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Review article

Pharmaceutical and medicinal significance of sulfur (S^{VI})-Containing motifs for drug discovery: A critical review

Chuang Zhao, K.P. Rakesh*, L. Ravidar, Wan-Yin Fang, Hua-Li Qin**

Department of Pharmaceutical Engineering, School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, 205 Luoshi Road, Wuhan, 430070, PR, China

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ABSTRACT

Sulfur (S^{VI}) 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 (S^{VI})-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, carbonic 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 (S^{VI}) based drugs against the numerous death-causing diseases.

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* Corresponding author.
** Corresponding author.
E-mail addresses: rakeshasg@gmail.com (K.P. Rakesh), qinhuali@whut.edu.cn (H.-L. Qin).

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1. Introduction

The sulfonamide or sulfonyl 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 agricultural and pharmaceutical agents [2,3]. The features of S^{VI}-containing species of strong electron withdrawing nature, stability against hydrolysis, resistance to reduction at sulfur, and crisp preference for two-electron processes over radical processes, have already made this group applicable to many productive fields. Sulfonamides as synthetic antifolic agents have been widely used for the anticipation and treat 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], antimalaria [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 (S^{VI}) motif are available in the market such as celecoxib, meloxicam, piroxicam, sulfasalazine, and so on [46]. The diverse pharmacological activity of S^{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 (S^{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 more new potent multi-targeted sulfonamide or sulfonyl drugs, many medicinal chemistry scholars focused on sulfonamide nucleus, which has importance in the area of medicinal chemistry, drug development as a core substituent of diverse biological agents [54]. In order to overcome the resistance and to reduce the adverse effects, continuous efforts are made to synthesize novel multi-targeted bioactive sulfonamide analogues. In this regard, combinations of certain sulfonamides and other drug molecules are being used to develop novel formulations with greater effectiveness as well as less toxicity [55].

This present comprehensive review aims to recapitulate the recent biological applications made towards the discovery of novel sulfonyl or sulfonamides functional group containing analogues as potential therapeutic agents and the critical aspects of design and structure-activity relationship (SAR) studies were also briefly explained.

2. Biological applications of sulfonyl or sulfonamides functionalities

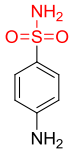
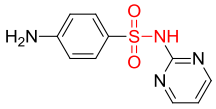
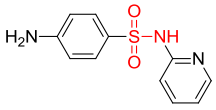
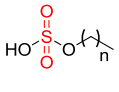
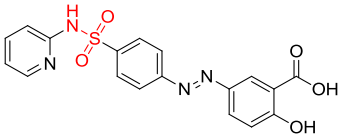
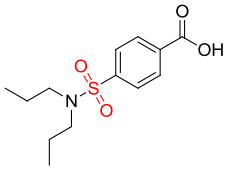
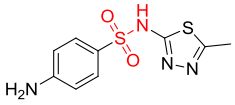
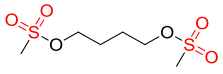
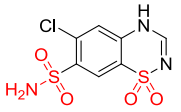
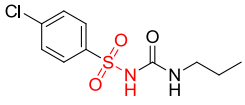
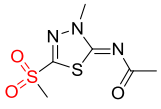
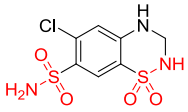
2.1. Antimicrobial agents

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 sulphonamide 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 develope 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 μg/mL. The replacement of 4-fluorobenzyl group (**107**) by 2,4-dichlorobenzyl group, **108** (Fig. 2) showed good antibacterial activity against *B. typhi* with MIC values 4 μg/mL. Compound **108** showed eight folds higher activity (MIC = 4 μg/mL) than standard Chloromycin against *B. typhi* [59]. The above same research group further developed a class of new type of sulphonamide-containing azoles analogues as potential antimicrobial agents. Compound **109** (Fig. 2) showed excellent antibacterial activity against *P. aeruginosa* with MIC value of 16 μg/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 μg/mL each. Compound **111** (Fig. 2) showed excellent antibacterial activity against different bacterial pathogens namely *B. subtillis* and *E. coli* with MIC value of 10 μg/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 Cl functional group, compound **111** was found to be highly active against another bacterial strains *B. subtillis* 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

Table 1
Sulfonamides or sulfonyl group containing FDA approved drugs from 1937 to 2012.

Sl No	Drug Name	Structure	Diseases	Approved Year
1	Streptozol		Dermatological	1937
2	Sulfadiazine		Antibiotic	1941
3	Sulfapyridine		Anti-infective	1942
4	Sotradecol	 n = 13	Cardiovascular	1946
5	Azulfidine		ALM/DER	1950
6	Benemid		Musculo-skeletal	1951
7	Thiosulfil		DER/BBO/AIN/SEN	1953
8	Myleran		Oncological	1954
9	Diuril		Cardiovascular	1957
10	Diabinese		Alimentary tract and metabolism	1958
11	Neptazane		Sensory organ	1959
12	Hydrochlorothiazide		CAR/END	1959

(*continued on next page*)

Table 1 (*continued*)

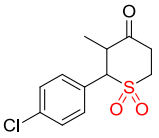
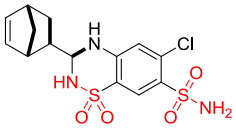
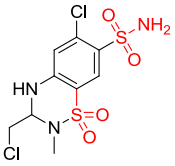
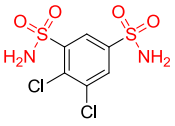
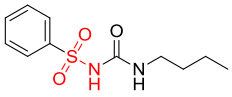
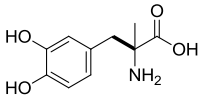
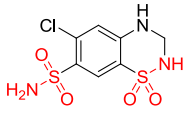
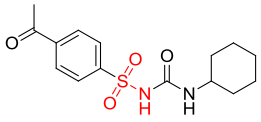
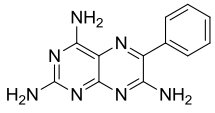
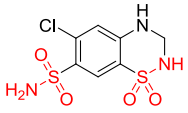
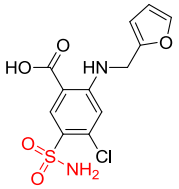
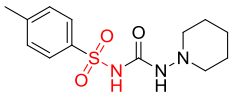
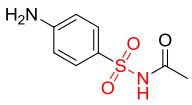
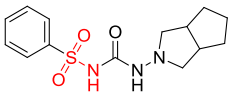
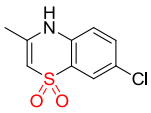
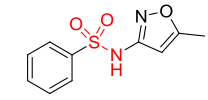
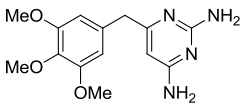
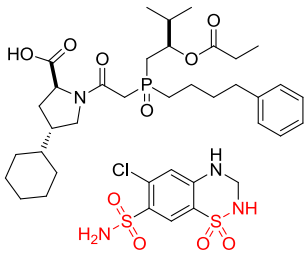
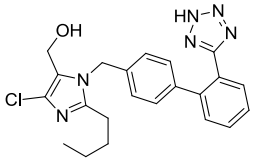
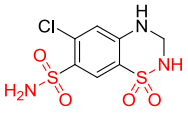
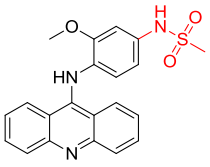
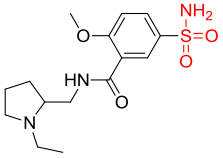
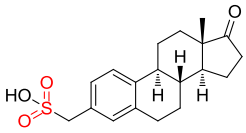
Sl No	Drug Name	Structure	Diseases	Approved Year
13	Trancopal		Musculo-skeletal	1960
14	Doburil		Cardiovascular	1960
15	Enduran		Cardiovascular	1960
16	Daranide		Sensory organ	1960
17	Orinase		Alimentary tract and metabolism	1961
18	Aldoril	 	Cardiovascular	1962
19	Dymelor		Alimentary tract and metabolism	1964
20	Dyazide	 	Cardiovascular	1965
21	Lasix		Cardiovascular	1966
22	Tolinase		Alimentary tract and metabolism	1966

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
23	Sulfacel-15		Sensory organ	1970
24	Gliclazide		Alimentary tract and metabolism	1970
25	Hyperstat		Cardiovascular	1973
26	Bactrim	 	Anti-infective	1973
27	Monopril HCT		Cardiovascular	1974
28	Hyzaar	 	Cardiovascular	1975
29	Amsacrine		Oncological	1976
30	Sulpiride		Nervous System	1978
31	Premarin		GUS/ONC	1978

(*continued on next page*)

Table 1 (*continued*)

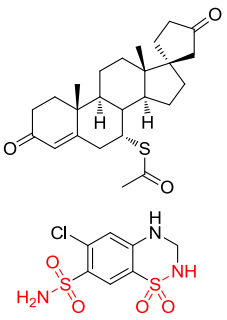
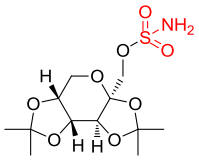
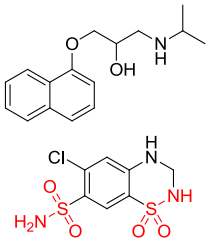
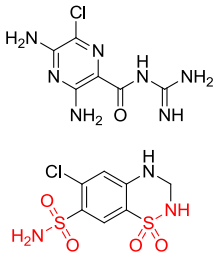
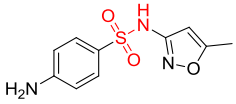
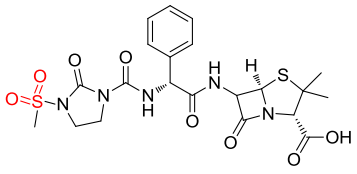
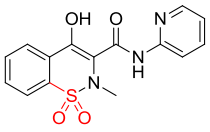
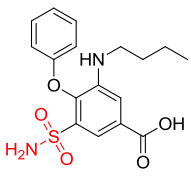
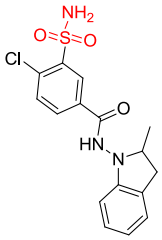
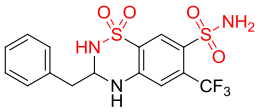
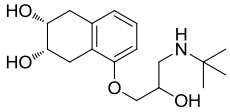
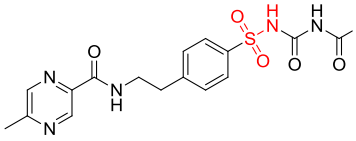
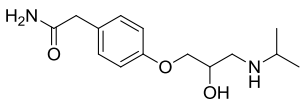
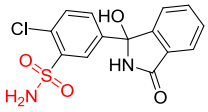
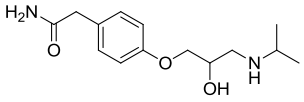
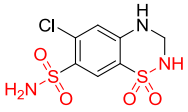
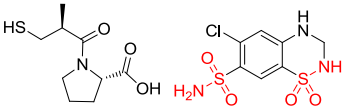
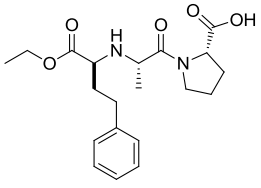
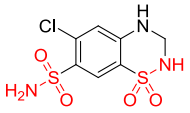
Sl No	Drug Name	Structure	Diseases	Approved Year
32	Aldactazide		Cardiovascular	1978
33	Topiramate		Nervous system	1979
34	Inderide		Cardiovascular	1979
35	Moduretic		Cardiovascular	1981
36	Sulfamethoxazole		Anti-infective	1982
37	Mezlin		Anti-infective	1982
38	Feldene		MSK/SEN	1982
39	Bumex		Cardiovascular	1983

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
40	Lozol		Cardiovascular	1983
41	Corzide	 	Cardiovascular	1983
42	Glucotrol		ALM/END	1984
43	Tenoretic	 	Cardiovascular	1984
44	Lopressor HCT	 	Cardiovascular	1984
45	Capozide		CAR/END	1984
46	Vaseretic	 	Cardiovascular	1986

(*continued on next page*)

Table 1 (*continued*)

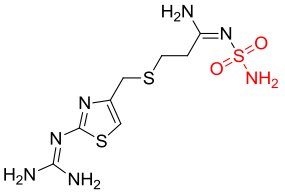
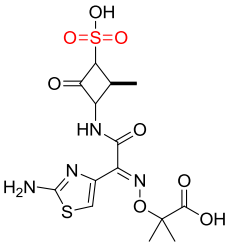
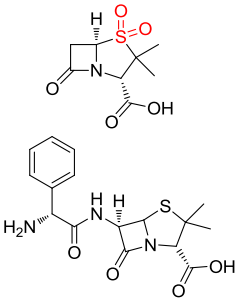
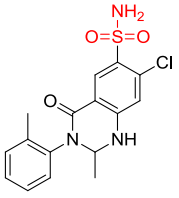
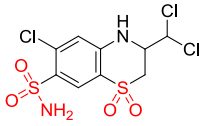
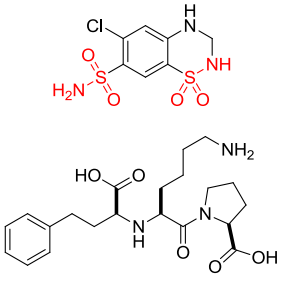
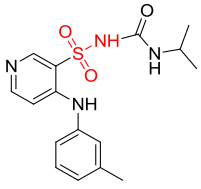
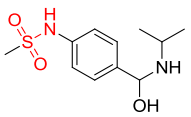
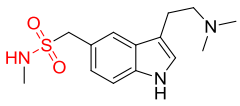
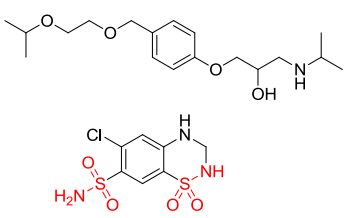
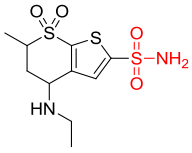
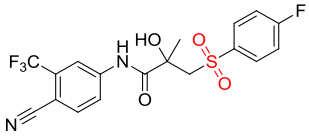
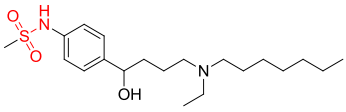
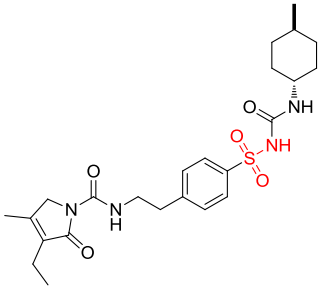
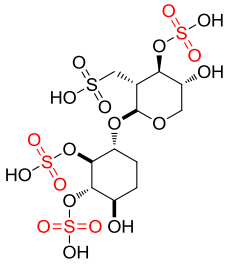
Sl No	Drug Name	Structure	Diseases	Approved Year
47	Pepcid		Alimentary tract and metabolism	1986
48	Cayston		AIN/ALM/RES	1986
49	Unasyn		Anti-infective	1986
50	Mykrox		Cardiovascular	1987
51	Metahydrin		Cardiovascular	1988
52	Prinzide		Cardiovascular	1989
53	Torasemide		Cardiovascular	1990

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
54	Sotalol		Cardiovascular	1992
55	Imitrex		Nervous system	1992
56	Ziae		Cardiovascular	1993
57	Trusopt		Sensory organ	1994
58	Casodex		Endocrine system	1995
59	Corvert		Cardiovascular	1995
60	Amaryl		ALM/END	1995
61	Pentosan polysulfate		Cardiovascular	1996

(*continued on next page*)

Table 1 (*continued*)

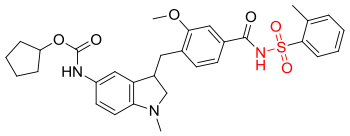
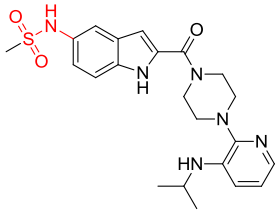
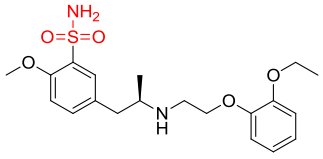
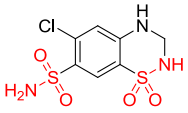
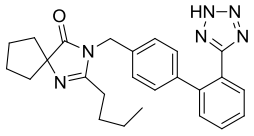
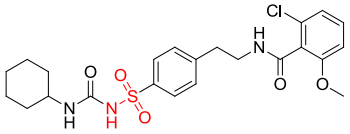
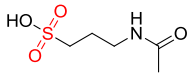
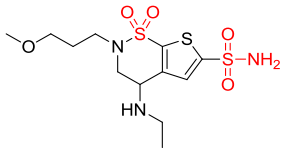
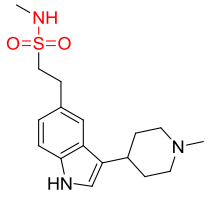
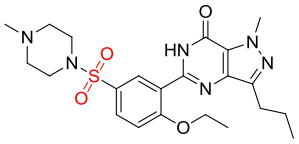
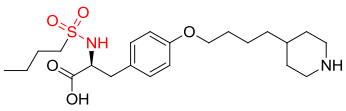
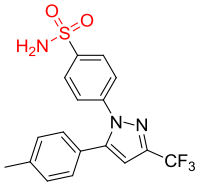
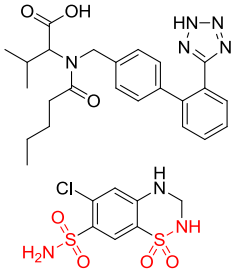
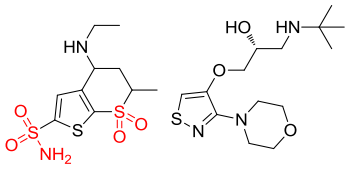
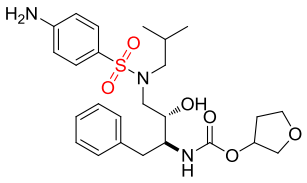
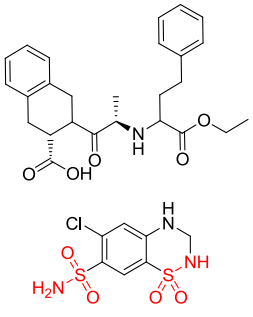
Sl No	Drug Name	Structure	Diseases	Approved Year
62	Aceolate		Respiratory system	1996
63	Rescriptor		Anti-infective	1997
64	Flomax		Genito-Urinary and Sex hormone	1997
65	Avalide	 	Cardiovascular	1997
66	Glyboride		BBO/END	1997
67	Acamprosate		Nervous system	1998
68	Azopt		Sensory organ	1998
69	Amerge		Nervous system	1998

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
70	Viagra		Genito-Urinary and Sex hormone	1998
71	Aggrastat		Blood and blood forming organ	1998
72	Celebrex		ONC/MSK	1998
73	Diovan HCT		Cardiovascular	1998
74	Cosopt		Sensory organ	1998
75	Agenerase		Anti-infective	1999
76	Accuretic		Cardiovascular	1999

(*continued on next page*)

Table 1 (*continued*)

