

hGlyT-1	98	LKRGNGWNGQIEFVLTSVGYAVGLGNVWRFPYLCYRNGGGAFMPPYFIMLIFCGIPLFFMELSPGQFASQCGLGWV-RISPMFKGVGYGMM	186
hGlyT-2	189	KARGNWSSKLDLFILSMVGYAVGLGNVWRFPYLAQNGGGAFILPYLMLLALAGLPIFFLEVSLGQFASQGFVSQVW-KAIPALQGGCIAML	277
hGlyT-1 (6ZPL/6ZBV)	98	LKRGNGWNGQIEFVLTSVGYAVGLGNVWRFPYLCYRNGGGAFMPPYFIMLIFCGIPLFFMELSPGQFASQCGLGWV-RISPMFKGVGYGMM	186
dDAT (4M48)	25	DERETWSGKVDFLLSVIGFAVDLANVWRFPYLCYRNGGGAFILVPGIMLAVGGIPLFYMBLALGQHNRKGAITCWGRILVPLFKGIGYAVV	114
dDAT (4XP4/4XP9)	25	DERETWSGKVDFLLSVIGFAVDLANVWRFPYLCYRNGGGAFILVPGIMLAVGGIPLFYMBLALGQHNRKGAITCWGRILVPLFKGIGYAVV	114
dDAT (4XPH)	25	DERETWSGKVDFLLSVIGFAVDLANVWRFPYLCYRNGGGAFILVPGIMLAVGGIPLFYMBLALGQHNRKGAITCWGRILVPLFKGIGYAVV	114
hSERT (5I73)	77	GERETWSGKVDFLLSVIGFAVDLANVWRFPYLCYRNGGGAFILVPGIMLAVGGIPLFYMBLALGQHNRKGAITCWGRILVPLFKGIGYAVV	166
hGlyT-1	187	VVSTYIGIYYNVVICIAFYFFSSMTHVLFWAYCNPWNTHDCAG---VLDASNLTNNGSRPAALPSNLHLLNHSLQRT-----	262
hGlyT-2	278	IISVLIAIYYNVVICIAFYFFSSMTHVLFWAYCNPWNTHDCAG---VLDASNLTNNGSRPAALPSNLHLLNHSLQRT-----	367
hGlyT-1 (6ZPL/6ZBV)	187	VVSTYIGIYYNVVICIAFYFFSSMTHVLFWAYCNPWNTHDCAG---VLDASNLTNNGSRPAALPSNLHLLNHSLQRT-----	262
dDAT (4M48)	115	LIAFYVDFFYNVIAWSLRFFFASTNSLPWTSCNNIWNTPNCRP---FES-----	208
dDAT (4XP4/4XP9)	115	LIAFYVDFFYNVIAWSLRFFFASTNSLPWTSCNNIWNTPNCRP---FES-----	208
dDAT (4XPH)	115	LIAFYVDFFYNVIAWSLRFFFASTNSLPWTSCNNIWNTPNCRP---FES-----	208
hSERT (5I73)	167	LIAFYIASYYNTIMAWALYLLISSFTDQLPWTSCNNIWNTPNCRP---FES-----	224
hGlyT-1	263	-SPSEYYWRLVYLKL--SDDIGNFGEVRLPLLGCLGVSWLVVFLCLIRGVKSSGKVYFTATFPYVVLTLFVRGVTLEGAFGIMYYLT	349
hGlyT-2	368	VSGSEYYWRLVYLKL--SAGIEYFGEIRWPLALCLFLAWVIVYASLAGIKTSQKVYFTATFPYVVLTLFVRGVTLEGAFGIMYYLT	455
hGlyT-1 (6ZPL/6ZBV)	263	-SPSEYYWRLVYLKL--SDDIGNFGEVRLPLLGCLGVSWLVVFLCLIRGVKSSGKVYFTATFPYVVLTLFVRGVTLEGAFGIMYYLT	349
dDAT (4M48)	209	QSAASEYFNRYILELNRSEGIHDLGAIKWDMALCLLIVLYLCYFSLWKGISTSGKVWVFTALFPYAVLLILLIRGLTLPGSFLGIQYYLT	298
dDAT (4XP4/4XP9)	209	QSAASEYFNRYILELNRSEGIHDLGAIKWDMALCLLIVLYLCYFSLWKGISTSGKVWVFTALFPYAVLLILLIRGLTLPGSFLGIQYYLT	298
dDAT (4XPH)	209	QSAASEYFNRYILELNRSEGIHDLGAIKWDMALCLLIVLYLCYFSLWKGISTSGKVWVFTALFPYAVLLILLIRGLTLPGSFLGIQYYLT	298
hSERT (5I73)	225	TSPAEEYFTRVLQIHRSKGLDGGISVQLALCLLIFTVIYFISWKGISTSGKVWVFTALFPYAVLLILLIRGLTLPGSFLGIQYYLT	314
hGlyT-1	350	PQWDKILEAKVWGDAAQIFYSLGCAWGLITMASYNKFNHNCYRDSVIIISITNCATSVYAGFVIFSIILGFMANHLLGVDSVRVADH-GPG	438
hGlyT-2	456	PKWEKLTDAVWGDAAQIFYSLSAAWGLITLSSYNKFNHNCYRDLTIVTCTNSATSIAGFVIFSVIGFMANERKVNIEVADQ-GPG	544
