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Synthesis of 4-hydroxy-3-[(*E*)-2-(6-substituted-9*H*-purin-9-yl)vinyl]-coumarins as lipoxygenase inhibitors

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ABSTRACT

The synthesis of 4-hydroxy-3-[(*E*)-2-(6-substituted-9*H*-purin-9-yl)vinyl] coumarins has been achieved from the reactions of 4-hydroxycoumarin with 2-(6-substituted-9*H*-purin-9-yl)acetaldehydes in DMF under heating. The new compounds showed significant lipoxygenase inhibitory activity (e.g., **6a**: IC_{50} = 6.25 μM).

The 3-substituted derivatives of 4-hydroxycoumarin possess a wide range of biological activities,[1–7] including anticoagulant, anticancer, HIV enzyme inhibition, and antibacterial. Warfarin (**I**) (Fig. 1) has been prescribed as an anticoagulant drug for more than 50 years.[8–10] The natural substance dicoumarol (**II**)[11] and the synthetic phenprocoumon (**III**)[9,10] (Fig. 1) are also anticoagulants. Compounds **I** and **II** also show anticancer activity.[3,6] Brodifacoum (**IV**) and its parent compound, difenacoum, are rodenticide drugs.[12] PD099560 (**V**) is an HIV-1 protease inhibitor,[13] while ferulenol (**VI**) (Fig. 1), isolated from nature, exhibits antimycobacterial activity.[14]

The 3-substituted 4-hydroxycoumarin derivatives such as warfarin (**I**) are prepared, mainly by Michael addition of 4-hydroxycoumarin (**5**) to α,β-unsaturated carbonyl compounds,[15–20] as racemic products in the presence of different catalysts[16a,18,19] or with enantioselectivity under organocatalysis.[20,21] Dicoumarol (**II**) and its methylene substituted derivatives are synthesized by this method through the initially formed 3-alkylidene-chroman-2,4-diones from the reaction of **5** with formaldehyde,[22,23] aromatic aldehydes[23–26] or aliphatic aldehydes[23,24,27] in ethanol,[22–25,27] other polar solvents,[25,27] without solvent,[25] or in acetic anhydride[26] at room temperature,[22,23,25] under heating,[24,26,27] or using microwave irradiation.[26] The direct alkylation of **5** with alkylhalides presents difficulties.[28–30] Alcohols as alkylating agents have been utilized to circumvent this problem leading to C3-alkylated[31–35] or O-alkylated[35,36] products under Lewis acid catalysis. 3-Aryl-4-hydroxycoumarin derivatives have been synthesized by the coupling of aryl lead compounds with 4-hydroxycoumarins,[37] while 3-benzyl-4-hydroxy coumarins have been prepared by the reduction of the intermediate 3-benzylidene-chroman-2,4-diones.[38] Another route to 3-alkylated-4-hydroxycoumarins is via cyclization starting from *o*-hydroxyarylcarbonyl compounds[30,39,40] or salicylates.[22]

Modified nucleosides present interesting biological activities, in particular antiviral, anticancer, and antimetabolic.[41–46] Through rational drug design approaches, hybrid molecules with dual functionality and/or targets have been developed.[47] Some of these hybrid drugs have been demonstrated to be potent agents, possessing no or minimum toxicity. In continuation of our previous studies[48–50] on modified nucleosides bearing two biologically active moieties, we decided to combine 4-hydroxycoumarin and the purine moieties in a new entity, a hybrid molecule, in an attempt to derive potent lipoxygenase inhibitors with possible anti-inflammatory activity. The new compounds are synthesized from the reactions of 4-hydroxycoumarin with (purin-9-yl)-acetaldehyde derivatives. The reactions studied and the products obtained are depicted in Scheme 1.

