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Article

Synthesis, Characterization, and Study of the Biological Activity of Pt(II) Dithiocarbamate Complexes With Dppe and Dppf

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Abstract: Theophylline-dithiocarbamate, a novel ligand, was synthesized by reacting theophylline with carbon disulfide in the presence of NaOH at low temperatures (7-0 °C). Platinum-based complexes of this ligand with tertiary phosphines (dppf and dppe) were prepared in a 1:1 molar ratio (phosphine). These complexes were characterized using physical methods (melting points, molar conductivity, elemental analysis) and spectroscopic techniques (FT-IR, ^{1}H-NMR, and ^{31}P{^{1}H}-NMR). The antibacterial activity of the ligands and complexes was tested against Escherichia coli and Enterococcus faecium, revealing varying inhibition rates compared to the standard antibiotic, Ciprofloxacin. This study highlights the potential of these complexes as antibacterial agents, contributing to the ongoing search for new antimicrobial compounds.

Keywords: Coordination chemistry, Tertiary phosphines, Biological activity

Introduction

Coordination chemistry has been interested in studying complexes containing sulfur as donor atoms. The dithiocarbamate ligand (DTC) is one of the important topics in this field [1] as it behaves as a bidentate ligand with many di- and tri-oxide metals [2] and can also behave as a monodentate sometimes, which is often due to steric hindrance around the central atom [3] and dithiocarbamate ligands can also be linked in a polydentate manner. Dithiocarbamate compounds have interesting biological properties and have been considered as an alternative to traditional antibiotics to mitigate the spread of antimicrobial resistance.

This explains the increasing interest in investigating the antimicrobial activity of different dithiocarbamate compounds [4]. Tertiary phosphines Organophosphorus chemistry has become very important in many sectors of industry and daily life over the past century. Phosphorus is found in the form of inorganic and organic phosphates [5] in most fertilizers, pesticides, detergents, food products

and pharmaceutical products. Thus, the chemistry of organophosphorus compounds has now grown to a level of complexity and sophistication similar in many respects to that of carbon (5). The British researcher Joseph Chatt [6] made several valuable contributions to organometallic chemistry, but perhaps his most important and widely applicable legacy was his high promotion of phosphine as a flexible ligand in the chemistry of transition elements [7] and its presence enabled chemists to develop reactions with the metal centre that was unique and resulted in the attachment of many unusual and new organic ligands and groups to metals.

Experimental part

Preparation of Theophylline (dithiocarbamate) (Th-DTC)

The ligand was prepared by adding 0.33g (5.5mmol) of carbon disulfide CS2 to 1g (5.5mmol) of theophylline dissolved in 10 ml of DMF in the presence of 0.22g (5.5mmol) of sodium hydroxide NaOH. The mixture was stirred for three hours using an ice bath at (0ºC -7ºC) until a light orange solution was formed. The solution was filtered and then evaporated to pre-dryness using a water bath at (50ºC). The resulting precipitate was collected and dried in an electric oven at (50ºC) for three hours as in the following reaction:

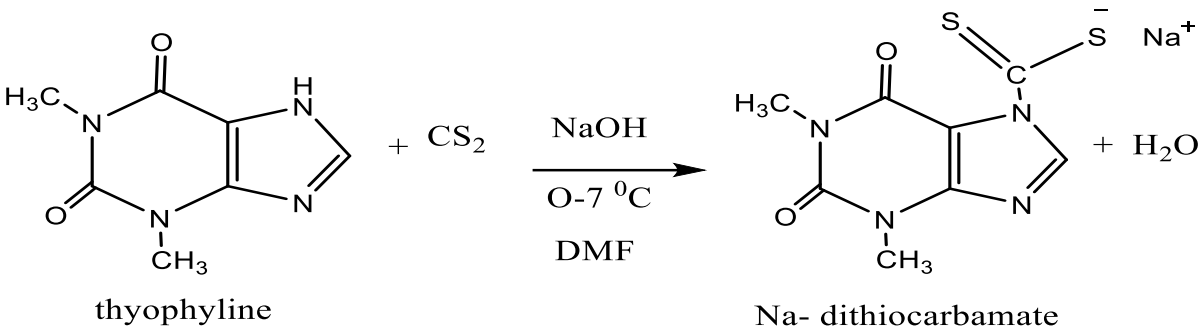


Figure 1. The resulting precipitate was collected and dried in an electric oven at (50ºC) for three hours as in the following reaction

