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Review Article

VARIOUS BIOLOGICAL ACTIVITIES OF COUMARIN AND OXADIAZOLE DERIVATIVES

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ABSTRACT

In this review article, data are collected regarding the various derivatives of coumarin and oxadiazole as both these have wide range of biological activities and they can be further modified to synthesize more effective and potent drugs. Coumarin class of organic compounds consists of 1,2-benzopyrone ring system as a basic parent scaffold. These benzopyrones are subdivided into alpha-benzopyrones and gamma-benzopyrones; with coumarin class of compounds belonging to alpha-benzopyrones, coumarins were synthesized in many of their derivative forms since the last few years. Their pharmacological, therapeutic, and biochemical properties depend on their pattern of substitution. Coumarins exhibit a wide range of pharmacological activities, which includes antidiabetic, antiviral, antimicrobial, anticancer, antioxidant, antiparasitic, antiproliferative, anticonvulsant, anti-inflammatory and antihypertensive activities, and anti-helminthic. 1,3,4-oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. It is derived from furan by substitution of two methylene groups with two pyridine type nitrogens. There are three known isomers: 1,2,3-oxadiazole, 1,2,4-oxadiazole, and 1,2,5-oxadiazole. Oxadiazole moiety shows antimicrobial, anticancer, and anti-inflammatory activity and suitably substituted 1,3,4-oxadiazole having biological activities such as antimicrobial, anticancer, and other biological activities.

Keywords: Coumarin derivatives, Oxadiazole derivatives, Biological activities, 1,3,4-oxadiazole, Hybrids.

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INTRODUCTION

As per the WHO reports, more than 10 million cancer cases occurred worldwide since 2002. This situation would get worse to 15 million over the next 20 years [1]. It can occur at all ages but more common with old age. Cancer results from uncontrolled growth of normal cells, so cancer cells closely resemble normal cells. Most of the drugs used in the treatment of cancer act against all rapidly proliferating cells, and therefore, along with the cancer cells, they also affect the normal cells. The most common problem in the cancer treatment is to kill the cancer cells selectively with no or less side effects [2].

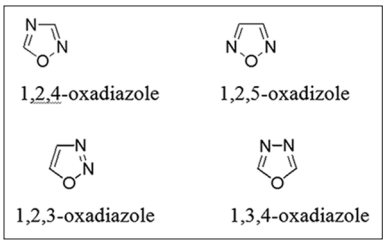
Coumarins are fused benzene and pyrone ring systems which prompt biological investigation to assess their potential therapeutic significance. It contains good anticancer potential with minimum side effects depending on the substitutions on the basic nucleus. Coumarins have a tremendous ability to regulate diverse range of cellular pathways that can be explored for selective anticancer activity [3]. Coumarin is a natural substance that has shown antitumor activity *in vivo*, with the effect believed to be due to its metabolites such as 7-hydroxycoumarin. Therefore, the focus will be on these relevant compounds and their therapeutic importance. A recent study has shown that coumarin-substituted benzothiazole inhibits the protein tyrosine kinase. This knowledge may lead to its use in cancer therapy. The most recent work involves 2 cell lines, MCF-7 a breast carcinoma and A549 lung carcinoma.

1,3,4-oxadiazole is a heterocyclic compound containing two nitrogen atoms and an oxygen atom in a five-membered ring. It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=). There are three known isomers: 1,2,4-oxadiazole, 1,2,3-oxadiazole, and 1,2,5-oxadiazole. Oxadiazole moiety shows anticancer, antimicrobial, and anti-inflammatory activity and suitably substituted 1,3,4-oxadiazole having biological activities such as antimicrobial, anticancer, and other biological activities. This work focused to develop efficient synthetic strategies to afford structurally diverse chalcone derivatives having improved antimicrobial activities by attaching other lead structure like oxadiazole heterocyclic moieties [4].

CHEMISTRY OF COUMARIN AND OXADIAZOLE

The fusion of benzene nucleus with pyrone ring gives rise to a class of heterocyclic compound known as benzopyrone with two distinct types recognized as benzo-α-pyrone (Fig. 1) commonly called as coumarin and benzo-γ-pyrone (Fig. 2) commonly called as chromon. They are different from each other only in the position of carbonyl group in heterocyclic ring. There are several methods which are developed for the synthesis of coumarin, such as the Pechmann, Perkin, Knoevenagel, Witting, and Reformastsky reaction. Among these, the Pechmann reaction has been the most widely used method in the synthesis of coumarin since it proceeds from very simple starting materials and gives good yield of variously substituted coumarin. Pechmann reaction consists of condensation of β-ketonic ester with phenol to give coumarin [5].

