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THEME

Synthesis and Characterization of Metal Complexes Derived from Codeine

Publicly defended before a jury composed of:

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إهداء

ها أنا أُكمل مرحلةً أخرى من حياتي، وأقف لوهلةٍ أتذكّر فيها كلّ الأشخاص الذين شاركوني اللحظات الجميلة، وخاصة في الأوقات الصعبة.
أولئك الأشخاص الذين أحبّونا بدون شروط، ومدّوا لنا يد العون حتى دون أن نطلب، وفي حياة مليئة بالفوضى والعشوائية، ظلّوا هم الثابتين.

ورغم أنني لست حزينًا على انتهاء هذه المرحلة، إلا أنني أخشى المجهول الذي تخبئه لنا الحياة، لكنّي على يقينٍ تام بأن نفس الأشخاص الذين وقفوا إلى جانبي لن يترددوا في تقديم المساعدة إذا احتجتُ إليها.

أُهدي هذا العمل إلى والديَّ العزيزين، تقديرًا لدعمهما المتواصل طوال مسيرتي الدراسية،
وإلى أختي،
وإلى أفراد عائلتي، وأصدقائي، وزملائي، الذين كان لدعمهم وتشجيعهم المعنوي ونصائحهم بالغ الأثر.

كما أوجّه شكري العميق إلى الأساتذة الذين لم يترددوا في تقديم يد العون، فإكمال هذه المرحلة الأكاديمية هو أيضًا تجسيدٌ لإرادتهم.

وفي الختام،شكر لكم جميعا

Summary

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Abbreviation	Definition
Cod.	Codeine
Cod.P	Codeine Phosphate
$FeCl_3$	Ferric Chloride
$(NH_4)_2Fe(SO_4)_2\cdot 6H_2O$	Ferrous Ammonium Sulfate
$Fe_2(SO_4)_3$	Ferric Sulfate
$CuCl_2\cdot H_2O$	Copper(II) Chloride Monohydrate
$MgCl_2$	Magnesium Chloride
$NiSO_4$	Nickel(II) Sulfate
Na_2CO_3	Sodium Carbonate
H_3PO_4	Phosphoric Acid
DMSO	Dimethyl Sulfoxide
EtOH	Ethanol
MeOH	Methanol
T	Temperature
FTIR	Fourier Transform Infrared Spectroscopy
UV–Vis	Ultraviolet–Visible Spectroscopy
DFT	Density Functional Theory
NEB	Nudged Elastic Band Method
LMCT	Ligand-to-Metal Charge Transfer

Fe–O bond	Iron–Oxygen Coordination Bond
λmax	Maximum Absorption Wavelength
nm	Nanometer
eV	Electronvolt
Ha	Hartree (unit of energy in quantum chemistry)
g	Gram
M	Molar Concentration (mol/L)
pH	Acidity/Basicity Scale (Power of Hydrogen)
Method 01	Protocol for synthesis based on the use of codeine or Cod.P in organic solvents
Method 02	Protocol for synthesis based on the use of codeine or Cod.P in the aqueous phase and the use of heating and pH adjustment.
Cod-M	Complex formed between pure codeine (Cod.) and a metal ion (M)
Cod.P-M	Complex formed between codeine phosphate (Cod.P) and a metal ion (M)
-M	Metal ion

Abstract

Codeine has many medical uses, such as pain relief and cough medicine. This study focused on the synthesis of complexes between codeine and metals. The published structure of the codeine-Fe(III) complex by (Ghamami et al). was used as the starting point for this study. First, the compound itself was modeled using DFT and NEB methods to evaluate its stability and energy interaction properties. Then, the Fe(III)-codeine compound was synthesized Practical, and different organic solvents were tested in the complex formation to evaluate the effect of the medium on the result. The resulting precipitates were then analyzed using UV-visible and FTIR spectroscopy.

An attempt was made to synthesize complexes between pure codeine and codeine phosphate with different metal ions such as Fe^{2+}, Cu^{2+}.Two methods were used to synthesize the complexes: the first in an organic medium (method 1) and the second in an aqueous medium with heating (method 2). The resulting precipitates were evaluated in terms of color and yield. The products were analyzed using FTIR and showed signs of possible codeine-metal coordination in several cases, although the nature of the resulting precipitates remained inconclusive in some cases.

Overall, this study demonstrates the possibility of forming codeine-metal complexes, and may serve as a starting point for pharmacological research based on the synthesis of new stable complexes.

Keywords: codeine, codeine phosphate, metal complexes, coordination chemistry.

Résumé

La codéine a de nombreuses utilisations médicales, telles que le soulagement de la douleur et le traitement de la toux. Cette étude s'est concentrée sur la synthèse de complexes entre la codéine et des métaux. La structure publiée du complexe codéine-Fe(III) par (Ghamami et al). a été utilisée comme point de départ pour cette étude. Tout d'abord, le composé lui-même a été modélisé à l'aide des méthodes DFT et NEB afin d'évaluer sa stabilité et ses propriétés d'interaction énergétique. Ensuite, le composé Fe(III)-codéine a été synthétisé expérimentalement, et différents solvants organiques ont été testés dans la formation du complexe afin d'évaluer l'effet du milieu sur le résultat. Les précipités obtenus ont ensuite été analysés par spectroscopie UV-visible et FTIR.

Nous avons ensuite tenté de synthétiser des complexes entre la codéine pure et le phosphate de codéine avec différents ions métalliques tels que Fe^{2+} et Cu^{2+}. Deux méthodes ont été utilisées pour synthétiser les complexes : la première dans un milieu organique (méthode 1) et la seconde dans un milieu aqueux avec chauffage (méthode 2). Les précipités obtenus ont été évalués en termes de couleur et de rendement. Les produits ont été analysés par FTIR et ont montré des signes d'une possible coordination codéine-métal dans plusieurs cas, bien que la nature des précipités obtenus soit restée incertaine dans certains cas.

Dans l'ensemble, cette étude démontre la possibilité de former des complexes codéine-métal et pourrait servir de point de départ à des recherches pharmacologiques basées sur la synthèse de nouveaux complexes stables.

Mots-clés : codéine, phosphate de codéine, complexes métalliques, chimie de coordination.

ملخص

الكودايين له العديد من الاستخدامات الطبية، مثل تسكين الألم وعلاج السعال. ركزت هذه الدراسة على توليف مركبات بين الكودايين والمعادن. استخدمت البنية المنشورة لمركب الكودين–الحديد الثلاثي بواسطة (غامامي و زملاءه) كنقطة انطلاق لهذه الدراسة. أولاً، تم نمذجة المركب نفسه باستخدام طريقتي نظرية الكثافة الوظيفية **DFT** و وطريقة النطاق المطاطي المدفوع **NEB** لتقييم استقراره وخصائص تفاعل الطاقة. ثم تم تصنيع مركب الكودين–الحديد الثلاثي تجريبياً، واختبار مذيبات عضوية مختلفة في تكوين المركب لتقييم تأثير الوسط على النتيجة. ثم تم تحليل الرواسب الناتجة باستخدام التحليل الطيفي بالأشعة فوق البنفسجية وطيف الأشعة التحت الحمراء.

ثم حاولنا تصنيع مركبات بين الكودين النقي وفوسفات الكوديين مع أيونات معدنية مختلفة مثل Fe^{2+} الحديد والنحاس Cu^{2+} تم استخدام طريقتين لتصنيع المركبات: الأولى في وسط عضوي (الطريقة 1) والثانية في وسط مائي مع تسخين (الطريقة 2). تم تقييم الرواسب الناتجة من حيث اللون والإنتاجية. تم تحليل المنتجات باستخدام وطيف الأشعة التحت الحمراء وأظهرت علامات على احتمال وجود تنسيق بين الكوديين والمعادن في عدة حالات، على الرغم من أن طبيعة الرواسب الناتجة ظلت غير حاسمة في بعض الحالات.

بشكل عام، تثبت هذه الدراسة إمكانية تكوين مركبات الكوديين والمعادن، وقد تكون نقطة انطلاق للبحوث الدوائية القائمة على تكوين مركبات جديدة مستقرة.

الكلمات المفتاحية: الكوديين، فوسفات الكوديين، مركبات معدنية، كيمياء التنسيق.

I. Introduction

Codeine is a drug that has many medical uses, such as pain relief and cough suppression, there has been growing interest in the scientific field in studying its ability to form coordination complexes within an important branch of chemistry known as “coordination chemistry.” This field is defined as the study of chemical compounds that arise from the binding of metal ions to molecules or ions called “ligands” through bonds known as coordination bonds [1]. Coordination compounds have specific spatial structures, such as octahedral, tetrahedral, or square planar shapes, and in addition, they have distinctive electronic properties that give them stability [2].Between a central metal atom and ligands, bonds called coordination covalent bonds are formed, where the ligand donates a shared pair of electrons to the central metal atom, which usually has empty orbitals, leading to the formation of a stable compound [3].In these compounds, d-d electron transitions or charge transfer (CT) can occur [4]. These electronic transitions can appear as specific absorption bands in ultraviolet and visible spectra. and any change in the geometry of the complex or the strength of the bond may lead to changes in the wavelength and intensity of absorption [4-5]. In this context, codeine is considered a molecule capable of acting as a ligand, opening the door to the possibility of synthesizing new metal complexes.

Previous studies have investigated the ability of codeine to form compounds with transition metals by (Zayed et al). [6] and [7] using combined physical-chemical analytical methods. They concluded that the compounds formed are highly stable.

A study on the formation of a complex between codeine and iron was also reported, and the complex was characterized by analytical methods by (GHAMAMI et al) [8].

(as shown in Figure 1). The results of their study indicate that the resulting complex has the ability to inhibit the growth of MCF-7 (breast cancer) and AGS (stomach cancer).

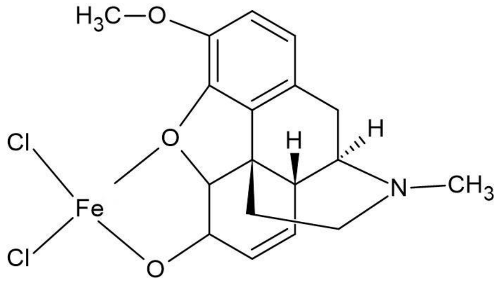

Figure 1 Molecular Structure of the Codeine-Fe(III) Complex

Codeine is an opioid known for its effectiveness in relieving pain and suppressing coughs. It is derived from the poppy plant and is specifically manufactured through the methylation of morphine. Although it is sometimes used in prescription medications, it is also found in a number of over-the-counter (OTC) medications [9]. The effectiveness of codeine lies in its conversion to morphine, which is the active ingredient through a metabolic process that occurs within the body [10]. Codeine can be considered one of the best pharmacological options for the treatment of mild to moderate pain, as studies have demonstrated its efficacy in cases such as post-operative pain and chronic pain [11] .It is also a reliable option for treating cough, especially when traditional treatments fail to control it [12] . As a "mild opiate," codeine offers a safer alternative in pain management strategies, especially in patients who are likely to be severely affected by the side effects of strong opioids [13].

Pharmaceutically, codeine can be found in two basic forms: pure codeine and codeine phosphate, both of which are the same active ingredient but with a slight difference in chemical composition. Pure codeine, known by its scientific name **3-methoxy-17-methylmorphinan**, has the molecular formula ($C_{18}H_{21}NO_3$) and is characterized by a four-ring structure that is a distinctive feature of the opium family, with a methoxy group at position 3 and a hydroxyl group at position 6 [14] As for codeine phosphate, its chemical formula is ($C_{18}H_{24}NO_7P$) [15], we note that a phosphate group (PO_4) has been introduced, which enhances the compound's solubility in water, facilitating its absorption into the body and increasing its pharmacological efficacy [16] . In summary, pure codeine retains its classic structure as a morphinan derivative (**as shown in Figure 2**), but is characterized by poor water solubility, which may limit its bioavailability.

