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Conventional Route for Synthesis of Novel Heterocyclic 2-(Substituted-2-oxo-2H-chromen-3-yl)-3-(4-(2-(substituted-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one Derivatives and Their Antimicrobial Activity

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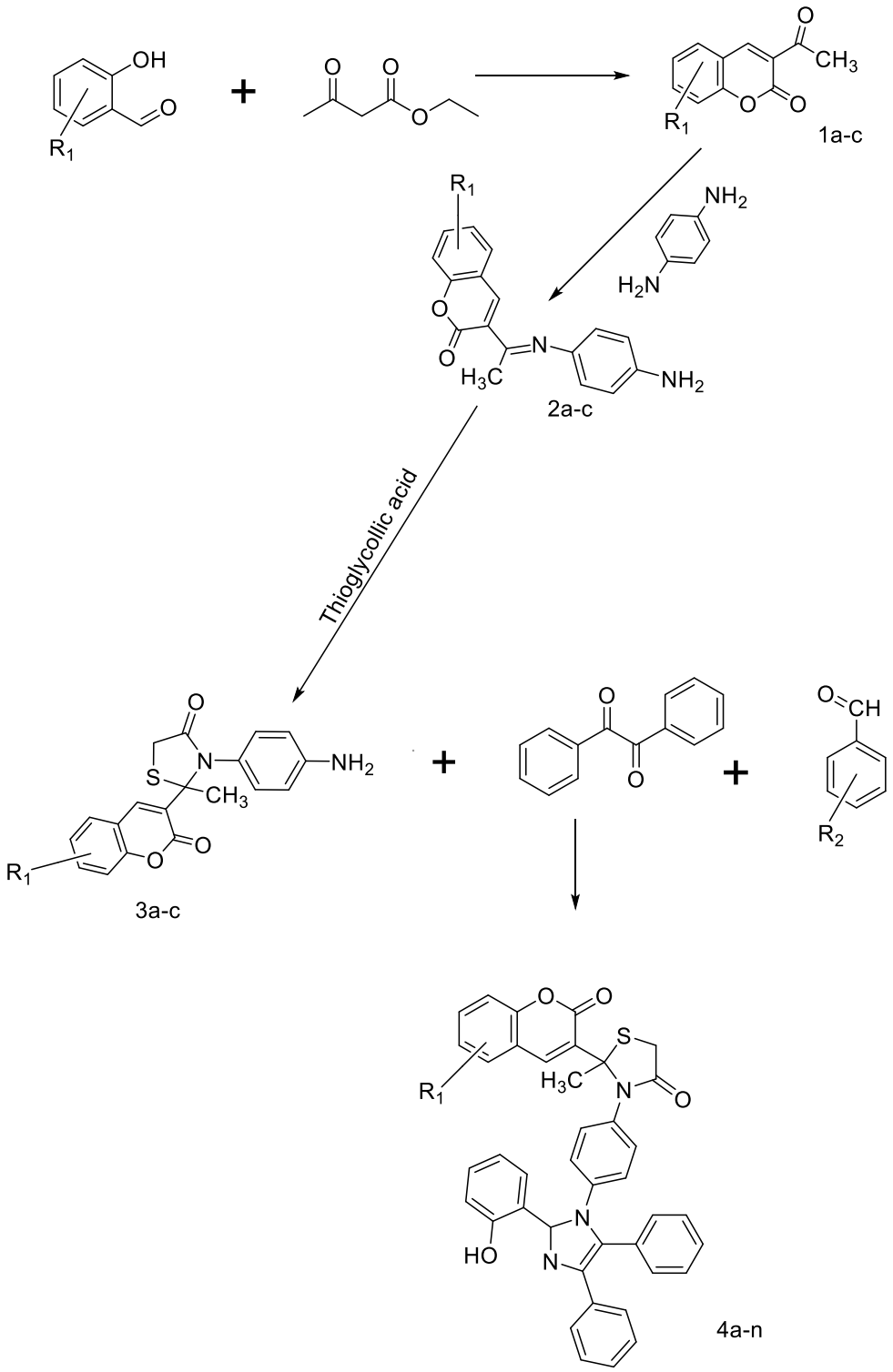
Abstract— *Conventional routes were achieved for the synthesis of methylthiazolidin-4-one derivatives starting through reaction of substituted salicylaldehyde and acetoacetic ester, which gives acetyl-coumarin. Upon further reaction with benzene-1,4-diamine, it was converted into imine, subsequently cyclized into a thiazole-amine in the presence of thioglycolic acid. The final derivatives were cyclized by a three-component one-pot reaction of amine, substituted aldehyde, and ketone, yielding 2-(8-fluoro-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one derivatives. The structures of the novel synthesized derivatives were established by elemental analysis, UV, FT-IR, ¹H-NMR, and mass spectra. The obtained derivatives displayed excellent to moderate antimicrobial activity.*

Keywords— Benzil, thioglycolic acid, coumarin, acetoacetic ester, substituted salicylaldehyde, benzene-1,4-diamine, acetic acid.

