

UNIVERSITY OF BAHRAIN

College of Science



Department of Chemistry

Evaluation of Sensing Efficiency of Selected Organic Acids Derivatives toward Metal Ions in Aqueous Medium

A Thesis Submitted in Partial Fulfilment of the Requirements for the M.Sc. Degree in
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ABSTRACT

Non-covalent organic heterosynthons show enhanced properties in contrast to their individual coformers, rendering them promising for various applications. Specifically, hydrogen-bonded heterosynthons have shown effective coordination behavior with diverse metal ions, hinting at their potential for rapid optical sensing. Their straightforward synthesis and the interactions between the coformers make them good candidates for detection purposes. In this study, five hydrogen-bonded heterosynthons, phthalic-2-amino-3-methylpyridine **1**, phthalic-imidazole **2**, dipicolinic acid-pyrazole **3**, dipicolinic acid-imidazole **4**, and dipicolinic acid-2-amino-3-methylpyridine **5**, of two distinct dicarboxylic acids were synthesized using slow evaporation method and characterized using FTIR, UV-Vis, ¹H-NMR, and PXRD spectroscopic techniques. Physical mixtures with different molar ratios, using the same coformers were prepared through a grinding method. Binary phase diagrams were constructed, and FTIR analysis was performed to propose the type of heterosynthons being formed. The colorimetric detection efficiency of the synthesized heterosynthons towards a wide range of metal ions was examined and compared to that of their individual acids. Interestingly, all heterosynthons demonstrated enhanced colorimetric sensing performance towards metal ions. However, dipicolinic acid-pyrazole **3** and dipicolinic acid-2-amino-3-methylpyridine **5**, did not show any significant color change in the presence of Ni(II) in contrast to their pure acid. This could be enhanced by improving the structural conjugation of the prepared heterosynthons and accordingly intensifying the obtained color and enhancing the naked-eye colorimetric detection results.

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Chapter 1 Introduction

Recently, heavy metal contamination has increased significantly, leading to detrimental consequences on the environment and the public health (Shamim, Zia, Zeeshan, Khan, & Shahid, 2022). Sources of heavy metals range from geological origins to anthropogenic, including industrial, agricultural, and domestic waste (Kobielska, Howarth, Farha, & Nayak, 2018). Water contamination with Fe, Cd, Ni, Cr, Co, Pb, etc. has been extensively investigated in terms of monitoring, sensing, and remediation applications (Bolisetty, Peydayesh, & Mezzenga, 2019; Pradeep & Anshup, 2009; Rudd et al., 2016). Many materials have been utilized for the detection of heavy metals in different environmental matrices (Shahat, Hassan, & Azzazy, 2013; Waheed, Mansha, & Ullah, 2018). Currently, studies have been conducted to synthesize new derivatives, that could interact with metal ions, to enhance the detection performance of their parental molecules. Hydrogen-bonded heterosynthons for instance, have shown successful coordination behaviour with diverse metal ions (Golbedaghi & Fausto, 2018; Therrien, 2020), suggesting the potential for rapid optical sensing results.

Cocrystals and/or molecular salts hereafter, collectively termed as heterosynthons, are crystalline materials of multimolecular components (co-formers) in a specific stoichiometric ratio, linked together via non-covalent interactions (Karimi-Jafari, Padrela, Walker, & Croker, 2018; E. Khan, 2024). Developing heterosynthons is an advanced methodology to enhance the physical properties of the co-formers, including melting point, stability, solubility, conductivity, optical and mechanical properties (Stoler & Warner, 2015). However, the intermolecular forces formed due to the interaction have no obvious impact on the chemical properties. Organic heterosynthons are synthesized using different routes including liquid phase, solid-phase, and vapor-phase methods. The liquid phase methods are advantageous due to their simplicity, cost-effectiveness and reproducibility (Jiang, Zhen, Li, Zhang, & Hu, 2021). The formation of heterosynthons is governed by the difference in pK_a values of the respective co-formers (Cruz-Cabeza, 2012; Islam et al., 2022). However, modifying

the synthesis and crystallization method is a feasible way to produce either molecular salt/cocrystals using the same precursors (Losev & Boldyreva, 2018).

Heterosynthons have been widely used in versatile applications due to their superior luminescent, magnetic, and electrical properties compared to their starting precursors **Figure 1.1** (Cruz-Cabeza, 2012; Islam et al., 2022). Non-covalent supramolecular assemblies are investigated for their sensing ability due to their facile, and short synthetic procedures, that could ease the formation of a chemosensor. Additionally, due to their weak interactions, the material could provide a quick bond formation with target analyte, leading to rapid detectable and measurable signals (Mako, Racicot, & Levine, 2019).

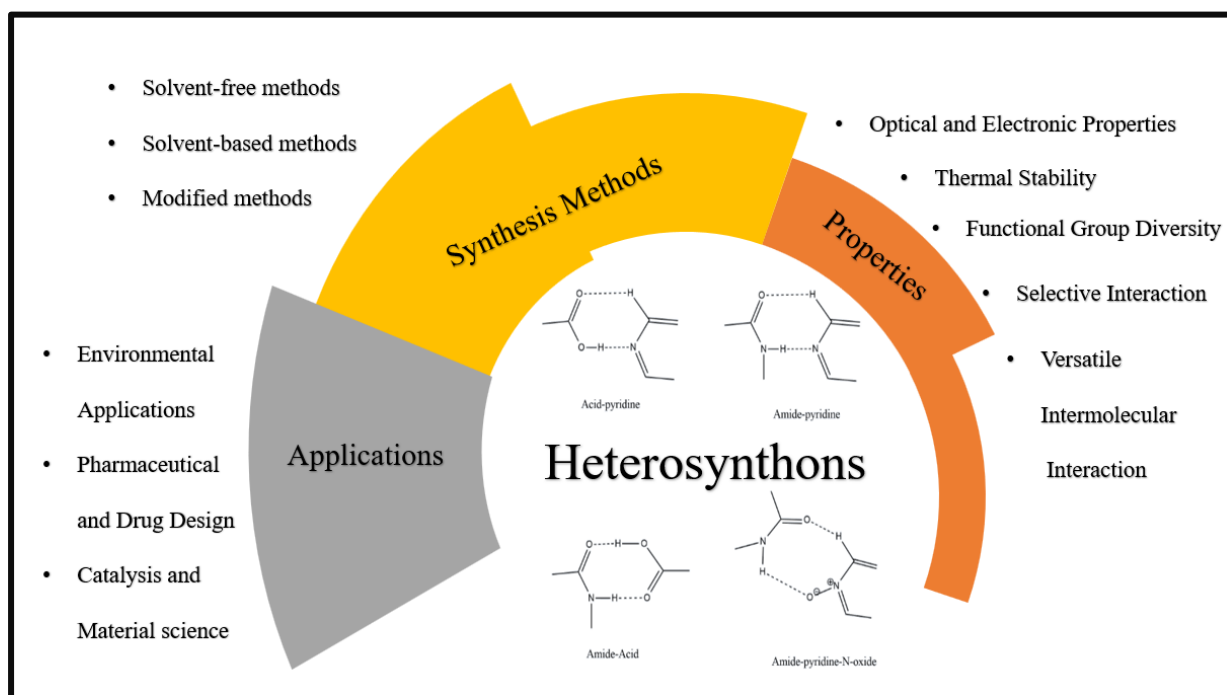


Figure 1.1 Schematic diagram of different heterosynthons and their properties, synthetic routes and applications

1.1 Research Problem

The detection and quantification of metal ions in environmental segments is critical and direly needed for various applications, including environmental monitoring and industrial processes. While organic acid derivatives have shown promise as potential sensing agents, there exists a gap in our understanding of their efficiency, specificity,

and reliability for metal ion detection in aqueous mediums. Few recent investigations have been conducted to implement polycarboxylate cocrystals in sensing applications (Abosedede et al., 2020; J. J. Wang, Zhang, Zhang, Jin, & Gao, 2014). Although, several research groups have discussed the coordination aspects of cocrystals and their ability to form coordination polymers (Garai & Biradha, 2019; Olayemi et al., 2021), still there is a notable literature gap in reporting their metal-ion sensing performance. Evaluation of hydrogen bonded heterosynthons on the optical sensing behaviour of acids is not studied thoroughly in literature. The research problem revolves around the need to systematically evaluate and compare the sensing efficiency of selected organic acid derivatives to address relevant questions.

1.2 Research Question

How does the sensing efficiency of specific organic acid derivatives for the detection of metal ions in aqueous medium improve?

1.3 Research Objectives

- To synthesize several hydrogen-bonded heterosynthons (molecular salts/cocrystals) based on dicarboxylic acids (dipicolinic and PHT) and nitrogen containing bases including 2-amino-3-methylpyridine (Ampy), Imidazole (Imd), and pyrazole (Pz).
- To characterize the synthesized multicomponent material using optical techniques i.e., (UV-Vis, FT-IR, PXRD) and ^1H -NMR spectroscopy.
- To evaluate the efficiency of the parental carboxylic acids and their derivatives as sensors for the detection of metal ions.

1.4 Research Significance

The significance of the research lies in its potential to address pressing environmental, industrial, and health challenges by providing valuable insights into the sensing efficiency of organic acid derivatives for metal ions. The outcomes of the study

may have practical implications for various sectors and contribute to the development of more effective sensing technologies.

1.5 The study's Setting

Dipicolinic and phthalic acids derivatives will be synthesized following the slow evaporation method with appropriate modifications, if needed[18]. Acid and base derivatives will be treated in an appropriate stoichiometric ratio. The material will be processed under ambient conditions followed by slow evaporation to obtain crystalline material. The synthetic route will be accordingly modified based on the obtained results and reflux for some material might be needed. The synthesized material will be characterized using UV-Vis, FTIR, ¹H-NMR spectroscopy, and PXRD analysis. Binary phase diagrams will be constructed as an approach to predict the type of heterosynthons formed. The material will be tested for the detection of metal ions using colorimetric sensing. Organic material as sensors will be added to different metal-ion solutions to test their colorimetric detection efficiency. Different metal ions will be tested during the study, successful sensing results will be documented accordingly. Rapid naked-eye detection is expected for the material however, changes in the absorption spectra will be measured as a governing factor in the detection process.

1.6 Research Terminology

The main research terminologies used in this study are abbreviated for simplicity and are listed in **Table 1.1**.

Table 1.1 list of abbreviation used in this research.

Abbreviation	Word
PHT	phthalic acid
DPA	dipicolinic acid
Ampy	2-Amino-3-methylpyridine

Imd	Imidazole
Pz	Pyrazole
UV-Vis	Ultraviolet-Visible Spectroscopy
FT-IR	Fourier Transform Infrared Spectroscopy
PXRD	Powder X-Ray Diffraction
¹ H-NMR	Proton Nuclear Magnetic Resonance

Chapter 2 Literature Review

2.1 Hydrogen-Bonded Heterosynthons of Polycarboxylic Acids

Recently, derivatization and functionalization of polycarboxylic acids have received considerable interest, for the sake of enhancing their respective properties and to expand the scope of their applications (Ali et al., 2022; Wu, Lin, & Lin, 2018; Yang, Yu, Liu, Chen, & Zhao, 2019). Synthesizing hydrogen-bonded heterosynthons is a simple method aimed at improving the physical properties of the parental coformers (Stoler & Warner, 2015). Polycarboxylic acids are potential candidates for the synthesis of hydrogen bonded homosynthons and heterosynthons due to their available hydrogen donor and acceptor groups (Hutchins, 2018; Lemmerer, Bernstein, & Kahlenberg, 2011). Dicarboxylic acids, for example phthalic or dipicolinic acid form well known cocrystals/proton transfer salts with different physical properties such as solubility (Kundu et al., 2018), stability (Bán, Bombicz, & Madarász, 2009) and optical properties (Dhawan et al., 2024; Feng et al., 2017; Singh & Baruah, 2022).

PHT, also known as 1,2-benzenedicarboxylic acid, consists of a benzene ring attached to two carboxylic acid (-COOH) groups in ortho position with respect to each other. On the other hand, dipicolinic acid, known as 2,6-pyridinedicarboxylic acid, consists of a pyridine ring with two carboxylic acid (-COOH) groups attached to position numbers 2 and 6. Their hydrogen donor groups (-OH) allow for the formation of different types of hydrogen bonded heterosynthons with nitrogen containing molecules (Hutchins, 2018). **Figure 2.1** shows two distinct dicarboxylic acids used along with heterocyclic nitrogen containing bases to synthesize hydrogen bonded heterosynthons.

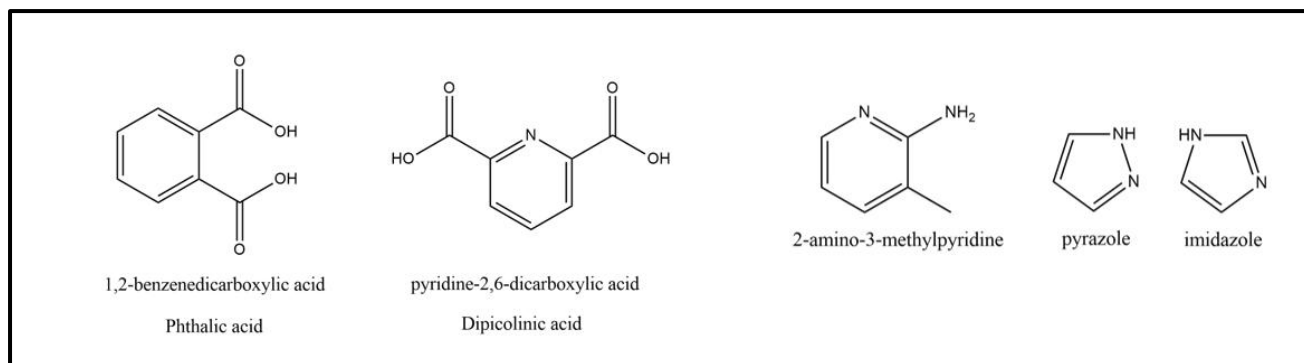


Figure 2.1 Acid and bases used in the preparation of hydrogen bonded heterosynthons.

Generally, hydrogen bonded heterosynthons could be either molecular salts, or cocrystals. Other classifications are also present and are discussed in the following sections. Hydrogen bonded molecular salts are compounds formed by reaction between an acid and a base, due to proton transfer and result in positively and negatively charged species (ions) in the main structure. In contrast, cocrystals are crystalline compounds formed due to the intermolecular non-covalent hydrogen bonding interactions between two or more molecules (Losev & Boldyreva, 2018). General structures of heterosynthons of monocarboxylic acid with nitrogen containing base are shown in **Figure 2.2**. According to literature reports, both types give varied properties in contrast to their individual coformers.

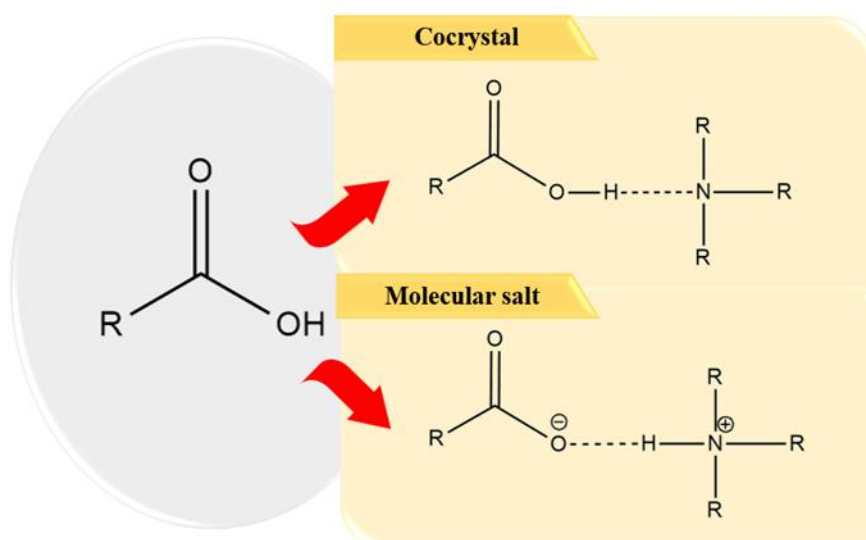


Figure 2.2 Hydrogen bonded heterosynthons of carboxylic acid and nitrogen containing compounds.

The governing factor to determine the type of the heterosynthons is the pK_a rule **Figure 2.3**, which depends on the difference in pK_a values of bases and acids to determine the type of the product formed. It states that if $\Delta pK_a < -1$, a cocrystal is more likely to form but if $\Delta pK_a > 4$, a molecular salt is formed. However, no accurate predictions could be made in the case of ΔpK_a being between $-1 < \Delta pK_a < 4$. Therefore, probabilities suggest the formation of either molecular salts or cocrystals (Cruz-Cabeza, 2012). Alteration in synthesis methods offer the ability to form either products (Losev & Boldyreva, 2018).

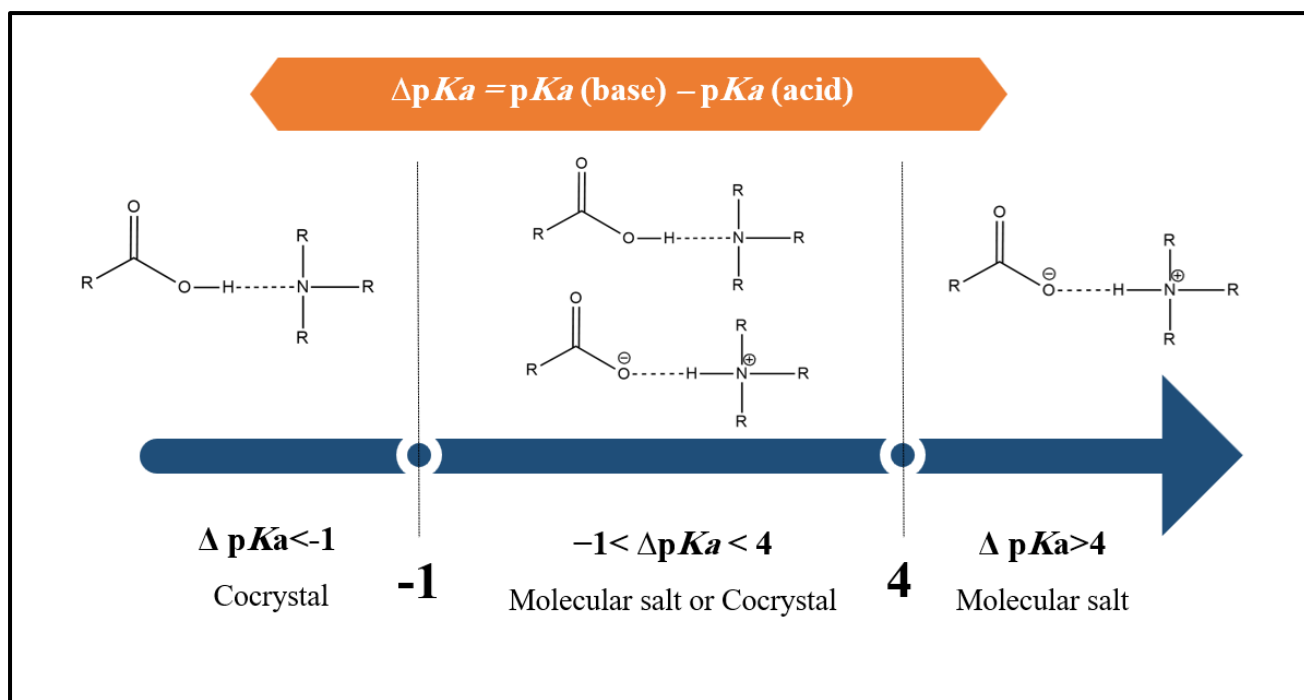


Figure 2.3 The pKa rule for the prediction of salt/cocrystal formation.

2.2 Classification of Hydrogen-Bonded Heterosynthons

Generally, multicomponent solids are classified based on different criteria including number of components (binary/ternary), nature of interactions (hydrogen bonding, ionic, others), and type of components (ions, coformers, solvents). Hydrogen-bonded binary heterosynthons are classified into three main classes and four subclasses. The main classes include salts, cocrystals and solvates, while the subclasses include solvated cocrystal, solvated salt cocrystal, non-solvated salt cocrystal, and solvated salt **Figure 2.4** Proton transfer salts are chemical compounds formed by at least two ions and involve a proton transfer. The cationic ion is derived from solid precursor and the anionic form is derived from either solid/liquid starting material. Hydrogen-bonded cocrystals are crystalline materials formed from solid precursors only. The solvates are chemical compounds formed from solid and liquid starting material with only one coformer and one or two solvents (Aitipamula et al., 2012; Grothe, Meekes, Vlieg, ter Horst, & de Gelder, 2016).

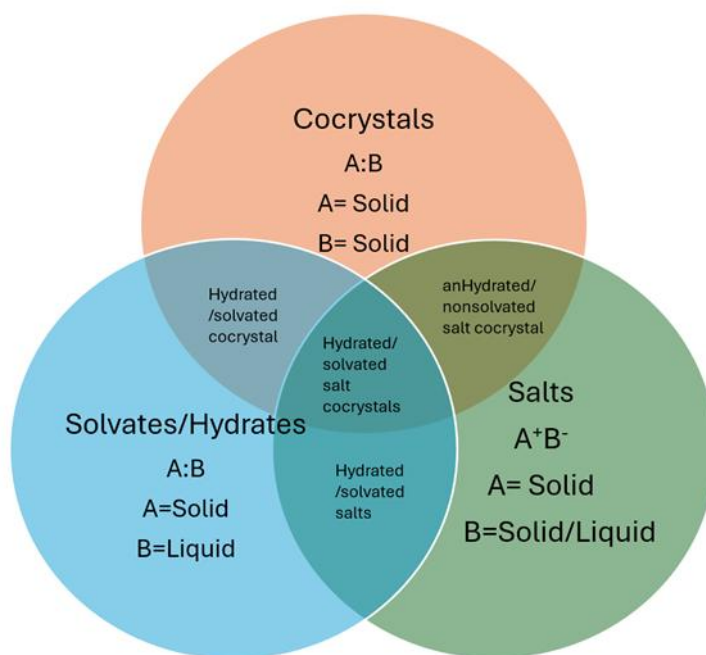


Figure 2.4 Classification of multicomponent solid forms.

Differences in the number and types of components (ions, coformers, and solvents) result in subclasses summarized in **Table 2.1**. All solvated components have at least one type of solvent molecules. Likewise, all salts (solvated/non-solvated) have at least two ionic species and all salt cocrystals have at least one coformer (Grothe et al., 2016).

Table 2.1 Classification of multicomponent solid forms based on the number and type of components.

	Class	Ion	Solvent	Coformer
Main classes	Salt	≥ 2	0	0
	Cocrystal	0	0	≥ 2
	Solvate	0	≥ 1	1
Sub classes	Solvated Salt	≥ 2	≥ 1	0
	Solvated Cocrystal	0	≥ 1	≥ 2
	Solvated salt cocrystal	≥ 2	≥ 1	≥ 1
	Anhydrous salt cocrystal	≥ 2	0	≥ 1

2.3 Synthetic Methods

Cocrystals are synthesized using different synthetic routes including solvent free methods, solvent based methods, and other modified methods such as supercritical fluids, spray drying, freeze drying, and high-pressure homogenization. Below **Figure 2.5** lists the three main synthetic methods with several examples of each type. Mechanochemical methods (grinding) and the slow evaporation methods are well-known for the synthesis of proton transfer salts, cocrystals, coordination complexes and networks (Marivel, Braga, Grepioni, & Lampronti, 2010). A comparison between the grinding methods and the slow evaporation method is summarized in **Table 2.2**

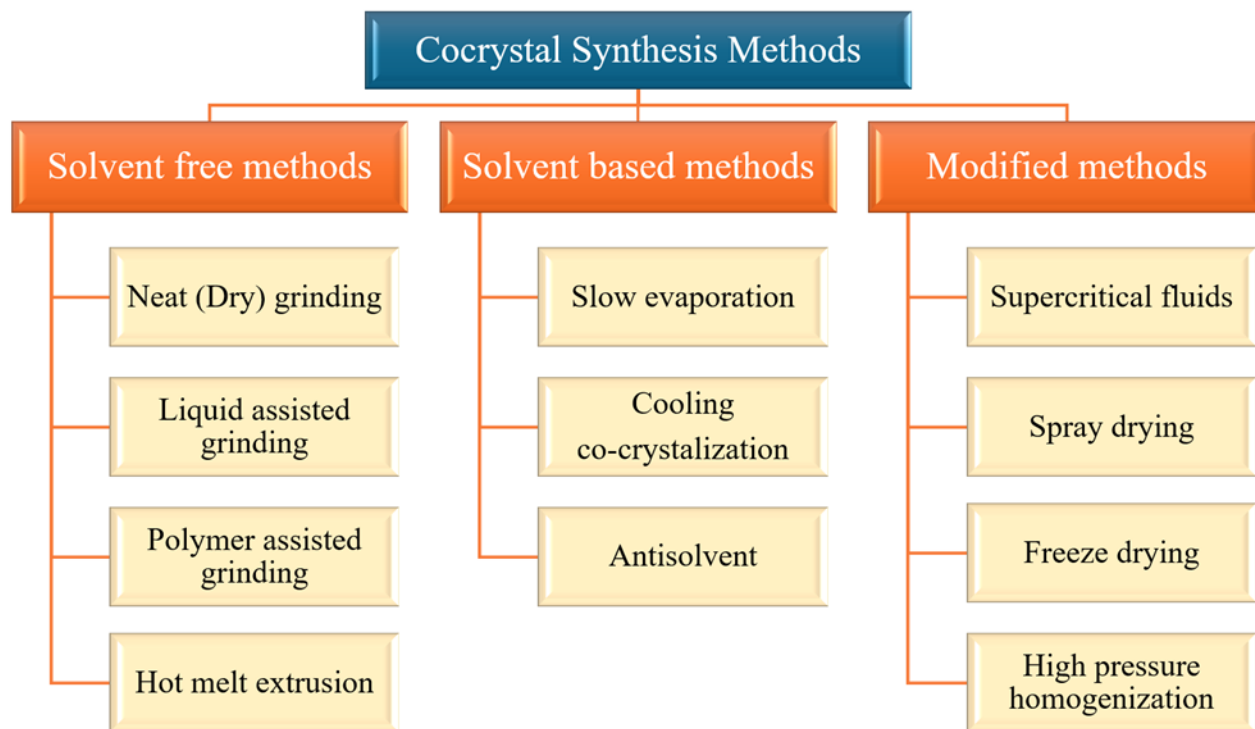


Figure 2.5 A list of cocrystal preparation methods.

