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DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF BENZYL HYDROXAMIC ACID ANALOGUES OF COUMARIN

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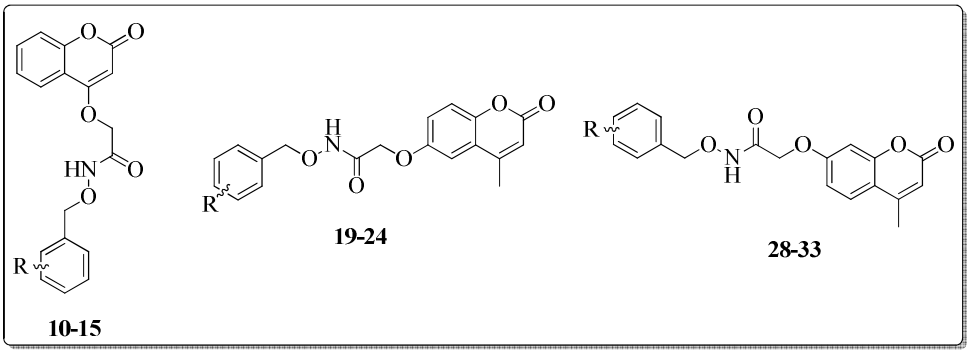
ABSTRACT
Hydroxamic acids (-CONHOH) are important components of many chemotherapeutic agents such as the succinate-based matrix metalloproteinase (MMP) inhibitors, class I/II histone deacetylase (HDAC) inhibitors and iron-containing antibiotics. N-(benzyloxy)-benzamide and its analogues with the O-benzylhydroxylamine moiety (-$CONHOCH_2$-Ar) possess antibacterial, herbicidal and enzyme inhibiting activities. We reported here the convenient synthesis of N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides (**10-15**), N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (**19-24**) and N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (**28-33**) in high yields by amide coupling of acids and oxyamines. The structures of the synthesized compounds are established based on IR, NMR, Mass spectrometric methods and elemental analysis. The antibacterial and antifungal activities of synthesized compounds were evaluated.

KEYWORDS: Coumarin, ethylester, hydrolysis, oxyamine, coupling, hydroxamic acid, anti microbial activity

INTRODUCTION
Coumarin and its derivatives are some of the most important oxygen heterocycles and are extensively found in various natural and synthetic products[i] . They are effective pharmacophores, widely used in the drug design and synthesis of novel bioactive compounds[ii] . Accordingly, different biological activities such as anticoagulation and cardiovascular activities[iii] and antimicrobial activities[iv] have been reported. They also possess anticancer[v], anti-inflammatory and antioxidant[vi], antiviral[vii] and enzyme-inhibition effects[viii]. At this juncture, fused coumarin derivatives have attracted attention because of their biological properties[ix]. Their antiproliferative[x], anti-inflammatory[xi], fluoroscent probe imaging[xii] have been reported in the literature.
Recent reports suggest that N-(benzyloxy)-benzamide and its analogues with the *o*-benzylhydroxylamine moiety (-$CONHOCH_2$-Ar) possess antibacterial, herbicidal and enzyme inhibiting activities[xiii, xiv]. The pharmacophore (-$CONHOCH_2$-) is generally considered to be the bioisosteric analog of (-$CONHCH_2CH_2$-) in drug design[xv]. Hydroxamic

acids (-CONHOH) are important components of many chemotherapeutic agents such as the succinate-based matrix metalloproteinase (MMP) inhibitors[xvi], class I/II histone deacetylase (HDAC) inhibitors[xvii] and iron-containing antibiotics[xviii]. Also hydroxamic acid analogues are important targets for the medicinal chemist because of the intrinsic chelating properties of this functional group with Zn^{++} at the active site of metalloproteins[xix, xx]. Recently various methods have been reported for the preparation of hydroxamic acids starting from carboxylic acids or their derivatives[xxi] and N-acyloxazolidinones[xxii]. The solution-phase hydroxyamination of esters is generally achieved via a two-step sequence; firstly preparation of a salt of hydroxylamine followed by addition of the ester in alcohol as solvent[xxiii] or activation of the acid by reaction with an acyl chloride or mixed anhydride and quenching with O-protected hydroxylamine derivatives[xxiv].