Oxadiazoles and their derivatives are simple five-membered heterocycles possessing one oxygen and two nitrogen atoms. The oxadiazoles exist in different isomeric forms such as 1,2,4-, 1,2,5-, 1,2,3-, and 1,3,4-oxadiazoles.



The five-member heterocyclic compounds containing nitrogen and oxygen heterocycles, particularly oxadiazoles have been successfully tested against several diseases and therefore received special attention in pharmaceutical chemistry due to their diverse medicinal potential. Among the oxadiazoles; 1,2,4-oxadiazoles continuously draws interest for the development of newer drug

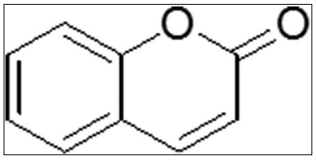


Fig. 1: Benzo-α-pyrone

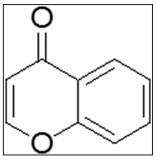


Fig. 2: Benzo-γ-pyrone

moiety. Substituted 1,3,4-oxadiazole derivatives have shown a broad spectrum of biological properties in pharmaceutical field. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and antidiabetic properties. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters, and carboxamides [6]. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. Two examples of compounds containing the 1,3,4-oxadiazole unit currently used in clinical medicine are Raltegravir®, an antiretroviral drug [7] and Zibotentan®, an anticancer agent [8]. Other market formulations are nesapidil, and furamizole. Oxadiazole is a very weak base due to the inductive effect of the extra-heteroatom. The replacement of two CH= groups in furan by two pyridine type nitrogen (N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibits character of conjugated diene. Electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low-electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However, the attack of electrophiles occurs at nitrogen if oxadiazole ring is substituted with electron releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergoes nucleophilic substitution with the replacement of halogen atom by nucleophiles. Oxadiazole undergoes nucleophilic substitution similarly as occurring at an aliphatic sp_2 carbon atom [9].

VARIOUS SYNTHETIC PATHWAYS OF COUMARIN AND OXADIAZOLE DERIVATIVES

Coumarins can be obtained by different extraction methods from the plants such as maceration under sonication, infusion, and supercritical fluid extraction. However, the extraction from plants is time-consuming and tedious job; hence, there is a need for sophisticated instrument for separation process to get the pure product. Chemically, coumarins can be synthesized by various methods such as the Pechmann reaction, Knoevenagel condensation, Claisen rearrangement, Perkin, Wittig, Reformatsky, and catalytic cyclization reactions.

Perkin reaction

The chemical synthesis of coumarin was first achieved by Perkin. In this reaction, Perkin used salicylaldehyde as synthon. Coumarin was obtained by heating salicylaldehyde with acetic anhydride and anhydrous sodium acetate. This reaction proceeds through the formation of an intermediated o-hydroxycinnamic acid derivative which converts spontaneously into the lactone ring [10].

Pechmann reaction

The reaction of a phenol with malic acid in the presence of concentrated sulfuric acid leads to the formation of hydroxyl phenyl coumarin derivatives. Many substituted phenols do not undergo this reaction; only coumarins unsubstituted in the pyrone ring are obtained [11].

Pechmann-Duisberg reaction

Pechmann and Duisberg found that phenols condense with para-ketonic esters in the presence of sulfuric acid, giving coumarin derivatives. This reaction has found extensive applications in the synthesis of various coumarin derivatives [12].

Knoevenagel reaction

This process is based on the synthesis of coumarin derivatives obtained from o-hydroxy (aryl/phenyl) aldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases [13].

Witting reaction

In the Wittig reaction, the alkene formation takes place from carbonyl compounds and phosphonium ylides, proceeding primarily through betaine and/or oxaphosphetane intermediates. This type of olefination of o-hydroxycarbonyl aromatic compounds followed by lactonization is a well-known method for the preparation of coumarin derivatives [14].

The synthesis of heterocyclic compounds involves multistructure in a molecule. The condensation reaction involves cyclization or ring formation. There are two free positions for the substitution in the oxadiazole heterocyclic ring system. 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles were prepared by both microwave-assisted and conventional method of synthesis. The starting material 2-methyl-4-nitro-imidazole, used in the preparation of hydrazide, was obtained commercially. The 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles were prepared by the microwave irradiation of 2-methyl-4-nitro-1-imidazo acetohydrazide, with appropriate carboxylic acids in the presence of phosphorous oxychloride [15].

