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Review article

Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review

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A B S T R A C T

Sulfur (SVI) based moieties, especially, the sulfonyl or sulfonamide based analogues have showed a variety of pharmacological properties, and its derivatives propose a high degree of structural diversity that has established useful for the finding of new therapeutic agents. The developments of new less toxic, low cost and highly active sulfonamides containing analogues are hot research topics in medicinal chemistry. Currently, more than 150 FDA approved Sulfur (SVI)-based drugs are available in the market, and they are widely used to treat various types of diseases with therapeutic power. This comprehensive review highlights the recent developments of sulfonyl or sulfonamides based compounds in huge range of therapeutic applications such as antimicrobial, anti-inflammatory, antiviral, anticonvulsant, antitubercular, antidiabetic, antileishmanial, carbolic anhydrase, antimalarial, anticancer and other medicinal agents. We believe that, this review article is useful to inspire new ideas for structural design and developments of less toxic and powerful Sulfur (SVI) based drugs against the numerous death-causing diseases.

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1. Introduction

The sulfonamide or sulfonamyl functional groups have been important motifs in medicinal chemistry since the early discovery of sulfonamide containing antibacterial drugs [1]. The applications of sulfonyl or sulfonamide functional groups in medicinal chemistry cannot be ignored, as it constitutes an important class of drugs used extensively as both veterinary and pharmaceutical agents [2,3]. The features of $\text{S}^\text{VI}$-containing species of strong electron withdrawing nature, stability against hydrolysis, resistance to reduction at sulfur, and high molecular weight have already made this group applicable to many productive fields. Sulfonamides as synthetic antifolic agents have been widely used for the anticipation and treatment of bacterial infections in biological systems and recently have evoked high favor in biology and medicine due to their wide array of biological activities such as antibacterial [4–6], antifungal [7], anti-inflammatory [8–10], antioxidant [11,12], diuretics [13–15], anticancer [16–19], carbonic anhydrases [20–22], antitumor [23–25], Alzheimer diseases [26,27], antitubercular [28,29], antidiabetic [30,31], HIV protease inhibitors [32,33], antiglaucoma [34–36], antiobesity [37,38], antiviral [39,40], antimalarial [41], MMP inhibitors [42,43], non-peptidic vasopressin receptor antagonists [44] and translation initiation inhibitors [45] etc. Up to date, more than 150 FDA approved drugs bearing Sulfur ($\text{S}^\text{VI}$) motif are available in the market such as celecoxib, meloxicam, piroxicam, sulfasalazine, and so on [46]. The diverse pharmacological activity of $\text{S}^\text{VI}$ in organic molecules makes it a first choice for incorporation by the hybrid approach, which is present in most of the required medicines that are accessible in the market [47].

Heterocyclic compounds play essential roles in life and biochemical processes [48]. Among them, a huge number of novel sulfonamide derivatives have been reported and tested for both in vivo and in vitro antitumor activities. Some of these highly potent analogues are tested in clinical trials. Hopefully, these may lead to new alternative anticancer drugs avoiding the side effects of the available pharmacological agents [49]. Sulfur ($\text{S}^\text{VI}$)-containing drugs are still widely used for circumstances of spots and urinary tract infections, and are receiving more renewed interest for the treatment of infections caused by bacterial resistance of other antibiotics [50,51]. The excellent biological profile, hydrolytic stability and crystalline nature of sulfonamides have grabbed significant attention from synthetic chemists [52,53]. These sulfonamide analogues can be traced in a number of well established potential drugs belonging to various types of therapeutic agents. Some of the representative sulfonamides or sulfonyl functional group containing FDA approved drugs are listed in Table 1.

In search of some new antibiotics, the sulfonamide functional groups have been fundamental motifs in medicinal chemistry since the early discovery of sulfonamide containing antibacterial drugs [1]. To date, a number of sulfonyl or sulfonamide bearing aromatic heterocycles such as quinazolinones, oxazoles, benzimidazole, thiazole and pyridazine have been successfully developed and employed in clinics with the presence of sulfadiazine, sulfachlorpyridazine, sulfathiazole and sulfisoxazole exhibiting excellent antimicrobial activities [58]. Because of the weak effectiveness and even loss of resistance power of old antibiotics against new and upcoming bacterial pathogens, urgent alternatives were needed to develop novel, less toxic and highly effective antimicrobial agents with distinct structures to fight with emerging antibiotic-resistant bacterial infections. In the first part of this review article, we have focused on sulfonamide analogues as a core substituent of antibacterial agents for drug development. In this regard, the combinations of sulfonamides and other heterocyclic drug molecules are being used to develop novel antibiotic drugs [54]. Some of the sulfonyl or sulfonamides containing heterocycles as potential antimicrobial agents are summarized in Fig. 1.

Zhou et al. designed and synthesized a novel series of benzimidazole-derived sulfonamide analogues and evaluated for in vitro antimicrobial activities against different microbial pathogens. Compound 107 (Fig. 2) showed excellent antibacterial activity against S. aureus with MIC values of 4 $\mu$g/mL. The replacement of 4-fluorobenzyl group by 2,4-dichlorobenzyl group, 108 (Fig. 2) showed good antibacterial activity against B. typhi with MIC values 4 $\mu$g/mL. Compound 108 showed eight folds higher activity (MIC = $4\mu$g/mL) than standard Chloromycine against B. typhi [59]. The above same research group further developed a class of novel sulfonamide-containing azoles analogues as potential antimicrobial agents. Compound 109 (Fig. 2) showed excellent antibacterial activity against P. aeruginosa with MIC value of $16\mu$g/mL [60]. Kamble et al. have reported pyrazole derived sulfonamide analogues as good antibacterial agents. Compound 110 (Fig. 2) showed potent antibacterial activity against tested bacterial strains S. aureus and S. typhimurium with MIC value of 10 $\mu$g/mL each. Compound 111 (Fig. 2) showed excellent antibacterial activity against different bacterial pathogens namely B. subtilis and E. coli with MIC value of 10 $\mu$g/mL each. To elucidate the structure activity relationship (SAR) of compounds 110 and 111, the presence of electron withdrawing (Br and CF$_3$) groups (EWG) on the sulfonyl attached phenyl ring, increases the bacterial resistance against the tested S. aureus and S. typhimurium strains. But the same moiety with replacement of the –Br functional group, and the inserting of the C1 functional group, compound 111 was found to be highly active against another bacterial strains B. subtilis and E. coli. The lipophilicity as well as nature and position of the substituent present on benzene ring of sulfonamide end affected the antimicrobial activity [61]. In 2014, Nasr et al. developed a new type of

2. Biological applications of sulfonyl or sulfonamides functionalities

2.1. Antimicrobial agents

The problem of antibiotic resistance among pathogenic bacteria is as old as antibiotics itself [56]. The antibiotic resistance which was accelerated by the use and misuse of antimicrobial drugs has been a major global challenge for public health. Dramatic increase of human pathogenic bacteria was observed from the past decades due to their resistance to one or more antibiotics. A number of infections caused by resistant organisms fail at responding to the conventional treatment and in few cases, the last resort antibiotics have also lost their power [57].

In search of some new antibiotics, the sulfonamide functional groups have been fundamental motifs in medicinal chemistry since the early discovery of sulfonamide containing antibacterial drugs [1]. To date, a number of sulfonyl or sulfonamide bearing aromatic heterocycles such as quinazolinones, oxazoles, benzimidazole, thiazole and pyridazine have been successfully developed and employed in clinics with the presence of sulfadiazine, sulfachlorpyridazine, sulfathiazole and sulfisoxazole exhibiting excellent antimicrobial activities [58]. Because of the weak effectiveness and even loss of resistance power of old antibiotics against new and upcoming bacterial pathogens, urgent alternatives were needed to develop novel, less toxic and highly effective antimicrobial agents with distinct structures to fight with emerging antibiotic-resistant bacterial infections. In the first part of this review article, we have focused on sulfonamide analogues as a core substituent of antibacterial agents for drug development. In this regard, the combinations of sulfonamides and other heterocyclic drug molecules are being used to develop novel antibiotic drugs [54]. Some of the sulfonyl or sulfonamides containing heterocycles as potential antimicrobial agents are summarized in Fig. 1.

Zhou et al. designed and synthesized a novel series of benzimidazole-derived sulfonamide analogues and evaluated for in vitro antimicrobial activities against different microbial pathogens. Compound 107 (Fig. 2) showed excellent antibacterial activity against S. aureus with MIC values of 4 $\mu$g/mL. The replacement of 4-fluorobenzyl group by 2,4-dichlorobenzyl group, 108 (Fig. 2) showed good antibacterial activity against B. typhi with MIC values 4 $\mu$g/mL. Compound 108 showed eight folds higher activity (MIC = $4\mu$g/mL) than standard Chloromycine against B. typhi [59]. The above same research group further developed a class of novel sulfonamide-containing azoles analogues as potential antimicrobial agents. Compound 109 (Fig. 2) showed excellent antibacterial activity against P. aeruginosa with MIC value of $16\mu$g/mL [60]. Kamble et al. have reported pyrazole derived sulfonamide analogues as good antibacterial agents. Compound 110 (Fig. 2) showed potent antibacterial activity against tested bacterial strains S. aureus and S. typhimurium with MIC value of 10 $\mu$g/mL each. Compound 111 (Fig. 2) showed excellent antibacterial activity against different bacterial pathogens namely B. subtilis and E. coli with MIC value of 10 $\mu$g/mL each. To elucidate the structure activity relationship (SAR) of compounds 110 and 111, the presence of electron withdrawing (Br and CF$_3$) groups (EWG) on the sulfonyl attached phenyl ring, increases the bacterial resistance against the tested S. aureus and S. typhimurium strains. But the same moiety with replacement of the –Br functional group, and the inserting of the C1 functional group, compound 111 was found to be highly active against another bacterial strains B. subtilis and E. coli. The lipophilicity as well as nature and position of the substituent present on benzene ring of sulfonamide end affected the antimicrobial activity [61]. In 2014, Nasr et al. developed a new type of
| Sl No | Drug Name   | Structure | Diseases               | Approved Year |
|-------|-------------|-----------|------------------------|---------------|
| 1     | Streptozol  | ![Structure](structure1.png) | Dermatological         | 1937          |
| 2     | Sulfadiazine| ![Structure](structure2.png) | Antibiotic             | 1941          |
| 3     | Sulfapyridine| ![Structure](structure3.png) | Anti-infective         | 1942          |
| 4     | Sotradecol  | ![Structure](structure4.png) | Cardiovascular         | 1946          |
| 5     | Azulfidine  | ![Structure](structure5.png) | ALM/DER                | 1950          |
| 6     | Benemid     | ![Structure](structure6.png) | Musculo-skeletal       | 1951          |
| 7     | Thiosulfil  | ![Structure](structure7.png) | DER/BBO/AIN/SEN        | 1953          |
| 8     | Myleran     | ![Structure](structure8.png) | Oncological            | 1954          |
| 9     | Diuril      | ![Structure](structure9.png) | Cardiovascular         | 1957          |
| 10    | Diabinese   | ![Structure](structure10.png) | Alimentary tract and metabolism | 1958 |
| 11    | Neptazane   | ![Structure](structure11.png) | Sensory organ          | 1959          |
| 12    | Hydrochlorothiazide | ![Structure](structure12.png) | CAR/END                | 1959          |

