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FULL PAPER

Recent advances in sulfadiazine's preparation, reactions and biological applications

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Sulfa drugs have great attraction due to their wide applications in medicine, pharmacology and other sciences. One of the most important compounds of Sulfa drugs family is sulfadiazine compound (SDA). It is considered as one of the most important antibiotics that is used in treatment of many diseases such as urinary tract infections (UTIs), toxoplasmosis, malaria and other cases. Due to vital role of sulfadiazine in our life, this review focused on the sulfadiazine properties, preparation methods, reactions and its biological applications.

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KEYWORDS

Sulfadiazine; preparation; reactions; biological activity.

Introduction

Sulfadiazine is one of the most important antibiotics in medicines, which is known as a sulfa drug or the sulfonamide group. According to the IUPAC system, this compound is called as 4-amino-N-pyrimidin-2-yl-benzenesulfonamide, as shown in **Figure 1**. Sulfadiazine compound has some physiochemical properties such as being a white, odorless crystalline powder, modestly soluble in acetone $(CH_3)_2CO$ and alcohol, dissolvable in water, molar mass; 250.28 g·mol^{-1} and melting point; 252-256 °C. This drug is used in the medical field to treat urinary tract infections, as a topical agent to the treatment of a burn and wound infections and in the veterinary and human therapy [1-11].

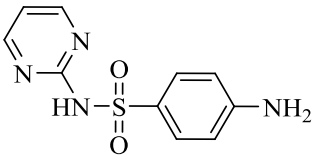


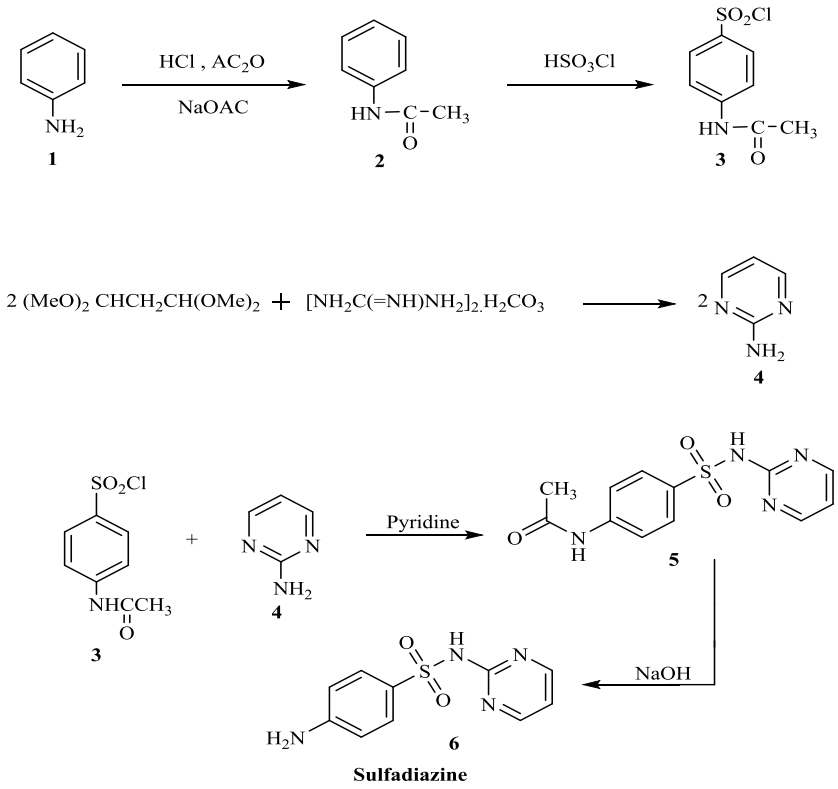
Figure 1 Structure of sulfadiazine

Numerous chemotherapeutically important sulfa compounds as sulfadiazine (silver sulfadiazine, Silvadene), Sulfamerazine, Sulfathiazole, etc, have (-SO_2NH-) part, as a toxophoric functional group [12]. Their heterocyclic moiety contains sulfur(S), oxygen (O) or nitrogen (N) atoms that improve their biological activities [13].

