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RESEARCH ARTICLE

Design and Synthesis of Novel Oxadiazole and Diphenyl Ether Hydrazone Derivatives of Coumarin as Potential Antibacterial Agents

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Abstract: ***Background:*** Coumarins, possesing antimicrobial activity are often used by the researchers to develop novel synthetic and semisynthetic coumarin based therapeutic agents. Molecular hybridization concept was used to design coumarin hybrid molecules. Synthesized molecules were evaluated for their invitro antibacterial activities. We designed Coumarin derivatives of diphenyl ether and oxadiazole. Most of the compounds showed antimicrobial activity against gram-positive as well as gram-negative bacteria.

Methods: ADME properties of the molecules calculated by Qikprop program. It predicts both physically appropriate descriptors and drug like properties. Oxadiazole and diphenyl ether hydrazone derivatives of coumarin were designed by molecular hybridization concept. Designed molecules were synthesized and confirmed by spectral data; further synthesized molecules were screened for antimicrobial activity by using the REMA plate method.

Results: We analyzed drug like properties with 44 physically relevant descriptors of coumarin derivatives by Qikprop, out of 28 ligands 14 all coumarin-oxadiazole derivatives structures exhibited allowed values for the properties analyzed and exhibited drug-like characteristics derived from Lipinski's rule of 5. Biological screening of coumarin-oxadiazole derivative of nitrophenyl **8g** was active against both gram positive and negative bacteria. It was seen that electron withdrawing substituent such as nitro group was important for activity. For coumarin –diphenyl hydrazone derivatives, halogens chloro substituent also exhibited significant activity as compare to fluoro substituted compounds. The most active hydrazone derivatives were **6c** and **6g** with chloro and trifluoromethoxy substitution on benzene ring. In part B, fluoro substitution at aromatic ring had no effect on improvement of antibacterial activity. However it showed that electron withdrawing group were more active and exhibited significant improvement in the antibacterial activity.

Conclusion: The efficient and instructive SAR study will provide deeper insight into further optimization of coumarin-oxadiazole and coumarin-diphenyl ether derivatives representing to promising leads for further exploration as antibacterial agents.

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1. INTRODUCTION

Infectious diseases pose a big challenge globally, because of resistance to a number of antimicrobial agents (beta - lactam antibiotics, macrolides, aminoglycosides, quinolones, and chloramphenicol) caused by clinically significant species of microorganisms leading to world health problem. Fight against this problem can be resolved by two ways, one is the use of currently marketed antimicrobial agents and other is the discovery of new antimicrobial agents. Many studies have shown that the occurrence of multidrug-resistant isolates is increasing in India and throughout the world. The development of multi drug resistant bacteria has produced a situation in which there are few or no treatment options for infections with certain microorganism. The development of resistance of marketed antibiotics could be solved by searching new targets using gene therapy, modifying available antibiotics by designing and discovery of novel antibacterial agents with novel structure and mechanism of action [1, 2]. The present studies focuses on the design and synthesis of the anti-infective agents which are active against microbial infections.

Especially, coumarin ring containing compounds have been increasingly attracting special interest due to their potential outstanding contributions in the prevention and treatment of diseases, and the related research and devel-

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opment have become an extremely attractive area [3, 4]. Coumarin compounds have ability to exhibit noncovalent interactions (hydrophobic, π-π and electrostatic interactions as well as hydrogen bonds, metal coordination, van der Waals force etc.) with the a range of active sites in organisms, and thus show a variety of biological activities such as anticoagulant [5], antineurodegenerative [6], antioxidant [7], anticancer [8] and antimicrobial [9] efficacies so on. In addition, coumarin scaffold with unique characteristic contains oxygen atom is also considered as a kind of ideal block to produce supramolecular assembly with interesting molecules and ions including bioactive species, thus is commonly used in the rational design and construction of supramolecular medicinal agents [10], particularly in antibacterial and antifungal fields which have shown preliminary application prospect and attracted much attention in recent years.