(continued on next page)
| Sl No | Drug Name | Structure | Diseases                          | Approved Year |
|-------|-----------|-----------|-----------------------------------|---------------|
| 13    | Trancopal | ![Trancopal](image) | Musculo-skeletal                  | 1960          |
| 14    | Doburil   | ![Doburil](image) | Cardiovascular                    | 1960          |
| 15    | Enduran   | ![Enduran](image) | Cardiovascular                    | 1960          |
| 16    | Daranide  | ![Daranide](image) | Sensory organ                     | 1960          |
| 17    | Orinase   | ![Orinase](image) | Alimentary tract and metabolism   | 1961          |
| 18    | Aldoril   | ![Aldoril](image) | Cardiovascular                    | 1962          |
| 19    | Dymelor   | ![Dymelor](image) | Alimentary tract and metabolism   | 1964          |
| 20    | Dyazide   | ![Dyazide](image) | Cardiovascular                    | 1965          |
| 21    | Lasix     | ![Lasix](image) | Cardiovascular                    | 1966          |
| 22    | Tolinase  | ![Tolinase](image) | Alimentary tract and metabolism   | 1966          |
| SI No | Drug Name | Structure | Diseases                        | Approved Year |
|-------|-----------|-----------|---------------------------------|---------------|
| 23    | Sulfacel-15 | ![Structure Image](image1.png) | Sensory organ                   | 1970          |
| 24    | Gliclazide | ![Structure Image](image2.png) | Alimentary tract and metabolism | 1970          |
| 25    | Hyperstat | ![Structure Image](image3.png) | Cardiovascular                  | 1973          |
| 26    | Bactrim   | ![Structure Image](image4.png) | Anti-infective                   | 1973          |
| 27    | Monopril HCT | ![Structure Image](image5.png) | Cardiovascular                   | 1974          |
| 28    | Hyzaar    | ![Structure Image](image6.png) | Cardiovascular                   | 1975          |
| 29    | Amsacrine | ![Structure Image](image7.png) | Oncological                      | 1976          |
| 30    | Sulpiride | ![Structure Image](image8.png) | Nervous System                   | 1978          |
| 31    | Premarin  | ![Structure Image](image9.png) | GUS/ONC                         | 1978          |

(continued on next page)
| Sl No | Drug Name | Structure | Diseases       | Approved Year |
|-------|-----------|-----------|----------------|---------------|
| 32    | Aldactazide | ![Structure](image) | Cardiovascular | 1978          |
| 33    | Topiramate | ![Structure](image) | Nervous system | 1979          |
| 34    | Inderide   | ![Structure](image) | Cardiovascular | 1979          |
| 35    | Moduretic  | ![Structure](image) | Cardiovascular | 1981          |
| 36    | Sulfamethoxazole | ![Structure](image) | Anti-infective | 1982          |
| 37    | Mezlin     | ![Structure](image) | Anti-infective | 1982          |
| 38    | Feldene    | ![Structure](image) | MSK/SEN        | 1982          |
| 39    | Bumex      | ![Structure](image) | Cardiovascular | 1983          |
| Sl No | Drug Name | Structure | Diseases         | Approved Year |
|-------|-----------|-----------|------------------|---------------|
| 40    | Lozol     | ![Structure of Lozol](image1) | Cardiovascular  | 1983          |
| 41    | Corzide   | ![Structure of Corzide](image2) | Cardiovascular  | 1983          |
| 42    | Glucotrol | ![Structure of Glucotrol](image3) | ALM/END         | 1984          |
| 43    | Tenoretic | ![Structure of Tenoretic](image4) | Cardiovascular  | 1984          |
| 44    | Lopressor HCT | ![Structure of Lopressor HCT](image5) | Cardiovascular  | 1984          |
| 45    | Capozide  | ![Structure of Capozide](image6) | CAR/END         | 1984          |
| 46    | Vaseretic | ![Structure of Vaseretic](image7) | Cardiovascular  | 1986          |

(continued on next page)
| Sl No | Drug Name | Structure | Diseases | Approved Year |
|-------|-----------|-----------|----------|---------------|
| 47    | Pepcid    | ![Pepcid Structure](image) | Alimentary tract and metabolism | 1986          |
| 48    | Cayston   | ![Cayston Structure](image) | AIN/ALM/RES | 1986          |
| 49    | Unasyn    | ![Unasyn Structure](image) | Anti-infective | 1986          |
| 50    | Mykrox    | ![Mykrox Structure](image) | Cardiovascular | 1987          |
| 51    | Metahydrin| ![Metahydrin Structure](image) | Cardiovascular | 1988          |
| 52    | Prinzide  | ![Prinzide Structure](image) | Cardiovascular | 1989          |
| 53    | Torasemide| ![Torasemide Structure](image) | Cardiovascular | 1990          |
| Sl No | Drug Name     | Structure | Diseases       | Approved Year |
|-------|---------------|-----------|----------------|---------------|
| 54    | Sotalol       | ![Sotalol Structure](image) | Cardiovascular | 1992          |
| 55    | Imitrex       | ![Imitrex Structure](image) | Nervous system | 1992          |
| 56    | Ziae          | ![Ziae Structure](image) | Cardiovascular | 1993          |
| 57    | Trusopt       | ![Trusopt Structure](image) | Sensory organ  | 1994          |
| 58    | Casodex       | ![Casodex Structure](image) | Endocrine system | 1995         |
| 59    | Corvert       | ![Corvert Structure](image) | Cardiovascular | 1995          |
| 60    | Amaryl        | ![Amaryl Structure](image) | ALM/END        | 1995          |
| 61    | Pentosan polysulfate | ![Pentosan polysulfate Structure](image) | Cardiovascular | 1996          |
| Sl No | Drug Name | Structure | Diseases                        | Approved Year |
|-------|-----------|-----------|---------------------------------|---------------|
| 62    | Aceolate  | ![Structure](image1) | Respiratory system               | 1996          |
| 63    | Rescriptor| ![Structure](image2) | Anti-infective                   | 1997          |
| 64    | Flomax    | ![Structure](image3) | Genito-Urinary and Sex hormone   | 1997          |
| 65    | Avalide   | ![Structure](image4) | Cardiovascular                   | 1997          |
| 66    | Glyboride | ![Structure](image5) | BBO/END                         | 1997          |
| 67    | Acamprosate| ![Structure](image6) | Nervous system                   | 1998          |
| 68    | Azopt     | ![Structure](image7) | Sensory organ                    | 1998          |
| 69    | Amerge    | ![Structure](image8) | Nervous system                   | 1998          |
| Sl No | Drug Name | Structure | Diseases                                | Approved Year |
|-------|-----------|-----------|-----------------------------------------|---------------|
| 70    | Viagra    | ![Viagra Structure](image) | Genito-Urinary and Sex hormone          | 1998          |
| 71    | Aggrastat  | ![Aggrastat Structure](image) | Blood and blood forming organ           | 1998          |
| 72    | Celebrex   | ![Celebrex Structure](image) | ONC/MSK                                 | 1998          |
| 73    | Diovan HCT | ![Diovan HCT Structure](image) | Cardiovascular                          | 1998          |
| 74    | Cosopt     | ![Cosopt Structure](image) | Sensory organ                           | 1998          |
| 75    | Agenerase  | ![Agenerase Structure](image) | Anti-infective                          | 1999          |
| 76    | Accuretic  | ![Accuretic Structure](image) | Cardiovascular                          | 1999          |
| Sl No | Drug Name | Structure | Diseases                              | Approved Year |
|-------|-----------|-----------|---------------------------------------|---------------|
| 77    | Tykosin   | ![Tykosin](image1) | CAR/RES                               | 1999          |
| 78    | Atacand   | ![Atacand](image2) | Cardiovascular                        | 2000          |
| 79    | Argatroban| ![Argatroban](image3) | Blood and blood forming organ         | 2000          |
| 80    | Micardis HCT | ![Micardis HCT](image4) | CAR/END                              | 2000          |
| 81    | Mobic Tablet | ![Mobic Tablet](image5) | Musculo-skeletal                      | 2000          |
| 82    | Zonegram  | ![Zonegram](image6) | Nervous system                        | 2000          |
| 83    | Axert     | ![Axert](image7) | Nervous system                        | 2001          |
Table 1 (continued)

| Sl No | Drug Name | Structure | Diseases                              | Approved Year |
|-------|-----------|-----------|---------------------------------------|---------------|
| 84    | Tracleer  | ![Structure of Tracleer](image1) | Cardiovascular                        | 2001          |
| 85    | Bextra    | ![Structure of Bextra](image2)   | GUS/MSK                               | 2001          |
| 86    | Teveten HCT | ![Structure of Teveten HCT](image3) | Cardiovascular                        | 2001          |
| 87    | Metaglip  | ![Structure of Metaglip](image4) | Alimentary tract and metabolism       | 2002          |
| 88    | Relpax    | ![Structure of Relpax](image5)   | Nervous system                        | 2002          |
| 89    | Levitra   | ![Structure of Levitra](image6)   | Genito-Urinary and Sex hormone        | 2003          |

(continued on next page)
Table 1 (continued)

| SI No | Drug Name | Structure | Diseases                     | Approved Year |
|-------|-----------|-----------|------------------------------|---------------|
| 90    | Benicar HCT | ![Structure](image1.png) | Cardiovascular               | 2003          |
| 91    | Crestor   | ![Structure](image2.png) | CAR/BBO                     | 2003          |
| 92    | Aptivus   | ![Structure](image3.png) | Anti-infective               | 2005          |
| 93    | Doribax   | ![Structure](image4.png) | Genito-Urinary and Sex hormone | 2007          |
| 94    | Treximet  | ![Structure](image5.png) | Nervous system               | 2008          |
| 95    | Multaq    | ![Structure](image6.png) | Cardiovascular               | 2009          |
sulfonamide containing sulfisoxazole analogues and evaluated for antibacterial activity. Compound 112 (Fig. 2) showed promising antibacterial activities against most of the tested bacterial strains. Compound 113 (Fig. 2) showed excellent antibacterial activity against the *S. epidermidis*, *P. vulgaris* and *K. pneumonia* bacterial strains. The analysis of the SAR, revealed that the presence of sulfonamide group with heterocyclic moiety increases the lipophilic characters of the synthesized compounds [62].

The research group of Padmaja [63] synthesized heterocycles containing sulfonamides analogues and evaluated for *in vitro* antimicrobial activities against various microbial pathogens using agar disc diffusion method. Among all the synthesized analogues, isoxazole containing sulfone analog 114 (S. aureus - 32 mm, B. subtilis - 31 mm, K. pneumoniae - 26 mm, P. vulgaris - 28 mm in diameter) (Fig. 3) was found to exhibit the highest inhibitory activity against tested bacterial strains. The presence of EWG (Cl) on phenyl ring of the sulfonyl end and sulfone group infatuated stronger antimicrobial activities compared to the other EDGs. In the continuation of the potent antimicrobial drug developments of sulfone containing heterocyclic derivatives, Lavanya et al. [64] reported 1,4-phenylene) bis (arylsulfonylisoxazoles analogues to have potent antimicrobial properties. Compound 115 (Fig. 3) was found to have the highest antibacterial activity against *B. subtilis* with zone of inhibition of 38 mm at 100 mg/mL. The elucidating of the SAR indicated that the presence of EWG (Cl) on the phenyl ring of the sulfone end showed maximum antibacterial activity against *B. subtilis* strain. In another study, a 2-ureidothiophene-3-carboxylic acid derivative was synthesized and screened as dual bacterial RNAP and HIV-1 RT inhibitors by Elgaher et al. [65]. Compound 116 (Fig. 3) displayed more potency against tested *S. aureus* with high cellular antiretroviral activity. This is probably due to the presence of non-bulky hydrophilic substituents at the ureido side chain for RT inhibition, the hydrophilic and hydrogen bond donor or acceptor substituents at the N-phenyl group are also

| Sl No | Drug Name | Structure | Diseases       | Approved Year |
|-------|-----------|-----------|----------------|---------------|
| 96    | Votrient  | ![Structure](image1) | ALM/MSK        | 2009          |
| 97    | Amturnide | ![Structure](image2) | Cardiovascular | 2010          |
| 98    | Zelborat  | ![Structure](image3) | ONC/DER       | 2011          |
| 99    | Erivedge  | ![Structure](image4) | Oncological    | 2012          |
| 100   | Qsymia    | ![Structure](image5) | Endocrine System | 2012      |
important for increasing the antibacterial activity. Hrast and co-workers developed novel sulfone based cyanothiophene analogues and established their inhibitors of MurF enzymes by using Malachite green assay [66,67]. Compound 117 (Fig. 3) displayed potent MurFsp inhibitory activities against MurFsp enzyme with IC50 0.30 μM. Compound 118 (Fig. 3) exhibited excellent MurF enzymes activity against two MurFsp and MurFEC with IC50 values of 20 μM and 25 μM, respectively. This is probably due to the presence benzylsubstituted derivatives of electron-donating groups (EDGs) to improve the inhibitory activity more than 2–3-fold compared with electron-withdrawing groups (EWGs).

