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Synthesis, characterization and study of biological activity of New Schiff base Compound from trimethoprim drug

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Abstract

reacting hydrazo-trimethoprim with various aldehydes, a series of trimethoprim derivatives were created, with a high yield of 74%. Several spectroscopic techniques, including FT-IR, were used to confirm the structures of these compounds. the scaffolds' physical characteristics, such as melting points.

Two trimethoprim's Schiff base scaffolds were successfully synthesized by single step with good yield 66% -76% and were characterized by spectroscopic methods. And we doing and studying the biological activity of trimethoprim.

Keywords: Biological activity, Schiff base, Trimethoprim drug

Introduction

The medication trimethoprim is a two-amine molecule made from a heterocyclic pyrimidine ring[1].The atoms that make up trimethoprim are arranged in accordance with the structural formula shown below, and its molecular formula is C14H18N4O3. It has a molar mass of 290.32 g/mol and it's melting points 240 C0 [2]. As a pyrimidine inhibitor of bacterial dihydrofolate reductase, trimethoprim strongly binds to the

bacterial enzyme, preventing the synthesis of tetrahydrofolic acid from dihydrofolic acid [3].

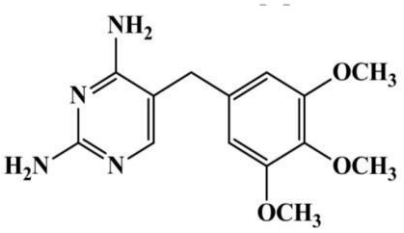


Fig1: Trimethoprim (5-(3,4,5-Trimethoxybenzyl) pyrimidine-2,4-diamine)

A member of the sulfonamide medication class, sulfamethoxazole directly affects the synthesis of folate in microorganisms like bacteria By inhibiting the enzyme dihydropteroate synthase, sulfamethoxazole directly accomplishes this by competing with p-aminobenzoic acid (PABA) during the formation of dihydrofolate Tetrahydrofolate is a crucial element in the synthesis of purines, which are vital for the formation of DNA and proteins By combining these two medications, it is intended to provide a synergistic anti-folate action [4].
These medications only have a bacteriostatic effect when taken by themselves. However, they can be bactericidal when used as combination sulfamethoxazole and trimethoprim because they obstruct two processes in the bacterial manufacture of vital nucleic acids and proteins [5-6].

The medication is used to both treat and prevent many bacterial illnesses. The FDA- Approved indications include: acute infectious exacerbation of chronic bronchitis, otitis media, travelers diarrhea for treatment and prophylaxis, shigellosis, pneumonia, toxoplasmosis, and most commonly used for urinary tract infections both as prophylaxis and treatment [7].
The substance that contains the azomethine group (-HC=N-) is called a Schiff base. Hugo Schiff initially described them in 1864; they are condensation products of ketones (or) aldehydes (aldehyde and ketones) with primary amines [8]. Schiff bases are typically formed under the catalysis of acids, bases, with heat. Crystalline solids are a frequent type of Schiff base; they are weakly basic, but at least some of them combine with strong acids to generate insoluble salts. Schiff bases are utilized as ligands for the formation of metal complexes with a variety of various structures or as intermediates in the synthesis of amino acids [9].

Materials & Methods

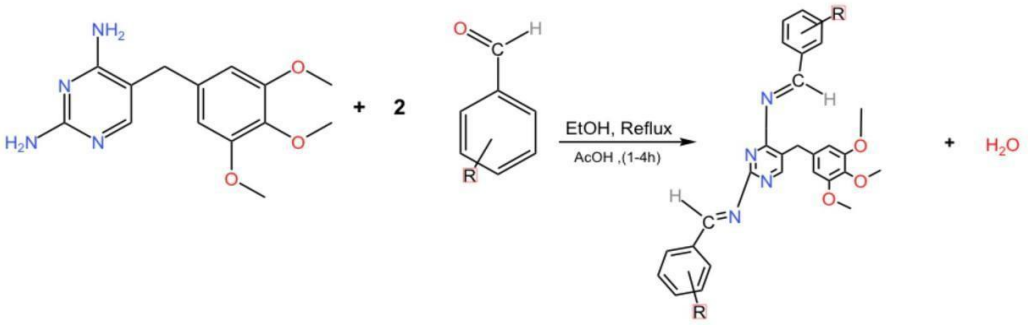
Materials:

All chemicals used on this study were of an analytical grade and directly used without further purification, otherwise stated. In contrast to 2,6-dichloro-benzaldehyde and 4-Dimethyl amino benzaldehyde, which were ordered from Merck in Germany, trimethoprim was ordered from Sigma-Aldrich. Glacial acetic acid was also bought from BDH limited in England.

