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1, 3-Dithiols and Oxoketene Gem-Dithiols Insertion into Au, Hg, Co and Ni; Synthesis and Biological Investigation of Some Metal Complexes

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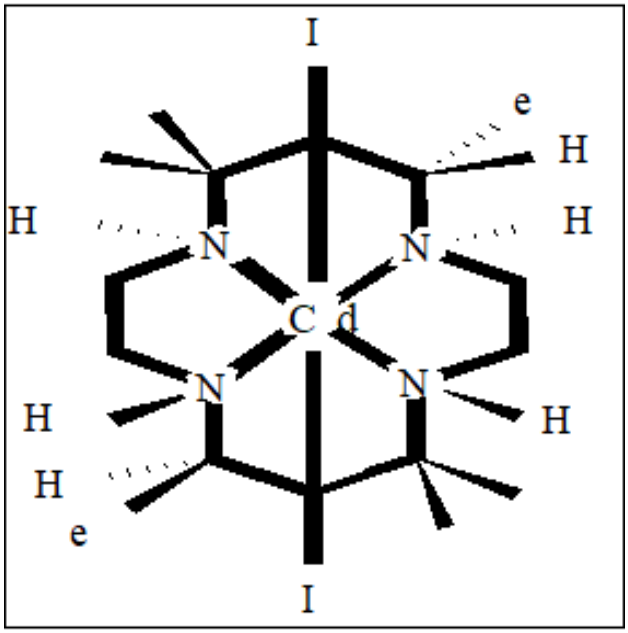
Abstract:- Reaction of dimethyl-2-(2-thien-2-yl-2-thioxoethylidene)-1,3-dithiole-4,5-dicarb- oxylate 1 and 1-(4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-dimercaptoprop-2-en-1-one 10 respectively with transition metal salts, e.g. $NaAuCl_4.2H_2O$, $NiCl_2.6H_2O$, $CoCl_2$ and $HgCl_2$ furnished the C-S-Metal complexes in a simple and a satisfactory manner. These complexes were screened as antimicrobial agents against a number of important bacteria such as Bacillus subtilus, Staphylococcus and Lactococcus and gave remarkable and observed inhibition zones.

Keywords:- *Oxoketene Gem-Dithiol, Metal Complexes, Ampicillin, Amphotericin, Sugar Manufacture, Biological Activities.*

I. INTRODUCTION

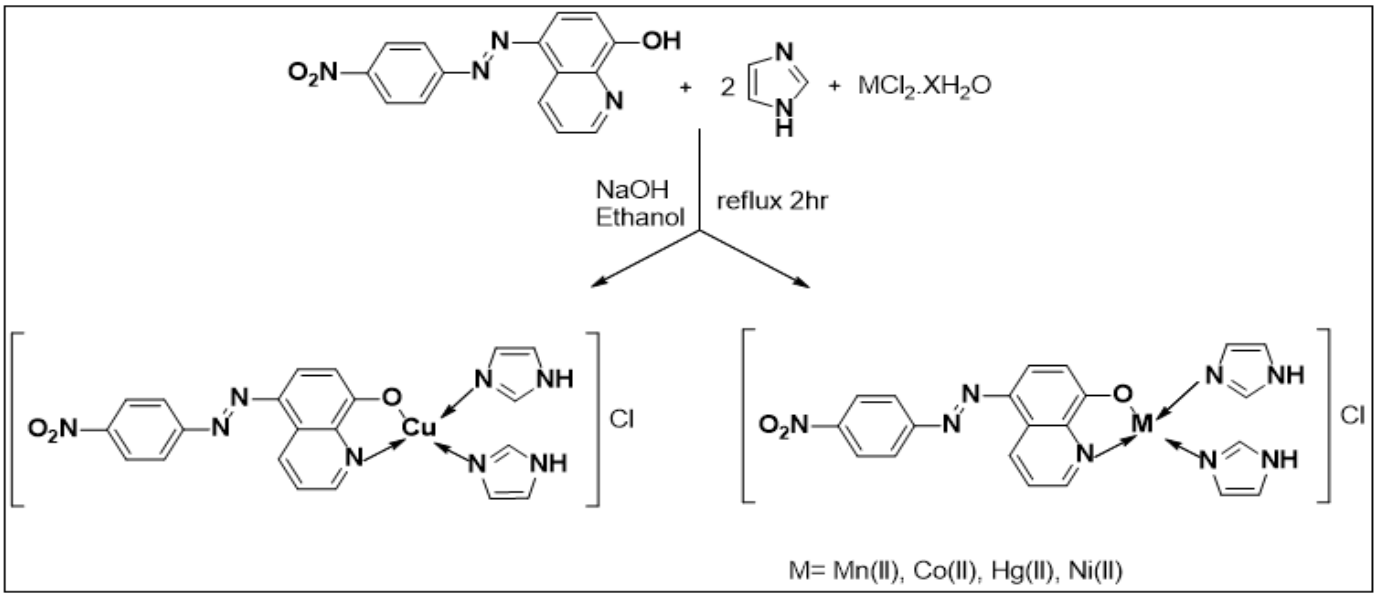
Recently, it has been found that metal coordination complexes [1-13] are useful in many fields such as physical and chemical purposes. These complexes are used as catalysts, for synthesizing of enormous different materials and in medicinal chemistry due to their biological activities [14-18]. Metal coordination complexes are used for treating many diseases that occur by different microorganisms [14,19]. It is found that heavy metals such as silver and copper in a minute quantity have the ability to exert a lethal effect on bacterial cells and kill cells of microorganisms present in water solutions.

