Bulgarian Chemical Communications, Volume 50, Special Issue C, (pp. 207 – 212) 2018

Radical scavenging activity toward 2,2-diphenyl-1-picrylhydrazyl and hydroxyl radicals of 5-aminoorotic acid and its Ga(III) complex

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Received September 28, 2017, Accepted October 31, 2017

Along with anti-tumor activity, flexible control over oxidative stress (OS) levels is a desirable quality of any anticancer drug. Radicals scavenging activity (RSA) toward 2,2-diphenyl-1-picrylhydrazyl radical (DPPH$^{\bullet}$) is widely used to evaluate the ability to eliminate free radicals by donating hydrogen. 5-aminoorotic acid (HAOA) is known to have antioxidant properties and has been used as a ligand in lanthanide(III) complexes possessing anticancer activity in cell cultures. Ga(III) salts are known for their anticancer activity. Thus, the Ga(III) complex with HAOA, GaAOA, might be a promising anticancer agent with antioxidant properties that have not been explored so far. In the present work, the UV spectra and RSA of HAOA and GaAOA toward DPPH$^{\bullet}$ and OH$^{\bullet}$ were evaluated and discussed. The stereochemistry of HAOA and its Ga(III) complex was evaluated, and compared by means of IR, Raman IR and Raman spectral data. Two factors affected the UV spectra of the molecules: their arrangement (steric properties) and their interaction with the solvent. As far as the RSA was determined in absolute ethanol (for DPPH$^{\bullet}$) and in water (for OH$^{\bullet}$), the UV spectra of the molecules in water and ethanol were compared and discussed. The hypochromicity in the UV spectra of GaAOA, compared to the expected intensities, indicated an arrangement of the ligands that diminished the dipole moment. The RSA of HAOA and GaAOA towards both radicals was concentration-dependent. GaAOA, at the lowest concentration in ethanol, exhibits signs of dissociation, manifested in an anomalous RSA increase. That demonstrates the potential of GaAOA for a controlled release of the antioxidant ligands.

Keywords: Ga(III) complex with 5-aminoorotic acid, Antioxidant activity, DPPH radical, OH radical, 5-Aminoorotic acid.

INTRODUCTION

The role of the reactive oxygen species (ROS) and oxidative stress (OS) in carcinogenesis [1-3] and cancer therapy [4,5] is very complex and intensively investigated. OS is involved in carcinogenesis *via* several pathways, but it is also able to kill malignant cells by altering their redox homeostasis. Disturbance of the redox homeostasis of the cancerous cells by using metal complexes is a promising approach in cancer therapy [5]. Metallodrugs based on Ga(III) are intensively investigated as promising anticancer agents [6,7], due to strong analogy between Ga(III) and Fe(III) in terms of ionic radius, electron affinity, electronegativity, coordination geometry, and Lewis base affinity. Ga(III) does not change its valent state in physiological conditions, unlike Fe(III). As the malignant cells have a greater requirement for iron than normal cells do [8], strategies to disrupt the iron-dependent metabolic pathways in malignant cells by introduction of Ga(III) are promising in cancer treatment. Lanthanide(III) complexes of 5-aminoorotic acid (HAOA) showed both antioxidant and anticancer activities [9-11]. Thus, the Ga(III) complex with HAOA might be a promising anticancer agent with antioxidant properties, that have not been explored so far. The hydroxyl radical, OH$^{\bullet}$, is the most reactive among ROS. It is formed as a result of interaction between H_2O_2 and free metal ions with variable valent states *via* the Fenton reaction [12]. The OH$^{\bullet}$ radical is easily recombined by molecules capable of donating hydrogen. The ability of GaAOA to donate hydrogen and react with OH$^{\bullet}$ has not been explored so far. The hydrogen-donor's total antioxidant capacity is often estimated by monitoring the radicals scavenging activity (RSA) toward the stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH$^{\bullet}$) [13-15], while the interaction with hydroxyl radicals may be estimated in the presence of various OH$^{\bullet}$ generating model systems [16-22].

