Antimicrobial Activity of Some 1,3,4-Thiadiazole Metal Complexes

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Abstract

Biological activities of Cu (II), Pt (IV), Zn (II) and V (IV) metal complexes with 1, 3, 4 – thiadiazole derivatives towards pathogenic bacteria (*Staph. aureus*, *Bacillus cereus*, *Pseudomonas aerogenosa* and *Escherichia coli*) and the fungus *Candida albicans* were studied. The investigation was conducted using plate agar method. Sulfadiazine was used as standard drug in this study. The results were referred to that the biological activities of the studied compounds are more effective than sulfadiazine. The minimum effective dose of the studied compounds against of the named bacteria was 50µg/ml, while the minimum effective dose of sulfadiazine was 100µg/ml. Moreover, *Candida albicans* was affected by all the studied compounds at 50µg/ml, but there is no significant effect of sulfadiazine toward *Candida albicans* even at the highest dose, 200µg/ml.

Keyword: biological activity, thiadiazole derivative, thiadiazole complexes, sulfadiazine.

Introduction

Thiadiazoles have been of a great interest as antitumor compounds for several years [1, 2]. Studies show that the fused derivatives of triazole and thia-diazole have various biological activities such as anti-bacterial, antifungal, antiviral, antitumor, and anti-inflammatory activities [3-6]. In more recent study, a series of 3, 6 disubstituted 1,2,4-triazole and 1,3,4- thiadiazole were prepared and estimated in their cytotoxicity against breast and ovarian human cell lines and other biological actvities [7-12].

The degree of toxicity for some new 1,3, 4-thiadiazole and 1, 2, 4- triazole derivatives was established and the potential anti-inflammatory activity for these compounds was also investigated [13]. Thiadiazole derivatives are well known to have a number of biological and pharmacological activities. Significant antimicrobial activities were observed for members of thiadiazole derivatives, which were prepared by incorporation of fluorobenzothiazole with 1,3,4 – thia-diazole derivatives [14].

The improvement in the method-logical study of heterocyclic compounds leads to the progress in synthesis of such compounds with high biological activity. It was reported that many thiadiazole and triazole derivatives have biological activity, with their antibacterial [15-17] and antifungal [18-19] action being notable. Recently researches were established an analgesic [20] and anti-inflammatory activity [21-22] for these heterocycles.

Asma and coworkers [23] were synthesized 2-N-arylimino -2, 3- dihydro 1,3,4- thiadiazole. A high Antimicrobial activity was found for the prepared compounds using the diffusion agar technique. In another study, various biological activities like antiinflammatory, antidiabetic and antifungal activities of some thaidiazole derivatives were evaluated [24].

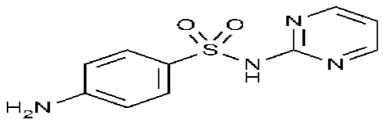
In another study, in vitro antibacterial and antifungal activity of sulfonamides and some of their metal complexes were screened against different types pathogenic bacteria and fungi. The results of this study were confirmed that the activity of complexes was more effective than uncomplexed derivative [25]. Mihai Barbuio and coworkers were synthesized and studied the biological activity for some metal complexes of 5-(2- amino ethyl)-2-amino -1,3,4-thiadiazole, the prepared complexes showed *in vitro* antifungal activity against *Aspergillus* and *Candida spp*. [26]. Zn (II) and Ag (I) complexes of aminobenzolamide-(5- sulfanilylamido –1,3,4– nthiadiazole -2-sulfonamide) were evaluated for their antifungal activity. The prepared complexes act as effective agents against several *Aspergillus* and *Candida spp*. in comparison with their ligand. The mechanism of antifungal activity for these complexes was suggested that the complexes act as inhibitors of

phosphomannose isomerase, a key enzyme in the biosynthesis of yeast cell walls [27].

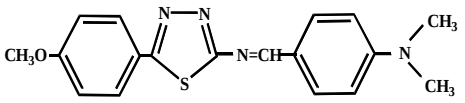
Thiadiazole complexes with Co (II), Cu (II), Ni (II), and Zn (II) were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *pseudomonas aeruginosa*. Anti-bacterial activity of thiadiazole derivative increased upon complexation in comparison to uncomplexed derivative against the tested bacterial species [28].