In addition, a lot of metallic elements have been used as inhibitors of the growth of microorganisms. Metallic elements were used in the manufacture as preservations for many substances like tomato juice, hides and cider [20-23]. In many chemotherapeutic aspects, it is found that coordination complexes of transition metals were used as antibacterial, antifungal agents. Pathogenic fungi and bacteria were subjected to treatment with these complexes and the results were remarkable. In addition to their uses for combating infections and neoplastic, they must serve a selective toxicity and chemical stability [24, 25]. The interaction of several compounds with metals ions leads to gather valuable moieties have antimicrobial characters and used as efficient drugs for treating of infections [26]. The complexes of macrocyclic ligands [27] figure 1 play an important and valuable role in different fields such as pharmacology [28] and industry [27,29]. On the other hand, these compounds are used as drugs for treatment of different diseases like tumors [30] and cancer [27, 31] In addition, they are used as antimicrobial agents which kill or inhibit the growth of microbes such as bacteria, fungi, or viruses [27, 32-34] as illustrated in **Scheme 1.**



Scheme 1 Complex $[Cd(teta)I_2]$

Some metal complexes [35,36] have the ability to treat the human diseases like leukemia, inflammation, cancer and infection [35, 37] The use of antibacterial drugs is required to avoid the different threats to the human health [32]. Compounds known as mixed ligand complexes of transition metal ions have been introduced as benefit characters as antibacterial agents [38] as shown in **Scheme 2**.

