Spatial characteristics and prediction of probable activity and toxicity of streptomycin and its derivatives using PASS-program

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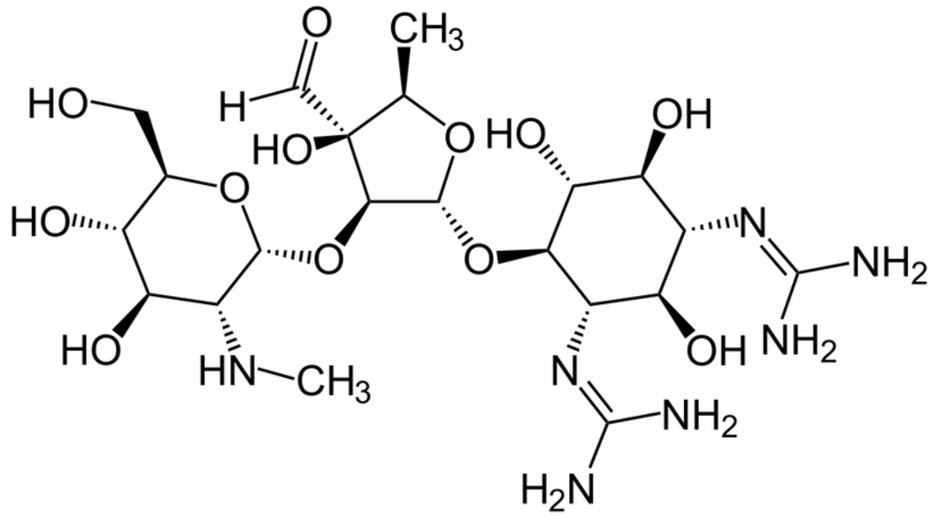
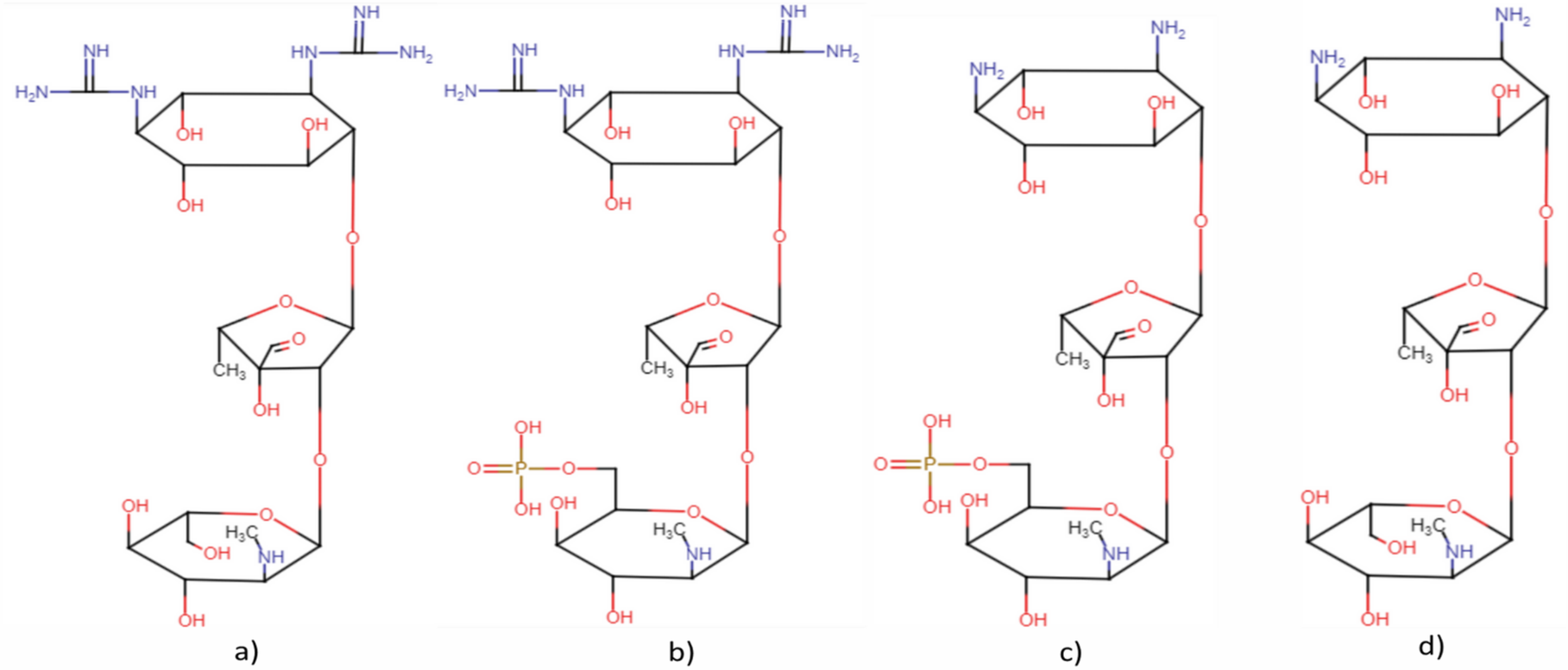
Streptomycin