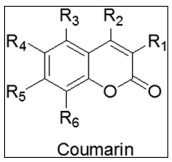
Similarly, the reaction was also carried out by the conventional method by refluxing an intimate mixture of hydrazide with an appropriate carboxylic acid in phosphrous oxychloride in an oil bath. Reactions of 4-substituted benzoic acid derivatives with (N-isocyanimino)-triphenyl phosphorane proceed smoothly at room temperature to lead to the corresponding 2-aryl-1,3,4-oxadiazoles through an intramolecular aza-Wittig reaction. Several synthetic methods have been reported for the preparation of (N-isocyanimino)-triphenyl phosphorane. There are several reports for the use of (N-isocyanimino)-triphenyl phosphorane in the synthesis of metal complexes. 2-Aryl-1,3,4-oxadiazole derivatives were prepared from 4-substituted benzoic acid derivatives and (N-isocyanimino)-triphenyl phosphorane in excellent yields under neutral conditions [16]. A suspension of salicylic hydrazide/thiosalicylic acid was prepared with toluene and acetic anhydride or with an acid chloride and an equimolar quantity of methanesulfonic acid. The suspension was refluxed at room temperature to give 1,3,4-oxadiazoles. Treatment of salicylic semicarbazides, which were readily obtainable by the reaction of salicylic hydrazide/thiosalicylic acid with isocyanates, under Appel's dehydration condition (Ph3P/CCl4/Et3N) smoothly afforded 1,3,4-oxadiazoles through carbodiimide intermediates followed by intramolecular cyclization reaction and hydride shift [17].

Synthesis of 3-carbethoxy coumarin salicylaldehyde and ethyl malonate was dissolved in absolute ethanol and to this mixture was added piperidine and glacial acetic acid. This mixture was heated under refluxed. The hot solution was transferred to an Erlenmeyer flask. Hot water was added to the solution, the product crystallized out rapidly as the solution cooled, the mixture was stirred from time to time as crystallization proceeded, and stored overnight in a refrigerator. The crystalline product was collected by filtration and washed with ethanol

and dried in air. Mol. Wt. 218; Yield: 82%; M.p: 245 0C; Rf. value: 0.65 (Ethyl acetate: acetone [9;1]) ; IR:(KBr v cm-1); 3090 (aromatic C-H stretching), 1680(C=O, coumarin), 1750(C=O ester), 1131(C-O ester), 800 (aromatic C-H bend).1H NMR (CDCl3) δ ppm1HNMR (DMSO) δ ppm: 2.4 (2H, CH3); 3.4(2H, OCH2: 6.2-8.2 (Ar-H, 9H) Mass- M+ synthesis of 2 – oxo – 2H – chromene -3 – carbohydrazide peak (m/z)218, Base peak (m/z)145 [18].

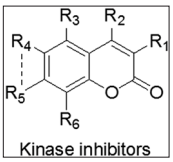
BIOLOGICAL ACTIVITIES OF COUMARIN AND OXADIAZOLE

Coumarin



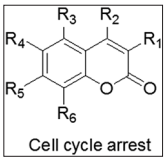
Kinase inhibitors

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. As all these effects are initiated by the activation of kinases, they are the key targets for inhibition by coumarins and their derivatives [19].



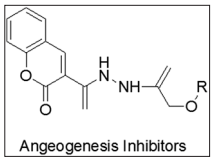
Cell cycle arrest

Coumarins are useful in arresting various phases of cell cycle such as G0, G1, S, and M phase that will eventually lead to apoptosis. They are found to initiate apoptosis by caspase-dependent intrinsic pathway and alteration in the cellular level of Bcl-2 family proteins [20]. Mitochondrial potential gets highly depleted due to an increased expression of proapoptotic Bax/Bak and intracellular reactive oxygen species. Further this, it results in release of cytochrome c from the mitochondria which lowers the matrix metalloproteinase and translocates into the cytoplasm with the activation of initiator caspase-9 and extracellular caspases-3/7. Tumour suppressor proteins p53 and its transcriptional target PUMA are upregulated. PUMA interacts with anti-apoptotic Bcl-2 family proteins, promotes the activation of Bax/Bak, and has necessary role in multiple apoptotic models [21].



