Appendix. Supplementary data

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An in silico protocol for identifying potential poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors from chemical databases

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Fig. S1. Structural formulas of test set compounds with IC_{50} (PARP-1) values and relevant citations for validation of the pharmacophore model Hypo1.

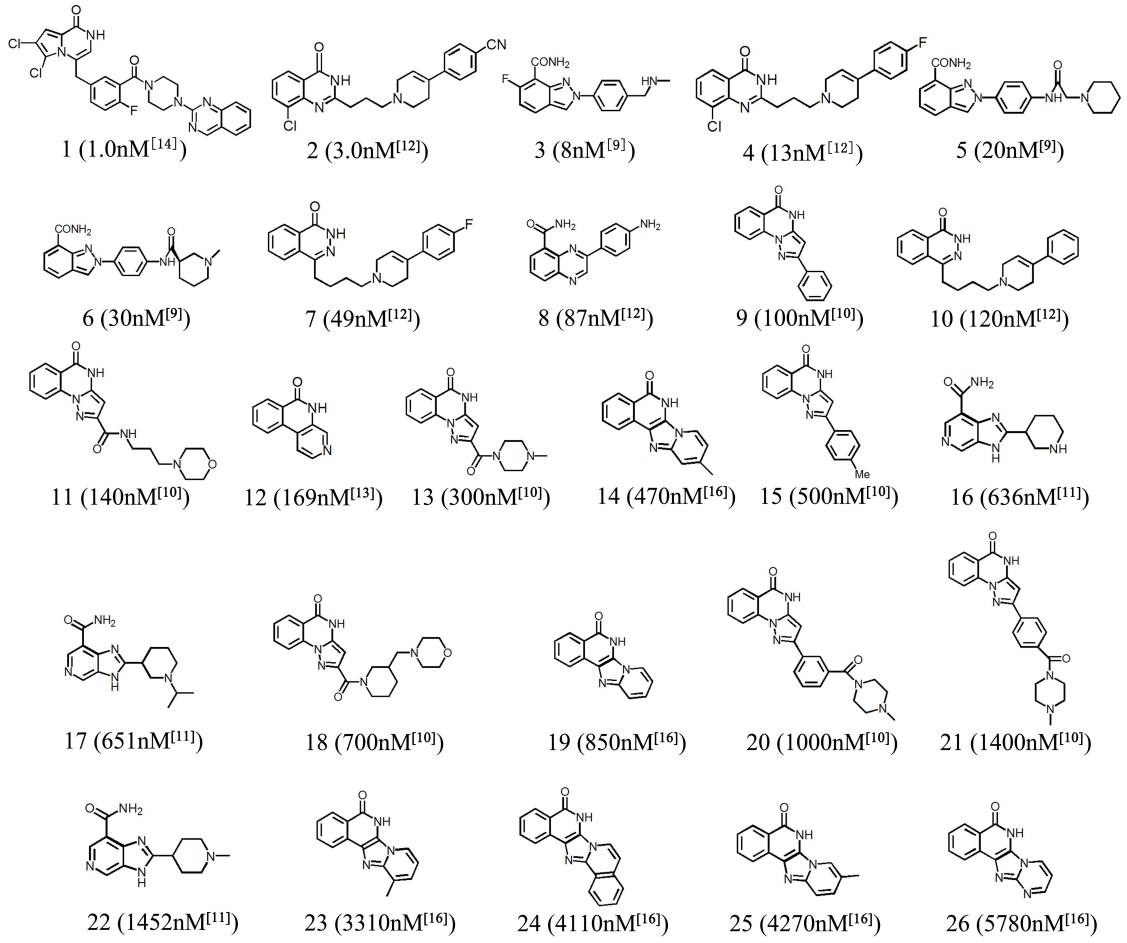


Fig. S2. The dose-response curves for compounds 4 and 5 against PARP-1. The bars indicate means ± S.D. (n= 3).