Treatment of 6-piperidinylpurine (**1a**)[48,51] with 2-bromo acetaldehyde diethyl acetal (**2**) and anhydrous K_2CO_3 in dry DMF at 90 °C under nitrogen for 8 h resulted in the formation of 9-(2,2-diethoxyethyl)-6-piperidin-1-yl-9*H*-purine (**3a**)[52] in 73% yield, while 14% of the starting material was recovered. The ^{1}H NMR spectrum of **3a** exhibited shifts at 1.05 (t, 6H, J = 7.0 Hz), 3.37 (dq, 2H, J_1 = 7.0 Hz, J_2 = 9.3 Hz), 3.62 (dq, 2H, J_1 = 7.0 Hz, J_2 = 9.3 Hz), 4.15 (d, 2H, J = 5.3 Hz), and 4.61 (t, 1H, J = 5.3 Hz) for the CH_3CH_2O–, CH_3CH_2O–, $–CH_2CH(OEt)_2$, and $–CH_2CH(OEt)_2$

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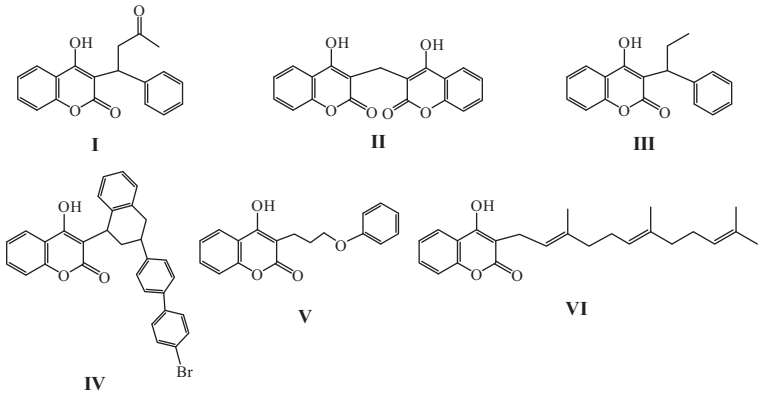
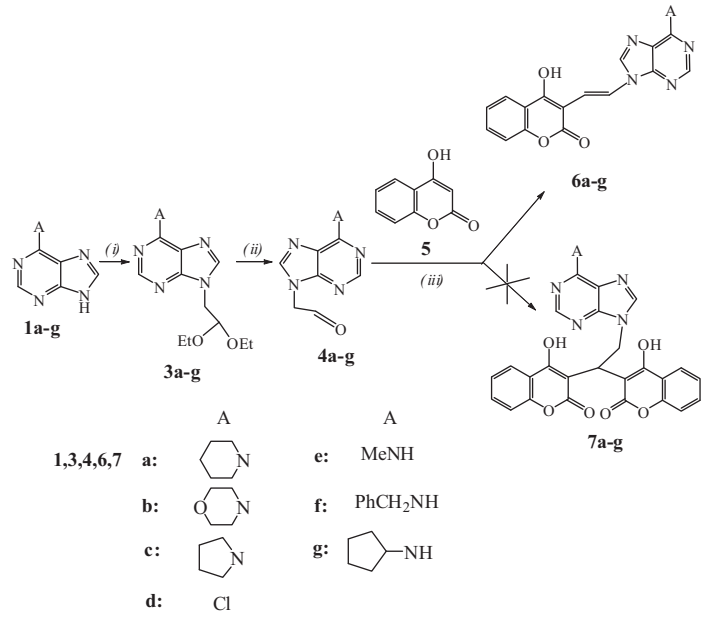


Figure 1.



Scheme 1. Reagents and conditions: (i) 2-bromoacetaldehyde diethyl acetal (**2**), anhydrous K_2CO_3, dry DMF, 90 °C under N_2, 8 h; (ii) HCl (1 M), reflux, 2 h [extraction with EtOAc (×10)]; (iii) 4-hydroxycoumarin (**5**), dry DMF, 90 °C, N_2, 2 h.

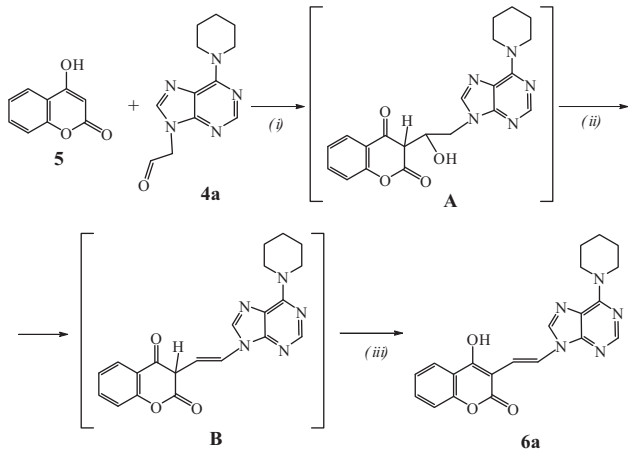
protons, respectively. Similar reactions[52] of 6-substituted purines **1b–g** gave the acetals **3b–g** in moderate to good yields (Table 1, entries 2–7).

