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Sulfonamide derivatives: Synthesis and applications

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Abstract

Sulfonamides belong to an important class of compounds which showed wide ranges of biological activities like antibacterial, antiviral, diuretic, hypo-glycemic, anticancer, anti-inflammatory and recently anti-covid-19. Over the last few decades, various pharmacological activities of sulfonamide conjugates were published. Moreover, many lead compounds with sulfonamide functionality are also in clinical trial for the treatment of various medical conditions. For these reasons, development of an efficient process for the synthesis of sulfonamides has always been in the focus for research in organic field synthesis. The most typical method for the synthesis involves reaction between primary or secondary amines and sulfonyl chloride in presence of organic or inorganic bases. Although this method is effective, but the nucleophilicity of amines may vary depending on the groups attached to it. In general, primary amines are highly reactive, whereas secondary amines show very low to almost nil reactivity. In this study, we have reviewed past and recent biological effects of some sulfonamide derivatives and some advances efficient synthetic procedures for some types of sulfonamides.

Keyword: Sulfonamide derivatives; Sulfa drug; Biological activity of sulfonamide; Sulfa drug synthesis; Antiviral

1 Introduction

Sulfonamides (sulfa drugs) firstly used systemically as preventive and chemotherapeutic agents against several illnesses (1). Many drugs containing this functional group are clinically used for treat different diseases including hypertension (2), bacterial infections (3), parasitic infection (4), inflammatory reactions (5), some types of tumors (6,7), Alzheimer's disease (8), several viral infections including corona virus (9) and, many other diseases (10). Sulfonamides are compounds which have a general structure represented by (fig 1) (10). After sulfonamides discovery, many chemical variations were studied and the best biological results were obtained from the compounds in which one hydrogen atom of the SO2NH2 group was replaced by heterocyclic ring (11). Recently thousands of sulfonamides derivatives have been discovered with various pharmacological actions. In this main structure R, R1 may be hydrogen, alkyl, aryl or hetero aryl etc.

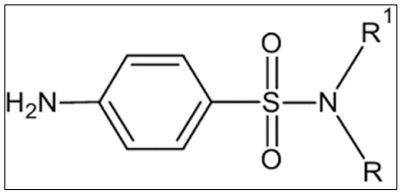

Figure 1 General structure of sulfonamides, if R=R1=H is sulfanilamide

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The aliphatic sulfonamides have the best antibacterial activity for Gram negative bacteria than Gram positive and this activity decreases as increasing length of carbon chain (12, 13). Several antimicrobial sulfonamides derivatives were prepared mainly by coupling between aromatic sulfonyl chlorides and heterocyclic primary amines like sulfacetamide, and sulfamoxole. While glipizide, and carbutamide which are anti-diabetic agents are synthesized by sulfonylureas pathway (fig 2) (14). Various novel and efficient strategies for the synthesis of sulfonamides are containing primary and secondary amine groups (14).

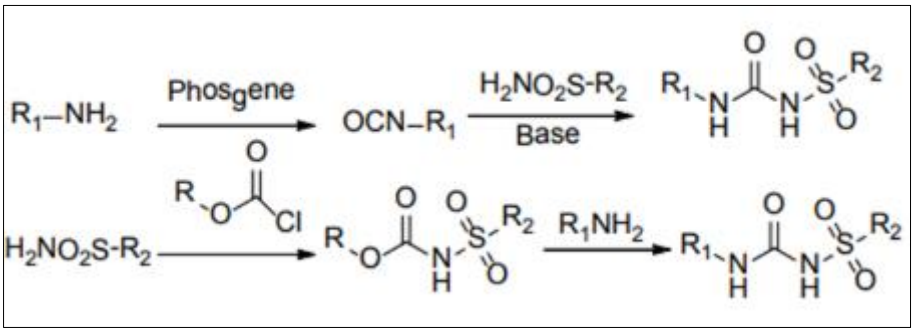

Figure 2 Synthesis of sulfonyl urea

The sulfonylation of amines with chlorides in the presence of base is the most typical preparing of sulfonamides. This method involves the nucleophilic attack by ammonia, primary or secondary amines with sulfonyl chlorides in the presence of a base. Although this method is efficient, it requires the availability of sulfonyl chloride, some of which are difficult to store or handle (15). The direct oxidative conversion of thiols into sulfonamides with H2O2-SOCL2 (fig 3) was reported by Bahrami *et al.,* (16) in which upon acts with amines, the corresponding sulfonamides were produced in excellent yield in very quickly (17). Sulfonamides were easily produced in good to high yield when aryl thiols carrying either electron withdrawing or electron donating substituents (18).

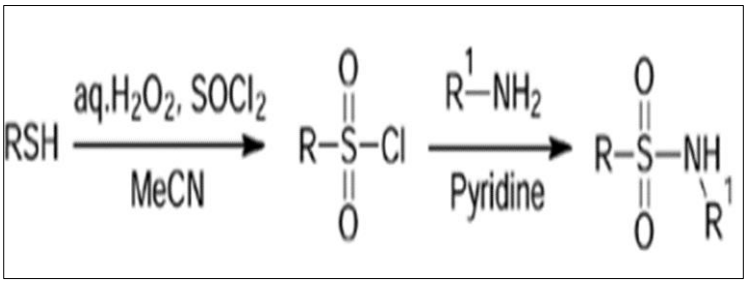

Figure 3 Conversion of thiols into sulfonamides with H2 O2 -SOCl2

In this study, we have focused on the synthesis, pharmacological mechanism of action of sulfonamides in number of diseases including Covid-19.

