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Synthesis of a Hybrid Molecule Based on 5Z,9Z-Eicosa-5,9-dienoic Acid and 1-Aminoadamantane and Study of Cytotoxic Activity †

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Abstract: One of the first adamantane derivatives used in medicine was amantadine (1-aminoadamantane), which showed good activity against the influenza virus. The introduction of an adamantane fragment into the structures of known drugs leads to an increase in lipophilicity and a noticeable improvement in pharmacological properties. Many adamantane derivatives have a wide range of biological activity, including antiviral, antidiabetic, antibacterial, antimalarial, anticancer, and anti-inflammatory properties. A hybrid molecule based on 5Z,9Z-eicosa-5,9-dienoic acid and 1-aminoadamantane was synthesized in high yield. Ti-catalyzed cross-cyclomagnesiation reaction of 2-(hepta-5,6-dien-1-yloxy)tetrahydro-2H-pyran and trideca-1,2-diene yielded dialkylidene-magnesacyclopentane, the hydrolysis of which led to 2-(((5Z,9Z)-eicosa-5,9-dien-1-yl)oxy)tetrahydro-2H-pyran. Oxidation of the resulting diene ester yielded (5Z,9Z)-eicosa-5,9-dienoic acid. The reaction of 1-aminoadamantane with dienoic acid was carried out in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl) and catalytic amounts of N,N-4-dimethylaminopyridine (DMAP) to obtain (5Z,9Z)-N-(adamantan-1-yl)eicosa-5,9-dienamide. The synthesized amide was tested for the viability of human tumor cells using the example of HEK293, Jurkat and K562 tumor lines. The drugs known as inhibitors of topoisomerase I and II, camptothecin and etoposide, were used as controls. Our data show that the synthesized hybrid molecule based on (5Z,9Z)-eicosa-5,9-dienoic acid and 1-aminoadamantane is a promising inducer of apoptosis in tumor cells.

Keywords: 5Z,9Z-eicosa-5,9-dienoic acid; cytotoxic activity; hybrid molecule

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1. Introduction

Adamantane derivatives are used as drugs with a wide range of biological activities, the most important of which are antiviral, antidiabetic, antimicrobial, anti-inflammatory and antiproliferative. Amantadine and memantine are well-known drugs used to treat neurodegenerative disorders [1–3].

The introduction of an adamantane fragment into the structures of known drugs increases their lipophilicity and improves their pharmacological properties. The lipophilicity of the adamantane core allows for interaction with biological membranes and hydrophobic regions of protein molecules that are part of the receptor structure [4].

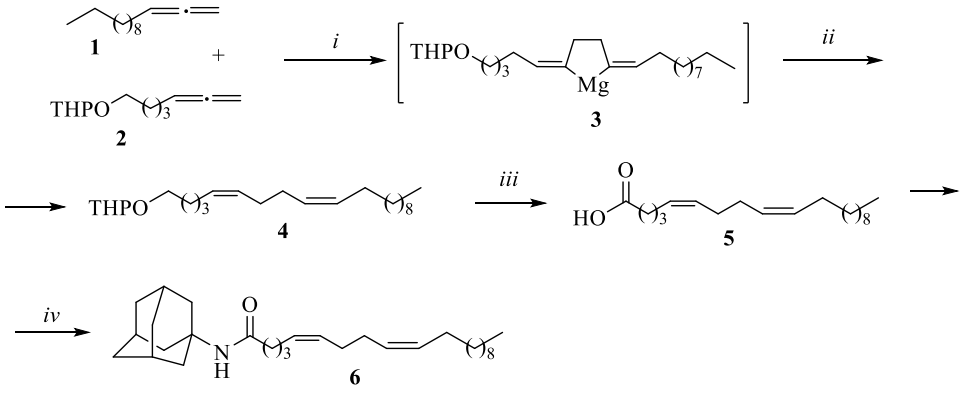
To date, a large number of studies have been published related to the search for effective antitumor drugs. Thus, in work [5], 5-adamantylthiadiazole derivatives were obtained and their antiproliferative activity in vitro was studied against cancer cells (MCF-

7, HepG-2 and A549). In [6], hybrid molecules containing adamantane and monoterpenoid residues linked via 1,2,4-triazole or 1,3,4-thiadiazole linkers were synthesized and tested against tyrosyl DNA phosphodiesterase 1 (Tdp1). Interesting results were obtained by a group of researchers in [7], where high antiproliferative activity in vitro of adamantane-linked thiazoles was demonstrated against five human tumor cell lines (PC-3, HCT-116, HepG-2, HeLa and MCF-7).

The development of new potential antitumor drugs is an important task, therefore we synthesized a hybrid molecule containing an adamantane fragment based on (5Z,9Z)-eicosa-5,9-dienoic acid, which, as shown in studies [8–14], has high inhibitory activity against topoisomerases I (hTop1) and II (hTop2α) in vitro.