Heating[52] 1 M HCl solution of acetal **3a** under reflux for two hours led to the aldehyde **4a**. Repeated extraction of the reaction mixture with ethyl acetate gave the pure aldehyde **4a** in 6% yield. The solid residue, after evaporation of the water layer, was a 1:1 mixture of **4a** (43% yield, totally 49% yield) and its hydrate (40% yield). In the ^{1}H NMR spectrum of **4a**, there were shifts at 5.09 (s, 2H) and 9.78 (s, 1H) for the C*H*$_2$ and C*H* protons of the acetaldehyde moiety, respectively. In the ^{1}H NMR spectrum of hydrate **4a** there were shifts at 4.19 (d, 2H, J = 4.8 Hz) and 5.12 (t, 1H, J = 4.8 Hz) for the C*H*$_2$ and C*H* protons of the hydrate unit. Analogous treatment of acetals **3b–g** gave aldehydes **4b–g** in good yields (Table 1, entries 9–14).

4-Hydroxycoumarin (**5**) was added to a solution of the crude mixture of aldehyde **4a** and its hydrate in dry DMF and the mixture was heated at 90 °C under nitrogen for two hours to give 4-hydroxy-3-[(*E*)-2-(6-piperidin-1-yl-9*H*-purin-9-yl)vinyl]-2*H*-chromen-2-one (**6a**)[52] in 81% yield (12% of the aldehyde **4a** and its hydrate were recovered). In the MS spectrum of compound **6a** there was

Table 1
Synthesis of the 4-hydroxy-3(9*H*-purin-9-yl)coumarin derivatives **3**, **4**, and **6**

Entry	Substrate	Product (Yield %)
1	**1a**[48,51]	**3a** (73)
2	**1b**[48,51]	**3b** (80)
3	**1c**[52,53]	**3c** (73)
4	**1d**	**3d** (41)
5	**1e**[54]	**3e** (75)
6	**1f**[51]	**3f** (80)
7	**1g**[55]	**3g** (74)
8	**3a**	**4a** (49), **4a** hydrate (40)
9	**3b**	**4b** (51), **4b** hydrate (43)
10	**3c**[56]	**4c** (47), **4c** hydrate (41)
11	**3d**[57]	**4d** (59), **4d** hydrate (28)
12	**3e**	**4e** (57), **4e** hydrate (33)
13	**3f**	**4f** (55), **4f** hydrate (32)
14	**3g**	**4g** (51), **4g** hydrate (38)
15	**4a**	**6a** (81)
16	**4b**	**6b** (89)
17	**4c**	**6c** (72)
18	**4d**	**6d** (65)
19	**4e**	**6e** (80)
20	**4f**	**6f** (76)
21	**4g**	**6g** (80)



Scheme 2. Conditions: (i) 'Aldol' type reaction; (ii) H_2O elimination; (iii) tautomerization.

an expected molecular ion at 390 $[M+H]^+$, while in the ^1H NMR spectrum there were two doublets at 7.73 (d, 1H, J = 14.8 Hz) and 8.46 (d, 1H, J = 14.8 Hz), which revealed that the product was the *trans*-isomer. Similar reactions of the crude mixtures of aldehydes **4b–g** (with their hydrates) with 4-hydroxycoumarin (**5**) resulted in the 3-substituted 4-hydroxycoumarin derivatives **6b–g** in good to excellent yields (Table 1, entries 16–21).