2 Chemistry and Chemical synthesis of sulfonamides

Chemically sulfonamides functional group is S(=O)2-NH2, a sulfonyl functional group is linked to an amine functional group. The general chemical formula is RSO2NH2, where R may be different organic group like alkyl or hetero-aryl, and may both of them are hydrogen, alkyl and aryl or hetero-aryl groups.

According to their roles, many synthetic methods have been developed for synthesis of sulfonamides and divided into two categories: 1st transition metal- free synthesis, 2nd transition metal catalyzed synthesis sulfonamide, which are subdivides reflecting to their kinds of chemical reaction by which they produced (19).

2.1 Transition metal-free synthesis of sulfonamide

Recently, sulfonamides prepared by nucleophilic reaction between amino compounds and sulfonyl chlorides in the presence of alkaline medium (fig 4) that considered as classical approach for synthesis of sulfonamides and has attracted big attention because its simplicity and good reactivity (19, 20, 21).

Figure 4 Nucleophilic reaction between amino compounds and sulfonyl chlorides in presence of a base

This synthesis pathway includes addition of base excess to scavenge (HCl) which generated through reaction, using heating is essential for less reactive substrate, purification steps often required because of side reaction product (22). The scope of this protocol is very wide which had covered construction of variety of primary, secondary and tertiary sulfonamides (23). Moreover, modifications of this standard method concern the using N-chlorosuccinimides (NCS) and tetrabutylammonium chloride-water system in acetonitrile delivered sulfonyl chloride in situ. Researchers have developed one pot-process for preparing sulfonyl azides from thiols under these conditions in the presence of NaN3. Jong *et al.,* reported this convenient one-pot synthesis of sulfonyl azides from sulfonic acids (24). The advantages of these modifications are excellent yields, availability and cheapest reagent, easy and clean workup, very fast reaction, and highly selectivity (fig 5) (25).

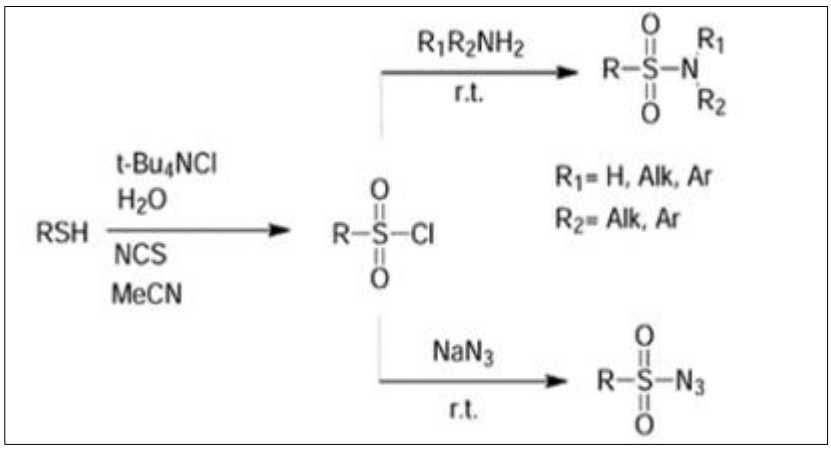

Figure 5 Modified method using t-Bu4 NCl and N-chlorosuccinimide (NCS)

Bonk *et al.,* used benzyltrimethyl ammonium chloride and trichloroisocyanuric acid (TCCA) in water to produce specific amount of chlorine into aprotic solvent (MeCN). The using of TCCA was provided the high purity of chlorine produced rather than hypochlorite. This modification through addition a subsequent amine into one-pot reaction, which producing chloride in situ and get sulfonamide within an hour (fig 6) (26).

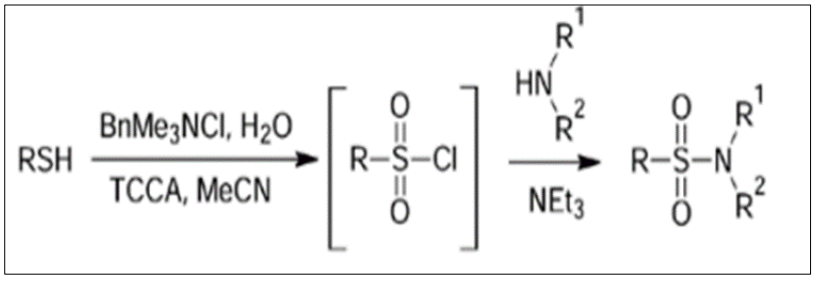

Figure 6 Sulfonamides synthesis by addition of (TCCA)

Renvankar *et al.,* illustrated another transition free metal method for sulfonamide preparation is by synthesis of 2-amino-9-H-purin-6-sulfonamides by using selective and moderate oxidants through oxidation of 2-amino-9H-purin-6-sulfenamide and using one equivalent of m-CPBA in nearly 50% (fig 7) (27).

