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1-Nicotinoylbenzotriazole: A Convenient Tool for Site-Selective Protection of 5,7-Dihydroxycoumarins

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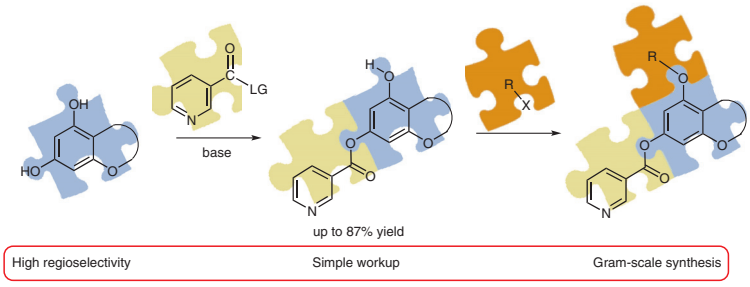

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Abstract 1-Nicotinoylbenzotriazole (NicBt) was uncovered as an efficient protecting agent for the site-selective acylation of resorcinol-type phenolic groups with almost equal reactivity. The use of NicBt allows selective protection of the 7-OH group in 5,7-dihydroxycoumarins in one simple scalable step, while combination of the nicotinoylation with tosylation–denicotinoylation or silylation–denicotinoylation yields 5-OH-protected 5,7-dihydroxycoumarins. Furthermore, nicotinoylated 5,7-dihydroxycoumarins proved useful in a gram-scale three-step preparation of a 2,2-dimethylpyrano[2,3-*f*]coumarin, a key intermediate for the synthesis of calanolide A, an HIV reverse transcriptase and *Mycobacterium tuberculosis* inhibitor, and its active analogues.

Key words esterification, protecting groups, phenols, acylation, natural products, total synthesis

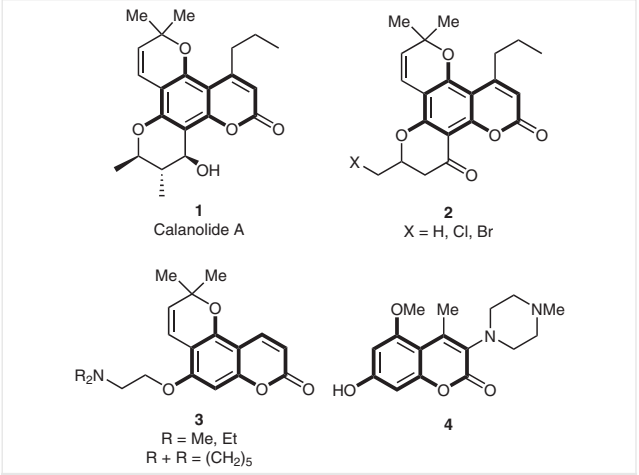

Figure 1 Biologically active compounds containing an asymmetrically substituted 5,7-dihydroxycoumarin core

Derivatives of asymmetrically O-substituted 5,7-dihydroxycoumarins attract immense attention as an important class of biologically active compounds. For example, tetracyclic coumarin natural products isolated from plants of the genus *Calophyllum* have anti-HIV activity.[1] Among them, calanolide A (**1**) (Figure 1) was identified as an inhibitor of HIV reverse transcriptase and *Mycobacterium tuberculosis*.[2] Synthetic calanolide analogue **2**[3] showed higher activity against HIV compared to the parent compound. *O*-Aminoalkyl derivatives **3**[4] demonstrated anticancer activity and compound **4** can be used for the prevention and treatment of brain lesions, in particular, stroke, dementia and Parkinson's disease.[5]

A general approach to asymmetrically substituted 5,7-dihydroxycoumarin derivatives is a deactivation of one hydroxyl group at position C5 or C7 of 5,7-dihydroxycoumarin. Usually, the deactivation of a hydroxyl group is carried out either by a Friedel–Crafts acylation of 5,7-dihydroxycoumarin at position C8 to give 8-acyl-5,7-dihydroxycoumarins[3,6] or by preparation of 7-monoprotected 5,7-dihydroxycoumarins.[3a,7] The latter approach is tedious, since the reactivity of hydroxyl groups in positions 5 and 7 is equal. For example, direct methylation with dimethyl sulfate in the presence of potassium carbonate[7c] or acylation with acyl chloride in the presence of aluminum chloride[7a] lead to a mixture of products with low yield of the desired compound. A general method for producing 7-monoprotected coumarins (Scheme 1) consists of an exhaustive tosylation followed by the selective removal of one of the protecting groups with tetrabutylammonium fluoride (TBAF).[3a,7] Thus, the drawbacks of known methods are multistep procedures. In addition, the purification of products can be carried out efficiently only using chromatography. Therefore,

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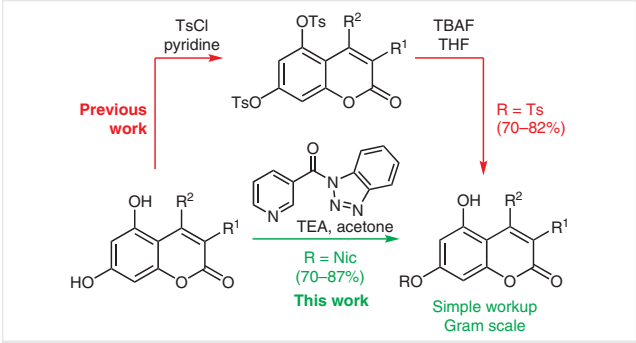
the development of a novel and efficient one-step strategy to access O-monosubstituted 5,7-dihydroxycoumarins is highly desirable.

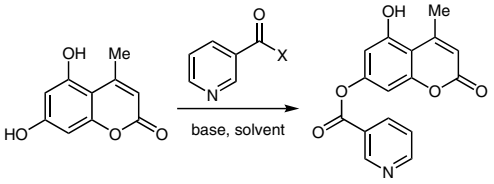
In continuation of our work on the site-selective modification of benzopyrones,[8] we aimed to develop a new method for the selective protection of the hydroxyl groups in 5,7-dihydroxycoumarins. To address the challenge of selectivity, we utilized a protective group capable of forming a hydrogen bond for the regioselective protection of 5,7-dihydroxycoumarins. In the present work (Scheme 1), we report a one-step scalable protocol for the direct nicotinoylation of the 7-OH group of 5,7-dihydroxycoumarins.



Scheme 1 Different approaches for the synthesis of 7-O-substituted 5,7-dihydroxycoumarins

It was found that the reaction of nicotinoyl azide with 5,7-dihydroxy-4-methylcoumarin (**5a**) in the presence of a slight excess of triethylamine (TEA) in THF at room temperature gave single product **6a** in moderate yield (Table 1, entry 1), while refluxing did not increase the yield (Table 1, entry 2). Next, we optimized the reaction conditions. A notable improvement in the product yield was achieved when acetone was used as solvent (Table 1, entry 3). When nicotinoyl azide was replaced with nicotinoyl chloride hydrochloride, and diisopropylethylamine (DIPEA) was used as base, the desired product **6a** and the 5,7-di-O-nicotinoylated product were obtained as a 4:1 mixture (Table 1, entry 4). Reaction with methyl nicotinate (Table 1, entry 5) gave a mixture of the starting materials. Further, our attention was drawn to the work of Katritzky and co-workers,[9] who described *N*-acylbenzotriazole derivatives as effective C-, N- and O-acylating agents. We found that using the benzotriazolyl moiety as leaving group gave very good yields of monoprotected product **6a** as a pure crystalline substance, without the formation of any byproducts (Table 1, entry 6). It should be noted that utilizing bases with close basicity (TEA, DIPEA and DMAP, conjugate acids in DMSO: pK_a = 9.0, 8.5[10a] and 7.9,[10b] respectively) in this reaction did not significantly affect the yield (Table 1, entries 7 and 8). However, using a stronger base (DBU, conjugate acid in DMSO: pK_a = 13.9[10a]) led to a complex mixture of mono- and diacylated products and reactants (Table 1, entry 9). On the other hand, weakly basic pyridine (pK_a = 3.3[10a]) produced the desired product **6a** in only 10% yield even after 72 hours (Table 1, entry 10). The use of an extra quantity of TEA also did not change the yield of **6a** (Table 1, entry 11).

