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Research Article

Synthesis and Characterization of Sulfamethoxazole Derivatives

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Abstract

Sulfamethoxazole (SMX) belongs to the sulfonamide group of antibiotics. It was chosen to represent this group because it is widely used and detected in aquatic environments. The thiazolidine ring has been incorporated into many well-known biologically active compounds, either as an additional component or by replacing another ring, prompting researchers to develop several compounds with this structure. Furthermore, the chemistry of chalcones has produced serious scientific readings throughout the world. Chiefly, interest has been concentrated on the creation and biodynamic actions of chalcones so that a diversity of novel heterocycles with favorable pharmaceutical shape can be designed. Synthetic procedures have been successfully developed for the generation of the target compounds. Six different aromatic para-benzaldehydes (H, OH, OCH3, NO2, Cl, & N(CH3)2) were used, following a multi-step reaction procedure. The purity of the products was checked by using thin-layer chromatography (TLC). The chemical structure of the intermediate and final compounds was identified and verified by checking their melting points, using FT-IR spectroscopy, performing elemental microanalysis (CHNS), and analyzing the final compounds with 1H NMR. A preliminary study of antimicrobial activity was conducted on three different strains of bacteria, revealing that the final compounds M3(a-f) exhibit significant activity compared to the standard drug sulfamethoxazole, with moderate to favorable activity.

Keywords: Sulfamethoxazole, Synthesis, Sulfamethoxazole Derivative, Antibiotic.

INTRODUCTION

Following Alexander Fleming's discovery of penicillin in 1928 and Domagk's introduction of sulfa drugs in 1932, the range of available antimicrobials expanded considerably from 1940 to 1960 [1]. This era, often referred to as 'the era of antibiotics,' was marked by optimism until the early 1970s[2]. However, infections remain the second biggest killer on Earth, accounting for more than 13 million deaths annually[3]. The rise of new illnesses, the return of old ones, and increasing antibiotic resistance demonstrate the complexities of the problem[4]. Antibiotics now include both naturally occurring, chemically modified compounds and synthetic antimicrobial agents[2]. Their specificity determines classification: Narrow-spectrum antibiotics target certain bacteria, like gram-positive or gram-negative strains, while broad-spectrum antibiotics affect a wider range[5]. Although science has significantly contributed to disease control through antibiotics, resistance is rising and spreading. Ampicillin and chloramphenicol are bactericidal agents, while penicillin is bacteriostatic. Bactericidal drugs destroy bacterial cells, whereas bacteriostatic agents inhibit bacterial growth[6].

Antibacterial agents act through various mechanisms: drugs like polymyxins and daptomycin disrupt the cytoplasmic membrane, causing cell lysis[7]. Fluoroquinolones inhibit DNA synthesis by targeting DNA gyrase, while rifampin interferes with RNA polymerase. β-Lactams and glycopeptides inhibit bacterial cell wall synthesis, targeting peptidoglycan cross-linking. Sulfonamides and trimethoprim interrupt folate metabolism, impeding DNA synthesis[8]. Protein synthesis inhibitors, such as oxazolidinones, macrolides, and chloramphenicol, target ribosomal subunits. Resistance arises from changes in bacterial cell structure, active efflux of drugs, target modification, enzymatic degradation, and use of alternative metabolic pathways[9].

Sulfanilamides resemble para-aminobenzoic acid (PABA) and competitively inhibit dihydropteroate synthase, preventing folic acid formation. They are bacteriostatic and active against both Gram-positive and Gram-negative bacteria[10]. Since prontosil's introduction over 70 years

ago, sulfa drugs especially N1-substituted sulfonamides have been used to treat microbial infections[11]. Sulfamethoxazole (SMX), a commonly used sulfonamide, inhibits dihydropteroate synthetase and blocks folic acid synthesis. Its combination with trimethoprim (TMP-SMX) is effective against Staphylococcus aureus[12]. SMX has both acidic and basic parts in its structure, and substances like N4-acetylsulfamethoxazole can be found in the blood[13].

