Thiophene-Cyclic and Sulfazane Derivatives (Preparation, Spectral Analysis, the Behavior in Organic Solvents, Microbial Testing)

Jalal Hasan Mohammed[1], Alaa Jawad Kadhim[2], Nagham Mahmood Aljamali[3]

[1]Lecturer, Department of Pharmaceutical Chemistry, College of Pharmacy, Karbala University, Iraq, [2]Lecturer, Department of Chemistry, College of Education for Pure Sciences, Karbala University, Iraq, [3]Assist. Professor ,Department of Chemistry, Iraq

Abstract

The thiophene core is the most broadly applied constructing blocks to the production of many biomolecules ,pharmaceutical drugs ,vitamins ,also in industrial compounds, in dyes compounds because of its high stability in environment. Thiophene derivatives were synthesized in present study from chalcone compound as a starting material from aldol reaction in first step, followed by cyclization reactions by using various conditions, and this paper involved new reaction for diazonium salts to producing (Sulfide- azo) compounds in same bond for the first time that we termed (Sulfazane) as a first and Novel preparation to this new type of compounds.,the synthesized derivatives were confirmed through numerous spectral techniques (FT.IR ,H.NMR ,C.NMR), other physic-chemical data for synthesized thiophene derivatives ,besides to studying of behavior of compounds in organic solvents and screening tests for efficiency of thiophene derivatives against microbes.

Keywords: *Microbial ,Sulphazane, Aldol, chalcone ,thiophene ,heterocyclic, phenylene diamine, coupling,Azo,new reaction of diazonium, sulfide- azo ,(-S-N=N-), seven membered ,five membered.*

Introduction

Thiophene is a colorless liquid in a benzene-like odor., with aromatic properties involving one hetero atom (sulfur) in the formula[1-3] structure(C_4H_4S), including a planar five-membered ring (four carbon atoms and one sulfur atom), it behaves in the reactions as a substitution reaction. Thiophene is stable in high temperatures and its nucleus in most natural molecules like biotin, numerous plant colors, natural dyes[4-8] ,besides various pharmaceuticals., some thiophene derivatives have applications[9-18] in antifungal fields.

Thiophene derivatives are important hetero-atom cyclic compounds[19-24] which are commonly used as structure in various agrochemicals in addition to pharmaceuticals., thiophene derivatives[21-25] appeared many uses and various applications[25-29] besides wide evaluations in microbial fields in medicinal and biological fields[29-32].

Experimental Part

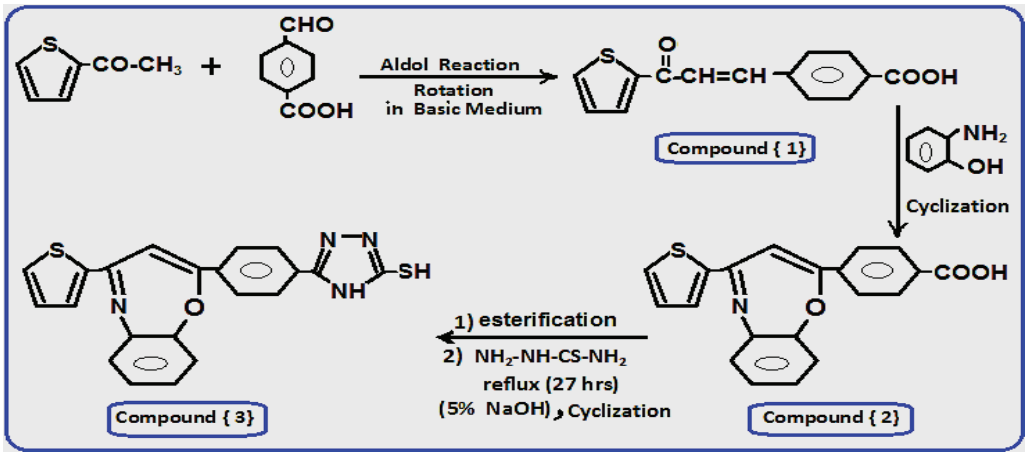
The routes of reaction carried out by many steps ,various conditions ,different catalysts to formation heterocyclic compounds from chalcone-thiophene , all formatted derivatives followed with (TLC) in addition to iodine vapor chamber. Thiophene derivatives {1-8} were established via various apparatuses: FT-IR spectra (FT-IR 8300 Shimadzu) with the range (400-4000)cm^{-1} using discs of KBr., ^{1}H.NMR–Spectra besides ^{13}C.NMR with solvent (d-DMSO).,besides to studying of behavior of compounds in organic solvents and microbial screening:

