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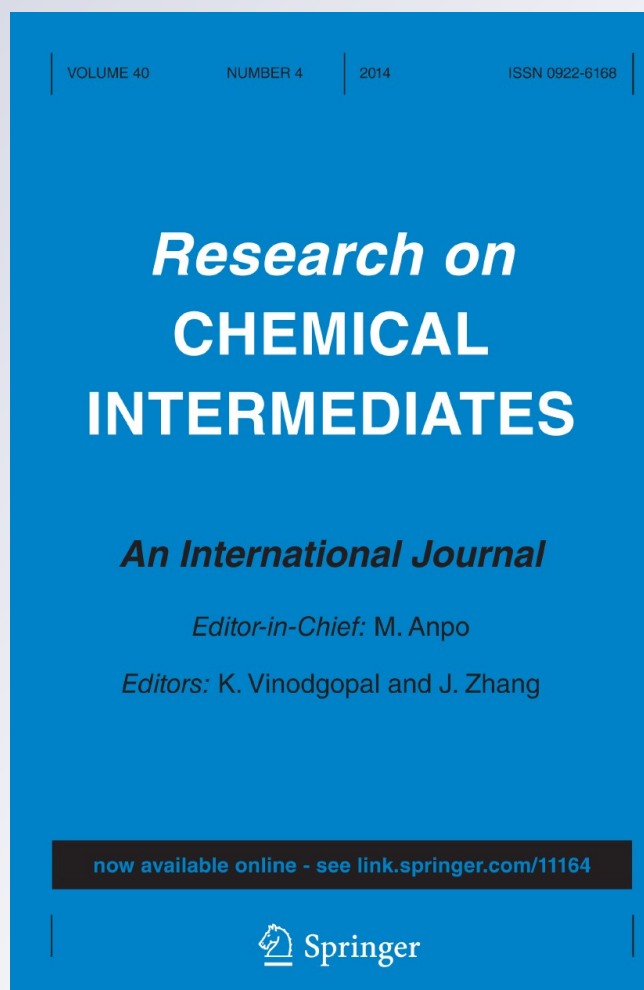
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Solvent-free synthesis, x-ray studies and in vitro inhibitory activities of copper(II) complexes of non-steroidal anti-inflammatory drugs

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Abstract Solid-state mechanochemical synthesis of $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complex **1a** and $[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complex **2a** were obtained by grinding stoichiometric amounts of $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$ and corresponding non-steroidal anti-inflammatory drugs[(caffeine (CAF) and codeine(COD))], respectively, in a mortar with pestle. Solvent-based synthesis of **1b** and **2b** was also carried out by reaction of metal acetate salt and each drug by refluxing at 70 °C in CH_3OH for 1 h for comparison purposes. The complexes **1a** and **2a** were characterized by comparison of elemental analysis, FT-IR, UV–Vis and ^1H NMR spectra with those of the free ligand and solvent-based products (**1b** and **2b**). The analytical and spectroscopic data of the complexes prepared via the two different methods are almost identical. X-ray diffraction patterns of the complexes prepared by mechanochemical method were different from that of the starting material suggesting formation of new metal complexes. In vitro inhibitory activities of both mechanochemical and solvent-based complexes were found to be higher than parent ligands, indicating that the antimicrobial effect of these drugs could be enhanced when they are chelated to the metal. The mechanochemical synthesis was carried out without the use of solvent or external heating. The method is faster and gives a higher yield than corresponding solvent-based reactions. The solid state reaction presented higher efficiency in terms of materials, energy and time compared to solvent-based synthesis.

Keywords Solvent-free synthesis · Caffeine · Codeine · ^1H NMR · XRPD patterns

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Introduction

The presence of copper in the human body and its functioning in different vital processes is connected with the copper atom ability to form complexes with different non-steroidal anti-inflammatory ligands such as caffeine and codeine [1]. Caffeine and codeine are of great pharmacological interest since they show a broad spectrum of biological activities including anti-inflammatory activities [2].

Caffeine is widely known as a white crystalline xanthine alkaloid and a substance used to stimulate the central nervous system and metabolic activities. Being the most commonly used energy drug, it constitutes about 90 % of all energy drinks world-wide. Chemically, it is an achiral molecule without stereoisomers and its IUPAC name is 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione. The two amide groups contained in the chemical structure of caffeine are double-bonded to each other so that both of these nitrogen atoms are potentially zwitterionic resonance structures and essentially planar (in sp^2 orbital hybridization) [2].

Codeine (morphine 3-methyl ether), on the other hand, is a member of the group of narcotics and a naturally occurring alkaloid found in opium poppy [3]. In addition to this, it is known in medicine as anti-tussive, an anti-diarrheal drug and a cough suppressant. It exerts its effects by acting on the central nervous system (brain and spinal cord). The biological activities of these ligands (caffeine and codeine) are greatly influenced by their molecular structures as well as by the coordination number of the copper moiety [4, 5].

Solvent-free mechanochemical methods represent viable green routes for the preparation of coordination compounds of pharmaceutical drugs. Most of these complexes have been synthesized by the traditional method using volatile organic compounds (VOCs) as solvents. Most research on solvent-free synthesis now focuses on the development of chemical reactions that minimize waste products [6–8]. A surprising aspect of these studies is that, in some cases, the reaction is faster and more environmentally friendly than the corresponding solvent-based synthesis. In the solvent-based synthesis of metal complexes, several different complexes can coexist in equilibrium in solution of volatile organic solvents (VOCs), and pollution by these solvents could lead to an acute problem of chemical waste [9, 10].

Metal complexes of various pharmaceutical active ingredients are reported in the literature [11–17]. Nevertheless, solid state mechanochemical methods have rarely been used in the preparation of these complexes. To the best of our knowledge, the first solvent-free synthesis of metal-drug complexes was reported by Braga et al. [18]. Zinc and copper complexes of the neuroleptic drug gabapentin were synthesized by Braga and co-workers by simply grinding solid gabapentin and the inorganic salts of $ZnCl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$. Amin et al. [19] described the mechanochemical synthesis of the Zn(II)–famotidine complex. Famotidine is an effective antiulcer drug having an excellent histamine H_2 receptor blocking effect. The reaction occurred within 30–40 s by grinding zinc acetate dihydrate and famotidine using a mortar and pestle.

