Research Article

Synthesis, Structural Elucidation, and Antibacterial Evaluation of Some New Molecules Derived from Coumarin, 1,3,4-Oxadiazole, and Acetamide

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Because of the reported biological activities of coumarin, 1,3,4-oxadiazole, and acetamides, some new compounds incorporating these moieties were synthesized and evaluated for their biological potential against Gram-positive and Gram-negative bacteria. In the present work, 4-chlororesorcinol (**1**) and ethyl acetoacetate (**2**) were mixed in a strong acidic medium to synthesize 6-chloro-7-hydroxy-4-methyl-2-oxo-2H-chromene (**3**) which was subjected to the intermolecular cyclization after consecutive three steps to synthesize 5-[[[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl]-1,3,4-oxadiazol-2-thiol (**6**). A series of acetamoyl electrophiles, **8a–o**, were synthesized from aralkyl/alkyl/aryl amines, **7a–o**, in an aqueous basic medium. The final compounds, **9a–o**, were synthesized by the reaction of compounds **6** and **8a–o** in DMF/NaH. The synthesized compounds were structurally elucidated by spectral data analysis of IR, ¹H-NMR, and EIMS. The most of the synthesized compounds remained moderate to excellent antibacterial agents. The molecules, **9e**, **9j**, and **9k**, were the most efficient ones against all the five bacterial strains taken into account.

1. Introduction

Coumarin is a naturally occurring heterocyclic class of compounds [1–3]. The compounds of this class were used by ancient Egyptians as drug [4]. The field of agriculture has also found the applications of these molecules [4, 5]. The different derivatives of various coumarins have been introduced synthetically and also by plant extraction to possess a number of biological activities including antibacterial, antioxidant, and anti-inflammatory activities [6–9]. The heterocyclic moiety, 1,3,4-oxadiazole, and its various 2,5-disubstituted products are also known to be biologically active compounds [10–12].

The presence of amide functionality is also known to boost up the potential of bioactive compounds including antifungal, anti-inflammatory, anticancer, antibacterial, and antioxidant activities [13–16].

The increased resistance by microbes against the existing drugs is the key point for search of new drug molecules [17, 18]. In continuation of our previous work on O-substituted derivatives [19] and notable bioactivity of ether derivatives of coumarin [6, 9, 20] this prompted us to incorporate coumarin with 1,3,4-oxadiazole and acetamides to evaluate their antibacterial activity.

2. Experimental

2.1. Material and Methods. 4-Chlororesorcinol, ethyl acetoacetate, ethyl 2-bromoacetate, hydrated hydrazine, carbon disulfide, aralkyl/alkyl/aryl amines, and 2-bromoacetyl bromide were purchased from Merck, Riedel-de Haen, Aldrich, and Alfa Aesar through local suppliers along with analytical grade solvents. The Jasco-320-A spectrophotometer was used to record IR spectra by KBr pellet method. The Bruker spectrometers at 125 and 400 MHz were used to record the ^{13}C and ^1H NMR spectra in CDCl_3 , respectively. The JMS-HX-110 spectrometer was used to record EIMS spectra. Silica plates coated on alumina were used for thin layer chromatography (TLC), run in mobile phase of *n*-hexane and ethyl acetate and observed under UV_{254} . Griffin-George apparatus was used to record the melting points in open capillary tubes which were uncorrected.

2.2. Synthesis of 6-Chloro-7-hydroxy-4-methyl-2-oxo-2H-chromene (3). 4-Chlororesorcinol (0.05 mol; **1**) was dissolved in ethyl acetoacetate (0.05 mol; **2**) on heating in an iodine flask (500 mL). Then concentrated H_2SO_4 (25 mL) was added on continuous shaking at low temperature. The mixture was aged for 12–16 hours. Excess cold distilled water was added to precipitate the title compound which was separated through filtration, washed by distilled water, and dried.

2.3. Synthesis of Ethyl 2-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetate (4). Compound **3** (0.045 mol) was dissolved in DMF (25 mL) in a round bottom (RB) flask (250 mL) and then NaH (0.045 mol) was added. The mixture was stirred for 0.5 hours and then ethyl 2-bromoacetate (0.045 mol) was added. The stirring was continued for 3–4 hours along with monitoring through TLC. Excess cold distilled water was added and the formed precipitates were filtered out, washed, and dried.

2.4. Synthesis of 2-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (5). The ethyl ester **4** (0.04 mol) was mixed with methanol (35 mL) in a RB flask (250 mL). The hydrated hydrazine (0.04 mol) was added and the mixture was set to stir for 2–3 hours. TLC was frequently developed to monitor the reaction. Solvent was evaporated to one-third and then excess of distilled water was added to precipitate the product. The precipitates were acquired through filtration and subjected to washing and drying.

2.5. Synthesis of 5-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl-1,3,4-oxadiazol-2-thiol (6). Compound **5** (0.035 mol) was added to absolute ethanol (50 mL) in a RB flask (250 mL) followed by solid KOH (0.035 mol). The mixture was homogenized on reflux and then cooled to room temperature and liquid CS_2 (0.07 mol) was added. The mixture was again set to reflux for 4–5 hours along with supervision by TLC. Solvent was evaporated to one-third and then excess cold distilled water was added. The pH of this homogeneous solution was adjusted to 6–7 by dilute HCl and aged for 0.5 hours to allow maximum precipitation. The

precipitates were filtered, washed with distilled water, and dried.

