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ANTIMICROBIAL ACTIVITY OF 2, 2-BIPYRIDINEDICHLOROPLATINUM (II), $C_{10}H_8CL_2N_2Pt$

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ABSTRACT

Antimicrobial activity of compound (2) was investigated against pathogenic microorganisms: *Staphylococcus aureus* (Gram (+), *Escherichia coli* (Gram (-) and fungal strain, *Candida albicans* using the Well Diffusion and the Poison plate methods. Compound (2) was shown to inhibit pathogenic growth, and judging from the area of the zone of inhibition, the susceptibility of the microorganism against compound (2) follows the sequence: *Staphylococcus aureus* > *Candida albicans* > *Escherichia coli*. The area of zone of inhibition ranging from (4.64 mm^2 to 6.47 mm^2) and (4.64mm^2 to 5.72 mm^2) for the Well Diffusion and Poison plates respectively. Both methods indicate that the area of the zone of inhibition for compound (2) is more potent than reference antibiotics: Nystatin and Ampicillin.

INTRODUCTION: In the field of medicine/Pharmacy, the syntheses of novel, potent selective antimicrobial drugs with least cell/tissue toxicity and adverse effects, [1-4] is of current interest . This stem from the fact that pathogenic microorganisms developed resistance to current antimicrobials [1, 2]. Pathogens also undergo genetic mutations which change proteins and other components of cells. In addition, pathogens produce enzymes that destroy or inactivate antimicrobials and alter the permeability of their cell membrane, making it difficult for antimicrobials to enter [2-4].

Antimicrobials act on pathogenic microorganisms via the inhibition of cell wall formation, leading to cell wall lysis. In addition, they damage the bacterial cell membrane, resulting in a loss of cell contents and death. At the molecular level, they inhibit nuclei acid and protein production and therefore arrest bacteria growth.

On aspect of drug discovery focuses on the modification of the structure of existing drug, resulting in a change in potency and selectivity with little side effects/ low toxicity.

Many synthetic antimicrobials reported to date are neutral organic molecules such as Penicillins, Vancomycin, Polymyxins etc. [2-4]. Plant extracts and isolated pure natural products, have also been used as initial antimicrobial agents [5-10, 37-39]. In addition, metal complexes have shown to possess biological activity [11-21] and there are several drugs that are metal complexes in nature [12-13].

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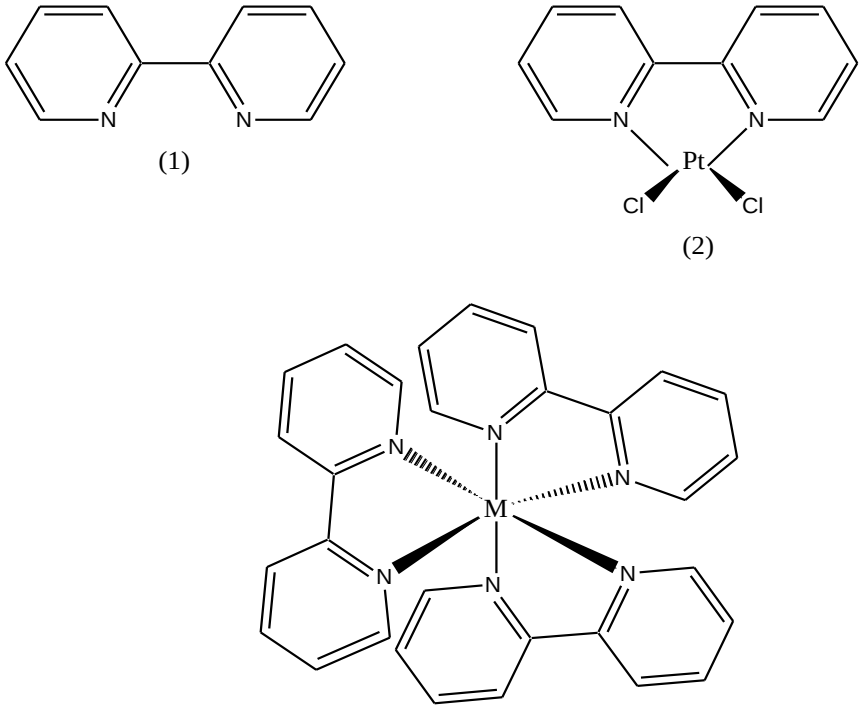
As part of our research program objectives, to find potent and selective antimicrobials of synthetic type that can be used locally and internationally, we report here the antimicrobial activity of 2, 2-Bipyridine dichloroplatinum (II), $C_{10}H_8Cl_2N_2Pt$ (2) against pathogenic microorganisms, *Candida albicans*, *S. aureus* and *E. coli*. Neutral mixed-ligand complexes of 2, 2'-bipyridinedichloroplatinum(II) with dianionic aromatic chelating ligands as potential photosensitizers have been reported [20].

