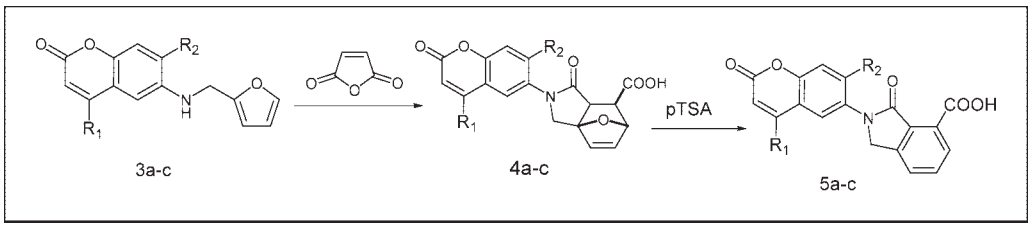
Synthesis and Antimicrobial Activity of Some Methyl-2-[*N*-Coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylates

Aabid Ali Mir,* Vinata V. Mulwad, and G. K. Trivedi

Department of Chemistry, The Institute of Science, Mumbai 400032, Maharashtra, India
*E-mail: aabidmir@gmail.com

Received June 26, 2009
DOI 10.1002/jhet.274
Published online 29 December 2009 in Wiley InterScience (www.interscience.wiley.com).



N-substituted furylmethylimines are prepared by condensing 6-aminocoumarins with furfural, these on sodium borohydride reduction afford *N*-[coumarin-6′-yl]-2-furylamines. Intramolecular [4+2] cycloaddition of these amines with maleic anhydride results into 3-[*N*-coumarin-6′-yl]-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids **4a–c**. The [4+2] cycloadducts on *p*-toluene sulphonic acid treatment followed by esterification yield the titled compounds. Compound **5a–c** was also reduced to isoindolone alcohol **7a–c** by sodium borohydride in the presence of a base. All the compounds have been tested *in vitro* for their antimicrobial activity against gram-positive bacteria *Bacillus subtilis, Staphylococcus aureus*, one gram-negative bacteria, *Escherichia coli*, and one fungal strain *Candida albicans* at 100 μg/mL concentration.

J. Heterocyclic Chem., **47**, 214 (2010).

INTRODUCTION

A variety of heterocyclic compounds bearing isoindolone skeleton reported to possess wide range of biological activities, such as antipsychotic [1], antihypertensive [2], antiviral [3], and antileukemic [4]. Furthermore, isoindolones have been widely used as building blocks for the synthesis of various drugs and natural products. Likewise, coumarins have also gained considerable synthetic and pharmacological interest for a long time because of their various biological activities [5–9]. In continuation of our work [10–15], keeping the biological profile of the two class of compounds in view, it appeared of interest to synthesize a molecular entity displaying the structural features of both the class of compounds.

Intramolecular Diels-Alder reaction of furan (IMDAF) methodology offers a facile way of constructing isoindolone moiety on a pre-existing 2-furylmethyl amine system [16]. In this article, we wish to report the synthesis of methyl-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylates using the IMDAF approach.

RESULTS AND DISCUSSION

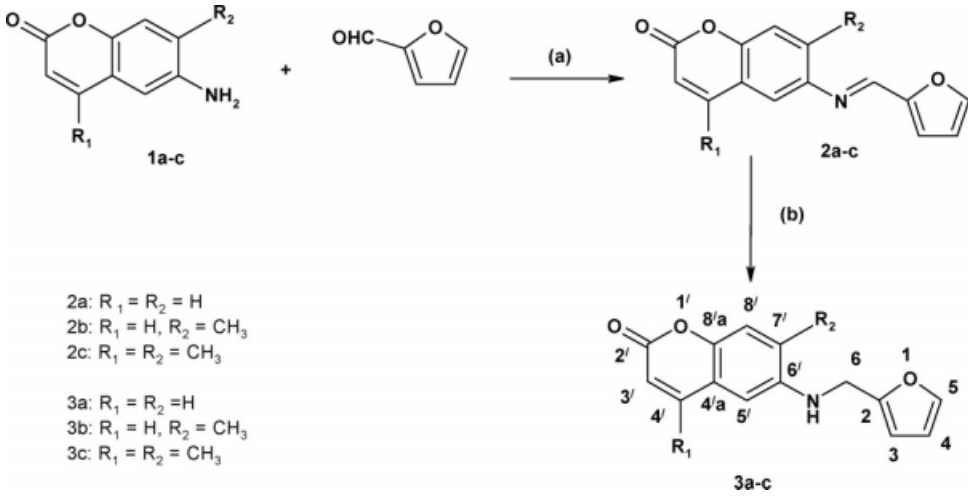
The required N-substituted 2-furylmethyl-amine **3a–c** was obtained by sodium borohydride reduction of the N-substituted 2-furylmethimines (**2a–c**) derived from 6-amino coumarin (**1a–c**) and furfural (Scheme 1). Capitalizing on the reactivity of the furan nucleus to words dienophiles in the Diels-Alder reaction, these furylmethyl amine were subsequently treated with maleic anhydride to afford compound **4a–c**.