The aim of this work is to evaluate the biological activity of some thiadiazole metal complexes against selective of pathogenic bacteria and fungi. Sulfa-diazine was used as standard drug in this study.

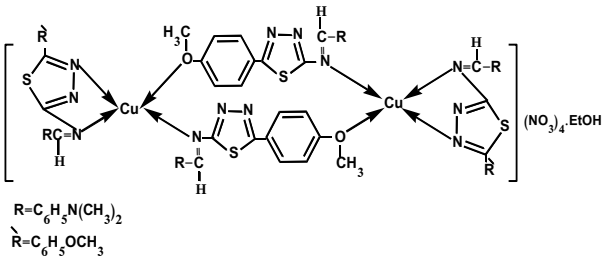
The suggested structural formulas, scientific names and abbreviations of the tested compounds were written as shown in Fig.(1).



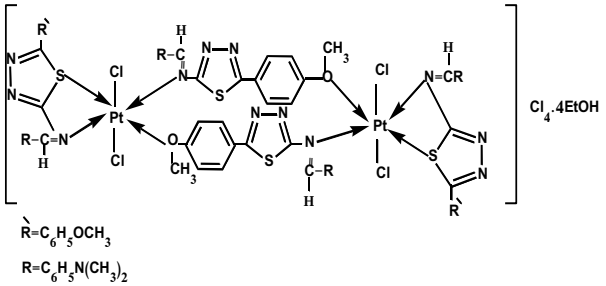
(S.D) (1)



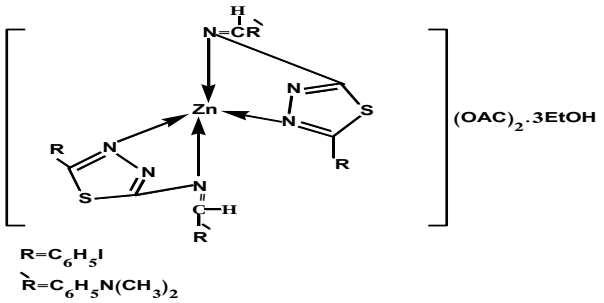
(L_A) (2)



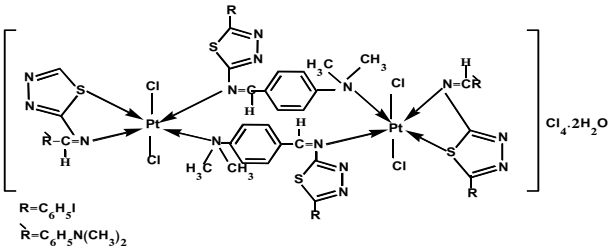
Cu (L_A) (3)



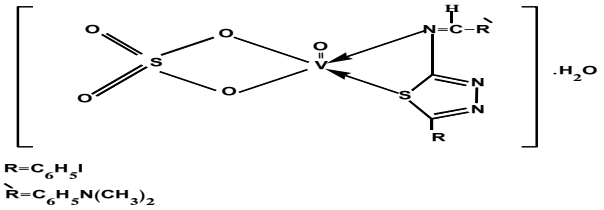
Pt (L_A) (4)



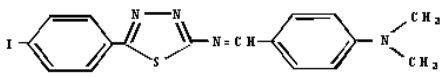
Zn (L_B) (5)



Pt (L_B) (6)



V (L_B) (7)



L_B (8)

Fig. (1) The structural formulas and scientific names of the studied compounds 29,31.