Table 2.2 A comparison between grinding and slow evaporation methods.

Method	Principle	Advantages	Disadvantages	Examples ^a	Ref
Grinding	This technique involves mixing different coformers in a specific stoichiometric ratios manually using (pestle and mortar) or mechanically using mill. Neat grinding and liquid assisted grinding are very common.	Environmentally friendly, rapid, less solvent and precursors consumption	Efficiency issues in neat grinding, incomplete cocrystallization, uncontrolled size and morphology, difficult scalability.	IsoPHT-DABCO (Cocrystal) DPA-DABCO (Salt) PHT-dimethylAmpy (salt) PHT-pyr (salt) TerePHT-pyr (cocrystal) PHT-pyrz (cocrystal)	(Marivel et al., 2010; Mohamed, Tocher, Vickers, Karamertzanis, & Price, 2009)
Slow evaporation method	involves evaporating a solvent over a period of time to obtain crystals. The coformers are allowed to react in a specific stoichiometric ratio and then the solvent is subjected to open air slow evaporation.	Cost-effective, efficient, enhanced purity, controlled crystal growth, scalability is possible using modified methods.	Time consuming, solvent consumption, efficiency depends on solubility of coformers in the selected solvent.	PHT-Theophy (cocrystal) DPA-Gly (cocrystal) DPA-Imd (salt)	(Bán et al., 2009; Bankiewicz & Wojtulewski, 2019; Thirumurugan & Anitha, 2018)

^aIsoPHT-DABCO = isoPHT-1,4-diazabicyclo-[2.2.2]-octane; DPA-DABCO= Dipicolinic acid-1,4-diazabicyclo- [2.2.2]-octane; PHT-dimethylAmpy= PHT-4,dimethylaminopyridine; PHT-pyr= PHT-pyridine; TerePHT-pyr= terePHT-pyridine; PHT-pyrz = PHT-pyrazine; PHT-Theophy= PHT- theophylline; DPA-Gly= Dipicolinic acid-Glycine; DPA-Imd= dipicolinic acid-Imidazole in 1:1 mole ratio.

Several DPA and PHT cocrystals/molecular salts are reported in literature using grinding and slow evaporation methods (Bán et al., 2009; Bankiewicz & Wojtulewski, 2019; Marivel et al., 2010; Mohamed et al., 2009; Thirumurugan & Anitha, 2018). The slow evaporation method is advantageous over the grinding technique due to its simplicity as it does not require any well-developed/sophisticated apparatus/equipments. Additionally, it is cost-effective, results in high purity crystals, and has feasible scalability when incorporated with other modified methods. However, it has several limitations including the long crystallization time and the large solvent consumption. Additionally, its efficiency depends on the solubility of the coformers in a particular solvent. For coformers having distinct solubility, the one with the lowest solubility will tend to precipitate first, forming a mixture of solid cocrystal and other components (Article, Sopyan, Kurniawansyah, Cikra, & Farmasi, 2021; Sultan et al., 2022; Walsh et al., 2003). Therefore, choosing coformers with similar solubility could enhance the efficiency of the method, and prevent the formation of a mixture of products. On the other hand, the grinding technique requires mechanical energy to obtain the crystals and could be performed manually or using mill chambers. This method is considered environmentally benign due to less consumption of starting materials and solvents. Although it is simple and fast, it has several drawbacks including the incomplete formation of the cocrystal and the efficiency issues attributed to the manual/mechanical grinding of the coformers. Controlling size and morphology is challenging too (Article et al., 2021). Despite the limitations in the grinding technique, it is still used as an assisted approach to obtain products and determine their phase (eutectic mixture, physical mixture or cocrystal) using phase diagrams (Article et al., 2021). This is discussed further in the characterization section.

2.4 Characterization Techniques

Characterization of hydrogen-bonded heterosynthons is crucial due to its importance in determining/confirming the structure and subsequently helps in predicting the properties and applications. Several techniques are reported in literature for the characterization of

such materials, and are summarized below (Cerreia Vioglio, Chierotti, & Gobetto, 2017; Pindelska, Sokal, & Kolodziejwski, 2017; Reutzel-Edens, 2011):

- X-ray Powder Diffraction (XRPD): XRPD is an important technique to determine the purity and crystallinity of powder products.
- Single Crystal X-ray Diffraction (SCXRD): SCXRD is used to provide information about the bond length between H and other electronegative atoms, angles, intermolecular interactions, and other structural features which helps determining the exact location of the proton.
- Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectroscopy is used to analyze the functional groups present in hydrogen-bonded heterosynthons. It provides information about the presence of O-H, N-H (in case of heterosynthons with nitrogen containing compounds) and protonated C=O group which is important in proposing the type of the corresponding heterosynthons.
- UV-Visible Spectroscopy: UV-Visible is used to study the electronic transitions and optical properties of the heterosynthons.
- Nuclear Magnetic Resonance (specifically ^1H -NMR): this technique is used to determine the molecular structure, presence of multicomponent in a mixture, purity, and insights on the presence of hydrogen bonding intermolecular interactions which results in altered splitting pattern and shifts. It could be used as a quantitative technique for determining the mole ratio between the components.
- Thermal Analysis techniques including differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA): These techniques are used to study the thermal behavior of the heterosynthons and can provide information about melting points, equilibrium phases, thermal stability, and the presence of hydrates or solvates.

In addition to these techniques, phase diagrams have played an important role in preliminary predicting the type of heterosynthons being prepared. The binary/ternary

phase diagrams are graphical representations used to study the relationship between the coformers. The different regions on the phase diagram correspond to different phases that can be obtained with specific composition. These phases can include pure components, cocrystals, salts, eutectic mixtures, and other solid-state forms (Reutzel-Edens, 2011). The binary eutectic mixture demonstrated a distinct V-shaped diagram, which showed a depression in the melting point known as the eutectic temperature. In contrast, a cocrystal (formed from two eutectic mixtures) characterized by a unique W-shaped graph (Solares-Briones et al., 2021). A W-shaped diagram indicates the presence of two eutectic points. Among these eutectic points, the cocrystal phase is identified

Figure 2.6

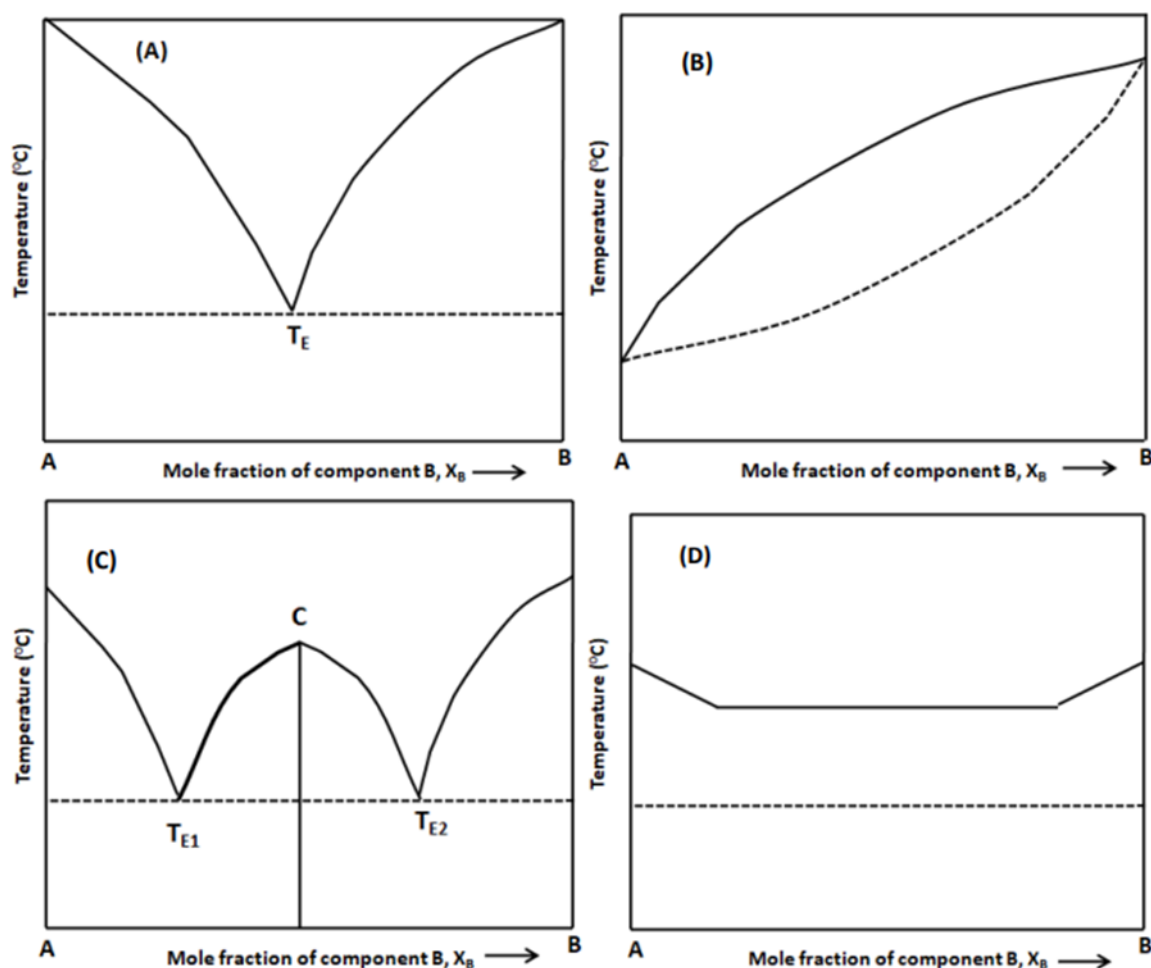


Figure 2.6 Schematic representation of Binary phase diagrams for (A) Eutectic mixture (B) solid solution (C) Cocrystal formation [C—Cocrystal phase] and (D)

Physical mixture [Dotted line-Onset of first component melting and dark line-Melting of the second component] . A and B represent the binary components; TE represent the eutectic temperatures. Reproduced with permission from (Reutzel-Edens, 2011).

2.5 Scope of the Study

The formation of hydrogen-bonded heterosynthons (molecular salts/cocrystals) is influenced by the difference in pK_a values of bases and acids. When $\Delta pK_a < -1$, a cocrystal is more likely to form. Conversely, when $\Delta pK_a > 4$, a molecular salt is formed. However, when the ΔpK_a falls within the range of $-1 < \Delta pK_a < 4$, accurate prediction is not possible. Therefore, either molecular salt or cocrystal may form. To determine the type of product, experimental investigation and characterization techniques are required. **Table 2.3** presents predictive results for heterosynthons based on pK_a values that are documented in the literature. It also includes a comparison of the reported results, highlighting their synthetic method and reaction conditions.

To determine the nature of the product formed in the reaction, the initial ΔpK_a (product) is taken into consideration. Accordingly, PHT-Ampy, DPA-Imd, and DPA-Ampy exhibit ΔpK_a value that suggests the potential formation of molecular salts. On the other hand, PHT-Imd and DPA-Pz exhibit pK_a values below 4, suggesting the possibility of forming heterosynthons. Therefore, constructing a binary phase diagram and measuring FTIR of each physical mixture would be beneficial in predicting the type of the product.

However, it is important to note that these considerations are based on theory and preliminary. Further experiments and characterizations are required to definitively determine the type of product being generated. According to the available literature, altering the synthesis and crystallization methods still allows for the possibility of both salt and cocrystal formation (Losev & Boldyreva, 2018).

Table 2.3 Calculated ΔpK_a of different acids and bases.

Acid	$pK_{a(\text{acid})}^*$	Base	$pK_{a(\text{base})}^{**}$	$\Delta pK_{a(\text{product})}$	Predicted/Reported result	Synthesis method	Reaction condition	Reference
PHT	$pK_{a1}(\text{PHT}) = 2.89$ $pK_{a2}(\text{PHT}) = 5.09$	Ampy	7.24	$\Delta pK_{a1} = 4.35$ $\Delta pK_{a2} = 2.15$	Molecular Salt Reported	Slow evaporation method	1:2 mol ratio, in water, heat, salt is formed by standing overnight.	(Jin, Pan, Hu, & Liang, 2001)
		Imd	6.8	$\Delta pK_{a1} = 3.91$ $\Delta pK_{a2} = 1.7$	Molecular salt/cocrystal/Not reported	-	-	-
DPA	$pK_{a1}(\text{DPA}) = 2.16$ $pK_{a2}(\text{DPA}) = 4.76$	Pz	2.52	$\Delta pK_{a1} = 0.36$ $\Delta pK_{a2} = -2.24$	Molecular salt/cocrystal/Not reported	-	-	-
		Imd	6.8	$\Delta pK_{a1} = 4.64$ $\Delta pK_{a2} = 2.04$	Molecular salt Reported	Slow evaporation method	Reaction 1: 1:1 mol ratio in water, heating for 2 hrs, salt is formed after evaporation of solvent.	(Thirumurugan & Anitha, 2018)
						Cooling crystallization	Reaction 2: 1:2 mole ratio in THF, heat, solution is cooled with water, salt is collected.	(Abdolmaleki, Ghadermazi, Ashengroph, Saffari, & Sabzkohi, 2018)
		Ampy	7.24	$\Delta pK_{a1} = 5.08$ $\Delta pK_{a2} = 2.48$	Molecular salt Reported		1:1 mole ratio, heat and reflux for 2 hrs, salt powder is formed.	(İlkimen, Salün, Gülbandılar, & Sarı, 2022)

* pK_a (PHT) $pK_{a(\text{PHT})}$ and $pK_{a(\text{DPA})}$ are reported in literature in references(Tummanapelli & Vasudevan, 2015), and (Packiaraj, Pushpaveni, Senthil, Govindarajan, & Rawson, 2015) respectively.

** $pK_{a(\text{bases})}$ are obtained from (Hanif et al., 2020; Martins et al., 2019; St. Jean & Fotsch, 2012).

2.6 Colorimetric Detection of Metal Ions Using Dicarboxylic Acids

The colorimetric detection of metal ions using N-containing molecules (Alorabi, Abdelbaset, & Zabin, 2020; Mergu & Gupta, 2015; Udhayakumari & Velmathi, 2014) and functionalized carboxylic acid derivatives (Buduru & Reddy B.C, 2016; Mondal & Yarger, 2019; Su et al., 2013) have been well-documented in the existing literature. However, the colorimetric detection of metal ions using PHT and DPA has not been thoroughly reported in literature yet. Besides, the coordination behavior of such compounds is prominent and well documented. Based on this fact and drawing upon the principle of coordination chemistry, the possibility of employing these compounds for colorimetric metal ion detection is proposed. Below, **Table 2.4** summarizes the coordination behavior of DPA, PHT, and several nitrogen containing compounds towards metal ions.

Table 2.4 Coordination behavior of dicarboxylic acids and nitrogen containing compounds.

Chemical compound	Coordinated metal	References
PHT	Mn(II), Co(II), Co(III) Ni(II), Cu(II), Zn(II), Cd(II), Cr(III), Cr(VI), Al(III), Au(I), Hg(II), Pb(II), Fe(III), and Ag(I)	(Svetlana G Baca et al., 2005; Svetlana G. Baca et al., 2004; Cheng, Sun, Zhang, Zhou, & Xin, 2021; Gao et al., 2017; Guo, Shu, Chuang, & Hong, 2021; Higashi, Hori, & Tsuchiya, 1967; Lövgren, 1991; Marandi, Ghorbanloo, & Soudi, 2007; Sun et al., 2011; Tong et al., 2020)
DPA	Co(II), Ni(II), Zn(II), and Cd(II), Pd(II), V(IV), Ca(II), Mn(II), Cu(II), Ga(II), Ru(II), Pt(II), Fe(II) and Fe(III), Ag(I), U(VI) and Cr(III)	(Chessa et al., 1991a, 1991b; Çolak, Çolak, Yeşilel, & Büyükgüngör, 2009; D'Ascenzo, Marino, Sabbatini, & Bica, 1978; Ghadermazi et al., 2015; Hakimi, Kukovec, Rezvaninezhad, Schuh, & Mohr, 2011; Mirzaei et al., 2014; Vargová, Almási, Gyepes, & Vetráková, 2019; J. Wang, de Kool, & Velders, 2015; Xie, Jia, Zhu, Shi, & Zhang, 2015; Xu, Tian, Teat, & Rao, 2013)

Ampy	Ag(I), Cu(II), and Co(II)	(Ahmadi, Safari, Khavasi, & Amani, 2011; Hanif et al., 2023)
Imd	Fe(III), Co(II), Ni(II), Zn(II), and Cd(II), Ag(I), Mn(II)	(Bauman Jr & Wang, 1964; M. S. Khan et al., 2021; H.-B. Zhang, Zhang, Chai, Tang, & Zhang, 2020)
Pz	Cu(II), Ni(II), Co(II), Fe(II) and Fe(III)	(Reedijk, 1969; Y.-P. Zhang et al., 2021)

PHT and DPA form well-known coordination complexes with diverse metal ions as outlined in **Table 2.4**, due to the availability of carboxylic acid groups. Similarly, nitrogen containing aromatic compounds such as Ampy, Imd, and Pz showed good coordination action with few transition metals due to the presence of the ligating nitrogen group. Based on this, the developing of hydrogen-bonded heterosynthons using these materials was proposed as an efficient approach to enhance the coordination behavior of the parental molecules and accordingly, increasing the efficiency towards the colorimetric detection of heavy metals.

Chapter 3 Research Methodology

3.1 Materials and Methods

All reagents and solvents are commercially available (purchased from Fluka, Sigma Aldrich, Emplura, and BDH chemicals Ltd), and were used without further purification. The chemicals used are PHT, DPA, absolute methanol, absolute ethanol, deionized water, distilled water, Ampy, Pz, and Imd. The metal salts used are iron(III) chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), nickel(II) chloride hexahydrate ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$), copper(II) chloride dihydrate ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$), cobalt(II) sulphate heptahydrate ($\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$), zinc(II) acetate ($\text{Zn}(\text{CH}_3\text{COO})_2$), silver nitrate (AgNO_3), Aluminum nitrate ($\text{Al}(\text{NO}_3)_3$), chromium(III) nitrate nonahydrate ($\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$), lead chloride (PbCl_2), and cadmium chloride (CdCl_2).

Round-bottom flasks, beakers, mortar and pestle, hot plates with stirrer and other glassware were used. BUCHI Rotary evaporator (B-480) with water bath was used to evaporate volatile solvents. Melting points were measured using FALC instrument and are uncorrected. UV-Vis spectra were recorded on ORION AQUAMATE 8000 spectrophotometer. Fourier transform Infrared (FT-IR) spectra were measured as KBr disc using SHIMADZU IR PRESTIGE 21 in the range of $400\text{-}4000\text{ cm}^{-1}$. Powder X-ray diffractograms were obtained using Phillips X'pert Pro PXRD, and ^1H -NMR spectra were measured using Bruker AVANCE spectrophotometer at 400 MHz in DMSO-d_6 .

General procedures were followed with minor modifications to synthesize PHT and DPA derivatives (İlkitmen et al., 2022; Islam et al., 2022; E. Khan, 2024; Ullah et al., 2023).

3.2 Synthesis of PHT derivatives

3.2.1 Synthesis of PHT-Ampy 1

Following the synthetic method reported in literature (Jin et al., 2001). PHT (2.003 g, 1.0 mmol) was dissolved in absolute methanol (25 mL) in a round bottom flask and stirred for few minutes to ensure complete dissolution. To the same flask, Ampy (2.4 mL, 2.0 mmol) was added, immediately white precipitates were formed. The precipitate was filtered and dried and then redissolved in a small amount of ethanol. The solution was kept undisturbed for slow evaporation under aerobic conditions. Few hours later, white crystalline material started to appear in the solution similar as the procedure reported (Jin et al., 2001). The flask was left for several days to ensure complete evaporation. The collected product was separated and dried in a vacuum desiccator. The melting point was measured, and the percentage yield was calculated. The compound was characterized using FT-IR, UV-Vis, PXRD and $^1\text{H-NMR}$.

Yield = 3.9 g (93.5%); m.p = 174-176°C; FT-IR, KBr disc, $\nu(\text{cm}^{-1})$ = 3348, 3227, 3149, 3069, 2972, 2730, 1658, 1544, 1392, 1358, 1309, 1265, 1038, 996, 878, 825, 787, 751, 588, 429; UV-Vis data (λ) = 233, 288 nm; PXRD 2θ (deg) = 11.24, 13.16, 14.6, 16.29, 18.76, 25.77, 26.48, 28.08, 32.72, 35.36, 41.2; $^1\text{H-NMR}(\text{DMSO-d}_6)$ $\delta(\text{ppm})$ = 2.49 s, 6.90 br, 7.00 q, 7.80 q, 8.20 q, 8.40 q.

3.2.2 Synthesis of PHT-Imd 2

PHT (2.00 g, 1.0 mmol) was dissolved in absolute methanol (10 mL) in a round bottom flask. In a separate flask, solid Imd (1.64 g, 2.0 mmol) was dissolved in methanol (10 mL) and clear solution was obtained. The prepared Imd solution was added to the PHT solution while stirring. The reaction was left stirring to continue overnight (12 h). The volume of reaction mixture was reduced to one-third using rotatory evaporator and the concentrated solution was allowed for slow evaporation. White crystals were grown after few days, they were collected from the mother liquor. The melting point was

measured, the percent yield was calculated, crystals were characterized using FT-IR, UV-Vis, PXRD, and NMR spectroscopy.

Yield = 2.31 g (63.5%); m.p = 101-103°C; FT-IR, KBr disc, $\nu(\text{cm}^{-1})$ = 3392, 3141, 3106, 2745, 1604, 1569, 1402, 1368, 1326, 1023, 966, 884, 793, 763, 698, 552, 427; UV-Vis data (λ) = 234, 285 nm; PXRD 2θ (deg) = 15.12, 19.24, 20.44, 22.48, 24.68, 27.88, 36.9, 37.8; $^1\text{H-NMR}(\text{DMSO-d}_6)$ $\delta(\text{ppm})$ = 8.20, 8.40, 7.30 s, 7.50 q, 8.00 q, 8.20 s.

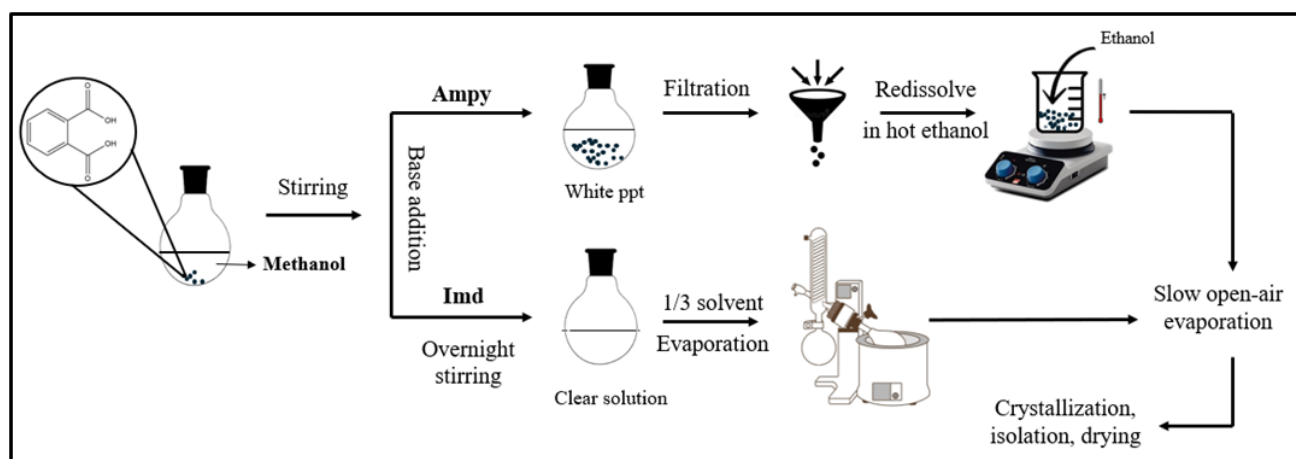


Figure 3.1 Heterosynthons containing PHT synthetic scheme.

