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synthesis of some a new azo derivative of paracetamol
تحضير وتشخيص بعض المشتقات الجديدة لدواء الباراسيتيمول

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Summery

In this work new derivatives of paracetamol drug were prepared that known high medicinal effectiveness, through coupling reaction between alkali solution of paracetamol and diazonium salt of some substituted aniline compounds (4-chloro -2-nitro aniline, 4-amino aniline , 2,3-di methyl aniline ,١-amino Naphthalene, 2-amino 1,3,4- thiadiazole-5-thiol).The identification of the prepared compounds was carried out by using UV-Visible and FTIR spectra.

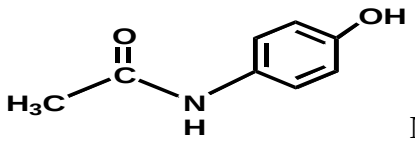
Key ward: paracetamol, new derivative, Biological activity

الخلاصة

تم في هذا البحث تحضير مركبات جديدة لدواء الباراسيتمول من خلال تفاعل ازدواج بين المحلول القاعدي للباراسيتمول و ملح الديازونيوم لبعض معوضات الانيلين(٤- كلورو-٢- نايترو انيلين ٤- امينو انيلين , ٢,٣ ثنائي مثيل انيلين ,١- امينو نفثالين ,٢- امينو ١,٣,٤- ثايادايازول-٥-ثايول) تم تشخيص المركبات المحضرة باستخدام مطيافية الأشعة تحت الحمراء ومطيافية الأشعة فوق البنفسجية.

1-Introduction

Paracetamol is 4-Hydroxyacetanilide with formulae structural explain below, it is used as an analgesic and antipyretic, in the treatment of a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain and in other painful disorders such as headache, dysmenorrhoea , myalgia and neuralgia[1,2].



N-(4- Hydroxyacetanilide

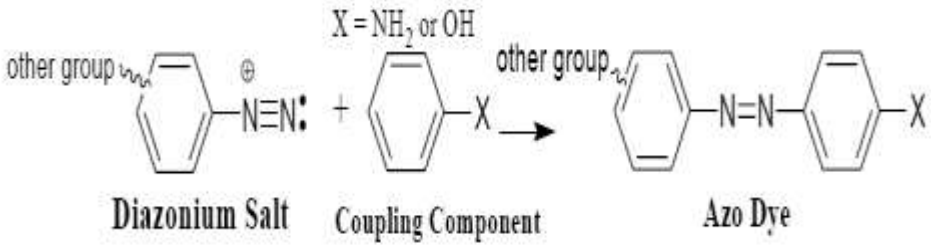
(paracetamol)

It is also indicated as an analgesic and antipyretic in diseases accompanied by generalized discomfort or fever, such as the common cold and other viral infections. Other uses include the manufacture of azo dyes and photographic chemicals, as an intermediate for pharmaceuticals and as a stabilizer for hydrogen peroxide[3]. Synthesis of paracetamol from acetylation of aminophenol[4]

The synthesis of an azo dye requires two organic compounds a diazonium salt and a coupling component. In this study, some new derivative of azo dyes for paracetamol were prepared by the interaction between paracetamol in alkali medium and coupling with daizonium salt of some substituted aniline compounds in nitrosyl hydrochloric acid.

In theory, a collection of different azo dyes should be able to make a complete rainbow of colors. In practice, azo dye compounds come in yellows, oranges, reds, browns, and blues. The color differences are caused by different substituent on the aromatic rings which lead to differences in the extent of conjugation of the π system in the azo dye[5.].

Azo compound is characterized by the presence of one or several R-N=N-R groups. The R groups are usually substituted aromatic hydrocarbons or aromatic heterocyclic compounds.[6] The general synthesis of azo dyes is shown below



Azo compounds are widely used as dyes and pigments since almost any colour can be obtained with this class of compounds. A comprehensive summary of the applicability of azo compounds as dyes and pigments is found in Reference .[6,7].

Another area of application of aromatic azo compounds is analytical chemistry where some of these compounds are used as indicators in pH, redox or complexometric titrations. The end point of an acid-base titration can be indicated by a colour change as a result of a change in the protonation of the indicator. In addition to titrations, direct and indirect determinations of transition metal ions in different matrices have also been presented utilising electroanalytical techniques such as polarography [7-12].

