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RESEARCH ARTICLE

Synthesis of prenylated homoisoflavonoids with a coumarin moiety

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Abstract: A series of prenylated homoisoflavonoid-coumarin hybrids were synthesized by developed cascade reactions of coumarin Mannich bases with 3-(dimethylamino)-1-(5-hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)prop-2-en-1-one. Obtained homoisoflavonoids might have a large potential for further investigations of their bioactivities.

Keywords: coumarins; homoisoflavonoids; inverse electron-demand Diels-Alder reaction.

Introduction

The development of new synthetic routes for the construction of natural product-like small-molecule libraries with structural complexity, diversity, and various physicochemical properties is attracting attention from the scientific community involved in chemical biology and drug discovery. The incorporation of privileged substructural motifs a concept that there exist preferred molecular scaffolds that can provide ligands for diverse receptors has been proven to be an essential tool for the discovery of bioactive molecules [1]. The naturally occurring homoisoflavonoids possess a broad spectrum of biological activities, such as antioxidant, anti-microbial, anti-diabetic, immunomodulatory effects, and protein kinase inhibition [2-4].

The sappanin-type homoisoflavonoids contain chromanone or chromone rings with 3-benzyl substituents. Like other flavonoid counterparts, naturally occurring homoiso-flavonoids typically bear hydroxylic, methoxy, and methylenedioxy groups in rings A and B. Isoprenyl and geranyl moieties, methyl groups, and aldehydes have been described as C-linked substituents [5].

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Isolated from the bulbs of *Ledebouria Floribunda* prenylated and geranylated flavonoids are very common in certain families of plants. The first examples of prenylated homoisoflavonoids are ledebourin A, B, and C **1a-1c** (Figure 1). These derivatives are the products of triple (acetate, shikimate, and mevalonate) biosynthetic pathways and have been reported as potent antioxidants. The expected activity due to the *ortho*-dihydroxy groups is probably enhanced by other factors introduced by the prenyl and geranyl groups [6].

Results and discussion

It should be noted that a few types of C-prenylated flavonoids have been isolated from natural sources. In most cases, naturally occurring flavonoids contain 2*H*-2,2-dimethylchromene or isopropylbenzofuran fragment, and ring-opening isoprenyl substituent which can be transformed to hydroxy or epoxy derivatives etc. Intramolecular cyclization of *ortho*-hydroxyprenylated flavonoids affords rarely isolated 2,2-dimethylchromane derivatives, which usually undergo oxidation to 2*H*-2,2-dimethylchromene derivatives. For example, a few C-isoprenyl flavonoids **2** [7, 8] as well as their cyclic isomers **3** [7, 9] were isolated from *Epimedium diphilum*, *Bursera leptophloes* (Figure 1).

Direct prenylation of phenols is a challenging problem for the synthesis of prenylated flavonoids. In the case of coumarins and chromones, direct prenylation was achieved using prenyl- or geranyl halides [10-14], 2-methyl-3-butene-2-ol [15], and enzyme-catalyzed prenylation with dimethylallyl diphosphate or geranyl diphosphate [16-18].

