MONO(AMINO ACID) DERIVATIVES OF FULLERENES, HYBRID STRUCTURES ON THEIR BASIS AND THEIR BIOLOGICAL ACTIVITY

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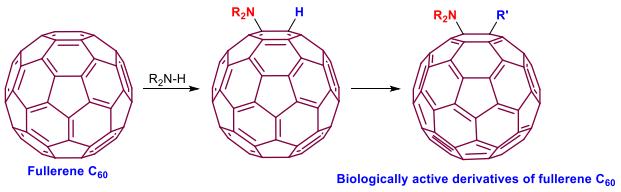
Abstract

The synthesis and biological properties of mono(amino acid) derivatives of fullerenes (MAADFs) as well as hybrid nanostructures (HNSs) on their basis are reviewed. It is shown that these derivatives are highly effective non-toxic compounds in various fields of medicine and can be further used as potential drugs.



Key words: amino acid derivatives of fullerenes, hybrid nanostructures, biological activity.

Introduction

A major challenge of modern nanotechnologies is the creation of new materials for medicine based on the production of hybrid nanostructures. Among modern nanomaterials, of particular interest are the nanocarbon structures, including fullerenes. Research in this filed is focused on the creation of water-soluble derivatives of fullerenes, which have high biocompatibility and exhibit a broad spectrum of biological activity. The number of amino acid or peptide moieties and the methods for their binding with a fullerene core can be different. Therefore, the physicochemical and biological properties of the resulting compounds will also differ significantly from each other.

It was found that the water-soluble derivatives of fullerene C_{60} display antioxidant [1, 2], membranotropic [3], anti-ischemic [4, 5], neuroprotective [6], antiviral [7], antibacterial [8], and antitumor [9] properties and can be used as effective low-toxic agents [10] for target-specific drug delivery in various diseases [11, 12]. The polyaddition of amino acids to a fullerene gives rise to new biologically active compounds. Thus, the penta(amino acid) derivatives of fullerene C_{60} show great promise as a basis for creating highly effective potential drugs for the treatment of pathological processes associated with the development of type 2 diabetes [13].

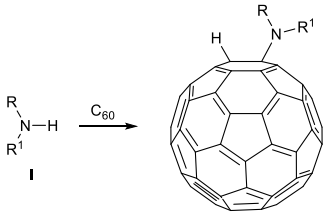
Mono(amino acid) derivatives of fullerenes

The mono(amino acid) and peptide derivatives of fullerene C_{60} (AADFs) stand somewhat apart. This is explained by the fact that the addition of one amino acid or peptide molecule leads to the appearance of a proton on the fullerene core, which readily enters the substitution reactions (Scheme 1).

These compounds were isolated and characterized for the first time in 1994 at the Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences (INEOS RAS) [12–15]. These derivatives exhibit high solubility in water, low toxicity, and different types of biological activity [16–21].

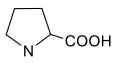
In experiments on mice and rabbits, it was demonstrated that the fullerene derivatives of L-alanine, L-serine, L-alanyl-L-alanine, which do not have their own immunogenicity, exhibit pronounced adjuvant activity [18, 20]. The presence of a free carboxy group in the amino acid and peptide moieties of AADFs allows one to conjugate the resulting derivatives with other biologically active compounds. The addition of the well-known adjuvant, namely, a peptide derivative of muramic acid widely used in biology and medicine, to *N*-(monohydro)fullerenyl-ε-aminocaproic acid led to the formation of a new adjuvant (compound **III**, Fig. 1) which displayed more than an order of magnitude higher activity than the initial adjuvant [19].

The conjugation of *N*-(monohydro)fullerenyl-ε-aminocaproic acid with a 24-mer peptide—a fragment of the foot-and-mouth disease (FMD) virus protein that exhibits the anti-FMD activity—afforded antigen H-C_{60}-Z-(136–159) (Z = -$NH(CH_2)_5C(O)$-) which immunogenicity was several orders of magnitude higher than that of the original 24-mer peptide—(136–159) = Y-S-A-G-G-M-G-R-R-G-D-L-E-P-L-A-A-R-V-A-A-Q-L-P [13].

