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Geometry, tautomerism and non-covalent interactions of the drug halofuginone with carbon-nanotubes and γ-Fe_2O_3 nanoparticles: A DFT study

SHIMA KAZERI-SHANDIZ, S. ALI BEYRAMABADI* and ALI MORSALI

Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

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Abstract: Halofuginone is a potential anti-malarial drug, which could exist as three possible tautomers. Herein, using density functional theory (DFT), and handling the solvent effects with the PCM model, the tautomerism of halofuginone was investigated. Intramolecular H-bonds play an important role in the stability of the tautomers. The conformer **H1a** is the most stable. Non-covalent interactions of the **H1a** conformer with the armchair (5,5) single-wall carbon nanotubes and γ-Fe_2O_3 nanoparticles were explored in several manners. The most stable form of them was determined. The intermolecular H-bonds play a substantial role in the energy behavior of the interaction between γ-Fe_2O_3 nanoparticles and halofuginone.

Keywords: halofuginone; DFT; PCM; tautomerism; γ-Fe_2O_3 nanoparticles; carbon nanotubes.

INTRODUCTION

In the 1960s, a number of analogues of febrifugine, such as halofuginone, were synthesized in the USA.[1–4] Halofuginone is a synthetic derivative of quinazolinone alkaloid febrifugine. Febrifugine has been used to treat fever and malaria for more than 2000 years. In 1967, the drug halofuginone was designed and synthesized by the American Cyanamid Company. Its commercial name is stenorol.[5,6]

Halofuginone is used as an anti-coccidial feed additive,[7,8] and was specifically shown to be an effective drug in malaria, cancer, fibrosis and inflammatory diseases.[9–11]

Nowadays, DFT methods are comprehensively used in many areas of computational chemistry, such as geometry optimization, spectroscopic assignments, drug science, investigations on the kinetics and mechanism of the chemical reactions, *etc*.[12–23] To date, the geometry and crystal structure of halofuginone

* Corresponding author. E-mail: beiramabadi@yahoo.com, beiramabadi6285@mshdiau.ac.ir
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have not been determined and therefore, a comprehensive computational investigation on the properties of halofuginone is of major importance. In this work, the molecular geometry and tautomers of halofuginone were investigated using valuable DFT approaches.

Because of the increasing use of nanotechnology in many areas especially in the drug delivery, exploring the interaction of nanoparticles with different molecules is of great importance. The covalent and non-covalent interactions of various molecules with the carbon nanotubes and iron-oxide nanoparticles have been theoretically investigated.[24–32] Herein, the non-covalent interactions of halofuginone with the carbon nanotubes and γ-Fe_2O_3 nanoparticles were theoretically explored using DFT methods.

THEORETICAL METHODS

In this work, all calculations were performed using the Gaussian 03 software package[33] and the B3LYP[34] functional of the density functional theory (DFT). The 6-311+G(d,p) basis set was used for an investigation of geometry optimization and tautomerism of the halofuginone molecule. Its interaction with the iron-oxide nanoparticles was investigated by employing the B3LYP and 6-31G(d) basis sets for all of the atoms except for the Fe atoms, where the LANL2DZ basis sets was used with effective core potential (ECP) functions. On the other hand, the interaction of halofuginone with a carbon-nanotube was investigated at the B3LYP/ /6-31G(d) level. The armchair (5,5) single wall carbon nanotube (SWCNT), comprising 150 atoms (16.6 Å length), was used.

The solvent effects in aqueous solution were considered using the sophisticated Polarized Continuum Model (PCM).[35] All of the geometries were fully optimized. The optimized geometries were confirmed to have no imaginary frequency, except for the transition state (TS), which has only one imaginary frequency of the Hessian. Zero-point corrections were considered in the evaluation of the energies. The Chemcraft 1.7 program was used for preparation of the figures.[36]

RESULTS AND DISCUSSION

Molecular geometry

A molecule of the halofuginone drug could exist as three possible tautomers, the geometries of which were fully optimized in aqueous solution. The **H1** tautomer of halofuginone has two different conformers, **H1a** and **H1b** (Fig. 1). In the optimized geometry of **H1a**, there is an intramolecular hydrogen bond between the O2 and H7 atoms. Since, the **H1a** conformer is more stable than the **H1b** one.

