

## Synthesis, Characterization and Antimicrobial activity Study Via some new Schiff bases for Trimethoprim

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### Abstract:

This search reports the synthesis of some new series of Schiff base compounds for trimethoprim derivatives which known high been known as a medicinal effectiveness. Trimethoprim was condensed with several substituted aldehydes compounds.(4-dimethyl amine benzaldehyde , propanal , salicaldehyde, 2,4 dimethoxy benzaldehyde and 4- methyl benzaldehyde) to obtain Schiff base products(1a-5a) and several substituted ketones compound (4-aminoacetophenone,4-chloroacetophenone, isobutyleketone, acetylacetone and acetophenone) to obtain Schiff base products(6b-10b) in ethanol in the presence of concentrated sulphuric acid as a catalyst to yield the Schiff base. The structure of synthesized compounds has been established on the basis of their Chemical structures of all products were confirmed by spectrophotometric methods such as U.V. visible and FTIR.. All these compounds were evaluated for their antibacterial activity *in vitro* against Gram + ve bacteria (bacillus) , Gram -ve bacteria (E-Coli).Most Compound under investigation exhibited potent antibacterial activity

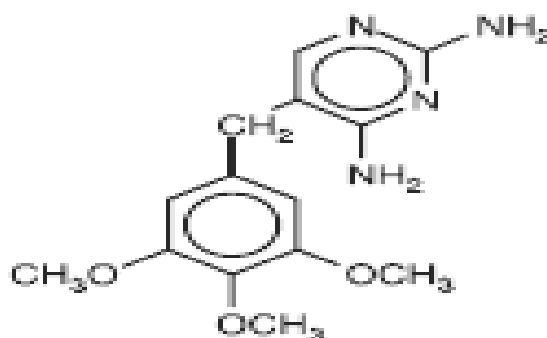
**Keywords:** Ttrimethoprim , Schiff bases , aldehyde .ketone, antibacterial activity.

### Introduction

Schiff bases are a class of important compounds in medicinal and pharmaceutical field. They show biological activities including antibacterial [1-4], antifungal [5,6], anticancer[7-9], and herbicidal[10] activities . Furthermore Schiff bases have been widely used as protective group of amino group in organic synthesis[11,12].

Trimethoprim and Trimethoprim derivative is a type of medicine called

an antibiotic[13]. It is used to treat infections with bacteria[14]., it is a significant antimicrobial activities [15,16], and its analogues[17].The chemical designation of Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxypenzyl)pyrimidine  $C_{14}H_{18}N_4O_3$  .was first describe by Roth and co-workers[15] It is a white to yellowish compound with bitter taste. The trade names of the combined product are Bactrim and Spectra[14].



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In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds, compounds containing azomethine group ( $-\text{CH}=\text{N}-$ ) are known Schiff bases. Schiff bases are usually formed by condensation of a primary amine with a carbonyl compounds [18], the general formula of Schiff bases  $\text{R}_1\text{R}_2\text{C}=\text{N}-\text{R}_3$ , where  $\text{R}_1, \text{R}_2, \text{R}_3$  may be an aliphatic or an aromatic group [19].

Schiff bases derived from aliphatic amines and salicylaldehyde drew the interest of many workers based on their antitumor activities which has been investigated on different Schiff-base ligands [20].

In current study we prepare some the new derivative of Schiff base compounds of Trimethoprim and study the effect of these compounds on the antimicrobial activity. It was thought that the new derivatives can provide a wide choice and flexibility to change structure in order to find a less toxic derivatives with enhanced activity.

The selection of bacterial strains was made because the trimethoprim possessed anti-microbial spectrum which include all gram positive and negative bacilli. Therefore, with altered structure, it was envisaged to see this modified structure could as well inhibit gram positive and negative bacteria.

## Material and Methods

All chemicals were high purity are used as the manufactures supplied them. The FTIR spectra in the range  $(4000-200) \text{ cm}^{-1}$  were recorded as KBr disc on a Shimadzu IR prestige -21 spectrophotometer. UV-visible spectra in the range  $(200-1100) \text{ nm}$  were recorded using Shimadzu UV-vis. 160A. Ultra-violet spectrophotometer. Melting point were recorded on a hot stage Gallen Kamp melting point apparatus.

carbonyl compound by mechanism of nucleophilic addition. The following Scheme explain the reaction:

## Material and methods

### Preparation of Schiff base

A series of Schiff base were prepared by reacting trimethoprim drug with different compounds of aldehydes and ketones by mixing equal amounts of (1mole) aldehydes compounds or (1mole) ketones compounds with (1mole) Trimethoprim, and dissolved with (25) ml Ethanol one drop of concentrated sulphuric acid was added, the mixture was refluxed for approximately 3 hour under  $70^\circ\text{C}$ .