Azo compounds are also used in the pharmaceutical industry. The pharmacological use of azo compounds originates from the discovery of the antibacterial action of Prontosil on streptococcal infections by Dogmagk.[13] The effect was later attributed to the sulfanilamide produced after bacterial reduction of the azo linkage in the colon. The search of other sulfanilamide preparations led to the discovery of Sulfasalazine (Salazosulfapyridine) for the treatment of rheumatoid arthrithtis and ulcerative colitis by Svarts in the beginning of the 1940's.[14] Sulfasalazine is still in use for treatment of these conditions [15,16].

2-Experimental methods

2.1-Apparatus

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.

2.2-Materials and Reagents

paracetamol 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 Aldrich companies.

2.3-Procedure

Preparation of azo compounds[17] (1-azo-[substituted benzene]5-paracetamol)

Various amines (0.021 mole) were added in beaker (100ml) contains (12.8 ml) from (50%)hydrochloric acid by using water path in temperatures (0-5) ^{0}C, and then added (8ml)from (20%) sodium nitrite solution was added drop wise with continuous stirring and cooling for production Diazonium salt.

Dilute (0.022 mole) paracetamol in 18 ml from(10%) sodium hydroxide in ice path at temperature zero centigrade ,then added Diazonium salt slowly with continuous stirring and cooling, the mixture was left for two hours in same temperature ,then added 2ml of (50%) hydrochloric acid was added Crystal precipitation apparent , after complete the reaction was left for one hour ,the mixture was filtered and washed with cooling water ,dry the crystal and crystallization with ethanol

3.1 Results and Discussion

The new derivative for paracetamol which prepared by reaction paracetamol with different amine compounds. The formula structure of paracetamol derivatives were identificated by using melting point which explain in table(1) and IR spectroscopy that explain in table(2) As well as UV-Visible spectroscopy.

Table (1):physical properties of azo compounds

Compounds No.	Color	Molecular weight	Molecular structure	Yield%	Melting point C^0
١	Browne-red	٣٣٤.٧١	$C_{14}H_{11}ClN_4O_4$	85	١٠٨-١١٠
٢	light Browne	٢٧٠.١١	$C_{14}H_{14}N_4O_2$	87	١٥٨-١٦٠
٣	light Yellow	٢٨٣.١٣	$C_{16}H_{17}N_3O_2$	77	١٠٢-١٠٤
٤	Dark violet	٣٠٥.٣٣	$C_{18}H_{15}N_3O$	85	١٢٨-١٣٠
٥	magenta (bright pink)	٢٩٥.٣٤	$C_{10}H_9N_5O_2S_2$	83	١٤٢-١٤٤

The stretching of O-H phenolic and al- alcoholic 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 (3000-3400) cm^{-1} [18].

The appearance of band 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 band at (1400-1410)cm^{-1} and bending for N=N group, as well as The appearance of different band that explain in table (2).Figures 1 ,2,3 are showed the spectrum of FTIR for paracetamol, new compound 2 and new compound 5 respectively.

Table (2):The value of IR spectroscopy for some functional group in paracetamol derivatives.

No.	Aromatic ringe ν(C=C) str cm^{-1}.	N=N str cm^{-1}	OH phenolic cm^{-1} str.	CH Aliphatic cm^{-1}	Other cm^{-1}
١	1504	١٤٠٨	٣٤٧٥	٢٩٩٧	Aromatic CH str.3114
٢	1510	١٤٠٠	٣٤٢٠	٢٩٣٨	NH str.3329,3388
٣	١٥٣١	١٤٠٠	٣٣٩٨	٢٨٢٣	Aromatic CH str.3047
٤	١٥٢٨	١٤٠٥	٣٣٧٧	٢٩٥٣	Aromatic CH str. 3020 Out of plan CH bend.742
٥	١٥٣٠	١٤٠٢	٣٣٩٢	٢٩٢٧	Aromatic CH str.3030
٦	١٤٩٦	١٤٠٨	٣٤١٤	٢٨٦٦	NH str.3329 In plan CH bend.813

The UV-Visible spectroscopy was demonstrated absorption bands at (288,360)nm belongs (n-π^*) transitions for (N=N) azo group and demonstrate other absorption bands at 230 nm belong to cycle benzene that result for (π-π^*) transitions

Figures 4 ,5,6,7 are showed the UV-visible spectrum of paracetemol, new compound 1,2 and 5 respectively

3.2-Biologcal Activities

The biological activity were studied, the effect of new paracetamol derivatives on two type of bacteria (G^-)E-coil and(G^+) Staphylococcus Aureus have been described in table3.,all the synthesized compounds were screened for their antibacterial activity by agar dilution methods[19]. The results showed all of these derivatives have shown high activity for Staphylococcus Aureus G^+ which showed in figure 8 but not shown Activity against G^- bacteria E^- Coil

Table 3 : biological activity of new paracetemol derivatives .