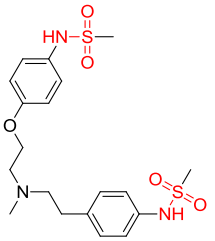
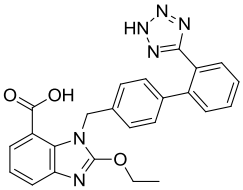
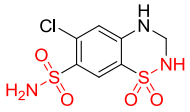
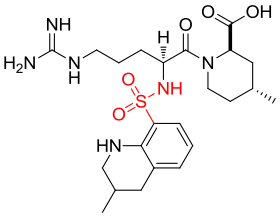
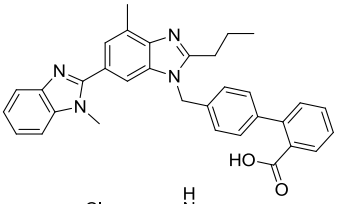
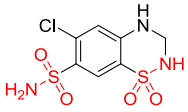
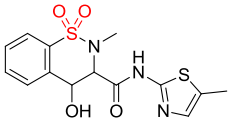
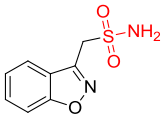
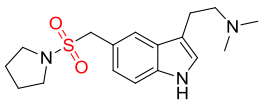
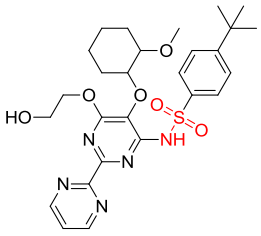
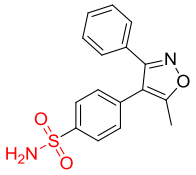
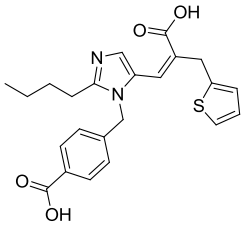
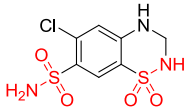
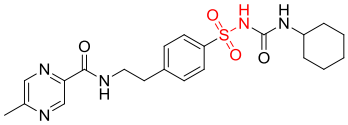
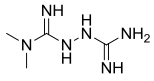
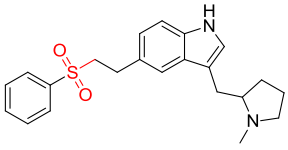
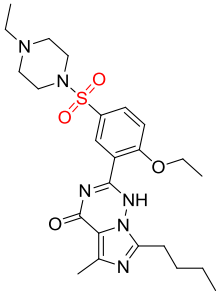
Sl No	Drug Name	Structure	Diseases	Approved Year
77	Tykosin		CAR/RES	1999
78	Atacand	 	Cardiovascular	2000
79	Argatroban		Blood and blood forming organ	2000
80	Micardis HCT	 	CAR/END	2000
81	Mobic Tablet		Musculo-skeletal	2000
82	Zonegram		Nervous system	2000
83	Axert		Nervous system	2001

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
84	Tracleer		Cardiovascular	2001
85	Bextra		GUS/MSK	2001
86	Teveten HCT	 	Cardiovascular	2001
87	Metaglip	 	Alimentary tract and metabolism	2002
88	Relpax		Nervous system	2002
89	Levitra		Genito-Urinary and Sex hormone	2003

(*continued on next page*)

Table 1 (*continued*)

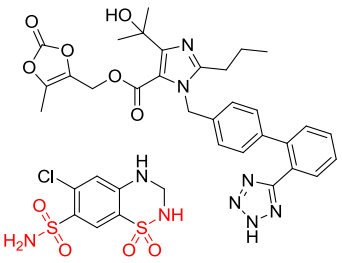
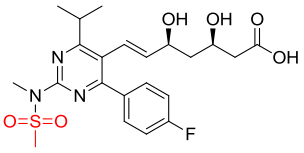
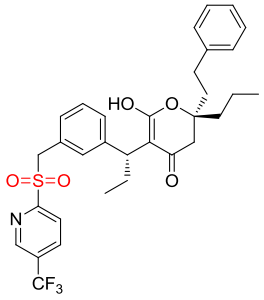
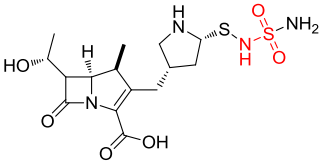
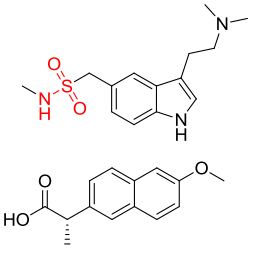
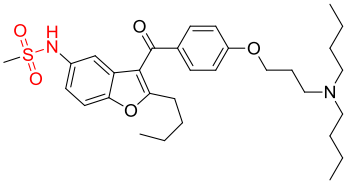
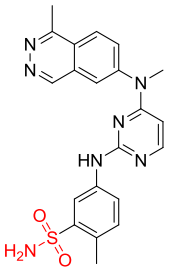
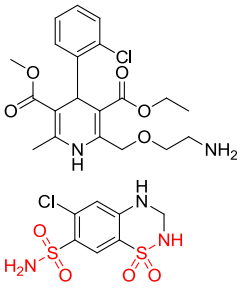
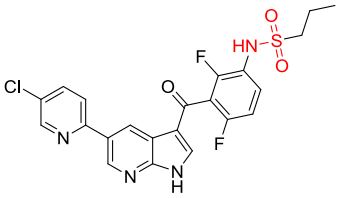
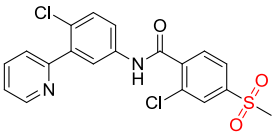
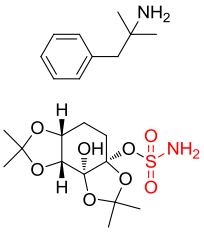
Sl No	Drug Name	Structure	Diseases	Approved Year
90	Benicar HCT		Cardiovascular	2003
91	Crestor		CAR/BBO	2003
92	Aptivus		Anti-infective	2005
93	Doribax		Genito-Urinary and Sex hormone	2007
94	Treximet		Nervous system	2008
95	Multaq		Cardiovascular	2009

Table 1 (*continued*)

Sl No	Drug Name	Structure	Diseases	Approved Year
96	Votrient		ALM/MSK	2009
97	Amturnide		Cardiovascular	2010
98	Zelborat		ONC/DER	2011
99	Erivedge		Oncological	2012
100	Qsymia		Endocrine System	2012

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

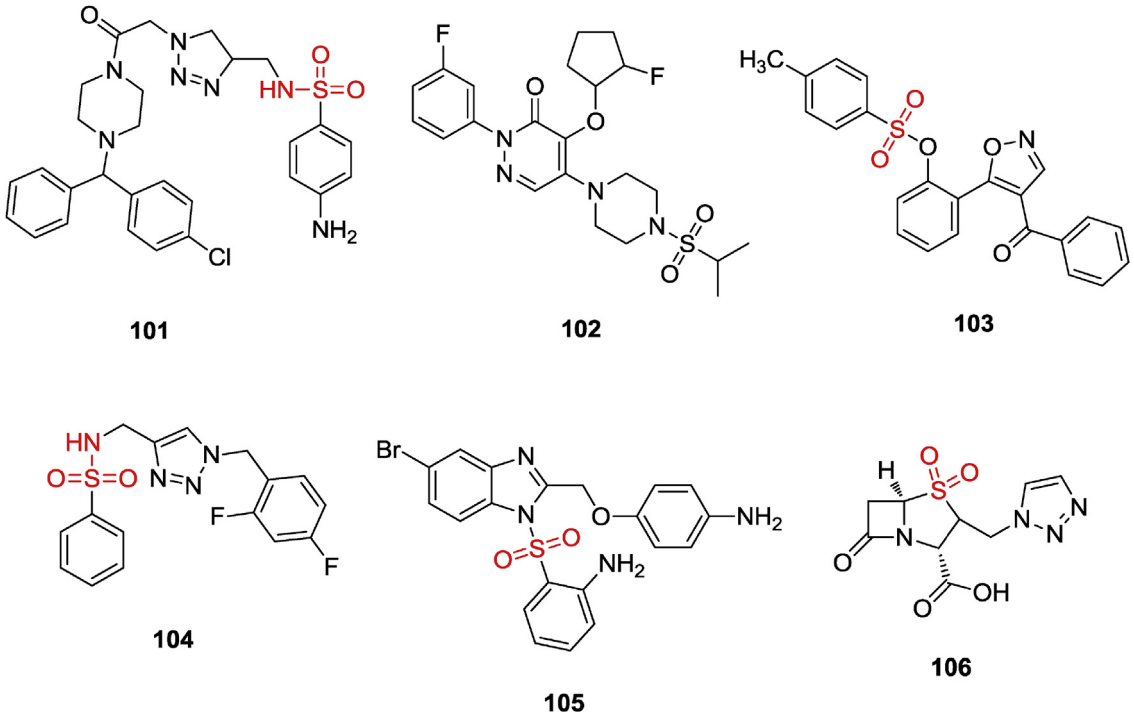


Fig. 1. Some of the sulfonyl or sulfonamides containing heterocycles as potential antimicrobial agents.

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 IC_{50} 0.30 μM. Compound **118** (Fig. 3) exhibited excellent MurF enzymes activity against two MurFSp and MurFEc with IC_{50} 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*-sulfonaminoethyloxime 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 tested five multidrug-resistances of *S. aureus* with MIC values between 0.78 and 1.56 μg/mL. The meta-CF_3 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 introduce of an electron withdrawing trifluoromethyl group (-CF_3) 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 CF_3 derivative 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 IC_{50} 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. fecalis* (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 benzothiazole 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 (-NH_2) and nitro group (-NO_2) 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 sulphonamide containing benzothiazole analogues as powerful antimicrobial properties, a new class of sulphonamide containing benzothiazole 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 -NO_2 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

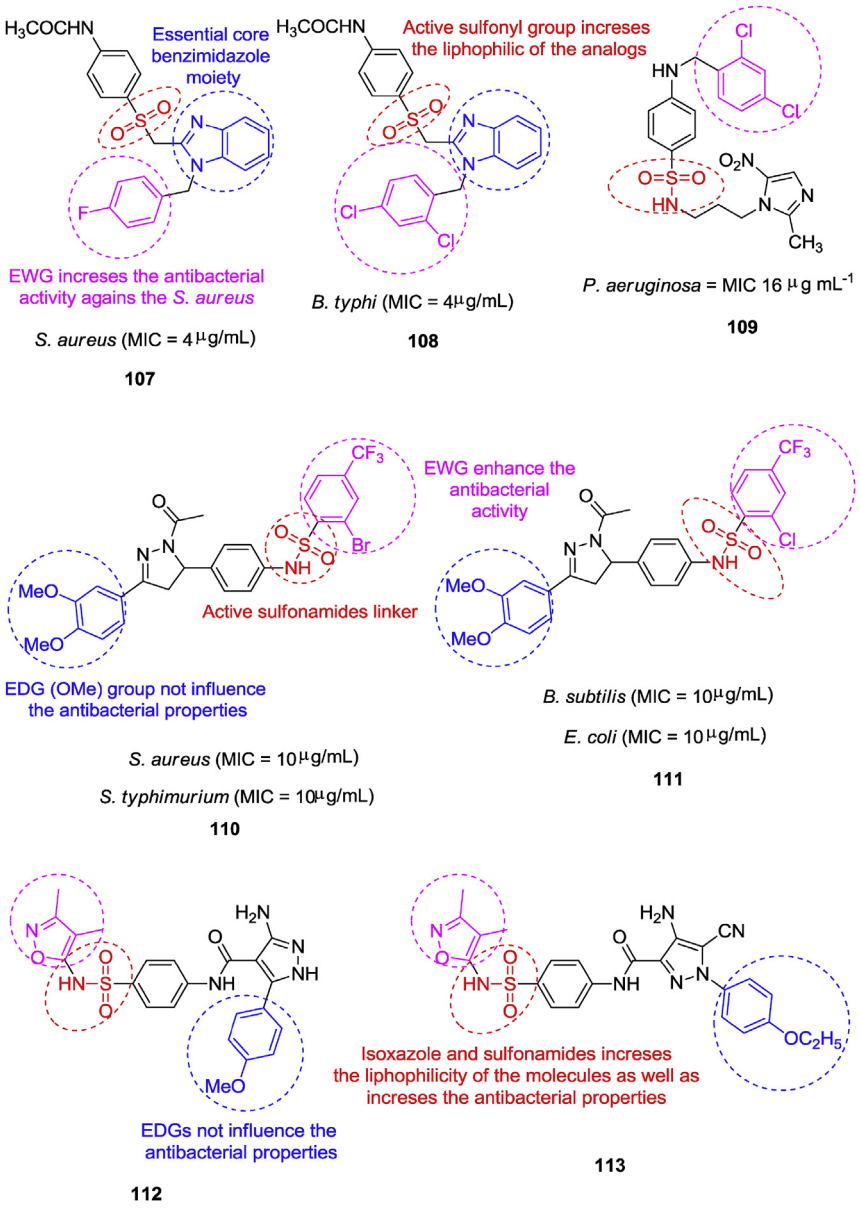


Fig. 2. Some antimicrobial activities of potent sulfonyl or sulfonamides hybrids.

presence of sulfonamide group at *para* position of the phenyl group has highly increases 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,

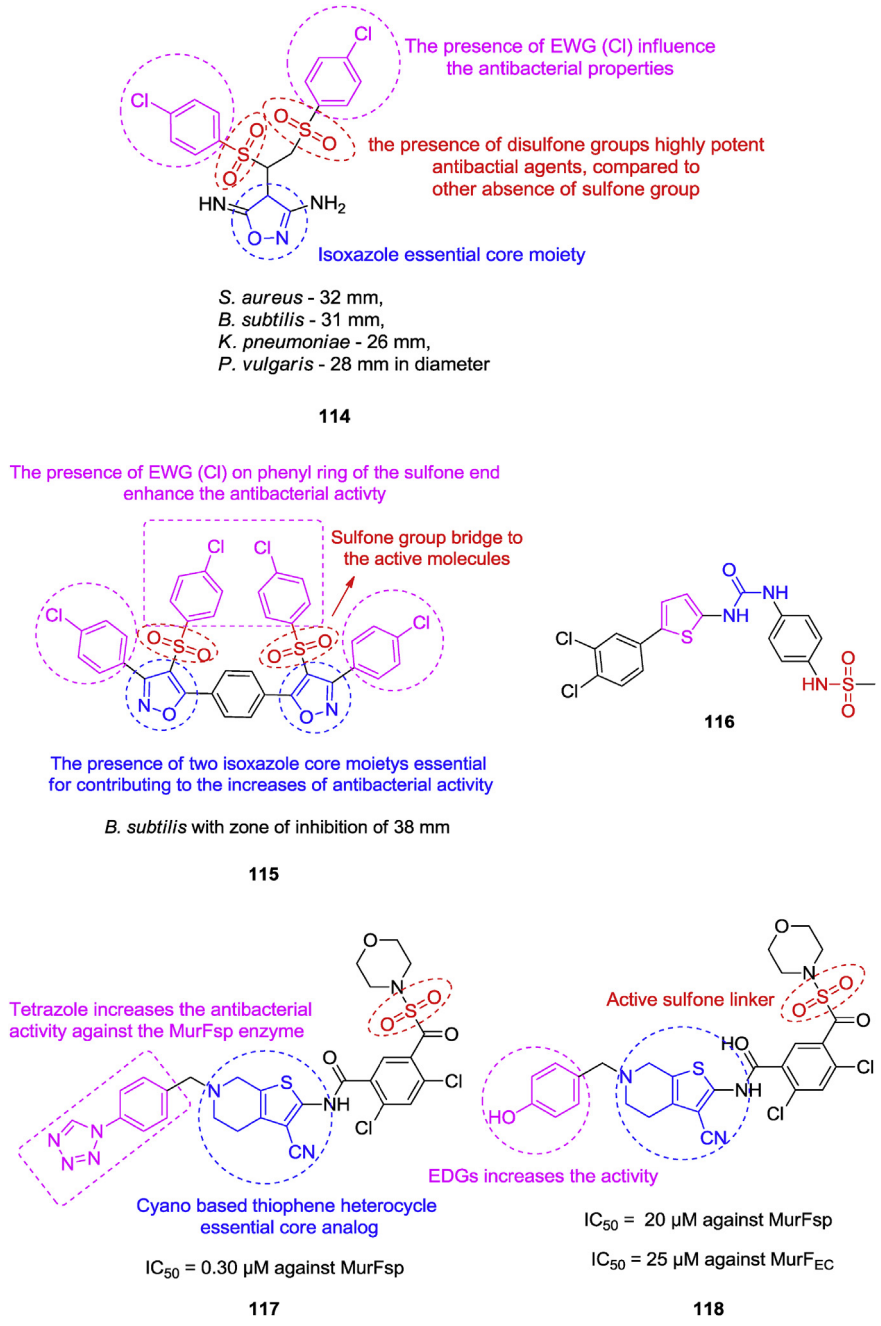


Fig. 3. Sulfonyl of sulfonamides with antimicrobial properties.

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 *in vivo* anti-diabetic activity in non-insulin dependent diabetes mellitus rat model was explored later by Moreno-Dıaz et al. in which compounds **142** and **143** (Fig. 8) showed promising antidiabetic properties. The SAR revealed that the presence of EDGs (-OMe and $-OC_2H_5$) 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 IC_{50} value is 19.5 and 40.9 μM respectively. The SAR revealed that the presence of EWGs ($-NO_2$) on the phenyl ring

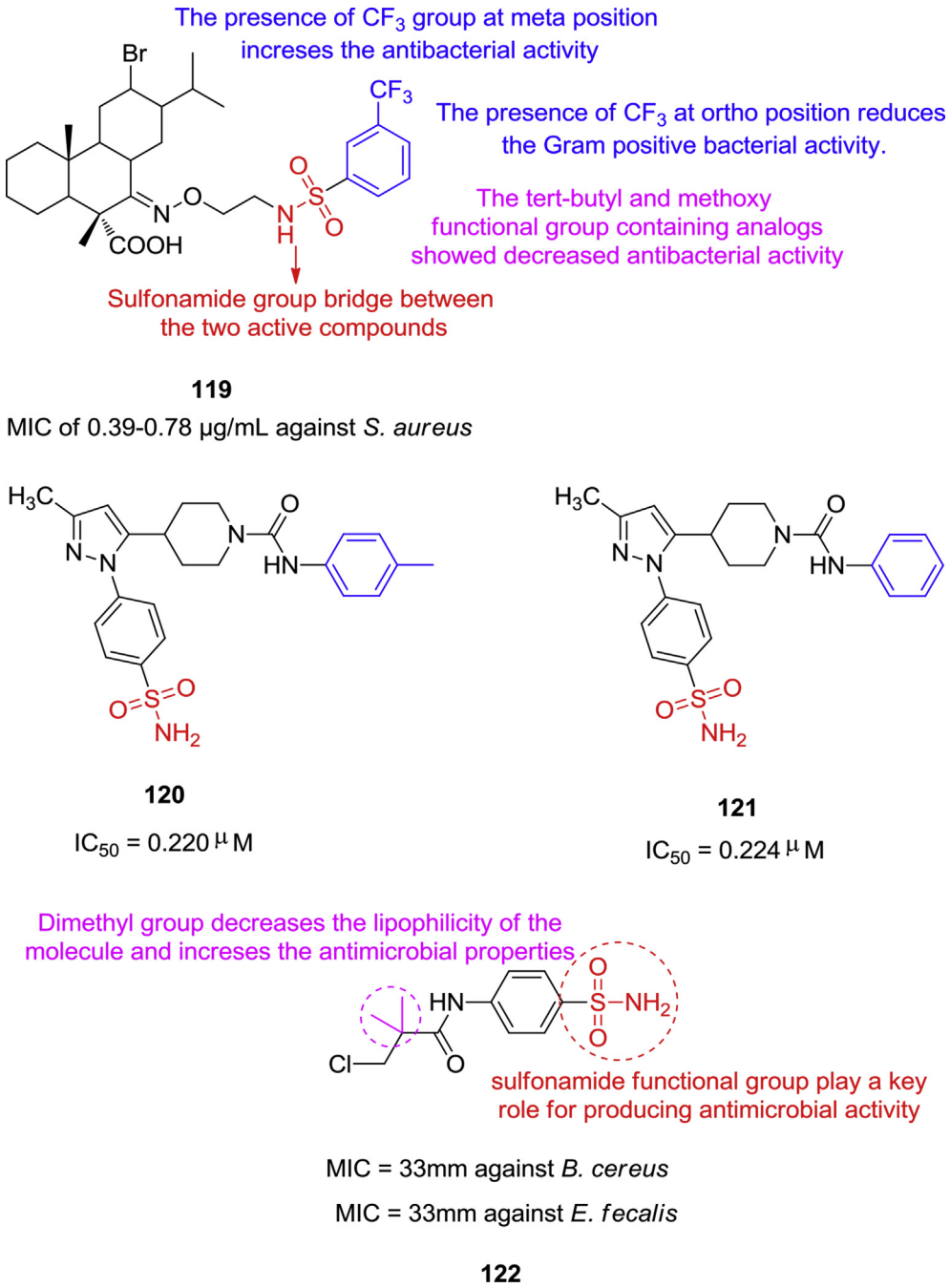


Fig. 4. Sulfonyl of sulfonamides as antimicrobial agents.

