Research Square

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Complexation process of lovastatin with metal ions (zinc, manganese, nickel) by NMR spectroscopy and MD

O. V. Aganova
Kazan Federal University
A. V. Rakova
Kazan Federal University
A. R. Yulmetov
Kazan Federal University
A. A. Troshkina
Kazan Federal University
V. V. Klochkov
vladimir.klochkov@kpfu.ru

Kazan Federal University

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Abstract

This work investigates the complexation process of transition metal ions (Zn2+, Mn2+, Ni2+) with lovastatin using high-resolution NMR spectroscopy and molecular dynamics (MD). Analysis of the 1H NMR spectra showed that the addition of Mn2+ and Ni2+ ions to a solution of lovastatin in deuterated acetone (C3D6O) leads to changes in the line shape and chemical shifts of the CH-15 and CH2-16 signals. In contrast, similar 1H NMR experiments with the lovastatin-Zn2+ system showed no such changes. The DOSY NMR spectra revealed changes in the self-diffusion coefficients (D) of lovastatin in the presence of Mn2+ and Ni2+ ions compared to lovastatin in pure deuterated acetone(C3D6O). Based on the experimental results a suggestion was proposed regarding possible binding locale for Mn2+ and Ni2+ ions on the lovastatin molecule. This assumption is confirmed by the results of molecular dynamics (MD) simulations of the corresponding systems.

1. Introduction

The study of drug interactions with metal ions is of considerable interest in modern medicine and pharmaceuticals, as such interactions can significantly affect the therapeutic efficacy and bioavailability of new drug compounds [1]. For instance, drugs based on manganese ions (Mn^{2+}) in combination with other components are used to treat anemia [2]. The addition of manganese dioxide (MnO_2) to other compounds constitutes a promising drug delivery system. This is possible due to the magnetic properties of the manganese within the compound, which can be used to guide the delivery system [3] Metal ion-based drugs (Zn^{2+}, Ni^{2+}) are widely used for the prevention and treatment of various diseases [4, 5]. Based on their efficacy in lowering low-density lipoprotein cholesterol (LDL-C) levels, statins are classified into three generations. Lovastatin, obtained from fungi, is a first-generation representative. It inhibits key stages of cholesterol biosynthesis in the liver, thereby contributing to reduced mortality from cardiovascular diseases [6]

High-resolution NMR spectroscopy is a powerful technique for investigating the structure of organic compounds in solution [4, 5]. This method allows for the identification of the binding nature of metal ions to specific protons and carbon atoms, as well as the study of conformational transformations, and the determination of coordination centers [7]. The study of the effects of Zn^{2+}, Mn^{2+} and Ni^{2+} ions on the structure of lovastatin by NMR spectroscopy is relevant for assessing potential drug-metabolic interactions. The obtained data reveal the mechanisms of statin interaction with Zn^{2+}, Mn^{2+} and Ni^{2+} ions at the molecular mechanisms may also be used in developing new diagnostic or therapeutic approaches.

2. Materials and methods

2.1. Materials

Lovastatin produced by «Sigma-Aldrich» was used in this work without additional purification. The chemical structure of lovastatin is presented in Fig. 1. The ^{1}H and ^{13}C NMR spectra of lovastatin in deuterated acetone are provided in Figures S1 and S2 (Supplementary materials), respectively.

The salts $MnCl_2$, $NiCl_2$, and $Zn(CH_3COO)_2$ were used to prepare solutions of lovastatin in deuterated acetone (C_3D_6O) for studying its complexation with Mn^{2+} and Ni^{2+}, Zn^{2+} ions, respectively. The initial salts were dissolved in a minimal amount of C_3D_6O, and the resulting solution was then added to the lovastatin sample by titration to achieve the target metal ion concentrations. All samples were prepared in standard 5-mm NMR tubes. The concentrations of the components in the C_3D_6O solution were as follows: lovastatin – 22.0 mM; $Zn(CH_3COO)_2$ – 22.0 mM; $MnCl_2$ – 0.44 mM and 4.4 mM; $NiCl_2$ – 0.44 mM and 4.4 mM. The solution volume for all samples was 0.5 ml.

2.2 Methods

Registration of one-and two-dimensional NMR (1D, 2D) spectra was recorded on a Bruker Avance II-500 pulsed NMR spectrometer (500 MHz for ^{1}H and 125.77 MHz for ^{13}C) at a temperature of 308 K. The spectrometer operated in internal stabilization mode along the ^{2}H resonance line. ^{1}H NMR spectra were acquired using a 90° pulse with a pulse delay of 2 s and a spectral width of 10 ppm. ^{13}C NMR spectra were acquired using a 90° pulse with a pulse delay of 2 s and a spectral width of 200 ppm. Chemical shifts were determined relative to tetramethylsilane (TMS). The “Bruker TopSpin 3.0” software was used for data acquisition and processing. Spectral line assignments were performed using standard high-resolution 1D and 2D NMR experimental protocols. All two-dimensional experiments were conducted with a data matrix of 2k*512 points; the number of scans (96) and the spectral width were optimized individually for each experiment [8–11].

The self-diffusion coefficients (D) in DOSY (Diffusion Ordered SpectroscopY) NMR experiments at a temperature of 308 K [12]. The following parameters were used: spectral width was 10 ppm; the number of gradient steps was 16; the duration of the gradient pulse was 2.5 ms; the diffusion delay time (Δ) was 0.27 s; the amplitude of the magnetic field gradient ranged from 0.24 to 4.57 T/m; the number of scans was 64. The D coefficients were determined using Bruker Topspin 3.6.1 software; to calculate the D for lovastatin, the average D value obtained from signals of different group of lovastatin was taken.

