Synthesis, Characterization and antibacterial Study of some Complexes Derivatives from 1,3,4–Thiadiazole Schiff base

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Abstract

The present study included preparing a new ligand from the thiadiazole derivatives from react between 1,2,5-dihydrazine, 1,3,4-thiadiazol with 4-Dimethyl amino benzaldehyde with a ratio of (1:2) to preparing the ligand (L1). Transition ions complexes (Co^{3+}, Cu^{2+}) were prepared with ligand (L1), the ligand and its complexes were characterized using the elemental analysis (C.H.N.S), Infrared spectrum (FTIR), proton nuclear magnetic resonance spectrum (1H-NMR), Mass spectroscopy, magnetic sensitivity, and molar conductivity, the practical results were exactly in line with the molecular formula and structural formulas for the compounds. The program (Hyper Chem) was used to draw ligands and their complexes and to show the distribution of electron density.

The results obtained from the study of magnetic sensitivity and molar conductivity of the prepared ligand complexes confirmed that the geometry shape of [L1CoCl3] is an octahedral complex, while [L1CuCl2] is a square planner complex. The results of molar conductivity also confirmed that the prepared cobalt complex is electrolytic, while the [L1CuCl2] complex is non-electrolytic.

The biological activity of the prepared ligand and its complexes were tested against two types of bacteria Staphylococcus aureus and Escherichia Coli in comparison with the standard inhibitor (Ciprofloxacin), the obtained results confirmed the biological activity of the prepared ligand was more than the standard inhibitor (Cipro) against Escherichia coli, also the complexes (A1, A2) showed higher biological activity than the standard inhibitor (Cipro) against Escherichia coli (Gram-negative), the ligand and its prepared complexes don't show biological activity against Staphylococcus aureus (Gram-positive).

Keywords: Thiadiazole, Schiff base, Biological Activity, Magnetic Sensitivity, Molar Conductivity, 1H-NMR, FTIR
1: Introduction

1-1: Schiff's bases

In the nineteenth century, Hugo Schiff managed to prepare a new group of organic compounds with various applications in various fields. These compounds were known as Schiff's bases in relation to this Scientist, many researchers have prepared various Schiff bases and their coordination compounds with transitional elements, most of these prepared complexes has various biological activities.

Schiff bases can be prepared from the condensation of carbonyl compounds with the primary amines, it contains the Azomethine group (RC=N) also called the Imine group and it is one of the very important classes of organic compounds. Schiff bases are considered distinctive, this is because of the ease of formation of ligands, in very simplified ways, and can coordinate with different metal ions, it is characterized by great stability and in various oxidative states and thus control of the minerals in various catalytic transformations and the ability to form chelating ligands by bonding with Imine nitrogen and another group like (O, N or S).

Schiff bases have an important role in the development of coordinated chemistry, Schiff bases compounds and their metallic complexes have many applications in many fields, including medicine and industry. These compounds are increasingly used, for example as catalysts in both homogeneous and heterogeneous reactions, intermediate compounds in organic synthesis, polymer stability, dyes, and corrosion inhibitors. Besides these applications, Schiff bases show great biological activities, such as antimalarial, antibacterial, antifungals, and anti-cancer properties, that the biological activities of Schiff bases have emerged during the recent period.

1-2: Schiff’ Bases Complexes

Research and study in coordination complexes are gaining increasing importance today and specifically, in the secrets they design or synthesized various activity, it is known that metallic ions are increasing the speed of drugs and the reaction of metallic ions with nucleic acids and DNA components has been studied extensively in the past few years. The reaction of metallic complexes with DNA is the subject of intense investigations for a long time, concerning the development of many reagents in biological and medical fields, the DNA strip can be split by hydrolysis or by oxidation methods. where play complexes Schiff bases a distinct role in the events of many changes in the composition and properties of DNA.

Schiff's Bases, or Azomethine, contain the double bond between carbon and nitrogen (C = N), it is the functional group, this type of system plays a crucial role in coordinate chemistry, due to its ability to bind with metal ions through donor atoms in their composition.

