Supporting Information

(Figures and Tables)

Bovine Serum Amine Oxidase and polyamine analogues: chemical synthesis and biological evaluation integrated with molecular docking and 3-D QSAR studies

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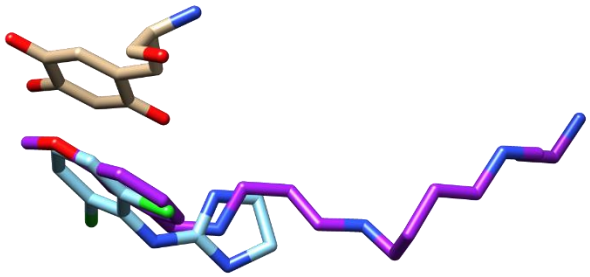

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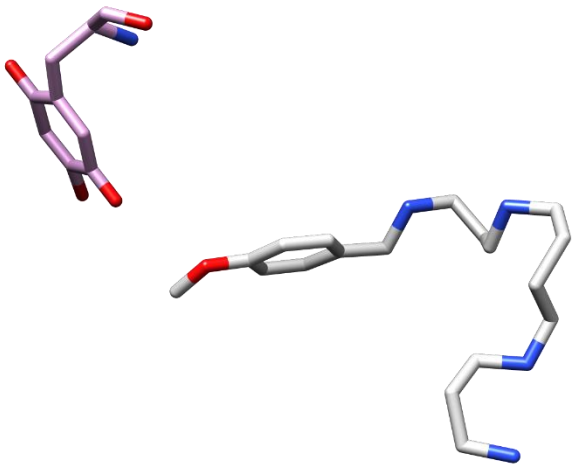

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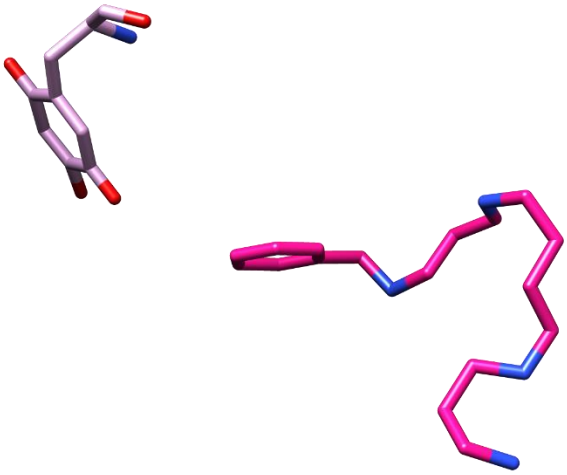

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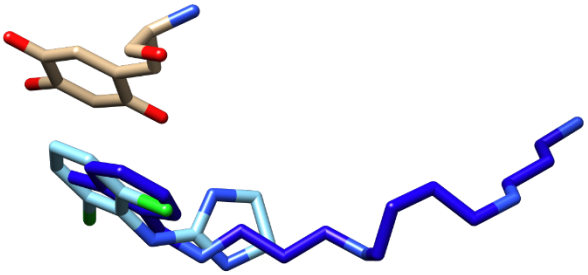

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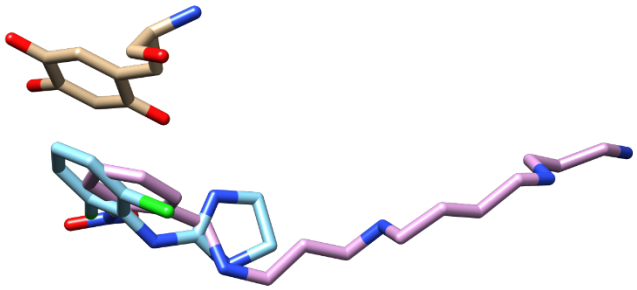

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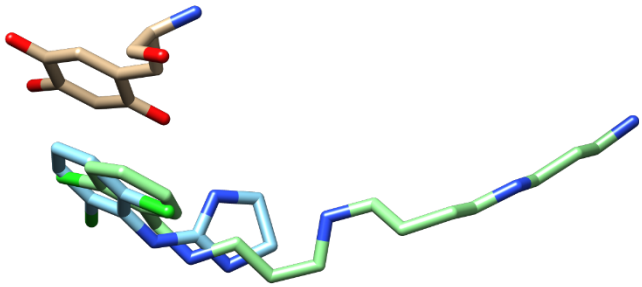

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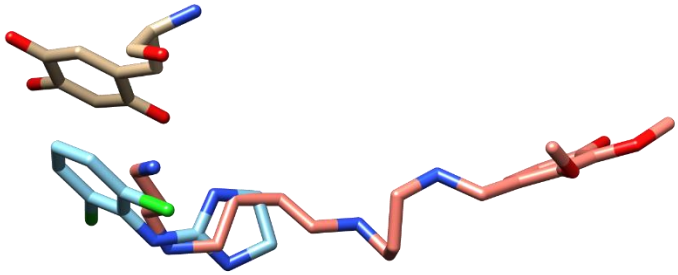

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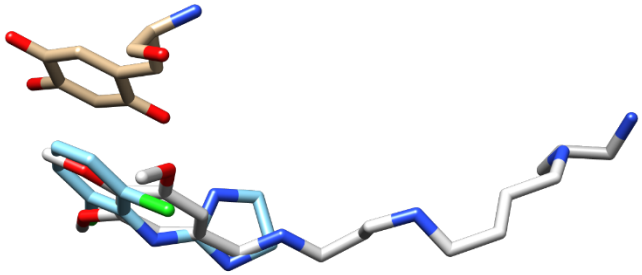

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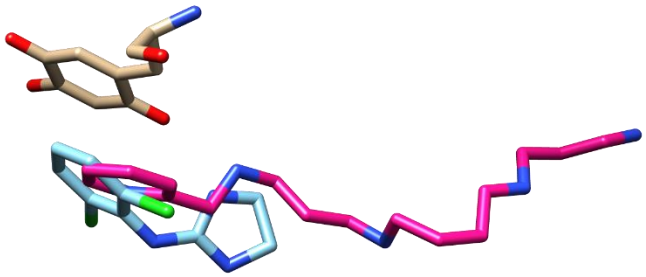

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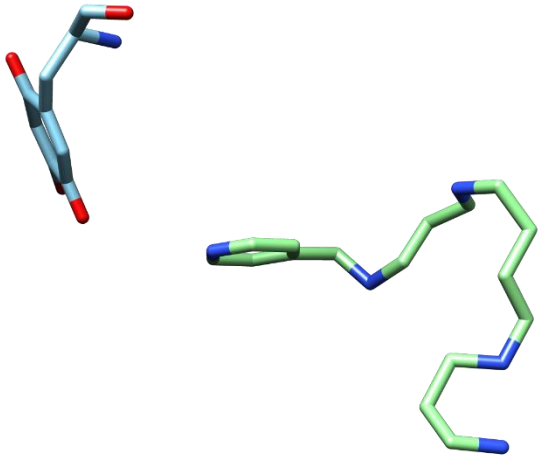

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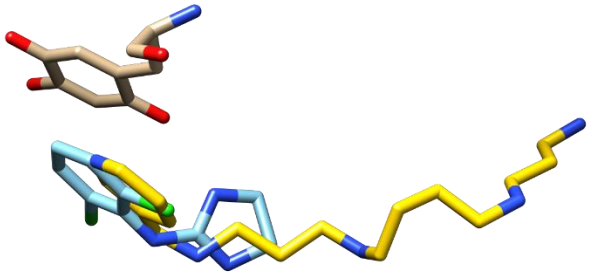

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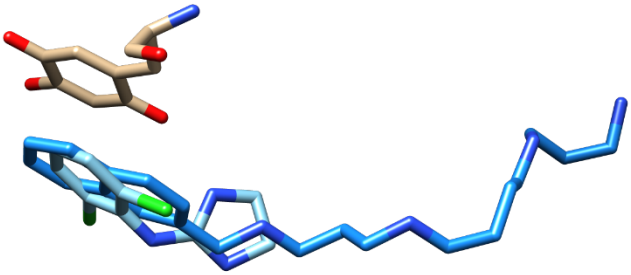

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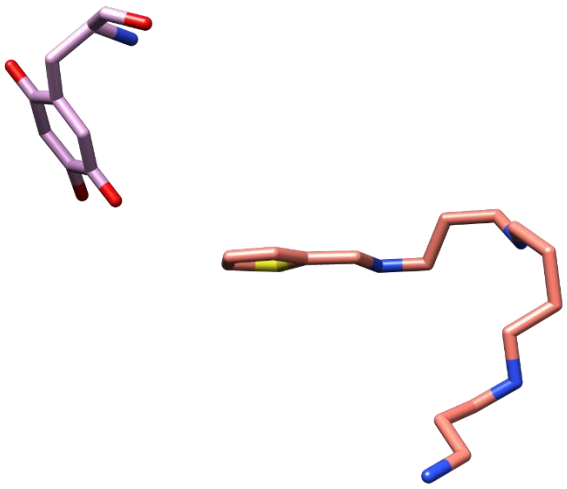

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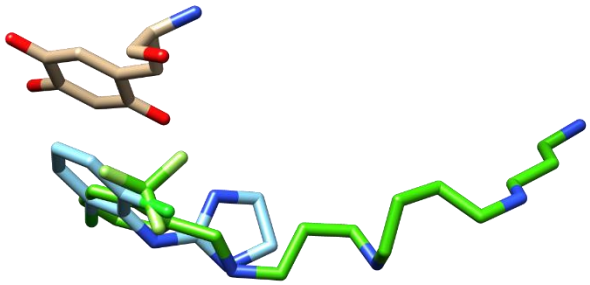

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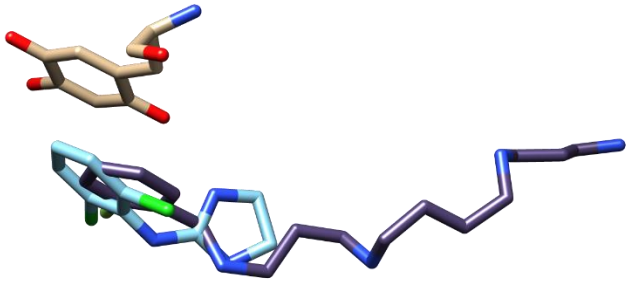

