Structural, Theoretical and Biological Studies of (Z)-3-Amino-N-(3-Amino Pyrazine-2-Carbonyl) Pyrazine-2-Carbohydrazonic Acid (APA; L) and Its Cu\(^{2+}\), Co\(^{2+}\), Pt\(^{4+}\) and Pd\(^{2+}\) Chelates

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Abstract

New chelates derived from the novel ligand, (Z)-3-amino-N-(3-amino pyrazine-2-carbonyl)pyrazine-2-carbohydrazonic acid (APA, L), with Cu\(^{2+}\), Co\(^{2+}\), Pt\(^{4+}\) and Pd\(^{2+}\) salts were investigated. The results suggest that APA acts as mononegative tridentate in the case of Cu\(^{2+}\), binegative tetradentate in the case of Co\(^{2+}\) and as mononegative bidentate towards Pt\(^{4+}\) and Pd\(^{2+}\) chelates. The results of the corrected \(\mu_{\text{eff}}\) and spectral suggest the geometries of the isolated chelates. The results of the corrected \(\mu_{\text{eff}}\) and spectral suggest the structures of the isolated chelates. Molecular modeling is deduced and chemical reactivity, energy components for chelates and also MEP for APA is illustrated. In Vitro, the SOD and radical scavengers like activity of the synthesized compounds Hep G2 liver cancer cells and cytotoxic activity were checked. Metal chelates show potent anti-oxidative activity. The results of cytotoxic activity assay against hepatocellular carcinoma cell line Hep G2 confirmed that Pt\(^{4+}\) complex has the highest value, while APA, Cu\(^{2+}\), Co\(^{2+}\) and Pd\(^{2+}\) chelates have no significant cytotoxic activity.

Keywords

Aminopyrazine, Density Function Theory Calculations, Antioxidant and Cytotoxic Activity, Biological Studies

1. Introduction

Heterocyclic compounds containing nitrogen show multidirectional pharmacological activity like diuretic [1] [2], antitumor [3] [4] [5] [6] and hypotensive [7]
On searching of the anticipated biologically active compounds, we had cared in 3-aminopyrazin-2-hydrazide [10]. The pyrazine derivatives are also utilized in many pharmaceuticals as well as the products used for plant protection [11] [12]. Our research devotes especially to the compounds having potential tuberculosis activity [10]. Pyrazinamide, as an example of pyrazine derivatives, is well known as an effective therapeutics in infections caused by $M.\text{tuberculosis}$.

The pervasive incidence of simple pyrazine molecules in nature, especially in the flavors of many food systems, their effectiveness at very low concentrations as well as the still increasing applications of synthetic pyrazines in the flavor and fragrance industry are queried for the high interest in these compounds [13]. Specific pyrazines, especially dihydropyrazines, are essential for all forms of life due to their DNA strand breakage activity and/or by their influencing of apoptosis [14]. Synthetic pyrazine derivatives have also been advantageous as drugs (antiviral, anticancer, antimycobacterial, etc.) fungicides, and herbicides [15]. Furthermore, 3-amino-6-chloro-pyrazine-6-carboxylic acid, as an example of a simple pyrazine compound, has shown an anti-auxin behavior. The significance of the pyrazine (1,4-diazine) ring for the activity of the biological herbicides can be assessed primarily according to the size of the investigated molecules. In this work, the potent active antioxidant and cytotoxic activities of the separated chelates on HepG2 liver cancer cells have been examined. The structures of the resulting APA and its chelates have been achieved on the basis of elemental analyses, spectral (IR, UV-vis., $^1$H-NMR, $^{13}$C-NMR mass), magnetic and thermal measurements and supported by Density Functional Theory (DFT) method.

The goal of our work is to check in detail the chelation behavior of the novel (Z)-3-amino-N-(3-aminopyrazine-2-carbonyl) pyrazine-2-carbohydrazonic acid (APA) and its chelates derived from Cu$^{2+}$, Co$^{2+}$, Pt$^{4+}$ and Pd$^{2+}$ ions, embedding structural articulation and molecular modeling of both APA and its chelates. Moreover, our attention is directed to evaluate the antioxidant and anticancer activity of the ligand as well as the detached chelates.

2. Experimental

2.1. Materials

All the chemicals are of AR quality and used as supplied. Elemental analyses (C, H, N), chloride and metal contents were determined by conventional methods [16]. Spectral and TGA studies were carried as reported in our previous work [17] [18]. Also, all the chemicals used in biological activity were reported earlier [18]. The diamagnetic corrections were determined using Pascal’s constants [19].

2.2. Synthesis of the Ligand (APA) and Its Complexes

2.2.1. Synthesis of (Z)-3-amino-N-(3-aminopyrazine-2-carbonyl) pyrazine-2-carbohydrazonic Acid (APA)

The novel organic compound, (Z)-3-amino-N-(3-aminopyrazine-2-carbonyl) pyrazine-2-carbohydrazonic acid ($\text{Figure 1(a), Figure 1(b)}$), was synthesized by adding slowly drop by drop of methyl 3-aminopyrazine-2-carboxylaste (1.53 g, 0.01
mol) in absolute ethanol to N₂H₄ (8 mL). A pale yellow solid of APA was obtained by continuous stirring of the reaction mixture on a heater at 60 °C for 1.5 h. Doubtless the addition of methyl 3-aminopyrazine-2-carboxylate to excess hydrazine hydrate assists of the formation of APA and excludes the formation of 3-amino-pyrazin-2-carbohydrazide (Figure 1(c)). The novel product was obtained and collected by filtration followed by continuous washing several times with hot EtOH and ether. The isolated product was kept in a drier over anhydrous phosphorous pentaoxide. APA was recrystallized from absolute EtOH (Yield: 60%). The purity of APA was checked by spectral, TLC and its melting point (159°C - 160°C).

2.2.2. Synthesis of Cu²⁺, Co²⁺, Pt⁴⁺ and Pd²⁺ Chelates
Metal chelates were acquired by reacting 0.001 mol of APA (0.274 g, 0.001 mol) to metal chlorides (CuCl₂·2H₂O; 0.17 g, CoCl₂·6H₂O; 0.24 g, PtCl₄; 0.34 g; PdCl₂; 0.18 g) in 1:1 M ratio. The pH of the solution was optimized at 2, 3, 2 and 5, respectively. The isolated metal chelates with the general formulae, C₁₀H₁₃Cu₂N₈O₄Cl₃, C₁₂H₁₈Co₂N₈O₅Cl₂, C₁₄H₂₅PtN₈O₆Cl₃ and C₁₁H₁₄PdN₈O₇/₂Cl, were isolated by filtration, rinsed continuously with EtOH and ether. The products were kept in a drier over P₄O₁₀. All the chelates are freely soluble in polar solvents and quite stable in air.

2.3. Biological Studies
2.3.1. Superoxide Dismutase Scavenging Activity
Both the metal chelates and APA were assessed against antioxidant activity [20]. The italicize of the ligand or its chelates to damped phenazine methosulphatemediated reduction of nitro blue tetrazolium dye was obtained from the results of
the assay. The determination of SOD was calculated as reported earlier [18].

2.3.2. Cell Cultures and Viability against HepG2
The safety of HepG2 cells in culture was carried out in triplicate and calculated by the MTT assay as reported in our earlier work [21].

2.4. Computational Details
DMOL³ program [22] in materials studio package [23] was acquired for the data which is resolved for large-scale DFT calculations. DFT semi core pseudopods calculations were elicited with double numerical basis sets in addition to polarization functional. DNP basis sets are of comparable quality to 6-31G Gaussian basis sets [24]. The data acquired by DNP basis sets are more accurate than Gaussian basis sets of the same size as reported by Delley et al. [22]. The RPBE functional [25] is considered the best exchange-correlation function [26] establish on the generalized descended approximation (GGA) and is used to take account of the exchange and correlation impacts of electrons. Hence the geometric optimization is officiated without any symmetry curb.