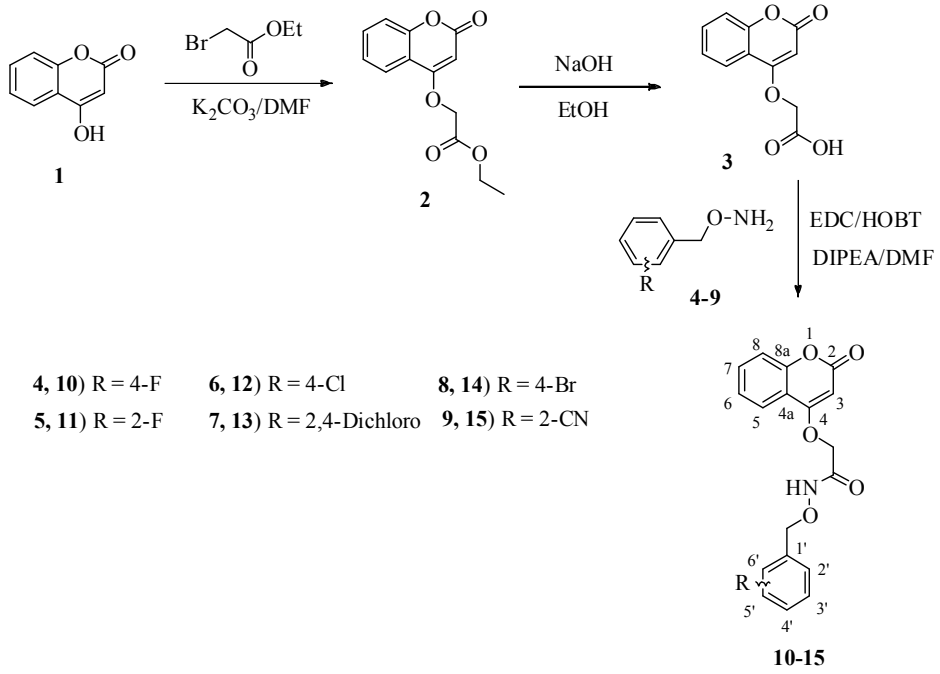
The above importance of hydroxamic acids encouraged us to investigate the synthesis of novel coumarin-hydroxamic acid analogues (**10-15, 19-24 & 28-33**) via amide coupling of acids with oxyamines. Coumarin system is present in various naturally occurring bioactive compounds[xxv] and thus it is expected that coumarin-hydroxamic acid analogues may possess interesting bioactivity. The synthesized compounds were screened for their antibacterial and antifungal activities.



RESULTS AND DISCUSSION

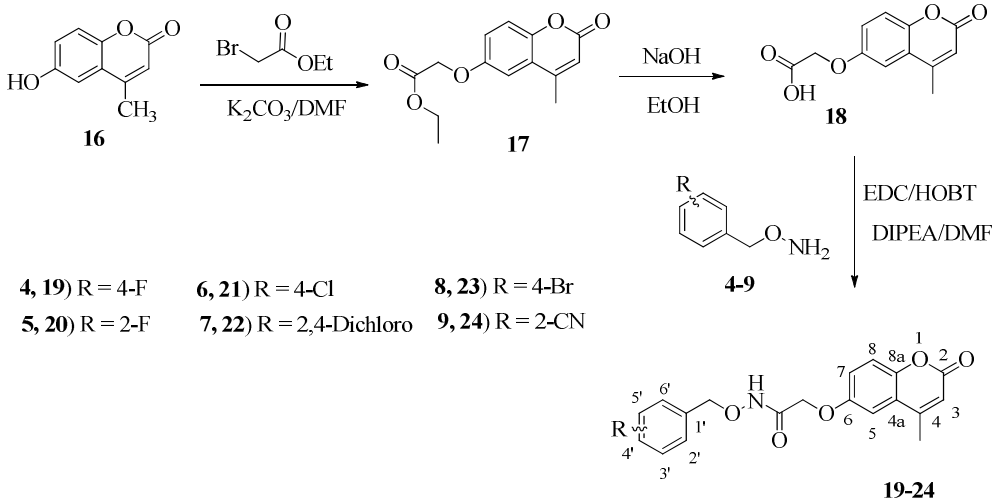
Chemistry. The synthetic route to the target compounds (**10-15, 19-24 & 28-33**) starting from substituted hydroxycoumarins (**3, 16 & 25**) was shown in Scheme 1, 2 & 3. O-Alkylation of compounds (**3, 16 & 25**) with ethyl-2-bromoacetate in the presence of K_2CO_3 in DMF afforded ethyl ester derivatives **4, 17 & 26** respectively. The esters **4, 17 & 26** were hydrolyzed with aqueous solution of sodium hydroxide in ethylalchol to yield the corresponding acids **5, 18 & 27**. Oxyamines were synthesized from N-hydroxy pthalimide and respective benzylhalides. The condensation of the carboxylic acids (**5, 18 & 27**) with appropriate oxy amines (**4-9**) were attempted by various reagents and conditions such as carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC), and N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC) / hydroxybenzotriazole (HOBT) in different solvents, but the best result was obtained by EDC/HOBT in DMF.

Scheme 1: Synthesis of N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides ***(10-15):***



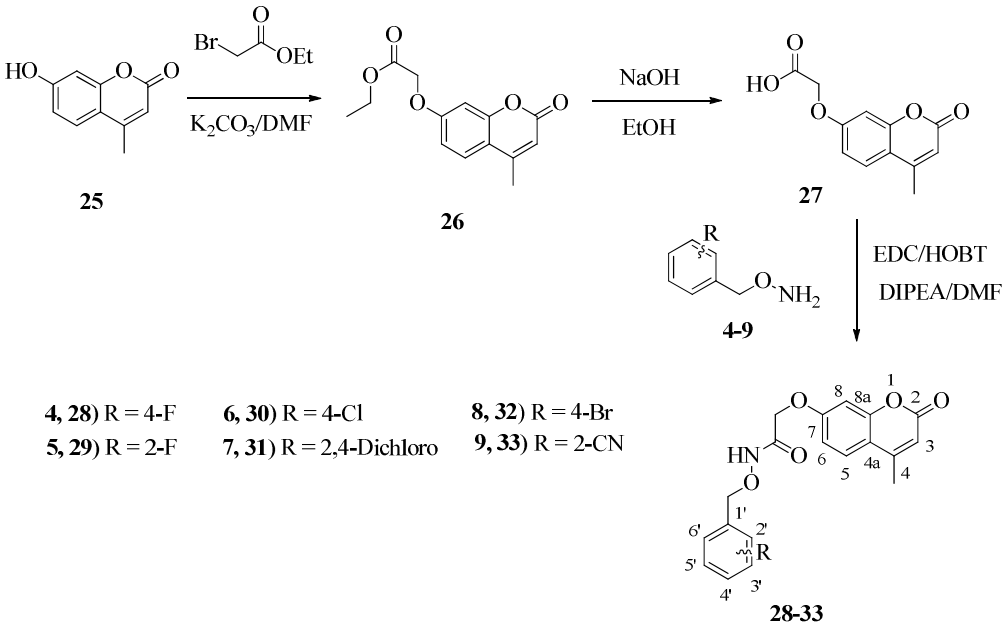
4, 10) R = 4-F **6, 12**) R = 4-Cl **8, 14**) R = 4-Br
5, 11) R = 2-F **7, 13**) R = 2,4-Dichloro **9, 15**) R = 2-CN