I. INTRODUCTION

Imidazole [1-6] molecule or more commonly known as 1,3-diazole belongs to a five-membered heterocyclic moiety bearing three carbon atoms, two nitrogen atoms, and four hydrogen atoms with two double bonds. It is amphoteric in nature and displays both acidic and basic properties. Since this molecule is amphoteric in nature, it greatly improves the solubility of its derivative molecules. The presence of positive charge on either of the two nitrogen atoms makes it amenable to exist in two tautomeric forms. It also goes by the name of glyoxaline as it was manufactured by using glyoxal and ammonia. Imidazole is an important molecule naturally as it is the edifice of many biologically significant compounds such as histidine [7], purines, and pyrimidines. Derivatives of imidazole [8-12] depict antiviral, antibacterial, anti-inflammatory, antitumor, antidiabetic, and antiallergic activities. Some of the most significant commercially available drugs are clemizole (antihistaminic agent), etonitazene (analgesic), enviroxime (antiviral), astemizole (antihistaminic agent), omeprazole, pantoprazole (antiulcer), thiabendazole (antihelmintic), nocodazole (antinematodal), metronidazole, nitroso-imidazole (bactericidal), megazol (trypanocidal), azathioprine (anti-rheumatoid arthritis), dacarbazine (Hodgkin's disease), tinidazole, ornidazole (antiprotozoal and antibacterial), etc. Thiazolidinone [13,14] heterocyclic compounds have a propensity to be engaged as drug motifs as most of them possess unique biological properties and have shown immense results in combating/curing various diseases. The pursuit of cheap, effective, and safe alternatives to expensive drugs is the reason behind the endless efforts of synthesizing various molecules. Thiazolidinone is a significant pharmacophore possessing tremendous biological [15-30] activities such as anticancer, antibacterial, antifungal, antiviral, antidiabetic, anticonvulsant, antioxidant, sedative, anti-inflammatory, antihypertension, and antituberculosis. The variations of substituents at positions 2, 3, and/or 5, and the substitution of carbon

at the second position, are responsible for the varied alterations in the structure and properties of the various thiazolidinone derivatives. Coumarins [31-33] are low molecular weight compounds bearing simple structure and high bioavailability, with excellent solubility in most organic solvents. These are compounds with negligible toxicity and various biological activities [34-37], and therefore they are amongst the pioneering scaffolds in the synthesis of new drug molecular synthons. They express profound pharmacological diversity such as anticoagulant, antimicrobial, anti-inflammatory, neuroprotective, antidiabetic, anticonvulsant, and antiproliferative activities.



SCHEME

II. CHEMISTRY

3-Acetyl-8-bromo-2H-chromen-2-one (1a-c) was synthesized by condensation reaction of substituted salicylaldehyde and acetoacetic ester, which was further converted into imine derivatives. One-pot three-component condensation for the preparation of 2-methylthiazolidin-4-one derivatives (3a-n): amine, substituted aldehyde, and ketone underwent cyclization to form thiazole by reaction with thioglycolic acid in the presence of $ZnCl_2$ in trace amount. The target derivatives were characterized by ^{1}H-NMR and infrared spectroscopic techniques. The structures of the novel compounds were established by their analytical and spectral data (IR, ^{1}H NMR, and mass). Characteristic peaks at 2988 (C-H, str., arom), 2895 (CH_3, str.), 1745 (C=O, str.), and 1190 (C-O-C str.) cm^{-1} region were observed in the FT-IR spectra of 1a-c. The FT-IR spectra of final derivatives 3a-n showed peaks for (C=N), (N-H), (C-O-C str.), (C-S-C), (str, C-N-C) at 1677, 3362, 1165, 1070, and 1146 cm^{-1}, respectively. The ^{1}H NMR of derivatives 4a-n showed a singlet at δ 3.34 for methyl, a doublet of doublets at δ 3.85 (dd, 2H, C-CH_2-S-) confirming the thiazolidine ring, and a broad singlet at δ 8.2 (br s, 1H, NH), which were in good agreement with theoretical and experimental data.

III. EXPERIMENTAL SECTION

The melting points of the novel synthesized methylthiazolidin-4-one derivatives were examined by the open capillary method. The progress of the reaction and purity of the prepared derivatives were determined using precoated TLC plates (Merck, 60F-254) with iodine vapor as visualizing agent and eluent chloroform/ethyl acetate (5:2). The ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO on a Bruker NMR spectrophotometer at 400 MHz. Tetramethylsilane was used as the internal standard and chemical shift values (δ) are given in parts per million (ppm). A Jasco FT-IR-470 spectrophotometer with KBr diffuse reflectance method was used. Mass spectra were recorded on a JEOL SX102 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the FAB gas and m-nitrobenzyl alcohol as the matrix. [Note to authors: UV and mass spectral data should be provided as supplementary material.]

