Coordination complexes constructed from pyrazole–acetamide and pyrazole–quinoxaline: effect of hydrogen bonding on the self-assembly process and antibacterial activity†

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Two mononuclear coordination complexes of N-(2-aminophenyl)-1-[5-methyl-1H-pyrazol-3-yl] acetamide (L1), namely [Cd(L1)2Cl2] (C1) and [Cu(L1)2(μ2-CH3OH)](NO3)2 (C2) and one mononuclear complex [Fe(L2)2(H2O)2](NO3)2·2H2O (C3), obtained after in situ oxidation of L1, have been synthesized and characterized spectroscopically. As revealed by single-crystal X-ray diffraction, each coordination sphere made of two heterocycles is completed either by two chloride anions (in C1), two ethanol molecules (in C2) or two water molecules (in C3). The crystal packing analysis of C1, C2 and C3 revealed 1D and 2D supramolecular architectures, respectively, via various hydrogen bonding interactions, which are discussed in detail. Furthermore, evaluation in vitro of the ligands and their metal complexes for their antibacterial activity against Escherichia coli (ATCC 4157), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923) and Streptococcus faecalis (ATCC 29212) strains of bacteria, revealed outstanding results compared to chloramphenicol, a well-known antibiotic, with a normalized minimum inhibitory concentration as low as 5 μg mL⁻¹.

1. Introduction

There is growing interest in the development of new active antibacterial compounds as current clinical treatments remain insufficient to meet the challenge of the increasing emergence and spread of antimicrobial resistance.¹ In Europe, antibiotic resistance is responsible for approximately 33,000 deaths per year.² In the United States, more than 2.8 million people suffer from antibiotic-resistant infections, resulting in more than 35,000 deaths each year.³ In 2019, the WHO identified 32 antibiotics in clinical development that address the WHO’s list of priority pathogens, of which only six were classified as innovative. Furthermore, a lack of access to quality antimicrobials remains a major issue. Antibiotic shortages are affecting countries of all levels of development and especially in healthcare systems.⁴ Therefore, there is an urgent need to develop new antimicrobial agents.

Nitrogen-based ligands are attracting growing attention due to their interesting properties in structural and inorganic chemistry.⁵ Pyrazole derivatives are biologically active heterocyclic compounds.⁶⁻⁷ This substance class has been the topic of numerous pharmaceutical studies being used for their medicinal properties such as anti-inflammatory,⁸ antidiabetic,⁹⁻¹¹ antiviral,¹² analgesic,¹¹ antitumor,¹³ catecholase,¹⁴ and antimicrobial properties.¹⁵⁻¹⁶ On the other hand, nitrogen systems have attracted more attention in recent years because of their interesting properties in coordination chemistry.¹⁷⁻¹⁹ However, many reports on transition metal complexes explain their efficient bioactivity against a range of bacterial and fungal species.²⁰⁻²² In particular, heterocyclic metal complexes dominated medicinal chemistry

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† Electronic supplementary information (ESI) available. CCDC 2095073 for C1, C2 and C3. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra09027e
due to their wide range of properties. Metal complexes tethered with heterocyclic moieties like imidazole, pyrazole, 1,2,4-triazoles and benzimidazole have received remarkable interest as broad spectrum antibacterial, antifungal and antiviral agents. Therefore, the antibacterial activity of many metal complexes has been demonstrated against several bacterial species both in vitro and in vivo, making it as promising antibacterial agents for use against these bacteria, pending a greater understanding of its safety upon systemic or topical administration in humans. Recently, a study investigated organometallic compounds submitted to the Community for Open Antimicrobial Drug Discovery (CO-ADD) databank, established a classification based on the nature of their metal element, activity, as well as toxicity. Metal-containing compounds show actually a significantly higher success rate (9.9%) compared to purely organic molecules (0.87%). Out of 906 compounds, 88 show activity against at least one of the tested strains, including fungi, while showing no cytotoxicity against mammalian cell lines or hemolytic properties. Amongst the metal complexes, cadmium, copper and iron, were the most frequent elements found in active ‘non-toxic’ compounds and show the highest overall success rate.

In order to search for new ligand candidates for assemblies of metal complexes, we considered the case of pyrazole acetamide ligands with O and N donor atoms. These molecules are particularly interesting as ligands for the construction of polynuclear complexes as models for bioinorganic systems. As a continuation of our research along this line, we have

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**Table 1** Refinement parameters and crystal data for C₁, C₂ and C₃

| CCDC number | C₁             | C₂             | C₃             |
|-------------|----------------|----------------|----------------|
|             | C₂H₂CdCl₂N₈O₂  | C₂₈H₄₀CuN₈O₄·2(NO₃) | C₂₄H₂₄FeN₈O₄·2(NO₃)·2(H₂O) |
| Crystal data |                |                |                |
| Chemical formula |                |                |                |
| M₀                    | 643.84         | 740.24         | 704.41         |
| Crystal system, space group | Monoclinic, Cc | Triclinic, P | Triclinic, P |
| T (K)                | 150            | 240            | 150            |
| a, b, c (Å)          | 13.7075(8), 21.2787(13), 9.1536(6) | 9.0258(5), 10.0091(6), 11.2402(6) | 8.392(3), 11.420(4), 15.823(6) |
| α, β, γ (°)          | 95.127(1)      | 74.769(1), 66.668(1), 80.782(1) | 78.679(4), 86.124(4), 1465.5(9) |
| V (Å³)               | 2659.2(3)      | 897.84(9)      | 1465.5(9)      |
| Z                     | 4              | 1              | 2              |
| μ (mm⁻¹)             | 0.96           | 0.67           | 0.60           |
| Crystal size (mm)    | 0.35 × 0.13 × 0.12 | 0.27 × 0.12 × 0.11 | 0.28 × 0.25 × 0.04 |

**Data collection**

| Diffractometer       | Bruker Smart APEX CCD |                  |                  |
| Absorption correction | Multi-scan SADABS     |                  |                  |
| Tmin, Tmax           | 0.75, 0.88            | 0.82, 0.93       | 0.73, 0.98       |
| No. of measured, independent and observed [I > 2σ(I)] | 25873, 7227, 6833 | 16816, 4438, 3338 | 12137, 6014, 3364 |
| Rint                  | 0.029                 | 0.031            | 0.042            |
| (sin θ/λ)max (Å⁻¹)   | 0.698                 | 0.668            | 0.629            |