The ligand solution (0.12 mmol, 0.047 g) dppe chloroform (10 ml) was added to the platinum salt solution (0.12 mmol, 0.05 g) K2PtCl4 in (10 ml) of distilled water, the mixture was stirred for an hour, then the prepared ligand (Th-dtc) (0.12 mmol, 0.047 g) dissolved in (10 ml) of distilled water was added and a pink precipitate was formed. The precipitate was filtered and washed with distilled water and then dried in an electric oven at a temperature of (50ºC) for three hours.

Preparation of the complex [Pt(Th-dtc) (dppf)]Cl

The ligand solution (0.12 mmol, 0.047 g) dppf chloroform (10 ml) was added to the platinum salt solution (0.12 mmol, 0.05 g) K2PtCl4 in (10 ml) of distilled water, the mixture was stirred for an hour, then the prepared ligand (Th-dtc) (0.12 mmol, 0.066 g) dissolved in (10 ml) of distilled water was added and a pink precipitate was formed. The precipitate was filtered and washed with distilled water and then dried in an electric oven at a temperature of (50ºC) for three hours.

Materials and Methods

The biological activity was measured by the Agar-well diffusion method as follows 1-Prepare the previously activated bacterial inoculum in nutrient broth medium a dilute to McFarland standard 0.5 at a concentration of 1.5 x108 bacterial cells per m.2- Spread the bacterial inoculum over the entire Mueller Hinton agar culture medium using a glass diffuser [8-10]. 3- Make wells in the agar medium using a sterile drill with a diameter of 6 mm. 4-Place the three diluted concentrations prepared from the solutions whose activity is to be measured inside the holes with a volume of 100 microliters in each hole on a single plate in which one bacterial model wasplanted separately. This step was repeated for all the prepared solutions with their concentrations and each of the bacterial models used under study [11-13].

Incubation and reading the results

The samples were incubated at a temperature of 35-37°C in a laboratory incubator for 24 hours. After the incubation period was over, the effectiveness was read by observing the diameter of inhibition around the holes loaded with the solutions and measuring it in millimetres using a ruler. As for the solutions that did not show an inhibition halo around them, they were considered ineffective solutions against the selected bacteria under study and were indicated by the symbol l n.a – no effectiveness. [14-18]

Results and Discussion

The two prepared complexes are thermally stable at normal temperatures and we note their solubility in Table (1)

Table 1. Shows the solubility of the two prepared complexes

Compound	C_2H_5OH	DMF	DMSO	H_2O
[Pt (Th dtc) (dppe)]Cl	-	+	+	-
[Pt(Th dtc) (dppf)] Cl	-	÷	+	-

Table (2) shows some of the physical properties and the percentage of the prepared ligands and complexes.

Table 2. Shows the percentage, melting point and colour of the prepared ligand and complexes.

Compound	Colour	m.p. °C	Yield%
Na-Th-dtc	**Yellow**	**200-198**	87%
[Pt (Th-DTC) (dppe)]Cl	**White**	282-280	68%
[Pt(Th dtc) (dppf)] Cl	Yellow	280*-278	60%

The prepared ligands and complexes were characterized by the C.H.N.S elemental analysis technique by measuring the percentage of carbon, hydrogen, nitrogen and sulfur. The results shown in Table (3) were obtained.

Table 3. Shows the conductivity measurement and C.H.N.S for the prepared ligand and complexes

Compound	ΛM DMSO	Elemental Analysis Found(cal)%			
		%C	%H	%N	%S
Na-Th-dtc	**30.7**	**34.53 (34.51)**	**2.54 (2.53)**	**20.13 (20.11)**	23.04 (23.03)
[Pt(Th- dtc)(dppe)]Cl	**32.7**	**46.18 (46.16)**	**3.53 (3.51)**	**6.34 (6.32)**	7.25 (7.22)
[Pt(Th- dtc)(dppf)]Cl	**37.8**	**48.90 (48.88)**	**3.72 (3.69)**	**5.30 (5.28)**	6.07 (6.04)

FT-IR Spectra for Complex

The FT-IR spectrum showed many bands for the prepared ligand and complexes at the positions shown in Table (4) and Figure (2).

