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

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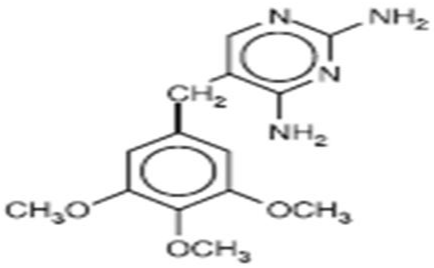
Abstract:
This search reports the synthesis of some new series of Schiff base compounds for trimetheprim derivatives which known high been known as a medicinal effectiveness. Trimetheprim was condensed with several substituted aldehydes compounds.(4-dimethyl amine benzaldehyde , propanal , salicaldehyde, 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: Ttrimetheprim , 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 is2,4-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 azomethin group(-CH=N-) are known Schiff bases . Schiff they are usually formed by condensation of a primary amine with a carbonyl compounds[18].,the general formula of Schiff bases $R_1R_2C=N-R_3$, where R_1,R_2 ,R_3 is 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 witch include all gram positive and negative bacilli. therfor, 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 spilled them The FTIR spectra in the range (4000-200) cm^{-1} were recorded as KBr disc on a Shimadzu IR prestige -21 spectrophotometer ,UV-visible spectra in the range (200-1100)nm were recorded using Shimadzu UV-vis.160A.Ultra-violet spectrophotometer. Melting point were recorded on a hot stage Gallen Kamp melting point apparatus.

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)aldehyds 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 3hour under 70C°.

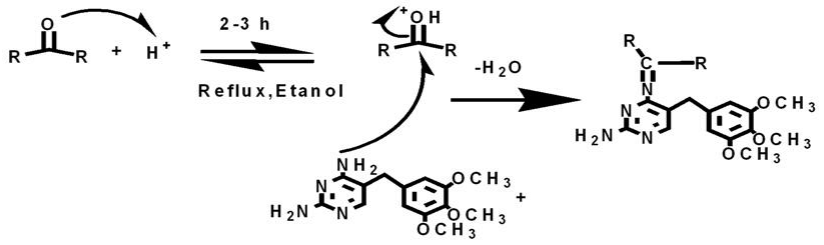
Then cool the products of trimetoprim schiff base , filtrated off , washed with ethanol , purification by re-crystallization in ethanol and dried under vacuum and kept in adesicator till further use.All derivatives of trimetoprim schiff base were given in table (1)

Bacteriology

Biological activity of new compound prepared were representative gram-positive and gram negative bacteria by agar plate methods [21].all compounds were prepared dissolving them with distill 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^0	Electronic spectra λ_{max} nm)/ Ethanol
1a	$C_{21}H_{22}N_4O_3$	light yellow	378.42	75-79	220,304,610
2a	$C_{17}H_{22}N_4O_3$	light Brown	330.38	-185 182	212,304,540
3a	$C_{21}H_{22}N_4O_4$	Organ	394.42	152-155	218,334,644
4a	$C_{23}H_{26}N_4O_5$	Dark Brown	438.48	105-108	221,301,331,819
5a	$C_{22}H_{24}N_4O_3$	Yellow	392.45	83-85	224,304,615
6b	$C_{22}H_{25}N_5O_3$	Light Yellow	407.47	108	213,332,403,570
7b	$C_{21}H_{20}ClN_4O_2$•	Brown	395.86	175	214,304,627
8b	$C_{18}H_{24}N_4O_3$	Dark Yellow	344.41	185	213,301,415
9b	$C_{19}H_{24}N_4O_4$	Yellow	372.42	176	302,348,720
10b	$C_{22}H_{24}N_4O_3$	Moderate Yellow	392.45	208	215,304,738

The formula structure of Schiff base Trimethoprim derivatives were identificated 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. cm^{-1}	C=N bend. cm^{-1}	CH Aldehayd	C=C Aromatic str. cm^{-1}	CH Aliphatic cm^{-1}	Other 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 cm^{-1}) band and the appearance of a strong band in the region of(1589–1654 cm^{-1}), assignable to the ν(C=N) imine group [22].