3.1 Synthesis of 3-acetyl-8-bromo-2H-chromen-2-one (1a-c)

Salicylaldehyde (20 mmol), ethyl acetoacetate (30 mmol), absolute alcohol (10 mL), and diethylamine (1 mL) were refluxed with continuous stirring for 3-4 hours. After filtering, the product was rinsed with excess water, allowed to air dry, and then recrystallized from ethanol. The characterization values of all derivatives are given below:

1a. 3-Acetyl-8-bromo-2H-chromen-2-one: Molecular Formula $C_{11}H_7BrO_3$, Mol. Wt 267, Yield 82%, M.Pt 96-97 °C. Analysis calcd: C, 49.47; Br, 29.92. Found: C, 49.44; Br, 29.90. IR (KBr) υ_max (cm^{-1}): 2988 (C-H, str., arom), 2895 (CH_3, str.), 1745 (C=O, str.), 1190 (C-O-C str.), 825 (C-Br).

1b. 3-Acetyl-8-fluoro-2H-chromen-2-one: Molecular Formula $C_{11}H_7FO_3$, Mol. Wt 206, Yield 74%, M.Pt 104-105 °C. Analysis calcd: C, 64.08; F, 9.21. Found: C, 64.04; F, 9.18. IR (KBr) υ_max (cm^{-1}): 2980 (C-H, str., arom), 2898 (CH_3, str.), 1740 (C=O, str.), 1194 (C-O-C str.), 812 (C-F).

1c. 3-Acetyl-8-chloro-2H-chromen-2-one: Molecular Formula $C_{11}H_7ClO_3$, Mol. Wt 223, Yield 68%, M.Pt 102-103 °C. Analysis calcd: C, 59.35; Cl, 15.92. Found: C, 59.31; Cl, 15.88. IR (KBr) υ_max (cm^{-1}): 2985 (C-H, str., arom), 2892 (CH_3, str.), 1748 (C=O, str.), 1190 (C-O-C str.), 735 (C-Cl).

3.2 Synthesis of imine (E)-3-(1-((4-aminophenyl)imino)ethyl)-substituted-2H-chromen-2-one (2a-c)

Equimolar quantities (0.01 mole) of 3-acetyl-substituted-2H-chromen-2-one and benzene-1,4-diamine in 25 mL ethanol were refluxed on a heating mantle for 7-8 hours with 1 mL glacial acetic acid. After being rinsed with cold water, the resulting products were recrystallized from ethanol. The characterization values are given below:

2a. (E)-3-(1-((4-Aminophenyl)imino)ethyl)-8-bromo-2H-chromen-2-one: Molecular Formula $C_{17}H_{13}BrN_2O_2$, Mol. Wt 357, Yield 60%, M.Pt 112-113 °C. Analysis calcd: C, 57.16; Br, 22.37; N, 7.84. Found: C, 57.12; Br, 22.32; N, 7.81. IR (KBr) υ_max (cm^{-1}): 2990 (C-H, str., arom), 2885 (CH_3, str.), 1755 (C=O, str.), 1185 (C-O-C str.), 780 (C-Br), 3345 (N-H), 1430 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.90-7.62 (m, 8H, aromatic), 3.45 (s, 3H, methyl), 6.12 (s, 1H, NH_2, D_2O exchangeable).

2b. (E)-3-(1-((4-Aminophenyl)imino)ethyl)-8-fluoro-2H-chromen-2-one: Molecular Formula $C_{17}H_{13}FN_2O_2$, Mol. Wt 296, Yield 55%, M.Pt 87-88 °C. Analysis calcd: C, 68.91; F, 6.41; N, 9.45. Found: C, 68.88; F, 6.37; N, 9.42. IR (KBr) υ_max (cm^{-1}): 2998 (C-H, str., arom), 2882 (CH_3, str.), 1750 (C=O, str.), 1190 (C-O-C str.), 740 (C-F), 3340

(N-H), 1435 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.92-7.64 (m, 8H, aromatic), 3.42 (s, 3H, methyl), 6.10 (s, 1H, NH_2, D_2O exchangeable).

2c. (E)-3-(1-((4-Aminophenyl)imino)ethyl)-8-chloro-2H-chromen-2-one: Molecular Formula $C_{17}H_{13}ClN_2O_2$, Mol. Wt 313, Yield 65%, M.Pt 106-107 °C. Analysis calcd: C, 65.29; Cl, 11.33; N, 8.96. Found: C, 65.24; Cl, 11.31; N, 8.92. IR (KBr) υ_max (cm^{-1}): 2995 (C-H, str., arom), 2875 (CH_3, str.), 1752 (C=O, str.), 1195 (C-O-C str.), 730 (C-Cl), 3335 (N-H), 1445 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.90-7.62 (m, 8H, aromatic), 3.43 (s, 3H, methyl), 6.14 (s, 1H, NH_2, D_2O exchangeable).

