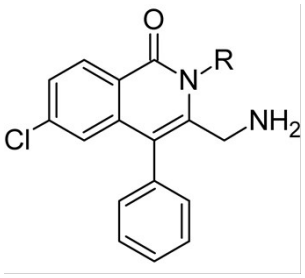
Electronic Supplementary Material (ESI) for Molecular BioSystems.

SUPPLEMENTARY MATERIAL

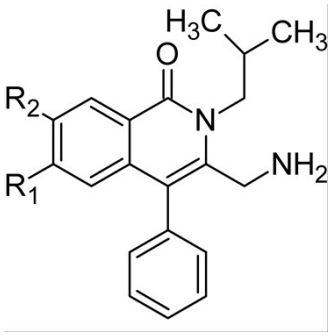
Supplementary Table 1. Structures and IC_{50} values for the compound set

Structure A



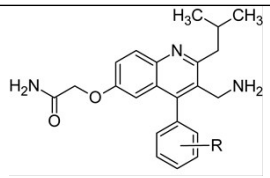
Compound	IC_{50} (nM)	R
1	8300	Et
2	1600	I-Bu

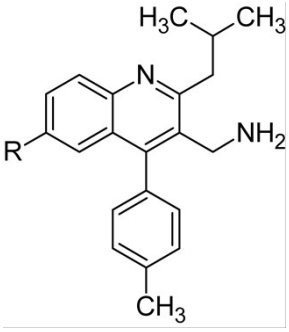
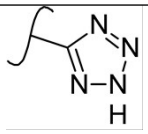
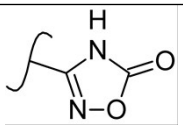
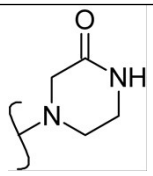
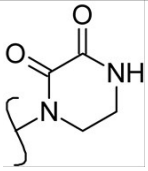
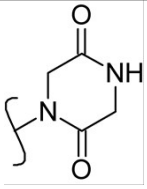
Structure B

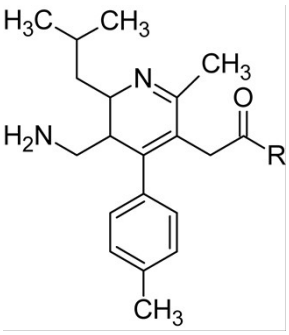
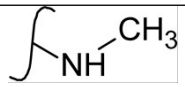
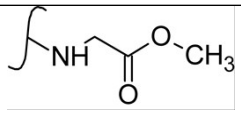
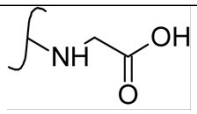
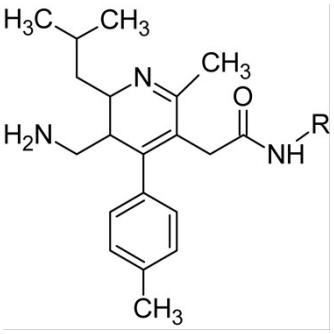
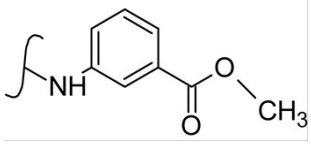
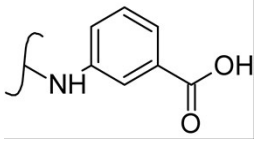
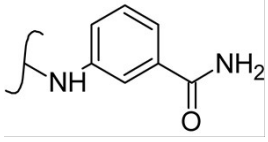


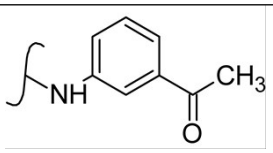
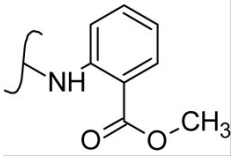
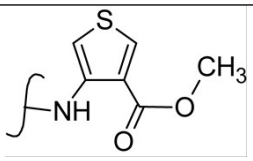
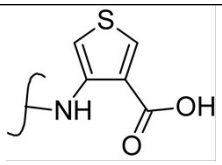
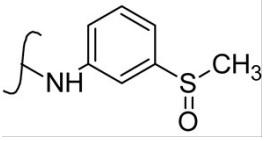
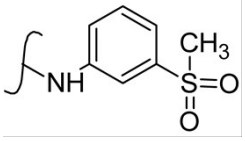
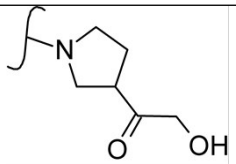
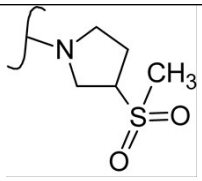
Compound	IC_{50} (nM)	R_1	R_2
3	980	CO_2H	H
4	360	$CONH_2$	H
5	1100	CN	H
6	2400	H	$CONH_2$
7	4000	$CONMe_2$	H
8	870	OMe	H
9	240	OCH_2CONH_2	H
10	1500	$CH_2CH_2CONH_2$	H