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 ureodo-sulfonamides based analogues. Among these, compounds **146** and **147** (Fig. 8) showed superior PTP1B inhibitors with IC_{50} values of 18.6 nM and 66.2 nM respectively. The SAR suggested 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 IC_{50} 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) ($IC_{50} = 20.1 \pm 0.19$ 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

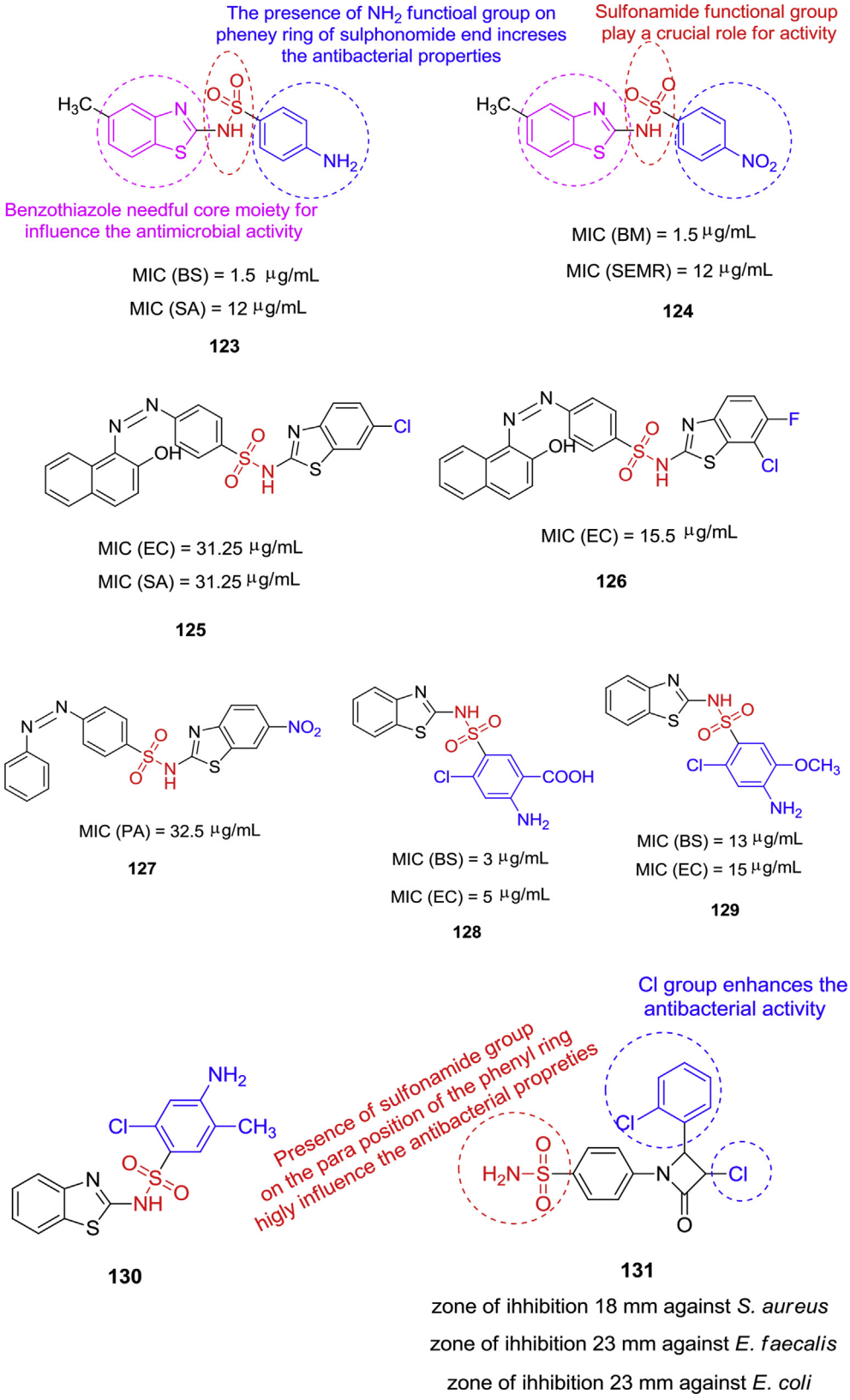


Fig. 4. (*continued*).

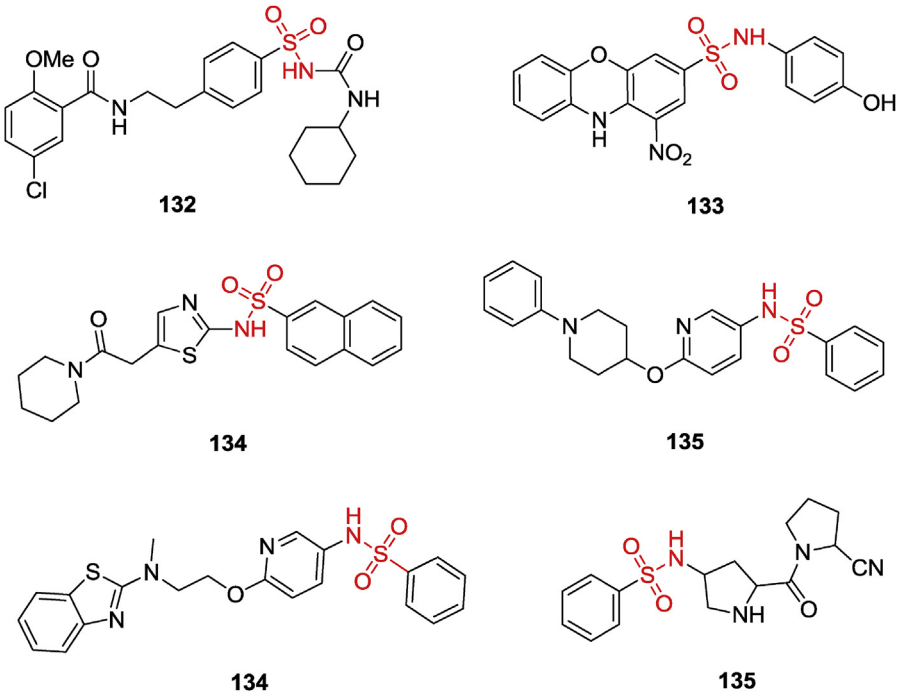


Fig. 5. Some representative sulfonyl of sulfonamides as potent anti-diabetic agents.

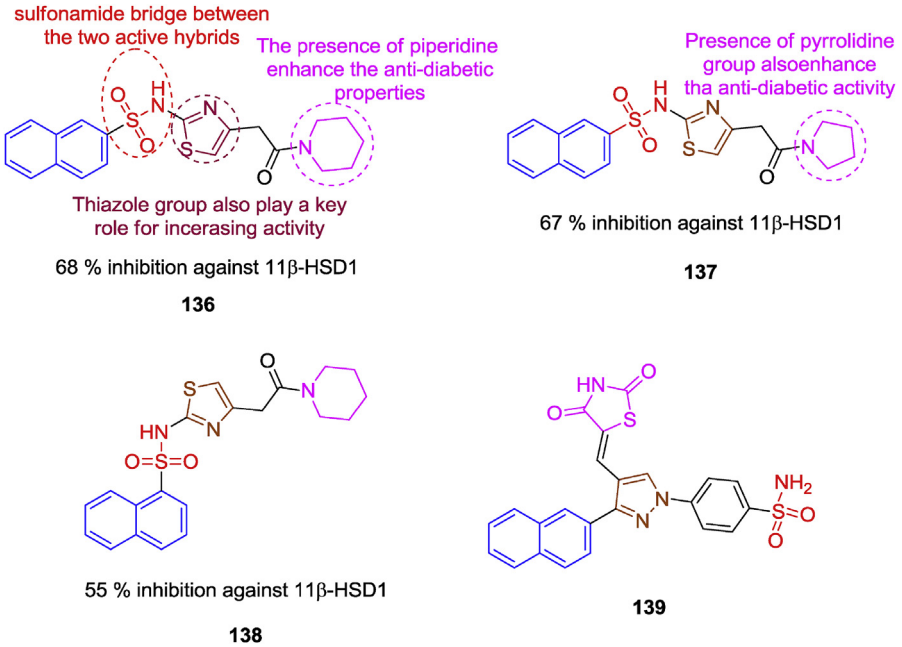


Fig. 6. Sulfonyl of sulfonamides as antidiabetic agents.

stronger cryptochrome modulator with $EC_{50} = 0.144\ \mu M$. 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 proliferatoractivated receptor γ (PPARγ). Among all the synthesized analogues, compounds **154** and **155** (Fig. 9) showed maximum PPARγ binding affinities (I_{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 PPARγ activity. In addition, the presence of electron withdrawing Cl and $-CF_3$ 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 $-OCH_3$) 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 PPARγ-targeted antidiabetics agents. Compound **156** (Fig. 10) showed the most potent active PPARγ inhibitor with EC_{50} values is 2 nM. The SAR

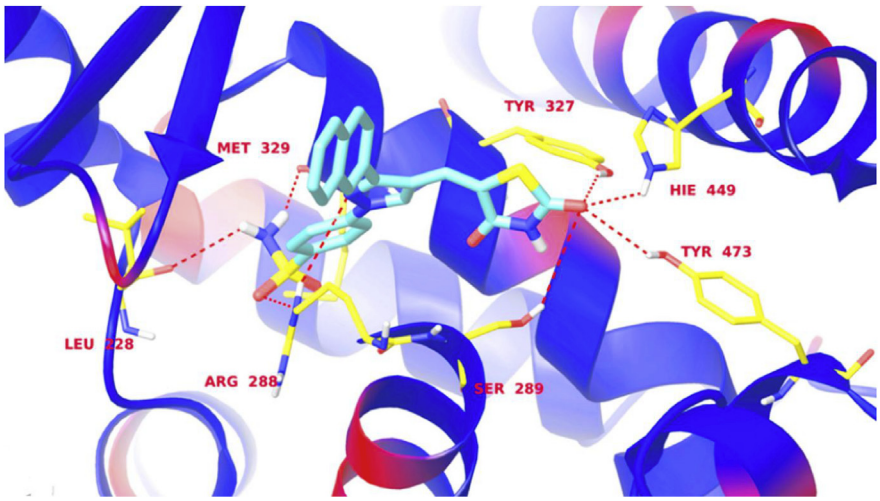


Fig. 7. Docked pose of compound **139** (turquoise colour) showing hydrogen bond interactions (red dashed lines) with amino acids in the binding site of PPARγ. The ligand and amino acids are represented as stick and thin tube model. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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 [90]. 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 IC_{50} 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, Iqbal 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 IC_{50} 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 glibenclamide (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 swellness, redness, heat with pain which is mediated by the release of proinflammatory mediators like bradykinin and cytosine 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 sulphonamide 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 sulphonamide moiety, SC-558 (**165**) 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 $NSAID_S$ 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 bioisosteric 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**

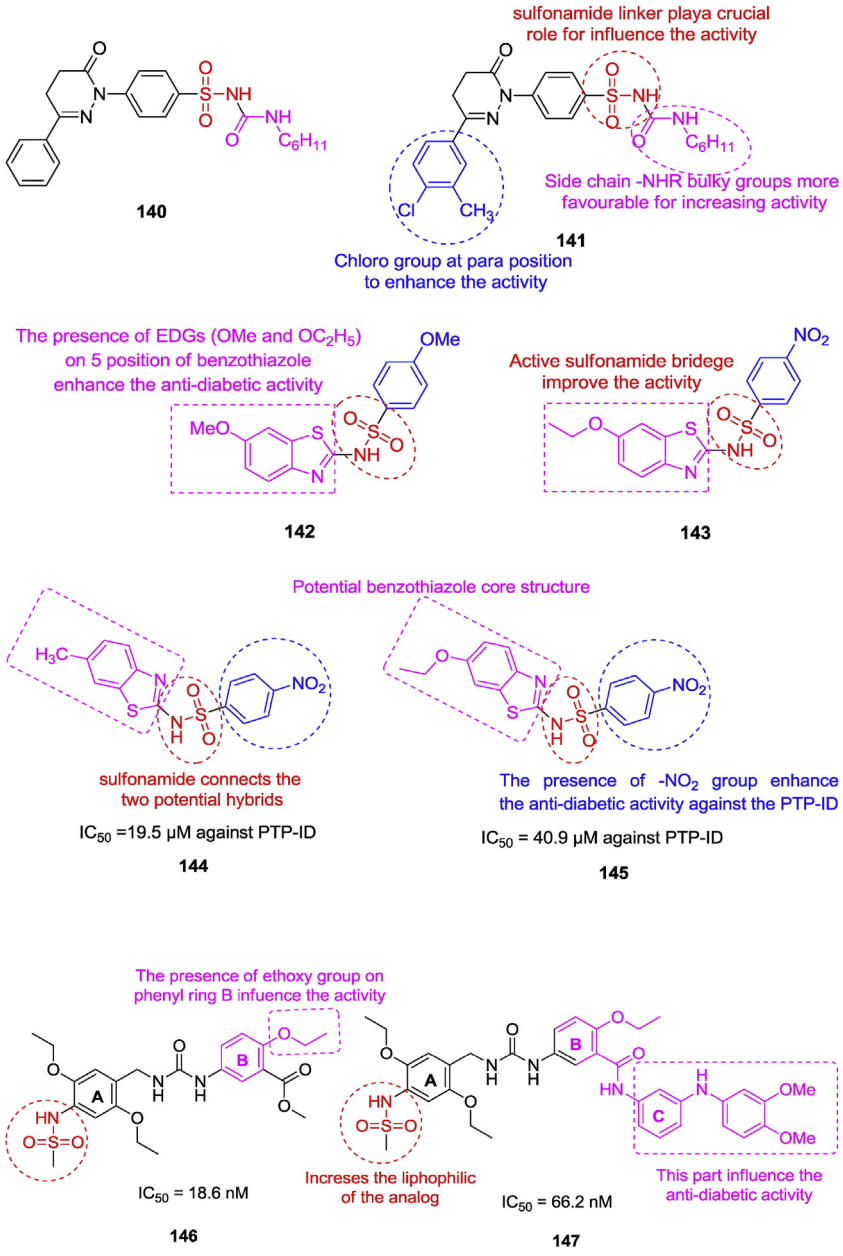


Fig. 8. Sulfonyl of sulfonamides as anti-diabetic agents.

($IC_{50} = 0.22$ mmoL/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 indomethacine. 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 pyrazolylpyrazolines 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.

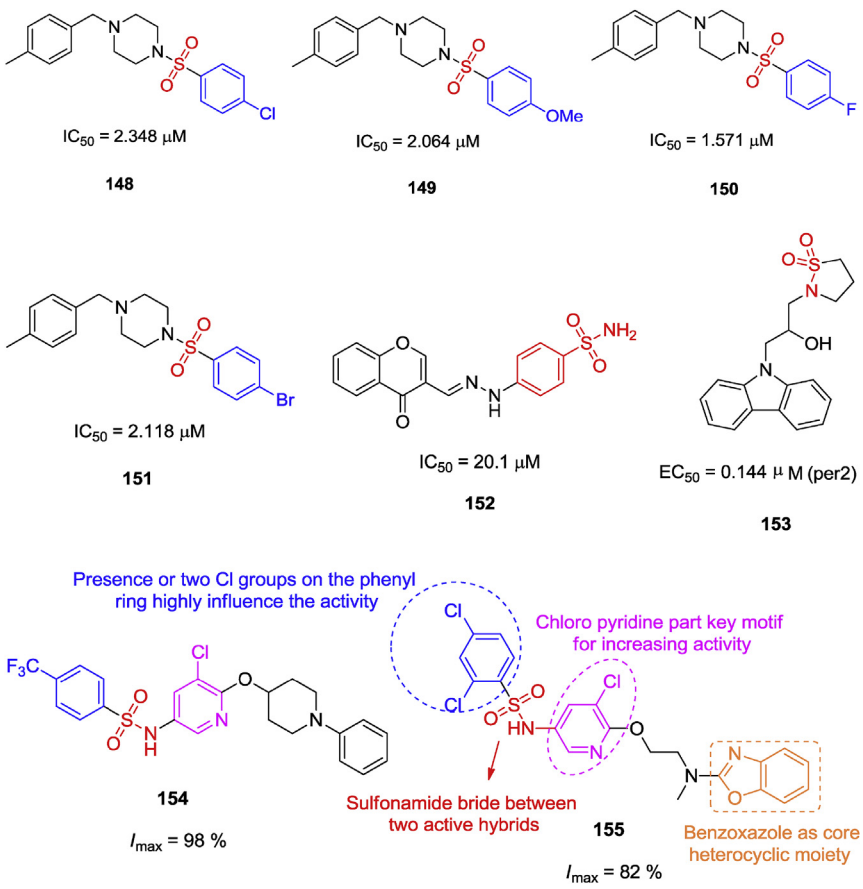


Fig. 9. Sulfonyl of sulfonamides as anti-diabetic agents.

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 μM 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 trifluoromethyl 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 μM 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 sulfonamide 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 μM. The structure activity studies concluded that the lipophilicity of dimethoxyphenyl and tetrahydroisoquinoline sulfonamide 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 μM, compared to a reference antimalarial drug chloroquine with IC_{50} value of 1.33 μM [125]. The screening of new *N*-(7-chloroquinolinyl-4-aminoalkyl)arylsulfonamides 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 μM, K1: 0.41 μM) and **199** (Fig. 16) (IC_{50} 3D7: 0.01 μM; K1: 0.36 μM) 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

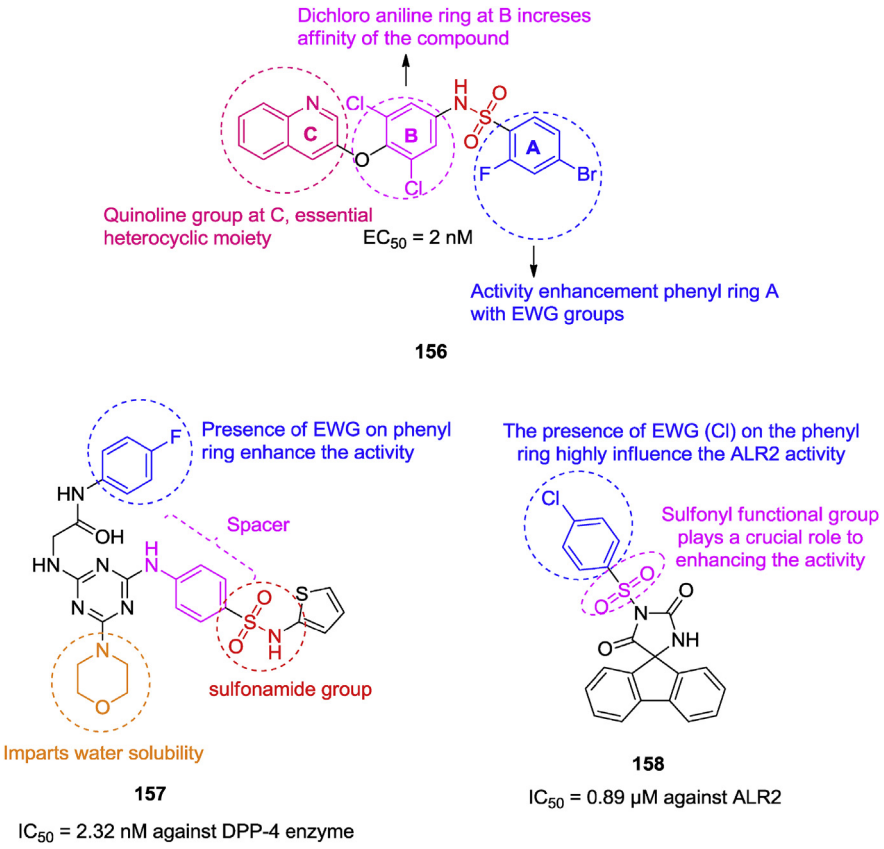


Fig. 10. Sulfonyl of sulfonamides as anti-diabetic agents.

