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Electronic Supplementary Information

Non-volatile pungent compounds isolated from *Zingiber officinale* and their action mechanisms

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1 Spectroscopic data of isolated new compounds

4(Z),8(Z)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)tetradecan-4,8-dien-3-one (1) light yellow oil; UV (MeOH) λ_{max} (log ε): 203 (4.16), 230 (3.31), 281 (3.97) nm; IR (KBr) v_{max}: 3349, 2943, 2865, 1632, 1597, 1568, 1510, 1281, 1029, 969 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 1; HRESIMS *m/z* 347.2217 $[M+H]^+$ (calculated for $C_{21}H_{31}O_4$, 347.2222).

4(Z),10(Z)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hexadecan-4,10-dien-3-one (2) light yellow oil; UV (MeOH) λ_{max} (log ε): 205 (4.24), 226 (3.89), 281 (3.73) nm; IR (KBr) v_{max}: 3332, 2940, 2358, 1629, 1565, 1508, 1284, 1154 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 1; HRESIMS *m/z* 375.2538 $[M+H]^+$ (calculated for $C_{23}H_{35}O_4$, 375.2535).

4(Z)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hexadec-4-en-3-one (3) light yellow power; UV (MeOH) λ_{max} (log ε): 204 (3.82), 229 (3.34), 281 (3.54) nm; IR (KBr) v_{max}: 3440, 2932, 2862, 1702, 1603, 1519, 1267, 1032, 803 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 1; HRESIMS *m/z* 377.2687 $[M+H]^+$ (calculated for $C_{23}H_{37}O_4$, 377.2692).

4(Z),11(Z),14(Z)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)eicos-4,11,14-trien-3-one (4) light yellow oil; UV (MeOH) λ_{max} (log ε): 204 (4.31), 229 (3.61), 281 (3.97) nm; IR (KBr) v_{max}: 3335, 2943, 1632, 1508, 1157, 966 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 2; HRESIMS *m/z* 451.2821 $[M+Na]^+$ (calculated for $C_{27}H_{40}O_4Na$, 451.2824).

4(E),11(Z),14(Z)-1-(4-hydroxy-3-methoxyphenyl)eicos-4,11,14-trien-3-one (5)

light yellow oil; UV (MeOH) λ_{max} (log ε): 204 (4.22), 229 (3.48), 280 (3.97) nm; IR (KBr) ν_{max}: 2935, 2859, 1668, 1513, 1447, 1267, 1029, 980, 808 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 2; HRESIMS *m/z* 435.2860 $[M+Na]^+$ (calculated for $C_{27}H_{40}O_3Na$, 435.2875).

1-(4-hydroxy-3-methoxyphenyl)-3-(4-nonanyl furan-1-yl)propan-3-one (6) light yellow oil; UV (MeOH) λ_{max} (log ε): 204 (4.37), 222 (3.67), 278 (3.76) nm; IR (KBr) ν_{max}: 3425, 2932, 2862, 1668, 1513, 1269, 1035, 806 cm^{-1}; ^{1}H (in $CDCl_3$, 600 MHz) and ^{13}C NMR (in $CDCl_3$, 150 MHz) data see Table 2; HRESIMS *m/z* 373.2379 $[M+H]^+$ (calculated for $C_{23}H_{33}O_4$, 373.2379).

Table S1 NMR spectroscopic data (in $CDCl_3$) of compounds 1-3

Pos.	1		2		3	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1′	132.6		132.6		132.7	
2′	110.9	6.67, d (1.9)	110.9	6.67, d (1.9)	110.9	6.67, d (2.0)
3′	146.4		146.4		146.3	
4′	144.0		144.0		143.9	
5′	114.3	6.82, d (8.2)	114.3	6.82, d (8.2)	114.3	6.83 d (8.1)
6′	120.8	6.69, dd (8.2, 1.9)	120.8	6.69, dd (8.2, 1.9)	120.8	6.69, dd (8.1, 2.0)
1	31.3	2.86	31.3	2.86	31.3	2.86
2	40.5	2.57	40.6	2.57	40.5	2.57
3	193.4		193.6		193.5	
4	99.6	5.45, s	99.4	5.45, s	99.4	5.45, s
5	193.4		194.0		194.3	
6	38.2	2.32	38.1	2.26	38.3	2.32
7	23.4	2.32	25.3	1.59	25.7	1.59
8	127.3	5.30	29.2	1.30	29.6	1.27
9	131.5	5.40	26.9	2.01	29.6	1.27
10	27.1	2.01	129.0	5.33	29.4	1.27
11	29.3	1.30	130.5	5.37	29.3	1.27
12	31.5	1.30	27.2	2.01	29.3	1.27

