Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supplementary material for

A molecular dynamics investigation of drug dissociation from SGLT and its implication in antidiabetic medication development

Ming-Hui Pang [a], Xue-Feng Liu [a, *], Xin-Guan Tan [a], Yu-Qing Wang [a]

a College of Mathematics and Physics, Chengdu University of Technology, Chengdu 610059, China

*Correspondence: liuxuefeng17@cdut.edu.cn (X.-F.L.);

Table S1. Hydrogen bond analysis with the equilibrium trajectories of the alpha-glucose at SGLT2 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
GLU99@OE2	α-glucose@O3	73.39	2.68	165.00
PHE98@O	α-glucose@O6	65.92	2.75	158.43
α-glucose@O3	ASN75@ND2	29.99	2.89	162.85
α-glucose@O2	TRP291@NE1	17.96	2.90	153.95
GLU99@OE1	α-glucose@O3	16.22	2.69	162.51
α-glucose@O2	LYS321@NZ2	13.25	2.87	154.31
α-glucose@O6	α-glucose@O2	13.02	2.78	147.93
α-glucose@O2	LYS321@NZ1	12.19	2.87	153.46
α-glucose@O2	LYS321@NZ3	11.01	2.87	153.31
α-glucose@O6	ALA102@N	9.90	2.91	147.67
ASN101@OD1	α-glucose@O6	9.25	2.80	158.36
ASN75@OD1	α-glucose@O2	7.87	2.75	152.41
GLU99@OE2	α-glucose@O4	7.16	2.70	156.34
GLU99@OE2	α-glucose@O2	7.02	2.66	161.30
α-glucose@O5	TRP291@NE1	4.80	2.89	151.92
α-glucose@O3	HIE80@NE2	4.48	2.89	154.76
SER287@OG	α-glucose@O2	3.80	2.80	157.50
α-glucose@O3	LYS321@NZ1	2.70	2.86	150.36
α-glucose@O6	ASN101@ND2	2.31	2.89	163.74
PHE98@O	α-glucose@O3	1.99	2.75	158.50
SER287@OG	α-glucose@O3	1.95	2.82	159.83
α-glucose@O3	LYS321@NZ2	1.81	2.84	147.38
α-glucose@O3	LYS321@NZ3	1.80	2.84	148.44
α-glucose@O5	ASN75@ND2	1.69	2.91	153.37
α-glucose@O4	LYS321@NZ3	1.52	2.89	155.14
PHE98@O	α-glucose@O4	1.19	2.80	153.62
ASN75@ND2	α-glucose@O2	0.94	2.92	155.05
SER287@OG	α-glucose@O6	0.77	2.84	154.32
PHE98@O	α-glucose@O2	0.65	2.79	161.16
α-glucose@O6	TYR291@OH	0.63	2.79	163.19
α-glucose@O4	ASN75@ND2	0.52	2.90	147.58
α-glucose@O6	SER287@OG	0.48	2.76	160.00
α-glucose@O2	α-glucose@O6	0.42	2.76	150.25
GLU99@OE1	α-glucose@O2	0.41	2.77	154.84
GLU99@OE1	α-glucose@O4	0.39	2.76	151.68
α-glucose@O4	GLN457@NE2	0.34	2.88	159.09
GLU99@O	α-glucose@O2	0.29	2.85	149.00
α-glucose@O2	ASN75@ND2	0.21	2.91	146.14
GLY79@O	α-glucose@O5	0.21	2.84	149.00

GLU99@OE2	α-glucose@O5	0.20	2.74	160.52
α-glucose@O1	TRP291@NE1	0.17	2.93	159.32
GLU99@O	α-glucose@O4	0.16	2.81	147.95
α-glucose@O5	LYS321@NZ3	0.13	2.89	143.34
α-glucose@O6	TRP291@NE1	0.11	2.91	149.24
α-glucose@O1	α-glucose@O6	0.06	2.60	136.94
α-glucose@O4	LYS321@NZ	0.06	2.84	144.36
α-glucose@O4	HIE80@NE2	0.06	2.87	151.68
α-glucose@O6	LYS321@NZ3	0.06	2.91	161.02
α-glucose@O4	LYS321@NZ2	0.05	2.86	156.80
α-glucose@O4	α-glucose@O5	0.05	2.73	137.65
GLN457@OE1	α-glucose@O4	0.04	2.72	157.20
α-glucose@O6	ASN101@ND2	0.04	2.87	161.69
SER287@OG	α-glucose@O5	0.04	2.86	156.85
α-glucose@O6	ASN101@N	0.04	2.94	139.86
α-glucose@O3	TRP291@NE1	0.04	2.94	160.54
ASN65@OD1	α-glucose@O4	0.03	2.85	162.12
α-glucose@O6	SER460@OG	0.03	2.85	162.61
α-glucose@O3	TYR290@OH	0.03	2.85	147.17
SER460@OG	α-glucose@O6	0.03	2.74	163.84
ASN101@OD1	α-glucose@O2	0.03	2.80	169.39
ASN101@OD1	α-glucose@O3	0.02	2.83	145.71
GLN457@OE1	α-glucose@O5	0.02	2.86	155.27
α-glucose@O1	GLN457@NE2	0.02	2.92	149.09
α-glucose@O6	LYS321@NZ1	0.01	2.88	156.81
α-glucose@O6	LYS321@NZ2	0.01	2.90	165.20
α-glucose@O3	α-glucose@O2	0.01	2.69	136.57
α-glucose@O5	α-glucose@O4	0.01	2.83	135.31
ASN75@ND2	α-glucose@O5	0.01	2.84	142.78
α-glucose@O4	LYS154@NZ	0.01	2.86	148.13
α-glucose@O2	HIE80@NE2	0.01	2.87	163.80
GLN457@OE1	α-glucose@O6	0.01	2.87	155.28

Table S2. Hydrogen bond analysis with the equilibrium trajectories of the beta-glucose at SGLT2 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
GLU99@OE2	β-glucose@O3	59.49	2.66	164.95
GLU99@OE2	β-glucose@O4	35.40	2.64	162.47
GLU99@OE1	β-glucose@O4	28.30	2.64	163.63
PHE98@O	β-glucose@O4	27.51	2.74	160.27
GLU99@OE1	β-glucose@O3	24.20	2.67	165.13
β-glucose@O2	β-glucose@O6	20.83	2.77	151.20
ASN101@OD1	β-glucose@O5	7.80	2.77	158.46
β-glucose@O4	LYS321@NZ1	7.30	2.86	155.05
β-glucose@O4	LYS321@NZ3	7.13	2.85	156.04
β-glucose@O4	LYS321@NZ2	6.68	2.87	154.63
β-glucose@O2	ASN75@ND2	6.18	2.90	153.26
SER287@OG	β-glucose@O6	5.77	2.81	159.69
GLN457@OE1	β-glucose@O6	5.60	2.75	157.45
GLU99@OE2	β-glucose@O2	4.94	2.65	164.48
ASN75@O	β-glucose@O2	4.69	2.83	154.70
PHE98@O	β-glucose@O5	4.09	2.75	159.43
GLU99@OE1	β-glucose@O5	3.84	2.71	166.21
β-glucose@O6	GLN457@NE2	3.84	2.88	160.20
ASN75@OD1	β-glucose@O3	3.41	2.72	161.39
β-glucose@O3	LYS321@NZ	2.69	2.86	146.27
β-glucose@O5	GLN457@NE2	1.79	2.90	155.05
ASN75@OD1	β-glucose@O2	1.77	2.80	157.34
β-glucose@O3	LYS321@NZ2	1.58	2.86	146.85
β-glucose@O6	GLN457@NE2	1.57	2.89	160.13
β-glucose@O3	LYS321@NZ1	1.54	2.85	147.58
β-glucose@O6	TYR290@OH	1.09	2.80	162.84
β-glucose@O6	SER287@OG	0.86	2.81	163.98
β-glucose@O5	ASN101@ND2	0.84	2.91	161.64
β-glucose@O2	TYR290@OH	0.72	2.81	158.53
β-glucose@O4	β-glucose@O5	0.66	2.74	137.94
β-glucose@O3	HIE80@NE2	0.58	2.87	147.03
β-glucose@O6	β-glucose@O2	0.38	2.79	147.15
β-glucose@O2	LYS321@NZ2	0.37	2.87	141.93
β-glucose@O6	ASN75@ND2	0.36	2.90	157.03
SER287@OG	β-glucose@O5	0.34	2.86	158.66
β-glucose@O1	GLN457@NE2	0.30	2.90	149.24
PHE98@O	β-glucose@O3	0.29	2.84	154.04
TYR290@OH	β-glucose@O6	0.18	2.83	161.60
β-glucose@O6	SER460@OG	0.18	2.85	157.33