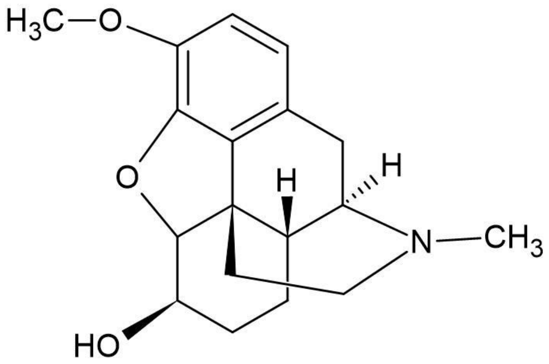

Figure 2 Molecular Structure of Pure Codeine

Codeine phosphate, on the other hand, thanks to its phosphate-enhanced structure (**as shown in Figure 3**), is more compatible with modern pharmaceutical uses, combining efficacy and rapid absorption—making it a smart choice in contemporary pharmaceutical practice.

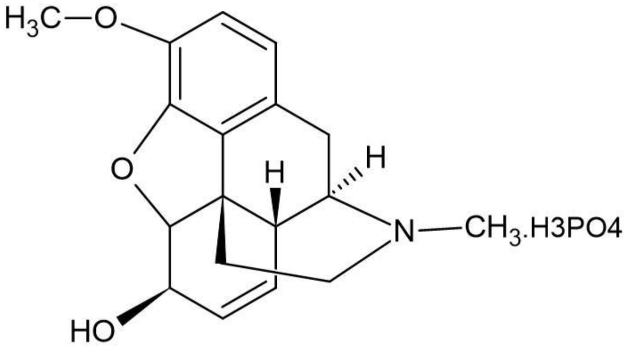

Figure 3 Molecular structure of codeine phosphate

The aim of our study was to synthesize quaternary complexes with different transition metals and study them using analytical techniques such as UV-visible and FTIR. The synthesis of the complexes involved the use of pure codeine and codeine phosphate to study the differences between them and the effect of phosphate ions on the coordination between codeine and the metal. During the study, synthesis was carried out using two different methods, the first in organic solutions and the second in aqueous solutions, to study the effect of the medium on the final results of the complexes and precipitates.

The study is divided into four main parts. The first section deals with a theoretical study of the stability of the codeine and iron complex, where the molecular structure of the complex described by GHAMAMI and his colleagues is considered the starting point for this study, relying on the density functional theory (DFT) to evaluate the stability of the complex. DFT enables us to calculate the total energy, electron density, and molecular geometry accurately and efficiently by expressing the energy of the system as a function of electron density instead of relying on complex wave functions such as the Schrödinger equation [17]. In this part of the study, geometry optimization of the complex was performed using Material Studio software, which allowed access to the most energetically stable structural configuration. In addition to evaluating the structure and energy, the theoretical analysis was extended using the driven rubber band theory (NEB), a technique used to plot the minimum energy path (MEP) between two steady states, such as reactants and products. This theory relies on creating a series of intermediate “images” of the compound along the reaction pathway, which are then progressively optimized to determine the transition state and energy barrier (Ea) of the reaction [18]. This has enabled analysis of the dynamic path that a complex may take during its reaction, helping to understand the possible reaction mechanisms. In addition, the reaction energy (Er) has been calculated to determine whether the reaction is exothermic or endothermic. After a theoretical study of the complex of codeine and iron (III), in the second section of the study, a codeine-iron complex was synthesized using different organic solvents during the reaction to evaluate the effect of the medium on the results of the complex. The precipitates and complexes were then analyzed using analytical techniques, including UV-Visible, where the complex was dissolved in DMSO, and the compounds were and the compounds were analyzed using FTIR. After the results obtained in the second section, the study was expanded in the third section to include the possibility of complex formation or coordination between codeine and different transition metals. The working conditions and reactions were the same as in the second section. In the fourth section of this study, codeine were synthesized in their pure form and codeine phosphate with different transition metals, where in this part, reactions are carried out in aqueous solutions instead of solvents. for studies and characterization of the differences between the compounds and to study the effect of codeine in its pure form or with phosphate on the results of complex coordination.

II. MATERIALS AND METHODS

2.1.Materials

All chemicals, reagents, and solvents used in this study were of analytical grade. Pure codeine was used as the starting material in the reactions and for the preparation of codeine phosphate (Cod.P). The metal salts used in the preparation of the complexes included the following: ferric chloride ($FeCl_3$), ferrous ammonium sulfate ($(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$), copper (II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$), nitrate hexahydrate nickel (II) chloride, magnesium chloride, cobalt chloride, The solvents used in these experiments included distilled water, acetone, acetonitrile, ethanol, 2-propanol, and DMSO, and Na_2CO_3 was prepared at a concentration of 10-2 molar. In the synthesis of codeine phosphate, phosphoric acid (H_3PO_4, 85%) was subsequently used. All glassware and reaction vessels were cleaned and thoroughly dried before each use

2.2. Study of complex stability using computational methods

Using the molecular structure of the compound codeine- Fe(III) as shown in **Figure 1** **(in part of the introduction)**, the complex was modeled using BIOVIA Materials Studio 2023 software, where the reaction between pure codeine ($C_{18}H_{21}NO_3$) and ferric chloride ($FeCl_3$) was simulated using the Nudged Elastic Band (NEB) method in 15 steps, allowing us to determine the transition states and reaction path. The reaction products were the complex $[Fe(C_{18}H_{21}NO_3)]Cl_2$ and the by-product HCl.

The structural and energetic properties of the complex were studied using density functional theory (DFT) with geometry optimization.

2.3. Preparation of the Codeine–Fe(III) Complex in Different Solvents (Method 1)

The codeine-Fe(III) complex was prepared with several different organic solvents (ethanol, acetonitrile, acetone, and 2-propanol) to verify the effect of the solvent medium on complex formation and reaction yield. Initially, tests were conducted to verify the solubility of both codeine and $FeCl_3$ and the possibility of precipitate formation with solvent change.

Then, a complexation reaction was performed, where 0.01 mol of pure codeine was mixed with 0.01 mol of $FeCl_3$ in 80 ml of organic solvent, and the reaction mixture was stirred for 4-5 hours at room temperature. The precipitate was then filtered using filter paper and dried overnight in an oven at 70 °C to obtain the final solid compound.

The solvents were changed to verify the effect of the reaction medium on the formation of the codeine-iron complex, and the results were compared based on visual observation and spectral analysis.

2.4. Preparation of Codeine Complexes with Different Metal Ions (Method 1)

We conducted a preliminary test to verify the possibility of precipitating and dissolving metal salts such as $NiSO_4$, $MgCl_2$, $CuCl_2$ in different organic solvents, including acetone, acetonitrile, and 2-propanol.

In the reaction, we mixed 0.01 mol of pure codeine with 0.01 mol of the selected metal salt in 70 ml of acetone solution with continuous stirring at room temperature for 4-5 hours. At the end of the reaction, the resulting precipitate is separated by filtration using filter paper, and then the precipitate is dried overnight in an oven at 70 °C to obtain the final compounds.

2.5. Preparation of Solid Complexes of Cod.P–M and Cod-M (M = Fe(II), Fe(III), Cu(II))

Synthesis of solid compounds of codeine phosphate (Cod.P) with selected metal ions — Fe(II), Fe(III), and Cu(II). In each reaction, 0.198 g of codeine phosphate was dissolved in 12 mL of distilled water, and the appropriate metal salt — either 0.196 g of ferro ammonium sulfate, 0.169 g of iron sulfate, or 0.170 g of copper (II) chloride — was dissolved in 15–17 ml of distilled water.

The metal solution was added to the binder solution, and the pH was adjusted using 0.1 molar Na_2CO_3 to values of 5.1, 5.0, and 6.5, respectively, depending on the metal ion. The reaction mixture was placed in a round-bottom flask, connected to a Vigreux column, and immersed in a hot water bath with continuous stirring and gentle reflux for 1–2 hours, depending on the rate of compound formation.

Instead of filtration, the resulting suspensions were centrifuged to separate the precipitated compounds from the supernatant. Each solid residue was then concentrated by redispersing it in a small volume of solvent and left to dry overnight at room temperature to obtain the final solid compounds.

Solid compounds were then synthesized from pure codeine with the same metal ions. In each reaction, 0.150 g of pure codeine was dissolved in 12 ml of distilled water, and the same laboratory procedures as above were followed.

2.6. Preparation of Codeine Phosphate from Pure Codeine

We prepared codeine phosphate (Cod.P) in the laboratory from pure codeine in order to carry out complexation reactions.

Working protocol To produce 0.01 mol of Cod.P, we need 0.01 mol of pure codeine, i.e. 2.99 g, and 0.67 ml of phosphoric acid (H_3PO_4, 85% concentration), as well as distilled water and ethanol.

Procedure In a 100 ml beaker, we dissolved 2.99 g (0.01 mol) of pure codeine in a small volume of warm distilled water with stirring. Then, 0.67 ml of 85% phosphoric acid (equivalent to 0.01 mol H_3PO_4) was added dropwise to this solution with continuous stirring.

The mixture was stirred at room temperature for 30-60 minutes until a homogeneous solution was formed and precipitation appeared.

The solution is then cooled in an ice bath to complete the precipitation of codeine phosphate.

The precipitate is separated by filtration, washed with only 2-5 ml of cold ethanol, and left to dry overnight at room temperature.

The final product is then stored and used in subsequent complexation reactions.

2.7 Characterization Techniques

2.7.1 Ultraviolet and visible spectroscopy: Electronic absorption spectra were recorded using a UV-Vis spectrophotometer in the range of 200-800 nm in DMSO solution to confirm the composition of the compounds. A UVline9400 spectrophotometer provided by Secomam was used.

2.7.2 Fourier transform infrared spectroscopy (FTIR): FTIR spectra were recorded in the range of 4000-400 cm^{-1} using the KBr pellet method to determine changes in the vibrations of functional groups indicating coordination. An FT/IR-4200 provided by Jasco was used.

III. Results and Discussion

3.1 Computational Study of Fe(+3)–Codeine Complex

To facilitate our understanding of the reaction mechanism and stability of the Fe–codeine complex, a quantitative chemical simulation was performed using the Nudged Elastic Band (NEB) method on 15 intermediate steps. The aim was to determine the reaction path and transition state, as well as the activation energy. The energy profile resulting from the NEB calculations is shown in **Figure 4** (which represents the evolution of energy along the reaction path).

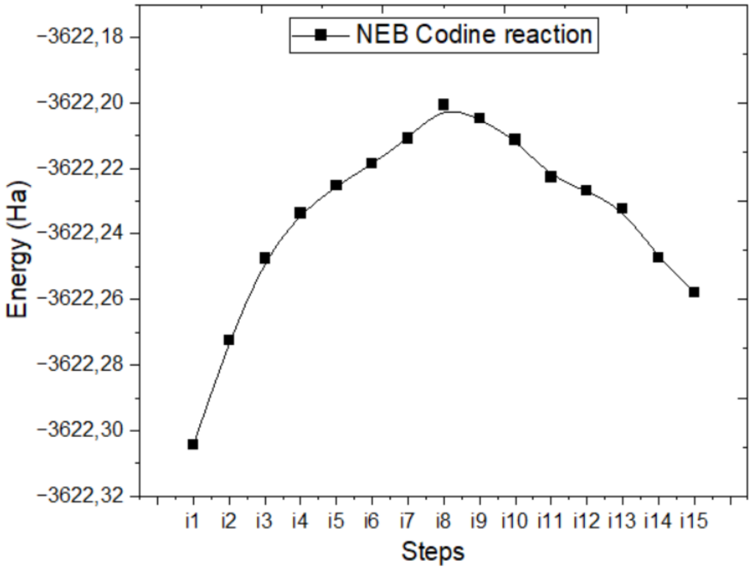

Figure 4 Reaction Energy Path of Fe(+3)–Codeine Complex

The energy curve obtained reveals that the reaction is endothermic, with a total change in reaction energy of **ΔE_s = (+1.26 eV or 0.04646 Ha),** indicating that the overall transition from the initial state to the final state requires energy absorption.

$$\mathbf{\Delta E_s = E}\boldsymbol{f}_{\mathbf{product}}\mathbf{ - E}\boldsymbol{f}_{\mathbf{reactant}}\mathbf{ = - 3622.25782 - (- 3622.30428)}$$

$$\mathbf{\Delta E_s = 0.04646\ Ha = + 1.26\ eV}$$

- **E*f*product :** Total energy of the product (**E*f*** (i15) = -3622.25782 Ha).
- **E*f*reactant :** Total energy of the reactant (**E*f*** (i1) = -3622.30428 Ha).