Going from the **H1a** conformer to the **H2** tautomer, the **H7** proton transfers from C11 atom to the O2 atom of the carbonyl group *via* an intermolecular proton transfer (IPT). Therefore, the C10–O2 bond length increases from 121.3 to 134.2 pm, while the C10–C11 bond length reduces from 149.7 to 134.3 pm in the **H2** conformer. Additionally, the hybridization of the C11 atom changes from sp^3 in the **H1a** tautomer to sp^2 in the **H2** tautomer. The C10–C11–C12 and

C10–C11–H6 angles are 118.8 and 107.7° for the **H1a** conformer, which are 125.5 and 117.9° in the **H2** tautomer, respectively.

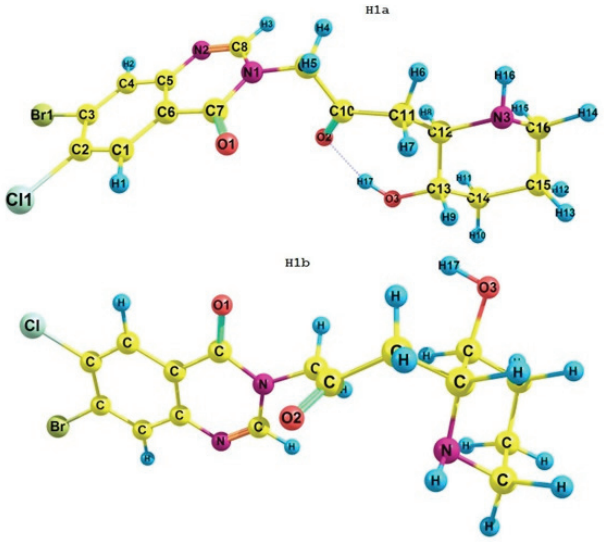

Fig. 1. Optimized geometries for the **H1a** and **H1b** conformers of the **H1a** tautomer of halofuginone.

In comparison with the **H1a** conformer, in the **H3** tautomer, the H5 proton transfers from the C9 atom to the O2 atom of the carbonyl group *via* an IPT. Since the C10–O2 bond length enlarges from 121.3 to 152.4 pm, the C9–C10 bond length decreases from 135.3 to 133.9 pm in the **H3** tautomer. The C9–C10––C11 and C10–C11–H5 angles are 114.8 and 52.1° for the **H1a** conformer, which are 120.5 and 22.7° in the **H3** tautomer, respectively. These angles confirm that the hybridization of the C9 atom changes from sp^3 in the **H1a** conformer to sp^2 for the **H3** tautomer.

In this work, the tautomerism of the halofuginone drug was investigated using valuable computational methods, which are useful in theoretical investigation of chemical reactions.[12–19,24–32,37–39] The relative energies of the optimized species are gathered in Table I. As could be seen, the **H1a** species is the most stable tautomer of halofuginone in aqueous solution.

There are three different tautomerization reactions for the three tautomers of halofuginone. The transition states of the **H1a** → **H2**, **H1a** → **H3** and **H2** → **H3** tautomerization reactions are named as **TSH1a-H2**, **TSH1a-H3** and **TSH2-H3**, respectively. In aqueous solution, the Gibbs energy change (ΔG) difference between the most stable conformer **H1a** with the **H2** and **H3** tautomers are 42.15 and 48.11 kJ mol^{-1}, respectively. Using the equation $K = \exp(-\Delta G / RT)$, the amounts of the **H2** and **H3** tautomers were predicted to be negligible in aqueous

solutions of halofuginone. The high barrier energies and large ΔG values demonstrate that conformer **H1a** is the kinetically and thermodynamically the most probable tautomer of halofuginone in aqueous solution.

TABLE I. The relative energies (kJ mol^{-1}) and the relative Gibbs energy change (kJ mol^{-1}) for the tautomerization reaction of halofuginone in the PCM model

Species	Relative energy	Relative Gibbs energy change
H1a	0.0	0.0
H1b	12.26	19.53
H2	37.04	42.15
H3	42.25	48.11
TSH1a-H2	282.04	–
TSH1a-H3	257.72	–
TS H2-H3	330.61	–

Non-covalent interactions of the halofuginone with the nanoparticles

Nowadays, nano-compounds are useful in many areas especially in drug delivery.[24–32,40–43] Herein, the non-covalent interaction of the **H1a** conformer of halofuginone with a carbon-nanotube and a magnetic γ-Fe_2O_3 nanoparticles have been investigated using the DFT methods.