The expected[23,24,27] 2:1 adducts **7a–g**, analogous to dicoumarol (**II**), were not isolated in the above experiments. In the proposed mechanism for this reaction (Scheme 2) the intermediate alcohol **A** is formed from the 'aldol' type[24] reaction of 4-hydroxycoumarin (**5**) and aldehyde **4a**. Elimination of H_2O from **A** gives the enamine **B**, which upon tautomerization leads to the final product **6a**. The formation of the intermediate enamine **B**, with the π-orbital overlapping with the heteroaromatic system,[56] and the subsequent tautomerization to give compound **6a**, with extended conjugation, is probably the driving force for the formation of products **6a–g** and not of the possible dicoumarol (**II**) derivatives **7a–g**.

The products **6** were tested as possible lipoxygenase inhibitors and antioxidant agents. Compounds **6b–c** showed significantly high reducing ability compared to the reference compound nordihydroguaiaretic acid [4,4′-(2,3-dimethylbutane-1,4-diyl)dibenzene-1,2-diol] (NDGA), whereas **6a** and **6d** showed similar results. All compounds **6** caused significant inhibition of lipid peroxidation (LPO). Compound **6a** (IC_{50} = 6.25 μM), which has a piperidinyl ring attached at C-6, is a very potent inhibitor compared to the standard reference compound NDGA. The next significant derivative is compound **6f** (IC_{50} = 20 μM). The antioxidant biological activities are correlated with their common structural characteristics, example the 4-OH coumarin and the purine ring. Although lipophilicity is referred[58] to as an important physicochemical property for LOX inhibitors, all the above tested derivatives do not follow this concept. In contrast, the stereochemistry of the 6-substituent might influence the activity. In the future, compound **6a** will be used as a lead for the design and the synthesis of more potent LOX inhibitors and multifunctional agents (Table 2).

In conclusion, we have developed an efficient method for the synthesis of 4-hydroxy-3-[(*E*)-2-(9*H*-purin-9-yl)vinyl] -2*H*-chromen-2-ones in good to excellent yields from the reactions of 4-hydroxycoumarin with 6-substituted (9*H*-purin-9-yl) acetaldehydes. Preliminary biological evaluation of these new compounds showed that they act as very good lipoxygenase inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.102.

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Table 2
Reducing activity % DPPH (RA%); % inhibition of lipid peroxidation (AAPH%); in vitro inhibition of soybean lipoxygenase (%LOX)/(IC_{50} μM)

Compound	Clog$P$[59]	RA% @ 100 μM 20 min (±SD)[a]	AAPH% @ 100 μM (±SD)[a]	IC_{50} μM or % LOX Inh. @ 100 μM (±SD)[a]
6a	3.81	66 ± 2	99 ± 4	6.25 μM (±0.2)
6b	2.43	93 ± 4	99 ± 3	45% (±2)
6c	3.25	73 ± 2	99 ± 2	100 μM (±3)
6d	2.91	68 ± 1	97 ± 2	24% (±1)
6e	3.09	52 ± 3	100 ± 5	37% (±2)
6f	4.54	44 ± 1	92 ± 4	20 μM (±1)
6g	4.56	45 ± 1	98 ± 3	NA
NDGA	—	83 ± 3	—	28 μM (±1)
Trolox	—	—	63 ± 1	—

NA: no activity under the reported experimental conditions.
[a] Values are the mean ± SD of three or four different determinations.

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52. *Selected data:* (a) General Procedure. Amination of chloropurine under MW irradiation. In a MW reaction vessel (30 ml) were placed a solution of 6-chloropurine (**1d**) (1 g, 6.45 mmol) in H_2O (10 ml) and pyrrolidine (0.916 g, 0.78 ml, 12.9 mmol). The mixture was irradiated [Biotage (Initiator 2.0) scientific MW oven] at 100 °C for 2 min. After cooling, the precipitate was filtered, washed thoroughly with H_2O (5 × 10 ml) and dried under vacuum to give 1.11 g (91% yield) of 6-pyrrolidin-1-yl-9*H*-purine (**1c**), mp 307–309 °C (dec.) (Lit.[53] mp 309–310 °C).

