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Sulfonamides: Synthesis and The Recent Applications in Medicinal Chemistry

Mohamed S. A. El-Gaby[a]*, Yousry A. Ammar[b], Mohamed I.H. El-Qaliei[a]*, Ahmed M. Ali[a] , Modather F. Hussein[a,c], Faraghally A. Faraghally[a]

[a]*Department of Chemistry, Faculty of Science, Al-Azhar University at assiut, 71524 , Assiut, Egypt.*

[b]*Department of Chemistry, Faculty of Science, Al-Azhar University , Nasr-City 11884, Cairo, Egypt.*

[c]*Chemistry Department, College of Science, Jouf University, P.O. Box 2014, Sakaka, Aljouf, Kingdom of Saudi Arabia*

Abstract

This review spotlights on sulfonamides from different sides, including history, structure-activity relationship, chemistry, methods of classification and up to date ways for their synthesis. Moreover, the review includes a discussion of the varied pharmacological effects of sulfonamides. Sulfonamides have a good range of pharmacological activities like oral diuretics (furosemide, indapamide, chlorthalidone, thiazides); anticancer (E7070), carbonic anhydrase (CA) inhibitors (CAIs) (acetazolamide, dichlorophenamide, dorzolamide and brinzolamide), antiepileptics (zonisamide and sulthiame), for rheumatoid arthritis (Sulfasalazine) antiviral (Darunavir) anti-inflammatory (celecoxib), antibacterial (Sulfadizine), as ophthamologicals (Dorzolamide) anticonvulsant (Zonisamide) cycloxygenase 2 (COX2) inhibitors (valdecoxib). These days, novel pills are launched, like apricoxib and pazopanib, which additionally include this organization. The sulfonamides competitively inhibit vitamin Bc synthesis in micro-organisms and subsequently inhibit multiplication of bacteria but donot actively kill them. They need been used against most gram-positive and lots of gram-negative bacteria, also as some fungi.

Keywords: sulfonamides.Medicinal Chemistry. Pharmacological activities. Micro-organisms.

Contents

*Corresponding authors e-mail: M_elgaby@azhar.edu.eg (Mohamed S. A. El-Gaby), Mohamedahmed.136@azhar.edu.eg (Mohamed I.H. El-Qaliei)
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1- Introduction

In 1932, in the patenting of Prontosil (Fig. 1) and numerous different azo dyes containing a sulfonamide organization induced by way of the knowledge that artificial azo dyes had been studied for his or her movement towards streptococci, domagk tested the new compounds and determined that mice with streptococcal and different infections could be blanketed with the aid of prontosil. in 1933, the primary medical case examine changed into reported through foerster, who gave prontosil to a ten month antique infant with staphylococcal septicemia and obtained a dramatic remedy. little attention was paid someplace else to the ones epoch-making advances in chemotherapy till Colebrook and kenny, additionally as buttle and coworkers, suggested their favorable scientific consequences with prontosil and its active metabolite, sulfanilamide, in puerperal sepsis and meningococcal infections. These reports wakened the medical career to the brand new field of antibacterial chemotherapy, and experimental and scientific articles soon appeared in profusion. the improvement of the carbonic anhydrase inhibitor–kind diuretics and the sulfonylurea hypoglycemic agents observed from observations accomplished with the sulfonamide antibiotics. Discovering the chemotherapeutic value of Prontosil, Domagk was awarded the Nobel Prize in Medicine in 1938 [1].

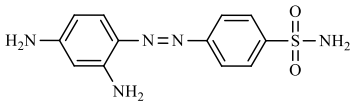


Fig. 1; Prontosil

These compounds have their familiarity as amide derivatives of sulphonic acid because they are synthesized by introduction of amino in sulphonic acid after replacing its hydroxyl group. The compounds which contain this functional group are called "sulfonamide". Theoverall formula of sulfonamide RSO_2NH_2,it is alsousually employed as a generic name for the derivatives of Para amino benzene are sulfonamide. The nitrogen atom of – RSO_2NH_2 is numbered as 1 and therefor the – NH_2 group as 4 [2] (**Fig. 2**). Individual members vary in the nature of N1 (sulfonamide N) substitution, which governs solubility, efficiency and pharmacokinetics property. a unfastened amino group within the p- position (N4) is needed for antibacterial activity [3].

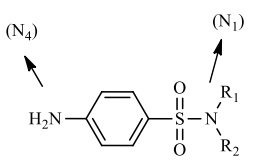


Fig. 2; the general structure of sulfonamides if R_1=R_2=H is sulfanilamides

Sulfonamides belong to a crucial class of compounds which show wide ranges of biological activities. Over previous couple of decades, various pharmacological activities of sulfonamide conjugates were published. Moreover, currently many lead compounds with sulfonamide functionality also are in clinical test for the treatment of varied medical conditions. For these reasons, the improvement of an efficient process for the synthesis of sulfonamides has continually been inside the recognition of studies in organic synthesis. Researchers published numerous articles over time to demonstrate the effectiveness of sulfonylation and n-alkylation tactics for the synthesis of sulfonamide. The foremost typical method for the synthesis involves a reaction between primary or secondary amines and sulfonyl chloride within the presence of organic or inorganic bases [4].

A big range of sulfonamide derivatives have in the long run been said to point out good sized protease inhibitory properties[5]. Sulfonamides are synthetic antimicrobial retailers which act as aggressive inhibitors of the enzyme dihydropteroate synthetase (DHPS).

the fundamental sulfonamide institution, SO_2NH, happens in various biological energetic compounds broadly used as antimicrobial capsules, antithyroid agents, antitumor, antibiotics, and carbonic anhydrase inhibitors[6, 7]. Clinically, sulfonamides arewontto treat several urinary tract infections and gastrointestinal infections [8]. Aromatic or heteroaromatic sulfonamide that are used as an antitumor agent act by inhibiting carbonicanhydrase.

Structurally, sulfonamides arealmost like to *p*-amino benzoic acid (PABA) which may be a cofactor neededby bacteria for the synthesis of vitamin Bc and thuscould compete for incorporation. Sulfonamide antibioticsare used as veterinary medicines to treat infectionsin livestock herds [9, 10]. Additionally, sulfonamides are extremely useful pharmaceutical compounds because they exhibit a good range of biological activities like anticancer, anti-inflammatory, and antiviral activity [11-15]. The sulphonylation of amines with sulphonyl chlorides within the presence of a base remains getting used because the method of choice due to high efficiency and ease of the reaction [16].Sulfonamide are used as protecting groups of OH or NH functionalities for straightforward removal under mild conditions [17, 18].

The sulfonamides application in therapy is partially limited by the bacterial resistance and sulfonamides side effects. so as to beat the resistance and to scale back the adverse effects, continuous efforts are made to synthesize novel antimicrobial compounds with the sulfonamide structure and to develop novel formulations with the prevailing sulfonamide substances [19, 20]. Resistance of *E. coli* strainsto sulfonamides has been shown due to their containing sulfonamides -resistant dihydropteroate synthase [21].Research has shown that each one things being equal, antibacterial activities of sulfonamide

decreases because the length of the carbon chain increases [22].

Structure-activity relationship

Sulfonamides have the general structure **(Fig. 3)**in which R may be alkyl, aryl or hetero aryl groups and R_1/R_2 may also be hydrogen, alkyl, and aryl or hetero aryl groups [23].

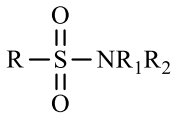


Fig. 3; the general structure of sulfonamides

Inside the initial phase of the sulfonamides studies, a big wide variety of sulfonamide derivatives have been synthesized, which made it viable to establish a correlation between specific structural characteristics and the antimicrobial hobby of newly created molecules. First of all, a free aromatic NH_2 group in the Para- position, relative to the sulfonamide group, is essential for the activity of sulfonamides [24]. The presence of the extra substituent in the ortho and meta position of the benzene ring reduces the sulfonamide activity. N1-monosubstituted derivatives of sulfanilamide are active compounds whose activity degree increases with the introduction of heteroaromatic substituents. A double substitution in the N1 position leads to inactive compounds. Additionally, the sulfonamide group must be directly attached to the benzene ring. A substitution of the benzene ring by using different cyclic system also results in the discount or a whole loss of activity. The first sulfanilamide (4-amino benzene sulfonamide) is the basic representation of sulfonamide antimicrobial drugs. The clinical significance of sulfanilamide is not large because it is very rarely applied in therapy nowadays due to the synthesis of more efficient products. But, sulfanilamide represents the essential structural and useful unit of the complete magnificence of antimicrobial sulfonamides. The structural formula of sulfanilamide and several sulfonamides are given in **(Fig.4).**

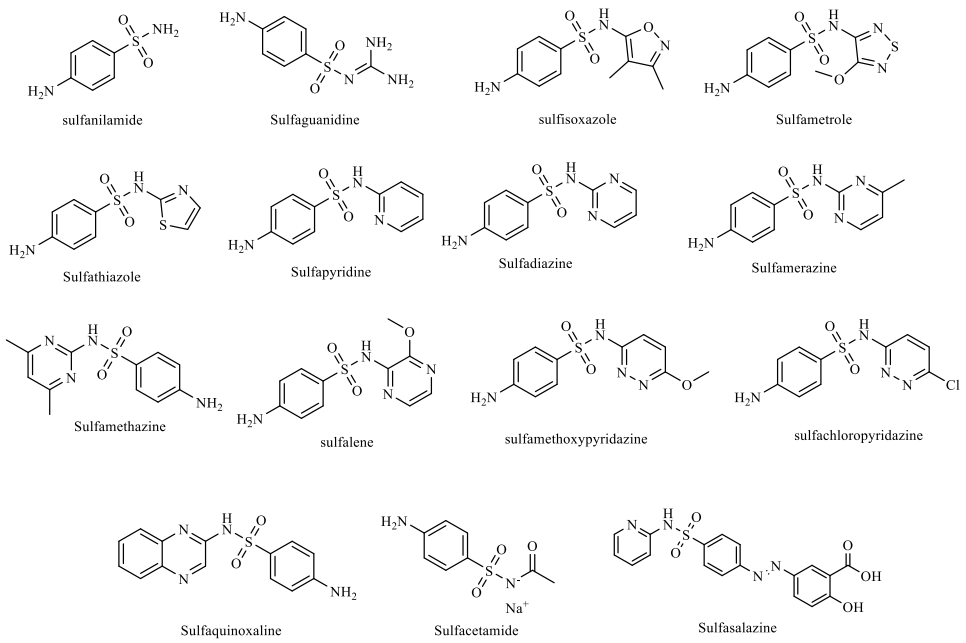


Fig. 4; Structure of several sulfonamide antimicrobial drugs

Sulfanilamide is a strong substance under ordinary temperature and pressure situations. It's far sensitive to light and incompatible with strong oxidizing agents. The solubility of sulfanilamide in ethanol (~27 mg/cm3) and acetone (~200 mg/cm3) is greater than in water [25]. Sulfanilamide is a weak acid (pKa= 10.4) due to the strong electron attractive effect of – SO_2 substituent and resonance stabilization of the resulting anion [26] Sulfanilamide ionization is given in **(Fig.5).**

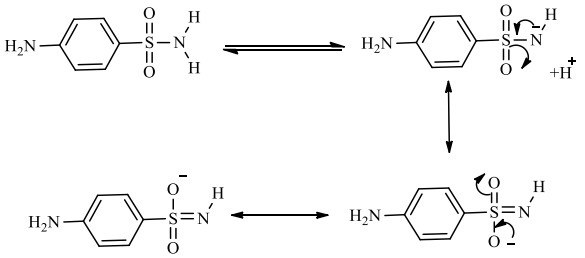


Fig. 5; ionization of sulfanilamide

1- Classification of sulfonamides

Most of the sulfonamides are used currently as*N1*-derivatives. supported the structural variations, [27]sulfonamides divided sulfonamides into three companies as follows:

a) Aryl derivatives (sulfamethoxazole, hydrochlorothiazide, sulphanilamide)

b) Heterocyclic derivatives containing six-membered rings (e.g. Pyridine, pyrimidines, pyridazines and pyrazines).

c) Heterocyclic derivatives containing five-membered rings (e.g. Thiazole, oxazole, isoxazole, 1,3,4- thiadiazole and pyrrazole).

The classification rate of absorption and half-life appears to be clinically relevant. Supported this, the sulfonamides are classified into three groups [28]:

1) Short Acting: Sulfonamides with a half-life less 10 hours (e.g. Sulfamethizole, sulfisoxazole, and sulfanilamide are used for the remedy of urinary tract infections)**(Fig.6)**.

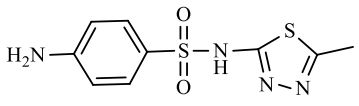


Fig. 6;Sulfamethizole

2) Intermediate Acting: Sulfonamides with a half-existence between 10-24 hours (e.g. Sulfamethoxazole, sulfacetamide and sulfadiazine are used for various infections, especially active against invasive aspergillosis in AIDS patients) **(Fig 7).**

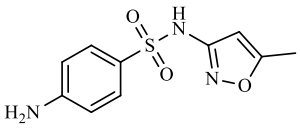


Fig. 7; Sulfamethoxazole

3) Long Acting: Sulfonamides with a half-existence longer than 24 hours (e.g. Sulfadimethoxine and Sulfadioxine have been used for the remedy of ulceration colitis) **(Fig.8).**

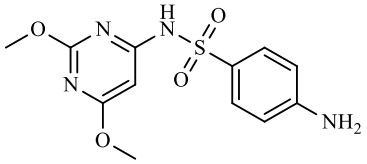


Fig. 8;Sulfadimethoxine

Sulfonamides are verified to be interesting scaffold that holds a wide variety of organic activities including anticancer, antimicrobial, antimalarial, and antiviral activities. This is owing to their potential structural features which are capable of multiple interactions with various biological targets. Moreover, sulfonamides are normally stable, easy to synthesize, whilst offering maximized pharma-cological profiles such as oral absorption and low side effects [29].

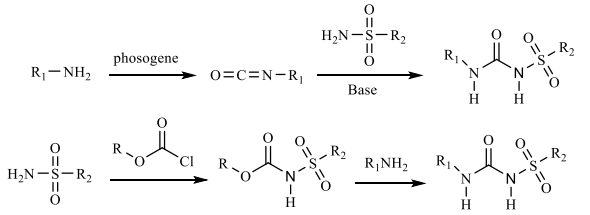
In chemistry the term sulfonamide is hired as a everyday name for derivatives of p-aminobenzene sulfonamide (sulfanilamide); the structural formulas of selected members of this class are shown in **(Fig 4).** Most of them are relatively insoluble in water, but their sodium salts are readily soluble. The minimal structural stipulations for antibacterial movement are all embodied in sulfonamide itself.. The RSO_2NH_2 group is not essential as such, but the important feature is that the sulfur is linked directly to the benzene ring. The Para- NH_2 group (the N of which has been designated as N4) is essential and can be replaced only by moieties that can be converted in vivo to a free amino group. Substitutions synthetic within the amide NH2 group (the N of which has been set as N1) have variable effects on antibacterial activity of the molecule. However, substitution of heterocyclic aromatic nuclei at N1 yields enormously amazing compounds.

