Coumarinsulfonamide : A Highly Versatile Scaffold In Drug Discovery

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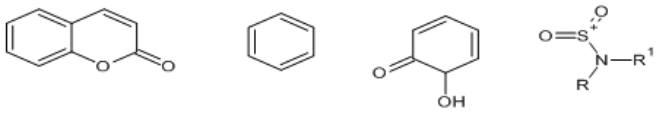
Abstract- *The heterocyclic pharmacophore coumarin sulfonamide serves as the central structural motif in a variety of medicinal scaffolds and analogues. Coumarin sulfonamides are privileged and essential templates with a wide range of uses in pharmacology, pharmaceutics, and medicine. The biomedical properties of coumarin sulfonamide are diverse and many, including anti-bacterial, antiviral, antifungal, anti-inflammatory, and anti-cancer. On the basis of structure-activity relationships (SAR), this review paper focuses on the structural characteristics of coumarin sulfonamide derivatives in the treatment of several fatal diseases. Numerous studies are cited in this review article that summarize and discuss the various substitutions around the coumarin sulfonamide nucleus. These substitutions have a wide range of biological activities and therapeutic potential, which has attracted many researchers looking to use the coumarin sulfonamide skeleton for drug discovery and the development of novel therapeutic agents.*

Keywords- coumarin sulfonamide, biological activities, antimicrobial, anti-cancer, anti-inflammatory, anti-oxidant.

I. INTRODUCTION

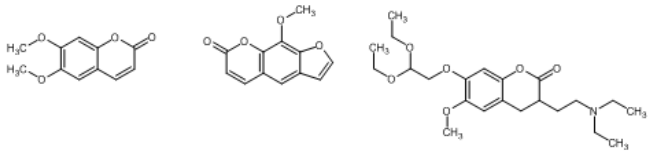
Natural lactones, coumarins are benzene rings fused to -pyrones in a class of fused six-membered oxygen-containing benzoheterocycles. Many therapeutic medications contain the pharmacologically active group found in sulfonamides, SO2 NH. Because of their intriguing, adaptable, and broad-spectrum biological actions, coumarins have attracted the attention of synthetic scientists as well as medicinal chemists and pharmacists. It has been demonstrated that coumarin and its derivatives are important starting points for the synthesis of a number of therapeutic medicines. Coumarin is the building block for a wide variety of chemical structures with intriguing biological properties, promising biological profiles, and therapeutic uses. These properties include those for anti-cancer, anti-HIV, anti-diabetic, antiviral, antiproliferative, antithrombotic, and antimicrobial agents, as well as anti-inflammatory, anti-psoriasis, anti-inflammatory, vasodilator, and anticoagulant properties. Figure 2 displays a few commercially available medications based on coumarin.



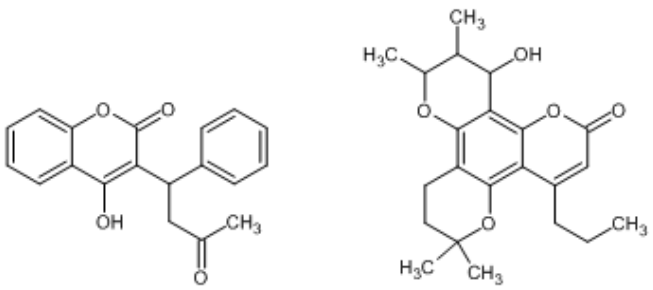
1 2 3 4

Figure 1 Structure of coumarin (1), benzene (2), α-pyrone (3) and sulfonamide (4).

Antibacterial, anti-inflammatory, anti-tumor, anti-carbonic anhydrase, anti-HIV, antimicrobial, anti-neoplastic, anti-convulsant, and anti-cancer properties are all exhibited by the sulfonamide molecule itself. Figure 3 displays some marketed medications with a sulfonamide structure.