2.6. General Synthesis of N-Aralkyl/alkyl/aryl-2-bromoacetamide (8a–o). Aralkyl/alkyl/aryl amines (0.005 mol; **7a–o**) were dispersed in distilled water (15 mL) in an iodine flask (125 mL). The pH was adjusted to 8–9 by aqueous Na_2CO_3 solution (15%, 4 mL). Then 2-bromoacetyl bromide (0.005 mol) was added on vigorous stirring and further set to stir for 1 hour on maintained pH. The precipitates of title products were filtered off, washed by distilled water and dried.

2.7. General Synthesis of N-Aralkyl/alkyl/aryl-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide (9a–o). Compound **6** (0.002 mol) was dissolved in DMF (12 mL) in a round bottom flask (50 mL) followed by NaH (0.002 mol). The mixture was stirred for 0.5 hours and then N-aralkyl/alkyl/aryl-2-bromoacetamide (0.002 mol; **8a–o**) were added. The stirring was continued for 4–6 hours along with monitoring through TLC. Excess cold distilled water was added and the precipitates were filtered out, washed, and dried.

2.8. Antibacterial Activity Assay. The sterilized 96-well microplates under aseptic conditions were used to evaluate the antibacterial activity by the reported method of Kaspady et al., 2009, and Yang et al., 2006, with slight modifications [21, 22]. The change in absorbance before and after the addition of sample compound was noted. The absorbance is varied with number of microbial cells which are varied with log phase microbial growth.

The clinically isolated three Gram-negative and two Gram-positive bacteria were stored on stock culture agar medium. A mixture of 200 μL was prepared by 180 μL fresh nutrient broth with suitable dilutions and 20 μg test samples with suitable dilutions. All the dilutions were performed using specific suited solvents. Before and after incubation at 37°C for 16–24 hrs with lid on the microplate, the absorbance (0.12–0.19 at beginning) was measured at 540 nm. The variation in absorbance was the criteria for bacterial growth. The percent inhibition was calculated by the following formula:

$$\text{Inhibition (\%)} = \frac{X - Y}{X} \times 100, \quad (1)$$

where X is absorbance in control with bacterial culture and Y is absorbance in test sample. Ciprofloxacin was taken as reference standard. Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5–30 $\mu\text{g}/\text{well}$) and results were calculated using EZ-Fit Perrella Scientific Inc., Amherst, USA, software.

2.9. Statistical Analysis. The antibacterial activity results were reported as percentage of age inhibition and minimum inhibitory concentration (MIC) values after performing each experiment three times. The results were reported as mean $\pm$ SEM after statistical analysis by Microsoft Excel 2010.

2.10. Characterization of the Synthesized Compounds

(3-6, 9a-o)

2.10.1. 6-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one (3). Light brown amorphous solid; Yield: 78%; M.P.: 262–264 °C; M.F.: $C_{10}H_7ClO_3$; M.M.: 210 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3310 (O-H), 3055 (Ar C-H), 1732 (ester C=O), 1586 (Ar C=C), 1146 (C-O), 703 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 7.54 (s, 1H, H-5'), 6.98 (s, 1H, H-8'), 6.17 (s, 1H, H-3'), 2.37 (s, 3H, CH_3 -11'); $^{13}\text{C-NMR}$ (125 MHz, CHCl_3 - d_1 , δ , ppm): 160.5 (C-2'), 157.7 (C-7'), 153.4 (C-4'), 151.5 (C-9'), 125.4 (C-5'), 118.7 (C-6'), 113.6 (C-10'), 112.7 (C-3'), 100.3 (C-8'), 18.5 (C-11'); EIMS (m/z): 212 (6%), 210 $[\text{M}]^{++}$ (17%), 193 (7%), 182 (5%), 175 (BP, 100%), 165 (3%), 149 (2%), 134 (5%).

2.10.2. Ethyl 2-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetate (4). Cream white amorphous solid; Yield: 73%; M.P.: 184–186 °C; M.F.: $C_{14}H_{13}ClO_5$; M.M.: 296 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3316 (O-H), 3062 (Ar C-H), 1735 (ester C=O), 1594 (Ar C=C), 1159 (C-O), 702 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 7.59 (s, 1H, H-5'), 6.71 (s, 1H, H-8'), 6.18 (s, 1H, H-3'), 4.74 (s, 2H, H-12'), 4.27 (q, $J = 7.2 \text{ Hz}$, 2H, H-1'''), 2.37 (s, 3H, CH_3 -11'), 1.30 (t, $J = 7.2 \text{ Hz}$, 3H, CH_3 -2'''); EIMS (m/z): 298 (6%), 296 $[\text{M}]^{++}$ (17%), 261 (19%), 251 (4%), 210 (91%), 193 (18%), 182 (BP, 100%), 165 (8%), 149 (7%), 134 (16%).

2.10.3. 2-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (5). Light yellow amorphous solid; Yield: 67%; M.P.: 190–192 °C; M.F.: $C_{12}H_{11}ClN_2O_4$; M.M.: 282 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3421 (N-H), 3061 (Ar C-H), 1735 (ester C=O), 1671 (amide C=O), 1594 (Ar C=C), 1159 (C-O), 703 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 8.84 (s, 1H, CON-H), 7.57 (s, 1H, H-5'), 6.72 (s, 1H, H-8'), 6.19 (s, 1H, H-3'), 4.72 (s, 2H, H-12'), 2.38 (s, 3H, CH_3 -11'); EIMS (m/z): 284 (7%), 282 $[\text{M}]^{++}$ (16%), 249 (7%), 247 (18%), 230 (4%), 214 (14%), 210 (89%), 193 (15%), 182 (BP, 100%), 165 (4%), 149 (7%), 134 (17%).