In the present work, the ability to donate hydrogen and the interaction with hydroxyl radicals of HAOA and GaAOA were estimated by measuring the Radical Scavenging Activities toward DPPH$^{\bullet}$ and OH$^{\bullet}$. The solvent effects of H_2O and C_2H_5OH on the investigated molecules were observed by recording the UV spectra of the solutions in both media. The interactions of HAOA and GaAOA with solvent molecules were visualized by steric energy minimization in

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presence of one molecule of solvent per ligand, using MM2 subroutine of a ChemOffice program package.

EXPERIMENTAL PART

The compounds used for preparing the solutions in this investigation were of finest purity (Sigma-Aldrich products), including $Ga(NO_3)_3$ and 5-aminoorotic acid. The latter was used as a ligand for the preparation of the metal complex.

The carbon, hydrogen and nitrogen contents of the compound were determined by elemental analysis.

The solid-state infrared spectra of the ligand and its Ga(III) complex were recorded in KBr in the 4000-400 cm^{-1} frequency range by FT-IR 113V Bruker spectrometer.

The Raman spectra of HAOA and its new Ga(III) complex were recorded with a Dilor microspectrometer (Horiba-Jobin-Yvon, model LabRam) equipped with a 1800 grooves/mm holographic grating. The 514.5 nm line of an argon ion laser (Spectra Physics, model 2016) was used for the probes excitation. The spectra were collected in a backscattering geometry with a confocal Raman microscope equipped with an Olympus LMPlanFL 50× objective and with a resolution of 2 cm^{-1}. The detection of Raman signal was carried out with a Peltier-cooled CCD camera. Laser power of 100 mW was used in our measurements.

Bi-distilled water and 96% ethanol were used as solvents and reaction media. Standard 10^{-3} M aqueous and ethanol solutions of both HAOA and GaAOA were prepared, and for the purpose of the experiment were further diluted to concentrations of 10^{-4} M, 10^{-5} M, 10^{-6} M and 10^{-7} M. Aqueous solutions, one of them containing 3 mM $FeCl_2$, 3 mM H_2O_2, and 0.3 mM EDTA, and another containing 4 mg/ml ascorbate, were prepared prior to the experiment and kept in ice bath. Standard 0.05 M $DPPH^{\bullet}$ solution was prepared in pure ethanol, covered with aluminum foil and kept at -25°C in a freezer. Before each experiment, this solution was diluted with 96% ethanol to give absorption between 0.7 and 0.9 a.u. at 517 nm.

All spectrophotometric measurements were performed using Shimadzu 1600 UV-VIS spectrophotometer (quartz cuvette) equipped with software, connected to a PC.

Assay for RSA toward $DPPH^{\bullet}$: The relative decrease in intensity of the signal at 517 nm (characteristic band for $DPPH^{\bullet}$) was monitored for 30 min, using the kinetics software of the apparatus. The absorption at 517 nm was recorded every 5 min. RSA (%) was determined using the formula:

$$RSA = \frac{A_{blank} - (A_{sam.} - A_{contr.})}{A_{blank}} * 100,$$

A_{blank} being the absorbance due to the presence of the sample's solvent in $DPPH^{\bullet}$ solution (2 ml $DPPH^{\bullet}$ solution and 0.02 ml sample's solvent), $A_{contr.}$ is the absorbance due to the sample alone (0.02 ml sample solution in 2 ml ethanol), and $A_{sam.}$ is the absorbance due to interaction of the sample with $DPPH^{\bullet}$ (2 ml $DPPH^{\bullet}$ solution and 0.02 ml sample solution). Data are presented as RSA (%) *vs* time. For further simplification, "RSA($DPPH^{\bullet}$)" will be used instead of "RSA toward $DPPH^{\bullet}$".