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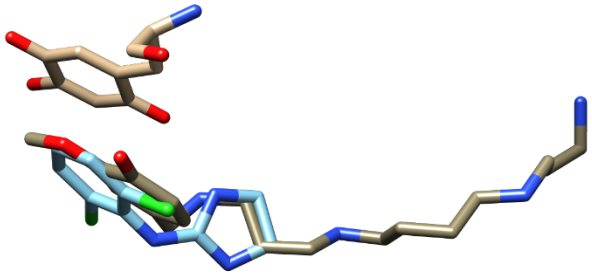

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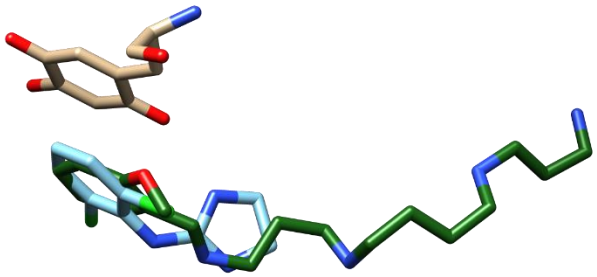

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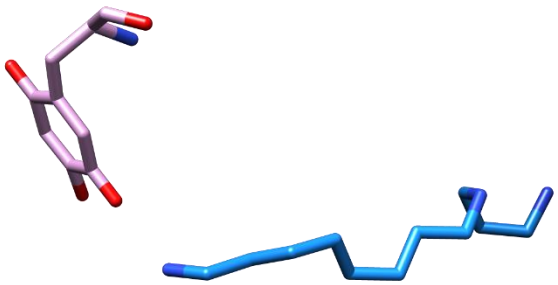

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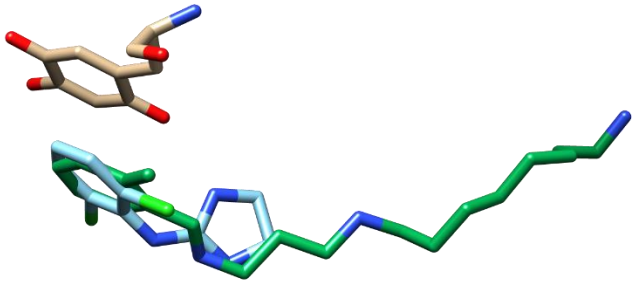

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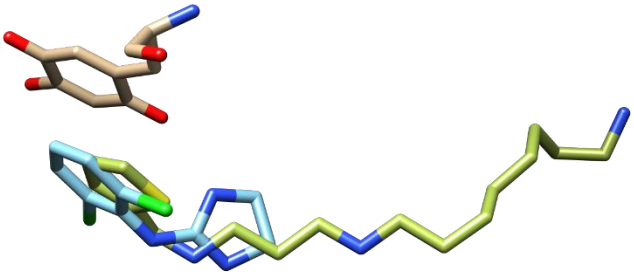

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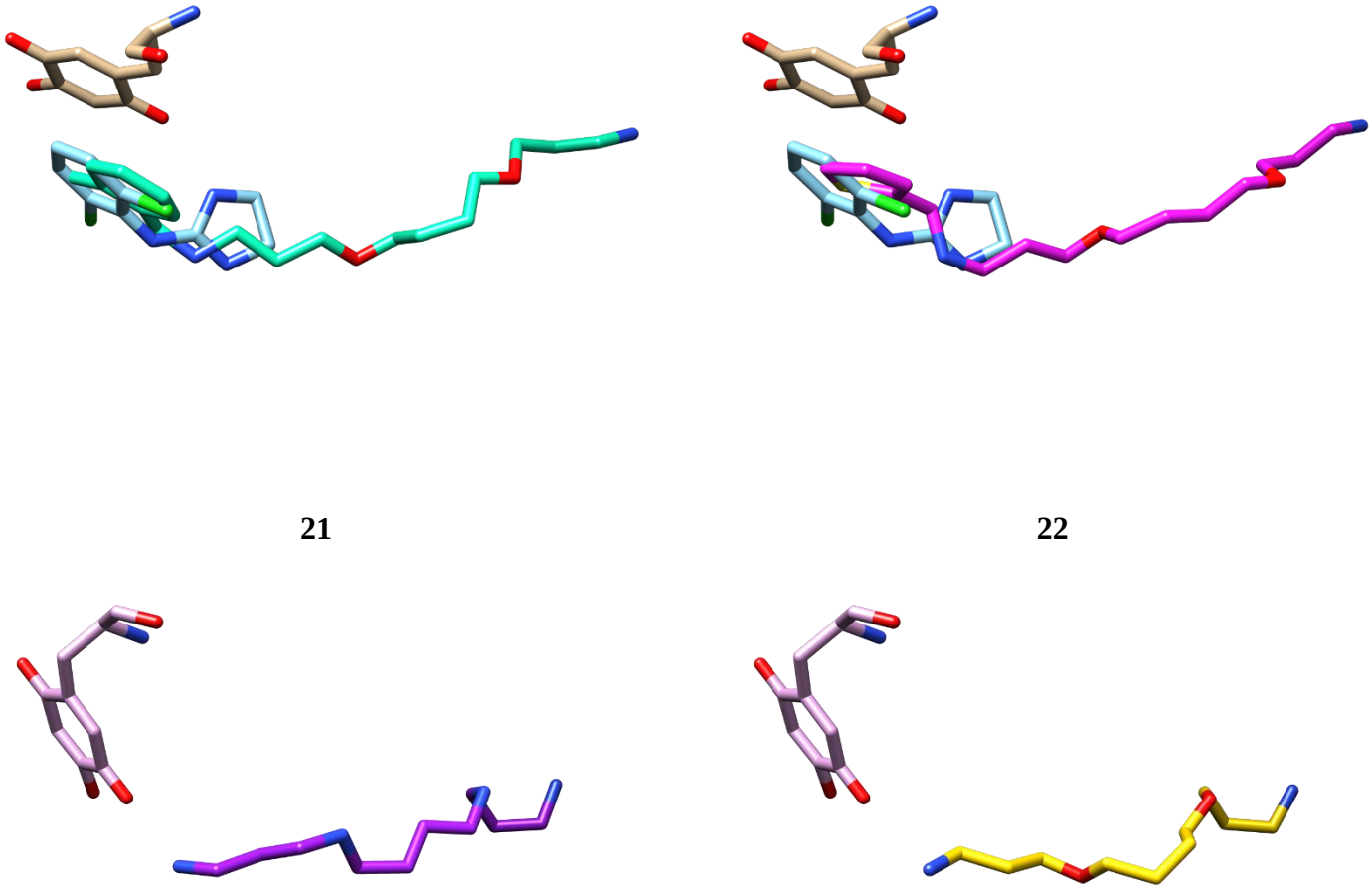


Figure S1. Docked PAa' conformations from the RMD runs. TPQ (dark khaki colored carbon atom for 2PCN while for 1TU5 carbon atoms were colored in orchid) and clonidine (light cyan colored carbon atoms) are also depicted.

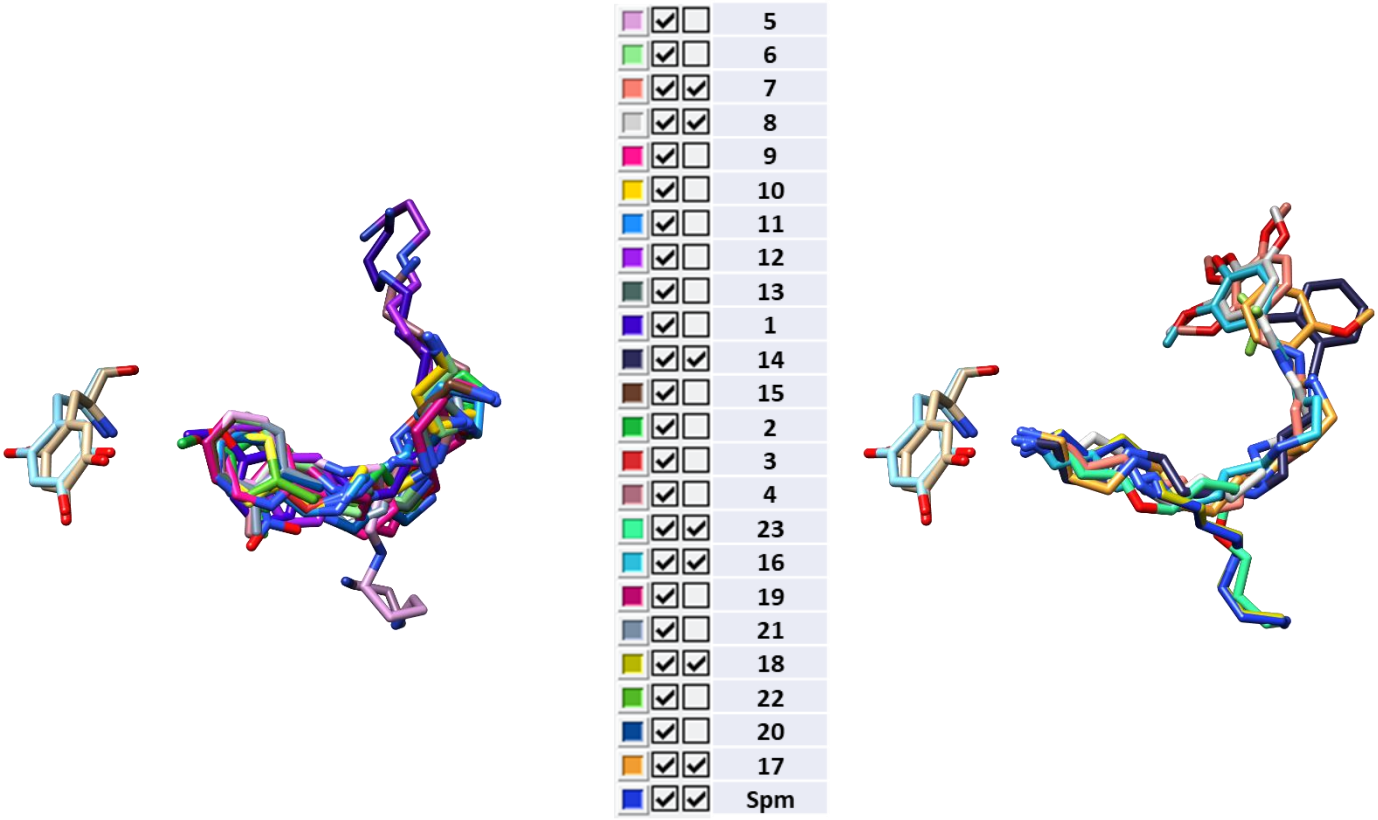


Figure S2. Docked PAa' conformations from the RMD runs into 1TU5 chains. TPQ (dark khaki and cyan colored carbon atoms) are also depicted. On the left panel (A) PAs' docked with the arymethyl head docked in the TPQ proximity. In panel C, PAs' docked with the primary amino group docked in the TPQ proximity. In panel B the color-coded legend, ticked boxes refer to molecules shown in panel C, empty boxes those in panel A.