The profile also shows us a high activation barrier (E*a*) of approximately **(2.82 eV or 0.10364 Ha),** indicating the presence of a high-energy transition state and the need for significant activation energy to initiate the reaction process.

$$\mathbf{E}\boldsymbol{a}\mathbf{ = E}\boldsymbol{f}_{\boldsymbol{transition\ state}}\mathbf{ - E}\boldsymbol{f}_{\mathbf{reactant}}\mathbf{ = - 3622.20064 - (- 3622.30428)}$$

$$\mathbf{E}\boldsymbol{a}\mathbf{ = 0.10364\ Ha = + 2.82\ eV}$$

- **E*a* :** Total energy of the highest point in the path - **E*f*** (i8) = -3622.20064 Ha.

We also performed density functional theory (DFT) calculations to evaluate the energetic stability of the final Fe–codeine complex. The optimized geometry of the complex shows a total energy of **–3161.789182 Hartree (Ha)** and a binding energy of **–8.5953721 Ha ‹Figure 5** shows that the geometric shape of the compound we obtained is the most stable in terms of energy, and this shape can be used later to calculate spectral or interactive properties. We can use the total energy of the compound to compare it with the energies of similar compounds or complexes to determine which is more stable, since the lower the total energy, the greater the stability.

Based on the interaction energy and activation energy, we conclude that the coordination reaction between the codeine and iron is an endothermic reaction. This result may explain how to select the Working protocol for future implementation of the reaction.

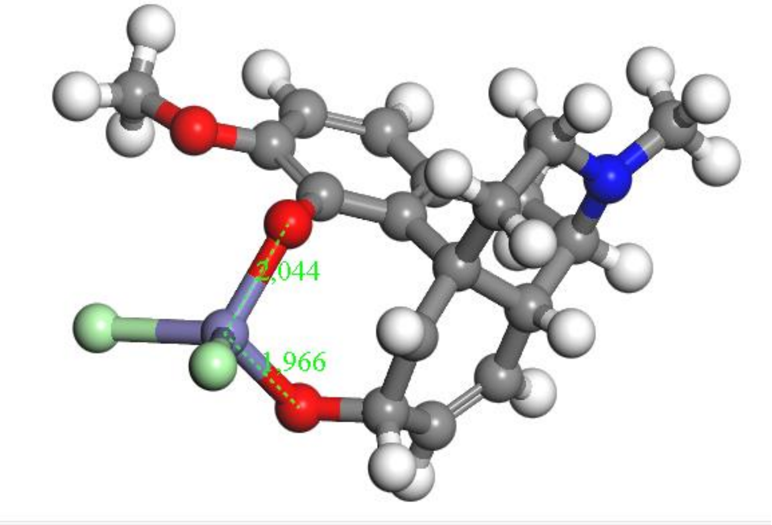

Figure 5 Optimized Geometry of Fe(+3)–Codeine Complex (DFT Calculation)

Atomes [Red = oxygen, purple = iron, green = chlorine, gray = carbon, white = hydrogen]

3.2 Solvent-Dependent Formation and Characterization of Fe–Codeine Complexes

The working results presented in this section correspond to the synthesis described under **Preparation of the Codeine–$FeCl_3$ Complex in Different Solvents (Method 1)** in the Materials and Methods section. In all cases, the reactions were carried out by mixing **0.01 mol of pure codeine** with **0.01 mol of $FeCl_3$** in different organic solvents to evaluate the impact of the solvent on complex formation, yield, and structural properties.

3.2.1 Preliminary Solubility and Precipitation Tests

We performed a quick test of the solubility of codeine and $FeCl_3$ compounds in various solvents, including ethanol, acetone, acetonitrile, and 2-propanol. All three compounds dissolved in the four solvents; however, brown precipitates were observed only in acetone, acetonitrile, and 2-propanol, while no precipitates formed in ethanol.

Table 1 Solubility of reactants and observation of precipitate formation in different solvents

Solvent	Solubility of Reactants	Precipitate Formation
Acetonitrile	Soluble	Brown precipitate
Acetone	Soluble	Brown precipitate
Ethanol	Soluble	No precipitate
2-Propanol	Soluble	Brown precipitate

3.2.2 Yield and Physical Characteristics of the Complexes

After the complexation reaction and drying process, we measured the dry masses of the solids obtained from the reactions. The results showed us a clear variation in yield depending on the solvent:

Table 2 Mass of dried Fe–codeine complexes obtained from different solvents

Solvent	Mass of Dried Complex (g)	Observed Color
Acetonitrile	0.366	Dark brown
Acetone	0.795	Dark brown
2-Propanol	1.552	Dark brown

We noticed that all precipitates were dark brown in color, but the 2-propanol solution yielded the highest mass, indicating that it promotes more efficient or stable precipitation of the complex.

3.2.3 UV-Visible spectra of codeine, $FeCl_3$, and Fe–codeine complex:

recorded the UV-visible spectra of pure codeine, $FeCl_3$, and the resulting Fe–codeine complex in DMSO in order to study the electronic transitions and confirm the formation of the complex.

The codeine spectrum showed a clear absorption band at λmax = 285 nm and λmax =260 nm, which is attributed to π → π* electronic transitions. and n → π*. In contrast, $FeCl_3$ showed a peak at λmax = 263 nm.

Upon integration, the Fe–codeine compound showed two main absorption bands at 265 nm and 285 nm, corresponding to π → π* and n → π* transitions, respectively. We also observed the appearance of a broad shoulder in the 310–425 nm range, which, despite its low intensity, is a characteristic feature of LMCT transitions involving Fe^{3+} and the codeine ligand.

The disappearance of the $FeCl_3$ peak at 265 nm, together with the appearance of new bands in the complex spectrum, provides clear evidence for the formation of an Fe–codeine coordination compound, which is consistent with the UV spectrum analysis in the work of (GHAMAMI et al) [8].

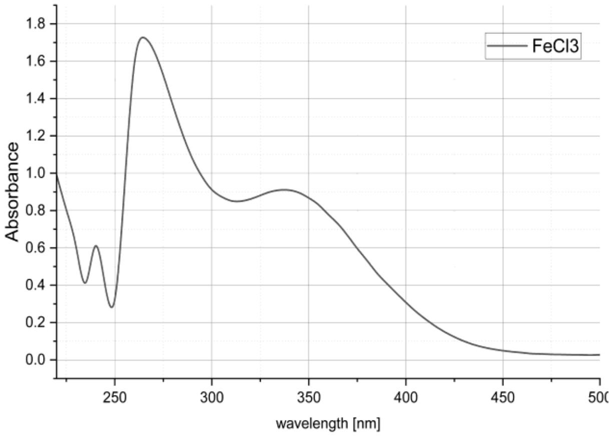

Figure 6 UV-Visible spectrum of $FeCl_3$ in DMSO

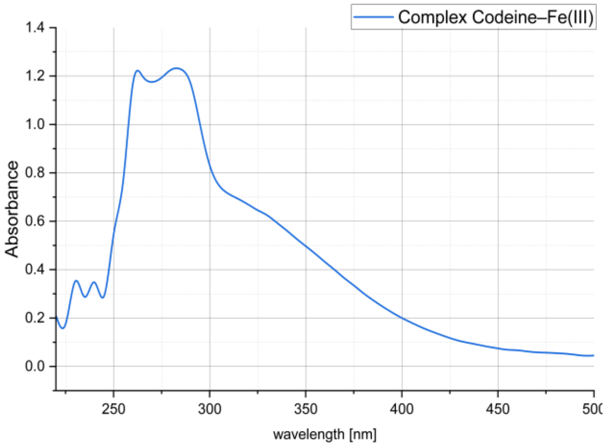

Figure 7 UV-Visible spectrum of the Fe–codeine complex in DMSO

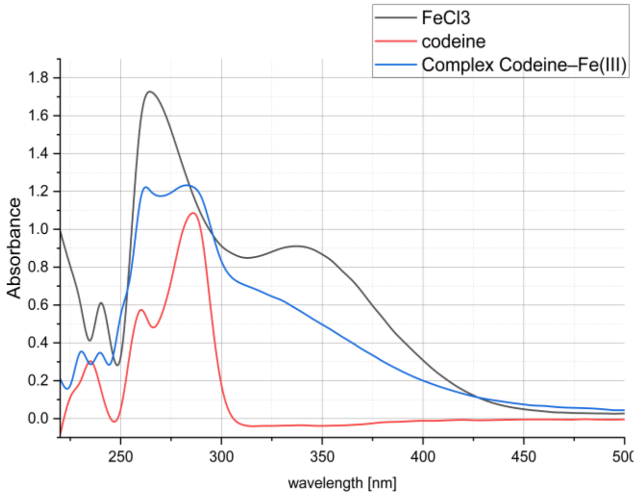

Figure 9 Comparative UV-Visible spectra of codeine, FeCl₃, and the Fe–codeine complex

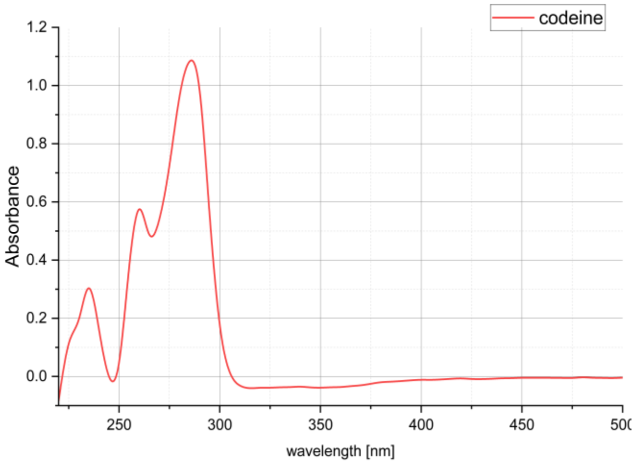

Figure 8 UV-Visible spectrum of pure codeine in DMSO

3.2.4 FTIR Analysis and Spectral Comparison of Fe–Codeine Complexes Synthesized in Different Solvents

3.2.4.1 Comparison Between Complexes Prepared in Different Solvents

FTIR spectra of Fe–codeine compounds prepared in acetonitrile, acetone, and 2-propanol showed a high degree of similarity in terms of characteristic absorption bands, indicating that the overall coordination pattern remained constant across different organic solvents.

Despite the similarity in peak locations, we observed slight changes in the intensity of the bands. These differences can be attributed to the effect of the solvent on molecular packing, degree of crystallization, or hydrogen bonding interactions during complex formation.

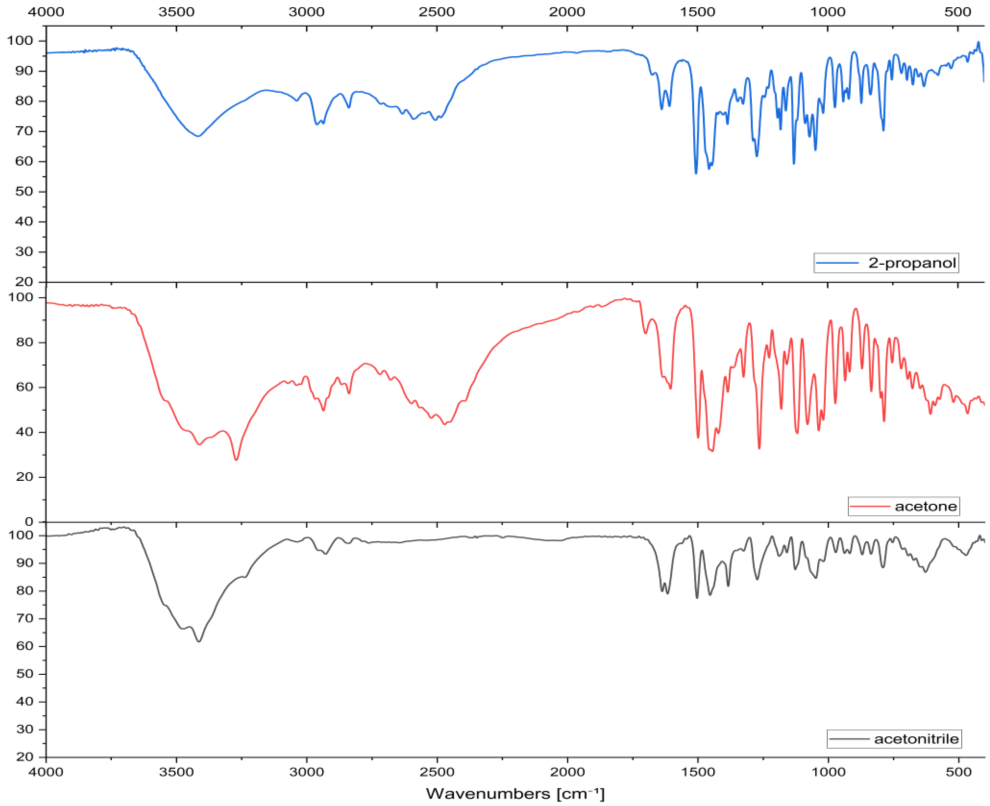

Figure 10 FTIR spectra of Fe–codeine complexes prepared in acetonitrile, acetone, and 2-propanol

3.2.4.2 Comparison Between Free Codeine and Fe–Codeine Complexes

To confirm the coordination between Fe^{3+} and codeine, a comparative FT-IR analysis was performed between pure codeine and the Fe–codeine complex synthesized in acetonitrile. The main observed functional groups and their associated absorption bands are summarized in the following tables.

