Supporting Information

Integrated Approach to Identify Selective PTP1B Inhibitors Targeting the Allosteric Site

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Table S1. MM-GBSA free energy decomposition of inhibitor-residue pairs with major contributions from individual residues (kcal/mol).

PTP1B-2					
Ligand/Residue	**vdW**	**ele**	**GB**	**SA**	**ΔE**
2	-20.16±0.10	-12.55±0.13	21.14±0.08	-3.36±0.01	-14.93±0.08
Phe280	-5.42±0.03	-0.33±0.02	1.45±0.02	-0.84±0.01	-5.14±0.04
Phe196	-2.11±0.03	-0.60±0.01	0.66±0.01	-0.24±0.01	-2.28±0.04
Leu192	-2.04±0.02	0±0.01	0.08±0.01	-0.11±0.01	-2.06±0.02
Asn193	-1.40±0.02	-1.04±0.08	0.79±0.04	-0.24±0.01	-1.89±0.03
Ala189	-1.20±0.01	-0.58±0.01	0.90±0.01	-0.21±0.01	-1.09±0.01
Met282	-0.93±0.02	-0.42±0.02	0.50±0.01	-0.16±0.01	-1.01±0.02
PTP1B-H3					
Ligand/Residue	**vdW**	**ele**	**GB**	**SA**	**ΔE**
H3	-22.67±0.08	-11.60±0.11	19.42±0.09	-3.67±0.02	-18.52±0.09
Phe280	-4.98±0.04	0.35±0.02	1.10±0.02	-0.76±0.01	-4.30±0.04
Phe196	-3.12±0.03	-0.77±0.01	0.84±0.01	-0.43±0.01	-3.48±0.04
Asn193	-2.17±0.02	-0.41±0.06	0.96±0.04	-0.31±0.01	-1.93±0.03
Leu192	-1.91±0.02	-0.09±0.01	0.24±0.01	-0.16±0.01	-1.92±0.02
Lys279	-1.62±0.02	-2.11±0.06	2.44±0.07	-0.19±0.01	-1.48±0.02
Glu276	-1.13±0.02	-4.78±0.08	4.74±0.10	-0.16±0.01	-1.33±0.03
Met282	-1.28±0.02	-0.15±0.01	0.44±0.01	-0.21±0.01	-1.20±0.03
Trp291	-1.17±0.02	-0.19±0.01	0.59±0.01	-0.23±0.01	-1.00±0.02
Ala189	-0.91±0.01	0.15±0.01	0.25±0.01	-0.16±0.01	-0.67±0.02
PTP1B-H9					
Ligand/Residue	**vdW**	**ele**	**GB**	**SA**	**ΔE**
H9	-22.12±0.10	-4.23±0.10	13.08±0.10	-3.62±0.01	-16.89±0.10
Phe280	-5.02±0.03	-0.46±0.01	1.13±0.01	-0.54±0.01	-4.89±0.03
Asn193	-4.27±0.02	-1.03±0.04	2.79±0.03	-0.45±0.01	-2.96±0.03
Phe196	-2.57±0.02	-0.69±0.02	0.60±0.01	-0.11±0.01	-2.76±0.03
Leu192	-2.11±0.02	-0.35±0.02	0.42±0.01	-0.08±0.00	-2.14±0.02
Ala189	-2.00±0.02	-0.60±0.01	0.98±0.01	-0.25±0.01	-1.88±0.02
Lys197	-2.13±0.02	1.48±0.05	-0.43±0.05	-0.16±0.01	-1.25±0.03

vdW = van der Waals contribution from MM.

ele = electrostatic energy as calculated by the MM force field.

GB = the electrostatic contribution to the solvation free energy calculated by GB.

SA = non-polar contribution to the solvation free energy calculated by an empirical model.

ΔE = sum of energetic contributions calculated from the terms above (kcal/mol).

Table S2. Comparisons of critical residues at the allosteric site of PTP1B with other pTyr-specific phosphatases.