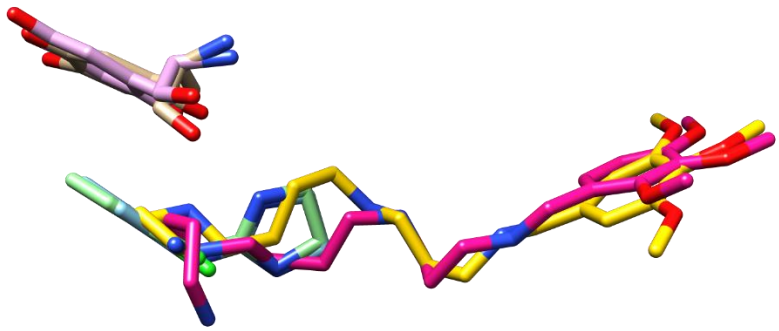
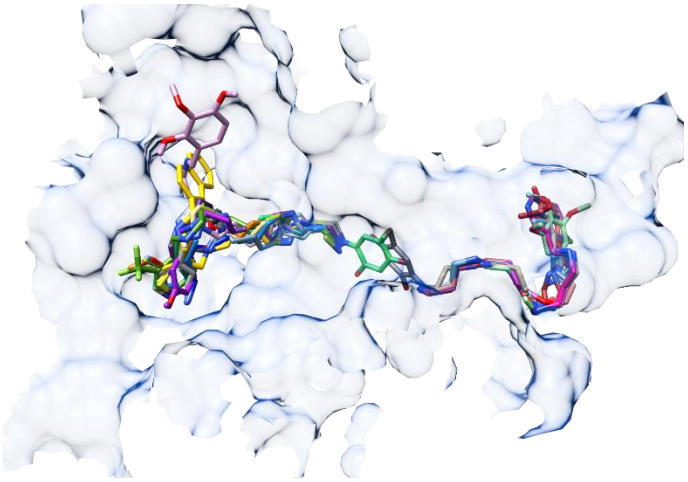
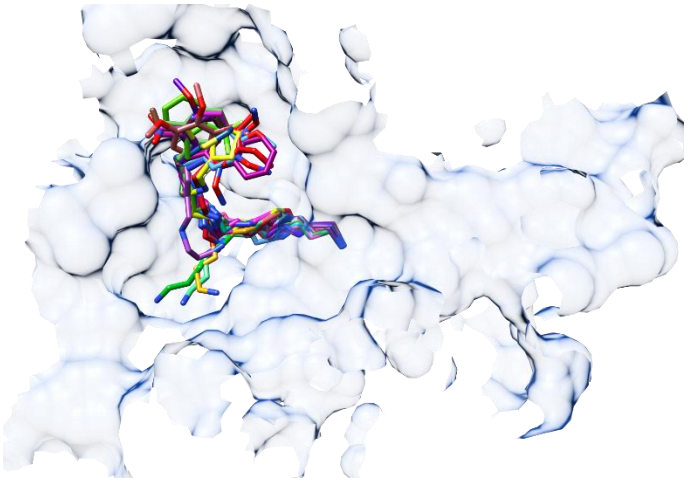


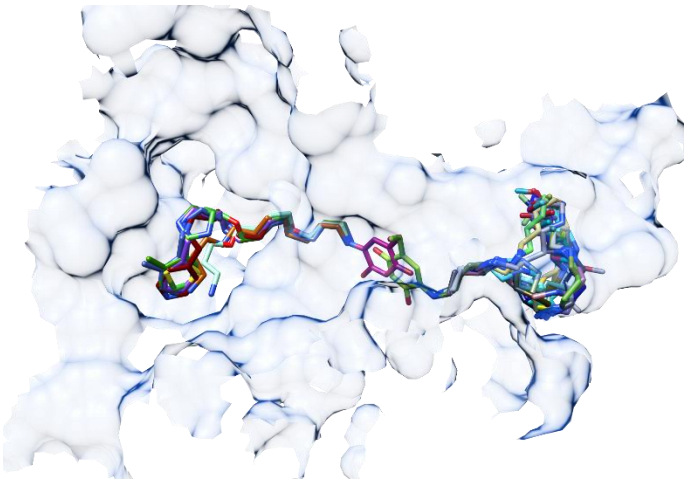
Figure S3. 2PNC docked PAa' conformations of **7** and **8**, the only two aryl methyl-PAs showing the aryl methyl head away from TPQ.



