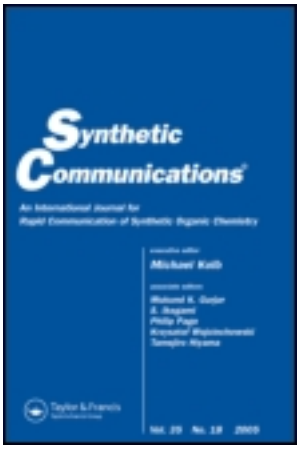

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Synthesis of 6,7-Diacylcoumarins via the Transformation of a Hydroxy into a Carbonyl Group

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Synthesis of 6,7-Diacylcoumarins via the Transformation of a Hydroxy into a Carbonyl Group

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Abstract: The synthesis of 6,7-diacylcoumarins is reported via the oxidation of 6-acetyl-7-hydroxycoumarin *N*-acylhydrazones with lead tetraacetate. The procedure involves transformation of hydroxy into an acyl group and formation of a new C–C bond.

Keywords: *N*-acylhydrazones, 6,7-diacyl-2*H*-chromen-2-ones, coumarins, lead tetraacetate, oxidation, transformation

Linear 6,7-disubstituted coumarins, a class of fused-ring heterocycles, also well known as chromen-2-ones, are widely found in the nature and show interesting biological activity.[1] Generally, naturally occurring coumarins are found in several plants, including grasses, orchids, citrus fruits, and legumes, and are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, and defense against infection.[2] In addition, these compounds exhibit a variety of pharmacological properties. Among these properties, their cytotoxic effects have been most extensively investigated.[3] However, they also play an important role in medicine as anti-HIV,[4] cytotoxic,[5] anticoagulant,[6] antibacterial,[7] oestrogenic,[8]

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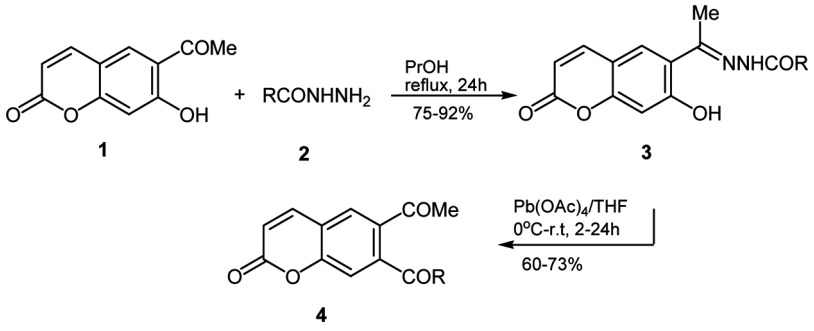
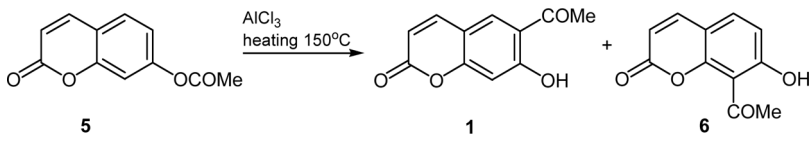
anti-inflammatory,[9] antioxidant,[10] and fluorescent[11] agents. Furthermore, several coumarins bearing different groups on the aromatic ring were synthesized and tested to find more active analogs. Psoralen and esculetin are typical examples among the natural 6,7-substituted coumarin derivatives with cytotoxic activity.[3] In addition, the linear furanocoumarins isopimpinellin and imperatorin are ingested regularly as part of the humandiet as they are present in the rind and pulp oflimes, in lemon and lime oils, and in celery, parsnip, and parsley; are analgesic;[12] and have been found to alter enzyme activities and reduce DNA adduct formation by polycyclic aromatic hydrocarbons in various tissues of mice.[13,14] On the other hand, 6,7-dimethylcoumarin derivatives are typical examples among the interesting synthetic analogs with antiangiogenic and simultaneous fluorescent activity, giving the ability for both imaging and inhibition against angiogenesis at the same time.[15] Because the pharmacological and biochemical properties and therapeutic applications of coumarins depend[2] upon the pattern of substitution and alterations in the structure of coumarins could change their cytotoxic properties, it is not difficult to understand why the design and the synthesis of substituted coumarin derivatives is of great importance to many researchers.