RSA toward Fe(II)-induced $OH^{\bullet}$ assay: $OH^{\bullet}$ was produced by the model system Fe(II)/H_2O_2/EDTA/ascorbate, in aqueous medium. MTT transformation into formazan was used as marker for the free radicals accumulation in the solution. The relative increase of the intensity at 578 nm (characteristic for the MTT formazan) was monitored each minute, for 10 minutes. RSA was evaluated using the formula:

$$RSA = \frac{\Delta A_{blank} - (\Delta A_{sam.} - \Delta A_{contr.})}{\Delta A_{blank}} * 100,$$

ΔA being the relative change of the absorbance at 578 nm for 10 min. ΔA_{blank} corresponded to ΔA in the presence of the $OH^{\bullet}$ - producing model system alone (0.05 ml Fe(II)/H_2O_2/EDTA, 0.05 ml ascorbate, 0.2 ml MTT, and H_2O to 2 ml), ΔA_{contr} describes the relative change of A(578 nm) in the presence of the sample solution and MTT (0.2 ml MTT, 0.2 ml sample solution and H_2O to 2.0 ml), and $\Delta A_{sam.}$ is the relative change of the 578 signal due to interaction between the free radicals in the model system and the sample solution (0.05 ml Fe(II)/H_2O_2/EDTA, 0.05 ml ascorbate, 0.2 ml sample solution, 0.2 ml MTT, and H_2O to 2.00 ml). For simplification in the text "RSA($OH^{\bullet}$)" will be used instead of "RSA toward $OH^{\bullet}$".

UV-spectral analysis: The UV-spectra were recorded within 400-200 nm, at very slow speed (λ_{step}= 0.5 nm) after base correction for the spectrum of the solvent in the cuvette. The instrumental errors were evaluated by scanning the spectrum of the solvent, with solvent base correction. The experimental error limits in position and absorbance of λ in the UV spectra were estimated by recording each spectrum for three times. These were found to be within ± 1 nm for λ position and ±0.001 a.u. for absorption.

Data management and presentation: For each concentration of each compound, RSA were

calculated based on 5 parallel measurements. Average values and standard deviations were calculated. Relative changes within the experimental error limits were not discussed. The concentration effects on RSA of the solutions of HAOA and GaAOA were statistically verified using One-way ANOVA, followed by Bonferoni post-test. The Bartlett test verified that all standard deviations belong to the same population. Differences due to the chemical composition at same concentration of solutions were statistically verified using non-parametric *t*-test with Welch correction.

ChemOffice program package v. 3.01 was used to build molecule models of the compounds investigated, as well as to illustrate their interactions with solvent molecules. The solvent effect on the molecular geometry was illustrated by presenting interaction of one solvent molecule per one HAOA or AOA ligand.

RESULTS

The complex was synthesized by reaction of Ga(III) salt and the ligand, in amounts equal to metal: ligand molar ratio of 1:3. The synthesis was made in different ratios (1:1, 1:2, 1:3) but in all the cases the final product was with the composition 1:3. The complex was prepared by adding an aqueous solution of Ga(III) to an aqueous solution of the ligand subsequently raising the pH of the mixture gradually to ca. 5.0 by adding dilute solution of sodium hydroxide. The reaction mixture was stirred with an electromagnetic stirrer at 25 °C for one hour. At the moment of mixing of the solutions, precipitate was obtained. The precipitate was filtered (pH of the filtrate was 5.0), washed several times with water and dried in a desiccator to constant weight. The obtained complex was insoluble in water, methanol and ethanol, but well soluble in DMSO.

Reaction of Ga(III) and 5-aminoorotic acid afforded a complex which was found to be quite stable both in solid state and in solution. The new Ga(III) complex was characterized by elemental analysis. The content of the metal ion was determined after mineralization. The used spectral analyses confirmed the nature of the complex.

The data of the elemental analysis of the Ga(III) complex serve as a basis for the determination of its empirical formula and the results are presented below. The elemental content of the Ga(III) complex of HAOA ($Ga(AOA)_3.H_2O$) is shown as % calculated/found: C= 30.10/30.04; H= 2,.34/2.55; N= 21.07/21.16; H_2O= 3.01/3.28; Ga= 11.66/11.19, where HAOA= $C_5N_3O_4H_5$ and AOA= $C_5N_3O_4H_4^-$.

