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Synthesis and Characterization of Co-Crystallization of Pyridine 2, 6- Dicarboxylic Acid with Different Bases

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ABSTRACT

Three novel co-crystals of pyridine-2,6-dicarboxylic acid were successfully synthesized with nicotinamide, 2-amino-6-chlorobenzothiazole, and caffeine in a stoichiometric ratio of 1:2. The synthesis was carried out using a suitable solvent evaporation technique, resulting in the formation of stable crystalline products with appreciable yield. These co-crystals were structurally characterized through various analytical techniques, including UV–visible spectroscopy and Fourier Transform Infrared (FT-IR) spectroscopy, to confirm the formation of intermolecular interactions and functional group involvement. In addition, melting point determination and solubility studies were performed to evaluate their physicochemical properties. The spectroscopic analysis revealed significant shifts in characteristic absorption bands, indicating the formation of hydrogen bonding and other non-covalent interactions between the carboxylic acid groups of pyridine-2,6-dicarboxylic acid and the functional groups of the co-formers. The presence of

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carboxylate groups (C=O and C–O) plays a crucial role in facilitating these bonding interactions, contributing to the stability of the co-crystals. Furthermore, variations in melting points compared to the pure components confirmed the successful formation of new crystalline phases. Overall, all synthesized co-crystals exhibited good yield and enhanced physicochemical characteristics, suggesting their potential applicability in pharmaceutical and material science fields, particularly in improving solubility and stability of active compounds.

Keywords: Co-crystals synthesis, Pyridine-2,6-dicarboxylic acid, FT-IR spectroscopy, Hydrogen bonding interactions, Cocrystal characterization

1. Introduction

Co crystals may be defined is its supramolecular crystalline entity that is comprises two or more crystalline forms with a particular stoichiometric ratio. Co crystals having components are in a neutral state and interact through non-ionic interaction. Co crystals are particularly utilized in industrial as well as academic application in order to modify some physical properties and some new solid structure. this contrast with polymorphisms which when observed can be difficult to overcome and really represent an opportunity significantly enhance physical properties such as studies of solubility of drugs substances for example showed that the ratio of polymorphisms solubility typically less than two (Taylor & Wood, 2019).

The crystallization of an active pharmaceutical ingredient (API) is fundamental step in the manufacturing of new drugs substance (Shamshina & Rogers, 2023). For most pharmaceutical active compound various crystals form can be come across polymorph of the pure compound (Devos et al., 2025).

Solvates/hydrate, salt or co crystal. The solids form a drug can be significantly modifying its physiochemical properties. This year and the years to come, solid-state sciences have also overcome the reward that come with versatile solid-state forms, particularly targeting physicochemical properties of a drug by modification of the solid form, without altering the biological functionality of the drug so-called “solid-state engineering”. Screening for different forms (e.g., viable salts) is a common approach in pharmaceutical development, with a high number of drugs currently administered as a salt (Michalchuk et al., 2021).

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Co-crystallization is one of the contemporary ideas in crystal engineering. Co crystal serves best scheme and strategy in the designing of new crystal having enormous and awful activate especially in the pharmaceutical field as well as pharmaceutical materials beyond as well. Co crystal having pharmaceutical purpose, in order to converge and adjoin the criteria of interested dynamic co crystals should have been a vigorous constituent such as active pharmaceutical ingredient (API). Increase in properties such as resistivity, bioavailability stability, solubility and other precious properties can best be accomplished by different techniques (Gazal et al., 2021).