Instrumentation:

Digital Stuart Scientific SMP30 melting point apparatus, UK, was used to measure the melting points of all derivatives. Additionally, utilizing the FTIR-800,

Fourier Transform Infrared (FTIR) analysis was carried out (SHIMADZU, Japan). Moreover.



Scheme 1: General scheme for synthesis of trimethoprim derivatives.

Classical Heating Method:

Preparation of Compound 1:

The conventional reflux method was performed according to Biagi, M. with slight modifications [10].The compound below was synthesized by reaction (0.001mol , 0.29mg)of trimethoprim with (0.002mol, 0.35mg) of (2,6-dicholorobenzaldehyde in (40ml) of ethanol, then (3) drops of glacial acetic acid, then refluxing the mixture to (4hrs) at (78C°), and the solution was filtered, dried with recrystallized to yield (88%) [11-14].

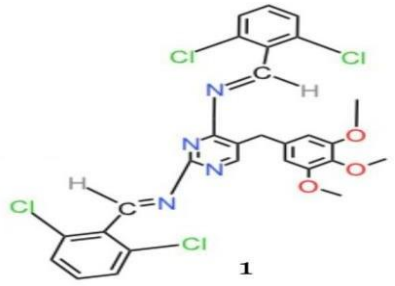


Fig2: N2,N6-bis(2,6-dichlorobenzylidene)-3-(3,4,5-trimethoxybenzyl) pyridine-2,6-diamine (Compound 1)

Preparation of Compound 2:

The same preparatory steps for the above mixture where done to the second aldehyde (4-dimethyl amino benzaldehyde) to prepare compound (2). (0.001mol, 0.29mg)of trimethoprim with (0.002mol, 0.29g) 4-dimethyl amino benzaldehyde in (40ml) of ethanol, then (3) drops of glacial acetic acid, then refluxing the mixture to

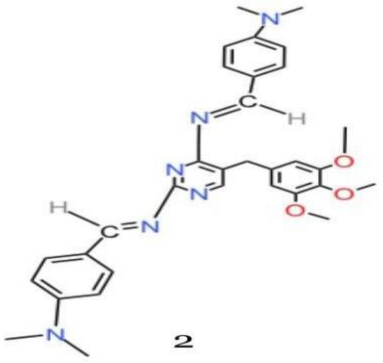
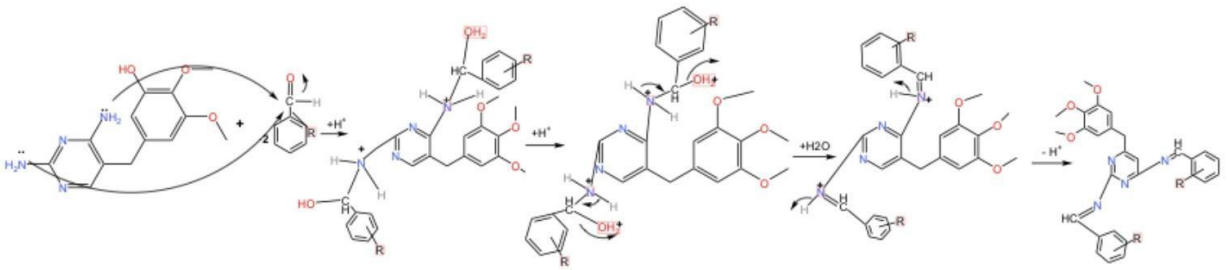


Fig 3: N2,N6-bis(4-(dimethylamino)benzylidene)-3-(3,4,5-trimethoxybenzyl) pyridine-2,6-diamine (Compound 2)



