Supporting Information for the paper

Cyclohexane-1,3-Dione derivatives as Future Therapists for NSCLC: QSAR Modeling, in silico ADME-Tox Properties, and structure-based drug designing approach

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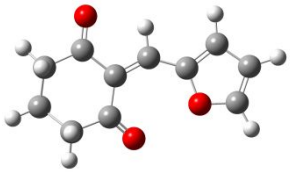
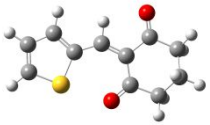
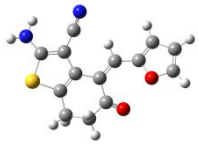
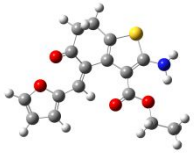
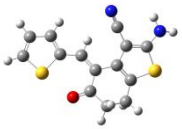
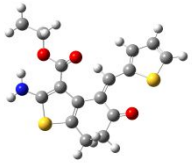
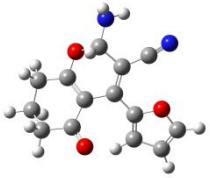
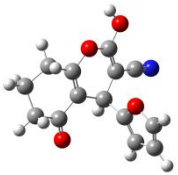
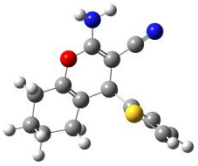
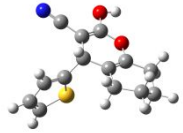
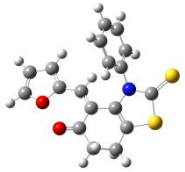
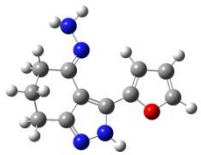
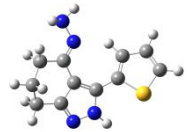
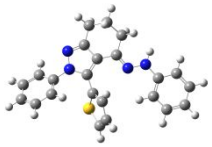
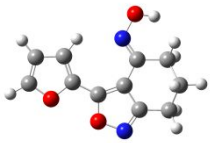
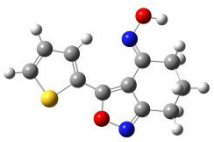
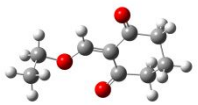
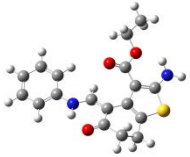
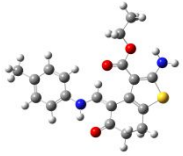
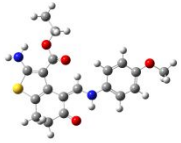
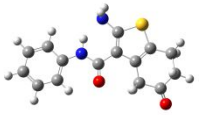
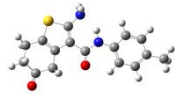
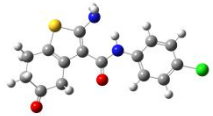
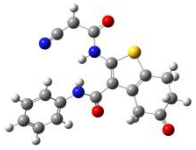
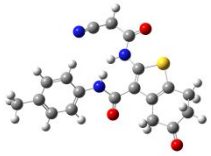
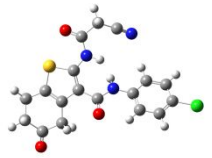
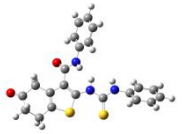
Table S1. Optimized molecular structures of cyclohexane-1,3-dione derivatives and in vitro data points of their pIC_{50} ($-LogIC_{50}$) inhibitory activity against the NSCLC cell line H460.

	3a	pIC_{50}=5.26		3b	pIC_{50}=6.41		5a	pIC_{50}=5.38		5b	pIC_{50}=5.93		5c	pIC_{50}=6.59
	5d	pIC_{50}=6.44		6a	pIC_{50}=5.24		6b	pIC_{50}=6.09		6c	pIC_{50}=6.43		6d	pIC_{50}=6.38
	8a	pIC_{50}=6.55		8b	pIC_{50}=6.54		10a	pIC_{50}=5.12		10b	pIC_{50}=5.42		10c	pIC_{50}=6.37

	10d	pIC_{50}=6.24		12a	pIC_{50}=5.97		12b	pIC_{50}=6.44		14	pIC_{50}=5.17		16a	pIC_{50}=5.27
	16b	pIC_{50}=5.14		16c	pIC_{50}=6.17		17a	pIC_{50}=5.20		17b	pIC_{50}=5.34		17c	pIC_{50}=5.58
	17d	pIC_{50}=5.78		17e	pIC_{50}=6.29		17f	pIC_{50}=6.48		19a	pIC_{50}=5.08		19b	pIC_{50}=5.64
														

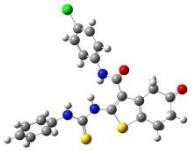
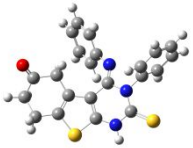
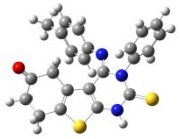
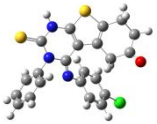
19c	pIC_{50}=6.49	20a	pIC_{50}=5.12	20b	pIC_{50}=5.24	20c	pIC_{50}=6.46	21a	pIC_{50}=5.19
									
21b	pIC_{50}=5.79	21c	pIC_{50}=5.06	22a	pIC_{50}=5.08	22b	pIC_{50}=5.63	22c	pIC_{50}=6.74

Table S2. Computed molecular descriptors used in this study to generate the predictive QSAR model.

	MV	n	d	*ae*	Stretch	Bend	S-B	Tor	NVDW	VDW	Dipole	MW	HBA	HBD	RoB	LogP	CCA
3a	150.00	1.59	1.27	20.16	1.33	17.94	0.14	4.68	1.93	9.88	4.09	190.06	3	0	1	1.12	367.60
3b	156.70	1.65	1.32	22.58	1.73	15.10	0.33	12.37	3.80	10.30	4.82	206.04	2	0	1	1.59	374.07
5a	188.50	1.68	1.43	28.21	1.28	21.24	0.08	9.12	1.80	9.36	2.92	270.05	4	1	2	1.50	434.23
5b	229.40	1.38	1.38	33.75	2.39	26.65	0.22	17.30	2.81	14.69	2.31	317.07	4	1	3	3.14	511.54
5c	196.30	1.71	1.45	30.45	1.54	17.36	0.24	18.90	3.18	9.61	3.68	286.02	3	1	2	1.97	439.67
5d	236.10	1.70	1.41	36.16	2.60	22.44	0.35	27.69	3.87	14.86	2.83	333.05	3	1	4	3.61	516.51
6a	186.20	1.62	1.37	26.07	1.93	17.25	0.04	11.97	1.94	13.15	-2.58	256.09	5	1	2	0.31	426.93
6b	180.00	1.63	1.42	25.24	0.71	14.14	-0.12	-4.16	-4.65	7.74	-2.40	257.07	5	1	2	0.63	438.95
6c	197.00	1.64	1.31	28.26	0.79	6.14	-0.03	5.36	-4.64	9.48	1.88	258.08	3	1	2	3.15	448.79
6d	190.80	1.65	1.35	27.44	0.71	6.83	-0.04	4.96	-5.00	6.78	0.01	259.07	3	1	2	2.85	445.32
8a	234.50	1.75	1.44	37.72	3.59	33.75	-0.25	14.76	5.50	17.70	1.00	339.04	2	0	2	4.15	506.16
8b	242.30	1.77	1.46	39.97	3.88	29.83	-0.11	24.65	6.52	17.95	1.68	355.02	1	0	2	4.62	509.55
10a	141.50	1.76	1.52	23.01	0.83	28.43	-0.07	-4.46	-0.43	5.74	-0.74	216.10	5	2	1	1.97	349.98
10b	291.50	1.68	1.26	43.72	2.89	30.36	0.03	-2.33	3.39	20.93	-0.27	368.16	5	1	4	5.64	587.82
10c	149.50	1.81	1.55	25.56	1.14	22.30	0.09	3.15	0.32	6.86	-0.36	232.08	4	2	1	2.73	359.77
10d	299.50	1.71	1.28	46.27	3.06	23.92	0.12	12.60	3.83	20.84	-0.06	384.14	4	1	4	6.37	594.24
12a	143.80	1.70	1.51	21.93	1.12	29.12	-0.02	-5.63	-0.15	6.46	4.27	218.07	5	1	1	2.89	378.97
12b	151.80	1.75	1.54	24.47	1.20	21.55	0.09	6.44	-0.13	7.16	4.73	234.05	4	1	1	3.62	388.44
14	139.50	1.56	1.21	17.91	1.19	4.45	0.27	5.85	0.76	11.68	3.20	168.08	3	0	2	0.41	369.16
16a	164.00	1.70	1.31	25.11	1.46	6.60	0.26	-4.60	2.13	14.06	2.42	215.10	3	1	2	2.00	413.82
16b	180.20	1.68	1.27	27.03	1.52	6.76	0.26	-5.33	1.93	14.72	2.41	229.11	3	1	2	2.50	445.52
16c	188.00	1.67	1.30	27.76	1.73	9.07	0.32	-4.60	2.52	16.81	2.41	245.11	4	1	3	2.10	459.84
17a	213.70	1.70	1.38	32.64	1.54	11.02	0.21	-1.36	2.08	13.72	1.81	295.08	4	2	3	2.12	475.64
17b	243.40	1.73	1.41	38.70	2.58	16.19	0.36	7.76	3.01	19.01	1.31	342.10	4	2	5	3.77	552.80
17c	229.50	1.68	1.34	34.47	1.60	11.19	0.21	-2.10	1.87	14.37	1.79	309.09	4	2	3	2.62	507.33
17d	259.70	1.72	1.37	40.61	3.06	18.84	0.44	9.56	4.41	19.81	1.26	356.12	4	2	5	4.26	581.98
17e	235.60	1.68	1.38	35.16	1.81	13.49	0.26	-1.36	2.47	16.46	1.83	325.09	5	2	4	2.22	521.65

