



# A new amino functionalized thio-modified $\beta$ -cyclodextrin based ligand and its Fe(III) complex with physico-chemical and antibacterial activity: an integrated experimental and computational investigation

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## Abstract

$\beta$ -Cyclodextrin plays a crucial role in augmenting the activity of metal complexes by ameliorating their solubility, stability, and reactivity, therefore the thio-functionalized  $\beta$ -cyclodextrin based amino ligand mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (4) was synthesized and analyzed by elemental analyses, AAS, UV–visible, FTIR, and <sup>1</sup>H NMR spectroscopy. The newly synthesized Fe(III) complex was soluble in water. The Fe(III) complex's spectral analysis using FTIR confirmed that the ligand aided the metal ion coordinate by way of the sulfur atom of the  $\beta$ -cyclodextrin moiety and the nitrogen atoms of the two ligand molecules, with two H<sub>2</sub>O occupying the fifth and sixth coordination sites. Additionally, the mass spectrometry verifies that the intended Fe(III) complex has synthesized. Density functional theory (DFT) was used to calculate different electronic parameters of the optimized structure of Fe(III) complex to reveal its stability. Antimicrobial metal complexes that are suitable for therapeutic application are known to be more stable and bioavailable when  $\beta$ -cyclodextrin is introduced, therefore studies have been done to inquire into the possible comparative in vitro antibacterial activity of the Fe(III) complex and free ligand against two gram positive (*Bacillus subtilis*, and *Staphylococcus aureus*) and two gram negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*) strains. Molecular docking was used to further corroborate these capabilities.

**Keywords**  $\beta$ -Cyclodextrin · Mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin · Fe(III) complex · DFT · Antibacterial activity · Molecular docking

## Introduction

In recent years, supramolecular chemistry has drawn more attention from several chemistry disciplines. After presenting their host–guest chemistry conclusions for the first time, Cram, Lehn, and Pedersen were granted the Nobel Prize in 1987 [1–5]. Cyclodextrins are cyclic oligosaccharides consisting a combination of six ( $\alpha$ -CD), seven ( $\beta$ -CD), eight ( $\eta$ -CD), or more glucose subunits connected by  $\alpha$ -1,4 glycosidic linkages [6, 7]. A non-toxic derivative having a hydrophilic surface and a hydrophobic internal cavity,  $\beta$ -cyclodextrin is the most affordable, most helpful, and

easily accessible when compared to other derivatives. The fact that  $\beta$ -CD, functionalized derivatives and its metal complex, can be yielded and applied to a variety of biological applications is the focus of extensive study currently underway in this field [8, 9]. A similar combination of hydrophobicity and molecular rearrangement capabilities is also shown when  $\beta$ -CD is substituted with a ligand at the primary face. On the other hand, other transformations in aqueous media have also been carried out using metal complexes of  $\beta$ -CD. The derivation of  $\beta$ -CD underwent a significant change with the introduction of mono tosylation, which made it possible to couple or derive  $\beta$ -CD at the site of the main hydroxyl group [5, 10].

Transition metal complexes with polydentate ligands have emerged as a major stay of chemistry [11]. In polydentate ligands, donor hetero atoms such as nitrogen, phosphine, oxygen, and sulfur tend to be the most frequent coordinating atoms [12, 13]. Due to the significant roles that nitrogen and sulfur ligands can play in a wide range of metallic biomolecules, chemists worldwide have

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recently focused their attention on the study of metal complexes containing these elements. Under excessive pressure, sulfur- and nitrogen-containing ligands and their transition metal complexes can be added to lubricants, functioning as additional corrosion inhibitors [14–16]. The metal complexes of certain chelating ligands, such as S and N, exhibit biological activities like antifungal [17], antibacterial [18], and anti-humentery [19] characteristics. Unfortunately, the potential applications of these complexes for biological activity can be restricted by their limited solubility in water. Enhancing the solubility of the aforementioned complexes can be achieved by tagging the  $\beta$ -cyclodextrin moiety [20–22] in the ligand structure and thereafter in the complex structure.

Overall, metal complexes based on  $\beta$ -cyclodextrin present encouraging prospects for the synthesis of potent antibacterial medicines that exhibit improved solubility, stability, targeting specificity, and synergistic activity. Their distinct qualities render those appealing options for battling bacterial infections and tackling issues related to antibiotic resistance. Therefore, this work focuses on the synthesis, physico-chemical characterization, and antibacterial activity of an intriguing Fe(III) complex and ligand that is soluble in water with components S and N. Computational simulation is an effective tool to understand the stability of the complex through different electronic property calculations [23]. In this study, different electronic properties e.g., highest occupied molecular orbital (HOMO)-lowest unoccupied molecular orbital (LUMO) gap, electrostatic potential (ESP) maps, Mulliken charge distribution, reduced density gradient (RDG) were calculated with computational simulation using density functional theory (DFT) to establish the stable geometry of the complex. Additionally, the antibacterial activity of both ligand and Fe(III) complex has been studied which was further supported with the help of molecular docking study. According to both experimental and theoretical studies, the ligand and complex may be an effective antibacterial agent, and small modifications to the ligand system could enhance the activity.

## Materials, reagents and methods

The chemicals  $\beta$ -cyclodextrin, *p*-Toluenesulfonyl chloride (TsCl), *o*-chloroaniline,  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , sodium hydroxide (NaOH), ammonium chloride ( $\text{NH}_4\text{Cl}$ ), thiourea, hydrochloric acid (HCl), trichloroethylene ( $\text{C}_2\text{HCl}_3$ ), sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) and ethanol were purchased from Sigma Aldrich in Germany. Double-distilled water was utilized in each experiment. Solvents were purified prior to their use following standard literature procedures.