The formation of stereochemically defined exo-tricyclic cycloadduct proceeds smoothly *via* initial N-acylation followed by intramolecular Diels-Alder reaction (one-pot reaction) [17–19] Scheme 2.

In the next step, ring opening followed by aromatization of the epoxy isoindolones was accomplished by subjecting the cycloadduct (**4a–c**) to *p*-toluene sulphonic acid (pTSA) in refluxing toluene [16]. The resultant product was characterized as 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylic acid (**5a–c**). The presence of carboxy function was confirmed by converting (**5a–c**) to their corresponding methyl esters (**6a–c**) and isoindolone alcohol (**7a–c**) Scheme 3.

Spectral characterization. Formation of furfural amines **3a–c** was confirmed by the IR spectra, which showed characteristic —NH stretching at 3438 cm^{-1}. In its ^{1}H NMR in $CDCl_3$, it showed a singlet at δ 4.34 ppm integrating for two methylene protons. The formation of cycloadduct was confirmed by the absence of —NH stretching in IR spectra and the presence of characteristic bands for the vibrations of the amide and carboxylic group in the regions of 1620–1690 and 1710–

Scheme 1. Reagents and conditions:(a) toluene, reflux, 5 h and (b) $NaBH_4$, MeOH, 0°C, 3 h.



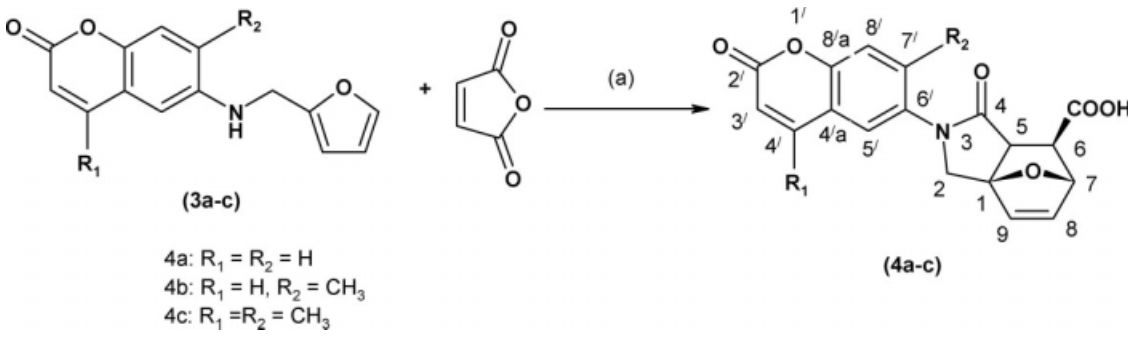
1726 cm^{-1}, respectively. The ^1H NMR spectra of compound **4c** contain three characteristic signals for mutually interacting protons 7-H, 8-H, and 9-H with chemical shifts of 5.07, 6.50, and 6.65 ppm, respectively, and coupling constants $J_{7,8} = 1.8$ Hz and $J_{8,9} = 5.7$ Hz, respectively. The absence of the $J_{6,7}$ spin–spin coupling constant indicates the endo arrangement of the 5-H and 6-H protons ($J_{5,6} = 9$ Hz) and the exo arrangement of the carboxyl and amide constituents. The C-2 protons of CH_2 are magnetically nonequivalent and are observed as an AB quartet at 4.57 and 3.84 ppm ($J_{AB} = 11.4$ Hz), respectively. Compound **5c** shows a singlet at δ 5.13 for the CH_2 protons along with other signals. Compounds **5a–c** were independently confirmed by converting them into their corresponding methyl-esters, showing stretching vibration between 1730 and 1735 cm^{-1} for carbonyl group of methyl ester. The ^1H NMR of compound **6c** shows an additional singlet at δ 3.83 ppm for three protons of methyl ester. 5-Hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone **7a–c** shows singlet at δ 4.68 for CH_2—OH protons along with the other signals.