**Refinement**

| R [F² > 2σ(F²)], wR(F²), S | 0.023, 0.053, 1.03 | 0.045, 0.129, 1.03 | 0.069, 0.215, 1.00 |
| No. of reflections       | 7227              | 4438             | 6014             |
| No. of parameters        | 337               | 241              | 427              |
| No. of restraints        | 2                 | 29               |                  |
| H-atom treatment        | H-atom parameters constrained | H-atom parameters constrained | H-atom parameters constrained |
| Δρmax, Δρmin (e Å⁻³)    | 1.09, −0.24       | 0.58, −0.22      | 1.35, −0.45      |
| Absolute structure      | Refined as an inversion twin |                  |                  |
| Absolute structure parameter | 0.267(16)        |                  |                  |
successfully synthesized three new Cd(n), Cu(n) and Fe(n) coordination complexes derived from the ligands, namely N-(2-aminophenyl)-2-(5-methyl-1H-pyrazol-3-yl)acetamide (L₁) and 3-(5-methyl-1H-pyrazol-3-yl)quinoxalin-2(1H)-one (L₂) (Fig. 1). The molecular structures of the complexes were confirmed by single-crystal X-ray diffraction. All ligands and metal complexes were evaluated in vitro for their antibacterial activity against *Escherichia coli* (ATCC 4157), *Pseudomonas aeruginosa* (ATCC

### Table 2 Hydrogen-bond geometry (Å, °) of C₁, C₂ and C₅

| D–H⋯A       | D–H    | H⋯A    | D⋯A    | D–H⋯A  | Symmetry codes                      |
|-------------|--------|--------|--------|--------|-------------------------------------|
| C₁          |        |        |        |        |                                     |
| N1–H1A⋯Cl2 | 0.91   | 2.57   | 3.469(3) | 169    | x – 1/2, −y + 3/2, z − 1/2          |
| N1–H1B⋯Cl1 | 0.91   | 2.52   | 3.259(3) | 139    | x, y, z                            |
| N2–H2A⋯Cl2 | 0.91   | 2.61   | 3.280(3) | 131    | x, y, z − 1                        |
| N4–H4A⋯N5  | 0.91   | 2.06   | 2.954(4) | 168    | x, y, z                            |
| N5–H5A⋯Cl2 | 0.91   | 2.59   | 3.473(3) | 157    | x, y, z                            |
| N5–H5B⋯Cl1 | 0.91   | 2.59   | 3.473(3) | 165    | x + 1/2, −y + 3/2, z + 1/2         |
| N6–H6A⋯O2  | 0.91   | 2.29   | 3.196(4) | 170    | x, −y + 1, z + 1/2                 |
| N8–H8A⋯N1  | 0.91   | 2.04   | 2.937(4) | 171    | x, y, z                            |
| C10–H10⋯Cl1| 0.95   | 2.74   | 3.617(3) | 154    | x + 1/2, −y + 3/2, z − 1/2         |
| C4–H4⋯Cg2  | 0.95   | 2.89   | 3.587(4) | 131    | x, y, z − 1                        |
| C22–H22⋯Cg5| 0.95   | 2.82   | 3.693(3) | 144    | x, −y + 1, z + 1/2                 |
| C₂          |        |        |        |        |                                     |
| N1–H1A⋯O2  | 0.91   | 2.17   | 3.062(3) | 166    | −x + 1, −y + 2, −z + 1             |
| N1–H1B⋯O3  | 0.91   | 2.12   | 3.028(6) | 173    | x − 1/2, y, z                      |
| N2–H2A⋯O2  | 0.91   | 1.96   | 2.857(2) | 167    | x, y, z                            |
| N4–H4A⋯N1  | 0.91   | 2.05   | 2.958(2) | 173    | −x + 1, −y + 1, −z + 1             |
| C5–H5⋯O4   | 0.94   | 2.54   | 3.431(8) | 158    | −x + 1, −y + 2, −z + 2             |
| C10–H10⋯O4 | 0.94   | 2.39   | 3.329(4) | 173    | −x + 2, −y + 2, −z + 1             |
| C12–H12B⋯O3| 0.97   | 2.46   | 3.388(6) | 161    | −x + 2, −y + 1, −z + 1             |
| O5–H5A⋯O2  | 0.87   | 2.17   | 2.898(2) | 141    | x, y − 1, z                        |
| O5–H5A⋯O4  | 0.87   | 2.45   | 3.262(5) | 156    | x, y − 1, z                        |
| C₃          |        |        |        |        |                                     |
| O3–H3A⋯N1  | 0.87   | 2.00   | 2.855(4) | 168    | −x + 1, −y + 1, −z + 1             |
| O3–H3B⋯O10 | 0.87   | 1.89   | 2.708(11)| 157    | x, y, z                            |
| O3–H3B⋯N10 | 0.87   | 2.52   | 3.381(17)| 173    | x, y, z                            |
| O4–H4A⋯O12 | 0.87   | 1.80   | 2.638(5) | 162    | x, y, z                            |
| O4–H4B⋯N5  | 0.87   | 1.99   | 2.856(4) | 174    | −x + 1, −y + 1, −z                 |
| N2–H2A⋯O7  | 0.91   | 1.91   | 2.805(4) | 166    | x, y + 1, z                        |
| N3–H3C⋯O11 | 0.91   | 2.02   | 2.917(4) | 169    | x, y − 1, z                        |
| N6–H6A⋯O11 | 0.91   | 1.94   | 2.845(4) | 173    | x, y − 1, z                        |
| N7–H7C⋯O7  | 0.91   | 1.98   | 2.885(4) | 176    | x, y + 1, z                        |
| C14–H14⋯O5 | 0.95   | 2.54   | 3.400(5) | 175    | x + 1, y, z                        |
| C24–H24A⋯O9| 0.98   | 2.49   | 3.47(3)  | 173    | −x + 1, −y + 2, −z                 |
| O11–H11A⋯O6| 0.87   | 2.05   | 2.833(4) | 153    | x + 1, y + 1, z                    |
| O11–H11B⋯O9| 0.87   | 1.76   | 2.61(2)  | 167    | x, y, z                            |
| O12–H12D⋯O5| 0.87   | 1.96   | 2.814(6) | 168    | x, y, z                            |
| O12–H12D⋯N9| 0.87   | 2.57   | 3.359(6) | 151    | x, y, z                            |
| O12–H12E⋯O9| 0.87   | 2.01   | 2.87(14)| 170    | x, y − 1, z                        |

a Cg2 and Cg5 are, respectively, the centroids of the N7/N8/C32/C21 and C1⋯C6 rings.
27853), Staphylococcus aureus (ATCC 25923) and Streptococcus fasciens (ATCC 29212) strains of bacteria.