The GROMACS software package was used for molecular dynamics (MD) simulations of the interaction of Zn^{2+}, Mn^{2+}, and Ni^{2+} ions with lovastatin in deuterated acetone (C_3D_6O). The starting system configuration was energy-minimized using the steepest descent algorithm until the maximum force fell below a threshold of 1000 kJ/(mol*nm). Then, each optimized molecular system was equilibrated in the canonical (NVT) at 300 K for 200 ps using a Berendsen thermostat with a coupling constant τ = 0.1 ps. The system was then equilibrated in the isothermal-isobaric (NPT) ensemble (T = 300 K and P = 1 bar) for 300 ps using a Berendsen thermostat τ = 0.1 ps and a Parrinello-Rahman barostat τ = 3.0 ps and pressure $4.5*10^{-6}$ bar. Finally, the resulting molecular system was simulated in the NPT ensemble without any restrictions. Periodic boundary conditions were applied in all MD simulations. Electrostatic

interactions were treated using the Particle Mesh Ewald (PME) method. The simulations were run for at least 250 ns and trajectories were taken every 2 ns [13–16].

3. Results and discussion

3.1 NMR experiments of lovastatin with Zn^{2+} ions in C_3D_6O

The Fig. 2 shows fragments of the ^1H NMR spectra of lovastatin in C_3D_6O and lovastatin in the presence of Zn^{2+} ions at a 1:1 molar ratio. No changes in the chemical shifts or line widths are observed upon the addition of Zn^{2+} ions. The chemical shifts in the ^1H, ^{13}C NMR spectrum of lovastatin in C_3D_6O at 300 K are provided in Table S1 (Supplementary materials).

The obtained results can be explained as follows: a slight change in the shielding constant of the resonant nuclei occurs for the ^1H NMR signals of lovastatin. This change, in turn, leads to a shift of the resonance signal in the NMR spectrum. Based on the NMR experiments it is not possible to determine the approximate location of the Zn^{2+} ion within the lovastatin structure, as no changes in the chemical shifts or signal line widths are observed, despite the lovastatin: Zn^{2+} molar ratio being close to 1:1.

3.2 NMR experiments of lovastatin with Mn^{2+} ions in C_3D_6O

Fragments of ^1H NMR spectra of lovastatin in C_3D_6O with Mn^{2+} ions at various statin: ion ratios presented in Fig. 3.

Spectral analysis of ^1H NMR spectra of lovastatin with varying concentrations of Mn^{2+} revealed the following changes: at a lovastatin: Mn^{2+} ratio = 5:1, broadening of all signals occurs, which is likely attributable to the paramagnetic nature of the manganese ion. Downfield shifts (increased ppm) were observed for the CH-13 and CH_2-16 signals, whereas the CH-15 signal shifted upfield (decreased ppm). The remaining signals either retained their positions or exhibited only minor variations. This behavior is presumably associated with the proximity of the Mn^{2+} ion to the CH-15 and CH_2-16 protons, resulting in an altered local magnetic environment around the CH_2-16 group. Chemical shifts and changes in the chemical shifts in the ^1H, ^{13}C NMR spectrum of lovastatin with Mn^{2+} ions at statin:ion ratios 1:0 (a), 50:1 (b), 5:1 (c) in C_3D_6O at 300 K are summarized in Table S2 (Supplementary materials). The remaining signals shift upfield. According to NMR spectroscopy, an interaction between lovastatin and the Mn^{2+} ion was observed. Mn^{2+} ions presumably interacting with lovastatin from its outer side. The most probable location of the Mn^{2+} ion near the lovastatin molecule is shown in Fig. 4.

3.3 NMR experiments of lovastatin with Ni^{2+} ions in C_3D_6O

Figure 5. Fragments of the ^{1}H NMR spectra (500 MHz) of lovastatin in C_3D_6O with Ni^{2+} ions: *a*) statin: Ni^{2+} ratio 1:0, *b*) statin: Ni^{2+} ratio 50:1, *c*) statin: Ni^{2+} ratio 5:1, *- the solvent signal.

Analysis of the ^{1}H NMR spectra revealed the following changes: at a lovastatin: Ni^{2+} ratio of 5:1, broadening of all signals is observed, which can be explained by the paramagnetic properties of the Ni^{2+} ion. Downfield shifts were observed for the CH-13 and CH_2-16 signals, in contrast to the CH-15 signal that has upfield shift. The remaining signals either showed no changes in their ^{1}H NMR chemical shifts or exhibited only minor variations. This behavior is presumably associated with the proximity of the Ni^{2+} ion to the CH-15 and CH_2-16 protons, resulting in an altered local magnetic environment around the CH_2-16 group. Chemical shifts and changes in the chemical shifts in the ^{1}H, ^{13}C NMR spectrum of lovastatin with Ni^{2+} ions at statin:ion ratios 1:0 (a), 50:1 (b), 5:1 (c) in C_3D_6O at 300 K are summarized in Table S3 (Supplementary materials).

The NMR spectroscopy revealed an interaction between lovastatin and the Ni^{2+} ion. It is presumed that the Ni^{2+} ions interact with the outer side of the lovastatin molecule. The most probable location of the Ni^{2+} ion next to the lovastatin molecule is shown in Fig. 6.