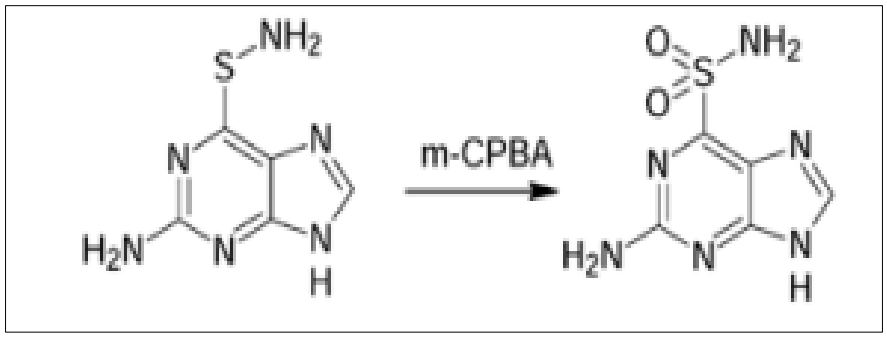

Figure 7 Synthesis of sulfonamides by m-CPBA oxidation of sulfonamides

2.2 Transition metal-catalyzed synthesis of sulfonamide

Although many efforts have been made towards the development of novel sulfonamide by metal free synthesis involving either the reaction of amino compounds with sulfonyl chlorides or by using sulfonate salts as intermediates. However, methods that have been used to produce sulfonyl chlorides such as electrophilic aromatic substitution with chloro-sulfonic acid, oxidative chlorination or organosulfur generally suffer from harsh conditions (19), the scope of limitation and always needs hazardous and oxidants or polluting chlorinating agents. Recently, however, a number of transition metals catalyzed reactions like use Pd, Rh, Ru, Fe, Ni, and Cu as transition metals catalyst have been evolved to overcome the problems in usual synthesis pathways. In principle, a transition metal catalyzed cross coupling C-N bond formation reaction and used for direct addition of SO2 moiety into suitably functionalized substrate, like aryl boronic acid or aryl halides (28, 29). Where the most well-known, palladium catalyzed N-arylation is the Buchwald reaction (30). Until now catalysts base on some transition metals have been checking for the N-arylation of sulfonamides. Pd is the first one like a bi-aryl phosphine ligand, t-BuXPhos and K3PO4 in tert-amyl alcohol was found to be optimal base-solvent combination for a Pd catalyzed sulfonamide production of aryl nonafluorobutane-sulfonates, the reaction conditions were tolerant of many different functional groups. The only disadvantage of this methodology is the 2, 6-disubstituted aryl nonaflates cannot efficiently participate in the reaction (fig 8) (31).

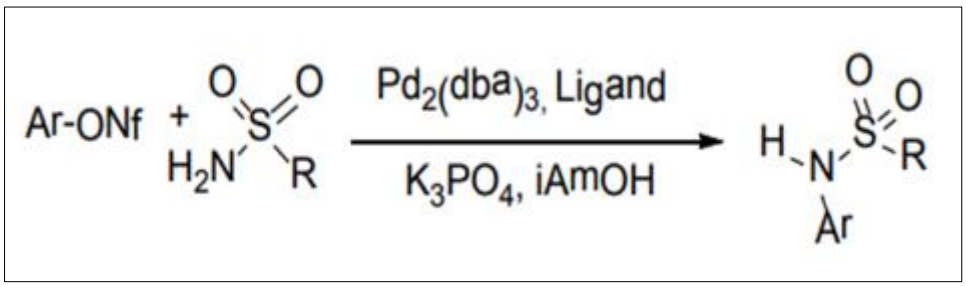

Figure 8 Synthesis of sulfonamide by Pd-catalyst

Rosen *et al.,* studied the Pd-catalyzed cross coupling reaction between substituted aryl halide and methane sulfonamide with high yield (fig 9) (32). It is more convenient method to produce aromatic derivatives of sulfonamide with eliminating using of aniline which can produce genotoxic impurities.

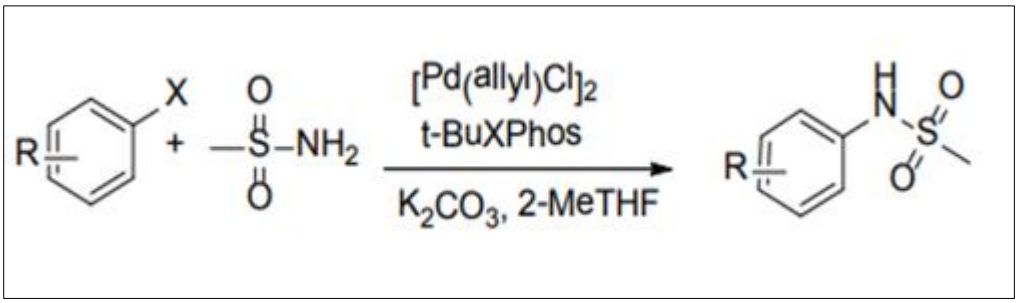

Figure 9 Synthesis of aromatic sulfonamides derivatives by Pd-catalyst

Watson *et al.,* reported the solvent free microwave assisted N-alkylation of primary sulfonamide with alcohol to produce secondary sulfonamide in very good yield (33). Ru-complex also was used to catalyze the reaction to get the proton from alcohol. Moreover, Cu catalyzed N-arylation of benzensulfonamide using boronic acid was reported by Lam et al., (34) in high yield. Various cross-coupling between aryl-boronic acid with numbers of primary sulfonamides using catalytic copper system is the main advantage of this protocol. In addition, Rh (II) catalyze the oxidative coupling reaction of sulfonamides and aldehydes to produce N-sulfonylcaroxamides in single step. Many sulfonamide derivatives able to react with aliphatic and aromatic aldehydes to synthesize good yields of desired compound (fig 10) (35,36).

