Antimicrobial Activity of New Cu(II) and Zn(II) Heteroleptic Complexes Containing Bipyridine, Benzimidazole and Thiadiazole Derivatives

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The synthesis and characterization of two new heteroleptic complexes of [M(II)L(tdz)$_2$] type (where M(II) is Cu or Zn ; L = 4,4'-dimethyl-2,2'—bipyridine or 2-hydroxymethyl-benzimidazole and tdz is 2,5-dimercapto-1,3,4-thiadiazole) have been described. The structures of the complexes were elucidated by elemental analysis, electronic absorption and infrared spectra, as well as molar electrical conductivities. All complexes are tetra-coordinated with N2S2 and NOS2 environment respectively in a square planar geometry and exhibit a strong ligand-to-ligand charge transfer band in 450-475 nm visible range. The biological (antibacterial and antifungal) activity of the synthesized complexes was compared with that of the heterocyclic ligands. The results indicated that the Cu(II) complexes have good biological activity similar or even higher than the clinical antibiotics.

Keywords: 2-hydroxymethyl-benzimidazole, 4,4'-dimethyl-bipyridine, 2,5-dimercapto-1,3,4-thiadiazole, antibacterial activity, antifungal activity

The increasing prevalence of antibiotic-resistant microbial strains leads to the need to find alternative methods to combat pathological potential they represent. The non-conventional methods of fighting against various microbial strains include the use of antibacterial nanoparticles (Ag, Au, ZnO etc), new organic compounds or complex compounds of known antimicrobial agents [1-19]. Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities and these are well-documented in literature. Several thousands of benzimidazole analogues have been synthesized and screened for pharmacological activity. These heterocyclic systems have different activities as they can act as bacteriostats or bactericides, as well as fungicides, and they are present in numerous, antiparasitic, antitumoral and antiviral drugs exhibiting significant activity against several viruses such as HIV, herpes (HSV-1), RNA, influenza, and human cytomegalovirus (HCMV) [20]. In addition, some of them present appreciable antiprotozoal activity. They show selective neuropeptides YY1 receptor antagonists, potent inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors, antitumor agents, gamma-amino butyric acid (GABA) agonists, and 5-HT3 antagonists. In addition, benzimidazoles are very important intermediates in organic synthesis; vitamin B12 constitutes a milestone in the chemistry of benzimidazoles [21].

The benzimidazole ring is an important pharmacophore in modern drug discovery as structural isosteres of nucleosides, this bioisosteric effect being responsible for improving drug potency and selectivity. The synthesis of novel benzimidazole derivatives remains a focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, show easy interactions with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in human [22].

1,3,4-thiadiazole exhibit diverse biological activities, possibly due to the present of =N-C-S moiety and present important applications in many pharmaceutical, biological and analytical field [23].

The azole ring has been demonstrated to be one of the most important pharmacophores for antifungal activity, and both the toxicity and activity of azole antifungal agents are mainly attributed to coordination binding of the nitrogen atom of the azole ring to the iron atom of heme [24]. Thiadiazole derivatives have occupied a unique position in medicinal chemistry: the naturally occurring B6-vitamins pyridoxine, pyrodoxal, pyridoxamine, and codecarbaxylase contain a thiadiazole nucleus.

Derivatives of 1,3,4-thiadiazoles have been recognized as molecules with potential antimicrobial utility most of the molecules studied contain substituents on the 2 and 5 position of the thiadiazole ring [25,26]. The synthesis of compounds containing 1,3,4- thiadiazole has attracted widespread attention due to their diverse applications as antifungal, anticancer agents, antibacterial agents, anti-inflammatory drugs, antidepressants [27], carbonic anhydrase inhibitors, anti-*Helicobacter pylori* agents, antitrypanosomals and leishmanicidal agents [28-30].

2,5-Dimercapto-1,3,4-thiadiazole (DMcT), also known as bismuthiol I, is used in synthesizing salts of strong bases, heavy metal salts, and polymers; as an ingredient in flame and scorch retardants; in cross linking halogenated polymers; as an additive in lubricating oils and greases; as a corrosion inhibitor; in electrode compositions; in photography; as an adhesion improver; as an intermediate or starting material for pharmaceuticals and dyes; as a chelating agent used to determine metals in samples; in purifying and treating waste; and as a biocide.