3.3 Synthesis of DPA derivatives

3.3.1 Synthesis of DPA-Pz 3

General procedures were followed to synthesize the product. DPA (2.001 g, 1.0 mmol) was prepared in absolute ethanol (30 mL) in a round bottom flask. In a separate flask, Pz (1.63 g, 2.0 mmol) was dissolved in ethanol (10 mL) and a clear solution was obtained. The prepared Pz solution was added to the DPA solution, and the reaction was heated to reflux for 9 hours before cooling to room temperature and then evaporation under vacuum was performed to afford the desired product as a white solid. The obtained product was weighed, and percent yield was calculated. Melting point was measured and FT-IR, UV-Vis, PXRD, and $^1\text{H-NMR}$ spectra were recorded.

Yield = 1.318 g (32.9%), m.p = 236-239°C. FT-IR, KBr disc, $\nu(\text{cm}^{-1})$ = 3437, 3278, 3139, 2993, 1728, 1631, 1573, 1427, 1383, 1301, 1243, 1038, 996, 886, 774, 755, 691,

645, 505. UV-Vis data (λ)= 222, 271 nm; PXRD 2θ (deg) = 11.24, 11.6, 14.2, 16.2, 17.7, 17.8, 18.4, 20.5, 22.5, 23.4, 24.1, 26.5, 27.0, 36.0, 37.3, 39.5; $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) = 6.20 t, 7.50 s, 8.00 q, 8.20 t.

3.3.2 Synthesis of DPA-Imd 4

Minor modifications in the synthetic methods reported in (Abdolmaleki et al., 2018; Thirumurugan & Anitha, 2018) were done to synthesize the desired product. DPA (2.00 g, 1.0 mmol) was prepared in absolute ethanol (20 mL) in a round bottom flask. In a separate flask, Imd (1.64 g, 2.0 mmol) was dissolved in ethanol (10 mL) and a clear solution was obtained. The prepared Imd solution was slowly added to the DPA solution, and the reaction mixture was refluxed. After 2-3 h reflux, white precipitates were obtained. The reaction was allowed to continue under reflux condition for 9 h. Gelatinous precipitates were filtered, dried, and crystallized in deionized water. White crystalline material was obtained. The percent yield was calculated, melting point was measured and FT-IR, UV-Vis, PXRD, and $^1\text{H-NMR}$ spectra were obtained. The structure and molar ratio of synthons in the product was deduced from the obtained consistent spectroscopic data.

Yield = 3.287 g (90%), m.p = 223-225°C. FT-IR, KBr disc, $\nu(\text{cm}^{-1})$ = 3435, 3147, 3092, 2745, 2360, 1734, 1588, 1458, 1425, 1379, 1309, 1294, 1195, 1047, 995, 905, 875, 852, 755, 691, 634, 543, 484; UV-Vis data (λ)= 220, 270 nm; PXRD 2θ (deg) = 19.00, 21.46, 29.36, 30.32, 37.72, 39.94, 52.12; $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) = 7.20 t, 8.00 s, 8.10 q, 8.20 t.

3.3.3 Synthesis of DPA-Ampy 5

Appropriate changes in the synthesis method reported in (İlkimen et al., 2022) were done to obtain the product. Solution of DPA (2.00 g, 1.0 mmol) was prepared in absolute ethanol (25 mL) in a round bottom flask. To the same flask, Ampy (2.4 mL, 2.0 mmol) was added, and the reaction mixture was refluxed for 2-3 h. White precipitates were formed in the reaction mixture. The reaction was continued for 9 h to complete. The

white gelatinous precipitate was filtered, dried, and redissolved in deionized water to get crystals. The obtained product was weighed, and studied as discussed above for compounds **1-4**.

Yield = 3.87 g (84.4%), m.p = 148-150°C. FT-IR, KBr disc, $\nu(\text{cm}^{-1})$ = 3369, 3247, 3103, 2969, 2709, 2419, 2360, 1939, 1736, 1681, 1652, 1633, 1559, 1542, 1472, 1419, 1365, 1332, 1254, 1170, 1002, 966, 894, 878, 797, 780, 744, 689, 592, 495, 421; UV-Vis data (λ_{max}) = 225, 295 nm (br); PXRD 2θ (deg) = 12.4, 13.0, 18.8, 24.6, 31.1, 37.2, 38.0; $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) = 2.90 s, 6.90 br, 7.70 t, 8.20 d, 8.50 q, 8.60 d

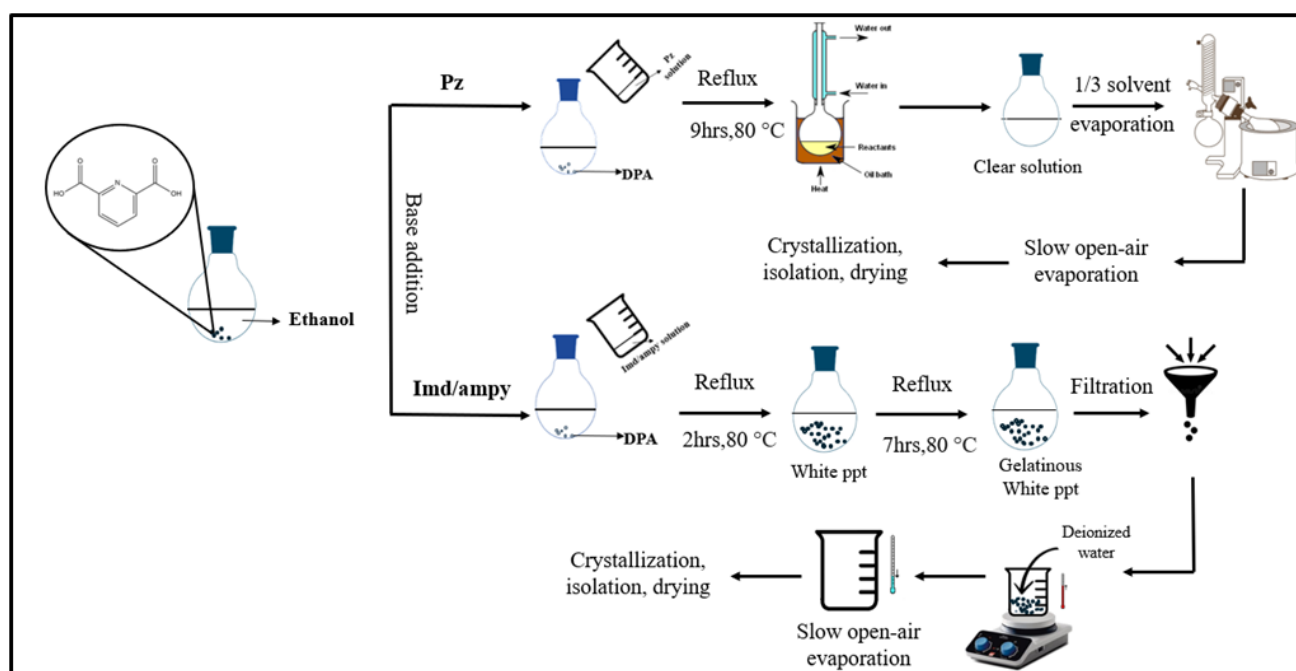


Figure 3.2 Synthetic procedure of heterosynthons containing DPA.

3.4 Melting point Determination and Binary Phase Diagrams

The physical mixtures of the coformers were prepared in different acid:base mole ratio (9:1-1:9) and manually grinded using a mortar and pestle for 10 min as reported in (Islam et al., 2022). The melting point of the mixture was determined using a thermal apparatus (FALC instrument). The melting point of the starting materials, and the heterosynthons prepared using slow evaporation method were measured in capillary tubes.

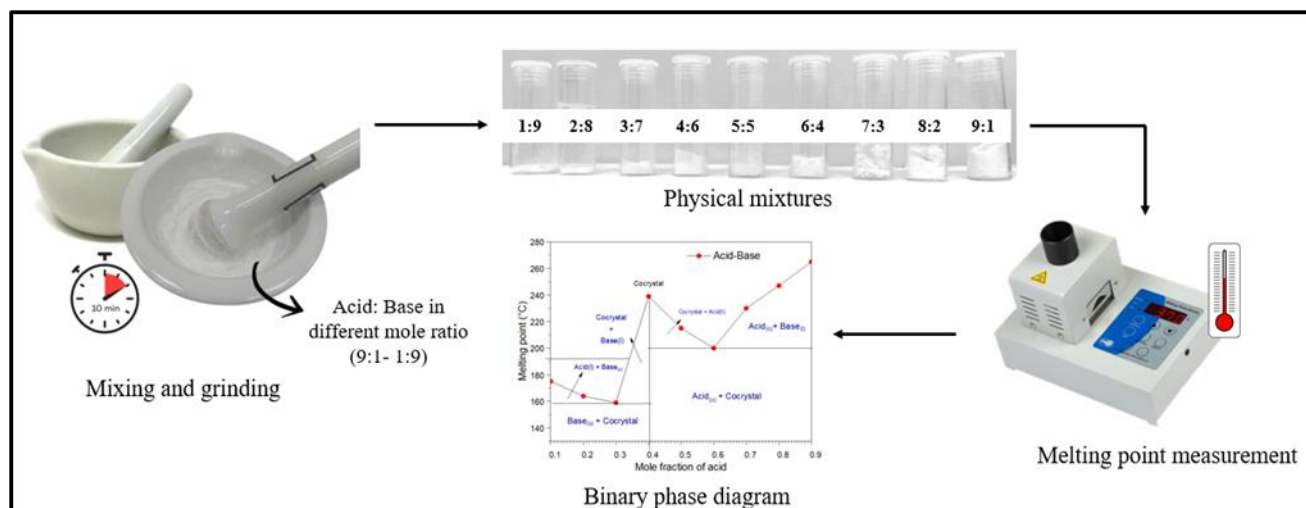


Figure 3.3 Preparation of physical mixtures and construction of binary phase diagrams.

3.5 Spectroscopic Characterization of Heterosynthons

Following the general procedures of the spectroscopic analysis reported in (Islam et al., 2022), FT-IR, $^1\text{H-NMR}$, and PXRD were measured.

3.5.1 FT-IR Spectroscopy

The FT-IR analysis was performed on SHIMADZU IR PRESTIGE 21 spectrophotometer. The spectra were measured using KBr disc in the range of 400-4000 cm^{-1} with accumulation of 90 scans.

3.5.2 $^1\text{H-NMR}$ Measurements

The $^1\text{H-NMR}$ spectra of the products were measured in (DMSO-d_6) solvent using Bruker AVANCE spectrophotometer at 400 MHz.

3.5.3 PXRD Analysis

The Powder X-ray diffractograms (PXRD) of the prepared products were obtained using Phillips X'pert Pro powder X-ray diffractometer, with $\text{Cu-K}\alpha$ radiation source ($\lambda = 0.15431 \text{ nm}$). The PXRD of starting acids and Imd were analysed for comparison purposes.

3.5.4 UV-Vis Spectroscopic Studies

Absorption spectra of all starting materials and products were recorded using ORION AQUAMATE 8000 spectrophotometer in quartz cuvette cells over the wavelength range of 200-800 nm using the method documented in (Alorabi et al., 2020). Stock solutions of 100 ppm were prepared by taking 10 mg of the sample in 100 mL ethanol, then 1.0 mL was transferred to a 10 mL volumetric flask and 10 ppm working solution was prepared. The absorption spectra were collected, and the wavelength was determined (λ_{max}).

3.6 Colorimetric Sensing of Metal Ions

Stock solutions containing different transition metals (Co(II), Ni(II), Cu(II), Pb(II), Zn(II), Cd(II), Ag(I), Fe(III), Al(III), and Cr(III)) of concentration 1×10^{-2} M in 100 mL deionized water were prepared. Likewise, stock solutions of compounds **1-5** with concentration of 1×10^{-2} M in 100 mL deionized water were also prepared. Following the literature procedure (Alorabi et al., 2020) for the colorimetric detection experiments, a fixed volume of 1.0 mL of metal solution was added to 2.0 mL of compounds **1-5** individually in a test tube. The change in color was observed and recorded. The same procedure was adopted for starting material, acids to get easy comparison between the material.

The UV-Vis experiments were conducted to observe the absorption behavior of compounds **1-5**. In a similar manner as discussed above, 1.0 mL of metal salt solution was added to 2.0 mL solution of the respective compound, **1-5**, the solutions were mixed, and 1 mL was taken to prepare an aqueous stock solution of each with the concentration of 1×10^{-4} M in 100 mL flask. The stock solution was diluted to 1×10^{-5} M to measure the absorption spectrum using quartz cuvette cell with 1 cm path length.

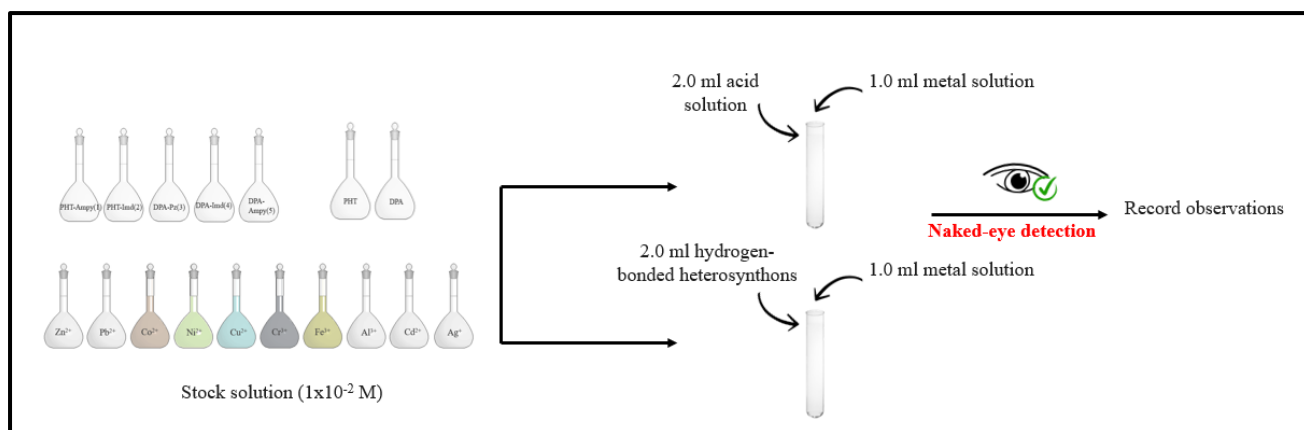


Figure 3.4 Procedure of the colorimetric sensing of metal ions

Chapter 4 Results and Discussion

4.1 Synthesis of PHT and DPA derivatives

The heterosynthons were prepared for a mixture of acid/base in a 1:2 stoichiometric ratio, respectively. Compounds **1,3,4** and **5** were obtained as solid precipitates, and were separated through filtration, collected and purified through recrystallization. However, in compound **2** white crystals were obtained directly after allowing the clear solution to evaporate in air for several days. For compounds **1,3,4**, and **5**, a solubility test was performed to choose a suitable solvent with high solubility and good recovery for recrystallization. A small amount of hot ethanol was chosen to redissolve compound **1**, and deionized water was chosen to recrystallize compounds **3**, **4**, and **5** under slight heat. The amount of deionized water was minimized as much as possible since water is slowly evaporating. Other solvents such as methanol, and acetonitrile were tested to recrystallize **3**, **4**, and **5** but the samples were insoluble in these solvents.

A rotatory evaporator was used to speed up the evaporation process. Solutions obtained in reaction **2** and **3** were evaporated to 1/3 of its original volume to obtain the product. A slow open-air crystallization was preferred over ice-assisted crystallization to obtain fine and good quality crystals and to prevent trapping of contaminants in the desired product.

White crystals were isolated for compound **2**, however, other compounds were collected as crystalline material, or gelatinous precipitates as isolating a single crystal was challenging **Figure 4.1** and **Figure 4.2**.

The compounds with dipicolinic acid were prepared under reflux conditions to facilitate the dissolution of the acid in ethanol. PHT containing synthons were easily prepared at room temperature under mild stirring conditions.

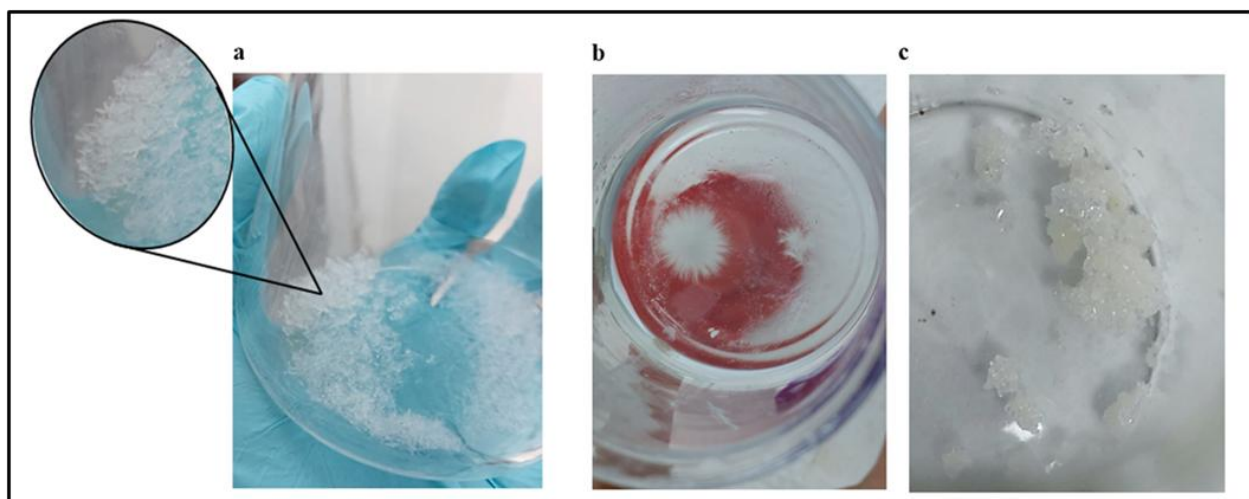


Figure 4.1 Products obtained of a) PHT-Ampy **1**, and c) PHT-Imd **2**, b) Crystal growth of PHT-Imd **2**.

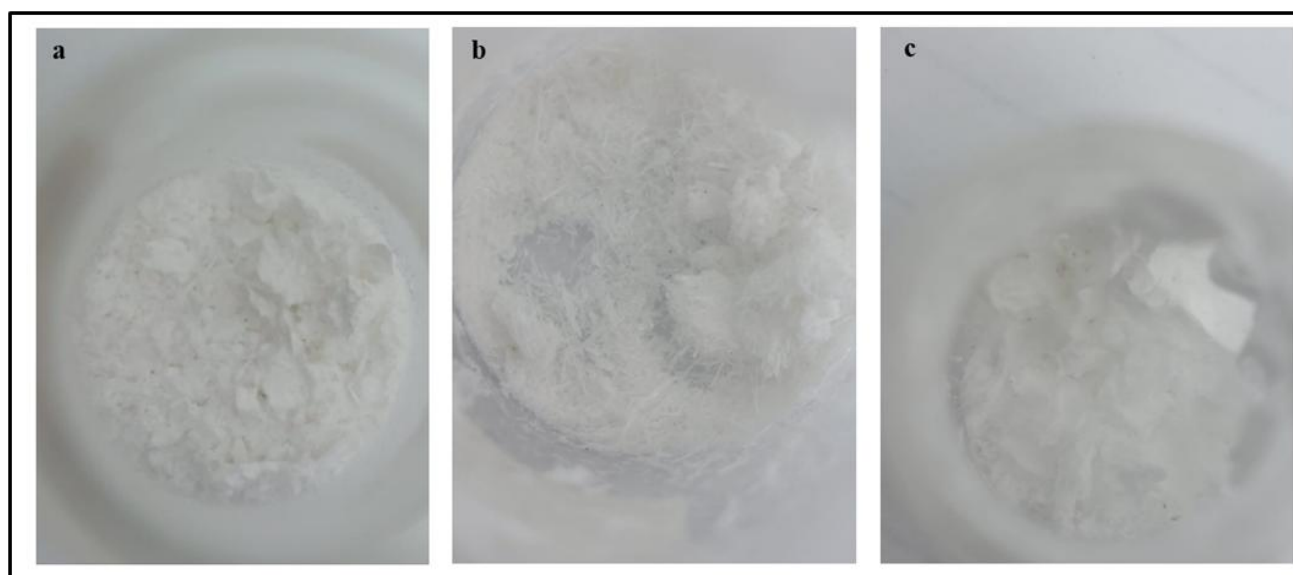


Figure 4.2 Products obtained of a) DPA-Pz **3**, b) DPA-Imd **4**, and c) DPA-Ampy **5**.

4.2 Melting point Determination and Binary Phase Diagrams

Measuring melting points is a simple, fast, and easy technique to preliminarily predict the formation of a new product, and to have an insight into the purity of a prepared compound. Below, **Table 4.1** provides a comparison between the melting points of the products and their respective starting precursors.

Table 4.1: Melting points (°C) of products, and their starting precursors.

Acid	Base	Product code/No.	Acid	Base	Product
PHT	Ampy	PHT-Ampy 1	210	29-32	171-174
	Imd	PHT-Imd 2		86-90	101-103
DPA	Pz	DPA-Pz 3	247-262	67-70	236-239
	Imd	DPA-Imd 4		86-90	223-225
	Ampy	DPA-Ampy 5		29-32	148-150

According to the results obtained, all compounds have sharp melting points indicating a pure crystalline product. All Compounds have a significant change in their melting points compared to their starting material, thus the formation of a new product is preliminarily confirmed. Other spectroscopic characterization techniques are also crucial to determine the successful formation of the product, detailed below.

The binary phase diagrams were constructed to find the optimal mole ratio for the synthesis of the heterosynthons and to predict the phase transformation and the type of the material formed, **Figure 4.3**. The melting point of the cocrystal can also be obtained from the diagram. Compounds **2**, **3** and **4** exhibited a W-shaped phase diagram, indicating the possible formation of a cocrystal. Compound **1** showed an irregular shape, suggesting the formation of a salt. Compound **5** showed a semi-W-shaped phase diagram, therefore further spectroscopic analysis is necessary to confirm the formation of the cocrystal or salt.

The optimal molar ratios of compounds **2**, **3**, **4**, and **5** were extracted from the graph, the optimal molar ratio of compound **2** and **4** was found to be 1:1, for compounds **3** and **5** it was determined to be 4:6 and 6:4; or 1:1.5 and 1.5:1; or 2:3 and 3:2, respectively. Obtaining the optimal mole ratio from the graph of compound **1** is somehow difficult due to the obtained shape. It is worth noting that the materials were synthesized in 1:1 mole ratio but the reactions were unsuccessful. According to the W-

shaped graphs, there is still a possibility to synthesize cocrystals in different mole ratios as the W-shaped diagrams showed different equilibrium phases of the product with acid, and the respective base derivative.

The melting point of cocrystals in the optimal mole ratio can be obtained from the graph as shown in **Figure 4.3**. The melting point range of cocrystal in different mole ratio can also be predicted, but it is not a viable approach as this technique is experimentally inaccurate. All compounds except compound **1**, showed a large difference in melting points measured compared to melting point predicted at molar ratios of 1:2, which might be attributed to the uncertainty of the measurement. However, melting points of **2**, **3**, and **4** obtained from slow evaporation technique in 1:2 mole ratio was found in cocrystal and liquid base region, which made it possible to have the expected product with equilibrium with the starting material. Therefore, wet products gave different melting points compared to the completely dried product. Unexpectedly, compound **5** showed melting point equals to 148-150°C, which is higher than the melting point being predicted from the graph. This also might be due to the inaccurate melting point measurements.

Synthesizing a cocrystal in equilibrium with liquid is advantageous over synthesizing a cocrystal in equilibrium with solids, due to the ease and efficiency of isolating crystals from liquid phase compared to the purification process required for cocrystal in equilibrium with solids.

The eutectic points, which are the lowest melting points can the mixture exhibit, were also obtained for compounds **2**, **3**, **4** and **5** from the graph. The eutectic points of compound **2** were found to be 59 and 116°C. The compound **3** showed eutectic points at 159 and 200°C, compound **4** at 172 and 228°C and **5** at 106 and 202°C. However, the value 202°C is higher than the melting point of the respective cocrystal at the optimal mole ratio, therefore it is not accepted, and errors may probably be attributed to the inaccurate measurement.

