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REVIEW ARTICLE

Review of the Syntheses and Activities of Some Sulfur-Containing Drugs

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Abstract: ***Background*:** Sulfur-containing compounds represent an important class of chemical compounds due to their wide range of biological and pharmaceutical properties. Moreover, sulfur-containing compounds may be applied in other fields, such as biological, organic, and materials chemistry. Several studies on the activities of sulfur compounds have already proven their anti-inflammatory properties and use to treat diseases, such as Alzheimer's, Parkinson's, and HIV. Moreover, examples of sulfur-containing compounds include dapsone, quetiapine, penicillin, probucol, and nelfinavir, which are important drugs with known activities.

***Objective*:** This review will focus on the synthesis and application of some sulfur-containing compounds used to treat several diseases, as well as promising new drug candidates.

***Conclusion*:** Due to the variety of compounds containing C-S bonds, we have reviewed the different synthetic routes used toward the synthesis of sulfur-containing drugs and other compounds.

Keywords: Sulfur, C-S bond, RN-18, quetiapine, 3-arylthioindoles, ebsulfur, dapsone.

1. INTRODUCTION

Sulfur-containing molecules are often found in nature. They are biologically and pharmacologically active and are used to treat several diseases [1]. The C-S bond is present in several drug molecules, which are used to combat cancer, HIV, and Alzheimer's disease (Fig. **1**) [2].

Due to the important applications of sulfur-containing compounds in several fields of science, a large number of research groups around the world have turned their attention to the development of efficient methods used to form C-S bonds [3].

Conventional methods used for C-S bond formation are quite inefficient due to the harsh reaction conditions used, such as elevated temperature, long reaction time, the use of polar and toxic solvents, as well as multistep syntheses [4]. In order to overcome such shortcomings, different methodologies have been proposed including cross-coupling reactions.

This review aims to present the different synthetic routes used to prepare C-S bond-containing drugs, as well as promising molecules with high pharmacological potential. Their main biological activities used in Medicine are also described.

2. SYNTHESIS AND ACTIVITY STUDIES OF RN-18 AND RN-19

2.1. Previous Reports on the Synthesis of RN-18

Since the very first cases of AIDS were identified in 1981, the disease has been the cause of more than 20 million deaths around the world, despite promising medicinal advances [5].

Over the last two decades, more than 25 anti-HIV drugs have been produced, which target the different phases of the HIV life cycle [6]. Among the main approaches to treating HIV-1, chemotherapy is used to inhibit protease and reverse transcriptase [7]. However, due to HIV-1 viral resistance and the toxicity associated with the inhibitors of these enzymes, more powerful and safe therapies have been developed [5]. Viral infectivity factor (VIF), a protein found in HIV and other retroviruses, is one of the regulatory elements encoded by the HIV-1 virus, which is essential for its replication [5].

Efficient HIV virus replication requires the presence of VIF, once it opposes the activity of the APOBEC3G (A3G) enzyme, which has the function of catalyzing hypermutations in viral DNA and acts as a "weapon" against retroviruses [8]. Cells with A3G are known as non-permissive toward viral replication. In such cells, the HIV-1 virus requires VIF for replication [8]. In the case of host cells without the A3G enzyme (known as permissive cells), virus replication is independent of VIF [5]. Once the cellular homologues of VIF HIV-1 are known, this protein represents a target for antiviral intervention [6].

Small molecules that specifically inhibit the functions of VIF and restore the cellular levels of AG3 have been studied as inhibitors of HIV-1 virus replication [7]. The most promising advances have involved studying the activity of 25 organic compounds [5].

Among the molecules studied, two compounds, RN-18 and RN-19 (Fig. **2**), stand out as antagonists of VIF, inhibiting HIV-1 virus replication in non-permissive cells [8]. Moreover, RN-18 increases the A3G levels in the cell, enabling its incorporation into the virus [6]. To date, data analysis has indicated that RN-18 is a specific VIF inhibitor during HIV-1 virus replication. Besides, by targeting the VIF–A3G interaction, RN-18 is a valuable compound for the development of antiviral therapies against HIV-1 [7].

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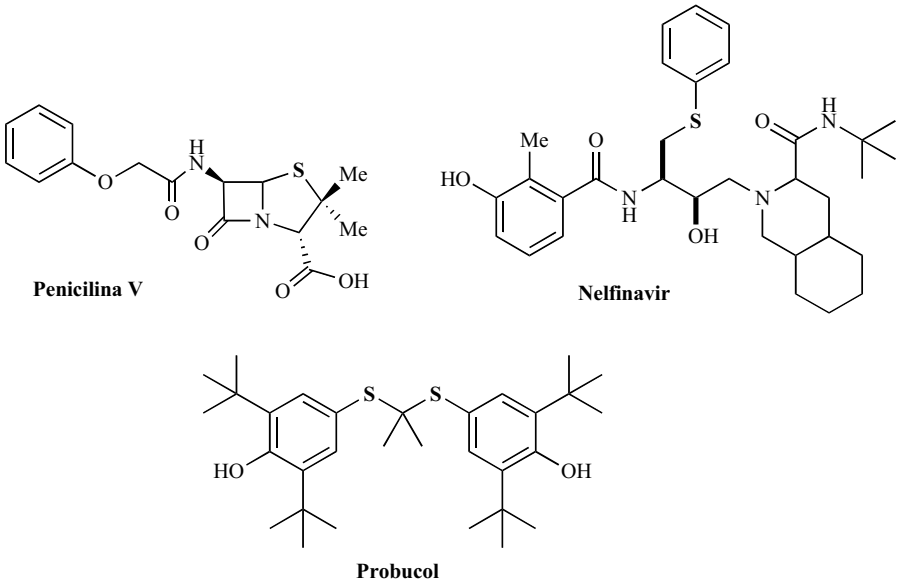


Fig. (1). Sulfur-containing drug molecules.

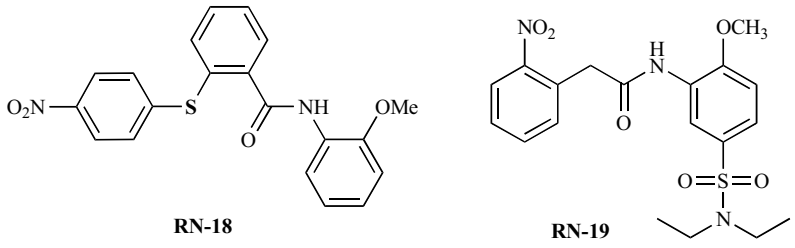
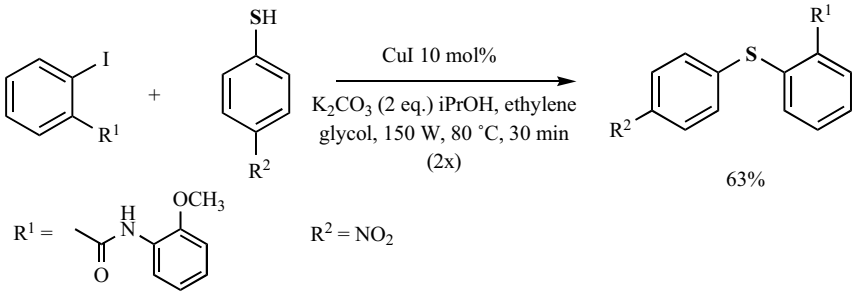
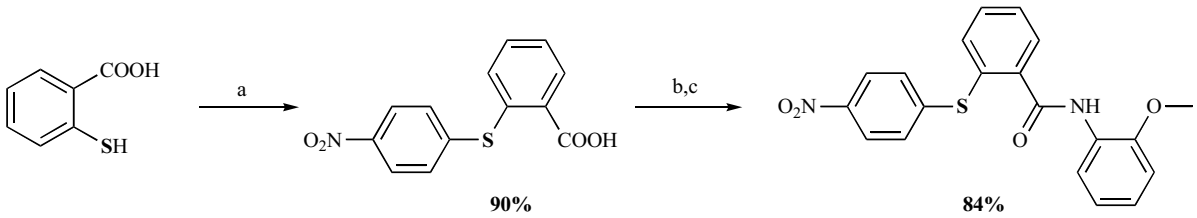


Fig. (2). Structure of compounds RN-18 and RN-19.



Scheme 1. Synthesis of RN-18 according to the procedure of Ali *et al*. [7].



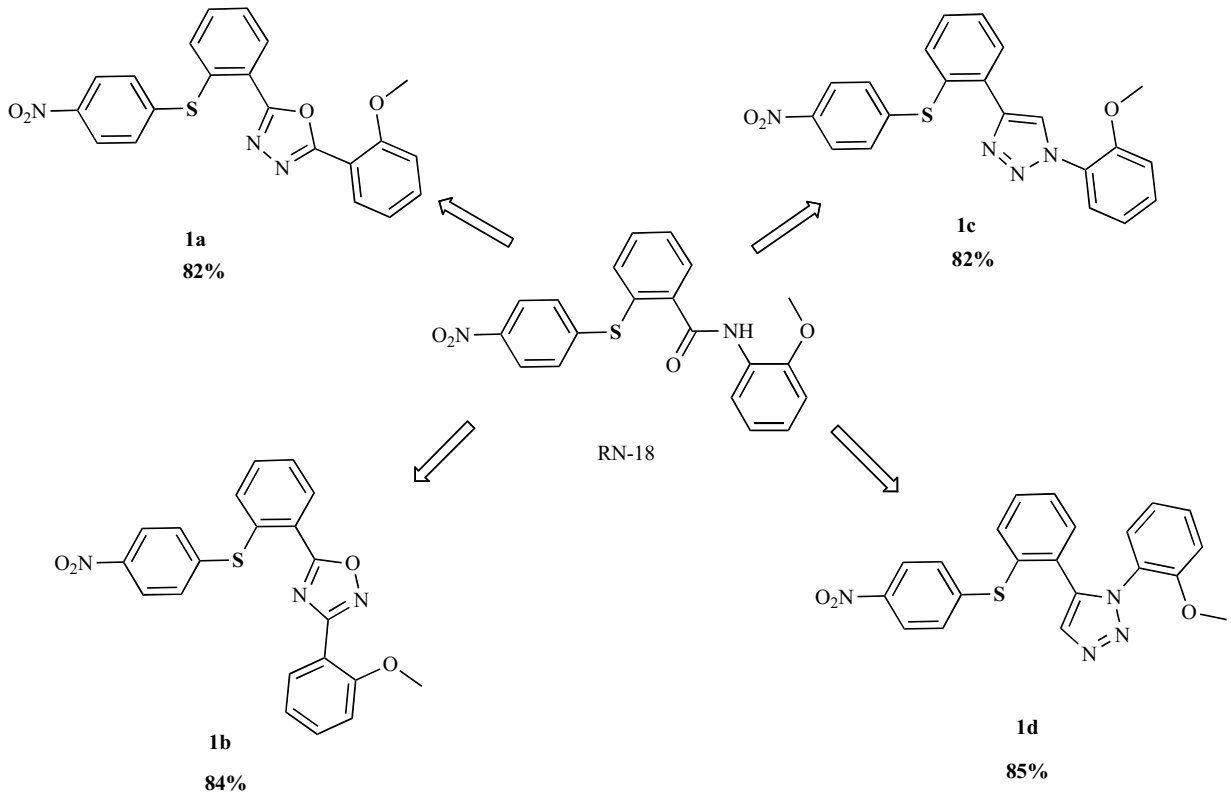
Scheme 2. Synthesis of RN-18 according to the procedure of Mohammed *et al*. [8] Reagents and conditions: (a) 4-Fluoronitrobenzene, K_2CO_3, DMF, 120 °C, 8 h; (b) $SOCl_2$, cat. DMF, benzene, 80°C, 2 h; (c) *ortho*-anisidine, Et_3N, benzene, 80°C, 5 h.

