Supporting Information

Molecular electrostatic potential and volume-aided drug design based on an isoindolinone-containing cyclopeptide S-PK6

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[1] Lei Zhao and Tingting Li contributed equally to this work.

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Table S1. Electrostatic potential distribution extreme of compound **1** (S-PK6).

Number of surface minima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})
1	-12.18	**1**	14.69	**20**	-13.21
2	-22.58	**2**	16.249	**21**	3.01
3	-56.01	**3**	45.71	**22**	11.69
4	-22.11	**4**	11.29	**23**	-22.29
5	19.04	**5**	13.05	**24**	5.68
6	-50.26	**6**	9.72	**25**	7.82
7	2.34	**7**	21.24	**26**	-24.19
8	-30.23	**8**	21.06	**27**	10.25
9	-37.963	**9**	-23.02	**28**	32.25
10	-39.26	**10**	12.14	*** 29**	52.04
11	5.66	**11**	22.92	**30**	21.70
12	-48.61	**12**	3.86	**31**	10.87
13	-5.30	**13**	20.32	**32**	29.70
***14**	-64.19	**14**	4.75	**33**	2.35
15	-33.459	**15**	19.06	**34**	12.30
16	29.61	**16**	-0.95	**35**	15.48
17	24.57	**17**	11.18	**36**	21.96
18	8.05	**18**	-26.68	**37**	14.54
		19	-30.99		

Note: The values in bold with * indicate the maximum or minimum extreme values

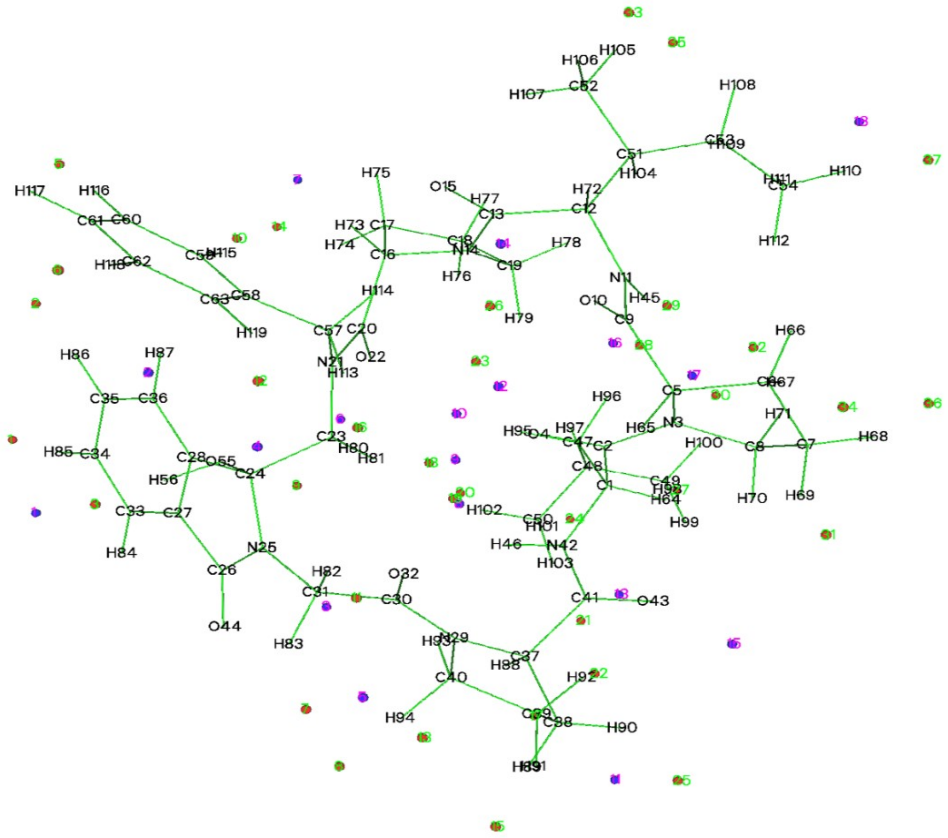

Fig.S1. Distribution of the surface electrostatic potential of compound **1** (S-PK6) with numbered atoms. The

blue points with pink numbers represent the minimum extreme, and the red points with green number represent the maximum extreme.

Table S2. Electrostatic potential distribution diagram of compound **2**.

Number of surface minima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})
1	-7.78	**1**	15.39	**22**	-3.60
2	-10.43	**2**	15.84	**23**	7.64
3	-2.60	**3**	22.04	**24**	8.39
4	-21.45	**4**	15.58	**25**	0.03
5	-4.64	**5**	15.58	**26**	12.58
6	-49.93	**6**	18.75	**27**	-1.78
7	-59.07	*** 7**	52.53	**28**	-9.49
8	6.77	**8**	17.44	**29**	4.44
***9**	-59.80	**9**	6.36	**30**	10.09
10	-9.65	**10**	10.12	**31**	-2.44
11	-43.94	**11**	9.86	**32**	8.99
12	-1.49	**12**	7.03	**33**	10.31
13	5.41	**13**	6.79	**34**	8.81
14	-38.76	**14**	-0.13	**35**	-0.61
15	0.47	**15**	2.24	**36**	10.77
		16	-3.34	**37**	9.53
		17	10.30	**38**	4.16
		18	7.29	**39**	2.18
		19	-36.19	**40**	33.60
		20	11.54	**41**	12.67
		21	8.46	**42**	11.88