2,2'-bipyridine and its 4,4' derivatives have been intensively used due to their high chemical stability and redox properties as ligands for complex compounds synthesis with various biological activity. By complexation of the nitrogen atoms, the pyridinic ring electrons become more delocalized and can be involved in stacking interactions with other aromatic systems [31-33].

Heterocyclic moieties can be found in a large number of compounds that display biological activity. The biological

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activity of the compounds is mainly dependent on their molecular structures [34-40].

Understanding the role of chemical structure in biological activity is very important. Prediction of biological and physico-chemical properties of molecules based on their structure represents one of the fundamental objectives of theoretical chemistry.

Intense efforts are dedicated to synthesize new derivatives of bioisosteric heterocyclic compounds with improved potency and selectivity against microorganisms. Another approach is combining the biological activity of a known compound with an essential metal [41-49].

The possible therapeutic properties of the metal complexes with biological active molecules have also excited wide interest [50-57]. It was found that the complexes of transition metals, especially chelates with biological active molecules showed larger antimicrobial activity than the ligands applied alone. This is usually assigned to their higher lipophilicity that eases the penetration of cells wall.

In the present paper we report the synthesis and characterization of two new heteroleptic complexes of [M(II)L(tdz)2] type (where M(II) is Cu or Zn ; L = 4,4'-dimethyl-2,2'-bipyridine (bpy) or 2-hydroxymethyl-benzimidazole (bzd) and tdz is 2,5-dimercapto-1,3,4-thiadiazole) and their antibacterial and antifungal activity against Gram negative and Gram positive bacteria and fungi tested. With this strategy, we expect that the new compounds present a synergetic effect of their antimicrobial power and much wider biological activity, than the components alone.

Experimental part

All chemicals were purchased from Sigma-Aldrich and used as received.

Synthesis of 2,5-dimercapto-1,3,4-thiadiazole [30]

A mixture of hydrazine hydrate (99%) (5 mL, 0.02 mol) and carbon disulphide (15 mL, 0.02 mol) with dry pyridine (50 mL) was refluxed for 5 h. The excess solvent was distilled off and the resulting solid was separated out by adding 25 mL water and 5 mL hydrochloric acid. The mixture was then filtered and the solid was recrystallized from ethanol.

Calc: C: 15,99%, N: 18,65%, S: 64,03%

Found: C: 15,96%, N: 18,68%, S: 64,08%

Synthesis of 2-hydroxybenzendithiol [23]

Synthesis of 2-hydroxymethyl-benzimidazole was achieved in two stages: condensation in reflux of o-phenylendiamine with glycolic acid in HCl solution and neutralization with conc. NH_3 at *p*H = 8.

A solution of 500 mg (4.62 mmol) of o-phenylenediamine and 703 mg (9.24 mmol) of glycolic acid in 10 mL of 4N HCl was heated at 100°C for 45 min. The reaction mixture was cooled and neutralized to pH = 8 with ammonia. The solution was filtered immediately and then chilled in an ice-bath resulting in white crystals.

Note: the reaction mixture must be filtered while still warm from the neutralization, otherwise the crystallization occurs before filtration and the product will be grey in colour. The crystallized product was filtered and air-dried. Recrystallization was carried out from hot ethylacetate and the pure-white crystals were filtered off and dried.

Calc: C: 64.85%, N: 18,91%, H: 5.44%

Found: C: 64.81%, N: 18,95%, H: 5.46%

Synthesis of [M(bpy)(tdz)$_2$] complexes

A solution of 4,4'-dimethyl-2,2'-bipyridine in dichlorethan was mixed with a methanolic solution of $CuCl_2 \cdot 4H_2O$ and H_2tdz (in 1:1:1 molar ratio) and then boiled in reflux at 60°C for 3 h. From the blue-green solution initially obtained it was separated at slowly evaporation of the solvents (room temperature) a light brown compound that was filtered, washed with methanol and chloroform and then dried in vacuum on P_4O_{10}.

The light pink complex [Zn(bpy)(tdz)$_2$] was obtained in similar conditions from $Zn(CH_3COO)_2$.

