

Proceeding Paper

# Catalytic Cycloaddition of Diazo Compounds Based on Pharmacologically Significant and Natural Compounds to C<sub>60</sub>-Fullerene <sup>†</sup>

Lilia L. Khuzina, Airat R. Tuktarov and Usein M. Dzhemilev

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**Abstract:** The data obtained by the authors in the field of carbon cluster chemistry, namely, the catalytic cycloaddition of diazo compounds of modern pharmacologically significant and natural compounds to C<sub>60</sub>-fullerene under the action of complex Pd-catalysts, are summarized. Cycloaddition reactions of diazoacetates, diazoamides, diazoketones with C<sub>60</sub>-fullerene, catalyzed by Pd(acac)<sub>2</sub>-PPh<sub>3</sub>-Et<sub>3</sub>Al, with selective formation of methano- and pyrazolinofullerenes, new and promising classes of biologically active derivatives of C<sub>60</sub>-fullerenes.

**Keywords:** fullerenes; diazo compounds; methanofullerenes; homofullerenes; pyrazolinofullerenes; antioxidant activity; cytotoxic activity; metal complex catalysis

## 1. Introduction

The discovery of fullerenes, a new allotropic form of carbon, is recognized as one of the amazing and most important discoveries in the science of the XX century. The interest in fullerenes and its derivatives is due to the possibility of their wide application in various fields of technology and science. At the same time, fullerene derivatives are of particular practical value for medicine. Thus, according to the literature data, functionally substituted fullerenes have high antioxidant, antitumor and antiviral properties, and are also of interest as X-ray reducing agents [1–12]. At the time of the beginning of our research, one of the popular directions in the synthesis of organic derivatives of C<sub>60</sub>-fullerene was the Bingel-Hirsch reaction [13,14] based on the cycloaddition of in situ generated  $\alpha$ -halocarbanions to C<sub>60</sub>-fullerene with the formation of corresponding methanofullerenes. As well as an alternative method for obtaining functionally substituted fullerenes C<sub>60</sub> was considered to be the cycloaddition of diazo compounds followed by thermolysis or photolysis of the resulting fullereneopyrazolines [15–17]. However, there was practically no information in the literature concerning the selective cycloaddition of diazo compounds of complex structure synthesized on the basis of pharmacologically significant compounds, including natural ones, to C<sub>60</sub>-fullerene in the presence of metal-complex catalysts.

## 2. Results and Discussion

To date, we have accumulated considerable experience in the catalytic method of selective citation of C<sub>60</sub>-fullerene under the action of Pd catalysts [18–22]. As a result of the research, effective preparative methods for the synthesis of functionally substituted fullerenes containing known natural and biologically active compounds as a substitute have been proposed.

Diazoacetates containing cholesterol in the ester group [23],  $\alpha$ -tocopherol, Trolox methyl esters, 20.29 dehydrobetulic and ursolic acids [24], which have antioxidant,

