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Review Article

SULFONES: AN IMPORTANT CLASS OF ORGANIC COMPOUNDS WITH DIVERSE BIOLOGICAL ACTIVITIES

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ABSTRACT

Sulfones have been studied broadly for various biological activities primarily as anti-inflammatory, antimicrobial, anticancer, anti-HIV, antimalarial, and anti-inflammatory. The review focused on the biological activity of various sulfones on different therapeutic targets. The aim of this review is to summarize the biological significance of sulfones, giving a comprehensive scenario and offer prospective in the development of new sulfone derivatives as therapeutic agents.

Keywords: Sulfone, Therapeutic agents, Biological activity.

INTRODUCTION

Sulfones are one of the members of organo sulfur compounds. Sulfones are S, S-dioxides of ether and represented by general structural formula R-S(O)$_2$-R', where R and R' are organic groups. The chemistry of sulfones has been explored due to their importance as synthetic intermediates for the production of a wide range of chemically and biologically active molecules. Sulfones are widely used as solvents, polymers, and biopharmaceutical agents. Several drug molecules containing sulfone groups are used for the treatment of leprosy, dermatitis herpetiformis, and tuberculosis. Researchers have also determined many therapeutic activities of sulfone containing compounds, including antibacterial, antifungal, antimalarial, cysteine protease inhibitor, anti-HIV, anti-proliferative, anti-cancer, protein phosphatase methylesterase-1 inhibitors, thyroid receptor antagonist, 11β-hydroxy steroid dehydrogenase type 1 inhibitors, M_1 positive allosteric modulators, cyclic nucleotide-gated channel agonist, EPAC2 antagonist, anti-inflammatory activity, PI3K/Akt/mTOR signaling pathways inhibitors, γ-secretase inhibitors, β-lactamase inhibitors and gelatinase inhibitors. In this review, we will briefly summarize the various sulfones reported in the literature over the past two decades and furthermore focus will be on the biological and pharmaceutical applications of these compounds.

Sulfones- anti-inflammatory activity

A series of 5-aryl-3-alkylthio-1,2,4-triazoles and corresponding sulfones (Fig.1) were synthesized and evaluated for their anti-inflammatory-analgesic activity by Tozkoparan *et al.*[1]. Many compounds of this series displayed potential anti-inflammatory-analgesic activity with minimum ulcerogenic risk.

In comparison to alkyl thio analogues the corresponding alkyl sulfones derivatives were reported as more potent anti-inflammatory-analgesic agents.

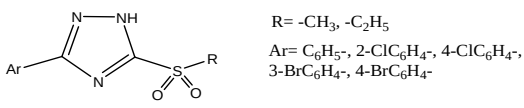


Fig. 1

Hwang *et al.* in 2011 reported a new series of molecules by combining diarylpyrazole, a COX-2 pharmacophore and urea; a soluble epoxide hydrolase (sEH) phramacophore (Fig. 2) and reported their inhibitory activity on both Cox-2 and sEH *in vitro* and *in vivo* [2].

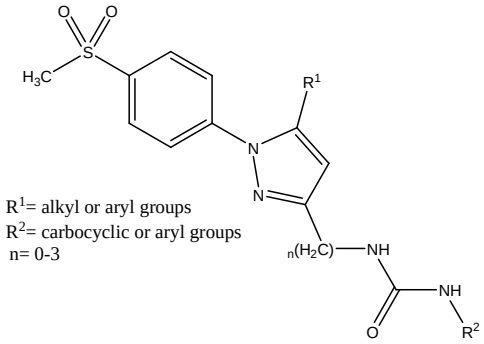


Fig. 2

Shaaban *et al.* synthesized 21 analogues of 4,5-dihydrothieno[*3,2-e*][1,2,4]triazolo[*4,3-a*]pyrimidine-2-carboxamide series (Fig.3) and reported their biological activity as anti-inflammatory and analgesic agents [3]. The compounds were evaluated for their anti-inflammatory activity by using acute and subacute model with diclofenac Na as reference. The results revealed that the sulfonyl analogues exhibited better anti-inflammatory activity, then its corresponding sulfanyl analogues. Further to rationalize the biological results the methyl and benzyl sulfonyl analogues with high anti-inflammatory activity was docked on human COX-2.

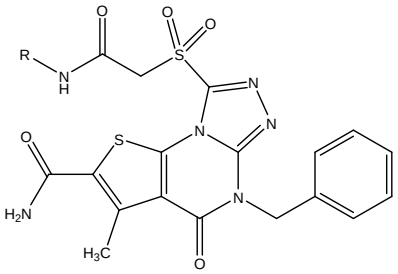


Fig. 3

Sulfones-antimicrobial activity

Curti *et al.* reported the one pot-microwave synthesis of sulfone derivatives in water [4]. The modified microwave irradiation method provided the desired product in 30 min and with good yields. These compounds were evaluated for their antibacterial and

antifungal activity and few sulfone derivatives (Fig.4) of this series depicted promising antimicrobial activity.

