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Original Article

SYNTHESIS OF 7-(2,3-EPOXYPROPOXY)COUMARIN DERIVATIVES AND EVALUATION OF THEIR RADICAL-SCAVENGING PROPERTIES BY EPR SPECTROSCOPY

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ABSTRACT

Coumarin derivatives are known for their broad biological activities, particularly their ability to influence oxidative stress pathways. In this work, a new series of 7-(2,3-epoxypropoxy)coumarin derivatives was synthesized and fully characterized by NMR and HRMS. The structural modification introduced a 3'-ethoxy-2'-hydroxypropoxy fragment, and the compounds were evaluated for their ability to modulate hydroxyl and methyl radical formation in the Fenton reaction using Electron Paramagnetic Resonance (EPR) spectroscopy. Comparative analysis revealed that derivative 1 and its precursor a (6-acetyl-4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one) exhibited the most pronounced radical-scavenging activity, demonstrating stronger antioxidant effects than their corresponding substrates. These findings highlight coumarin epoxide derivatives as promising scaffolds for redox-modulating agents, and confirm the utility of EPR as a sensitive tool for probing antioxidant potential.

KEYWORDS: coumarin, Electron Paramagnetic Resonance.

1. Introduction

Extensive research on coumarin derivatives has been carried out worldwide for many years. These studies have confirmed their significant role in the pharmacotherapy of various diseases, owing to their broad spectrum of biological activities [1, 2]. It has been established that the introduction of specific fragments into the coumarin molecule can alter its biological activity, and the presence of certain moieties within the structure may determine a range of pharmacological effects.

It is well established that coumarin derivatives containing a 2-hydroxypropyl fragment in their structure exhibit diverse biological activities. The 2-hydroxypropyl group alone is a common pharmacophore for most ß-blockers. Such derivatives with satisfactory activity can be obtained through an epoxide ring-opening reaction. A representative example of a drug containing this fragment is the indole derivative, pindolol (Figure 1), a non-selective ß-adrenolytic agent that acts on $ß_1$, $ß_2$, and $ß_3$ receptors. Moreover, the presence of the epoxide moiety in the penultimate step of the synthesis allows the introduction of an isopropylamine group into the structure, which in turn enables the desired biological activity [3]. Coumarin derivatives incorporating a 2-hydroxypropyl linker have been shown to possess a broad spectrum of scientifically documented biological properties. Reported examples of bioactive coumarins include compounds with antimicrobial activity [4—6], anticancer and antioxidant agents [4], antiparasitic compounds [7,8], cardiovascular agents [9—11], antihistamine compounds [12], α-glucosidase inhibitors [13], as well as anti-inflammatory and analgesic agents [14]. A literature review indicates that the topic is current and that in recent years many review articles and patent reports relevant to coumarin derivatives have been published, both in terms of structural studies, biological activity, and structure–activity analyses [15—18].

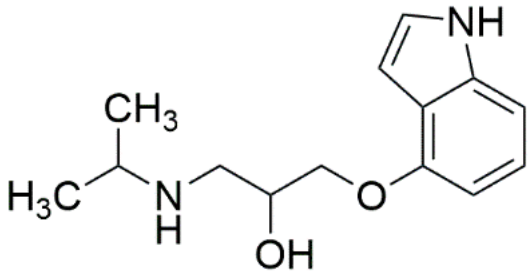


Fig. 1. Pindolol structure.

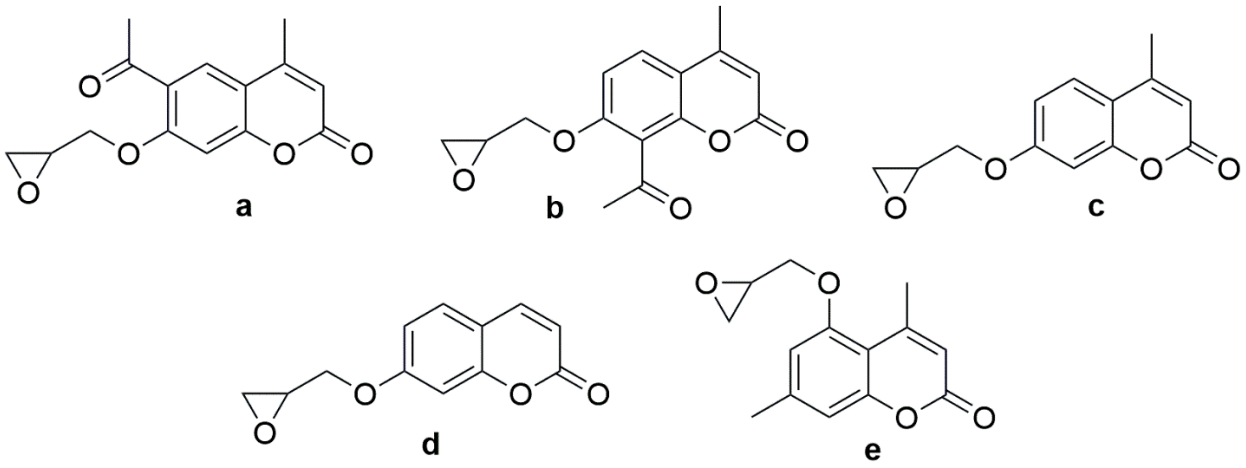


Fig. 2. The starting compounds' structures.

Based on data from scientific publications and previous research conducted at the Department of Organic and Physical Chemistry, Medical University of Warsaw [19], a ring-opening reaction of the epoxide moiety with ethanol was designed and carried out to obtain compounds with anticipated biological activity. A one-step synthesis on a millimolar scale was employed to produce a series of new derivatives by attempting the epoxide ring opening of coumarin derivatives using absolute ethanol. The substrates for this synthesis were 2,3-epoxycoumarins: 6-acetyl-4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one (a), 8-acetyl-4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one (b), 4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one (c), 7-(oxiran-2-ylmethoxy)-2H-chromen-2-one (d), and 4,7-dimethyl-5-(oxiran-2-ylmethoxy)-2H-chromen-2-one (e). The reactions were designed to yield (3′-ethoxy-2′-hydroxypropoxy) coumarin derivatives (Figure 2, Scheme 1).

2. Materials and Methods

All chemicals were purchased from major chemical suppliers (Merck, Aldrich, CHEMPUR or POCH) as high or the highest purity grade and used without further purification. Prefabricated silica gel sheets (Merck Kieselgel 60 F254) were used for TLC. Melting points were determined with a Digital Melting Point Apparatus 9001 and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded at 25 ºC with a Varian NMRS-300, and standard Varian software was employed. High-resolution mass spectra were recorded on a Quattro LCT (TOF). The TLC spots were detected under UV light at wavelengths of 254 and 365 nm. The ^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds are available in the Appendix.

2.1. General procedure for preparing compounds a—e

The starting compounds a—e (Figure 2) bearing the (oxiran-2-yl)methoxy group were prepared by the previously reported procedures [19—20].

2.2. General procedure for preparing compounds 1—5

The corresponding 2',3'-epoxypropoxycoumarin (a—e) (1 mmol) was dissolved in absolute ethanol (10 ml). The mixture was heated under reflux for 15 h (for compound 4), 18 h (for compounds 1 and 5), or 20 h (for compounds 2 and 3). The mixture was monitored by TLC on silica gel plates (eluent: $CHCl_3$: MeOH; volume ratio: 10:0.25). After completion of the reaction, the solvent was evaporated. The residue was purified by column chromatography (eluent $CHCl_3$). ^{1}H NMR and ^{13}C NMR spectra and atom numbering of all synthesized compounds are available in the Appendix.