β-glucose@O3	ASN75@ND2	0.17	2.89	147.60
β-glucose@O5	SER287@OG	0.16	2.87	164.51
β-glucose@O3	TYR290@OH	0.15	2.78	165.77
SER287@OG	β-glucose@O4	0.14	2.80	154.63
β-glucose@O6	LYS154@NZ	0.14	2.87	147.58
β-glucose@O2	LYS321@NZ1	0.14	2.88	142.33
ASN75@OD1	β-glucose@O6	0.13	2.85	154.63
ASN101@OD1	β-glucose@O4	0.11	2.90	155.83
β-glucose@O6	LYS154@NZ	0.09	2.88	146.07
β-glucose@O5	ASN101@ND2	0.09	2.91	160.06
GLN457@NE2	β-glucose@O6	0.09	2.91	151.99
β-glucose@O1	β-glucose@O6	0.08	2.62	137.41
β-glucose@O1	SER287@OG	0.07	2.83	144.28
β-glucose@O6	LYS154@NZ	0.07	2.89	147.73
β-glucose@O2	LYS321@NZ3	0.06	2.88	140.63
β-glucose@O4	β-glucose@O3	0.06	2.72	137.35
ASN75@O	β-glucose@O3	0.06	2.80	143.69
β-glucose@O1	GLN457@NE2	0.06	2.89	146.23
β-glucose@O2	HIE80@NE2	0.05	2.86	145.02
GLU99@OE1	β-glucose@O2	0.04	2.77	140.08
GLN457@OE1	β-glucose@O5	0.04	2.86	154.90
β-glucose@O4	ALA102@N	0.04	2.87	145.09
ASN75@O	β-glucose@O6	0.03	2.81	148.21
β-glucose@O5	GLN457@NE2	0.02	2.90	149.81
ASN75@OD1	β-glucose@O5	0.02	2.92	150.03
GLU99@O	β-glucose@O3	0.02	2.92	144.42
ASN75@ND2	β-glucose@O2	0.02	2.90	141.26
β-glucose@O2	β-glucose@O3	0.01	2.72	139.71
ASN75@ND2	β-glucose@O3	0.01	2.82	164.19
β-glucose@O4	ASN75@ND2	0.01	2.96	138.03
ASN75@OD1	β-glucose@O4	0.01	2.70	168.72
β-glucose@O4	HIE80@NE2	0.01	2.81	154.07
SER74@O	β-glucose@O6	0.01	2.84	169.16
TYR290@OH	β-glucose@O2	0.01	2.85	166.68
SER460@OG	β-glucose@O6	0.01	2.93	151.74
β-glucose@O2	ASN75@ND2	0.01	2.97	147.10
HIE80@ND1	β-glucose@O2	0.01	2.98	154.37

Table S3. Hydrogen bond analysis with the equilibrium trajectories of the Empagliflozin at SGLT2 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
GLU99@OE2	Empagliflozin@O3	95.65	2.63	165.44
PHE98@O	Empagliflozin@O2	90.60	2.75	162.02
SER287@OG	Empagliflozin@O4	72.86	2.80	153.94
GLN457@OE1	Empagliflozin@O5	68.48	2.78	161.19
Empagliflozin@O2	TRP291@NE1	44.27	2.89	161.03
Empagliflozin@O4	TRP291@NE1	6.00	2.89	146.69
Empagliflozin@O3	LYS321@NZ1	4.81	2.89	145.40
Empagliflozin@O3	HIE80@NE2	4.37	2.89	153.72
Empagliflozin@O3	LYS321@NZ2	3.93	2.89	145.08
Empagliflozin@O3	LYS321@NZ3	3.65	2.89	144.90
Empagliflozin@O1	GLN457@NE2	2.35	2.92	157.47
Empagliflozin@O7	THR87@OG1	1.74	2.87	157.63
Empagliflozin@O2	LYS321@NZ3	1.57	2.89	161.72
GLU99@OE1	Empagliflozin@O3	0.62	2.73	161.84
Empagliflozin@O4	SER287@OG	0.57	2.74	159.43
GLU99@OE2	Empagliflozin@O2	0.38	2.68	159.73
Empagliflozin@O2	LYS321@NZ2	0.37	2.90	160.78
PHE98@O	Empagliflozin@O4	0.36	2.80	154.96
Empagliflozin@O2	LYS321@NZ1	0.34	2.89	159.83
GLU99@OE1	Empagliflozin@O2	0.27	2.70	161.38
Empagliflozin@O6	TYR526@OH	0.25	2.80	147.77
ASN75@OD1	Empagliflozin@O3	0.20	2.76	154.43
Empagliflozin@O3	ASN75@ND2	0.20	2.91	163.06
Empagliflozin@O5	GLN457@NE2	0.19	2.90	146.86
ASN75@O	Empagliflozin@O3	0.10	2.82	151.26
Empagliflozin@O6	THR87@OG1	0.08	2.80	163.27
SER287@OG	Empagliflozin@O5	0.04	2.85	153.76
Empagliflozin@O3	TYR290@OH	0.01	2.85	156.73
Empagliflozin@O1	Empagliflozin@O5	0.01	2.59	136.44
Empagliflozin@O2	ASN75@ND2	0.01	2.88	156.82
ASN101@OD1	Empagliflozin@O4	0.01	2.89	161.70