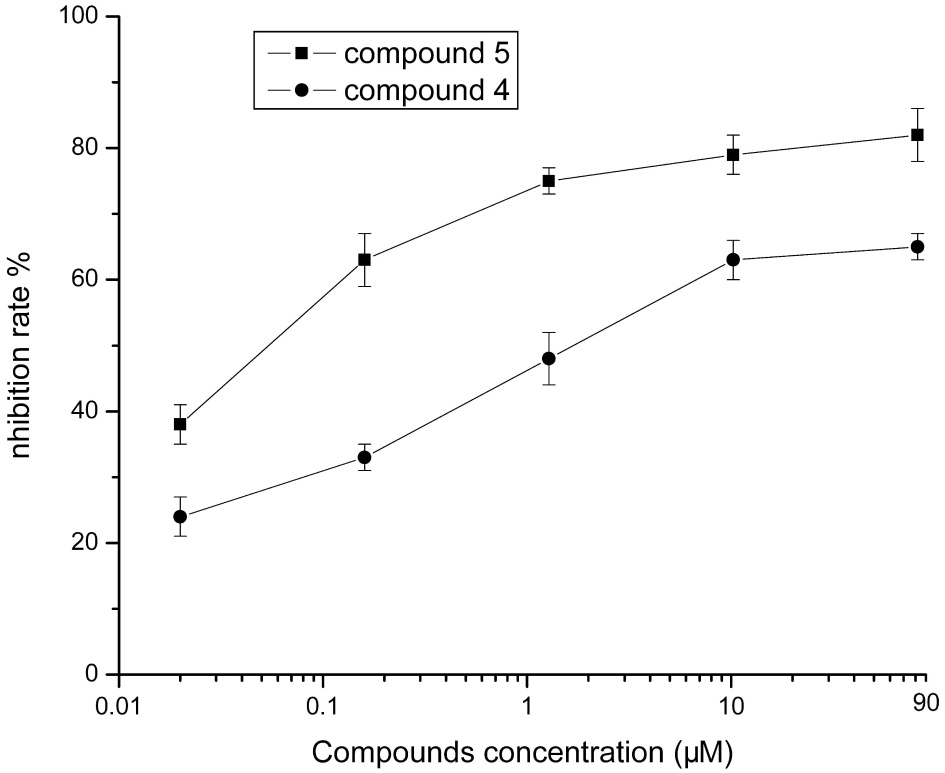
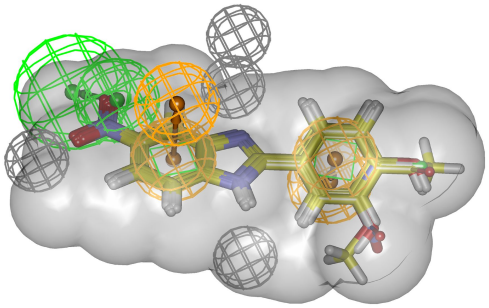


Fig. S3. Mapping of screened compounds on Hypo1 with a steric constriction. (A) Eight hit compounds chosen for biological testing. (B) Two hits (AJ-333/13050060 and AR-434/42808022) screened from Specs database. (C) Structural formulas of two hits.

A



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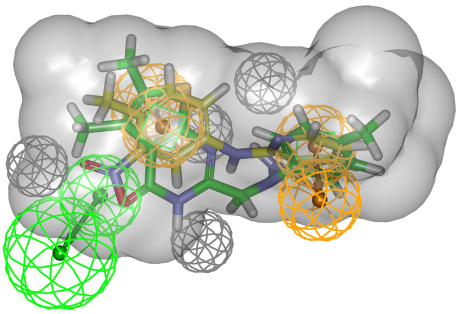
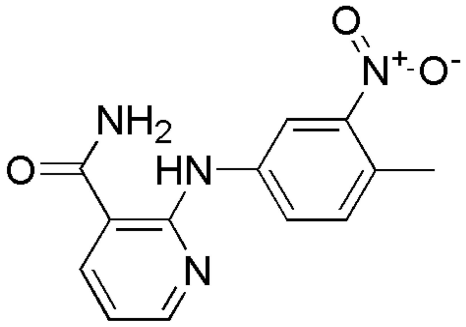


C



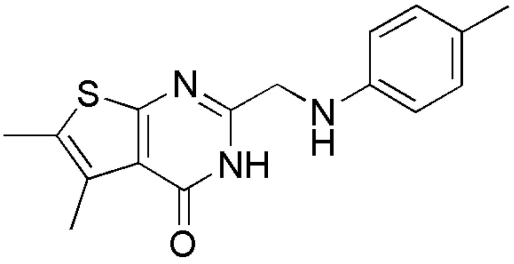


Table S1. Experimental and estimated IC_{50} values of the training set compounds based on best pharmacophore hypothesis Hypo1