The lipophilicity of the N1 institution has the largest impact on protein binding, and usually, the extra lipids

soluble a sulfonamide are, the extra of it is going to be protein certain [30]. The aniline (N4) amino group is very essential for activity because any modification of it other than to make prodrugs outcomes in a loss of interest [31]. Moreover, sulfonamides also are inactive if p-amino group is acylated, benzene is substituted, sulfonamide group now not connected immediately to a benzene ring. Greater advanced studies found out that modified sulfonamides showing excessive to moderate antibacterial activity [32]. Aliphatic sulfonamides have maximum powerful antibacterial interest for Gram (-) bacteria than Gram (+) and antibacterial activity decreases due to the fact the period of the carbon chain will increase [33].

Drugs containing sulfonamides of primary amines

Sulfonamides are used as a center structural moiety or a crucial fragment in many marketed drugs. Numerous antimicrobial drugs have been prepared mainly by using coupling among heterocyclic primary amines and aromatic sulfonyl chlorides e.g. sulfacetamide, sulfadiazine, sulfamethoxazole, sulfamoxole and so on.Another important use of sulfonamide was noticed in the synthesis of sulfonylureas **(scheme1),** which were evolved as good anti-diabetic agents. Few crucial drugs on this series are glipizide, acetohexamide, carbutamide.



Scheme 1; Synthesis of Sulfonyl urea

Sultiame, also known as sulthiame, is a sulfonamide prepared from simple starting material paminobenzene sulfonamide. It is an inhibitor of the enzyme carbonic anhydrase and currently in use as an anticonvulsant. . Dorzolamide, acetozolamide and brinzolamide are a few different crucial collection of drugs in which primary sulfonamide side chains are attached to heterocyclic ring. those are used to deal with glaucoma or ocular high blood pressure. Zonisamide has been advanced as a essential drug in which the methane sulfonamide group is attached with benzoisoxazole moiety. The drug has been authorized in many countries for numerous essential diseases. In **US** and **UK**zonisamide has received approval for adjunctive treatment of partial seizures. In Japan, the same molecule has marketed for the treatment of Parkinson's disease. In recent years, it is also being investigated for other diseases like migraine, obesity and bipolar depression.

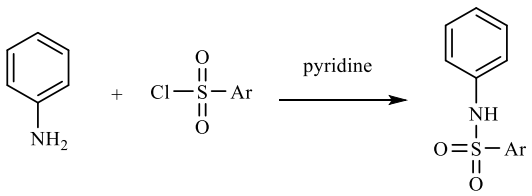
Drugs containing sulfonamides of secondary amines

Several crucial drugs containing sulfonamide moiety have also been marketed wherein the coupling response among sulfonyl chloride and secondary amine was considered as the important thing artificial step. Two important drugs in this class are amprenavir and darunavir. Amprenavir (original brand name Agenerase) released through Glaxo-Smithkline acts as a protease inhibitor. it's far already in use to treat **HIV** infection. Darunavir is every other drug in this category that is evolved by means of Tibotec, bought beneath the emblem call Prezista. It's far being used for antiretroviral medicinal drug to treat and prevent **HIV/AIDS** patient. The secondary sulfonamide side chain is connected with benzoic acid inside the structure of probenecid that's utilized in treating gout and hyperuricemia. Various novels and efficient strategies for the synthesis of sulfonamides containing primary and secondary amine groups have been identified and discussed in this review.

2- Synthesis of sulfonamides

a- Synthesis of sulfonamide using primary amines and aryl sulfonyl chloride

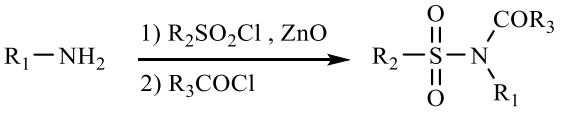
Youn et al.reported [34] the preparation of sulfonamide using aryl primary amine and aryl sulfonyl chloride **(scheme 2)** employing pyridine as a base at 0-25 °C. They've discovered 100% yield when aniline is used as a primary amine and benzene sulfonyl chloride or 4-nitrobenzyl sulfonyl chloride as sulfonylation agent. Quantitative yield additionally stated for the reaction between p-toluidine and tosylchloride. The purpose of the take a look at changed into a regioselective synthesis of 3-Arylindoles from N-Ts-Anilines and styrenes.



Scheme 2; Synthesis of sulfonamides using primary amine and sulfonyl chloride

Rattanaburi et al. reported [35] Fe_3O_4-DIPA catalyzed sulfonamide preparation with excellent yield (98%) where the reactant and Fe_3O_4-DIPA in dichloro

methane (DCM) were shaken at room temperature (RT) for reaction completion. The catalyst became separated with the aid of magnetic separation and reused. Chemo selective solvent free synthesis of sulfonamide **(scheme 3)** using zinc oxide-nanoparticle was prepared [36] with 95% yield. Synthesis started with primary amines, sulfonylation accompanied by way of acylation produced N-acylsulfonamides. Reusability of environmental-friendly catalyst turned into the principle advantage of the protocol. Also the invention of surprisingly efficient catalyst CsF-Celite for sulfonylation reaction was reported by [37] Chemoselective solvent free neat reaction has been demonstrated for the preparation of various sulfonamides with high yield.

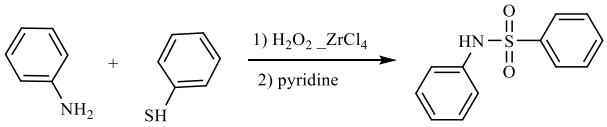


Scheme 3: solvent free synthesis of sulfonamides using ZnO- nanopartic

Over the decades, researchers suggested use of neat pyridine or its combination with polar solvents for the synthesis of sulfonamides of primary amines e.g., [38] filed a patent on ramoplanin derivatives having antibacterial activity in 2006 where they have reported the synthesis of N-phenylbenzene sulfonamide with 90% yield. Neat pyridine changed into delivered to amine substrate at 0^{o}C and the reaction became performed at room temperature (RT) after addition of sulfonyl chloride. Kato et al. [39] suggested synthesis of a chiral aromatic sulfonamide that are in addition passed through spontaneous fast resolution to provide chiral crystal. Polymer supported pyridine became used as a base and dichloromethane as a solvent to afford 92% yield. Alba et al. [40] synthesis a mono-sulfonamide and bis-sulfonamide with 90% yield where sulfonamide prepared using pyridine as a base in **THF**-solvent. The synthesized sulfonamides were used as an organo-catalyst, i.e. hydrogen-bond donors in organo-catalyzed ROP of locations. Moderate to suitable yield was stated in numerous articles for the sulfonylation of primary amines using another commercially considerable organic base triethylamine (**TEA**). Tosylation was carried out by**TEA** as a base in **THF** solvent 86% yield was obtained by Kurkin et al. [41] Synthesis procedure was simple; **TEA** was added drop wise to the solution of aniline in **THF**, the mixture was stirred in ice bath. Benzenesulfonyl chloride was added drop wise and stirred at RT for 6 h for reaction completion. Conway and Gribble [42] reported 85% yield of N-phenylbenzene sulfonamide by reaction between aniline and benzene sulfonyl chloride in diethyl ether at 0 °C. Qiu et al. [43] reported reaction between domino Aryan precursor and sulfonamide where sulfonamides were prepared with 85% yield using **TEA** as a base in DCM. The use of an inorganic base like potassium carbonate was also explored in sulfonylation reaction [44] where the researchers achieved up to 78% yield yield whilst reactions have been done in PEG-400 solvent. The evolved protocol turned into handy because of heterogeneous response mass in which the bottom may be easily separated from the reaction mass through filtration. Recovery and reuse of PEG-400 is another advantage of the reported method from economic and environmental aspect. Newcomer et al.[45] reported poor yield (only 44%) when strong inorganic base like sodium hydroxide was employed for the sulfonamide synthesis reaction. In a magnetic stirrer acid chloride and amine were mixed collectively. The addition of 10% NaOH changed into performed in quantities and the response combination stirred for 1 h at RT to produce N-phenylbenzenesulfonamide. The main intention of the study was to prepare unalkylated benzene sulfonanilides to check rearrangement of the same to sulfones. Sulfonamide synthesis by reaction between aqueous solutions of primary amine and sulfonyl chloride at RT using sodium carbonate as a base was reported [46] The research group prepared a series of sulfonamide- 4-substituted-1, 2, 3-trizolyl nucleosides and evaluated their activity against tumor cell lines RCC4 and MDA-MB-231.

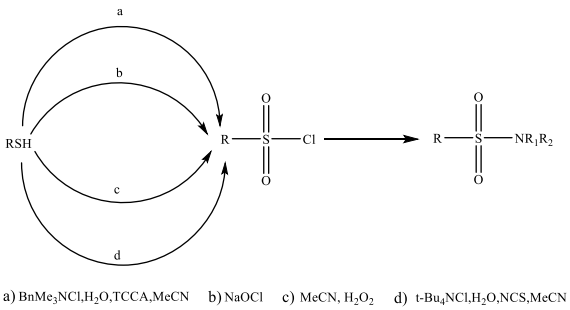
b- Synthesis of sulfonamide using amines and thiol

Another method for the synthesis of sulfonamide of primary amines has been explored by way of the researchers where SH group of aromatic thiol was in-situ oxidized through the use of oxidizing agent and chlorinated before the amide bond formation. Bahrami et al.[47] reported stage wise reaction between aniline and benzene thiol **(scheme 4)** using hydrogen peroxide as an oxidizing and zirconium chloride as a chlorinating agent. In degree-2, pyridine used as a base and typical 98% yield changed into completed. They have claimed environmentally green and economical protocol where the novel H_2O_2-$ZrCl_4$ reagent system offered fast reaction at room temperature to furnish excellent yield (92-98%).



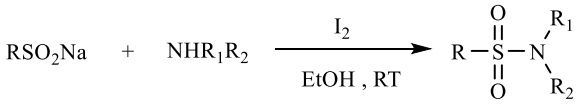
Scheme 4: synthesis of sulfonamides using primary amine and thiol

The same studies also mentioned [48] a stage wise process **(scheme 5, path c)** where in stage 1, a combination of hydrogen peroxide and thionyl chloride reagent system were used for direct oxidative chlorination of various thiol derivatives to the corresponding sulfonyl chloride intermediates, which had been in addition converted to sulfonamide in level 2 *via* reacting with one of a kind amines using pyridine as a base in acetonitrile or water solvent to afford 94-98% normal yield. Thiol may be transformed to sulfonyl chloride in many methods (**scheme 5**). Aside from the oxidative chlorination of thiol to sulfonyl chloride , in-situ conversion of heteroaromatic thiols to sulfonyl choride the use of sodium hypochlorite as an oxidizing agent **(path b)** was reported [49] to prepare sulfonyl chloride at low temperature, which was immediately trapped with benzyl amine to produce sulfonamide in almost quantitative yield.(Scully and Bowdring [50] prepared organic chloramines by mixing sodium hypochlorite and aq. The solution of a mine which has reacted rapidly with sodium arene sulfinate to form arene sulfonamide. Veisi et al. [51] developed a novel method where an oxidizing chlorinating system was developed to synthesize sulfonyl chloride from various thiols by mixing N-Chlorosuccinamide and tertbutylammonium chloride-water system in acetonitrile solvent (path d). The sulfonyl chloride is in situ transformed to the corresponding sulfonamide in a single pot. Bonk et al. [52] reported novel system for controlling liberation of chlorine in combination of trichloroisocyanuric acid and benzyltrimethylammonium chloride in MeCN solvent **(path a).** The sulfonyl chloride turned into generated and in-situ reacted with diverse amines to diversify the scope of the protocol.



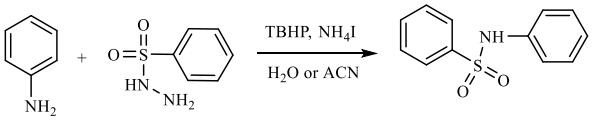
Scheme 5; Converstion of thiol to sulfonyl chloride using various reagents

The concept of green chemistry was applied for the first time in sulfonylation reaction wherestage wise reaction using iodine and ethanol was investigated [53] the reported procedure was novel and efficient since any metal, base, ligand or additive was not used in the reaction. The scope of the protocol was also very wide which had covered the construction of a variety of primary, secondary and tertiary sulfonamides.



Scheme 6; Metal free sulfonamides synthesis using sodium sulfinate and amines

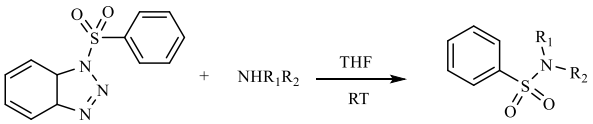
Yu and Zhang [54] mentioned for the first time that use of benzene sulfonyl hydrazide **(scheme 7)** for sulfonylation of various amines in presence of tertbutylhydroperoxide (**TBHP**) and ammonium iodide in water or acetonitrile (**ACN**) with moderate to good yield. **TBHP** was used as an oxidant and ammonium iodide (NH_4I) as a catalyst to produce aryl sulfonyl hydrazide which is further reacted with amines to produce corresponding sulfonamides.



Scheme 7; synthesis of sulfonamides using benzene sulfonyl hydrazide

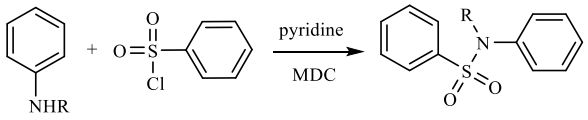
c- Synthesis of sulfonamide using secondary amines

A novel reagent 1-phenylsulfonylbenzotriazolewas synthesized [55] **(scheme 8)** for the conversion of various aliphatic and aromatic aminesand phenols to their corresponding benzenesulfonamides and benzenesulfonates.



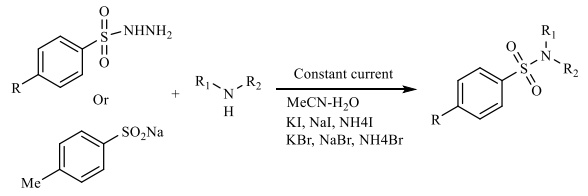
Scheme 8; synthesis of sulfonamides using 1-phenyl sulfonyl benzotrizole

Sulfonamide synthesis using secondary amineslike *N*-methyl aniline or diphenyl aniline **(scheme 9)** was synthesized by [56] The aim of the study was to explore the hemolytic cleavage and intermolecular radical-radical coupling reaction mechanism of 1,3- and 1,5-sulfonyl migration of *N*-arenesulfonyl phenothiazines and *N*-arenesulfonylphenoxazines. Excellent yield (97%) was achieved using pyridine as a base in chlorinated solvent by portion wise adding of benzenesulfonyl chloride.



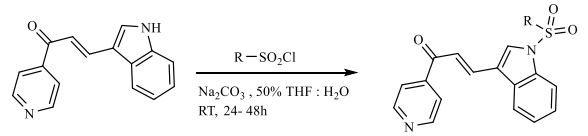
Scheme 9; Synthesis of sulfonamides using secondary amine

Terent'ev et al. [57] reported an effective electrochemical synthesis of sulfonamides from arenesulfonohydrazidesor sodium *p*-methylbenzene sulfinate and amines**(scheme 10)**. The reactions were carried out in an undivided cell using graphite anode and iron cathode at constant current density 35-40 mA cm^{-2} to efficiently produce fourteen various sulfonamides in 56-98%.