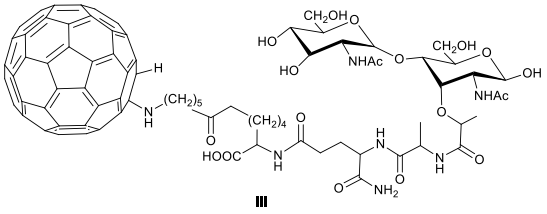


a: R = CH_2CO_2H
b: R = $C_6H_4CO_2H$
c: R = $(CH_2)_5CO_2H$
d: R = L-$CH(CH_3)CO_2H$
e: R = L-$CH(CH_3)CO_2Me$
R^1 = H

f: R = *L*-$CH(CH_3)C(O)$-*L*-$NHCH(CH_3)COOH$
g: R = *D*,*L*-$CH(CH_3)C(O)$-*D*,*L*-$NHCH(CH_3)COOH$
h: R = $CH_2C(O)$-*L*-$NHCH[CH(CH_3)_2]COOH$
i: RR^1N =

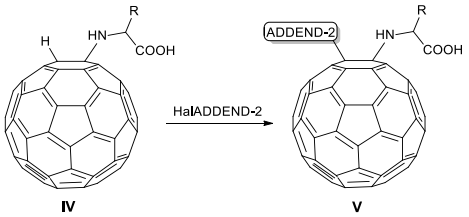


Scheme 1. Synthesis of amino acid derivatives of fullerenes.



III

Figure 1. Adjuvant based on a fullerene and muramic acid.



IV **V**

Scheme 2. Synthesis of hybrid fullerene nanostructures.

It is known that human cytomegalovirus (CMV) can cause severe illness in adults, especially in immunodeficient conditions, affect young children, and lead to death of the fetus and newborns. The CMV infection is one of the most common opportunistic infections in AIDS. The drugs used in the treatment of the CMV infection are ganciclovir and foscarnet, which are highly toxic. Furthermore, their application is often associated with the development of the drug-resistant CMV infection. To expand the range of substances with the anti-CMV activity, the fullerene derivatives of aminobutyric and aminocaproic acids were explored. The antiviral activity was studied using a primary culture of human embryonic diploid lung fibroblasts (HELFs). The sodium salts of the mentioned acids were studied. These compounds do not have acute cytotoxicity both *in vitro* and *in vivo* up to high concentrations (the experiments were carried out on cells, mice, and rabbits), while the chronic cytotoxicity is observed at doses 2–3 orders of magnitude higher than the effective antiviral dose. It was shown that the introduction of the aminobutyric acid derivative into infected HELFs results in a decrease in the concentration of the viral proteins in cells to the values approaching the protein concentration in an uninfected cell culture [21]. In HIV infection, the best results were demonstrated by *N*-(monohydro)fullerenyl-ε-aminocaproic acid, which, in ultra-low doses, effectively inhibited intracellular reproduction of HIV under conditions of acute and chronic infection and suppressed the infectivity of the mature extracellular virus [21].

Tritium-labeled fullerene derivative of aminocaproic acid T-C_{60}-NT$(CT_2)_5$COOK was shown to be excreted from the body in 72 h *via* the kidneys [22].

However, the presence of a proton on the fullerene core promotes significant expansion of the application scope of these substances in biology and medicine by creating biocompatible hybrid nanostructures through binding of the second addend to the fullerene core instead of a proton.

Hybrid nanostructures of fullerenes

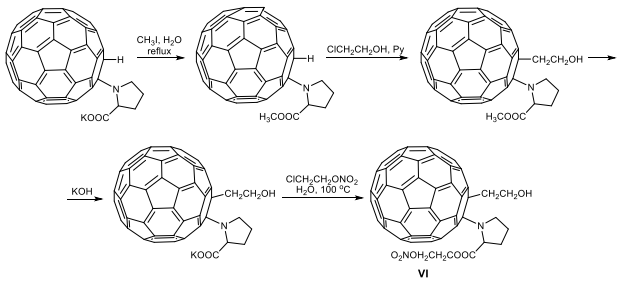
Kotel'nikov *et al.* [23, 24] suggested a new approach to further modification of the amino acid derivatives of fullerenes. A significant expansion of the range of AADFs was found to be possible by creating hybrid structures based on fullerenes (for example, **V**) obtained by the addition of the second addend (**ADDEND-2**) to fullerene derivative **IV** by replacing the hydrogen atom introduced into the fullerene structure in the process of the amino acid addition (Scheme 2). These hybrid fullerene derivatives (HFDs) or hybrid fullerene compounds (HFCs) opened the way to a wide range of biocompatible compounds using combinations of two different addends: one of them, the amino acid component, imparts water solubility and membranotropic properties to the fullerene core, while the second one imparts additional biological activity, in particular, antioxidant activity, which gives the ability to release nitric oxide, to act as a photosensitizer, or to inhibit key enzymes.