The structural-activity relationships of sulfonamides indicate that the paraposition of amine and sulfonamide groups on the benzene ring is essential for antibacterial activity. N1-substituents influence pharmacokinetics, toxicity, and solubility[14]. Schiff bases, characterized by an azomethine group (–CH=N–), are synthesized by reacting carbonyl compounds with primary amines[15]. They exhibit diverse biological activities due to their ability to form chelates with metals and their utility in coordination chemistry[16]. Schiff bases derived from sulfonamides possess antibacterial, antifungal, antitubercular, anticancer, anti-inflammatory, and antiviral properties[17].

Heterocyclic compounds, especially those containing nitrogen, oxygen, or sulfur, are integral to life and medicines. They are found in nucleic acids, vitamins, antibiotics, agrochemicals, dyes, and pigments[18]. Thiazolidinones, particularly 4-thiazolidinones, derived from thiazolidine, are versatile and present in drugs like penicillin[19]. These compounds show antiviral, antidepressant, anticonvulsant, antitubercular, anticancer, antibacterial, antifungal, anti-inflammatory, and analgesic activities, depending on substituents at C-2 and N-3 positions[20].

Chalcones, compounds with α,β-unsaturated carbonyl groups, are synthesized primarily via Claisen Schmidt condensation and act as precursors to various heterocycles[21]. They have shown antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, antileishmanial, and other pharmacological effects[22]. Substituted 5-arylidene-thiazolidinones have shown stronger antibacterial and anti-inflammatory effects, particularly when they have certain groups that pull electrons away at specific spots[23]. Their ability to inhibit cyclooxygenase (COX) enzymes makes them relevant for anti-inflammatory drug design[24].

Aim and Objective

Based on sulfamethoxazole, a novel class of sulfa medicines called 5-arylidene-4-thiazolidinone has been created. Because of their pharmacophore, these new drugs should outperform sulfamethoxazole in antibacterial activity. The chemical make-up of these substances

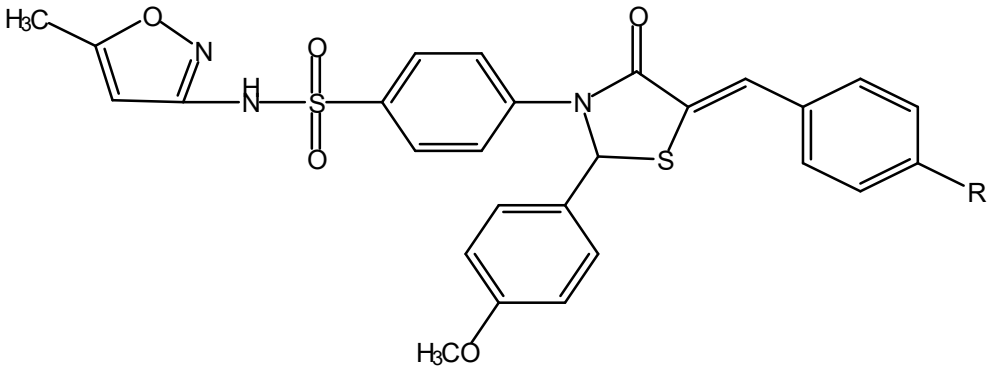


Figure 1: 5-arylidene-4-thiazolidinone

Compound	R
R1	-H
R2	-OH

EXPERIMENTAL WORK

Chemicals

p-Methoxybenzaldehyde, Sulfamethoxazole, Ethanol (absolute), Glacial Acetic Acid, Petroleum Ether, Ethyl Acetate, Thioglycolic Acid, Dimethylformamide (DMF), Anhydrous Zinc Chloride ($ZnCl_2$), Diethyl Ether, Toluene, Methanol, Chloroform, Piperidine

Equipment

Magnetic Stirrer with Heating Mantle—for controlled heating and reflux during synthesis

Reflux Condenser Setup—for safe and consistent heating during condensation and cyclization reactions

Thin Layer Chromatography (TLC) Apparatus—for monitoring reaction progress

UV Chamber (254 nm / 365 nm)—for visualization of TLC spots

Büchner Funnel with Vacuum Filtration Setup—for efficient solid product collection

Melting Point Apparatus

FT-IR Spectrophotometer (e.g., Bruker IFS66)—for structural confirmation using IR spectra

NMR Spectrometer (e.g., VARIAN VNMRS 400-MR)—for ^{1}H and ^{13}C NMR spectral analysis

Elemental Analyser (e.g., Carlo Erba)—for CHNS analysis

Analytical Balance (±0.1 mg accuracy)—for precise weighing of reagents

Rotary Evaporator—for solvent removal (DMF, ethanol, etc.)