## Instruments

The Euro VECTOR EA 3000 analyzer was used to conduct elemental microanalyses of C, H, and N. The Perkin-Elmer Spectrum FTIR spectrometer (RX-1) was used to record IR spectra in the  $4000\text{--}400\text{ cm}^{-1}$  range at room temperature using KBr pellets. The JascoV-530 double beam spectrophotometer was used to record UV–visible spectra using a quartz cell with a path length of 1 cm that was equipped with a thermostated bath (maintained at  $25 \pm 0.1\text{ }^\circ\text{C}$ ) using DMSO and water as solvent references. Using  $\text{D}_2\text{O}$  and  $\text{DMSO-d}^6$  as solvents at room temperature,  $^1\text{H}$  NMR spectra were acquired on a Bruker Advance-II 400 MHz spectrometer, and chemical shifts ( $\delta$ ) were stated in ppm with respect to TMS. The Waters ZQ-40000 equipment was utilized to measure the ESI–MS of both the complex and ligand. AAS (Varian, SpectraAA 50B) was used to determine the metal content using a standard metal solution from Sigma-Aldrich, Germany. A magnetic susceptibility balance (Magway MSB Mk1) made by Sherwood Scientific Ltd. was used to test the magnetic susceptibility at room temperature. A Systronics conductivity meter (TDS-308) was used to evaluate the synthesized complex's specific conductance in room-temperature water. The generated ligand and complex's antibacterial activity (in vitro) against four distinct bacterial species—gram positive (*Staphylococcus aureus*, *Bacillus subtilis*) and gram negative (*Escherichia coli*, *Klebsiella pneumoniae*)—was examined using the disc diffusion method.

## Synthesis of mono-6-deoxy-6-(*p*-tosylsulfonyl)- $\beta$ -cyclodextrin ( $\beta$ -CDOTs) (1)

*p*-Toluenesulfonyl chloride (2.5 g, 1.5 equiv.) was added drop wise to a round bottom flask containing  $\beta$ -cyclodextrin ( $\beta$ -CD) (10.0 g, 8.8 mmol) dissolved in pyridine (500 mL) and stirred overnight at room temperature. After 24 h, the solution gave three components as observed by TLC ( $\text{SiO}_2$ ; butanol:ethanol:water = 5:4:3 (vol.)) and the reaction was ceased by adding 10 mL water. Then the reaction mixture was concentrated to one-fifth in volume and acetone was added dropwise until the precipitation was over. The precipitate was filtered, washed with acetone and dried under vacuum. The precipitate was dissolved in DMF and purified on a reversed-phase column (silica gel 60 silanized, 200 g in dry weight,  $4.1 \times 30\text{ cm}_2$ ) using 5–40% DMF (aq) as eluent. The fraction of 5–10% contained  $\beta$ -CD while TsO- $\beta$ -CD was in 10–20% and 20–40% contained (TsO) $_2$ - $\beta$ -CD. Then the fraction of 10–20% was concentrated and poured into acetone to obtain white pure product. The product was filtered, dried and stored in a vacuum desiccator. Color: white; yield (45%); IR

$\text{cm}^{-1}$ , KBr: 3391 (OH), 2926 (C–H), 1646 (C=C), 1366 (SO<sub>2</sub> asym), 1153 (SO<sub>2</sub> sym)  $\text{cm}^{-1}$ ; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C),  $\delta$  (ppm): 7.49 (m, 2H Ph), 7.12 (m, 2H Ph), 5.94–5.72 (m, 14H, OH2 and OH3 CD), 4.87–4.76 (m, 7H, H1 CD), 4.58–4.43 (m, 6H, OH6 CD), 4.27 (m, 2H, H6/CD), 4.02 (m, 1H, H5/CD), 3.92–3.54 (m, 25H, H3, H5 and H6 CD), 3.47–3.14 (m, H2, H4 overlap with water), 2.28 (s, 3H, Ph-CH<sub>3</sub>) [13]; <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  (ppm): 146.52, 143.15, 127.91, 124.26 (aromatic), 101.84 (C1), 81.06 (C4), 73.03, 72.06, 71.68 (C3, C2, C5), 62.88 (C6/), 60.16 (C6), 23.18 (C9) [14]; Anal. Calcd for C<sub>49</sub>H<sub>76</sub>O<sub>37</sub>S: C, 45.65; H, 5.94; O, 45.92. Found: C, 45.05; H, 5.29; O, 45.53.

### Synthesis of mono-6-deoxy-6-mercapto- $\beta$ -cyclodextrin (2)

After dissolving 2 g of powdered  $\beta$ -CDOTs (1) and 2 g of thiourea in 100 mL of 80% aqueous methanol, the mixture was refluxed for two days at 60 °C. The solution was refluxed and then evaporated in a vacuum. The residue was combined with 30 mL of methanol and stirred for 1 h. The residue was filtered and dissolved to 34 mL of 10% NaOH and was kept at 50–60 °C for 5 h. By adding 2.5 mL of trichloroethylene (CHCl<sub>3</sub>) and 10% HCl, the pH of the solution was kept at 2. It was then stirred all night at room temperature. The precipitate that was produced was filtered and repeatedly cleaned with water. After that the trichloroethylene (CHCl<sub>3</sub>) was eliminated in a vacuum, compound 2 was produced by repeatedly recrystallizing it from water.

Color: White; Yield (56%); IR, KBr  $\text{cm}^{-1}$ : 2562 (-SH), 1650, 1365–1200  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C): 5.95–5.86 (m, 14H, OH2 and OH3 CD), 4.92–4.85 (m, 7H, H1 CD), 4.59–4.51 (m, 6H, OH6 CD), 4.35 (m, 2H, H6/CD), 3.98 (m, 1H, H5/CD), 3.71–3.61 (m, 25H, H3, H5 and H6 CD), 3.43–3.34 (m, H2, H4 overlap with water), 2.14 (s, 1H, SH), ppm [21, 24]. Anal. Calcd for C<sub>42</sub>H<sub>70</sub>O<sub>34</sub>S: C, 43.82; H, 6.12; O, 47.25; S, 2.78. Found: C, 43.28; H, 5.87; O, 46.86; S, 2.27. *m/z* (ESI): calculated 1151.02 found 1152.24 [M + H]<sup>+</sup>.