(Scoparone) 5 (8-Methoxypsoralen) 6 (Carbochromen) 7



(Warfarin) 8 (Calanolide A) 9

The anti-metastatic properties of various coumarin sulfonamide hybrid structures, including CAI17, were demonstrated.

Against human carbonic anhydrase IX and XII, sulfocoumarin and chlorophenyl modified coumarinsulonamide scaffolds shown astounding selectivity. The recent research on the medicinal value of multifunctional coumarin sulfonamide complexes, which showed significant anti-cancer, anti-bacterial, antiviral, antifungal, and anti-inflammatory actions, is summarized in this piece of literature.

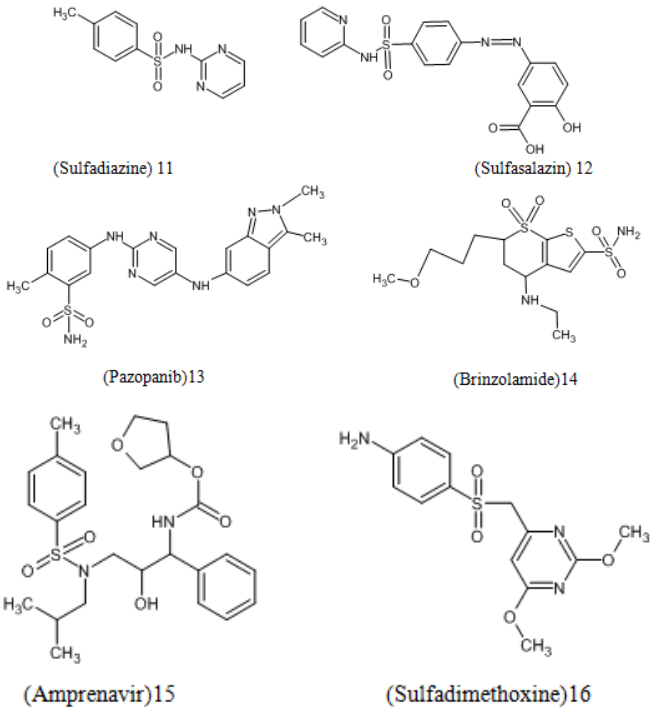


Figure 3 Structures of different sulfonamide based marketed drugs

Review of the Literature on the Pharmacological Characteristics of Coumarin Sulfonamide Frameworks:The Coumarin sulfonamide moiety can be thought of as a "Master Key" since it is a significant and favoured structural motif that is a vital component of numerous hybrid structural libraries of compounds intended to elicit a variety of pharmacological effects. The following classes can be used to categorize coumarin sulfonamide's pharmacological profile:

1. Anti-cancer activities
2. Anti-oxidant activities
3. Alkaline phosphatase inhibitory effects
4. Anti-inflammatory activities
5. Anti-bacterial activities
6. Antifungal activities

Anti-cancer Activities of Coumarin Sulfonamide Derivatives

The medical R&D (research and development) scientific community faces a huge difficulty in developing medications, medicinal therapeutic agents, and processes for safer treatment because cancer is a complex and occasionally fatal disease. Hybrid structures and scaffolds based on coumarin sulfonamide show great therapeutic potential against different cancer cell lines and carbonic anhydrases (CA). Carbonate dehydratases (CAs) are metalloenzymes that come in a variety of forms, including secreted CA isozymes, five membrane-bound isozymes, two mitochondrial forms, and five cytosolic forms. Specific isoenzymes displayed a variety of biological responses, while isozymes themselves had different and broad-spectrum inhibitory patterns. Diuretics, glaucoma medications, obesity and epilepsy medications, and anticancer treatments all have CAI inhibitory potential. Metalcomplexing anions and unsubstituted sulfonamides and their bioisosteres are the two primary types of CAIs. In order to produce a tetrahedral adduct with a non-protein zinc ligand, CAIs either bind to the enzyme's Zn2+ ion or create a trigonal bipyramidal species by adding to the metal coordination sphere.