The Schiff bases complexes and the changing transitional elements are distinguished in the coordination structure, and oxidation states and spectral changes, these properties give a wide space for the design of suitable symmetric ligands, capable of binding to DNA and RNA. Other applications of HEV bases complexes that act as catalysts for many organic reactions, models for interaction with enzymatic metallic centers are effective catalysts in the synthesis of identical molecules.
chemically\(^{15,16}\), agricultural pesticides, analytical chemistry, Dyes, and polymers industry, Food industries, synthetic magnetic chemistry, biological fields, and many other applications\(^{17,18}\). Transition metals can form complexes with Schiff’s bases and also used as chelating ligands in the field of coordination Chemistry, atoms (N, O, and S) play a fundamental role in the coordinate of the metals with the active sites, that is the metals of multiple biological molecules\(^{19,20}\).

1-2-1: Thiadiazole

Thiadiazole is a type of heterocyclic five-member ring compound that contains two nitrogen atoms, one sulfur atom, and two carbon atoms. This type of compound and its complexes are distinguished by a wide range of biological activities and industrial applications, heterocyclic five-member ring compounds, which specifically contain nitrogen and sulfur, are of special importance, Thiadiazole has been successfully tested against many diseases, so it has received more attention in research and study in pharmaceutical and medicinal chemistry because of its various applications\(^{21}\).

The heterocyclic compound 1,3,4-Thiadiazole is a class of thiazoles and this family includes many compounds such as thiadiazole, oxadiazole, and triazole...etc, 1,3,4-thiadiazole was first discovered by Fischer in 1882, but the true form of this type of ring system was introduced in 1890 by both Freund and kuh\(^{22-24}\).

1-2-2: 1,3,4–Thiadiazole

The compound 1,3,4-Thiadiazole has four isomers, and the 1,3,4-Thiadiazole derivatives are the most common among the other isomers in the applications of ligands in coordination chemistry, isomers 1,2,5-Thiadiazole derivatives are used in materials that give a narrow gap in polymers with interesting physical properties, such as conductivity and good nonlinear optical properties in nonlinear nanotechnology\(^{25}\), on the other hand, 1,2,3-thiadiazole isomer derivatives have wide applications in agricultural chemistry\(^{26}\), while many isomer derivatives 1,2,4-Thiadiazole are particularly effective in selectivity and effective inhibitors of enzyme 2-Cyclooxygenase\(^{27}\). Figure (1) shows the structural formulas for the 1,3,4-Thiadiazole isomers.

![Thiadiazole isomers](image)

2: Procedure

2-1: Synthesis compound (A) 2,5-dithiole -1, 3, 4- thadiazole

The potassium hydroxide (22g, 0.4 mole) was dissolved in ethanol (100ml) in the reaction flask (reflex), then adding hydrazine (16 ml) and heating the reaction mixture for (10-15hr), then cooling at room temperature and then adding (50ml) carbon Disulfide (gradually and in small batches with stirring) heating the reaction mixture for (6-8 hr.) The follow-up of the reaction should be monitored using thin layer chromatography (TLC) or the removal the smell similar to the smell of rotten eggs resulting from the release of hydrogen sulfide gas, or by using lead acetate solution
(CH₃COOPb) when the blackening of the leaf a filtration moistened with a solution resulting from the formation of hydrogen sulfide gas (H₂S), this indicates the end of the reaction and the formation of the product of the derivative of thiadiazole, cooling by ice for about an hour and then adding a solution of hydrochloric acid (HCl) 10% of the reaction mixture, heating the reaction mixture for one hour and then cooling the reaction mixture, we note the deposition of yellow crystals due to the thiadiazole derivative (2,5-dithiole-1,3,4- thiadiazole)²⁸,²⁹. Filter the solution and then wash it with distilled water, and recrystallize it using ethanol, and drying. The weight of the formed product is (22gm, 0.25mole), with a yield about (78%), and the melting point (m.p) ranges from (163-165) ºC as in Figure (2).

![Figure 2](synthesis_2_5_dithiole-1_3_4_thiadiazole.png)

**Figure (2) Synthesis 2,5-dithiole-1, 3, 4- thiadiazole**

2-1-1: Synthesis compound (B) 2,5-dihydrazinel-1,3,4-thiadiazole

The compound (A) was dissolved in ethanol absolute (100ml) and adding hydrazine (5 ml) and heating the reaction mixture (Reflux) for (9-12hr), Follow the reaction progress until the reaction endpoint is reached by TLC, after making sure the end of the reaction and the formation of pale white crystals (yellowish), evaporating the solution to the half, and then conducting agent filtration and washing the precipitate with distilled water, and re-crystallization using absolute ethanol and distilled water ³⁰. The obtained crystals (B) (2,5-dihydrazone-1,3,4-thiadiazole) with a pale white (yellowish) color (5.2 g, 0.03 mole) weighed their melting point (172-174)ºC With yield (71%), as shown in Figure (3).