A comparison of the FT-IR spectra of pure codeine and the codeine-Fe(III) complex synthesized in acetonitrile solution reveals clear spectral modifications confirming the formation of a coordination complex

Table 3 FT-IR data for codeine

Wavenumber (cm^{-1})	Vibration Assignment
3532	O–H (free alcohol)
3469, 3415	O–H (intermolecular hydrogen bond)
3019	=C–H (aromatic ring)
2928	C–H (sp^3, aliphatic)
1636	C=C (cis-alkene)
1605, 1502, 1453	C=C (aromatic)
1276	C–N (aromatic amine)
1250	C–O–C (cyclic ether)
1056	C–O–Me (ether)

One of the most important observations is the disappearance of the sharp O–H stretching band at 3532 cm^{-1}, which is characteristic of free hydroxyl groups in codeine. This suggests that the hydroxyl group has participated in coordination with the Fe^{3+} ion, most likely leading to the formation of an Fe–O bond.

In addition, the band at 1250 cm^{-1} corresponding to the cyclic ether C–O–C stretching present in the codeine spectrum is absent in the compound, indicating to us a change in the environment surrounding the ether function, possibly due to structural rearrangement resulting from coordination or bond polarization.

The complex spectrum also shows two new bands at 628 cm^{-1} and 472 cm^{-1}, which are not present in the codeine curve and can be said to be related to Fe–O vibration modes.

These new signals provide direct evidence for the formation of a metal-oxygen bond, which is a characteristic feature of Fe–O coordination in such compounds.

Slight shifts were also observed in other functional groups such as C=C (aromatic), C–N, and C–O–Me, further supporting the alteration of the electronic environment around these groups as a result of complexation.

Overall, these spectral characteristics confirm that Fe^{3+} coordinates with codeine through its oxygen-containing groups, resulting in a stable Fe–codeine complex, with clear changes in both the high-frequency (O–H) and low-frequency (metal–bond) regions of the infrared spectrum , This is consistent with the results obtained in the infrared spectrum analysis in the work of (GHAMAMI et al) [8].

Table 4 FT-IR data for codeine-Fe(III) complex

Wavenumber (cm^{-1})	**Vibration Assignment**
3476, 3414	O–H (intermolecular hydrogen bond)
2928	C–H (sp^3, aliphatic)
1638	C=C (cis-alkene)
1617, 1504, 1454	C=C (aromatic)
1273	C–N (aromatic amine)
1049	C–O–Me (ether)
628, 472	Fe–O (metal–ligand coordination)

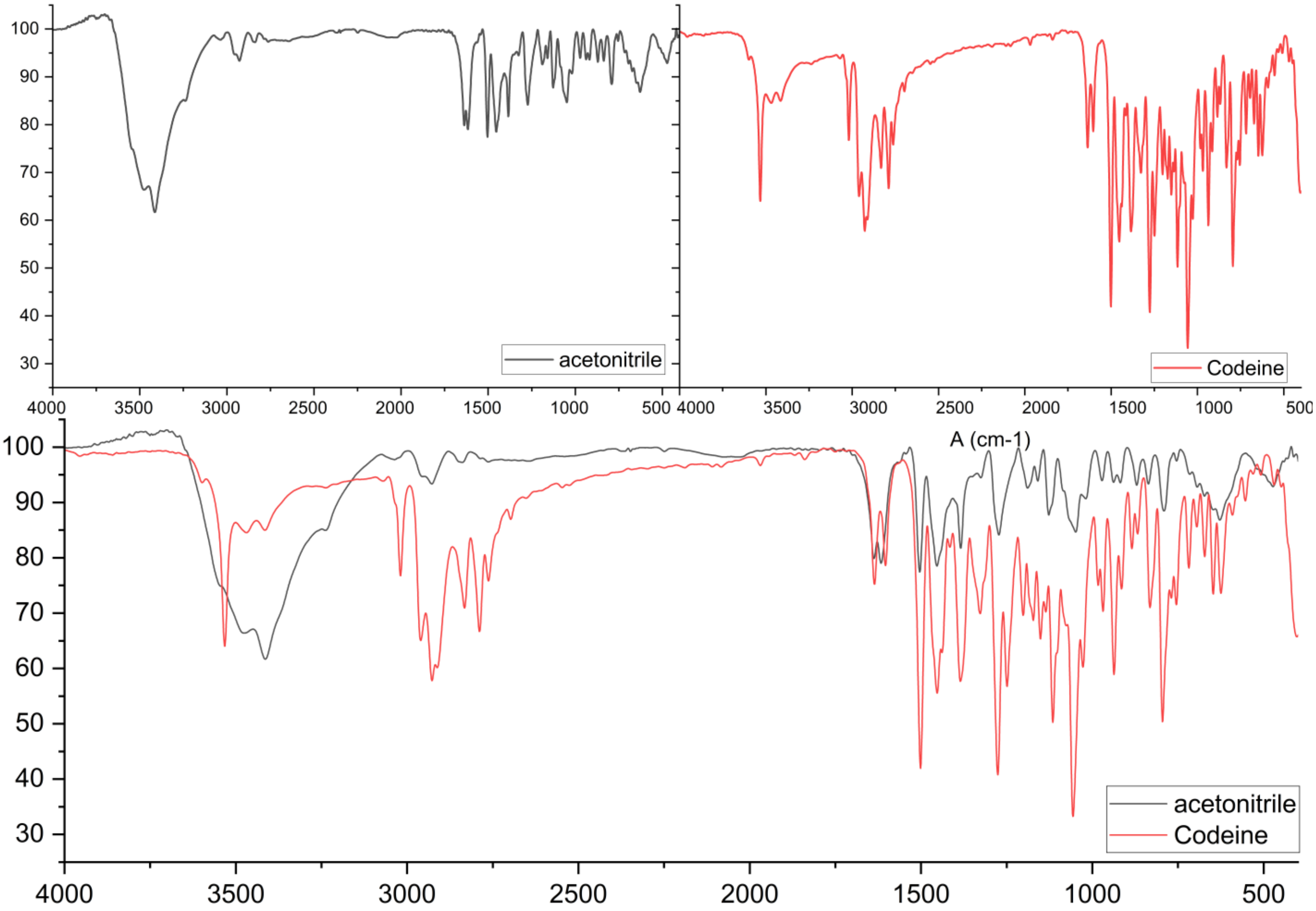

Figure 11 FTIR spectra of codeine and its Fe(III) complex in acetonitrile (Showing key spectral differences confirming complex formation)

3.3 Preparation and Characterization of Codeine Complexes with Different Metal Ions (Method 1)

In the scope of our research conducted in the previous section on the formation of Fe(III)–codeine complexes, we expanded our study to explore the possible interactions between codeine and other metal ions. Our goal was to evaluate whether it is possible to obtain similar complexes with metals such as Cu^{2+}, Ni^{2+}, and Mg^{2+}, as well as to analyze the properties of the resulting precipitates through FTIR. This examination provides insight into the coordination behavior of codeine with various metals and solvents.

3.3.1 Preliminary Solubility and Precipitation Screening with Different Metal Ions

First, we performed a series of initial solubility tests and rapid line tests to evaluate the behavior of codeine with different metal salts (Ni^{2+}, Mg^{2+}, Cu^{2+}) in different solvents (2-propanol, acetonitrile, acetone).

3.3.1.1 Solubility Tests :

All tested metal salts and codeine dissolved in the selected solvents except for Ni^{2+} and Mg^{2+} salts, which were either completely insoluble or had very low solubility.

3.3.1.2 Precipitation Tests:

We prepared mixtures of equal molar solutions of codeine and soluble metal salts to test for the possibility of precipitation.

Table 5 Effect of solvent on precipitation in the $CuCl_2$-codeine system

System	Solvent	Observed Precipitate
codeine + $CuCl_2$	2-propanol	Brown precipitate
codeine + $CuCl_2$	acetone	Blue precipitate
codeine + $CuCl_2$	acetonitrile	Brown precipitate

We observed the appearance of solid precipitates in most systems, indicating an interaction between codeine and metal ions, which may lead to the formation of various complexes.

3.3.2 Solid Product Preparation and Yield Determination

Based on the preliminary observations, selected systems were scaled up to prepare isolated solid products. In each case, 0.01 mol of codeine was mixed with 0.01 mol of the metal salt in acetone, stirred at room temperature for 4 hours. The resulting precipitates were collected, dried, and weighed.

Table 6 Physical Properties of the Dried Precipitate Formed with $CuCl_2$-codeine system

Metal Ion	**Color of Dried Precipitate**	**Mass of Dried Precipitate (g)**
Cu^{2+}	Green	2.1067

3.3.3 UV-Visible of codeine, $CuCl_2$, and the precipitated solid product

We recorded the visible ultraviolet radiation of codeine, $CuCl_2$, and the precipitate resulting from the Codeine-Cu Complex coordination process, where the codeine spectrum showed a clear absorption range at λ max = 285 nm and also a value at 260 nm, which is attributed to $\pi \rightarrow \pi^*$ electronic transitions. and $n \rightarrow \pi^*$. The $CuCl_2$ spectrum showed a peak at λ max = 290 nm.

In comparison, the spectrum of the precipitate resulting from the Codeine-Cu Complex coordination process showed a clear absorption range at λ max = 285 nm and a value at 260 nm. We note a match between the codeine and the complex, which indicates the presence of a codeine structure in the complex. We also observed the appearance of a broad shoulder in the 300-400 nm range, which, despite its low intensity, is a characteristic feature of LMCT transitions involving the copper and the codeine ligand. This may indicate the formation of a complex.