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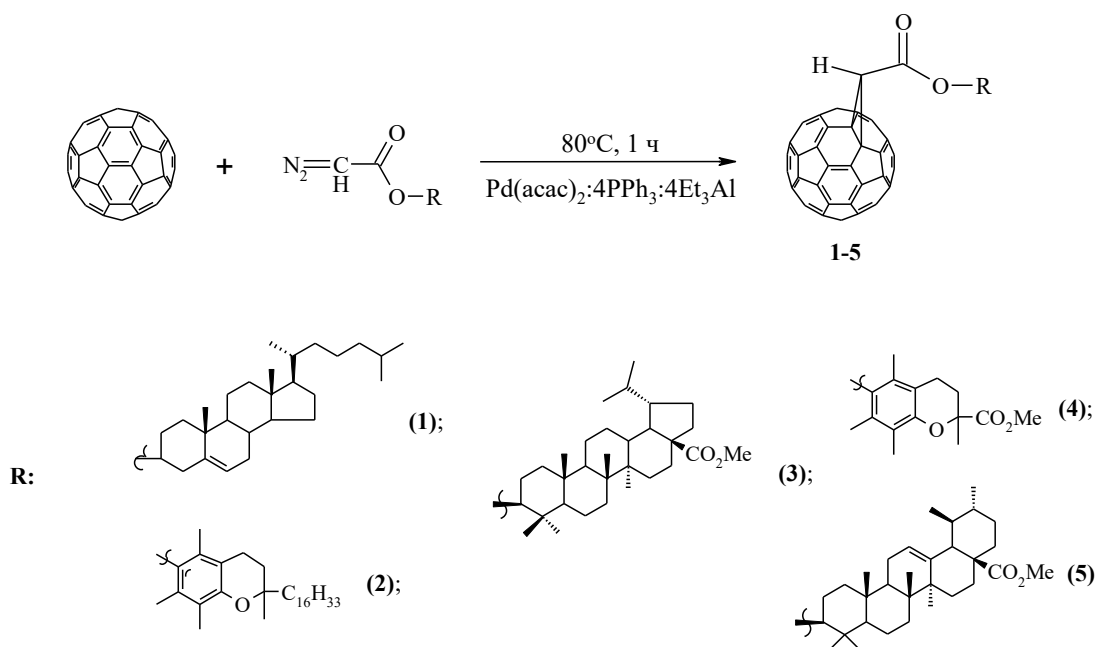
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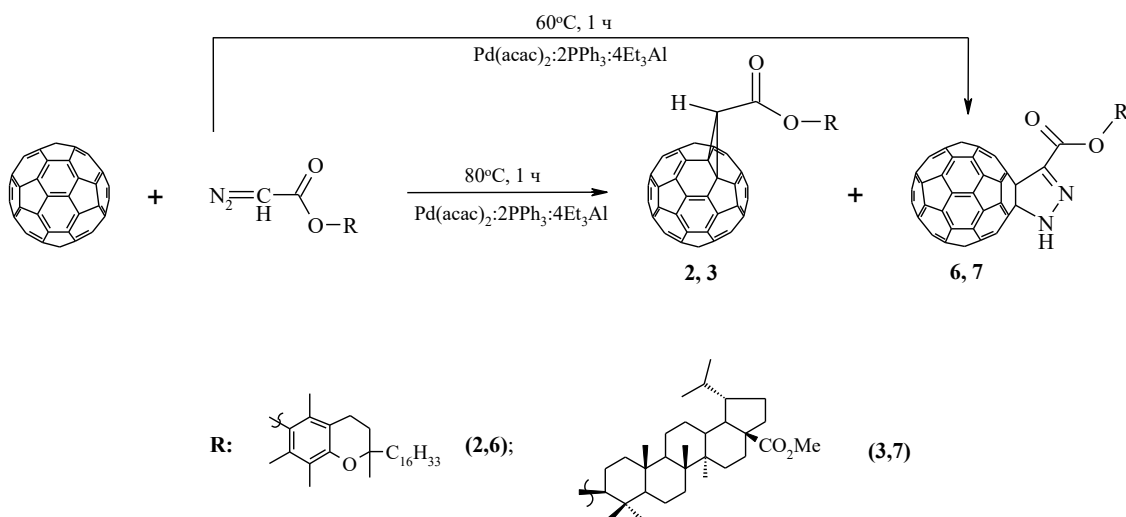
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antitumor, and antiviral properties, were used as the initial pharmacological objects of the study. It has been shown that the above diazo compounds interact with C<sub>60</sub>-fullerene (molar ratio 5:1) in the presence of 20 mol.% of the three-component catalyst Pd(acac)<sub>2</sub>-PPh<sub>3</sub>-Et<sub>3</sub>Al, taken in a ratio of 1:4:4 at 80 °C, for 1 h in 1,2-dichlorobenzene, the corresponding methanofullerenes **1–5** are selectively formed with a yield of 60–75%.