Novel N-sulfonaminoethylxime derivatives of dehydroabietic acid were developed by Zhang et al. [68] and tested for antibacterial activity against various bacterial pathogens. Among those, compound 119 (Fig. 4) exhibited the superior activity against five multidrug-resistances of *S. aureus* with MIC values between 0.78 and 1.56 μg/mL. The meta-CF3 phenyl derivative 119 showed the highest activity with MIC of 0.39–0.78 μg/mL against *S. aureus* Newman. To elucidate the SAR, they demonstrated that the introduction of an electron withdrawing trifluoromethyl group (-CF3) at meta position on the phenyl ring is more beneficial for the increasing antibacterial activity and selectivity compared to other substituents such as chloro, bromo, fluoro, methyl or methoxy groups. Very interestingly, the ortho substituted CF3 derivative 119 exhibited no in vitro activity against any of the Gram-positive bacterial strains at 50 μg/mL. The tert-butyl and methoxy functional group containing analogues showed decreased antibacterial activity. In addition, the substitution position appeared to have slight influence on the antibacterial activity of electron withdrawing functional group substituted derivatives. Nimbarte and co-workers [69] developed novel sulfonamide linked piperidine and pyrazole analogues and evaluated for the inhibition of soluble epoxide hydrolysis. Compounds 120 and 121 (Fig. 4) showed the highest inhibitory activity against tested bacterial strains with IC50 values of 0.220 μM and 0.224 μM, respectively. Zengin and co-workers found a new class of sulfanilamide as potent antimicrobial agents against tested bacterial and fungal strains. Compound 122 (Fig. 4) was found to have the highest antimicrobial activities against *B. cereus* (MIC value is 33 mm) and *E. faecalis* (MIC value is 33 mm). The SAR studies revealed that the lipophilicity of the analogues played a crucial role for producing antimicrobial activities. The dimethyl substituted compound 122 had high antimicrobial activity but low lipophilic character [70]. Series of sulfonamide containing benzoazole hybrids were evaluated for in vitro antimicrobial properties against some microbial pathogens.

Compounds 123 and 124 (Fig. 4) and were found to have higher antimicrobial activities compared to the reference Sulfamethoxazole-trimethoprim mixture. The SAR studies revealed that the presence of sulfonamides with an amino group (-NH2) and nitro group (-NO2) at the para position of the phenyl ring showed excellent antimicrobial properties. The replacement of the amino group with nitro group led to the decrease of the antibacterial activity [71]. In continuous study of sulfonamide containing benzoazole analogues as powerful antimicrobial properties, a new class of sulfanilamide containing benzoazole hybrids were synthesized and screened for antimicrobial activity by Patel et al. Compound 126 (Fig. 4) was found to be antimicrobially active with MIC values in the range of 15.5–31.25 μg/mL. Compounds 125 and 127 (Fig. 4) showed reasonable antimicrobial activity with MIC values in the range of 31.25–62.5 μg/mL. The SAR studies revealed that the presence of strong EWGs such as -F, -Cl, and –NO2 showed superior antimicrobial activities compared to the EDGs [72]. Various sulfonamide based analogues were synthesized and tested for their in vitro antimicrobial agents by Bhusari et al. Among these, compounds 128–130 (Fig. 4) displayed superior antimicrobial agents against the tested microbial pathogens [73]. Subudhi et al. developed a class of novel sulphonamide based analogues and evaluated for their in vitro antimicrobial activities. Compound 131 (Fig. 4) showed superior antimicrobial activity against the *S. aureus* (zone of inhibition 18 mm), *E. faecalis* (zone of inhibition 23 mm), *E. coli* (zone of inhibition 18 mm) and *P. aeruginosa* (zone of inhibition 17 mm). The preliminary SAR study revealed that the

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Fig. 1. Some of the sulfonyl or sulfonamides containing heterocycles as potential antimicrobial agents.
presence of sulfonamide group at para position of the phenyl group has highly increased the antibacterial properties of all the tested bacterial pathogens. Furthermore, the presence of EWG (Cl) group on the phenyl ring also contributes to increasing the antibacterial activity [74].

2.2. Anti-diabetic activity

Diabetes is one of the most severe diseases rising in the world. According to the estimation data obtained in 2010, around 285 millions of people are suffering from diabetes all over the world and it may increase to 439 million by 2030 [75,76]. Change in the blood glucose due to the insulin resistance is observed as the characteristic of being diabetic in 95% of the cases [77] which give raise to several more problems like high blood pressure, heart problem, kidney failure, stroke and blindness [78]. Therefore, it is highly demanded to develop additional electronic and steric requirements of arylsulfonamidothiazoles with antidiabetic effect [79]. Fig. 5 showed some representative sulfonyl of sulfonamides as potent anti-diabetic agents.

In 2014, Navarrete-Vázquez and co-workers designed and developed naphthalene containing sulfonamides as potent anti-diabetic agents against 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1). Among them, compounds 136, 137 and 138 (Fig. 6) showed promising anti-diabetic activity against 11β-hydroxysteroid dehydrogenase type-1 with % inhibition of 68, 67 and 55 at 10 μM respectively better than the standard drug BVT.14225 (55% inhibition). The SAR studies suggested that both piperidine and pyrrolidine core attached at the amide group were more active compounds to the tested all hybrids [80]. A novel class of thiazolidinedione based sulfonamide hybrids were evaluated for anti-diabetic activity against the Peroxisome Proliferator Activated Receptor (PPARγ) by Naim et al. [81]. Among these, compound 139 (Fig. 6) was found to be excellent PPAR-γ inhibitor of 61.2% with 1.9 folds increase in gene expression. In docking studies, compound 139 displayed good interaction with amino acids Tyr 473, Ser 289,
Hie 449, Tyr 327, Arg 288, Met 329 and Leu 228 (Fig. 7). This observation indicates that the presence of hydrophobic moiety in 139 is surrounded by hydrophobic amino acids. It is believed that such hydrophobic interactions enhances the ligand receptor complex as well as binding affinity of ligand towards PPARγ.

Rathish et al. reported the synthesis and anti-diabetic activity of sulfonamide based pyridazinone derivatives. Compounds 140 and 141 (Fig. 8) showed excellent anti-diabetic agents with more than 50% reduction in the rise of blood glucose levels. The SAR may be summarized as the introduction of electron withdrawing Cl at para position of phenyl group caused slightly reduction in the activity. On the other hand, the presence of electron releasing functional groups such as methoxy or methyl functional group at phenyl ring slightly caused reduction in the activity. Moreover, the compounds containing less bulky side chains were found to be more favourable for increasing anti-diabetic activity [82]. The effect of \textit{in vivo} anti-diabetic activity in non-insulin dependent diabetes mellitus rat model was explored later by Moreno-Díaz et al. in which compounds 142 and 143 (Fig. 8) showed promising antidiabetic properties. The SAR revealed that the presence of EDGs (-OMe and -OC2H5) at position 5 of the benzothiazole ring, enhanced the antidiabetic activity [83]. Navarrete-Vazquez et al., in 2009 designed and synthesized a series of new 2-arylsulfonylaminobenzothiazole analogues and screened for protein tyrosine phosphatase-1D inhibitory activity (PTP-1D). Compounds 144 and 145 (Fig. 8) showed the most promising activity against PTP-1D with IC50 value is 19.5 and 40.9 μM respectively. The SAR revealed that the presence of EWGs (-NO2) on the phenyl ring
of sulfonamide end enhanced the anti-diabetic properties [84]. Recently, how to improve the drug resistance of potent anti-diabetic drugs against PTP-1B, has emerged as a key role of insulin signalling target for type 2-diabetes. In 2018, Du and co-workers reported novel PTP-IB inhibitors of a series of ureido-sulfonamides based analogues. Among these, compounds 146 and 147 (Fig. 8) showed superior PTP1B inhibitors with IC50 values of 18.6 nM and 66.2 nM respectively. The SAR implied that, compound 146 with 2-ethoxy group on B ring was identified to possess 10.9 fold more potent inhibitory activity against the PTP1B enzyme. Compound 147, with the presence of -CONH-(3,4-di-MeO-Ph) group on ring B displayed high potent activity [85].

A series of piperazine-sulfonamide analogues were studied for in vitro α-amylase inhibition activity by Nawaz et al. [86]. Compounds 148, 149, 150 and 151 (Fig. 9) displayed promising inhibitory effects with IC50 value 2.348, 2.064, 1.571 and 2.118 μM, respectively. The SAR implied that the EWGs, -Cl, -F and -Br enhanced, while the EDGs decreased the α-amylase inhibition activity. In 2017, Wang and co-workers developed novel potential α-glucosidase inhibitors of sulfonamide based chromone hydrazones. Compound 152 (Fig. 9) (IC50 = 20.1 ± 0.19 μM) bearing a 4-sulfonamide substitution at phenyl part of hydrazide was the
most efficient α-glucosidase inhibitor. Docking results revealed that, compound 152 was interacting with the amino acids residues Glu-276, Asp-214, Asp-349 and Arg-439 through hydrogen bonds and π-π interactions [87]. In a study by Humphries et al. carbazole-containing sulfonamides as assayed for potent cryptochrome modulators of antidiabetic agents. Compound 153 (Fig. 9) showed

![Chemical structures and MIC values](image)

**Fig. 4.** (continued).
stronger cryptochrome modulator with EC\textsubscript{50} \(= 0.144\) \(\mu\)M. The SAR suggested that, the presence of sulfonamides functional group improved lipophilic efficiency of the potent analog [88]. Recently, Deka and co-workers have prepared a new series of thiazolidinediones hybrids and screened for potent peroxisome proliferator-activated receptor \(\gamma\) (PPAR\(\gamma\)). Among all the synthesized analogues, compounds 154 and 155 (Fig. 9) showed maximum PPAR\(\gamma\) binding affinities (\(I_{\text{max}}\)) with 98% and 82% respectively. The SAR revealed that, the introduction of diverse aryl sulfonamides as the polar head group and 1-phenylpiperidine on the tail part highly influenced the PPAR\(\gamma\) activity. In addition, the presence of electron withdrawing Cl and \(-\text{CF}_{3}\) groups on the phenyl ring of the sulfonamide linker also played a major role for the increases of activity. The presence of electron releasing (OH and \(-\text{OCH}_{3}\)) groups decreased the activity [89].