Table 1 Optimization of the Nicotinoylation Reaction Conditions[a]



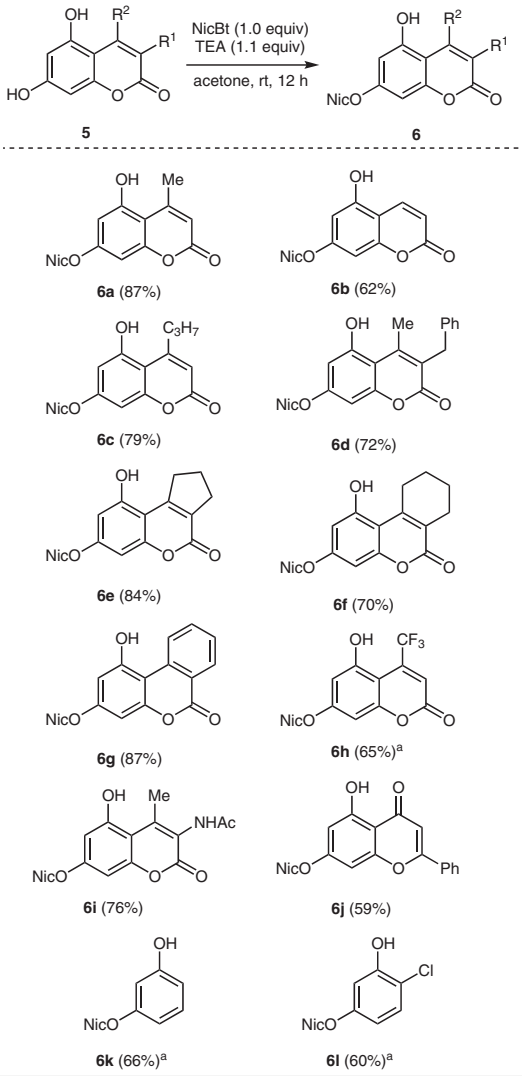
5a **6a**

Entry	X	Base (equiv)	Solvent	Yield (%)[b]
1	N_3	TEA (1.1)	THF	46
2[c]	N_3	TEA (1.1)	THF	44
3	N_3	TEA (1.1)	acetone	71
4	Cl	DIPEA (2.2)	acetone	38, mixture[d,e]
5	OMe	TEA (1.1)	acetone	NR[f]
6	 (1-benzotriazolyl, Bt)	TEA (1.1)	acetone	87
7	Bt	DIPEA (1.1)	acetone	86
8	Bt	DMAP (1.1)	acetone	87
9	Bt	DBU (1.1)	acetone	complex mixture[e]
10[g]	Bt	pyridine (1.1)	acetone	10
11	Bt	TEA (1.5)	acetone	85

[a] Reaction conditions, unless otherwise noted: **5a** (0.5 mmol), nicotinoyl derivative (0.5 mmol), base, solvent (5 mL), room temperature, overnight.
[b] Yield of isolated product based on **5a**.
[c] Temperature: 66 °C.
[d] 4:1 mixture of **6a** with 5,7-di-O-nicotinoylated product.
[e] Based on NMR study.
[f] NR: no reaction.
[g] Reaction time: 72 h.

Since the use of DIPEA or DMAP did not provide any advantages over TEA in terms of yield or convenience, we later used TEA (Table 1, entry 6) for the selective protection of various 5,7-dihydroxycoumarin derivatives (Scheme 2). All of the 5,7-dihydroxycoumarins afforded 7-*O*-nicotinoyl derivatives **6a–i** as pure crystalline substances in fair to very good yields. 5,7-Dihydroxy-4-(trifluoromethyl)coumarin (**5h**) did not form a crystalline precipitate of **6h** from acetone due to its high solubility. However, a solid was obtained when acetone was replaced with ethyl acetate. Coumarins with other positions of the hydroxyl groups, such as 6,7-dihydroxycoumarin and 7,8-dihydroxycoumarin, yielded a mixture of isomers in this nicotinoylation reaction. 5,7-Dihydroxyflavone (chrysin, **5j**) was used in the reaction and gave the anticipated product **6j** in 59% yield. Interestingly, the acylation of resorcinol and its 4-chloro derivative

with 1-nicotinoylbenzotriazole in the presence of TEA in ethyl acetate gave the monosubstituted products **6k**, **6l** in good yields.



Scheme 2 Scope of the nicotinoylation. [a] EtOAc used as solvent.

The site of nicotinoylation was established using 2D ^{1}H–^{13}C HMBC experiments. Thus, compounds **6** were characterized by cross peaks between the OH hydrogen and the C6 and C4a benzene ring carbons (see Supporting Information, Figure S7). Obviously, if a free hydroxyl group was present at the 7-position, cross peaks between OH and both C6 and C8 would be registered in the HMBC spectrum.

To gain insight into the selective nature of this reaction, the role of the type and position of the heteroatom for the regioselectivity was investigated. When the pyridine ring was replaced by furan or benzene, a mixture of the 5,7-diprotected product and the starting 5,7-dihydroxycoumarin **5a** was formed (according to ^{1}H NMR data) and thus no selectivity was observed. Reactions with 1-isonicotinoyl-, picolinyl-, pyrazinylcarbonyl- and 2-(indol-3-yl)acetylbenzotriazole also failed. These results indicated the crucial role of one nitrogen heteroatom in the 3-nicotinoyl ring for the selectivity of this reaction.

In order to demonstrate the opportunities of this method, we modified the free 5-OH group and removed the nicotinoyl protective group (Scheme 3). Acylation of coumarin **6c** with acetic anhydride yielded the corresponding derivative **7** in 94% yield. Unfortunately, upon deprotecting with HCl, compound **7** lost both the nicotinoyl and acetyl groups, yielding 5,7-dihydroxycoumarin **5c**. However, the acetyl derivative **7** formed single crystals and such a single crystal was used in an X-ray diffraction experiment which provided solid evidence for the 7-OH nicotinoylated structure (Figure 2).