3. Results and Discussion

Table 1 summarized the elemental analyses (C, H, M, and Cl) of the isolated metal chelates and some physical properties. The empirical formulae of the chelates are rimmed by elemental analyses (C, H, N, M, Cl) and confirmed by thermal gravimetric data. The low values of molar conductance (8 - 13 ohm⁻¹·cm²·mol⁻¹ range) of the chelates in DMSO (Table 1) suggest their non-electrolytic nature [27]. Doubtless, the lower pH of the solution during complex formation (pH = 2, 3, 2 and 5 for Cu²⁺, Co²⁺, Pt⁴⁺ and Pd²⁺, respectively) causes the block of the NH₂ groups and consequently the enolization of the carbonyl group occurred with the liberation of a proton during complex formation. Hence, all the compounds were obtained by losing one or two protons as shown in Table 1. The results

| Compound; (empirical formula) | % Found (Calcd.) | A⁺⁺ (DMSO) | Yield (%) |
|-------------------------------|------------------|------------|----------|
| **APA**; C₁₀H₁₀N₈O₂         |                  |            |          |
| (F. Wt) 274.246 | Color Blue Yellow 156 - 157 | 44.6 (43.8) 4.6 (3.7) --- --- 70 |
| | M.p. (°C) | % Found (Calcd.) | A⁺⁺ (DMSO) | Yield (%) |
| **[Cu₂(APA-H)(H₂O)Cl₃]·H₂O**; C₁₀H₁₃Cu₂N₈O₄Cl₃ | 542.721 Brown > 300 | 22.9 (22.1) 3.1 (2.4) 23.1 (23.4) 20.0 (19.6) 9 83 |
| **[Co₂(APA-2H)(H₂O)Cl₃·EtOH]**; C₁₂H₁₈Co₂N₈O₅Cl₂ | 543.098 Olive-green > 300 | 26.01 (26.5) 4.2 (3.3) 20.96 (21.7) 13.7 (13.1) 10 76 |
| **[Pt(APA-H)(H₂O)Cl₃]·H₂O·2EtOH**; C₁₄H₂₅PtN₈O₆Cl₃ | 702.849 Light-brown > 300 | 23.2 (23.9) 4.1 (3.2) --- 16 (15.1) 13 90 |
| **[Pd(APA-H)(H₂O)C]·2/1EtOH**; C₁₁H₁₄PdN₈O₇/₂Cl | 456.162 Olive-green > 300 | 29.6 (28.9) 3.3 (3.1) 23.5 (23.3) 8.5 (7.8) 8 69 |
suggest that the comparatively high pH values of the Co$^{2+}$ and Pd$^{2+}$ (pH = 3 and 5) complexes stay for the liberations of two protons while the decline pH of Cu$^{2+}$ and Pt$^{4+}$ complexes give the chance to lose only one electron during the formation of the reactants.

3.1. IR Spectra

Two tautomer shapes [keto (a) and enol (b)] as elucidated in Figure 1(a). Figure 1(b) are suggested for APA on the basis of the results of IR spectra. The infrared spectrum of APA (KBr) shows three bands at 3416, 3306 and 3200 cm$^{-1}$ imputable to $\nu$(OH), $\nu$(NH$_2$) and $\nu$s(NH$_2$) [28] vibrations, respectively. The band at 3150 cm$^{-1}$ is attributed to $\nu$(NH$_2$) vibration [29]. The possibility of keto/enol tautomers (HN-C=O/N=C-OH) is reinforced by the observation of two NH group bands. The $\nu$(C=O), $\nu$(C=N)$_{azom}$. And $\nu$(C=N) vibrations of the pyrazine ring are observed at 1695, 1643 and 1562 cm$^{-1}$, respectively [30] [31]. All these basics were ascertained and supported by studding the modeling of the ligand as shown in Figure 2.

Figure 2. Molecular modeling of (a) APA (b) electron density.
The infrared spectra of APA and the isolated metal chelates (Table 2) show that the ligand binds to Cu\(^{2+}\) and Co\(^{2+}\) metal ions in 2:1 (M:L) ratio and 1:1 in case of Pt\(^{4+}\) and Pd\(^{2+}\) metal ions. APA behaves as mononegative tetradeinate coordinating via the two nitrogen of NH\(_2\) groups and two oxygen atoms with losing only one proton from the OH group (Figure 3) in case of C\(_{10}\)H\(_{13}\)Cu\(_2\)N\(_8\)O\(_4\)Cl\(_3\). The bonding sites are revealed by: 1) the NH\(_2\) and C=O groups are relocated to lower wavenumbers indicating that these groups are participate in chelation; 2) the observation of new band at 1331 cm\(^{-1}\) attributed to (C-O) group; 3) new bands are traced at 532 and 467 cm\(^{-1}\) assigned to M-O and M-N, respectively [32]. The spectrum of copper(II) chelate exhibits a broad band at 3416 cm\(^{-1}\) attributable to the water of coordination and water of solvation [33]. APA coordinates in a bi-negative tetradeinate ligand via two NH\(_2\) groups and two oxygen atoms with losing two protons from the two OH groups in case of Co\(^{2+}\), with the general formulae, C\(_{12}\)H\(_{18}\)Co\(_2\)N\(_8\)O\(_5\)Cl\(_2\) (Figure 4). This conduct revealed by:

1) The hiding of the (CO) group indicates this group is taking part in coordination after deprotonation.

2) The bands at 3285 - 3262 cm\(^{-1}\) attributable to (NH\(_2\)) are observed at lower wave numbers indicating that this group participates in bonding.

### Table 2. The most important IR bands of APA and its metal chelates.

| Compound                  | \(\nu(\text{OH})\) | \(\nu(\text{NH}_2)\) | \(\nu(\text{NH})\) | \(\nu(C=O)\) | \(\nu(C=C)_{a,m}\) | \(\nu(C=N)_{pyr}\) | \(\nu(C=O)\) | \(\nu(M-O)\) | \(\nu(M-N)\) |
|--------------------------|---------------------|-----------------------|---------------------|--------------|---------------------|---------------------|--------------|--------------|--------------|
| APA; C\(_{10}\)H\(_{10}\)N\(_8\)O\(_2\) | 3451                | (3381)\(_s\) (3313),| 3187                | 1695         | 1643                | ----                | ----         | ----         | ----         |
| C\(_{10}\)H\(_{13}\)Cu\(_2\)N\(_8\)O\(_4\)Cl\(_3\) | 3416                | (3306)\(_s\) (3197),| 3150                | 1686         | 1650                | 1556                | 1331         | 532          | 467          |
| C\(_{12}\)H\(_{16}\)Co\(_2\)N\(_8\)O\(_5\)Cl\(_2\) | 3401                | (3285)\(_s\) (3262),| ----                | ----         | 1652                | 1556                | 1335         | 1315         | 536          | 464          |
| C\(_{14}\)H\(_{25}\)PtN\(_8\)O\(_6\)Cl\(_3\) | 3405                | (3312)\(_s\) (3293)\(_s\) | 3150                | 1711         | 1614                | 1562                | 1317         | 544          | 473          |
| C\(_{11}\)H\(_{14}\)PdN\(_8\)O\(_7\)Cl\(_2\) | 3422                | (3326)\(_s\) (3309)\(_s\) | 3145                | 1708         | 1622                | 1569                | 1323         | 494          | 461          |

Note: azo: azomethine; pyrz: pyrazine ring.

![Figure 3. Molecular airing of C\(_{10}\)H\(_{13}\)Cu\(_2\)N\(_8\)O\(_4\)Cl\(_3\).](image)
3) The NH band is obscured with the simultaneous observation of a new band in the 1652 - 1616 cm⁻¹ region assigned to the (C=N) azom groups confirming the enolization of the NH groups together with the dislocation of a hydrogen atom from both OH groups.

4) Nouveau bands attributed to the (C-O) group are noticed in the 1553 - 1315 cm⁻¹ regions.

5) Nouveau bands at 536 and 464 cm⁻¹ are attributed to M-O and M-N [32].

6) The chelates exhibit a broad band at 3401 cm⁻¹ assignable to H₂O and EtOH [33].

In the complexes, C₁₄H₂₅PtN₈O₆Cl₃ and C₁₁H₁₄PdN₈O₇/₂Cl (Figure 5, Figure 6), APA coordinates as a mononegative bidentate ligand through (N) of NH₂ group and (O) atom of deprotonated C-OH group. The chelation is suggested by the displacement of the NH₂ group to lower wavenumber together with the observation of new bands in the scale 1317 - 1323 cm⁻¹ assigned to ν(C-O) vibration. The medium broad band at 3405 and 3422 cm⁻¹ are assigned to the coordinated water as well as ethanol [33]. Also, the bands observed in the range 544 - 494 and 473 - 461 cm⁻¹ are assigned to M-O and M-N, respectively [32].

3.2. Nuclear Magnetic Resonance Spectra (¹H-NMR and ¹³C-NMR)

Three signals at 9.8, 7.5 and 4.5 ppm, relative to TMS, are observed in the ¹H-NMR spectrum of APA in d₆-DMSO (Figure S1) and attributed to the protons of OH [34], NH and NH₂ [28] groups and obscured on adding D₂O (Figure S2). The protons of pyrazine ring are noticed in the (7.7 - 8.3) region ppm. The observation of the OH signal suggests that APA is existed in the keto/enol forms as illustrated in Figure 7. Additional backing for the composition of the ligand is attested from the arising of ten signals in the ¹³C-NMR spectrum (Figure 1) and the chemical shift of carbon (C=O) is observed at 167.02 ppm [35]. The signals assigned to C₁₁, C₂, C₄ and C₅ are noticed at 155.3, 133.0, 123.7 and 156.4 ppm, respectively. The existences of (OH) group adduced a great downfield shift of the (C₁₄ and C₁₈) and the up field shifts of C₁₁ and C₁₅ in accord with the
Figure 5. Molecular airing of C_{14}H_{25}PtN_{8}O_{6}Cl_{3}.

