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Synthesis of Aromatic Macrodiolides and Study of Their Antitumor Activity In Vitro †

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Abstract: Based on (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid, previously undescribed polyether aromatic macrodiolides were synthesized in good yields (53–67%). The cytotoxicity of the resulting macrocyclic compounds in vitro against tumor Jurkat cells, K562 cells, conditionally normal Hek293 cell lines and normal fibroblasts was the assessment carried out. The ability of the most active macrodiolide to induce apoptosis toward Jurkat cells and influence the cell cycle was studied.

Keywords: 1,5-dienoic compounds; homo-cyclomagnesiation; Grignard reagents; macrodiolides; crown ether

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1. Introduction

Unsaturated fatty acids, due to their wide variety and outstanding biological activity, are considered by researchers as the basis for the creation of modern drugs. Recent studies conducted in various scientific centers have shown that fatty acids with bis-methylene-separated cis–cis double bonds in the structure exhibit antibacterial, antitumor, fungicidal and antimalarial activities [1–3].

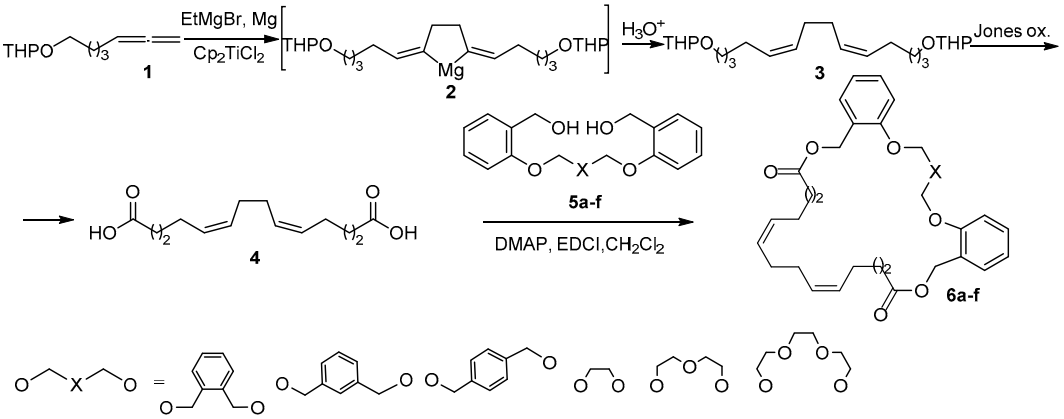
Previously, using the original cyclomagnesiation reaction, we developed effective methods for obtaining natural 5*Z*,9*Z*-dienoic fatty acids and their semi-synthetic analogs that exhibit antitumor properties. In the development of these studies, new biologically active hybrid molecules and macrocyclic compounds with a 1*Z*,5*Z*-diene fragment in the structure were synthesized [4–7].

This work presents the synthesis of previously undescribed multifunctional macrodiolides and provides preliminary results of an in vitro analysis of the antitumor activity of the resulting macrocyclic compounds.

2. Results and Discussion

To accomplish the tasks set for the synthesis of new polyfunctional macrodiolides, we have preliminarily carried out the synthesis of (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid **4**. Further, using the conditions at a molar ratio of reagents [diacid (4):diol (5):DMAP:EDCI = 1:1:0.5:2] with a strong dilution in dichloromethane ([5 mM]), new polyether unsaturated macrocyclic compounds **6a–f** were synthesized (Scheme 1).

With the aim of studying the polyether macrocycles for their antitumor activity and assessing their potential clinical applicability, we tested the products for their in vitro cytotoxicity and ability to influence the cell cycle and induce apoptosis (Table 1).



Scheme 1. Synthesis of aromatic polyether macrodiolides.

Table 1. Cytotoxic activities in vitro of synthesized cyclophanes **6a**–**f** measured on cell cultures (Jurkat, K562, Hek293 and normal fibroblasts) (μM).