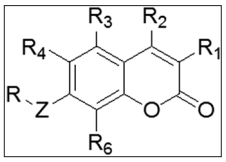
Angiogenesis inhibitors

Coumarin derivatives also act through angiogenesis. They have been found to prevent angiogenesis by inhibiting fibroblast growth factor-2-mediated proliferation, migration, and tubule formation. Coumarin derivatives were also observed to decrease the expression of vascular endothelial growth factor at mRNA level through nuclear factor-κB and phosphorylation of IKKα; interestingly, with this phosphatidylinositide 3-kinases (PI-3K)/Akt, signalling pathway remains unaffected [22].



HSP90 inhibitors

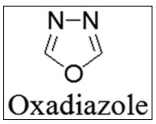
A number of experiments are already been carried out and many are still going in progress to inhibit all the eight hallmarks of cancer by targeting HSP90. Coumarins are found to bind directly on HSP90 which is upregulated in many cancers. Many proteins are also responsible for transformation of normal cells to cancerous cells. Coumarins also degrade cochaperone and proteins which ultimately results in antiproliferative effect. Coumarins are reported to cause *in vivo* and *in vitro* depletion of the key regulatory HSP90-dependent kinases including Src, Raf-1, and ErBB2-a protein in humans encoded by ErBB2 gene [23].



Antimicrobial agents

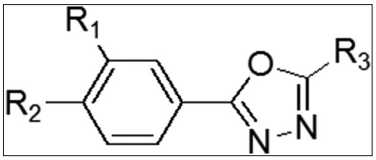
The thioemicarbazones acts as a key intermediate in the novel preparation of important compounds with good antimicrobial activity such as thiazolidin-4-one derivatives. These thiazolidine-4-one derivative possessed comparable activity to ampicillin and chloramphenicol at a concentration 25 µg/ml. Also, 4-methylcoumarin-thiazolidine-4-one hybrids were reported to exhibit good antimicrobial activity; the thiazolidine-4-one had comparable activity to ciprofloxacin and griseofulvin at 10 µg/ml and the 4-methylcoumarin-thiazolidine-4-one possessed potent antifungal activity with minimum inhibitory concentration value of 0.10 µg/ml. Therefore, the purpose of this work was to study the effect of hybridizing 7-hydroxy-4-methylcoumarin and their 7-alkoxy analogs with different N4-substituted thiosemicarbazone that were cyclized into the C5-substituted-thiazolidine-4-one ring. The antimicrobial activity of new compounds was evaluated [24].

Oxadiazole

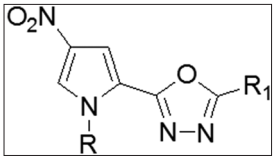


Antimycobacterial activities

Macaev *et al.* had been reported with synthesis of 5-aryl-2-thio-1,3,4-oxadiazole derivatives were screened for their antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv [25].



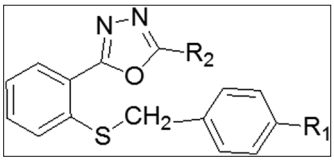
Rane *et al.* had been reported with synthesis and antimicrobial evaluation of 42 novel 4-nitropyrrole-based 1,3,4-oxadiazoles. The synthesized molecules were evaluated for antibacterial, antifungal, and antitubercular activities [26].



Anticonvulsant activity

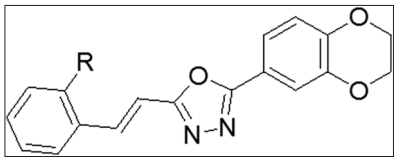
A series of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles was designed and synthesized as anticonvulsant agents.

The introduction of an amino group in position two of 1,3,4-oxadiazole ring and a fluoro substituent at para position of benzylthio moiety had the best anticonvulsant activity [27].

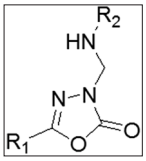


Antitumor activity

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. Among them, compound 7a showed the most potent biological activity against human umbilical vein endothelial cells [28].

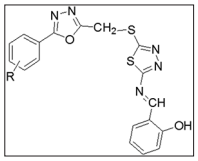


Recently, some new 3-(2-methoxyphenylaminomethyl)-5-(2-bromophenyl)-1,3,4-oxadiazoline-2-thione derivatives has been found to possess considerable anti-tumor agents property [29].