Table 4. Shows the infrared measurement of the prepared complex.

Compound	υ (C-H)	υ C=O	υ C-S	υ C=S	υ C=C	υ C=N	υ (P-Ph)	υ (C-P)
Na-Th-dtc	**3049m**	**2891W 2935m**	**1639 (S) 1687S**	**1533 m**	**1612 m**	**1045 W 1060m**	977	
[Pt(Th dtc) (dppe)] Cl	**2899M 2953M**	**1685S 1643S**	**968M**	**1026w 1064M**	**1531 S**	**1606 M**	**1435S 1103S**	690 S
[Pt(Th dtc) (dppf)] Cl	**2895W 2945W**	**1687S 1643S**	**968M**	**1043W 1070M**	**1535 M**	**1610 M**	**1435M 1101M**	696 M

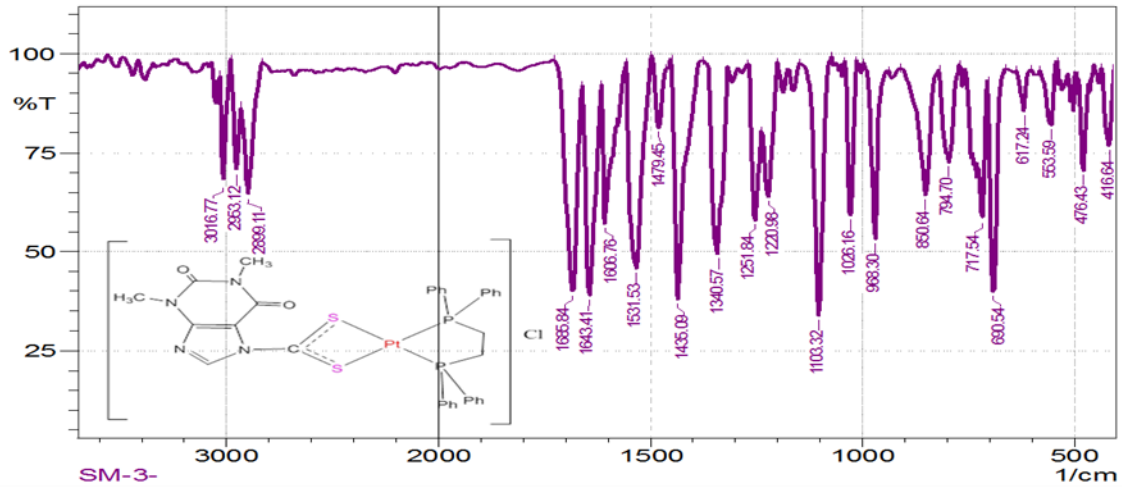


Figure 2. Infrared spectrum of the complex [Pt(Th-dtc)(dppe)]Cl 1H-NMR spectrum of Pt(Th-dtc)(dppe)]Cl] complex

The 1H-NMR spectrum of Pt(Th-dtc)(dppe)]Cl) complex showed two signals at position (3.24 ppm 3.44,) which are due to six protons of the two methyl groups in the ligand and the appearance of a multiple signal within the range (7.87-7.73 ppm) with an integration corresponding to 20 protons of dppe which are due to the protons of the phenyl rings and the proton of the (N-CH) group in the theophylline ring, in addition to a signal at position (2.95 ppm) with an integration corresponding to four protons which are due to the protons of the (CH2) group in dppe, as shown in Figure (3).

