



## Review Article

### Synthesis and Study Biological Activities of Sulfur - Containing Drugs

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#### ABSTRACT

The importance of developing sulfur therapy is crucial to achieving the progress of pharmaceutical works - functional groups produced from sulfur can be found in a wide range of medicines due to the components of various biological and pharmaceutical effects.

Sulfur compounds are an important class of chemical molecules. It can be used in various areas of chemistry.

As a result of the widespread of pharmaceutical compounds containing sulfur, it gave great importance, as there are many drugs that have been developed, such as mafenide, sulfacetamide, Sulfadiazine, sulfamethazine, Sulfasalazine, sulfisoxazole. The study dealt with collecting the most important methods of preparing organic sulfur compounds.

The focus was on thiols, thiones and sulfones, and a comparison was made between the pharmaceutical compounds that are included in their compositions in terms of synthesis and medical uses as antibacterial, antifungal and anticancer cells.

**Keywords:** sulfonamide, sulfone, pharmaceutical, drugs sulfur.

## INTRODUCTIONS

Sulfur-containing compounds frequently exhibit. With diverse biological action and critical roles in medicinal applications, a vast range of sulfur-containing scaffolds may be found in natural goods and pharmaceuticals.

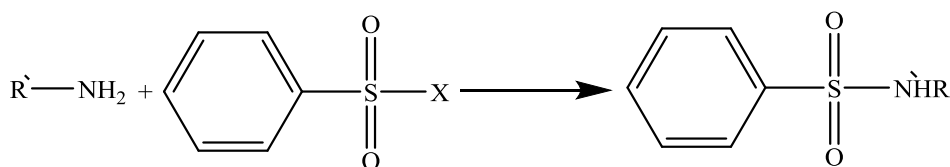
For several years, sulfur has retained its stat as a compact heterocyclic atom that has been able to dominate over 362 FDA-approved sulfur-containing drugs along with oxygen or nitrogen to this day through sulfonamide, sulfones and C-S containing derivatives compounds. Recent developments will be presented talk (Kumar *et al.*, 2020).

Sulfonamides have been a key component in the development of novel medications since their introduction in 1930 (Beale *et al.*, 2010), spanning six decades during the Last century sulfonamide antibiotics were the first to be administered systemically paving the modern antibiotic revolution in medicine sulfonamides (sulfmedicines were the first pharmaceuticals that were willy and chemotherapies agents a wide range of disorders (Hai *et al.*, 2021) over 30 medicines with activity are in clinical use including the antifungal (Qadir *et al.*, 2016) antibacterial (Abdul Qadir *et al.*, 2015) anti-inflammatory (Alaa *et al.*, 2019) sulfonamides have lately been employed as an anticancer drug (Peerzada *et al.*, 2018).

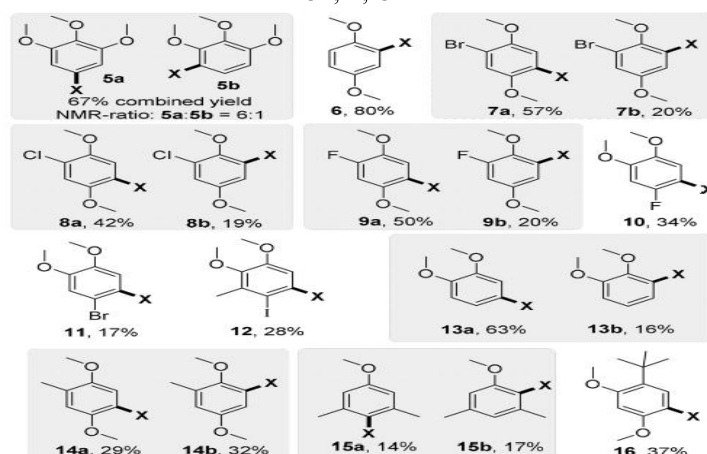
### Synthesis of sulfonamides.

One of the most common approaches to sulfonamides includes the production of straight N-S bonds via an addition - elimination.

A mechanism in this sort of reaction is sulfonyl chloride is a common substrate that combines with aryl or alkyl amines to yield the appropriate sulfonamide on a massive scale (Blum *et al.*, 2021).



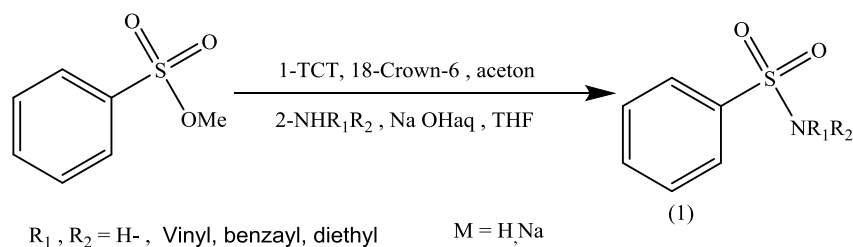
X = Cl, f, OR



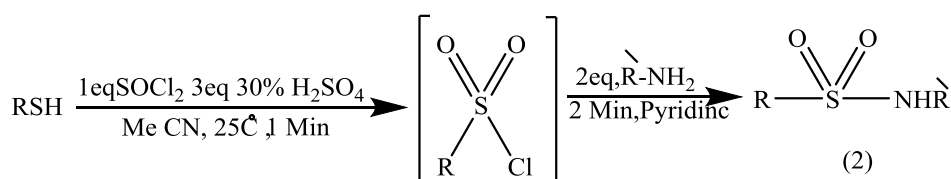
Until today, such a technique is the typical method for producing sulfonamide in the pharmaceutical business, although it still has to be improved in the past few decades, much effort has been put into discovering new synthetic methods to efficiently prepare sulfonamides. Traditionally sulfonamides were synthesis

It still needs to be improved and a lot of effort has been made to discover new synthetic methods for preparing sulfonamides.

Several sulfonamides can be prepared directly from sulfonic acids or the sodium salts of sulfonic acids under the influence of microwave radiation for a high yield (De Luca and Giacomelli, 2008).