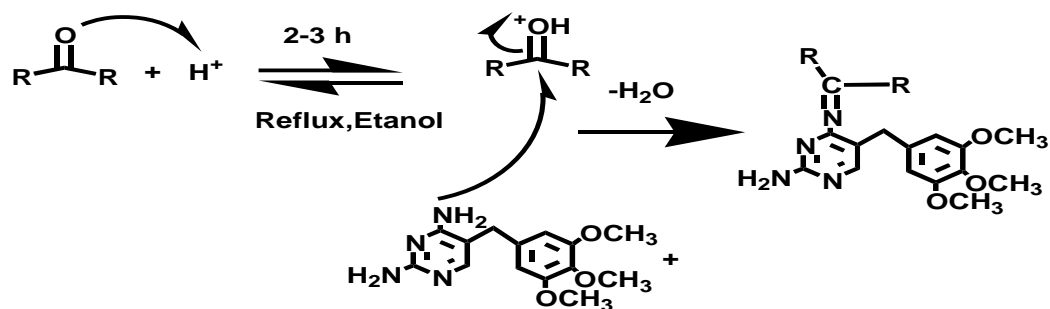
Then cool the products of trimethoprim schiff base, filtrated off, washed with ethanol, purification by recrystallization in ethanol and dried under vacuum and kept in a desiccator till further use. All derivatives of trimethoprim schiff base were given in table (1)

### Bacteriology

Biological activity of new compound prepared were representative gram-positive and gram negative bacteria by agar plate methods <sup>(21)</sup>. All compounds were prepared dissolving them with distilled water to obtain final concentration of 30 ppm and cultivated in nutrient agar. The results are found in table (3).

## Discussion

The new derivative for Trimethoprim Schiff bases can be synthesized from condensing Trimethoprim with varies



**R=H,Alkyl,Aryl**

Many anew compounds of Schiff base were isolated and characterized by ,melting point and spectroscopic data ..all compounds prepared were found to be stable at room temperature.The

physical properties of the new Schiff base of trimethoprim compounds with varies aldehydes(1a-5a) and ketones (6b-10b)compound, which prepared, are listing in table (1).

**Table Physo-Chemical data of synthesized Schiff Base of anew Trimethoprim Schiff bases**

No.	Molecular structure	Color	Molecular weight	Melting point C <sup>0</sup>	Electronic spectra $\lambda_{\max}$ nm)/ Ethanol
<b>1a</b>	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>	light yellow	378.42	75-79	220,304,610
<b>2a</b>	C <sub>17</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>	light Brown	330.38	-185 182	212,304,540
<b>3a</b>	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub>	Organ	394.42	152-155	218,334,644
<b>4a</b>	C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub>	Dark Brown	438.48	105-108	221,301,331,819
<b>5a</b>	C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub>	Yellow	392.45	83-85	224,304,615
<b>6b</b>	C <sub>22</sub> H <sub>25</sub> N <sub>5</sub> O <sub>3</sub>	Light Yellow	407.47	108	213,332,403,570
<b>7b</b>	C <sub>21</sub> H <sub>20</sub> ClN <sub>4</sub> O <sub>2</sub> •	Brown	395.86	175	214,304,627
<b>8b</b>	C <sub>18</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub>	Dark Yellow	344.41	185	213,301,415
<b>9b</b>	C <sub>19</sub> H <sub>24</sub> N <sub>4</sub> O <sub>4</sub>	Yellow	372.42	176	302,348,720
<b>10b</b>	C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub>	Moderate Yellow	392.45	208	215,304,738

The formula structure of Schiff base Trimethoprim derivatives were

identified by IR spectroscopy which explain in table(2)

**Table (2):**The value of IR spectroscopy for some functional group in trimethoprim Schiff bases.

No.	C=N str. $\text{cm}^{-1}$	C=N bend. $\text{cm}^{-1}$	CH Aldehyd	C=C Aromatic str. $\text{cm}^{-1}$	CH Aliphatic $\text{cm}^{-1}$	Other $\text{cm}^{-1}$
1a	1654	1636	3475	1458	2997	Aromatic CH str.3114
2a	1636	1597 1566	3420	1508	2938	NH str.3329,3388
3a	1589	1504	3379	1458	2823	Aromatic CH str.3047
4a	1640	1634	3377	1451	2953	Aromatic CH str. 3020 Out of plan CH bend.742
5a	1640	1635	3392	1433	2927	Aromatic CH str.3030 Out of plan C=C bend.502
6b	1636	1589	-	1423	2835	NH str.3394,3329 Aromatic CH str.3120
7b	1644	1625	-	1458	2877	Aromatic CH str.3030 C-Cl str.1000-1100
8b	1651	1544	-	1488	2865	Aromatic CH str.3108
9b	1654	1458	-	1508	2855	Aromatic CH str.3124 Out of plan C=C bend.505
10b	1635	1597	-	1458	2836	NH str.3491 Aromatic CH str.3109