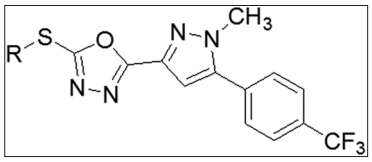


Anticancer activity

Chen *et al.* had been reported with the synthesis of novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff base moiety were designed, synthesized, and evaluated for their *in vitro* antitumor activities against SMMC-7721, MCF-7, and A549 human tumor cell lines by CCK-8 assay [30].



Poojary *et al.* had been reported with the design, synthesis, and biological evaluation of a novel series of 1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl-)phenyl pyrazole moiety as cytotoxic agents [31].



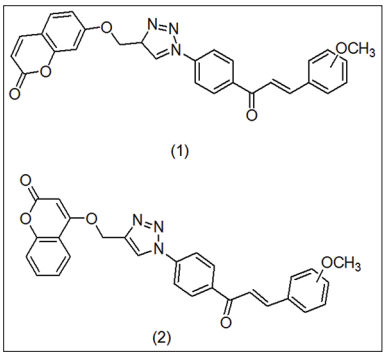
COUMARIN AND OXADIAZOLE HYBRIDS WITH DIFFERENT HETEROCYCLIC COMPOUNDS

Indolyl–coumarin hybrids

Sangshetti *et al.* [32] synthesized series of some new combination of hetrocycles having the coumarin and indole linked through chalcone-like chain and same were evaluated in vitro antileishmanial activity. Since the entire three nucleuses were also found to possess antioxidant activities; therefore, their antioxidant screening too performed using DPPH-radical scavenging method. To clarify and understand the probable binding mode of synthesized compounds for their antileishmanial activity, the compounds were docked for possible targets for anti-leishmanial activity. We had also predicted their ADME properties *in silico* to suggest the suitability of any of the new compounds for further drug development.

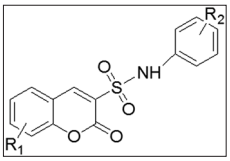
Coumarin-chalcone hybrids

A series of coumarin-chalcone hybrids has been synthesized and evaluated for their *in vitro* cytotoxicity against a set of four human cancer cell lines and normal fibroblasts. Pingaew *et al.* synthesized two sets of coumarin chalcone derivatives (1,2) linked by a 1,2,3-triazole ring through the azide/alkyne dipolar cycloaddition and their cytotoxicity was screened *in vitro* against a panel of four cancer cell lines, including HuCCA-1 (cholangiocarcinoma), HepG2 (hepatocellular carcinoma), A549 (lung carcinoma) using MTT assay, and MOLT-3 (lymphoblastic leukemia) using XTT assay [15]. It was revealed that majority of the hybrid compounds showed cytotoxicity against MOLT-3 cells with IC50 values ranging between 0.53 and 79.49 μM; among them, compounds bearing trimethoxy-substituted B-ring selectively inhibited growth of MOLT-3 cells. The most potential compound bearing 4-triazole on A-ring and 2,3-DiOCH3 on B-ring of (2) displayed significant cytotoxicity against HuCCA-1 (IC50 = 4.81 μM), followed by A549 (IC50=7.95 μM) and HepG2 (IC50 = 8.18 μM) with non-toxic to non-cancerous vitro cell line [33].



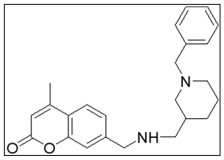
Coumarin-sulfonamide hybrid

Reddy *et al*. synthesized coumarin-3-(N-aryl)-sulfonamides. The effect of all the compounds on the growth of human tumor cells in culture was evaluated using androgen receptor negative prostate (DU145), non-small cell lung carcinoma (H157), estrogen-receptor negative breast (BT20), colorectal (DLD-1), and chronic myeloid leukemia (K562) cell lines. The establishment of dose-response of each cell line was done by determining the number of viable cells after 96 hrs of continuous treatment against five different concentrations (1-100 μM range) of each compound. The activation of JNK1 by these compounds as shown in immune complex kinase assay clearly showed that they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway [34].



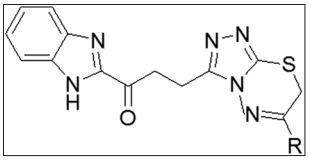
Donepezil-coumarin hybrids

On combining the N-benzylpiperidine moiety of donepezil with coumarin into in a single molecule, novel hybrids with ChE and MAO-B inhibitory activity were designed and synthesized. The biological screening results indicated that the most of compounds displayed good potent inhibitory activity for AChE and BuChE, and clearly selective inhibition to MAO-B [35].