Analytical data for $CuC_{16}N_6S_6H_{10}$: Calcd: Cu 11.72 %; S 35.45 % Found Cu 11.28 %; S 36.12 %

Analytical data for $ZnC_{16}N_6S_6H_{10}$: Calcd: Zn 11.79 %; S 35.48 % Found Zn 11.34 %; S 36.05 %

Synthesis of [M(bzd)(tdz)$_2$] complexes

A solution of 2-hydroxymethylbenzimidazole in methanol was mixed with a methanolic solution of $CuCl_2 \cdot 4H_2O$ and H_2tdz (in M(II) : bzd : H_2tdz = 1 : 1 : 1 molar ratio) and boiled at 80°C for one hour. From the blue-green solution initially obtained it was separated at slowly evaporation of the solvents (room temperature) a brown green compound that was filtered, washed with methanol and chloroform and then dried in vacuum on P_4O_{10}.

The light pink complex [Zn(bzd)(tdz)$_2$] was obtained in similar conditions from $Zn(CH_3COO)_2$.

Analytical data for $MC_{12}N_6S_6H_{12}$: Calcd: Cu 12.82 %; S 38.75 % Found Cu 11.25 %; S 39.15 %

Analytical data for $ZnC_{12}N_6S_6H_{12}$: Calcd: Zn 11.79 %; S 35.48 % Found Zn 11.34 %; S 36.05 %

Elemental analyses were performed by means of *EuroEA elemental* analysers *EA3000.*

FTIR spectra were recorded on Bruker Tensor 27 apparatus, using KBr pellets technique.

UV-Vis reflectance spectra were recorded on Able Jasco V560 spectrophotometer.

Electrical conductivities were recorded in DMSO solutions at 25°C, with an OK 102/1 Radelkis Conductometer with a 0.1 S – 0.5 S measuring range.

Magnetic measurements were carried out using a Faraday balance at room temperature using Mohr salt as standard.

Biological determinations

All the newly synthesized compounds were evaluated for their in vitro antibacterial activity against Gram negative bacteria strains: *Escherichia coli* (EC) (ATCC 10536), *Salmonella Typhimurium* (ST) (ATCC 13311), *Proteus Vulgaris* (PV) (ATCC 29905), Gram positive bacteria strains: *Staphylococcus aureus* (SA) (ATCC 6538) *Bacillus Cereus* (BC) (ATCC 10876), *Bacillus Subtilis* (BS) (PTCC 1023); *Streptococcus Pneumoniae* (SP) (ATCC 6305), *Enterococcus Faecalis* (EF) (ATCC 29212) and fungi strains *Candida albicans* (CA) (ATCC 10231); *Aspergillus Niger* (AN) (ATCC 22343); *Saccharomyces Cerevisiae* (SC) (ATCC 204508).

Antibacterial activities of the compounds were tested by the disc-diffusion method under standard conditions using agar medium. The investigated isolate of Gram-negative, Gram-positive bacterial and fungal strains was pre-seeded in the Petri dishes with nutrient broth. The compounds have been tested in solid phase in acetone solution (concentration 1%). Acetone is highly volatile and its effect on microorganisms is therefore negligible.

The discs of Millipore filter paper (diameter 5 mm) were impregnated (200μg/microdisc) with acetone solution of tested compound.

Complex compound	λ , nm (cm^{-1})	Assignment	μ_{eff} (MB)	Λ_m ($\Omega^{-1}cm^2mol^{-1}$)
[Cu(bpy)(tdz)$_2$]	240 (41 666) 310 (32 258) 450 (22 223) 650 (15 385)	bpy band tdz band LLCT (tdz → bpy) broad band d-d $d_{xy} \rightarrow d_{x2-y2}$ $d_{xz,yz} \rightarrow d_{x2-y2}$	1.85	20
[Zn(bpy)(tdz)$_2$]	240(41 666) 310 (32 258) 470 (21 277)	bpy band tdz band LLCT (tdz → bpy)	diamagnetic	25
[Cu(bzd)(tdz)$_2$]	260 (38 462) 310 (32 258) 450 (22 223) 690 (14 493)	bzd band tdz band LLCT (tdz→ bzd) broad band d-d $d_{xy} \rightarrow d_{x2-y2}$ $d_{xz,yz} \rightarrow d_{x2-y2}$	2.08	22
[Zn(bzd)(tdz)$_2$]	270 (37 037) 300 (33 330) 475 (21 053)	bzd band tdz band LLCT (tdz→ bzd)	diamagnetic	24