In vitro antimicrobial evaluation of newly synthesized compounds was done against three bacterial and one fungal strain by agar-well diffusion method [20] at 100 μg/mL concentration. Antibacterial activity of the test compounds was evaluated against two gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus,* and one gram-negative bacteria, *Escherichia coli*, using ampicillin as standard drug. Antifungal activity was screened against one fungal strain, *Candida albicans*, using clotrimazole as standard drug. The results are given in Table 1.

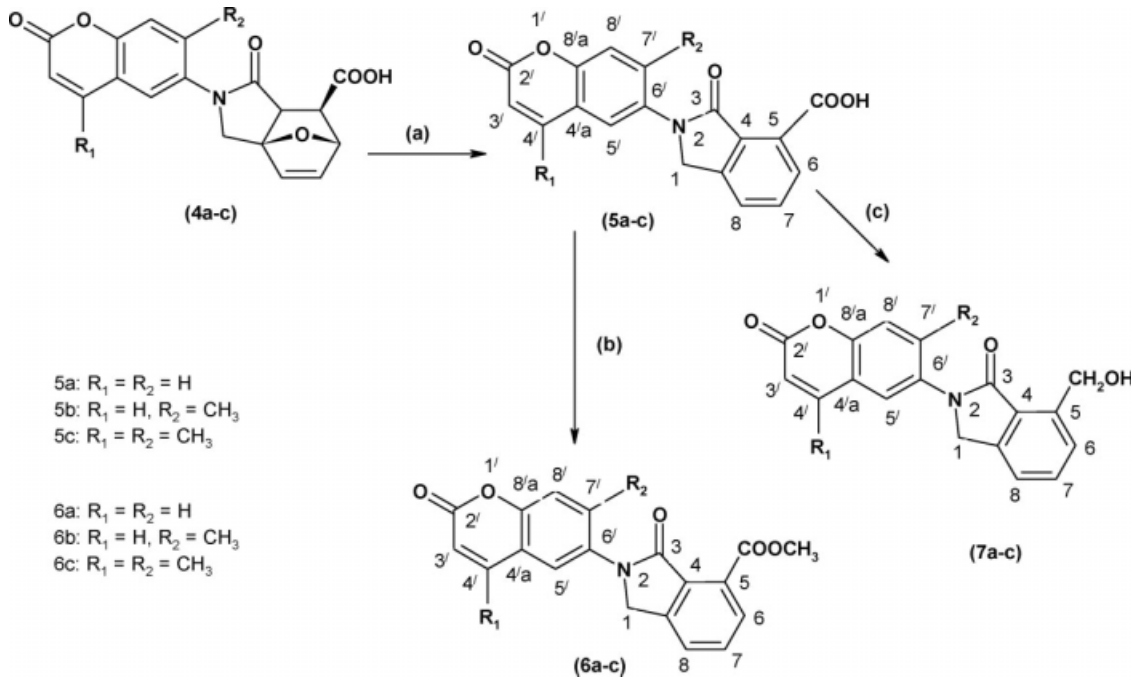
CONCLUSIONS

In conclusion, a series of novel 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylic acid (**5a–c**), methyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylate (**6a–c**), and 5-hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone (**7a–c**) were synthesized by IMDAF, and their antimicrobial activities have been evaluated.

Scheme 2. Reagents and conditions: (a) maleic anhydride, benzene.



Scheme 3. Reagents and conditions: (a) pTSA, toluene, reflux, (b) MeOH, Conc. H_2SO_4, reflux, 8 h, and (c) THF, ethylchloroformate, TEA/$NaBH_4$/MeOH, r.t, 24 h.