hGlyT-1 (6ZPL/6ZBV)	350	PQWDKILEAKVWGDAAQIFYSLGCAWGLITMASYNKFNHNCYRDSVIIISITNCATSVYAGFVIFSIILGFMANHLLGVDSVRVADH-GPG	438
dDAT (4M48)	299	PNFSAIYKAEVWDAATQVFFSLGPGFGVLLAYASYNKYHNNVYKDALLTSFINSATSFIAAGFVIFSVLGYMAHTLGVRIEDVATE-GPG	387
dDAT (4XP4/4XP9)	299	PNFSAIYKAEVWDAATQVFFSLGPGFGVLLAYASYNKYHNNVYKDALLTSFINSATSFIAAGFVIFSVLGYMAHTLGVRIEDVATE-GPG	387
dDAT (4XPH)	299	PNFSAIYKAEVWDAATQVFFSLGPGFGVLLAYASYNKYHNNVYKDALLTSFINSATSFIAAGFVIFSVLGYMAHTLGVRIEDVATE-GPG	387
hSERT (5I73)	315	PNWQKLELTGVWIDAAQIFYSLGPGFGVLLAFASYNKFNHNCYQDALVTSVVCMTSFVSGFVITVLGYMAEMRNEDEVSEVAKDAGPS	404
hGlyT-1	439	LAFAVYFPAALTLPLISPLWSLLFFFMILLGLGTQFCLETLVTAIVDEVGNEWILQKTYVTLGAVAGFLLGIPLTSQAGIYWLMLD	528
hGlyT-2	545	LAFAVYFPAALTLPLISPLWSLLFFFMILLGLGTQFCLETLVTAIVDEVGNEWILQKTYVTLGAVAGFLLGIPLTSQAGIYWLMLD	633
hGlyT-1 (6ZPL/6ZBV)	439	LAFAVYFPAALTLPLISPLWSLLFFFMILLGLGTQFCLETLVTAIVDEVGNEWILQKTYVTLGAVAGFLLGIPLTSQAGIYWLMLD	528
dDAT (4M48)	388	LVFVYVPAAIATMPASTFWALIFFMMLATLGLDSSFGGSEAIITALSDEFP-KIKRNR-ELFVAGLFSLYFVVGASCTQGGFYFFHLLD	475
dDAT (4XP4/4XP9)	388	LVFVYVPAAIATMPASTFWALIFFMMLATLGLDSSFGGSEAIITALSDEFP-KIKRNR-ELFVAGLFSLYFVVGASCTQGGFYFFHLLD	475
dDAT (4XPH)	388	LVFVYVPAAIATMPASTFWALIFFMMLATLGLDSSFGGSEAIITALSDEFP-KIKRNR-ELFVAGLFSLYFVVGASCTQGGFYFFHLLD	475
hSERT (5I73)	405	LLFTIYAEAIANMPASTFFAIIFFMLITLGLDSSFAGLEGVITAVLDEFP-VWAKRRERFVLAVVITCFGSLVTLTFGGAYYVKLLE	493
hGlyT-1	529	NYAASFSLVVISIMCVAIMYIYGHNRNYFDIQMMLGFPPLFFQICWRVSPAIIFFILVFTVIQYQPIYNYHYQYQWAVAGIFLMAL	618
hGlyT-2	634	TYAASYALVIAIFELVGISYVYGLQRFCEDEIMMIGFQPNIFWKCWAFVTPILTIFILCFSEFYQWEMPTYSYGRYPNWSMVLGWLMLA	723
hGlyT-1 (6ZPL/6ZBV)	529	NYAASFSLVVISIMCVAIMYIYGHNRNYFDIQMMLGFPPLFFQICWRVSPAIIFFILVFTVIQYQPIYNYHYQYQWAVAGIFLMAL	618
dDAT (4M48)	476	RYAAGYSILVAVFEEAIAVSWIYGTNRFSIEDIRDMIGFPPGRYWCQVRFVAPIFLFFITVYLLIGYEPLTYADYVYPSWANALGWCIAG	565
dDAT (4XP4/4XP9)	476	RYAAGYSILVAVFEEAIAVSWIYGTNRFSIEDIRDMIGFPPGRYWCQVRFVAPIFLFFITVYLLIGYEPLTYADYVYPSWANALGWCIAG	565
dDAT (4XPH)	476	RYAAGYSILVAVFEEAIAVSWIYGTNRFSIEDIRDMIGFPPGRYWCQVRFVAPIFLFFITVYLLIGYEPLTYADYVYPSWANALGWCIAG	565
hSERT (5I73)	494	EYATGPAVLTVLIEAVAVSWFYGITQFCRDVKEMLGFSFGWFWRICWVAISPLFLFFIISFLMSPQQLRLFYQNYPYWSIILGYAIGT	583
hGlyT-1	619	SSVLCIPLYAMFRLCRTDGDITLLQRLKNAATKPSRD	653
hGlyT-2	724	CSVWIPIPMFVIMHLAGG-RFIERIKLVCSQPQD	757
hGlyT-1 (6ZPL/6ZBV)	619	SSVLCIPLYAMFRLCRTDGDITLLQRLKNAATKPSRD	653
dDAT (4M48)	566	SSVVMIPAVAIKLLSTPG-SLRQRFTILTTPWRD	599
dDAT (4XP4/4XP9)	566	SSVVMIPAVAIKLLSTPG-SLRQRFTILTTPWRD	599
dDAT (4XPH)	566	SSVVMIPAVAIKLLSTPG-SLRQRFTILTTPWRD	599
hSERT (5I73)	584	SSFICIPYIAYRLIITPG-TFKERIISITPBT	617