Recently, we synthesized[16] 7,8-diacylcoumarins in our laboratory, and we would like further to synthesize linear 6,7-diacyl derivatives.

Depending on this knowledge, on our interest in coumarin derivatives,[16] and on the applications of the reactions of *o*-hydroxy arylketone *N*-acylhydrazones[17] with lead tetraacetate (LTA) in organic synthesis, we studied the synthesis of 6,7-diacylcoumarins **4** according to Scheme 1. The synthetic scheme proceeds via reaction of 6-acetyl-7-hydroxycoumarin *N*-acylhydrazones **3** with LTA and involves transformation of a hydroxy into a carbonyl group.



Scheme 1. Preparation of 6,7-diacylcoumarins **4**.

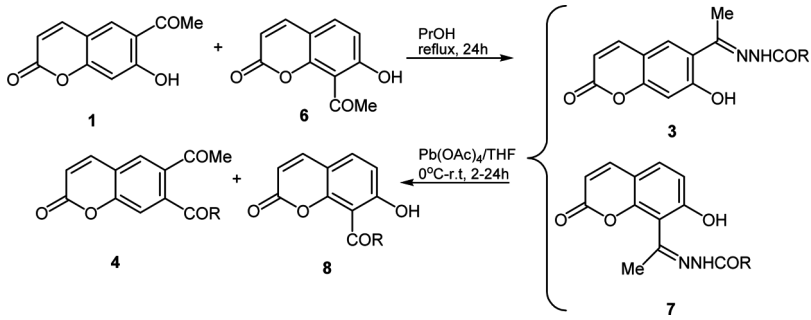


Scheme 2. Preparation of 6- and 8-acetyl-7-hydroxycoumarin **1** and **6**.

Starting coumarin **1** has been reported in the literature as obtained as a mixture with the isomer 7-hydroxy-8-acetylcoumarin **6** under treatment of 7-acetoxycoumarin **5** with aluminum chloride (Scheme 2).[18]

Recrystallization of this mixture results in the isolation of 7-hydroxy-8-acetylcoumarin **6** in 74% yield as a solid, whereas the desired 6-acetyl derivative **1** remains in the filtrate along with some quantity of 8-acetyl isomer **6** and 7-hydroxycoumarin. Removal of the solvent and subjection of the filtrate mixture to column chromatography afforded the desired 6-acetyl derivative **1** in only minor traces to 5% pure yield, whereas the most quantity of the product is obtained as a mixture with the isomer 7-hydroxy-8-acetylcoumarin. Trying to optimize the yield for coumarin **1**, we applied two subsequent purifications via column chromatography as well as recrystallization from ethanol. In this way, 6-acetyl isomer **1** could be isolated in 14% yield. However, because the yield was still low, we decided to run two series of experiments to synthesize 6,7-diacylcoumarins using as the starting carbonyl substrate: (i) pure 6-acetyl-7-hydroxycoumarin (method A, Scheme 1) and (ii) the mixture of 6- and 8-acetyl-7-hydroxycoumarin as it was in the filtrate without any further purifications (method B, Scheme 3).

In method A, a series of 6-acetyl-7-hydroxycoumarin *N*-carbonylhydrazones **3** were prepared in very good yields, 92 to 75% (Scheme 1). Hydrazones **3** are new compounds, and they were identified by their



Scheme 3. Alternative preparation of 6,7-diacylcoumarins **4**.

spectral data and by either exact mass measurement or elemental analysis. Hydrazones **3** were subsequently oxidized with LTA to lead to the formation of the desired products **4** in good yields, 60–73%. The reaction conditions, the yields of formation of the new compounds **3** and **4**, and their melting points are presented in Table 1. The desired linear 6,7-diacylcoumarins were isolated by column chromatography and identified by their spectral data and by either exact mass measurement or elemental analysis.