3.4 DOSY NMR study of lovastatin with Zn^{2+}, Mn^{2+} and Ni^{2+} ions in C_3D_6O

The translational mobility of lovastatin-ion systems in C_3D_6O was investigated using DOSY NMR spectroscopy. It is expected that if there is an interaction between lovastatin and the ions, the self-diffusion coefficients (D) will change compared to those of the pure statin in acetone. The measured self-diffusion coefficients of lovastatin, water (H_2O), and acetone (C_3D_6O) at different ratios of statin: Zn^{2+}, Mn^{2+}, Ni^{2+} ion at a temperature of 300 K are summarized in Table S4 (Supplementary materials). The absence of some values for H_2O is attributed to the difficulty of accurately determining its self-diffusion coefficient under these experimental conditions.

Thus, the self-diffusion coefficients (D) of lovastatin were measured in the presence of metal ions Mn^{2+}, Ni^{2+} and Zn^{2+}. The observed changes in the coefficients indicate an interaction between lovastatin molecules and these ions. The measured self-diffusion coefficients (D) of lovastatin in the absence and presence of metal ions at maximum concentrations are summarized in Table S4. Analysis of the obtained data revealed no significant changes in the self-diffusion coefficient (D) of lovastatin in the presence of Zn^{2+} ions ($D = 1.28*10^{-9}$ m^2/s) consistent with the absence of observable effects in 1D NMR spectra. This suggests that Zn^{2+} does not significantly affect the translational dynamics of lovastatin under these experimental conditions.

In contrast, upon addition of Mn^{2+} and Ni^{2+} ions at lovastatin:ion ratio of 5:1, there was a significant decrease in the self-diffusion coefficient (D) were observed. For the lovastatin: Mn^{2+} system, D

decreased to $1.6*10^{-10}$ m^2/s, while for lovastatin: Ni^{2+} (D) decreased to $5.4*10^{-10}$ m^2/s compared to pure lovastatin ($D = 1.28*10^{-9}$ m^2/s). These obvious changes in diffusion coefficients (D) indicate altered translational mobility of lovastatin in the presence of paramagnetic ions consistent with ion-statin association in solution.

Notably, the more significant decrease in (D) for Mn^{2+} compared to Ni^{2+} ion the same statin: ion ratio = 5:1 suggests differences in the association behavior. We suppose that Mn^{2+} ion can form higher molecular weight associates, whereas Ni^{2+} primarily forms complexes with fewer statin molecules. This would explain the more significant decrease in translational mobility observed in the lovastatin-Mn^{2+} system.

3.5 NOESY NMR study of lovastatin with Zn^{2+}, Mn^{2+} and Ni^{2+} ions in C_3D_6O

Interproton distances in lovastatin were calculated based on two-dimensional NOESY spectra recorded with different mixing times: t_m = 0.1, 0.2, 0.25, and 0.3 s for free lovastatin, and t_m = 0.1, 0.2, 0.3, and 0.4 s for lovastatin in the presence of metal ions [17, 18].

The distance between nonequivalent protons of the CH_2-11 group (2.49 Å) was used as an internal reference. ^1H-^{13}C NOESY distances (r) and cross-relaxation rates (σ) for lovastatin in C_3D_6O at 300 K in the absence and presence of metal ions (Mn^{2+}, Ni^{2+}) determined from 2D NOESY NMR experiments are presented in Tables S5 (Supplementary materials).

Analysis of the 2D NOESY NMR data revealed that the reference distance *11a-11b remains constant at 2.49 Å across all experimental conditions (pure statin, Mn^{2+}, and Ni^{2+} systems) confirming the reliability of the 2D NOESY NMR measurements. For other interproton distances (e.g., 3–4, 3–18, 9–15 groups) variations within 0.1–0.9 Å were observed depending on the ion type and concentration. These changes fall within the range of experimental uncertainty and do not indicate substantial structural rearrangements of the lovastatin molecule.

The absence of significant changes in interproton distances indicates that the overall spatial structure of lovastatin remains practically unchanged in the presence of paramagnetic ions (Ni^{2+}, Mn^{2+}). Thus, the effects observed in the ^1H NMR spectra (line broadening and chemical shift variations) are predominantly due to the influence of ions located in close proximity to the molecule and are not associated with conformational rearrangements of the statin itself.

3.6 Modeling of MD of lovastatin with Zn^{2+}, Mn^{2+}, Ni^{2+} ions in C_3D_6O

To confirm the proposed binding location for the metal ions, molecular dynamics (MD) simulations were performed on systems containing lovastatin and each metal ion (Zn^{2+}, Mn^{2+} or Ni^{2+}) separately. The model system consisted of 20 lovastatin molecules, with the addition of Mn^{2+}, Ni^{2+}, Zn^{2+} ions (statin: ion ratios are 1:1 for Zn^{2+}, 5:1 for Mn^{2+} and 5:1 for Ni^{2+} corresponding to experimentally studied solutions by NMR). The system was solvated in a periodic cubic box (10 × 10 × 10 nm) containing 32.284 water molecules which corresponds to the experimentally used solution concentration. The CHARMM36 force field was employed for parameterization.

To analyze the binding dynamics between lovastatin and the metal ions radial distribution functions (RDFs) were calculated from the MD trajectories. RDFs were constructed for Mn^{2+}, Ni^{2+} and Zn^{2+} ions with respect to the hydrogen atoms of lovastatin. For each frame of the MD trajectory all interatomic distances between the statin molecules and the metal ions were compiled. These distance data were then averaged over the entire simulation trajectory to compute the RDFs for specific “statin-ion” pairs. The resulting RDF plots are shown in Figure S3 (Supplementary Material).