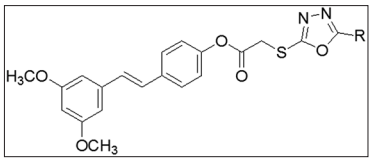
Benzimidazole-oxadiazole hybrid

Depending on the heterocyclic nucleus of bendamustine, a series of four benzimidazole derivatives was designed and synthesized starting from 4-(1H-benzo-imidazol-2-yl)-4-oxo-butanehydrazide. In the rational design of target molecules, the benzimidazole ring of bendamustine was retained and the bis-(chloroethyl) amine group (mechlorethamine) was substituted with several biologically active scaffolds such as oxadiazole, thiadiazole, and triazolothiadiazines, in the hope of obtaining novel cytotoxic agents with improved efficacy and safety. Cytotoxic activities of the designed analogs were carried out at the National Cancer Institute (NCI), USA, against full NCI 60 human cell lines [36].



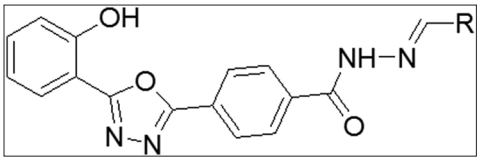
Resveratrol-oxadiazole hybrid

Novel classes of resveratrol-oxadiazole hybrid compounds were synthesized to screen for their *in vitro* antiproliferative activity against human cancer cell lines. All the compounds showed good antiproliferative activity than the reference compound resveratrol. Resveratrol-oxadiazole hybrid compounds may possibly be used as a good leads for the development of new antiproliferative agents. Resveratrol-oxadiazole analogs were prepared from reaction of resveratrol bromides and with 1,3,4-oxadiazole-2-thiones. These two coupling partners resveratrol bromides and 1,3,4-oxadiazole-2-thiones were synthesized from commercially available starting materials [37].



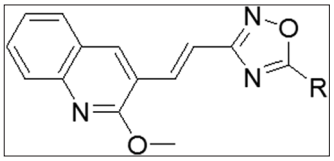
Oxadiazole-benzohydrazone hybrids

A series of novel compounds consisting of oxadiazole-benzohydrazone hybrids was synthesized through a five-step reaction sequence and then evaluated for their β-glucuronidase inhibitory potential. β-glucuronidase is an enzyme that catalyzes cleavage of glucuronosyl-O-bonds. This enzyme is involved in many diseases such as inflammation of joints such as rheumatoid arthritis. While in some cases, overexpression of this enzyme is reported to cause liver diseases and AIDS. Besides that, β-glucuronidase also plays an important role in diseases such as urinary tract infection, epilepsy, renal disease, rejection of transplantation, larynx, and breast. Various studies had been carried out to show that bacterial β-glucuronidase inhibitor decreases carcinogen-induced colonic tumors [38].



Quinoline-oxadiazole hybrids

Novel quinoline-oxadiazole hybrid compounds were designed based on stepwise rational modification of the lead molecules and to enhance bioactivity and improve drug likeness. The hybrid compounds synthesized were screened for biological activity against mycobacterium tuberculosis H37Rv and for cytotoxicity in HepG2 cell line [39].



CONCLUSION

Coumarin and oxadiazole derivatives have received increasing attention for their wide biological and pharmacological activities. We summarized the anti-inflammatory, anticoagulant, and anticancer activity for natural and synthesized coumarins and oxadiazoles. The anticancer effect of the coumarins and oxadiazoles is the most important one in these biological activities and the G-quadruplex interacting with coumarins may be a new target of the proto-oncogene for further cancer treatment and 1,3,4-oxadiazoles derivatives are also potent anticancer agents. The review is of importance for the design and development of the coumarin and oxadiazole derivatives as novel lead molecules for disease therapy.

