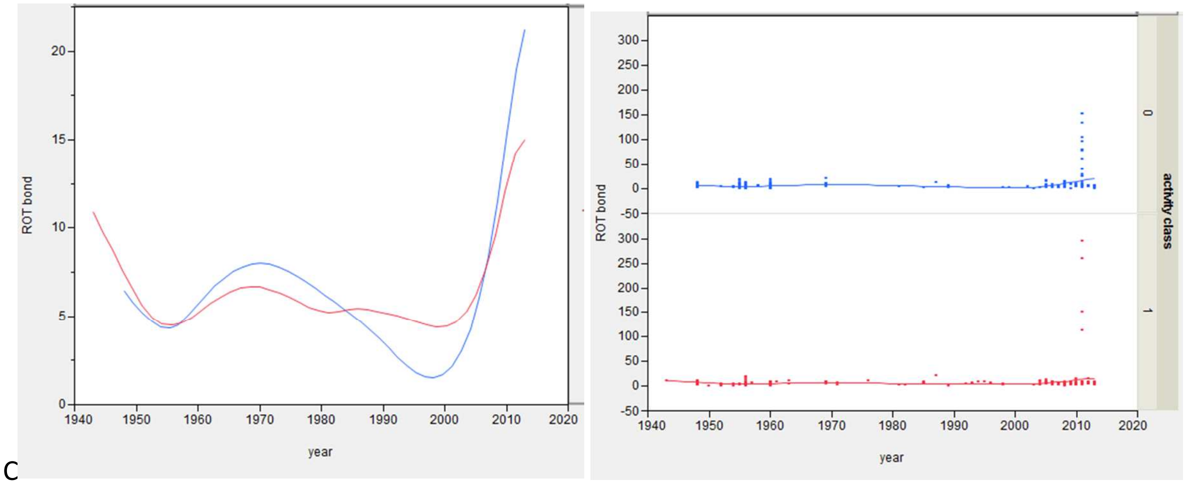
Figure S1. Average differences and trends between molecular descriptors versus year of publication of the source paper (as a surrogate for year of discovery) to illustrate historical progress and temperospatial effects (left plot = smoothed data; right plot = individual data points; red = active *in vivo*; blue = inactive *in vivo*). A, AlogP; B, MWT; C, rotatable bond number; D, number of rings; E, number of aromatic rings; F, hydrogen bond acceptors; G, hydrogen bond donors; H, fractional polar surface area.



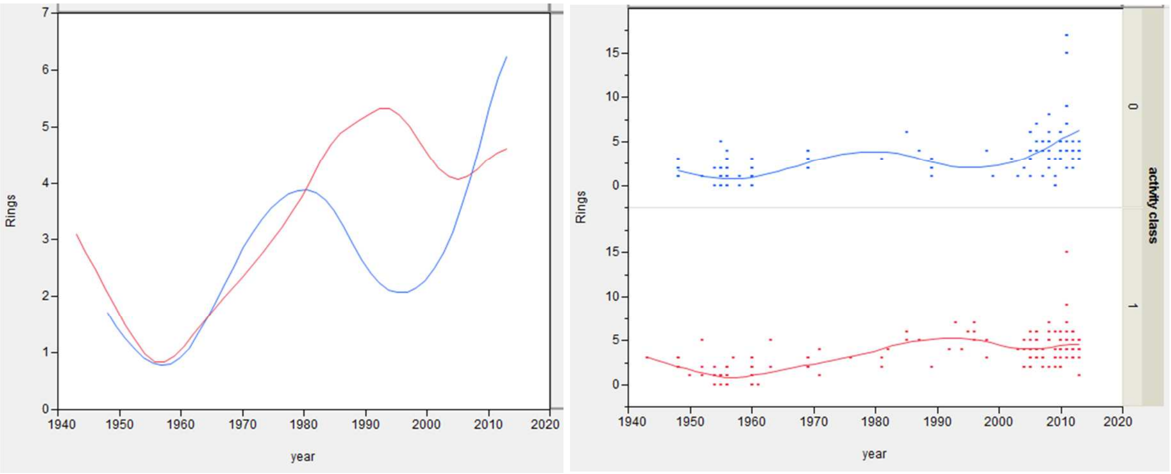
A


MWT
1000
900
800
700
600
500
400
300
200
100
1940
1950
1960
1970
1980
1990
2000
2010
2020
year
MWT
5000
4000
3000
2000
1000
0
-1000
activity class
0
1
year