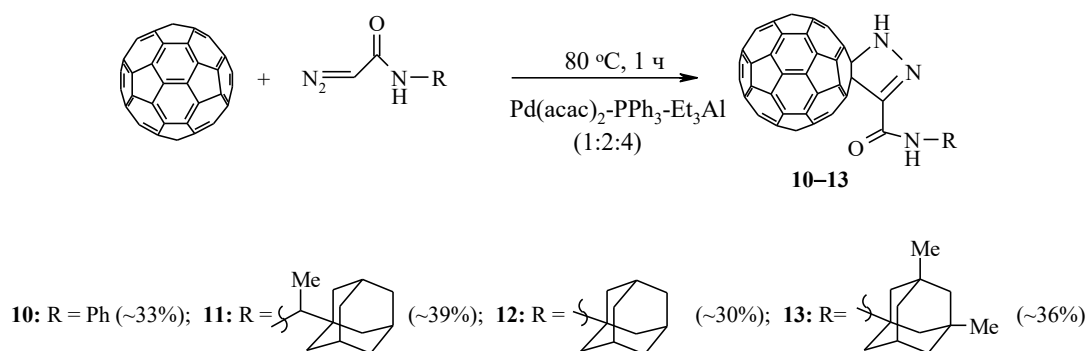
**Scheme 1.** Catalytic cycloaddition of diazoacetates to C<sub>60</sub>-fullerene.

Previously, we found that a change in the ratio of the components of the Pd(acac)<sub>2</sub>-PPh<sub>3</sub>-Et<sub>3</sub>Al catalytic system, taken in a ratio of 1:4:4 to 1:2:4 in the reactions of cycloaddition of diazoacetates to fullerene C<sub>60</sub>, leads to the predominant formation of 5,6-open cycloadducts [18–22]. However, in our experiments under these conditions, the interaction of diazo-derived  $\alpha$ -tocopherol and methyl ester 20,29-dehydrobetulin with C<sub>60</sub>-fullerene, instead of the expected homofullerenes, obtained the corresponding methanofullerenes **2, 3** and pyrazolinofullerenes **6** and **7** with a total yield of 58 and 65%. When the reaction temperature drops to 60 °C, pyrazolinofullerenes **6** and **7** are predominantly formed with yields of 35 and 41%, respectively.



**Scheme 2.** Synthesis of [2+3]-cycloadducts of C<sub>60</sub>-fullerene.

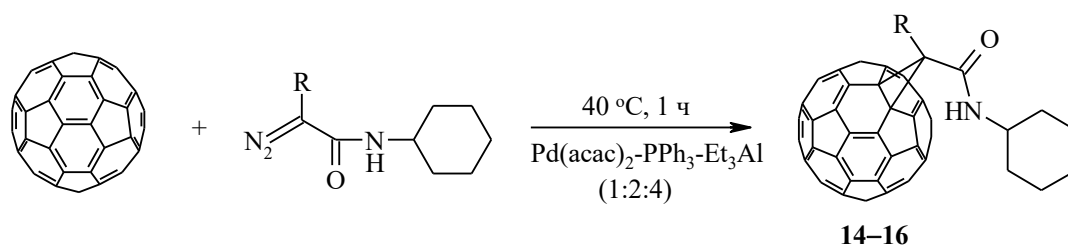
In the development of our research, and also taking into account the lack of information in the literature on the catalytic cycloaddition of diazoamides to fullerenes, we studied the possibility of catalytic cycloaddition to C<sub>60</sub>-fullerene of diazoamides synthesized on the basis of glycine and cyclohexylamine, aniline, or adamantane-containing amines [25]. As a result of the reactions, we isolated individual pyrazolinofullerenes 9–13. In the absence of a catalyst, this reaction proceeds with the formation of a mixture of methane and stereoisomerichomofullerenes [26].