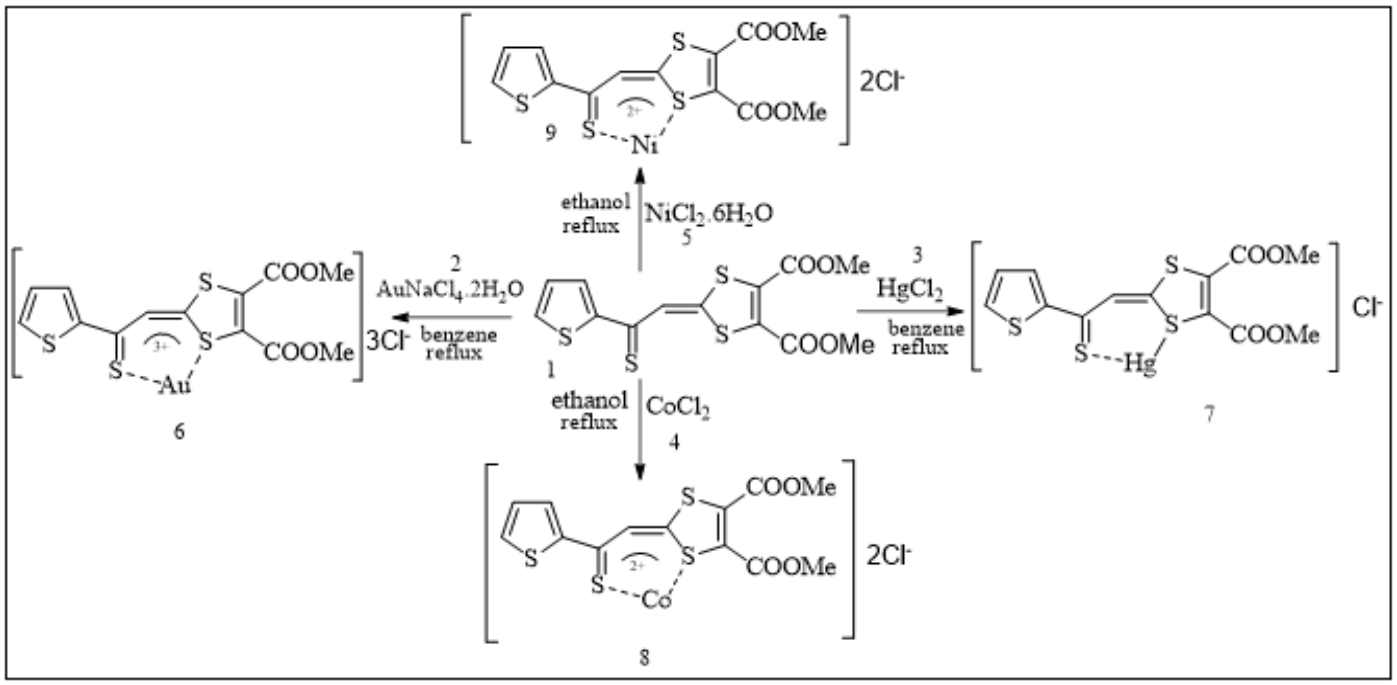


Scheme 2 $[M(L_1)(L_2)_2]Cl$ Complexes

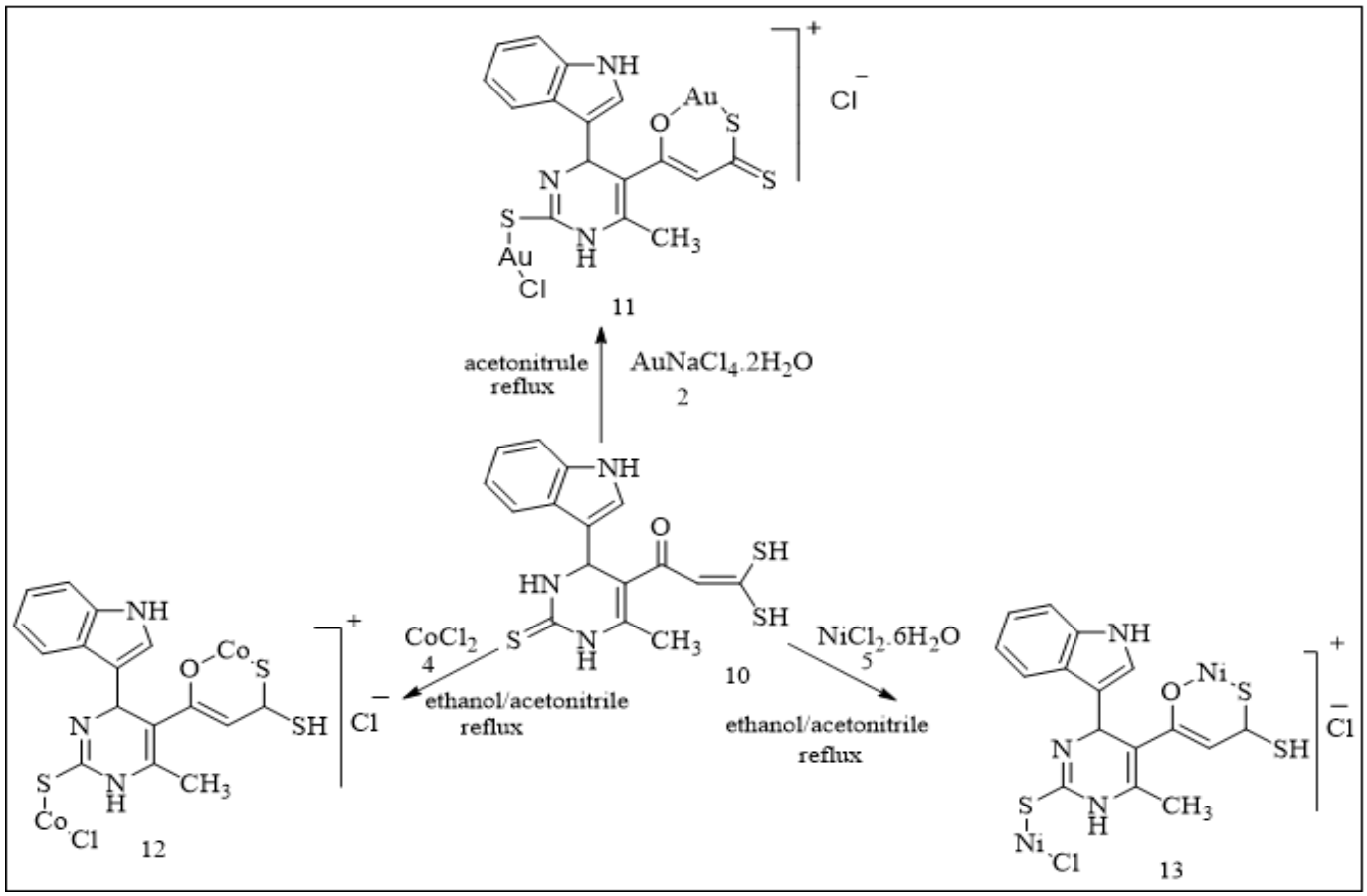
It was taken into consideration of most research how to face the resistance of microorganisms to action of drug [39], macrocyclic compounds were subjected to these studies [27]. Besides their biological activities. the importance of macrocyclic compounds due to their nature which resembles the natural macrocyclic complexes like vitamin B_{12}, heme and chlorophyll [27] In addition, macrocyclic complexes are used in industrial, pharmacological, and analytical purposes [27].