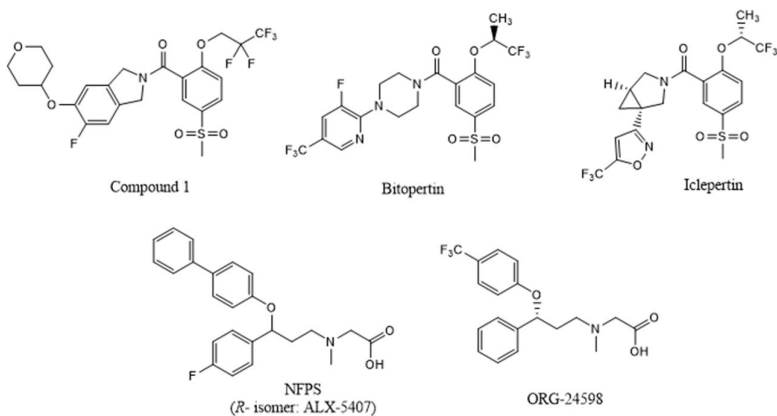
Figure S1. Amino acids sequence alignment used to build models of glycine transporters.

Table S1. Assessment of the selected models and their templates. Models and matrices were evaluated without considering the N- and C-terminus and the EL2 loop fragment.

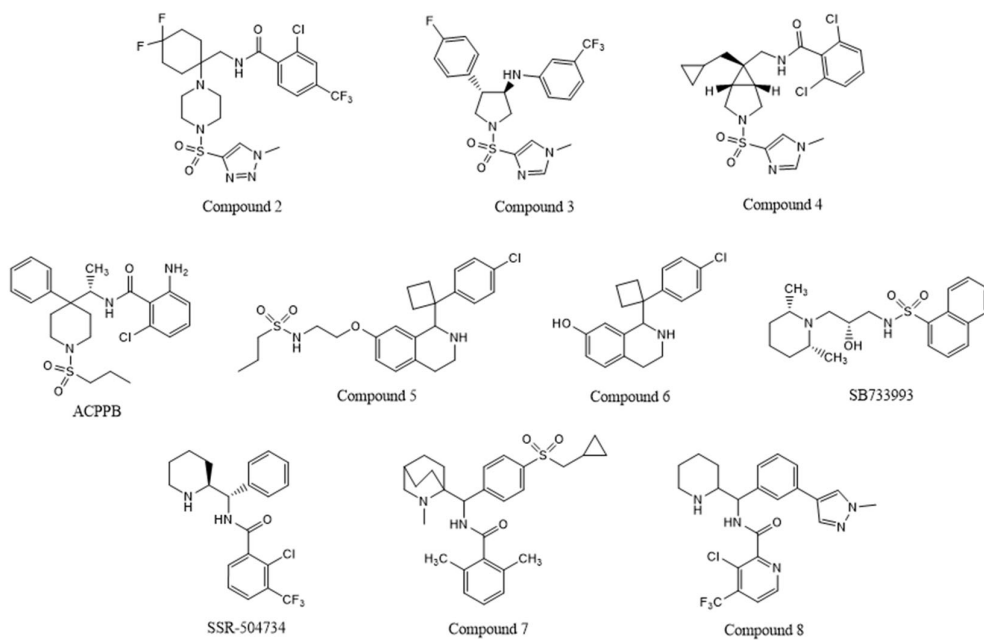
		Verify3D	QMEAN	DopeScore	Ramachandran plot	
					favoured	disallowed
models	GlyT-1 (4M48)	80.96	-3.84	-82413.5	91.5	0.4
	GlyT-1 (6ZPL)	77.65	-4.03	-79792.9	92.3	0.0
	GlyT-2 (4XP9)	88.61	-3.17	-84396.3	93.5	0.0
	GlyT-2 (6ZPL)	81.89	-4.02	-80678.7	93.0	0.0
templates	GlyT-1 (6ZPL)	79.17	-3.83	-79239.2	93.8	0.2
	DAT (4M48)	93.85	-2.68	-83617.4	90.7	0.2
	DAT (4XP9)	91.73	-2.62	-83761.5	94.7	0.0

GlyT-1 inhibitors

non-competitive



competitive



GlyT-2 inhibitors

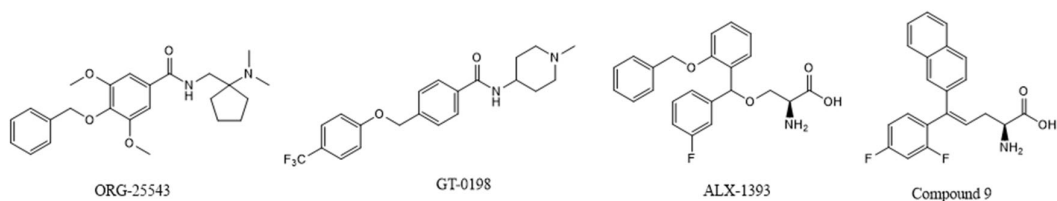


Figure S2. Structures of the compounds for which the detailed binding modes with glycine transporters were presented herein.