**Scheme 3.** Cycloaddition of diazoamides to C<sub>60</sub>-fullerene.

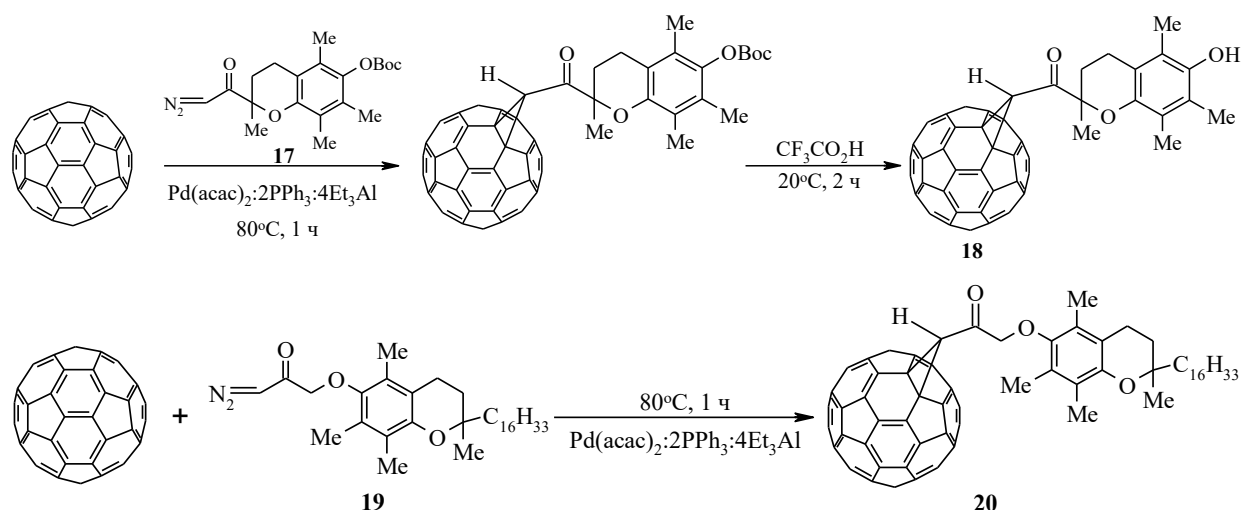
It is known from the literature that pyrazolinofullerenes thermally transformed into the corresponding methanofullerenes [27,28]. By boiling the synthesized [2+3]-cycloadducts 9–13 in 1,2-dichlorobenzene for 100 h, the formation of the corresponding methanofullerenes does not was found.

It is known [28] that the presence of a substituent in the  $\alpha$ -position to the diazo group of the initial diazocompound leads to destabilization of the pyrazolinofullerene and the formation of the corresponding [2+1] cycloadducts. To this end, we have been involved in the reactioncatalytic cycloaddition of diazoamides,synthesized from  $\alpha$ -alanine,  $\alpha$ -leucine or  $\alpha$ -methionine andcyclohexylamine. It was found that these diazoamides react with C<sub>60</sub>-fullerene in the developedconditions (40 °C, 1 h) in the presence of 20 mol.% of a three-component catalyst Pd(acac)<sub>2</sub>-PPh<sub>3</sub>-Et<sub>3</sub>Al (1:2:4) to formexclusively methanofullerenes 14–16 with a yield of 40-50%.



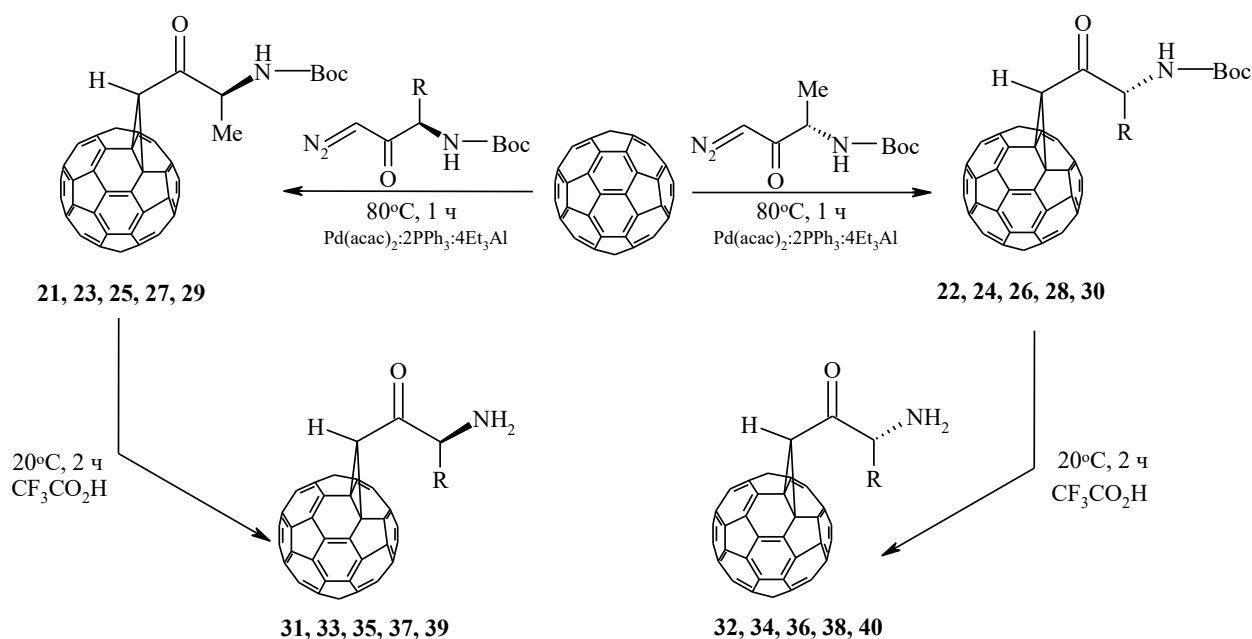
**Scheme 4.** Cycloaddition of  $\alpha$ -substituted diazoamides to C<sub>60</sub>-fullerene under the action of the [Pd] complex.