II. RESULT AND DISCUSSION

Metal complexes [40] have versatile coordination behavior [41-43]. In ligands metals tend to form specific compounds of certain structures of desired properties [44]. In the present work we have found that, reaction of heterocyclic compounds containing sulfur and/or nitrogen atoms with some metal halides e.g., aurine sodium chloride $NaAuCl_4$. $2H_2O$, $NiCl_2.6H_2O$, $CoCl_2$ and $HgCl_2$ give rise to new complexes that possess biological activities towards some microorganisms. Reaction of dimethyl-2-(2-thien-2-yl-2-thioxoethyliden-e)-1,3-dithiole-4,5-dicarboxylate **1** [45] with $AuNaCl.2H_2O$ **2**, $HgCl_2$ **3**, $CoCl_2$ **4** and $NiCl_2.6H_2O$ **5** proceeded through insertion of metal and furnished the complexes **6**, **7**, **8** and **9** respectively as illustrated in **Scheme 3.** Also, the reaction of 1-[4-(1*H*-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-3,3-dimercapto-propenone **10** with $AuNaCl.2H_2O$ **2**, $CoCl_2$ **4** and $NiCl_2.6H_2O$ **5** gave the complexes **11**, **12** and **13** respectively as illustrated in scheme **4.**



Scheme 3 Reaction of dimethyl-2-(2-thien-2-yl-2-thioxoethyliden-e)-1,3-dithiole-4,5-dicarboxylate 1 with $AuNaCl.2H_2O$ 2, $HgCl_2$ 3, $CoCl_2$ 4 and $NiCl_2.6H_2O$



Scheme 4 Reaction of 3,3-dimercaptopropenone derivative 10 with AuNaCl.2H_2O 2, $CoCl_2$ 4 and $NiCl_2.6H_2O$ 5

➢ *Microbiological Survey*

Sugar loss due to microbial infection has always been a problem encountered by the industry and monitoring is very important. Microorganisms present in cane and beet juices, raw sugar and sugar refinery which utilize source and other sugars as a source of energy are classified as bacteria, yeast, and molds. According to temperature range for microorganism maximum growth, psychrophiles grow generally between 4 and 20ºC, mesophiles, 20-45ºC and thermophiles 45-100 [46].

- *Bacteria*

Bacillus subtilis and Bacillus cereus are examples of spore-forming bacteria [47-49] Spore-forming bacteria can survive the processing conditions because their spores are heat resistant [50].

