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| D:\Rinat\Rinat\доки\журнал\статьи\logo.jpg | HYBRID NANOSTRUCTURES BASED ON MONO(AMINO ACID) DERIVATIVES OF FULLERENE C60 AND VITAMIN B12 | | |
| Cite this: *INEOS OPEN*,  **2025**, *8 (1–3)*, XX–XX  DOI: 10.32931/ioXXXXx  *Received XX Month 20XX,*  *Accepted 2 March 2025*  http://ineosopen.org | | N. Yu. Shepeta\* | |
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| Abstract  This minireview highlights the author's own works on the synthesis and investigations of the properties of hybrid nanostructures (HNSs) based on mono(amino acid) derivatives of fullerene C60 and vitamin B12. The synthetic routes to monoderivatives of fullerene C60 with various amino acids and the methods for obtaining their hybrid nanostructures with vitamin B12 derivatives were developed. The structures of the resulting compounds and the sizes of their nanoparticles were studied by different physicochemical methods. It was shown that the HNSs with catalytically active derivatives of vitamin B12 retain the activity in the autoxidation of ascorbic acid, which is characteristic of some derivatives of vitamin B12. | | |  |
| **Key words:** amino acids, vitamin B12, fullerene C60, hybrid nanostructures. | | | |

**Introduction**

Fullerene derivatives are known to exhibit a broad spectrum of biological activity [1, 2]. Water-soluble derivatives of fullerene C60 exhibit antioxidant, membranotropic, neuroprotective, antiviral, antibacterial, and antitumor properties and also act as effective low-toxic delivery systems of drugs for various diseases to their targets [3, 4].

This work was envisioned by the full member of the Academy of Sciences of USSR M. E. Volpin and carried out by his colleagues at INEOS RAS. V. S. Romanova was the first to develop a unique method for the synthesis of mono(amino acid) and peptide derivatives of fullerene [5]. The resulting compounds appeared to be non-toxic, are easily excreted from the body, and display different types of biological activity.

**Mono(amino acid) derivatives of fullerene C60 and vitamin B12**

According to M. E. Volpin [6], the catalytic sources of reactive oxygen species (ROS), which selectively accumulate in a tumor, can actively suppress the growth of malignant cells. Of particular interest are natural macrocyclic complexes of cobalt: vitamin B12 and its derivatives (cobalamins, including B12 e-monocarboxylic acid (e-COOH-Cbl-CN, **1**) and e-carboxy-dihydroxycobinamide (e-COOH-Cbi-(OH)2, **2**), Fig. 1).

It was established that cobalamins can be used as delivery systems of drugs to a tumor [7]. However, the molecule of vitamin B12 itself hardly passes through cell membranes. This can be mitigated by the partial hydrophobization of the vitamin molecule, which, in turn, can be achieved by attaching it to a



**Figure 1.** Structures of B12 e-carboxylic acid (**1**) and e-carboxy-dihydroxycobinamide (**2**).

hydrophobic compound, for example, a derivative of fullerene C60.

At the first stage of investigations, the principal possibility of obtaining new compounds based on a conjugate of catalytically inactive B12 e-carboxylic acid **1** and a derivative of fullerene C60 with ε-aminocaproic acid [8] in two ways was demonstrated.

After that, a hybrid nanostructure combining a catalytically active form of vitamin B12, e-carboxy-dihydroxycobinamide **2**, and *N*-(monohydrofullerenyl)-ε-aminocaproic acid was synthesized. It was found that the resulting HNS retains the catalytic activity in the oxidation of a natural substrate, namely, ascorbic acid, inherent in compound **2** [9].

It was shown that the biological activity of the resulting conjugate changes upon variation of the structure of the amino acid incorporated into the composition of the fullerene C60 derivative [10]. Recently, the successful production of a hybrid nanostructure based on a salt of fullerene-l-phenylalanine acid and e-carboxy-dihydroxycobinamide **2** was reported [11]. This HNS was also found to be catalytically active, just like initial compound **2**.

The introduction of a fluorine atom into an amino acid molecule usually imparts new biological properties to the final product [12, 13]. To expand the spectrum of biological activity of amino acid and peptide derivatives of fullerenes, the following amino acids were used as starting compounds for the synthesis of water-soluble derivatives of fullerene C60: l-phenylalanine, *o*-fluoro-l-phenylalanine, and *p*-fluoro-l-phenylalanine. The first stage was the synthesis of the fullerene derivatives with *o*-fluoro-l-phenylalanine and *p*-fluoro-l-phenylalanine. l-Phenylalanine derivatives of fullerene C60 [14] were obtained by our research group (Scheme 1) according to the earlier suggested method [5].



**Scheme 1.** Synthesis of the salts of the fullerene-substituted l-phenylalanine acids.

Next, the resulting nanostructures of *N*-(monohydrofullerenyl)amino acids (**3**, **4**) were combined with a derivative of vitamin B12, namely, e-carboxy-dihydroxycobinamide (**2**). Since complex **2** contains several free hydroxy groups, the addition should be carried out without the use of thionyl chloride. Therefore, a synthetic approach based on the introduction of an ethylene spacer and the application of DCC as a coupling agent was suggested (Scheme 2).



**Scheme 2.** Synthesis of the derivatives of *N*-(monohydrofullerenyl)-l-phenylalanine and e-carboxy-dihydroxycobinamide (**5**, **6**).

The structures of all HNSs obtained based on mono(amino acid) derivatives of fullerene C60 and e-carboxy-dihydroxycobinamide were confirmed by various physicochemical methods [14].

It was found that the resulting HNSs exhibit catalytic activity in the autoxidation of ascorbic acid, but their activity is slightly lower than that of the derivatives of vitamin B12 [9, 14]. This can be explained by a decrease in the relative concentration of a vitamin B12 moiety in the molecules of the hybrid nanostructures and partial deactivation of the resulting ROS by the fullerene framework. It should be noted that the data obtained by us are consistent with the results for similar structures based on pure chlorin and its fullerene derivative [15]. The substituted fullerene unit in the resulting conjugate will likely to be able to compensate for a decrease in the catalytic activity by imparting the lipophilic properties to a hybrid nanostructure, which is facilitated by amino acid derivatives of fullerene, capable of entering the cell without destroying a lipid bilayer of the cell membrane.

**Conclusions**

The effective chemical strategies for the synthesis of hybrid nanostructures based on e-carboxy-dihydroxycobinamide and *N*-(monohydrofullerenyl)amino acids were developed. The monoderivatives of fullerene C60 with ε-aminocaproic acid, l-phenylalanine, *o*-fluoro-l-phenylalanine, and p-fluoro-l-phenylalanine, as well as their hybrid nanostructures with the vitamin B12 derivatives were obtained and characterized. The catalytic activity of the resulting nanostructures in the ascorbic acid autooxidation was demonstrated.

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