Evaluation of Different Virtual Screening Programs for Docking in a Charged Binding Pocket

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Supporting Information:

Table S1. Results of docking binders and non-binders to CCPW191G, using FRED with Chemgauss3 scoring function. Non-binders are label with "-NB".

(*: Chemgauss3 unable to assign atom types, due to the small number of heavy atoms. Therefore their score do not include contributions other than steric interactions.)

With HOH308		Without HOH308	
Name	Total Score	Name	Total Score
benzimidazole	-51.40	benzimidazole	-52.82
2,5-diaminopyridine hydrochloride	-50.00	4-amino-5-imidazole carboxamide-NB	-51.92
phenol	-49.09	2,5-diaminopyridine hydrochloride	-51.41
2-iminopiperidine hydrochloride	-48.49	4,5-diaminopyrimidine	-51.22
2,4-diaminopyrimidine	-47.97	indazole-NB	-50.75
3-pyridylcarbinol	-47.37	phenol	-50.47
2-amino-5-methylpyridine	-47.32	4-aminopyridine	-49.88
4-aminopyridine	-47.29	3,4-diaminopyridine	-49.31
4-amino-5-imidazole carboxamide-NB	-47.21	2-amino-5-methylpyridine	-48.70
3,4-diaminopyridine	-46.63	2-iminopiperidine hydrochloride	-47.83
4-pyridylcarbinol	-46.39	1-methyl-1,6-dihydropyridin-3-amine	-47.64
cyclopentylamine	-45.80	2-amino-4-methylpyridine	-47.61
4-aminopyrimidine	-45.61	imidazo[1,2-a]pyridine	-47.48
3-aminopyridine	-45.60	cyclopentylamine	-47.37
4-aminoresorcinol hydrochloride-NB	-45.32	3-aminopyridine	-47.34
3-cyanopyridine-NB	-45.25	3,5-difluoroaniline-NB	-47.11
benzylamine	-45.15	benzylamine	-47.00
1-vinylimidazole	-45.03	2,4-diaminopyrimidine	-46.89
3-methylthiazole	-45.00	3-cyanopyridine-NB	-46.34
toluene-NB	-44.75	1-vinylimidazole	-46.29
3-fluorocatechol	-44.31	3-pyridylcarbinol	-45.76
indazole-NB	-44.16	aniline	-45.72
2,6-diaminopyridine	-44.05	4-pyridylcarbinol	-45.71
3,5-difluoroaniline-NB	-44.01	4-aminoresorcinol hydrochloride-NB	-45.64
2-ethylimidazole	-43.76	2-amino-5-methylthiazole	-45.15
aniline	-43.54	3-fluorocatechol	-45.02
2-cyanoaniline-NB	-43.54	toluene-NB	-44.92
2-thiolpyrimidine-NB	-43.23	2-cyanoaniline-NB	-44.86
1H-imidazol-2-ylmethanol hydrochloride	-43.22	2-ethylimidazole	-44.60
2-aminothiazole	-43.20	2-thiolpyrimidine-NB	-44.39
1-methylimidazole	-42.23	1H-imidazol-2-ylmethanol hydrochloride	-44.34
imidazo[1,2-a]pyridine	-42.15	4-aminopyrimidine	-44.19
2-thiolimidazole-NB	-41.80	2-aminothiazole	-44.04
1-methyl-1,6-dihydropyridin-3-amine	-41.56	2,6-diaminopyridine	-43.75
3-chlorophenol-NB	-41.41	1,2-dimethylimidazole	-43.72
indoline	-41.31	pyridine	-43.66
2-amino-4-methylpyridine	-40.78	1-methylimidazole	-43.49
pyridine	-40.53	3-chlorophenol-NB	-43.27
4-methylimidazole	-40.42	2-aminopyridine	-43.10
2-methylimidazole	-40.34	indoline	-42.21
2-amino-5-methylthiazole	-40.31	isoniazide-NB	-41.75
isoniazide-NB	-40.17	2-thiolimidazole-NB	-41.39
4,5-diaminopyrimidine	-39.59	2-methylimidazole	-40.83
3-methylthiazole	-39.30	imidazole	-40.64

