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Synthesis, Reactions and Medicinal Importance of Cyclic Sulfone Derivatives: A Review

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Abstract

Sulfones or the cyclic sulfones are the type of organosulfur compounds that attract the special interest to organic chemists. Vast applications are observed in different fields with these types of sulfone containing compounds and their derivatives like in medicinal chemistry and also give the importance to many kinds of biological activity. The sulfones and their derivatives are used in many other fields as pharmaceutical and polymeric agents. Sulfone containing compounds are also used for the treatment of different diseases like dermatitis herpetiformis, leprosy, tuberculosis and others. The researchers have been giving much concentration to synthesize many types of sulfone compounds because of their various strong medicinal activities like as biological, antimalarial, antimicrobial, anti-inflammatory, anticancer, anti-HIV, and anti-inflammatory and in other sectors also. These kinds of vast importance encourage us to study about the synthesis, reactions and applications of cyclic sulfones and their derivatives. The present article will provide some important information about the synthesis, reactions and applications of cyclic sulfone type compounds to the chemists to facilitate them in advance research works with more concentration which will be more beneficial for the society as well as for upcoming science generation.

Keywords: Cyclic sulfones; Anticancer activity; Biological activity; Medicinal chemistry

Introduction

The sulfone compound is formed by a sulfonyl group and with the attachment of two carbon atoms. The sulfur atom is connected with two oxygen atoms through double bond and with two carbon atoms through single bond [1]. That means, the sulfones are S, S-dioxides of ether which is represented by the general structural formula R-S(O)$_2$-R^1, where R and R^1 are organic groups. The cyclic sulfone compounds have some common criteria which gives the emphasis to the chemists as well as drug designers.

Among the various criteria like the strong H-bond acceptor sulfone compounds interacts with the potential biological targeted molecules. Various membered ring can fix the functional group easily to reduce the entropy of other molecules. Sometimes other groups are also present. Additionally, it is also possible to interact the biological compounds by H-bonding. There exists a distance between the H-bonding units.

There are many types of cyclic sulfone compounds. These may be different according to the number of ring in cyclic sulfones. Some simple six membered cyclic sulfone ring type of compounds are also formed. Sulfones are the major class of organosulfur compounds [2] that are used as the important intermediates in the synthetic organic chemistry [3]. There are many interest exist to develop different methods with the sulfone and their derivatives in the area of synthetic organic chemistry. Also, the subsequent transformation of the molecules can be done with the presence of sulfonyl functional group.

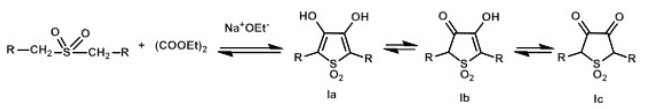
Cyclic sulfones, particularly, have some unique synthetic utilities. Various types of substituted sulfones are the important source for the conjugated dienes with the help of SO_2 extraction. These are used as the masked dienes for intramolecular type Diels-Alder reactions in various synthetic procedures [4-6]. It is also possible to construct cyclic olefins through the usage of cyclic sulfones ring [7-11] by the well-established Ramberg-Bäcklund reaction [12-15]. The biologically active molecules such as protease and β-lactamase inhibitors are also designed by doing good research of cyclic sulfones and their derivatives [16-19].

Although different methods for the synthesis of cyclic sulfones are exists [2,3], it is still highly required to do research for establishing more and more effective and well-organized approach for the synthesis of various ring sizes cyclic sulfones which will be so much effective in the field of biological as well as medicinal.

Literature Review

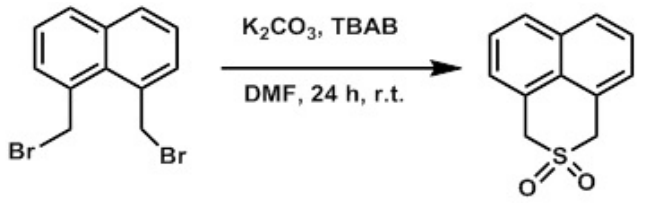
Synthesis and reactions of cyclic sulfones

The preparation of thiophene-l-dioxides in order to study the attack of free radicals on a vinyl sulfone group (-CH=CH-SO$_2$-) contained in a ring has been undertaken by Overberger et al. [20]. The condensation of ethyl oxalate with arylmethyl sulfones (R=o-naphthyl, phenyl, p-chlorophenyl) to give 2,5-diaryl-3,4-dihydroxythiophene-1-dioxides (I) is described in Scheme 1.