Figure 6. Molecular airing of C_{11}H_{14}PdN_{8}O_{7/2}Cl.

Figure 7. $^{13}$C-NMR spectrum of APA in d$_6$-DMSO.
The trend of \( \pi \)-electron densities [36], which is taken as a strong guide that APA is existed in the keto/enol forms.

The \(^1\)H-NMR spectrum of Pt\(^{4+}\) chelate (Figure S3) shows signals at 9.01, 3.93 and 3.56 ppm attributed to NH, NH\(_2\) and OH (EtOH and H\(_2\)O) protons, respectively. The protons of pyrazine ring are noticed in the 8.55 - 7.96 ppm range. The protons signal of ethanol (CH\(_3\) and CH\(_2\)) are observed at 1.35 and 4.38 ppm indicating the existence of EtOH outside the coordination sphere [37]. The Pd\(^{2+}\) chelate spectrum (Figure S4) exhibits three signals at 8.27, 3.85 and 3.89 ppm assigned to NH, NH\(_2\) and OH (EtOH and H\(_2\)O) protons, respectively. The protons of the pyrazine ring are traced in the 7.98 - 7.59 ppm range. The monitor of the proton signals of CH\(_3\) and CH\(_2\) (EtOH) outside the coordination sphere at 1.05 and 3.45 ppm verify the proposed formula [37].

3.3. Mass Spectra

Molecular ion peak noticed at m/z = 274 (10%) corresponds to (C\(_{10}\)H\(_{10}\)N\(_8\)O\(_2\)), M. wt. = 274.246, as shown in the mass spectrum of APA (Figure 8). Elemental analyses and spectral are taken as strong brochure for the suggested geometry.

APA (C\(_{10}\)H\(_{10}\)N\(_8\)O\(_2\)) fragmentation pattern shows successive segments. The peak at m/z 274.9 (10% abundance) represents the molecular ion (Calcd. 274.25). Also, the peak at 242 (46% abundance) symbolizes to [C\(_{10}\)H\(_{8}\)N\(_6\)O\(_2\)]\(^+\) (Calcd. 242.2) and the peak in 224 (48% abundance) symbolizes to the fragment [C\(_{10}\)H\(_{6}\)N\(_6\)O\(_2\)]\(^+\) (Calcd. 224.2). The peak at 135 (100% abundance) represents to [C\(_{3}\)H\(_2\)N\(_2\)O\(_4\)]\(^+\) (Calcd. 134.1) portions. The peak in 102 with 46% abundance corresponds to [C\(_{5}\)H\(_2\)N\(_4\)O\(_2\)]\(^+\) (Calcd. 106.1). The molecular ion peaks in the mass spectrum of C\(_{12}\)H\(_{18}\)Co\(_2\)N\(_8\)O\(_5\)Cl\(_2\) approves with its formula. The mass spectrum of the Co\(^{2+}\) complex (Figure S5) elucidates the fragmentation example of the successive degradation of the chelate. The first peak at m/z 543.2 (0.02% abundance) represents the molecular ion (Calcd. 543.098). The peaks at 413, 299, 255, 199, 183, 153,
96, 77 and 51 with 2, 23, 10, 24, 15, 53, 89, 46 and 100% abundance (Calcd. 413.548, 301.149, 255.079, 199.054, 181.038, 153.027, 94.097, 78.074 and 51.048) correspond to \([\text{C}_8\text{H}_{14}\text{Co}_2\text{N}_5\text{O}_5\text{Cl}]^{+}\), \([\text{C}_8\text{H}_{12}\text{CoN}_5\text{O}_4]^{+}\), \([\text{C}_6\text{H}_6\text{CoN}_5\text{O}_3]^{+}\), \([\text{C}_5\text{H}_6\text{CoN}_3\text{O}_2]^{+}\), \([\text{C}_5\text{H}_4\text{CoN}_3\text{O}]^{+}\), \([\text{C}_4\text{H}_4\text{CoN}_3]^{+}\), \([\text{C}_4\text{H}_4\text{N}_3]^{+}\), \([\text{C}_4\text{H}_2\text{N}_2]^{+}\) and \([\text{C}_3\text{HN}]^{+}\) parts, respectively. Also, the mass spectrum of \(\text{C}_{14}\text{H}_{25}\text{PtN}_8\text{O}_6\text{Cl}_3\) (Figure S6) shows a molecular ion peak at 702.6 which coincides with the theoretical value (702.849). The segment path of \(\text{C}_{14}\text{H}_{25}\text{PtN}_8\text{O}_6\text{Cl}_3\) is illustrated in Scheme S1. \(\text{C}_{11}\text{H}_{14}\text{PdN}_8\text{O}_7/2\text{Cl}\) (Figure S7) exhibits a molecular ion peak equals 456 which is agreed with the calculated value (456.162) as illustrated from the mass spectrum. Scheme S2 depicts peaks corresponding to the successive degradation of Pd\(^{2+}\) chelate.

### 3.4. Spectral and Magnetic Results

All the electronic spectra of APA and its chelates were arises in Nujol mull. The chelates are distinctive by intense charge-transfer bands. The absorption band at 300 - 344 nm (33,333 - 28,901 cm\(^{-1}\)) is raised to \(\pi \to \pi^*\) transition of pyrazine rings are shown in the spectrum of APA. The absorption band observed at 402 nm (24,815 cm\(^{-1}\)) is assigned to \(n \to \pi^*\) of the NH\(_2\) group, which shifts in chelates toward lower frequencies, supporting the chelation of the NH\(_2\) group in bonding. Another two bands appear at 452 and 548 nm (22,123 and 18,284 cm\(^{-1}\)) are assigned to \(\pi \to \pi^*\) of \((\text{C}=\text{N})_{\text{asym}}\) and \(n \to \pi^*\) transitions of the carbonyl group, respectively [38] [39]. The \(^2B_2 \to ^2E\) and \(^2B_2 \to ^2B_1\) transitions at 728 and 574 nm (13,736 and 17,421 cm\(^{-1}\)) in the electronic spectrum of the Cu\(^{2+}\) chelate (Nujol) confirms the presence of tetrahedral structure around the Cu\(^{2+}\) ion [40]. The band at 525 nm (19,047 cm\(^{-1}\)) is attributed to type \(L \to M\) transition. The corrected magnetic moment value (\(\mu_{\text{eff}} = 1.6\) BM) is calculated for each Cu\(^{2+}\) ion [41]. Also, the Co\(^{3+}\) chelate shows three bands at 691, 562 and 418 nm (14,471, 17,793 and 23,923 cm\(^{-1}\)). The first two bands are assigned to \(4A_2 \to 4T_1\) (\(F\)) and \(4A_2 \to 4T_1\) (\(P\)) transitions in a tetrahedral geometry around the Co\(^{3+}\) ion. The band at 23,923 cm\(^{-1}\) is raised to charge-transfer (\(L \to M\)) [42]. The corrected magnetic moment (\(\mu_{\text{eff}} = 4.4\) BM) of Co\(^{4+}\) ion supports a tetrahedral geometry around the Co\(^{2+}\) [43]. The values of to be 10 Dq, B and \(\beta\) (519.9 cm\(^{-1}\), 736.1 and 0.76), were calculated. Pt\(^{4+}\) chelate exhibits two bands at 486 and 440 nm (20,576 and 22,727 cm\(^{-1}\)) refers to the d-d transition bands \(^1A_{1g} \to ^1T_{1g}\) and \(^1A_{1g} \to ^1T_{2g}\) respectively [17]. Two bands at 388 and 592 nm (25,773 and 16,891 cm\(^{-1}\)) assigned to \(^1A_{1g} \to ^1B_{2g}\) and \(^1A_{1g} \to ^1E_{g}\) transitions in a square-planar configuration for the diamagnetic \(\text{C}_{11}\text{H}_{14}\text{PdN}_8\text{O}_7/2\text{Cl}\) [17] [44].

### 3.5. Molecular Modeling

#### 3.5.1. DFT Calculations for Optimization of the Geometry

The optimization of APA and its metal chelates are displayed in Figures 2-6. The bond lengths and angles calculated by optimized molecular geometry are given in Tables S1-S10. The important points are summarized as follow:

1) On chelation the bond angles of APA are shifted; the most important effective changes are shown in C(15)-N(20)-C(14), C(14)-C(11)-O(12), O(12)-C(11)-
N(9), O(10)-C(7)-C(4), N(19)-C(5)-C(4) and N(8)-C(7)-O(10), which are affected (decrease or increase) on chelation due to chemical bonding [45].

2) Tetrahedral geometry of the Cu(II) and Co(II) chelates, \( \text{C}_{10}\text{H}_{13}\text{Cu}_{2}\text{N}_{8}\text{O}_{4}\text{Cl}_{3} \) and \( \text{C}_{12}\text{H}_{18}\text{Co}_{2}\text{N}_{8}\text{O}_{5}\text{Cl}_{2} \), is proposed on the basis of the values of bond angles, while octahedral geometry is propounded for \( \text{C}_{14}\text{H}_{25}\text{PtN}_{8}\text{O}_{6}\text{Cl}_{3}, 2\text{EtOH} \) and a square-planar for \( \text{C}_{11}\text{H}_{14}\text{PdN}_{8}\text{O}_{7/2}\text{Cl} \).