Routes of Preparation[8-15]:

Route of Preparation for Thiophene Derivatives{ 1, 2 , 3}

P-Formal benzoic acid(0.01 mole) rotated with 2-acetothiophene (0.01 mole) at room temperature via mechanical rotation for (8 hrs) according to processes[14] in basic medium to yield product that acts chalcone Compound{1},the next step, drying, re crystallized

,weigh (0.01 mole) cyclized with (0.01 mole) of ortho-aminophenol in refluxing step, the resulting filtered ,dried followed by re crystallized to give seven-membered ring from compound{2}, which (0.01 mole) condensed for (26 hrs) with (0.01 mole) of thiosemicarbazide in basic medium (5% NaOH) in two steps according to processes[8-12] ,then filtered ,dried,then recrystallized to obtain triazole derivative as a compound{3}.



Scheme.1:Preparation of Thiophene Derivatives{1, 2 , 3}

Route of Preparation for new compound (Sulfazane) Derivatives{4 , 5}

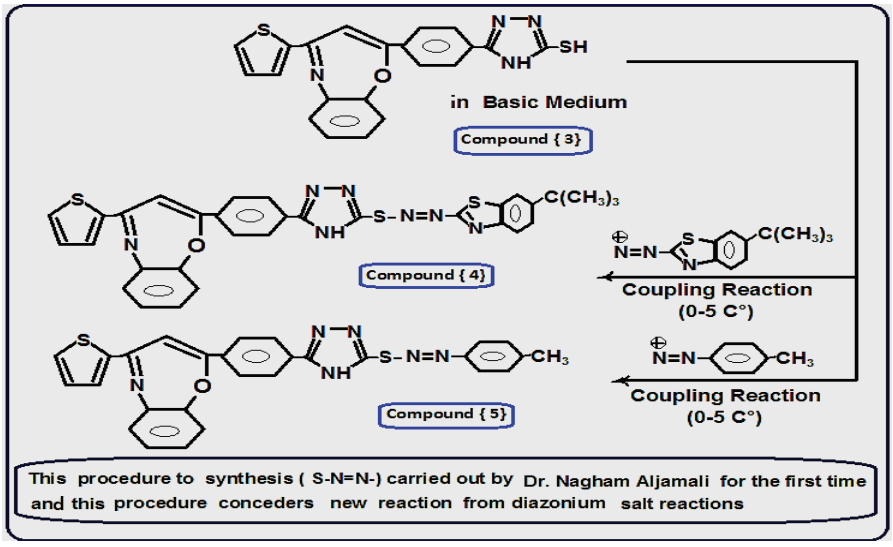
In new procedure (for the first time) and new reaction step in this paper by (Dr. Nagham Aljamali -new reaction for diazonium reaction) to synthesis of Sulfide–Azo (S-N=N-) derivative in same linkage that we termed (Sulfazane) as a first and Novel preparation to this new type of compounds :

Compound{3} (0.01 mole) reacted in basic medium via coupling reaction with (0.01 mole) of

Benzothiazole diazonium salt-derivative at (0-5) C° according to approaches[15] ,after (24 hrs)

The resulting compound washed in distilled water ,dried, to give (S-N=N-)Sulfazane compound {4} .

Compound{3} (0.01 mole) reacted in basic medium via coupling reaction with (0.01 mole) of p-methyl phenyl diazonium salt-derivative at (0-5) C° according to approaches[9, 15] ,after (24 hrs) .,The resulting compound washed in distilled water ,dried, recrystallized to give(S-N=N-) Sulfazane compound {5} .