Among the tested compounds, compounds **5c**, **6c,** and **7c** with methyl substitution on fourth and seventh positions of benzopyran ring have showed significant activities.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. FTIR spectra (V_{max} in cm^{-1}) were recorded on a Perkin Elmer 400 spectrometer using KBr. NMR spectra were recorded on JEOL NMR AL300 (300 MHz) using TMS as standard and mass spectra on a Shimadzu GC-MS QP-2010. Elemental analyses were carried out in IIT, Mumbai. The reactions are followed up and purity of the products is carried out on precoated TLC plates (Silica gel 60 F254, Merck), visualizing the spots in ultraviolet light. All the new compounds gave satisfactory elemental analyses.

Synthesis of *N*-[coumarin-6′-yl]-2-furylmethinimine (2a–c). Imines (**2a–c**) were prepared by refluxing a mixture of freshly distilled furfuraldehyde and appropriate 6-amino coumarin in toluene using Dean-Stark apparatus, refluxing was continued for 5 h. Toluene was distilled off on a rotary evaporator and the crude imine was used in the next step without purification.

Table 1

Antibacterial and antifungal activities of the compounds as zone of inhibition (mm) (100 μg/mL).

Comp.	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*
5a	14	14	15	16
5b	14	15	14	15.5
5c	18	19	22	18
6a	9	13	13	14
6b	11	14	14	15
6c	16	17.5	18	16
7a	8	10	13	13
7b	10	12	14	15.5
7c	15	14	15	16.5
DMSO	Control	Control	Control	Control
Ampicillin	18	19	16	–
Clotrimazole	–	–	–	22

Synthesis of *N*-[coumarin-6′-yl]-2-furylmethylamine (3a–c). Sodiumborohydride was added in small portions to a solution of imine (**2a–c**) in methanol at 0°C for 30 min and there after at room temp for 3 h, and then acidified with 10% HCl to pH 1. The resulting mixture was adjusted to pH 11 with aq NH_3 solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give off white solid.

3a. Yield 68%; mp 118–120°C. IR (KBr, cm^{-1}): 3438, 2950, 1710; ^1H NMR ($CDCl_3$): δ 4.10 (s, 1H, NH, D_2O-exchangable), 4.34 (s, 2H, C_6—CH_2), 6.25 (d, 1H, J = 9 Hz C_3'—H), 6.30–6.85 (m, 3H, furfural-H), 6.80 (d, IH, J = 8.7 Hz, C_8'—H), 7.12 (d, 1H, J = 8.7 Hz, C_7'—H), 7.30 (s, 1H, C_5'—H), 7.64 (d, 1H, J = 9 Hz, C_4'—H). Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.41; H, 4.68; N, 5.65.

3b. Yield 65%; mp 122–124°C. IR (KBr, cm^{-1}): 3435, 2945, 1713; ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, C_7'—CH_3), 4.05 (s, 1H, NH, D_2O-exchangable), 4.28 (s, 2H, C_6—CH_2), 6.21 (d, 1H, J = 9 Hz, C_3'—H), 6.28–6.85 (m, 3H, furfural-H), 7.08 (s, 1H, C_8'—H), 7.18 (s, 1H, C_5'—H), 7.68 (d, 1H, J = 9 Hz, C_4'—H). Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.41; H, 5.20; N, 5.30.

3c. Yield 62%; mp 123–125°C. IR (KBr, cm^{-1}): 3431, 2950, 1708; ^1H NMR ($CDCl_3$): δ 2.24 (s, 3H, C_7'—CH_3), 2.35 (s, 3H, C_4'—CH_3), 3.96 (s, 1H, NH, D_2O-exchangable), 4.38 (s, 2H, C_6—CH_2), 6.19 (s, 1H, C_3'—H), 6.30–6.88 (m, 3H, furfural-H), 7.08 (s, 1H, C_8'—H), 7.28 (s, 1H, C_5'—H); ms: m/z = 269 (35%) [M^+], 188 (25%), 160 (20%), 117 (10%), 81 (100%). Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found C, 71.15; H, 5.66; N, 5.31.