Scheme 2: Synthesis of N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides ***(19-24):***



4, 19) R = 4-F **6, 21**) R = 4-Cl **8, 23**) R = 4-Br
5, 20) R = 2-F **7, 22**) R = 2,4-Dichloro **9, 24**) R = 2-CN

Scheme 3: Synthesis of N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides ***(28-33):***



Initially, 7-hydroxy substituted coumarins[xxvi] were synthesized from the substituted resorcinols, β-keto esters in the presence of Con.H_2SO_4 (Pechmann reaction) followed by alkylation with ethyl bromoacetate to give ethyl esters which are converted into acids via base hydrolysis[xxvii]. Oxyamines are prepared as per literature[xxviii]. N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides (**10-15**), N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (**19-24**) and N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (**28-33**) in high yields by amide coupling of acids and oxyamines in EDC, HOBT/DMF system.

Spectral analysis. The structural assignment of the title compounds (**10-15, 19-24 & 28-33)** has been made on the basis of ^{1}H-NMR and mass studies. The structure of **10** is interpreted from spectroscopic data. In the ^{1}H-NMR spectra of **10**, the newly formed amide proton appeared at δ 11.59 (s, O=C-NH), 4-OCH_2 & 1'-OCH_2 appeared at δ 4.79 (s), 4.85 (s) and other protons at δ 5.86 (s, H-3), 7.19-7.24 (m, H-3' & H-5'), 7.38-7.5 (m, H-2', H-3' & H-6, H-8), 7.67-7.71 (m, H-7), 7.96 (d, J = 9.2 Hz, H-5). Mass spectrum was consistent with assigned structure showing [M+H$^+$] peak at 344.0. In the ^{1}H-NMR spectra of **19**, the newly formed amide proton appeared at δ 9.15 (s, O=C-NH). 4-CH_3, 6-OCH_2 & 1'-OCH_2 appeared at δ 2.38 (s), 4.61 (s) and 4.95 (s). Other protons appeared at δ 6.30 (s, H-3), 7.01-7.06 (m, H-5 & H-7, H-3' & H-5'), 7.24 (d, J = 1.6 Hz, H-2'), 7.37-7.41 (m, H-8 & H-6'). Mass spectrum was consistent with assigned structure showing [M+H$^+$] peak at 358.4. In the ^{1}H-NMR spectra of **28**, the newly formed amide proton appeared at δ 9.13 (s, O=C-NH); 4-CH_3, 7-OCH_2 & 1'-OCH_2 appeared at δ 2.4 (s), 4.62 (s) & 4.95 (s), other protons appeared at δ 6.17 (s, H-3), 6.81 (s, H-8), 6.83 (d, J = 2.4 Hz, H-6), 7.01-7.05 (m, H-3' & H-5'), 7.37-7.4 (m, H-2' & H-6'), 7.51 (d, J = 8.8 Hz, H-5). Mass spectrum was consistent with assigned structure showing [M+H$^+$] peak at 358.0.

EXPERIMENTAL

All melting points were obtained on a Polmon instrument, India (model MP96) and are uncorrected. The IR spectra were measured on a fourier transform infrared spectroscopy Perkin-Elmer 337 (Perkin Elmer instrument company, Massachusetts, USA). ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz, Switzerland using TMS as an internal

standard (Chemical shift in δ, ppm). *J*-Values are given in Hz. Mass spectral data were obtained with Agilent 6310 ion trap mass spectrometer, USA. All the materials and solvents were used directly unless otherwise stated. All the compounds synthesized were purified by recrystallization or column chromatography on silica gel (60-120 mesh, Spectrochem, Mumbai, India).

General procedure for the synthesis of O-benzyl hydroxamic acid analogues (10-15), (19-24) & (28-33). To a stirred solution of acid (0.3 g, 1 eq) in DMF (3 ml),. EDC (1.2 eq), HOBT (1.2 eq), DIPEA (1.5 eq) were added along with O-(substitutedbenzyl)-hydroxylamine (1.5 eq) and stirred for 24 h at room temperature. After completion of the reaction by TLC detection, water (30 mL) and ethylacetate (2x30 ml) was added and layers separated. Organic layer was washed with 1N HCl (30 mL), 10% $NaHCO_3$ (30 mL), brine solution (30 mL), dried over Na_2SO_4 and concentrated to yield the crude oxyamide. Crude oxyamide was taken into 30 ml of diethylether, stirred for 1 h. Filtered to get pure compound as solid.

