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SYNTHESIS AND BIO- SPECTRAL STUDY OF NEW LIGANDS FROM BIS - (THIAZOLE – HETERO CYCLES) AND FORMAZAN LIGANDS

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ABSTRACT

Various and new eight ligands from bis –(thiazole –heterocycles) and formazan were synthesized in this work by using benzil compound as a starting material for preparation of thiazole derivative which converted to bis (anil compound) via condensation reaction with para-formal benzaldehyde , the last compound reacted with (sodium azid , mercapto acetic acid , o-hydroxy benzoic acid ,phthalamide)via condensation reaction to produce various ligands including bis heterocycles (five, six, seven)_ membered ring in their structures like (tetrazole ,thiazolone ,oxazine , diazepine). The structure of the newly synthesized compounds were monitored by (TLC) and identified by many techniques (Uv.Vis-spectro ,FT.IR- spectro , ^{1}H.NMR-spectro) , melting points , solubility in different solvents , study of bio- activity for synthesized ligands.

KEYWORDS: Thiazole, Tetrazole, Oxazine, Diazepine, Formazan

INTRODUCTION

Thiazoles and their derivatives have been discovered as a vital component of natural products that exhibit a wide variety of biological applications. The exceptional range of antitumor, antiviral, and antibiotic activities, as well as their presence in peptides, or ability to bind to biological molecules, DNA, and RNA, have directed numerous synthetic studies and new applications of these heterocycles[(1-4)]., this heterocyclic nucleus is a very important group because of its potent antitumor activity [(5-10)] and other pharmaceutical uses, like treatment of inflammatory diseases, analgesia Additionally, thiazoles are frequently appearing in peptide research. Thiazoles can also serve as a protected formyl group that can be liberated in the late stages of a complex natural product synthesis.

A large number of the derivatives of these thiazole compounds have been investigated for analytical purposes , and have been used as analytical reagents in addition to being interesting complexing agents[(11-16)] in coordination chemistry.

The chemistry of hetero cyclic compounds which linked with (diazepine[(6)] ,thizole , ,tetrazole , oxazine) are studied extensively because of its high synthesis and are used to design medicinal compounds .many of hetero cyclic compounds are synthesized , hundreds of them which have been tested to find new prospective leads for different pharmacy , therapeutic areas[(8-12)] .

Experimental

All measurement were carried out by : **melting** points in electro thermal 9300 ,LTD, U.K., **Uv.Vis** –Specrta ,**TLC**- Techniques , all **physical properties** like **solubility** in different solvent , **study of bio- activity** for synthesized ligands and **FT.IR** ,KBr –disc , shimadzu 8300 were tested in Iraq ., ^{1}**H.NMR** –spectra in DMSO –solvent in **Canada**.

Synthesis of Compound [1] as Starting Material

Starting material [1] was synthesized according to studies[8-10] ,benzil compound (0.01 mole) reacted with (0.01 mole) of thiourea in presence of absolute ethanol with mechanical stirring and reflux for (3 hrs), then the precipitate was filtered and dried to yield(82%) of compound [1] .

Synthesis of Ligand [2]

(0.02 mole) of compound [1] and para- formal benzaldehyde were mixed in (50ml) of absolute ethanol in presence of drops glacial acetic acid , the mixture was refluxed and stirred for (2 hrs) , then filtered and dried to give (86%) of ligand [2].

Synthesis of Ligand [3]

A mixture of (0.01mole) of compound [2] and sodium azide (0.02mole) was heated in presence of (50ml) of tetrahydrofuran , the precipitate was filtered and dried ,re crystallized from dioxane to give (82%) of compound [3].

Synthesis of Ligand [4]

A mixture of (0.01mole) of compound [2] and mercapto acetic acid (0.02mole) was refluxed for (5hrs) in presence of (50ml) of dry benzene, the precipitate was filtered and dried ,then re crystallized to give (%82) of compound [4].

Synthesis of Ligand [5]

Ligand [2] (0.01mole) refluxed with (0.02mole) of O-hydroxy benzoic acid in presence of dry benzene for (5hrs) ,the precipitate was filtered and dried ,then re crystallized to produce (%84) of compound [5].

Synthesis of Ligand [6]

A mixture (0.01mole) of ligand [2] and (0.02mole) of phthalamide refluxed for (6hrs) in presence of dry benzene ,the precipitate was filtered and dried ,then re crystallized from benzene to produce (%86) of ligand [6].