In the development of ongoing research aimed at developing effective methods for covalent binding of C<sub>60</sub> fullerene with modern pharmacologically significant compounds, we studied the catalytic cycloaddition to the latter of diazoketones synthesized on the basis of biologically active carboxylic acids. Trolox, a synthetic analogue of  $\alpha$ -tocopherol, and tocopherylacetic acid, were chosen as model pharmacons. As a result of the interaction of C<sub>60</sub> fullerene with diazoketones 17 and 19, individual methanofullerenes 19 and 20 were obtained in ~40% yield and 37% respectively.

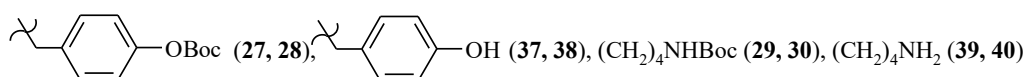


**Scheme 5.** Catalytic cycloaddition of diazoketones to C<sub>60</sub>-fullerene.

In order to obtain previously undescribed optically active methanofullerenes [29], we implemented a catalytic cycloaddition of C<sub>60</sub> fullerene with optically active diazoketones synthesized from L- and D-  $\alpha$  amino acids: alanine, leucine, methionine, tyrosine and lysine, in which the amino group is protected with butyloxycarbonyl (Boc) group.



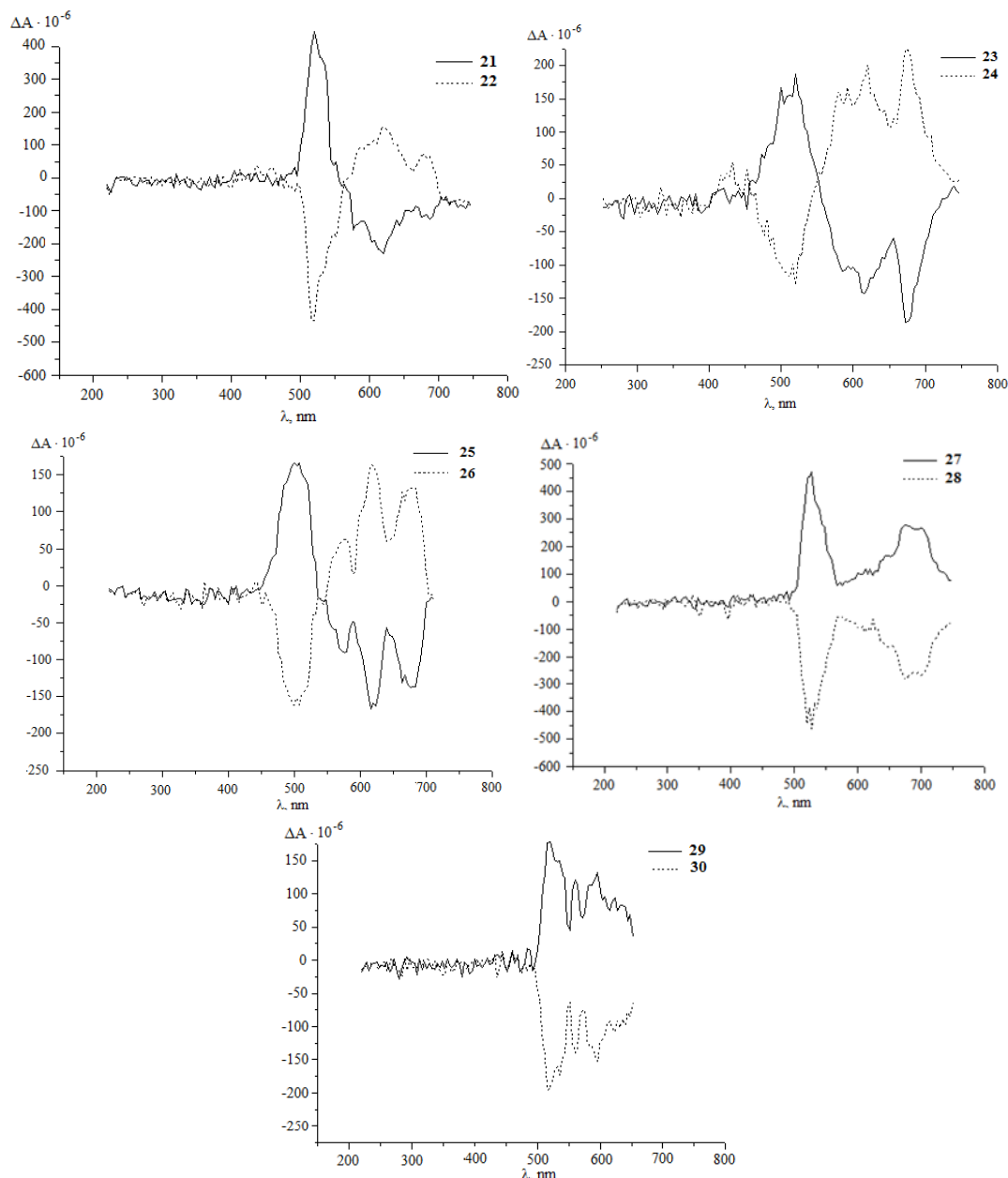
R = Me (21, 22, 31, 32), *i*-Bu (23, 24, 33, 34), (CH<sub>2</sub>)<sub>2</sub>SMe (25, 26, 35, 36)