3.3 Synthesis for the cyclization of imine: 3-(4-aminophenyl)-2-(substituted-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one (3a-c)

Methylthiazolidin-4-one was synthesized by using equimolar quantities (0.01 mole) of (E)-3-(1-((4-aminophenyl)imino)ethyl)-substituted-2H-chromen-2-one (a-c) with thioglycolic acid in the presence of a trace amount of $ZnCl_2$ in 20 mL DMF, refluxed on a heating mantle for 11-12 hours. The obtained final product was poured into crushed ice and recrystallized from ethanol. The characterization values are given below:

3a. 3-(4-Aminophenyl)-2-(8-bromo-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula $C_{19}H_{15}BrN_2O_3S$, Mol. Wt 431, Yield 60%, M.Pt 102-103 °C. Analysis calcd: C, 52.91; Br, 18.53; N, 6.50; S, 7.43. Found: C, 52.87; Br, 18.50; N, 6.47; S, 7.40. IR (KBr) υ_max (cm^{-1}): 3050 (C-H, str., arom), 2890 (CH_3, str.), 1760 (C=O, str.), 1185 (C-O-C str.), 810 (C-Br), 1050 (C-S-C), 1150 (str, C-N-C), 2930 (str, CH_2). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.90-7.62 (m, 8H, aromatic), 3.43 (s, 3H, methyl), 6.14 (s, 1H, NH_2, D_2O exchangeable), 3.88 (dd, 2H, C-CH_2-S- thiazolidine ring).

3b. 3-(4-Aminophenyl)-2-(8-fluoro-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula $C_{19}H_{15}FN_2O_3S$, Mol. Wt 370, Yield 72%, M.Pt 108-109 °C. Analysis calcd: C, 61.61; F, 5.13; N, 7.56; S, 8.66. Found: C, 61.57; F, 5.11; N, 7.53; S, 8.62. IR (KBr) υ_max (cm^{-1}): 3065 (C-H, str., arom), 2895 (CH_3, str.), 1762 (C=O, str.), 1180 (C-O-C str.), 760 (C-F), 1055 (C-S-C), 1160 (str, C-N-C), 2935 (str, CH_2). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.90-7.64 (m, 8H, aromatic), 3.44 (s, 3H, methyl), 6.16 (s, 1H, NH_2, D_2O exchangeable), 3.88 (dd, 2H, C-CH_2-S-thiazolidine ring).

3c. 3-(4-Aminophenyl)-2-(8-chloro-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula $C_{19}H_{15}ClN_2O_3S$, Mol. Wt 387, Yield 68%, M.Pt 101-102 °C. Analysis calcd: C, 58.99; Cl, 9.16; N, 7.24; S, 8.29. Found: C, 58.95; Cl, 9.12; N, 7.20; S, 8.25. IR (KBr) υ_max (cm^{-1}): 3060 (C-H, str., arom), 2898 (CH_3, str.), 1765 (C=O, str.), 1187 (C-O-C str.), 768 (C-Cl), 1060 (C-S-C), 1150 (str, C-N-C), 2940 (str, CH_2). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.88-7.67 (m, 8H, aromatic), 3.40 (s, 3H, methyl), 6.12 (s, 1H, NH_2, D_2O exchangeable), 3.86 (dd, 2H, C-CH_2-S- thiazolidine ring).

3.4 Synthesis of final derivatives: 2-(Substituted-2-oxo-2H-chromen-3-yl)-3-(4-(2-(substituted-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one (4a-n)

Synthesis of final derivatives was carried out using 0.01 mole equimolar quantities of imine 3-(4-aminophenyl)-2-(substituted-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one (a-c), with slow addition of benzil, ammonium acetate, and substituted aldehyde in 15 mL acetic acid. The reaction was stirred for 1 hour at room temperature, then heated at 90 °C for 11-12 hours, and quenched with ice water. The residues obtained were extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by column chromatography (hexane:ethyl acetate) to obtain the desired product. The characterization values are given below:

4a. 2-(8-Bromo-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-hydroxyphenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula $C_{40}H_{29}BrN_3O_4S$, Mol. Wt 727, Yield 68%, M.Pt 101-102 °C. Analysis calcd: C, 66.03; Br, 10.98; N, 5.77; S, 4.41. Found: C, 66.01; Br, 10.96; N, 5.74; S, 4.38. IR (KBr) υ_max (cm^{-1}): 3050 (C-H, str., arom), 2880 (CH_3, str.), 1760 (C=O, str.), 1675 (C=N), 3370 (N-H), 1170 (C-O-C str.), 732 (C-Br), 1070 (C-S-C), 1130 (str, C-N-C), 2955 (str, CH_2). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.85-7.65 (m, 22H, aromatic), 3.40 (s, 3H, methyl), 3.87 (dd, 2H, C-CH_2-S- thiazolidine ring), 8.3 (br s, 1H, NH), 3.62 (s, 1H, Ar-OH).

4b. 2-(8-fluoro-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{41}H_{31}FN_3O_5S$, Mol. Wt-697, Yield-62 %, M.Pt-121-122

°C Analysis calcd- C, 70.68; F, 2.73; N, 6.03; S, 4.60 Found- C, 70.64; F, 2.71; N, 6.00; S, 4.56 IR (KBr) υ_{max}/per-cm- 3053 (C-H, str.,arom), 2885 (CH_3, str.), 1765 (C=O, str.), 1678 (C=N), 3374 (N-H), 1175 (C-O-C str.), 765 (C-F), 1072 (C-S-C) 1135 (str,C-N-C), 2958 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.68 (m,21 H, Aromatic), 3.42(s,3H, methyl), 3.88 (dd,2H, C-CH_2-S- thiazol ring), 8.1 (br s, 1H, NH)), 3.64 (1H,s, Ar-OH), 7.22 (s, 3H, OCH_3).