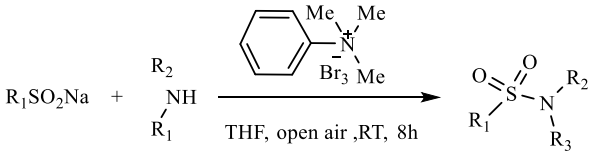
Scheme 10; Synthesis of sulfonamides using arenesulfonohydrazides or p- methylbenzensulfinate and secondary amine

Recently in 2018, various tertiary sulfonamide derivatives of pyridyl-indolebased heteroaryl chalcone in 60-90% yield was discovered by [58] **(scheme 11)**. Reactions were carried out room temperature (RT) using weak inorganic base Na_2CO_3 in 50% THF:H_2O solvent mixture. All the compounds were evaluated for carbonic anhydrase IX inhibitors and anticancer agents.



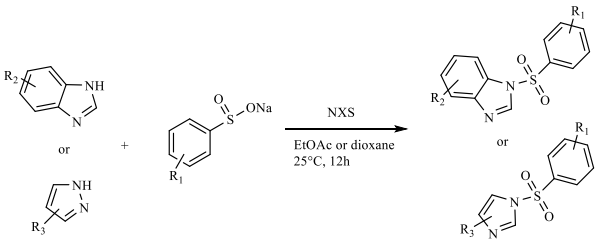
Scheme 11; Synthesis of sulfonamide derivatives of pyridyl-indole based heteroaryl chalcone

An open air, metal free oxidative coupling for the synthesis of sulfonamide mediated by phenyl trimethyl ammonium tribromide (PTAB) [59] **(scheme 12**). Initially benzene sulfinatereacted with PTAB to produce forms the corresponding sulfonyl bromide, then the nucleophilic reaction of amineswith sulfonyl bromide produced the desired products in 54-82% yield.



Scheme 12;synthesis of sulfonamide mediated by PTAB

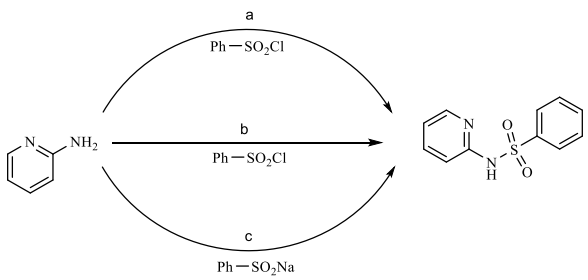
Metal free direct *N*-sulfonylationof azoles or benzimidazolesby sodium sulfinates **(scheme13)** was reported by [60] A diverse range of azoles and pyrazoles were convertedto sulfonamides following simple and green procedure. Initially, aromatic sodium sulfinatewas reacted with *N*-Iodo or *N*-bromosuccinimide (NBS) to produce sulfonyl bromide or iodide, which was finally converted to sulfonamides by means of nucleophilic assault of azoles or benzimidazoles.



Scheme 13; Synthesis of sulfonamides using substituted azole or benzimidazole and sodium sulfinates

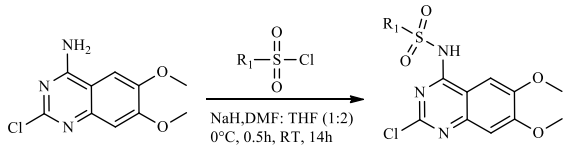
d- **Synthesis of sulfonamide using heteroaryl amine**

Reaction between 2-aminopyridineand benzene sulfonyl chloride was reported by [61, 62] using organic base pyridine in 63% yield **(scheme 14, path a)**. Comparable low yield (29%) obtained when the same sort of reactions were carried out applying microwave irradiation **(scheme 14, path b)** [63]. Iodine catalyzed reaction between heteroaryl amine and the sodium salt of benzenesulfonate (**scheme 14, path c**) was reported [64] in 52% yield.



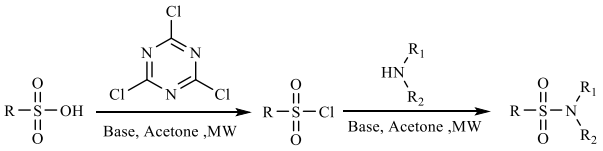
Scheme 14; synthesis of sulfonamides using heteroaryl amine

Recently in 2017, [65] synthesized various quinazoline sulfonamide derivativesand evaluated them as an anticancer agent against SKOV3, DU145, THP1, U937and COLO205 cell lines. Few compounds had been found to be energetic against THP1 and U937 cell lines. Different aryl, heteroaryl, alkyl and cyclopropyl sulfonyl chlorides were reacted with 2-chloro-6,7-dimethoxyquinazolin-4-aminein **DMF** and **THF** solvent mixture using sodium hydride as a base to produce the corresponding sulfonamide in 72-96% yield **(scheme 15)**.



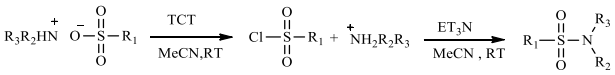
Scheme15; Synthesis of substituted quinazoline sulfonamide of secondary amines starting from sulfonic acid

Microwave assisted preparation of sulfonamide starting from sulfonic acid was explored by [66] in high yield. The reaction proceeded via sulfonyl chloride intermediate. 2, 4, 6-trichloro-[1, 3, 5]-triazine was added to a solution of p-toluenesulfonic acid in acetone, followed by TEA. The reaction mass was irradiated at 80 °C for 20 min, thesulfonyl chloride is isolated by filtration and further reacted with an allylamine to produce corresponding sulfonamide in 95% yield **(Scheme 16)**.



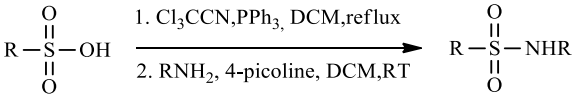
Scheme 16; Microwave assisted preparation of sulfonamide from sulfonic acid

Rad et al. [67] reported one pot synthesis of sulfonamide from primary or secondaryamine by preparing amine sulfonate saltusing cyanuric chloride.Usinga classical heating method with excellent yield **(scheme 17)**. The reaction mechanism has also been explained by the research group. The reaction proceeds via a SNAr - type reaction between sulfonate anion and cyanuric chloride. The chloride ion attacks the sulfur atom to produce the corresponding sulfonyl chloride. In the next step, the amine liberates from ammonium in the presence of **TEA**, which reacts with sulfonyl chloride to afford sulfonamide product.



Scheme 17; preparation of sulfonamide from amine sulfonate salt using cyanuric chloride

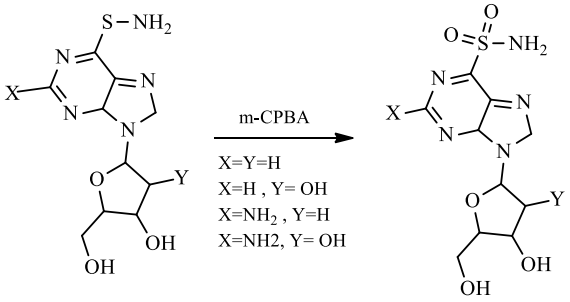
Chantarasriwong et al. [68] prepared a novel method for sulfonamide preparation where the scope of the study was widened by using aliphatic, aromatic and heterocyclic amines. In the first step, sulfonic acid was treated with trichloroacetonitrile, triphenylphosphine in dichloromethane (DCM) to produce the corresponding sulfonyl chloride, which is subsequently transformed to sulfonamide by reacting with amine and a base **(scheme 18)**.



Scheme 18; synthesis of sulfonamide from sulfonic acid using trichloroacetonitrile

e- Synthesis of sulfonamide by oxidation of sulfenamides

Revankar et al. [69] reported elimination of 2'-deoxy-6-thioinosine and 9-*β*-Darabinofuranosyl-6-thiopurine with chloramine to prepare corresponding 6-sulfenamides which on oxidation by excess meta-chloroperbenzoic acid (**mCPBA**) produced corresponding sulfonamide in 48% yield **(scheme 19)**. (**mCPBA**) was used as an oxidizing agent for the oxidation of sulfur to produce the corresponding sulfone.

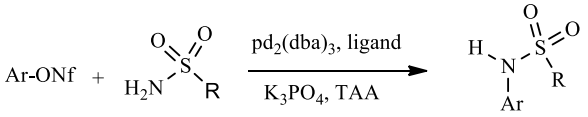


Scheme 19; Synthesis of sulfonamide from sulfenamide

f- Synthesis of sulfonamide by Metal catalyzed sulfonamidation

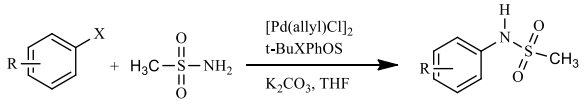
Preparation of secondary and tertiary sulfonamides using a metal catalyst Pd catalyzed sulfonamidation of aryl nonafluorobutanesulfonates **(scheme 20)** has been

investigated [70] The optimal reaction condition was established for N-arylation where combinations of Tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and binary phosphine ligand, t-BuXPhOS were used as highly active catalyst and K_3PO_4 in *tert*-amyl alcohol (TAA) was found as an optimal base solvent combination for the reaction. Though the instability of di-substituted aryl nonaflates is a major limitation, the wide substrate scope is the advantage of the protocol.



Scheme 20; Pd catalyzed synthesis of sulfonamide

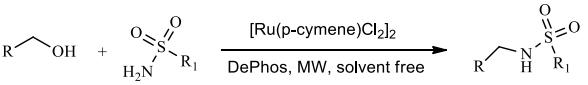
Pd-catalyzed cross coupling reaction between substituted aryl halide and methane sulfonamide **(scheme 21)** was studied [71] with high yield.



Scheme 21; Sulfonamide synthesis using borrowing Hydrogen catalyst

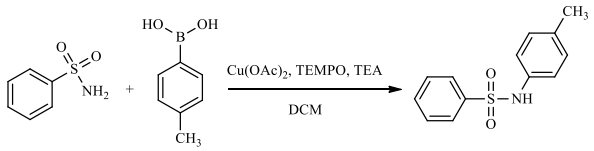
Solvent free microwave assisted *N*-alkylation of primary sulfonamide with alcohol to produce secondary sulfonamide in very good yield **(scheme 22)** was reported [72].

The Ru-complex was used as a catalyst in the reaction to borrow the hydrogen from alcohol. The intermediate aldehyde reacted with an amine to generate imine, which is eventually reduced by the catalyst to produce sulfonamide of the secondary amine.



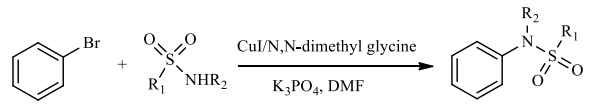
Scheme 22; Synthesis of secondary amine sulfonamide by hydrogen auto transfer

Lam et al. [73] reportedCu catalyzed *N*-arylation of benzenesulfonamide using aryl boronic acid in quantitative yield **(scheme 23)**. Diversity of cross-coupling between arylboronic acid with a wide range of primary sulfonamide using the catalytic copper system is the main advantage of the invented protocol. Catalytic $Cu(OAc)_2$/TEMPO in the air and catalytic $Cu(OAc)_2/O_2$ system worked well for the majority of the substrate.



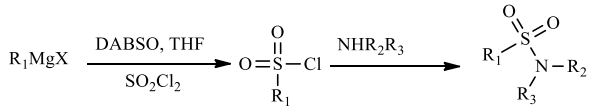
Scheme 23; Cu- catalyzed N-arylation of sulfonamide using boronic acid

Another example of Cu catalyzed N-arylation of sulfonamide was disclosed by [74] where coupling between aryl bromideor iodide and sulfonamide was carried out in excellent yield. **DMF** used as a solvent, K_3PO_4 and amino acid as a base and ligand **(scheme 24)**. Invention of less expensive and more environmentally benign Cu(**I**)/amino acid catalyst system for C-N cross-coupling reaction is the novelty of the protocol.



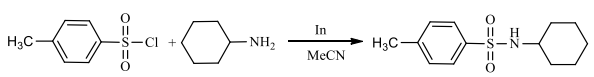
Scheme 24; Synthesis of N-arylsulfonamide using CuI

Woolven et al. [75] synthesized a stable complex **DABSO**, which was prepared by reaction between **DABCO** and gaseous sulfur dioxide. The complex was used as a safer source of sulfer dioxide, which was combined with Grignard reagent to produce sulfinate. Sulfuryl chloride was used to convert sulfinates to sulfonyl chloride, which was in-situ reacted with various amines to produce corresponding sulfonamides **(scheme 25).**



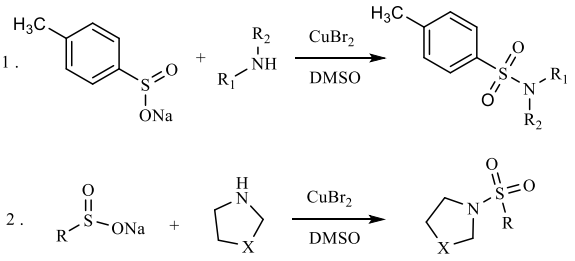
Scheme 25; Synthesis of sulfonamide using DABSO-Bis (sulfurdioxide complex)

Indium catalyzed sulfonylation of sterically hindered and less nucleophilic amines were reported by [76] in excellent yield. A A wide variety of sulfonamides was synthized by using the new methodology. The research group claimed reusability of the catalyst up to five times. They proposed that, eletrophilic species RSO_2^+ might be generated by reaction between sulfonyl chloride and indium metal, which is further reacted with aminesto furnish sulfonylated product and active indium metal **(scheme 26).**



Scheme 26; synthesis of sulfonamide using catalytic Indium

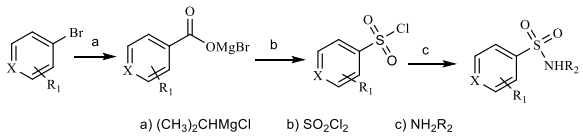
Cu catalyzed oxidative coupling between various aminesand sodium sulfonates **(scheme 27)** were investigated by [77]. Good yield and excellent chemo selectivity were observed since the transformation happened via a single electron transfer pathway.



Scheme 27; synthesis of sulfonamide via Cu-catalyzed oxidative coupling

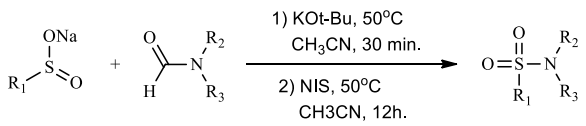
g- Synthesis of sulfonamide *via* Grignard

Pandya et al. [78] discovered an innovative method for the preparation of sulfonyl chloride followed by sulfonamide. Aryl and heteroaryl bromides had been first converted into the corresponding Grignard reagents the usage of isopropylmagnesium chloride, which had been subsequently reacted with sulfuryl chloride and amines to produce sulfonamides **(scheme 28).**



Scheme 28; synthesis of sulfonamide via Grignard

Recently [79] reported a two-step sequential metal free process for the synthesis of sulfonamides using *N*,*N*-disubstituted formamides as an amine and sodium sulfinates as sulfone source. Initially, formamide was decarbonylated by Potassium tert-butylate (KOt-Bu) to produce the corresponding amine in acetonitrile solvent. At the same time sodium sulfinatereacted with *N*-Iodosuccinamide (NIS) to afford sulfonyl iodide which was eventually generated sulfonyl radical. Finally, nucleophilic attack of amine to sulfonyl radical provided desired sulfonamide in 24-91% yield (**scheme 29**).