Table S4. Hydrogen bond analysis with the equilibrium trajectories of the Ertugliflozin at SGLT2 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
HIE80@ND1	Ertugliflozin@H2	58.90	2.85	155.82
GLY79@O	Ertugliflozin@H3	33.06	2.82	154.19
Ertugliflozin@O1	GLN457@HE22	29.22	2.86	150.57
HIE80@O	Ertugliflozin@H3	8.22	2.82	157.34
Ertugliflozin@O3	Ertugliflozin@H4	7.95	2.75	149.77
Ertugliflozin@O6	GLN457@HE22	2.17	2.88	156.63
PHE453@O	Ertugliflozin@H1	2.09	2.80	158.16
PHE453@O	Ertugliflozin@H4	0.78	2.83	158.49
Ertugliflozin@O3	THR87@HG1	0.51	2.88	148.57
TYR526@OH	Ertugliflozin@H4	0.44	2.85	152.98
Ertugliflozin@O6	TYR526@HH	0.37	2.83	151.46
GLY83@O	Ertugliflozin@H1	0.32	2.87	147.16
Ertugliflozin@O6	Ertugliflozin@H1	0.31	2.75	146.74
Ertugliflozin@O1	Ertugliflozin@H4	0.12	2.66	138.18
GLY79@O	Ertugliflozin@H2	0.10	2.83	155.25
Ertugliflozin@O5	GLN457@HE22	0.06	2.93	157.73
Ertugliflozin@O4	Ertugliflozin@H3	0.02	2.81	137.27
Ertugliflozin@O7	ASN75@HD22	0.02	2.83	155.06
THR87@OG1	Ertugliflozin@H1	0.02	2.90	145.48
PHE453@O	Ertugliflozin@H3	0.02	2.73	160.70
Ertugliflozin@O5	GLN457@HE21	0.02	2.93	138.96
GLN457@NE2	Ertugliflozin@H4	0.02	2.93	142.79
ASP454@OD1	Ertugliflozin@H4	0.01	2.73	161.35
LEU84@N	Ertugliflozin@H1	0.01	2.94	143.03
HIE80@NE2	Ertugliflozin@H2	0.01	2.95	135.22
Ertugliflozin@O1	GLN457@HE21	0.01	2.97	137.43
GLN457@OE1	Ertugliflozin@H4	0.01	2.99	145.10

Table S5. Hydrogen bond analysis with the equilibrium trajectories of the LX2761 at SGLT2 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
LX2761@O6	ASN75@ND2	74.23	2.86	164.43
LX2761@O6	TYR290@OH	63.38	2.73	160.71
ASP454@OD1	LX2761@O2	27.22	2.68	165.63
LX2761@O5	LX2761@N2	25.07	2.78	148.88
HIE80@ND1	LX2761@N1	22.82	2.91	150.67
LX2761@O5	GLN457@NE2	19.96	2.85	157.97
LX2761@N3	TRP291@NE1	10.69	2.93	157.57
GLN451@OE1	LX2761@O4	10.16	2.74	161.69
GLY509@O	LX2761@O4	9.66	2.74	155.88
GLN457@OE1	LX2761@N2	7.56	2.83	159.15
LX2761@O4	GLN451@NE2	6.29	2.90	159.09
GLY509@O	LX2761@O3	3.40	2.73	159.47
ASP454@OD2	LX2761@O2	3.08	2.69	163.99
GLY450@O	LX2761@O2	1.31	2.77	161.87
SER508@OG	LX2761@O3	1.12	2.82	158.07
SER510@O	LX2761@O3	1.06	2.78	154.86
SER510@O	LX2761@O4	0.67	2.81	154.00
LX2761@O5	GLN457@NE2	0.65	2.89	149.68
GLN451@OE1	LX2761@O3	0.42	2.73	160.13
SER508@OG	LX2761@O4	0.42	2.85	154.24
GLN451@OE1	LX2761@O2	0.33	2.77	162.98
LX2761@O3	GLN451@NE2	0.30	2.90	159.52
LX2761@O4	SER510@N	0.26	2.93	150.67
LX2761@O3	SER508@OG	0.20	2.79	161.87
GLY450@O	LX2761@O4	0.16	2.76	162.21
LX2761@O2	LX2761@O3	0.14	2.72	137.98
LX2761@O2	GLN451@NE2	0.06	2.95	155.70
LX2761@O4	SER508@OG	0.05	2.79	156.78
LX2761@O4	GLY509@N	0.03	2.97	140.51
LX2761@O4	GLN451@NE2	0.02	2.91	144.68
HIE80@ND1	LX2761@N2	0.02	2.97	144.95
LX2761@O3	GLY509@N	0.02	2.86	163.82
CYS511@O	LX2761@O4	0.02	2.90	153.13
LX2761@O4	SER510@OG	0.02	2.93	157.20
LX2761@N2	ASN75@ND2	0.02	2.93	144.76
LX2761@O1	THR87@OG1	0.01	2.91	153.59
LX2761@N1	GLN457@NE2	0.01	2.97	139.05
LX2761@O3	LX2761@O4	0.01	2.77	136.71
ASP454@OD1	LX2761@O4	0.01	2.84	170.18

Table S6. Hydrogen bond analysis with the equilibrium trajectories of the alpha-glucose at SGLT1 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
ASP161@OD2	α-glucose@O6	75.02	2.72	164.49
ASN78@O	α-glucose@O2	53.28	2.69	165.06
ASN78@O	α-glucose@O5	16.31	2.80	159.74
THR156@O	α-glucose@O4	15.77	2.77	160.75
ASP161@OD1	α-glucose@O6	13.40	2.72	163.54
α-glucose@O2	α-glucose@O3	11.82	2.68	139.54
THR156@O	α-glucose@O5	6.62	2.72	163.28
α-glucose@O3	TYR290@OH	4.01	2.81	161.91
α-glucose@O6	α-glucose@O2	3.90	2.75	147.71
ASP161@OD1	α-glucose@O2	2.77	2.62	167.65
α-glucose@O6	HIE83@N	2.61	2.91	142.43
α-glucose@O6	GLY82@N	1.66	2.91	140.23
ASP161@OD2	α-glucose@O2	1.63	2.61	167.65
HIE83@ND1	α-glucose@O2	1.61	2.83	160.23
α-glucose@O2	TYR290@OH	1.57	2.79	149.79
α-glucose@O3	LYS157@NZ2	1.16	2.83	156.55
α-glucose@O3	LYS157@NZ3	0.87	2.87	154.15
TYR290@OH	α-glucose@O3	0.85	2.88	144.94
HIE83@ND1	α-glucose@O3	0.67	2.88	146.73
α-glucose@O3	LYS157@NZ1	0.60	2.85	155.96
α-glucose@O4	α-glucose@O3	0.43	2.73	138.91
α-glucose@O4	α-glucose@O5	0.31	2.72	137.76
GLY82@O	α-glucose@O3	0.11	2.85	144.54
α-glucose@O5	TYR290@OH	0.11	2.87	157.81
α-glucose@O5	ASN78@ND2	0.09	2.89	150.39
ASN78@O	α-glucose@O6	0.07	2.80	151.54
GLY82@O	α-glucose@O5	0.05	2.74	165.86
THR156@O	α-glucose@O3	0.04	2.87	142.31
HIE83@ND1	α-glucose@O5	0.04	2.91	153.02
α-glucose@O2	GLY82@N	0.04	2.95	139.93
α-glucose@O2	ASN78@ND2	0.03	2.95	140.80
α-glucose@O3	GLN457@NE2	0.01	2.87	162.07
ASN78@ND2	α-glucose@O3	0.01	2.93	138.87
α-glucose@O5	α-glucose@O4	0.01	2.65	136.56
TYR290@OH	α-glucose@O2	0.01	2.73	138.74
GLU102@OE2	α-glucose@O4	0.01	2.82	164.20
ASN78@ND2	α-glucose@O5	0.01	2.84	173.10
α-glucose@O2	LYS157@NZ3	0.01	2.85	152.24
α-glucose@O1	TYR290@OH	0.01	2.86	147.63

α-glucose@O3	ASN78@ND2	0.01	2.89	135.25
ASN78@O	α-glucose@O3	0.01	2.93	160.17
ASN78@ND2	α-glucose@O2	0.01	2.93	142.00
HIE83@N	α-glucose@O3	0.01	2.94	135.60
α-glucose@O2	HIE83@N	0.01	2.96	136.17
α-glucose@O4	LYS157@NZ3	0.01	2.98	137.66