Based on the RDF plots in Figure S3 a distinct maximum is observed for the Mn^{2+} ion at 0.59 nm (for H-15) and 0.49 nm (for H_2-16). This indicates a high probability of finding the Mn^{2+} ion at these specific distances from the respective protons, consistent with its localization in the vicinity of the C-15 and C-16 fragment of the lovastatin molecule. Metal binding site can be rationalized by the presence of the ring group in this region that possesses a large dipole moment and is capable of coordinating metal ions.

The RDF profiles for Ni^{2+} exhibit a similar pattern with well-defined maximum at 0.68 nm (for H-15) and 0.70 nm (for H_2-16), indicating a high probability of Ni^{2+} localization near the same molecular region.

In contrast, the RDFs for Zn^{2+} show no pronounced maxima and display a uniform distribution starting from approximately 0.8 nm (for H-15) and 0.7 nm (for H_2-16). This behavior suggests that Zn^{2+} does not exhibit a preferred binding site near these protons and remains solvated in the pure solution. Thus, only Mn^{2+} and Ni^{2+} ions demonstrate a high probability of specific localization near the H-15 and H_2-16 protons of lovastatin which is in full agreement with the results obtained from 1D and 2D NMR spectroscopy.

Conclusion

High-resolution NMR spectroscopy combined with MD simulations revealed interactions of lovastatin with Mn^{2+} and Ni^{2+} ions, but not with Zn^{2+}. The ^1H NMR spectra showed line broadening and chemical shift variations for the H-15 and H_2-16 protons signals upon addition of Mn^{2+} and Ni^{2+} indicating spatial proximity of these ions to the CH-15 and CH_2-16 fragment of the molecule. The DOSY NMR data confirmed the formation of ion-statin associates in solution. MD simulations supported the preferential localization of Mn^{2+} and Ni^{2+} near the H-15 and H_2-16 protons, while no such localization was observed for Zn^{2+}. The 2D NOESY derived interproton distances demonstrated that the overall spatial structure of

lovastatin remains unchanged in the presence of paramagnetic ions, suggesting that the observed NMR effects are primarily due to the proximity of the ions to CH-15 and CH_2-16 rather than to conformational rearrangements of the statin.

Declarations

Author contributions section

O.V.: Investigation, Visualization, Writing-Original draft preparation

A.V.: Methodology, Investigation, Validation

A.R.: Investigation, Methodology, Validation

A.A.: Writing - review editing, Validation.

V.V.: Funding acquisition, Resources, Conceptualization, Writing-Reviewing and Editing, Supervision.

All authors discussed the results and contributed to the final manuscript.

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Conflict of interest: The authors declare that they have no conflicts of interest.

Financial interests: The authors declare they have no financial interests.

Non-financial interests: none.

Ethics declaration: not applicable.