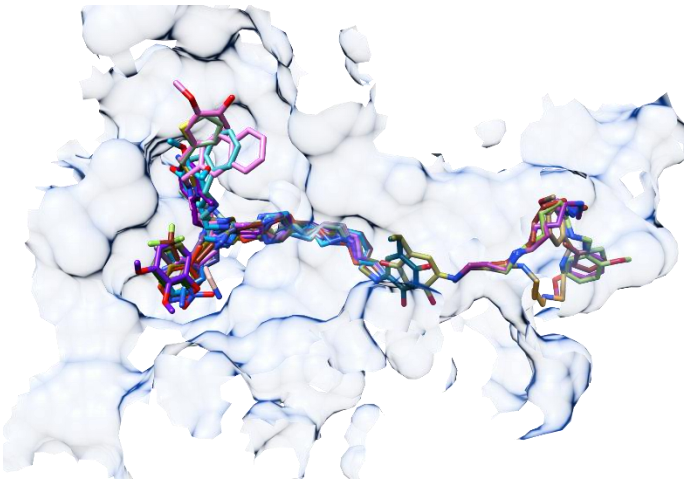
1TU5A vina



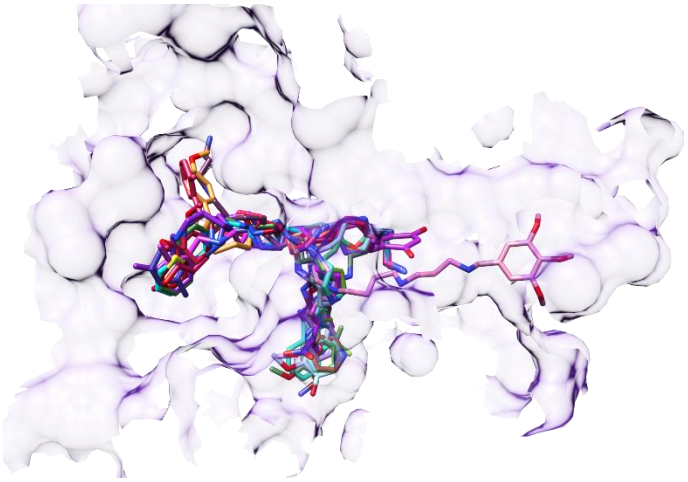
1TU5A vinardo



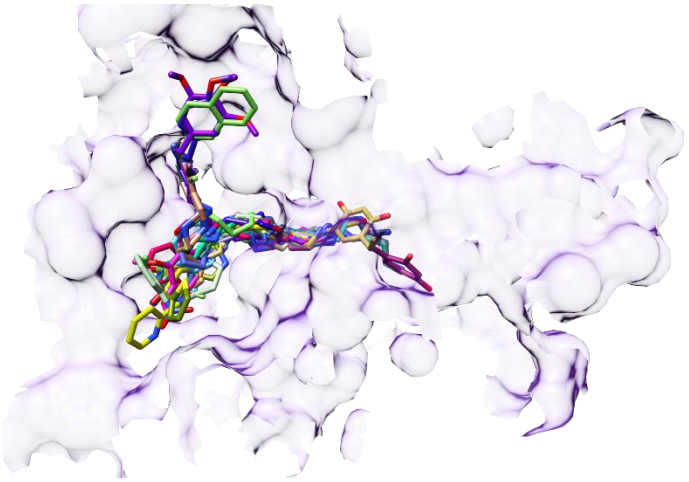
1TU5B vina



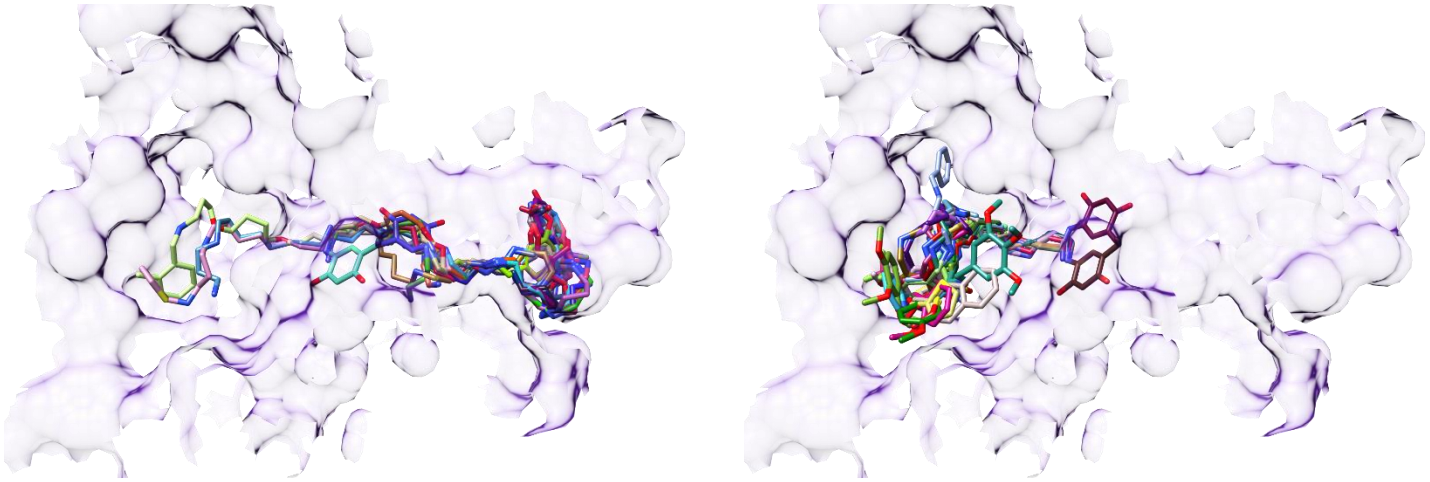
1TU5B vinardo



2PNCA vina



2PNCA vinardo



2PNCB vina 2PNCB vinardo

Figure S4. CMD docked PAs into the four BSAO chains from 1TU5 and 2PNC

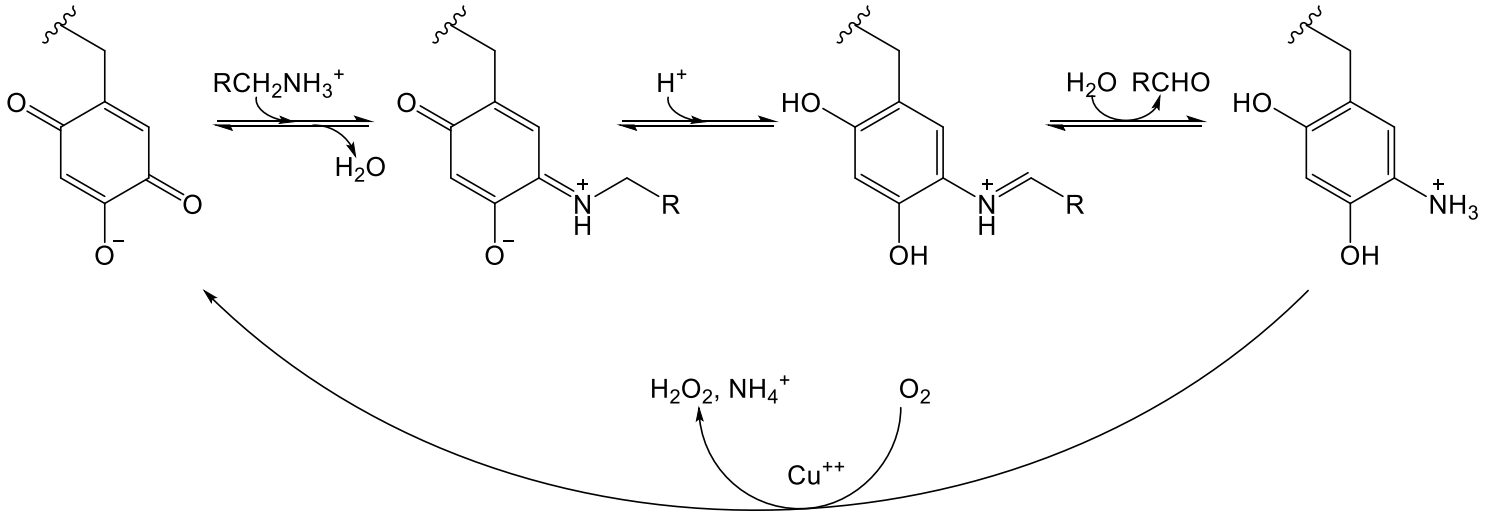


Figure S5. Scheme of the PA oxidation exerted in the BSAO and catalyzed by TPQ and copper ion.

