Ministry of higher education and scientific research University of Babylon College of pharmacy

GRADUATION RESEARCH

Preparation and identification of derivative for Trimethoprim drug

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الاهداء

الحمد الله حباً وشكرا وامتنان على البدء والختام وآخر دعواهم أن (الحمد لله رب العالمين) بعد تعب ومشقة دامت خمس سنوات في سبيل الحلم والعلم حملي في طياتها امنيات الليالي، واصبح عنائي اليوم للعين قرة، ها انا اليوم اقف على عتبة تخرجي اقطف ثمار تعبي وارفع قبعتي بكل فخر ، فاللهم لك الحمد قبل أن ترضى ولك الحمد اذا رضيت ولك الحمد بعد الرضا لأنك وفقتني على إتمام هذا النجاح وتحقيق حلمي.....

وبكل حب اهدي ثمرة نجاحي وتخرجي

إلى الذي زين اسمي بأجمل الألقاب ، من دعمني بلا حدود واعطاني بلا مقابل إلى من علمني أن الدنيا كفاح وسلاحها العلم والمعرفة، داعمي الأول في مسيرتي وسندي وقوتي وملاذي بعد الله فخري واعتزازي

(ابينا العزيز)

إلى من جعل الله الجنة تحت أقدامها، واحتضنني قلبها قبل يديها وسهلت ل الشدائد بدعائها، إلى القلب الحنون والشمعة التي كانت لي في الليالي المظلمات سر قوتي ونجاحي جنتي

(امنا الغالية)

إلى من ساندني بكل حب عند ضعفي وازاح عن طريقي المتاعب ممهدا لي الطريق زرع الثقة والإصرار بداخلي الى من شد الله به عضدي فكان خير معين

(إخوتي)

إلى ملائكة رزقني الله بهن لأعرف من خلالهن طعم الحياة الجميلة، تلك الملائكة التي غيرن مفاهيم الحب والصداقة والسند في حياتي

(أخواتي)

واخيراً من قال: أنا لها نالها، وأنا لها إن أبت رغما عنيا، فمن فيها مثلي لم يبال بمن فيها، فلا يضيق دنياه ولا يوسعا."

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ABSTRACT

The work included the innovation and development of the drug trimethoprim by linking it with the innovative compound sulfazane and creation of several derivatives of sulfazane –trimethoprim for the first time then studying
the behavior and impact of innovative compounds on vital activities as anti-cancer tumors by following an innovative procedures of preparation for sulfazane compounds ,then linking them with several chemical reactions with the drug trimethoprim to develop its effectiveness and efficiency. Several spectral techniques were used to diagnose and demonstrate the formation
of innovative derivatives (sulfazane- trimethoprem) thereof (FT.IR - Spectra ,H.NMR – Spectra , HMBC- Spectrum ,Mass Spectra), chemical properties, Flowing through TLC ,in addition to laboratory study of cancerous tumors. The results indicated to formation of these drug derivatives by appearance of new bands and disappearance of bands in starting compounds., besides to conclusions from our paper that gave good data for inhibition efficiency for these drug derivatives against cancer cells. in this research work continued to prepare other
drug derivatives by linking sulfazane to the drug trimethoprim via (-S-N=N-) sulfazane group to study its effect on cancerous tumors.Trimethoprim contains the active ingredient trimethoprim, an antibiotic used to treat infections with bacteria. Bacterial cells in order to grow and multiply need a genetic material (DNA) to produce DNA and need folic acid (folate).3-10 Methoprim works by preventing bacteria from producing folic acid .

