PREPARATION AND STUDYING OF (CHARACTERIZATION ,CHROMATOGRAPHY ,MICROBIAL BEHAVIOR) FOR NEWENAMINE DERIVATIVES

Nuha Salman Salih[1] , Dr. Nagham Mahmood Aljamali*[2]

[1]*Chemistry Department ,College of sciences., university of Kufa, Iraq.*
[2]Faculty of Education for Girls ,Kufa University, Iraq.

ABSTRACT

Enamine Compounds were prepared in this work (new six compounds) from reaction between two amino compounds like aminobenzothiazole derivatives and benzaldehyde compound to yield mannich bases (have various terminal like: hydroxyl , carboxyl , halogen ,…groups) . all enamine compounds investigated through many techniques like (I.R , H.NMR , Mass)- Spectra and studied) by (chromatography , microbial) ., which gave good results and good evidences for their formation.

Keywords:bacteria,benzothiazole , enamine , mannich base.

INTRODUCTION

Enamine: The first molecule containing the(N-C=C) active group. The name is a contraction of alkene amine. Secondary amines are usually used in enamine synthesis due to the preferential preparation of the more thermodynamically stable imine species [1-3] . Alkyl ketone self-condensation is a side-reaction which can be avoided via the addition of some element chloride into the reaction mixture (to act as a water scavenger[4-6] An example of an aldehyde reacting with a secondary amine to form an enamine via a carbinolamine intermediate is shown below:

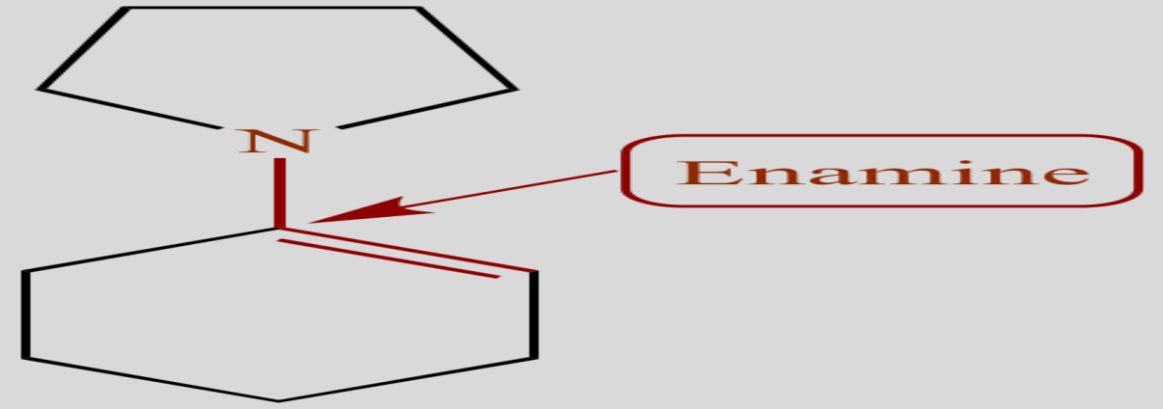


Fig .1 :Enamine Compound

The (enamine-imine)tautomerismmay be considered analogous to the keto-enoltautomerism. In both cases, a hydrogen atom switches its location between the heteroatom (oxygen or nitrogen) and the second carbon atom.

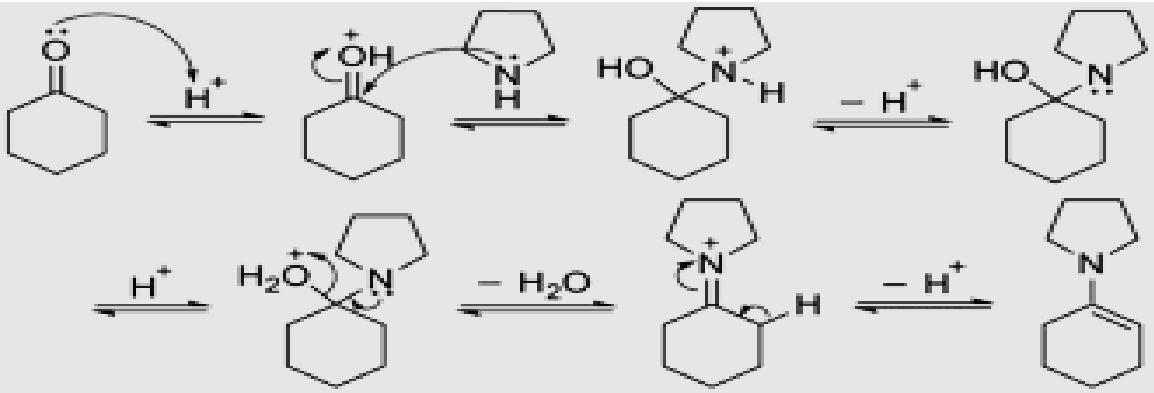


Fig .2 :Mechanism - Formation of Enamine Compound

Enamine behave good nucleophile and actgood bases in its reactions . Its behavior as carbon-based nucleophiles is explained with reference to resonance structures. Enamines act as nucleophiles that require less acid/base activation for reactivity than their enolate counterparts.

