

Ga(III) complexes of methoxy substituted aroylhydrazones: synthesis, characterization and DFT calculations

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The study reports the synthesis and physicochemical characterization of Ga (III) complexes with 3-, 4- and 5-methoxy substituted salicylaldehyde based aroylhydrazones designed by varying the position of methoxy group in salicylaldehyde moiety. The complexes were obtained by reaction of Ga(NO₃)₃.H₂O with the ligands in 1:2 metal-to-ligand molar ratio. The coordination behaviour of 3-, 4- and 5-methoxysalicylaldehyde-4-hydroxybenzoylhydrazones towards Ga (III) ions was investigated at theoretical and experimental level. Density Functional Theory calculations with Becke's 3-parameter hybrid functional and 6-31+G (d,p) basis set were carried out to investigate the structural features of the methoxy substituted at different positions aroylhydrazones ligands and Ga (III) complexes. The predicted metal-ligand binding mode was confirmed by spectral data. The complexes are mononuclear with the Ga (III) ions being surrounded by two tridentate ligands. The analysis revealed coordination binding through deprotonated salicylaldehyde phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms. A general formula [Ga(L-H)₂]₂NO₃ for the complexes obtained was suggested on the basis of the experimental data.

Key words: gallium (III) complexes, aroylhydrazones, DFT calculations.

INTRODUCTION

Over the last few years gallium was widely studied due to the versatile applications of this metal and its complexes as bioactive compounds, materials for optoelectronic devices, catalysts, etc. [1–3]. The ability of simple metal salt gallium (III) nitrate to inhibit tumor cell growth *in vitro* and *in vivo* provides a strong motivation for continued research into the development of new gallium compounds with antitumor activities [3–6]. However, in aqueous media and under physiological conditions, the small and highly charged Ga (III) ion hydrolyzes nearly completely over a wide pH range, forming various hydroxide species [1]. To prevent hydrolysis processes, coordination of gallium with polydentate organic ligands has been proposed since Ga (III) complexes possess improved oral bioavailability, hydrolytic stability and membrane penetration ability [1, 3]. Hydrazones are effective ligands as they easily form stable complexes with many metals. The coordination modes of the hydrazone ligands depend on different factors like reaction conditions, stability of the complex formed, number and nature of the substituents on hydrazone skeleton. Aroylhydrazones of the type R-CO-NH-N=CH-R', derived by condensation of aromatic aldehydes and acid hydrazides form a series of biologically active ligands used in medicinal chemistry

[7–10]. Furthermore, suitable substituents can improve the coordination properties. Especially interesting hydrazones were synthesized by salicylaldehyde (2-hydroxybenzaldehyde). The additional hydroxy group in the aldehyde part increases the number of donor atoms and enhances coordination ability of the ligands. Various derivatives of salicylaldehyde have been used in order to discover new pharmacologically active compounds [11–13]. The substitutions slightly change the compounds but give rise to a diversity of biological effects and various pharmacological and potential therapeutic properties. It has been demonstrated that the introduction of a methoxy group into a salicylaldehyde results in derivatives with high antiproliferative and antioxidant activity [13–15]. Hence the methoxy substituted hydrazones would be suitable to prepare cytotoxic Ga complexes.

In the study herein we describe the synthesis and physicochemical characterization of Ga (III) complexes with 3-, 4- and 5-methoxy substituted salicylaldehyde based hydrazones. DFT calculations were carried out to examine the coordination ability of methoxy hydrazones and to investigate how the position of the methoxy group in salicylaldehyde affects the structural features of the complexes. The obtained gallium complexes were characterized by elemental analysis, NMR- and IR-spectroscopy.

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EXPERIMENTAL PART

3-methoxysalicylaldehyde, 4-ethoxysalicylaldehyde, 5-methoxysalicylaldehyde and 4-hydroxybenzylhydrazone used for the preparation of the ligands 3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**¹), 4-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**²) and 5-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**³) were purchased from Sigma-Aldrich and used without further purification. Gallium (III) nitrate monohydrate used for the synthesis of the complexes was purchased from Sigma-Aldrich. All other chemicals used were of analytical reagent grade.