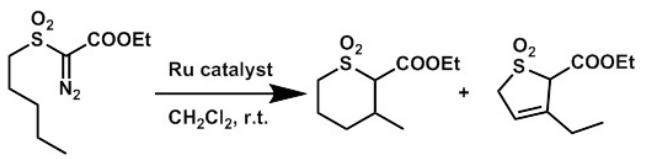
Scheme 1: Cyclic sulfones from the condensation of ethyl oxalate with arylmethyl sulfones.

A series of symmetrical sulfones were prepared by Kotha et al. [21] from rongalite (Scheme 2). It is mentioned that rongalite is the trade name of sodium hydroxymethanesulfinate or sodium formaldehydesulfoxylate which is commonly used in the textile industry as a decolorizing agent.



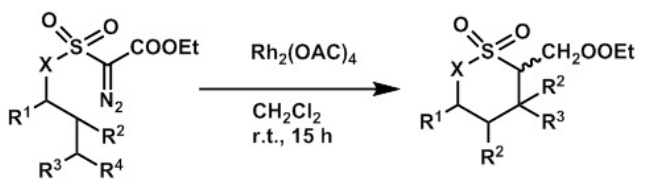
Scheme 2: Preparation of cyclic sulfone from rongalite.

The C-H insertion on the alkyl sulfonyl diazoacetate substrates has demonstrated by Jungong et al. [22]. The formation of five and six membered cyclic sulfones are shown here Scheme 3. The substitution is occurred in this procedure with the help of $Rh_2(pfb)_4$ catalyst. The produced thiofuran or thiopyran 1,1-dioxides can act as the important intermediates in the synthetic pathways.



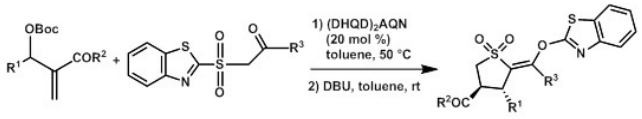
Scheme 3: Formation and catalyst effectivity on ive- *vs.* six-membered sulfone rings.

John and Novikov demonstrated the formation of six membered cyclic sulfones and sulfonates with the help of C-H insertion (Scheme 4) [23].



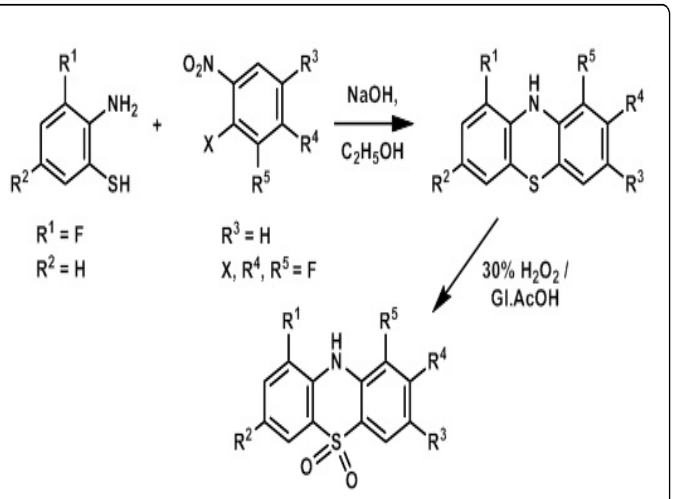
Scheme 4: Formation of six-membered cyclic sulfones by C-H insertion.

The researchers Chen et al. investigated and found the asymmetric allylic alkylation of Morita-Baylis-Hillman carbonates and β-keto sulfones through the catalysis of modified cinchona alkaloids [24]. The product implies an addition of rearrangement-sulfinate to formulate the highly functionalized five-membered cyclic sulfones which was done in the presence of DBU. The moderate to excellent enantioselectivity and good diastereoselectivity was also found (Scheme 5).



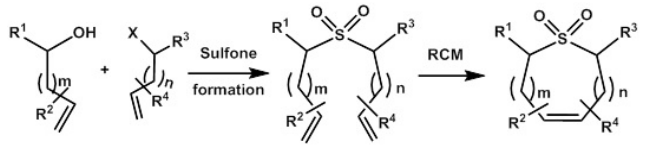
Scheme 5: Formation of chiral cyclic sulfones.

