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Research Article

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

Shivanand Merugu,[1] Vijaya Kumar Ponnamaneni,[2] Ravi Varala,[3] Syed Farooq Adil,[4] Mujeeb Khan,[4] Mohammed Rafiq H. Siddiqui,[4] and Ravikumar Vemula[1]

[1]*Department of Chemistry, Kamala Institute of Technology and Science, Huzurabad, Karimnagar 505 468, Telangana, India*
[2]*Synocule Research Labs Private Limited, Plot No. 16, CFC Area, IDA Nacharam, Hyderabad 500 076, Telangana, India*
[3]*Scrips Pharma, Mallapur, Hyderabad 500076, Telangana, India*
[4]*Department of Chemistry, King Saud University, Riyadh 11451, Saudi Arabia*

Correspondence should be addressed to Syed Farooq Adil; sfadil@ksu.edu.sa and Ravikumar Vemula; vemularavi97@gmail.com

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A series of (E)-3-(2-((5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) acetyl)-2*H*-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. H_2SO_4. 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], anthelmintic [17], antitubercular [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 dodecatungstosilicic acid/P_2O_5 [21], $Cu(NO_3)_2$, $6H_2O$ [22], silica sulfuric 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-yl) thio) acetyl)-2*H*-chromen-2-ones and derivatives were prepared from 3-(2-bromoacetyl)coumarin, 5-amino-1,3,4-thiadiazole-2-thiol and substituted benzaldehydes by method I and II with a catalytic amount of conc. H_2SO_4 in ethanol.

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 KBr disks on a Bruker WM-200 MHz spectrometer. ^{1}H- and ^{13}C-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).* 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. H_2SO_4 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).

*2.1.1. (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}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.56 (s, 2H, -CH_2-), 5.57 (s,1H, -NH-), 7.41–7.54 (m, 2H, of C_6 & C_8-H coumarin), 7.75 (m, 1H, of C_7-H), 7.78–7.81 (m, 3H, Ar-H); 7.84 –7.91 (m, 2H, Ar-H); 7.94 (m, 1H, of C_5-H), 8.60 (s, 1H, C_4-H of coumarin) and 11.61 (s, 1H, of –CH=N-); ^{13}C NMR (400 MHz, DMSO-d_6): δ 43.56, 116.51, 118.31, 125.42, 127.94, 128.42, 128.84, 128.86, 129.42, 129.47, 131.12, 131.21, 136.41, 137.51, 153.10, 159.64, 160.10, 160.94, 164.12, 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}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3), 4.51 (s, 2H, -CH_2-), 7.42–7.54 (m, 2H, of C_6&C_8-H coumarin), 7.75 (m, 1H, Ar-H of C_7-H), 7.78–7.91 (m, 4H, Ar-H); 7.94–7.98 (m, 1H, Ar-H of C_5-H), 8.64 (s, 1H, C_4-H of coumarin), and 11.64 (s, 1H, of –CH=N-); ^{13}C NMR (400 MHz, DMSO-d_6): δ 21.35, 43.60, 116.41, 118.35, 125.37, 127.84, 128.21, 129.12, 129.15, 129.49, 129.53, 131.20, 133.21, 137.56, 140.21, 153.10, 159.46, 160.12, 164.51, 166.12, 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), 1671 (-C=O), 1725 (lactone, -C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.58 (s, 2H, -CH_2- of Sulfer), 7.49–7.55 (m, 2H, of C_6&C_8-H coumarin), 7.71 (m, 1H, Ar-H of C_7-H), 7.91 (m, 1H, Ar-H of C_5-H), 7.97–8.24 (m, 3H, Ar-H), 8.56 (m, 1H, Ar-H), 8.67 (s, 1H, C_4-H of Coumarin), 11.66 (s, 1H, of –CH=N).

*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}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.96 (s, 3H, -OCH_3), 4.51 (s, 2H, -CH_2-), 7.12–7.26 (m, 4H, Ar-H), 7.46–7.65 (m, 2H, of C_6&C_8-H coumarin), 7.71 (m, 1H, of C_7-H coumarin), 7.85–7.91 (m, 1H, C_5-H of coumarin), 8.64 (s, 1H, C_4 –H of Coumarin), and 11.70 (s, 1H, of –CH=N).

