Research Article

Metal-free Catalyzed One-Pot Multicomponent Synthesis of (E)-3-(2-((5-(Benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one Derivatives and Their Biological Evaluation

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A series of (E)-3-(2-((5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) acetyl)-2H-chromen-2-one and its derivatives (4a-h) have been obtained using a one-pot multicomponent reaction with good yields. The compounds have been synthesized from 3-(2-bromoacetyl)chromen-2-ones (1), 5-amino-1,3,4-thiadiazole-2-thiol (2), and substituted benzaldehydes (3) in anhydrous ethanol and conc. H2SO4. Subsequently, all the synthesized compounds have been screened for their antimicrobial activity and characterized by analytical and spectral data.

1. Introduction

Over the several decades, the interest of the scientific community in the heterocyclic compounds and their various derivatives has been persistent due to their broad applications in pharmaceutical and chemical industries [1]. Among various heterocyclic compounds such as pyrazole, tetrahydroquinoline, and benzotriazole, thiadiazole has gained prominent importance which consists of an important five-membered heterocyclic system containing two nitrogen atoms and a sulfur atom [2]. Particularly, among various thiadiazole, the 1,3,4-thiadiazole has been studied more than any other counterpart, due to its biologically significance [3]. The 1,3,4-thiadiazole and most of their derivatives are important heterocyclic entities in pharmaceutical as well as in medicinal chemistry, due to their diverse biological activities as well as inhibition properties against a variety of specific enzymes [4], several of which are known to possess excellent antibacterial [5], antimicrobial [4, 6], anti-inflammatory [7], anticonvulsant [8], antidepressant and anxiolytic [9], anti-tuberculosis [10], anticancer [11], and CNS depressant activities [12]. In this regard, various coumarin (benzopyran-2-one) derivatives have particularly shown remarkable biological activities due to their privileged structure which facilitates high affinity and specificity to different molecular targets [13]. Besides, the presence of planar aromatic ring fused with lactone functionality, availability of highly interactive functional groups which enhances the interactions with foreign moieties including proteins makes this heterocycle a unique pharmacophore in the field of medicinal chemistry.

In view of this importance, the present study focused on a facile one-pot multicomponent reaction of Schiff base containing heterocyclics. A multicomponent reaction
involves three or more reactants to generate a single product only in one operation. These reactions can be performed under mild reaction conditions, shorter reaction times with maximum selectivity, atom economy, and a high percentage of yields in a single synthetic operation. Currently, multicomponent reactions constitute a large number of important organic reactions. Recently, these types of reactions have become more popular in chemical biology and drug discovery due to the growing environmental concerns, as majority of these reactions comply with the principles of green chemistry. Therefore, the quest for finding new MCRs and/or improvising the already known multicomponent reactions is of considerable interest.

In this regard, a great deal of effort has been made by chemists for the facile synthesis of Schiff bases involving MCRs. Schiff bases are a class of compounds with an imine group, which are very important compounds in organic chemistry. These types of heterocyclic systems which were reported by Hugo Schiff are commonly prepared by the condensation reaction of primary amines with carbonyl compounds. They are also known as azomethine or imine (C=N-) types of compounds which have demonstrated several important biological properties including antimicrobial [14], anticonvulsant [15], antioxidant [16], antiherpetic [17], antitumor [18], anticancer [19], and anti-inflammatory [20] properties. Apart from this, Schiff bases have also been used in different applications such as urease inhibitors [A], antiglycating agents [B, C, D], pesticidal agents [E, F], Schiff base containing sulfadiazine [G], and Trimethoprim [H] drugs (Figure 1).

A variety of catalysts have been reported for the synthesis of Schiff base containing scaffolds such as dodecatungstostilic acid/P2O5 [21], Cu(NO3)2, 6H2O [22], silica sulfonic acid [23], and hydrotalcites [24]. Therefore, in this study, we have developed a novel facile methodology for the synthesis of Schiff base containing scaffolds by one-pot multicomponent reaction (MCR) employing metal-free catalyst. The target compounds, such as (E)-3-(2-((5-(Benzylideneamino)-1,3,4-thiadiazol-2-y1)thio) Acetyl)-2H-chromen-2-one and Its Derivatives (4a-h) (Method I). A mixture of 5-amino-1,3,4-thiadiazole-2-thiol (1 mmol), derivatives of aromatic benzaldehydes (1 mmol), and 3-(2-bromoacetyl)-chromen-2-one (1 mmol) was taken in 5 ml of ethanol. A catalytic amount of conc. H2SO4 was added to the reaction mixture. This is refluxed for 4 hours and monitored by TLC and allowed to cool to room temperature to get the solid, which was filtered, dried, and recrystallized from ethanol to get title compounds (Table 1).