6-Acetyl-7-(3'-ethoxy-2'-hydroxypropoxy)-4-methyl coumarin (1)

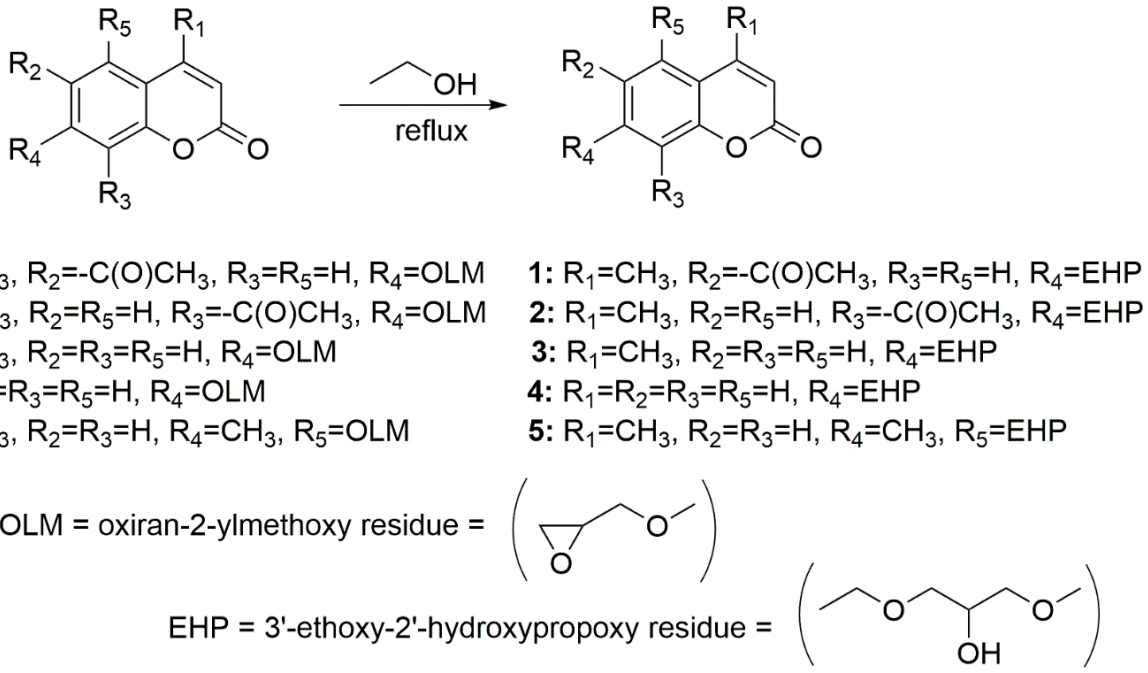
Creamy solid, mp 90-91 ºC, Rf=0.48, yield 31.7 %, ^{1}H NMR (300 MHz, CDCl3) δ ppm: 8.03 (t, J = 6 Hz, 1H, H-5), 6.90 (s, 1H, H-8), 6.21 (s, 1H, H-3), 4.23 (m, 3H, H-2', H-1'), 3.62 (m, 4H, H3', H4'), 2.72 (s, 3H, H-11), 2.46 (s, 3H, H-9), 1.26 (t, J = 6 Hz, 3H, H-5'); ^{13}C NMR (75 MHz, CDCl3) δ ppm: 197.8 (C-10), 161.0 (C-7), 160.5 (C-2), 157.7 (C-8a), 152.7 (C-4), 113.9 (C-5), 113.5 (C-6), 113.2 (C-3), 101.3 (C-4a), 100.9 (C-8), 71.3 (C-3'), 70.7 (C-1'), 69.7 (C-2'), 67.4 (C-4'), 32.3 (C-11), 31.9 (C-9), 19.0 (C-5'); TOF MS ES +: $[M + H]^{+}$calcd for $C_{17}H_{21}O_6$ 321.1332, found 321.1340.

8-Acetyl-7-(3'-ethoxy-2'-hydroxypropoxy)-4-methyl coumarin (2)

Creamy solid, mp 116-117 ºC, Rf=0.62, yield 15.2 %, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.59 (d, J = 9 Hz,1H, H-5), 6.96 (d, J = 6 Hz, ^{1}H, H-6), 6.21 (s, ^{1}H, H-3), 4.17 (m, 3H, H-1', H2'), 3.58 (m, 4H, H-4', H-3'), 2.65 (s, 3H, H-11), 2.43 (s, 3H, H-9), 1.24 (m, H-5'); ^{13}C NMR (75 MHz, CDCl3) δ ppm: 199.7 (C-10), 160.0 (C-2), 158.1 (C-7), 152.3 (C-8a), 151.1 (C-4), 127.2 (C-5), 119.9 (C-8), 113.3 (C-6), 113.1 (C-3), 109.5 (C-4a), 71.0 (C-3'), 69.0 (C-1'), 67.4 (C-2'), 67.2 (C-4'), 32.8 (C-11), 19.1 (C-9), 15.3 (C-5'); TOF MS ES +: $[M + H]^{+}$calcd for $C_{17}H_{21}O_6$ 321.1332, found 321.1341.

7-(3'-Ethoxy-2'-hydroxypropoxy)-4-methylcoumarin (3)

Creamy solid, mp 73-74 ºC, Rf=0.53, yield 35.5 %, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.54 (d, J = 9 Hz, 1H, H-5), 6.90 (m, 2H, H-6, H-8), 6.17 (s, 1H, H-3), 4.15 (m, 1H, H-1'), 4.08 (m, 2H, H-2'), 3.67 (m, 4H, H-3', H-4'), 2.42 (s, 3H, H-9), 1,.25 (t, J = 6 Hz, 3H, H-5'); ^{13}C NMR (75 MHz, CDCl3) δ ppm: 161.8 (C-2), 161.5 (C-7), 155.4 (C-8a), 152.7 (C-4), 125.8 (C-5), 114.1 (C-3), 112.7 (C-4a), 112.4 (C-6), 101.9 (C-8), 71.2 (C-3'), 69.7 (C-1'), 69.1 (C-2'), 67.3 (C-4'), 18.9 (C-9), 15.3 (C-5'); TOF MS ES +: $[M + H]^{+}$calcd for $C_{15}H_{19}O_5$ 279.1227, found 279.1230.



Scheme 1. Synthesis of compounds 1—5.

7-(3'-Ethoxy-2'-hydroxypropoxy)coumarin (4)

Oil, Rf=0.52, yield 33.3 %, ^{1}H NMR (300 MHz, CDCl3) δ ppm: 7.67 (d, J = 9 Hz, 1H, H-4), 7.39 (d, J = 6 Hz, 1H, H-5), 6.88 (m, 2H, H-6, H-8), 6.27 (d, J = 9 Hz, 1H, H-3), 4.18 (m, 1H, H-1), 4.08 (m, 2H, H-2'), 3.67 (m, 4H, H-3', H-4'), 1.25 (t, J = 6 Hz, 3H, H-5'); ^{13}C NMR (75 MHz, CDCl3) δ ppm: 162.0 (C-2), 161.4 (C-7), 156.0 (C-8a), 143.6 (C-4), 129.0 (C-5), 113.6 (C-3), 113.0 (C-6, C-8a), 101.9 (C-8), 71.2 (C-3'), 69.8 (C-1'), 69.1 (C-2'), 67.3 (C-4'), 15.3 (C-5'); TOF MS ES +: $[M + H]^+$calcd for $C_{14}H_{17}O_5$ 265.1070, found 265.1075.

5-(3'-Ethoxy-2'-hydroxypropoxy)-4,7-dimethyl coumarin (5)Creamy solid, mp 80-812 ºC, Rf=0.03, yield 17.7 %, ^{1}H NMR (300 MHz, CDCl3) δ ppm: 6.78 (s, 1H, H-6), 6.57 (s, 1H, H-8), 6.07 (s, 1H, H-3), 4.23 (m, 1H, H-1'), 4.10 (m, 2H, H-2'), 3.63 (m, 4H, H-3', H-4'), 2.36 (s, 1H, H-9), 2.41 (s, 1H, H-10), 1.26 (t, J = 7.5 Hz, 3H, H-5'); ^{13}C NMR (75 MHz, CDCl3) δ ppm: 161.1 (C-7), 157.0 (C-4), 155.5 (C-5), 154.1 (C-8a), 143.3 (C-7), 113.8 (C-4a), 110.8 (C-6), 108.5 (C-3), 108.3 (C-8), 71.6 (C-3'), 70.3 (C-1'), 69.1 (C-2'), 67.3 (C-4'), 24.9 (C-10), 22.2 (C-9), 15.3 (C-5'); TOF MS ES +: $[M + H]^+$calcd for $C_{16}H_{21}O_5$ 293.1385, found 293.1388.

2.3. Electron Paramagnetic Resonance

For the Fenton reaction inhibition studies, 20 µl of 5 mM $FeSO_4$ aqueous solution, 20 µl of 10 mM FDMPO (4-hydroxy-5,5-dimethyl-2-trifluoromethylpyrroline-1-oxide) spin trap aqueous solution, 20 µl of 10 mM studied compound solution in DMSO. and 20 µl of 20 mM hydrogen peroxide aqueous solution were mixed in an Eppendorf tube (1.5 ml). The time of addition of hydrogen peroxide was taken as the reaction start.

