ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Schiff's Bases Containing Sulphamethoxazole Nucleus.

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ABSTRACT

Schiff bases are condensation products of primary amines with carbonyl compounds gaining importance day by day in present scenario. Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group and are found to be a versatile pharmacophore for design and development of various bioactive lead compounds. Schiff bases exhibit useful biological activities such anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, antiglycation, and antidepressant activities. Schiff bases are also used as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers, and corrosion inhibitors. The present review summarizes information on the diverse biological activities and also highlights of some Schiff bases synthesized.

Keywords: Schiff base, amines, sulphamethoxazole nucleus.

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ISSN: 0975-8585

GENERAL INTRODUCTION

Schiff's bases are the compounds, which contain –C=N- group. These compounds were named after the German chemist Hugo Schiff and are produced by reacting the aldehyde or ketone with primary amines [1], Structurally, a Schiff base (also known as imine or azomethine or anils) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C,O) has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers [2]. Schiff bases are reported to show.

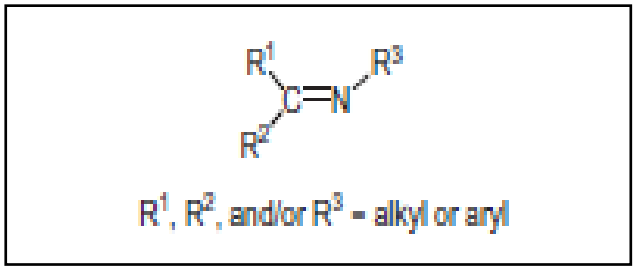
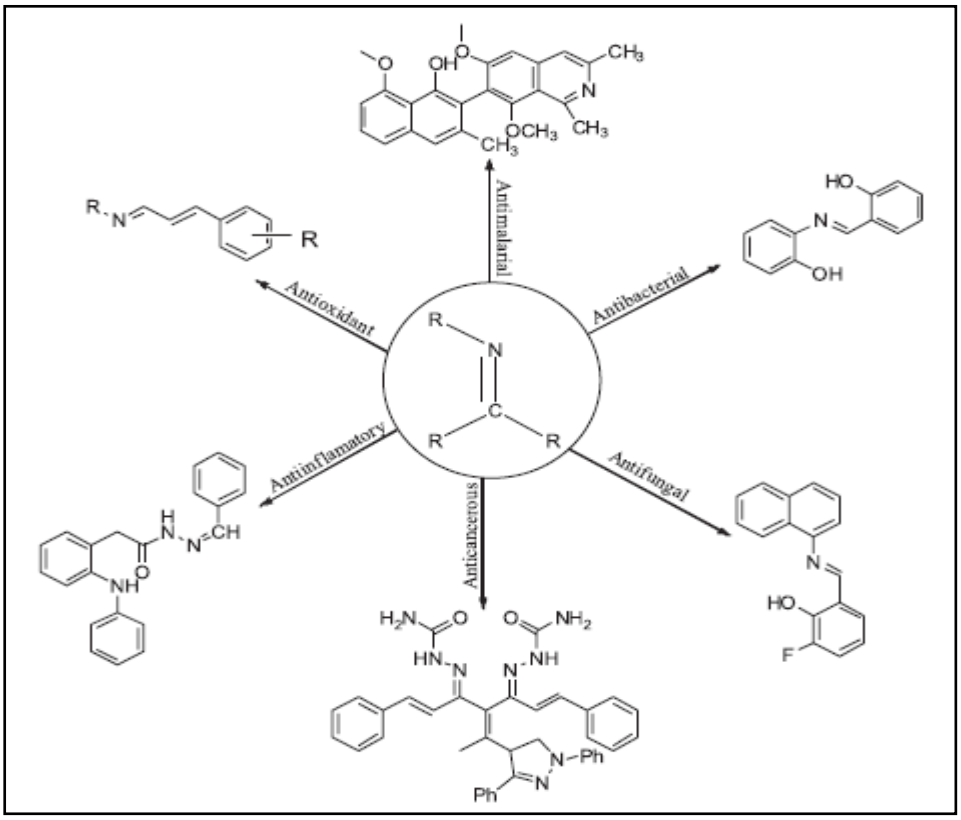


Figure 1: General structure of a Schiff's bases.



Scheme 1: Pharmacologically active schiff's bases [1,5,6,7].