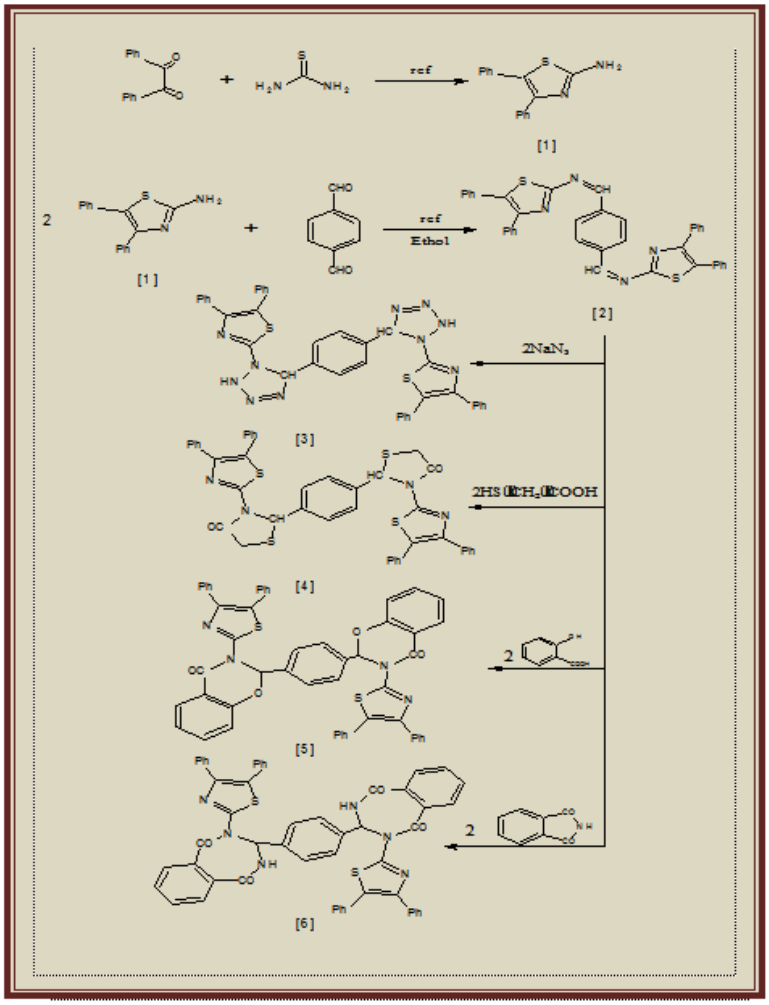
Synthesis of Ligand [7]

Equimolar mixture (0.01mole) of 0- phenylene di amine and para-hydroxy benzaldehyde were refluxed in presence of absolute ethanol with drops glacial acetic acid for (2hrs) , the resulting compound reacted with mixture of ortho-methoxy diazonium salt at (0-5)C° , to produce fromazane compound (85%) of ligand [7] .

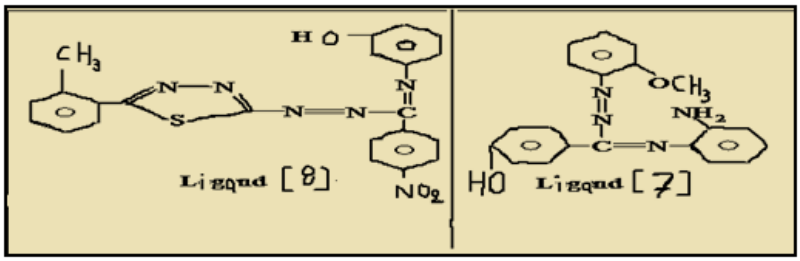
Synthesis of Ligand [8]

A mixture of ortho-methyl benzoic acid (0.01mole) and thiosemicarbazide (0.01mole) were reacted in refluxing for (10 hrs) ,the resulting precipitate was amino compound , which dissolved in (2ml) of hydrochloric acid with (0.6gm) solution of sodium nitrite at (0-5)C° , ethanolic solution of 3-(hydroxy benzene)-4-nitro phenyl imine added to mixture to

produce fromazane compound (84%) of ligand [8] .