Streptomycin is an antibiotic that is an organic base whose molecule consists of three parts: streptidine, streptose, and N-methylglucosamine.
These components are linked together by the same glycosidic bonds as in polysaccharides (starch, cellulose and glycogen). Streptomycin has three secondary amino groups: two of the streptamine amino groups are part of guanidine groups [H2N-C(= NH)-NH-], and one, which is part of glucosamine, is methylated.

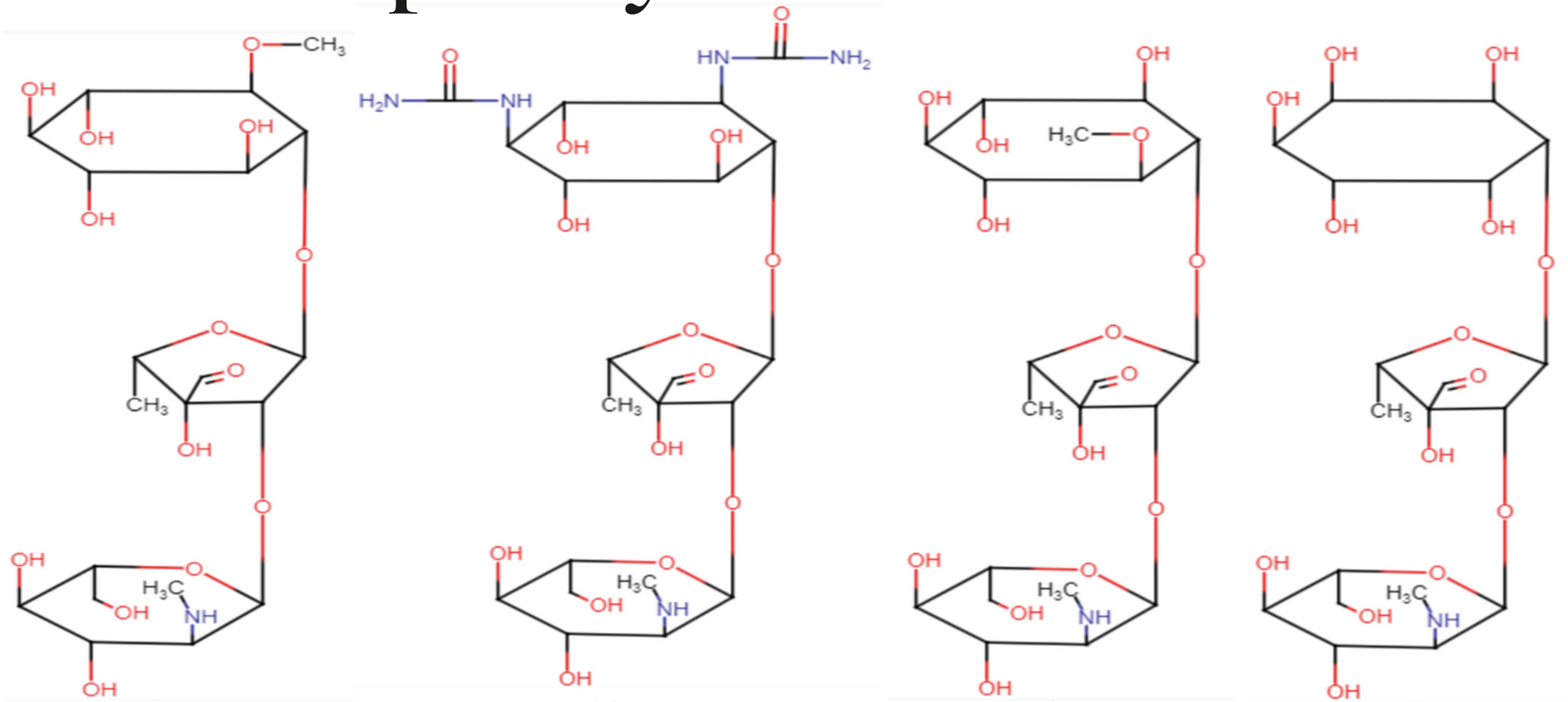


Models of streptomycin derivatives



(a) No.1 streptomycin (O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-N,N'-bis(aminoiminomethyl)-D-streptamine); ***(b) No.2*** D-galactose-6-phosphate(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-N,N'-bis(aminoiminomethyl)-D-streptamine); ***(c) No.3*** - D-galactose-6-phosphate(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-N,N'-D-streptamine); ***(d) No.4*** - (O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-N,N'-D-streptamine)