![Figure 3](synthesis_2_5_dihydrazine-1_3_4_thiadiazole.png)

**Figure (3) Synthesis 2,5-dihydrazine-1,3,4-thiadiazole**

2-1-2: Synthesis ligand (1) 4,4'-(1E,1'E)-((1,3,4-thiadiazole-2,5-diyl)bis (hydrazin-2-yl-1-ylidene))bis(methaneylylidene))bis(N,N dimethylaniline)

Mix (3g, 0.02 mole) of the 4-Dimethyl amino benzaldehyde dissolved in (50ml) of ethanol absolute with (1.46g, 0.01mole) of compound (B) dissolved in (50ml) of ethanol absolute then added glacial acetic acid (3-4 drops) gradually to the reaction flask and in small batches, then heating for (3-4hr), Follow the reaction progress until the reaction endpoint is reached by TLC, after confirming the end of the reaction and the precipitate being formed, the cooling process is carried out by placing the reaction flask in the ice for about an hour, and then the precipitate is filtered after its concentration (vaporization) to approximately half its volume, washing, and re-crystallization, and the result is in the form of a yellow powder of (3.2 g) The melting point (174-176)ºC and with a yield about (80%), as shown in Figure (4).
2-1-3: Synthesis ligand (L₁) complexes

Add (mole 0.02) of ligand (L₁) in the reaction flask dissolved in (50 ml) of absolute and hot ethanol to (0.001 mole) of salts (CuCl₂.2H₂O), (CoCl₂.6H₂O) to the reaction flask periodically and heat the reaction mixture (Reflux) for (3-4 hr). Follow the reaction progress until the reaction endpoint is reached by TLC, the cooling process is carried out by placing the reaction flask in the ice for about an hour, and then the precipitate is filtered after its concentration (vaporization) to approximately half its volume, washing and re-crystallization using absolute ethanol. The yield obtained from the crystals of the transitional elements complexes with the ligand (L₁) with some physical properties as shown in Table (1).

| Chemical Formula and some physical properties | Symbol | Chemical Formula | M.wt  | Color          | m.p  °C | Yield |
|----------------------------------------------|--------|-----------------|-------|----------------|--------|-------|
|                                              | L₁     | C₂₀H₂₄N₈S      | 408.5 | Light yellow   | 176-174 | 80%   |
|                                              | L₁Cl₁  | [L₃CoCl₂]Cl     | 573.3 | Light brown    | 290-293 | 78%   |
|                                              | L₁C₂   | [L₃CuCl₂]       | 542.1 | Olive green    | 280-283 | 74%   |

3: Result and Discussion

3-1: Characterize of prepared compounds

The prepared ligand and its metal complexes were diagnosed based on the results of the Elemental Analyzer Instrument, the infrared spectrum, the proton nuclear magnetic resonance spectrum, and the mass spectrum.

3-2: Elemental Analysis

The results of the Elemental Analyzer Instrument for the prepared ligand shows the extent of congruence between the practical percentages of the elements (S, N, H, C) with the theoretical percentages calculated for this ligand

| Elemental Analyzer Instrument Data for prepared ligand (1) |
|-----------------------------------------------------------|
| Sym. | Practical Percentages | Theoretical Percentages |
|------|-----------------------|-------------------------|
| L₁   | C % 58.65     | H % 5.85    | N % 27.29   | S % 7.85   | C % 58.80 | H % 5.92 | N % 27.43 | S % 7.85 |