Binary Phase Diagrams

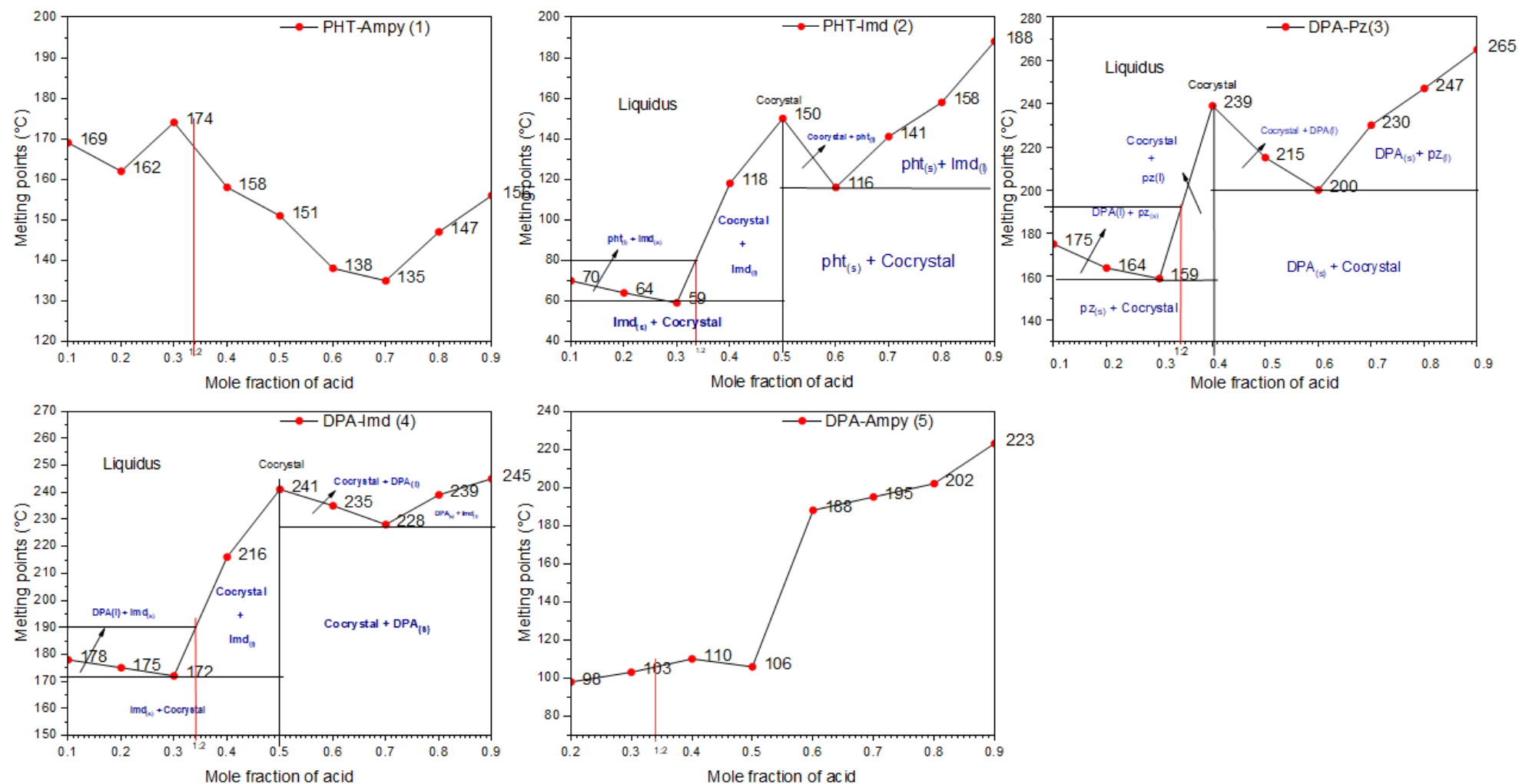


Figure 4.3 Binary phase diagrams of the compounds.

A spectroscopic FT-IR analysis was conducted to determine and characterize the type of interaction between the coformers. The physical mixtures, with different molar ratios, were prepared and subjected to analysis to determine the presence or absence of distinct O-H and N-H bands, as well as the protonated C=O group, which normally exists in cocrystals. According to the literature reports, cocrystals have both N-H and O-H bands in addition to protonated C=O group due to the formation of non-covalent hydrogen bond interactions. However, salts showed N-H bands and deprotonated C=O, indicating a proton transfer between the coformers (da Silva, Guimarães, Ribeiro, & Martins, 2016; Islam et al., 2022).

According to the obtained spectrum, PHT-Imd **2** showed overlapped N-H and O-H bands at the range of 3000-3700 cm^{-1} , the protonated C=O group was insignificant due to the broadness of the spectrum however, it was proposed as cocrystal due to the presence of both N-H and O-H bands. In DPA-Pz **3**, a band at approximately 3100 cm^{-1} started to appear with the O-H band at 4:6 mole ratio, also it showed protonated C=O group at $<1700 \text{ cm}^{-1}$, suggesting the formation of a cocrystal. In DPA-Imd **4** spectra, N-H, O-H and protonated C=O ($<1730 \text{ cm}^{-1}$) bands are noticeable. The difference in pKa rule suggests the formation of a salt. Therefore, salt cocrystal was proposed as the protonated carbonyl group was observed at higher frequency compared to carboxylic acids. Single crystal XRD analysis is required to confirm the structure, however good quality was not obtained. The DPA-Ampy **5** showed overlapped peaks in the range of 2800-3700 cm^{-1} , making the identification of the O-H band cumbersome. Consequently, it was difficult to assume the formation of a salt based solely on the insignificant O-H band. This is because the $\nu(\text{C}=\text{O})$ was found at 1700-1760 cm^{-1} , which is higher than deprotonated $\nu(\text{C}=\text{O})$, therefore the formation of a normal proton salt is contradicted. Based on this, it was proposed that a cocrystal salt was obtained. PHT-Ampy **1** showed broad N-H band, and absence of O-H and protonated C=O, therefore salt formation was suggested **Figure 4.4** and **Figure 4.5**

For compounds **2-5**, at high mole ratios of acid, the O-H band is significant and showed as a broad signal. As the mole ratio is shifted gradually towards higher mole ratios of the base, both N-H and O-H bands became evident, and exhibiting overlapping features, indicating the presence of both bonds in the heterosynthon. The DPA-Ampy, **5** was also assumed as salt cocrystal, due to the presence of the protonated C=O group. Most of the DPA derivatives obtained, showed very broad overlapped bands at mole ratio 1:9 and this could be attributed to the higher concentration of sample taken during the analysis, however, the presence of both bands is still noticeable at a mole ratio of 3:7. In PHT-Ampy, **1** as the mole ratio of base increases, the presence of the broad N-H became significant. The absence of the protonated C=O also became clear starting from mole ratio of 4:6.

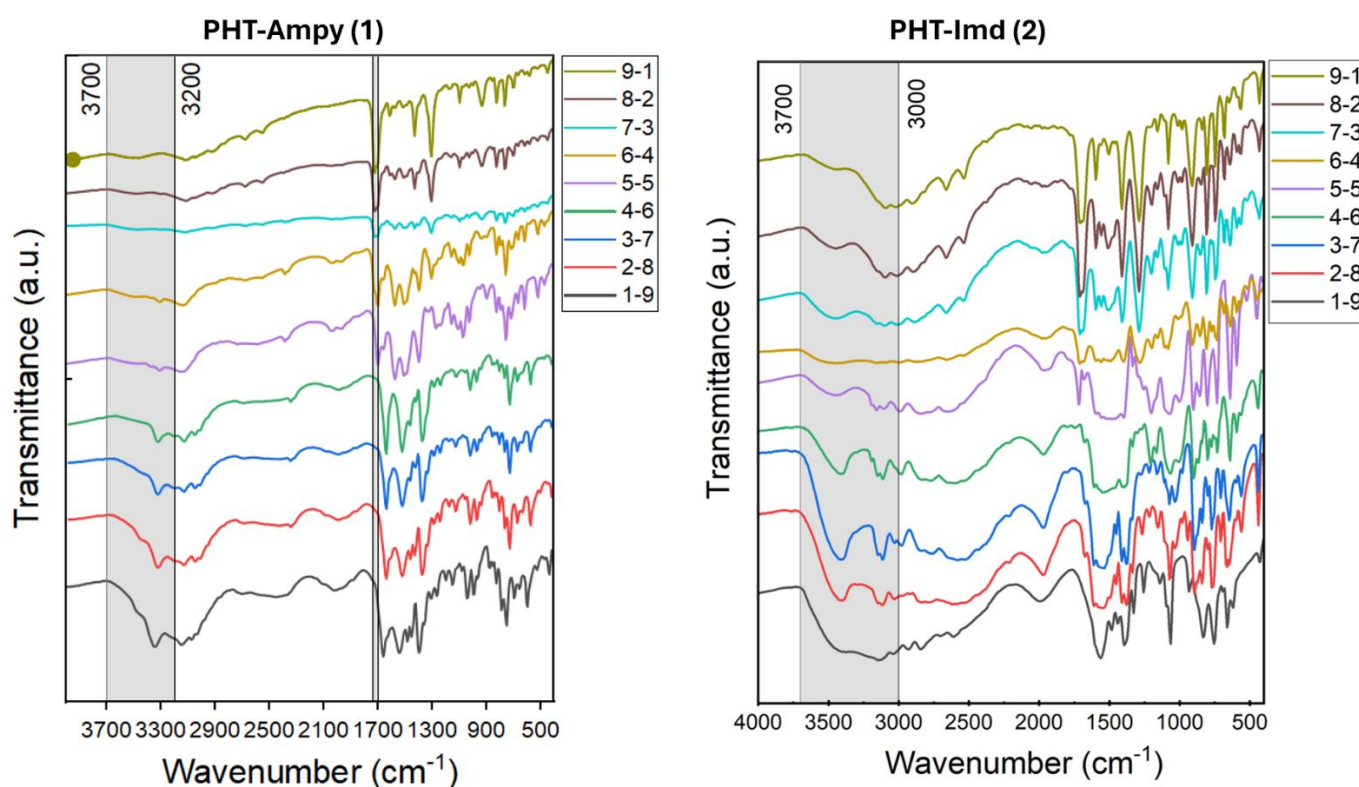


Figure 4.4 FT-IR of PHT physical mixtures with different mole ratios

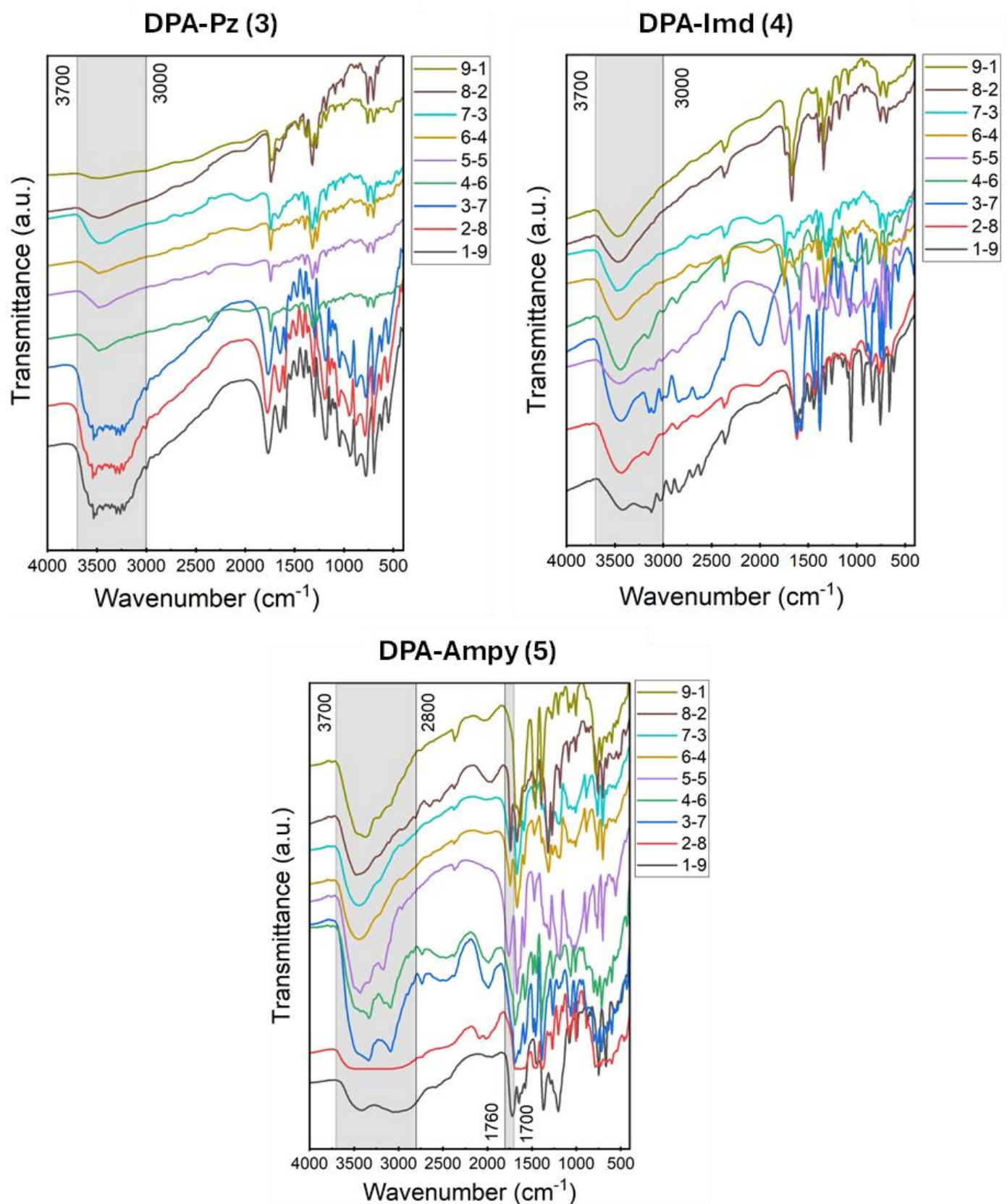


Figure 4.5 FT-IR of DPA physical mixtures in different mole ratios.

4.3 Spectroscopic Characterization of Heterosynthons

4.3.1 FT-IR Studies

4.3.1.1 PHT

The spectrum of m-PHT was obtained for comparison purposes **Figure 4.6**. A strong broad band at 3464 cm^{-1} was assigned to O-H stretching (Kundu et al., 2018). The stretching band of carbonyl group, C=O was observed at 1700 and 1681 cm^{-1} . Bands at 1586 , 1404 , and 1277 cm^{-1} were assigned to $\nu_{\text{as}}(\text{COO}^-)$ asymmetric stretching, $\nu_{\text{s}}(\text{COO})$ symmetric stretching, and C-O stretching, respectively (**Table 4.2**).

Table 4.2 The significant stretching bands (in cm^{-1}) associated with PHT.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	comments
3464	O-H	Carboxylic acid	strong and broad	
3090	C-H sp^2	Conjugated aromatic	medium	
1700 1681	COOH (C=O)	Carboxylic acid	strong	Lower than free carboxylic acid due to conjugation
1586	$\nu_{\text{as}}(\text{COO}^-)$	Carboxylic acid	strong	
1404	$\nu_{\text{s}}(\text{COO})$	Carboxylic acid	strong	
1277	C-O	Carboxylic acid	strong	

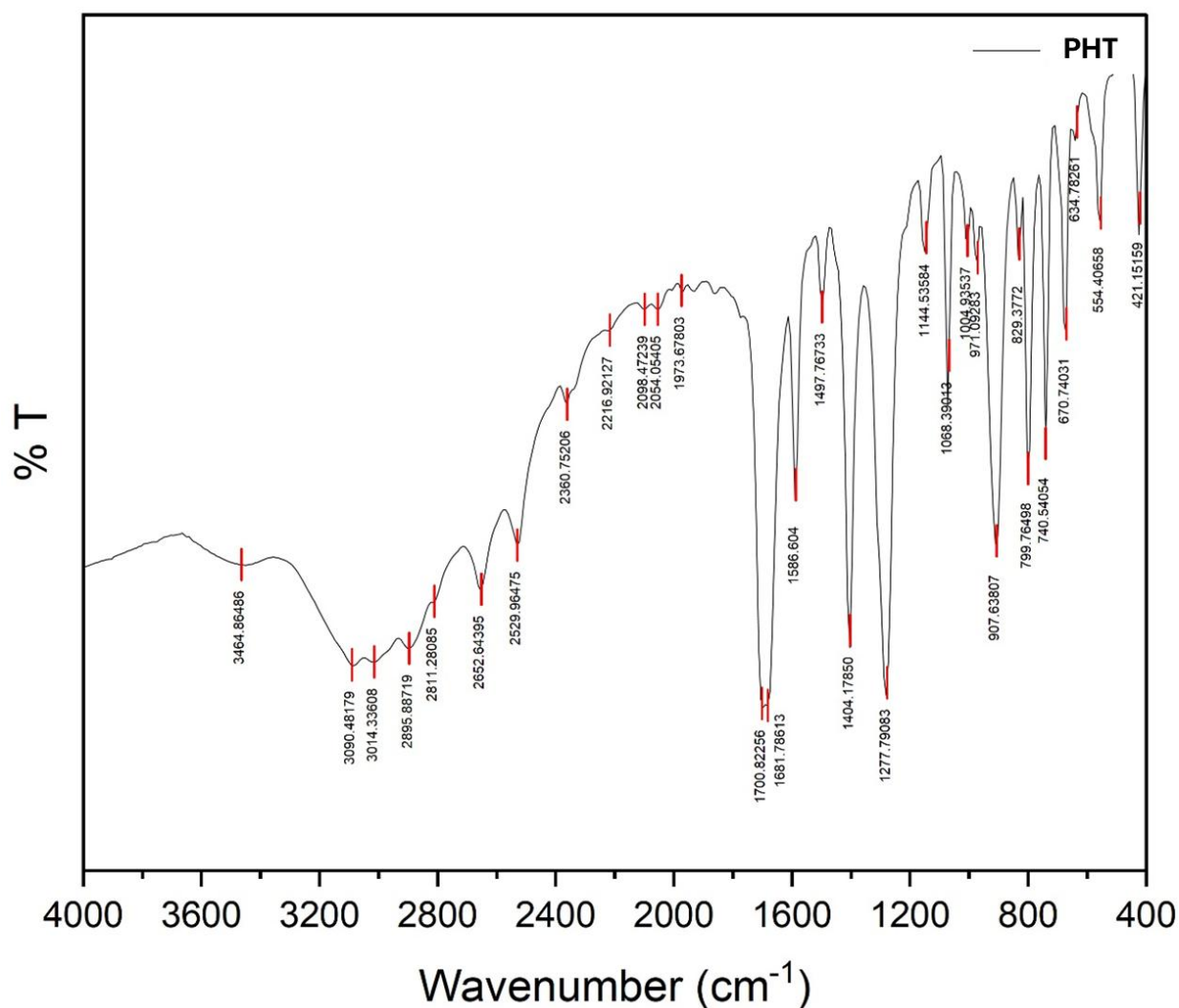


Figure 4.6 FT-IR spectrum of PHT.

4.3.1.2 Compound 1, PHT-Ampy

The obtained spectrum is shown in **Figure 4.7** and reveals the most significant peaks which were assigned accordingly, **Table 4.3**. Shifts, attenuation, or overlapping were noticed in comparison to bands in the parental materials. Overlapped peaks were noticed for N-H, C-H (sp²) aromatic, C-H (sp³) at 3348-3149, and 3060, 2972 cm⁻¹, respectively. A sharp and strong band at 1658, 1544, 1392 cm⁻¹ were assigned to C=N stretching of pyridine ring in the respective product, $\nu_{as}(\text{COO}^-)$ asymmetric, and $\nu_s(\text{COO}^-)$ symmetric stretching, respectively. Medium band at 1358 cm⁻¹ was assigned to C-N stretching. According to the obtained data, salt is proposed and assigning C-O band is difficult as several bands are overlapped in the expected region.

Table 4.3 The most significant stretching bands (ν in cm^{-1}) in PHT-Ampy, compound 1.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	Comments
3348 3149	N-H	primary amine	strong	Overlapped with C-H sp^2 aromatic, and C-H sp^3
3060	C-H sp^2	aromatic	medium	Overlapped with N-H, and C-H sp^3
2972	C-H sp^3	aliphatic	medium	Overlapped with N-H, and C-H sp^2
1544	$\nu_{\text{as}}(\text{COO}^-)$	Carboxylic acid	strong, sharp	
1392	$\nu_{\text{s}}(\text{COO}^-)$	Carboxylic acid	strong, sharp	
1658	C=N	pyridine	strong, sharp	
1358	C-N	pyridine	medium	

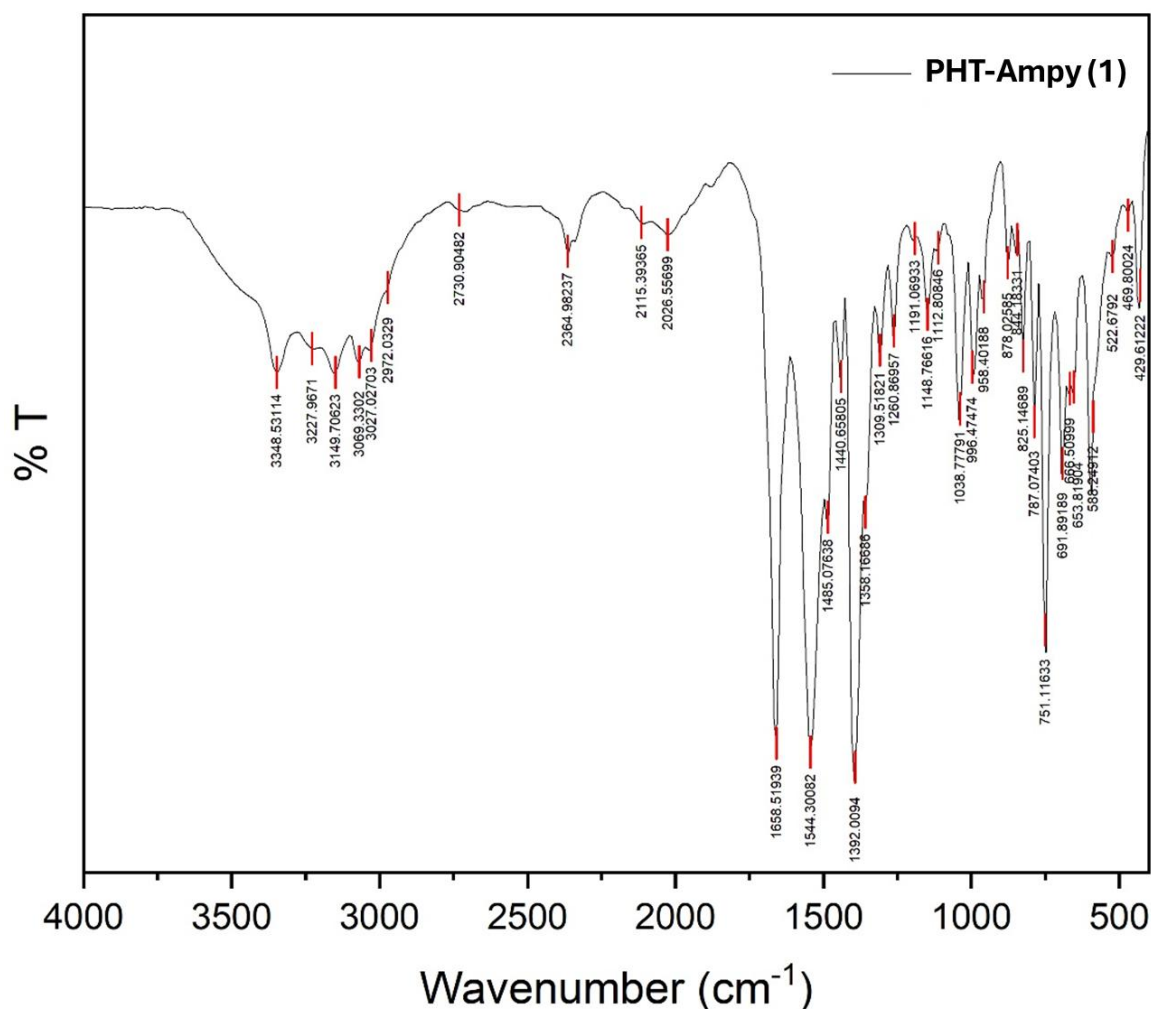


Figure 4.7 FT-IR spectrum of compound **1**.

4.3.1.3 Compound **2**, PHT-Imd

In FT-IR spectrum of the product **2** shift, attenuation, or overlapping in the respective peaks was observed in comparison to bands in the parental molecules as given in **Figure 4.8**. A broad band at 3392 cm^{-1} was assigned to O-H group and the N-H was found as a sharp peak at 3141 cm^{-1} . Strong and sharp bands at 1604 , 1569 , 1402 cm^{-1} were assigned to C=C (Imd ring), $\nu_{\text{as}}(\text{COO}^-)$ asymmetric, and $\nu_{\text{s}}(\text{COO}^-)$ symmetric stretching, respectively. Aromatic C-N was found overlapped around 1334 cm^{-1} , **Table 4.4**.