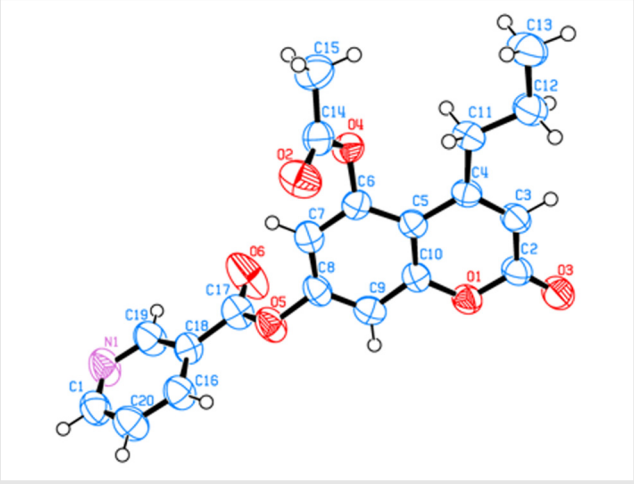
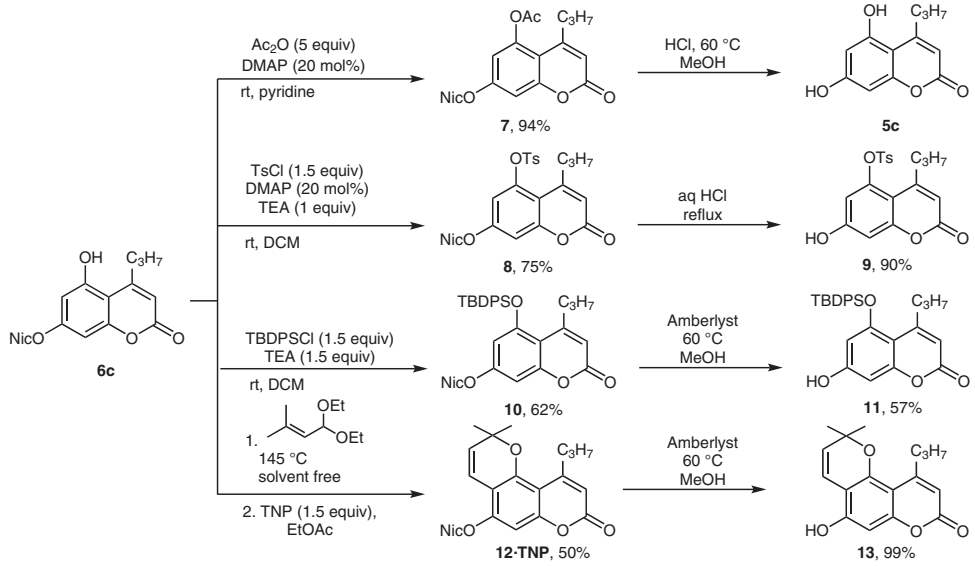


Figure 2 X-ray crystal structure (CCDC 1894797) of **7**

Tosylation and silylation of **6c** with *p*-toluenesulfonyl chloride and *tert*-butyldiphenylsilyl chloride (TBDPSCl), orthogonal protecting groups, yielded more promising derivatives **8** and **10**. Compound **8** was deprotected with HCl solution to obtain 5-*O*-tosylated product **9** completing the exchange of protective groups in the 7-OH and 5-OH positions. Silylated derivative **10**, upon treatment with Amberlyst 16 resin, yielded 5-*O*-silylated product **11** (Scheme 3). Thus, the proposed method can also be considered as a simple tool to 5-OH-protected derivatives of 5,7-dihydroxycoumarins, a class of compounds characterized by tedious multistep preparation and not previously substantially described (to our knowledge, the only published article[6c] presented a selective synthesis of 5-benzyloxy-7-hydroxycoumarins).

Since the 5,7-dihydroxycoumarin scaffold is part of the anti-HIV calanolide-type alkaloids **1**, **2**, we exploited selectively protected **6c** for the synthesis of the calanolide A precursor 2,2-dimethylpyranocoumarin **13**. Annulations of a 2,2-dimethylpyran ring are usually carried out with 3-



Scheme 3 Synthetic opportunities of the novel method

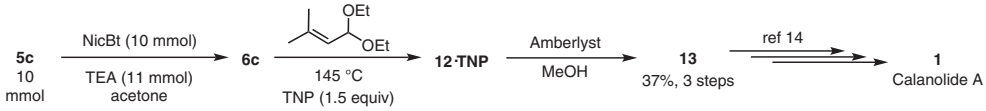
chloro-3-methylbut-1-yne[7a] in the presence of various catalysts or with 3-methylbut-2-enal[11] or its diethyl acetal[3a,4,7b,12] in the presence of pyridine or picoline[13] in high boiling solvents (e.g., toluene). Since the pyridine core was present in compounds **6** as the nicotinoyl moiety, one may assume that the reaction may be carried out without additional bases. We used 1,1-diethoxy-3-methylbut-2-ene in the Claisen rearrangement with coumarin **6c** under solvent- and base-free conditions at 145 °C, yielding pyranocoumarin **12** (Scheme 3). Compound **12** was isolated from the reaction mixture by addition of picric acid (2,4,6-trinitrophenol, TNP), giving pure pyranocoumarin **12** as the solid crystalline picrate. Removal of the nicotinoyl group with Amberlyst 16 resin in methanol yielded the desired pyranocoumarin **13** in almost quantitative yield (Scheme 3).

Notably, the synthesis of **13** from **5c** on a 10-mmol scale gave **13** in 37% overall yield (1.05 g), demonstrating the practical applicability of the method for the large-scale synthesis of calanolide-type pyranocoumarins and the stereoselective synthesis of calanolide A itself[14] (Scheme 4).

In summary, we have developed a method for the site-selective protection of one of the hydroxyl groups in benzopyrones using a benzotriazole derivative of pyridinecarboxylic acid. The scope of the reaction was demonstrated by the conversion of various coumarins and 1,3-dihydroxybenzenes with 1-nicotinoylbenzotriazole. Combination of the nicotinoylation with tosylation–denicotinoylation or silylation–denicotinoylation allows the preparation of 5-OH-protected 5,7-dihydroxycoumarins.

^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 or DMSO-d_6/CCl_4 as a solvent. Chemical shifts (δ) are given in parts per million (ppm) relative to the deuterated solvent [δ = 2.5 ppm for DMSO-d_6 and for the mixture of DMSO-d_6/CCl_4 (1:1) for ^{1}H and δ = 39.52 ppm for DMSO-d_6 and for the mixture of DMSO-d_6/CCl_4 (1:1) for ^{13}C]. Abbreviations are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), m (multiplet), q (quartet), quint (quintet), br s (broad signal). Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Bruker Alpha (ATR, ZnSe) IR-Fur spectrophotometer. Elemental analyses were carried out using a CHNS/O analyzer Perkin-Elmer 2400 Series II instrument. Reactions were monitored using TLC (silica gel plates). Visualization was accomplished with UV light (254 or 365 nm).

1*H*-1,2,3-Benzotriazol-1-yl(pyridin-3-yl)methanone, 1*H*-1,2,3-benzotriazol-1-yl(pyridin-4-yl)methanone, 1*H*-1,2,3-benzotriazol-1-yl(pyridin-2-yl)methanone, 1*H*-1,2,3-benzotriazol-1-yl(furan-2-yl)methanone and 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-(1*H*-indol-3-yl)ethanone were synthesized in accordance with procedures described by Katritzky and co-workers.[9] All of the NMR spectra of the known compounds were in full accordance with the published data. Resorcinol (**5k**), 4-chlororesorcinol (**5l**) and 5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (**5j**) were purchased from Sigma-Aldrich and used



Scheme 4 Gram-scale synthesis of **13**

without further purification. 5,7-Dihydroxy-2*H*-chromen-2-one (**5b**),[12b] 1,3-dihydroxy-6*H*-benzo[*c*]chromen-6-one (**5g**)[15] and 5,7-dihydroxy-4-(trifluoromethyl)-2*H*-chromen-2-one (**5h**)[16] were prepared according to known methods. Other coumarins **5a**,**c**–**f**,**i** were synthesized according to the modified procedure described by Sharghi and Jokar.[17]

Nicotinoyl Derivatives 6; General Procedure

To a solution of coumarin **5** (0.5 mmol) and 1-nicotinoylbenzotriazole (112 mg, 0.5 mmol) in anhydrous acetone (5 mL) was added TEA (76 μL, 0.55 mmol). The mixture was then stirred overnight at room temperature. The formed precipitate was collected by filtration, washed with acetone and dried under air to give the corresponding **6**.