Models of streptomycin derivatives



(a) No.5 - (O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-L-1-O-methyl-myo-inositol); ***(b) No.6*** - O-2-Deoxy-2-(amino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-N,N'-bis(carbamyl)-D-streptamine; ***(c) No.7*** O-2-Deoxy-2-(amino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-D-1-O-methyl-myo-inositol); ***(d) No.8*** O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1"2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1"4)-L-myo-inositol

Calculations of enthalpy of formation models of new streptomycin derivatives

No. of compounds	AM 1 - Δ H (kcal/mol)	PM 3 - Δ H (kcal/mol)
No. 1	-484,041	**-443,25**
No. 2	-522,68	**-655,76**
No.3	–855,88	**–701,611**
No. 4	–545,36	**–491,2**
No. 5	-613,44	**-576,568**
No. 6	-489,5	**-449,9**
No. 7	-619	**-577,697**
No. 8	-646,86	**-586,17**

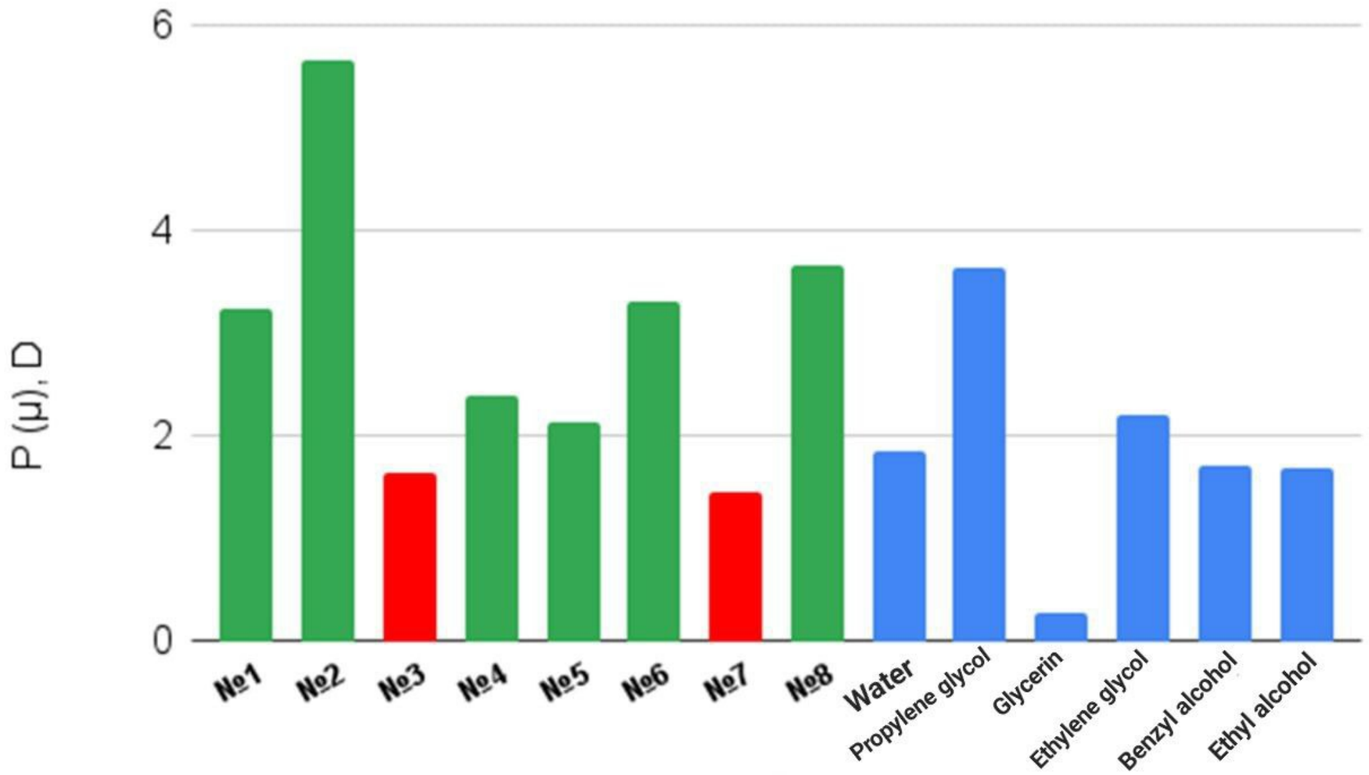
Energies of the HOMO and LUMO in the investigated models of new streptomycin derivatives

