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Coumarine Oxadiazole Derivatives: Review on Antimicrobial activity

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A B S T R A C T
Emergence of resistance by microbial and fungal stains towards existing antimicrobial agents is one of the major complication as well as stimulation to developing a latest class of antimicrobial agents possessing strong activity compared to commonly used treatment. Coumarine oxadiazole derivatives shows antimicrobial, anticancer and anti-inflammatory activity. The derivatives with strong antibacterial activity were put through molecular docking studies to study the structural activity relationship between the active derivatives and biological targets.
Keywords: Coumarin, Antimicrobial activity, Molecular docking studies, Oxadiazole.

A R T I C L E I N F O

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CONTENTS

1. Introduction

Coumarins are an important group of heterocyclic compounds that are known for their properties such as antimicrobial, anti-inflammatory and anticancer disease. Oxadiazole moiety in association with various heterocyclic rings. 1,3,4-oxadiazole is a heterocyclic compound containing one oxygen atom and two nitrogen atoms in a five membered ring. Oxadiazole rings contain two carbon atoms, two nitrogen atoms, one oxygen atom. The compounds containing 1,3,4-oxadiazole unit presently used in clinical medicine are:-Nevirapine an antiretroviral drug and Zibotentan an anticancer agent. Oxadiazole nucleus is present in antihypertensive drugs such as nesadipil and antibiotics such as furamizole [1-2]. Coumarin and its derivatives represent one of the most active classes of compound belonging to a broad spectrum of biological activity. This day, additional antimicrobial drugs such as cephalosporins, oxazolidinones, fluconazole and ketoconazole are available. Coumarin derivatives belongs to one of the most wide spread classes of natural compounds they have been found to exhibit antitumor, antioxidant, anti-inflammatory, antimicrobial and antidiabetic activities. [3-5]

1,3,4-oxadiazoles are five-membered heterocyclic compounds. Cancer is a leading disease in which abnormal cells grow and can occur in all the living cells. Coumarins present a variety of bioactivities including antimicrobial, antihelmintic and hypothermic actions. Coumarin and related derivatives are identified as inhibitors. Five membered rings have constitute the substantial profits [6-7]. Erythrocytic phase is responsible for indications in humans Coumarins via inhibition of retroviral enzymes. Antibacterial activities of new coumarin derivatives were tested invitro activity. The electronic range of the 1,3,4-oxadiazole system is equivalent to that of benzene. Oxadiazoles are useful targets. The derivatives have been studied for their anti-human immunodeficiency virus ability [8-10]. The chemical structures of the synthesized compounds were determined by spectroscopic techniques [11].

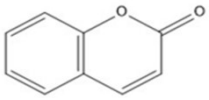


Figure 1

Coumarin compounds have shown to inhibit replication of HIV steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of rheumatoid arthritis and anti-inflammatory diseases. 1,3,4-oxadiazoles Schiff bases to get the synergistic effect. Coumarin derivatives have numerous therapeutic applications Coumarin with 1,3,4-oxadiazole and acetamides to assess their antibacterial activity [12-13].Coumarin is a a toxic white crystalline lactone with an odor of new-mown found in plants or made synthetically and used especially in perfumery and as a parent compound in anticoagulant agents.

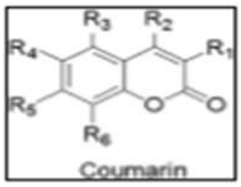


Figure 2

Kinase inhibitors:

Kinases are those enzymes that catalyze the transfer of a phosphate group to the target protein. They play a critical role in the modulation of growth factor signaling. Activated forms of these enzymes can cause increase in cell proliferation, promote angiogenesis, prevent apoptosis and metastasis in several cancers, and their activation by the somatic mutation is a basic mechanism of tumor genesis [14-15]. As all these effects are initiated by the activation of kinases, they are the key targets for inhibition by coumarins and their derivatives.

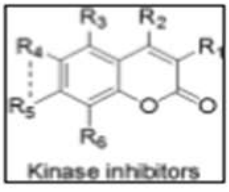


Figure 3

Angiogenesis inhibitors:

Coumarin derivatives also act through angiogenesis. They have been found to prevent angiogenesis by inhibiting fibroblast growth factor2-mediated proliferation, migration, and tubule formation [16]. Coumarin derivatives were also observed to decrease the expression of vascular endothelial growth factor at mRNA level through nuclear factor-κB.