REFERENCES

1. American Institute for Cancer Research Diet and Cancer Project, Food, Nutrition and the Prevention of Cancer: A Global Perspective American Institute for Cancer Research. p997.
2. Cooper GM. Elements of Human Cancer. Boston; Jones and Bartlett Publishers; 199.
3. Chohan ZH, Supuran CT. Synthesis, docking study and anticancer activity of coumarin substituted derivatives of benzothiazole. J Comput Methods Mol Des 2012;2 (1):51-60.
4. Thasneem CK, Biju CR, Babu G. Synthesis and antimicrobial study of chalcone linked 1,3,4-oxadiazole derivatives. World J Pharm Pharm Sci 2014;4(1):643-55.
5. Shah RC. New Synthetical Methods in Coumarins Chemistry. Symposium; 1938. p. 26-7.
6. Sandhu S, Bansal Y, Silakari O, Bansal G. Coumarin hybrids as novel therapeutic agents. Bioorg Med Chem 2014;22(15):3806-14.
7. Boström J, Hogner A, Llinàs A, Wellner E, Plowright AT. Oxadiazoles in medicinal chemistry. J Med Chem 2012;55(5):1817-30.
8. Savarino A. A historical sketch of the discovery and development of HIV-1 integrase inhibitors. Expert Opin Investig Drugs 2006;15:1507-22.
9. Rajagopalan V, Corpuz EO, Hubenschmidt MJ, Townsend CR, Asai DJ, Wilkes DE. Analysis of properties of cilia using *Tetrahymena thermophila*. Methods Mol Biol 2009;586:283-99.
10. Chand M, Gupta A, Subhash C. Jain biological profile of coumarins (7-hydroxy-4-methyl-2hbenzopyran-2-ones). W H J Chem Soc 1868;21:53.
11. Krishna MH, Thriveni P. Synthesis of coumarins via Pechmann reaction using Cr(NO3)3. 9H2O as a catalyst under microwave irradiation. H Chem Ber 1884;17:929-6.
12. Pechmann H, Duisberg C. Synthesis of the fluorescent amino acid rac-(7-hydroxycoumarin-4-yl)ethylglycine. Berichte 1883;16:119.
13. Knoevenagel E. Berichte knoevenagel reaction in [MMIm][MSO4]: Synthesis of coumarins. Molecules 1898;31:2585-96.
14. Ferroud D, Collard J, Klich M, Dupuis-Hamelin C, Mauvais P, Lassaigne P, *et al.* Synthesis and biological evaluation of coumarincarboxylic acids as inhibitors of gyrase B. L-rhamnose as an effective substitute for L-noviose. Bioorg Med Chem Lett 1999;9(19):2881-6.
15. Aboraia AS, Abdel-Rahman HM, Mahfouz NM, El-Gendy MA. Novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: Promising anticancer agents. Bioorg Med Chem 2006;1:1236-46.
16. Ramazani A, Ahmadi E, Kazemizadeh AR, Dolatyari L, Noshiranzadeh N, Eskandari I, *et al*. Phosphorus, sulphur. Silicon Relat Elem 2005;180:2419.
17. Aydogan F, Turgut Z, Ocal N. Synthesis and electronic structure of new aryl- and alkyl-substituted 1,3,4-oxadiazole-2-thione derivatives. Turk J Chem 2002;26:159-69.
18. Biju CR, Ilango K. Docking investigation, synthesis and cytotoxic studies of substituted oxadiazole derivatives. Int J Pharm Pharm Sci 2012;4(3):262-5.

