Supplementary information

Comprehensive structure-activity relationship (SAR) investigation of C-aryl glycoside derivatives for the development of SGLT1/SGLT2 dual inhibitors

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Table of Contents

Table S1 SMILES notation for the designed compounds

Comp.	SMILES
C1	ClC1=CC=C([C@H]2O[C@H](SCC(N)=O)[C@@H](O)[C@H](O)[C@H]2O)C=C1CC3=CC=C(OCC)C=C3
C2	ClC1=CC=C([C@H]2O[C@H](SCCCO)[C@@H](O)[C@H](O)[C@H]2O)C=C1CC3=CC=C(OCC)C=C3
C3	ClC1=CC=C([C@H]2O[C@H](SC[C@H](O)CO)[C@@H](O)[C@H](O)[C@H]2O)C=C1CC3=CC=C(OCC)C=C3
C4	ClC1=CC(OC)=C([C@H]2O[C@H](SC[C@H](O)CO)[C@@H](O)[C@H](O)[C@H]2O)C=C1CC3=CC=C(OCC)C=C3
C5	O[C@@H]([C@H](O)[C@H]1O)[C@@H](SC[C@@H]2OC2)OC1C3=CC=C(Cl)C(CC4=CC=C(OCC)C=C4)=C3
C6	O[C@@H]([C@H](O)[C@H]1O)[C@@H](SC[C@@H]2OC2)OC1C3=C(OC)C=C(Cl)C(CC4=CC=C(OCC)C=C4)=C3
Sotagliflozin	O[C@@H]([C@H](O)[C@H]1O)[C@@H](SC)OC1C2=CC=C(Cl)C(CC3=CC=C(OCC)C=C3)=C2

Table S2 Docking results of all SGLT1 inhibitors

Comp.	IC_{50} (nM)	Exp. PIC_{50}	Docking Score (kcal/mol)
A1	13137	4.8815	-5.136
A2	12335	4.9089	-5.462
A3	5314	5.2746	-6.337
A4	4987	5.3022	-6.563
A5	18679	4.7282	-4.878
A6	81487	4.889	-3.904
A7	24146	4.6172	-4.618
A8	5902	5.2290	-5.553
A9	158	6.8013	-7.333
A10	126	6.8996	-7.241
A11	3086	5.5106	-5.696
A12	6281	5.202	-5.210
A13	2050	5.6882	-5.814
A14	546	6.2628	-6.685
A15	4	8.3979	-9.981
A16	5	8.301	-10.380
A17	5	8.301	-10.032
A18	53	7.2757	-8.448
A19	58	7.2366	-8.745
A20	32	7.4949	-7.886
A21	33	7.3468	-8.842
A22	48	7.3188	-8.997
A23	49	7.3098	-8.582
A24	37	7.4318	-7.570
A25	96	7.0177	-8.113
A26	34	7.4685	-8.572
A27	112	6.9508	-7.774

A28	269	6.5702	-7.082
A29	165	6.7825	-7.269
A30	93	7.0315	-8.291
A31	221	6.6556	-7.198
A32	25	7.6021	-7.662
A33	287	6.5421	-7.091
A34	31	7.5086	-7.679
A35	36.2	7.4413	-7.889

Table S3 Docking results of all SGLT2 inhibitors

Comp.	IC_{50} (nM)	Exp. pIC_{50}	Docking Score (kcal/mol)
B1	5.9	8.2291	-8.718
B2	22.3	7.6517	-8.764
B3	6.8	8.1675	-8.802
B4	28.4	7.6517	-8.010
B5	0.882	9.0545	-9.191
B6	43.1	7.3655	-8.023
B7	0.927	9.0329	-9.228
B8	1.1	8.9586	-8.586
B9	76.3	7.1175	-7.912
B10	17.4	7.7595	-8.143
B11	10.8	7.9666	-8.593
B12	1.37	8.8633	-8.882
B13	18.8	7.7258	-8.209
B14	1.16	8.9355	-8.742
B15	1.71	8.7670	-9.250
B16	2.68	8.5719	-8.331
B17	1.51	8.8210	-8.304
B18	1.77	8.8355	-8.366
B19	1.78	8.821	-8.194
B20	1	9	-9.494
B21	1	9	-9.244
B22	2	8.6990	-9.302
B23	1	9	-8.377
B24	1	9	-8.430
B25	1	9	-8.630
B26	1	9	-9.111
B27	3	8.5229	-8.689

B28	221	6.6556	-7.697
B29	2.2	8.6576	-8.749
B30	7.4	8.1308	-8.382
B31	0.88	9.0555	-8.845
B32	2.3	8.6383	-8.583
B33	2251	5.6476	-6.047
B34	2300	5.6383	-6.999
B35	5478	5.2614	-6.093
B36	1520	5.8182	-7.051
B37	3296	5.4820	-6.138
B38	32	7.4949	-8.121
B39	8.1	8.0915	-8.102
B40	17	7.7696	-7.937
B41	2.4	8.6198	-8.197
B42	24.6	8.1675	-7.771
B43	2.39	8.767	-9.844
B44	10	8.1291	-8.911
B45	3.9	8.57169	-8.278
B46	1.8	8.7447	-8.188