3-3: Infrared Spectra

The infrared spectra of ligand (L₁) and its complexes showed the presence of groups (CH=N) and (NH), and we note the stretch vibration peak of the group (C=N) in all of these compounds as a clear package in the area (1634-1603) cm⁻¹, the stretch vibration peak of the (N-H) group, it appeared in the region (3198-3197) cm⁻¹, the stretch vibration peak was shown at (3080-3027) cm⁻¹ returns to the aromatic group (C-H), and
the ligand also contains a stretch in the region (2898-2821) cm\(^{-1}\) due to the stretch vibration of the aliphatic group (C-H), and a peak appears at the region (1603-1489) cm\(^{-1}\) returns to the vibration of the stretch of the group (C=C) present in the aromatic rings of all prepared compounds. The five-ring spectrum of thiadiazole was distinguished by the appearance of absorption peaks in the regions (1338,1320,1319,1304) cm\(^{-1}\) it returns to the structural movement of the ring and the symmetric and asymmetric stretch vibration for the C-S-C group. The infrared spectra are very important in determining the type of correlation in the case of complexes, where shifting to a higher peak of the highest vibration of the group (C=N) appeared in the complexes shifting towards higher wavenumber compared to their location in the prepared ligand, and this confirms bound nitrogen azomethine group for the dual electronic component to form coordination bond, the complex spectrum was distinguished by the appearance of the stretch vibration M-Cl in addition to (M-N) which were not present in the ligand this confirm that the complexation process has occurred, as these peaks appeared at the sites (621-508)cm\(^{-1}\), (298-265)cm\(^{-1}\) are due to stretch vibration (M-N), (M-C1), respectively, as shown in Table (3).

Table (3) Shown the most important peaks in the infrared spectra of the Schiff bases and their complexes prepared in units (cm\(^{-1}\))

| Sym | Chemical Formula | N-H | Ar. C-H | Aliph C-H | C=N | M-N | M-Cl |
|-----|-----------------|-----|---------|----------|-----|-----|------|
| L1  | C\(_{20}\)H\(_{24}\)N\(_8\)S | 3198 | 3080    | 2821     | 1603|      |      |
| A1  | Cl [L1CoCl\(_2\)] | 3197 | 3050    | 2898     | 1634| 509  | 294  |
| A2  | [L1CuCl\(_2\)]   | 3197 | 3027    | 2850     | 1631| 508  | 273  |

Figure (5) Infrared spectrum of the complex [L1CuCl\(_2\)] in the cesium iodide disk.

3-4: Nuclear Magnetic Resonance Spectra (\(^1\)H-NMR)

The nuclear magnetic resonance spectra for the ligand (L1) was distinguished by the appearance of multiple peaks at (7.77-8.19 ppm) and is due to the aromatic ring protons, a peak at (8.98 ppm) is due to the proton of the group (CH=N), a beam at (10.58 ppm) is due to the proton of the group (N-NH-C=), the spectrum also showed another peak at (2.66-3.32ppm) returning to 12 protons of (-CH\(_3\)) groups, in addition to another peak at (2.5ppm), returning to the solvent Dimethyl sulfoxide (DMSO)\(^{34,35}\) as shown in the Table (4).
Table (4) The peaks shown in the Nuclear Magnetic Resonance Spectra of the prepared ligand.

| Compound | Group       | Kind of signal | Shift (ppm) | Integration |
|----------|-------------|----------------|-------------|-------------|
| L1       | N-NH-C=     | Singlet        | 10.5        | 2H          |
|          | CH3-N       | Singlet        | 3.3         | 12H         |
|          | CH=N-       | Singlet        | 8.9         | 2H          |
|          | Benzene ring| Multiple       | 7.7-8.4     | 8H          |

Figure (6) Nuclear magnetic resonance spectrum (1H-NMR) for the ligand L1 (C20H24N8S)

3-5: Mass Spectra

Most of the research that is concerned with studying and preparing complexes of transition elements depends on the mass spectrum to confirm the structural formulas of the complexes as this spectrum confirms the structural formulas for the prepared Schiff’s bases and their complexes by noticing the molecular ion peak (M⁺) and the appearance of the main peak of the ions separated from the mother molecule, therefore, the mass spectrum was used to diagnose thiadiazole derivatives.