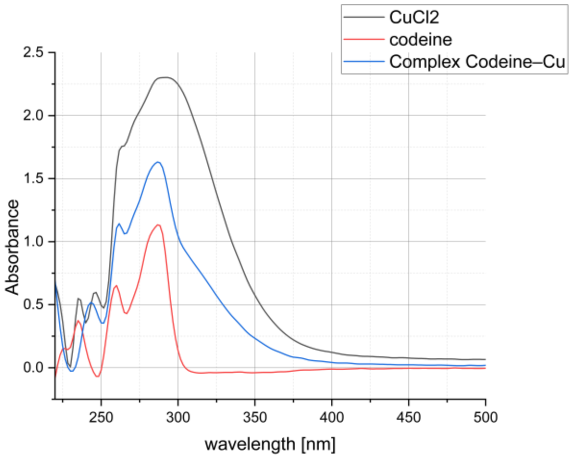

Figure 15 Comparative UV-Visible spectra of codeine, $CuCl_2$, and the copper–codeine complex

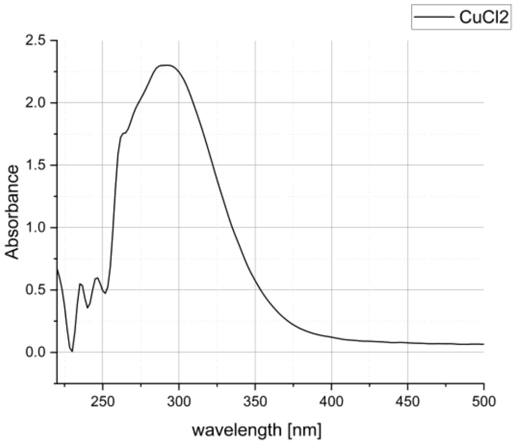

Figure 14 UV-Visible spectrum of $CuCl_2$ in DMSO

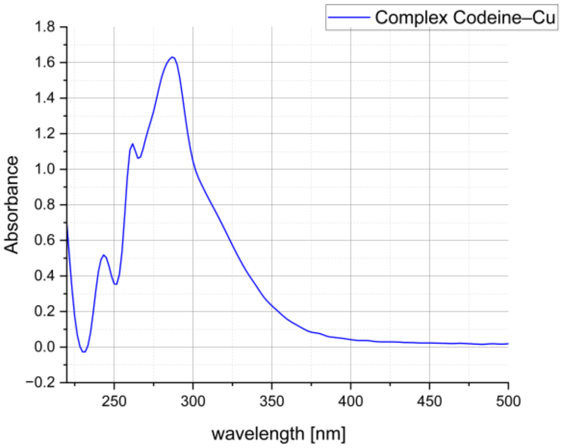

Figure 12 UV-Visible spectrum of the copper–codeine complex in DMSO

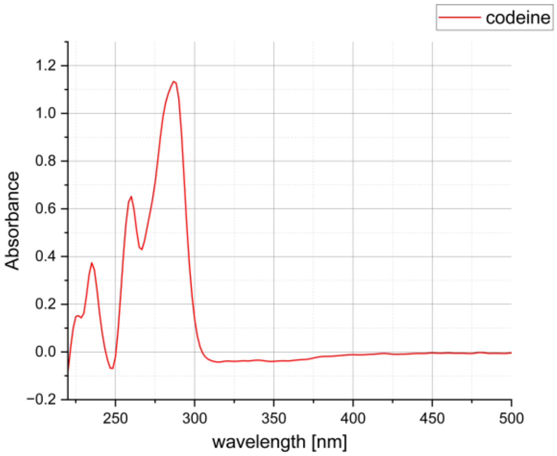

Figure 13 UV-Visible spectrum of pure codeine in DMSO

3.3.4 FTIR Analysis of Solid Products

Comparison of FT-IR spectra of pure codeine and the codeine-copper complex synthesized in acetone solution reveals clear spectral modifications confirming the formation of a coordination complex. One of the most important observations is the shift of the sharp O–H stretching band at

3524 cm⁻¹, which is characteristic of free hydroxyl groups in codeine. This indicates that the hydroxyl group did not participate in coordination with the copper ion.

In addition, the band at 1250 cm⁻¹ corresponding to the C–O–C periodic ether extension present in the codeine spectrum is absent in the compound, indicating a change in the environment surrounding the ether function, which may indicate the contribution of oxygen in the formation of a coordination bond between codeine and copper.

The complex spectrum also shows two new bands at 608 cm⁻¹, 520 cm⁻¹, and 464 cm⁻¹, which are not present in the codeine curve and can be said to be related to Cu–O vibration patterns.

These new signals provide direct evidence for the formation of a metal-oxygen bond, which is a characteristic feature of Cu–O coordination in such compounds.

Slight changes were also observed in other functional groups such as C=C (aromatic), C–N, and C–O–Me, further supporting the change in the electronic environment around these groups as a result of complexation.

Overall, these spectral characteristics confirm that copper coordinates with copper through its oxygen-containing groups, resulting in a stable codeine-copper complex, with clear changes in the cyclic ether C–O–C region and low frequency (metal bond) of the infrared spectrum.

Table 7 FT-IR data for codeine-copper complex

Wavenumber (cm^{-1})	**Vibration Assignment**
3524	O–H (free alcohol)
1642	C=C (cis-alkene)
1606, 1501, 1454	C=C (aromatic)
1267	C–N (aromatic amine)
1073	C–O–Me (ether)
608, 520,464	Cu–O (metal–ligand coordination)

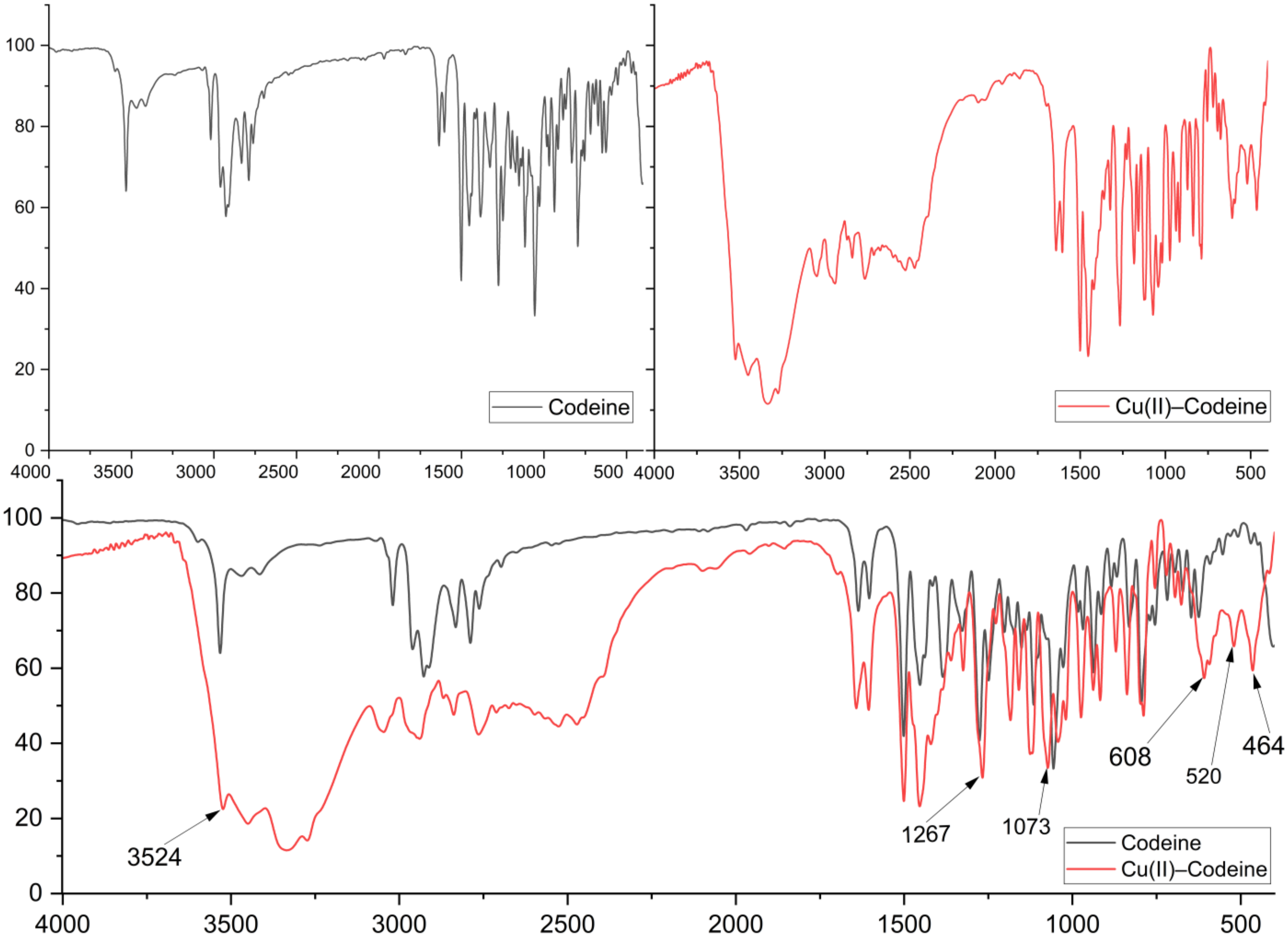

Figure 16 FTIR spectra of codeine and its copper complex in acetone (Showing key spectral differences confirming complex formation)

3.4 Characterization of Solid Products Obtained by Mixing Codeine or Codeine Phosphate with Selected Metal Ions (Method 2)

This section aims to evaluate the ability of both codeine phosphate (Cod.P) and pure codeine to interact with selected metal ions (Fe^{2+}, Fe^{3+}, Cu^{2+}) under aqueous reaction conditions (Method 2). The resulting precipitates were collected and analyzed to assess their color and FTIR spectral characteristics, enabling a comparison of the coordination behavior of each ligand type.

3.4.1 Visual Observation of the Precipitates

The difference in the color of the precipitates suggests that the nature of the ligand (neutral or phosphate form) strongly influences the type of solid product obtained, possibly indicating differences in the mode of interaction or the composition of the precipitate.

Table 8 Visual observation of the precipitates obtained from the reaction of codeine or codeine phosphate with selected metal ions (Method 2).

Ligand	**Fe^{2+}**	**Fe^{3+}**	**Cu^{2+}**
Codeine (pure)	Orange	Dark red	Green
Codeine phosphate (Cod.P)	White	White	White

3.4.2 FTIR Spectral Analysis

3.4.2.1 Precipitates from Codeine Phosphate + Metals

To assess the possible formation of coordination interactions between codeine phosphate and selected metal ions (Fe^{2+}, Fe^{3+}, Cu^{2+}), the FTIR spectra of the obtained precipitates were recorded and compared to that of the free ligand. The main bands and observed shifts are summarized below.

3.4.2.1.1 FTIR Spectral Analysis of Fe(II)-Codeine Phosphate Precipitate

As shown in **Figure 17**, the FTIR spectrum of the Fe(II)–Codeine Phosphate precipitate reveals the disappearance of the free O–H stretching band (3532 cm^{-1}), with a broad band emerging at 3413 cm^{-1}, which may suggest the involvement of the hydroxyl group in interaction with Fe^{2+} and/or the presence of coordinated water molecules.

Table 9 FTIR bands of Fe(II)–Codeine Phosphate precipitate

Functional group	**Wavenumber (cm^{-1})**
O–H (coordinated or H-bonded)	3413
C=C (cis-alkene)	1637
C=C (aromatic)	1505, 1401
C–O–C (cyclic ether)	1050
M–O (metal–oxygen)	598, 790

The C=C bands (cis-alkene and aromatic) remain visible at 1637 cm^{-1}, 1505 cm^{-1}, and 1401 cm^{-1}, indicating that the aromatic structure of the ligand is largely preserved.

A notable shift of the C–O–C ether band from 1250 cm^{-1} to 1050 cm^{-1} may reflect potential coordination through the ether oxygen.

Moreover, the appearance of new bands in the 598–790 cm^{-1} region could correspond to M–O vibrations, suggesting the possible formation of Fe–O bonds in the precipitate.