Note: The value in bold with * indicates the maximum or minimum value

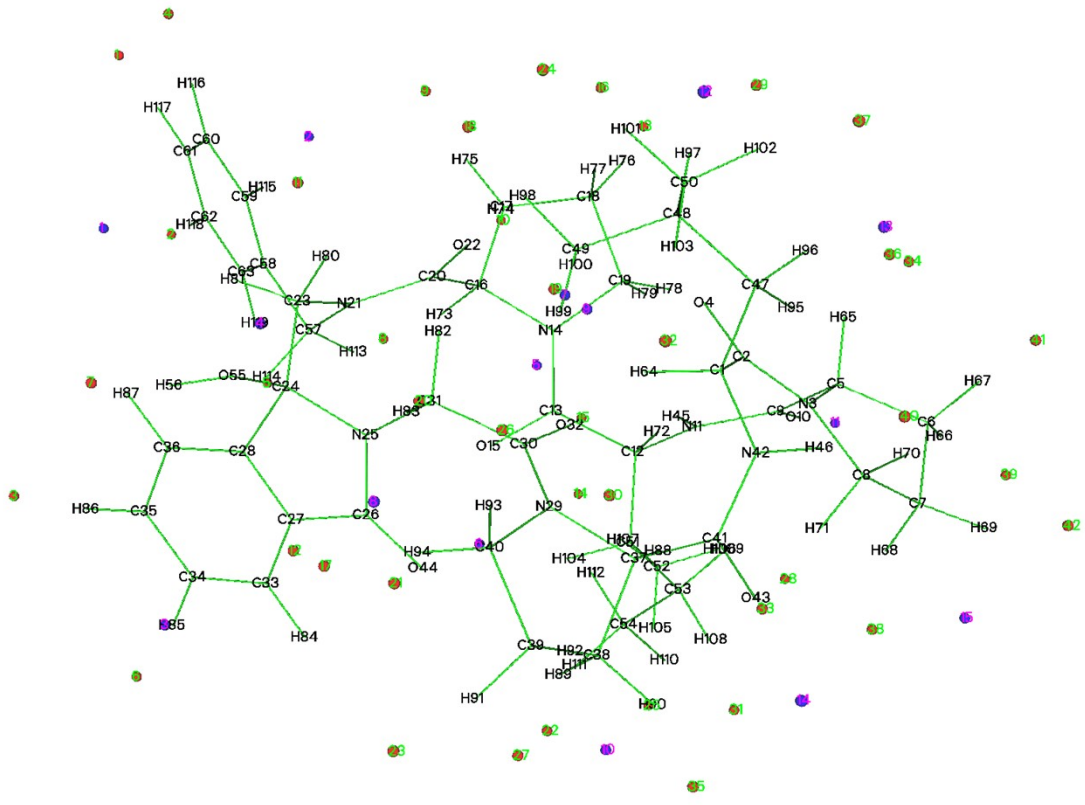

Fig.S2. Distribution of the surface electrostatic potential extreme of compound **2** with numbered atoms. The blue points with pink numbers represent the minimum extreme, and the red points with green number represent the maximum extreme.

Table S3. Electrostatic potential distribution diagram of compound **3**.

Number of surface minima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})
1	-14.09	**1**	13.77	**25**	19.20
2	-11.27	**2**	13.60	***26**	34.89
3	6.52	**3**	13.50	**27**	-6.88
4	-2.54	**4**	10.62	**28**	-15.33
5	-12.09	**5**	9.55	**29**	16.60
6	-1.77	**6**	12.49	**30**	17.44
7	-1.77	**7**	4.24	**31**	15.50
8	-47.38	**8**	10.72	**32**	2.75
9	9.84	**9**	10.99	**33**	16.28
10	-32.09	**10**	7.12	**34**	-2.29
11	10.99	**11**	-0.58	**35**	-1.11
***12**	-55.87	**12**	12.67	**36**	15.67
13	-3.97	**13**	10.83	**37**	14.64
14	-40.75	**14**	14.83	**38**	11.83
15	14.89	**15**	10.72	**39**	2.22
16	-30.03	**16**	12.09	**40**	2.26
17	8.12	**17**	-6.35	**41**	0.38
18	-7.07	**18**	18.65	**42**	7.00
19	-5.28	**19**	5.54	**43**	0.81
20	0.85	**20**	7.02	**44**	8.98
21	-36.27	**21**	-18.06	**45**	4.13
		22	8.21	**46**	2.82
		23	4.69	**47**	3.30
		24	7.39		

Note: The value in bold with * indicates the maximum or minimum value

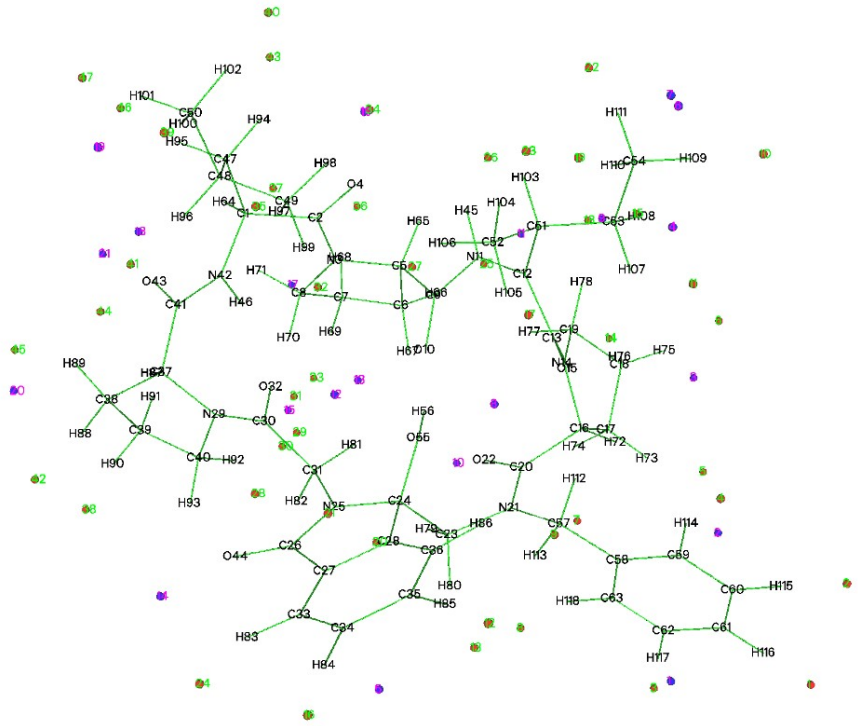

Fig.S3. Distribution of the surface electrostatic potential extreme of compound **3** with numbered atoms. The blue points with pink numbers represent the minimum extreme, and the red points with green numbers represent the maximum extreme.