The synthesis and spectroscopic studies of potential antiviral [Pt(2,2'-bipyridyl)(amino acid)] Cl complexes have also been reported [21]. However, the antimicrobial activities of 2, 2-Bipyridinedichloro platinum (II), $C_{10}H_8Cl_2N_2Pt$ (2) against pathogenic microorganisms has not been reported to date. We have previously reported neutral molecules as antimicrobial agents [22-27, 28].

2, 2'- bipyridine (bipy), an organic bidentate chelating ligand with general formula $C_{10}H_8N_2$, forms complexes with many transition metals such as ruthenium and platinum. Some complexes of 2, 2' bipyridine include $Mo(CO)_4(bipy)$, $RuCl_2(bipy)_2$, $Fe(bipy)_3)^{2+}$. In *tris* (bipy) complexes, $[M(bipy)_3]n+$ (M = metal ion: Cr, Fe, Co, Ru, Rh, three bipyridine molecules coordinate to a metal ion (3). These complexes are six coordinate and are octahedrally shaped.

Platinum is a silvery white malleable ductile transition metal and the third element of group 10. It is found in certain copper and nickel ores from which it is recovered during refining. It is resistant to oxidation and is not attacked by acids, except *aqua regia* or alkalis. It is used as a catalyst for ammonia oxidation and in catalytic converters and as thermocouples [31-32].



(1) (2) (3)

FIG. 1.0. 2, 2' BIPYRIDINE, 2, 2-BIPYRIDINEDICHLOROPLATINUM (II), $C_{10}H_8CL_2N_2PT$ AND *TRIS* (BIPY) COMPLEX

E. coli can cause several intestinal and extra intestinal infections such as urinary tract infections, meningitis, peritonitis, mastitis, septicemia and gram-negative pneumonia[33-34]. It also causes gastroenteritis and haemorrhagic colitis. *E. coli* can affect all age groups and causes more than 20,000 infections and as many 250 deaths each year in the USA alone [33-34].

Staphylococcus aureus, the yellow type induce furuncles (boils), carbuncles (a collection of furuncles) [35]. In infants, *Staphylococcus aureus* can cause a severe disease Staphylococcal scalded skin syndrome (SSSS). *Staphylococcal endocarditis* (infection of the heart valves) and pneumonia may be fatal. *Staphylococcus aureus* can cause food poisoning.

Candida albicans, a diploid fungus (a form of yeast) and is a casual agent of opportunistic oral and genital infections in humans [36]. It is responsible for the infectious disease, *candidiasis*, thrush etc.

PROCEDURE: Compound (2), commercially available was made up to a concentration of 0.1 mg/L in C_2H_5OH and its antimicrobial activity was investigated using the Well Diffusion and Poison Plate assay under asceptic conditions [29-30]. These are described in previously published paper, [5-11, 15, 22-27, 37-39] and don't need further description here.