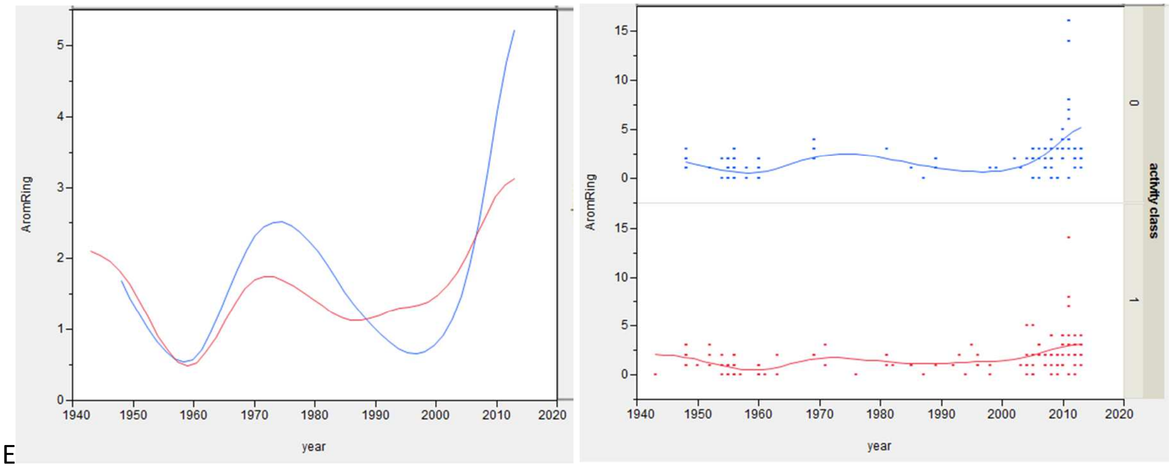
B


ROT bond
20
15
10
5
0
1940
1950
1960
1970
1980
1990
2000
2010
2020
year
ROT bond
300
250
200
150
100
50
0
-50
activity class
0
1
year

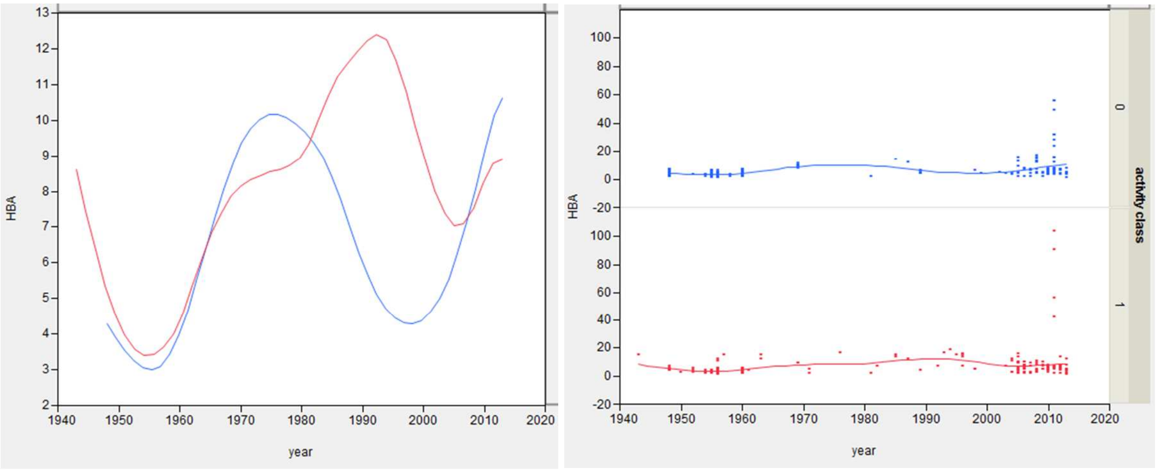
C


Rings
0
1
2
3
4
5
6
7
1940
1950
1960
1970
1980
1990
2000
2010
2020
year
Rings
0
5
10
15
0
5
10
15
0
1
activity class

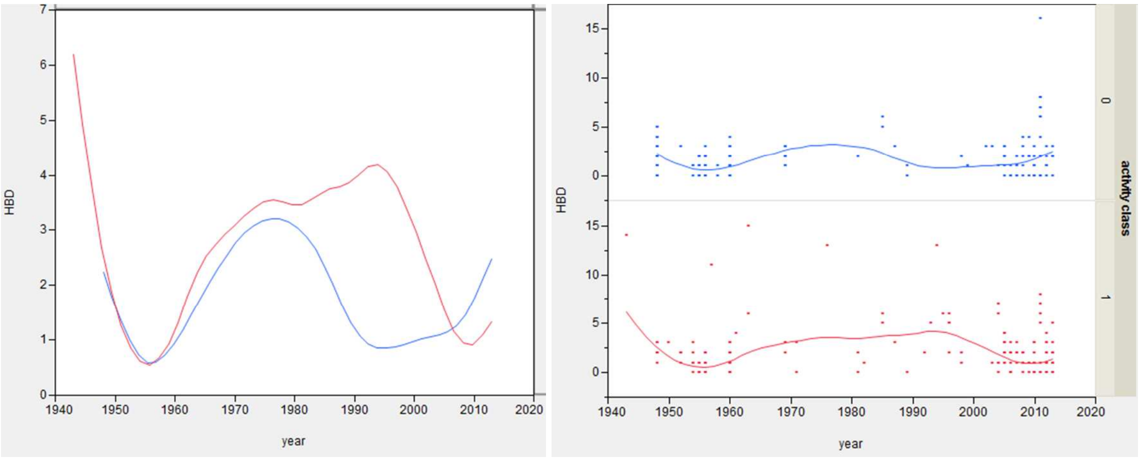
D


AromRing
0
1
2
3
4
5
1940
1950
1960
1970
1980
1990
2000
2010
2020
year
AromRing
0
5
10
15
0
5
10
15
0
1
activity class