Table S7. Hydrogen bond analysis with the equilibrium trajectories of the beta-glucose at SGLT1 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
GLU102@OE1	β-glucose@O5	83.41	2.65	165.22
β-glucose@O6	TRP291@NE1	26.12	2.90	160.74
GLN457@OE1	β-glucose@O4	18.90	2.72	157.37
GLU102@OE1	β-glucose@O4	11.36	2.65	164.99
GLN457@OE1	β-glucose@O3	10.47	2.75	157.16
β-glucose@O6	LYS321@NZ1	9.82	2.88	151.80
β-glucose@O6	LYS321@NZ2	8.06	2.88	151.41
β-glucose@O4	GLN457@NE2	6.69	2.87	157.40
β-glucose@O6	LYS321@NZ3	6.68	2.88	149.13
THR460@OG1	β-glucose@O5	6.02	2.78	160.89
GLU102@OE2	β-glucose@O5	4.49	2.71	153.89
GLN457@OE1	β-glucose@O2	4.49	2.77	160.12
β-glucose@O1	ASN78@ND2	3.62	2.91	158.42
β-glucose@O5	LYS157@NZ	1.90	2.84	156.18
β-glucose@O1	LYS321@NZ3	1.60	2.91	144.76
β-glucose@O5	LYS157@NZ	1.24	2.84	155.32
GLU102@OE1	β-glucose@O3	1.23	2.75	156.82
β-glucose@O1	LYS157@NZ	1.23	2.83	150.32
HIE83@ND1	β-glucose@O6	0.94	2.87	156.09
β-glucose@O5	LYS157@NZ	0.90	2.84	154.18
β-glucose@O3	GLN457@NE2	0.89	2.91	159.19
β-glucose@O5	ASN78@ND2	0.89	2.92	159.24
β-glucose@O6	LYS157@NZ	0.86	2.84	150.76
β-glucose@O1	LYS157@NZ	0.84	2.85	152.17
HIE83@ND1	β-glucose@O2	0.71	2.89	159.72
β-glucose@O1	LYS321@NZ1	0.67	2.92	144.25
β-glucose@O1	LYS157@NZ	0.60	2.85	149.91
ASN78@O	β-glucose@O6	0.51	2.76	157.31
β-glucose@O5	HIE83@NE2	0.49	2.86	152.40
β-glucose@O6	LYS157@NZ3	0.45	2.87	152.52
β-glucose@O6	LYS157@NZ2	0.31	2.87	150.68
β-glucose@O1	LYS321@NZ1	0.29	2.91	146.68
LEU286@O	β-glucose@O6	0.24	2.88	157.72
GLN457@OE1	β-glucose@O5	0.22	2.71	161.11
GLY82@O	β-glucose@O3	0.21	2.77	146.93
β-glucose@O5	GLN457@NE2	0.12	2.91	150.87
THR287@OG1	β-glucose@O6	0.09	2.76	162.00
GLY82@O	β-glucose@O2	0.07	2.77	153.83
β-glucose@O4	GLN457@NE2	0.07	2.87	158.15

β-glucose@O1	β-glucose@O6	0.05	2.61	137.49
GLN457@NE2	β-glucose@O4	0.05	2.89	156.89
β-glucose@O4	THR460@OG1	0.04	2.79	153.51
LEU286@O	β-glucose@O2	0.04	2.85	140.51
β-glucose@O4	β-glucose@O3	0.03	2.70	137.09
β-glucose@O6	ASN78@ND2	0.03	2.93	160.61
β-glucose@O5	LYS321@NZ3	0.03	2.93	138.73
GLU102@OE2	β-glucose@O4	0.02	2.85	139.65
β-glucose@O2	LYS157@NZ1	0.02	2.86	148.87
HIE83@ND1	β-glucose@O5	0.02	2.85	151.87
β-glucose@O2	LYS157@NZ2	0.01	2.82	155.62
β-glucose@O5	LYS321@NZ1	0.01	2.93	138.12
GLU102@OE1	β-glucose@O6	0.01	2.72	156.02
β-glucose@O4	β-glucose@O5	0.01	2.77	135.59
THR460@OG1	β-glucose@O4	0.01	2.80	145.95
β-glucose@O3	β-glucose@O2	0.01	2.85	135.86
ASN78@ND2	β-glucose@O6	0.01	2.90	152.10
β-glucose@O4	HIE83@NE2	0.01	2.90	147.30
β-glucose@O2	GLN457@NE2	0.01	2.91	146.52
SER461@OG	β-glucose@O6	0.01	2.91	146.58
β-glucose@O5	THR156@OG1	0.01	2.92	163.98
β-glucose@O6	GLY80@N	0.01	2.93	148.11
HIE83@NE2	β-glucose@O5	0.01	2.93	142.08
β-glucose@O2	LYS157@NZ3	0.01	2.95	156.56

Table S8. Hydrogen bond analysis with the equilibrium trajectories of the LX2761 at SGLT1 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
PHE101@O	LX2761@O4	70.21	2.81	164.20
THR287@OG1	LX2761@O3	69.00	2.81	151.00
LX2761@O2	GLN457@NE2	49.27	2.89	159.25
LX2761@O1	HIE83@NE2	39.97	2.89	154.72
LX2761@O4	TRP291@NE1	28.23	2.91	159.68
LX2761@O5	SER94@OG	24.49	2.77	159.12
ASP454@OD1	LX2761@N1	22.15	2.87	164.95
LX2761@O6	SER94@OG	4.64	2.80	152.53
ASP454@OD2	LX2761@N1	2.57	2.88	163.65
LX2761@O3	LX2761@O2	1.31	2.72	137.72
GLN457@OE1	LX2761@O2	1.27	2.82	152.59
LX2761@O6	GLN451@NE2	0.82	2.86	157.74
LX2761@N3	THR362@OG1	0.28	2.88	151.00
GLU102@OE2	LX2761@O4	0.21	2.74	161.15
LX2761@O6	GLN451@NE2	0.07	2.90	159.28
LX2761@O3	THR287@OG1	0.05	2.88	164.43
LX2761@O4	THR287@OG1	0.04	2.80	162.30
PHE101@O	LX2761@O3	0.02	2.82	158.10
GLN457@NE2	LX2761@O2	0.02	2.90	146.80
LX2761@N3	GLN451@NE22	0.02	2.93	158.62
LX2761@N3	GLN451@NE21	0.01	2.94	158.21
ASP273@OD2	LX2761@N2	0.01	2.75	146.56
LX2761@O5	LX2761@N2	0.01	2.76	142.31
LX2761@O6	THR90@OG1	0.01	2.78	163.72
LX2761@N3	ASN363@ND2	0.01	2.90	135.22
LX2761@N2	GLN451@NE2	0.01	2.97	147.80
LX2761@O2	GLN457@NE2	0.01	2.98	144.36

Table S9. Hydrogen bond analysis with the equilibrium trajectories of the Empagliflozin at SGLT1 site complex.