13	22.5	1.28	29.3	1.30	29.2	1.27
14	14.0	0.88, t (7.0)	31.5	1.30	31.9	1.27
15			22.6	1.30	22.7	1.27
16			14.1	0.88, t (7.0)	14.1	0.88, t (7.0)
3′-OCH_3	55.9	3.87, s	55.8	3.87, s	55.8	3.87, s
4′-OH		5.48, br s		5.48, br s		5.47, br s
5-OH		15.47, br s		15.50, br s		15.51, br s

Multiplets and or overlapped signals are reported without designating multiplicity

Table S2 NMR spectroscopic data (in $CDCl_3$) of compounds 4-6

Pos.	4		5		6	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1′	132.6		133.2		133.3	
2′	110.9	6.67,d (1.9)	111.1	6.69, d (1.9)	111.1	6.74, d (1.9)
3′	146.4		146.4		146.4	
4′	143.9		143.8		143.9	
5′	114.3	6.82, d (7.8)	114.3	6.82, d (7.8)	114.3	6.83, d (8.2)
6′	120.8	6.69, dd (7.8, 1.9)	120.8	6.71, dd (7.8, 1.9)	120.8	6.72, dd (8.2, 1.9)
1	31.3	2.86	29.8	2.85	29.6	2.93
2	40.5	2.57	42.0	2.86	43.4	3.01
3	193.5		199.7		195.6	
4	99.4	5.45, s	130.3	6.09, d (15.9)	120.2	
5	194.1		147.7	6.83, d (15.9)	140.2	7.23, d (2.0)
6	38.2	2.24	32.4	2.19	109.9	6.58, d (2.0)
7	25.6	1.59	28.0	1.45	162.9	
8	28.8	1.31	28.8	1.59	28.0	3.01
9	29.3[a]	1.31[b]	29.4[a]	1.31[b]	27.8	1.65
10	27.0	2.05	27.0	2.05	29.5	1.30
11	129.7	5.35	129.7	5.35	29.3	1.30

12	128.3	5.36	128.3	5.36	29.3	1.30
13	25.6	2.76	25.6	2.76	29.3	1.30
14	127.8	5.32	127.8	5.32	31.9	1.30
15	130.3	5.38	130.3	5.38	22.7	1.30
16	27.2	2.05	27.2	2.05	14.3	0.89, t (7.0)
17	29.3[a]	1.31[b]	29.3[a]	1.31[b]		
18	31.5	1.31	31.5	1.31		
19	22.6	1.31	22.6	1.31		
20	14.0	0.87, t (7.0)	14.0	0.87, t (7.0)		
3′ - **OCH_3**	55.8	3.87, s	55.8	3.87, s	55.9	3.86, s
4′- **OH**		5.48, br s		5.48, br s		5.48, br s
5-OH		15. 50, br s				

[a,b] Signals could be interchangeable with the corresponding position in one compound

Multiplets and or overlapped signals are reported without designating multiplicity

