

Structure and germicidal property of a novel guanidine organomercury complex

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Abstract

A novel guanidine organomercury complex **1**, $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3\cdot\text{CH}_3\text{CN}$ **1** (DNP = 2,4- dinitrophenol), has been synthesized. Each mercury(II) atom is tricoordinated to one chlorine atom, one carbon atom of the benzene ring, and one oxygen atom from 2, 4-dinitrophenol. The coordination arrangement around the mercury atom is Y-shaped. This is the first structural report on an organomercury derivative of 2, 4-dinitrophenol and guanidine. The distance of Hg-Cl between the two Hg ions groups is 3.272 Å, which indicates the presence of weak Hg \cdots Cl interactions. Secondary bonds make complex **1** form 3D interspersed network structure, which is 2D $[\text{HgCl}(\text{DNP})\text{CH}_5\text{N}_3]_n$ plane and 1D solvent $[(\text{CH}_3\text{CN})_2]_\infty$ broadband. The antibacterial activity of **1** were studied. It shows complex **1** has very good bactericidal activity, and is also a potential antimicrobial agents.

Introduction

Guanidine is a strong organic base, which is found in urine and is a metabolite of protein [1]. Guanidine, commonly used in the form of salt, is an intermediate in organic synthesis (synthetic heterocyclic compounds), drug synthesis, and dye synthesis [2]. Many derivatives of guanidine are physiologically important, such as *p*-aminobenzene sulfonyl guanidine, an anti-inflammatory intestinal drug [3]. The antiviral morpholine guanidine also contains guanidine. Guanidine is used as a nucleophile and catalyst in various reactions [4]. Many compounds of biological significance were synthesized by nucleophilic reaction of guanidine [5–7]. Guanidine ligands containing CN_3 have been widely used in the synthesis of a variety of metal complexes, using them as neutral, single or double anion ligands to form a variety of new complexes with metal structures [8, 9]. Guanidine compounds are a kind of super-base compounds, which can be used as organic catalysts, as carriers of transition metals, and as main group elements to form guanidine complexes [10–13].

Compounds formed by d^{10} metal ions Zn(II), Cd(II) and Hg(II), with organic ligands have attracted wide attention due to their excellent properties and can be used in organic light-emitting diodes [14–15], photocatalytic reaction catalysts [16] and fluorescence sensor materials [17–19]. However, Hg(II) ionic complexes have been less studied, mainly because mercury (II) ions are harmful to both the environment and human health. Analysis of the concentration of mercury ions in the environment has become the mainstream of chemists. Hg(II) ions have a flexible coordination environment, reported from two to eight coordination, and can be used to construct coordination polymers and frames. When combined with mercury ions, organic compounds can significantly change their properties for high sensitivity and selective mercury sensors. However, complexes of guanidine and mercury have been rarely reported.

2,7-dibromo-4'-(hydroxymercurio)-fluorescei disodium salt (Mercurochrome) is the oldest organic mercury topical disinfectant, which is used for disinfecting superficial wounds. Mercurochrome is the most common bacteriostatic agent in China. Antimicrobial resistance has become a serious threat to human health and economic development [20]. Many strategies involving the development of new antimicrobial

agents [21], the revival of old antibiotics [22], and combination therapy had been putting forward to fight or delay resistance [23].

As we can know, the crystallographic structural studies should provide much more detailed information characterizing rather than the spectroscopic investigations. Interaction between ligands, metal ions or host molecules plays a vital role in the nucleation and growth of a molecular crystal. Up to date guanidine organic mercury compounds are rarely reported [24]. Herein, we have reported the crystal structure and germicidal property of $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3\cdot\text{CH}_3\text{CN}$.