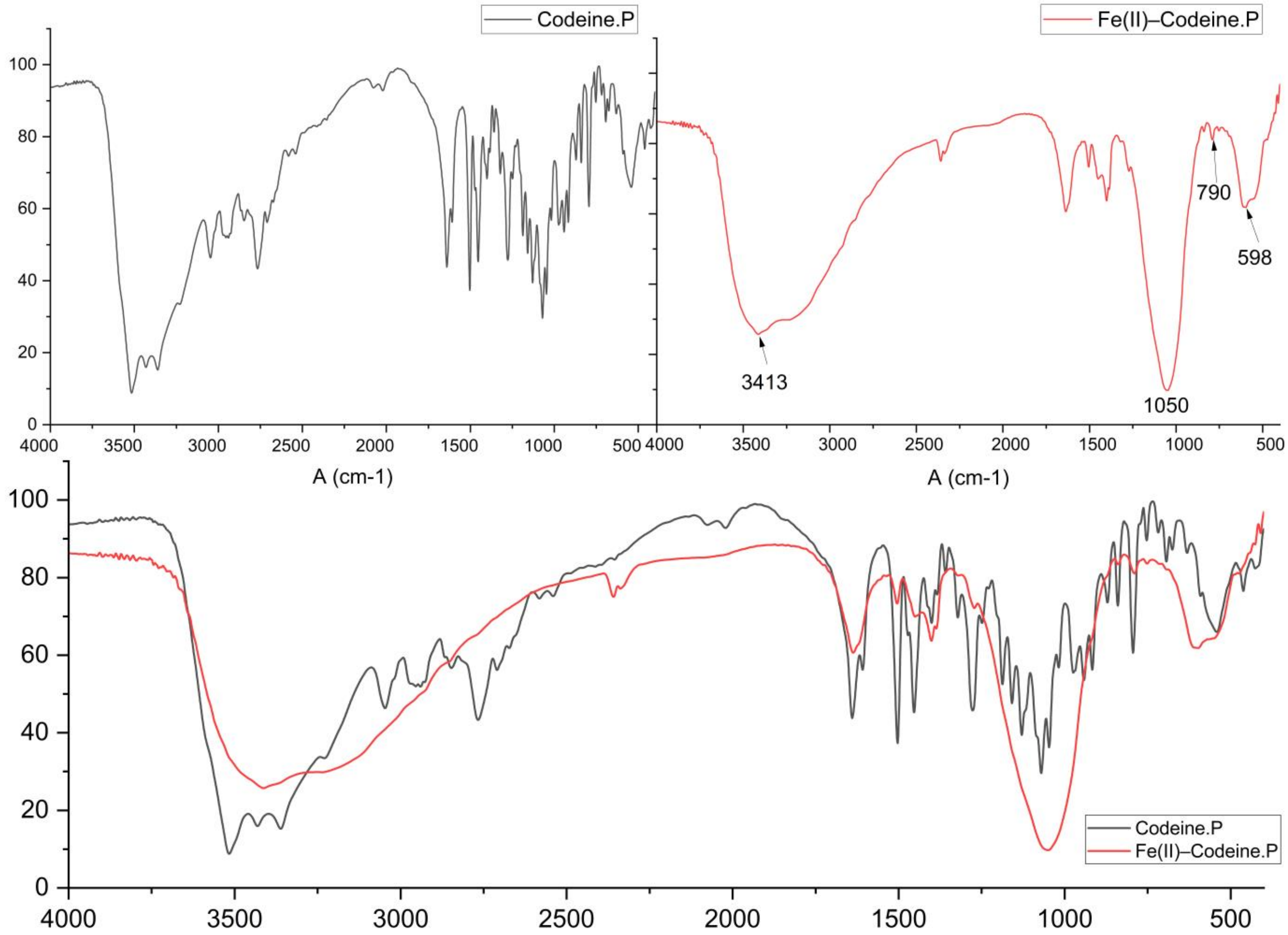

Figure 17 Overlay FTIR spectra of codeine phosphate and the solid product obtained from its reaction with Fe(II).

3.4.2.1.2 FTIR Spectral Analysis of Fe(III)–Codeine Phosphate Precipitate

The FTIR spectrum presented in **Figure 18** for the Fe(III)–Codeine Phosphate precipitate shows a similar pattern: disappearance of the free O–H band and appearance of a broad band at 3391 cm^{-1}, suggesting possible coordination of Fe^{3+} with the hydroxyl group and/or water molecules.

Table 10 FTIR bands of Fe(III)–Codeine Phosphate precipitate

Functional group	**Wavenumber (cm^{-1})**
O–H (coordinated or H-bonded)	3391
C=C (cis-alkene)	1633
C=C (aromatic)	1504, 1405
C–O–C (cyclic ether)	1049
M–O (metal–oxygen)	796, 598, 440

The C=C bands remain essentially unchanged, and the C–O–C band shift from 1250 cm^{-1} to 1049 cm^{-1} may indicate interaction involving the ether oxygen.

New absorptions observed at 796, 598, and 440 cm^{-1} may be indicative of M–O interactions, suggesting the potential formation of Fe–O bonds in the solid product.

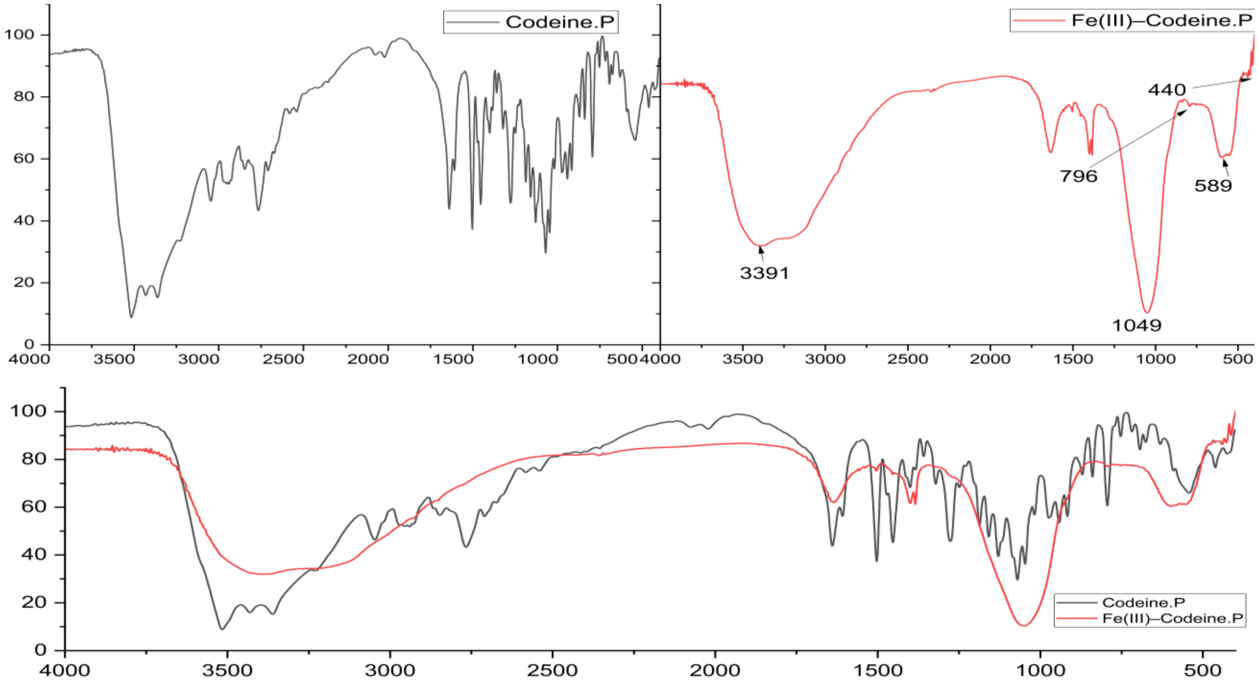

Figure 18 Overlay FTIR spectra of codeine phosphate and the solid product obtained from its reaction with Fe(III).

3.4.2.1.3 FTIR Spectral Analysis of Cu(II)–Codeine Phosphate Precipitate

Table 11 FTIR bands of Cu(II)–Codeine Phosphate precipitate

Functional group	**Wavenumber (cm^{-1})**
O–H (coordinated or H-bonded)	3470
C=C (cis-alkene)	1632
C=C (aromatic)	1500, 1384
C–O–C (cyclic ether)	1052
M–O (metal–oxygen)	607, 557, 484

In the Cu(II)–Codeine Phosphate precipitate **(Figure 19)**, the disappearance of the free O–H band and the emergence of a band at 3470 cm^{-1} may suggest the participation of the phenolic hydroxyl group in interaction with Cu^{2+}.

The C=C bands are retained, and the C–O–C shift to 1052 cm^{-1} may reflect coordination through the ether oxygen.

The presence of new bands in the 607–484 cm^{-1} region may be attributed to Cu–O stretching modes, implying that a coordination interaction may be occurring in the precipitate.

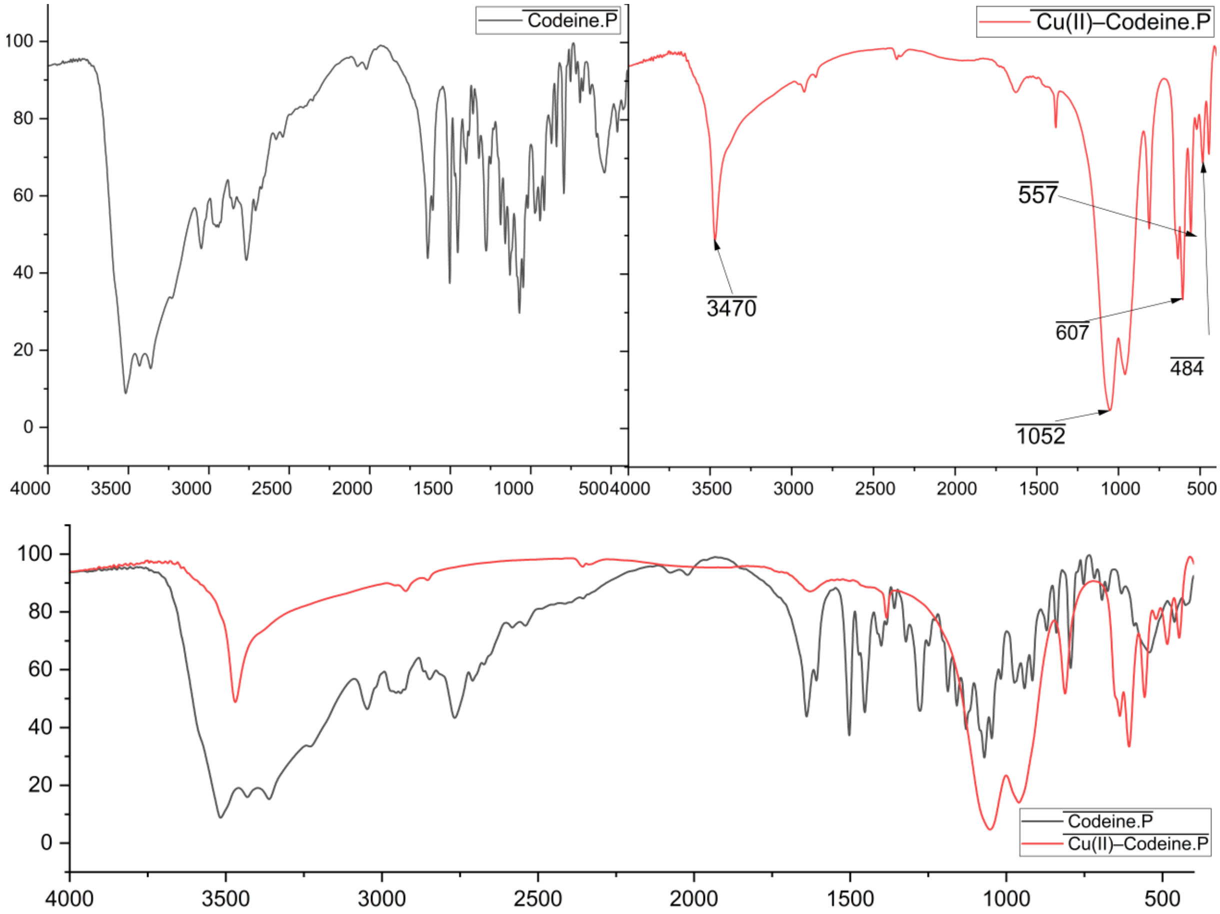

Figure 19 Overlay FTIR spectra of codeine phosphate and the solid product obtained from its reaction with Cu(II).

3.4.2.2 Precipitates from Codeine Pure + Metals

In parallel to the experiments with codeine phosphate, the interaction of **pure codeine** with selected metal ions (**Fe^{2+}, Fe^{3+}, Cu^{2+}**) was investigated. The resulting precipitates were dried and analyzed by FTIR spectroscopy to assess potential changes in functional groups indicative of metal-ligand interactions. The results are discussed below.

3.4.2.2.1 FTIR Spectral Analysis of Fe(II)–Codeine Puree Precipitate

The interaction of pure codeine with Fe^{2+} resulted in a reddish-brown precipitate. The FTIR spectrum of the solid product **(Figure 20)** showed a notable reduction and shift in the 3500–3000 cm⁻¹ region, corresponding to O–H or N–H stretching, along with new peaks in the 600–400 cm⁻¹ region. These observations may suggest the occurrence of metal-ligand interactions, although the possibility of partial metal oxide formation cannot be excluded.

