

From intermolecular forces to physical properties via crystal engineering

by

Nayani Aloka Amarasooriya Marasinghe Prins

BSc (Honors), University of Kelaniya, 2019

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2026

Abstract

Acetylated 2-aminopyridine derivatives tend to form two distinct types of homomeric interactions in the solid state. To elucidate why these specific assemblies form, we examined the structural landscape of two families of acetylated 2-aminopyridines; 5-NO₂ and 3-Cl, 5-CF₃. In the NO₂ series, increasing steric demands induce a switch from N-H···C=O chains to N-H···N(pyridine) dimers. In contrast, the 3-Cl, 5-CF₃ series consistently formed infinite N-H···O=C chains, indicating that electrostatics governs the assembly. In addition, we also noted that IR spectroscopy may be used to predict the type of interaction formed. To verify this observation, two more series were examined using IR spectroscopy and crystallography. It was found that chain-forming compounds exhibited C=O stretching modes at 1655-1688 cm⁻¹, whereas the dimers appeared at 1697-1709 cm⁻¹. 20 of 22 compounds (91%) fit this behavior, confirming that IR spectroscopy can serve as a useful diagnostic structural tool when suitable single crystals are unavailable.

The effect of chain vs dimer motifs on cocrystallization was then studied using extensive cocrystallization experiments (~500 grindings), and results revealed that dimer-forming targets formed significantly more cocrystals (66%) than chain-forming targets (10%), likely due to weaker interactions, an explanation which was validated through interaction energy calculations.

A study on acetylated 2-aminopyrimidine derivatives introduced an additional acceptor site relative to the pyridine system, enhancing the structural complexity. Across 22 crystal structures, variations in alkyl chain length and halogen-atom substitution did not alter primary hydrogen-bonding motifs. Notably, strong hydrogen bonds can be replaced by halogen bonds without disrupting the overall crystal assembly, and halogen bonds exhibit greater directionality, highlighting their potential as reliable alternatives in crystal engineering.

Stoichiometric control in cocrystals was examined using mechanochemical and solution methods. Varying coformer ratios during grinding enabled the selective cocrystal formation with distinct stoichiometries. However, solution crystallizations were strongly influenced by solubility, solvation, nucleation, and coformer strength. These findings emphasize the interplay between thermodynamic stability and kinetic accessibility in determining crystallization outcomes.

A structure-property study of 2-aminopyrazine derivatives examined the odd-even effect on bulk properties. The results demonstrate that the odd-even effect clearly influences thermal stability but does not affect hygroscopicity; subtle variations in molecular structure can significantly affect macroscopic thermal and hygroscopic properties.

A structure-property analysis of an iodo analogue of the antiviral drug favipiravir, showed an increased crystal form diversity and produced cocrystals with generally higher thermal stability than those of favipiravir.

Finally, nine cocrystals of *N*-(5-nitropyridin-2-yl) amide derivatives with two different coformers were synthesized and characterized. Coformer changes exhibited notable color differences during grindings, supported by UV-visible spectroscopy and photoluminescence studies. The photophysical properties can be rationalized and predicted using calculated HOMO-LUMO gaps, demonstrating a strategy for controlled bottom-up design of functional cocrystals.

From intermolecular forces to physical properties via crystal engineering

by

Nayani Aloka Amarasooriya Marasinghe Prins

BSc (Honors), University of Kelaniya, 2019

A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2026

Approved by:

Major Professor
Dr. Christer B. Aakeröy

Copyright

© Nayani Aloka Marasinghe Prins 2026.

Abstract

Acetylated 2-aminopyridine derivatives tend to form two distinct types of homomeric interactions in the solid state. To elucidate why these specific assemblies form, we examined the structural landscape of two families of acetylated 2-aminopyridines; 5-NO₂ and 3-Cl, 5-CF₃. In the NO₂ series, increasing steric demands induce a switch from N-H···C=O chains to N-H···N(pyridine) dimers. In contrast, the 3-Cl, 5-CF₃ series consistently formed infinite N-H···O=C chains, indicating that electrostatics governs the assembly. In addition, we also noted that IR spectroscopy may be used to predict the type of interaction formed. To verify this observation, two more series were examined using IR spectroscopy and crystallography. It was found that chain-forming compounds exhibited C=O stretching modes at 1655-1688 cm⁻¹, whereas the dimers appeared at 1697-1709 cm⁻¹. 20 of 22 compounds (91%) fit this behavior, confirming that IR spectroscopy can serve as a useful diagnostic structural tool when suitable single crystals are unavailable.

The effect of chain vs dimer motifs on cocrystallization was then studied using extensive cocrystallization experiments (~500 grindings), and results revealed that dimer-forming targets formed significantly more cocrystals (66%) than chain-forming targets (10%), likely due to weaker interactions, an explanation which was validated through interaction energy calculations.

A study on acetylated 2-aminopyrimidine derivatives introduced an additional acceptor site relative to the pyridine system, enhancing the structural complexity. Across 22 crystal structures, variations in alkyl chain length and halogen-atom substitution did not alter primary hydrogen-bonding motifs. Notably, strong hydrogen bonds can be replaced by halogen bonds without disrupting the overall crystal assembly, and halogen bonds exhibit greater directionality, highlighting their potential as reliable alternatives in crystal engineering.

Stoichiometric control in cocrystals was examined using mechanochemical and solution methods. Varying coformer ratios during grinding enabled the selective cocrystal formation with distinct stoichiometries. However, solution crystallizations were strongly influenced by solubility, solvation, nucleation, and coformer strength. These findings emphasize the interplay between thermodynamic stability and kinetic accessibility in determining crystallization outcomes.

A structure-property study of 2-aminopyrazine derivatives examined the odd-even effect on bulk properties. The results demonstrate that the odd-even effect clearly influences thermal stability but does not affect hygroscopicity; subtle variations in molecular structure can significantly affect macroscopic thermal and hygroscopic properties.

A structure-property analysis of an iodo analogue of the antiviral drug favipiravir, showed an increased crystal form diversity and produced cocrystals with generally higher thermal stability than those of favipiravir.

Finally, nine cocrystals of *N*-(5-nitropyridin-2-yl) amide derivatives with two different coformers were synthesized and characterized. Coformer changes exhibited notable color differences during grindings, supported by UV-visible spectroscopy and photoluminescence studies. The photophysical properties can be rationalized and predicted using calculated HOMO-LUMO gaps, demonstrating a strategy for controlled bottom-up design of functional cocrystals.

Table of Contents

List of Figures	xvi
List of Tables	xxii
Acknowledgements	xxiv
Dedication	xxviii
Preface	xxix
Chapter 1 - Introduction	1
1.1 Structure-property relationship	1
1.2 Polymorphism	3
1.2.1 Conformational polymorphism	3
1.2.2 Packing polymorphism	4
1.3 Covalent vs supramolecular chemistry	5
1.4 Non-covalent interactions	6
1.4.1 Hydrogen bonds	7
1.4.2 Halogen bonds	7
1.4.3 Charge-transfer interactions	9
1.5 Supramolecular synthons	10
1.6 Cocrystals and their importance	12
1.6.1 Formation and characterization of cocrystals	12
1.6.2 Hydrogen-bond-based cocrystals	14
1.6.3 Halogen-bond-based cocrystals	16
1.6.4 Charge-transfer-based cocrystals	20
1.6.5 Applications of cocrystals	20
1.6.5.1 Pharmaceutical cocrystals	20
1.7 Goals of the dissertation	22
1.8 References	24
Chapter 2 - The structural landscape of 2-aminopyridine derivatives: Chains or Dimers?	32
2.1 Introduction	32
2.2 Experimental section	35
2.2.1 General	35

2.2.2 Syntheses of the 5-NO ₂ series.....	35
2.2.2.1 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)acetamide (NO ₂ -methyl).....	35
2.2.2.2 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)propionamide (NO ₂ -ethyl).....	36
2.2.2.3 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)butyramide (NO ₂ -propyl)	36
2.2.2.4 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)pentanamide (NO ₂ -butyl)	37
2.2.2.5 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)hexanamide (NO ₂ -pentyl).....	37
2.2.2.6 Synthesis of <i>N</i> -(5-nitropyridin-2-yl)benzamide (NO ₂ -phenyl).....	37
2.2.3 Syntheses of the Cl-CF ₃ series	38
2.2.3.1 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)acetamide (Cl-CF ₃ -methyl)	38
2.2.3.2 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)propionamide (Cl-CF ₃ -ethyl)	38
2.2.3.3 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)butyramide (Cl-CF ₃ -propyl).....	39
2.2.3.4 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)pentanamide (Cl-CF ₃ -butyl).....	39
2.2.3.5 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)hexanamide (Cl-CF ₃ -pentyl)	40
2.2.3.6 Synthesis of <i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)benzamide (Cl-CF ₃ -phenyl)	40
2.2.4 Reaction conditions for obtaining the polymorphs	41
2.2.4.1 <i>N</i> -(5-nitropyridin-2-yl)acetamide-Polymorph II.....	41
2.2.4.2 <i>N</i> -(5-nitropyridin-2-yl)butyramide-Polymorph II.....	41
2.2.5 Molecular electrostatic potential calculations (MEP).....	42
2.3 Results.....	42
2.3.1 MEP values	42
2.3.1.1 MEP values of the NO ₂ series.....	42
2.3.1.2 MEP values of the Cl-CF ₃ series	42
2.3.2 SCXRD analysis of target materials	43
2.3.3 FTIR results of target materials	46
2.4 Discussion.....	46

2.5 Conclusions.....	51
2.6 References.....	52
Chapter 3 - Can FTIR spectroscopy be used as a diagnostic tool to identify bonding modes of	
amide derivatives of 2-aminopyridine in the solid-state?	57
3.1 Introduction.....	57
3.2 Experimental section.....	59
3.2.1 General	59
3.2.2 Syntheses of the 3,5-dibromo series	60
3.2.2.1 Synthesis of <i>N</i> -(3,5-dibromopyridin-2-yl)propionamide (3,5-diBr-ethyl)	60
3.2.2.2 Synthesis of <i>N</i> -(3,5-dibromopyridin-2-yl)butyramide (3,5-diBr-propyl).....	60
3.2.2.3 Synthesis of <i>N</i> -(3,5-dibromopyridin-2-yl)pentanamide (3,5-diBr-butyl).....	60
3.2.2.4 Synthesis of <i>N</i> -(3,5-dibromopyridin-2-yl)hexanamide (3,5-diBr-pentyl)	61
3.2.3 Syntheses of the 3-iodo series.....	61
3.2.3.1 Synthesis of <i>N</i> -(3-iodopyridin-2-yl)acetamide (3-I-methyl)	61
3.2.3.2 Synthesis of <i>N</i> -(3-iodopyridin-2-yl)butyramide (3-I-propyl)	61
3.2.3.3 Synthesis of <i>N</i> -(3-iodopyridin-2-yl)pentanamide (3-I-butyl)	62
3.2.3.4 Synthesis of <i>N</i> -(3-iodopyridin-2-yl)hexanamide (3-I-pentyl)	62
3.2.4 Molecular electrostatic potential calculations (MEP).....	63
3.3 Results.....	63
3.3.1 MEP values of target materials	63
3.3.1.1 MEP values of the 3,5-dBr series	64
3.3.1.2 MEP values of the 3-iodo series	64
3.3.2 SCXRD analysis of target materials	64
3.4 Discussion.....	68
3.5 Conclusions.....	69
3.6 References.....	70
Chapter 4 - How do dimer and chain motifs of 2-aminopyridine derivatives influence cocrystal	
formation with carboxylic acids?.....	73
4.1 Introduction.....	73
4.2 Experimental section.....	76
4.2.1 Cocrystal screening with liquid-assisted grinding	76

4.2.2 Interaction energy calculations	78
4.3 Results.....	78
4.3.1 FTIR analysis of the ground samples.....	78
4.3.2 Crystal growth.....	81
4.3.3 SCXRD analysis of cocrystals	83
4.3.4 Interaction energies of the targets	84
4.4 Discussion.....	85
4.5 Conclusions.....	88
4.6 References.....	89
Chapter 5 - How molecular complexity governs the intermolecular interactions of amide-	
substituted 2-aminopyrimidine derivatives?	91
5.1 Introduction.....	91
5.2 Experimental section.....	93
5.2.1 General	93
5.2.2 Syntheses of the PM Series	94
5.2.2.1 Synthesis of <i>N</i> -(pyrimidin-2-yl)acetamide (PM-methyl).....	94
5.2.2.2 Synthesis of <i>N</i> -(pyrimidin-2-yl)propionamide (PM-ethyl).....	94
5.2.2.3 Synthesis of <i>N</i> -(pyrimidin-2-yl)butyramide (PM-propyl)	95
5.2.2.4 Synthesis of <i>N</i> -(pyrimidin-2-yl)pentanamide (PM-butyl)	95
5.2.2.5 Synthesis of <i>N</i> -(pyrimidin-2-yl)hexanamide (PM-pentyl).....	95
5.2.2.6 Synthesis of <i>N</i> -(pyrimidin-2-yl)heptanamide (PM-hexyl).....	96
5.2.2.7 Synthesis of <i>N</i> -(pyrimidin-2-yl)octanamide (PM-heptyl)	96
5.2.3 Syntheses of the Cl-PM Series.....	97
5.2.3.1 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)acetamide (Cl-PM-methyl).....	97
5.2.3.2 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)propionamide (Cl-PM-ethyl)	97
5.2.3.3 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)butyramide (Cl-PM-propyl).....	97
5.2.3.4 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)pentanamide (Cl-PM-butyl).....	97
5.2.3.5 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)hexanamide (Cl-PM-pentyl).....	98
5.2.3.6 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)heptanamide (Cl-PM-hexyl).....	98
5.2.3.7 Synthesis of <i>N</i> -(5-chloropyrimidin-2-yl)octanamide (Cl-PM-heptyl).....	98
5.2.4 Syntheses of the Br-PM Series	99

5.2.4.1 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)acetamide (Br-PM-methyl)	99
5.2.4.2 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)propionamide (Br-PM-ethyl).....	99
5.2.4.3 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)butyramide (Br-PM-propyl)	99
5.2.4.4 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)pentanamide (Br-PM-butyl)	100
5.2.4.5 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)hexanamide (Br-PM-pentyl)	100
5.2.4.6 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)heptanamide (Br-PM-hexyl)	100
5.2.4.7 Synthesis of <i>N</i> -(5-bromopyrimidin-2-yl)octanamide (Br-PM-heptyl)	101
5.2.5 Molecular electrostatic potential calculations (MEP).....	102
5.3 Results.....	102
5.3.1 MEP values of the target materials	102
5.3.1.1 MEP values of the PM Series	102
5.3.1.2 MEP values of the Cl-PM series.....	103
5.3.1.3 MEP values of the Br-PM series.....	103
5.3.2 SCXRD analysis of the target materials	103
5.4 Discussion.....	108
5.5 Conclusions.....	111
5.6 References.....	112
Chapter 6 - Can the stoichiometry of cocrystals be controlled?	116
6.1 Introduction.....	116
6.2 Experimental section.....	119
6.2.1 General	119
6.2.2 Synthesis of the 5-(pyridin-3-yl) pyrimidin-2-amine (PM)	120
6.2.3 Cocrystal screening by liquid-assisted grinding (LAG)	120
6.3 Results.....	121
6.3.1 MEP values of the target molecule and coformers	121
6.3.1.1 Correlations of coformer donor and acceptor MEPs with pKa values	121
6.3.2 FTIR evidence for cocrystal formation.....	122
6.3.3 DSC analysis of cocrystals.....	124
6.3.4 SCXRD analysis of target material (PM) and its cocrystals.....	126
6.3.4.1 Target material/PM	126
6.3.4.2 Cocrystals.....	127

6.3.4.2.1 Crystal structure of PM-3,5-dNBA (1:1)	128
6.3.4.2.2 Crystal structure of PM-3,4-dClBA (1:1)	128
6.3.4.2.3 Crystal structures of PM-4-IBA (1:1)	129
6.3.4.2.4 Crystal structure of PM-BA (1:1).....	131
6.3.4.2.5 Crystal structures of PM-3-MBA (1:1) and PM-3-MBA (1:2).....	131
6.3.4.2.6 Crystal structures of PM-3-dMABA (1:1) and PM-3-dMABA (1:2).....	132
6.4 Discussion.....	134
6.5 Conclusions.....	138
6.6 References.....	138
Chapter 7 - Can the odd-even effect be used to dial in the structure-property relationship of	
acetylated 2-aminopyrazine derivatives?.....	141
7.1 Introduction.....	141
7.2 Experimental section.....	142
7.2.1 General	142
7.2.2 Synthesis of the PZ Series.....	142
7.2.2.1 Synthesis of <i>N</i> -(pyrazin-2-yl)acetamide (PZ2).....	142
7.2.2.2 Synthesis of <i>N</i> -(pyrazin-2-yl)propionamide (PZ3).....	143
7.2.2.3 Synthesis of <i>N</i> -(pyrazin-2-yl)butyramide (PZ4).....	143
7.2.2.4 Synthesis of <i>N</i> -(pyrazin-2-yl)pentanamide (PZ5).....	144
7.2.2.5 Synthesis of <i>N</i> -(pyrazin-2-yl)hexanamide (PZ6).....	144
7.2.2.6 Synthesis of <i>N</i> -(pyrazin-2-yl)heptanamide (PZ7).....	144
7.2.2.7 Synthesis of <i>N</i> -(pyrazin-2-yl)octanamide (PZ8).....	145
7.2.2.8 Synthesis of <i>N</i> -(pyrazin-2-yl)nonanamide (PZ9).....	145
7.2.3 Thermal Stability Analysis	146
7.2.4 Hygroscopicity Studies	146
7.3 Results.....	147
7.3.1 SCXRD analysis of target materials	147
7.3.2 Thermal stability of target materials	148
7.3.3 Hygroscopicity of target materials.....	149
7.4 Discussion.....	150
7.5 Conclusions.....	153

7.6 References.....	154
Chapter 8 - Analogue of favipiravir and its cocrystals: Insights into structure-property relationships.....	158
8.1 Introduction.....	158
8.2 Experimental section.....	161
8.2.1 General.....	161
8.2.2 Synthesis	161
8.2.2.1 Synthesis of 2-hydroxy-5-iodobenzamide (I-Fav).....	161
8.2.2.2 Cocrystal synthesis by liquid-assisted grinding (LAG).....	162
8.3 Results.....	162
8.3.1 FTIR and DSC analysis of I-Fav	162
8.3.2 SCXRD analysis of I-Fav	163
8.3.3 Cocrystallization results of I-Fav	166
8.3.4 SCXRD results of cocrystals.....	168
8.3.5 Thermal stability of cocrystals	170
8.4 Discussion.....	170
8.5 Conclusions.....	173
8.6 References.....	174
Chapter 9 - Can we modulate some photophysical properties of cocrystals?.....	176
9.1 Introduction.....	176
9.2 Experimental section.....	178
9.2.1 General.....	178
9.2.2 Preparation of the cocrystals	179
9.2.3 Solid-state replacement studies.....	180
9.3 Results.....	181
9.3.1 Physical appearance	181
9.3.2 Infrared spectra (IR) analysis.....	182
9.3.3 Crystal structure analysis (SCXRD)	183
9.3.4 Powder X-ray diffraction (PXRD) analysis	187
9.3.5 HOMO-LUMO calculations	187
9.3.5 Charge transfer character	189

9.3.6 Photophysical properties	191
9.3.6.1 Solid-state UV absorption.....	191
9.3.6.2 Photoluminescence studies	192
9.3.7 Solid-state replacement studies.....	193
9.4 Discussion.....	193
9.5 Conclusions.....	195
9.6 References.....	196
Chapter 10 - Future work.....	200
10.1 References.....	203
Appendix A - Additional information for Chapter 1	205
Appendix B - Additional information for Chapter 2	215
Appendix C - Additional information for Chapter 3	227
Appendix D - Additional information for Chapter 4	233
Appendix E - Additional information for Chapter 5.....	245
Appendix F - Additional information for Chapter 6.....	263
Appendix G - Additional information for Chapter 7	266
Appendix H - Additional information for Chapter 8	272
Appendix I - Additional information for Chapter 9.....	280
Appendix J - Additional information for Chapter 10.....	294

List of Figures

Figure 1.1. Correlation of the melting points with the α,ω -Alkanedicarboxylic acids chain length. ¹²	1
Figure 1.2. Enantiomers of thalidomide	2
Figure 1.3. Categorization of polymorphism.	3
Figure 1.4. Intermolecular interactions of form I and form II of ritonavir. ²³	4
Figure 1.5. Two polymorphs of aspirin. ²⁶	5
Figure 1.6. Covalent vs supramolecular synthesis.	5
Figure 1.7. Schematic representation of a hydrogen bond.	7
Figure 1.8. Schematic representation of a halogen bond.	8
Figure 1.9. Triply activated XB donors, showing the σ -hole potentials on the iodine atom computed using DFT at the B3LYP/6-311++G** level of theory at iso = 0.002. ⁴⁹	9
Figure 1.10. Illustration of the energy gap.	10
Figure 1.11. Supramolecular synthons.	11
Figure 1.12. Schematic representation of recrystallization and cocrystallization.	11
Figure 1.13. An illustration of a cocrystal.	12
Figure 1.14. Summary of the synthetic methods, supramolecular interactions, and characterization methods used to study cocrystals in this dissertation.	13
Figure 1.15. A schematic representation of the caffeine-oxalic acid cocrystal. ⁷⁷	14
Figure 1.16. Representative hydrogen-bonding motifs: (a) sulfonamide...pyridine (N-H...N), (b) sulfonamide...amide (N-H...O), and (c) sulfonamide...amine (N-H...N). ⁷⁸	15
Figure 1.17. Cocrystal structures of IDP with (a) 4,4'-dipyridyl, showing sulfonamide...pyridine (N-H...N) heteromeric synthons and <i>N</i> -methylpyridone, showing sulfonamide...amide (N-H...O) heterosynthons. ⁷⁸	15
Figure 1.18. A cocrystal capsule held together by multiple carboxylic acid-aminopyrimidine interactions. ⁶¹	16
Figure 1.19. Representation of infinite chains between 4,4'-dipyridyl with (a) 1,4-dibromotetrafluorobenzene, (b) 1,3-dibromotetrafluorobenzene, and (c) 1,2-dibromotetrafluorobenzene.	17
Figure 1.20. Halogen-bond donor and acceptors of the study. ⁸³	18

Figure 1.21. Halogen bonding motifs in (a) α -(titfb)(2bzpy) (b) α -(titfb)(3bzpy), and (c) α -(titfb)(4bzpy). ⁸³	18
Figure 1.22. Molecular structures of the XB acceptor (left) and donor (right) used for the construction of the capsule. ⁸⁰	19
Figure 1.23. Representation of the molecular capsule where I $\cdots$ N XB bonds are shown as dotted black lines. Color code: carbon, gray; nitrogen, blue; oxygen, red; iodine, purple; fluorine, yellow; hydrogen, white. ⁸⁰	19
Figure 1.24. Charge-transfer cocrystals formed between the 9-(3-(pyren-1-yl)phenyl)-9H-carbazole (1PY-mCzB) and 1,2,4,5-tetracyanobenzene (TCNB). ⁸⁵	20
Figure 1.25. Indomethacin-saccharin cocrystal, interactions, and vapor sorption and desorption isotherms. ⁹⁹	21
Figure 1.26. The Entresto cocrystal. ¹⁰⁰	22
Figure 2.1. Examples of pharmaceutically relevant molecules containing <i>N</i> -(pyridin-2-yl) amides.	33
Figure 2.2. Two prevalent modes of self-aggregation of 2-aminopyridine amides, (a) i & ii; chains, (b) dimer.	34
Figure 2.3. Schematic diagram of molecular structures of compounds in this study.	35
Figure 2.4. MEP values (kJ/mol) at the most likely hydrogen bond donor and acceptor sites in the twelve targets.	42
Figure 2.5. Primary hydrogen-bond interactions in the crystal structures of (a) NO ₂ -methyl, (b) NO ₂ -ethyl, (c) NO ₂ -propyl, (d) NO ₂ -butyl, (e) NO ₂ -pentyl, and (f) NO ₂ -phenyl.	43
Figure 2.6. Chain motif in polymorph II of NO ₂ -methyl;(b) ribbon motif in polymorph II of NO ₂ -propyl.	44
Figure 2.7. Primary hydrogen bonds in the crystal structures of (a) Cl-CF ₃ -methyl, (b) Cl-CF ₃ -ethyl, (c) Cl-CF ₃ -propyl, (d) Cl-CF ₃ -butyl, (e) Cl-CF ₃ -pentyl, and (f) Cl-CF ₃ -phenyl.	45
Figure 2.8. Conformational difference between the NO ₂ series (left) and the Cl-CF ₃ series (right) with respect to the amide group.	47
Figure 2.9. MEP summary of series 1 and 2.	48
Figure 2.10. Schematic representation of the range of bands for dimers and chains.	49
Figure 2.11. Summary of key findings of the study.	51
Figure 3.1. Schematic representation of the range of bands for dimers and chains.	58

Figure 3.2. MEP values (kJ/mol) at the most likely hydrogen-bond donor and acceptor sites in the eight targets.	64
Figure 3.3. Primary hydrogen-bond interactions in the crystal structures of (a) 3,5-diBr-ethyl, (b) 3,5-diBr-propyl, (c) 3,5-diBr-butyl, and (d) 3,5-diBr-pentyl.....	65
Figure 3.4. Primary hydrogen bonds in the crystal structures of (a) 3-iodo-methyl, (b) 3-iodo-propyl, (c) 3-iodo-butyl, and (d) 3-iodo-pentyl.....	66
Figure 3.5. Different C=O groups observed in 3-iodo-methyl and 3-iodo-pentyl.....	68
Figure 3.6. Schematic representation of the range of bands for dimers and chains.	69
Figure 4.1. Interactions observed among target molecules.....	73
Figure 4.2. Target molecules used in this study.....	74
Figure 4.3. Possible outcomes of cocrystallization experiments.	75
Figure 4.4. Some of the cocrystal structures of T2, T3, T4, and T5 targets.	83
Figure 4.5. Bonding motifs and their influence on cocrystal formation based on interaction energy calculations.....	85
Figure 4.6. Influence of chain and dimer motifs on cocrystal formation.	86
Figure 4.7. The most common synthon observed between the target and coformer.	87
Figure 4.8. Influence of chain and dimer motifs on cocrystal formation.	87
Figure 4.9. Influence of coformers.	88
Figure 4.10. Key findings of the study.	88
Figure 5.1. Some FDA-approved pharmaceutical drugs with 2-aminopyrimidine moieties.....	92
Figure 5.2. Potential hydrogen bond donor-acceptor sites.	93
Figure 5.3. Postulated primary hydrogen bond motifs.	93
Figure 5.4. MEP values (kJ/mol) at the likely donor-acceptor sites in the 21 target compounds.	103
Figure 5.5. The intermolecular interactions in three different types of single crystal structures appeared in the PM series.	104
Figure 5.6. The intermolecular interactions in five different types of single crystal structures appeared in the Cl-PM series.	106
Figure 5.7. The intermolecular interactions in four different types of single crystal structures appeared in the Br-PM series.....	107
Figure 5.8. The primary intermolecular interactions in all the crystal structures.	109