1, 3, 4-oxadiazole has become an important moiety for the development of new drugs. The moiety containing 1, 3, 4-oxadiazole compounds have wide range of biological activity such as under antimicrobial, antibacterial; antifungal and antiviral, analgesic, anti inflammatory, antihypertensive, antidiabetics and anticonvulsant [11].

Since 30 years, diphenyl ether, triclosan 5-chloro-2-(2,4-dichloro- phenoxy) phenol ether, is a broad-spectrum biocide that has been used as a part of antimicrobial wash in consumer products such as toothpastes, mouthwashes, deodorant soaps and lotions [12]. Triclosan absorption by diffusion into the bacterial cell wall, since it is small hydrophobic molecule and that its antibacterial activity was the result of a non-specific disruption of the organism's cell wall [13-14]. However, the first evidence that this diphenyl ether inhibits fatty acid biosynthesis came when a genetic analysis of an *Escherichia coli* strain resistant to triclosan linked the resistance to the FabI gene which encodes for ENR [15]. Many studies have been carried out to confirm that triclosan is a specific inhibitor of E. coli ENR with respect to biochemical and structural features [16-18]. ENR from Staphylococcus aureus was directly inhibited by triclosan [19], *Haemophilus influenza* [20], *M. tuberculosis* and *Mycobacterium smegmatis* [21-23] (encoded by InhA) and *Plasmodium falciparum*, the malaria parasite [24-26]. NADþ cofactor is essential requirement for triclosan to inhibit ENR. The interaction of triclosan with ENR is stabilized by the pi-pi stacking interaction between the hydroxyl chloro phenyl ring and hydrogen bonding between the hydroxyl groups of a tyrosine with the hydroxyl group of triclosan. The ether oxygen of triclosan may also be critical in the formation of the stable ENRe triclosane NADþ complex, since the bioisosteric replacement of the oxygen atom by a sulfur atom diminishes the inhibitory activity [16].

To improve efficacy more than parent compound by hybrid molecule this is evolved from combining two pharmacophoric moieties of bioactive molecules by concept of molecular hybridization [27]. A series of novel molecules containing Coumarin-oxadiazole and Coumarin-diphenyl ether moiety were designed. These moieties were combined with the help of amide and hydrazone linkage and depicted in Fig. (**1**) and Fig. (**2**) respectively.

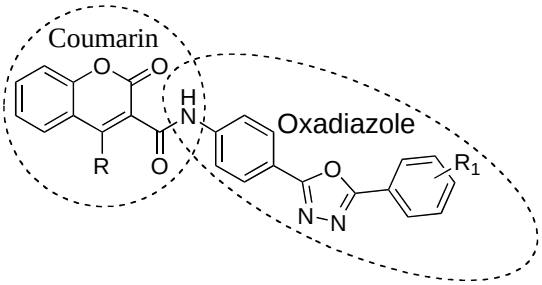


Fig. (1). Coumarin-Oxadiazole hybrid molecule.

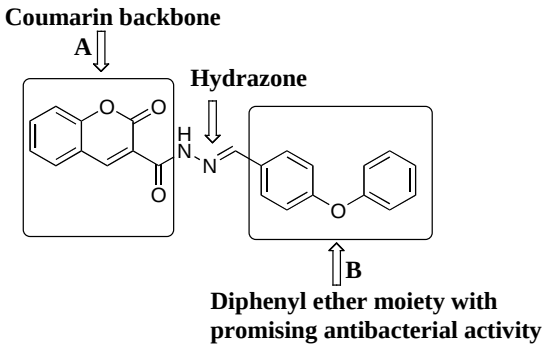


Fig. (2). coumarin-diphenyl ether hybrid molecule.