17f	267.40	1.71	1.39	41.34	2.85	18.64	0.41	7.79	3.41	21.75	1.24	372.11	5	2	6	3.87	598.77
19a	203.30	1.72	1.41	31.85	0.74	10.98	0.05	3.12	-1.93	8.95	-12.79	286.08	3	2	3	1.67	469.56
19b	219.60	1.70	1.37	33.77	0.77	10.99	0.04	2.50	-2.29	9.58	-13.11	300.09	3.00	2.00	3.00	2.17	500.85
19c	215.30	1.72	1.49	33.79	0.74	10.88	0.06	3.22	-2.20	9.37	-12.14	320.04	3.00	2.00	3.00	2.55	493.45
20a	244.00	1.71	1.45	37.64	0.85	12.36	0.08	5.89	-4.13	9.56	-9.31	353.08	4.00	2.00	7.00	0.89	551.47
20b	260.30	1.69	1.41	39.55	0.91	12.52	0.08	5.18	-4.34	10.21	-9.56	367.10	4.00	2.00	7.00	1.39	583.14
20c	256.00	1.71	1.51	39.58	0.86	12.40	0.08	5.80	-4.43	9.98	-8.21	387.04	4.00	2.00	7.00	1.77	575.28
21a	289.40	1.79	1.46	48.44	1.03	13.45	0.11	-3.32	-4.39	17.21	-18.08	421.09	4.00	3.00	7.00	2.99	632.41
21b	305.60	1.77	1.42	50.36	1.08	13.60	0.10	-3.93	-4.82	17.82	-17.90	435.11	2.00	3.00	7.00	3.49	0.00
21c	301.30	1.79	1.51	50.38	1.01	13.36	0.10	-3.21	-4.85	17.60	-17.15	455.05	2.00	3.00	7.00	3.86	655.78
22a	284.60	1.76	1.41	46.47	3.38	21.60	-0.02	21.71	1.62	28.51	-8.61	403.08	2.00	1.00	2.00	4.26	518.96
22b	299.80	1.75	1.39	48.23	3.42	21.69	-0.02	21.01	1.26	29.15	-8.72	417.10	2.00	1.00	2.00	4.76	543.59
22c	293.90	1.77	1.48	48.30	3.38	21.63	-0.01	21.79	1.25	28.96	-8.18	437.04	2.00	1.00	2.00	4.97	547.67

Table S2. continuation

	CMA	**MR**	**LogS**	**BI**	**MTI**	**PSA**	**TC**	**wi**	**ET**	**DM**	**E_{HOMO}**	**E_{LUMO}**	**E_{gap}**	**x**	**μ**	**η**	**ω**
3a	181.05	5.17	-1.39	41807	2238	43.37	6.9E-03	301	-17710.04	1.71	-6.19	-2.41	3.78	4.30	-4.30	1.89	4.89
3b	187.01	5.76	-1.87	41807	2238	34.14	6.9E-03	301	-26498.79	0.96	-6.28	-2.50	3.78	4.39	-4.39	1.89	5.10
5a	226.14	7.37	-2.23	128856	4763	76.11	9.4E-04	652	-32588.14	3.59	-5.31	-1.86	3.45	3.58	-3.58	1.73	3.72
5b	272.70	8.47	-3.07	256718	7003	78.62	3.8E-04	983	-37348.83	5.58	-4.99	-1.51	3.48	3.25	-3.25	1.74	3.03
5c	231.81	7.96	-2.66	128856	4763	66.88	9.4E-04	652	-41376.86	4.03	-5.39	-2.01	3.38	3.70	-3.70	1.69	4.06
5d	278.72	9.07	-3.49	256718	7003	69.39	3.8E-04	983	-46137.56	5.85	-5.05	-1.67	3.38	3.36	-3.36	1.69	3.34
6a	223.62	6.63	-1.80	120455	4472	85.34	9.4E-04	609	-23832.64	4.05	-5.79	-1.98	3.81	3.88	-3.88	1.91	3.96
6b	225.88	6.64	-1.88	120455	4397	79.55	9.4E-04	609	-24373.25	7.77	-5.98	-1.71	4.27	3.84	-3.84	2.14	3.46
6c	234.80	7.34	-2.93	9546	4052	59.04	1.1E-03	535	-31147.81	4.81	-5.69	-0.53	5.16	3.11	-3.11	2.58	1.88
6d	231.52	7.13	-2.87	95461	3983	72.25	1.1E-03	535	-46130.76	6.46	-6.01	-0.69	5.32	3.35	-3.35	2.66	2.11
8a	274.42	9.90	-4.37	259095	8073	29.54	1.4E-04	1094	-46130.76	4.72	-5.25	-2.16	3.09	3.71	-3.71	1.55	4.45
8b	279.04	10.49	-4.79	259095	8073	20.31	1.4E-04	1094	-54919.50	4.01	-5.29	-2.28	3.01	3.78	-3.78	1.51	4.76
10a	171.13	6.17	-2.32	57370	3030	72.00	2.0E-03	402	-19607.80	2.35	-5.14	-0.83	4.31	2.99	-2.99	2.15	2.07