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** ($IC_{50} = 2.06$ 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 hydroxyethypiperazines bearing benzenesulfonyl hybrids as antimalarial agents. All the synthesized compounds were tested *in vitro* antimalarial activity against a *W2 P. falciparum clone*. Among those, compound **201** (IC_{50} of 16.9 μM, Fig. 16) displayed superior antimalarial activity with IC_{50} 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 *Pf*3D7 and *Pf*K1 strains. Among those, compounds **202**, **203**, **204** and **205** (Fig. 17) with sulfonyl pharmacophore showed promising activity with IC_{50} of 1.87, 1.93, 2.00, 2.17 μM against CQ sensitive *Pf*3D7 strain and 1.69, 2.12, 1.60, 2.19 μM against CQ resistant *Pf*K1 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 IC_{50} 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 ($IC_{50} = 7.0$ μM) and DHFR ($IC_{50} = 6.3$ 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 *Pf*CDK 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 IC_{50} 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 worldwidely 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

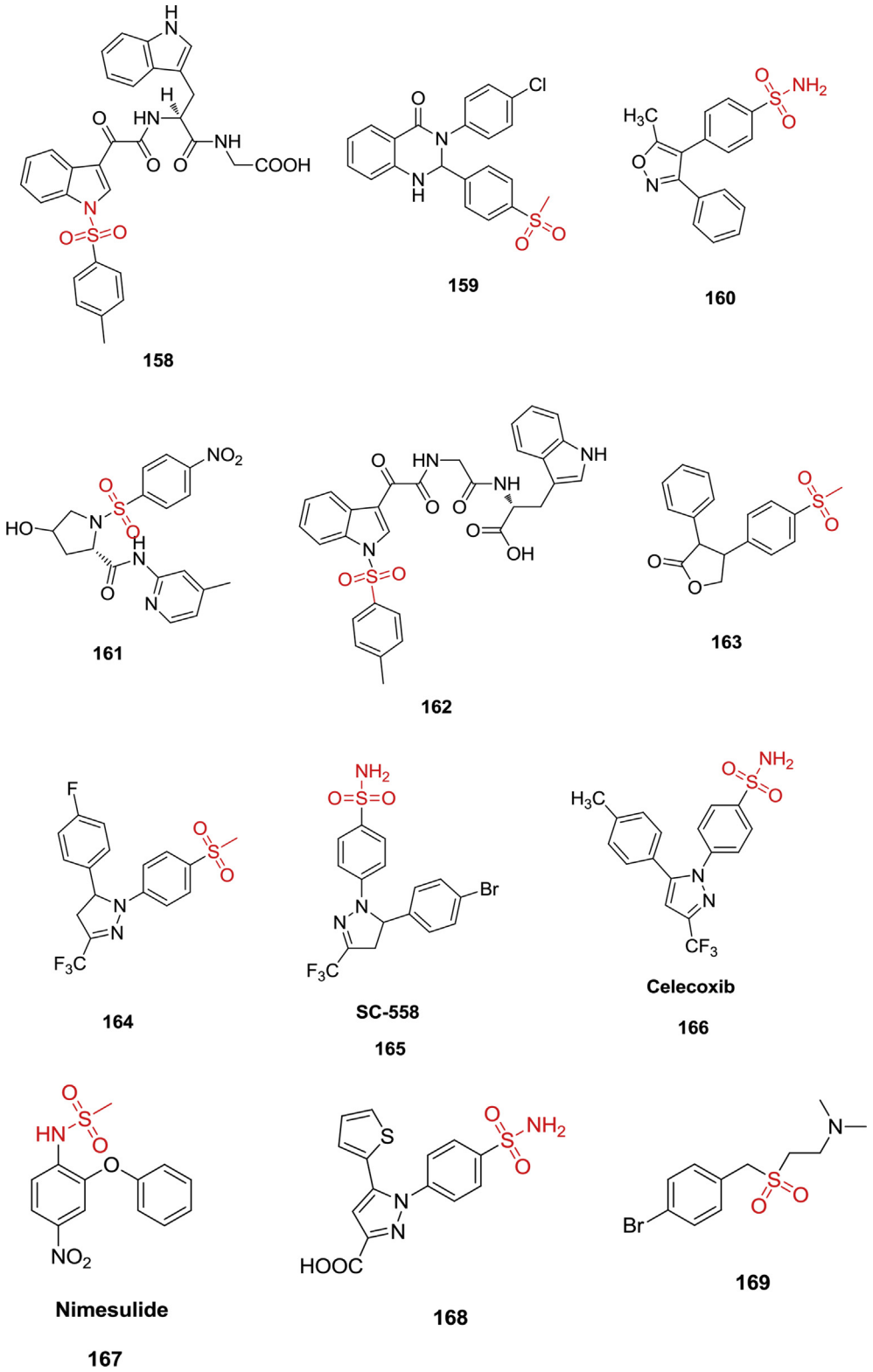


Fig. 11. Some representative sulfonyl or sulfonamides containing potential anti-inflammatory agents.

(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.

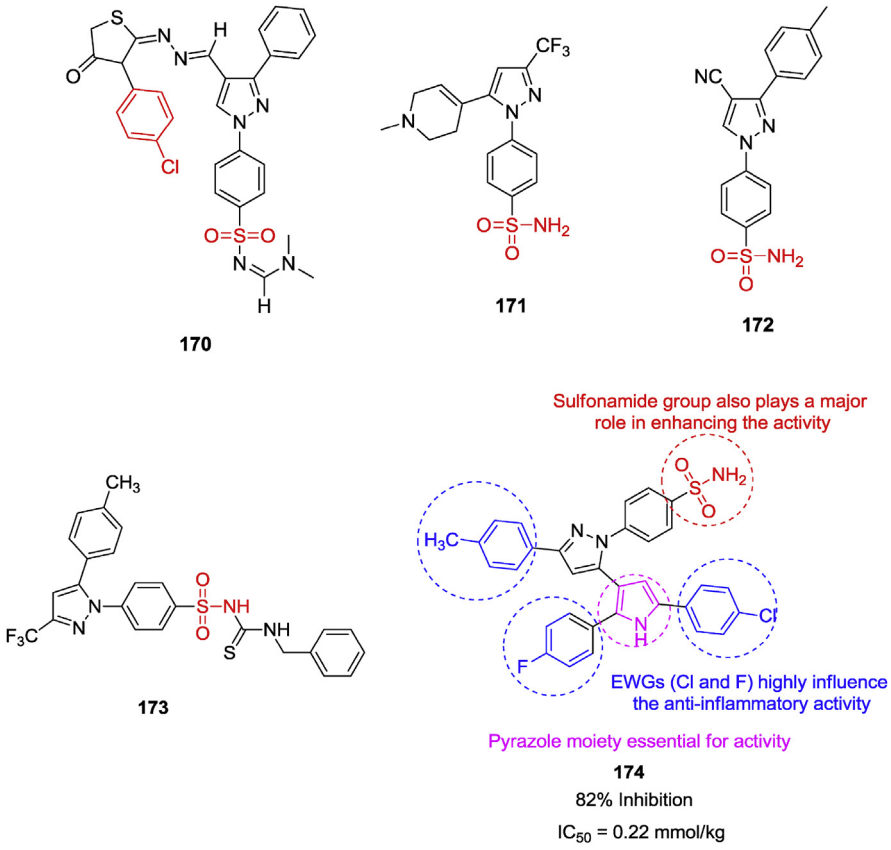


Fig. 12. Some of the representative potent sulfonyl of sulfonamides as anti-inflammatory agents.

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 BChE (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 and Tyr334 from peripheral anionic site (PAS). 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 BChE. The binding of the tested compound **217** with AChE and BChE 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 BChE 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

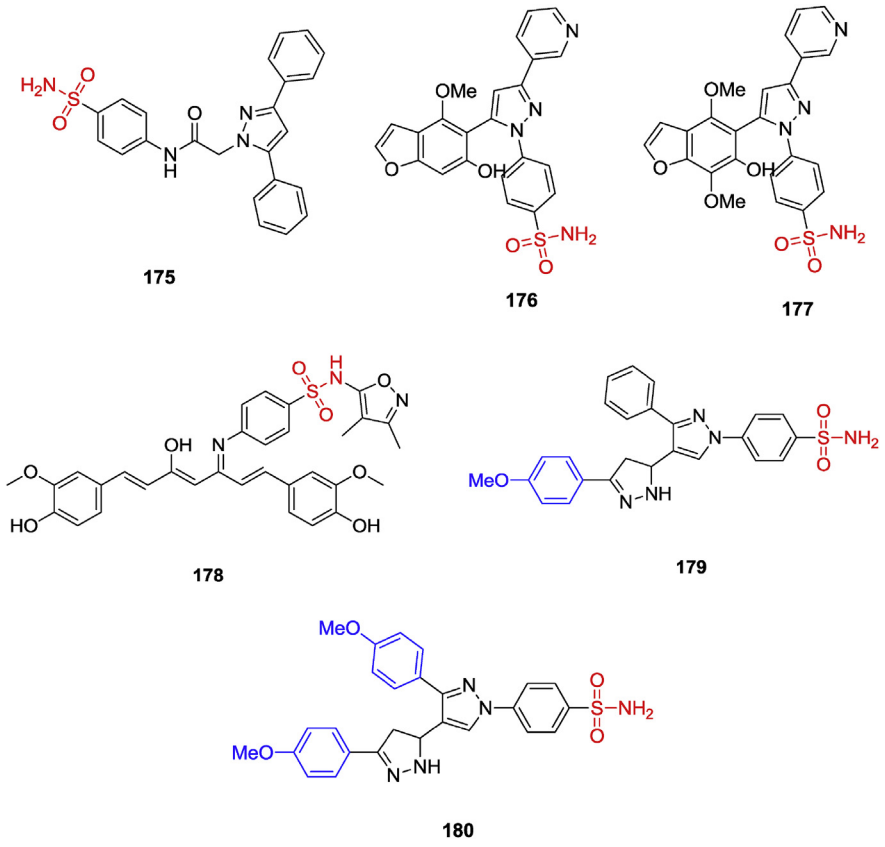


Fig. 13. Sulfonyl of sulfonamides as anti-inflammatory agents.

$IC_{50} = 0.009\ \mu M$). 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 μM and BChE 4.81 μM. 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 intra molecular 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 $(CH_2)_2OMe$ 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 sulfonamide chalcones analogues as potent β-secretase and acylcholinesterase inhibitors. Compounds **225** ($IC_{50} = 0.21\ \mu M$), **226** ($IC_{50} = 0.62\ \mu M$) and **227** ($IC_{50} = 0.69\ \mu M$) (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-HT6 receptor antagonist with a cholinesterase inhibitor. Among these, compound **228** (Fig. 26) was found to be the most potent agent against the 5-HT6 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

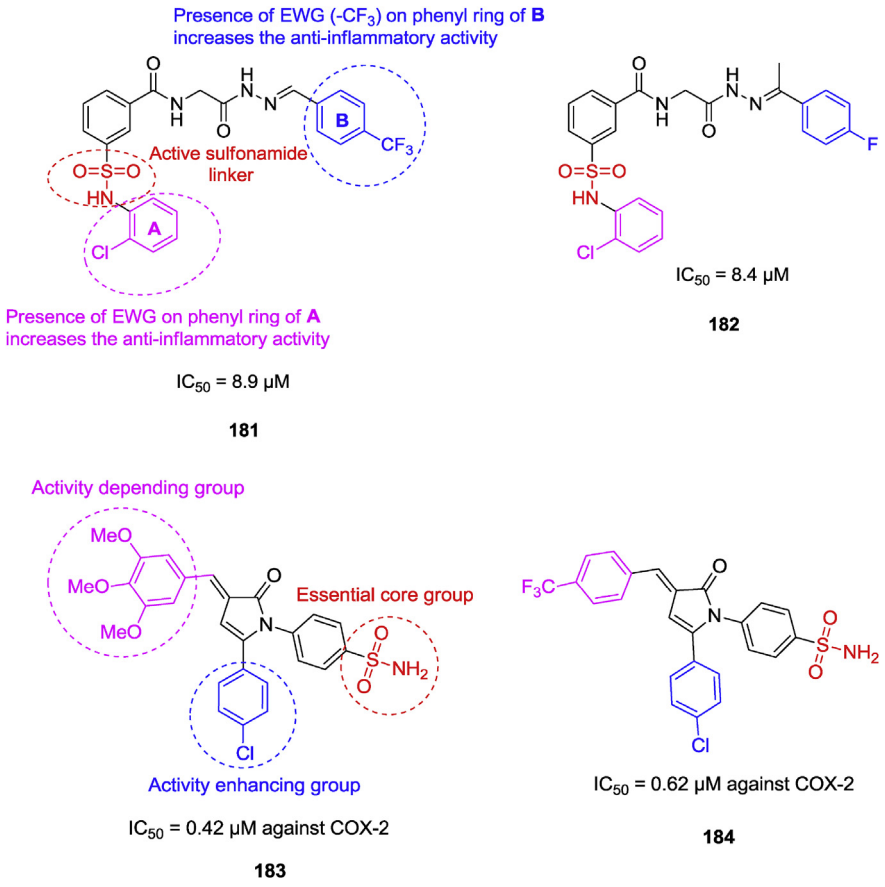


Fig. 14. Sulfonyl of sulfonamides as anti-inflammatory agents.

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 chemotherapic treatment [155]. Sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®), the two pentavalent antimonial [Sb(V)] compounds, 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 act 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-(1*H*-pyrazol-1-yl)benzenesulfonamide hybrids against the *L. infantum* and *L. amazonensis* strains. Compounds **230** ($IC_{50} = 0.059\ \mu M$ against *L. infantum*, $IC_{50} = 0.070\ \mu M$ against *L. amazonensis*) and **231** ($IC_{50} = 0.065\ \mu M$ against *L. infantum*, $IC_{50} = 0.072\ \mu M$ 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 benzenesulfonamide hybrids as potent antileishmanially active candidates against *Leishmania amazonensis*. Among these, compound **232** (IC_{50} value is 6.7 μM) (Fig. 27) was found to have the most potent activity against *Leishmania amazonensis* with IC_{50} value higher than reference drug ketoconazole [165]. González-Rosende et al. developed a new series of naphthalene-sulfonamide analogues as potent antileishmanial and trypanocidal inhibitors. Compound **233** (Fig. 27) displayed most potent inhibition on three Leishmania species entitled *L. infantum* ($IC_{50} = 23.0\ \mu M$), *L. amazonensis* ($IC_{50} = 42.9\ \mu M$) and *T. cruzi* ($IC_{50} = 223.7\ \mu M$). 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 ($IC_{50} = 2.8\ \mu M$), 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 antileishmanial agents. Compound **235** (Fig. 27) was found to be the best profile against *L. braziliensis promastigotes* with IC_{50} 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].

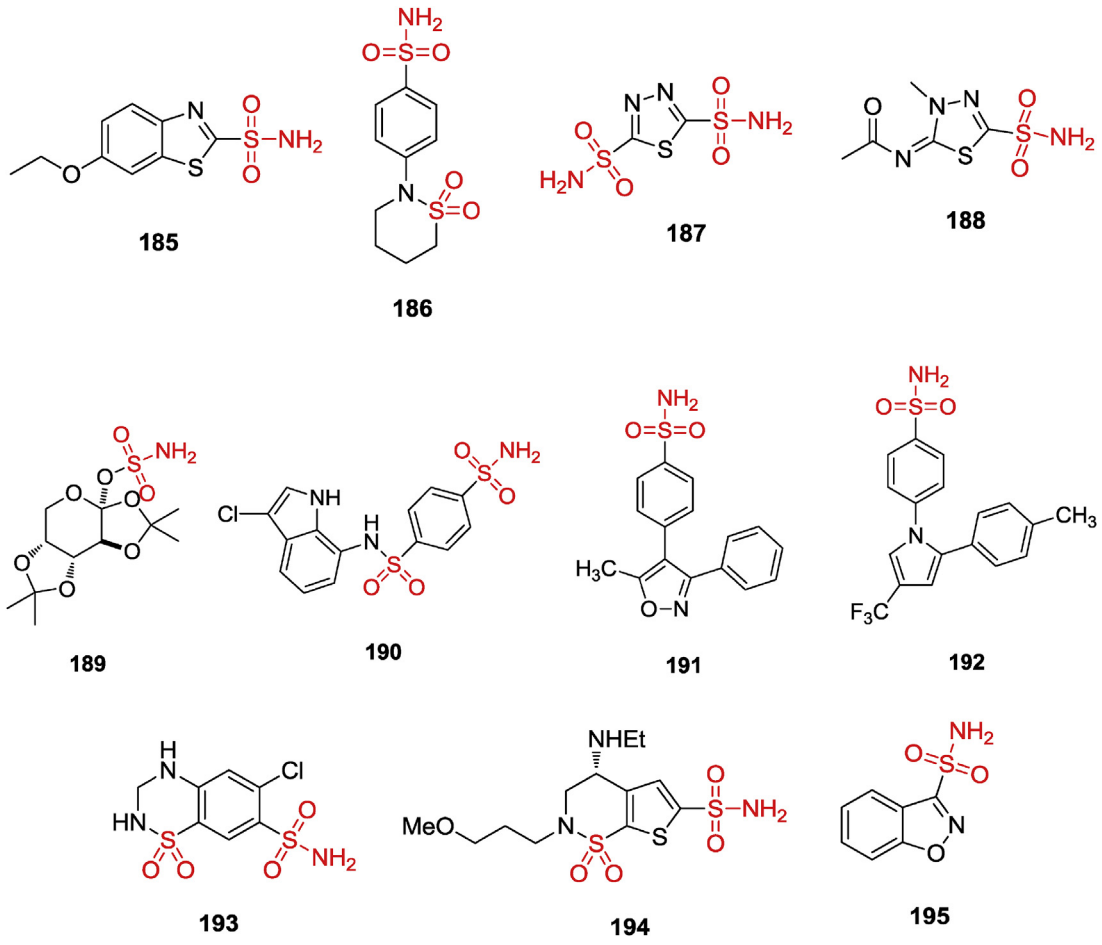


Fig. 15. Some representative potential anti-malarial sulfonyl or sulfanamide agents.