The carbon, nitrogen and hydrogen contents of the compounds were determined by elemental analyses on Euro EA 3000 – Single, EuroVector SpA analyzer. The IR spectra were recorded on a Thermo Scientific Nicolet iS10 spectrophotometer in the range of 4000–400 cm⁻¹ as ATR. The ¹H NMR spectra were recorded on a Bruker Avance DRX 250 spectrometer in DMSO-d₆ as solvent, chemical shifts were referenced to the solvent signal. Chemical shifts (δ) are reported in parts per million (ppm), *J* values are given in Hz. Splitting patterns were indicated by the symbols: s (singlet), d (doublet), t (triplet) and m (multiplet).

The synthesis of the ligands was published in our previous works [13–14, 16].

The gallium (III) complexes were obtained by reaction of Ga(NO₃)₃·H₂O with the ligands in 1:2 metal-to-ligand molar ratios using the following general procedure: Solution of gallium nitrate monohydrate (0.5 mmol) in methanol (50 mL) was added to the respective solutions of the ligands (1 mmol) in methanol (100 mL). The resulted solutions were stirred for 1 h at room temperature to complete the reaction and then were kept at room temperature for 48 h. During this time crystals of the product were obtained. Fine crystals were collected after filtration, washed with methanol and dried in a vacuum desiccator.

Bis-(3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone) gallium (III) nitrate,
[Ga(L¹-H)₂](NO₃)

Yield: 58%; Colour: Yellow-greenish; IR (ν cm⁻¹): 3400 (OH_{hydrazide}), 3200 (NH), 1607 (C=O), 1588 (C=N), 1391 (NO₃⁻). ¹H NMR (250 MHz, DMSO-d₆) δ ppm: 3.77 (s, 3H, -OCH₃), 6.83 (m, 2H, ArH_{hydrazide}, 3H, ArH_{aldehyde}), 7.90 (d, 2H, *J* = 8 Hz, ArH_{hydrazide}), 8.76 (s, 1H, CH=N), 10.00 (s, 1H, OH_{hydrazide}), 11.11 (s, 1H, NH). Calculated for [Ga(C₁₅H₁₃N₂O₄)₂](NO₃): C, 51.31; H, 3.73; N, 9.97. Found: C, 51.58; H, 3.89; N, 9.59.

Bis-(4-methoxysalicylaldehyde 4-hydroxybenzoylhydrazone) gallium (III) nitrate,
[Ga(L²-H)₂](NO₃)

Yield: 65 %; Colour: Yellow-greenish; IR (ν cm⁻¹): 3401 (OH_{hydrazide}), 3179 (N-H), 1618 (C=O), 1593 (C=N), 1392 (NO₃⁻). ¹H NMR (250 MHz, DMSO-d₆) δ ppm: 3.67 (s, 3H, -OCH₃), 6.31 (s, 1H, ArH_{aldehyde}), 6.35 (d, 1H, *J* = 8 Hz, ArH_{aldehyde}), 6.86 (d, 2H, *J* = 8 Hz, ArH_{hydrazide}), 7.31 (d, 1H, *J* = 9 Hz, ArH_{aldehyde}), 7.80 (d, 2H, *J* = 6.5 Hz, ArH_{hydrazide}), 8.56 (s, 1H, CH=N), 9.96 (s, 1H, OH_{hydrazide}), 11.78 (s, 1H, NH). Calculated for [Ga(C₁₅H₁₃N₂O₄)₂](NO₃): C, 51.31; H, 3.73; N, 9.97. Found: C, 51.18; H, 3.95; N, 9.62.