4c. 3-(4-(2-(4-chlorophenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(8-fluoro-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{40}H_{28}ClFN_3O_3S$, Mol. Wt-685, Yield-55 %, M.Pt-117-118 °C Analysis calcd- C, 70.12; Cl, 5.17; F, 2.77; N, 6.13; S, 4.68 Found- C, 70.08; Cl, 5.14; F, 2.73; N, 6.11; S, 4.64 IR (KBr) υ_{max}/per-cm- 3058 (C-H, str.,arom), 2882 (CH_3, str.), 1769 (C=O, str.), 1673 (C=N), 3370 (N-H), 1178 (C-O-C str.), 762 (C-Cl), 1077 (C-S-C) 1140 (str,C-N-C), 2960 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.63 (m,22 H, Aromatic), 3.40 (s,3H, methyl), 3.85 (dd,2H, C-CH_2-S- thiazol ring), 8.3 (br s, 1H, NH)), 3.64 (1H,s, Ar-OH).

4d. 3-(4-(2-(4-bromophenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(8-fluoro-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{40}H_{28}BrFN_3O_3S$, Mol. Wt-730, Yield-51 %, M.Pt-106-107 °C Analysis calcd- C, 65.85; Br, 10.95; F, 2.60; N, 5.76; S, 4.39 Found- C, 65.81; Br, 10.92; F, 2.57; N, 5.73; S, 4.35 IR (KBr) υ_{max}/per-cm- 3057 (C-H, str.,arom), 2885 (CH_3, str.), 1755 (C=O, str.), 1670 (C=N), 3378 (N-H), 1165 (C-O-C str.), 730 (C-Br), 1070 (C-S-C) 1145 (str,C-N-C), 2962 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.65 (m,22 H, Aromatic), 3.43 (s,3H, methyl), 3.82 (dd,2H, C-CH_2-S- thiazol ring), 8.5 (br s, 1H, NH)), 3.60 (1H,s, Ar-OH).

4e. 3-(4-(4,5-diphenyl-2-(p-tolyl)-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(8-fluoro-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{41}H_{31}FN_3O_3S$, Mol. Wt-665, Yield-53 %, M.Pt-114-115 °C Analysis calcd- C, 74.08; F, 2.86; N, 6.32; S, 4.82 Found- C, 74.05; F, 2.83; N, 6.28; S, 4.81 IR (KBr) υ_{max}/per-cm- 3057 (C-H, str.,arom), 2885 (CH_3, str.), 1755 (C=O, str.), 1670 (C=N), 3378 (N-H), 1165 (C-O-C str.), 730 (C-F), 1070 (C-S-C) 1145 (str,C-N-C), 2962 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.60 (m,22 H, Aromatic), 3.48 (s,6H, methyl), 3.81 (dd,2H, C-CH_2-S- thiazol ring), 8.2 (br s, 1H, NH)), 3.62 (1H,s, Ar-OH).

4f. 2-(8-bromo-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-hydroxyphenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{40}H_{29}BrN_3O_4S$, Mol. Wt-728, Yield-45 %, M.Pt-108-109 °C Analysis calcd- C, 66.03; Br, 10.98 ; N, 5.77; S, 4.41 Found- C, 66.01; Br, 10.96 ; N, 5.74; S, 4.38 IR (KBr) υ_{max}/per-cm- 3060 (C-H, str.,arom), 2880 (CH_3, str.), 1758 (C=O, str.), 1675 (C=N), 3365 (N-H), 1160 (C-O-C str.), 732 (C-Br), 1075 (C-S-C) 1140 (str,C-N-C), 2968 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.66 (m,22 H, Aromatic), 3.46 (s,3H, methyl), 3.81 (dd,2H, C-CH_2-S- thiazol ring), 8.4 (br s, 1H, NH)), 3.64 (1H,s, Ar-OH).

4g. 2-(8-bromo-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-3l2-imidazol-1(2H)-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{41}H_{31}BrN_3O_5S$, Mol. Wt-758, Yield-52 %, M.Pt-103-104 °C Analysis calcd- C, 64.99; Br, 10.55; N, 5.55; S, 4.23 Found- C, 64.96; Br, 10.52; N, 5.51; S, 4.20 IR (KBr) υ_{max}/per-cm- 3062 (C-H, str.,arom), 2885 (CH_3, str.), 1765 (C=O, str.), 1680 (C=N), 3360 (N-H), 1168 (C-O-C str.), 736 (C-Br), 1065 (C-S-C) 1130 (str,C-N-C), 2962 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.82-7.61 (m,22 H, Aromatic), 3.45 (s,3H, methyl), 3.82 (dd,2H, C-CH_2-S- thiazol ring), 8.3 (br s, 1H, NH)), 3.61 (1H,s, Ar-OH), 7.15 (s, 3H, OCH_3).