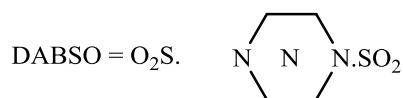
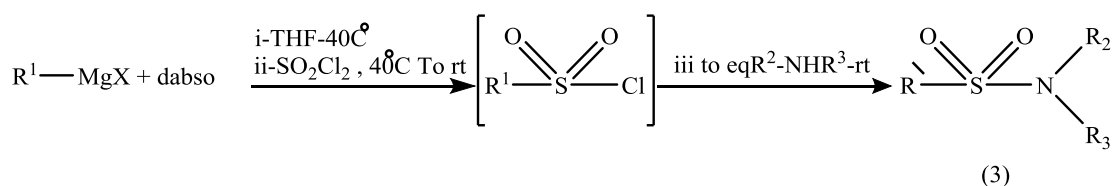
By using a mixture of hydrogen peroxide and thionyl chloride, it gives a highly effective reagent for oxidation directly by converting thiol derivatives to the corresponding sulfonic chloride with high purity, which in turn reacts with amines through oxidative chlorination, which leads to obtaining the corresponding sulfonamides in a short period of time (Bahrami *et al.*, 2009).



$R = \text{Ar}, \text{alkyl}$

$R' = \text{Ar}, \text{alkyl}$

The mixture of DABCO and sulfur dioxide also gave the charge transfer compound DABCO [1.4 Diazobicyclo [2,2,2-octane] which can replace the gaseous sulfur dioxide used in the organic synthesis where DABCO was combined with Krinkard reagent to form sulfate and the possibility of converting it to sulfonamides derivatives. (Woolven *et al.*, 2011).

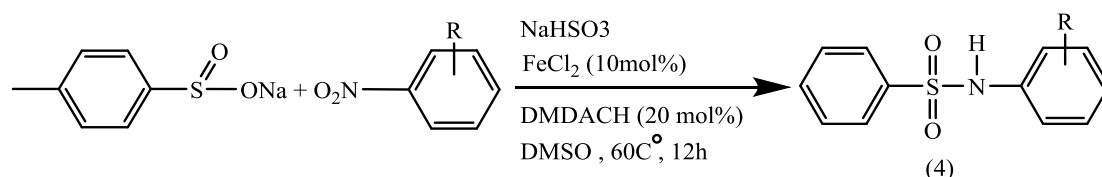


$R_1 = \text{Ar}, \text{allyl}, \text{Bu}, \text{alkyl}$

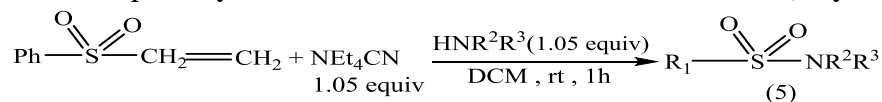
$R_2 = \text{alkyl}, \text{allyl}$

$R_3 = \text{alkyl}, \text{H}$

In one-step reaction was developed to form sulfonamides directly from sodium sulinate with nitroarenes the presence  $\text{FeCl}_2$  and  $\text{NaHSO}_3$  as a catalyst (Zhang *et al.*, 2015).



The researchers (Ray and Woonglee) were able to prepare the sulfonate, ticket sulfonate and sulfonamides from vinyl sulfonamides by removing the addition in a series where the sanides mediate the generation of the sulfate ion kanchylophil in the presence of N-bromosuccinamide and it was possible to use the primary amines in the formation of the sulfomides (Roy and Lee, 2020).



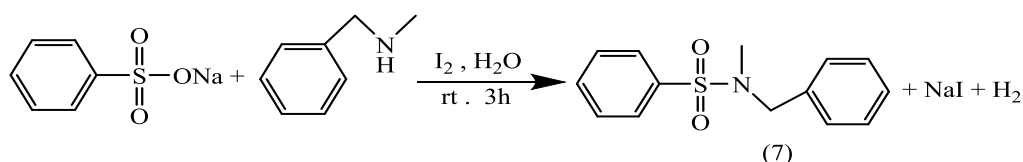
$\text{R}_1 = \text{1alkyl, BU}$

$\text{R}_2 = \text{H.1alkyl, BU}$

By applying the chain coupling reaction and in the presence of metal catalysts between nitroarenes and aryl boric acid, a wide range of sulfonamides were obtained (Hosoya *et al.*, 2019).



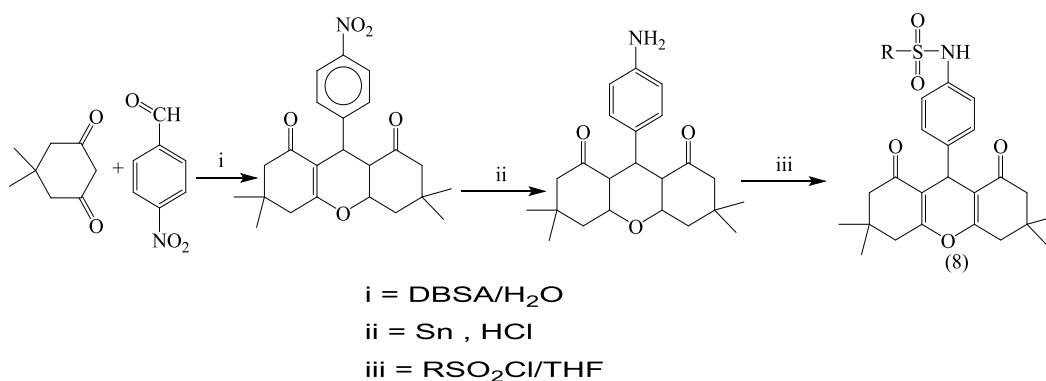
By applying green chemistry, the sulfonamides were prepared using I2 and water as solvents and at room temperature, which is an easy, simple and environmentally friendly method (Pan *et al.*, 2015).