2. Materials and Methods

The chemicals were purchased from commercial sources, used without further purification. The purity of prepared materials was checked by TLC on silica plates (E-Merk, Mumbai, India). Melting points were checked with an open capillary tube with a "Cintex" melting point apparatus, Mumbai, India, and were uncorrected. IR spectra were recorded in KBrs on a Bruker WM-200 MHz spectrometer. 1H- and 13C-NMR spectra were recorded on a Bruker WM-400 spectrometer (in δ ppm) using TMS as an internal standard. Mass spectra (EI-MS) were determined on a Jeol-D-300 spectrometer at 70 eV.

2.1. Synthesis of (E)-3-(2-((5-(Benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one and Its Derivatives (4a-h) (Method I). 2.1.1. (E)-3-(2-((5-(Benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (4a). IR (KBr):1607 (C=N), 1680 (C=O), 1720 (lactone, C=O) cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d\(_6\)): δ 6.51 (s, 2H, -CH=), 5.57 (s, 1H, -CH=N), 7.41–7.54 (m, 2H, of C6 & C8-H coumarin), 7.35 (m, 1H, of C7-H), 7.78–7.81 (m, 3H, Ar-H); 7.84–7.91 (m, 2H, Ar-H); 7.94–7.98 (m, 1H, Ar-H of C5-H); 8.60 (s, 1H, C2-H of coumarin) and 11.61 (s, 1H, of –CH=N); 13C NMR (400 MHz, DMSO-d\(_6\)): δ 35.36, 43.56, 61.51, 118.31, 129.47, 129.48, 131.12, 131.21, 131.26, 131.51, 135.10, 159.60, 160.10, 160.94, 161.12, 196.65; EI (MS): m/z 407.

2.1.2. (E)-3-(2-((5-((3-Methylbenzylidene)amino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (4b). IR (KBr); 1610 (C=N), 1679 (C=O), 1717 (lactone, C=O) cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d\(_6\)): δ 2.26 (s, 3H, -CH3), 4.51 (s, 2H, -CH2-), 7.42–7.54 (m, 2H, of C6 & C8-H coumarin), 7.75 (m, 1H, Ar-H of C5-H); 7.78–7.91 (m, 4H, Ar-H); 7.94–7.98 (m, 1H, Ar-H of C5-H); 8.64 (s, 1H, C4-H of coumarin), and 11.64 (s, 1H, of –CH=N); 13C NMR (400 MHz, DMSO-d\(_6\)): δ 31.26, 34.48, 43.56, 61.51, 116.41, 118.35, 125.37, 127.84, 128.84, 128.86, 129.42, 129.47, 131.12, 131.21, 131.26, 131.51, 135.10, 160.94, 161.12, 196.64.

2.1.3. (E)-3-(2-((5-((4-Nitrobenzylidene)amino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (4c). IR (KBr); 1610 (C=N), 1679 (C=O), 1720 (lactone, C=O) cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d\(_6\)): δ 2.26 (s, 3H, -CH3), 4.51 (s, 2H, -CH2-), 7.42–7.54 (m, 2H, of C6 & C8-H coumarin), 7.75 (m, 1H, Ar-H of C5-H); 7.78–7.91 (m, 4H, Ar-H); 7.94–7.98 (m, 1H, Ar-H of C5-H); 8.64 (s, 1H, C4-H of coumarin), and 11.64 (s, 1H, of –CH=N); 13C NMR (400 MHz, DMSO-d\(_6\)): δ 21.35, 34.56, 43.56, 61.51, 116.41, 118.35, 125.37, 127.84, 128.84, 129.42, 129.47, 131.12, 131.21, 131.26, 131.51, 135.10, 160.94, 161.12, 164.51, 166.12, 196.64.