2.10.4. 5-[(6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl-1,3,4-oxadiazol-2-thiol (6). Light brown amorphous solid; Yield: 73%; M.P.: 188–190 °C; M.F.: $C_{13}H_9ClN_2O_4S$; M.M.: 324 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3078 (Ar C-H), 1736 (ester C=O), 1689 (C=N), 1595 (Ar C=C), 1158 (C-O), 697 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 7.59 (s, 1H, H-5'), 6.75 (s, 1H, H-8'), 6.21 (s, 1H, H-3'), 4.74 (s, 2H, H-12'), 2.39 (s, 3H, CH_3 -11'); EIMS (m/z): 326 (7%), 324 $[\text{M}]^{++}$ (16%), 289 (14%), 251 (3%), 249 (7%), 230 (2%), 214 (13%), 210 (86%), 193 (13%), 182 (BP, 100%), 165 (7%), 149 (4%), 134 (16%).

2.10.5. N-Cyclohexyl-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (9a). White amorphous solid; Yield: 78%; M.P.: 100–102 °C; M.F.: $C_{21}H_{22}ClN_3O_5S$; M.M.: 463 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3445 (N-H), 3073 (Ar C-H), 1739 (ester C=O), 1676 (amide C=O), 1684 (C=N), 1596 (Ar C=C), 1159 (C-O),

697 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 8.71 (s, 1H, CON-H), 7.57 (s, 1H, H-5'), 7.04 (s, 1H, H-8'), 6.23 (s, 1H, H-3'), 5.33 (s, 2H, H-12'), 4.05 (s, 2H, H-2'''), 3.76–3.73 (m, 1H, H-1''), 2.38 (s, 3H, CH_3 -11'), 1.85–1.82 (m, 2H, $H_{\text{eq}}-2''$ & $H_{\text{eq}}-6''$), 1.67–1.56 (m, 4H, H-3''' & H-5''), 1.35–1.32 (m, 2H, $H_{\text{ax}}-2''$ & $H_{\text{ax}}-6''$), 1.22–1.16 (m, 2H, H-4''); EIMS (m/z): 465 (9%), 463 $[\text{M}]^{++}$ (20%), 428 (16%), 251 (4%), 249 (8%), 230 (4%), 214 (13%), 210 (90%), 193 (17%), 182 (BP, 100%), 165 (4%), 149 (8%), 134 (17%), 126 (28%), 98 (34%).

2.10.6. N-Benzyl-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (9b). Light yellow amorphous solid; Yield: 84%; M.P.: 126–128 °C; M.F.: $C_{22}H_{18}ClN_3O_5S$; M.M.: 471 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3464 (N-H), 3053 (Ar C-H), 1736 (ester C=O), 1672 (amide C=O), 1689 (C=N), 1609 (Ar C=C), 1156 (C-O), 704 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 8.64 (s, 1H, CON-H), 7.61 (s, 1H, H-5'), 7.25–7.19 (m, 5H, H-2'' to H-6''), 7.06 (s, 1H, H-8'), 6.23 (s, 1H, H-3'), 5.37 (s, 2H, H-12'), 4.37 (s, 2H, H-7''), 4.06 (s, 2H, H-2'''), 2.34 (s, 3H, CH_3 -11'); EIMS (m/z): 473 (8%), 471 $[\text{M}]^{++}$ (24%), 436 (13%), 251 (5%), 249 (9%), 230 (3%), 214 (8%), 210 (84%), 193 (11%), 182 (BP, 100%), 165 (7%), 149 (5%), 134 (47%), 106 (35%).

2.10.7. N-(2-Phenylethyl)-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (9c). Light grey amorphous solid; Yield: 87%; M.P.: 126–128 °C; M.F.: $C_{23}H_{20}ClN_3O_5S$; M.M.: 485 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3441 (N-H), 3065 (Ar C-H), 1743 (ester C=O), 1659 (amide C=O), 1684 (C=N), 1602 (Ar C=C), 1174 (C-O), 702 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 8.62 (s, 1H, CON-H), 7.61 (s, 1H, H-5'), 7.15–7.10 (m, 5H, H-2'' to H-6''), 7.05 (s, 1H, H-8'), 6.21 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.07 (s, 2H, H-2'''), 3.43 (t, $J = 7.6 \text{ Hz}$, 2H, H-8''), 2.73 (t, $J = 7.6 \text{ Hz}$, 2H, H-7''), 2.38 (s, 3H, CH_3 -11'); EIMS (m/z): 487 (6%), 485 $[\text{M}]^{++}$ (17%), 450 (13%), 251 (4%), 249 (8%), 230 (1%), 214 (9%), 210 (88%), 193 (15%), 182 (BP, 100%), 165 (7%), 149 (8%), 148 (31%), 134 (9%), 120 (34%).

2.10.8. N-Phenyl-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (9d). Light grey amorphous solid; Yield: 77%; M.P.: 94–96 °C; M.F.: $C_{21}H_{16}ClN_3O_5S$; M.M.: 457 gmol^{-1} ; IR (KBr, ν_{max} , cm^{-1}): 3436 (N-H), 3046 (Ar C-H), 1735 (ester C=O), 1667 (amide C=O), 1681 (C=N), 1588 (Ar C=C), 1121 (C-O), 704 (C-Cl); $^1\text{H-NMR}$ (400 MHz, CHCl_3 - d_1 , δ , ppm): 8.59 (s, 1H, CON-H), 7.63 (s, 1H, H-5'), 7.57 (d, $J = 7.6 \text{ Hz}$, 2H, H-2'' & H-6''), 7.34 (t, $J = 7.6 \text{ Hz}$, 2H, H-3''' & H-5''), 7.17 (t, $J = 7.6 \text{ Hz}$, 1H, H-4''), 7.05 (s, 1H, H-8'), 6.20 (s, 1H, H-3'), 5.36 (s, 2H, H-12'), 4.07 (s, 2H, H-2'''), 2.39 (s, 3H, CH_3 -11'); EIMS (m/z): 459 (6%), 457 $[\text{M}]^{++}$ (21%), 422 (18%), 251 (6%), 249 (10%), 230 (4%), 214 (12%), 210 (87%), 193 (15%), 182 (BP, 100%), 165 (7%), 149 (4%), 134 (17%), 120 (37%), 92 (29%).