10b	328.20	11.20	-6.54	581104	15254	49.22	1.205	1968	-32182.29	0.74	-4.88	-1.11	3.77	2.99	-2.99	1.88	2.38
10c	178.01	6.77	-2.76	57370	3030	62.77	0.002	402	-28396.28	2.49	-5.28	-1.07	4.21	3.17	-3.17	2.11	2.39
10d	332.81	11.79	-6.96	581104	15254	39.99	1.205	1968	-40970.84	0.85	-4.85	-1.09	3.76	2.97	-2.97	1.88	2.34
12a	190.89	5.74	-2.28	57370	2915	63.41	2.0E-03	402	-20687.32	3.27	-5.69	-1.51	4.17	3.60	-3.60	2.09	3.11
12b	197.59	6.34	-2.71	57370	2915	54.18	2.0E-03	402	-29475.94	3.46	-5.77	-1.69	4.08	3.73	-3.73	2.04	3.42
14	181.03	4.45	-1.04	28907	1498	43.37	2.4E-02	203	-15583.15	1.84	-6.00	-1.40	4.60	3.70	-3.70	2.30	2.97
16a	210.95	6.25	-2.35	84372	3577	46.17	3.4E-03	469	-19277.68	1.68	-5.91	-1.73	4.18	3.82	-3.82	2.09	3.48
16b	230.01	6.71	-2.70	114101	4304	46.17	2.8E-03	564	-20347.64	2.18	-5.78	-1.66	4.12	3.72	-3.72	2.06	3.35
16c	237.97	6.87	-2.40	152719	4966	55.40	2.0E-03	676	-22394.01	3.45	-5.56	-1.55	4.01	3.55	-3.55	2.00	3.15
17a	255.13	8.45	-3.34	219802	6885	78.91	4.7E-04	919	-34155.64	3.07	-5.06	-1.38	3.68	3.22	-3.22	1.84	2.82
17b	303.24	9.55	-4.19	406980	9641	81.42	1.9E-04	1319	-38916.38	4.97	-4.73	-0.99	3.74	2.86	-2.86	1.87	2.19
17c	274.21	8.92	-3.70	278685	8004	78.91	3.9E-04	1066	-35225.59	2.57	-4.99	-1.33	3.67	3.16	-3.16	1.83	2.72
17d	322.02	10.02	-4.54	501289	11015	81.42	1.6E-04	1502	-39986.33	4.82	-4.67	-0.94	3.73	2.81	-2.81	1.87	2.11
17e	282.15	9.07	-3.40	351436	8992	88.14	2.7E-04	1235	-37271.94	1.62	-4.88	-1.24	3.64	3.06	-3.06	1.82	2.57
17f	330.25	10.17	-4.24	615292	12207	90.65	1.1E-04	1710	-42032.68	4.21	-4.58	-0.86	3.72	2.72	-2.72	1.86	1.98
19a	248.93	7.96	-2.97	175434	5948	72.19	6.6E-04	805	-33692.83	6.73	-5.75	-1.26	4.48	3.50	-3.50	2.24	2.74
19b	268.04	8.42	-3.32	224578	6960	72.19	5.4E-04	939	-34762.77	6.64	-5.57	-1.23	4.34	3.40	-3.40	2.17	2.66
19c	263.86	8.45	-3.68	224578	6555	72.19	5.4E-04	939	-46198.85	7.72	-5.85	-1.43	4.42	3.64	-3.64	2.21	3.00
20a	300.66	9.40	-3.26	496961	10783	99.06	1.4E-04	1490	-40356.60	4.36	-6.05	-1.54	4.51	3.80	-3.80	2.25	3.20
20b	319.79	9.86	-3.61	604608	12216	99.06	1.1E-04	1681	-41426.55	4.40	-5.94	-1.51	4.43	3.72	-3.72	2.22	3.13
20c	315.64	9.89	-3.97	604608	11640	99.06	1.1E-04	1681	-52862.63	5.20	-6.15	-1.67	4.48	3.91	-3.91	2.24	3.41
21a	353.15	12.19	-5.54	845619	17054	70.23	1.968	2304	-53358.46	5.51	-5.78	-1.65	4.13	3.71	-3.71	2.07	3.34
21b	0.00	12.66	-5.89	998530	18937	70.23	1.607	2551	-54428.41	5.80	-5.75	-1.61	4.13	3.68	-3.68	2.07	3.28
21c	368.48	12.69	-6.24	998530	18193	70.23	1.607	2551	-65864.48	4.38	-5.87	-1.76	4.12	3.82	-3.82	2.06	3.53
22a	284.06	11.93	-5.24	535954	13596	44.70	1.607	1813	-51278.37	5.26	-5.71	-1.39	4.32	3.55	-3.55	2.16	2.91
22b	298.86	12.40	-5.59	637839	15189	44.70	1.312	2021	-52347.95	3.89	-4.29	-1.29	2.99	2.79	-2.79	1.50	2.60
22c	302.57	12.43	-5.95	637839	14562	44.70	1.312	2021	-63784.01	3.10	-5.76	-1.53	4.23	3.64	-3.64	2.12	3.14

Table S3. Correlation matrix generated by PCA analyses.