E

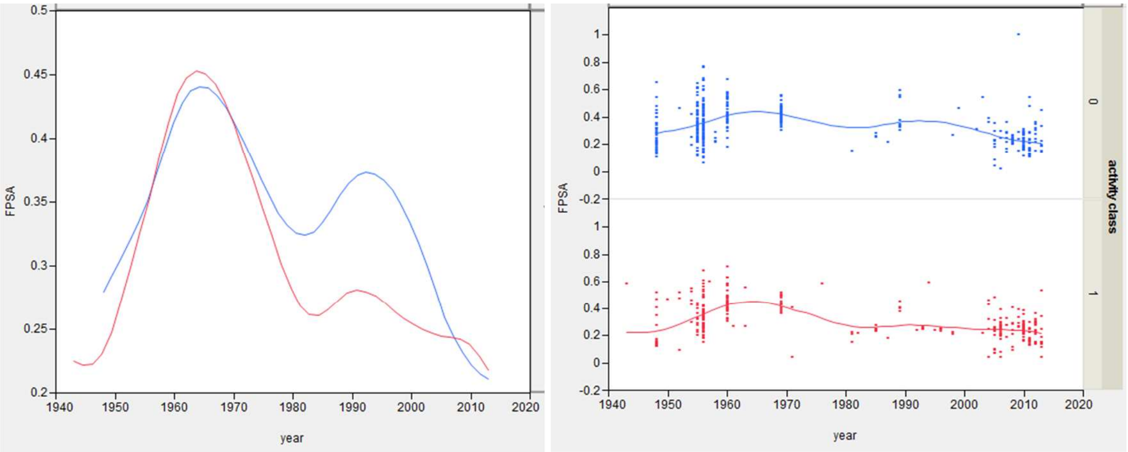

HBA
year
1940
1950
1960
1970
1980
1990
2000
2010
2020
activity class
0
1

F


HBD
year
1940
1950
1960
1970
1980
1990
2000
2010
2020
activity class
0
1

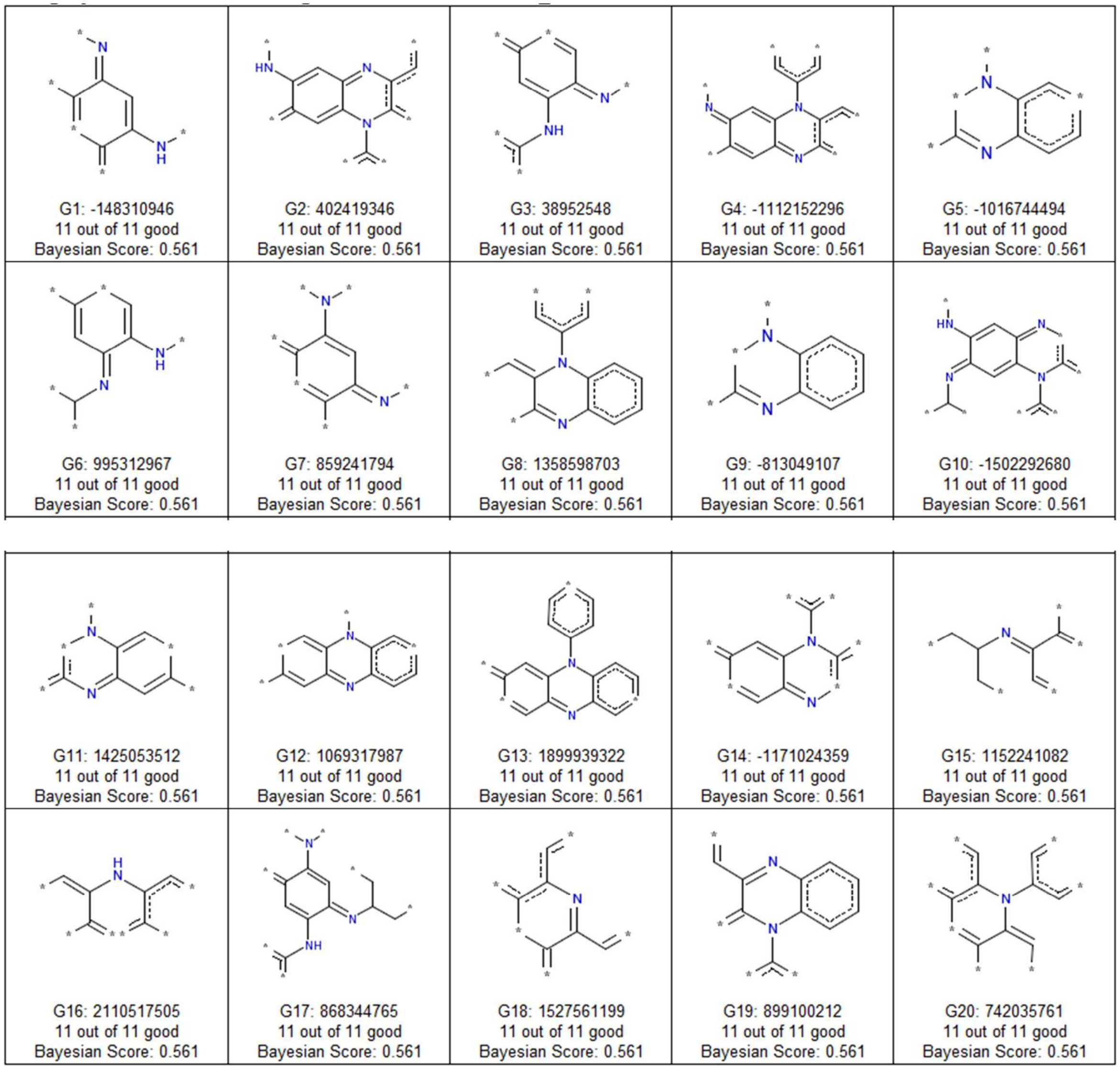
G

H



FPSA
0.5
0.45
0.4
0.35
0.3
0.25
0.2
1940
1950
1960
1970
1980
1990
2000
2010
2020
year
FPSA
1
0.8
0.6
0.4
0.2
0
-0.2
1
0.8
0.6
0.4
0.2
0
-0.2
0
1
activity class
1940
1950
1960
1970
1980
1990
2000
2010
2020
year

Figure S2. Mouse *in vivo Mtb* activity Bayesian model: good features from FCFP_6.