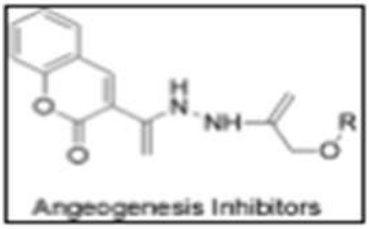


Figure 4

Oxadiazole:

1,2,4-oxadiazoles are known in medicinal chemistry for their use as bioisosters of esters and amides. 1,3,4-oxadiazole nucleus shows a broad spectrum of pharmaceutical applications.

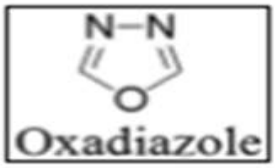


Figure 5

2. Anti-Tumour Activity

A series of 1,3,4-oxadiazole derivatives containing 1,4-benzodioxan moiety has been designed, synthesized, and evaluated for their antitumor activity. Most of the synthesized compounds were proved to have potent antitumor activity and low toxicity [17].

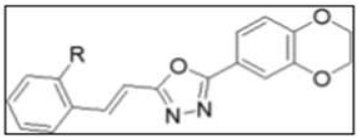


Figure 6

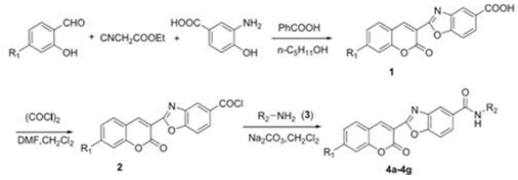
Synthesis of coumarin derivatives:

Table 1 Synthesis of various coumarin-benzoxazole derivatives.

Entry	R_1	R_2	Yield[b] (%)
4a	$-NEt_2$		52.3
4b	$-NEt_2$		53.4
4c	$-NEt_2$		61.1
4d	$-NEt_2$		63.4
4e	$-NEt_2$		43.0
4f	$-NEt_2$		41.2
4g	-H		62.8

[a] Reaction conditions: A mixture of **2** (1 mmol), **3** (1.1 mmol), Na_2CO_3 (1.1 mmol) was added in DCM (20 mL) and stirred at rt for 12 h.

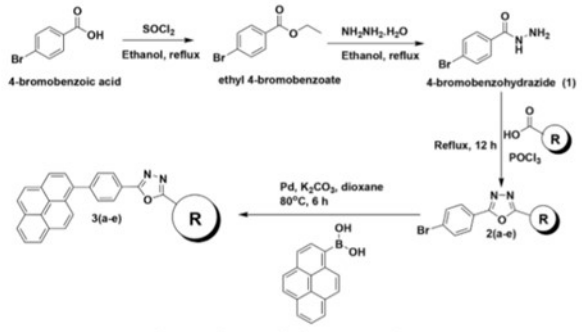
[b] Isolated yield.



Scheme 1: Synthetic routes to coumarin benzoxazole derivatives

Which the 7-Position is alternate with N,N-diethyl donor group, while the 3-position is alternate with benzoxazole group to increase the π- conjugation length, and the 4-position of benzoxazolyl is alternate with nitrobenzene derivatives served as accept group.The effects of the structure on the optical properties and third-order NLO properties were measured. All the properties of these compounds were also calculated using semi- empirical (ZINDO), Time- dependant density functional theory (TDDFT), and density functional theory(DFT), showing a good accordance with experimental data [18-19].

A comparatively simple and efficient synthetic procedure was adopted for the synthesis of compounds , 4-bromobenzoic acid was esterified to obtain ethyl 4-bromobenzoate which is further treating with hydrazine hydrate to obtain the required precursor 4-bromobezohydrazide. Conversion of 4-bromobenzohydrazide to key intermediates were attain by treatment of 4-bromobenzohydrazide with different aryl/heteroaryl carboxylic acids in refluxing $Pocl_3$. In the final step compounds were treat with to pd- catalyzed Suzuki-Miyaura cross-coupling reaction with pyren-1-ylboronic acid to provide the final compounds with 75-85% yields [20].



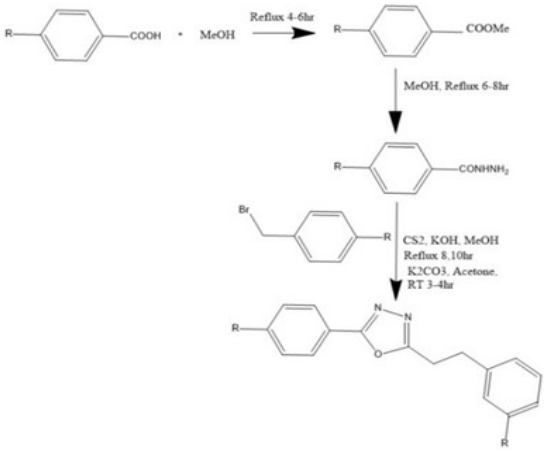
Scheme 2: Synthetic route for the target compounds

General Procedure for the synthesis of Coumarine Oxdiazole derivatives:

The corresponding carboxylic acid (0.02mol) as a starting material is dissolved in methanol (30ml) and concentrated sulfuric acid (0.5ml) is added followed by reflux for 8-10 hours. To monitor the progress of reaction TLC is utilize at regular intervals. Then the mixture is concentrated on rotary evaporator upon completion. The reaction mixture is washed with saturated aqueous sodium bicarbonate solution (150ml) and remove with ethyl acetate (3×50ml), organic layer is dried over anhydrous sodium sulfate and concentrated under vaccum to obtain pure product [21].