2.10.9. *N*-(2-Methylphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9e). White amorphous solid; Yield: 69%; M.P.: 100–102°C; M.F.: C₂₂H₁₈ClN₃O₅S; M.M.: 471 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3442 (N-H), 3069 (Ar C-H), 1733 (ester C=O), 1678 (amide C=O), 1691 (C=N), 1603 (Ar C=C), 1150 (C-O), 701 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.73 (s, 1H, CON-H), 7.72 (d, *J* = 8.0 Hz, 1H, H-6''), 7.63 (s, 1H, H-5'), 7.21 (d, *J* = 8.0 Hz, 1H, H-3''), 7.15 (t, *J* = 8.0 Hz, 1H, H-5''), 7.07 (t, *J* = 8.0 Hz, 1H, H-4''), 7.02 (s, 1H, H-8'), 6.22 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.06 (s, 2H, H-2'''), 2.38 (s, 3H, CH₃-11'), 2.28 (s, 3H, CH₃-7''); EIMS (*m/z*): 473 (7%), 471 [M]⁺⁺ (24%), 436 (12%), 251 (4%), 249 (7%), 230 (5%), 214 (16%), 210 (81%), 193 (13%), 182 (BP, 100%), 165 (8%), 149 (3%), 134 (47%), 106 (32%).

2.10.10. *N*-(3-Methylphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9f). Yellowish grey amorphous solid; Yield: 83%; M.P.: 88–90°C; M.F.: C₂₂H₁₈ClN₃O₅S; M.M.: 471 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3432 (N-H), 3067 (Ar C-H), 1736 (ester C=O), 1668 (amide C=O), 1689 (C=N), 1591 (Ar C=C), 1153 (C-O), 703 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.82 (s, 1H, CON-H), 7.61 (s, 1H, H-5'), 7.33 (s, 1H, H-2''), 7.30 (d, *J* = 7.6 Hz, 1H, H-6''), 7.17 (t, *J* = 8.0 Hz, 1H, H-5''), 7.04 (s, 1H, H-8'), 6.91 (d, *J* = 7.6 Hz, 1H, H-4''), 6.21 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 3.98 (s, 2H, H-2'''), 2.37 (s, 3H, CH₃-11'), 2.30 (s, 3H, CH₃-7''); EIMS (*m/z*): 473 (5%), 471 [M]⁺⁺ (19%), 436 (13%), 251 (7%), 249 (8%), 230 (2%), 214 (15%), 210 (83%), 193 (14%), 182 (BP, 100%), 165 (9%), 149 (5%), 134 (42%), 106 (28%).

2.10.11. *N*-(4-Methylphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9g). White amorphous solid; Yield: 79%; M.P.: 98–100°C; M.F.: C₂₂H₁₈ClN₃O₅S; M.M.: 471 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3435 (N-H), 3061 (Ar C-H), 1734 (ester C=O), 1668 (amide C=O), 1689 (C=N), 1584 (Ar C=C), 1141 (C-O), 703 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.66 (s, 1H, CON-H), 7.59 (s, 1H, H-5'), 7.36 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 7.17 (d, *J* = 8.4 Hz, 2H, H-3'' & H-5''), 7.05 (s, 1H, H-8'), 6.21 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.06 (s, 2H, H-2'''), 2.36 (s, 3H, CH₃-11'), 2.26 (s, 3H, CH₃-7''); EIMS (*m/z*): 473 (8%), 471 [M]⁺⁺ (23%), 436 (15%), 251 (7%), 249 (9%), 230 (3%), 214 (15%), 210 (87%), 193 (14%), 182 (BP, 100%), 165 (9%), 149 (4%), 134 (49%), 106 (31%).

2.10.12. *N*-(2-Ethylphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9h). Light brown amorphous solid; Yield: 84%; M.P.: 92–94°C; M.F.: C₂₃H₂₀ClN₃O₅S; M.M.: 485 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3447 (N-H), 3069 (Ar C-H), 1738 (ester C=O), 1677 (amide C=O), 1689 (C=N), 1606 (Ar C=C), 1149 (C-O), 705 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.61 (s, 1H, CON-H), 7.58 (s, 1H, H-5'), 7.16 (d, *J* = 8.0 Hz, 1H, H-6''), 7.11 (t, *J* = 8.0 Hz, 1H, H-5''), 7.07 (t, *J* = 8.0 Hz, 1H, H-4''), 7.04 (s, 1H, H-8'), 6.98 (d, *J* = 8.0 Hz, 1H, H-3''), 6.21 (s, 1H, H-3'), 5.35 (s, 2H, H-12'), 4.09 (s, 2H, H-2'''), 2.46 (q,

J = 7.2 Hz, 2H, H-7''), 2.36 (s, 3H, CH₃-11'), 1.03 (t, *J* = 7.2 Hz, 3H, CH₃-8''); EIMS (*m/z*): 487 (6%), 485 [M]⁺⁺ (17%), 450 (13%), 251 (4%), 249 (5%), 230 (2%), 214 (13%), 210 (88%), 193 (14%), 182 (BP, 100%), 165 (6%), 149 (7%), 148 (33%), 134 (16%), 120 (32%).