Genaral Genaral account of the summary of reaction of aldehydes with amine (aromatic or aliphatic) has been reviewed by Murry [8]. Some azomethines from amphetine and procaine were reported by Giovambattista and Rabassa [9]. Savich [10] at el. gave the detail study report of azomethines from 2-hydroxy-1-napthaldehyde and arylamides. Takeo and Yuh [11] have been synthesized azomethines of 3,5-dibromosalicyladehyde. Some complexes of azomethines have also been synthesized from hetero aromatic amine and salicylaldehyde [12]. Sreenivasulu and Rao[13] have studied the characterization of azomethines and its ability of complexing with cadmium(II) by polarography. Electrochemical behavior of platinum complexes of azomethines has also been reported by Shagisultanova et al. [14] .

Parra et al. [15] have studied the mesomorphic properties of some azomethines compounds derived from phenyl and thienyl-1,3,4,-thiadiazol. Some other azomethines have also been synthesized by Hussain and Shaukat from p-dimethylamino cinnamaldehyde [16] .

Importance of Schiff Bases in Organic Synthesis, Bio-Processes and Pharmaceutical Chemistry

1. **Schiff Bases as Precursors of Countless Versatile Organic Processes for the Production of Intermediates/Products.**

As a versatile precursor for organic synthesis, we can identify, in an oversimplification, four different types of reactions in which Schiff bases have been found extremely important applications:

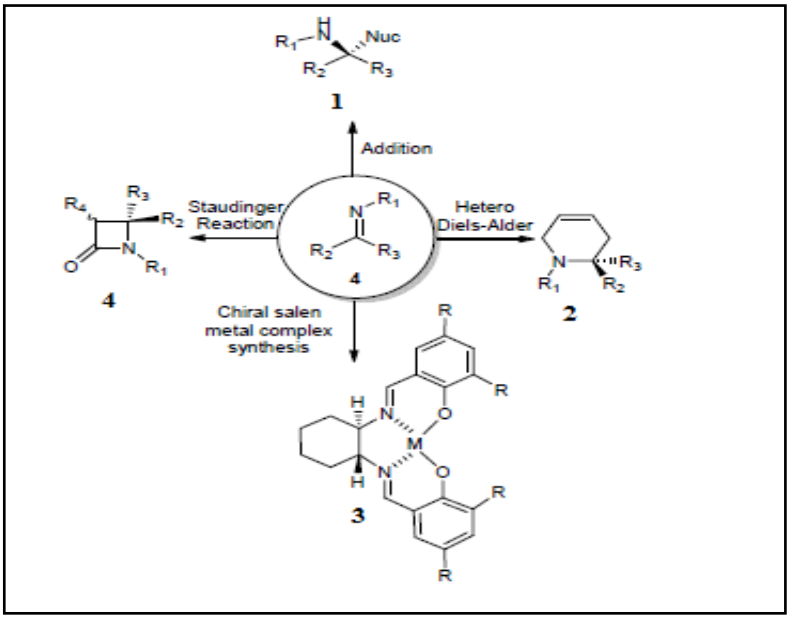
a. Addition of organometallic reagents or hydride to C=N bond to afford compounds of structure **1**;
b. Hetero Diels-Alder reaction to furnish six membered nitrogen containing heterocyclic compounds of general formula **2**;
c. Skeletons for the building-up scaffolds, as the very famous *salen scaffold*, to be used as "*privileged ligand*" [17] for the formation of the corresponding *chiral salen metal complexes* **3**;
d. Staudinger reaction with ketene to furnish biologically important β-lactam ring **4** (Scheme 2). It must be underlined for point (c) that we are reporting only the applications of chiral salen complexes [17-21].

For different complex catalysts, as salophen [22,23] , or for the use of Schiff bases, different from salen backbone, we refer the interested reader to the following up-to-date survey survey of extremely good and dedicated reviews on the subject authored by specialists in the field [24-30].

The same criteria have been used for all the applications reported in Scheme 10. Accordingly we have grouped the references reported in:

a. Reduction of C=N bond, focused on asymmetric formation of carbon-carbon bond [31-34];
b. Hetero Diels-Alder reactions with the formation of heterocyclic compounds [35-41] ;
c. Use of chiral salen metal complexes in the asymmetric synthesis [42,43];
d. Staudinger reactions for the preparation of β-lactams [44-48].

In the following paragraphs we will emphasize the importance of imines, first discovered by the Hugo Schiff, providing the reader with relevant information highlighting the importance of Schiff bases and their applications in a wide range of organic and pharmaceutical chemistry fields.