Table S3 14 key cancer-related targets

Uniprot ID	Gene Name	GO Function
P04150	NR3C1	apoptotic process, cell division, cell cycle
Q09472	EP300	apoptotic process, B cell differentiation, lung development, fat cell differentiation
P21554	CNR1	positive regulation of apoptotic process, G protein-coupled receptor signaling pathway
Q9NR56	MBNL1	myoblast differentiation, nervous system development
P10636	MAPT	regulation of autophagy, positive regulation of neuron death, negative regulation of kinase activity
Q9BYJ1	ALOXE3	fat cell differentiation, peroxisome proliferator activated receptor signaling pathway
P61981	YWHAG	regulation of G2/M transition of mitotic cell cycle, regulation of neuron differentiation
P14555	PLA2G2A	positive regulation of ERK1 and ERK2 cascad, positive regulation of macrophage derived foam cell differentiation
O15296	ALOX15B	negative regulation of cell proliferation, negative regulation of cell migration
Q04760	GLO1	negative regulation of apoptotic process, osteoclast differentiation
P35968	VEGFR2	cell differentiation, positive regulation of cell migration
Q9UBM7	DHCR7	cell differentiation
P08908	HTR1A	cell proliferation
Q16236	NFE2L2	negative regulation of endothelial cell apoptotic process, negative regulation of hematopoietic stem cell differentiation