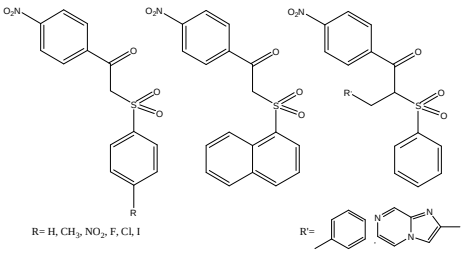
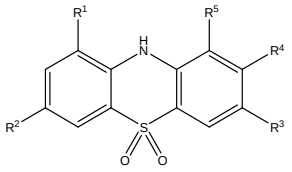


Fig. 4

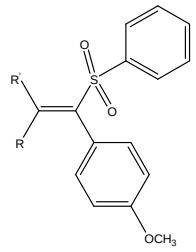
Dixit *et al.* have synthesized a series of fluorinated 10*H*-Phenothiazines and their sulfone derivatives (Fig.5). The compounds were tested for antimicrobial activity and all the compounds showed good to moderate results [5].



R^1= H, F, $(CH_3)_2CH$; R^2= H, $(CH_3)_2CH$; R^3= H, NO_2; R^4= H, F; R^5= H, F

Fig. 5

Kumar *et al.* reported the efficient and selective oxidation of sulfide into sulfoxides and sulfones (Fig. 6) and their *in vitro* antibacterial activities against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa* and antifungal activities against *Aspergillusniger* and *Candida albicans* [6].



R = H, Br, C_6H_5, $C_6H_5SO_2$; R' = H, Br, C_6H_5, $C_6H_5SO_2$

Fig. 6

Pilyugin *et al.* synthesized a series of bis-(2-arylcarbonylamino-1*H*-benzimidazol-5-yl) sulfones (Fig.7) by reacting the corresponding substituted benzoyl chloride with sodium cyanamide to afford N-cyanobenzamide and further treating the prepared N-cyanobenzamide with 3,3',4,4'-tetraaminodiphenyl sulfone in acid medium [7]. The synthesized compounds were screened for fungicidal activity.

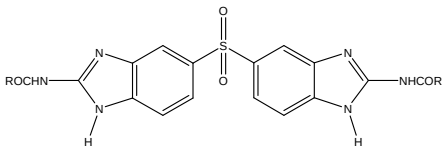


Fig. 7

Stecoza *et al.* reported the synthesis, characterization and antimicrobial activity of derivatives of 6,11-dihydrodibenzo[b,e] thiepin 5,5 dioxide [8]. These cyclic sulfones (Fig.8) exhibited significant antimicrobial activity, with MICs values ranging from 15.6 µg/ml to 250 µg/ml.

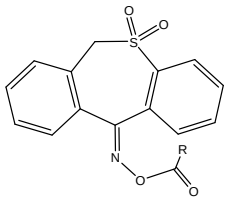


Fig. 8

Barbuceanu et al. [9] reported the antimicrobial activity of a series of S-alkylated 1,2,4-triazoles (Fig.9) which were synthesized by alkylation of sulfone bearing compound *i. e.* 5-{4-[(bromophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones with various alkylating agents such as ethyl bromide, phenacyl bromide and ethyl chloroacetate. These compounds were evaluated by using different standard microorganism and showed promising results in comparison to parent triazoles and ampicillin.

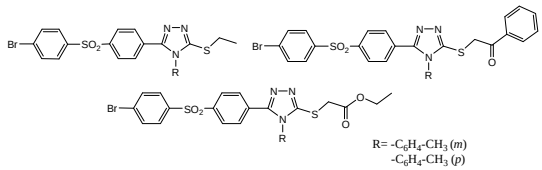


Fig. 9

Kudryavtsev *et al.* reported the *in vitro* inhibitory activity of the *Staphylococcus aureus* sortase SrtA transpeptidase by aseries of *cis*-5-phenyl prolinates [10]. In these compounds the fourth position of the pyrrolidine ring was functionalized by electron withdrawing groups such as vinyl sulfone (Fig.10) and nitrile group. The compounds were synthesized by performing 1,3-dipolar cycloaddition reaction of an arylamino ester with divinylsulfone and acrylonitrile. Compounds inhibited *S. aureus* sortase Srt A irreversibly by modification of enzyme Cys 184 and thus shows promising future as antibacterial and antivirulence agent.

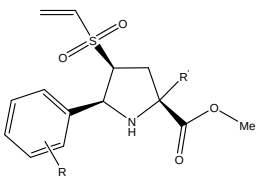
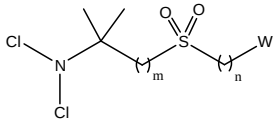


Fig. 10

Low *et al.* synthesized sulfone-containing analogues (Fig.11) of taurine-based chloroamines and explored their structure activity relationship for antimicrobial activity against *Escherichia coli, Staphylococcus aureus* and *Candida albicans* [11]. The stability of these compounds in aqueous solution was maintained by incorporating quaternary ammonium or sulfonate group.



m= 1, 2, 3
n = 0, 2, 3, 8
W= SO_3H, NMe_3^+

Fig. 11

A series of phthalyl substituted aryl sulphones (fig. 12) was synthesized from phthalimide and evaluated for their antibacterial and antifungal activity by Soni *et al.* [12]. The compounds were screened against the pathogenic strains *E. coli, S. aureus* and *S. typhii* for antibacterial activity and against *A. niger, Penicillium sp.* and *C. albicans* for antifungal activity.