2.1.4. (E)-3-(2-((5-((4-Methoxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (4d). IR (KBr); 1608 (C=N), 1678 (C=O), 1726 (lactone, C=O) cm\(^{-1}\); 1H NMR (400 MHz, DMSO-d\(_6\)): δ 3.96 (s, 3H, -OCH3), 4.51 (s, 2H, -CH2-), 7.12–7.26 (m, 4H, Ar-H); 7.46–7.65 (m, 2H, of C6 & C8-H coumarin), 7.71 (m, 1H, Ar-H of C5-H); 7.91 (m, 1H, Ar-H of C5-H); 7.85–7.91 (m, 1H, C4-H of coumarin), 8.64 (s, 1H, C4 –H of Coumarin), and 11.70 (s, 1H, of –CH=N).

2.1.5. (E)-3-(2-((2,4-Dichlorobenzylidene)amino)-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (4e). IR (KBr); 1611 (C=N), 1681 (C=O), 1724 (lactone, C=O) cm\(^{-1}\); 1H
NMR (400MHz, DMSO-$d_6$): δ 4.52 (s, 2H, -CH$_2$-), 7.39–7.57 (m, 4H, Ar-H of C6 and C8-H of coumarin & Ar-H), 7.67 (m, 1H, of C7-H of coumarin), 7.84 (d, 1H, $J_\text{H-H} = 2$Hz, C5-H of coumarin), 7.87–7.98 (m, 2H, Ar-H), 8.67 (s, 1H, C4-H of coumarin), and 11.63 (s, 1H, of –CH=N-).

2.1.6. (E)-3-(2-((5-((3-Methoxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)thio)Acetyl)-2H-chromen-2-one (4g).

IR (KBr); 1610 (-C=N), 1681 (-C=O), 1725 (lactone, -C=O) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.94 (s, 3H, -OCH$_3$), 4.52 (s, 2H, -CH$_2$-), 7.10–7.36 (m, 3H, Ar-H), 7.44–7.65 (m, 2H, of C$_6$&C$_8$-H coumarin), 7.76 (m, 1H, of C$_7$-H coumarin), 7.86–7.93 (m, 2H, C$_5$-H of coumarin & Ar-H), 8.66 (s, 1H, C$_4$-H of coumarin), and 11.62 (s, 1H, of –CH=N-).

2.2. Preparation of 3-(2-((5-Amino-1,3,4-thiadiazol-2-yl)thio)Acetyl)-2H-chromen-2-one, (Method-II) (5). To a solution of 3-(2-bromoacetyl) chromen-2-one (1mmol) and 5-amino-1,3,4-thiadiazole-2-thiol (1mmol) in a 5 ml of ethanol was refluxed for 30 minutes. The reaction mixture was checked by TLC, then allowed to cool room temperature to get the solid, and was filtered. The crude product was recrystallised from ethanol.

| Compounds 4a-h and 5 | R$_1$ | R$_2$ | R$_3$ | R$_4$ | Molecular formula | Molecular weight g mol$^{-1}$ | Yield (%) method | M.P. (°C) |
|----------------------|------|------|------|------|------------------|------------------|---------------|----------|
| a                    | H    | H    | H    | H    | C$_{20}$H$_{13}$N$_3$O$_3$S$_2$ | 407.47           | 70            | 65       | 218–220  |
| b                    | H    | H    | CH$_3$| H    | C$_{21}$H$_{15}$N$_3$O$_3$S$_2$ | 421.49           | 86            | 80       | 223–225  |
| c                    | H    | H    | H    | NO$_2$| C$_{20}$H$_{12}$N$_4$O$_5$S$_2$ | 452.46           | 83            | 71       | 215–217  |
| d                    | H    | H    | OCH$_3$| H    | C$_{21}$H$_{15}$N$_3$O$_3$S$_2$ | 437.49           | 84            | 76       | 219–221  |
| e                    | Cl   | H    | Cl   | H    | C$_{20}$H$_{12}$N$_3$O$_3$S$_2$Cl$_2$ | 476.36           | 80            | 66       | 235–237  |
| f                    | Cl   | H    | H    | H    | C$_{20}$H$_{12}$N$_3$O$_3$S$_2$Cl | 441.91           | 83            | 70       | 234–236  |
| g                    | H    | H    | H    | OCH$_3$| C$_{21}$H$_{12}$N$_3$O$_3$S$_2$ | 437.49           | 84            | 78       | 225–227  |
| h                    | H    | H    | Br   | H    | C$_{20}$H$_{12}$BrN$_3$O$_3$S$_2$ | 486.36           | 80            | 76       | 241–243  |
| s                    |      |      |      |      | C$_{13}$H$_8$N$_3$O$_3$S$_2$ | 319.36           | 85            | —        | 212–215  |

