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Proceeding Paper

A New Hybrid Molecules Based on (5*Z*,9*Z*)-icosa-5,9-dienoic Acid and Monocarbonyl Derivatives of Curcuminoids †

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Abstract: Efficient methods for the synthesis of previously undescribed hybrid compounds based on monocarbonyl derivatives of curcumin and 5*Z*,9*Z*-dienoic acid with yields of 58–66% was presented. The key monomer, (5*Z*,9*Z*)-icosa-5,9-dienoic acid was prepared using the stereoselective cross-cyclomagnesiation reaction of aliphatic and oxygen-containing 1,2-dienes catalyzed by Cp_2TiCl_2.

Keywords: 1,5-dienoic compounds; cross-cyclomagnesiation; Grignard reagents; fatty acids; curcuminoids

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1. Introduction

Over the past years, a strategy has been actively developed for obtaining molecular hybrids containing pharmacophore groups of known biologically active compounds in the structure. The rationale for this approach is based on the supposed synergistic interaction of two pharmacologically active components with the intended target, which can significantly increase the effectiveness of the compounds obtained [1,2].

It is believed that the use of hybrid molecules minimizes the risk of interactions between different drugs when used together, and each component of the hybrid is able to balance the side effects of the other and avoid potential drug resistance [3–7].

Since ancient times, curcumin has been of great interest among researchers, exhibiting a variety of pharmacological activities. However, high metabolic instability, poor absorption and bioavailability of natural curcumin are a deterrent to active use in pharmacology and medicinal chemistry. In this regard, new synthetic analogs are being developed, for example, by changing the number of carbon atoms in the middle linker chain, monocarbonyl derivatives of curcuminoids have been obtained, which exhibit high antitumor and antibacterial properties, while having low toxicity and greater bioavailability compared to curcumin [8–12].

A large number of hybrid compounds based on curcuminoids have been synthesized, which show high cytotoxic, neuroprotective, antibacterial, antiviral activities in vitro and in vivo, while maintaining low toxicity. It should be noted that the activity of hybrid compounds is much higher than the activity of the original derivatives. Moreover, this approach allows to improve the bioavailability of compounds and transport through the membranes of cell organelles, as well as to protect active substances from enzymatic degradation [13–18].

It is known that 5*Z*,9*Z*-dienoic acids belonging to the class of bis-methylene-interrupted fatty acids exhibit antimalarial, antimicrobial, antibacterial and antitumor activities [19–22].

A low-step stereoselective method for the preparation of natural and synthetic 5*Z*,9*Z*-dienoic fatty acids has recently been developed [23]. The studies performed have shown that the unsaturated acids synthesized by us and new derivatives obtained on their basis demonstrate antitumor activity in vitro against a number of tumor cell lines [24–28].

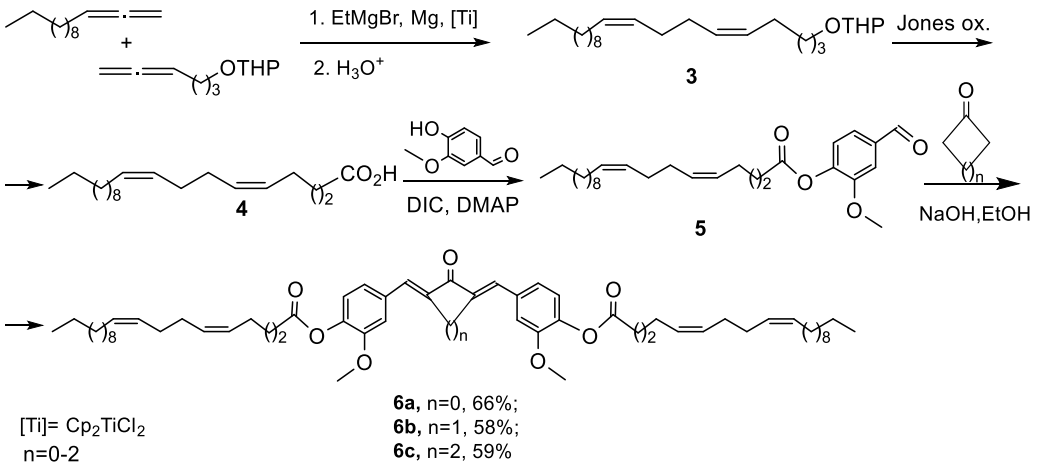
In the development of our research, taking into account the above, in the framework of this work, we decided to implement the idea of synthesizing new hybrid molecules based on biologically active (5*Z*,9*Z*)-icosa-5,9-dienoic acid and curcumin monocarbonyl derivatives.