Acceptor	Donor	Occupancy (%)	Average Distance(Å)	Average Angle(°)
GLU102@OE2	Empagliflozin@O3	96.47	2.63	165.53
PHE101@O	Empagliflozin@O2	86.98	2.72	161.16
THR287@OG1	Empagliflozin@O4	84.61	2.79	157.16
Empagliflozin@O3	HIE83@NE2	46.21	2.86	151.76
Empagliflozin@O6	TYR526@OH	37.18	2.77	151.62
GLN457@OE1	Empagliflozin@O5	34.25	2.80	163.77
Empagliflozin@O3	ASN78@ND2	26.09	2.88	158.60
Empagliflozin@O2	LYS321@NZ3	23.20	2.87	156.99
Empagliflozin@O2	LYS321@NZ1	20.10	2.86	157.72
Empagliflozin@O2	LYS321@NZ2	19.89	2.87	157.35
Empagliflozin@O1	GLN457@NE2	10.12	2.91	160.32
Empagliflozin@O4	TRP291@NE1	9.11	2.90	150.84
GLU102@OE1	Empagliflozin@O3	1.71	2.85	147.51
ASN78@O	Empagliflozin@O3	1.56	2.81	156.47
Empagliflozin@O7	THR90@OG1	0.69	2.86	161.25
ASN78@OD1	Empagliflozin@O2	0.55	2.83	149.74
Empagliflozin@O1	Empagliflozin@O5	0.42	2.59	138.30
GLU102@OE2	Empagliflozin@O2	0.34	2.68	156.80
Empagliflozin@O3	LYS321@NZ2	0.19	2.88	141.78
Empagliflozin@O3	LYS321@NZ1	0.18	2.89	141.33
Empagliflozin@O3	LYS321@NZ3	0.16	2.90	142.36
THR287@OG1	Empagliflozin@O5	0.11	2.86	154.80
Empagliflozin@O5	GLN_441@NE2	0.09	2.95	141.52
Empagliflozin@O4	ASN78@ND2	0.04	2.89	163.99
MET283@O	Empagliflozin@O5	0.03	2.86	156.01
PHE101@O	Empagliflozin@O5	0.02	2.87	150.95
Empagliflozin@O4	Empagliflozin@O2	0.01	2.74	135.43
Empagliflozin@O2	ASN78@ND2	0.01	2.83	141.98

Table S10. The energy component of binding free energy (MM/GBSA method).

complex(SGLT2)	ΔE_{vdW}	ΔE_{ele}	$\Delta G_{pol,\ GB}$	ΔG_{nonpol}	ΔG_{gas}	ΔG_{sol}	ΔG_{total}
alpha-glucose	-16.62 ± 0.15	-48.78 ± 0.36	43.95 ± 0.26	-3.25 ± 0.01	-65.40 ± 0.35	40.69 ± 0.26	-24.70 ± 0.26
beta-glucose	-11.63 ± 0.17	-44.23 ± 0.47	44.63 ± 0.31	-2.97 ± 0.01	-55.86 ± 0.48	41.66 ± 0.30	-14.20 ± 0.34
empagliflozin	-58.23 ± 0.17	-64.36 ± 0.32	62.70 ± 0.22	-8.22 ± 0.01	-122.58 ± 0.29	54.49 ± 0.22	-68.10 ± 0.23
ertugliflozin	-56.97 ± 0.14	-24.22 ± 0.33	47.03 ± 0.24	-7.28 ± 0.01	-81.19 ± 0.32	39.74 ± 0.24	-41.45 ± 0.25
LX2761	-72.20 ± 0.20	-49.22 ± 0.62	67.70 ± 0.50	-9.70 ± 0.02	-121.42 ±0.56	58.00 ± 0.50	-63.42 ± 0.30

[a]All values are in kcal/mol

Table S11. The energy component of binding free energy (MM/GBSA method).

complex(SGLT1)	ΔE_{vdW}	ΔE_{ele}	$\Delta G_{pol,\ GB}$	ΔG_{nonpol}	ΔG_{gas}	ΔG_{sol}	ΔG_{total}
alpha-glucose	-16.85 ± 0.13	-31.43 ± 0.43	42.52 ± 0.30	-3.03 ± 0.01	-48.29 ± 0.38	39.50 ± 0.30	-8.79 ± 0.19
beta-glucose	-15.55 ± 0.15	-42.77 ± 0.41	45.72 ± 0.40	-3.40 ± 0.01	-58.32 ± 0.36	42.32 ± 0.40	-16.01± 0.38
LX2761	-82.30 ± 0.22	-52.46 ± 0.45	59.10 ± 0.37	-11.00 ± 0.02	-134.76 ± 0.44	48.09 ± 0.37	-86.67 ± 0.30
empagliflozin	-54.60 ± 0.20	-64.44 ± 0.56	44.74 ± 0.33	-7.93 ± 0.01	-119.04 ± 0.55	36.82 ± 0.33	-82.23 ± 0.43

[a]All values are in kcal/mol

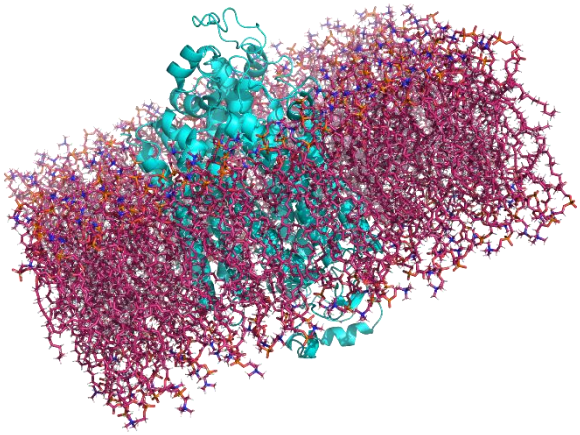

Fig. S1. The model of the membrane protein of SGLT2. the protein is inserted into DOPC lipid bilayer used by CHARMM-GUI. lipid bilayer was colored in pink and blue with stick representation. Sodium-dependent glucose cotransporters (SGLT) was colored cyan in cartoon representation. The same is true in the SGLT1 system