In 2017, Bruning and co-workers designed and synthesized a class of novel 2,4-dichloro-\(N\)-(3,5-dichloro-4-(quinolin-3-yloxy) phenyl)benzenesulfonamide analogues for potent PPAR\(\gamma\)-targeted antidiabetics agents. Compound 156 (Fig. 10) showed the most potent active PPAR\(\gamma\) inhibitor with EC\textsubscript{50} values is 2 nM. The SAR
revealed that, the presence of EWGs (F and Br) on phenyl ring A increased the activity. The sulfonamide moiety and a bromine atom at the para position on the aromatic benzene ring A contributed the potent active PPARγ inhibitor [98]. Gao and co-workers synthesized a novel series of sulfonamide-1,3,5-triazine-thiazoles derivatives and tested for in vitro inhibitory activity against several DPP enzymes, such as DPP-4, DPP-8 and DPP-9. Compound 157 (Fig. 10) was found to be highly potent against DPP-4 enzyme with IC₅₀ value of 2.32 nM compared to standard drug alogliptin. The SAR suggested that, compounds containing EWGs had superior inhibitory activity compared to those with EDGs substituent. Furthermore, the presence of additional aromaticity did not influence the activity. Moreover, molecular docking results indicated that, ligand 157 was efficiently docked into the active site of the catalytic triad of Ser 630, Asp 708 and His 740 encompassing both S1 and S2 pocket with CDOCKER interaction energy of 57.80 [91]. At last, Iqlbal and co-workers have developed arylsulfonylspiroimidazolidine-2,4-dione hybrids as potent hypoglycemic and ALR2 agents. Compound 158 (Fig. 10) was found to have the most potent inhibitory activity against ALR2 with an IC₅₀ value of 0.89 μM. The in vivo hypoglycaemic activity of compound 158 exhibited 72.24% reduction in blood glucose, which was more potent than standard drug glimepiride (60.92% reduction). The SAR suggested that, the presence of EWG (Cl) on the phenyl ring highly influenced the ALR2 activity. Replacing the halogen atom by methyl or methoxy group led to a reduced activity which was attributable to the lower lipophilicity of these substituents compared to the chlorine atom, and lesser interaction with the active site of aldose reductase. Activity was not really affected when the 2-naphthyl group replaced the para substituted phenyl ring; however, 2-anthraquinyl group was found to be detrimental to the activity. The large size of the 2-anthraquinyl group might be responsible for this negative effect [92].

2.3. Anti-inflammatory activity

Inflammation is a localised physical condition causing swelling, redness, heat with pain which is mediated by the release of proinflammatory mediators like bradykinin and cytokine increasing the prostaglandin synthesis rate [93,94]. Nonsteroidal anti-inflammatory drugs (NSAIDs) existing in two isomeric forms, constitutive form (COX-1) and an inducible form (COX-2) inhibits cyclooxygenases (COX) and thereby inhibiting the biosynthesis of prostaglandins (PGs) [95,96]. The role of COX-1 enzyme is maintaining the gastric integrity and kidney functioning whereas COX-2 is involved in inflammation and pain [97,98]. The sulfonamide moiety exists as one of the most ubiquitous pharmacophoric functional groups in medicinal chemistry. Sulfonamide group shows a diverse pharmacological activity in the organic molecules and hence it has become a priority while choosing functional group to incorporate in the optimizations by hybrid approach. It was reported earlier that a number of sulfonyl or sulfonamide functional group containing heterocyclic compounds were utilised to demonstrate potential anti-inflammatory activity [99–103]. Moreover, among the highly marketed COX-2 inhibitors that comprise the sulfonamide moiety, SC-558 (155) and celecoxib (166) (Fig. 11) are the major determinant for COX-2 selectivity and in vivo efficacy. Nimesulide (167) (Fig. 11) is an example of small molecule NSAID sold in the market today that has the sulfonamide functionality [104,105]. Some of them were potential anti-inflammatory analogues as showed in Fig. 11.

A class of novel sulfonamides as potent anti-inflammatory agents were designed and synthesized bearing pyrazolyl derivatives by Bekhit et al. [106]. The para-chlorophenyl substituted compound 170 (Fig. 12) emerged as a potent anti-inflammatory agent with protection 77.4% exceeding that of indomethacin. Chowdhury and co-workers reported a family of pyrazole bearing sulfonamides analogues and evaluated for in vitro anti-inflammatory activity. Compound 171 (Fig. 12) displayed attractive anti-inflammatory activity compared to the standard anti-inflammatory drugs celecoxib and aspirin. SAR studies revealed that the presence of N-methyl-1,2,3,6-tetrahydropyridyl ring significantly increased the biosisosteric effects in the active analogues [107]. Next, the research group of El-Din et al. developed sulfonamides based hybrids with potent anti-inflammatory activity [108]. Compound 172 (Fig. 12) was found to be most significant candidate, no ulcerogenic effect and with minimal effects on renal function. Novel pyrazole based sulfonamides derivatives were prepared by Küçükgüzel and co-workers and screened for their in vitro anti-inflammatory activity. Among those, compound 173 (Fig. 12) showed promising anti-inflammatory activity [109]. In 2013, Ragab et al. prepared and evaluated some novel 1,3,4-trisubstituted pyrazoles derivatives with potent anti-inflammatory and analgesic activities. Compound 174.
(IC$_{50}$ = 0.22 mM/kg) (Fig. 12) showed excellent anti-inflammatory activity (82% inhibition) and promising analgesic activity. The SAR suggested that, compounds containing 4-chlorophenyl pharmacophore exhibited higher activity than other functional substituted analogues (except for benzenesulfonamide azomethine). The effect of the nature of substituent at the 3-position of the pyrazole nucleus also played a major role in enhancing the anti-inflammatory activity [110].

Mohammed and Nissan reported novel pyrazole bearing sulphonamide-hydrazones derivatives as potent anti-inflammatory agents. Compound 175 (Fig. 13) was found to be a better anti-inflammatory agent than the standard anti-inflammatory drug diclofenac and indomethacin. In addition, molecular docking study revealed that the compound 175 interacted with Tyr 385 and Ser 530 [111]. Hassan et al. synthesized a series of benzofuran bearing celecoxib-sulfonamides for the development of novel anti-inflammatory agents. Among those, compound 176 and 177 (Fig. 13) exposed the highest anti-inflammatory activities. Anti-inflammatory data revealed that an essential role of compounds 176 and 177 bearing pyridine moiety enhanced the anti-inflammatory efficiency in animal models [112]. Ahmed and co-workers synthesized a new class of curcumin-containing sulfonamides analogues to investigate the activity against anti-inflammatory. Compound 178 (Fig. 13) was identified as a successful anti-inflammatory agent by 82% inhibition of induced edema which is comparable to standard drug indomethacin (84.4% inhibition) [113]. In 2014, Kumar et al. reported an eighteen pyrazolopyrazolines bearing benzenesulfonamide as potent anti-inflammatory agents. Among those, compounds 179 and 180 (Fig. 13) showed excellent anti-inflammatory effects [114]. Compounds containing sulfonamides based heterocycles have been highlighted for the search of new anti-inflammatory agents.
Korupolu et al. reported a structural investigation of sulfonamide hydrazones as potent anti-inflammatory agents. Among all the synthesized analogues, compounds 181 and 182 (Fig. 14) showed superior anti-inflammatory activities with IC_{50} values of 8.9 and 8.4 \mu M respectively. Compound 181 was found to be the strongest and the most selective COX-2 inhibitor among the fluorinated derivatives. SAR suggested that the presence of tri-fluoromethyl group at para position in compound 181 showed good selectivity with COX-2 inhibition activity [115].

Recently, Abdellatif and co-workers reported the synthesis and anti-inflammatory activity study of sulfonamides based imidazolone analogues as selective COX-2 inhibitors. Based on in vitro evaluation, compounds 183 and 184 (Fig. 14) displayed excellent COX-2 potency with IC_{50} values of 0.42 and 0.62 \mu M respectively and the most COX-2 selective indexes as S.I. values of 10.76 and 10.87 respectively. SAR suggested that the presence of EWGs on the phenyl ring influenced the anti-inflammatory activity [116].

2.4. Anti-malarial activity

Malaria is a parasitic infection which is spread worldwide mostly affecting and causing serious problems in the tropical and subtropical parts of Asia, Central and South America, Africa and also millions of people are affected in the parts of Middle East [117,118]. A parasitic species called Plasmodium which is carried by the female of Anopheles mosquito is the cause of this disease which enters into bloodstream of humans by an infected mosquito. The treatment and management of this disease is unreasonably high not only because of medication but also due to low production [119]. The difficulty in controlling malaria lies at growing resistance of malaria parasite to most of the antimalarial drugs used [120].

Hence there is a strong need to treat this drug-resistant disease by developing better performing drugs. A continued effort including exploration of potentially bioactive natural product derived compounds is required. Most of the biologically active antimalarial agents contains sulphonamide group [121–123]. The sulphonamide group present in a number of potential anti-malarial analogues were showed in Fig. 15.

Pingaew et al. described a synthesis and biological properties of compounds with in vitro antimalarial activity against P. falciparum. Compound bearing sulfonamide analog 196 (Fig. 16) with 6,7-dimethoxy groups exhibited the most potent antimalarial activity with IC_{50} values of 2.8 \mu M. The structure activity studies concluded that the lipophilicity of dimethoxyphenyl and tetrahydroisoquinoline sulphonamide may be contributing to enhance the activity [124]. Eleven analogues of sulphonamide bearing chalcones were tested for their effects as inhibitors of β-hematin formation against cultured P. falciparum parasites by Domínguez et al. The substituted trimethoxyl aromatic compound 197 (Fig. 16) was found to be the most active antimalarial agent with IC_{50} value of 0.48 \mu M, compared to a reference antimalarial drug chloroquine with IC_{50} value of 1.33 \mu M [125]. The screening of new N-(7-chloroquinolinyl-4-aminokyl)arylsulphonamides analogues were developed by Verma et al. All the synthesized analogues were tested in vitro antimalarial activity against P. falciparum 3D7 and K1 strains. Two compounds 198 (Fig. 16) (IC_{50} 3D7: 0.05 \mu M; K1: 0.41 \mu M) and 199 (Fig. 16) (IC_{50} 3D7: 0.01 \mu M; K1: 0.36 \mu M) showed promising antimalarial activity better than the positive control. Results from the study indicated that alkyl chain length was critical for antimalarial activity and also the presence of isopropyl groups.
on the phenyl ring of the sulfonamide end highly enhanced the antimalarial activity [126]. Recently, Oliveira and co-workers reported the potent sulfonamide containing chaclcone hybrids and evaluated for in vitro anti-malarial activity against P. falciparum. Compound 200 (IC50 = 2.06 μM) (Fig. 16) was found to be the best antimalarial agent with good selectivity index [127]. Muthas and co-workers reported a class of new potent hydroxyethylpiperazines bearing benzenesulfonyl hybrids as antimalarial agents. All the synthesized compounds were tested in vitro antimalarial activity against W2 P. falciparum clone. Among those, compound 201 (IC50 of 16.9 μM, Fig. 16) displayed superior antimalarial activity with IC50 values of 4.80 μM against W2 P. falciparum clone [128].