Synthesis of 3-[*N*-coumarin-6′-yl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1.5}$]dec-8-ene-6-carboxylic acid (4a–c). To a stirred solution of **3a–c** in anhydrous benzene was added maleic anhydride at r.t. The solution was stirred at r.t. for 10 h. The product was filtered and washed with benzene to yield cycloadduct **4a–c**. Recrystallization from hexane-ethyl acetate gave desired acids **4a–c** as colorless solids.

4a. Yield 88%; mp 220–222°C, IR (KBr, cm^{-1}): 3076, 1725, 1665; ^1H NMR (DMSO-d_6): δ 2.87 (d, 1H, J = 9 Hz, C_6—H), 3.01 (d, 1H, J = 9 Hz, C_5—H), 3.80 (d, 1H, J = 11.4 Hz, C_{2a}—H), 4.52 (d, 1H, J = 11.4 Hz, C_{2b}—H), 5.05 (d, 1H, J = 1.8 Hz, C_7—H), 6.50 (dd, 1H, J = 5.7 and 1.8 Hz, C_8—H), 6.65 (d, 1H, J = 5.7 Hz, C_9—H), 6.25 (d, 1H, J = 9 Hz, C_3'—H), 6.81 (d, 1H, J = 9 Hz, C_8'—H), 7.08 (d, 1H, J = 9 Hz, C_7'—H), 7.20 (s, 1H, C_5'—H), 7.85 (d, 1H, J = 9 Hz, C_4'—H), 12.30 (s, 1H, COOH). Anal. Calcd. for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13. Found C, 63.51; H, 3.92; N, 4.22.

4b. Yield 86%; mp 225–227°C, IR (KBr, cm^{-1}): 3070, 1722, 1672; ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H, C_7'—CH_3), 2.86 (d, 1H, J = 9 Hz, C_6—H), 3.05 (d, 1H, J = 9 Hz, C_5—H), 3.77 (d, 1H, J = 11.4 Hz, C_{2a}—H), 4.50 (d, 1H, J = 11.4 Hz, C_{2b}—H), 5.09 (d, 1H, J = 1.8 Hz, C_7—H), 6.51 (dd, 1H, J = 5.7 and 1.8 Hz, C_8—H), 6.62 (d, 1H, J = 5.7 Hz, C_9—H), 6.21 (d, 1H, J = 9 Hz, C_3'—H), 6.89 (s, 1H, C_8'—H), 7.22 (s, 1H, C_5'—H), 7.82 (d, 1H, J = 9 Hz, C_4'—H), 12.25 (s, 1H, COOH). Anal. Calcd. for $C_{19}H_{15}O_6N$: C, 64.59; H, 4.28; N, 3.96. Found C, 64.29; H, 4.42; N, 4.11.

4c. Yield 82%; mp 221–223°C, IR (KBr, cm^{-1}): 3072, 1720, 1671, ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H, C_7'—CH_3), 2.40(s, 3H, C_4'—CH_3), 2.95 (d, 1H, J = 9 Hz, C_6—H), 3.02 (d, 1H, J = 9 Hz, C_5—H), 3.84 (d, 1H, J = 11.4 Hz, C_{2a}—H), 4.57 (d, 1H, J = 11.4 Hz, C_{2b}—H), 5.07 (d, 1H, J = 1.8 Hz, C_7—H), 6.50 (dd, 1H, J = 5.7 and 1.8 Hz, C_8—H), 6.19 (s, 1H, C_3'—H), 6.65 (d, 1H, J = 5.7 Hz, C_9—H), 7.32 (s, 1H, C_8'—H), 7.64 (s, 1H, C_5'—H), 12.28 (s, 1H, COOH); ^{13}C NMR(DMSO—d_6, δ): 17.55 (C_7'—CH_3), 17.99 (C_4'—CH_4), 44.88 (C-2), 50.0 (C-6), 51.50 (C-5), 80.26 (C-7), 88.75 (C-1), 113.80 (C-3′), 118.0 (C-8′), 123.41 (C-4′a), 128 (C-5′), 134.10 (C-8), 135.44 (C7′), 136.80 (C-6′), 141.43 (C-9), 151.75 (C-8′a), 153.0 (C-4′), 159.80 (C-2′, C=O), 170.23 (C-4, C=O), 174.0 (COOH); ms: m/z = 367 (45%) [M^+], 160 (35), 188 (25), 91(60). Anal. Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found C, 65.18; H, 4.77; N, 3.94.