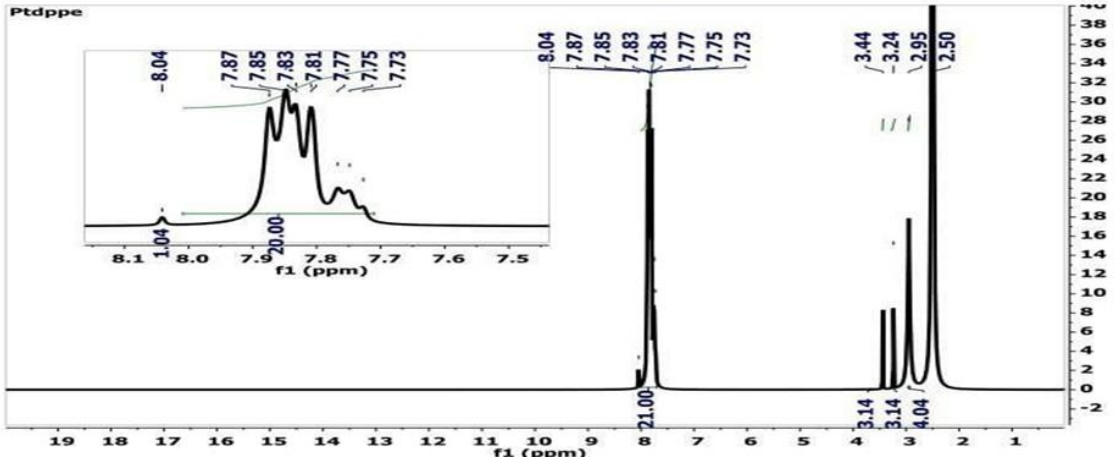


Figure 3. 1H-NMR spectrum of the complex [Pt(Th-dtc)(dppe)]Cl measured in DMSO-d6 solvent. The 31P-NMR spectrum of the complex [Pt(Th-dtc)(dppe)]Cl

The 31P-NMR spectrum measured in DMSO-d6 solvent and shown in Figure (4) showed a single signal at the displacement δP = 40.28 ppm. This indicates the presence of one isomer of the complex and the phosphorus atoms in the dppe ligand are equivalent and coordinated in a chelating manner[19]. The spectrum showed the presence of platinum tracers.

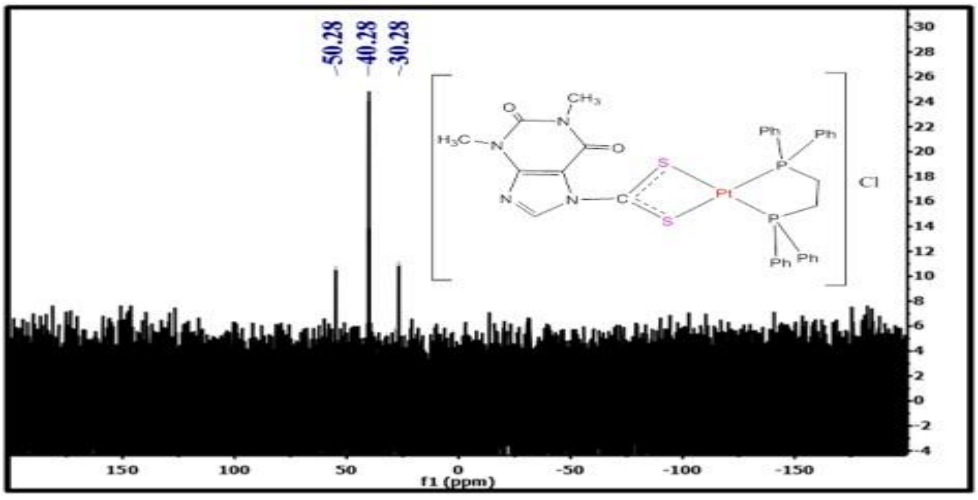


Figure 4. 31P-{1H}nmr spectrum of the complex [Pt(Th-dtc)(dppe)]Cl measured in DMSO-d6 solvent. 1H-NMR spectrum of Pt(Th-dtc)(dppf)]Cl] complex

The 1H-NMR spectrum of Pt(Th-dtc)(dppf)]Cl) complex showed two multiple signals at positions (3.30, 3.20 ppm) due to the protons of the (CH3) groups of the ligand with an integration corresponding to six protons, and the spectrum showed four single signals at positions δH=4.47 ppm, δH=4.56 ppm, δH=4.81 ppm, δH=4.94 ppm. The integration of each signal indicates two protons for a total of eight protons, which were attributed to the protons of the two cyclopentadienyls (Cp) rings in the (dppf) ligand. The appearance of two single signals indicates that the two pentadiene rings are

staggered. If it was identical (eclipsed), it would have appeared in the form of a single signal [20] and multiple signals would have appeared within the range (8.15-7.49 ppm) with an integration corresponding to 20 protons of dppf indicating the protons of the phenyl ring [21] and the proton of the (N-CH) group in the theophylline ring, as in Figure (5).