2. MATERIALS AND METHODS

2.1. ADME Screening

ADME properties of the molecules were calculated by Qikprop program. It predicts both physically appropriate descriptors and drug like properties. All the molecules were subjected to Ligprep before being used by Qikprop [28].

The program was processed in normal mode, and predicted 44 properties for the 28molecules, consisting of principal descriptors and physiochemical properties with a detailed analysis of the log P (Octanol/Water), QP%, and log HERG. Acceptability of the analogues was evaluated based on Lipinski's rule of 5 [29], which are crucial for rational drug design.

2.2. Experimental Section

2.2.1. Synthesis of Coumarin-Oxadiazole Hybrid

2.2.1.1. Synthesis of Coumarin Derivatives

The staring material salicyladehyde/2-hydroxyacetophenone **1** was reacted with diethyl malonate **2** in basic condition provided by piperidine and acetic acid in ethanol as solvent at 70°C. The substituted ethyl coumarin-3-carboxylate derivatives were further hydrolyzed in the presence of base 1N NaOH and acidified to get substituted ethyl coumarin-3-carboxylic acids **4a-4b**.

2.2.1.2 Synthesis of Oxadiazole Derivatives (7a-7g)

A mixture of 0.69 g (0.005 mole) of 4-amino benzoic acid and substituted benzoic acid hydrazides (0.005 mole) in 5 mL of phosphorus oxychloride was refluxed on water bath for 7–10 h. The mobile phase toluene: ethyl acetate: metha-

nol (70:20:10) used to monitor progress of reaction by TLC. After the completion of reaction, it was cooled and poured onto crushed ice with continuous stirring. The separated solid was neutralized with 10% w/v sodium bicarbonate solution. Finally solid obtained was filtrated, washed with cold water, dried and recrystallized from absolute ethanol, **7a-7g** as shown in Scheme **1**.

2.2.1.3 Synthesis of Coumarin and Oxadiazole Hybrids

The coumarin and oxadiazole hybrids were synthesized as depicted in Scheme **1**, to compound 4a in dry acetonitrile stirred at room temperature, DCC (coupling reagent) was added and then catalytic amount of DMAP was added. Then **7a** subsequently added to the reaction mixture was refluxed for 4-5 hrs. The reaction completion indicated by TLC. The mixture was filtered and the filtrate was extracted with dichloromethane and concentrate in vaccum. Recrystallisation with ethanol, gave compound **8a**. Compounds **8b-8n** were further prepared using the same method.

2.2.2 Synthesis of Coumarin Hydrazide Derivative

As described in Scheme **2**, the ethyl coumarin-3- caroxylate was stirred in ethanol, then hydrazine hydrate was added in presence of triethylamine and then reaction mixture was refluxed for 3-4 hrs the resulting product obtained as **(2)** shown in Scheme **2**.

2.2.2.1 Synthesis of Diphenyl Ether Derivatives

The diphenyl ether derivatives were synthesized as depicted in Scheme **2** by using 4-flourobenzaldehyde in DMSO as a solvent, and various phenol derivatives in the presence of K_2CO_3 afforded to correspond diphenyl ether derivatives in moderate to good yields.