Fume Hood—for safe handling of volatile solvents and acids

Ice Bath Setup/Cooling Bath—for precipitation and crystallization steps

Glassware Set (250 mL RBF, measuring cylinders, pipettes, beakers, etc.)—for general lab operations

Methods of characterization and identification

Standard techniques were employed to characterize and identify the synthesized compounds, which include the following:

Thin-layer chromatography (TLC)

For TLC, we utilized Kieselgel GF254 (60) aluminum plates from E. Merck (Germany) to monitor the reactions' progression and ensure the purity of the chemicals we made. Exposure to iodine vapor or UV254 light allowed for the detection of compounds. We used these solvent systems to create the chromatograms: a) Ethyl acetate: petroleum ether (7:3): toluene (3:1): ether (3:1).

Melting points

The Thomas Hoover Electronic Apparatus for measuring melting points was passed down for use in determining the melting points specified in the subsequent work.

Infrared bands

The KBr picture was created by identifying infrared bands using an FTIR Shimadzu spectrophotometer.

Proton Nuclear Magnetic Resonance (^{1}H-NMR)

A 300 MHz spectrometer was used to produce the 1HNMR spectra in DMSO-d6. Bruker spectrophotometer measurements were obtained, with TMS acting as the internal standard.

Chemical synthesis

The substances were synthesized by adhering to the processes and techniques described in units (2.3.1) through (2.3.3).

3.9. Synthesis of Schiff Base [4-((4-methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide] (R)

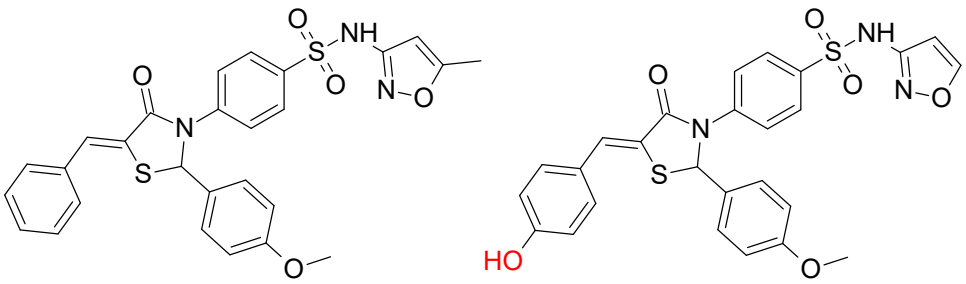
Equal amounts of p-methoxybenzaldehyde (0.01 mol, 1.362 g) and sulfamethoxazole (0.01 mol, 2.533 g) were combined in a small amount of ethanol to make the Schiff base. After refluxing for five to eight hours, 1 mL of glacial acetic acid was added. Reaction progress was monitored by TLC using a 7:3 ethyl acetate:petroleum ether system. The cooled mixture was poured over crushed ice and filtered to yield a crystalline product (mp 234–236°C, 88% yield). The physicochemical properties, yield %, and Rf values are listed in Table 3. FT-IR spectra are shown in Table 3-2 and Figure 3. Table 3 and Figure 3-10 provide the 1H-NMR data for compound [R].