### Synthesis of mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (3)

After dissolving 344.7 mg of mono-6-deoxy-6-mercapto- $\beta$ -cyclodextrin (2) and 38.25 mg of *o*-chloroaniline in 70 mL of aqueous Na<sub>2</sub>CO<sub>3</sub> (pH 10) with 20 mL ethanol, the mixture was stirred under nitrogen for two days at room temperature. The pH of the solution was adjusted to 3 by adding 1N HCl, and was vacuum-concentrated to about 40 mL. After adding 5 mL of trichloroethylene, the liquid was stirred for an entire day. The precipitate formed was collected with trichloroethylene using separating funnel. After the trichloroethylene

was evaporated in vacuo, the solid product that remained was obtained and purified by repeated recrystallization.

Color: White; Yield (78%); IR  $\text{cm}^{-1}$ : 1612, 1262, 753  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 25 °C):  $\delta$ =7.53 (m, 1H, Ph), 7.28 (m, 1H, Ph), 7.12 (m, 1H, Ph), 6.91 (m, 1H, Ph), 5.93–5.89 (m, 14H, OH2 and OH3 CD), 4.71–4.64 (m, 7H, H1 CD), 4.45–4.38 (m, 6H, OH6 CD), 4.25 (s, 2H, NH<sub>2</sub>), 4.11 (m, 2H, H6/CD), 3.89 (m, 1H, H5/CD), 3.78–3.64 (m, 25H, H3, H5 and H6 CD), 3.54–3.41 (m, H2, H4).; UV: 206 nm, 312 nm; Anal. Calcd for C<sub>48</sub>H<sub>75</sub>NO<sub>34</sub>S: C, 46.41; H, 6.08; N, 1.12; O, 43.79; S, 2.58. Found: C, 46.03; H, 5.19; N, 0.97; O, 43.24. *m/z* (ESI): calculated 1242.13, found 1242.63 [M]<sup>+</sup>.

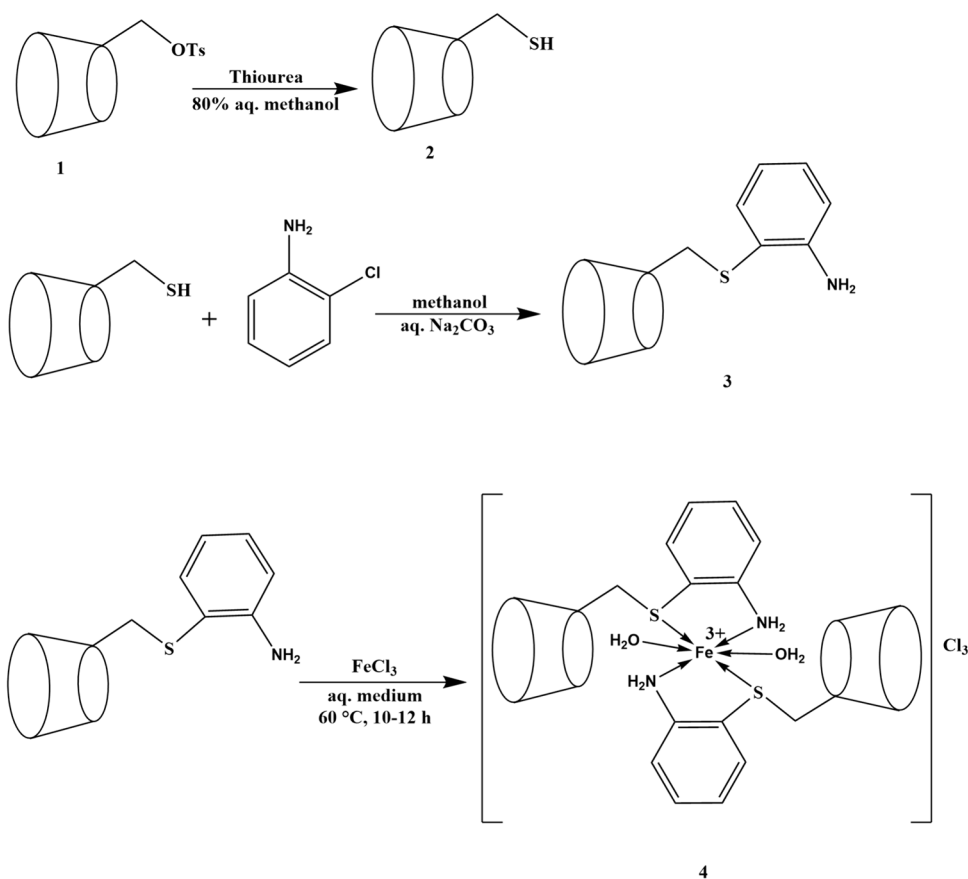
### Synthesis of Fe(III)-complex of mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (4)

An aqueous solution containing 0.1 mmol (27.03 mg) FeCl<sub>3</sub>·6H<sub>2</sub>O was stirred at room temperature and then was added drop wise to a stirred aqueous solution containing 2 mmol (248 mg) of ligand (3). Afterwards, the mixture was refluxed at 60 °C for 10 to 12 h. The solution was then concentrated to a volume of 15 mL. Then, by adding 100 mL of acetone, white precipitate appeared. After being vacuum-filtered through a Buchner funnel and twice being washed with acetone, the precipitate was dried in a desiccator to yield a purple color product.

