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Hybrid Molecules Based on Fullerene C_{60} and Spiropyrans as a Promising Approach to the Creation of Anticancer Drugs †

Artur A. Khuzin *, Liliya L. Khuzina, Airat R. Tuktarov and Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis of RAS, 450075 Ufa, Russia; khuzinall@mail.ru (L.L.K.); tuktarovar@gmail.com (A.R.T.); dzhemilev@anrb.ru (U.M.D.)

* Correspondence: artur.khuzin@gmail.com

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Abstract: In this work, we present a novel spiropyran–containing photochromic pyrrolidinofullerene as a promising agent for the photodynamic therapy of cancer.

Keywords: [60]fullerene; spiropyrane; merocyanine; Prato reaction; pyrrolidinofullerene; photochromism; cytotoxicity; antitumor activity

1. Introduction

Cancer is one of the leading causes of mortality among the working–age population around the world. To date, a huge number of chemotherapeutic drugs have beenused to treat oncological diseases, but most of the known and widely used anticancer drugs in medical practice are extremely toxic and non–selective. One of the possible approaches to solving this problem is the use of photoactivated molecules, which, under the action of light, can isomerize and pass from an inactive form to an active one in certain targets.

Currently, the literature describes a wide range of different classes of compounds that exhibit antitumor activity under the influence of UV light [1–3]: dithienylethenes [4], fulgimides [4], azobenzene [5], etc. [6–9].

The cytotoxicity of spiropyrans and their photoinduced merocyanine forms is poorly studied due to the limited number of studies and therather narrow range of photochromic molecules, which does not allow us to revealthe pattern of the structure–cytotoxic activity. Therefore, to date, the only successful application of photoswitching of the cytotoxicity of spirophotochromes in relation to cancer cells is the work [10], devoted to the synthesis of water–soluble spiropyran, which penetrates into Hek293 cells without showing a cytotoxic effect, as long as under the influence of thermostable UV light, the form of spiropyran is not isomerized to merocyanine.

Due to their structural features, spiropyrans penetrate poorly through cell membranes. Taking this into account, we assumed that the chemical binding of spiropyrans with fullerenes can contribute not only to the better penetration of a new hybrid molecule into a cancer cell, but also to an increase in cytotoxicity due to the unique transport properties of the original molecule of the carbon cluster.

In order to confirm the proposed idea, in this work, we carried out the synthesis of previously undescribed pyrrolidinofullerenes containing spiropyran addends.

2. Results and Discussion

As the main method for the preparation of pyrrolidinofullerenes, we chose the Prato reaction based on 1,3–dipolar cycloaddition to the carbon cluster of azomethine ylides generated in situ throughthe interaction of an aldehyde with sarcosine. Thus, the reaction of C_{60} fullerene with spiropyrans 1–3 in the presence of sarcosine leads to the formation of pyrrolidinofullerenes 4–6 with a yield of 56–62% (Figure 1). The choice of these starting

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monomers is due to several reasons. The presence of the NO_2-group, as shown in our previous work [11], promotes the manifestation of the photochromic properties of the new hybrid molecule. The use of alkyl bromide substituents of various lengths at the nitrogen atom of the indole fragment makes it possible to establish the effect of the arrangement of the ammonium group in the hybrid molecule on the water–soluble properties of the latter.

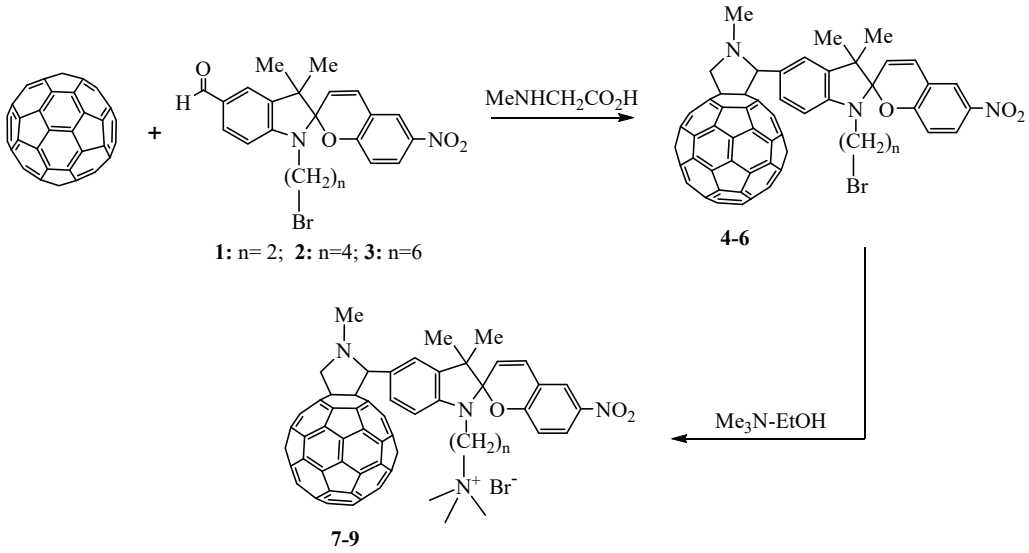

Figure 1. Synthesis of pyrrolidinofullerenes containing spiropyrane moieties.

At present, physicochemical studies of the photochromic properties of new hybrid molecules are being carried out in order to identify the most promising samples for the subsequent study of their cytotoxic activity.

3. Materials and Methods

All reactions were performed under an argon atmosphere and in anhydrous solvent. The solvents and reagents were dried or refined according to the literature procedures. Commercially available C_{60} fullerene (99.5% pure, Sigma–Aldrich) was used. The reaction products were analyzed on a HPLC chromatograph Shimadzu SPD–20A (Japan). The 1H and 13C NMR spectra were run on a Bruker Avance-500 spectrometer. The mass spectra were obtained on an UltraFlex III TOF/TOF (Bruker Daltonik GmbH, Bremen, Germany) operating in linear (TOF) and reflection (TOF/TOF) positive and negative ion modes.

Procedure for the synthesis of pyrrolidinofullerenes 4–6.

To a solution of 0.1 g (0.139 mmol) C_{60} in 15 mL chlorobenzene, 0.025 g (0.278 mmol) sarcosine and 0.695 mmol corresponding spiropyran aldehyde 1–3 were added. The resulting mixture was heated for two hours at 100–110 °C. The reaction products 4–6 and the starting fullerene C_{60} were separated usingthe semi-preparative HPLC, and the eluent was toluene.

Procedure for the synthesis of pyrrolidinofullerenes 7–9.

Trimethylamine–EtOH solution (0.5 mL, 35% Et_3N in EtOH) was added to a flask containing compounds 4–6 (50 mg, 0.04 mmol) in 5 mL toluene, and the solution was stirred at rt for 24 h in darkness. The formed precipitate was collected by filtration and washed with EtOH (90% yield).

4. Conclusions

Under the conditions of the Prato reaction, the synthesis of new pyrrolidinofullerenes containing spiropyran addends, potentially possessing light–regulated cytotoxic activity, was carried out.

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