In our previous work the geometry of 5-aminoorotic acid was computed and optimized with the Gaussian 03 program employing the B3PW91 and B3LYP methods with the 6-311++G** and LANL2DZ basis sets [23]. In the present study the binding mode of the HAOA ligand to Ga(III) ions was elucidated by recording the IR and Raman spectra.

The stability of HAOA and GaAOA, dissolved in water and ethanol, was evaluated by recording the spectra of their solutions. HAOA was stable in both solvents. All aqueous solutions, and ethanol solutions of GaAOA above 10^{-6} M, were stable too. UV spectra were resolved according to data in existing literature [24-28]. Characteristic bands for 5-aminoorotic acid (individual, and as a ligand) are seen in all the spectra, as illustrated in Fig. 1 for the 10^{-4} M concentrations.

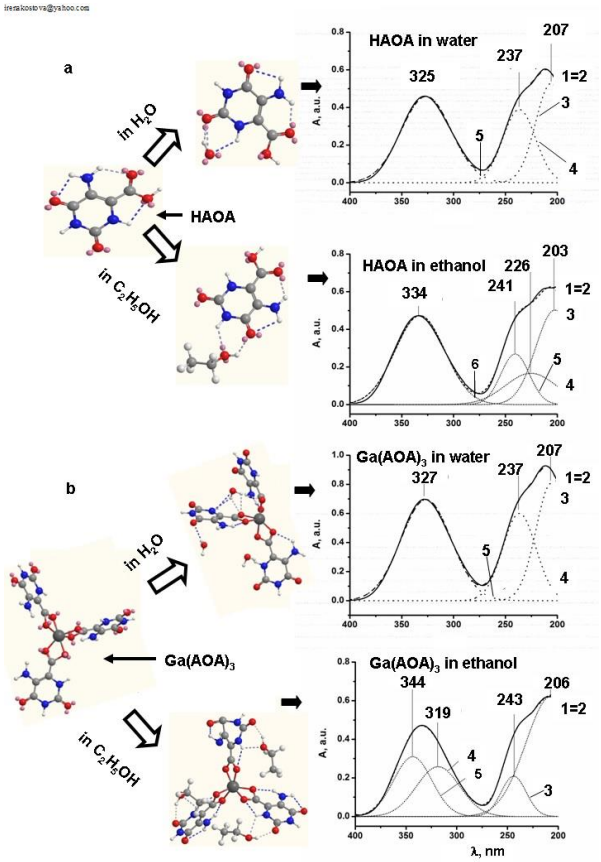

Figure 1. Solvent effects of water and ethanol on the geometry and UV-spectra of HAOA (a) and GaAOA (b).

In the UV spectrum of 10^{-6} M GaAOA in ethanol some bands indicating ionization (Fig. 2) were observed.

After subtraction of the HAOA spectrum (Fig. 2, spectrum 1) from this of GaAOA (Fig. 2, spectrum 2), a new component appeared (spectrum 3), with a sharp, intensive maximum at about 206 nm, and broad, low-intensive band at 376 nm. In agreement with literature, these new bands may be associated

with the appearance of ionized AOA^- in the solution.

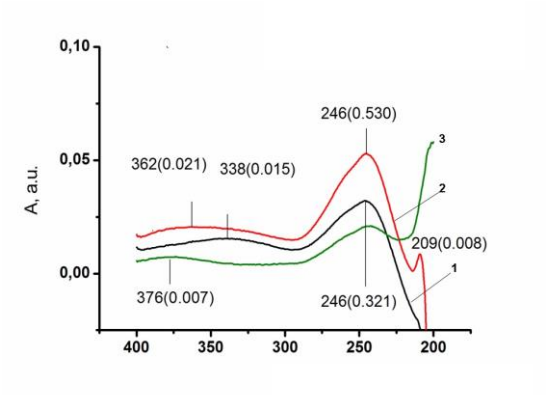

Figure 2. UV spectra of 10^{-6} M ethanol solutions of HAOA (1), GaAOA (2) and the result of the subtraction (3) of (1) from (2), in the interval of 400-200 nm.