Figure 5.9. Thermal stability variation of three series.	109
Figure 5.10. Key findings of the study.	111
Figure 6.1. Chemical structure of the selected target, 5-(pyridin-3-yl) pyrimidin-2-amine.	118
Figure 6.2. Chemical structures of selected coformers.	119
Figure 6.3. MEP values of the target/PM molecule. (kJ/mol).	121
Figure 6.4. The relationship between the donor MEPs and the pKa values of the coformers...	122
Figure 6.5. The relationship between the acceptor MEPs and the pKa values of the coformers.	122
Figure 6.6. FTIR analysis of PM-3-MBA (1:1) ground sample with its starting materials.....	123
Figure 6.7. DSC analysis of PM-3-MBA (1:1 and 1:2) ground samples with their starting materials.	125
Figure 6.8. The asymmetric unit and a fragment of the crystal structure of 5-(pyridin-3-yl) pyrimidin-2-amine.	127
Figure 6.9. The asymmetric unit and a fragment of the crystal structure of PM-3,5-dNBA (1:1).	128
Figure 6.10. The asymmetric unit and a fragment of the crystal structure of PM-3,4-dCIBA (1:1).	129
Figure 6.11. The asymmetric units of the crystal structures of (a) PM-4-IBA (1:1) form I, (b) PM-4-IBA (1:1) form II.	129
Figure 6.12. Schematic representation of cocrystal formation observed in the 1:1 and 1:2 slow evaporation samples.	130
Figure 6.13. The asymmetric unit and a fragment of the crystal structure of PM-BA (1:1).....	131
Figure 6.14. The asymmetric unit and fragments of the crystal structures of PM-3-MBA (1:1 and 1:2).	132
Figure 6.15. The asymmetric unit and fragments of the crystal structures of PM-3-dMABA (1:1 and PM-3-dMABA (1:2).	133
Figure 6.16. Two schematics showing (a) donor and acceptor sites of the target molecule, and (b) possible binding sites of the target molecule.	134
Figure 6.17. Schematic of nicotinamide and suberic acid.	135
Figure 6.18. A summary of cocrystal stoichiometries obtained from slow evaporation.	136
Figure 6.19. A schematic showing target binding sites of coformers with different strengths.	137

Figure 6.20. Roadmap of the key findings.....	138
Figure 7.1. Primary hydrogen-bond interactions in the crystal structures of (a) PZ2, (b) PZ3, and (c) PZ5.	147
Figure 7.2. Melting point and crystal density for PZ2-PZ9.....	149
Figure 7.3. The TGA curves of PZ2 confirming the presence of water absorption.	149
Figure 7.4. Melting point and crystal density for PZ2-PZ9 (red = melting point, black = density).	151
Figure 7.5. PXRD and SCXRD of PZ2.	151
Figure 7.6. (a) The anticipated hydrogen bonding pattern and (b), (c), (d) observed hydrogen bonding patterns.....	152
Figure 7.7. Key findings of the study.	153
Figure 8.1. The mechanism of action of favipiravir.	158
Figure 8.2. The enol (a) and keto (b) isomers of favipiravir.....	159
Figure 8.3. Chemical structure of the iodo analogue of favipiravir (2-hydroxy-5- iodobenzamide).....	160
Figure 8.4. Coformers used for the cocrystallization studies.....	160
Figure 8.5. IR spectrum of the ground mixture.	162
Figure 8.6. DSC of the ground mixture.	163
Figure 8.7. Forms of I-Fav.....	164
Figure 8.8. Form I and Form II of I-Fav with labels.....	165
Figure 8.9. Form III and Form IV of I-Fav with labels.	165
Figure 8.10. PXRD patterns of I-Fav -Theo and its starting materials.	166
Figure 8.11. IR spectra of I-Fav-Theo ground mixture and its starting materials.	167
Figure 8.12. Asymmetric units of (a) I-Fav-Theo cocrystal, (b) I-Fav-5-flu cocrystal, and (c) I- Fav-Tro cocrystal.	169
Figure 8.13. Asymmetric unit of (a) Fav-Theo cocrystal, (b) Fav-5-flu cocrystal, and (c) Fav-Tro cocrystal.	169
Figure 8.14. Thermal stability comparison of I-Fav and Fav cocrystals (* = outliers).	170
Figure 8.15. Two reported forms of favipiravir.....	171
Figure 8.16. General structure of favipiravir analogues with the 6-position labeled.	172
Figure 9.1. Chemical structures of donor and acceptor molecules.	178

Figure 9.2. Anticipated R22 (8) dimeric hydrogen-bonding motif.....	178
Figure 9.3. Physical appearance of starting materials: T3, 3DMABA, 4ABA, and their ground mixtures.....	181
Figure 9.4. Physical appearance of resultant ground mixtures.	182
Figure 9.5. (a) i. Asymmetric unit of T2-3DMABA-PI, (a) ii. $\pi\cdots\pi$ stacking, (b) i. Asymmetric unit of T2-3DMABA-P II, (b) ii. $\pi\cdots\pi$ stacking, (c) i. Asymmetric unit of T3-3DMABA, (c) ii. $\pi\cdots\pi$ stacking (blue = donor, green = acceptor).	185
Figure 9.6. (a) i. Asymmetric unit of T2-4ABA, (a) ii. $\pi\cdots\pi$ stacking (blue = donor, green = acceptor), (b) i. Asymmetric unit of T3-4ABA-P II, (b) ii. $\pi\cdots\pi$ stacking (green = donor, blue/red = acceptors), (c) i. Asymmetric unit of T5-4ABA, (c) ii. Charge-transfer structure.	186
Figure 9.7. HOMO and LUMO energy level diagrams of 3DMABA cocrystals and their starting materials.	188
Figure 9.8. HOMO and LUMO energy level diagrams of 4ABA cocrystals and their starting materials.	189
Figure 9.9. Molecular orbitals contributing to the transitions.	191
Figure 9.10. Summary of findings of the study.	195
Figure 10.1. Schematic of planned future work for Chapter 6.	200
Figure 10.2. Comparison of the growth of (1:1) and (2:1) cocrystals of benzoic acid and isonicotinamide in different solvent compositions. ⁷	202
Figure 10.3. Schematic of planned future work for Chapter 8.	203

List of Tables

Table 1.1. Estimated strengths of intermolecular interactions.....	6
Table 2.1. Solvents used for crystal growth and crystal descriptions.....	41
Table 2.2. Hydrogen bond parameters of crystal structures in the NO ₂ series	45
Table 2.3. Hydrogen bond parameters of crystal structures in the Cl-CF ₃ series.....	45
Table 2.4. The IR stretching frequency for the amide C=O group in twelve target molecules. ..	46
Table 3.1. Solvents used for crystal growth and crystal descriptions.....	63
Table 3.2. Hydrogen-bond parameters of C=O...H-N chain interaction of crystal structures in the 3,5-diBr series	66
Table 3.3. Hydrogen-bond parameters of C=O...H-N chain interaction of crystal structures in the 3-iodo series	67
Table 3.4. The IR stretching frequency for the amide C=O mode in fourteen compounds	67
Table 4.1. Coformers used in this study	76
Table 4.2. Results for strong aromatic acids.....	79
Table 4.3. Results for weak aromatic acids	79
Table 4.4. Results for aliphatic acids	80
Table 4.5. Influence of coformers.....	80
Table 4.6. Influence of targets	81
Table 4.7. Solvents used for crystal growth and crystal descriptions.....	81
Table 4.8. Interaction energy among target molecules	84
Table 4.9. Selected coformers for SCXRD analysis.....	86
Table 5.1. Solvents used for crystal growth and crystal descriptions.....	101
Table 5.2. Inter-dimer hydrogen or halogen bond angles and distances	107
Table 6.1. pK _a values of selected coformers	119
Table 6.2. MEPs of the acceptor and donor sites of the carboxylic group of coformers.....	121
Table 6.3. IR frequencies of ground samples	124
Table 6.4. Summary of positive cocrystals based on IR analysis.....	124
Table 6.5. Melting points of ground mixtures	126
Table 6.6. Summary of positive cocrystals based on DSC analysis	126
Table 6.7. Solvents used for crystal growth and crystal descriptions.....	127

Table 6.8. Summary of cocrystal formation in solution	133
Table 7.1. Solvents used for crystal growth and crystal descriptions.....	146
Table 7.2. Melting points and crystallographic densities.	148
Table 8.1. Solvents used for crystal growth and crystal descriptions.....	163
Table 8.2. Some crystallographic parameters and enol/keto ratios of four forms	164
Table 8.3. Summary of grinding experiments	167
Table 8.4. Solvents used for crystal growth and crystal descriptions.....	168
Table 8.5. Summary of key findings of the study.....	173
Table 9.1. Solvents used for crystal growth and crystal descriptions.....	179
Table 9.2. Crystallographic data	180
Table 9.3. IR frequencies of acceptors, donors and ground mixtures.....	182
Table 9.4. Calculated electronic absorption parameters	190

Acknowledgements

I believe the past few years have been among the most wonderful times of my life, during which I met so many people for whom I am truly grateful for being part of shaping who I am today. But above all, it is my advisor and mentor, Professor Christer Aakeröy, whose guidance, trust, patience, kindness, and care made this journey so rewarding, and without him, it simply would not have been the same. Therefore, first and foremost, I would like to express my deepest gratitude to him for his immense support, for believing in me, and for accepting me as I am. I am grateful to him for giving me this opportunity to join his amazing research group, and I consider myself incredibly fortunate and privileged to learn and grow under his guidance. I am also thankful that he has remained the same genuine and welcoming person I first met throughout all these years. I have learned so much from him, and if I am a better researcher, writer, and presenter today, it is all thanks to him. Thank you for helping me grow into a more confident individual and for always being there for me whenever I felt lost. His incredible ability to lighten the mood during extremely stressful times, along with his sense of humor, made the journey much easier. Finally, thank you for being my family away from home.

I am especially grateful to Dr. Boris Averkiev for his immense contributions in collecting and solving so many of my crystal structures, and for his genuine excitement about them; without his support, my dissertation would not have been possible.

I would also like to thank my Ph.D. advisory committee members, Dr. Tendai Gadzikwa, Dr. Christine Aikens, and Dr. Bret Flanders, for their valuable time, feedback, support, flexibility, and encouragement throughout my Ph.D.

I would also like to acknowledge Dr. Jun Li and Mr. Zahirul Saddam for their support with the solid-state UV-Vis absorption experiments, Dr. Daniel Higgins and Ms. Sorour Salehi for their

support with the photoluminescence experiments, and Mr. Sulalith Samarasinghe for helpful discussions and guidance regarding the theoretical calculations.

Many thanks to the Department of Chemistry and the Johnson Cancer Research Center for funding my research throughout my time at K-State, and the NSF-MRI Grant CHE-2018414, to purchase the Rigaku XtaLAB Synergy-S single-crystal X-ray diffractometer. I would also thank the Graduate Student Council, the College of Arts and Sciences, the Johnson Cancer Research Center, and Phi Lambda Upsilon for funding numerous conferences.

I want to thank everyone in the Department of Chemistry for creating such a warm and welcoming environment. I am grateful to all the professors, especially Dr. Tendai Gadzikwa, Dr. Peter Sues, Dr. Christine Aikens, Dr. Ryan Rafferty, and Dr. Om Prakash. Special thanks to Dr. Yasmin Patell for being so caring and supportive, and for making our group gatherings so much fun. I would like to thank Dr. Higgins (former HOD) and Dr. Aakeröy for their leadership and for keeping the department running efficiently and to Mr. Micheal Hinton, Dr. Tingting Liu, Dr. Simon Sham (former NMR manager), Dr. Tomohiro Kimura, Mr. Bart Bath, Dr. Sadish Karunaweera, Mr. Tobe Eggers, and Mr. Jim Hodgson for their hard work to keep the department running smoothly. Your dedication has made my time at K-State much easier and more enjoyable. Finally, I would like to thank Ms. Kathy Roeser and Ms. Mary Dooley for assisting with paperwork when I first joined, and Ms. Kimberly Ross for creating a friendly and supportive atmosphere in the department and for always being someone I could talk to.

Special thanks to the Aakeröy group members, past and present, for their support throughout my time at K-State. I am thankful to Dr. Viraj de Silva for his guidance when I first started in the lab, and to Dr. Amila Abeysekara for her support, even though we never met in person in the lab. I would also like to thank Dr. Vinu Panikkattu, Dr. Kelly Shunje, and Dr. Nandini Sarkar for helping

me in many ways. I owe a big thank you to Trupti Patel and Marrissa Raynesford for being through all the ups and downs. I never felt lonely thanks to you both, and I will always cherish the memories we shared. I am also grateful to Jane, Daniel, Jack, Thomas, Stella, Sebastian, Ravi, Asanga, Katie, Jordan, Bella, Audrey, and Michelle for being the best.

I want to thank Kushan and Nishadi for helping me with everything when I first arrived at K-State, and Asantha and Shashika for their constant support as I adjusted to a new country. I am also grateful to all my friends in Manhattan, too many to mention individually, for being a family away from home, for making this journey enjoyable, and for always being there through the ups and downs. Life here would have been so different without you.

I am deeply grateful to my undergraduate supervisor, Dr. Shashikala Rajapakse, for believing in me even more than I did, and for encouraging me to come to the USA when I doubted myself. I am also thankful to the other amazing professors I met during my undergraduate time, as well as my inspiring teachers from school, who helped shape who I am today and believed in me.

I am deeply grateful to my mom for her unconditional love and countless blessings, for all the sacrifices she has made by putting her own dreams aside, and for giving me the strength to achieve my success. She is the strongest, bravest, yet the softest and most generous woman I have ever met in my life. I would not be who I am today without her, and she is the pillar behind every step I take. I am also deeply grateful to my dad, who has passed away. Thank you for being my best friend, the sweetest, kindest, funniest, and most wonderful person I have ever met, and for always being such a good listener. Thank you for loving me unconditionally, and your love continues to carry me wherever I go. Last but not least, I am deeply grateful to my sisters for their endless love and support. I could not have completed this journey without you.

I also want to thank all the other friends I made during this time, from my undergraduate university and school, who have been part of my journey, and I am grateful to everyone I met, though not mentioned here, who helped shape me into the person I am today. In the end, I want to thank myself for not giving up and for finally achieving my childhood dream.



Dedication

To my beloved mom and dad

for their endless love and sacrifices

&

To my sisters,

for always being there



Preface

Research carried out at Kansas State University for this dissertation led to the following publications in scientific journals:

1. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers? *Crystal Growth & Design* **2025**, 25 (20), 8703-8711. <https://doi.org/10.1021/acs.cgd.5c01222>. (Chapter 2)
2. A. Marasinghe, A.; B. Averkiev, B.; B. Aakeröy, C. Examining Intermolecular Interactions in Crystal Structures of Amide-Substituted 2-Aminopyrimidine Derivatives. *CrystEngComm* **2025**, 27 (43), 7000-7011. <https://doi.org/10.1039/D5CE00839E>. (Chapter 5)
3. A. Marasinghe, A.; B. Averkiev, B.; B. Aakeröy, C. Modulating some photophysical properties of cocrystals. *CrystEngComm* **2026**. <https://doi.org/10.1039/d6ce00063k>. (Chapter 9)

Chapter 1 - Introduction

1.1 Structure-property relationship

The relationship between molecular structure and macroscopic properties has long been recognized as a foundational concept in chemistry, dating back to the pioneering work of Wiener, who demonstrated systematic variations in boiling points with molecular size and branching.^{1,3}

Since then, structure-property relationships have become central to understanding and predicting the behavior of compounds across chemistry, biology, materials science, and engineering, etc.^{4,7}

In the solid state, crystal structure dictates many of the fundamental characteristics of a material, such as solubility, thermal and chemical stability, hygroscopicity, mechanical strength, and bioavailability, *etc.* Even small structural variations can significantly influence the physical and chemical properties of bulk materials.^{8,11}

A well-known example of how changes in molecular structure translate directly into material properties comes from alkane dicarboxylic acids.¹² It has been shown that the melting points of alkane dicarboxylic acids decrease monotonically with increasing number of methylene groups in the chain (Figure 1.1).

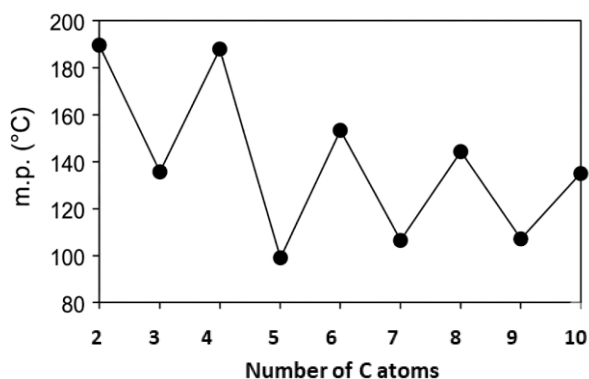


Figure 1.1. Correlation of the melting points with the α,ω -Alkanedicarboxylic acids chain length.¹²

At the same time, diacids with an even number of carbon atoms in their chains exhibit higher melting points than those with an odd number. Thus, altering the molecular structure just by adding one methylene group can result in significant and predictable changes in bulk melting properties. (Figure 1.1).

The importance of structure-property relationships is particularly evident in many pharmaceuticals, where small structural changes can have profound consequences on performance and biological activities. A well-known example of this is the thalidomide tragedy in the late 1950s, where administration of the teratogenic (S)-enantiomer alongside the therapeutic (R)-enantiomer led to severe birth defects.¹³⁻¹⁵

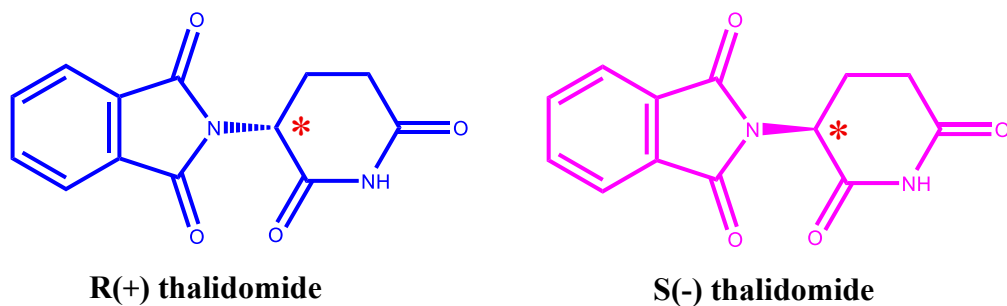


Figure 1.2. Enantiomers of thalidomide

In bulk materials, structure-property relationships arise from the inherent properties of molecules as well as from the way molecules are arranged and interact with one another in the three-dimensional solid-state. These relationships can be classified into two main fundamental categories.¹⁶ In the first category, variations in material properties originate from changes in molecular structure and conformation, such as differences in functional groups, stereochemistry, or molecular flexibility.¹⁶ In the second category, property changes come from differences in intermolecular arrangement, including molecular packing, intermolecular interactions, and spatial organization within the crystal lattice.¹⁶

1.2 Polymorphism

A specific aspect of the solid-state is the existence of polymorphism, defined as the ability of a substance to exist in more than one crystalline form.¹⁷ Polymorphism can be categorized into two main groups: conformational polymorphism and packing polymorphism (Figure 1.3).¹⁸⁻²⁰

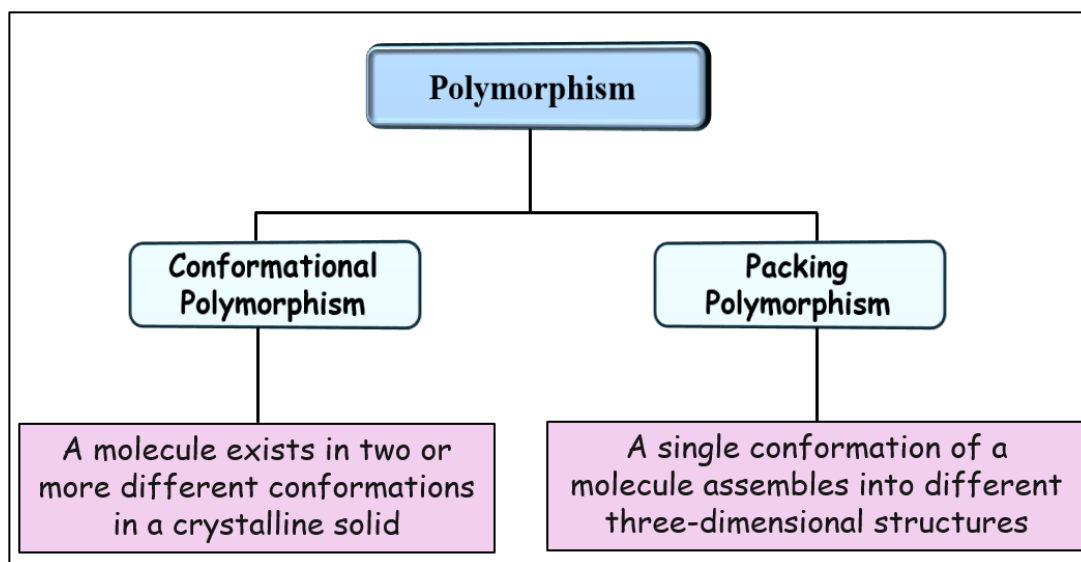


Figure 1.3. Categorization of polymorphism.

The molecules showing packing polymorphs tend to be more rigid compared to those showing conformational polymorphism.¹⁸

1.2.1 Conformational polymorphism

The antiviral drug ritonavir (Norvir), which was introduced in 1996 for the treatment of Acquired Immunodeficiency Syndrome (AIDS), provides a striking example of conformational polymorphism. The discovery of the second polymorph of ritonavir led to the temporary withdrawal of this drug from the market in 1998.²¹ In form I, ritonavir molecules assemble into β -like stacks stabilized by intermolecular hydrogen bonds. In contrast, in form II, conformational changes allow hydroxyl groups to participate more effectively in hydrogen bonding (Figure 1.4). These structural differences result in pronounced variations in physicochemical properties. For

example, form I exhibits a solubility of approximately 90 mg/mL in a 99:1 ethanol-water mixture at 5 °C. In comparison, form II shows a drastically reduced solubility of only 19 mg/mL under identical conditions.²² This example shows how subtle conformational changes can significantly alter material properties.

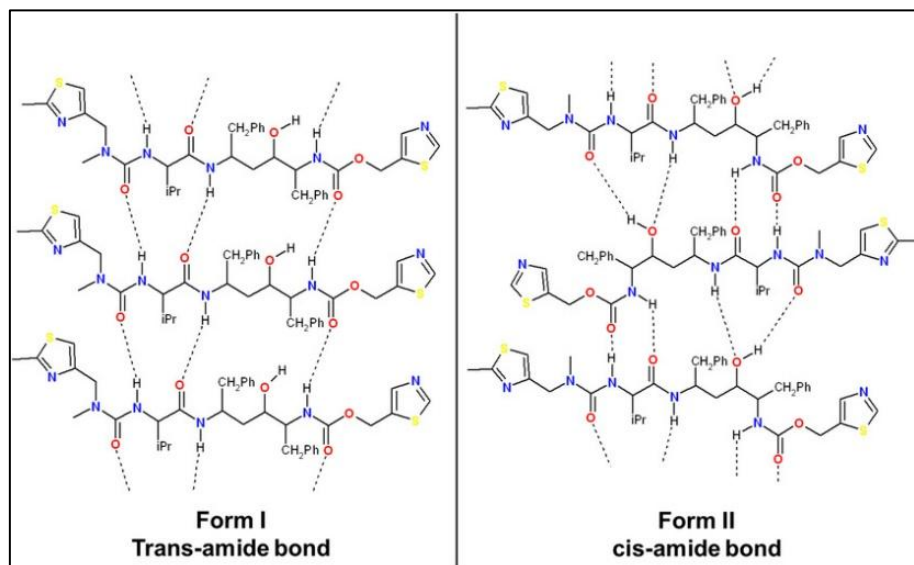


Figure 1.4. Intermolecular interactions of form I and form II of ritonavir.²³

Interestingly, in 2014, a third polymorph of this drug was discovered and subsequently fully characterized in 2022.²⁴

1.2.2 Packing polymorphism

An important example of packing polymorphism can be found in aspirin. Aspirin has two well-known polymorphs. Forms I and II consist of molecules with nearly identical conformations and similar hydrogen-bonding interactions.²⁵ Despite their structural similarity, the primary difference between the two forms is how the layers are stacked and the orientation of aspirin dimer pairs within each layer (Figure 1.5). These small differences significantly change their mechanical properties. Aspirin form II is mechanically unstable and readily converts to the more stable form I under external stress.²⁶

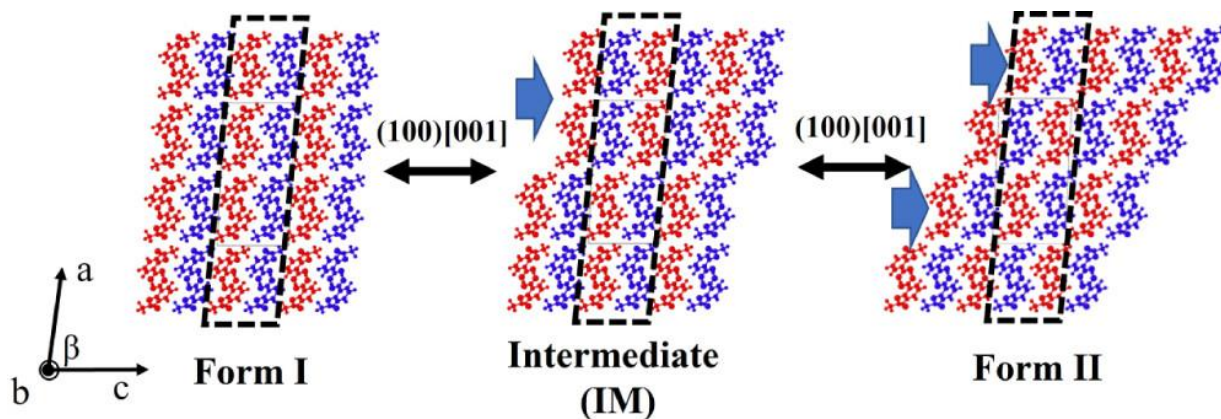


Figure 1.5. Two polymorphs of aspirin. ²⁶

Consequently, the properties of bulk materials can be tuned by either modifying the molecular structure through covalent chemistry or altering crystal packing via supramolecular approaches.