Name	IC_{50} nM		Error[a]	Activity scale[b]	
	Experimental	Estimated		Experimental	Estimated
1	1.4	5	+3.6	++++	++++
2	5	5.5	+1.1	++++	++++
3	10	5.8	-1.7	++++	++++
4	16	14	-1.1	++++	++++
5	33	54	+1.6	+++	+++
6	54	51	-1.1	+++	+++
7	68	62	-1.1	+++	+++
8	82	110	+1.3	+++	+++
9	90	200	+2.2	+++	+++
10	101	56	-1.8	+++	+++
11	131	190	+1.5	+++	+++
12	150	230	+1.5	+++	+++
13	200	30	-6.7	+++	+++
14	300	540	+1.8	++	++
15	350	270	-1.3	++	+++
16	400	550	+1.4	++	++
17	540	1300	+2.4	++	++
18	600	540	-1.1	++	++
19	651	1100	+1.7	++	++
20	825	650	-1.3	++	++
21	938	790	-1.2	++	++
22	1100	550	-2.0	++	++
23	2500	550	-4.5	++	++
24	5000	6600	+1.3	+	+
25	7500	9000	+1.2	+	+
26	11200	9100	-1.2	+	+

[a] Positive value indicates that the estimated IC_{50} is higher than the experimental IC_{50}; negative value indicates that the estimated IC_{50} is lower than the experimental IC_{50}.

[b] Activity scale: $IC_{50} < 30$nM (Most active, ++++); $30 \leq IC_{50} < 300$nM (Active, +++); $300 \leq IC_{50} < 3000$nM (Moderately active, ++); ≥ 3000nM (Inactive, +).

Table S2. Test set compounds listed with their experimental, estimated activities and error values.

Name	IC_{50} nM		Error[a]	Activity scale[b]	
	Experimental	Estimated		Experimental	Estimated
1	1	4	+4.0	++++	++++
2	3	12	+4.0	++++	++++
3	8	5	-1.6	++++	++++
4	13	5	-2.6	++++	++++
5	20	6	-3.3	++++	++++
6	30	14	-2.1	+++	++++
7	49	15	-3.3	+++	++++
8	87	24	-3.6	+++	++++
9	100	126	+1.3	+++	+++
10	120	20	-6.0	+++	++++
11	140	270	+1.9	+++	+++
12	169	260	+1.5	+++	+++
13	300	280	-1.1	++	+++
14	470	574	+1.2	++	++
15	500	360	-1.4	++	++
16	636	190	-3.3	++	+++
17	651	165	-3.9	++	+++
18	700	280	-2.5	++	+++
19	850	570	-1.5	++	++
20	1000	550	-1.8	++	++
21	1400	610	-2.3	++	++
22	1452	290	-5.0	++	+++
23	3310	608	-5.4	+	++
24	4110	5100	+1.2	+	+
25	4270	3670	-1.2	+	+
26	5780	9100	+1.6	+	+

[a] Positive value indicates that the estimated IC_{50} is higher than the experimental IC_{50}; negative value indicates that the estimated IC_{50} is lower than the experimental IC_{50}.

[b] Activity scale: $IC_{50} < 30$nM (Most active, ++++); $30 \leq IC_{50} < 300$nM (Active, +++); $300 \leq IC_{50} < 3000$nM (Moderately active, ++); ≥ 3000nM (Inactive, +).

Table S3. Analyses of critical amino acids for PARP-1 inhibition from 7 co-crystal structures deposited in protein databank.

PDB ID	Tyr246	Tyr235	Ser243	Asp105	Ser203	Gly202	Lys242	Glu327
1UK0	√	√	√	√	√	√		
2RCW	√	√	√	√		√	√	√
2RD6	√	√	√			√	√	√
3GJW	√	√	√	√	√	√	√	√
3L3L	√	√	√			√	√	√
3L3W	√	√	√	√		√		√
4HHY	√	√	√			√		√

Table S4. Docking sores and fit values of eight molecules (compounds 1-8) identified using the screening protocol.

Compounds	ID	Fit value	Docking sore (kcal·mol^{-1})	% Inhibition (MDA-MB-231)
1	AF-407/32482005	4.7045	-12.5794	<50
2	AJ-077/33269004	4.9507	-15.5242	81
3	AN-353/12702001	4.9613	-15.5831	89
4	0109-0039	4.9792	-15.8314	95
5	0109-0037	4.9819	-17.7167	97
6	8005-3004	4.7266	-13.9736	<50
7	0568-0770	4.8235	-13.0253	63
8	0568-0769	4.7496	-13.4665	54