3-thienylmethylamine	-38.44	3-methylthiazole	-40.12
1,2-dimethylimidazole	-38.31	2-ethyl-4-methylimidazole	-39.86
imidazole	-38.19	4-methylimidazole	-39.77
3,4-dimethylthiazole	-37.70	3,4,5-trimethylthiazole	-39.66
pyrazole-NB	-37.42	3-thienylmethylamine	-39.26
3-aminopyrazole-NB	-36.98	3,4-dimethylthiazole	-39.04
3-thiophenecarboxamide hydrochloride	-36.70	2-amino-4-methylthiazole	-39.03
Quinoline	-35.46	3-thiophenecarboxamide hydrochloride	-37.94
3-amino-4-cyanopyrazole-NB	-35.38	2,3,4-trimethylthiazole	-37.85
2-ethyl-4-methylimidazole	-31.40	pyrazole-NB	-37.82
tetrazole-NB	-31.37	3-aminopyrazole-NB	-37.70
3,4,5-trimethylthiazole	-31.30	Quinoline	-37.27
2,3,4-trimethylthiazole	-30.94	3-amino-4-cyanopyrazole-NB	-35.98
2-amino-4-methylthiazole	-28.41	tetrazole-NB	-31.36
dimethylammonium-NB	-19.30	dimethylammonium-NB	-19.92
methylammonium-NB	-8.84	methylammonium-NB	-15.07

Table S2 Results of docking binders and non-binders to CCPW191G, using FRED with Zapbind scoring function. Non-binders are label with "-NB".

With HOH308		Without HOH308	
Name	Total Score	Name	Total Score
2-amino-5-methylthiazole	-21.63	2-amino-5-methylthiazole	-23.06
benzimidazole	-20.61	benzimidazole	-20.21
1-methyl-1,6-dihydropyridin-3-amine	-19.40	2-aminothiazole	-19.43
4-methylimidazole	-18.67	3-methylthiazole	-19.01
3-methylthiazole	-18.65	4-methylimidazole	-18.79
2-aminothiazole	-18.44	Quinoline	-18.29
dimethylammonium-NB	-18.06	3-methylthiazole	-18.22
Quinoline	-17.99	dimethylammonium-NB	-17.86
3-methylthiazole	-17.30	imidazo[1,2-a]pyridine	-17.71
2-ethylimidazole	-17.28	2-ethylimidazole	-17.56
2-ethyl-4-methylimidazole	-17.21	2-ethyl-4-methylimidazole	-17.05
aniline	-16.60	aniline	-16.80
2-methylimidazole	-16.24	2-amino-5-methylpyridine	-16.26
2-amino-5-methylpyridine	-16.13	2-methylimidazole	-16.05
methylammonium-NB	-15.81	2,3,4-trimethylthiazole	-15.99
3-thienylmethylamine	-15.57	indoline	-15.88
indoline	-15.51	3-thienylmethylamine	-15.59
benzylamine	-15.50	benzylamine	-15.40
imidazole	-15.23	imidazole	-15.32
1-methylimidazole	-15.13	1H-imidazol-2-ylmethanol hydrochloride	-15.11
1H-imidazol-2-ylmethanol hydrochloride	-15.07	1-methylimidazole	-15.07
1,2-dimethylimidazole	-14.52	2,5-diaminopyridine hydrochloride	-14.79
2-aminopyridine	-13.34	1,2-dimethylimidazole	-14.64
2,3,4-trimethylthiazole	-12.40	2-amino-4-methylthiazole	-14.60
2-amino-4-methylthiazole	-12.08	methylammonium-NB	-14.22
1-vinylimidazole	-10.34	2-aminopyridine	-13.40
imidazo[1,2-a]pyridine	-10.07	3,4,5-trimethylthiazole	-12.74
3-thiophenecarboxamide hydrochloride	-9.25	3-pyridylcarbinol	-12.54
2,5-diaminopyridine hydrochloride	-9.16	2,6-diaminopyridine	-12.43
2,6-diaminopyridine	-7.85	1-methyl-1,6-dihydropyridin-3-amine	-11.58
3,4-dimethylthiazole	-7.72	2-amino-4-methylpyridine	-11.31
4-aminopyrimidine	-7.50	3-thiophenecarboxamide hydrochloride	-10.35
pyridine	-7.34	1-vinylimidazole	-10.18
4,5-diaminopyrimidine	-7.21	3,4-diaminopyridine	-9.15
2,4-diaminopyrimidine	-5.05	2-iminopiperidine hydrochloride	-9.04
3-aminopyrazole-NB	-4.93	3-aminopyridine	-8.98
3,4,5-trimethylthiazole	-4.09	3,4-dimethylthiazole	-8.04
2-iminopiperidine hydrochloride	-3.58	pyridine	-7.96
phenol	-2.50	3,5-difluoroaniline-NB	-7.18