N-(4-fluorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (10). Yield: 80 %; light brown solid; mp 164-168 °C; IR (KBr) cm^{-1}: 1186 (C-O-C), 1672 (-CONH), 1724 (-C=O), 3179 (-CONH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (s, 4-OCH_2), 4.85 (s, 1'-OCH_2), 5.86 (s, H-3), 7.19-7.24 (m, H-3' & H-5), 7.38-7.5 (m, H-2', H-3' & H-6, H-8), 7.67-7.71 (m, H-7), 7.96 (d, *J* = 9.2 Hz, H-5), 11.59 (s, O=C-NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 66.8 (4-OCH_2), 76.7 (1'-OCH_2), 91.7 (C-3), 115.3 (C-8), 115.3 (C-4a), 115.7 (C-5), 116.8 (C-6), 123.9 (C-2' & C-6'), 124.8 (C-4'), 131.7 (C-7), 132.3 (C-3' & C-5'), 133.3 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 164.7 (C-4), 163.5 (O=C-NH); ESI–MS: *m/z* 344 [M+H^+]; Anal.calc. for $C_{18}H_{14}FNO_5$: C, 62.97; H, 4.11; N, 4.08. Found: C, 62.28; H, 4.12; N, 4.17.

N-(2-Fluorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (11). Yield: 75 %; brown solid; mp 140-141 °C; IR (KBr) cm^{-1}: 1027 (C-O-C), 1621 (-CONH), 1712 (-C=O), 3087 (-CONH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.65 (s, 4-OCH_2), 5.15 (s, 1'-OCH_2), 5.64 (s, H-3), 7.04-7.34 (m, H-5', H-6 & H-6'), 7.37-7.51 (m, H-8 & H-3'), 7.68-7.71 (m, H-4' & H-7), 7.78-7.81 (m, H-5), 11.59 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 66.8 (4-OCH_2), 76.7 (1'-OCH_2), 91.7 (C-3), 115.9 (C-3'), 116.8 (C-4a), 122.8 (C-8), 123.0 (C-5), 123.9 (C-5'), 124.6 (C-6), 124.9 (C-1'), 131.5 (C-7), 132.5 (C-6'), 133.3 (C-4'), 133.3 (C-8a), 153.1 (C-2'), 161.8 (2-C=O), 163.6 (O=C-NH), 164.7 (C-4); ESI–MS: *m/z* 344 [M+H^+]; Anal.calc. for $C_{18}H_{14}FNO_5$: C, 62.97; H, 4.11; N, 4.08. Found: C, 62.28; H, 4.12; N, 4.17.

N-(4-Chlorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (12). Yield: 85 %; off-white solid; mp 218-219 °C; IR (KBr) cm^{-1}: 1077 (C-O-C), 1669 (-CONH), 1728 (-C=O), 3176 (-CONH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (s, 4-OCH_2), 4.86 (s, 1'-OCH_2), 5.86 (s, H-3), 7.38-7.42 (m, H-2', H-6' & H-3'), 7.43-7.46 (m, H-5' & H-6, H-8), 7.67-7.69 (m, H-7), 7.96 (d, *J* = 7.6 Hz, H-5), 11.59 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 66.8 (4-OCH_2), 76.6 (1'-OCH_2), 91.8 (C-3), 115.3 (C-8), 116.8 (C-4a), 123.9 (C-5), 124.6 (C-6), 128.8 (C-7), 131.2 (C-3' & C-5'), 133.4 (C-2' & C-6'), 133.5 (C-4'), 135.1 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.5 (O=C-NH), 164.7 (C-4); ESI–MS: *m/z* 360 [M+H^+], 362 [M+2+H^+]); Anal.calc. for $C_{18}H_{14}ClNO_5$: C, 60.09; H, 3.92; N, 3.89. Found: C, 60.08; H, 3.82; N, 3.79.

N-(2,4-Dichlorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (13). Yield: 90 %; white solid; mp 168-169 °C; IR (KBr) cm^{-1}: 1029 (C-O-C), 1666 (-CONH), 1714 (-C=O), 3086 (-CONH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.78 (s, 4-OCH_2), 4.97 (s, 1'-OCH_2), 5.85 (s, H-3), 7.37-7.47 (m, H-5', H-6' & H-8), 7.58-7.7 (m, H-3' & H-6, H-7), 7.93 (d, J=7.2Hz, H-5), 11.59 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 66.7 (4-OCH_2), 73.7 (1'-OCH_2), 91.7 (C-3), 115.3 (C-8), 116.8 (C-4a), 123.8 (C-5), 124.6 (C-6), 127.8 (C-5'), 129.3 (C-7), 132.8 (C-6'), 133.2 (C-3'), 133.3 (C-2'), 134.4 (C-4'), 134.8 (C-1'), 153.1 (C-8a), 161.8

(2-C=O), 163.7 (O=C-NH), 164.7 (C-4); ESI–MS: *m/z* 394 [M+H$^+$], 396 [M+H$^+$+2]; Anal.calc. for $C_{18}H_{13}Cl_2NO_5$: C, 54.84; H, 3.32; N, 3.55. Found: C, 54.81; H, 3.22; N, 3.49.