Recently, our group reported solvent-less mechanically-induced synthesis of Ni(II) and Co(II) complexes of cimetidine with high quantitative yield in the absence of volatile organic solvents [20]. However, the experiments described here

demonstrate the utility of a mechanochemical method (grinding in a mortar and pestle or ball-milling at room temperature) for rapidly achieving complete reactions between copper(II) ion and two ligands (caffeine and codeine) in 15 min, and comparing the analytical and spectroscopic data thus obtained from a mechanochemical method with those of the free ligands and solution-based conventional synthesis products. To our knowledge, solvent-free solid state reactions have never been used to produce $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ and $[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$, and we have applied for the first time solid-state reactions to synthesize metal complexes of non-steroidal anti-inflammatory drugs(caffeine and codeine).

Experimental

Materials and instrumentation

All reagents and chemicals were of analytical grade and used as obtained from Aldrich. The ligands (caffeine and codeine) were obtained as gift from Tuyil Pharmaceutical, Ilorin, Nigeria. FT-IR spectra of the ligands and the complexes were recorded in KBr pellets in the range of $4,000\text{--}400\text{ cm}^{-1}$ on a SHIMADZU scientific model 500 FITR spectrophotometer. Electronic spectra were done on an Aquamate Spectrophotometer, Model V4.60. Conductivity measurements were carried out using a WTW Conductimeter Bridge. ^1H NMR(400 MHz) spectra were recorded with a Bruker DPX-NMR spectrometer. Chemical shifts for proton resonances are reported in ppm(δ) relative to tetramethylsilane. Thin layer chromatography (TLC) was carried out using TLC plates coated with silica gel. AAS analysis was carried out on Atomic Absorption Spectrophotometer Model 6503 Jenway. X-ray diffraction analysis was carried out on a Bruker AVS D8 graphite diffractometer. Elemental analysis was performed on a Perkin-Elmer CHN Analyzer 2400 Series II. *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Candida albicans* and *Aspergillus niger* were obtained as gifts from University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Experimental procedure

The methods described by Amin et al. [19] and Stuart et al. [21] were modified and adopted for mechanochemical or solvent-free synthesis. The method described by Obaleye et al. [11–13]; Tella and Obaleye [14–17] was used for solution-based synthesis. The stoichiometry of reactants used was in the ratio of 1:2 metal to ligand.

Mechanochemical synthesis of $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ (**1a**)
(OAc= OOCCH_3)

Caffeine (2 mmol, 0.388 g) and copper acetate ($\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$) (1 mmol, 0.199 g) were weighed into a mortar that had been previously washed and dried.

The reactants were ground continuously in the mortar with a pestle for 15 min to a fine paste at room temperature. The progress of the reaction was monitored by TLC until no traces of the reactants were found. A bluish-green powder obtained was washed with methanol to remove unreacting starting materials and dried at room temperature. The equation of the reaction is shown in Scheme 1.

Yield: 91.3 %, anal. calcd. m.wt. = 587.38 g/mol, m.pt. = 245 °C. Anal. calcd. (found) % for (C₂₀H₂₈N₈O₉Cu); C, 40.86 (40.24); H, 4.77 (4.96); N, 19.07 (18.96); Cu, 10.73 (11.20); IR (KBr, cm⁻¹): 3,400–3,249, 3,118, 2,956, 1,705, 1,654, 1,600, 1,548, 1,350, 746, 422; UV–Vis(DMSO) λ, nm: 676; ¹H NMR(DMSO-*d*₆): δ(N1–CH₃) 3.29 ppm, δ(N3–CH₃) 3.67 ppm, δ(N7–CH₃) 3.92 ppm, δ(C8–H) 8.20, δ(OH) 12.9 pp.

Solvent-based synthesis of [Cu(CAF)₂(H₂O)(OAc)]OAc (**1b**) (OAc=OOCCH₃)

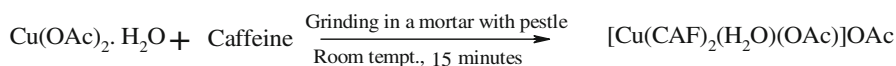
A solution of caffeine (2 mmol, 0.388 g) in methanol (10 ml) was added to a solution of copper acetate (Cu(CH₃COO)₂·H₂O) (1 mmol, 0.199 g) in methanol (10 ml). The resulting solution was refluxed for 1 h at 70 °C, filtered, and allowed to evaporate for 2 days at room temperature. A crystalline deep green product obtained was washed with methanol and dried at room temperature. The equation of the reaction is shown in Scheme 2.

Yield: 77.9 %, anal. calcd. m.wt. = 587.38 g/mol, m.pt. = 242 °C. Anal. calcd. (found) % for (C₂₀H₂₈N₈O₉Cu); C, 40.86 (40.01); H, 4.77 (4.49); N, 19.07 (19.00); Cu, 10.73 (11.1.2); IR (KBr, cm⁻¹): 3,400–3,250, 2,950, 1,705, 1,662, 1,608, 1,550, 1,345, 746, 426; UV–Vis(DMSO) λ, nm : 670. ¹H NMR(DMSO-*d*₆): δ(N1–CH₃) 3.28 ppm, δ(N3–CH₃) 3.69 ppm, δ(N7–CH₃) 3.90 ppm δ(C8–H)8.15, δ(OH) 12.9 ppm.

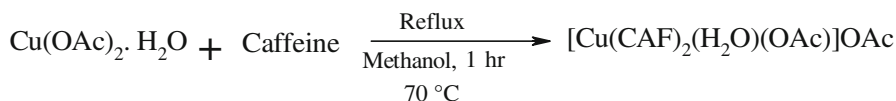
Mechanochemical synthesis of [Cu(COD)₂(H₂O)(OAc)]OAc (**2a**) (OAc=OOCCH₃)

Codeine (1 mmol, 0.299 g) and copper acetate (Cu(CH₃COO)₂·H₂O) (1 mmol, 0.199 g) was weighed into a mortar that has been previously washed and dried. The reactant mixture was then ground continuously in the mortar with a pestle for 15 min to a fine paste at room temperature. The progress of the reaction was monitored by TLC until no traces of the reaction were found. A light blue powder obtained was washed with methanol to remove unreacting starting materials and dried at room temperature. The equation of the reaction is shown in Scheme 3.