Scheme 1: Synthesis of Ligands [1-6]



Scheme 2: Synthesis of Ligands [7, 8]

RESULTS AND DISCUSSIONS

In this work, we have synthesized eight compounds as a ligands from bis (thiazole – heterocycles) and formazane , via condensation reaction and coupling reactions.

All synthesized ligands were characterized by { Uv. Vis , FT.IR, ^{1}H.NMR } spectra and other studies like

solubility of ligands in various solvents , other physical properties and biological activity:

(Uv.Vis) –Spectra and Physical Properties

Uv. Visible spectra of these compounds, data of analysis, products %, melting points are listed in Table (1), Figures (1-4).

Table 1: Physical Properties & Λ_{max} of Ligands[1-8]

Ligands	M.P (C^0)	λ_{max}	Product%
[1]	160	365	82
[2]	188	410	86
[3]	204	435	82
[4]	218	422	82
[5]	230	455	84
[6]	246	460	86
[7]	202	382	85
[8]	226	398	84

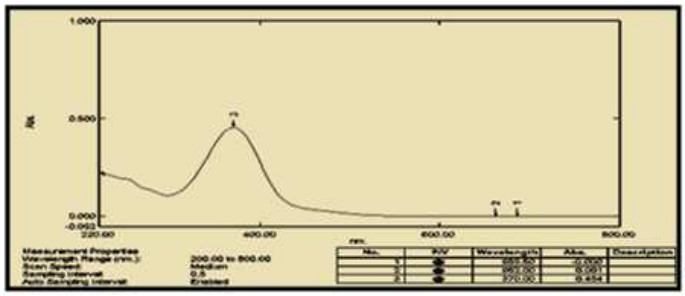


Figure 1: Uv.Vis – Spectra of Ligand [1]

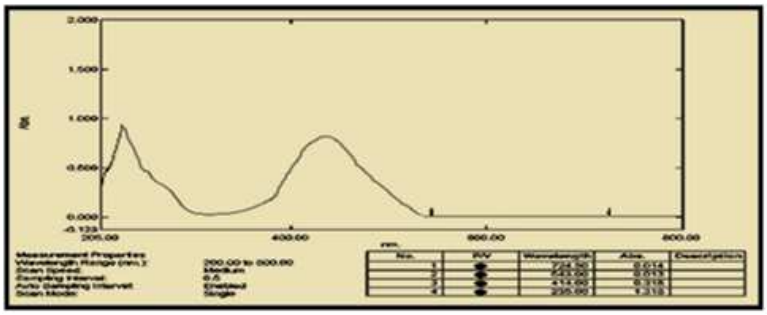


Figure 2: Uv.Vis – Spectra of Ligand [5]

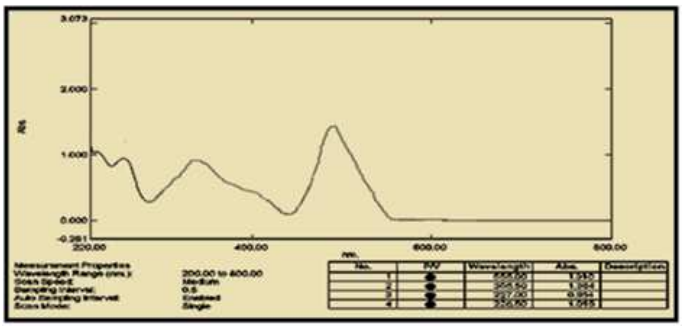


Figure 3: Uv.Vis – Spectra of Ligand [6]

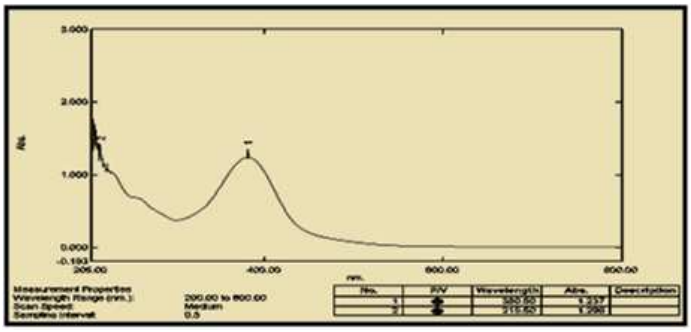


Figure 4: Uv.Vis – Spectra of Ligand [7]