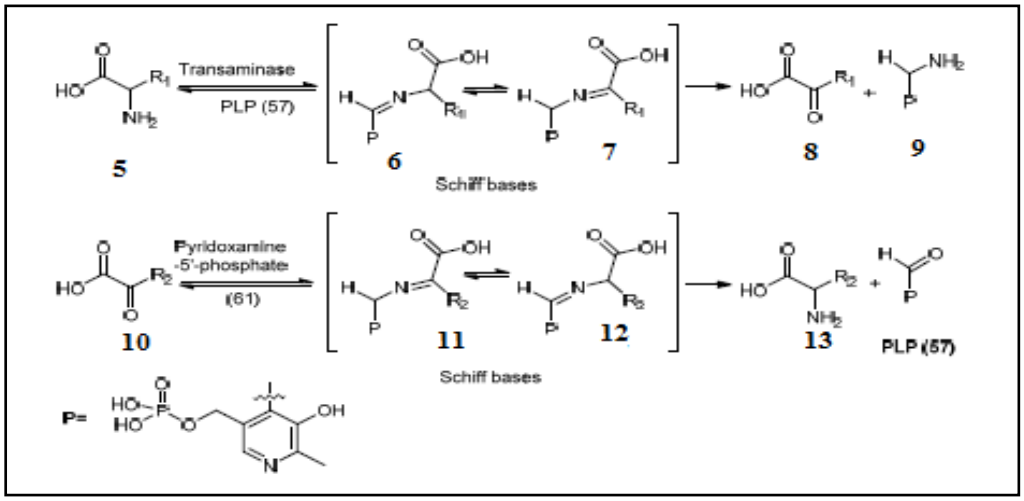


Scheme 2: Application of schiff bases in organic synthesis.

ISSN: 0975-8585

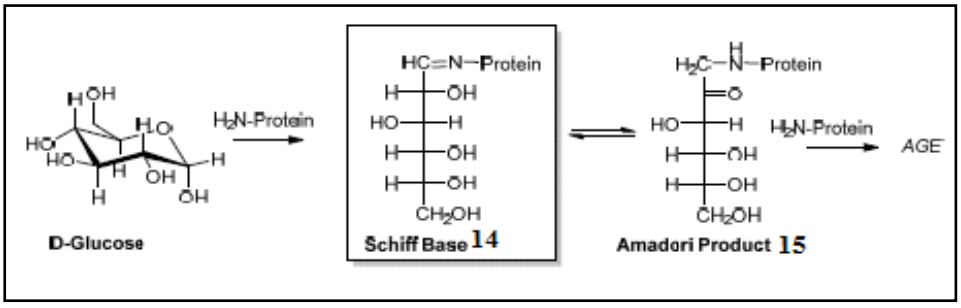
2. Schiff Bases as Intermediate of Bio-Processes

The importance of Schiff bases as intermediates in bio-processes is very well established: suffice it to mention one of the very basic process of life: the transamination reaction (Scheme 3) [49].



Scheme 3: Transamination reaction through Schiff bases from amino-acid to ketoacid and vice versa.

Other important bio-processes, that lately are attracting the interest of chemists and biologists, are related to the glycation of albumin that leads to the formation of important biomarkers, which are predictive of type II diabetes [50] or to the reaction between sugars and biologically relevant amines with the formation of Schiff bases. These intermediates Schiff bases **14**, in turn, evolve to **A**dvanced **G**lycation **E**ndproducts ***(AGE)*** through Amadori compounds (Scheme 4).



Scheme 4: Protein glycation by glucose.

AGEs are involved in many pathological conditions such as cardiovascular disease [51], Alzheimer [52].

3. Pharmacologcal Significance of Schiff's Bases

Antimicrobial activities

Schiff base derived from furylgloxyl and p-toludine show antibacterial activitiy against Esherichia coli,. Some heterocyclic Schiff base [53-55] can act as a antibacterial agent. Isatin derived Schiff base [56, 57] posses anti-HIV activity and anti-bacterial activity. Schiff bases (banzimidazole [58], toluidinones [59], quin-azolinones [60], furaldehyde [61], thiazole [62, 63] pyrimidine [64], indole [65], show antibacterial activity. Schiff base [66-68] with thiophene carboxaldehyde and aminobenzoic acid show anti-bacterial activity. Lysine based Schiff bases and their complexes [69] with La, Co, Fe, show bacteriostatic activity to B. subtilis, E.coli and S. aureus. Zn (II), Cd (II), Ni (II) and Cu (II) complexes with furfural and semicarbazide [70], and with furfurylidene diamine [71] Shiff bases show antibacterial activities. Organo-silicon (IV) complexes [72] with bidentate Schiff bases, organo-lead (IV) complexes [73] with nitrogen donar legands of sulpha drugs posses antibacterial activities.

