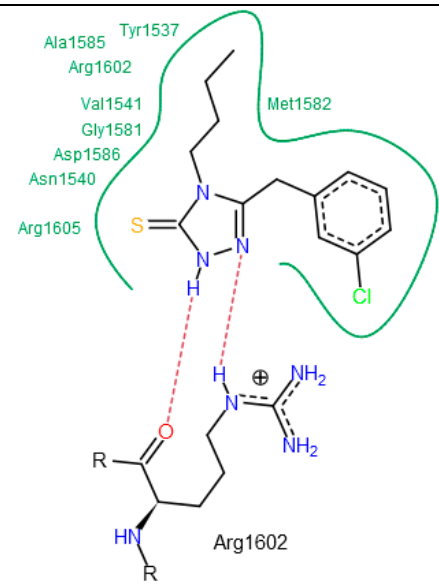
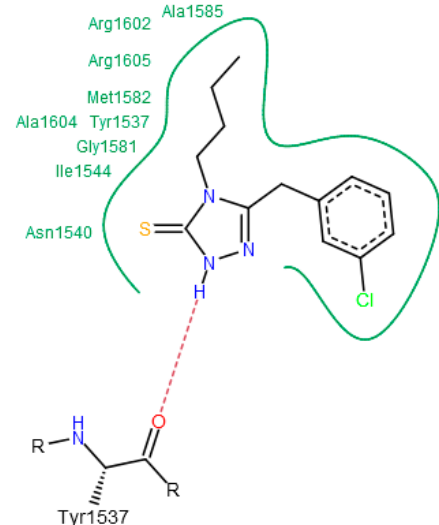


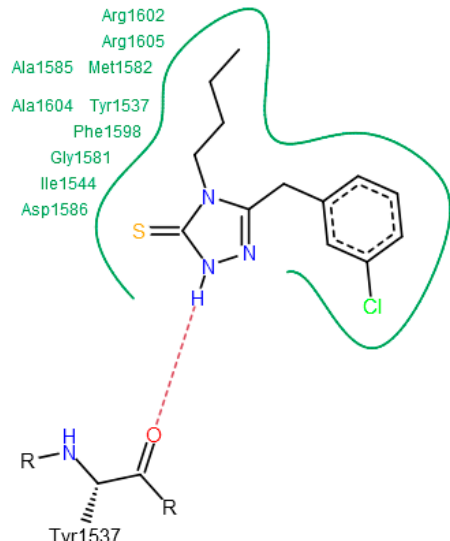
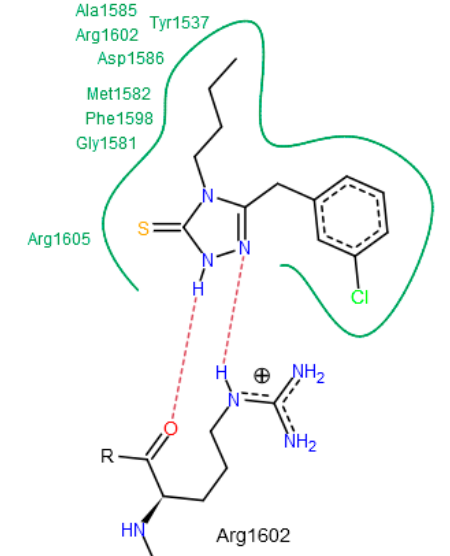
SUPPORTING INFORMATION

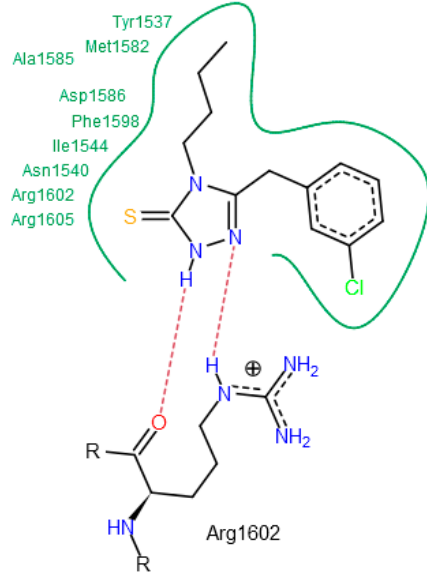
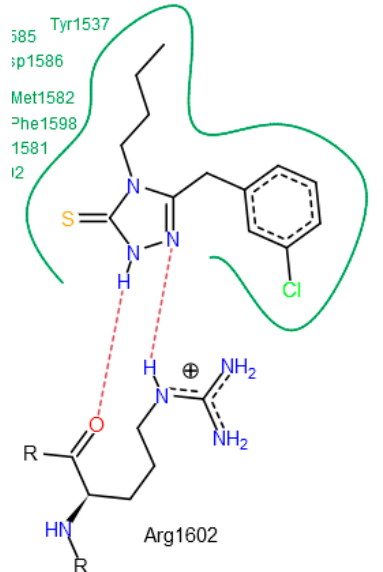
Table S1. Docking results of the *s*-triazoles **1-4** in human Nav1.7-VSD4-NavAb protein (pdb id 5EK0)