The sample was transferred to a 50 µl haematocrit capillary (Brand InterMark), and the EPR spectra were registered using the MS200 Miniscope benchtop X-band EPR spectrometer (Magnettech) equipped with the Espect+ multiharmonic analyzer accessory (Novilet). The first spectrum was registered after 2 minutes from the start of the reaction, then after 5 minutes of reaction time, and then every 5 minutes for up to 45 minutes. The parameters of EPR spectra registration were: central field 335 mT, field sweep 10 mT, modulation amplitude 500 µT, scan time 11 s, 2 scans. The experiments were performed in replicates only for the reference system.

EPR spectra simulations were performed using the EasySpin toolbox for Matlab.

3. Results and Discussion

The synthesis of the products proceeded in two stages. In the first step, the appropriate coumarins — 6-acetyl-7-hydroxy-4-methylcoumarin, 8-acetyl-7-hydroxy-4-methylcoumarin, 7-hydroxy-4-methylcoumarin, 7-hydroxycoumarin, or 4,7-dimethyl-5-hydroxycoumarin — and epichlorohydrin were heated in a flask in the presence of anhydrous potassium carbonate using either a microwave reactor or conventional heating. The reactions were monitored by thin-layer chromatography (TLC). Upon completion, inorganic salts were filtered off, the reaction mixture was evaporated to dryness using a rotary evaporator, and the products were purified by column chromatography [15, 16]. In the next step, the previously obtained epoxycoumarin derivatives **a**—**e** were reacted with absolute ethanol. The conducted syntheses required prolonged and gentle heating, along with constant monitoring, and each time, a significant amount of unreacted substrate remained in the reaction mixture. The final fraction collected from the column after the reaction was always an oily mixture of low-polarity byproducts. The opening of the epoxide ring by an alcohol is a well-known and well-documented process that proceeds via an SN2 mechanism. The reaction often occurs with inversion of configuration at the attacked carbon, and the resulting products have trans stereochemistry. It is also known that the opening of the epoxide ring by ethanol usually proceeds with moderate efficiency, and since no

catalyst was used under the reaction conditions, the obtained yields were relatively low (15.2—35.3%).

The analyses revealed that the obtained compounds had structures containing the 3'-ethoxy-2'-hydroxypropoxy moiety (Scheme 1). In the ^{1}H NMR spectra, a signal was observed around 3.5 ppm with an integration of approximately 4, along with an additional signal around 1.2 ppm with an integration of approximately 3. Conclusions were drawn about the presence of two methylene groups in proximity to oxygen, as well as a methyl group attached to an aliphatic chain. Additionally, the obtained MS spectra confirmed that the masses of the products were consistent with the expected values.

To estimate the redox-modulating properties of the investigated compounds (a—e and 1—5), we used X-band Electron Paramagnetic Resonance (EPR) spectroscopy to follow the generation of hydroxyl (•OH) and C-centered radicals in the Fenton reaction in the presence of DMSO. This approach allows for a sensitive, direct, and non-invasive quantification of radical species in situ, enabling differentiation between antioxidant and pro-oxidant activities based on the suppression or enhancement of radical signal intensities.

The Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$) is a well-established in vitro model of oxidative stress, generating highly reactive hydroxyl radicals. When DMSO is added to this system, •OH abstracts a hydrogen atom to form methyl radicals ($\bullet CH_3$), which are efficiently trapped by FDMPO (4-hydroxy-5,5-dimethyl-2-trifluoromethylpyrroline-1-oxide) to form the FDMPO/$\bullet CH_3$ adduct.

In the reference system (Fenton reaction in the presence of DMSO), a typical triplet of quartets signal from FDMPO spin adducts was observed. The signal is a superpositon of two spin adducts (FDMPO/$\bullet CH_3$ and FDMPO/•OH) with A_n = 1.42 mT and A_F = 0.19 mT, and A_n = 1.36 mT and A_f = 0.27 mT correspondingly (Figure 3). The same components were observed in all studied systems.

Figure 4 presents EPR kinetic curves showing the decay of total FDMPO radical adducts signal intensity over 45 minutes for five sets of compounds tested in a Fenton-DMSO system (Figure 4). Each plot includes a substrate compound (s-) and its corresponding modified derivative, allowing comparison of their antioxidant effects based on radical trapping efficiency.

Previously, it was shown that even small modifications of the coumarin derivatives could lead to distinctive radical scavenging properties [21—22]. Compounds 1—4 and their precursors a—d generally exhibited comparable antiradical activity in the Fenton-DMSO system, as shown by similar decay profiles of the EPR spin adduct signals. In contrast, compound 5 and its precursor e did not demonstrate any radical-scavenging properties, suggesting that substitution at the 5-position with methyl groups is less favorable for redox modulation. Notably, compound 1 displayed stronger antiradical activity than its precursor a. This enhancement can be attributed to the combined influence of the 6-acetyl substituent and the newly introduced 3'-ethoxy-2'-hydroxypropoxy fragment, which likely facilitates hydrogen atom donation and stabilizes radical intermediates more effectively than the unmodified epoxide precursor. These observations indicate that while the introduction of the hydroxypropoxy group alone does not universally improve radical scavenging, its effect can be amplified in specific substitution patterns, with the 6-acetyl group playing a decisive role.

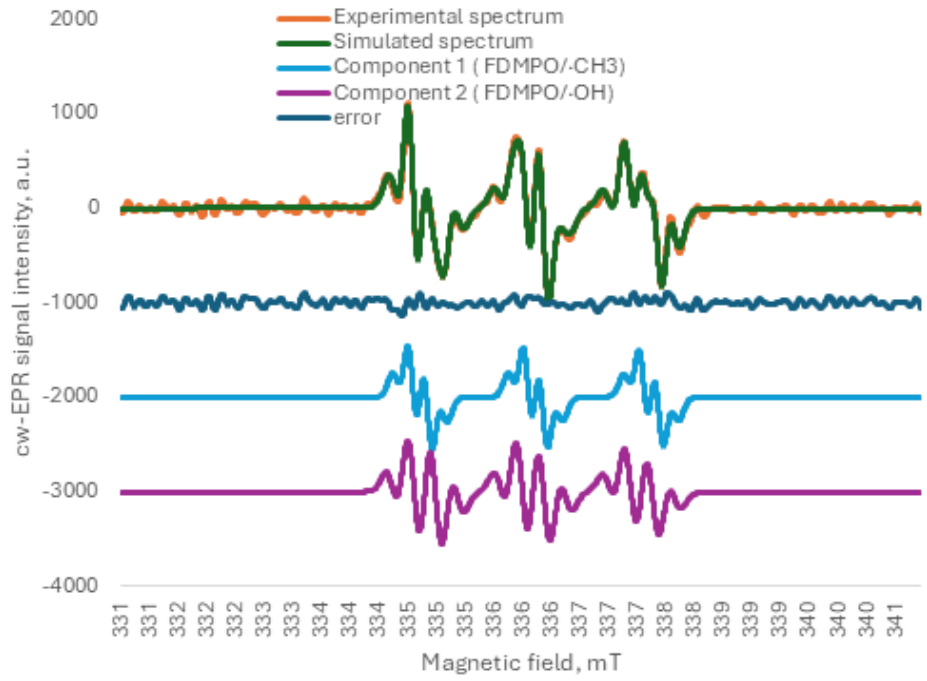


Fig. 3. Experimental spectrum, simulation, and individual components (FDMPO/$\bullet CH_3$ and FDMPO/•OH).

