Anti-bacterial activity for trimethoprim Cefixime and trimethoprim tin And its complexes

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Abstract

Background: The biological assessment of trimethoprim organotin complexes is the subject of the work discussed in this publication.

Objective: The purpose of this project is to investigate the properties of trimethoprim tin complexes and via characterizing their IR and NMR elemental analysis sensitivity.

Material and methods: These complexes combine octahedral ML6 and pyramidal ML5 tin complexes by allowing amino groups present in the medicinal ingredients to react with organotin (IV).

Results: The complex conductivity was also determined for the prepared complexes and displayed low values.

Discussions: Two concentrations of these complexes were screened for antibacterial activity against Gram+ve (*Bacillus Pumilus*) and (*Candida albicans*) by the Agar diffusion disc technique and showed a significant activity.

In conclusion: the synthesized compounds proven to be more effective in inhibiting bacteria such as a) Bacillus Pumilus and b) Candida albicans at two concentrations (1×10-2, 1×10-4M).

Keywords: Tin complex, Trimethoprim, biological activity, tin (IV).

1. Introduction

Trimethoprim, also known as 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine, consists of 2,4-diamino-5-methyl pyrimidine and 3,4,5-trimethoxytoluene. It belongs to the category of chemotherapy drugs called dihydrofolate reductase inhibitors which are applied to treat urinary tract infections and as a prophylactic measure (1). A synthetic antibacterial combination drug called trimethoprim is classified as a bacteriostatic inhibitor because it prevents the bacterial enzyme dihydrofolate reductase from producing tetrahydrofolic acid. In the de novo production of the intermediate thymidine monophosphate, a precursor to the DNA metabolite thymidine triphosphate, which is a crucial precursor (2)? In essence, bacteria must produce folic acid on their own because they are unable to absorb it from the environment. When the enzyme is inhibited, the bacteria are deprived of the nucleotides needed for DNA replication, which can occasionally result in cell death. An earlier stage of the synthesis of folate is inhibited by the combination of trimethoprim and organotin. Through the inhibition of the subsequent steps in folate production, this combination has an in-vitro synergistic antibacterial impact. It's possible that general clinical use won't reveal this benefit (3). Trimethoprim has stronger antibacterial and antifungal effects against various fungi and gram-positive and gram-negative bacteria (4). The synthesis of trimethoprim complexes with (Fe, Cu, Zn, and Sn) (5) was the focus of earlier work on trimethoprim metal complexes. Therefore, this work aimed to study the properties of trimethoprim tin complexes were discussed and identified using IR, NMR, and elemental analysis susceptibility measurements in this study. The ligand's and its complexes' biological activity has been investigated.

2.1. Materials

All the chemicals or solvents were purchased from Fluka and Sigma-Aldrich.

2.2. Synthesis of Complex 1

A stirred solution of trimethoprim (0.29 g, 1.0 mmol) in methanol (MeOH) was added to a solution of Ph3SnCl (0.39 g, 1.0 mmol) in MeOH (10 mL). It took 6 hours to reflux this mixture. After cooling, the solid was generated, and it was filtered, washed with MeOH (2–5 mL), and dried to give 1 (Figure 1) (6).

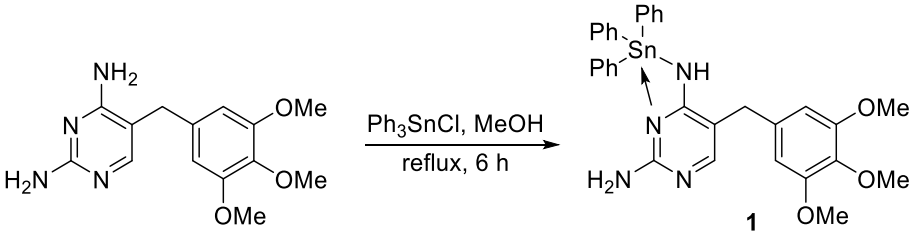

Figure (1): Trimethoprim-tin complex 1 synthesis

2.3. Complexes 1 and 2 preparation

Trimethoprim (0.58 g, 2.0 mmol) in MeOH was mixed with a solution of Ph2SnCl2 (0.35 g, 1.0 mmol) or n-Bu2SnCl2 (0.30 g, 1.0 mmol) before the addition (10 mL). Refluxing the mixture took six hours. After cooling, the resulting solid was filtered, washed with MeOH (2 5 mL), and dried to produce 2 or 3 (Scheme 2), respectively (6).