Comp 30 mg/l	Activity against G^- bacteria E^- Coil	Activity against G^+ Staphylococcus Aureus
1	-	+ +
2	-	+ + +
3	-	+ +
4	-	+ +
5	-	+ +

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

4-Conclusion

In this study was prepared a new derivative compounds of paracetamol through the interaction coupling between alkali solution of paracetamol and daizonium salt of some substituted aniline compounds. These new derivative have high activity for Staphylococcus Aureus G^+.

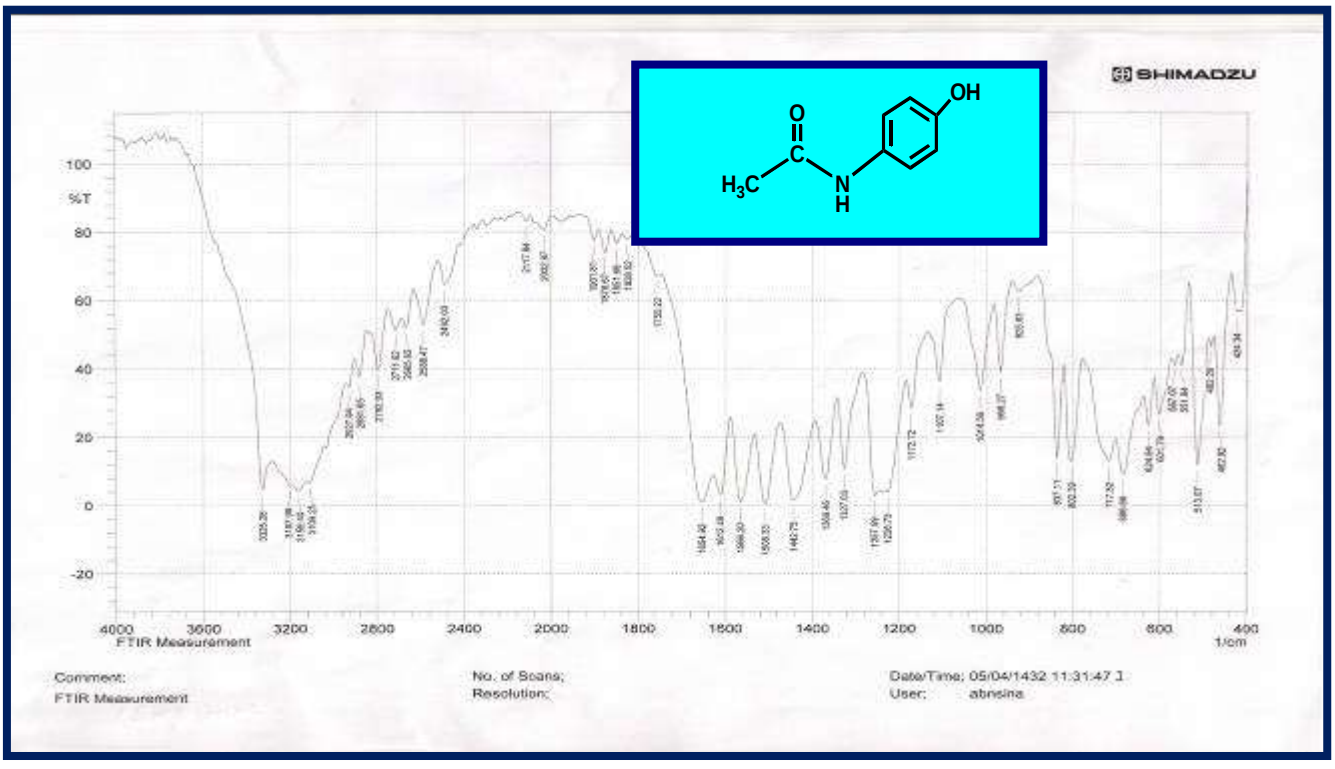


Figure (1) FTIR spectrum of paracetamol