Wang, et al. more information on the anti-cancer CAI properties of coumarin sulfonamide scaffolds is provided below.These synthetic scaffolds were tested against the MCF-7 and B16-F10 breast cancer cell lines. An analog of coumarin benzene sulfonamide based on substituted pyrimidines.

With an IC50 value of 0.024 M, scaffold (21) had the most anti-cancer action against the trans membrane tumor-associated isoform (hCAs-IX), outperforming AZA and SA (whose IC50 values were 0.028 and 0.29 M, respectively). hCA-I (cytosolic), hCA-II, hCA-IX, and hCA-XII (trans membrane, tumor-associated isozymes) were among the carbonic anhydrase inhibitor isoforms that Wagner et al. attempted to produce and test against.

The most effective inhibitor of the synthetic derivatives was the amino-based coumarindisulfonamide scaffold (22), which showed good inhibition against the hCA-IX inhibitor with a Ki value of 14 nM as opposed to AZA, which had a Ki value of 25 nM. In contrast to AZA, which had a Ki value of 2.5 nM, scaffold (22) demonstrated good inhibitory action against the hCA-XII inhibitor with a Ki value of 6 nM.

Kurt, et al. [54] created hybrid coumarylthiazole structures based on substituted benzene sulfonamides and established their anti-cancer action for various human carbonic anhydrase isoforms, including hCA I and hCA II. With an IC50 value of 5.63 M, the thiazole-based coumarin naphthalene sulfonamide scaffold (23) demonstrated the highest inhibition against hCA I. With an IC50 value of 8.48 M, derivative (23) likewise displayed impressive inhibition against hCA II.

(24) sulfonamide-bearing coumarin scaffolds that showed inhibition against distinct human carbonic anhydrase isoforms (hCA I, II, IX, and XII) were examined by Chandak et al. in their study published in Science [55]. In comparison to the reference chemical AZA, which had a Ki value of 25 nM,

the amino thiazole-based coumarin benzene sulfonamide compound (24) had strong inhibitory effect against hCA IX. When compared to AZA, scaffold (24) exhibited stronger inhibitory efficacy against hCA XII, with Ki values of 3.94 and 5.7 nM, respectively. Zaib and co.[56] variants of the produced amino benzene sulfonamide and thiourea were examined for their ability to inhibit carbonic anhydrase. Compared to AZA (IC50 value 0.96 0.18 M), the substituted amino sulfonylphenyl base coumarinthiourea (25) demonstrated to be the most effective inhibitor against hCA II (cytosolic enzymes). Due to the replacement of 3-aminosulfonylphenyl on the ortho position of the thiourea ring, scaffold (25) demonstrated the best inhibition.

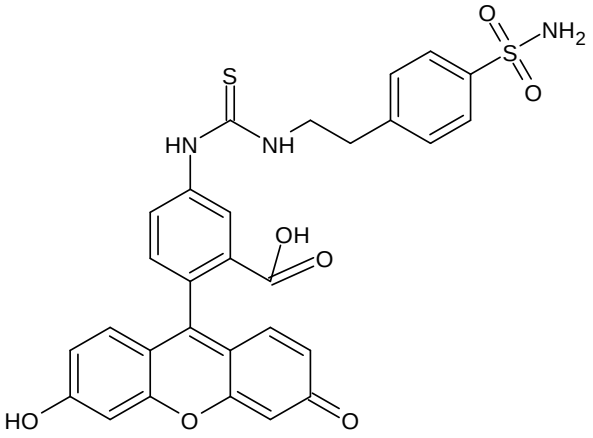
According to the research cited in this article, cancer treatment may benefit from the suppression of tumor-associated CA isozymes. The coumarin sulfonamides, which serve as anti-proliferative and therapeutic agents as detailed below, have proved a critical role in the treatment and management of numerous types of malignant tumors.