3.10. Synthesis of 4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (R(A))

We combined a small amount of anhydrous zinc chloride, thioglycolic acid (0.022 mol, 2.5 mL), and Schiff base (0.01 mol, 2.98 g) in dimethylformamide (20 mL) and heated the mixture under reflux for 12 hours. Reaction progress was tracked by TLC using an ether:toluene (1:3) solvent system. After cooling to room temperature, the mixture was poured over crushed ice, filtered, and washed with water repeatedly. The product had a 95% yield and a melting point of 136–137°C. Table (3) lists physical characteristics, yield %, and Rf values of R(A). FT-IR spectra are shown in Table (3) and Image (3). 1H-NMR data are presented in Figures 3-7 and Table 4 for compound [R(A)].

3.11. Synthesis of Derivatives R1 & R2

An aromatic aldehyde (0.012 mol) was mixed with compound R(A) (0.01 mol, 4.455 g) in about 50–55 mL of pure ethanol and heated for 6–14 hours with 1–3 drops of piperidine in a 250 mL round-bottom flask, depending on the type of derivatives. Reaction progress was monitored by TLC using a methanol/chloroform/ether (4:3:3) solvent system. After filtration and washing with cold, dry toluene or ethanol, recrystallization from ethanol was performed (mp 138–140°C). Table 3 provides physical characteristics, percent yield, and Rf values of compounds [R1 & R2]. FT-IR spectra are shown in Tables 3-2 and Figures 3-4 to 3-9. 1H-NMR data for [R1 & R2] are in Tables (3-5) to (3-7) and corresponding images.



R1 R2

Figure 2: Structures of the synthesised compounds

3.12. Biological study

3.12.1. Antimicrobial study:

Initial assessments of antibacterial characteristics were carried out using the well diffusion method. To find out how effective the newly synthesized chemicals were against bacteria, we ran in vitro tests against three distinct species: gram-negative Escherichia coli, gram-positive Pseudomonas aeruginosa, and gram-positive Staphylococcus aureus. These bacteria were cultivated on nutrient agar and then activated clinically to see how effective they were as an antibiotic. All of these tests of antibacterial activity were conducted using sulfamethoxazole as the reference medication.

Sensitivity Assay:

Antibacterial Activity

An agar diffusion test was used to assess the antibacterial properties of every chemical derivative. Pure isolates of three bacterial species were subcultured in Brain Heart Infusion broth at 37°C for 18–24 hours. Three to five colonies were selected and mixed with 3 mL of normal saline. Using a glass spreader, we spread about 100 µL of the prepared bacterial mixture (1.5 × 10^8 CFU/mL) on Mueller Hinton Agar (MHA) plates, following the 0.5 McFarland turbidity standard. Excess liquid was either spread again or left to dry in a controlled environment. After drying, five 6 mm holes were punched into the agar, and the bacteria were placed in each well. Then, 100 µL of various dilutions (500, 250, 125, 62.5) of the derivative compounds were added. Demersal monohydrate served as the negative control. Plates were incubated at 37°C for 24 hours. The inhibition zone (IZ) in mm was measured to evaluate antibacterial effectiveness.

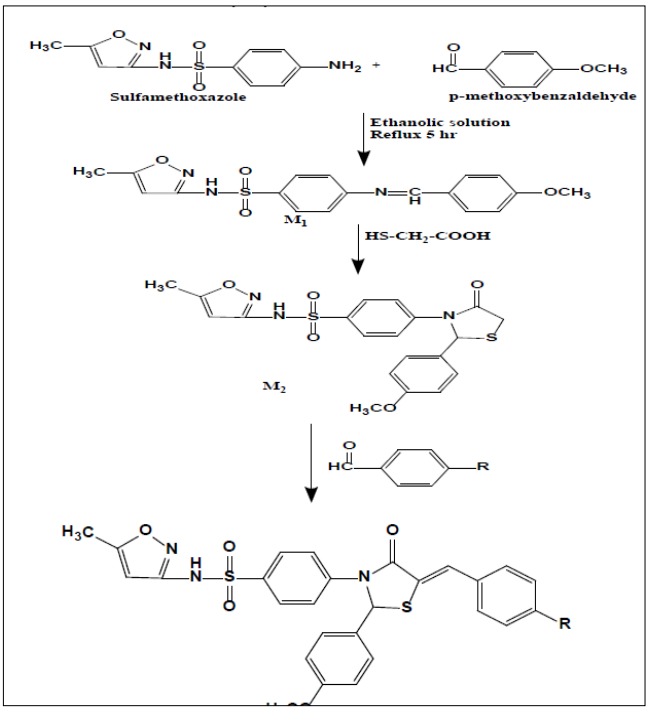
3.12.3. Preparation of Serial Dilutions of Newly Synthesised Compounds

