Synthesis and Identification of Some New Derivative of Trimethoprim and Paracetemol Drugs

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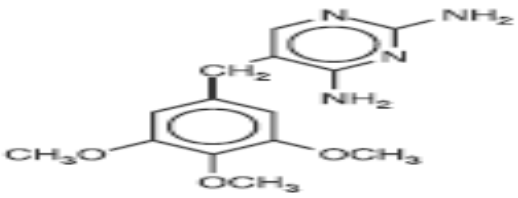
Abstract:

In this research two series of the new derivatives of Trimethoprim and paracetamol drugs have been prepared which known as a high medicinal effectiveness. Series (A) is including the interaction of diazonium salt of trimethoprim and coupling with some substituted phenol compounds (2-amino phenol, 3-ethyl phenol, 1-naphthol, 2-nitro phenol, Salbutamol). Series (B) is including the interaction coupling alkali solution of paracetamol with diazonium salt of some substituted aniline compounds (Benzedine, 2, 3-di chloro aniline, Trimethoprim, Anilinium chloride, 2-nitro- 4-chloro aniline).Chemical structures of all synthesized compounds were confirmed by UV-visible and FTIR spectroscopy.

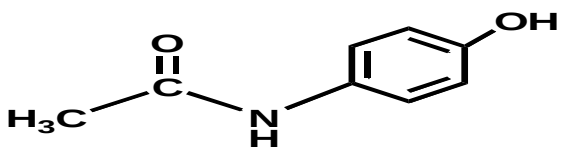
Key word: Azo compound, Trimethoprim, Synthesis, paracetemol

Introduction

Trimethoprim and its derivatives are type of medicine called an antibiotic[1] they are used to treat infections with bacteria[2], they are significant antimicrobial activities[3,4], and its analogues[5].The chemical designation of trimethoprim is 5-[(3, 4, 5-trimethoxyphenyl) methyl]-2, 4-diaminopyrimidine. It is a white to yellowish compound with bitter taste. The trade names of the combined product are Bactrim and Spectra[2].



5-[(3, 4, 5-trimethoxyphenyl) methyl]-2, 4- diaminopyrimidine



4 -Hydroxyacetanilide

Paracetamol is 4 -Hydroxyacetanilide used as antipyretic[6] It has commercial applications in the pharmaceutical industry as an analgesic and an antipyretic; it and related compounds are used in the manufacture of azo dyes and photographic chemicals[7,8]In current study some of the new derivatives of trimethoprim were prepared that known high medicinal effectiveness, after convert it to diazonium salt in alkali medium and coupling with substituted phenol compounds to produce azo compounds[9]. Also a new derivative of paracetamol was prepared, through the interaction between paracetemol in alkali medium and coupling with daizonium salt of some substituted aromatic amine compounds.Azo compounds have the potential to act as drug carriers that facilitate the selective release of therapeutic agents to the colon, and also to effect the oral administration of

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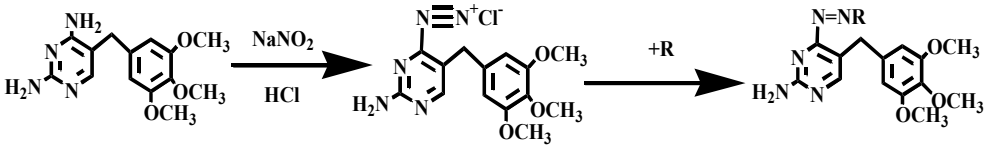
those macromolecular drugs that require colon-specific drug delivery[10]. Diazonium salt is the most widely used in industrial reaction in the production of dyes, lakes and pigments. Aromatic diazonium ions act as electrophiles in coupling reactions with activated aromatics such as anilines or phenols. Phenols common compounds that associated in coupling reaction, this reaction happened in alkali medium [11]. The substitution normally occurs at the para position, except when this position is already occupied, in which case *ortho* position is favored. The pH of solution is quite important; it must be mildly acidic or neutral, since no reaction takes place if the pH is too low[12].