1.3 Covalent vs supramolecular chemistry

A covalent bond is a chemical bond formed when atoms share electrons instead of fully transferring them, as in ionic bonding. ²⁷Covalent chemistry relies on forming or breaking covalent bonds to generate new molecular entities, often requiring multistep reactions and extensive synthetic optimization. While covalent synthesis allows modification of molecular structure, supramolecular chemistry controls material properties by manipulating intermolecular interactions and multi-component assembly (Figure 1.6). ²⁸

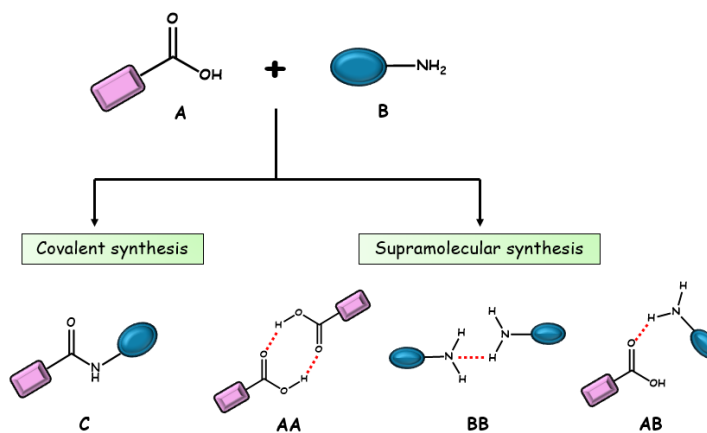


Figure 1.6. Covalent vs supramolecular synthesis.

Supramolecular chemistry has evolved rapidly over the past few decades. Jean-Marie Lehn, who won the Nobel Prize in 1987 for his outstanding contributions to the field, defined supramolecular chemistry as “the chemistry of molecular assemblies and of the intermolecular bond.”^{29,30} Supramolecular synthesis utilizes reversible non-covalent interactions to assemble existing molecules into new solid forms with modified properties.²⁸ In 2016, the Nobel Prize in Chemistry was awarded to Jean-Pierre Sauvage, Sir Fraser Stoddart, and Bernard Feringa for the design and synthesis of molecular machines. This achievement further underscores the power of supramolecular principles in creating functional systems from intermolecular interactions.³¹

1.4 Non-covalent interactions

Non-covalent interactions are relatively weak attractions between molecules or parts of a molecule that do not involve the transfer of electrons. These interactions can be classified into different categories, such as hydrogen bonds, halogen bonds, chalcogen bonds, charge-transfer interactions, van der Waals interactions, π - π interactions, *etc.* An approximate strength of each interaction is given in Table 1.1.³²⁻⁴¹

Table 1.1. Estimated strengths of intermolecular interactions.

Type of Interaction	Strength/kJ/mol
Covalent bond ³⁶	100-1100
Hydrogen bond ³⁷	2-170
Halogen bond ³⁸	5-180
Charge transfer interactions ³⁹	10-180
π - π interaction ⁴⁰	0-50
Van der Waals interaction ⁴¹	<5

This dissertation primarily focuses on three main types of non-covalent interactions: hydrogen bonds, halogen bonds, and charge-transfer interactions.

1.4.1 Hydrogen bonds

The hydrogen bond (HB) is defined as “an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule in which there is evidence of bond formation.”⁴² It is commonly represented as X-H $\cdots$ A, where X-H is the hydrogen-bond donor, and A is the hydrogen-bond acceptor (Figure 1.7).³⁷

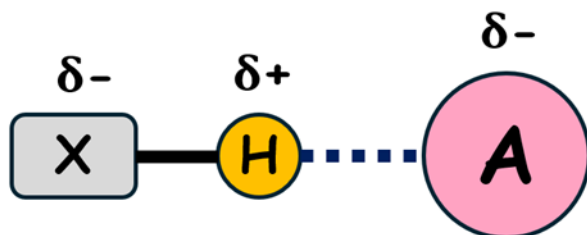


Figure 1.7. Schematic representation of a hydrogen bond.

The nature of the interaction is not constant and exhibits broad transition regions that merge continuously with covalent, van der Waals, and ionic interactions. Therefore, the strength of hydrogen bonds can vary widely, from very weak to much stronger, ranging approximately 0.5 - 40 kcal mol⁻¹. In addition, strong hydrogen bonds typically adopt a nearly straight geometry, with the X-H $\cdots$ A angle close to 180°. Since hydrogen bonds are strong enough to hold molecules together yet weak enough to break and reform easily, they are among the most studied intermolecular interactions in supramolecular chemistry.^{37,43,44}

1.4.2 Halogen bonds

A halogen bond (XB) is a weak, but highly directional attraction between a halogen atom (usually Cl, Br, or I) (σ -hole of a polarized halogen atom) and an electron-rich site (like a lone pair or π system), along the extension of the halogen atom's covalent bond. This interaction arises from the presence of a σ -hole on the halogen atom. A σ -hole is the small, localized positive region on the

surface of an atom that lies directly opposite a covalent bond of halogen atoms. This positive region forms because electron density is depleted along the bond axis, making that area electrostatically positive.⁴⁵

Halogen bonds are typically written as: $R-X\cdots A$, where $R-X$ is the halogen-bond donor, and A is an electron-rich acceptor (Figure 1.8). These bonds are usually highly directional, with $R-X\cdots Y$ angles ranging from 160° to 180° . The strength of halogen bonding largely depends on the polarizability of the halogen ($I > Br > Cl \gg F$) and the electronic nature of the substituent attached to it. As a result, halogen bonds can range from weak to relatively strong interactions.^{35,38,46-48}

Halogen bonds can be detected and characterized using several experimental techniques. Infrared (IR) and Raman spectroscopy monitor changes in molecular vibrations, nuclear magnetic resonance (NMR) spectroscopy observes chemical shifts and couplings in solution and solids, nuclear quadrupole resonance (NQR) spectroscopy probes quadrupolar halogen nuclei, and single-crystal X-ray diffraction (SCXRD) directly reveals molecular geometry and short $X\cdots A$ contacts.

38

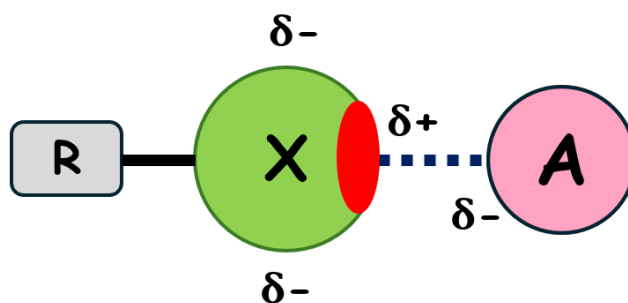


Figure 1.8. Schematic representation of a halogen bond.

Over the past few years, halogen bonding has attracted significant attention as a promising tool for crystal engineering in the design and synthesis of new functional supramolecular materials.^{38,46,48}

An interesting feature of the halogen bond is that its strength can be effectively increased by “activating” the halogen atom by attaching electron-withdrawing substituents (Figure 1.9).⁴⁹

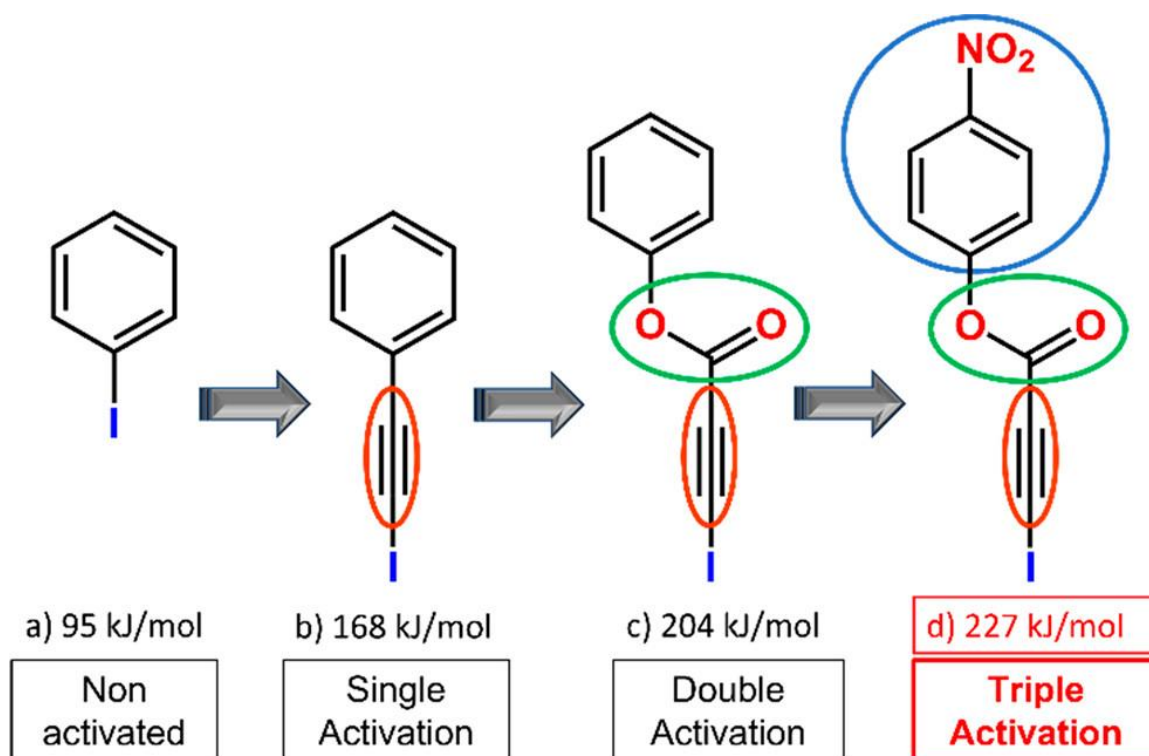


Figure 1.9. Triply activated XB donors, showing the σ -hole potentials on the iodine atom computed using DFT at the B3LYP/6-311++G** level of theory at iso = 0.002.⁴⁹

1.4.3 Charge-transfer interactions

Charge-transfer interactions involve the partial transfer of electrons from an electron-rich molecule (donor) to an electron-deficient molecule (acceptor). This can occur between two different molecules or within a single molecule with both electron-rich and electron-deficient regions.⁵⁰ In organic compounds, charge-transfer interactions often produce a visible color change due to alterations in the energy gap between molecular orbitals.^{51,52} The energy difference between the donor molecule's highest occupied molecular orbital (HOMO) and the acceptor molecule's lowest unoccupied molecular orbital (LUMO) is largely responsible for this color change (Figure 1.10).⁵³⁻
⁵⁵⁻ Such complexes have been used in applications such as sensors and optical devices.^{56,57} Additionally, altering the structures of the donor and acceptor molecules can control the desired

colors. Although the energy gap primarily determines the emission color, other factors also influence color, including molecular structure, conjugation, intermolecular interactions, and environmental conditions.^{50,54}

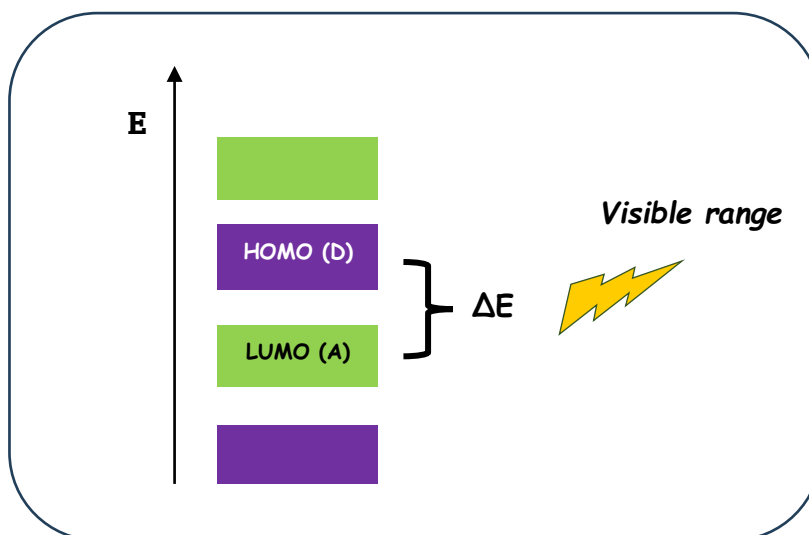


Figure 1.10. Illustration of the energy gap.

1.5 Supramolecular synthons

The effective design of supramolecular assemblies with precise stoichiometry and structure relies on the use of supramolecular synthons, defined as a recurring structural unit within a crystal that arises from specific intermolecular interactions.⁵⁸ Synthons can be classified as homosynthons, formed between identical functional groups, or heterosynthons, formed between complementary but different functional groups (Figure 1.11). The robustness and transferability of these synthons are critical due to the weak and reversible nature of non-covalent interactions. Nevertheless, successful identification of reliable synthons enables rational design of new crystalline materials.

^{59,60}

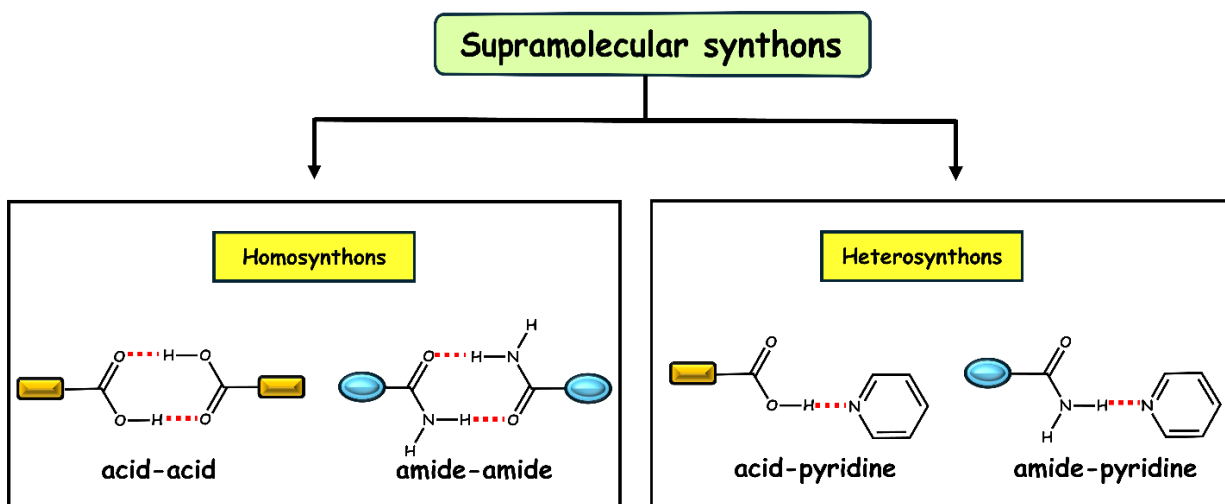


Figure 1.11. Supramolecular synthons.

Non-covalent supramolecular assemblies fall broadly into two categories. If the participating molecules are the same kind, the process is called “recrystallization”, and if the molecules are different, it is called “cocrystallization” (Figure 1.12).⁶¹

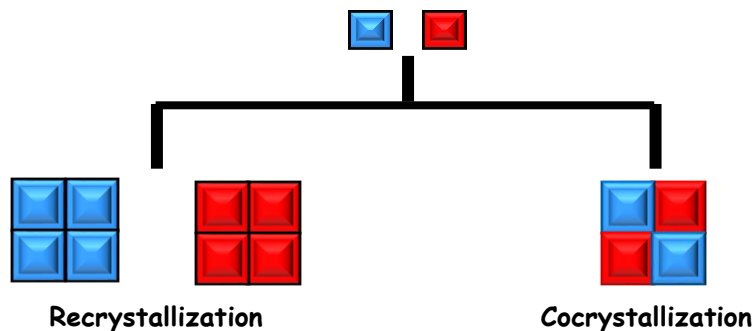


Figure 1.12. Schematic representation of recrystallization and cocrystallization.

In a suitable medium, cocrystallization occurs when heteromeric interactions predominate over homomeric interactions, providing opportunities to modify spatial relationships between molecules. They provide a versatile strategy for tuning optical, mechanical, and electronic properties of materials.⁶¹

1.6 Cocrystals and their importance

A cocrystal is a crystalline material composed of two or more different molecular compounds held together by non-covalent interactions, generally in a precise stoichiometric ratio (Figure 1.13). Cocrystals are formed by breaking the homomeric interactions and subsequently replacing them with more favorable heteromeric interactions.⁶²⁻⁶⁴ However, in solution, many potential cocrystals fail to form because recrystallization of the individual components is generally favored, even though cocrystals may be thermodynamically more stable. This is due to kinetic barriers that hinder nucleation and differences in solubility that can prevent cocrystallization. Successful cocrystallization requires a supersaturation region for the cocrystal while the individual components remain saturated or undersaturated. Otherwise, the pure components crystallize first. This challenge is particularly pronounced when solubilities are highly mismatched.⁶⁵⁻⁷⁰ Therefore, cocrystallization requires rational design strategies.

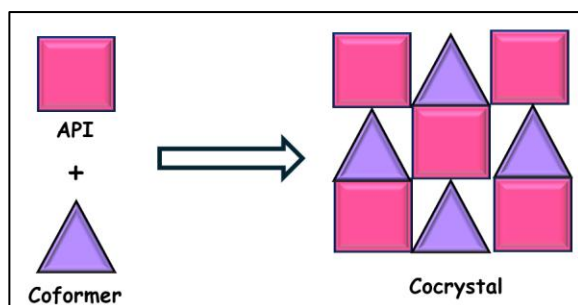


Figure 1.13. An illustration of a cocrystal.

Importantly, cocrystals can alter the physicochemical properties of a material without disrupting the molecular-level chemical structure.⁶²

1.6.1 Formation and characterization of cocrystals

The primary requirement for cocrystal synthesis is the presence of complementary functionalities. The formation of a cocrystal depends on multiple experimental variables, including the choice of

coformer, stoichiometric ratio, solvent, temperature, pressure, and crystallization technique. Cocrystal synthesis methods can be generally categorized into green synthesis techniques (such as liquid-assisted grinding, neat grinding, extrusion, and hot-melt extrusion), solvent-based methods (including spray drying, solvent evaporation, and slurry cocrystallization), and supercritical fluid approaches.⁷¹⁻⁷³ Cocrystal characterization can be carried out using several methods such as single crystal X-ray diffraction (SCXRD), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), nuclear magnetic spectroscopy (NMR), and Raman spectroscopy, differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetry analysis (TGA), scanning electron microscopy (SEM) and optical microscopy (Figure 1.14).⁷⁴⁻⁷⁶ Among these, SCXRD provides the most definitive structural evidence for cocrystal formation by directly resolving the intermolecular interactions and packing motifs.

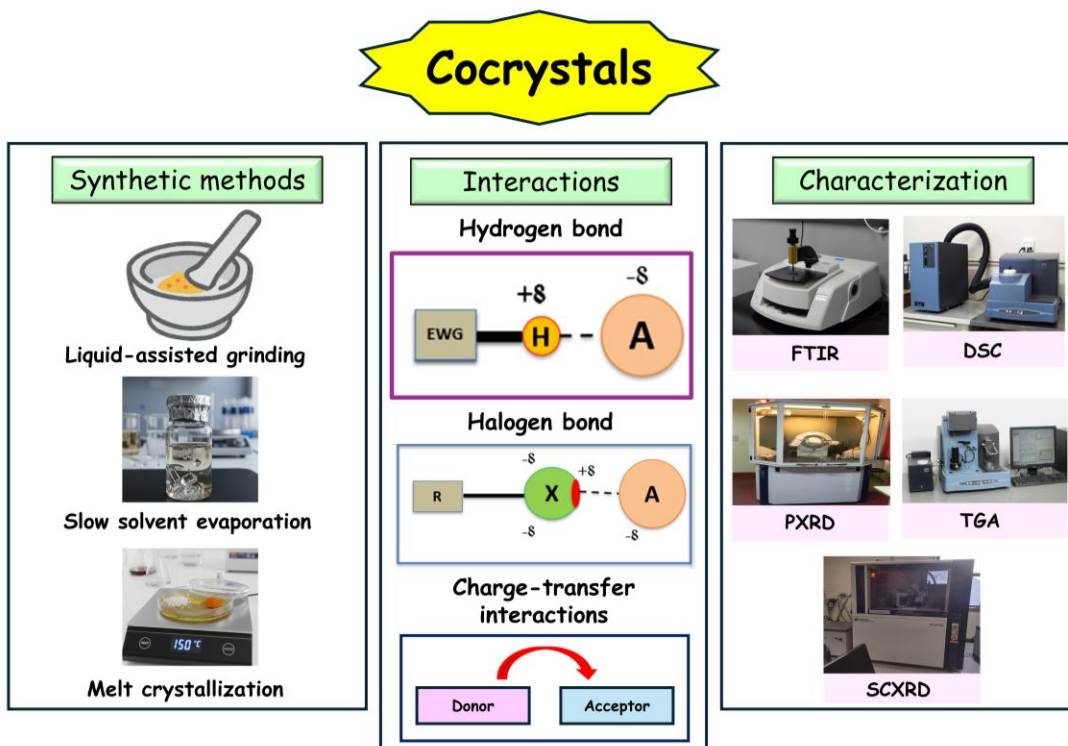


Figure 1.14. Summary of the synthetic methods, supramolecular interactions, and characterization methods used to study cocrystals in this dissertation.

1.6.2 Hydrogen-bond-based cocrystals

Figure 1.15 illustrates a hydrogen-bonded cocrystal formed between caffeine and oxalic acid, in which the components assemble in a 2:1 caffeine-to-oxalic acid stoichiometry.⁷⁷ Specifically, strong O-H $\cdots$ N hydrogen bonds form between the carboxylic acid group of oxalic acid and the imidazole nitrogen atom of caffeine, while weaker C-H $\cdots$ O interactions further stabilize the crystal packing. These interactions lead to the formation of planar trimeric caffeine-acid-caffeine units, often described as a “dumbbell” motif, in which oxalic acid serves as the central handle and the caffeine molecules form the terminal weights. The trimers stack in an ordered arrangement within the crystal lattice, creating a robust hydrogen-bonded network. As a result of this well-organized supramolecular structure, the cocrystal exhibits significantly improved moisture stability compared with pure caffeine, remaining unchanged for up to seven weeks without structural alteration. This example demonstrates how even a relatively simple hydrogen-bonded cocrystal system can significantly enhance the physical stability of a compound.

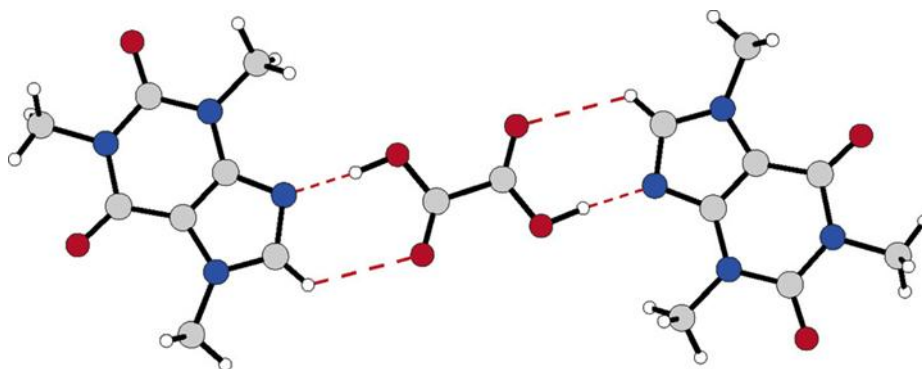


Figure 1.15. A schematic representation of the caffeine-oxalic acid cocrystal.⁷⁷

Another example of a hydrogen-bonded cocrystal involves indapamide (IDP) and different coformers.⁷⁸ IDP's sulfonamide group can act as both a hydrogen bond donor (N-H) and acceptor (O), allowing it to interact with pyridine, amide, and amine coformers (Figure 1.16). The study finds that strong heterosynthons, such as sulfonamide-pyridine (N-H $\cdots$ N) and sulfonamide-

carboxamide ($\text{N-H}\cdots\text{O}=\text{C}$), direct the formation of well-ordered cocrystals, whereas weaker, sulfonamide-amine ($\text{N-H}\cdots\text{NH}$) interactions do not form stable cocrystals (Figure 1.17). This example highlights how the strength of hydrogen bonds plays an important role in cocrystal formation and how deliberate manipulation of supramolecular synthons can predictably control solid-state outcomes.