G1: -148310946
11 out of 11 good
Bayesian Score: 0.561

G2: 402419346
11 out of 11 good
Bayesian Score: 0.561

G3: 38952548
11 out of 11 good
Bayesian Score: 0.561

G4: -1112152296
11 out of 11 good
Bayesian Score: 0.561

G5: -1016744494
11 out of 11 good
Bayesian Score: 0.561

G6: 995312967
11 out of 11 good
Bayesian Score: 0.561

G7: 859241794
11 out of 11 good
Bayesian Score: 0.561

G8: 1358598703
11 out of 11 good
Bayesian Score: 0.561

G9: -813049107
11 out of 11 good
Bayesian Score: 0.561

G10: -1502292680
11 out of 11 good
Bayesian Score: 0.561

G11: 1425053512
11 out of 11 good
Bayesian Score: 0.561

G12: 1069317987
11 out of 11 good
Bayesian Score: 0.561

G13: 1899939322
11 out of 11 good
Bayesian Score: 0.561

G14: -1171024359
11 out of 11 good
Bayesian Score: 0.561

G15: 1152241082
11 out of 11 good
Bayesian Score: 0.561

G16: 2110517505
11 out of 11 good
Bayesian Score: 0.561

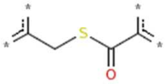
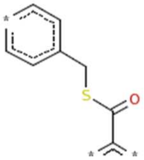
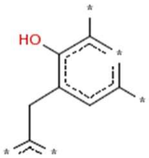
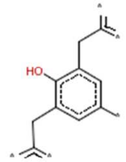
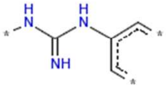
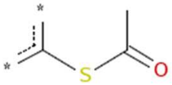
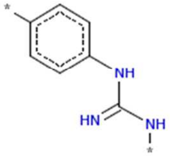
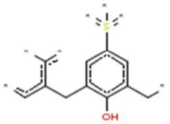
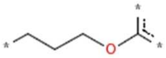
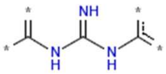
G17: 868344765
11 out of 11 good
Bayesian Score: 0.561

G18: 1527561199
11 out of 11 good
Bayesian Score: 0.561

G19: 899100212
11 out of 11 good
Bayesian Score: 0.561

G20: 742035761
11 out of 11 good
Bayesian Score: 0.561

Supplemental Figure S3. Mouse *in vivo Mtb* activity Bayesian model: bad features from FCFP_6.

 B1: 1569499252 0 out of 10 good Bayesian Score: -1.843	 B2: -935558029 0 out of 10 good Bayesian Score: -1.843	 B3: 1713697850 0 out of 10 good Bayesian Score: -1.843	 B4: -1638460559 0 out of 10 good Bayesian Score: -1.843	 B5: -1630517516 0 out of 9 good Bayesian Score: -1.755
 B6: -1539730963 0 out of 9 good Bayesian Score: -1.755	 B7: -980712074 0 out of 8 good Bayesian Score: -1.659	 B8: -1877850085 0 out of 7 good Bayesian Score: -1.552	 B9: 368675221 0 out of 7 good Bayesian Score: -1.552	 B10: -1878095589 0 out of 7 good Bayesian Score: -1.552