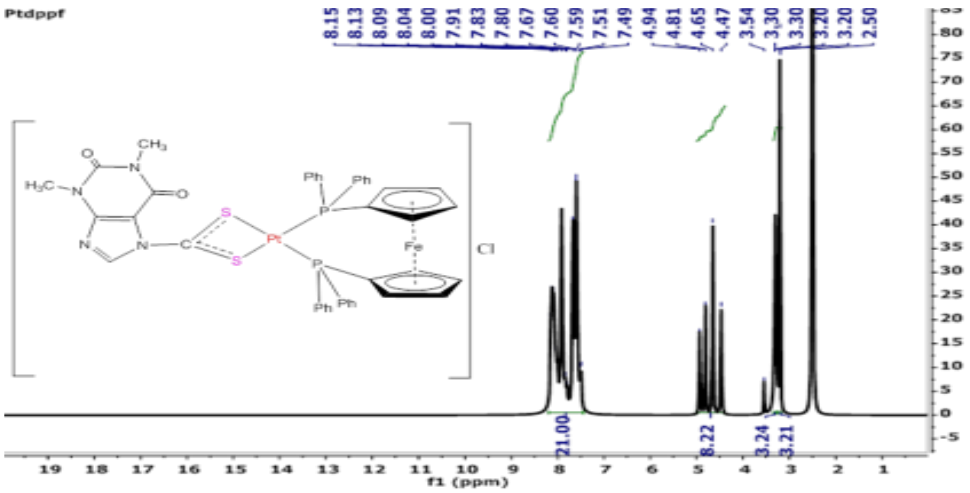


Figure 5. 1H-NMR spectrum of the Pt(Th-dtc)(dppf)]Cl] complex.

The 31P-{1H}-NMR spectrum of the complex [Pt(Th-dtc) (dppf)Cl] measured in DMSO-d6 solvent and shown in Figure (6) showed a single signal at a chemical shift of 12.45 ppm δP= indicating the presence of one isomer and that the two phosphorus atoms are equivalent and coordinated in a chelate form [21] The spectrum showed the presence of platinum tracers.

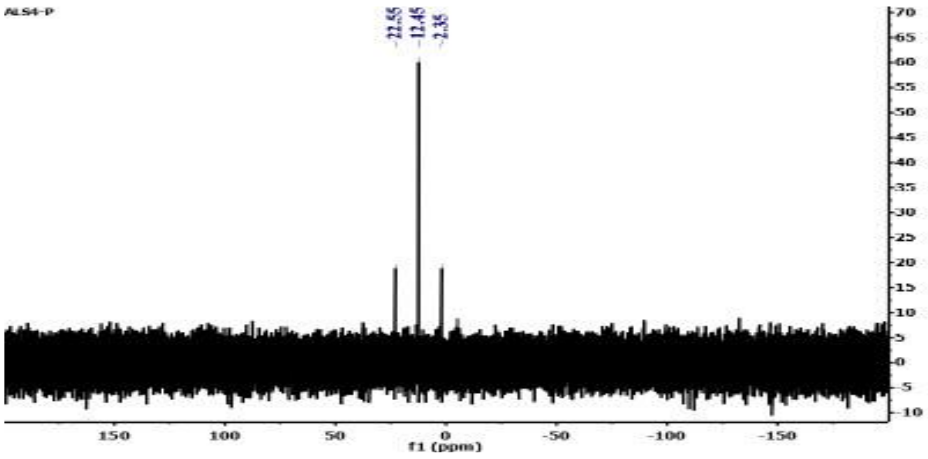


Figure (6): 31P-{1H}-NMR spectrum of the complex [Pt(Th-dtc)(dppf)]Cl measured in DMSO-d6 solvent. Study of the bacterial effect of the ligand and the prepared complexes