3-5-1: Mass spectra of the ligand (L1)

The ligand mass spectrum was characterized by the appearance of the molecular ion (M⁺) [C20H24N8S]+ at (408 m/z). The spectrum also showed the following peaks 77,178, 218, 269, 334, 378 m/z which due to, [C6H5]+, [C8H6N3S]+, [C9H8N5S]+, [C12H9N6S]+, [C16H12N7S]+, [C18H18N8S]+, respectively, as shown in Table (5) and Figure (7).
3-5-2: Mass spectra of the complex $[\text{L}_1\text{CoCl}_2]\text{Cl}$

The mass spectrum of the molecular ion complex, $[\text{L}_1\text{CoCl}_2]\text{Cl} (M^+)$, showed a peak at (573 m/z) as noted in the spectrum of the following ion peaks (468, 503, 538 m/z) due to the loss of chlorine atoms $([\text{L}_1\text{Co}]^+, [\text{L}_1\text{CoCl}]^+, [\text{L}_1\text{CoCl}_2]^+)$ respectively, as shown in Table (6) and Figure (8).

**Table (6) Mass spectra of the complex $[\text{L}_1\text{CoCl}_2]\text{Cl}$**

| M/Z   | M/Z                      |
|-------|--------------------------|
| 573   | $[\text{L}_1\text{CoCl}_2]\text{Cl}$ |
| 538   | $[\text{L}_1\text{CoCl}_2]^+$ |
| 503   | $[\text{L}_1\text{Co}]^+$    |
| 468   | $[\text{L}_1\text{Co}]^+$    |
3-5-3: Mass spectra of the complex [L₁CuCl₂]Cl

The mass spectrum of the molecular ion complex, [L₁CuCl₂]Cl (M⁺) showed a peak at (542 m/z) as noted in the spectrum of the following ion peaks (472, 507 m/z) due to the loss of chlorine atoms [L₁Cu]⁺, [(L₁CuCl)⁺] respectively, as shown in table (7) and figure (9).

Table (7) Mass spectra of the complex [L₁CuCl]Cl

| M/Z | Ion |
|-----|-----|
| 542 | [L₁CuCl₂]⁺ |
| 507 | [L₁CuCl]⁺ |
| 472 | [L₁Cu]⁺ |

3-6: Molar Conductivity

The conductivity values indicate that the complex [L₁CuCl₂] exhibits the behavior of neutral compounds (non-electrolytic) because there is no ion trait. The complex [L₁CoCl₂]Cl exhibits the behavior of the ionic compounds and the conductivity is different between them (1:1) depending on the number of chloride ions outside the...
consistency ball as Counter Ions for the central ion, the presence of chlorine outside the coordination ball was also confirmed by adding the aqueous solution AgNO₃ to the complex solution (dissolved in DMSO), where a white precipitate was observed in the presence of chlorine outside the coordination ball, and the turbidity increases with the increase in the number of chlorine atoms outside the coordination ball, and the absence of a precipitate or a non-turbidity of the solution indicates that there is no chloride ion outside the coordination ball as a conjugated ion. The results obtained were consistent with the molecular formula and stereo formula of the proposed prepared complexes.

Table (8) Molar conductivity values Λm for ligand complexes (L₁) in the solvent DMSO (10⁻³ M) at a temperature of 298K.

| Electrolyte Type | Λm (S. cm².mole⁻¹ In (DMSO)) | Complexes |
|------------------|-------------------------------|------------|
| 1:1              | 38                            | [L₁CoCl₂]Cl |
| Non Electrolyte  | 14.3                          | [L₁CuCl₂]  |

3-7: Magnetic sensitivity

Effective magnetic moment values (μ_eff) were calculated for the prepared complexes to obtain additional evidence that strengthens the conclusion of the proposed structural formulas for them. The results are shown in Table (9) show a decrease in the values of magnetic moments of the prepared complexes, which confirms that these complexes are of a low spin this means that the prepared ligand is classified as a strong ligand. The low values of the magnetic momentum calculated for the cobalt confirmed that its complexes are of the low spin, because the ligand is strong, which leads to makes electrons pair, as the cobalt showed an octahedral shape. While the magnetic sensitivity values calculated for the copper complex were characterized by having one single electron, the magnetic moment values must be close to the calculated theoretical values where there is no orbital contribution, it suggests that the shape of the copper complex is the square planner and not a tetrahedral, because the strong ligand will push the electron in the 3d orbital to 4p, and this is confirmed by the theoretical study.