5-Hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl Nicotinate (6a)

White solid; yield: 129 mg (87%); mp 269–271 °C.

IR-Fur (neat): 1737, 1615, 1428, 1292, 1085 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.85 (s, 1 H, OH-5), 9.25 (d, *J* = 1.6 Hz, 1 H, H-2′), 8.85 (dd, *J* = 1.6, 4.9 Hz, 1 H, H-6′), 8.44 (dt, J_d = 8.0 Hz, J_t = 1.9 Hz, 1 H, H-4′), 7.60 (dd, *J* = 4.9, 8.0 Hz, 1 H, H-5′), 6.71 (d, *J* = 2.3 Hz, 1 H, H-8), 6.69 (d, *J* = 2.3 Hz, 1 H, H-6), 6.01 (d, *J* = 1.0 Hz, 1 H, H-3), 2.62 (d, *J* = 1.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.5 (C=O), 158.8 (C-2), 157.4 (C-8a), 155.2 (C-5), 153.8 (C-6′), 153.7 (C-4), 152.3 (C-7), 150.3 (C-2′), 137.1 (C-4′), 124.6 (C-3′), 123.5 (C-5′), 112.2 (C-3), 107.0 (C-4a), 104.6 (C-6), 100.7 (C-8), 23.1 (CH_3).

Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.71; H, 3.64; N, 4.78.

5-Hydroxy-2-oxo-2*H*-chromen-7-yl Nicotinate (6b)

White solid; yield: 88 mg (62%); mp 246–248 °C.

IR-Fur (neat): 1737, 1614, 1444, 1287, 1109, 1075 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 11.16 (s, 1 H, OH-5), 9.25 (d, *J* = 1.3 Hz, 1 H, H-2′), 8.88 (dd, *J* = 1.3, 4.8 Hz, 1 H, H-6′), 8.45 (dt, J_d = 8.0 Hz, J_t = 1.7 Hz, 1 H, H-4′), 8.10 (d, *J* = 9.7 Hz, 1 H, H-4), 7.64 (dd, *J* = 4.8, 8.0 Hz, 1 H, H-5′), 6.85 (d, *J* = 1.7 Hz, 1 H, H-8), 6.72 (d, *J* = 1.7 Hz, 1 H, H-6), 6.32 (d, *J* = 9.7 Hz, 1 H, H-3).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.9 (C=O), 159.8 (C-2), 155.5 (C-5), 155.1 (C-8a), 154.2 (C-6′), 153.3 (C-7), 150.6 (C-2′), 138.8 (C-4), 137.5 (C-4′), 124.8 (C-3′), 123.9 (C-5′), 113.0 (C-3), 106.6 (C-4a), 104.2 (C-6), 100.9 (C-8).

Anal. Calcd for $C_{15}H_9NO_5$: C, 63.61; H, 3.20; N, 4.95. Found: C, 63.50; H, 3.34; N, 4.83.

5-Hydroxy-2-oxo-4-propyl-2*H*-chromen-7-yl Nicotinate (6c)

White solid; yield: 128 mg (79%); mp 229–231 °C.

IR-Fur (neat): 1739, 1613, 1434, 1290, 1150, 1082 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.90 (s, 1 H, OH-5), 9.27 (s, 1 H, H-2′), 8.91–8.83 (m, 1 H, H-6′), 8.52–8.45 (m, 1 H, H-4′), 7.68–7.60 (m, 1 H, H-5′), 6.72 (s, 2 H, H-6 + H-8), 5.97 (s, 1 H, H-3), 3.00–2.90 (m, 2 H, C-4-CH_2), 1.75–1.61 (m, 2 H, $CH_2CH_2CH_3$), 1.09–0.96 (m, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.2 (C=O), 159.0 (C-2), 157.3 (C-4), 157.0 (C-8a), 155.6 (C-5), 153.3 (C-6′), 152.1 (C-7), 150.0 (C-2′), 137.8 (C-4′), 124.9 (C-3′), 123.7 (C-5′), 111.7 (C-3), 106.4 (C-4a), 104.8 (C-6), 100.9 (C-8), 37.3 (C-4-CH_2), 22.3 ($CH_2CH_2CH_3$), 13.7 (CH_3).

Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.53; H, 4.79; N, 4.29.

3-Benzyl-5-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl Nicotinate (6d)

White solid; yield: 139 mg (72%); mp 223–225 °C.

IR-Fur (neat): 1743, 1700, 1604, 1428, 1285, 1157 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.80 (s, 1 H, OH-5), 9.30–9.22 (br s, 1 H, H-2′), 8.88–8.81 (m, 1 H, H-6′), 8.47–8.42 (m, 1 H, H-4′), 7.63–7.57 (m, 1 H, H-5′), 7.28–7.10 (m, 5 H, Ph), 6.72 (d, *J* = 2.3 Hz, 1 H, H-8), 6.70 (d, *J* = 2.3 Hz, 1 H, H-6), 3.97 (s, 2 H, CH_2), 2.65 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.4 (C=O), 160.2 (C-2), 157.3 (C-5), 153.8 (C-8a), 153.7 (C-6′), 151.5 (C-7), 150.5 (C-2′), 149.2 (C-4), 138.8 (C_i), 137.1 (C-4′), 127.9 (C_m), 127.6 (C_o), 125.6 (C_p), 124.6 (C-3′), 123.4 (C-5′), 121.7 (C-3), 107.5 (C-4a), 104.8 (C-6), 100.4 (C-8), 31.8 (CH_2), 19.3 (CH_3).

Anal. Calcd for $C_{23}H_{17}NO_5$: C, 71.31; H, 4.42; N, 3.62. Found: C, 71.21; H, 4.53; N, 3.49.

9-Hydroxy-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-7-yl Nicotinate (6e)

White solid; yield: 136 mg (84%); mp 255–257 °C.

IR-Fur (neat): 1744, 1735, 1712, 1615, 1292, 1112 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.71 (s, 1 H, OH-9), 9.24 (d, *J* = 1.4 Hz, 1 H, H-2′), 8.84 (dd, *J* = 1.4, 4.7 Hz, 1 H, H-6′), 8.44 (dt, J_d = 7.9 Hz, J_t = 1.9 Hz, 1 H, H-4′), 7.60 (dd, *J* = 4.7, 7.9 Hz, 1 H, H-5′), 6.74 (d, *J* = 1.8 Hz, 1 H, H-8), 6.66 (d, *J* = 1.8 Hz, 1 H, H-6), 3.35 (t, *J* = 7.5 Hz, 2 H, CH_2-1), 2.72 (t, *J* = 7.5 Hz, 2 H, CH_2-3), 2.1 (quint, *J* = 7.5 Hz, 2 H, CH_2-2).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.6 (C=O), 158.4 (C-4), 156.0 (C-9), 155.3 (C-5a), 155.1 (C-9b), 153.9 (C-6′), 151.9 (C-7), 150.5 (C-2′), 137.2 (C-4′), 124.7 (C-3′), 124.1 (C-3a), 123.6 (C-5′), 106.4 (C-9a), 104.1 (C-8), 100.5 (C-6), 35.6 (C-1), 29.1 (C-3), 22.1 (C-2).

Anal. Calcd for $C_{18}H_{13}NO_5$: C, 66.87; H, 4.05; N, 4.33. Found: C, 66.78; H, 4.15; N, 4.28.

1-Hydroxy-6-oxo-7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-3-yl Nicotinate (6f)

White solid; yield: 118 mg (70%); mp 223–225 °C.