Table 12 FTIR bands for Codeine + Fe^{2+} precipitate

Wavenumber (cm⁻¹)	**Codeine (Pure)**	**Codeine–Fe^{2+} Precipitate**	**Assignment**
3400–3500	Strong	Weak / Shifted	O–H or N–H stretching
2949	Present	Present	C–H stretching
1500–1400	Multiple peaks	Shifted (e.g., 1384)	C–H bending / Aromatic ring
1111	Absent	Present	Possible C–O or metal-ligand
600–400	Weak	Possible new peaks	Metal-ligand bonding

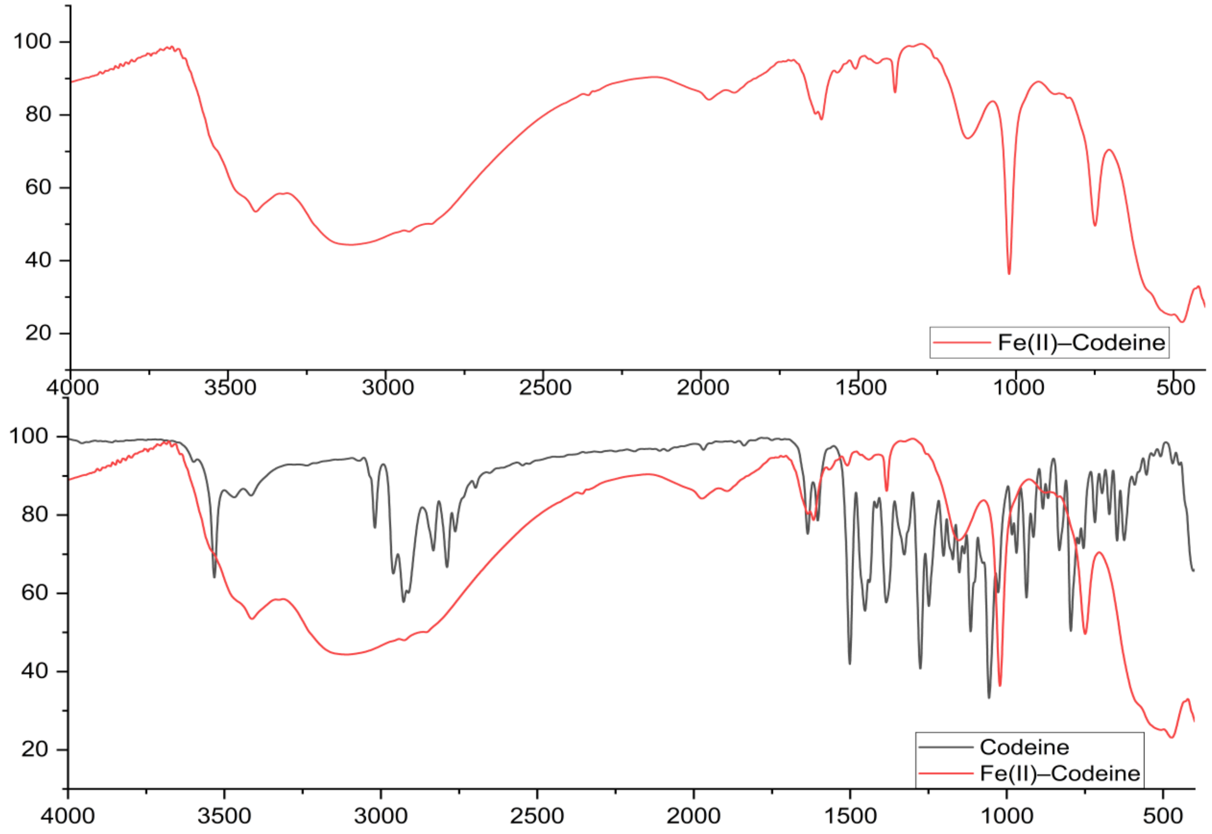

Figure 20 Overlay FTIR spectra of codeine pure and the solid product obtained from its reaction with Fe(II).

3.4.2.2.2 FTIR Spectral Analysis of Fe(III)–Codeine Pure Precipitate

The reaction of pure codeine with Fe^{3+} yielded a reddish-brown precipitate. The FTIR spectrum **(Figure 21)** displayed a weakened and shifted O–H / N–H stretching band (3500–3000 cm^{-1}), with new peaks observed at 1344 and 1163 cm^{-1}, and weak absorptions in the 600–400 cm^{-1} region. These spectral changes may indicate possible metal-ligand interactions, though the formation of metal hydroxide phases is also possible.

Wavenumber (cm^{-1})	**Codeine (Pure)**	**Codeine–Fe^{3+} Precipitate**	**Assignment**
3400–3500	Strong	Weak / Shifted	O–H or N–H stretching
1353	Present	Absent / Shifted (1344)	C–H bending
1163	Absent	Present	Possible C–O or metal-ligand
600–400	Weak	Possible new peaks	Metal-ligand bonding

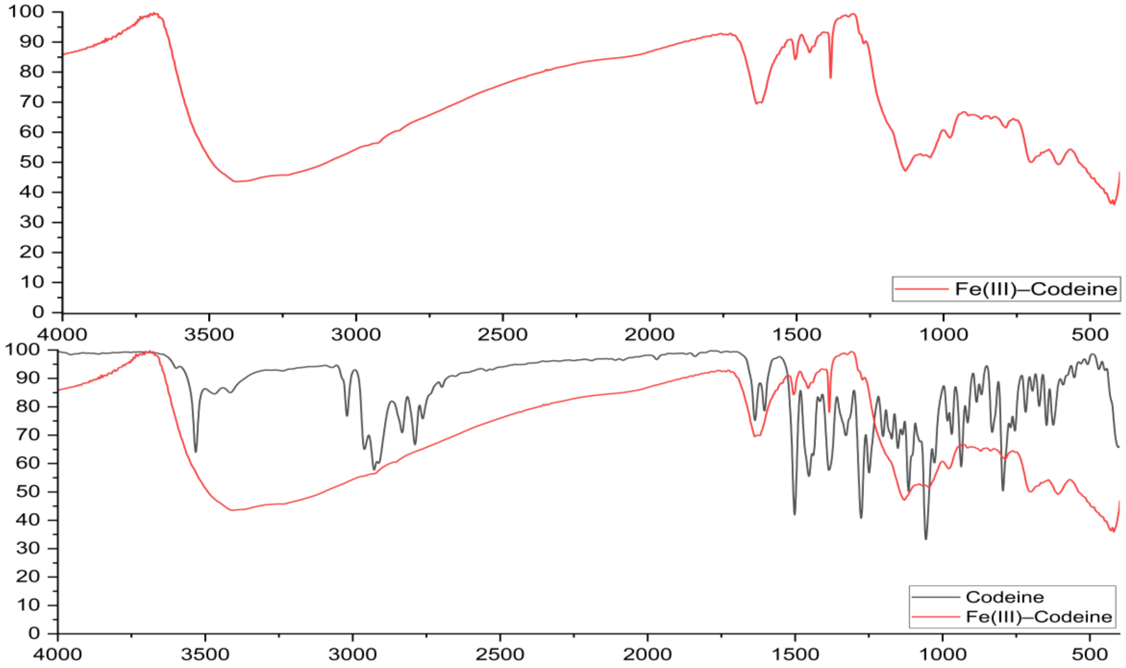

Figure 21 Overlay FTIR spectra of codeine pure and the solid product obtained from its reaction with Fe(III).

3.4.2.2.3 FTIR Spectral Analysis of Cu(II)–Codeine Pure Precipitate

Notably, the green color of the precipitate obtained from the reaction between codeine and Cu^{2+} is very similar to that of the starting material $CuCl_2 \cdot H_2O$, while pure codeine is white. This visual resemblance suggests that the precipitate may retain characteristics of the original copper salt, and not necessarily represent a new coordination compound.

Although the FTIR spectrum shows a weakened O–H/N–H stretching band (~3448 cm^{-1}), along with new absorptions at 1505, 1434, 497, and 407 cm^{-1}—possibly indicative of metal–ligand interactions—the intensity and specificity of these bands remain limited.

Therefore, it remains uncertain whether a true Cu–codeine complex has formed. The observed product may instead represent a physical mixture, an incomplete reaction product, or adsorbed $CuCl_2$ co-precipitating with codeine. Further structural analysis would be necessary to clarify the exact nature of this precipitate.

Table 13 Overlay FTIR spectra of codeine pure and the solid product obtained from its reaction with Cu(II).

Wavenumber (cm^{-1})	**Codeine (Pure)**	**Codeine–Cu^{2+} Precipitate**	**Assignment**
3400–3500	Strong	Weak / Shifted (3448)	O–H or N–H stretching
1505	Absent	Present	Possible aromatic ring or metal-ligand
1434	Absent	Present	C–H bending or metal-ligand
600–400	Weak	Present (497, 407)	Metal-ligand bonding

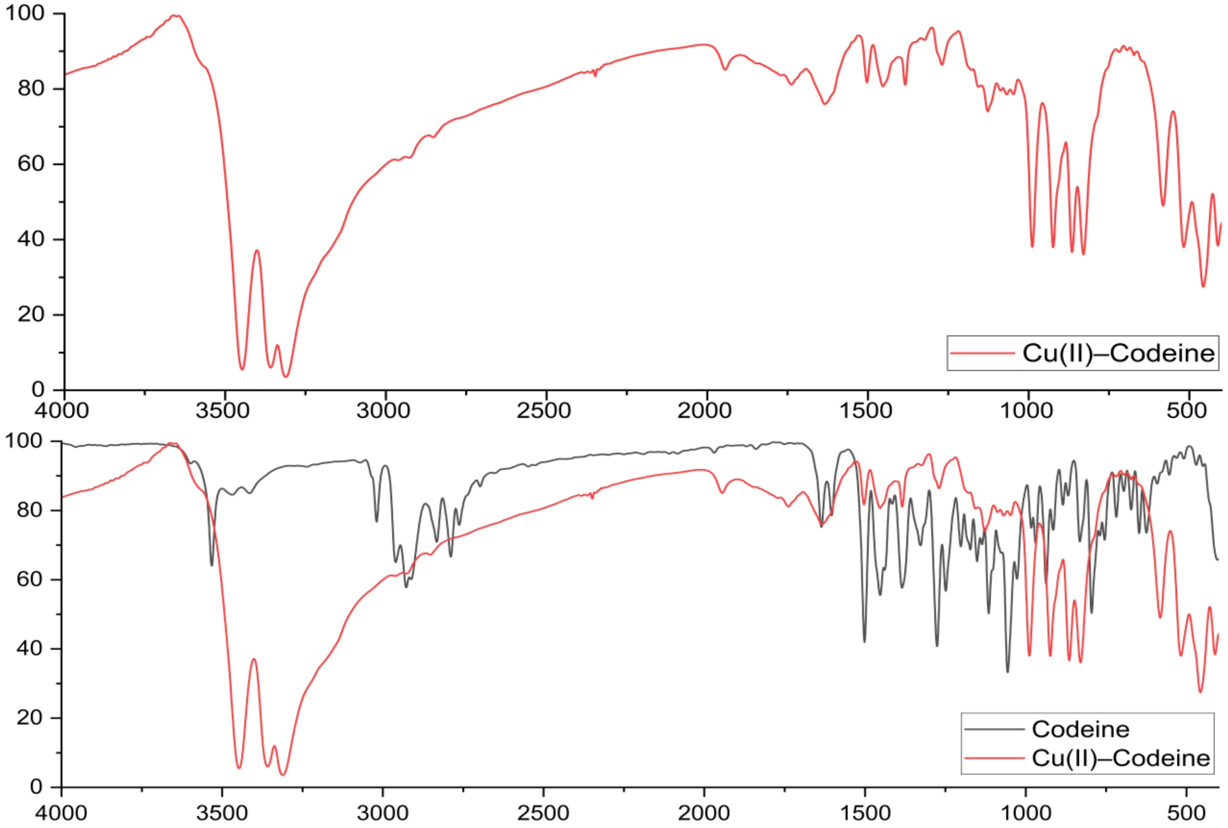

Figure 22 Overlay FTIR spectra of codeine pure and the solid product obtained from its reaction with Cu(II).