Table S4 Docking results of SGLT2 inhibitors (marked drugs)

Comp.	Docking Score	Hydrogen bonds interaction
Sotagliflozin	-8.188	SER400 SER293
Dapagliflozin	-8.425	SER400 SER293 TYR150
Empagliflozin	-7.187	SER393 SER396 LYS154 ASP294
Ertugliflozin	-5.772	SER393 SER396 LYS154 ASP294 GLY77
Luseogliflozin	-6.013	SER393SER396 LYS154 ASP294 GLY77
Ipragliflozin	-7.191	SER393 SER396 LYS154 GLY77
tianagliflozin	-7.655	SER400 SER293
Rongliflozin	-7.587	SER396 SER74 TYR150 LYS154 ASP194
Hengliflozin	-6.765	SER393 SER396 LYS154 ASP294
Bexagliflozin	-8.087	SER393 SER146 LYS154 ASP294 SER74

Table S5 Hydrogen bonds interactions of designed compounds with SGLT1

Comp.	Hydrogen Bonds interaction
C1	SER396 HIS83
C2	ASP294 GLN295 ARG300
C3	SER396 LYS157
C4	ASP204 SER396 ALA76
C5	SER396 HIS83 GLY82
C6	SER396 SER400 LYS157
Sotagliflozin	ASP204 SER396

Table S6 Hydrogen bonds interactions of designed compounds with SGLT2

Comp.	Hydrogen bonds interaction
C1	ASP294 SER400
C2	ASP294 SER293 TYR150 SER400
C3	ASP294 SER400 TYR150 ALA73
C4	ASP294 SER396 SER393 LYS154 ASP201
C5	SER400 SER293 LYS154
C6	SER293 SER400 LYS154
Sotagliflozin	SER400 SER293

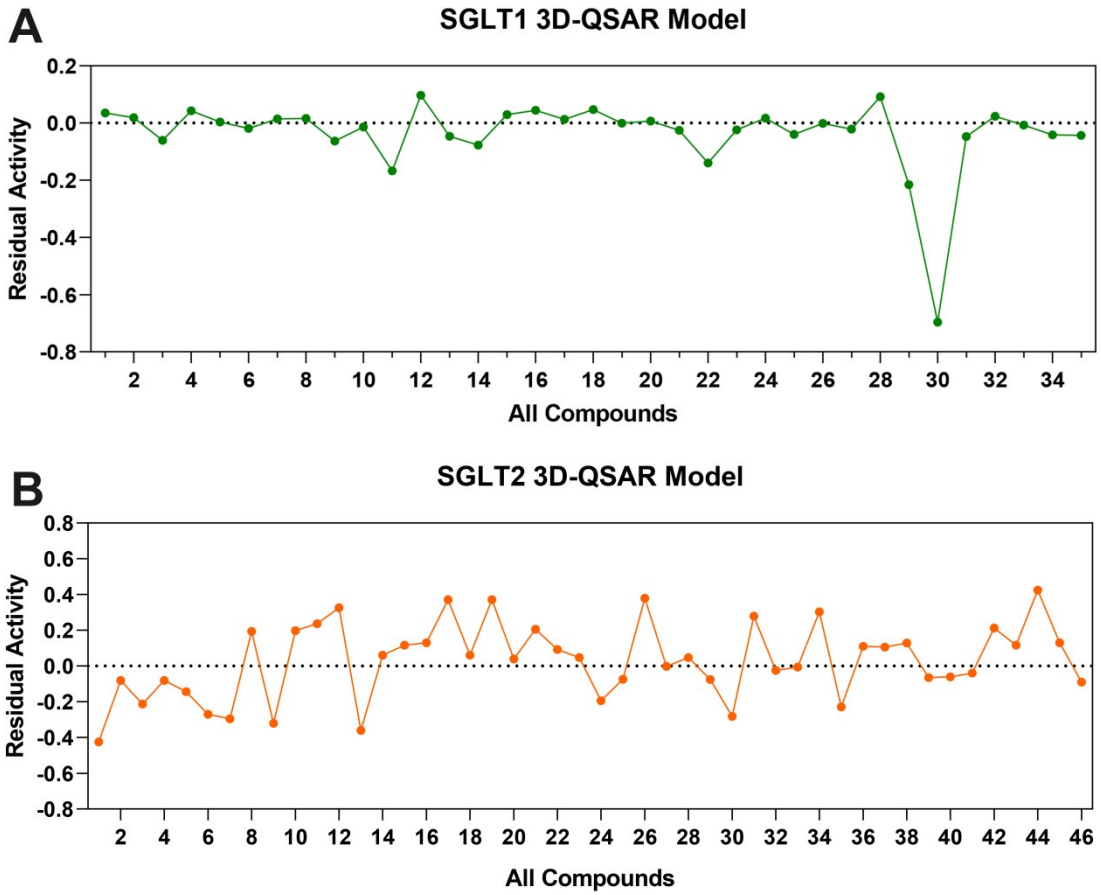

Fig. S1 Residual plots between the experimental and predicted values for SGLT1 (A) and SGLT2 (B) 3D-QSAR models.