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Antifungal activities

Benzothiazole Schiff bases [74] posses effective antifungal activity. Schiff bases and their metal complexes [75] formed between furan or furylglycoxal with various amines show antifunagal activity against Helminthsorium gramineum (causing stripe disease in barely) Syncephalostrum racemosus (causing fruit rot in tomato).

Antiviral activities

Schiff base of gossypol [76] show high antiviral activity. Flourination [77] on aldehyde part of shiff base enhances insectoacracidal activity. Schiff bases (thiadiazole derivatives with salicylaldehyde) and their metal complexes [78] with Mo (IV) show insecticidal activities against bollworn and promote cell survival rate of mung bean spouts.

Sulphonamides

A sulfonamide grouping is derived from a sulfonic acid group by replacing its hydroxyl group with an amino group. Sulfonamides, also known as sulfa drugs, have a history that dates back to almost 70-80 years. A sulfonyl group plays a very important role as a key constituent of number of biologically active molecules. sulfonamide used to treat various infections caused by bacteria and fungai. They have an active functional group $–S(=O)_2–NH_2$ i.e. sulfonyl group connected with a free amino group on the apposite side thus forming a general formula RSO_2NH_2, where R is an organic group. Moreover, the free amino group has a tendency to give condensation products, if reacted with carbonyl containing moieties e.g., aldehydes, ketones and/or acids. The sulfonamide family includes active members as sulfamethazine, sulfadiazine, sulfathiazole, sulfanilamide, sulfamethaxazole, 4-(2-aminoethyl)benzenesulfonamide, 4-(aminomethyl)benzinesulfonamide, sulfisoxazole (gantrisin), sulfaguanidine, sulfasalazine (azulfidine), sulfadimethoxine, sulfamethoxypyridazine, sulfacetamide, sulfadoxine, sulfasalazine, sulfafurazole, sulfamoxole and sulfamerazine. We can classify sulfa drugs in two ways, one is based on the chemical structure i.e., sulfonylartylamine, non sulfonylarylamine and sulfonamide moiety containing drugs (Figure. 1) [79] and the other is based on cross reactivity theory i.e., Sulfonamides Antibiotics (SA) and Sufonamides Non-Antibiotics (SNA) (Table 1) [80].

Table 1: Sulfa drugs

Antibiotic sulfonamide	أ- **Subgroups**	**Drugs Sulfadiazine, sulfisoxazolesulfamethoxazole, sulfapyridine**
Non antibiotic sulfonamide	Carbonicanhydrase inhibitors	Acetazolamide, Brinzolamide, Dichlorphenamide, Dorzolamide,
	Loop diuretics	Methazolamide, Sulthiame Bumetanide, Furosemide,
	Thiazides and related compounds	Piretanide, Torsemide Bendroflumethiazide, Benzthiazide, Chlorothiazide, Chlorthalidone, Clopamide, Diazoxide, hydrochlorothiazide,
	Sulfonylureas	Hydroflumethiazide, Indapamide, methyclothiazide, metolazone, Polythiazide, Xipamide
	Cyclooxygenase 2 (COX-2) inhibitors	Acetohexamide, Chlorpropamide
	protease inhibitors	Gliclazide, Glibornuride, Glipizide,
	Triptans	Glimepiride, Gliquidone, Glyburide,
	Other agents	Glymidine, Tolazamide, Tolbutamide Celecoxib, rofecoxib, valdecoxib Amprenavir, Fosamprenavir Naratriptan, Sumatriptan Amprenavir, Dapsone, Fosamprenavir, Ibutilide, Probenecid, Sotalol, Sulfasalazine, Topiramate, Zonisamide