The events of cocrystals have been initiated from a germen chemist friedric wholer in 1884, and Ar. Ling 1893 with the discovery of quinhydrone as conformer. Later in the year of 1894 the lock-and –key hypothesis was proposed in supra molecular chemistry by F. Email, afterwards crystal was engineering and designing was introduced in 1955 and imposed by J Schmidt in 1964.Various terms like molecular complex, solvates, inclusions compound, calthrates, channel compound was reached to the zenithal point in that such period. The term cocrystal was for the first time introduced by J. Schmidt in1967 and vulgarized by MC Etter in 1995. In the year of 2003-2007 cocrystillizations was serving an indispensable role and get more and more fashionable in the field of pharmaceutical drug designing. Today and the days to come cocrystillizations is not merely used for the designation of crystal but also playing a vital role in the endowing and formulation of drugs properties like density, stability, bioavailability, solubility and some other precious properties. Furthermore, the non-ionic cocrystal was nominated by Braga 2010. In the outline guidance of USFDA, polymorphs are compound having the capability of various and different arrangements in their lattice in opponent to cocrystal and various salts. It subsists in aggregate crystalline form such as solvates, amorphous, hydrates and as well as pseudoploymorphs forms. Due to lattice properties they also have various sorts of physiochemical properties. in contrast to cocrystal, the acid base interaction involves the complete transfer of proton from acid to base resulting ionic interaction in salts. In such case various salts are different s from cocrystal by the proton position. In cause of cocrystal, the constituents are keep and bond together via non-covalent interaction like Vander Wall interaction, pi-pi stacking, hydrogen bonding,

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and halogen bonding etc. (Edwardson et al., 2022).

Whenever a designing co-crystal comprises two or more components have an enlightened advantages of superior therapeutic effect over which are govern discretely or one by one. Co-crystal having fixed-dose amalgamation, or combination drugs, are of two or more active pharmaceutical ingredients (APIs) combined in a single dose, and have become gradually more admired in current times. Co-crystal also extends its help in therapeutic effect, so it also made assistance in this field of therapy is well (Xiao et al., 2023).

Experimental Work

2.1 Chemicals Used

The chemical utilized right through this project are nicotinamide, 2-Amino-6-cholrobenzothiazole (TCI) and acid such as pyridine-2, 6-dicarboxylic acid from Alfa Aesar (Germany) and caffeine were purchased. These precious chemical are used as such as it received or without any further purification. Solvents such as methanol and chloroform were used all the way through the synthetic processes which are required to use. For MP, FT-IR, and UV of already been synthesized compounds Stuart SMP- 10 (japan), schimdzu (1802 japan) were used during this whole project.

2.2 Synthetic Preference Approach

We have already been study diverse and sundry plains which are easily available in the literature in the way of formation of co-crystals and molecular salts, thus we have been choose the slow evaporation technique. Slow evaporation technique is one of the competent and best techniques regarded for appreciable quality of cocrystal formation. We have selected this direction because after studying environment of starting materials. It was trouble-free and soft to handle circumstances in such strategy, because of all the given chemicals are easily dissolvable in the specific amount of solvent. So we did not suffer from any sort of dilemma which are frantic and mystery in the above approach.

2.3 Preparative Methods

2.3.1 General Methods

Generally, we used straightforward methods which are really easy to handle while making sure the formation of aspired cocrystal for which we use one of the fair and

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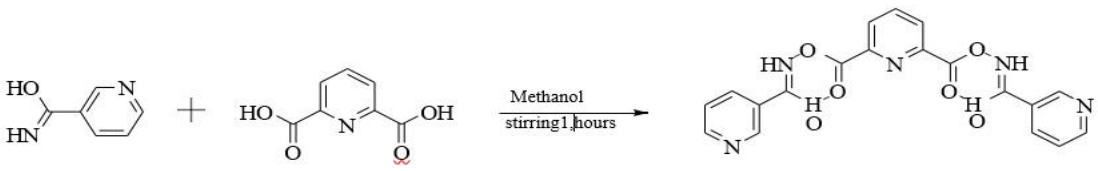
square technique known as slow evaporation technique. The stoichiometric ratio of the reacting compounds was get dissolved in a specific and known volume of solvent which are kept on stirring, in terms to get clear solution. Upon heating on reflux as well as regular stirring the components of the reacting compounds which is in the forms of clear solution will slowly and gradually mixed up, the reflux was as possible as for 8 hours for some reacting compound and other was for just 4 hours. After that the mixture we get was remained for slow and steady evaporation in order to get desirous crystalline product. The ultimate product we acquired was characterized by getting the improvement of melting point (Stuart SMP-10, Japan), FT-IR.