Table 4.4 The most significant stretching bands (ν in cm^{-1}) in PHT-Imd compound 2.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity
3392	O-H	Carboxylic acid	Strong, broad
3141	N-H	Secondary amine	Strong
3106	C-H sp^2	aromatic	medium
overlapped	C=O	Carboxylic acid	Strong
1569	$\nu_{\text{as}}(\text{COO}^-)$	Carboxylic acid	strong
1402	$\nu_{\text{s}}(\text{COO}^-)$	Carboxylic acid	strong
1604	C=C Imd	imidazole	strong
1368	C-N	imidazole	medium

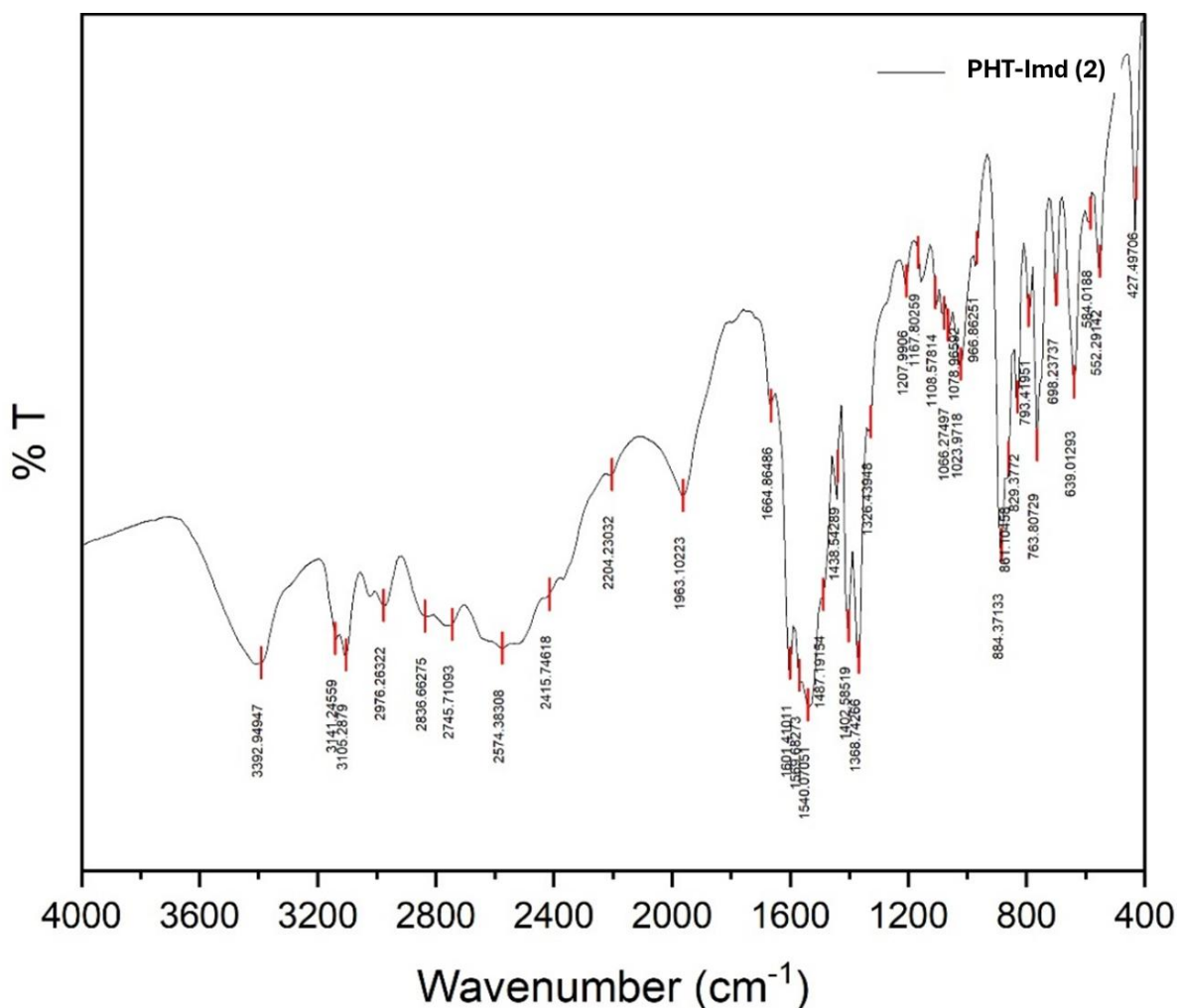


Figure 4.8 The FT-IR spectrum of compound 2.

4.3.1.4 DPA

The spectrum of pure DPA was obtained for comparison purposes, and it was also compared to reported data (İlkimen & Saygili Canlidinç, 2020) shown in **Figure 4.9A** broad and strong band at 3409 cm^{-1} was assigned to symmetric and asymmetric stretching of O-H. Strong vibrational bands at 1707 , and 1459 cm^{-1} were assigned to COOH and $\nu_s(\text{COO})$ symmetric stretching, respectively. The $\nu(\text{C}=\text{N})$ band was noticed within its expected region at 1571 cm^{-1} . Stretching bands at 1326 , 1411 cm^{-1} were assigned to $\nu(\text{C}-\text{O})$, and $\nu(\text{C}=\text{C})$, respectively as summarized in **Table 4.5**

Table 4.5 The summarized stretching bands (ν in cm^{-1}) correspond to DPA.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	comments
3409	O-H	Carboxylic acid	Strong and broad	Overlapped with C-H sp^2
3124	C-H sp^2	aromatic	Broad due to overlapping	Overlapped with O-H
1707	COOH	Protonated carboxylic acid	Broad, overlapped	Overlapped with asymmetric COO^-
overlapped	$\nu_{\text{as}}(\text{COO})$	Carboxylic acid	Strong, broad	
1459	$\nu_{\text{s}}(\text{COO})$	Carboxylic acid	strong	
1571	C=N	Pyridine ring	medium	
1296	C-O	Carboxylic acid	strong	
1411	C=C	Aromatic alkene	medium.	
778	Pyridine ring wagging		strong	

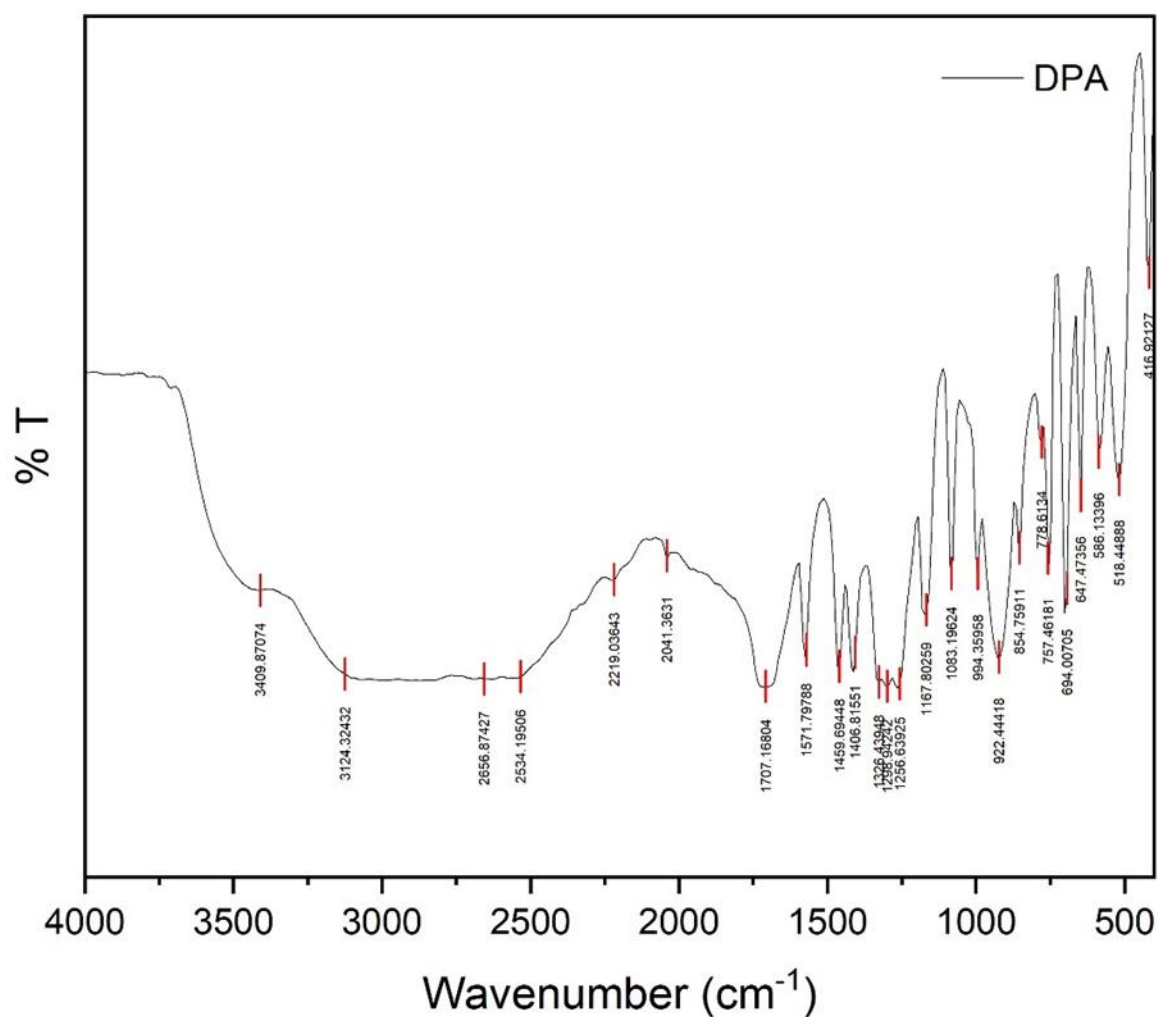


Figure 4.9 The FT-IR spectrum of DPA.

4.3.1.5 Compound 3, DPA-Pz

A broad and overlapped peaks were observed at 3139 and 3437 cm^{-1} and assigned to $\nu(\text{N-H})$, $\nu(\text{O-H})$, respectively. Protonated carboxylic acid $\nu(\text{C=O})$ was observed at 1728 cm^{-1} . $\nu_{\text{as}}(\text{COO})$ asymmetric vibration was found at 1631 cm^{-1} and it overlapped with COOH. Band at 1428 cm^{-1} was assigned to C=C , while $\nu_{\text{s}}(\text{COO})$ symmetric was overlapped and insignificant. The C-O stretching band was obtained at 1301 cm^{-1} . The $\nu(\text{C=N})$ stretching band was found at 1573 cm^{-1} , **Table 4.6** and **Figure 4.10**

Table 4.6 The important stretching bands (ν in cm^{-1}) correspond to compound **3**.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	comments
3139	N-H	Secondary amine	expected to be sharp and strong	Overlapped with O-H, and C-H sp^2 stretching.
3437	O-H	Carboxylic acid	Strong and broad	Overlapped with N-H, C-H sp^2
~ 3080	C-H sp^2	aromatic	Broad due to overlapping	Overlapped with N- H, O-H
1728	COOH	Carboxylic acid	Strong, sharp	
1631	$\nu_{\text{as}}(\text{COO})$			
overlapped	$\nu_{\text{s}}(\text{COO})$	Carboxylic acid	strong	
1301	C-O	Carboxylic acid	Strong, sharp	
1573	C=N	Pyridine ring	medium	
1427	C=C			

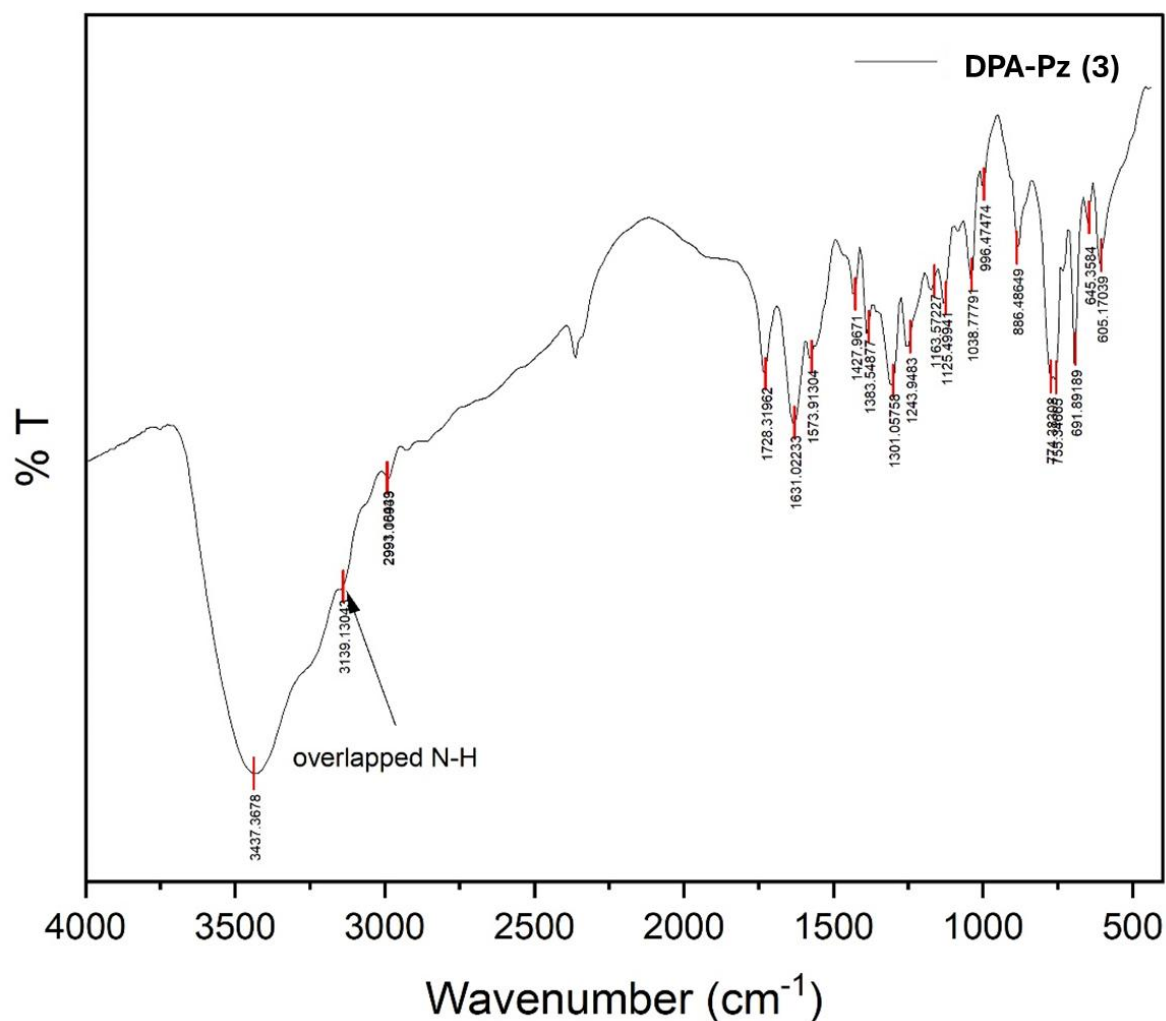


Figure 4.10 The FT-IR spectrum of compound **3**.

4.3.1.6 Compound **4**, DPA-Imd

The spectrum of compound **4** shows a broad band at 3435 cm^{-1} which is predominantly assigned to $\nu(\text{O-H})$. Band at 3147 cm^{-1} was assigned to $\nu(\text{N-H})$, while $\nu(\text{C=O})$ stretching band was obtained at 1734 cm^{-1} , $\nu_{\text{as}}(\text{COO})$ antisymmetric was overlapped with protonated COOH and not correctly assigned. Band at 1458 cm^{-1} was assigned to $\nu_{\text{s}}(\text{COO})$ symmetric. The C-O stretching band was obtained at 1309 cm^{-1} . Bands at 1586 , and 1425 cm^{-1} were assigned to $\nu(\text{C=N})$ and $\nu(\text{C=C})$, respectively **Figure 4.11** and **Table 4.7**

Table 4.7 The important stretching bands (ν in cm^{-1}) correspond to compound 4.

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	comments
3147	N-H	Secondary amine	expected to be sharp and strong	
3435	O-H	Carboxylic acid	Strong and broad	
3092	C-H sp^2	aromatic	medium	
1734	COOH	Carboxylic acid	Strong, sharp	
Overlapped	$\nu_{\text{as}}(\text{COO})$			Overlapped with protonated COOH
1458	$\nu_{\text{s}}(\text{COO})$	Carboxylic acid	strong	
1309	C-O	Carboxylic acid	Strong, sharp	
1586	C=N	Pyridine ring	medium	
1425	C=C	Aromatic alkene	medium	

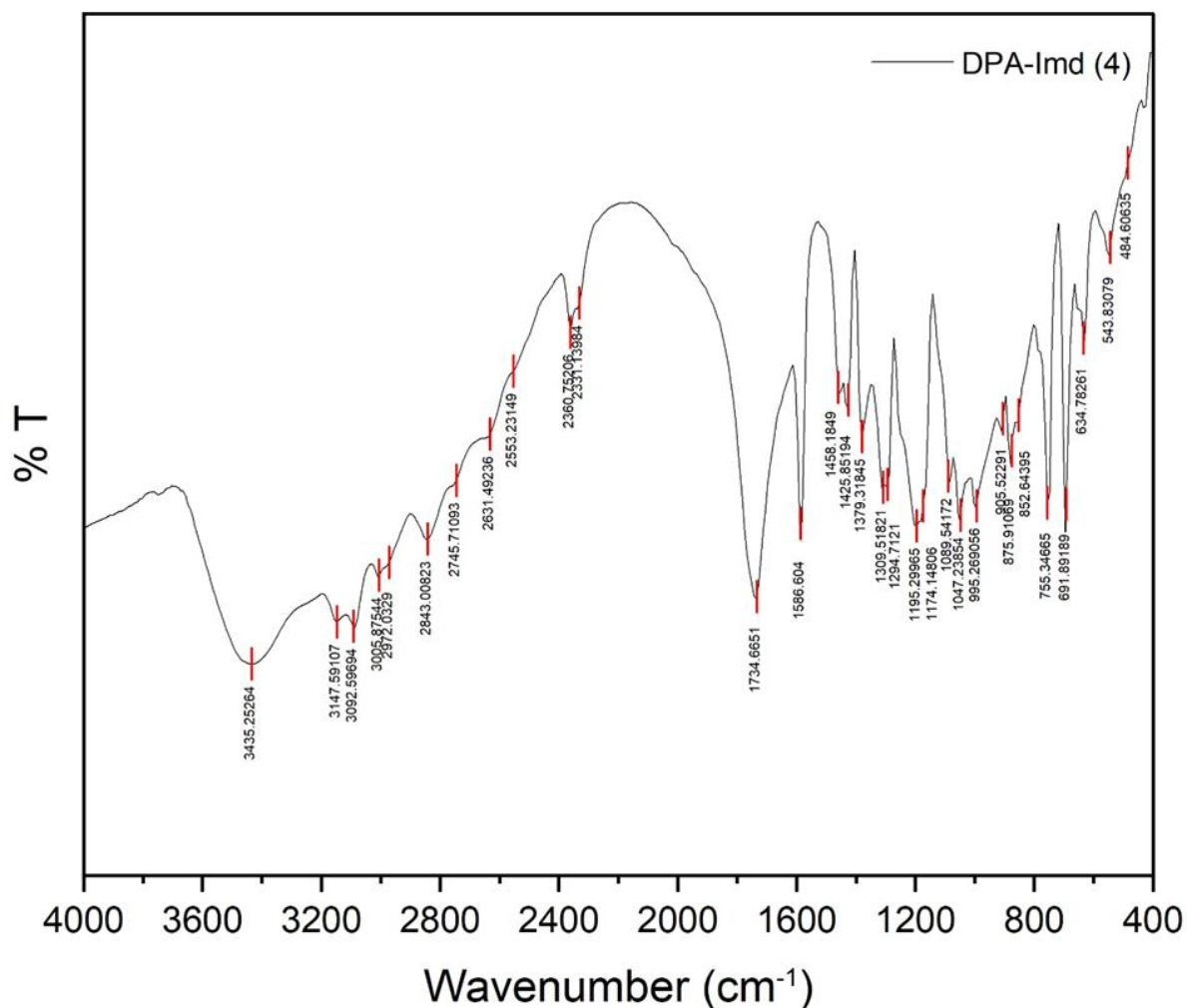


Figure 4.11 The FT-IR spectrum of compound 4.

4.3.1.7 Compound 5, DPA-Ampy

In the case of compound 5, the same trend in its FT-IR spectrum was observed as for previously discussed compounds. A broad peak at 3369, and 3247 cm⁻¹ is assigned to N-H group of primary amin. The assignment of band correspond to $\nu(\text{O-H})$ was ambiguous due to the broad nature of the peak over a wide area. Bands at 1736, 1652, and 1472 cm⁻¹ were assigned to COOH, $\nu_{\text{as}}(\text{C=O})$ and $\nu_{\text{s}}(\text{COO})$ stretching vibrations, respectively. The C-O stretching band was obtained at 1332 cm⁻¹ which is characteristic region for this group (İlkimen et al., 2022). Bands at 1633, 1578, 1419 cm⁻¹ were assigned to $\nu(\text{C=N})_{\text{Ampy}}$, $\nu(\text{C=N})_{\text{DPA}}$, and $\nu(\text{C=C})$, respectively **Table 4.8** and **Figure 4.12**.

Table 4.8 Summarized FT-IR bands (ν in cm^{-1}) correspond to compound **5**

Wavenumber (cm^{-1})	Functional group	Compound class	Intensity	Comments
3369 3247	N-H	primary amine	expected to be sharp and strong	Very broad, assumed overlapped with O-H.
3103	C-H sp^2	aromatic	medium	
1736	COOH	acid	Strong, sharp	
1652	vas(COO)			
1472	vs(COO)	acid	strong	
1332	C-O	acid	Strong, sharp	
1578	C=N	Pyridine ring of DPA	medium	
1633	C=N	Pyridine ring of Ampy	strong	
1419	C=C	Aromatic alkene	medium	

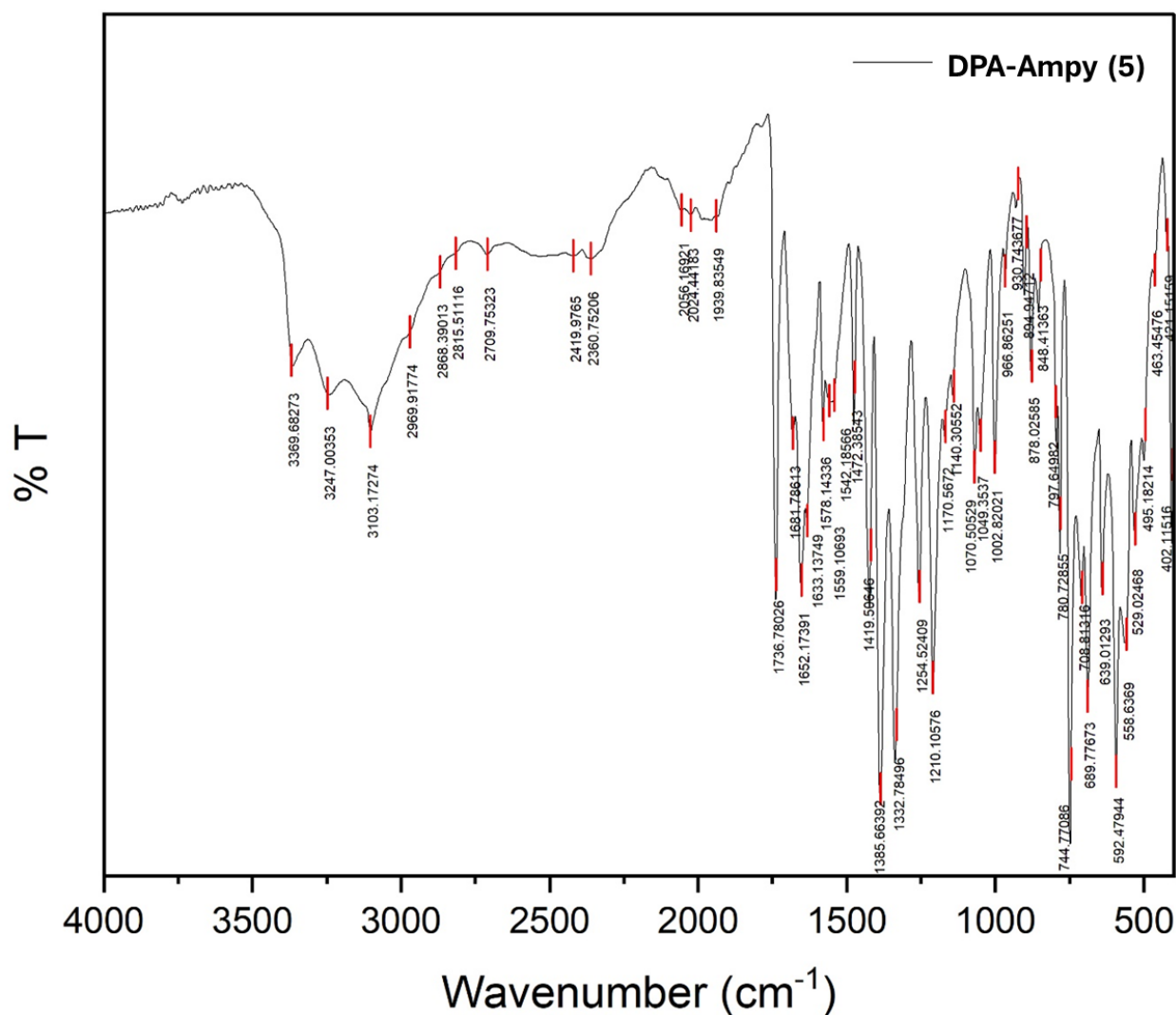


Figure 4.12 The FT-IR spectrum of compound **5**.

4.3.2 ^1H -NMR Spectroscopic Studies

The ^1H -NMR spectroscopy is one of the reliable techniques to confirm the presence of the components and their molar ratio in a mixture. The obtained ^1H -NMR spectra were interpreted to find the molar ratio of acid: base expected in the reaction mixture. The spectra of compounds **1-5** were recorded in DMSO-d_6 , a polar solvent with greater solubility of the synthesized compounds. The solvent DMSO exhibits a characteristic peak at around δ 2.5 ppm which is due to its residual protons and is considered during interpretation as a reference peak.

All expected signals were present in spectra of compounds and were assigned to their respective protons. Additionally, the integration values of each signal helped to calculate the ratio of acid and base in their mixture.