Synthesis of sulfadiazine

The common synthesis of sulfadiazine compound usually starts from acetylation of aniline derivatives **1** by reaction with acetic anhydride to give acetanilide derivative **2**. Acetanilide derivatives react with Chlorosulfonic acid to produce 4-acetylaminobenzenesulfonyl chloride **3**. On the other hand, the 2-aminopyrimidine **4** was prepared by reaction two molecules of tetramethoxypropane with guanidine salt. In the final stage, the 4-acetylaminobenzenesulfonyl chloride was reacted with 2-aminopyrimidine to give an

acetanilide derivative **5** which hydrolyzed by using NaOH solution to form sulfadiazine compound (6), Scheme 1[14-15].



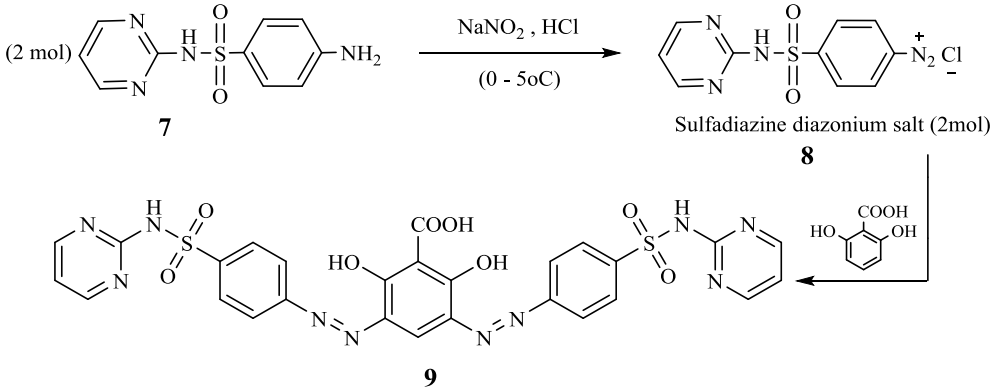
SCHEME 1 Synthesis of sulfadiazine compound

Reactions of sulfadiazine

There are two reactive groups in sulfadiazine compounds by which sulfadiazines involve in many chemical reactions; one is the aromatic amine and another is sulfonamide group.

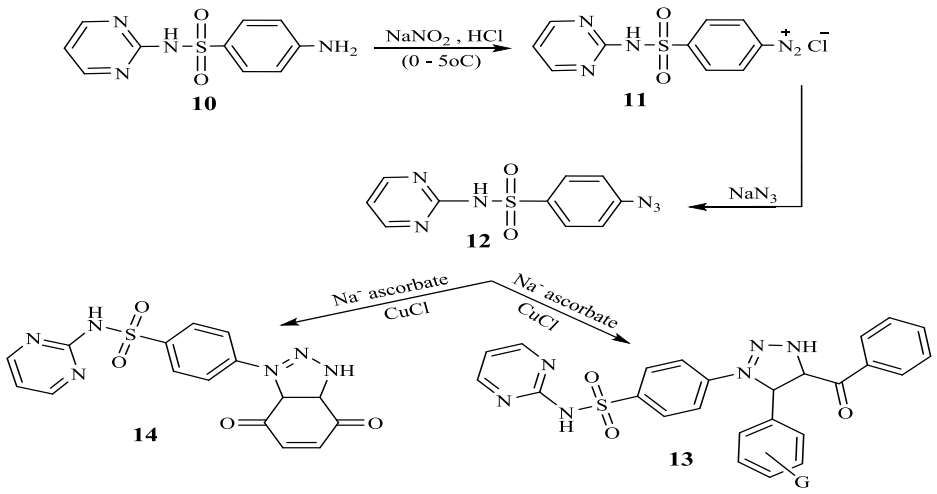
Reaction of amine group

Salim *et al.* [17], Synthesized azo derivative by treatment of sulfadiazine **7** with solution of nitrite in the presence of acidic medium to afford diazonium salt **8**, the latter reacts with Gamma-resorsolic acid in the presence of basic medium to produce compound **9**, Scheme 2.