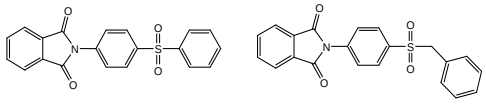


Fig. 12

Guruswamy *et al.* synthesized β-hydroxy benzimidazolyl sulfones (Fig.13) containing 7-piperazine fluoroquinolones by doing selective oxidation in the presence of ammonium molybdate catalyzed H_2O_2. The antimicrobial activity of synthesized compounds was evaluated against different bacteria and fungi strains and many of the compounds showed significant activity [13].

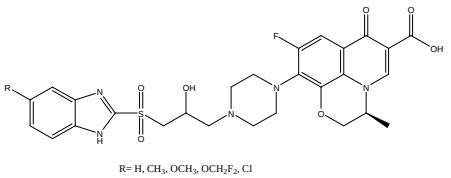


Fig. 13

Synthesis of a series of 2,5- disubstituted 1,3,4-oxadiazoles by cyclocondensation of aromatic carboxylic acids with arylsulfonyl propanehydrazide were done by Kumar *et al.* [14]. Several compounds showed promising antimicrobial activity (fig. 14).

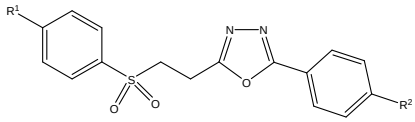


Fig. 14

Wani *et al.* in 2014 synthesized diaryl sulfones (Fig.15) by reacting aromatic substrate and aromatic sulphonyl chlorides in the presence of anhydrous aluminum chloride and screened them for antibacterial activity, individually, and in combination with trimethoprim [15]. They performed the QSAR study and identified the physicochemical parameter/s contributing towards the antibacterial activity of diaryl sulfones.

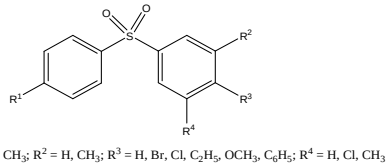


Fig. 15

Sulfones- anti HIV activity

Meadows *et al.* reported a series of vinyl geminal disulfones (Fig.16) as HIV-1 inhibitors [16]. To analyze the effect of structure on inhibitory mechanism a range of compounds bearing different ring substituents was synthesized by reacting bis-phosphonate reagent and an appropriate aromatic aldehyde under Horner-Emmons-Wadsworth reaction conditions. Inhibitors possessing electron withdrawing substituents or no substituents on the aromatic rings displayed promising cytotoxicity and antiviral activity.

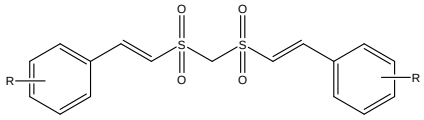


Fig. 16

Sulfones- antiproliferative activity

Usera *et al.* synthesized trifluoromethyl, methyl and isopropyl sulfone analogues of 1α,25-dihydroxyvitamin D_3 (fig. 17) and reported their comparison of *in vitro* antiproliferative activities and *in vivo* calcemic activities [17]. By comparing their *in vitro* antiproliferative activities, it was evident that trifluoromethylsulfone analogue showed the maximum whereas methyl sulfone analogue minimum activity and their antiproliferative activity increases in the following order CH_3<*t*-Bu≅i-Pr<CF_3. In comparison to calcemic *t*-butyl sulfone analogue the methyl sulfone and triflorimethyl sulfone showed desirable low calcemic levels.

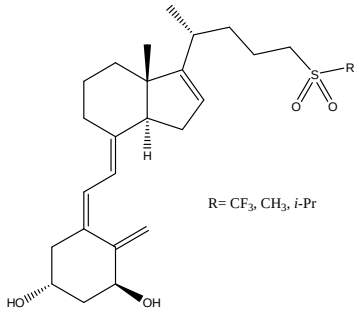


Fig. 17

Barbosa *et al.* replaced the alkene spacer group between the two aromatic rings of antitubulin agent combretastatin A-4 by sulfide spacer using the coupling reaction between iodobenzene and thio phenol [18]. The further sulfide group was oxidized to sulfoxide and sulfone using m-CPBA. The compounds (Fig.18) were evaluated for antiproliferative and antitubulin activity and comparative study with CA4 for inhibitory effect on cell growth, tubulin polymerization, and the binding of [^{3}H]colchicine to tubulin were also reported.

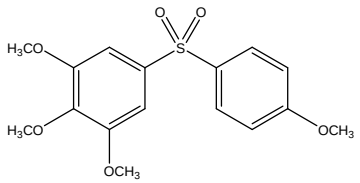


Fig. 18

Cohen *et al.* reported the antiproliferative activity of sulfonyl derivatives of 5-nitro-1,3-thiazole series [19]. The compounds were synthesized by reacting 4-chloromethyl-2-methyl-5-nitro-1,3-thiazole with different sulfinate anions in water and under microwave irradiation. The promising antiproliferative activity was observed for these compounds (Fig.19) towards the HepG-2 cell lines in comparison to the CHO cell lines.

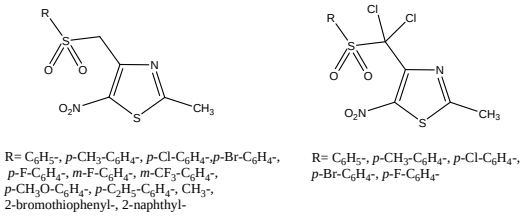


Fig. 19

Sulfones- anticancer activity

Al-Said *et al.* synthesized sulphonyl compounds bearing biologically active 1,3-dihydropyridine, chromene and chromenopyridine moieties [20]. These compounds (Fig.20) were evaluated against human breast cell line (MCF7) by using dextrorubicin as reference drug and exhibited potential anticancer activity. Docking study of these compounds on the active site of farnesyltransferase and arginine methyl transferase were performed and results provided the support in understanding the mechanism of action of these compounds as anticancer agents.