Table 1
ELECTRONIC SPECTRA, MAGNETIC MOMENTUM AND MOLAR ELECTRICAL CONDUCTIVITY FOR SYNTHESIZED COMPLEX COMPOUNDS

After incubation for 24 h in thermostat at 37°C, inhibition (sterile) zone diameters (including disc) were measured (in mm) and compared with standard antibiotics control samples, specific for each type of microorganism. An inhibition zone diameter over 8 mm indicates that the tested compound is active against microorganism.

Parallel with the antimicrobial investigations of the complexes, the free ligands were also tested. Every test was done in three replications.

Results and discussions

Molar electrical conductivity for all complexes in DMF solution (10^{-3}M, 25°C) established their non-electrolyte nature (table 1).

Electronic spectra bands recorded in reflection in 200-900 nm range and magnetic moments values calculated from experimentally measured magnetic susceptibility for all synthesized complex compounds are presented in table 1.

Electronic spectra of copper complex compounds exhibit in visible range a *d-d* broad band with a maximum at 650 nm and 690 nm respectively, corresponding to a square-planar coordination of Cu(II) ion. Magnetic momentum values of 1.85 MB and 2.08 MB respectively support this assumption of d^9 ion in square-planar geometry. Electronic spectra also show in UV range the characteristic bands for the ligands (strong absorption band at about 240 nm attributed to the ligand centred π-π* transitions on the 4,4'-dimethyl-bipyrydine, one band at 310 nm due to the π- π* of C=S on 2,5-dimercapto-1,3,4-thiadiazole and one band at 260 nm assigned to π- π* transition on 2-hydroxymethyl-benzimidazole). A charge transfer band (CT) ligand to metal (L→M) or ligand-to-ligand (L→L) with a maximum at 450 nm occurs in electronic spectra of both copper complexes.

Electronic spectra of zinc complex compounds presents in UV range the two characteristic bands for ligands and ligand to ligand charge transfer band at 450 nm and 470 nm respectively.

Compound	ν_{NH}	$\nu_{Carom-N}$ $\nu_{as,simCH3}$ δ_{CH3}, ν_{C-H}	ν_{S-H}	$\nu_{C=N}$	$\nu_{C=C}$	$\nu_{Py\ cycle}$ ν_{N-N}	$\nu_{tdz\ cycle}$ $\nu_{S-C=N}$ ν_{C-S-C} $\nu_{asS-C=S}$ $\nu_{=C-S-C=}$	$\nu_{Py\ cycle}$ Δ,Γ
bpy		2960 2850	-	1650	1556	1480;1260 1440;1240		675 420
H_2tdz	3200	2852	2480			1263	1585;1320 1040; 740	
[Cu(bpy)(tdz)$_2$]	3070	2960 2850	-	1665	1560	1475;1443 1246	1500,1116 1046,773	480 (ν_{Cu-S})
[Zn(bpy)(tdz)$_2$]	3060	2920 2850	-	1675	1559	1470;1445 1243	1498,1110 1056,770	512 450 (ν_{Zn-S})

Table 2
CHARACTERISTIC IR FREQUENCIES FROM bpy, tdz, [M(II)(bpy)(tdz)$_2$] SPECTRA AND THEIR ASSIGNMENT

Compound	$\nu_{as,sOH}$	$\nu_{as,sNH}$	ν_{S-H}	bzd cycle $\nu_{C=N}$ δ_{H-O-H}	tdz cycle $\nu_{S-C=N}$ ν_{C-S-C} $\nu_{asS-C=S}$ $\nu_{=C-S-C=}$	ν_{C-OH}	$\nu_{Carom-N}$ δ_{C-OH}
bzd	3350 3450	3230 3160		1670 1620		1150	1265 1210
H_2tdz		3200	2480	-	1585;1320 1040; 740	-	-
[Cu(bzd)(tdz)$_2$]	3300	3052	-	1650 1615	1500,1116 1046,773	1120	1250 1200
[Zn(bzd)(tdz)$_2$]	3290	3060	-	1653 1614	1500,1116 1046,773	1120	1250 1200