Experimental

Synthesis

The commercially available $\text{Hg}(\text{CH}_3\text{COO})_2$ (0.01 mol, 3.19 g), 2,4-dinitrophenol (DNP, 0.01 mol, 1.84 g) and guanidine hydrochloride ($\text{CH}_5\text{N}_3\text{Cl}$, 0.01 mol, 0.96 g), was dissolved in 30 mL CH_3CN solution, by using a pot in the teflon in the reaction kettle, and then set at 180°C in 8 hours. Then, temperature control to reduce the rate of $60^\circ\text{C}/\text{h}$ to room temperature, opening the reaction kettle get acicular red block crystal, the yield of 78.5% based on $\text{Hg}(\text{CH}_3\text{COO})_2$. The red block crystals suitable for diffraction is obtained directly. The single crystals X-ray confirmed that the red block crystal was $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3\cdot\text{CH}_3\text{CN}$. The elemental analysis supports this formulation. Anal. Calc. for $\text{C}_9\text{H}_{10}\text{ClHgN}_6\text{O}_5$: C, 20.84%; H, 1.93%; N, 16.21%; Cl, 6.85%; Hg, 38.70%; O, 15.44%. Found: C, 20.67%; H, 1.89%; N, 16.04%.

Structure determination

The diffraction data were collected on an SMART APEXII diffractometer with graphite monochromatic $\text{Mo-K}\alpha$ ($\lambda = 0.71073 \text{ \AA}$, $T = 293\text{K}$) radiation. Empirical absorption correction was carried out by using the SADABS program. Their structures were solved by direct methods and refined by least squares on F_{obs}^2 with SHELXTL software package. All non-H atoms were anisotropically refined. The hydrogen atoms were located by difference synthesis and refined isotropically. The molecular graphics were plotted using SHELXTL. Atomic scattering factors and anomalous dispersion corrections were taken from International Tables for X-ray Crystallography. A summary of the key crystallographic information was given in Supporting Information (SI) Table S1. The CCDC number is 2042589.

Antibacterial property test for guanidine derivative

Main instruments and equipment: High temperature and high pressure steam sterilizer (Hirayama VE-50). Multi-function marker (Switzerland TECAN SPARK 10M). Clean table (SW-CJ-2FD). Constant temperature vibration Swing device (IS-RDV1). Analytical Electronic balance (FA2004).

The main reagent: Tryptone (AR), Yeast powder (AR), Agar powder (AR), NaCl (AR).

Bacterial strain: E. coli, Staphylococcus aureus.

Sample to be tested: Sample **1** to **9**, for the structure of compounds **1-9** see Supporting Information (SI) page 4-6.

Preparation of LB medium

LB liquid medium: Using a measuring cylinder, 100 mL distilled water was poured into a 250 mL reagent bottle, and 1 g tryptone, 0.5 g yeast powder and 1 g sodium chloride were weighed by analytical electronic balance, respectively. The above weighing reagent was added to mix well, and sterilized in a high-temperature and high-pressure steam sterilization pot at 121 °C for 15 minutes.

LB solid medium: Using a measuring cylinder, 100 mL distilled water was poured into a 250 mL reagent bottle, and then 1 g tryptone, 0.5 g yeast powder, 1 g sodium chloride and 1.5 g AGAR powder were weighed by analytical electronic balance. The above weighing reagent was added to mix well, and put in a high temperature and high pressure steam sterilization pot at 121°C for 15min to be used after sterilization.

Preparation of bacterial suspension

Three 12 mL bacterial culture tubes were added into 3 mL LB liquid medium. 6 L *Staphylococcus aureus* and *Escherichia coli* freezers were added to two of them, and the other one was used as blank control. It was placed in a thermostatic oscillator (37 °C, 200 RPM) and incubated overnight (15 h). OD 460 (1.25 for *E. coli* OD 460, corresponding concentration of 5.9×10^8 CFU/mL) was measured on a multifunctional microplate reader. *Staphylococcus aureus* OD 460 was 1.5 and the corresponding bacterial liquid concentration was 5.8×10^8 CFU/mL. Then LB medium was used to dilute the bacterial suspension to 5×10^6 CFU/mL for later use.