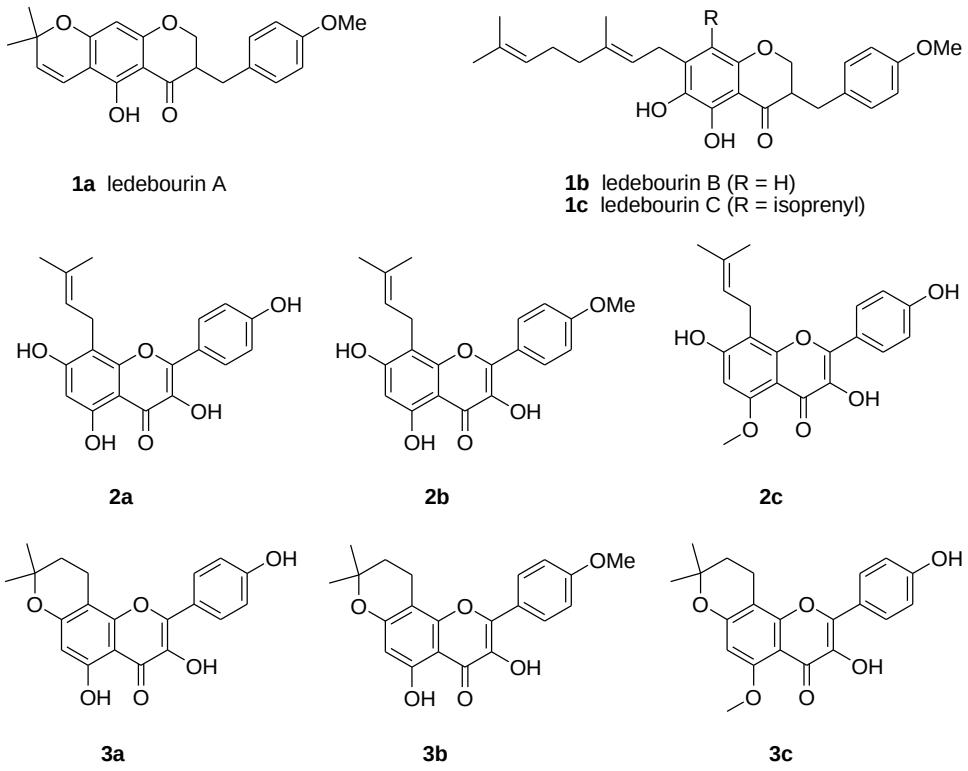
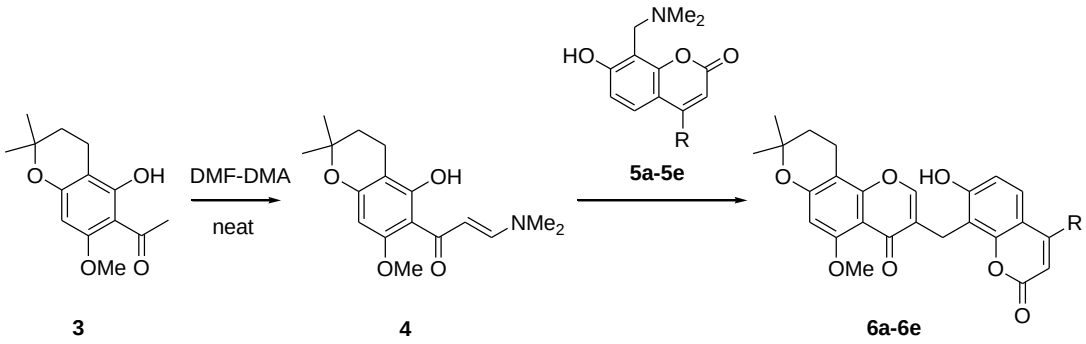


Figure 1. Chemical structures of some prenylated sappanin-type natural homoisoflavonoids and ring-chain isomeric prenylated flavones.



Scheme 1. Synthesis of homoisoflavonoid-coumarin hybrids.

However, in a similar condition, the formation of isoprenyl-substituted compounds and/or 2,2-dimethylchromanes was observed. It should be noted, these reactions had poor selectivity and yield; the formation of O-prenylated, 6,6- or 8,8-bisprenylated compounds was observed using 5,7-dihydroxycoumarins [11, 19] and 5,7-dihydroxychromones [20]; C-3 prenylation of coumarins also was observed [10].

Moreover, this reaction is impossible in the case of A- and B- ring flavonoids due to the low selectivity of prenylation. For the synthesis of A-ring prenylated homoisoflavonoids-coumarin hybrids, we used described one-pot procedure which includes inverse electron-demand Diels-Alder reaction with subsequent intramolecular cascade reactions (Scheme 1) [21].

Started enaminone **4** was synthesized by a reaction of 1-(5-hydroxy-7-methoxy-2,2-dimethylchroman-6-yl)ethan-1-one (**3**) with dimethylformamide dimethyl acetal. 8-Dimethylaminomethyl-7-hydroxycoumarins were synthesized by aminomethylation of 7-hydroxycoumarins with bis(dimethylamino)methane in propanol-2 solution.