No. of compounds	HOMO	LUMO	χ (HOMO +LUMO)/2	μ (–χ)	η (HOMO – LUMO)/2	S 1/(2η)
No. 1	-9,1115	0,4258	-4,3428	4,3428	4,7686	0,1048
No. 2	-8,9169	-0,1069	-4,5119	4,5119	4,405	0,113
No. 3	–9,4639	0,08543	–4,4689	4,4689	4,7746	0,104
No. 4	-9,256	0,287	-4,4845	4,4845	4,7715	0,105
No. 5	–9.4867	0,5074	–4,4896	4,4896	4,997	0,1
No. 6	-9,0465	0,1997	-4,4234	4,4234	4,6231	0,108
No. 7	–9.6165	0,2993	–4,6586	4,6586	4,9579	0,1
No. 8	–9,7357	0,1926	–4,7715	4,7715	4,9641	0,1007

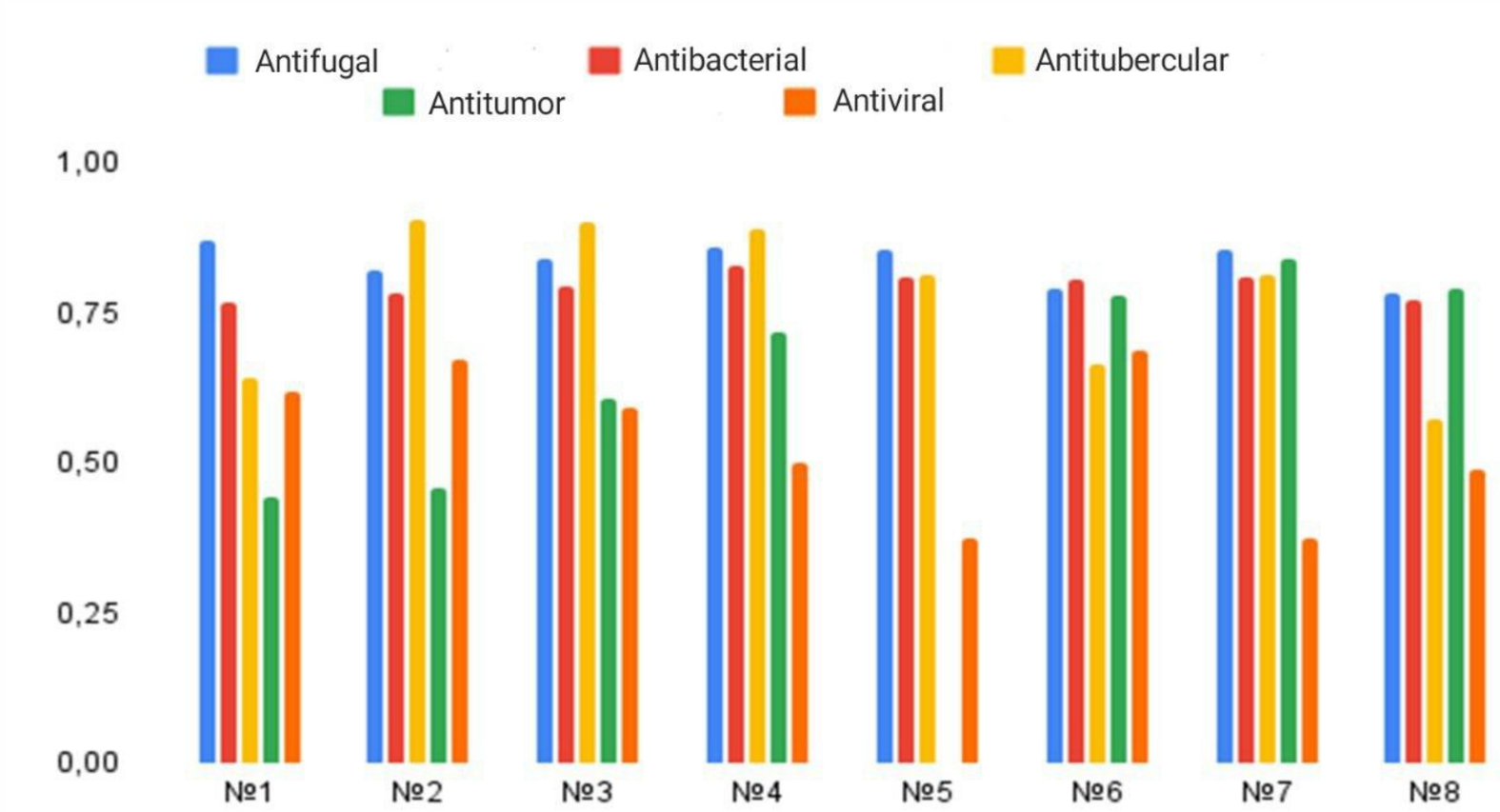
Values of charge characteristics on atoms in the investigated streptomycin derivatives

№ of compound	–Δ q, units of charge	+Δ q, units of charge
№1	13 O –0,3233 19 O –0,2733 26 N –0,1982 31 O –0,2965 52 O –0,3129 4 N –0.1863	45 C 0,2615 51 C 0.2443
№2	19 O –0,2791 66 O – 0.6580 80 O – 0.6473 82 O – 0.6845 84 O – 0.8547	34 C 0.3175 24 C 1.0117 79 P 2.1925
№3	21 O –0,2881 64 O –0.6458 66 O –0.6834 68 O –0.8565	22 C 0,3194 63 C 0,3054 63 P 2.1917
№4	21 O –0,2893 42 O –0,3132 37 O –0,2642	22 C 0,3177 35 C 0,2625
№5	27 O –0,3007 48 O –0,3132 76 O –0,3923 77 O –0,4018	28 C 0,3180 41 C 0,2603
№6	31 O –0,3003 47 O –0,2629 52 O –0,3078 19 O –0,2603 26 N –0.1988	32 C 0,3265 45 C 0,2592
№7	27 O –0,3048 48 O –0,3080 73 O –0,4027 74 O –0,3927	24 C 0,3667 25 C 0,3612
№8	19 O –0,2854 21 O –0,2983 37 O –0,2616 42 O –0,3101	24 C 0,3238 25 C 0,2614