Treatment of samples to be tested

5 mg samples to be tested were respectively weighed and placed in a 15 mL centrifuge tube according to groups, and then sterilized at 121°C for 20 min in a high temperature and high pressure steam sterilization pot.

Plate coating count test

The LB liquid medium was used to dilute the bacterial suspension to a concentration of 5×10^6 CFU/mL, and then 1 mL of the bacterial suspension was absorbed and added to a 15 mL centrifuge tube with the sterilized sample. The suspension was placed in a thermostatic oscillator at 37°C and oscillated at 200 RPM for 18 h.

After the culture was completed, 100 L bacterial suspension was diluted with a ratio of 10 times (10^{-5} , 10^{-6} and 10^{-7} were used in this test), and 100 L was uniformly coated on LB solid medium. Placed in a constant temperature incubator for 18 h at 37°C, the number of colonies was recorded and photos were taken.

Results And Discussion

Crystal structure

Single crystal X-ray analysis showed that the structural unit of title compound **1** was composed of the host $[\text{HgCl}(\text{DNP})]^{1-}$ anion, the guest guanidine $(\text{CH}_6\text{N}_3)^{1+}$ cation and the solvent molecule CH_3CN . The bond lengths and bond angles, ORTEP diagram and corresponding atomic numbers are shown in Supplementary Materials Table S1, Table S2 and Figure S1. As a bidentate ligand, DNP is best described as $(\text{DNP})^{2-}$, it should lose two protons in OH group and CH group to provide two negative charges. The host is expressed as $[\text{HgCl}(\text{DNP})]^{1-}$ anion. The guest guanidine absorbs a proton with a positive charge, and the whole molecule is electrically neutral. The metal Hg is in triangular coordination with the oxygen atoms on the hydroxyl group, the carbon atoms on the benzene ring and the Cl^- anion. The length of Hg-C bond is $2.058(5)\text{\AA}$, and the length of Hg-Cl bond is $2.328(1)\text{\AA}$, both of which are consistent with similar structures reported previously [25-27]. The Hg-O bond distance is $2.981(1)\text{\AA}$, which is significantly longer than the commonly reported bond distance (average 2.07\AA) [28-29], indicating the existence of a weak chemical bond between Hg and O atoms. Considering the long-term force, Hg atoms form chemical bonds with Cl along the *b* axis, and the length of the Hg-Cl bond is $3.272(3)\text{\AA}$, which can be considered as electrostatic force. Thus, the coordination environment of Hg atoms can be described as a tetragonal pyramid structure, and the host can be represented as the $[\text{HgCl}(\text{DNP})]_n^{n-}$ one-dimensional trapezoidal polymer (Fig. 1).

In the crystal, each unit contains one $[\text{HgCl}(\text{DNP})]^{1-}$, one $(\text{CH}_6\text{N}_3)^{1+}$ cation and one CH_3CN molecules. $(\text{CH}_6\text{N}_3)^{1+}$ cation and CH_3CN is forming the strong hydrogen bonds with donor and acceptor distance of 3.054\AA and 2.845\AA , respectively. CH_3CN molecules are joined end to end to form one dimensional chains $(\text{CH}_3\text{CN})_\infty$, which then form double-chains $[(\text{CH}_3\text{CN})_2]_\infty$ structures by strong $\pi\cdots\pi$ action of the $\text{C}\equiv\text{N}$ groups. The $(\text{CH}_6\text{N}_3)^{1+}$ cation is located on both sides of double-chains, like a railing around CH_3CN molecules in the middle (Figure 2).