2. Experimental

2.1. General methods

Melting points were measured using a Buchi B-545 digital capillary melting point apparatus and used without correction. Reactions were checked with TLC using aluminum sheets with silica gel 60 F254 from Merck. IR spectra were recorded on a PerkinElmer VERTEX 70 FT-IR spectrometer covering field 400–4000 cm⁻¹. ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ on a Bruker spectrometer (300 MHz). Mass spectra were collected using an API 3200 LC/MS/MS system, equipped with an ESI source. Chemical reagents were purchased from Fluka, Sigma and Aldrich chemicals. ⁵⁷Fe Mössbauer spectra were measured in transmission geometry at room temperature with a constant acceleration mode conventional spectrometer equipped with a 50 mCi ⁵⁷Co(Rh) source and a Reuter Stokes proportional counter. A microcrystalline sample of C₃ was sealed in a Plexiglas sample holder. The spectrum was fitted using Recoil 1.0 Mössbauer Analysis software (Lagarec K., Rancourt D. G.: Recoil, Mössbauer spectral analysis software for Windows 1.0. Department of Physics, University of Ottawa, Canada (1998)). The isomer shift is given with respect to α-Fe at room temperature. X-Ray powder diffraction patterns were recorded on a D8-Advance diffractometer (Bruker, Germany) working with a Cu Kα radiation (λ = 1.5148 Å).

2.2. Synthesis

2.2.1. Synthesis of (Z)-4-(2-oxopropylidene)-4,5-dihydro-1H-1,5-benzodiazepin-2(3H)-one (3). A solution of dehydroacetic acid (3.36 g, 0.02 mol) and of o-phenylenediamine (4.32 g, 0.04 mol) in xylene (80 mL) was refluxed for 4 h. Next, the precipitated product was filtered under reduced pressure and then recrystallized from ethanol. Yield: 75% (2.52 g); m.p. (°C): 236–238; IR (ATR, γ (cm⁻¹)): 1671, 1607, 1575; ¹H NMR (300 MHz, DMSO-d₆, δ (ppm)): 2.00 (s, 3H, CH₃); 3.00 (s, 2H, CH₂); 5.20 (1H, s); 7.10 (4H, m); ESI-MS: m/z = 217 [M + H]+.

2.2.2. Synthesis of N-(2-aminophenyl)-2-(5-methyl-1H-pyrazol-3-yl)acetamide (L₁). A mixture of (Z)-4-(2-oxopropylidene)-4,5-dihydro-1H-1,5-benzodiazepin-2(3H)-one (2 g, 0.92 mmol) and stoichiometric amount of hydrazine hydrate (0.46 g, 0.92 mmol) in ethanol (40 mL) were refluxed for 2 h. After concentration of the solvent volume to 20 mL, the solution was allowed to stand; the precipitate formed was filtered off and then recrystallized from ethanol. Single crystals were obtained after recrystallization from ethanol. Yield: 80% (1.6 g); m.p. (°C): 170–172; IR (ATR, (cm⁻¹)): 3000–3400 (NH, NH₂), 1737 (C=O), 1655 (C=N), 1625, 1604, 1586 (C=C), 608 (Cd–Cl), 541 (Cd–N), 404 (Cd–O); ESI-MS: m/z = 231 [M + H]+.

2.2.3. Synthesis of [Cd(L₁)₂Cl₂] (C₁). CdCl₂·2.5H₂O (100 mg, 0.44 mmol, 1 eq.) was dissolved in water (10 mL) and added to a solution of L₁ (200 mg, 0.87 mmol, 2 eq.) in ethanol (15 mL). The resulting light yellow solution was left at room temperature. Colorless column-like single crystals were obtained by slow evaporation of a clear light yellow solution of the reaction mixture after 48 h. Yield = 88% (490 mg); FT-IR (ATR, (cm⁻¹)): 3391–3291 (NH, NH₂), 3117–2866 (CH), 1746 (C=O), 1653 (C=N), 1625, 1604, 1586 (C=C), 608 [Cd–Cl], 541 (Cd–N), 404 (Cd–O); ESI-MS: m/z = 607.1030 [M – Cl + H]+ for C₂₄H₂₈CdCl₂N₈O₂ in MeOH.

2.2.4. Synthesis of [Cu(L₁)₂(C₂H₅OH)₂(NO₃)₂] (C₂). Cu(NO₃)₂·3H₂O (110 mg, 0.46 mmol, 1 eq.) was dissolved in

Scheme 2 Plausible reaction mechanism for the formation of L₂.
water (10 mL) and added to a solution of L1 (200 mg, 0.87 mmol, 2 equiv.) in ethanol (15 mL). The resulting solution was stirred and warmed slightly. The light green precipitate was filtered and then recrystallized from ethanol and left at room temperature. Light green single crystals were obtained by slow evaporation of the reaction mixture after 24 h. Yield: 90% (580 mg); FT-IR (ATR, cm\(^{-1}\)): 3398–3217 (NH, NH\(_2\)), 3121–2905 (CH), 1746 (C=O), 1614 (C=N), 1549, 1499, 1453 (C=C), 427 (Cu–N); ESI-MS: \(m/z = 615.2382 \text{ [M + H]}^+\) for C\(_{28}\)H\(_{40}\)CuN\(_8\)O\(_4\) in MeOH.