- *Filamentous Fungi (Molds)*

They are particularly prevalent in rotting piles of organic material such as bagasse. They can be serious plant pathogens and cause human health hazard due to spores and toxin production. Examples are Penicilium and Apergillus [51,52].

➢ *Microbial Problems in Sugar Manufacture*

- *Processing Problems:*

Problem associated with organisms causing slime are acid inversion of sucrose, clogging of pipes, strainers and pumps and increasing liquors viscosity [53] due to its metabolic products including organic acids, reducing sugars and polymers such as gums.

- *Quality Control Problem*

They may cause deterioration in the foods or beverages to which they are added. Some of the volatile and non-volatile constituents responsible for the flavor and odour of cane sugar products such as table syrups, molasses and refinery brown sugar are due to microbial activity [54].

➢ *Biocides and biocidal agents [55]*

The term biocides denote chemical agents that have antiseptic, disinfectant, or preservative activity. Chlorine releasing biocides such as hypochlorite and quaternary ammonium compounds are commonly used in sugar processing. They help in breaking up biofilms and prove to be economically more efficient than without their use. The composition of a typical commercial biocide is as follows: (Midland Laboratories PCS 6001).

- Sodium dimethyldithiocarbamate 15%
- Disodium ethylenebisdithiocarbamate 15%
- Inert ingredient 70%

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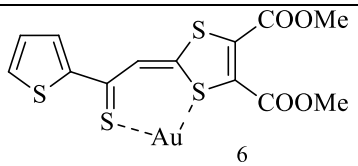
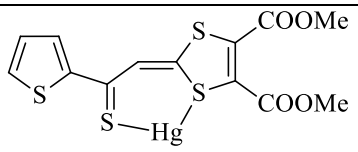
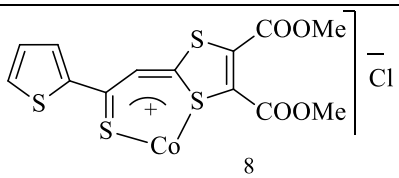
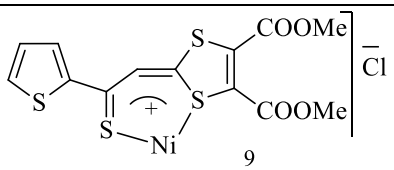
III. THE EXPECTED SAVINGS UPON USING THE NEWLY PREPARED COMPOUNDS AS ANTIMICROBIAL AGENTS IN SUGAR MANUFACTURE.

Sugar losses by infection may amount to at least 1% cane [56] and 0.4% beet during the extraction process as this microbiological degradation reaction is an autocatalytic chain reaction and when it starts it is very difficult or impossible to stop. The following example shows the volume of financial damage which demonstrates the importance of avoiding such infection reaction. e.g., In the case of manufacturing ten million tons of sugar cane per season, the expected sugar losses only in the extraction process as estimated above by 1%.

Cane is equal to $10x10^6x1/100$= 100,000 tons sugar which is equivalent to financial fund = 100,000 x 2250 pounds/ton sugar = 225 x 10^{62} Egyptian pounds according to the sugar price in the Egyptian local market. The following table shows the biological comparison studies of the tested compounds (**Table 1**).

Table 1 Shows the Biological Comparison Studies of the Tested Compounds

Chemicals 1000 ppm	Bacillus subtillis 37°C Gram +ve	Bacillus subtillis 37°C Gram -ve	Escerchia coli 37°C Gram +ve	Escerchia coli 37°C Gram -ve	Aspregillus niger 28°C
 6	100%	92%	100%	89%	91%
 7	100%	83%	100%	87%	83%
 8	100%	88%	100%	88%	87%
 9	84%	87%	77%	79%	72%

In the last forty decades, the development in the pharmaceutical fields has increased. Because of the development in different class areas of drug discovery. Antimicrobial substances have been discovered, and they are found to have a wide effect on microorganisms such as Gram-positive and Gram-negative bacteria. Gram-positive bacteria differ in their resistance to antibacterial substances from Gram-negative bacteria due to the differences in the structure of their cell walls. Gram-negative bacteria endow their surface with strong hydrophilic due to its lipopolysaccharide content, which acts as a permeability barrier to lipophilic splits. Gram-positive bacteria have only an outer peptidoglycan layer, which is not an effective permeability barrier [57]. According to these reasons various studies were carried out to increase the activity and the effects of the antimicrobial substances.

Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method [58] (**Table 2**). Briefly, 100 µl of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately 108 cells/ ml for bacteria or 105 cells/ml for fungi [59]. 100 µl of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method [60]. Plates inoculated with filamentous fungi as Aspergillus flavus at 25°C for 48 hrs.; Gram (+) bacteria as Staphylococcus aureus, Bacillus subtilis; Gram (-) bacteria as Escherichia coli, Pseudomonas aeruginosa they were incubated at 35-37°C for 24-48 hrs., and yeast as Candida albicans incubated at 30°C for 24-48 hrs., and then the diameters of the inhibition zones were measured in millimeters [61]. Standard discs of Ampicillin (Antibacterial agent),

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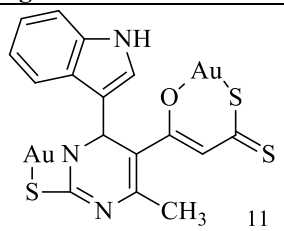
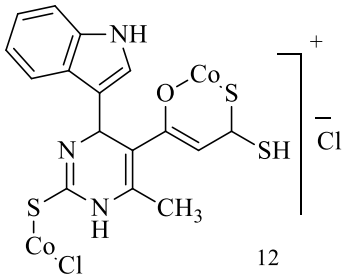
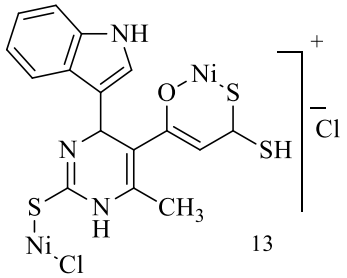
Amphotericin B (Antifungal agent) served as positive controls for antimicrobial activity, but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control. Blank paper disks (Schleicher & Schuell, Spain) with a diameter of 8.0 mm were impregnated 10µ of tested concentration of the stock solutions. When a filter paper disc impregnated with a tested chemical is placed on agar the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc. If an organism is placed on the agar, it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as a "Zone of inhibition" or" Clear zone". For the disc diffusion, the zone diameters were measured with slipping calipers of the National Committee for Clinical Laboratory Standards [62]. Agar based methods such as Test and disk diffusion can be good alternatives because they are simpler and faster than broth-based methods [63-95].

Table 2 Antimicrobial Activity on the Tested Samples using a Modified Kirby-Bauer Disc Diffusion Method

Sample		Inhibition zone diameter (mm/mg Sample)			
		Escherichia Coli (G)	**Staphylococcusaureus (G^+)**	**Aspergillus flavus (Fungu)**	**Candida albicans (Fungu)**
Control: DMSO		0.0	0.0	0.0	0.0
Standard	**Ampicillin: Antibacterial agent**	30	24	--	--
	Amphotericin B: Antifungal agent	--	--	16	19
 11		14	15	0.0	0.0
 12		14	14	0.0	12
 13		12	13	0.0	*11*