Secondary bonds play an important role in the construction of organomercury compounds [30]. Compound **1** exhibits a variety types of secondary interactions between host $[\text{HgCl}(\text{DNP})]$ and guest CH_5N_3 and CH_3CN . First, nitro-oxygen atoms in DNP formed strong hydrogen bonds with guanidine hydrogen atoms, and the $\text{O}\cdots\text{H}$ bond lengths were 2.106\AA , 2.068\AA , 2.256\AA and 2.105\AA , respectively. The corresponding donor and acceptor were established as $\text{N}4\cdots\text{O}1$ distance of 2.856\AA , $\text{N}3\cdots\text{O}1$ 2.831\AA , $\text{N}5\cdots\text{O}3$ 2.991\AA , and $\text{N}3\cdots\text{O}2$ 2.920\AA , respectively. These strong hydrogen bonds between host $[\text{HgCl}(\text{DNP})]$ and guest guanidine form a plane with symmetrical structure (Figure 3a). Second, the plane of $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3$ connected double-chains $[(\text{CH}_3\text{CN})_2]_\infty$ by strong hydrogen bond, with the $\text{N}6\cdots\text{H}$ of 2.237\AA , and the $\text{N}6\cdots\text{N}4$ of 3.054\AA . Finally, double-chains $[(\text{CH}_3\text{CN})_2]_\infty$ and $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3$ plane form interpenetration structure as shown in Figure 3b. Detailed data for the hydrogen bonds are given in **SI** Table S3. All the above-mentioned secondary interactions and the hydrogen bonds at the supramolecular level lead to a three-dimensional network (Figure 3c).

The antibacterial results show

Bacterial infections are responsible for a large number of deaths every year worldwide. Both *Escherichia coli* and *Staphylococcus aureus* are important human pathogens and representatives of Gramobacteria. The human infections caused by them rank the first and second in the world. These two bacteria are also prone to develop drug resistance. As a result, they are the most studied bacteria in modern biology [31]. Guanidine complex have been experimentally documented to possess broad-spectrum antibacterial and antifungal activities, and they can remarkably inhibit the growth of Gram-positive bacteria, yeast, and fungi [32-35]. Moreover, they also show antitrichomonal and antitumor activities [36]. Our research group has been engaged in the synthesis and properties research of guanidine derivatives, and found that guanidine compounds have certain bactericidal activity [37]. The antibacterial tests of guanidine compounds were carried out by plate coating counting method.

The antibacterial experiment data of guanidine compounds, and *coli* and *staphylococcus aureus* experiment photo, are found in SI Table S4 and Page 8-11. Figure 4 shows the comparative data of bactericidal efficacy of *Escherichia coli* and *Staphylococcus aureus*. From Figure 4 we can clearly see that the bactericidal properties of the title compound are almost 100%, which antibacterial property was significantly better than those of other guanidine compounds synthesized by us. It is expected that the title complex is a potential and candidate drug for new fungicides.

Conclusions

In summary, a new organomercury complex $[\text{HgCl}(\text{DNP})]\cdot\text{CH}_5\text{N}_3\cdot\text{CH}_3\text{CN}$ was synthesized and prepared through a simple method. Crystal structure analysis showed that interspersed with each other 3D network structure formed by host $[\text{HgCl}(\text{DNP})]$ and guest CH_5N_3 2D plane and solvent molecules $[(\text{CH}_3\text{CN})_2]_\infty$ 1D broadband through strong secondary bonds is rare and novel. Also, guanidine stability in crystal structure as an electroneutral molecule is reported for the first time. This could be helpful for future research on drug release inhibitors. The study on bioactivity of guanidine derivatives shows that the complex **1** has very good bactericidal activity, and is also a potential antimicrobial agents.

Declarations

Supporting Information Available: CCDC 2042589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Detailed experimental procedure, crystal data, bond length, bond angle, hydrogen bond and antibacterial property test data of the compounds are shown in the supplementary materials.