2. Results and Discussion

Ti-catalyzed cross-cyclomagnesiation reaction of trideca-1,2-diene **1** and 2-(hepta-5,6-dien-1-yloxy)tetrahydro-2H-pyran **2** afforded dialkylidenemagnesacyclopentane **3**, the hydrolysis of which led to 2-(((5Z,9Z)-eicosa-5,9-dien-1-yl)oxy)tetrahydro-2H-pyran **4**. Oxidation of the resulting diene ester **4** with Jones reagent afforded (5Z,9Z)-eicosa-5,9-dienoic acid **5**. The reaction of 1-aminoadamantane with dienoic acid was carried out in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl) and catalytic amounts of N,N-4-dimethylaminopyridine (DMAP) to give (5Z,9Z)-N-(adamantan-1-yl)eicosa-5,9-dienamide (Scheme 1).



Reagents and reaction conditions: *i.* Cp_2TiCl_2 (5 mol.%), EtMgBr (2 eq.), Mg (2 eq.), Et_2O, 20-22 °C, 10 h; *ii.* HCl 5%, 72-86%; *iii.* Jones reagent; *iv.* 1-aminoadamantane, DMAP, EDC, CH_2Cl_2, 2 h, 0 °C.

Scheme 1. Synthesis of a hybrid compound based on (5Z,9Z)-eicosa-5,9-dienoic acid and 1-aminoadamantane.

The synthesized amide 6 was tested for viability of human tumor cells using the example of tumor lines HEK293, Jurkat and K562. The drugs known as inhibitors of topoisomerase I and II, camptothecin and etoposide, were used as controls. Our data show that the synthesized hybrid molecule based on (5Z,9Z)-eicosa-5,9-dienoic acid and 1-aminoadamantane is a promising inducer of apoptosis in tumor cells (Table 1).

Table 1. Cytotoxicity of amide **6** towards tumor cells, IC_{50} (μM) ± SE.

Compound	IC_{50} (μM) HeLa	IC_{50} (μM) Jurcat	IC_{50} (μM) K562	IC_{50} (μM) U937	IC_{50} (μM) Fibroblasts
6	2.5 ± 0.09	1.2 ± 0.018	1.21 ± 0.004	1.34 ± 0.002	7.44 ± 0.02
Camptotecin	25.17 ± 0.9	45.4 ± 1.6	33.6 ± 2.3	60.9 ± 1.6	82.9 ± 1.3
Etoposide	19.45 ± 0.8	48.6 ± 2.5	34.7 ± 1.5	74.5 ± 1.8	68.5 ± 1.4

3. Conclusions

Thus, we have synthesized a hybrid compound based on (5Z,9Z)-eicosa-5,9-dienoic acid and 1-aminoadamantane with a high yield, using at the key stage a new reaction of intermolecular cross-cyclomagnesiation of aliphatic and O-containing 1,2-dienes, catalyzed by Cp_2TiCl_2 (Dzhemilev reaction).

4. Experimental Part

Commercially available reagents (Sigma-Aldrich and Acros) were used. Reactions with organomagnesium compounds were carried out under dried argon atmosphere. 1,2-dienes was prepared according to the known procedure. Reaction products were analyzed on a Carlo Erba chromatograph (a Hewlett Packard Ultra-1 glass capillary column, 25 m × 0.2 mm, flame ionization detector, operating temperature 50–170 °C, carrier gas helium). TLC was performed on Silufol UV-254 plates. Elemental composition of compounds was determined using a Carlo Erba-1106 instrument. Mass spectra were obtained using a Bruker MALDI-TOF/TOF Autoflex III instrument. 1H and 13C NMR spectra were recorded on a Bruker Avance 400 spectrometer (100.62 MHz for 13C and 400.13 MHz for 1H). Chemical shifts of 1H and 13C nuclei (δ) are given relative to the residual signals of the deuterated solvent (δ 7.28 for protons and 77.2 for carbon nuclei). All experimental data obtained for compounds **4** and **5** are in good agreement with the previously described 13C, 1H NMR spectral parameters for structurally identical compounds [8].

(5Z,9Z)-N-1-adamantyl-1-icosa-5,9-dienamide (6). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 6.6 Hz, 3H), 1.27–1.36 (m, 16H), 1.65–1.68 (m, 12H), 2.00–2.03 (m, 8H), 2.05–2.09 (m, 3H), 2.10–2.13 (m, 2H), 2.23 (t, *J* = 6.4 Hz, 2H), 5.33–5.42 (m, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 172.37, 130.50, 130.14, 129.24, 128.98, 51.75, 41.71, 37.85, 36.38, 31.92, 29.66, 29.58, 29.45, 29.36, 29.31, 29.21, 27.45, 27.34, 27.30, 26.61, 22.69, 14.13. MS (MALDI-TOF), *m*/*z*: 442 $[M]^+$. $C_{30}H_{51}NO$. Found (%): C 81.50; H 11.68**.** Calcd for $C_{30}H_{51}NO$ (%): C 81.57; H 11.64.

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