2.10.13. *N*-(4-Ethylphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9i). Cream white amorphous solid; Yield: 84%; M.P.: 104–106°C; M.F.: C₂₃H₂₀ClN₃O₅S; M.M.: 485 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3432 (N-H), 3067 (Ar C-H), 1736 (ester C=O), 1671 (amide C=O), 1689 (C=N), 1606 (Ar C=C), 1147 (C-O), 702 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.72 (s, 1H, CON-H), 7.61 (s, 1H, H-5'), 7.09 (d, *J* = 8.0 Hz, 2H, H-2'' & H-6''), 7.04 (s, 1H, H-8'), 6.96 (d, *J* = 8.0 Hz, 2H, H-3'' & H-5''), 6.21 (s, 1H, H-3'), 5.36 (s, 2H, H-12'), 4.08 (s, 2H, H-2'''), 2.54 (q, *J* = 7.2 Hz, 2H, H-7''), 2.36 (s, 3H, CH₃-11'), 1.13 (t, *J* = 7.2 Hz, 3H, CH₃-8''); EIMS (*m/z*): 487 (8%), 485 [M]⁺⁺ (17%), 450 (15%), 251 (4%), 249 (7%), 230 (5%), 214 (9%), 210 (92%), 193 (17%), 182 (BP, 100%), 165 (7%), 149 (5%), 148 (35%), 134 (11%), 120 (38%).

2.10.14. *N*-(2-Methoxyphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9j). Cream yellow amorphous solid; Yield: 78%; M.P.: 106–108°C; M.F.: C₂₂H₁₈ClN₃O₆S; M.M.: 487 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3437 (N-H), 3069 (Ar C-H), 1733 (ester C=O), 1683 (amide C=O), 1689 (C=N), 1603 (Ar C=C), 1158 (C-O), 703 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.59 (s, 1H, CON-H), 8.22 (d, *J* = 8.0 Hz, 1H, H-6''), 7.62 (s, 1H, H-5'), 7.05 (s, 1H, H-8'), 7.01 (t, *J* = 7.6 Hz, 1H, H-5''), 6.92 (t, *J* = 7.6 Hz, 1H, H-4''), 6.81 (d, *J* = 8.0 Hz, 1H, H-3''), 6.21 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.06 (s, 2H, H-2'''), 3.82 (s, 3H, CH₃-7''), 2.37 (s, 3H, CH₃-11'); EIMS (*m/z*): 489 (5%), 487 [M]⁺⁺ (17%), 452 (16%), 251 (4%), 249 (6%), 230 (2%), 214 (13%), 210 (86%), 193 (12%), 182 (BP, 100%), 165 (4%), 150 (31%), 149 (8%), 134 (18%), 122 (39%).

2.10.15. *N*-(2-Ethoxyphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9k). Light grey amorphous solid; Yield: 86%; M.P.: 96–98°C; M.F.: C₂₃H₂₀ClN₃O₆S; M.M.: 501 g mol⁻¹; IR (KBr, $\nu_{\max}$, cm⁻¹): 3453 (N-H), 3056 (Ar C-H), 1736 (ester C=O), 1667 (amide C=O), 1681 (C=N), 1606 (Ar C=C), 1155 (C-O), 702 (C-Cl); ¹H-NMR (400 MHz, CHCl₃-d₁, δ , ppm): 8.66 (s, 1H, CON-H), 7.59 (s, 1H, H-5'), 7.43 (d, *J* = 8.4 Hz, 1H, H-6''), 7.17 (t, *J* = 8.4 Hz, 1H, H-4''), 7.03 (s, 1H, H-8'), 6.84 (t, *J* = 8.4 Hz, 1H, H-5''), 6.75 (d, *J* = 8.0 Hz, 1H, H-3''), 6.20 (s, 1H, H-3'), 5.35 (s, 2H, H-12'), 4.04 (s, 2H, H-2'''), 3.74 (q, *J* = 7.2 Hz, 2H, H-7''), 2.37 (s, 3H, CH₃-11'), 1.11 (t, *J* = 7.2 Hz, 3H, CH₃-8''); EIMS (*m/z*): 503 (8%), 501 [M]⁺⁺ (22%), 466 (11%), 251 (4%), 249 (7%), 230 (2%), 214 (14%), 210 (85%), 193 (18%), 182 (BP, 100%), 165 (8%), 164 (30%), 149 (9%), 136 (28%), 134 (17%).

2.10.16. *N*-(4-Ethoxyphenyl)-2-[(5-{[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)sulfany]acetamide (9l). Reddish purple amorphous solid; Yield: 74%;

M.P.: 108–110°C; M.F.: $C_{23}H_{20}ClN_3O_6S$; M.M.: 501 $gmol^{-1}$; IR (KBr, ν_{max} , cm^{-1}): 3443 (N-H), 3078 (Ar C-H), 1734 (ester C=O), 1679 (amide C=O), 1688 (C=N), 1597 (Ar C=C), 1155 (C-O), 705 (C-Cl); 1H -NMR (400 MHz, $CHCl_3-d_1$, δ , ppm): 8.82 (s, 1H, CON-H), 7.59 (s, 1H, H-5'), 7.39 (d, $J = 8.0$ Hz, 2H, H-2'' & H-6''), 7.03 (s, 1H, H-8'), 6.81 (d, $J = 8.4$ Hz, 2H, H-3'' & H-5''), 6.20 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 3.98 (s, 2H, H-2'''), 3.97 (q, $J = 6.8$ Hz, 2H, H-7''), 2.37 (s, 3H, CH_3 -11'), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3 -8''); EIMS (m/z): 503 (9%), 501 $[M]^{++}$ (21%), 466 (13%), 251 (6%), 249 (8%), 230 (3%), 214 (15%), 210 (81%), 193 (19%), 182 (BP, 100%), 165 (9%), 164 (32%), 149 (6%), 136 (25%), 134 (19%).