RESULTS: Results obtained are tabulated in **tables 1-4** below as follows:

TABLE 1: RANDOM CHECK FOR REFERENCE STANDARD ANTIBIOTICS: NYSTATIN AND AMPICILLIN

Sample	*E. coli*		*Staphylococcus aureus*		*Candida albicans*	
	Average of Triplicates	Area of Inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$
	2.63	5.43	2.4	4.15	2.5	4.91

TABLE 2: POISON PLATE, ED_{50} VALUE AND THE AREA OF ZONE OF INHIBITION FOR COMPOUND (2)

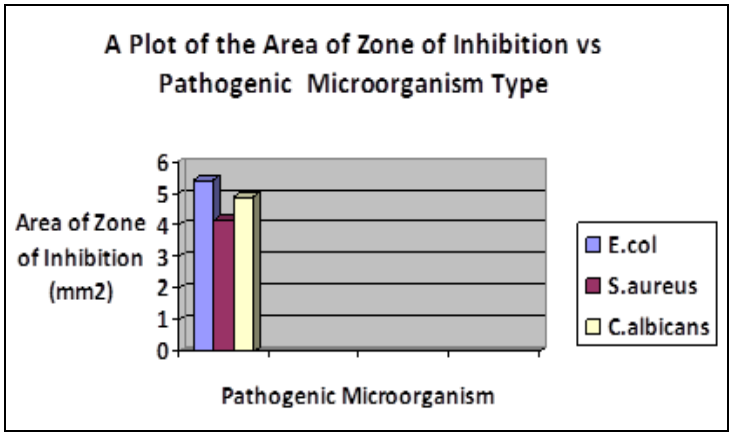
Sample	*E. coli*		*Staphylococcus aureus*		*Candida albicans*	
	Average of Triplicates	Area of Inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$
	2.43	4.64	2.63	5.43	2.7	5.72

TABLE 3: WELL DIFFUSION: ED_{50} VALUE AND AREA OF ZONE OF INHIBITION FOR COMPOUND (2)

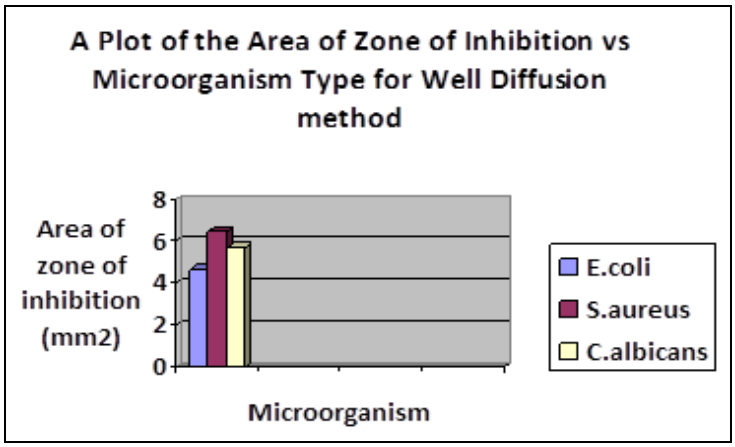
Sample	*E.coli*		*Staphylococcus aureus*		*Candida albicans*	
	Average of Triplicates, ED_{50}	Area of Inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$	Average of Triplicates, ED_{50}	Area of inhibition $(mm)^2$
	2.4	4.64	2.0	6.47	2.7	5.72

TABLE 4: MEAN DIAMETER, STANDARD DEVIATION (SD) AND THE AREA OF ZONE OF INHIBITION FOR COMPOUND (2)

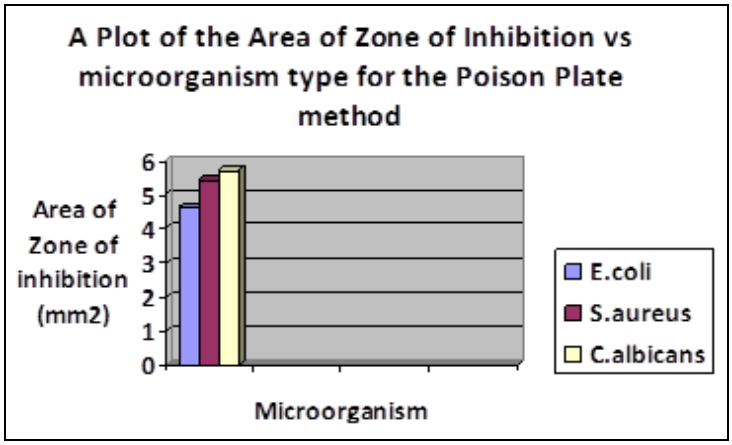
Microorganisms	Type of Experiment	Compound Type	Diameter of zone of inhibition (mm) as triplicates	Mean diameter of zone of inhibition with Standard Deviation	Area of Zone of inhibition $(mm)^2$
E. coli	Reference (Positive control)	(2)	2,5, 2.8, 2.6	2.63 ± 0.207	5.43
S.aureus	Reference (Positive control)	(2)	2.1, 2.4, 2.4	2.3 ± 0.173	4.15
C. albicans	Reference (Positive control)	(2)	2.8, 2.7, 2.0	2.5 ± 0.435	4.91
E. coli	Poison Plate	(2)	2.2, 2.4, 2.7	2.43 ± 0.259	4.64
S .aureus	Poison Plate	(2)	2.3, 2.7, 2.9	2.63 ± 0.31	5.43
C. albicans	Poison Plate	(2)	2.7, 2.8, 2.6	2.7 ± 0.1	5.72
E. coli	Well Diffusion	(2)	2.3, 2.4, 2.6	2.43 ± 0.1528	4.64
S. aureus	Well Diffusion	(2)	3.0, 2.9, 2.7	2.86 ± 0.153	6.47
C. albicans	Well Diffusion	(2)	2.7, 2.6, 2.8	2.7 ± 0.1	5.72