Table (9): Effective magnetic moments (μ_eff) of prepared ligand complexes

| Symbol | Complexes   | Effective magnetic moments (μ_eff) |
|--------|-------------|-----------------------------------|
| A₁     | [CoL₁Cl₃]  | 0.6                               |
| A₂     | [CuL₁Cl₂]  | 1.8                               |

3-8: A study of the electronic density of ligands using the Hyperchem program

The Hyperchem program was used to draw the prepared ligands using the PM3 method and demonstrate the Electrostatic Potential. The study of the electrical potential of the molecule is very important for finding effective sites in the molecular system. The voltage of the prepared ligand is drawn, as shown in Figure (10).
Electronic density of Ligand L₁

Ligand L₁(C₂₀H₂₄N₈S)

Figure (10): Distribution of the electronic density in the L₁ ligand

Through the spectroscopic and analytical studies of the prepared thiadiazole derivative and its complexes, it was concluded that ligand (L₁) has its octahedral complexes with salts of three-oxidant transition elements (Co⁺³) while square complexes are level with elements of transition salts triple oxidation (Cu⁺²), as shown in Figure (11).

Figure (11): The geometric shape of the copper and cobalt complexes with ligand

3-9: Evaluation Biological Activity of Schiff Bases and its complex

The activity of ligand (L₁) and its complexes prepared against two types of pathogenic bacteria, Gram-negative and Gram-positive, it is a dye that treats bacteria those that respond to this dye take the dye and do not put it outside the cell wall they are positive, which do not respond to this dye so that they take the dye and put it outside the cell wall, which is negative towards this dye. This difference between the bacteria is due to the nature of its external walls. For this reason, two types of bacteria were used, the first sensitive and positive Gram (Staphylococcus aureus) and the second sensitive and negative for Gram (Escherichia coli).

Dissolve (0.05g) of ligand or complex in (1ml) of DMSO and inject the bacteria dishes after making holes in them using a Cork Borer with (0.1ml) of these solutions in each hole and incubated at a temperature (37°C) for 24 hours, then measured diameters of inhibition zones compared to the inhibition of these materials with standard inhibitor is (Cipro) and the same concentration, as shown in the table (10) and Figure (12).

1- The prepared ligand showed higher biological efficacy than the standard inhibitor (Cipro) against Escherichia coli (Gram-negative).

2- The complexes (A1, A2) showed higher biological efficacy against Escherichia coli (Gram-negative) than standard inhibitor (Cipro).
3- The prepared ligand and its complexes don't show any biological efficacy than against *Staphylococcus aureus* (Gram-positive).

**Table (10) The biology effect of compounds prepared against *Escherichia coli* and *Staphylococcus aureus* compared to the standard inhibitor (Cipro).**

| Symbol | *Escherichia coli* Inhibition zone(mm) | *Staphylococcus aureus* Inhibition zone(mm) |
|--------|----------------------------------------|--------------------------------------------|
| 8(A1)  | 15+++                                  | 0-                                         |
| 9(A2)  | 11++                                   | 0-                                         |
| 10(L1) | 17+++                                  | 0-                                         |
| Cipro  | 9+                                     | 7+                                         |

Note: +++ Very good Inhibition, ++ Good Inhibition, + middle Inhibition, - Not Inhibition.

**Figure (12): Biological effectiveness of complexes 8,9 and 10 against *E. coli* on the right and *Staph.* at the left**

4: Conclusion

1- The new ligand prepared from (1,3,4-Thiadiazole) formed stable metal complexes with a short time with two-and-three-positively charged metallic ions, this consider to be an indication that the prepared ligand has a great ability to coordinate with the metal ions.

2- The triple metal ion (Co$^{3+}$) gave an octahedral complex, while (Cu$^{2+}$) gave a square planner complex.

3- By the results of the measured magnetic sensitivity of the prepared complexes, it was found that the prepared ligand possesses a strong ligand field.

4- Spectroscopic and analytical studies have included the results of the infrared spectrum, elemental analysis, NMR spectroscopy, and mass spectrometry, as well as measurements of molar conductivity and magnetic sensitivity confirmed the proposed molecular and structural formulas for the prepared compounds.

5- The ligand prepared from 1,3,4-Thiadiazole and its complexes showed a strong to moderate inhibition activity against *Escherichia coli*, which encourages future studies on the biological efficacy of metallic complexes and similar types of prepared ligands.

6- The current study showed that the prepared derivatives of 1,3,4-Thiadiazole and its complexes do not have an inhibitory biological activity towards a *Staphylococcus aureus*. 
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