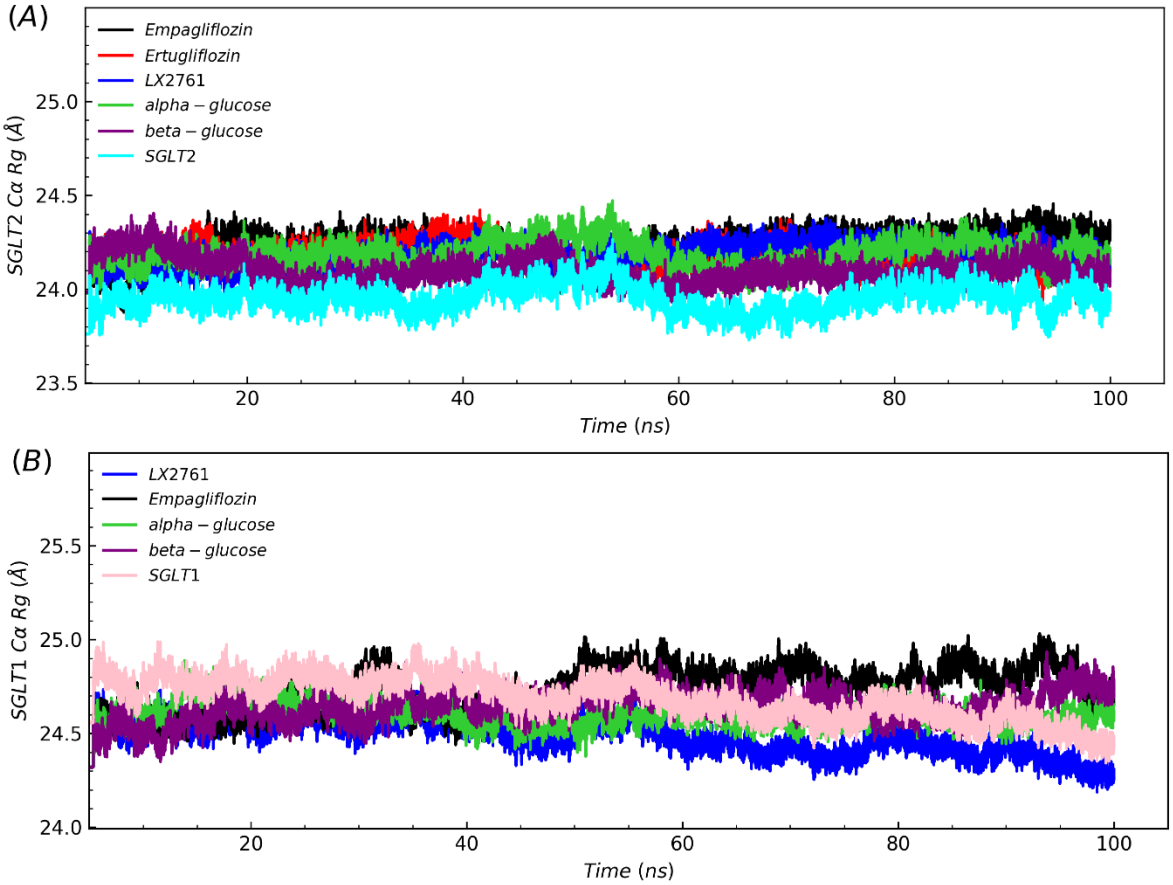

Fig. S2. The radius of gyration (Rg) of (A)SGLT2, (B)SGLT1.

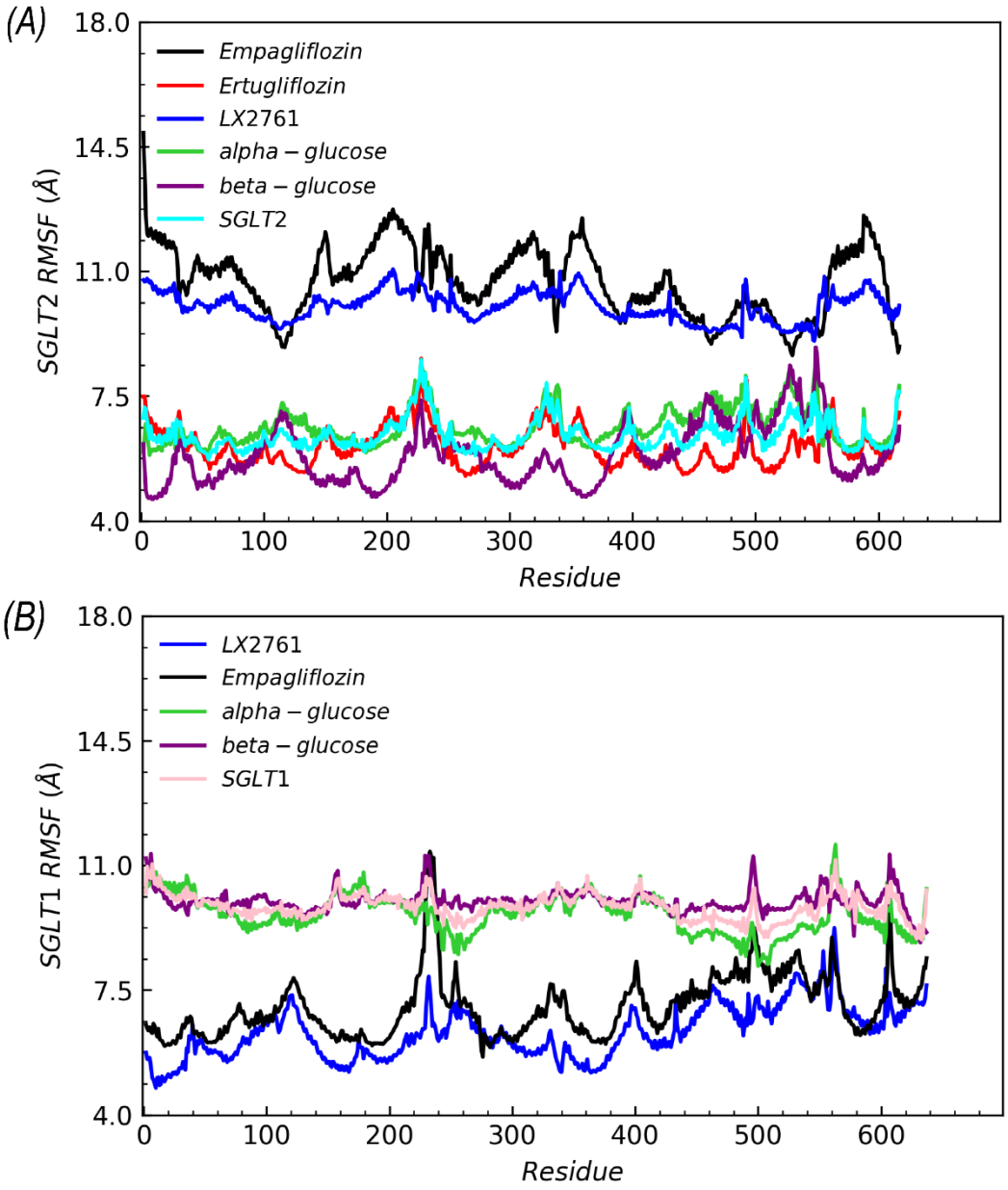

Fig. S3. The root-mean-square fluctuation (RMSF) of (A)SGLT2, (B)SGLT1.