2.4. Formation of Compounds

2.4.1 Preparation of Compound 1

Formation of compounds 1 involve here are, pyridine-2,6-dicarboxylic acid was reacted with nicotinamide having stoichiometric ratio 1:2. Pyridine-2,6-dicarboxylic acid of 0.16 g was dissolved in 20 mL of methanol upon stirring and shaking it give us a clear solution. Correspondingly in order to make base solution which acts also as co-former of nicotinamide was dissolved in 20 mL methanol. The solution we made both mixed with each other at room temperature and at constant stirring for in 1 hour. After that the clear mixture was then kept on reflux for 4 hours. The solution was as such as before reflux, so no obvious change was observed. Furthermore, the solution was kept for slow evaporation at place which was safe and sound. After 10 days' white crystal was formed. These solutions were then characterized with different techniques such as melting point, FTIR and UV-vis.

MP = 210 °C



Scheme 2.1: Expected structure & scheme of compound 1

Preparation of Compound 2

The production of compound 2 involved the treating of pyridine-2,6-dicarboxylic acid with 2-Amino-6-cholrobenzothiazole in stoichiometric ratio 2:1. pyridine-2,6-

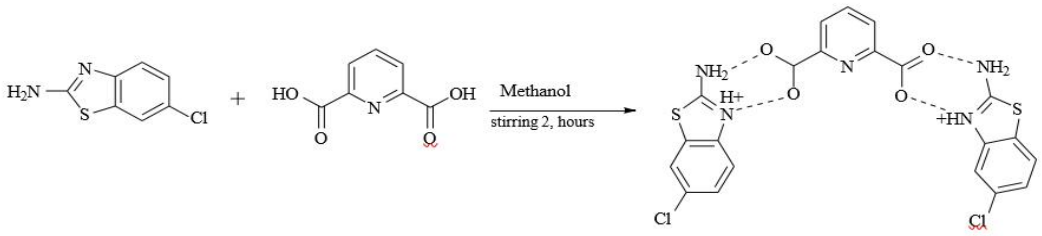
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dicarboxylic acid 0.25 g was dissolved in 15 mL methanol. A clear solution was acquired, both solution was mixed at room temperature (RT) and stirred were almost 2 hours, hence after one week a white cluster were achieved rather than a clear crystal. Furthermore, for getting clear crystal the already obtained cluster was dissolved again in 10 mL mixture of methanol and chloroform and refluxed for 4 hours. After 2 weeks' crystal were obtained, having white color same as starting materials. The solution was slowly and gradually cooled up at room temperature and allowed to kept for slow evaporation. These crystals were then characterized by melting point (MP), FT-IR and UV-vis.

MP = 237 °C



Scheme 2.2: Expected structure & scheme of compound 2

Preparation of Compound 3

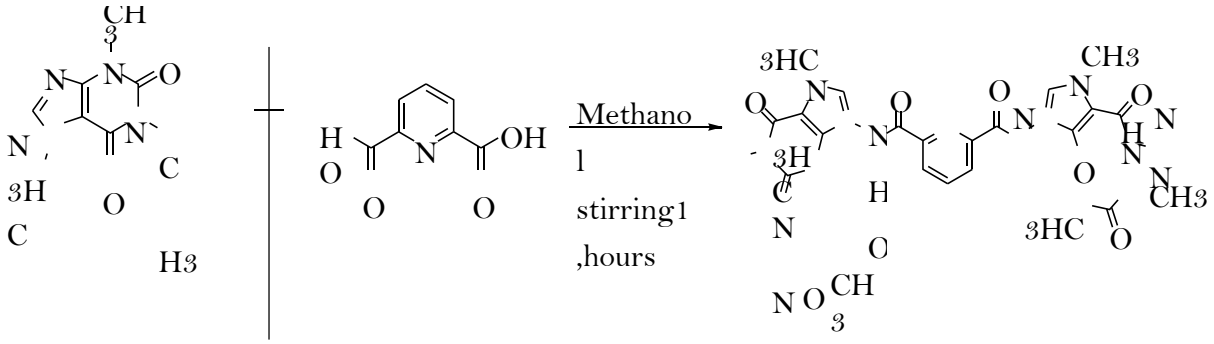
For the creation of compound 3, pyridine-2,6-dicarboxylic was treated with caffeine in 1:1 stoichiometric ratio. pyridine-2,6-dicarboxylic 0.043g was dissolved in 20 mL of methanol pursue by stirring as well as shaking in order to make clear solution. Correspondingly for making solution of caffeine (as conformer) were dissolved in MeOH. Obviously both of the solutions were mixed at RT (room temperature) for almost 1 hour. The clear mixture of acid and caffeine was obtained. The acquired solutions were then kept for slow evaporation at safe and sound place in terms of getting clear and sophisticated crystal. After 2 weeks' agglutinate cluster were gained rather than that of clear crystal. That cluster was not being capable for characterization, means it was just white like powder. In order to get clear crystal that specific cluster was again dissolved in mixture of chloroform and methanol again clear solutions were prepared upon shaking for 10 minutes. Furthermore, it was refluxed for 4 hours, colorless solution was gained thus solution was kept for slow evaporation process and after 2 and half weeks' white crystal were obtained.