N-(4-Bromobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (14). Yield: 85 %; light orange solid; mp 228-229 °C; IR (KBr) cm^{-1}: 1072 (C-O-C), 1628 (-CONH), 1728 (-C=O), 3175 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.78 (s, 4-OCH_2), 4.84 (s, 1'-OCH_2), 5.86 (s, H-3), 7.38-7.43 (m, H-2', H-6' & H-6, H-8), 7.58-7.6 (m, H-3' & H-7, H-5'), 7.95 (d, *J* = 7.2 Hz, H-5), 11.59 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 66.8 (4-OCH_2), 76.7 (1'-OCH_2), 91.8 (C-3), 115.3 (C-8), 116.8 (C-4a), 122.1 (C-4'), 123.9 (C-5), 124.6 (C-6), 131.5 (C-7), 131.7 (C-2' & C-6'), 133.4 (C-3' & C-5'), 135.5 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.5 (O=C-NH), 164.7 (C-4); ESI–MS: *m/z* 404 [M+H$^+$], 406 [M+H$^+$+2); Anal.calc. for $C_{18}H_{14}BrNO_5$: C, 53.49; H, 3.49; N, 3.47. Found: C, 53.81; H, 3.22; N, 3.49.

N-(2-Cyanobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (15). Yield: 70 %; off white solid; mp 150-151 °C; IR (KBr) cm^{-1}: 1022 (C-O-C), 1622 (-CONH), 1714 (-C=O), 2232 (-CN), 3093 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.77 (s, 4-OCH_2), 5.05 (s, 1'-OCH_2), 5.83 (s, H-3), 7.37-7.41 (m, H-6' & H-8), 7.6-7.69 (m, H-4', H-5' & H-7, H-6), 7.8-7.85 (m, H-3' & H-5), 11.59 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 66.8 (4-OCH_2), 76.7 (1'-OCH_2), 91.7 (C-3), 112.5 (C-2'), 115.3 (-CN), 116.9 (C-8), 117.7 (C-4a), 123.9 (C-5), 124.6 (C-6), 129.9 (C-6'), 131.3 (C-7), 133.5 (C-4'), 133.6 (C-3'), 133.7 (C-5'), 139.1 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.8 (O=C-NH), 164.7 (C-4); ESI–MS: *m/z* 351 [M+H$^+$]; Anal.calc. for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.19; H, 4.12; N, 8.09.

N-(4-fluorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (19). Yield: 75 %; white solid; mp 120-121 °C; IR (KBr) cm^{-1}: 1052 (C-O-C), 1571 (-CONH), 1675 (-C=O), 3271 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 4-CH_3), 4.61 (s, 6-OCH_2), 4.95 (s, 1'-OCH_2), 6.3 (s, H-3), 7.01-7.06 (m, H-3' & H-5', H-5 & H-7), 7.24 (d, *J* = 9.2 Hz, H-2'), 7.37-7.41 (m, H-6' & H-8), 9.15 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.8 (6-OCH_2), 76.6 (1'-OCH_2), 109.9 (C-5), 115.4 (C-3), 115.6 (C-7), 117.9 (C-3' & C-5'), 120.1 (C-4a), 120.5 (C-8), 131.5 (C-2' & C-6'), 132.4 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 161.3 (C-4'), 164.9 (O=C-NH); ESI–MS: *m/z* 358.4 [M+H$^+$]; Anal.calc. for $C_{19}H_{16}FNO_5$: C, 63.86; H, 4.51; N, 5.32. Found: C, 63.91; H, 4.52; N, 5.49.

N-(2-fluorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (20). Yield: 70 %; white solid; mp 150-151 °C; IR (KBr): 1062 (C-O-C), 1682 (-CONH), 1715 (-C=O), 3314 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 4-CH_3), 4.61 (s, 6-OCH_2), 4.95 (s, 1'-OCH_2), 6.3 (s, H-3), 7.01-7.06 (m, H-3' & H-5', H-5 & H-7), 7.24 (d, *J* = 9.2 Hz, H-2'), 7.37-7.41 (m, H-6' & H-8), 9.15 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.8 (6-OCH_2), 76.6 (1'-OCH_2), 109.9 (C-5), 115.4 (C-3), 115.6 (C-7), 117.9 (C-3' & C-5'), 120.0 (C-4a), 120.5 (C-8), 131.5 (C-2' & C-6'), 132.4 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 161.3 (C-4'), 164.9 (O=C-NH); ESI–MS: *m/z* 358.3 [M+H+]; Anal.calc. for $C_{19}H_{16}FNO_5$: C, 63.86; H, 4.51; N, 5.32. Found: C, 63.91; H, 4.52; N, 5.49.

N-(4-chlorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (21). Yield: 90 %; white solid; mp 115-116 °C; IR (KBr): 1088 (C-O-C), 1678 (-CONH), 1712 (C=O), 3323 (CONH) cm $^{-1}$;^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 4-CH_3), 4.61 (s, 6-OCH_2), 4.95 (s, 1'-OCH_2), 6.3 (s, H-3), 6.99-7.01 (m, H-5 & H-7), 7.24 (d, *J* = 9.2 Hz, H-2'), 7.37-7.45 (m, H-5', H-3' & H-6' & H-8), 9.07 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.8 (6-OCH_2), 76.6 (1'-OCH_2), 109.92 (C-5), 115.4 (C-3), 115.6 (C-7), 117.9 (C-3' & C-5'), 120.0 (C-4a), 120.5 (C-8), 131.5 (C-2' & C-6'), 132.4 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 161.3 (C-4'), 164.9 (O=C-NH); ESI–MS: *m/z* 374.3 [M+H$^+$], 376.3 [M+H$^+$+2); Anal.calc. for $C_{19}H_{16}ClNO_5$: C, 61.05; H, 4.31; N, 3.75. Found: C, 61.11; H, 4.42; N, 3.79.