2-amino-4-methylpyridine	-2.31	3-aminopyrazole-NB	-5.40
3,5-difluoroaniline-NB	-2.03	2,4-diaminopyrimidine	-5.04
tetrazole-NB	-0.42	4,5-diaminopyrimidine	-3.16
cyclopentylamine	-0.25	phenol	-2.94
2-cyanoaniline-NB	-0.24	3-fluorocatechol	-2.65
2-thiolimidazole-NB	-0.04	tetrazole-NB	-1.61
3-aminopyridine	0.24	2-thiolimidazole-NB	-1.31
toluene-NB	0.61	pyrazole-NB	-1.10
4-amino-5-imidazole carboxamide-NB	0.72	2-cyanoaniline-NB	-0.58
3-pyridylcarbinol	1.08	toluene-NB	-0.26
pyrazole-NB	1.25	4-pyridylcarbinol	1.53
3-chlorophenol-NB	1.74	4-aminopyridine	1.66
4-aminopyridine	2.20	3-cyanopyridine-NB	1.92
indazole-NB	2.43	isoniazide-NB	2.52
3-cyanopyridine-NB	3.18	3-chlorophenol-NB	2.94
isoniazide-NB	3.65	indazole-NB	3.18
2-thiolpyrimidine-NB	5.12	2-thiolpyrimidine-NB	3.61
4-pyridylcarbinol	6.88	4-amino-5-imidazole carboxamide-NB	7.45
3-fluorocatechol	8.32	4-aminopyrimidine	8.05
4-aminoresorcinol hydrochloride-NB	13.55	3-amino-4-cyanopyrazole-NB	9.59
3-amino-4-cyanopyrazole-NB	14.58	4-aminoresorcinol hydrochloride-NB	10.73

Table S3 Results of docking binders and non-binders to CCPW191G, using QXP/FLO. Non-binders are label with "-NB".

With HOH308		Without HOH308	
Name	Total Score	Name	Total Score
3-pyridylcarbinol	-50.80	3-pyridylcarbinol	-49.20
cyclopentylamine	-49.10	2,5-diaminopyridine hydrochloride	-47.50
2,5-diaminopyridine hydrochloride	-48.40	2-amino-5-methylpyridine	-46.60
2-amino-5-methylpyridine	-46.90	2-iminopiperidine hydrochloride	-46.10
3,4-diaminopyridine	-46.80	4-pyridylcarbinol	-45.70
2-iminopiperidine hydrochloride	-46.30	2-amino-5-methylthiazole	-45.50
2,6-diaminopyridine	-45.80	3-thienylmethylamine	-43.90
3-thienylmethylamine	-44.90	2-aminopyridine	-43.70
benzimidazole	-43.90	imidazo[1,2-a]pyridine	-43.30
4-aminopyridine	-43.90	2,6-diaminopyridine	-42.90
benzylamine	-43.90	benzimidazole	-41.90
2-aminopyridine	-43.70	3,4-diaminopyridine	-41.90
imidazo[1,2-a]pyridine	-43.70	3-aminopyridine	-41.70
2-aminothiazole	-43.50	2-aminothiazole	-41.60
3-aminopyridine	-42.60	4-aminopyridine	-39.70
2-amino-5-methylthiazole	-42.60	imidazo[1,2-a]pyridine	-39.70
1H-imidazol-2-ylmethanol hydrochloride	-42.50	2,4-diaminopyrimidine	-39.60
2,4-diaminopyrimidine	-42.40	cyclopentylamine	-39.40
4-aminopyrimidine	-42.30	2-amino-4-methylpyridine	-39.20
4,5-diaminopyrimidine	-42.20	pyridine	-38.20
4-pyridylcarbinol	-41.40	1H-imidazol-2-ylmethanol hydrochloride	-38.00
dimethylammonium-NB	-41.20	1-vinylimidazole	-37.70
2-amino-4-methylpyridine	-40.90	2-amino-4-methylthiazole	-37.40
1-vinylimidazole	-40.00	3-thiophenecarboxamide hydrochloride	-36.60
1,2-dimethylimidazole	-39.50	1,2-dimethylimidazole	-36.40
methylammonium-NB	-39.40	4-aminopyrimidine	-36.30
4-methylimidazole	-38.80	4-methylimidazole	-35.70
pyridine	-38.50	4,5-diaminopyrimidine	-35.50
2-ethyl-4-methylimidazole	-38.40	1-methylimidazole	-34.70
2-amino-4-methylthiazole	-38.20	2-ethyl-4-methylimidazole	-34.50
3-thiophenecarboxamide hydrochloride	-37.80	2-methylimidazole	-34.10
2-ethylimidazole	-36.90	2-ethylimidazole	-34.10
1-methylimidazole	-36.20	dimethylammonium-NB	-33.70
2-methylimidazole	-35.40	1-methyl-1,6-dihydropyridin-3-amine	-31.60
1-methyl-1,6-dihydropyridin-3-amine	-34.50	imidazole	-31.00
3-methylthiazole	-34.10	methylammonium-NB	-30.50
imidazole	-32.60	3-methylthiazole	-30.10
Quinoline	-32.20	3,4-dimethylthiazole	-29.80
4-aminoresorcinol hydrochloride-NB	-28.60	4-aminoresorcinol hydrochloride-NB	-29.50
3-aminopyrazole-NB	-27.90	3-fluorocatechol	-27.10
3,4-dimethylthiazole	-27.50	4-amino-5-imidazole carboxamide-NB	-26.30