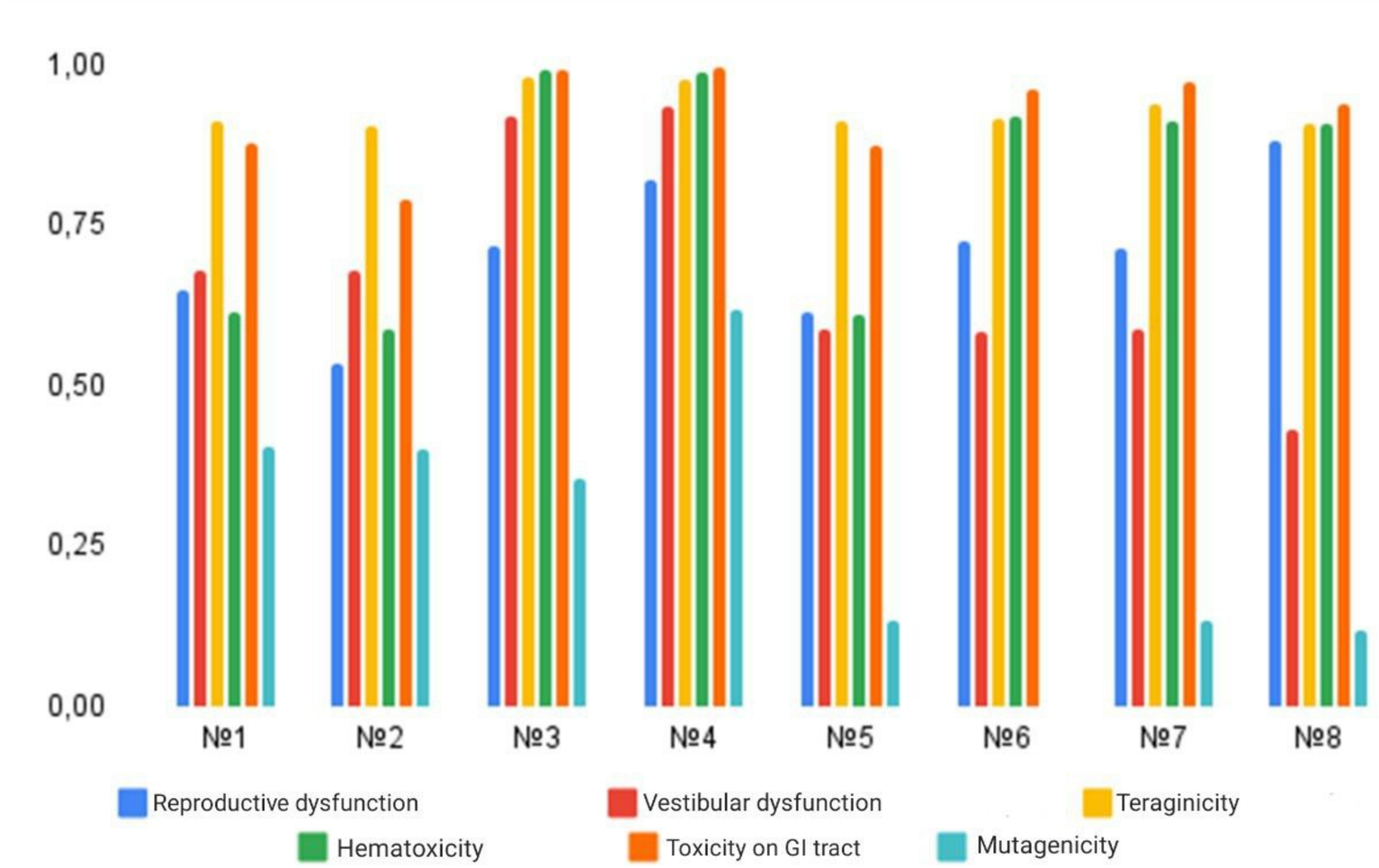
Dipole moment in investigated models of new streptomycin derivatives and polar solvents