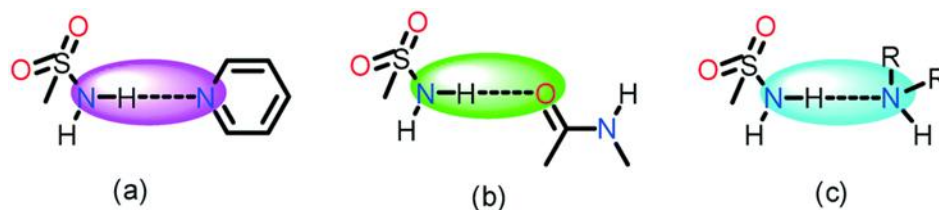


Figure 1.16. Representative hydrogen-bonding motifs: (a) sulfonamide $\cdots$ pyridine ($\text{N-H}\cdots\text{N}$), (b) sulfonamide $\cdots$ amide ($\text{N-H}\cdots\text{O}$), and (c) sulfonamide $\cdots$ amine ($\text{N-H}\cdots\text{N}$).⁷⁸

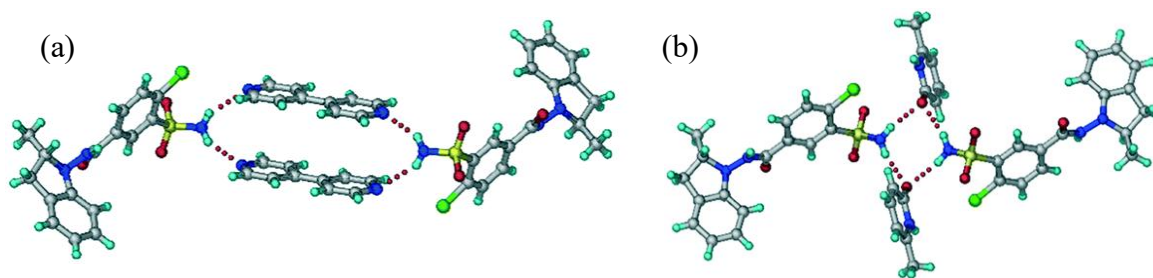


Figure 1.17. Cocrystal structures of IDP with (a) 4,4'-dipyridyl, showing sulfonamide $\cdots$ pyridine ($\text{N-H}\cdots\text{N}$) heteromeric synthons and *N*-methylpyridone, showing sulfonamide $\cdots$ amide ($\text{N-H}\cdots\text{O}$) heterosynthons.⁷⁸

An additional example is a supramolecular capsule formed through hydrogen-bonding. In this study, two molecules of a cavitand tetracarboxylic acid and four molecules of 2-aminopyrimidine self-assemble via 16 hydrogen bonds to form a discrete capsule in a 2:1 stoichiometry.^{61,79} Single-crystal X-ray diffraction (SCXRD) revealed two cavitand subunits held rim-to-rim by four 2-

aminopyrimidine molecules, which act as hydrogen-bonded linkers (Figure 1.18). These findings demonstrate that hydrogen-bonded cocrystals can form well-defined capsules capable of encapsulating guest molecules, offering potential applications in molecular recognition, stabilization of reactive intermediates, and the creation of controlled microenvironments for host-guest chemistry

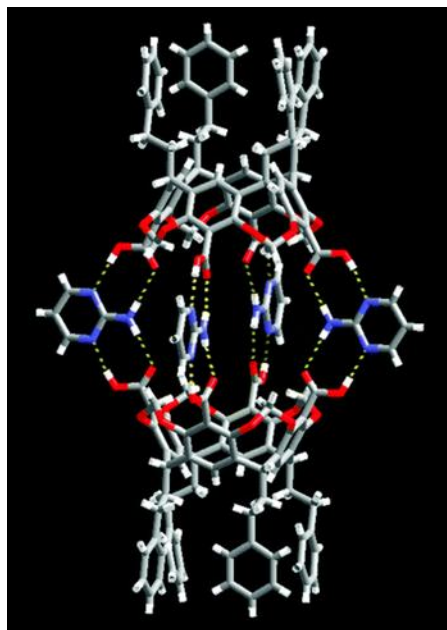


Figure 1.18. A cocrystal capsule held together by multiple carboxylic acid-aminopyrimidine interactions.⁶¹

1.6.3 Halogen-bond-based cocrystals

This example of a halogen-bonded cocrystal (Figure 1.19) illustrates how the strong directionality of halogen bonding translates into supramolecular architecture.⁸⁰⁻⁸² In this, the acceptor molecule 4,4'-bipyridine forms a linear halogen-bonded chain when cocrystallized with the donor 1,4-dibromotetrafluorobenzene. However, when the same acceptor interacts with 1,3-dibromotetrafluorobenzene or 1,2-dibromotetrafluorobenzene, the resulting cocrystals form zigzag or wavy supramolecular chains instead of straight ones. This difference occurs because the

positions of the bromine atoms in the donor molecules are different, which changes the direction of the halogen bonds. This example highlights that by choosing molecular building blocks with specific geometries, the shape and organization of halogen-bonded cocrystals can be controlled.

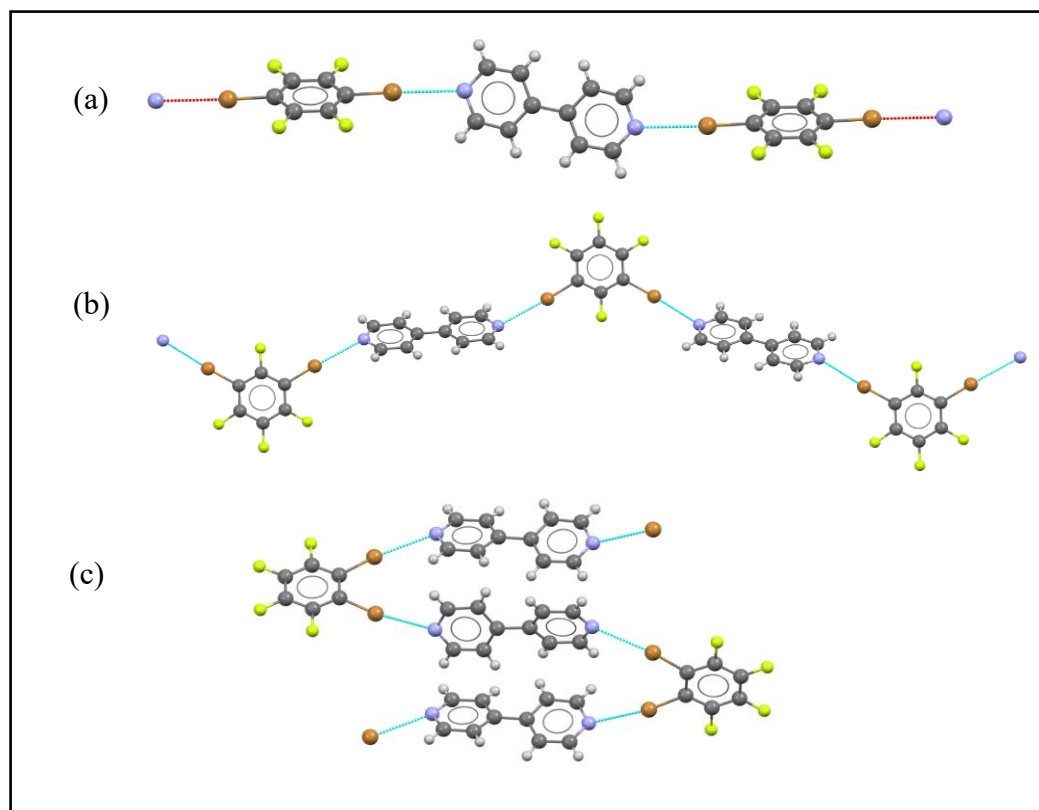


Figure 1.19. Representation of infinite chains between 4,4'-dipyridyl with (a) 1,4-dibromotetrafluorobenzene, (b) 1,3-dibromotetrafluorobenzene, and (c) 1,2-dibromotetrafluorobenzene.

Another example of halogen-bonded cocrystals involves the structures formed between 1,3,5-triiodo-2,4,6-trifluorobenzene (titfb) and the three structural isomers of benzoylpyridine (2-, 3-, and 4-), which are N, O-ambidentate halogen-bond acceptors (Figure 1.20).⁸³ In most cocrystals formed, benzoylpyridine accepts halogen bonds at both pyridyl nitrogen and carbonyl oxygen, demonstrating that the carbonyl O atom can reliably compete with N as a halogen-bond acceptor in the same molecule (Figure 1.21).

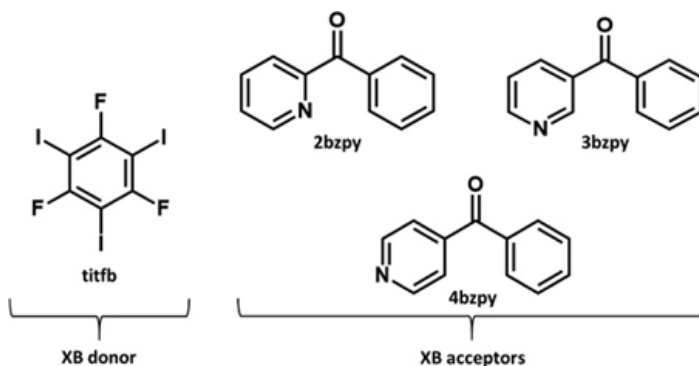


Figure 1.20. Halogen-bond donor and acceptors of the study.⁸³

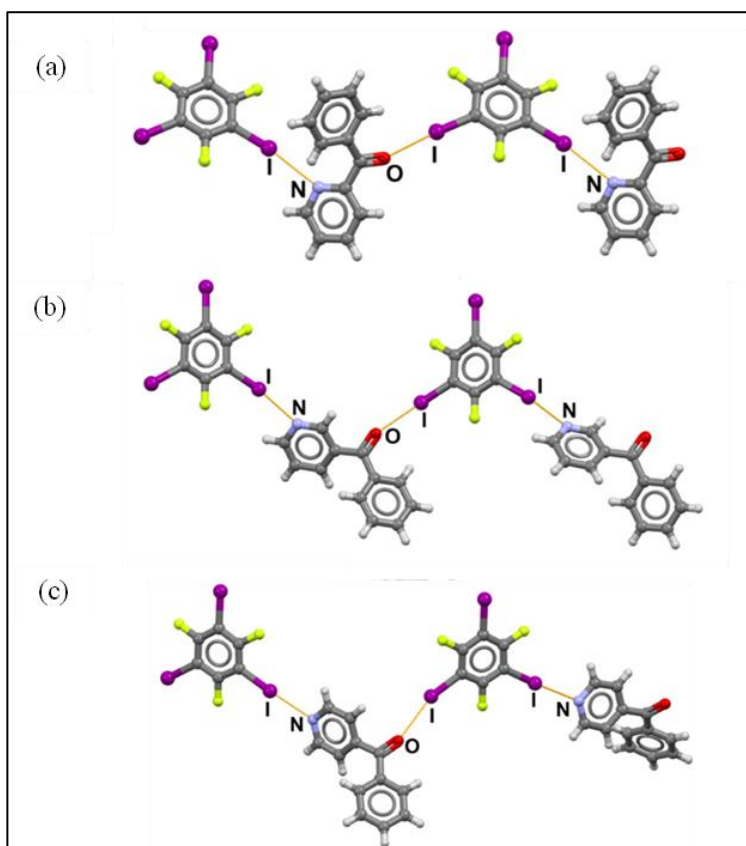


Figure 1.21. Halogen bonding motifs in (a) α -(titfb)(2bzpy) (b) α -(titfb)(3bzpy), and (c) α -(titfb)(4bzpy).⁸³

Another notable halogen-bonded cocrystal is the first halogen-bonded capsule reported in 2012 by Christer Aakeröy, Pierangelo Metrangolo, and Giuseppe Resnati.^{80,84} In this study, a heteromeric capsule formed via the self-assembly of the XB acceptor *C*-pentyltetrakis(4-pyridyl)cavitand and

the XB donor *p*-tert-butylcalix[4]arenetetrakis[2-(4-iodotetrafluorophenoxy)ethyl ether] (Figure 1.22). The rigid frameworks of the donor and acceptor allowed multiple halogen bonds to form simultaneously, while flexible -OCH₂CH₂O- linkers allowed shape adjustment, enabling four strong and directional I⋯N halogen bonds (C-I⋯N angles 169°-177°) to stabilize the capsule, and solvent molecules occupy the inner cavities (Figure 1.23). This work demonstrated that directional halogen bonds can be used to develop capsules capable of guest encapsulation, highlighting applications in supramolecular design.

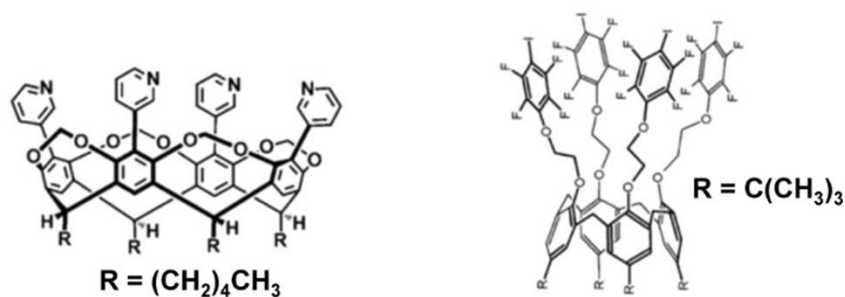


Figure 1.22. Molecular structures of the XB acceptor (left) and donor (right) used for the construction of the capsule.⁸⁰

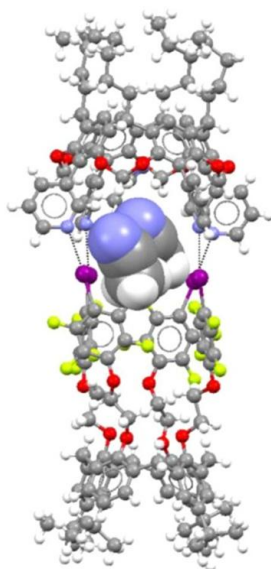


Figure 1.23. Representation of the molecular capsule where I⋯N XB bonds are shown as dotted black lines. Color code: carbon, gray; nitrogen, blue; oxygen, red; iodine, purple; fluorine, yellow; hydrogen, white.⁸⁰

1.6.4 Charge-transfer-based cocrystals

Charge-transfer cocrystals are formed by combining electron donors and acceptors into a single crystal, resulting in partial electron transfer from the HOMO of the donor to the LUMO of the acceptor through non-covalent interactions, such as π -stacking (Figure 1.17).^{54,57}

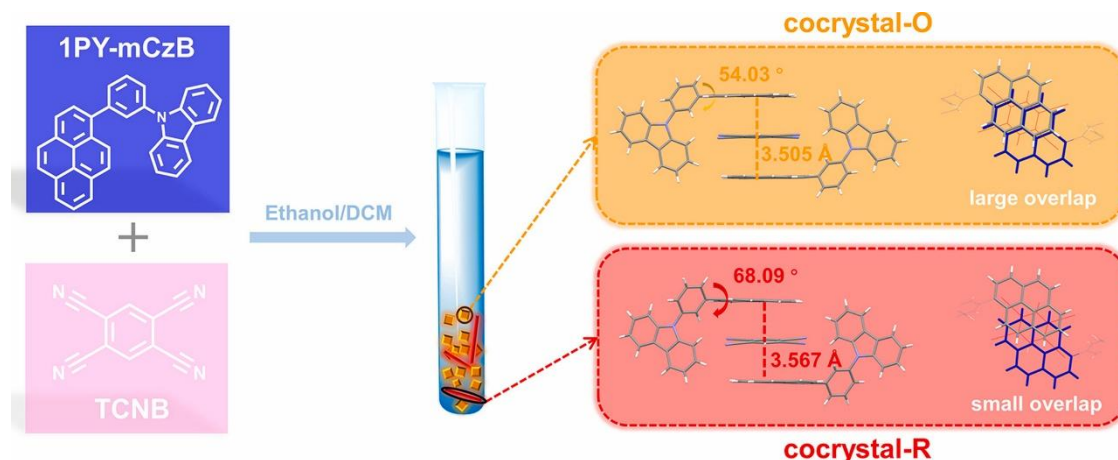


Figure 1.24. Charge-transfer cocrystals formed between the 9-(3-(pyren-1-yl)phenyl)-9H-carbazole (1PY-mCzB) and 1,2,4,5-tetracyanobenzene (TCNB).⁸⁵

1.6.5 Applications of cocrystals

Cocrystallization has found widespread applications across diverse fields, including pharmaceuticals,⁸⁶ energetic materials,⁸⁷ agrochemicals,⁸⁸ organic semiconductors,⁸⁹ and optoelectronic materials.⁹⁰ Beyond property modulation, cocrystallization has been employed in chiral resolution,⁹¹ solid-state solvent-free synthesis⁹² and separation and purification processes.

93

1.6.5.1 Pharmaceutical cocrystals

Drug development is an expensive and time-consuming process, requiring the evaluation of thousands of compounds to yield a single FDA-approved drug.⁹⁴ The primary reason for the late-stage failure of many drugs is their sub-optimal physical properties, such as low aqueous solubility, stability, or bioavailability.^{95,96} Therefore, cocrystal synthesis has gained significant interest in the

pharmaceutical industry as a powerful tool to improve the physical properties of drugs.^{97,98} For example, indomethacin (γ -form) is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic and analgesic properties, is practically insoluble in water (2.5-4 $\mu\text{g/ml}$), and is classified as a BCS class II drug. Several methods have been employed to enhance the solubility and dissolution rate of indomethacin, and cocrystal formation has proven to be an effective approach. The cocrystal formed with saccharine had a significantly higher dissolution rate (200 mM, pH 7.4) compared to that of indomethacin, which was 50 times lower, indicating greater stability over time (Figure 1.18). This demonstrates how cocrystals can improve the properties of pharmaceuticals without changing their inherent structure.⁹⁹

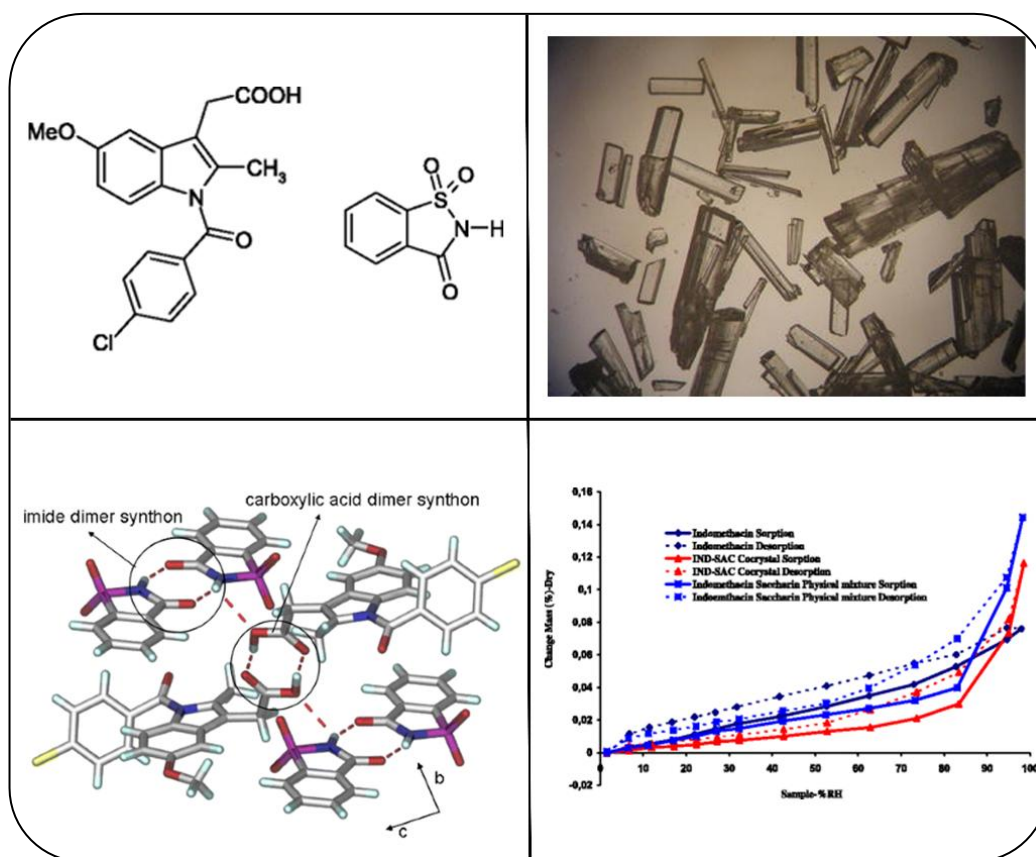


Figure 1.25. Indomethacin-saccharin cocrystal, interactions, and vapor sorption and desorption isotherms.⁹⁹

As a result of these advances in cocrystals, the first cocrystal drug, Entresto, was approved by the FDA in 2015. This drug is used to treat chronic heart failure. It comprises a 1:1 combination of *Sacubitril*, a neprilysin inhibitor, and *Valsartan*, an angiotensin receptor blocker (Figure 1.19).^{100,101} Sacubitril alone is not very effective as it can unintentionally increase hormones that tighten blood vessels. Valsartan itself helps block these harmful hormones but does not boost the body's natural protective hormones that help relax blood vessels. Together in Entresto, they balance each other and work better than either drug alone.

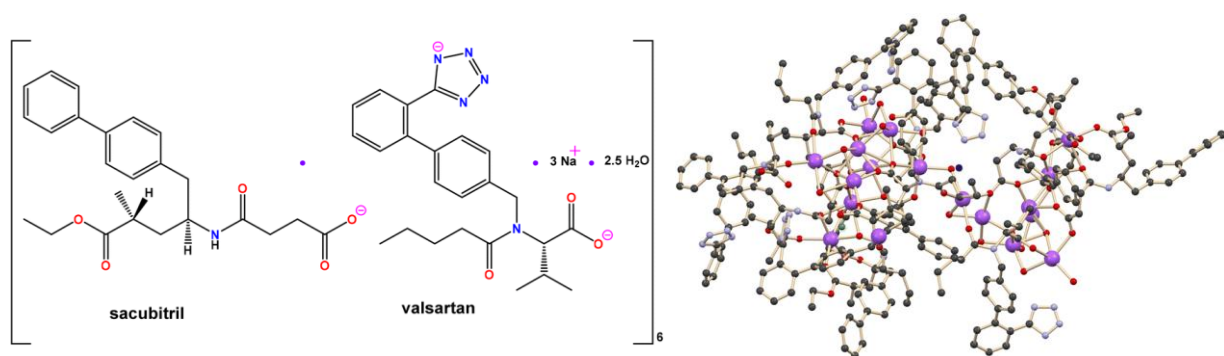


Figure 1.26. The Entresto cocrystal.¹⁰⁰

1.7 Goals of the dissertation

Establishing robust structure-property relationships in the solid-state remains essential for the rational ‘bottom-up’ development and optimization of functional materials. Since supramolecular synthesis is a relatively new concept and involves manipulating intermolecular interactions, it is still evolving compared to traditional organic transformations. In this dissertation, systematic structural modifications were employed to investigate how small, deliberate molecular modifications impact crystal structures and their landscapes. The primary focus is on structural analysis, examining how subtle changes affect hydrogen/halogen bonding motifs, molecular packing, and overall crystal architecture. Based on these structural insights, the dissertation further

explores how such variations influence cocrystal formation and the properties of the resulting cocrystals.

This dissertation is organized as follows:

- ✓ **Chapter 2** examines the structural landscape of two libraries of 2-aminopyridine derivatives, with a focus on identifying preferred supramolecular motifs.¹⁰²
- ✓ **Chapter 3** extends the structural investigation by examining two more series of 2-aminopyridine derivatives to investigate whether FTIR spectroscopy can be used as a definitive diagnostic tool to identify bonding modes of amide derivatives of 2-aminopyridine in the solid-state.
- ✓ **Chapter 4** evaluates the influence of chain and dimer motifs of 2-aminopyridine derivatives on cocrystal formation.
- ✓ **Chapter 5** investigates how molecular complexity governs the intermolecular interactions of amide-substituted 2-aminopyrimidine derivatives.¹⁰³
- ✓ **Chapter 6** explores synthetic avenues for achieving stoichiometric control in cocrystal formation.
- ✓ **Chapter 7** demonstrates that the odd-even effect can be used to dial in the structure-property relationship of acetylated 2-aminopyrazine derivatives.
- ✓ **Chapter 8** investigates an analogue of favipiravir and its cocrystals, with insights into structure-property relationships.
- ✓ **Chapter 9** demonstrates how photophysical properties of cocrystals can be altered through controlled structural and supramolecular modifications.
- ✓ **Chapter 10** discusses future research directions.

1.8 References

1. Wiener, H. Structural Determination of Paraffin Boiling Points. *Journal of the American Chemical Society* **1947**, 69 (1), 17–20.
2. Wiener, H. Vapor Pressure–Temperature Relationships among the Branched Paraffin Hydrocarbons. *The Journal of Physical and Colloid Chemistry* **1948**, 52 (2), 425–430.
3. Katritzky, A. R.; Kuanar, M.; Slavov, S.; Hall, C. D.; Karelson, M.; Kahn, I.; Dobchev, D. A. Quantitative Correlation of Physical and Chemical Properties with Chemical Structure: Utility for Prediction. *Chemical Reviews* **2010**, 110 (10), 5714–5789.
4. Lehn, J.-M. Toward Self-Organization and Complex Matter. *ChemInform* **2002**, 33 (40), 281–281.
5. Glotzer, S. C.; Solomon, M. J. Anisotropy of Building Blocks and Their Assembly into Complex Structures. *Nature Materials* **2007**, 6 (8), 557–562.
6. Whitesides, G. M. Self-Assembly at All Scales. *Science* **2002**, 295 (5564), 2418–2421.
7. Ball, P. Water an Enduring Mystery. *Nature* **2008**, 452 (7185), 291–292.
8. Hancock, B. C.; Zograf, G. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. *Journal of Pharmaceutical Sciences* **1997**, 86 (1), 1–12.
9. Yu, L. Polymorphism in Molecular Solids: An Extraordinary System of Red, Orange, and Yellow Crystals. *Accounts of Chemical Research* **2010**, 43 (9), 1257–1266.
10. S. Byrn, R. Pfeiffer and J. Stowell, “Solid State Chemistry of Drugs,” 2nd Edition, SSCI, Inc., West Lafayette, 1999. - References - Scientific Research Publishing. Scirp.org.
11. *Polymorphism in the Pharmaceutical Industry*; Hilfiker, R., Raumer, M. von, Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2018.
12. Thalladi, V. R.; Nüsse, M.; Boese, R. The Melting Point Alternation in α,ω -Alkanedicarboxylic Acids. *Journal of the American Chemical Society* **2000**, 122 (38), 9227–9236.
13. Blaschke, G.; Kraft, H. P.; Fickentscher, K.; Köhler, F. [Chromatographic Separation of Racemic Thalidomide and Teratogenic Activity of Its Enantiomers (Author's Transl)]. *Arzneimittel-Forschung* **1979**, 29 (10), 1640–1642.
14. Franks, M. E.; Macpherson, G. R.; Figg, W. D. Thalidomide. *The Lancet* **2004**, 363 (9423), 1802–1811.
15. Lucas Rosa Fraga; Rafipay, A.; Vargesson, N. *Thalidomide and Birth Defects*. ResearchGate. https://www.researchgate.net/publication/291135885_Thalidomide_and_Birth_Defects. (accessed 12/28/25)

16. Bernstein, J. Crystal Growth, Polymorphism and Structure-Property Relationships in Organic Crystals. *Journal of Physics D* **1993**, 26 (8B), B66–B76.
17. Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon Press: Oxford, 2010.
18. Zimmer, G. C.; Pagliari, A. B.; Solner, V. B.; Manfredo Hörner; Bonacorso, H. G.; Zanatta, N.; Marcos. Packing and Conformational Polymorphism in 1,2-Bis(Aminocarbonyl(1-*Tert*-Butyl-1*H*-Pyrazol(3)5-Yl))Ethanes: Illuminating Examples of Highly Flexible Molecules. *Crystal Growth & Design* **2021**, 21 (8), 4690–4706.
19. Cruz-Cabeza, A. J.; Bernstein, J. Conformational Polymorphism. *Chemical Reviews* **2013**, 114 (4), 2170–2191.
20. Braun, D. E.; Gelbrich, T.; Kahlenberg, V.; Laus, G.; Wieser, J.; Griesser, U. J. Packing Polymorphism of a Conformationally Flexible Molecule (Aprepitant). *New Journal of Chemistry* **2008**, 32 (10), 1677–1677.
21. Chemburkar, S. R.; Bauer, J.; Deming, K.; Spiwek, H.; Patel, K.; Morris, J.; Henry, R.; Spanton, S.; Dziki, W.; Porter, W.; Quick, J.; Bauer, P.; Donaubauber, J.; Narayanan, B. A.; Soldani, M.; Riley, D.; McFarland, K. Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development. *Organic Process Research & Development* **2000**, 4 (5), 413–417.
22. Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. Ritonavir: An Extraordinary Example of Conformational Polymorphism. *Pharmaceutical Research* **2001**, 18 (6), 859–866.
23. *Ritonavir Near Disaster and Polymorphism*. Openochem.org. <https://learn.openochem.org/learn/the-alchemy-of-drug-development/ritonavir-near-disaster>. (accessed 12/28/25)
24. Parent, S. D.; Smith, P. A.; Purcell, D. K.; Smith, D. T.; Bogdanowich-Knipp, S. J.; Bhavsar, A. S.; Chan, L. R.; Croom, J. M.; Bauser, H.; McCalip, A.; Byrn, S. R.; Radocea, A. Ritonavir Form III: A Coincidental Concurrent Discovery. *Crystal Growth & Design* **2022**, 23 (1), 320–325.
25. Bond, A. D.; Boese, R.; Desiraju, G. R. On the Polymorphism of Aspirin: Crystalline Aspirin as Intergrowths of Two “Polymorphic” Domains. *Angewandte Chemie (International Ed. in English)* **2007**, 46 (4), 618–622.
26. Hattori, S.; Zhu, Q. Revisiting Aspirin Polymorphic Stability Using a Machine Learning Potential. *ACS Omega* **2024**, 9 (34).
27. Nordholm, S.; Bacskey, G. B. The Basics of Covalent Bonding in Terms of Energy and Dynamics. *Molecules* **2020**, 25 (11), 2667.
28. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons, Inc: Chichester, West Sussex ; Hoboken, 2022.