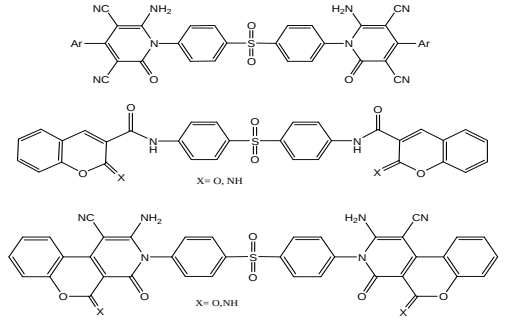


Fig. 20

Sulfones- antimalarial activity

Rosenthal *et al.* have synthesized 6 dimeric trioxane sulfones in 5-6 step from the natural trioxaneartemisinin [21]. These series of compounds (Fig.21) showed promising activity in malaria infected mice and were effectively and selectively cytotoxic to cancer cell lines.

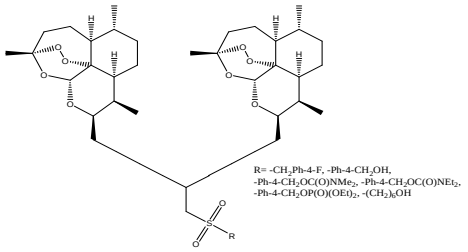


Fig. 21

Capela *et al.* prepared a series of artemisinin-dipeptidyl vinyl sulfone hybrid molecules by combining dipeptidyl vinyl sulfone and artemisinin cores and screened them for antiplasmodial activity and falcipain-2 inhibition [22]. These compounds (Fig.22) displayed potent antiplasmodial activity in the range of 2 to 5 nM (IC_{50}) against a panel of *Plasmodium falciparum* chloroquine-sensitive and multidrug-resistant strains and additionally in thelow micromolar range were able to inhibit falcipain-2.

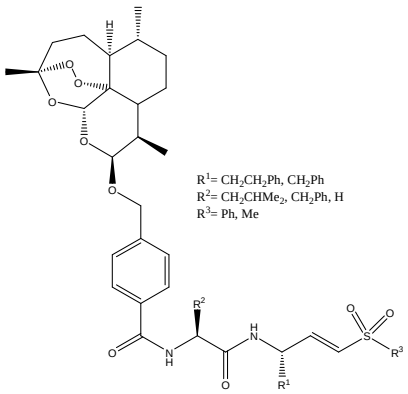


Fig. 22

Lee *et al.* identified several sulfonyl compounds as antimalarial agents by targeting the fatty acid biosynthesis enzyme, β-ketoacyl-acyl carrier protein synthase III (PfKASIII). Two classes of compounds, i.e. benzene-sulfonyl-naphthalenes and benzene-sulfonyl-benzenes (Fig.23) displayed potency to inhibit PfKASIII and parasite growth [23].

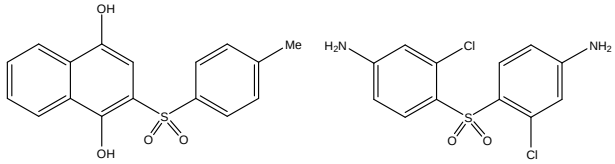


Fig. 23

Sulfones- cysteine protease inhibitors

Shenai *et al.* have reported the inhibition of the *Plasmodium falciparum* cysteine proteases falcipain-2, falcipain-3, and parasite development by 39 new peptidyl vinyl sulfones (Fig.24) and established their structure-activity relationships (SAR) [24].

The compounds were synthesized by using Horner-Wads-worth-Emmons reaction and standard peptide coupling conditions.

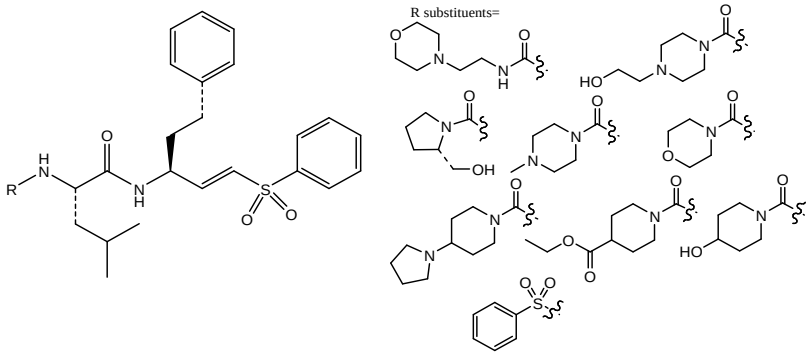


Fig. 24

Chen *et al.* in 2008 used the major cysteine protease of Trypanaosoma cruzi to design and synthesize conformationally constrained inhibitors for the treatment of Chaga's disease [25]. Vinyl sulphone containing macrocyclic trypanosomal cysteine protease inhibitors (Fig.25) were synthesized by using a ring closing metathesis reaction. These compounds were evaluated against cruzain and rhodesain, a closely related cysteine protease.