GRAPH 1: A PLOT OF THE AREA OF ZONE OF INHIBITION VS. PATHOGENIC MICROORGANISM FOR REFERENCE EXPERIMENT



GRAPH 2: A PLOT OF THE AREA OF ZONE OF INHIBITION VS MICROORGANISM TYPE FOR DISC DIFFUSION



GRAPH 3: A PLOT OF THE AREA OF ZONE OF INHIBITION VS MICROORGANISM TYPE FOR POISON PLATE

DISCUSSION: Antimicrobial activity of compound (2) was investigated using the Well diffusion and Poison Plate microbial assays, [29-30]. The zone of inhibition (mm) is quoted at the ED_{50} value and as the area of inhibition (mm^2), **Table 1, 2 and 3**. Also, the Standard Deviation (SD) of the mean is expressed in **Table 4**. Each test was performed in triplicates and expressed as the mean.

The zone of inhibition in mm at the ED_{50} value was measured and converted into the area of inhibition, mm^2. ED_{50} is the effective dose concentration of the sample required to kill 50% of the pathogen growth [29]. Initially, a Random Check of the microorganism potency against standard antibiotic Nystatin and Ampicillin was investigated and are presented in Table 1.

Also, to check whether solvents had any effect on antimicrobial activity, another experiment was conducted. Negligible zone of inhibition (< 5mm) was observed. Thus, the area of zone of inhibition observed was due to compound (2) antimicrobial properties rather than to a solvent effect. Ampicillin and Nystatin were used as the reference (positive control) for bacterial (*S. aureus* and *E. coli*) and fungal species (*C. albicans*) respectively. *E. coli* produces a larger zone of inhibition compared with *S. aureus*.

The above results indicate that for both methods, the susceptibility of the microorganism to a solution of compound (2) followed the sequence: *S. aureus* > *C. albicans* > *E. coli.* This trend is opposite to our previously published paper, showing that the metal does modulate antimicrobial selectivity of a complex [15].

For example, for the Poison plate method, at an ED_{50} value of 2.63 mm and 2.7 mm, area of zone of inhibition of 5.43 mm^2 and 5.72 mm^2 were obtained for *S.aureus* and *C. albicans* respectively. In comparison, the Well-Diffusion assay at an ED_{50} value of 2.86mm and 2.7 mm, induces area of zone of inhibition of 6.47 mm^2 and 5.72 mm^2 against *S.aureus* and *C. albicans* respectively.

Thus, both methods support the antimicrobial susceptibility selectivity trend mentioned above. For comparison purposes, compound (2) antimicrobial potency has been found to be greater than that for standard antibiotics Nystatin and Ampicillin against *S. aureus* and *C. albicans* but less than against *E. coli*.

CONCLUSION: In conclusion, based on the above results, future work should target the syntheses of compounds incorporating the 2, 2-bipyridinedichloro platinum (II) unit as an important moiety of the synthetic skeleton of antimicrobil drugs since antimicrobial selectivity and potency greater than that against standard antibiotics have been achieved.

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