3) The metal chelates of APA are arraying according to M-O bond length as follows: O-Cu > O-Pt > O-Pd > O-Co.

4) According to M-N bond lengths the chelates of APA are arranged as follows: N-Cu > N-Pt > N-Pd > N-Co.

5) The angles around the metal centers while the bond angles in APA backbone do not change significantly.

3.5.2. Chemical Reactivity

1) Methods of Describing the Global Reactivity

The most important parameters in quantum calculations depend mainly on both the energies of the HOMO (\( \pi \)-donor) and LUMO (\( \pi \)-acceptor). These parameters are essentially behaved as an electron donor and electron acceptor, respectively, and these orbitals are known as Frontier Molecular Orbitals (FMOs).

1) The negative values of \( E_{\text{HOMO}} \) and \( E_{\text{LUMO}} \) and their neighboring orbitals (Table 3) anticipate the stability of the synthesized molecules [18].

2) The coordination sites (electrophilic attack) on aromatic compounds are easily anticipated using FMOs theory. The uttermost overlap between the HOMO on one molecule and the LUMO on the other illustrates that the reaction takes place. The most important factor in any reaction depends essentially on the interaction between HOMO and LUMO. The goal of the computations is to find out the highest values of molecular orbital coefficients. Consequently, the elevated value of molecular orbital coefficients for the ligand orbitals indicates its activity for chelation. All these keynotes are deduced from the data obtained.

### Table 3. Calculated \( E_{\text{HOMO}} \), \( E_{\text{LUMO}} \), energy band gap \( (E_{\text{L}} - E_{\text{H}}) \), chemical potential \( (\mu) \), electronegativity \( (\chi) \), global hardness \( (\eta) \), global softness \( (S) \), global electrophilicity index \( (\omega) \) and softness \( (\sigma) \) for APA and its complexes.

| Compound   | \( E_{\text{H}} \) eV | \( E_{\text{L}} \) eV | \( (E_{\text{L}} - E_{\text{H}}) \) eV | \( \chi \) eV | \( \mu \) eV | \( H \) eV | \( S \) eV\(^{-1} \) | \( \Omega \) eV | \( \sigma \) eV |
|------------|----------------------|------------------|-------------------------------|------------|----------|-----------|----------------|-------------|---------|
| APA        | −5.027               | −2.493           | −2.534                        | 3.76       | −3.76    | 1.267     | 0.6335         | 8.95617    | 0.789266 |
| Cu complex | −5.199               | −3.265           | −1.934                        | 4.232      | −4.232   | 0.967     | 0.4835         | 8.6594     | 1.034126 |
| Co complex | −4.885               | −3.632           | −1.053                        | 4.0585     | −4.0585  | 0.4265    | 0.21325        | 3.512531   | 2.344666 |
| Pt complex | −5.316               | −4.034           | −1.282                        | 4.775      | −4.775   | 0.741     | 0.3705         | 8.447632   | 1.349528 |
| Pd complex | −4.909               | −3.462           | −1.447                        | 4.1855     | −4.1855  | 0.7235    | 0.36175        | 6.337285   | 1.38217  |

\( H = \text{HOMO}, \ L = \text{LUMO}. \)
from calculations indicating that the nitrogen of NH₂ groups, oxygen of deprotonated C-OH and carbonyl groups with largest values of molecular orbital coefficients.

3) Linert et al. [45] showed that the bond strength increases as the adjacent bonds become weaker according to Gutmann’s variation rules. This view agrees with the results of increasing of the value of E_{HOMO} accompanying by elongation followed by the weakness of the metal-ligand bonds and the narrowness of the positions abutted to the metal-ligand centers and thus becomes quite strong.

4) The level of HOMO is essentially domestic on the N(20), N(19) and O(10) and O(12) atoms (Figure 9) suggesting that these atoms are the most active nucleophile sites on the central metal ion. This indicates that these centers have high values of HOMO density coefficients and in face of the metal ions.

5) The energy gap (E_{HOMO}-E_{LUMO}) [45] is used to calculate the kinetic stability and chemical reactivity of the APA. The theoretical model for illustrating the geometry and approval barriers in different modulate, which governs the biological bustle of the molecule, depends mainly on the energy gap. The softness of the molecule (more polarized) is known from the small gap. Accordingly, the reactivity of soft molecules than hard ones is mainly due to the easily offer electrons to an acceptor. The charge-transfer is easily occurred due to the small energy gap in case of APA suggests which effectuating the biological activity of the molecule. The groups that enter into conjugation causes the low value of energy gap.

![Figure 9. 3D plots frontier orbital energies using DFT method for APA.](image-url)
6) The donating electron capacity is weaker due to the lowering of the HOMO energy values. Contrarily, the molecule becomes good electron donor when the HOMO energy becomes higher. The ability of a molecule to receive electron depends on the LUMO energy [45].

Both the site selectivity and chemical reactivity of the molecular systems is figured out from DFT. The energies of both \((E_{\text{HOMO}} + E_{\text{LUMO}})\) and \((E_{\text{HOMO}} - E_{\text{LUMO}})\) construe the charge-transfer interaction, electronegativity \(\chi\), chemical potential \(\mu\), global hardness \(\eta\), global softness \(S\) and global electrophilicity index \(\omega\) within the molecule [46] [47]. The results are depicted in Table 3.

\[
\chi = -\frac{1}{2}(E_{\text{LUMO}} + E_{\text{HOMO}}) \\
\mu = -\chi = \frac{1}{2}(E_{\text{LUMO}} + E_{\text{HOMO}}) \\
\eta = \frac{1}{2}(E_{\text{LUMO}} - E_{\text{HOMO}}) \\
S = \frac{1}{2}\eta \\
\omega = \mu^2 / 2\eta
\]

The inverse value of the global hardness bestowed the softness \(\sigma\) as follow:

\[
\sigma = 1/\eta
\]

The electrophilicity index is considered the most important quantum chemical factor which describes the toxicity of different pollutants in relation to their reactivity and site selectivity [48]. The biological activity of drug receptor interaction is illustrated from the value of electrophilicity. The new reactivity index is utilized to measure the stabilization energy when additional electronic charge from the environment from the system is needed. The measurements of the molecular stability and reactivity depend on the values of \(\eta\) and \(\sigma\). The metal ion acts as a Lewis acid while APA behaves as a Lewis base in chelate formation.

### 3.5.3. Molecular Electrostatic Potential (MEP)

The electrostatic potential mapped onto the constant electron density surface is obtained from the plot of MEP. Also, it is important in disquisition of the molecular structure with its physiochemical property nexus and hydrogen bonding interplay [49] [50] [51]. The values of \(V(r)\) at \(r\) \((x, y, \text{and} z)\) is mooted in terms of the interaction energy between the electrical charge formed from the electrons of molecule, nuclei and proton located at \(r\) [52] [53]. The plot of 3D of MEP for APA is labeled in Figure 10. The results showed that the maximum negative
region suggests the most suitable site for electrophilic attack which symbolized by a red color. The blue color represents the maximum positive region prefers site for nucleophile attack. Equivocally the increase of potential is in the order red < green < blue, where blue depicts the strongest attraction and red shows the strongest repulsion. The negative potential regions are existed over the more electronegative atoms meanwhile the regions with positive potential are found over the hydrogen atoms.

3.5.4. Other Molecular Properties
Binding energy estimations detect that the increase of the value of calculated binding energy of complexes in comparison to that of APA indicating that the stability of the formed metal chelate is higher than that of APA. DFT calculations conjecture this energy as shown in Table 4.

3.6. Thermal Studies (TGA/DTG)
The degradable stages, temperature ranges degradable products as well as the weight loss percentages of Cu²⁺ chelate are shown in Table S11. Also, Figure S8 illustrates the TGA/DTG curves of the chelate. The results suggest that the experimental weight loss agrees with the calculated values. The residue was confirmed by chemical analysis. The first stage at 32°C - 102°C with weight loss of 3.3 (Calcd. 3.3%) matches to the loss of H₂O (lattice molecules) was shown from the TG thermogram of C₈H₁₄Cu₄N₈O₄Cl₂. The weight loss of 27.1 (Calcd. 27.2%) at 102°C - 246°C is assigned to the loss of the coordination water molecules and (C₄H₃N₃ + Cl) portions as shown from the second step. The removal of (C₈H₁₄N₁) portions with weight loss of 17.1 (Calcd. 17.2%) at 247°C - 336°C is obtained from the third step. The fourth step at 336°C - 416°C with weight wastage of 14.1 (Calcd. 13.4%) indicates the removal of 2HCl molecules. Finally, the fifth step is noticed in the 417°C - 569°C range with gradual mass loss corresponds to (N₂ + C) fragments, 7.3 (Calcd. 7.4%). The final remainder is [Cu₂(O)₂] + C (Found 31.1, Calcd. 31.5%).