IR-Fur (neat): 1742, 1733, 1703, 1614, 1292, 1277, 1080 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.63 (s, 1 H, OH-1), 9.26 (d, *J* = 1.6 Hz, 1 H, H-2′), 8.85 (dd, *J* = 1.6, 4.8 Hz, 1 H, H-6′), 8.45 (dt, J_d = 7.9 Hz, J_t = 1.9 Hz, 1 H, H-4′), 7.60 (dd, *J* = 4.8, 7.9 Hz, 1 H, H-5′), 6.70–6.65 (m, 2 H, H-2 + H-4), 3.20–3.12 (br s, 2 H, CH_2-10), 2.48–2.40 (br s, 2 H, CH_2-7), 1.81–1.70 (br s, 4 H, CH_2-8 + CH_2-9).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.6 (C=O), 159.8 (C-6), 156.9 (C-1), 153.9 (C-6′), 153.4 (C-4a), 151.0 (C-3), 150.4 (C-2′), 148.9 (C-10a), 137.2 (C-4′), 124.7 (C-3′), 123.6 (C-5′), 119.8 (C-6a), 107.2 (C-10b), 104.7 (C-2), 100.5 (C-4), 29.1 (CH_2-10), 24.1 (CH_2-7), 21.6 (CH_2-9), 20.7 (CH_2-8).

Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.57; H, 4.57; N, 4.03.

1-Hydroxy-6-oxo-6*H*-benzo[*c*]chromen-3-yl Nicotinate (6g)

White solid; yield: 145 mg (87%); mp >300 °C.

IR-Fur (neat): 1744, 1735, 1608, 1416, 1289, 1087 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.54 (s, 1 H, OH-1), 9.31–9.25 (br s, 1 H, H-2′), 9.15–9.11 (m, 1 H, H-10), 8.94–8.89 (m, 1 H, H-6′), 8.50–8.46 (m, 1 H, H-4′), 8.30–8.26 (m, 1 H, H-7), 7.96–7.92 (m, 1 H, H-9), 7.69–7.62 (m, 2 H, H-5′ + H-8), 6.98 (d, *J* = 2.4 Hz, 1 H, H-4), 6.90 (d, *J* = 2.4 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.1 (C=O), 160.2 (C-6), 157.3 (C-1), 154.4 (C-6′), 152.5 (C-4a), 151.0 (C-3), 150.7 (C-2′), 137.6 (C-4′), 135.2 (C-9), 134.2 (C-10a), 129.5 (C-7), 128.1 (C-8), 126.8 (C-10), 125.0 (C-3′), 124.1 (C-5′), 119.7 (C-6a), 105.7 (C-2), 104.5 (C-10b), 101.8 (C-4).

Anal. Calcd for $C_{19}H_{11}NO_5$: C, 68.47; H, 3.33; N, 4.20. Found: C, 68.25; H, 3.66; N, 4.03.

5-Hydroxy-2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl Nicotinate (6h)

EtOAc used as solvent.

Pale yellow solid; yield: 114 mg (65%); mp 257–259 °C.

IR-Fur (neat): 1738, 1614, 1402, 1279, 1229, 1148, 1084 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.61–11.44 (br s, 1 H, OH-5), 9.26 (d, *J* = 1.8 Hz, 1 H, H-2′), 8.91 (dd, *J* = 1.8, 4.8 Hz, 1 H, H-6′), 8.47 (dt, J_d = 1.8 Hz, J_t = 8.0 Hz, 1 H, H-4′), 7.66 (dd, *J* = 4.8, 8.0 Hz, 1 H, H-5′), 7.02 (d, *J* = 2.3 Hz, 1 H, H-8), 6.87 (s, 1 H, H-3), 6.83 (d, *J* = 2.3 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9 (C=O), 158.4 (C-2), 155.9 (C-5), 155.5 (C-8a), 154.4 (C-6′), 153.7 (C-7), 150.7 (C-2′), 138.6 (q, *J* = 33.8 Hz, C-4), 137.7 (C-4′), 124.8 (C-3′), 124.1 (C-5′), 121.7 (q, *J* = 274 Hz, CF_3), 115.6 (q, *J* = 7.4 Hz, C-3), 105.7 (C-6), 101.8 (C-4a), 101.7 (C-8).

Anal. Calcd for $C_{16}H_8F_3NO_5$: C, 54.71; H, 2.30; N, 3.99. Found: C, 54.52; H, 2.67; N, 3.79.

3-Acetamido-5-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-ylNicotinate (6i)

White solid; yield: 135 mg (76%); mp >300 °C.

IR-Fur (neat): 1732, 1716, 1670, 1614, 1292, 1088 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 11.30–11.01 (br s, 1 H, OH-5), 9.40 (s, 1 H, NH), 9.31–9.21 (br s, 1 H, H-2′), 8.91–8.86 (m, 1 H, H-6′), 8.51–8.42 (m, 1 H, H-4′), 7.70–7.63 (m, 1 H, H-5′), 6.91 (d, *J* = 2.1 Hz, 1 H, H-8), 6.79 (d, *J* = 2.1 Hz, 1 H, H-6), 2.44 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3(Ac)).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 168.6 (C=O(Ac)), 163.0 (C=O), 157.8 (C-2), 157.5 (C-5), 154.3 (C-6′), 153.1 (C-8a), 152.1 (C-7), 150.6 (C-2′), 147.2 (C-4), 137.6 (C-4′), 124.9 (C-3′), 124.1 (C-5′), 119.3 (C-3), 107.2 (C-4a), 105.4 (C-8), 101.1 (C-6), 22.5 (CH_3(Ac)), 18.5 (CH_3).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.80; H, 4.13; N, 7.87.

5-Hydroxy-4-oxo-2-phenyl-4*H*-chromen-7-yl Nicotinate (6j)

Recrystallized from DMF.

Pale yellow solid; yield: 106 mg (59%); mp 188–190 °C.

IR-Fur (neat): 1737, 1652, 1617, 1280, 1147, 1079 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.88 (s, 1 H, OH-5), 9.27 (d, *J* = 1.6 Hz, 1 H, H-2′), 8.92 (dd, *J* = 1.6, 4.8 Hz, 1 H, H-6′), 8.48 (dt, J_d = 8.0 Hz, J_t = 1.6 Hz, 1 H, H-4′), 8.13–8.08 (m, 2 H, Ph), 7.70–7.54 (m, 4 H, H-5′ + Ph), 7.31 (d, *J* = 1.8 Hz, 1 H, H-8), 7.15 (s, 1 H, H-3), 6.90 (d, *J* = 1.8 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.6 (C-4), 164.3 (C-2), 162.8 (C=O), 160.8 (C-5), 156.3 (C-8a), 155.6 (C-7), 154.5 (C-6′), 150.7 (C-2′), 137.6 (C-4′), 132.4 (C(Ph)), 130.4 (C_i(Ph)), 129.2 (C(Ph)), 126.6 (C(Ph)), 124.8 (C-3′), 124.1 (C-5′), 108.5 (C-4a), 105.8 (C-3), 105.5 (C-6), 101.8 (C-8).

Anal. Calcd for $C_{21}H_{13}NO_5$: C, 70.19; H, 3.65; N, 3.90. Found: C, 70.31; H, 3.53; N, 3.79.

3-Hydroxyphenyl Nicotinate (6k)

EtOAc used as solvent. Recrystallized from EtOAc.

White solid; yield: 71 mg (66%); mp 182–184 °C (Lit.[18] 183–183.5 °C).