EXPERIMENTAL &MATERIALS

Our compoundssupplied from chemical Company in high purity .

EXPERIMENTALPART:

Synthesis of Compound (1):

P-Methyl aniline (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) androtationin ice path according to literature[21] ,to give precipitation which filtered and dried then re

crystallized to yield aminecompounds , which (0.02 mole) reacted with (0.01 mole) of benzaldehyde to give compound(1).

Synthesis of Compound (2):

P-Hydroxy aniline (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) and rotationin ice path according to literature[21] ,to give precipitation which filtered and dried then re crystallized to yield amine compounds , which (0.02 mole) reacted with (0.01 mole) of benzaldehyde to give compound (2).

Synthesis of Compound (3):

P-Nitro aniline (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) and rotationin ice path according to literature[21] ,to give precipitation which filtered and dried then re crystallized to yield amine compounds , which (0.02 mole) reacted with (0.01 mole) of benzaldehyde to give compound (3).

Synthesis of Compound (4):

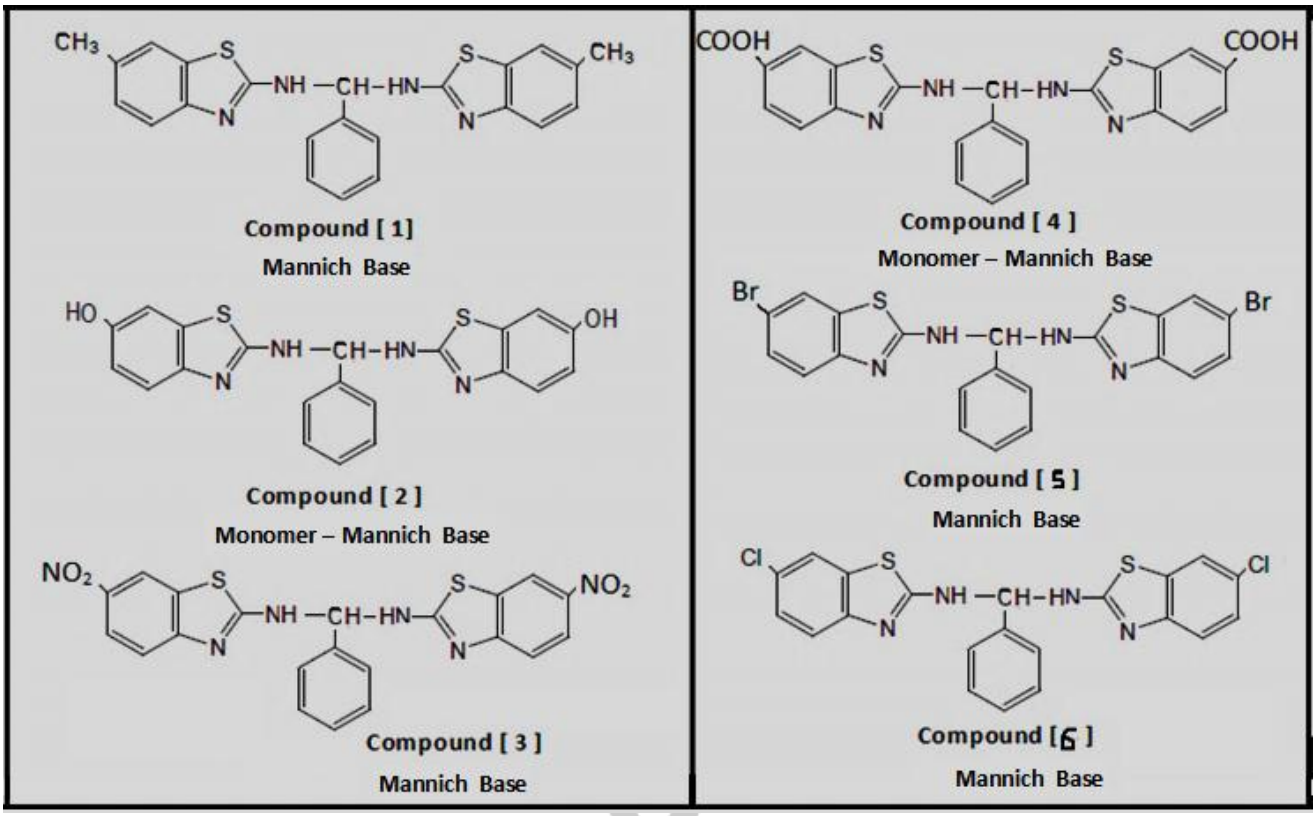
P-Amino benzoic acid (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) and rotationin ice path according to literature[21] ,to give precipitation which filtered and dried then re crystallized to yield amine compounds ,which (0.02 mole) reacted with (0.01 mole) ofbenzaldehyde to give compound (4).