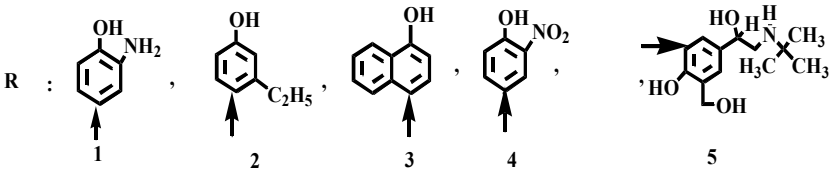
Materials and Methods:

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 points were recorded on a hot stage Gallen Kamp melting point apparatus.Trimethoprim standard. with (99% purity) was obtained from (BDH), it was provid from Al-Nahrain company industrial drug , other All chemical were high purity are used in this work as the manufactures, supplied from BDH, Fluka and or Aldrich companies.For production Series (A), diazonium salt of trimethoprim, (0.021 mole, 5.2g) Trimethoprim is added in beaker contain (12.8 ml) of (50%) hydrochloric acid at temperatures (0-5) C^0, and then (8ml) of (20%) sodium nitrate solution is added , drop by drop with continuous stirring and cooling (0-5) C^0. (0.022 mole) of substituted phenol compounds were taken with 18 ml of (10%) sodium hydroxide in ice path at zero centigrade ,then diazonium salt is added slowly with continuous stirring and cooling. Set aside the mixture for two hours and same temperature ,then (30%) hydrochloric acid is added crystal precipitation apparent , leave it to stabile for one hour then filter and wash with cooling water ,dry the crystal and recrystalization with ethanol For production Series (B), variation amines (0.021 mole, 5.2g) were added in beaker contain (12.8 ml) of (50%)hydrochloric acid by using water path in temperatures (0-5)C^0, and then added (8ml)from (20%) sodium nitrate solution ,is added drop by drop with continuous stirring and cooling for production Diazonium salt. Dissolve (0.022 mole) of paracetemol in 18 ml (10%) sodium hydroxide in ice path at temperature zero centigrade ,then added diazonium salt slowly with continuous stirring and cooling. leave the mixture for two hours in same temperature ,then added 2ml of (30%) hydrochloric acid . crystal precipitation apparent , after complete the reaction for one hour ,the mixture was filtered and washed with cooling water ,dry the crystal and recrystalation with ethanol. table (1) showed a new derivative compounds were prepared .

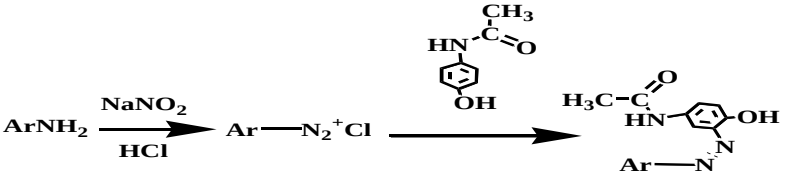
Discussion

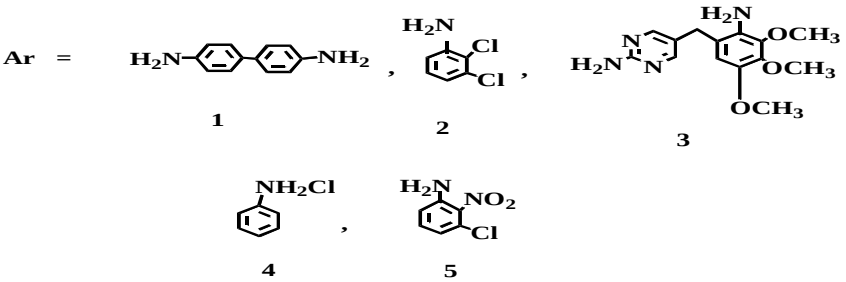
The new derivatives for Trimethoprim were prepared by reaction Diazonium salt of Trimethoprim with different phenol compounds. The following mechanism explains the reaction.





The new derivatives of paracetemol were prepared by reaction of paracetemol with different amine compounds. The following mechanism explains the reaction .





The formula structure and other physical properties of new derivatives of trimethoprim and paracetamol were identificated by using melting point that explains in table (1).