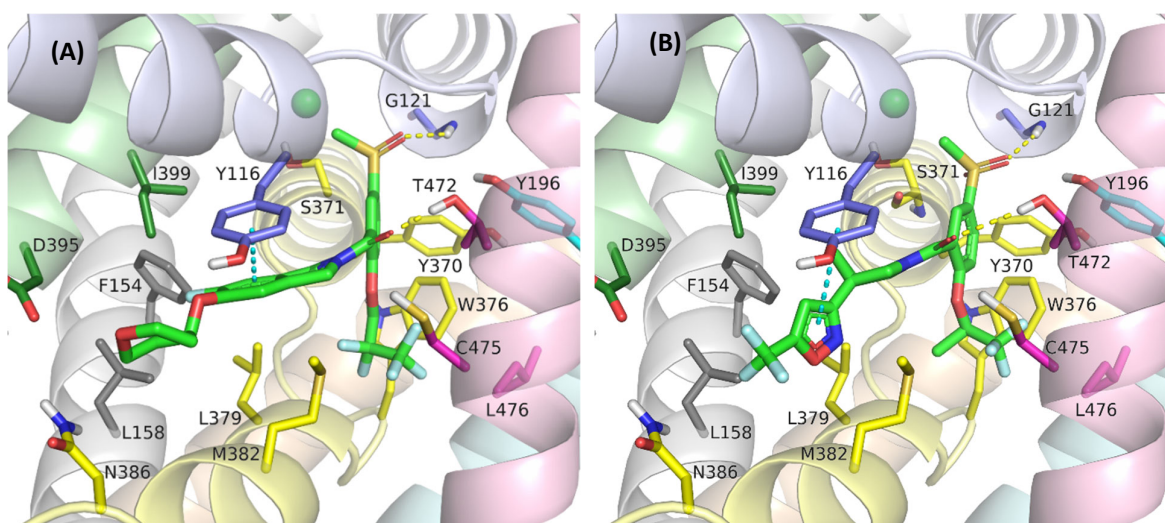


Figure S3. Binding mode of the compound **1** (A) and iclepertin (B) within GlyT-1 in inward-open state.

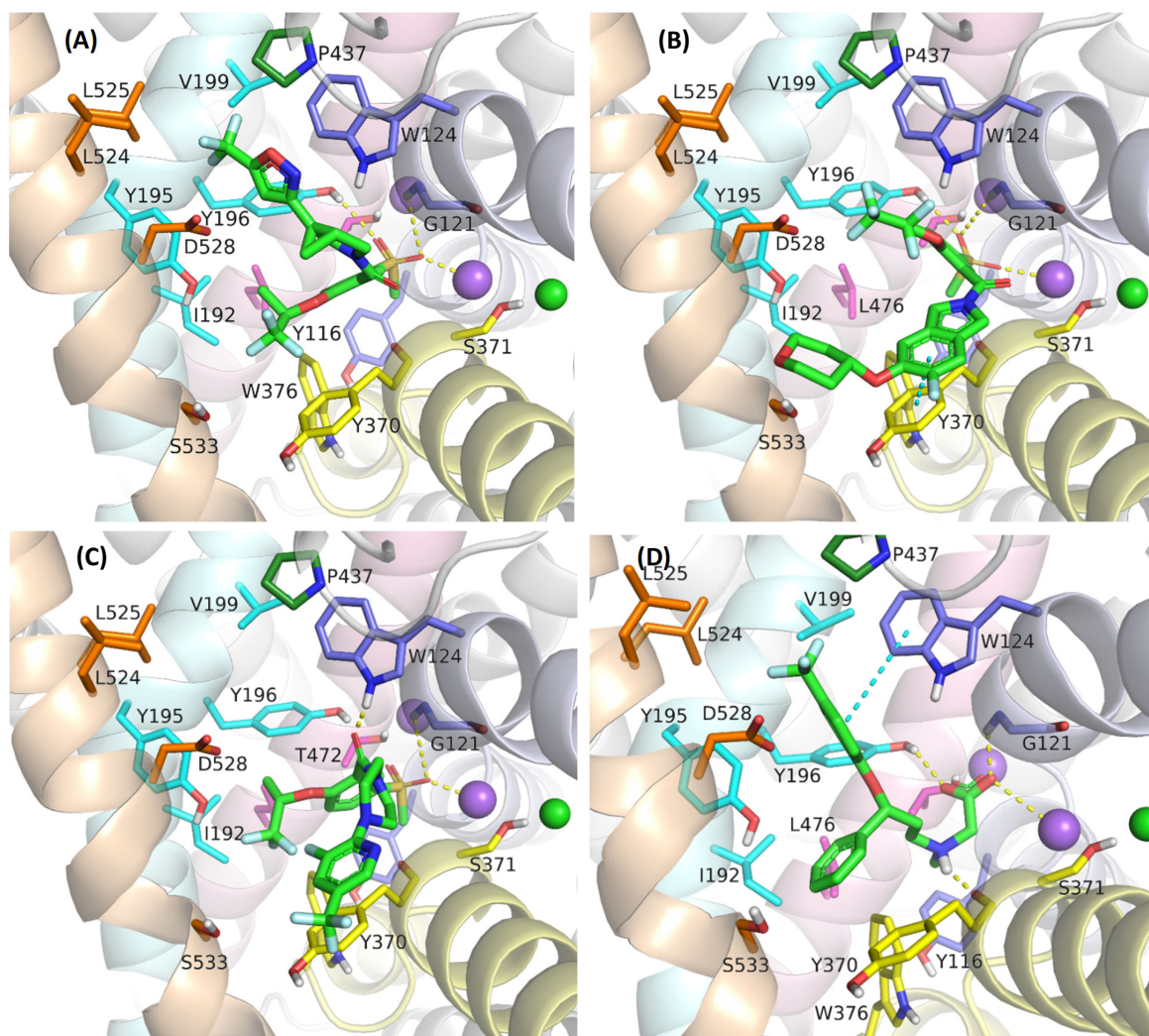


Figure S4. Binding mode of the iclepertin (A), compound **1** (B), bitopertin (C), and ORG-24598 (D) within GlyT-1 in outward-open state.