Synthesis of Compound (5):

P-Bromo aniline (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) and rotationin ice path according to literature[21] ,to give precipitation which filtered and dried then re crystallized to yield amine compounds , which (0.02 mole) reacted with (0.01 mole) of benzaldehyde to give compound (5).

Synthesis of Compound (6):

P-Chloro aniline (0.01 mole) reacted with (0.01mole) of ammonium thiocyanate in presence of bromine with glacial acetic acid (drop by drop) and rotationin ice path according to literature[21] ,to give precipitation which filtered and dried then re crystallized to yield amine compounds , which (0.02 mole) reacted with (0.01 mole) of benzaldehyde to give compound (6).



Scheme .1 :Mannich Base[1 - 6]

Organic Investigation:

The FT.IR- Investigation : absorption bands appeared at (NH-) Amine : 3183 ., (C=N) Endocycle: 1639 ., (CH) Aliphatic : 2974 in compound(1) , bands are appeared at (NH-) Amine : 3200 ., (C=N) Endocycle: 1641 ., (OH)Phenol: 3397 in compounds (2) ,while other bands appeared at (NH-) Amine : 3195 ., (C=N) Endocycle: 1653 ., (NO_2) : (1345 , 1511) in compound (3) ., bands at (NH-) Amine : 3178 ., (C=N) Endocycle: 1632 ., (CO-) Carboxyl : 1711 in compound (4) , bands at (NH-) Amine : 3205 ., (C=N) Endocycle: 1630 ., (Br) : 742 in compound (5) ., bands at (NH-) Amine : 3197 ., (C=N) Endocycle: 1637 ., (Cl): 798 in compound [6] , all bands summarized in Table (1) .

Table (1): FT.IR- data (cm^{-1}) of Compounds (1-6).

Comp	Other Groups
(1)	(NH-) Amine : 3183 ., (C=N) Endocycle: 1639 ., (CH) Aliphatic : 2974.
(2)	(NH-) Amine : 3200 ., (C=N) Endocycle: 1641 ., (OH)Phenol: 3397.
(3)	(NH-) Amine : 3195 ., (C=N) Endocycle: 1653 ., (NO_2) : (1345 , 1511).
(4)	(NH-) Amine : 3178 ., (C=N) Endocycle: 1632 ., (CO-) Carboxyl : 1711
(5)	(NH-) Amine : 3205 ., (C=N) Endocycle: 1630 ., (Br) : 742
(6)	(NH-) Amine : 3197 ., (C=N) Endocycle: 1637 ., (Cl): 798

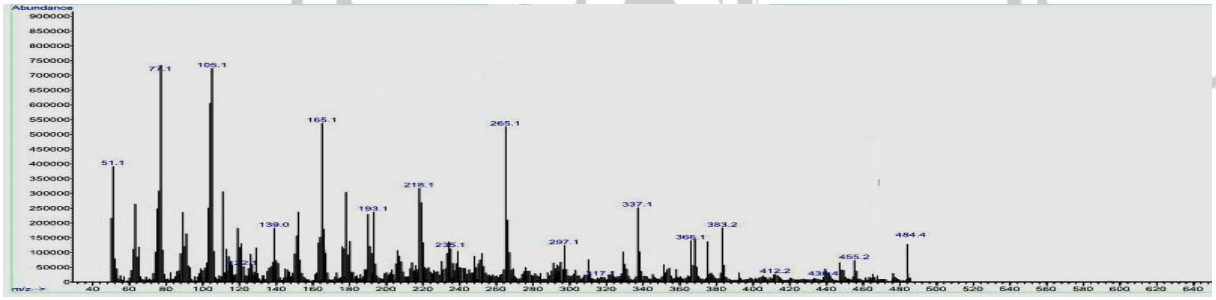
The ^{1}H.NMR- Spectra: showed peaks at δ DMSO-d6(solvent): 2.50 .,(NH) Proton of amine: 5.44 .,Protons of Phenyl ring : (6.79-7.52) , (CH_3): 0.91in compound (1) ,but

compound (2) gave peaks at (NH) Proton of amine: 5.91 , (OH) Proton of Phenol : 11.04 .,Protons of Phenyl ring : (6.83 -7.77) ., compound(3) appeared peak at (NH-) Proton of amine: (5.73) .,Protons of Phenyl ring: (6.76 -7.84), while compound (4) showed signals at Protons of (NH) amine: 5.76 .,Protons of Phenyl ring : (6.90 -7.74) ., While compound (5) showed signals at(NH) Proton of amine: 5.81.,Protons of Phenyl ring : (6.62-7.75) , compound[6] appeared peaks at (NH) Proton of amine: 5.86 .,Protons of Phenyl ring : (6.94-7.88) , and other peaks in table (2) .