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Figures

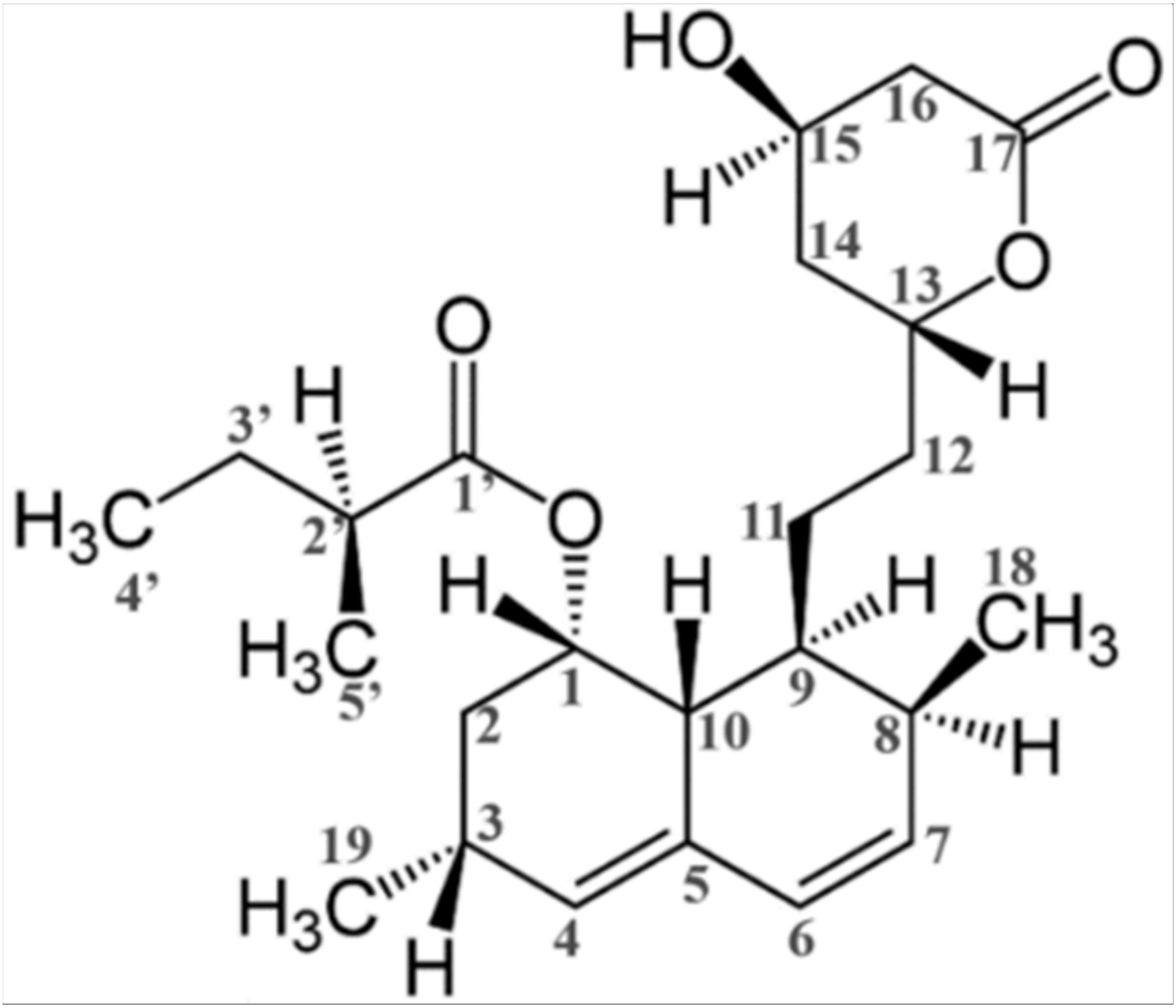


Figure 1

Chemical structure of lovastatin.

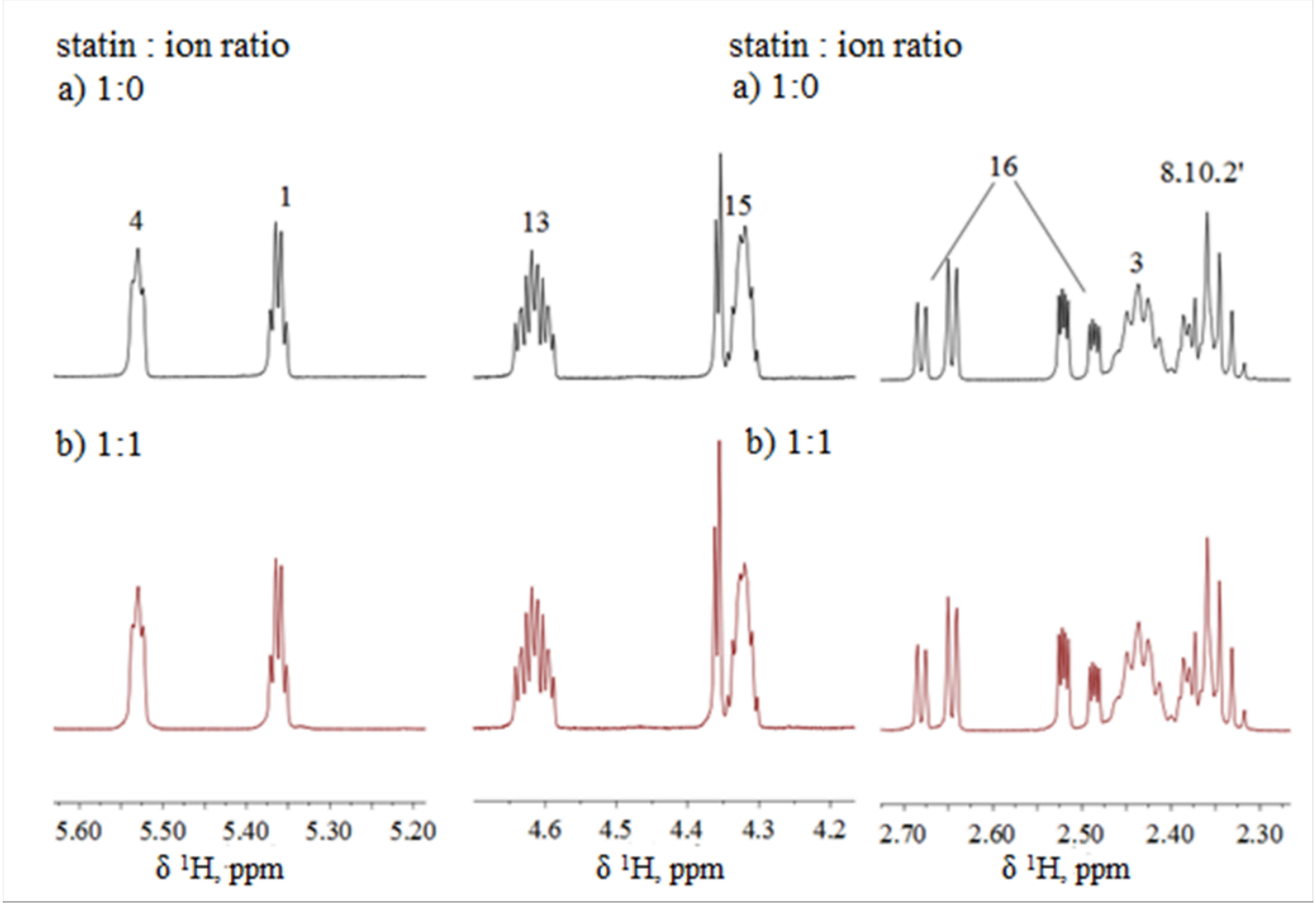


Figure 2

Fragments of the ^{1}H NMR spectra (500 MHz) of lovastatin in C_3D_6O a) statin: Zn^{2+} ratio = 1:0, b) statin: Zn^{2+} ratio= 1:1