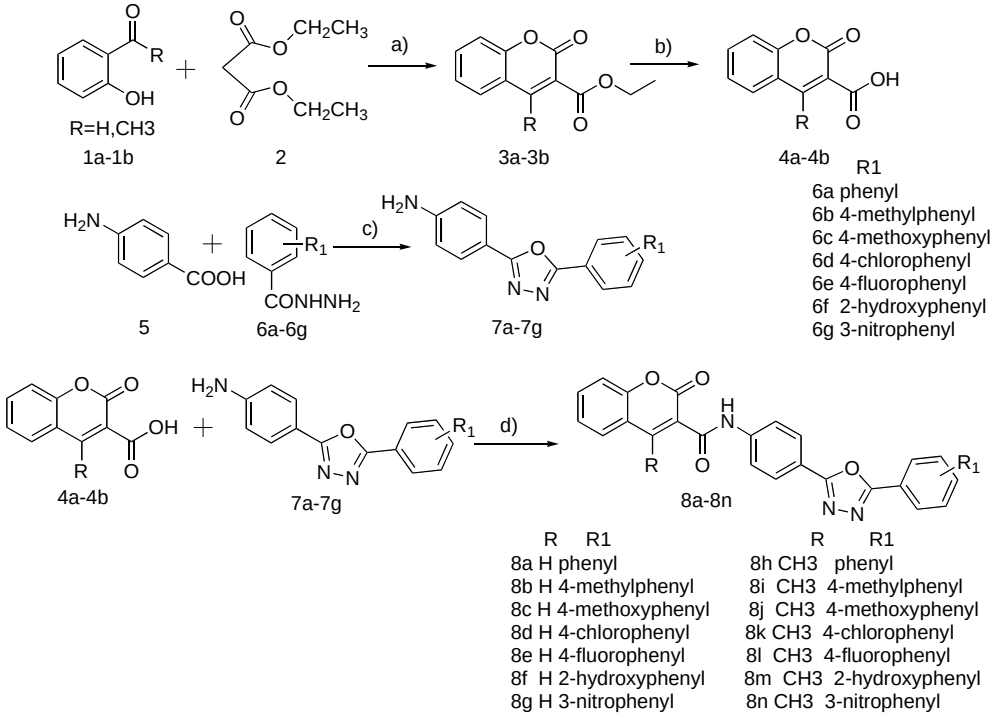
2.2.2.2. Synthesis of Coumarin-Diphenyl Ether Derivatives

The coumarin and diphenyl ether derivatives were synthesized as depicted in Scheme **2** by using coumarin hydrazide **(2)** and diphenyl ether aldehyde **(5a)** in ethanol and glacial acetic acid added at reflux condition afforded to corresponding coumarin diphenyl ether hydrazone hybrid **(6a)** in moderate to good yields. The coumarin diphenyl ether analogs **6b-6n** were also prepared using the same method.

This paper work represents synthesis and antibacterial evaluation of series of coumarin-oxadiazole and coumarin-diphenyl ether hybrid. The synthesized molecules were confirmed analytical methods like IR, NMR and Mass Spectroscopy.