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 (EMB0), 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 sulfonamides 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 (IC_{50} = 1.9 μM). The SAR revealed that the presence of electron withdrawing (CF_3) 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)benzo[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 IC_{50} 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** (IC_{50} = 18 μM), **248** (IC_{50} = 21 μM), **249** (IC_{50} = 39 μM) and **250** (IC_{50} = 41 μM) (Fig. 24) showed the most potent PtpB inhibitors. The SAR suggested that the presence of EWGs (Cl, F and NO_2) 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. Compound

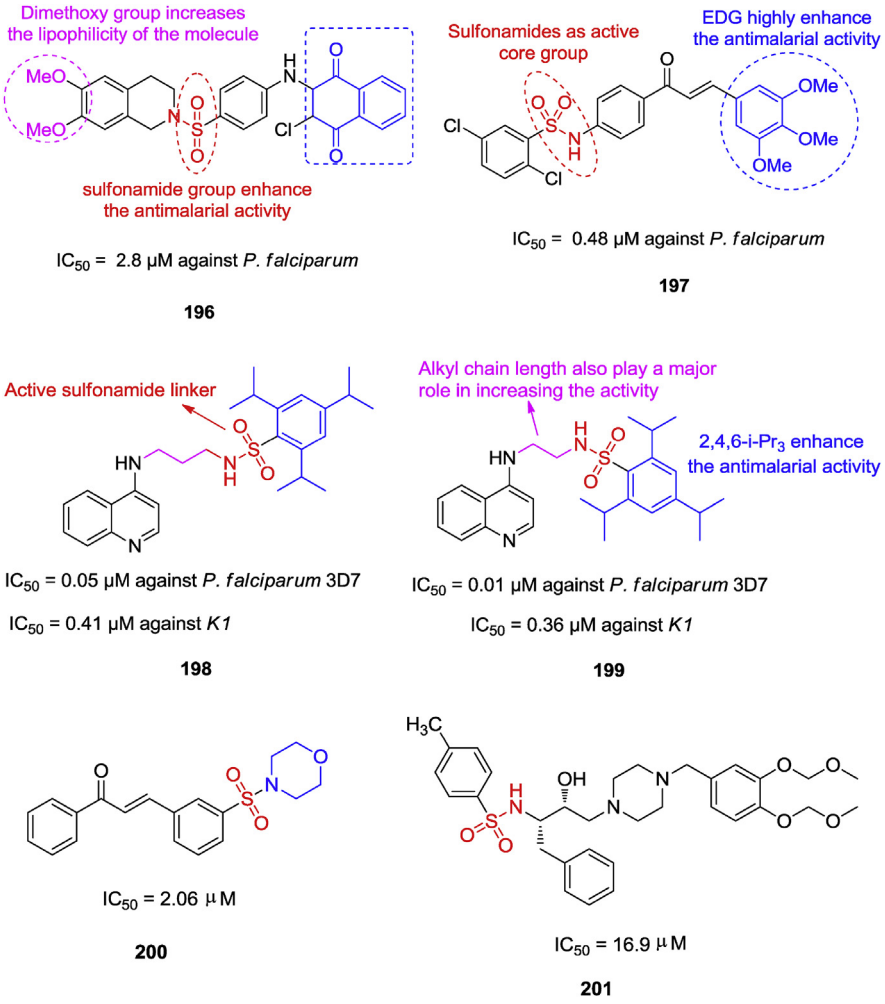


Fig. 16. Sulfonyl of sulfonamides as anti-malarial agents.

251 (Fig. 29) was found to be the most active anti-TB agents with $IC_{50} = 17.02$ μM. 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 μM. 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 *Mtb*CM. Compound **253** ($Ki = 5.7$ μM) (Fig. 29) was found to be the best inhibitor against *Mtb*CM. The SAR showed that the indole containing an *o*-(RSO_2NH) C_6H_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 *in vitro* anti-mycobacterial activity against $MTBH_{37}Rv$. Among these, compound **254** (Fig. 29) showed excellent anti-TB activity with MIC value of 0.78 μg/mL, eight fold more potent than EMB (MIC: 1.56 μg/mL) and PZA (MIC: 6.25 μg/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 *in vitro* HIV-1 replication by Loh et al. Compounds **261** ($IC_{50} = 93$ μM against HIV-I and $IC_{50} = 91$ μM against NL4.3) and **262** ($IC_{50} = 75$ μM against HIV-I

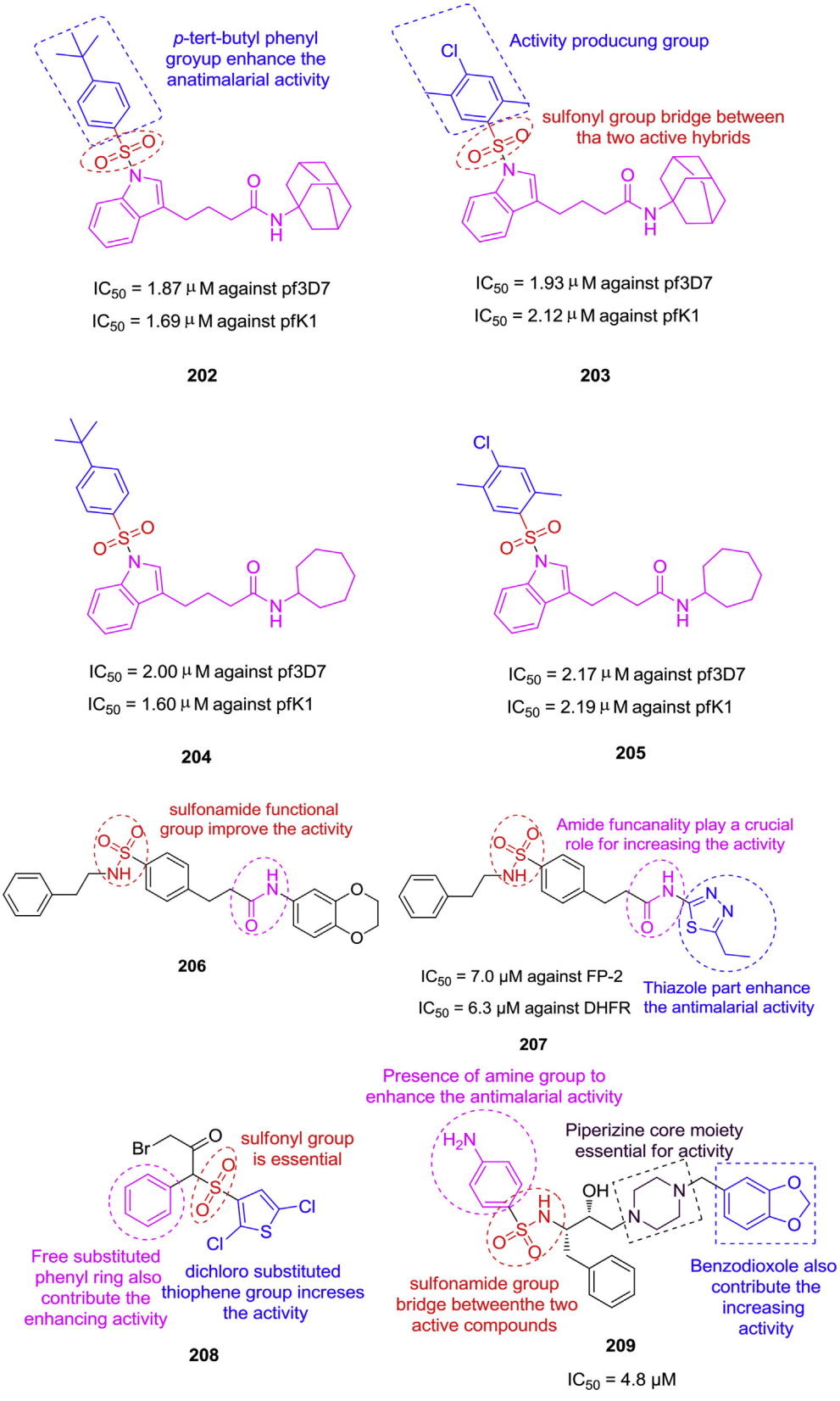


Fig. 17. Sulfonyl of sulfonamides as anti-malarial agents.

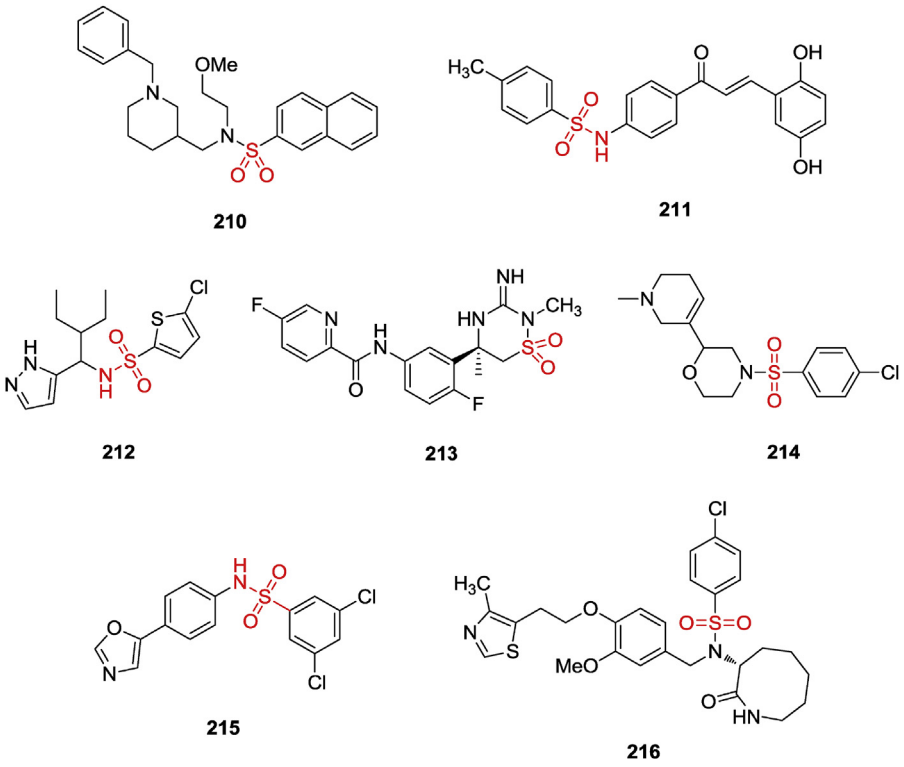


Fig. 18. Some of the sulfonyl or sulfonamides containing heterocycles as potential Alzheimer's agents.

and $IC_{50} = 71\ \mu M$ 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 K_i 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** ($EC_{50} = 8.1\ \mu M$ and $CC_{50} = >224\ \mu M$), **265** ($EC_{50} = 4.8\ \mu M$ and $CC_{50} = >186\ \mu M$) (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 $EC_{50} = 0.428$ and $0.675\ \mu M$, respectively, more potent than reference drug AZT. These results are expected to be helpful in the design of thiophenepyrimidine-based NNRTIs with more potent activity against HIV strains with RT mutations [188]. Zhang et al. explored pyridine-sulfonamides as potent Hepatitis C (HCV) NS4B inhibitor. Compound **267** (Fig. 31) has showed outstanding potency against the HCV 1b replicon, with an $EC_{50} = 2\ nM$ and a selectivity index of >5000 with respect to cellular GAPDH. The overall profile of compound **267** makes it a good aspirant for future drug development program [189].

Several thiadiazole bearing sulfonamides 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 sulfonamide 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 EC_{50} 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 ($Ki = 0.8\ nM$, $IC_{50} = 1.5\ \mu M$) antiviral activity. Oral bioavailability of this compound ranged from 42% (rat) to 77% (dog) with $t_{1/2} = 6\ h$ [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 ED_{50} 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** ($EC_{50} = 10.2\ \mu M$) and **274** ($EC_{50} = 13\ \mu M$) (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 $-SO_2$ linker was fundamental to their anti-CHIKV activity. Bezouracil derivatives **273** (Fig. 32) had better selectivity indexes compared to uracil **274** (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

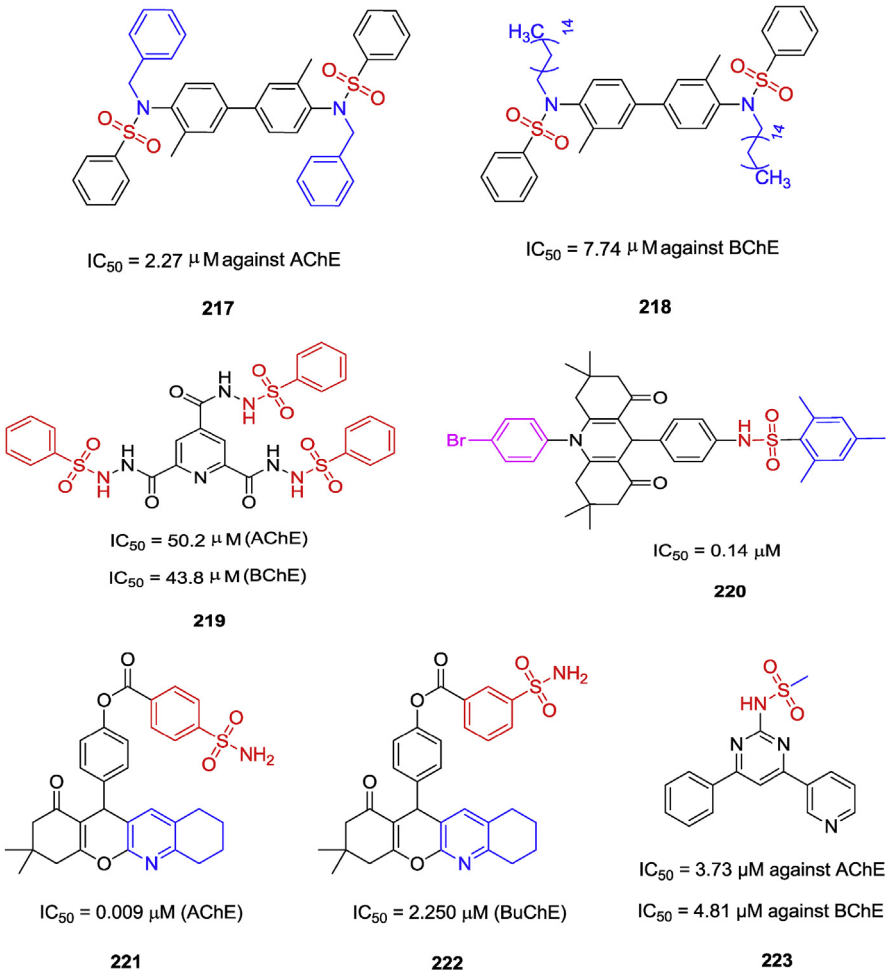


Fig. 19. Sulfonyl of sulfonamides as Alzheimer's agents.

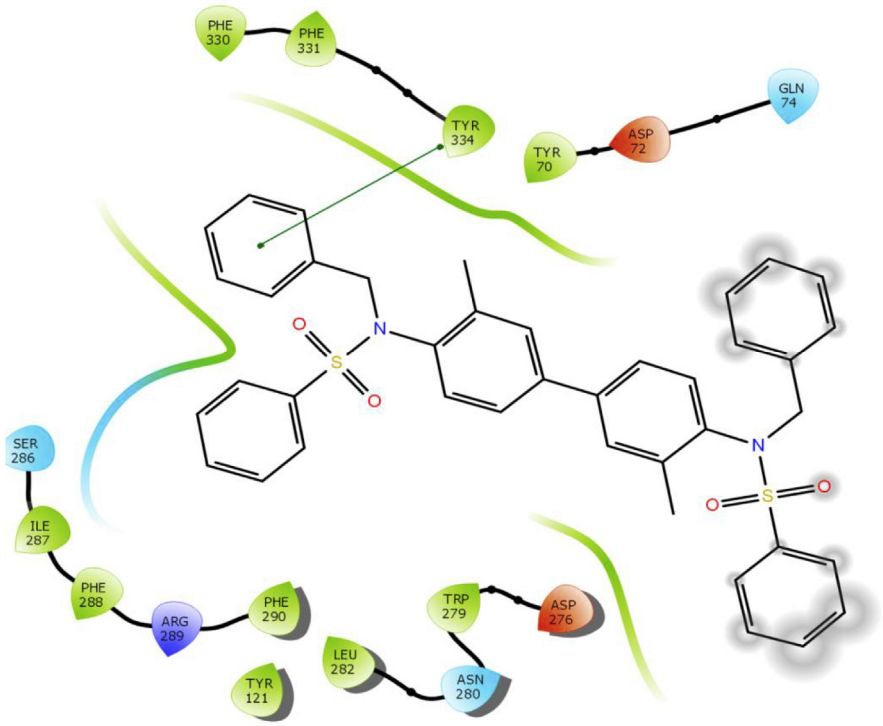


Fig. 20. 2D-binding mode of compound **217** within the active site of AChE.

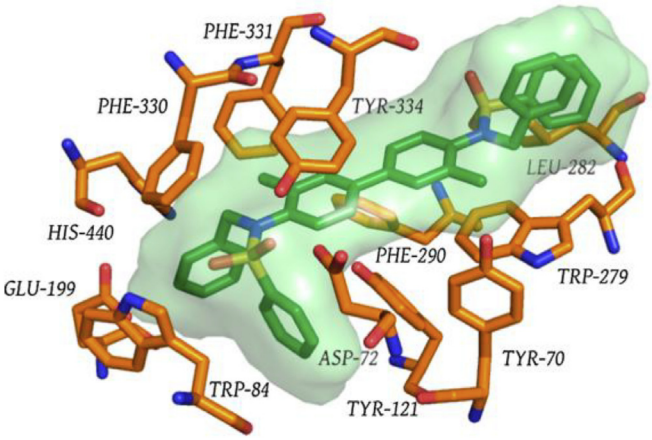


Fig. 21. 3D-binding mode of compound **217** with in the active site of AChE.

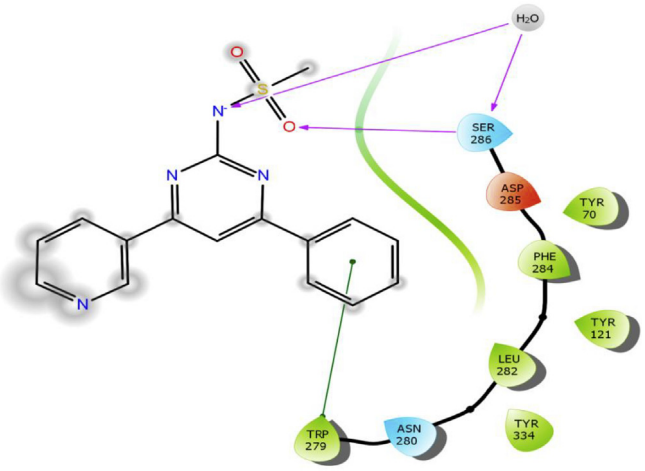


Fig. 22. Best 2D-docked pose of compound **223** within the AChE active site (PDB code: 3I6Z).

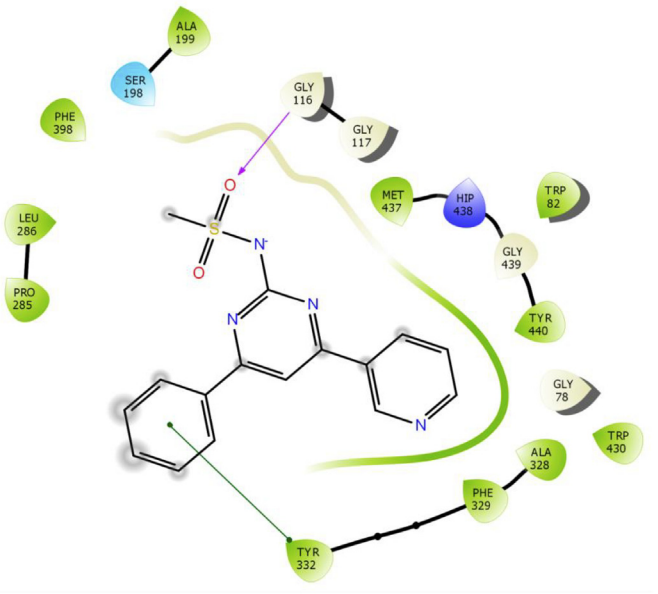


Fig. 23. Best 2D-docked pose of compound **223** within the BChE active site (PDB code: 4BDS).

