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THE RECENT PROGRESS OF SULFONAMIDE IN MEDICINAL CHEMISTRY

Khulood H. Oudah[a*], Mazin A.A. Najm[a], Ali B. Roomi [b,c], Hussein A.Al-sa'idy [d] and Fadi M. Awadallah[e]

[a] Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq.
[b] Ministry of Education, Directorate of Education Thi-Qar, Thi-Qar-64001, Iraq.
[c] College of Health and Medical Technology, Al-Ayen University, Thi-Qar-64001, Iraq.
[d]Marsh Research Center, University of Thi-Qar, Iraq.
[e] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Egypt.

Abstract
Sulfonamide compounds exhibit a wide range of targets and expansive biological activities. Chemistry of sulfonamide has a role in its manufacture in various forms as well as its integration with other compounds to increase the effectiveness against different diseases. Currently directed attention towards sulfonamide derivatives to act as an anti-cancer in addition to its previous action as an anti-inflammatory and its use in the treatment of Alzheimer's disease. There are various derivatives associated with sulfonamide and modern strategies to manufacture it in different forms so, in this review article, the major focus has been paid to the usage of sulfonamide compounds in treating multiple diseases, including anticancer, antimicrobial, anti-inflammatory, etc. Strategies for various designed compounds were discussed.

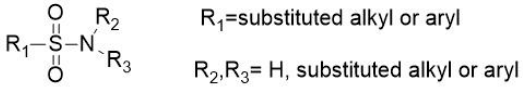
Keywords: Sulfonamide, CAIs, antibacterial, anticancer.

Corresponding Author:
Dr. Khulood H. Oudah
Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq.
E-mail: dr.khulood@alayen.edu.iq
ORCID: 0000-0002-5014-7129

1. INTRODUCTION

Due to the recent outbreak of diseases, researchers have been exploring for powerful compounds known to affect most diseases and developing them to become widespread and include different areas of diseases and for several targets.
Sulfonamide, a chemical class containing -SO_2N in its structure (figure 1), is one of these groups that have a wide range in the treatment of diseases ranging from antibiotics to modern use as an anti-cancer. An assortment of sulfonamide drugs has been combined because of their amazingly productive antimicrobial nature (1). To battle drug-resistance microorganism, best logical procedures incorporate release and advancement of new, economically, and progressively strong spearheading antibacterial specialists with least adverse effects (2). Sulfonamide derivatives have been the focal point of consideration for scientists and researchers for quite a while because of their wide group of biological activity. A new candidate was generated from a combination of a sulfonamide group with other known scaffolds. This leads to an extension of the use of the sulfa drug to covering disease rather than bacterial infection such as Alzheimer's disease (3).

Figure 1. The general structure of sulfonamide derivatives

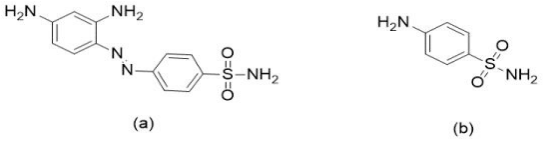


New era of sulfonamide uses is carbonic anhydrase inhibitors (CAIs) which enter many fields for instance antiglaucoma and anticancer (4). Despite the fact that this is demonstrated to be accomplished by numerous other medication atoms that don't have a sulfonamide centre, sulfonamides are still of extraordinary pertinence here since there is a fundamentally enormous library of biologically active and synthetically adaptable sulfa drugs. They can undoubtedly be adjusted at least one site to present multi-target properties combat an assortment of diseases(5).

2. Sulfonamide chemistry

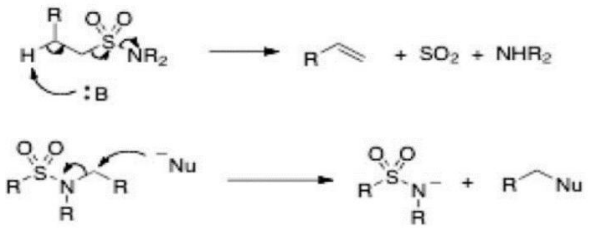
From 1935 discovery of the azo dye, **Prontosil** (figure 2) by *Gerhard Domagk* was the historical breakthrough of sulfonamide about medicinal chemists. Since then the presentation of the so-called "sulfa-drugs" had widespread uses such as antibiotic drugs(6).
It is frequently accepted that the sulfonamide component performs comparably to carbonyl compounds such as esters and amides and related sulfur compounds such as sulfones, sulfoxides and sulfonate esters. Whereas there's a few truth in this presumption, there are numerous more curiously contrasts in their reactivity, which can be the factor in spread uses of sulfonamide as a basic built in synthesis (7).