Table 3
CHARACTERISTIC IR FREQUENCIES FROM bzd, tdz, [M(II)(bzd)(tdz)$_2$] SPECTRA AND THEIR ASSIGNMENT

A comparative study of FTIR spectra of the complex compounds with FTIR spectra of ligands provides meaningful information about the coordination sites of the ligands (table 2, 3).

Usually bpy coordinates to metals in a bidentate mode by the two heterocyclic nitrogen atoms. In case of bzd bonding occurs through the nitrogen atom in a monodentate form, regardless of the metal ion or the heteroatom (N, S, O) present in the molecule, or in a bidentate mode, giving place to a variety of metal-ligand coordination modes. Tdz can coordinate monodentate to one metal ion or bidentate as bridge between two metal ions.

By comparison between IR spectra of heteroleptic complex compounds $[M(bpy)(tdz)_2]$ and free ligands bpy and H_2tdz several conclusions can be drawn:

- IR spectra of both complex compounds contain frequencies belonging to both ligands;
- in the region 1570-1670 cm^{-1} in the spectra of complexes all bands assigned to $\nu(C=C)$, $\nu(C=N)$ are shifted towards higher frequencies in comparison to unbounded bpy what indicates that these N-donors are coordinated to metal;
- the spectroscopic signature of tdz is complicated by simultaneous vibrational coupling between bands of similar frequency (especially those involving thione moieties) and extensive delocalization of electron density in the heterocycle due to the large number of possible resonance structures. The FTIR spectrum of tzd showed a medium intensity band at 1585 cm^{-1} that could correspond with (C=N) stretching near 1,3,4-thiadiazole ring [30]. In this spectrum, there are two other characteristic bands at 3200 and 2480 cm^{-1} due to (N-H) and (S-H) stretching vibrations, respectively. From this, we can say that this free ligand can exist in the thiol and thion form. The complex compounds did not show any (SH) stretching band in the region (2300-2500) cm^{-1}, confirming the deprotonation of thiol group and bonding of sulphur to the metal ion is confirmed by the presence of characteristic band ν_{M-S}. Metal complexes exhibit small shift to a lower region for the two (C=N) stretching, which were weakened as well by sulphur complexation.

Considering all these, we can conclude that in both complex compounds bpy is bidentate coordinated and tdz coordinates by deprotonated sulphur of exocyclic thiol group.

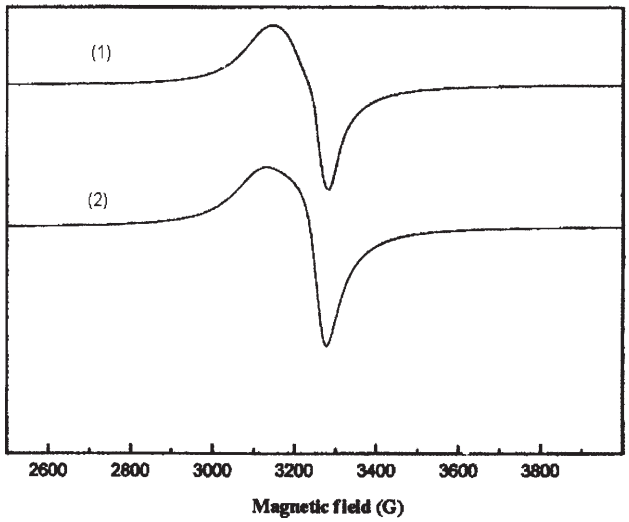

Fig. 1. ESR spectra of (1) $[Cu(bpy)(tdz)_2]$ and (2)$[Cu(bzd)(tdz)_2]$ complexes

By comparison between IR spectra of heteroleptic complex compounds $[M(bzd)(tdz)_2]$ and free ligands bzd and H_2tdz several conclusions can be drawn:

- IR spectra of both complex compounds contain frequencies belonging to both ligands.
- lower shift of ν_{OH} and ν_{C-OH} bands belonging to bzd in the complex compounds spectra is a proof of OH group coordination to metallic ion. Also, lower shift of $\nu_{Carom-N}$ and $\nu_{C=N}$ bands indicate that nitrogen coordinate. The presence of several bands in the 400– 500 cm^{-1} region in both complexes should suggest the coordination of oxygen and nitrogen of the ligand to the metal.
- the absence of characteristic ν_{S-H} band of tdz in complex compounds spectra and the lower shift of ν_{C-S} band confine with coordination by S of tdz to the metal.