Recently, the combination of indoleamides with sulfonyl has been reported as the most active antimalarial agents against P3D7 and PfK1 strains. Among those, compounds 202, 203, 204 and 205 (Fig. 17) with sulfonyl pharmacophore showed promising activity with IC50 of 1.87, 1.93, 2.00, 2.17 μM against CQ sensitive P3D7 strain and 1.69, 2.12, 1.60, 2.19 μM against CQ resistant PfK1 strain, respectively. SAR revealed that the presence of sulfonyl analogues containing bulky groups such as p-ter-butylphenyl (202 and 204) and 4-chloro-2,5-dimethyl phenyl groups (203 and 205) showed the most promising antiplasmodial activity with IC50 values range between 1.60 and 2.19 μM [129]. Huang and co-workers reported sulphonamide bearing small analogues as potent dual inhibitors of FP-2 and DHFR. Compounds 206 and 207 (Fig. 17) bearing amide and sulphonamide moieties were found to be the most active FP-2 inhibitors. Compound 207 containing thiazole group on amide moiety was most active analogues against FP-2 (IC50 = 7.0 μM) and DHFR (IC50 = 6.3 μM). In addition, compound 207 showed reasonable in vivo antimalarial activities compared to standard drug chloroquine diphosphate salt. SAR suggested that the presence of amide, sulphonamide and thiazole groups played a crucial role for enhancing the antimalarial activity [130]. Caridha and co-workers reported potent thiophene and benzene sulfonamides as antimalarial agents. Among these, bromohydrosulfonylacetamides 208 (Fig. 17) was found to be promising growth inhibition of drug resistant P. falciparum W2 strain as well as low toxicity profiles against mammalian cell lines. Further exploration of 208 with variation in the thiophene and benzene ring substitutions may produce more potent P3CDK inhibitors [131]. Cunico and co-workers have developed hydroxyethylpiperazine analogues and evaluated in vitro anti-malarial agents against a W2 Plasmodium falciparum clone. Compound 209 was found to be the most potent anti-malarial agent with IC50 value of 4.8 μM against W2 Plasmodium falciparum clone almost as active as standard lopinavir. The SAR revealed that the presence of amine group on the phenyl ring influenced the anti-malarial activity. In addition, the presence of piperazine moiety was also an essential for increases the activity. The sulfonamide functional groups were bridged between the two bioactive analogues [132].

2.5. Alzheimer’s disease (AD)

Alzheimer’s disease (AD) is a neurodegenerative disorder featured with cognitive dysfunction and memory lapse which accounts for the major dementia cases. According to the present estimation, about 45 million people are going through this disease worldwide and it may reach up to 131 million by 2050 as per the documentation if left untreated [133–135]. Actual etiology for the AD progression is not known yet but a number of pathophysiology factors are believed to be responsible for the progression of this disease. Deficits of acetylcholine (Ach), inflammation, β-amyloid
(Aβ) deposits, oxidative stress, dyshomeostasis of biometals, tau-protein aggregation are considered to be such pathophysiological factors [136–138]. Unfortunately the medicines for the cure of AD and its progression are not discovered yet. But certain medicines are approved and prescribed for the AD patients for the temporary relief [139,140]. In this part of the review article, sulfonamide nucleus is focused as a core substituent of Alzheimers agents for the development of drug [141–144]. Some of the sulfonyl or sulfonamides containing heterocycles represented as potential Alzheimer’s agents are summarized in Fig. 18.
Mutahir and co-workers performed novel biphenyl bis-sulfonamide derivatives as potent acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) agents. Among the tested compounds, compound 217 (Fig. 19) was found to be the most potent activity against AChE (IC$_{50}$ 2.27 ± 0.01 µM), whereas 218 (Fig. 19) exhibited the highest inhibition for BuChE (IC$_{50}$ 7.74 ± 0.07 µM). SAR studies revealed that both the 3,30-dimethylbiphenyl functionality as well as benzyl moiety on nitrogens played a crucial role for the higher activity of compound 217. The higher activity of 218, bearing n-hexadecanyl moiety on nitrogens, is a similar trend as the case in AChE inhibition which could be attributed to the hydrophobic bulkiness of the n-hexadecanyl group. In addition, molecular docking studies were also performed for the analysis of the binding mode and hydrogen bonding interactions of compound 217 in both cholinesterases enzymes. Ligand binding within the active site of AChE was limited to hydrophobic interactions with Tyr334, Phe331, and Phe330 from anionic sub-site, Tyr70 from acyl pocket as well as Tyr121, Trp279, Asp276, and Phe228 from peripheral anionic site. Biphenyl fragment was engaged in more specific π–π and CH–π interactions with Tyr334. The arrangement of the most active compound 217 in the active gorge of AChE is shown in Fig. 20. Ligand binding within the active site of AChE was limited to hydrophobic interactions with Trp84, Phe330, and Phe331 from anionic sub-site, Phe290 from acyl pocket as well as Tyr121, Trp279, Asp276, and Phe228 from peripheral anionic site. Biphenyl fragment was engaged in more specific π–π and CH–π interactions with Trp279, Phe331, and Tyr334. Oxygen atoms in sulfonamide groups might create weak H-bonds with hydroxyl group of Tyr70 or unionized form of Asp72. The arrangement of the most active compound 217 in the active gorge of AChE is shown in Fig. 21. And similar results were observed in case of docking to the active site of BuChE. The binding of the tested compound 217 with AChE and BuChE was mainly provided due to the presence of hydrophobic interactions. Summing up, it can be assumed that the binding of the tested compounds with AChE and BuChE was mainly provided due to the presence of hydrophobic interactions. However, the obtained compounds are interesting starting point for their further development and synthesis of potent cholinesterase inhibitors. Structural modifications leading to increase of number of hydrogen bond donors and acceptors should augment the strength and specificity of binding to enzymes [145].

Yar et al. reported the novel potent pyridine 2,4,6-tricarbohydrazide analogues as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) agents. Compound 219 (Fig. 19) exhibited the most potent activity against tested enzymes such as AChE (IC$_{50}$ 50.2 µM) and BChE (IC$_{50}$ 43.8 µM). Overall the compound 219 bearing phenyl group was found to be active against all these tested enzymes [146]. On the other hand, Ulus et al. described acridine-sulfonamide hybrids as potent acetylcholinesterase inhibitor for the treatment of Alzheimer’s disease. Compound 220 (Fig. 19) displayed superior activity against AChE with an IC$_{50}$ of 0.14 µM [147]. Later, the same research group (Ulus et al.) continued the development of new type of alzheimer’s agents in which, sulfonamid bearing tacrine derivatives were synthesized and evaluated for in vitro acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities. Compound 221 (Fig. 19) was found to have the highest inhibitory activity on AChE with IC$_{50}$ value of 0.009 µM. This value is 220-fold higher than that of galantamine (IC$_{50}$ = 2.054 µM). Compound 222 (Fig. 19) displayed the strongest inhibition of BuChE with IC$_{50}$ value of 2.250 µM. To elucidate SAR, sulfonamide group present on the para position at the phenyl ring showed good acetylcholinesterase activity (AChE...
When sulfonamide group moved from para to meta-position of phenyl ring the butyrylcholinesterase activity was increased [148]. Rehman et al. also evaluated the ability of some pyrimidine-based sulfonamides against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes. They designed and tested compound 223 (Fig. 19) as a potent agent with IC$_{50}$ values of AChE 3.73 mM and BChE 4.81 mM. SAR studies suggested that the presence of electron releasing moiety was crucial for the higher activity of 223 and EWGs inactive against the AChE and BChE enzymes. At the next level of investigation, the authors also performed the molecular docking analysis of potent compound 223 for detailed exploration of its binding pattern within the active sites of AChE and BChE. In addition, docking technique is considered efficient in accurately predicting binding mode of small molecules. The most potent compound 223 was showed detailed exploration of its binding pattern (2D and 3D binding mode of interaction) within the active sites of AChE and BChE. Compound 223 had two hydrogen-bond interactions with the peripheral anionic site residue Tyr279 upon binding to AChE (Fig. 22). Additionally, the docked complex of BChE with 223 showed that the hydrophobic patch residue Tyr332 and the catalytic triad residue Gly116 were involved in intramolecular hydrogen bonding (Fig. 23). The docking results showed that 223 were capable of establishing two hydrogen-bond interactions with the peripheral anionic site (PAS) residue Tyr121 upon binding to AChE (Fig. 24). Additionally, the docked complex of BChE with 6j (BChE-6j) showed that the hydrophobic patch residue Tyr128 and the catalytic triad residue Ser198 were involved in intramolecular hydrogen bonding (Fig. 25) [149].

Gobec et al. realized the synthesis of N-propargyl-piperidines containing naphthalene-2-carboxamide or naphthalene-2-sulfonamide hybrids and tested for multi-functional Alzheimer's agents. The most potent hBChE inhibitor of the series, compound 224 (Fig. 26) (IC$_{50}$ = 127 nM) is 1,3 disubstituted piperidine with a sulphonamide group and (CH$_2$)$_2$OMe chain on the sulfonamide nitrogen. SAR revealed that the absence of the N-alkyl chain on the carboxamide and sulfonamide nitrogen was imperative for MAO-B inhibition, as compounds bearing the N-alkyl chain were inactive [150]. Since 2013, Park et al. has reported the generation of sulfonyl chalcones analogues as potent β-secretase and acylcholinesterase inhibitors. Compounds 225 (IC$_{50}$ = 0.21 mM), 226 (IC$_{50}$ = 0.62 µM) and 227 (IC$_{50}$ = 0.69 µM) (Fig. 26) showed most potent BACE1 inhibitor. To elucidate the SAR, the presence of 3,4-dihydroxy group in the B ring of the chalcone, produced more potent agent than the corresponding 4-hydroxy derivatives. Smaller electron donating groups (CH$_3$, OH and NH$_2$) were more favoured than larger species such as OCH$_3$ and EWGs such as NO$_2$ [151]. Recently, Wieckowska et al. reported the sulfonamide based piperidine hybrids as potent 5-HT$\text{6}$ receptor antagonist with a cholinesterase inhibitor. Among these, compound 228 (Fig. 26) was found to be the most potent agent against the 5-HT$\text{6}$ receptor ($K_b$ = 27 nM), AChE and BuChE (hAChE: IC$_{50}$ = 12 nM, hBuChE: IC$_{50}$ = 29 nM). In a further drug development program, a novel class of multi-functional ligands were evaluated, in which compound 229 (Fig. 26) the best derivative from the series, represented an excellent starting point for the development of an effective treatment for AD [152].

### 2.6. Antileishmanial activity

Disseminated leishmaniasis has become an emerging infectious disease, mostly due to Leishmania braziliensis. L. braziliensis has caused both cutaneous and mucocutaneous leishmaniasis in
several Latin American countries [153]. Presently, this parasitic disease causes morbidity and mortality, mainly in the developing world [154]. Toxicity, high costs, and development of drug resistance have become obstacles in the prevailing chemotherapeutic treatment [155]. Sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®), the two pentavalent antimonials [Sb(V)], were first introduced in the 1940s and are being used for all forms of leishmaniasis through parenteral administration [156]. Therefore, drugs that are safe, inexpensive and easily available need to be developed immediately. Lead compounds are also now having taken important roles for the future treatment of this disease globally.

Sulfonamides, according to literature, have shown versatile antileishmanial activity and have become a structural core in leishmanicidal therapy [157–160]. The sulfonamide group acts as a chemical link that allows binding of other potential “active components” such as aromatic and heteroaromatic systems along with the demonstration of antiparasitic activity [161–163].