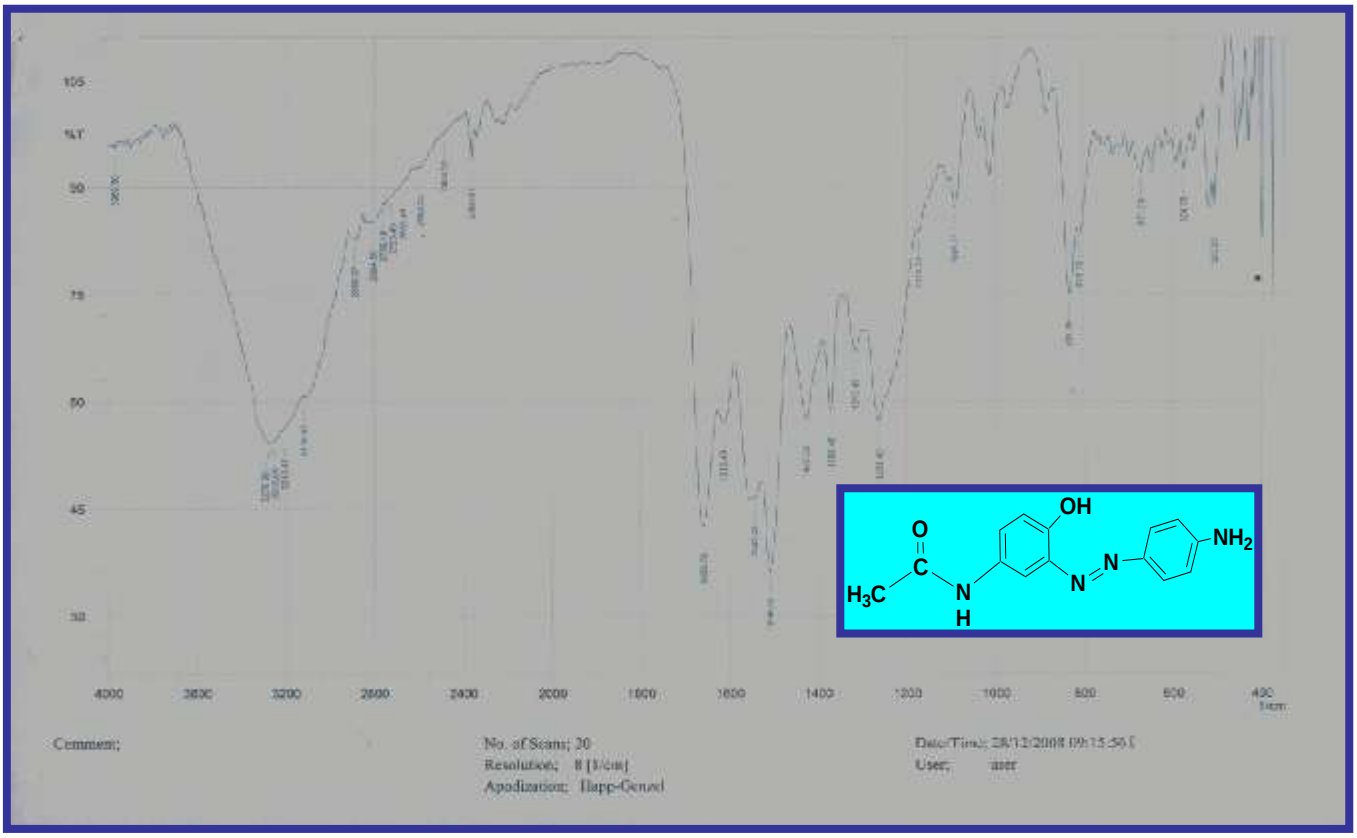


Figure (2) FTIR spectrum of N-[3-(4-Amino-phenylazo)-4-hydroxy-phenyl]-acetamide

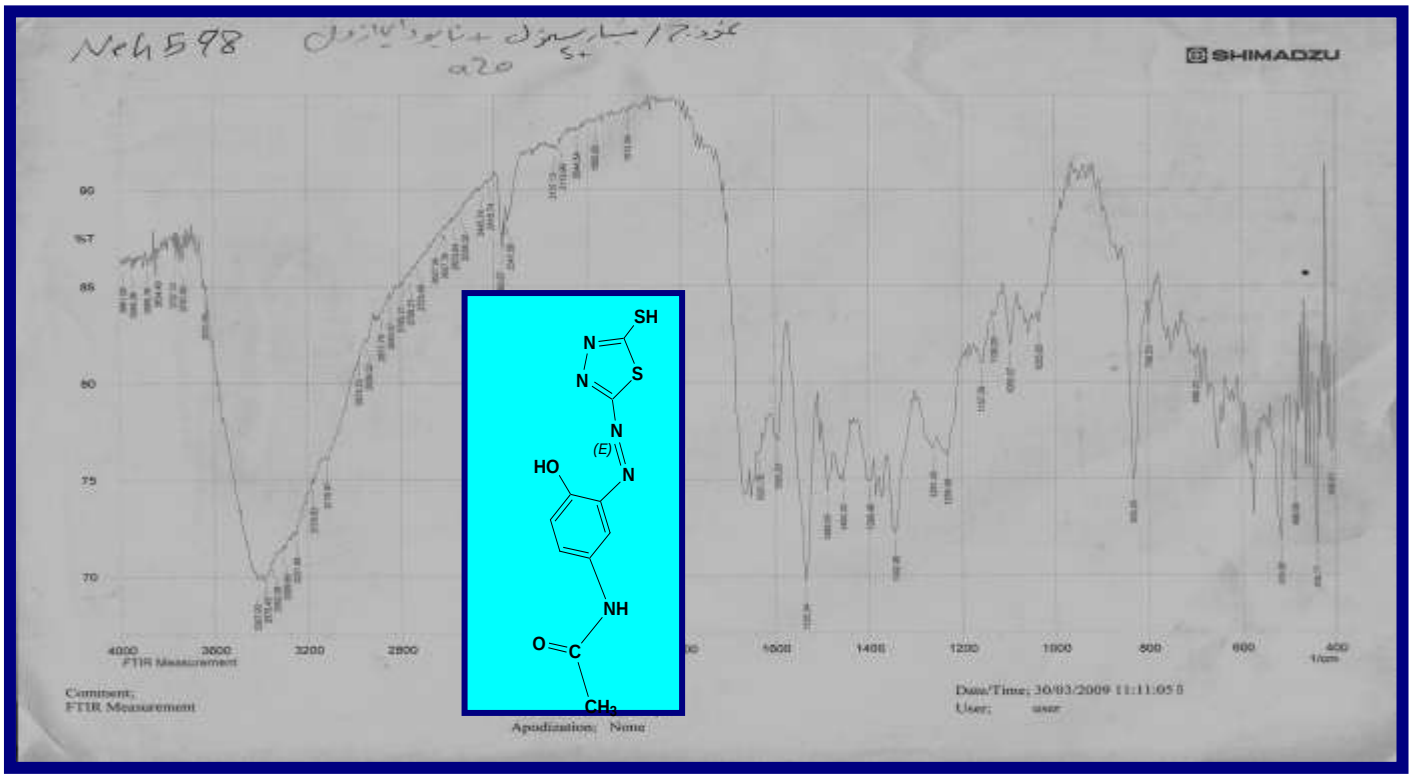


Figure (3) FTIR spectrum of N-[4-Hydroxy-3-(5-mercapto-[1,3,4]thiadiazolyl-2-azo)-phenyl]-acetamide