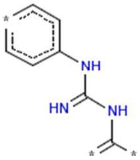
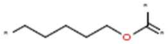
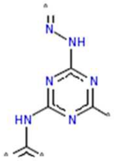
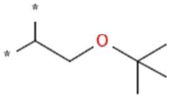
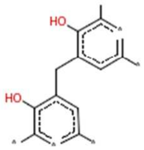
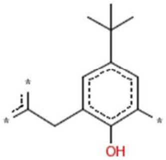
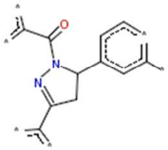
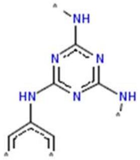
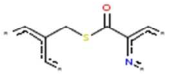
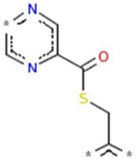
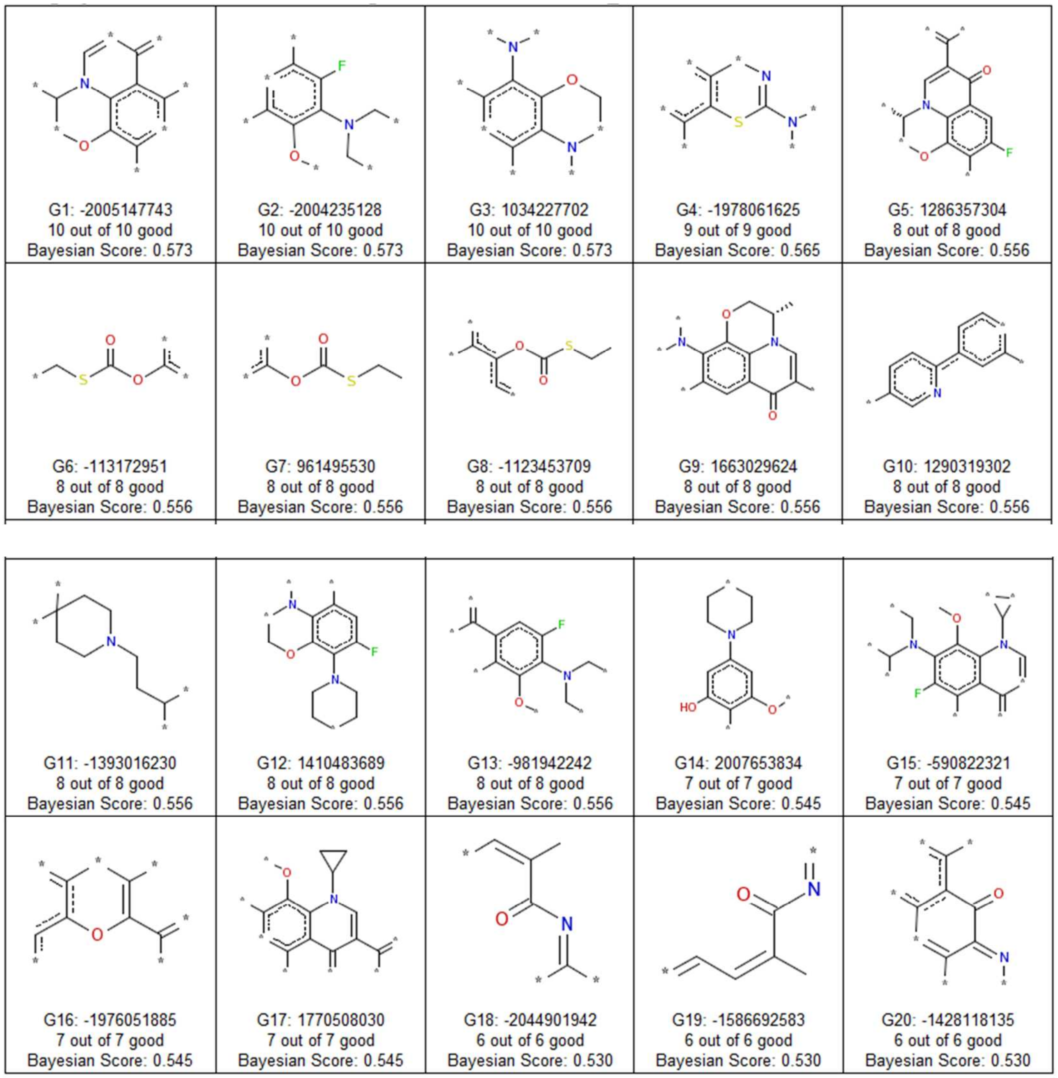
 B11: -1674330733 0 out of 7 good Bayesian Score: -1.552	 B12: -447202965 1 out of 14 good Bayesian Score: -1.440	 B13: -1931998982 0 out of 6 good Bayesian Score: -1.433	 B14: 1267353621 0 out of 6 good Bayesian Score: -1.433	 B15: -541372719 0 out of 6 good Bayesian Score: -1.433
 B16: -484806247 0 out of 6 good Bayesian Score: -1.433	 B17: -1230639123 0 out of 6 good Bayesian Score: -1.433	 B18: 385180118 0 out of 6 good Bayesian Score: -1.433	 B19: -731926398 0 out of 6 good Bayesian Score: -1.433	 B20: 215090317 0 out of 6 good Bayesian Score: -1.433

Figure S4. Mouse *in vivo Mtb* activity Bayesian model after removal of Clofazamine and 10 analogs from the dataset: good features from FCFP_6. ROC score was -0.76, 5 fold cross validation ROC score was 0.73 (Sensitivity 73.8%, Specificity 87.1%, Concordance 81.0%).



G1: -2005147743
10 out of 10 good
Bayesian Score: 0.573

G2: -2004235128
10 out of 10 good
Bayesian Score: 0.573

G3: 1034227702
10 out of 10 good
Bayesian Score: 0.573

G4: -1978061625
9 out of 9 good
Bayesian Score: 0.565

G5: 1286357304
8 out of 8 good
Bayesian Score: 0.556

G6: -113172951
8 out of 8 good
Bayesian Score: 0.556

G7: 961495530
8 out of 8 good
Bayesian Score: 0.556

G8: -1123453709
8 out of 8 good
Bayesian Score: 0.556

G9: 1663029624
8 out of 8 good
Bayesian Score: 0.556

G10: 1290319302
8 out of 8 good
Bayesian Score: 0.556

G11: -1393016230
8 out of 8 good
Bayesian Score: 0.556

G12: 1410483689
8 out of 8 good
Bayesian Score: 0.556

G13: -981942242
8 out of 8 good
Bayesian Score: 0.556

G14: 2007653834
7 out of 7 good
Bayesian Score: 0.545

G15: -590822321
7 out of 7 good
Bayesian Score: 0.545

G16: -1976051885
7 out of 7 good
Bayesian Score: 0.545

G17: 1770508030
7 out of 7 good
Bayesian Score: 0.545

G18: -2044901942
6 out of 6 good
Bayesian Score: 0.530

G19: -1586692583
6 out of 6 good
Bayesian Score: 0.530

G20: -1428118135
6 out of 6 good
Bayesian Score: 0.530

Figure S5. Mouse *in vivo Mtb* activity Bayesian model after removal of Clofazamine and 10 analogs from the dataset: bad features from FCFP_6. ROC score was -0.76, 5 fold cross validation ROC score was 0.73 (Sensitivity 73.8%, Specificity 87.1%, Concordance 81.0%).