Figure 2. The structure of (a) Prontosil prodrug (b) sulfanilamide



Carbonyl compounds, sulfones, sulfonate esters and sulfonamides all apply an electron-withdrawing impact on encompassing particles both mesomerically and inductively. In any case, the action of the sulfonamide is the slightest electron-withdrawing ingredient of all of these series. *Roush et al* demonstrated that sulfonate ester which is very similar compounds are the greatest electron-withdrawing. They revealed that the activity of sulfonate was less towards nucleophilic addition reaction to simple thiol nucleophile compounds. Whereas carbonyl compound was the more active than sulfonate ester but less than sulfonamide in the rate of the reaction (8). Usually, beneath certain circumstances, it can act as a leaving group frequently with the removal of SO_2 (figure 3)(9).

Figure 3. Mechanism of action of sulfonamide (9)



One of the remarkable differences between carbonyl compounds and sulfonyl compounds is the resistance of the last mentioned to a nucleophilic displacement of leaving groups at the location α- to the sulfonyl unit. The sulfonyl group deactivates this location but nitrile and other withdrawing groups activate it (6).

3. Sulfonamide derivatives as target agents

From 1940 up-to-date the application of sulfonamide focuses on medicinal purposes for the treatment of various conditions such as antibacterial, antifungal, antiviral, and recently as anticancer. The discovery of large groups of sulfonamides with various biological activity is the most popular advantage of sulfonamide-derived drugs. Also, sulfonamide widespread use in many other diseases such as Alzheimer's disease (AD), new hit sulfonamide derivatives was designed their activity was in low concentrations (10). Other uses, central nervous system (CNS) disorders(11), psychosis,(12) diabetes,(13), and different cancers types(14). There have been numerous sulfa-derived compounds synthesized and distinguished as a multi-target candidate against different conditions, particularly within the past ten a long time. In spite of their action as a single target drug sulfonamide used widely as a multi-target agent due to their forced action on complex diseases such as cancers (15). The multi-target approach was introduced to the treatment of complex diseases because the later affected by different factors and not by a single factor. Moreover, medicinal chemistry lately focused on the treatment of various malignant growth types with one drug candidate (16).

Although numerous other medication particles that don't have a Sulfonamide centre, sulphonamides are still of incredible importance in this range since there is a fundamentally enormous library of biologically active and synthetically flexible sulfa-drug. They can effectively be adjusted at one or more destinations to present multi-target properties against various diseases (5).

4. Sulfonamide derivatives as antimicrobial agents

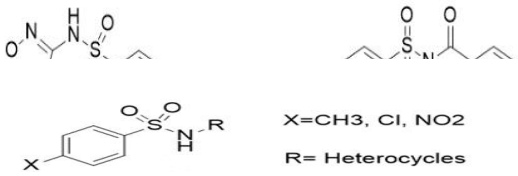
An important use of sulfonamide after its first discovery is its use as an antimicrobial drug. Important factors that make researchers interested in the production of Sulfonamide as an antibiotic, the first being the infinite progressively bacterial strains and their development. The second is the truth that sulfa-drugs are water-insoluble, which may be a property that supports to determine their dosage in addition to therapeutic efficiency because it may crystallize in the kidneys (1).

Ibrahim, H.R., *et al.* demonstrated an example of the coupling between sulfa drugs sulfamethoxazole (SMZ) and sulfobenzamide (SBM) (figure 4) with Ovotransferrin, transferrin proteins, the procedure depended on earlier information about the transferrin receptors (TfR) accordingly coupling these mixes would build their capacity to target pathogens when utilized as anti-microbial medications. The combination was evaluated with known target compounds triclosan (TCS), antimicrobial agents, which inhibit fatty acid synthesis by inhibition of enoyl-ACP reductase, to powerful their antimicrobial activity (17).

The associated structures were assessed in changing molar concentration against three bacterial strains (*E. coli, S. aureus* and *P. acnes*) in human colon epithelial cells HCT-116. They diminished the cell suitable quantities of the bacterial strains, even deleted them totally at higher molar proportions (17).

Figure 4. The structure of (a) sulfamethoxazole, (b) sulfobenzamide.