(b) *General procedure for the synthesis of the acetals **3a–g**.* To a solution of 6-piperidinopurine (**1a**) (0.88 g, 3.88 mmol) in dry DMF (20 ml), anhydrous K_2CO_3 (0.539 g, 3.88 mmol) was added followed by 2-bromo acetal dehyde diethyl acetal (**2**) (0.764 g, 0.58 ml, 3.88 mmol). The mixture was heated at 90 °C under an N_2 atmosphere for 8 h, filtered under vacuum while hot, and washed with CH_2Cl_2. The filtrate was evaporated and the residue separated by column chromatography [silica gel No 60, hexane/EtOAc (4:1)] to give *9-(2,2-diethoxyethyl)-6-piperidin-1-yl-9H-purine* (**3a**) (0.908 g, 73% yield), white solid, mp 42–44 °C (CH_2Cl_2), IR (Nujol): 3060, 1570, 1540 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (t, 6H, J = 7.0 Hz); 1.54-1.67 (m, 6H); 3.37 (dq, 2H, J_1 = 7.0 Hz, J_2 = 9.3 Hz); 3.62 (dq, 2H, J_1 = 7.0 Hz, J_2 = 9.3 Hz); 4.07–4.19 (m, 4H); 4.15 (d, 2H, J = 5.3 Hz); 4.61 (t, 1H, J = 5.3 Hz); 7.71 (s, 1H); 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2; 24.9; 26.1; 46.2; 46.4; 63.8; 100.5; 119.5; 139.1; 151.0; 152.5; 154.0; MS (ESI): 320 $[M+H]^+$, 342 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{25}N_5O_2$: C, 60.17; H, 7.89; N, 21.93. Found: C, 60.32; H, 7.64; N, 22.09.

(c) *General procedure for synthesis of the aldehydes **4a–g**.* A solution of acetal **3a** (0.45 g, 1.41 mmol) in HCl (1 M) (8 ml) was heated under reflux for 2 h. After cooling, the mixture was extracted with EtOAc (10 × 5 ml). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to give (6-piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde (**4a**) (20 mg, 6% yield). The aqueous layer was evaporated to give a crude 1:1 mixture of aldehyde **4a** (0.3 g, yield 43%, totally 49%) and its hydrate (0.3 g, 40% yield).

Compound **4a**, white solid, mp 100–101 °C (EtOAc), IR (Nujol): 3040, 2750, 1710, 1610, 1580, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.64–1.83 (m, 6H), 4.19-4.37 (m, 4H), 5.09 (s, 2H), 7.75 (s, 1H), 8.32 (s, 1H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.8, 26.2, 46.7, 52.4, 119.5, 138.1, 150.7, 152.3, 153.7, 193.6; MS (ESI): 268 $[M+Na]^+$, 300 $[M+Na+MeOH]^+$. Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.54; H, 6.42; N, 28.83.

(d) *Genral procedure for the synthesis of 4-hydroxy-3-[(E)-2-(6-substituted-9H-purin-9-yl)vinyl]coumarins (**6a–g**).* 4-Hydroxycoumarin (**5**) (64 mg, 0.39 mmol) was added to a solution of a mixture of aldehyde **4a** (50 mg, 0.2 mmol) and its hydrate (50 mg, 0.19 mmol) in dry DMF (5 ml). The mixture was heated at 90 °C under an N_2 atmosphere for 2 h. After cooling, CH_2Cl_2 (1 ml) was added and *4-hydroxy-3-[(E)-2-(6-piperidin-1-yl-9H-purin-9-yl)vinyl]-2H-chromen-2-one* (**6a**) (0.124 g, 81% yield) precipitated; light yellow solid, mp 210–212 °C, IR (Nujol): 3380, 3040, 1661, 1632, 1580, 1515 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.60-1.68 (m, 6H), 4.18–4.28 (m, 4H), 7.39–7.44 (m, 2H), 7.66 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.6 Hz), 7.73 (d, 1H, J = 14.8 Hz), 7.96 (br s, 1H), 8.10 (d, 1H, J = 7.6 Hz), 8.33 (s, 1H), 8.46 (d, 1H, J = 14.8 Hz), 8.69 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 25.9, 34.1, 46.4, 100.2, 111.0, 115.3, 116.1, 119.1, 121.6, 122.8, 123.7, 123.9, 131.0, 132.2, 137.3, 151.7, 152.2, 161.5, 162.6; MS (ESI): 390 $[M+H]^+$. Anal. Calcd for $C_{21}H_{19}N_5O_3$ C, 64.77; H, 4.92; N, 17.98. Found: C, 64.53; H, 4.76; N, 17.88.
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