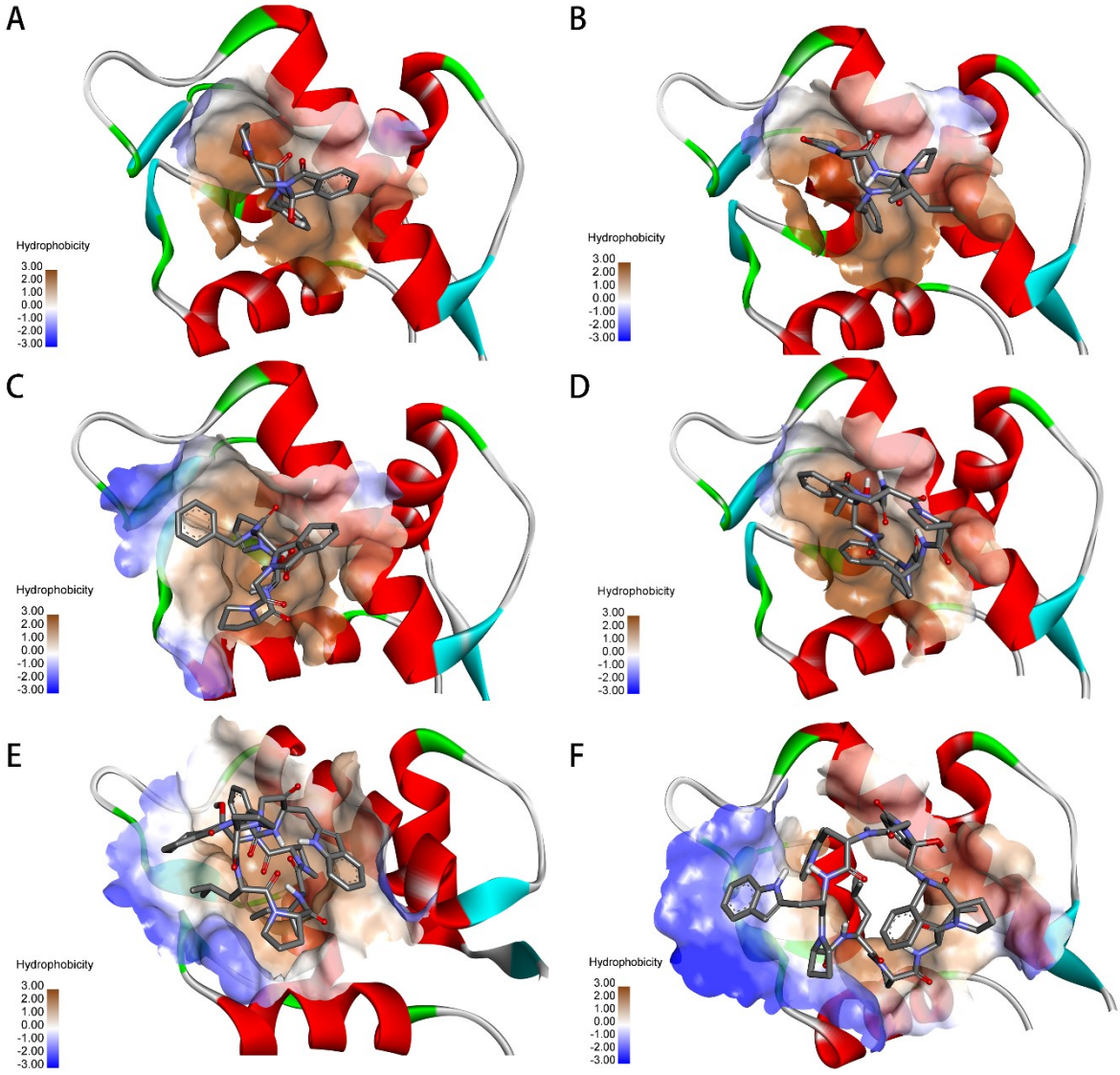

Fig.S4. The three-dimensional (3D) molecular docking between compounds **4**(A), **5**(B), **6**(C), **7**(D), **8**(E), and **9**(F) with MDM2.