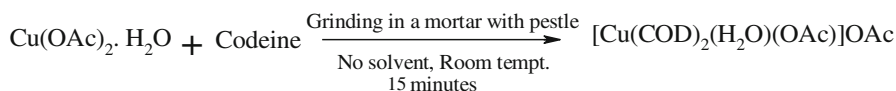
Yield: 96.2 %, anal. calcd. m.wt. = 797.72 g/mol, m.pt. = 192 °C. Anal.calcd. (found) % for (C₄₀H₅₀N₂O₁₁Cu); C, 50.17 (49.20); H, 6.26 (6.00); N, 3.51 (3.42), Cu 13.77 (14.10); IR (KBr, cm⁻¹): 3,400–3,250, 3,036, 2,949, 1,602, 1,325, 1,057, 754, 473; UV–Vis(DMSO) λ, nm: 682.



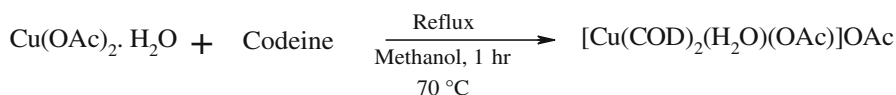
Scheme 1 Equation of reaction for solvent-drop synthesis of [Cu(CAF)₂(H₂O)(OAc)]OAc



Scheme 2 Equation of reaction for solvent-based synthesis of $[\text{Cu(CAF)}_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$



Scheme 3 Equation of reaction for mechanochemical synthesis of $[\text{Cu(COD)}_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$



Scheme 4 Equation of reaction for solvent-based synthesis of $[\text{Cu(COD)}_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$

Solvent-based synthesis of $[\text{Cu(COD)}_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ (**2b**) ($\text{OAc}=\text{OOCCH}_3$)

A solution of codeine (1 mmol, 0.299 g) in methanol (10 ml) was added to a solution of copper acetate ($\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$) (1 mmol, 0.199 g) in methanol (10 ml). The resulting solution was refluxed for 1 h at 70 °C, filtered, and allowed to evaporate for 2 days at room temperature. A crystalline bluish-green product obtained was washed with methanol and dried at room temperature.

The equation of the reaction is shown in scheme 4.

Yield: 78.6 %, anal. calcd. m.wt. = 797.72 g/mol, m.pt. = 188 °C. Anal. calcd. (found) % for ($\text{C}_{40}\text{H}_{50}\text{N}_2\text{O}_{11}\text{Cu}$); C, 50.17 (50.68); H, 6.26 (6.45); N, 3.51 (3.34); Cu, 13.77 (14.00); IR (KBr, cm^{-1}): 3,400–3,250, 3,036, 2,918, 1,602, 1,325, 1,055, 754, 470; UV–Vis(DMSO) λ , nm: 679. ^1H NMR (DMSO-*d*₆): δ (1H) 6.80 ppm, δ (2H) 6.98 ppm, δ (7H) 5.86 ppm, δ (8H) 5.50 ppm, δ (9H) 4.40 ppm, δ (OCH₃) 3.10 ppm, (NCH₃) 2.95 ppm.

Antibacterial and antifungal activities study

The antibacterial and antifungal activities study of caffeine and codeine and their complexes were determined using the agar well diffusion method described by Wasi et al. [22] and Agwara et al. [23]. Solutions of two different concentrations (50 and 25 $\mu\text{g/ml}$) consisting of the caffeine, codeine and the two complexes were prepared in methanol. The sterile Mueller–Hinton agar for bacteria (*E. coli*, *S. aureus* and *K. pneumonia*) and Sabouraud dextrose agar for fungi (*Aspergillus niger* and *Candida albicans*) were separately inoculated with the test microorganisms. Each of the test compounds was placed in wells (10 mm) dug in the agar media. The plates were incubated at 37 °C for bacterium (24 h) and at 25 °C for fungi (72 h). The resulting inhibition zones on the plates were measured with a zone reader. Methanol was used as control instead of sample. Triplicate measurements were done.

Results and discussion

The $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complex **1a** was synthesized by mechanochemical grinding of copper acetate and caffeine in a mortar with a pestle for 15 min at room temperature, while the solvent-based product **1b** was obtained by reaction of copper acetate and caffeine by refluxing in methanol for 1 h at 70 °C. Analysis of UV–Vis, FT-IR and ^1H NMR spectra clearly shows the formation of 1:2 complexes. It also appears from our results that both methods gave similar spectra data in comparison with the free ligand caffeine. The elemental analysis for C, H, and N were also found to be consistent with the formular units of the products (Table 1). Both complexes show interesting properties that have been correlated with those in the literature [24–35].

The $[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complexes **2a** was also synthesized by mechanochemical grinding of copper acetate and codeine in a mortar with a pestle for 15 min at room temperature. The solvent-based product **2b** was obtained by reaction of copper acetate and caffeine by refluxing in methanol for 1 h at 70 °C.

The analytical data of complexes **1a**, **1b** and **2a**, **2b** obtained via the different methods are shown in Table 1.