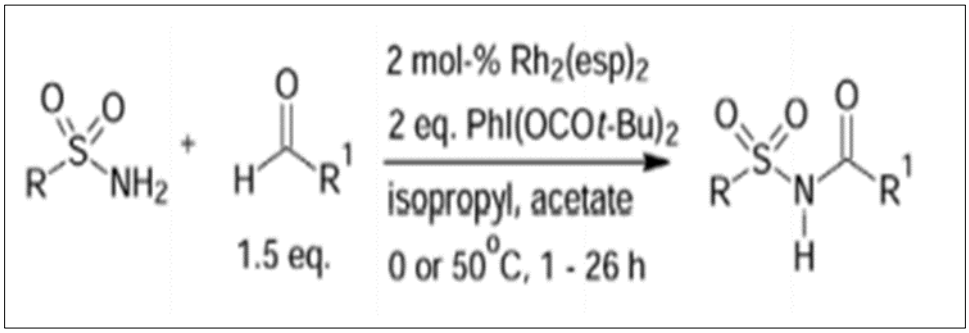

Figure 10 Rh (II) catalyzed production of secondary sulfonamide derivatives.

Beside all above metal discussed, Luo *et al.,* reported an iron catalyzed production of N-aryl sulfonamide complex by induction of N-S bonds by coupling of nitroarenes with aryl sulfinates which were used as a source of nitrogen in this reaction (fig 11) (37).

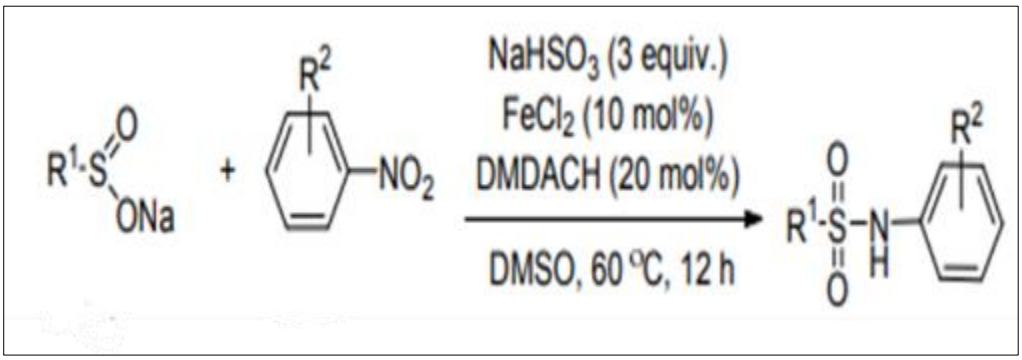

Figure 11 Fe-metal catalyzed synthesis of N-aryl sulfonamide

3 Biological activity of sulfonamides

3.1 Antibacterial effect

Sulfonamides are very important class of drugs because having very wide range of antibacterial activity such as Gram negative and Gram-positive bacteria (38). Klebsiella, Escherichia coli, Enterobacter species, and Salmonella are some

sulfonamides susceptible Gram-negative bacteria (39). Sulfa drugs have affinity to treat septicemia, tonsillitis, bacillary dysentery, meningitis, and many urinary tract infections (40, 41). Sulfonamide and its derivatives like sulfamethazine, sulfadiazine showed antibacterial activity against Staphylococcus aureus and Escherichia coli (42, 43). Antibacterial activity of sulfonamide derivatives can increase by addition of electron withdrawing substitution such as nitro group (44, 45). As been known antibiotics are chemotherapeutics agent used to kill or inhibit bacterial growth. The antibacterial mechanism of sulfonamides is through competitive inhibitor and structural analogues to P-aminobenzoic acid (PABA) which is essential for folic acid synthesis for further bacterial DNA production (46). The structural similarity of PABA and sulfonamides (fig 12) allows sulfonamides to replace and inhibit PABA in dihydropteroate synthetase enzymes (which have important activity to produce of folic acid) that lead to inhibit formation of tetrahydrofolate, dihydrofolate and subsequently inhibit bacterial production and cell replication and cell division (47,48). Because sulfonamides inhibit cell division, making these drugs bacteriostatic rather than bactericidal (49, 50).