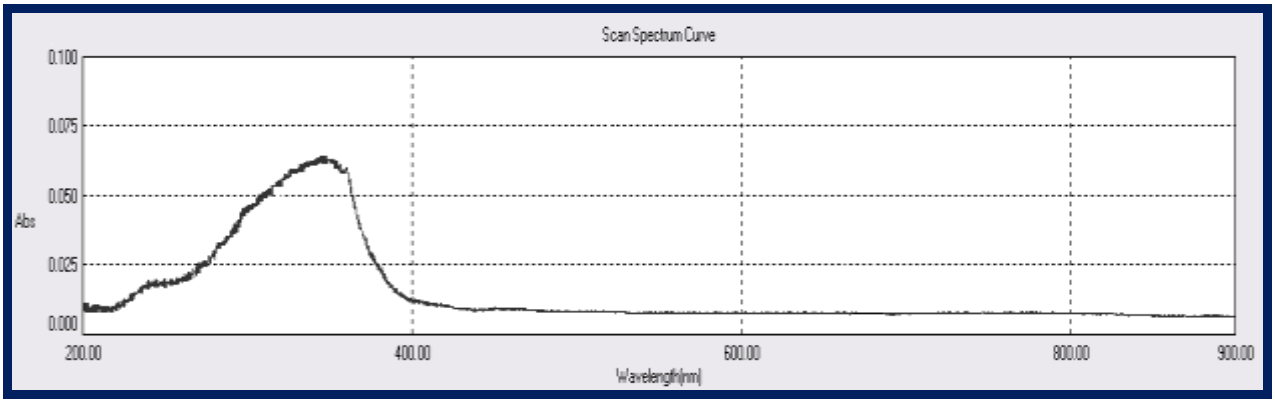


Figure 4. Absorption spectra of paracetamol

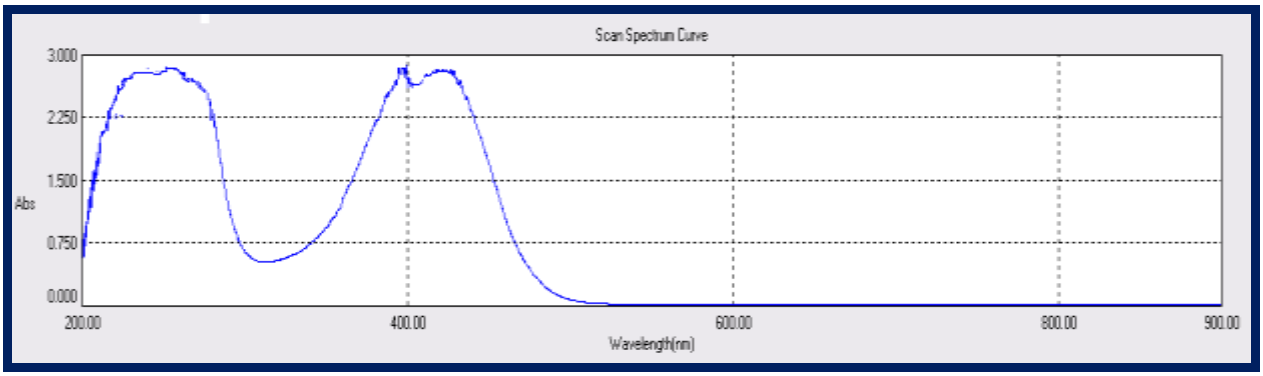


Figure 5. Absorption spectra of N-[3-(4-Chloro-3-nitro-phenylazo)-4-hydroxy-phenyl]-acetamide

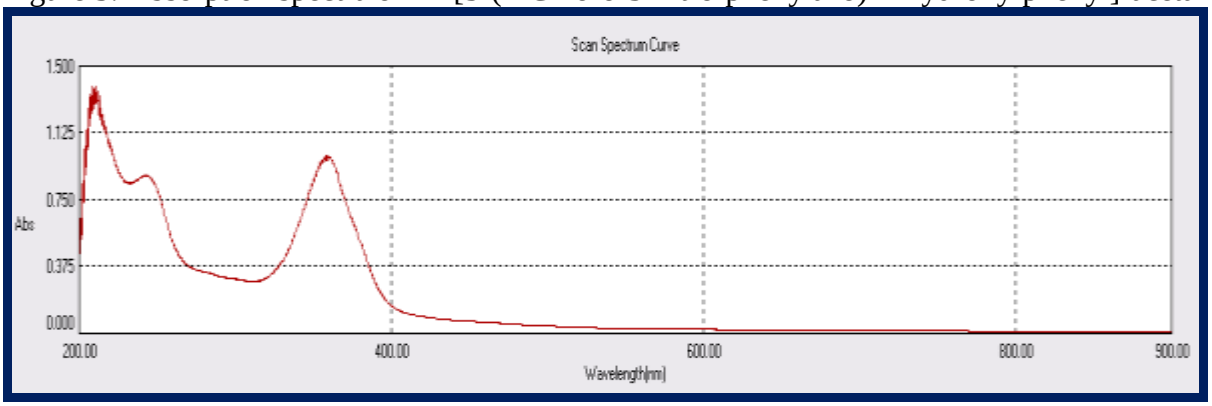


Figure 6. Absorption spectra of N-[3-(4-Amino-phenylazo)-4-hydroxy-phenyl]-acetamide