Color: Purple; Yield (80%); IR  $\text{cm}^{-1}$ , KBr: 840, 735, 525, 466; UV: 232 nm, 370 nm, 524 nm; Anal. Calcd for C<sub>84</sub>H<sub>142</sub>N<sub>2</sub>O<sub>70</sub>S<sub>2</sub>Cl<sub>3</sub> Fe: C, 39.94; H, 5.66; N, 1.10; O, 44.31; S, 2.53, Fe, 2.21. Found: C, 39.42; H, 5.11; N, 0.94; O, 44.07; S, 2.06; Fe, 1.93. *m/z* (ESI): calculated 2525.80, found 2525.54 [M]<sup>+</sup>.

### Computational study

Gaussian 09 software was used for the DFT calculation of the optimized Fe(III) complex structure with B3LYP hybrid functional [25]. 6–31 g (d,p) basis set was used for non-metals (C H O N S) while an effective core potential LANL2DZ basis set was used for Iron metal in aqueous medium [26, 27]. Frequency calculation of optimized geometry (no imaginary frequencies) revealed that the geometry of the complex lies on the minima to the potential energy surface [27]. To reduce the computational cost we have considered one unit of thio-functionalized  $\beta$ -cyclodextrin attached with Fe(III) for computational simulation [28, 29]. Different electrochemical parameters like highest HOMO–LUMO energy gap, Mulliken charge distribution, and ESP maps, RDG of the Fe complex were also analyzed with same level of theory.

**Scheme 1** Synthesis of compound 1, 2, 3 and 4

## Antibacterial activity

Two pathogenic gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and two pathogenic gram negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* were used for assessing the antibacterial activities using well diffusion method. The Mumbai, India-based Hi-media laboratory Pvt Ltd was the supplier of the nutrient agar (NA) medium. Boiling NA (2.8 g) in 100 mL of distilled water while suspended in it resulted in its complete dissolution. It was then autoclaved for 15 min at 15 lbs of pressure (121 degrees Celsius) and transferred onto a sterile Petri plate to set. A sterility check was carried when the agar solidified [30]. Pure cultures of each bacteria were prepared in nutrient broth and kept at 37 °C for the duration of the night. After incubation, each of the required plates was inoculated using a non-toxic, sterile cotton swab dipped into the microbial growth. Extra inoculate was removed by firmly pressing and spinning the swab against the tube wall above the liquid's level. To inoculate the media, the swab was equally streaked across the whole surface of the plate in three distinct directions. The antibacterial activity assay was carried out using the agar well diffusion method. Sterile nutritional agar (NA) was applied to sterile Petri dishes containing the test organisms after they had been inoculated. Using a sterile cork borer, every Petri plate (9 mm) was carefully prepared.

Each well (microorganism-inoculated plate) received approximately 200  $\mu$ l of a synthetic chemical (10 mg/mL) using a sterile pipette. The combination was then incubated for 24 h at 37 °C. After the incubation period, all tested plates were inspected and the inhibitory zone widths were measured.

## Molecular docking

The selected protein PDB ID (<https://www.rcsb.org>) was utilized to carry out the molecular docking of the complex using the Auto Dock Vina tool (version 1.1.2). The grid dimensions for all the proteins were kept 1 Å spacing were all the proteins dimensions to being stiff for the receptor structure. The dimensions of X, Y, and Z for 5ZH8 (*Staphylococcus aureus*) was 62, 58, and 60 for 2GCX (*Klebsiella pneumoniae*) was 40, 44, and 40, for 2BH0 (*Bacillus subtilis*) was 56, 54, and 40 and for 1XFF (*Escherichia coli*) was 40, 46, and 48, respectively.

## Results and discussion

Mono-6-deoxy-6-(*p*-tosylsulfonyl)- $\beta$ -cyclodextrin ( $\beta$ -CDOTs) (1) was converted into mono-6-deoxy-6-mercapto- $\beta$ -cyclodextrin (2). After synthesis, *o*-chloroaniline



reacts with the mercapto modified  $\beta$ -cyclodextrin (2) to generate mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (3). Later, it is permitted to react with  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in aqueous medium to give amino functionalized mercapto modified  $\beta$ -cyclodextrin based Ferric complex(4) (Scheme.1). The structure of Fe(III) complexes was verified by a variety of analytical spectroscopic techniques, such as elemental analysis, FTIR,  $^1\text{H}$  NMR, UV–visible spectra, ESI–MS, and molar conductance.