Considering all these we can conclude that in both complex compounds bzd is N, O bidentate coordinated and tdz coordinates by deprotonated sulphur of exocyclic thiol group.

The X-band ESR spectra of Cu(II) complexes recorded in the solid state are shown in the figure 1.

From the observed g values of Cu(II) complexes at room temperature it is evident that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital and the ground state is $^2B_{1g}$.

The $g_{||} < 2.3$ value confirms the covalent character of the metal-ligand bond. The axial symmetry parameter, G, is less than 4 and indicates considerable exchange interaction in the solid complex.

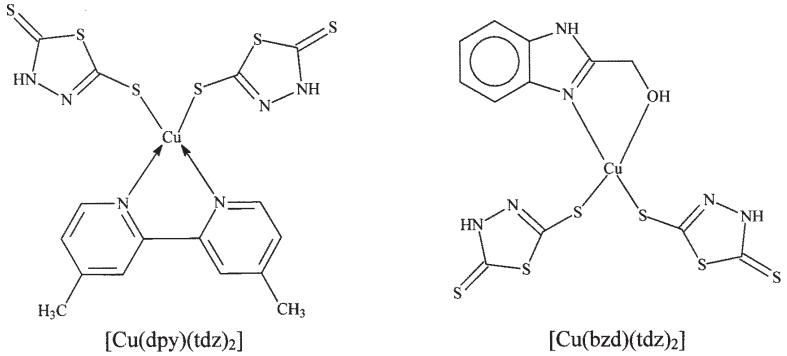

Fig. 2. Probable formula of the complex compounds

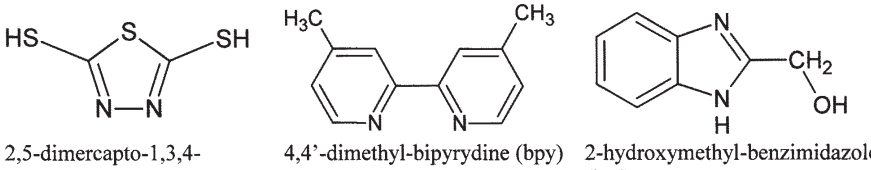

Fig. 3. Ligands formula

Square planar complexes (D_{3h})

Complex (1)	$g_{\parallel} = 2.127$	$g^{\perp}$=2,050	G=2.54
Complex (2)	$g_{\parallel} = 2.139$	$g^{\perp}$=2,053	G=2.62

In the figure 2 are depicted the probable formula of the complex compounds and in figure 3 the formula of ligands.

Biological activity measurements

The tests were aimed to study the antimicrobial activity of four complex compounds and three ligands against pathogenic and conditioned pathogenic strains. With these purpose eight bacteria strains and three fungi, strains have been selected, purified, identified and grown on appropriate culture media.

The obtained results allowed a classification of tested compounds based on their antimicrobial activity against different strains of bacteria and fungi, with the purpose of identifying the specific activity of each complex compound.

The microbiologic studies have been focused on qualitative estimation of the antimicrobial activity and its type for each tested compound: bactericidal, bacteriostatic and fungistatic activity.

Several parameters have been varied: i) the microorganism type; ii) the type of biological active ligand; iii) metallic ions.

Antimicrobial activity has been estimated based on inhibition diameter values (Φ, mm) as:

Inhibition diameter (Φ, mm)	Antimicrobial activity
11-15	week
16-20	medium
>20	strong

The tested strains have been selected based on their different shape (cocci and bacilli), different cellular wall (Gram positive and Gram negative) and fungi that are responsible for most commune human infections.