Phenothiazines are the important class of bioactive heterocycles. These belongs to a variety of pharmacological or biological activities [25-37] and their many derivatives are also used in the clinical purposes. These type of phenothiazines have been widely possess in various types of medicinal activities as antibacterial and antifungal, antivirals, aneshetic, anti-inflammatories, anticancer, tuberculostatic, CNS depressants, antipyretics, antidepressants, tranquilizers, antihistamines, diuretics, analgesics, neurolepitcs, sedatives, antipsychotics, anthelmintics, antiemetics, antiparkinson drugs. The newly synthesized 10H-phenothiazines and sulfone derivatives have been used for antimicrobial activity by Kerby Bauer procedure [38,39] as well as Dixit et al. [40] (Scheme 6).



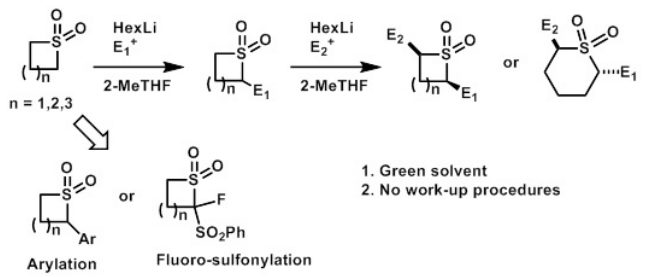
Scheme 6: Antimicrobial active 10H-phenothiazines and sulfone derivatives.

To synthesize the cyclic sulfones a novel and versatile strategy was constructed by Yao [41]. Here the ring-closing metathesis (RCM) of acyclic sulfones was followed. The cyclic sulfones were prepared from alkenyl alcohols and alkenyl halides by the functional group transformations (Scheme 7).



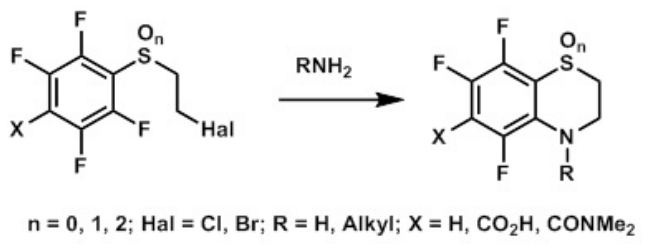
Scheme 7: Synthesis of cyclic sulfones by Ring-Closing Metathesis (RCM) technique.

Luisi R and his co-workers investigated the regioselective functionality of four- and six-membered cyclic sulfones (Scheme 8) [42] with the strategy of lithiation/electrophile trapping. They used here 2-Me-THF which is more eco-friendly than other solvents and a lithiating agent as n-hexyllithium which is safer than other alkyllithium compounds. A number of derivatives were prepared spanning a range of 5 log P units, and these were characterized through RP-HPLC for lipophilicity checking.



Scheme 8: Greener and efficient access for four- and six-membered cyclic sulfones.

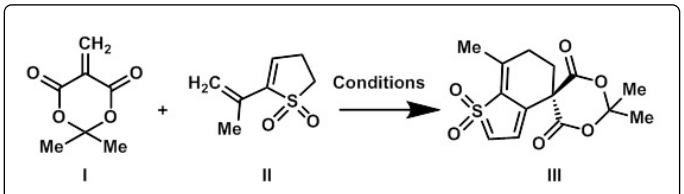
Kondratyev et al. [43] demonstrates a general synthetic approach to a variety of unsubstituted and 4-substituted 5,7,8-trifluoro-3,4-dihydro-2H-1,4-benzothiazines and the corresponding sulfoxides and sulfones starting from available [(2-haloethyl) sulfanyl]-2,3,5,6-tetrafluorobenzene derivatives (Scheme 9).



Scheme 9: formation of cyclic sulfones through the reaction of (2-haloethyl) polyfluorophenyl sulfides, sulfoxides, and sulfones in presence of ammonia or amines.