Figure 1: Various biologically active Schiff bases.

Table 1: Physical data of compounds (4a-h and 5).
2.2.1. 3-(5-Amino-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (5). IR (KBr); 3416 (-NH 2), 1610 (-C=O), 1726 (lactone, -C=O), 3416 (-NH 2) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆); δ 4.56 (s, 2H, -CH₂-), 5.57 (s, 1H, -CH₂-), 7.39–7.46 (m, 2H, C₆&C₈-H, Coumarin), 7.65 (m, 1H, C₇-H of coumarin), 7.76 (d, 1H, C₅-H of coumarin), 7.81 (s, 2H, NH₂), 8.67 (s, 1H, C₄-H of coumarin); 13C NMR (400 MHz, DMSO-d₆); δ 42.76, 116.61, 118.20, 122.51, 125.44, 131.09, 135.38, 144.96, 152.16, 155.21, 159.00, 196.65; EI (MS): m/z 319.

2.3. Preparation of 4a-h from (5) (Method-II). A mixture of 3-(5-amino-1,3,4-thiadiazol-2-yl)thio)acetyl)-2H-chromen-2-one (5, 1 mmol) and appropriate aromatic aldehyde (1 mmol) was taken in 5 mL of ethanol, and a catalytic amount of conc. H₂SO₄ was refluxed for 4 hours. The reaction mixture was checked by TLC, then allowed to cool room temperature to get the solid, and was filtered. The crude product was recrystallized from ethanol to get the title compounds (Table 1).

3. Results and Discussion

The present protocol involved in one-pot multicomponent acid catalyzed condensation reaction of 3-(2-bromoacetyl) coumarins 1, with 5-amino-1,3,4-thiadiazole-2-thiol 2 and substituted benzoaldehyde 3 and a catalytic amount of conc. H₂SO₄ in ethanol. The yields of the products 4a-h are good (70–86%). In the one-pot multicomponent method, it is believed that 3-(2-bromoacetyl)coumarins 1 react with 5-amino-1,3,4-thiadiazole-2-thiol 2 and substituted benzaldehyde 3 in the presence of conc. H₂SO₄/ethanol to give corresponding (E)-3-(2-(5-benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) acetyl)-2H-chromen-2-ones. In this regard, first method (Method-I) presents an efficient acid catalyzed condensation reaction and a simple, easy workup procedure, without any side products. The reaction takes place under reflux conditions (Scheme 1) to yield 4 which is formed by S-alkylation subsequent to that condensation reaction to give the corresponding Schiff bases containing heterocyclic.

Title compounds 4a-h can also be synthesized through an alternative method involving 3-(2-bromoacetyl)chromen-2-one 1 with 5-amino-1,3,4-thiadiazole-2-thiol 2 in ethanol to give the corresponding 3-(2-(5-amino-1,3,4-thiadiazol-2-yl)thio)acetyl)-2H-chromen-2-one 5. This, on further reaction with substituted benzoaldehydes and Conc. H₂SO₄ in ethanol, result in the formation of 4a-h through a two-step process (Method -II) by S-alkylation and condensation reaction. The yields of products (Method -II) 4a-h are in between 65 and 80%, while both the methods to give the target compounds were found to be identical by their mixed m.p. measurements, co-TLC and IR spectra (Scheme 2).

In the present work, Method-I was preferred over Method II, in terms of higher yields of the products and less time. Unlike the literature methods, we have first time synthesized title compounds 4a-h in one step to expand the scope of synthetic transformation and offer a new convenient method for synthesis of title compounds 4a-h.