The results are presented in figures 4-6 and some conclusions can be drawn:

2,5-dimercapto-1,3,4-thiadiazole presents a higher antibacterial and antifungal activity by comparison with 4,4'-dimethyl-bipyrydine and 2-hydroxymethyl-benzimidazole. The same trend is observed for the complex compounds of the three ligands.

Copper complexes exhibit a much higher antimicrobial activity than zinc complexes, up to three fold higher in case of complex compounds of $[M(bzd)(tdz)_2]$ type.

The antibacterial activity is higher against Gram-positive strains, especially against Staphylococcus aureus and Streptococcus Pneumoniae. Compared with Gram-positive bacteria, Gram negative are more resistant against antibodies, because of their impenetrable wall. This outer membrane is composed primarily of lipopolysaccharide molecules and forms a hydrophilic permeability barrier, providing protection against the effect of highly hydrophobic drugs that would normally damage the inner membrane or cell wall. Both copper complexes present strong antimicrobial activity against Gram-negative bacteria and fungi, exception $[Cu(dmdpy)(tdz)_2]$ against ST and $[Cu(hmbzd)(tdz)_2]$ against PV.

The highest antifungal activity presents $[Cu(hmbzd)(tdz)_2]$ against AN.

The lowest values of inhibition diameter are obtained against the gram-positive bacteria BC for all tested compounds.