Comp.	Jurkat (CC_{50}, μM) *	K562 (CC_{50}, μM) *	Hek293 (CC_{50}, μM) *	Fibrobl. (CC_{50}, μM) *	Selectivity Index	$CC50_{max}$/ $CC50_{min}$
6a	0.21 ± 0.02	0.16 ± 0.03	1.91 ± 0.21	2.98 ± 0.31	0.21–2.98	14.19
6b	0.17 ± 0.02	0.22 ± 0.02	1.86 ± 0.19	2.69 ± 0.26	0.17–2.69	15.82
6c	0.67 ± 0.07	0.41 ± 0.04	2.84 ± 0.28	3.72 ± 0.36	0.41–3.72	9.07
6d	2.12 ± 0.22	2.49 ± 0.24	9.07 ± 0.91	10.11 ± 1.01	2.02–10.11	5.00
6e	2.49 ± 0.24	3.02 ± 0.31	9.51 ± 0.93	11.59 ± 1.19	2.44–11.59	4.75
6f	2.81 ± 0.29	3.18 ± 0.30	9.28 ± 0.93	11.24 ± 1.26	2.74–11.24	4.10
Staurosporin	1.72 ± 0.15	4.35 ± 0.85	8.16 ± 0.88	18.08 ± 2.12	1.72–18.08	10.51

* Data are presented as the mean_SEM calculated from results of at least three independent experiments.

It was shown that macrodiolides **6a**,**b** exhibit the most pronounced cytotoxicity, while the introduction of one, two or three ethylene glycol fragments into the macrodiolide molecules instead of the central benzene fragment in the aromatic diol leads to a significant decrease in the cytotoxicity of the macrodiolides (**6d**–**f**) (Table 1).

To conduct further studies on the Jurkat cell lines of apoptosis-inducing activity and the ability to influence the cell cycle, the most active macrocyclic compounds **6a**–**c** were selected. As a result, it was established that the synthesized compounds are inducers of apoptosis and help slow down the process of cell division due to a block at the G1/S checkpoint.

3. Materials and Methods

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^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 spectrometer. The mass spectra were obtained using an ultraflex III TOF/TOF (Bruker Daltonik GmbH, Bremen, Germany). The macrocyclic compounds were synthesized similarly according to the procedure described in the literature [7]. Studies of antitumor activity (induction of apoptosis tests, cell cycle analysis) were carried out following the known procedures [6].

(11*Z*,15*Z*)-8,9,10,13,14,17,18,19,28,33-decahydro-5*H*,22*H*-tribenzo[*c*,*g*,*k*][1,5,10,14]tetraoxacyclooctacosine-7,20-dione **(7a)**. White waxy solid; yield 54%. R_f = 0.55, hexane/EtOAc 5:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59–7.50 (m, 2H), 7.43–7.25 (m, 6H), 7.02–6.91 (m, 4H), 5.38–5.15 (m, 12H), 2.37–1.90 (m, 8H), 1.72–1.65 (m, 4H), 1.65–1.55 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.7, 156.9, 134.9, 131.0, 130.2, 129.9, 128.9, 128.4, 128.3, 124.6, 120.9, 111.9, 68.1, 61.9, 33.4, 27.3, 26.3, 24.6. ESI-MS: calcd. for $C_{36}H_{40}O_6$ + Na^+ $[M + Na]^+$ 591.2717; found 591.2731.

(14*Z*,18*Z*)-2,6,9,24-tetraoxa-1,7(1,2),4(1,3)-tribenzenacyclopentacosaphane-14,18-diene-10, 23-dione **(7b)**. White waxy solid; yield 58%. R_f = 0.54, hexane/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.24 (m, 8H), 7.03–6.88 (m, 4H), 5.48–4.94 (m, 12H), 2.33 (t, *J* = 7.4 Hz, 4H), 2.15–1.86 (m, 8H), 1.74–1.59 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 156.6, 137.4, 130.2, 129.9, 129.6, 128.9, 128.8, 126.5, 125.6, 124.8, 120.8, 111.9, 69.8, 61.7, 33.7, 27.2, 26.6, 24.9. ESI-MS: calcd. for $C_{36}H_{40}O_6 + NH_4^+$ $[M + NH_4]^+$ 586.3163; found 586.3187.