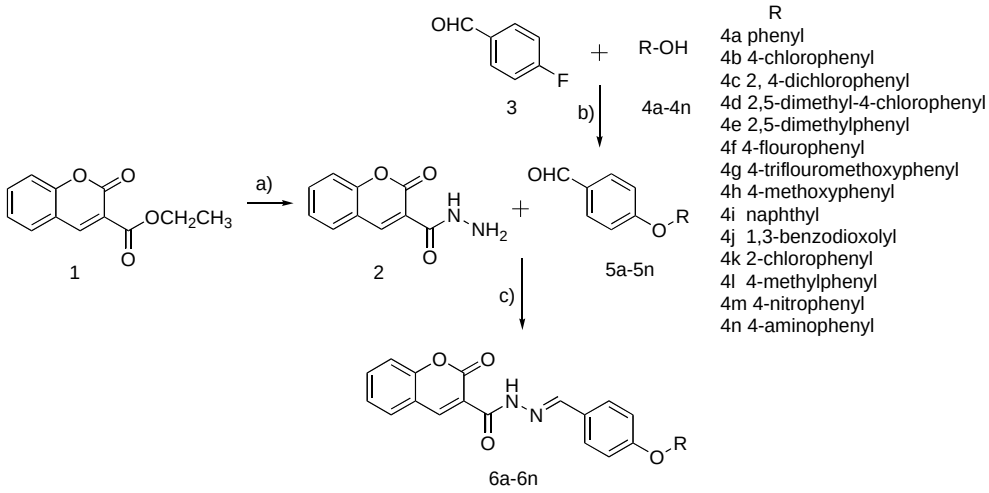
2.2.3. Antimicrobial Activity

Resazurin Microtitre Assay (REMA) plate method with serial dilution method was used to determine minimum inhibitory concentration (MIC) for series of synthesized molecules that were tested against S.aureus and E.coli. The test compounds were serially diluted on plates with DMSO as a solvent. Homogeneous bacterial culture with 10^5 cell per well were suspended in microtitre plates. MIC was the lowest inhibition concentration and was observed by the colour change of resazurin dye from blue to pink was represented by the lowest MIC value of inhibitory concentration. The reference drug was used as ciprofloxacin.



a Reagents: a) Piperidine, EtOH, AcOH; reflux, 2h; b)1N NaOH, dil HCl; reflux 2h; c) $POCl_3$, DCM, reflux, 4 h; d) ACN, DCC, DMAP, Reflux for 8-10 h.

Scheme 1. Synthetic scheme of coumarin-oxadiazole derivatives.



[a] Reagents: Reagents and Conditions: a) $NH_2NH_2.H_2O$, reflux for 3-4 h; b) K_2CO_3, DMSO, reflux for 6-7 h; c) glacial acetic acid, Ethanol, reflux for 7-8 h

R	R
6a phenyl	6h 4-methoxyphenyl
6b 4-chlorophenyl	6i naphthyl
6c 2, 4-dichlorophenyl	6j 1,3-benzodioxolyl
6d 2,5-dimethyl-4-chlorophenyl	6k 2-chlorophenyl
6e 2,5-dimethylphenyl	6l 4-methylphenyl
6f 4-flourophenyl	6m 4-nitrophenyl
6g 4-triflouromethoxyphenyl	6n 4-aminophenyl

Scheme 2. Synthesis of coumarin diphenyl ether derivatives.

3. RESULTS AND DISCUSSION

3.1. Predicted ADME Properties

Qikprop thereotically predicts ADME properties. We analyzed drug like properties with 44 physically relevant descriptors of coumarin derivatives, among which were molecular weight, H-bond donors, H-bond acceptors, log P (octanol/water), QPPCaCO, human oral absorption and their position according to Lipinski's rule of 5 (Table **1**). Lipinski's rule of 5 is a rule of thumb helps in evaluating drug likeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule explains molecular properties like molecular mass, hydrogen bond acceptor–donor and lipophilicity are crucial for a drug's pharmacokinetics in the human body, including its ADME. However, the rule does not predict if a compound is pharmacologically active [29].

Current study, out of 28 ligands, 14 all coumarin-oxadiazole derivatives structures exhibited allowed values for the properties analysed and exhibited drug-like characteristics derived from Lipinski's rule of 5. Some coumarin-diphenyl ether derivatives eg. **6b, 6c, 6d, 6e, 6f, 6g, 6i, 6k** and **6l** did not show drug-like characteristics. The program indicates specific limit values for each property, which acts as a cut- off filter for the acceptance or rejection of the produced results.

3.2. Antibacterial Evaluation for Coumarin-Oxadiazole Hybrid Derivatives

REMA protocol was used to determine the MIC of all the synthesized coumarin-oxadiazole derivatives. The results of biological screening are summarized in Table **2**. From the antibacterial screening, it was found that the highest active compounds 8g was having a MIC of 31.25 and 62.5 μg/ml against *S.aureus* and *E.coli* respectively. The most active compound was amide derivatives 8g with nitro substitution at para position of the benzene ring. The other compounds like **8b, 8c, 8e, 8f, 11f, 8h, 8i, 8j, 8k, 8l, 8m** and **8n** were inactive against both gram-positive and gram negative strain. The coumarin oxadiazole derivative **8d** also exhibited promising antibacterial activity against *S.aureus* for chloro substituent on benzene ring. The substituted aryl derivatives of the oxadiazole **8b, 8c, 8e** and **8f** contain methyl, methoxy, fluoro and hydroxyl on benzene ring which were found to be inactive even at 125 μg/ml. This may be attributed to the electron releasing group on the benzene ring.