Begin by adding 0.01 g of each component into a test tube and dissolving in 10 mL of DMSO to prepare a stock solution (1000 µg/mL). For the first dilution (500 µg/mL), mix 2.5 mL of stock solution with 2.5 mL of DMSO. To prepare the second dilution (250 µg/mL), mix 2.5 mL of the first dilution with 2.5 mL of DMSO. Repeat this by mixing 2.5 mL of the second dilution with 2.5 mL of DMSO to obtain a third dilution (125 µg/mL). Finally, mix 2.5 mL of the third dilution with 2.5 mL of DMSO to get the fourth dilution (62.5 µg/mL). This method was applied to all synthesized compounds (M3–8), with sulfamethoxazole as the reference drug.

RESULTS AND DISCUSSION

General Methodology

The reaction sequences for creating the desired sulfamethoxazole derivatives are illustrated in diagrams.



Scheme 1 Synthesis of intermediates and target compound R1=H & R2=OH

Synthetic Studies

Scheme (1) shows the synthesis methods of the target compounds. Melting points, percentage yields, and Rf values related to purity and characterization of intermediates are included in Table 3. Functional groups were identified using FT-IR spectroscopy (Figures 3–9), with interpretations in Table 3. Table (3) also shows the results of elemental microanalysis (CHNS), while Figures 1 and 2, along with Tables (4) to (7), display 1H-NMR spectra to confirm the structure.

The synthesized molecules involve

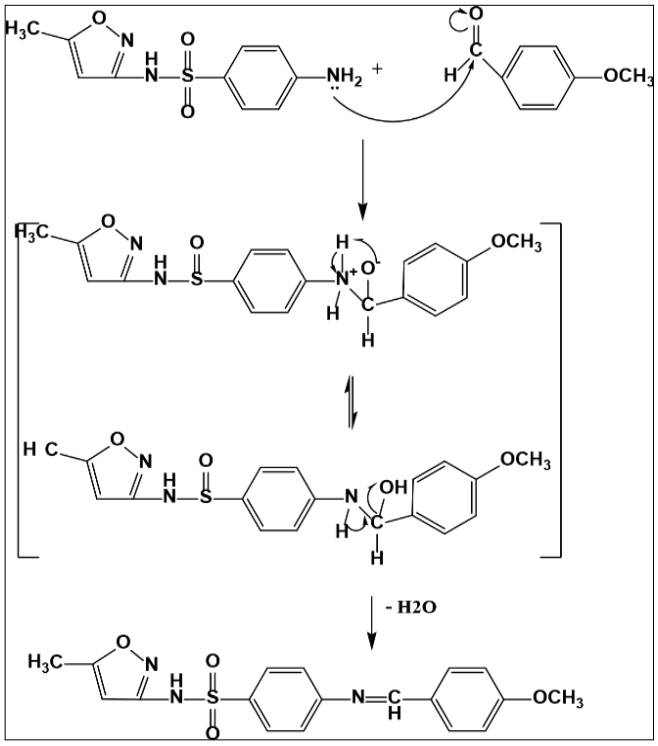
- Schiff base formation via reflux of sulfamethoxazole and para-methoxybenzaldehyde.
- We synthesize 4-thiazolidinone from sulfamethoxazole.
- The pharmacophores of substituted 5-arylidene-4-thiazolidinone are constructed.

Synthesis of Schiff Base (R)

Hydrazones, Schiff bases, or imines are formed by reacting an aromatic aldehyde with sulfamethoxazole. This acid-catalyzed reversible process starts with nucleophilic addition of a primary amine to a carbonyl group, forming carbinolamine. Acid catalysis adds a proton to the oxygen in carbinolamine, making it easier to create an iminium ion after removing water. The final product results from proton loss from nitrogen and regeneration of the acid catalyst, as illustrated in Scheme (2).