SCHEME 2 Synthesis of Azo dye from sulfadiazine compound

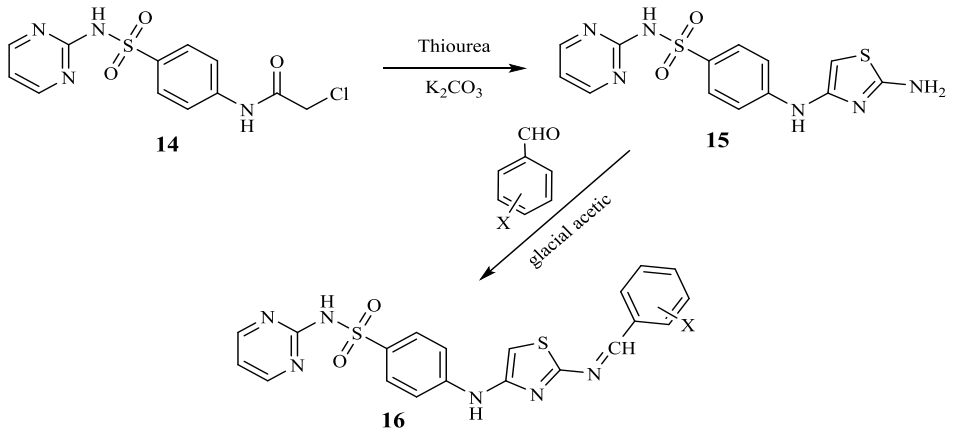
In Scheme 3, Ahmed [18], Synthesized of (4-azido-N-(pyrimidin-2-yl) phenylsulfon-amid) derivatives by coupling reaction, in the first step, sulfadiazine **10** reacted with sodium nitrite in the presence of HCl solution, then, the result compound **11** reacted with sodium azide. In addition, 1,2,3-Triazoline derivatives was prepared by reaction of azido **12** derivative with chalcones and unsaturated compounds.



G =-4-N,N-dimethyl , -4-bromo, -4-methyl , -4-nitro, 2-4-dichloro, -4-hydrox

SCHEME 3 Synthesis of Azo and 1,2,3-triazoline derivatives

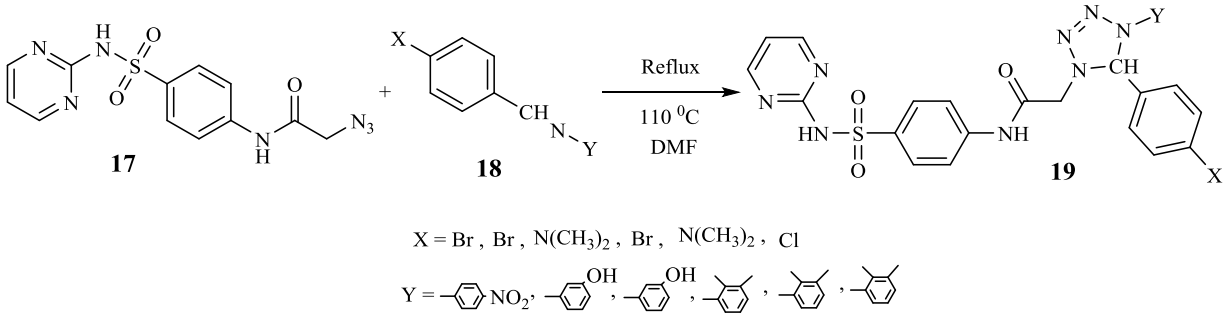
The [Chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide]compound, thiourea and anhydrous potassium carbonate (K_2CO_3) in absolute ethanol were heated under reflux on water bath for 12 hours to form [4-(2-aminothiazol-4-ylamino)-N-(pyrimidin-2-yl)benzene sulfonamide]. This derivative reacted with different aromatic aldehydes in the presence of glacial acetic acid to form Schiff bases derivatives, Scheme 4 [19].