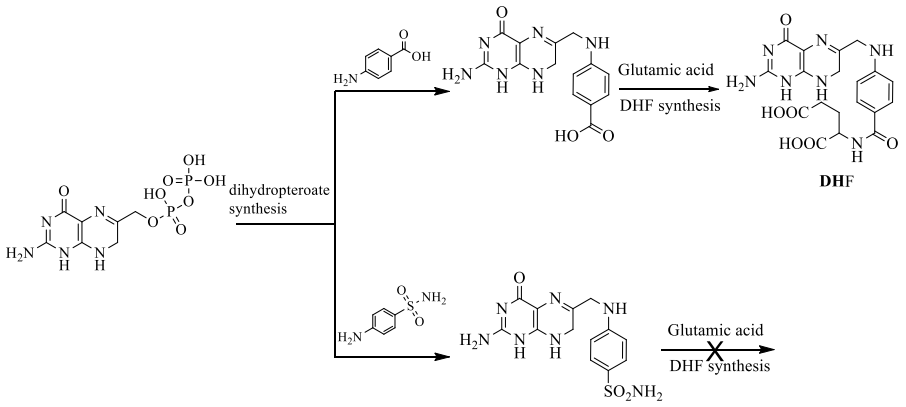


Scheme 29; Synthesis of sulfonamide via Gignard

3- Medicinal chemistry applications

a- Antimicrobial

Sulfonamide compounds are a big class of synthetic bacteriostatic antibiotics which are still used today for the therapy of bacterial infections and other infections caused by different microorganisms. Additionally they're referred to as sulfa drugs and were the most source of therapy against bacterial infections, before the introduction of penicillin in 1941. Additionally, the primary sulfonamide section is found in many clinically used drugs like diuretics, carbonic anhydrase inhibitors and antiepileptics. Sulfonamides are antimicrobial drugs with a broad spectrum of action, effective against Gram-positive and certain Gram-negative bacteria, like intestinal species [80]. Sulfonamides show a good activity against E. coli, moderate towards Proteus *mirabilis* and Enterobacter species and weak towards Klebsiella, however they display no inhibitory activity in opposition to pseudomonas aeruginosa and Serratia species. They are effective against species of Chlamydia genus. Sulfonamides also are powerful towards fungi (Pneumocystis carinii) and protozoa (Toxoplasma gondii).Sulfonamides differ in potency, but not in the spectrum of the antimicrobial activity [81, 82]. Because of the lack of ability of bacteria to gather dihydrofolic acid from their environment, as part of microorganism's DNA biosynthesis, inhibition of dihydrofolic acid synthesis poses a desirable target for bacteriostatic agents **(Scheme 30).** Inhibition of these enzymes has been achieved with early sulfonamides such as sulfanilamide. The formation of dihydrofolic acid is initiated with the aid of coupling pteridine diphosphate with p-aminobenzoic acid, which can then go through amide coupling with glutamic acid to shape dihydrofolic acid. Sulfanilamide displays comparable core structure to that of p-aminobenzoic acid and act as a competitive inhibitor. The Dihydrofolic acid formation is interrupted during the second step; because of a lack of acidic terminal to be had to couple with glutamic acid, hence dihydrofolic acid formation is interrupted [83].



Scheme 30; Inhibition of DHF formation by sulfonamide

Some compounds used as anti-microbial

El-Gaby et al. [84] Synthesized and studied Antimicrobial Activity of some novel thiourea, hydrazine, bisthiourea andfused pyrimidine derivatives containing sulfonamide moieties **(Fig. 9)**. Fourteen compounds were screened In vitrofor their antimicrobial activities against four strains of bacteria *staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579), *Serratia marcesens* (IMRU-70), *Proteus mirabilis* (NCTC-289) and two strains of the fungi *Aspergillus ochraceus Wilhelm* (AUCC-230) and *Penicilliumchrysogenum Thom* (AUCC-530) by the agar diffusion technique.

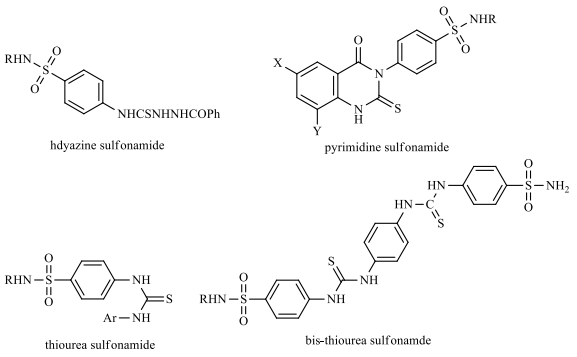


Fig. 9; some derivatives containing sulfonamido moieties

New aryldisulfonamides **(Fig 10**) were synthesized showing antibacterial activities against Gram positive bacteria (*S.aureus* ATCC 25953), (*B.aureus* ATCC 6633) and Gram negative bacteria (*E.coli* ATCC 11230) were done by Alyar*et al*. [85].

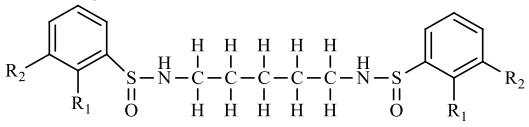


Fig. 10; structure of arydisulfonamides

1,3-diaryl-4-formylpyrazoles **(Fig 11)** synthesized and evaluated for their antibacterial activity against *S.aureus, B.subtilis* (Gram positive), *E.coli, P.aeruginosa* (Gram negative) and antifungal activity for *A.niger* and *A.flavus* by Sharma *et al* [86].

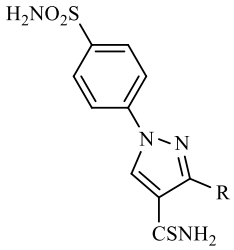


Fig. 11; Structure of 1,3-diaryl-4-formylpyrazoles

A series of new and novel coumarin-6-sulfonamides **(Fig. 12)** have been synthesized as antimicrobials such as antibacterial and antifungal activity [87].

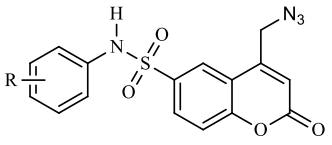


Fig. 12; Structure of chromene-6-sulfonamide

Series of Schiff's base **(Fig. 13)** have been prepared via reaction between substituted sulfonamides and aromatic aldehydes, which showed good antibacterial and antifungal activity [88].

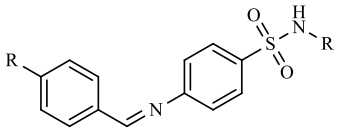


Fig. 13;N(2-substituted benzylidine)-4-sulfonamides benzenamine.

A series of novel heterocyclic thioureas containing sulfonamide moiety (**Fig. 14**) has been synthesized [89] through condensation of isothiocyanatobenzene sulfonamide with a variety of heterocyclic amines The newly synthesized compounds had been evaluated for their in *vitro* antibacterial activity against Streptococcus pneumoniae and *Bacillus subtilis* as examples of Gram-positive bacteria and Pseudomonas *aeruginosa* and *Escherichiacoli* as examples of Gram negative bacteria. They were also evaluated for their in vitro antifungal capacity towards a consultant panel of fungal strains i.e. *Aspergillusfumigatus*, and *Candida albicans*. Interestingly, some compounds showed similar or better activity comparison with the reference drug against the examined microorganisms.

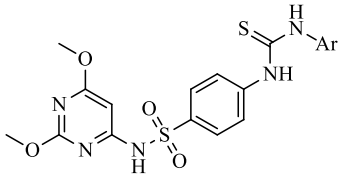


Fig. 14; structure of heterocyclic thioureas containing sulfonamide moiety

In the next year Ghorab et al. [90] described a new series of novel fluorinated thiourea derivatives carrying sulfonamide moieties (**Fig. 15**). Fluorinated pyridine derivative showed the highest antimicrobial activity (with MIC values ranged from 1.95 to 15.63 μg/mL). Interestingly, thiadiazole derivative and coumarin derivative exhibited selective antibacterial activities against Gram positive bacteria. Fluorinated pyridine derivative was the most active against HepG2 with IC_{50} value of 4.8μg/mL Molecular docking was performed on the active site of MK-2 with good results.

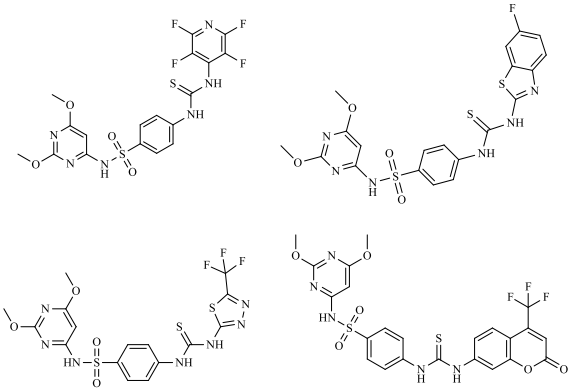


Fig. 15; new series of novel fluorinated thiourea derivatives carrying sulfonamide moieties

Recently, [91] synthesized a series of 4-((4-ydroxynaphthalen-1-yl)diazenyl)benzenesulfon-amides which have been prepared by subsequent diazotization of sulfonamide derivatives and coupling with 1-naphthol in alkaline medium. Cyclization of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzene sulfon-amides with cinnamic acidin the presence of a basic catalyst afforded the novel naphtho[1,2-b]furans.Also,4-((4-hydroxynaphthalen-1-yl)diazen-yl)benzenesulfonamide can be cyclized with α-cyanocinnamonitrilesto afford 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromenes.4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)benzenesulfon amides were obtained at room temperature by treatment of 2-amino-1,1,3-tricyanopropene with a diazonium salt of sulfonamide derivatives (**Fig. 16**).

Thenewly synthesized compounds tested displayed variable invitro antimicrobial activities under these screening conditions. Interestingly, the tested compounds exhibited significant antifungal activities against the filamentous fungus (Aspergillus fumigatus) and unicellular yeast (Candida albicans).

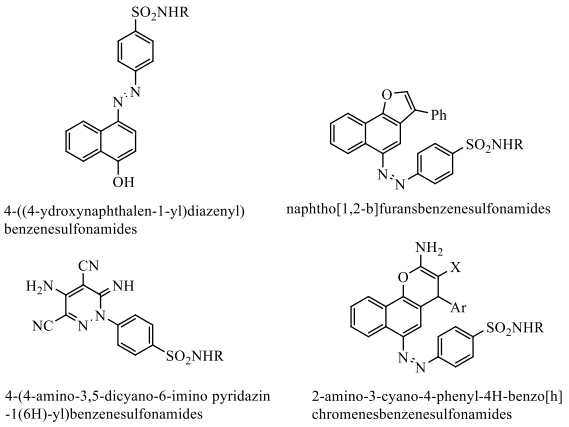


Fig. 16; derivatives of diazenylbenzenesulfonamides

In the same year they described the new series of sulfonamides drugs linked with thiourea-carbamate side chains as a drug delivery system was synthesized**(Fig. 17)** [92]. The thiourea-carbamate hybrid was connected to para-amino group which act as a prodrug to enhance sulfonamides activity. The novel hybrids sulfonamide-carbamates were synthesized by treatment of *N*-substituted 4-isothiocyanatophenyl sulfonamides (which synthesized in high yield *via* thiophosgenation of sulfonamides at room temperature in acidic medium (HCl), according to literature procedure) with ethyl carbamate in dry 1,4-dioxan at reflux temperature in the presence of triethylamine. Some Compounds exhibited activity against tested bacteria.

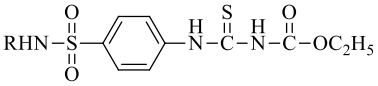
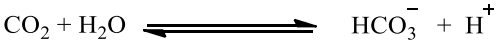


Fig. 17; structure of thiourea-carbamate benzene sulfonamides

b- Carbonic anhydrase inhibitors

Carbonic anhydrases catalyze the interconversion of carbon dioxide and bicarbonate. The main function of carbonic anhydrases is to modulate physiological pH, respiration, CO_2 transport, electrolyte excretion, regulation and homeostasis. Sixteen CA isozymes have been identified in humans, CA **I** to CA **XV**, with different sub-cellular localization[93-95].



The role of CAs in cancer can be explained thinking about the metabolic conditions required by a cancer growing cell, i.e., a cell developing with a higher rate of replication with respect to a normal one. any such circumstance calls for a excessive flux of bicarbonate into the cellular itself to be able to offer substrate for the synthesis of either nutritionally crucial components N (nucleotides) or cellular structural components (membrane lipids) [96]. On the other hand, H^+ ions produced by metabolism are pumped from the intracellular compartment into the interstitial one, subsequently flowing into the blood. Still, the level of H^+ ions in the interstitial compartment is higher in tumors compared with normal tissue [96].

Among the CAs, CA **IX** and **XII**show close association with tumors, therefore, believed that inhibition of CA **IX**/CA **XII** could be an attractive alternative option for anticancer therapy. Sulfonamides **97-100** have anti-carbonic anhydrase activity in nanomolar concentration **(Fig. 18)**[93, 95].However, due to their low selectivity, these CA inhibitors show good inhibitory activity against several isozymes including CA **I**, CA **II**, CA **IX**, and to some extent, CA **XII**.

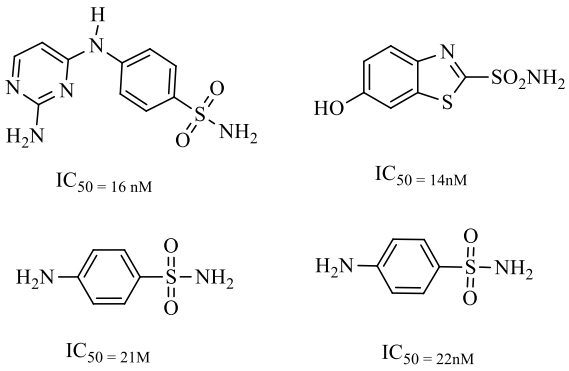


Fig. 18; structure and biological activity of CAI/CAII/CA IX inhibitors

Thiry et al. [97] later synthesized another class of sulfonamides and carried out an investigation of their potency against CA **I**, CA **II** and CA **IX**. It was found that even though the compounds were ineffective against CA **I** they were very effective against both CA **II** and CA **IX(Fig. 19).** Furthermore, a docking study of 33 within CA **II** and CA **IX**, by the same group, indicates that the binding pockets of the two isozymes (CA **II** and CA **IX**) are very similar; if this is the case then it will make it difficult to target one isozyme over the other.

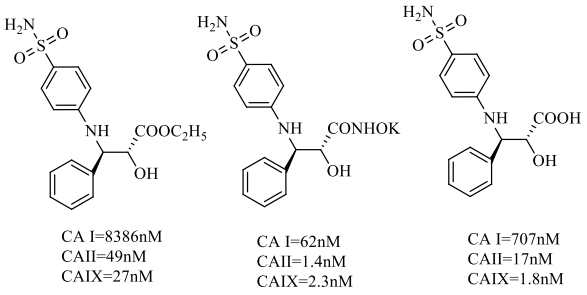


Fig. 19; Non-selective inhibition of CA I/CAII/CAIX

Supuran et al. [98] most recently reported that, by introducing a pyridinium moiety to the CA **II**/CA **IX** inhibitor**,** tumor acidification can be reduced by specifically inhibiting CA **IX**. **(Fig.20)**.Were reported and display good inhibition of CA **IX** over CA **II**.