Amin, et al. [57] created coumarin-pyrazoline analogs with a phenylsulfonyl moiety and tested them against several tumor cell lines to see whether they had any anti-cancer properties. Remarkable anti-cancer activity was shown over the colon cancer cell line HCT-116 and the breast cancer cell line MCF7 by the chloro-phenylsulfonyl substituted pyrazol based methoxycoumarin scaffold (26). In contrast to the standard drug, doxorubicin, which had an IC50 value of 0.63 M, scaffold (26) demonstrated activity against the HCT-116 cell line with an IC50 value of 0.01 M. Aoki, et al. [58] developed a coumarin derivative-containing sulfonamide moiety and tested it for inhibitory efficacy. Scaffold (27) effectively inhibited the proliferation of HCT-116 cells with an IC50 value of 8 nM. Additionally, Scaffold (27) showed strong in vivo anticancer efficacy against the HCT 116 xenograft ED_{50} of 4.8 mg/kg.

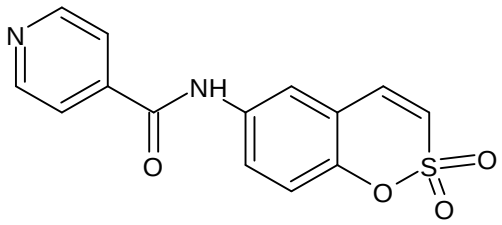
Pingaew, et al. [59] created 1, 2, and 3-triazole-based coumarin sulfonamide compounds and tested them against several cell lines for potential anti-cancer properties. When compared to the standard drugs ketoconazole and letrozole, which had IC50 values of 2.6 0.7 M and 0.0033 0.0004 M, accordingly, the dimethoxy substituted dihydroisoquinolin based coumarintriazole scaffold (28) demonstrated aromatase anti-cancer activities with Met374 and Ser478. A number of sulfonyl coumarin derivatives were tested against the HepG2 (hepatocellular carcinoma) cell line by Sawy, et al. [60]. HepG2 was resistant to the spread of the anti-angiogenic drug substituted amino sulfonyl coumarinpyrazol (29), which relied on MMP.

In order to study their anti-proliferative efficacy against the HepG2 (hepatocellular carcinoma), MCF-7 (breast cancer), and Caco-2 (colon cancer) cell lines, Sabt et al. [61] produced coumarin substituted sulfonamide derivatives. Comparing the IC50 value of the coumarin sulfonamide scaffold (30) based on phenyl thiazole to that of the reference medication doxorubicin, which had an IC50 value of 5.43 0.24 M, revealed that it had a remarkable high level of activity against HepG2 cells. The in-vitro anti-cancer and antibacterial effects of cyano-acetohydrazonoethyl-N-ethyl-N-methyl benzene sulfonamide analogues were studied by Debbabi, et al. [62]. With an IC50 value of 1.08 g/mL compared to the reference medication MTX (methotrexate), which had an IC50 value of 12.3 g/mL, the hydrazono-based coumarin benzene sulfonamide scaffold (31) demonstrated the best activity against MCF-7 When compared to the reference drug MTX (methotrexate), which had an IC50 value of 12.3 g/mL, MCF-7 had an IC50 value of 1.08 g/mL.

A variety of coumarin-benzimidazole hybrid structures were created by Holiyachi et al. [63] and their anti-cancer properties were assessed. When compared to the reference drug Adriamycin (ADR), the tosyl-benzimidazole substituted methyl coumarin scaffold (32) had excellent anti-cancer action against the HeLa (human cervix cancer cell line). When compared to ADR, the tosyl-benzimidazole substituted methoxycoumarin scaffold (33) likewise exhibited anti-cancer action against HeLa. When compared to ADR, the tosyl-benzimidazole substituted based bromo coumarin imidazole (34) had a surprisingly strong activity against HT 29. The SAR investigations revealed that the electronic effects of the CH3, OCH3, and Br substituents connected to the coumarin rings were responsible for the diverse anti-cancer action against various cell lines demonstrated by the synthesized compounds (32), (33) and (34).