The armchair (5,5) single wall carbon nanotube (SWCNT) was used as a model for a carbon-nanotube. The optimized geometry of the SWCNT is shown in Fig. 2. The **H1a** conformer could interact with the SWCNT in different manners. Herein, two possible interactions between **H1a** and the SWCNT were investigated. These interactions, named as **NANO-CNT1** and **NANO-CNT2**, optimized geometries, are shown in Fig. 3.

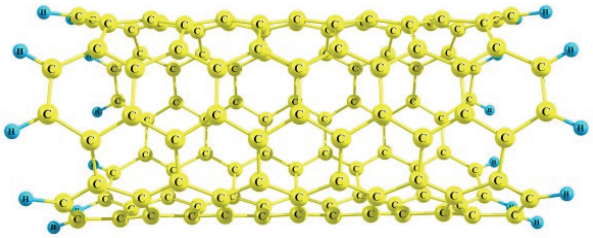

Fig. 2. Optimized geometry for the investigated SWCNT.

In the optimized geometry of the **NANO-CNT1** form, the aromatic rings of **H1a** are parallel with respect to the SWCNT. The minimum distance between the **H1a** species and the SWCNT is about 400 pm. In the optimized geometry of the **NANO-CNT2** form, the **H1a** is like a cap on the SWCNT. The Br and Cl substitutions are closer to the SWCNT than in the **NANO-CNT1** form. The nearest atoms of the halofuginone molecule to the carbon atoms of the SWCNT are shown in Fig. 3.

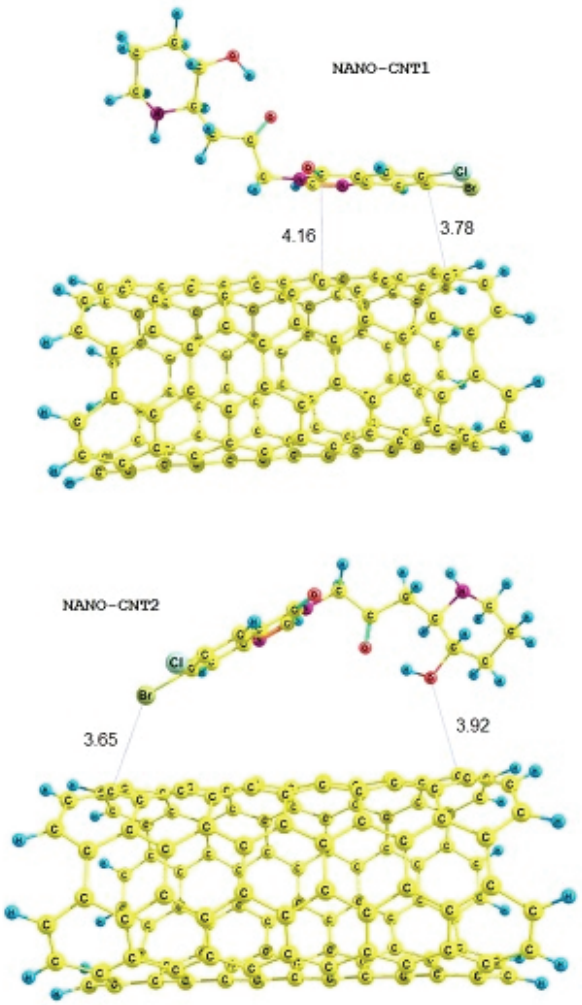

Fig. 3. Optimized geometries of two possible non-covalent interactions between the **H1a** conformer and a SWCNT.

The computed electronic energies for the investigated species together with the binding energies are gathered in Table II. The binding energy could be defined as:

$$\Delta E = E_{(\text{NANO-CNT*})} - (E_{(\text{H1a})} + E_{(\text{SWCNT})})$$

where $E_{(\text{NANO-CNT*})}$, $E_{(\text{H1a})}$ and $E_{(\text{SWCNT})}$ are the electronic energies of the investigated species, either NANO-CNT1 or NANO-CNT2 forms, the **H1a** conformer and free SWCNT, respectively.