In order to obtain the bioactive compound (RN-18) and consequently upgrade our knowledge of its biological activity, some reports from the literature are described in the following section.

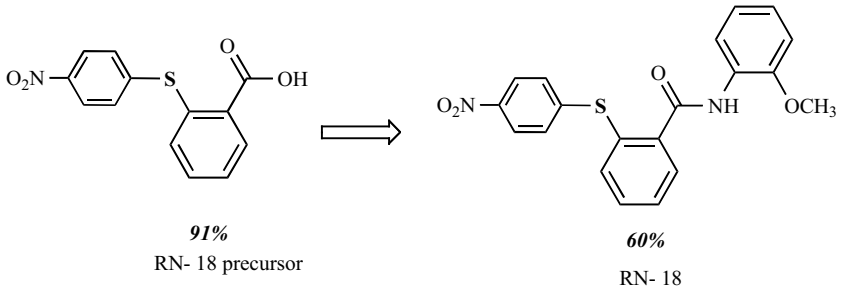
Ali *et al.* [7] have described the synthesis of RN-18 and its derivatives using two synthetic routes, which both involve the cross-coupling of an aryl halide substituted with a thiol or phenol using copper iodide as the catalyst (Scheme **1**). RN-18 was obtained as a yellow crystalline solid in 63% yield.

Mohammed *et al*. [8] also carried out the synthesis of RN-18 from a precursor compound synthesized *via* a C-S cross-coupling reaction, followed by amidation (Scheme **2**).

Consequently, the same authors described the synthesis of four RN-18 derivatives by modifying the amide functionality as well as



Scheme 3. The synthesis of RN-18 derivatives according to the procedure of Mohammed *et al*. [6].



Scheme 4. Synthesis of RN-18 according to the procedure of Santos *et al.* [9].

introducing a heterocyclic system: 1,3,4-oxadiazole (1a), 1,2,4-oxadiazole (1b), 1,2,3-triazol-1,4-dissubstituído (1c), and 1,2,3-triazol-1,5-dissubstituído (1d) [6] (Scheme **3**).

Recently, Santos *et al.* [9] also synthetized RN-18, from a synthetic precursor *via* a cross-coupling reaction between thiosalicylic acid and 1-iodo-4-nitrobenzene using a minimum amount of a recyclable catalyst consisting of palladium and ethanol as a green solvent (Scheme **4**). RN-18 was then obtained *via* an amidation reaction using *ortho*-anisidine in anhydrous toluene and Et_3N.

2.2. Studies on the Activity of RN-18

The family of VIF antagonist molecules based on RN-18 reduce the viral infectivity and increases the degradation of VIF, which proportionally increases the incorporation of A3G into the virus and increases cytidine deamination in the viral genome [6].

RN-18 and RN-19 inhibit HIV-1 replication in a dose-dependent manner (IC_{50} = 6 and 25 μM, respectively) in non-permissive cells only (H9, CEM) [7].

In permissive cells (MT4), RN-18 does not inhibit the viral infectivity at 100 μM, showing that this family of inhibitors are specific for VIF [6]. Once RN-18 has the capacity to inhibit HIV-1 replication in non-permissive cells only, it is considered a VIF antagonist [5].

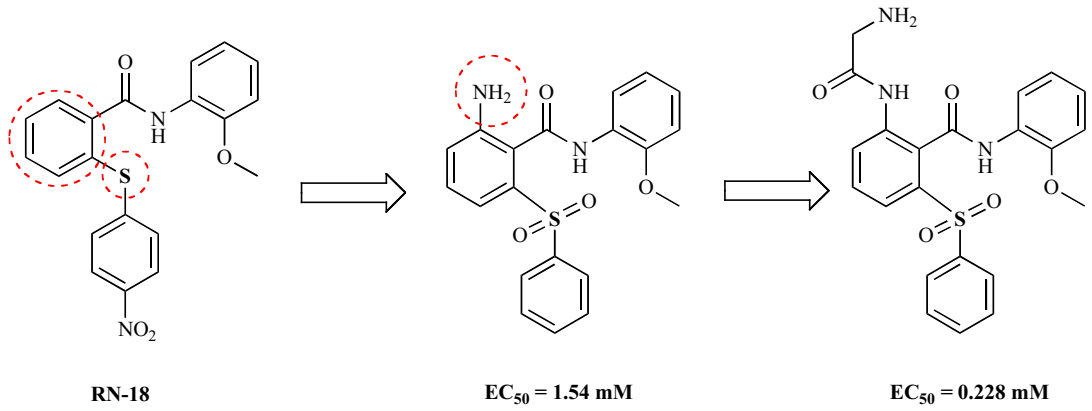
Zhou *et al*. [10] discovered a potent compound (EC_{50} = 1.54 μM) *via* sulfur oxidation and modification of the RN-18 thioether ring. This resulted in an increase in the antiviral activity of >150-fold when compared to RN-18 in non-permissive H9 cells. Subsequently, glycine-based amidation gave a compound exhibiting high water solubility, which inhibited HIV-1 virus replication with EC_{50} = 0.228 μM (Scheme **5**).

To date, data analysis has indicated that RN-18 is a specific VIF inhibitor of HIV-1 replication and the VIF–A3G interaction is a valuable target for the development of antiviral therapies for HIV-1 infections [7].

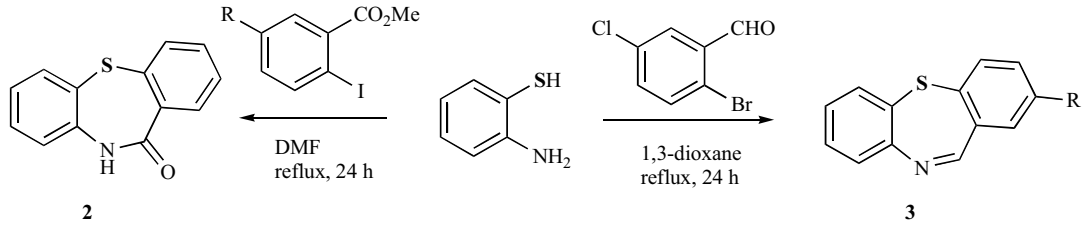
3. SYNTHESIS AND ACTIVITY STUDIES OF QUETIAPINE

3.1. Previous Reports on the Synthesis of Quetiapine

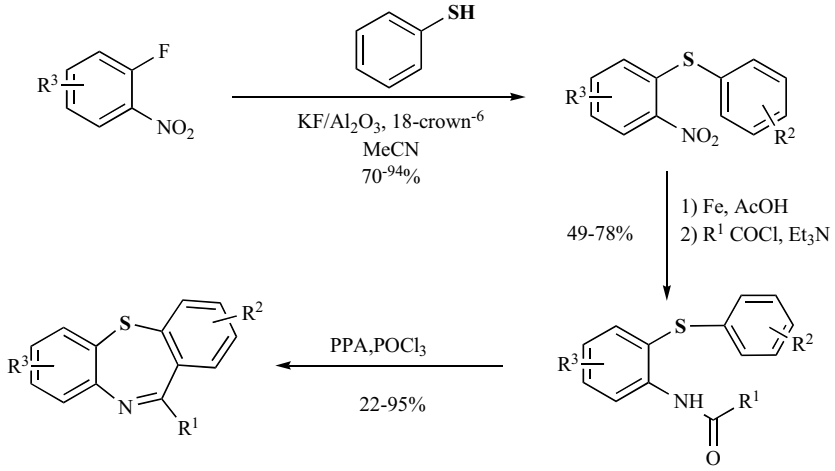
Dibenzothiazepines have been widely studied due to their large number of biological applications, which makes this class of compounds very important for pharmaceutical purposes [11]. One



Scheme 5. Synthesis of RN-18 derivatives according to the procedure of Zhou *et al*. [10].



Scheme 6. Synthesis of dibenzothiazepines using 10 mol% $CuFe_2O_4$ and KO^{t}Bu in N_2 atmosphere according to the procedure of Panda *et al*. [16].



Scheme 7. Synthesis of dibenzothiazepines according to the procedure of Guo *et al*. [17].

of the first dibenzothiazepines synthesized was clotiapine, a compound used to treat schizophrenia, which showed serious adverse reactions in patients [12]. For this reason, new compounds were developed including olanzepine, quetiapine, and ziprasidone (Fig. **3**) [12].

Among them, quetiapine fumarate presented the best efficiency for this disease, which significantly decreased the adverse reactions due to its neurotropic and psychotropic properties [13].

Some studies have revealed the potential application of quetiapine to treat acute cases of bi-polarity in addition to the anti-emetic activity of the dibenzothiazepine core [14].

Quetiapine fumarate, also known as 2-(2-(4-dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl-ethoxy), is obtained from a dibenzo[b,f][1,4]thiazepin-11[10*H*]-one intermediate and is composed of a seven-member ring bearing an amide group, which is usually prepared *via* a C-S cross-coupling reaction [15].

Due to the pharmaceutical importance of quetiapine, other synthetic routes have been proposed in the literature aimed at preparing the dibenzothiazepine core.

Panda *et al*. [16] described two synthetic routes using $CuFe_2O_4$ particles as the catalyst. In both routes, 2-aminobenzenethiol was used as the nucleophile; for final product 2, the researchers used methyl 2-iodobenzoate as the electrophile and for product 3, 2-bromo-5-chlorobenzaldehyde was used (Scheme **6**).

According to Guo *et al*. [17], the synthesis of the dibenzothiazepine core may be accomplished upon treating *ortho*-fluoronitrobenzene with thiophenol, reduction of the nitro group using Fe/AcOH, followed by acylation of the resulting amine to give the amide of interest. This amide is treated with polyphosphoric acid to give the dibenzothiazepine product (Scheme **7**).

Lin *et al*. [18] have described the synthesis of dibenzo[b,f][1,4]thiazepines using ortho-aminothiophenol and an ortho-halobenzaldehyde under microwave irradiation. During the cyclo-condensation reaction, several reaction parameters such as the base, solvent, and temperature were investigated and the use of a strong base such as KO^{t}Bu was required to give a significant product yield (Scheme **8**).