(CAI 17)



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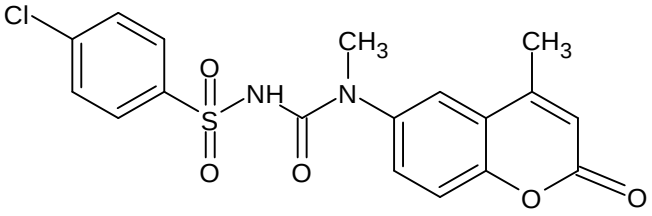

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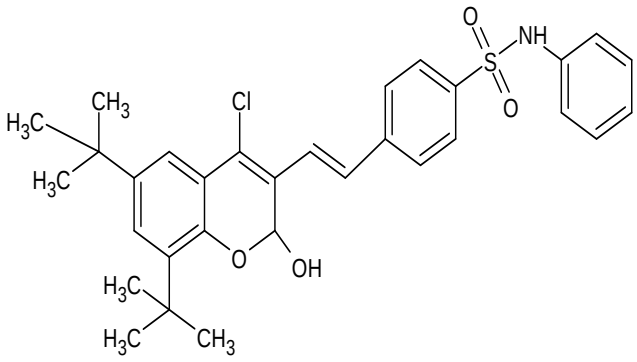

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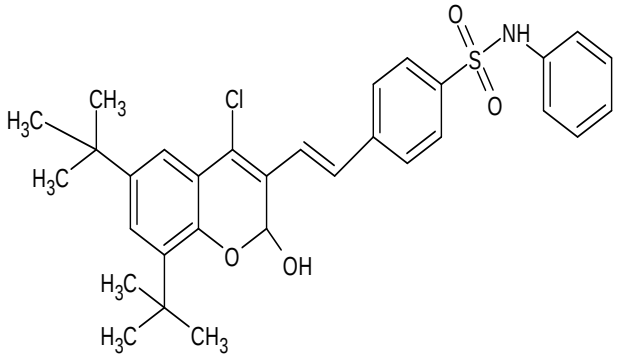

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Figure 5 Pyrimidine and coumarinyl sulfonamide scaffolds 20 and 21 which displayed anti-cancer activity.

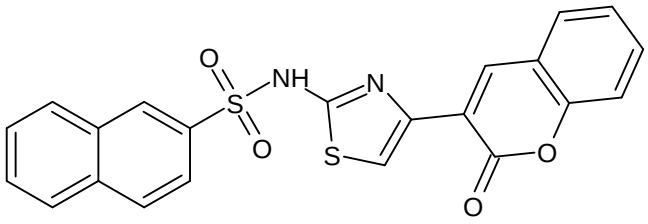

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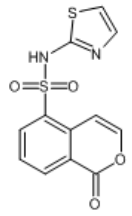
Figure 6 Thiazole based coumarin analogue 22 which displayed anti-cancer activity

Anti-bacterial activities of coumarin sulfonamide derivatives

Mostajeran, et al. [1] described the synthesis of coumarin-6-sulfonamide compounds and evaluated their in vitro anti-bacterial activity against the bacteria ATCC6538 (Staphylococcus aureus) and ATCC35218 (Escherichia coli). The zone of inhibition (ZI) value of 24 mm for the thiazole-based coumarin sulfonamide scaffold (23) against S. aureus (ATCC6538) was remarkably high compared to that of the reference drugs ampicillin and chloramphenicol, which had ZI values of 28 mm and 19 mm, respectively. In comparison to ampicillin and chloramphenicol, which had ZI values of 15 and 22 mm, respectively, scaffold (23) demonstrated high anti-bacterial action against E. coli (ATCC35218).