Scheme (2): Synthesis mechanism of Schiff bases

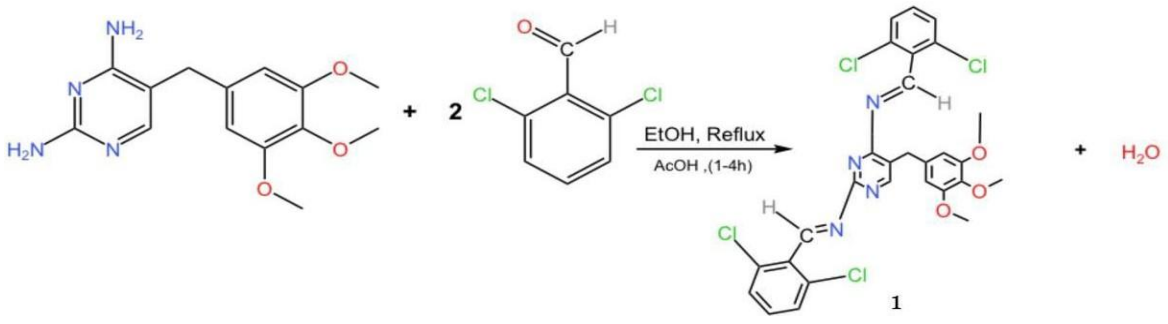
(4hrs) at (78Co), and the solution was filtered, dried with recrystallized to yield 92%.

Results and Discussion:

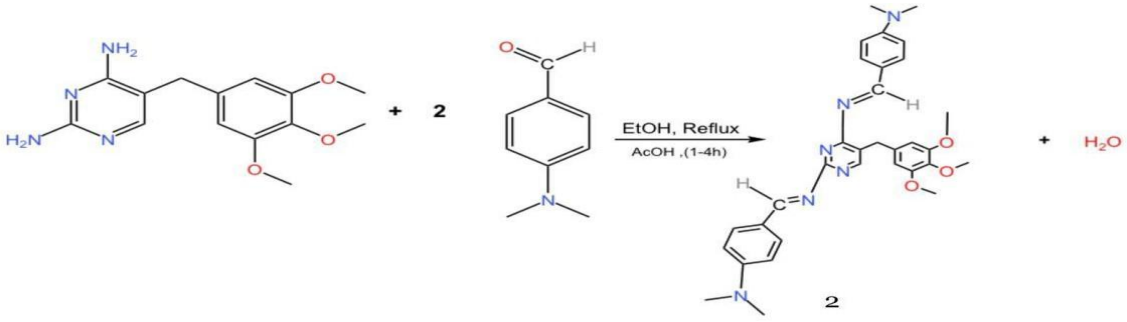
According to Scheme 3 and 4, trimethoprim was used to create a series of two derivatives of compounds (1-2) by reacting it with various aldehydes derivatives in the presence of glacial acetic acid as a catalyst and methanol as a solvent.

The compounds were identified by studying their physical characteristics (melting point) as well as spectroscopic (FTIR) According to the mechanism of schiff bases as shown in Scheme 2 and the reaction of prepared compounds (1-2) as shown in scheme (3-4) the manufacture of Schiff bases (1–2) included the nucleophilic addition of trimethoprim to the carbonyl group.

The two compounds were obtained as powder the first as white powder m.p (67-72) yield 66% and the second is yellow powder m.p (64-69); yield 76%.



Scheme (3): Synthesis mechanism of Schiff bases (1) from reaction of trimethoprim with 2,6-dichloro benzaldehyde



Scheme (4): Synthesis mechanism of Schiff bases (2) from reaction of trimethoprim with 4-dimethyl amino.