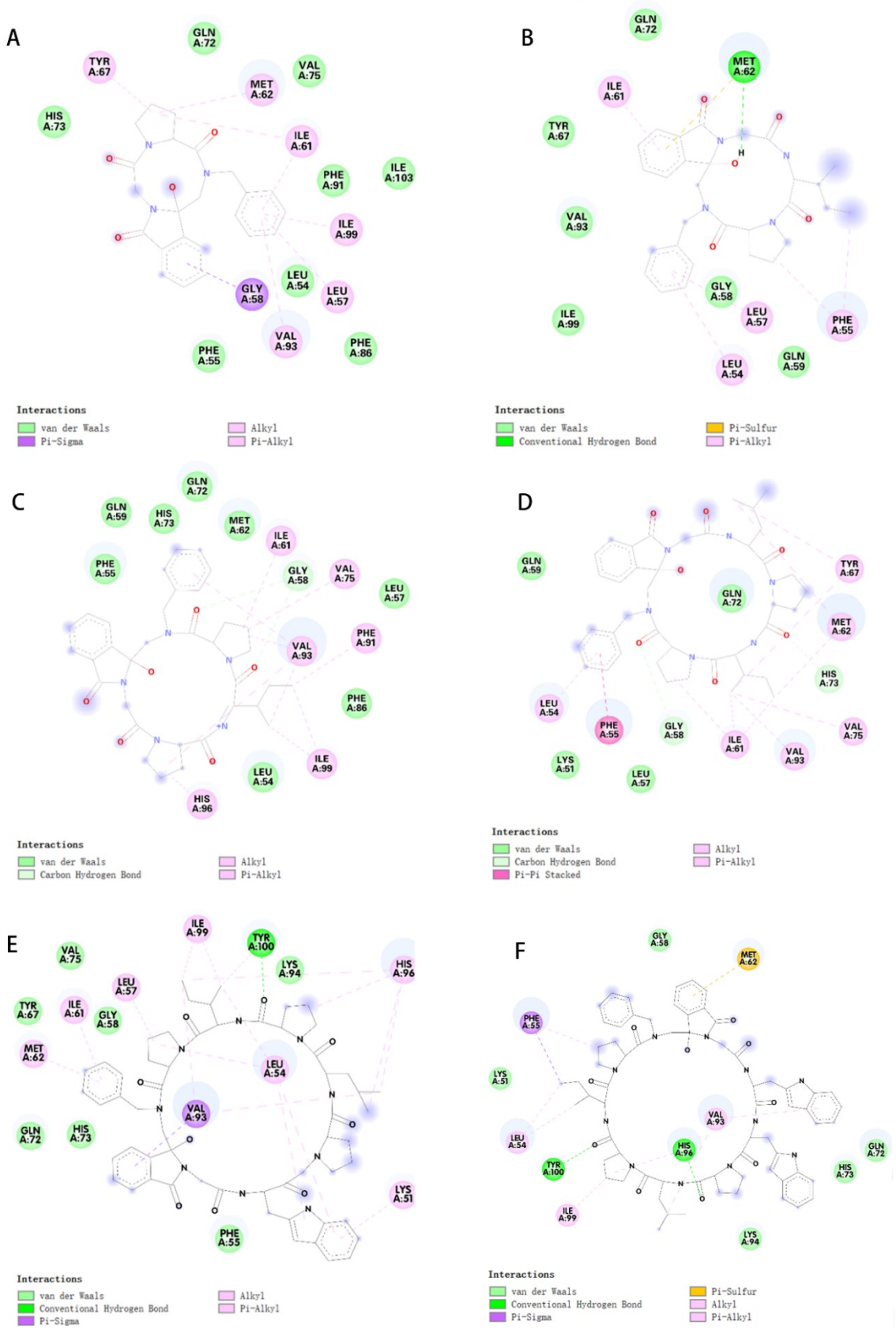

Fig.S5. The 2D molecular docking sites between compounds **4**(A), **5**(B), **6**(C), **7**(D), **8**(E), and **9**(F) with MDM2.

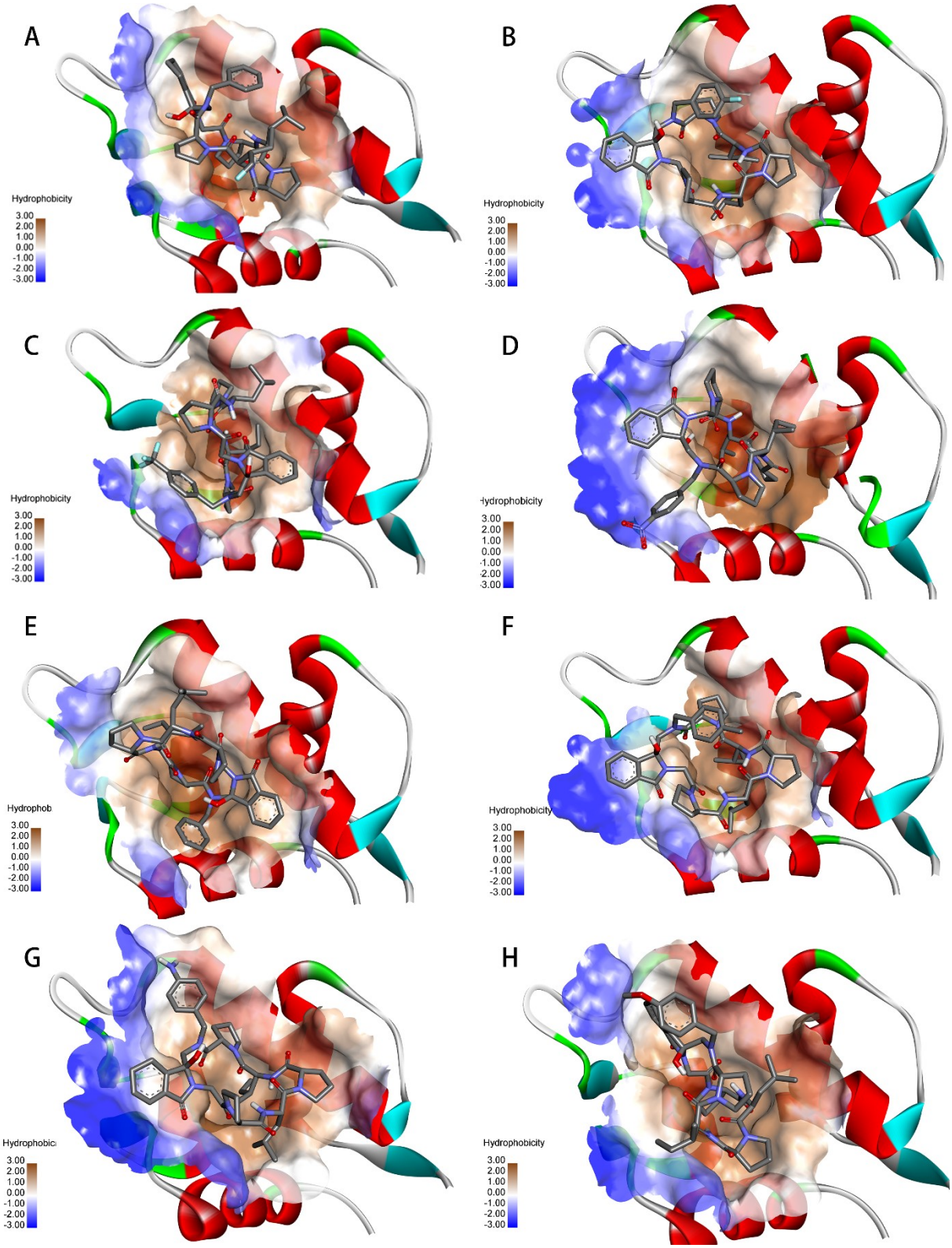

Fig.S6. The three-dimensional (3D) molecular docking between compounds **11**(A), **12**(B), **13**(C), **14**(D), **15**(E), **16**(F), **17**(G), and **18**(H) with MDM2.