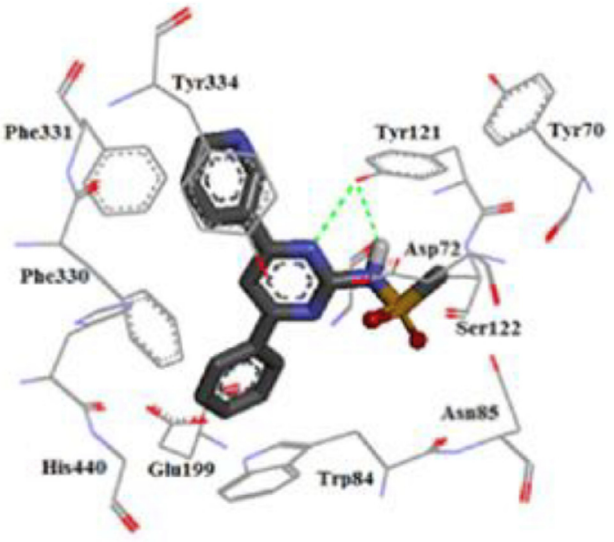


Fig. 24. Best 3D-docked pose of compound **223** within (**24**) the AChE active site, and (**25**) the BChE active site. Green dashed lines represent hydrogen bond interactions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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 CO_2 hydrase catalytic activity which is inhibited by CA inhibitors belonging to sulphonamide, 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 IC_{50} 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 anydrases (CAs, EC 4.2.1.1) I, II, IV and IX by a stopped-flow CO_2 hydrase assay [204]. Compounds **276** and **277** (Fig. 33) showed the most potent active against hCAII with IC_{50} values of KIs of 0.41 and 0.46 nM which may be due to the presence of EWGs (Cl and NO_2) 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

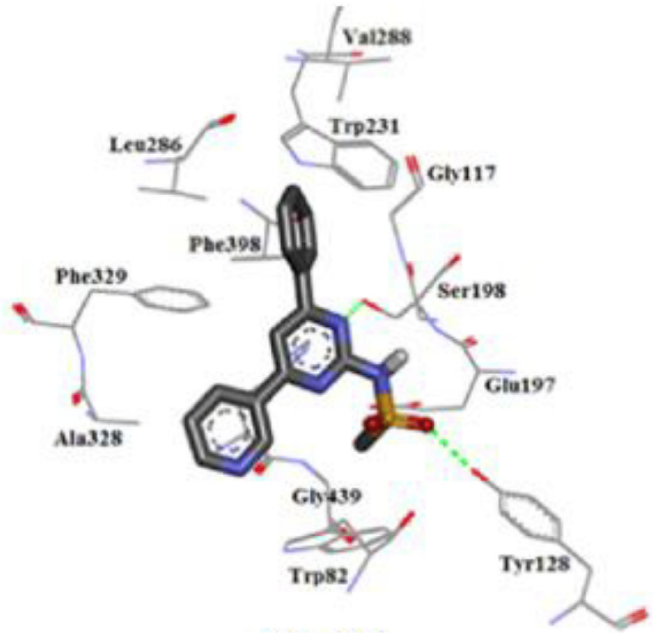


Fig. 25. Best 3D-docked pose of compound **223** within (**24**) the AChE active site, and (**25**) the BChE active site. Green dashed lines represent hydrogen bond interactions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

anhydrase isozymes by Seok et al. Compound **278** (Fig. 33) was found to be incorporated with amino, hydrazino, ethylamino, dimethylamino or amino acyl moieties, and showed promising CA activity but incorporation of bulky groups viz., *n*-propyl, *n*-butyl, diethylaminoethyl, piperazinylethyl, pyridoxal amine or phenoxy 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 (CB_1 and CB_2, 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 CB_1/CB_2 dual agonists for the administration of pain [214]. Very recently, Watson and co-workers from Pfizer have reported sulfonylbenzimidazole

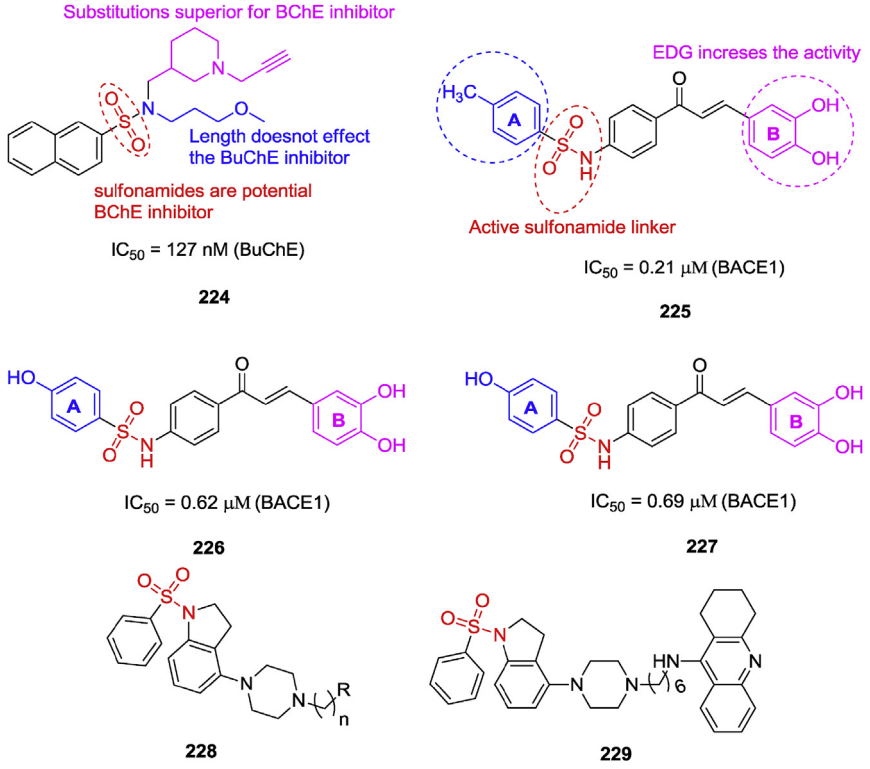


Fig. 26. Sulfonyl of sulfonamides as Alzheimer's agents.

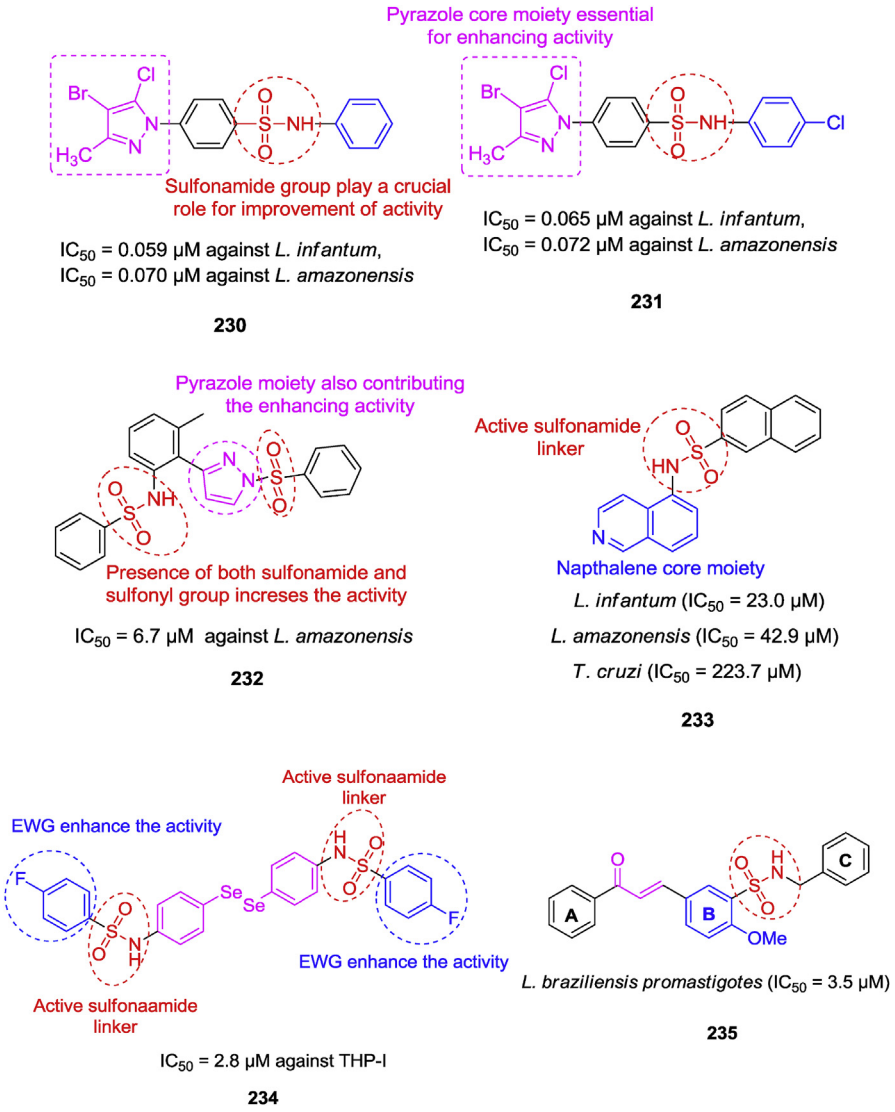


Fig. 27. Sulfonyl of sulfonamides as Antileishmanial agents.

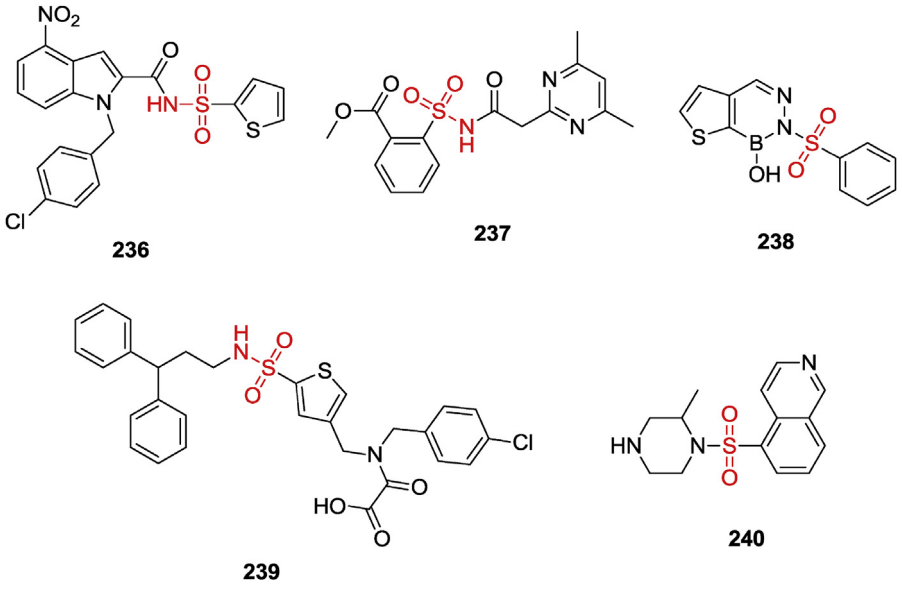


Fig. 28. Some of the sulfonyl or sulfonamides containing heterocycles as potential TB agents.

hybrids (**288** and **289**) (Fig. 34) as selective CB_2 agonists and as potential analgesic agents devoid of the side effects associated with CB_1 agonists [215]. In 2012, Verbist and co-workers identified sulfonylbenzimidazole analogue **290** (Fig. 34) as potent CB_2-receptor agonists. The compound **290** was found to have no analgesic effect which was demonstrated in pain models. Furthermore, to improve the metabolic stability and solubility, the same group optimized the compound **290** and led to the discovery of relatively polar and peripherally acting CB_2 agonists of compounds **291** and **292** (Fig. 34) [216]. Greig et al. designed and produced a new class of indole sulfonamides as potent cannabinoid receptor. Compounds **293** and **294** (Fig. 34) 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 hCB_2 receptor, compound **295** ($EC_{50} = 5.1$ nM) and **296** ($EC_{50} = 7.0$ nM) (Fig. 34) being the most potent hCB_2 receptor agents. These results inspired further development of *in vitro* profiling of sulfonamides on the hCB_1 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 **297** (Fig. 34) was found to be most potent cannabinoid-1 receptor antagonist with K_i values of 0.3 nM (hCB1R), 21.0 nM (hCB2R) and EC_{50} of 3 nM (CB1R). Compound **297** 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 seizers [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 **298** protected all animals better than the reference drug phenobarbital and did not show mortality. Other active compounds **299** and **300** 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 **301** and **302** (Fig. 35) 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 sulfonyl hybrids as potent anticancer agents. Among them, some of the compounds showed superior anticancer activity against human cervical HeLA cell lines. Compounds **303** and **304** (Fig. 36) were extensively inhibiting to the cell growth and GI_{50} values were found to be 0.22 and 0.6 μM respectively. The SAR studies revealed that the presence of EWGs (NO_2) on the phenyl ring and two sulfonyl 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 **305** and **306** (Fig. 36) showed

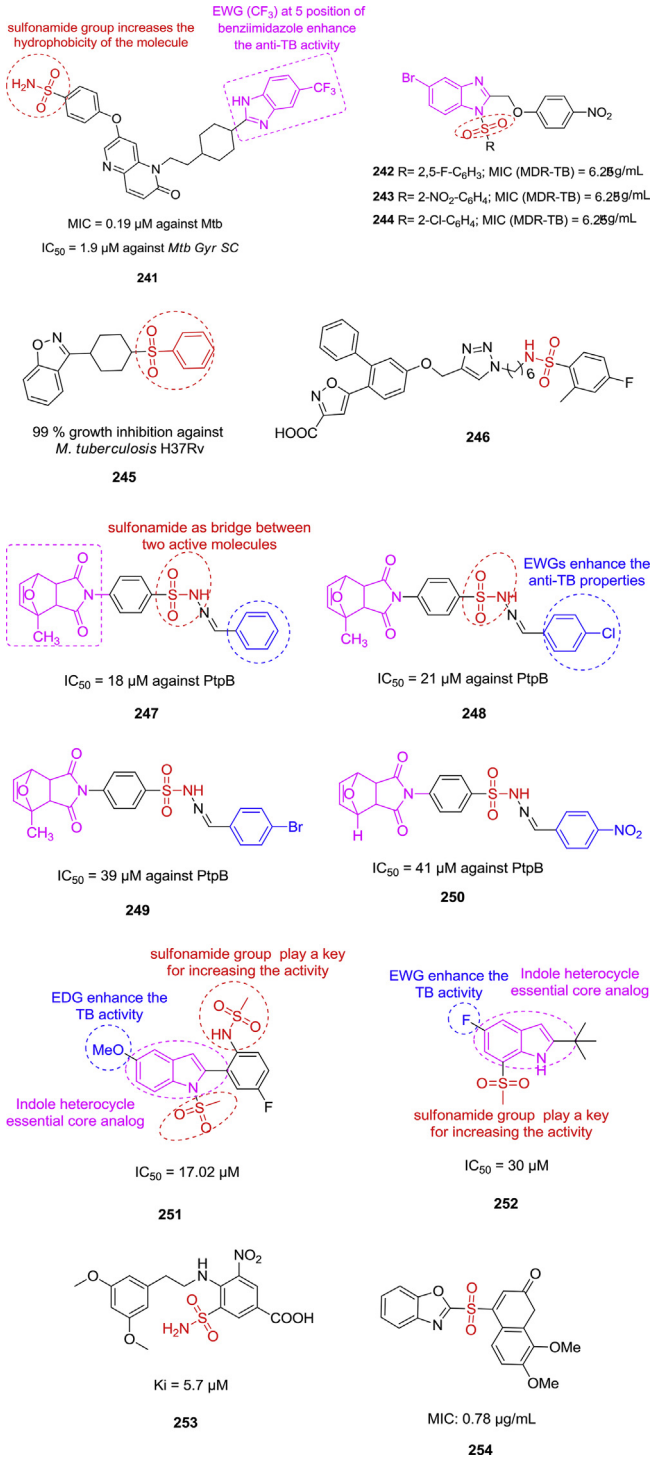


Fig. 29. Sulfonyl or sulfonamides as potent anti-Tuberculosis agents.

good carbonic anhydrases inhibition to the cell lines hCA IX ($K_i = 15.7$ and 7.4 nM, respectively) and hCA XII ($K_i = 3.7$ and 5.4 nM, respectively). The SAR studies suggested that the presence of EWGs (NO_2) on the phenyl ring to increased the activity and sulphonamide played a major role in the enhancing the CA activity [231]. In 2014, Tiangong and co-workers developed compound (**307** and **308**) (Fig. 36), a new class of styrylsulfonyl-methylpyridines hybrids with the anticancer activity against A2780, MCF7 and HCT-116 cell lines by using MTT assay. Compound **307** was found to have the best antitumor activity in a xenograft HCT-116 colon cancer model with GI_{50} value of 0.570 μmoL/L. Compound **308** displayed potent antitumor efficacy in the xenograft A2780 with GI_{50} value of 0.007 μmoL/L. The SAR studies revealed that compounds containing 2,4,6-trimethoxy and two sulfoonamide group 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. Pingaew et al. [124] reported a new class of sulfonyl containing thiosemicarbazone and tetrahydroisoquinoline hybrids as potent anticancer agents. Some of the synthesized thiosemicarbazone analogues showed good cytotoxic potency against MOLT-3 cell lines with IC_{50} value of 2.13 μg/mL. Compound **309** (Fig. 36) was found to have the best cytotoxic activity against HuCCA-1 and HepG2cells with IC_{50} 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 IC_{50} values in the range of 0.055–0.105 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** ($IC_{50} = 14$ μM) and **314** ($IC_{50} = 3.9$ 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 sulphonamide 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

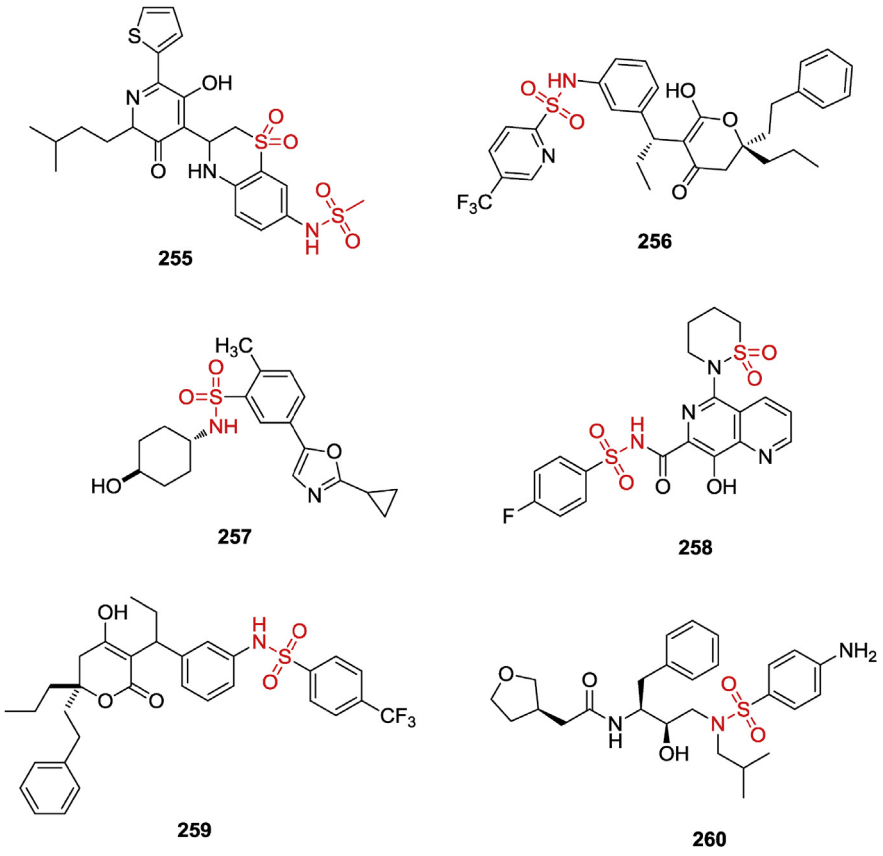


Fig. 30. Sulfonyl or sulfonamides potent anti-viral agents.