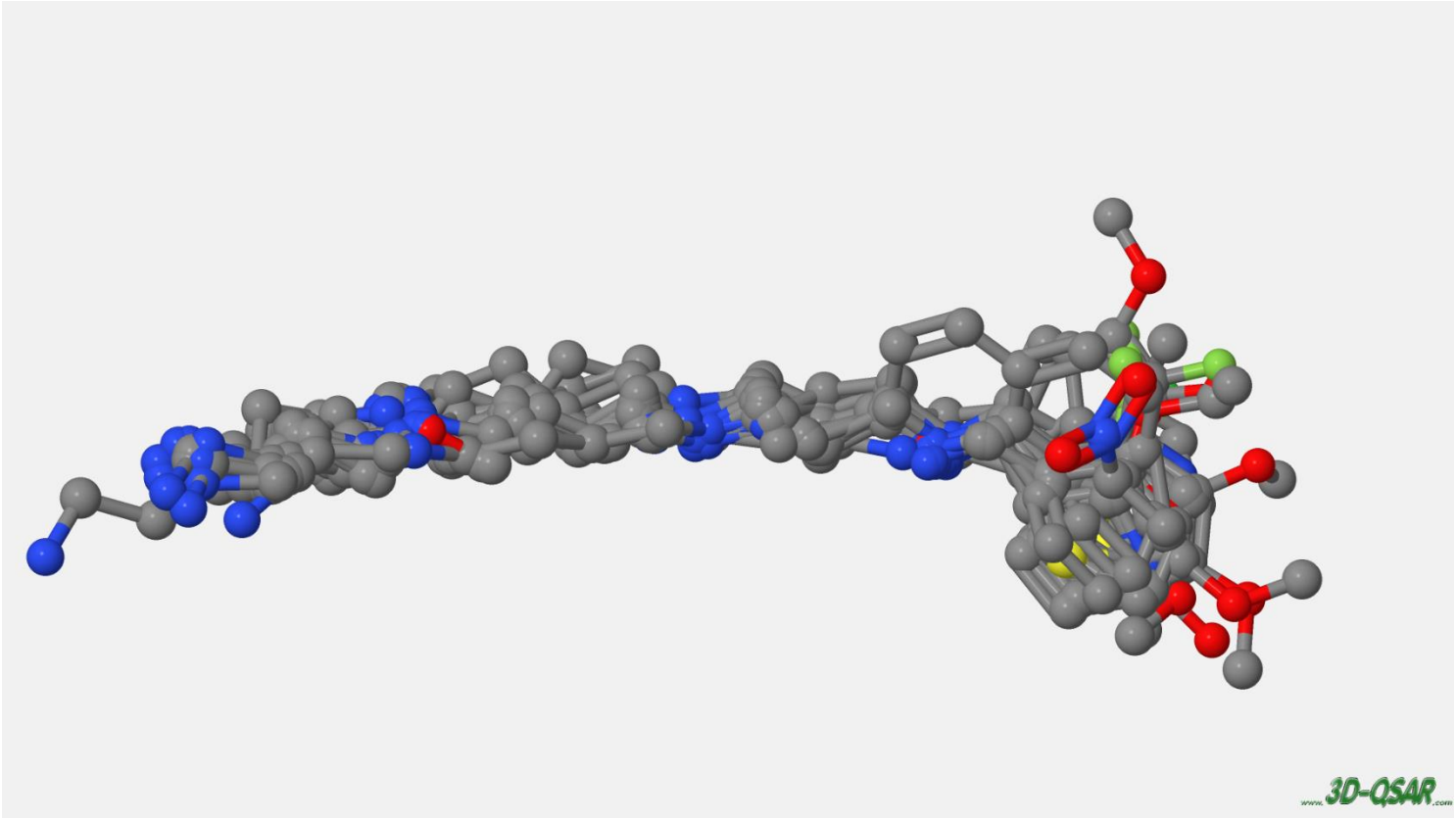


Figure S6. The aligned PAs for the model LB1

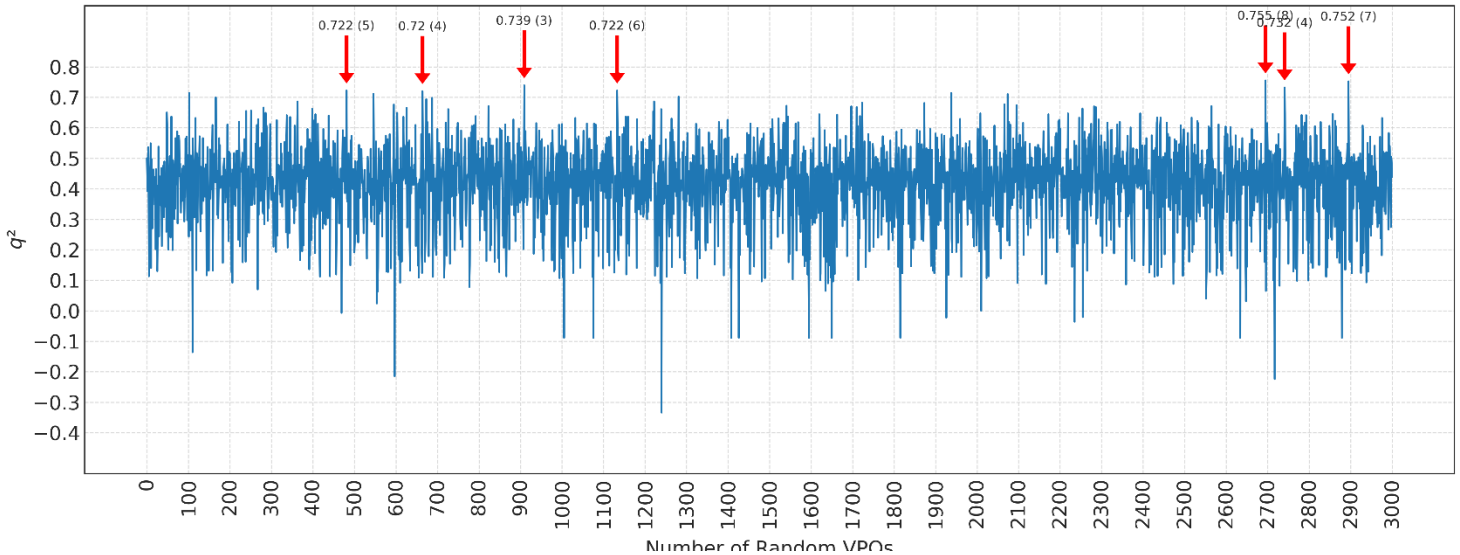


Figure S7. Distribution of the 3000 random VPO runs on model LB1

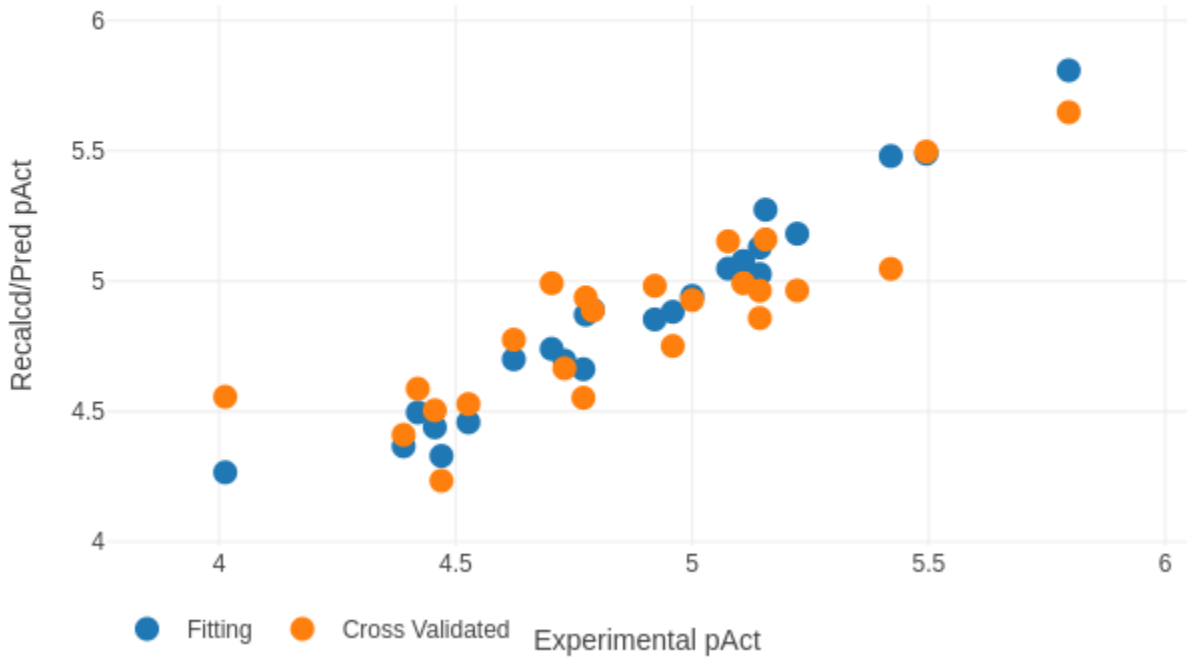


Figure S8. Recalculated/Predicted versus experimental pK_M values for model LB3 (pAct = pK_M in the axis)

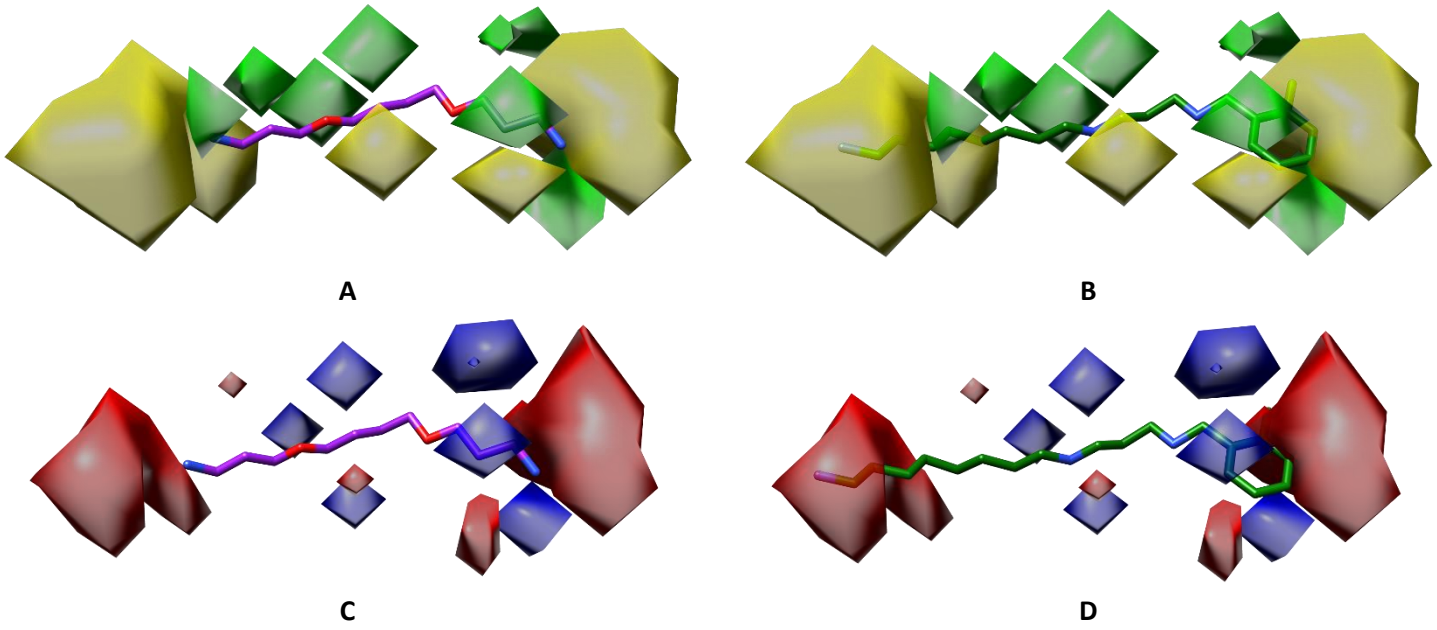


Figure S9. STE (A and B) and ELE (C and D) MIFs for model LB3 overlapped to **23** (A and C) and **19** (B and D), the most and least active PAs, respectively. The polyhedrons represent the AAC obtained by the product of the PLS coefficient with the average MIF values.

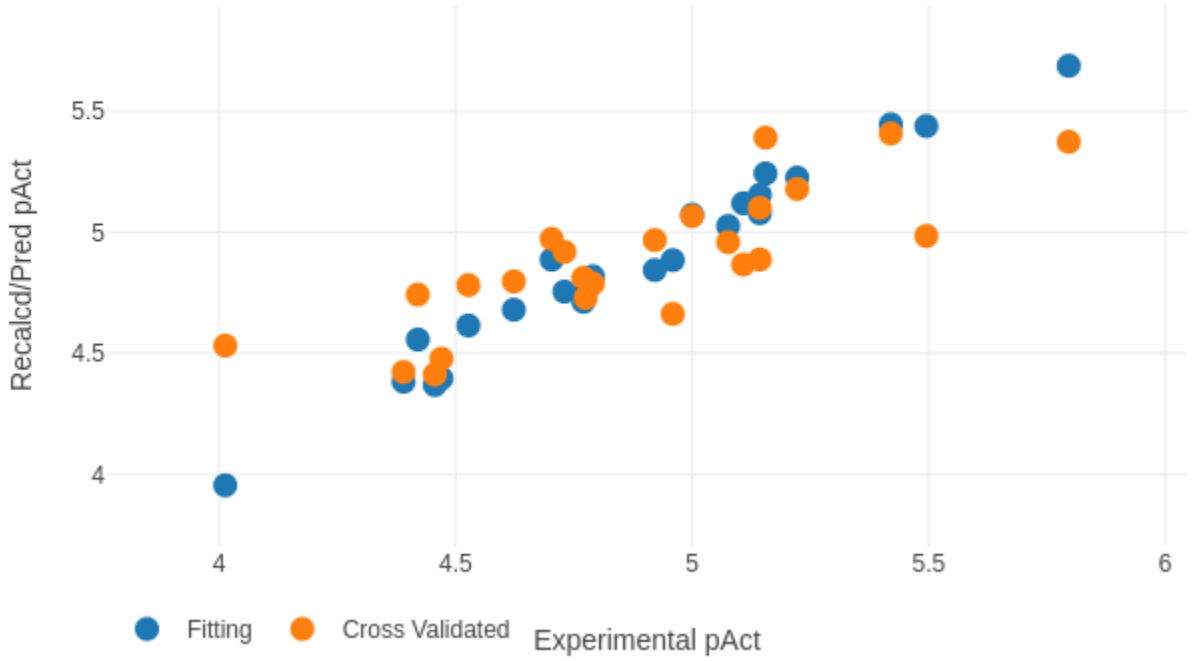


Figure S10. Recalculated/Predicted versus experimental pK_M values for the SB derived Py-CoMFA model (pAct in the axis)

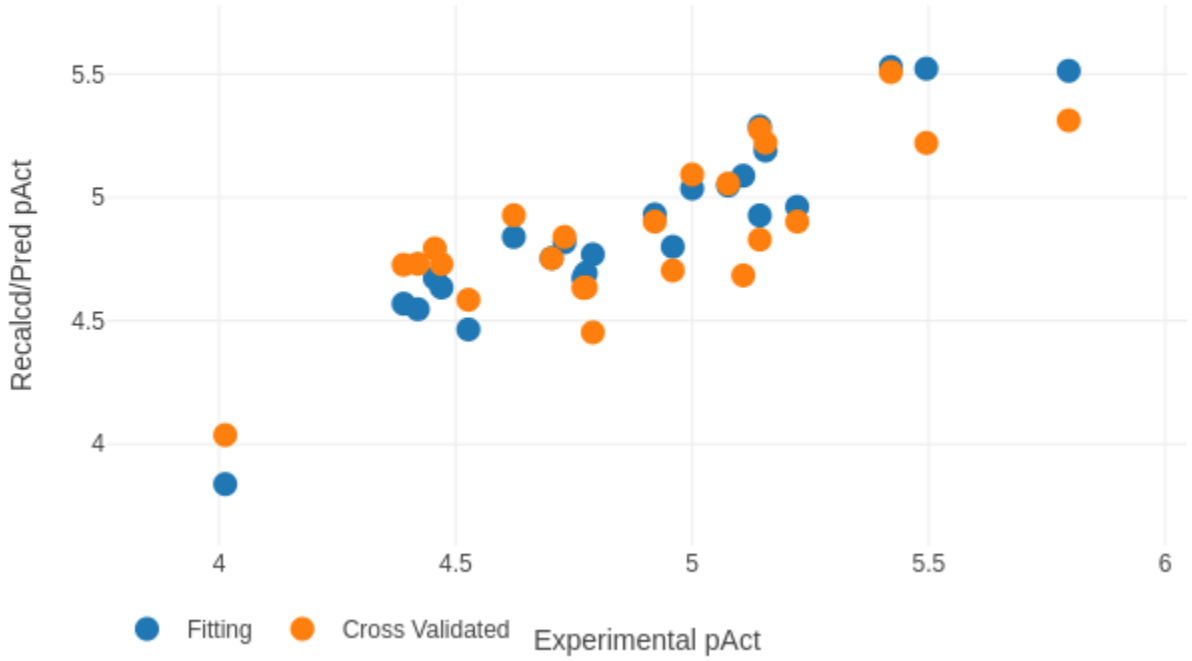


Figure S11. Recalculated/Predicted versus experimental pK_M values for the Py-ComBinE model (pAct in the axis)