The disappearance of absorption for the NH_2 group that it be secondary demonstrate in the region (3000-3400) cm^{-1} [23] is not clearly that to give reason for one of the 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 (C=C) aromatic when (1423-1508) cm^{-1} and frequencies of the benzene ring substitutes, the C–X (X = Cl,) bond on the phenyl ring led to the appearance of a strong absorption band at 1000–1100 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 λ_{max} = 212-224 nm can be assigned to the medium energy π-π* transition of the aromatic ring, while the second band at λ_{max} = 301-348 nm. is due to the low energy π-π* transition.. Other absorption bands that weak absorbance demonstrate in the visible region up 403 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 G^- bacteria E^- Coil	Activity against G^+ bacteria Bacillus
1a	++	++
2a	—	+
3a	+	++
4a	++	++
5a	—	+
6b	++	++
7b	++	++
8b	+	++
9b	+	+
10b	—	+

(-) No inhibition
(+) Inhibition diameter of 20-25 mm
(++) Inhibition of 25-30 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.

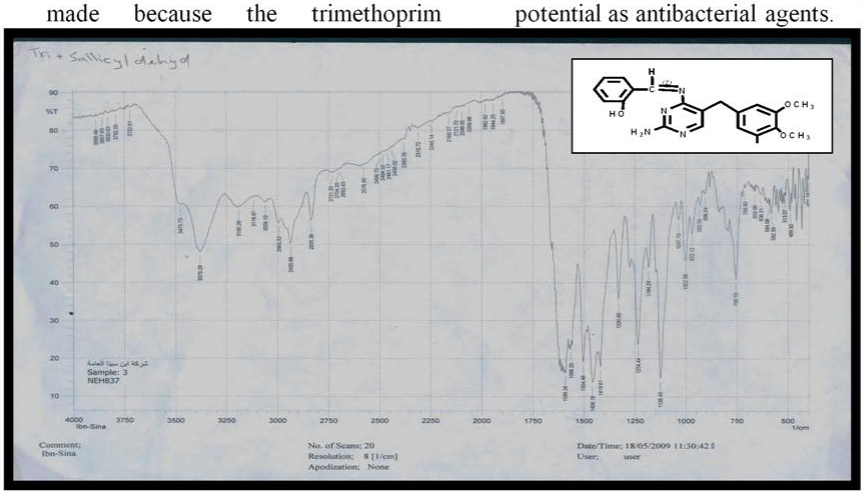


Figure1:Salicylidene trimethoprim

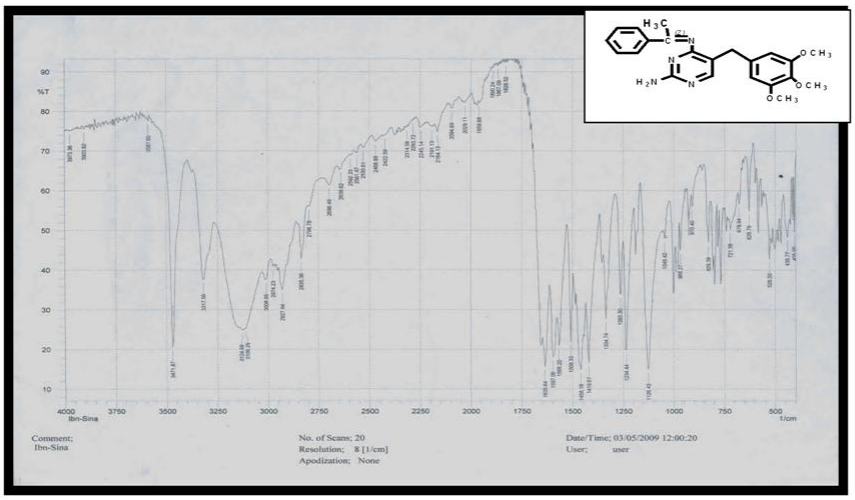


Figure2: Phenyl-ethylidene trimethoprim

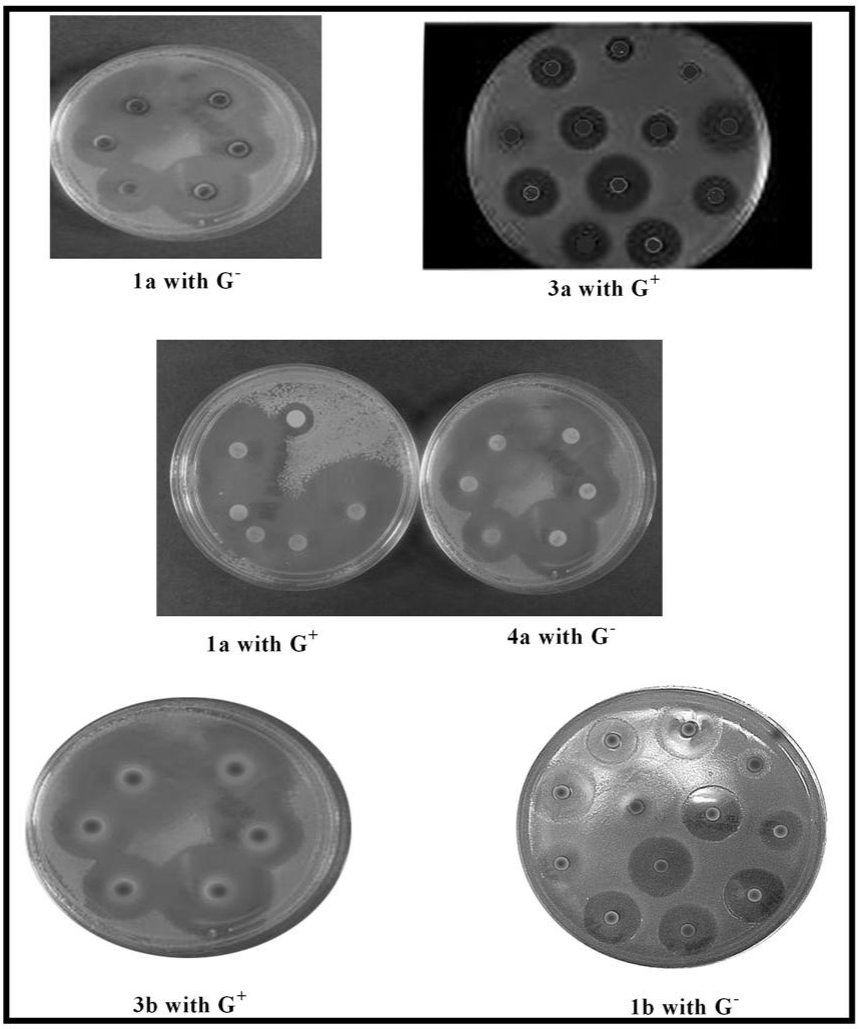


Figure 3:the biological activity of some compounds prepared.

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تحضير وتشخيص ودراسة الفعالية البايولوجية لبعض مركبات قواعد شف لـ 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 بنزلديهايد , بروبانال , سلسلك الدهايد , 2.4 ثنائي ميثوكسي بنزلدهايد , 4- مثيل بنزلدهايد) لنحصل على نواتج قواعد شف(5a -1a) .والكيتونات(4- امينواسيتوفينون,4-كلورو اسيتوفينون,ازوبيوتايل 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 الأنشطة البايولوجية قد تم بحثها أيضا لهذه مركبات مع البكتريا الموجبة bacillus والبكتريا السالبة E-Coli. f . حيث تبين إن معظم المركبات تحت البحث لها فعالية تثبيط.