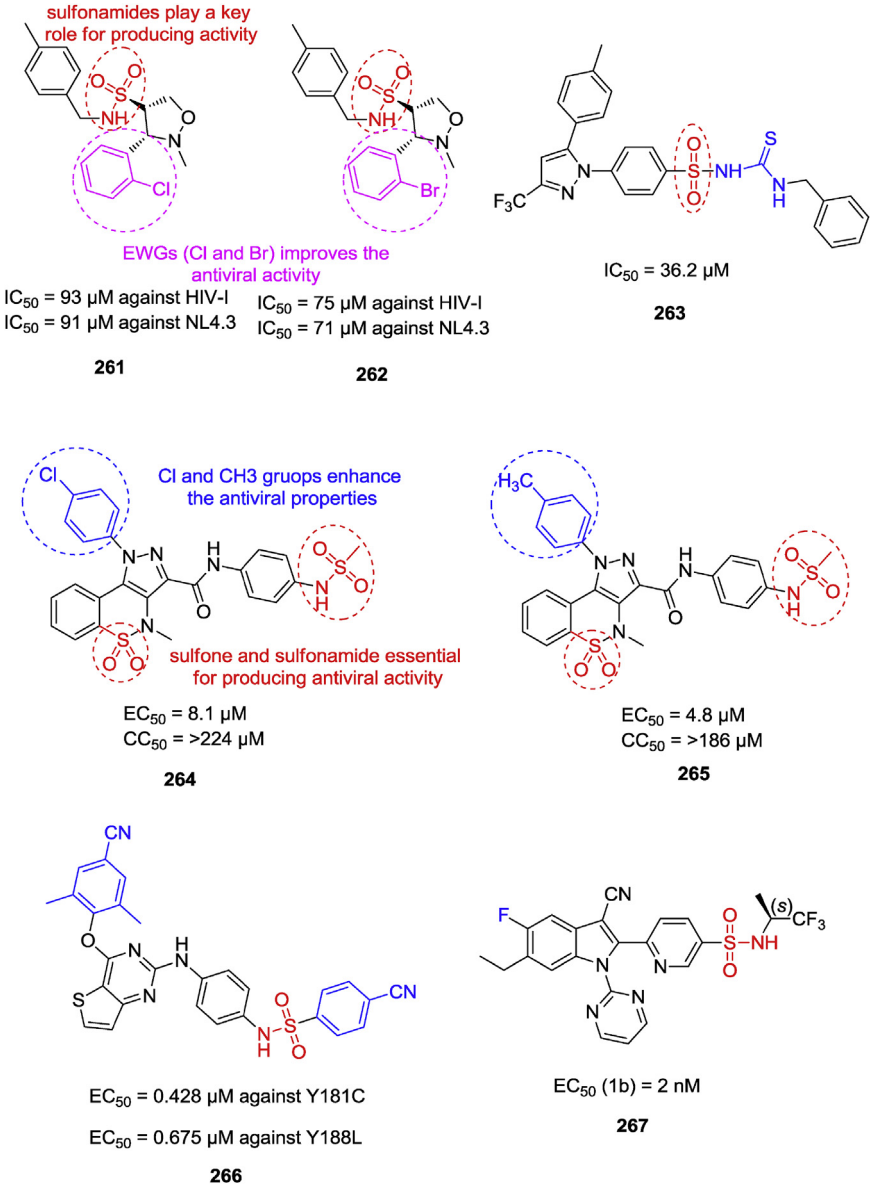
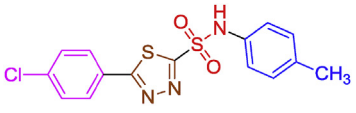


Fig. 31. Sulfonyl or sulfonamides potent anti-viral agents.



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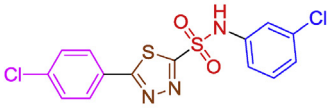

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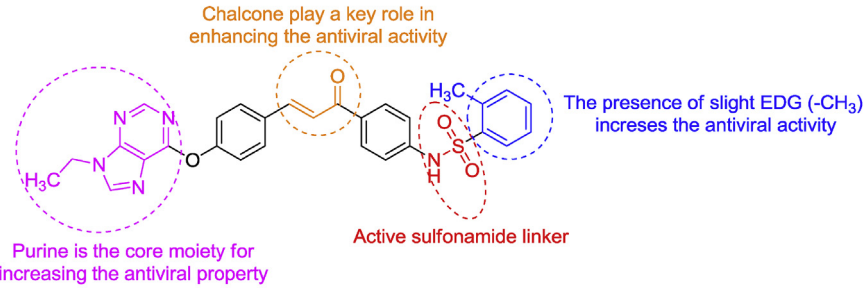
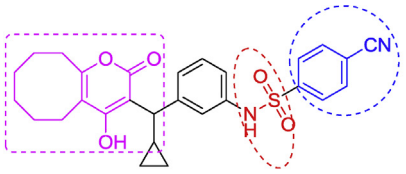


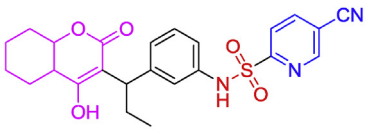
EC_{50} = 51.65 μg/mL

270



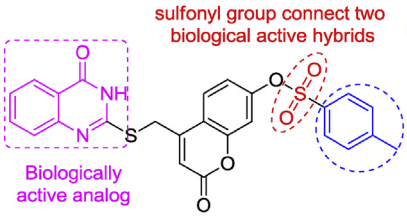
K_i = 0.8 nM, IC50 = 1.5 μM

271



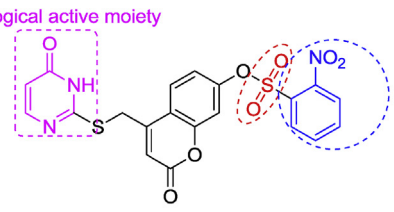
ED_{50} = 0.95 μM

272



EC_{50} = 10.2 μM

273



EC_{50} = 13 μM

274

Fig. 32. Sulfonyl or sulfonamides potent anti-viral agents.

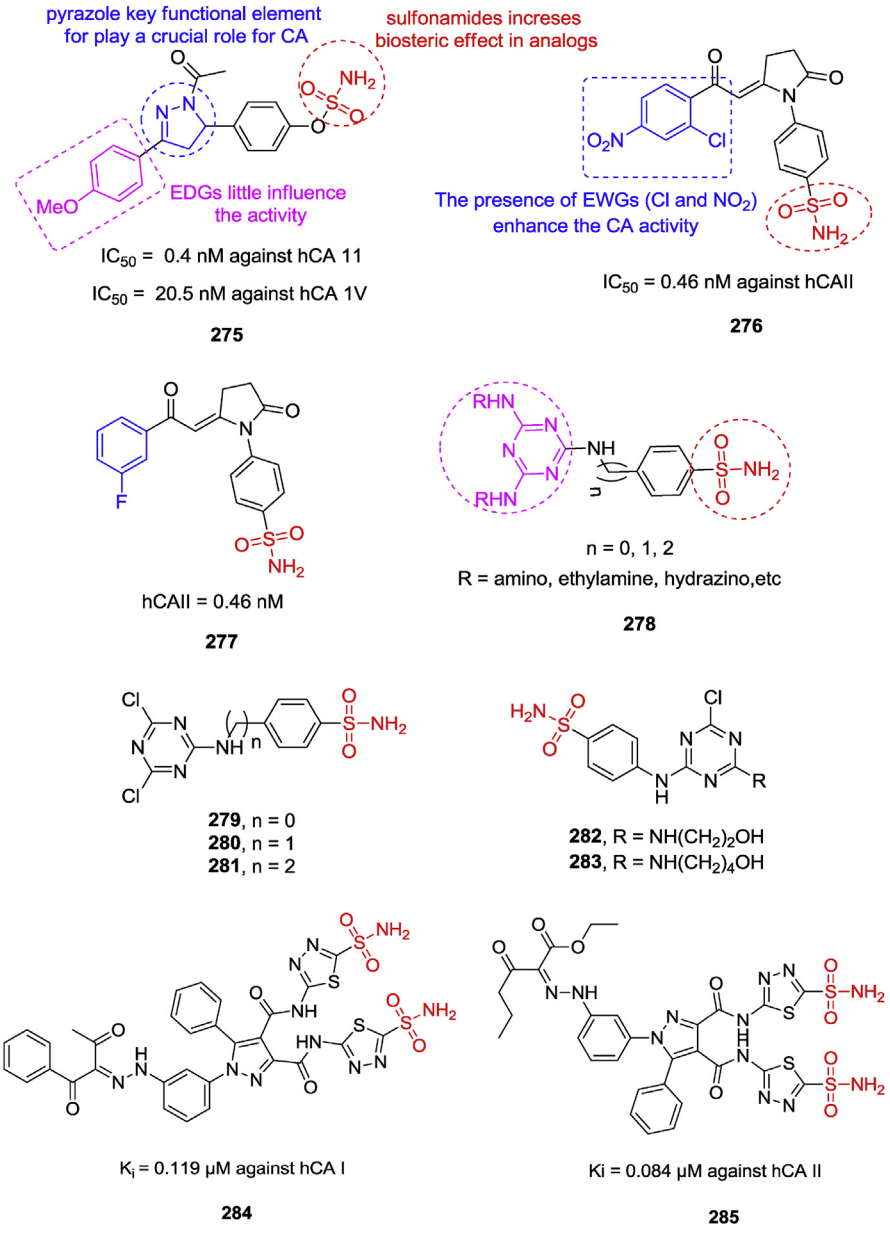


Fig. 33. Sulfonyl or sulfonamides potent carbonic anhydrase agents.

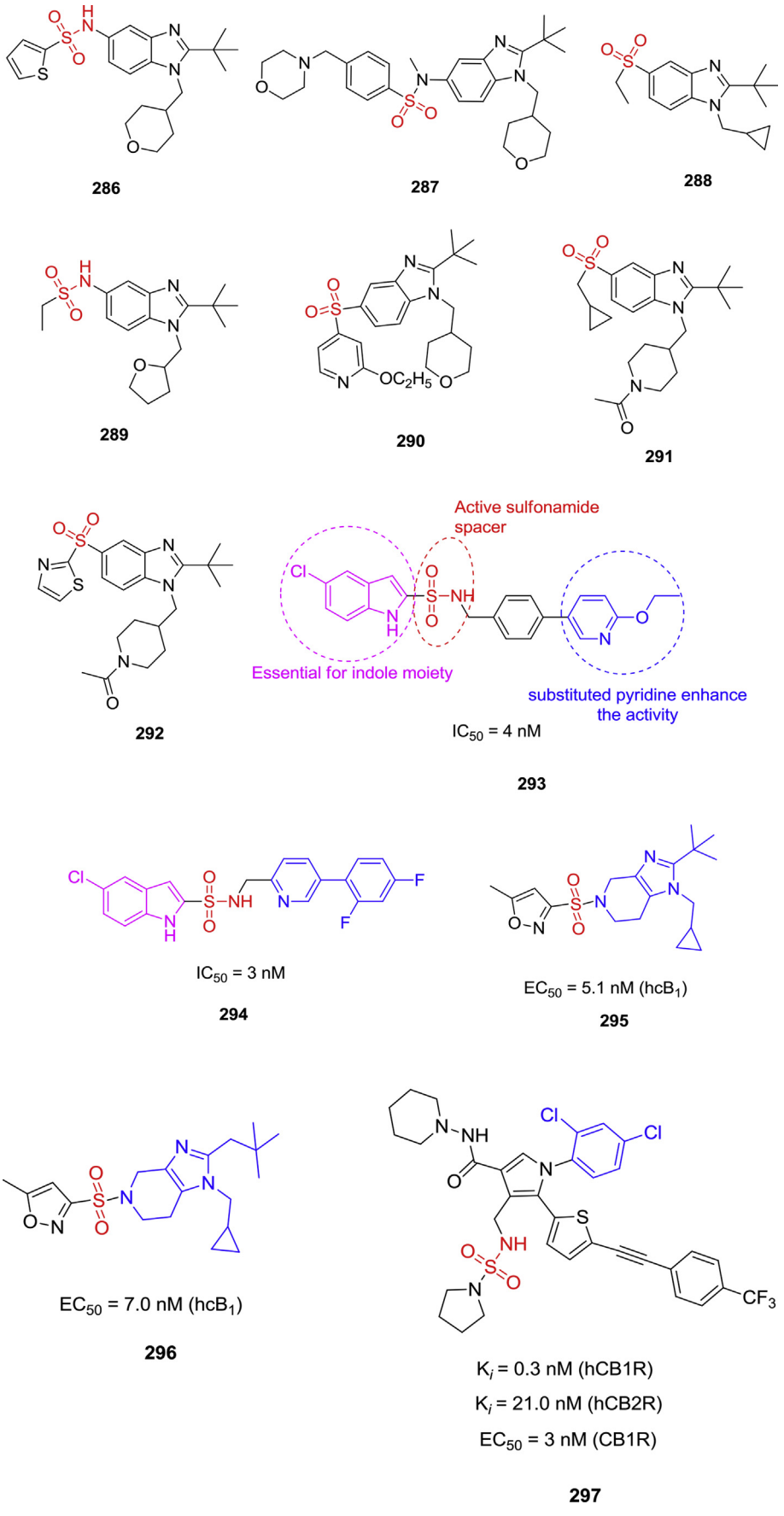


Fig. 34. Sulfonyl or sulfonamides as potent Cannabinoid receptor agonists.

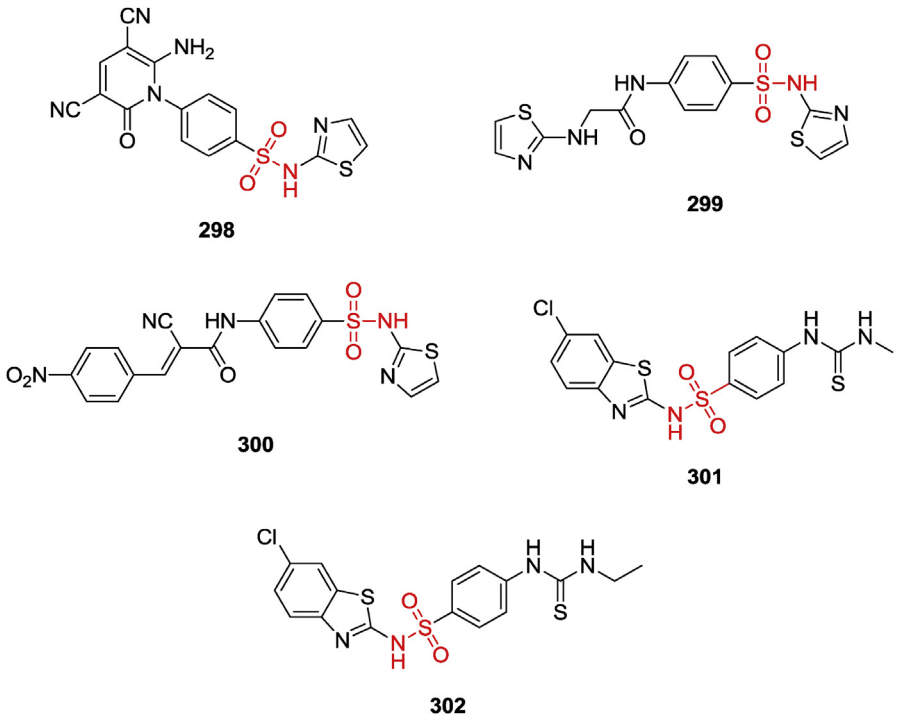


Fig. 35. Sulfonyl or sulfonamides as potent anticonvulsant agents.

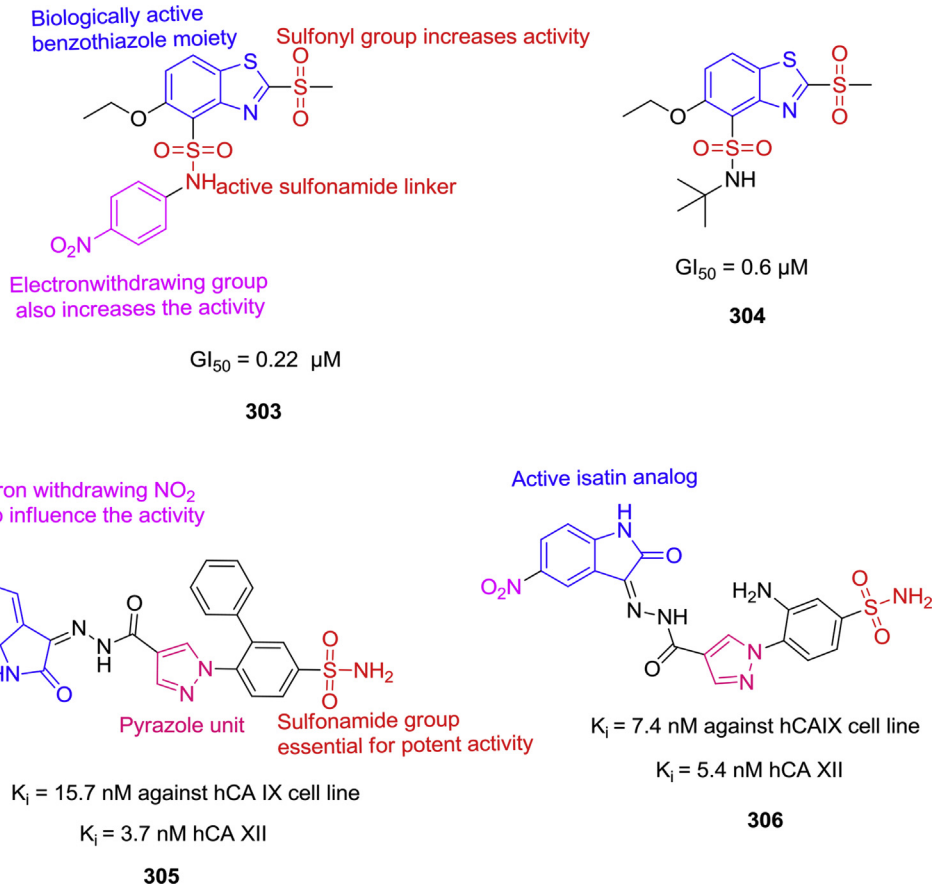
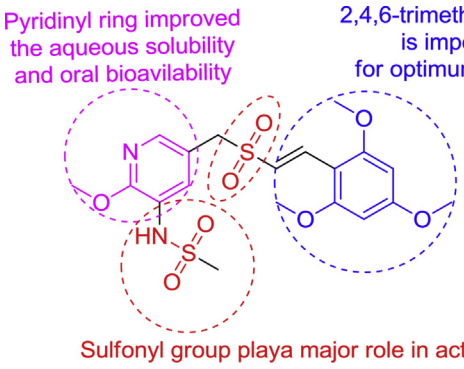
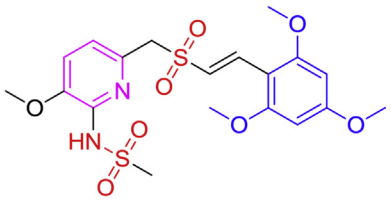


Fig. 36. Sulfonyl or sulfonamides as potent anticancer agents.