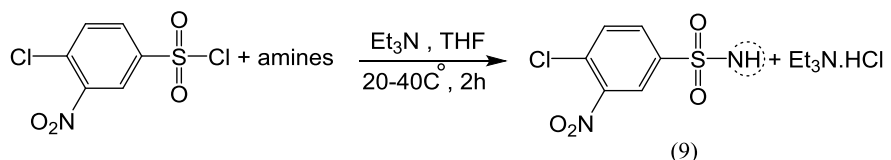
### Biological Activities of sulfonamides:

#### A- Sulfonamides as antimicrobial.

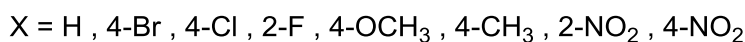
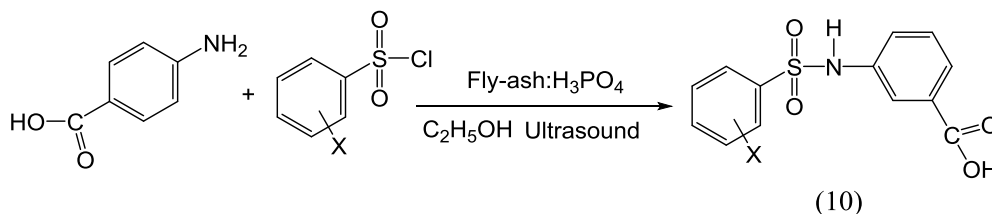
A series of sulfonamides and carboxamides containing a xanthine ring. All the prepared compounds were tested as antimicrobials for this activity. The results were compared with standard antibiotics erythromycin and nystatin, some of which showed activity against bacteria, microbes, and fungi (Kaya *et al.*, 2013).



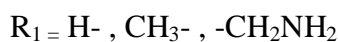
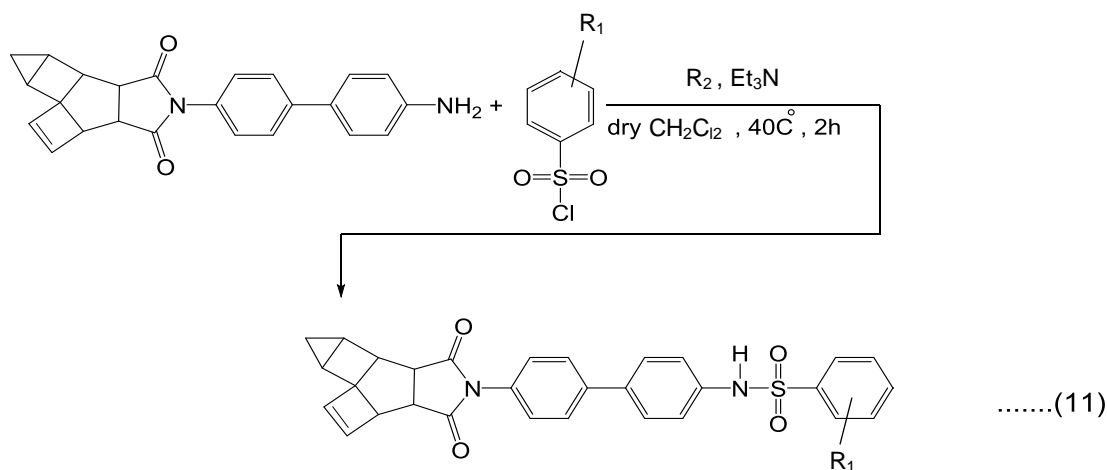
Recently, it was found that a series of sulfonamides derivatives resulted from the reactor of 4-chloro-3-nitrobenzene sulfonyl chloride with esters of various amino acids and amines. They are good against microbes and affinity for DNA (Kumar *et al.*, 2020).



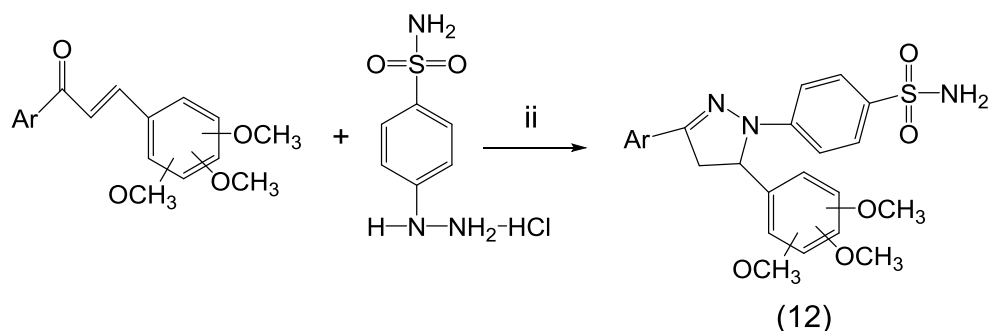
With equal concentrations of substituted benzene sulfonyl chloride, phenyl sulfonyl chloride and 4-aminobenzoic acid, and in the presence of fly ash,  $H_3PO_4$ , and ply - ash -  $H_3PO_3$  in the ethanol solvent, this mixture was subjected to ultrasonic irradiation to produce 4- (substituted phenyl) benzoic acid. The antimicrobial activities of all sulfonamides were measured, and some of them showed activity against microbes and fungi (Dineshkumar and Thirunarayanan, 2019).



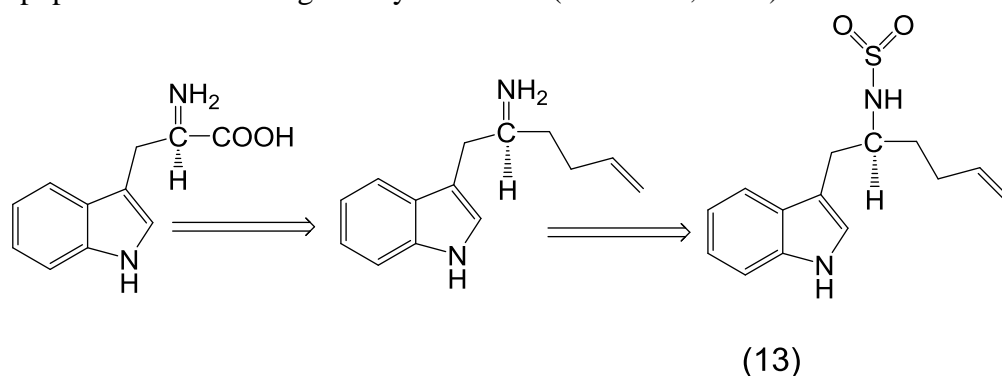
This review included the preparation of cyclic heptatriptamine derivatives of sulfa amides containing amines, and their biological activity was evaluated for types of pathogenic bacteria. In addition, others did not show effectiveness as anti-bacterial used in the experiment (Khediar *et al.*, 2021).



