Supporting information

(-)-Kusunokinin as a potential aldose reductase inhibitor: Equivalency observed via AKR1B1 dynamics simulation

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Table S1. AKR1B1 ligands used in molecular docking studies

Ligand	PubChem CID	Molecular weight (g/mol)
(-)-Kusunokinin	384876	370.4
Zenarestat	5724	441.6
Zopolrestat	1613	419.4
Sulindac	11245227	356.4
Lidorestat	157839	376.4
IDD1219	10150300	366.4
Epalrestat	1549120	319.4
IDD740	10150441	377.3
IDD594	4369325	416.2
IDD552	448658	414.3
Tolrestat	53359	357.3
Tolmetin	5509	257.3
Alrestatin	2120	255.2
Minalrestat	190816	449.2
Ranirestat	153948	420.2
Fidarestat	160024	279.2

Ligand	PubChem CID	Molecular weight (g/mol)
Sorbinil	337359	236.2
Oleanolic acid	10494	456.7
AD5467	197383	307.4
γ-mangostin	13873657	380.4
Arctiin	100528	534.6
Arctigenin	64981	372.4
10C	76370315	328.4
Caffeic acid phenethyl ester	5281787	284.3
Retinol	445354	286.5
PGH_2	445049	352.5
UVI2008	124081750	427.4
PGA1	5281912	336.5

Table S2. Predicted binding energy of (-) kusunokinin with 41 proteins associated with CSF1R and AKT pathways

Protein	PDB code	Resolution (Å)	Binding energy (kcal/mol)		ΔΔG (kcal/mol)
			(-)-kusunokinin	Native ligand	
Cell proliferation					
AKR1B1	1US0	0.66	-11.11	-9.83	-1.28
MEK2	1S9I	3.20	-10.14	-9.56	-0.58
TrkC	3V5Q	2.20	-9.67	-13.51	3.84
TrkB	4AT3	1.77	-9.60	-9.94	0.34
FGFR3	4K33	2.34	-9.49	-8.60	-0.89
TRα	3ILZ	1.85	-9.41	-11.48	2.07
EphA3	3DZQ	1.75	-9.42	-12.9	3.48
SHIP-1	6IBD	1.48	-9.32	-10.85	1.53
TRβ	1N46	2.20	-9.31	-11.48	2.17
EP3	6M9T	2.50	-9.22	-8.08	-1.14
EP4	5YHL	4.20	-9.18	-11.86	2.68
PDGFRA	5GRN	1.77	-9.10	-12.28	3.18
PLA2	1POE	2.10	-8.92	-9.10	0.18

Protein	PDB code	Resolution (Å)	Binding energy (kcal/mol)		ΔΔG (kcal/mol)
			(-)-kusunokinin	Native ligand	
ALK	5FTO	2.22	-8.75	-11.65	2.90
DDR2	6FER	2.87	-8.74	-10.35	1.61
INSR	3EKK	2.10	-8.72	-10.18	1.46
DDR1	3ZOS	1.92	-8.70	-10.79	2.09
RON	3PLS	2.24	-8.67	-8.15	-0.52
MER	3BPR	2.80	-8.52	-7.62	-0.90
AKT2	2JDO	1.80	-8.39	-9.54	1.15
PLCB	2ZKM	1.62	-8.27	-9.38	1.11
LYN	3A4O	3.00	-8.25	-8.34	0.09
c-RAF	3OMV	4.00	-8.24	-9.41	1.17
EphA7	3DKO	2.00	-8.16	-10.47	2.31
PLCG	4FBN	2.40	-8.15	-7.82	-0.33
B-Raf	5CSW	2.66	-8.13	-10.96	2.83
FGFR2	1OEC	2.40	-8.07	-10.1	2.03
FGFR4	6JPJ	2.64	-8.05	-7.52	-0.53
SHP2	5EHR	1.70	-8.03	-10.74	2.71

Protein	PDB code	Resolution (Å)	Binding energy (kcal/mol)		ΔΔG (kcal/mol)
			(-)-kusunokinin	Native ligand	
EphB1	5MJA	2.14	-7.78	-9.16	1.38
EphB3	5L6O	1.88	-7.78	-7.62	-0.16
AXL	5U6B	2.84	-7.75	-9.82	2.07
BTK	6O8I	1.42	-7.68	-8.99	1.31
FAK2	3FZR	2.70	-7.67	-7.93	0.26
IRS-1	1QQG	2.30	-7.42	-7.21	-0.21
SHIP-2	4A9C	2.10	-7.21	-12.79	5.58
MYC	6G6K	1.35	-5.57	-4.90	-0.67
Cell migration					
WASP*	1T84	-	-8.75	-9.77	1.02
CDC42	1DOA	2.60	-8.36	-7.67	-0.69
Angiogenesis					
VEGFR1	3HNG	2.70	-8.92	-11.68	2.76
TIE2	3L8P	2.40	-8.42	-13.04	4.62

* WASP structure was taken from the first conformer of the solution NMR structure.