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Conflicts of Interest:

No conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Figures

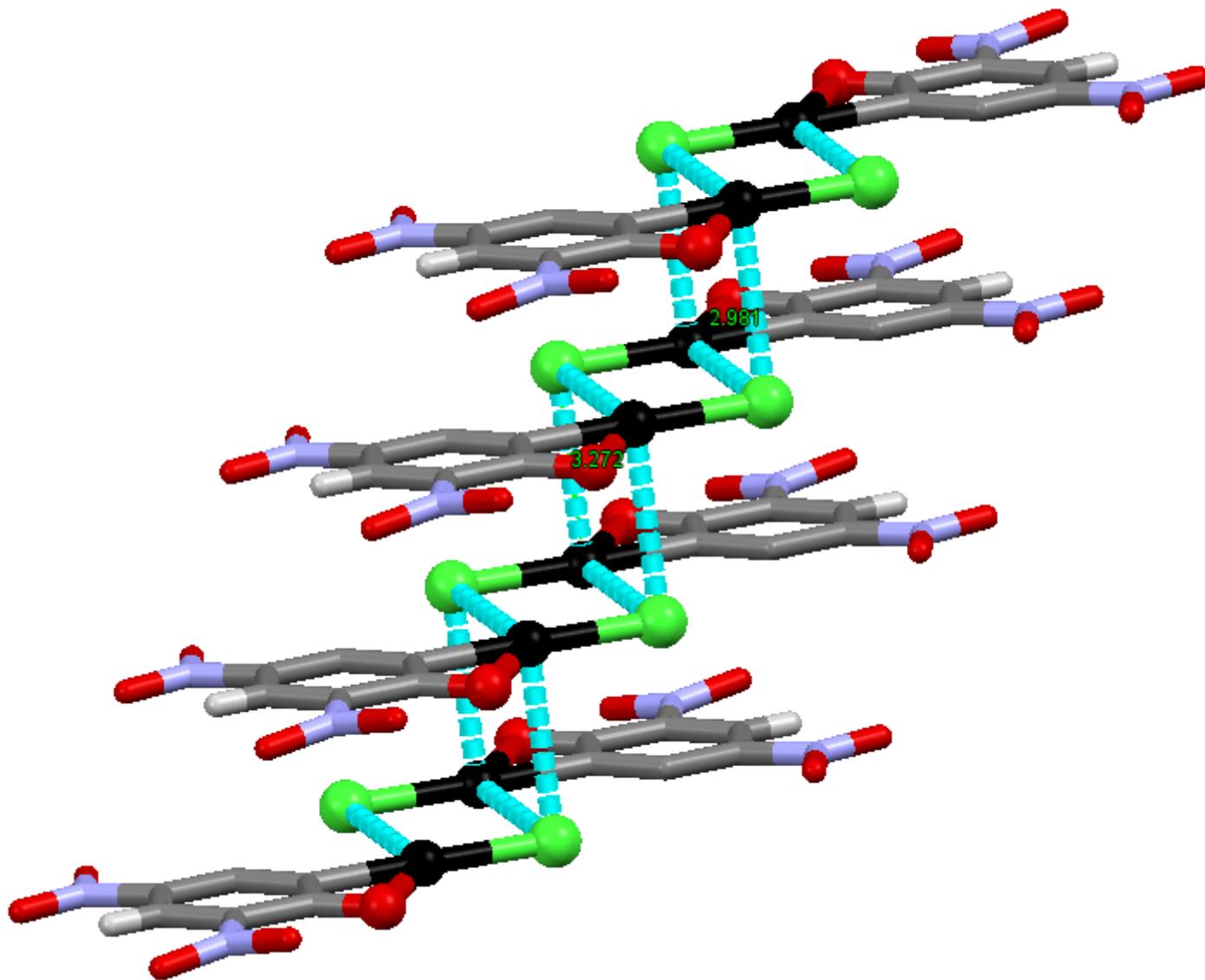
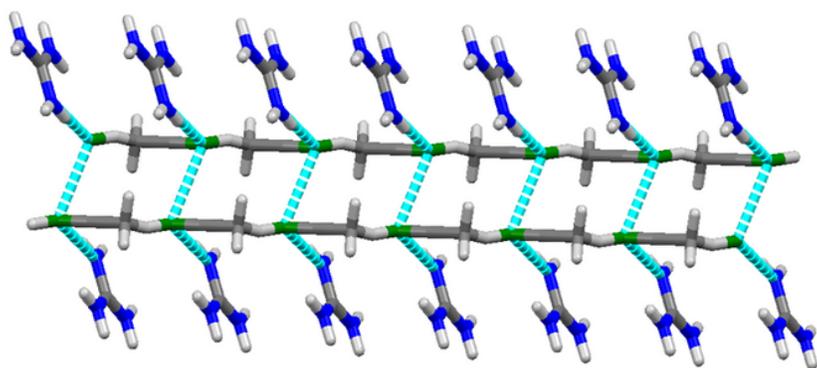
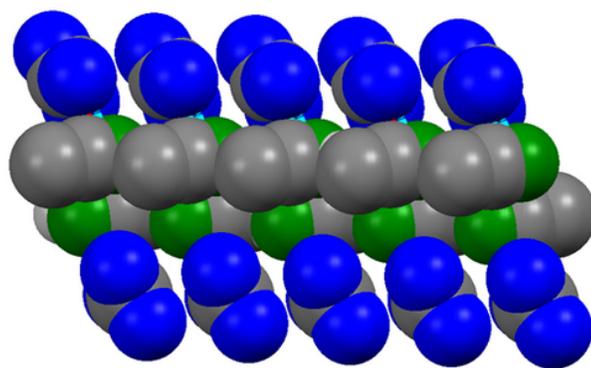