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The gained crystal was then characterized via MP, FT-IR and UV.

MP = 220 °C



Scheme 3.3: Expected structure & scheme of compound 3

Results and Discussion

General Characterization of Compound 1-3

All of the prepared compound from 1-3 were characterized by solubility, melting point, FT-IR and UV-vis spectroscopic techniques. The aspects of characterization for each and every synthesized compound are quashing as below. For the determination of melting point, the apparatus Stuart SMP-10 (Japan) was used.

Compounds Characterization

The compounds were confirmed and characterized by Solubility, MP, FT-IR and UV- vis.

FT-IR Spectrum of compound 1

The FT-IR spectrum of compound 1 is shown in figure 1 which having all the precious values of peaks. The spectrum reflects a broad peak at 3447 cm-1 which are correspond to O-H bond stretching, while the N-H stretching can be seen at the 3361 cm-1. The aromatic and aliphatic hydrogen bond in the spectra of compound 1 are confirmed from the broad and medium peaks 3174-3077 cm-1 and 2950 cm-1 respectively. The two different stretching in the regions of 3174-3077 cm-1 confirm the presence of two different environment of aromatic hydrogen in the desire product. Similarly, the remaining peaks 1715, 1674 and 1620 cm-1 are corresponding to C=O, C=O and C=C bonds respectively.

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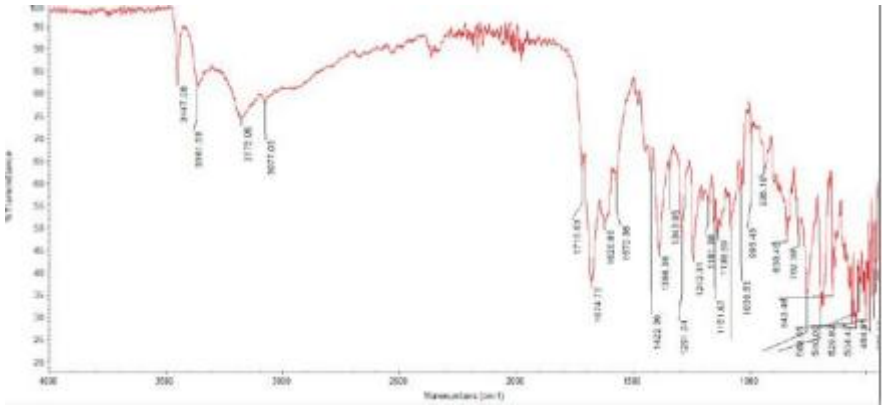


Figure 3.1: FT-IR spectrum of compound 1

FT-IR Spectrum of Compound 2

The FT-IR spectrum of compound 2 shown in figure 2 which having all the precious values of peaks. The spectrum reflects a weak absorption peak at 3544 cm-1 which are correspond to O-H bond stretching, while the N-H stretching can be seen at the 3448 cm-1. The aromatic and aliphatic hydrogen bond's stretching in compound 2 are found in the region of 3129-3082 cm-1 and 2955 cm-1 respectively. The two different stretching in the regions of 3129-3082 cm-1 confirm the presence of two different environment of aromatic hydrogen (thiazole and pyridine hydrogens) in the desire product. Similarly, the remaining peaks 1738, 1699 and 1659 cm-1 are corresponding to C=O, C=O and C=C bonds respectively.