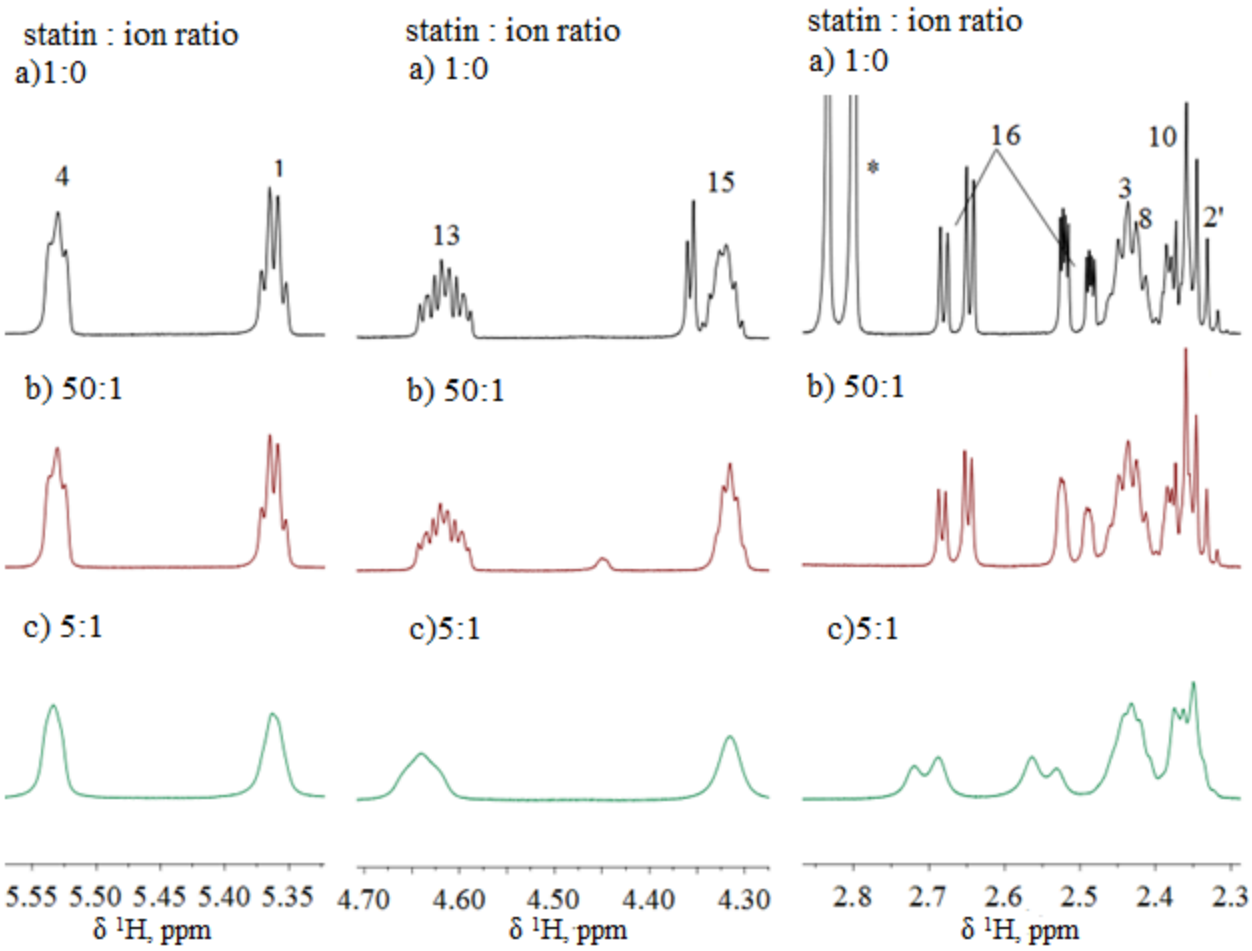


Figure 3

Fragments of the ^{1}H NMR spectra (500 MHz) of lovastatin in C_3D_6O: *a*) statin: Mn^{2+} ratio 1:0, *b*) statin: Mn^{2+} ratio 50:1, *c*) statin: Mn^{2+} ratio 5:1, *- the solvent signal.