2.2.5. Synthesis of \([\text{Fe}(\text{L}_2)\text{H}_2\text{O}_2]\text{NO}_3\cdot2\text{H}_2\text{O}\) (C\(_3\)). Fe(NO\(_3\))\(_3\)·9H\(_2\)O (180 mg, 0.45 mmol, 1 eq.) was dissolved in water (10 mL) and added to a solution of \(\text{L}_1\) (200 mg, 0.87 mmol, 2 eq.) dissolved in ethanol (15 mL). The resulting red solution was stirred and warmed slightly, and left at 10 °C. Red orange single crystals were obtained by slow evaporation of the reaction mixture after 24 h, and filtered. Yield: 45% (280 mg); FT-IR (ATR, cm\(^{-1}\)): 3198–2860 (CH), 1663 (C=O), 1624 (C=N), 1575, 1537, 1518 (C=C), 505 (Fe–N); ESI-MS: \(m/z = 566.1096 \text{ [M + Na]}^+\) for C\(_{24}\)H\(_{24}\)FeN\(_8\)O\(_4\) in MeOH. When the reaction was carried out at 40 °C, a black powder precipitated which was filtered and analyzed by X-ray powder diffraction and \(^{57}\)Fe Mössbauer spectroscopy. From this black powder, red orange crystals could be isolated, presenting the same structure as C\(_3\).

2.3. X-ray analysis

X-ray single-crystal data were collected on single crystals using Mo K\(\alpha\) (\(\lambda = 0.7107\) Å) radiation on a Bruker SMART APEX diffractometer equipped with CCD area detector. Unit cell refinement data reduction (SAINT) and structure solution as well as refinement (SHELXTL)\(^{19}\) were carried out using the software package of SMART APEX. The structures of C\(_1\), C\(_2\) and C\(_3\) were solved by direct method and refined in a routine manner. In both structures, non-hydrogen atoms were treated anisotropically. Molecular graphics were generated by using the softwares MERCURY 3.9 (ref. 46) and POV-Ray. The details of the X-ray crystal data and the structure solution as well as the refinement are given in Table 1. CCDC 2095071–2095073 for C\(_1\), C\(_2\) and C\(_3\), respectively contain the supplementary crystallographic data for these compounds.

2.4. Antibacterial activity

The antibacterial activity of the synthesized compounds was determined according to the method described in our previous work.\(^{43}\)

3. Result and discussion

3.1. Synthesis of pyrazole–acetamide ligands L\(_1\)

Our strategy was to develop a simple, high-yield, synthetic procedure in a few steps to prepare the desired acetamide derivative. The development of the synthesis of L\(_1\) is given in Scheme 1. The major product \(^3\) was produced in good yield by condensation of o-phenylenediamine with dehydroacetic acid (DHA) in refluxing xylene for 4 h. The second step consists in the condensation of a stoichiometric amount of hydrazine monohydrate with the benzodiazepine compound 3 in refluxing ethanol for 2 h to give the ligand pyrazole–acetamide L\(_1\) in good yield\(^{44}\) (Scheme 1).

3.2. Synthesis of coordination complexes C\(_1\), C\(_2\) and C\(_3\)

The three coordination complexes \([\text{Cd}(\text{L}_1)_2\text{Cl}_2]\) (C\(_1\)), \([\text{Cu}(\text{L}_1)_2(\text{C}_2\text{H}_2\text{OH})_2]\text{NO}_3\cdot2\text{H}_2\text{O}\) (C\(_2\)) and \([\text{Fe}(\text{L}_2)_2(\text{H}_2\text{O})_2]\text{NO}_3\cdot2\text{H}_2\text{O}\) (C\(_3\)) were obtained as single crystals after recrystallization from ethanol during the reaction carried out in an aqueous ethanolic solution.
solution involving pyrazole acetamide L₁ and Cd(II), Cu(II) and Fe(III) (metal/ligand ratio 1 : 2), respectively (Table 2).

While classic coordination occurred for L₁ with cadmium and copper, an unexpected oxidation reaction followed by an intramolecular cyclization of the formed intermediate was presumably observed when iron nitrate was used as chelating agent. Thus, the iron(II) complex C₃ was synthesized in low yield by the reaction of Fe(NO₃)₃·9H₂O with L₁ in a 1 : 2 molar ratio using ethanol as a solvent. The low yield of the compound is attributed to the involvement of the L₁ ligand in the redox reaction with Fe(III) ion, where the Fe(III) ion was reduced to Fe(II) ion. The Fe(II) ion produced was complexed with the ligand L₂ formed by the oxidation of L₁ (Scheme 2). The first Fe(III) promoted in situ oxidation of a thiazoline-2-thione to the corresponding hetero-disulphide with concomitant coordination to Fe(II) was reported by Raper et al.,⁴⁹ Several studies have been conducted mainly to characterize the products of reactions between nitrogen-containing ligands and Fe(III) ions under aerobic conditions.⁵⁰–⁵³ The presence of the electron-withdrawing groups increases the reduction potential of the Fe³⁺ + e⁻ → Fe²⁺ redox couple, making the reduction product thermodynamically more stable.⁵⁴

A plausible mechanism (Scheme 2) is proposed to explain the original transformation of pyrazole acetamide L₁ into the new ligand L₂. Thus, the participation of the ligand L₁ in redox reaction with Fe(III) ion, where Fe(III) ion was reduced to Fe(II) ion and L₁ was oxidized to L₁′, is proposed. Afterwards, air oxygen reacted with the carbon–carbon double bond of the tautomeric form L₁′ affording spiro oxetane pyrazole A which undergoes a ring opening of the oxetane moiety under the effect of a base to lead to the hydroxy pyrazoline B. The latter compound aromatizes by the loss of a water molecule to give the ketonic amide C which undergoes an intramolecular cyclization to afford after a loss of a water molecule pyrazolyl quinoxaline acting as coordination compound towards Fe(II) ion produced by reduction of Fe(III). It should be noted that a similar oxidation reaction has already been observed in our previous work on 1,2,4-triazolo pyrimidines.⁴³

3.3. Description of the crystal structures of the complexes [Cd(L₁)₂Cl₂] (C₁), [Cu(L₁)₂(C₂H₅OH)₂][NO₃]₂ (C₂) and [Fe(L₂)₂(H₂O)₂][NO₃]₂·2H₂O (C₃)

The crystal structures of C₁, C₂ and C₃ are shown in Fig. 2. Crystallization of all the three coordination compounds was
obtained by reaction of the ligand L₁ (for C₁ and C₃) or L₂ (for C₄) and metal salts in aqueous ethanolic solution (metal : ligand = 1 : 2) by slow evaporation.