Variables	MV	n	d	αe	Stretch	Bend	S-B	Tor	NVDW	VDW	Dipole	MW	HBA	HBD	RoB	LogP	CCA	CMA	MR	LogS	BI	MTI	PSA	TC	wi	ET	DM	EHOMO	ELUMO	Egap	x	μ	η	ω
MV	**1.0**	0.3	0.1	1.0	0.5	0.2	0.0	0.3	-0.1	0.8	-0.6	1.0	-0.2	0.4	0.7	0.6	0.5	0.6	1.0	-0.9	0.9	1.0	0.1	0.7	1.0	-0.8	0.2	0.4	0.2	-0.2	-0.3	0.3	-0.2	-0.2
n	0.3	**1.0**	0.5	0.4	0.1	0.1	-0.2	0.0	-0.1	0.2	-0.4	0.4	-0.2	0.4	0.2	0.4	0.1	0.1	0.5	-0.5	0.4	0.4	-0.1	0.4	0.4	-0.5	0.0	0.1	0.1	0.0	-0.1	0.1	0.0	-0.1
d	0.1	0.2	**1.0**	0.2	-0.1	0.4	-0.4	0.1	-0.3	-0.2	-0.3	0.3	0.0	0.4	0.1	0.1	0.0	0.0	0.2	-0.1	0.2	0.1	0.3	0.1	0.2	-0.4	0.4	0.0	-0.1	0.0	0.1	-0.1	0.0	0.0
αe	1.0	0.2	0.2	**1.0**	0.5	0.2	-0.1	0.3	-0.1	0.7	-0.6	1.0	-0.3	0.5	0.7	0.7	0.4	0.5	1.0	-0.9	0.9	1.0	0.1	0.7	1.0	-0.9	0.2	0.4	0.1	-0.2	-0.3	0.3	-0.2	-0.2
Stretch	0.5	0.1	-0.1	0.5	**1.0**	0.6	0.0	0.7	0.8	0.8	0.2	0.4	-0.3	-0.4	-0.1	0.7	0.3	0.4	0.5	-0.5	0.3	0.4	-0.4	0.3	0.3	-0.4	-0.2	0.6	-0.1	-0.7	-0.3	0.3	-0.7	0.1
Bend	0.2	0.1	0.4	0.2	0.6	**1.0**	-0.3	0.4	0.5	0.3	0.2	0.2	0.0	-0.3	-0.2	0.5	0.1	0.1	0.2	-0.3	0.1	0.2	-0.3	0.2	0.1	-0.2	-0.2	0.5	-0.2	-0.6	-0.2	0.2	-0.6	0.1
S-B	0.0	-0.2	-0.4	-0.1	0.0	-0.3	**1.0**	0.0	0.3	0.1	0.3	-0.1	0.2	0.2	0.2	-0.1	0.1	0.1	-0.1	0.1	0.0	-0.1	0.3	-0.2	0.0	0.2	-0.3	0.2	0.1	-0.2	-0.2	0.2	-0.2	-0.1
Tor	0.3	0.0	0.1	0.3	0.7	0.5	0.0	**1.0**	0.5	0.4	0.1	0.3	-0.5	-0.5	-0.2	0.3	0.2	0.2	0.3	-0.2	0.0	0.1	-0.3	0.1	0.1	-0.4	0.1	0.2	-0.2	-0.4	0.0	0.0	-0.4	0.2
NVDW	-0.1	-0.1	-0.3	-0.1	0.8	0.6	0.3	0.7	**1.0**	0.4	0.6	-0.1	-0.1	-0.5	-0.4	0.3	0.1	0.1	-0.1	0.0	-0.2	-0.2	-0.4	-0.2	-0.2	0.2	-0.5	0.6	-0.2	-0.8	-0.2	0.2	-0.8	0.2
VDW	0.8	0.2	-0.2	0.7	0.8	0.3	0.1	0.5	0.7	**1.0**	-0.2	0.7	-0.3	0.0	0.2	0.7	0.4	0.4	0.7	-0.7	0.6	0.7	-0.3	0.6	0.7	-0.5	-0.1	0.5	0.1	-0.4	-0.3	0.3	-0.4	-0.1
Dipole	-0.6	-0.4	-0.3	-0.6	0.2	0.2	0.3	0.1	0.6	-0.2	**1.0**	-0.6	0.3	-0.7	-0.6	-0.1	-0.1	-0.2	-0.6	0.5	-0.7	-0.7	-0.3	-0.6	-0.7	0.6	-0.5	0.2	-0.1	-0.3	-0.1	0.1	-0.3	0.1
MW	1.0	0.3	0.3	1.0	0.4	0.2	-0.1	0.3	-0.1	0.7	-0.6	**1.0**	-0.2	0.5	0.7	0.6	0.5	0.5	1.0	-0.9	0.9	1.0	0.2	0.7	1.0	-0.9	0.3	0.3	0.1	-0.2	-0.3	0.3	-0.2	-0.2
HBA	-0.2	-0.2	0.0	-0.3	-0.3	0.0	0.2	-0.5	-0.1	-0.3	0.3	-0.2	**1.0**	0.3	0.1	-0.3	0.1	0.1	-0.3	0.3	-0.2	-0.2	0.6	-0.3	-0.2	0.5	-0.1	0.2	0.4	0.1	-0.4	0.4	0.1	-0.4
HBD	0.4	0.3	0.6	0.5	-0.4	-0.3	0.2	-0.5	-0.5	0.0	-0.7	0.5	0.3	**1.0**	0.7	0.0	0.1	0.2	0.4	-0.4	0.6	0.5	0.7	0.3	0.5	-0.4	0.3	0.1	0.4	0.2	-0.3	0.3	0.2	-0.5
RoB	0.7	0.2	0.1	0.7	-0.1	-0.2	0.2	-0.2	-0.4	0.2	-0.6	0.7	0.1	0.7	**1.0**	0.1	0.4	0.4	0.6	-0.5	0.8	0.7	0.6	0.3	0.7	-0.5	0.3	0.0	0.2	0.1	-0.1	0.1	0.1	-0.2
LogP	0.6	0.4	0.1	0.7	0.7	0.5	-0.1	0.3	0.5	0.7	-0.1	0.6	-0.3	0.0	0.1	**1.0**	0.3	0.4	0.7	-0.8	0.5	0.6	-0.4	0.5	0.6	-0.5	-0.1	0.6	0.3	-0.3	-0.5	0.5	-0.3	-0.3
CCA	0.5	0.1	0.0	0.4	0.3	0.1	0.1	0.2	0.1	0.4	-0.1	0.5	0.1	0.1	0.4	0.3	**1.0**	1.0	0.4	-0.4	0.3	0.4	0.2	0.1	0.4	-0.4	0.1	0.3	0.2	-0.1	-0.3	0.3	-0.1	-0.2
CMA	0.6	0.1	0.0	0.5	0.4	0.1	0.1	0.2	0.1	0.4	-0.2	0.5	0.1	0.2	0.6	0.4	1.0	**1.0**	0.5	-0.5	0.4	0.5	0.2	0.2	0.5	-0.5	0.1	0.3	0.2	-0.2	-0.3	0.3	-0.2	-0.2
MR	1.0	0.4	0.2	1.0	0.5	0.2	-0.1	0.3	-0.1	0.7	-0.6	1.0	-0.3	0.6	0.8	0.8	0.6	0.2	**1.0**	-1.0	0.9	1.0	0.1	0.8	1.0	-0.9	0.2	0.4	0.1	-0.2	-0.3	0.3	-0.2	-0.2
LogS	-0.9	-0.5	-0.1	-0.9	-0.5	-0.3	0.1	-0.2	0.0	-0.7	0.5	-0.9	0.3	-0.4	-0.5	-0.8	-0.4	-0.5	-1.0	**1.0**	-0.8	-0.9	0.1	-0.8	-0.9	0.8	0.0	-0.4	-0.2	0.2	0.4	-0.4	0.2	0.2
BI	0.9	0.4	0.2	0.9	0.3	0.1	0.0	0.0	-0.2	0.6	-0.7	0.9	-0.2	0.6	0.8	0.5	0.5	0.4	0.9	-0.8	**1.0**	1.0	0.2	0.8	1.0	-0.8	0.2	0.2	0.1	-0.1	-0.2	0.2	-0.1	-0.2
MTI	1.0	0.4	0.1	1.0	0.4	0.2	-0.1	0.1	-0.2	0.7	-0.7	1.0	-0.2	0.5	0.7	0.7	0.4	0.5	1.0	-0.9	1.0	**1.0**	0.1	0.8	1.0	-0.8	0.1	0.3	0.1	-0.2	-0.3	0.3	-0.2	-0.2
PSA	0.1	-0.1	0.3	0.1	-0.4	-0.3	0.3	-0.3	-0.4	-0.3	-0.3	0.2	0.6	0.7	0.6	-0.4	0.2	0.2	0.1	0.1	0.2	0.1	**1.0**	-0.2	0.2	-0.1	0.4	0.1	0.3	0.2	-0.2	0.2	0.2	-0.4
TC	0.7	0.3	0.1	0.7	0.3	0.2	-0.2	0.1	-0.2	0.6	-0.6	0.7	-0.3	0.3	0.3	0.5	0.1	0.2	0.8	-0.8	0.8	0.8	-0.2	**1.0**	0.8	-0.6	0.0	0.1	0.0	0.0	-0.1	0.1	0.0	-0.1
wi	1.0	0.3	0.2	1.0	0.3	0.1	0.0	0.1	-0.2	0.7	-0.7	1.0	-0.2	0.5	0.7	0.6	0.4	0.5	1.0	-0.9	1.0	1.0	0.2	0.3	**1.0**	-0.8	0.2	0.3	0.1	-0.1	-0.2	0.2	-0.1	-0.2

ET	-0.8	-0.5	-0.4	-0.9	-0.4	-0.2	0.2	-0.4	0.2	-0.5	0.6	-0.9	0.5	-0.4	-0.5	-0.5	-0.4	-0.5	-0.9	0.8	-0.8	-0.8	-0.1	-0.2	-0.9	**1.0**	-0.4	-0.1	0.0	0.1	0.1	-0.1	0.1	0.0
DM	0.2	0.0	0.8	0.2	-0.2	-0.2	-0.3	0.1	-0.5	-0.1	-0.5	0.3	-0.1	0.3	0.3	-0.1	0.1	0.1	0.2	0.0	0.2	0.1	0.4	0.0	0.2	-0.4	**1.0**	-0.1	0.1	0.3	0.0	0.0	0.3	-0.1
EHOMO	0.4	0.1	0.0	0.4	0.6	0.5	0.2	0.2	0.6	0.5	0.2	0.3	0.2	0.1	0.0	0.7	0.3	0.3	0.4	-0.4	0.2	0.3	0.1	0.1	0.6	-0.1	-0.1	**1.0**	0.4	-0.6				
ELUMO	0.2	0.1	-0.1	0.1	-0.1	-0.2	0.1	-0.2	-0.2	0.1	-0.1	0.1	0.4	0.4	0.2	0.3	0.2	0.2	0.1	-0.2	0.1	0.1	0.3	0.0	0.1	0.0	0.1	0.4	**1.0**	0.5				
Egap	-0.2	0.0	0.0	-0.2	-0.7	-0.6	-0.2	-0.4	-0.8	-0.4	-0.3	-0.2	0.1	0.2	0.1	-0.3	-0.1	-0.2	-0.2	0.2	-0.1	-0.2	0.2	0.0	-0.1	0.1	0.3	-0.6	0.5	**1.0**				
x	-0.3	-0.1	0.1	-0.3	-0.3	-0.2	-0.2	0.0	-0.2	-0.3	-0.1	-0.3	-0.4	-0.3	-0.1	-0.5	-0.3	-0.3	-0.3	0.4	-0.2	-0.3	-0.2	-0.1	-0.2	0.1	0.0	-0.9	-0.8	0.1	**1.0**			
μ	0.3	0.1	-0.1	0.3	0.3	0.2	0.2	0.0	0.2	0.3	0.1	0.3	0.4	0.3	0.1	0.6	0.3	0.3	0.3	-0.4	0.2	0.3	0.2	0.1	0.2	-0.1	0.0	0.9	0.8	-0.1	-1.0	**1.0**		
η	-0.2	0.0	0.0	-0.2	-0.7	-0.6	-0.2	-0.4	-0.8	-0.4	-0.3	-0.2	0.1	0.2	0.1	-0.3	-0.1	-0.2	-0.2	0.2	-0.1	-0.2	0.2	0.0	-0.1	0.1	0.3	-0.6	0.5	1.0	0.1	-0.1	**1.0**	
ω	-0.2	-0.1	0.0	-0.2	0.1	0.1	-0.1	0.2	0.2	-0.1	0.1	-0.2	-0.4	-0.5	-0.2	-0.3	-0.2	-0.2	-0.2	0.2	-0.2	-0.2	-0.4	-0.1	-0.2	0.0	-0.1	-0.5	-1.0	-0.4	0.8	-0.8	-0.4	**1.0**