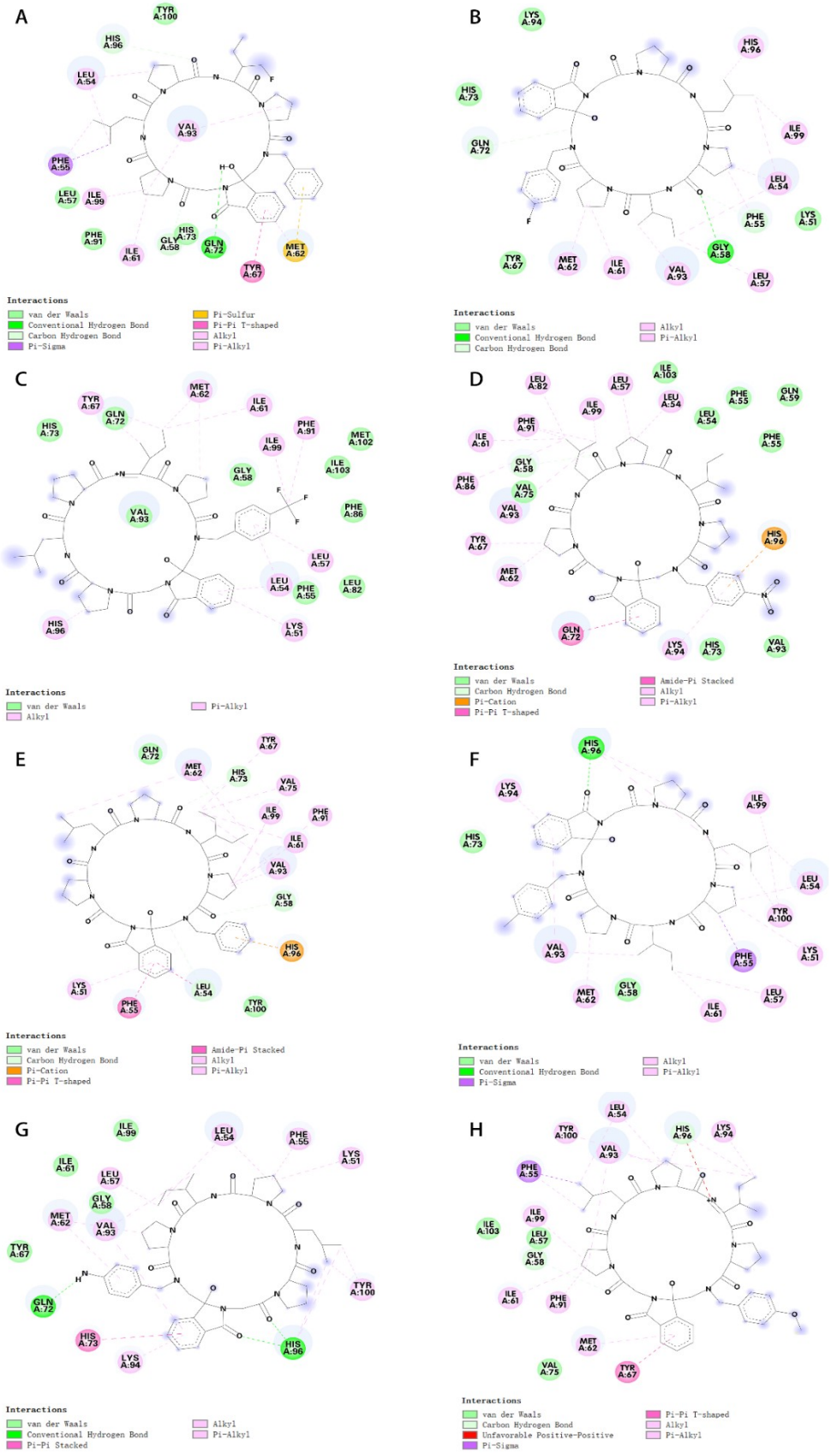

Fig.S7. The two-dimensional (2D) molecular docking sites between compounds **11**(A), **12**(B), **13**(C), **14**(D), **15**(E), **16**(F), **17**(G), and **18**(H) with MDM2.

