Investigation of Lovastatine with transition metal by NMR

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Introduction

One of the current tasks is to find ways to modernize existing drugs in order to reduce their toxicity by adding metals to their structure. The choice of ligand for the synthesis of the metal complex will allow you to adjust lipophilicity, solubility and reactivity, thereby enhancing the positive properties of the drug and reducing toxicity [1]. Statins are the most common class of drugs used to lower low-density lipoprotein cholesterol levels.

Object

The statin group is represented by a wide variety of molecules that differ in medical activity, solubility, etc. Lovastatin is the first approved HMG-CoA reductase inhibitor, clinical trials of which have provided evidence of the ability of drugs in this class to reduce morbidity and mortality associated with cardiovascular diseases [2]. Its structure with the numbering of carbon atoms is presented in Figure 1 a.

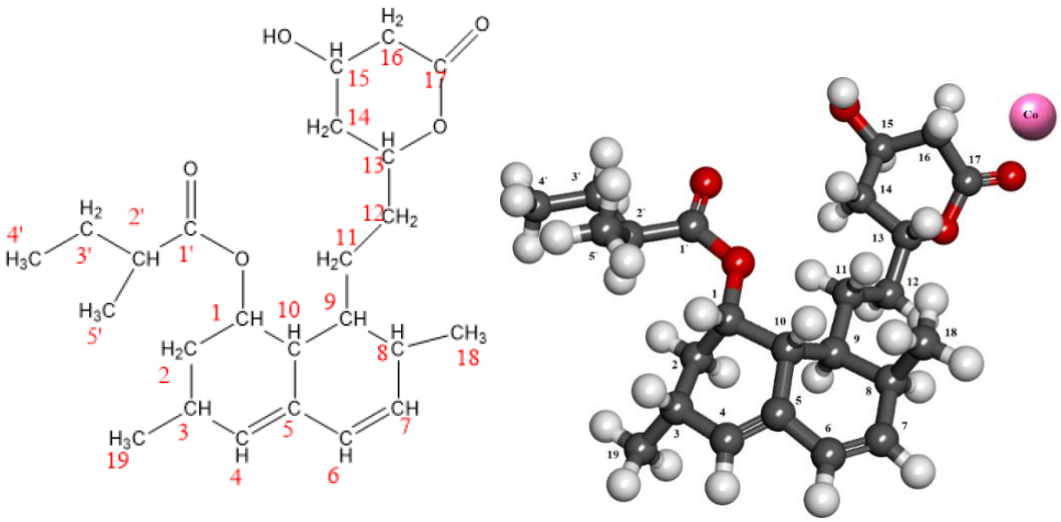

Fig. 1. Structural formula of Lovastatin (a) and schematic representation of the cobalt (Co^{+2}) – lovastatin complex (b).

The main requirement for a ligand is low toxicity of the ion. Transition group metals, such as cobalt, are present in the body as part of vitamin B_{12} and are involved in hematopoiesis [1,2].

Method

The study of complex formation in the cobalt (Co^{+2}) - lovastatin system was carried out using one-dimensional ^{1}H NMR spectroscopy within the framework of the approach discussed in our previous works [3,4].

Recording of ^{1}H NMR spectra of lovastatin in deuterated acetone at various concentrations of cobalt chloride $CoCl_2$ (cobalt/lovastatin: 1/5, 1/10) was carried out on a Bruker Avance II 500 NMR spectrometer at a temperature of 308 K. ^{1}H NMR spectrum was recorded using 90 ° pulse, delay between pulses 2 with spectral width 10 ppm. The correlation of one-dimensional spectra was performed using TopSpin software.

Result

The one-dimensional ^{1}H NMR spectrum of the prepared solutions is shown in Figure 2.