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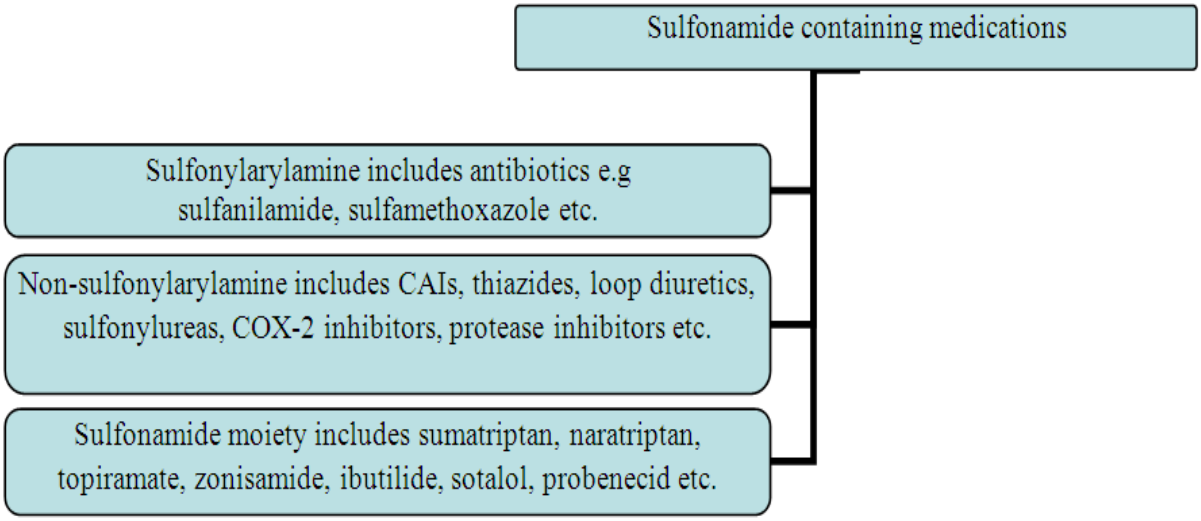


Figure 2: Classification of sulfonamides, CAI = carbonic anhydrase inhibitors; COX-2 = cyclooxygenase-2; thiazides = thiazide diuretics and related compounds.

Sulphanomides as Antibacterial

Sulfonamides were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. Among the many and so different families of organic–inorganic chemicals being currently investigated today because of their applications, sulfonamides and their N-derivatives are one of the outstanding groups.

Sulfonamides represent an important class of medicinally important compounds which are extensively used as antibacterial agent. It interferes with PABA (p-aminobenzoic acid) in the biosynthesis of tetrahydrofolic acid, which is a basic growth factor essential for the metabolic process of bacteria.

Sulphamethoxazole Derivative of Sulphonamide

Sulfamethoxazole (4-amino-N-(5-methylisoxazol-3-yl)-benzenesulfonamide), one of the sulfonamides is a class of drugs whose molecular structure contain the sulfanilamide analog [81]. Sulfamethoxazole is most often used as part of combination with Trimethoprim [82], which act synergistically against a wide variety of bacteria [83-84], although other combinations of sulfonamides are also available. It has found widespread use in animal husbandry [85] and, to a lesser extent [86], in the treatment of human infections such as bronchitis and urinary tract infections [87]. It is also applicable for antiseptique [88], atituberculr [89] and anti-inflammatory agent [90]. Thus, significant biological properties associated with azomethines derivatives have aroused considerable interest to design the compounds in which therapeutically active Sulfamethoxazole nucleus. (Figure 7) shows the general structure of sulphamethoxazole.