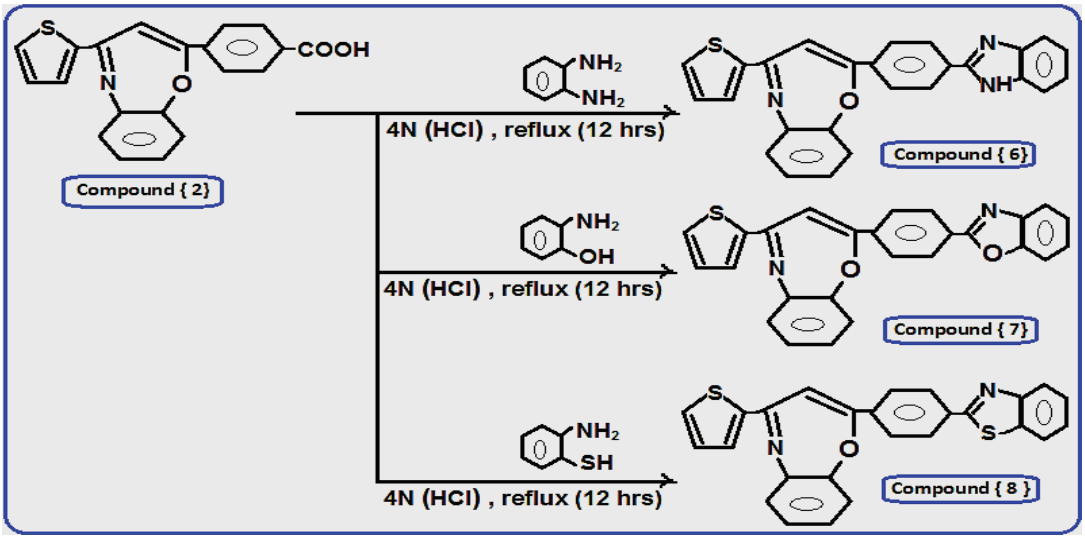
Scheme.2:Preparation of Sulfide-Azo(-S-N=N-) Derivatives{4, 5}

Route of Preparation for Thiophene Derivatives{ 6,7,8}

Thiophene Compound{2}(0.01 mole) cyclized with (0.01 mole) of ortho-phenyl diamine in refluxing step in (4N of HCl) in refluxing process according to approaches[9-12], the resulted compound filtered ,dried followed by re crystallized to produce compound {6}.

Thiophene Compound {2}(0.01 mole) cyclized with (0.01 mole) of ortho-aminophenol in refluxing step in (4N of HCl) in refluxing process according to approaches[9-12], the resulted compound filtered ,dried followed by re crystallized to produce compound {7}.

Thiophene Compound {2}(0.01 mole) cyclized with (0.01 mole) of ortho-thiol aniline in refluxing step in (4N of HCl) in refluxing process according to approaches[8-10], the resulted compound filtered ,dried followed by re crystallized to produce compound {8}.



Scheme.3:Preparation of Thiophene Derivatives{6,7,8} RESULTS AND DISCUSSION:

The products of thiophene compounds prepared via cyclization reaction of chalcone compound which prepared in previously step (aldol reaction)[14], followed by cyclization with amino derivative to yield seven membered ring ,then cyclization reaction with thiosemicarbazide to yield triazole derivative with thiol (SH)- terminal that reacted with various diazonium salts–derivatives in new reaction step in this paper by (Dr. Nagham Aljamali –as a new reaction for diazonium salt) that we termed (Sulfazane) as a first and Novel preparation to this new type of compounds.

All Thiophene-heterocyclic and sulfide-azo compounds examined by spectral characterization besides microbial screening:

Spectral Description :

FT.IR- Description of Spectra : From spectral analysis , that noted disappearance of bands while appearance of new bands to indicate to formation of Thiophene-cyclic and that improve formation of (sulfide–Azo) compounds as a new band and as evidence for new reaction**:**

Thiophene –Chalcone Compound **{1}:** bands at (-CO-O) carbonyl of carboxyl group: 1706 ,(CO-) carbonyl of chalcone : 1667 ,(C-S)thiophene : 753 ,(-CH=CH-) Alkene of chalcone : 3049 .

Thiophene –Seven Membered ring Compound **{2}:** bands at (-CO-O) carbonyl of carboxyl group: 1710 ,(C-O-C) : 1117 ,(C-S)thiophene : 780 ,(=CH-) Alkene : 3058 ,(C=N) endocycle: 1661 .

Thiophene –Triazole Compound **{3}:** bands at (C-O-C) : 1126 ,(C-S)thiophene : 774 ,(=CH-) Alkene: 3063 ,(C=N) endocycle: 1651 ,(NH) amine : 3292 ,(SH) Thiol : 2389 .