No	*Scientific name*	*abbreviation*
1	Standard drug (sulfadiazine)	S.D
2	2-N (4-N, N-dimethylenzyliden-5-(p-methoxy phenyl) -1, 3, 4-thiadiazole	L_A
3	Bis µ-(2-N (4-N, N-dimethyl benzyliden-5-(p- methoxy phenyl)-1, 3, 4-thia diazole bis (2- N (4 – N, N dimethyl benzyliden – 5 - (p- methoxy phenyl) -1, 3, 4-thiadiazole dicupper (II) nitrate, ethanol	$Cu(L_A)$
4	Bis µ-(2-N (4-N, N-dimethyl benzyliden-5-(p-methoxy phenyl)-1 3,4thiodiazole bis(dichloro(2-N(4-N,N-dimethyl benzyliden-5-(p-methoxyphenyl)-1,3,4-thiodiazole diplatinum (IV) chloride .ethanol	$Pt (L_A)$
5	Bis(2-N(4-N,Ndimethylbenzyliden-5-(p-Iodophenyl)-1,3,4thiodiazole)Zinc (II).acetate.ethanol	$Zn (L_B)$
6	Bis µ-(2-N (4-N, Ndimethylbenzyliden-5-(p-Iodophenyl)-1, 3, 4 thiodiazole bis (dichloro (2-N (4-N, N- dimethyl benzyliden-5-(p-Iodophenyl)-1, 3, 4-thiodiazole diplatinum (IV) chloride.water	$Pt (L_B)$
7	Sulphato(2-N(4-N,N-dimethyl benzyliden-5-(p-Iodo phenyl)-1,3,4thiodiazole Vindyl(IV).water	$V (L_B)$
8	2-N(4-N,Ndimethylbenzyliden-5-(p-Iodophenyl)- 1,3,4thiodiazole	L_B*

* The biological activity 0f L_B (ligand B) was not evaluated in this study.

Experimental

1, 3, 4 – thiadiazole derivatives, (L_A & L_B) and their complexes with Cu (II), Zn (II), Pt (IV) and V (IV) were prepared, purified and characterized as reported in elsewhere [29]. Sulfadiazine of the highest available quality was purchased from Merck Company.

Staphylococcus aureus, Bacillus cereus (gram-positive), *Pseudomonas* and *Escherichia coli* (gram- negative) bacteria, and *Candida albicans* were obtained from the Biotechnology Department, Collage of Science, University of Baghdad. The anti-microbial activity was achieved by plate agar method [30]. Microorganisms were cultured aerobically at 37C for 24 hours in nutrient agar medium. The plates containing agar medium were inoculated by microorganism suspensions, which are spreading on the surface. Each sample (100µl) was placed in a hole (3mm depth, 4 mm diameter) made in the agar layer. Under the same conditions, solutions of sulfadiazine were used as standard. The diameter of inhibition zones was measured using a ruler with an accuracy of 0.5 mm. A control using only inoculation by solvent (DMSO) was also carried out.

Results and Discussion

It was reported that the active concentration 100 µg/ ml and the upper allowed concentration for sulfadiazine drug was 150 µg/ml [31]. Accordingly, four different concentrations of the studied compounds were prepared, 200 µg/ml (C_1), 150 µg/ml (C_2), 100 µg/ml (C_3) and 50 µg/ml (C_4).

It can be seen from Tables (1–4) that sulfadiazine was not effective toward all types of the studied bacteria at concentration lower than100 µg/ ml, on the other hand, the biological activity of the 1, 3, 4-thiadiazole and its complexes against the studied bacteria was detected even at the lower concentration, 50 µg/ ml.

The results also showed that the Pt (L_B) complex was appeared high activity against to *Staph. aureus, Bacillus cereus* and *Escherichia coli* in comparison to other compounds as shown in Tables (1-3). Both Cu (L_A) and V(L_B) complexes were found to be the most active compounds against to *Pseudomonas* as shown in Table (4).

Table (5) showed that there is no significant effect of sulfadiazine against the fungus *Candida albicans* even at the highest dose 200 µg/ ml. However, the biological activity of the studied compounds against *Candida albicans* was detected at the lowest dose 50 µg / ml. The biological activity of Pt (L_B) complex was recorded as the highest one against this type of fungus.

Antibacterial and antifungal activities for some thaidiazoles were evaluated *In vitro*. The variations in their activities were elucidated on the base of the different substituted functional groups [32]. Antibacterial and antifungal activities were reported for another series of thiadiazole compounds. They exhibited moderate to good antibacterial antifungal activity [33]. More recently, a study reported the successful synthesis of fluorinated azoles, which was described as novel classes of microbial agents [34].

The differences in biological activity towards certain types of microorganism between thiadiazole derivative and its complexes may be attributed to synergetic effect that occurred between metal ion and ligand. Therefore, metal ion may be reduce or enhance the biological activity of the prepared compound. However, such behavior is affected by types of bacteria [26, 35].