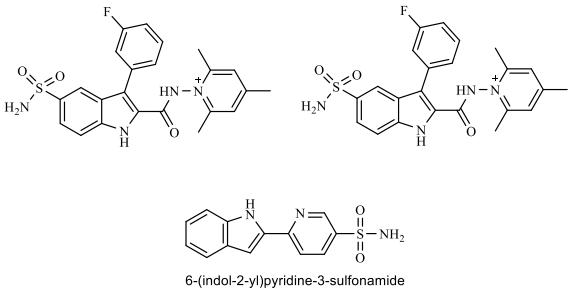


Fig. 20; Specific inhibitors for CAIX

Acetazolamide (AZA, anti- glaucoma), Zonisamide (ZNS, anti-convulsant) and Topiramate (TPM, anti-convulsant) **(Fig.21).**Are known for their ability to inhibit CAs, and their X-ray crystal structures have been determined, which show tight binding of the inhibitors to CA **II**, CA **VA** and CA VB[99][100]. Interestingly, it has been noted that, during clinical studies, obese patients experienced dramatic weight loss as a side effect.Therefore inhibiting CA **II**, VA and VB can reduce the rate of lypogenesis, and in turn, can be used as anti-obesity drugs[101, 102].

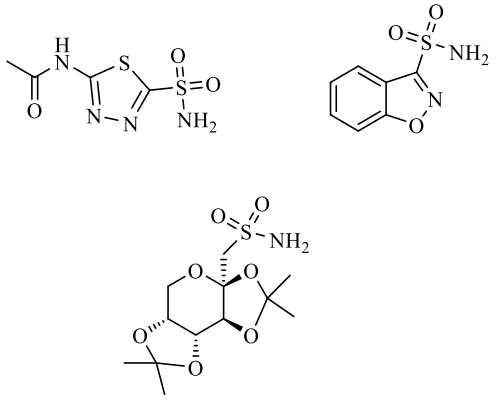


Fig. 21; commercially available inhibitors for CAV

Vullo*et al*. have synthesized a wide range of sulfonamides such as and for anti-CA **V** activity, and it was found that several aminobenzolamides display low-nanomolar potency compare to registered CA inhibitors **(Fig. 22)**[101, 103].

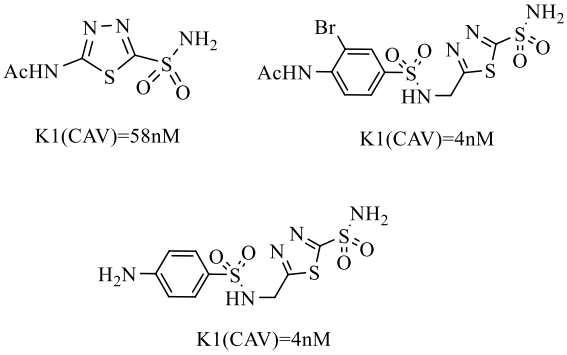


Fig.22; Structure and biological activity of CA inhibitors

c- Antiviral

i- HIV inhibitors

Sulfonamides also possess activity against **HIV** proteases. **HIV** protease consists of a homodimer with aspartyl active sites (Asp and Asp), which have the ability to cleave difficult bonds, such as Tyr-Pro and Phe-Pro2. Thus far, several **HIV** protease inhibitors are clinically available, and are often used in conjunction with reverse transcriptase inhibitors to deliver the multi-drug treatment known as the Highly Active Anti-Retroviral Therapy. It was found that non-peptidic protease inhibitors display higher bioavailability as well as slower excretion rate compared to the conventional peptide-base protease inhibitors. Among those protease inhibitors Amprenavir and Tipranavir aresulfonamide derived drugs [11][104, 105].

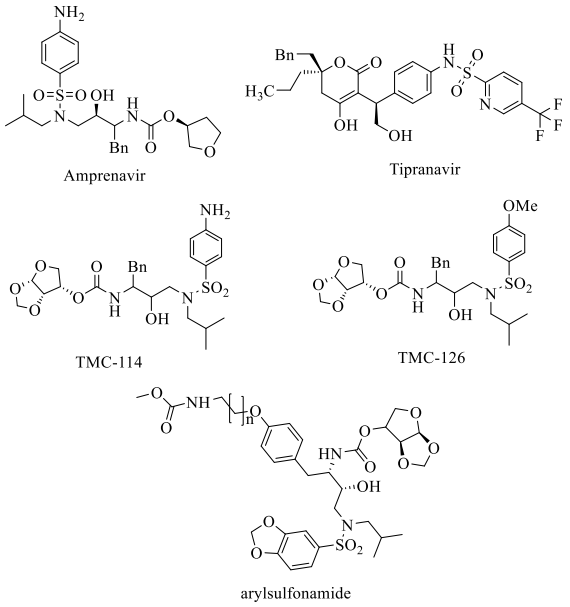


Fig. 23; structure of HIV protease inhibitors

Most drugs achieved their high potency due to their ability to bind rigidly and optimally into an active site. However, high mutation rates within **HIV** viral particles render many anti **HIV** drugs inactive, furthermore, they pose tremendous challenge to antiretroviral therapy. A more recent idea of overcoming this problem is to synthesize a drug that, instead of binding tightly to the protease active site, binds tightly with the protein backbone since the protein backbone are only minimally deformed during mutation [106]. An example of this approach can be seen in the investigations of derivatives of Amprenavir which are currently being investigated; these include TMC-114 (a.k.a Darunavir) and TMC-126. X-ray crystallography of TMC-114 bound to **HIV** protease showed that the bis-THF moiety of TMC-114 forms strong H-bonds with Asp and Asp amides within the protein backbone, and showed 10-fold higher potency than Amprenavir and Tipranavir[106][107].Ohtaka*et al*. also showed that TMC-126 displays 13-fold higher potency than that for Amprenavir[107, 108].Meanwhile, another class of arylsulfonamide, which are structurally related to TMC-114 and TMC-126, also displaysthe low Nanomolar concentration during a QSAR study **(Fig. 23**) [109].

Apart from the numerous studies as **HIV** protease inhibitors, sulfonamides in recent years, are also found to inhibit **HIV** reverse transcriptase [110] and cell entry [111]. (Wang H-G. et al. and Wang T. et al. have modified a previously known viral fusion inhibitor BMS806 by replacing the α-ketoamide with a sulfonamide and a biaryl moiety to further improve the potency (**Fig.24**) [112, 113].

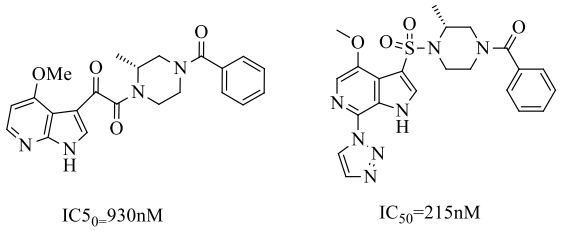


Fig.24; structures and biological of HIV cell entry inhibitors

ii- Herpes viruses (HSV and HCMV) protease inhibitors

The herpes viruses are enveloped, linear double-strand DNA viruses with a distinctive morphology, containing an icosadeltahedral capsid surrounded by an amorphous tegument. the viral genomes range in size from 125 to 230 kilobases (kb), encoding for 70–200 gene products 115 [114].

Eight human herpes viruses have been identified so far, divided in three sub-families as follows:

i) α-Herpes viruses, which include **HSV-1, HSV-2**, and varicella-zoster virus (**VZV**). They cause widespread disease in either immunocompetent and immunocompromised patients, such as mucosal-labial herpes (cold sores) –HSV-1, or genital herpes–**HSV-2**, respectively. VZV infection is also widespread in the human population, causing chickenpox following primary infection in children and shingles (herpes zoster) upon reactivation in adults [115].

ii) β-herpesviruses include **HCMV**, human herpes viruses 6 and 7 **(HHV-6** and **HHV-7).HCMV** provokes serious pulmonary (pneumonitis) or ocular (retinitis) diseases, mainly in immunocompromised patients or transplant recipients115-117 [114, 116]. In addition, congenital **CMV** infection provokes morbidity in approximately 15% of babies asymptomatic at birth115(Smith 2002).**HHV-6** (and to a lesser extent **HHV-7**) is the primary cause of roseola, infecting greater than 95% of babies, whereas its reactivation is associated with complications in transplant recipients115[114].

iii) ɤ-herpes viruses include Epstein–Barr virus (**EBV**) and the newly identified human herpesvirus 8 (**HHV-8**) [117].

Primary **EBV** infection is the leading cause of infectious mononucleosis in adolescence and early adulthood, but this virus is also associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease [114]. **HHV-8** is associated

with Kaposi's sarcoma in **AIDS** and solid organ transplant populations[117]and may be a significant factor in the development of multiple myeloma [114, 117]. A sulfonamide-based antivirals were also recently designed against the **HCMV** protease [118].

In contrast to the **HIV PR** discussed earlier, this enzyme belongs to the serine PR family, and together with similar proteases isolated from other herpes viruses, it is characterized by a particular catalytic triad, of the type His, His-Ser within the active site [119].

It was observed that α-methylpyrrolidine-5,5-trans-lactam derivatives of type (**I**) act as mechanism-based inhibitors of the **HCMV**δAlaprotease, acylating reversibly and in a time dependent manner the active site nucleophile Ser 132 [118].This serine **PR** hydrolyzes peptide bonds of the type Ala-Ser. Compounds of type **(II)** bind to this PR with the 6-Me group within the S_1 sub site, the N-4-cyclopropylcarbonyl moiety within the S_1 , sub site and the bulky, hydrophobic arylsulfonylpyrrolidine-2-carbonyl moiety within the S_3 sub site[118]. Derivatives incorporating the dansyl-(S) - proline moiety in this position showed the best activity (IC_{50} of 0.34 uM) and also specificity over related serine proteases (such as elastase, thrombin, or acetyl cholinesterase), which were inhibited with IC_{50} values in the range of 10–200 uM. [118]. Some halogeno-ketone sulfonamide derivatives **(II-IV)** were also reported as potent inhibitors (inactivates) of the **HCMV** protease, but no precise biological data are provided.35 These compounds incorporate either secondary sulfonamide (**II, III**) or secondary and primary sulfonamide groups **(IV)** in their molecules, in addition to the reactive halogeno-ketone moiety responsible for inactivation of the protease, by reaction with the active site, catlytically critical Ser 132(**Fig. 25**) [119].

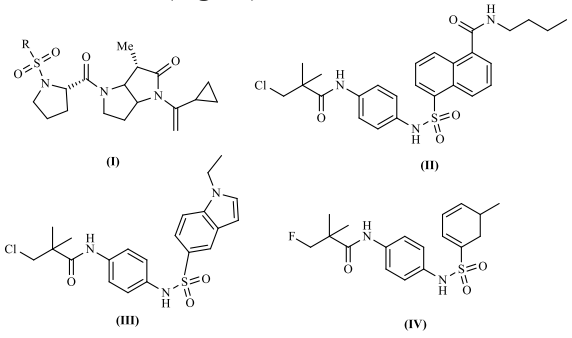


Fig. 25; some selected compounds as HIV inhibitors

iii- HCV inhibitors

Hepatitis C virus (**HCV**) is a major cause of acute hepatitis and chronic liver disease, including fibrosis, cirrhosis and liver cancer [120].Globally, up to 3% of the world's population is chronically inflamed with HCV and 3–4 million people are newly infected every year [121].

a singular collection of 6-(indol-2-yl)pyridine-3-sulfonamides (**Fig. 26**) turned into prepared and evaluated for his or her capability to inhibit HCV, RNA replication in the HCV Replicon cell culture assay by Chen et al.The target compounds were synsized through a Suzuki coupling strategy by treatment of the boronic acid, generated from the key intermediate, with the corresponding aryl halides. Preliminary optimization of this collection furnished compounds with low nanomolar potency against the HCV genotype(1b Replicon.,some compounds have diagnosed as a powerful HCV Replicon inhibitor with a selectivity index with appreciate to cellular GAPDH of more than 2500 [122].

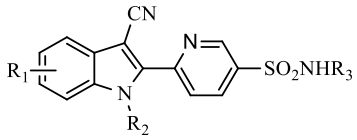


Fig. 26; structure of 6-(indol-2-yl)pyridine-3-sulfonamides

d- **COX-II specific inhibitors**

Cyclooxygenase (COX) is involved in the synthesis of prostaglandins and thromboxane from arachidonic acid. Cyclooxygenase exist in three isoforms: COX**(I-III).** Cyclooxygenase-**I** is expressed in platelet aggregation and mucosal protection by prostaglandin production, thus an undesirable side effect of COX-**I** inhibition can be gastric damage. Cyclooxygenase-**II** is induced and expressed during inflammation, cell proliferation and angiogenesis. Cyclooxygenase-**III** is identified as a COX-**I** variant, and it's known to be inhibited by paracetamol [123-125].

Conventional COX inhibitors along with ibuprofen are acknowledged to have low selectivity and as a result might also result in ulcer, bleeding and gastroduodenal erosion. However, COX-**II** specific inhibitors can relieve symptoms such as pain, caused by inflammation, but without the undesirable side effects of traditional COX inhibitors [126]. Celecoxib and Valdecoxib (**Fig.27**) have been developed by Pfizer as COX-**II** specific inhibitors for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) [127, 128].

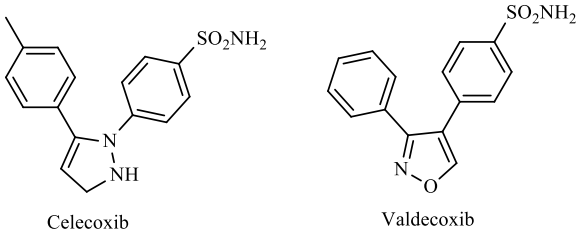


Fig. 27; commercially available COX-II inhibitors

Normally, prostacyclin (PGI2) and thromboxane (TxA2) are both produced, but the traditional COX-**II** specific inhibitors may disrupt the optimum balance of the two species and an increase in the amount of thromboxane, can elevate the risk of cardiovascular disease, heart attack and stroke; which it is the case for Valdecoxib. Recently a new approach has been to utilize an inhibitor, which is mainly COX-**II**selective, but with mild COX-**I** inhibitory properties. Yang *et al*. [129] Have synthesized a range of 4-Phenyliminomethyl benzenesulfonamide, based on the natural product Resveratrol (**Fig. 28**), that have 7-80 fold selectivity for COX-II over COX-**I**.

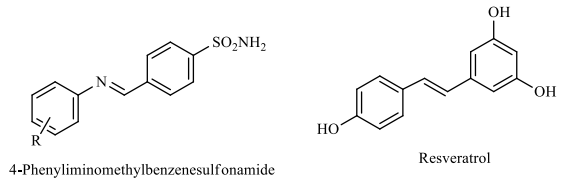


Fig. 28; COX-II selective inhibitors with mild COX-II inhibitor properties

Ghorab et al. in 2017 was prepared novelthiourea derivatives bearing sulfonamide moiety as anticancer agents through **COX-II** inhibition **(Fig. 29)** [130]. a number of examined compounds confirmed a large selective cytotoxicity against HepG2, MCF-7, Caco-2 and PC-3 cancer cells. The target compounds were further screened in vitro for their anti COX-**I**/COX-**II** activity and investigated in vivoas anti-inflammatory agents against carrageenan-induced rat paw oedema model.