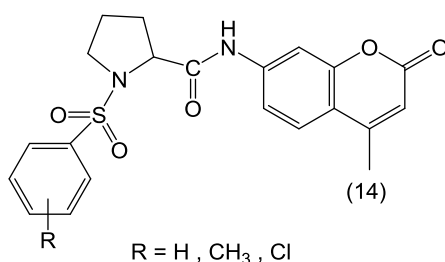
In this study, the researchers focused on the preparation of a selective anti-cancer drug by inhibiting isoenzymes associated with cancer. The new sulfonamides contain a derivative of 4-hydrazinobenzen sulfonamide hydrochloride in an acidic medium and examined their biological activity if they have anti-cell effects. Human squamous cell carcinoma by MTT test and the conclusion was that most of the compounds have antitumor activity (Gul *et al.*, 2018).



A series of (S) S-tryptamine derivatives containing an allyl and aryl sulfonamide group were prepared and evaluated for their potential aryl or allyl sulfonamide use as anticancer agents for four human cancer cell lines HepG2, A549, CNE1, Hela, and some of them showed moderate to good activities against these species. 6ag could stop the HepG2 cell cycle in the G1 phase by promoting apoptosis and inhibiting colony formation (Guo *et al.*, 2021).

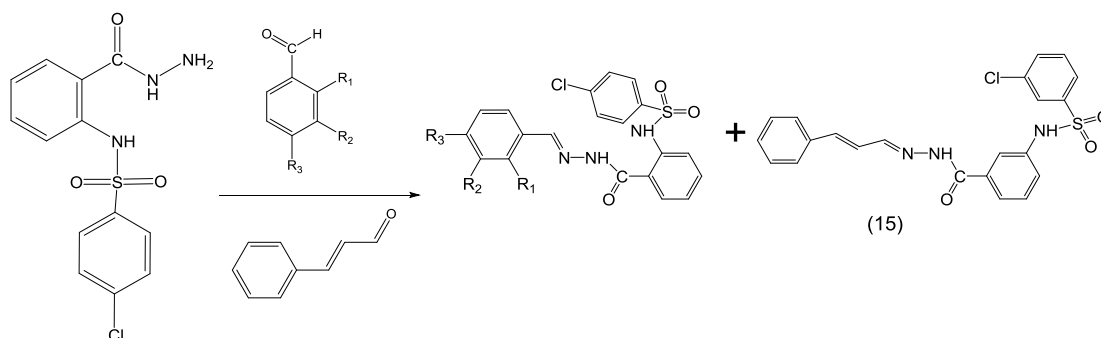


New amino-hybrids of coumarin-proline were prepared and selected as anti-cancer and anti-diabetic agents, and the MTT method was used to search for activity against lung cancer cell lines A549 and breast cancer cells MCF-7 with a value of  $I_{c50}$  1.07 $\mu$ m. While all compounds showed moderate activation of DPP-IV (Durgapal and Soman, 2019).

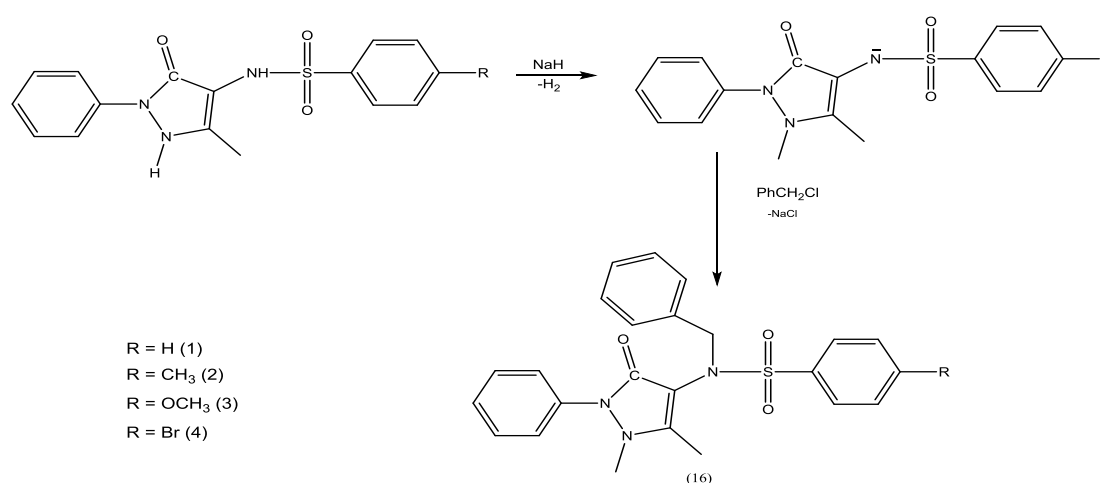


### C-Sulfonamide as Enzymeinhibitors

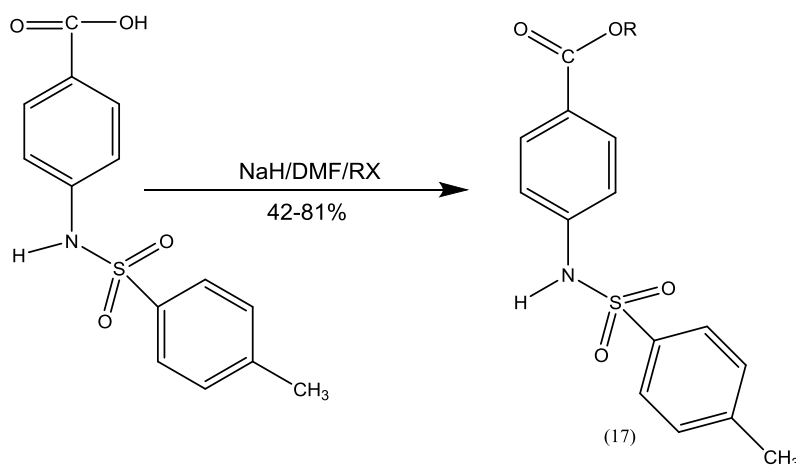
The ability of sulfonamide-containing drugs to inhibit different enzymes depends on the tendency of the sulfonamide group to instigate through electrostatic and non-covalent bonding interactions with the receptor binding site. Several sulfonamides were selected for their ability to inhibit enzymes only. It was noted that a series of Schiff bases and their derivatives of sulfonamides and through preliminary analysis and their effects on inhibitors of angiotensin degrading enzymes AchE and BchE and carbonic dehydrate I and II and determine their activity for these antioxidant derivatives by running scan tests using ABTS and DppHb is highly effective in inhibiting it, which opens the door for the development of new drugs for neurodegenerative disorders (Kausar *et al.*, 2019).