3.3.1. [Cd(L₁)₂Cl₂] (C₁). Colorless column-like single crystals of C₁ crystallized in the monoclinic space group Cc (Table 1). The asymmetric unit contains one crystallographically unique Cd(n) ion, two molecules of ligand L₁ and two chloride anions. The Cd(n) metal center showed distorted octahedral geometry \[
\left[ \angle \text{N–Cd–Cl} = 100.78(7)\text{°}–106.73(7)\text{°}; \angle \text{N–Cd–O} = 77.13(8)\text{°}–78.18(8)\text{°}; \angle \text{Cl–Co–Cl} = 100.22(3)\text{°}; \angle \text{O–Cd–O} = 86.72(10)\text{°}; \angle \text{O–Cd–Cl} = 83.69(6)\text{°} \right]
\] in which the coordination sites are occupied by two chloride anions, and N atoms of pyrazole and O atoms of amide moiety of the ligand L₁. The equatorial coordination sites of Cd(n) are occupied with the two N atoms and one O atom of the pyrazole and amide functionalities of the ligand L₁, respectively, and one Cl⁻ anion, and the axial position are coordinated to one Cl⁻ anion and one O atom of amide moiety of L₁. Basically, the non-planar ligand L₁ [torsion angle between the planes of the aromatic rings = 47.84(2) and 60.33(8)° for crystallographically independent ligands] coordinates to Cd(n) in an N, O-chelating mode, generating the six-membered chelate ring as expected. Such chelation was strongly supported by strong intramolecular hydrogen bonding involving amino group of L₁ with the metal bound Cl⁻ anion \([\text{N–H…Cl} = 3.259(3)\text{Å}]; \angle \text{N–H–Cl} = 139°\] O atom of amide functionality of L₁ \([\text{N–H…O} = 2.934(3)\text{Å}; \angle \text{N–H–O} = 109°]\) and N atom of pyrazole \([\text{N–H…N} = 2.937(4)\text{Å}; \angle \text{N–H–N} = 171°]\) resulted in a four-membered, six-membered and five-membered rings, respectively. Moreover, supramolecular assembly in the crystal structure of C₁ is mainly driven by N–H…Cl hydrogen-bonding interactions comprising N–H of the amide moiety of L₁ and metal bound Cl⁻ anion \([\text{N–H…Cl} = 3.280(3)\text{Å}; \angle \text{N–H–Cl} = 131°]\), resulting in a one-dimensional (1D) hydrogen bonded chain structure. Such chains are further assembled in parallel fashion with the support of various van der Waals interactions (Fig. 3).

3.3.2. [Cu(L₁)₂(C₂H₅OH)₂][NO₃]₂ (C₂). Light green colored single crystals of C₂ belong to triclinic centrosymmetric space group P1. The asymmetric unit contains one-half of Cu(n) ion, one full molecule of ligand (coordinated to the metal center Cu(n) through N atom of pyrazole and O atom of amide functionality of L₁ in a chelate fashion), one molecule of ethanol (also coordinated to Cu²⁺) and one nitrate counter anion. Thus the entire octahedral coordination complex is generated by the inversion center of symmetry located on the metal ion Cu²⁺. The Cu(n) metal center showed slightly distorted octahedral geometry \([\angle \text{N–Cu–O} = 89.48(7)°–90.52(7)°]; \angle \text{O–Cu–O} = 89.40(6)°–90.60(6)° \right]\) in which the equatorial coordination positions of Cu(n) are occupied by the O and N atoms of L₁ through its amide and pyrazole moieties resulted in N,O-chelated six membered ring, and axial positions of the metal center are coordinated to the O atoms of ethanol ([EtOH]). As expected the ligand showed nonplanar geometry, revealed from the torsion angle [68.62(6)°] between the planes of the aromatic rings. The amine and amide N–H of the coordination complex form hydrogen bonding with O atoms of the nitrate anion \([\text{N–H…O} = 3.028(7)\text{Å}; \angle \text{N–H–O} = 173°]\); the nitrate anion also involved in bifurcated hydrogen bonding with N–H of amine \([\text{N–H…O} = 2.857(2)\text{Å}; \angle \text{N–H–O} = 167°]\) and O–H of metal bound ethanol molecule \([\text{O–H…O} = 2.898(2)\text{Å}; \angle \text{O–H–O} = 141°]\) resulted in \(R_2^1(9)\) ring (Fig. 4a). Supramolecular assembly in the crystal structure of C₂ is mainly directed by intermolecular N–H…O and O–H…O hydrogen-bonding interactions involving the nitrate anion with amide, metal bound ethanol and amine resulted in three synthons.

![Crystal structure illustration of C₂](image-url)
having graph-sets of $R_{2}^{2}(11)$, $R_{2}^{2}(9)$ and $R_{2}^{2}(8)$ (Fig. 4b). Self-assembly through these three synthons lead to the formation of a two-dimensional (2D) hydrogen bonded sheet structure. If the discrete [Cu(L$_{1}$)$_{2}$](EtOH)$_{3}$ complex, and nitrate anions are taken as nodes, 2D hydrogen bonded network in this coordination compound can be simplified to a 2D $(3,6)$-connected kgd net with a point (Schläfli) symbol of {4$^{3}$}$_{2}$4$^{6}$6$^{6}$8$^{3}$ (Fig. 4c). Such 2D layers are stack up each other along crystallographic axis ‘a’ with the support of C–H···O hydrogen bonding involving aromatic C–H and O atom of nitrate anion [C–H···O = 3.431(8) Å, ∠C–H–O = 158°] (Fig. 4d).