(14*Z*,18*Z*)-2,6,9,24-tetraoxa-1,7(1,2),4(1,4)-tribenzenacyclopentacosaphane-14,18-diene-10, 23-dione **(7c)**. White waxy solid; yield 67%. R_f = 0.54, hexane/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 4H), 7.42–7.21 (m, 4H), 7.00 (t, *J* = 7.4 Hz, 4H), 5.43–5.08 (m, 12H), 2.42–2.27 (m, 4H), 2.15–1.92 (m, 8H), 1.76–1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 157.1, 136.6, 130.9, 130.2, 129.9, 129.0, 127.3, 127.3, 124.7, 120.8, 111.9, 69.7, 62.2, 33.6, 27.3, 26.4, 24.8.ESI-MS: calcd. for $C_{36}H_{40}O_6 + Na^+$ $[M + Na]^+$ 591.2717; found 591.2694

(11*Z*,15*Z*)-8,9,10,13,14,17,18,19,28,29-decahydro-5*H*,22*H*-dibenzo[*e*,*y*][1,4,8,23]tetraoxacyclo hexacosine-7,20-dione **(7d)**. White waxy solid; yield 53%. R_f = 0.57, hexane/EtOAc 3:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 13.6, 7.4 Hz, 4H), 7.03–6.93 (m, 4H), 5.49–5.27 (m, 4H), 5.20 (d, *J* = 9.5 Hz, 4H), 4.38 (s, 4H), 2.36–2.26 (m, 4H), 2.13–1.94 (m, 8H), 1.72–1.62 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 156.7, 130.2, 130.1, 129.6, 129.1, 125.0, 121.0, 111.8, 66.9, 61.5, 33.4, 27.5, 26.4, 24.8. ESI-MS: calcd. for $C_{30}H_{36}O_6 + Na^+$ $[M + Na]^+$ 515.2404; found 515.2391.

(11*Z*,15*Z*)-8,9,10,13,14,17,18,19,28,29,31,32-dodecahydro-5*H*,22*H*-dibenzo[b_1,*h*][1,4,7,11,26] pentaoxacyclononacosine-7,20-dione **(7e)**. White waxy solid; yield 60%. R_f = 0.49, hexane/EtOAc 3:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 4H), 7.03–6.85 (m, 4H), 5.47–5.27 (m, 4H), 5.19 (s, 4H), 4.22–4.10 (m, 4H), 3.96 (t, *J* = 4.6 Hz, 4H), 2.33 (t, *J* = 7.2 Hz, 4H), 2.18–1.87 (m, 8H), 1.77–1.59 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.5, 157.1, 130.5, 130.3, 129.8, 129.0, 124.8, 120.8, 111.9, 70.1, 68.3, 61.8, 33.6, 27.4, 26.4, 24.8. ESI-MS: calcd. for $C_{32}H_{41}O_6 + H^+$ $[M + H]^+$ 537.2847; found 537.2858

(11*Z*,15*Z*)-8,9,10,13,14,17,18,19,28,29,31,32,34,35-tetradecahydro-5*H*,22*H*-dibenzo[e_1,*k*][1,4,7, 10,14,29]hexaoxacyclodotriacontine-7,20-dione **(7f)**. White waxy solid; yield 67%. R_f = 0.38, hexane/EtOAc 3:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 16.2, 6.8 Hz, 4H), 7.01–6.87 (m, 4H), 5.45–5.29 (m, 4H), 5.19 (d, *J* = 6.1 Hz, 4H), 4.17 (t, *J* = 4.6 Hz, 4H), 3.89 (t, *J* = 4.7 Hz, 4H), 3.77 (s, 4H), 2.40–2.28 (m, 4H), 2.15–1.96 (m, 8H), 1.77–1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$)): δ = 173.5, 157.0, 130.4, 130.2, 129.7, 129.0, 124.6, 120.7, 111.7, 71.1, 69.8, 68.1, 61.8, 33.6, 27.3, 26.5, 24.9. ESI-MS: calcd. for $C_{34}H_{44}O_8 + Na^+$ $[M + Na]^+$ 603.2928; found 603.2943.

4. Conclusions

As a result of the research, the synthesis of polyether aromatic macrodiolides was carried out in good yields for the first time. Biological studies have shown that the synthesized macrocycles have cytotoxicity against tumor cell lines, are capable of slowing down the cell cycle and can act as inducers of apoptosis.

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