In the preparation of a new series of N-benzylated derivatives, the prepared compounds were evaluated, and included biological studies, antioxidants, and inhibition of Butyryl choline esterase enzyme, as well as studies of DNA methylation reactions using the well-known Elman method and a direct relationship between the enzyme inhibition activity and the concentration of the compounds was observed through experimental molecular docking (Abbas *et al.*, 2016).

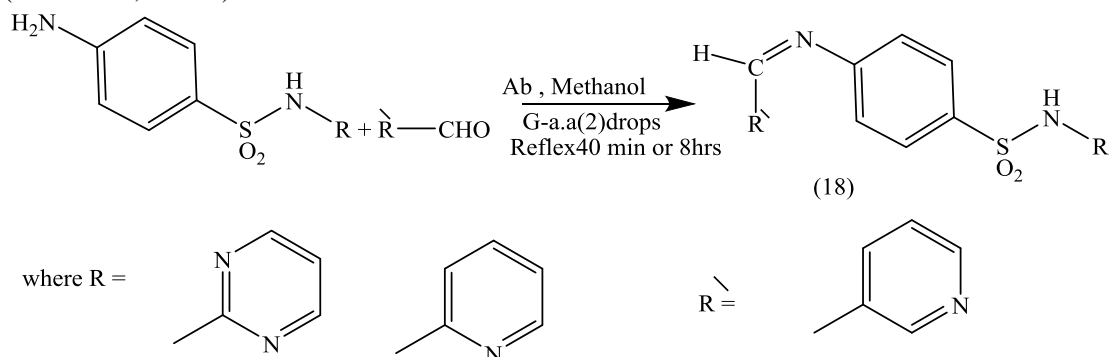


A new study to prepare new inhibitors of the enzyme lipoxygenase resulting from the reaction of p-aminobenzoic acid with para-chloride coloring sulfonyl and the product was subsequently reacted with various alkylating and acylation agents and gave 13 new derivatives of sulfonamides with good yields, and it was verified that Lipoxygenase inhibited these derivatives. The new sulfonamides showed 4m, 4g, 4j, 4e, 4f inhibitory activities for this enzyme with IC<sub>50</sub> values ranging from 15.8 to 0.57.  $\bar{x}$  and 91.7 0.01  $\bar{x}$  > imol (Mustafa *et al.*, 2012).

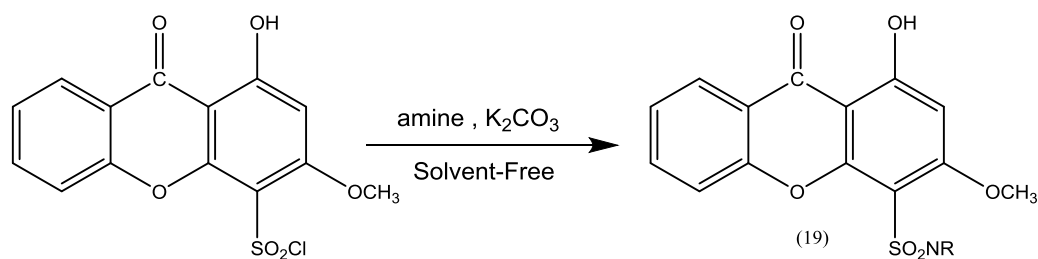


### D-Sulfonamides as Antibacterial:

New compounds prepared from Schiff bases obtained from the reaction of some sulfa drugs with different aldehydes and conducting antibacterial tests on them against two types of pathogenic bacteria (Tram positive - Tram negative) by measuring their inhibition area Against certain types of standard antibiotics with different concentrations of compounds, it was noted that the compound SH<sub>7</sub> best activity, while SH<sub>8</sub> showed moderate activity, while the remaining compounds were less active (Ali *et al.*, 2020).

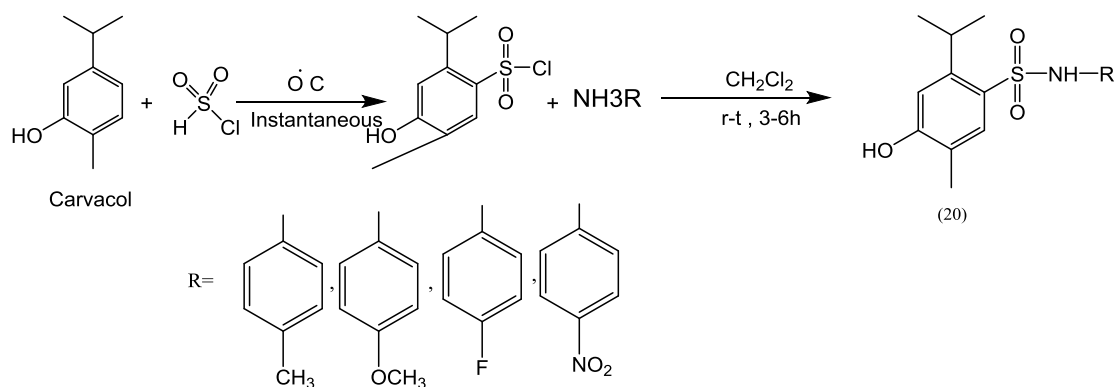


Twenty compounds of xanthene sulfonamides were prepared in a simple way by mixing xanthan sulfonyl chloride with an amine in the presence of K<sub>2</sub>CO<sub>3</sub> at room temperature, and a search for activity against types of pathogenic bacteria showed different results. (Malekpoor *et al.*, 2015).



R = Cyclohexylamin , benzylamine , piprazine , Ph-NH- , 2-aminothiazole

Sulfonamides resulting from the reaction of sulfonamides Carvacol 4- hydroxy-4- 2-isopropyl- 5- methyl gasoline-1- Sulfonyl chloride with a difference of Amin. It is a well -known antibacterial, with useful results (de Oliveira *et al.*, 2016).