Marra et al. conducted a study aimed at the preparation and evaluation of potent novel 4-(1H-pyrazol-1-yl)benzenesulfonamide hybrids against the L. infantum and L. amazonensis strains. Compounds 230 (IC50 = 0.059 μM against L. infantum, IC50 = 0.070 μM against L. amazonensis) and 231 (IC50 = 0.065 μM against L. infantum, IC50 = 0.072 μM against L. amazonensis) (Fig. 27) showed most potent activity against the tested L. infantum and L. amazonensis strains. In this case, both compounds 230 and 231 pyrazole baring sulfonamide groups were active for treating infections caused by these two Leishmania strains [164]. Borges and co-workers reported a new class of pyrazolyl benzensulfonamide hybrids as potent antileishmanially active candidates against Leishmania amazonensis. Among these, compound 232 (IC50 value is 6.7 μM) (Fig. 27) was found to have the most potent activity against Leishmania amazonensis with IC50 value higher than reference drug ketoconazole [165]. González-Rosende et al. developed a new series of naphthalene-sulfonamide analogues as potent anti-leishmanial and trypanocidal inhibitors. Compound 233 (Fig. 27) displayed most potent inhibition on three Leishmania species entitled L. infantum (IC50 = 23.0 μM), L. amazonensis (IC50 = 42.9 μM) and T. cruzi (IC50 = 223.7 μM). In addition, compound 233 was found to be an excellent anti-T. cruzi candidate, and further clinical investigation could be useful in the development of new antichagasic drugs [166]. The group of Palop reported diselenide containing sulfonamide derivatives, which exhibited in vitro leishmanicidal activities against Leishmania infantum intracellular amastigotes and THP-1 cells. Compound 234 (Fig. 27) emerged as the most active compound (IC50 = 2.8 μM), showing higher activity and much less toxicity against THP-1 cells than reference drug edelfosine. SAR studies, no clear-cut relationship was found but, mutually these results suggested that the sulfonamide scaffold could be a valuable linker for the connection of parent diselenide and para-fluoro phenyl ring attaching both sulfonamide ends [167]. In addition, Rodrigues et al. designed and developed chalcone-sulfonamised analogues as potent anti-leishmanial agents. Compound 235 (Fig. 27) was found to be the best profile against L. braziliensis promastigotes with IC50 value of 3.5 μM. Moreover, the presence of benzylamino group extensively contributed to this activity. These results revealed the sulfonamide based methoxychalcone hybrids as lead compounds for designing new candidates for leishmaniasis treatment [168].

![Fig. 14. Sulfonyl of sulfonamides as anti-inflammatory agents.](image-url)
2.7. Tuberculosis activity

Tuberculosis is a highly infectious chronic deadly disease caused by a bacteria called *Mycobacterium tuberculosis* (MTB). This disease is a threat to the human life affecting lungs primarily (pulmonary TB) apart from other vital organs. Drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and totally drug resistant TB (TDR) are emerging now a day’s which are completely resistant for the action of presently available standard drugs [169]. The infection of TB is so high that it has caused deaths of around 1.4 million and 10.4 million clinical cases all over globe as reported in 2015 [170,171]. However the treatment of TB with the drugs such as Isoniazid (INH), Ethambutol (EMB), Rifampicin (RIF) and Pyrazinamide (PZA) is observed to be highly effective for TB. Discovery of Rifampicin (RIF) have helped in obtaining handful of Anti-TB drug compounds to the humans. However, still a number of derivatives are to be explored to stop the activity of bacteria and further spreading of TB.

Fig. 28 showed some of the sulfonyl or sulfonamide containing heterocycles as potential TB agents.

Shahul and co-workers reported aminoperidines with benzimidazole derivatives as potent anti-TB agents against Mtb and Mtb DNA gyrase. Compound 241 (Fig. 29) displayed superior anti-tuberculosis activities against Mtb and (MIC = 0.19 μM) Mtb DNA gyrase (IC₅₀ = 1.9 μM). The SAR revealed that the presence of electron withdrawing (CF₃) substituent at 5-position of benzimidazole ring was crucial for producing potent Mtb and introduction of other hydrophobic substituents such as methyl or fluorine enhanced the antiTB potency by 4-fold [172]. Another new class of sulfonyl containing benzimidazole derivatives were evaluated for in vitro anti-TB activity against *M. fortuitum*, *Mtb* H37Rv, MDR-TB and *M. smegmatis* strains by Ranjith et al. The compounds 242–244 (Fig. 29) showed an excellent activity against Mtb H37Rv strain with the MIC of 6.25 μg/mL. This may be due to the presence of sulfonyl group and bromine at 5 or 6-position of central benzimidazole as the key factor for the improving the activity [173]. A set of new 3-(4-(phenylsulfonyl) cyclohexyl]benzol[d]isoxazole hybrids 245 (Fig. 29) were designed and tested for their anti-TB against *M. tuberculosis* H37Rv strain by Naidu et al. in which compound 245 with benzenosulfonyl moiety inhibited growth of 99% bacteria at 3.125 μg/mL [174]. MTB Protein Tyrosine Phosphatase B (MptpB), a familiar protein tyrosine phosphatase determined by Mtb, is a promising target for new anti-TB agents. Yao et al. has screened around 3500 compounds as MptpB inhibitor, and some of them displayed potent activities which are exemplified by 246 (Fig. 29) with IC₅₀ of 0.15 μM. Thus, both of them could act as leads to be further exploited [175]. Several sulfonyl-hydrazones were also tested for in vitro anti-TB agents against *Mycobacterium tuberculosis*-PtpB. Among all the synthesized molecules, compounds 247 (IC₅₀ = 18 μM), 248 (IC₅₀ = 21 μM), 249 (IC₅₀ = 39 μM) and 250 (IC₅₀ = 41 μM) (Fig. 24) showed the most potent PtpB inhibitors. The SAR suggested that the presence of EWGs (Cl, F and NO₂) on the phenyl ring of sulfonamide end enhanced the anti-TB properties [176]. As the continuous search of new type of potent anti-TB agents, Reddy and co-workers designed and developed new sulfonamide based indole hybrids as potent anti-TB agents.
251 (Fig. 29) was found to be the most active anti-TB agents with IC\textsubscript{50} = 17.02 M. The SAR study revealed that (i) N-mesyl indoles showed better activities compared to N-tosyl analogues and (ii) the presence of EDGs at C-5 position of the indole ring was favourable for chorismate mutase (CM) inhibition [177]. Compound 252 (Fig. 29) displayed promising anti-TB activity with 45% inhibition at 30 \mu M. In silico study suggested that the carbonyl oxygen of 252 participated in H-bond interactions with CM [178]. Nakhi et al. explored potent anti-TB agents against \textit{Mtb}CM. Compound 253 (Ki = 5.7 M) (Fig. 29) was found to be the best inhibitor against \textit{Mtb}CM. The SAR showed that the indole containing an \textit{o}-(RSO\textsubscript{2}NH) \textsubscript{C\textsubscript{6}}H\textsubscript{4} group at C-2 position and a sulfonamide moiety played a key role during its interaction with the active site of CM [179]. At last, novel 4-aryl/alkylsulfonylmethylcoumarins hybrids were synthesized and screened for \textit{in vitro} anti-mycobacterial activity against MTBH\textsubscript{37Rv}. Among these, compound 254 (IC\textsubscript{50} = 2.06 \mu M) showed excellent anti-TB activity with MIC value of 0.78 \mu g/mL, eight fold more potent than EMB (MIC: 1.56 \mu g/mL) and PZA (MIC: 6.25 \mu g/mL) [180].

2.8. Antiviral activity

Viruses are infectious agents affecting the life forms. They are responsible for causing various dangerous diseases like human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV, respectively), severe acute respiratory syndrome (SARS), corona viruses (Middle east respiratory Syndrome, MERS); influenza (seasonal, pandemic), viral haemorrhagic fevers (Ebola), dengue, and chikungunya etc. These diseases have caused adverse impact on human health leading to unexpected illnesses and deaths, troubling day-to-day normal life activities. Viruses are the major cause for the emergence of newer pandemics e.g. H1N1 influenza, Ebola, and Zika virus etc. threatening the public health [181,182].

On the same hand, more than 60 antiviral drugs of diverse chemical classes have been approved by the FDA, mainly for the management of HIV, the hepatitis B and C, herpes and influenza A and B viruses and still many molecules are in various stages of clinical trials. But there is still a pressing need for the development of new drugs acting through several mechanisms and combat the viral resistance as viruses are constantly evolving [183]. However it is always challenging for the medicinal chemists to develop newer drugs understanding unique biological features of viruses and treat the emerging viral disease in one or the other way without harming the host cells [184]. Fig. 30 showed some of the sulfonyl or sulfonamides potent anti-viral agents.

In recent years, various sulphonamide based isoxazolidines hybrids were synthesized and evaluated for \textit{in vitro} HIV-1 replication by Loh et al. Compounds 261 (IC\textsubscript{50} = 93 \mu M against HIV-I and IC\textsubscript{50} = 91 \mu M against NL4.3) and 262 (IC\textsubscript{50} = 75 \mu M against HIV-I...
Fig. 17. Sulfonyl of sulfonamides as anti-malarial agents.
and IC50 = 71 μM against NL4.3 (Fig. 31) blocked the transcriptional activation of HIV-1. The SAR suggested that the presence of size of the halogen and aromatic rings seemed to be significant for the antiretroviral activity against HIV-1 vector and wild-type NL4.3 HIV-1 [185]. Ali et al. designed and developed new potent antiviral agents of potent phenyloxazolidinones hybrids against wild-type HIV-1 protease and MDR variant. Among them, compound 263 (Fig. 31) was found to have excellent antiviral properties with Ki values of 0.003 nM against wt and 2.45 nM against MDR variant [186]. Manfroni and co-workers synthesized a new class of potent pyrazolobenzothiazines hybrids as antiviral activity against HCV. Compounds 264 (EC50 = 8.1 μM and CC50 > 224 μM), 265 (EC50 = 4.8 μM and CC50 > 186 μM) (Fig. 31) were identified as successful anti-HCV agents [187]. Kang et al. designed and synthesized thiophene-pyrimidine analogues and evaluated their activity against a panel of mutant HIV-1 strains. All the analogues were found to exhibit reasonable to outstanding potency against wild-type (WT) HIV-1 in MT-4 cells. Compound 266 (Fig. 31) was found to be the most potent activity against the single mutants Y181C and Y188L with EC50 = 0.428 and 0.675 μM, respectively, more potent than reference drug AZT. These results are expected to be helpful in the design of thiophene-pyrimidine-based NNRTIs with more potent activity against HIV-1 strains. The overall profile of compound 266 makes it a good aspirant for future drug development program [188].

Several thiadiazole bearing sulfonylamides analogues have also demonstrated promising antiviral activity against tobacco mosaic virus by the half leaf method explored by Yang et al. Compounds 268 (42%) and 269 (42%) (Fig. 32) showed promising TMV inhibition compared to the reference drug Ningnanmycin (54%). The SAR, structural modification in the sulfonylamide moiety has a wide impact on anti-viral activity of the compounds [190]. Hu et al. developed and prepared a new class of chalcone-containing purines and benzenesulfonamide hybrids and tested for antiviral properties against TMV and CMV. Compound 270 (Fig. 32) was found to possess outstanding activity against TMV with the EC50 value of 51.65 μg/mL, which was better than that of ribavirin (150.45 μg/mL). The SAR analysis showed that introducing EDGs at the 2-position of benzenesulfonamide aromatic rings and low steric hindrance group promoted antiviral properties. These findings indicated that chalcone derivatives were worthy of further research and development as templates for new antiviral agents [191]. Compound 271 (Fig. 32) was found to have potent (Ki = 0.8 nM, IC50 = 1.5 μM) antiviral activity. Oral bioavailability of this compound ranged from 42% (rat) to 77% (dog) with t1/2 = 6 h [192,193]. Saturation of the 5,6-double bond in the pyrone ring led to the identification of a compound 272 (Fig. 32) with excellent binding affinity for the HIV protease (Ki values in the 0.05 nM) and excellent antiviral activity in cell culture, with significantly less ED50 value of 0.95 μM [194]. At last, the continuation of finding new class of potent coumarin-benzimidazole hybrids as potent anti-HCV activity by Hwu et al. Among these, compounds 273 (EC50 = 10.2 μM) and 274 (EC50 = 13 μM) (Fig. 32) displayed excellent antiviral activity against chikungunya virus (CHIKV). The SAR revealed that the extension of the doubly conjugated uracilecoumarins to triply conjugated uracilecoumarinearenes by use of the -SO2 linker was fundamental to their anti-CHIKV activity. Bezouacil derivatives 275 (Fig. 32) had better selectivity indexes compared to uracil 276 (Fig. 32) or thymine [195].