Thiophene (Sulfide- Azo) Compound **{4}:** new bands improved formation of (sulfide–Azo) (S-N=N-)

at (1389 ,1454, 1515) as a new band in new reaction .,(C-O-C): 1134 ,(C-S)thiophene : 779 ,(=CH-) Alkene : 3067 ,(C=N) endocycle: 1657 , (NH) amine : 3273 ,(CH) aliphatic : 2985 .

Thiophene (Sulfide- Azo) Compound **{5}:** new bands improved formation of (sulfide–Azo) (S-N=N-) at (1384 ,1467,1509).,(C-O-C): 1165 ,(C-S)thiophene : 786 ,(=CH-) Alkene : 3092 ,(C=N) endocycle: 1655 , (NH) amine : 3256 ,(CH) aliphatic : 2976 .

Thiophene –imidazole Compound **{6}:** bands at (C-O-C): 1155 ,(C-S)thiophene : 769 ,(=CH-) Alkene : 3071 ,(C=N) endocycle: 1642 , 1663 , (NH) in imidazole : 3310 .

Thiophene –Oxazole Compound **{7}:** bands at (C-O-C): 1135 ,(C-S)thiophene : 796 ,(=CH-) Alkene : 3078 ,(C=N) endocycle: 1639 , 1658 ,(C-O-) Oxazole : 1189.

Thiophene –Thiazole Compound **{8}:** bands at (C-O-C) : 1147 ,(C-S)thiophene : 791 ,(=CH-) Alkene : 3069, (C=N) endocycle: 1635 , 1650 ,(C-S-) in Thiazole : 763.

Other functional groups appeared in some spectra figure(1) .

^{1}H.NMR- Description of Spectra : From spectral analysis , that noted disappearance of peaks while appearance of new peaks to indicate to formation of Thiophene-cyclic and (sulfide–Azo) compounds ,all spectra appeared signal at (2. 50) due to solvent (d-DMSO), and other signals like:

Thiophene–Chalcone Compound **{1}:** appearance signals at (12. 66) due to proton of carboxyl group (COOH).,(6.14 , 6. 33) to protons of chalcone (CO-CH=CH-).,(6. 63 – 7. 99) to protons of aromatic ring.

Thiophene–Seven Membered ring Compound **{2}:** appearance signals at (12. 20) due to proton of carboxyl group (COOH).,(2. 83) to proton of alkene (-C=CH-).,(6. 65 – 7. 51) to protons of aromatic ring.

Thiophene–Triazole Compound **{3}:** appearance signals at (8. 24) due to proton of amine in Triazole ring (NH) .,(13.54) due to proton of Thiol group (SH).,(2. 64) to proton of alkene (-C=CH-).,(6. 72 – 7. 67) to protons of aromatic ring.

Thiophene (Sulfide- Azo) Compound **{4}:** appearance signals at (8. 19) due to proton of amine in Triazole ring (NH).,(0. 98) due to protons of methyl groups (CH_3).,(2. 68) to proton of alkene (-C=CH-).,(6. 90 – 7. 74) to protons of aromatic ring.

Thiophene (Sulfide- Azo) Compound **{5}:** appearance signals at (8. 27) due to proton of amine in Triazole ring (NH) .,(0. 63) due to protons of methyl group (CH_3).,(2. 72) to proton of alkene (-C=CH-).,(6. 85 – 7. 81) to protons of aromatic ring.

Thiophene –Imidazole Compound **{6}:** appearance signals at (8. 11) due to proton of amine group (NH) in Imidazole.,(2. 81) to proton of alkene (-C=CH-).,(6. 77 – 7. 67) to protons of aromatic ring.

Thiophene –Oxazole Compound **{7}:** appearance signals at (2. 64) to proton of alkene (C=CH-) .,(6. 95 – 7. 87) to protons of aromatic ring.

Thiophene –Thiazole Compound **{8}: }:** appearance signals at (2. 61) to proton of alkene (C=CH-).,(6. 90 – 7. 73) to protons of aromatic ring.

Other protons of functional groups appeared in some spectra figure (1) .

The ^{13}C.NMR Description of Spectra : From spectral analysis , that noted disappearance of peaks while appearance of new peaks to indicate to formation of Thiophene-cyclic and signals that improve formation of (sulfide–Azo) compounds ,all spectra appeared signal at (40. 00) due to solvent (d- DMSO), and other signals like:

Thiophene–Chalcone Compound **{1}:** appearance peaks at (171. 04) due to carbon atom of (COOH) carboxyl group .,(110.0 , 112. 1) due to carbon atoms of chalcone (-CH=CH-).,(179.7) due to carbonyl in chalcone (-CO-).,(120- 132) due to carbon atoms of aromatic ring .,(136–142) due to carbon atoms of heterocycles.