3.3.3. [Fe(L$_{2}$)$_{2}$(H$_{2}$O)$_{2}$](NO$_{3}$)$_{2}$·2H$_{2}$O (C$_{3}$). Orange colored single crystals of C$_{3}$ got crystalized in the centrosymmetric triclinic space group $P	ext{1}$ (Table 1). The asymmetric unit comprises of one Fe(ii) ion, two molecules of ligand L$_{2}$, two water molecules (both water and L$_{2}$ are coordinated to Fe(ii)), two nitrate counter anions and two solvated water molecules. The Fe(ii) metal center showed distorted octahedral geometry [∠O–Fe–O = 88.91(11)–91.62(11)$^\circ$; ∠O–Fe–N = 84.56(11)–97.20(11)$^\circ$] in which the equatorial and axial coordination sites are occupied by ligand L$_{2}$ and water molecules, respectively. In the crystal structure, the ligand L$_{2}$ showed slightly non-planar structure in which the torsion angle between the plane of quinoxaline and pyrazole is 11.43–13.11$^\circ$. The O atom of quinoxaline and N atom of pyrazole moiety of L$_{2}$ are coordinated to the Fe(ii) resulted in a N,O-chelated six membered ring. The hydrogen bonding interactions of nitrate anions with solvated water molecule [N–H···O = 2.885(5) Å, ∠N–H–O = 177$^\circ$; O–H···O = 2.813(5)–2.87(3) Å, ∠O–H–O = 168–170$^\circ$] and nitrate···π interaction [3.454(6) Å] of nitrate with pyrazole ring of metal coordinated L$_{2}$ resulted in an twelve membered ring which contains the four donor and acceptor atoms with a graph-set symbol $R_{2}^{2}(12)$ (Fig. 5a). This synthon is connected to the discrete [Fe(L$_{2}$)$_{2}$(H$_{2}$O)$_{2}$] complex unit node through nitrate anions, metal bound water molecule and quinoxaline moiety via N–H···O and O–H···O interactions [N–H···O = 2.805(4) Å, ∠N–H–O = 166$^\circ$; O–H···O = 2.708(12) Å, ∠O–H–O = 157$^\circ$], the same synthon is further assembled with the neighboring [Fe(L$_{2}$)$_{2}$(H$_{2}$O)$_{2}$] complex unit node through another twelve membered ring having a graph-set of $R_{2}^{2}(12)$ N–H···O [N–H···O = 2.845(4) Å, ∠N–H–O = 173$^\circ$] and O–H···O [O–H···O = 2.613(3)–2.87(3) Å, ∠O–H–O = 162–170$^\circ$] hydrogen bonding involving nitrate anions, solvated water molecules, quinoxaline N–H and Fe(ii) coordinated water molecule (Fig. 5a).

The hydrogen bonding interactions through these two synthons resulted in the self-assembly of C$_{2}$ along crystallographic axis “b” lead to the formation of one-dimensional hydrogen bonded chain (Fig. 5a). The self-assembly further follow through these
two twelve membered ring synthons along crystallographic axis “a” resulted in a 2D hydrogen bonded sheet network structure (Fig. 5b and c). Interestingly, such 2D network structure further self-assembled through O–H···N hydrogen bonding [O–H···N = 2.856(4) Å, \( \angle O\text{–}H\text{–}N = 174^\circ \)] involving metal bound water and N atom of quinoxalinone (along crystallographic axis “c”) lead to the formation of a 3D hydrogen bonded network (Fig. 5d). If the discrete [Fe(L2)(H2O)2] complex, and twelve membered ring synthons are taken as nodes, the 3D hydrogen bonded network can be simplified to a 3D \([3\times 6\text{c}]\)-connected net having point (Schläfli) symbol of \([4\times 8]^2[4^2\times 6]^2[4^2\times 8]^10\times 10^3\) (Fig. 5e).

### 3.4. Hirshfeld surface analysis

To further explore the supramolecular interactions in the crystal structure of the coordination compounds, we have constructed their Hirshfeld surface and 2D-fingerprint plots by using Crystal Explorer program.\(^{25}\) The surface where the electron density \(\rho_{\text{int}}(r)\) of the molecules is larger than the electron density \(\rho_{\text{ext}}(r)\) of the adjacent molecules is called the Hirshfeld surface.\(^{26}\) Hirshfeld surfaces (HS) of the coordination compounds \(C_1, C_2\) and \(C_4\) are shown in Fig. 6, displaying the surface map over the normalized contact distance \((d_{\text{norm}})\) in which the red and white colors indicating strong proximity and intermediate closeness of atoms to the HS from outside, respectively. We have used the following equation to calculate \(d_{\text{norm}}\) from the values of \(d_e\) (distance between the Hirshfeld surface and external molecule), \(d_i\) (distance between the Hirshfeld surface and inside molecule), \(r_{vdw}^i\) or \(r_{vdw}^e\) van der Waals radii of the atoms. From the value of \(d_{\text{norm}}\) we can easily determine the regions participating in the intermolecular interactions in the complexes.

\[
d_{\text{norm}} = \frac{d_i}{r_{vdw}^i} + \frac{d_e}{r_{vdw}^e}
\]

In other words, these two colors indicating strong and intermediate hydrogen bonding interactions present between HS and neighboring atoms outside, respectively. The blue color regions in the HS meaning the longer distances than the van der Waals radii. The HS of \(C_1\) was generated by using a standard (high) surface resolution with 3D \(d_{\text{norm}}\) surfaces mapped to a range \(-0.3180\) to \(1.5585\) a.u. From the \(d_{\text{norm}}\) mapping, it is

![Fig. 6](image)
revealed that strong N–H···Cl hydrogen bonding interaction (between amide moiety of L4 and chloride anion) was present in the crystal structure of C1, as observed from the bright red spots on the HS. The 3D \( d_{\text{norm}} \) surfaced mapping of C2 was done within the range of \(-0.5718\) to 1.7268 a.u which showed bright red spots at amine and amide N–H (due to strong N–H···O hydrogen bonding with nitrate counter anion), and metal bound water molecule (O–H···O hydrogen bonding with nitrate). In the case of complex C3, the 3D \( d_{\text{norm}} \) surfaced mapping (range of \(-0.7131\) to 1.2768 a.u.) showed red spots near to metal bound water molecule and quinoxalinone moiety (due to strong O···H···O and O···H···N hydrogen bonding). We have also plotted the shape index and curvedness of the coordination complexes by using Crystal Explorer program; the red concave surface surrounded by the receptors and blue convex surface surrounding receptors on the HS in the shape index of the coordination complexes further confirm the presence of such hydrogen bonding (Fig. 7 and S13, S14† ESI).