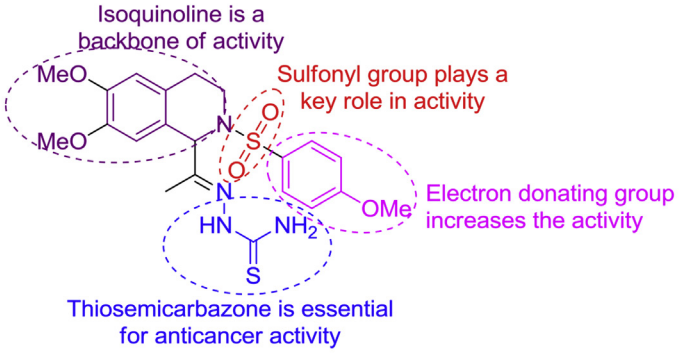
GI_{50} = 0.570 μmol/L

307



GI_{50} = 0.007 μmol/L

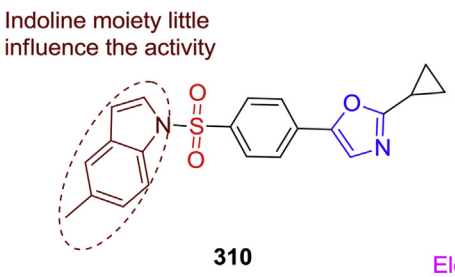
308



IC_{50} = 31.00 μg/mL against HuCCA-I

IC_{50} = 10.50 μg/mL against HepG2

309



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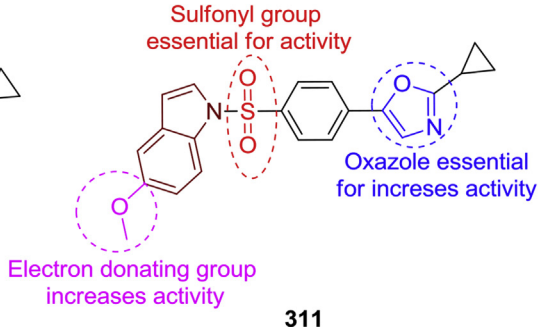

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Fig. 36. (*continued*).

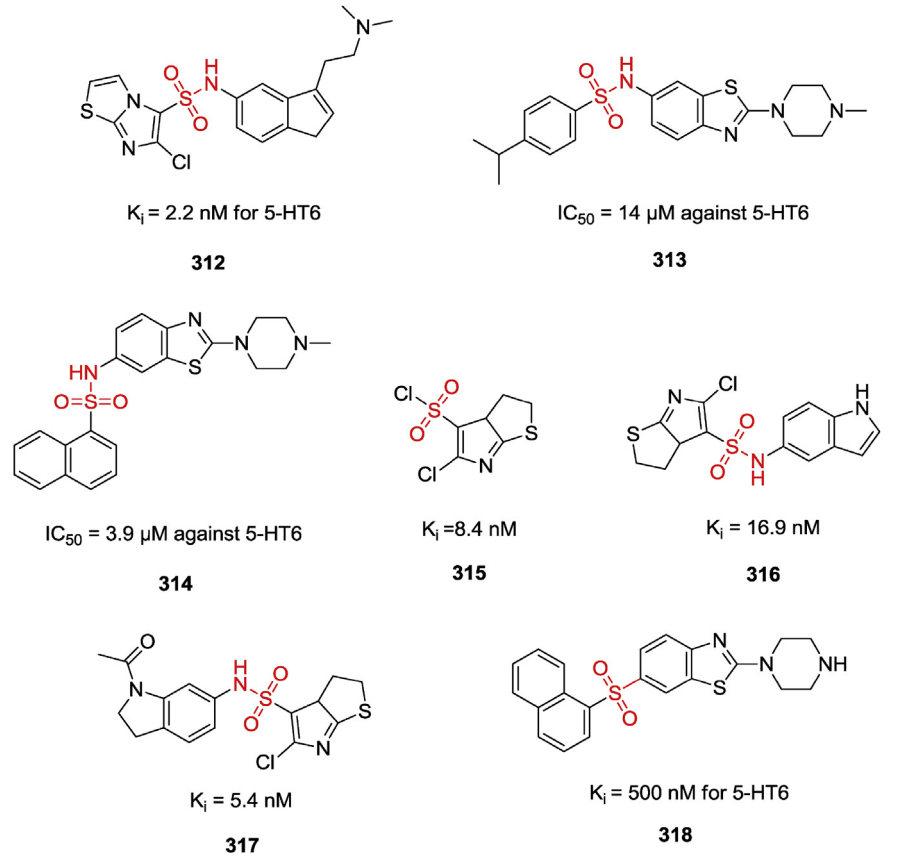


Fig. 37. Sulfonyl or sulfonamides as potent 5-HT6 receptor.

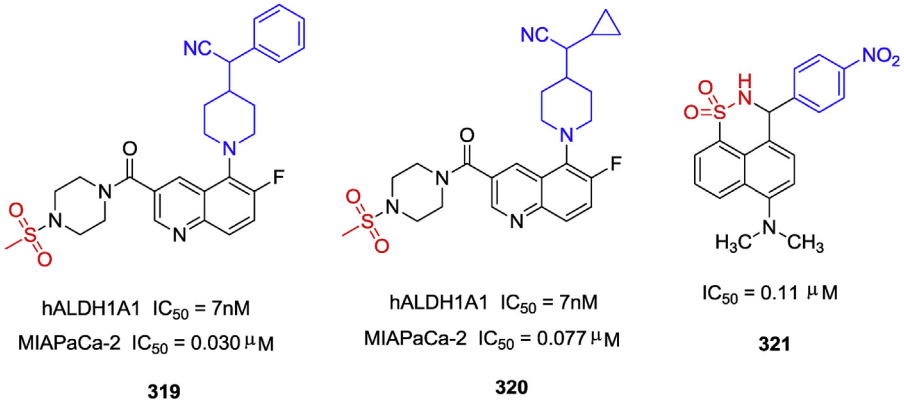


Fig. 38. Sulfonyl or sulfonamides showed diverse biological properties.

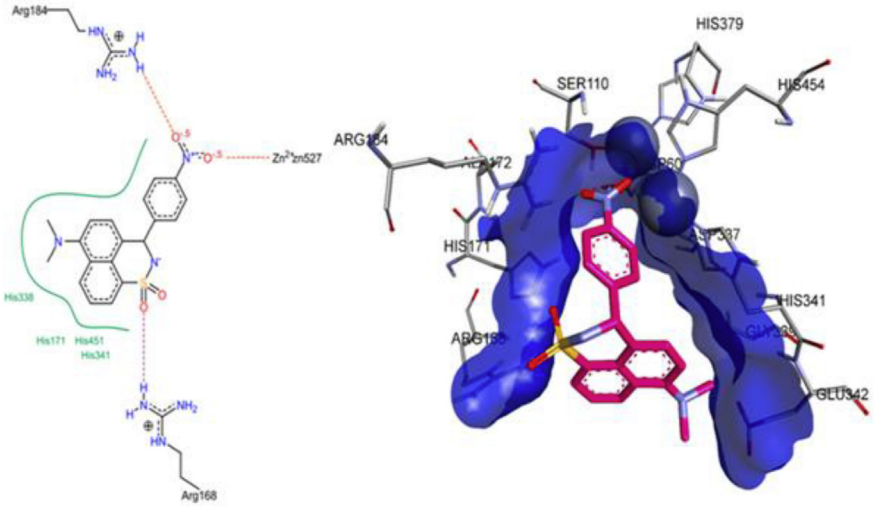


Fig. 39. 2D (left) and 3D (right) interactions of most active bTNAP inhibitor **321**.

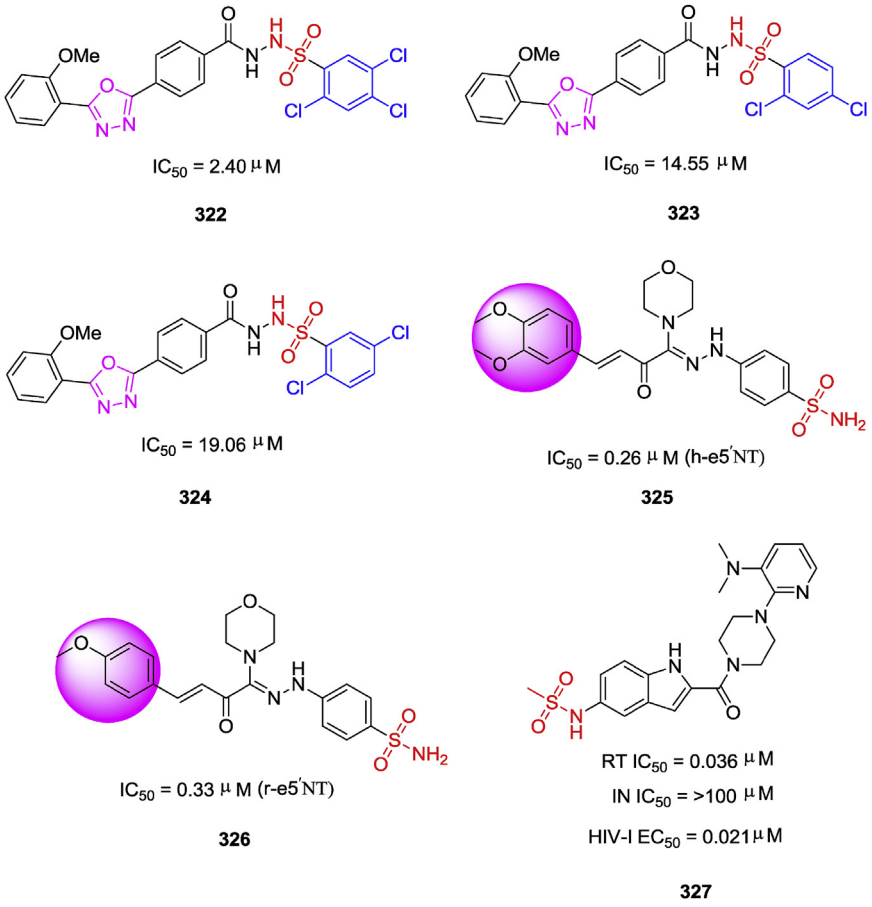
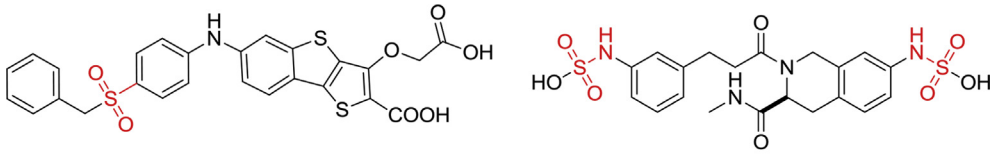


Fig. 40. Sulfonyl or sulfonamides with diverse pharmacological properties.



328 329

Fig. 41. Sulfonyl or sulfonamides showed diverse biological properties.

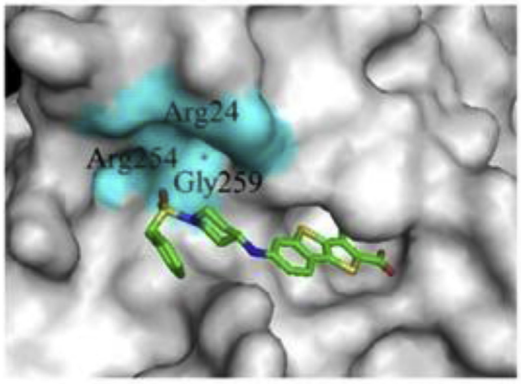


Fig. 42. X-ray crystal structures of PTP1B/compound complex (Fig. 42). PTP1B/5 (2B07); (Fig. 43) PTP1B/6 (2F6Z) The residues related to selectivity are labeled with black words and coloured by cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

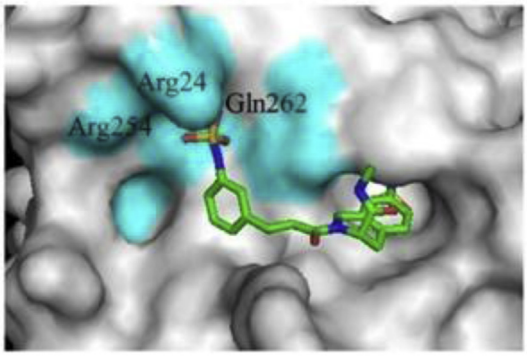


Fig. 43. X-ray crystal structures of PTP1B/compound complex (Fig. 42). PTP1B/5 (2B07); (Fig. 43) PTP1B/6 (2F6Z) The residues related to selectivity are labeled with black words and coloured by cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the physiological and pathophysiological actions of this enzyme [239]. Very recently, Iqbal and co-workers found the sulfonamide bearing sultams 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 IC_{50} 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 NO_2 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 Zn^{2+} 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 Zn^{2+} 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** ($IC_{50} = 2.40 \pm 0.01$ μM) (Fig. 40) was found to be the most potent which was twenty folds more active than the reference standard drug. Compound **323** ($IC_{50} = 14.55 \pm 0.30$ 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 coworkers 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 IC_{50} 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 **4e** also showed strong 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].

Moretto et al. identified a novel pyridothiophene inhibitor of PTP1B with a K_i 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,

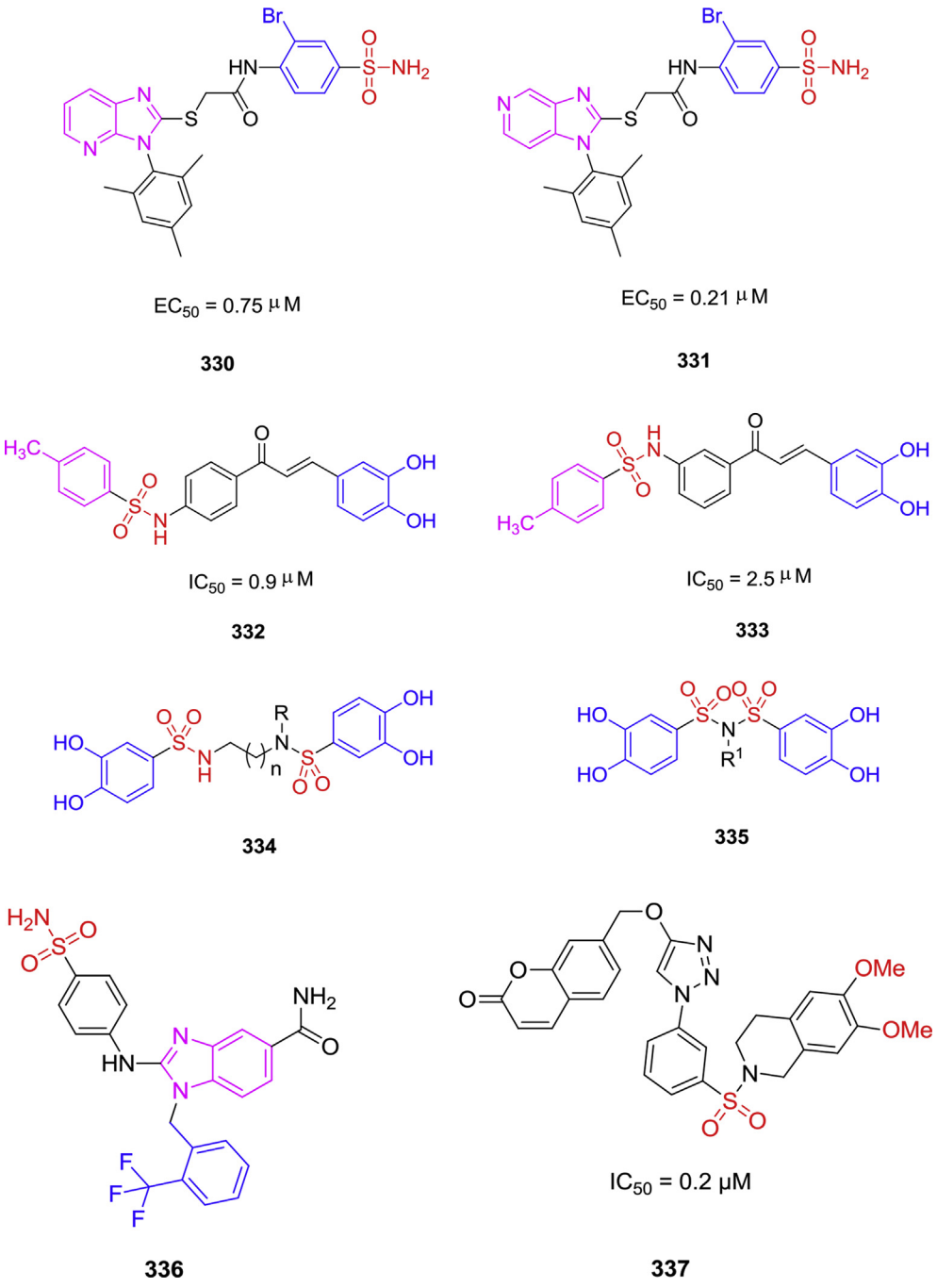


Fig. 44. Sulfonyl or sulfonamides showed diverse biological properties.

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 μM and 0.21 μM, 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 μM [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 bisarylsulfonamide **334** (Fig. 44) or sulfonimide **335** (Fig. 44) which showed potent PAI-1 inhibitory activity. Compound **334** (IC_{50} = 0.284 μM) and **335** (IC_{50} = 0.594 μM) 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 μM). The SAR revealed that the presence of 1-benzylic

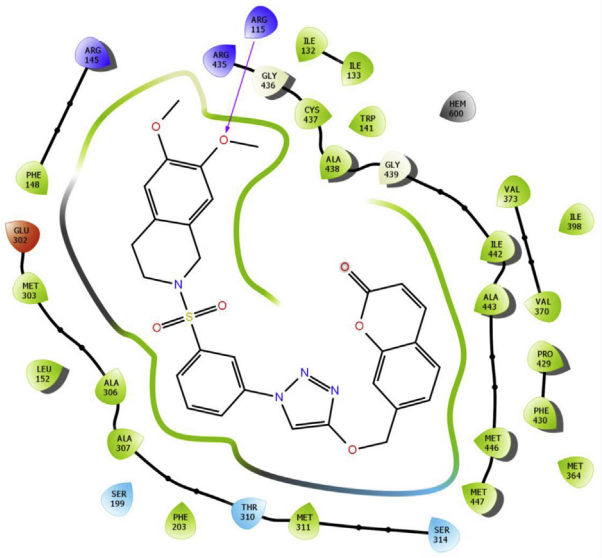


Fig. 45. 2D-ligand protein interaction scheme of compound **337** (PDB code: 3EQM).

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, Prachayasittikul 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 ($IC_{50} = 0.2\ \mu M$) 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** was arranged in such a way to appropriately form hydrogen bonding of the sulfonyl group with the amino group of Ala306 and Ala307 as well as hydrogen bonding of oxycoumarinyl 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 coumarinyl 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-coumaryloxymethyl at position 4 of the triazole ring, and *m*-substitution of triazole and sulfonyl 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 (S^{VI} 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 (S^{VI} 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.

Acknowledgements

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