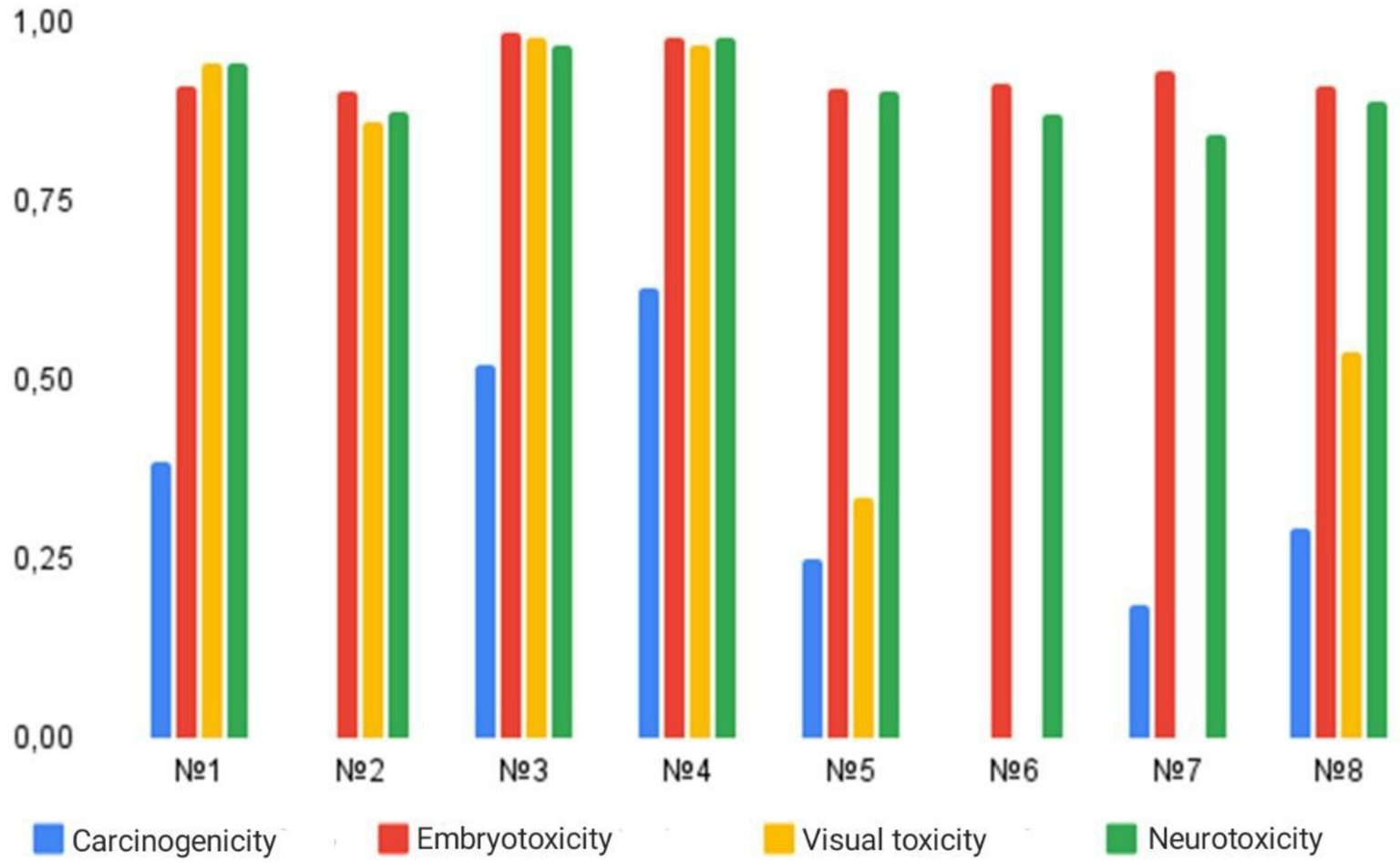
Values of pharmacologic effects of streptomycin models



Toxicity values of streptomycin models



Toxicity values of streptomycin models



Correlation of antifungal activity of streptomycin derivatives with charge (qC) and dipole moment (μ)

№ of compound	Pa	qC, units of charge	P (μ), D
№ 1	0,869	-0,1315 (31)	3,2258
№ 4	0,857	-0,1375 (41)	2,384
№ 5	0,856	-0,1801 (49)	2,1262

Correlation of antituberculosis activity of streptomycin derivatives with charge (qC) and dipole moment (μ)

№ of compound	Pa	qC, units of charge	P (μ), D
№ 2	0,905	-0,1281 (43)	5,65
№ 4	0,890	-0,1375 (41)	2,384
№ 5	0,813	-0,1801 (49)	2,1262

Conclusion

Thus, as a result of the studies of streptomycin derivatives, correlations between electronic structure and pharmacological activities have been established by combining quantum-chemical calculations and predictions of PASS biological activity spectra. The obtained correlations on the structure-property system can be used in the planning of scientific research and in the synthesis of drugs.