The reaction of enaminone **4** with coumarin Mannich bases **5a-5e** was carried out in DMF at reflux for 6 h. The formation of compounds **6a-6e** could be considered as cascade reactions which include: the thermally generated formation of quinone methides **7** from coumarin Mannich bases **5**, inverse electron-demand Diels-Alder reaction of compounds **7** with enaminone **4**, deamination of hemiaminals **8** with the formation of 4*H*-chromeno derivatives **9**, and intramolecular nucleophilic attack of C-4 with the

phenolic group. As result, compounds **6a-6e** were alone products of the reaction of enaminone **4** with 8-dimethylaminomethylcoumarins **5a-5e** (Scheme 2).

Conclusions

As a result, we demonstrated the efficient synthesis of 3-(7-hydroxy-2-oxo-2*H*-chromen-8-ylmethyl)-5-methoxy-8,8-dimethyl-9,10-dihydro-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-ones as isomers of prenylated homoisoflavonoid-coumarin hybrids by the cascade reaction of (2*E*)-3-(dimethylamino)-1-(5-hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)prop-2-en-1-one with 7-hydroxycoumarin Mannich bases.

Experimental section

^{1}H and ^{13}C spectra were recorded on Bruker 500 (500/125 MHz) or Bruker 400 (400/100 MHz) spectrometers in $CDCl_3$ [residual $CHCl_3$ (δ_H = 7.26 ppm) or $CDCl_3$ (δ_C = 77.16 ppm) as internal standard] or DMSO-d_6 [residual $SO(CD_3)(CD_2H)$ (δ_H = 2.50 ppm) or $SO(CD_3)_2$ (δ_C = 39.52 ppm) as internal standard]. Melting points were determined in open capillary tubes using Buchi B-535 apparatus and were uncorrected. Mass spectra were obtained using an Agilent 1100 spectrometer using APCI (atmospheric-pressure chemical ionization). Elemental analysis was performed on a Vario MICRO cube automated CHNS-analyzer. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04-0.063 mm silica gel.

Compound **5a** was synthesized as reported previously [21].

(2E)-3-(Dimethylamino)-1-(5-hydroxy-7-methoxy-2,2-di-methyl-3,4-dihydro-2H-chromen-6-yl)prop-2-en-1-one **(4)**.

A mixture of 0.75 g (3 mmol) in 2 ml DMF-DMA was heated at reflux for 1 h, cooled, and formed residue was filtered off and washed with MeOH. Compound 4 was recrystallized from MeOH.

