

# Ionic derivatives of insulin-mimetic vanadium(V) complexes with Schiff base ligands

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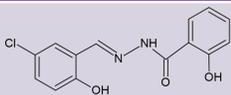
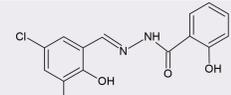
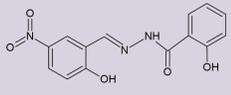
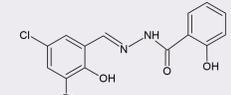
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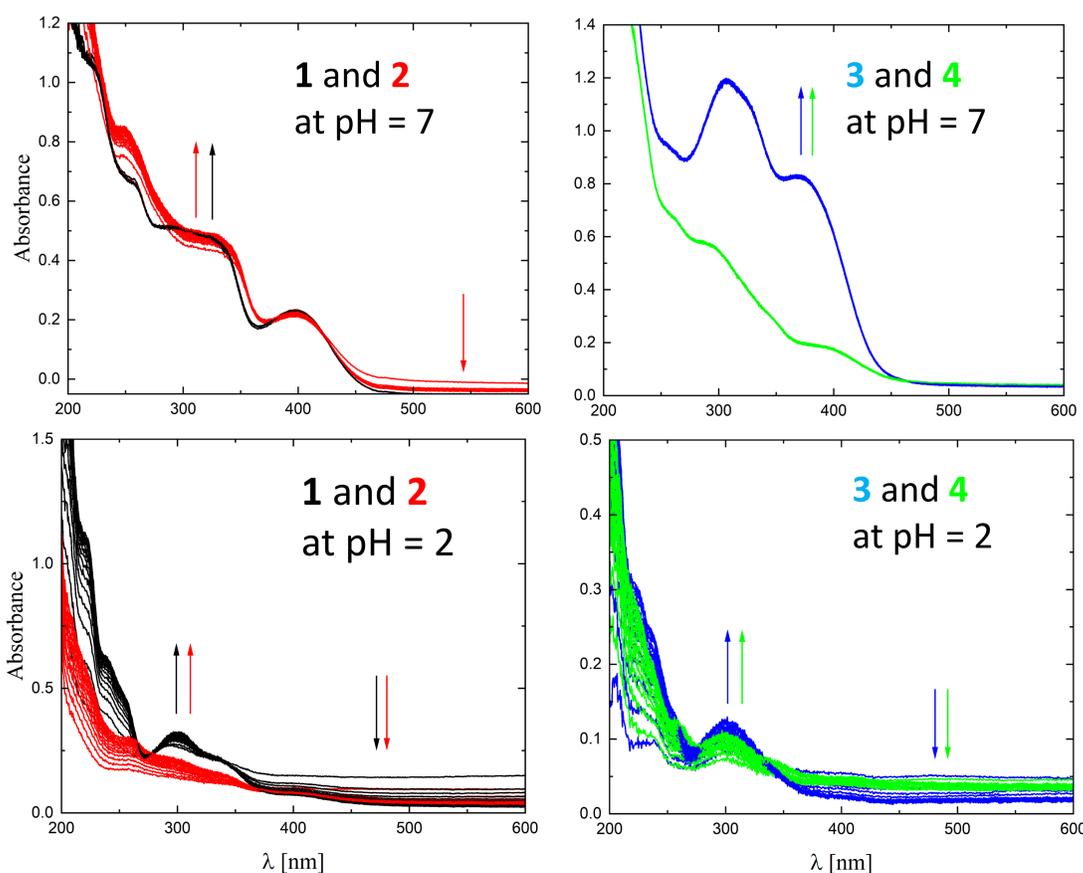
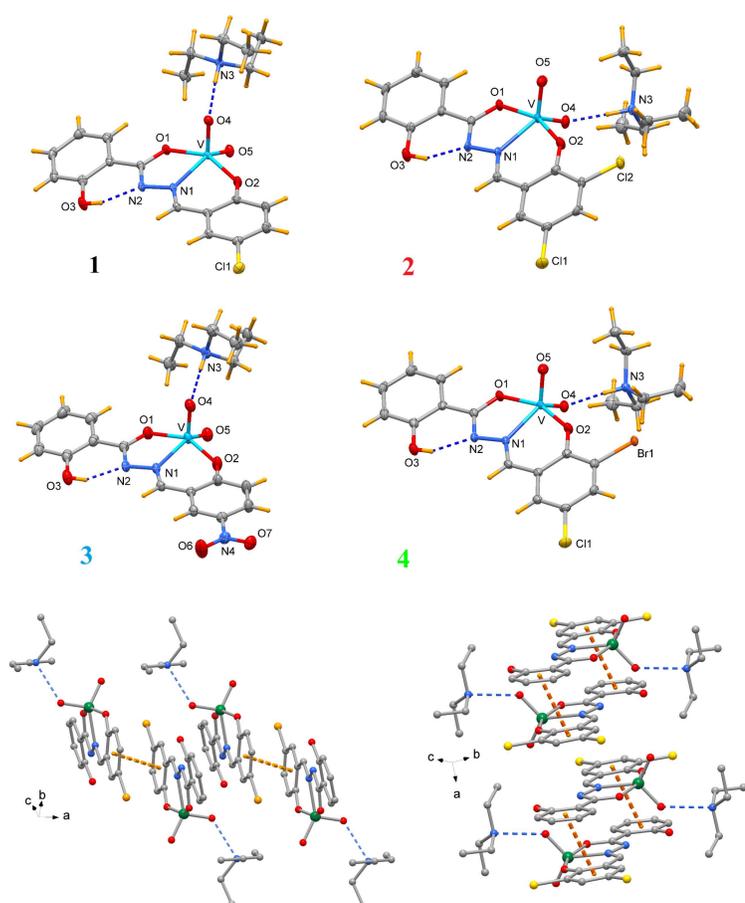
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The biological activity of the vanadium Schiff base complexes, which can be potentially used as insulin-mimetic compounds, was extensively studied in the last decade. Pharmacological data showed that these compounds produced a significant decrease in blood glucose level and improved liver and kidney function after two weeks of daily use. The vanadium complexes obtained so far with Schiff bases create problems, most often with cytotoxicity, very low solubility in water, difficulties in studying the crystal structure, instability at pH = 2 and in transport to cells. Therefore, it is necessary to search for new organic vanadium compounds to optimize their pharmaceutical activity. Lastly, several hundred vanadium(III- V) complexes with Schiff bases were tested, controlling both the starting vanadium compound for the synthesis of complexes, as well as changing the substituents in the aromatic ring of aldehyde and hydrazide - Schiff base components. The obtained neutral compounds were highly soluble in organic solvents, however, they were insoluble in water. Therefore, the DMSO-H<sub>2</sub>O mixture was used to test the stability of the complexes. In the last studies, the synthesis and physicochemical characterization of the vanadium(V) complex with triethylamine as a cation - HTEA[VO<sub>2</sub>(L)] (where L = Schiff base formed from 5-bromosalicylaldehyde and 2-hydroxybenzhydrazide) was described. In the formed ionic complexes, the crystal studies show additional hydrogen interactions between the cation and the complex anion. The ionic structure of such compounds should increase the solubility of the complexes in water, thus maximizing their availability in the biological systems studied. Here, we present a series of vanadium(V) complexes with Schiff base ligands, and protonated triethylamine (HTEA) as cation, along with the structural and physicochemical characterization. In particular, the stability of complexes at pH = 2 and 7 was investigated.