The replacement of a hydrogen atom for the second substituent usually proceeds in pyridine under the action of the corresponding halogen-containing compound.

The quantum-chemical calculations showed that the addition of amino acids or peptides to fullerene C_{60} occurs at the double bond of six-membered rings of the polyene system with the formation of 1,2-isomers [25]. However, a hydrogen atom of the fullerene core in the resulting adduct is labile [26]; therefore, the introduction of the second substituent instead of it can lead to steric hindrances in vicinal positions 1 and 2, facilitating the appearance of 1,4-isomers. The structure of the second substituent affects not only the chemical properties of the ensuing compounds, but also the contact area of the fullerene core with water and, as a consequence, the solvation mechanism [27].

To improve the biological efficacy of fullerene derivatives, recent advances in the field of the physiological activity of nitric oxide were used. It is known that nitric oxide controls vascular tone, serves as a modulator of oxidative reactions, apoptosis process, and immune responses [28].

The nitro derivative of fullerene C_{60} HO-CH_2CH_2-C_{60}-Pro-$C(O)CH_2CH_2ONO_2$ (**VI**) (Scheme 3) was tested as an antihypertensive agent. The effect of this compound on blood pressure and heart rate in Wistar rats was studied. A lower effect on the NO-dependent indicators of the cardiovascular system of rats than in the case of nitroglycerin was detected. These results indicate the possibility of creating original vasodilating compounds for antihypertensive therapy based on this class of compounds [29, 30].



VI

Scheme 3. Synthesis of the nitro derivatives of *N*-(monohydro)fullerenyl-L-proline.

The synthesis of compounds **VII**–**X** (Fig. 2) was carried out analogously.

To evaluate the antitumor potential of fullerene derivatives, the hybrid structures based on a fullerenyl-substituted proline (**VII**–**X**) with the biologically active NO donors and antioxidant carnosine (**XI**) were used.