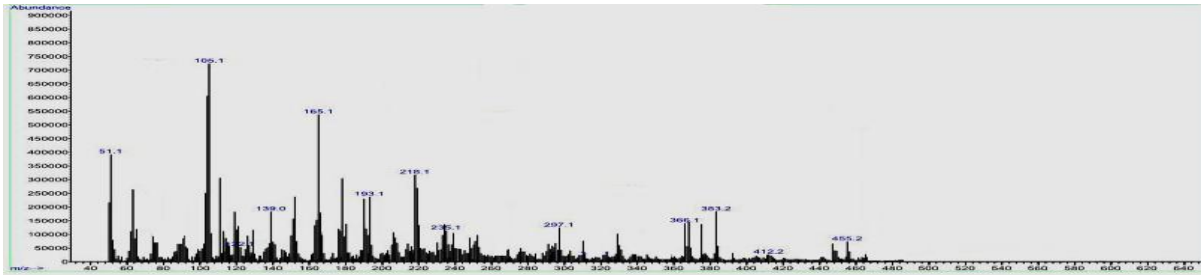
Table (2): H.NMR-data (δ - ppm) of Compounds (1-6)

Comp	Other groups
(1)	DMSO-d6(solvent): 2.50 ., (NH) Proton of amine: 5.44 .,Protons of Phenyl ring : (6.79-7.52) , (CH_3): 0.91.
(2)	DMSO-d6(solvent): 2.50 ., (NH) Proton of amine: 5.91 , (OH) Proton of Phenol : 11.04 .,Protons of Phenyl ring : (6.83 -7.77).
(3)	DMSO-d6(solvent): 2.50 ., (NH-) Proton of amine: (5.73) .,Protons of Phenyl ring: (6.76 -7.84).
(4)	DMSO-d6(solvent): 2.50 ., (NH) Proton of amine: 5.76 .,Protons of Phenyl ring : (6.90 -7.74) .
(5)	DMSO-d6(solvent): 2.50 ., (NH) Proton of amine: 5.81 .,Protons of Phenyl ring : (6.62-7.75) .
(6)	DMSO-d6(solvent): 2.50 ., (NH) Proton of amine: 5.86 .,Protons of Phenyl ring : (6.94-7.88) .

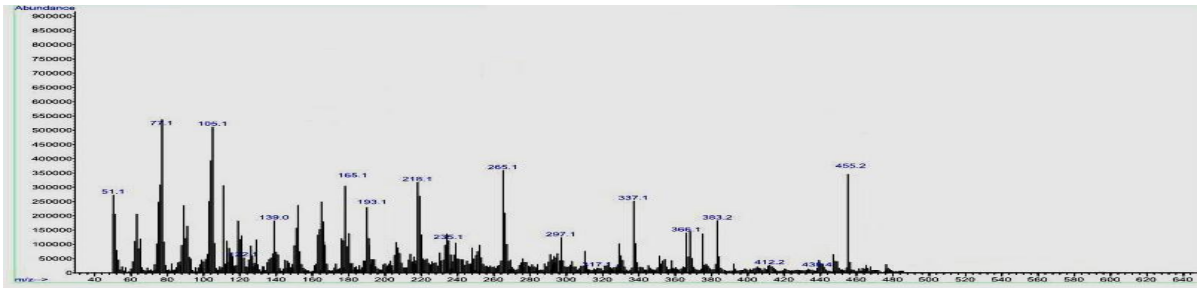
The Mass Spectra : Showed all fragments about parts of our formatted compounds in figures(1-3):



Fig(1): Mass Spectra of Compound (2)



Fig(2): Mass Spectra of Compound (4)



Fig(3): Mass Spectra of Compound (6)

Microbial studying :

In this paper , we studied bio-effect of benzothiazole derivatives for their antibacterial activities by using agar biological methods[16] . The antibacterial activities were done at (50 mg.ml^{-1}) concentrations in (DMSO) - solvent through using two types of bacteria ((***Streptococcus Salivarius ,Streptococcus Mutans***)). Bacteria were incubated for 24 hrat 37^{o}C.

RESULTS AND DISCUSSION

The formatted enaminecompounds tested forBiological Activityagainst two types of bacteria .

Collection of Samples and Antibacterial Assay :

According to procedures[18-20] ,the biological activity forcompounds was tested on two types of bacteria , The antimicrobial results are summarized in table (1). From results of antibacterial studies it was found to be potentially activity against all types of bacteria at concentrations (20, 30, 50 mg.ml^{-1})were summarized in table (1).