X = 4- Br , N,N-Me , 4-OH-3-OCH_3 , 4-OH, 2,4-diCl

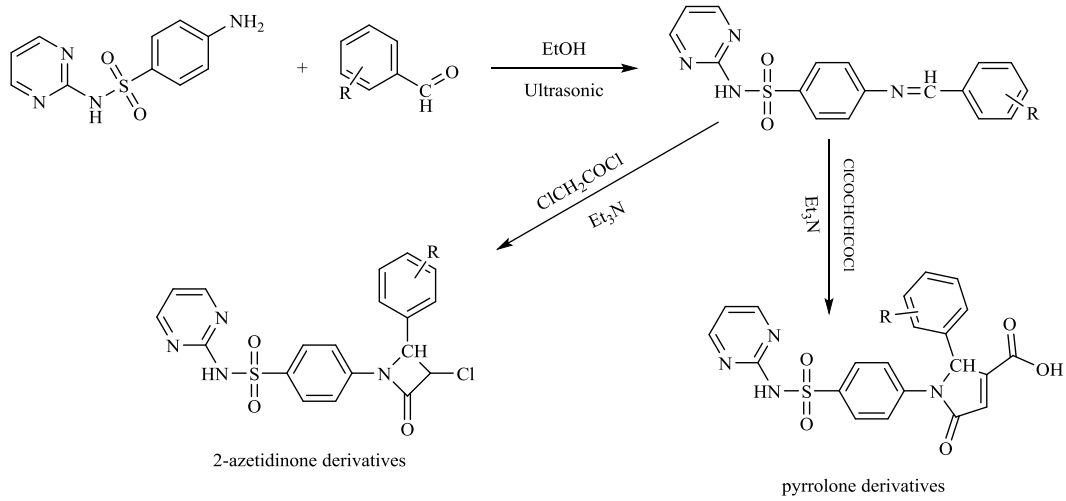
SCHEME 4 Synthesis of Sulfadiazine derivatives

Tetrazole derivative was prepared in good yields by 1,3- dipolar_cyclo addition reactions of 2-azido-N(4-(N-pyrimidin-2ylsulfamoyl)-phenyl) acetamid and Schiff bases derivatives, Scheme 5 [20].



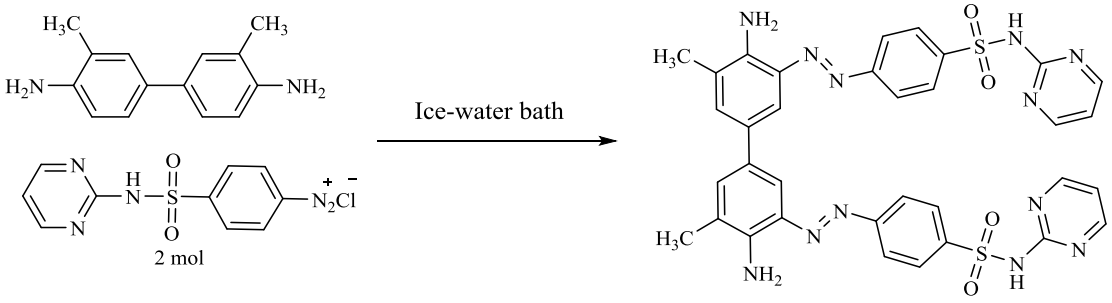
SCHEME 5 Synthesis of Tetrazole derivatives

Sangar A. *et al*. [21] prepared 2-azetidinone derivatives and pyrrolone derivatives as antioxidant agents with antibacterial activity against two kinds of bacteria (*Staphylococcus aureus* and *Escherichia coli*) via condensation of sulfadiazine with different substituted aldehydes to form schiff base derivatives; the latter compounds were reacting with chloroacetyl chloride and fumaryl chloride in the presence of triethylamine, respectively, Scheme 6.