In order to quantify the contribution of various supramolecular interactions in the coordination complexes C1, C2 and C3, we have plotted their 2D fingerprints by using Crystal Explorer program (Fig. 7 and S15–S17† ESI). The internal \( d_i \) and external \( d_e \) distances between the HS and atom contacts are given in Å. We found that two strong hydrogen bonding N–H···O and N–H···Cl are presented in the crystal structure of C1 which corroborated well with their 2D fingerprints; meaning the contributions of the interatomic contacts to the HF such as Cl···H/H···Cl (16.1%) and O···H/H···O (7.3%). Moreover, other weak interatomic contacts to the HF of C1 such as N···H/H···N (4.5%), C···H/H···C (17.6%), H···H/H···H (49.6%) and C···C/C···C (2.9%) are also present in the 2D fingerprint. Similarly, the main contributions of the compounds C2 and C3 to the HS are assigned to the close contacts of O···H/H···O (25% for C2 and 25.5% for C3), N···H/H···N (2.3% for C2 and 6.7% for C3), C···H/H···C (13.9% for C2 and 10% for C3), H···H/H···H (57.5% for C2 and 40.5% for C3), C···C/C···C (1.3% for C2 and 8.8% for C3) and N···C/N···C (6.7% for C2). The interatomic contacts such as O···H/H···O, N···H/H···N, C···H/H···C, H···H/H···H, C···C/C···C present in the 2D fingerprints of C2 and C3 corroborate well with the supramolecular interactions such as N···H···O, C···H···N, C···H···π, other van der Waals interactions and C···H···π/π···π stacking, respectively present in their crystal structures (Fig. 7).

3.5. Mössbauer spectroscopy

A powdered sample of C3 was recorded at 298 K. The spectrum shows a quadrupole doublet with isomer shift \( \delta = 0.346(3) \) mm s\(^{-1}\) and quadrupole splitting \( \Delta E_Q = 0.72(1) \) mm s\(^{-1}\) (Fig. 8). Such a doublet is characteristic of high-spin Fe(II) species. Measurements were also recorded at high velocity up to \( v_{\text{max}} = 10 \) mm s\(^{-1}\) but no oxides were detected. This result contrasts with the one offered by single crystal X-ray diffraction which revealed Fe(II) species only. A microscope analysis shows that the powder contains few orange single crystals, whereas the majority of the powder is black. A crystal cell parameters analysis of orange crystals revealed similar parameters as those given in Table 1. This result is confirmed by powder X-ray diffraction of the powdered sample which shows an amorphous pattern plus diffraction peaks. These diffraction peaks correspond to the simulated ones from the cif file of C3 (Fig. 9). Worth to note that the amount of C3 detected in the powder was evaluated below the detection limit of Mössbauer spectroscopy, i.e. ca. 2%.
3.6. Antibacterial activity

The antibacterial activities of the synthesized molecules (3 and L1) and metal complexes (C1, C2 and C3) were tested against E. coli and P. aeruginosa as Gram-negative and S. aureus and S. fasciens as Gram-positive microorganisms by the diffusion method disk. Table 3 reports the minimum inhibitory concentration (MIC) which is the lowest concentration for which no growth is detected for 24 h at 37 °C. The results were compared with a standard, chloramphenicol, an antibiotic, e.g. used for the treatment of eyelid infection, at various concentrations.

Overall the three complexes showed higher antibacterial activities against the four strains tested, compared to 3 and L1 ligand, except in the case of S. fasciens with a remarkable MIC = 5 µg mL⁻¹ for 3 (Table 3). Such antibacterial activity of the C1–C3 complexes compared to the ligand, could be due to the coordination of cadmium, copper and iron metal ions to the condensed ring system (as shown by single crystal X-ray diffraction), thus increasing the delocalization of π electrons throughout the chelated ring and improving the lipophilicity of the complexes and thus the penetration of the complexes into the lipid membrane and further limiting the multiplicity of microorganisms, following Overtone’s concept on cell permeability, and Tweedy’s chelation theory.

Remarkably, C1 reveals an outstanding activity against both Gram-negative (E. coli and P. aeruginosa) and Gram-positive (S. aureus) bacteria, compared to C2, C3 complexes, with a MIC value of 5 µg mL⁻¹. This value is even better compared to chloramphenicol, a well-known antibiotic. Similarly, C2 reveals

| Compound | E. coli | P. aeruginosa | S. aureus | S. fasciens |
|----------|--------|--------------|----------|------------|
| 3        | 10     | 10           | 20       | 5          |
| L1       | 20     | 20           | 20       | 20         |
| C1       | 5      | 5            | 5        | 10         |
| C2       | 5      | 10           | 5        | 20         |
| C3       | 20     | 5            | 10       | 20         |
| Chloramphenicol | 6.25 | 6.25 | 12.5 | 6.25 |

Table 3 Antibacterial activity of ligand and complexes (MIC, µg mL⁻¹)
an identical MIC for *E. coli* and *S. aureus*, whereas C₃ show excellent activity against *P. aeruginosa* (MIC = 5 μg mL⁻¹) and very good activity towards *S. aureus*.

Most excitingly, superior values are found compared to earlier literature reports on Cd[0], Cu[0] and Fe[0] complexes (Table 4).