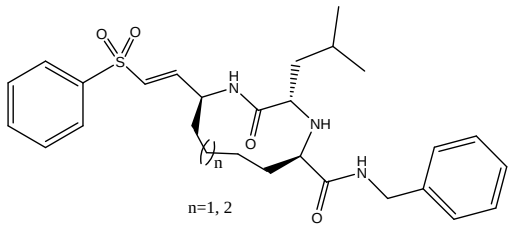


Fig. 25

In 2008, Brak *et al.* identified a new class of nonpeptidic inhibitors of cruzain [26]. The 2,3,5,6-tatrafluorophenoxymethyl ketone (Fig.26) was reported as apotent irreversible inhibitor that completely eradicates *T. cruzi* parasites in cell culture. Further to convert the most efficient substrates to inhibitors several pharmacophores such as vinyl sulfone, β-chloro vinyl sulphone, acyl- and aryloxymethyl ketone were explored. The β-chloro vinyl sulphone pharmacophore led to the key mechanistic insight and resulted in the development of nonpeptidic inhibitors.

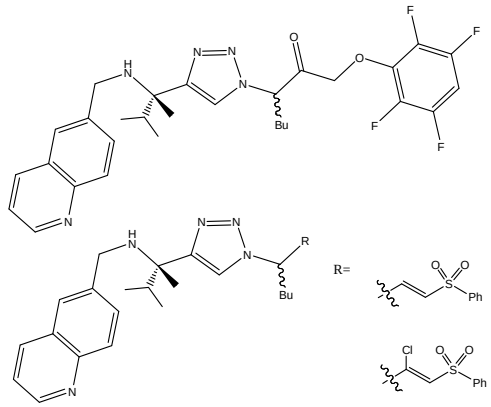


Fig. 26

In 2013, Chen *et al.* reported that WRR 483 (Fig.27), an analog of K11777(a potent inhibitor of cruzain), an effective cysteine protease inhibitor with trypanocidal activity in cell culture and animal model. The crystal structure of WRR 483 bound to cruzain provided the evidence that its mode of action is by targeting the active site of cruzain [27].

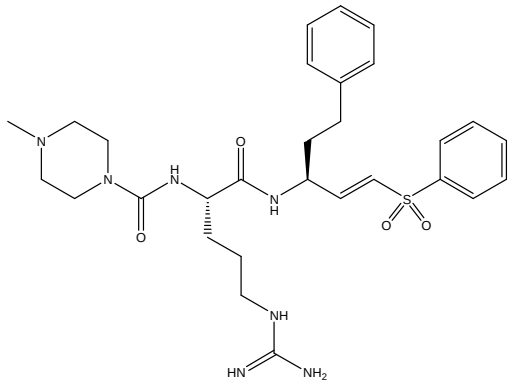


Fig. 27

Bryant *et al.* discovered the two new classes of non-peptidic vinyl sulfone (Fig.28) that inhibit cysteine protease in vitro and inhibit the growth of *T. brucei* parasites in culture. The co-crystal structure of non peptidic vinyl sulfone inhibitor bound to cruzain reveals the importance of targeting S2 and S3 subsites of parasite cysteine proteases [28].

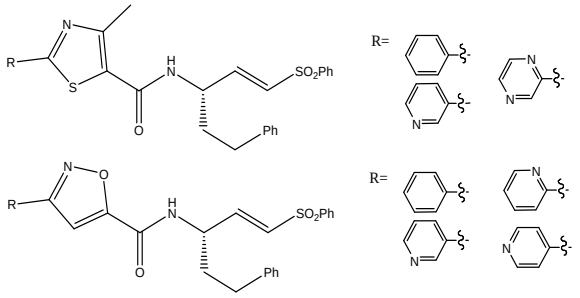
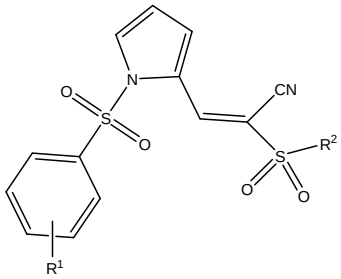


Fig. 28

Sulfones- protein phosphatase methylesterase-1 (pme-1) inhibitors

The reports suggest that the serine hydrolase protein phosphatase methylesterase-1 (PME-1) is involved in the regulation of the methyl esterification state of protein phosphatase 2A (PP2A) and thus can act as an attractive therapeutic target for cancer and Alzheimer's disease. Bachovchin *et al.* synthesized a series of compounds of sulfonyl acrylonitrile scaffold (Fig.29) and reported their selective PME-1 inhibitory activity [29].



R^1= H, 3-CN, 4-CN, 4-Cl, 3-NO_2, 4-NO_2, 2,3,4,5,6-$(F)_5$
R^2= Me, *t*-Bu, Ph, 4-F-Ph

Fig. 29

Sulfones- thyroid receptor antagonist

Hwang *et al.* in 2011 reported the methylsulfonylnitrobenzoates (MSNB's) (Fig. 30A) as a new class of thyroid receptor antagonist that inhibit the interaction of the thyroid hormone with its coactivators by irreversibly modifying cysteine 298 of thyroid hormone receptor [30]. In a further study, they synthesized series of 5-carboxamide-sulfonylnitrophenylthiazoles (SNPTs) and 4-carboxamide-SNTPs (Fig.30B) by replacing the ester linkage of MSNBs with a thiazole moiety and evaluated them for antagonism toward thethyroid receptor-coactivators [31].