Table S1. RMSD and docking scores values for the docking assessment from clonidine experimental conformation

Key Code	Program	SF	Min	1TU5B		1TU5A		2PNCA		2PNCB		Best Docked Lock Code	3Best Docked		Average RMSD
				RMSD	Score	RMSD	Score	RMSD	Score	RMSD	Score		RMSD	Score	
2PNCA	Plants	ChemPLP	NoMin	13.67	-62.62	14.88	-62.36	2.69	-79.30	2.73	-70.92	2PNCA	2.69	-79.30	1.74
2PNCB	Plants	ChemPLP	NoMin	13.31	-61.75	7.79	-61.26	0.79	-78.98	0.84	-69.67	2PNCA	0.79	-78.98	
2PNCA	Plants	PLP	NoMin	15.34	-58.72	15.53	-59.99	2.69	-77.13	2.74	-66.52	2PNCA	2.69	-77.13	1.56
2PNCB	Plants	PLP	NoMin	7.86	-59.58	15.12	-59.19	0.42	-77.04	2.48	-65.91	2PNCA	0.42	-77.04	
2PNCA	Plants	PLP95	NoMin	7.46	-83.74	14.40	-85.69	2.27	-108.63	2.76	-97.58	2PNCA	2.27	-108.63	2.13
2PNCB	Plants	PLP95	NoMin	13.06	-84.28	14.17	-86.58	1.99	-108.73	0.58	-97.35	2PNCA	1.99	-108.73	
2PNCA	Smina	AD4	NoMin	10.04	-22.30	10.11	-22.10	25.86	-21.90	13.11	-23.00	2PNCB	13.11	-23.00	6.75
2PNCB	Smina	AD4	NoMin	10.41	-22.40	10.32	-22.30	0.38	-28.50	0.20	-27.00	2PNCA	0.38	-28.50	
2PNCA	Smina	Vina	NoMin	13.42	-6.10	13.72	-6.30	14.31	-6.10	13.95	-6.80	2PNCB	13.95	-6.80	13.68
2PNCB	Smina	Vina	NoMin	13.13	-6.20	13.34	-6.40	13.72	-6.10	13.40	-6.70	2PNCB	13.40	-6.70	
2PNCA	Smina	Vinardo	NoMin	14.06	-5.70	14.15	-5.70	0.49	-7.80	14.02	-6.10	2PNCA	0.49	-7.80	7.04
2PNCB	Smina	Vinardo	NoMin	14.15	-5.70	14.21	-5.60	14.12	-5.70	13.59	-5.90	2PNCB	13.59	-5.90	
2PNCA	Smina	AD4	Min	25.25	-2.11	14.48	-2.05	10.33	-2.04	13.12	-2.11	1TU5B	25.25	-2.11	20.01
2PNCB	Smina	AD4	Min	14.77	-2.11	14.91	-2.11	2.47	-1.93	2.46	-2.03	1TU5B	14.77	-2.11	
2PNCA	Smina	Vina	Min	12.80	-0.27	13.43	-0.26	14.04	-0.27	13.82	-0.27	2PNCB	13.82	-0.27	13.75
2PNCB	Smina	Vina	Min	13.68	-0.31	13.31	-0.27	19.01	-0.27	14.44	-0.26	1TU5B	13.68	-0.31	
2PNCA	Smina	Vinardo	Min	13.60	-0.37	12.43	-0.34	25.52	-0.36	14.13	-0.36	1TU5B	13.60	-0.37	13.96
2PNCB	Smina	Vinardo	Min	13.34	-0.36	14.88	-0.38	10.36	-0.38	14.32	-0.39	2PNCB	14.32	-0.39	

Table S2. RMSD and docking scores values for the docking assessment from clonidine random conformation

Key Code	Program	SF	Min	1TU5B		1TU5A		2PNCA		2PNCB		Best Docked Lock Code	Best Docked		Average RMSD
				RMSD	Score	RMSD	Score	RMSD	Score	RMSD	Score		RMSD	Score	
2PNCA	Plants	ChemPLP	NoMin	12.56	-66.08	14.70	-64.53	2.60	-81.20	1.51	-75.06	2PNCA	2.60	-81.20	1.87
2PNCB	Plants	ChemPLP	NoMin	12.81	-66.07	13.54	-64.62	1.14	-80.92	1.33	-75.06	2PNCA	1.14	-80.92	
2PNCA	Plants	PLP	NoMin	12.22	-61.60	11.80	-62.69	0.56	-79.83	2.57	-67.62	2PNCA	0.56	-79.83	0.62
2PNCB	Plants	PLP	NoMin	13.54	-61.03	11.28	-61.80	0.67	-79.83	1.15	-67.06	2PNCA	0.67	-79.83	
2PNCA	Plants	PLP95	NoMin	14.49	-86.88	14.51	-88.69	2.02	-111.39	12.66	-96.29	2PNCA	2.02	-111.39	2.06
2PNCB	Plants	PLP95	NoMin	14.21	-86.88	14.22	-86.08	2.09	-111.39	2.53	-96.69	2PNCA	2.09	-111.39	
2PNCA	Smina	AD4	NoMin	11.28	-23.90	10.14	-21.50	11.29	-24.10	13.27	-22.10	2PNCA	11.29	-24.10	11.41
2PNCB	Smina	AD4	NoMin	11.49	-23.90	14.81	-21.60	11.53	-24.20	12.98	-22.10	2PNCA	11.53	-24.20	
2PNCA	Smina	Vina	NoMin	13.98	-6.20	14.09	-6.20	13.64	-6.10	13.99	-6.30	2PNCB	13.99	-6.30	8.30
2PNCB	Smina	Vina	NoMin	13.71	-6.20	13.61	-6.20	2.60	-7.50	13.71	-6.30	2PNCA	2.60	-7.50	
2PNCA	Smina	Vinardo	NoMin	15.01	-5.90	15.03	-6.00	0.64	-7.60	14.08	-5.80	2PNCA	0.64	-7.60	7.54
2PNCB	Smina	Vinardo	NoMin	14.71	-5.90	14.76	-6.00	9.98	-5.90	14.43	-6.10	2PNCB	14.43	-6.10	
2PNCA	Smina	AD4	Min	25.53	-2.53	15.18	-2.69	15.33	-2.49	13.38	-2.63	1TU5A	15.18	-2.69	15.21
2PNCB	Smina	AD4	Min	25.57	-2.50	14.86	-2.59	15.05	-2.49	15.23	-2.60	2PNCB	15.23	-2.60	
2PNCA	Smina	Vina	Min	15.75	-0.41	14.17	-0.41	14.07	-0.41	14.35	-0.41	2PNCA	14.07	-0.41	16.84
2PNCB	Smina	Vina	Min	15.14	-0.40	19.60	-0.41	13.72	-0.41	14.07	-0.41	1TU5A	19.60	-0.41	
2PNCA	Smina	Vinardo	Min	15.63	-0.61	15.89	-0.61	17.13	-0.61	2.80	-0.55	1TU5A	15.89	-0.61	15.76
2PNCB	Smina	Vinardo	Min	15.41	-0.61	15.62	-0.61	15.64	-0.56	15.39	-0.57	1TU5A	15.62	-0.61	

Table S3. PAs docking energies into 1TU5 chains

PA	1TU5B Score	1TU5A Score	Best Docked Score	Best Docking Protein Chain
1	-101.73	-101.16	-101.73	1TU5B
2	-106.81	-108.63	-108.63	1TU5A
3	-109.68	-111.44	-111.44	1TU5A
4	-100.43	-99.64	-100.43	1TU5B
5	-97.19	-99.72	-99.72	1TU5A
6	-98.14	-102.9	-102.9	1TU5A
7	-100.44	-100.81	-100.81	1TU5A
8	-102.73	-99.92	-102.73	1TU5B
9	-104.59	-104.83	-104.83	1TU5A
10	-102.96	-96.64	-102.96	1TU5B
11	-103.46	-102.81	-103.46	1TU5B
12	-112.28	-107.52	-112.28	1TU5B
13	-99.29	-103.59	-103.59	1TU5A
14	-103.28	-102.21	-103.28	1TU5B
15	-113.15	-101.86	-113.15	1TU5B
16	-102.43	-97.49	-102.43	1TU5B
17	-99.4	-101.79	-101.79	1TU5A
18	-87.67	-86.57	-87.67	1TU5B
19	-108.35	-106.09	-108.35	1TU5B
20	-101.04	-103.75	-103.75	1TU5A
21	-105.46	-107.13	-107.13	1TU5A
22	-100.8	-104.12	-104.12	1TU5A
23	-81.12	-80.66	-81.12	1TU5B
Spm	-83.07	-82.02	-83.07	1TU5B