In method B, the mixture of 6- and 8-acetyl-7-hydroxycoumarin **1** and **6** was treated with the appropriate hydrazides **2** to produce mixtures of the corresponding hydrazones **3** and **7**, which subsequently afforded mixtures of the corresponding 6,7- and 7,8-diacylcoumarins **4** and **8** under treatment with LTA. The desired linear pure 6,7-diacyl-coumarins **4** were isolated by column chromatography in 35–48% yield (Table 1) and identified by comparison of their spectral data with those of the authentic samples prepared by method A. Isomers **8** that were also formed during the reactions are known compounds, and their synthesis was recently reported.[16]

In addition, reaction of hydrazone **4e** with phenyliodosodiacetate (PID) led to the formation of **4e** in yields comparable to the LTA yield (Table 1). This is in accordance with our previous findings about the transformation of the hydroxy into a carbonyl group.[17]

Concerning the mechanism of the transformation reactions, it is not unreasonable to assume that it works analogously to the mechanism that we proposed for the transformation of *o*-hydroxyacetophenone *N*-benzoylhydrazone into 1-acetyl-2-benzoylbenzene.[19]

In conclusion, the transformation of a hydroxy into an acyl group (**1** → **3** → **4** in Scheme 1) was applied in coumarins, giving the ability for the synthesis of linear *ortho*-diacylsubstituted derivatives. The presence of two acyl groups at neighboring positions is always desirable in aromatic derivatives. However, there are no other general methods for such derivatives.[20] The transformation has been proven to be the most appropriate way to synthesize *ortho*-diacylsubstituted heterocycles. The simplicity of the method, the low cost of the reagents, and the good yield add to the synthetic value of the transformation. In addition, 6,7-diacyl-coumarins **4** could also serve as very useful intermediates to various heterocycles with possible pharmaceutical properties.

EXPERIMENTAL

All the solvents for the reactions and chromatography were purchased from Merck, whereas all hydrazides **2** from Aldrich. Compound **5** was

Table 1. Preparation of 6-acetyl-7-hydroxycoumarin *N*-acylhydrazones **3** and 6,7-diacylcoumarins **4**

Compound	R	Reagents method A (Method B)	Reagent molar ratio	Reaction time (h)	Solvent	Reaction temp. (°C)	Yield (%) method A (Method B)	Mp (°C)[a]
3a	Ph	**1** + **2a**	1/1	24	PrOH	Reflux	92	286–288
3b	2′-HOC_6H_4	**1** + **2b**	1/1	24	PrOH	Reflux	80	328–330
3c	2′-$O_2NC_6H_4$	**1** + **2c**	1/1	24	PrOH	Reflux	88	251–252
3d	2′-furyl	**1** + **2d**	1/1	24	PrOH	Reflux	89	227–228.5
3e	2′-thienyl	**1** + **2e**	1/1	24	PrOH	Reflux	83	284–286
3f	Me	**1** + **2f**	1/1	24	PrOH	Reflux	75	319–321
4a[b]	Ph	**3a** + LTA	1/1.5	2	THF	rt rt	68	166–167
		(**3a** + **7a** + LTA)				rt	(44)	
4b[b]	2′-HOC_6H_4	**3b** + LTA	1/1.5	24	THF	rt	67	186–188
		(**3b** + **7b** + LTA)					(48)	
4c[b]	2′-$O_2NC_6H_4$	**3c** + LTA	1/2	2	THF	rt	61	152–154
		(**3c** + **7c** + LTA)					(36)	
4d[b]	2′-furyl	**3d** + LTA	1/2.3	24	THF	rt	60	194–196
		(**3d** + **7d** + LTA)					(35)	
4e[b]	2′-thienyl	**3e** + LTA	1/1.5	24	THF	rt	64	178.5–180
		(**3e** + **7e** + LTA)					(38)	
		3e + PID	1/2	24	CH_2Cl_2	rt	60	
4f[b]	Me	**3f** + LTA	1/2	24	THF	0	73	128–130
		(**3f** + **7f** + LTA)					(48)	