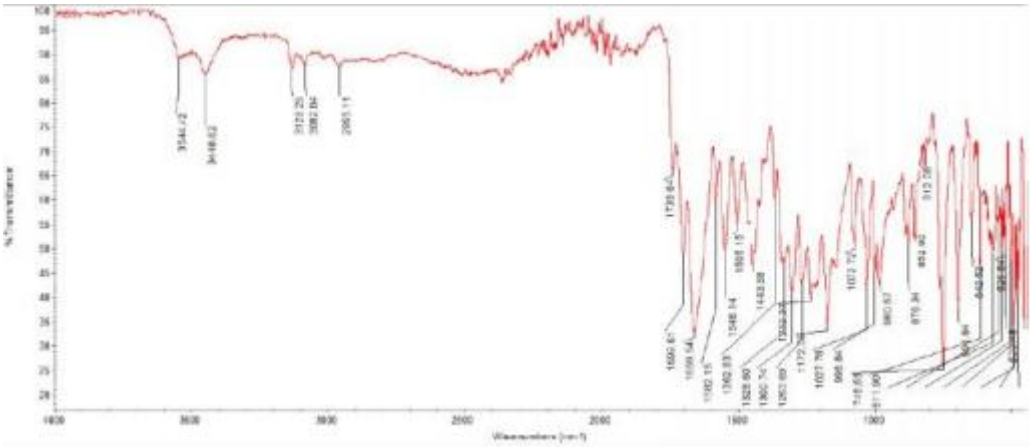


Figure. 3.2: FT-IR spectrum of compound 2

FT-IR Spectrum of Compound 3

The FT-IR spectrum of compound 3 shown in figure 3 shows a sharp and strong absorption peak at 3643 cm-1 which confirm the presence of O-H bond stretching.

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The absence of N-H bond stretching confirms the formation of cocrystal because there is no N-H bond in the reactants. The caffeine has basic character tend to abstract proton from acid via N-atom of aromatic ring, but their absence confirm that no transfer of hydrogen occurred here, and their coformer are interlinked with each other via hydrogen bonding. The aromatic and aliphatic hydrogen bond's stretching in compound 3 can be seen at the region of 3192-2910 cm-1 this broadness of peaks is perhaps of coupling of aromatic and aliphatic hydrogen via hydrogen bonding. Similarly, the remaining peaks 1726, 1651 and 1573 cm-1 are corresponding to C=O, C=O and C=C bonds respectively.

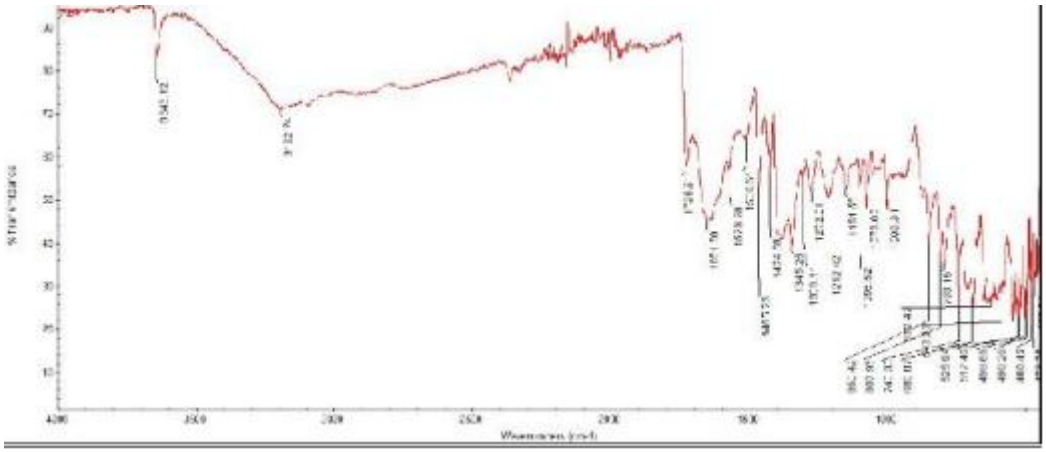


Figure. 3.3: FT-IR spectrum of compound 3

Melting Point

Melting Point of Compound 1

First of all, the melting point of pyridine-2, 6-dicarboxylic acid was determined by apparatus SMP (10) Japan, having value in the range of 248-255 °c which is also outlined in the literature and amines which is nicotinamide having melting point value 128 °c, after designing the cocrystal of the above acid and amines the melting point of specific cocrystal was enhanced and reached to the value of 210 °c, which demarcates clear difference between the starting materials and that of products.