3.3. SAR of Coumarin-Oxadiazole Derivatives

From the biological screening of coumarin-oxadiazole derivative of nitrophenyl **8g** was active against both gram positive and negative bacteria. It was seen that electron withdrawing substituent such as nitro group was important for activity. Among halogens chloro substituent also exhibited significant activity as compare to fluoro substituted compounds.

3.4. Antibacterial Evaluation of Coumarin-Diphenyl Ether Derivatives

REMA protocol was used to determine the MIC of all the synthesized coumarin diphenyl ether derivatives. The results of biological screening are summarized in Table **3**. From the antibacterial screening, it was found that the most active compounds **6c** and **6g** had 31.25 μg/ml activity against

Table 1. QikProp analysis data.

Title	#Stars[a]	QPlogPo/w[b]	QPPCaco[c]	% Human Oral Absorption[d]	Rule of Five[e]
6a	2	4.797	733.292	100	0
6b	3	5.302	733.322	96.317	1
6c	3	5.667	733.274	100	1
6d	1	5.778	733.257	100	1
6e	2	5.337	733.25	96.521	1
6f	2	5.037	733.328	94.761	1
6g	2	5.963	733.321	100	1
6h	1	4.855	733.314	100	0
6i	3	5.655	733.22	100	1
6j	2	4.217	733.323	100	0
6k	2	5.162	733.269	95.492	1
6l	2	5.123	733.306	95.266	1
6m	1	4.041	87.747	85.386	0
6n	1	3.994	190.578	91.141	0
8a	1	3.902	393.45	96.237	0
8b	2	4.228	393.418	100	0
8c	1	3.96	393.272	96.575	0
8d	2	4.408	393.468	100	0
8e	1	4.142	393.467	100	0
8f	1	3.512	176.139	87.706	0
8g	1	3.147	47.147	75.322	0
8h	1	4.219	477.478	100	0
8i	2	4.545	477.446	100	0
8j	1	4.278	477.282	100	0
8k	2	4.725	477.519	100	0
8l	2	4.459	477.497	100	0
8m	2	3.819	212.204	90.949	0
8n	1	3.464	57.209	78.682	0

[a]#Stars: #stars are MW, dipole, IP, EA, SASA, FOSA, FISA, PISA, WPSA, PSA, volume, donorHB, accptHB, QPlogPoct, QPlogPw, QPlogPo/w, logS, QPLogKhsa, QPlogBB. The range predicted for this parameter using QikProp is 0–5; where 0–1 indicates no violation or best candidate.
[b] QPlogPo/w: This gives the predicted octanol/water partition coefficient. The range predicted for this parameter using QikProp is -2.0–6.5.
[c] QPPCaco: QikProp predictions are for nonactive transport, where <25 is considered poor and >500 is considered excellent.
[d] % Human-Oral Absorption: This gives the predicted human oral absorption on 0–100% scale where >80% is considered high and <25% is considered poor.
[e] Rule of Five: This property denotes the number of violations of Lipinski's rule of five

Table 2. Antibacterial activity of coumarin-oxadiazole derivatives

Compounds	R	R_1	MIC (µg/ml)	
			S. aureus	*E. coli*
8a	H	phenyl	62.5	>125
8b	H	4-methylphenyl	>125	>125
8c	H	4-methoxyphenyl	>125	>125
8d	H	4-chlorophenyl	62.5	>125
8e	H	4-fluorophenyl	>125	>125
8f	H	2-hydroxyphenyl	>125	>125
8g	H	3-nitrophenyl	31.25	62.5
8h	CH_3	phenyl	>125	>125
8i	CH_3	4-methylphenyl	>125	>125
8j	CH_3	4-methoxyphenyl	>125	>125
8k	CH_3	4-chlorophenyl	>125	>125
8l	CH_3	4-fluorophenyl	>125	>125
8m	CH_3	2-hydroxyphenyl	>125	>125
8n	CH_3	3-nitrophenyl	62.5	125
Ciprofloxacin[b]	-	-	0.5	0.5

Table 3. Antibacterial activity of coumarin-diphenyl ether derivatives.