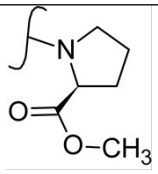
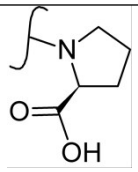
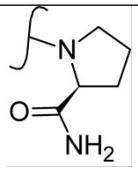
Structure C



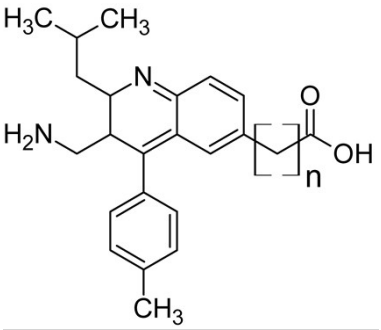
Compound	IC_{50} (nM)	R
11	34	H
12	49	3-F
13	57	3-CH_3
14	4.2	4-CH_3
Structure D		
Compound	**IC_{50} (nM)**	**R**
15	84	$OCH_2CO_2CH_3$
16	52	$OCH_2CONHCH_3$
17	7.5	$CH_2CH_2CONH_2$
18	1.8	(E)$CH{=}CHCOCH_2CO_2$
19	55	$CONH_2$
20	100	CO_2H
21	9.2	
22	11	
23	2.2	
24	2.7	
25	1.3	

Structure E		
		
Compound	**IC_{50} (nM)**	**R**
26	69	
27	17	
28	73	
Structure F		
		
Compound	**IC_{50} (nM)**	**R**
29	3.7	
30	19	
31	8.1	

32	1.8	
33	19	
34	23	
35	30	
36	2.8	
37	8.2	
Structure G		
Compound	**IC_{50} (nM)**	**R**
38	11	
39	53	

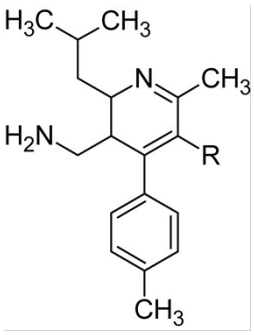
40	1.1	
41	2.9	
42	1.1	

Structure H

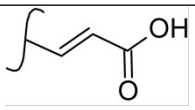
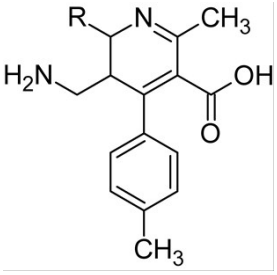
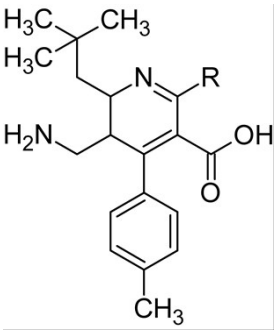


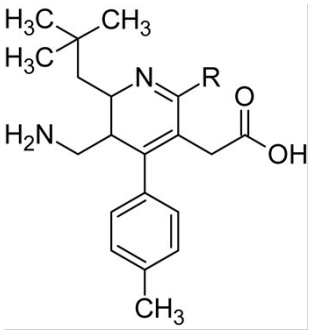
Compound	IC_{50} (nM)	n
43	23	2
44	8.7	3
45	9.6	4
46	6.6	5

Structure I



Compound	IC_{50} (nM)	R
47	18	COOH
48	20	CH_2COOH

49	39	CH_2CH_2COOH
50	66	
Structure J		
Compound	**IC_{50} (nM)**	**R**
51	57	Pr
52	58	Bu
53	18	Neopentil
Structure K		
Compound	**IC_{50} (nM)**	**R**
54	5.7	Et
55	4.4	Pr
56	19	i-Pr
57	4.6	i-Bu
58	2.5	Bn