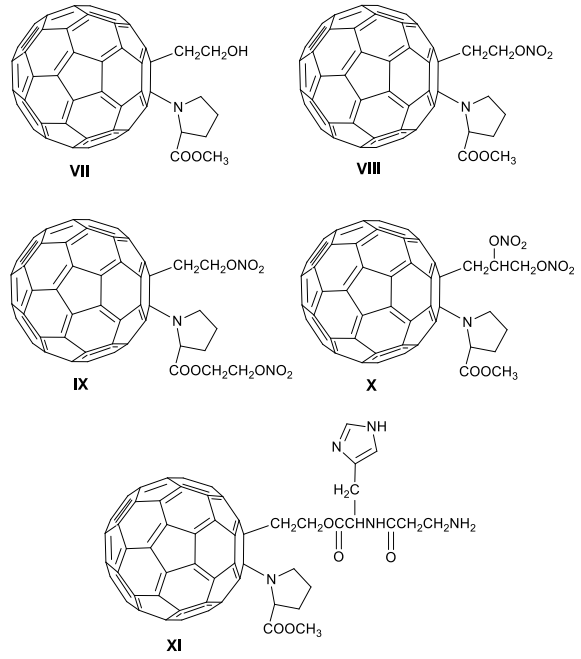


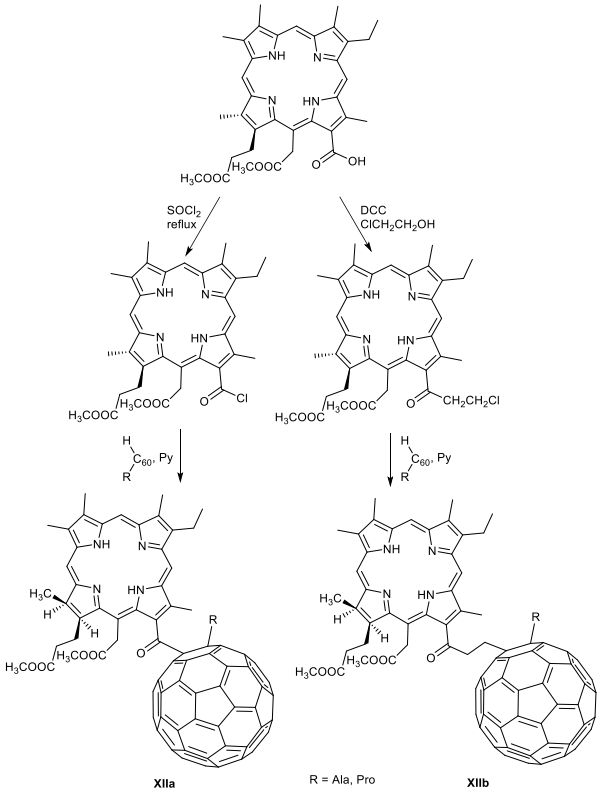
Figure 2. HNSs based on *N*-(monohydro)fullerenyl-L-proline methyl ester.

These nanostructures exhibited significant antitumor effects. Hybrid nanostructures **VII**–**XI** acted as effective chemosensitizers, which caused the recovery of up to 67% of animals with P388 leukemia when the compounds were administered in combination with the clinically used cytostatic cyclophosphamide. Similar hybrid molecules act as pronounced inhibitors of metastasis when administered in combination with a cytostatic. Therewith, the therapeutic dose of the cytostatic agent is decreased tenfold, which reduces its toxicity and prevents the development of resistance [31]. The fullerene derivative of proline **IIi** showed no antitumor activity under these conditions.

The effect of nitroxy HFDs $O_2NOCH_2CH_2$-C_{60}-L-Pro-OMe (**VIII**) and $O_2NOCH_2CH(ONO_2)CH_2$-C_{60}-L-Pro-OMe (**X**) on the enzymatic activity of the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase was studied. These HFDs were shown to be the inhibitors of the SR Ca^{2+}-ATPase [32]. Thus, mononitrate **VIII** decelerates the ATP hydrolysis with the inhibition constant K_i = $1.92 \cdot 10^{-6}$ M and the transmembrane transfer of Ca^{2+} ions with the inhibition constant $K_i = 3.79 \cdot 10^{-6}$ M. Dinitrate **X**, although it is a close analog of mononitrate **VIII** and noncompetitively inhibits both functions of the enzyme, differs from mononitrate by the lower values (by two orders of magnitude) of the inhibition constants (K_i): $2.38 \cdot 10^{-8}$ and $3.08 \cdot 10^{-8}$ M, respectively. These experimental facts suggest an increased sensitivity of the enzyme hydrolytic function to the action of dinitrate **X** and may indicate a partial uncoupling of the SR Ca^{2+}-ATPase function. It was noted that the results on the induced modulation of the activity of the SR Ca^{2+}-ATPase, associated with a change in the ratio of extra- and intracellular contents of Ca^{2+} ions, suggest the existence of the antimetastatic properties of the nitroxy HFD explored.

Photodynamic therapy (PDT) is an actively developing area of medicine, which is based on the selective effect of low-toxic dye molecules, photosensitizers (PS), on tumors or microorganisms, when they are excited by light of a certain wavelength—in the tissue transparency window of 700–950 nm. The photoexcitation results in the generation of highly toxic free radicals: singlet oxygen, superoxide anion radical, and other reactive oxygen species (ROS), which inhibit the growth of tumors or microorganisms. The main advantages of PDT over the conventional methods of treating malignant neoplasms (surgery, chemotherapy, and radiotherapy) are non-invasiveness, high efficiency, and selectivity of the effect on a tumor in the absence of a noticeable effect on healthy body tissues, the absence of toxicity of the drugs in use, and the possibility of multiple application [33–44].