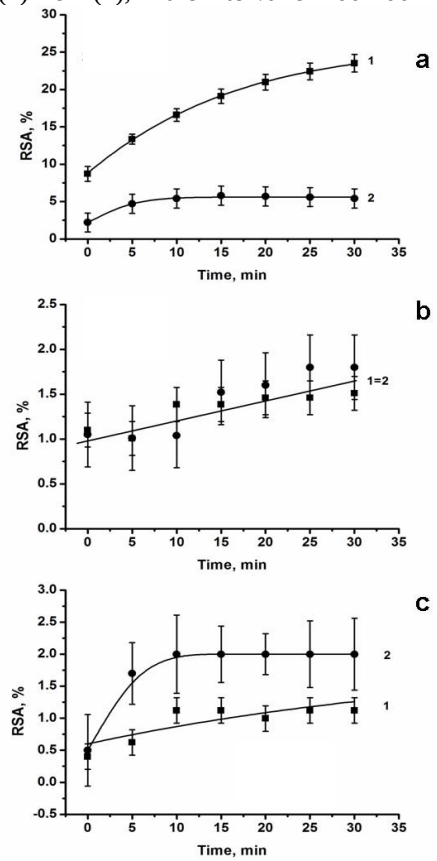

Figure 3. Radicals scavenging activity of 10^{-4} M (a), 10^{-5} M (b), and 10^{-6} M (c) solutions of HAOA (1) and GaAOA (2).

The RSA($DPPH^•$) of HAOA (1) and GaAOA (2) at different concentrations are seen in Fig. 3. The 10^{-7} M solutions of HAOA and GaAOA did not show any significant RSA($DPPH^•$). In Fig. 3 a-c it is seen that the RSA($DPPH^•$) of HAOA decreased in the order: 10^{-4} M>10^{-5} M (p<0.001)=10^{-6} M (p>0.05). RSA($DPPH^•$) in the presence of GaAOA decreased in the order: 10^{-4} M>10^{-6} M (p<0.001)>10^{-5} M (p<0.05). The RSA($DPPH^•$) of 10^{-4} M HAOA was much higher than this of GaAOA of the same concentration (Fig. 3a). The 10^{-5} M solutions of both HAOA and GaAOA exhibited the same RSA($DPPH^•$) (p>0.05, Fig. 3b), while this of the 10^{-6} M solution of GaAOA was slightly, but noticeably higher than this of 10^{-6} M HAOA (Fig. 3c).

The RSA($OH^•$) of HAOA and GaAOA are presented in Fig. 4b and compared with RSA($DPPH^•$) for the same time period (Fig. 4a). RSA toward both radicals of HAOA was higher than this of its Ga(III) complex. RSA($DPPH^•$) was significantly lower than RSA($OH^•$) for each compound at any given concentration (in all comparisons p was less than 0.01).

DISCUSSION

The UV spectra of HAOA and GaAOA showed that in aqueous medium both compounds were stable. The Gauss deconvolution of the spectra revealed components typical for the 5-aminoorotic acid, similarly to UV spectra of HAOA complexes with lanthanide ions [26-28]. The band at 330-340 nm was assigned to $\pi \rightarrow \pi^*$ transitions in the ring structure of 5-aminoorotic acid. The band at about 230-240 nm may be associated with $\pi \rightarrow \pi^*$ transitions of the triple-conjugated double bond system in AOA and $–NH_2$. The 207 nm band was related to possible E2-type ($\pi \rightarrow \pi^*$) band of the C=O and C=C in the molecule. The band around 201 nm might be a $\pi \rightarrow \pi^*$ transition of isolated C(OH)=O groups. In general, the solvent effects of H_2O and C_2H_5OH on the UV spectra of both molecules were consistent with the higher polarity of water compared to ethanol, and specificities in location and hydrogen bonding of the solvent toward solute. This is illustrated on the simple molecular models shown in Fig. 1. In Fig. 1a it is seen that the attachment of C_2H_5OH to HAOA affected mainly the $\pi \rightarrow \pi^*$ transitions of the triple-conjugated double bond system in AOA and $–NH_2$, the band related to possible E2-type ($\pi \rightarrow \pi^*$) band of the C=O and C=C in the molecule, and the $\pi \rightarrow \pi^*$ transition of isolated C(OH)=O groups. The UV spectra of aqueous and ethanol solutions of GaAOA (Fig. 1b) were much less intensive than expected for a compound containing three AOA ligands. This might be related with solvents' effect on the ligands orientation in the complex, as illustrated by the molecule models. The specific geometry of one AOA^- ligand in the ethanol solution of $Ga(AOA)_3.H_2O$ might be the reason for the appearance of two components in the characteristic band for the $\pi \rightarrow \pi^*$ ring transitions in the UV