2. Results and Discussion

The synthetic strategy for obtaining the target hybrid molecules includes preliminary synthesis of (5*Z*,9*Z*)-icosa-5,9-dienoic acid **4** based on the use of original Ti-catalyzed intermolecular cross-cyclomagnesiation of aliphatic and O-containing 1,2-dienes with Grignard reagents.

Thus, the reaction of 1,2-tridecadiene **1** and 2-(5,6-heptadien-1-yloxy)tetrahydropyran **2** with EtMgBr in the presence of magnesium metal and the Cp_2TiCl_2 catalyst and subsequent acid hydrolysis received 2-(((5*Z*,9*Z*)-icosa-5,9-dien-1-yl)oxy)tetrahydro-2*H*-pyran **3**. Jones oxidation of tetrahydropyran ester **3** leads to the formation of (5*Z*,9*Z*)-icosa-5,9-dienoic acid **4** (Scheme 1).

The reaction of intermolecular esterification of vanillin with acid **4** according to Steglich using N,N′-diisopropylcarbodiimide (DIC) and 4-(Dimethylamino)pyridine (DMAP) gave conjugate **5**. At the final stage, to Claisen-Schmidt condensation of ester **5** in an alkaline medium with various ketones (acetone, cyclopentanone, cyclohexanone), the target hybrid compounds **6** were synthesized (Scheme 1).



Scheme 1. Synthesis of hybrid molecules.

The structure of the resulting compounds **6** was established by combined experimental methods, including one-dimensional (^1H, ^{13}C) and two-dimensional heteronuclear correlation NMR experiments (HSQC, HMBC), as well as mass spectrometry (HRMS).

3. Materials and Methods

Reactions were carried out in an inert atmosphere. Solvents were dried (diethyl ether over Na, dichloromethane over P_2O_5) and freshly distilled before use. Commercial 5-hexyn-1-ol and Cp_2TiCl_2 (Aldrich) were used without preliminary purification. Individuality and purity of the synthesized compounds were controlled using TLC on Silufol UV-

254 plates; anisic aldehyde in acetic acid was used as a developer. One- (^{1}H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on Bruker Avance-400 ((400.13 MHz (^{1}H), 100.62 MHz (^{13}C)) instruments. 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. S_8 and DCTB (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenyliden]malononitrile) were used as the matrix.

General procedure of Steglich esterification.

Vanillin (4.2 mmol, 1 eq.) in an argon atmosphere dissolved in dry methylene chloride (50 mL), then added (5*Z*,9*Z*)-icosa-5,9-dienoic acid **4** (5 mmol, 1.2 eq.) and DMAP (5 mmol, 1.2 eq.). The reaction mixture was cooled to 0 °C and for 30 min. dropwise DIC (4.2 mmol, 1 eq.) dissolved in methylene chloride (10 mL) was added. The resulting reaction mass was stirred at room temperature (8 h), the reaction was controlled using TLC. The resulting precipitate was filtered, the solvent was evaporated and the remaining product was purified by column chromatography (SiO_2, eluent PE:EA = 8:1).

4-formyl-2-methoxyphenyl-(5*Z*,9*Z*)-icosa-5,9-dienoate (5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.90 (s, 1H, COH), 7.45 (dd, *J* = 11.1, 3.0 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 5.44–5.38 (m, 4H, CH=CH), 3.86 (s, 3H, OCH_3), 2.58 (t, 2H, CH_2-COO, *J* = 7.2 Hz), 2.11–2.03 (m, 8H, CH_2CH=), 1.73 (q, 2H, CH_2, *J* = 7.2 Hz), 1.37–1.27 (m, 16H, CH_2), 0.90 (t, 3H, CH_3, *J* = 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.0, 171.2, 152.0, 145.1, 135.1, 130.5, 130.6, 129.9, 129.7, 124.7, 123.4, 110.8, 56.0, 33.9, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 27.2, 27.2, 27.1, 24.9, 22.7, 14.1. HRMS (ESI-TOF), $[M + Na]^+$ calcd. for: $C_{28}H_{42}O_4Na$ 465.2975; found 465.2983. Yield 68%.

General procedure for the synthesis of hybrid molecules.