Classification of pTyr-specific phosphatases	PDBcode[a]	Position1	Position2	Position3
PTP1B (Protein tyrosine phosphatase 1B)	1T4J	Asn193	Phe196	Phe280
TC-PTP (T-Cell Protein Tyrosine Phosphatase)	1L8K	Asn194	Phe197	Cys278[b]
SHP2 (Src homology-2 domain-containing protein tyrosine phosphatase-2)	3O5X	Asp437	Glu440	Thr524
LAR (Receptor-type tyrosine-protein phosphatase F, Leukocyte common antigen related)	1LAR	Ala1502	Arg1505	Cys1584
CD45 (Receptor-type tyrosine-protein phosphatase C, CD antigen CD45)	1YGR	Lys808	Arg811	Phe890
LYP (lymphoid-specific protein tyrosine phosphatase)	2P6X	Glu207	Trp210	Arg292
VHR (human vaccinia H1-related phosphatase)	1VHR	Arg104	Asp107	Glu180
PTPN9/MEG2 (protein tyrosine phosphatase PTPN9)	2PA5	Asp482	Arg485	Lys577
PTPα (Receptor-type tyrosine-protein phosphatase alpha)	6UZT	Lys413	Lys416	Tyr495

[a] Organism sources: Homo sapiens; [b] not determined in the crystal structure of 1L8K.

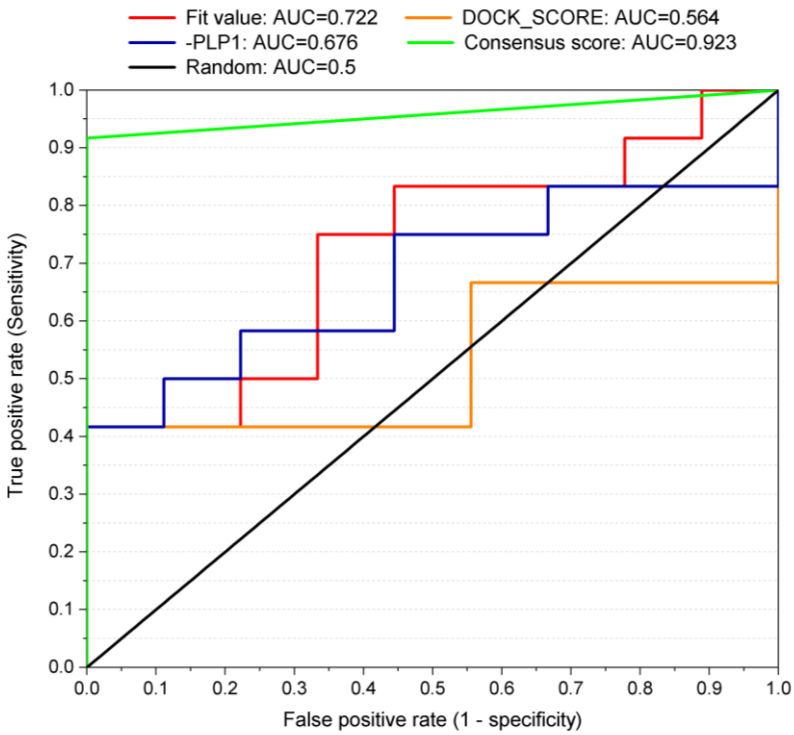
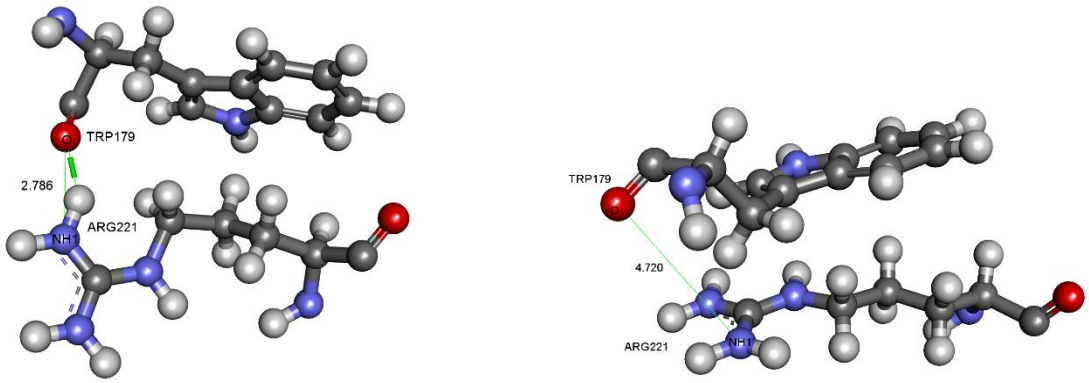
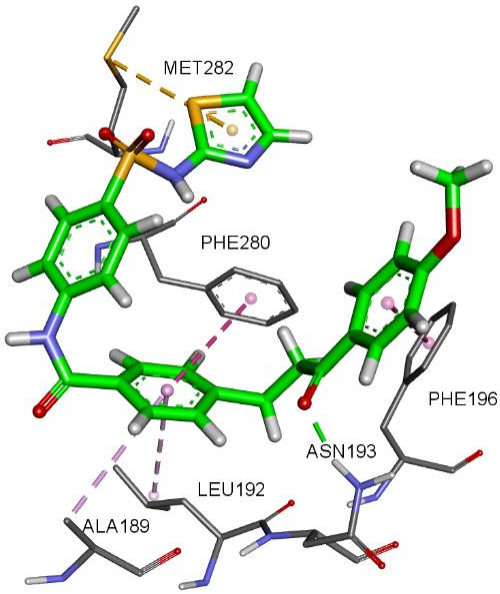