## FTIR spectra

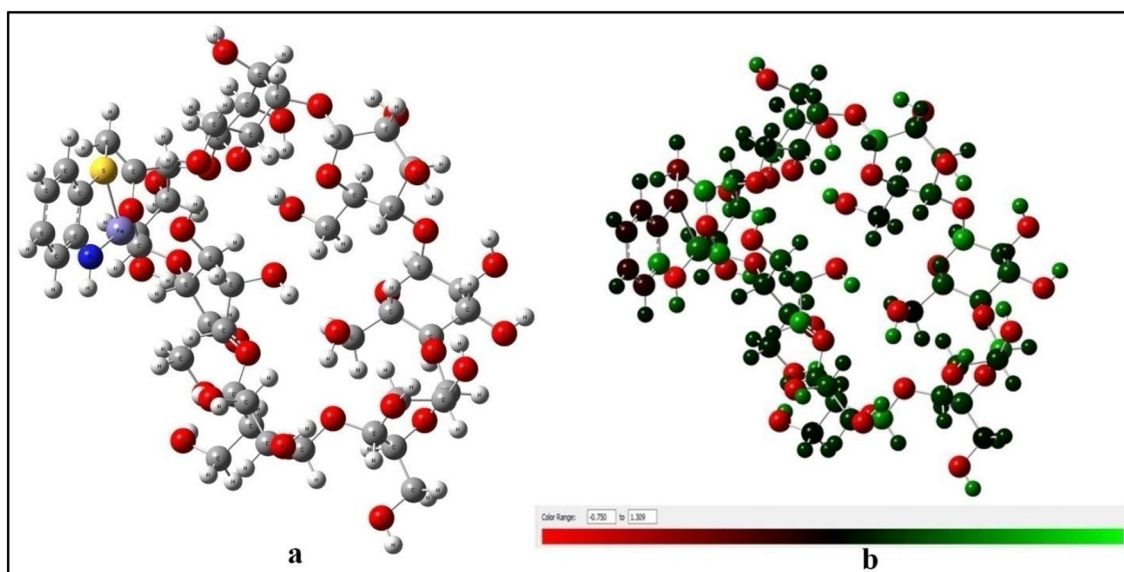
The FTIR spectra of compounds 1 and 2 were shown in (Fig. S1 and Fig. S2). The usual absorption peaks at  $3391\text{ cm}^{-1}$  is due to the presence of OH of the  $\beta$ -cyclodextrin moiety. The other peaks such as 1646, 1366, and  $1153\text{ cm}^{-1}$  in the IR spectra of 6-OTs- $\beta$ -CD (1) is due to presence of C=C,  $\text{SO}_2$  Asymmetric and  $\text{SO}_2$  Symmetric respectively [31]. Owing to the thio group (–SH) substitution for the tosyl group, these peaks are absent from the compound 2 IR spectra. On the other hand, the characteristic absorption peak of  $2562\text{ cm}^{-1}$  is visible in the spectra of 2. The absorption peak at  $2562\text{ cm}^{-1}$ , which was found to match with SH stretching vibrational bands [24], suggesting the detection of a thiolated  $\beta$ -cyclodextrin. The absorption peak at  $1200\text{--}1055\text{ cm}^{-1}$ , appears along this because of the C–O vibration in polysaccharide and antisymmetric glycosidic (C–O–C) bond [32]. The polysaccharide C–C stretching is responsible for the band at  $1650\text{ cm}^{-1}$ . In the FTIR spectra of compound 3 (Fig S3), three new, distinct absorption peaks appeared at 1612 (N–H bending), 1262 (C–N stretching), and  $753\text{ cm}^{-1}$  (N–H wagging)  $\text{cm}^{-1}$ . The absorption peaks at  $2562\text{ cm}^{-1}$  in

compound 2 disappeared. The results showed that the thiol group had been replaced with the aniline group. The coordinated wagging and rocking vibration of the water molecule was identified as the cause of the bands that appeared at  $840$  and  $735\text{ cm}^{-1}$  in the infrared spectra of 4 (Fig. S4) [21]. In complex 4,  $\nu(\text{M–S})$  vibrations were identified in the bands at  $466\text{ cm}^{-1}$  and  $\nu(\text{M–N})$  vibrations were identified in the band at  $525\text{ cm}^{-1}$  [33].