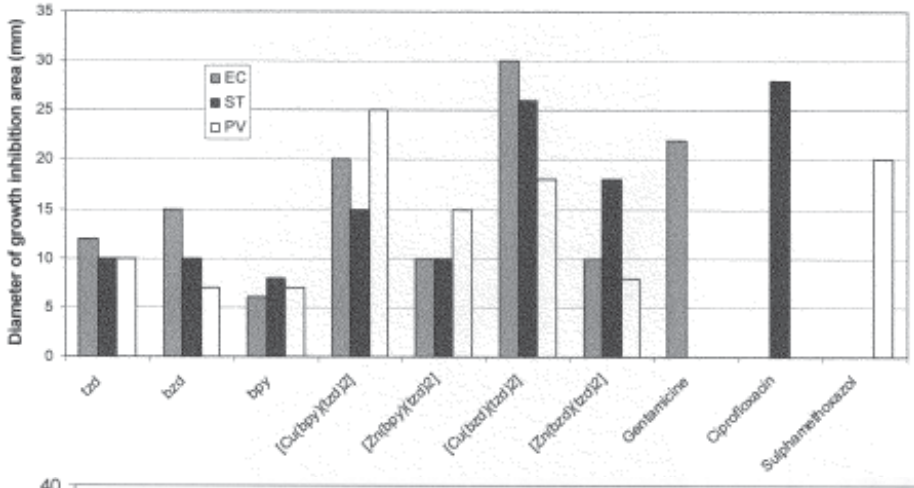

Fig. 4. Antibacterial activity against Gram-negative bacteria

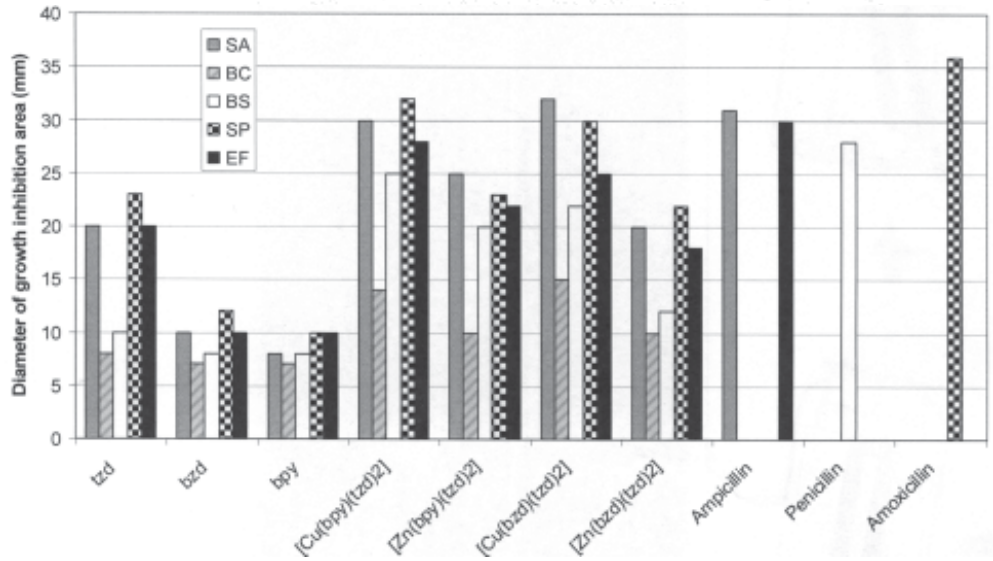

Fig. 5. Antibacterial activity against Gram-positive bacteria

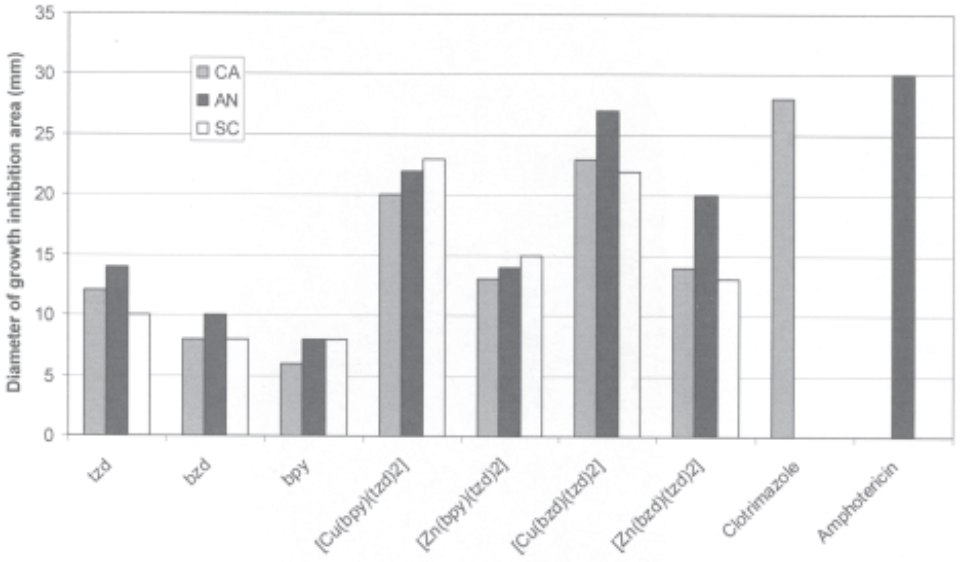

Fig. 6. Antifungal activity

By comparing the antimicrobial activity of the ligands and their complexes, it was found that the complexes were more effective against all the bacteria. In some cases, a synergetic effect is observed for complex compounds. This fact suggests that coordinated metallic ion may play a significant role for antimicrobial activity. This can be explained in terms of the chelation theory, which states that a decrease in the polarizability of the metal can change the lipophilicity of the complexes. It is well known that this property is responsible for the transport and distribution of drugs in a biological system. However, this can also be a result of delocalization of electrons of heterocyclic ring by complexation that is known that increase the antimicrobial activity of the compound [58,59]. Of importance for their biological activity could be the square planar geometry of the complex compounds; heteroleptic complex compounds of Ni(II) having square planar geometries and charge transfer between different ligands showed a biological activity being regarded as metalloenzyme model [60,61] and also an increase antibacterial activity by comparison with antibacterial activity of ligands [62,63].

Conclusions

Heteroleptic complex compounds of two essential metallic ions Cu and Zn with three biological active heterocyclic compounds 2,5-dimercapto-1,3,4-thiadiazole, 2-hydroxymethylbenzimidazole and 4,4'-dimethyl-bipyridine have been synthesized and characterized by means of elemental analysis, electronic absorption and infrared spectra, as well as molar electrical conductivities. Their antibacterial and antifungal activity has been measured as inhibition diameter and the best results have been obtained in case of copper complexes which display a higher antibacterial activity than the corresponding antibiotic for EC and SA. This behaviour can be due to a synergetic effect of the both ligands as well as the presence of copper ion.

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