29. Lehn, J.-M. Supramolecular Chemistry—Scope and Perspectives Molecules, Supermolecules, and Molecular Devices(Nobel Lecture). *Angewandte Chemie International Edition in English* **1988**, 27 (1), 89–112.
30. Lehn, J.-M. Toward Complex Matter: Supramolecular Chemistry and Self-Organization. *Proceedings of the National Academy of Sciences* **2002**, 99 (8), 4763–4768.
31. Leigh, D. A. Genesis of the Nanomachines: The 2016 Nobel Prize in Chemistry. *Angewandte Chemie* **2016**, 55 (47), 14506–14508.
32. Desiraju, G. R.; Steiner, T.; International Union Of Crystallography. *The Weak Hydrogen Bond : In Structural Chemistry and Biology*; Oxford University Press: Oxford, 2006.
33. Hunter, C. A.; Sanders, J. K. M. The Nature of .Pi.-Pi. Interactions. *Journal of the American Chemical Society* **1990**, 112 (14), 5525–5534.
34. Metrangolo, P.; Resnati, G. Halogen Bonding: A Paradigm in Supramolecular Chemistry. *Chemistry - A European Journal* **2001**, 7 (12), 2511–2519.
35. Politzer, P.; Murray, J. S.; Clark, T. Halogen Bonding: An Electrostatically-Driven Highly Directional Noncovalent Interaction. *Physical Chemistry Chemical Physics* **2010**, 12 (28), 7748.
36. *Covalent Bond Energies*. gchem.cm.utexas.edu. <https://gchem.cm.utexas.edu/data/section2.php?target=bond-energies-table4.php>. (accessed 02/12/26)
37. Steiner, T. The Hydrogen Bond in the Solid State. *Angewandte Chemie International Edition* **2002**, 41 (1), 48–76.
38. Riley, K. E.; Merz, K. M. Insights into the Strength and Origin of Halogen Bonding: The Halobenzene–Formaldehyde Dimer. *The journal of physical chemistry. A/The journal of physical chemistry. A.* **2007**, 111 (9), 1688–1694.
39. Ji, X.; Wang, W.; Hedi Mattoussi. Controlling the Spectroscopic Properties of Quantum Dots via Energy Transfer and Charge Transfer Interactions: Concepts and Applications. *Elsevier* **2016**, 11 (1), 98–121.
40. Wilson, K. A.; Kellie, J. L.; Wetmore, S. D. DNA–Protein π -Interactions in Nature: Abundance, Structure, Composition and Strength of Contacts between Aromatic Amino Acids and DNA Nucleobases or Deoxyribose Sugar. *Nucleic Acids Research* **2014**, 42 (10), 6726–6741.
41. Hunter, C. A. Van Der Waals Interactions in Non-Polar Liquids. *Chem. Sci.* **2013**, 4 (2), 834–848.
42. Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.;

- Nesbitt, D. J. Defining the Hydrogen Bond: An Account (IUPAC Technical Report). *Pure and Applied Chemistry* **2011**, 83 (8), 1619–1636.
43. Desiraju, G. R. A Bond by Any Other Name. *Angewandte Chemie International Edition* **2010**, 50 (1), 52–59.
 44. Desiraju, G. R. Hydrogen Bridges in Crystal Engineering: Interactions without Borders. *Accounts of Chemical Research* **2002**, 35 (7), 565–573.
 45. Clark, T. Halogen Bonds and σ -Holes. *Faraday Discuss.* **2017**, 203, 9–27.
 46. Gilday, L. C.; Robinson, S. W.; Barendt, T. A.; Langton, M. J.; Mullaney, B. R.; Beer, P. D. Halogen Bonding in Supramolecular Chemistry. *Chemical Reviews* **2015**, 115 (15), 7118–7195.
 47. Politzer, P.; Lane, P.; Concha, M. C.; Ma, Y.; Murray, J. S. An Overview of Halogen Bonding. *Journal of Molecular Modeling* **2006**, 13 (2), 305–311.
 48. Priimagi, A.; Cavallo, G.; Metrangolo, P.; Resnati, G. The Halogen Bond in the Design of Functional Supramolecular Materials: Recent Advances. *Accounts of Chemical Research* **2013**, 46 (11), 2686–2695.
 49. Panikkattu, V. V.; Huber, A. S.; Sinha, A. S.; Averkiev, B. B.; Aakeröy, C. B. “Triply Activated” Phenyl 3-Iodopropiolates: Halogen-Bond Donors with Remarkable σ -Hole Potentials. *Crystal Growth & Design* **2022**, 22 (3), 1538–1542.
 50. John R.G. Sander; Dejan-Krešimir Bučar; Henry, R. F.; Baltrusaitis, J.; Geoff G.Z. Zhang; Macgillivray, L. R. A Red Zwitterionic Co-Crystal of Acetaminophen and 2,4-Pyridinedicarboxylic Acid. *Journal of pharmaceutical sciences* **2010**, 99 (9), 3676–3683.
 51. Zheng, K.; Gao, S.; Chen, M.; Li, A.; Wu, W.; Qian, S.; Pang, Q. Color Tuning of an Active Pharmaceutical Ingredient through Cocrystallization: A Case Study of a Metronidazole–Pyrogallol Cocrystal. *CrystEngComm* **2020**, 22 (8), 1404–1413.
 52. Guan, X. How Does the Conjugated Structure in Organic Compounds Affect Its Color. *2021 3rd International Conference on Biology, Chemistry and Medical Engineering (ICBCME 2021)*.
 53. Shi, W.; Deng, T.; Wong, Z. M.; Wu, G.; Yang, S.-W. A Molecular Roadmap towards Organic Donor-Acceptor Complexes with High-Performance Thermoelectric Response. *npj Computational Materials* **2021**, 7 (1).
 54. Wang, Y.; Wu, H.; Jones, L. O.; Mosquera, M. A.; Stern, C. L.; Schatz, G. C.; Stoddart, J. F. Color-Tunable Upconversion-Emission Switch Based on Cocrystal-To-Cocrystal Transformation. *Journal of the American Chemical Society* **2023**, 145 (3), 1855–1865.

55. Lyakurwa, M.; Numbury, S. B. DFT and TD-DFT Study of Optical and Electronic Properties of New Donor–Acceptor–Donor (D–A–D') Monomers for Polymer Solar Cells. *Oxford Open Materials Science* **2023**, *3* (1).
56. Yang, X.-G.; Zhai, Z.-M.; Lu, X.-M.; Ma, L.-F.; Yan, D. Fast Crystallization-Deposition of Orderly Molecule Level Heterojunction Thin Films Showing Tunable Up-Conversion and Ultrahigh Photoelectric Response. *ACS Central Science* **2020**, *6* (7), 1169–1178.
57. Barman, D.; Annadhasan, M.; Anil Parsram Bidkar; Pachaiyappan Rajamalli; Barman, D.; Ghosh, S. S.; Chandrasekar, R.; Iyer, P. K. Highly Efficient Color-Tunable Organic Co-Crystals Unveiling Polymorphism, Isomerism, Delayed Fluorescence for Optical Waveguides and Cell-Imaging. *Nature Communications* **2023**, *14* (1).
58. Desiraju, G. R. Supramolecular Synthons in Crystal Engineering-a New Organic Synthesis. *Angewandte Chemie International Edition in English* **1995**, *34* (21), 2311–2327.
59. Vânia André; Fernandes, A.; Santos, P. P.; Duarte, M. T. On the Track of New Multicomponent Gabapentin Crystal Forms: Synthon Competition and PH Stability. *Crystal Growth & Design* **2011**, *11* (6), 2325–2334.
60. Draguta, S.; Fonari, M. S.; Bejagam, S. N.; Storms, K.; Lindline, J.; Timofeeva, T. V. Structural Similarities and Diversity in a Series of Crystalline Solids Composed of 2-Aminopyridines and Glutaric Acid. *Structural Chemistry* **2016**, *27* (4), 1303–1315.
61. Aakeröy, C. B.; Salmon, D. J. Building Co-Crystals with Molecular Sense and Supramolecular Sensibility. *CrystEngComm* **2005**, *7* (72), 439.
62. Aakeröy, C. B.; Desper, J.; Fasulo, M.; Hussain, I.; Levin, B.; Schultheiss, N. Ten Years of Co-Crystal Synthesis; the Good, the Bad, and the Ugly. *CrystEngComm* **2008**, *10* (12), 1816.
63. Guo, M.; Sun, X.; Chen, J.; Cai, T. Pharmaceutical Cocrystals: A Review of Preparations, Physicochemical Properties and Applications. *Acta Pharmaceutica Sinica B* **2021**, *11* (8).
64. Schultheiss, N.; Newman, A. Pharmaceutical Cocrystals and Their Physicochemical Properties. *Crystal Growth & Design* **2009**, *9* (6), 2950–2967.
65. Taylor, C. R.; Day, G. M. Evaluating the Energetic Driving Force for Cocrystal Formation. *Crystal Growth & Design* **2017**, *18* (2), 892–904.
66. Yulia Pimonova; Carpenter, J. E.; Gruenwald, M. Thermodynamic Stability Is a Poor Indicator of Cocrystallization in Models of Organic Molecules. *Journal of the American Chemical Society* **2024**, *146* (4), 2805–2815.
67. Xuan, B.; Chee, Y.; Wong, K. C.; Chen, R.; Lo, P. S.; Lakerveld, R.; Hoi, H.; Chow, S. F. Impact of Cocrystal Solution-State Stability on Cocrystal Dissociation and Polymorphic Drug Recrystallization during Dissolution. *International Journal of Pharmaceutics* **2021**, *610*, 121239–121239.

68. Guérain, M.; Guinet, Y.; Correia, N. T.; Paccou, L.; Danède, F.; Hédoux, A. Polymorphism and Stability of Ibuprofen/Nicotinamide Cocrystal: The Effect of the Crystalline Synthesis Method. *International Journal of Pharmaceutics* **2020**, *584*, 119454.
69. Sun, S.; Zhang, H.; Xu, J.; Wang, S.; Wang, H.; Yu, Z.; Zhao, L.; Zhu, C.; Sun, J. The Competition between Cocrystallization and Separated Crystallization Based on Crystallization from Solution. *Journal of Applied Crystallography* **2019**, *52* (4), 769–776.
70. Zhao, X.; Li, J.; Quan, S.; Fu, X.; Meng, S.; Jiang, L.; Fan, X. Study on the Effect of Solvent on Cocrystallization of CL-20 and HMX through Theoretical Calculations and Experiments. *RSC Advances* **2022**, *12* (33), 21255–21263.
71. Karimi-Jafari, M.; Padrela, L.; Walker, G. M.; Croker, D. M. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. *Crystal Growth & Design* **2018**, *18* (10), 6370–6387.
72. Malamataris, M.; Ross, S. A.; Douroumis, D.; Velaga, S. P. Experimental Cocrystal Screening and Solution Based Scale-up Cocrystallization Methods. *Advanced Drug Delivery Reviews* **2017**, *117*, 162–177.
73. MacEachern, L.; Kermanshahi-pour, A.; Mirmehrabi, M. Supercritical Carbon Dioxide for Pharmaceutical Co-Crystal Production. *Crystal Growth & Design* **2020**, *20* (9), 6226–6244.
74. Sarathi, P.; Padhi, S. Insight of the Various *in Silico* Screening Techniques Developed for Assortment of Cocrystal Formers and Their Thermodynamic Characterization. *Drug Development and Industrial Pharmacy* **2021**, *47* (10), 1523–1534.
75. Myz, S. A.; Mikhailenko, M. A.; Mikhailovskaya, A. V.; Bulina, N. V.; Gerasimov, K. B.; Politov, A. A.; Kuznetsova, S. A.; Shakhtshneider, T. P. Cocrystals of Betulin with Adipic Acid: Preparation and Thermal Behavior. *Journal of Thermal Analysis and Calorimetry* **2021**, *147* (15), 8235–8242.
76. Vaksler, Ye. A.; Benedis, D.; Dyshin, A. A.; Oparin, R. D.; Correia, N. T.; Capet, F.; Shishkina, S. V.; Kiselev, M. G.; Idrissi, A. Spectroscopic Characterization of Single Co-Crystal of Mefenamic Acid and Nicotinamide Using Supercritical CO₂. *Journal of Molecular Liquids* **2021**, *334*, 116117.
77. Trask, A. V.; Motherwell, W. D. S.; Jones, W. Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration. *Crystal Growth & Design* **2005**, *5* (3), 1013–1021.
78. Allu, S.; Suresh, K.; Bolla, G.; Mannava, M. K. C.; Nangia, A. Role of Hydrogen Bonding in Cocrystals and Coamorphous Solids: Indapamide as a Case Study. *CrystEngComm* **2019**, *21* (13), 2043–2048.
79. Kobayashi, K.; Shirasaka, T.; Horn, E.; Furukawa, N.; Yamaguchi, K.; Sakamoto, S. Molecular Capsule Constructed by Multiple Hydrogen Bonds: Self-Assembly of Cavitand Tetracarboxylic Acid with 2-Aminopyrimidine. *Chemical Communications* **2000**, No. 1, 41–42.

80. Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. The Halogen Bond. *Chemical Reviews* **2016**, *116* (4), 2478–2601.
81. Liantonio, R.; Metrangolo, P.; Pilati, T.; Resnati, G. 4,4'-Bipyridine 1,2-Diiodo-3,4,5,6-Tetrafluorobenzene. *Acta Crystallographica Section E Structure Reports Online* **2002**, *58* (5), o575–o577.
82. Alessandra De Santis; Forni, A.; Liantonio, R.; Pierangelo Metrangolo; Pilati, T.; Resnati, G. N $\cdots$ Br Halogen Bonding: One-Dimensional Infinite Chains through the Self-Assembly of Dibromotetrafluorobenzenes with Dipyridyl Derivatives. *Chemistry: A European Journal* **2003**, *9* (16), 3974–3983.
83. Baus Topić, N.; Bedeković, N.; Lisac, K.; Stilinović, V.; Cinčić, D. Halogen-Bonded Cocrystals of 1,3,5-Triiodo-2,4,6-Trifluorobenzene and Structural Isomers of Benzoylpyridine. *Crystal Growth & Design* **2022**, *22* (6), 3981–3989.
84. Aakeröy, C. B.; Rajbanshi, A.; Metrangolo, P.; Resnati, G.; Parisi, M. F.; Desper, J.; Pilati, T. The Quest for a Molecular Capsule Assembled via Halogen Bonds. *CrystEngComm* **2012**, *14* (20), 6366.
85. Shen, Y.; Hou, J.; Liu, Y.; Wan, X.; Bai, M.; Jiang, X.; Duan, W.; Yan, F. Deep Insight into the Charge-Transfer Cocrystals: Decreasing Structural Overlap Induced Bathochromically Shift Emission. *Dyes and Pigments* **2023**, *215*, 111277.
86. Aakeröy, C. B.; Forbes, S.; Desper, J. Altering Physical Properties of Pharmaceutical Co-Crystals in a Systematic Manner. *CrystEngComm* **2014**, *16* (26), 5870–5877.
87. Bennion, J. C.; Matzger, A. J. Development and Evolution of Energetic Cocrystals. *Accounts of Chemical Research* **2021**, *54* (7), 1699–1710.
88. Mazzeo, P. P.; Carraro, C.; Monica, A.; Davide Capucci; Paolo Pelagatti; Bianchi, F.; Agazzi, S.; Careri, M.; Raio, A.; Carta, M.; Menicucci, F.; Belli, M.; Michelozzi, M.; Bacchi, A. Designing a Palette of Cocrystals Based on Essential Oil Constituents for Agricultural Applications. *ACS Sustainable Chemistry & Engineering* **2019**, *7* (21), 17929–17940.
89. Sokolov, A. N.; Tomislav Friščić; Blais, S. P.; Ripmeester, J. A.; MacGillivray, L. R. Persistent One-Dimensional Face-To-Face π -Stacks within Organic Cocrystals. *Crystal Growth & Design* **2006**, *6* (11), 2427–2428.
90. Yu, Y.; Xia, X.-Y.; Xu, C.-F.; Lv, Z.-J.; Wang, X.-D.; Liao, L.-S. Customizable Organic Charge-Transfer Cocrystals for the Dual-Mode Optoelectronics in the NIR (II) Window. *Journal of the American Chemical Society* **2024**, *146* (17), 11845–11854.
91. Springuel, G.; Leyssens, T. Innovative Chiral Resolution Using Enantiospecific Co-Crystallization in Solution. *Crystal Growth & Design* **2012**, *12* (7), 3374–3378.

92. Hutchins, K. M.; Sumrak, J. C.; MacGillivray, L. R. Resorcinol-Templated Head-To-Head Photodimerization of a Thiophene in the Solid State and Unusual Edge-To-Face Stacking in a Discrete Hydrogen-Bonded Assembly. *Organic Letters* **2014**, *16* (4), 1052–1055.
93. Sinha, A. S.; Aakeröy, C. B. Chapter 9. Co-Crystallization as a Versatile Tool in Separations Technology. *Monographs in Supramolecular Chemistry* **2018**, 302–335.
94. Hay, M.; Thomas, D. W.; Craighead, J. L.; Economides, C.; Rosenthal, J. Clinical Development Success Rates for Investigational Drugs. *Nature Biotechnology* **2014**, *32* (1), 40–51.
95. Wu, K.; Kwon, S. H.; Zhou, X.; Fuller, C.; Wang, X.; Jaydutt Vadgama; Wu, Y. Overcoming Challenges in Small-Molecule Drug Bioavailability: A Review of Key Factors and Approaches. *International Journal of Molecular Sciences* **2024**, *25* (23), 13121–13121.
96. Sun, D.; Gao, W.; Hu, H.; Zhou, S. Why 90% of Clinical Drug Development Fails and How to Improve It? *Acta Pharmaceutica Sinica B* **2022**, *12* (7).
97. Buddhadev, S. S.; Garala, K. C. Pharmaceutical Cocrystals-a Review. *Proceedings* **2021**, *62* (1), 14.
98. Chettri, A.; Ankita Subba; Singh, G.; Partha Pratim Bag. Pharmaceutical Co-Crystals: A Green Way to Enhance Drug Stability and Solubility for Improved Therapeutic Efficacy. *Journal of Pharmacy and Pharmacology* **2023**, *76* (1).
99. Basavoju, S.; Boström, D.; Velaga, S. P. Indomethacin–Saccharin Cocrystal: Design, Synthesis and Preliminary Pharmaceutical Characterization. *Pharmaceutical Research* **2007**, *25* (3), 530–541.
100. Shaikh, T. R.; George, C. P.; Priyanka Bhukya; Shelke, N.; Pawar, K.; Garai, A.; Rambabu Dandela; Gonnade, R. G.; Nangia, A. K. Novel Crystal Forms of Entresto: A Supramolecular Complex of Trisodium Sacubitril/Valsartan Hemi-Pentahydrate. *CrystEngComm* **2022**, *24* (42), 7387–7393.
101. Che, A. *Entresto: The first FDA-approved Drug-Drug Co-crystal (DDC) in the New Century*. Medium. <https://medium.com/@allen-che/entresto-the-first-fda-approved-drug-drug-co-crystal-ddc-in-the-new-century-ea75298f5813> (accessed 01/03/2026).
102. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers? *Crystal Growth & Design* **2025**, *25* (20).
103. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Examining Intermolecular Interactions in Crystal Structures of Amide-Substituted 2-Aminopyrimidine Derivatives. *CrystEngComm* **2025**, No. 43.

Chapter 2 - The structural landscape of 2-aminopyridine derivatives: Chains or Dimers?

2.1 Introduction

Non-covalent interactions, notably hydrogen-, halogen- and chalcogen bonds are well established¹⁻⁷ as synthetic drivers for the systematic construction of multi-component molecular solids such as binary and higher-order molecular cocrystals.⁸⁻¹² The delicate balance between these forces underpins intentional assembly of diverse structural arrangements with a range of desirable bulk properties.¹³⁻¹⁴ Specific spatial arrangements of molecules in a crystal lattice may be controlled via “bottom-up” strategies by promoting favorable intermolecular interactions and limiting unfavorable intermolecular interactions.¹⁵⁻¹⁶ Such scenarios need to be systematically examined and carefully interpreted in order to identify reliable synthons that can be related to precise steric¹⁷⁻²⁰ thermodynamic²¹⁻²³, and supramolecular demands.²⁴⁻²⁷ Even very subtle changes in molecular geometry can have dramatic effects on how molecules self-assemble into a highly ordered and periodic crystal lattice.²⁸⁻³¹

One of the key reasons behind a hierarchical view of intermolecular interactions stems from the importance of electrostatics for identifying and ranking the relative competition between different intermolecular interactions.³²⁻³⁴ However, since many molecules contain numerous sites capable of forming electrostatically-driven intermolecular bonds, it is a challenge to predict which binding will be the most likely pairing of regions of positive and negative electron density.³⁵⁻³⁷ In addition, even parts of a molecule that do not directly interact electrostatically can play a significant role in stabilizing and directing intermolecular recognition and communication.

To advance our understanding and control of specific non-covalent interactions in the solid-state, it is important to conduct structural investigations on closely related molecules that allow us to

systematically analyze how different factors influence their structural properties without making too many molecular modifications at once. To this end, we carried out a structural examination of twelve acetylated derivatives of 2-aminopyridine, grouped into two series (5-NO₂ and 3-Cl,5-CF₃) of increasing molecular weight and steric complexity. 2-Aminopyridine has been used extensively for creating low-molecular-weight pharmacophores effective against different biological targets that undergo minimal side reactions during the synthesis.³⁸⁻⁴² Therefore, derivatives of 2-aminopyridine have been used in developing anticancer, anti-inflammatory, antioxidant, antidiabetic, antifungal, antibacterial, antiviral, antimalarial, antileishmanial, and antitrypanosomal drugs.^{38-39,43-45} However, systematic structural examinations of closely related homologous series of 2-aminopyridine are relatively uncommon.^{20,38} Amide derivatives of 2-aminopyridine have also received considerable interest in recent years due to their varied medicinal and pharmacological applications, notably molecules containing *N*-(pyridin-2-yl) amides, Figure 2.1.⁴⁰

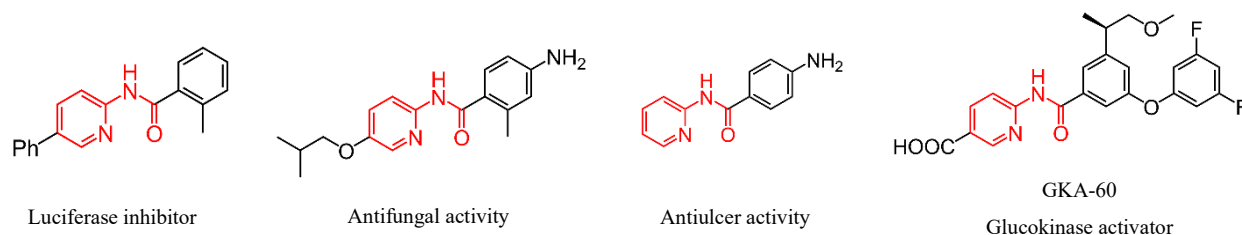


Figure 2.1. Examples of pharmaceutically relevant molecules containing *N*-(pyridin-2-yl) amides.

The amide moiety is also frequently employed in supramolecular chemistry due to its ability to form different structural assemblies in the solid-state.^{20,46-51} It predominantly forms either N-H $\cdots$ O=C infinite chain-like interactions or N-H $\cdots$ N(py)/N(py) $\cdots$ H-N dimeric interactions, Figure 2.2.

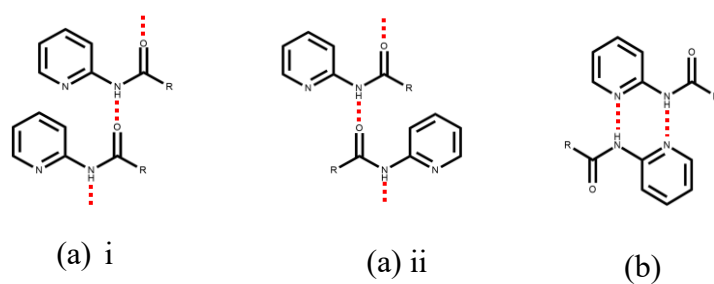


Figure 2.2. Two prevalent modes of self-aggregation of 2-aminopyridine amides, (a) i & ii; chains, (b) dimer.