INTRODUCTION

Trimethoprim and its derivatives are type of medicine called an ntibiotic. Trimethoprim is a dihydropyridine antimicrobial and antiparasitic agent. It is the prototype of a group of nonsulfonamide drugs that inhibit dihydrofolate reductase in bacterial and protozoal cells(1).The chemical designation of trimethoprim is 5- [(3, 4, 5trimethoxyphenyl) methyl]-2, 4-diaminopyrimidine. It is a white to yellowish compound with bitter tas). Trimethoprim, 2,4-diamino-5-(3',4',5'-trimethoxybenzyl) pyrimidine), is synthesized in various ways. The first scheme of synthesis begins with ethyl ester of 3,4,5-trimethoxydehydrocinnamic acid, which is formylated with ethyl format using sodium as a base to make an enol of the semialdehyde 3′,4′,5′-trimethoxybenzylmalonic ester (33.1.49), which undergoes a heterocyclization reaction with guanidine to make 2-amino-4-hydroxy-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (33.1.50) (2). Subsequent replacement of the hydroxyl group in the resulting product with chlorine using phosphorous oxychloride and then with an amino group using ammonia gives the desired trimethoprim. All of the other syntheses begin with 3,4,5- rimethoxybenzaldehyde. According to one of them, condensation of 3,4,5-trimethoxybenzaldehyde with 3-ethoxy- or 3-anilinopropionitrile gives the corresponding benzylidene derivative (33.1.52), which upon direct reaction with guanidine gives trimethoprim(3). trimethoprim has also been synthesized by condensing 3,4,5- trimethoxybenzaldehyde with malonic acid dinitrile in a Knoevenagel reaction, which forms the derivative (33.1.53), which is partially reduced to the enamine (33.1.54) by hydrogen using a palladium on carbon catalyst, which upon being reacted with guanidine is transformed into trimethoprim. Finally,(4) trimethoprim can be synthesized in a manner that also uses a Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde as the first step, but this time with ethyl cyano-acetate, which gives an ylidene derivative (33.1.55). The double bond in this product is reduced by hydrogen over a palladium on carbon catalyst, giving 3′,4′,5′- trimethoxy-benzylcyanoacetic ester (33.1.56). Reacting this in a heterocyclization reaction with guanidine gives the desired trimethoprim(5). The diaminopyrimidine derivative trimethoprim (TMP) is a selective inhibitor of bacterial dihydrofolate reductase (DHFR), which is widely conserved and essential in bacterial pathogens (6).

Trimethoprim is an antibiotic used to treat bacterial infections. It works by stopping the growth of bacteria.This antibiotic treats only bacterial infections. It will not work for viral infections (such as common cold,

flu). Using any antibiotic when it is not needed can cause it to not work for future infections .(7)

Take this medication by mouth with or without food as directed by your doctor, usually once or twice daily. The dosage is based on your medical condition and response to treatment. In children, the dosage is also based on their weight.

If you are using the liquid form of this medication, carefully measure the dose using a special measuring device/spoon. Do not use a household spoon because you may not get the correct dose.(8)

For the best effect, take this antibiotic at evenly spaced times. To help you remember, take this medication at the same time(s) every day.

Continue to take this medication until the full prescribed amount is finished, even if symptoms disappear after a few days. Stopping the medication too early may result in a return of the infection.

SIDE EFFECTS(9)

Diarrhea, nausea, vomiting, stomach upset, loss of appetite, changes in taste, and headache may occur. If any of these effects last or get worse, tell your doctor or pharmacist promptly.

Remember that this medication has been prescribed because your doctor has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects(10). Tell your doctor right away if you have any serious side effects, including: new signs of infection (such as sore throat that doesn't go away, fever), easy bruising/bleeding, pale skin, unusual tiredness, fast/irregular heartbeat, mental/mood changes, signs of liver disease (such as nausea/vomiting that doesn't stop, dark urine, stomach/abdominal pain, yellowing eyes/skin), stiff neck, headache that doesn't go away, muscle weakness, extreme drowsiness, signs of low blood sugar (such as sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling hands/feet).