The mole ratio can be calculated for molecules in a mixture with the same number of equivalent protons according to **Eq. 1**. However, errors may arise if the protons are not chemically equivalent, or the number of the equivalent protons are not the same. Moreover, extra care shall be taken in selecting the peak area when integrating a spectrum.

$$\text{Molar ratio} = \frac{\frac{I_{acid}}{N_{acid}}}{\frac{I_{base}}{N_{base}}} \quad \text{Eq. 1}$$

Where, I_{acid} is Integration Value of Acid; N_{acid} = Number of Equivalent Protons in Acid; I_{base} = Integration Value Base; N_{base} = Number of Equivalent Protons in Base.

4.3.2.1 Compound 1, PHT-Ampy

A singlet signal in the aliphatic region at 2.49 ppm was assigned to methyl group of Ampy. A broad signal was observed downfield at 6.90 ppm for N-H bond, due to the de-shielding effect caused by the anisotropy of the pyridine ring, which increases the chemical shift compared to N-H bond in aliphatic alkyl (Sathya, Ponnusamy, & Dhandapani, 2018). The C-H in ortho position to carboxylic acid, **-CH-C-COOH**, was observed at higher shift (8.40 ppm) compared to C-H at meta position of the PHT i.e., **-CH=CH-C-COOH** (7.90 ppm). This is due to the presence of strong electron withdrawing groups (EWG, i.e., carboxylic acid) that decreases the electron density at the nucleus, resulting in deshielding and higher chemical shift. The integration values of these equivalent protons were not reliable as they were shown as ^1H only. Protons correspond to **-CH-N-**, **-CH=CCH₃**, and **-CH-CH= CCH₃** signals in Ampy were observed at 8.2, 7.8, and 6.9 ppm, respectively **Figure 4.13**.. The mole ratio can be calculated using the integration values from the respective spectrum however, errors may arise due to the absence of the same number of equivalent protons in Ampy and

PHT, in addition to the unreliable integration values of equivalent protons of PHT, **Table 4.9.**

Table 4.9 Number of protons in PHT-Ampy 1.

	PHT		Ampy			
Number of protons	2	2	3	1	1	1
Integration	1	1	6	1	1	1

Molar Ratio = $(1 / 2) / (1 / 1) = 1/2$

Molar Ratio = $(1 / 2) / (6 / 3) = 1/4$ (unacceptable)

Mole ratio assuming the integration of equivalent protons of PHT is $2 = (2 / 2) / (6 / 3)$
 $= 1/2$

Therefore, the mole ratio of Acid: Base matches the mole ratio used in the reaction.

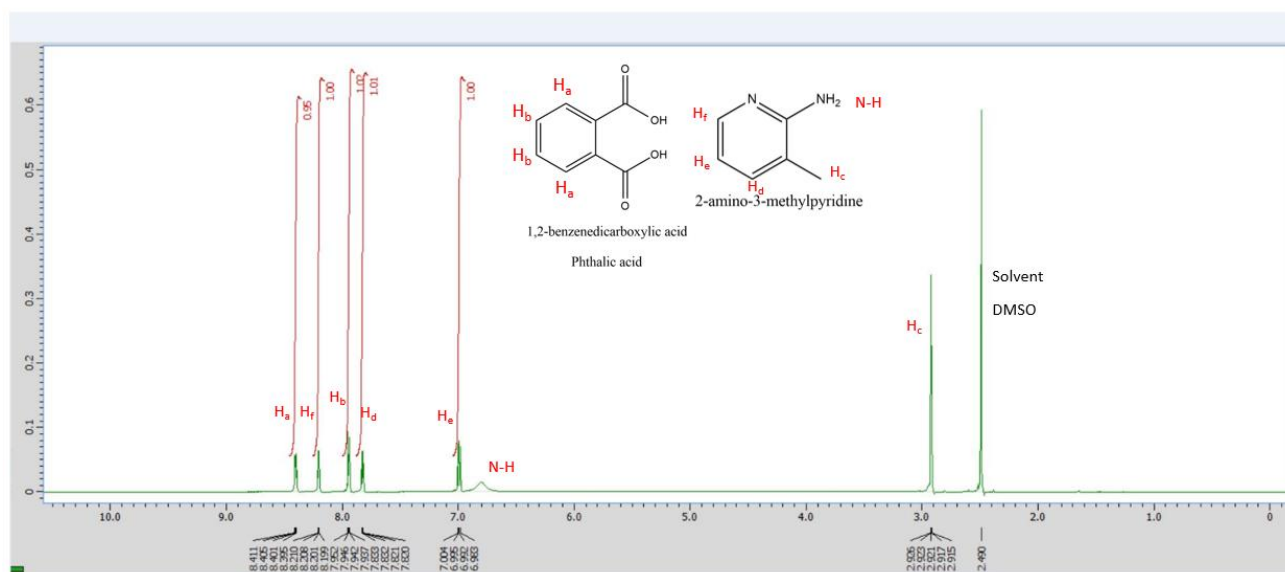


Figure 4.13 ^1H -NMR spectrum measured in DMSO- d_6 of compound **1**

4.3.2.2 Compound 2, PHT-Imd

PHT protons observed at 8.20 ppm correspond to ortho protons, **-CH-C-COOH** and 8.00 ppm for **-CH=CH-C-COOH** in meta position to carboxylic acid. Signals at

7.50 and 7.30 ppm were assigned to -NCH=CHNH- and -N=CHNH- protons of Imd **Figure 4.14**.

Since both compounds have equivalent protons, the determination of the molar ratio is possible using the spectra. The integration values are shown in **Table 4.10** which shows the integration, and number of protons contribute to each signal.

Table 4.10 Number of protons in PHT-Imd **2**

	PHT		Imd	
Number of protons	2	2	1	2
Integration	1	1	1	2

$$\text{Molar Ratio} = (1 / 2) / (2 / 2) = 1/2$$

Therefore, the mole ratio of Acid: Base is 1:2.

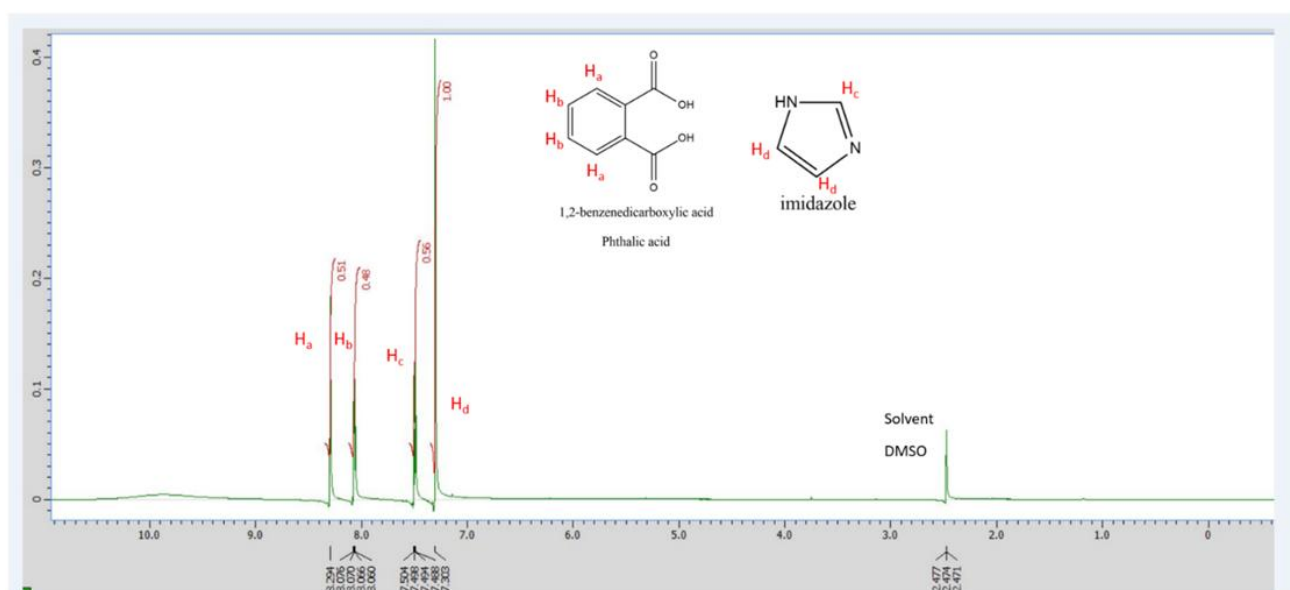


Figure 4.14 ¹H-NMR spectrum, measured in DMSO-d₆ of compound **2**

4.3.2.3 Compound 3, DPA-Pz

Protons NMR chemical shift at 8.20 ppm, corresponds to DPA and the those of pyrazole were found at 7.50 ppm. The chemical shift of -CH=CHN of pyrazole was found

relatively up field, 6.20 ppm **Figure 4.15** The integration of the peaks and the number of protons are summarized in **Table 4.11**,

Table 4.11 Number of protons in DPA-Pz **3**

	DPA		Pz	
Number of protons	2	1	1	2
Integration	6	2	1	2

Molar Ratio = $(6 / 2) / (2 / 2) = 3$ (unacceptable)

Therefore, the mole ratio obtained of Acid: Base is 3:1 which is unexpected and unreliable as the mole ratio used in the reaction is 1:2.

This error may be attributed to the choice of solvent that led to a proton exchange resulting in alteration in peak intensities and probably incorrect integration values. Repeating the run with other solvents could enhance the quality of the result. The ambiguous signals noticed at 1-2 ppm, and 4-5 ppm may have appeared due to impurities such as the unevaporated ethanol solvent during the analysis.

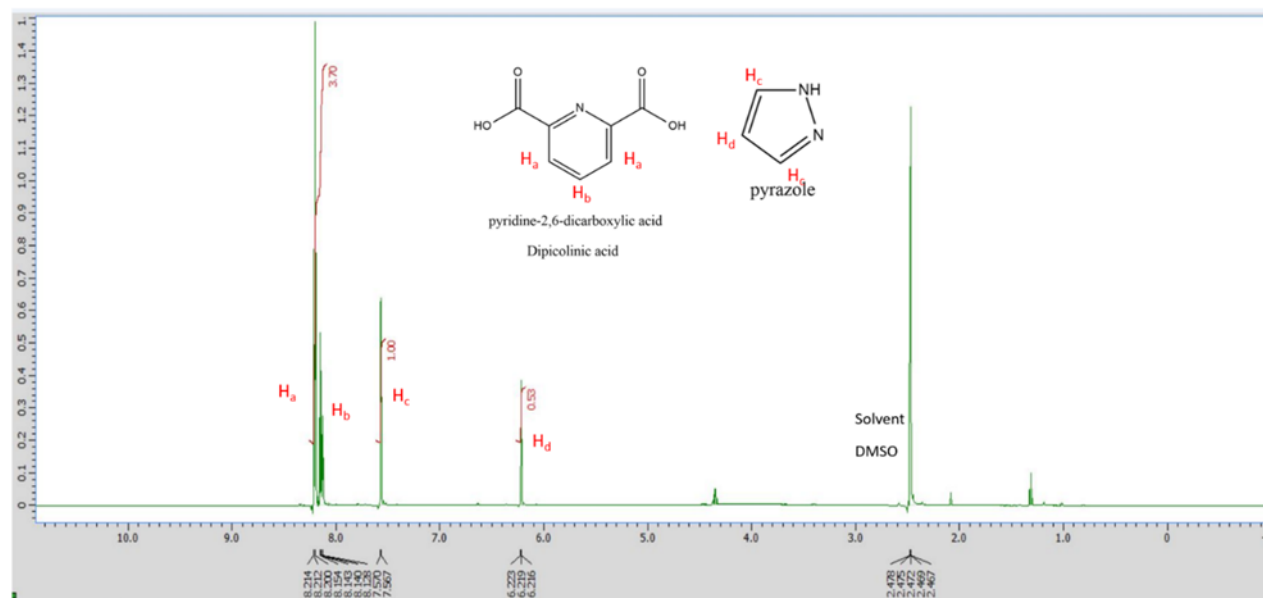


Figure 4.15 ^1H -NMR spectrum, measured in DMSO-d_6 of compound **3**

4.3.2.4 Compound 4, DPA-Imd

Two signals at 8.20 and 7.20 ppm were assigned to aromatic protons of DPA and imidazole, respectively. A singlet signal downfield at 8.00 ppm was assigned to NH-CH=NCH of imidazole. The -CH at meta position with respect to carboxylic acid was found at 8.10 ppm **Figure 4.16**.

The integration of the peaks and the number of protons is summarized in **Table 4.12**

Table 4.12 Number of protons in DPA-DPA-Imd 4

	DPA		Imidazole	
Number of protons	2	1	1	2
Integration	4	2	1	2

Molar Ratio Acid:Base = $(4 / 2) / (2 / 2) = 2$ (unacceptable)

Therefore, the mole ratio obtained from the spectra of Acid: Base is 2:1 which is not reliable as the mole ratio used in the reaction is 1:2. This may be due to the maximum overlapping of proton signals in the upfield, resulting in difficulties in obtaining their exact integration values. However, the presence of both cofomers is still confirmed in the obtained spectrum.

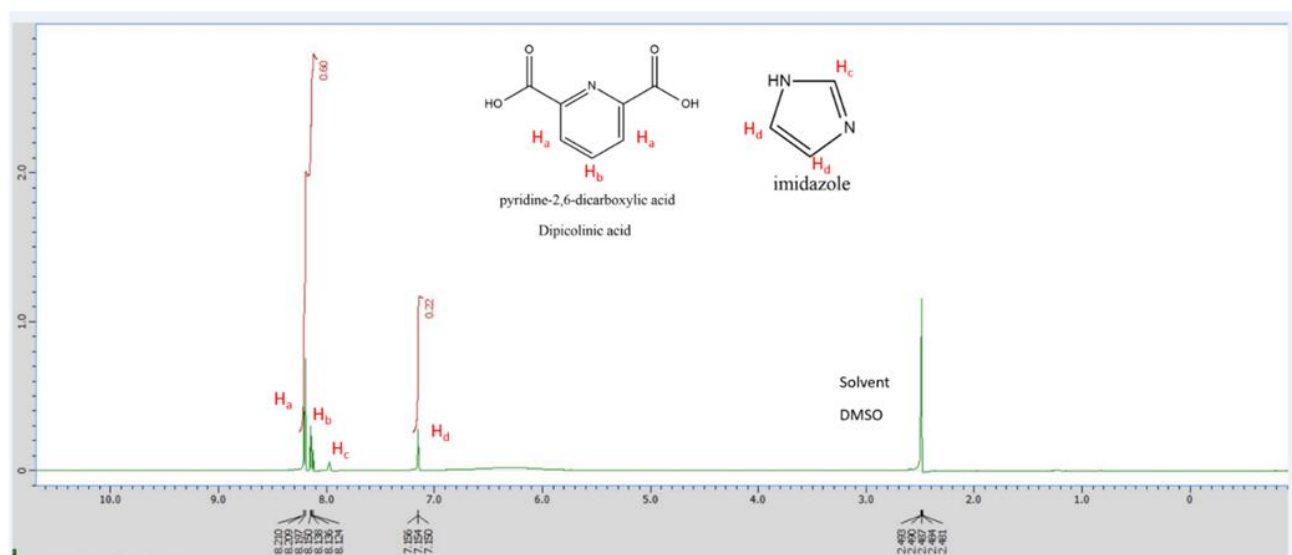


Figure 4.16 ¹H-NMR spectrum, measured in DMSO-d₆ of compound 4

4.3.2.5 Compound 5, DPA-Ampy

A broad band relatively downfield at 6.80 ppm was unambiguously assigned to N-H. A doublet signal at 8.60 ppm was assigned to protons of DPA. While aromatic -CH at meta position to carboxylic acid was observed at 8.50ppm. Different signals at 7.70, 6.90, and 8.20 ppm were assigned to -CH=CCH₃CNH₂, -CHCH=CCH₃CNH₂, -CHN=CNH₂ of Ampy, respectively. A singlet band at 2.90 ppm was assigned to -CH₃ group of Ampy, **Figure 4.17**. The mole ratio can be calculated using the integration values from the spectrum **Table 4.13**

Table 4.13 Number of protons in DPA-Ampy 5

	DPA		Ampy			
Number of protons	2	1	3	1	1	1
Integration	2	1	6	1	1	1

$$\text{Molar Ratio} = (2 / 2) / (6 / 3) = 1/2$$

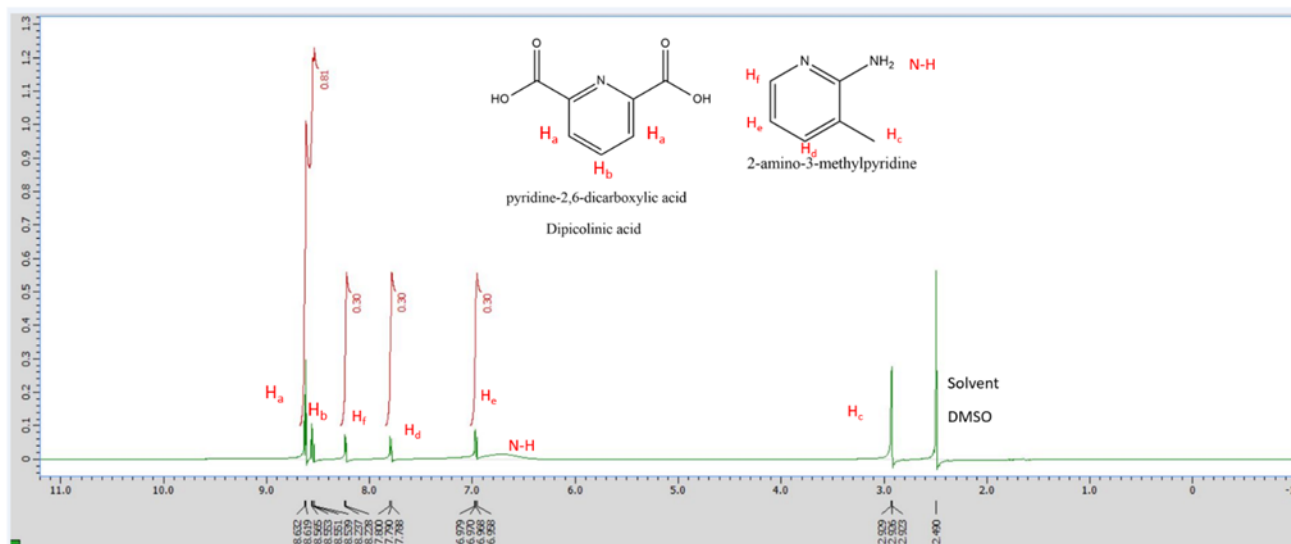


Figure 4.17 ¹H-NMR spectrum, measured in DMSO-d₆ of compound 5

4.3.3 PXRD Studies

The powder X-ray diffractograms of all the synthesized heterosynthons were obtained to determine their bulk purity and crystallinity. The XRD of acids and Imd were also obtained to make the comparison easy **Figure 4.18**. However, XRD

measurements could not be conducted on Ampy and pyrazole due to specific reasons, the Ampy, being a liquid. On the other hand, the starting pyrazole was unavailable, preventing its inclusion in the XRD analysis. Therefore, compounds **2** and **4** were compared with their parental acid and base while others were compared to the acid only. All compounds showed sharp peaks with high intensities, indicating pure and crystalline bulk nature. Shifts/disappearance in peaks, and alteration in intensity were noticed in the diffractograms of the product compared to their individual coformers, indicating the formation of a new crystalline products. New peaks with considerable intensity were observed in compound **2** at 22.48, 24.68, 27.88, and 37.8° Likewise, new high intensity peaks were shown in compound **4** at 29.36, 30.32, and 39.00° which further supports the formation of a new product.

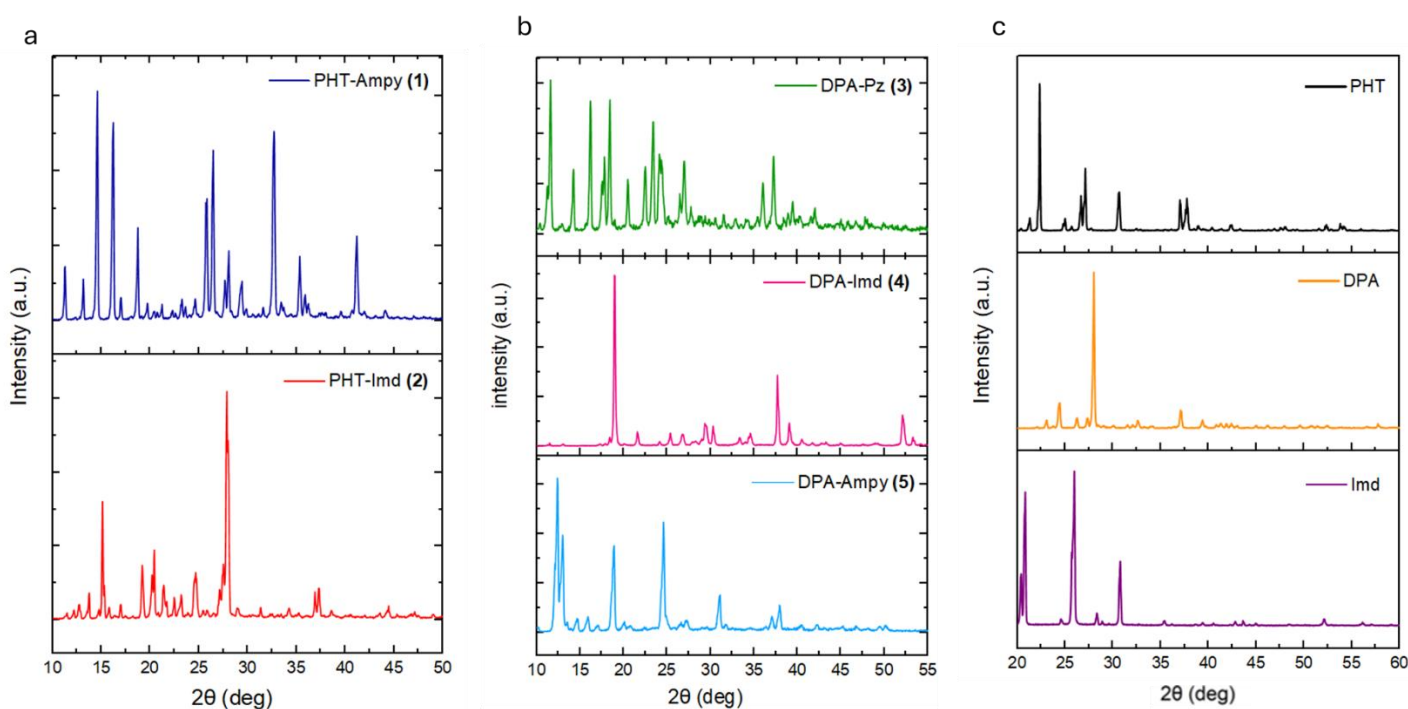


Figure 4.18 PXRD pattern of compounds a): PHT-Ampy **1** and PHT-Imd **2**, b) DPA-Pz **3**, DPA-Imd **4**, and DPA-Ampy **5** c) Starting precursors PHT, DPA, and Imd.

4.3.4 UV-Vis spectroscopic studies

The absorption spectra of all starting materials and products were obtained, as shown in respective figures below. **Figure 4.19a** reveals the absorption spectra of PHT, with two significant bands at 221 and 280 nm, assigned to $\pi \rightarrow \pi^*$ transition of the

aromatic ring and $n \rightarrow \pi^*$ transition of the carboxylic acid group, respectively. Similarly, bands in absorption spectra of DPA at 221 and 270 nm were assigned to $\pi \rightarrow \pi^*$ transition of the aromatic pyridine ring, and $n \rightarrow \pi^*$ transition of the carboxylic acid group **Figure 4.19b** (Ruderman, Caffarena, Mogilner, & Tolosa, 1998). Higher intensities and shorter wavelengths were observed for $\pi \rightarrow \pi^*$ transitions compared to $n \rightarrow \pi^*$, due to relatively greater difference in energy between the bonding and antibonding π -orbitals compared to the difference in energy between the non-bonding orbitals to antibonding π -orbital. Better results could be obtained using less polar solvents as high polarity solvents form H-bonds with the sample, leading to broadness in peaks and concealing the fine details in the spectra. The polar solvents also usually shift $n \rightarrow \pi^*$ to shorter wavelength.