Bis-(5-methoxysalicylaldehyde 4-hydroxybenzoylhydrazone) gallium (III) nitrate,
[Ga(L³-H)₂](NO₃)

Yield: 62 %; Colour: Orange-greenish; IR (ν cm⁻¹): 3370 (OH_{hydrazide}), 3190 (N-H), 1616 (C=O), 1593 (C=N), 1392 (NO₃⁻). ¹H NMR (250 MHz, DMSO-d₆) δ ppm: 3.70 (s, 3H, -OCH₃), 6.80 (m, 2H, ArH_{hydrazide}, 2H, ArH_{aldehyde}), 7.00 (s, 1H, ArH_{aldehyde}), 7.90 (d, 2H, *J* = 7.5 Hz, ArH_{hydrazide}), 8.62 (s, 1H, CH=N), 9.97 (s, 1H, OH_{hydrazide}), 10.80 (s, 1H, NH). Calculated for [Ga(C₁₅H₁₃N₂O₄)₂](NO₃): C, 51.31; H, 3.73; N, 9.97. Found: C, 51.51; H, 4.04; N, 9.62.

The B3LYP/31+G(d,p) (Becke's three-parameter hybrid exchange-correlation functional [17] with diffuse function augmented double-ζ polarized basis set) method was used to optimize the geometry of each ligand and metal complex. Local minima were verified by establishing that all vibrational frequencies are real. All calculations were performed using Gaussian 09 [18]. PyMOL molecular graphics software was used for generating the molecular graphics images [19].

RESULTS AND DISCUSSION

The ligands 3-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**¹), 4-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**²) and 5-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone (**L**³), shown on Figure 1, were synthesized as already reported [13, 14, 16].

Three gallium (III) complexes with the ligands **L**¹, **L**² and **L**³ were prepared by a direct reaction of the hydrazones and gallium (III) nitrate monohydrate in absolute methanol with good yields (58–65 %) (Scheme 1).

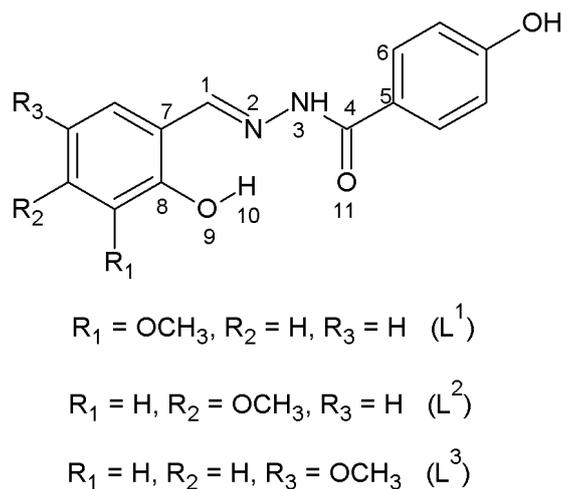
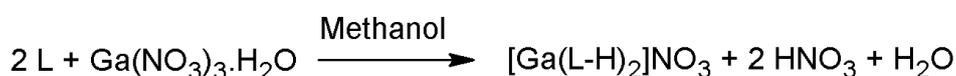


Figure 1. Structure of the 3-, 4- and 5-methoxy substituted ligands.



Scheme 1. Synthesis of the gallium (III) complexes with the ligands.

The complexes were characterized by elemental analysis as a basis for the determination of their empirical formulas. Experimental and calculated C, H, N values are in good agreement and reveal molar ratio metal:ligand = 1:2 in the complexes. Analyses suggest the following molecular formula of the compounds $[\text{Ga}(\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4)_2]\text{NO}_3$. The data from the elemental analysis of the gallium (III) complexes are summarized in the Experimental section.

The coordination behaviour of 3-, 4- and 5-methoxysalicylaldehyde benzoylhydrazones towards Ga (III) ions was investigated at theoretical and

experimental level. DFT calculations were carried out to predict the molecular structure of the new gallium (III) complexes and to investigate how the position of the methoxy group in the salicylaldehyde affects the structural features of the complexes. The optimized geometry of the Ga-complex ions $[\text{Ga}(\text{L}^1-\text{H})_2]^+$, $[\text{Ga}(\text{L}^2-\text{H})_2]^+$ and $[\text{Ga}(\text{L}^3-\text{H})_2]^+$ are shown on Figure 2.

Selected geometrical parameters for the studied ligands and complexes (bond lengths (Å) and angles (°)) are presented in Table 1.