The important diagnostic bands in the IR spectra were assigned and the band positions are compiled in Table 2. and figures The infrared absorption spectra of all the trimethoprim Schiff bases(1a-10b) compounds indicate the formation of Schiff base product by the absence of the carbonyl group ( $1700\text{ cm}^{-1}$ ) band and the appearance of a strong band in the region of( $1589\text{--}1654\text{ cm}^{-1}$ ), assignable to the  $\nu(\text{C}=\text{N})$  imine group <sup>(22)</sup>.

The disappearance of absorption for the  $\text{NH}_2$  group that it be secondary demonstrate in the region ( $3000\text{--}3400\text{ cm}^{-1}$ ) <sup>(23)</sup> is not clearly that to give reason for one of the  $\text{NH}_2$  group that is situated in position 4 between two nitrogen atoms in the pyrimidine cycle is not inter reaction , may be the hydrogen atom in this amine group enter tautomerism with the neighboring nitrogen atoms

The frequency of stretch ( $\text{C}=\text{C}$ ) aromatic when ( $1423\text{--}1508\text{ cm}^{-1}$ ) and frequencies of the benzene ring substitutes, the  $\text{C-X}$  ( $\text{X} = \text{Cl},$ ) bond on the phenyl ring led to the appearance of a strong absorption band at  $1000\text{--}1100\text{ cm}^{-1}$  as in Table (2)

The electronic absorption spectra of the Schiff bases under investigation were measured in ethanol the Schiff

bases in ethanol are characterized by mainly bands (Table 1).

The first band at  $\lambda_{\text{max}} = 212\text{--}224\text{ nm}$  can be assigned to the medium energy  $\pi\text{--}\pi^*$  transition of the aromatic ring, while the second band at  $\lambda_{\text{max}} = 301\text{--}348\text{ nm}$ . is due to the low energy  $\pi\text{--}\pi^*$  transition.. Other absorption bands that weak absorbance demonstrate in the visible region up  $403\text{ nm}$  which is present in the spectrum of the free amine, is assigned to an intermolecular charge transfer absorption involving the whole molecule. for Schiff bases . this weak peak give reason of produce color

**Table 3 :** biological activity of trimethoprim Schiff bases.

Comp 30 mg/l	Activity against $\text{G}^-$ bacteria E- Coil	Activity against $\text{G}^+$ bacteria Bacillus
1a	++	++
2a	—	+
3a	+	++
4a	++	++
5a	—	+
6b	++	++
7b	++	++
8b	+	++
9b	+	+
10b	—	+

(-) No inhibition

(+) Inhibition diameter of  $20\text{--}25\text{ mm}$

(++) Inhibition of  $25\text{--}30\text{ mm}$  in diameter

The biological activity were studied the effect of some Schiff base compounds on two type of bacteria ( $G^-$ )E-coil and( $G^+$ )Bacillus have been described in table3.and showed in figure 3,all the synthesized compounds were screened for their antibacterial activity by agar dilution methods. the selection of the bacterial strains was made because the trimethoprim

processed antimicrobial spectrum witch included all gram positive bacilli. Therefore with altered structure could as well inhibit gram negative bacteria.

some of these derivatives have shown high activity These results confirm the fact that compounds with ( $NH$ , and  $OH$ )with Schiff base have great potential as antibacterial agents.