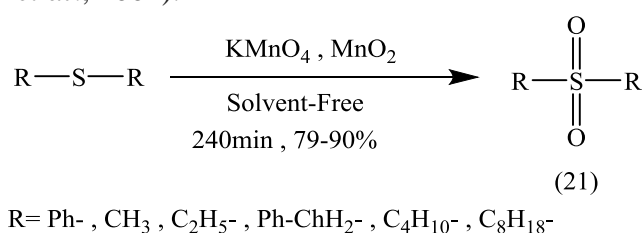


**Sulfones:**

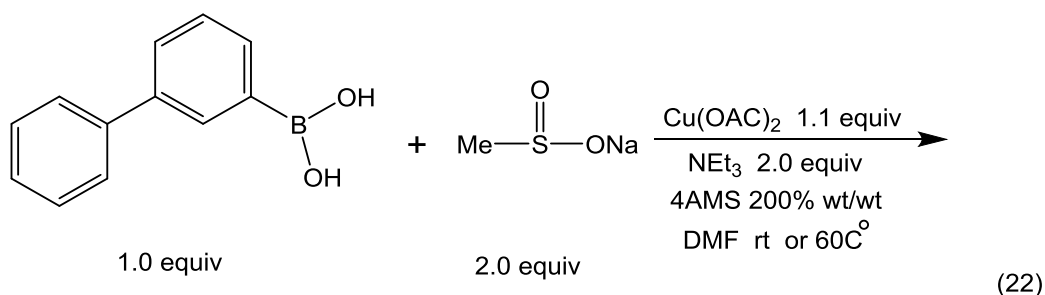
They are one of the important organic compounds containing sulfur and oxygen. They have the general structural formula  $ASO_2R_1$  where  $R^1$  and  $R$  are two organic groups. Sulfones have gained great importance in organic synthesis due to their importance as synthetic mediators for the production of a wide range of chemically and biologically active molecules. It has been widely used for various biological activities as anti-inflammatory (Wen *et al.*, 2010), anti-bacterial (Konduru *et al.*, 2013), anti-cancer (Shaaban *et al.*, 2022), anti-malarial (Aratikatla *et al.*, 2020) and anti-fungal (Xu *et al.*, 2011), as well as used in industry as solvents (Ludot *et al.*, 2013) and polymers (Meng *et al.*, 2013).

**Synthesis of Sulfones:**

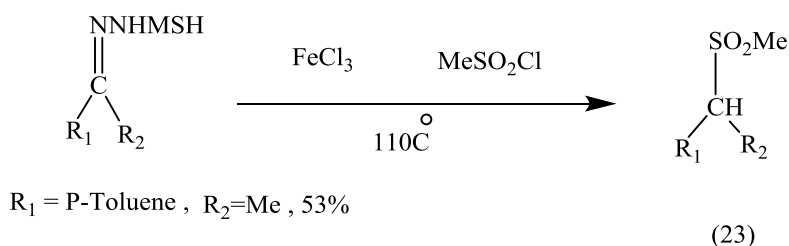
Using green chemistry techniques sulfonates was prepared in the presence of potassium permanganate and active manganese dioxide, effectively to oxidize organic compounds under solvent-free conditions (Shaabani *et al.*, 2004).



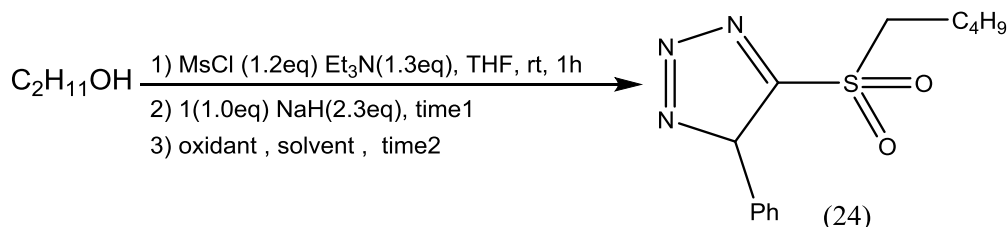
A new series of sulfonates by reacting boronic acid and sulfonic acid salts via acid coupling by  $Cu(OAc)_2$  questionnaire to produce various groups of sulfonates with distinct productivity ratios (Beaulieu *et al.*, 2004).



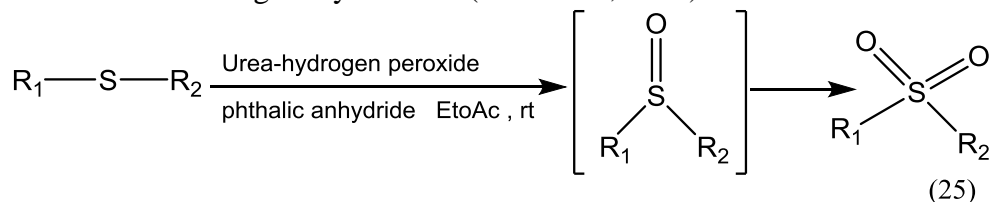
A group of scientists explained that a variety of sulfonates can be prepared through the Hydrazon Ariel, Alkil, alpha, and unsaturated ketones through inexpensive and environmentally friendly chloride, which helped form a large group of sulfonates (Barluenga *et al.*, 2011).



Developed a one-step method of sulfide (Julia-Kocienski) by converting a variety of primary alcohol transitions or thiols to the corresponding sulfonate (Ando and Hattori, 2019).



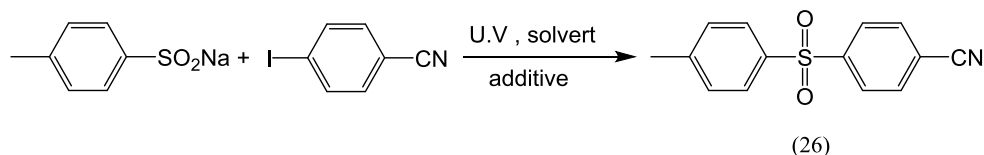
The substituted sulfides were converted to the corresponding sulfonates by oxidation that is free of metals and is environmentally friendly in the presence of hydrogen peroxide, urea, and phthalic acid in a solvent through ethyl alcohol (Lutz *et al.*, 2018).