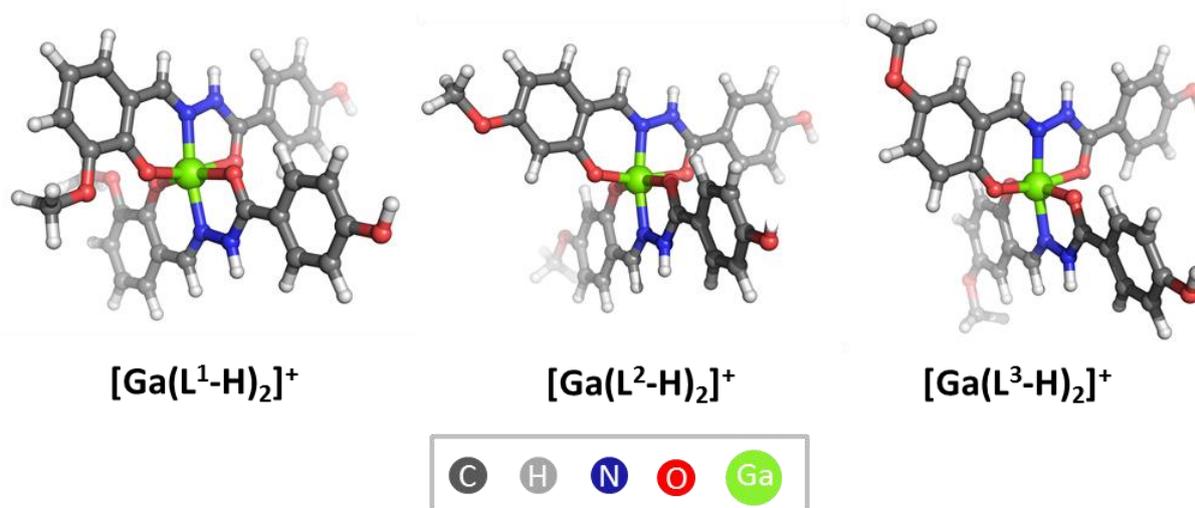


Figure 2. B3LYP/6-31+G(d,p) optimized geometries of the Ga (III) complexes.

Table 1. Selected B3LYP/6-31+G(d,p) calculated parameters for the ligands and complexes. Atom numbering is shown on Figure 1.

	Ligand			Complex		
	L ¹	L ²	L ³	[Ga(L ¹ -H) ₂] ⁺	[Ga(L ² -H) ₂] ⁺	[Ga(L ³ -H) ₂] ⁺
dipole moment, μ [D]	4.36	5.93	6.38	5.14	4.11	6.79
bond length [Å]						
C1-N2	1.290	1.291	1.291	1.305	1.308	1.307
N2-N3	1.359	1.361	1.359	1.376	1.377	1.377
N3-C4	1.388	1.387	1.389	1.357	1.357	1.357
C4-C5	1.497	1.496	1.496	1.463	1.464	1.464
C4-O11	1.223	1.224	1.223	1.263	1.262	1.263
C5-C6	1.406	1.406	1.406	1.410	1.410	1.464
C1-C7	1.453	1.448	1.451	1.421	1.415	1.420
C7-C8	1.416	1.428	1.416	1.432	1.446	1.434
C8-O9	1.343	1.346	1.350	1.303	1.309	1.309
O9-H10/O9-Ga	0.986	0.987	0.985	1.903	1.902	1.901
N1-Ga	-	-	-	2.014	2.022	2.024
O11-Ga	-	-	-	2.031	2.034	2.029
angle [°]						
C1-N2-N3	118.68	118.60	118.68	120.26	120.06	119.95
N2-N3-C4	120.21	120.17	120.09	116.40	116.14	116.23
N3-C4-O11	122.12	122.18	122.06	117.72	117.84	117.80
N3-C4-C5	114.99	114.97	115.03	120.39	120.11	120.14
C5-C4-O11	122.88	122.85	122.90	121.89	122.05	122.06
C1-C7-C8	121.37	122.18	121.83	121.92	122.99	122.15
dihedral angle [°]						
N2-C1-C7-C8	0.80	0.77	1.03	0.09	0.77	0.66
N3-C4-C5-C6	24.14	24.77	23.97	2.56	11.48	10.59