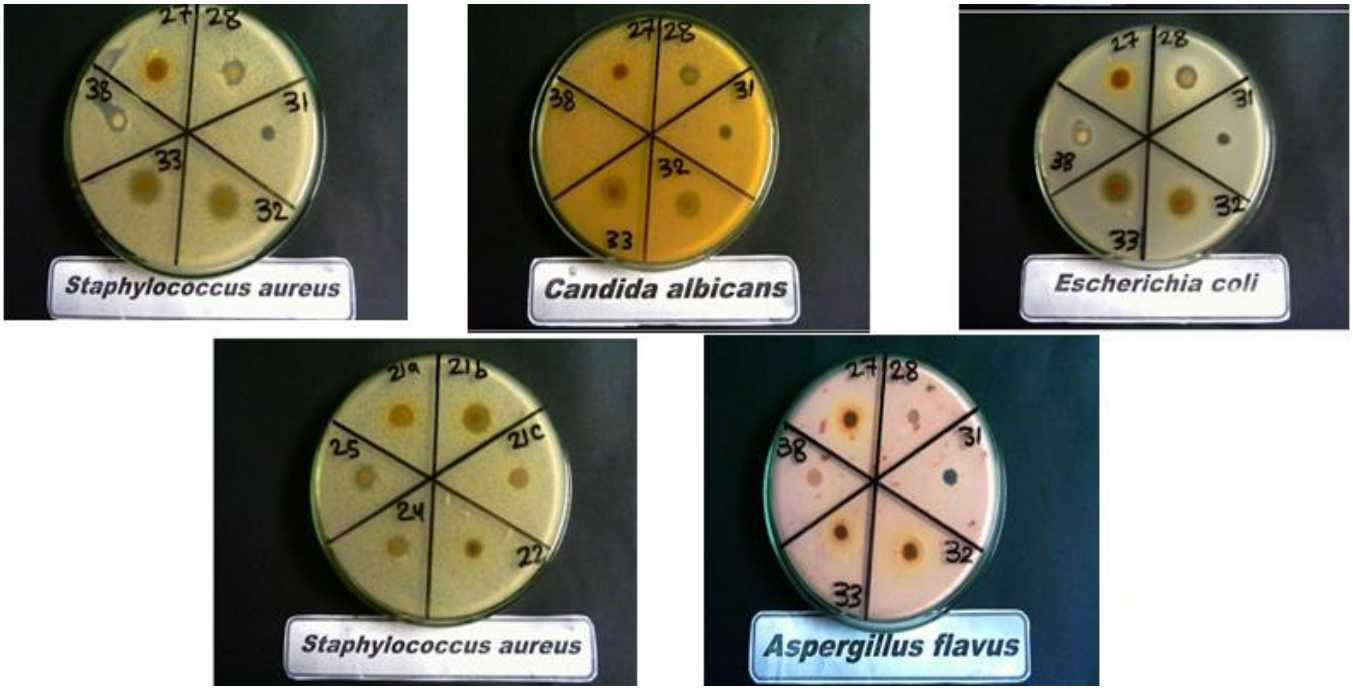


Fig 1 Growth Inhibition Pattern of the Complexes

IV. CONCLUSION

The search discussed the synthesis of some metal complexes joined to 1,3-dithiols and dihydropyrimidines. The obtained complexes were investigated for their biological activity against some microorganism present in sugar cane juice and their biological activity was compared with the known Ampicillin and Amphotericin; satisfied results were achieved.

➢ *Experimental*

All melting points are uncorrected and were determined on Kofler melting point apparatus. The progress of the reactions was followed up by TLC technique. IR spectra were determined with Shimadzu IR 408 infrared spectrophotometer using KBr wafer technique. ^{1}HNMR spectra were recorded on Perkin Elmer 300 MHz spectrometer using TMS as an internal reference and chemical shifts are expressed as δ. The electron impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. Biolgical activity was carried out at Microbiology Lab., South Valley University and Cairo University.

➢ *Synthesis of C-S-Gold Complex (6) and (11)*

- *Complex (6)*

(0.5 gm, 0.001 mol) of Compound 1 was dissolved in 20 ml acetone/water (4:1), to this solution was added (0.56 gm, 0.001 mol) of $NaAuCl_4.2H_2O_2$. The mixture was heated under reflux for 2 hrs., the product precipitated while heating. The product was separated and recrystallized from DMF as brown solid. m.p. 210-212°C, IR, (cm^{-1}): 1635 C=O; MW, $C_{13}H_{10}O_4S_4Au$ (555.44), MS, 555.22; ^{1}H-NMR: δ 3.85 (s, 6H, $2CH_3$), 7.00-7.50 (m, 3H, thienyl-H), 8.40 (s, 1H, ylide-CH).

- *Complex (11)*

A mixture of (0.36 gm, 0.001 mol) of compound 10 and (0.27 gm, 0.001 mol) of $NaAuC_{l4}.2H_2O_2$ in 30 ml ethanol/acetonitrile (3:2) was heated under reflux for 4 hrs. The new adduct was followed up by TLC. The reaction mixture was left to cool, and the product was collected and recrystallized from ethanol/toluene as a dark brown solid. m.p. 200-202°C, IR, (cm-1): 1636 C=O, 3393 NH; MW, $C_{16}H_{11}N_3OS_3Au_2$ (751.40), MS, 751.0, ^{1}H-NMR: δ 2.10 (s, 3H, CH_3), 3.41 (s, 1H, pyrimidinyl-H), 6.05 (s, 1H, ylide-CH), 7.00-8.09 (m, aromatic protons), 8.25 (s, 1H, NH).