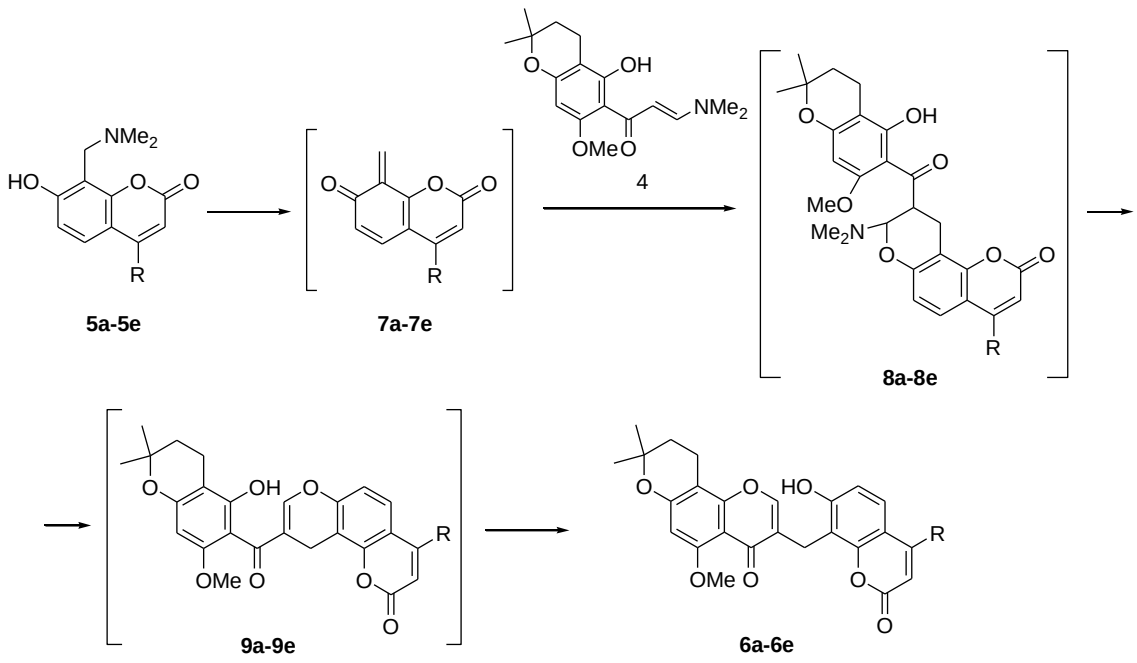
Yield 513 mg, 56%; mp 187-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.98 (s, 1H), 7.88 (d, *J* 12.4 Hz, 1H), 6.26 (d, *J* 12.4 Hz, 1H), 5.82 (s, 1H), 3.79 (s, 3H), 3.09 (s, 3H), 2.91 (s, 3H), 2.60 (d, *J* 6.7 Hz, 2H), 1.77 (t, *J* 6.7 Hz, 2H), 1.32 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 165.1, 159.9, 158.4, 154.0, 104.5, 102.0, 97.0, 91.1, 75.4, 55.5, 45.1, 37.3, 32.4, 26.8, 16.4. LC/MS (APCI) *m/z* 306.2 $[M+H]^+$. Anal. calcld. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.71; H, 7.48; N, 4.81.

*General procedure for the synthesis of 8-dimethylaminomethylcoumarins **5**.*

To a stirred suspension of coumarins **5c-5e** (2 mmol) in 10 mL of isopropanol was added 0.3 mL (2.2 mmol, 1.1 eq) of bis(N,N-dimethylamino)methane at 70 °C. The mixture was heated at 80 °C for 2 h and cooled, and diluted with hexane. The formed residue was filtered off and washed with hexane. The Mannich bases **5** were recrystallized from isopropanol-hexane.

*8-[(Dimethylamino)methyl]-7-hydroxy-4-methyl-2H-chromen-2-one **(5b)**.*

Yield 271 mg, 58%; mp 95-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 7.33 (d, *J* 8.7 Hz, 1H), 6.68 (d, *J* 8.7 Hz, 1H), 5.98 (s, 1H), 3.92 (s, 2H), 2.33 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 161.1, 153.3,



Scheme 2. Plausible reaction mechanism.

152.3, 124.6, 113.3, 112.0, 110.4, 108.0, 55.1, 44.4, 18. LC/MS (APCI) *m/z* 234.2 $[M+H]^+$. Anal. calcld. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.31; H, 6.71; N, 6.25.

8-[(Dimethylamino)methyl]-7-hydroxy-4-(methoxymethyl)-2H-chromen-2-one ***(5c)***.

Yield 448 mg, 85%; mp 126-128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.33 (d, *J* 8.7 Hz, 1H), 6.73 (d, *J* 8.7 Hz, 1H), 6.30 (s, 1H), 4.56 (s, 2H), 4.00 (s, 2H), 3.48 (s, 3H), 2.38 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 161.3, 152.6, 152.3, 123.8, 113.5, 109.6, 108.5, 108.3, 70.4, 59.1, 55.2, 44.5. LC/MS (APCI) *m/z* 264.0 $[M+H]^+$. Anal. calcld. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.13; H, 6.26; N, 5.44.

8-[(Dimethylamino)methyl]-7-hydroxy-4-isopropyl-2H-chromen-2-one ***(5d)***.