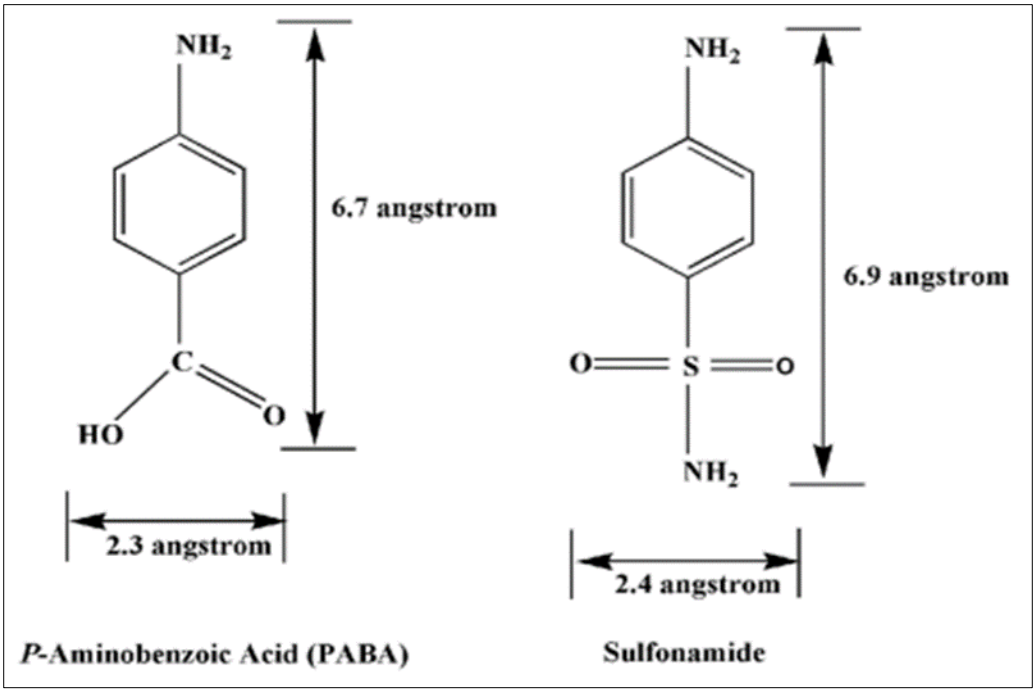

Figure 12 Approximate matching between Sulfonamides and PABA structure

3.2 Anti-corona virus

Corona virus affected hundreds of millions of humans and caused death for a large number of millions. Sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect humans and animals and cause many of sever and highly prevalent diseases (51). Because the number of infections and deaths still increasing with time around the world, therefor preparations of prophylactic and curative drugs or vaccines is the only way to overcome and reduce number of morbidity and mortality. In this context, various drug classes were tested for opposition this virus, but low success rate and highly toxicity is the challenge till now (52, 53). SARS-CoV-2 is a mutual of huge number of corona virus and it is relatively large enveloped, positive sense, single RNA strand (nearly 30 kilobases) (54). They are 4 structural proteins and 16 non-structural proteins translated from it. The protease of corona-virus is main protease (Mpro) enzyme is also called 3CL protease which is one of the essential non-structural proteins which represent an excellent target for drug designing due to playing a critical role in processing the polyproteins that are translated from the viral RNA, therefore important in replication of virus (55, 56). The SARS-CoV-2 replicase gene encodes two overlapping polyproteins-pp1a and pp1ab that are very essential for viral transcription and replication (57). Since its structurally different from human protease enzyme, so inhibiting this target approve less toxic and less side effects treatment and making Mpro an attractive target for design anti-coronavirus drug (58). The main protease Mpro enzyme have the ability to cleave specific amide bonds of polyproteins which enable viral replication process, for this reason sulfonamides have the ability to bind this enzyme, and it can be designed and used as SARS-CoV-2 Mpro inhibitor (54). The affinity of sulfonamides to produce good binding with the active site of covid-19 Mpro had been explored by AL HOQUE *et al.*, using molecular docking (fig 13), this binding ability can get a possible range of new sulfa drugs derivatives to treat SARS-CoV-2. Moreover, because sulfonamides mimic PABA structure and can stop bacterial growth (secondary infection) may accompany with CoV-2 that provide another important role in reduction severity of this disease. For

these reasons, some studies using in silico methods that screen some sulfonamide derivatives these able to act against corona virus. Darunavir is a sulfonamide derivative being able and considered to fight against corona virus (59).

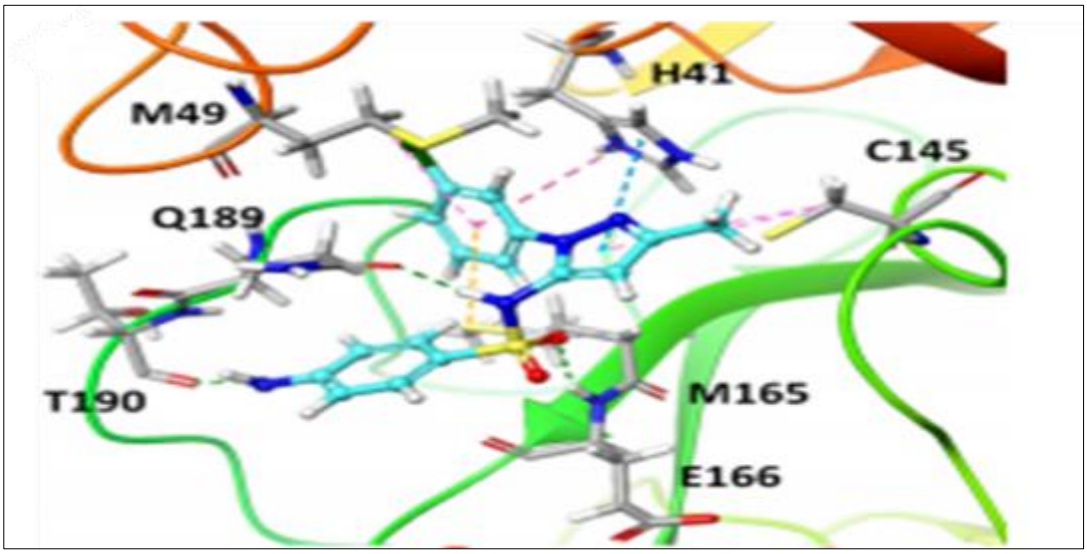

Figure 13 Docking study of one sulfonamide derivative with active site of SARS-CoV -2Mpro