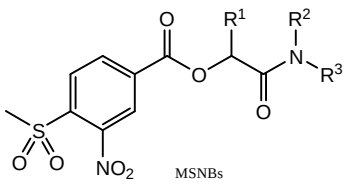


Fig. 30A

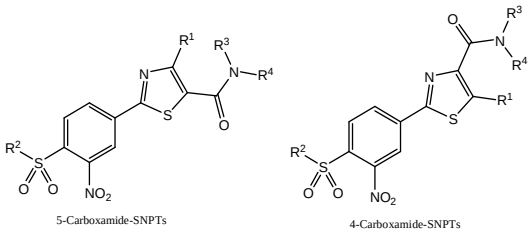


Fig. 30B

Sulfones- 11β-hydroxysteroid dehydrogenase type 1 inhibitors

During the last decade the pharmaceutical companies were highly interested in the development of small molecules as selective inhibitors of 11-β-Hydroxysteroid Dehydrogenase Type 1(HSD 1) for the treatment of type 2 diabetes, obesity and other metabolic disorders. X. Su *et al.* synthesized series of adamantly ethanone pyridyl derivatives (Fig.31) by linking pyridyl ring to an adamantly ethanones, through sulfur, oxygen, sulfoxide, sulfoneand amide linker [32]. These compounds were evaluated for their inhibitory activity against human and mouse11β-HSD1. Adamantyl ethanone pyridyl derivatives with sulfone linker were identified as potent and selective inhibitors of human and mouse 11β-HSD1.

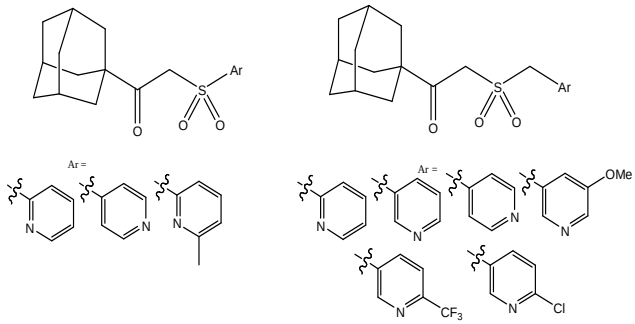


Fig. 31

Sulfones- M_1 positive allosteric modulators

G-protein coupled receptors (GPCRs) family members' muscarinic acetylcholine receptors (mAChRs) contain five subtypes known as M_1 –M_5. All five subtypes are considered as therapeutic targets for various peripheral and CNS pathologies. Reid *et al.* reported several compounds on the novel indole scaffold bearing sulfone group (Fig.32) as M_1 positive allosteric modulator (PAM) [33].

One of the compounds of this series, ML169 showed potent, selective and brain penetrant M_1 PAM activity and *in vitro* results demonstrate promising brain to plasma ratio in comparison to prototypical M_1 PAM, BQCA.

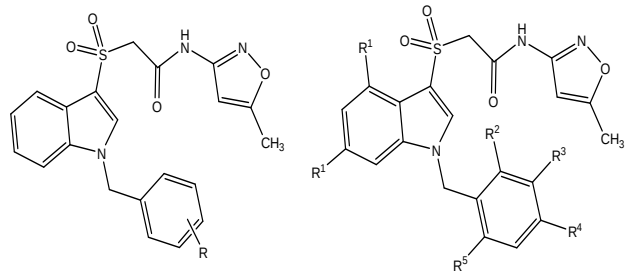


Fig. 32

Sulfones- cyclic nucleotide-gated channel agonist

The Cyclic nucleotide-gated (CNG) channels play very important role in olfactory sensory neurons and retinal photoreceptors. Changes in the concentration of cyclic nucleotide due to odorant and light produce electric signals that are transmitted to the brain. Continuous efforts are being made to develop pharmacological agents in order to explain the role of CNG channels in cellular signaling. In this regard Strassmaier *et al.* designed and synthesized several cGMP derivatives by doing a modification at N-1 and N-7 position [34]. Their results displayed that the two novel sites of cGMP *i.e.* N1 and N7 (Fig. 33) are acquiescent for further variation in order to develop novel CNG channel agonist and to understand the cGMP and CNG channels interactions.

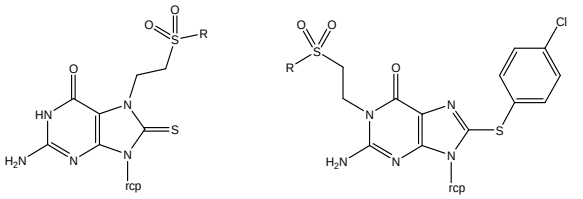


Fig. 33

Sulfones- EPAC2 antagonist

EPAC represents two isoforms of exchange protein directly activated by cAMP *i.e.* EPAC1 and EPAC2 and are involved in number of intracellular processes and are promising targets for the development of new therapies for human disorders such as diabetes, heart disease and cancer. H. Chen*et al.* designed and synthesized several analogues on three different scaffolds *i.e.* i) diarylsulfone scaffold using Friedal-Crafts sulfonylation, Suzuki coupling and Mitsunobu reactions ii) N,N-diarylamines iii) arylsulfonamides and reported their potency, selectivity towards EPAC-2 and established structure activity relationship [35]. Through hit to lead optimization process these compounds (Fig.34) exhibited potent and selective antagonist activity for EPAC-2.