Melting Point of Compound 2

The melting point of pyridine-2, 6-dicarboxylic acid was determined by apparatus SMP (10) Japan, having value in the range of 248-255 °c which is also outlined in the literature and amines which is 2-amino-6-cholrobenzothiazole having melting point value 199-201°c, after designing the cocrystal of the above acid and amines the

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melting point of specific cocrystal having the value of 237 °c, which shows clear difference between the starting materials and that of products.

Melting Point of Compound 3

The melting point of pyridine-2, 6-dicarboxylic acid was determined by apparatus SMP (10) Japan, having value in the range of 248-255 °c, which is also outlined in the literature and that of caffeine having melting point value 235-238 °c, after formation of the cocrystal of above acid and caffeine the melting point of cocrystal having the value of 220 °c, which reflects clear difference between the starting materials and that of products.

Solubility

Solubility of pyridine-2, 6-dicarbooxylic acid was confirmed in many of organic solvents such as methanol, ethanol, acetone, dimethylsulphoxide (DMSO), acetonitrile, chloroform. It is also soluble in water, but it is completely miscible in mixture of chloroform and methanol.

Solubility of Compound 1

The solubility of compound 1 has been confirmed in various solvents such as methanol, ethanol, chloroform, acetone, dimethylsulphoxide (DMSO), as well as in acetonitrile.It also having less solubility in water but upon heating it dissolved completely in water.

Solubility of Compound 2

The solubility of compound 2 has been confirmed in various solvents such as methanol, ethanol, chloroform, acetone, dimethylsulphoxide (DMSO), as well as in acetonitrile. It is also soluble in water.

Solubility of Compound 3

The solubility of compound 3 has been confirmed in various solvents such as methanol, ethanol, chloroform, acetone, dimethylsulphoxide (DMSO), as well as in acetonitrile. It is completely soluble in all proportion in mixture of chloroform and methanol. It is also soluble in water upon stirring and also on heating.

UV-vis Spectra of Compounds 1

In the spectra of compounds 1, the product formation was confirmed by formation of new absorption peaks at lower energy (higher wave length) from respective

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reactants. The spectra of compounds 1 are shown in Figure 4.

In the case of compound 1 the reactants absorption maxima lay at 262 and 266 nm while the new absorption peak arises on 276 nm which confirmed the formation of product.

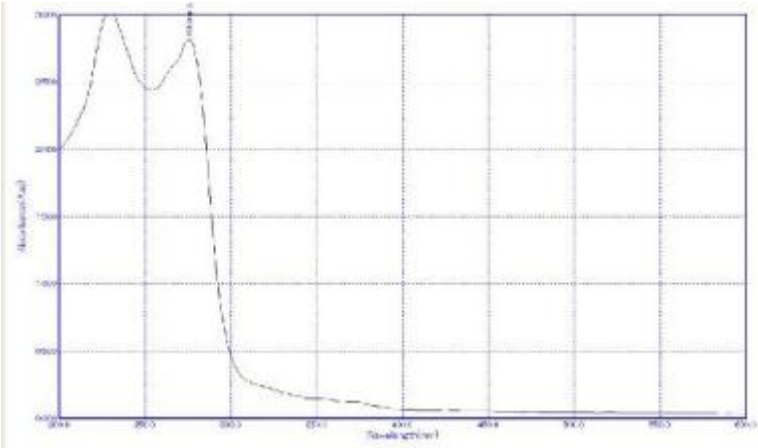


Figure. 3.4: Electronic absorption spectra of compound 1

UV-Vis Spectra of Compounds 2

In the spectra of compounds 2, the product formation was confirmed by formation of new absorption peaks at lower energy (higher wave length) from respective reactants. The spectra of compounds 2 are shown in Figure 5. In the case of compound 2 the reactants absorption maxima lay at 273 and 266 nm while the new absorption peak arises on 278 nm which confirmed the formation of product. After the formation of products these peaks were shifted.