2.9. Carbonic anhydrase inhibition

Carbonic anhydrases (CAs) are a class of metalloenzymes containing zinc as the metal. The roles of these metalloenzymes are the
Fig. 19. Sulfonyl of sulfonamides as Alzheimer’s agents.

IC$_{50} = 2.27 \ \mu$M against AChE

IC$_{50} = 7.74 \ \mu$M against BChE

IC$_{50} = 50.2 \ \mu$M (AChE)
IC$_{50} = 43.8 \ \mu$M (BChE)

IC$_{50} = 0.14 \ \mu$M

IC$_{50} = 0.009 \ \mu$M (AChE)

IC$_{50} = 2.250 \ \mu$M (BuChE)

IC$_{50} = 3.73 \ \mu$M against AChE
IC$_{50} = 4.81 \ \mu$M against BChE

Fig. 20. 2D-binding mode of compound 217 within the active site of AChE.
interconversion of carbon dioxide and water to bicarbonate and proton maintaining the acid-base balance in tissues and blood. This enzyme is a multidomain protein containing CA subdomain situated outside the cell. It also possesses high CO2 hydrase catalytic activity which is inhibited by CA inhibitors belonging to sulfonamide, sulfamate and sulfamide classes of compounds [199].

Today around 15 different human CAs are known which are widely distributed in different tissues involving in different physiological process such as cell differentiation and proliferation, pH homeostasis, neurotransmission and pathologies like diuretics, epilepsy, glaucoma, obesity and cancer [196–198].

Sulfonamide is considered to be a significant moiety due to its diverse pharmacological activities [200] and these have clinical use as carbonic anhydrase inhibitors (CAIs) primarily as diuretics and anti-glaucoma agents. Heterocyclic ring or the aromatic ring containing sulfonamide moieties as zinc binding group as tail approach afford CAIs possessing both high affinity and desired pharmacologic properties and have been already explored in literature [201,202].

Very recently, a family of sulfonamide based heterocycles hybrids were designed and biologically evaluated as potent carbonic anhydrase activity against hCA 11 and hCA 1V by Nocentini et al. Compound 275 (Fig. 33) was found to have superior activity with IC50 values of hCA 11 is 0.4 nM and hCA 1V is 20.5 nM. The SAR revealed that the presence of key functional elements such as pyrazole, isoxazole and sulfonamide functional moiety was beneficial for the enhancing carbonic anhydrase activity [203]. Khalifah and co-workers designed and developed potent iminothiazolidinone-sulfonamide hybrids and evaluated for their inhibitory effect against four relevant human (h) isoforms of carbonic anhydrases (CAs, EC 4.2.1.1) I, II, IV and IX by a stopped-flow CO2 hydrase assay [204]. Compounds 276 and 277 (Fig. 33) showed the most potent active against hCAII with IC50 values of KIs of 0.41 and 0.46 nM which may be due to the presence of EWGs (Cl and NO2) for highly influencing the strongest inhibitors of hCAII [205].

In 2008, a series benzenesulfonamide linked 1,3,5-triazine hybrids were synthesized in good yield and tested for in vitro carbonic
showed least CA activities against hCA I, II and IX inhibitors [206]. Supuran et al. reported sulfonamides linked triazine moieties (279–283) (Fig. 33) and tested for carbonic anhydrase transmembrane isoforms IX, XII and XIV over cytosolic isoforms I and II. The longer spacer compound \( (n = 2) \) has shown more effectiveness as an inhibitor than the intermediate spacer \( (n = 1) \), which in turn was more effective than the shorter spacer derivative \( (n = 0) \). The short amino alcohol derivative 279 (Fig. 33) has also shown more effective than the bulkier compound 281 [207]. Mert et al. reported the new class of 5-amino-1,3,4-thiadiazole-2-sulfonamide containing pyrazole hybrids and tested for in vitro inhibitory activity against the isoforms of human cytosolic carbonic anhydrase I and II. Compounds 284 (Fig. 33) for hCA I \( (K_i = 0.119 \, \mu M) \) and the compound 285 (Fig. 33) for hCA II \( (K_i = 0.084 \, \mu M) \) showed the highest inhibitory activity compared to the rest of the analogues [208].

2.10. Cannabinoid receptor agonists

Cannabinoid receptors 1 and 2 (CB1 and CB2, respectively) were considered to be the members of the G protein-coupled receptor (GPCR) superfamily in the early of 1990’s [209,210]. Cannabinoid-1 receptor (CB1R) being most abundant neuroregulatory receptors present in the brain, peripheral organs such as adipose tissues, muscle and liver [211] regulates feeding and appetite [212]. Whereas cannabinoid-2 receptor (CB2R) is mostly expressed in the immune system regulating immunity and neurodegeneration [213].

Compound 286 (Fig. 34) was the best example of sulfonamide group claimed potent cannabinoid receptor agonist. In addition to this finding of new sulfonamides containing cannabinoid receptor drugs, scientists from AstraZeneca have also reported a potent sulphonamide based drug 287 (Fig. 34) acts as both CB1/CB2 dual agonists for the administration of pain [214]. Very recently, Watson and co-workers from Pfizer have reported sulfonylbenzimidazole
Fig. 27. Sulfonyl of sulfonamides as Antileishmanial agents.
proved to be an extremely potent agonists at the hCB2 receptor, the presence of sulfonamides functionalities has therapeutic potential of allosteric modulation of the cannabinoid receptor. Compounds and indole sulfonamides as potent cannabinoid receptor. The compound was found to have no agonistic effect which was demonstrated in pain models. Furthermore, to improve the metabolic stability and solubility, the same group optimized the compound and led to the discovery of relatively polar and peripherally acting CB2 agonists of compounds and (Fig. 34) [216]. Greig et al. designed and produced a new class of indole sulfonamides as potent cannabinoid receptor. Compounds and displayed outstanding potencies of 4 and 3 nM respectively, and showed good oral exposure and CNS penetration, making them highly versatile tools for investigating the therapeutic potential of allosteric modulation of the cannabinoid system [217]. The presence of sulfonamides functionalities has proved to be an extremely potent agonists at the hCB2 receptor, compound (EC50 = 5.1 nM) and (EC50 = 7.0 nM) (Fig. 34) being the most potent hCB2 receptor agents. These results inspired further development of in vitro profiling of sulfonamides on the hCB1 receptor and on rat liver microsomes (RLM) [218]. Chang et al. developed pyrazole bearing sulfonamide hybrids and evaluated for potent cannabinoid-1 receptor antagonist. Compound (Fig. 34) was found to be most potent cannabinoid-1 receptor antagonist with Kᵢ values of 0.3 nM (hCB1R), 21.0 nM (hCB2R) and EC₅₀ of 3 nM (CB1R). Compound is currently under development for treating obesity and the related metabolic syndrome [219].

2.11. Anticonvulsant activity

Epilepsy is a family of neurological disorders caused due to disturbances in the nerve cell activity which is associated with progressively impaired cognition and function, brain damage and other neurological deficits. It has become a common neurological condition affecting 45–100 million people [220]. Fortunately there is availability of antiepileptic drugs [AED’s] which allow epileptic patients to maintain a normal and undisturbed life by having satisfied control and total relief of seizures [221,222]. Further improvement in the development of antiepileptic drugs is a requirement for the complete prevention of epilepsy and its progression. 

Farag and co-workers developed a set of compounds (298–300) (Fig. 35) with pharmacophore hybrids and tested for picrotoxin (PIC)-induced convulsions (10 mg/kg, i.p.) in mice. Among them, compound protected all animals better than the reference drug phenobarbital and did not show mortality. Other active compounds and also showed reasonable protections and they decreased the mortality rate up to fifty percent [223]. In continuation, the authors have further modified benzothiazole pharmacophore by introducing sulfonamide group and tested those molecules for their anticonvulsant activity using MES, sc-PTZ seizure tests in Swiss albino mice [224]. Compounds and were found to be the most active in both seizure tests at variant doses and were neurotoxic at the higher doses of 300 mg/kg as similar to standard drug carbamazepine [225].

2.12. Anticancer activity

Cancer is been universally known as a disease or a group of diseases causing death. It is found to exist all over the world [226,227]. Cancer is meant to be a bunch of cells originated from a single cell due to its uncontrolled growth and rapid proliferation properties [228]. The problem with the drugs is that it is unable to differentiate between normal and cancerous cell type leading to several serious side effects [229]. Development of anticancer therapeutic agents has become a challenge for the medicinal chemists. But a continuous effort is being carried in this area of research to save millions of lives.

In 2017, Nitin and co-workers designed and developed a new class of benzothiazole derived methyl sulfonil hybrids as potent anticancer agents. Among them, some of the compounds showed superior anticancer activity against human cervical HeLa cell lines. Compounds and (Fig. 36) were extensively inhibiting to the cell growth and GI₅₀ values were found to be 0.22 and 0.6 μM respectively. The SAR studies revealed that the presence of EWGs (NO₂) on the phenyl ring and two sulfonil groups in the analogues increased the anticancer activity [230]. In addition, the search of novel class of potent sulfonamides bearing hybrids, Ibrahim and co-workers reported isatin-pyrazole benzenesulfonamide derivatives as potent CA inhibitors. Compounds and (Fig. 36) showed...
5.4 nM, respectively). The SAR studies suggested that the presence of EDGs (OMe) on the phenyl ring to increased the activity and the presence of oxazole moiety also favourably increased the anticancer activity. The presence of EDGs was necessary for to increases the activity and also the presence of pyridine ring in the derivatives increased the oral bioavailability and solubility of the synthesized compounds [232]. R. Pingaea et al. [124] reported a new class of sulfonyl containing thiosemicarbazone and tetrahydroisquinoline hybrids as potent anticancer agents. Some of the synthesized thiosemicarbazone analogues showed good cytotoxic potency against MOLT-3 cell lines with IC50 value of 2.13 µg/mL. Compound 309 (Fig. 36) was found to have the best cytotoxic activity against HuCCA-1 and HepG2 cells with IC50 values of 31.00 µg/mL and 10.50 µg/mL respectively. The SAR displayed the presence of EDGs (OMe) and sulfonyl functionalities increased the cytotoxic activity [233]. At last, in 2014, Jun and co-workers designed and produced novel 1-sulfonyl indolines analogues in good yields and tested for their antiproliferative activity against various cancer cell lines. Among them, compounds 310 and 311 (Fig. 36) showed good cytotoxicity with IC50 values in the range of 0.955–0.105 µM and 0.039–0.112 µM, respectively against four human cancer cell lines HCT116, PC3, HepG2 and SK-OV-3. The SAR demonstrated that the presence of EDGs (OMe) significantly increased the activity and the presence of oxazole moiety also influenced the antiproliferative activity [234].