4h. 2-(8-bromo-2-oxo-2H-chromen-3-yl)-3-(4-(2-(4-chlorophenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{40}H_{28}BrClN_3O_3S$, Mol. Wt-746, Yield-54 %, M.Pt-95-96 °C Analysis calcd- C, 64.39; Br, 10.71; Cl, 4.75; N, 5.63; S, 4.30 Found- C, 64.35; Br, 10.68; Cl, 4.72; N, 5.60; S, 4.26 IR (KBr) υ_{max}/per-cm- 3065 (C-H, str.,arom), 2884 (CH_3, str.), 1760 (C=O, str.), 1672 (C=N), 3368 (N-H), 1168 (C-O-C str.), 738 (C-Br), 1077 (C-S-C) 1145 (str,C-N-C), 2964 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.85-7.63 (m,22 H, Aromatic), 3.48 (s,3H, methyl), 3.83 (dd,2H, C-CH_2-S- thiazol ring), 8.2 (br s, 1H, NH)), 3.61 (1H,s, Ar-OH).

4i. 2-(8-bromo-2-oxo-2H-chromen-3-yl)-3-(4-(4,5-diphenyl-2-(p-tolyl)-3λ^2-imidazol-1(2H)-yl)phenyl)-2-methylthiazolidin-4-one: Molecular Formula-$C_{41}H_{31}BrN_3O_3S$
Mol. Wt-726, Yield-58 %, M.Pt-106-107 °C Analysis calcd- C, 67.86; Br, 11.01; N, 5.79; S, 4.42 Found- C, 67.82; Br, 11.00; N, 5.74; S, 4.37 IR (KBr) υ_{max}/per-cm- 3060 (C-H, str.,arom), 2888 (CH_3, str.), 1762 (C=O, str.), 1670 (C=N), 3366 (N-H), 1160 (C-O-C str.), 732 (C-Br), 1071 (C-S-C) 1140 (str,C-N-C), 2967 (str, CH_2), 1H NMR-

$CDCl_3$-300 MHz, δ, ppm: 6.82-7.65 (m,22 H, Aromatic), 3.34 (s,6H, methyl), 3.81 (dd,2H, C-CH_2-S- thiazol ring), 8.4 (br s, 1H, NH)), 3.63 (1H,s, Ar-OH).

4j. 2-(8-bromo-2-oxo-2H-chromen-3-yl)-2-methyl-3-(4-(2-(4-nitrophenyl)-4,5-diphenyl-3l2-imidazol-1(2H)-yl)phenyl)thiazolidin-4-one: Molecular Formula- $C_{40}H_{28}BrN_4O_5S$, Mol. Wt-757, Yield-42 %, M.Pt-103-104 °C Analysis calcd- C, 63.50; Br, 10.56; N, 7.40; S, 4.24 Found- C, 63.47; Br, 10.52; N, 7.36; S, 4.21 IR (KBr) υ_{max}/per-cm- 3070 (C-H, str.,arom), 2875 (CH_3, str.), 1760 (C=O, str.), 1560 (N=O str.asym-nitro-benzene),1286 (N=O str, sym, nitro-benzene) 1678 (C=N), 3368 (N-H), 1160 (C-O-C str.), 1070 (C-S-C) 1155 (str,C-N-C), 2960(str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.81-7.63 (m,22 H, Aromatic), 3.32 (s,3H, methyl), 3.80 (dd,2H, C-CH_2-S-thiazol ring), 8.1 (br s, 1H, NH)).

4k. 3-(4-(2-(4-fluorophenyl)-4,5-diphenyl-3l2-imidazol-1(2H)-yl)phenyl)-2-(6-methoxy-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{41}H_{31}FN_3O_4S$
, Mol. Wt-681, Yield-48 %, M.Pt-119-120 °C Analysis calcd- - C, 72.34; F, 2.79; N, 6.17; S, 4.71 Found C, 72.30; F, 2.75; N, 6.14; S, 4.68 IR (KBr) υ_{max}/per-cm- 3066 (C-H, str.,arom), 2887 (CH_3, str.), 1762 (C=O, str.), 1684 (C=N), 3362 (N-H), 1164 (C-O-C str.), 737 (C-Br), 1062 (C-S-C) 1134 (str,C-N-C), 2964 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.82-7.64 (m,22 H, Aromatic), 3.47 (s,3H, methyl), 3.83 (dd,2H, C-CH_2-S- thiazol ring), 8.5 (br s, 1H, NH)), 3.63 (1H,s, Ar-OH), 7.11 (s, 3H, OCH_3).

4l. 3-(4-(2-(4-bromophenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(6-methoxy-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one: Molecular Formula- $C_{41}H_{31}BrN_3O_4S$, Mol. Wt-742, Yield-45 %, M.Pt-112-113 °C Analysis calcd- C, 66.40; Br, 10.77; N, 5.67; S, 4.32 Found- C, 66.35; Br, 10.73; N, 5.65; S, 4.28 IR (KBr) υ_{max}/per-cm- 3064 (C-H, str.,arom), 2881 (CH_3, str.), 1750 (C=O, str.), 1677 (C=N), 3362 (N-H), 1165 (C-O-C str.), 734 (C-Br), 1070 (C-S-C) 1146 (str,C-N-C), 2970 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.81-7.62 (m,22 H, Aromatic), 3.34 (s,6H, methyl), 3.85 (dd,2H, C-CH_2-S- thiazol ring), 8.2 (br s, 1H, NH)), 3.61 (1H,s, Ar-OH).