A previous study of the self-aggregation in ten 2-acylaminopyridines decorated with supramolecularly ‘innocuous’ (but sterically relevant) groups (methyl, ethyl, i-propyl, t-butyl, and 1-adamantyl) established that these molecules form $\text{N-H}\cdots\text{O}=\text{C}$ chains and $\text{N-H}\cdots\text{N}(\text{py})/\text{N}(\text{py})\cdots\text{H-N}$ dimers.²⁰ It was also noted that chain formation is dominant in order to prevent steric clash. In addition, it was also reported that the vibrational behavior of the $\text{C}=\text{O}$ bond, as detected by infrared spectroscopy, could possibly be used as a marker for identifying specific bonding modes in the solid-state. In order to examine these observations, we began to further map out the structural landscape of 2-aminopyridine derivatives containing the amide functionality. Therefore, in this study, we have synthesized and structurally characterized twelve molecules, Figure 2.3, and we also address additional questions regarding intermolecular molecular recognition and assembly, including;

- Does the length of the alkyl chain at the R position influence the chain vs dimer?
- Does the electrostatic nature of the pyridine nitrogen affect self-assembly?
- Can infrared spectroscopy alone be used as a tool to determine the bonding mode?

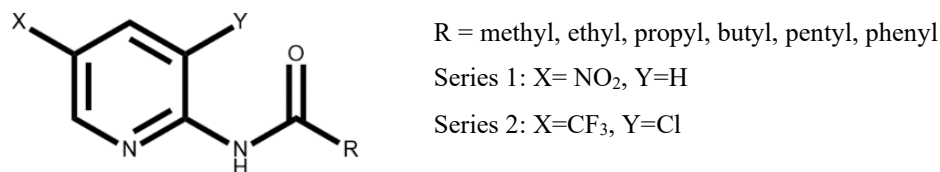


Figure 2.3. Schematic diagram of molecular structures of compounds in this study.

2.2 Experimental section

2.2.1 General

All precursors and solvents were purchased from commercial sources and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on Bruker 400 and 600 MHz spectrometers. Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra were recorded with a Nicolet 380 FTIR spectrometer using attenuated total reflection (ATR) with a ZnSe crystal. Electrostatic potentials were calculated with density functional B3LYP level of theory using 6-311++G** basis set in vacuum, using Spartan'14 software.

2.2.2 Syntheses of the 5-NO₂ series

Syntheses of the *N*-(pyridin-2-yl)acylamides were carried out according to a literature procedure.

52

2.2.2.1 Synthesis of *N*-(5-nitropyridin-2-yl)acetamide (NO₂-methyl)

A solution of 2-amino-5-nitropyridine (1.41 g, 9.84 mmol) in acetic anhydride (5.00 mL, 52.65 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 86.91%, M.P: 197-199 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.22 (s, 1H), 9.16 (d, *J* = 2.6 Hz, 1H), 8.59

(dd, $J = 9.3, 2.8$ Hz, 1H), 8.29 (dd, $J = 9.3, 0.0$ Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 170.7, 156.6, 145.2, 140.2, 134.7, 112.8, 24.6.

2.2.2.2 Synthesis of *N*-(5-nitropyridin-2-yl)propionamide (NO₂-ethyl)

A solution of 2-amino-5-nitropyridine (1.39 g, 9.66 mmol) in propionic anhydride (6.00 mL, 46.34 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 92.59%, M.P: 172-174 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 11.17 (s, 1H), 9.15 (d, $J = 2.9$ Hz, 1H), 8.59 (dd, $J = 9.3, 2.8$ Hz, 1H), 8.30 (d, $J = 9.3$ Hz, 1H), 2.47 (q, $J = 7.5$ Hz, 2H), 1.08 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 174.3, 156.7, 145.2, 140.1, 134.6, 112.8, 29.9, 9.5.

2.2.2.3 Synthesis of *N*-(5-nitropyridin-2-yl)butyramide (NO₂-propyl)

A solution of 2-amino-5-nitropyridine (4.00 g, 28.75 mmol) in butyric anhydride (4.90 mL, 30 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 83.46 %, M.P: 105-107 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 9.16 (d, $J = 2.7$ Hz, 1H), 8.59 (dd, $J = 9.3, 2.8$ Hz, 1H), 8.31 (d, $J = 9.3$ Hz, 1H), 2.45 (t, $J = 7.3$ Hz, 2H), 1.62 (h, $J = 7.4$ Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 174.5, 156.6, 145.2, 140.1, 134.6, 112.9, 38.5, 18.6, 13.9.

2.2.2.4 Synthesis of *N*-(5-nitropyridin-2-yl)pentanamide (NO₂-butyl)

A solution of 2-amino-5-nitropyridine (1.11 g, 7.98 mmol) in pentanoic anhydride (2.00 mL, 10 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 83.46%, M.P: 83-85 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 9.15 (d, *J* = 2.8 Hz, 1H), 8.57 (dd, *J* = 9.3, 2.8 Hz, 1H), 8.30 (d, *J* = 9.3 Hz, 1H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.57 (p, *J* = 7.4 Hz, 2H), 1.31 (h, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.6, 156.7, 145.2, 140.1, 134.6, 112.8, 36.4, 27.2, 22.2, 14.1.

2.2.2.5 Synthesis of *N*-(5-nitropyridin-2-yl)hexanamide (NO₂-pentyl)

A solution of 2-amino-5-nitropyridine (1.04 g, 7.23 mmol) in hexanoic anhydride (2.40 mL, 10.0 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 90.25%, M.P: 89-91 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 9.15 (d, *J* = 2.8 Hz, 1H), 8.58 (dd, *J* = 9.3, 2.9 Hz, 1H), 8.30 (d, *J* = 9.3 Hz, 1H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.59 (p, *J* = 7.3 Hz, 2H), 1.29 (q, *J* = 3.6 Hz, 4H), 0.91 - 0.83 (m, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.6, 156.7, 145.2, 140.1, 134.7, 112.9, 36.6, 31.2, 24.8, 22.3, 14.3.

2.2.2.6 Synthesis of *N*-(5-nitropyridin-2-yl)benzamide (NO₂-phenyl)

A solution of 2-amino-5-nitropyridine (1.00 g, 7.19 mmol) and benzoic anhydride (1.63 g, 7.19 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was

filtered off and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, ice-cold water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 52.68%, M.P: 165-167 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.53 (s, 1H), 9.23 (s, 1H), 8.66 (d, *J* = 9.3 Hz, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 2H), 7.64 (t, 1H), 7.55 (t, *J* = 7.8 Hz, 2H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.2, 157.0, 145.0, 140.6, 134.6, 133.8, 133.0, 128.9, 128.8, 114.1.

2.2.3 Syntheses of the Cl-CF₃ series

2.2.3.1 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)acetamide (Cl-CF₃-methyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (0.21 g, 1.05 mmol) in acetic anhydride (2.00 mL, 21.05 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 94.42 %, M.P: 138-140 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.53 (s, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.50 (d, *J* = 1.8 Hz, 1H), 2.13 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 169.1, 152.3, 144.2, 144.2, 136.7, 136.7, 126.0, 124.2, 123.9, 123.7, 122.4, 23.8.

2.2.3.2 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)propionamide (Cl-CF₃-ethyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (1.44 g, 7.12 mmol) in propionic anhydride (5.00 mL, 38.80 mmol) was stirred for 1.5 h at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with

dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 94.44 %, M.P: 131-133 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 8.81 - 8.78 (m, 1H), 8.50 (d, *J* = 2.2 Hz, 1H), 2.43 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.7, 152.4, 144.3, 144.2, 144.2, 144.1, 136.7, 136.7, 136.6, 136.6, 126.1, 124.7, 123.9, 123.6, 121.9, 29.3, 9.8.

2.2.3.3 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)butyramide (Cl-CF₃-propyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (0.21 g, 1.07 mmol) in butyric anhydride (1.50 mL, 8.99 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 78.25%, M.P: 108-110 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.52 (s, 1H), 8.80 (s, 1H), 8.49 (s, 1H), 2.42 - 2.36 (m, 2H), 1.66 - 1.61 (m, 2H), 0.94 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 171.8, 152.4, 144.2, 136.7, 126.4, 124.3, 123.9, 122.4, 37.9, 18.8, 14.0.

2.2.3.4 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)pentanamide (Cl-CF₃-butyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (1.21 g, 6.17 mmol) in pentanoic anhydride (2.00 mL, 10.0 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate

the pure product. Yield 52.02 %, M.P: 110-112 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.51 (s, 1H), 8.80 (s, 1H), 8.50 (d, *J* = 2.1 Hz, 1H), 2.44 - 2.38 (m, 3H), 1.59 (p, *J* = 8.1, 7.7 Hz, 4H), 1.35 (h, *J* = 7.8 Hz, 4H), 0.90 (t, *J* = 7.4 Hz, 5H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.9, 152.4, 144.2, 144.2, 136.7, 136.6, 126.3, 124.7, 124.0, 123.7, 121.9, 35.7, 27.4, 22.2, 14.1.

2.2.3.5 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)hexanamide (Cl-CF₃-pentyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (1.28 g, 6.30 mmol) in hexanoic anhydride (2.40 mL, 10.0 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, brine, water and dried with anhydrous magnesium sulfate, filtered and concentrated to isolate the product. Yield 63.80 %, M.P: 107-109 °C ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.51 (s, 1H), 8.80 (s, 1H), 8.50 (s, 1H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.61 (h, *J* = 7.1 Hz, 2H), 1.34 - 1.28 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 171.9, 152.4, 144.3, 144.3, 136.7, 136.7, 126.4, 124.3, 122.5, 35.9, 31.2, 24.9, 22.3, 14.3.

2.2.3.6 Synthesis of *N*-(3-chloro-5-trifluoromethylpyridin-2-yl)benzamide (Cl-CF₃-phenyl)

A solution of 2-amino-3-chloro-5-trifluoromethylpyridine (1.00 g, 5.09 mmol) and benzoic anhydride (1.15 g, 5.09 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, ice-cold water and dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to isolate the pure product. Yield 48.34%, M.P: 152-154 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 8.90

(s, 1H), 8.60 (s, 1H), 8.02 (d, $J = 7.7$ Hz, 2H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.57 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 165.7, 152.5, 144.0, 136.5, 132.9, 132.5, 129.3, 128.6, 128.2, 127.7.

Additionally, within each series, the melting points of these compounds decrease as the alkyl chain length increases, as a result of the increasing nonpolar contribution.

Crystals suitable for single-crystal X-ray diffraction for all twelve compounds were obtained by slow evaporation from a variety of solvents, Table 2.1. Details of crystallographic experiments are given in Appendix B.

Table 2.1. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology
<i>N</i> -(5-nitropyridin-2-yl)acetamide-Polymorph I	NO₂-methyl - Polymorph I	Ethyl acetate	Colorless, needle
<i>N</i> -(5-nitropyridin-2-yl)acetamide-Polymorph II	NO₂-methyl - Polymorph II	Acetonitrile	Colorless, irregular block
<i>N</i> -(5-nitropyridin-2-yl)propionamide	NO₂-ethyl	Ethyl acetate	Pale yellow, needle
<i>N</i> -(5-nitropyridin-2-yl)butyramide-Polymorph I	NO₂- propyl -Polymorph I	Ethyl acetate	Colorless, block
<i>N</i> -(5-nitropyridin-2-yl)butyramide-Polymorph II	NO₂- propyl -Polymorph II	Methanol	Colorless, plates
<i>N</i> -(5-nitropyridin-2-yl)pentanamide	NO₂- butyl	Methanol	Colorless, plate
<i>N</i> -(5-nitropyridin-2-yl)hexanamide	NO₂- pentyl	Ethanol	Colorless, block
<i>N</i> -(5-nitropyridin-2-yl)benzamide	NO₂- phenyl	Methanol	Colorless, plate
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)acetamide	Cl-CF₃-methyl	Acetone	Colorless, needle
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)propionamide	Cl-CF₃-ethyl	Ethanol	Colorless, needle
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)butyramide	Cl-CF₃-propyl	Dioxane	Colorless, block
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)pentanamide	Cl-CF₃-butyl	Methanol	Colorless, needle
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)hexanamide	Cl-CF₃-pentyl	Hexane	Colorless, needle
<i>N</i> -(3-chloro-5-trifluoromethylpyridin-2-yl)benzamide	Cl-CF₃-phenyl	Ethanol	Colorless, needle

2.2.4 Reaction conditions for obtaining the polymorphs

2.2.4.1 *N*-(5-nitropyridin-2-yl)acetamide-Polymorph II

Equimolar amounts of *N*-(5-nitropyridin-2-yl)acetamide and copper iodide were dissolved in acetonitrile and allowed to slowly evaporate for about a week to get crystals of polymorph II.

2.2.4.2 *N*-(5-nitropyridin-2-yl)butyramide-Polymorph II

Liquid-assisted grinding was performed on equimolar amounts of *N*-(5-nitropyridin-2-yl)butyramide and 4-aminobenzoic acid in the presence of a few drops of methanol. Then, the

grinding mixture was allowed to slowly evaporate in methanol for about a week to get crystals of polymorph II.

2.2.5 Molecular electrostatic potential calculations (MEP)

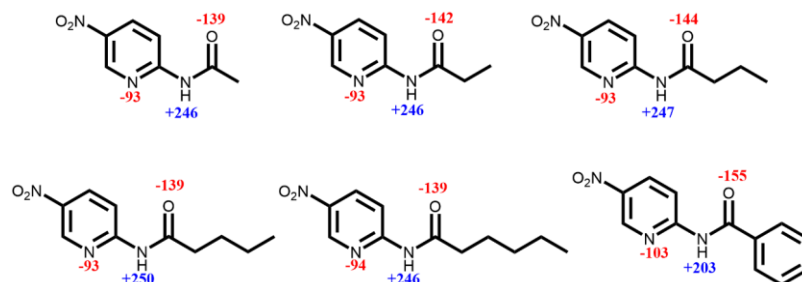
MEP surfaces were generated for all molecules explored in this study using Spartan'14 Version 1.1.4. The molecular skeleton was first loaded into the software from a ChemDraw file, which was then geometry-optimized using DFT with the B3LYP functional and the 6-311++G** triple-zeta basis set in vacuum. On this optimized structure, the maxima and minima on the MEP surface (0.002 e/au isosurface) were determined using a positive point charge in the vacuum as a probe.

2.3 Results

2.3.1 MEP values

The calculated molecular electrostatic potentials (MEPs) are shown in Figure 2.4.

2.3.1.1 MEP values of the NO₂ series



2.3.1.2 MEP values of the Cl-CF₃ series

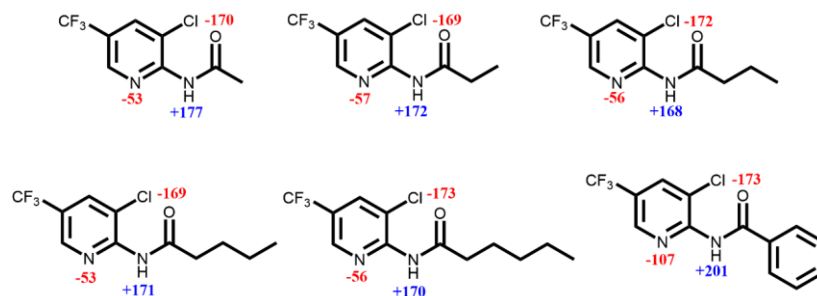


Figure 2.4. MEP values (kJ/mol) at the most likely hydrogen bond donor and acceptor sites in the twelve targets.

2.3.2 SCXRD analysis of target materials

The primary hydrogen bonds in the crystal structures of the six nitro-substituted target compounds are displayed in Figure 2.5a-f.

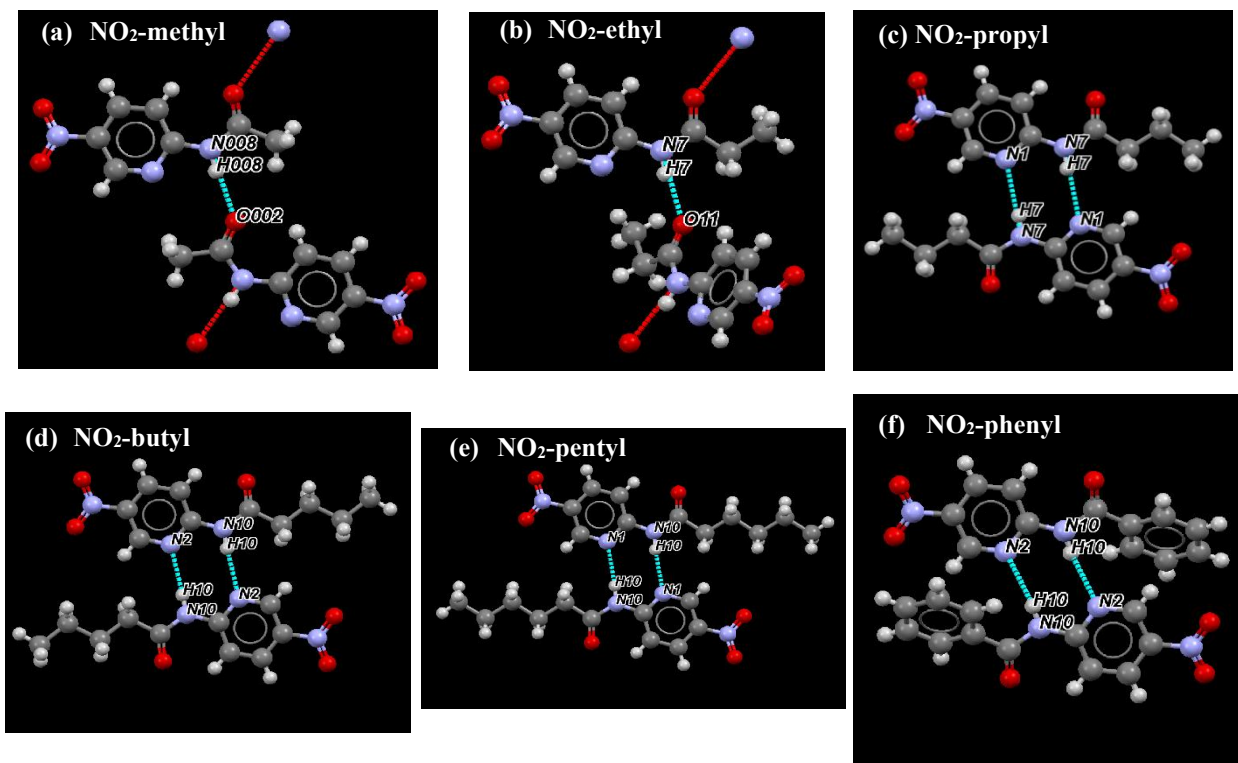


Figure 2.5. Primary hydrogen-bond interactions in the crystal structures of (a) NO₂-methyl, (b) NO₂-ethyl, (c) NO₂-propyl, (d) NO₂-butyl, (e) NO₂-pentyl, and (f) NO₂-phenyl.

In the six crystal structures from the NO₂ family (Figure 2.5), an infinite N-H $\cdots$ O=C chain is the primary supramolecular motif in the first two members of this family (methyl and ethyl alkyl groups). However, with an increase in chain length and thus more prominent steric influences, an N-H $\cdots$ N(py)/ N(py) $\cdots$ H-N dimer becomes the dominant supramolecular unit. The relevant hydrogen bond parameters in these crystal structures are given in Table 2.2.

Additionally, polymorphs of NO₂-methyl and NO₂-propyl were found in parallel studies of these compounds, but only the NO₂-methyl displayed a motif that was consistent with the initial form; a chain motif in polymorph II of NO₂-methyl but an unexpected ribbon motif in polymorph II of NO₂-propyl, Figure 2.6 (see Discussion).

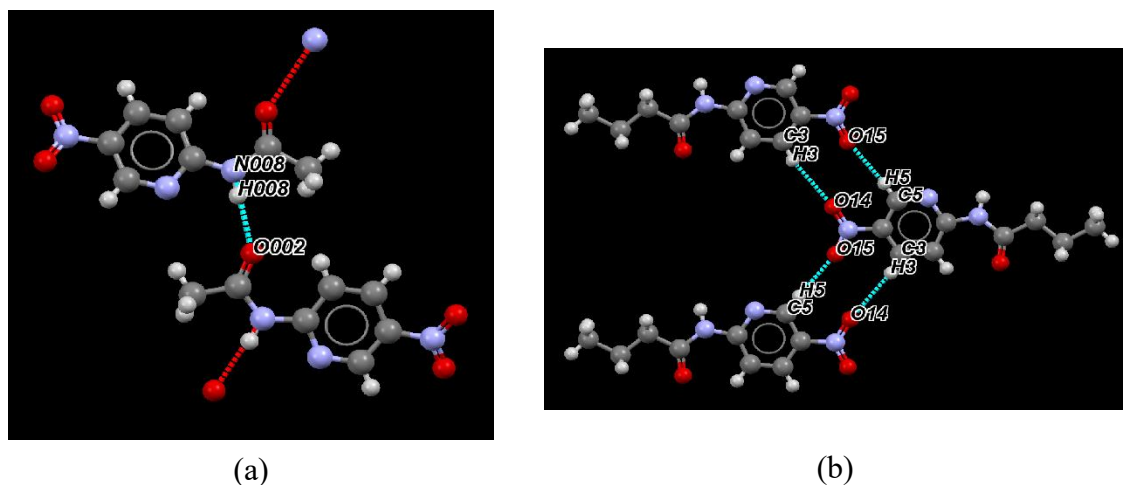
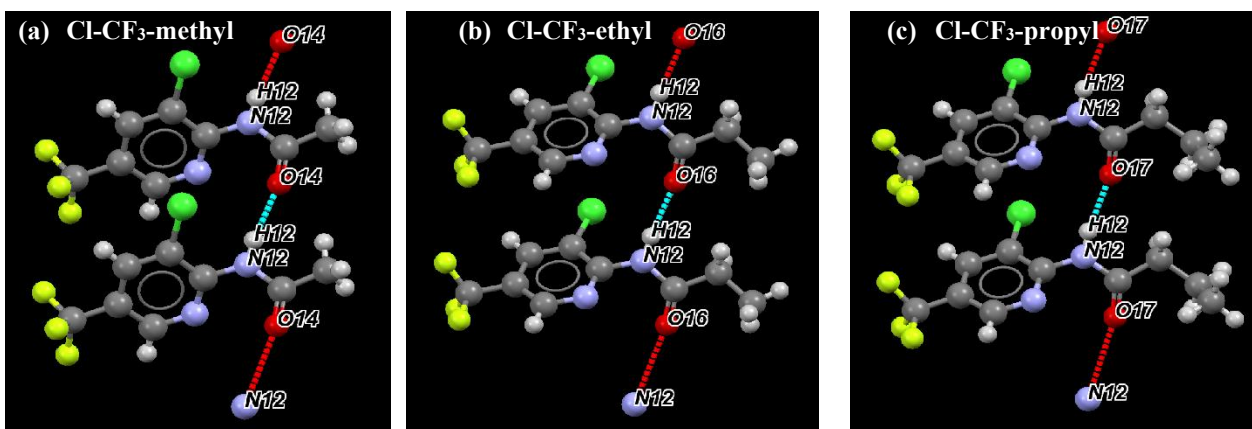


Figure 2.6. Chain motif in polymorph II of NO₂-methyl;(b) ribbon motif in polymorph II of NO₂-propyl.

The primary intermolecular interactions in the six crystal structures of the Cl-CF₃ series are shown in Figures 2.7a-f. In every crystal structure from this family, the primary intermolecular interaction is an infinite N-H···O=C chain. The relevant hydrogen bond parameters in these six crystal structures are given in Table 2.3.



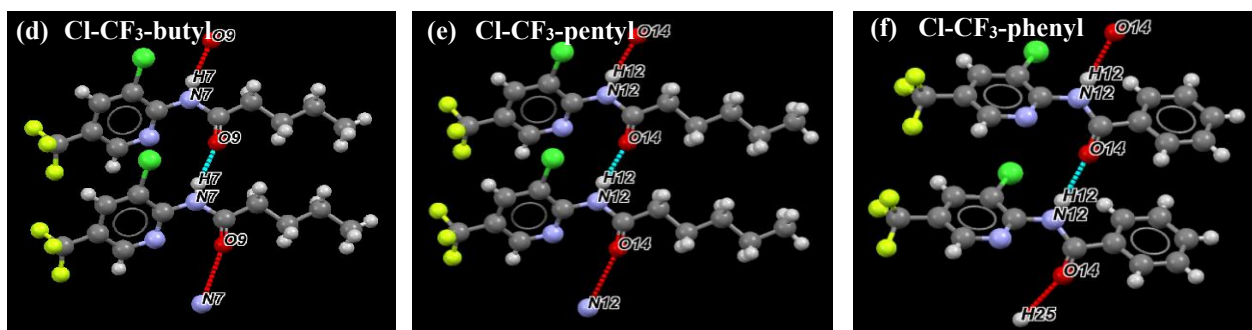


Figure 2.7. Primary hydrogen bonds in the crystal structures of (a) Cl-CF₃-methyl, (b) Cl-CF₃-ethyl, (c) Cl-CF₃-propyl, (d) Cl-CF₃-butyl, (e) Cl-CF₃-pentyl, and (f) Cl-CF₃-phenyl.

Table 2.2. Hydrogen bond parameters of crystal structures in the NO₂ series

	D-H...A	D...A/Å	D-H...A/°
methyl	N008-H008...O002	2.9442(15)	173.0(19)
ethyl	N7-H7...O11	2.8841(11)	166.97(6)
propyl	N7-H7...N1	3.2130(18)	173.54(9)
butyl	N10-H10...N2	3.180(3)	175.0(3)
pentyl	N10-H10...N1	3.189(2)	175.0(2)
phenyl	N10-H10...N2	3.297(3)	135.0(3)

Table 2.3. Hydrogen bond parameters of crystal structures in the Cl-CF₃ series

	D-H...A	D...A/Å	D-H...A/°
methyl	N12-H12...O14	2.876(2)	168.0(3)
ethyl	N12-H12...O16	2.874(2)	173.56(11)
propyl	N12-H12...O17	2.899(3)	168.03(16)
butyl	N7-H7...O9	2.8880(18)	164.0(2)

pentyl	N12-H12...O14	2.897(3)	165.79(16)
phenyl	N12-H12...O14	2.916(2)	163.0(3)

A graph-set notation⁵³ was employed to characterize the hydrogen-bond motifs, and among the twelve crystal structures, all chain structures displayed the $C_1^1(4)$ pattern, the dimers exhibited the $R_2^2(8)$ motif, and the unexpected ribbon motif was assigned $R_2^2(10)$.