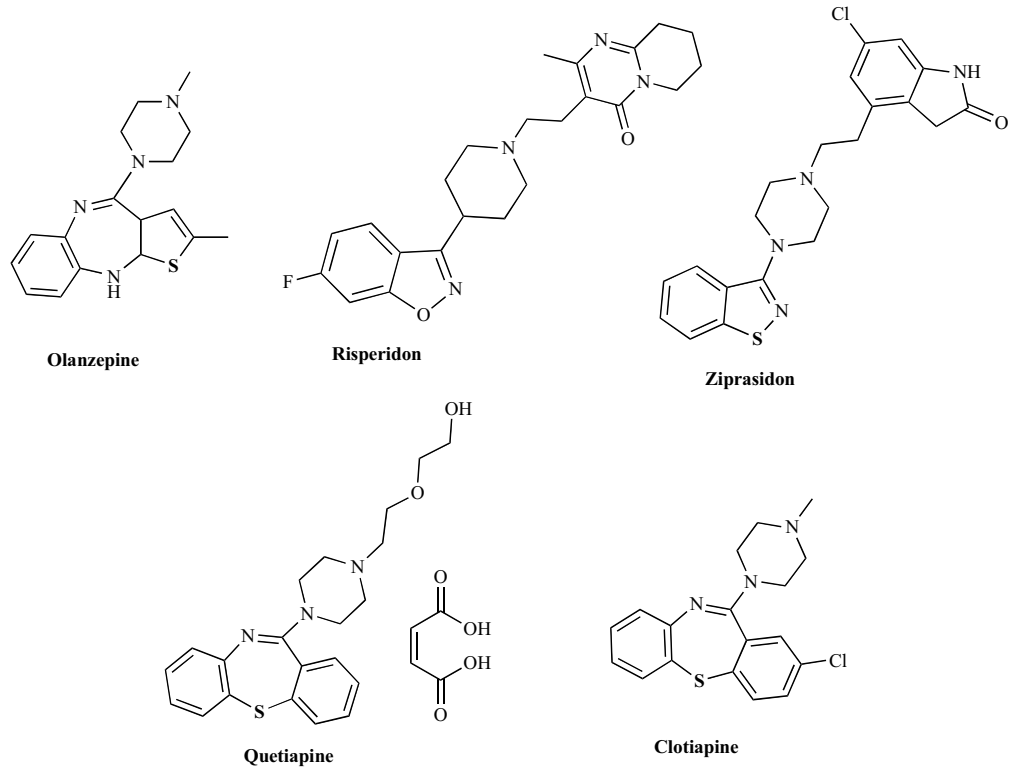
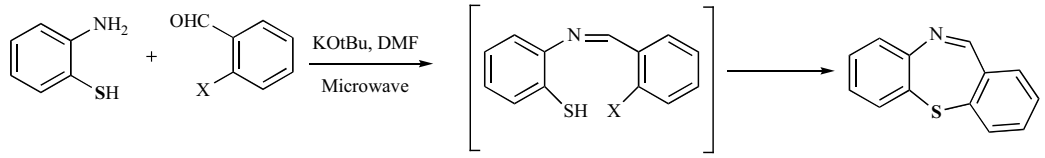
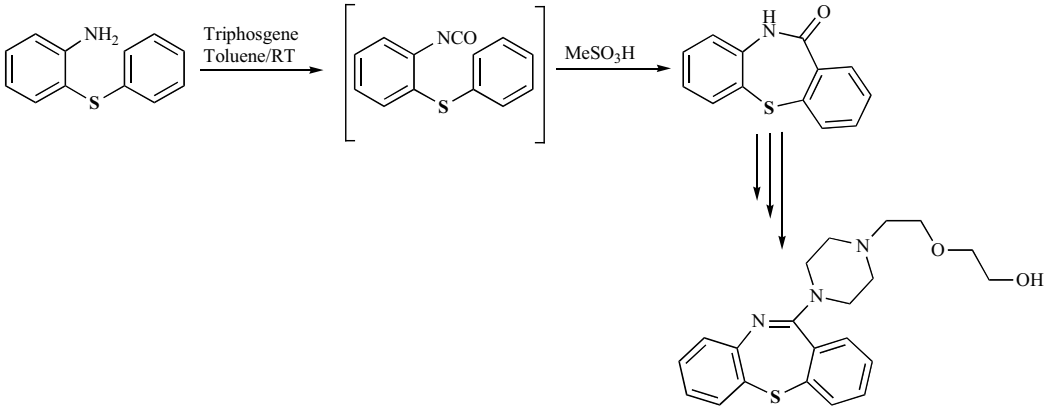


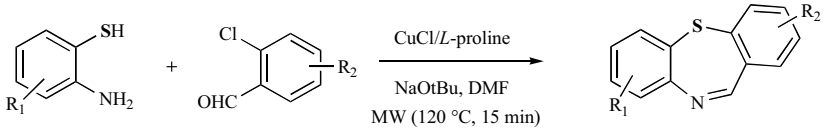
Fig. (3). Representive drugs used to treat schizophrenia [12].



Scheme 8. Synthesis of dibenzo[b,f][1,4]thiazepines according to the procedure of Lin *et al*. [18].

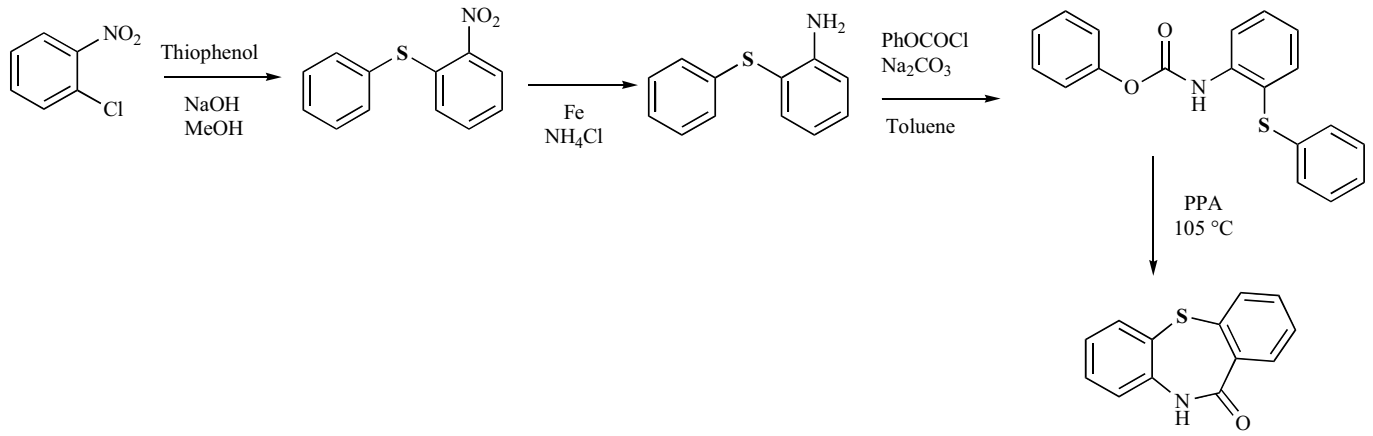


Scheme 9. Synthesis of dibenzo[b,f][1,4]thiazepine-11[10H]-one according to the procedure of Kandula [15].

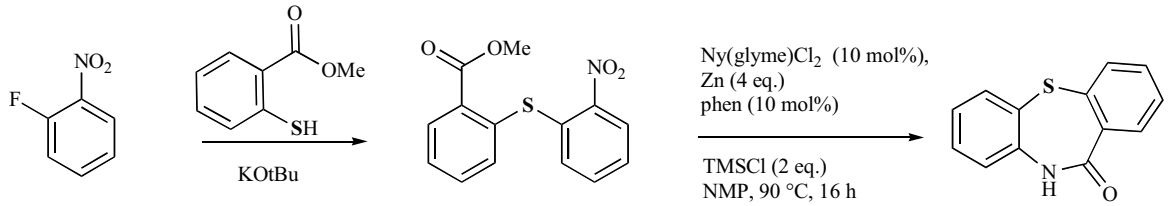


Scheme 10. Synthesis of dibenzo[b,f][1,4]thiazepine according to the procedure of Saha *et al*. [19].

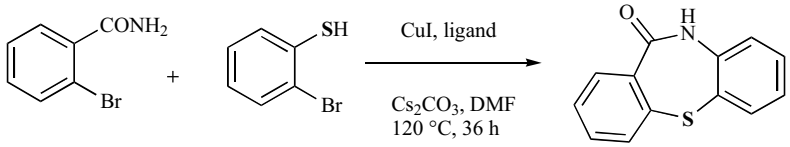
Due to the problems found in the synthetic route used to prepare the dibenzothiazepine core, Kandula proposed an efficient route to dibenzo[b,f][1,4]thiazepine-11[10H]-one [15]. This route succeeded in obtaining the dibenzothiazepine core using 2-(phenylthio)aniline and triphosgene in toluene, followed by the addition of methanesulfonic acid to carry out the cyclization reaction to give the compound of interest, thus enabling quetiapine fumarate to be prepared in three steps (Scheme **9**).



Scheme 11. Synthesis of dibenzo[b,f][1,4]thiazepine-11(10H)-one according to the procedure of Gudisela *et al*. [14].



Scheme 12. Synthesis of the diazepine core according to the procedure of Cheung *et al*. [20].



Scheme 13. Synthesis of dibenzothiazepine according to the procedure of Chen *et al.* [21].

Saha *et al*. [19] described the synthesis of dibenzothiazepine starting from ortho-aminothiophenol and ortho-chloro-benzaldehyde *via* a cyclization reaction using a copper catalyst. This reaction was performed over two steps, including the formation of the requisite imine, followed by the addition of the catalyst (Scheme **10**).

Gudisela *et al.* [14] proposed the synthesis of the benzothiazepine core in order to study its capacity as a cancer inhibitor using a cross-coupling reaction between 1-chloro-2-nitrobenzene and thiophenol in the presence of a strong base in MeOH. The as-obtained compound was reduced using iron powder and ammonium chloride, the resulting amine converted into its 2-(phenylthio)phenylcarbamate, and then treated with polyphosphoric acid (PPA) to give dibenzo[b,f][1,4]thiazepine-11[10*H*]-one (Scheme **11**).

Recently, Cheung *et al*. [20] proposed the synthesis of the diazepine core *via* the reduction of nitrobenzene using zinc and trimethylsilyl chloride (TMSCl). The resulting product was then cyclized to form the diazepine core (Scheme **12**).

Chen *et al.* [21] described the synthesis of diazepine in a single process *via* a Goldberg intramolecular reaction using a substituted 2-bromobenzamine and 2-bromothiophenol as starting materials in the presence of a *N*,*N*-dimethylglycine ligand and copper iodide catalyst (Scheme **13**).

3.2. Studies on the Activity of Quetiapine

Quetiapine fumarate has been successfully used to treat schizophrenia due to its high affinity with serotonin compared to dopamine [12]. This drug is considered efficient in patients resistant to the side effects of schizophrenia, unlike clonazepine, which seems to be ineffective [12].

Antipsychotic studies have been performed using quetiapine, and its efficacy in relation to common antipsychotics, such as chlorpromazine and haloperidol, was investigated [22]. One of the main advantages related to the use of quetiapine is the minimization of any side effects [22].