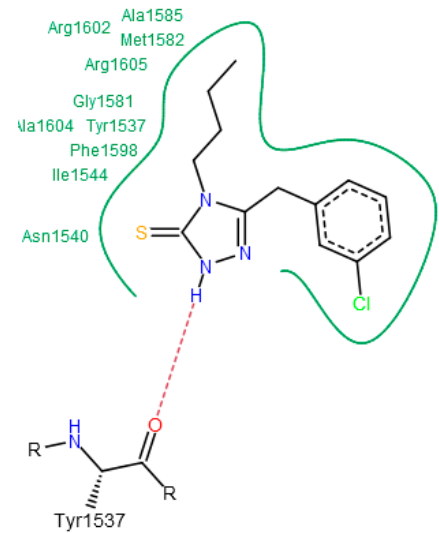
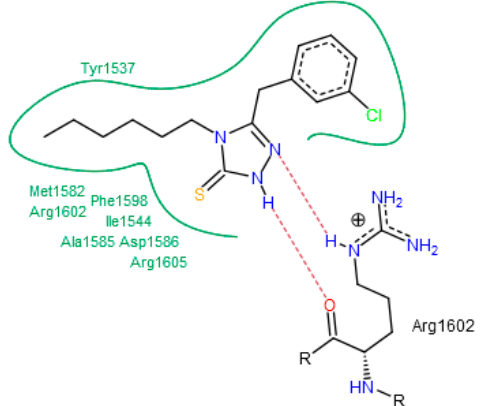
<i>s</i> -triazole	Posename #	docking score	Hyde (ΔG) in kJ/mol	PoseView
1	1	-13.4	-37	

	2	-13.0	-36	<p>Tyr1537</p> <p>Met1582 Phe1598 Val1541 Asp1586 Asn1540 Arg1602 Arg1605</p> <p>Arg1602</p>
	3	-12.7	-37	<p>Tyr1537</p> <p>Arg1602</p> <p>Asp1586 Met1582 Phe1598 Ile1544 Asn1540 Ala1585 Arg1605</p> <p>Arg1602</p>

	4	-12.4	-25	
	5	-12.0	-28	

	6	-12.0	-28	<p> Arg1602 Arg1605 Ala1585 Met1582 Ala1604 Tyr1537 Phe1598 Gly1581 Ile1544 Asp1586 </p>  <p>Tyr1537</p>
	7	-11.8	-23	<p> Ala1585 Tyr1537 Arg1602 Asp1586 Met1582 Phe1598 Gly1581 Arg1605 </p>  <p>Arg1602</p>

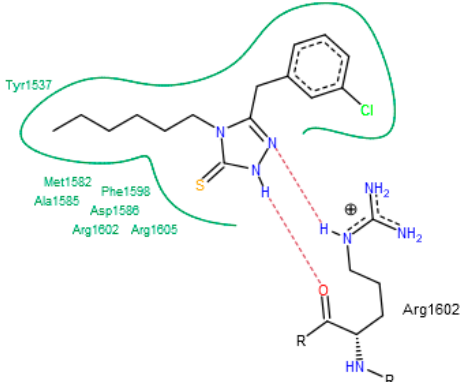
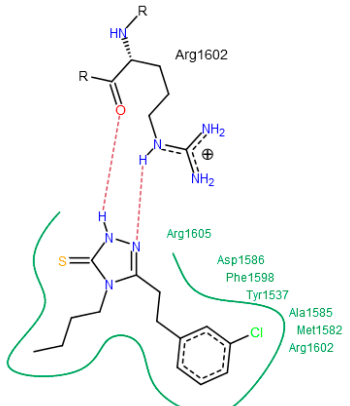
	8	-11.8	-10	
	9	-11.8	-28	