The complexes **1a**, **1b** and **2a**, **2b** were coloured ranging from light bluish-green to bluish-green and deep green. All the products are stable, non-hygroscopic, soluble in methanol, ethanol and DMSO. The complexes **1a**, **1b** and **2a**, **2b** were dissolved in DMSO and the molar conductivity values of 10^{-3} M solution at 25 °C of the complexes are in the range $64.5\text{--}69.1\ \Omega^{-1}\text{mol}^{-1}\text{cm}^2$ for **1a**, **1b** and $94.6\text{--}98.2\ \Omega^{-1}\text{mol}^{-1}\text{cm}^2$ for **2a**, **2b**, respectively. This data show that the complexes **1** and **2** are electrolytes. The test for acetate was carried out by addition of 1 mg of complexes **1** and **2** to 1 ml of 2.0 M $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ (1:1 v/v), [19]. The acetate test for **1a** and **1b** was positive with the formation of a white precipitate that has the odor of vinegar, indicating that the acetate is outside the coordination sphere. When the same test was carried out with **2a** and **2b**, the addition of 1 mg of complex to 1 ml of 2.0 M $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ (1:1 v/v), it appears that there is no difference in the formation of precipitate between the mechanochemically synthesized complexes and the solution-based products. In an attempt to test for presence of coordinated water, we activated both complexes **1** and **2** to 110 °C for 15 min and monitored the reaction progress by using FT-IR spectroscopy [36]. The test was negative for **1a**, **1b** and **2a**, **2b** without changes in composition and vibrational frequency, indicating that H_2O was present inside the coordination sphere. This showed that the water is coordinated with the metal ion and not present as lattice water. The R_f values for complexes **1a**, **1b** and **2a**, **2b** obtained via both methods also showed single spots indicating the purity of the mechanochemically synthesized complex. In addition, the % yield of the mechanochemical products **1a** and **2a** is higher than the solvent-based products **1b** and **2b**. The melting points of the complexes are higher than the parent ligand.

Infra-red spectra

Figures 1 and 2 show a comparison of the FT-IR spectra of the free caffeine and codeine ligands with the complexes obtained via mechanochemical and solvent-based methods (reflux in methanol).

Table 1 Analytical data of caffeine, codeine and complexes **1a**, **1b** and **2a**, **2b**

Analytical data	Caffeine	Codeine	[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc mechanochemical 1a	[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc solvent-based 1b	[Cu(COD) ₂ (H ₂ O)(OAc)]OAc mechanochemical 2a	[Cu(COD) ₂ (H ₂ O)(OAc)]OAc solvent-based 2b										
Color	White	White	Light bluish green	Deep green	Bluish green	Deep green										
Conductivity $\Omega^{-1} \text{ mol}^{-1} \text{ cm}^2$	0.50	0.70	69.1	64.5	98.2	94.6										
R _f	0.75	0.84	0.93	0.90	0.68	0.65										
Yield (%)	–	–	91.3	77.9	96.2	78.6										
M.pt. (°C)	225	299	245	242	192	188										
M.wt. (g/mol)	194	299	587.38	587.38	797.72	797.72										
Copper (%)	–	–	11.20	11.12	14.10	14.00										
			Anal. calcd. (found) %		Anal. calcd. (found) %											
			C	H	N	C	H	N								
Elemental analysis			–	–	40.86 (40.24)	4.77 (4.96)	19.07 (18.96)	40.86 (40.55)	4.77 (4.49)	19.07 (19.00)	50.17 (49.20)	6.26 (6.00)	3.51 (3.42)	50.17 (50.68)	6.26 (6.45)	3.51 (3.34)
<i>M.wt.</i> Molecular weight, <i>M.pt.</i> melting point, <i>R_f</i> retention factor (TLC)																

M.wt. Molecular weight, M.pt. melting point, R_f retention factor (TLC)

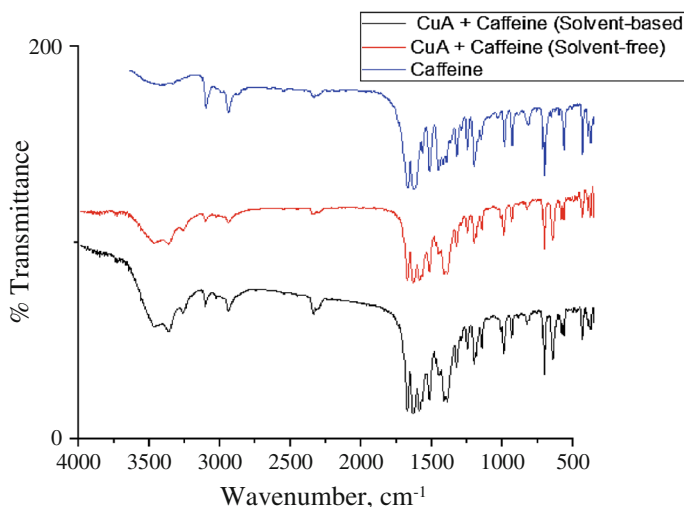


Fig. 1 FT-IR spectrum of caffeine and its Cu(II) complexes

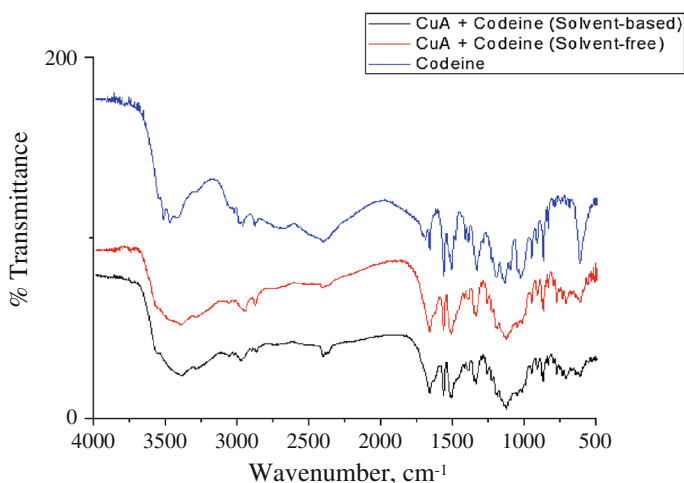


Fig. 2 FT-IR spectra of codeine and its Cu(II) complexes

It can be seen in Figs. 1 and 2 that FT-IR spectra of complexes **1a**, **1b** and **2a**, **2b** synthesized via the two methods are identical, but different from the free ligands (caffeine and codeine). The selected FT-IR data of caffeine, codeine and complexes **1a**, **1b** and **2a**, **2b** are collected in Tables 2 and 3. The data presented below are consistent with the ones in the literature, [3, 26, 28, 30–33].