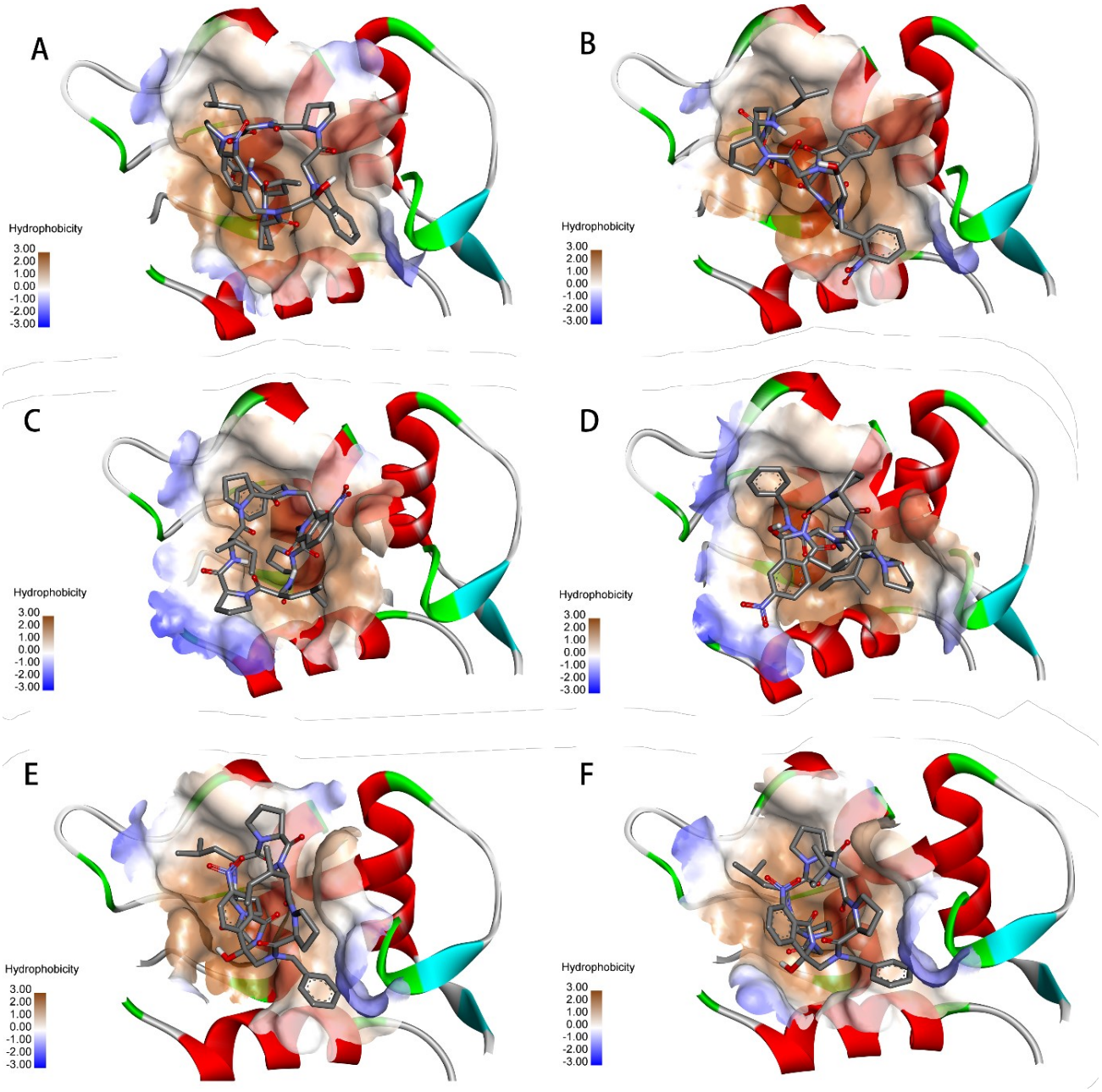

Fig.S8. The three-dimensional (3D) molecular docking between compounds **19**(A), **20**(B), **21**(C), **22**(D), **23**(E), and **24**(F) with MDM2.