### 4. Conclusions

In conclusion, three new Cd[0], Cu[0] and Fe[0] complexes formulated as [Cd(L₁)₂Cl₂] (C₁), [Cu(L₂)₂(C₆H₅OH)₂]NO₃]₂ (C₂) and [Fe(L₃)₂(H₂O)₂]NO₃]₂ (C₃) have been synthesized and their crystal structures have been studied. Crystal structure and Hirshfeld Surface analysis have shown that the crystal lattices of all the complexes are influenced for the presence of several intermolecular interactions, including hydrogen bonds. The N–H···O and N–H···Cl hydrogen bonding interactions benefits to C₁, which is the first coordination complex with L₁, to assemble to form a 1D chain as a primary supramolecular architecture. On the other hand, in complex C₂, N–H···O and O–H···O hydrogen bonding play a role to self-assemble the crystallographically independent molecules of complexes and ethanol molecules to form a 2D corrugated hydrogen bonded sheet. The layers are joined by inversion-related C–H–O and O–H–O hydrogen bonding interactions. In conclusion, three new Cd[0], Cu[0] and Fe[0] complexes showed notable activity against all four strains of bacteria studied. Thus, the best result was shown by

### Table 4 Antibacterial activity of C₁, C₂, C₃ and other model complexes

| Metal complexes | *E. coli* MIC (μg mL⁻¹) | *P. aeruginosa* MIC (μg mL⁻¹) | *S. aureus* MIC (μg mL⁻¹) | Ref. |
|-----------------|------------------------|-----------------------------|--------------------------|-----|
| C₁              | 5                      | 5                           | 5                        | This work |
| C₂              | 5                      | 10                          | 5                        | This work |
| C₃              | 20                     | 5                           | 10                       | This work |
| [CuCl₂(Fpy)₂]   | 310                    | —                           | 150                      | 60  |
| Cu(2,5-xil)₂   | —                      | 31.2                        | 31.2                     | 61  |
| Cu(3,5-xil)₂   | —                      | 31.2                        | <15.6                    | 62  |
| [Cu(Ligand)₂(bipy)]ClO₄H₂O | — | —                           | 125                      | 62  |
| [Cu(Ligand)₂(bpy)]ClO₄bipy  | — | —                           | 62                       | 62  |
| [Cu(Ligand)₂(bipy)]ClO₄3H₂O  | — | —                           | 62                       | 62  |
| [Cu(Ligand)₂(bipy)]ClO₄  | 256                    | 256                         | 64                       | 64  |
| [Fe(C₂H₃O₂N₆)₀][Cl]  | 64                     | 64                          | 32                       | 65  |
| [Fe(C₂H₃O₂N₆)(NO₃)]₂ | 128                   | >128                        | 64                       | 65  |
| Cu(naph₁ppc)  | 256                    | 256                         | 64                       | 66  |
| Cu(naph₂ppc)  | >512                   | 512                         | 66                       | 66  |
| Cu(dansyl)₄  | >512                   | >512                        | 69                       | 69  |
| [Cu(HL)₃(CH₃CH₂OH)][CH₃COO]  | 128                    | 128                         | 67                       | 67  |
| [[CdCl(HATtsc)]2(m-CI)]₂ | 25          | >100                        | 25                       | 68  |
| [[Cd(NO₃)]₂(HATtsc)]2(m-N0₃)₂ | 25        | >100                        | 25                       | 68  |
| [Cd(brmesal)₂][Cl]  | 125                    | —                           | 70                       | 70  |
| [Cd(bdu)₄]  | 250                    | —                           | 70                       | 70  |
| [Cu(pdpho)[NO₃][H₂O]₄]  | 256                    | 256                         | 71                       | 71  |
| [Cu(pdpho)[SCN][H₂O]₄]  | 512                    | 256                         | 71                       | 71  |
| [Cu(pdpho)[ClO₄][H₂O]₄]  | 512                    | 256                         | 71                       | 71  |
| Cu(DL₃)₂  | >32                    | —                           | 72                       | 72  |
| Fe(L₄)₄  | >512                   | >512                        | 73                       | 73  |
| Fe(L₅)₄  | >512                   | >512                        | 73                       | 73  |

* Fpy = 2-fluoropyridine. *₂ 2,5-xil = 2,5-dimethylaniline, 3,5-xil = 3,5-dimethylaniline. *₃ bipy = 2,2’-bipyridine; ligand = reaction between meso-1,2-diphenyl-1,2-ethylenediamine with salicylaldehyde (1), 5-bromosalicylaldehyde (2) or 3-methoxysalicylaldehyde (3). *₄ TL = reaction of 2-aminoisofluorene with 2-pyridinecarboxaldehyde. *₅ bcmpo = 3-bis(3-carboxyl-5'-methyl-1'-pyrazolyl)propan-2-ol; bcmp = 1,3-bis(3-carboxyl-5'-methyl-1'-pyrazolyl)-2-methyl propane. *₆ naph₁pp = 3-hydroxy-2-methyl-1-naphthyrylpyridinonate; naph₂pp = 1-{N-naphthyrylcarbamoylpropyl}-3-hydroxy-2-methyl-4-pyridinonate; dansylpp = 2-{N-dansylaminomethyl}-3-hydroxy-1,6-dimethyl-4-pyridinonate. *₇ HL₄ = N,N'-bis(salicylidene)diethylenetriamine. *₈ HATtsc = 2-acetyl-2-thiazoline thiosemicarbazone. *₉ bmesal = N,N'-bis(3-methoxysalicylidene)-1,3-diamino propane. *₁₀ bdu = 1,3-diethyl-1,3-bis(4-nitrophenyl)urea. *₁₁ pdpho = 1-phenyl-2,3-dimethyl-4-(N-2-hydroxy-4-methoxybenzaldehyde)-3-pyrazolin-5-one. *₁₂ DL₃ = N,N'-bis(1-{4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl})ethylenediamine; malonaldehydraze. *₁₃ L₄ = 2-[(2-hydroxynaphthalen-1-yl)methylene]amino e andthane-1,1-diol. *₁₄ L₅ = 2-[[2-hydroxynaphthalen-1-yl]methylen]amino)-2-phenylethane-1,1-diol.

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C1, against E. coli, P. aeruginosa and S. aureus bacterial strains, with a remarkable MIC of 5 μg mL⁻¹.

**Conflicts of interest**

The authors declare no competing financial interest.

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