*2.1.5. (E)-3-(2-((5-((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}; ^{1}H

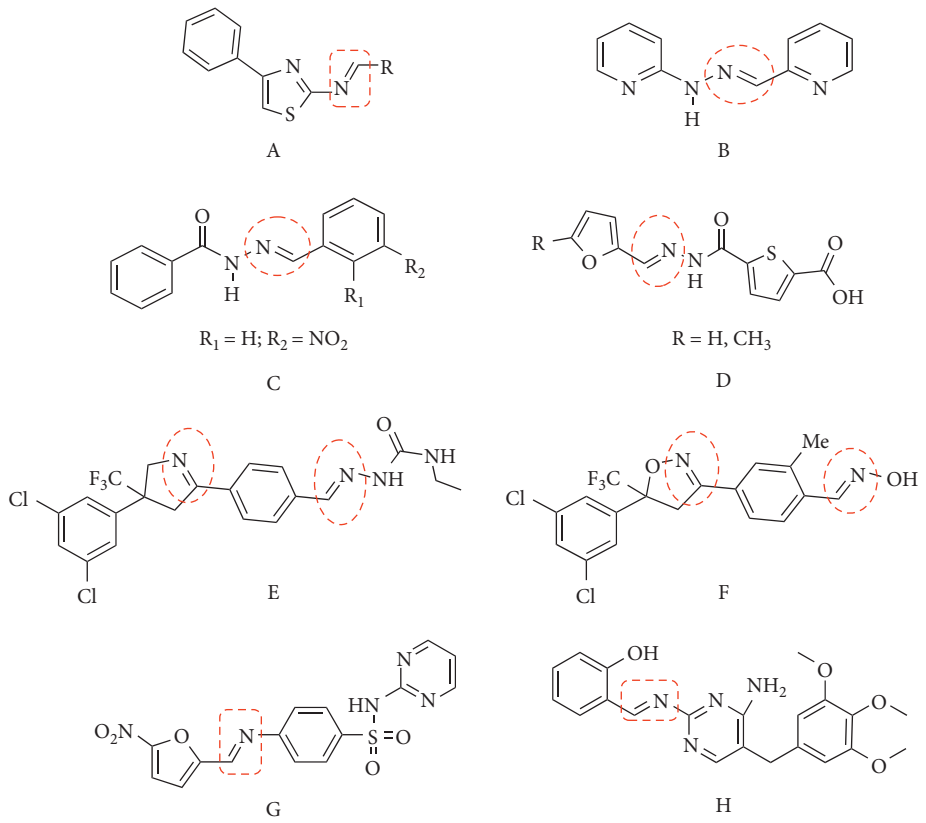


Figure 1: Various biologically active Schiff bases.

Table 1: Physical data of compounds (**4a-h** and **5**).

Compounds **4a-h** and **5**	R_1	R_2	R_3	R_4	Molecular formula	Molecular weight g mol^{-1}	Yield (%) method I	Yield (%) method II	M.P. (°C)
a	H	H	H	H	$C_{20}H_{13}N_3O_3S_2$	407.47	70	65	218–220
b	H	H	CH_3	H	$C_{21}H_{15}N_3O_3S_2$	421.49	86	80	223–225
c	H	H	H	NO_2	$C_{20}H_{12}N_4O_5S_2$	452.46	83	71	215–217
d	H	H	OCH_3	H	$C_{21}H_{15}N_3O_4S_2$	437.49	84	76	219–221
e	Cl	H	Cl	H	$C_{20}H_{11}N_3O_3S_2Cl_2$	476.36	80	66	235–237
f	Cl	H	H	H	$C_{20}H_{12}N_3O_3S_2Cl$	441.91	83	70	234–236
g	H	H	H	OCH_3	$C_{21}H_{15}N_3O_4S_2$	437.49	84	78	225–227
h	H	H	Br	H	$C_{20}H_{12}BrN_3O_3S_2$	486.36	80	76	241–243
5	—	—	—	—	$C_{13}H_9N_3O_3S_2$	319.36	85	—	212–215

NMR (400 MHz, DMSO-d_6): δ 4.52 (s, 2H, -CH_2-), 7.39–7.57 (m, 4H, Ar-H of C_6 and C_8-H of coumarin & Ar-H), 7.67 (m, 1H, of C_7-H of coumarin), 7.84 (d, 1H, J = 2 Hz, C_5-H of coumarin), 7.87–7.98 (m, 2H, Ar-H), 8.67 (s, 1H, C_4-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 (1 mmol) and 5-amino-1,3,4-thiadiazole-2-thiol (1 mmol) 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.

*2.2.1. 3-(2-((5-Amino-1,3,4-thiadiazol-2-yl)thio) Acetyl)-2H-chromen-2-one (**5**).* IR (KBr); 1610 (-C=N), 1680 (-C=O), 1726 (lactone, -C=O), 3416 (-NH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.76 (s, 2H, -CH_2-), 5.76 (s, 1H, -NH-), 7.39–7.46 (m, 2H, C_6&C_8-H, Coumarin), 7.65 (m, 1H, C_7-H of coumarin), 7.76 (d, 1H, C_5-H of coumarin), 7.81 (s, 2H, NH_2), 8.67 (s, 1H, C_4-H of coumarin); ^{13}C NMR (400 MHz, DMSO-d_6): δ 42.76, 116.61, 118.20, 122.51, 125.44, 131.09, 135.38, 146.54, 149.46, 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-(2-((5-amino-1,3,4-thiadiazol-2-yl)thio)acetyl)-2*H*-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. H_2SO_4 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 benzaldehyde **3** and a catalytic amount of conc. H_2SO_4 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. H_2SO_4/ethanol to give corresponding (*E*)-3-(2-((5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)thio) acetyl)-2*H*-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)-2*H*-chromen-2-one **5**. This, on further reaction with substituted benzaldehydes and Conc. H_2SO_4 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).