This medication may rarely cause a severe intestinal condition due to a bacteria called C. difficile. This condition may occur during treatment or weeks to months after treatment has stopped. Tell your doctor right away if you develop: diarrhea that doesn't stop, abdominal or stomach pain/cramping, blood/mucus in your stool.(11)

If you have these symptoms, do not use anti-diarrhea or opioid products because they may make symptoms worse.

Use of this medication for prolonged or repeated periods may result in oral thrush or a new yeast infection. Contact your doctor if you notice white patches in your mouth, a change in vaginal discharge, or other new symptoms.

Get medical help right away if you have any very serious side effects, including: seizures.

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.(12)

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

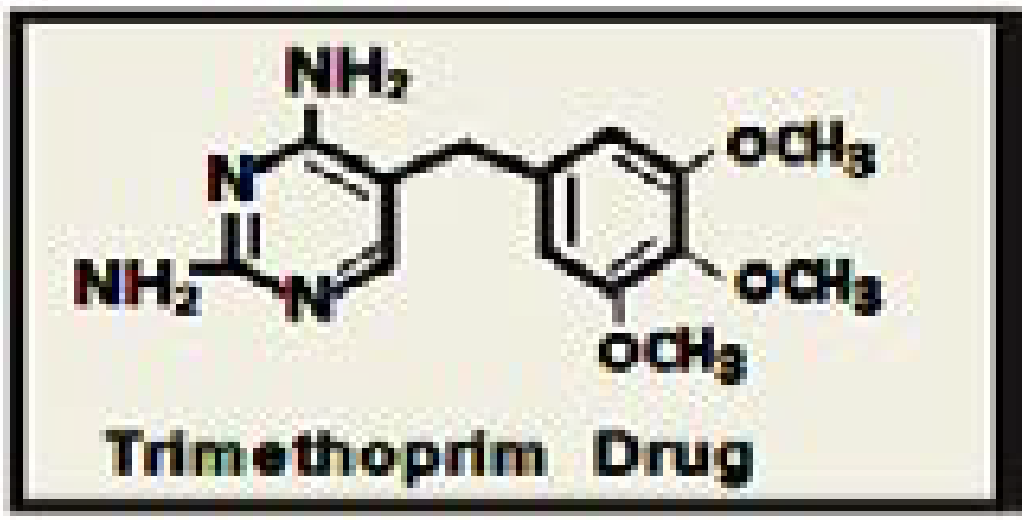


Fig "1" Trimethoprim Drug

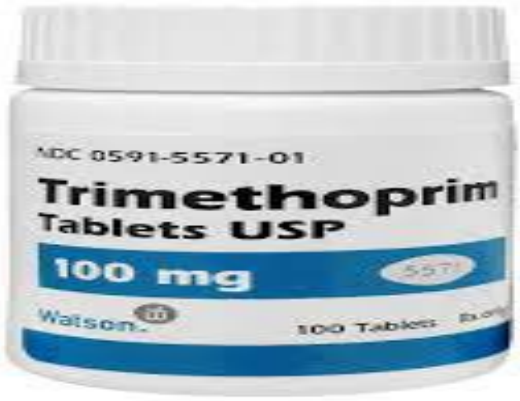


Fig "2" Trimethoprim 100 MG

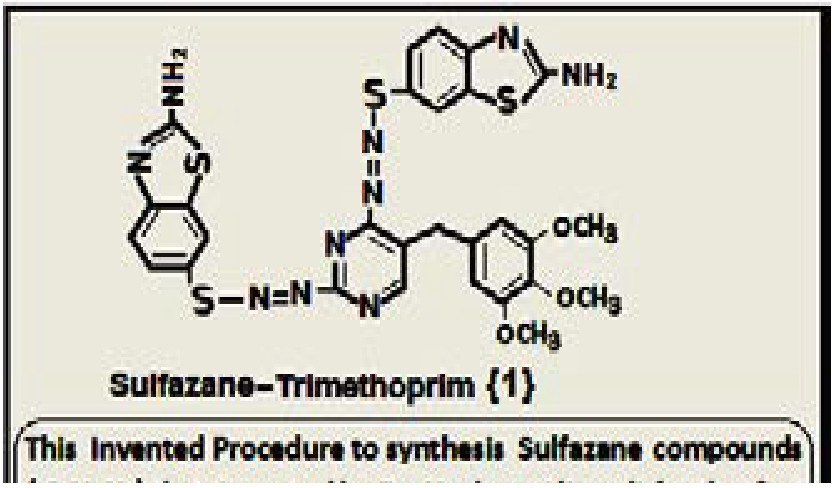
EXPERIMENTAL PART

An innovative method1, 2 was used to develop the trimethoprim drug by linking it to an innovative sulfazane compounds through several steps, chemical reactions and reaction conditions that differ for each of the innovative derivatives prepared in this research. The chemical composition of the innovative derivatives prepared in this research was proven by several investigation techniques (FT-IR spectra) with the range (400-4000)cm-1 using discs of KBr., and in solvent (d-DMSO) .

PATHS OF SYNTHESIS