The FT.IR–spectra shown absorption band at (1630)cm^{-1} due to (CH=N) imine group[16,17] in ligand [2] ,which disappeared and other bands appeared in synthesized ligands such as [(3242)cm^{-1} due to (-NH-)[6] ., [(1294)cm^{-1} due to (N=N-N)cm^{-1} to tetrazole in ligand [3]., band at [(1689)cm^{-1} due to (-CO-N-) of] in amide ligand [4]., bands at [(1693)cm^{-1} to (-CO-N) amide and (1222)cm^{-1} due[6] to (-C-O-C) of ether] in ligand [5] ., bands at [(1688)cm^{-1} due to (-CO-N-) amide and (3298)cm^{-1} due to (-NH)] in ligand [6]., bands at [(3420)cm^{-1} to hydroxyl group (-OH-) ., (3355 ,3330)cm^{-1} to (amine[19] (-NH_2) and (1468 ,1482)cm^{-1} due to (-N=N-) azo] in ligand [7]., bands at [(3436)cm^{-1} to (-OH-) hydroxyl group of phenol ., (1612)cm^{-1} due to (C=N)of endo thiadiazole and (1457 ,1485)cm^{-1} due to (-N=N-) azo group] in ligand [8] ., and other data in table (2) and figures (5-8).

Table 2: FT.IR data (cm^{-1}) of Ligands

Ligands	Only Important Groups
[1]	(NH_2) amine : 3395 ,3380
[2]	(CH=N)imine group:1630
[3]	(NH) endo cycle of tetrazole:3242 , (N=N-N) :1294 .
[4]	(CH-S):1268 , (CO-N) carbonyl of amide : 1689
[5]	(CO-N) carbonyl of amide : 1693 , (C-O-C) ether :1222 .
[6]	(-CO-N-) carbonyl of amide:1688 .,(NH) :3298
[7]	(OH) hydroxyl group:3420 ,(NH_2) :3355 ,3330 ,(-N=N-) azo: 1468, 1482 , (-OCH_3)ether : 1235.
[8]	(OH) hydroxyl group:3436 , (C=N) endo thiazole: 1612 ,(-N=N-) azo: 1457, 1485.

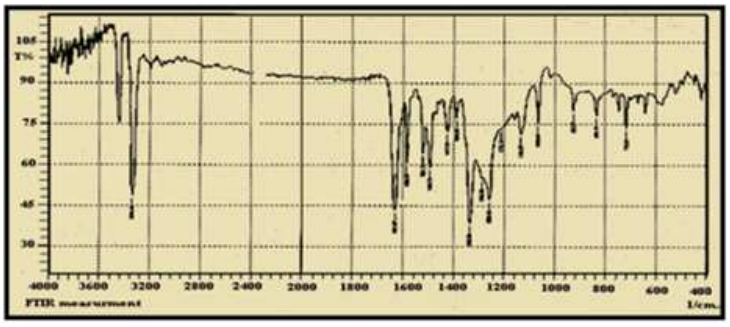


Figure 5: FT.IR spectra of Compound [1]

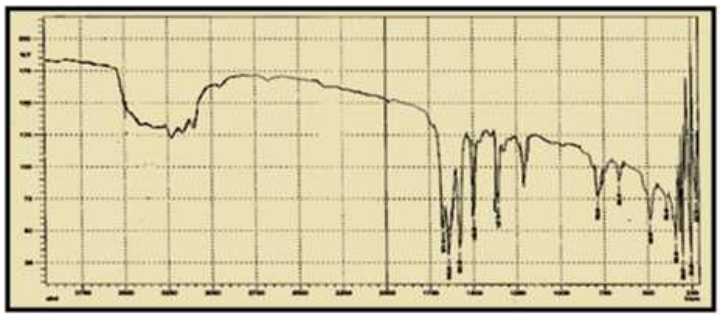


Figure 6: FT.IR Spectra of Ligand [2]

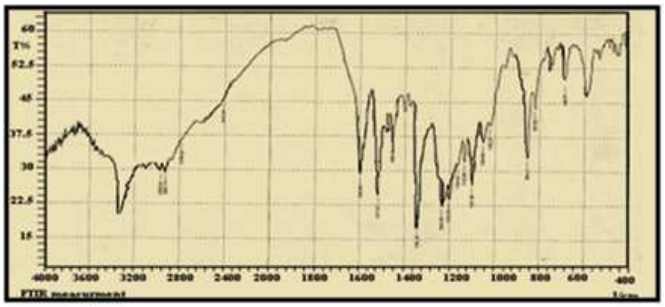


Figure 7: FT.IR spectra of Ligand [3]