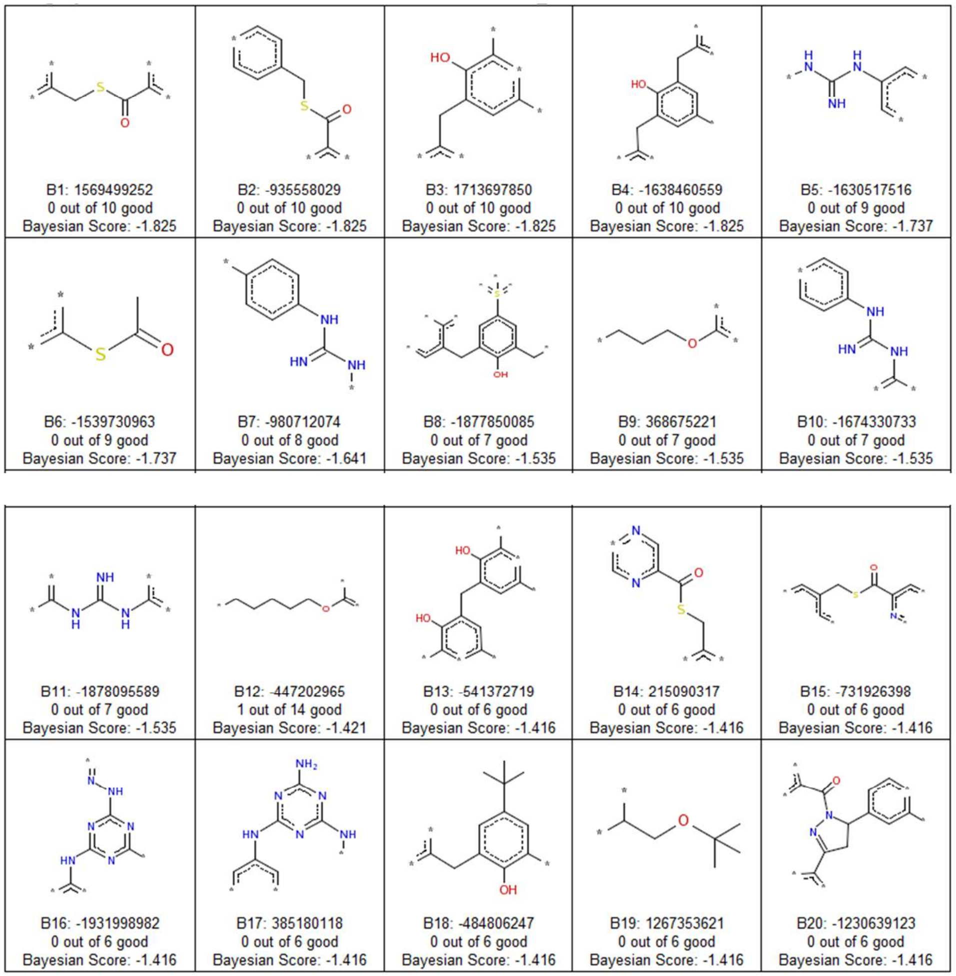
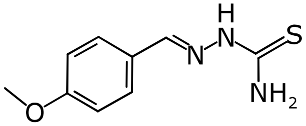
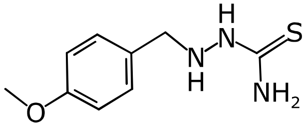
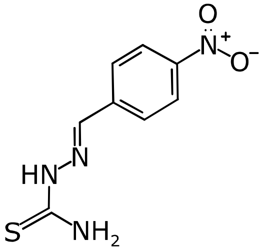
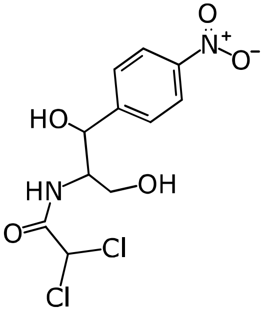
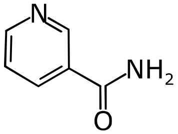
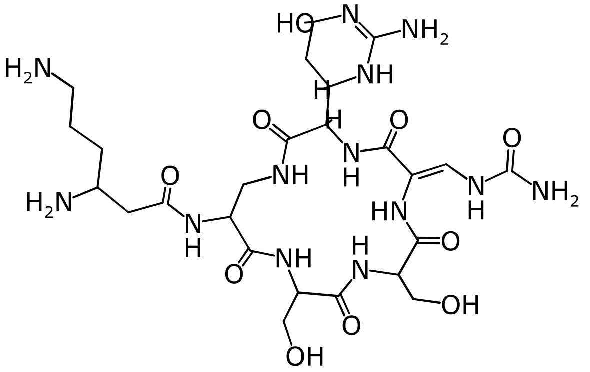
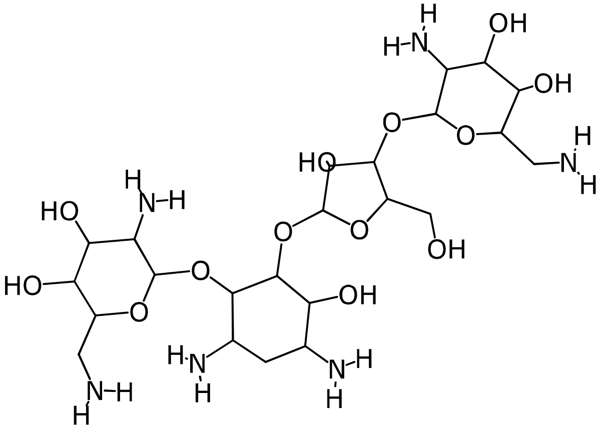
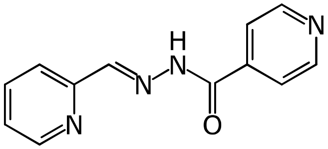


Figure S6. Molecules from very recent and historic publications used as a test set for the machine learning models.