IR-Fur (neat): 1735, 1597, 1484, 1427, 1238, 1143 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 9.57 (s, 1 H, OH), 9.23 (d, *J* = 1.5 Hz, 1 H, H-2′), 8.84 (dd, *J* = 1.5, 4.8 Hz, 1 H, H-6′), 8.43 (dt, J_d = 7.9 Hz, J_t = 1.9 Hz, 1 H, H-4′), 7.60 (dd, *J* = 4.8, 7.9 Hz, 1 H, H-5′), 7.24–7.17 (m, 1 H, H-5), 6.73–6.61 (m, 3 H, H-2 + H-4 + H-6).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 163.0 (C=O), 158.3 (C-1), 153.7 (C-6′), 151.0 (C-3), 150.4 (C-2′), 137.1 (C-4′), 129.5 (C-5), 125.1 (C-3′), 123.6 (C-5′), 113.0 (C-2 or C-4 or C-6), 111.6 (C-2 or C-4 or C-6), 108.8 (C-2 or C-4 or C-6).

4-Chloro-3-hydroxyphenyl Nicotinate (6l)

EtOAc used as solvent. Recrystallized from acetonitrile.

White solid; yield: 75 mg (60%); mp 171–173 °C.

IR-Fur (neat): 1741, 1612, 1391, 1221, 1094, 727 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.28 (s, 1 H, OH), 9.28–9.19 (br s, 1 H, H-2′), 8.88–8.79 (m, 1 H, H-6′), 8.47–8.37 (m, 1 H, H-4′), 7.62–7.53 (m, 1 H, H-5′), 7.31 (d, *J* = 8.6 Hz, 1 H, H-5), 6.86 (d, *J* = 1.8 Hz, 1 H, H-2), 6.67 (dd, *J* = 8.6, 1.8 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6/CCl_4, 1:1): δ = 162.8 (C=O), 153.7 (C-6′ + C-3), 150.4 (C-2′), 149.1 (C-1), 137.0 (C-4′), 129.6 (C-5), 124.8 (C-3′), 123.4 (C-5′), 117.4 (C-4), 112.5 (C-6), 109.9 (C-2).

Anal. Calcd for $C_{12}H_8ClNO_3$: C, 57.73; H, 3.23; N, 5.61. Found: C, 57.63; H, 3.41; N, 5.53.

Functionalization of the Free 5-OH Group of Compound 6c

5-Acetoxy-2-oxo-4-propyl-2*H*-chromen-7-yl Nicotinate (7) by Acylation of 6c

To a suspension of **6c** (162.5 mg, 0.5 mmol) in pyridine (4 mL) was added Ac_2O (236 μL, 2.5 mmol), and 4-dimethylaminopyridine (12 mg, 0.1 mmol) and the mixture was stirred at room temperature until reaction completion, as monitored by TLC (about 2 h). Then, the reaction mixture was poured into ice and the formed precipitate was collected by filtration, washed with water and dried under air to give **7**.

White solid; yield: 172 mg (94%); mp 169–171 °C.

IR-Fur (neat): 1769, 1743, 1714, 1612, 1256, 1182, 1139, 1108, 1070 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 9.27 (d, *J* = 1.5 Hz, 1 H, H-2′), 8.88 (dd, *J* = 1.5, 4.8 Hz, 1 H, H-6′), 8.47 (dt, J_d = 7.9 Hz, J_t = 1.5 Hz, 1 H, H-4′), 7.63 (dd, *J* = 4.8, 7.9 Hz, 1 H, H-5′), 7.36 (d, *J* = 2.3 Hz, 1 H, H-8), 7.21 (d, *J* = 2.3 Hz, 1 H, H-6), 6.28 (s, 1 H, H-3), 2.86–2.78 (m, 2 H, C-4-CH_2), 2.38 (s, 3 H, CH_3(Ac)), 1.73–1.60 (m, 2 H, $CH_2CH_2CH_3$), 1.10–1.02 (m, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8 (C=O(Ac)), 162.9 (C=O(Nic)), 158.7 (C-2), 154.8 (C-8a), 154.5 (C-4), 154.4 (C-6′), 151.6 (C-7), 150.6 (C-2′), 147.8 (C-5), 137.6 (C-4′), 124.6 (C-3′), 124.1 (C-5′), 115.2 (C-3), 114.5 (C-6), 110.8 (C-4a), 108.8 (C-8), 36.3 (C-4-CH_2), 21.6 ($CH_2CH_2CH_3$), 21.1 (CH_3(Ac)), 13.6 (CH_2CH_3).

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.24; H, 4.65; N, 3.67.

2-Oxo-4-propyl-5-(tosyloxy)-2*H*-chromen-7-yl Nicotinate (8) by Tosylation of 6c

To a suspension of **6c** (162.5 mg, 0.5 mmol) in DCM (5 mL) were added sequentially TEA (70 μL, 0.5 mmol), DMAP (12.0 mg, 0.1 mmol) and TsCl (142.9 mg, 0.75 mmol). The resulting mixture was stirred at room temperature until reaction completion, as monitored by TLC (about 0.25 h). Then, the reaction mixture was diluted with DCM (20 mL), washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was recrystallized from MeOH to give **8**.

White solid; yield: 180 mg (75%); mp 145–147 °C.

IR-Fur (neat): 1740, 1724, 1588, 1473, 1371, 1258, 1013 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.28–9.23 (br s, 1 H, H-2′), 8.95–8.89 (m, 1 H, H-6′), 8.50–8.44 (m, 1 H, H-4′), 7.92–7.84 (m, 2 H, H_o(Ts)), 7.71–7.63 (m, 1 H, H-5′), 7.58–7.48 (m, 3 H, H-8 + H_m(Ts)), 7.27–7.21 (m, 1 H, H-6), 6.36 (s, 1 H, H-3), 2.81–2.71 (m, 2 H, C-4-CH_2), 2.41 (s, 3 H, CH_3(Ts)), 1.54–1.40 (m, 2 H, $CH_2CH_2CH_3$), 0.87–0.77 (m, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7 (C=O), 158.4 (C-2), 154.9 (C-8a), 154.5 (C-6′), 154.1 (C-4), 151.6 (C-7), 150.7 (C-2′), 146.8 (C_p(Ts)), 145.8 (C-5), 137.7 (C-4′), 130.8 (C_i(Ts)), 130.5 (C_m(Ts)), 128.5 (C_o(Ts)), 124.6 (C-3′), 124.1 (C-5′), 115.6 (C-3), 112.5 (C-6), 111.0 (C-4a), 110.0 (C-8), 36.2 (C-4-CH_2), 21.6 ($CH_2CH_2CH_3$), 21.2 (CH_3(Ts)), 13.3 (CH_2CH_3).

Anal. Calcd for $C_{25}H_{21}NO_7S$: C, 62.62; H, 4.41; N, 2.92; S, 6.69. Found: C, 62.50; H, 4.77; N, 2.79; S, 6.60.

5-((*tert*-Butyldiphenylsilyl)oxy)-2-oxo-4-propyl-2*H*-chromen-7-yl Nicotinate (10) by Silylation of 6c

To a suspension of **6c** (195 mg, 0.6 mmol) in DCM (5 mL) were added TEA (125 μL, 0.9 mmol) and TBDPSCl (247 mg, 0.9 mmol). The mixture was stirred at room temperature until reaction completion, as monitored by TLC (about 5 h). Then, the mixture was washed with water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was crystallized from MeOH to give **10**.

Colourless crystals; yield: 210 mg (62%); mp 153–155 °C.