phenol	-26.70	phenol	-26.10
aniline	-25.50	3-aminopyrazole-NB	-26.10
3-fluorocatechol	-25.20	3-amino-4-cyanopyrazole-NB	-25.50
3-amino-4-cyanopyrazole-NB	-24.30	Quinoline	-25.40
tetrazole-NB	-23.60	aniline	-25.00
4-amino-5-imidazole carboxamide-NB	-23.00	3,5-difluoroaniline-NB	-24.60
3,4,5-trimethylthiazole	-22.50	3,4,5-trimethylthiazole	-24.50
3,5-difluoroaniline-NB	-21.70	tetrazole-NB	-21.20
3-cyanopyridine-NB	-21.50	3-cyanopyridine-NB	-20.30
pyrazole-NB	-21.10	3-chlorophenol-NB	-19.70
indazole-NB	-21.10	indazole-NB	-19.60
3-chlorophenol-NB	-21.00	pyrazole-NB	-19.20
toluene-NB	-19.80	toluene-NB	-19.00
2,3,4-trimethylthiazole	-18.90	2,3,4-trimethylthiazole	-18.10
2-cyanoaniline-NB	-17.90	2-cyanoaniline-NB	-17.80
indoline	-15.80	2-thiolimidazole-NB	-14.30
2-thiolimidazole-NB	-10.20	indoline	-13.40
2-thiolpyrimidine-NB	-6.60	2-thiolpyrimidine-NB	-11.00
isoniazide-NB	6.20	isoniazide-NB	7.50

Table S4 Results of docking binders and non-binders to CCPW191G, using GLIDE with Standard Precision Scoring Function. *Non-binders are label with "-NB".*