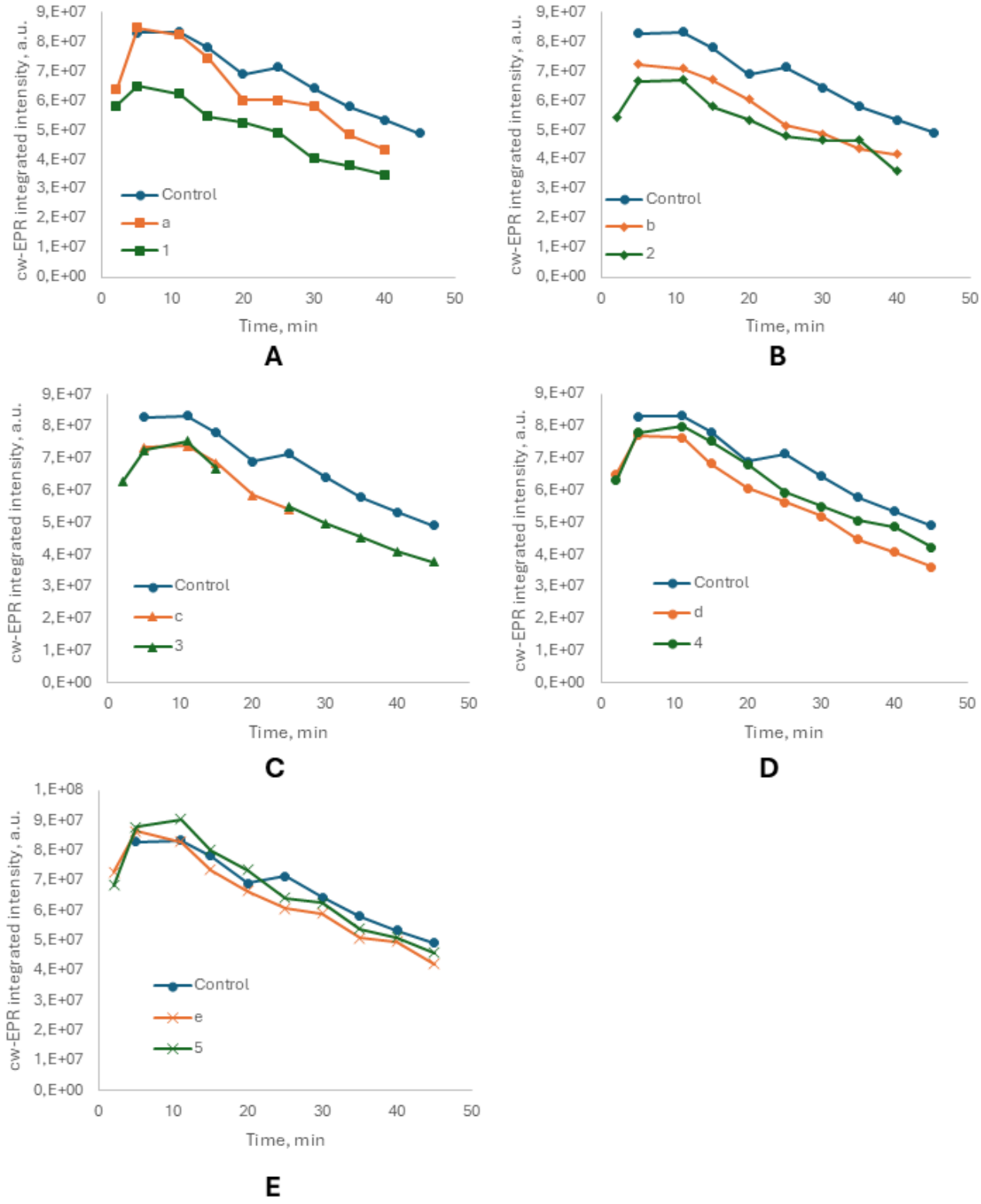


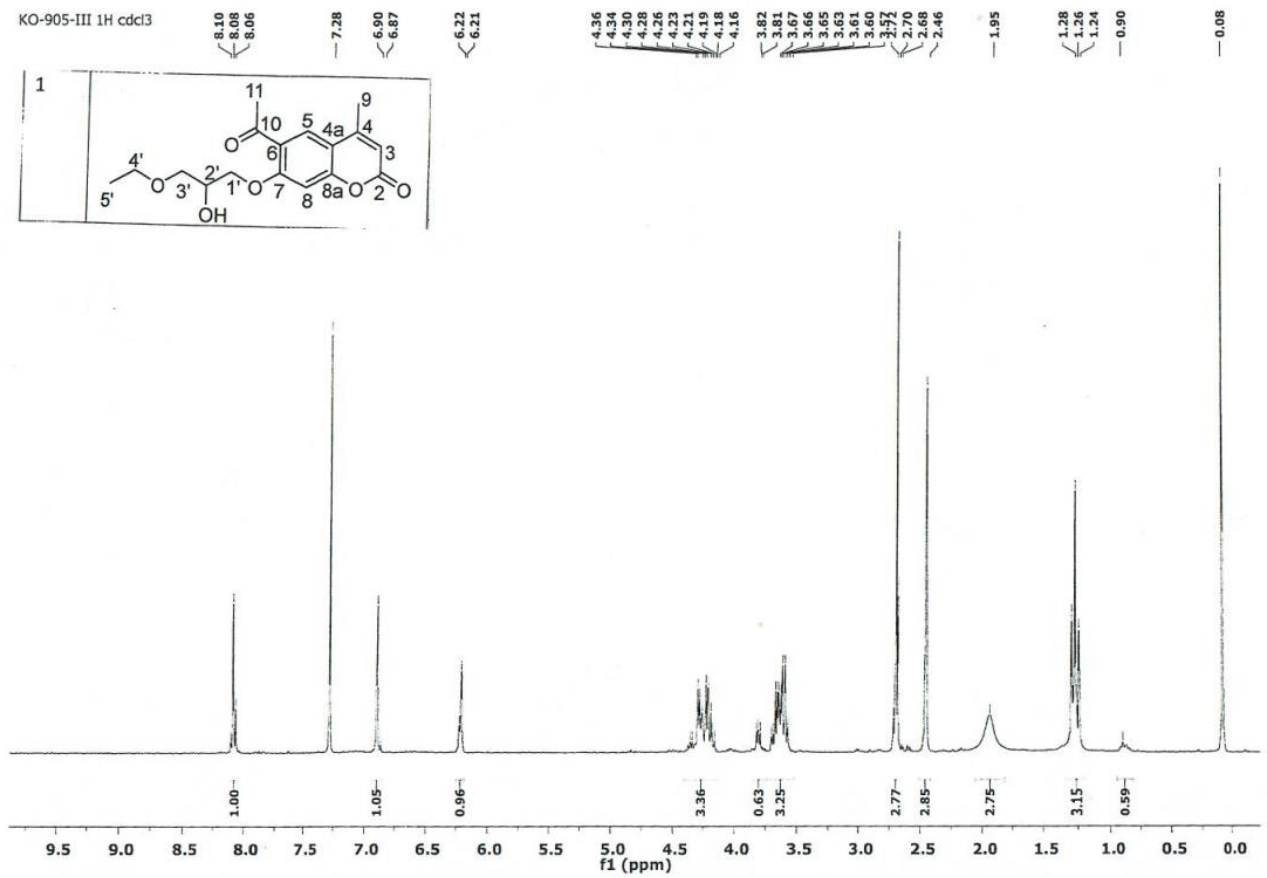
Fig. 4. Time-dependent integrated EPR signal intensities of FDMPO spin adducts formed in the Fenton reaction with DMSO in the presence of substrate compounds and their corresponding derivatives.