Caffeine consists of two heterocyclic systems, a six-membered pyrimidine ring and a five-membered imidazole ring. Caffeine has a methyl group at N7, N1, and N3. All these sites are blocked by the CH₃ group which prevents interaction of the metal atoms. Hence, the likely binding sites in caffeine are N9, O2, and O6. Caffeine acts as an

Table 2 Selected FT-IR absorption band (cm^{-1}) data for caffeine and its complexes

S/N	Ligand/complex	$\nu\text{C}=\text{N}$	$\nu\text{C}=\text{O}$	$\nu\text{C}=\text{H}$ (aromatic)	$\nu\text{H}_2\text{O}$	νsCOO	νasCOO	$\nu\text{M}-\text{O}$	$\nu\text{Cu}-\text{OH}_2$
1.	Caffeine	1,687	1,720s	3,118	—	—	—	—	—
2.	$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ mechanochemical 1a	1,654	1,705b	3,110	3,400–3,249	1,600	1,350	422	746m
3.	$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ solvent-based 1b	1,662	1,705b	3,109	3,400–3,250	1,608	1,345	426	746m

Table 3 Selected FT-IR absorption band (cm^{-1}) data of codeine and its complexes

S/N	Ligand/complex	$\nu\text{O}-\text{H}$	$\nu\text{C}-\text{O}-\text{C}$	$\nu\text{C}-\text{O}$ (CH_3O)	$\nu\text{asC}-\text{H}$ (aliphatic)	$\nu\text{sC}-\text{H}$ (aromatic)	$\nu\text{M}-\text{O}$	$\nu\text{Cu}-\text{OH}_2$
1.	Codeine	3,690s	1,066s	1,271	2,937b	3,043m,b	—	—
2.	$[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ mechanochemical 2a	—	1,057b	—	2,949b	3,036m,b	473m,b	754b
3.	$[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ solvent-based 2b	—	1,055b	—	2,918s	3,036m,b	470m,b	754b

ambidentate ligand. In caffeine, either N9 or N9/O6 usually participate in coordination [27, 29, 33]. Therefore, caffeine acts as a bidentate ligand and binds through N9 of the imidazole group and O6 of the pyrimidine group with copper atom using one molecule of H_2O and acetate ion to complete octahedral geometry. The infra-red spectra of caffeine exhibited a strong band at $1,687\text{ cm}^{-1}$ which is attributed to $\nu\text{C}=\text{N}$. This band shifted to lower wavenumbers in the two complexes by $25\text{--}33\text{ cm}^{-1}$, indicating that the ($\text{C}=\text{N}$) group is involved in complex formation [32]. The absorption band of carbonyl $\nu\text{C}=\text{O}$ at $1,720\text{ cm}^{-1}$ attributed to carbonyl oxygen in the ligand is shifted to $1,705\text{ cm}^{-1}$ in both complexes, suggesting the involvement of this group in coordination. The presence of acetate in the coordination sphere in the two complexes is confirmed by band $\nu\text{as}(\text{COO})$ band at $1,600\text{--}1,610\text{ cm}^{-1}$ compared to $1,578\text{ cm}^{-1}$ for CH_3COONa and $\nu\text{s}(\text{COO})$ at $1,345\text{--}1,350\text{ cm}^{-1}$ compared to $1,414\text{ cm}^{-1}$ for CH_3COONa . The difference in $\nu\text{as} - \nu\text{s}$ is around $\Delta\nu 255\text{--}260\text{ cm}^{-1}$, showing that $\Delta\nu$ values in this case were found to be greater than 200 indicating monodentate coordination of the acetate group in both **1a** and **1b** [35]. The N1, N3, and N7 belonging to the amide group in both pyrimidine and imidazole rings are blocked due to the methyl group attached to them and they cannot participate in the coordination with the metal [32]. The $[\text{M}-\text{N}]$ and $[\text{M}-\text{O}]$ bonds were indicated by the appearance of new bands $\nu[\text{M}-\text{N}]$ at 543 cm^{-1} and $\nu[\text{M}-\text{O}]$ at 422 and 426 cm^{-1} in both complexes [34, 38]. The vibrational band due to ($\nu\text{M}-\text{OH}_2$) at 746 cm^{-1} in both complexes confirms involvement of water molecules in the coordination sphere [37]. The vibrational band due to $\nu\text{M}-\text{OH}_2$ at 746 cm^{-1} in **1a** and **1b** did not significantly shift to

a lower or higher frequency after heating both complexes at 110 °C for 15 min. In other words, the water is not present as lattice molecules outside the coordination sphere but was coordinated with Cu(II) ion. Figure 2 and Table 3 show a comparison of the IR spectra of the free codeine ligand with mechanochemical product **2a** and the product **2b** obtained from the solution method. In the complexes resulting from the two methods, codeine acts as a bidentate ligand and binds through deprotonated phenolic OH and oxygen of the methoxy group. One molecule of water and a molecule of acetate ion are outside the coordination sphere. The band due to $\nu\text{O-H}$ of the ligand at $3,690\text{ cm}^{-1}$ is absent in the two products, indicating coordination through the deprotonated phenolic OH of the ligand. The band due to $\nu(\text{C-O})$ at $1,271\text{ cm}^{-1}$ due to the methoxy group which in the free ligand is also absent in both complexes, suggesting coordination via the methoxy group oxygen [30]. The band at the free codeine ligand ($1,066\text{ cm}^{-1}$) due to $\nu(\text{C-O-C})$ is positive with little shift to lower frequency values indicating non-involvement of this group in the bonding. In addition, in the far FT-IR spectra of both codeine complexes (Table 5, below), the non-ligand bands at $528\text{--}474\text{ cm}^{-1}$ can be assigned to the $[\text{M-O}]$ stretch of the attributed acetate group. The coordinated bond between the water molecule and the cation results in the appearance of vibrational band at 754 cm^{-1} $\nu(\text{M-OH}_2)$ in the codeine complexes. This result is an indicative of the coordination of oxygen of the water molecules to the metal ion as indicated by Bojidarka et al. [27]. The very broad band at $3,250\text{--}3,400\text{ cm}^{-1}$ observed in the codeine complexes has been assigned to $\nu(\text{O-H})$ and is characteristic of coordinated water molecules [23]. Hence, codeine complexes generally show 6-coordinate geometry with the ligand acting as bidentate.