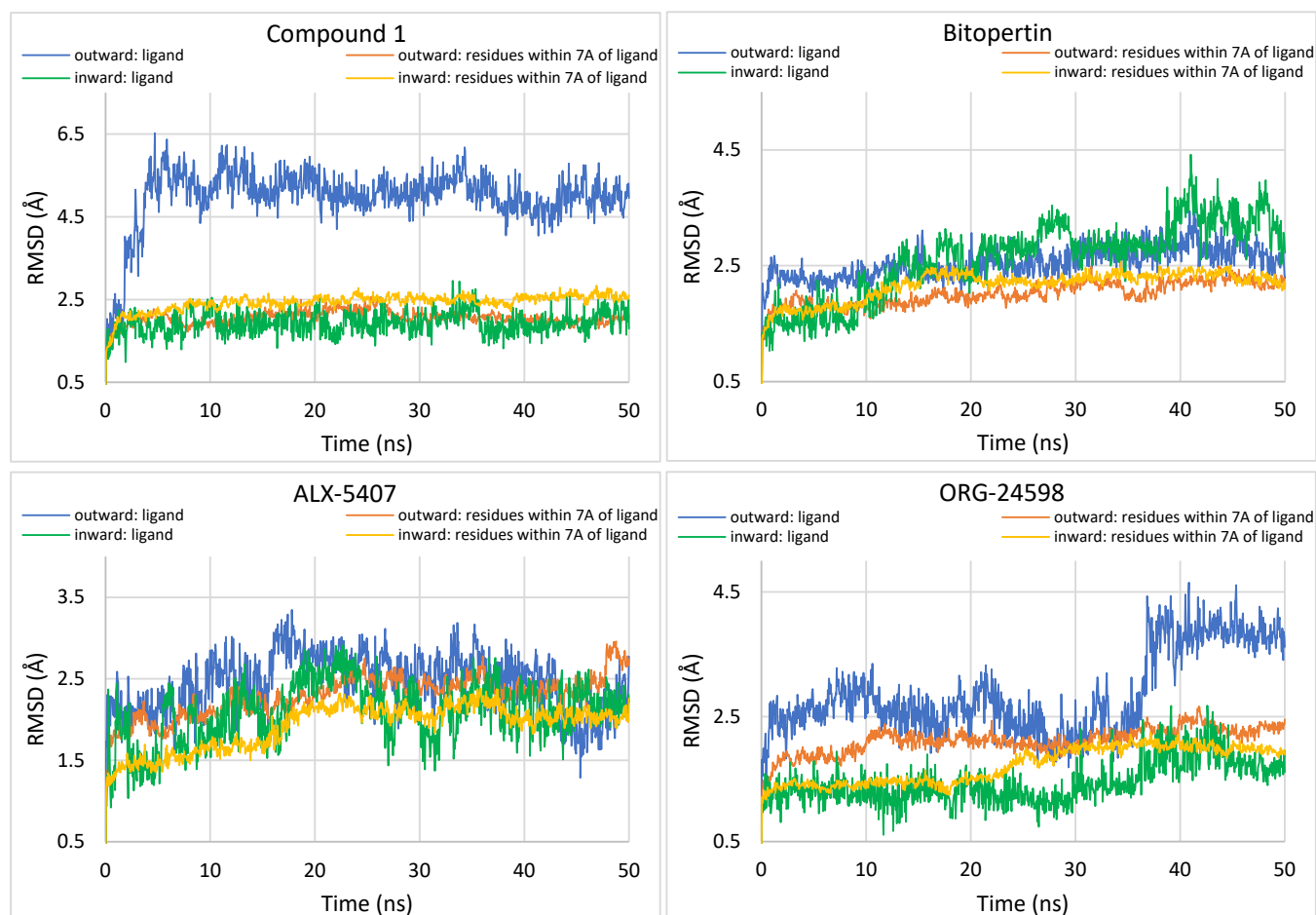


Figure S5. Comparison of RMSD changes in the course of molecular dynamics for compound **1**, bitopertin, ALX-5407, and ORG-24598 in complex with GlyT-1 in outward-open and inward-open states.