With HOH308		Without HOH308	
Name	Total Score	Name	Total Score
benzylamine	-7.17	3-thiophenecarboxamide hydrochloride	-7.60
4-pyridylcarbinol	-7.13	isoniazide-NB	-7.49
3-thiophenecarboxamide hydrochloride	-7.03	benzylamine	-7.19
2-iminopiperidine hydrochloride	-6.83	3-fluorocatechol	-7.13
4-aminoresorcinol hydrochloride-NB	-6.82	4-aminoresorcinol hydrochloride-NB	-7.11
4-amino-5-imidazole carboxamide-NB	-6.77	3-thienylmethylamine	-7.04
isoniazide-NB	-6.72	4-pyridylcarbinol	-6.80
1H-imidazol-2-ylmethanol hydrochloride	-6.66	4-amino-5-imidazole carboxamide-NB	-6.80
2-amino-4-methylpyridine	-6.62	2-thiolimidazole-NB	-6.70
3-pyridylcarbinol	-6.62	3,4-diaminopyridine	-6.59
2-thiolimidazole-NB	-6.42	2-iminopiperidine hydrochloride	-6.59
3-thienylmethylamine	-6.41	2,6-diaminopyridine	-6.55
3-aminopyridine	-6.32	3-pyridylcarbinol	-6.55
2,5-diaminopyridine hydrochloride	-6.28	2-amino-4-methylpyridine	-6.48
cyclopentylamine	-6.19	cyclopentylamine	-6.35
1-vinylimidazole	-6.18	2,5-diaminopyridine hydrochloride	-6.32
3-fluorocatechol	-6.18	3-aminopyridine	-6.21
imidazo[1,2-a]pyridine	-6.14	1-vinylimidazole	-6.20
2-aminopyridine	-6.11	1H-imidazol-2-ylmethanol hydrochloride	-6.18
2,6-diaminopyridine	-6.04	imidazo[1,2-a]pyridine	-6.16
2-amino-5-methylpyridine	-6.03	2-aminopyridine	-6.11
1-methyl-1,6-dihydropyridin-3-amine	-6.02	2-amino-5-methylpyridine	-6.06
benzimidazole	-5.93	1-methyl-1,6-dihydropyridin-3-amine	-6.05
2-ethylimidazole	-5.91	2-ethylimidazole	-6.01
4-methylimidazole	-5.90	benzimidazole	-6.01
3,4-diaminopyridine	-5.89	4-aminopyridine	-5.97
3,4,5-trimethylthiazole	-5.89	indazole-NB	-5.88
4-aminopyridine	-5.87	4-methylimidazole	-5.88
2,3,4-trimethylthiazole	-5.84	3,4,5-trimethylthiazole	-5.87
indoline	-5.84	2,3,4-trimethylthiazole	-5.84
indazole-NB	-5.83	indoline	-5.77
3-cyanopyridine-NB	-5.78	2-methylimidazole	-5.75
3,5-difluoroaniline-NB	-5.74	pyridine	-5.73
2-methylimidazole	-5.73	3,5-difluoroaniline-NB	-5.70
pyridine	-5.71	3-chlorophenol-NB	-5.69
3-chlorophenol-NB	-5.65	1,2-dimethylimidazole	-5.69
1,2-dimethylimidazole	-5.61	2-cyanoaniline-NB	-5.68
imidazole	-5.61	2-ethyl-4-methylimidazole	-5.67
2-ethyl-4-methylimidazole	-5.59	imidazole	-5.60
4,5-diaminopyrimidine	-5.57	3,4-dimethylthiazole	-5.57

2-cyanoaniline-NB	-5.54	2,4-diaminopyrimidine	-5.55
3,4-dimethylthiazole	-5.51	2-amino-5-methylthiazole	-5.53
2,4-diaminopyrimidine	-5.49	phenol	-5.52
aniline	-5.47	aniline	-5.51
2-amino-5-methylthiazole	-5.46	4,5-diaminopyrimidine	-5.51
phenol	-5.45	3-amino-4-cyanopyrazole-NB	-5.46
2-amino-4-methylthiazole	-5.40	2-thiolpyrimidine-NB	-5.43
3-amino-4-cyanopyrazole-NB	-5.40	3-cyanopyridine-NB	-5.42
2-thiolpyrimidine-NB	-5.35	3-aminopyrazole-NB	-5.40
Quinoline	-5.34	2-amino-4-methylthiazole	-5.38
1-methylimidazole	-5.22	1-methylimidazole	-5.29
3-methylthiazole	-5.07	2-aminothiazole	-5.17
3-aminopyrazole-NB	-5.03	Quinoline	-5.15
2-aminothiazole	-5.02	3-methylthiazole	-5.13
4-aminopyrimidine	-5.00	4-aminopyrimidine	-5.05
toluene-NB	-4.80	methylammonium-NB	-4.97
dimethylammonium-NB	-4.78	toluene-NB	-4.83
methylammonium-NB	-4.64	dimethylammonium-NB	-4.80
pyrazole-NB	-4.37	pyrazole-NB	-4.41
tetrazole-NB	-3.91	tetrazole-NB	-4.04

Table S5 Results of docking binders and non-binders to CCPW191G, using GLIDE with Extra Precision Scoring Function. *Non-binders are label with "-NB".*