R = aryl, alkyl

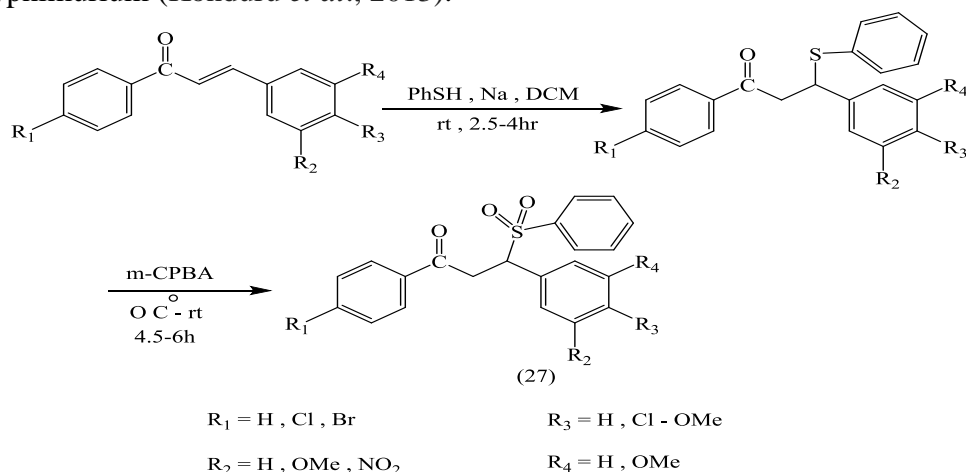
R<sub>1</sub> = R<sub>2</sub> and R<sub>1</sub> ≠ R<sub>2</sub>

Without a metal catalyst and using UV-UV rays, a number of sulfates were prepared from sulfonates and aryl halides as a result of the withdrawal of the sodium iodide molecule and the formation of new sulfone compounds (Chen *et al.*, 2019).



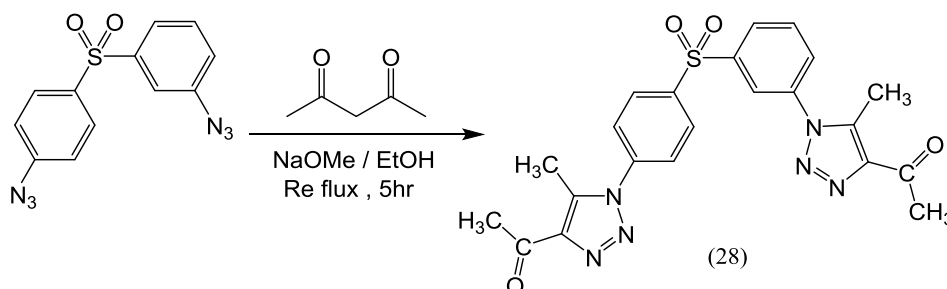
### Sulfones anti microbiological activity

The scientist Konduru and others prepared two series of derivatives of sulfones and bisulfones using galcon with thiophenol and sodium at room temperature. The product was entered by oxidation of galcon sulfide using the factor M - CPBA at zero centigrade, and their antimicrobial and antifungal activities were evaluated where the compounds showed 3C, 6C and 2C. High antifungal activity, 7C, 8C, 9C, and the compounds 5C, 6C, and 7C gave high antibacterial activity against *S*-typhimurium (Konduru *et al.*, 2013).



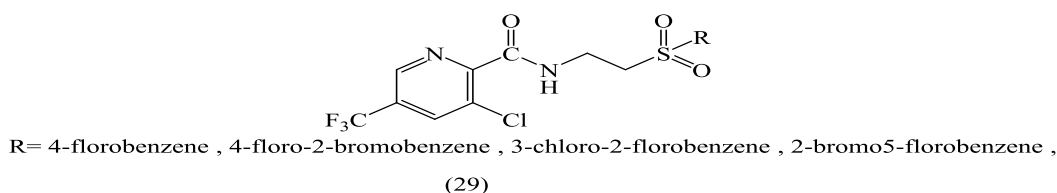
From the compound Dapsone, a disulfone compound of 1, 2, 3 - triazole was prepared. The compound was evaluated and its ability to be used as an anti-bacterial. Six types of pathogenic

bacteria were selected. The results were high capabilities as an anti-bacterial, as the studied compound had a strong impact on all bacterial strains used and through Molecular docking study against two vital enzymes, dihydropteroate rate, DNA gyrase, where the study showed that the compound is an outstanding candidate for fighting a wide range of pathogenic bacterial strains and the possibility of its use in the fields of medicine and pharmaceutical application (Berning *et al.*, 2021).



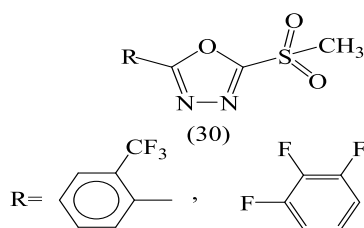
### From trifluoro methylpyridine amide

New sulfur-containing derivatives were prepared that were selected against bacteria such as *Xanthomonas*, *Oryzae pr*, *Oryzae xoo*, *Ralstonia Solanacearum*, *R-solanacearum* And it was chosen as a type of insecticide, as the sulfone-containing Flo compound showed the highest activity against Xoo bacteria (Guo *et al.*, 2020).

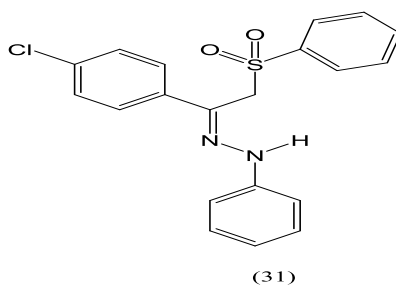


### b- sulfone antifungal

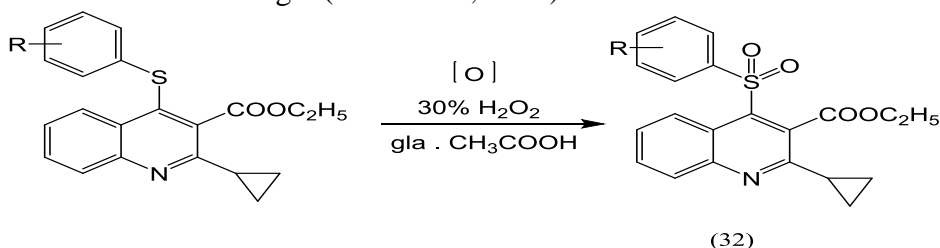
A series of 1,3,4-oxadiazole sulfone compounds have been evaluated as antifungals found in the Chinese ecosystem including: That was *R-Solani*, *C-mandshurica*, *F-oxysporum* and others. The compounds 5b, 5d and 5e showed their superiority over the commercial pesticide hymexazol, while the compounds 5d, 5e, 5f and 5i were highly active against *B-cinerea* (Xu *et al.*, 2011).