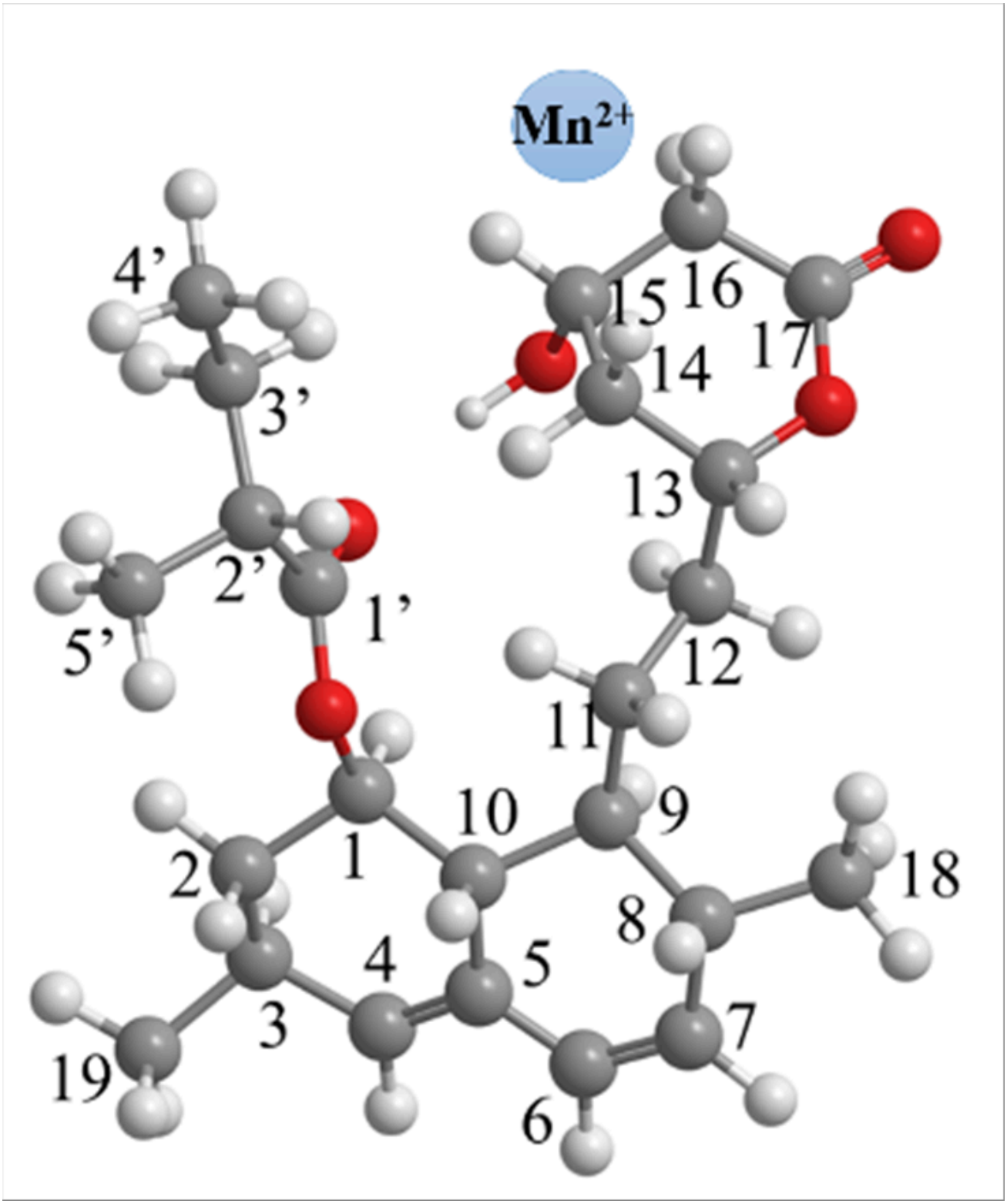


Figure 4

Scheme of localization of Mn^{2+} ions (blue ball) with the lovastatin molecule.