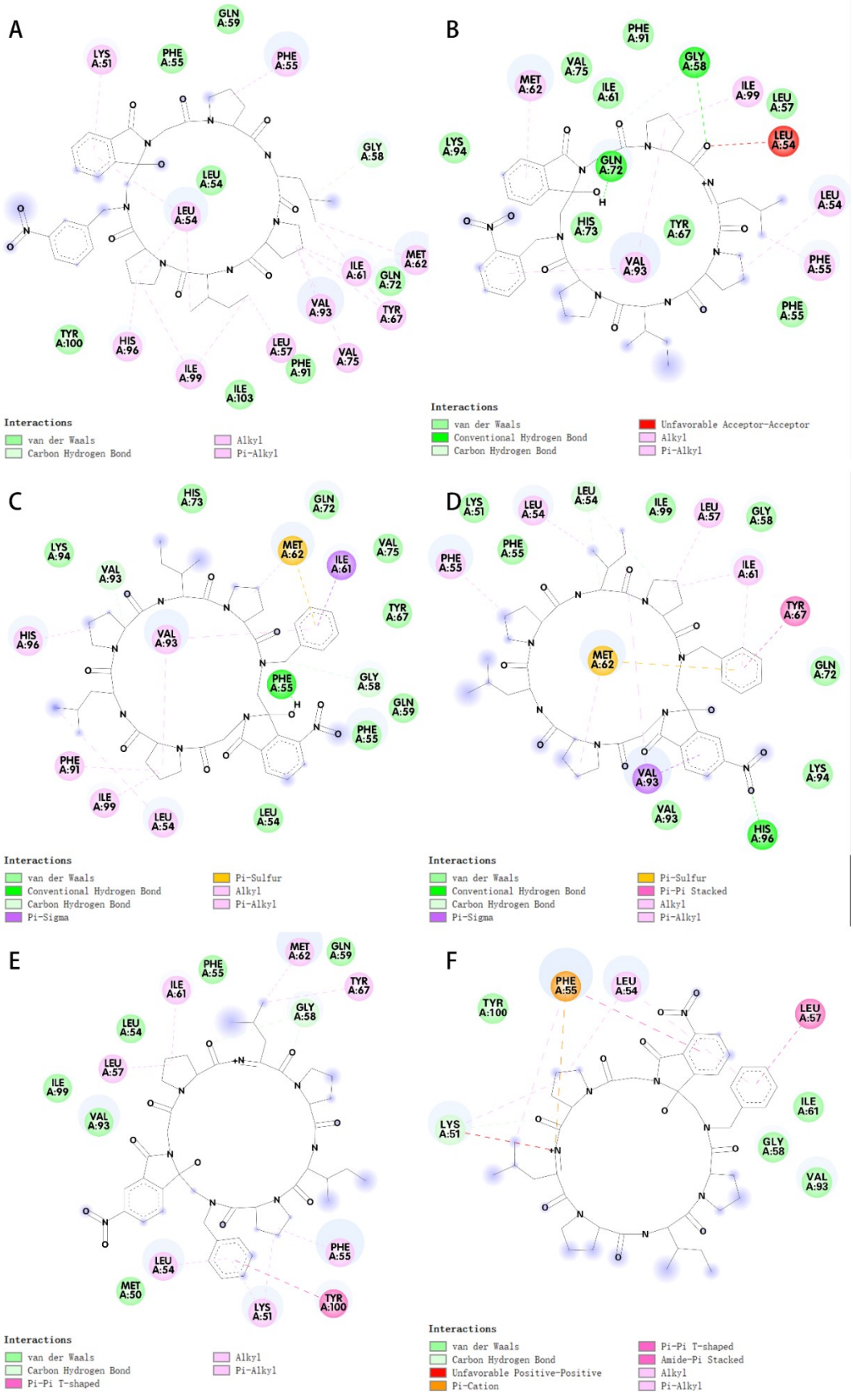

Fig.S9. The two-dimensional (2D) molecular docking sites between compounds **19**(A), **20**(B), **21**(C), **22**(D), **23**(E), and **24**(F) with MDM2.

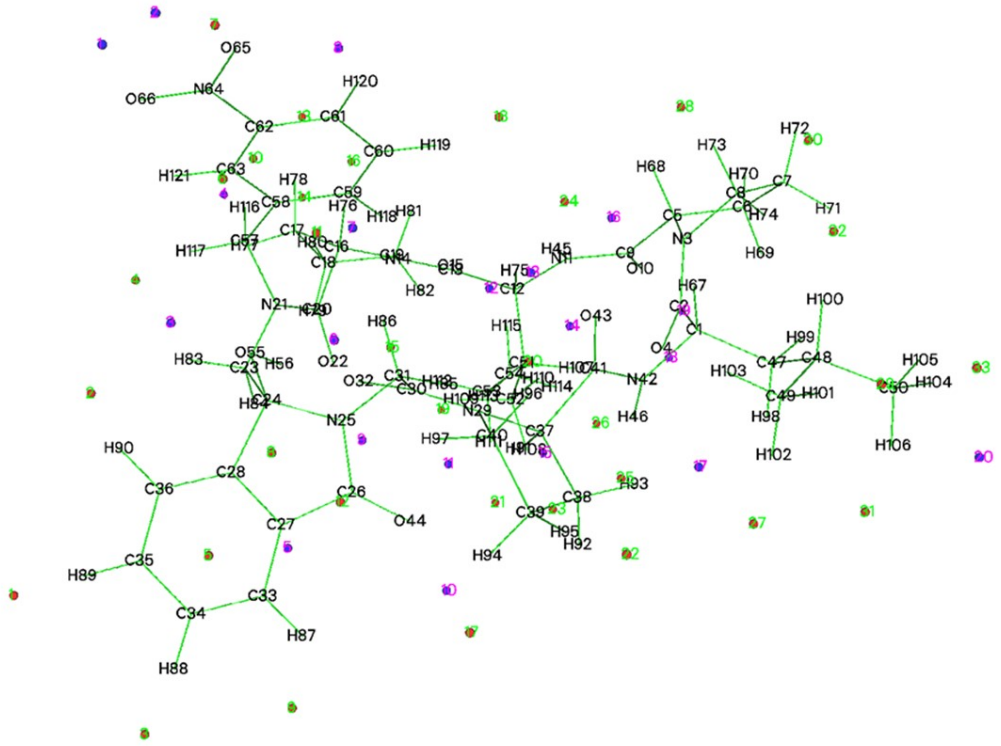

Fig.S10. Distribution of the surface electrostatic potential extreme of compound **19** with numbered atoms. The blue points with pink numbers represent the minimum extreme, and the red points with green number represent the maximum extreme.

Table S4. Electrostatic potential distribution diagram of compound **19**.

Number of surface minima	Potential (kcal·mol-1)	Number of surface maxima	Potential (kcal·mol-1)	Number of surface maxima	Potential (kcal·mol-1)
1	-42.84	**1**	18.91	**21**	-1.43
2	-43.21	**2**	18.95	**22**	13.67
3	-33.61	**3**	17.33	**23**	-4.58
4	22.23	**4**	27.27	**24**	23.31
5	-13.75	**5**	-14.77	**25**	34.21
6	-43.51	**6**	-2.36	**26**	-3.46
7	-19.42	**7**	7.24	**27**	13.99
8	-2.09	**8**	-11.87	**28**	26.93
9	-43.33	**9**	9.97	**29**	10.76
10	-42.19	***10**	35.31	**30**	24.88
11	-25.42	**11**	-17.15	**31**	12.57
12	-24.66	**12**	-9.26	**32**	28.06
13	-43.37	**13**	29.11	**33**	12.52
14	-3.13	**14**	25.32		
15	-6.17	**15**	-20.27		
16	-3.32	**16**	28.24		
17	6.28	**17**	4.34		
18	-47.05	**18**	16.13		
***19**	-49.73	**19**	7.13		
20	3.68	**20**	9.25		