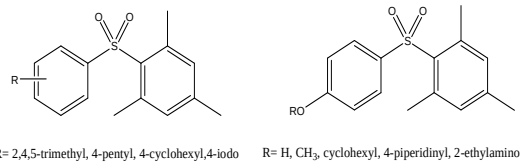


Fig. 34

Sulfones- PI3K/Akt/mTOR signaling pathways inhibitors

The PI3K/Akt/mTOR signaling pathways are really important in cancer biology due to their involvement in the regulation of cell growth, proliferation and survival, angiogenesis and therefore offer an attractive therapeutic target for tumor growth inhibition [36].

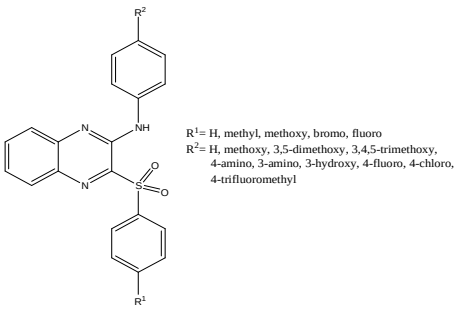


Fig. 35

A series of novel 2-arylamino-3-(arylsulfonyl) quinoxalines (Fig.35) was synthesized as PI3Kα inhibitors by Wu *et al.* in 2011 [37]. Most of the targeted compounds of this series displayed favorable cytotoxicities and excellent cellular potencies.

Finlay and his group in 2012 reported the synthesis and structure activity relationship study of a series of sulfonyl-morpholino-pyrimidines (Fig.36) as selective mTOR kinase inhibitors [38].

To increase the mTOR potency and selectivity over PI3K two libraries of compounds was prepared by changing the pyridyl moiety and by using different substituents on sulfone moiety. Introduction of 5-indole and urea moiety increases the mTOR inhibition in both enzyme and cellular assays.

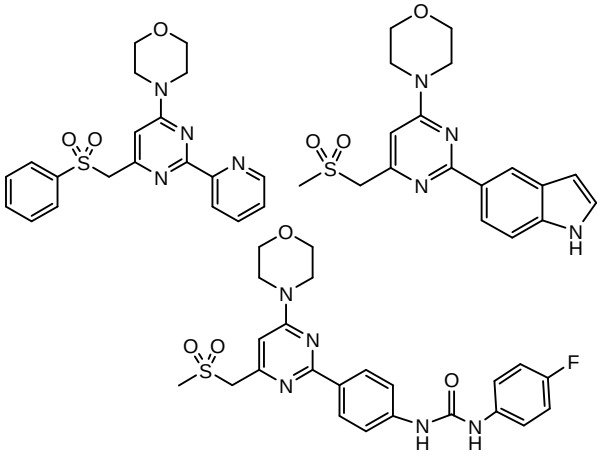


Fig. 36

In 2012, Liu *et al.* restricted the movement of the sulphonylside chain through the design and synthesis of conformationally restricted cyclic sulfones(Fig.37) and reported their potency and selectivity asmTOR kinase inhibitors [39]. One of the compounds of this series PF-05139962 showed significant mTOR inhibition, more than 500 fold selectivity against PI3Kα, cellular potency and *in vitro* ADME profile.

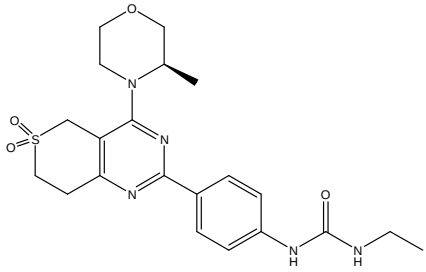
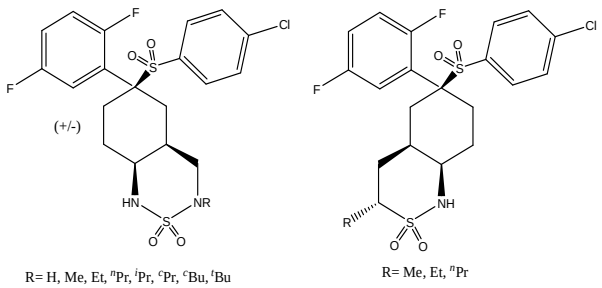


Fig. 37

Sulfones- γ-secretase inhibitors

Shaw *et al.* reported the synthesis of 3,4-fused cyclohexyl sulfones (Fig.38). The compounds of this series were reported as potent γ-secretase inhibitors [40]. Structure activity relationship was established for these series of compounds and result provided the compounds with significantly reduced brain Aβ in transgenic mouse study and therefore exhibited potential as possible treatments for Alzheimer's disease.



R= H, Me, Et, ^{n}Pr, ^{i}Pr, ^{c}Pr, ^{c}Bu, ^{t}Bu

R= Me, Et, ^{n}Pr

Fig. 38

Sulfones- β-lactamase inhibitors

The main mechanism behind the bacterial resistance to β-lactam antibiotics is β-lactamase production. One of the strategies to overcome β-lactamase mediated resistance is to use suicide inhibitors that inhibit β-lactamase. Setti*etal*. synthesized series of 2β-alkoxycarbonylpenicillanic acid sulfone derivatives (Fig.39) by modifying the C (2) carbon atom of penamsulfone as broad spectrum β-lactamase inhibitors with increased cephalosporinase activity [41].