Studies on the dibenzothiazepine core have demonstrated that the presence of heterocyclic or aliphatic groups containing nitrogen, oxygen, and sulfur results in compounds with bactericidal activity [23].

Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa, and Serratia marcescens [23] were tested as Gram-negative and Gram-positive bacteria. To prove the efficiency of this bactericidal agent, tetracycline was used as a reference. Thus, the activity of the test compounds was observed by the evolution of the inhibition zone on agar plates inoculated with these bacteria [23] (Fig. **4**).

Gudisela *et al.* have recently described the efficiency of the dibenzodiazepine core as an anti-emetic for nausea and vomiting during the treatment of advanced breast cancer (MDA-MB 231). The antiproliferative activity of the tested compound was also assessed in cancer cells, which exhibited the effective inhibition of leukemic cells. It is worth mentioning that the data demonstrate the anticancer potential of the compound [14] (Fig. **5**).

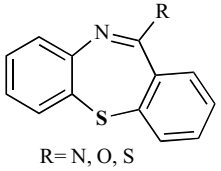


Fig. (4). Anti-bactericidal agent derived from dibenzothiazepine [13].

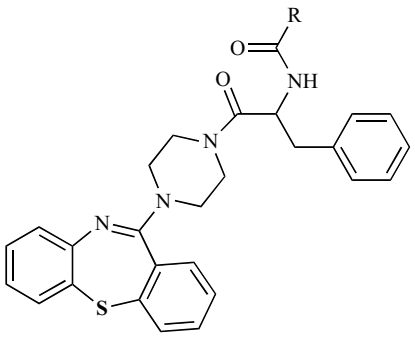


Fig. (5). A quetiapine derivative with anticancer activity [14].

4. SYNTHESIS AND ACTIVITY STUDIES OF 3-ARYLTHIOINDOLE DERIVATIVES

4.1. Synthesis of 3-arylthioindole Derivatives

Indoles constitute an important class of compounds found in natural products and medicinal chemistry [24, 25]. Due to their importance, a lot of research attention has been drawn to the synthesis of this family of compounds *via* the total construction or modification of the indole ring [26]. Their structure, which is electron-rich, enables them to react with electrophiles to form new C-C or C-heteroatom bonds [27]. Among the numerous indole derivatives reported to date, it is known that the 3-position of indole may be functionalized by heteroatoms, more specifically, a sulfur atom, which is the case for 3-acylthioindoles and 3-arylthioindoles [28] (Fig. **6**).

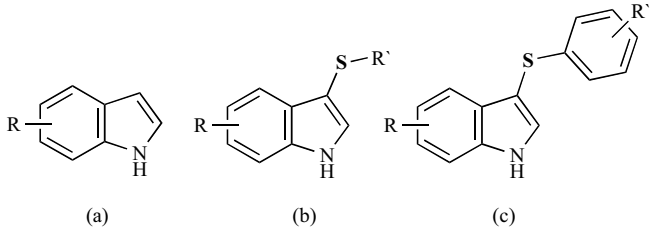


Fig. (6). (a) Indole, (b) 3-alkylthioindole, and (c) 3-arylthioindole.

3-Thioindoles have attracted considerable interest from the pharmaceutical industry due to their therapeutic value in the treatment of HIV [29, 30], cancer [31], obesity [32], heart disease [33], and allergies [34] (Fig. **7**). With this perspective, the sulfenylation of indole leads to the formation of important precursors used toward the synthesis of new compounds.

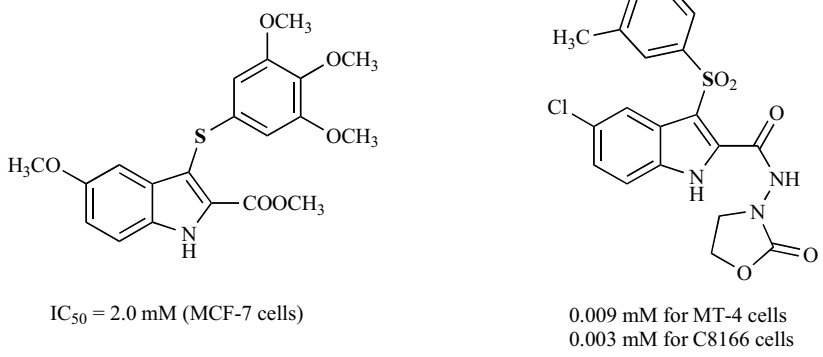
Currently, these compounds have been the object of important experimental studies and many methodologies have been developed to achieve them, including: a) The electrophilic substitution of indoles with sulfenylating agents in the presence of metal catalysts such as copper [35], palladium [36], cerium [37], magnesium [38], iron [39], ruthenium [40], and vanadium [27], and strong bases (KOH, triethylamine) or Lewis acids (Bu_3SnH, TMSS) [41, 42]; (b) electrophilic cyclization of 2-alkynylanilines with arylsulfenyl or disulfide chlorides [36, 43]; c) the addition of sulfanilic radicals to acinilazides [44]; and d) the use of aryl Grignard reagents and disulfide lithiated heteroaromatics [45].

In this context, the direct sulfenylation of indoles using sulfenylating agents such as thiols [27], disulfides [46], sulfenyl halides [47], quinone containing mono-*O,S*-acetals groups [48], *N*-thioarylphthalimides [35, 38, 49], *in situ* activated thiols using *N*-chlorosuccinamide, bis(trifluoroacetate) phenyl(III)iodide [50], sulfonyl hydrazides [51, 52], sulfinic acids [53, 54], arylsulfonyl chlorides [55, 56], *para*-arylsulfinates [57], and α-acylthiones [58].

Among the as-mentioned methodologies, we observed that transition-catalyzed cross-coupling reactions involving aryl halides and thiols had become one of the most important methods for the synthesis of diaryl sulfides. Over recent years, direct sulfenylation *via* functionalization of the C-H bond has drawn a great deal of interest since it can lead to a more efficient synthesis and a reduced number of steps [54-40]. Although several synthetic approaches have been developed, many are still considered impractical in view of the high cost of reagents, severe reaction conditions, large quantities of reagents, inert atmosphere requirements, and long reaction times [27, 46-58]. Thus, several researchers have developed novel synthetic strategies that enable the installation of 3-(alkylsulfonyl) and 3-(arylsulfonyl) functionalities on an indole substrate starting from suitable and readily available precursors.

Golzar *et al*. [59] have described the sulfenylation of indole using an inexpensive copper-based catalyst (CuI) and aryl halides in the presence of thiourea under normal atmospheric conditions to give the target products in 80–90% yield. The same reagents and a Pd(II)-(KCC-1/BTB/Pd) catalyst consisting of fibrous nanosilica (KCC-1) as a functionalized support containing 1,3-bis (dimethylthiocarbamoyloxy) benzene (BTB) groups complexed with Pd(II) were used. Zhiani *et al*. [60] also described the synthesis of various 3-sulfenylindoles derivatives under green conditions, which gave the target products in up to 90% yield (Scheme **14**).

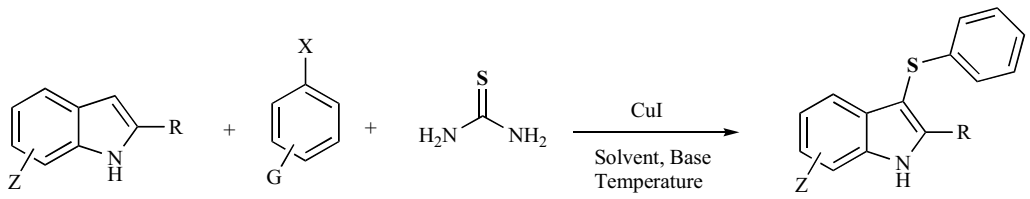
Studies performed by Devi *et al*. [61] have revealed the differences observed using Pd(II) and Ni(II) catalysts in the C-S cross-coupling reaction compared to the sulfenylation of indoles with active methylenes using iron salts. The Pd(II) complex shows slightly better reactivity when compared to Ni(II). The conditions were also based on the use of non-toxic solvents, aryl halides, and thiourea as alternatives to conventional sulfur sources, which result



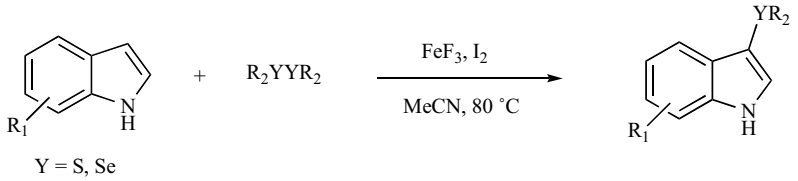
IC_{50} = 2.0 mM (MCF-7 cells)

0.009 mM for MT-4 cells
0.003 mM for C8166 cells

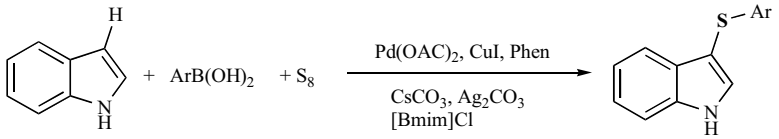
Fig. (7). Some biologically active 3-(arylthio)indole and 3-(arylsulfonyl)indole compounds.



Scheme 14. Synthesis of 3-arylthioindoles according to the procedure of Golzar *et al.* [59].



Scheme 15. Synthesis of 3-arylthioindoles according to Fang *et al.* [39].



Scheme 16. Sulfenylation of indoles proposed by Li *et al.* [63].

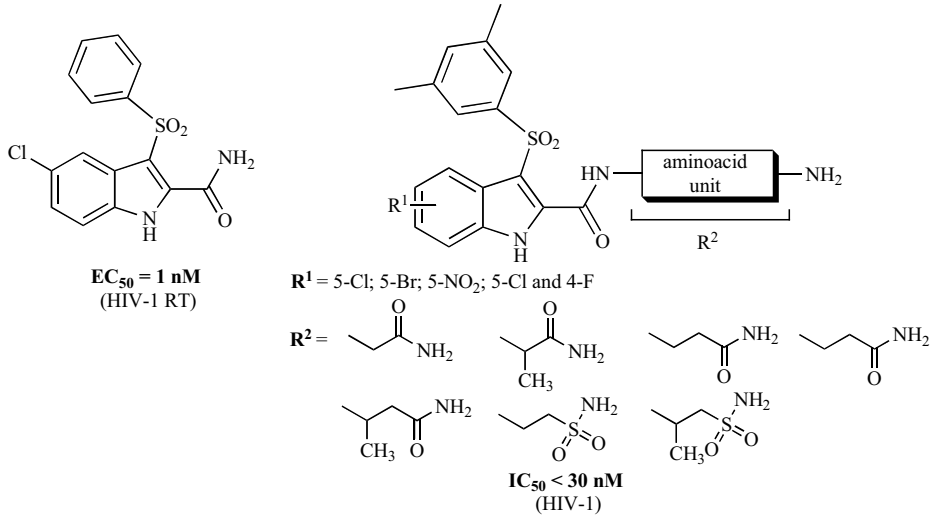


Fig. (8). IASs' derivatives with antiviral potential.

in a very fast reaction (3 h), high efficiency (yields from 80–95%), and profitability in terms of the high reactivity of the catalyst.