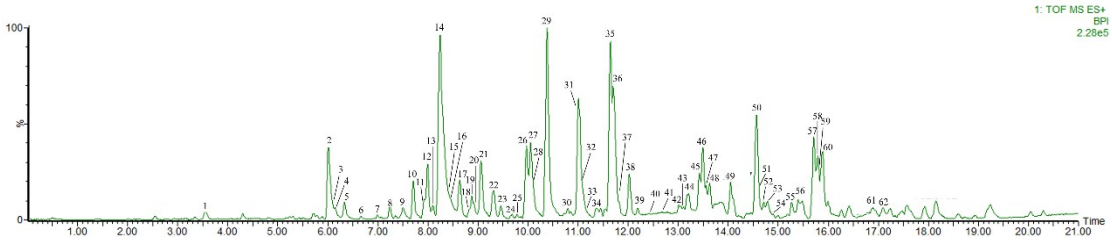

Figure S1. BPI chromatogram of the ZO-2 by UPLC-Q/TOF-MS

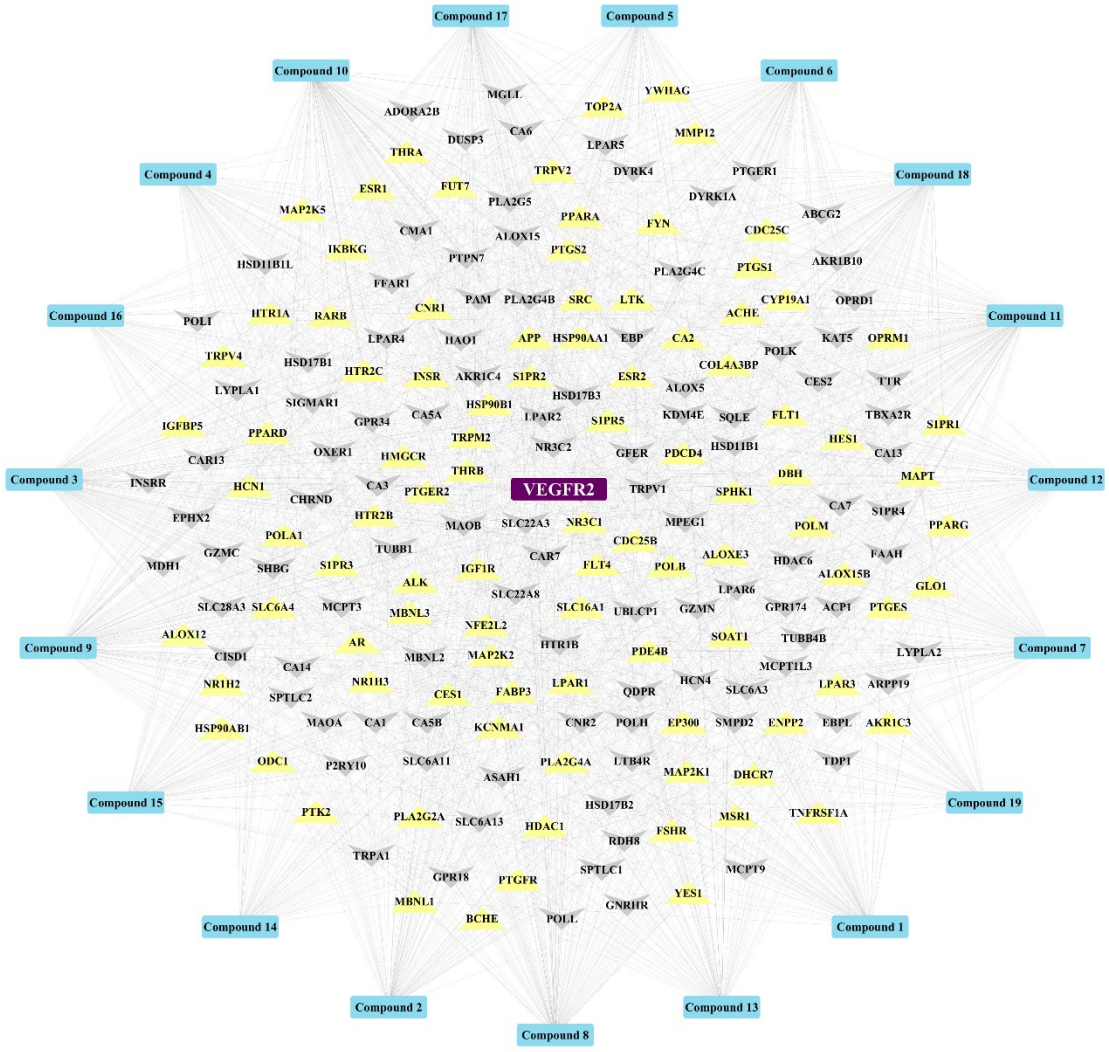

Figure S2. Potential active compound-target network (cyan round rectangles stand for the compounds, yellow triangles represent the cancer related targets, and gray V shape are other targets)