3.3 Anti-HIV

The worldwide emergence of AIDS epidemic focused huge number of studies and great progress in this area, presently many antiviral drugs are available, most of them used to treat HIV infection (60). Most of these agents contain in their molecules have sulfonamide moiety which have substantial antiviral activity in vivo and in vitro (61). Because the diversity of chemical motif of sulfa drugs of heterocyclic\aromatic derivatives, there are many different anti-viral action and lesser side effects (61). Viral DNA is integrated in chromosomal DNA of host cell is an essential step in the virus life cycle is mediated by integrase (IN), a 32 kDa enzyme which catalyze 2 separate chemical reactions Known as DNA strand transfer and 3-processing (62, 63). 1st reaction involves IN binds to a short sequence at each end of viral DNA known as the long terminal repeat (LTR) and catalysis an ednonucleotide cleavage known as 3-processing in which a dinucleotide is removed from each end of viral DNA. The final cleaved DAN is then used as a substrate for integration or strand transfer leading to the covalent insertion of viral DNA to infected cell genome. This second reaction occurs simultaneously at both end of viral DNA molecule, with an offset of precisely five base pairs between the two opposite points of insertion. IN is good target for developing novel antiviral drug because there is no human counterpart of HIV IN (62). Delelis and Neamati groups identified many sulfonamides classes such as sulfisoxazole and sulfasalazine that used clinically for their interaction with IN with IC50 values in range of 50-100 µg/Ml (62-64). Moreover, they also investigate that the derivative which having the bulkier groups having the much better inhibitory action (65). Neamati *et al.,* identified that most of sulfonamide derivatives contribute in hydrogen bonds with active site residue Gln 148, as in compound in (fig 14), in which the NH group of sulfonamide motif donates the H-bond to the oxygen of O= CNH2 group of Gln 148, one of the sulfonamide oxygen atoms accepts H-bond from GL62 and the other oxygen of SO2 accepts hydrogen bond by His 114 (65).

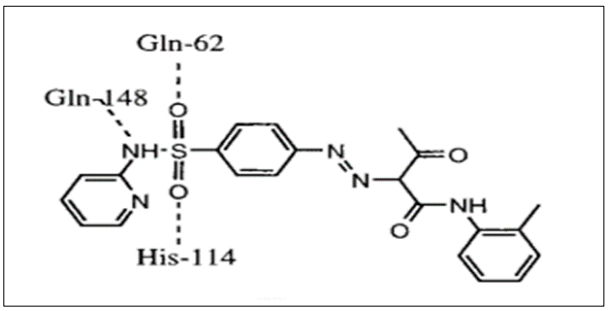

Figure 14 Structure of compound as IN inhibitor

Recently, the excellent IN inhibitory action was detected by johnston *et al.,* in compound in (fig 15) tris-sulfonamide, this compound is an interesting lead to develop much better IN inhibitors by IC50 of 5.5 μM for integration reaction (61).