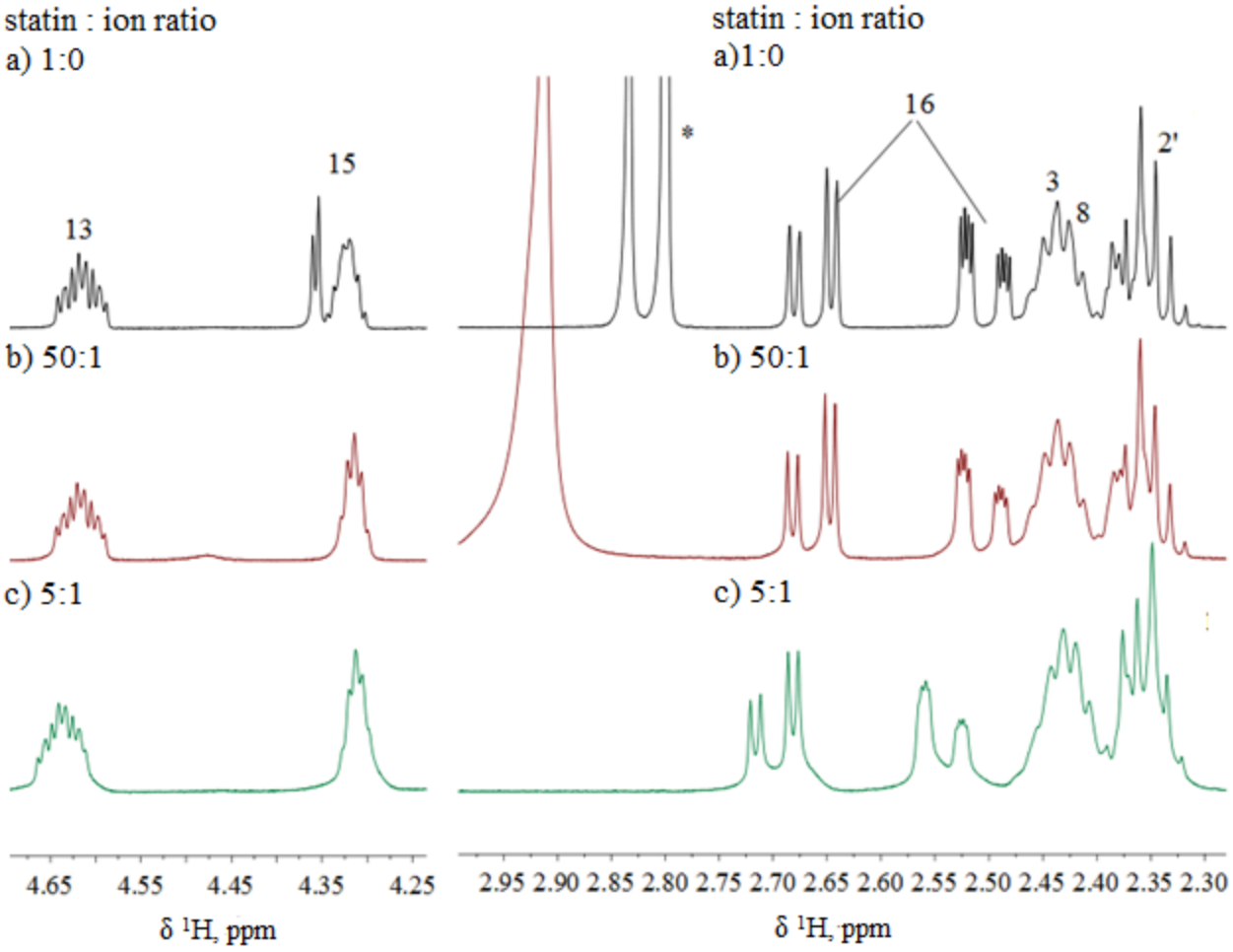


Figure 5

Fragments of the ^{1}H NMR spectra (500 MHz) of lovastatin in C_3D_6O with Ni^{2+} ions: *a*) statin: Ni^{2+} ratio 1:0, *b*) statin: Ni^{2+} ratio 50:1, *c*) statin: Ni^{2+} ratio 5:1, *- the solvent signal.

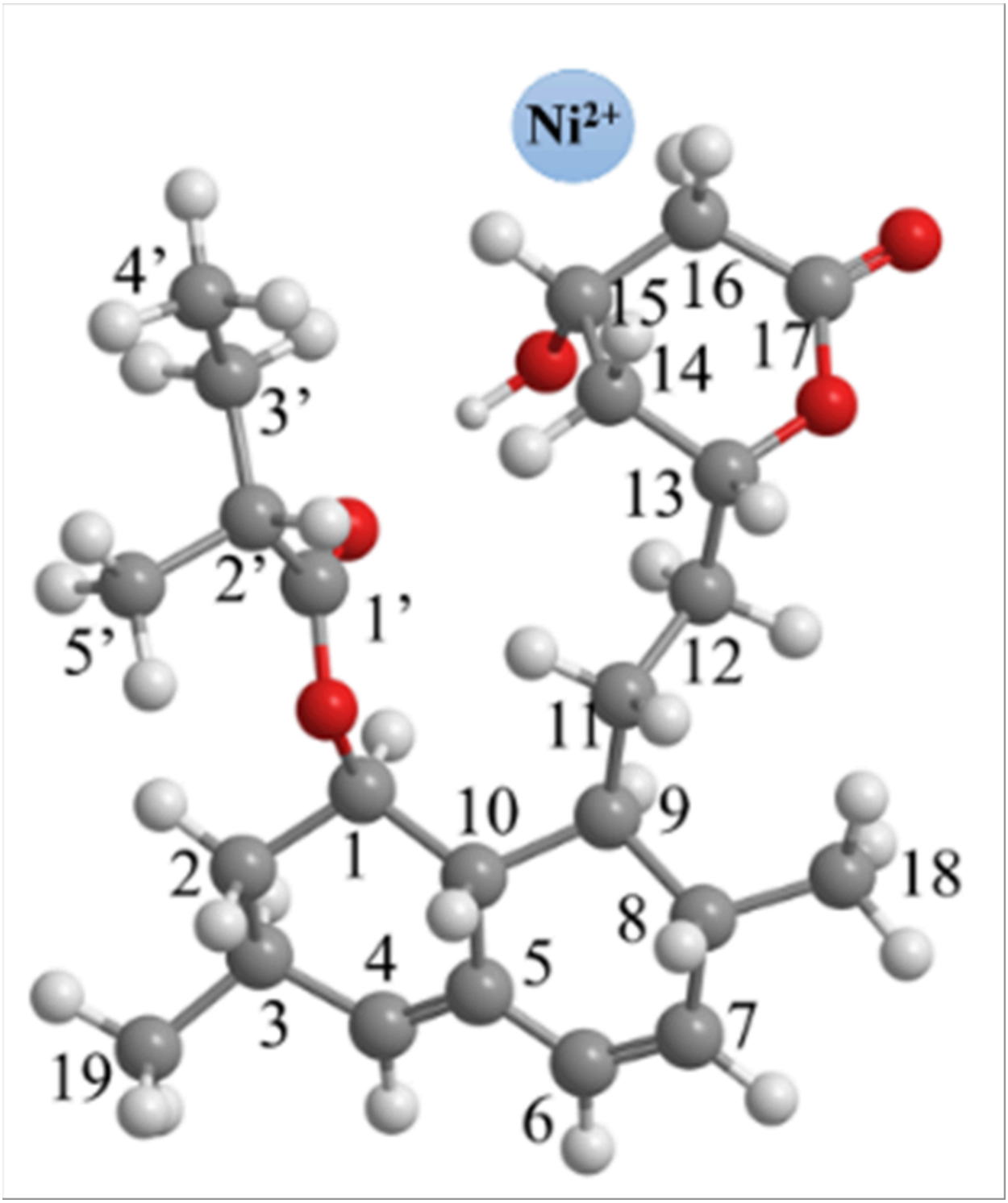


Figure 6

Scheme of localization of Ni^{2+} ions (blue ball) with the lovastatin molecule.

Supplementary Files

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