Another selective indole sulfenylation reaction involving disulfides using iron(III) fluoride as a catalyst was presented by Fang *et al*. in 2009 [39]. Using the disulfide starting materials under the reported reaction conditions, the authors obtained the corresponding sulfenyl indole products in excellent yield (70–96%) (Scheme **15**).

In the search for clean methodologies, Ge *et al.* [62] reported the use of sodium sulfinate, an inexpensive, odorless, and stable solid, as the sulfenylation agent in a $Cu(OAc)_2$-catalyzed reaction in the presence of D-glucosamide, which lead to the formation of the target product in 91% yield.

Li *et al.* [63] have also described an efficient methodology (60–90% yield) using the oxidative sulfenylation of indoles with different heteroarenes bound to boronic acids and elemental sulfur in a reaction catalyzed by Pd(II) (Scheme **16**). Thus, the authors presented a more effective synthetic approach to obtain biologically important 3-arylthioindoles.

4.2. Antiviral Activity of 3-arylthioindoles Derivatives

The 3-arylthioindole core is present in many important biologically active synthetic derivatives. Recognition of the antiviral potential of this structural core has been confirmed in the work published in 1993 by Merck Research Laboratories describing the discovery of 5-chloro-3- (benzenesulfonyl)indole-2-carboxamide (HIV-1 RT), a novel and potent, selective inhibitor for HIV-1 WTIIIB with an EC_{50} value of 1 nM (Fig. **8**) [64].

Also known as indolylarylsulfones (IASs), Silvestri *et al*. [65] and Psictelli *et al*. [66] published a number of novel indole derivatives, which, in addition to the presence of the C-S bond at the 3-position, contain carboxamide groups similar to glycine, D

and L-alanine, and unnatural amino acids attached at the 2-position. Studies involving these derivatives have shown excellent replication activity against HIV-1 WT, and NNRTI-resistant viruses, some with nanomolar inhibition concentration values (Fig. **8**).

Thus, studies on the structure–activity relationships (SARs) have led to the identification of three structural regions in IASs that can enhance the spectrum of their activity against HIV-1 replication: Region A – introducing methoxy groups at positions 3 and 5 of the 3-phenylsulfonyl moiety [67]; region B – 2-carboxamide coupling with different natural or synthetic amino acids [65,66]; and region C – changing the substitution pattern at positions 4 and 5 on the indole ring, such as 5-chloro-4-fluoro [47] (Fig. **9**).

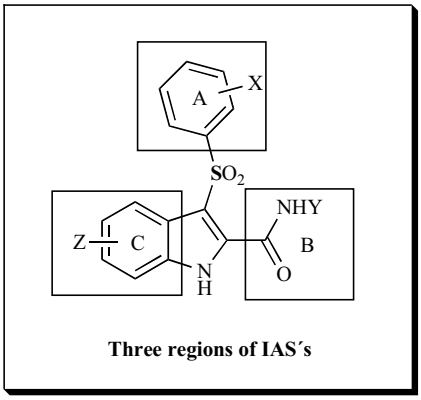


Fig. (9). Important structural regions in the IAS derivatives used for SAR studies in the fight against HIV.

Thus, IASs are considered as a potent class of non-nucleoside reverse transcriptase type 1 inhibitors of HIV [47].

4.3. Antitumor Activity of 3-arylthioindoles Derivatives

Besides their previously reported antiviral potential, the 3-aryl-substituted indole core has attracted a great deal of interest from researchers because of its antitumor potential. In the works carried out by La Regina *et al*. [68-70] and De Martino *et al*. [31], the authors presented a series of arylthioindoles (ATIs) with the potential to inhibit the polymerization of tubulin and cancer cell growth (MCF-7), in which the substituent at the 2-position of the indole ring, as well as the presence of the 3-aryl substituent lead to the formation of potentially active compounds (Fig. **10**).

La Regina *et al*. [47] further disclosed that substituents at the 5-position of the indole moiety such as a halogen or ether group lead to compounds that significantly inhibit the growth of MCF-7 tumor cells with IC_{50} values <50 nM.

It is known that some structural features result in the improvement in the antitumor activity of the indole core, such as the presence of a 3-arylthio group substituent in (A) attached *via* a C-S bond (C), the inclusion of an ether or halogen substituent in (D), and a substituent at the 5-position of the indole moiety in (D) (Fig. **11**) [31, 70, 71].

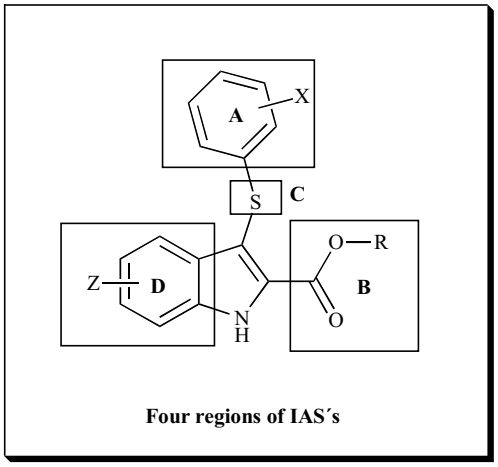


Fig. (11). Structural regions in IASs with potential antitumor activity.

5. SYNTHESIS AND ACTIVITY STUDIES OF EBSULFUR AND ITS DERIVATIVES

5.1. Previous Reports on the Synthesis of Ebsulfur

Ebselen (1,2-benzoselenazol-3(2H)-one) (Fig. **12a**) is an important compound, which has attracted a great deal of research interest in medicine and biology in view of its promising potential as an antioxidant, inflammatory agent, anti-stroke drug, bipolar disorder preventor, Mycobacterium tuberculosis Ag85 inhibitor, and anticancer agent [71]. Ebselen is lipid soluble, exhibits glutathione peroxidase-like (Gpx) activity, and is the first known organoselenium compound with minimal toxicity [72]. The synthesis of 1,2-benzoselenazol-3(2H)-one has been developed due to these fascinating properties [73]. Ebselen derivatives have been synthesized *via* the ortho-lithiation of benzamides, annulation of ortho-selanylbenzoyl chloride with primary amines, radical

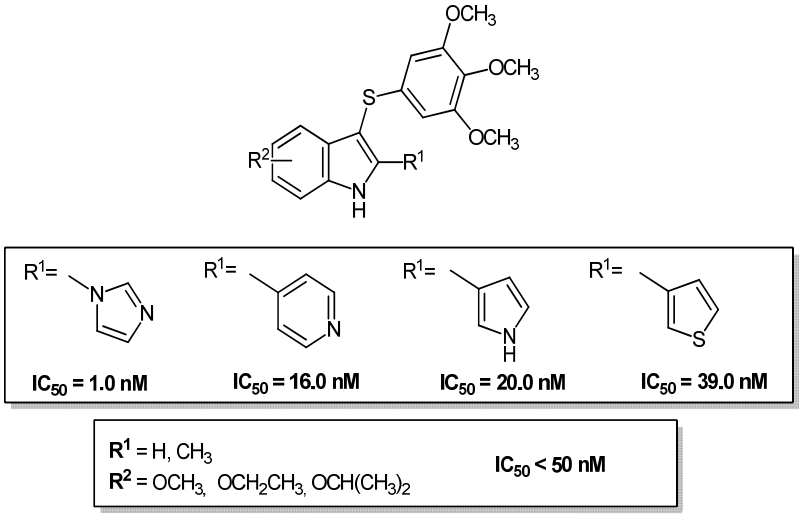
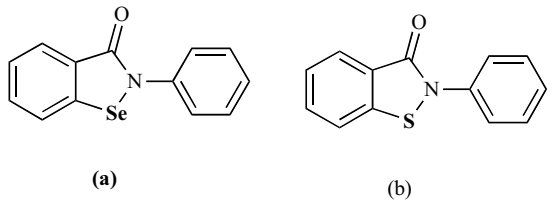


Fig. (10). The structures of the ATIs derivatives developed by La Regina *et al*. [68-70].

cyclization of diselenides and transition metal-mediated cross-coupling reactions [74]. In order to reduce the accumulation of selenium in the organism, ebsulfur (1,2-benzoisothiazol-3(2H)-one) (Fig. **12b**) was developed, in which the selenium atom of ebselen is replaced by a sulfur atom. Thus, ebsulfur and its derivatives have been the focus of interest for application against several diseases [75].



(a) (b)

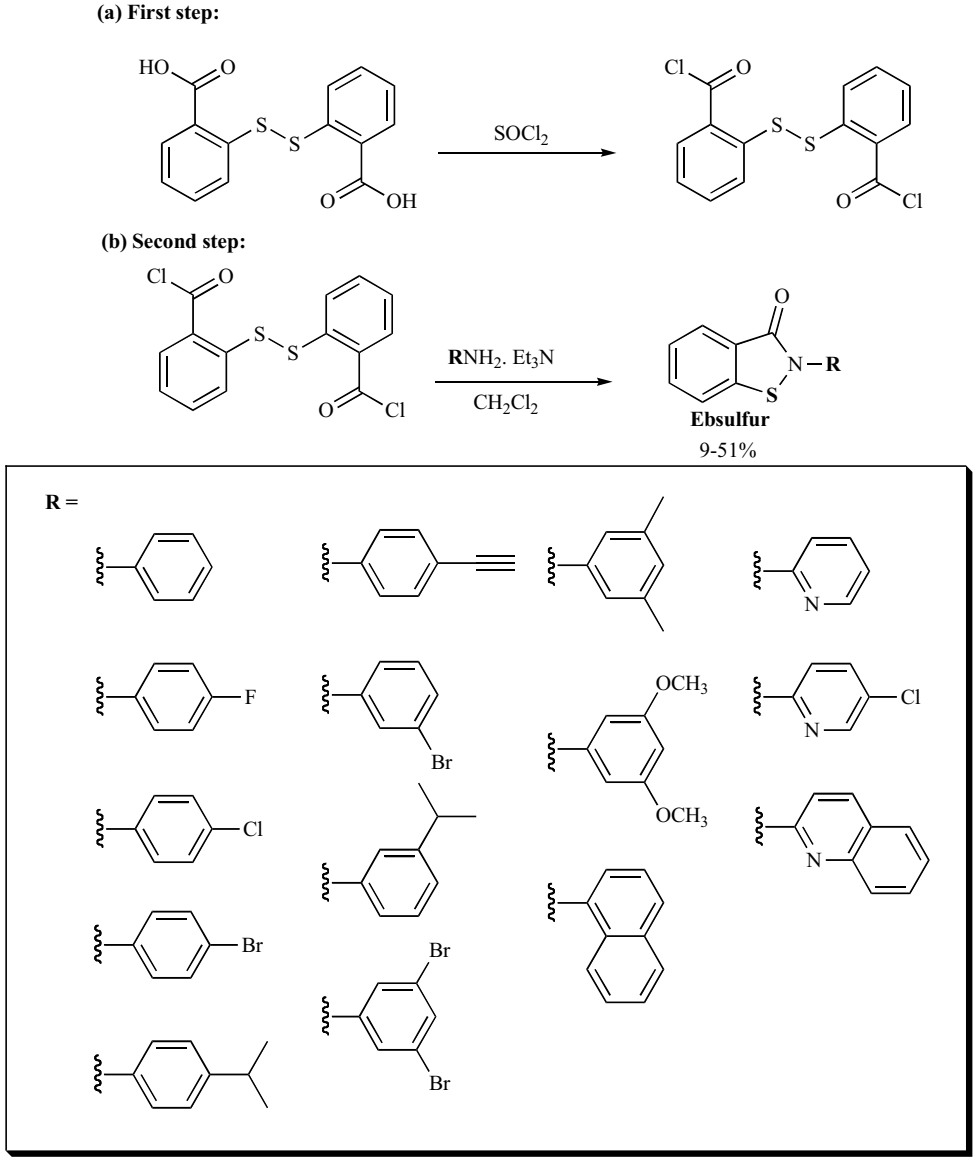
Fig. (12). The structures of (**a**) ebselen and (**b**) ebsulfur.