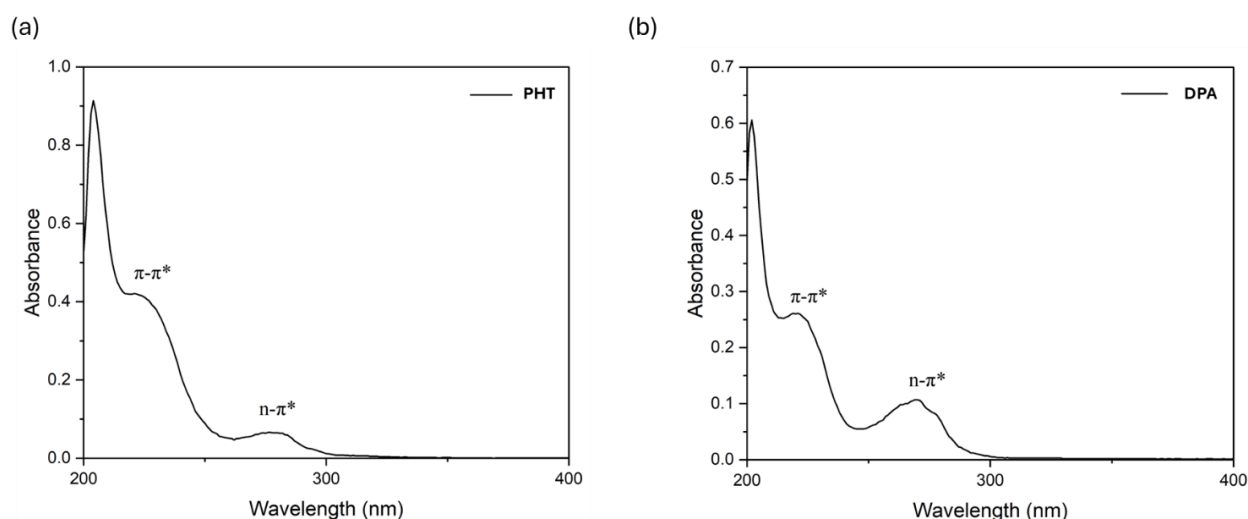


Figure 4.19 Absorption spectra of a): Phthalic acid and b): DPA

The absorption spectra of all products were recorded and compared to the absorption spectra of their respective precursors. Noticeable differences were observed in UV-Vis absorption behavior of products compared to their individual coformers. In , PHT-Ampy **1**, a hypochromic shift was observed for the $\pi \rightarrow \pi^*$ band as the intensity decreased to around 0.2, also the same band was red-shifted by ~ 12 nm to 233 nm. Similarly, in PHT-Imd **2** both hypochromic and red shifts were observed for $\pi \rightarrow \pi^*$ transition. A

decrease in intensity to less than 0.2 was noticed, and an increase in wavelength to 234 nm was recorded (red shift by 13 nm) **Figure 4.20**

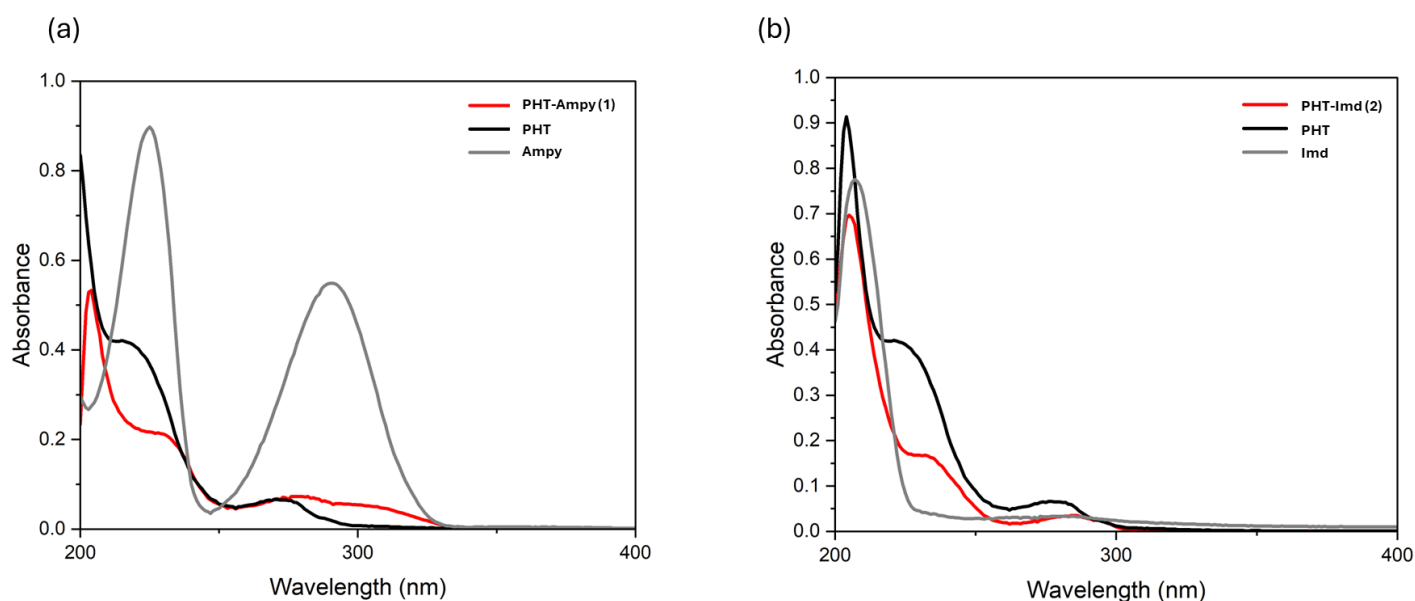


Figure 4.20 Absorption spectra of a): PHT-Ampy **1** and b): PHT-Imd **2**.

Significant differences were also noticed in the absorption spectra of DPA derivatives and their coformers. **Figure 4.21**. A hypochromic shift was observed in UV-vis spectrum of DPA-Pz **3**, DPA-Imd **4** and DPA-Ampy **5** compared to the absorption spectrum of DPA. In DPA-Ampy **5**, a slight bathochromic (red shift) was also noticed in the same spectrum compared to the spectrum of pure acid.

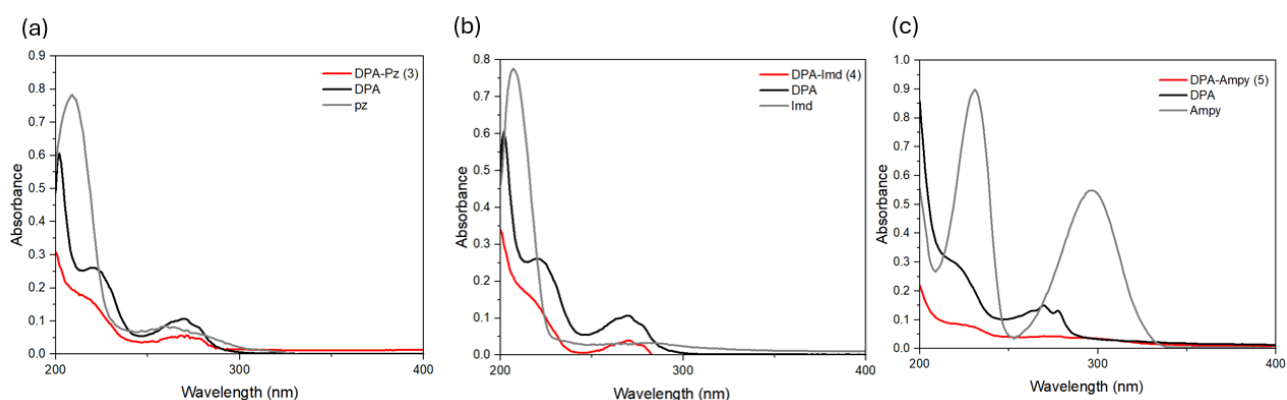


Figure 4.21 UV-Vis spectra of a): DPA-DPA-Pz **3**, b): DPA-DPA-Imd **4**, and c): DPA-Ampy **5**.

4.4 Proposed Structures

Based on the characterization results, particularly on FT-IR and ^1H -NMR spectra, the structures of the heterosynthons were proposed as given in **Figure 4.22** and **Figure 4.23**. For hydrogen bonded heterosynthons PHT-Imd **2** and DPA-Pz **3** the FT-IR spectra show O-H and N-H bands which indicates the absence of any proton transfer, suggesting the formation of a cocrystal where the coformers are held together through hydrogen bonding interactions. However, in the case of DPA-Imd **4** both OH, and N-H bands are significant in addition to the protonated C=O group at 1732 cm^{-1} . The large difference in pK_a values, and the shape of the binary phase diagram suggest the formation of a salt cocrystal. Further experimental investigations are required to confirm the structure, specifically single crystal X-ray diffraction. In DPA-Ampy **5**, only N-H band was observed. Additionally, the protonated C=O was also present at 1736 cm^{-1} . Based on these results and considering the nature of the components used (liquid Ampy and solid DPA), in addition to the large difference in pK_a values and the shape obtained in the binary phase diagram, the structure was suggested as a salt cocrystal. Additional characterization could also support this finding. The higher protonated carbonyl C=O frequencies of both compound **4** and **5** compared to **3**, $\nu(\text{C=O})$ at 1728 cm^{-1} also points to the formation of a salt cocrystal.

In contrast, PHT-Ampy **1**, showed only an N-H band, with absence of the protonated COOH group, which suggests a proton transfer and supports predominantly the formation of a molecular salt, where the acidic protons from the COOH group of the PHT were transferred to the amine group of Ampy.

The obtained results could be preliminarily considered for proposing the structure, as mentioned above, further confirmation is crucial using advanced spectroscopic techniques, such as the single crystal X-ray diffraction to determine the distance between the electronegative atom and H, and accordingly confirming the structure.

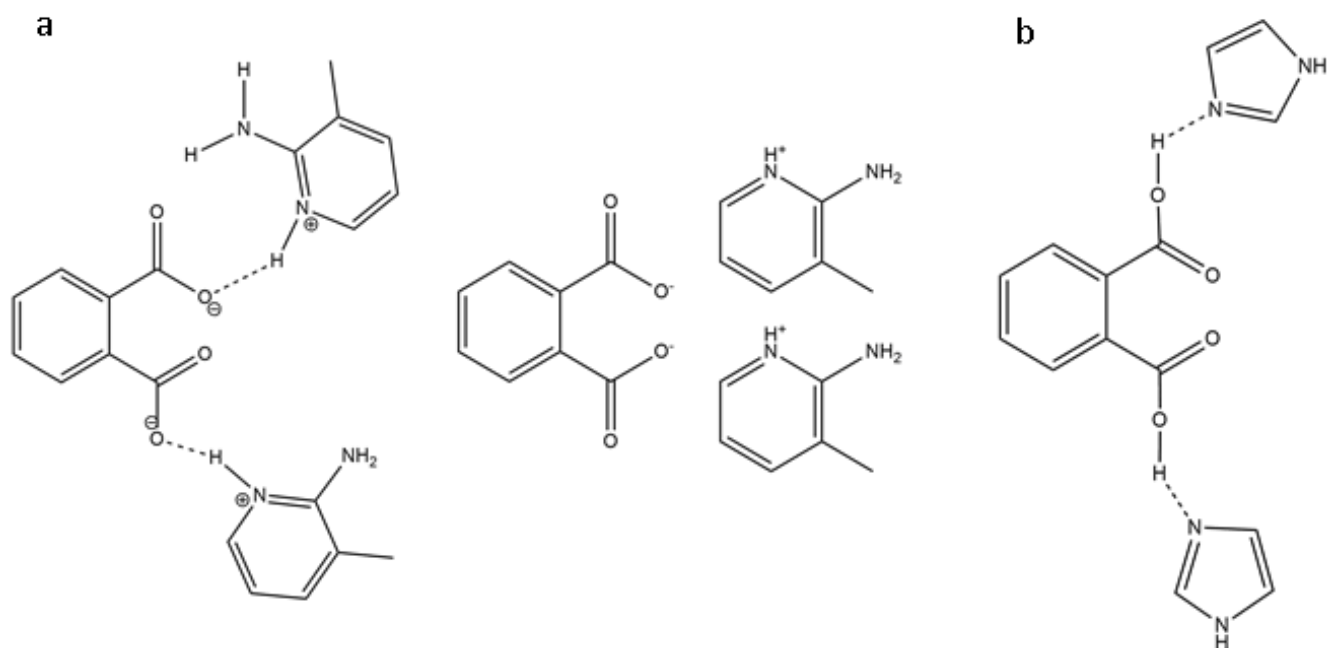


Figure 4.22 Proposed structures of a): molecular salt of PHT-Ampy **1** and b): cocrystal PHT-Imd **2**.

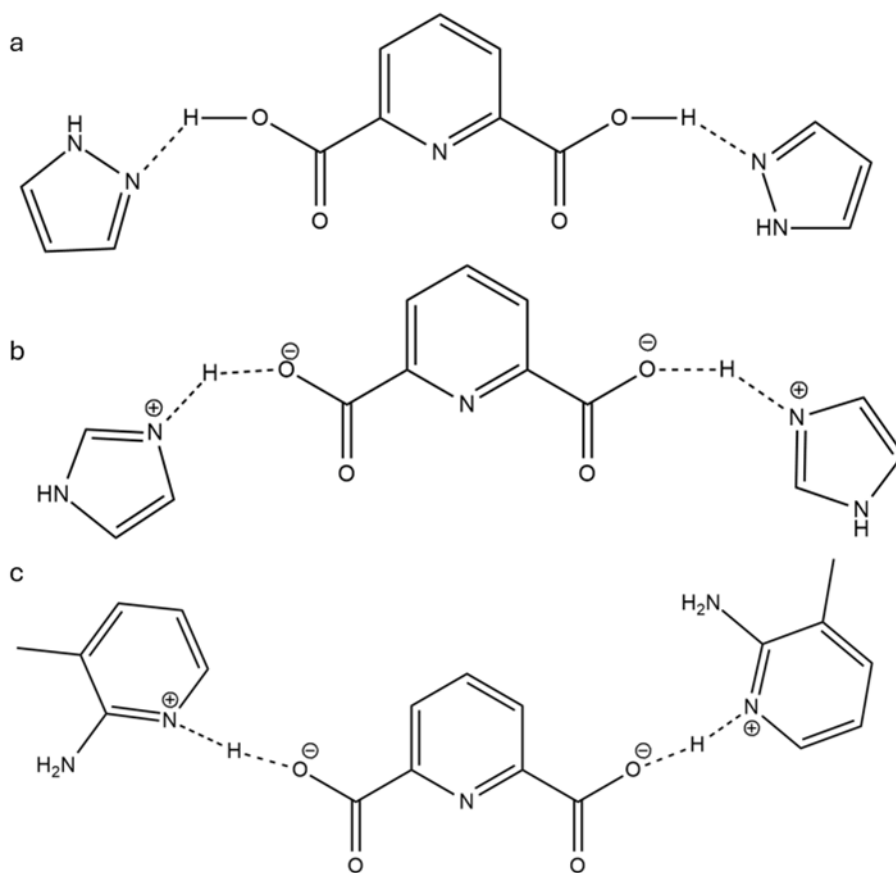


Figure 4.23 Proposed structures of cocrystal of a): DPA-Pz **3**, and salt cocrystals of b): DPA-Imd **4**, c): DPA-Ampy **5**

4.5 Results Comparison

A comparison between the predicted results based on pK_a values, reported literature results, and results obtained in this work is presented in **Table 4.14**. The PHT-Ampy **1** gave a molecular salt and showed agreement with the predicted and reported results. Prediction of PHT-Imd **2** and DPA-Pz **3** products were not decisive according to pK_a rule due to their values being between -1 and 4. However, based on the characterization, the structures were proposed to be cocrystals. The DPA-Imd **4** and DPA-Ampy **5** were proposed to form salt cocrystals. Prediction of results using pK_a could not provide accurate determination of the subclass as it is limited to the prediction of salt/cocrystal only. The results obtained showed agreement with literature reports as the coformers afforded white precipitates of salt after two hours reaction time. However, modification in reaction time in this work was performed as the time was elongated to 9 h to test for the possibility to form cocrystal. The FT-IR characterization results of physical mixtures showed agreement with results obtained using slow evaporation method, which further supports findings of this study.

Table 4.14 Comparison between results obtained, literature results and results predicted

Acid	$pK_{a(acid)}^*$	Base	$pK_{a(base)}^{**}$	$\Delta pK_{a(product)}$	Product predicted	Reported result	Synthesis method	Reaction condition	Reference	Product proposed in this work	Methodology used in this work
PHT	$pK_{a1 (PHT)} = 2.89$ $pK_{a2 (PHT)} = 5.09$	Ampy	7.24	$\Delta pK_{a1} = 4.35$ $\Delta pK_{a2} = 2.15$	Molecular Salt	Reported as molecular salt	Slow evaporation method	1:2 mol ratio, in water, heat, salt is formed by standing overnight.	(Jin et al., 2001)	Molecular salt	1:2 mol ratio in methanol, white precipitate is collected directly after the addition of Ampy, crystalline material
		Imd	6.8	$\Delta pK_{a1} = 3.91$ $\Delta pK_{a2} = 1.7$	Molecular salt/cocrystal	Not reported	-	-	-	Cocrystal	1:2 mole ratio in methanol, overnight stirring, evaporation of solvent is allowed using rotatory evaporator, crystals are collected after few days.
DPA	$pK_{a1 (DPA)} = 2.16$ $pK_{a2 (DPA)} = 4.76$	Pz	2.52	$\Delta pK_{a1} = 0.36$ $\Delta pK_{a2} = -2.24$	Molecular salt Cocrystal/	Not reported	-	-	-	Cocrystal	1:2 mol ratio in ethanol, reflux for 9 hrs, evaporation of solution using rotatory evaporator, precipitate is obtained, recrystallization, crystalline material is collected.
		Imd	6.8	$\Delta pK_{a1} = 4.64$ $\Delta pK_{a2} = 2.04$	Molecular salt	Reported as molecular salt	Slow evaporation method	Reaction 1: 1:1 mol ratio in water, heating	(Thirumurugan & Anitha, 2018)	Salt Cocrystal	1:2 mol ratio in ethanol, reflux for 2-3 hrs, white precipitate was formed, reflux was

								for 2 hrs, salt is formed after evaporation of solvent.			continued to complete 9 hrs, precipitate was collected and recrystallised, crystalline material was obtained.
							Cooling crystallization	Reaction 2: 1:2 mole ratio in THF, heat, solution is cooled with water, salt is collected.	(Abdolmaleki et al., 2018)		
		Ampy	7.24	$\Delta pK_{a1} = 5.08$ $\Delta pK_{a2} = 2.48$	Molecular salt	Reported as molecular salt		1:1 mole ratio, heat, and reflux for 2 hrs, salt powder is formed.	(İlkinen et al., 2022)	Salt cocrystal	1:2 mol ratio in ethanol, reflux for few hrs, white precipitate was formed, reflux was continued to complete 9 hrs, precipitate was collected and recrystallized, crystalline material was obtained.

* $pK_{a(PHT)}$ and $pK_{a(DPA)}$ are reported in literature in references (Tummanapelli & Vasudevan, 2015), and (Packiaraj et al., 2015) respectively.

** $pK_{a(bases)}$ are obtained from (Hanif et al., 2020; Martins et al., 2019; St. Jean & Fotsch, 2012)

4.6 Colorimetric Sensing of Metal Ions.

The sensing ability of heterosynthons towards different metal ions was examined using naked-eye experiments. As given in **Table 4.15** the obtained colorimetric sensing results for final products and their starting acidic precursors are promising.

According to the optical results being obtained in this study, acids and their heterosynthons have high potential to rapidly detect metal ions using colorimetric sensing techniques. All results were obtained in seconds, directly after the addition of metal solutions to heterosynthons. PHT showed rapid naked-eye sensing ability towards Fe(III) ion in its aqueous solution, as the color of the sensor turned yellow from colorless. Both heterosynthons of PHT showed further sensing ability towards M(II) ions, Cu, Co and Cr(III). A noticeable change in color of the sensor was observed for DPA in the presence of Cu(II), and Ni(II) in their solutions as the color changed to cyan and light green, respectively. Both Pz and Imd compounds were expected to show very analogous detection results due to similarity in their structures. However, compound DPA-Pz **3** showed successful detection results of Cu(II), and Co(II) as the color of the solution changed to cyan and light pink, respectively. Unexpectedly, no noticeable color change was observed in the presence of Ni(II), which might be due to the faintness nature of the color. Compound **4** containing DPA-Imd showed further coordination behavior with Co(II) compared to DPA. Interestingly, Compound DPA-ampy **5** showed good detection results towards Cr(III) in addition to Cu(II). Detection results were also recorded after minutes and days to observe the change as reported in **Table 4.15**. Colors of the solutions are shown within each UV-vis spectra in the following section.

Table 4.15 Colorimetric sensing results of acids and their derivatives towards metal ions*.

Compounds	Detectable ions (within sec.)	Color Change	Detectable ions (after min or days)	Change
PHT	Fe(III)	Colorless to yellow	-	-
PHT-Ampy 1	Fe(III), Cu, Cr(III), Co	Fe(III): colorless to orange Cu: colorless to light blue (cyan) Cr(III): colorless to yellow- green turned to blue after few days. (figure of blue color is provided) Co: colorless to very light pink	Pb	fine crystals started to appear after few minutes (turned to turbid)
PHT-Imd 2	Fe(III), Cu, Cr(III), Co	Fe(III): colorless to orange Cu: colorless to light blue (cyan) Cr(III): colorless to green turned to blue after few days. (figure of blue color is provided) Co: colorless to very light pink	Pb	fine crystals started to appear after few minutes (turned to turbid)
DPA	Cu, Ni	Cu: colorless to light blue (cyan) Ni: colorless to light green	Cd, Cr(III)	Cd: fine crystals started to appear after 15-30 minutes. Cr(III): colorless to violet after 5-7 days.
DPA-Pz 3	Cu, Co	Cu: colorless to light blue (cyan) Co: colorless to very light pink	Cr(III) Cd	Cr(III): colorless(after 2-3 days turned to violet)

				Cd: fine crystals started to appear after 15-30 min
DPA-Imd 4	Cu, Ni, Co	Cu: colorless to light blue (cyan) Ni: colorless to light green Co: colorless to very light pink	Cr(III) Cd	Cr(III): colorless(after 5-7 days turned to violet) Cd: fine crystals started to appear after 15-30 min
DPA-Ampy 5	Cu, Co, Cr(III)	Cu: colorless to light blue Co: colorless to very light pink Cr(III): colorless to green	Cr(III) Cd	Cr(III): from colorless to green (after 2-3 days turned to violet) Cd: fine crystals started to appear after days.

*The oxidation state if not mentioned, is +2, for other metal ions their oxidation state is given.

Within a short time of less than 5 min, the addition of PHT derivatives to a Pd(II) solution resulted in the rapid formation of fine crystals. This phenomenon was accompanied by the solution turning turbid and the subsequent development of crystals. In contrast, when the respective acid was added individually, no such crystal formation or turbidity occurred. These observations strongly suggest the possible formation of a metal complex between Pd (II) and the PHT derivatives and accordingly good detection results.

Similarly, when compounds of DPA and its pure form were introduced to a Cd(II) solution separately, crystals were obtained within 15-30 min. This outcome further supports the successful formation of a metallic complex involving Cd(II) and DPA/DPA compounds. The prompt crystal growth indicates a positive sensing result.

While these observed results may not align directly with colorimetric sensing, documenting them is still beneficial for the development of remediation strategies of metal ions based on Phthalic and DPA heterosynthons.

Compound DPA-Ampy **5** showed rapid colorimetric detection of Cr(III) as the color of the sensor turned from colorless to green. However, the other two derivatives and their respective acid showed positive optical sensing results after few days (2-3 days for compounds **3** and **4** and 5-7 days for the acid) as the solution turned violet, which suggests a decrease in detection time using DPA with Ampy compared to others.

4.4.1 UV-Vis Studies

To evaluate the efficiency of the synthesized heterosynthons for detecting a range of metal ions and to compare their performance with the corresponding acids, absorption spectra were measured. Optical changes including increase/decrease in intensity, shifting/broadening/narrowing in peaks were observed due to the successful formation of a metal complex, which align with colorimetric sensing studies reported in literature (Alorabi et al., 2020). Additionally, it worth-mentioning that the main purpose of the absorption spectra is to assign the maximum wavelength of the detectable ions in the visible range, and thereby proceeding further to perform sensitivity tests.

According to available literature, PHT has the potential to form metallic complexes with diverse metal ions, which also include the specific ions used in the experiment. This was clearly observed in **Figure 4.24** which shows the absorption spectra of PHT with different metal ions. Alteration in intensity, broadening/narrowing in peaks were observed in all spectra, suggesting the formation of the coordination bond. Similarly, coordination complexes of Ampy and Imd with several metal ions have been reported in literature **Table 2.4**. Interestingly, developing heterosynthons of PHT-with Ampy and Imd showed enhanced coordination behavior with a wide range of metals compared to their individual coformers. Distinctive variations in absorption intensity and peak sharpening were noticed in PHT-Ampy1-Mⁿ⁺ spectrum compared to PHT-Ampy alone. Slight differences in intensities, peak broadening/sharpening were also observed in PHT-Imd-Mⁿ⁺ spectrum due to the possible coordination interaction. However, few colorimetric sensing results were obtained using PHT and its derivatives. This is mainly attributed to the several factors of the color developments governed by

crystal field theory in Coordination Chemistry. These factors include the oxidation state of the metal (distribution of electrons in d-orbitals of the metal), geometry of the metal complex, and the strength of the ligand. Comprehensive understanding of these factors in each case remains an area for future investigations.