To conjugate **5** (10 mmol, 2 equiv.) dissolved in 10 mL of ethanol (96%) was added ketone (5 mmol, 1 equiv.) and stirred for 15 min at room temperature. Then, a solution of sodium hydroxide (0.4 g) in water (10 mL) was added dropwise and the reaction mixture was stirred for 48 h at room temperature. The progress of the reaction was monitored by TLC. At the end of the reaction water (20 mL) was added to the reaction mass and extracted with methylene chloride (3*50 mL). The organic layer was dried over $MgSO_4$, the product was isolated by column chromatography (SiO_2, eluent PE:EA = 4:1)

((1*E*,4*E*)-3-oxopenta-1,4-diene-1,5-diyl)bis(2-methoxy-4,1-phenylene) (5*Z*,5′*Z*,9*Z*,9′*Z*)-bis(icosa-5,9-dienoate) (6a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.61–7.56 (m, 2H), 7.47–7.38 (m, 4H), 7.18–7.04 (m, 4H), 5.46–5.36 (m, 8H, CH=CH), 3.87 (s, 6H, OCH_3), 2.58 (t, 4H, CH_2-COO, J = 7.2 Hz), 2.14–2.02 (m, 16H, CH_2CH=), 1.75–1.68 (m, 4H, CH_2), 1.38–1.26 (m, 32H, CH_2), 0.90 (t, 6H, CH_3, J =6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.9, 174.9, 151.7, 147.2, 130.2, 130.1, 129.9, 128.0, 127.9, 127.6, 124.8, 123.4, 114.4, 108.8, 56.1, 33.9, 31.5, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 27.2, 27.2, 27.1, 24.9, 22.6, 14.2. HRMS (ESI-TOF), $[M + Na]^+$ calcd. for: $C_{59}H_{86}O_7Na$ 929.6266, found 929.6271. Yield 66%.

((1*E*,1′*E*)-(2-oxocyclopentane-1,3-diylidene)bis(methanylylidene))bis(2-methoxy-4,1-phenylene) (5*Z*,5′*Z*,9*Z*,9′*Z*)-bis(icosa-5,9-dienoate) (6b)

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.65–7.58(m, 2H), 7.44–7.35 (m, 4H), 7.10–6.99 (m, 2H), 5.43–5.32 (m, 8H, CH=CH), 3.90 (s, 6H, OCH_3), 2.96–2.85 (m, 4H, CH_2), 2.62 (t, 4H, CH_2-COO, *J* = 7.1 Hz), 2.12–2.01 (m, 16H, CH_2CH=), 1.76–1.64 (m, 4H, CH_2), 1.36–1.18 (m, 32H, CH_2), 0.91 (t, 6H, CH_3, *J* = 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 195.4, 174.7, 151.8, 141.9, 134.8, 130.1, 130.0, 129.8, 128.4, 128.1, 126.2, 124.7, 115.4, 108.6, 56.4, 33.8, 31.6, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.8, 27.3, 27.2, 27.1, 24.9, 24.5, 22.6, 14.1. HRMS (ESI-TOF), $[M + Na]^+$ calcd. for: $C_{61}H_{88}O_7Na$ 955.6422, found 955.6434. Yield 58%.

((1*E*,1′*E*)-(2-oxocyclohexane-1,3-diylidene)bis(methanylylidene))bis(2-methoxy-4,1-phenylene) (5*Z*,5′*Z*,9*Z*,9′*Z*)-bis(icosa-5,9-dienoate)

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.64–7.57 (m, 2H), 7.43–7.35 (m, 4H), 7.11–7.01 (m, 2H), 5.44–5.32 (m, 8H, CH=CH), 3.89 (s, 6H, OCH_3), 2.89–2.78 (m, 4H, CH_2), 2.61 (t, 4H, CH_2-COO, *J* = 7.1 Hz), 2.12–2.01 (m, 16H, CH_2CH=), 1.86–1.64 (m, 6H, CH_2), 1.37–1.22 (m, 32H, CH_2), 0.91 (t, 6H, CH_3, *J* = 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 189.9, 174.9,

151.9, 139.8, 136.8, 130.1, 130.0, 129.8, 128.4, 127.5, 126.9, 124.4, 114.8, 108.2, 56.2, 33.9, 31.5, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 28.8, 28.4, 27.3, 27.2, 27.1, 24.9, 23.1, 22.6, 14.1. HRMS (ESI-TOF), $[M + Na]^+$ calcd. for: $C_{62}H_{90}O_7Na$ 969.6579, found 969.6568. Yield 59%.

4. Conclusions

As a result of the research, hybrid molecules based on biologically active monocarbonyl derivatives of curcumin and (5Z,9Z)-icosa-5,9-dienoic acid were synthesized for the first time. The resulting conjugates may be of potential interest as synthetic precursors in the development of drugs with antitumor activity.

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