The three types of bacteria which tested: (***Streptococcus Salivarius , Streptococcus Mutans***):

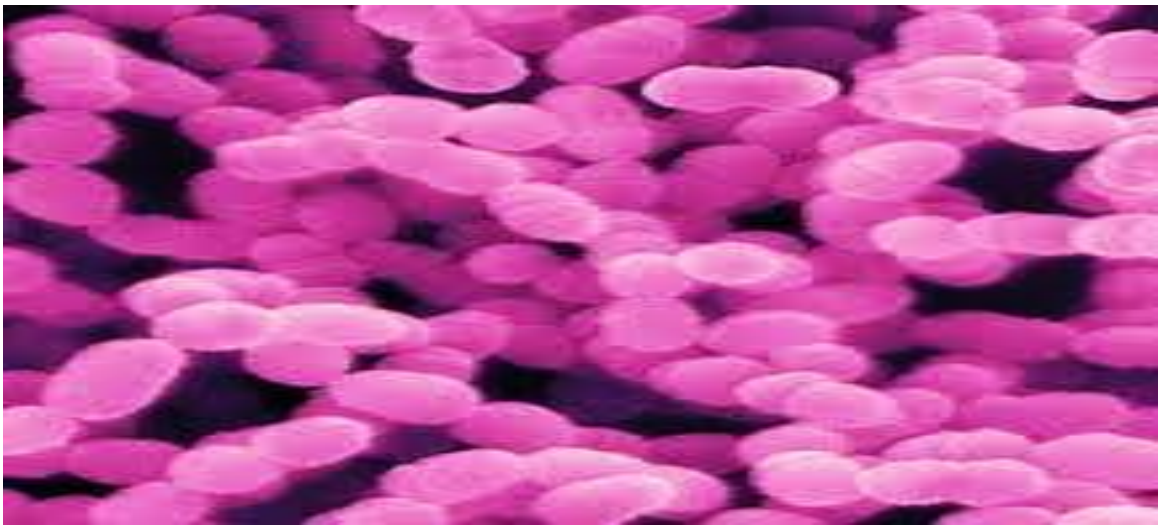


Fig .4 :*Streptococcus Salivarius*

Fig .5 :*Streptococcus Mutans*

Effect ofSynthesized Compounds on Bacteria :

Our compounds [1- 6] were screened according to their action against bacteria are described table (1). The presence of functional groups like (Cl , Br , COOH ,….) which increase antibacterial effect of benzothiazole and functional groups.

The antimicrobial results are listed at table (1). From results of antibacterial studies it was found to be potentially activity against towards four types of bacteria ,which gave good indicators from the results that the biological activity of all compounds have high biological activity which inhibit the growth of bacteria .

Our compounds [5 , 6] have higher activity than other compounds which due to presence of (Br , Cl) atoms in their structures[18-20] ,the mechanism of action for this compounds involved formation of hydrogen bonding with the active centers of the cell constituents resulting in the interference with the normal cell process.

Table(1):Antibacterial Activity of Compounds (Inhibition Zone in (mm))as average of three Concentrations (20, 30, 50 mg.ml^{-1})

Compounds	(average of three Measurements) *Streptococcus Salivarius*	(average of three Measurements) *Streptococcus Mutans*
[1]	6	4
[2]	6	4
[3]	6	6
[4]	8	8
[5]	12	8
[6]	12	10

Chromatographic Studies of Compounds :

Solutions of heterocyclic compounds were diluted in concentration (1 ppm), and injected through a syringe (Hamilton) in capacity (10ml) by nitrogen (gas flow 25 ml/min) . Our cyclic compounds separated according to their interactions or polarity of terminal compounds and their molecular weight ., for this reason , compound [1]separated in the first time due to[21] its polarity (less than other compounds), while the last one compounds [2] and 4] , because of their high polarity and molecular weight more than other compounds , figures (7-9).

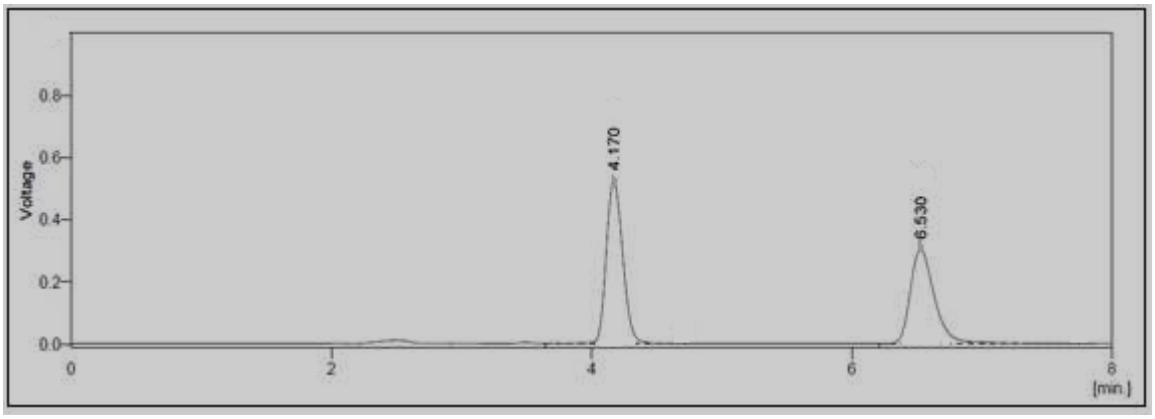


Fig (7): Chromotogram of Compound [1]