Another attempt to increase activation of sulfa drug of sulfomethoxazole and sulfobenzamide by modification of their branches with various groups such as methyl-, chloro-, and nitro-groups to the benzene ringside, while heterocycle



compounds were added to the other side of the drug in combination with N- (figure 5).

Figure 5. Sulfamethoxazole derivatives

This study proved that all substituent with an electron-withdrawing group was more active against strains of bacteria than donating groups that may be due to the high electronic effect of these groups (18). Moreover, Schiff-bases reactions were used to synthesize two sulfa derivatives through condensation of salicylaldehyde with sulfonamide derivatives and molecular docking was evaluated for the compounds (19).

5. Sulfonamide as scaffold for various diseases

Inhibitor properties of sulfonamide derivatives in many biological pathways lead to produced it as enzyme inhibitors such as carbonic anhydrase inhibitors (20) that used in various diseases conditions as well as uses as anti-hyperthyroidism (21), anticancer (20), and used in Alzheimer's disease.

5.1. Sulfonamide derivatives in the treatment of Alzheimer's disease

Although the correct mechanism of Alzheimer's disease is still indistinguishable, many compounds have been detailed to block different pathways related to it. a γ-secretase inhibitor is the main target for sulfonamide for the treatment of Alzheimer's. A few N-bridged bicyclic sulfonamides were synthesized and assessed as inhibitors of γ-secretase in comparison to a reference compound, GammaAPP, an exceedingly powerful known inhibitor of the enzyme.

The basic change of a progression of [3.3.1] bicyclic sulfonamide based γ-secretase (figure 6) inhibitors is depicted. Enhanced potency and in vitro stability was shown in the structure–activity-relationship (SAR) studies for modified ester compounds (3).

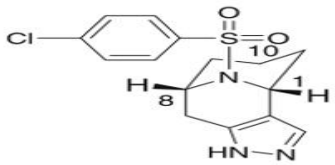


Figure 6. Representative N-bicyclic sulfonamide γ -secretase inhibitor. (GammaAPP) IC_{50}= 2nM, $t_{1/2}$ = 24min (3)

5.2. Sulfonamide derivatives as anticancer agents

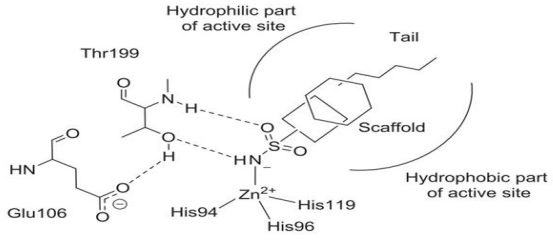
Since 1998, great attention occurred on utilizing sulfonamides for carbonic anhydrase (CA) inhibitors. CAs enzymes are zinc enzymes act by keeping a balance between carbon dioxide to bicarbonate in the tissue ($H_2O+CO_2 \rightleftharpoons H^+ + HCO_3^-$). They are consisting of more than 15 isoforms type of them. Every type may affect a different kinds of diseases and can use as a target for the treatment of these conditions such as antiglaucoma drugs, antimicrobial drugs, and anticancer drugs (22).

Supuran's group was confirmed that two main classes can inhibit CAs one of them is the metal complexing anions and the other is sulfonamides and other sulfa compounds with the general formula **RXSO2NH2,** whereas (X = O, NH or nothing) while (R = aryl; hetaryl; perhaloalkyl) (22).

The main isoform that acts as a target for anticancer drugs are hCA I, hCA II, hCA IX, hCA XII isozymes (23). In addition to overexpression of CAXII in many types of cancer (24), it's overexpression in breast cancer makes it target attraction for treatment of breast cancer especially after showing that CAXII isozymes regulated by Estrogen receptors in breast cancer cells (25).

There are four mechanisms of Carbonic anhydrase inhibitors; Zinc binding mechanism is the first, which include sulfonamides and bioisosteres, carboxylates, dithiocarbamates, and hydroxamates. Other mechanisms either by occlusion of the active site entrance, out of the active site binding, or anchoring to the metal-bound nucleophile (figure 7) (26).

Figure 7. Schematic illustration of the key interactions



between a primary sulfonamide and the hCA II active site as determined by X-ray crystallography(26)

C. T. Supuran *et al.*in 2001, with an extension of previous researches, reported the first systematic study of sulfonamide as CAIs with high strength of inhibition against a variety of cancer cell lines growth (4).