3.7. Biological Studies
3.7.1. The Antioxidant Activity
Antioxidant activity utilizing superoxide dismutase like activity assay was used

Table 4. Some of energetic properties of APA and its complexes calculated by DMOL³ using DFT-method.

| Compound          | HOMO (eV) | LOMO (eV) | Binding energy (Kcal/mol) | Total energy (Kcal/mol) | Dipole moment (D) |
|-------------------|-----------|-----------|---------------------------|-------------------------|-------------------|
| APA               | −5.027    | −2.493    | −3368.8                   | −6.1 × 10⁵              | 6.9624            |
| C₈H₁₄Cu₂N₈O₄Cl₂  | −5.199    | −3.265    | −4185.1                   | −1.8 × 10⁶              | 6.6597            |
| C₆H₁₃Co₂N₈O₃Cl₂  | −4.485    | −3.632    | −4043.2                   | −1.4 × 10⁶              | 5.0550            |
| C₇H₁₅PtN₈O₆Cl₂   | −5.516    | −4.034    | −3756.7                   | −1.6 × 10⁶              | 8.9002            |
| C₈H₁₄PdN₈O₇/2Cl  | −4.909    | −3.462    | −3619.9                   | −1.0 × 10⁶              | 7.6981            |
to check out all the chelates. In contrarily, the Pd\(^{2+}\) chelate shows no antioxidant activity while APA showed from low to mediate anti-oxidative activity as shown in Figure 11.

The Cu\(^{2+}\), Co\(^{3+}\) and Pt\(^{4+}\) chelates have the highest activity of quenching phenazine methosulphate radicals at 76.3%, 83.0% and 88.1% inhibition, respectively. The high potency of antioxidant is due to the fared of chelation. This is due to structure-activity relationship: they differ in the coordination geometries and stability and distortion. Moreover, the difference in the dipole moment of the complexes affects the stability, the distortion and the activity of the complexes. The compounds under investigation are considered as important group of promising antioxidants and also help to attenuate oxidative stress and used in protection against the harmful action of reactive oxygen species, mainly oxygen free radicals.

**Figure 11.** Superoxide dismutase scavenging radicals like activity of APA and its chelates.

**Figure 12.** Cytotoxic activity of APA and its chelates.
3.7.2. Cytotoxic and Antitumor Activity

APA and its metal chelates were tried against hepatocellular carcinoma cell line HepG2 for their antitumor activity (Figure 12). After few days’ incubation of the HepG2 liver cancer cells using different concentrations of APA and its chelates, Pt4+ proved to have the highest cytotoxic activity with IC50 of 79.8 µM.

The viability of HepG2 tumor cells after incubation with Pt4+ chelate is highly affected. The cell layer partially condensed forming cell-free areas and finally detached from the culture plate. APA and its chelates (Cu2+, Co2+ and Pd2+) show no significant cytotoxic activity. The data indicate that there is no significant difference in cell death in comparison to the untreated control (negative control).

4. Conclusion

Metal chelates (Cu2+, Co2+, Pt4+ and Pd2+) derived from the novel ligand, (Z)-3-amino-N-(3-aminopyrazine-2-carbonyl) pyrazine-2-carbohydrazonic acid (APA, L) were synthesized and achieved by conventional physical and chemical, spectroscopic, magnetic and TGA studies. APA behaves in tridentate and tetrade ntate manners as in the case of Cu2+ and Co2+, respectively. Also, the ligand acts in a bidentate manner towards Pt4+ and Pd2+ chelates. Both the corrected µeff. and spectral data propose the geometries of the chelates and the molecular modeling. The chemical activity, energy components and also MEP for APA are figured out. In Vitro, cytotoxic activity and superoxide dismutase radical scavenger-like activity of the synthesized compounds HepG2 liver cancer cells were examined. Metal chelates show the potent anti-oxidative activity. The results of cytotoxic activity assay against hepatocellular carcinoma cell line HepG2 confirmed that Pt4+ complex has the highest value, while APA, Cu2+, Co2+ and Pd2+ chelates have no significant cytotoxic activity.

Conflicts of Interest

The authors declare that they have no conflict of interests that could influence this work.

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Appendix

Figure S1. $^1$H-NMR spectrum of APA in d$_6$-DMSO.

Figure S2. $^1$H-NMR spectrum of APA in d$_6$-DMSO and D$_2$O.
Figure S3. $^1$H-NMR spectrum of $[\text{Pt(APA-H)(H}_2\text{O)Cl}_3]\cdot\text{H}_2\text{O}\cdot2\text{EtOH}$ in d$_6$-DMSO.

Figure S4. $^1$H-NMR spectrum of $[\text{Pd(APA-H)(H}_2\text{O)Cl}]\cdot1/2\text{EtOH}$ in d$_6$ DMSO.
**Figure S5.** Mass spectrum of $\text{[Co}_2(\text{APA}-2\text{H})(\text{H}_2\text{O})_2\text{Cl}_2]\cdot\text{EtOH}$. 

**Figure S6.** Mass spectrum of $\text{[Pt(APA-H)(H}_2\text{O})\text{Cl}_3]\cdot\text{H}_2\text{O}\cdot2\text{EtOH}$. 
Figure S7. Mass spectrum of [Pd(APA-H)(H$_2$O)Cl]·1/2EtOH.

Figure S8. Thermal analysis curves (TGA, DTG) of [Cu$_2$(APA-H)(H$_2$O)Cl$_2$]·H$_2$O.
Scheme S1. The main fragments in mass spectrum of [Pt(APA)-H(H2O)Cl3]·H2O·2EtOH.
Scheme S2. The main fragments in mass spectrum of \([\text{Pd(APA-H)(H}_2\text{O)}\text{Cl]}\cdot\frac{1}{2}\text{EtOH}\).
Table S1. Bonds lengths (Å) of (APA) using DFT-method from DMOL³ calculations.

| Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) |
|---------------|------------|---------------|------------|---------------|------------|---------------|------------|
| N(20)-H(30)  | 1.1078     | C(15)-N(20)   | 1.5109     | N(9)-C(11)    | 1.5095     | C(4)-C(5)     | 1.5426     |
| N(20)-H(29)  | 1.1098     | C(15)-N(16)   | 1.5098     | N(8)-H(23)    | 1.1087     | N(3)-C(4)     | 1.5095     |
| N(19)-H(28)  | 1.1089     | C(14)-C(15)   | 1.5438     | N(8)-N(9)     | 1.479      | C(2)-H(22)    | 1.1399     |
| N(19)-H(27)  | 1.1099     | C(18)-N(13)   | 1.5095     | C(7)-O(10)    | 1.5103     | C(2)-N(3)     | 1.5102     |
| C(18)-H(26)  | 1.14       | N(13)-C(14)   | 1.5098     | C(7)-N(8)     | 1.5099     | C(1)-H(21)    | 1.1399     |
| C(17)-H(25)  | 1.1398     | O(12)-H(24)   | 1.11       | C(5)-N(19)    | 1.5107     | N(6)-C(1)     | 1.5094     |
| C(17)-C(18)  | 1.5383     | C(14)-C(11)   | 1.5419     | C(5)-N(6)     | 1.5095     | C(1)-C(2)     | 1.539      |
| N(16)-C(17)  | 1.5088     | C(11)-O(12)   | 1.5079     | C(4)-C(7)     | 1.542      |              |            |

Table S2. Bonds angles (°) of (APA) using DFT-method from DMOL³ calculations.

| Angle          | Degree (°) | Angle          | Degree (°) | Angle          | Degree (°) |
|----------------|------------|----------------|------------|----------------|------------|
| H(30)-N(20)-H(29) | 119.8083   | N(16)-C(15)-C(14) | 119.8481   | N(8)-C(7)-C(4) | 120.0328   |
| H(30)-N(20)-C(15) | 120.4091   | C(15)-C(14)-N(13) | 119.7604   | N(5)-N(6)-C(1) | 120.1135   |
| H(29)-N(20)-C(15) | 119.7821   | C(15)-C(14)-C(11) | 120.849    | N(19)-C(5)-N(6) | 119.4975   |
| H(28)-N(19)-H(27) | 119.8783   | N(13)-C(14)-C(11) | 119.3906   | N(19)-C(5)-C(4) | 120.6217   |
| H(28)-N(19)-C(5)  | 120.2226   | C(18)-N(13)-C(14) | 120.2529   | N(6)-C(5)-C(4) | 119.8576   |
| H(27)-N(19)-C(5)  | 119.8853   | H(24)-O(12)-C(11) | 109.5015   | C(7)-C(4)-C(5) | 120.6503   |
| H(26)-C(18)-C(17) | 120.0106   | C(14)-C(11)-O(12) | 120.5572   | C(7)-C(4)-N(3) | 119.6208   |
| H(26)-C(18)-N(13) | 120.0344   | C(14)-C(11)-N(9)  | 120.2337   | C(5)-C(4)-N(3) | 119.7171   |
| C(17)-C(18)-N(13) | 119.955    | O(12)-C(11)-N(9)  | 119.1791   | C(4)-N(3)-C(2) | 120.108    |
| H(25)-C(17)-C(18) | 120.0382   | C(11)-N(9)-N(8)   | 118.9125   | H(22)-C(2)-N(3) | 120.0437   |
| H(25)-C(17)-N(16) | 120.0359   | H(23)-N(8)-N(9)   | 119.5355   | H(22)-C(2)-C(1) | 120.0059   |
| C(18)-C(17)-N(16) | 119.9258   | H(23)-N(8)-C(7)   | 119.8885   | N(3)-C(2)-C(1) | 119.9495   |
| C(17)-N(16)-C(15) | 120.2461   | N(9)-N(8)-C(7)    | 120.5228   | H(21)-C(1)-N(6) | 120.041    |
| N(20)-C(15)-N(16) | 119.2623   | O(10)-C(7)-N(8)   | 119.9566   | H(21)-C(1)-C(2) | 120.0285   |
| N(20)-C(15)-C(14) | 120.8896   | O(10)-C(7)-C(4)   | 119.9196   | N(6)-C(1)-C(2) | 119.9277   |