Electronic spectra

The selected UV-Vis spectral data of caffeine, codeine, and complexes **1a**, **1b** and **2a**, **2b** are collected in Tables 4 and 5.

It can also be seen in Tables 4 and 5 that the UV-Vis spectra of both complexes synthesized via the two methods are identical.

The UV-Vis spectra of caffeine in solid state form presents one absorption band at 295 nm which is assigned to $n \rightarrow \pi^*$ transition, respectively, within the organic ligand. For the two complexes, the visible region produced a broad band at 676 and 670 nm which is attributed to ${}^2E_g \rightarrow {}^2T_{2g}$ suggesting an octahedral structure for the complexes **1a** and **1b**, (Table 4). In addition, the UV-Vis spectra of codeine in solid state form also present one absorption band at 286 nm which is assigned to $\pi \rightarrow \pi^*$

Table 4 Selected UV-Vis spectra data of caffeine and its complexes

Ligand/complex	Wavelength (nm)	Energy (cm^{-1})	Absorbance	Assignment
Caffeine	295	33,898	1.415	$n \rightarrow \pi^*$
$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ mechanochemical 1a	676	14,793	0.238	${}^2E_g \rightarrow {}^2T_{2g}$
$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ solvent-based 1b	670	14,925	0.379	${}^2E_g \rightarrow {}^2T_{2g}$

Table 5 Selected UV–Vis spectra data of codeine and its complexes

Ligand/complex	Wavelength (nm)	Energy (cm ⁻¹)	Absorbance	Assignment
Codeine	286	34,965	1.071	$\pi \rightarrow \pi^*$
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc mechanochemical 2a	682	14,663	0.376	$^2E_g \rightarrow ^2T_{2g}$
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc solvent-based 2b	679	15,898	0.338	$^2E_g \rightarrow ^2T_{2g}$

transition, respectively. Electronic transitions occurred in the moiety of the complexes at the wavelength of 682 and 679 nm in **2a** and **2b**, which are assigned to $^2E_g \rightarrow ^2T_{2g}$ transitions respectively, this also suggests an octahedral structure (**2a** and **2b**) as shown in Table 5.

X-ray diffraction studies

Figures 3 and 4 shows a comparison of the X-ray diffraction patterns of the product obtained via the mechanochemical method (solid state complex) and the starting materials (caffeine, codeine ligand, and **1a** and **2a**).

In Fig. 3, it can be seen that the X-ray powder diffraction patterns of the mechanochemical product (solid state complex) were different from the XRPD patterns of the starting materials (free caffeine ligand and Cu(II) salt). New peaks corresponding to the complex are observed. The XRPD of the complex showed peaks at $2\theta = 5^\circ, 12^\circ, 14^\circ$, and 25° indicating formation of a new phase.

In Fig. 4, the X-ray powder diffraction patterns of the mechanochemical product (solid state complex) were different from the XRPD patterns of the free codeine and Cu(II) ion. This is evidence of the formation of a new product.