spectrum. The appearance of new components in the spectrum of 10^{-6} M ethanol solution of GaAOA (Fig. 2) might be related with some dissociation of GaAOA in this medium. If true, this will result in higher RSA(DPPH$^{\bullet}$) of the 10^{-6} M GaAOA ethanol solution than this of 10^{-6} M HAOA. (Fig. 3c).

In presence of 10^{-4} M solutions, in which the intact Ga(III) complex dominated (Fig. 1b - spectrum in ethanol) RSA(DPPH$^{\bullet}$) decreased in the order HAOA>GaAOA (p<0.0001) (Fig. 3a). The smaller size and less complicated geometry of HAOA in comparison with these of GaAOA suggested an increased probability for the formation of the transition state needed for the hydrogen transfer to DPPH$^{\bullet}$. In the presence of 10^{-5} M solutions (Fig. 3b) HAOA and GaAOA exhibited the same (p>0.05) radical scavenging activity, while in the presence of 10^{-6} M solutions (Fig. 3c) the latter decreased in the order GaAOA>HAOA (p<0.01). Data in Figs. 2 and 3b indicated that a small amount of the Ga(III) complex might dissociate in ethanol, thus leading to higher RSA(DPPH$^{\bullet}$) than expected at a concentration of 10^{-6} M. Based on data in Figs. 1b, 2 and 3 it was proposed that the simpler the geometry and the higher the stability of the compound in ethanol environment, the higher RSA(DPPH$^{\bullet}$) would be. Comparisons between radicals scavenging activities of HAOA and GaAOA (Fig. 4) indicated that in presence of a given free radical and environment, the geometry and the size of the radical scavenger may influence the radical scavenging effectiveness. Data about RSA of HAOA in Fig. 4a,b suggested that the size and the geometry of the free radical, as well as the solvent effect on the scavenger also may play a role regarding the effectiveness.

The anticancer activity of Ga(III) [8], in combination with the antioxidant activity of the AOA ligands, as well as the weak instability of the GaAOA complex in ethanol environment suggest that the Ga(III) complex with 5-aminoorotic acid might be a promising anticancer agent.

CONCLUSIONS

1. The complex of Ga(III) with 5-aminoorotic acid has been synthesized and characterized by elemental, UV-VIS and vibrational spectral analyses, including IR and Raman spectra.

2. The 5-aminoorotic acid alone and as a ligand in the complex with Ga(III) exhibited hydrogen donor activity toward DPPH$^{\bullet}$ and OH$^{\bullet}$.

3. The better radicals scavenging activity of HAOA than this of GaAOA at concentrations above 10^{-5} M toward DPPH$^{\bullet}$ might be related with the smaller size and simpler geometry of the individual compound than those of the complex. Below this concentration, the effect of the complex was stronger than this of the individual compound, probably due to some dissociation in ethanol environment.