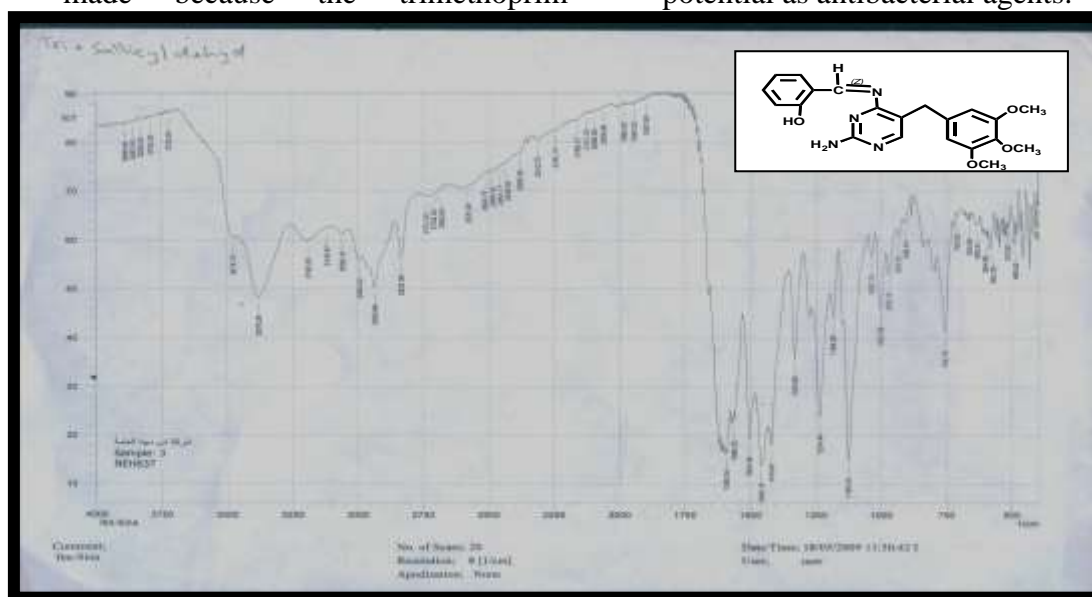


Figure1:Salicylidene trimethoprim

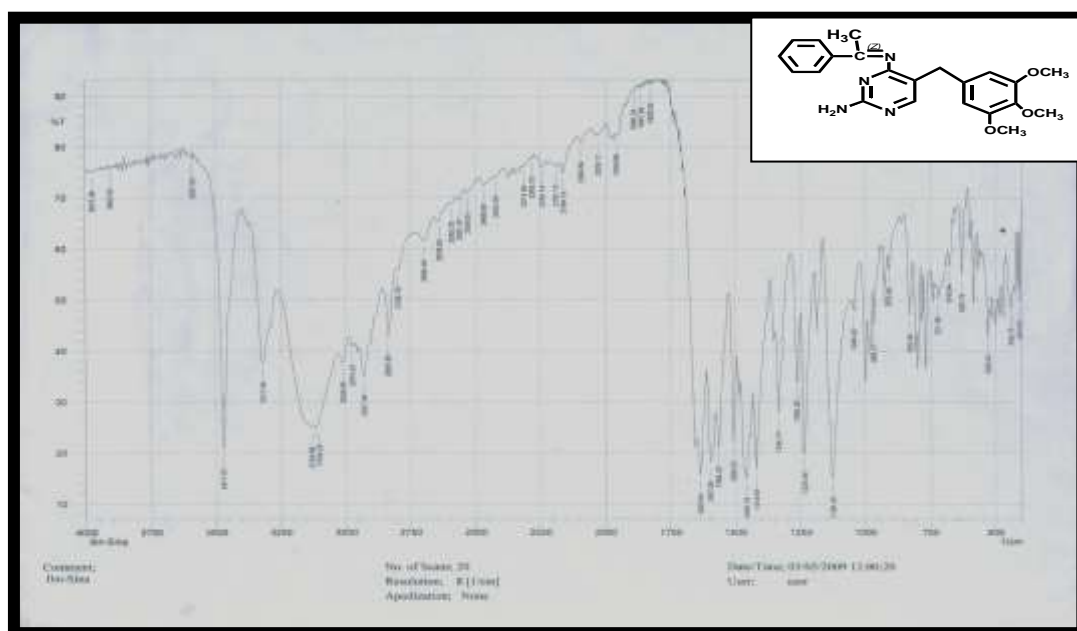
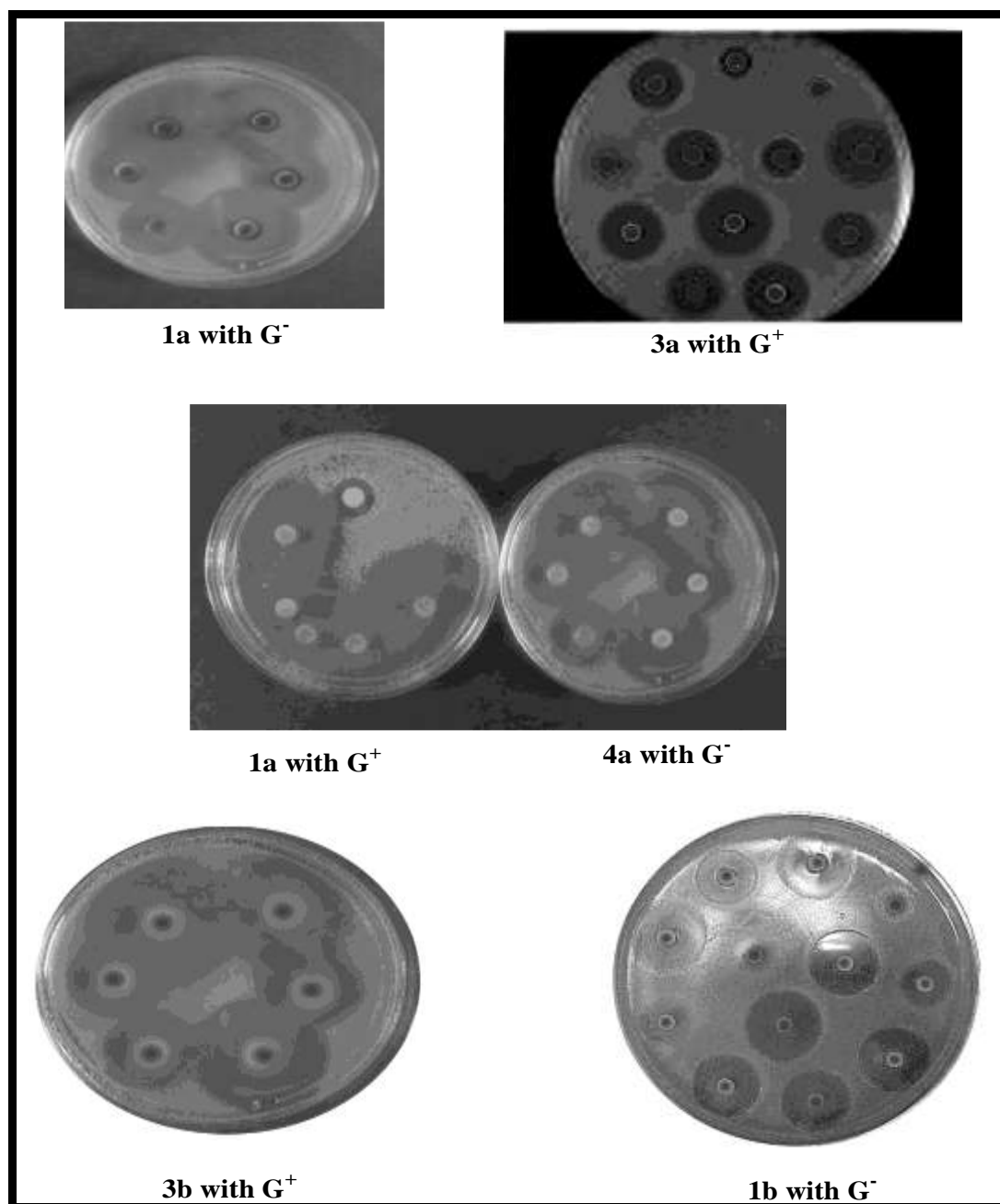


Figure2: Phenyl-ethylidene trimethoprim



**Figure 3:the biological activity of some compounds prepared.**

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## تحضير وتشخيص ودراسة الفعالية البيولوجية لبعض مركبات قواعد شف ل- تراي مثبرين

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### الخلاصة

تم في هذا البحث تحضير أنواع من قواعد شف جديدة للمركب الدوائي التراي مثبرين المعروف بفعاليته الدوائية العالية من خلال تكثيف التراي مثبرين مع بعض الالدهايدات (4- ثنائي مثيل امينو بنزليدهايد , بروبانال , سلسلك الدهايد , 2,4 ثنائي ميثوكسي بنزليدهايد , 4- ميثيل بنزليدهايد ) لنحصل على نواتج قواعد شف (1a- 5a) والكينونات (4- امينواسيتوفينون, 4-كلورو اسيتوفينون, ازوبيوناتيل كيتون, استايل اسيتون, واسيتوفينون) لنحصل على نواتج قواعد شف (6b- 10b) بوجود حامض الكبريتيك كعامل مساعد وبوجود الايثانول كمذيب. تم تشخيص المركبات المحضرة باستخدام بعض الطرق الطيفية UV-Visible, FTIR والأنشطة البيولوجية. قد تم بحثها أيضا لهذه مركبات مع البكتريا الموجبة bacillus والبكتريا السالبة E-Coli. حيث تبين إن معظم المركبات تحت البحث لها فعالية تثبيط.