Thiophene –Seven Membered ring Compound **{2}:** appearance peaks at (171. 05) due to carbon atom of (COOH) carboxyl group .,(100.0 ,105. 7) due to carbon atoms of alkene (-CH=C-).,(149) due to carbon atom of (-C=N-).,(112- 127) due to carbon atoms of aromatic ring .,(132–144) due to carbon atoms of heterocycles.

Thiophene –Triazole Compound **{3}:** appearance peaks at (101. 22 ,104. 83) due to carbon atoms of alkene (-CH=C-).,(152. 12) due to carbon atom of (-C=N-).,(116- 130) due to carbon atoms of aromatic ring

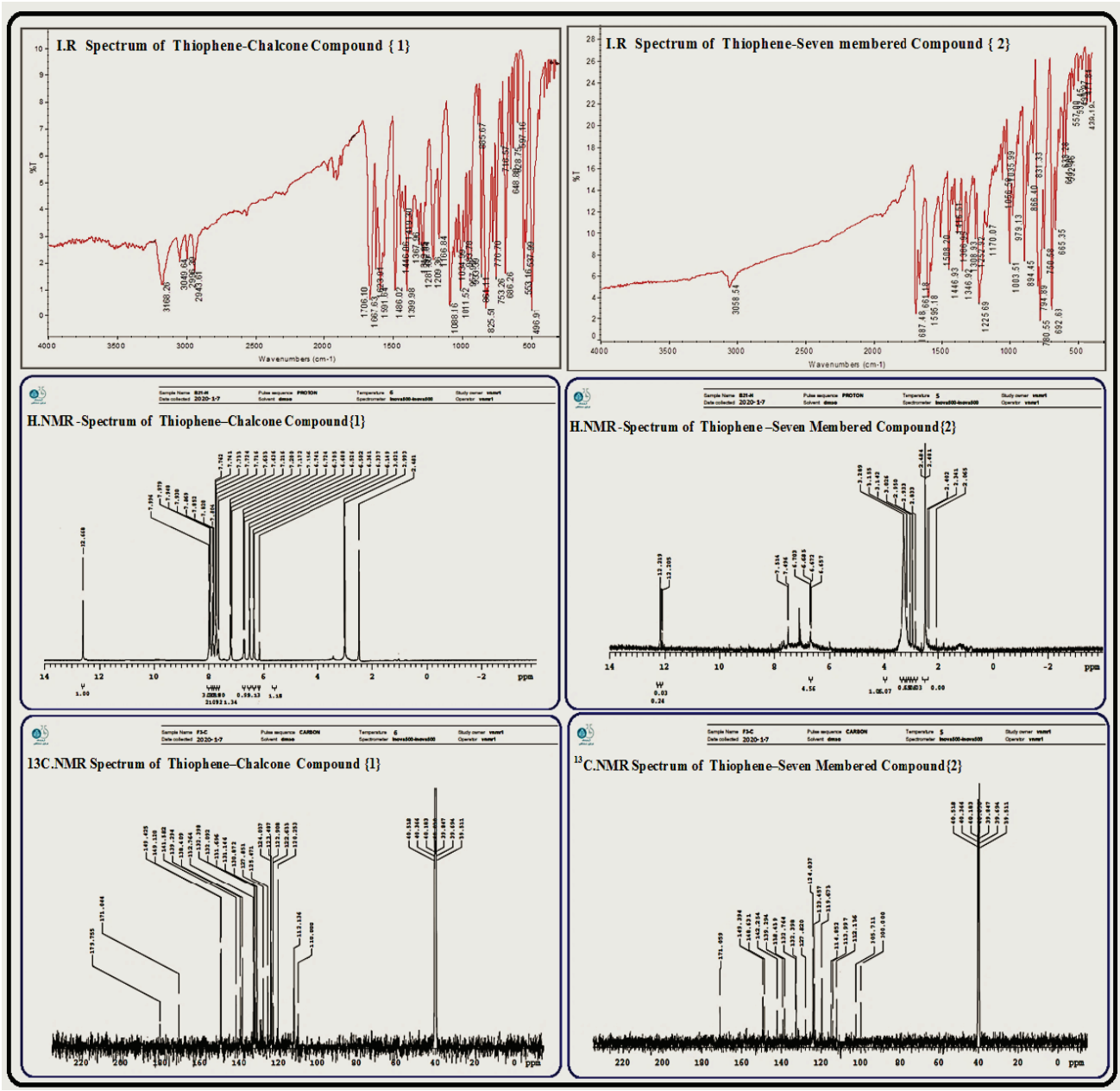
.,(134–148) due to carbon atoms of heterocycles.