IR-Fur (neat): 1716, 1607, 1139, 1098, 1076, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (br s, 1 H, H-2′), 8.79–8.78 (m, 1 H, H-6′), 8.21–8.18 (m, 1 H, H-4′), 7.73–7.71 (m, 4 H, Ph), 7.48–7.36 (m, 7 H, H-5′ + Ph), 6.83 (d, *J* = 2.3 Hz, 1 H, H-8), 6.24 (s, 1 H, H-3), 6.23 (d, *J* = 2.3 Hz, 1 H, H-6), 3.33 (t, *J* = 7.4 Hz, 2 H, C-4-CH_2), 1.79 (sextet, *J* = 7.4 Hz, 2 H, CH_2CH_3), 1.14 (s, 9 H, ^{t}Bu), 1.04 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.5 (C=O), 160.5 (C-2), 157.3 (C-4), 156.0 (C-8a), 154.9 (C-5), 154.2 (C-6′), 151.7 (C-7), 151.4 (C-2′), 137.6 (C-4′), 135.4 (4 C, Ph), 131.2 (2 C, C_i(Ph)), 130.6 (2 C, Ph), 128.4 (4 C, Ph), 125.0 (C-3′), 123.5 (C-5′), 112.5 (C-3), 110.24 (C-6), 110.21 (C-4a), 104.3 (C-8), 37.6 (C-4-CH_2), 26.8 (C(CH_3)$_3$), 21.3 (CH_2CH_3), 19.5 (C(CH_3)$_3$), 13.7 (CH_2CH_3).

Anal. Calcd for $C_{34}H_{33}NO_5Si$: C, 72.44; H, 5.90; N, 2.48. Found: C, 72.28; H, 6.05; N, 2.37.

2,2-Dimethyl-8-oxo-10-propyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-5-yl Nicotinate Hydropicrate (12·TNP) by Annulation of a 2,2-Dimethylpyran Ring to 6c

A mixture of **6c** (325 mg, 1.0 mmol) and 3-methylbut-2-enal diethyl acetal (708 μL, 3.75 mmol) was heated at 145 °C for 50 min. Then, the mixture was cooled, diluted with EtOAc (7 mL) and filtered. The resulting solution was added to a solution of picric acid (TNP; 344 mg, 1.5 mmol) in EtOAc (10 mL). The obtained crystals were collected by filtration, washed with EtOAc and dried to give **12** as a salt with TNP.

Yellow crystals; yield: 310 mg (50%); mp 193–195 °C.

IR-Fur (neat): 1765, 1717, 1523, 1361, 1275, 1118 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6/CCl_4, 1:1): δ = 10.40–10.16 (br s, 1 H, OH(TNP)), 9.32 (d, *J* = 1.4 Hz, 1 H, H-2′), 8.91 (dd, *J* = 1.4, 4.8 Hz, 1 H, H-6′), 8.58 (s, 2 H, H_m(TNP)), 8.55 (dt, J_d = 7.9 Hz, J_t = 1.5 Hz, 1 H, H-4′), 7.69 (dd, *J* = 7.9, 4.8 Hz, 1 H, H-5′), 6.89 (s, 1 H, H-6), 6.43 (d, *J* = 10 Hz, 1 H, H-4), 6.08 (s, 1 H, H-9), 5.76 (d, *J* = 10 Hz, 1 H, H-3), 2.97–2.87 (m, 2 H, C-10-CH_2), 1.76–1.63 (m, 2 H, $CH_2CH_2CH_3$), 1.54 (s, 6 H, C-2-(CH_3)$_2$), 1.10–1.03 (m, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6 (C=O), 160.7 (C_i(TNP)), 159.1 (C-8), 156.7 (C-10), 154.2 (C-6a), 153.3 (C-6′), 151.3 (C-10b), 149.7 (C-2′), 147.9 (C-5), 141.8 (C_o(TNP)), 139.1 (C-4′), 130.2 (C-3), 125.2 (C_m(TNP)), 125.0 (C-3′), 124.6 (C-5′), 124.2 (C_p(TNP)), 115.3 (C-4), 113.5 (C-9), 110.8 (C-4a), 107.5 (C-10a), 103.6 (C-6), 78.4 (C-2), 37.4 (C-10-CH_2), 27.3 (C-2-(CH_3)$_2$), 22.8 ($CH_2CH_2CH_3$), 13.7 (CH_2CH_3).

Anal. Calcd for $C_{29}H_{24}N_4O_{12}$: C, 56.13; H, 3.90; N, 9.03. Found: C, 56.07; H, 4.09; N, 8.93.

Removal of the Nicotinoyl Group

7-Hydroxy-4-propyl-5-(tosyloxy)-2*H*-chromen-2-one (9)

Compound **8** (479 mg, 1 mmol) was added to 5 N HCl and the reaction mixture was refluxed for 8 h. Then, the reaction mixture was cooled to room temperature and diluted with water. The formed precipitate was collected by filtration, washed with water and dried under air to give **9**.

White solid; yield: 337 mg (90%); mp 179–181 °C.

IR-Fur (neat): 1684, 1626, 1449, 1375, 1262, 1183, 1008 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.97 (s, 1 H, OH-7), 7.85 (d, *J* = 8.2 Hz, 2 H, H_o(Ts)), 7.54 (d, *J* = 8.2 Hz, 2 H, H_m(Ts)), 6.68 (d, *J* = 2.4 Hz, 1 H, H-8), 6.52 (d, *J* = 2.4 Hz, 1 H, H-6), 6.08 (s, 1 H, H-3), 2.75–2.65 (m, 2 H, CH_2), 2.44 (s, 3 H, CH_3(Ts)), 1.52–1.37 (m, 2 H, CH_2), 0.85–0.74 (m, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (C-7), 159.0 (C-2), 156.0 (C-8a), 155.0 (C-4), 146.7 (C_p(Ts) or C-5), 145.6 (C-5 or C_p(Ts)), 131.5 (C_i(Ts)), 130.5 (C_m(Ts)), 128.6 (C_o(Ts)), 111.9 (C-3), 106.4 (C-6 or C-8), 105.0 (C-4a), 102.0 (C-8 or C-6), 36.3 (C-4-CH_2), 21.7 ($CH_2CH_2CH_3$), 21.2 (CH_3(Ts)), 13.4 (CH_3).

Anal. Calcd for $C_{19}H_{18}O_6S$: C, 60.95; H, 4.85; S, 8.56. Found: C, 60.83; H, 4.99; S, 8.46.

5-((*tert*-Butyldiphenylsilyl)oxy)-7-hydroxy-4-propyl-2*H*-chromen-2-one (11)

Compound **10** (165 mg, 0.293 mmol) was dissolved in MeOH, Amberlyst 16 resin, 4.8 eq/kg (165 mg) was added and the mixture was refluxed with stirring until reaction completion, as monitored by TLC (about 5 h). Then, the reaction mixture was cooled to room tempera-

ture and the Amberlyst resin was filtered off. The filtrate was cooled to –15 °C and the precipitate formed was collected by filtration and dried under air to give **11**.

Colourless crystals; yield: 76 mg (57%); mp 205–207 °C.

IR-Fur (neat): 1694, 1582, 1449, 1355, 1168, 813 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 4 H, Ph), 7.46–7.37 (m, 6 H, Ph), 6.56 (d, *J* = 2.3 Hz, 1 H, H-8), 6.48 (s, 1 H, OH), 6.05 (s, 1 H, H-3), 5.90 (d, *J* = 2.3 Hz, 1 H, H-6), 3.29 (t, *J* = 7.3 Hz, 2 H, C-4-CH_2), 1.76 (sextet, *J* = 7.3 Hz, 2 H, CH_2CH_3), 1.11 (s, 9 H, ^{t}Bu), 1.03 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (C-2), 159.4 (C-4), 159.0 (C-7), 156.7 (C-8a), 155.3 (C-5), 135.4 (4 C, Ph), 131.4 (2 C, C_i(Ph)), 130.4 (2 C, Ph), 128.3 (4 C, Ph), 108.9 (C-3), 105.8 (C-6 or C-4a), 105.7 (C-4a or C-6), 97.8 (C-8), 37.6 (C-4-CH_2), 26.7 (C(CH_3)$_3$), 21.4 (CH_2CH_3), 19.5 (C(CH_3)$_3$), 13.8 (CH_2CH_3).