Table 1: Physical analysis of Schiff bases **(1 and 2).**

Compounds	Molecular formula	Molecular weight	Meting point	Physical appearance
1	$C_{29}H_{24}O_3Cl_4N_4$	Mol.Wt=618.34	M.P=(67-72 C^0)	White powder
2	$C_{33}H_{38}O_3N_6$	Mol.Wt=566.71	M.P=(64-69 C^0)	Yellow powder

Table 2: Infrared frequencies of the major functional groups **(1-2)**

Compound	Important FTIR frequencies Frequency/wavelength (υmax in cm^{-1})				
	C-H(Aromatic)	-C-H (Aliphatic)	C=N	$O-CH_3$	C-Cl
1	3048	2913	1657	1230	742
2	3473	2904	1696	123	-

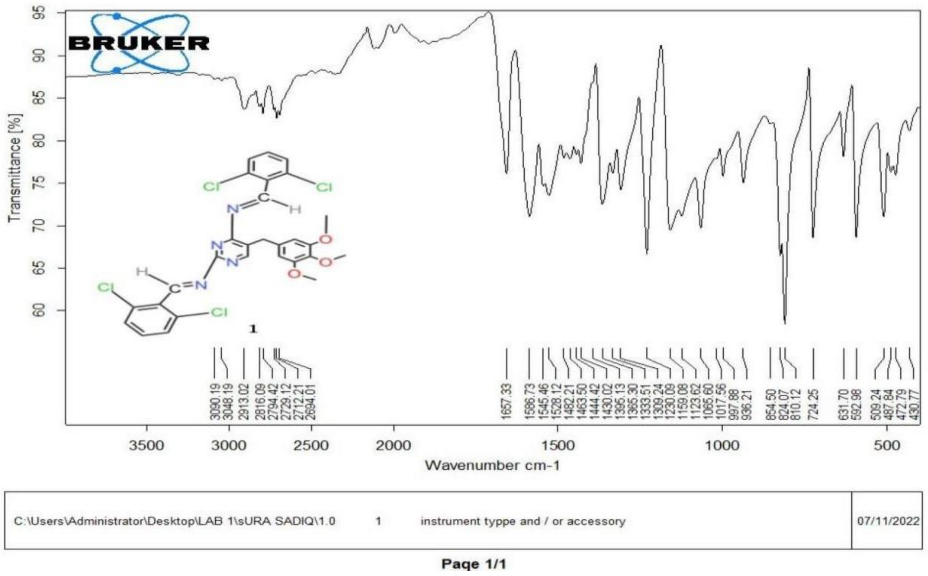


Figure 4: FTIR of N2,N6-bis(2,6-dichlorobenzylidene)-3-(3,4,5-trimethoxybenzyl) pyridine-2,6-diamine (Compound 1)

FT-IR Spectrum data for derivative (1): bands for (3048 cm-1) for (C-H) aromatic, (2913 cm-1) for (-C-H) aliphatic, (1657 cm-1) for C=N, (1230 cm-1) for O-CH3 ether, (742 cm-1) for C-Cl……

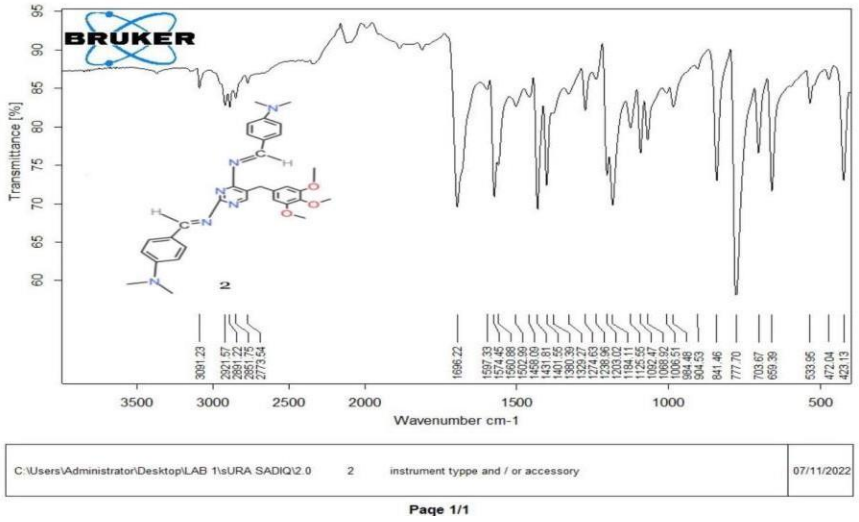


Figure 5: FTIR of N2,N6-bis(4-(dimethylamino)benzylidene)-3-(3,4,5-trimethoxybenzyl) pyridine-2,6-diamine (Compound 2)

FT-IRSpectrum data for derivative (2): bands for (3473 cm-1) for (C-H) aromatic, (2904 cm-1) for (-C-H) aliphatic , (1696 cm-1) for C=N , (123 cm-1) for (O-CH3) ether….