Table S4. Y-randomization test

Model	R	R^2	Q^2
Original	0.919239	0.849502	0.637215
Random 1	0.562271	0.316149	-0.51072
Random 2	0.500554	0.250554	-2.92671
Random 3	0.562972	0.316937	-0.42633
Random 4	0.498081	0.248085	-0.78709
Random 5	0.560655	0.314334	-0.3577
Random 6	0.375947	0.141336	-1.09184
Random 7	0.414505	0.171814	-0.92186
Random 8	0.56627	0.320662	-0.83537
Random 9	0.44976	0.202284	-2.48887
Random 10	0.577905	0.333974	-0.52828
Random 11	0.604269	0.365141	-0.39359
Random 12	0.58246	0.339259	-0.42915
Random 13	0.552771	0.305556	-0.67212
Random 14	0.34803	0.121125	-1.05833
Random 15	0.545193	0.297235	-1.59849
Random 16	0.432948	0.187444	-0.77693

Random 17	0.463728	0.215044	-0.54455
Random 18	0.712514	0.507676	0.073181
Random 19	0.544496	0.296476	-0.53499
Random 20	0.523704	0.274266	-0.57623
Random 21	0.499014	0.249015	-0.52583
Random 22	0.504403	0.254422	-0.79175
Random 23	0.35815	0.128272	-1.0279
Random 24	0.545471	0.297539	-1.19761
Random 25	0.423384	0.179254	-1.70443
Random 26	0.445998	0.198914	-1.25732
Random 27	0.494131	0.244166	-0.67882
Random 28	0.708799	0.502396	-0.11524
Random 29	0.360453	0.129926	-2.21103
Random 30	0.450221	0.202699	-0.88592
Random 31	0.391635	0.153378	-0.82959
Random 32	0.601248	0.361499	-0.84461
Random 33	0.411347	0.169206	-0.89074
Random 34	0.491667	0.241736	-0.57399
Random 35	0.616555	0.38014	-0.6623
Random 36	0.540618	0.292267	-2.8335
Random 37	0.533226	0.28433	-0.5478
Random 38	0.429846	0.184767	-2.22508
Random 39	0.569186	0.323973	-0.56803
Random 40	0.652215	0.425384	-0.13947
Random 41	0.637915	0.406936	-1.17984
Random 42	0.500904	0.250905	-0.91362
Random 43	0.579826	0.336198	-1.03692
Random 44	0.4158	0.172889	-0.84945
Random 45	0.884647	0.7826	0.611637

Random 46	0.470167	0.221057	-0.62506
Random 47	0.535329	0.286577	-0.75863
Random 48	0.569813	0.324687	-1.27268
Random 49	0.564393	0.31854	-0.27371
Random 50	0.689367	0.475227	-0.24844
Random Models Parameters			
Average R:	0.525095		
Average R^2 :	0.286085		
Average Q^2 :	-0.88887		
$^cR_p^2$:	0.690867		

Table S5. Similarity between the pIC_{50} range of in vitro-observed cyclohexan-1,3-dione derivatives and that predicted in silico using MLR-QSAR and ANN-QSAR models..

	2D-QSAR model descriptors								IC_{50} (µM)	Obs(pIC_{50})	pred(pIC_{50})	
	S-B	HBA	CMA	PSA	TC	E_T	E_{HOMO}	E_{LUMO}			MLR	ANN
3a	0.14	3.00	181.05	43.37	6.9E-03	-17710.04	-6.19	-2.41	5.42	5.26	5.283	5.244
3b	0.08	4.00	226.14	76.11	9.4E-04	-32588.14	-5.31	-1.86	0.39	6.41	6.035	6.598
5a	0.22	4.00	272.70	78.62	3.8E-04	-37348.83	-4.99	-1.51	4.18	5.38	5.412	5.291
5b	0.24	3.00	231.81	66.88	9.4E-04	-41376.86	-5.39	-2.01	1.17	5.93	5.667	5.923
5c	0.35	3.00	278.72	69.39	3.8E-04	-46137.56	-5.05	-1.67	0.26	6.59	6.084	6.557
5d	0.04	5.00	223.62	85.34	9.4E-04	-23832.64	-5.79	-1.98	0.36	6.44	6.277	6.332
6a	-0.12	5.00	225.88	79.55	9.4E-04	-24373.25	-5.98	-1.71	5.73	5.24	5.200	5.222
6c	-0.03	3.00	234.80	59.04	1.1E-03	-31147.81	-5.69	-0.53	0.82	6.43	6.814	6.398
8a	-0.25	2.00	274.42	29.54	1.4E-04	-46130.76	-5.25	-2.16	0.37	6.55	6.362	6.558
8b	-0.11	1.00	279.04	20.31	1.4E-04	-54919.50	-5.29	-2.28	0.42	6.54	6.988	6.457
10b	0.03	5.00	328.20	49.22	1.2	-32182.29	-4.88	-1.11	0.28	5.42	5.470	5.422
10d	0.12	4.00	332.81	39.99	1.2	-40970.84	-4.85	-1.09	0.29	6.24	6.039	6.199
12a	-0.02	5.00	190.89	63.41	2.0	-20687.32	-5.69	-1.51	7.6	5.97	6.195	5.932
14	0.27	3.00	181.03	43.37	2.4E-02	-15583.15	-6.00	-1.40	3.8	5.17	5.538	5.132
16a	0.26	3.00	210.95	46.17	3.4E-03	-19277.68	-5.91	-1.73	0.43	5.27	5.419	5.375
16b	0.26	3.00	230.01	46.17	2.8E-03	-20347.64	-5.78	-1.66	0.58	5.14	5.363	5.096
16c	0.32	4.00	237.97	55.40	2.0E-03	-22394.01	-5.56	-1.55	1.06	6.17	5.983	6.335
17a	0.21	4.00	255.13	78.91	4.7E-04	-34155.64	-5.06	-1.38	0.36	5.20	5.498	5.168
17b	0.36	4.00	303.24	81.42	1.9E-04	-38916.38	-4.73	-0.99	6.7	5.34	5.775	5.499