N-(2,4-dichlorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (22). Yield: 90 %; white solid; mp 150-151 °C; IR (KBr): 1058 (C-O-C), 1692 (-CONH), 1730 (-C=O), 3313 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.4 (s, 4-CH_3), 4.62 (s, 6-OCH_2), 5.09 (s, 1'-OCH_2), 6.32 (s, H-3), 7.02 (s, H-5), 7.07 (d, J = 8.8 Hz, H-7), 7.25-7.29 (m, H-5' & H-6'), 7.4-7.45 (m, H-3' & H-8), 9.12 (s, O=C-NH); ^{13}C NMR ((DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.8 (6-OCH_2), 76.6 (1'-OCH_2), 109.9 (C-5), 115.2 (C-3), 117.9 (C-7), 120.0 (C-4a), 120.5 (C-8), 127.8 (C-5'), 129.2 (C-6'), 132.8 (C-3'), 132.9 (C-2'), 134.2 (C-4'), 134.5 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.1 (O=C-NH); ESI–MS: *m/z* 408.3 [M+H$^+$], 410.3 [M+H$^+$+2); Anal.calc. for $C_{19}H_{15}Cl_2NO_5$: C, 55.90; H, 3.70; N, 3.43. Found: C, 55.99; H, 3.72; N, 3.49.

N-(4-Bromobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (23). Yield: 85%; orange solid; mp 155-156 °C; IR (KBr): 1065 (C-O-C), 1680 (-CONH), 1715 (-C=O), 3329 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.4 (s, 4-CH_3), 4.61 (s, 6-OCH_2), 4.93 (s, 1'-OCH_2), 6.32 (s, H-3), 7.01-7.06 (m, H-5 & H-7), 7.26-7.29 (m, H-8, H-2' & H-6'), 7.47-7.5 (d, J = 8.4 Hz, H-5' & H-3'), 9.01 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.6 (4-CH_3), 66.8 (6-OCH_2), 76.6 (1'-OCH_2), 109.9 (C-5), 115.2 (C-3), 117.9 (C-7), 120.0 (C-4a), 120.5 (C-4'), 122.0 (C-8), 131.3 (C-2' & C-6'), 131.6 (C-3' & C-5'), 135.6 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.0 (O=C-NH); ESI–MS: *m/z* 419.2 [M+H$^+$], 421.2 [M+H$^+$+2]; Anal.calc. for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86; N, 3.35. Found: C, 54.99; H, 3.82; N, 3.39.

N-(2-cyanobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (24). Yield: 75%; white solid; mp 181-182 °C; IR (KBr): 1064 (C-O-C), 1681 (-CONH), 1709 (-C=O), 2225 (CN), 3273(-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 4-CH_3), 4.64 (s, 6-OCH_2), 5.19 (s, 1'-OCH_2), 6.30 (s, H-3), 7.06-7.12 (m, H-5 & H-7), 7.26 (d, J = 9.2 Hz, H-3'), 7.34-7.38 (m, H-6'), 7.64-7.7 (m, H-8, H-4' & H-5'), 9.43 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.7 (4-CH_3), 66.7 (6-OCH_2), 74.8 (1'-OCH_2), 109.9 (C-5), 112.2 (C-2'), 115.2 (C-3), 117.7 (C-7), 117.9 (-CN), 119.9 (C-4a), 120.5 (C-8), 129.8 (C-6'), 131.2 (C-4'), 133.7 (C-3'), 133.8 (C-5'), 139.3 (C-1'), 148.1 (C-8a), 153.3 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.2 (O=C-NH); ESI–MS: *m/z* 365.4 [M+H$^+$]; Anal.calc. for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.99; H, 4.62; N, 7.79.

N-(4-fluorobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (28). Yield: 85%; orange solid; mp 156-158 °C; IR (KBr): 1077 (C-O-C), 1679 (-CONH), 1716 (-C=O), 3320 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.4 (s, 4-CH_3), 4.62 (s, 7-OCH_2), 4.95 (s, 1'-OCH_2), 6.17 (s, H-3), 6.81 (s, H-8), 6.83 (d, J = 2.4 Hz, H-6), 7.01-7.05 (m, H-3' & H-5'), 7.37-7.4 (m, H-2' & H-6'), 7.51 (d, J = 8.8 Hz, H-5), 9.13 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.3 (7-OCH_2), 76.6 (1'-OCH_2), 102.1 (C-8), 112.8 (C-6), 114.1 (C-4a), 115.6 (C-3), 126.9 (C-3' & C-5'), 131.5 (C-5), 131.6 (C-2' & C-6'), 132.4 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.4 (2-C=O), 161.1 (C-7), 161.3 (C-4'), 164.6 (O=C-NH); ESI–MS: *m/z* 358 [M+H$^+$]; Anal.calc. for $C_{19}H_{16}FNO_5$: C, 63.86; H, 4.51; N, 5.32. Found: C, 63.99; H, 4.62; N, 5.39.