Table S3. Bonds lengths (Å) of [Cu₂(APA-H)(H₂O)Cl₃]·H₂O using DFT-method from DMOL calculations.

| Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) |
|---------------|------------|---------------|------------|---------------|------------|---------------|------------|
| O(24)-H(37)  | 0.9973     | N(19)-H(32)  | 1.0338     | N(13)-C(14)   | 1.3817     | C(5)-N(19)   | 1.4295     |
| O(24)-H(36)  | 0.9973     | N(19)-Cu(21) | 2.2537     | O(12)-Cu(22)  | 2.1144     | C(5)-N(6)    | 1.3596     |
| O(24)-Cu(22) | 2.307      | C(18)-H(31)  | 1.0959     | C(14)-C(11)   | 1.4721     | C(4)-C(7)    | 1.4618     |
| Cl(23)-Cu(22)| 2.3418     | C(17)-H(30)  | 1.0955     | C(11)-O(12)   | 1.3259     | C(4)-C(5)    | 1.4461     |
| Cl(26)-Cu(21)| 2.35       | C(17)-C(18)  | 1.4239     | O(10)-Cu(21)  | 2.1479     | N(3)-C(4)    | 1.383      |
| Cl(25)-Cu(21)| 2.3589     | N(16)-C(17)  | 1.3642     | N(9)-C(11)    | 1.3743     | C(2)-H(28)   | 1.097      |
| N(20)-H(35)  | 1.0358     | C(15)-N(20)  | 1.4392     | N(8)-H(29)    | 1.0488     | C(2)-N(3)    | 1.3584     |
| N(20)-H(34)  | 1.0389     | C(15)-N(16)  | 1.3612     | N(8)-N(9)     | 1.35      | C(1)-H(27)   | 1.0968     |
| N(20)-Cu(22) | 2.2372     | C(14)-C(15)  | 1.4531     | C(7)-O(10)    | 1.3055     | N(6)-C(1)    | 1.3614     |
| N(19)-H(33)  | 1.0382     | C(18)-N(13)  | 1.359      | C(7)-N(8)     | 1.4       | C(1)-C(2)    | 1.4276     |
**Table S4.** Bonds angles (˚) of \([\text{Cu}_2(\text{APA}-\text{H})(\text{H}_2\text{O})\text{Cl}_3]\)·\(\text{H}_2\text{O}\) using DFT-method from DMOL³ calculations.

| Angle | Degree (˚) | Angle | Degree (˚) | Angle | Degree (˚) |
|-------|------------|-------|------------|-------|------------|
| H(37)-O(24)-H(36) | 104.086 | H(33)-N(19)-C(5) | 113.632 | C(11)-N(9)-N(8) | 119.668 |
| H(37)-O(24)-Cu(22) | 104.421 | H(32)-N(19)-Cu(21) | 111.1704 | H(29)-N(8)-N(9) | 118.3853 |
| H(36)-O(24)-Cu(22) | 109.2731 | H(32)-N(19)-C(5) | 109.4936 | H(29)-N(8)-C(7) | 119.973 |
| O(24)-Cu(22)-Cl(23) | 106.4758 | Cu(21)-N(19)-C(5) | 114.9949 | N(9)-N(8)-C(7) | 121.6032 |
| O(24)-Cu(22)-N(20) | 105.1124 | H(31)-C(18)-C(17) | 121.7454 | O(10)-C(7)-N(8) | 119.7595 |
| O(24)-Cu(22)-O(12) | 111.9968 | H(31)-C(18)-N(13) | 117.0667 | O(10)-C(7)-C(4) | 125.3761 |
| Cl(23)-Cu(22)-N(20) | 121.7634 | C(17)-C(18)-N(13) | 121.1866 | N(8)-C(7)-C(4) | 114.8569 |
| Cl(23)-Cu(22)-O(12) | 128.4852 | H(30)-C(17)-C(18) | 122.0378 | C(5)-N(6)-C(1) | 118.0727 |
| N(20)-Cu(22)-O(12) | 79.4743 | H(30)-C(17)-N(16) | 117.5059 | N(19)-C(5)-N(6) | 116.2464 |
| Cl(26)-Cu(21)-Cl(25) | 121.4286 | C(18)-C(17)-N(16) | 120.4563 | N(19)-C(5)-C(4) | 121.8344 |
| Cl(26)-Cu(21)-N(19) | 111.2144 | C(17)-C(18)-N(13) | 117.5879 | N(6)-C(5)-C(4) | 121.8838 |
| Cl(26)-Cu(21)-O(10) | 116.7568 | N(20)-C(15)-N(16) | 114.1991 | C(7)-C(4)-C(3) | 123.8584 |
| Cl(25)-Cu(21)-N(19) | 102.41 | N(20)-C(15)-C(14) | 123.0835 | N(19)-C(5)-C(4) | 118.0727 |
| Cl(25)-Cu(21)-O(10) | 114.7559 | N(16)-C(15)-C(14) | 121.9146 | N(19)-C(5)-C(4) | 119.8421 |
| N(19)-Cu(21)-O(10) | 81.0071 | C(15)-C(14)-N(13) | 117.6974 | N(6)-C(5)-C(4) | 118.7355 |
| H(35)-N(20)-H(34) | 108.6316 | C(15)-C(14)-C(11) | 124.0972 | H(28)-C(2)-N(3) | 118.012 |
| H(35)-N(20)-Cu(22) | 117.1723 | N(13)-C(14)-C(11) | 118.1901 | H(28)-C(2)-C(1) | 120.6356 |
| H(35)-N(20)-C(15) | 108.4625 | C(18)-N(13)-C(14) | 119.8418 | N(3)-C(2)-C(1) | 121.3278 |
| H(34)-N(20)-Cu(22) | 99.8601 | C(22)-O(12)-C(11) | 122.14 | H(27)-C(1)-N(6) | 117.6961 |
| H(34)-N(20)-C(15) | 112.5589 | C(14)-C(11)-O(12) | 120.358 | H(27)-C(1)-C(2) | 121.5398 |
| Cu(22)-N(20)-C(15) | 110.0307 | C(14)-C(11)-N(9) | 126.3113 | N(6)-C(1)-C(2) | 120.7567 |
| H(33)-N(19)-H(32) | 108.7155 | O(12)-C(11)-N(9) | 113.1607 |
| H(33)-N(19)-Cu(21) | 98.3312 | Cu(21)-O(10)-C(7) | 125.5608 |

**Table S5.** Bonds lengths (Å) of \([\text{Co}_2(\text{APA}-2\text{H})(\text{H}_2\text{O})\text{Cl}_2]\)·\(\text{EtOH}\) using DFT-method from DMOL³ calculations.