2.3.3 FTIR results of target materials

The IR carbonyl stretching frequencies of these twelve compounds are given in Table 2.4.

Table 2.4. The IR stretching frequency for the amide C=O group in twelve target molecules.

Amide group	C=O frequency/cm ⁻¹		
	NO ₂ series		Cl-CF ₃ series
methyl	<i>Polymorph I</i>	1685	1688
	<i>Polymorph II</i>	1670	
ethyl	1681		1688
propyl	<i>Polymorph I</i>	1709	1684
	<i>Polymorph II</i>	1688	
butyl	1697		1688
pentyl	1697		1687
phenyl	1686		1672

2.4 Discussion

Initially, we hypothesized that amide derivatives of 2-aminopyridine compounds would engage in one of two different intermolecular events, N-H...O=C or N-H...N(py)/N(py)...H-N hydrogen bonds, resulting in infinite chains or discrete dimers, respectively. Indeed, both interactions were present to varying degrees in the crystal structures that were obtained.

In the first series (NO₂), we increased the length of substituted alkyl chains from one to five carbon atoms to probe how this steric increase would affect the supramolecular assembly. Since the MEP values of the molecules remained almost constant throughout the series, we could rule out any obvious electrostatic influence and directly connect changes in molecular structure to changes in crystal structure. The first two crystal structures, with the shorter methyl and ethyl alkyl groups, favor the formation of N-H···O=C infinite chains. However, the addition of lengthier alkyl chains from three to five carbon atoms promotes the formation of dimeric N-H···N(py)/ N(py)···H-N motifs. Thus, it is reasonable to conclude that the steric effects from the larger alkyl chains impact the supramolecular assemblies. But what if we have a simple aromatic ring instead of an alkyl chain? Hence, we investigated that question by adding an aromatic group instead of an alkyl chain and it resulted in a dimeric N-H···N(py)/N(py)···H-N motif. Therefore, we can deduce that sterics alone have a significant impact on the formation of supramolecular assemblies in this family of compounds.

In contrast, in the second series (Cl-CF₃), the infinite N-H···O=C chains were present in all five structures, despite differences in alkyl chain length. Clearly then, the increasing chain length itself is not affecting the molecular assemblies in the crystal structures in this series. The other main structural difference observed in this series compared to the structures of the (NO₂) group is that the N-H and C=O groups have rotated with respect to each other, Figure 2.8. The MEP values for each series were calculated for the given conformations.

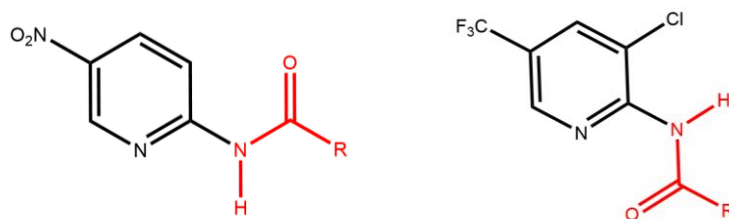


Figure 2.8. Conformational difference between the NO₂ series (left) and the Cl-CF₃ series (right) with respect to the amide group.

The reason for this change could be due to the steric effect and electrostatic preferences resulting from the Cl group attached to the third position of the pyridine ring. However, another factor disfavoring the $\text{N-H}\cdots\text{N}(\text{py})/\text{N}(\text{py})\cdots\text{H-N}$ dimeric interaction type could be the reduced hydrogen-bond acceptor strength of the pyridine ring nitrogen atom in this series, which would diminish its H-bonding tendencies. And also, in series 2, the carbonyl group acts as a strong hydrogen-bond acceptor and is therefore expected to participate in hydrogen bonding, whereas in series 1, steric effects arising from the alkyl chain are the primary influencing factor (Figure 2.9). The presence of a phenyl ring instead of an alkyl chain does not change the supramolecular assembly and the result is an infinite $\text{N-H}\cdots\text{O}=\text{C}$ chain.

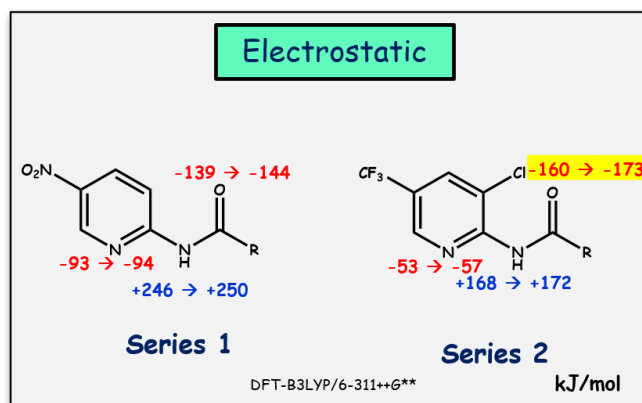


Figure 2.9. MEP summary of series 1 and 2.

Compared to the NO_2 series, the presence of the CF_3 and Cl groups on the aromatic ring of the second series altered the MEP of the acceptor and donor sites by decreasing the acceptor (py-N) potential (less negative) and decreasing the donor (N-H) potential (less positive) and increasing the C=O acceptor potential (more negative). Although the NO_2 group is a strongly electron-withdrawing moiety, the CF_3 and Cl combination has a greater impact on the charge distribution across the molecular backbone than the NO_2 group alone.

To determine if the structural outcomes could be rationalized using a simple electrostatic model, we then inspected all twelve compounds and noted that eight molecules display motifs that involve the best donor/highest positive (N-H) and the best acceptor/highest negative (C=O) moieties indicating that the simple electrostatic model provides reasonable guidance for predicting the structural outcome.

In addition, we also explored if vibrational spectroscopy could be used as a diagnostic tool for determining the bonding mode (chain vs. dimer) of amide derivatives of 2-aminopyridines in the solid-state. We observed a significant difference between the C=O stretching frequencies of dimers and chains (Figure 2.10). Chains had lower C=O IR stretching frequencies (red shifted) and dimers had higher stretching frequencies (blue shifted). (The highest number observed for chains is 1688 cm^{-1} , and the lowest number observed for dimers is 1697 cm^{-1}).

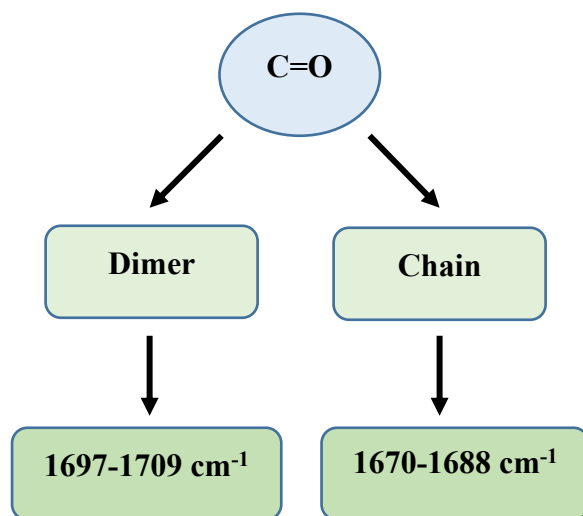


Figure 2.10. Schematic representation of the range of bands for dimers and chains.

There is only one outlier among the acylated analogues, the unexpected ribbon form, which suggests that IR spectroscopy can indeed be used as a tool to indicate the bonding mode of amide derivatives of 2-aminopyridine in the absence of crystallography. The aromatic compounds show only slight variation, with the NO₂-phenyl derivative as the sole exception, while the Cl-CF₃-

phenyl analogue follows the observed trend. Overall, twelve out of fourteen compounds agreed with the observations, demonstrating that IR spectroscopy can reliably indicate the bonding mode of amide derivatives of 2-aminopyridine. Moreover, for the two compounds that form polymorphs, IR spectroscopy showed two distinct carbonyl stretching values, indicating that IR can also be used to indicate polymorph formation.

As noted previously, our crystallization experiments yielded two polymorphs of the NO₂-methyl compound and two polymorphs of the NO₂-propyl compound. Polymorphs I and II of NO₂-methyl crystallize in the same space group (triclinic, *P*-1); however, they differ in their unit cell dimensions and total cell volumes. Polymorphs I and II of NO₂-propyl crystallize in different space groups (Polymorph I: monoclinic, *P*21/*c*, with molecules occupying general positions; Polymorph II: orthorhombic, *Pnma*, with molecules lying in mirror planes) and also differ in their unit cell dimensions and total cell volumes. The NO₂-methyl polymorphs follow the trend observed for small alkyl groups in this series, with molecules in both polymorph I and polymorph II linked into N-H···O=C chains. Strikingly different behavior is observed in the NO₂-propyl polymorphs. Polymorph I crystallizes as dimers linked by N-H...N(py) interactions, following the trend observed for large alkyl groups in this series, but polymorph II crystallizes not as dimers but in a unique ribbon motif in which the NO₂ group interacts intermolecularly with ring hydrogens rendered slightly acidic due to their proximity with the ring nitrogen atom and with the ring carbon atom bearing the nitro group.

2.5 Conclusions

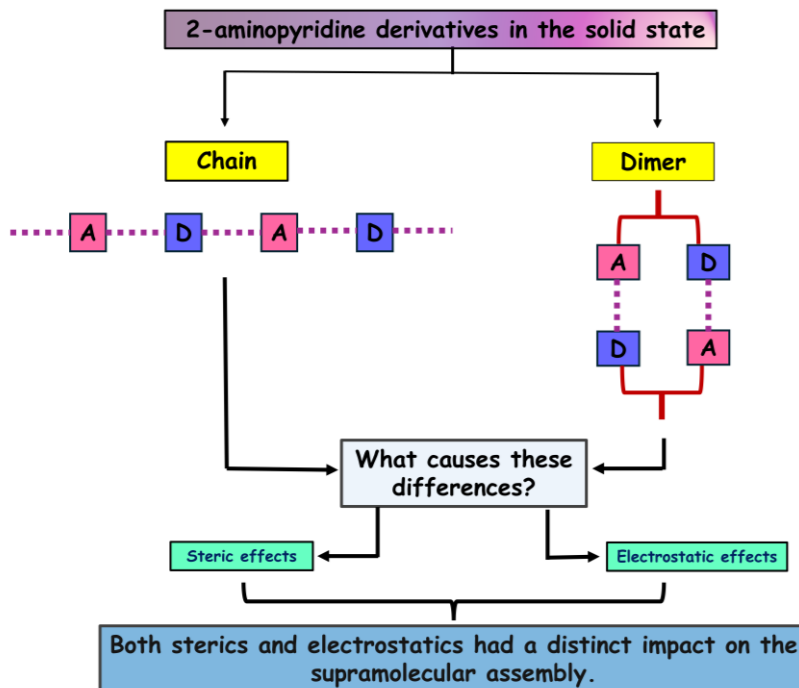


Figure 2.11. Summary of key findings of the study.

In this study, we investigated 12 different target molecules in two closely related series. The NO₂ series indicated that sterics do play an important role in determining the bonding mode by changing the self-assembly in the solid-state from N-H...O=C chains to N-H...N(py)/N(py)...H-N dimers as the chain length increased. The Cl-CF₃ series demonstrated that the charge of the pyridine nitrogen has a significant influence on the formation of supramolecular assemblies. Overall, these two series indicated that both sterics and charge have a great impact on the determination of final supramolecular assembly and that minor alterations to a molecular framework can result in profound changes to supramolecular assemblies (Figure 2.11).

In addition, we also established that IR spectroscopy is an indicative tool for determining the H-bonding mode of amide derivatives of 2-aminopyridines in the solid-state. Our investigations revealed that chains possess lower C=O IR stretching frequencies (1670-1688 cm⁻¹) and dimers

possess higher stretching frequencies (1697-1709 cm⁻¹). Although these findings provide a useful dataset and promising insights, the current molecular library is insufficient to confirm the applicability of this approach. Therefore, further studies involving a wider range of molecules should be conducted.

2.6 References

- ((1) Liu, Y.; Wang, L.; Zhao, L.; Zhang, Y.; Li, Z.-T.; Huang, F. Multiple Hydrogen Bonding Driven Supramolecular Architectures and Their Biomedical Applications. *Chemical Society Reviews* **2024**, *53* (3), 1592–1623. <https://doi.org/10.1039/d3cs00705g>.
- (2) Steiner, T. The Hydrogen Bond in the Solid State. *Angewandte Chemie International Edition* **2002**, *41* (1), 48–76. [https://doi.org/10.1002/1521-3773\(20020104\)41:1%3C48::aid-anie48%3E3.0.co;2-u](https://doi.org/10.1002/1521-3773(20020104)41:1%3C48::aid-anie48%3E3.0.co;2-u).
- (3) Ichiro Hisaki; Suzuki, Y.; Gomez, E.; Ji, Q.; Norimitsu Tohnai; Nakamura, T.; Abderrazzak Douhal. Acid Responsive Hydrogen-Bonded Organic Frameworks. *Journal of the American Chemical Society* **2019**, *141* (5), 2111–2121. <https://doi.org/10.1021/jacs.8b12124>.
- (4) Wang, H.; Bisoyi, H. K.; Urbas, A. M.; Bunning, T. J.; Li, Q. The Halogen Bond: An Emerging Supramolecular Tool in the Design of Functional Mesomorphic Materials. *Chemistry - A European Journal* **2018**, *25* (6), 1369–1378. <https://doi.org/10.1002/chem.201802927>.
- (5) Meazza, L.; Foster, J. A.; Fucke, K.; Pierangelo Metrangolo; Resnati, G.; Steed, J. W. Halogen-Bonding-Triggered Supramolecular Gel Formation. *Nature Chemistry* **2012**, *5* (1), 42–47. <https://doi.org/10.1038/nchem.1496>.
- (6) Scilabra, P.; Terraneo, G.; Resnati, G. The Chalcogen Bond in Crystalline Solids: A World Parallel to Halogen Bond. *Accounts of Chemical Research* **2019**, *52* (5), 1313–1324. <https://doi.org/10.1021/acs.accounts.9b00037>.
- (7) Vogel, L.; Wonner, P.; Huber, S. M. Chalcogen Bonding: An Overview. *Angewandte Chemie International Edition* **2018**, *58* (7), 1880–1891. <https://doi.org/10.1002/anie.201809432>.
- (8) Cheney, M. L.; Weyna, D. R.; Shan, N.; Hanna, M.; Wojtas, L.; Zaworotko, M. J. Supramolecular Architectures of Meloxicam Carboxylic Acid Cocrystals, a Crystal Engineering Case Study. *Crystal Growth & Design* **2010**, *10* (10), 4401–4413. <https://doi.org/10.1021/cg100514g>.
- (9) Yousef, M. A. E.; Vangala, V. R. Pharmaceutical Cocrystals: Molecules, Crystals, Formulations, Medicines. *Crystal Growth & Design* **2019**, *19* (12), 7420–7438. <https://doi.org/10.1021/acs.cgd.8b01898>.

- (10) Wong, S. N.; Fu, M.; Li, S.; Kwok, W. T. C.; Chow, S.; Low, K.-H.; Chow, S. F. Discovery of New Cocrystals beyond Serendipity: Lessons Learned from Successes and Failures. *CrystEngComm* **2024**, *26* (11), 1505–1526. <https://doi.org/10.1039/d4ce00021h>.
- (11) Ng, Z. X.; Tan, D.; Teo, W. L.; León, F.; Shi, X.; Sim, Y.; Li, Y.; Ganguly, R.; Zhao, Y.; Mohamed, S.; García, F. Mechanochemistry of Higher-Order Cocrystals: Tuning Order, Functionality and Size in Cocrystal Design**. *Angewandte Chemie International Edition* **2021**, *60* (32), 17481–17490. <https://doi.org/10.1002/anie.202101248>.
- (12) Wilson, A. J. Non-Covalent Polymer Assembly Using Arrays of Hydrogen-Bonds. *Soft Matter* **2007**, *3* (4), 409. <https://doi.org/10.1039/b612566b>.
- (13) Lehn, J.-M. From Matter to Life: Chemistry?! *Resonance* **1996**, *1* (3), 39–53. <https://doi.org/10.1007/bf02835621>.
- (14) Edwards, A. J.; Mackenzie, C. F.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A. Intermolecular Interactions in Molecular Crystals: What's in a Name? *Faraday Discussions* **2017**, *203*, 93–112. <https://doi.org/10.1039/c7fd00072c>.
- (15) Corpinot, M. K.; Bučar, D.-K. A Practical Guide to the Design of Molecular Crystals. *Crystal Growth & Design* **2018**, *19* (2), 1426–1453. <https://doi.org/10.1021/acs.cgd.8b00972>.
- (16) Lee, I. S.; Shin, D. M.; Chung, Y. K. Self-Assembly of Organometallic–Organic Hybrid Supramolecular Arrays from Ferrocenyl Dipyridines and Aromatic Carboxylic Acids. *Crystal Growth & Design* **2003**, *3* (4), 521–529. <https://doi.org/10.1021/cg0340695>.
- (17) Borys Ośmiałowski; Kolehmainen, E.; Kowalska, M. 2-Acylamino-6-Pyridones: Breaking of an Intramolecular Hydrogen Bond by Self-Association and Complexation with Double and Triple Hydrogen Bonding Counterparts. Uncommon Steric Effect on Intermolecular Interactions. *The Journal of Organic Chemistry* **2012**, *77* (4), 1653–1662. <https://doi.org/10.1021/jo201800u>.
- (18) McQuade, D. T.; McKay, S. L.; Powell, D. R.; Gellman, S. H. Indifference to Hydrogen Bonding in a Family of Secondary Amides. *Journal of the American Chemical Society* **1997**, *119* (36), 8528–8532. <https://doi.org/10.1021/ja9711019>.
- (19) Adams, H.; Bernad Jr., P. L.; Hembury, G. A.; Hunter, C. A.; McCabe, J. F.; Eggleston, D. S.; Haltiwanger, R. C.; Livingstone, D. J.; D. M. Harris, K.; Kariuki, B. M. Substituent Effects on Aromatic Interactions in the Solid State. *Chemical Communications* **2001**, No. 16, 1500–1501. <https://doi.org/10.1039/b101575n>.
- (20) Borys Ośmiałowski; Kolehmainen, E.; Dobosz, R.; Ryszard Gawinecki; Kauppinen, R.; Arto Valkonen; Juha Koivukorpi; Rissanen, K. Self-Organization of 2-Acylaminopyridines in the Solid State and in Solution. *The Journal of Physical Chemistry A* **2010**, *114* (38), 10421–10426. <https://doi.org/10.1021/jp1063116>.
- (21) Kaur, R.; Row, G. Polymorphic Anhydrous Cocrystals of Gallic Acid and Acetamide from Methanol: Pointers toward a Stable Cocrystal Form. *Crystal Growth & Design* **2012**, *12* (6), 2744–2747. <https://doi.org/10.1021/cg300536n>.

- (22) Feng, Z.; Fan, A.; Valiyaveetil, S.; Vittal, J. J. Interplay of Weak Interactions and Structural Features in the Solid State Self-Assembly of Symmetric Diamides. *Crystal Growth & Design* **2003**, *3* (4), 555–565. <https://doi.org/10.1021/cg034045y>.
- (23) Jarzemska, K. N.; Hoser, A. A.; Radosław Kamiński; Madsen, A. Ø.; Durka, K.; Krzysztof Woźniak. Combined Experimental and Computational Studies of Pyrazinamide and Nicotinamide in the Context of Crystal Engineering and Thermodynamics. *Crystal Growth & Design* **2014**, *14* (7), 3453–3465. <https://doi.org/10.1021/cg500376z>.
- (24) Parra, N.; Guarda, L.; Belmar, J. B.; Hidalgo, P. I.; Jiménez, C. A.; Pasán, J.; Ruiz-Pérez, C. Conformational Influence of Quinoline Moieties in the Crystal Packing of Bis(Quinolinecarboxamide)Alkane Derivatives. *CrystEngComm* **2013**, *15* (36), 7212–7212. <https://doi.org/10.1039/c3ce40807h>.
- (25) Hartlieb, M.; Edward; Perrier, S. A Guide to Supramolecular Polymerizations. *Polymer Chemistry* **2020**, *11* (6), 1083–1110. <https://doi.org/10.1039/c9py01342c>.
- (26) Bicknell, J.; Agarwal, S. A.; Petersen, K. J.; Loya, J. D.; Lutz, N.; Sittinger, P. M.; Teat, S. J.; Settineri, N. S.; Campillo-Alvarado, G. Engineering Lipophilic Aggregation of Adapalene and Adamantane-Based Cocrystals via van Der Waals Forces and Hydrogen Bonding. *Crystal Growth & Design* **2024**, *24* (12), 5222–5230. <https://doi.org/10.1021/acs.cgd.4c00457>.
- (27) Ishigaki, Y.; Asai, K.; Jacquot de Rouville, H.; Shimajiri, T.; Hu, J.; Heitz, V.; Suzuki, T. Solid-State Assembly by Chelating Chalcogen Bonding in Quinodimethane Tetraesters Fused with a Chalcogenadiazole. *ChemPlusChem* **2022**, *87* (4). <https://doi.org/10.1002/cplu.202200075>.
- (28) Aakeröy, C. B.; Rajbanshi, A.; Li, Z. J.; Desper, J. Mapping out the Synthetic Landscape for Re-Crystallization, Co-Crystallization and Salt Formation. *CrystEngComm* **2010**, *12* (12), 4231. <https://doi.org/10.1039/c0ce00052c>.
- (29) Friščić, T. Supramolecular Concepts and New Techniques in Mechanochemistry: Cocrystals, Cages, Rotaxanes, Open Metal–Organic Frameworks. *Chemical Society Reviews* **2012**, *41* (9), 3493. <https://doi.org/10.1039/c2cs15332g>.
- (30) G. Thompson, H. P.; M. Day, G. Which Conformations Make Stable Crystal Structures? Mapping Crystalline Molecular Geometries to the Conformational Energy Landscape. *Chemical Science* **2014**, *5* (8), 3173–3182. <https://doi.org/10.1039/C4SC01132E>.
- (31) Mukherjee, A.; Teyssandier, J.; Hennrich, G.; Steven De Feyter; Mali, K. S. Two-Dimensional Crystal Engineering Using Halogen and Hydrogen Bonds: Towards Structural Landscapes. *Chemical science* **2017**, *8* (5), 3759–3769. <https://doi.org/10.1039/c7sc00129k>.
- (32) Aakeröy, C. B.; Spartz, C. L.; Dembowski, S.; Dwyre, S.; Desper, J. A Systematic Structural Study of Halogen Bonding *Versus* Hydrogen Bonding within Competitive Supramolecular Systems. *IUCrJ* **2015**, *2* (5), 498–510. <https://doi.org/10.1107/s2052252515010854>.

- (33) Zojer, E. Tuning the Electrostatic Energy Landscape within the Pores of Covalent Organic Frameworks: Post-Synthetic Modification Reactions and Structural Imperfections. *Journal of Materials Chemistry A* **2024**, *12* (17), 10166–10184. <https://doi.org/10.1039/d3ta06996f>.
- (34) Tiwari, M. K.; Kumar Vanka. Exploiting Directional Long Range Secondary Forces for Regulating Electrostatics-Dominated Noncovalent Interactions. *Chemical Science* **2016**, *8* (2), 1378–1390. <https://doi.org/10.1039/c6sc03642b>.
- (35) Perera, M. D.; Desper, J.; Sinha, A. S.; Aakeröy, C. B. Impact and Importance of Electrostatic Potential Calculations for Predicting Structural Patterns of Hydrogen and Halogen Bonding. *CrystEngComm* **2016**, *18* (44), 8631–8636. <https://doi.org/10.1039/c6ce02089e>.
- (36) Varadwaj, A.; Marques, H. M.; Varadwaj, P. R. Is the Fluorine in Molecules Dispersive? Is Molecular Electrostatic Potential a Valid Property to Explore Fluorine-Centered Non-Covalent Interactions? *Molecules* **2019**, *24* (3), 379. <https://doi.org/10.3390/molecules24030379>.
- (37) Brinck, T. The Use of the Electrostatic Potential for Analysis and Prediction of Intermolecular Interactions; Elsevier, 2007; Vol. 5, pp. 51–93. [https://doi.org/10.1016/S1380-7323\(98\)80005-8](https://doi.org/10.1016/S1380-7323(98)80005-8).
- (38) Rao, R. N.; Chanda, K. 2-Aminopyridine – an Unsung Hero in Drug Discovery. *Chemical Communications* **2022**, *58* (3), 343–382. <https://doi.org/10.1039/d1cc04602k>.
- (39) Kibou, Z.; Aissaoui, N.; Daoud, I.; Seijas, J. A.; Vázquez-Tato, M. P.; Klouche Khelil, N.; Choukchou-Braham, N. Efficient Synthesis of 2-Aminopyridine Derivatives: Antibacterial Activity Assessment and Molecular Docking Studies. *Molecules* **2022**, *27* (11), 3439. <https://doi.org/10.3390/molecules27113439>.
- (40) Liu, Y.; Lu, L.; Zhou, H.; Xu, F.; Ma, C.; Huang, Z.; Xu, J.; Xu, S. Chemodivergent Synthesis of *N*-(Pyridin-2-yl)Amides and 3-Bromoimidazo[1,2-*A*]Pyridines from α -Bromoketones and 2-Aminopyridines. *RSC Advances* **2019**, *9* (59), 34671–34676. <https://doi.org/10.1039/c9ra06724h>.
- (41) Bis, J. A.; McLaughlin, O. L.; Vishweshwar, P.; Zaworotko, M. J. Supramolecular Heterocatemers and Their Role in Cocrystal Design. *Crystal Growth & Design* **2006**, *6* (12), 2648–2650. <https://doi.org/10.1021/cg060516f>.
- (42) Mishra, A.; Gupta, R. Supramolecular Architectures with Pyridine-Amide Based Ligands: Discrete Molecular Assemblies and Their Applications. *Dalton Trans.* **2014**, *43* (21), 7668–7682. <https://doi.org/10.1039/c4dt00277f>.
- (43) Abate, C.; Savina Ferorelli; Niso, M.; Cesarea Lovicario; Infantino, V.; Paolo Convertini; Perrone, R.; Berardi, F. 2-Aminopyridine Derivatives as Potential σ_2 Receptor Antagonists. *ChemMedChem* **2012**, *7* (10), 1847–1857. <https://doi.org/10.1002/cmdc.201200246>.
- (44) Saidahmatov, A.; Li, J.; Xu, S.; Hu, X.; Gao, X.; Kan, W.; Gao, L.; Li, C.; Shi, Y.; Sheng, L.; Wang, P.; Zhou, Y.; Liang, X.; Li, J.; Liu, H. Discovery of Novel 2-Aminopyridine-Based and 2-Aminopyrimidine-Based Derivatives as Potent CDK/HDAC Dual Inhibitors for the Treatment of Refractory Solid Tumors and Hematological Malignancies. *Journal of Medicinal Chemistry* **2024**, *67* (17), 15220–15245. <https://doi.org/10.1021/acs.jmedchem.4c00837>.