Innovation and Creation of Sulfazane-Trimethoprim {1}

P-thiol aniline (0.01 mole) with (0.01mole) ammonium thiocyanate in bromine with glacial acetic acid ,after rotation for (2 hrs) at (10C°) via three reactions ,then precipitation filtered,washed, dried, purification by recrystallization, then (0.01 mole) from precipitation dissolved in basic alcoholic solution, and added to acidic diazo- trimethoprim salt in three steps according to invented procedure in papers(1, 2) ,after (3 days), filtered ,washed ,dried ,recrystallized to yield sulfazane- trimethoprim {1}.



Scheme 1. Creation of Sulfazane- Trimethoprim {1}

SPECTRAL EVIDENCES "FT.IR- SPECTRA"

The infrared spectrum is the first technique that has demonstrated, with certain evidence, the creation of innovative, advanced derivatives in this study through the emergence of effective and functional grouping frequencies in derivatives indicating the reason for the accuracy of their preparation and the correctness of the innovative procedure to prepare them :-

Sulfazane- Trimethoprim {1}

Bands at (-OCH3) methoxy group: 1183 ,(-N=N-S-) Azo-Sulfide: (1398, 489), 1500) , (S-CH-) Sulfide : 1226 ,(C-S) endocyle of benzothiazole : 756 (C=N) endocycle of pyrimidine: 1652 ,(-NH2) amine group: (3358,3409).

physical properties and information about TLC for invented derivatives in Table(1)

Table 1. All chemical with physical properties and information of TLC

Invented Derivatives	*Product %*	*Color*	*M .P(C °)*	*Rf Solvents(TLC)*
Sulfazane-Trimethoprim {1}	74	Deep Yellow	202	0.68 Ethanol : Benzene