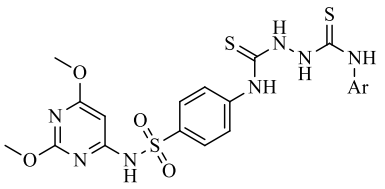


Fig. 29; thiourea-sulfonamide moiety derivatives

e- Protease inhibitors

Cysteine proteases are a class of biologically important enzymes, which are involved in inflammation, cell apoptosis and protein degradation[131-133].These enzymes also are implicated in numerous disorder states which includes arthritis, osteoporosis, Alzheimer's disease, cancer and malaria.

Examples of cysteine protease enzymes include caspase, a cysteine protease which cleaves at the Ala-Asp residue (hence caspase), and is strongly associated with bapoptosis, necrosis and infection. There are 11 caspases now realize, specifically caspase 1-10 and 13. Not all caspases are directly concerned in apoptosis; in which the initiator caspases **(CASP-2, CASP-8 and CASP-9)**are liable for activating the effector (executioner) caspases **(CASP-3, CASP-6 and CASP-7)**in advance than the apoptosis. Therefore, apoptosis occurs through a network cascade of caspases instead of an individual enzymatic reaction[131, 133].

Another example is the interleukins illustrated by interleukin-**1β** (**IL-1β**), a cytokine implicated in various neurodegenerative diseases such as Alzheimer's disease. However, **IL-1β** is normally present in its inactive pro-form and needs to be converted into the active cytokine by an **IL-1β** converting enzyme (**ICE**), now known as **caspase-1**. Early studies from various corporations have found that a deficiency of **caspase-1** on animal version (transgenic mice) were related to reduced neuronal apoptosis, suggesting an oblique affiliation of**caspase-1** with neuronal cell death. Therefore if **caspase-1** level can be moderated, this will then be possible to treat Alzheimer's disease[134-136].

It's clean that inhibition/interference with caspases offers a number of therapeutic possibilities and this prompted [137] to develop an approach toward a library of diphenyl ether sulfonamides and these were shown to exhibit micromolar inhibition against **caspase-1**.However **SAR** study by [13] Suggested that, by increasing the number of H-bonding on a known peptide-based **caspase-1** inhibitor, increases the rigidity of the molecule as well as potency **(Fig.30).** In addition, K_I and IC_{50} are further decreased by introducing a sulfonamide group and a C_2H_4Ph side arm. Thus, improvements in potency can be achieved, rendering sulfonamides potentially therapeutically useful.

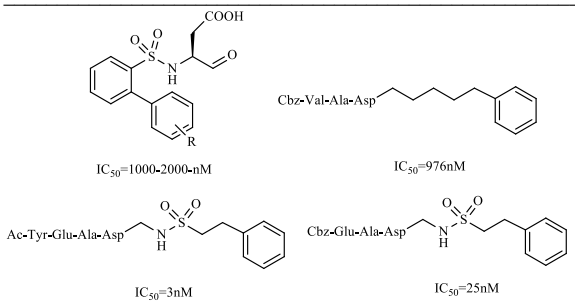


Fig. 30; structures and biological activity of caspase -1 inhibitors

A high-throughput screen at GSK identified two 5-nitroisatin based compounds and as potent caspase-3 inhibitor **(Fig.31).**

Caspase-3 is an effector **caspase** that directly linked to apoptosis. Lee et al. have synthesized several analogues with different substituents on the 5-*C* position, and found that replacing a nitro group with a sulfonamide group can improve the potency to low-nanomolar range, for example the pyrrolidine sulfonamide exhibited potent caspase-3 and caspase-7 inhibition [138, 139].

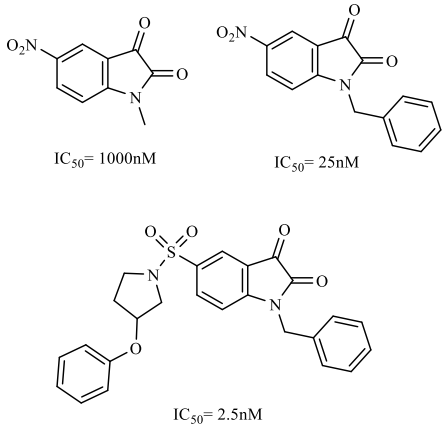


Fig. 31; Structures and biological activity of Caspase -3 inhibitors

Cysteine proteases are also important to the life cycle of pathogenic protozoa such as Trypanosoma Curzi, which was found to be the cause of Chagas' disease in South America. Cruzain, a form of cysteine protease in T. Cruzi, was found to be a potential therapeutic target for treatment of Chagas' disease. Roush *et al.* [140] have synthesized several vinyl sulfones, sulfonates and sulfonamides and these were screened against Cruzain. It was found that several of these compounds were very potent inhibitors (**Fig.32**).especially vinyl sulfonamide and vinyl sulfonate. Furthermore, the second generation of the vinylsulfonamidesare found to be active in vitro and in vivo [141].

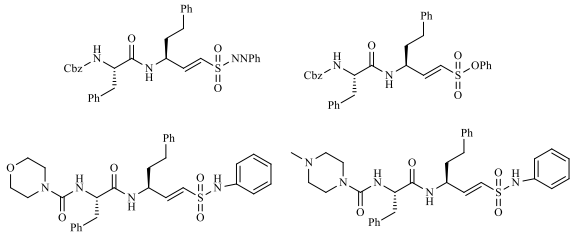


Fig. 32; structures of Cruzaininhibitirots

f- Histone deacetylase 6 inhibitors

Autosomal dominant polycystic kidney disease (ADPKD) is associated with the advanced magnitude of numerous renal cysts, mostly give rise to the renal disorder that can't be put a stop to by a common therapy. Two protein chains encoded by two genes are associated with ADPKD: PC2 (pkd2), a Ca^{2+} channel, and PC1 (pkd1), a signaling molecule. Derangement of cAMP signaling is focal to ADPKD, but the molecular process is undetermined. [142] a model recorded which histone deacetylase 6 inhibitors (HDAC6i) decreases intracellular Ca^{2+} via inhibition of ER Ca^{2+} release [143]. They propose that HDAC6i inhibits proliferation and cell growth primarily by significantly decreasing Ca^{2+} and cAMP levels.Their results determined therapeutic purposes that can be beneficial as potential therapies for ADPKD. At one of the new progress in cancer therapy recorded the role of epigenetic modifiers in the adjustment of immuno-modulatory pathways. Between these, HDACs are marvelous goals due to the accessibility of multiple marketed, broad spectrum inhibitor compounds of these zinc-containing enzyme [144]. Diverse HDAC is such as quisinostat, panobinostat, and vorinostat have newly been tested in early Phase II or Phase I trials for melanoma, hence most of these demonstrate limited effect and acceptability as single factors, with nausea, fatigue, laboratory abnormalities, and hematological toxicity happening as repeatedly harmful effects. The Histone deacetylase 6 inhibitors of sulfonamides patent applications were filed by Lee et al. [145] which developed AU2016299484 (A1), (Applicant: Chong Kun Dang Pharmaceutical Corp) a potent, selective, competitive, and reversible Histone deacetylase 6 inhibitor. on this patent, the winning invention relates to novel compounds represented with the aid of using the method I having histone deacetylase 6 (HDAC6) inhibitory interest, stereoisomers thereof, or pharmaceutically appropriate salts thereof, the use thereof for the guidance of healing medicaments, pharmaceutical

compositions containing the equal, a way for treating illnesses using the composition, and strategies for making ready the unconventional compound.

The novel compounds, stereoisomers thereof, or pharmaceutically acceptable salts thereof, according to the present invention have histone deacetylase (HDAC) inhibitory activity and are effective for the prevention or treatment of HDAC6-mediated diseases (**Fig.33**) [145].

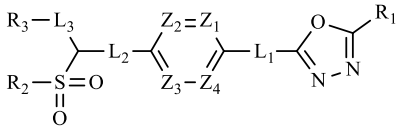


Fig. 33;

g- Sphingosine kinase inhibitors

Two isoenzymes of sphingosine kinase have been recognized (**SphK1** and **SphK2**). However, they showed accurate differences in the subcellular localization and substrate specificity, **SphK1** and **SphK2** isoforms catalyze the identical reaction, i.e., the phosphorylation action of sphingosine to generate sphingosine-1-phosphate (**S1P**) compound. **S1P** compound is a bioactive lipid which activates a class of G protein-coupled receptors, called **S1P1–5** [146]. The **SphK1** enzyme is predominantly localized to the cytosol part while **SphK2** isoform is principally nuclear. **SphK1** and **SphK2** isoforms double knockout rats exhibit a seriously damaged angiogenesis and neurogenesis, causing embryonic lethality. Thus, mice knocked out for just one of the two kinase enzymes are fertile, viable, and without any evident disturbances, clearly because of some compensatory acts of the two isozymes [147]. Experiments obtained knocking down SphK1 and SphK2 indicate the being of a compensatory process for the two isoenzymes (**Table 1**).

Table 1. Issued patents claiming SphK* inhibitors

Title	US patent	Assignee
Sphk inhibitors	7,220,764	Apogee Biotechnology
Sphk inhibitors and method of their use	7,338,961	Apogee Biotechnology
Sphk inhibitors and method of their use	8,063,248	Apogee Biotechnology
Sphk inhibitors and method of their use	8,577,800	Apogee Biotechnology
Sphk inhibitor prodeug	8,685,936	Apogee Biotechnology
Thiazolyle piperidine derivatives	8,436,186	Merck Patent GmBH
Inhibitors of Sphk	8,907,098	Merck Patent GmBH
Inhibitors of Sphk	9,062,015	Merck Patent GmBH
Sphk1 inhibitors and processes using the same	8,314,151	Enzo Therapeutics
Novel Sphk1 inhibitors ,compositions and processes	8,372,888	Enzo Therapeutics
Composition and method for inhibiting Sphk	8.686,066	University of Virginia

*Sphk = sphingosine kinase

Therefore, multiple types of research have centered their consideration on the expansion of dual inhibitor compounds to study this mechanism further [148]. The observation of the SphK1 structure has given a raise to the discovery of new SphK inhibitor compounds, newly give rise to the exploration of newisoenzyme elective inhibitors. The inhibitor compounds have been beneficial in clarifying the important roles of SphK enzymes in the involvement in inflammatory signaling and in the egulation of key oncogenes. Indeed, the most generally utilized inhibitors failed to induce Cancer cell death (**Table 2**).

Table 2. Pending Applications Claiming SphK inhibitors.

Title	Application	Applicant
Long chain Sphk inhibitors	WO 2013/119946	University of Virginia
Selective inhibitors and allosteric activation of Sphk	WO 2014/118556	City University of New York & University of Strathclyde (UK)
Sphk inhibitor	WO 2014/157382	Ajinomoto
Benzene sulfonamide- based inhibitor of Sphk	WO 2016/007993	Univ South Australia

The Sphingosine kinase inhibitor of sulfonamides patent applications was filed by [149] which developed WO2016007993(A1), (Applicant: Univ south Australia [au] central Adelaide local health network INC [au]) a potent, selective, competitive, and reversible sphingosine kinase inhibitor (**Fig.34**).

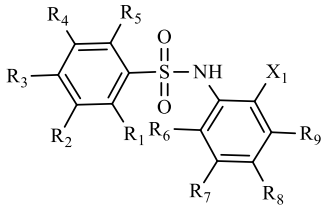


Fig. 34; reversible sphingosine kinase inhibitor

h- Sulfonamides as a cure of some diseases

Sulfonamides also have substantial value in the treatment of more complex diseases. After the belief that sulfonamide derivatives could have enzyme inhibitor residences in a broad variety of biological pathways, they have been applied as carbonic anhydrase inhibitors (**CAI**) in diverse applications as well as anti-hyperthyroidism, antitumor and anticancer agents [150-157].

i- Alzheimer's disease

Inside the beyond decade, there have been substantial new tendencies in drug discovery closer to the treatment of dementia and Alzheimer's disease using sulfonamide derivatives in multi-target procedures. Following the work of [150] on N-bridged bicyclic sulfonamide-based inhibitors of γ-secretase as new anti-AD drug candidates, the attention was divided between γ-secretase inhibition to prevent amyloid β accumulation and inhibition of two cholinesterase enzymes of the cholinergic system that is responsible for neurotransmission and is related to memory and other cognitive activities. The hydrolysis of the neurotransmitter acetylcholine (**ACh**) terminates the cholinergic neurotransmission in the brain and is catalyzed by acetylcholinesterase (**AChE**) and butyrylcholinesterase (**BChE**) The accumulation of tau and amyloid-β protein deposits, oxidative stress and other contributors lead to a decrease in the amount of **AChE** in **AD**. Therefore, for symptomatic treatment purposes, some of the focus shifted towards the development of **AChE** and **BChE** inhibitors [158]. Košak*et al*. highlighted the significance of noncovalent binding in the efficiency of cholinesterase inhibitors derived from sulfonamides **(Fig. 35)** in their publications from 2016 to 2018 [158-160].Mutahir *et al*. [161] also demonstrated that binding of the inhibitor molecule to **AChE** and **BChE** via interactions in the hydrophobic pocket is quite significant in the inhibitor activities.They synthesized new biphenyl bis-sulfonamide analogues and tested their inhibitory activities, as well as utilized molecular modeling in their evaluation. It was found that the replacement of the acetyl moiety with a propyl group improved the activity, and adding n-butyl groups to the nitrogen further enhanced it. This indicated that electron donating alkyl groups, especially on the nitrogen, positively influence the binding, thus noncovalent interactions are significant in the complex formation between the enzyme and inhibitor [161]. In 2016, Košak and co-workers reported several sulfonamide derivatives of the in vivo active cymserine drug, a **BChE** inhibitor that has passed Phase I trials. One of the compounds obtained by replacing 2,3-dihydro-1H-inden-2-yl ring with benzyl groups **(Fig.35),** showed to be the most potent drug candidate with 4.9 nM IC_{50} against human **BChE** [158]. It was able to successfully inhibit **BChE** activity, while protecting neuronal cells from toxic amyloid-β species, and also had low cytotoxicity, good Caco-2 cell permeability (rat brain cells) and high plasma binding, thus longer half-time in human plasma [158].

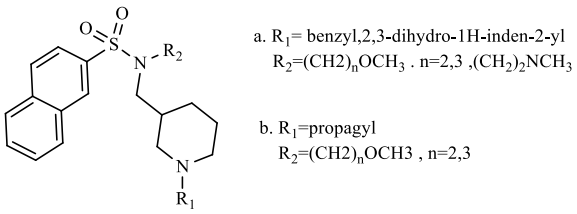


Fig. 35; structure of sulfonamides-derived AChE and BChE inhibitor candidates (a) [158, 159], (b)[161]

The same group developed sulfonamide derivatives of another hit compound, **PDB4TPK**, a potent human BChE inhibitor, and reported an in vivo active noncovalent **BChE** inhibitor with picomolar IC50 value.2 The crystal structural characterizations revealed two strong cation-π interactions, when it makes a complex with the target enzyme, as the source of its highly improved inhibitory properties [159].In parallel to the developments discussed above, [162] reported significant addition to the library of sulfonamide drugs that showed activity towards cholinesterase modulation, amyloid-β self-assembly inhibition and free-radical scavenging aspects of **AD** treatments. Among the tested compounds was the well-known **AChE** inhibitors donepezil and galantamine as references, and a variety of commercially available and newly synthesized novel cyclic and long chain aliphatic sulfonamides [162](**Fig.36**) summarizes similar reports, each group utilizing a slightly different base structure for their sulfa-drug candidates in **SAR** studies.