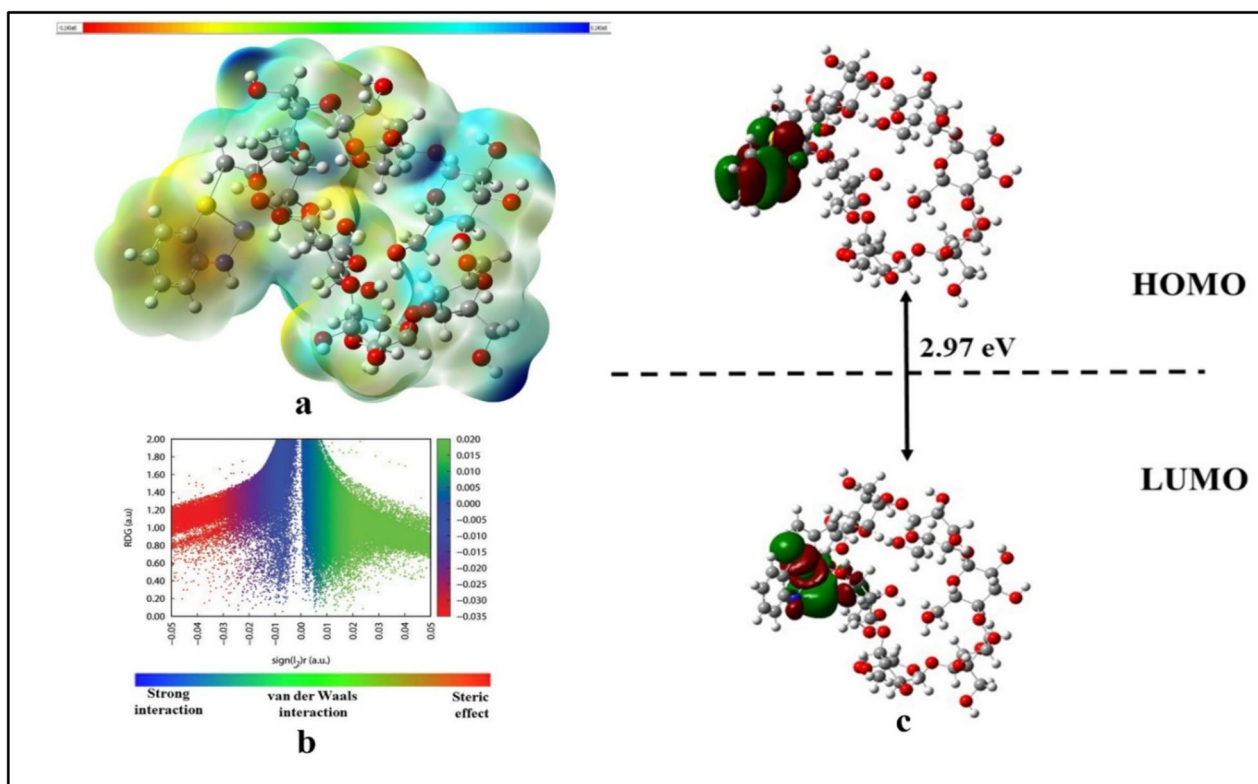
## NMR spectra

For the mono-tosylated  $\beta$ -cyclodextrin (1), mono-6-deoxy-6-mercapto- $\beta$ -cyclodextrin (2), and mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (3), the  $^1\text{H}$  NMR spectra were recorded in  $\text{D}_2\text{O}$  and  $\text{DMSO-d}_6$ . The metal compound is paramagnetic, so its  $^1\text{H}$  NMR spectra were not able to be obtained. The  $^1\text{H}$  NMR of the mono-tosylated  $\beta$ -cyclodextrin (1) is shown in figure S5. The  $^1\text{H}$  NMR spectra of Compound 2 (figure S6) shows that the –SH group peak is situated at  $\delta = 2.14\text{ ppm}$  [24]. It is proposed that the signals of the H6 protons with a thiol group (H6'a, H6'b) that occur at 0.74 ppm lower field than those of the H6 protons of other rings of  $\beta$ -cyclodextrin suggesting the formation of mono-6-deoxy-6-mercapto- $\beta$ -cyclodextrin (2).

Compound (3)  $^1\text{H}$  NMR spectrum (figure S7) reveals that the aromatic protons' signals showed as multiplets in the range of  $\delta \approx 6.91\text{--}7.53\text{ ppm}$ , and the – $\text{NH}_2$  group appeared as a singlet at 4.25 ppm [21]. This observation supports the theory that compound 3 substituted the thiol proton with an aromatic amine. In compound (3)  $^1\text{H}$  NMR spectra, the peak of the –SH proton that was present in compound (2) disappeared.



**Fig. 1** a Optimized structure of the Fe(III) complex, b Mulliken charge analysis of the complex



**Fig. 2** **a** Molecular electrostatic potential maps of the synthesized complex. **b** Reduced density gradient (RDG) of the synthesized complex. **c** HOMO–LUMO energy gap calculation

### UV–visible spectra and magnetic moment studies

The UV–visible spectra of the mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin(3) and Fe(III)-complex of mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin (4) were recorded in water, (figure S8 and S9). Two bands are visible at 312 and 206 nm in compound 3, which are caused by the  $n \rightarrow \pi^*$  and  $\pi \rightarrow \pi^*$  transitions. Fe(III) complex (4) exhibits a band shift from 206 to 232 nm (bathochromic), indicating a coordinated behavior of the metal ion ( $\text{Fe}^{3+}$ ) with ligand. The coordination of Fe and the ligand's N-atom was shown by the complexes' disappearance of their peaks at 312 nm relative to the ligands. The MLCT/LMCT transition is responsible for the complex (4) peaks that appear at 370 nm. In contrast, transitions at 714–625 nm have been discovered to characterize the low-spin ( $S = 1/2$ ) form, while transitions at 555–500 nm have been shown to represent the high spin ( $S = 5/2$ ) form in distinct spin equilibrium systems [34]. The Fe(III) complexes' spectra show a single band at 524 nm, which is consistent with the  ${}^6\text{A}_1\text{g} \rightarrow {}^4\text{T}_1\text{g}$  transition characteristic of the octahedral structure [34]. As a result, the Fe-complex has octahedral, high spin geometry. A computation of the magnetic moment of the synthesized Fe(III) complex showed that it was paramagnetic. The magnetic moment value ( $\mu_{\text{eff}}$ ) at room temperature is 5.88 B.M.

According to these values, the Fe(III) complex has a high spin octahedral structure.