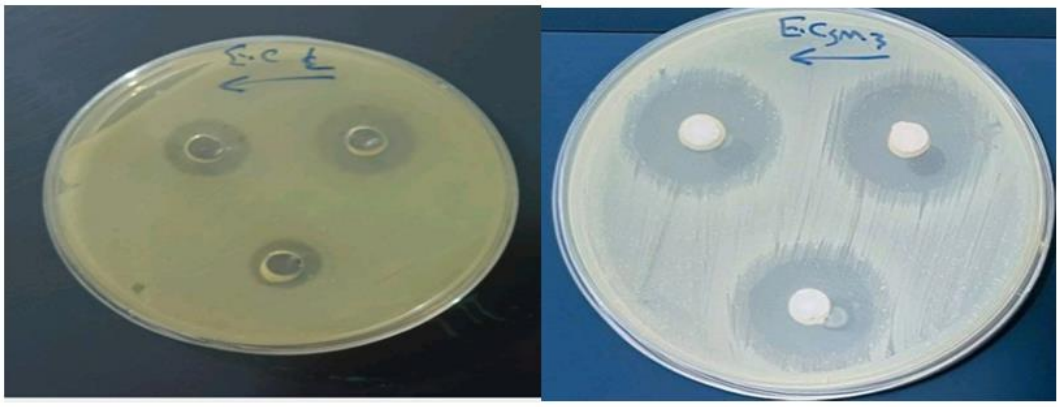
The effect of the ligand and the complex Pt(Th-dtc)(dppe)]Cl] was studied as antibacterial agents against two types of bacteria, namely Gram-negative bacteria, namely E. coli, and Gram-positive bacteria, namely Enterococcus faecium [22-25]. The optimal concentration was determined as (10-3 mg/mol) and was relied upon to determine the radius of inhibition in (mm) units. The ligand and the prepared complex showed a difference in their effect on the bacteria used in the study, [26] as shown in Table (5), Figure (7) and Figure (8)

Table 5. Compounds with biological activity that gave positive results against Gram-positive and negative bacteria.

Complex	Solution concentration and inhibition diameter towards bacterial species					
	E.Coli			Enterococcus faecium		
	25%	50%	100%	25%	50%	100%
Th-DTC	14	15	18	13	15	20
[Pt(Th-dtc)(dppe)]Cl	21	25	25	15	15	19
DMSO	No.activity					

complex [Pt(Th-dtc)(dppe)]Cl ligand Th-dtc

Figure 7. The inhibitory effect of the ligand and the complex against Escherichia coli bacteria.

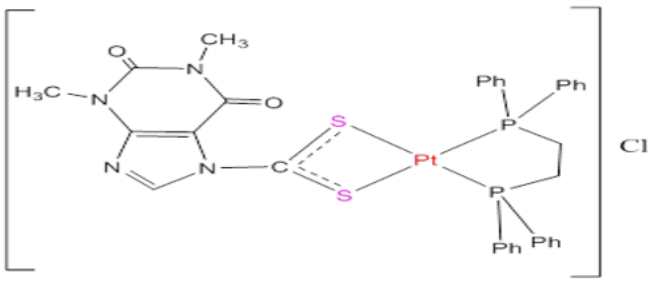


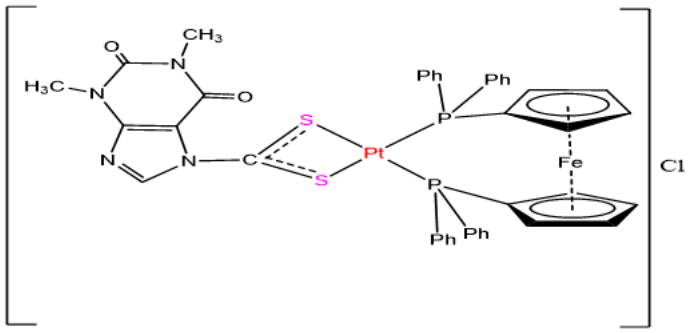
complex [Pt(Th-dtc)(dppe)]Cl ligand Th-dtc

Figure 8. Inhibitory effect of ligand and complex against Enterococcus Faecalis bacteria.

Conclusion

Through the measurements, it was shown that (dppe, pdf) behaved in a double-toothed manner when bound to the metal through the two phosphorus atoms, and this was confirmed by the results of the nuclear magnetic resonance spectra of phosphorus 13P{1H}-NMR, while the ligand Th-dtc was bound to the metal ion in a double-toothed chelate manner through the two sulfur atoms, and the platinum complexes have a square-planar shape.





The results obtained through measuring the biological activity also showed that the [Pt(Th-dtc)(dppe)]Cl complex has a high inhibitory activity towards Escherichia - Coli bacteria, while for Enterococcus faecium bacteria, it was found that the ligand has a higher inhibition rate than the complex.

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