Table (3): Biological activity of trimethoprim

componds	s.aureus (µg/ml)			Staph.aureus (µg/ml)			E.Coli (µg/ml)			Klebsiella (µg/ml)		
	100	50	25	100	50	25	100	50	25	100	50	25
1	16.2	13.4	20.8	17.3	11.7	11.5	_	_	9.1	11.2	9.6	_
2	9.3	_	_	19.6	11.3	11.6	21.7	20.4	20.3	15.6	13.3	15.2
ciprofloxacin		11.8			11.5			11.2			11.7	
DMSO (negative)		___			___			___			___	

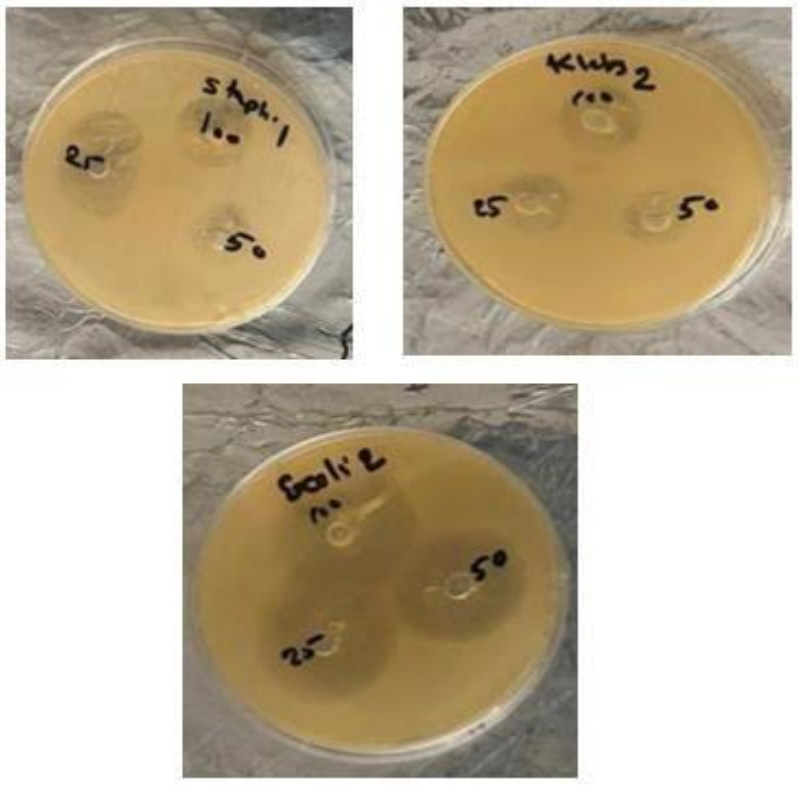


Figure (6): Staphylococcus aureus for compound (1) and E. coli for compound (2) and klebsiella species compound (2) it shows the good result for antimicrobial activity.

Antimicrobial Activity:

The compounds synthesis were screened for their antibacterial activity using was tested against gram (+) (Staphelococcus aureus, streptococcus aureus) and gram (-) (Escherichia coli and klebsiella pneumonia). The activities of these compound were tested using disc diffusion method at concentration using 5mm filter paper disc and filled with (100,50,25) of compound. The solvent (DMSO) were used as a negative control while ciprofloxacin (10µg/disc) was used as positive control, plates were incubated at 370C for 18-24 hr the area of inhibition of zone was measured compound (1) for staphylocoocus aureus (2) for E.coli and klebsiella showed good antibacterial activity [15].

Conclusion:

Two trimethoprim's Schiff base scaffolds were successfully synthesized by single step with good yield 66% -76% and were characterized by spectroscopic methods. And we doing and studying the biological activity of trimethoprim.

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