[a]Mps are uncorrected.
[b]Compounds **4a**–**4f** were recrystallized from ethanol.

prepared according to the literature procedure.[18] Compound **1** was prepared according to the literature procedure[18] with additional two columns of chromatography and a recrystallization of the final obtained fraction mixture of **1** + **6** (Scheme 2). Thin-layer chromatography (TLC) plates were Merck plastic plates with silica gel 60 F_{254} (70–230 mesh). Column chromatography was performed on silica gel 60 F_{254} (70–230 mesh). The NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H MHz 400.15, ^{13}C 100.62 MHz) in dimethyl sulfoxide (DMSO) using the signal of the solvent as the internal standard (residual DMSO for ^{1}H: δ 2.50 ppm, ^{13}C δ 39.5 ppm). Either elemental analysis or exact mass measurement have been provided for all the new compounds **3** and **4**.

Typical Procedure for Formation of 6-Acetyl-7-hydroxycoumarin *N*-Acylhydrazones 3

A mixture of 6-acetyl-7-hydroxycoumarin **1** (5 mmol) and the corresponding hydrazide in molar ratio 1:1 were refluxed in propanol-1 (20 ml) for 24 h. The mixture was allowed to cool, and the precipitate was filtered and subsequently dried to afford the pure products **3** as white solids (Table 1).

Typical Procedure for Formation of 6,7-Diacylcoumarins 4 (Method A)

Lead tetracetate was added to a stirred solution of hydrazone **3** (1 mmol) in tetrahydrofuran (THF) (20 ml), in an ice bath. The molar ratio of hydrazone/lead tetraacetate (LTA) and the reaction times are presented in Table 1. The mixture was then stirred at rt. The oily product obtained after filtration of lead diacetate and condensation of the filtrate was subjected to column chromatography (silica gel 70–230 mesh) and was eluted with a mixture of petroleum ether/ethylacetate 1:1 to afford the pure products **4** as white solids (Table 1).

Typical Procedure for Formation of 6,7-Diacylcoumarins 4 (Method B)

A mixture of 6- and 8-acetyl-7-hydroxycoumarin **1** and **6** (5 mmol), prepared according to the literature procedure,[18] was treated with the appropriate hydrazide **2**, in molar ratio 1:1, under reflux in propanol-1 (20 ml), for 24 h. The mixture was allowed to cool, and the precipitate was filtered and subsequently dried to afford mixtures of hydrazones **3** and **7**. These mixtures of hydrazones were further used without any purification. Thus, lead tetracetate was added to a stirred solution of

the mixture of **3** and **7** (1 mmol) in THF (20 ml), in an ice bath. The molar ratio of the mixture of hydrazones/LTA and the reaction time are presented in Table 1. The reaction mixture was then stirred at rt. The oily product obtained after filtration of lead diacetate and condensation of the filtrate was subjected to column chromatography (silica gel 70–230 mesh) and was eluted with a mixture of petroleum ether/ethylacetate 1:1 to afford the pure products **4** as white solids (Table 1).

Oxidation of Hydrazone 3e with PID

Phenyliodosodiacetate (PID) was added to a stirred solution of hydrazone **3e** (1 mmol) in dichloromethane (20 ml) in an ice bath. The molar ratio of hydrazone/LTA and the reaction time are presented in Table 1. The mixture was then stirred at rt. The oily product obtained after condensation of the solvent was subjected to column chromatography (silica gel 70–230 mesh) and was eluted with a mixture of petroleum ether/ethylacetate 1:1 to afford the pure coumarin **4e** as white solid (Table 1).