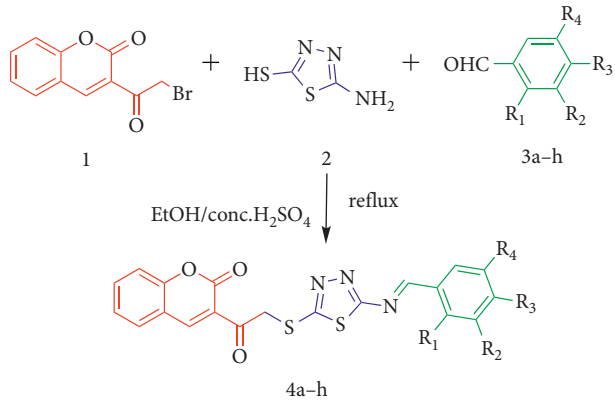
In the present work, Method-I was preferred over Method II, in terms of higher yields of the products and less time. Unlike the literature methods, we have first time synthesized title compounds **4a-h** in one step to expand the scope of synthetic transformation and offer a new convenient method for 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=N), 1680 (-C=O), 1720 (lactone, -C=O), 3411 (-NH) cm^{-1}, consistent with the assigned structures. The ^{1}H NMR (DMSO-d_6) spectrum of **4a** confirmed signals around δ 4.56 (s, 2H, -CH_2-), 5.57 (s, 1H, -NH-), 7.39–7.41 (m, 4H, Ar-H), 7.69–7.73 (m, 2H, of C_6 &C_8-H coumarin), 7.79 (m, 1H, Ar-H of C_7-H), 7.81 (m, 1H, Ar-H of C_5-H), 8.61 (s, 1H, C_4-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%). The IR spectra of compounds **5** confirmed prominent peaks at 1610 (-C=N), 1680 (-C=O), 1726 (lactone, -C=O), and 3416 (-NH) cm^{-1}, CH_2 protons appeared around δ 4.76 in the ^{1}H NMR spectra, and –NH- proton appeared at δ 5.76 which is D_2O exchangeable. The mass spectrum of **5** showed the molecular ion at *m/z* 319.

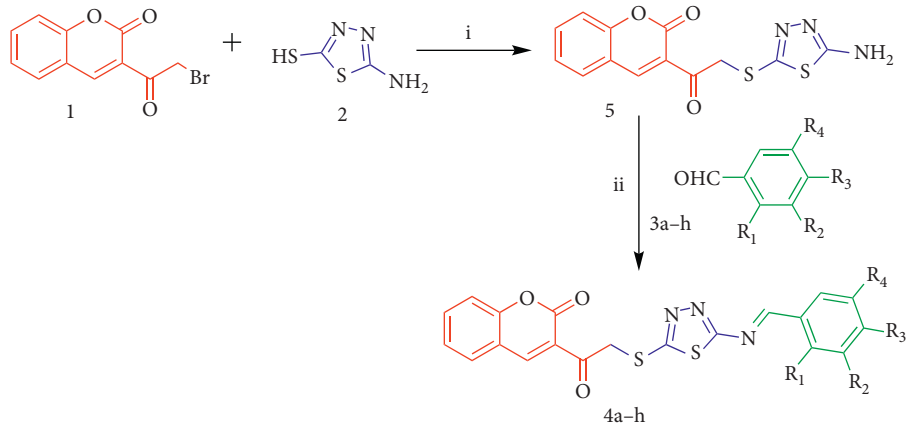
3.1. Biological Activity

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/mlon 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 simple 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



Scheme 1: *Method-I*. Experimental condition: (i) EtOH/Conc. H_2SO_4, reflux for 30 minutes.



Scheme 2: *Method-II*. Experimental condition: (i) EtOH, Reflux for 30 minutes; (ii) EtOH/Conc. H_2SO_4, reflux for 4 hours.

Table 2: Antimicrobial activity data of compounds from **4a-h**.

Compound	Concentration (μg/ml)	Zone of inhibition (in mm)					
		Gram-positive		Gram-negative		Fungal strain	
		B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. abicans*	*A. niger*
4a	100	24	25	23	26	24	21
b	100	24	18	21	23	21	19
c	100	25	29	24	28	24	21
d	100	21	24	23	25	23	20
e	100	25	29	26	29	23	21
f	100	26	28	25	28	25	22
g	100	21	24	24	26	21	19
h	100	25	29	24	27	23	21
Ciprofloxcin	50	26	28	24	28	—	—
Miconazole	50	—	—	—	—	25	25

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 antifunal 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 compoundswere 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.

Acknowledgments

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