In 2014 and 2015, novel aryl sulfonamide derivatives were reported that can act as antagonists of **5-HT6/5-HT7** to treat dementia [163] as well as methods that combine these antagonists and cholinesterase inhibitors to find drugs that can have potent activity against Alzheimer's disease [164]. Following this report by [165] prepared and tested sixteen new sulfonamide derivatives of a known **AD** drug molecule to obtain both serotonergic subtype 4 receptor **(5-HT4R**) agonist and **5-HT6R** antagonist properties. Later, further tacrine-based and donepezil-like structures for producing sulfonamide based potential drug candidates, as well as N-propargylpiperidines with naphthalene-2-sulfonamide moieties for potential multi-target agents against **AD** were described.[160, 162], [166] More recently, Knez*et al*. reported a highly merged chimeric multi-target directed ligand synthesis that are sulfonamide derivatives. The goal was to obtain both **BChE** inhibition and good antioxidant, i.e. good radical scavenging properties. Two of their compounds showed promising results, which can be developed into new **BChE** inhibitor drugs that are also antioxidants and show neuroprotective properties [167].It was followed by another study on the metabolism of a sulfonamide derivative SAM-760, a serotonin receptor subtype 6 (**5-HT6R**) antagonist. Mathematical models were developed to learn about its pharmacokinetics and drug-drug interactions [168].

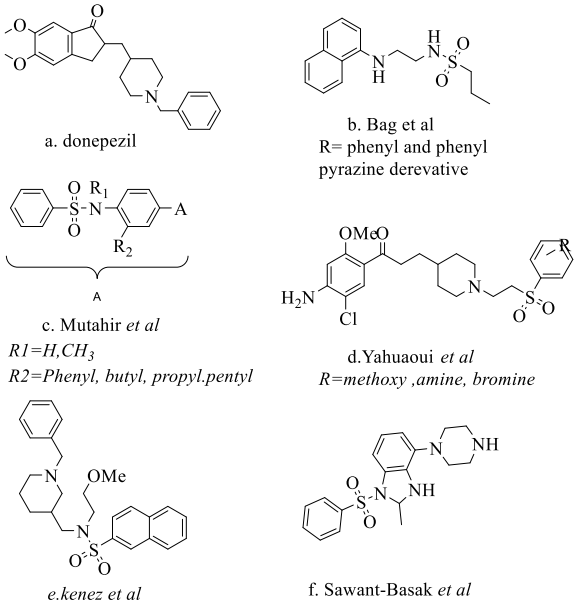


Fig.36; Donepezil (a), a well -known inhibitor of AChE and BChE, is an inspiration for the design of many sulfonamide derivatives as potential anti -AD drugs (b,c,d,e,f) [161, 162], [167, 168]

j- Anticancer

most cancers is a group of the most deadly kinds of sicknesses characterised by means of odd and uncontrolled cellular proliferation. most cancers is the second one most public reason of death after cardiovascular illnesses internationally for men and women. on the other hand, incidence ratio is anticipated to growth dramatically inside the close to future. The high incidence and mortality ratio of cancer are due to the fact that there are more than 200 types of cancer and it is very hard to discover most of them in the early stage. For all these reasons, the vast majority of current research focused on cancer treatment with biologically more potent and less toxic way by using specific methods and sulfonamides had been additionally having an crucial region in drug discovery research and continue to be the one of the maximum investigated compounds owning pharmacological activities as anticancer.

In 2018, novel 5-amino-1,3,4-thiadiazole-2-sulfonamide derivatives of acridine sulfonamide/ carboxamide compounds with inhibitory effects on human carbonic anhydrases were reported [154] **(Fig. 37**). Using sulfonamides for carbonic anhydrase (**CA**) inhibition dates back to and has gained increasing attention since 2005. Supuran's group demonstrated that aromatic sulfonamides show increased activities towards **CA IX** isozyme, after confirming that it was a drug gable target. The study was carried out with a library of aromatic sulfonamides with various substituents at the triazine moiety (**Fig. 37)** [152, 169]. In a follow-up work, they persisted to synthesize similar derivatives for checking out as human **CA I, II**, and **IX** inhibitors increase their investigation (**Fig. 37**) [169]. To increase the selectivity of **CA** inhibitors, numerous tactics had been developed, one in every of which turned into to utilize the truth that tail moieties of the ligand (**Fig. 37**) interact with the amino acid residues on the rim of the enzyme cavity [170]. The same researchers reported a detailed evaluation of sulfonamide derivatives that were effective towards **CA IX** as they promoted oxygen species-mediated apoptosis in cervical cancer HeLa cells **(Fig. 37).** Important points regarding the mechanism were revealed, such as the change in pH leading to the reduction of cell proliferation and increased cell apoptosis. It also supplied a useful approach for the inhibition of **CA IX** activity in human tumors that specific this enzyme at a high rate [171]. In every other latest report, tertiary sulfonamide derivatives of pyridyl-indole based totally heteroaryl chalcone were synthesized and tested as **CA IX** inhibitors (**Fig. 37**) [58]. The results of this observe served as an illustration that tertiary arylsulfonamides may also function lead compounds within the improvement of non-zinc-binding inhibitors with anticancer properties that can also selectively bind to **CA IX** isoforms [58].

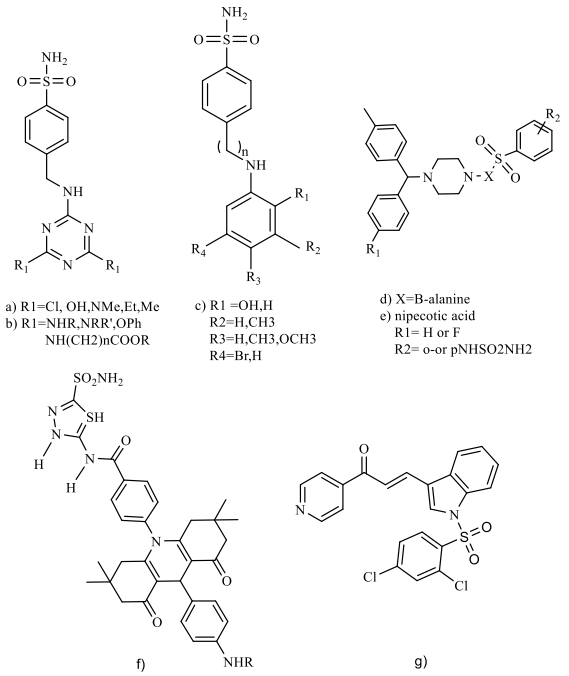


Fig. 37; Sulfonamide derivative with varying groups (a [152] and b[169]at the triazine moiety that are active towards CA I,II,IX isozymase , and their expanded library by varying R and X groups as indicated (c, d and e) [170, 171]. Acridine - derivative sulfonamides tested for their inhibitory effects towards human CAI, II, IV and VII isozymase f [154]. Pyridyl -indole -based sulfonamides derivatives studied for their anticancer properties g [58]

Okolotowicz et al. in 2018,synthesis novel tertiary sulfonamides as potent anti-cancer agents (**Fig. 38**) [172].

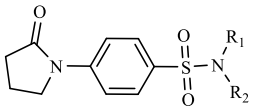


Fig. 38; general structure of pyrrolidinone phenylsulfonamides.

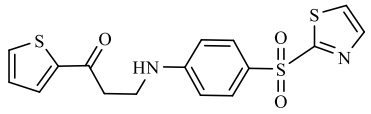
Some important Sulfonamide derivative as potent anticancer agent

Sulfonamide based drugs are clinically used in the cure and treatment of various types of cancer cells of different body parts. Cancer is a disease which deals with the growth of abnormal cells that quickly proliferate to other body parts. There are different types of cancers such as lung cancer, liver cancer, prostate cancer, breast cancer, pancreatic cancer, skin cancer, and lymphoma [173]. Each type of cancer has different symptoms. Cancer is a worldwide health problem and the most fatal disease

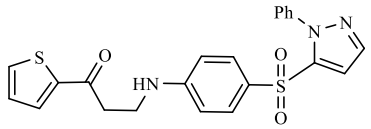
in humans. The causes of cancer are environmental pollution, poor food quality, unawareness in public and different sources of carcinogens. Cancer is increasing regularly day by day due to the increase of these factors. Cancer can be treated via radiotherapy, surgery and chemotherapy [174].

The literature survey of the last decade mentioned in this review article provides a comprehensive insight to the effect that the heterocyclic moieties substituted with the sulfonamide core have an effect on the therapeutic potential of sulfonamide derivatives against different types of cancer cell lines. The present study shows that the synthesized anti-cancer sulfonamide combinatorial libraries, analogs and scaffolds, can be helpful tothe development of new drug design and future drug discovery in pharmaceutics and medicine Praxis.

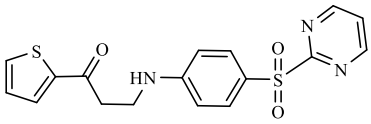
Ghorab et al. in 2014, synthesized sulfonamide derivatives having antitumor activity against Michigan Cancer Foundation-7 (MCF-7) cell line. The thiophene based thiazole sulfonamide scaffold, thiophene based pyrazole sulfonamide derivative, and thiophene based pyrimidin sulfonamide derivative **(Fig.39)**, exhibited best activity against MCF-7 cell line from all the synthesized derivatives with IC_{50} values 10.25, 9.70 and 9.55 μmol L^{-1} respectively as compared with reference doxorubicin [175].



thiophene based thiazole sulfonamide derivatives



thiophene based pyrazole sulfonamide derivatives



thiophene based pyrimidine sulfonamide derivatives

Fig. 39; sulfonamide derivatives having antitumor activity against Michigan Cancer Foundation-7 (MCF-7) cell line

Bonakdar et al. in 2017, screened chalcone based sulfonamide derivatives as anticancer agents against MCF-7 (Breast cancer) cell line **(Fig. 40)**.Among all these derivatives, the substituted acryloyl sulfonamide scaffold showed potent anti-cancer activity as compared to the reference compound Tamoxifen with IC_{50} value 2.5 μM [176].

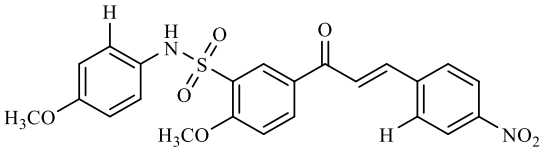


Fig. 40; Substituted acryloyl sulfonamide derivatives

Reddy et al. in 2016, prepared cinnamyl sulfonamide hydroxamate derivatives as anticancer activity against breast ER^+ adenocarcinoma (MCF-7), breast epithelial (MCF-10A), ER^- adeno carcinoma (MDA-MB-231), and lung cancer (A549). Among these derivatives, the NMJ-2 (cinnamylsulfonamidehydroxamate derivative) showed potent antitumor activity with the IC_{50} value 5.5 ± 0.43, 8.9 ± 0.80, 5.8 ± 0.27 and 6.5 ± 0.87 and for the MCF-7, MCF-10A, MDA-MB-231and A549 respectively**(Fig. 41)** [177].

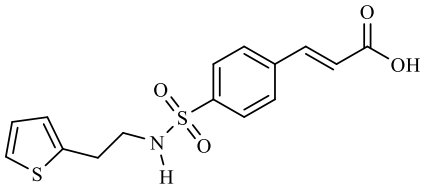


Fig. 41; cinnamyl sulfonamide hydroxamate derivative

Sławiński et al. in 2013, synthesized heterocyclic substituted pyridine sulfonamide derivatives and studied their anticancer activity against 26 cell lines. Among these derivatives, the piperazine based pyridine sulfonamide **(Fig.42)** scaffold showed best antitumor activity against of melanoma (SK-MEL-5), breast cancer (T-47D), ovarian cancer (OVCAR-4) and leukemia (K-562) cell lines with the IGP 89%, 72%, 65% and 65% respectively [178].

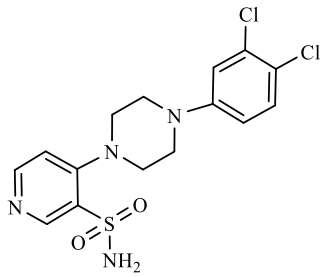
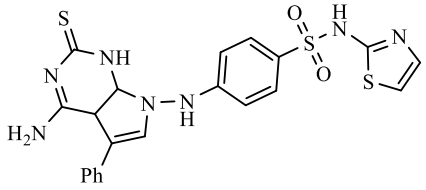


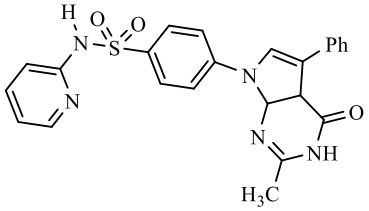
Fig. 42; piperazine based pyridine sulfonamide derivative

Ghorab et al. in 2010, afforded sulfonamide derivatives as anticancer activity against liver cancer cell line (HEPG2) and MCF-7 (breast cancer) cell line. Among all synthesized derivatives, pyrimidine

basethiazole sulfonamide scaffold showed significant antitumor activity against liver cell with the IC50 value 3.12 μM and pyrimidine base pyridine sulfonamide derivatives **(Fig.43)** against breast cancer cell with the IC_{50} value 3.15 μM [179].



pyrimidine based thiazole sulfonamide derivative



pyrimidine based pyridine sulfonamide derivative

Fig. 43; sulfonamide derivatives as anticancer activity against liver cancer cell line (HEPG2) and MCF-7 (breast cancer) cell line

Luo et al. in 2011, afforded cinnamic acyl sulfonamide derivatives as anticancer agents. The substituted acryl sulfonamide derivative **(Fig.44)** showed best antitumor active agents against B16-F10 cell line (melanoma) having IC_{50}values 0.8μg/ml [180].

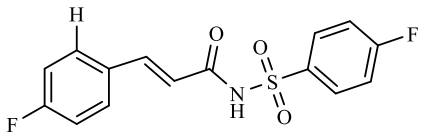


Fig. 44; Substituted Acryl sulfonamide derivative

Zayed et al. afforded quinazolinone sulfonamide derivatives and evaluated their anticancer activities. The pyrimidine based quinazolin sulfonamide derivative **(Fig. 45)** showed best antitumor active agents against NCI (National Cancer Institute) lung cancer cell line with the IC_{50} value 2.51 ± 0.48 μM. The methotrexate used as reference drug with the IC_{50} value 2.4 ± 0.23 μM [181].

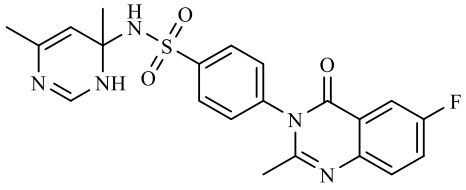


Fig. 45; pyrimidine base quinazoline sulfonamide derivative

Lu et al. in 2011 synthesized pyridine acyl sulfonamide derivatives were tested for anticancer therapeutic potential against different cancer cell lines. Among the series of derivatives, pyridine based sulfonamide scaffold**(Fig. 46)** demonstrated best antitumor activity against MCF-7 and HepG2 cell line having IC_{50} value 1.8 and 1.2μM [182].