Table 3 shows the melting point and Rf values of the Schiffbase. FT-IR spectra (Figure 2, Table 3) display bands at ~3400 cm^{-1} (υNH amide), 2854.74 cm^{-1} (methyl υC–H), and 1658.84–1600.97 cm^{-1} (υC=N), with the absence of ϕNH_2 stretching at 3468.13 cm^{-1}.

Figure (6) and Table (4) display the 1H-NMR spectra of compound [R], which has a wide NH amide peak at 11.41 ppm and an imine (CH=N) proton at 8.97 ppm.



Scheme 2: Mechanism of Schiff base synthesis

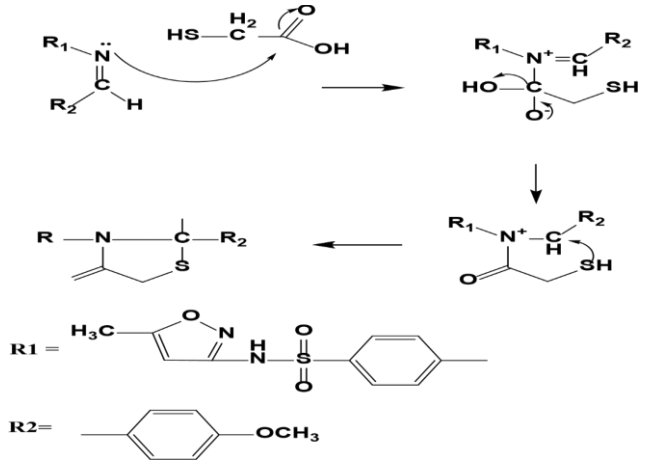
Synthesis of 4-thiazolidine (R)

The 4-thiazolidinone chemical was created by heating a mix of thioglycolic acid, a Schiff base, and a small amount of anhydrous $ZnCl_2$ in N,N-dimethylformamide for 12 hours. Scheme (3) shows the suggested process for making these chemicals. The compound probably forms this way because the carbon in the carbonyl group is more reactive than the carbon in the imine, which makes it easier for the nitrogen atom's lone pair to attack it compared to the sulfhydryl group.

The structure of compound R(A) was characterized by melting point and Rf values.

The spectra of compound R(A), shown in Figure 3 and Table 3, show absorption bands at 3377.47 cm^{-1} (amide υNH), 2968.55 cm^{-1} (asymmetric methyl υC–H), and about 1702.13 cm^{-1} (υC=O). The υC=N stretching band The υC=N stretching band at 1658.84 cm^{-1} is absent.

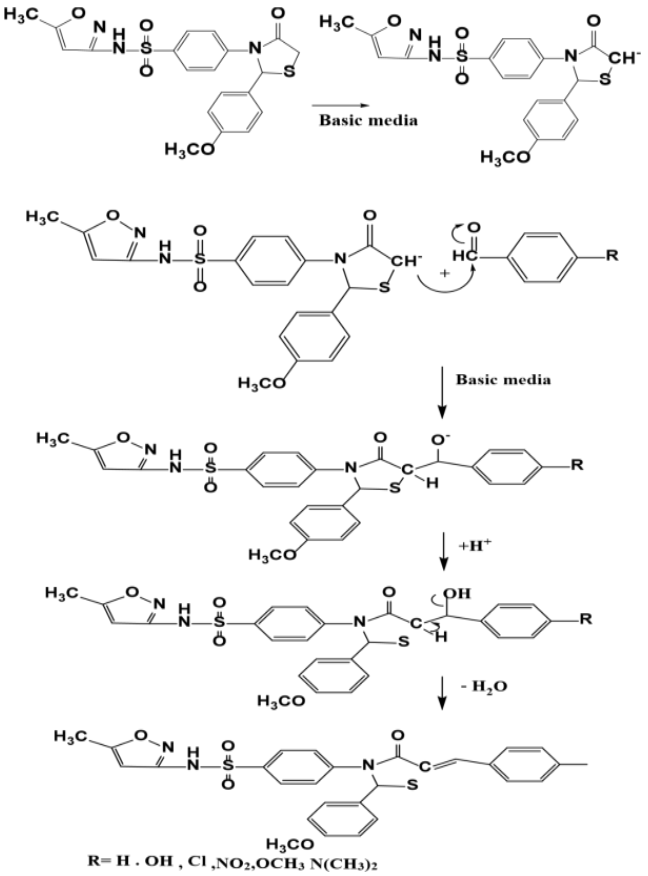
A wide peak at 10.97 ppm for the NH amide proton appears in the 1H-NMR spectra of compound [R(A)], as shown in Figure and Table 4. The imine signal at 8.9 ppm is no longer there. The imine signal at 8.9 ppm is no longer present. Signals at 6.02 ppm and 6.51 ppm indicate CH_2 and CH of thiazolidinone.