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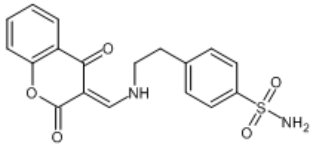

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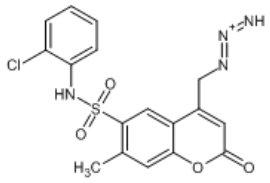

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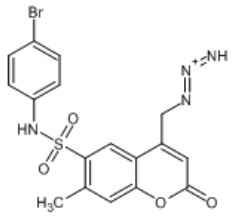

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The creation of coumarin-6-sulfonamide compounds was disclosed by Mostajeran, et al. [1] who also assessed their in vitro anti-bacterial effectiveness against the bacteria ATCC6538 (Staphylococcus aureus) and ATCC35218 (Escherichia coli). Comparing the zone of inhibition (ZI) values of the reference medications ampicillin and chloramphenicol, which had ZI values of 28 mm and 19 mm, respectively, the ZI value for the thiazole-based coumarin sulfonamide scaffold (24) against S. aureus (ATCC6538) was unusually high at 24 mm. displayed strong anti-bacterial effect against E. coli (ATCC35218) in comparison to ampicillin and chloramphenicol, which had ZI values of 15 and 22 mm, respectively.

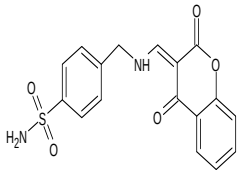
Numerous 4-azidomethyl coumarin compounds with sulfonamide content were created by Basanagouda, et al. [64] and have antibacterial action. The group of recently reported substances demonstrated in vitro anti-bacterial activity against

various bacteria strains, including Streptococcus faecalis (MTCC 3382), Staphylococcus aureus (MTCC 3160), Bacillus subtilis (MTCC 297), Pseudomonas aeruginosa (MTCC1034), Klebsiella pneumonia (MTCC 3384), and Escherichia coli (MTCC1089). The reference medication ciprofloxacin also had a MIC value of 1 g/mL, but the azidomethyl substituted coumarin based amide scaffold (25) demonstrated anti-bacterial action against S. faecalis via a MIC value of 1 g/mL. In contrast to ciprofloxacin, which had a MIC value of 1.0 g/mL, scaffold (25) demonstrated antibacterial efficacy toward P. aeruginosa.

When compared to ciprofloxacin, which likewise had a MIC value of 1.0 g/mL, scaffold (26) demonstrated anti-bacterial efficacy against K. pneumonia. Comparing the substituted azidomethyl coumarin-based amide to ciprofloxacin, which also had a MIC value of 1.0 g/mL, revealed that it was more effective at combating germs against S. faecalis. Comparing the antibacterial activity of scaffold (27) to ciprofloxacin, which had a MIC value of 1 g/mL, scaffold (27) had the strongest antibacterial activity against P. aeruginosa. When compared to ciprofloxacin, which also reported a MIC value of 1 g/mL against K. pneumonia, scaffold (27) demonstrated antibacterial efficacy.

Antifungal activities of coumarin sulfonamide derivatives

4-hydroxycoumarin sulfonamide hybrids were tested by Chohan et al. [65] for their antifungal efficacy in-vitro against the fungi A. flavus, T. longifusus, C. glaberata, M. canis, F. solani, and C. albicans. When compared to the reference medicine miconazole (MIC = 98.4 g/mL), the amino substituted coumarin benzene sulfonamide scaffold (28) shown significant effectiveness against M. canis with a MIC value of 74 g/mL. When compared to miconazole (MIC = 98.4 g/mL), the amino substituted pyrimidinyl based coumarin sulfonamide derivative (28) shown significant effectiveness against M. canis. When compared to miconazole (MIC = 73.25 g/mL), the substituted amino isoxazolylcoumarin benzene sulfonamide (29) had extremely strong efficacy against F. solani. Compound (29), which had a MIC value of 82 g/mL, outperformed the reference standard medicine miconazole, which had a MIC value of 73.25 g/mL, in terms of its strong anti-fungal efficacy against F. solani.