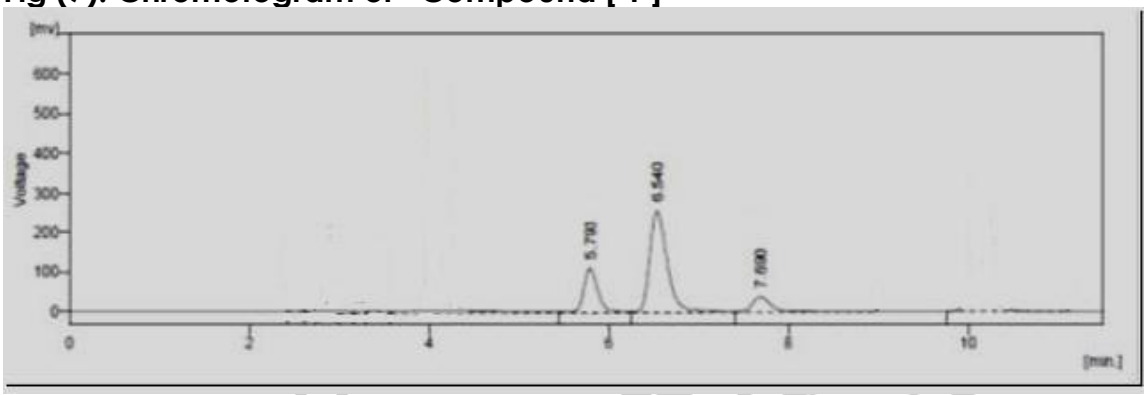


Fig (8): Chromotogram of Compound [3]

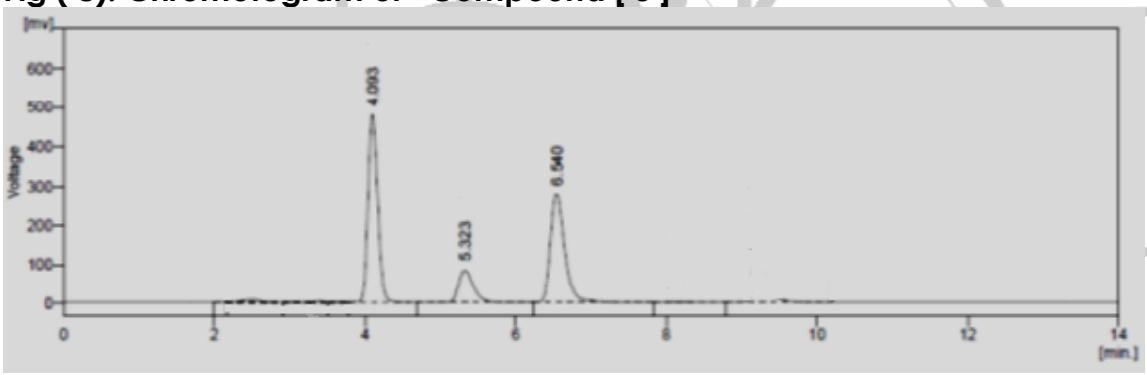


Fig (9): Chromotogram of Compound [5]

Conclusions

The prepared compounds separated according to interactions with polarity of terminal compounds and their molecular weight ., for this reason , and most of our synthesized compounds gave good results against selected bacteria.

REFERENCES

1.Clayden, Jonathan (2001). Organic chemistry. Oxford, Oxfordshire: Oxford University Press. ISBN 0-19-850346-6.

2. *Smith, Michael B.;* March, Jerry *(2007),* Advanced Organic Chemistry: Reactions, Mechanisms, and Structure *(6th ed.), New York: Wiley-Interscience,* ISBN 0-471-72091-7

3.Enamines: Synthesis: Structure, and Reactions, Second Edition, Gilbert Cook (Editor). 1988, Marcel Dekker, NY. ISBN 0-8247-7764-6

4. Guo, Fenghai; Clift, Michael D.; Thomson, Regan J. (September 2012). "Oxidative Coupling of Enolates, EnolSilanes, and Enamines: Methods and Natural Product Synthesis". European Journal of Organic Chemistry. **2012** (26): 4881–4896. doi:10.1002/ejoc.201200665.

5. Y. Filali Baba, H. Elmsellem, Y. KandriRodi, H. Steli, C. AD5, Y. Ouzidan,F. OuazzaniChahdi, N. K. Sebbar, E. M. Essassi and B. Hammouti., Der PharmaChemica, 8,4, 2016, 159-169**.**

6.Kiran M. Kulkarni, Sagar A. Jadhav, Pramod B. Patil, Vikas R. Dholeand Shitalkumar S. Patil, Der PharmaChemica, 8,4, 2016, 1-5.

7. Chao jun-shu, Huia ping-xin, Liashuo, "Synthesis and Antibacterial Activities of Novel Biphenyltetrazole Derivatives Bearing 1,3,4- Oxadiazole." Journal of the Chinese Chemical Society, 52, 2005, 539-544.

8. Srinivas K, Srinivas U, Bhanuprakash K, Harakishore K. "Synthesis and antibacterial activity of various substituted s-triazines". Eur J Med Chem; 41, 2016, 1240-1246.