Table S4. PAs docking energies into 2PNC chains

PA	1TU5B Score	1TU5A Score	Best Docked Score	Best Docking Protein Chain
1	-113.34	-108.09	-113.34	2PNCA
2	-113.16	-99.48	-113.16	2PNCA
3	-111.05	-98.91	-111.05	2PNCA
4	-115.17	-102.98	-115.17	2PNCA
5	-114.84	-102.26	-114.84	2PNCA
6	-114.86	-101.59	-114.86	2PNCA
7	-104.75	-101.55	-104.75	2PNCA
8	-109.25	-101.84	-109.25	2PNCA
9	-105.57	-100.56	-105.57	2PNCA
10	-109.14	-99.95	-109.14	2PNCA
11	-107.63	-102.63	-107.63	2PNCA
12	-115.55	-107.25	-115.55	2PNCA
13	-103.66	-98.83	-103.66	2PNCA
14	-114.41	-103.61	-114.41	2PNCA
15	-115.61	-97.80	-115.61	2PNCA
16	-115.56	-108.78	-115.56	2PNCA
17	-113.17	-102.02	-113.17	2PNCA
18	-83.03	-79.19	-83.03	2PNCA
19	-116.03	-103.88	-116.03	2PNCA
20	-107.70	-100.99	-107.70	2PNCA
21	-112.71	-103.01	-112.71	2PNCA
22	-105.24	-99.34	-105.24	2PNCA
23	-76.55	-72.29	-76.55	2PNCA
Spm	-77.44	-76.66	-77.44	2PNCA

Table S5. PAs docking energies from cross-docking into 1TU5 and 2PNC chains

PA	1TU5B Score	1TU5A Score	2PNCA Score	2PNCB Score	Best Docked Score	Best Docking Protein Chain
1	-107.17	-99.56	-113.23	-104.75	-113.23	2PNCA
2	-109.81	-109.44	-107.04	-101.84	-109.81	1TU5B
3	-113.26	-107.24	-108.76	-101.81	-113.26	1TU5B
4	-107.40	-104.32	-114.93	-101.32	-114.93	2PNCA
5	-102.43	-100.24	-116.98	-98.61	-116.98	2PNCA
6	-103.51	-102.11	-112.10	-102.62	-112.10	2PNCA
7	-102.73	-101.07	-106.21	-92.39	-106.21	2PNCA
8	-101.74	-99.39	-110.91	-101.66	-110.91	2PNCA
9	-101.59	-96.76	-104.21	-95.13	-104.21	2PNCA
10	-101.15	-106.64	-106.31	-100.03	-106.64	1TU5A
11	-103.67	-103.09	-106.13	-100.78	-106.13	2PNCA
12	-114.77	-112.62	-118.46	-108.85	-118.46	2PNCA
13	-103.97	-100.92	-103.34	-98.66	-103.97	1TU5B
14	-102.14	-103.27	-115.50	-106.44	-115.50	2PNCA
15	-105.72	-105.21	-112.71	-103.21	-112.71	2PNCA
16	-102.97	-89.88	-119.50	-108.90	-119.50	2PNCA
17	-99.08	-100.45	-113.34	-99.79	-113.34	2PNCA
18	-87.63	-87.29	-80.50	-80.10	-87.63	1TU5B
19	-108.61	-108.83	-117.29	-107.98	-117.29	2PNCA
20	-102.07	-103.84	-109.92	-102.86	-109.92	2PNCA
21	-105.94	-105.45	-114.66	-98.18	-114.66	2PNCA
22	-98.78	-102.91	-105.63	-100.55	-105.63	2PNCA
23	-81.44	-80.59	-78.52	-74.67	-81.44	1TU5B
Spm	-82.78	-82.07	-79.62	-75.91	-82.78	1TU5B

Table S6. Py-CoMFA model LB1 statistical coefficients

# PC	r^2 [b]	SDEC [c]	q^2 [d]	SDEP [e]	SDEP Decrement
1	0.30	0.11	0.15	0.13	
2	0.70	0.05	0.21	0.12	7.46%
3	0.86	0.02	0.38	0.10	20.97%
4	0.96	0.01	0.42	0.09	7.14%
5* [a]	0.98	0.00	0.47	0.08	8.79%
6	1.00	0.00	0.49	0.08	2.41%
7	1.00	0.00	0.49	0.08	0.00%
8	1.00	0.00	0.50	0.08	2.47%

a: optimal number of PLS principal components
b: squared correlation coefficient
c: Standard error of calculation by the model
d: cross-validated squared correlation coefficient
e: Standard error of prediction during cross-validation

Table S7. PAs'chemical physical features calculated to select the templates for the best LB alignments

PA	pK_M	MW	HA	HD	LogP	TPSA	RBs	MR	Length	Max Length
1	4.73	322.27	5.00	4.00	1.48	71.34	17.00	97.96	11.24	22.64
2	4.39	322.27	5.00	4.00	1.48	71.34	17.00	97.96	11.37	23.99
3	4.47	292.26	4.00	4.00	1.48	62.11	15.00	91.41	11.07	21.50
4	5.14	306.28	4.00	4.00	1.78	62.11	16.00	96.15	10.12	21.37
5	4.78	337.25	6.00	4.00	1.91	107.93	16.00	100.23	10.34	22.38
6	4.53	326.22	4.00	4.00	2.13	62.11	15.00	96.42	9.85	22.83
7	4.46	382.29	7.00	4.00	1.50	89.80	21.00	111.07	11.07	24.49
8	4.96	382.29	7.00	4.00	1.50	89.80	21.00	111.07	11.99	23.59
9	4.92	293.26	5.00	4.00	0.87	75.00	15.00	89.21	10.89	21.07
10	5.14	293.26	5.00	4.00	0.87	75.00	15.00	89.21	9.51	21.75
11	4.62	293.26	5.00	4.00	0.87	75.00	15.00	89.21	9.72	22.40
12	5.11	342.28	4.00	4.00	2.63	62.11	15.00	108.92	11.17	24.45
13	5.22	298.22	5.00	4.00	1.54	62.11	15.00	89.29	10.55	21.92
14	4.77	360.25	4.00	4.00	2.49	62.11	15.00	96.41	9.62	22.76
15	4.42	310.25	4.00	4.00	1.61	62.11	15.00	91.37	9.80	20.40
16	4.79	338.27	6.00	5.00	1.19	91.57	18.00	99.63	12.68	23.60
17	4.70	322.27	5.00	4.00	1.48	71.34	17.00	97.96	11.81	21.93
18	5.00	201.22	3.00	3.00	1.22	64.07	13.00	63.30	9.46	17.80
19	4.01	305.28	3.00	3.00	3.36	50.08	16.00	97.13	10.57	20.95
20	5.08	297.22	4.00	3.00	3.12	50.08	15.00	90.27	10.10	21.94
21	5.42	308.25	4.00	2.00	2.64	56.51	16.00	92.05	10.72	21.53
22	5.16	300.19	5.00	2.00	2.39	56.51	15.00	85.19	12.21	21.02
23	5.80	204.18	4.00	2.00	0.50	70.50	13.00	58.22	8.42	16.30
Spm	5.50	202.22	4.00	4.00	-0.36	76.10	13.00	62.32	9.83	16.60

Table S8. Py-CoMFA model LB2 statistical coefficients

# PC	r^2 [b]	SDEC [c]	q^2 [d]	SDEP [e]	SDEP Decrement
1	0.63	0.06	0.41	0.09	
2	0.91	0.01	0.69	0.05	47.31%
3* [a]	0.95	0.01	0.74	0.04	16.33%
4	0.98	0.00	0.70	0.05	-17.07%
5	0.99	0.00	0.65	0.05	-12.50%
6	1.00	0.00	0.61	0.06	-12.96%
7	1.00	0.00	0.59	0.07	-6.56%
8	1.00	0.00	0.59	0.07	0.00%

a: optimal number of PLS principal components
b: squared correlation coefficient
c: Standard error of calculation by the model
d: cross-validated squared correlation coefficient
e: Standard error of prediction during cross-validation

Table S9. Top 20 Full LB Py-CoMFA model obtained with VPO

r^2 (# PC)	q^2 (# PC)	Probe	Charge Model	Min Sigma	Grid Spacing	Grid Extension	Diel Const	CutOff
0.997 (8)	0.755 (8)	N.am	mmff94	0.80	2.70	1.00	3	2
0.997 (7)	0.752 (7)	N.am	qtpie	0.90	3.30	7.00	49	29
0.952 (3)	0.739 (3)	N.am	eem2015ha	0.30	2.50	2.00	4	25
0.940 (4)	0.732 (4)	H.P	eem2015bn	0.90	3.40	4.00	9	4
0.982 (6)	0.722 (6)	O.2	gasteiger	0.70	3.30	4.00	18	26
0.990 (5)	0.722 (5)	N.am	qeq	0.70	2.30	6.00	8	24
0.984 (4)	0.720 (4)	N.am	mmff94	0.20	2.60	6.00	3	4
0.992 (8)	0.714 (8)	N.am	mmff94	0.70	3.40	4.00	72	23
0.995 (6)	0.714 (6)	O.2	eem2015ba	0.80	2.90	8.00	6	20
0.983 (4)	0.711 (4)	N.am	eem2015ha	0.70	2.60	6.00	9	4
0.997 (8)	0.710 (8)	N.am	openbabel	0.80	3.20	10.00	69	25
0.986 (5)	0.702 (5)	C.3.H3	eem2015hn	0.10	3.30	4.00	64	3
0.992 (8)	0.700 (8)	C.3.H3	eem2015ha	0.80	3.10	10.00	8	6
0.996 (6)	0.698 (6)	N.am	qeq	0.50	2.40	5.00	28	9
0.991 (6)	0.694 (6)	N.am	eem2015ha	0.40	2.70	1.00	49	1
0.986 (7)	0.686 (7)	O.2	eem	1.00	3.40	4.00	65	28
0.987 (5)	0.686 (5)	N.am	qeq	0.10	2.30	6.00	45	15
0.988 (7)	0.682 (7)	C.3.H3	mmff94	0.40	3.40	5.00	10	18
0.979 (6)	0.681 (6)	O.2	mmff94	0.60	3.40	3.00	23	7
0.999 (7)	0.677 (7)	C.3.H3	eem2015ba	0.20	1.80	3.00	9	14