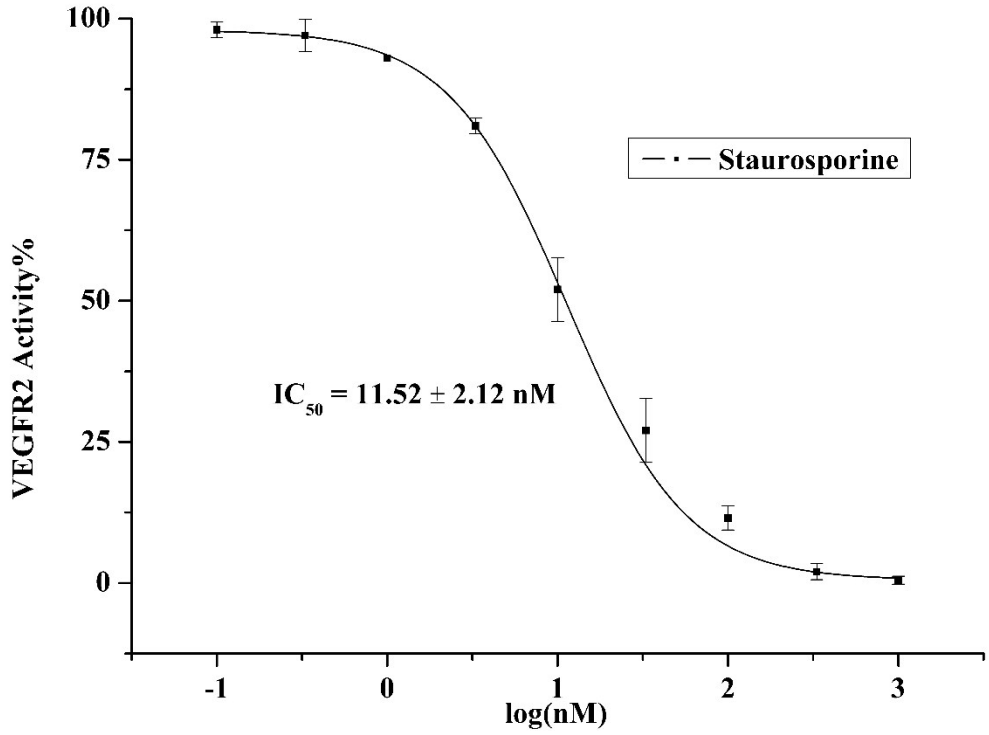

Figure S3. Effect of VEGFR2 enzyme inhibitory activity of Staurosporine

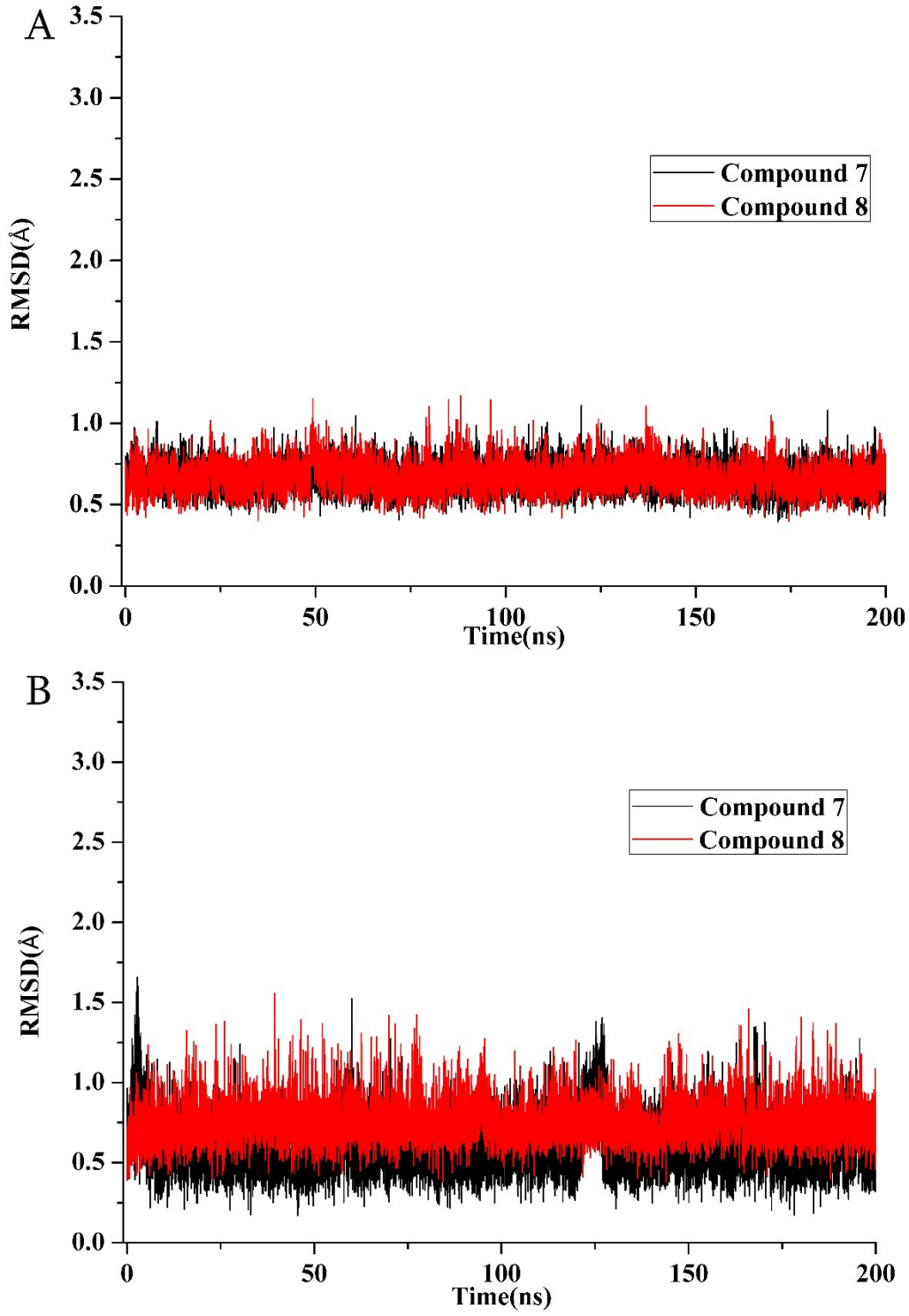

Figure S4.The monitoring of the equilibration for the MD trajectories: (A) the time series of the RMSD of Cα atoms for the residues in 5 Å around of ligand from the initial structure; (b) time evolution of the RMSD of heavy atoms for the ligand.