With HOH308		Without HOH308	
Name	Total Score	Name	Total Score
benzylamine	-8.00	3-fluorocatechol	-7.33
3-fluorocatechol	-7.43	4-pyridylcarbinol	-7.29
4-pyridylcarbinol	-7.36	1-methyl-1,6-dihydropyridin-3-amine	-7.23
2-amino-5-methylpyridine	-7.16	3-pyridylcarbinol	-7.21
3,4-diaminopyridine	-7.06	2-amino-4-methylpyridine	-7.14
2,5-diaminopyridine hydrochloride	-6.77	2-amino-5-methylpyridine	-7.10
3-aminopyridine	-6.76	benzylamine	-7.01
2-aminopyridine	-6.73	3-thienylmethylamine	-6.92
3-chlorophenol-NB	-6.72	4-aminoresorcinol hydrochloride-NB	-6.91
indazole-NB	-6.70	2-aminopyridine	-6.75
2,6-diaminopyridine	-6.68	3-aminopyridine	-6.75
cyclopentylamine	-6.62	2,5-diaminopyridine hydrochloride	-6.75
isoniazide-NB	-6.62	3-chlorophenol-NB	-6.68
4-aminoresorcinol hydrochloride-NB	-6.55	indazole-NB	-6.64
2-amino-4-methylpyridine	-6.51	isoniazide-NB	-6.63
3-thiophenecarboxamide hydrochloride	-6.45	2,6-diaminopyridine	-6.59
Quinoline	-6.41	2-cyanoaniline-NB	-6.41
indoline	-6.40	indoline	-6.36
aniline	-6.17	3-thiophenecarboxamide hydrochloride	-6.24
2-iminopiperidine hydrochloride	-6.15	Quinoline	-6.17
3,5-difluoroaniline-NB	-6.13	3-cyanopyridine-NB	-6.06
3-pyridylcarbinol	-6.10	phenol	-6.05
3-thienylmethylamine	-6.09	aniline	-6.05
phenol	-6.07	4-aminopyridine	-5.95
2-cyanoaniline-NB	-6.00	cyclopentylamine	-5.86
4-aminopyridine	-5.90	3,4-diaminopyridine	-5.81
benzimidazole	-5.88	pyridine	-5.79
1-methyl-1,6-dihydropyridin-3-amine	-5.74	3,5-difluoroaniline-NB	-5.78
2-amino-4-methylthiazole	-5.57	benzimidazole	-5.71
4-amino-5-imidazole carboxamide-NB	-5.54	imidazo[1,2-a]pyridine	-5.65
toluene-NB	-5.46	toluene-NB	-5.51
1-vinylimidazole	-5.27	1,2-dimethylimidazole	-5.49
2,3,4-trimethylthiazole	-5.20	4-amino-5-imidazole carboxamide-NB	-5.43
3,4,5-trimethylthiazole	-5.18	1-vinylimidazole	-5.28
2-amino-5-methylthiazole	-5.14	2-amino-5-methylthiazole	-5.25
imidazo[1,2-a]pyridine	-5.13	2-amino-4-methylthiazole	-5.22
imidazo[1,2-a]pyridine	-5.01	3-aminopyrazole-NB	-5.17
3-aminopyrazole-NB	-4.95	3,4,5-trimethylthiazole	-5.12
2-ethyl-4-methylimidazole	-4.93	2,3,4-trimethylthiazole	-5.12
4,5-diaminopyrimidine	-4.90	imidazo[1,2-a]pyridine	-5.04

3-amino-4-cyanopyrazole-NB	-4.89
2,4-diaminopyrimidine	-4.86
3-cyanopyridine-NB	-4.82
2-thiolpyrimidine-NB	-4.82
4-aminopyrimidine	-4.73
1-methylimidazole	-4.72
3,4-dimethylthiazole	-4.64
2-ethylimidazole	-4.62
2-aminothiazole	-4.61
pyridine	-4.55
4-methylimidazole	-4.55
pyrazole-NB	-4.41
2-methylimidazole	-4.40
2-thiolimidazole-NB	-4.36
1,2-dimethylimidazole	-4.33
imidazole	-3.98
3-methylthiazole	-3.98
dimethylammonium-NB	-3.60
tetrazole-NB	-3.05
methylammonium-NB	-2.95