Thiophene (Sulfide- Azo) Compound **{4}:** appearance peaks at (100. 14 ,103. 92) due to carbon atoms of alkene (-CH=C-).,(150. 36) due to carbon atom of (-C=N-).,(111.32 – 129. 08) due to carbon atoms of aromatic ring .,(133. 8–148. 75) due to carbon atoms of heterocycles , (17. 45 , 19. 61 , 19. 92) due to carbon atoms of methyl groups.

Thiophene (Sulfide- Azo) Compound **{5}:** appearance peaks at (100. 76 ,102. 38) due to carbon atoms of alkene (-CH=C-).,(149. 52) due to carbon atom of (-C=N-).,(115. 76 – 130. 17) due to carbon atoms of aromatic ring .,(134. 41–146. 27) due to carbon atoms of heterocycles ,(16. 96) due to carbon atom of methyl group.

Thiophene –imidazole Compound **{6}:** appearance peaks at (101. 54 , 103. 21) due to carbon atoms of alkene (-CH=C-).,(150. 56) due to carbon atom of (-C=N-).,(109. 73- 130. 94) due to carbon atoms of aromatic ring .,(135. 87–146. 89) due to carbon atoms of heterocycles.

Other carbon atoms of functional groups appeared in some spectra ,figure (1).



Fig(1):Spectra of Antimicrobial Compounds{1,2}

Behavior of Thiophene Derivatives in Organic Solvents

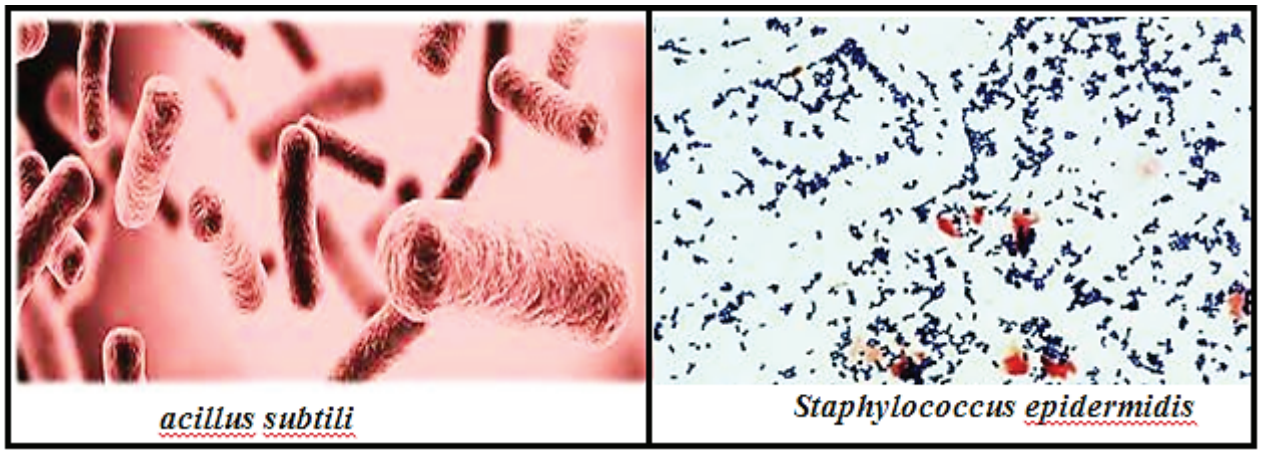
Thiophene–Cyclic and Sulfide- Azo (Sulphazane compounds) screened and tested in various organic solvents, the solvents that selected have various polarities for this reason ,some of prepared thiophene compounds have solubility in polar solvents while other compounds have no solubility in these solvents.,Table(1).