Molecule	Name
	1070
	1493
	2403
	2406
	2875

	viomycin
	neomycin
	PCIH

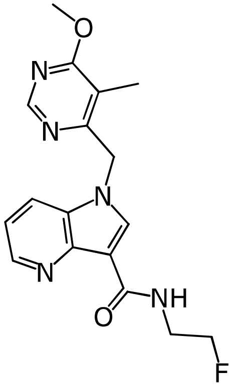
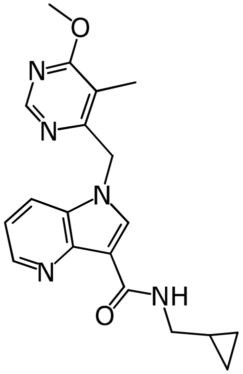
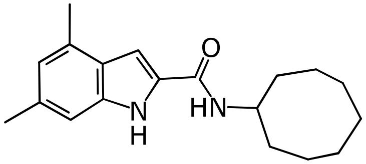
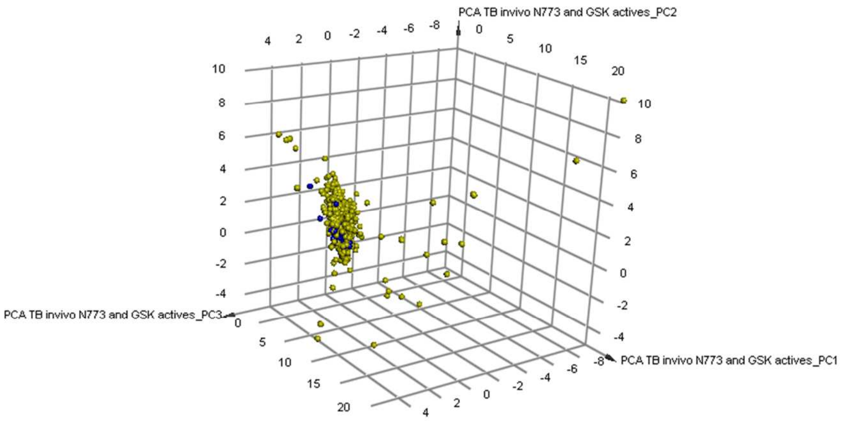
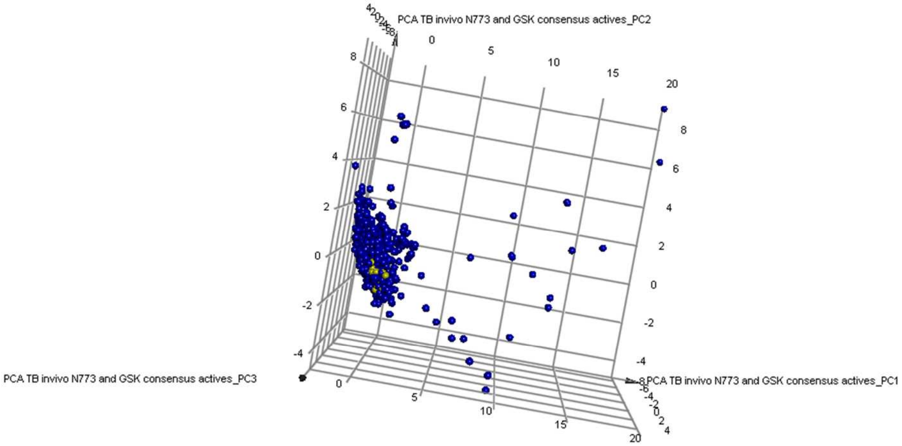
	cpd 3
	cpd 4
	indoleamide

Figure S7. GSK *in vitro* active compounds and coverage of *Mtb in vivo* space. A. Overlap of GSK compounds (blue) with 773-molecule TB *in vivo* dataset (yellow) PCA. 3PCs explain 86.4% of variance. B. PCA of 24 GSK Consensus actives (yellow) and TB in vivo data (blue). 3 PCs explain 87% of variance. Consensus actives (yellow) are buried in the major cluster of *in vivo* data.