Figure 1

The host $[\text{HgCl}(\text{DNP})]_n^-$ is shown the trapezoidal structure by Hg-Cl electrostatic force along the b axis. The guest $(\text{CH}_6\text{N}_3)^+$ and solvent CH_3CN are omitted for clarity.



(a)



(b)

Figure 2

(a) CH₃CN molecules are joined end to end by the C≡N···H hydrogen bond and π···π action to form a 1D broadband, guanidine molecule located on either side of the broadband. (b) Spacefill view of [CH₅N₃·CH₃CN]_n like “highway with guardrail”. The host HgCl(DNP) are omitted for clarity.

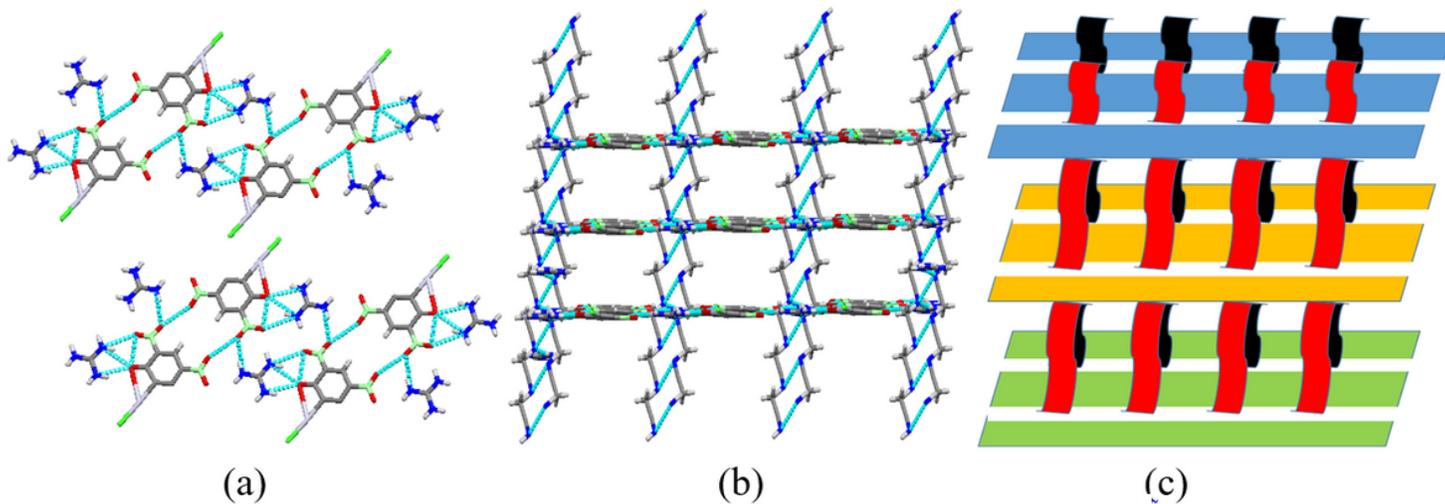
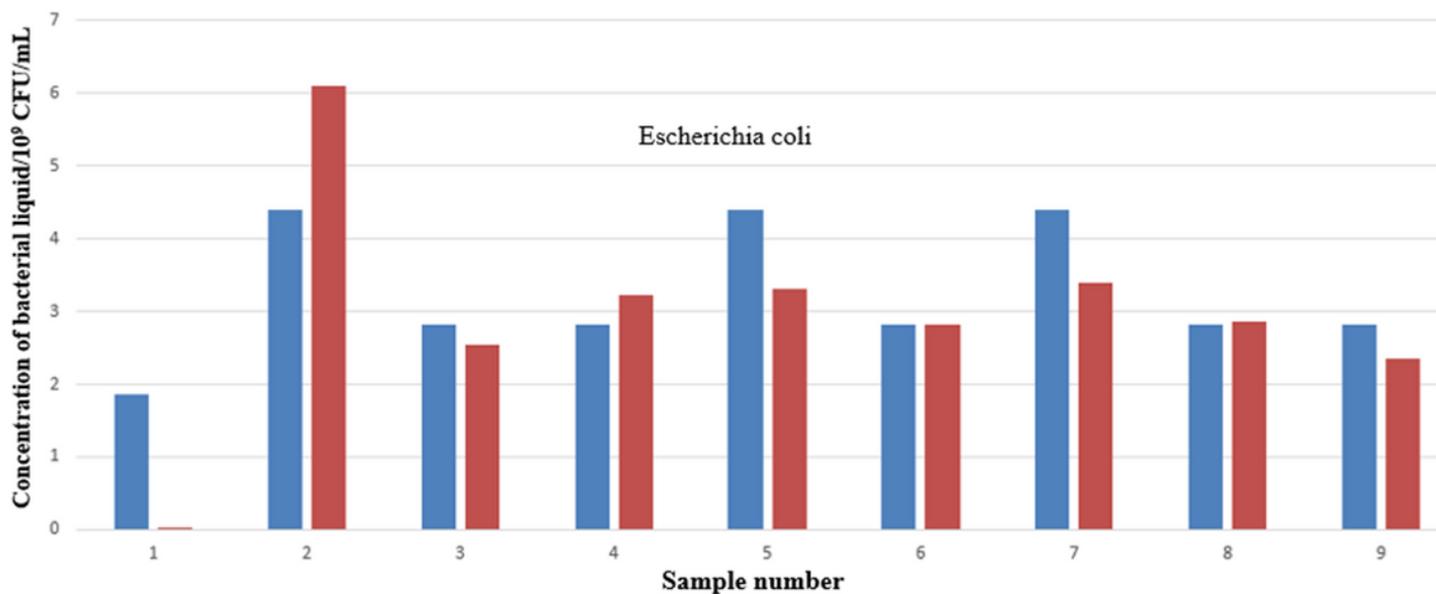
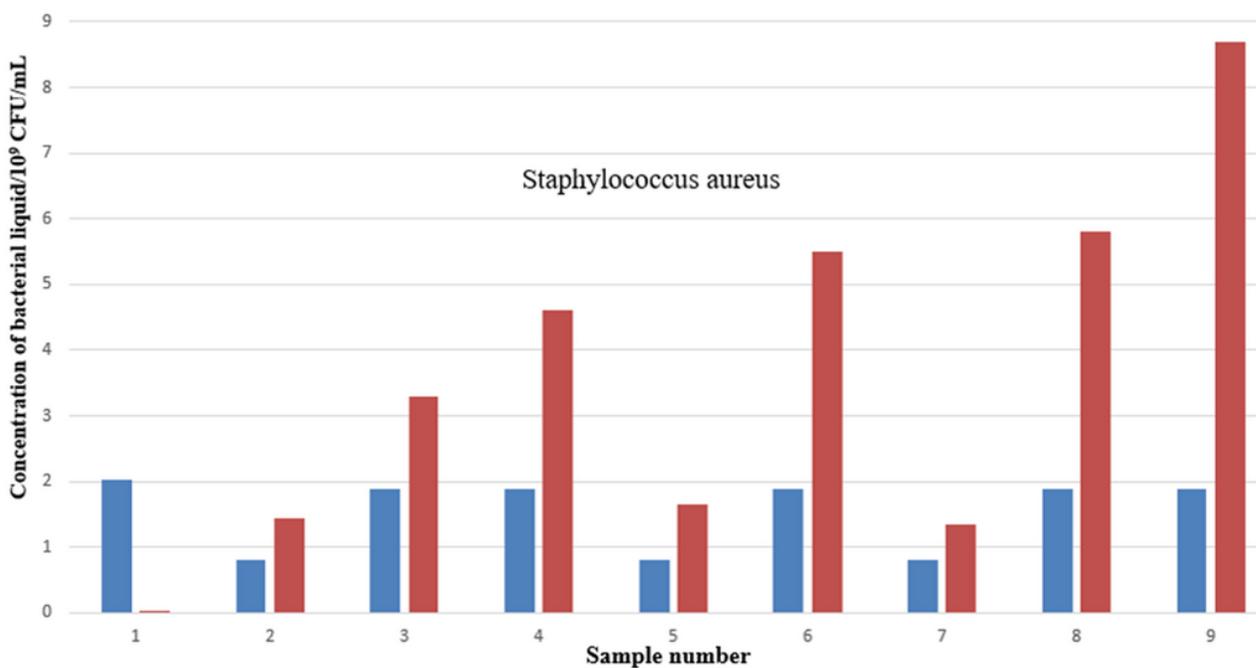