Table 1: Properties of Thiophene Derivatives and Solubility

Compds	Product %	Color	M .P (C °)	Solubility in solvents				
				Ethyl Alcohol	Methyl Alcohol	Chloroform	Carbon Tetrachloride	Toluene
{ 1 }	80	Yellow	168	+	+	-	-	-
{ 2 }	74	Deep Yellow	176	+	+	-	-	-
{ 3 }	70	Yellowish Brown	184	+	+	-	-	-
{ 4 }	72	Deep Yellow	230	+	+	-	-	-
{ 5 }	70	Yellowish Orange	218	+	+	-	-	-
{ 6 }	68	Orange	190	+	+	-	-	-
{ 7 }	64	Reddish Orange	194	+	+	-	-	-
{ 8 }	70	Yellowish Orange	200	+	+	-	-	-

Assay of Bacterial Growth[20-23]

The antimicrobial activity was tested via incubation of two types of bacteria anaerobically at 37°C for (48 hr) by using three concentrations ,each plate was measured[20-24] for the zone of inhibition (diameters of the discs to the nearest whole number)[28-32].,Table (2)



Fig(2):*Selected Bacteria*

Table.2:Antibacterial Assay of Thiophene compounds in Concentration (10 µ .gm)

Compounds	Bacillus subtilis	Staphylococcus epidermidis.
{ 1 }	8	8
{ 2 }	8	8
{ 3 }	14	16
{ 4 } Sulfazane	18	20
{ 5 } Sulfazane	18	18
{ 6 }	12	12
{ 7 }	12	10
{ 8 }	14	14

The results indicated to high inhibition for (Sulfide–Azo) derivatives {4,5} than other thiophene derivatives due to new band sulfide linked with azo group(S-N=N-) which gave high efficiency in decreasing resistance of bacteria towards these new compounds (Sulfide- Azo).

Conflict of Interest: There is no any Conflict of Interest

Ethical Clearance:Ethics committee refer that there is no plagiarism and there is no mistakes or wrong results in this work.

Source of Funding:Self funding.

References

1. *Swanston J. "Thiophene". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH., 2006.*doi:10.1002/14356007.a26_793.pub2. ISBN 3527306730.
2. *Daniel L. The Organic Chemistry of Drug Synthesis. New York: Wiley Interscience. 1999,187.* ISBN:0-471-24510-0.
3. Asiri AM, Khan SA. Synthesis and anti-bacterial activities of a bis-chalconederived from thiophene and its bis-cyclized products. Molecules. 2011,12;16(1):523-31.
4. Bondock S, Fadaly W, Metwally MA. Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety. Eur J Med Chem. 2010,45(9):3692-701.
5. Takemoto, Y. Org; Enantio-selective Organo-catalysis: Reactions and Experimental Procedures Biomol. Chem. 2005(3),4299.
6. William J G, Anticonvulsant action of tiagabine, a new GABA-uptake inhibitor, Journal of Epilepsy,1994,(7),3,161-166.
7. Christine D W, Tioconazole, In xPharm: The Comprehensive Pharmacology Reference, edited by S.J. Enna and David B. Bylund, Elsevier, New York, 2007,1-4.
8. Nagham M A, Alaa J K, Jalal H M, Rajaa AA G ,Rajaa Abdul Ameer Ghafil , Alaa J K , Rajaa A A G , Nagham Mahmood Aljamali, Alaa Jawad K. Review on Preparation and Applications of Formazan Compounds. International Journal of Thermodynamics and Chemical Kinetics. 2019; 5(2): 23–33p.
9. Nagham M A .,"The Various Preparation Methods in Synthetic Chemistry".,1 Edt. ,Evincepub Publishing house, 2019., ISBN:978-93-88277-82-2 .
10. Nagham M A, Rasha NH, Aafaq Jaber Alnajem, Ali Jassim, Afaq J K.,Studying of (Chemical ,Physical ,Biological)–Applications of Oxo-Sulfur Derivatives., Journal of Natural Sciences Research.,2016,(6),7.
11. Nagham M A. "Reactions and Mechanisms".,1 Edt., IJMRA Publication ,2018.,**ISBN: 978-93-87176-25-6 .**
12. Nagham M A. "Synthesis and Biological Study

of Hetero (Atoms and Cycles) Compounds", Der Pharma Chemica, 2016,(8),6,40-48.

13. Nagham M A., "Synthesis and Chemical Identification of Macro Compounds of (Thiazol and Imidazol)".,Research J.Pharm. and Tech, 2015,(8),1,78-84., DOI:10.5958/0974-360X.2015.00016.5 .