3.4.3 Comparison of codeine and codeine phosphate in coordination behavior

After analyzing the precipitated products with infrared spectroscopy, we dissolved the precipitates in several organic solvents such as DMSO, ethanol, or acetone, even with the addition of heat, but they did not dissolve. This suggests that the precipitated products in this part of the study have a **strong coordination structure** that makes them **insoluble** in organic or aqueous solvents. Therefore, we were unable to analyze these samples using ultraviolet spectroscopy.

Although pure codeine and codeine phosphate have the same active ingredient, the working results showed us that their reactions and results are different. Even when using the same metal salts, reaction conditions, and working conditions, observations showed differences in the color of the precipitates as well as differences in the infrared spectrum curves, indicating that phosphate greatly affected the coordination of metals with codeine and the structure of the resulting solid materials.

The following two tables summarize this part of the study on codeine coordination with metal salts :

Table 14 FTIR Summary for Complexes of Codeine Phosphate with Metal Ions

Metal Ion	**O–H (cm^{-1})**	**C–O–C (cm^{-1})**	**M–O (cm^{-1})**	**Precipitate Color**	**Interpretation**
Cod.P	**3532**	1250, 1056	**--**	**--**	**--**
Fe^{2+}	-	1050	598, 790	white	High probability of complex formation
Fe^{3+}	-	1049	796, 598, 440	White	High probability of complex formation
Cu^{2+}	-	1052	607, 557, 484	White	High probability of complex formation

Table 15 FTIR Summary for Complexes of Pure Codeine with Metal Ions

Metal Ion	**O–H / N–H (cm^{-1})**	**Additional Peaks**	**M–O (cm^{-1})**	**Precipitate Color**	**Interpretation**
Fe^{2+}	Weak / shifted	1384, 1111	Broad (600–400)	Orange	Possible weak compound
Fe^{3+}	Weak / shifted	1344, 1163	Broad (600–400)	Dark red	Possible weak compound
Cu^{2+}	Shifted (3448)	1505, 1434	497, 407	Green ($CuCl_2$-like)	Possible weak compound or copper hydroxide

IV. Conclusion

This study discusses in detail the possibility of complex formation between codeine and certain metal ions, combining computer modeling and laboratory experiments to obtain a comprehensive view. The research was organized into four main parts, each focusing on a different aspect of how codeine molecules bind to metals and how this can be exploited.

Using the molecular structure of codeine-Fe(III) published by Ghamami et al. as a starting point for this study, the stability of the compound was analyzed and verified using computational methods. The Nudged Elastic Band (NEB) method was applied, which showed that the reaction is an endothermic reaction. Optimized Geometry was performed for the complex, where we obtained a more energetically stable shape, which is later used in the calculation of another theory. We also obtained the potential energy of the system in its geometrically stable state, which is equal to 3161.789182 Hartree and a binding energy of –8.5953721 Ha. This value is used to compare the stability of Codeine-metal coordination in theory.

The Fe(III)–codeine complex was synthesized in the laboratory using method 1, and this reaction was tested in different solvents—acetonitrile, acetone, and 2-propanol—to determine the effect of each on the reaction outcome and yield. The resulting compound was analyzed using UV spectroscopy and FTIR, and the results of the analysis of the resulting compound were consistent with the results of the analysis in the study by (GHAMAMI et al) [8]. indicating the successful formation of the Fe(III)-codeine compound.

After the positive results obtained during the synthesis of Fe(III)-codeine complex, which are consistent with the results of the study by Ghamami et al., the synthesis of codeine complexes with metals was tested. The conclusion of this study was the coordination of codeine complex-copper complex. The reaction was carried out in an Aston solution, and the compound was analyzed using UV–Vis and FTIR spectroscopy , showing two main absorption bands at wavelengths of 260 and 285 nm, corresponding to π → π* and n → π* transitions, respectively. A broad extension in the 300–400 nm range also appeared. Although its intensity was low, it is a characteristic feature of

LMCT transitions involving copper and covalent bonds. The FTIR spectrum of the compound showed the appearance of new peaks at 608 cm^{-1}, 520 cm^{-1}, and 464 cm^{-1}, indicating the formation of Cu-O metal-oxygen bonds, as well as the disappearance of the band at 1250 cm^{-1} corresponding to the C–O–C ring ether extension, and the non-disappearance of the O-H value and its appearance at 3524 cm^{-1}. This may indicate that coordination between the codeine and copper metal occurred in the oxygen atom present in the ring ether of the codeine C-O-C.

In a second approach, complex compounds of codeine and metals were synthesized without the use of solvents, where codeine phosphate reacted with Fe^{2+}, Fe^{3+}, and Cu^{2+} metals. In parallel with this study, pure codeine was also used to synthesize complex compounds. Interestingly, the color of the resulting precipitates differed depending on whether pure codeine or codeine phosphate was used. The FTIR results also differed. For codeine phosphate-based precipitates, the spectra showed that the results were consistent with the infrared spectrum results of the study conducted by (Zayed et al). [6] .For pure codeine-based precipitates, the results were more ambiguous, with some FTIR spectra (e.g., with Cu^{2+} or Fe^{2+}) showing weak shifts, and the metal oxygen bands were weak or broad, indicating a lower degree of coordination or the possibility of incomplete product formation. In some cases, the color of the precipitate was almost identical to that of the initial metal salt (e.g., green with $CuCl_2 \cdot H_2O$), which may indicate incomplete reaction or physical mixing rather than the formation of a true compound. In the case of Fe^{3+}, more pronounced shifts were found, indicating partial coordination. Overall, the FTIR results indicate clear signs of metal coordination with codeine phosphate. Under the same conditions, pure codeine showed signs of limited or inconsistent reactions depending on the metal ion.

In the part where organic solvents were used to synthesize the complexes (method 1) in the second and third parts of this study, the complexes showed solubility, especially in DMSO, compared to the use of aqueous solutions and heat for complex synthesis. (method 2). In the fourth part of the study, the complexes showed insolubility, indicating that the method of complex formation may play an important role in the formation of the coordination structure between the codeine and metals. This can be concluded from the result of the codeine complex-copper complex in an organic acetone solution and the precipitate obtained by mixing codeine and $CuCl_2$ in an aqueous solution with heat, where despite using the same pure codeine and $CuCl_2$ compound, the results of UV-visible and FTIR analyses showed that the nature of the coordination was different.

It can also be concluded that the type of codeine can affect the coordination product between codeine and metals, as shown in the fourth part of this study, where coordination products between pure codeine and metals, and coordination products between codeine phosphate and metals, showed significant differences in the color of the precipitates and FTIR analysis, indicating a difference in the coordination structure of the obtained precipitates.

In the second part of this study, a complex synthesis of codeine- Fe(III) was carried out in several organic solvents, with 2-propanol showing the highest yield. This is due to the fact that **a protic solvent** promotes complex precipitation and reduces side reactions with the metal, compared to non-protic solvents that reduce complex precipitation. The dielectric constant also plays a role in **salt dissociation and charge distribution** in the medium, affecting reaction efficiency and solubility. The dielectric constant of 2-propanol is ≈ 18, acetone is lower (≈ 21), and acetonitrile has a high dielectric constant (≈ 36). FTIR and UV-visible analyses were performed, and no significant differences were found between the complexes, indicating that the type of solution does not affect the coordination between the ligands and metals but does affect the reaction yield.

In summary, this study demonstrates that the type of solution or reaction medium and the type of codeine used, whether pure codeine or phosphate codeine, can affect the coordination of the resulting complexes. This study shows that codeine has the ability and potential to bind to transition metals under appropriate conditions. Although further structural analysis is needed in this study, these results may be a starting point for further studies to develop stable codeine-metal complexes that can be used in the medical field.

V. References

[1] Shahzadi, S., Ali, S., Shahid, K., Yousaf, M., Sharma, S., & Qanungo, K. (2010). Interaction of di- and triorganotin(iv) compounds with carboxylate ligand: synthesis, spectral characterization, semi-empirical study and in vitro antimicrobial activities. Journal of the Chinese Chemical Society, 57(4A), 659-670. **https://doi.org/10.1002/jccs.201000092**.

[2] Perilli, D., Breglia, R., & Valentin, C. (2022). Using coordination chemistry concepts to unravel electronic properties of sacs in bidimensional materials. The Journal of Physical Chemistry C, 126(23), 9615-9622. https://doi.org/10.1021/acs.jpcc.2c02307.

[3] Lepetit, C., Maraval, V., Canac, Y., & Chauvin, R. (2016). On the nature of the dative bond:coordination to metals and beyond. the carbon case. Coordination Chemistry Reviews, 308, 59-75. https://doi.org/10.1016/j.ccr.2015.07.018.

[4] Choi, J. and Park, Y. (2003). Electronic and vibrational spectroscopy of cis-diisothiocyanato(1,4,8,11-tetraazacyclotetradecane)chromium(iii) thiocyanate. Bulletin of the Korean Chemical Society, 24(3), 384-388. https://doi.org/10.5012/bkcs.2003.24.3.384.

[5] Marchione, D., Belpassi, L., Bistoni, G., Macchioni, A., Tarantelli, F., & Zuccaccia, D. (2014).The chemical bond in gold(i) complexes with n-heterocyclic carbenes. Organometallics, 33(16), 4200-4208. https://doi.org/10.1021/om5003667.

[6] M.A. Zayed, M.F. Hawash, M.A. Fahmey. Spectrochem. Acta. 363–371 (2006).

[7] M.A. Zayed, M.S. El-Morsy. J. Chem. 23, 1-11 (1980).

[8] Ghamami, S., Golzani, M., & Lashgari, A. (2016). Synthesis, characterization and biological properties of new codeine fe(iii) complex.Journal of the Chilean Chemical Society, 61(2), 2954-2957. https://doi.org/10.4067/s0717-97072016000200020.

[9] R, A. and O, A. (2019). A narrative review of codeine and preventive measures in mitigating against the widespread of its abuse and misuse. Journal of Alcoholism and Drug Dependence, 07(01 https://doi.org/10.4172/2329-6488.1000323.

[10] Kirchheiner, J., Schmidt, H., Tzvetkov, M., Keulen, J., Lötsch, J., Roots, I., … & Brockmöller, J. (2006). Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to cyp2d6 duplication. The Pharmacogenomics Journal, 7(4), 257-265. https://doi.org/10.1038/sj.tpj.6500406.

[11] Vries, F., Reeskamp, L., Ruler, O., Arum, I., Kuin, W., Dijksta, G., … & Serlie, M. (2017). Systematic review: pharmacotherapy for high-output enterostomies or enteral fistulas. Alimentary Pharmacology & Therapeutics, 46(3), 266-273. https://doi.org/10.1111/apt.14136.

[12] Sobczak, Ł. and Goryński, K. (2020). Pharmacological aspects of over-the-counter opioid drugs misuse. Molecules, 25(17), 3905. https://doi.org/10.3390/molecules25173905.

[13] Alzahrani, H. (2023). Patterns of prescribing postoperative analgesic medication after thyroid surgery: a retrospective cohort study. International Journal of General Medicine, Volume 16, 405-410. https://doi.org/10.2147/ijgm.s401828.

[14] J.M. Gulland, R. Robinson, M. Mem, Lit. Philos. Soc. 69 (1925) 75.

[15] Langes, C., Gelbrich, T., Griesser, U., & Kahlenberg, V. (2009). Codeine dihydrogen phosphate hemihydrate.Acta Crystallographica Section C Crystal Structure Communications, 65(8), o419-o422. https://doi.org/10.1107/s0108270109027164.

[16] Dahan, A., Wolk, O., Zur, M., Amidon, G., Abrahamsson, B., Cristofoletti, R., … & Dressman, J. (2014). Biowaiver monographs for immediate-release solid oral dosage forms: codeine phosphate. Journal of Pharmaceutical Sciences, 103(6), 1592-1600. https://doi.org/10.1002/jps.23977.

[17] Ullrich, C. and Yang, Z. (2013). A brief compendium of time-dependent density functional theory. Brazilian Journal of Physics, 44(1), 154-188. https://doi.org/10.1007/s13538-013-0141-2.

[18] Zarkevich, N. and Johnson, D. (2015). Nudged-elastic band method with two climbing images: finding transition states in complex energy landscapes. The Journal of Chemical Physics, 142(2). https://doi.org/10.1063/1.4905209.