Yield 392 mg, 75%; mp 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 7.41 (d, *J* 8.9 Hz, 1H), 6.68 (d, *J* 8.8 Hz, 1H), 6.02 (s, 1H), 3.93 (s, 2H), 3.17 (hept, *J* 6.8 Hz, 1H), 2.32 (s, 6H), 1.21 (d, *J* 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.6, 161.9, 152.6, 124.1, 113.3, 110.7, 108.3, 106.4, 55.2, 44.4, 28.5, 21.9. LC/MS (APCI) *m/z* 262.2 $[M+H]^+$. Anal. calcld. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.52; N, 5.21.

4-Cyclopropyl-8-[(dimethylamino)methyl]-7-hydroxy-2H-chromen-2-one ***(5e)***.

Yield 482 mg, 93%; mp 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 7.67 (d, *J* 8.8 Hz, 1H), 6.72 (d, *J* 8.8 Hz, 1H), 5.75 (s, 1H), 3.94 (s, 2H), 2.34 (s, 6H), 2.11-1.88 (m, 1H), 1.16-0.97 (m, 2H), 0.87-0.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 161.9, 158.7, 152.2, 124.7, 113.3, 112.3, 108.0, 105.4, 55.2, 44.5, 12.0, 8.1. LC/MS (APCI) *m/z* 260.2 $[M+H]^+$. Anal. calcld. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.73; H, 6.45; N, 5.67.

General procedure for the synthesis of homoisoflavonoids ***6***.

A mixture of enaminone **4** (1 mmol) and corresponding Mannich base **5a-e** (1 mmol) in DMF (10 mL) was stirred at reflux for 6 h. The reaction mixture was cooled, the solvent was evaporated, and formed residue was washed with water and purified by recrystallization from DMF-MeOH mixture.

3-[(7-Hydroxy-2-oxo-2H-chromen-8-yl)methyl]-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-pyrano[2,3-f]-chromen-4-one ***(6a)***.

Yield 326 mg, 75%; mp 263-265 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 7.92 (d, *J* 9.4 Hz, 1H), 7.53 (s, 1H), 7.44 (d, *J* 8.5 Hz, 1H), 6.87 (d, *J* 8.5 Hz, 1H), 6.32 (s, 1H), 6.20 (d, *J* 9.4 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 2H), 2.58 (t, *J* 6.7 Hz, 2H), 1.75 (t, *J* 6.7 Hz, 2H), 1.27 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.6, 160.4, 159.2, 158.4, 157.9, 156.4, 153.6, 150.4, 144.8, 127.7, 122.0, 112.9, 111.6, 111.5, 111.2, 107.5, 100.8, 96.8, 75.9, 55.9, 31.0, 26.2, 18.8, 15.7. LC/MS (APCI) *m/z* 435.2 $[M-H]^-$. Anal. calcld. for $C_{25}H_{22}O_7$: C, 69.12; H, 5.10. Found: C, 69.03; H, 5.38.

3-[(7-Hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methyl]-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-pyrano-[2,3-f]chromen-4-one ***(6b)***.

Yield 309 mg, 69%; mp 268-270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.56-7.48 (m, 2H), 6.88 (d, *J* 8.8 Hz, 1H), 6.31 (s, 1H), 6.12 (s, 1H), 3.77 (s, 3H), 3.70 (s, 2H), 2.58 (t, *J* 6.6 Hz, 2H), 2.35 (s, 3H), 1.75 (d, *J* 6.6 Hz, 2H), 1.27 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.6, 160.2, 159.0, 158.4, 157.9, 156.4, 153.7, 152.9, 150.3, 124.4, 122.1, 112.6, 112.3, 111.5, 110.1, 107.5, 100.8, 96.8, 75.9, 55.9, 31.0, 26.2, 18.9, 18.2, 15.7. LC/MS (APCI) *m/z* 449.0 $[M+H]^+$. Anal. calcld. for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found: C, 69.84; H, 5.53.

3-{[7-Hydroxy-4-(methoxymethyl)-2-oxo-2H-chromen-8-yl]methyl}-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-pyrano[2,3-f]chromen-4-one ***(6c)***.