Carboxylic acid hydrazides are synthesized following a modified procedure already described in the literature. Hydrazine hydrate (80%, 0.06 mol) is added slowly to a solution of carboxylate esters (0.02 mol) in methanol (30 ml). The reaction mixture is subjected to reflux for 6-8 hours. Upon completion of reaction. The mixture is cooled down to the room temperature and ice water is added [22]. The precipitated solid product obtained was filtered, dried and recrystallized from methanol. Hydrazide is disestablish in methanol and a methanolic solution of potassium and ice water is added. The precipitated solid product obtained was filtered, dried and recrystallized from methanol.

The corresponding hydrazide is dissolved in methanol and a methanolic solution of potassium hydroxide (0.03 mol) is added. After ten minutes, CS2 (0.06, mol) is added drop wise into the stirring mixture. The color of mixture turned yellow and treated with further reflux for 12-14 hours until the completion of reaction. The mixture is cooled to room temperature and concentrated then provideinto ice cold water. Crude solid product precipitated out on treatment with dilute HCl up to pH 2 [23]. The precipitates are filtered, washed with warm water and recrystallized from methanol to provide target oxadiazole derivatives.

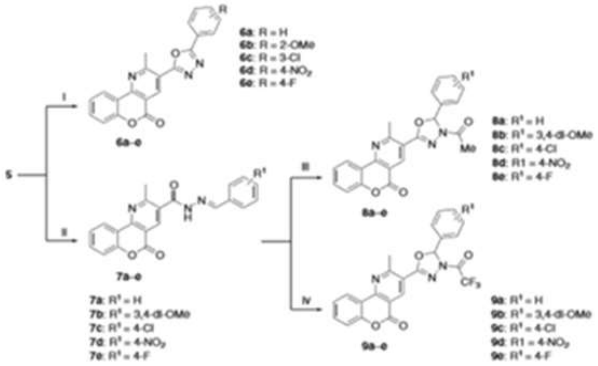


Scheme 3: Synthetic route for the synthesis of 1,3,4-oxadiazole

3. Antimicrobial activity

The antimicrobial activity was assessed by agar-well diffusion method using Mueller Hinton agar medium. Zone of inhibition and MIC's were measured for compounds and against bacterial strains Staphylococcus areus(Gram-positive), Escherichia coli (Gram-negative) and fungal strains Candida albicans and Aspergillus nigerwith reference to standard drugs (streptomycin and griseofulvin). Compounds possess a good antibacterial activity at 5 μg/mL against the tested strains of Gram-positive S. areus as close lead when compared with standard drug streptomycin whereas other derivatives are moderately active. Compounds displaya good potency with respect to streptomycin whereas compounds show moderate activity against Gram-negative bacteria E. coli. For fungal strains, compounds shows a good inhibitory activity against C. albicans, whereas compounds shows moderate inhibition with respect to standard drug griseofulvin [24]. Compounds are moderately active against the tested strain of A. niger, whereas other compounds are less active with respect to

griseofulvin. In summary, the structureactivity relationship (SAR) analysis of antimicrobial screening shows that compound with R1 as p-chloro andp-fluoro substituents display good antimicrobial activity for S. aureus. Against E. coli, compounds containing R1 as p-chloro and p-fluoro along with N-substituted COCF3 group on the oxadiazole ring display good activity. For the same organism, moderate activity is displayed when the R group is hydrogen or p-chloro. For C. albicans, compounds containing R1 as p-NO2, N-substituted COCH3 or p-fluoro group display good antimicrobial activity [25]. Compounds containing R1 as p-fluoro substituent display good to moderate antimicrobial activity against A.niger.



Scheme 4

4. Conclusion

Coumarine derivatives containing Oxadiazole ring shows antimicrobial, anticancer and anti-inflammatory activity. The current review mainly focused on the antimicrobial activity of 1, 3, 4-oxodiazol containing coumarine derivatives, which leads to help our further research on the new oxodiazol coumarine derivatives with more biological activity.

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