N-(2-fluorobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (29). Yield: 75%; orange solid; mp 162-163 °C; IR (KBr): 1079 (C-O-C), 1681 (-CONH), 1715 (-C=O), 3323 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 4-CH_3), 4.62 (s, 7-OCH_2), 5.07 (s, 1'-OCH_2), 6.17 (s, H-3), 6.81 (s, H-8), 7.26 (dd, J = 2.8 Hz, 2.8 Hz, H-6), 7.06-7.08 (m, H-5'), 7.14 (d, J = 7.2 Hz, H-6'), 7.34 (d, J = 6.8 Hz, H-3'), 7.42-7.46 (m, H-4'), 7.52 (d, J = 8.8 Hz, H-5), 9.24 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.2 (7-OCH_2), 70.9 (1'-OCH_2), 101.9 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 115.9 (C-3'), 122.9 (C-5'), 123.0 (C-5), 124.8 (C-1'), 126.9 (C-6'), 131.3 (C-4'), 132.4 (C-4), 153.7 (C-8a), 154.9 (C-

2'), 161.0 (2C=O), 162.5 (C-7'), 164.7 (O=C-NH); ESI–MS: *m/z* 358 [M+H$^+$]; Anal.calc. for $C_{19}H_{16}FNO_5$: C, 63.86; H, 4.51; N, 5.32. Found: C, 63.99; H, 4.62; N, 5.39.

N-(4-chlorobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (30). Yield: 85%; orange solid; mp 156-157 °C; IR (KBr): 1080 (C-O-C), 1684 (-CONH), 1716 (-C=O), 3322 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 4-CH_3), 4.62 (s, 7-OCH_2), 4.95 (s, 1'-OCH_2), 6.17 (s, H-3), 6.80-6.83 (m, H-6 & H-8), 7.3-7.35 (m, H-2' & H-6', H-3' & H-5'), 7.51 (d, *J* = 8.8 Hz, H-5), 9.12 (s, O=C-NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 18.6 (4-CH_3), 66.2 (7-OCH_2), 76.5 (1'-OCH_2), 101.9 (C-8), 111.9 (C-6), 114.1 (C-4a), 126.9 (C-3), 128.9 (C-5), 129.0 (C-3' & C-5'), 131.1 (C-2' & C-6'), 133.4 (C-4'), 135.2 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.5 (2-C=O), 161.0 (C-7), 164.6 (O=C-NH); ESI–MS: *m/z* 374 [M+H$^+$], 376 (M+2); Anal.calc. for $C_{19}H_{16}ClNO_5$: C, 61.05; H, 4.31; N, 3.75. Found: C, 61.19; H, 4.32; N, 3.79.

N-(2,4-dichlorobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (31). Yield: 90%; orange solid; mp 190-191 °C; IR (KBr): 1080 (C-O-C), 1683 (-CONH), 1718 (-C=O), 3317 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 4-CH_3), 4.58 (s, 7-OCH_2), 5.04 (s, 1'-OCH_2), 6.15 (s, H-3), 6.85 (s, H-8), 6.9 (d, *J* = 8.4 Hz, H-6), 7.25 (d, *J* = 6.4 Hz, H-5'), 7.38 (d, *J* = 8.8 Hz, H-6'), 7.48 (d, *J* = 8.0 Hz, H-5), 7.55 (s, H-3'), 11.07 (s, O=C-NH); ^{13}C NMR ((DMSO-d_6, 100.6 MHz): δ 14.4 (4-CH_3), 66.2 (7-OCH_2), 73.7 (1'-OCH_2), 101.9 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 126.9 (C-5), 127.8 (C-5'), 129.2 (C-6'), 132.9 (C-3'), 133.0 (C-2'), 134.3 (C-4'), 134.6 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.4 (2-C=O), 161.0 (C-7), 164.8 (O=C-NH); ESI–MS: *m/z* 408 [M+H$^+$], 410 [M+H$^+$+2]; Anal.calc. for $C_{19}H_{15}Cl_2NO_5$: C, 55.90; H, 3.70; N, 3.43. Found: C, 55.97; H, 3.62; N, 3.49.

N-(4-bromobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (32). Yield: 90%; orange solid; mp 176-177 °C; IR (KBr): 1073 (C-O-C), 1684 (-CONH), 1717 (-C=O), 3325 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 4-CH_3), 4.62 (s, 7-OCH_2), 4.93 (s, 1'-OCH_2), 6.17 (s, H-3), 6.81-6.83 (m, H-6 & H-8a), 7.27 (d, *J* = 6.8 Hz, H-2'), 7.45-7.51 (m, H-5 & H-5', H-3' & H-6'), 9.22 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.5 (4-CH_3), 66.2 (7-OCH_2), 76.6 (1'-OCH_2), 102.0 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 122.0 (C-4'), 126.9 (C-5), 131.4 (C-2' & C-6'), 133.8 (C-3' & C-5'), 135.6 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.5 (2-C=O), 161.0 (C-7), 164.6 (O=C-NH); ESI–MS: *m/z* 418 [M+H+], 420 [M+H$^+$+2); Anal.calc. for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86; N, 3.35. Found: C, 54.67; H, 3.86; N, 3.49.