The phenyl ring in the ligand structure is rotated about 25 degrees (23.97° – 24.77°), so the ligands are not planar. One mode of coordination with octahedral arrangement between the optimized structures of the deprotonated free ligands and the Ga cations was considered: the metal is bound to the oxygen atoms of salicylaldehyde phenolic and amide groups and to the azomethine nitrogen atom of each of the two ligands. In the resulting complexes the ligands are positioned almost perpendicularly to each other. The calculated Ga–O and Ga–N distances are indicative of a stronger interaction of Ga cations with the deprotonated OH-groups – in all cases the O9–Ga bonds ($<2 \text{ \AA}$) are shorter than the O11–Ga and N1–Ga bonds ($>2 \text{ \AA}$) (Table 1). Some structural changes are observed in the ligands upon complex formation, as the most pronounced one is the change observed in the L¹ structure – the ligand becomes almost planar (the N3–C4–C5–C6 dihedral angle changes from 24.14° to 2.56°). Ga cation is positioned at almost equal distance from O9 and O11 atoms in all complexes. A little bit shorter N1–Ga bond is predicted for the $[\text{Ga}(\text{L}^1\text{-H})_2]^+$ complex. The coordination realized between L¹ (with methoxy group in position 3) and Ga cation seems to be slightly stronger than that with the other ligands.

The predicted mode of coordination of the ligands to the gallium ions was verified by IR and ¹H NMR spectral data for the metal-free ligands as well as their Ga (III) complexes.

The ligands show a band at $3300\text{--}3360 \text{ cm}^{-1}$ due to salicylaldehyde phenolic OH group. The absence of these bands in the IR spectra of the Ga (III) complexes supports the suggestion for deprotonation of the ligands during the coordination and displacement of a proton by the Ga (III) ion. The $\nu(\text{C}=\text{O})$ band, observed at $1634\text{--}1662 \text{ cm}^{-1}$ in the spectra of the ligands, is shifted to lower wavenumbers by $18\text{--}44 \text{ cm}^{-1}$ in the gallium complexes, indicating coordination of the carbonyl group to the metal ion. The bands attributed to azomethine C=N group of the ligands ($1602\text{--}1608 \text{ cm}^{-1}$) were shifted by $9\text{--}20 \text{ cm}^{-1}$ to lower wavenumbers in the spectra of the complexes ($1588\text{--}1593 \text{ cm}^{-1}$) indicating the involvement of N-atom of the azomethine group in the complex formation. Absorptions at $1391\text{--}1392 \text{ cm}^{-1}$ in the spectra of the complexes were attributed to the nitrate group as counter-ion. The IR spectra of ligand L³ and its Ga-complex are given on Figure 3.