	Complex formula	Scheme of synthesis	Elemental analysis [%] found and calculated	Hydrazide	Aldehyde	Ligand L <sub>n</sub> formula
1	HTEA[VO <sub>2</sub> (L1)]	<b>1 mmol of hydrazide</b> <b>+ 1 mmol of aldehyde</b> ↓ 50 mL MeOH, reflux <b>yellow solution</b> ↓ 0.5 mmol of V <sub>2</sub> O <sub>5</sub> , reflux <b>dark red solution</b> ↓ 2 mL of triethylamine (TEA) <b>crystals</b>	C, 50.96; 50.59 H, 5.21; 5.52 N, 8.71; 8.85	2-hydroxy-benzhydrazide	5-chloro-salicylaldehyde	
2	HTEA[VO <sub>2</sub> (L2)]		C, 47.31; 47.17 H, 4.90; 4.95 N, 8.24; 8.25		3,5-dichloro-salicylaldehyde	
3	HTEA[VO <sub>2</sub> (L3)]		C, 49.55; 49.49 H, 5.51; 5.40 N, 11.49; 11.54		5-nitro-salicylaldehyde	
4	HTEA[VO <sub>2</sub> (L4)]		C, 43.30; 43.38 H, 4.46; 4.55 N, 7.43; 7.59		3-bromo-5-chloro-salicylaldehyde	



**Discussion and conclusions:** Ionic dioxido vanadium(V) complexes **1-4** have a close comparable structure. Compounds **1** and **3** reveal a square pyramidal geometry, while compounds **2** and **4** a trigonal bipyramid. Ionic complexes, unlike neutral ones, have, apart from intramolecular hydrogen bonds, also intermolecular hydrogen bonds, which contributes to increasing the solubility of the complexes in water. The stability of the complexes was measured by UV-Vis spectroscopy in water (pH ca. 7) as well as in 0.01 M HCl (pH ca. 2, imitating the environment in the stomach). All measurements were performed at 37 °C. The stability of complexes in water is very good (the band at 400 nm does not change with time), however, they are unstable at pH = 2 (the disappearance of the bands at ca. 400 nm, combined with an increase in the intensity of the bands at ca. 300 nm, suggests the decomposition of Schiff bases into components). Complex **2** showed the best solubility, due to the additional chlorine substituent.

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