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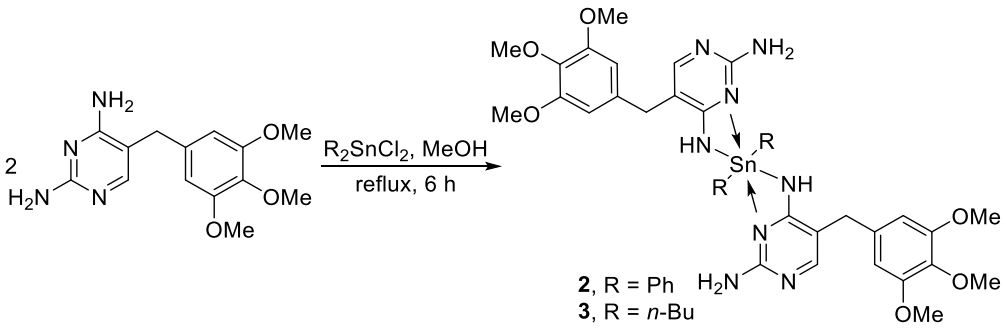

Figure (2): Trimethoprim-tin complexes 2 and 3 synthesis

2.4. Cultural media preparation

(28gm) of the seeded nutrient agar were dissolved in a liter of distilled water to make the nutrient agar. The composition of nutrient agar was arbitrarily chosen for well-defined zones. The composition of nutrient agar employed with *B. subtilis* was for liter: 1.5 g of beef extracts (Difco), 6.0 g of peptone (Difco), 3.0 g of yeast extract (Difco), and 20.0g of agar (BBL). This was adjusted to 6.0 with dilute HCl or NaOH and was unbuffered. The prepared solution was then put into a culture plate at a temperature of (45 C^o) and allowed to cool to room temperature before being placed in the refrigerator for 15 minutes to better suit creating the diameters of the control sites within the limits of spreading. The culture media were then perforated and injected with both bacterial and fungal inoculums. Before pouring it, it was incubated for an hour at a temperature of (37 C^o) in the incubator (7). The weights of the aforementioned ingredients were then dissolved in one liter of distilled water to create Media 1 (8).

2.5. Preparation of chemical solutions

The dimethyl sulfoxide solution was utilized to prepare the chemical solutions for the biological study (DMSO). From each sample, the two concentrations of 10-2 M and 10-4 M were created. The preparation was carried out in glass tubes that were sterilized for 15 minutes at a temperature in an autoclave (121 C^o). The antibiotic Cefixime served as the basis for the comparison. A control model of (DMSO) alone was performed and its effect on bacteria and fungi was studied under the same conditions.

2.6. Technique for evaluating the synthesized compounds' sensitivity

After making wells in the culture medium with two different antibiotic concentrations (1×10^{-2}, 1×10^{-4}M), 50 µl of each was poured into the holes and allowed to absorb. The culture medium was then stored in the incubator at a temperature of (37 C^o), which is the appropriate degree for bacterial growth for a period of (24) hours.

2.7. The damping area's measurement

To create solutions with different concentrations, the stock solution was aseptically transferred and diluted twice. The diameters of the inhibition zone (mm) were measured in order to calculate the antibacterial activity using the filter paper disc technique (9). The DMF-containing media served as a control. At 37 °C, all cultures were maintained on nutritional agar (NA). By letting the culture develop overnight at 37 °C in Nutrient Agar (NA) broth, the bacterium inoculums were produced. On NA plates, a homogeneous layer of 0.1 mL of diluted bacterial culture solution was applied. Ten milligrams of each compound were dissolved in

ten milliliters of DMF to create solutions of the reference medications and the tested compounds. Each sample was pipetted into a 3 mm-deep hole drilled in the agar in a 100-L container. Test chemicals were infused throughout sterile 8 mm discs from Himedia Pvt. Ltd. On the plate was where the disc was. One control disc was soaked in solvent on each plate. The plates were incubated for 18–48 hours at 37 °C. Filter discs soaked in 10 L of the solvent DMSO were used as a negative control, and standard discs containing Cefixime and trimethoprim tin complexes (an antibacterial agent; 10 g/disc) were used as positive controls for antimicrobial activity. The results of each experiment were averaged after being run at least three times.