9. KD Tripathi. Essentials of medical pharmacology. Jaypee Brothers Medical Publishers Ltd, New Delhi, India, 2008, 189.

10. AateshÈznur, KocabalkanliAysËe, CesurNesrin, "Synthesis and antimicrobial activity of some 5-aryl-2-[(N,N-disubstitutedthiocarbamoylthio) acylamino]-1,3,4-oxadiazoles" , Farmaco , 53 (1998), 541-544.

11. Montalbetti, Christian A. G. N.; Falque, Virginie, "Amide bond formation and peptide coupling". Tetrahedron. 61 (46), 2005, 10827–10852., doi:10.1016/j.tet. 2005.08.031

12. Valeur, Eric; Bradley, Mark., "Amide bond formation: beyond the myth of coupling reagents". Chem. Soc. Rev., 38, 2009, 606–631., doi:10.1039/B701677H.

13. Nanjunda S, Swamy S, Basppa, PriyaBs, Prabhuswamy B, DoreswamyBH.,"Crystal Structure of Novel2-butyl-4-chloro-1Hlmidazolyl-5-Carboxaldehyde" . European Journal. of Medicinal Chemistry ,41, 2006, 531-538.3.

14. Jin, Jiang Chen, Baoan Song, Zhuo Chen, Song Yang, "Synthesis, structure, and bioactivity of N0-substituted benzylidene-3,4,5-Trimethoxybenzo hydrazide and -acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives.", Bioorganic & Medicinal Chemistry Letters 16 (2006) 5036–504.

15. NaghamMahmoodAljamali ,SaherMahmoodJawd ,ZainabMahmoodJawad ., "Bacterial Studying of Anil–(Sugar and Thiophene) Derivatives Against Mouth and Teeth"., J.Bio.Innov6 (3), 2017, pp: 391-398.

16. Aboraia S. Ahmed, Rahman-abdel.Mhamdy, Mahouz M. nadia, "Novel 5-(2 hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: Promising anticancer agents." Bioorganic & Medicinal Chemistry 14 (2006) 1236–1246.

17. NaghamMahmoodAljamali .," Synthesis of Antifungal Chemical Compounds from Fluconazole with (Pharma- Chemical) Studying" ., Research journal of Pharmaceutical, biological and chemical sciences., 8 (3)., 2017 , p. 564 -573 .

18. NaghamMahmoodAljamali, "Synthesis and Biological Study of Hetero (Atoms and Cycles) Compounds", Der PharmaChemica, 2016, 8(6), 2016,40-48.

19. B. J. Hathaway and D. E. Billing, "The electronic properties and stereo chemistry of mono-nuclear complexes of the copper(II) ion," Coordination Chemistry Reviews, vol. 5, no. 2, 1970, pp. 143–207.

20. R. V. Singh, R. Dwivedi, and S. C. Joshi, "Synthetic, magnetic, spectral, antimicrobial and antifertility studies of dioxomolybdenum(VI) unsymmetrical imine complexes having a N=N donor system," Transition Metal Chemistry, vol. 29, no. 1, 2004,pp. 70– 74.

21. NaghamMahmoodAljamali , Intisar O , "Synthesis of Sulfur Heterocyclic Compounds and Study of Expected Biological Activity" , Research J. Pharm. and Tech., 8(9) ,2015,1225-1242 .,**DOI:** 10.5958/0974-360X.2015.00224.3.

22. NaghamMahmoodAljamali , SaherMahmood, ZainabMahmood, Seena K. , "Microbial Studying of (Thiazole ,Oxadiazole, Thiadiazole)–Derivatives on Mouth and Teeth Bacteria ", International Journal of Medical Research and Pharmaceutical Sciences, 3, 8 ,2016,30-39 , **DOI**:10.5281/zenodo.61357 .

23. NaghamMahmoodAljamali , "Methods of preparation and identification of various membered ring ", 1th Ed., Alnoor publishing , Germany , **(2017**).

24. H. Nozaki; H. Takaya; S. Moriuti; R. Noyori., "Homogeneous catalysis in the decomposition of diazo compounds by copper chelates: Asymmetric carbenoid reactions". Tetrahedron. 24 (9), 1968, 3655–3669. , **doi:**10.1016/S0040-4020(01)91998-2.

25. J.C. Hindson; B. Ulgut; R.H. Friend; N.C. Greenham; B. Norder; A. Kotlewskic; T.J. Dingemans ., "All-aromatic liquid crystal triphenylamine-based poly(azomethine)s as hole transport materials for opto-electronic applications". J. Mater. Chem. 20 (5), 2010, 937–944., doi:10.1039/B919159C.

26. Cremlyn, R. J. (1996). "An Introduction to Organosulfur Chemistry. Chichester: John Wiley and Sons. ISBN 0-471-95512-4.