The scientist Hazen and his colleagues prepared the derivatives of Schiff bases that contain the sulfone group and these compounds were studied on four types of fungi based on the data compound 13 showed excellent results against the types used and the results were compared with the standard drug Fluconazole (fluconazole) (Ghabbour *et al.*, 2014).

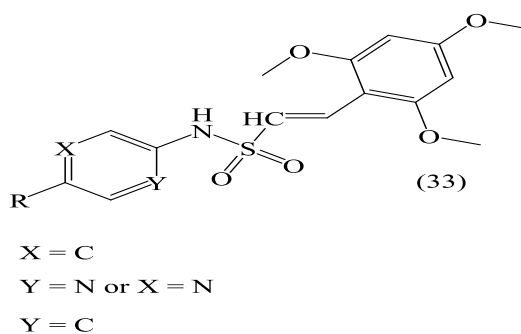


Sulfone derivatives containing quinolone and (silcobrobyl) ring had high activity against bacteria and fungi strains used in this study, as most of the compounds gave good efficacy as anti-bacterial and anti-fungal (Patel *et al.*, 2022).

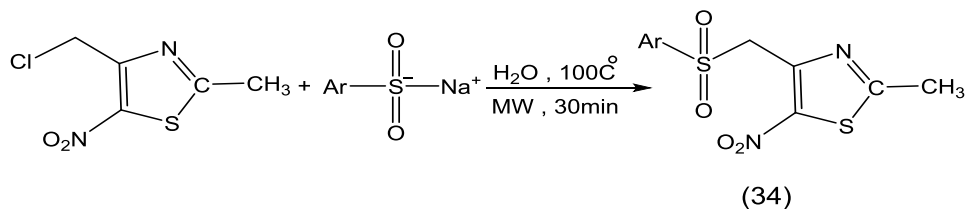


### Sulfone anti-cancer

Here (Hereon) series of N-hetero arystyryl sulfone derivatives were prepared and studied as anti-cancer agents. 14F was tested against a range of cancerous strains in which cell cycle arrest was observed at ( $G_2 / M$ ) phase and induced apoptosis by targeting CDC<sub>25</sub>C and MCl-1 proteins in 2780 (Long *et al.*, 2016).



An effective and environmentally friendly method was developed based on the use of green chemistry by emitting microwave radiation to produce (4-alkyl-, 4-aryl) sulfonyl methyl-2-methyl - 5-nitro-1,3-thiazoles, and the biological evaluation revealed by the MTT method by studying the prepared compounds Against cancer cell lines doxorubicin, HepG<sub>3</sub>, Cho as a reference drug, the compounds showed promising selective activity in vitro towards human cell lines HepG<sub>2</sub> by hydrogen sulfonate It also needs more studies to find out whether the anti -cancer compounds can be used to treat liver cancer (Cohen *et al.*, 2012).

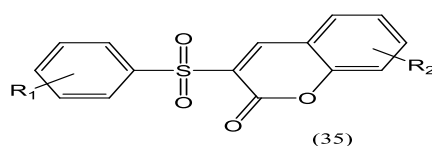


2a Ar = C<sub>6</sub>H<sub>5</sub>

2b Ar = p-CH<sub>3</sub> C<sub>6</sub>H<sub>4</sub>

2c Ar = p-Cl C<sub>6</sub>H<sub>4</sub>

Various studies have been conducted on five types of cancer cell lines MCF<sub>7</sub>, HcT<sub>166</sub>, H<sub>1299</sub>, HepG<sub>2</sub> and Hel<sub>2</sub> by MTS assay for a series of Benzyl sulfone coumarins derivatives. The results were analyzed, and compound 5h showed more effective activity against the above cancer lines (Wang *et al.*, 2019).



R<sub>1</sub> = 2-Cl

R<sub>2</sub> = NO<sub>2</sub>

R<sub>1</sub> = 2-Br

R<sub>2</sub> = NO<sub>2</sub>

R<sub>1</sub> = 2-F

R<sub>2</sub> = NO<sub>2</sub>

## CONCLUSIONS

A review has been done focusing on the compounds which sulfur - containing drugs such as sulfonamides, Sulfones. The review was concentrated on the Synthesis and pharmaceutical applications of these compounds as well as their use in many medical tests, including MTT and their significant characteristics as a drug.

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## تحضير ودراسة الأنشطة البيولوجية للأدوية المحتوية على الكبريت

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### الملخص

تعد أهمية تطوير العلاج بالكبريت أمراً بالغ الأهمية لتحقيق تقدم الأعمال الصيدلانية - يمكن العثور على المجموعات الوظيفية المنتجة من الكبريت في مجموعة واسعة من الأدوية بسبب مكونات التأثيرات البيولوجية والصيدلانية المختلفة. تعتبر مركبات الكبريت فئة مهمة من الجزيئات الكيميائية يمكن استخدامها في مجالات الكيمياء المختلفة. نتيجة الانتشار الواسع للمركبات الصيدلانية المحتوية على الكبريت، فقد أعطت أهمية كبيرة، حيث يوجد العديد من الأدوية التي تم تطويرها، مثل عقار مافينيد، سلفاسيتاميد، سلفاديازين، سلفاميثيزول، سلفاسالازين، سلفيزوكسازول. تطرقت الدراسة الى جمع اهم طرق تحضير مركبات الكبريت العضوية. تم التركيز على مركبات الثايول والثايون والسلفون وتمت المقارنة بين المركبات الدوائية التي تدخل في تركيبها من حيث التخليق والاستخدامات الطبية كمضادات للبكتريا والفطريات والخلايا السرطانية.

**الكلمات الدالة:** سلفوناميد، سلفون، المركبات الدوائية.