17c	0.21	4.00	274.21	78.91	3.9E-04	-35225.59	-4.99	-1.33	5.41	5.58	5.475	5.427
17d	0.44	4.00	322.02	81.42	1.6E-04	-39986.33	-4.67	-0.94	7.24	5.78	5.886	5.649
17e	0.26	5.00	282.15	88.14	2.7E-04	-37271.94	-4.88	-1.24	0.68	6.29	6.167	6.254
17f	0.41	5.00	330.25	90.65	1.1E-04	-42032.68	-4.58	-0.86	6.28	6.48	6.469	6.599
19a	0.05	3.00	248.93	72.19	6.6E-04	-33692.83	-5.75	-1.26	4.61	5.08	5.194	5.209
19c	0.06	3.00	263.86	72.19	5.4E-04	-46198.85	-5.85	-1.43	2.63	6.49	6.466	6.461
20b	0.08	4.00	319.79	99.06	1.1E-04	-41426.55	-5.94	-1.51	1.65	5.24	5.281	5.390
20c	0.08	4.00	315.64	99.06	1.1E-04	-52862.63	-6.15	-1.67	0.51	6.46	6.630	6.429
21a	0.11	4.00	353.15	70.23	2.0	-53358.46	-5.78	-1.65	0.33	5.19	5.175	5.096
21b	0.10	2.00	0.00	70.23	1.6	-54428.41	-5.75	-1.61	8.29	5.79	5.858	5.739
21c	0.10	2.00	368.48	70.23	1.6	-65864.48	-5.87	-1.76	2.28	5.06	5.018	5.210
22a	-0.02	2.00	284.06	44.70	1.6	-51278.37	-5.71	-1.39	0.32	5.08	5.068	5.124
22c	-0.01	2.00	302.57	44.70	1.3	-63784.01	-5.76	-1.53	7.62	6.54	6.681	6.448
6b*	0.33	2.00	187.01	34.14	6.9E-03	-26498.79	-6.28	-2.50	5.72	6.09	5.950	6.206
6d*	-0.04	3	231.52	53.25	1.10E-03	-36130.76	-6.01	-0.69	0.35	6.38	6.888	6.354
10a*	-0.07	5.00	171.13	72.00	2.0E-03	-19607.80	-5.14	-0.83	6.39	5.12	5.578	5.050
10c*	0.09	4.00	178.01	62.77	2.0E-03	-28396.28	-5.28	-1.07	1.64	6.37	6.248	6.342
12b*	0.09	4.00	197.59	54.18	2.0E-03	-29475.94	-5.77	-1.69	8.69	6.44	6.786	6.446
19b*	0.04	3.00	268.04	72.19	5.4E-04	-34762.77	-5.57	-1.23	8.25	5.64	5.343	5.575
20a*	0.08	4.00	300.66	99.06	1.4E-04	-40356.60	-6.05	-1.54	2.37	5.12	5.343	5.128
22b*	-0.02	2.00	298.86	44.70	1.3E+00	-52347.95	-4.29	-1.29	0.29	5.63	5.462	5.768
	* Items of the test set											

Table S6. Molecular descriptor sizes and pIC_{50} range predicted using the optimal QSAR model for the designed novel cyclohexan-1,3-dione derivatives.

	2D-QSAR model descriptors								pred(pIC50)
	S-B	HBA	CMA	PSA	TC	ET	E_{HOMO}	E_{LUMO}	MLR
H01	-0.0995	5	235.517	75.34	9.5E-04	-33833.326	-6.35	-1.53	7.06
H02	-0.189	4	242.169	76.11	9.5E-04	-42622	-5.95	-1.6	6.50
H03	-0.0144	4	250.114	76.11	6.7E-04	-33893.9	-6.03	-1.56	5.88
H04	-0.0167	4	269.405	76.11	5.5E-04	-34963.73	-5.91	-1.51	5.81
H05	-0.0189	5	276.958	85.34	3.9E-04	-37010.03	-5.67	-1.49	6.30
H06	-0.0113	4	265.181	75.11	5.5E-04	-46400.14	-6.17	-1.71	7.22
H07	-0.0113	5	281.959	87.85	3.9E-04	-38594.28	-5.49	-1.23	6.30
H08	-0.183	4	287.916	78.62	3.9E-04	-37382.98	-5.65	-1.3	5.47
H09	-0.183	4	296.708	78.62	2.7E-04	-38654.7	-5.8	-1.26	5.69
H10	-0.0107	4	315.887	78.62	9.6E-06	-39724.84	-5.72	-1.23	5.92

H11	-0.0133	5	323.218	87.85	1.6E-04	-31771.25	-5.39	-1.19	5.28
H12	-0.0065	4	311.964	58.62	2.2E-04	-41161.12	-5.92	-1.4	7.19
H13	-0.0929	5	231.496	79.55	9.5E-04	-24373.62	-5.97	-1.72	5.50
H14	-0.182	4	238.369	70.32	9.4E-04	-33162.29	-6.13	-1.78	5.87
H15	-0.006	4	246.324	70.32	6.7E-04	-24434.2	-6.34	-1.74	5.34
H16	-0.0084	4	265.524	70.32	5.5E-04	-26483.76	-6.22	-1.74	5.36
H17	-0.0082	5	271.907	79.55	3.8E-04	-27398.61	-5.73	-1.7	5.56
H18	-0.0041	4	261.531	70.32	5.5E-04	-39940.29	-6.46	-1.73	7.01
H19	-0.09	5	279.905	82.06	3.8E-04	-29134.42	-5.65	-1.89	5.30
H20	-0.18	4	286.306	62.83	3.8E-04	-47923.16	-5.81	-1.41	7.49
H21	-0.005	4	293.666	62.83	2.7E-04	-39195.07	-6.16	-1.48	7.02
H22	-0.0067	4	312.825	62.83	2.2E-04	-30265.04	-6.02	-1.49	5.84
H23	-0.0091	5	320.428	82.06	1.6E-04	-32311.36	-5.61	-1.45	5.70
H24	-0.00267	4	308.982	68.83	2.2E-04	-44701.47	-6.27	-1.43	7.32
H25	-0.00448	5	224.427	82.68	9.5E-04	-33801.13	-6.22	-1.63	6.76
H26	-0.0046	4	234.812	63.45	1.10E-5	-33589.81	-6.18	-2.05	6.49
H27	0.8214	4	243.926	73.45	6.6E-04	-23861.73	-6.37	-1.88	6.41
H28	0.8214	4	244.664	73.45	5.4E-04	-24931.71	-6.22	-1.81	6.44
H29	0.8214	5	270.182	82.68	3.8E-04	-26978.15	-5.84	-1.83	6.70
H30	0.8214	4	259.138	73.45	5.4E-04	-36367.94	-6.42	-2.04	7.62
H31	0.8214	5	273.294	82.19	3.8E-04	-28661.91	-5.94	-1.63	7.05
H32	0.8214	4	281.39	75.96	3.8E-04	-37350.58	-5.96	-1.64	7.31
H33	0.8214	4	292.914	75.96	2.7E-04	-28622.48	-6.1	-1.51	6.47
H34	0.8214	4	311.347	75.96	2.2E-04	-29692.45	-5.96	-1.48	6.39
H35	0.8214	5	318.565	85.19	1.5E-04	-31738.88	-5.63	-1.46	6.81
H36	0.8214	4	308.372	71.96	2.2E-04	-41128.7	-6.18	-1.66	7.92
*6d	-0.04	3	231.52	53.25	1.1E-03	-36130.76	-6.01	-0.69	**6.88**