Scheme 3: Mechanism of Schiff base synthesis

Synthesis of chalcones R (1 & 2)

The main method for making chalcones is the classic Claisen-Schmidt condensation with a water-based alkaline solution. Scheme (4) illustrates our research in basic media.



Scheme 4: Mechanism of Schiff base synthesis

Analysis and recognition of the target compounds and their interpretation

Table (1) displays the produced compounds and their intermediates, along with their physical characteristics, melting temperatures, and Rf values. A thin-layer chromatography (TLC) test using two solvent systems tracked the transformation of reactants into products and checked for unwanted reactions. A single spot with distinct Rf values confirmed the process, as shown in Table 1.

Interpretation of the Results of FT-IR Spectral Data

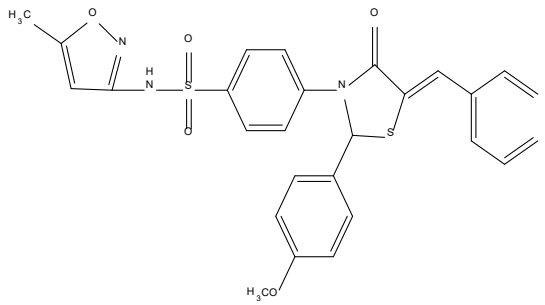
The special absorption bands in the FT-IR spectra of the created compounds and their intermediates matched the expected structures. Table 1 summarizes the band values, supported by literature studies on related substances and a reference book.

Interpretation of the Results of the 1H-NMR

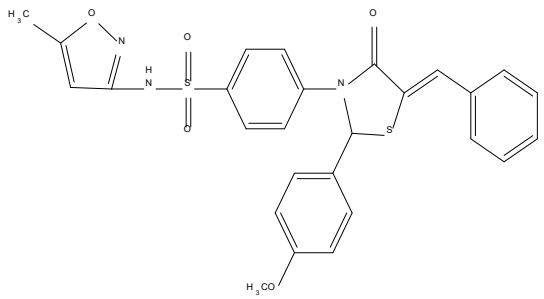
Using 1H-NMR analysis, the produced chemicals and their precursors were identified. Spectra were recorded in DMSO, and chemical shifts were compared with a reference book and research on similar compounds. Results are summarized in Tables (1).

Table 1: Analysis and physical characteristics of the intermediates and the final products

Comp No.	R	Mol. Formula	Yield %	Color, physical appearance	M.P /ºC	R_f value
R	**-**	C18H17N3O4S	88	Yellow crystalline	234-235	A: 0.54 B: 0.52
R(a)	**-**	C20H19N3O5S2	90	Off-white powder	136-137	A: 0.64 B: 0.62
R1	H	C27H22N3O5S2	67	Pale-yellow powder	244-245	A:0.71 B: 0.70
R2	OH	C27H22N3O6S2	62	Yellowish-brown powder	180-181	A: 0.52 B: 0.49



R1 Compound



R2 Compound

Table 2: FT-IR Spectral data for intermediate and final compounds (R1)