| Bond | Length (Å) | Bond | Length (Å) | Bond | Length (Å) | Bond | Length (Å) |
|------|------------|------|------------|------|------------|------|------------|
| O(26)-H(38) | 1.1101 | N(19)-H(32) | 1.11 | N(13)-C(14) | 1.5122 | C(4)-C(7) | 1.553 |
| O(26)-H(37) | 1.11 | N(19)-H(31) | 1.11 | O(12)-Co(22) | 1.9364 | C(4)-C(5) | 1.5571 |
| O(24)-H(36) | 1.11 | N(19)-Co(21) | 1.9399 | C(14)-C(11) | 1.5538 | N(3)-C(4) | 1.5121 |
| O(24)-H(35) | 1.11 | C(18)-H(30) | 1.1399 | C(11)-O(12) | 1.5096 | C(2)-H(28) | 1.1401 |
| O(24)-Co(22) | 1.9502 | C(17)-H(29) | 1.14 | O(10)-Co(21) | 1.9361 | C(2)-N(3) | 1.5089 |
| Cl(23)-Co(22) | 2.2011 | C(17)-C(18) | 1.536 | N(9)-C(11) | 1.5101 | C(1)-H(27) | 1.14 |
| O(26)-Co(21) | 1.9497 | N(16)-C(17) | 1.5075 | N(8)-N(9) | 1.4791 | N(6)-C(1) | 1.5077 |
| Cl(25)-Co(21) | 2.2004 | C(15)-N(20) | 1.5119 | C(7)-O(10) | 1.5099 | C(1)-C(2) | 1.5364 |
| N(20)-H(34) | 1.1101 | C(15)-N(16) | 1.5114 | C(7)-N(8) | 1.5086 |
| N(20)-H(33) | 1.1099 | C(14)-C(15) | 1.557 | C(5)-N(19) | 1.5121 |
| N(20)-Co(22) | 1.9391 | C(18)-N(13) | 1.5087 | C(5)-N(6) | 1.5113 |
### Table S6. Bonds angles (˚) of [Co(APA-2H)(H2O)Cl]-EtOH using DFT-method from DMOL3 calculations.

| Angle                     | Degree (˚) | Angle                     | Degree (˚) | Angle                     | Degree (˚) |
|---------------------------|------------|---------------------------|------------|---------------------------|------------|
| H(38)-O(26)-H(37)         | 109.4302   | Co(22)-N(20)-C(15)        | 109.6599   | C(14)-C(11)-N(9)          | 119.5847   |
| H(38)-O(26)-Co(21)        | 109.2133   | H(32)-N(19)-H(31)         | 109.4227   | O(12)-C(11)-N(9)          | 117.9303   |
| H(37)-O(26)-Co(21)        | 109.4171   | H(32)-N(19)-Co(21)        | 109.3682   | Co(21)-O(10)-C(7)         | 107.6198   |
| H(36)-O(24)-H(35)         | 109.4408   | H(32)-N(19)-C(5)          | 108.9992   | C(11)-N(9)-N(8)           | 121.5672   |
| H(36)-O(24)-Co(22)        | 109.4173   | H(31)-N(19)-Co(21)        | 109.802    | N(9)-N(8)-C(7)            | 118.5908   |
| H(35)-O(24)-Co(22)        | 109.4902   | H(31)-N(19)-C(5)          | 109.8154   | O(10)-C(7)-N(8)           | 118.0668   |
| O(24)-Co(22)-Cl(23)       | 111.0168   | Co(21)-N(19)-C(5)         | 109.4161   | O(10)-C(7)-C(4)           | 122.6228   |
| O(24)-Co(22)-N(20)        | 111.9964   | H(30)-C(18)-C(17)         | 120.029    | N(8)-C(7)-C(4)            | 119.2666   |
| O(24)-Co(22)-O(12)        | 112.0431   | H(30)-C(18)-N(13)         | 120.0525   | C(5)-N(6)-C(1)            | 120.6745   |
| Cl(23)-Co(22)-N(20)       | 111.4271   | C(17)-C(18)-N(13)         | 119.9185   | N(19)-C(5)-N(6)           | 117.9891   |
| Cl(23)-Co(22)-O(12)       | 110.4816   | H(29)-C(17)-C(18)         | 120.0868   | N(19)-C(5)-C(4)           | 122.2724   |
| N(20)-Co(22)-O(12)        | 99.3834    | H(29)-C(17)-N(16)         | 120.1165   | N(6)-C(5)-C(4)            | 119.6257   |
| N(20)-Co(21)-Cl(25)       | 111.2416   | C(18)-C(17)-N(16)         | 119.7966   | C(7)-C(4)-C(5)            | 123.4378   |
| O(26)-Co(21)-N(19)        | 111.6896   | C(17)-N(16)-C(15)         | 120.7084   | C(7)-C(4)-N(3)            | 117.4794   |
| O(26)-Co(21)-O(10)        | 110.682    | N(20)-C(15)-N(16)         | 117.9179   | C(5)-C(4)-N(3)            | 119.0759   |
| Cl(25)-Co(21)-N(19)       | 111.7693   | N(20)-C(15)-C(14)         | 122.3096   | C(4)-N(3)-C(2)            | 120.8485   |
| Cl(25)-Co(21)-O(10)       | 111.351    | N(16)-C(15)-C(14)         | 119.6592   | H(28)-C(2)-N(3)           | 120.0426   |
| N(19)-Co(21)-O(10)        | 99.6008    | C(15)-C(14)-N(13)         | 118.9783   | H(28)-C(2)-C(1)           | 120.035    |
| H(34)-N(20)-H(33)         | 109.4637   | C(15)-C(14)-C(11)         | 123.3267   | N(3)-C(2)-C(1)            | 119.9222   |
| H(34)-N(20)-Co(22)        | 109.562    | N(13)-C(14)-C(11)         | 117.6894   | H(27)-C(1)-N(6)           | 120.0678   |
| H(34)-N(20)-C(15)         | 109.9549   | C(18)-N(13)-C(14)         | 120.9323   | H(27)-C(1)-C(2)           | 120.0938   |
| H(33)-N(20)-Co(22)        | 109.2137   | Co(22)-O(12)-C(11)        | 107.1183   | N(6)-C(1)-C(2)            | 119.8385   |
| H(33)-N(20)-C(15)         | 108.9691   | C(14)-C(11)-O(12)         | 122.4387   |

### Table S7. Bonds lengths (Å) of [Pt(APA-H)(H2O)Cl]-H2O·2EtOH using DFT-method from DMOL3 calculations.

| Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) | Bond          | Length (Å) |
|---------------|------------|---------------|------------|---------------|------------|---------------|------------|
| O(23)-H(36)  | 1.11       | N(19)-H(31)  | 1.1101     | O(12)-Pt(21)  | 2.0993     | C(4)-C(7)    | 1.5419     |
| O(23)-H(35)  | 1.11       | C(18)-H(30)  | 1.1401     | C(14)-C(11)  | 1.5548     | C(4)-C(5)    | 1.5449     |
| Cl(25)-Pt(21)| 2.3556     | C(17)-H(29)  | 1.1399     | C(11)-O(12)  | 1.5088     | N(3)-C(4)    | 1.5104     |
| Cl(24)-Pt(21)| 2.3582     | C(17)-C(18)  | 1.5356     | N(9)-C(11)   | 1.5147     | C(2)-H(27)  | 1.14       |
| O(23)-Pt(21) | 2.109      | N(16)-C(17)  | 1.5073     | N(8)-H(28)  | 1.1071     | C(2)-N(3)   | 1.5094     |
| Cl(22)-Pt(21)| 2.3583     | C(15)-N(20)  | 1.5138     | N(8)-N(9)   | 1.4809     | C(1)-H(26)  | 1.14       |
| N(20)-H(34)  | 1.1102     | C(15)-N(16)  | 1.512      | C(7)-O(10)  | 1.5089     | N(6)-C(1)   | 1.5094     |
| N(20)-H(33)  | 1.1102     | C(14)-C(15)  | 1.5575     | C(7)-N(8)   | 1.5096     | C(1)-C(2)   | 1.539      |
| N(20)-Pt(21) | 2.1059     | C(18)-N(13)  | 1.508      | C(5)-N(19)  | 1.511      |
| N(19)-H(32)  | 1.1079     | N(13)-C(14)  | 1.5112     | C(5)-N(6)   | 1.5111     |

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Table S8. Bond angles (˚) of [Pt(APA-H)(H2O)Cl3]·H2O·2EtOH using DFT-method from DMOL3 calculations.