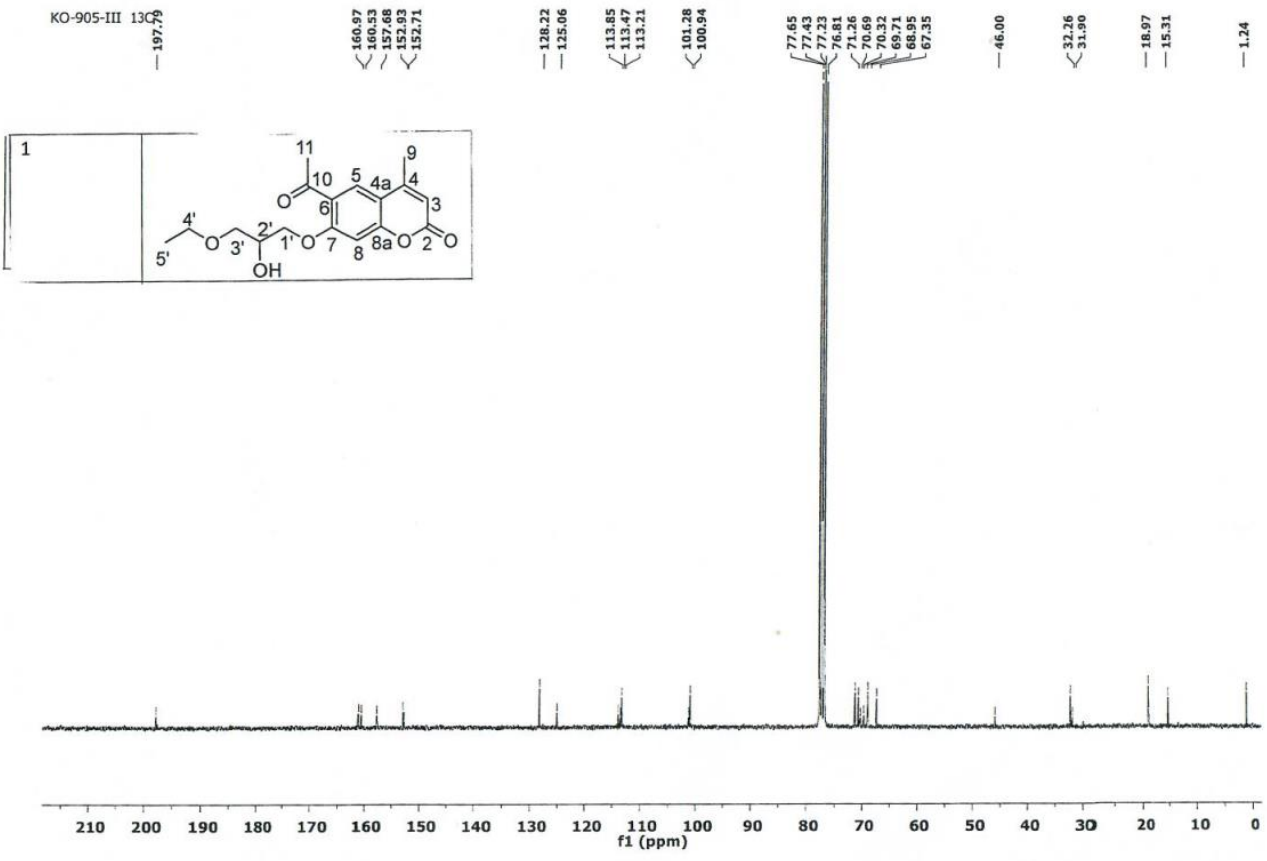
4. Conclusions

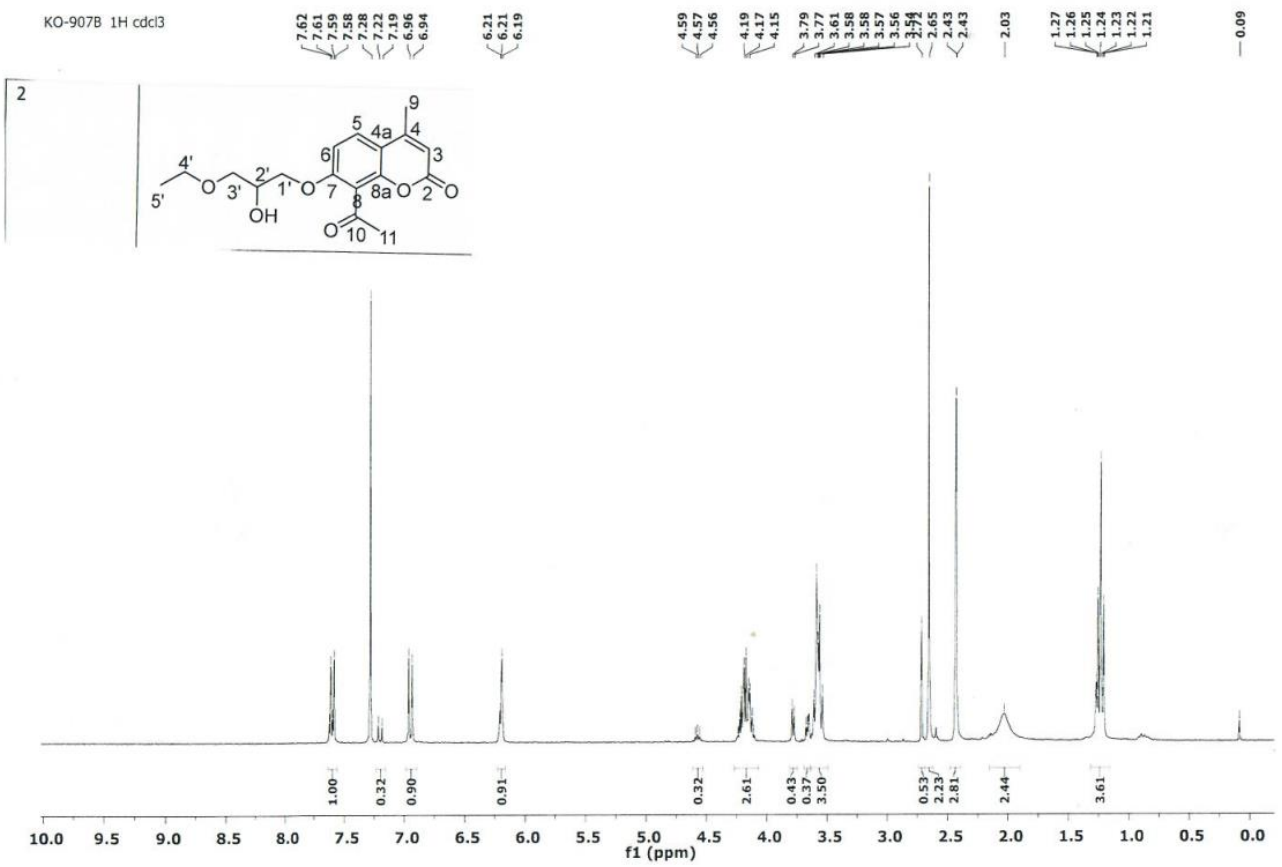
Five new derivatives of 2,3-epoxycoumarins containing a 3'-ethoxy-2'-hydroxypropoxy fragment were synthesized. Electron Paramagnetic Resonance (EPR) spectroscopy showed that among all studied compounds the most pronounced differences between the properties of the substrates and the final products were observed for the substrate a (6-acetyl-4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one) and its derivative 1 (6-acetyl-7-(3'-ethoxy-2'-hydroxypropoxy)-4-methylcoumarin).

Appendix

^{1}H NMR and ^{13}C NMR spectra in solution were recorded at 25 ºC with a Varian NMRS-300, standard Varian software was employed and $CDCl_3$ was used as the solvent.