Yield 388 mg, 81%; mp 261-263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.54 (s, 1H), 7.46 (d, *J* 8.7 Hz, 1H), 6.87 (d, *J* 8.7 Hz, 1H), 6.33 (s, 1H), 6.19 (s, 1H), 4.62 (s, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 3.41 (s, 3H), 2.60 (t, *J* 6.7 Hz, 2H), 1.76 (t, *J* 6.7 Hz, 2H), 1.28 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.6, 160.3, 159.0, 158.4, 157.9, 156.4, 153.1, 152.8, 150.4, 123.7, 122.0, 112.7, 111.7, 109.9, 107.8, 107.5, 100.9, 96.9, 76.0, 69.5, 58.4, 55.9, 31.0, 26.2, 19.0, 15.7. LC/MS (APCI) *m/z* 479.0 $[M+H]^+$. Anal. calcld. for $C_{27}H_{26}O_8$: C, 67.77; H, 5.48. Found: C, 67.53; H, 5.65.

3-[(7-Hydroxy-4-isopropyl-2-oxo-2H-chromen-8-yl)-methyl]-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-pyrano-[2,3-f]chromen-4-one ***(6d)***.

Yield 372 mg, 78%; mp 246-248 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.64 (d, *J* 7.2 Hz, 1H), 7.55 (s, 1H), 6.90 (d, *J* 8.7 Hz, 1H), 6.34 (s, 1H), 6.09 (s, 1H), 3.78 (s, 3H), 3.71 (s, 2H), 3.34 3.26 (m, 1H), 2.61 (d, *J* 6.6 Hz, 1H), 1.77 (d, *J* 6.6 Hz, 3H), 1.28 (s, 6H), 1.23 (d, *J* 6.7 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.6, 162.9, 160.7, 158.8, 158.4, 158.0, 156.4, 153.2, 150.4, 123.9, 122.1, 112.8, 111.9, 111.0, 107.5, 106.3, 100.8, 96.9, 75.9, 55.9, 31.0, 28.0, 26.2, 21.7, 19.0, 15.7. LC/MS (APCI) *m/z* 477.0 $[M+H]^+$. Anal. calcld. for $C_{28}H_{28}O_7$: C, 70.58; H, 5.92. Found: C, 70.36; H, 6.17.

3-[(4-Cyclopropyl-7-hydroxy-2-oxo-2H-chromen-8-yl)-methyl]-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-pyrano[2,3-f]chromen-4-one ***(6e)***.

Yield 266 mg, 56%; mp 244-246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.81 (d, *J* 8.8 Hz, 1H), 7.53 (s, 1H), 6.91 (d, *J* 8.8 Hz, 1H), 6.31 (s, 1H), 5.81 (s, 1H), 3.77 (s, 3H), 3.71 (s, 2H), 2.56 (t, *J* 6.6 Hz, 2H), 2.27-2.12 (m, 1H), 1.73 (d, *J* 6.6 Hz, 2H), 1.25 (s, 6H), 1.13-1.00 (m, 2H), 0.91-0.77 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.6, 160.7, 159.0, 158.9, 158.4, 157.9, 156.4, 152.8, 150.4, 124.3, 122.1, 112.7, 112.5, 111.6, 107.5, 104.5,

100.8, 96.8, 75.9, 55.9, 31.0, 26.2, 19.0, 15.7, 11.5, 8.6. LC/MS (APCI) *m/z* 475.0 $[M+H]^+$. Anal. calcld. for $C_{28}H_{26}O_7$: C, 70.87; H, 5.52. Found: C, 70.63; H, 5.76.

Notes

The authors declare no conflict of interest.

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Синтез пренільованих гомоізофлавоноїдів із кумариновим фрагментом

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Резюме: Синтезовано ряд пренільованих гомоізофлавоноїд-кумаринових гібридів шляхом каскадних реакцій кумаринових основ Манніха з 3-(диметиламіно)-1-(5-гідрокси-7-метокси-2,2-диметил-3,4-дигідро-2*H*-хромен-6-іл)проп-2-ен-1-оном. Отримані гомоїзофлавоноїди можуть мати великий потенціал для подальших досліджень їх біологічної активності.

Ключові слова: кумарини; гомоізофлавоноїди; обернена за електронними вимогами реакція Дільса-Альдера.