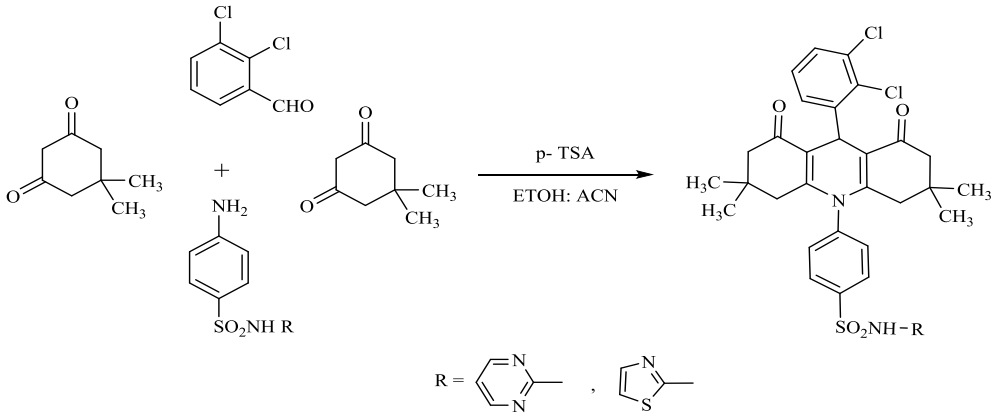
SCHEME 6 Synthesis of 2-azetidinone derivatives and pyrrolone derivatives

Iman K *et al.* [22] prepared a series of 1,3-oxazepine derivatives and 1,3-dizepene derivatives. The first step was the reaction of dizaonium slat of sulfadiazine with O-tolidine, Scheme 7.



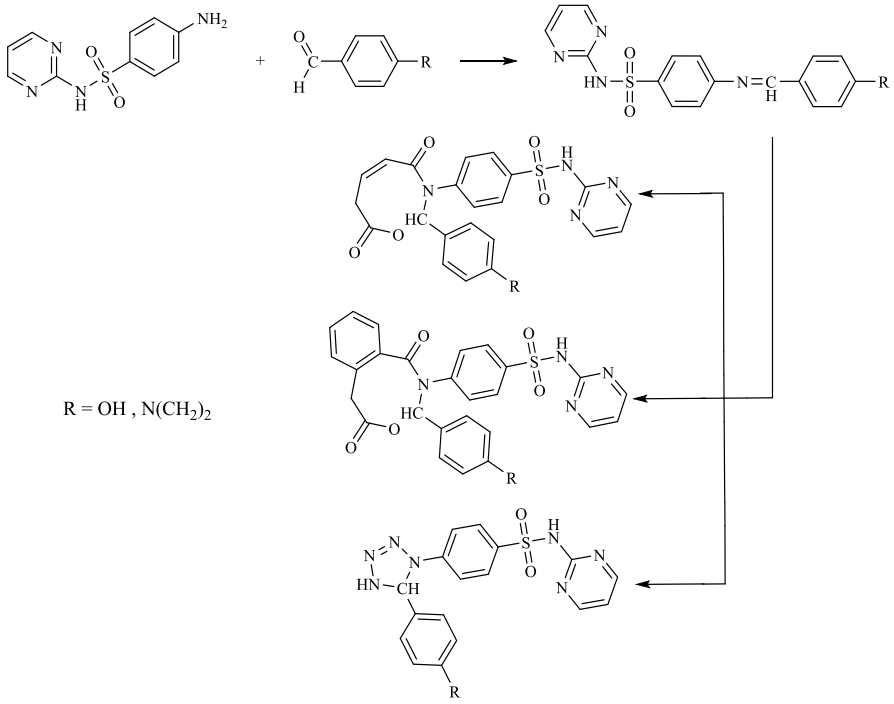
SCHEME 7 Synthesis of O-tolidine derivatives

M.G. Gündüz *et al*. [23] prepared two novel acridine and sulfonamide scaffolds from reaction 5,5-dimethyl-1,3-cyclohexanedione, 2,3-dichlorobenzaldehyde with sulfadiazine /sulfathiazole compounds in the presence of a catalytic amount of p-toluene sulfonic acid, Scheme 8.