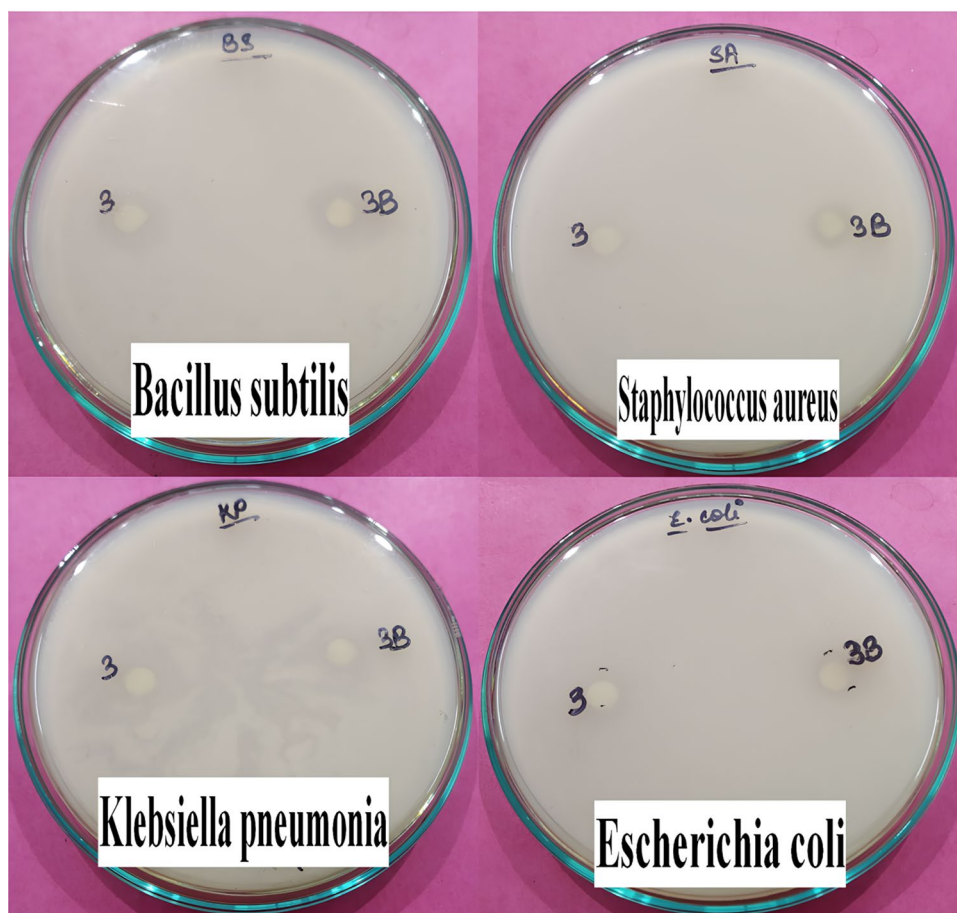
### ESI–MS

The ESI–MS spectra of compounds 2, 3, and 4 were recorded and are shown in figure S10, S11 and S12 respectively. Compounds 2 and 3 includes  $m/z$  peaks at 1152.24 and 1242.63 corresponding to  $[\text{M} + \text{H}]^+$  and  $[\text{M}]^+$ , respectively. In Fe(III) complex (4), an additional peak was found at 2525.54  $[\text{M}]^+$  which corresponds to the molecular weight of the complexes. Consequently, these results were in good agreement with the comparable structures that had been earlier demonstrated by the elemental and other spectrum examinations.

### Molar conductance

After dissolving the synthesized Fe(III) complex in water, the molar conductance of  $10^{-3}$  mol  $\text{dm}^{-3}$  complex solutions was measured at room temperature. A 1:3 electrolytic behavior was suggested by the conductance value of  $405 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$  of the Fe(III) complex (4) [35].

**Fig. 3** Antibacterial activity of ligand and complex (denoted as 3 and 3A respectively) against *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumonia* and *Escherichia coli*



**Table 1** Antibacterial screening results

Compounds	Inhibition zone (mm)			
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Klebsiella pneumonia</i>
Ligand	11	6	6	7
Complex	12	9	8	8

### Electronic properties study using DFT

Optimized structure of the complex [considering one unit of thio-functionalized  $\beta$ -cyclodextrin attached with Fe(III)] is represented by the Fig. 1a. Metal Iron is well capped by the Sulphur, Oxygen and Nitrogen atoms. A strong binding reflects by the bond distances of 1.83 Å (N-Fe) and 2.27 Å (S-Fe). Two Oxygen atoms are also apart from Fe with an average distance of 2.1 Å. Mulliken charge analysis data (Fig. 1b) also supports the compact structure of the complex. Positive Fe (green) is well attached with the negative N, O and S (reddish).

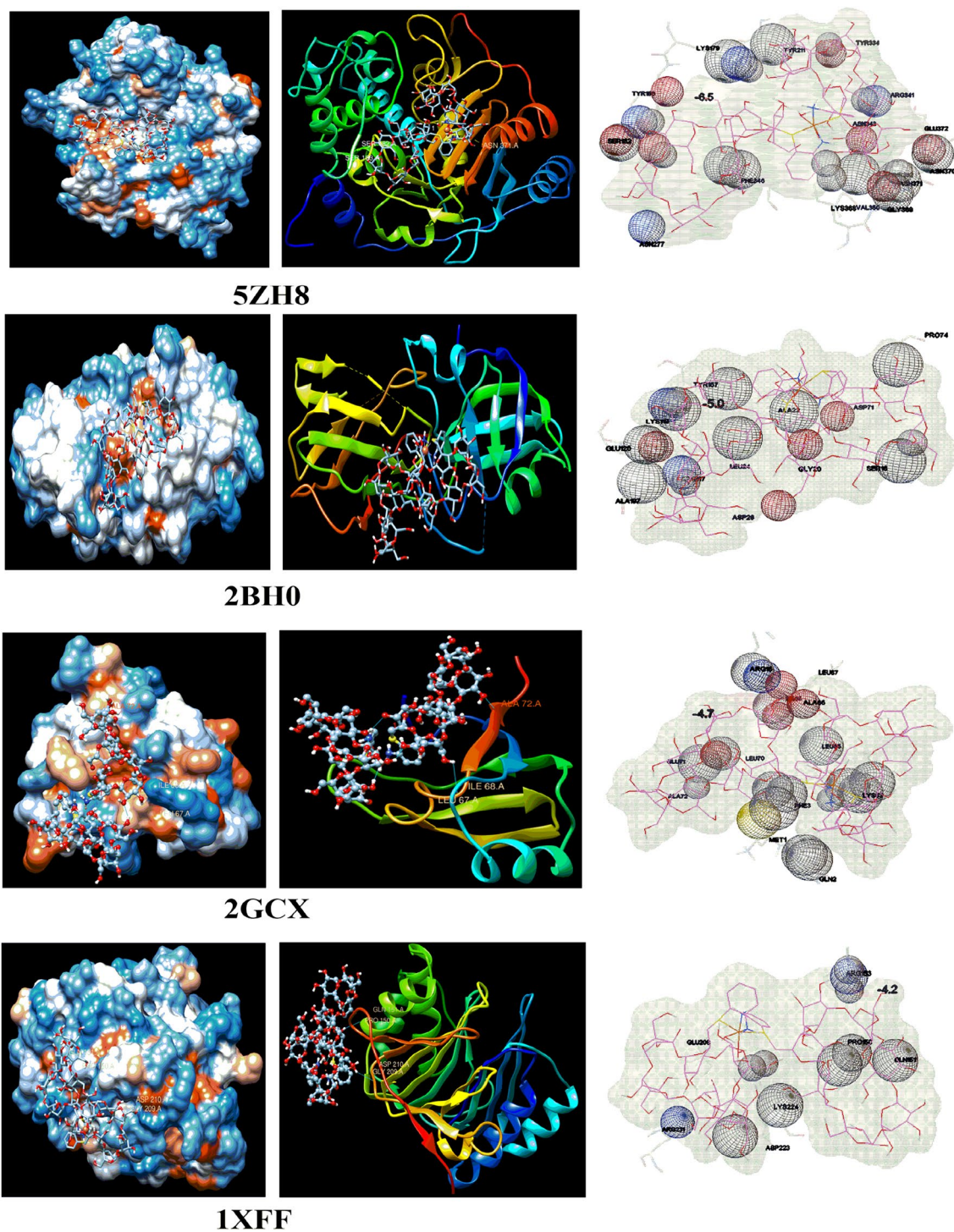
ESP study (Fig. 2a) reflects a moderate negative surface present in the thio end of the complex. As per RDG analysis, van der Waals and strong interaction majorly dominate the