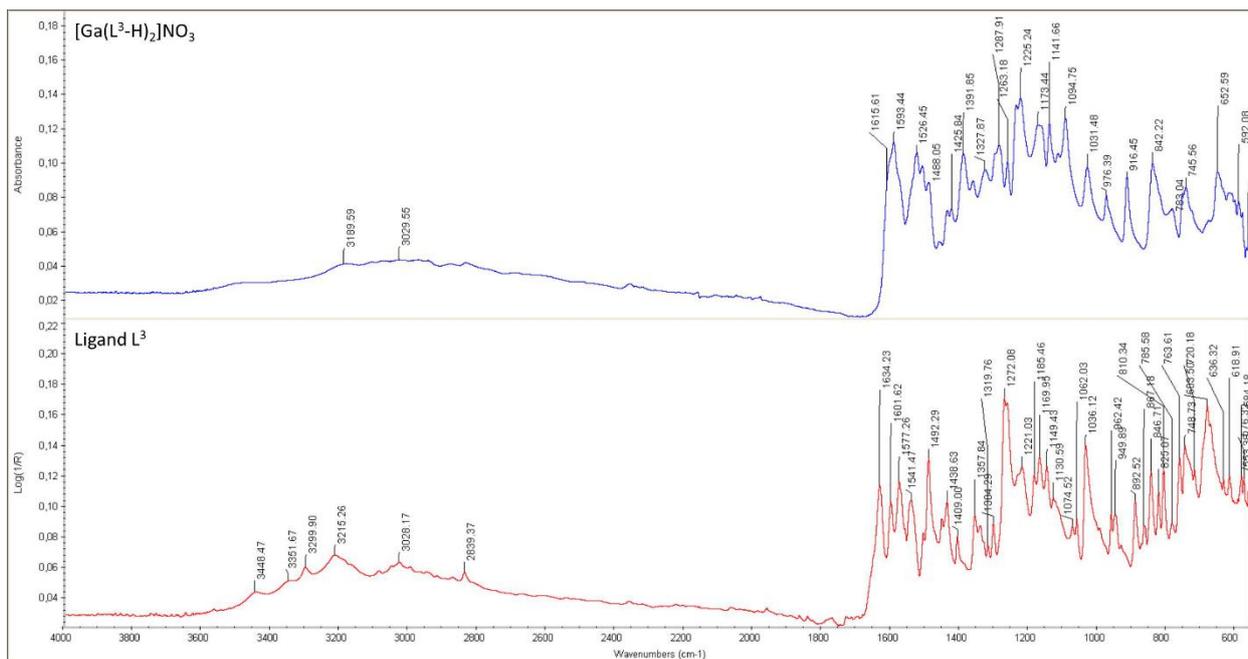


Figure 3. The IR spectra of ligand L^3 and its Ga-complex.

^1H NMR spectra of the Ga (III) complexes give additional information about structural changes in the ligands upon complexation. In the ^1H NMR spectra of the ligands the signal for the proton of the salicylaldehyde phenolic OH group was observed as a singlet at 11.78-11.89 ppm. The disappearance of these signals in the ^1H NMR spectra of the complexes supposes coordination of Ga (III) ion to the salicylaldehyde phenolic oxygen atom after deprotonation. The singlets at 8.51-8.61 ppm in the spectra of the ligands, assigned to azomethine group – $\text{CH}=\text{N}$, were downfield shifted (by 0.05-0.15 ppm) in the complexes to 8.56-8.76 ppm, indicating the involvement of the azomethine nitrogen in bonding with the Ga (III) ion. The signals for the protons of the methoxy-group in salicylaldehyde ring in the spectra of the complexes were slightly upshifted by 0.02-0.10 ppm compared to those of the ligands.

The observed changes in the experimental IR and ^1H NMR spectra of the ligands and their Ga (III) complexes suggest that 3-methoxy-, 4-methoxy- and 5-methoxysalicylaldehyde-4-hydroxybenzoylhydrazones chelate the metal ions through deprotonated salicylaldehyde phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms and thus forming stable six-membered chelates.

CONCLUSION

Three novel Ga (III) complexes with 3-, 4- and 5-methoxysalicylaldehyde-4-hydroxybenzoylhydrazone ligands were synthesized and structurally characterized. The analytical data reveal that complexes are mononuclear with molar ratio metal:ligand = 1:2 and general formula $[\text{Ga}(\text{L-H})_2]\text{NO}_3$. The ligands act as

tridentate ligands and chelate Ga (III) ion through deprotonated phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms forming a six-membered chelate ring. The molecular geometries of the ligands and gallium (III) complexes were studied at the B3LYP/6-31+G(d,p) level of theory. Selected geometrical parameters for the studied ligands and complexes are compared and the structural changes in the ligands upon complex formation are discussed. On the basis of the calculated Ga–O and Ga–N distances stronger interaction of Ga (III) with the deprotonated salicylaldehyde OH-groups can be concluded.