Characteristics bands of IR spectra (cm^{-1}, KBr disk)	
Bands	**Interpretation**
3367	**NH** Stretching vibration of 2° sulfonamide
3190	**C-H** stretching of aromatic
2951	**CH** asymmetric stretching of CH_3
1668	**C=O** stretching of thiazolidinone
1589	Aromatic **C=C** stretching
1163	**C-S** stretching

Table 3: FT-IR Spectral data for intermediate and final compounds (R2)

Characteristics bands of IR spectra (cm^{-1}, KBr disk)	
Bands	**Interpretation**
1680	**C=O** stretching of thiazolidinone
2928	**CH** asymmetric stretching of CH_3
3076	**C-H** stretching of aromatic
3223	**NH** Stretching vibration of 2° sulfonamide
3452	Phenolic **O-H** stretching

Table 4: 1H-NMR data and their interpretation of compound [R]

Signal	Signal Position (δppm)	Relative No. of proton	Multiplicity	Inference
a	2.131	3H	Singlet	CH_3 of the isoxazole ring
b	3.88	3H	Singlet	Para-OCH3

Table 5: 1H-NMR data and their interpretation of compound [R1]

Signal	Signal Position (δppm)	Relative No. of proton	Multiplicity	Inference
a	2.4	3H	Singlet	CH_3 of isoxazole ring
b	3.48	3H	Singlet	Para-OCH3

Table 6: 1H-NMR data and their interpretation of compound [R2]

Signal	Signal Position (δppm)	Relative No. of proton	Multiplicity	Inference
a	2.2	3H	Singlet	CH_3 of isoxazole ring
b	3.74	3H	Singlet	Para-OCH3

Antimicrobial activity evaluation

The antibacterial results revealed that the compounds tested had effects at different concentrations. In contrast to the original compound sulfamethoxazole, all the tested compounds were effective against the gram-negative bacterium Pseudomonas aeruginosa. Among these, the para-chloro and nitro derivatives exhibited the greatest activity, whereas the derivatives of para-H and OH exhibited the lowest levels of activity. To evaluate the efficacy of the antibacterial agent, the inhibition zone around the well was measured. The findings demonstrated that when the concentration of the substances under study increased, the inhibition zone grew.

Table 7: Antibacterial activity of sulfamethoxazole and compounds (R1f) against the tested bacteria

Compound No.	Concentration (µg/ml)	The zone of inhibition for Escherichia coli exists.	Inhibition zone of Pseudomonas aeruginosa (mm)	Inhibition zone (mm) for Staphylococcus aureus (Gm+ve)
	500	**20**	**_____**	**20**
SMX	**250**	**15**	**_____**	**16**
	125	**14**	**_____**	**15**
	62.5	**12**	**_____**	**_____**
DMSO	**Pure**	**_____**	**_____**	**_____**
	500	**20**	**18**	**20**
R1	**250**	**20**	**16**	**18**
	125	**18**	**16**	**15**
	62.5	**10**	**10**	**13**
	500	**18**	**17**	**20**
R2	**250**	**17**	**16**	**19**
	125	**17**	**15**	**16**
	62.5	**15**	**12**	**15**

CONCLUSION

The compounds under consideration have been synthesized successfully. To describe and identify the target compounds, we looked at their physical features, 1H-NMR spectra, FT-IR spectroscopy, and elemental microanalysis. Based on our findings, compounds R1 & R2 might be good candidates for future antibiotic research and development.

List of Symbols and Abbreviations

Abbreviation	Full Form
API	Active Pharmaceutical Ingredient
DMSO	Dimethyl Sulfoxide
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
HPLC	High-Performance Liquid Chromatography
IR	Infrared Spectroscopy
LC-MS	Liquid Chromatography–Mass Spectrometry
LOD	Limit of Detection
LOQ	Limit of Quantification
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
pKa	Acid Dissociation Constant
RP-HPLC	Reverse Phase High-Performance Liquid Chromatography
SEM	Scanning Electron Microscopy
TLC	Thin Layer Chromatography
UV	Ultraviolet
UV-Vis	Ultraviolet–Visible Spectroscopy
XRD	X-ray Diffraction

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