Synthesis of 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolene-5-carboxylic acid (5a–c). A mixture of cycloadduct **4a–c** (1 mmol), toluene, and pTSA (3 mmol) in a flask equipped with reflux condenser was stirred at refluxing temperature. The progress of the reaction was monitored by TLC. When the reaction was complete, toluene was distilled off on a rotary evaporator. The resulting residue was dissolved in CH_2Cl_2 and washed thoroughly with water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give solid mass, which was purified by column chromatography (ethyl acetate–pet ether) to give the desired product.

5a. Yield 50%; mp 280–282°C, IR (KBr, cm^{-1}): 2995, 1716, 1675, 1500; ^1H NMR (DMSO-d_6): δ 5.10 (s, 2H, C_1—CH_2), 6.30 (d, 1H, J = 9 Hz, C_3'—H), 7.15 (d, 1H, J = 9 Hz, C_7'—H), 7.20 (d, 1H, J = 9 Hz, C_8'—H), 7.38 (s, 1H, C_5'—H), 7.75–7.99 (m, 3H, Arom-H), 7.89 (d, 1H, J = 9 Hz, C_4'—H), 11.89 (s, 1H, COOH). Anal. Calcd. for $C_{18}H_{11}NO_5$: C, 67.29; H, 3.45; N, 4.36. Found C, 67.12; H, 3.51; N, 4.48.

5b. Yield 48%; mp 284–286°C, IR (KBr, cm^{-1}): 2995, 1720, 1670; ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, C_7'—CH_3), 5.15 (s, 2H, C_1—CH_2), 6.28 (d, 1H, J = 9 Hz, C_3'—H), 7.20 (s, 1H, C_8'—H), 7.35 (s, 1H, C_5'—H), 7.70–7.95 (m, 3H, Arom-H), 7.84 (d, 1H, J = 9 Hz, C_4'—H), 11.80 (s, 1H, COOH). Anal. Calcd. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found C, 67.89; H, 3.96; N, 4.27.

5c. Yield 45%; mp 285–287°C, IR (KBr, cm^{-1}): 2991, 1723, 1674; ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H, C_7'—CH_3), 2.38 (s, 3H, C_4'—CH_3), 5.13 (s, 2H, C_1—CH_2), 6.38 (s, 1H, C_3'—H), 7.30 (s, 1H, C_8'—H), 7.39 (s, 1H, C_5'—H), 7.70–7.99 (m, 3H, Arom-H), 12.05 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, δ): 17.70 (C_7'—CH_3), 18.01 (C_4'—CH_4), 54.28 (C-1), 114.18 (C-3′), 118.17 (C-8′), 124. 71 (C-4′a), 127.0 (C-5′), 130.10 (C-8), 132.0 (C-7), 133.80 (C-7′), 135.60 (C-4), 136.44 (C-7′), 138.0 (C-5), 138.10 (C-6′), 139.20 (C-6), 152.75 (C-8′a), 154.0 (C-4′), 159.640 (C-2′, C=O), 165.0 (C-3, C=O), 170.20 (COOH); ms. m/z = 349 (65%) [M^+], 338(55%), 217(100%), 161 (70%). Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found C, 68.52; H, 4.41; N, 4.09.

Synthesis of methyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolene-5-carboxylate (6a–c). Mixture of compound (**5a–c**) (1 mmol), conc. H_2SO_4 (0.5 mL), and absolute methanol (10 mL) was refluxed for 8 h. Excess methanol was distilled off by rotary evaporation. The resulting mass was diluted with ethyl acetate and washed with aq. $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the corresponding esters (**6a–c**), which were purified by recrystallization using ethyl acetate–pet ether.

6a. Yield 62%; mp 170–172°C, IR (KBr, cm^{-1}): 3050, 1730, 1685; ^1H NMR (DMSO-d_6): 3.80 (s, 3H, OCH_3), 4.92 (s, 2H, C_1—CH_2), 6.32 (d, 1H, J = 9 Hz, C_3'—H), 7.21 (d, 1H, J = 9 Hz, C_7'—H), 7.28 (d, 1H, J = 9 Hz, C_8'—H), 7.50 (s, 1H, C_5'—H), 7.65–7.87 (m, 3H, Arom-H), 7.85 (d, 1H, J = 9 Hz, C_4'—H). Anal. Calcd. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found C, 67.89; H, 3.96; N, 4.29.