**Scheme 5.** Catalytic cycloaddition of optically active diazoketones to C<sub>60</sub>-fullerene.

It was established that under the developed conditions (80°C, 1 h, chlorobenzene) C<sub>60</sub> interacts with diazoketones of the indicated amino acids (molar ratio 1:5) under the action of 20 mol.% Pd(acac)<sub>2</sub>·2PPh<sub>3</sub>·4Et<sub>3</sub>Al, selectively forming the corresponding methanofullerenes 21–30 with yields of 30–77%. Unfortunately, all attempts to measure the optical angles

of rotation of the polarization plane of synthesized methanofullerenes with protected amino groups were unsuccessful. Therefore, for a more reliable proof of the stereochemistry of optically active methanofullerenes, we turned to the circular dichroism (CD) method [30,31]. As expected, in the CD spectra for the synthesized enantiomers **21–30**, a mirror image of the Cotton effects (EC) was obtained.



**Figure 1.** CD spectra of methanofullerenes **21–30** in chloroform with  $c = 1.0$  g/L.

Using the derivatizing shift reagent (tris [3-(heptafluorobutyryl)-L-camphorato]europium (III)), using the example of compound **21**, we established a high enantiomeric purity (more than 98%).

Deprotection of functional groups in methanofullerenes **21–30** with  $\text{CF}_3\text{CO}_2\text{H}$  leads to the formation of cycloadducts **31–40** in the form of a solid powder, hardly soluble in traditional solvents for fullerenes and its derivatives (toluene, chlorobenzene, 1,2 dichlorobenzene, chloroform, carbon disulfide). In the case of compounds **31–40**, we failed to record the CD spectra of their solutions in pyridine, but the saponification of the amino

group associated with the chiral center made it possible to measure the optical rotation angles of the polarization plane of these methanofullerenes.

The development and implementation of new highly effective drugs is one of the priority areas of modern medicine and pharmacology. In connection with the foregoing, within the framework of this work, antioxidant activity was studied for adducts **2** and **19**, as well as antitumor and anti-inflammatory activity for derivatives **3**, **7**, and **20**.

### 3. Conclusions

Thus, based on the results obtained, it can be concluded that the hybrid molecules synthesized by us based on C<sub>60</sub>-fullerene and pharmacologically significant compounds are of exceptional interest for the development of a new generation of targeted drugs.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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