Some HNSs based on poly(amino acid) derivatives of fullerenes were reported, for which the possibility of a significant increase in the photodynamic activity of the dye owing to the interaction with the fullerene core was demonstrated [45–49]. But not all of the compounds obtained appeared to be water-soluble. To expand the panel of HNSs, the conjugates of chlorin (**XII**) (Scheme 4) and pyropheophorbide (**XIII**) with the fullerene mono(amino acid) derivatives were synthesized that showed high efficiency in PDT.



Scheme 4. Synthesis of the HNSs based on chlorin and fullerene mono(amino acid) derivatives.

The fullerene derivatives of pyropheophorbide **XIIIa** and **XIIIb** were obtained analogously (Fig. 3).

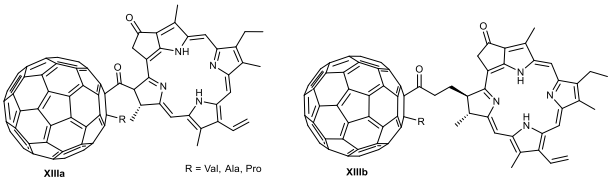
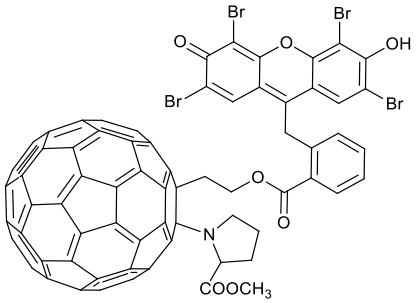


Figure 3. HNSs based on pyropheophorbide and fullerene mono(amino acid) derivatives.

Hybrid nanostructures facilitate the creation of compounds with specific photophysical and biological properties [50]. The addition of eosin dye to fullerenyl-substituted proline was carried out (compound **XIV**, Fig. 4) [51, 52].



XIV

Figure 4. HNS based on eosin and *N*-(monohydro)-fullerenyl-L-proline methyl ester.

Eosin is effectively excited to the triplet state; then the excited state can be transferred to the fullerene or lead to an electron transfer from eosin to the fullerene core. As a result, this hybrid structure allows one to effectively generate singlet oxygen or a superoxide anion radical upon excitation of the dye in the green spectral region at a wavelength of 533 nm. It was found that such a hybrid derivative penetrates the blood–brain barrier (BBB), and its maximum content in brain tissues is reached in two hours and significantly decreases in five hours after injection. All this makes these hybrid structures the promising candidates for photodynamic therapy of cancer and pharmacokinetic studies [51, 53].

The membranotropic properties of both MAADFs [2] and HNSs based on them [52] were studied.

Using the triplet probe method, it was shown that the HNSs act as phosphorescence quenchers for the triplet probes in aqueous solutions and in the composition of phosphatidylcholine liposomes. By changes in the intensity of fluorescence of the triplet excited state of erythrosin, the ability of the HNSs to penetrate through the lipid bilayer into the interior of liposomes was revealed.

It is known that the blood–brain barrier regulates the penetration of biologically active substances, metabolites, chemical compounds which affect the sensitive structures of the brain, and also prevents foreign agents from entering the brain. However, in the case of certain types of cerebral pathology: injuries, inflammatory lesions of brain tissues, or various neoplasms, it is necessary to overcome the BBB for the administration of therapeutic drugs.

Yamago *et al.* [54] reported that water-soluble fullerene C_{60} can pass through the BBB of rats. Hsieh *et al.* [55] showed *in vivo* that water-soluble pentasubstituted derivatives of fullerene C_{60} can pass through the BBB and act as neuroprotective agents. It was demonstrated that the HNSs based on MAADFs also pass through the BBB [51].

Fullerenes were found to have antioxidant properties. Moreover, this concerns both the MAADFs and HNSs based on fullerenes [56]. The antioxidant properties of HNSs and the BBB permeability for them suggested the prospects of their use for the treatment of neurodegenerative diseases, in particular, Alzheimer's disease.

One of the causes of Alzheimer's disease is the aggregation of amyloid proteins, which results in the formation of plaques. Using high-resolution electron microscopy in *in vitro* amyloid systems of brain Aβ(1-42)-peptide and muscle X-protein of the titin family, the anti-amyloid ability of the HNSs with nitro groups (**VIII**–**X**) to prevent the formation of amyloid fibrils by Aβ(1-42)-peptide of the brain and X-protein, as well as to decompose the amyloid structures already formed by them was studied [57].