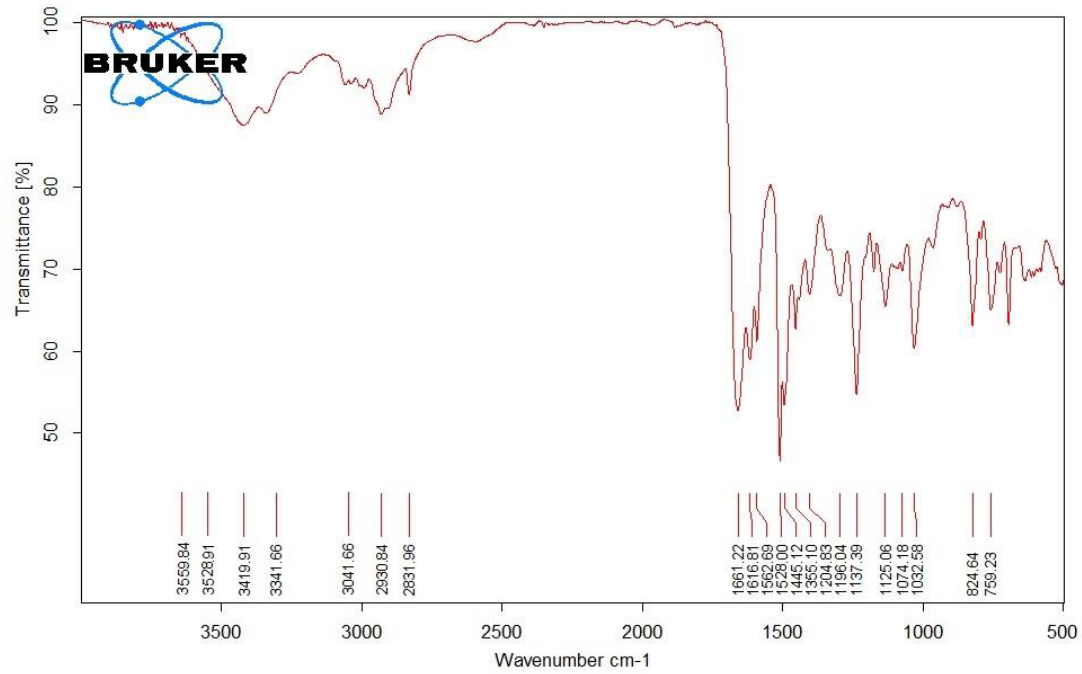


Fig. 1. I.R Spectrum of Invented Sulfazane-Trimethoprim{1}

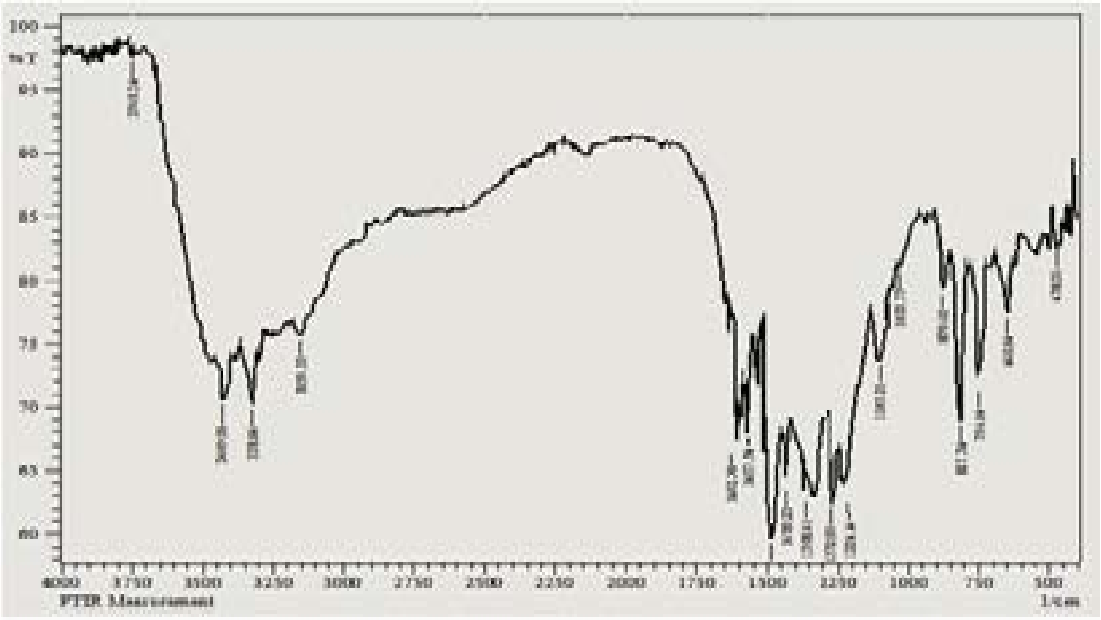


Fig. 1. I.R Spectrum of Invented Sulfazane-Trimethoprim{1}

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