Figure 3

(a) View of 2D plane structure of [HgCl(DNP)CN₅H₃]_n. (b) 2D [HgCl(DNP)CN₅H₃]_n plane and 1D [(CH₃CN)₂]_∞ broadband interpenetrate 3D network through N-H···O, C-H···N, N-H···N and π···π interactions (dash lines). (c) 2D layer and 1D broadband are interpenetrating 3D network.



(a)



(b)

Figure 4

The bactericidal effect of compounds 1-9 was tested by plate coating counting method. (a) *Escherichia coli*. (b) *Staphylococcus aureus*. 1 = [HgCl(DNP)]·CH₅N₃·CH₃CN; 2 = 1,3-Bis(3,5-di-tert-butyl-2-hydroxyphenyl-methylideneamino) ; 3 = 1,3-Bis(3-hydroxy-phenyl-methylideneamino) guanidine ; 4 = 1,3-Bis(5-chloro-2-hydroxyphenyl-methylideneamino) guanidine hydrochloride ; 5 = Tri-(5-chloro-2-hydroxyphenyl-methylideneamino)guanidine ; 6 = Tri-3,5-dibromo-2-hydroxyphenyl-methylideneamino ;

guanidine⁷= Tri-(3-phenyl-allylideneamino) guanidine⁸= Tri-3,5-di-tert-butyl-2-hydroxyphenyl-methylideneamino⁹guanidine⁹= Tri-(3-hydroxy-phenyl-methylideneamino) guanidine hydrochloride.

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