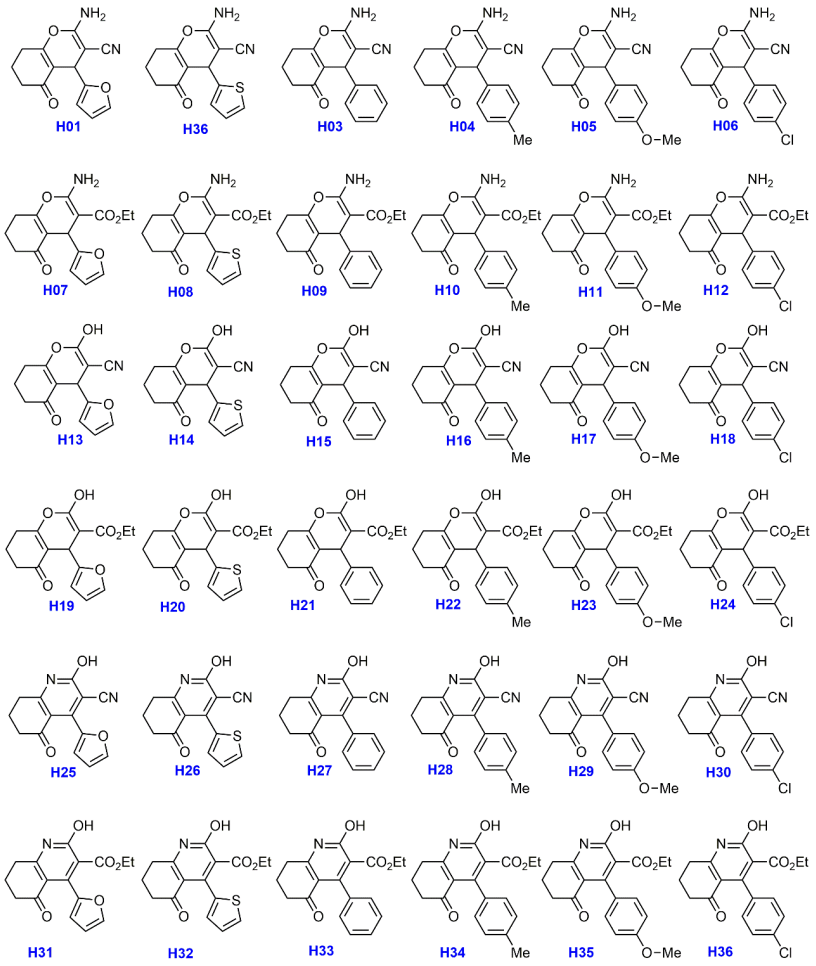
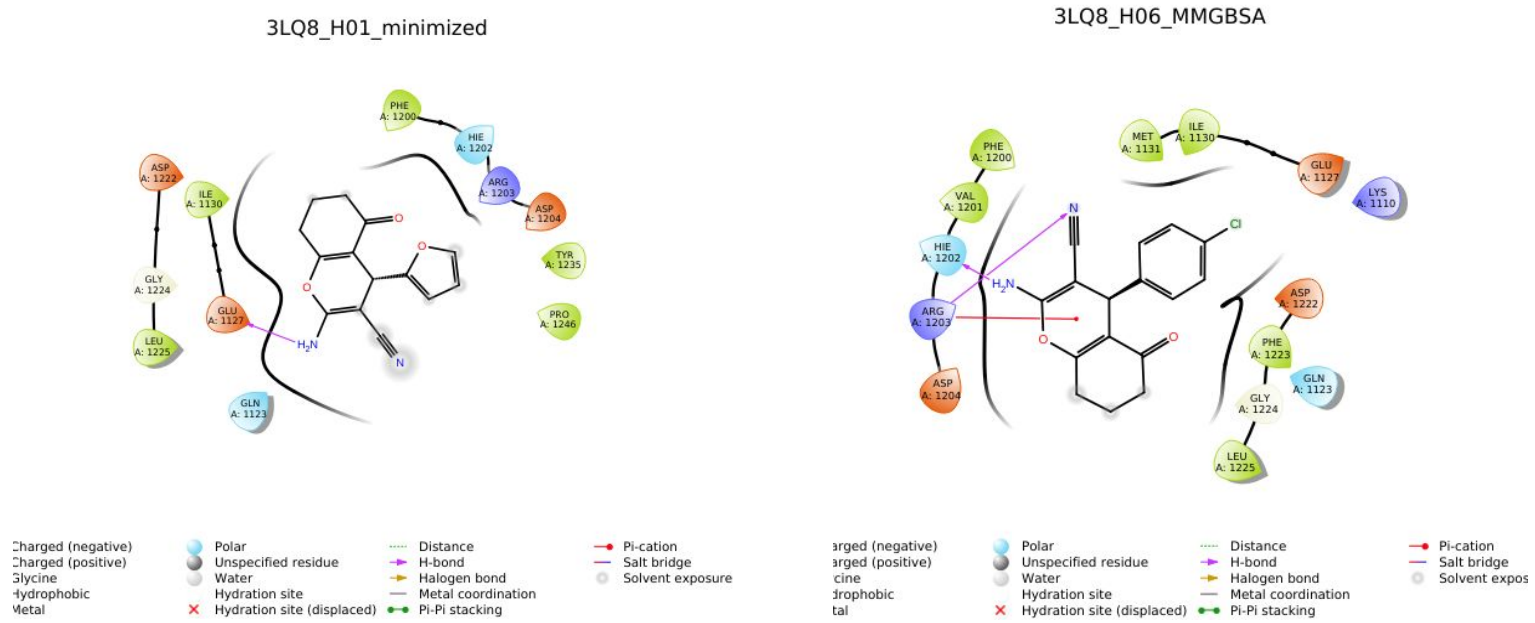
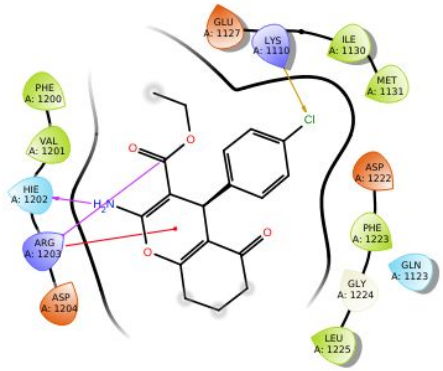


Figure S1. Heterocyclic structures of the 36 designed compounds (H01-H36) based on scaffold 6d.