As could be seen, the **NANO-CNT2** form involves more binding energy than the NANO-CNT1 form by 1.53 kJ mol^{-1}. Thus, **NANO-CNT1** is the more stable and favorable form for non-covalent interaction of halofuginone with SWCNT.

TABLE II. The electronic and binding energies of the optimized geometries for the non-covalent interactions of the **H1a** conformer with the SWCNT in aqueous solution

Species	Electronic energy, Hartree	Binding energy, kJ mol^{-1}
SWCNT	–4966.2215459	–
H1a conformer	–4041.828239	–
SWCNT+ **H1a** conformer	–9008.083114[a]	–
NANO-CNT1	–9008.0843194	–3.16
NANO-CNT2	–9008.0849021	–4.69

[a]Sum of electronic energies of the free SWCNT and the **H1a** conformer

In addition, non-covalent interaction between nano-magnetic γ-Fe_2O_3 particles and the **H1a** conformer of halofuginone was investigated theoretically. Previously, a model was presented for γ-Fe_2O_3 nanoparticles based on a $Fe_6(OH)_{18}(H_2O)_6$ ring cluster. This model has good consistency with the experimental data, such as the vibration frequencies and bond lengths.[29,31,32] This model was employed in this research. The geometry of the used model for γ-Fe_2O_3, shown in Fig. 4, was fully optimized.

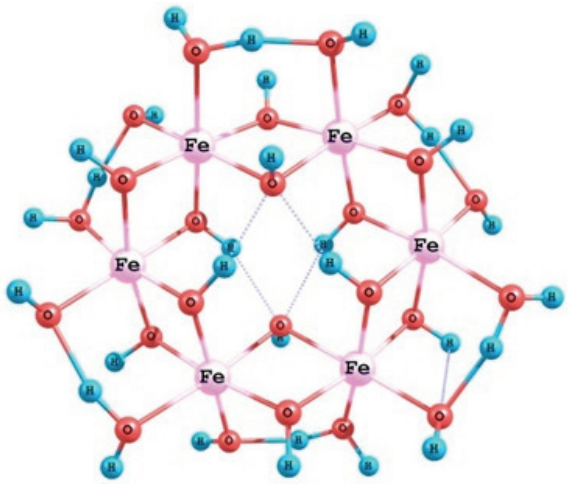

Fig. 4. Optimized geometry of the γ-Fe_2O_3 nano-particle.

For the investigation of the non-covalent interactions of the **H1a** conformer with the γ-Fe_2O_3, the proposed geometry of this tautomer in the presence of the γ-Fe_2O_3 was optimized in three different forms. These forms are named **NANO--Fe1** to **NANO-Fe3** and their optimized geometries are shown in Fig. 5. In the

NANO-Fe1 form, the **H1a** conformer is close to the SWCNT *via* the carbonyl and hydroxyl group. Three intermolecular hydrogen bonds are seen in Fig. 5. Two of them are between the oxygen atom of the drug and the hydrogen atoms of the H_2O and the –OH ligands of the nano-particle. The lengths of these H-bonds are 176.9 and 214.2 pm. The remaining one is between the hydrogen atom of the hydroxyl group and oxygen atom of the –OH ligand in the nano-particle, which is a strong H-bond (174.1 pm).