Conclusion

The biological activity of thiadiazole derivative was increased when it coordinated with metal ion to form metal complex.

Thiadiazoles are considered to be among active antibacterial and antifungal agents. Generally, the basic of anti-bacterial agents action can be attributed to one or more of the following factors: inhibition of essential metallic reactions within the cytoplasm of microorganism, inhibition of cell wall synthesis and inhibition of RNA synthesis which involve the inhibition of replication of DNA. We concluded that the behavior of our compounds in this work were bactericidal not bacteriostatic.

Table (1)

Biological activity of the studied compounds against Staph. Aureus.

No	*Compounds*	*C1*	*C2*	*C3*	*C4*	*Control*
1	S.D.	15mm	12mm	10mm	--	--
2	L_A	20	15	13	10	--
3	Cu (L_A)	21	15	12	10	--
4	Pt (L_A)	17	15	11	10	--
5	Zn (L_B)	15	11	10	9	--
6	Pt(L_B)	23	17	15	12	--
7	V (L_B)	11	10	10	10	--

(--) Effective killing area is not significant.

***** (mm) = Inhibition zone diameter***

Table (2)

Biological activity of the studied compounds against Bacillus cerus.

No	*Compounds*	*C1*	*C2*	*C3*	*C4*	*Control*
1	S.D.	17mm	14mm	12mm	--	--
2	L_A	19	13	11	10	--
3	Cu (L_A)	25	20	15	12	--
4	Pt (L_A)	20	18	16	15	--
5	Zn (L_B)	22	19	15	10	--

6	Pt(L_B)	22	18	18	17	--
7	V (L_B)	15	13	10	10	--

Table (3)

Biological activity of the studied compounds against Escherichia coli.

No	*Compounds*	*C1*	*C2*	*C3*	*C4*	*Control*
1	S.D.	20mm	17mm	15mm	--	--
2	L_A	20	15	13	12	--
3	Cu (L_A)	20	19	15	14	--
4	Pt (L_A)	22	19	18	14	--
5	Zn (L_B)	20	20	17	16	--
6	Pt(L_B)	20	20	20	19	--
7	V (L_B)	21	20	20	15	--

Table (4)

Biological activity of the studied compounds against Pseudomonas aerogenosa.

No	*Compounds*	*C1*	*C2*	*C3*	*C4*	*Control*
1	S.D.	18mm	15mm	13mm	--	--
2	L_A	20	15	13	10	--
3	Cu (L_A)	17	16	15	15	--
4	Pt (L_A)	22	18	15	10	--
5	Zn (L_B)	18	17	15	14	--
6	Pt(L_B)	19	17	16	14	--
7	V (L_B)	23	20	18	15	--

Table (5)

Biological activity of the studied compounds against Candida albicans.

No	*Compounds*	*C1*	*C2*	*C3*	*C4*	*Control*
1	S.D.	-- mm	-- mm	-- mm	-- mm	--
2	L_A	15	14	12	11	--
3	Cu (L_A)	20	19	18	15	--
4	Pt (L_A)	18	17	16	16	--
5	Zn (L_B)	35	30	18	16	--
6	Pt(L_B)	25	23	20	18	--
7	V (L_B)	30	21	21	14	--

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الخلاصة

درست الفعالية الحيوية لمعقدات Cu (II) و Zn (II) و Pt (IV) و V (IV) مع مشتق 4,3,1 – ثايادايازول تجاه عزلات مختارة من البكتريا المرضية (بكتريا المكورات العنقودية والعصوية وزائفة القيح الازرق واشريكيا القولون) وفطر المبيضات البيض.

اجريت الدراسة بطريقة اطباق بتري وباستخدام السلفادايازين كعقار قياسي. اشارت النتائج الى ان الفعالية الحيوية للمركبات المحضرة تجاه البكتريا كانت ذات تاثير عالي في التركيز الاوطأ (50 مايكروغرام/ مل) مقارنة بعقار السلفادايازين الذي لم يكن مؤثرا في تركيز يقل عن 100 مايكروغرام/ مل، فضلا عن تاثيرها على فطر المبيضات البيض الذي لم يؤثر عليه السلفادايازين حتى في التركيز الاعلى، 200 مايكروغرام/ مل.