Study of the interaction of lovastatin with a transition group metal - gadolinium in solution using NMR spectroscopy

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Introduction

Modification of biologically active compounds through the use of metal complexes is one of the promising directions in the development of drugs that must have certain previously known properties. Statins, being the most effective way to relieve atherosclerosis, have a wide range of side effects, such as myositis, increased production of liver enzymes. Studying the interaction of statins with transition group metals will help clarify ways to create a stable metal complex and subsequent studies on changes in pharmacokinetics.

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.

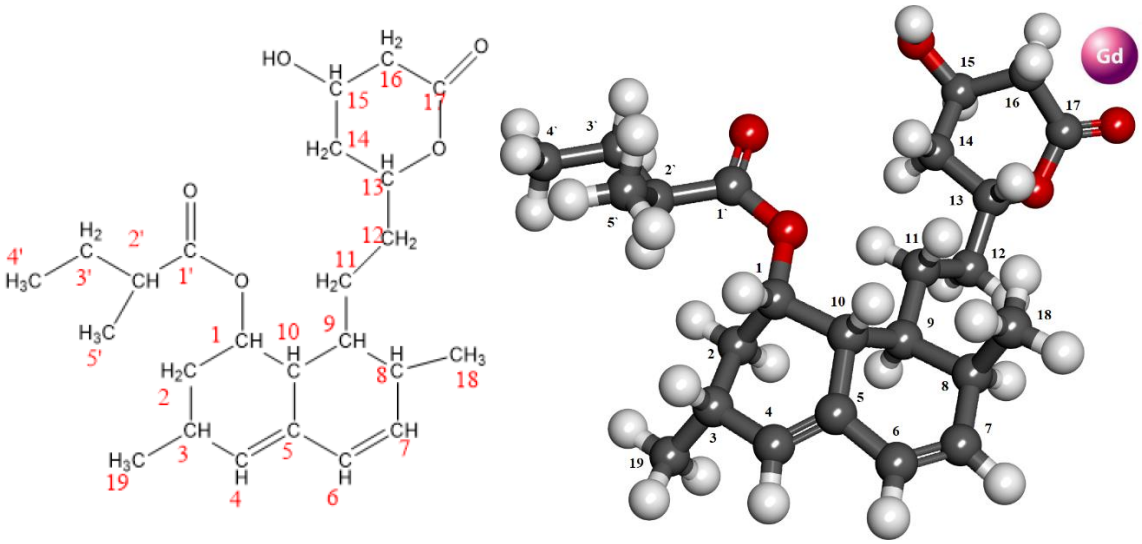

Figure 1 – The chemical structure of Lovastatin (a) and schematic representation of the gadolinium (Gd^{+2}) – lovastatin complex (b).

The main requirement for a ligand is low toxicity of the ion. Transition group metals, such as gadolinium, are widely used as a contrast agent for MRI and are a low-toxic element.

Method

^{1}H (700 MHz), ^{13}C (175 MHz), $^{1}H–^{13}C$ HMBC NMR spectra of lovastatin in deuterated acetone at various concentrations of gadolinium chloride $GdCl_2$ (gadolinium/lovastatin: 1/5, 1/10) at temperature of 308 K were recorded using Bruker "Avance -700 III TM" spectrometer. ^{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.

The study of complex formation in the gadolinium (Gd^{+2}) – lovastatin system was carried out using two-dimensional $^{1}H–^{13}C$ HMBC NMR spectroscopy within the framework of the approach discussed in our previous works [3,4].

Result

Figure 2 shows heteronuclear experiment $^{1}H–^{13}C$ HMBC spectra of lovastatin with gadolinium ion Gd^{2+} in deuterated acetone (C_3H_6O) with different solution concentrations.

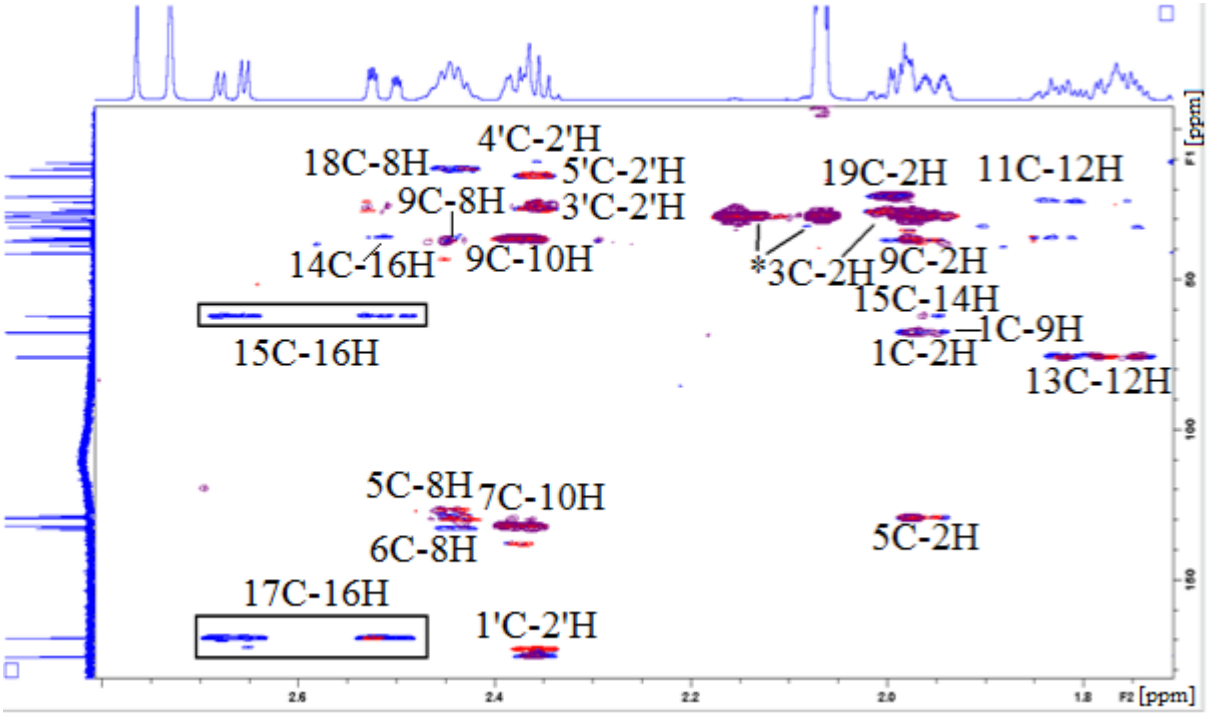

Figure 2 – Fragment of the ^{1}H –^{13} C HMBC NMR spectra (^{1}H, 700 MHz) of lovastatin in a solution of acetone (C_3H_6O) with gadolinium (blue – pure lovastatin, red – lovastatin with gadolinium ion in a molar ratio of 1/75 ion/statin, purple – lovastatin with ion gadolinium in a molar ratio of 1/50 ion/statin, * - solvent signal)

When comparing $^{1}H–^{13}C$ HMBC NMR spectra, the following differences can be identified: signals from 15C-16H, 17C-16H, 14C-16H are present only in “pure lovastatin”, while they are not observed in other samples. The signal from 15C-14H is also not observed when gadolinium ion Gd^{2+} is added. The signals of the remaining peaks change slightly. Thus, it can be assumed that the localization of the gadolinium ion will be located in the environment of C-14, C-15 and C-16 atoms (figure 1b).

References

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