Structure L	
	

Compound	IC_{50} (nM)	R
59	10	Me
60	5.3	Et

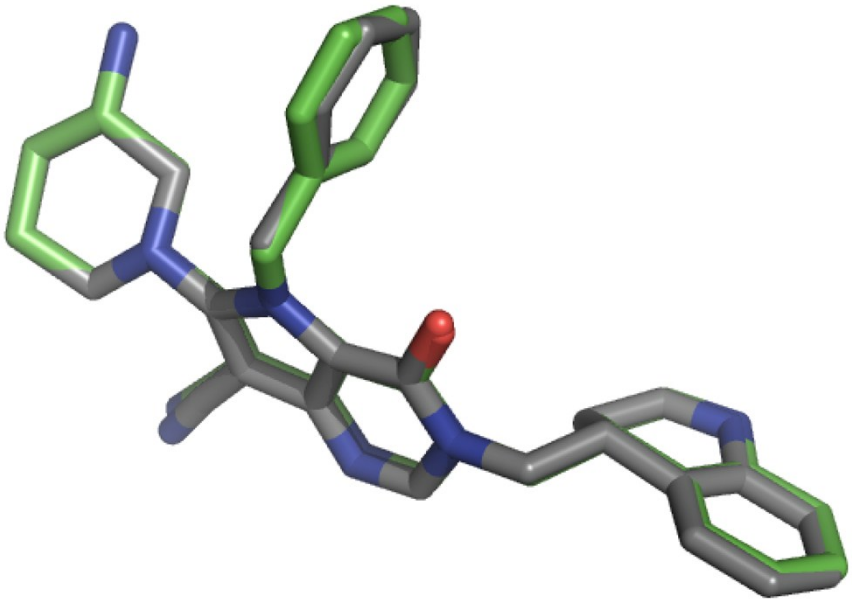
Supplementary Table 2. RMSD values obtained from the redocking validation employing five different docking protocols

Protocol	Flexible sidechain residues	Presence of structural water	Redocking – RMSD
1	Tyr547, Ser630 and Tyr666	H_2O 1 and 2	0.657 Å
2	Tyr547, and Tyr666	H_2O 1 and 2	2.260 Å
3	Ser630 and Tyr666	H_2O 1 and 2	0.733 Å
4	Tyr547, Ser630 and Tyr666	No structural water	2.262 Å
5	No flexibility	No structural water	4.603 Å

Supplementary Table 3. Compounds of the test set in each training/test splitting employed in the chance correlation validation

training / test set splitting	Compound											
1*	**10**	**15**	**17**	**20**	**23**	**28**	**29**	**35**	**38**	**51**	**58**	**60**
2	3	8	16	19	22	37	42	45	46	47	50	57
3	3	11	18	20	21	25	30	38	40	53	57	59
4	1	12	14	18	20	25	35	38	44	48	51	58
5	1	18	20	25	31	39	43	47	52	54	58	59
6	2	8	25	26	32	34	36	37	38	48	51	58
7	4	8	11	14	16	23	24	31	44	47	49	56
8	4	9	11	12	14	24	33	37	41	44	48	52
9	9	10	15	16	17	30	37	43	44	46	53	58
10	1	16	20	21	22	23	28	37	42	46	50	52
11	6	9	12	14	16	23	29	35	52	53	54	57
12	6	16	18	20	28	38	39	44	45	46	54	59
13	7	14	20	21	28	30	37	38	41	42	43	49
14	6	12	16	20	29	31	36	40	41	43	48	59
15	7	20	35	39	40	42	44	52	53	56	58	60
16	3	8	11	23	34	36	38	42	43	51	57	60
17	4	8	13	15	19	22	24	25	35	42	44	55
18	2	9	13	17	18	27	35	40	49	53	57	60
19	6	8	11	12	17	30	31	37	41	48	53	58
20	5	13	20	22	23	29	36	38	39	45	52	57

*test compounds employed in the external validation



Supplementary Figure 1. Redocking pose (carbon atoms showed in gray) of the crystallographic ligand (C atoms in dark green) - PDB: 4A5S - obtained with the best docking protocol.