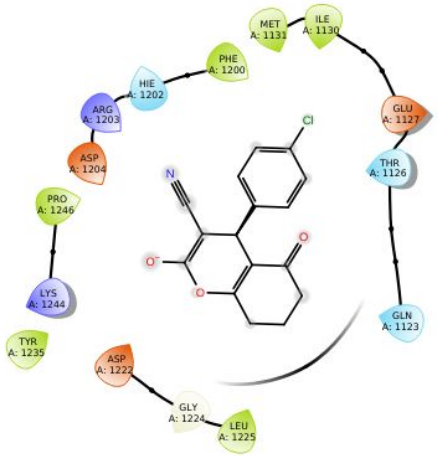
H01-3LQ8 : (A) **H06-3LQ8 : (B)**

3LQ8_H12_MMGBSA

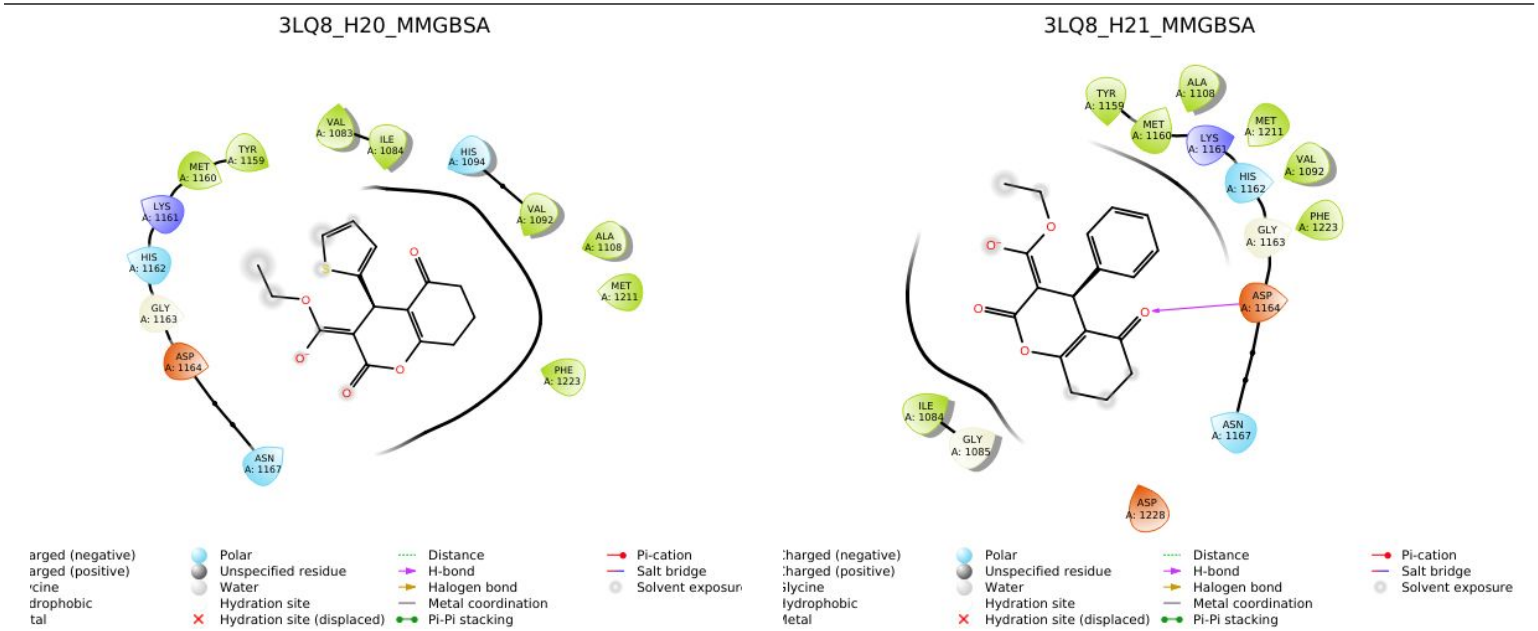


H12-3LQ8 :(C)

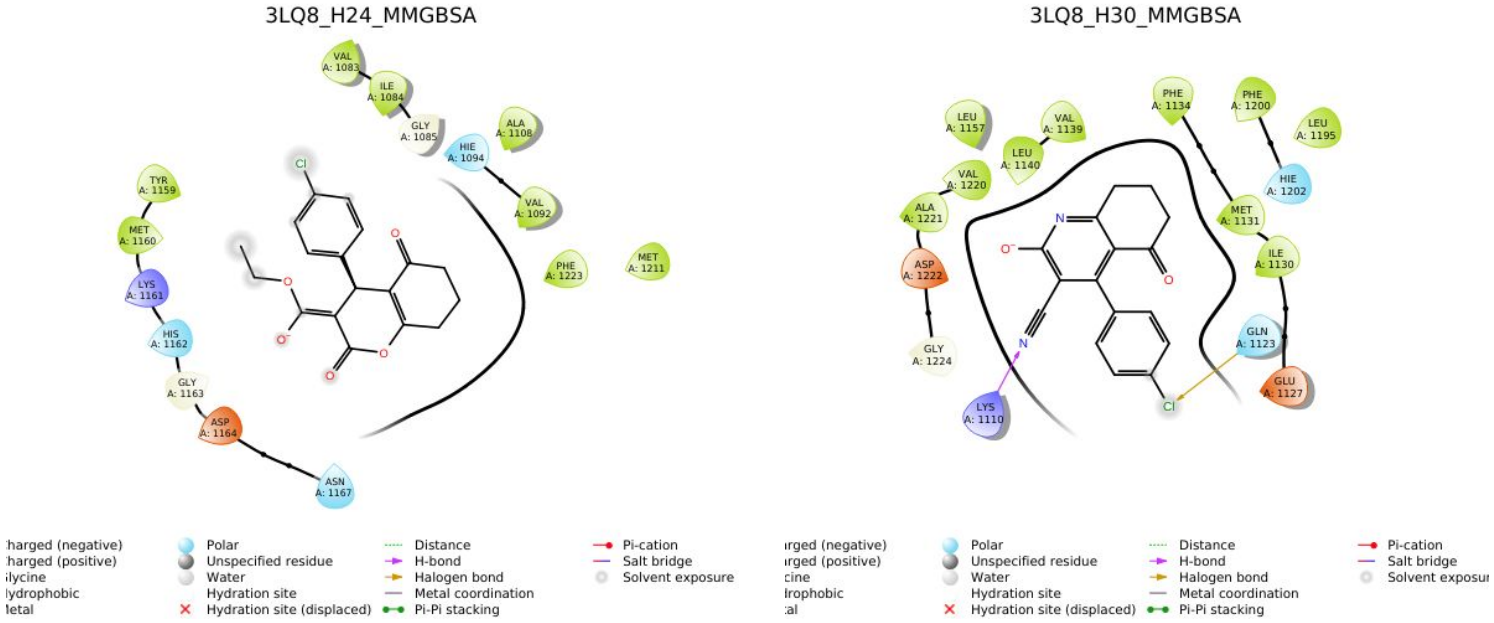
3LQ8_H18_MMGBSA



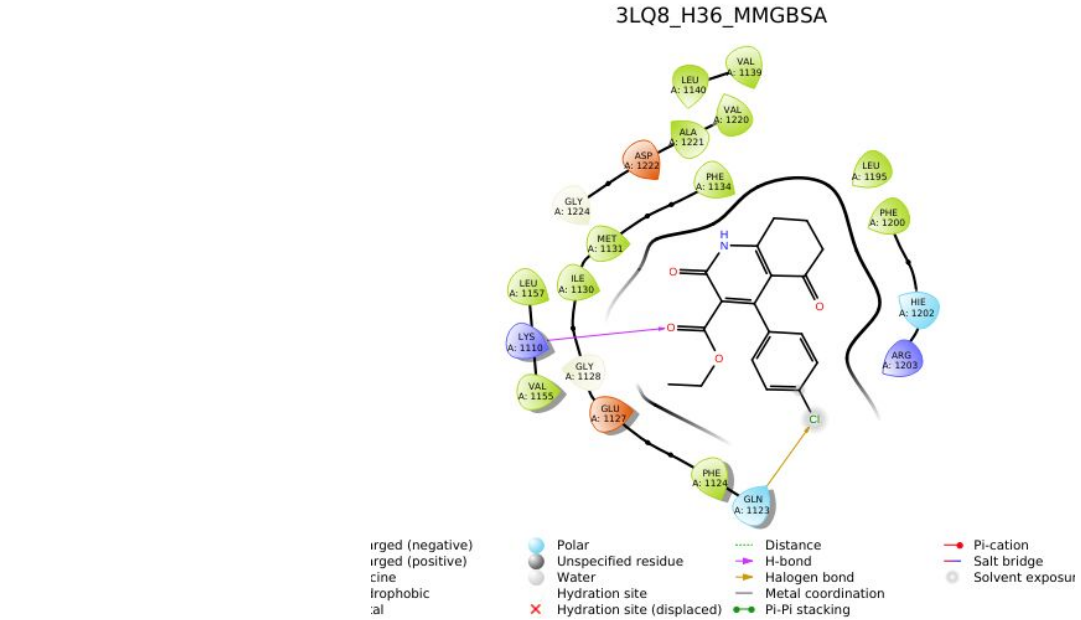
H18-3LQ8 :(D)



H20-3LQ8 :(E) **H21-3LQ8 : (F)**


3LQ8_H24_MMGBSA
VAL A: 1083
ILE A: 1084
GLY A: 1085
ALA A: 1108
HIE A: 1094
VAL A: 1092
PHE A: 1223
MET A: 1211
TYR A: 1159
MET A: 1160
LYS A: 1161
HIS A: 1162
GLY A: 1163
ASP A: 1164
ASN A: 1167
Cl
O
O⁻
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure
3LQ8_H30_MMGBSA
LEU A: 1157
VAL A: 1139
LEU A: 1140
PHE A: 1134
PHE A: 1200
LEU A: 1195
VAL A: 1220
HIE A: 1202
ALA A: 1221
MET A: 1131
ASP A: 1222
ILE A: 1130
GLY A: 1224
GLN A: 1123
GLU A: 1127
LYS A: 1110
N
O⁻
O
Cl
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge

H24 : (G) **H30 : (H)**



H36-3LQ8 : (I)

Figure S2. The key interactions predicted from MM-GBSA simulation between 3LQ8 and the designed compounds (A) H01, (B) H06, (C) H12, (D) H18, (E) H20, (F) H21, (G) H24, (H) H30, (I) H36.