	10	-11.7	-31	 <p>Arg1602 Ala1585 Met1582 Arg1605 Gly1581 Val1604 Tyr1537 Phe1598 Ile1544 Asn1540</p> <p>Tyr1537</p>
2	1	-12.1	-40	 <p>Tyr1537</p> <p>Met1582 Arg1602 Phe1598 Ile1544 Ala1585 Asp1586 Arg1605</p> <p>Arg1602</p>

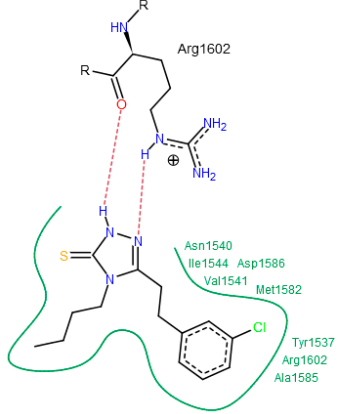
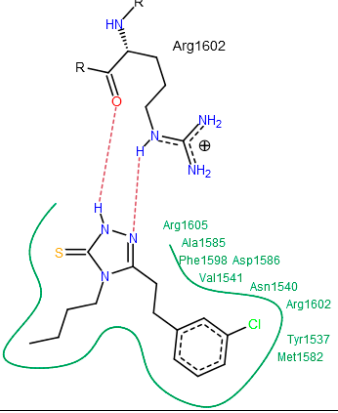
	2	-12.0	-6	<p>This diagram shows a thiazole derivative molecule docked in a protein binding pocket. The molecule features a thiazole ring with a 4-chlorophenyl group at position 4 and a heptyl chain at position 2. A red dashed line indicates a hydrogen bond between the thiazole NH and the guanidinium group of Arg1602. A green outline highlights the interaction with Tyr1537. Other residues shown include Met1582, Val1541, Asn1540, Phe1598, Arg1605, Ile1544, and Asp1598. The Arg1602 side chain is shown with its characteristic guanidinium group and a carbonyl-containing side chain.</p>
	3	-11.3	-41	<p>This diagram shows the same thiazole derivative molecule docked in a protein binding pocket. The interactions are similar to the first diagram, with a red dashed line indicating a hydrogen bond between the thiazole NH and the guanidinium group of Arg1602. A green outline highlights the interaction with Tyr1537. Other residues shown include Met1582, Val1541, Arg1602, Phe1598, Ala1585, Ile1544, Asp1586, and Arg1605. The Arg1602 side chain is shown with its characteristic guanidinium group and a carbonyl-containing side chain.</p>