In terms of its synthesis, ebsulfur can be prepared upon the reaction of 2,2'-disulfanediyldibenzoic acid followed by treatment with thionyl chloride, amidation with a primary amine, and intramolecular cyclization. A classic approach involves two steps: (a) Starting from 2,2'-disulfanediyldibenzoic acid to give 2,2'-disulfanediyldibenzoyl chloride and (b) annulation of the *ortho*-sulfanylbenzoyl chloride with primary amines using triethylamine in dichloromethane (Scheme **17**) [76].

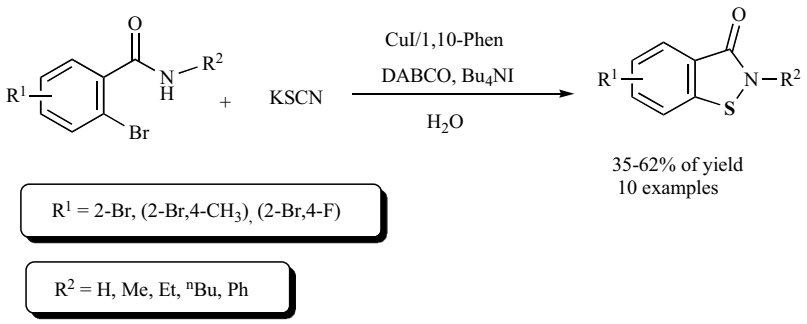
The toxicity of the reagents used in the classical synthesis of ebsulfur has restricted their application on an industrial scale. Therefore, new methodologies have been developed to obtain ebsulfur, for example a copper-mediated sulfur-nitrogen coupling reaction using 2-halo-arylamides, sulfur powder, and copper iodide/1,10-phenanthroline has been reported by Kumar *et al.* in 2009 (Scheme **18**) [77].

Aiming to make the synthetic route environmentally friendly, Xi *et al.* [78] proposed the synthesis of ebsulfur and its derivatives in water using ortho-bromobenzamide derivatives and potassium thiocyanate (KSCN) with copper iodide/1,10-phenantroline as the catalyst. Nine compounds of interest were prepared (Scheme **19**).

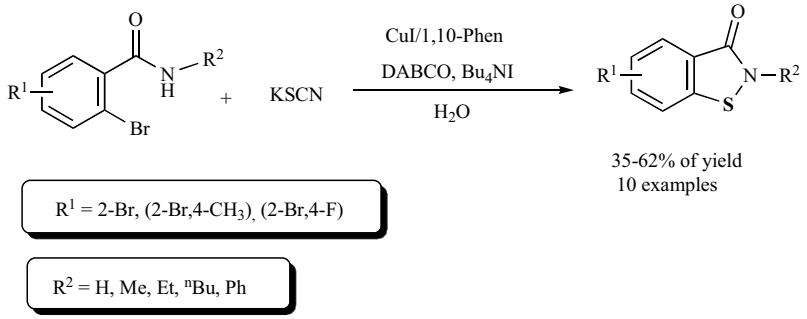
Another strategy to obtain ebsulfur is based on C-S/S-N bond formation mediated by C-H activation. In 2014, Shi *et al.* [79] described the synthesis of ebsulfur using N-(2-(pyridin-2-yl)propan-2-yl)benzamides and sulfur in the presence of $Cu(OAc)_2$



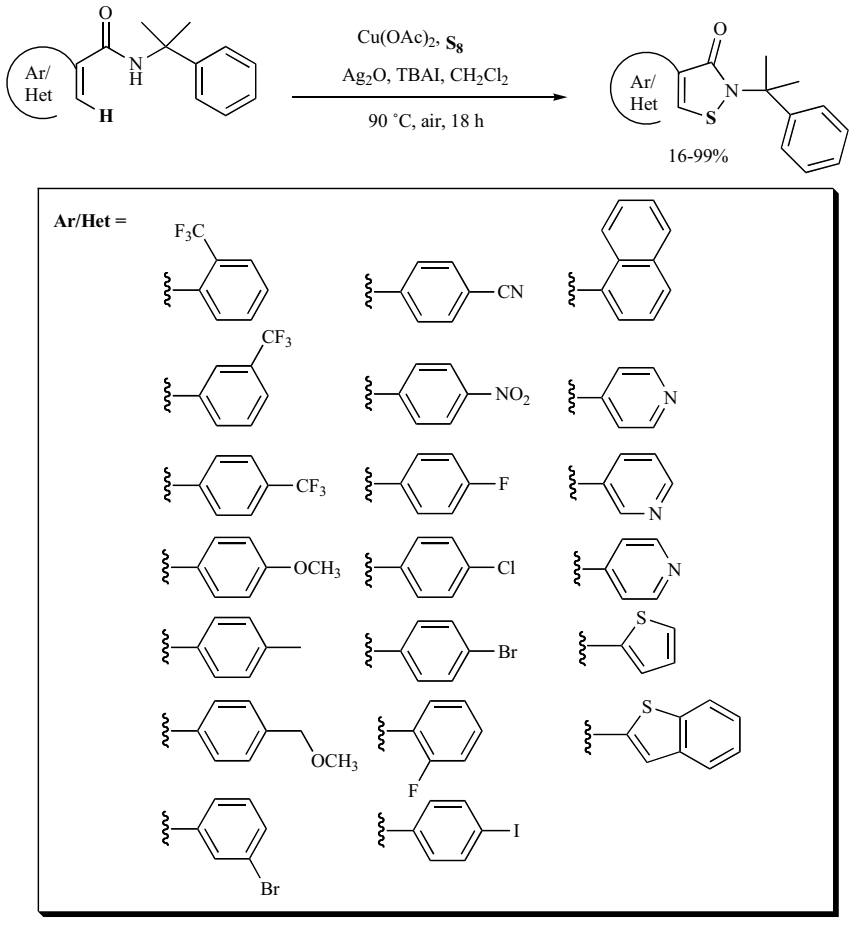
Scheme 17. Classical synthesis of 1,2-benzoisothiazol-3(2*H*)-one.



Scheme 18. S-N coupling reaction of ebsulfur.



Scheme 19. Copper-catalyzed synthesis of ebsulfur derivatives using ortho-bromobenzamides and potassium thiocyanate.



Scheme 20. Synthesis of ebsulfur *via* C-H activation.

and Ag_2O. The authors reported the synthesis of thirty examples of ebsulfur derivatives in moderate yield (16–99%). Moreover, the reactions were performed on a multi-gram scale, which enabled the introduction of several functional groups resulting in the efficient synthesis of several important compounds in medicinal chemistry (Scheme **20**).

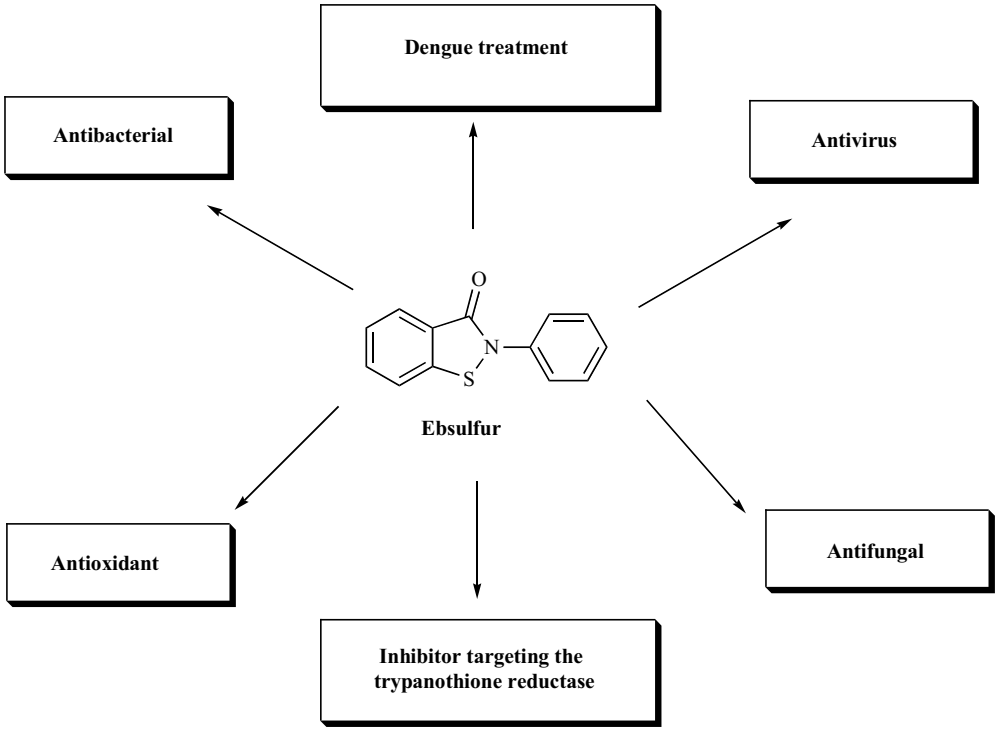
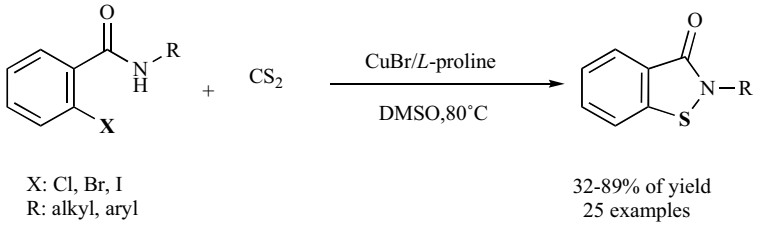


Fig. (13). Important biological properties of ebsulfur and its derivatives.



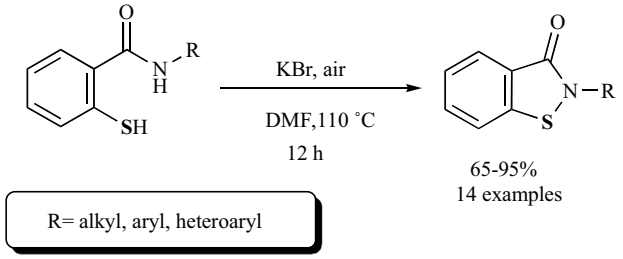
Scheme 21. CS_2 promoted the synthesis of ebsulfur derivatives.