Nowadays, the main criteria for screening potential drugs for the treatment of neurodegenerative disorders, in addition to the inhibition of *β*-amyloid protein aggregation, are antioxidant activity and an inhibitory effect on the catalytic activity of the mitochondrial enzyme of oxidative deamination of biogenic amines, namely, monoamine oxidase B (MAO B) [58].

Lipid peroxidation (LPO) in Alzheimer's disease is one of the most important processes that accompanies the disease. A relationship was established between a decrease in the content of mitochondrial superoxide dismutase (Cu, Zn-SOD) and the intensification of superoxide generation in Alzheimer's disease [59]. The role of SOD in this process is explained by its main function: the inactivation of superoxide anion radicals. The antioxidant activity of the compounds was determined by the change in the content of malondialdehyde (MDA) in the rat brain homogenates.

Our research group showed [60] that compound **XI** exerts the highest effect, considerably reducing the specific content of MDA and suppressing LPO two times more effectively than complexes **VIII** and **X**, as well as neat carnosine.

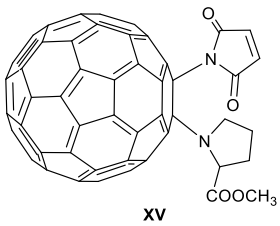
This result is caused by the binary antioxidant action of compound **X**: on the one hand, the C_{60} fullerene carbon spheroid acts as an acceptor of peroxyl radicals [58], which leads to chain termination, on the other hand, carnosine binds with hydroperoxides to form an intermediate that undergoes heterolytic decomposition without the formation of free radicals, which excludes the possibility of a degenerate branching during LPO [61–63]. The mono(amino acid) derivatives of fullerenes had no effect on the treatment of neurodegenerative diseases.

It was found that compound **X** inhibits glutamate-induced Ca^{2+} uptake into synaptosomes of the rat brain cortex better than other derivatives and significantly increases the amplitude of AMPA receptor currents. This indicates the potential ability of structure **X** to positively affect the memory of animals and is of undoubted interest for further investigation of its neuroprotective activity [60].

Of considerable interest is the introduction of a maleimide unit into the hybrid structures, which enables binding of the fullerene structures to proteins and peptides through the SH groups of cysteine residues or amino groups of other amino acid residues [64, 65].

Compound **XV** (Fig. 5) was covalently bound to hemoglobin through the SH group. This technique can be used to covalently bind fullerenes to various carriers, including proteins, peptides, and nucleic acids, which opens up great opportunities for the application of fullerenes in new immunological and molecular genetic methods [66].

The same approaches can be used to create regular monolayers and organized structures from fullerenes on the surface of metals and films, for grafting them to polymers, synthetic and natural fibers [67].



XV

Figure 5. HNS based on *N*-(monomaleimidyl)fullerenyl-L-proline methyl ester.

Using the principle of binding of biologically active moieties to MAADFs, the methods for synthesizing potentially biologically active substances based on the derivatives of fullerenes and vitamin B_{12} were developed.

The full member of the Academy of Sciences of USSR M. E. Vol'pin suggested [68] that the catalytic sources of reactive oxygen species, able to selectively accumulate in a tumor, can actively suppress the growth of malignant cells. Of particular interest are natural macrocyclic complexes of cobalt: vitamin B_{12} and its derivatives (cobalamins, in particular, *e*-carboxylic acid B_{12} (*e*-COOH-Cbl-CN, **XVI**) and *e*-carboxydioxy cobinamide (*e*-COOH-Cbi- $(OH)_2$, **XVII**), Fig. 6).