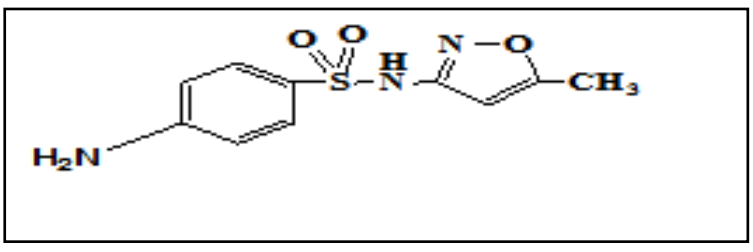
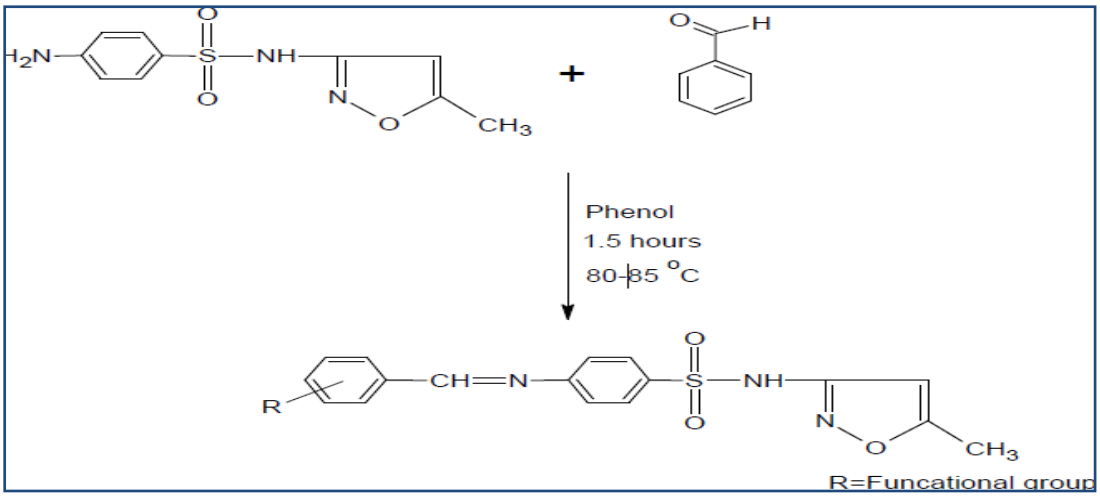


Figure 3: Structure of sulphamethoxazole [91].

Some of Schiff's Bases Containing Sulfamethoxazole Nucleus.

1. 4-[(4-methoxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzene sulfonamide.
2. 4-{[4-(dimethylamino)benzylidene]amino}-N-(5-methyl-1,2-oxazol-3- yl) benzenesulfonamide.

3. 4-[(4-fluorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3- yl) benzene sulfonamide.
4. 4-[(4-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3- yl) benzene sulfonamide.
5. N-(5-methyl-1,2-oxazol-3-yl)-4-[(3-nitrobenzylidene)amino] benzene sulfonamide.
6. N-(5-methyl-1,2-oxazol-3-yl)-4-[(2-nitrobenzylidene)amino] benzene sulfonamide.
7. 4-(benzylideneamino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide.
8. 4-[(2-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzene sulfonamide.
9. 4-[(3-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzene sulfonamide.
10. 4-[(3-bromobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzene sulfonamide.



Scheme 5: Synthesis of compounds above.

11) Sulphamethoxazole-Salicyladimine.

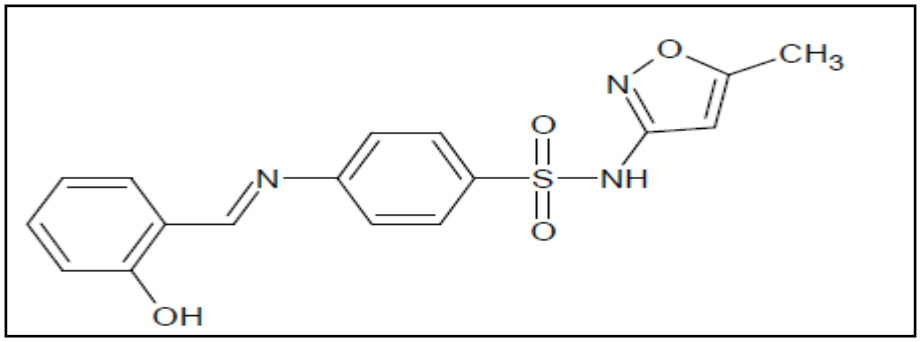
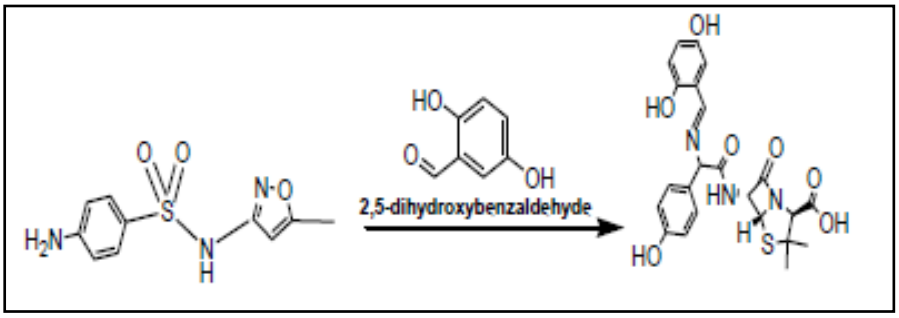


Figure 4: Structure of 4-[(2-hydroxy-benzylidene)-amino]-N-(5-methyl-isoxazol- 3-yl)benzenesulfonamide

*12) 2, **5-dihydroxybenzalidenesulphamethoxazole***



Scheme 6: Synthesis of 2, 5-dihydroxybenzalidenesulphamethoxazole.