| Angle | Degree (˚) | Angle | Degree (˚) | Angle | Degree (˚) |
|-------|------------|-------|------------|-------|------------|
| H(36)-O(23)-H(35) | 109.5042 | H(33)-N(20)-C(15) | 108.6103 | O(12)-C(11)-N(9) | 117.6962 |
| H(36)-O(23)-Pt(21) | 109.4916 | Pt(21)-N(20)-C(15) | 113.8931 | C(11)-N(9)-N(8) | 122.2549 |
| H(35)-O(23)-Pt(21) | 109.4627 | H(32)-N(19)-H(31) | 119.8452 | H(28)-N(8)-N(9) | 120.5454 |
| Cl(25)-Pt(21)-Cl(24) | 89.944 | H(31)-N(19)-C(5) | 119.8198 | N(9)-N(8)-C(7) | 119.7369 |
| Cl(25)-Pt(21)-O(23) | 89.9361 | H(31)-N(19)-C(5) | 119.8198 | N(9)-N(8)-C(7) | 119.7369 |
| Cl(25)-Pt(21)-Cl(22) | 89.5533 | H(30)-C(18)-C(17) | 120.0703 | O(10)-C(7)-N(8) | 119.6681 |
| Cl(25)-Pt(21)-N(20) | 179.3994 | H(30)-C(18)-N(13) | 120.0682 | O(10)-C(7)-C(4) | 119.556 |
| Cl(25)-Pt(21)-O(12) | 90.3169 | C(17)-C(18)-N(13) | 119.8615 | N(8)-C(7)-C(4) | 119.556 |
| Cl(24)-Pt(21)-O(23) | 89.7542 | H(29)-C(17)-C(18) | 120.1036 | C(5)-N(6)-C(1) | 120.2071 |
| Cl(24)-Pt(21)-Cl(22) | 179.2842 | H(29)-C(17)-N(16) | 120.1069 | N(9)-C(5)-N(6) | 119.3033 |
| Cl(24)-Pt(21)-N(20) | 90.2003 | C(18)-C(17)-N(16) | 117.7893 | N(9)-C(5)-C(4) | 120.859 |
| Cl(24)-Pt(21)-O(12) | 90.071 | C(17)-N(16)-C(15) | 120.7419 | N(5)-C(4)-N(3) | 119.8377 |
| O(23)-Pt(21)-Cl(22) | 89.7357 | N(20)-C(15)-N(16) | 117.5192 | C(7)-C(4)-N(3) | 119.7369 |
| O(23)-Pt(21)-N(20) | 60.4674 | N(20)-C(15)-C(14) | 122.7561 | C(7)-C(4)-N(3) | 119.7369 |
| O(23)-Pt(21)-O(12) | 179.6923 | N(16)-C(15)-C(14) | 120.0077 | C(5)-C(4)-N(3) | 119.7369 |
| Cl(22)-Pt(21)-N(20) | 90.3076 | C(15)-C(14)-N(13) | 118.9046 | C(4)-N(3)-C(2) | 120.233 |
| Cl(22)-Pt(21)-O(12) | 90.4413 | C(15)-C(14)-C(11) | 122.9298 | H(27)-C(2)-N(3) | 120.005 |
| N(20)-Pt(21)-O(12) | 89.0999 | N(13)-C(14)-C(11) | 118.1577 | C(7)-C(2)-C(1) | 119.9873 |
| H(34)-N(20)-H(33) | 108.6236 | C(18)-N(13)-C(14) | 121.0771 | N(9)-C(5)-N(6) | 120.192 |
| H(34)-N(20)-H(33) | 108.5445 | Pt(21)-O(12)-C(11) | 109.3031 | C(7)-C(2)-C(1) | 119.9873 |
| H(34)-N(20)-C(15) | 108.4817 | C(14)-C(11)-O(12) | 121.8095 | C(7)-C(2)-C(1) | 119.9873 |
| H(33)-N(20)-Pt(21) | 108.5761 | C(14)-C(11)-N(9) | 120.4931 | N(6)-C(1)-C(2) | 119.9495 |

Table S9. Bond lengths (Å) of [Pd(APA-H)(H2O)Cl]-EtOH_{1/2} using DFT-method from DMOL3 calculations.

| Bond | Length (Å) | Bond | Length (Å) | Bond | Length (Å) | Bond | Length (Å) |
|------|------------|------|------------|------|------------|------|------------|
| O(22)-H(34) | 1.1099 | C(18)-H(28) | 1.14 | O(12)-Pd(21) | 2.087 | C(5)-N(6) | 1.5108 |
| O(22)-H(33) | 1.11 | C(17)-H(27) | 1.1399 | C(14)-C(11) | 1.5573 | C(4)-C(7) | 1.5418 |
| Cl(23)-Pd(21) | 2.3458 | C(17)-C(18) | 1.5354 | C(11)-O(12) | 1.5099 | C(4)-C(5) | 1.5446 |
| O(22)-Pd(21) | 2.0975 | N(16)-C(17) | 1.5069 | N(9)-C(11) | 1.5149 | N(3)-C(4) | 1.5108 |
| N(20)-H(32) | 1.1101 | C(15)-N(20) | 1.5106 | N(8)-H(26) | 1.1067 | C(2)-H(25) | 1.1401 |
| N(20)-H(31) | 1.11 | C(15)-N(16) | 1.5116 | N(8)-N(9) | 1.4808 | C(2)-N(3) | 1.5091 |
| N(20)-Pd(21) | 2.0895 | C(14)-C(15) | 1.5571 | C(7)-O(10) | 1.5092 | C(1)-H(24) | 1.1401 |
| N(19)-H(30) | 1.1079 | C(18)-N(13) | 1.5082 | C(7)-N(8) | 1.5095 | N(6)-C(1) | 1.5095 |
| N(19)-H(29) | 1.11 | N(13)-C(14) | 1.5106 | C(5)-N(19) | 1.5108 | C(1)-C(2) | 1.539 |
**Table S10.** Bonds angles (°) of [Pd(APA)(H2O)Cl]·1/2EtOH using DFT-method from DMOL3 calculations.

| Angle | Degree (°) | Angle | Degree (°) | Angle | Degree (°) |
|-------|-----------|-------|-----------|-------|-----------|
| H(34)-O(22)-Pd(21) | 109.4642 | C(17)-C(18)-N(13) | 119.9035 | N(9)-N(8)-C(7) | 119.82 |
| H(33)-O(22)-Pd(21) | 109.613 | H(27)-C(17)-C(18) | 120.1288 | O(10)-C(7)-N(8) | 119.7379 |
| Cl(23)-Pd(21)-O(22) | 89.8849 | H(27)-C(17)-N(16) | 120.1279 | O(10)-C(7)-C(4) | 120.8417 |
| Cl(23)-Pd(21)-N(20) | 179.3931 | C(18)-C(17)-N(16) | 119.7434 | N(8)-C(7)-C(4) | 119.4171 |
| Cl(23)-Pd(21)-O(12) | 90.4317 | C(17)-N(16)-C(15) | 120.6591 | C(5)-N(6)-C(1) | 120.1962 |
| O(22)-Pd(21)-N(20) | 90.7193 | N(20)-C(15)-N(16) | 117.897 | N(19)-C(5)-N(6) | 119.3221 |
| O(22)-Pd(21)-O(12) | 179.545 | N(20)-C(15)-C(14) | 122.1352 | N(19)-C(5)-C(4) | 120.8546 |
| N(20)-Pd(21)-O(12) | 88.9638 | N(16)-C(15)-C(14) | 119.8389 | N(6)-C(5)-C(4) | 119.8231 |
| H(32)-N(20)-H(31) | 109.7835 | C(15)-C(14)-N(13) | 118.7078 | C(7)-C(4)-C(5) | 121.1058 |
| H(32)-N(20)-Pd(21) | 109.6259 | C(15)-C(14)-C(11) | 123.0671 | C(7)-C(4)-N(3) | 119.0913 |
| H(32)-N(20)-C(15) | 109.8928 | N(13)-C(14)-C(11) | 118.2251 | C(5)-C(4)-N(3) | 119.8015 |
| H(31)-N(20)-Pd(21) | 109.7371 | C(18)-N(13)-C(14) | 121.1457 | C(4)-N(3)-C(2) | 120.2436 |
| H(31)-N(20)-C(15) | 109.7275 | Pd(21)-O(12)-N(13) | 107.612 | H(25)-C(2)-N(3) | 120.0226 |
| Pd(21)-N(20)-C(15) | 108.0494 | C(14)-C(11)-N(13) | 121.8715 | H(25)-C(2)-C(1) | 120.0318 |
| H(30)-N(19)-H(29) | 119.8485 | C(14)-C(11)-N(9) | 120.5024 | N(3)-C(2)-C(1) | 119.9452 |
| H(30)-N(19)-C(5) | 120.3039 | O(12)-C(11)-N(9) | 117.5862 | H(24)-C(1)-N(6) | 120.0049 |
| H(29)-N(19)-C(5) | 119.8476 | C(11)-N(9)-N(8) | 122.5354 | H(24)-C(1)-C(2) | 120.0056 |
| H(28)-C(18)-C(17) | 120.0458 | H(26)-N(8)-N(9) | 120.5353 | N(6)-C(1)-C(2) | 119.9892 |
| H(34)-O(22)-Pd(21) | 109.4642 | C(17)-C(18)-N(13) | 119.9035 | N(9)-N(8)-C(7) | 119.82 |

**Table S11.** Decomposition steps with the temperature range and weight loss for Cu2+ complex of APA.

| Compound | Decomp. Step | Temperature Range (°C) | Remove Species | Wt. Loss % (Calcd.) | % Found |
|----------|--------------|------------------------|----------------|---------------------|---------|
| [Cu2(APA-H)(H2O)Cl3]·H2O | 1st | 32 - 102 |−(H2O) | 3.3 | 3.3 |
| | 2nd | 102 - 246 |−(C3H3N3 + Cl + H2O) | 27.2 | 27.1 |
| | 3rd | 247 - 336 |−(C2H3N3) | 17.2 | 17.1 |
| | 4th | 336 - 416 |−(2HCl) | 13.4 | 14.1 |
| | 5th | 417 - 569 |−(N2 + C) | 7.4 | 7.3 |
| | residue | ========= | [Cu2(O)2] + C | 31.5 | 31.1 |