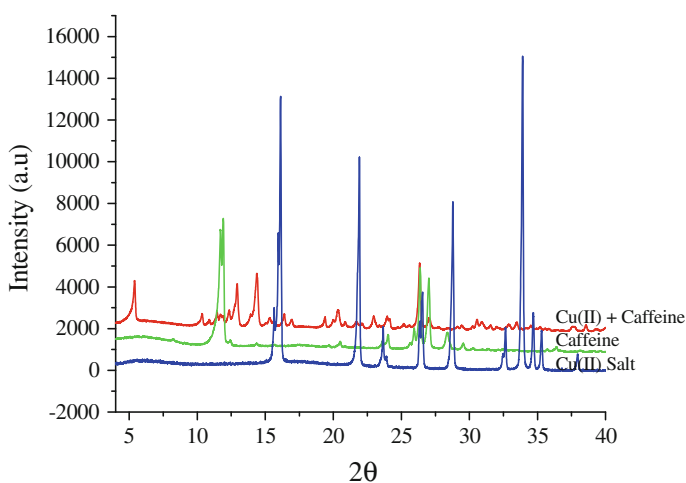


Fig. 3 Powder X-ray diffraction patterns of **1a** and the starting materials

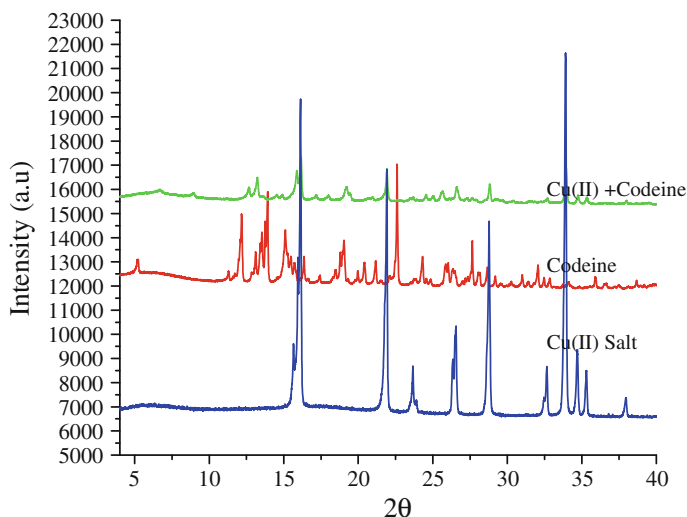


Fig. 4 Powder X-ray diffraction patterns of **2a** and the starting materials

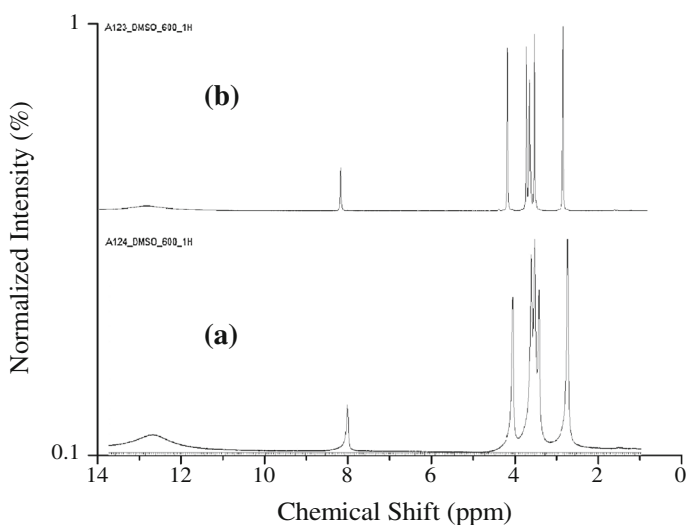


Fig. 5 Comparison of ^1H NMR spectral (DMSO- d_6) for (a). Solution state synthesized $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ **1b** (b). Mechanochemically synthesized $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ **1a**

^1H NMR spectra

Figure 5 shows a comparison of the ^1H NMR spectrum of the mechanochemical product **1a** and the product obtained by solution method **1b**, while Fig. 6 shows the ^1H NMR spectrum of codeine and its mechanochemical product **2b**.

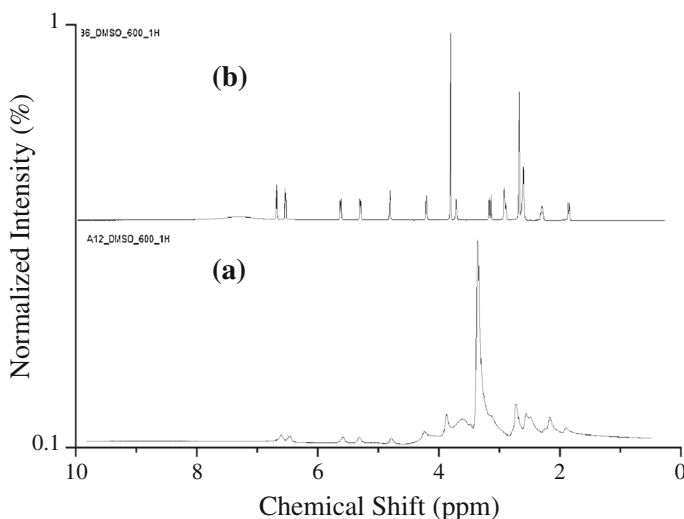


Fig. 6 Comparison of ^1H NMR spectral (DMSO- d_6) for (a). Solution state synthesized $[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ **2b** (b) codeine

From Figs. 5 and 6, it can be seen that ^1H NMR spectral of both complexes **1a** and **1b** synthesized via the two methods are similar. The ^1H NMR spectral of complex **2b** is different from that of the codeine ligand.

All the chemical shifts and the assignment of the individual ^1H resonance of caffeine, and complexes **1a** and **1b** in acetone are listed in Table 6.

From Table 6, the ^1H NMR spectrum of the caffeine in acetone showed four prominent proton signals at $\delta(\text{N1-CH}_3)$ 3.31, $\delta(\text{N3-CH}_3)$ 3.56, $\delta(\text{N7-CH}_3)$ 3.90 and $\delta(\text{C8-H})$ 8.04 ppm, respectively. The assignment of caffeine is shown below.

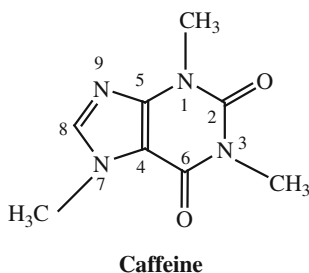


Table 6 Selected ^1H NMR spectral data (δ , ppm) of caffeine and its complexes **1a** and **1b**

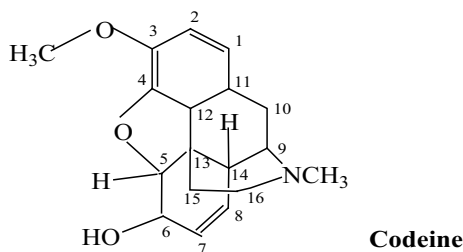
Ligand/complex	N1-CH ₃	N3-CH ₃	N7-CH ₃	C8-H	OH
Caffeine	3.31	3.56	3.90	8.04	—
$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ mechanochemical 1a	3.29	3.67	3.92	8.20	12.9
$[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ solvent-based 1b	3.28	3.69	3.93	8.15	12.9

In the complexes of **1a** and **1b**, the signals of N1–CH₃, N7–CH₃ are not significantly shifted, the sites are blocked by methyl groups, which prevents interaction of the metal atoms. However, N3–CH₃ which is also blocked by CH₃ shifted slightly to 3.67 ppm in **1a** and 3.69 ppm in **1b**. This lower field shift is as a result of its closeness to the binding site of C6=O. A similar mode of coordination has been reported in the literature [31]. The signal due to C8–H was shifted to 8.20 ppm in **1a** and 8.15 ppm in **1b**; the downfield shift indicates the coordination of caffeine with metal ion through the N(9) atom [39]. The new broad signal at 12.00 ppm due to the proton of OH appearing in the complex indicates probable coordination of H₂O to the metal ion [17]. Thus, ¹H NMR study reinforces the conclusions drawn from the IR spectra.

It can be inferred from the spectroscopic studies that caffeine is coordinated with the Cu(II) ion through the nitrogen of the imidazole group, N9 and oxygen of the pyrimidine group, C6=O with the ligand acting as bidentate.

The ¹H NMR data (chemical shifts and the assignment) of the individual ¹H resonance of Codeine and the solvent-based complex **2b** in DMSO-*d*₆ are listed in Table 7.

The assignments of ¹H NMR spectra of codeine (Table 7) were performed with reference to a previous study [3]. The ¹H NMR spectrum of codeine showed proton signals at 6.78, 6.95, 5.78, 5.40, 4.40, 3.87, and 3.00 ppm corresponding to 1H, 2H, 7H, 8H, 9H, OCH₃, and NCH₃, respectively.