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13) N-[3-Chloro-4-(4-methoxyphenyl)-2-oxo-azetine-1-yl]-2-(N'-5-methyl-3-isoxazolyl) sulfonamide

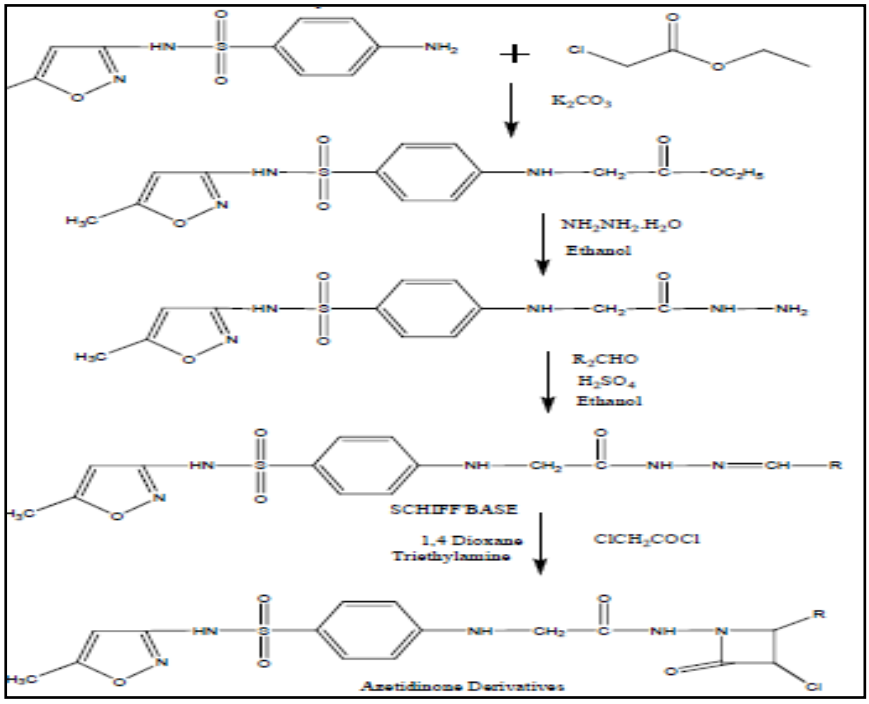
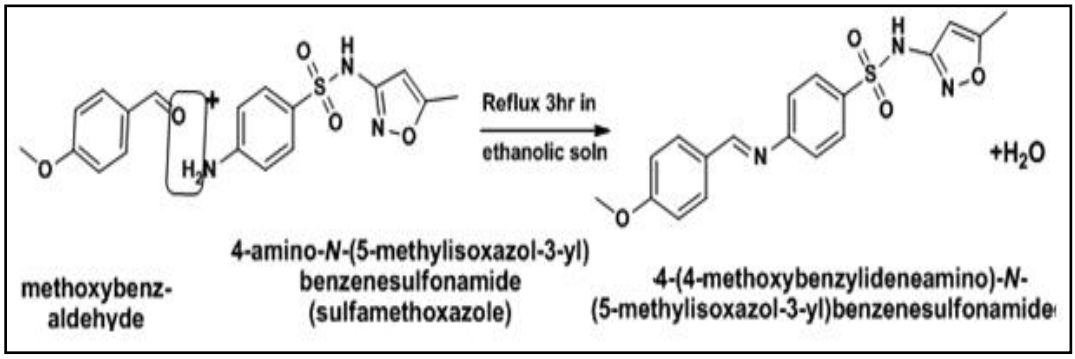


Figure 5: Structure of *N*-[3-Chloro-4-(4-methoxyphenyl)-2-oxo-azetine-1-yl]-2-(*N*'-5-methyl-3-isoxazolyl) sulfonamide.

14) 4-(4-methoxybenzylideneamino)-N-5-(meethylisoxazol-3-yl)benzenesulphanomide.