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REFERENCES

1. L. R. Bernstein, in: The Use of Metals in Medicine, M. Gielen, B. R. T. Tiekink. (eds), vol. 14, John Wiley & Sons, Ltd., New York, 2005, 259.
2. F. Zhang, X. Liu, F. Huang, Z. Zhuo, L. Lu, Z. Xu, Y. Wang, X. Tao, W. Bian, W. Tang, , *Chin. Sci. Bull.*, **56**, 479 (2011).
3. M. A. Jakupec, M. Galanski, V. B. Arion, G. C. Hartinger, B.K. Keppler, *Dalton Trans.*, **2**, 183 (2008).
4. L. R. Bernstein, T. Tanner, C. Godfrey, B. Noll, *Met. Based Drugs*, **7**, 33 (2000).
5. P. Collyer, B. K. Keppler, C. Madoulet, B. Desoize, *Crit. Rev. Oncol. Hematol.*, **42**, 283 (2002).
6. M. A. Jakupec, B. K. Keppler, *Curr. Top. Med. Chem.*, **4**, 1575 (2004).

7. P. Ponka, D. Richardson, E. Baker, H. M. Schulman, J. T. Edward, *Biochim. Biophys. Acta*, **967**, 122 (1988).
8. E. Baker, D. R. Richardson, S. Gross, P. Ponka, *Hepatology*, **15**, 492 (1992).
9. D. R. Richardson, P. Ponka, *J. Lab. Clin. Med.*, **131**, 306 (1998).
10. J. L. Buss, E. Arduini, P. Ponka, *Biochem. Pharmacol.*, **64**, 1689 (2002).
11. D. B. Lovejoy, D. R. Richardson, *Blood*, **100**, 666 (2002).
12. D. R. Richardson, K. Milnes, *Blood*, **89**, 3025 (1997).
13. B. Nikolova-Mladenova N. Halachev, R. Iankova, G. Momekov, D. Ivanov, *J. Arzneim.-Forsch.*, **61**, 714 (2011).
14. B. Nikolova-Mladenova, G. Momekov, D. Ivanov, *Pharmacia*, **LVIII**, 41 (2011).
15. N. G. Hristova-Avakumova, B. I. Nikolova-Mladenova, V. A. Hadjimitova, *Bulg. Chem. Comm.*, **47**, 1053 (2015).
16. B. Nikolova-Mladenova, G. Momekov, D. Ivanov, A. Bakalova, *J. Appl. Biomed.*, in press (2017).
17. A. D. Becke, *J. Chem. Phys.*, **98**, 5648 (1993).
18. M. J. Frisch et al., Gaussian 09, Revision D.01; Gaussian, Inc., Wallingford CT, 2013.
19. The PyMOL Molecular Graphics System, Version 1.7.6.6 Schrödinger, LLC.

Ga(III) КОМПЛЕКСИ С МЕТОКСИ-ЗАМЕСТЕНИ АРОИЛХИДРАЗОНИ: СИНТЕЗ, ОХАРАКТЕРИЗИРАНЕ И ИЗЧИСЛЕНИЯ С ТФП

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(Резюме)

В това изследване се описва синтезът и физикохимичното охарактеризиране на Ga (III) комплекси с метокси заместени ароилхидразони, получени чрез вариране на мястото на метокси групата в салицилалдехидния фрагмент. Комплексите са получени чрез взаимодействие на Ga(NO₃)₃·H₂O с лигандите в молно отношение метал:лиганд = 1:2. Координационното поведение на 3-, 4- и 5-метоксисалицилалдехид-4-хидроксibenзоилхидразоните спрямо Ga (III) йони беше изследвано теоретично и експериментално. За изследване на структурните характеристики на лигандите (метокси-заместени в различни позиции ароилхидразони) и Ga (III) комплекси бяха направени изчисления с използване на Теория на функционала на плътността, B3LYP функционал и базисен набор 6-31+G (d,p). Предсказаното координиране метал-лиганд беше потвърдено от спектралните данни. Комплексите са моноядрени, като Ga (III) йоните са свързани с два тридентатни лиганда. Доказаната координация е чрез кислороден атом от депротонираната алдехидна хидроксилна група, азотен атом от азометинова група и кислороден атом от amidна група. На базата на експерименталните данни за комплексите беше предложена обща формула [Ga(L-H)₂]NO₃.