The proton signals in the 6–7 ppm range are typical of the hydrogen attached to the aromatic ring. Comparison of ¹H NMR data for **2b** with those for codeine shows that there is a little or no change in the chemical shift of each of these protons (aromatic 1H, 2H), 7H, 8H, and 9H which is due to the non-involvement of this group in coordination. However, the signal due to the CH₃O (methoxyl group) was shifted from 3.87 to 3.10 ppm, and the upfield shift was attributed to coordination of copper with codeine through the oxygen of the methoxyl group. The observed chemical shift for the compound is in good agreement with values reported earlier [30]. All these observations put together lead us to propose the structures shown in Figs. 8 and 9.

Table 7 Selected ¹H NMR spectral data (δ, ppm) of codeine and complex **2b**

Ligand/complex	1H	2H	7H	8H	9H	OCH ₃	NCH ₃
Codeine	6.78	6.95	5.78	5.40	4.40	3.87	3.00
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc solvent-based 2b	6.80	6.98	5.86	5.50	4.40	3.10	2.95

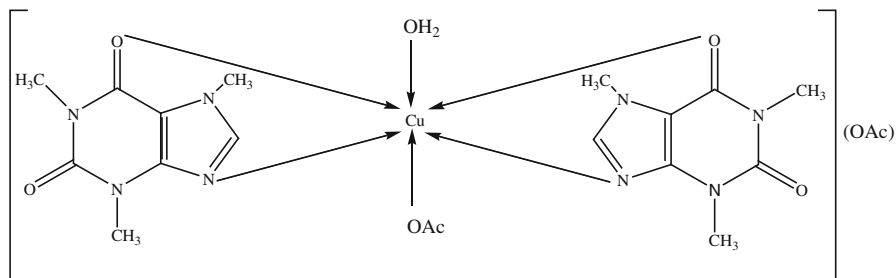


Fig. 8 Proposed structure of synthesized $[\text{Cu}(\text{CAF})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complex obtained via solvent-free and solvent-based

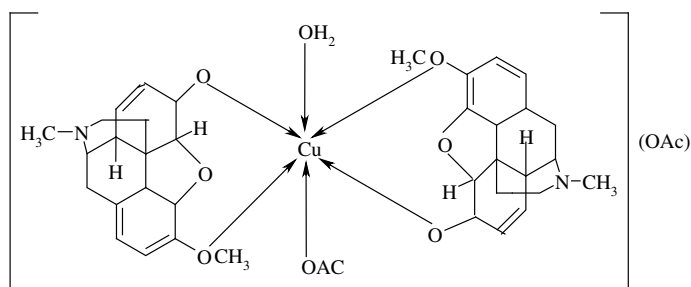


Fig. 9 Proposed structure of $[\text{Cu}(\text{COD})_2(\text{H}_2\text{O})(\text{OAc})]\text{OAc}$ complexes **2a** and **2b** obtained via mechanochemical and solvent-based methods

Table 8 Antibacterial activity of codeine, caffeine and their complexes

	<i>E. coli</i>		<i>S. aureus</i>		<i>K. pneumonia</i>	
	Zone of inhibition (mm)					
Complex/ligand (μg/ml)	50	25	50	25	50	25
Caffeine	13	11	16	10	15	10
Codeine	12	9	14	12	14	12
[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc mechanochemical 1a	21	14	20	14	18	13
[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc solvent-based 1b	20	15	18	13	20	14
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc mechanochemical 2a	22	15	17	14	21	12
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc solvent-based 2b	24	14	20	16	22	15

Antibacterial and antifungal activities study

The antibacterial and antifungal activities of the free ligands and the complexes were tested *in vitro* against the bacteria *E. coli*, *S. aureus* and *K. pneumonia* and the fungi *Candida albican* and *A. niger* by the diffusion method. The results are summarized in Tables 8 and 9.

Table 9 Antifungi Activities of Caffeine, Codeine and their Complexes

Complex/ligand (μg/ml)	<i>Aspergillus niger</i>		<i>Candida albican</i>	
	Zone of inhibition (mm)			
Complex/ligand (μg/ml)	50	25	50	25
Caffeine	9	7	7	5
Codeine	8	8	6	5
[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc mechanochemical 1a	13	11	13	10
[Cu(CAF) ₂ (H ₂ O)(OAc)]OAc solvent-based 1b	12	10	18	13
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc mechanochemical 2a	15	13	17	13
[Cu(COD) ₂ (H ₂ O)(OAc)]OAc solvent-based 2b	16	12	15	14

The results show that the zones of inhibition of the products from both methods are higher than those of the ligands and that the results are in good agreement with previous findings [40]. This indicates that metal complexes of both mechanochemical and solution-based methods are more active than the free ligands.

Such enhanced activity of metal chelates is due to the lipophilic nature of metal ions in complexes. The chelation increases the lipophilic nature of the central atom which subsequently favors its permeation through the lipid layer of the cell membrane. The chelation theory accounts for the increased activities of the metal complexes [15]. It can be observed from the results that the activity of the compounds increases with concentration, which is due to the effect of metal ions on the normal processes. Tables 8 and 9 shows that both complexes possess higher antifungi activity than their parent ligands.

Conclusions

It can be seen from the study that solvent-free synthesis is quick, and gives a quantitatively high yield without the need for solvent. Caffeine coordinated with the copper ion through nitrogen of the imidazole group and oxygen of the pyrimidine group of the ligand, and codeine coordinated with the copper ion through the deprotonated phenolic OH group and carbonyl (methoxy group) of the ligand, with the ligand acting as bidendate. The presence of the water molecule and acetate inside the coordination sphere completed an octahedral geometry. One molecule of acetate is outside the coordination sphere. Both antibacterial and antifungi activity study of the metal–drug complexes showed that they possessed higher inhibitory activity against strains of pathogenic organisms than their parent ligands at concentrations of 50 and 25 μg/ml.

In conclusion, solvent-free synthetic routes present higher efficiency in terms of energy and time compared to classical solution phase synthesis. The mechanochemical technique appears to open a pathway to new processes where chemical transformations are performed in an environmental benign manner.

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