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3.56
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2.43
2.43
2.03
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4
6
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6.0
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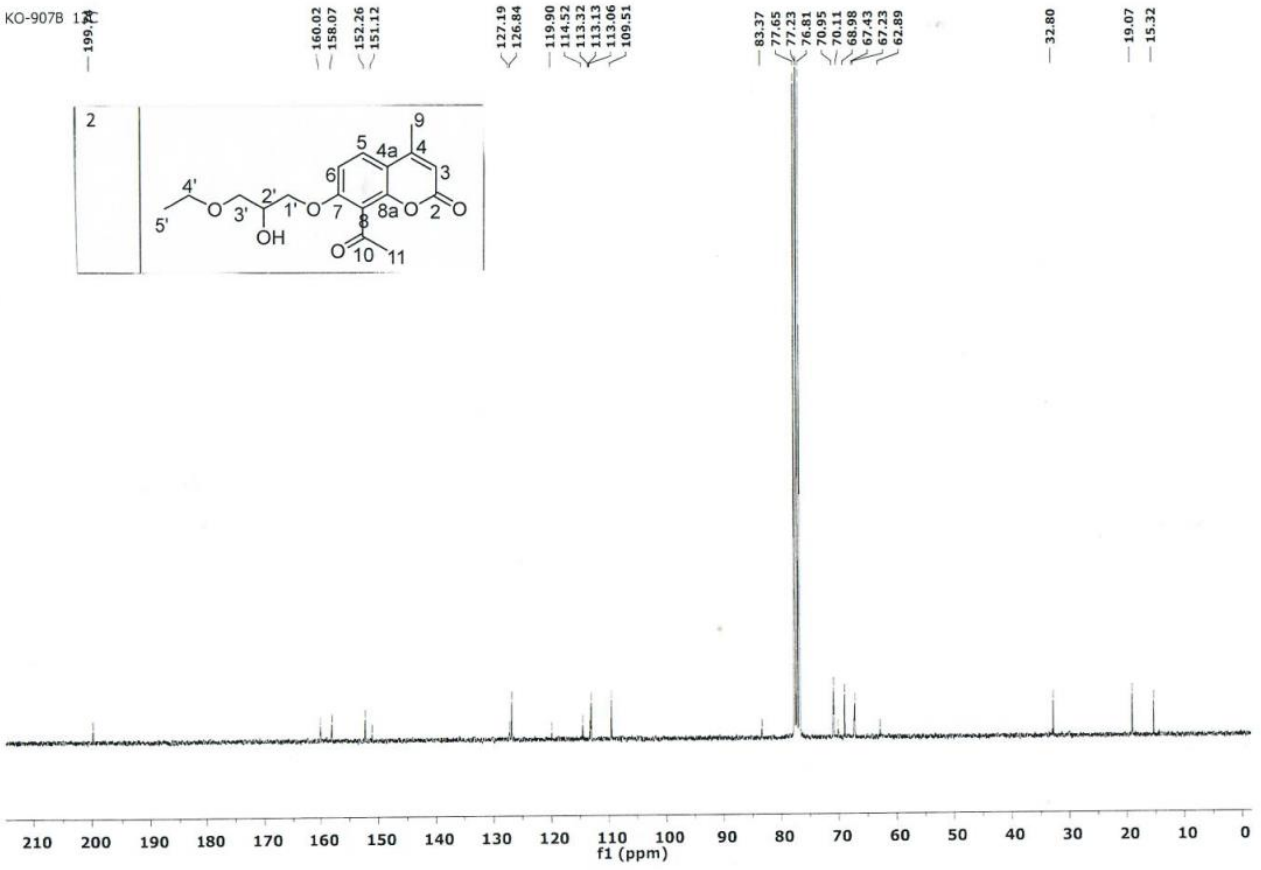
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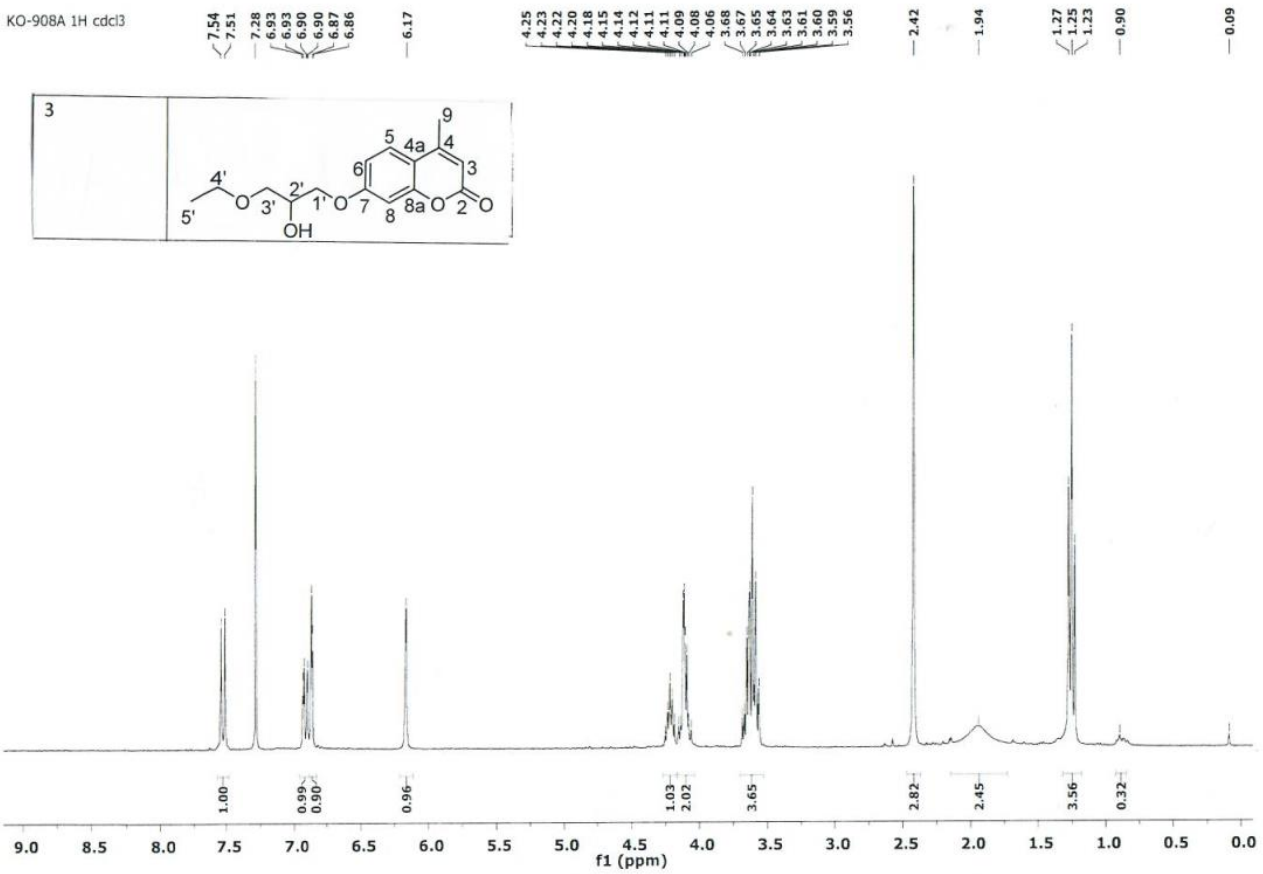
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0.09
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5
4a
4
6
3
4'
2'
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1'
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8a
2
5'