Their researches were based on the association of different branches of the aromatic and heterocyclic compounds of sulfonamide with different tails (figure 8). Thus, we obtain a good compound in terms of the physical properties required for medications such as water solubility, membrane impermeability, and other requirements for drug manufacturers that are important in drug design for new pharmacologically effective drugs (4).

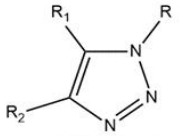
Figure 8. Sulfonamide tail with different substitutions

Lately many sulfonamide derivatives for example Pazopanib (figure 9) approved on 19 October 2009 for treatment of or use as a treatment for advanced/metastatic renal cell carcinoma and advanced soft tissue sarcomas(27). E7010, and E7070 have been stated as powerful anticancer agents and they are entered in progression clinical trials (figure 10).

Figure 9. The structure of FDA approval drug Pazopanib

Also Peerzada *et al.* in 2018 showed that tertiary aryl sulfonamides might serve as lead compounds within the advancement of non-zinc-binding inhibitors with anticancer properties that can moreover specifically inhibit CA IX isoforms (28).

Figure 10. The structure E7010, E7070 sulfonamide in



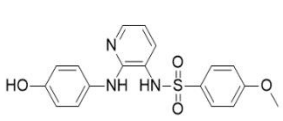
1,2,3-triazole

R_1,R_2=H ,electron withdrawingl, electrone donating, alkyl,aryl, others

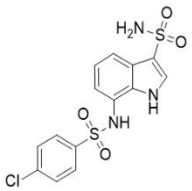
Pazopanib

clinical trials

Other strategies of sulfonamide design, N-sulfonamide ligand with copper (II) complex recently reported by Hangan AC *et al.* and their activity against cancer cells were validated (29).



E7010



E7070

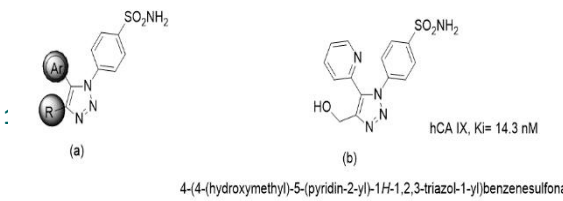
Furthermore, 1,2,3-triazole derivatives with sulfonamide moieties are very commonly utilized in anticancer drug development, particularly focusing on certain types of cancer. For instance, in 2017, Vats, Sharma *et al.* synthesized a series of 1,2,3-triazole with different derivatives (figure 11) such as sulfonamides, hydroxamates, carboxamides, carboxylic acids, carboxylic acid hydrazides, and CAIs inhibitors were considered for hCA I, II, IV, IX isoform (30).

Figure 11. The structure of triazole bearing hybrids

Their previous studies on sulfonamide compounds urged them to complete research in this field and manufacture new 1,2,3-triazole compounds with sulfonamides. When they compared the later study with their previous studies, they found that compounds with sulfonamide derivatives had more inhibitor action against hCA IX isoforms (31).

Also, a methyl group or small derivative in 1,2,3-triazole sulfonamide (figure 12) had great inhibitor action against CA IX isoforms than derivatives with large groups or heterocycle branches that cause crowding on the compound and thus hinder the binding with the enzyme also they were less effective inhibitors for all hCA isoforms. Also, sulfonamide compounds have been shown to display more efficacy on enzyme IX, which is considered a target for anticancer therapy (31).

Figure 12. (a) The general design of compounds, (b) activity



against CA enzyme

6. CONCLUSION

Sulfonamides and their subordinates keep on staying a critical some portion of novel medication structure and advancement against an assortment of complex ailments, alongside the progressing upgrades in their traditional use as anti-infection agents, antiviral or antifungal specialists. As multi-target approaches in medicate disclosure began to increase a lot of merited consideration as of late, so increased the work of sulfonamide subsidiaries as multi-target specialists.

In addition to their classical use of sulfonamide derivatives as antibacterial and antifungal, they have taken the spotlight to develop them to other uses such as treatment of Alzheimer's disease and as anticancer.

All through this overview, it was demonstrated that sulfonamide derivatives are utilized in different fields of drug detection. Also, we highlight some of their modern uses and some applications that are still being developed by researchers. We hope soon that there will be a larger breakthrough in the field of treatment on a wider level despite the side effects that have been proven on it.

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Competing interest statement

The authors declare no conflict of interest.

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