Data on Compound 3a

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H), 6.27 (d, 1H, $J = 9.3$ Hz), 6.85 (s, 1H), 7.55–7.63 (m, 3H), 7.93–8.05 (m, 4H), 11.45 (s, 1H), 14.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 103.8, 111.1, 112.3, 117.2, 128.1 128.4, 129.3, 132.1, 132.7, 144.4, 155.7, 156.9, 160.0, 162.4, 164.5; MS m/z (ES+): 345 (M+23), 323 (M+1); CHN: C, 67.01%; H, 4.43%; N, 8.70%. Calculated for $C_{18}H_{14}N_2O_4$: C, 67.07%; H, 4.38%; N, 8.69%.

Data on Compound 3b

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H), 6.27 (d, 1H, $J = 9.4$ Hz), 6.86 (s, 1H), 6.96–7.02 (m, 2H), 7.41–7.45 (m, 1H), 7.93–7.98 (m, 2H), 8.03 (s, 1H), 11.40 (s, 1H), 11.69 (s, 1H), 12.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ too insoluble; HRMS (ESI+) m/z: calcd. for $C_{18}H_{14}N_2O_5$: 699.16976 (2M+Na); 361.07949 (M+Na); found: 699.16964 (2M+Na); 361.07891 (M+Na).

Data on Compound 3c

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H), 6.27 (d, 1H, $J = 9.4$ Hz), 6.62 (s, 1H), 7.77–7.89 (m, 3H), 7.97 (d, 1H, $J = 9.7$ Hz), 8.04 (s, 1H), 8.19

(d, 1H, $J = 8.0$ Hz), 11.4 (s, 1H), 11.8 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 103.8, 111.2, 112.35, 117.1, 124.3, 129.5, 130.1, 130.5, 131.4, 134.2, 144.3, 146.6, 155.75, 156.3, 160.1, 162.2, 162.9; HRMS (ESI+) m/z calcd. for $C_{18}H_{13}N_3O_6$: 757.15009 (2M+Na), 390.06966 (M+Na); found: 757.15059 (2M+Na), 390.06929 (M+Na).

Data on Compound 3d

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H), 6.27 (d, 1H, $J = 9.5$ Hz), 6.71 (d, 1H, $J = 3.1$ Hz), 6.84 (s, 1H), 7.41 (d, 1H, $J = 3.3$ Hz), 7.96–7.98 (m, 2H), 8.06 (s, 1H), 11.31 (s, 1H), 14.06 (s, 1H). Compound **3a** was too insoluble for ^{13}C NMR; HRMS (ESI +) m/z calcd. for $C_{16}H_{12}N_2O_5$: 647.13847 (2M+23), 335.06380 (M+Na);found: 647.13924 (2M+Na), 335.06370 (M+Na).

Data on Compound 3e

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (s, 3H), 6.27 (d, 1H, $J = 9.5$ Hz), 7.24 (s, 1H), 7.91–7.92 (m, 2H), 7.95–7.98 (m, 2H), 8.05 (s, 1H), 11.37 (s, 1H), 14.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 103.7, 111.1, 112.3, 117.2, 128.1, 129.4, 130.5, 132.6, 136.6, 144.35, 155.7, 156.8, 158.9, 160.0, 162.3; HRMS (ESI +) m/z calcd. for $C_{16}H_{12}N_2O_4S$: 679.09339 (2M+Na), 351.04155 (M+Na); found: 679.09440 (2M+Na), 351.04099 (M+Na).

Data on Compound 3f

Compound **3a** was too insoluble for H^1 and ^{13}C NMR; HRMS (ESI+) m/z calcd. for $C_{13}H_{12}N_2O_4$: 543.14863 (2M+Na), 283.06893 (M+Na); found: 543.14873 (2M+2Na), 283.06915 (M+Na).

Data on Compound 4a

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H), 6.64 (d, 1H, $J = 9.7$ Hz), 7.43–7.61 (m, 6H), 8.17 (d, 1H, $J = 9.7$ Hz), 8.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.6, 116.6, 118.5, 119.8, 129.3, 129.4, 129.5, 130.2, 132.1, 133.0, 133.8, 137.0, 144.1, 144.2, 156.5, 159.9, 195.8, 197.4; HRMS (ESI+) m/z calcd. for $C_{18}H_{12}O_4$: 293.08058 (M+H); found: 293.08084 (M+H).