Anal. Calcd for $C_{28}H_{30}O_4Si$: C, 73.33; H, 6.59. Found: C, 73.21; H, 6.68.

5-Hydroxy-2,2-dimethyl-10-propyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-8-one (13)

To a solution of **12·TNP** (1.00 g, 1.61 mmol) in MeOH (50 mL) was added Amberlyst 16 resin (1.0 g) and the resulting mixture was stirred overnight at 60 °C. Then, the Amberlyst resin was filtered off and washed with MeOH. The combined MeOH solution was diluted with water (250 mL) and cooled to 0 °C. The formed precipitate was collected by filtration, washed with water and dried under air to provide **13** (457 mg, 99%) as a white solid. The ^1H and ^{13}C NMR spectra were in full accordance with the published data.[4]

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Supporting Information

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References

(1) Reviews: (a) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev.* **2003**, *23*, 322. (b) Kostova, I. *Curr. HIV Res.* **2006**, *4*, 347. (c) Su, X.-H.; Zhang, M.-L.; Li, L.-G.; Huo, C.-H.; Gu, Y.-C.; Shi, Q.-W. *Chem. Biodivers.* **2008**, *5*, 2579. (d) Kontogiorgis, C.; Detsi, A.; Hadjipavlou-Litina, D. *Expert Opin. Ther. Pat.* **2012**, *22*, 437.

(2) Xu, Z.-Q.; Barrow, W. W.; Suling, W. J.; Westbrook, L.; Barrow, E.; Lin, Y.-M.; Flavin, M. T. *Bioorg. Med. Chem.* **2004**, *12*, 1199.

(3) (a) Ma, T.; Liu, L.; Xue, H.; Li, L.; Han, C.; Wang, L.; Chen, Z.; Liu, G. *J. Med. Chem.* **2008**, *51*, 1432. (b) Xue, H.; Lu, X.; Zheng, P.; Liu, L.; Han, C.; Hu, J.; Liu, Z.; Ma, T.; Li, Y.; Wang, L.; Chen, Z.; Liu, G. *J. Med. Chem.* **2010**, *53*, 1397.

(4) Zheng, P.; Somersan-Karakaya, S.; Lu, S.; Roberts, J.; Pingle, M.; Warrier, T.; Little, D.; Guo, X.; Brickner, S. J.; Nathan, C. F.; Gold, B.; Liu, G. *J. Med. Chem.* **2014**, *57*, 3755.

(5) Ostrowska, K.; Olejarz, W.; Wrzosek, M.; Głuszko, A.; Nowicka, G.; Szczepański, M.; Materek, I. B.; Kozioł, A. E.; Struga, M. *Biomed. Pharmacother.* **2017**, *95*, 1412.

(6) (a) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L.; Xu, Z.-Q. *J. Med. Chem.* **1996**, *39*, 1303. (b) Zembower, D. E.; Liao, S.; Flavin, M. T.; Xu, Z.-Q.; Stup, T. L.; Buckheit, R. W.; Khilevich, A.; Mar, A. A.; Sheinkman, A. K. *J. Med. Chem.* **1997**, *40*, 1005. (c) Zhang, J.; Kirchhoff, E. W.; Zembower, D. E.; Jimenez, N.; Sen, P.; Xu, Z.-Q.; Flavin, M. T. *Org. Process Res. Dev.* **2000**, *4*, 577.

(7) (a) Fox, M. E.; Lennon, I. C.; Meek, G. *Tetrahedron Lett.* **2002**, *43*, 2899. (b) Liu, Z.-J.; Guo, X.-Y.; Liu, G. *Chin. Chem. Lett.* **2016**, *27*, 51. (c) Sun, I.; Hua, J.; Song, X.; Wu, D.; Kong, L.; Sun, Y.; Wang, D.; Wang, Y.; Chen, N.; Liu, G. *Eur. J. Med. Chem.* **2013**, *67*, 39.

(8) (a) Khalymbadzha, I. A.; Chupakhin, O. N.; Fatykhov, R. F.; Charushin, V. N.; Schepochkin, A. V.; Kartsev, V. G. *Synlett* **2016**, *27*, 2606. (b) Khalymbadzha, I. A.; Fatykhov, R. F.; Chupakhin, O. N.; Charushin, V. N.; Tseitler, T. A.; Sharapov, A. D.; Inytina, A. K.; Kartsev, V. G. *Synthesis* **2018**, *50*, 2423. (c) Gorbunov, E. B.; Rusinov, G. L.; Ulomskii, E. N.; El'tsov, O. S.; Rusinov, V. L.; Kartsev, V. G.; Charushin, V. N.; Khalymbadzha, I. A.; Chupakhin, O. N. *Chem. Nat. Compd.* **2016**, *52*, 708.

(9) (a) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (b) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720. (c) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617. (d) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656. (e) Katritzky, A. R.; Khelashvili, L.; Munawar, M. A. *J. Org. Chem.* **2008**, *73*, 9171.

(10) (a) Lepore, S. D.; Khoram, A.; Bromfield, D. C.; Cohn, P.; Jairaj, V.; Silvestri, M. A. *J. Org. Chem.* **2005**, *70*, 7443. (b) Augustin-Nowacka, D.; Makowski, M.; Chmurzynski, L. *J. Chem. Thermodyn.* **2002**, *34*, 391.

(11) (a) Sakthivel, P.; Ilangovan, A.; Kaushik, M. P. *Eur. J. Med. Chem.* **2016**, *122*, 302. (b) Mun, J.; Jabbar, A. A.; Devi, N. S.; Yin, S.; Wang, Y.; Tan, C.; Culver, D.; Snyder, J. P.; Van Meir, E. G.; Goodman, M. M. *J. Med. Chem.* **2012**, *55*, 6738. (c) Yan, J.; Chen, J.; Zhang, S.; Hu, J.; Huang, L.; Li, X. *J. Med. Chem.* **2016**, *59*, 5264. (d) Yang, Z.; Wu, W.; Wang, J.; Liu, L.; Li, L.; Yang, J.; Wang, G.; Cao, D.; Zhang, R.; Tang, M.; Wen, J.; Zhu, J.; Xiang, W.; Wang, F.; Ma, L.; Xiang, M.; You, J.; Chen, L. *J. Med. Chem.* **2014**, *57*, 7977. (e) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 16720.

(12) (a) Nayak, M.; Kim, I. *J. Org. Chem.* **2015**, *80*, 11460. (b) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.

(13) (a) Bulman Page, P. C.; Appleby, L. F.; Day, D.; Chan, Y.; Buckley, B. R.; Allin, S. M.; McKenzie, M. J. *Org. Lett.* **2009**, *11*, 1991. (b) Strong, A. L.; Jiang, Q.; Zhang, Q.; Zheng, S.; Boue, S. M.; Elliott, S.; Burow, M. E.; Bunnell, B. A.; Wang, G. *ACS Med. Chem. Lett.* **2014**, *5*, 143.

(14) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

(15) Krzeszewski, M.; Vakuliuk, O.; Gryko, D. T. *Eur. J. Org. Chem.* **2013**, 5631.

(16) Bayer, V.; Pactor, R.; Cambon, A. *J. Fluorine Chem.* **1982**, *20*, 187.

(17) Sharghi, H.; Jokar, M. *Heterocycles* **2007**, *71*, 2721.

(18) Fiedler, H. *Pharmazie* **1965**, *20*, 401.