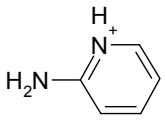
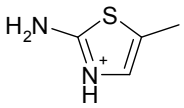
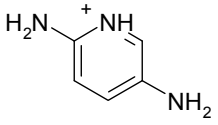
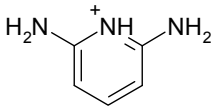
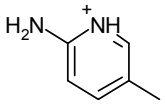
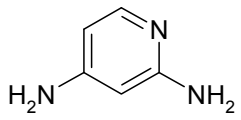
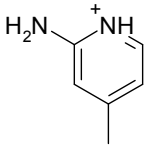
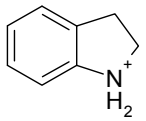
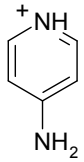
3-amino-4-cyanopyrazole-NB	-4.92
2-ethylimidazole	-4.90
2-ethyl-4-methylimidazole	-4.88
4,5-diaminopyrimidine	-4.83
2-thiolpyrimidine-NB	-4.82
4-aminopyrimidine	-4.79
1-methylimidazole	-4.73
2-aminothiazole	-4.73
3,4-dimethylthiazole	-4.69
2,4-diaminopyrimidine	-4.65
4-methylimidazole	-4.58
2-thiolimidazole-NB	-4.46
pyrazole-NB	-4.39
2-methylimidazole	-4.39
3-methylthiazole	-4.02
imidazole	-3.98
2-iminopiperidine hydrochloride	-3.89
dimethylammonium-NB	-3.51
tetrazole-NB	-3.04
methylammonium-NB	-3.02

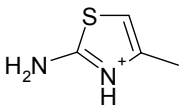
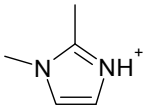
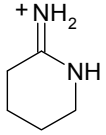
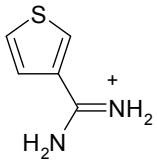
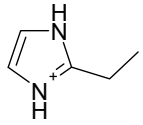
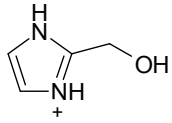
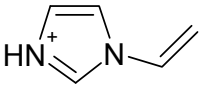
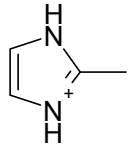
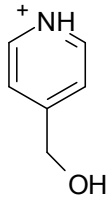
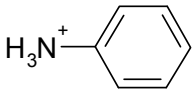
Table S6. Binding Site Marker Atoms (colored pink) during QXP/FLO Docking.

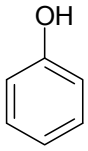
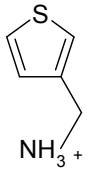
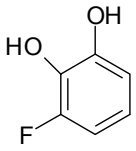
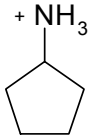
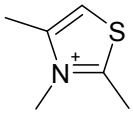
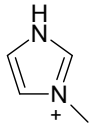
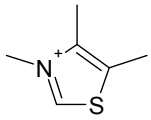
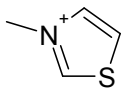
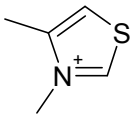
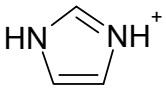
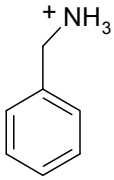
Residue	Atom	Coordinates
HIS175	C (gamma)	(-8.465, 55.895, 108.988)
GLY191	C (alpha)	(-12.672, 49.299, 108.141)
MET230	S (delta)	(13.473, 51.401, 113.299)
HOH308*	O	(-9.249, 48.848, 107.796)
HEM	C	(-4.195, 51.712, 111.171)

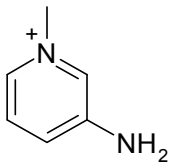
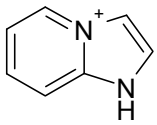
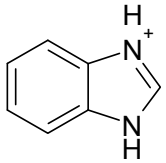
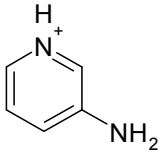
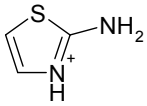
* Removed when docking without HOH308

Table S7 Summary of the 35 crystal structures with bound ligands.

PDB ID	Ligand Name	MBC (mM)	Kd (mM)	Ligand Structure	Crystal Resolution (Å)	R-value	R_{free}	Ref.
1AEO	2-aminopyridine	——	0.05		2.10	——	——	a
1AEN	2-amino-5-methylthiazole	——	0.006		2.10	——	——	a
2AQD	2,5-diaminopyridine	0.25	——		1.35	0.134 (obs.)	0.163	b
2ANZ	2,6-diaminopyridine	——	0.06		1.75	0.192 (obs.)	0.210	b
2EUP	2-amino-5-methylpyridine	——	0.04		1.40	0.153 (obs.)	0.181	b
2EUN	2,4-diaminopyrimidine	——	0.05		1.70	0.194 (obs.)	0.226	b
2EUT	2-amino-4-methylpyridine	0.25	——		1.12	0.143 (obs.)	0.152	b
1AEK	indoline	——	0.16		2.10	——	——	a
1AEG	4-aminopyridine	——	0.04		2.10	——	——	a