4m. 3-(4-(2-(4-chlorophenyl)-4,5-diphenyl-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(6-methoxy-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one:Molecular Formula- $C_{41}H_{31}ClN_3O_4S$, Mol. Wt-697, Yield-62 %, M.Pt-117-118 °C Analysis calcd- C, 70.63; Cl, 5.08; N, 6.03; S, 4.60 Found- C, 70.60; Cl, 5.04; N, 6.01; S, 4.56 IR (KBr) υ_{max}/per-cm- 3067 (C-H, str.,arom), 2883 (CH_3, str.), 1754 (C=O, str.), 1679 (C=N), 3360 (N-H), 1160 (C-O-C str.), 736 (C-Br), 1074 (C-S-C) 1140 (str,C-N-C), 2978 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.81-7.61 (m,22 H, Aromatic), 3.35 (s,6H, methyl), 3.82 (dd,2H, C-CH_2-S- thiazol ring), 8.4 (br s, 1H, NH)), 3.62 (1H,s, Ar-OH), 7.22 (s, 3H, OCH_3).

4n. 3-(4-(4,5-diphenyl-2-(p-tolyl)-3λ^2-imidazol-1(2H)-yl)phenyl)-2-(6-methoxy-2-oxo-2H-chromen-3-yl)-2-methylthiazolidin-4-one:Molecular Formula- $C_{42}H_{34}N_3O_4S$
Mol. Wt-677, Yield-62 %, M.Pt-108-109 °C Analysis calcd- C, 74.54; N, 6.21; S, 4.74 Found- C, 74.51; N, 6.16; S, 4.70 IR (KBr) υ_{max}/per-cm- 3060 (C-H, str.,arom), 2888 (CH_3, str.), 1762 (C=O, str.), 1670 (C=N), 3366 (N-H), 1160 (C-O-C str.), 732 (C-Br), 1071 (C-S-C) 1140 (str,C-N-C), 2967 (str, CH_2), 1H NMR- $CDCl_3$-300 MHz, δ, ppm: 6.82-7.65 (m,22 H, Aromatic), 3.34 (s,6H, methyl), 3.81 (dd,2H, C-CH_2-S- thiazol ring), 8.4 (br s, 1H, NH)), 3.63 (1H,s, Ar-OH), 7.22 (s, 3H, OCH_3).

IV. ANTIMICROBIAL ACTIVITY

4.1 Determination of MIC

The broth microdilution method was used to determine the MIC of synthesized 2-(substituted-2-oxo-2H-chromen-3-yl)-3-(4-(2-(substituted-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one derivatives, as per CLSI guidelines. Twofold serial dilutions of the samples were made directly in a microtiter plate filled with Mueller-Hinton broth. After adding the bacterial inoculum, each well had a final concentration of 5×10^5 CFU/mL. Ciprofloxacin, a common medication, was used as the standard. The plate was incubated at 37°C for 24 hours. After adding resazurin to each well, the microtiter plate was incubated for 30 minutes at 37°C. While the well without bacterial growth remained blue, the wells with bacterial growth became pink. The minimum inhibitory concentration (MIC) was defined as the extract concentration that completely stops bacterial growth. The derivatives to be tested were diluted twofold in a series. The test samples were dissolved in DMSO to obtain a 10 mg/mL stock solution. Sabouraud's broth was prepared for antifungal testing. The solution of the test material (0.2 mL) was added to 1.8 mL of the seeded broth, forming the first dilution. Subsequently, 1.0 mL of this was diluted with a further 1.0 mL of the seeded broth to give the second dilution, and so on until 10-12 such dilutions were obtained. A set

of tubes containing only seeded broth and the standard containing fluconazole were also maintained under identical conditions. The tubes were incubated at 28°C and the MICs of the products (based upon visual appearance of growth) were noted after 48-96 hours post-incubation. The last tube with no apparent growth of the microorganism was taken to represent the MIC of the test compound expressed in µg/mL.

TABLE 1
ANTIMICROBIAL ACTIVITY OF 2-(SUBSTITUTED-2-OXO-2H-CHROMEN-3-YL)-3-(4-(2-(SUBSTITUTED-PHENYL)-4,5-DIPHENYL-4,5-DIHYDRO-1H-IMIDAZOL-1-YL)PHENYL)-2-METHYLTHIAZOLIDIN-4-ONE DERIVATIVES (4A-N): MIC (µg/mL)