Note: The value in bold with * indicates the maximum or minimum value

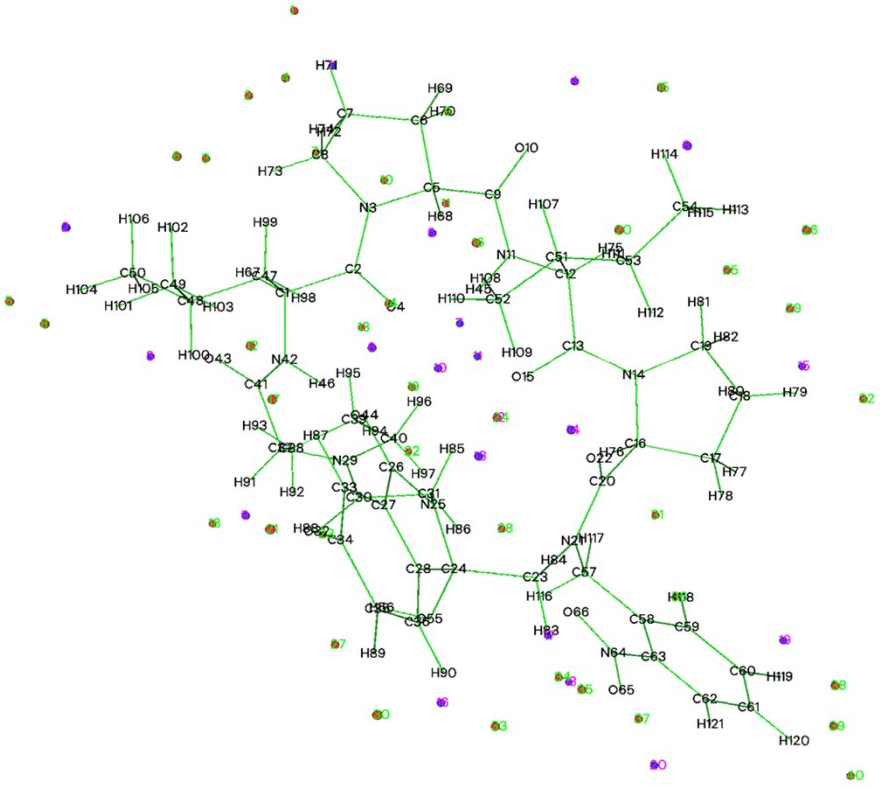

Fig.S11. Distribution of the surface electrostatic potential extreme of compound **20** with numbered atoms. The blue points with pink numbers represent the minimum extreme, and the red points with green number represent the maximum extreme.

Table S5. Electrostatic potential distribution diagram of compound **20**.

Number of surface minima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})	Number of surface maxima	Potential (kcal·mol^{-1})
1	6.81	**1**	14.70	**21**	16.10
2	-6.76	**2**	15.68	**22**	11.14
3	-51.19	**3**	16.47	**23**	6.35
4	-47.28	**4**	13.90	**24**	-39.66
5	-16.60	**5**	-0.98	**25**	23.07
6	-40.20	**6**	4.84	**26**	9.081
7	-28.01	**7**	12.13	**27**	8.97
8	-4.43	**8**	0.71	**28**	15.75
*** 9**	-49.05	**9**	11.07	**29**	22.99
10	-57.72	**10**	10.66	**30**	19.52
11	-32.13	**11**	10.10	**31**	31.04
12	-42.55	**12**	0.57	**32**	26.21
13	-22.01	**13**	0.49	**33**	20.86
14	-41.13	**14**	-19.63	**34**	20.24
15	18.16	**15**	-1.48	**35**	21.77
16	-25.06	**16**	-2.60	**36**	22.93
17	-30.34	**17**	7.60	**37**	11.51
18	-32.10	**18**	-2.24	*** 38**	34.18
19	12.14	**19**	-38.87	**39**	32.47
20	6.99	**20**	0.66	**40**	32.37

Note: The value in bold with * indicates the maximum or minimum value

Table S6. Docking process parameter settings for those with relative high binding energy.

Parameter	Compound **1**	Compound **2**	Compound **3**	Compound **8**	Compound **14**	Compound **19**
Grid box (nm)	40×40×40	40×40×40	40×40×40	40×40×40	40×40×40	40×40×40
spacing	0.375	0.375	0.375	0.375	0.375	0.375
grid center x	-7.442	-7.442	-7.442	-7.442	-7.442	-7.442
grid center y	0.621	0.621	0.621	0.621	0.621	0.621
grid center z	6.892	6.892	6.892	6.892	6.892	6.892
GA runs	20	20	20	20	20	20
population size	150	150	150	150	150	150

Table S7. Drug-likeness prediction of compounds **1-24**

Compounds	Number of HBA	HBD	MolLogP	MolPSA (A^2)	BBB Score	Drug-likeness model score
Compound **1**	8	3	1.86	150.95	1.00	0.36
Compound **2**	8	3	1.86	150.95	1.00	0.36
Compound **3**	8	3	1.86	150.95	1.00	0.36
Compound **4**	4	1	1.71	66.26	3.55	0.22
Compound **5**	5	2	1.95	91.64	2.11	0.47
Compound **6**	6	2	1.59	108.58	1.64	0.47
Compound **7**	7	3	2.31	134.02	1.00	0.36
Compound **8**	9	5	3.18	185.97	0.20	0.3
Compound **9**	10	7	4.39	221.21	0.00	0.3
Compound **10***	-	-	-	-	-	-
Compound **11**	8	3	1.48	150.95	1.00	0.49
Compound **12**	8	3	1.92	150.95	1.00	0.88
Compound **13**	8	3	2.79	150.95	1.00	0.44
Compound **14**	10	3	1.78	184.34	1.00	0.18
Compound **15**	8	3	2.46	150.95	1.00	0.49
Compound **16**	8	5	2.30	150.95	1.00	0.47
Compound **17**	8	5	0.77	171.76	1.17	0.51
Compound **18**	9	3	1.81	158.50	1.00	0.54
Compound **19**	10	3	1.71	184.34	1.00	0.24
Compound **20**	10	3	2.01	184.03	1.00	-0.07
Compound **21**	10	3	1.16	184.03	1.00	-0.29
Compound **22**	10	3	1.97	184.03	1.00	-0.31
Compound **23**	10	3	1.91	184.34	1.00	-0.06
Compound **24**	10	3	1.27	184.03	1.00	0.12

* The druglikeness of compound 10 could be not predicted by MolSoft programme due to it large molecular weight.