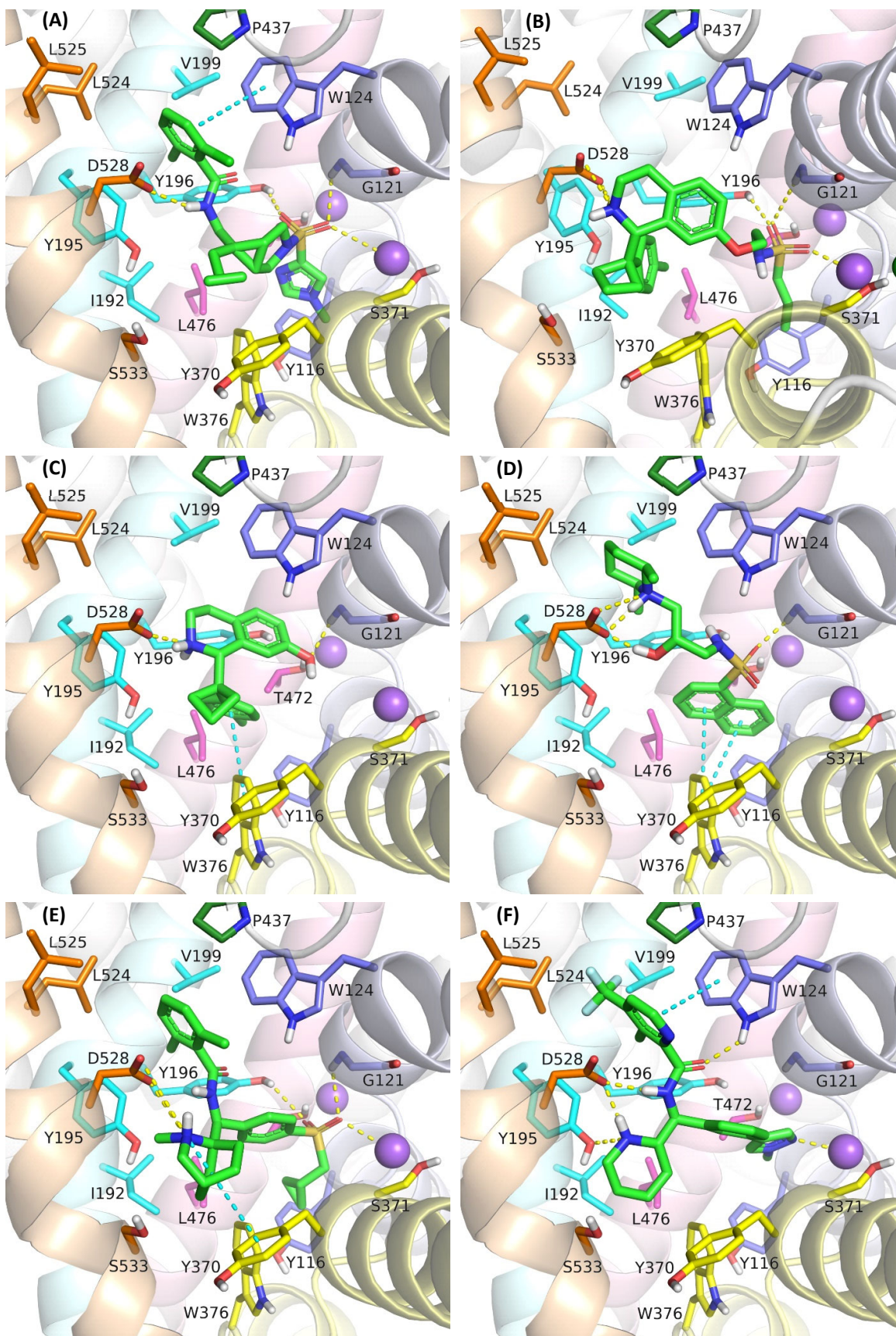


Figure S6. Binding mode of the compound 4 (A), compound 5 (B), compound 6 (C), SB733993 (D), compound 7 (E), and compound 8 (F) within GlyT-1 in outward-open state.

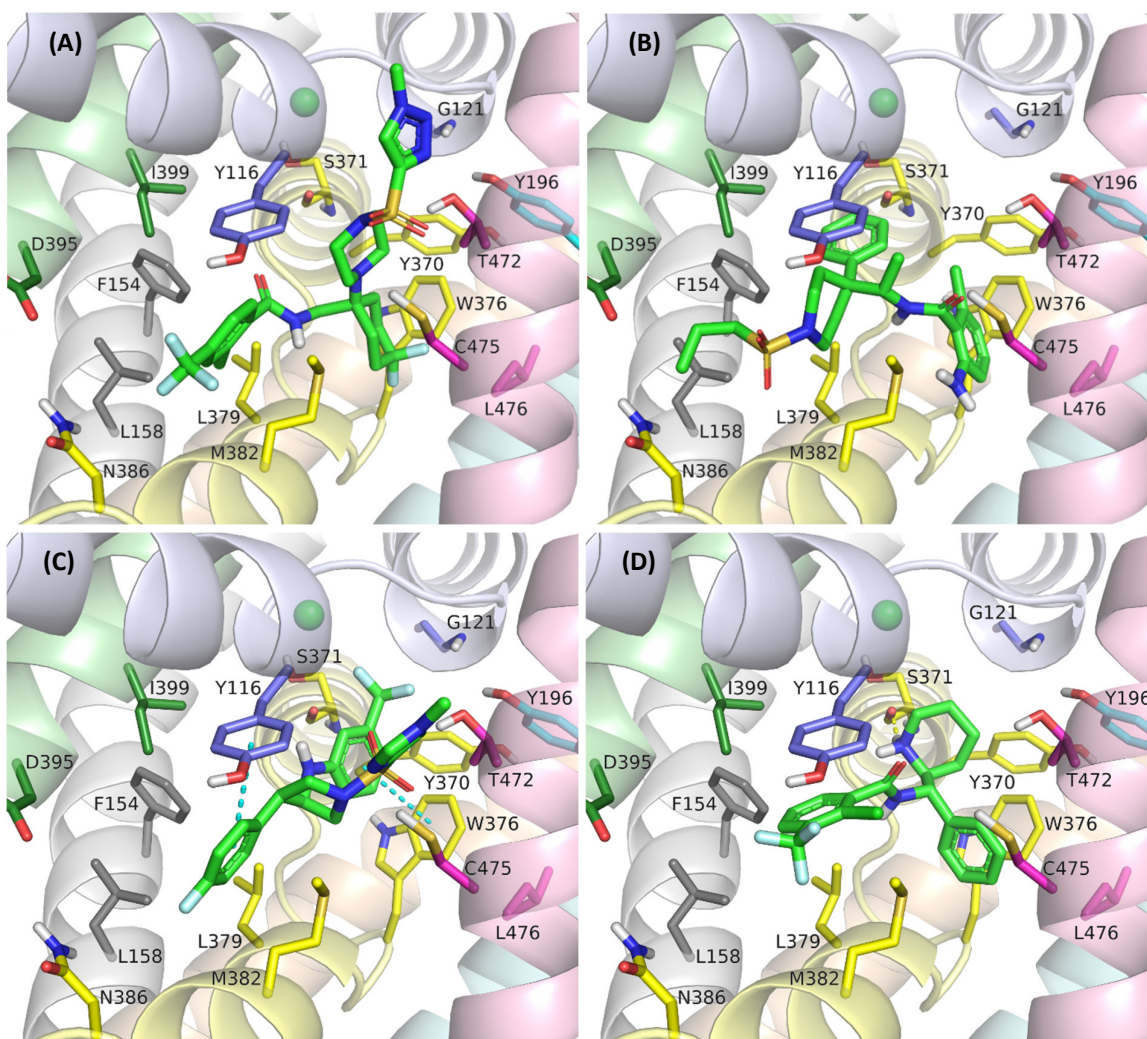


Figure S7. Binding mode of the compound **2** (A), ACPPB (B), compound **3** (C), and SSR-504734 (D) within GlyT-1 in inward-open state.