Table (1): physical properties of compounds prepared

Compound No s	Color	Molecular weight	Molecular structure	Melting point C^0
1A	light Brown	410.43	$C_{20}H_{22}N_6O_4$	260-258
2A	Black	423.47	$C_{22}H_{25}N_5O_4$	248-250
3A	Green	434.47	$C_{23}H_{24}N_5O_4$	230
4A	Yellow	440.41	$C_{20}H_{20}N_6O_6$	262-264
5A	Brown	540.61	$C_{27}H_{36}N_6O_6$	265
6B	Browne	346.38	$C_{20}H_{18}N_4O_2$	108-110
7B	Orange	324.16	$C_{14}H_{11}C_{l2}N_3O_2$	158-160
8B	Orange	452.46	$C_{22}H_{24}N_6O_5$	102-104
9B	Light Yellow	255.27	$C_{14}H_{13}N_3O_2$	128-130
10B	Yellow	334.71	$C_{14}H_{11}ClN_4O_4$	142-144

The stretching of O-H phenolic demonstrate wide absorption band in the region (3125-3275)cm^{-1} . of absorption for the NH_2 group which it be secondary demonstrate in the region (3000-3400) cm^{-1} [13]is not clearly that to give reason for one of the NH_2 group that is situated in position 4 between tow nitrogen atoms in the pyrimidine cycle is not diazonate , may be the hydrogen atom in this amine group enter tautomerism with

the neighboring nitrogen atoms .The appearance of that medium intensity band in the region (1595-1490) cm^{-1} belong to the frequency matched stretching for N=N group, so The appearance of medium bands at (1400-1410)cm^{-1} bending for N=N group, as well as The appearance of different bands which explain in table (2).

Table (2): The value of IR spectroscopy of compounds prepared.

No.	N=N str. cm^{-1}	C=C Aromatic cm^{-1}	N-H str.sym. cm^{-1}	OH phenolic str. cm^{-1}	CH Aliphatic cm^{-1}	CH Aromatic str cm^{-1}	Other cm^{-1}
1 A	1504	1605		3275	2997	3114	
2 A	1419asym 1531sym.	1558	3395	3212	2938	3100	NH str.3329,3388
3 A	1531	1610	3425	3125	2823	3047	
4 A	1528	1602		3177	2953	3020	Out of plan CH bend.742
5 A	1530	1605		3212	2927	3030	Out of plan C=C bend.502

Table (3): The value of IR spectroscopy of paracetemol derivatives.

No.	N=N cm^{-1} str.	C=C Aromatic cm^{-1}	OH phenolic cm^{-1} str.	CH Aliphatic cm^{-1}	CH Aromatic str cm^{-1}	Other cm^{-1}
6B	1507	1590	3445	2988	3100	
7B	1510	1578	3455	2972	3059	NH str.3330,3390
8B	1540	1607	3383	2843	3047	
9B	1533	1603	3351	2921	3024	
10B	1522	1620	3401	2911	3020	

The stretching of O-H phenolic demonstrate wide absorption band in the region (3400-3100)cm^{-1} with disappearance of absorption for NH_2 group that it be secondary demonstrate in the region (3000-3300) cm^{-1}[13].The appearance of beam that intensity medium in the region (1595-1490)cm^{-1} belong to the frequency matched stretching for N=N group, so The appearance of medium beam at (1400-1410) cm^{-1} and bending for N=N group, as well as The appearance of different beam that explain in table (3). The UV-Visible spectroscopy was demonstrated absorption beams at about (288,360) nm belongs (Π-Π^*) and (n-Π^*) The transitions for (N=N) azo group demonstrate the absorption bands at 230 nm belong to cycle benzene as a result of (Π-Π^*) transitions other absorption beams that weak absorbance demonstrate in the visible region up 420 nm this weak peak give reason of produce color. The color differences are caused by different substituents on the aromatic rings which lead to differences in the extent of conjugation of the π system in the azo dye. In general, the less extensive the conjugated π system of a molecule, the shorter the wavelength of visible light it will absorb[14].