2.10.17. *N*-(2-Methoxycarbonylphenyl)-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfany]acetamide (**9m**). Yellow amorphous solid; Yield: 75%; M.P.: 122–124°C; M.F.: $C_{23}H_{18}ClN_3O_7S$; M.M.: 515 $gmol^{-1}$; IR (KBr, ν_{max} , cm^{-1}): 3429 (N-H), 3050 (Ar C-H), 1731 (ester C=O), 1671 (amide C=O), 1683 (C=N), 1601 (Ar C=C), 1159 (C-O), 703 (C-Cl); 1H -NMR (400 MHz, $CHCl_3-d_1$, δ , ppm): 8.81 (s, 1H, CON-H), 8.68 (d, $J = 8.4$ Hz, 1H, H-6''), 8.10 (d, $J = 7.6$ Hz, 1H, H-3''), 7.62 (s, 1H, H-5'), 7.51 (t, $J = 7.6$ Hz, 1H, H-5''), 7.18 (t, $J = 7.6$ Hz, 1H, H-4''), 7.05 (s, 1H, H-8'), 6.21 (s, 1H, H-3'), 5.36 (s, 2H, H-12'), 4.07 (s, 2H, H-2'''), 3.81 (s, 3H, CH_3 -8''), 2.37 (s, 3H, CH_3 -11'); EIMS (m/z): 517 (9%), 515 $[M]^{++}$ (19%), 480 (13%), 251 (6%), 249 (9%), 230 (2%), 214 (14%), 210 (92%), 193 (17%), 182 (BP, 100%), 178 (37%), 165 (6%), 150 (33%), 149 (7%), 134 (15%).

2.10.18. *N*-(4-Bromophenyl)-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfany]acetamide (**9n**). Light grey amorphous solid; Yield: 73%; M.P.: 102–104°C; M.F.: $C_{21}H_{15}BrClN_3O_5S$; M.M.: 535 $gmol^{-1}$; IR (KBr, ν_{max} , cm^{-1}): 3422 (N-H), 3056 (Ar C-H), 1734 (ester C=O), 1662 (amide C=O), 1684 (C=N), 1593 (Ar C=C), 1143 (C-O), 702 (C-Cl), 639 (C-Br); 1H -NMR (400 MHz, $CHCl_3-d_1$, δ , ppm): 8.28 (s, 1H, CON-H), 7.62 (s, 1H, H-5'), 7.47 (d, $J = 8.4$ Hz, 2H, H-2'' & H-6''), 7.41 (d, $J = 8.4$ Hz, 2H, H-3'' & H-5''), 7.05 (s, 1H, H-8'), 6.22 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.08 (s, 2H, H-2'''), 2.36 (s, 3H, CH_3 -11'); EIMS (m/z): 539 (7%), 537 (18%), 535 $[M]^{++}$ (20%), 500 (14%), 251 (6%), 249 (8%), 230 (4%), 214 (13%), 210 (92%), 198 (33%), 193 (13%), 182 (BP, 100%), 170 (31%), 165 (6%), 149 (8%), 134 (11%).

2.10.19. *N*-(4-Nitrophenyl)-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfany]acetamide (**9o**). Light yellow amorphous solid; Yield: 81%; M.P.: 108–110°C; M.F.: $C_{21}H_{15}ClN_4O_7S$; M.M.: 502 $gmol^{-1}$; IR (KBr, ν_{max} , cm^{-1}): 3438 (N-H), 3053 (Ar C-H), 1735 (ester C=O), 1678 (amide C=O), 1688 (C=N), 1606 (Ar C=C), 1163 (C-O), 703 (C-Cl); 1H -NMR (400 MHz, $CHCl_3-d_1$, δ , ppm): 9.34 (s, 1H, CON-H), 8.41 (d, $J = 8.0$ Hz, 2H, H-3'' & H-5''), 8.06 (d, $J = 8.0$ Hz, 2H, H-2'' & H-6''), 7.62 (s, 1H, H-5'), 7.05 (s, 1H, H-8'), 6.22 (s, 1H, H-3'), 5.34 (s, 2H, H-12'), 4.07 (s, 2H, H-2'''), 2.36 (s, 3H, CH_3 -11'); EIMS (m/z): 504 (5%), 502 $[M]^{++}$ (17%), 467 (18%), 251 (8%), 249 (7%), 230 (5%), 214 (11%), 210 (91%), 193 (18%), 182 (BP, 100%), 165 (42%), 149 (8%), 137 (32%), 134 (17%).

3. Results and Discussion

The different *N*-aralkyl/alkyl/aryl acetamides incorporating coumarin and 1,3,4-oxadiazole rings, **9a–o**, were synthesized by the multistep protocol given in Scheme 1. The synthesis was aimed at combining multiple functionalities in a single molecule so these may be able to demonstrate more efficient biological activity. The antibacterial behavior of these molecules was tested against Gram-bacteria including positive and negative strains. The three negative and two positive bacterial strains have been reported to be the cause of various diseases [23–27].