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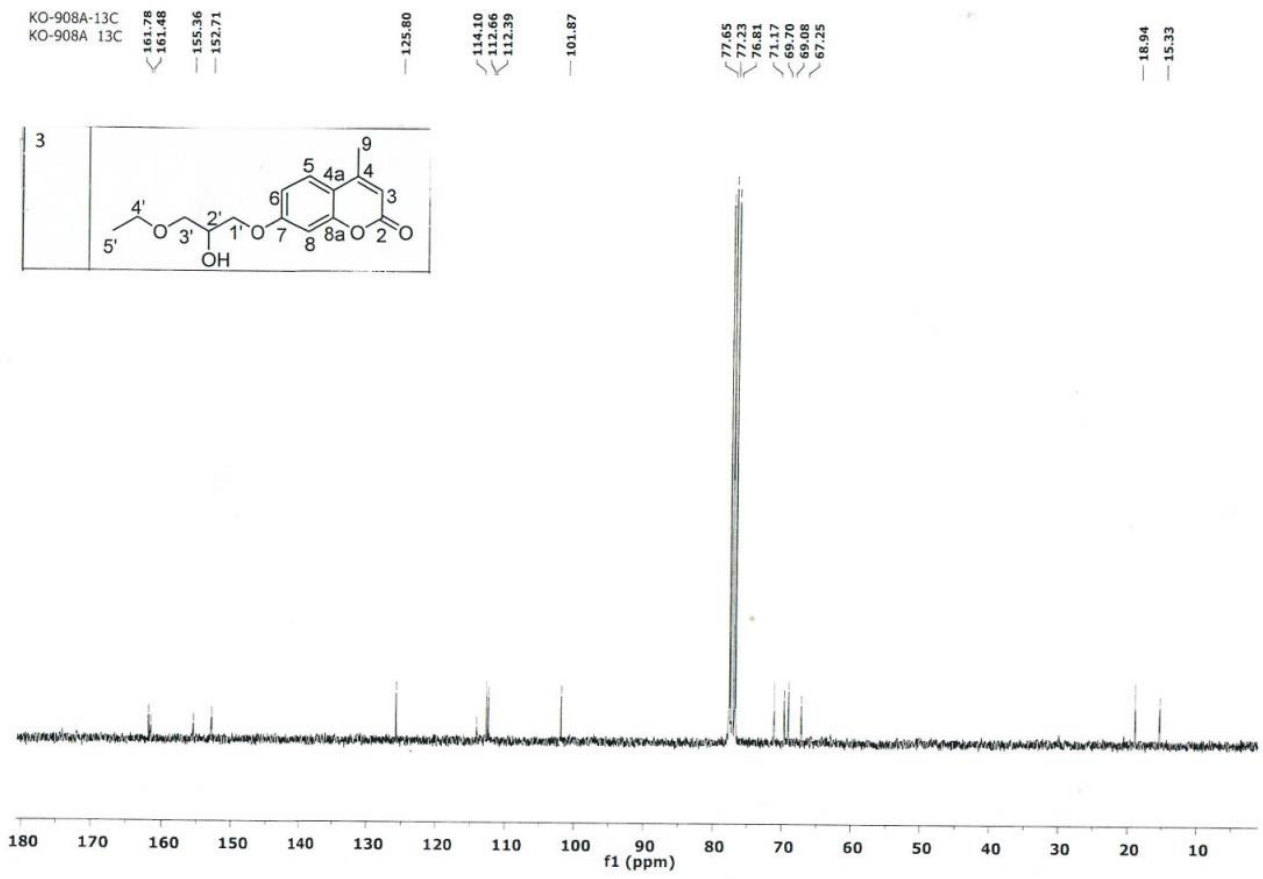
f1 (ppm)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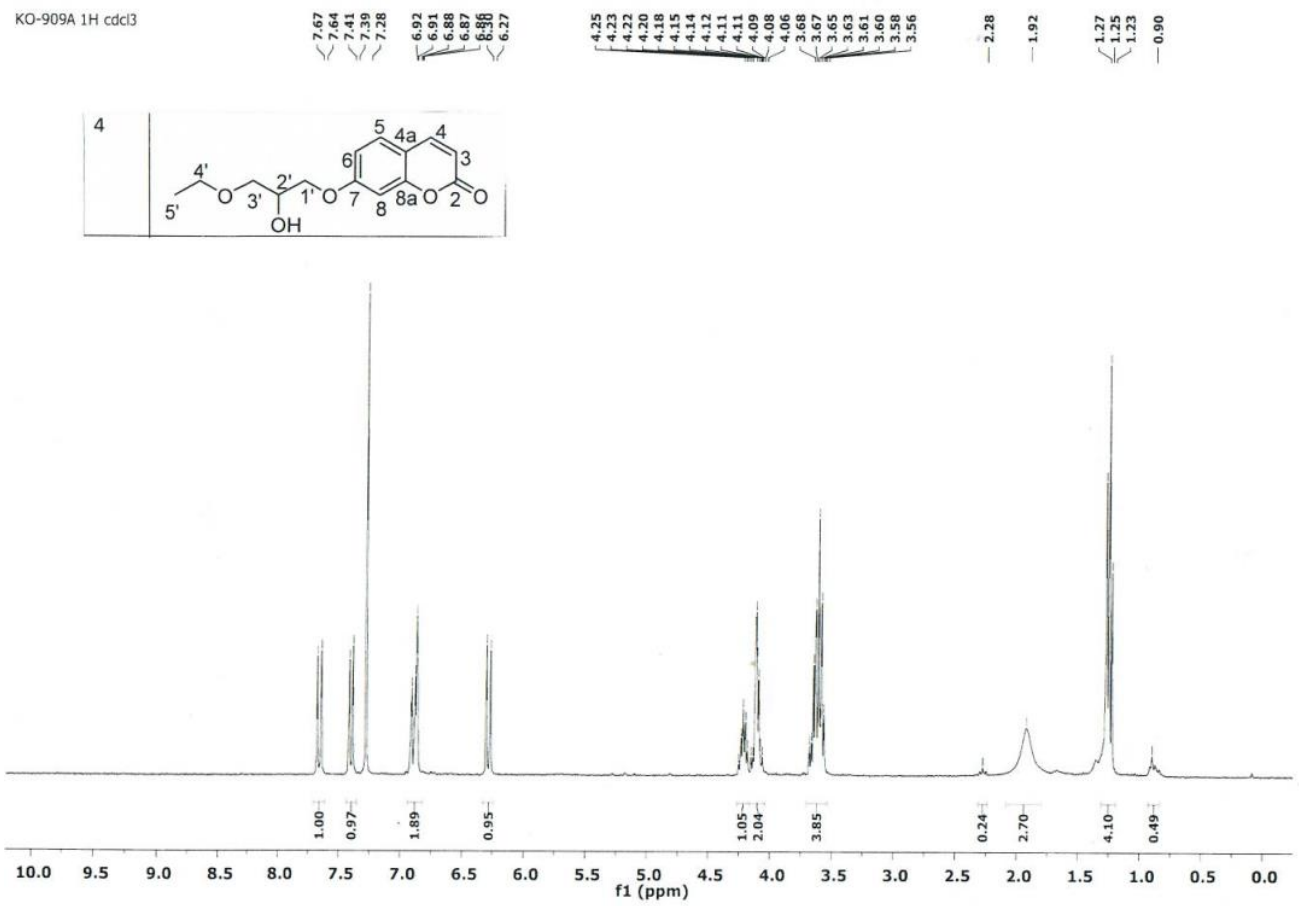
f1 (ppm)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4.22
4.20
4.18
4.15
4.14
4.12
4.11
4.11
4.09
4.08
4.06
3.68
3.67
3.65
3.63
3.61
3.60
3.58
3.56
2.28
1.92
1.27
1.25
1.23
0.90
4
5
4a
4
6
3
4'
2'
5'
O
3'
1'
O
7
8
8a
O
2
O
OH
1.00
0.97
1.89
0.95
1.05
2.04
3.85
0.24
2.70
4.10
0.49
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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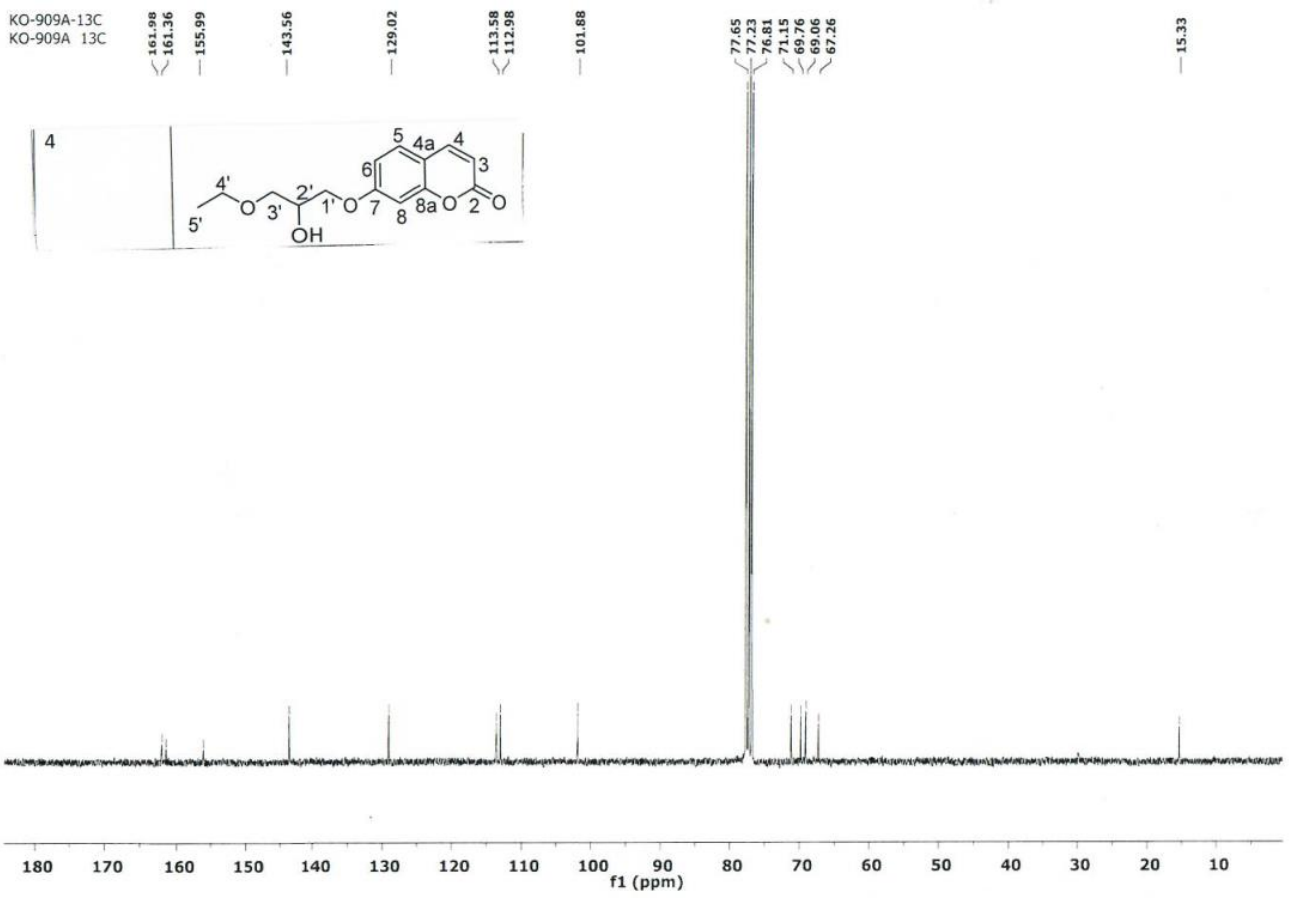
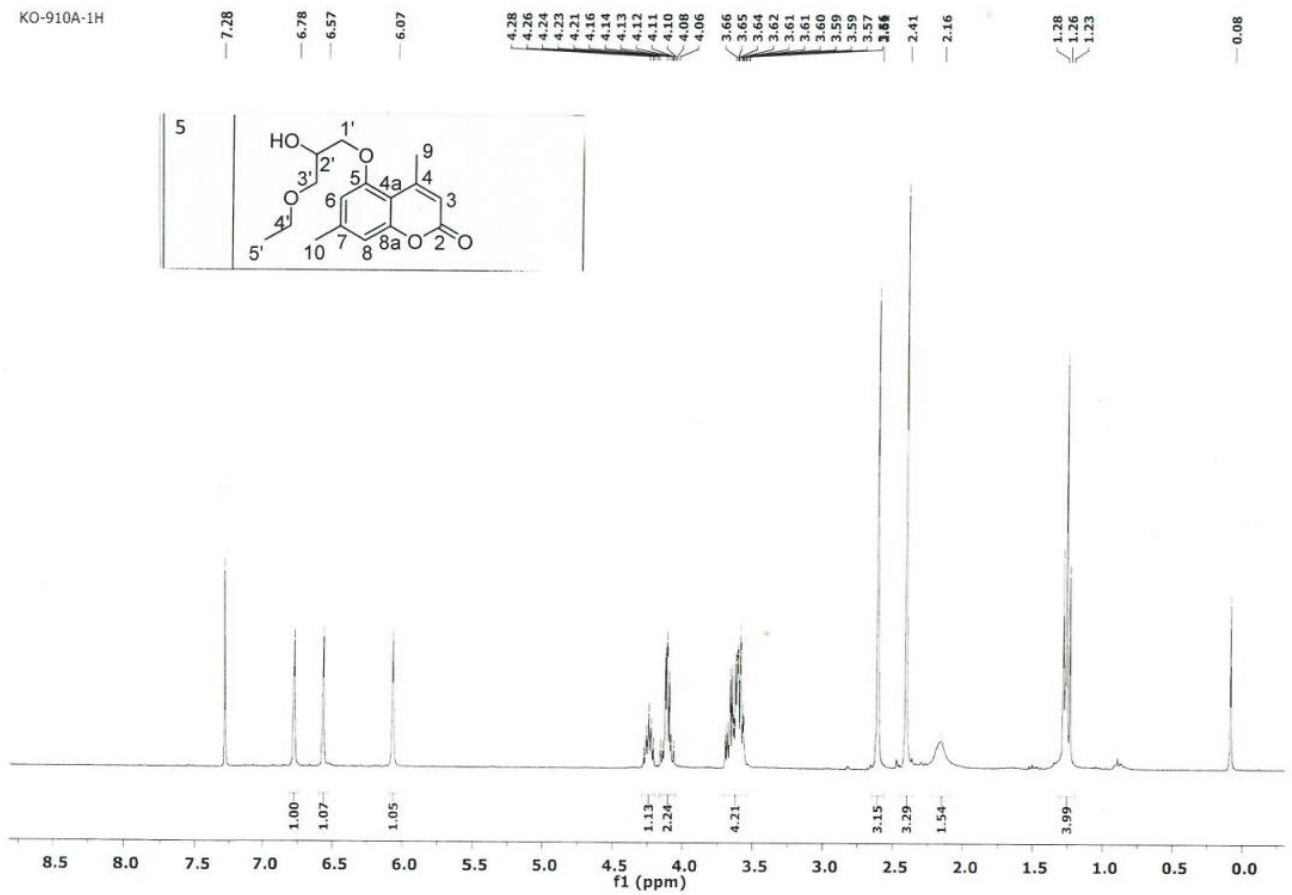
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