14. Aseel M J ,Mostafa N. Mohamed Salih , Nagham M A, Thanaa A. H, Aseel Mahmood Jawad ,Nadia H O, Nagham Mahmood Aljamali. Review on Chalcone (Preparation ,Reactions, Medical and Bio Applications). International Journal of Chemical Synthesis and Chemical Reactions.; 2019,5,(1):16–27p.

15. Nawfel M B ,Hayder H K, Noor H D, Nawfel Muhammed Baqer ,Nagham Mahmood Aljamali., "Preparation of Chemical Inhibitors to Treat the Corrosion and Erosion of Machines", International Journal of Engineering, Applied and Management Sciences Paradigms.,2019, 54,3,89-93.

16. Farmer LJ, Bemis G, Britt SD, Cochran J, Connors M, Harrington EM, Hoock T, Markland W, Nanthakumar S, Taslimi P, Ter Haar E, Wang J, Zhaveri D, Salituro FG. Bioorg Med Chem Lett,2008,18:6231–6235.

17. Eicher T H. The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications.,2003, ISBN:978-3-527-30720-3.

18. Schwarz G. "2,4-Dimethylthiazole". Organic Syntheses., Collective ,1945,19,3,332

19. Srinivas K, Srinivas U, Bhanuprakash K, Harakishore K. "Synthesis and antibacterial activity of various substituted s-triazines". Eur.J.Med. Chem ;**2006**,(41),1240-1246.

20. Mieaad M ,Nagham M A ,Sabreen AA ,Wassan AS. "Formation of Oxadiazole Derivatives Ligands from Condensation and Imination Reaction with References To Spectral Investigation, Thermal and Microbial Assay".,Biochem.Cell. Arch.,2018,(18),1,847-853.

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

22. Rajaa A A G ,Ghafil R A. "Schiff-chalcone derivatives(preparation, investigation, antibacterial assay)".,Int.J.Pharm. Res.,2019,(11),1,657-666.

23. Nagham M A, Saher M J ,Zainab M J, Intisar O A."Inhibition Activity of (Azo–Acetyl acetone) on Bacteria of Mouth",Research J.Pharm. and Tech.,2017,(10),6,1683-1686.,DOI:10.5958/0974-360X.2017.00297.9 .

24. Gitai Z. "The new bacterial cell biology: moving parts and sub cellular architecture". Cell,2005, (120),5,577–86.

25. Vanita S, Supriya M. "Development of furfural formazan as potential antitubercular agents ".,Der Pharma Chemica, 2016,(8),18,144-148.

26. Park S, Park B, Yun S, Kang H, Yun S. "Antimicrobial activities of honey bee venom against pathogens isolated from clinical bovine mastitis in Korea",Planta Med.,2013,79, PL16.

27. Hegazi AG, Abdou A. "Evaluation of the antibacterial activity of bee venom from different sources", World Applied Sciences Journal, 2014,(30),3,266-270.

28. Intisar O A ,Nuha S S, Zainab M J ,Nagham M A. Synthesis of New Organic Compounds Via Three Components Reaction with Studying of (Identification ,Thermal Behavior, Bioactivity on Bacteria of Teeth).,Journal of Global Pharma Technology. 2017;(11),9,157-164.

29. Mieaad M, Nagham M A , Nadheema A A."Preparation, Spectral Investigation, Thermal Analysis, Biochemical Studying of New (Oxadiazole-Five Membered Ring)-Ligands".,Journal of Global Pharmacy Technology, 2018;(10),1,20-29.

30. Mieaad M, Nagham M A ,Wassan A S,Sabreen A A ."New Azomethine- Azo Heterocyclic Ligands Via Cyclization of Ester".,Research J.Pharm.and Tech.2018,(11),6.

31. Rana N ,Nagham M A ,Rana Neama Atiya ,Mjed Jeri ,Rana N A .Synthesis, Identification of Heterocyclic Compounds and Study of Biological Activity.,*Asian J.Research Chem.2014,(7),7,664-676.*

32. Nagham M A ,Shireen R R ,Rana Neama Atiya, Rana N A. Synthesis and Investigation of (Five, Six, Seven and Eight)–Membered Rings Containing Di Nitrogen Atoms.,Asian J.Pharm. Tech. 2014;(4),3,141-146.