	4	-11.0	-14	
	5	-11.0	-26	
	6	-10.9	-8	

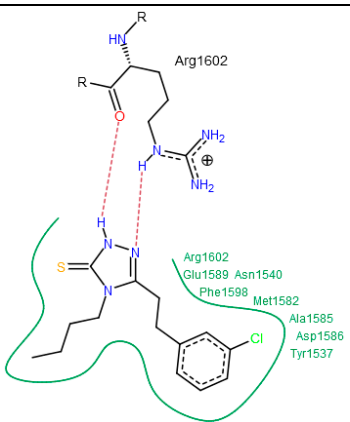
	7	-10.8	-17	
	8	-10.7	-32	
	9	-10.6	-8	

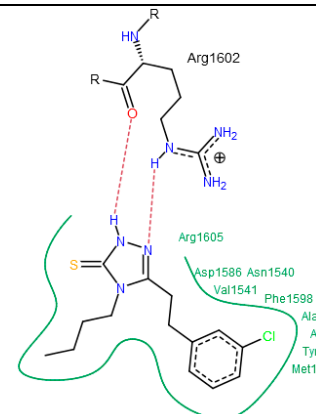
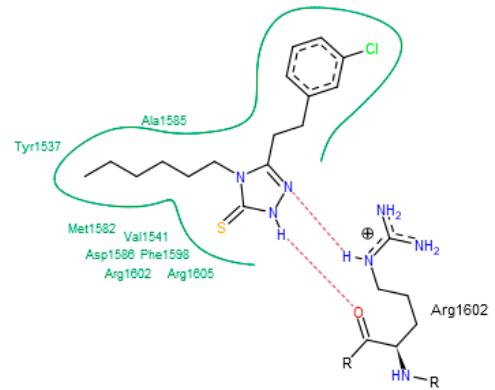
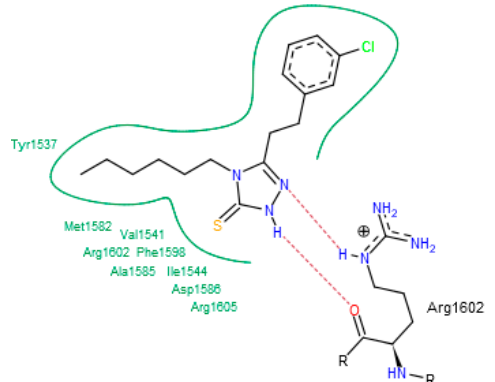
	10	-10.4	-29	
3	1	-13.2	-13	

	2	-12.4	-21	
	3	-11.4	-11.0	

	4	-11.0	-34	
	5	-10.8	-24	

	6	-10.7	-36	
	7	-10.7	-34	

	8	-10.6	-34	
	9	-10.6	-17	

	10	-10.2	-27	
4	1	-11.6	-25	
	2	-11.6	-22	

	3	-11.5	-39	
	4	-11.4	-30	
	5	-11.3	-14	

	6	-10.9	-16	<p>Tyr1537</p> <p>Met1582 Phe1598 Arg1602 Asp1598 Ala1585 Arg1605</p> <p>Arg1602</p>
	7	-10.6	-31	<p>Tyr1537 Val1541 Met1582 Phe1598 Arg1602 Asp1598 Ala1585 Arg1605</p> <p>Arg1602</p>

	8	-10.5	-14	
	9	-10.5	-12	
	10	-10.3	-10	

Table S2. Statistical evaluation of differences between means of IC₅₀ values reflecting VGSC affinity.

Tukey's multiple comparisons test	Mean diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P value
1 vs. 2	9.63	9.152 to 10.11	Yes	****	<0.0001
1 vs. 3	3.9	3.422 to 4.378	Yes	****	<0.0001
1 vs. 4	-3.1	-3.578 to -2.622	Yes	****	<0.0001
1 vs. veratridine	-2	-2.478 to -1.522	Yes	****	<0.0001
2 vs. 3	-5.73	-6.208 to -5.252	Yes	****	<0.0001
2 vs. 4	-12.73	-13.21 to -12.25	Yes	****	<0.0001
2 vs. veratridine	-11.63	-12.11 to -11.15	Yes	****	<0.0001
3 vs. 4	-7	-7.478 to -6.522	Yes	****	<0.0001
3 vs. veratridine	-5.9	-6.378 to -5.422	Yes	****	<0.0001
4 vs. veratridine	1.1	0.622 to 1.578	Yes	****	<0.0001

Table S3. Statistical evaluation of differences between means of ED₅₀ values of compounds **3**, **4** and valproate measured at the peak of their anticonvulsant activity.

Tukey's multiple comparisons test	Mean diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P value
ED ₅₀ of 3 vs ED ₅₀ of valproate	-92.4	-102 to -82.82	Yes	****	<0.0001
ED ₅₀ of 4 vs ED ₅₀ of valproate	-73.6	-83.18 to -64.02	Yes	****	<0.0001
ED ₅₀ of 3 vs ED ₅₀ of 4	-18.8	-28.38 to -9.218	Yes	****	<0.0001

Table S4. Statistical analysis of differences between ED₅₀ values showing anticonvulsant activity of compounds containing methylene linker (**1**, **2**) and ethylene linker (**3**, **4**)

Tukey's multiple comparisons test	Mean diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P value
ED ₅₀ of 1 vs ED ₅₀ of 3 (<i>butyl derivatives</i>)	-53.4	-61.25 to -45.55	Yes	****	<0.0001
ED ₅₀ of 2 vs ED ₅₀ of 4 (<i>hexyl derivatives</i>)	-43.3	-51.15 to -35.45	Yes	****	<0.0001