6b. Yield 58%; mp 175–177°C, IR (KBr, cm^{-1}): 3045, 1732, 1689; ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, C_7'—CH_3), 3.78 (s, 3H, OCH_3), 4.95 (s, 2H, C_1—CH_2), 6.30 (d, 1H, J = 9 Hz, C_3'—H), 7.32 (s, 1H, C_8'—H), 7.50 (s, 1H, C_5'—H), 7.62–7.89 (m, 3H, Arom-H), 7.80 (d, 1H, J = 9 Hz, C_4'—H). Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found C, 68.58; H, 4.39; N, 4.12.

6c. Yield 55%; mp 173–175°C, IR (KBr, cm^{-1}): 3045, 1735; ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, C_7'—CH_3), 2.25 (s, 3H, C_4'—CH_3), 3.82 (s, 3H, OCH_3), 4.98 (s, 2H, C_1—CH_2), 6.36 (s, 1H, C_3'—H), 7.40 (s, 1H, C_8'—H), 7.60 (s, 1H, C_5'—H), 7.72–7.87 (m, 3H, Arom-H); ^{13}C NMR (DMSO-d_6, δ): 18.20 (C_7'—CH_3), 18.91 (C_4'—CH_4), 53.28 (OCH_3), 53.63 (C-1), 114.84 (C-3′), 118.83(C-8′), 125. 64 (C-4′a), 126.0 (C-5′), 131.10 (C-8), 133.0 (C-7), 133.90 (C-7′), 135.60 (C-4), 136.44 (C-7′), 136.0 (C-5), 137.10 (C-6′), 138.20 (C-6), 150.75 (C-8′a), 152.0 (C-4′), 158.80 (C-2′, C=O), 160.0 (C-3, C=O), 168.0 (C=O); ms. m/z = 363 (50%) [M^+], 304 (30%), 188 (60%), 160 (25%). Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found C, 69.22; H, 4.79; N, 3.98.

Synthesis of 5-hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone (7a–c). To a suspension of the acid **5a–c** (0.3 mmol) in tetrahydrofuran (THF) (6 mL) at −20°C were added ethyl chloroformate (0.36 mmol) and triethlyamine (TEA) (0.45 mmol), and the reaction mixture was stirred at 0°C for 1 h. To the reaction mixture at 0°C were slowly added solid $NaBH_4$ (0.6 mmol) and MeOH (2 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with $NaHCO_3$. The organic layer was washed with brine solution, dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatographic purification gave compound (**7a–c**).

7a. Yield 55%; mp 260–262°C, IR (KBr, cm^{-1}): 3372, 2995, 1716; ^1H NMR (DMSO-d_6): δ 5.12 (s, 2H, C_1—CH_2), 6.31 (d, 1H, J = 9 Hz, C_3'—H), 7.13 (d, 1H, J = 9 Hz, C_7'—H), 7.21 (d, 1H, J = 9 Hz, C_8'—H), 7.38 (s, 1H, C_5'—H), 7.75–7.89 (m, 3H, Arom-H), 7.83 (d, 1H, J = 9 Hz, C_4'—H), 4.78 (s, 2H, CH_2—OH). Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.36; H, 4.23; N, 4.56. Found C, 70.61; H, 4.35; N, 4.76.

7b. Yield 52%; mp 264–266°C, IR (KBr, cm^{-1}): 3378, 2958, 1718; ^1H NMR (DMSO-d_6): δ 2.33 (s, 3H, C_7'—CH_3), 5.13 (s, 2H, C_1—CH_2), 6.21 (d, 1H, J = 9 Hz, C_3'—H), 7.25 (s, 1H, C_8'—H), 7.32 (s, 1H, C_5'—H), 7.70–7.88 (m, 3H, Arom-H), 7.80 (d, 1H, J = 9 Hz, C_4'—H), 4.72 (s, 2H, CH_2—OH). Anal. Calcd. for $C_{19}H_{15}NO_4$: C, 71.03; H, 4.68; N, 4.36. Found C, 71.25; H, 4.78; N, 4.52.