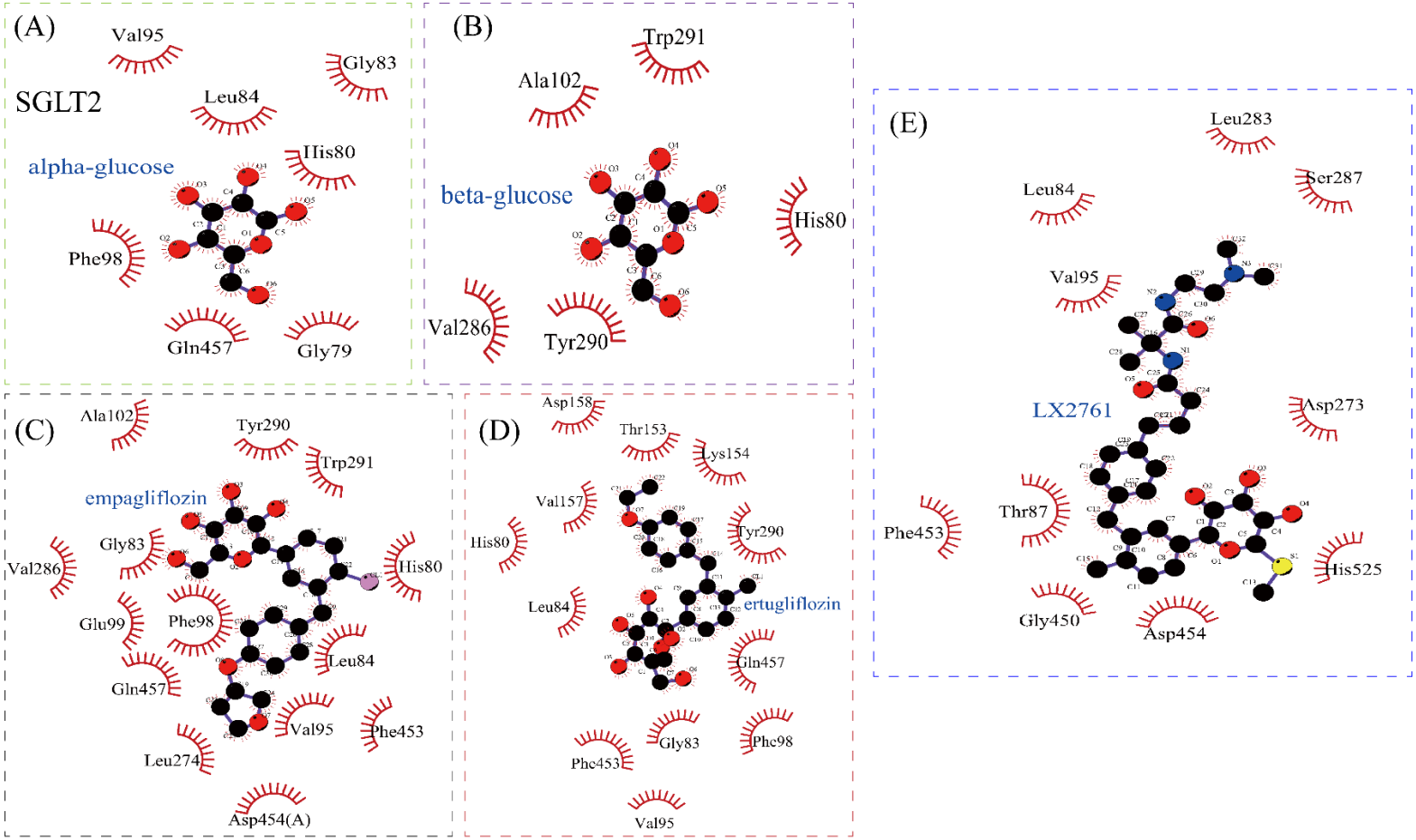

Fig.S4. The hydrophobic interaction between the five ligands bounded at the SGLT2. The stick (in the middle) and red arc represented ligands and SGLT2 residues, respectively. (A) SGLT2-alpha-glucose complex. (B) SGLT2-beta-glucose complex. (C) SGLT2-Empagliflozin complex. (D) SGLT2-Ertugliflozin complex. (E) SGLT2-LX2761 complex.

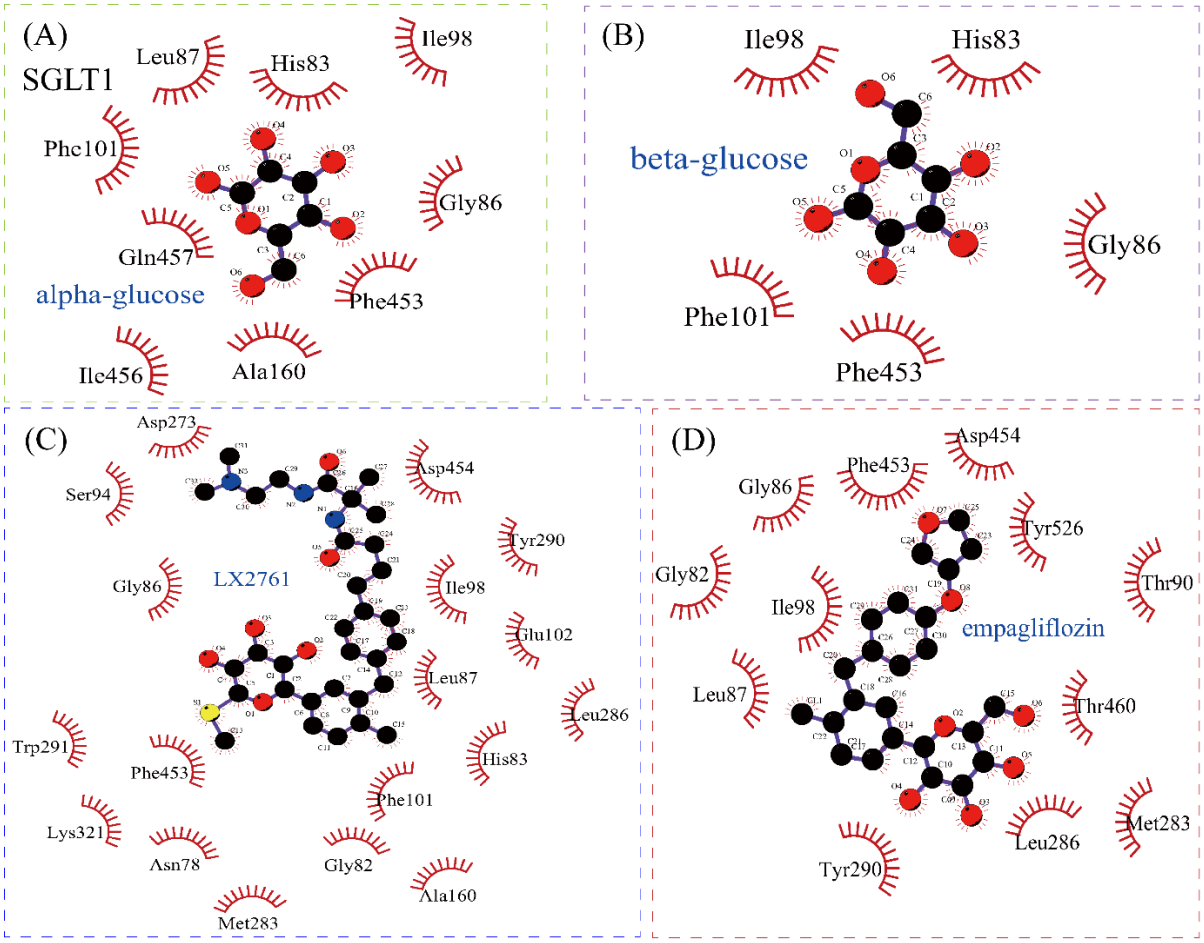

Fig.S5. The hydrophobic interaction between the four ligands bounded at the SGLT1. The stick (in the middle) and red arc represented ligands and SGLT1 residues, respectively. (A) SGLT1-alpha-glucose complex. (B) SGLT1-beta-glucose complex. (C) SGLT1-LX2761 complex. (D) SGLT1-Empagliflozin complex.