3. Results

All the compounds were evaluated for their antibacterial activity *in vitro* by using the zone inhibition technique against *Bacillus-Pumilus* (+) and *Candida-albicans* at two concentrations (1×10^{-2}, 1×10^{-4}M) as described above. The results obtained were compared with the results from the standard drug Cefixime.

4. Discussion

Upgrading the action of Cefixime and trimethoprim tin complexes including: (**Cefixime**, **Complexes-1, Complexes-2, and Complexes-3**). All the prepared complexes gave a relatively higher inhibiting rate for the bacteria used, while they gave a relatively weaker inhibiting rate for the used fungi as shown in Table (1).

Table (1): Biological activity for Cefexim and trimethoprim tin complexes

Compound	**Conc. (mg/ml)**	**Inhib. Zone (mm)** *Bacillus-Pumilus*	**Inhib. Zone (mm)** *Candida-Albicans*
Cefixime	1×10^{-2}	24.6	26.0
	1×10^{-4}	22.8	25.5
Complex-1	1×10^{-2}	12.5	12.0
	1×10^{-4}	12.0	11.2
Complex-2	1×10^{-2}	12.5	11.8
	1×10^{-4}	10.1	11.5
Complex-3	1×10^{-2}	12.0	0.0
	1×10^{-4}	11.2	0.0

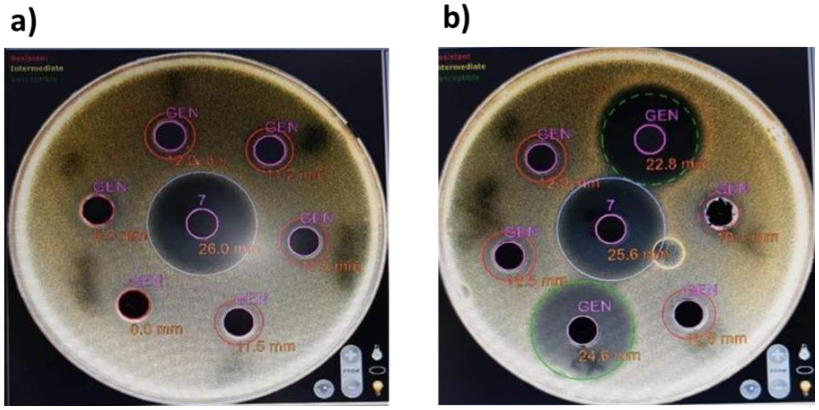

Figure (3): Biological activity for trimethoprim tin complexes against a) *Bacillus Pumilus* and b) *Candida albicans.*

4. Conclusions

Three trimethoprim tin complexes of trimethoprim with three different organo-tin compounds were prepared. The prepared compounds have proven to be more effective in inhibiting bacteria such as a) *Bacillus Pumilus* and b) *Candida albicans* at two concentrations (1×10^{-2}, 1×10^{-4}M).

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6. References

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نشاط مضاد للبكتيريا لتريميثوبريم سيفكسيم وتريميثوبريم قصدير ومعقداته

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الخلاصــة:

الخلفية عن الموضوع: التقييم البيولوجي لمجمعات القصدير العضوي تريميثوبريم هو موضوع العمل الذي تمت مناقشته في هذا المنشور.
الهدف : الغرض من هذا المشروع هو فحص خصائص معقدات القصدير تريميثوبريم ومن خلال توصيف حساسية تحليل عناصر الأشعة تحت الحمراء والرنين المغناطيسي النووي.
المواد والطرق: تجمع هذه المجمعات بين معقدات ML6 ثمانية السطوح ومركب القصدير ML5 الهرمي من خلال السماح للمجموعات الأمينية الموجودة في المكونات الطبية بالتفاعل مع القصدير العضوي (IV).
النتائج: تم تحديد الموصلية المعقدة للمجمعات المعدة وعرض قيم منخفضة. أخيرًا ، تم فحص تركيزين من هذه المجمعات بحثًا عن النشاط المضاد للبكتيريا ضد Bacillus Pumilus (Gram + ve) و Candida albicans) باستخدام تقنية قرص انتشار Agar وأظهرت فعالية كبيرة المناقشة ، أثبتت المركبات المركبة أنها أكثر فاعلية في تثبيط البكتيريا مثل أ) Bacillus Pumilus و Candida albicans (b بتركيزين (1 × 10-2 ، 1 × 10-M4).

الكلمات المفتاحية: مجمع القصدير ، تريميثوبريم ، النشاط البيولوجي ، القصدير (IV).