All the synthesized materials were characterized by their analytical and spectral data. The IR spectra of compounds 4a showed prominent peaks 1607 (-C=O), 1680 (-C=O), 1720 (lactone, -C=O), 3411 (-NH) cm⁻¹, consistent with the assigned structures. The ¹H NMR (DMSO-d₆) spectrum of 4a confirmed signals around δ 4.56 (s, 2H, -CH₂-), 5.57 (s, 1H, -CH₂-), 7.39–7.41 (m, 4H, Ar-H), 7.69–7.73 (m, 2H, of C₆ &C₈-H coumarin), 7.79 (m, 1H, Ar-H of C₅-H), 8.61 (s, 1H, C₇-H of coumarin), and 11.64 (s, 1H, of –CH=N-) in the mass spectrum 4a confirmed the molecular ion peak at m/z 407 (100%).

3.1. Biological Activity

3.1.1. Antimicrobial Activity. All the synthesized compounds (Table 1) 4a-h were screened for antibacterial and antifungal activity by using measurement of zone of inhibition by the agar well diffusion method [25] against bacterial species (Gram-positive and Gram-negative) were cultured on nutrient agar plates at 37°C. All the synthesized compounds were assayed using cup plate technique in the nutrient agar at 100 μg/ml concentration, as shown in (Table 2). Ciprofloxacin standard was active at 50 μg/ml on all the bacterial strains tested, i.e., Gram (+ve) bacteria Bacillus subtilis and Staphylococcus aureus, and Gram (–ve) bacteria Pseudomonas aeruginosa and Escherichia coli, while antibacterial screening zone of inhibition created by active compounds were measured after 24–48 h. Miconazole standard was active at 50 μg/ml on all the fungal strains tested, i.e., Candida albicans and Aspergillus niger, and the zone of inhibition created by active compounds was measured after 24–48 h.

3.1.2. Results. All the synthesized compounds of 1,3,4-thiadiazole derivatives were screened for their antimicrobial activity. The antibacterial studies were carried out against Gram-positive species, i.e., B. subtilis and S. aureus and Gram-negative species, i.e., P. aeruginosa and E. coli, while C. albicans and A. niger species were used for antifungal studies. Ciprofloxacin was used as the standard antibacterial agent while Miconazole was used as a standard antifungal agent. Among all the compounds tested, 4c, 4e, 4f, and 4h (Table 2) were found to be active for all bacterial strains, and the presence of a single phenyl ring and substitution of nitro group at the metaposition of phenyl ring yielded satisfactory results. In the case of Gram-positive bacteria, the electron withdrawing group present at phenyl ring increases the bacterial activity of the compounds, while in the case of Gram-negative bacteria, substitution of a methoxy group present at phenyl ring decreases the antimicrobial activity of
compounds. Though, all the synthesized compounds possess a coumarin moiety on one side and a phenyl ring on the other side, the compounds with substituted rings have better activity as compared to those with unsubstituted rings. Moreover, the 4c, 4e, 4f, and 4h exhibited the maximum activity because in these compounds, on phenyl ring, they were substituted by electron withdrawing groups as well as electron donating groups at R position, whereas the phenyl ring of compound 4d was substituted by methoxy groups, and it exhibited less activity as compared to 4c, 4e, 4f, and 4h. Compounds 4a and 4b exhibited less activity due to no substitution on aryl ring and methyl group, respectively.
Moreover, in the case of the anifungal studies carried out, only the compound 4f was found to be active against C. abicans fungal strain, as compared to the standard used, while none of the prepared compounds showed appreciable antifungal activity against A. niger fungal strain.

4. Conclusion
In the present work, we have described the preparation of Schiff base containing different kind of heterocyclic moieties which are prepared by two methods from readily available starting materials. The advantages of this protocol are mild reaction conditions, single step, shorter reaction times, good yields, and easy workup procedure, without any side products. Further, all the synthesized compounds were screened for their antimicrobial activity, among that 4c, 4e, 4f, and 4h exhibited maximum activity, while 4a and 4b exhibited less activity against bacterial strains, while only 4f was found to be active against C. abicans fungal strain.

Data Availability
The data of the research work carried out is presented in the manuscript itself.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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