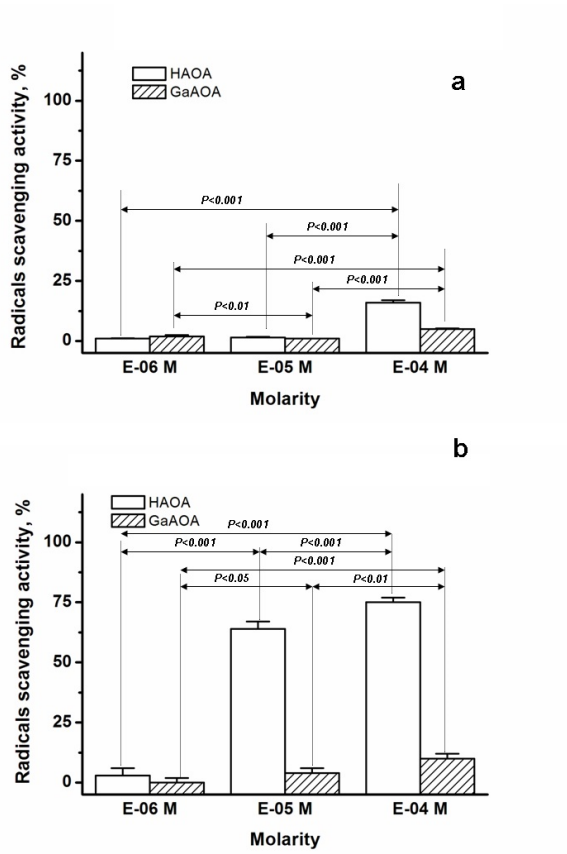

Figure 4. Radicals scavenging activity (RSA, %) of HAOA and GaAOA toward DPPH$^{\bullet}$ and OH$^{\bullet}$ radicals; reaction time – 10 min.

4. The better radicals scavenging activity of each compound toward OH$^{\bullet}$ than this toward DPPH$^{\bullet}$ might result from the smaller size, higher chemical reactivity and much simpler geometry of the hydroxyl radical than these of the stable and large DPPH$^{\bullet}$.

5. The combination of anticancer activity of Ga(III) and antioxidant activity of 5-aminoorotic acid, along with the instability of the complex depending on the environment suggest that GaAOA might be a promising anticancer agent.

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РАДИКАЛОПРИХВАЩАЩ ЕФЕКТ НА 5-АМИНООРОТОВА КИСЕЛИНА И НЕЙНИЯ Ga(III) КОМПЛЕКС СПРЯМО 2,2-ДИФЕНИЛ-1-ПИКРИЛХИДРАЗИЛОВ И ХИДРОКСИЛЕН РАДИКАЛ

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Постъпила на 28 септември, 2017 г. ; приета на 31 октомври, 2017 г.

(Резюме)

Освен противотуморна активност, гъвкав контрол върху нивата на оксидативен стрес е желано качество на всяко противораково лекарство. Радикалоприхващащият ефект (RSA) спрямо 2,2-дифенил-1-пикрилхидразилов радикал (DPPH$^{\bullet}$) е широко използван за преценка на способността да се елиминират свободни радикали чрез отдаване на водород. 5-аминооротовата киселина (AOA) притежава антиоксидантни свойства и е използвана като лиганд в лантанидни(III) комплекси, които проявяват противоракови свойства в клетъчни култури. Солите на Ga(III) са известни със своята противоракова активност. По тази причина комплексът на Ga(III) с AOA (GaAOA) може да бъде обещаващо противораково съединение с антиоксидантни свойства, които не са проучвани до този момент. В настоящата работа са изследвани и анализирани УВ спектрите и RSA на HAOA и GaAOA спрямо DPPH$^{\bullet}$ и хидроксилен радикал (OH$^{\bullet}$). Стереохимията на HAOA и нейния Ga(III) комплекс са изследвани и сравнени с ИЧ, Раманови ИЧ и Раманови спектрални данни. Два фактора влияят върху УВ спектрите на молекулите: тяхното подреждане (стерични свойства) и тяхното взаимодействие с разтворителя. Тъй като RSA е определен в абсолютен алкохол (DPPH$^{\bullet}$) и вода (OH$^{\bullet}$), УВ спектрите на съединенията във вода и етанол са изследвани и анализирани. Хипохромното отместване на УВ спектрите на GaAOA, в сравнение с очакваните интензитети, свидетелства за подреждане на лигандите, намаляващо диполния момент. RSA на HAOA и GaAOA спрямо двата радикала е концентрационно-зависимо. GaAOA в най-ниската концентрация в етанол дава признаци за дисоциация, изразени чрез аномално нарастване на RSA Това показва потенциала на GaAOA за контролирано освобождаване на антиоксидантни лиганди.