As an alternative synthetic route, the carbon-disulfide bond has been used as a building block for sulfur compounds in organic synthesis due to its simplicity, economy of materials, and efficiency. In this context, Chen *et al*. [80] used CS_2 as a starting material for the construction of C-S/N-S bonds during the synthesis of ebsulfur from 2-halo-benzamides. The reaction was conducted in the presence of CuBr and L-proline at 80°C in DMSO and 25 ebsulfur derivatives were obtained (Scheme **21**).

Considering the importance of ebsulfur, researchers have searched for a methodology without requiring the use of a copper salt and toxic reagents because the presence of small amounts of these metals (even on a ppm scale) can cause disorders of the human immunological system. Wang *et al*. [81] have reported the synthesis of a variety of ebsulfur derivatives using KBr as a catalyst *via* an intramolecular oxidative dehydrogenation cyclization reaction under air conditions at 110°C to form the N-S bond (Scheme **22**).

5.2. Ebsulfur

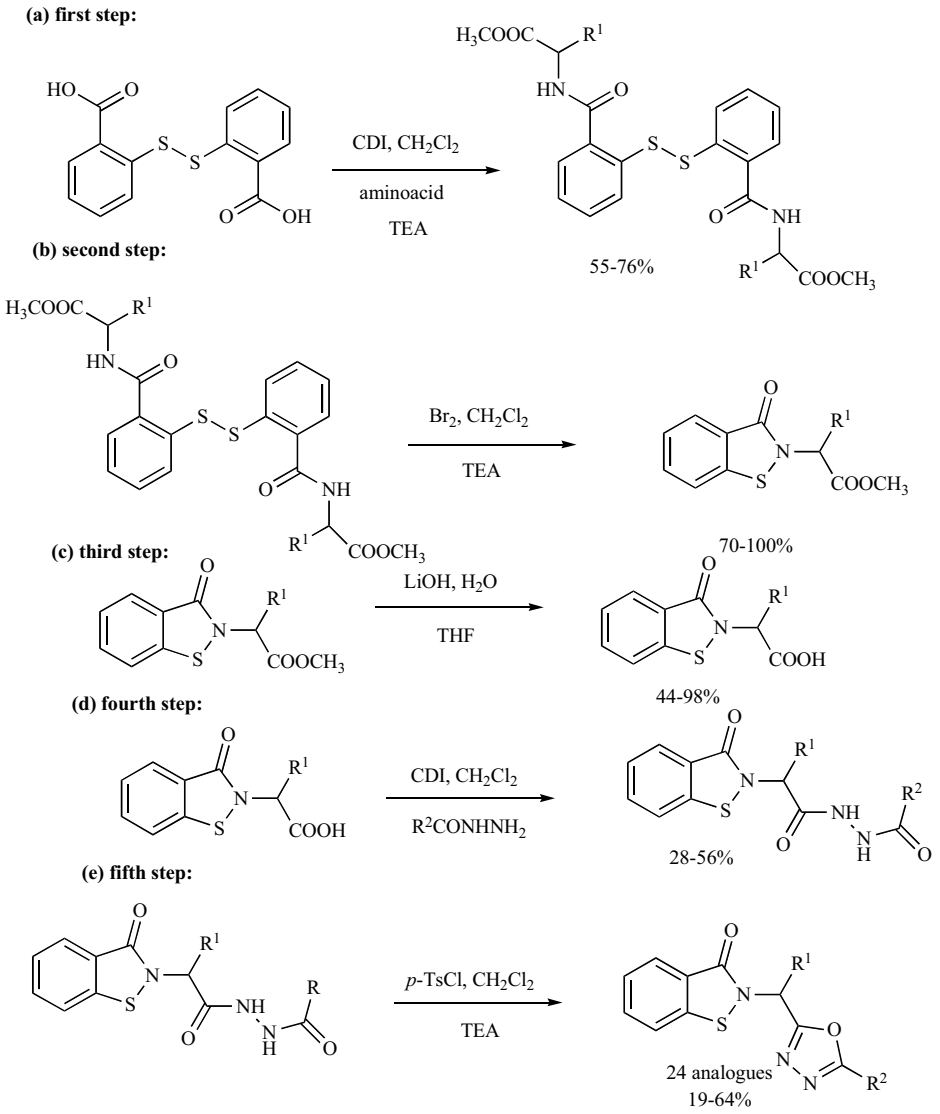
Ebsulfur derivatives act as important compounds for pharmaceutical applications due to their proven bioactivity, such as antiviral, antifungal and antibacterial properties, inhibitory activity toward trypanothione reductase [82], and use as a treatment for dengue fever. Focusing on the value of the ebsulfur core, significant attention from medicinal chemists has led to the functionalization of 1,2-benzoisothiazol-3(2*H*)-one (Fig. **13**) [83].



Scheme 22. KBr-catalyzed N-S bond formation.

5.2.1. Ebsulfur Derivatives Used to Treat Parasitic Infections

Infections caused by the protozoan parasite Trypanosoma brucei can result in African trypanosomiasis and human sleeping sickness. African trypanosomiasis has two stages in humans: (1) Parasites are found in the blood in the first stage and (2) the parasites cross the blood–brain barrier causing neurological symptoms in the second stage, leading to death if left untreated [84]. These parasites require a unique thiol redox system for DNA synthesis and defense against oxidative stress. This involves trypanithione and trypanothione reductase (TrxR) rather than the thioredoxin and glutaredoxin systems of mammalian hosts [85]. Thus, ebsulfur derivatives have emerged as a promising option for the development of drugs used to treat African trypanosomiasis. Holmgren and co-workers [85] showed that ebsulfur (EbS) is a potent inhibitor of Trypanosoma brucei growth with a high



Scheme 23. Synthesis of 1,2-benzisothiazol-3(2*H*)-one-1,3,4-oxadiazoles according to the procedure of Groutas *et al*.

selectivity index over mammalian cells. During their analysis, Halmgren's group observed that ebsulfur inhibited TryR activity. Soluble ebsulfur derivatives have been synthesized and used to treat Trypanosoma brucei infection in mice in combination with nifurtimox. Therefore, ebsulfur derivatives interrupt the trypanothione system, hampering their defense against oxidative stress [86].

5.2.2. Ebsulfur Derivatives with Antifungal Activity

Fungi-based infections have become a public health threat, mainly due to the increased number of immunocompromised patients. Among these are the AIDS patients, those with primary immunodeficiency, and those undergoing chemotherapy or organ transplantation [87]. The most common infections are Candida fungi, Cryptococcus neoformans, Aspergillus fuminatus, and Aspergillus nidulas. The most common therapeutic compounds used to treat fungal infections are azoles, nystatin (NYS), and (3) candicidin (CAN) [88].

Due to inadequate use, such as the dose and duration of treatment using these fungicidal agents, new fungal strains resistant to these drugs have evolved. Thus, the need to develop new compounds with antifungal activity has increased. In this scenario, ebsulfur appears to be structurally similar to ebselen with a new mechanism of action, which is distinct from the fungicidal agents previously mentioned [89].

The antifungal activity of ebsulfur has not been fully elucidated, but Garneau-Tsodikova *et al*. [90], investigated the antifungal activity of ebselen, esulfur and 32 derivatives against strains of Candida and Aspergillus in 2016. The ebsulfur derivatives exhibit increased fungicidal activity against all the fungal strains studied when compared to ebselen and the reference drugs. Thus, we can consider ebsulfur and its derivative as a powerful tool to fight fungi-based diseases.

5.2.3. Ebsulfur Derivatives Used to Treat Dengue Fever

The dengue virus mostly affects humans and belongs to the Flaviviridae family (genus Flavivirus). Dengue fever is a relatively mild illness with rash. However, infection by the dengue virus can evolve into a more severe illness causing bleeding [91]. There are four kinds of serotypes, which react in the same way in humans. Approximately 2.5 billion people live in the endemic regions of the dengue virus. Annually between 50 to 100 million cases of this virus occur worldwide, causing around 500,000 cases of dengue hemorrhagic fever (DHF) and 22,000 deaths. The transmission of the dengue virus occurs through mosquito bites from the Aedes aegypti genus [92]. Classic dengue fever has some common clinical

manifestations: Fever, headache, vomiting, muscular pain, fatigue, and malaise [93]. In view of the disease caused by the dengue virus, there is a need to develop an inhibitor of virus replication. Ebsulfur derivatives play an important role in various pharmaceutical applications and have shown a broad range of bioactivity against various diseases [94]. In this context, Groutas *et al*. [95] described 24 ebsulfur derivatives containing the 1,2-benzisothiazol-3(2H)-one-1,3,4-oxadiazole core and studied them against dengue virus proteases. During their analysis, ten compounds showed >50% inhibition against the dengue virus. 1,2-Benzisothiazol-3(2H)-one-1,3,4-oxadiazole can be obtained from 2,2'-disulfanediyldibenzoic acid (Scheme **23**).

6. SYNTHESIS AND ACTIVITY STUDIES OF DAPSONE

6.1. Previous Synthesis of Dapsone

Diarylsulfones and derivatives are an important class of compounds due to their wide range of applications in pharmaceuticals and polymers [96]. These compounds possess several biological activities and are used as drugs for the treatment of some diseases. An important example of a diarylsulfone is 4,4-aminodiylsulfone, known as dapsone (Fig. **14**), which is a well-known antibacterial, anti-inflammatory, and antiprotozoal drug whose action against various diseases has been widely studied [97]. It is used to treat infectious diseases (such as leprosy and malaria), non-infectious inflammatory diseases, and skin diseases [98].

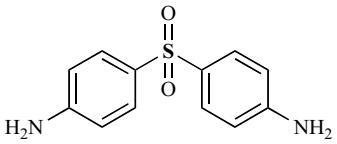


Fig. (14). The structure of dapsone.

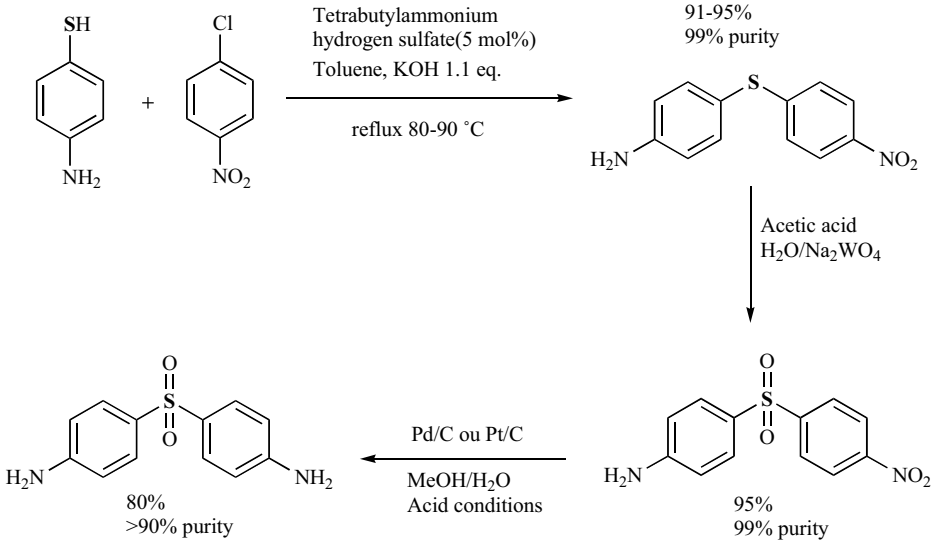
The very first synthesis of this compound was performed in 1908 by Fromm and Wittmann [99] using 10 g of para-nitro-chlorobenzene and 1 g of sulfur dissolved in a mixture of ethanol and sodium hydroxide solution. The compound was obtained, but in low yield (~6%). Despite this synthesis, its biological activity was first tested in 1937.