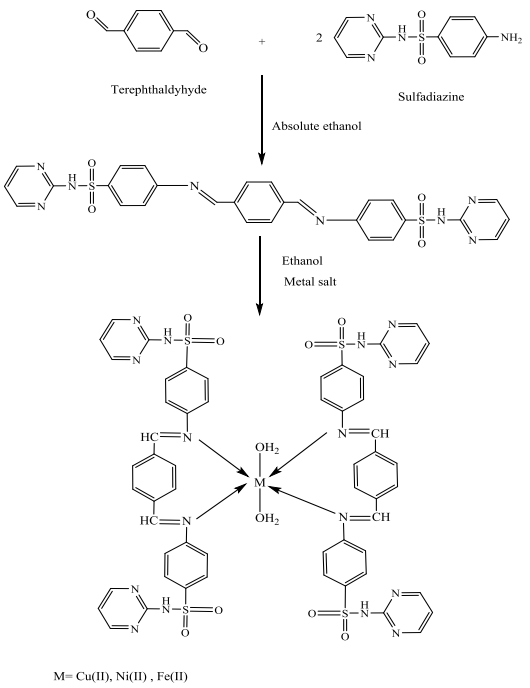
SCHEME 8 Synthesis of acridine-(sulfadiazine/sulfathiazole) Derivatives

Wissam [24] showed the reaction of sulfadiazine as starting material with substituted benzaldehydes to yield Schiff base derivatives. These derivatives reacted with (maleic anhydride, phthalic anhydride) and sodium azide to give (Oxazepine) and Tetrazole derivatives, respectively, Scheme 9.



SCHEME 9 Synthesis of Oxazepine and Tetrazole derivatives

Hawraa [25] synthesized new complexes of Schiff base derived from sulfadiazine (Scheme 10).

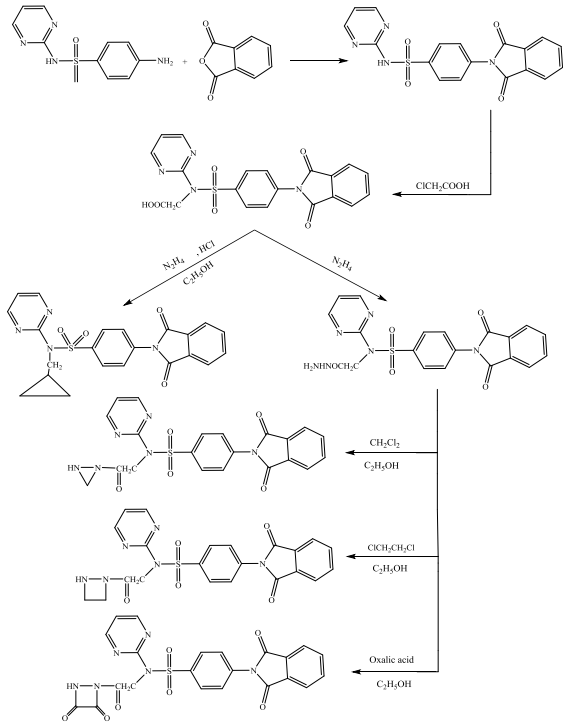


SCHEME 10 Synthesis of Oxazepine and Tetrazole derivatives

Reaction of sulfonamide group

In these reactions, the amine group must be protected and blocked before the sulfomide group interacts with other compounds.