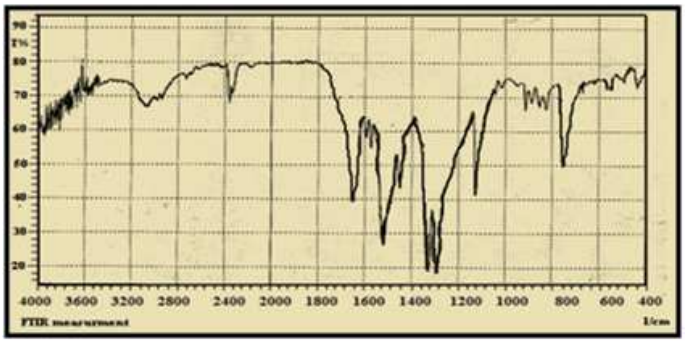


Figure 8: FT.IR spectra of Ligand [4]

^{1}H.NMR - spectra for some of synthesized compounds ., shown signal at ϭ (5.03) due to amine group (NH_2) in compound [1] ., signal at ϭ (8.5) due to proton[8,9] of imine group (CH=N) in ligand [2] ., which disappeared and other signals appeared in synthesized ligands such as : signals at **{**ϭ**(** 3.05 due to (N-CH-N) ., 5.0 due to (NH) of tetrazole] in ligand [3]., signals at { ϭ 3.72 due to (S-CH-N) and (2.6) due to (CH_2-CO-)} in ligand [4]., signals at[ϭ 3.98 due to (N-CH-O) in ligand [5] ., signals at { ϭ 10.11) due to protons of amide (NH-CO-) and 3.08 due to proton of (N-CH-CO-)} in ligand [6]., signal at { ϭ 11.06 due to (OH) of phenol in ligand [7]., signals at[ϭ 11.12 due to (OH)of phenol and 5.54 due to amine (NH_2) in ligand [8] , and other signals in Table (3) and Figures (9-11) .

Table 3:^{1}H.NMR data (ϭ ppm) of Compounds

Comps	Important Peaks "Only"
[1]	5.03(NH_2) amine group.
[2]	8.5 (CH=N) imine group.
[3]	5.00 (NH) ., 3.05(N-CH-N) of tetrazole cycle

[4]	3. 72(N-CH-S) of cycle ., 2.6 (CH_2-CO-) of cycle .
[5]	3.98 (N-CH-O) of cycle.
[6]	10.11 (NH-CO) aimde ., 3.08 (N-CH-CO-) .
[7]	11.06 (OH) of phenol ., 0.98 (CH_3) .
[8]	11.12 (OH) of phenol ., 5.54 (NH_2) ., 3.10 (-OCH_3).

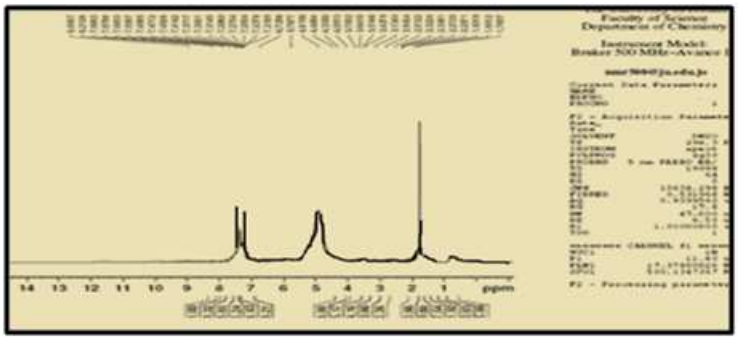


Figure 9: ^{1}H.NMR Spectra of Compound [1]