N-(2-cyanobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (33). Yield: 70%; orange solid; mp 162-163 °C; IR (KBr): 1080 (C-O-C), 1684 (-CONH), 1714 (-C=O), 2226 (-CN), 3310 (-CONH) cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 4-CH_3), 4.6 (s, 7-OCH_2), 5.15 (s, 1'-OCH_2), 6.16 (s, H-3), 6.84 (s, H-8), 6.91 (dd, *J* = 2.4 Hz, 2.4 Hz, H-6), 7.48-7.51 (m, H-3'), 7.53 (d, *J* = 8.8 Hz, H-5), 7.62-7.72 (m, H-4', H-5' & H-6'), 10.96 (s, O=C-NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 18.6 (4-CH_3), 66.2 (7-OCH_2), 74.9 (1'-OCH_2), 101.9 (C-8), 111.9 (C-6), 112.8 (C-2'), 114.1 (C-4a), 117.7 (C-3), 126.9 (-CN), 129.8 (C-5), 131.1 (C-6'), 133.4 (C-4'), 133.7 (C-3'), 133.8 (C-5'), 139.2 (C-1'), 153.7 (C-4), 154.1 (C-8a), 160.5 (2-C=O), 161.0 (C-7'), 164.8 (O=C-NH); ESI–MS: *m/z* 365 [M+H$^+$]; Anal.calc. for $C_{20}H_{16}NO_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.97; H, 4.46; N, 7.69.

Antimicrobial activity. The *in vitro* antimicrobial activity[xxix-xxxi] of all the synthesized compounds was carried out using paper disk method. These compounds were screened against *Staphylococus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) for antibacterial activity where as *Aspergillus terreus* and *Rhizoctonia solani* for antifungal activity. The strains used for the activity procured from the Institute of Microbial Technology (IMT), Chandigarh. Cultures of test organisms were maintained on nutrient agar (bacterial) and potato dextrose agar (fungal) media and subcultured in petri dishes prior to testing. The

compounds were tested at the concentrations of 200 µg/mL and 100 µg/ mL using DMSO as solvent. After solidification of media, petri plates inoculated with actively growing cultures of *S. aureus* (Gram-positive), *E. coli* (Gram-negative) *A. terreus* and *R. solani* separately. Filter paper disks of 5 mm diameter dipped in the test solution of different concentrations. After drying the disk, kept on nutrient agar broth. Potato dextrose broth in petri plates seeded with 1 mL culture of *S. aureus* (Gram-positive), *E. coli* (Gram-negative), *A. terreus* and *R. solani* incubated for 24 h at 27 ℃. Then the petri dishes were tested for growth of inhibition. The presence of clear zone of growth inhibition around the paper disk indicated the inhibition of growth of organisms. The diameter of zone of inhibition was calculated in millimeters. Ampicillin is used as standard antibacterial drug, where as clotrimazole used as standard antifungal drug. The observed data of antimicrobial activity of compounds and the standard drugs are given in Table 1. From the obtained results it was evident that most of the compounds showed good antibacterial activity (12, 14, 19, 23, 24, 28, 29 and 33) and antifungal activity (12, 14, 15, 23, 24, 28 and 33) in higher concentrations comparable with that of standard drugs tested. Although with respect to standard drugs, all the tested compounds were found to be moderate to poor in their activity. So, the result of all preliminary study indicated that the N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides (**10-15**), N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (**19-24**) and N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (**28-33**) moiety represent a new class of pharmacophore for broad spectrum of antibacterial and antifungal activity.

Table 1
Antimicrobial activity of compounds **(10-15), (19-24)** and **(28-33)**

		Antibacterial activity		Antifungal activity	
Compd. No.	Conc.(µg/ mL)	*S.aureus*[a]	*E.coli*[a]	*A.terreus* [a]	*R. solani*[a]
10	200	16	30	26	25
	100	11	23	18	18
11	200	19	26	32	32
	100	13	17	23	23
12	200	19	28	27	21
	100	10	20	19	17
13	200	18	30	30	30
	100	12	22	21	21
14	200	22	30	33	30
	100	12	24	26	24
15	200	16	27	26	29
	100	10	18	17	11
19	200	27	24	21	16
	100	13	19	11	10
20	200	21	32	28	28
	100	10	23	19	19
21	200	13	21	39	39
	100	8	13	26	27
22	200	18	28	26	26
	100	12	21	15	15
23	200	28	32	34	24

	100	19	24	25	27
24	200	31	28	28	25
	100	11	22	19	19
28	200	29	28	26	29
	100	11	17	20	20
29	200	31	24	13	17
	100	11	16	16	16
30	200	19	21	26	15
	100	13	32	15	34
31	200	27	25	34	25
	100	19	31	25	28
32	200	18	21	29	19
	100	12	28	19	26
33	200	28	27	26	21
	100	11	24	20	22
Ampicillin	20 µg/mL	19	21	NA	NA
Clotrimazole	20 µg/mL	NA	NA	20	22

[a]Zone of inhibition

S. aureus - Staphylococus aureus, E.coli - Escherichia coli, A.terreus - Aspergillus terreus and R.solani - Rhizoctonia solani

Conclusion

Herewith, we report the simple and efficient method for synthesis of hydroxamic acid analogues, N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides (**10-15**), N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (**19-24**) and N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (**28-33**). Some of these compounds have shown good antimicrobial activity.

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