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Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity

Jalpa C. Trivedi,[a] Jitender B. Bariwal,[a] Kuldip D. Upadhyay,[b] Yogesh T. Naliapara,[a] Sudhir K. Joshi,[c] Christophe C. Pannecouque,[d] Erik De Clercq[d] and Anamik K. Shah[a,*]

[a]*Department of Chemistry, Saurashtra University, Rajkot 360 005, India*
[b]*Torrent Research Center, Gandhinagar 382 428, India*
[c]*H & H. B. Kotak Institute of Science, Rajkot 360 005, India*
[d]*Rega Institute for Medical Research, Katholieke Universiteit, Leuven B-3000, Belgium*

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Abstract—Two closely structurally related coumarins, 4-hydroxy-8-isopropyl-5-methylcoumarin and 4-hydroxy-6-chloro-7-methylcoumarin were acylated at C-3 and further converted to the respective chalcones and two series of eighteen new compounds, which were evaluated for possible antiviral activity.

The incidence of HIV-1 infection leading to acquired immunodeficiency syndrome (AIDS) is one of the world's greatest threats to human health and there is no complete effective remedy for this disease.[1] Coumarins and structurally related compounds have been shown to inhibit replication of HIV and thus exhibit a therapeutic potential.[2] A large number of structurally novel coumarin derivatives have been reported to show substantial cytotoxic and anti-HIV activity in vitro and in vivo.[3,4] A variety of synthetic coumarins have unique mechanisms of action referring to the different stages of HIV replication.[5] Thus coumarins are important lead compounds for the development of antiviral and/or virucidal drugs against HIV.[6–8] Some phenyl coumarins and chalcones have been proposed as suppressors of LTR-dependent transcription, but the mechanism of action has not been fully characterized.[9] (+)-Calanolide A, a natural dipyranocoumarin is also currently undergoing anti-AIDS clinical trials.[10] In our work on anti-HIV compounds, the 3-acetyl-4-hydroxycoumarin system was used for the synthesis of potent anti-HIV compounds using an easy and rapid method, which improves the yields to a significant level.

All the compounds were synthesized according to Scheme 1. Substituted coumarins **2** were prepared by the literature method using an appropriately substituted phenol and malonic acid, a Lewis acid and as condensing agent, phosphorus oxychloride ($POCl_3$). For acetylation of the substituted coumarin, the method of Dholakia et al.[11] was employed using glacial acetic acid as acetylating agent in the presence of $POCl_3$. In conventional methods for chalcone synthesis, the time for completion of reactions is very long, ranging from 24 to 36 h at rt.[12,13] A small alteration in reaction conditions, using chloroform as solvent with a mild organic base, for example, piperidine, reduced the reaction time in most cases, from 1 to 1.5 h (Table 1). Moreover, the isolation of product **4** or **5** was also easy. Biological assessments were carried out against HIV-I (III B) and HIV-2 (ROD) and the results are shown in Tables 2 and 3 in the Supplementary data. The cut-off point for such specific antiviral activity was $\geqslant$5-fold lower than the cytotoxic concentration. However, no specific antiviral effects were noted for any of the compounds against any of the viruses evaluated.

Our improved method for the synthesis of coumarinyl chalcones was effective in terms of time and yields of the products. Unfortunately, all the compounds were inactive against HIV.

Keywords: Antiviral; Anti-HIV; Chalcones; 4-Hydroxycoumarins.
* Corresponding author. Tel.: +91 281 2581013; e-mail: anamik_shah@hotmail.com