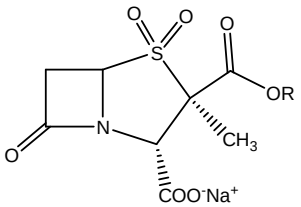


Fig. 39

Phillips *et al.* have synthesized a series of new penamsulfone derivatives (Fig.40) enclosing a 2β-substituted-oxyimino and -hydrazine substituents and reported their β-lactamase inhibitory activity against class A and C β-lactamases enzymes [42]. The oxime containing penamsulfones showed promising activity against *Escherichia coli* TEM-1 and *Klebsiella pneumonia* cefotaximase (CTX-1) enzymes, however displayed moderate activity against *Pseudomonas aeruginosa* 46012 cephalosporinase. In comparison to this 2β-substituted hydrazone derivatives exhibited very less activity against these enzymes. The inhibitors of this series were able to enhance the antibacterial activities of piperacillin (PIP) and ceftazidime (CAZ) mostly against TEM-1 and CTX-1 producing bacterial strains.

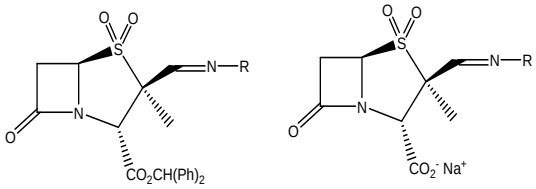


Fig. 40

In order to understand the mechanism of action of known inhibitors and to obtain more potent compounds, 6β-(hydroxymethyl) penicillanic acid sulfone (6β-HM-sulfone) (Fig.41) was designed and synthesized by Papp-Wallace *et al.* in 2012 [43]. The sulfone was tested against isolates expressing the class A TEM-1 β-lactamase and clinically important variant of the AmpC cephalosporinase of *Pseudomonas aeruginosa*, PDC-3. 6β-HM-sulfone inhibited TEM-1 with an IC_{50} of 12 ± 2 nM and PDC-3 with an IC_{50} of 180 ± 36 nM.

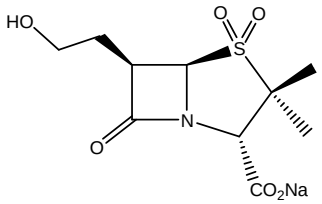


Fig. 41

Sulfones- gelatinase inhibitors

The enzymes gelatinases are family members of matrix metelloproteinases (MMPs) and have been associated with many pathological and physiological functions, including cancer and

cardiovascular diseases. SB-3CT is considered as potent and selective gelatinase inhibitors both *in vitro*. To support the mechanistic study of this inhibitor Lee *et al.* performed the conformational analysis of SB-3CT and its two methyl substituted (Fig.42) by using x-ray crystallography and molecular dynamics simulation [44]. In 2009, they reported that thiirane ring act as a caged thiol and unmasked selectively in the active site of gelatinases [45].

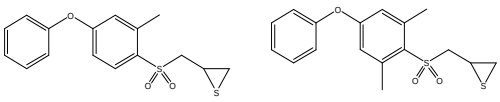


Fig. 42

Further to improve metabolic stability and to support mechanistic study, α-methyl variants of SB-3CT (fig. 43) were synthesized and evaluated as potent gelatinases inhibitors [46]. Introduction of methyl group α to the sulfonyl moiety prohibited the oxidation at that position as well as prevented the hydroxylation of the terminal phenyl ring. These compounds showed the ability to inhibit MMP-2, MMP-9 and MMP-14 and thus considered important for cancer progression.

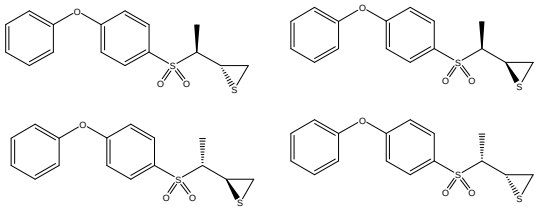
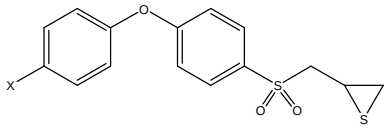


Fig. 43

In 2011 Gooyit *et al.* reported the selective water soluble gelatinase inhibitor pro drugs (fig. 44) with promising pharmacokinetic properties and thus making them suitable for intravenous administration in the treatment of acute gelatinase-dependent diseases [47].



X= OH, NH_2

Fig. 44

CONCLUSION

As far as my information this is the first review in last two decades, where various biological activities of sulfone derivatives have been summarized. It is evident from this review that sulfone group is having diversified application and immense potentiality. Sulfone group has attracted much attention in medicinal chemistry and provided numerous potent sulfone derivatives for different therapeutic targets. We can conclude that this review will provide complete knowledge to the researchers about the biological importance of sulfone derivatives, which further help in the design and synthesis of more number of sulfone derivatives with strong effect in the development of drug candidates for many fatal diseases.

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CONFLICT OF INTERESTS

Declared None

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