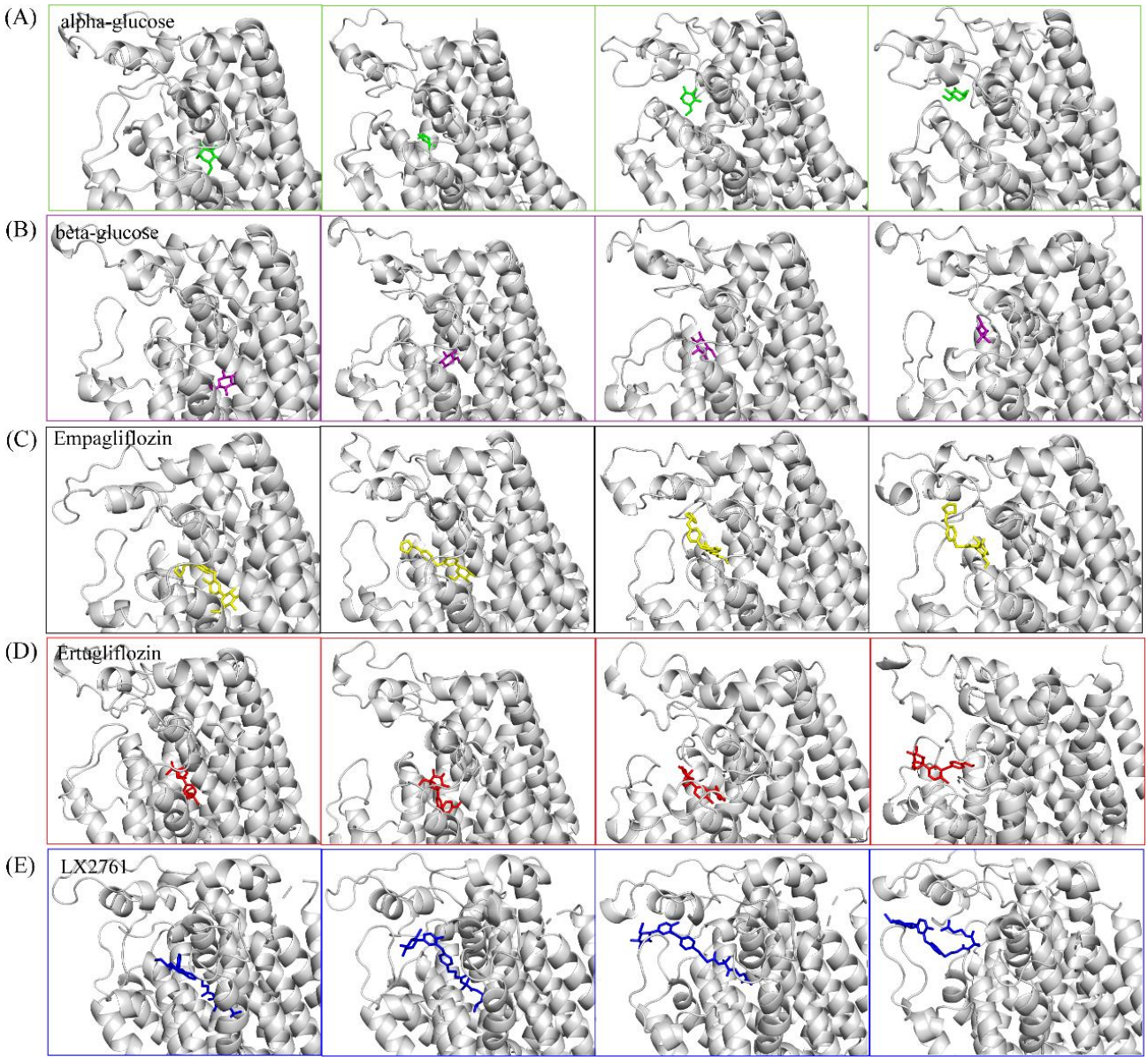

Fig.S6. Intermediate snapshots of the five systems during PMF simulations, SGLT2 and ligand are represented as gray cartoons and colo red sticks, respectively. The selected windows are respectively 1, 20, 40, 50ns. All molecules move between TM1b, TM2, TM6a and TM10. (A) SGLT2-alpha-glucose system, alpha-glucose is in green. (B) SGLT2-beta-glucose system, beta-glucose is in purple. (C) SGLT2-Empagliflozin system, empagliflozin is yellow. (D) SGLT2-Ertugliflozin system, ertugliflozin in red. (E) SGLT2-LX2761 system, LX2761 in blue.

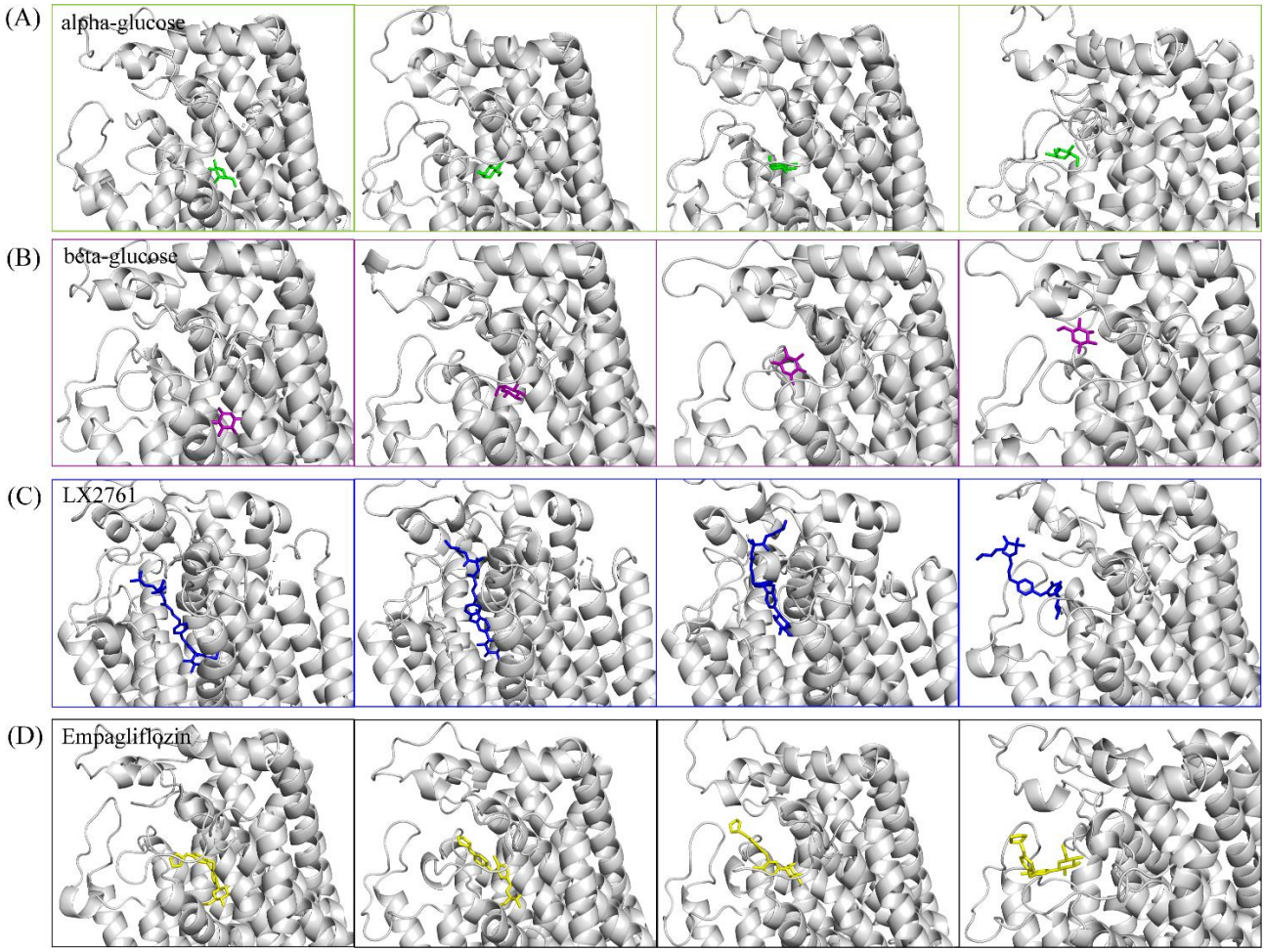

Fig.S7. Intermediate snapshots of the four systems during PMF simulations, SGLT1 and ligand are represented as gray cartoons and colored sticks, respectively. The selected windows are respectively 1, 20, 40, 50ns. All molecules move between M1b, M2, M6a and M10. (A) SGLT1-alpha-glucose system, alpha-glucose is in green. (B) SGLT1-beta-glucose system, beta-glucose is in purple. (C) SGLT1-LX2761 system, LX2761 in blue. (D) SGLT1-Empagliflozin system, empagliflozin is yellow.