2.13. 5-HT6 receptor

Romero and co-workers reported a new class of thiazole-containing tryptamine hybrids as potent 5-HT6 receptor agonist. Compound 312 (Fig. 37) was found to have good Ki value of 2.2 nM against 5-HT6 receptor. Compound 312 displayed partial agonistic property in cAMP functional assay with pKi value 6.96 in HEK-293 F cell line. Further in vivo studies indicated that compound 312 effectively improved recognition memory by combined modulation of cholinergic as well as glutamatergic neurotransmission in rats [235]. Hayat et al. found that the benzothiazole-sulfonamide hybrids displayed powerful 5-HT6 receptor antagonists against HeLa cell line. Compounds 313 (IC50 = 14 µM) and 314 (IC50 = 3.9 µM) (Fig. 37) bearing 4-isopropylphenyl and 1-naphthylsulfonamide group at C-6 position of benzothiazole ring, respectively, showed promising inhibition of 5-HT6 receptor antagonists against HeLa cell line [236]. Prio et al. patented various N-phenyl-2,3-dihydroimidazol [2,1-b]thiazole-5-sulfonamide derivatives as 5-HT6 receptor ligands. Numerous substitution on phenyl as well as imidazole ring provided suitable ligands and some of them displayed excellent affinity for 5-HT6 receptor. Particularly compounds 315, 316 and 317 (Fig. 37) showed good Ki value of 8.4, 16.9 and 5.4 nM, respectively [237]. At last, Liu et al. explored a number of sulfonamide based benzothiazole hybrids as 5-HT6 receptor agents. All the produced hybrids possessed nanomolar range affinity for 5-HT6 receptor. Among them, compound 318 (Fig. 37) was found to be the best potent 5-HT6 receptor with Ki value of 500 nM. In addition, in vitro and in vivo studies of this compound 318 (Fig. 37) may provide promising leads in future [238].

2.14. Miscellaneous

Yang et al. designed and developed a class of potent quinoline-based ALDH1A1 inhibitors. The pharmacokinetics (PK) study demonstrated that compounds 319 and 320 (Fig. 38) had realistic drug exposure via po administration and would be suitable for in vivo proof of concept animal studies for a better understanding of
Fig. 30. Sulfonyl or sulfonamides potent anti-viral agents.
Fig. 31. Sulfonyl or sulfonamides potent anti-viral agents.
Fig. 32. Sulfonyl or sulfonamides potent anti-viral agents.
Fig. 33. Sulfonyl or sulfonamides potent carbonic anhydrase agents.
Fig. 34. Sulfonyl or sulfonamides as potent Cannabinoid receptor agonists.

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Fig. 35. Sulfonyl or sulfonamides as potent anticonvulsant agents.

Fig. 36. Sulfonyl or sulfonamides as potent anticancer agents.
Fig. 36. (continued).

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$\text{GI}_{50} = 0.570 \, \mu\text{mol/L}$

$\text{IC}_{50} = 31.00 \, \mu\text{g/mL} \text{ against HuCCA-I}$

$\text{IC}_{50} = 10.50 \, \mu\text{g/mL} \text{ against HepG2}$
Fig. 37. Sulfonyl or sulfonamides as potent 5-HT6 receptor.

Fig. 38. Sulfonyl or sulfonamides showed diverse biological properties.
Fig. 39. 2D (left) and 3D (right) interactions of most active bTNAP inhibitor \textbf{321}.

Fig. 40. Sulfonyl or sulfonamides with diverse pharmacological properties.
the physiological and pathophysiological actions of this enzyme [239]. Very recently, Iqbal and co-workers found the sulfonamide bearing sulfams analogues as potent alkaline phosphatase (bTNAP and bIAP) inhibitors. Among these, compound 321 (Fig. 38) containing a p-nitro substituent was found to be the best active inhibitor with IC50 value of 0.11 ± 0.005 μM. This examination highlighted the significance of the presence of EWGs on the para position of phenyl ring for effective bTNAP inhibition. The presence of NO2 on the para position of phenyl ring 321 was found to be very efficient and selective inhibitor of bTNAP over bIAP. Moreover, the homology built models were then used for the docking studies in order to rationalize the most probable binding interactions of inhibitors with the enzyme. Compound 321 was the most active bTNAP inhibitor, the sulfonamide group found to be oriented towards the Zn2+ metal ions. Fig. 39 displayed the detailed binding site interactions of most active bTNAP inhibitor of compound 321. Compound 321 was the only compound in which not the sulfonamide group, but the oxygen atom of the p-nitro group was in direct contact (2.1 Å) with the Zn2+ ion of the active site, since 321 is the most active bTNAP inhibitor, this interaction might be responsible for exceptional inhibitory activity observed for this compound. The presence of a sulfonamide group, as a zinc binding function, is suggested to be the most prominent structural feature in the design of potent AP inhibitors [240].

Taha et al. also discovered a new class of oxadiazole containing sulfonamides hybrids as potent in vitro β-glucuronidase inhibitory activity. The 2,4,5-trichloro substituted compound 322 (IC50 = 2.40 ± 0.01 μM) (Fig. 40) was found to be the most potent which was twenty folds more active than the reference standard drug. Compound 323 (IC50 = 14.55 ± 0.30 μM) (Fig. 40) which only lacked the chloro at 5-position, was observed to be seven-fold decline in the activity. Another compounds 324 (Fig. 40) lacked chloro at position 4 was perceived to be nine times decline in the activity. The SAR revealed that the decrease of chloro substitution from tri- to di- substituted decreased the activity. It is worth displaying in that the synthesized hybrids of biologically active analogues such as oxadiazole ring, sulfone group, hydrazide moiety and aryl rings cordially played their role in exhibiting the activity. Compound 322 was identified as a lead compound for bglucuronidase inhibitory activity and may be used for further research for finding a powerful inhibitor [241]. Very recently, Iqbal and co-workers developed a class of chalcone-sulfonamide hybrids as potent alkaline phosphatase inhibitors. Among them, compounds 325 and 326 (Fig. 40) showed maximum inhibition of human and rat e5 NT with IC50 values of 0.26 and r5 NT with 0.33 μM, respectively. The SAR studies suggested that the presence of EDGs at meta position of phenyl ring displayed greater inhibition. Likewise, the presence of di-substituted bulky electron donating group i.e., methoxy group at 3/4 position showed greater inhibition of ~161 fold higher than that of the standard compound sulfamic acid. The most potent inhibitor of 325 and 326 were analyzed in the active pocket of enzyme where its docking poses elaborate the presence of five strong hydrogen bonds with various amino acid residues. Compound 325 showed strongly electrostatic interactions. The two zinc ions within active pocket of h-e5 NT showed interaction with nitrogen of sulfonamide moiety by forming a metal acceptor phenomenon [242]. In 1997, the FDA approved compound Delavirdine (327) (Fig. 40) was found to be the second NNRTI agent authorized for treatment of HIV-1 [243]. Further, crystallographic analysis confirmed that methyl-sulfonamide group at indole ring was essential for enhancing the activity [244].

Morenetto et al. identified a novel pyridothienophene inhibitor of PTP1B with a K value of 0.370 μM [245]. The X-ray co-crystal structures of compounds 328 and 329 (Fig. 41) showed one of the sulphonamide oxygens hydrogen bonded to the backbone nitrogen of Gly259 and the other entered into interactions with Arg24 and Arg254 through bridging water molecules (Fig. 42). These interactions could increase the inhibitor activity up to 25-fold more.
but would not bring selectivity over TCPTP. In 2006, Klopfenstein and co-workers developed compound 329 as PTP1B inhibitors with 2-fold selectivity over TCPTP, in which the sulfamic acid moiety picked up hydrogen bonding interactions with Arg24, Arg254, and Gln262 (2F6Z, Fig. 43) \[246\].

With the aim at further investigating the diverse chemical space, the introduction of imidazopyridine ring as a scaffold led to the discovery of two novel series of imidazopyridinylthioacetanilides hybrids. Among these, compounds 330 and 331 (EC\(_{50}\) = 0.75 \(\mu\)M and 0.21 \(\mu\)M, respectively) (Fig. 44) were identified as the most potent inhibitors in suppressing HIV-1 replication. These compounds 330 and 331 (Fig. 44) had higher anti-HIV-1 potency compared to reference drug dideoxycytidine [247]. Later, Kim et al. designed and developed sulfonamide containing hydroxylated chalcones 332 and 333 (Fig. 44) with potential inhibition of trans-sialidase enzyme which was demonstrated by IC\(_{50}\) values 0.9 and 2.5 \(\mu\)M [248]. In continuous search of potential sulfonamide based chalcone hybrids as potent drugs against some diseases causing pathogens, in 2010, El-Ayache [249] reported polyphenol bearing two polyphenolic moieties separated by a bis-aryl sulfonamide 334 (Fig. 44) or sulfonimide 335 (Fig. 44) which showed potent PAI-1 inhibitory activity. Compound 334 (IC\(_{50}\) = 0.284 \(\mu\)M) and 335 (IC\(_{50}\) = 0.594 \(\mu\)M) showed the most potent PAI-1 inhibitory activity. Compound 336 (Fig. 44) was developed by Lahue et al. as potent and selective inhibitors of Eg5 (IC\(_{50}\) = 7.4 \(\mu\)M). The SAR revealed that the presence of 1-benzylic...
moiety was essential for the activity and the substitution at the benzylic methylene was detrimental to the inhibitory activity. Also, the presence of ortho substituent on the aromatic ring of the benzyl group especially trifluoromethyl group enhanced the Eg5 inhibitory activity [250]. Finally, Prachayasitakul and co-workers found triazoles derived sulfonamide analogues as potent aromatase inhibitory activity. Compound 337 (Fig. 44) bearing 6,7-dimethoxy substituents on the isoquinoline ring showed the most potent aromatase inhibitory activity (IC₅₀ = 0.2 µM) without affecting normal cell. The SAR suggested that the lipophilic effect of dimethoxy groups enhanced the activity of compound 337. In addition, molecular docking studies were performed the most active compound 337 and mode of binding interaction of compound 337 was revealed that, the investigated triazoles could closely engage the active site of aromatase through the interactions of hydrophobic, π-π stacking and H-bonding. Furthermore, hydrophobic interactions with Arg115 were observed 2D-ligand protein interaction (Fig. 45). The compound 337 showed in such a way to appropriately form hydrogen bonding of the sulfonil group with the amino group of Ala306 and Ala307 as well as hydrogen bonding of oxycomarilin moiety with Ser119. These hydrophobic and hydrogen bonding interactions were suggested to play pertinent roles contributing to the most potent activity of compound 337. Interestingly, isomeric oxycomarilin and naphthalenyl triazoles play crucial roles in exerting more potent aromatase inhibitory activity than other tested compounds. This could be attributed to their binding interactions with the aromatase enzyme. The molecular requirements for the most potent triazole inhibitor 337 which contains 6,7-dimethoxy groups, 7-coumaroyloxymethyl at position 4 of the triazole ring, and m-substitution of triazole and sulfonil moieties on the phenyl ring. Such structural features were essential for engaging in hydrophobic, π-π stacking and H-bonding interactions with the aromatase enzyme, particularly, hydrogen bond forming with Arg115 and Ser119 [251].

3. Conclusion

This review updates and summaries the importance of the sulfonyl or sulfonamide based scaffolds (SVI based moieties) in bioactive compounds. As described above, sulfonamide based hybrids have huge range of biological activities such as antimicrobial, anti-diabetic, anti-inflammatory, anti-malarial, anti-tubercular, antiviral, Alzheimer’s activity, anti-convulsant, anti-cancer, anti-tubercular and other activities. Theoretically, sulfonyl or sulphonamide (SVI moieties) based drugs possess the immense potential therapeutic values on diversity of drug targets. The SAR based work will probably continue to play an important role to further optimize the full potential of sulfonamide hybrids. Many of these potential drugs are not yet in clinical trials, but emphasize the exigency in the need for their further derivatization to provide an opportunity for managing therapeutic values more efficiently and with greater efficacy in the future. In addition, these biological agents with promising activity and well-defined mechanisms of action can be considered valuable candidates as prototypes in the design and development of novel and more effective synthetic compounds based potent inhibitors.

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