Data on Compound 4b

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H), 6.64 (d, 1H, $J = 9.7$ Hz), 6.80–6.81 (m, 1H), 6.96 (d, 1H, $J = 8.2$ Hz), 7.15 (d, 1H, $J = 7.7$ Hz), 7.44–7.49 (m, 2H), 8.16 (d, 1H, $J = 9.7$ Hz), 8.54 (s, 1H), 11.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.6, 116.4, 118.2, 118.5, 119.8, 119.9, 121.2, 132.1, 132.4, 132.7, 136.7, 143.1, 144.1, 156.4, 159.9, 161.2, 197.4, 200.6; MS m/z (ES+): 331 (M+23), 309 (M+1), 215; CHN: C, 69.84%; H, 3.72%. Calculated for $C_{18}H_{12}O_5$: C, 70.13%; H, 3.92%.

Data on Compound 4c

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H), 6.69 (d, 1H, $J = 9.7$ Hz), 7.45 (s, 1H), 7.56 (d, 1H, $J = 8.2$ Hz), 7.78–7.85 (m, 2H), 7.11 (d, 1H, $J = 8.2$ Hz), 8.16 (d, 1H, $J = 9.7$ Hz), 8.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.4, 117.7, 119.0, 121.0, 124.5, 129.6, 130.6, 131.2, 133.2, 133.4, 135.7, 138.7, 143.0, 147.6, 154.6, 159.2, 192.25, 199.5; HRMS (ESI+) m/z calcd. for $C_{18}H_{11}NO_6$: 697.10650 (2M+Na), 360.04786 (M+2Na); found: 697.10710 (2M+Na), 360.04790 (M+Na).

Data on Compound 4d

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56 (s, 3H), 6.65–6.67 (m, 2H), 7.07 (d, 1H, $J = 3,5$ Hz), 7.53 (s, 1H), 7.96 (m, 1H), 8.16 (d, 1H, $J = 9.7$ Hz), 8.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.3, 113.1, 118.1, 119.4, 119.5, 122.0, 129.6, 131.0, 133.05, 141.8, 149.3, 151.6, 155.4, 159.25, 181.1, 197.3; HRMS (ESI+) m/z calcd. for $C_{16}H_{10}O_5$: 587.09487 (2M+23), 305.04204 (M+Na); found: 587.09477 (2M+Na), 305.04183 (M+Na).

Data on Compound 4e

^{1}H NMR(400 MHz, DMSO-d_6): δ 2.53 (s, 3H), 6.64 (d, 1H, $J = 9.7$ Hz), 7.43–7.57 (m, 2H), 7.59–7.61 (m, 2H), 8.17 (d, 1H, $J = 9.7$ Hz), 8.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.6, 116.6, 118.5, 119.8, 129.3, 129.4, 132.1, 133.0, 133.85, 137.0, 144.1, 144.2, 156.5, 159.9, 195.8, 197.4; MS (ESI+) m/z: 321 (M+Na), 215; CHN: C, 64.06%; H, 3.30%. Calculated for $C_{16}H_{10}O_4S$: C, 64.42%; H, 3.38%.

Data on Compound 4f

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H), 2.52 (s, 3H), 6.60 (d, 1H, $J = 9.5$ Hz), 7.54 (s, 1H), 8.07 (d, 1H, $J = 9.5$ Hz), 8.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.6, 30.2, 116.0, 116.7, 120.2, 130.6, 133.8, 143.7, 144.4, 155.8, 159.9, 199.4, 202.0; MS (ESI+) m/z: 253 (M+Na), 231 (M+H); CHN: C, 67.66%; H, 4.30%. Calculated. for $C_{13}H_{10}O_4$: C, 67.82%; H, 4.38%.

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