Compounds	R_1	MIC (µg/ml)	
		S. aureus	*E. coli*
6a	phenyl	62.5	125
6b	4-chlorophenyl	>125	>125
6c	2, 4-dichlorophenyl	31.25	62.5
6d	2,5-dimethyl-4-chlorophenyl	62.5	>125
6e	2,5-dimethylphenyl	>125	>125
6f	4-flourophenyl	>125	>125
6g	4-triflouromethoxyphenyl	31.25	62.5
6h	4-methoxyphenyl	>125	>125
6i	naphthyl	>125	>125
6j	cisamol	>125	>125
6k	2-chlorophenyl	>125	>125
6l	4-methylphenyl	>125	>125
6m	4-nitrophenyl	62.5	62.5
6n	4-aminophenyl	>125	>125
Ciprofloxacin[b]	-	0.5	0.5

S.aureus. We observed that compounds such as **6a, 6d** and **6m** were having a MIC of 62.5 μg/ml against *S.aureus*. Other compounds such as **6c, 6g** and **6m** were having a MIC of 62.5 μg/ml against *E. coli*. However, analogs like **6b, 6e, 6f, 6h, 6i, 6j, 6k, 6l** and **6n** were inactive against both strains.

3.5. SAR of Coumarin-Diphenyl Ether Derivatives

From the biological screening of diphenyl ether derivatives of coumarin, it was found that coumarin derivative of diphenyl ether **6c** and **6g** were active against both *S. aureus* and *E. coli*. The most active hydrazone derivatives were **6c** and **6g** with chloro and trifluoromethoxy substitution on benzene ring. In part B, fluoro substitution at aromatic ring had no effect on improvement of antibacterial activity. However it showed that electron withdrawing group were more active and exhibited significant improvement in the antibacterial activity. It was also found that compound **6c** and **6g** with 2,4-dichlorophenyl and trifluoromethoxy substitutions on diphenyl ether moiety leads to highest antibacterial activity of coumarin diphenyl ether hydrazone derivatives.

4. CONCLUSION

The present study revealed that coumarin-oxadiazole derivatives possess good to moderate activity against *S. aureus*. Out of 14 synthesized coumarin-oxadiazole derivatives, compound 8g with nitro substitution emerged with antibacterial activity of 31.25 μg/ml. In case of aryl derivatives of oxadiazole moiety, the compounds with electron releasing functional group substitutions were inactive. The promising activity of the coumarin-oxadiazole derivatives established them as crucial pharmacophore which can be used as a lead for further development of novel derivatives of coumarin with better antibacterial activity. Considering this as a pharmacophore, the further expansion of the coumarin-oxadiazole series is underway to find a potent antibacterial agent.

Coumarin-diphenyl ether derivatives possess good to moderate activity against *S. aureus* and *E. coli*. Since 14 synthesized coumarin-diphenyl ether derivatives, compound **6c** and **6g** with 2, 4-dichlorophenyl and trifluoromethoxy substitution emerged with antibacterial activity of 31.25 μg/ml. In case of diphenyl ether derivatives, the compounds with electron withdrawing functional group substitutions were more active and exhibited significant improvement in the antibacterial activity as compared to bulkier group. Moreover diphenyl ether containing fluoro group were inactive than chloro derivatives.

Moreover, the efficient and instructive SAR study will provide deeper insight into further optimization of coumarin-oxadiazole and coumarin-diphenyl ether derivatives representing to promising leads for further exploration as antibacterial agents.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Spectral data for synthesized compounds.

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