Throughout the years, the biological activity displayed by this compound has been discovered. Thus, several syntheses have sought to improve the synthesis and yield as well as decrease the cost. Over the last 15 years, several methodologies have been developed, and due to its large-scale use as a medicine, several patents have been applied for due to their application on an industrial scale.

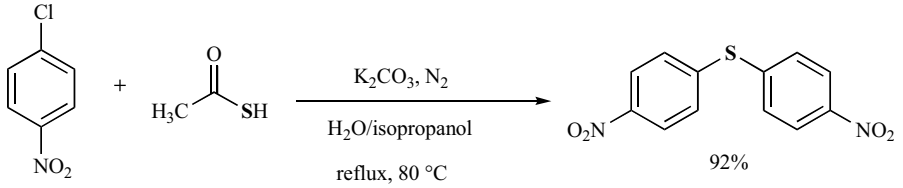
In 2009, Villa and colleagues [100] applied for a patent for the synthesis of dapsone, attempting to implement it at a low cost and high yielding industrial process. The process consists of 3 steps: 1) A condensation reaction between 4-mercaptoaniline and 4-chloro-nitrobenzene to give 4-(4-nitrophenylsufanyl) phenylamine, 2) oxidation of 4-amino-4'-nitro-diphenylsulfide using H_2O/Na_2WO_4 to give 4-amino-4'-nitro-diphenylsulfone, and 3) reduction of 4-amino-4'-nitro-diphenylsulfone to give dapsone (Scheme **24**).

In 2014, Allegrini and Mantegazza [101] described the preparation of 4-4'-dinitrophenylsulfide and its use in the synthesis of dapsone. This work proposed two different syntheses of 4-4'-dinitrophenylsulfide. One starts from nitrothiophenol and chloro-nitrobenzene (Scheme **25**) and the other from 4-chloronitrobenzene and thioacetic acid (Scheme **26**). Both approaches were carried out under a nitrogen atmosphere at reflux using a mixture of water and isopropanol as the reaction solvent and potassium carbonate as the base.

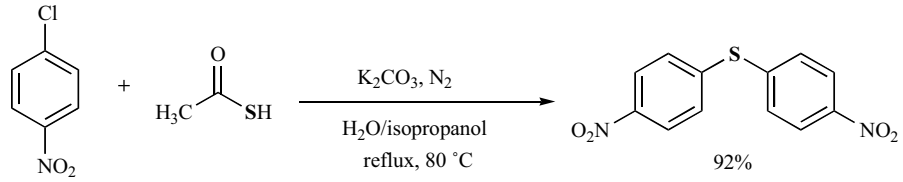
The authors proceeded to use 4-4'-dinitrophenylsulfide in the synthesis of dapsone, which required two steps. The first step involves the oxidation of the sulfur atom using several reagents to obtain 4-4'-diamino-diphenylsulfone. In this step, a solution of sodium tungstate in acetic acid, hydrogen peroxide, and methyl isobutyl ketone was used. The second step involves the reduction of



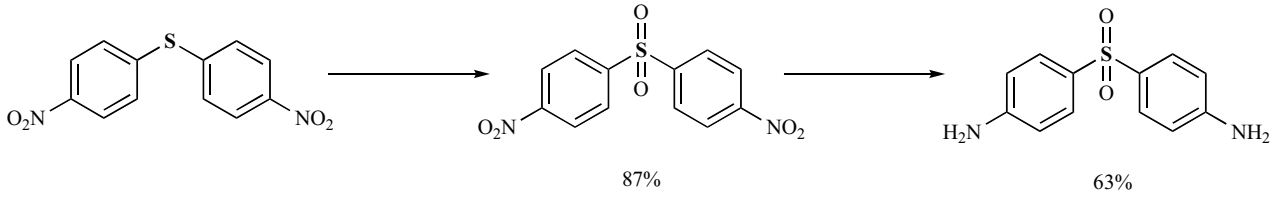
Scheme 24. Synthesis of dapsone according to the procedure of Villa *et al.* [100].



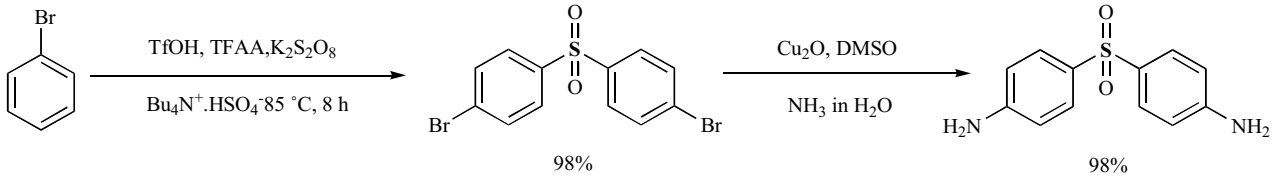
Scheme 25. Synthesis of 4-4'-dinitrophenylsulfide according to the procedure of Allegrini and Mantegazza [101].



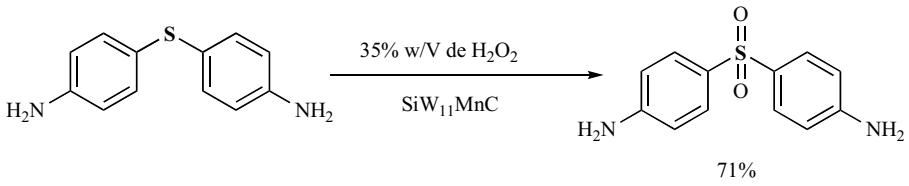
Scheme 26. Synthesis of 4-4'-dinitrophenylsulfide according to the procedure of Allegrini and Mantegazza [101].



Scheme 27. Synthesis of dapsone according to the procedure of Allegrini and Mantegazza [101].



Scheme 28. Synthesis of dapsone by Yang *et al*. [96].



Scheme 29. Synthesis of dapsone by Frenzel *et al.* [102].

the nitro groups to the amino group (Scheme **27**). For this purpose, the compound obtained in procedure was placed in an autoclave using 5% palladium on 50% wet carbon and a methanesulfonic acid solution. After active carbon treatment and adjusting the pH with sodium hydroxide, the product of interest was obtained.

Both syntheses proposed by the authors to prepare 4-4'-dinitrophenylsulfide are inexpensive and result in high yield and purity. However, the dapsone synthesis requires many steps, which may result in the loss of yield during the process, which makes the synthesis of this compound not viable.

Yang and co-workers [96] described the synthesis of diarylsulfones from arenes and potassium persulfate in 2014 (Scheme **28**). The authors performed the synthesis of dapsone and its derivatives, as well as the large-scale synthesis of dapsone. Several reaction conditions were tested, and they found the optimal conditions for the synthesis, as shown in Scheme 28. The stoichiometric amounts of the reagents used in the synthesis were: 1.0 eq of $K_2S_2O_8$, 4.0 eq of TfOH, 11.0 eq of TFAA, and 0.1 eq of PTC.

Frenzel and co-workers [102] used different catalysts for the selective oxidation of sulfides, sulfoxides, and sulfones. The catalysts used were transition metal-modified lacunary tungstosilicic polyoxometallate (TMPOM) with different transition metals supported or not supported on carbon. The metals used were manganese, iron, cobalt, and copper. The manganese catalyst ($SiW_{11}MnC$) showed the highest selectivity for the conversion of sulfones to sulfoxides. For the synthesis of dapsonde, 1 mmol of 4,4'-diaminosulfide, 0.2 mL of a 35% solution of H_2O_2, 100 mg of the manganese catalyst in 9 mL of acetonitrile were used, under stirring at 50°C in a 3 h reaction, which is illustrated in Scheme **29**.

6.2. Biological Activity of Dapsone

Dapsone is currently used as a drug for several diseases, mainly skin diseases, and is on the list of essential medicines of the World Health Organization [103]. Although its synthesis was carried out in 1908, its biological activity was only tested in 1937 by Buttle *et al*. [104], in whose research its antibacterial activity was described, as well as its activity against *Streptococcus* infections.

From these results, several studies have been performed, aiming to use this drug in the treatment of other diseases. Tests against leprosy showed the high toxicity of this compound in animals, however, when tested in humans, this toxicity was not observed. Dapsone was first used in humans in 1945 and was used orally in 1949 [105]. The drug showed a great reduction or inhibition of leprosy symptoms [106] and has become a popular and widely used treatment for this disease.

After its efficacy in the treatment of leprosy was proven, studies on the activity of this drug for various skin diseases were carried out [107]. It is known that the antibacterial action of dapsone is due to its ability to inhibit the conversion of *para*-aminobenzoic acid to folic acid.

The anti-inflammatory activity of this drug was also studied, in which its effective action was discovered in 1997. Debol *et al*. [108] proposed a mechanism of action for the anti-inflammatory activity presented by dapsone, which has not been confirmed to date.

Dapsone has also been shown to be effective in treating malaria [109] and pneumocytosis in HIV patients [103].

CONCLUSION

In general, sulfur-containing compounds present great therapeutic potential due to their broad spectrum of biological properties.

A comprehensive review of the studies on sulfur compounds reported to date has revealed that there is a structure–activity relationship, which may be useful in the search for new therapeutic agents.

In this review, we have reported the major synthetic routes and biological activities of some sulfur drugs already marketed and other molecules with great potential as future drugs, indicating that sulfur-containing compounds may be a chemical tool for many other biological treatments.

LIST OF ABBREVIATIONS

AIDS	=	Acquired Immune Deficiency Syndrome
CAN	=	candicidin
CDI	=	1,1'-Carbonyldiimidazole
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DHF	=	Dengue hemorrhagic
DMF	=	Dimethylformamide
DMSO	=	Dimethyl sulfoxide
EbS	=	Ebsulfur
HIV	=	Human Immunodeficiency Virus
iPrOH	=	Isopropyl alcohol
NMP	=	*N*-Methyl-2-pyrrolidone
NYS	=	Nystatin
PPA	=	polyphosphoric acid medium
p-TsCl	=	*p*-Toluenesulfonyl chloride
TBAI	=	Tetrabutylammonium Iodide
TEA	=	Triethylamine
TFAA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TMPOM	=	Tungstosilicic polyoxometallate
TMSCl	=	Trimethylsilyl chloride
VIF	=	Viral infectivity factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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