Figure S1. The ROC curve derived from different scores. When the number of highly active compounds (IC_{50} < 1 μM) identified versus the number of compounds screened by different scoring functions was monitored, the area under the ROC curve (AUC) was measured by plotting ROC curves. The consensus score was consisted of -PLP1, DOCK_SCORE from LigandFit docking and Fit value from the CBP model.



A **B**

Figure S2. The distance was measured in (A) the closed conformation (PDB code: 1PTY) and (B) the open conformation (PDB code: 1T4J).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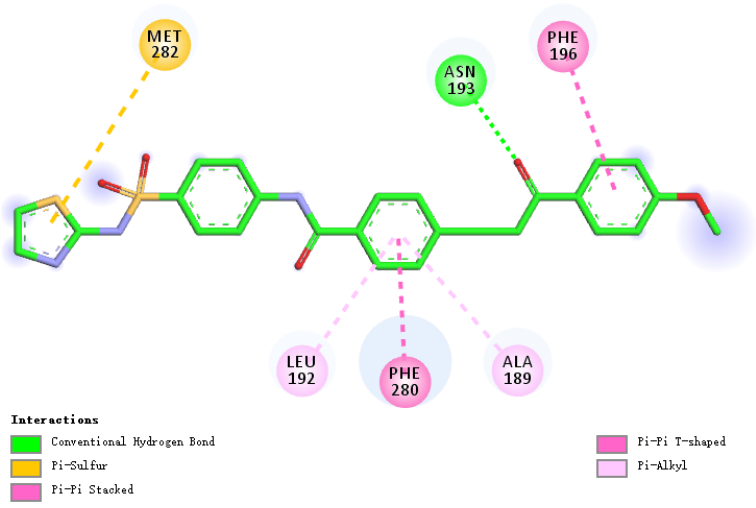
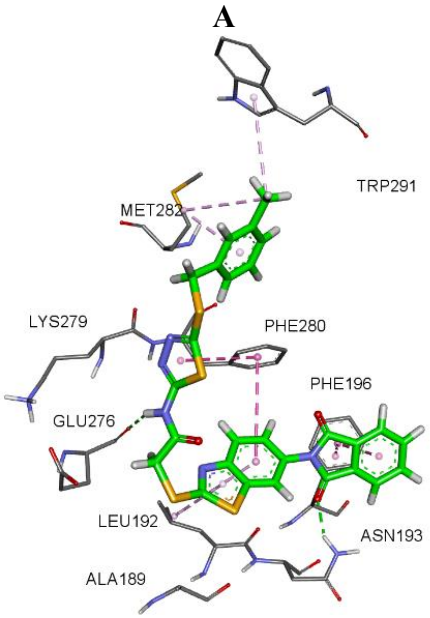
PHE280
PHE196
ASN193
LEU192
ALA189


MET 282
ASN 193
PHE 196
LEU 192
PHE 280
ALA 189
Interactions
Conventional Hydrogen Bond
Pi-Sulfur
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl

A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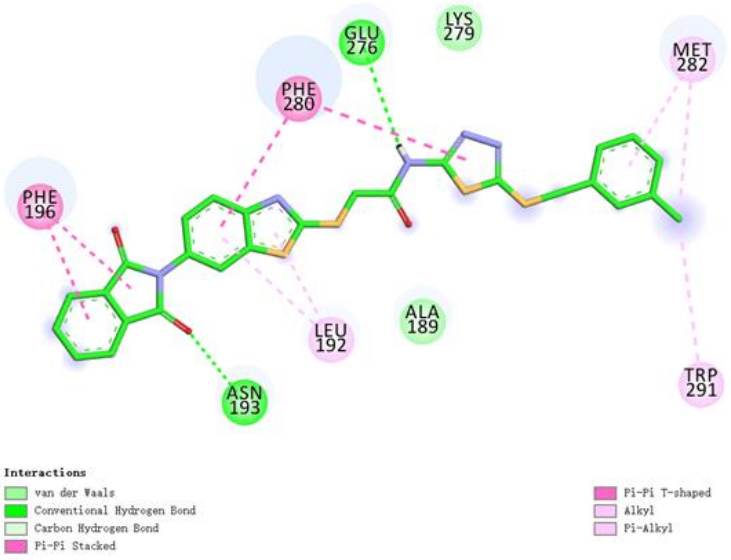
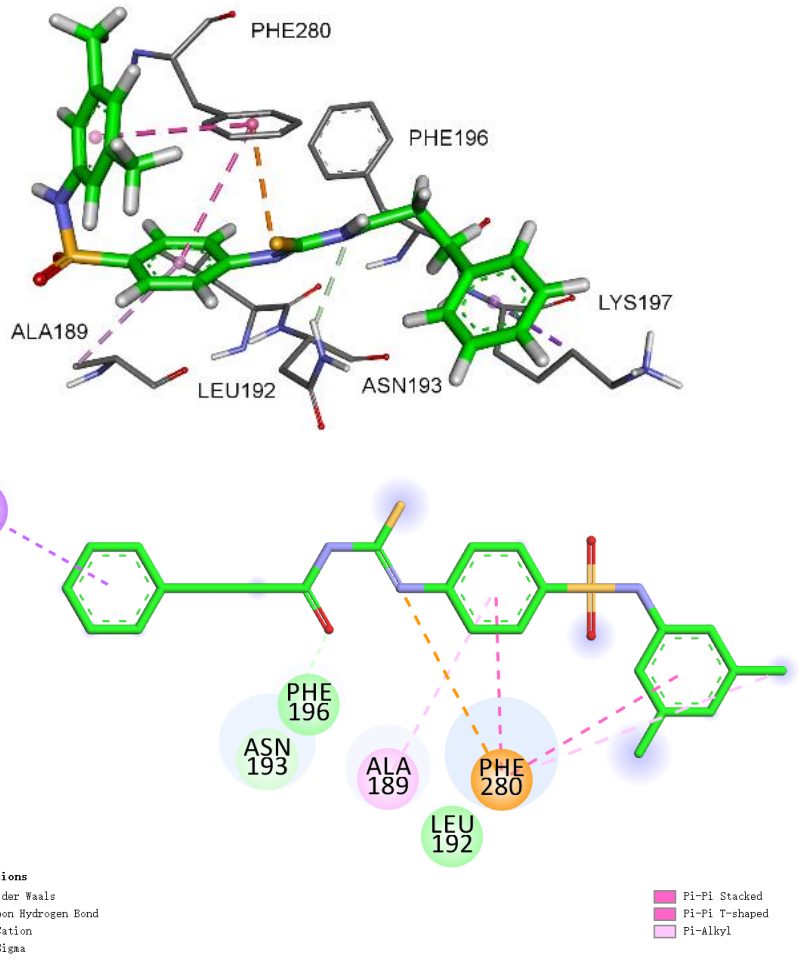
LYS279
PHE280
PHE196
GLU276
LEU192
ASN193
ALA189



B



C

Figure S3. The 3D graphics and 2D plots for binding modes of (A) **2**, (B) **H3** and (C) **H9** at PTP1B allosteric site with representative conformations from MD simulations.