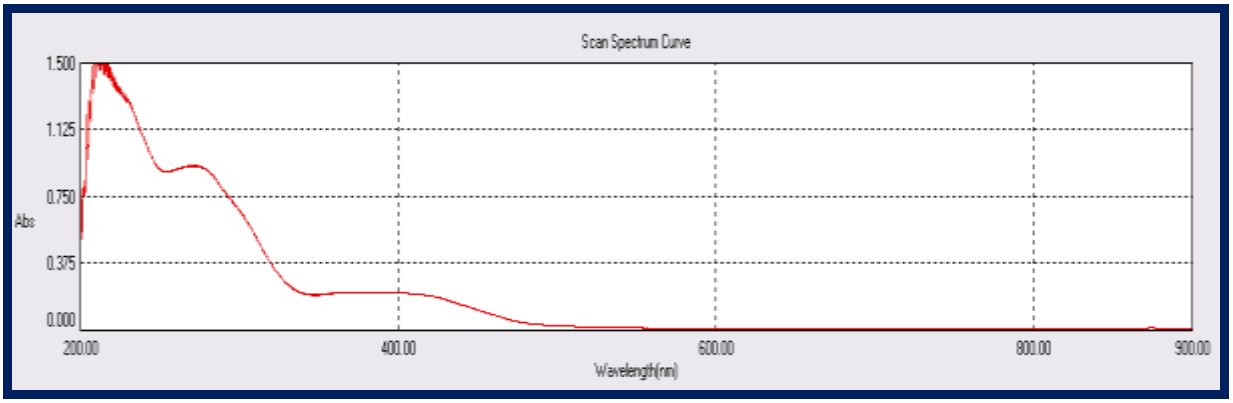


Figure 7. Absorption spectra of N-[4-Hydroxy-3-(5-mercapto-[1,3,4]thiadiazolyl-2-azo)-phenyl]-acetamide

Figure 8: the biological activity of some new compounds against G^+ Staphylococcus Aureus

References

1.National Toxicology Program NTP Chemical Repository Data Sheet: Acetaminophen (4- Hydroxyacetanilide), Research Triangle Park, NC, (1991).

2.P. R.Kumar, M. M Krishna, P. B Prakash, B. A Kumar and P. Madhusudhan, E-Journal of Chemistry,Vol. 3, No.12, pp 134.,(2006).

3. Sohrabi M R, Abdolmaleki P, Davallo M, Tadayyon F and Hay nollahi F, *Asian J.Chem*, 17(1), 117,(2003).

4.W. O. Foye, T. L. Lemke and D. A. Williams (eds.), Principles of Medicinal Chemistry, 4th Ed., Lippincott Williams & Wilkins Publishers, USA, P. 543,(1995).

5. March J "Advanced Organic Chemistry" $th Ed. J. Wiley and Sons, New York. (1992)

6. Zollinger H., Color Chemistry.,2nd Ed. VCH, Weinheim, p105,(1991).

7. Zollinger H., Azo and diazo chemistry. Aliphatic and aromatic compounds. Interscience, New York p144,(1961).

8. Krueger P.J., Basicity, hydrogen bonding and complex formation involving hydrazo, azo and azoxy groups. in The chemistry of the hydrazo, azo and azoxy groups. Part I, John Wiley & Sons, London(1975).

9. Florence T.M. and Aylward G.H., Aust. J. Chem.,Vol. 15 ,p 6,(1962).

10. Florence T.M., Johnson D.A. and Batley G.E., J. Electroanal. Chem.,Vol.50**,**p113,(1974).

11. Florence T.M., J. Electroanal. Chem.,Vol.52 p115,(1994).

12. Choi D., Lee S.K. Chung T.D. and Kim H., Electroanalysis.,Vol.12 ,p 477,(2000).

13. Solomons T.W.G., Organic Chemistry 2nd Ed. John Wiley & Sons, New York,(1980).

14. Svarts N., Acta Med. Scand.,Vol.110,p 577,(1942).

15. Klotz U., Eur. J. Pharmacol.,Vol.56 ,p353,(2000).

16. Krüger K., Schmerz,Vol.14 p193,(2005).

17. Sauder, K.H. Allen and R.L.M.., Aromatic diazo compounds,2nd Ed.(1985).

18**.** Silverstein .G.T.,Spectrophometric identification of organic compounds.,4 nd Ed,(1981).

19.Mbata, T.I.,African J. of Biotech.,Vol.6 No 3,p278,(2007).