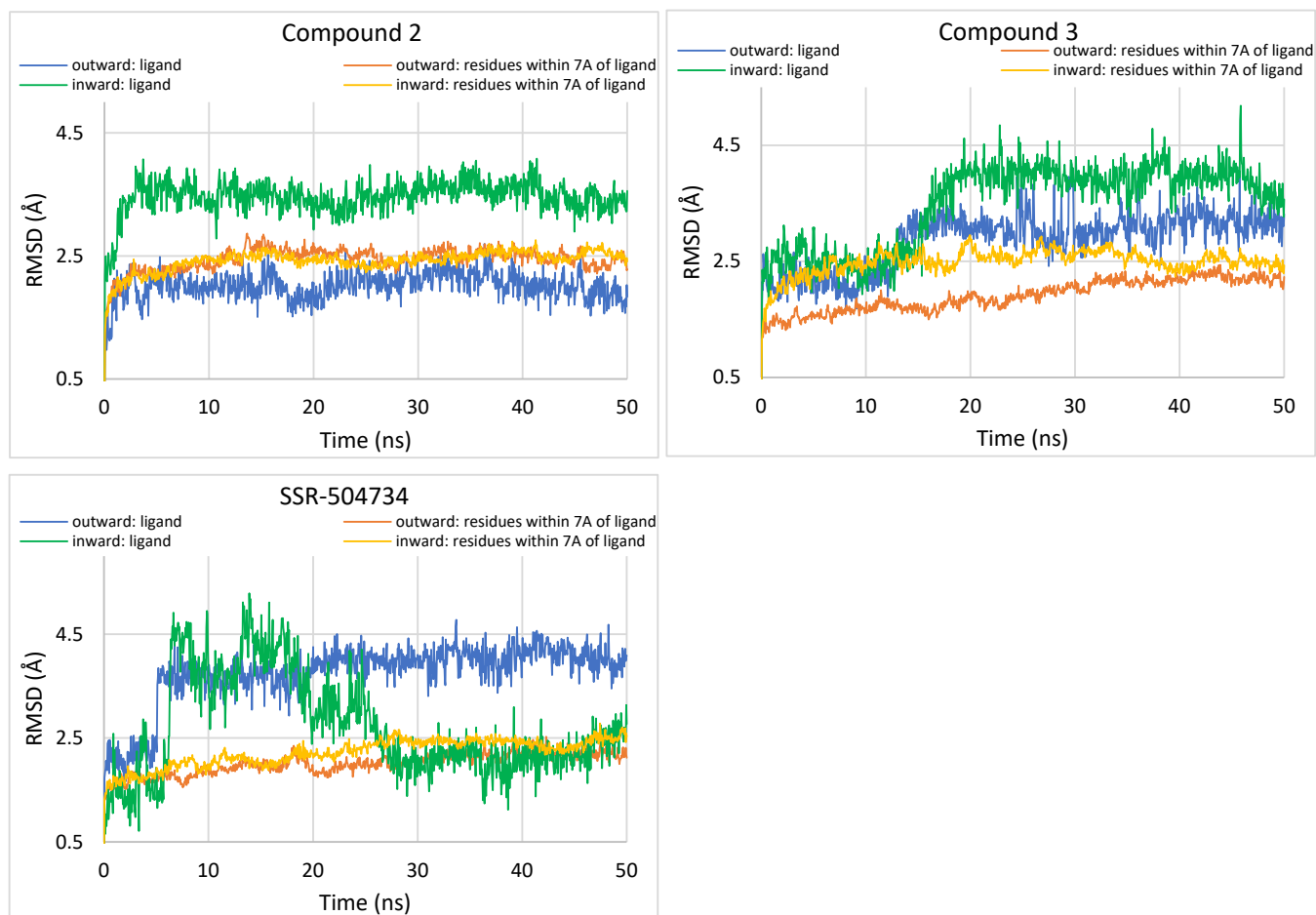


Figure S8. Comparison of RMSD changes in the course of molecular dynamics for compound **2**, compound **3**, and SSR-504734 in complex with GlyT-1 in outward-open and inward-open states.