Scheme 7: Synthesis of 4-(4-methoxybenzylideneamino)-*N*-(5-methylisoxazol-3-yl)benzenesulphanomide [92].

15) 4-[(4-dimethylamino-benzylidene)-amino]-N-(5-methyl-isoxazol- 3-yl)-benzenesulfonamide.

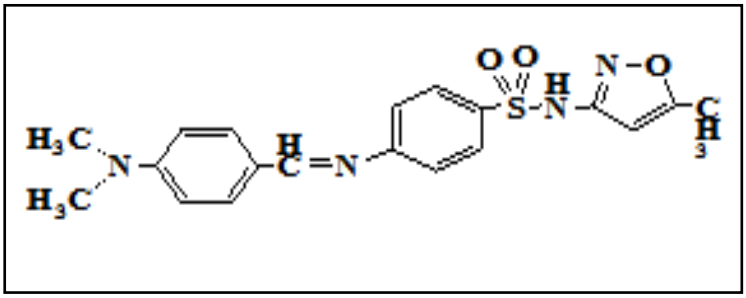


Figure 6: Structure of 4-[(4-dimethylamino-benzylidene)-amino]- *N*-(5-methyl-isoxazol-3-yl)-benzenesulfonamide.

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16) N-(5-methyl-isoxazol-3-yl)-4-[(3-nitro-benzylidene)-amino]-benzenesulfonamide.

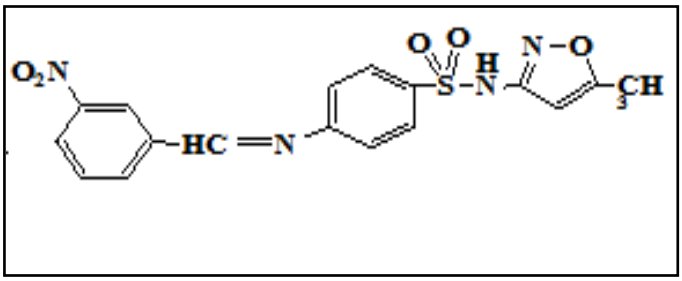

Figure 7: Structure of *N*-(5-methyl-isoxazol-3-yl)-4-[(3-nitro-benzylidene)-amino]-benzenesulfonamide.

17) 4-[(4-bromo-benzylidene)-amino]-N-(5-methyl-isoxazol-3-yl)-benzenesulfonamide.

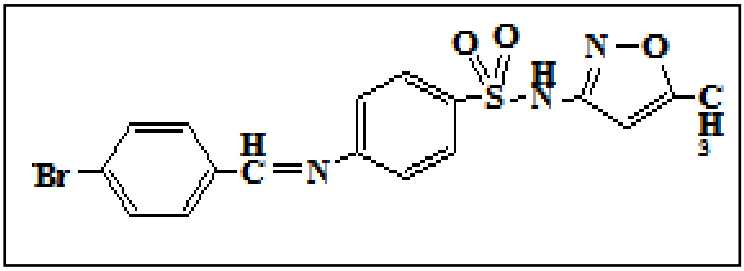

Figure 8: Structure of 4-[(4-bromo-benzylidene)-amino]-*N*-(5-methyl-isoxazol-3-yl)-benzenesulfonamide.

18) N-(5-methyl-isoxazol-3-yl)-4-[(4-nitroox-benzylidene)-amino]-benzenesulfonamide.

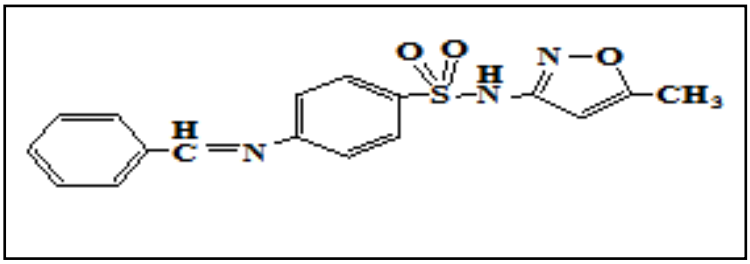

Figure 9: Structure of *N*-(5-methyl-isoxazol-3-yl)-4-[(4-nitroox-benzylidene)-amino]-benzenesulfonamide.

ACKNOWLEDGEMENTS

The authors acknowledge Misan University, Thi-Qar University, University Malaya and Al-Nahrain University and for their encouragement.

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