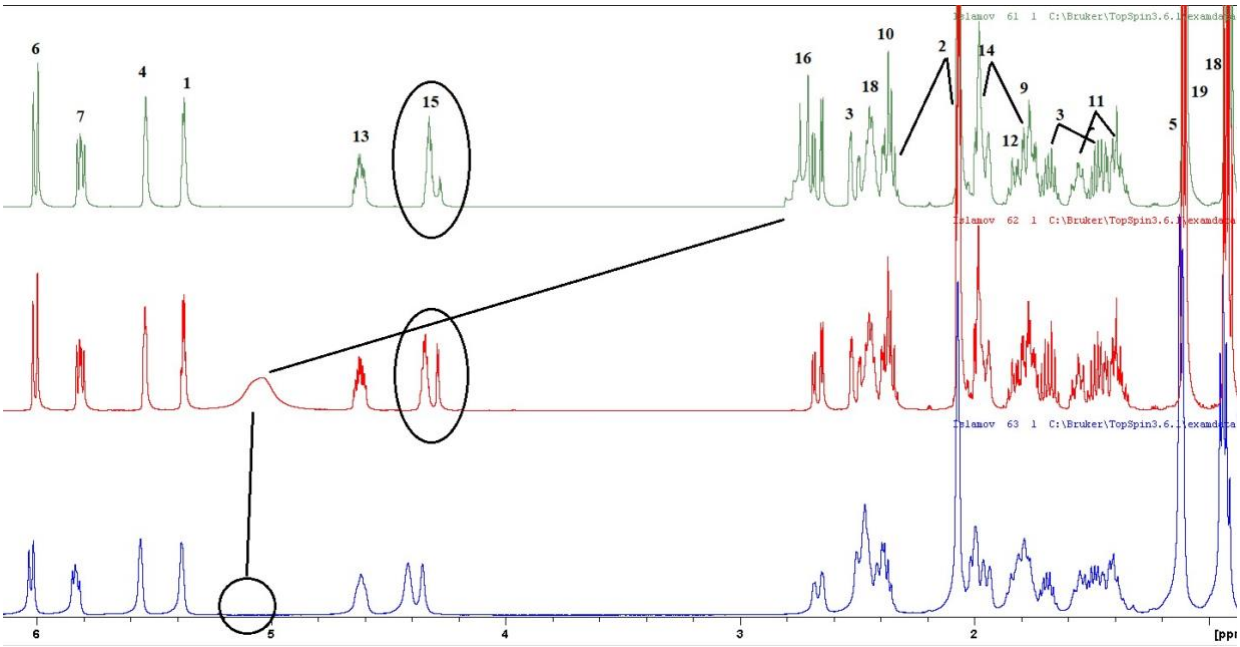

Fig. 2. NMR spectra (^{1}H, 500 MHz) of lovastatin in deuterated acetone (a – lovastatin, b – lovastatin solution with cobalt chloride in a ratio of 1/10, c – lovastatin mixed with cobalt chloride in a ratio of 1/5)

The ^{1}H NMR spectra of lovastatin in a solution of deuterated acetone (a) and in a solution of deuterated acetone with the addition of Co^{+2} ions (b and c) have a number of differences. The following changes are observed in the NMR spectra: the ^{1}H NMR signal ^{15}CH changes in intensity (while the integral intensity remains unchanged), the ^{16}CH signal shifts towards higher ppm. The shift of the ^{1}H NMR signal of ^{16}CH during the transition from sample a to sample b (ion/statin ratio 1/10) is 2.6 ppm; at a concentration of 1/5, the ^{1}H NMR signal disappears. Changes in the ^{1}H NMR signals of the remaining protons of lovastatin are insignificant. The spatial proximity of paramagnetic Co^{+2} ions leads to a decrease in the proton

relaxation time, which, in turn, causes a broadening of the spectral lines. Thus, it can be assumed that cobalt is predominantly located near the 15-16th carbon atoms (Figure 1 b).

Acknowledgments

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References

1. Kuranova N. N. et al. Complexation of Gold (III) with Pyridoxal 5′-Phosphate-Derived Hydrazones in Aqueous Solution //Molecules. – 2022. – Т. 27. – №. 21. – С. 7346.

2. Hamelin B.A., Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. // Trends Pharmacol. Sci. England, 1998. Vol. 19, № 1. P. 26–37.

3. Abdrakhmanov, Rustam, Modeling the Co^{2+} Binding to Amyloid Peptide Aβ13-23 in Water Environment by NMR Spectroscopy [text] / Rustam Abdrakhmanov, Dmitriy Blokhin, Konstantin Usachev, Vladimir Klochkov// BioNanoScience. – 2018.- V. 8, Issue 1.- P. 423-427. DOI 10.1007/s12668-017-0475-2. IF = 1.08 Scopus.

4. Tarasov, A.S. The effect of gadolinium ion on micelles and reverse micelles by NMR spectroscopy [text] /A.S. Tarasov, I.Z. Rakhmatullin, G.S. Shurshalova, A.V. Klochkov, K.A. Il'yasov, V.V. Klochkov// BioNanoScience.- 2021. – V.11, Issue1. - P.136-141. Q4; SiteScore = 2.20. (Scopus). https://doi.org/10.1007/s12668-020-00813-2.