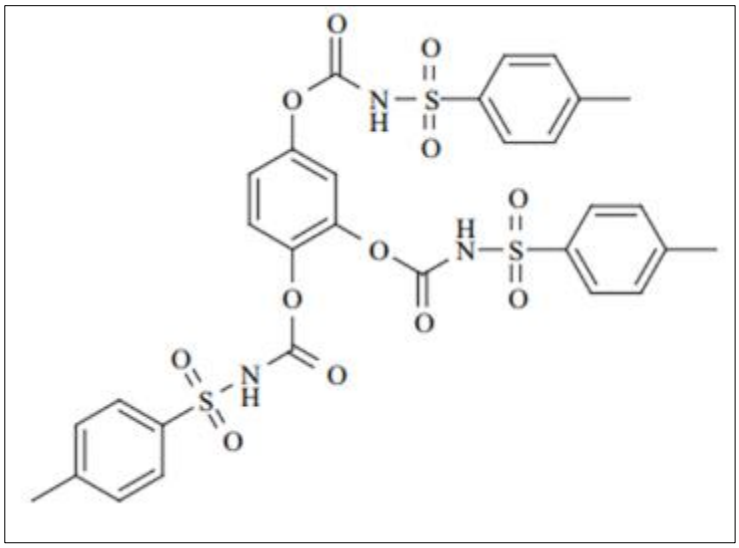

Figure 15 Structure of compound as IN inhibitor

3.4 Anticancer

Cancer is a term that refer to class of complex diseases because cells undergo rapid, uncontrollable, unusual division (66). Cancer is one of the most severe illnesses can threat human life. The mortality from this disease would exceed that from cardiovascular disease (67). According to the new reports of world health organization (WHO), more than 9.6 million deaths and near 20 million new cases have been determined in 2018 (68). Anticancer agents are very important cancer therapy, over one hundred drugs have been approved by U.S. Food and Drug Administration (FDA) for this disease (69). Among them, drugs containing sulfonamides moiety have occupied a prominent role in development for many FDA approved anticancer agent. For example, Bellinostat was approved to treat T-cell lymphoma (70). Sulfonamide derivatives have a potential anticancer action based on different targeting and mechanisms, such as Aromatase inhibitors, antiapoptotic Bcl-2 proteins, topoisomerase inhibitor and others. Breast cancer is very serious type of cancer that threat life among females with different age ranges around the world (71) and most of breast cancer appears in postmenopausal females due to high estrogen concentration (72). Estrogens, estrones are class of steroidal types of sex hormones those could be synthesized by their corresponding androgens in human body. Aromatase, an essential member of cytochrome P450 family which called (CYP19), plays an important role in estrogen biosynthesis (73). Inhibition of aromatase result in decreasing the estrogen levels so it has been an effective strategy for breast cancer therapy. Recently there are many aromatase inhibitors (AIs) have been designed and developed as anti-breast cancer compounds. Although some of these agents produce excellent clinical efficacy against breast cancer but the prolong used of these agent produces drug resistant and cause some side effects, that making challenging for drug designer (74, 75). Because this reason, it is urgent for medicinal chemist researchers to develop more novel AIs with more selectivity, higher efficiency and potency, and lower toxicity. Considering the potential structural features of sulfonamide motif, various derivatives of sulfonamides act as AIs have been developed in last few years. Pingaew *et al.,* designed and synthesize 2 series of 1,2,3-triazole-based sulfonamide derivatives through the click reaction then they evaluated their AIs (76). Most of these compounds produce an excellent aromatase inhibitor with IC50 values ranges from (0.2-9.4) Mm. Moreover, the SARs study showed the compounds with open chain sulfonamides displayed significant inhibitory activity against aromatase (77). Sulfonamides can also target the B-cell lymphoma-2 protein (Bcl-2) (78, 79, 80, 81) which is a class of an essential regulators in the mitochondria-mediated apoptotic pathway. In respect to their functions and structures, this family can be classified to group by pro-apoptotic multi-domain Bcl-2 proteins (like Bok, Bax, and Bak), anti-apoptotic Bcl02 proteins (like Bcl-2, Mcl-1, and Bcl-Xl) and BH3-only protein (like Bid, Bim, and Puma) (82). Apoptosis escaping is one of important cancers hallmark, that can also resist chemotherapies for cancer cells. In particular, the sequestration of pro-apoptotic Bcl-2 protein by unusual overexpression anti-apoptotic Bcl-2 protein is very related to the progression and development of cancer such as cervical cancer, leukemia, breast cancer, and lung cancer (83) therefore, agents that act as anti-apoptotic Bcl-2 protein have been considered as promising strategies for cancer therapy. In the last few decades, different small-molecule inhibitors targeting anti-apoptotic Bcl-2 protein have been developed by many strategies, and the drugs containing sulfonamides moiety as mentioned above is one of these

strategies. Moreover, topoisomerase enzymes are a class that play an important role is sparking modifying and controlling some DNA topological which appeared in various cell processing such as cell proliferation, differentiation and survival (84) because that any increasing in enzymes activity may observed in many cancers. In respect to their differences such as structures, mechanism of actions, and their catalytic functions, topoisomerase class could be further dividing into topoisomerase I and II. Topoisomerase I break single DNA strand at one time, while topoisomerase II could cleave double DNA strand simultaneously (85). Scientific research based on searching of compounds with anticancer action through inhibition of topoisomerase enzymes family. In addition to first line DNA topoisomerase inhibitors that identified like Camptothecin, Doxorubicin, Amsacrine, and Etoposide, they are many kinds of topoisomerase inhibitors including sulfonamide derivatives have been developed by medicinal chemists (84).

3.5 Anti-inflammatory

NSAIDs sulfonamides derivatives such as Celecoxib, Rofecoxib, and Valdecoxib have been developed by Pfizer as Cox-II specific inhibitors for treatment of rheumatoid arthritis and osteoarthritis (86). Their anti-inflammatory mechanism of action is selectively inhibiting of Cyclo-oxygenase-2 enzyme (COX-2 enzyme) (87) which is an enzyme represent a key player in inflammation. Under physiological conditions, Cox-2 is nearly absent in most tissues, but its expression is induced by proliferative stimuli and inflammation to provide Cox-2 derived locally for the regulation of inflammatory process. Over expression of Cox-2 is associated with acute and chronic inflammatory illness, cancer, and some neurological disorders (88, 89 ,90). Yang *et al.,* have synthesized of 4-phenyliminomethyl benzenesulfonamide based on Resveratrol a natural Cox-2 inhibitor product which have nearly 80-fold selectivity for Cox-II over Cox-1 (fig 16) (91). Moreover, the majority of selective Cox-2 inhibitors are belonged to tricyclic sulfone \sulfonamide compounds containing 1,2diaryl substitution on carbocyclic ring system or on a central heterocyclic (92) (fig 17).