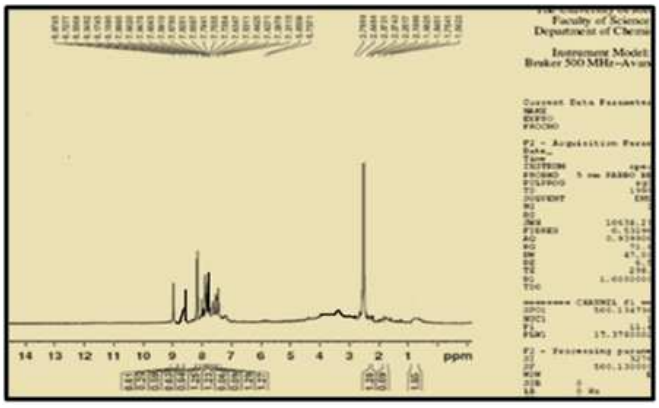


Figure 10: ^{1}h.Nmr Spectra of Ligand [2]

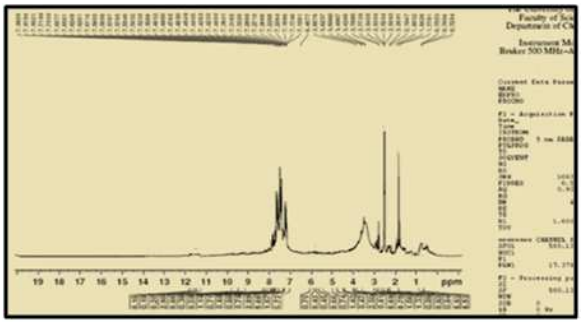


Figure 11: ^{1}H.NMR Spectra of Ligand [4]

Solubility of Ligands

The solubility of synthesized ligands was tested in different solvents according polarity of solvents , the results are shown in Table (4).

Table 4: Solubility of Synthesized Ligands

Ligands	Solvents					
	Ethanol	Methanol	DMSO	Benzene	Dioxane	THF
[1]	+	+	+	-	-	-
[2]	+	+	+	+	+	+
[3]	+	+	+	+	+	-
[4]	+	+	+	+	+	-
[5]	+	+	+	+	+	-
[6]	+	+	+	+	+	+
[7]	+	+	+	-	-	-
[8]	+	+	+	-	-	-

Biological Test [8, 9]

Bacteria supplied from bio-Lab in college of Education .,antimicrobial activity was tested by the filtered paper disc diffusion method against gram (+) positive bacteria (*Staphylococcus aureus*) and gram (-) negative bacteria (*E-coli*) .,(0.1mol) of the bacterial suspensions was seeded on agar .To determine minimum inhibitory concentration (MIC) for each ligands [1-8] were performed with two replicates .

Generally, the results showed that the ligands [1-8] have good inhibitory effect against tested bacteria .

Table (5) and Picture (1) showed the zone of inhibition of the ligands [1-8] in this study ranged (from 36 to 10) mm . from results , we noted the ligands [3 , 4, 8] have higher antibacterial activity against two type of bacteria (G+ and G-) due to their structures (consist of thiadiazole and thiazolone rings with tetrazole rings) consequently ,which it become more effective in precipitating proteins on bacteria

Table 5: Antibacterial Activity of Ligands [1-8]

Compounds	Diameter of Zone (Mm)	
	G+ : Staphylococcus Aureus	G- : E-Coil
Ligand [1]	16	10
Ligand [2]	18	14
Ligand [3]	36	26
Ligand [4]	36	24
Ligand [5]	22	16
Ligand [6]	26	16
Ligand [7]	12	10
Ligand [8]	30	20

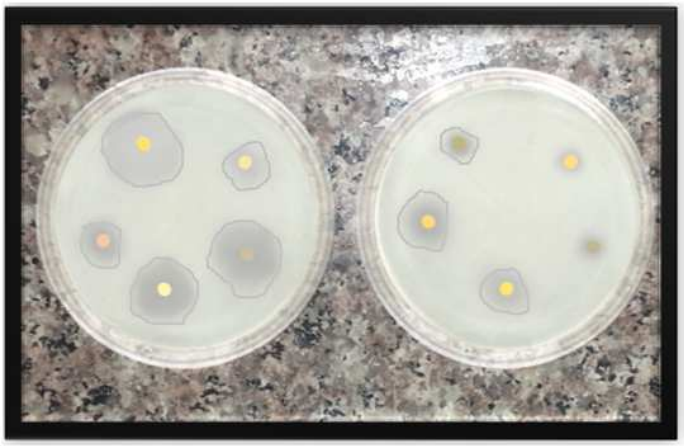


Figure 1: Showed the Zone of Inhibition of S.Aureus

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