1AEH	2-amino-4-methylthiazole	——	0.23		2.10	——	——	a
1CMP	1,2-dimethylimidazole	——	0.027		1.90	0.190 (obs.)	——	c
2AS2	2-iminopiperidine hydrochloride	0.13	——		1.45	0.134 (obs.)	0.177	b
2AS1	3-thiophenecarboxamide hydrochloride	——	0.02		1.55	0.152 (obs.)	0.199	b
1AEQ	2-ethylimidazole	——	0.73		2.10	——	——	a
2EUU	1H-imidazol-2-ylmethanol hydrochloride	0.50	——		1.45	0.146 (obs.)	0.161	b
1AEJ	1-vinylimidazole	——	0.15		2.10	——	——	a
1AEU	2-methylimidazole	——	0.07		2.10	——	——	c
2EUR	4-pyridylcarbinol	0.50	——		1.39	0.148 (obs.)	0.171	b
1AEE	aniline	——	0.03		2.10	——	——	a

2AS3	phenol	——	4.1		1.40	0.144 (work)	0.188	b
2EUQ	3-thienylmethylamine	——	0.05		1.30	0.147 (obs.)	0.166	b
2AS4	3-fluorocatechol	——	7.7		1.30	0.138 (work)	0.175	b
2AS6	cyclopentylamine	0.50	——		1.45	0.142 (work)	0.183	b
1AC4	2,3,4-trimethylthiazole	——	1.5		2.10	——	——	c
1AET	1-methylimidazole	——	0.07		2.10	——	——	c
1AC8	3,4,5-trimethylthiazole	——	0.2		2.10	——	——	c
1AEB	3-methylthiazole	——	0.3		2.10	——	——	a
1AED	3,4-dimethylthiazole	——	0.05		2.10	——	——	a
1AES	imidazole	——	0.07		2.10	——	——	c
2EUS	benzylamine	0.25	——		1.55	0.149 (obs.)	0.178	b

2EUO	1-methyl-1,6-dihydropyridin-3-amine	0.25	——		1.45	0.153 (obs.)	0.181	b
1AEM	imidazo[1,2-a]pyridine	——	0.09		2.10	——	——	a
1RYC	benzimidazole	——	0.15		1.80	0.163 (obs.)	——	c
1AEF	3-aminopyridine	——	0.05		2.10	——	——	a
1AEV	2-aminothiazole	——	0.04		2.10	——	——	d

a = Musah, R.A.; Jensen, G.M.; Bunte, S.W.; Rosenfeld, R.J.; Goodin, D.B. Artificial protein cavities as specific ligand-binding templates: characterization of an engineered heterocyclic cation-binding site that preserves the evolved specificity of the parent protein. J.Mol.Biol. **2002,** 315, 845-857.

b = Brenk, R.; Vetter, S.W.; Boyce, S.E.; Goodin, D.B.; Shoichet, B.K. Probing molecular docking in a charged model binding site. J.Mol.Biol. **2006,** 357, 1449-1470.

c = Fitzgerald, M.M.; Musah, R.A.; McRee, D.E.; Goodin, D.B. A ligand-gated, hinged loop rearrangement opens a channel to a buried artificial protein cavity. Nat.Struct.Biol. **1996,** 3, 626-631.

d = Musah, R.A.; Goodin, D.B. Introduction of novel substrate oxidation into cytochrome c peroxidase by cavity complementation: oxidation of 2-aminothiazole and covalent modification of the enzyme. Biochemistry **1997,** 36, 11665-11674.

—— = N/A

MBC = Minimum Bactericidal Concentration

(The PDB code, ligand name, MBC, Kd, Ligand structure, are downloaded from Shoichet's laborarty homepage*. The crystal resolution, R-value, R_{free}, references are obtained from PDB website.** The authors have noticed the slight inconsistence of crystal resolutions between the reference and PDB website.

* Shoichet Laboratory Homepage. University of California, San Francisco: San Francisco, CA, USA. http://shoichetlab.compbio.ucsf.edu/ (accessed Apr 19, 2007), Under "Take Aways -> CCP binders".

** RCSB PDB web service. http://www.rcsb.org (accessed Jun 18, 2008).)