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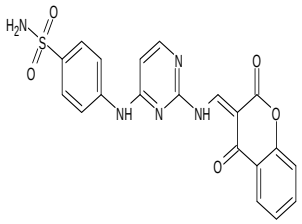

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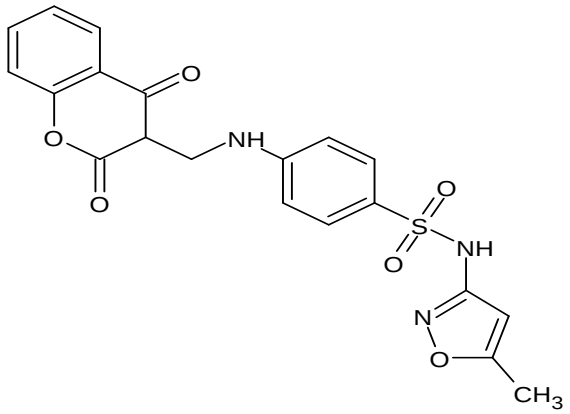

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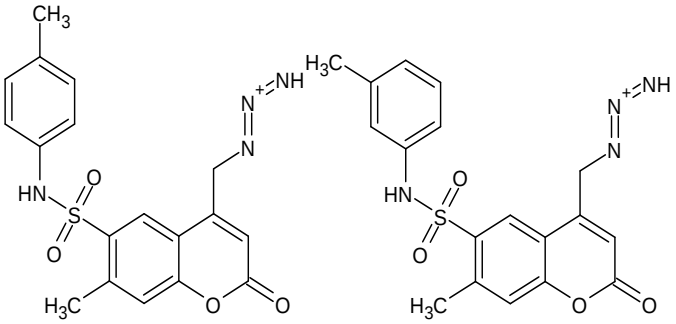
Coumarin sulfonamide derivatives with 4-azidomethyl substitutions were synthesized, according to Basanagouda et al. [64]. The antifungal activity of each of the produced coumarin sulfonamide derivatives was examined in vitro against a variety of fungal species, including Mucorfuscus, Candida albicans, Fusariumoxysporum, Aspergillusfumigatus, Penicilliumchrysogenum, and Aspergillusniger. Compared to the reference medication fluconazole (MIC = 8 g/mL), the substituted azidomethyl coumarin sulfonic acid scaffold (30) demonstrated excellent anti-fungal action against Candida albicans. With a MIC value of 4 g/mL compared to fluconazole's 8 g/mL, substituted azidomethyl-based coumarin sulfonic acid (31) demonstrated the highest anti-fungal effectiveness against C. albicans. Comparing its MIC value to fluconazole, which was 8 g/mL, the azidomethyl-based coumarin sulfonic acid derivative (31) showed action against C. albicans with a value of 4 g/mL.

II. CONCLUSION

The research reviewed in this article showed that coumarin sulfonamide scaffolds and their analogs exhibited a wide range of biological activities. As a result, these derivatives have a significant potential for the creation of novel therapeutic agents for the treatment of various illnesses. The enzyme inhibitory and anti-cancer activity profiles of the coumarin sulfonamide derivatives were encouraging. A wide range of biological actions in the areas of medicine, pharmaceutics, and pharmacology were demonstrated by the

coumarin sulfonamide scaffolds. According to the research described in this review article, some coumarin sulfonamide compounds are more potent and have superior therapeutic indices than the standard medications. On the basis of SAR, derivatives of coumarin sulfonamide showed good and promising activity against several bacterial and fungal strains as well as cancer cell lines. The biological profile of coumarin sulfonamide derivatives serves as a useful framework for the creation and development of improved therapeutics for the more secure management of a variety of disorders.



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