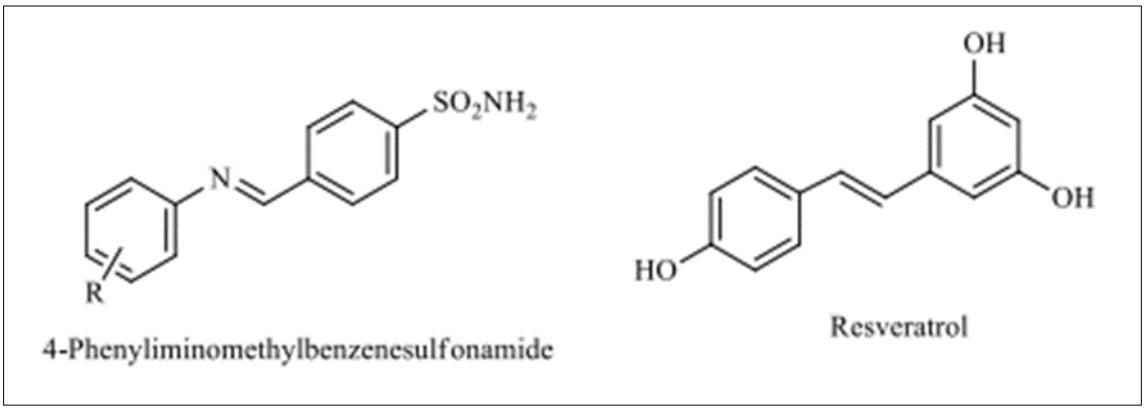

Figure 16 Cox-II selective inhibitor with mild Cox-I inhibitor properties

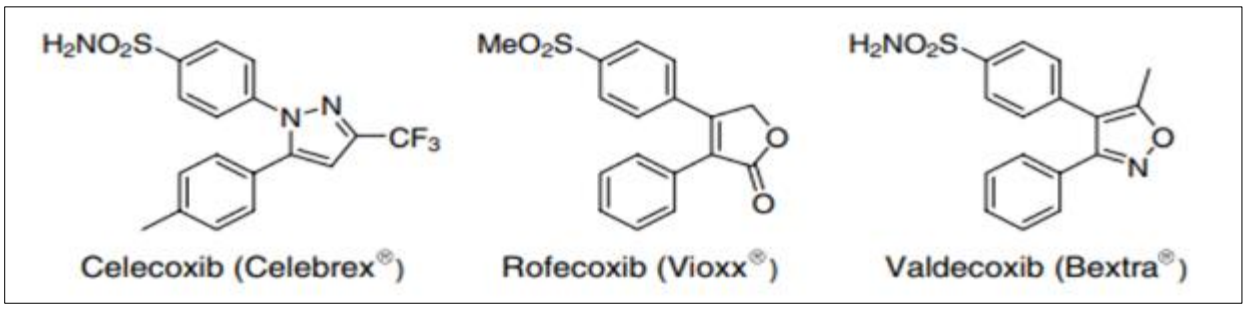

Figure 17 Selective Cox-2 inhibitors tricyclic sulfone \sulfonamide compounds

3.6 Anti-diabetic effect

Studies on sulfonamide bioactivities expanded to a proved that sulfa drugs can stimulate beta cells to release insulin. In 1950s carbutamide was first sulfonamide (sulfonylurea) compound presented in clinical use for diabetic mellitus (93). Sulfonamide (sulfonylurea) derivatives have been developed into more than ten anti-hyperglycemic drugs that usually classified into 2 generations. 1st includes carbutamide, tolbutamide, tolazamide, and chlopropamide (94) while 2nd

generation includes glipizide, gliclazide, glienclamide, and glibornuride (95). Beta cells transmembrane in pancreas are essential in glucose homeostasis and insulin secretion. ATP sensitive potassium channels (KATP) exist in a number of tissues and play very important role in many cell functions due to they combine membrane potential with cell metabolism (96). When ATP cell level decreases, KATP channels open then making cell membrane hyperpolarize (97). When the pancreatic beta cells in physiological state, the activity of KATP is balanced. The elevation of this KATP activity leads to stop insulin secretion, while reducing it leads to stimulate insulin secretion (98) in addition, intracellular calcium concentration (Ca2+) can also affect insulin secretion (99, 100, 101). In case of non-stimulated B-cells, Ca2+ sustained in low level controlled by Ca2+ ATPase on endoplasmic reticulum and plasma membrane. Elevation of blood sugar to stimulating level result in depolarization of cytoplasmic membrane that leads a voltage dependent Ca2+ influx through its channels. Subsequently, result in increasing an intracellular calcium concentration that triggers exocytosis. For this reason, KATP channel is play a critical role in maintaining glucose level in blood by secretion of insulin. The destruction of the coupling between the KATP channel and cell metabolism can cause two types of disease state. 1st diabetic, if the KATP gate unable to close by increasing glucose metabolism, and 2nd hyperinsulinemia, which come from closing the KATP gate when level of blood glucose is low (102). Thus, sulfonamide (sulfonylurea) derivative is a class of medications with ability to make an alteration in cell membrane potential and stimulate insulin release, through make depolarization of cell membrane (103). The scaffold of these compounds is presented in (fig 18). From this scaffold, it was known that these sulfonylurea compounds are derived from sulfonamide by some changes in parent sulfonamide structure like replacing R1with (-CO-NHR2) and R2 with H, NH2 with R3. R1, R2, R3 in sulfonylurea structure play essential role in different sulfonylurea compounds properties.

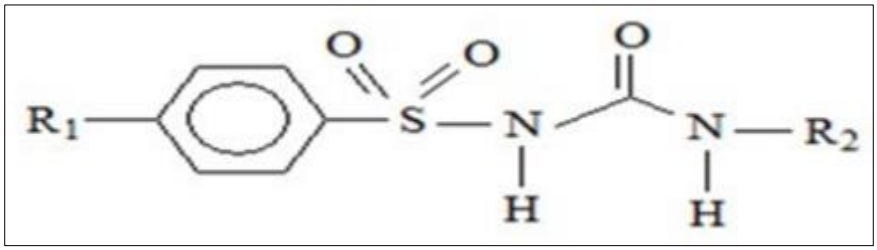

Figure 18 Sulfonamides scaffold in antihyperglycemic compounds

4 Conclusion

In this review, data were collected to demonstrate some synthesis pathways, examines modern method for preparation and multiplicity actions displayed by sulfonamide derivatives to improve and treat some diseases, infections and metabolic disorders.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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