3.1. *Chemistry*. First 4-chlororesorcinol (**1**) was treated with ethyl acetoacetate (**2**) in a strong acidic medium to yield 6-chloro-7-hydroxy-4-methyl-2H-chromen-2-one (**3**) which was separated through filtration. Compound **3** was further O-substituted by ethyl 2-bromoacetate in a polar aprotic solvent with the aid of a weak base. This substituted ester, **4**, was converted to corresponding carbohydrazide, **5**, after a simple nucleophilic substitution reaction by hydrazine in methanol. The carbohydrazide was cyclized to 5-substituted-1,3,4-oxadiazol-2-thiol by CS_2 in an alcoholic KOH medium on reflux. A list of electrophiles, **8a–o**, was synthesized from different aralkyl/alkyl/aryl amines, **7a–o**, on simple stirring with 2-bromoacetyl bromide in aqueous Na_2CO_3 medium. The final compounds were geared up by stirring **6** with **8a–o** again in DMF in the presence of NaH and separated through filtration after addition of excess distilled water.

All the compounds were structurally corroborated through IR, 1H -NMR, and EIMS spectral data. Compound **3** is also aided by ^{13}C -NMR data. One molecule description is given for **9h**. Its molecular formula was nominated as $C_{23}H_{20}ClN_3O_5S$, elucidated with the aid of molecular ion peak in EIMS spectrum and integration of protons in 1H -NMR spectrum. The suggested fragmentation pattern of this molecule is also sketched in Figure 1. The specific absorption bands for different functionalities in the molecule appeared in IR spectrum at ν_{max} (cm^{-1}) 3447 (N-H), 3069 (Ar C-H), 1738 (ester C=O), 1677 (amide C=O), 1689 (C=N), 1606 (Ar C=C), 1149 (C-O), and 705 (C-Cl). In aromatic region of 1H -NMR spectrum, the three singlets with single proton integration resonating at δ 7.58 (H-5'), 7.04 (H-8'), and 6.21 (H-3') were allocated for the chlorinated coumarin part of the molecule. The other four signals in the same region with single proton integration resonated at δ 7.16 (d, $J = 8.0$ Hz, H-6''), 7.11 (t, $J = 8.0$ Hz, H-5''), 7.07 (t, $J = 8.0$ Hz, H-4''), and 6.98 (d, $J = 8.0$ Hz, H-3'') for 2-ethylphenyl part of the molecule. The ethyl group was confirmed through a quartet and a triplet, both with coupling constant of 7.2 Hz, appearing at δ 2.46 (2H, H-7'') and 1.03 (3H, CH_3 -8''), respectively, in the aliphatic region. The protons of two methylene groups linked to oxygen and sulfur appeared as two singlets at δ 5.35 (H-12') and 4.09 (H-2'''), respectively. The three protons of methyl group attached to coumarin nucleus resonated as singlet at δ 2.36 (CH_3 -11'). The whole discussion confirmed **9h** as *N*-(2-Ethylphenyl)-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl)sulfany]acetamide.

SCHEME 1: Synthesis of *N*-aralkyl/alkyl/aryl-2-[(5-[(6-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl)-1,3,4-oxadiazol-2-yl]sulfa-nyl]acetamide (**9a-o**).

FIGURE 1: Mass fragmentation pattern of *N*-(2-ethylphenyl)-2-[(5-[[[(6-chloro-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (**9h**).

3.2. Antibacterial Activity (In Vitro). The results of antibacterial activity evaluation against Gram-bacteria were presented as percentage of age inhibition and MIC values in Tables 1 and 2. The ciprofloxacin was used as reference standard. All the compounds demonstrated moderate to excellent activity except a few. The Gram-negative strain, *S. typhi*, was not inhibited by **9b** and **9d**. It was the most efficiently inhibited by **9e**, **9f**, **9h**, **9j**, **9k**, and **9m**. The best activity against it was observed for **9j** with MIC value of $8.87 \pm 1.20 \mu\text{g/mL}$ and **9k** as $8.84 \pm 2.00 \mu\text{g/mL}$ with respect to that of reference as $8.00 \pm 2.54 \mu\text{g/mL}$. Only **9o** was inactive against *E. coli* and remaining moderate to good with the efficient ones as **9e**, **9f**, **9j**, **9k**, and **9m**. The most active one was **9f** with MIC of 10.15 ± 4.12 relative to $7.96 \pm 1.14 \mu\text{g/mL}$. Against

P. aeruginosa, **9b** and **9o** were inactive and remaining weakly moderate. The efficient ones against this strain were **9a**, **9c**, **9e**, **9f**, **9h**, **9j**, and **9m**. It was most actively inhibited by **9e** presenting MIC of $10.22 \pm 3.33 \mu\text{g/mL}$ as compared to $8.05 \pm 1.60 \mu\text{g/mL}$. *B. subtilis* was moderately inhibited by all the molecules and efficiently by **9n** with MIC of $11.95 \pm 4.71 \mu\text{g/mL}$ in comparison with $8.32 \pm 1.00 \mu\text{g/mL}$. The compounds against *S. aureus* were moderate to excellent inhibitors including **9c**, **9e**, **9j**, **9k**, and **9l**. The molecule **9e** was the most efficient with MIC of $8.90 \pm 2.08 \mu\text{g/mL}$ relative to $7.43 \pm 0.45 \mu\text{g/mL}$. The three compounds **9d**, **9i**, and **9n** were inactive at all against this strain. Overall the Gram-negative strains were efficiently inhibited by the synthesized molecules relative to Gram-positive ones. The best activity

TABLE 1: The % age inhibition for antibacterial activity.