Table S10. Py-CoMFA model LB3 statistical coefficients

# PC	r^2 [b]	SDEC [c]	q^2 [d]	SDEP [e]	SDEP Decrement
1	0.83	0.03	0.67	0.05	
2	0.92	0.01	0.75	0.04	25.00%
3* [a]	0.95	0.01	0.82	0.03	25.64%
4	0.96	0.01	0.79	0.03	-13.79%
5	0.99	0.00	0.81	0.03	9.09%
6	0.99	0.00	0.78	0.04	-16.67%
7	0.99	0.00	0.71	0.05	-28.57%
8	1.00	0.00	0.74	0.04	6.67%

a: optimal number of PLS principal components
b: squared correlation coefficient
c: Standard error of calculation by the model
d: cross-validated squared correlation coefficient
e: Standard error of prediction during cross-validation

Table S11. Py-CoMFA model LB3 recalculated/predicted vs experimental pK_M values

PA	pK_M				
	Exp	**Exp**	**Exp**	**Exp**	**Exp**
1	4.73	4.70	0.04	4.67	0.07
2	4.39	4.37	0.03	4.41	-0.02
3	4.47	4.33	0.14	4.23	0.24
4	5.14	5.13	0.01	4.96	0.18
5	4.78	4.87	-0.10	4.94	-0.16
6	4.53	4.46	0.07	4.53	0.00
7	4.46	4.44	0.02	4.50	-0.05
8	4.96	4.88	0.08	4.75	0.21
9	4.92	4.85	0.07	4.98	-0.06
10	5.14	5.03	0.12	4.86	0.29
11	4.62	4.70	-0.08	4.78	-0.15
12	5.11	5.08	0.03	4.99	0.12
13	5.22	5.18	0.04	4.96	0.26
14	4.77	4.66	0.11	4.55	0.22
15	4.42	4.50	-0.08	4.59	-0.17
16	4.79	4.89	-0.10	4.89	-0.10
17	4.70	4.74	-0.04	4.99	-0.29
18	5.00	4.94	0.06	4.93	0.07
19	4.01	4.27	-0.25	4.56	-0.54
20	5.08	5.05	0.03	5.15	-0.08
21	5.42	5.48	-0.06	5.05	0.37
22	5.16	5.27	-0.12	5.16	-0.01
23	5.80	5.81	-0.01	5.65	0.15
Spm	5.50	5.49	0.01	5.50	0.00

Table S12. Top 20 Full LB Py-CoMFA model obtained with VPO

r^2 (# PC)	q^2 (# PC)	Probe	Charge Model	Min Sigma	Grid Spacing	Grid Extension	Diel Const	CutOff
0.999 (8)	0.762 (8)	N.am	qeq	0.4	2.9	5	59	28
0.999 (8)	0.760 (8)	C.3.H3	qtpie	0.2	3.5	10	48	20
0.997 (8)	0.755 (8)	H.P	eem2015ha	0.4	3.4	8	74	27
0.974 (4)	0.752 (4)	H.P	eem2015ba	0.9	3.4	8	60	5
0.987 (7)	0.724 (7)	H.P	mmff94	0.3	3.4	8	42	18
0.986 (6)	0.724 (6)	H.P	eem2015hn	0.5	3.4	8	80	10
0.975 (5)	0.722 (5)	N.am	openbabel	0.3	3.4	8	65	20
0.971 (4)	0.706 (4)	O.2	qtpie	1	3.5	5	60	28
0.979 (5)	0.705 (5)	H.P	qeq	0.5	2.9	2	22	29
0.959 (6)	0.699 (6)	H.P	eem2015hm	0.2	3.4	3	25	14
0.999 (8)	0.695 (8)	C.3.H3	qeq	0.5	2.5	1	35	20
0.982 (6)	0.685 (6)	H.P	eem2015hn	0.5	3.4	8	55	15
0.989 (6)	0.681 (6)	O.2	qeq	0.6	2.9	2	59	29
0.955 (4)	0.674 (4)	H.P	gasteiger	0.5	3.4	8	4	12
0.998 (8)	0.671 (8)	N.am	openbabel	0.1	3.5	8	35	29
0.972 (5)	0.663 (5)	O.2	eem2015ha	0.4	3.4	8	72	19
0.984 (6)	0.659 (6)	O.2	qeq	1	2.9	2	51	9
0.999 (8)	0.651 (8)	N.am	openbabel	0.1	2.8	4	55	29
0.955 (5)	0.649 (5)	H.P	eem2015hn	0.3	3.4	8	19	17
1.000 (7)	0.647 (7)	N.am	mmff94	0.3	2.5	6	13	7

Table S13. Py-CoMFA SB model derived model statistical coefficients

# PC	r^2 [b]	SDEC [c]	q^2 [d]	SDEP [e]	SDEP Decrement	# PC
1	0.66	0.05	0.37	0.10		
2	0.85	0.02	0.59	0.07	35.00%	59.84%
3	0.94	0.01	0.73	0.04	35.38%	25.13%
4* [a]	0.95	0.01	0.78	0.03	19.05%	6.97%
5	0.99	0.00	0.81	0.03	11.76%	3.19%
6	0.99	0.00	0.84	0.03	16.67%	4.46%
7	1.00	0.00	0.83	0.03	-8.00%	-2.13%
8	1.00	0.00	0.86	0.02	18.52%	3.75%

a: optimal number of PLS principal components
b: squared correlation coefficient
c: Standard error of calculation by the model
d: cross-validated squared correlation coefficient
e: Standard error of prediction during cross-validation

Table S14. Py-CoMFA SB model recalculated/predicted vs experimental pK_M values

PA	pK_M				
	Exp	**Exp**	**Exp**	**Exp**	**Exp**
1	4.73	4.76	-0.03	4.92	-0.19
2	4.39	4.38	0.01	4.42	-0.03
3	4.47	4.40	0.07	4.48	-0.01
4	5.14	5.08	0.06	4.89	0.25
5	4.78	4.75	0.02	4.73	0.05
6	4.53	4.62	-0.09	4.78	-0.26
7	4.46	4.37	0.09	4.41	0.04
8	4.96	4.89	0.07	4.66	0.30
9	4.92	4.84	0.08	4.97	-0.05
10	5.14	5.16	-0.01	5.10	0.04
11	4.62	4.68	-0.06	4.80	-0.17
12	5.11	5.12	-0.01	4.87	0.24
13	5.22	5.23	0.00	5.18	0.04
14	4.77	4.71	0.06	4.81	-0.04
15	4.42	4.56	-0.14	4.74	-0.32
16	4.79	4.82	-0.03	4.79	0.00
17	4.70	4.89	-0.18	4.97	-0.27
18	5.00	5.07	-0.07	5.07	-0.07
19	4.01	3.96	0.06	4.53	-0.52
20	5.08	5.03	0.05	4.96	0.12
21	5.42	5.45	-0.03	5.41	0.01
22	5.16	5.24	-0.09	5.39	-0.24
23	5.80	5.69	0.11	5.37	0.42
Spm	5.50	5.44	0.06	4.99	0.51

Table S15. Py-ComBine model recalculated/predicted vs experimental pK_M values

PA	pK_M				
	Exp	**Recald**	**Err Fit/Pred**	**CV Pred**	**Err CV**
1	4.73	4.82	-0.09	4.84	-0.11
2	4.39	4.57	-0.18	4.73	-0.34
3	4.47	4.64	-0.17	4.73	-0.26
4	5.14	5.29	-0.15	5.28	-0.13
5	4.78	4.69	0.08	4.64	0.14
6	4.53	4.47	0.06	4.59	-0.06
7	4.46	4.67	-0.22	4.79	-0.34
8	4.96	4.80	0.16	4.70	0.26
9	4.92	4.93	-0.01	4.90	0.02
10	5.14	4.93	0.22	4.83	0.31
11	4.62	4.84	-0.22	4.93	-0.31
12	5.11	5.09	0.02	4.68	0.42
13	5.22	4.96	0.26	4.90	0.32
14	4.77	4.67	0.10	4.63	0.14
15	4.42	4.55	-0.13	4.73	-0.31
16	4.79	4.77	0.02	4.45	0.34
17	4.70	4.75	-0.05	4.75	-0.05
18	5.00	5.04	-0.04	5.09	-0.09
19	4.01	3.84	0.18	4.04	-0.02
20	5.08	5.05	0.03	5.06	0.02
21	5.42	5.53	-0.11	5.51	-0.09
22	5.16	5.19	-0.04	5.22	-0.07
23	5.80	5.51	0.28	5.31	0.48
Spm	5.50	5.52	-0.03	5.22	0.27

Table S16. SMILES structures of derivatives **1-24**

#	SMILES
1	COC1=CC=CC(CNCCCNCCCCNCCCN)=C1
2	COC1=CC=C(CNCCCNCCCCNCCCN)C=C1
3	NCCCNCCCCNCCCNCC1=CC=CC=C1
4	CC1=C(CNCCCNCCCCNCCCN)C=CC=C1
5	NCCCNCCCCNCCCNCC1=C(C=CC=C1)N(=O)=O
6	NCCCNCCCCNCCCNCC1=C(Cl)C=CC=C1
7	COC1=C(OC)C(OC)=C(CNCCCNCCCCNCCCN)C=C1
8	COC1=CC(CNCCCNCCCCNCCCN)=CC(OC)=C1OC
9	NCCCNCCCCNCCCNCC1=NC=CC=C1
10	NCCCNCCCCNCCCNCC1=CC=NC=C1
11	NCCCNCCCCNCCCNCC1=CC=CN=C1
12	NCCCNCCCCNCCCNCC1=CC2=CC=CC=C2C=C1
13	NCCCNCCCCNCCCNCC1=CC=CS1
14	NCCCNCCCCNCCCNCC1=C(C=CC=C1)C(F)(F)F
15	NCCCNCCCCNCCCNCC1=C(F)C=CC=C1
16	COC1=C(O)C=CC(CNCCCNCCCCNCCCN)=C1
17	COC1=C(CNCCCNCCCCNCCCN)C=CC=C1
18	NCCCCCCCCNCCCN
19	CC1=C(CNCCCNCCCCCCCCN)C=CC=C1
20	NCCCCCCCCNCCCNCC1=CC=CS1
21	CC1=C(CNCCCOCCCCOCCCN)C=CC=C1
22	NCCCOCCCCOCCCNCC1=CC=CS1
23	NCCCOCCCCOCCCN
Spm	NCCCNCCCCNCCCN