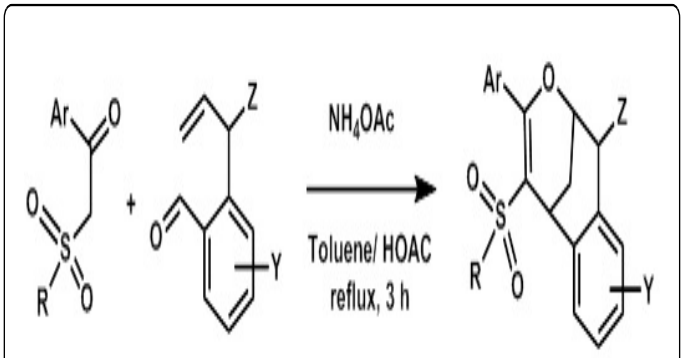
Synthesis of cyclic sulfones through Diels-Alder reactions

To find out various tri- and tetracyclic type compounds containing a fused tetrahydrothiophene 1,1-dioxide fragment, the Diels–Alder reactions with 2,3-dihydrothiophene 1,1-dioxide derivatives were used as dienophiles and dienes [44-49]. Some of the prepared compounds were found to exhibit a high antiphlogistic, antiulcer, and psychotropic activity together with low toxicity [50-52]. Shul'ts et al. [53] synthesized such compounds by the cycloaddition of 5-methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (I) [54] and 5-isopropenyl-2,3-dihydrothiophene-1,1-dioxide (II) [55]. The reaction of diene II with dienophile I was regioselective and found result in formation of 93% of adduct III (Scheme 10).



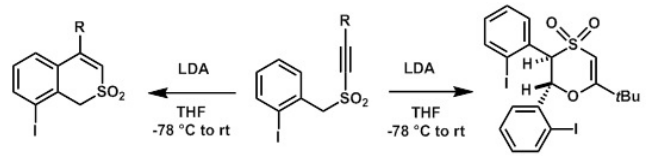
Scheme 10: Diels-Alder reactions of cyclic sulfones.

Recently, a one-pot easy-operational route for the synthesis of diversified carbocyclic or heterocyclic benzofused frameworks was developed by Chang et al. [56] with the functionalization of β-ketosulfones (α-sulfonyl ketones) [57,58] or o-formyl allylbenzenes (o-allyl benzaldehydes) building blocks under a series of domino benzannulation processes [59-62]. Knoevenagel condensation of active α-methylene compounds with carbonyl compounds has been described with the help of ammonium salts [63-67]. In particular, due to carbonyl compounds associating with an o-allyl arm such that the resulting intermediate (E)-3 has a chalcone motif we can proceed with further intramolecular annulation to provide the unexpected bridged skeleton with the oxabenzo [3.3.1] bicyclic core under single vessel conditions *via* a sequential intramolecular Diels-Alder cycloaddition (Scheme 11).



Scheme 11: Knoevenagel cyclocondensation procedure for the formation of cyclic sulfones.

The LDA-mediated intramolecular cyclization of selected benzyl alkyl sulfones was presented by the group of Schwan et al. [68]. They showed the direct or indirect formation of a carbanion at the benzylic position brought a new approach for the formation of ^{1}H-2-benzothiopyran S,S-dioxides [69]. The similarities and differences of this cyclization were found compared to anionic cyclizations with the dearomatization of aryl sulfones [70-74]. They attempted and found the way to prepare 5,6-dihydro-1,4-oxathiin S, S-dioxides (Scheme 12) [75].



Scheme 12: Divergent directions benzyl alkynyl sulfones cyclizations.

Biological, pharmaceutical and medicinal importance of cyclic sulfones

Sulfones are useful synthons for the construction of carbon–carbon bonds via anionic, cationic, and radical intermediates [76-81]. Fused or 3-substituted sulfolenes are a latent source of conjugated dienes. Therefore, they are useful partners in Diels-Alder reactions for the synthesis of complex synthetic targets containing six-membered rings [82-84]. Due to the electron-withdrawing nature of the sulfone moiety, neighboring methylene or methyl group(s) can be alkylated with various electrophiles. This unique reactivity coupled with the ease of desulfonylation has been exploited in several instances for the construction of various theoretically interesting and biologically active molecules [85].

Chiral cyclic sulfones are the key scaffolds in a number of pharmaceutically important compounds and natural products as those exemplified (Figure 1) [86-89], which exhibit broad biological activities such as inhibiting HIV-1 protease, hepatitis C virus, influenza neuraminidase, and human carbonic anhydrase II.

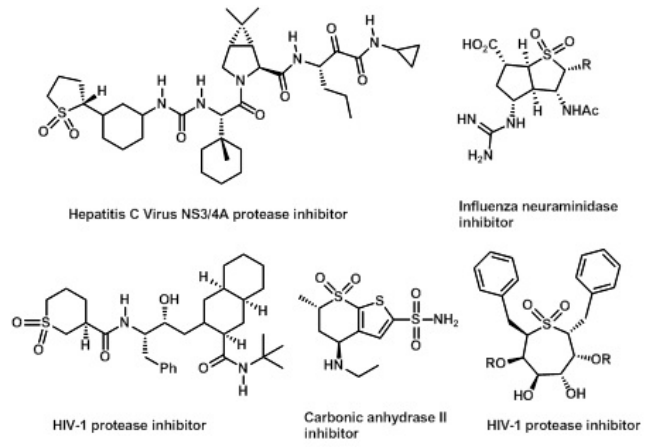


Figure 1: Cyclic sulfone containing compounds which showed strong biological activity.