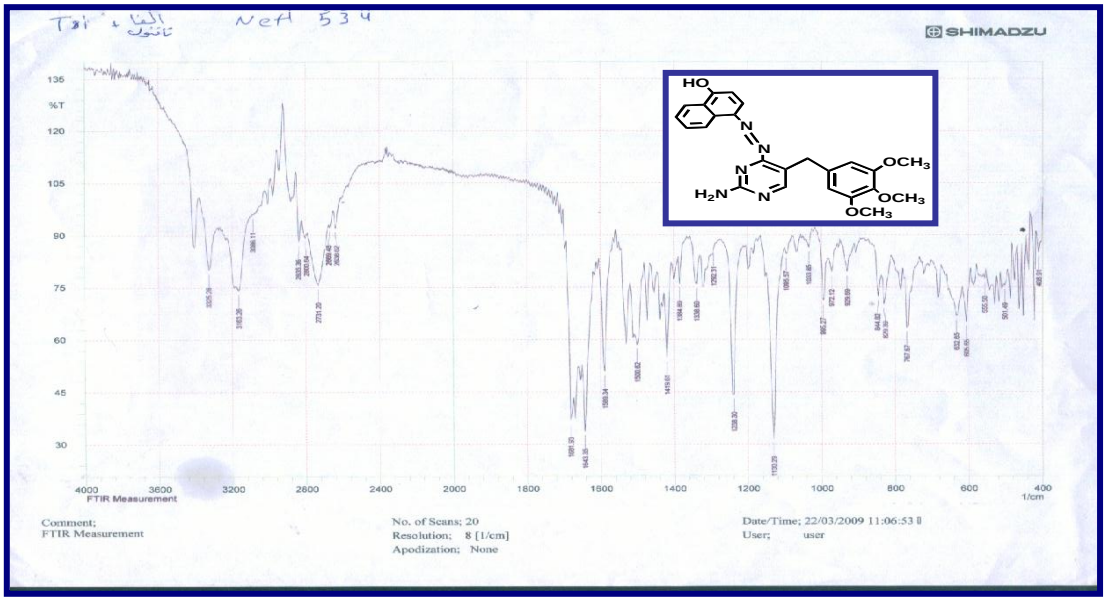


Fig. (1) IR spectrum of4-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4,4a-dihydro-naphthalen-1-ol.

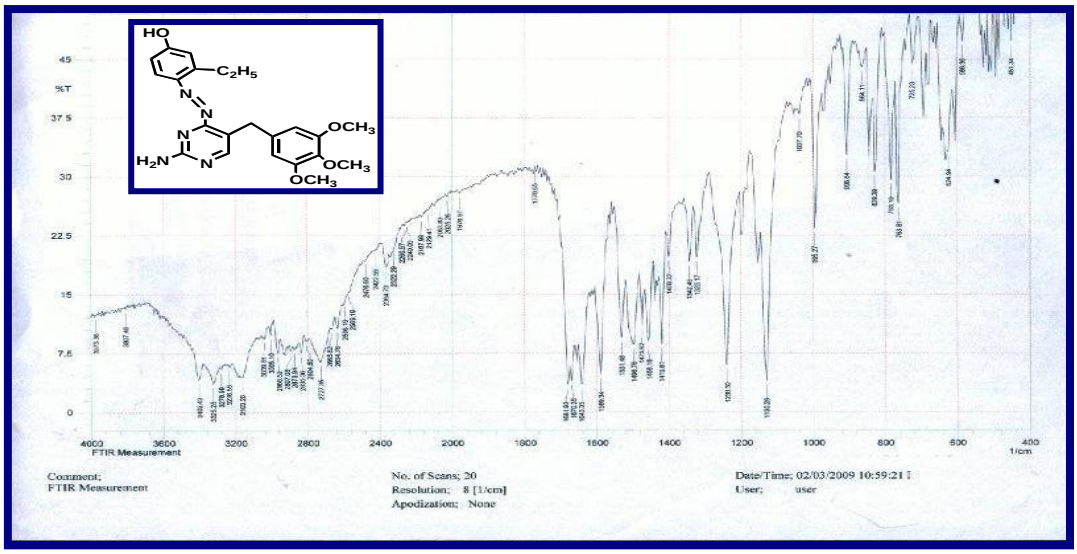


Fig. (2) IR spectrum of 4-[4-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-3-ethyl-phenol.