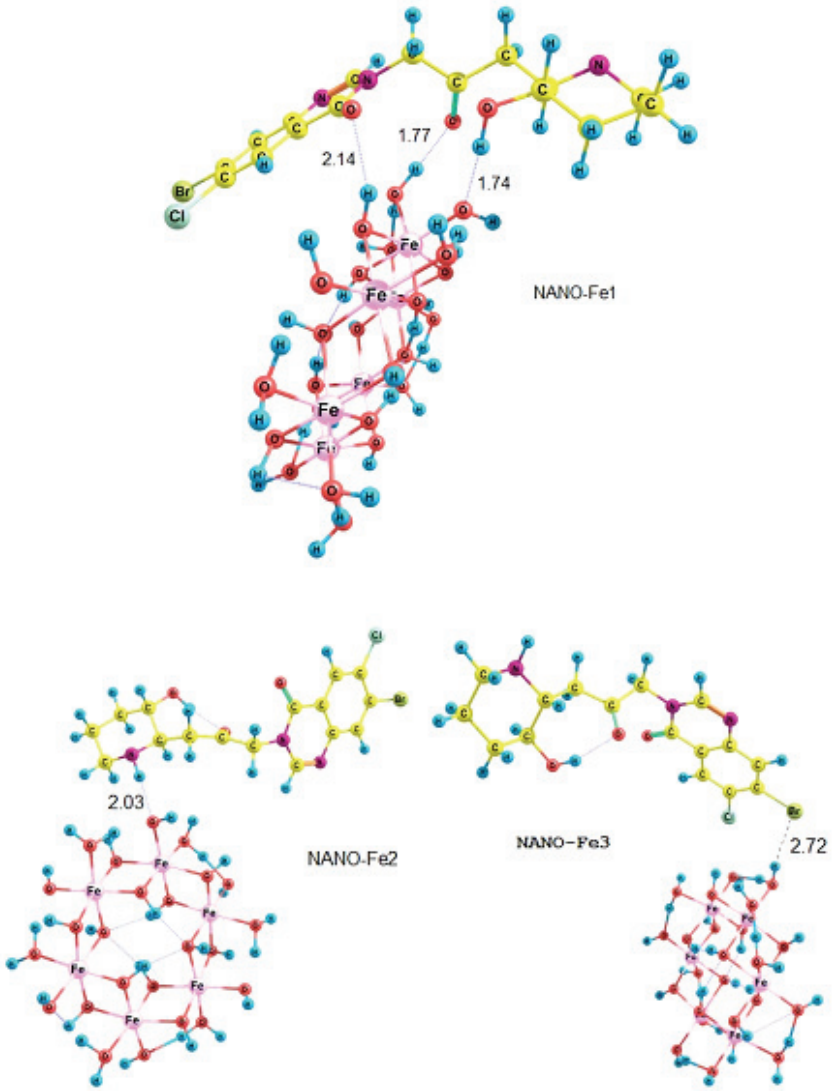

Fig. 5. Optimized geometries of three possible non-covalent interactions between the **H1a** species and the γ-Fe_2O_3 nano-particle.

In the **NANO-Fe2** form, contrary to the **NANO-Fe1** form, the aromatic rings are far from the SWCNT. There is only a weak hydrogen bond between H37 of the –NH group in **H1a** and oxygen atom of the –OH ligand of the γ-Fe_2O_3 nano--particle. The bond length of this hydrogen bond is 203.4 pm. In the **NANO-Fe3** form, the **H1a** molecule is close to the SWCNT *via* the Cl and Br substitutions on the benzene ring. As could be seen, there is no H-bond between the drug molecule and the nano-particle. The computed distance between the **H1a** and nano-particle is about 300 pm.

The calculated electronic energies and binding energies are listed in Table III. As could be seen, the **NANO-Fe1** form is the most stable form of the three investigated forms, which involves the greatest number of intermolecular hydrogen bonds. There are three hydrogen bonds between the carbonyl and hydroxyl groups of the drug and oxygen and hydrogen atoms of the –OH and H_2O ligands of the nano-particle.

TABLE III. The electronic and binding energies of the optimized geometries for the non-covalent interactions of the **H1a** tautomer and a γ-Fe_2O_3 nano-particle in aqueous solution

Species	Electronic energy, Hartree	Binding energy, kJ mol^{-1}
Free nano-Fe_2O_3	–2654.5173599	–
H1a conformer	–4041.828239	–
Free nano-Fe_2O_3+ **H1a** conformer	–6606.0245989[a]	–
NANO-Fe1	–6606.0469129	–58.53
NANO-Fe2	–6606.0277126	–8.17
NANO-Fe3	–6606.0253233	–1.90

[a]Sum of the electronic energies of the proposed model for the γ-Fe_2O_3 nano-particle and the **H1a** tautomer