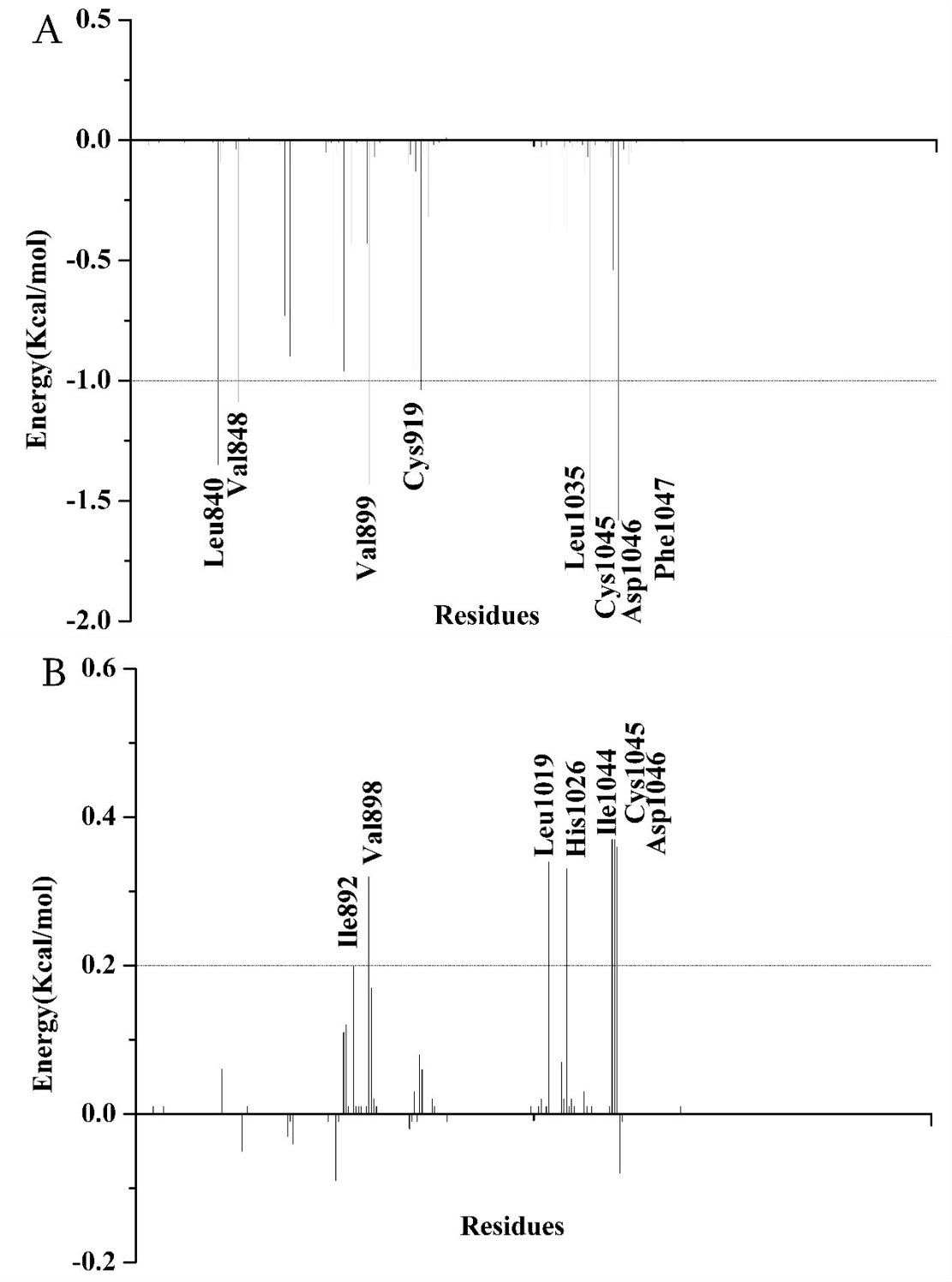

Figure S5. (A) The residue contributions of VEGFR2 to compound 8 binding; (B) the energy difference of each residue contribution for the compound 8-VEGFR2 relative to the compound 7-VEGFR2.