Compound	Percentage inhibition (%)				
	Gram-negative bacteria			Gram-positive bacteria	
	<i>S. typhi</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>B. subtilis</i>	<i>S. aureus</i>
9a	59.72 ± 0.17	58.71 ± 0.89	63.30 ± 1.65	51.35 ± 1.05	51.68 ± 0.95
9b	47.06 ± 3.50	69.65 ± 1.14	40.52 ± 5.00	75.60 ± 3.10	57.32 ± 0.79
9c	51.61 ± 0.28	66.63 ± 0.20	56.03 ± 0.67	66.55 ± 2.25	61.11 ± 4.47
9d	46.89 ± 3.33	50.05 ± 4.50	51.91 ± 1.19	54.35 ± 3.05	43.32 ± 0.05
9e	74.22 ± 0.44	74.26 ± 0.40	71.80 ± 0.26	72.00 ± 2.50	67.89 ± 0.32
9f	73.00 ± 0.44	75.15 ± 2.28	71.91 ± 1.39	69.95 ± 2.95	64.32 ± 0.21
9g	58.00 ± 1.44	55.54 ± 4.85	50.57 ± 4.90	56.35 ± 2.85	50.68 ± 1.63
9h	67.56 ± 2.22	70.25 ± 2.03	68.45 ± 0.82	64.00 ± 0.60	62.21 ± 3.05
9i	51.28 ± 2.50	50.84 ± 4.60	50.05 ± 3.66	56.55 ± 0.85	47.32 ± 0.58
9j	73.11 ± 0.89	73.22 ± 0.15	67.42 ± 0.41	64.95 ± 1.65	62.58 ± 0.89
9k	71.89 ± 0.44	73.91 ± 0.25	67.89 ± 2.63	64.55 ± 0.75	57.32 ± 1.95
9l	67.56 ± 4.94	59.50 ± 2.87	53.51 ± 4.12	53.00 ± 0.80	69.21 ± 0.89
9m	69.89 ± 0.89	71.29 ± 0.05	66.29 ± 1.34	66.35 ± 2.25	50.32 ± 2.95
9n	60.50 ± 0.28	60.84 ± 0.54	56.80 ± 2.37	58.75 ± 0.05	43.63 ± 2.26
9o	50.17 ± 1.83	44.31 ± 3.71	44.85 ± 1.13	45.35 ± 3.55	53.00 ± 2.89
Ciprofloxacin	92.43 ± 1.07	90.67 ± 0.65	90.33 ± 0.22	91.99 ± 2.00	91.00 ± 1.65

TABLE 2: The MIC values for antibacterial activity.

Compound	MIC ($\mu\text{g/mL}$)				
	Gram-negative bacteria			Gram-positive bacteria	
	<i>S. typhi</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>B. subtilis</i>	<i>S. aureus</i>
9a	12.59 ± 4.60	12.98 ± 1.56	11.30 ± 2.25	19.58 ± 1.08	17.86 ± 0.65
9b	—	13.41 ± 5.00	—	14.47 ± 5.00	13.35 ± 2.25
9c	14.46 ± 1.10	11.07 ± 1.94	11.42 ± 3.17	13.19 ± 1.83	10.91 ± 2.87
9d	—	19.93 ± 1.81	15.40 ± 5.00	16.51 ± 1.98	—
9e	10.61 ± 5.00	10.39 ± 1.62	10.22 ± 3.33	12.86 ± 3.85	8.90 ± 2.08
9f	9.50 ± 1.30	10.15 ± 4.12	10.43 ± 4.65	15.94 ± 3.06	13.18 ± 2.17
9g	17.19 ± 3.70	14.86 ± 5.00	19.50 ± 2.67	12.12 ± 4.00	19.53 ± 1.65
9h	9.16 ± 2.20	11.28 ± 1.06	11.52 ± 3.42	15.32 ± 5.00	12.95 ± 3.15
9i	19.07 ± 0.40	14.24 ± 1.25	19.97 ± 3.50	14.87 ± 2.71	—
9j	8.87 ± 1.20	10.41 ± 1.44	10.54 ± 0.80	14.58 ± 1.87	11.14 ± 2.22
9k	8.84 ± 2.00	10.94 ± 1.25	12.00 ± 1.33	12.96 ± 1.82	12.14 ± 1.48
9l	12.75 ± 4.50	12.07 ± 5.00	15.61 ± 5.00	15.75 ± 3.35	11.35 ± 2.00
9m	9.01 ± 1.40	10.86 ± 1.19	11.04 ± 4.17	14.18 ± 4.35	18.62 ± 1.00
9n	17.64 ± 5.00	15.97 ± 5.00	17.56 ± 2.00	11.95 ± 4.71	—
9o	19.92 ± 3.21	—	—	—	18.32 ± 1.11
Ciprofloxacin	8.00 ± 2.54	7.96 ± 1.14	8.05 ± 1.60	8.32 ± 1.00	7.43 ± 0.45

Note: minimum inhibitory concentration (MIC) was measured with suitable dilutions (5–30 μg /well) and results were calculated using EZ-Fit Perrella Scientific Inc., Amherst, USA, software.

was presented by the three molecules, **9e**, **9j**, and **9k** and their activity might be owed to the presence of *ortho*-substituted phenyl rings attached to nitrogen of acetamoyl linkage.

The alkyl substitution resulted in moderate to good activity against all the strains. Among aralkyl groups, the long aliphatic chain containing was moderate to good against all the strains. The molecules bearing *ortho*-substituted phenyl rings remained active against all the strains, also good to excellent and more efficient against the Gram-negative

strains. The *meta*-substituted ones were also good against negative strain. The *para*-substituted phenyl rings presented varying activities but moderate ones.

4. Conclusion

The multistep synthesis was carried out to incorporate different functionalities with an aim to obtain more potent molecules. The most of the synthesized molecules remained

efficient against all the strains specially Gram-negative bacteria. The most of the compounds were pharmacologically important including **9e**, **9j**, and **9k**. These molecules may be further modified to get more comparable or even better MIC results by more variation to the group linked to nitrogen of acetamoyl functionality. So the above listed compounds along with some others might be considered for drug designing program in search of new drug candidates.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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