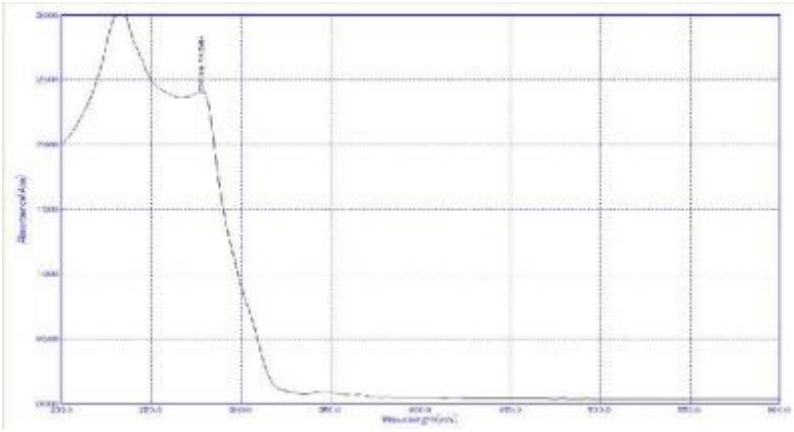


Figure 3.5: Electronic absorption spectra of compound 2

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UV-Vis Spectra of Compounds *3*

In the spectra of compounds *3*, the product formation was confirmed by formation of new absorption peaks at lower energy (higher wave length) from respective reactants. The spectra of compounds *3* are shown in Figure 6.

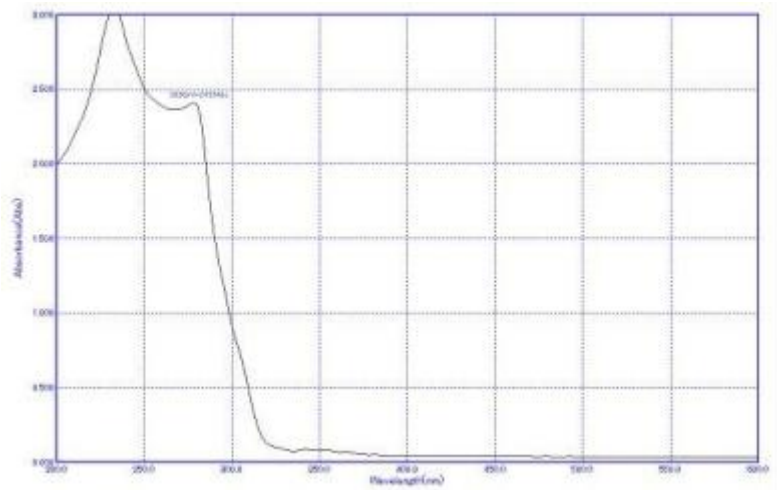


Figure 3.6: Electronic absorption spectra of compound 3

In the case of compound *3* the reactants absorption maxima lay at 275 and 266 nm while the new absorption peak arises on 283 nm which confirmed the formation of product. After the formation of products these peaks were shifted.

Conclusion

In this study, three novel co-crystals of pyridine-2,6-dicarboxylic acid with nicotinamide, 2-amino-6-chlorobenzothiazole, and caffeine were successfully synthesized in a 1:2 molar ratios. The formation of these co-crystals was confirmed through UV–visible spectroscopy and FT-IR analysis, which indicated the presence of strong intermolecular interactions, particularly hydrogen bonding involving carboxylic acid functional groups. The characteristic shifts in the C=O and C–O stretching vibrations further supported the successful formation of new crystalline entities. The physicochemical evaluation, including melting point determination and solubility studies, demonstrated noticeable differences between the co-crystals and their individual components, confirming the development of distinct solid phases. All synthesized co-crystals showed good yield, indicating efficient and reproducible synthesis methods. Overall, the results suggest that pyridine-2,6-dicarboxylic acid is a promising co-former capable of interacting effectively with various bioactive

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molecules. The improved properties observed in the synthesized co-crystals highlight their potential significance in pharmaceutical and material science applications, particularly for enhancing solubility, stability, and overall performance of active compounds. Further studies such as crystallographic analysis and biological evaluation may provide deeper insight into their structural and functional properties.

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