Alzheimer's disease (AD) is one kind of severe disease by which the brain disorders occur and loss the intellectual and social skills. One of the major hypotheses for the progression of AD is that the extracellular accumulation of Aβ is the primary pathological event leading to neurodegeneration, dementia and ultimately death. The inhibition of Aβ production is so much needed to stop the progress of this severe disease. The Aβ is produced by the result of β-amyloid precursor protein (β-APP) cleavage from two proteases. The first cleavage of β-APP by β-secretase produces a β-APP C terminal fragment which is cleaved within the cell membrane by the aspartyl protease γ-secretase to release Aβ. The identification of a selective orally active γ-secretase inhibitor has been targeted as an attractive way to test the amyloid hypothesis [90,91].

Scientist Shaw D and his co-workers found the highly potent γ-secretase inhibitors which identified 3,4-fused sulfamides, sulfonamides and sulfone (Figure 2). They investigated and found the substituted SAR as the potential treatment for these types of severe Alzheimer's diseases through these series which help to reduce the brain Aβ [92].

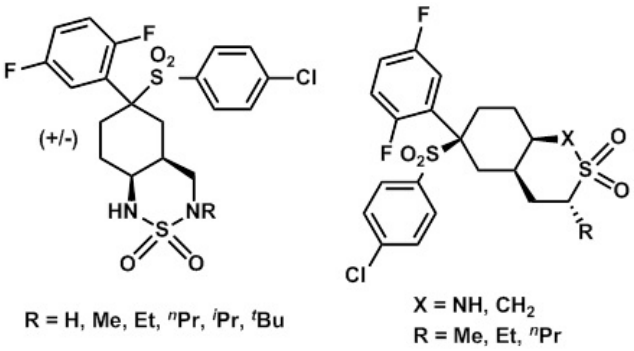


Figure 2: Fused sulfones which act as highly potent γ-secretase inhibitors.

More than 170 million people are afflicting through the infection of Hepatitis C virus (HCV) worldwide [93-95]. The severe problem like liver failure and liver cancer are infecting by this chronic HCV. The hospitals and health care centers are increasing the budget of the cost because of increasing the number of patients infected by HCV. The peginterferon and ribavirin are the result through the present HCV care [96,97]. Therefore, to vanish this severe infection the innovative treatment is necessary. To fill up this necessity scientist Francisco Velazquez and his co-workers are continuously trying to find the potent compounds with improved pharmacokinetic profiles [98]. And the cyclic sulfone P3-cap containing HCV NS3 protease inhibitors have been discovered by the researchers (Figure 3). The Ki values were found and the cellular potency was also improved in these newly HCV NS3 protease inhibitor.

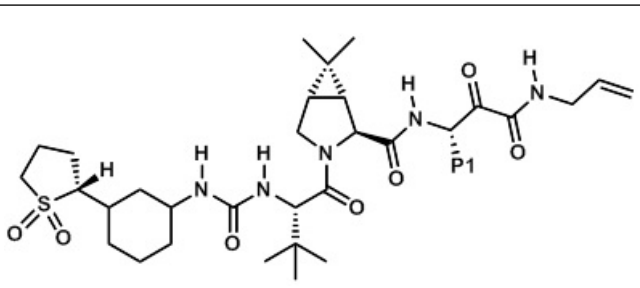


Figure 3: The cyclic sulfone inhibitors with the evaluation of P1-allyl group.

Structure-based design of a series is allowed the rational incorporation of prime- and nonprime-side fragments to a central core

template without any amide functionality. The core scaffold selection and the structure-activity relationship development were supported by molecular modeling studies and by X-ray analysis of BACE1 complexes with various ligands to expedite the optimization of the series. The direct extension from P1-aryl- and heteroaryl moieties into the S3 binding pocket allowed the enhancement of potency and selectivity over cathepsin D. Restraining the design and synthesis of compounds to a physicochemical property space consistent with central nervous system drugs led to inhibitors with improved blood-brain barrier permeability.