Compd	R^1 (Coumarin substituent)	R^2 (Imidazole substituent)	*B. subtilis*	*S. aureus*	*E. coli*	*C. albicans*
4a	8-Bromo	4-Hydroxyphenyl	100	50	25	25
4b	8-Bromo	4-Hydroxy-3-methoxyphenyl	100	50	100	100
4c	8-Bromo	4-Chlorophenyl	50	25	50	100
4d	8-Bromo	4-Methylphenyl	100	25	50	25
4e	8-Bromo	4-Nitrophenyl	25	100	50	25
4f	8-Fluoro	4-Hydroxyphenyl	100	100	100	100
4g	8-Fluoro	4-Hydroxy-3-methoxyphenyl	100	50	25	12.5
4h	8-Fluoro	4-Chlorophenyl	50	25	25	100
4i	8-Fluoro	4-Bromophenyl	25	12.5	25	6.25
4j	8-Fluoro	4-Methylphenyl	25	6.25	100	100
4k	6-Methoxy	4-Fluorophenyl	12.5	100	100	100
4l	6-Methoxy	4-Bromophenyl	100	100	50	100
4m	6-Methoxy	4-Chlorophenyl	50	50	50	100
4n	6-Methoxy	4-Methylphenyl	25	50	25	50
Standards		**Ciprofloxacin**	**50**	**100**	**50**	—
		Fluconazole	—	—	—	**50**

Note: MIC values are presented as µg/mL. All tests were performed in duplicate; variation was within ±1 dilution.

V. RESULTS AND DISCUSSION

Fourteen methylthiazolidin-4-one derivatives were synthesized, out of which five derivatives of bromo-3-acetyl coumarin, five derivatives of fluoro-3-acetyl coumarin, and four derivatives of methoxy-3-acetyl coumarin were evaluated for their antimicrobial activity against Gram-positive bacteria (*B. subtilis*, *S. aureus*), Gram-negative bacteria (*E. coli*), and fungus (*C. albicans*).

When the synthesized derivatives were tested against *Candida albicans*, only four derivatives exhibited good activity. Derivative **4i** (R^1 = 8-F, R^2 = 4-Br) showed superior activity with an MIC of 6.25 µg/mL. Derivative **4g** (R^1 = 8-F, R^2 = 4-OH,3-OCH_3) showed excellent activity with an MIC of 12.5 µg/mL. Derivatives **4a** (R^1 = 8-Br, R^2 = 4-OH) and **4d** (R^1 = 8-Br, R^2 = 4-CH_3) showed MIC values of 25 µg/mL. The remaining derivatives reflected only satisfactory activity.

Against *B. subtilis*, out of fourteen derivatives, only five were active. Derivatives **4e** (R^1 = 8-Br, R^2 = 4-NO_2), **4i** (R^1 = 8-F, R^2 = 4-Br), **4j** (R^1 = 8-F, R^2 = 4-CH_3), and **4n** (R^1 = 6-OCH_3, R^2 = 4-CH_3) displayed MIC values of 25 µg/mL. Derivative **4k** (R^1 = 6-OCH_3, R^2 = 4-F) showed excellent activity with an MIC of 12.5 µg/mL. The remaining nine derivatives demonstrated moderate activity.

Against *S. aureus*, five synthesized derivatives were found to be highly active. Derivatives **4c** (R^1 = 8-Br, R^2 = 4-Cl) and **4d** (R^1 = 8-Br, R^2 = 4-CH_3) showed MIC values of 25 µg/mL. Derivatives **4h** (R^1 = 8-F, R^2 = 4-Cl), **4i** (R^1 = 8-F, R^2 = 4-Br), and **4j** (R^1 = 8-F, R^2 = 4-CH_3) showed MIC values of 25, 12.5, and 6.25 µg/mL, respectively. Derivative **4j** was the most lethal against *S. aureus*, achieving an MIC of 6.25 µg/mL.

Against *E. coli*, derivatives **4a** (R^1 = 8-Br, R^2 = 4-OH), **4g** (R^1 = 8-F, R^2 = 4-OH,3-OCH_3), **4h** (R^1 = 8-F, R^2 = 4-Cl), **4i** (R^1 = 8-F, R^2 = 4-Br), and **4n** (R^1 = 6-OCH_3, R^2 = 4-CH_3) demonstrated good activity with MIC values of 25 µg/mL. The other ten derivatives displayed moderate activity.

Among all active compounds, one common factor is that either R^1 or R^2 or both contain electronegative substituents (halogens, nitro, methoxy), which appears to be the main cause of enhanced activity. It is clear that the presence of electronegative groups is very vital in eliciting the desired biological effect. Therefore, it is suggested here that the synthesis of more such compounds containing additional electronegative groups (chloro, fluoro, bromo, OCH_3, etc.) is required for further ascertaining the potentials of such derivatives.

TABLE 2
MOST ACTIVE COMPOUNDS

Compound	Most Significant Activity	MIC (µg/mL)
4i	*S. aureus* and *C. albicans*	12.5 and 6.25
4j	*S. aureus*	6.25
4k	*B. subtilis*	12.5
4g	*C. albicans*	12.5

VI. CONCLUSION

All synthesized derivatives (4a-n) of 2-(substituted-2-oxo-2H-chromen-3-yl)-3-(4-(2-(substituted-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)phenyl)-2-methylthiazolidin-4-one were evaluated for antimicrobial activity. Compounds **4i**, **4j**, and **4k** demonstrated the most promising antimicrobial activity. Exclusively, compound **4i** displayed broad-spectrum antibacterial and antifungal potency, suggesting that incorporation of halogen substituents, especially bromine and fluorine, may create potentially more active compounds. These findings indicate that the synthesized thiazolidinone-coumarin-imidazole hybrids may serve as potential lead molecules for the development of new antimicrobial agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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