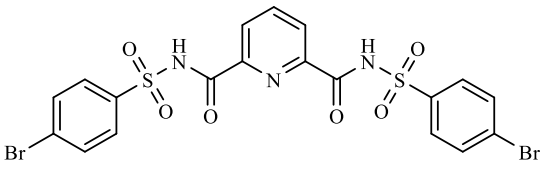


Fig. 46;pyridine based sulfonamide derivative

Ghorab et al. in 2015 afforded sulfonamide derivatives and demonstrated their anti-tumor activities. The substituted hydrazinyl sulfonamide scaffold **(Fig. 47)** showed highest anticancer active agents against the HEPG-2 cell line (liver cancer) having IC_{50}values 11.0 μM and doxorubicin used as the reference drug [183].

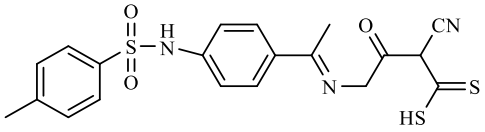
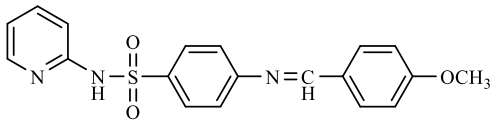
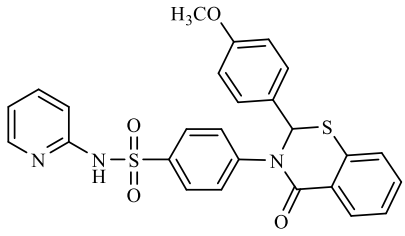


Fig. 47; Substituted hydrazinyl sulfonamide derivative

Kamel et al. in 2010 afforded sulfonamide Shiff's base derivatives and evaluated their anticancer active agents against cervix carcinoma HeLa cell line and MCF-7 cell line. In these derivatives, substituted pyridine sulfonamide scaffold showed best antitumor activity against MCF-7 with the IC_{50} value 0.74 m/mL and thiazine based pyridine sulfonamide derivative **(Fig.48)** showed highest antitumor active agents against HeLa having IC_{50} value 1.48 mg/ mL. The compounds 5-flurouracil and doxorubincin are used as reference drugs [184].



Substituted Pyridine sulfonamide derivative



Thiazine based pyridine sulfonamide derivative

Fig. 48; sulfonamide Shiff's base derivatives and evaluated their anticancer activity against cervix carcinoma HeLa cell line and MCF-7 cell line

Sun et al. in 2017 synthesized carbazole sulfonamide derivatives and studied their anti-tumor activity against hepatoma cancer (HepG2), MCF-7, pancreatic cancer (MIA PaCa-2) and liver cancer (Bel-7402). The substituted carbazole sulfonamide derivatives **(Fig.49)** showed potent antitumor activities. The IC_{50} values of the scaffold **93** were 0.012, 0.051, 0.014 and 0.056 μM for HepG2, MIA PaCa-2, MIA PaCa-2, and Bel-7402 cell lines respectively. The compound 25 have IC_{50} value 0.071 μM for HepG2, 0.092 μM for MIA PaCa-2, 0.036 μM for MIA PaCa-2, and 0.18 μM for Bel-7402 cell line [185].

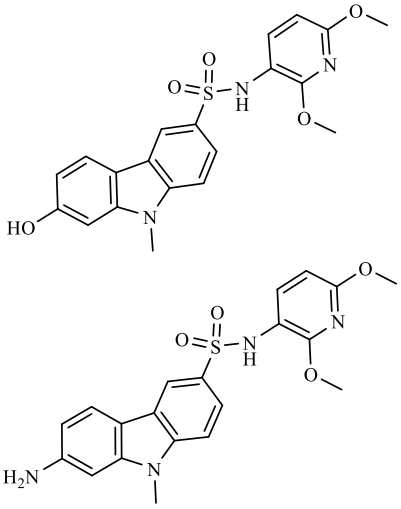


Fig. 49; Substituted Carbazole sulfonamide derivatives

A series of quinoline sulfonamide combinatorial libraries were afforded by Ghorab*et al* in 2009 [186]. They studied their antitumor activity against the MCF-7 cell line. In the series of these derivatives, quinolone based pyrimidine sulfonamide derivative **(Fig.50)** showed potent anticancer activity with the IC_{50} value 2.37 μM and doxorubicin was used as a reference compound.

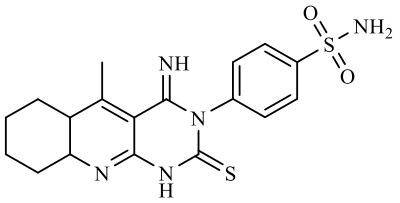


Fig. 50; Quinoline based pyrimidine sulfonamide derivative

Khan et al. afforded tosyl sulfonamide derivatives and evaluated their anticancer activity. The Zn(**II**) complex based tosyl sulfonamide derivative **(Fig.51)** were evaluated as a best anticancer activity against H-157 (lung carcinoma cancer cell line), BHK-21 (kidney fibroblast cell line), and vero cell line with IC_{50} ± SEM value 1.82 ± 0.11 μM, 2.19 ± 0.15 μM and 13.7 ± 1.8 % when compared with vincristine [187].

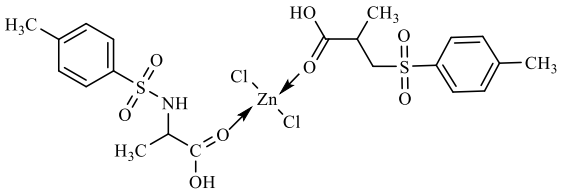


Fig. 51;Zn(II)complex of tosyl sulfonamide derivative

Ghorab et al. in 2011 synthesized a series of sulfonamide derivatives and tested these derivatives as potential anti-tumor agents. The pyran moiety containing thiazole sulfonamide scaffold **(Fig. 52)** showed best antitumor active agents against MCF-7 cell line with the IC_{50} value 34.64 μM when compared to doxorubicin as reference [188].

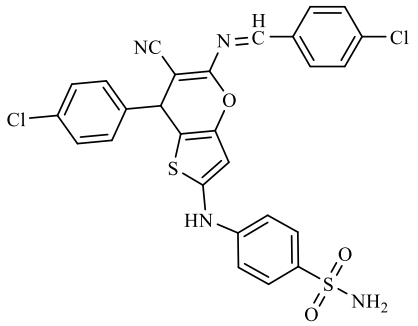


Fig. 52;Pyrane based thiazole sulfonamide derivative

El-Sayed et al. in 2011 synthesized thiadiazolo based pyrimidine sulfonamide derivatives as anti-cancer activity. Among all these derivatives, substituted thiadiazolo based pyrimidine sulfonamide scaffolds **(Fig.53)** showed potent antitumor activity in mice against Ehrlich ascites carcinoma (EAC) and increase the lifespan of the mice [9].

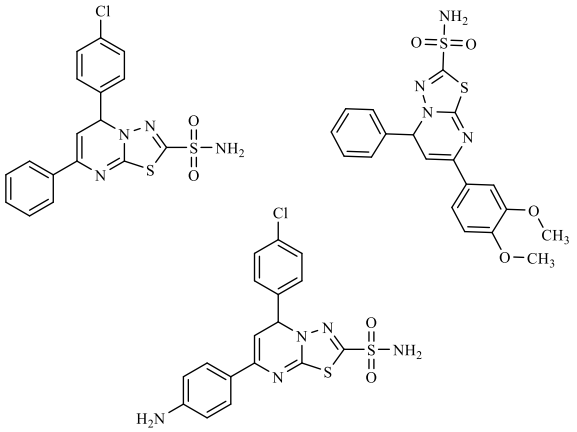
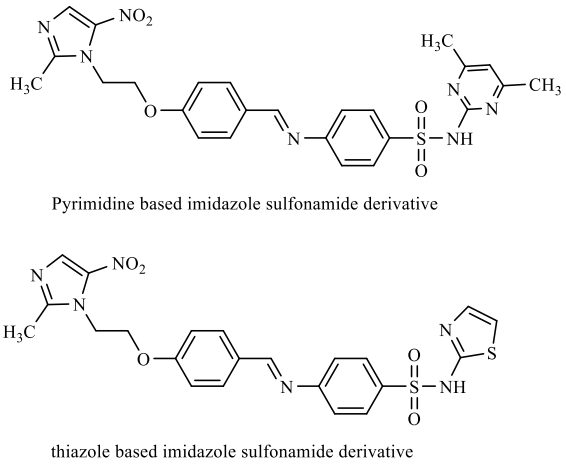


Fig. 53; Substituted Thiazolo based pyrimidine sulfonamide derivative

Wang et al. in 2014 synthesized metronidazole sulfonamide derivatives and evaluated their anticancer activities. The scaffold pyrimidine based imidazole sulfonamide and thiazole based imidazole sulfonamide **(Fig.54)** showed highest antitumor active agents against MCF-7 and B16-F10 (mouse melanoma cells) with the IC_{50} value 6.5 nM for MCF-7 and 150 nM for B16-F10 cell lines respectively when compared with semaxanib and doxorubicin as reference drugs [189].



Pyrimidine based imidazole sulfonamide derivative

thiazole based imidazole sulfonamide derivative

Fig. 54; metronidazole sulfonamide derivatives evaluated their anticancer activities

Bavadi et al. in 2017 synthesized pyrrole sulfonamide derivatives as anticancer active agents against MCF-7, acute lymphoblastic leukemia (MOLT-4) and promyelocytic leukemia cell (HL-60). The substituted pyrimidine based pyrrole sulfonamide derivative **(Fig. 55)** showed potent antitumor activity with the IC_{50} value 39.0 ± 4.5 μM for the MCF-7, 25.5 ± 1.1 μM for MOLT-4 and 30.6 ± 3.6 μM for HL-60 cell lines when compared with cisplatin reference drug [190].

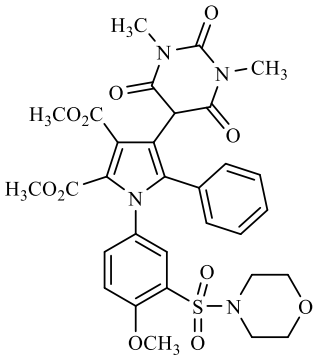


Fig. 55; Substituted Pyrimidine based pyrrole sulfonamide derivative

k- Other diseases

In keeping with different latest studies, the sulfonamide derivatives of metformin may also have anticoagulant and antifibrinolytic properties, tconsequently, may be tested in the improvement of capacity drug candidates for remedy of Type 2 diabetes mellitus (T2DM), which isn't best defined with the aid of its traditional signal of

hyperglycemia however additionally by way of its impaired balance between coagulation and fibrinolysis [191]. Ji *et al*. [192] prepared a series of acyl sulfonamide derivatives of quinoxalinone and demonstrated potent multi-functional inhibition of aldose reductase (ALR2)/ aldehyde reductase (ALR1).This development is important for treatment of diabetes mellitus as ALR_2 is a rate determining enzyme in the polyol pathway, through which glucose is phosphorylated under euglycemic conditions. Euglycemic conditions occur in patients with metabolic acidosis, hyperglycemia and increased ketone our bodies in the bloodstream once they still have serum glucose tiers within normal limits. it's far a regular case for numerous factors gambling a role inside the circumstance of the affected person, consequently the multi-goal healing method and multitarget compounds can provide significant benefits [192].

l- Other applications of sulfonamides

A large number of sulfonamides have been used for therapeutic intervention and more recently a very well-known example is that of as Sildenafil (Viagra) (**Fig.56**) for the treatment of erectile dysfunction. Erection is caused by binding of nitric oxide NO (released from the brain) to guanylate cyclase, causing the build-up of cyclic guanosine monophosphate (cGMP) resulting in smooth muscle relaxation and increase blood flow to the male organ. Viagra works by inhibiting phosphor diesterase- 5; which is responsible for metabolizing cGMP, resulting in prolonged erection [193].

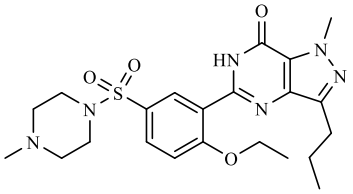


Fig. 56; structure of Sildenafil

The synthesis of benzosulfonamide analogs that incorporate ring moieties, with changed tail systems isn't always the only method in sulfonamide chemistry to broaden novel drug candidates for complex diseases. lately, copper(II) complexes with N-sulfonamide ligand have been synthesized and their antitumor activities towards HeLa cells were demonstrated [156]. Quinoline derivatives with sulfonamide moieties are also pretty usually utilized in anticancer drug development, especially targeting certain types of breast cancer.For instance, [194] Synthesized and executed molecular docking studies on a chain of acetylenic quinolinesulfonamide derivatives and identified pretty effective molecules. Naphthalene-1-sulfonamide derivatives were lately evolved as potent and selective inhibitors of fatty acid binding protein 4, a capability therapeutic target for diabetes and atherosclerosis [195]. Novel design and synthesis of 3,4-disubstituted pyrrolidone sulfonamide derivatives were additionally stated.The compounds were found to be selective and potent competitive inhibitors of glycine transporter [196] and promising applicants for drug improvement to deal with schizophrenia and different mental ailments. In another observe, sulfone pyrrolidine sulfonamides have been utilized as antagonists of temporary receptor capacity vallinoid- 4 (TRPV4) with in vivo activity in a pulmonary edema model [197].

Finally sulfonamides and their derivatives continue to remain a significant part of the novel drug design and development against a variety of complex diseases, in conjunction with the ongoing improvements of their classical use as antibiotics, antiviral or antifungal agents. As a multi-target approach in drug discovery started to gain much deserved attention recently, so did the increase of the employment of sulfonamide derivatives as multi-target agents. for the duration of this review, it has been shown that sulfonamide derivatives are used in diverse areas of drug discovery. at the same time as the single-target programs are enormously huge and frequent, their usage as multitarget agents are expanded simplest lately. Sulfa-drugs have the benefit of being well-studied retaining one among the biggest biologically applicable compound libraries. Their flexible structure may be altered easily and even small chemical modifications might also lead to an advanced model of an already present drug. The multi-target applications gained greater traction, in general due to these benefits. The well described compound libraries blended with the identification of key objectives in various diseases can be carried out to design novel sulfonamide derivatives to be examined for multi-goal activities and advantage acclaim for drug trials more rapidly than inside the case of a completely unknown middle shape. however, sulfonamides aren't with out drawbacks. they can be pretty poisonous and harmful to the surroundings which should be taken into consideration cautiously and responsibly during drug development. For instance, they are known to remove bilirubin from the transport protein albumin in humans, which then leads to high levels of bilirubin in the body, causing toxic side-effects on CNS, liver and kidneys. The waste from their synthesis can also

be harmful to the environment due to the Extensive use of organic solvents (e.g. Dimethylformamide) or surprisingly reactive poisonous beginning substances (e.g. thionyl chloride)[198].Recently, promising methods for synthesizing sulfonamide compounds in a"green" or non-toxic way have been published that demonstrated the synthesis without any organic solvents or reactive sulfur-sources like sulfonyl chloride [198, 199].

To summarize, a sulfonamide-based compounds have one of the broadest ranges of biological activities among drug molecules.This assets of sulfa-drugs combined with their structural versatility and big amount of data available cause them to splendid applicants for developing extra effective and more secure alternatives to the modern drugs for numerous diseases, complex or higher understood alike. Research on both single- and multi-target applications of sulfonamides is anticipated to remain on an upward trajectory.

4.Conclusion

This review article contains the medical, biological, pharmaceutical and industrial significance of sulfonamide derivatives in recent years. Also, this research examines modern methods for preparing sulfonamides.

Mohamed S. A. El-Gaby : ORCID iD

https://orcid.org/0000-0002-4902-5546

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