Nabeel jebor ALganabi *et al* [26] prepared a series of sulfadiazine derivatives by alkylated the nitrogen atom in the sulfonamide group to form diaziridine, diazirine and diazetidin derivatives, Scheme 11.

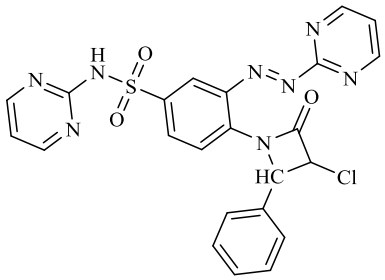


SCHEME 11 Synthesis of Sulfadiazine derivatives

Biological applications of sulfadiazine

Sulfadiazine is considered as standard therapy for the conservative treatment of burn wounds [27]. The drug sulfadiazine inhibits bacteria from making folic acid, so bacteria cannot manufacture DNA so it is not a step to increase the numbers. Thus, sulfadiazine prevents infection from spreading. The remaining bacteria either die in the end or are repelled by the immune system [28-29].

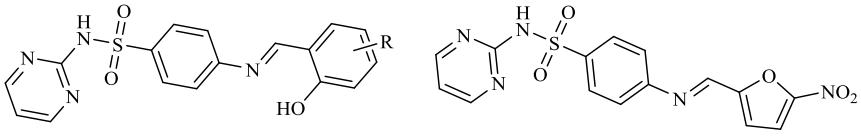
A.Khdur *et al.* [30] prepared some new β-Lactam derivatives from Azo Sulfadiazine as anticancer compounds, Figure 2.



R= (p-$N(CH_3)_2$), (p-Cl), (p-OH-m-OCH_3), (p-Br) , (p-NO_2)

FIGURE 2 Synthesis of β-Lactam Derivatives

Martin *et al.* [31] prepared Sulfadiazine-derived Schiff bases by the condensation between sulfadiazine with Salicylaldehydes & 5-nitrofuran-2-carbaldehyde. These compounds show antimicrobial activity and cytotoxicity properties, Figure 3.



R = H, 5-F, 5-Cl, 5-Br, 5-I, 5-NO_2 ,5-Me, 5-MeO, 5-OH,
5-tert-Bu, 3-Cl, 6-Cl, 3,5-Cl_2 , 3-Br-5-Cl, 3-I-5-Cl, 3,5-I_2

FIGURE 3 Synthesis of Sulfadiazine-derived Schiff bases

Mahmood *et al.* [32] synthesized Barbituric acids derivatives by reaction of 2-chloro-N-(4-(4-(N-pyrimidin-2-yl-sulfamoyl)phenyl-amino)thiazol-2-yl) acetamide compound with barbital, phenobarbital and their derivatives in the presences NaOH and K_2CO_3 respectively. The yield products show antibacterial and antifungal activity, Figure 4.

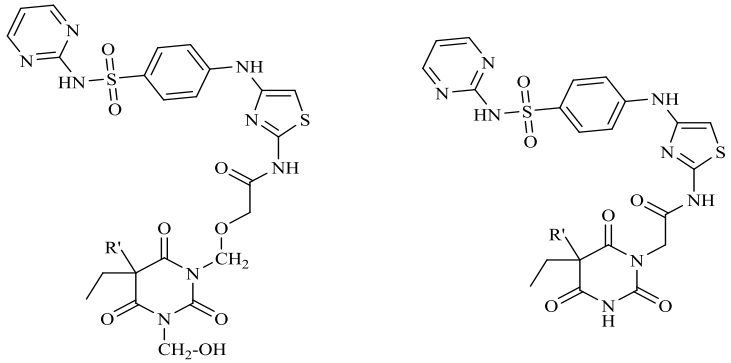


FIGURE 4 Synthesis of Barbituric acids derivatives

Conclusion

In sum, Sulfadiazine can be considered as starting material for Schiff base, Azo, Azetidinone, Oxazepine, Dizepene, Tetrazole, and Barbituric acids derivatives creation.

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