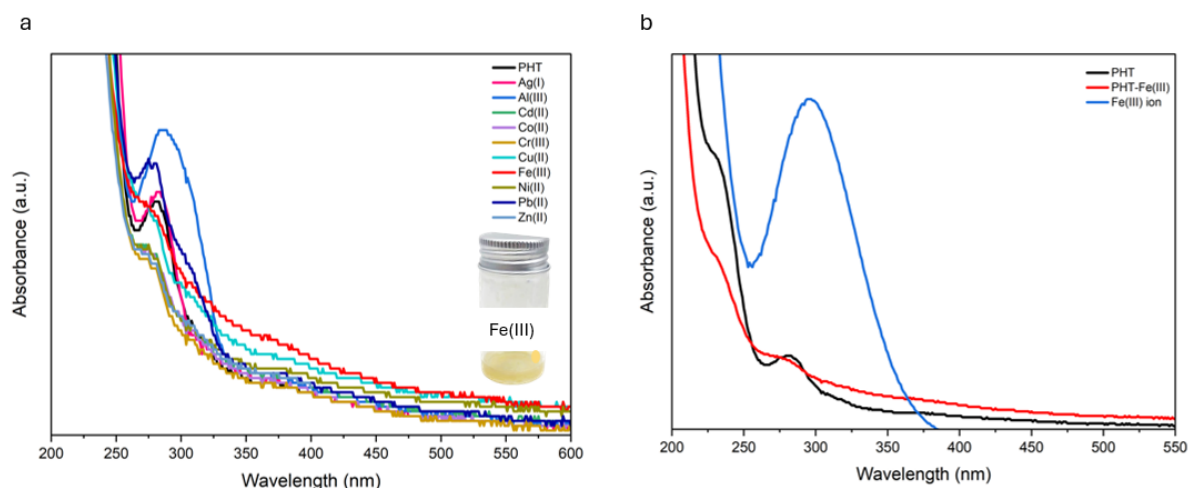


Figure 4.24 a): UV-Vis of PHT with diverse metal ions. b): UV-Vis of PHT, PHT-Fe(III), and Fe(III) metal ion.

PHT with Fe(III) showed the highest absorption in the visible range of 380-440 nm compared to others **Figure 4.24a**, which would suggest the formation of a yellow solution. This was also supported by the fact that this compound did not absorb light in the yellow region (around 600 nm). All other compounds displayed minimal absorption in the visible region and did not exhibit any significant colour change. Below **Figure 4.24b** shows the alteration in intensity of PHT-Fe(III) compared to the spectrum of the respective pure acid.

Very slight absorption throughout the visible region was observed for Cr(III) with PHT derivatives (at 400-450 nm), which would exhibit green-yellow solution **Figure 4.25.d**. Likewise, Fe(III) with PHT and PHT-base showed minimal light absorption in the range of 380-435 nm, suggesting a yellow/orange solutions **Figure 4.25c**. Similarly, PHT-Ampy **1** and PHT-Imd **2** exhibited cyan hue, therefore it was expected to have absorption peaks in the range of 490-520 nm **Figure 4.25b**. However, very minimal absorption was noticed (approaching zero), due to the weak color obtained. **Figure 4.25f**

The PHT containing derivatives with Co(II) gave very faint pink color, therefore spectral differences were not very clear and absorption peak was not noticeable in the visible region **Figure 4.25e**.

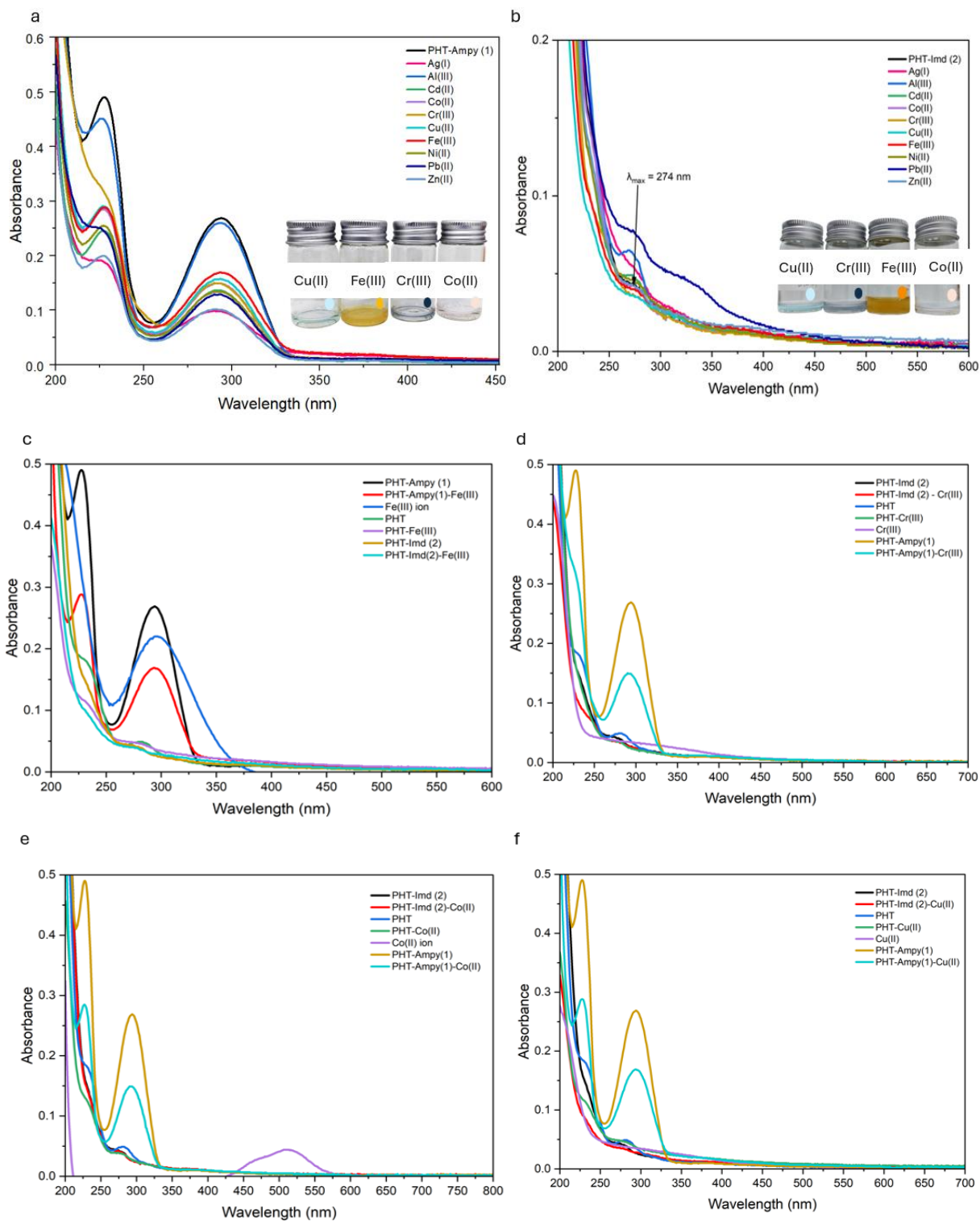


Figure 4.25 a): UV-Vis of PHT-Ampy **1** with diverse metal ions. b): UV-Vis of PHT-Imd **2** with different metal ions c): Fe(III) with PHT and PHT derivatives d): Cr(III)

with PHT and PHT derivatives. e): Co(II) with PHT and PHT derivatives. e): Cu(II) with PHT and PHT derivatives.

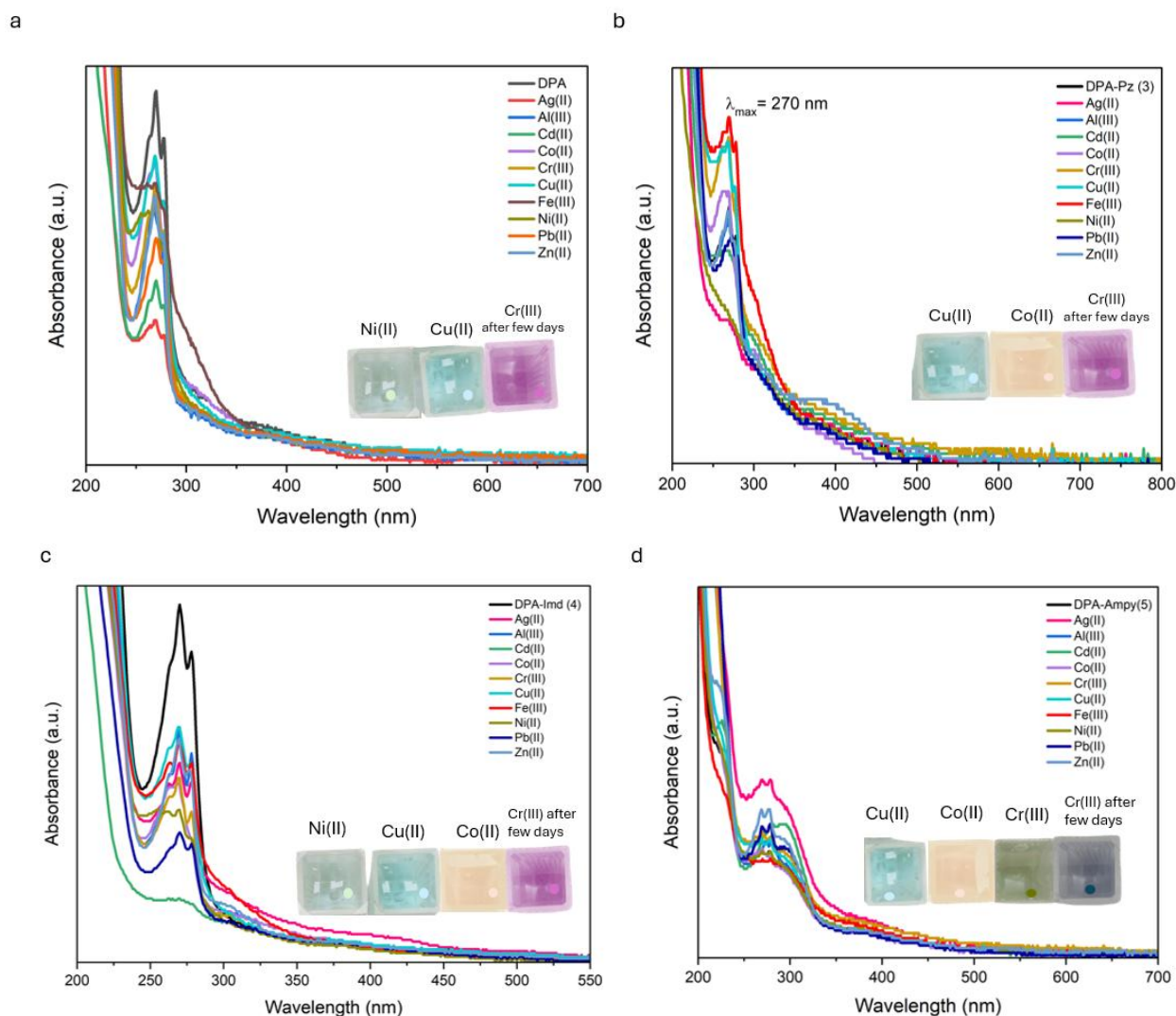


Figure 4.26 a): UV-Vis of a): DPA, b): DPA-Pz **3**, c): DPA-Imd **4** and d): DPA-Ampy **5** with different metal ions.

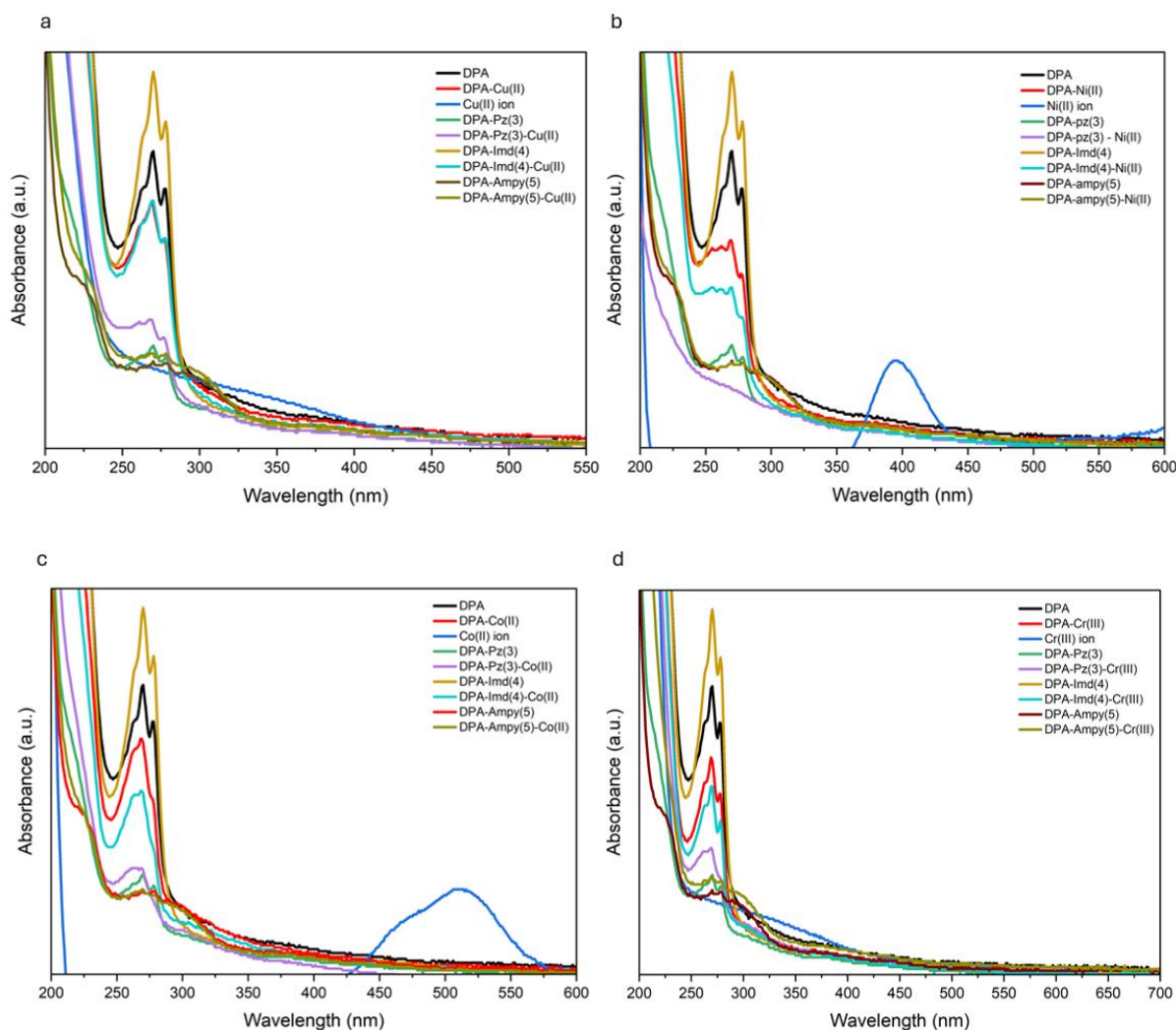


Figure 4.27 a): UV-Vis of a): Cu(II) with DPA and DPA derivatives b): Ni(II) with DPA and DPA derivatives. c): Co(II) with DPA and DPA derivatives. e): Cr(III) with DPA and DPA derivatives.

The coordination behavior of DPA has been studied extensively in literature due to the ability of the acid to form metallic complexes with a wide range of metal ions **Table 2.4**. This was also shown in **Figure 4.26a** which presents the absorption spectra of DPA with different metal ions. Distinct absorption patterns were observed in the absorption spectrum of DPA- M^{n+} in contrast to uncoordinated DPA, suggesting the formation of metallic complexes and accordingly aligning with the available literature (Abdolmaleki et al., 2018; Ghadermazi et al., 2015; Xu et al., 2013). Hypochromic shifts were noticed in the λ_{max} of the coordinated DPA due to the formation of coordination covalent bonds with metals **Figure 4.26a**. Likewise, absorption spectra of DPA-Pz **3**, DPA-Imd **4** and DPA-Ampy **5** with various metal ions showed hypochromic and

hyperchromic shifts compared to uncoordinated heterosynthons **Figure 4.26b, c, and d**. However, limited colorimetric sensing results were obtained using DPA and its derivatives due to the several factors of color developments explained formerly.

The possible adducts/complexes, DPA-Cu(II), DPA-pz**3**-Cu(II), DPA-Imd**4**-Cu(II), and DPA-ampy-Cu(II) showed cyan color, therefore it was expected to observe absorption peaks in the range of 490-520 nm, however, due to the subtle nature of the color, very slight absorption was noticed in visible region range **Figure 4.27a**.

The DPA-Ni(II), DPA-Imd**4**-Ni(II) exhibited light green color showed as broad and minimal absorption peaks in the range of 400-424 nm. The DPA-Pz**3**-Ni(II) was expected to show color change due to the similarity of the Imd compound. According to the absorption spectra, DPA-Pz**3**-Ni(II) showed hypochromic shift in the spectrum compared to uncoordinated DPA-Pz, pointing to its ability to form coordination complex with Ni(II). The negligible color change in DPA-Pz**3**-Ni(II) solution is possibly attributed to the faintness nature of the color. The adduct DPA-Ampy**5**-Ni(II) showed almost identical absorption pattern compared to that of the individual heterosynthon, indicating unsuccessful coordination complex formation. This is also aligned with current literature as there have been no reported studies of Ampy exhibiting notable coordination complexity with Ni(II) **Figure 4.27b**.

The mixture of DPA-Pz**3**-Co(II), and DPA-Imd**4**-Co(II) exhibited very light pink color and was expected to have absorption peaks in the range of 450-550 nm. However, slight differences in the optical spectra were observed in the ultraviolet region and very similarly to others, due to the weak color, the absorption peaks in the visible range were broad with small intensities (approaching to zero in the anticipated range). The DPA-Co(II) showed clear hypochromic shift, indicating the possible formation of a metal complex **Figure 4.27c**

Compound **5** and its interaction with Cr(III) i.e., DPA-Ampy**5**-Cr(III) showed clear yellow green solution and was anticipated to have absorption peaks in the range of 400-

424 nm **Figure 4.27d.** None of the other Cr(III) derivatives displayed rapid color changes within a short time of seconds during the experiment. However, after a few days, they exhibited a clear purple color.

As a summary of this part, absorption spectra were crucial to observe the optical differences result due to the formation of a metal complex. In the ultraviolet region, notable shifts in intensity, as well as the broadening and narrowing of peaks, were clearly observed. However, in the visible region, the spectral differences were insignificant due to the minimal absorption. Despite this, subtle and broad absorption bands were still observable for the detectable ions, which contributed to the appearance of faint colors in the complexes. The weak colors observed can be attributed to d-d transitions and charge transfer processes, which vary depending on the metal center (with its distinct electron configuration in the d orbitals) and the nature of the ligands involved, in addition to the geometry of the metal-complex. A detailed understanding of these variations for each specific metal-ligand complex formation remains a topic for future research. To enhance the intensity of the obtained colors, several strategies could be considered. For instance, incorporating highly conjugated systems into the heterosynthons could help in shifting the absorption into the visible region. Additionally, using stronger ligands could increase the splitting of d orbitals, leading to more shifts in the visible range and therefore better colorimetric sensing results.

Chapter 5 Future Work and Conclusion

5.1 Future Work

Based on the results obtained from this research, there are still several potential directions for future work to enrich the knowledge in the field of synthesizing hydrogen-bonded heterosynthons for sensing applications, as well as addressing the limitations encountered in this study.

Comprehensive understanding of the probabilities of salt/cocrystal formation would provide insights into the products formed and facilitate the selection of appropriate precursors for the desired applications. Although some studies have addressed the reliability of the pK_a rule, there is still a need for thorough investigations particularly focused on acids with multiple pK_a values within the range of 1-4, which remains relatively underexplored. The pK_a rule is also limited for the prediction of salt/cocrystals formation. Exact prediction of subclasses of salts/cocrystals is not possible.

Comparative studies evaluating the effectiveness of cocrystals/salts in detecting metal ions are crucial for drawing more definitive conclusions.

In addition, In-depth study of the effect of synthesis and cocrystalization methods on the type of the product formed, is still necessary. Even though FT-IR can provide valuable insights into the salt/cocrystal structure, incorporating single crystal XRD is a strong demand for confirmation purposes. To optimize the synthetic method, researchers should focus on preparing hydrogen-bonded heterosynthons using the optimal mole ratios predicted from the binary phase diagrams.

Moreover, enhancing the color intensities of the developed heterosynthons is a key area for improvement. Most of the colors obtained in this study were weak, with broad and minimal absorption peaks in the visible range. Increasing the conjugation within the heterosynthons structures can lead to a large shift in the absorption

wavelength to the visible range, thereby increasing color strength and enhancing the overall efficiency as a colorimetric sensor.

It is also crucial to conduct sensitivity and selectivity tests to implement these sensors effectively in real environmental sensing applications. These studies were not performed in the current work due to the slight absorption and lack of a prominent peak in the visible range, future research should focus on determining the maximum wavelength in the visible range and calculating the limit of detection.

5.2 Conclusion

A series of hydrogen-bonded heterosynthons were successfully synthesized using the slow evaporation method and all compounds were characterized using various analytical techniques, including FT-IR, UV-Vis, ^1H -NMR, and PXRD. Additionally, physical mixtures of the same precursors were prepared, and binary phase diagrams were constructed to determine the optimal mole ratio for synthesizing the heterosynthons and to identify the equilibrium phases.

The proposed structures of the heterosynthons were determined based on the presence or absence of specific functional groups, such as O-H, N-H, and protonated C=O, in the IR spectra of both the physical mixtures and the heterosynthons, in addition to the theoretical suggestions made depending on the difference in pK_a values. Further characterization using single crystal XRD could provide additional confirmation of the type of the product. It was found that all heterosynthons, except PHT-Ampy, formed cocrystals or salt cocrystal, while PHT-Ampy was identified as a molecular salt. The products obtained were confirmed to be pure and crystalline based on the spectral patterns observed in the PXRD diffractograms.

Furthermore, almost all heterosynthons demonstrated enhanced colorimetric sensing efficiency towards metal ions. However, two of the heterosynthons, namely DPA-Pz and DPA-Ampy, did not show notable color changes in the presence of Ni(II) as the acid. The DPA-Pz showed hypochromic shifts in the absorption spectra, pointing to its possibility to form a metal complex. Improvement in structural conjugation could

lead to more discernible detection results for Ni(II). It is worth noting that Ampy has not been reported as capable ligand of forming Ni(II) complexes, However, with PHT it showed spectral shifts suggesting the possible formation of the coordination bond while in DPA it exhibited identical spectral pattern. This may be due to the higher affinity of PHT to Ni(II) compared to DPA.

In conclusion, this research showed that hydrogen-bonded heterosynthons formed between acids and specific bases could enhance the coordination aspect of the parental molecules and accordingly, the colorimetric detection results could be enhanced in some cases. However, it is worth mentioning that this phenomenon could be improved by enhancing the conjugation in the prepared heterosynthons, to intensify the obtained color and thereby moving the wavelength to visible region.

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مُلخص البحث

تُظهر التركيبات العضوية غير المتجانسة غير التساهمية خصائص محسنة على التقيض من مكوناتها الفردية، مما يجعلها واعدة لمختلف التطبيقات. على وجه التحديد، أظهرت المركبات غير المتجانسة المرتبطة بالهيدروجين سلوكًا تنسيقًا فعالاً مع أيونات معدنية متنوعة، مما يشير إلى قدرتها على الاستشعار البصري السريع. إن تركيبها الكيميائي وطريقة تحضيرها تجعلها مرشحة جيدة لأغراض الكشف الكيميائي. في هذه الدراسة، تم تحضير خمسة مركبات غير متجانسة مرتبطة بالهيدروجين، حمض الفثاليك-٢-أمينو-٣-ميثيل بيريدين ١، حمض الفثاليك-إيميدازول ٢، حمض ديبيكولينيك-بيرازول ٣، حمض ديبيكولينيك-إيميدازول ٤، وحمض ديبيكولينيك-٢-أمينو-٣-ميثيلبيريدين ٥ باستخدام اثنين من الأحماض الثنائية الكربوكسيلية المتميزة عن طريق التبخر البطيء وتم تشخيصهما باستخدام التقنيات الطيفية مثل التحليل الطيفي للأشعة تحت الحمراء والتحليل الطيفي للأشعة فوق البنفسجية و المرئية و الرنين المغناطيسي النووي للهيدروجين و تحليل الأشعة السينية لمسحوق المادة المحضرة. كما تم تحضير المخاليط الفيزيائية بنسب مولية مختلفة، باستخدام نفس المواد الكيميائية من خلال طريقة الطحن. إضافة على ذلك تم إنشاء مخططات الطور الثنائي، وتم إجراء التحليل الطيفي للأشعة الحمراء للمخاليط الفيزيائية لاقتراح نوع التركيب الغير متجانس الذي تم تحضيره. علاوةً على ذلك تم فحص كفاءة الكشف اللونية للمركبات المصنعة تجاه مجموعة واسعة من أيونات المعادن ومقارنتها بكفاءة أحماضها الفردية. ومن المثير للاهتمام أن جميع المركبات الغير متجانسة المرتبطة بالهيدروجين التي تم تصنيعها أظهرت أداءً محسناً للاستشعار اللوني تجاه الأيونات المعدنية مقارنةً بالمواد الأولية. ومع ذلك، حمض ديبيكولينيك-بيرازول ٣ وحمض ديبيكولينيك-٢-أمينو-٣-ميثيلبيريدين ٥، لم يظهر أي تغير ملحوظ في اللون في وجود أيون النيكل. يمكن تعزيز ذلك من خلال تحسين الاقتران الهيكلي للمركبات المحضرة وبالتالي تكثيف اللون الذي تم الحصول عليه وتعزيز نتائج الكشف اللوني بالعين المجردة.

جامعة البحرين

قسم الكيمياء



كلية العلوم

تقييم الكفاءة الاستشعارية لمشتقات أحماض عضوية مختارة تجاه أيونات المعادن في الوسط المائي

رسالة مقدمة لاستكمال جزئي لمتطلبات درجة الماجستير في الكيمياء البيئية

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