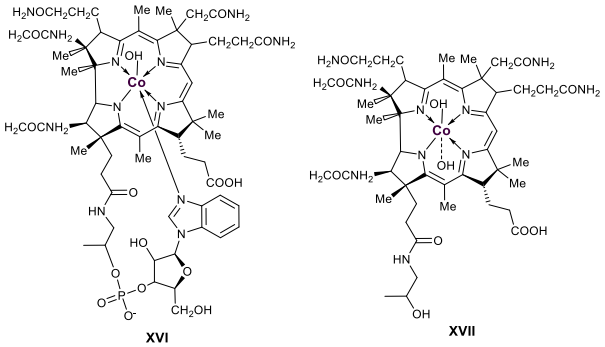


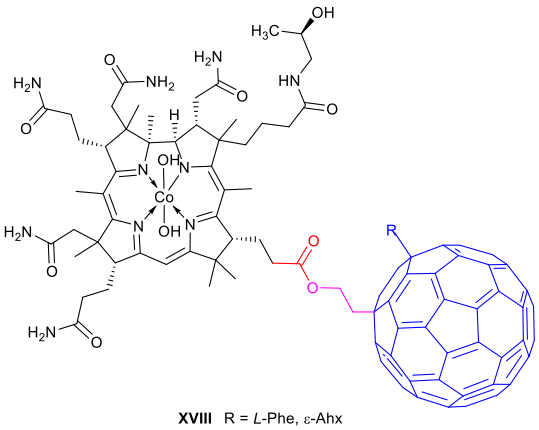
Figure 6. *e*-Carboxylic acid B_{12} (**XVI**) and *e*-carboxydioxy cobinamide (**XVII**).

The results of investigations, in particular, the study of the catalytic activity of corrin complexes in the oxidation of natural substrates [69] and the formation of ROS [70] in these processes, the oxidative cleavage of nucleic acids in the presence of these metal complexes [71–73] and medical and biological tests (evaluation of the antitumor activity of corrin complexes of cobalt and their compositions with L-ascorbic acid) confirmed that the catalytic systems generating reactive oxygen species based on cobalt complexes with corrin ligands and L-ascorbic acid can be very effective antitumor and related agents [74].

Therefore, it was suggested that the introduction of a pharmacophore catalytically active derivative of the fullerene and vitamin B_{12} into the molecule would significantly improve the antitumor efficacy of the complexes and afford the compounds with a new set of biological properties.

Based on this, the methods for obtaining the following hybrid nanostructures were developed (Fig. 7).

The results obtained in the oxidation of ascorbic acid in the presence of the ensuing HNS were comparable with the data for the unmodified vitamin B_{12} derivatives and confirmed the prospects of further investigations of these nanostructures as



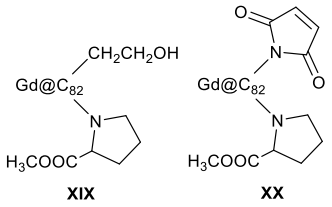
XVIII R = *L*-Phe, ε-Ahx

Figure 7. HNS based on *e*-carboxydioxy cobinamide and mono(amino acid) derivatives of fullerenes.

biologically active substances [75–77].

Besides the derivatives of fullerene C_{60}, the endohedral metallofullerene (EMF) derivatives are also used as HNSs. These HNSs are especially attractive for magnetic resonance imaging (MRI). This direction is very promising [78] since the EMF carbon backbone protects the metal atom, preventing its release into the body and thereby reducing the toxicity of the drug. For MRI the contrast agents that exhibit relaxation (paramagnetic) properties are used. In clinical practice, the contrast agents containing gadolinium chelate complexes gained popularity. However, a serious drawback of these compounds is their toxicity caused by the possible appearance of free gadolinium ions in the body [79].

The HNSs based on gadolinium proline derivatives H-Gd@C82-Pro hydroxyethyl-Gd@C82-Pro (**XIX**) and maleimidyl-Gd@C82-Pro (**XX**) were obtained (Fig. 8) [80].



XIX **XX**

Figure 8. HNSs based on methyl esters of the proline derivatives of endometallofullerenes with gadolinium.

The relaxation ability of these water-soluble compounds was determined from their effect on the spin-lattice relaxation time of water protons in an NMR spectrometer. The relaxation coefficients *R* for aqueous solutions of **XIX** and **XX** were 0.757 l/mol/s and 1.091 l/mol/s, respectively. The relaxation ability of the hybrid nanostructures is comparable to that of the commercial contrast agent magnevist (*R* = 2.041 l/mol/s) used in MRI, which increases the attractiveness of their use as contrast agents [80–83].

Conclusions

Thus, the mono(amino acid) derivatives of fullerenes and hybrid nanostructures on their basis are non-toxic compounds that offer ample opportunities for their application in biology and medicine.

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