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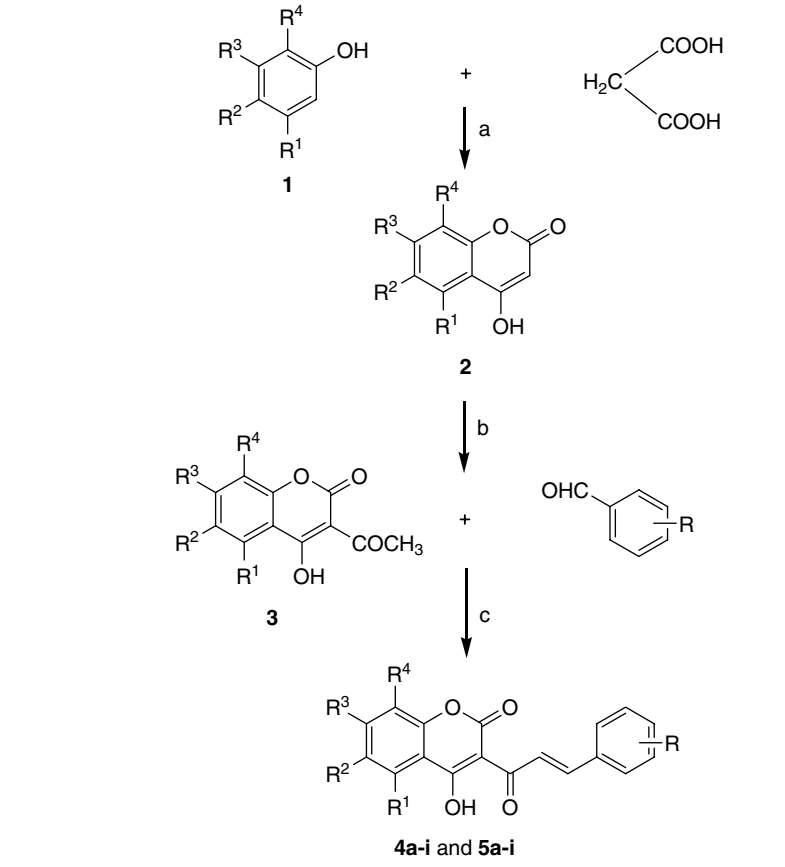
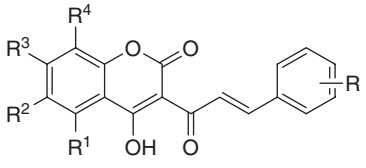


4 a-i, R^1=CH_3, R^2=H, R_3=H, R^4=$CH(CH_3)_2$
5 a-i, R^1=H, R^2=Cl, R^3=CH_3, R^4=H

R =H
=4-OH
=4-OCH_3
=3-OC_6H_5
=2-NO_2
=3-NO_2
=4-$N(CH_3)$, 4-OH
=3-OCH_3, 4-OH
=3,4-di OCH_3

Scheme 1. Synthesis of compounds **4a**–**i** and **5a**–**i**. Reagents and conditions: (a) Anhydrous $ZnCl_2$, $POCl_3$, 70 °C; (b) glacial acetic acid, $POCl_3$; (c) $CHCl_3$, piperidine, 80 °C.

Table 1. Physical properties of the synthesized coumarinyl chalcone derivatives



Compd.	Substitution					Yield (%)	Mol. wt.	Mp (°C)
	R^1	R^2	R^3	R^4	R			
4a	CH_3	H	H	$CH(CH_3)_2$	H	79	350	170–172
4b	CH_3	H	H	$CH(CH_3)_2$	4-OH	75	366	246–248
4c	CH_3	H	H	$CH(CH_3)_2$	4-OCH_3	76	378	215–217
4d	CH_3	H	H	$CH(CH_3)_2$	3-OC_6H_5	71	440	96–98
4e	CH_3	H	H	$CH(CH_3)_2$	2-NO_2	73	377	120–124
4f	CH_3	H	H	$CH(CH_3)_2$	3-NO_2	69	377	235–237
4g	CH_3	H	H	$CH(CH_3)_2$	4-$N(CH_3)_2$	72	391	245–247
4h	CH_3	H	H	$CH(CH_3)_2$	3-OCH_3, 4-OH	71	394	214–216

(*continued on next page*)

Table 1 (*continued*)

Compd.	Substitution					Yield (%)	Mol. wt.	Mp (°C)
	R^1	R^2	R^3	R^4	R			
4i	CH_3	H	H	$CH(CH_3)_2$	3,4-di-OCH_3	74	408	195–197
5a	H	Cl	CH_3	H	H	73	340.5	180–182
5b	H	Cl	CH_3	H	4-OH	68	356.5	246–248
5c	H	Cl	CH_3	H	4-OCH_3	76	370.5	220–222
5d	H	Cl	CH_3	H	3-OC_6H_5	69	432.5	188–190
5e	H	Cl	CH_3	H	2-NO_2	67	385.5	178–180
5f	H	Cl	CH_3	H	3-NO_2	70	385.5	230–232
5g	H	Cl	CH_3	H	4-$N(CH_3)_2$	77	383.5	235–237
5h	H	Cl	CH_3	H	3-OCH_3, 4-OH	79	386.5	220–222
5i	H	Cl	CH_3	H	3,4-di-OCH_3	81	416.5	258–260

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.175.

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