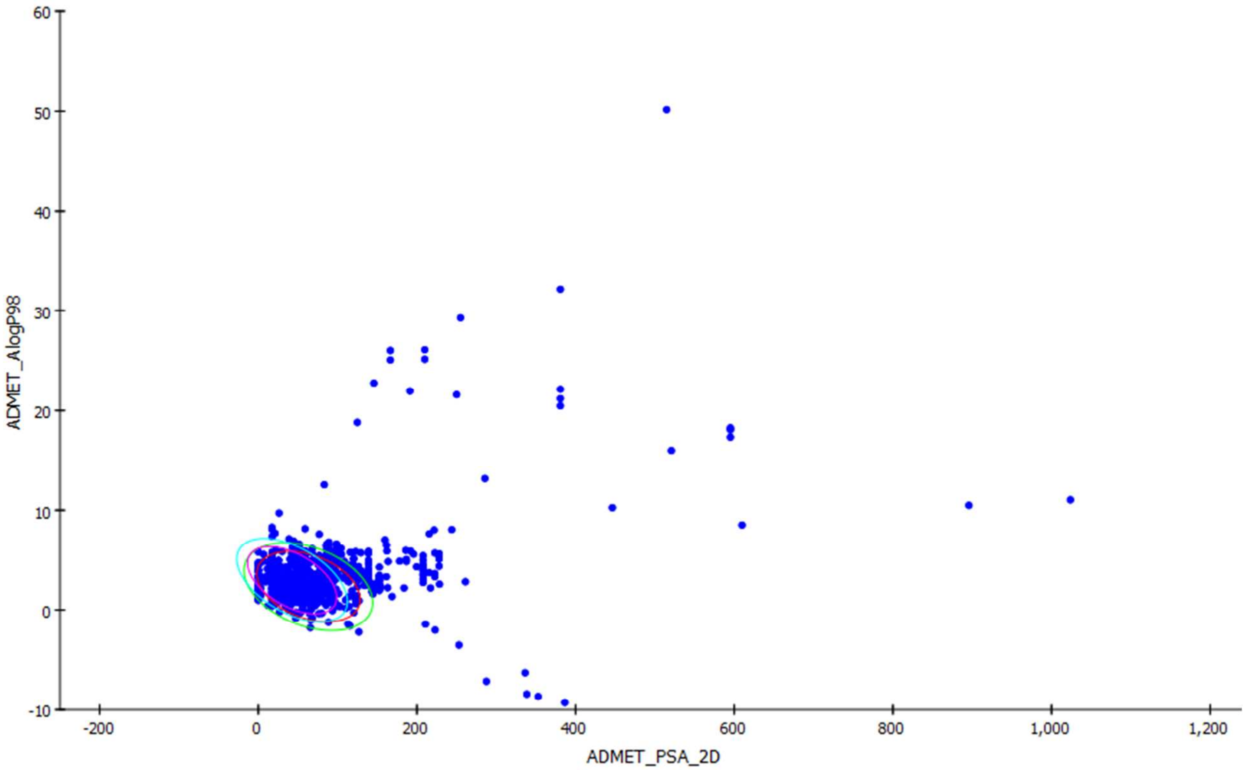


A

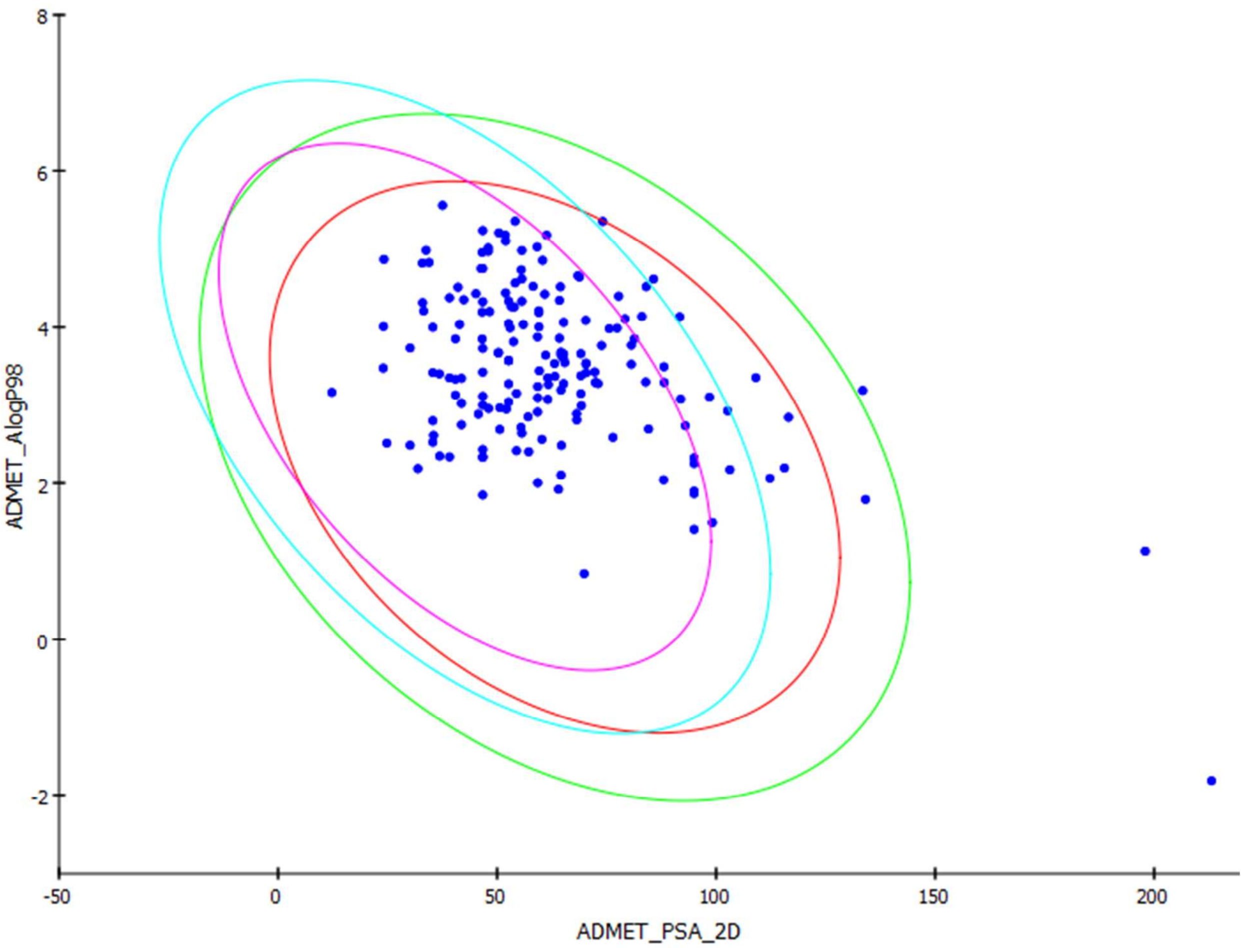


B

Figure S8. 2D Plot of AlogP98 and PSA for predicting human intestinal absorption and blood brain barrier penetration (BBB) in Discovery Studio A. *in vivo* dataset; B. GSK 177 cpds. Shown are 95% (blue, green) and 99% (magenta or red) confidence ellipses for human intestinal absorption and BBB, respectively.



A.



B.

Supplemental References for all molecules in training and test set

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