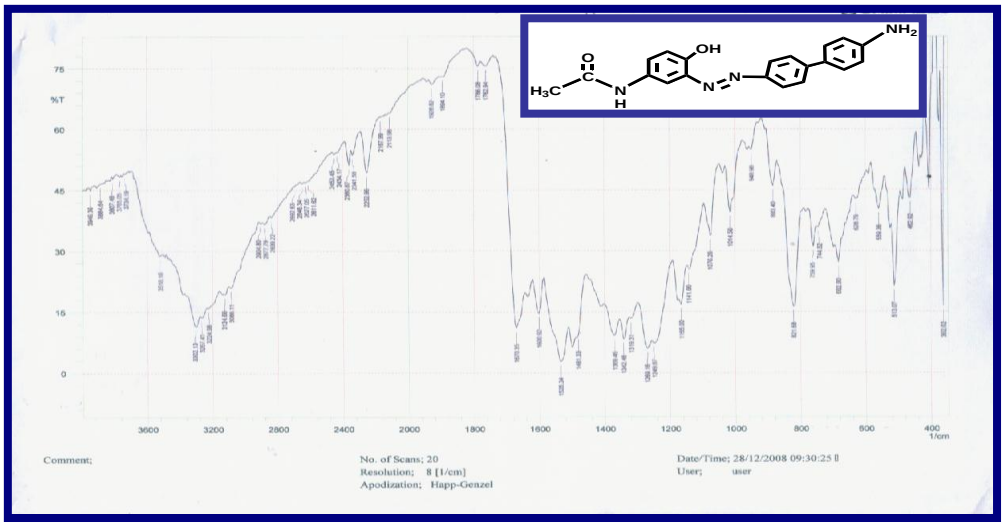


Fig.(3) IR spectrum of N-[3-(4'-Amino-biphenyl-4-azo)-4-hydroxy-phenyl]-acetamide.

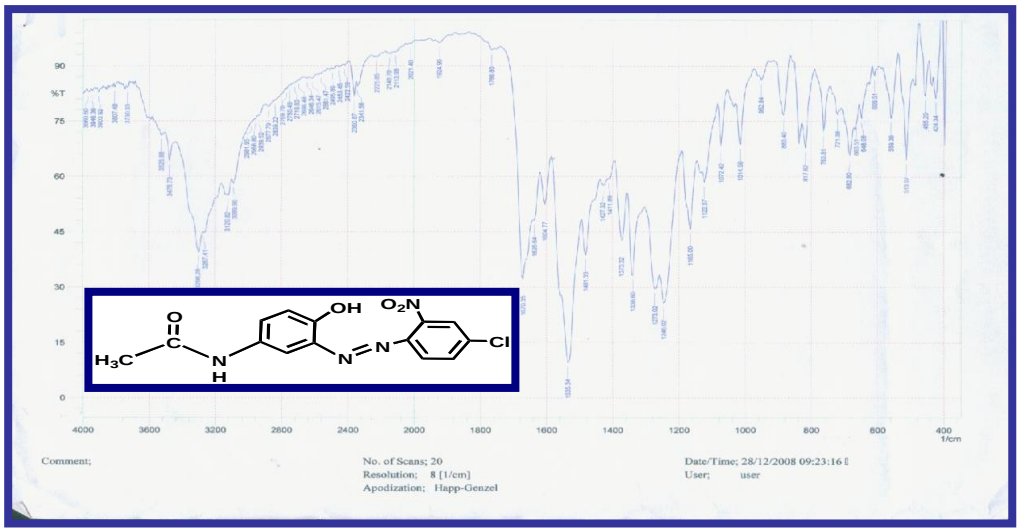


Fig.(4) IR spectrum of N-[3-(4-Chloro-2-nitro-phenylazo)-4-hydroxy-phenyl]-acetamide.

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تحضير وتشخيص بعض المشتقات الجديدة لأدوية التراي مثبرين والباراسيتمول

هند فاضل ثامر ***سعدية أحمد ظاهر ****

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الخلاصة:

في هذا البحث حضرت سلسلتين من المشتقات الجديدة للمركب التراي مثبرين والباراسيتمول المعروفة بفعاليتها الدوائية العالية.السلسلة (A)تتكون من خلال تفاعل ازدواج ملح الديازونيوم للتراي مثبرين مع بعض معوضات الفينولات (2- امينو فينول ,3- اثيل فينول ,1 -نفثول,2-نايترو فينول ,سالبيتيمول). السلسلة (B) تتضمن تفاعل ازدواج المحلول القاعدي للباراسيتمول مع ملح الديازونيوم لبعض معوضات الانيلين مع (بنزيدين , 3,2 - داي كلورو انيلين , تراي مثبرين, كلوريد الانلين ,2-نايترو4-كلوروانيلين). تم تشخيص المركبات المحضرة باستخدام بعض الطرق الطيفية UV-Visible, FTIR.