KO-909A-13C
KO-909A 13C
161.98
161.36
155.99
143.56
129.02
113.58
112.98
101.88
77.65
77.23
76.81
71.15
69.76
69.06
67.26
15.33
4
5
4a
4
6
3
4'
2'
5'
O
3'
1'
O
7
8
8a
O
2
O
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


KO-910A-1H
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6.78
6.57
6.07
4.28
4.26
4.24
4.23
4.21
4.16
4.14
4.13
4.12
4.11
4.10
4.08
4.06
3.66
3.65
3.64
3.62
3.61
3.61
3.60
3.59
3.59
3.57
2.41
2.16
1.28
1.26
1.23
0.08
5
HO
1'
2'
3'
O
4'
5'
O
5
4a
6
9
4
3
10
7
8
8a
O
2
O
1.00
1.07
1.05
1.13
2.24
4.21
3.15
3.29
1.54
3.99
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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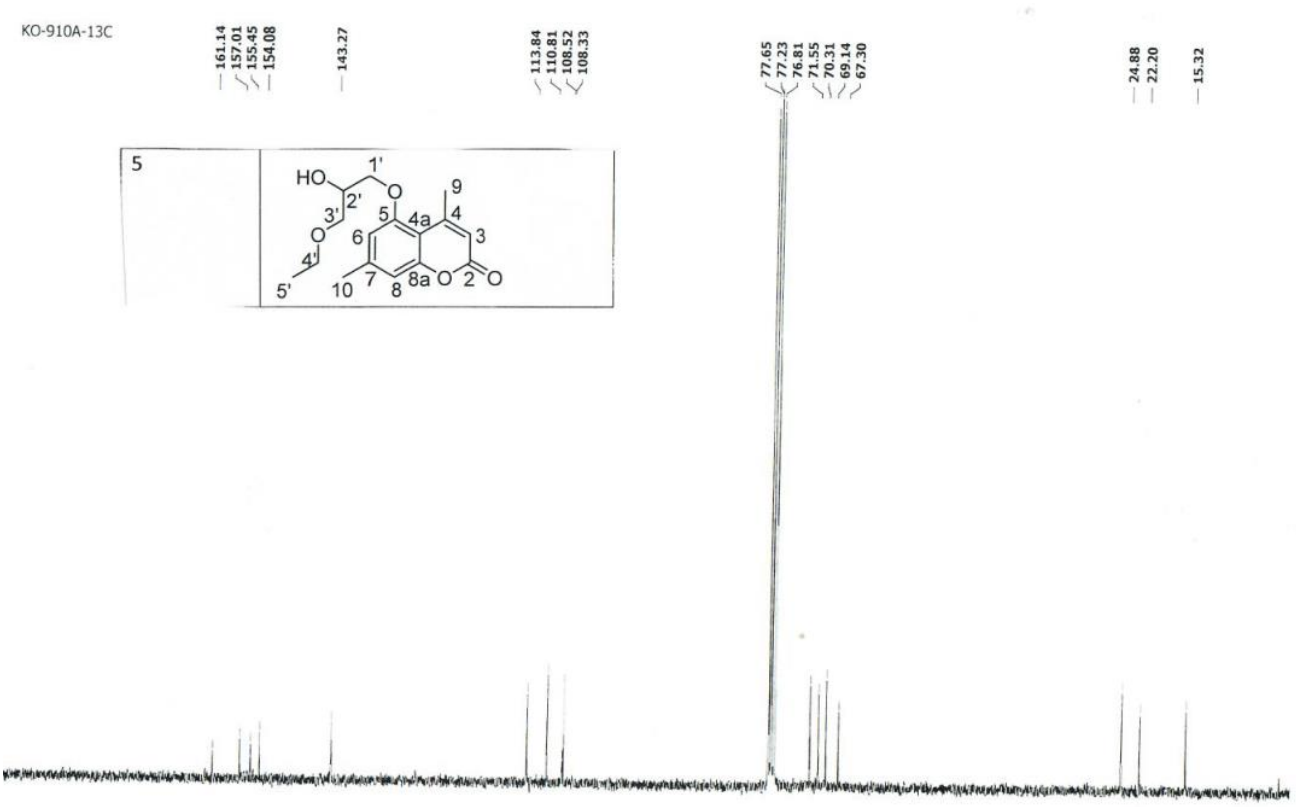
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


KO-910A-13C
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154.08
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110.81
108.52
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77.23
76.81
71.55
70.31
69.14
67.30
24.88
22.20
15.32
5
HO
1'
2'
3'
O
4'
5'
O
5
4a
6
9
4
3
10
7
8
8a
O
2
O

Author Contributions: Conceptualization, K.O. and K.M.; methodology, K.O. and K.M. ; validation, K.O. and K.M.; investigation, K.O., K.M., A.D. and M.K. ; resources, K.O. and K.M.; data curation, K.O. and K.M.; writing—original draft preparation, K.O. and K.M.; writing—review and editing, K.O. and K.M.; visualization, K.O. and K.M.; supervision, K.O. All authors have read and agreed to the published version of the manuscript.

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