complex as green and blue color covers the maximum part of Fig. 2b. Repulsive steric interaction (red color) is very less as per RDG analysis. Hence, RDG analysis reflects a stable complex was synthesized. HOMO–LUMO energy gap (Fig. 2c) is quite small in the complex as reflected from the DFT study [36].

### Antibacterial activity

The antibacterial activity of the ligand and complex was assessed using two gram positive (*Staphylococcus aureus*, *Bacillus subtilis*) and gram negative (*Escherichia coli*, *Klebsiella pneumonia*) bacteria. Given the existence of biologically active donor sites (N and S), it was highly expected that the ligand and complex would have good activity against bacteria, as shown in Fig. 3 and Table 1. Comparing two gram-positive bacteria with complex and ligand activity, *Staphylococcus aureus* and *Bacillus subtilis* had a stronger response than the other two gram-negative bacteria. The ligand and complex have demonstrated inhibitory zones of 11 and 12 mm against *Staphylococcus aureus* and 6 and 9 mm against *Bacillus subtilis*. The inhibitory zones obtained for *Escherichia coli* have been calculated to be 6 and 8 mm, while *Klebsiella pneumonia* showed





**Fig. 4** Complex's docking image with *Staphylococcus aureus* (PDB ID: 5ZH8), *Bacillus subtilis* (PDB ID: 2BH0), *Klebsiella pneumoniae* (PDB ID: 2GCX), and *Escherichia coli* (PDB ID: 1XFF)

similar patterns of diminishing ligand and complex activity sequences at 7 and 8 mm. The efficiency of common medications against various bacterial strains was investigated in a previous paper. The results suggested that small adjustments

to the ligand and complex might enhance the antibacterial activity [37–39].



**Table 2** Docking score with interaction profile

Protein name	PDB ID	Binding energy (Kcal/mol)	Amino acid residues
Crystal structure of FmtA from <i>Staphylococcus aureus</i> at 2.58 Å	5ZH8	−6.5	LYS179, TYR180, SER 182, TYR211, ASN277, TYR334, ARG341, ASN343, PHE346, VAL350, THR352, LYS368, GLY369, ASN370, ASN371, GLU372
Crystal structure of a SeMet derivative of EXPA from <i>Bacillus subtilis</i> at 2.5 Å	2BH0	−5.0	SER16, GLY20, ALA22, LEU24, ASP26, ASP71, PRO74, ARG117, LYS119, TYR157, LYS119, GLU120, ALA197
Solution structure of ferrous iron transport Protein A (FeoA) of <i>Klebsiella pneumoniae</i>	2GCX	−4.7	MET1, GLN2, PHE3, ARG16, LYS62, LEU65, ALA66, LEU67, ILE68, LEU70, GLU71, ALA72,
Glutaminase domain of glucosamine 6-phosphate synthase complexed with glutamate ( <i>Escherichia coli</i> )	1XFF	−4.2	PRO150, ARG153, GLN151, GLU208, ASP223, LYS224, ARG231

## Molecular docking

The complex was examined for interactions with different bacteria using the Auto Dock Vina tool (Fig. 4; Table 2). The molecular docking data further validate our previous claims. The receptor proteins of *Staphylococcus aureus* (5ZH8), *Bacillus subtilis* (2BH0), *Klebsiella pneumoniae* (2GCX), and *Escherichia coli* (1XFF), were used for the molecular docking of the complex. According to reports, the binding affinities were −6.5, −5.0, −4.7, and −4.2 in that order. Overall, the data point to the complex's strong interactions with a variety of bacterial protein receptors, supporting its claimed antibacterial efficacy.

## Conclusions

To summarize, a water soluble octahedral Fe(III) complex was synthesized using mono-6-deoxy-(*o*-aminobenzylthio)- $\beta$ -cyclodextrin, an amino ligand derived from thio modified  $\beta$ -cyclodextrin. FTIR spectra of the Fe(III) complexes confirmed that the ligands coordinate the metal ion via the sulfur and nitrogen atoms of the  $\beta$ -cyclodextrin moiety and amino groups respectively of the two ligand molecules and two H<sub>2</sub>O occupied the fifth and sixth coordination. The ESI-MS study suggested that it was a 1:2 metal-ligand complex. Electronic properties study using DFT also reflected a stable complex was synthesized. The synthesized compounds show potentiality to inhibit the bacterial efflux systems and enhancing the antibiotic activity which was further supported with the help of molecular docking.

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**Availability of data and materials** All data generated or analyzed during this study are included in the manuscript.

## Declarations

**Conflict of interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Ethics approval** This is an observational study. The University of North Bengal Ethics Committee has confirmed that no ethical approval is required.

**Consent to participate** This declaration is “not applicable”.

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