➢ *Synthesis of C-S-Mercury Complex (7)*

(0.38 gm, 0.001 mol) Of $HgCl_2$ 2 was added to a solution of (0.5 gm, 0.001 mol) of compound 1 in 20 ml of benzene. The mixture was refluxed for 3 hrs., then it was left to settle. The product was collected and recrystallized from methanol as violet solid. m.p. 180-182°C; IR, (cm^{-1}): 1640 C=O; MW, $C_{13}H_{10}O_4S_4Hg$ (559.07), MS, 559.0; ^{1}H-NMR: δ 3.89 (s, 6H, $2CH_3$), 7.53 (m, 3H, thienyl-H), 8.69 (s, 1H, ylide- CH).

➢ *Synthesis of C-S-Cobalt Complex (8) and (12)*

- *Complex (8)*

A mixture of (0.5 gm, 0.001 mol) of compound 1 and (0.129 gm, 0.001 mol) of CoCl2 4 in 20 ml ethanol was heated under reflux for 2 hrs. The solution was left to cool and settle. The product collected and recrystallized from benzene as brown solid. m.p. 160-162°C; IR, (cm-1): 1650 C=O; MW, $C_{13}H_{10}O_4S_4CoCl$ (542.45), MS, 453.0; ^{1}H-NMR: δ 3.90 (s, 6H, $2CH_3$), 7.20-7.52 (m, 3H, thienyl-H), 8.72 (s, 1H, ylidenic CH).

- *Complex (12)*

(0.36 gm, 0.001 mol) Of compound 10 was dissolved in 30 ml of ethanol/ aceronitrile (3:2); to this solution was added (0.129 gm, 0.001 mol) of $CoCl_2$ 4. The mixture was refluxed for 4 hrs. and then it was left to cool. The product precipitated and it was collected and recrystallized from ethanol/toluene as dark brown solid. m.p. > 360ºC, IR, (cm-1): 1635 C=O, 3396 NH; MW, $C_{16}H_{13}N_3OS_3Co_2Cl_2$ (550.27), MS, 550.0; 1-H-NMR: δ 1.15 (s, 1H, SH), 2.86 (s, 3H, CH3), 4.01 (s, 1H, CH), 6.65 (s, 1H, ylidenic CH), 6.97-7.50 (m, aromatic protons), 9.99 (s, 1H, NH),11.94 (s, 1H, NH).

➢ *Synthesis of C-S-Nickel Complex (9) and (13)*

- *Complex (9)*

(0.5 gm, 0.001 mol) compound 1 was dissolved in 20 ml of ethanol, to this solution was added (0.237 gm, 0.001 mol) of $NiCl_2.6H_2O$ 5. The mixture was heated under reflux for 2 hrs. and then it was left to cool. The product was separated and recrystallized from benzene as dark brown solid. m.p. 172-174ºC; IR, (cm^{-1}): 1650 C=O; MW, $C_{13}H_{10}O_4S_4NiCl$ (542.21), MS, 543.0; ^{1}H-NMR: δ 3.89 (s, 6H, $2CH_3$), 7.20-7.91 (m, 3H, thienyl-H), 8.70 (s, 1H, ylide-CH).

- *Complex (13)*

(0.36 gm, 0.001 mol) Compound 10 was dissolved in 30 ml of ethanol/ aceronitrile (3:2); to this solution was added (0.237 gm, 0.001 mol) of $NiCl_2.6H_2O$. The mixture was refluxed for 4 hrs. and then it was left to cool. The product precipitated and it was collected and recrystallized from ethanol/toluene as dark brown solid. m.p. 180ºC, IR, (cm-1): 1636 C=O, 3396 NH; MW, $C_{16}H_{13}N_3OS_3Ni_2Cl_2$ (549.79), MS, 550.0; ^{1}H-NMR: δ 1.15 (s, 1H, SH), 2.70 (s, 3H, CH_3), 3. 21 (s, 1H, CH), 4.01 (s, 1H, CH), 6.05 (s, 1H, ylidenic CH), 7.00-8.09 (m, aromatic protons), 8.27 (s, 1H, NH), 9.93 (s, 1H, NH).

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