The binding energy is defined as:

$$\Delta E = E_{(\text{NANO-Fe*})} - (E_{(\text{H1a})} + E_{(\text{Fe}_2\text{O}_3)}),$$

where $E_{(\text{NANO-Fe*})}$, $E_{(\text{H1a})}$ and $E_{(\text{Fe}_2\text{O}_3)}$ are the electronic energies of one of the three NANO-Fe forms, the electronic energies of the **H1a** conformer of halofuginone and the optimized model for a free γ-Fe_2O_3 nano-particle, respectively. The **NANO-Fe1** form involves three H-bonds, while the **NANO-Fe2** form involves only one H-bond and the **NANO-Fe3** form has no hydrogen bond. The intramolecular hydrogen bonds stabilize the investigated system. Since, the **NANO-Fe1** form has the lowest energy value and the highest stability, it is the favorite model for the non-covalent interaction of the **H1a** conformer of halofuginone with a γ-Fe_2O_3 nano-particle. In aqueous solution, the **NANO-Fe1** form is more stable than the **NANO-Fe2** and **NANO-Fe3** forms by 50.36 and 56.63 kJ mol^{-1}, respectively.

CONCLUSIONS

Halofuginone is a beneficial and effective drug in the therapy of the malaria, cancer, fibrosis and inflammatory disease. This drug could exist as three different tautomers that may be converted to each other *via* the IPT. In this work, their geometries as well as the kinetics of its tautomerization were evaluated using DFT methods. The PCM model was used for considering the solvent effects in aqueous solution.

In aqueous solution, **H1** is the most stable tautomer of halofuginone, which has two different conformers, **H1a** and **H1b**. The **H1a** conformer involving an intramolecular H-bond is more stable than the **H1b** one.

Tautomerization of the **H1a** tautomer to each of the **H2** and **H3** tautomers progresses *via* IPT. These tautomerization reactions involve high activation energies, confirming that the **H1a** species is kinetically and thermodynamically the most favorable tautomer of halofuginone. The amount of the **H2** and **H3** tautomers is predicted to be negligible.

The non-covalent interactions between the armchair (5,5) single wall carbon nanotube (SWCNT) and **H1a** conformer of halofuginone were investigated in two different forms. The calculated binding energies show that the non-covalent interactions slightly stabilize the system.

Furthermore, non-covalent interactions of the **H1a** conformer with the magnetic γ-Fe_2O_3 nanoparticles in the proposed model were investigated in three different manners. All of three forms involve intermolecular hydrogen bonds in their optimized geometries. The most stable form is the **NANO-Fe1** one. In the optimized geometry of the **NANO-Fe1** form, there are three intermolecular H-bonds between the drug and nano-particle, two strong and one weak H-bond. The two carbonyl groups and hydroxyl group of the **H1a** species are engaged in these H-bonds. The **NANO-Fe2** form involves only one weak H-bond between the –NH amine group of the **H1a** and oxygen atom of the –OH ligand of the γ-Fe_2O_3 nano-particle. The bond length of this H-bond is 2.03 Å. In the structure of the **NANO-Fe3** form there is no intermolecular H-bond between the drug molecule and the investigated nano-particle, resulting in the most unstable form for non-covalent interaction.

ИЗВОД

ГЕОМЕТРИЈА, ТАУТОМЕРИЈА И НЕКОВАЛЕНТНЕ ИНТЕРАКЦИЈЕ ЛЕКА ХАЛОФУГИНОНА СА УГЉЕНИЧНИМ НАНОЦЕВИМА И γ-Fe_2O_3 НАНОЧЕСТИЦАМА: DFT СТУДИЈА

SHIMA KAZERI-SHANDIZ, S. ALI BEYRAMABADI и ALI MORSALI

Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

Халофугинон је моћан лек против маларије, који може да постоји у три могућа таутомера. Овде смо, користећи теорију функционала густине (DFT), и уводећи ефекте растварача помоћу PCM модела, истраживали таутомерију код халофугинона. Интра-

молекулске H-везе имају значајну улогу у стабилизацији таутомера. **H1a** је најстабилнији конформер. Нековалентне интеракције конформера **H1a** са столичастом (5,5) једнозидном угљеничном наноцеви и са γ-Fe_2O_3 наночестицом истраживане су на више начина. Одређен је њихов најстабилнији облик. Међумолекулске H-везе имају суштинску улогу у енергетском понашању интеракције γ-Fe_2O_3 наночестице и халофугинона.

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