7c. Yield 50%; mp 268–270°C, IR (KBr, cm^{-1}): 3389, 2990, 1721, 1674; ^1H NMR (DMSO-d_6): δ 2.23 (s, 3H, C_7'—CH_3), 2.36 (s, 3H, C_4'—CH_3), 5.10 (s, 2H, C_1—CH_2), 6.36 (s, 1H, C_3'—H), 7.31 (s, 1H, C_8'—H), 7.35 (s, 1H, C_5'—H), 7.70–7.99 (m, 3H, Arom-H), 4.68 (s, 2H, CH_2—OH); ^{13}C NMR (DMSO-d_6, δ): 17.70 (C_7'—CH_3), 18.09 (C_4'—CH_4), 53.28 (C-1), 60.1 (CH_2OH) 113.18 (C-3′), 118.17 (C-8′), 124. 71 (C-4′a), 127.0 (C-5′), 131.10 (C-8), 132.0 (C-7), 134.80 (C-7′), 135.60 (C-4), 136.44 (C-7′), 138.0 (C-5), 138.10 (C-6′), 139.20 (C-6), 152.75 (C-8′a), 153.0 (C-4′), 159.6 (C-2′,C=O), 164.0 (C-3, C=O). Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found C, 71.88; H, 5.25; N, 4.40.

Acknowledgments. The authors thank the Department of Microbiology, Institute of Science, Mumbai, for carrying out antimicrobial testing and SAIF Department, IIT Bombay, for carrying out elemental analysis.

REFRENCES AND NOTES

[1] Bellioti, T. R.; Brink, W.A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Bioorg Med Chem Lett 1998, 8, 1499.

[2] Ferland, J. M.; Demerson, C. A.; Humber, L. G. Can J Chem 1985, 63, 361.

[3] Zhuang, Z. P.; Kung, M. P.; Kung, H. F. J Med Chem 1998, 41, 57.

[4] Norman, M. H.; Minick, D. J.; Rigdon, G. C. J Med Chem 1996, 39, 149.

[5] Yun, B. S.; Lee, I. K.; Ryoo, I. J.; Yoo, I. D. J Nat Prod 2001, 64, 1238.

[6] Zhao, H.; Neamati, N.; Hong, H. X.; Mazumder, A.; Wang, S. M.; Pommier, Y. J Med Chem 1997, 40, 242.

[7] El-Sayed, A. M.; Abd-Allah, O. A. Phosphorus Sulfur Silicon Relat Elem 2001, 170, 75.

[8] Nofal, Z. M.; El-Zahar, M. I.; Abd El-Karim, S. S. Molecules 2000, 5, 99.

[9] El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. Molecules 2001, 6, 519.

[10] Mulwad, V. V.; Shirodkar, J. M. J Heterocycl Chem 2003, 40, 377.

[11] Mulwad, V. V.; Pawar, R. B.; Chaskar, A. C. J Korean Chem Soc 2008, 52, 249.

[12] Mulwad, V. V.; Mir, A. A. J Chem Res 2008, 5, 292.

[13] Mulwad, V. V.; Satwe, D. S. Indian J Chem B 2004, 43, 2727.

[14] Choudhari, B. P.; Mulwad, V. V. Indian J Chem B 2006, 45, 309.

[15] Mulwad, V. V.; Chaskar, A. C.; Shirodkar, J. M. Indian J Chem B 2005, 44, 1465.

[16] Sarang, P. S.; Yadav, A. A.; Patil, P. S.; Trivedi, G. K. Synthesis 2007, 7, 1091.

[17] Zylber, J.; Tubel, A.; Brun, P. Tetrahedron: Asymmetry 1995, 6, 377.

[18] Prajapati, D.; Borthakur, D. R.; Sandhu, J. S. J Chem Soc Perkin Trans 1993, 1, 1197.

[19] Murli, R.; Surya Prakash Rao, H.; Scheeren, H. W. Tetrahedron 2001, 57, 3165.

[20] Hugo, W. B.; Russel, A. B. Pharmaceutical Microbiology, 4th ed.; Blackwell Scientific Publications: London, 1987; p 26.