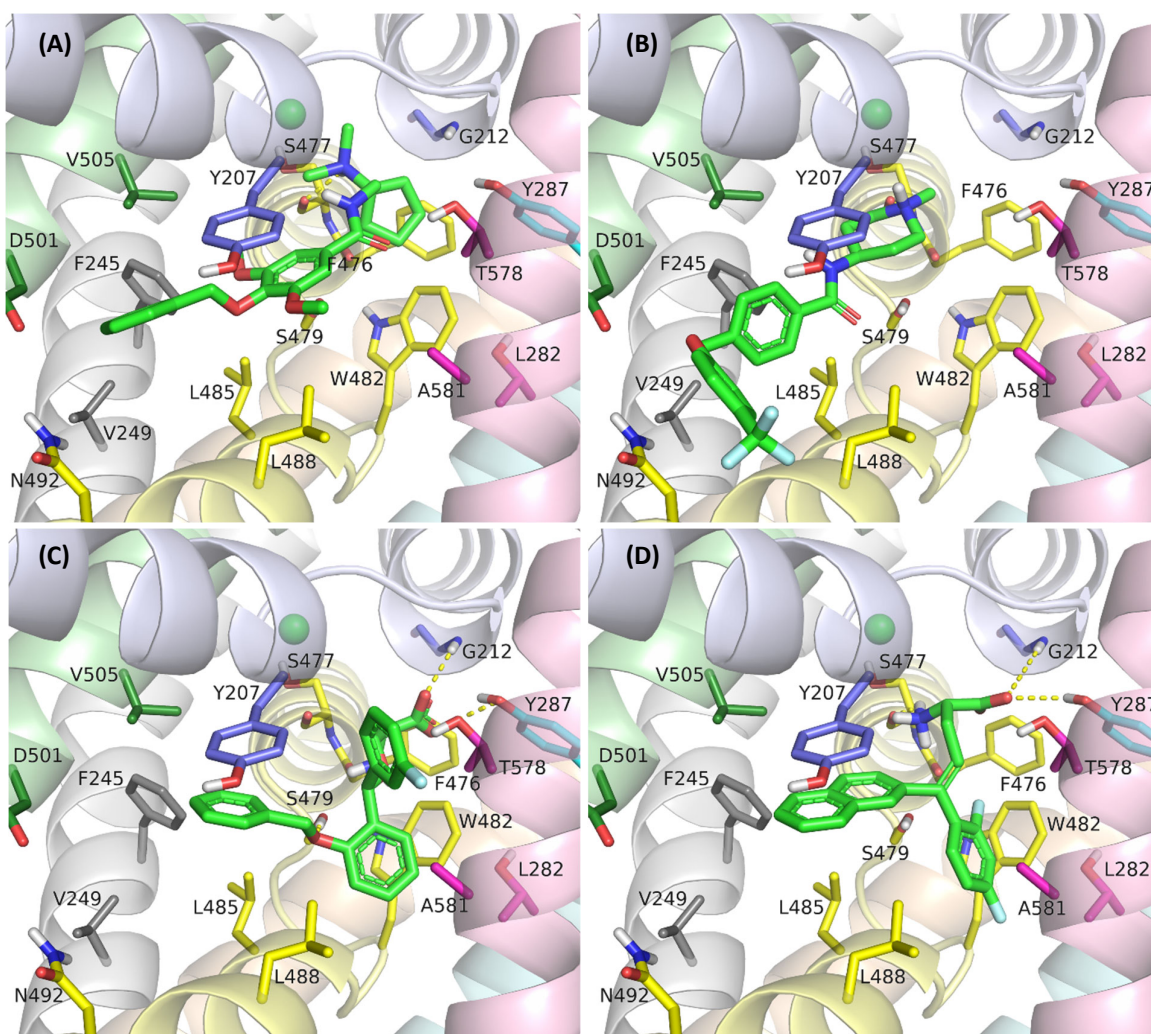


Figure S9. Binding mode of the ORG-25543 (A), GT-0198 (B), ALX-1393 (C), and compound 9 (D) within GlyT-2 in inward-open state.

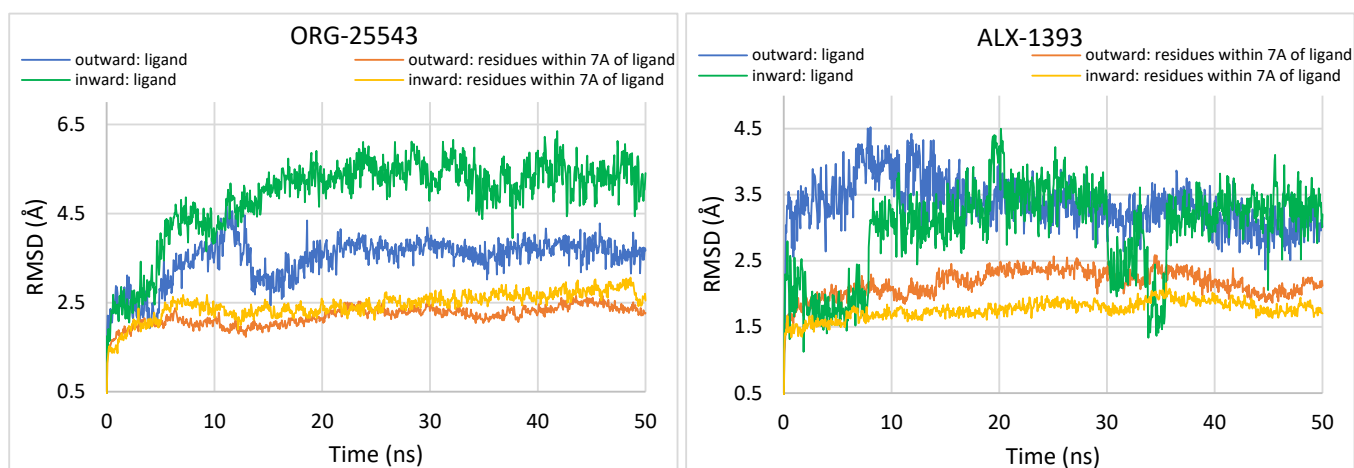


Figure S10. Comparison of RMSD changes in the course of molecular dynamics for ORG-25543 and ALX-1393 in complex with GlyT-2 in outward-open and inward-open states.