Rueeger and his co-workers [99] obtained the highly potent compounds like 60p with enzymatic and cellular IC_{50} values of 2 and 50 *n*M, respectively, as well as 200-fold selectivity through the structure-based optimization of the compounds. The cyclic hydroxyethylamine BACE1 inhibitors showed the better result against the diseases (Figure 4). The significant reduction of brain Aβ levels was observed through the oral doses of 180 μmol/kg in APP51/16 transgenic mice which was found by the Pharmacodynamic study.

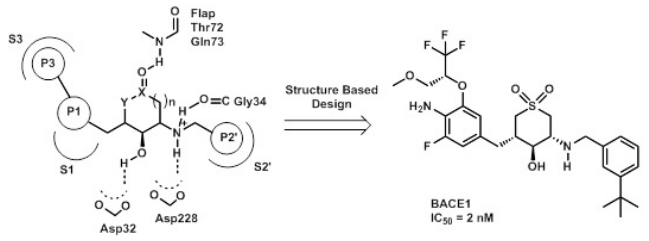


Figure 4: Structure based cyclic sulfones and β-Site APP-cleaving enzyme 1 (BACE1) inhibitors.

Liu et al. designed a series of novel cyclic sulfones [100] based on the concept of conformational restriction to generate potent and selective mTOR inhibitors (Figure 5). Among these inhibitors, PF-05139962 has more than 500-fold selectivity against PI3Ka and good *in vitro* ADME profile and cellular potency.

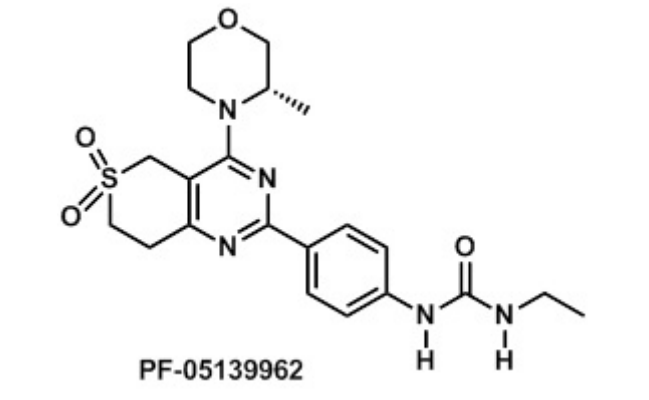


Figure 5: Cyclic sulfones as mTOR kinase inhibitors.

Several new sulfonebiscompounds having a biologically active 1,2-dihydropyridine-2-one, acrylamide, chromene and chromenopyridine moieties were formulated and showed as potential anticancer agents by Al-Said MS and his co-workers [101]. The results of their screening tests found that the obtained biscompounds can act as good anticancer activity against the human breast cell line (MCF7) comparable to the reference drug like doxorubicin. Following three compounds (**I, II, III**) showed IC_{50} values as 35.40 μM, 29.86 μM and 30.99 μM, respectively (Figure 6). For clarifying the method of action as anticancer agents, the docking of farnesyltransferase and arginine methyltransferase was also carried out and found good results.

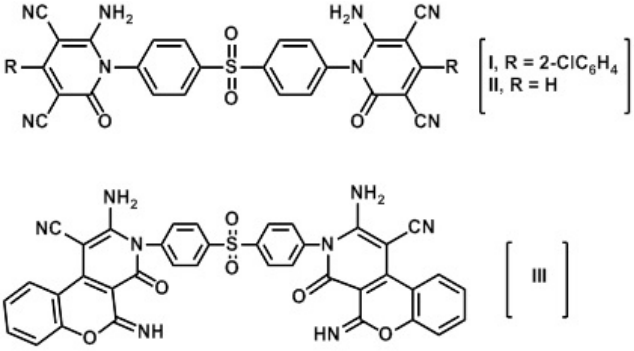


Figure 6: Sulfones moiety acts as anticancer activity.

Discussion and Conclusion

Here, the authors reported a brief review on the synthesis, reactions and medicinal importance of sulfones specially the cyclic sulfones and their derivatives. Sulfones and their derivatives have vast applications in biological, pharmaceutical, medicinal and in many other fields. Authors believe that the researchers including chemists, biologists and pharmacists will take this review study as one of their desirable and valuable materials for undergoing the works on sulfones specially the cyclic sulfones and their derivatives.

Conflicts of Interest

Authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

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