19. Singh N, Sarkar J, Sashidhara K, Ali S, Sinha S. Anti-tumour activity of a novel coumarin–chalcone hybrid is mediated through intrinsic apoptotic pathway by inducing PUMA and altering Bax/Bcl-2 rati. Apoptosis 2014;19:1017-23.
20. Saidu NE, Valente S, Bana E, Kirsch G, Bagrel D, Montenarh M. Coumarin polysulfides inhibit cell growth and induce apoptosis in HCT116 colon cancer cells. Bioorg Med Chem 2012;20:1584-94.
21. Vazquez R, Riveiro ME, Vermeulen M, Mondillo C, Coombes PH, Crouch NR, *et al.* Toddaculin, a natural coumarin from *Toddalia asiatica*, induces differentiation and apoptosis in U-937 leukemic cells. Phytomedicine 2012;19:737-43.
22. Pan R, Dai Y, Gao XH, Lu D, Xia YF. Inhibition of vascular endothelial growth factor-induced angiogenesis by scopoletin through interrupting the auto phosphorylation of p53 and its transcriptional target PUMA are up regulated receptor 2 and its downstream signaling pathways. Vasc Pharmacol 2011;54:18-26.
23. Kusuma BR, Khandelwal A, Gu W, Brown D, Liu W, Vielhauer G, *et al*. Synthesis and biological evaluation of coumarin replacements of novobiocin as HSP90 inhibitors. Bioorg Med Chem 2014;22:1441-51.
24. Amin KM, Abou-Seri SM. Synthesis and biological evaluation of novel coumarin derivatives as potential antimicrobials agents. Int J Pharm Pharm Sci 2016;8(4):109-16.
25. Fliur M, Zinaida R, Serghei P, Veaceslav B, Ghenadie R, Nathaly S, *et al*. The structure–antituberculosis activity relationships study in a series of 5-aryl-2-thio-1,3,4-oxadiazole derivatives, Bioorg Med Chem 2011;19:6792-807.
26. Rane RA, Bangalore P, Borhade SD, Khandare PK. Synthesis and evaluation of novel 4-nitropyrrole-based 1,3,4-oxadiazole derivatives as antimicrobial and anti-tubercular agents. Eur J Med Chem 2013;70:49-58.
27. Zarghi A, Faizi M, Shafaghi B, Ahadian A, Khojastehpoor HR, Zanganeh V, *et al*. (2005) Design and synthesis of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles as benzodiazepine receptor agonists. Bioorg Med Chem Lett 2005;15:3126-9.
28. Sun J, Li MH, Qian SS, Guo FJ, Dang XF, Wang XM, *et al*. Synthesis and antitumor activity of 1,3,4-oxadiazole possessing 1,4-benzodioxan moiety as a novel class of potent methionine aminopeptidase type II inhibitors. Bioorg Med Chem Lett 2013;23:2876-9.
29. Shahzad SA, Yar M, Bajda M, Jadoon B, Khan ZA, *et al*. Synthesis and biological evaluation of novel oxadiazole derivatives: A new class of thymidine phosphorylase inhibitors as potential anti-tumor agents. Bioorg Med Chem 2014;22:1008-15.
30. Salimon J, Salih N, Yousif E, Hameed A, Kreem A. Synthesis and pharmacological evaluation of 9(10H)-acridone bearing 1,3,4-oxadiazole derivatives as antimicrobial agents. Arab J Chem 2010;3:205-10.
31. Ren J, Wu L, Xin WQ, Chen X, Hu K. Synthesis and biological evaluation of novel 4b-(1,3,4-oxadiazole-2-amino)- podophyllotoxin derivatives. Bioorg Med Chem Lett 2012;22:4778-82.
32. Vaso K, Behrami A, Govori SN. Synthesis and antibacterial activity of 4-(4 hydroxyphenylamine)-3-[1-(phenylhydrazine]-2H-[1]-benzopyran-2-one. The comparison of the antibacterial activity with standard drugs. Montenegro Podgorica 2012;11:93.
33. Pingaew R, Saekee A, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, *et al.* Synthesis, biological evaluation and molecular docking of novel chalcone-coumarin hybrids as anticancer and antimalarial agents. Eur J Med Chem 2014;85:65-76.
34. Agarwal R. Synthesis and biological screening of some novel Coumarin derivatives. Biochem Pharmacol 2000;6:1042-51.
35. Pisani L, Muncipinto G, Miscioscia TF, Nicolotti O, Leonetti F, Catto M, *et al.* Discovery of a novel class of potent coumarin monoamine oxidase B inhibitors: Development and biopharmacological profiling of 7-[(3-chlorobenzyl)oxy]-4-[(methylamino)methyl]-2H-chromen-2-one methanesulfonate (NW-1772) as a highly potent, selective, reversible, and orally active monoamine oxidase B inhibitor. J Med Chem 2009;52:6685-706.
36. Husain A, Rashid M, Shaharyar M, Siddiqui AA, Mishra R. Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: New anticancer agents. Eur J Med Chem 2013;62:785-98.
37. Reddy MA, Jain N, Yada D, Kishore C, Vangala JR, P Surendra R, *et al.* Design and synthesis of resveratrol-based nitrovinylstilbenes as antimitotic agents. J Med Chem 2011;54:6751-60.
38. Zawawi NK, Taha M, Ahmat N, Wadood A, Ismail NH, Rahim F, *et al*. Novel 2, 5-disubtituted-1, 3, 4-oxadiazoles with benzimidazole backbone: A new class of β-glucuronidase inhibitors and in silico studies. Bioorg Med Chem 2015;23:3119-25.
39. Jain PP, Degani MS, Raju A, Ray M, Rajan MG. Rational drug design based synthesis of novel arylquinolines as anti-tuberculosis agents. Bioorg Med Chem Lett 2013;23(22):6097-105.