27. GarcíaRuano, J. L.; Cid, M. B.; Martín Castro, A. M.; Alemán, J. (2008). "Acyclic S,S-Dialkylsulfimides". In Kambe, N. Science of Synthesis. 39. Thieme. pp. 352–375. ISBN 978-1-58890-530-7.

28. NaghamMahmoodAljamali , SaherMahmoodJawd, ZainabMahmoodJawad,Intisar ObaidAlfatlawi ., " Inhibition Activity of (Azo – Acetyl acetone) on Bacteria of Mouth"., Research J. Pharm. and Tech. 10, 6, 2017, 1683-1686 ., **DOI:**10.5958/0974-360X.2017.00297.9

29. Drabowicz, J.; Lewkowski, J.; Kudelska, W.; Girek, T. (2008). "S,S-Dialkylsulfoximides". In Kambe, N. Science of Synthesis. 39. Thieme. pp. 154–173. ISBN 978-1-58890-530-7.

30. Drabowicz, J.; Lewkowski, J.; Kudelska, W.; Girek, T. (2008). "S,S-Dialkylsulfonediimines". In Kambe, N. Science of Synthesis. 39. Thieme. pp. 173–180. ISBN 978-1-58890-530-7.

31. Zhang, Y.; Hogg, N., "S-Nitrosothiols: cellular formation and transport". Free Radical Biol. Med. 38 (7), 2005, 831–838. doi:10.1016/j.freeradbiomed.2004.12.016. PMID 15749378.

32. Braverman, S.; Cherkinsky, M.; Levinger, S. (2008). "AlkylsulfurTrihalides". In Kambe, N. Science of Synthesis. 39. Thieme. pp. 187–188. ISBN 978-1-58890-530-7.

33. Sheppard, W. A. ,"ArylsulfurPentafluorides". J. Am. Chem. Soc. 84, 1962, 3064–3072. , doi:10.1021/ja00875a006.

34. Drabowicz, J.; Lewkowski, J.; Kudelska, W.; Girek, T. (2008). "DialkylsulfurTetrahalides". In Kambe, N. Science of Synthesis. 39. Thieme. pp. 123–124. ISBN 978-1-58890-530-7.

35. NaghamMahmoodAljamali , Mohammed Alaa A , Jalal H M , ZainabMahmoodJawad ., Studying of (Bacterial and Chromatographic)-Behavior for (Nitrogen ,Sulfur)-Heterocycles on Mouths· Bacteria" ., International Journal Of Advanced Research In Medical & Pharmaceutical Sciences , 2, 9, 2017 .

36. Moltzen, E. K.; Klabunde, K. J.; Senning, A., "Carbon monosulfide: a review". Chem. Rev. 88 (2), 1988, 391. doi:10.1021/cr00084a003.

37. Pötter, B.; Seppelt, K., "Trifluoroethylidynesulfur Trifluoride, F3C−C≡SF3". Angew. Chem. Int. Ed. Engl. 23 (2), 1984, 150., doi:10.1002/anie.198401501.

38. NaghamMahmoodAljamali and DhuhaRahi .,"New Formazan Compounds (Synthesis, Identification, Physical Properties)"., Journal of Chemical and Pharmaceutical Sciences , 10 , 3, 2017, 1461-1472 .

39. NaghamMahmoodAljamali and Ahmed Adnan Abdul Hussein .,"ANTIBACTERIAL STUDYING OF SOME NEW VARIOUS MANNICH BASE DERIVATIVES" , J.Bio.Innov, 6, 1, 2017, pp: 91- 99 .

40. S. Sreedaran, K. S. Bharathi, A. K. Rahiman et al., "Synthesis, electrochemical, catalytic and antimicrobial activities of novel unsymmetrical macrocyclicdicompartmental binuclear nickel(II) complexes," Polyhedron, vol. 27, no. 7, 2008,pp. 1867–1874.

41. NaghamMahmoodAljamali ., " SYNTHESIS AND CHEMICAL STUDY OF NEW SULFONE COMPOUNDS " ., Int. J. Curr.Res.Chem.Pharma.Sci. 1(9): (2014):78–87 .

42. NaghamMahmoodAljamali .," Review in Azo Compounds and its Biological Activity " ., Biochem Anal Biochem 2015, 4:2 ., http://dx.doi.org/10.4172/2161-1009.1000169.

43. Nakamoto, N. Infrared and Raman Spectra of Inorganic and Coordination Compounds, 6thEd, Part 2 John Wiley and Sons, Inc., New Jersy, 2009.

44. NaghamMahmoodAljamali , SaherMahmoodJawd ., (Chromatographic-Biochemical)-Studying of (Five, Six ,Seven)-Cycles" ., International Journal Of Advanced Research In Medical & Pharmaceutical Sciences , 2, 9, 2017 .

45. Arora P, Arora V, Lamba HS and WadhwaD,"Importance of Heterocyclic Chemistry: A Review". *Int J Pharm Res Sci*. 3,9 ,2012; 2947-2955., DOI: http://dx.doi.org/10.13040/IJPSR.0975-8232.3(9).2947-54