- (45) Khalid, T.; Malik, A.; Rasool, N.; Kanwal, A.; Nawaz, H.; Almas, I. Cracking the Code: The Clinical and Molecular Impact of Aminopyridines; a Review (2019–2024). *RSC Advances* **2025**, *15* (1), 688–711. <https://doi.org/10.1039/d4ra07438f>.
- (46) Fun, H.-K.; Shahani, T.; Kumar, R.; Isloor, A. M.; Shivananda, K. N. *N*-(5-Bromopyridin-2-Yl)Acetamide. *Acta Crystallographica Section E Structure Reports Online* **2011**, *67* (8), o2043–o2043. <https://doi.org/10.1107/s1600536811027553>.
- (47) Lüning, U.; Köhl, C.; Uphoff, A. Four Hydrogen Bonds – DDAA, DADA, DAAD and ADDA Hydrogen Bond Motifs. *European Journal of Organic Chemistry* **2002**, *2002* (23), 4063–4070. [https://doi.org/10.1002/1099-0690\(200212\)2002:23%3C4063::aid-ejoc4063%3E3.0.co;2-l](https://doi.org/10.1002/1099-0690(200212)2002:23%3C4063::aid-ejoc4063%3E3.0.co;2-l).
- (48) Mocilac, P.; Tallon, M.; Lough, A. J.; Gallagher, J. F. Synthesis, Structural and Conformational Analysis of a 3 × 3 Isomer Grid Based on Nine Methyl-*N*-(Pyridyl)Benzamides. *CrystEngComm* **2010**, *12* (10), 3080. <https://doi.org/10.1039/c002986f>.
- (49) Abeysekera, A. M.; Day, V. W.; Sinha, A. S.; Aakeröy, C. B. Mapping out the Relative Influence of Hydrogen and Halogen Bonds in Crystal Structures of a Family of Amide-Substituted Pyridines. *Crystal Growth & Design* **2020**, *20* (11), 7399–7410. <https://doi.org/10.1021/acs.cgd.0c01086>.
- (50) Katz, J. L.; Post, B. The Crystal Structure and Polymorphism of *N*-Methylacetamide. *Acta Crystallographica* **1960**, *13* (8), 624–628. <https://doi.org/10.1107/s0365110x60001485>.
- (51) Eckert, J.; Barthes, M.; Klooster, W. T.; Albinati, A.; Aznar, R.; Koetzle, T. F. No Evidence for Proton Transfer along the N–H···O Hydrogen Bond in *N*-Methylacetamide: Neutron Single Crystal Structure at 250 and 276 K. *The Journal of Physical Chemistry B* **2000**, *105* (1), 19–24. <https://doi.org/10.1021/jp000267k>.
- (52) Kadirova, Sh. A.; Nuralieva, G. A.; Alieva, M. A.; Talipov, S. A.; Tilyakov, Z. G.; Parpiev, N. A. Synthesis and Crystal Structure of 2-Aminoacetyl-1,3,4-Thiadiazole. *Russian Journal of General Chemistry* **2005**, *75* (12), 1962–1964.
- (53) Etter, M. C. Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds. *Accounts of Chemical Research* **1990**, *23* (4), 120–126. <https://doi.org/10.1021/ar00172a005>.

Chapter 3 - Can FTIR spectroscopy be used as a diagnostic tool to identify bonding modes of amide derivatives of 2-aminopyridine in the solid-state?

3.1 Introduction

Several studies have explored the possibility of using FTIR spectroscopy as a predictive tool for identifying bonding modes of amide derivatives in the solid-state, as an alternative to single-crystal X-ray diffraction (SCXRD).¹⁻⁴ Although some trends and guidelines have been suggested; there is still insufficient data to make more definitive statements about clear connections between solid-state structure and vibrational IR modes.

Chapter 2 revealed that IR spectroscopy can serve as an indicative tool for identifying hydrogen-bonding motifs in amide derivatives of 2-aminopyridine in the solid state. However, due to the limited data available, the findings of this study remain uncertain and should be interpreted cautiously, to consider this as an alternative for SCXRD. To further investigate these observations and evaluate the predictive capability of the trends observed in Chapter 2, additional studies involving a wider range of amide derivatives were undertaken.

In the previous study, we embarked on a systematic structural-spectroscopic study of fourteen amide derivatives of 2-aminopyridine, divided into two different groups.⁵ The compounds comprised alkyl amides derived from 2-amino-5-nitropyridine and from 2-amino-3-chloro-5-trifluoromethylpyridine. Within each group, structural variations were introduced by systematically varying the alkyl chain length up to five carbons. In addition, aromatic substitution was introduced by the addition of a phenyl group. In the solid-state, some structures formed dimer-like interactions, and some formed infinite chains.

We found that crystal structures that formed dimer-like or chain-like interactions displayed distinctly different carbonyl stretching vibrations (Figure 3.1), with chain motifs exhibiting lower C=O stretching frequencies (1670-1688 cm^{-1}) and dimer motifs exhibiting higher frequencies (1697-1709 cm^{-1}). Specifically, the highest C=O stretching frequency observed for chain structures was 1688 cm^{-1} , whereas the lowest for dimers was 1697 cm^{-1} , creating a non-overlapping range of frequencies for the two interaction modes. Out of the fourteen structures studied, twelve followed the defined trend, suggesting that FTIR spectroscopy could be a reliable tool to identify bonding modes.

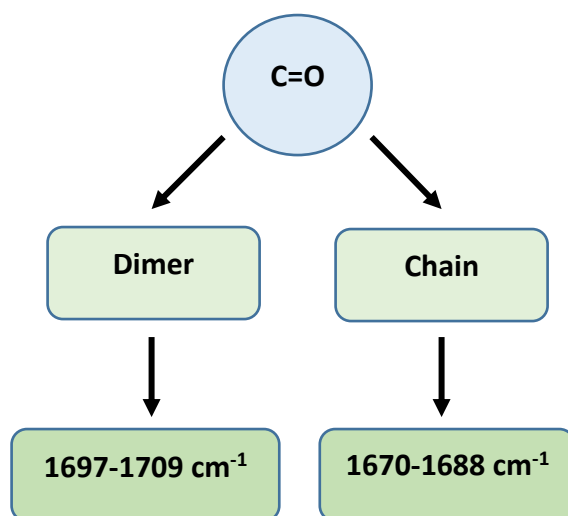


Figure 3.1. Schematic representation of the range of bands for dimers and chains.

However, given the limited number of experimental data, the present study expands the molecular library by incorporating eight more new alkyl amides of 2-aminopyridine derivatives belonging to 2-amino-3-iodopyridine and 2-amino-3,5-dibromopyridine series to further evaluate the robustness of the observed trend. Incorporation of heavy halogen substituents, such as iodine and bromine, was expected to modify both the electronic environment and the steric nature of the pyridine ring by adding bulky groups,⁶⁻⁹ thereby influencing intermolecular amide hydrogen

bonding and the resulting supramolecular organization. In addition, the high polarizability of these substituents introduces the potential for halogen bonding, which may compete with hydrogen bonding¹⁰⁻¹⁶ and alter the expected bonding pattern. By systematically varying the alkyl chain length, this approach will enable a broader evaluation of the factors governing the formation of hydrogen-bonded dimers versus chain motifs and provide a more diverse structural platform for assessing the predictive capability of IR spectroscopy.

As mentioned in Chapter 2, 2-aminopyridine is a widely used molecular scaffold in the pharmaceutical industry for drug development, yet its solid-state landscape remains underexplored.¹⁷⁻²⁵ However, a better understanding of how these molecules behave in the solid-state could facilitate drug development by reducing both time and cost. However, predicting bonding patterns/structural studies without crystal structures remains challenging, and growing suitable crystals for SCXRD is not always easy. Therefore, using an alternative, readily available technique, such as FTIR spectroscopy, as a predictive tool would offer a convenient approach for analyzing these materials. Thus, this study investigates whether FTIR can be used as a predictive tool to determine the bonding modes of 2-aminopyridine derivatives.

3.2 Experimental section

3.2.1 General

All precursors and solvents were purchased from commercial sources and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra were recorded using a Nicolet 380 FTIR spectrometer with attenuated total reflection (ATR) and a ZnSe crystal. Electrostatic potentials were calculated with density functional B3LYP level of theory using 6-311++G** basis set in vacuum, using Spartan'14 software.

Synthesis of the *N*-(pyridin-2-yl)acylamides was carried out according to an available literature procedure.²⁶

3.2.2 Syntheses of the 3,5-dibromo series

3.2.2.1 Synthesis of *N*-(3,5-dibromopyridin-2-yl)propionamide (3,5-diBr-ethyl)

A solution of 2-amino-3,5-dibromopyridine (3.00 g, 11.90 mmol) in propionic anhydride (1.28 mL, 11.00 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 61.65%, M.P: 165-167 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 2.35 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.58, 149.20, 148.57, 144.04, 118.28, 117.33, 29.10, 9.91.

3.2.2.2 Synthesis of *N*-(3,5-dibromopyridin-2-yl)butyramide (3,5-diBr-propyl)

A solution of 2-amino-3,5-dibromopyridine (1.00 g, 3.96 mmol) in butyric anhydride (0.58 mL, 3.56 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 49.58 %, M.P: 133-137 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.62 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.72, 149.21, 148.59, 144.04, 118.36, 117.38, 37.75, 18.84, 14.12.

3.2.2.3 Synthesis of *N*-(3,5-dibromopyridin-2-yl)pentanamide (3,5-diBr-butyl)

A solution of 2-amino-3,5-dibromopyridine (1.01 g, 4.01 mmol) in pentanoic anhydride (0.71 mL, 3.61 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 50.78%, M.P: 135-137 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.58 (p, *J* = 7.4 Hz, 2H), 1.35 (h, *J* = 7.3 Hz, 2H), 0.90 (t, *J* =

7.4 Hz, 3H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 171.85, 149.21, 148.59, 144.04, 118.35, 117.37, 35.54, 27.52, 22.24, 14.21.

3.2.2.4 Synthesis of *N*-(3,5-dibromopyridin-2-yl)hexanamide (3,5-diBr-pentyl)

A solution of 2-amino-3,5-dibromopyridine (5.00 g, 19.80 mmol) in hexanoic anhydride (4.32 mL, 18.00 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 66.67%, M.P: 117-123 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.18 (s, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.47 (d, J = 2.2 Hz, 1H), 2.32 (t, J = 7.4 Hz, 2H), 1.59 (q, J = 7.4 Hz, 2H), 1.31 (hept, J = 3.6, 3.1 Hz, 4H), 0.92 - 0.84 (m, 3H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 171.85, 149.20, 148.59, 144.03, 118.32, 117.36, 35.79, 31.29, 25.05, 22.34, 14.34.

3.2.3 Syntheses of the 3-iodo series

3.2.3.1 Synthesis of *N*-(3-iodopyridin-2-yl)acetamide (3-I-methyl)

A solution of 2-amino-3-iodopyridine (0.05 g, 0.23 mmol) in acetic anhydride (0.03 mL, 0.25 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 68.99%, M.P: 105-109 °C. ^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 8.37 (dd, J = 4.7, 1.7 Hz, 1H), 8.11 (dd, J = 7.8, 1.7 Hz, 1H), 7.91 (s, 1H), 6.83 (dd, J = 7.8, 4.7 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 169.02, 149.50, 146.71, 146.44, 119.83, 84.61, 22.86.

3.2.3.2 Synthesis of *N*-(3-iodopyridin-2-yl)butyramide (3-I-propyl)

A solution of 2-amino-3-iodopyridine (0.05 g, 0.23 mmol) in butyric anhydride (0.10 mL, 0.61 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 71.64%, M.P: 74-77 °C. ^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 8.41 (dd, J = 4.7, 1.7 Hz, 1H), 8.12 (dd, J = 7.8, 1.7 Hz,

1H), 7.79 (s, 1H), 6.84 (dd, $J = 7.9, 4.7$ Hz, 1H), 2.61 (t, $J = 7.4$ Hz, 2H), 1.80 (h, $J = 7.4$ Hz, 2H), 1.05 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 172.37, 150.95, 148.08, 148.04, 121.30, 86.47, 38.97, 18.63, 13.87.

3.2.3.3 Synthesis of *N*-(3-iodopyridin-2-yl)pentanamide (3-I-butyl)

A solution of 2-amino-3-iodopyridine (0.20 g, 0.91 mmol) in pentanoic anhydride (0.89 mL, 4.55 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C, after which the remaining solvent was allowed to evaporate. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 57.04 %, M.P: 67-70°C. ^1H NMR (400 MHz, Chloroform- d) δ 8.41 (dd, $J = 4.7, 1.7$ Hz, 1H), 8.12 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.69 (s, 1H), 6.84 (dd, $J = 7.8, 4.7$ Hz, 1H), 2.65 (t, $J = 7.6$ Hz, 2H), 1.76 (p, $J = 7.5$ Hz, 2H), 1.45 (dt, $J = 14.7, 7.4$ Hz, 2H), 0.98 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 175.20, 150.89, 148.07, 148.04, 121.25, 86.26, 36.83, 27.25, 22.42, 13.86.

3.2.3.4 Synthesis of *N*-(3-iodopyridin-2-yl)hexanamide (3-I-pentyl)

A solution of 2-amino-3-iodopyridine (0.20 g, 0.91 mmol) in hexanoic anhydride (1.05 mL, 4.55 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C, after which the remaining solvent was allowed to evaporate. The precipitate was filtered off and purified by column chromatography to obtain the pure product. Yield: 43.52%, M.P: 61-63 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 10.06 (s, 1H), 8.42 (d, $J = 4.6$ Hz, 1H), 8.30 (d, $J = 7.8$ Hz, 1H), 7.09 - 7.01 (m, 1H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.61 (t, $J = 7.3$ Hz, 2H), 1.37 - 1.29 (m, 4H), 0.88 (q, $J = 5.3$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 171.89, 152.90, 148.69, 148.55, 123.74, 94.46, 35.87, 31.37, 25.05, 22.36, 14.35.

Crystals suitable for single-crystal X-ray diffraction were obtained by slow evaporation from a variety of solvents for all compounds, as shown in Table 3.1. Details of crystallographic experiments are given in Appendix C.

Table 3.1. Solvents used for crystal growth and crystal descriptions.

Compound	Code	Solvent	Color and morphology
<i>N</i> -(3,5-dibromopyridin-2-yl)propionamide	3,5-dibromo-ethyl	Methanol	Yellow, block
<i>N</i> -(3,5-dibromopyridin-2-yl)butyramide	3,5-dibromo- propyl	Methanol	Colorless, needle
<i>N</i> -(3,5-dibromopyridin-2-yl)pentanamide	3,5-dibromo- butyl	Chloroform	Yellow, needle
<i>N</i> -(3,5-dibromopyridin-2-yl)hexanamide	3,5-dibromo- pentyl	Methanol	Colorless, needle
<i>N</i> -(3-iodopyridin-2-yl)acetamide	3-iodo-methyl	Methanol/heat	Colorless, needle
<i>N</i> -(3-iodopyridin-2-yl)butyramide	3-iodo-propyl	Hexane+Ethyl acetate	Pale green, plate
<i>N</i> -(3-iodopyridin-2-yl)pentanamide	3-iodo-butyl	Methanol	Dark yellow needle, needle
<i>N</i> -(3-iodopyridin-2-yl)hexanamide	3-iodo-pentyl	Methanol	Colorless, needle

3.2.4 Molecular electrostatic potential calculations (MEP)

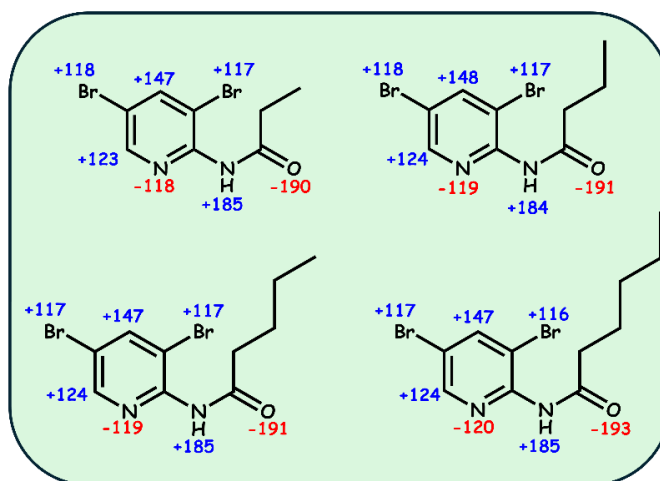
MEP surfaces were generated for all molecules explored in this study using Spartan'14 Version 1.1.4. The molecular skeleton was first loaded into the software from a ChemDraw file, which was then geometry-optimized using DFT with the B3LYP functional and the 6-311++G** triple-zeta basis set in vacuum. On this optimized structure, the maxima and minima on the MEP surface (0.002 e/au isosurface) were determined using a positive point charge in the vacuum as a probe.

3.3 Results

3.3.1 MEP values of target materials

The calculated molecular electrostatic potentials (MEPs) are shown in Figure 3.2.

3.3.1.1 MEP values of the 3,5-dBr series



3.3.1.2 MEP values of the 3-iodo series

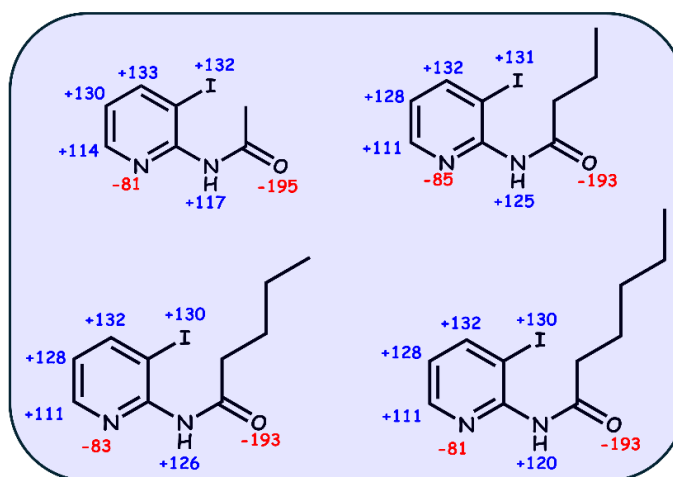


Figure 3.2. MEP values (kJ/mol) at the most likely hydrogen-bond donor and acceptor sites in the eight targets.

3.3.2 SCXRD analysis of target materials

The primary intermolecular interaction modes in the four crystal structures of the 3,5-diBr series are shown in Figures 3.3, a-d. All structures display infinite N-H $\cdots$ O=C chain-like motifs. Additionally, they also form C-H $\cdots$ N/N $\cdots$ H-C dimers with the neighboring molecules. The relevant hydrogen-bond parameters are given in Table 3.2.

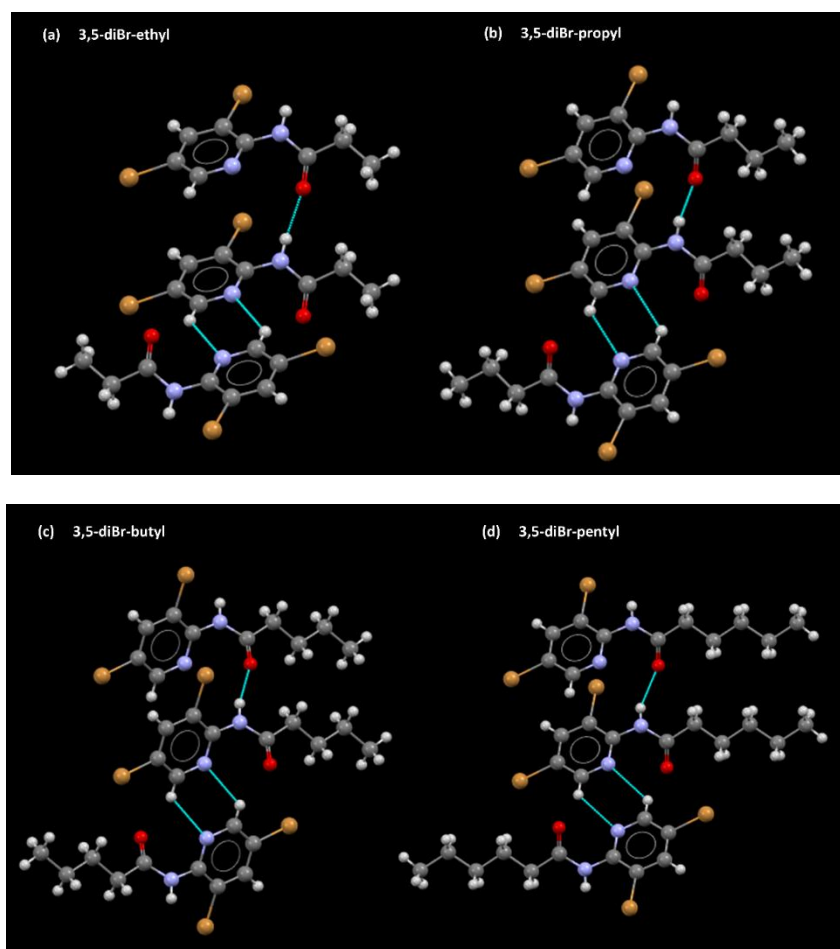


Figure 3.3. Primary hydrogen-bond interactions in the crystal structures of (a) 3,5-diBr-ethyl, (b) 3,5-diBr-propyl, (c) 3,5-diBr-butyl, and (d) 3,5-diBr-pentyl.

The four structures from the 3-iodo family (Figure 3.4) also display infinite $\text{N-H}\cdots\text{O}=\text{C}$ chains as the primary supramolecular motif, although they exhibit slight variations in packing from each other. Within these structures, only 3-iodo-methyl contained halogen bonds. The relevant hydrogen-bond and halogen-bond parameters and data for these four crystal structures are given in Table 3.3.

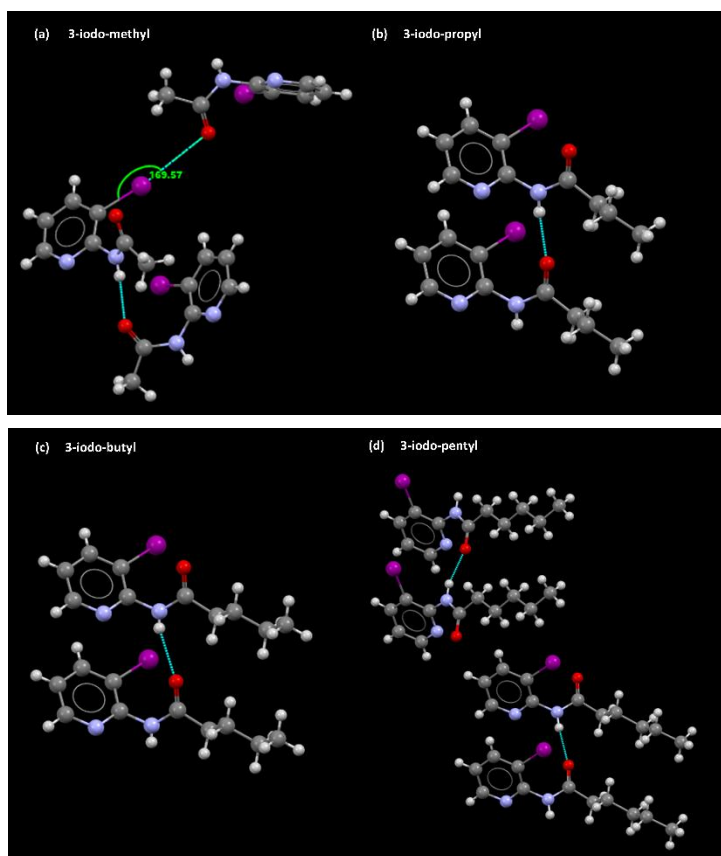


Figure 3.4. Primary hydrogen bonds in the crystal structures of (a) 3-iodo-methyl, (b) 3-iodo-propyl, (c) 3-iodo-butyl, and (d) 3-iodo-pentyl.

Table 3.2. Hydrogen-bond parameters of C=O...H-N chain interaction of crystal structures in the 3,5-diBr series

Compound	d(D-A)/Å	d(D-A)/Å	D-H-A/°	Space group	# of molecules in the AU
3,5-dibromo-ethyl	N9-H9...O13	2.890(4)	171.4(2)	P 2 ₁ /n	1
3,5-dibromo- propyl	N7-H7...O9	2.869(6)	164.4(3)	P 2 ₁ /c	1
3,5-dibromo- butyl	N9-H9...O11	2.907(11)	163.6(5)	P-1	1
3,5-dibromo- pentyl	N9-H9...O16	2.928(3)	150.0(4)	P-1	1

Table 3.3. Hydrogen-bond parameters of C=O...H-N chain interaction of crystal structures in the 3-iodo series

Compound	d(D-A)/Å	d(D-A)/Å	D-H-A/°	Space group	# of molecules in the AU
3-iodo-methyl	N7-H7...O9	2.893(5)	174.0(5)	P 2 ₁ /c	2
	C6-I1...I1	3.782	157.0		
3-iodo-propyl	N8-H8...O13	2.849(7)	154.8(4)	P 2 ₁ /c	1
3-iodo-butyl	N6-H6...O8	2.921(3)	159.0(5)	P 2 ₁ /c	1
3-iodo-pentyl	N7B-H7B...O9B	2.863(7)	158.6(4)	P-1	2

The key IR vibrational modes of all these eight compounds are given in Table 3.4.

Table 3.4. The IR stretching frequency for the amide C=O mode in fourteen compounds

C=O frequency/cm ⁻¹			
3,5-diBr series		3-iodo series	
3,5-dibromo-ethyl	1677	3-iodo-methyl	1715/1701/1693/1675
3,5-dibromo- propyl	1674	3-iodo-propyl	1655
3,5-dibromo- butyl	1674	3-iodo-butyl	1656
3,5-dibromo- pentyl	1676	3-iodo-pentyl	1670/1659

For the 3,5-diBr series, a single carbonyl stretching band was observed in the IR spectrum of each compound, and it was consistent with the presence of only one type of carbonyl group in the asymmetric unit. In contrast, for the 3-iodo series, both the 3-iodo-methyl and 3-iodo-pentyl derivatives consist of two independent molecules in the asymmetric unit, and the carbonyl groups of these two molecules exhibit multiple bands in IR spectra as they have different vibrations (Figure 3.5).

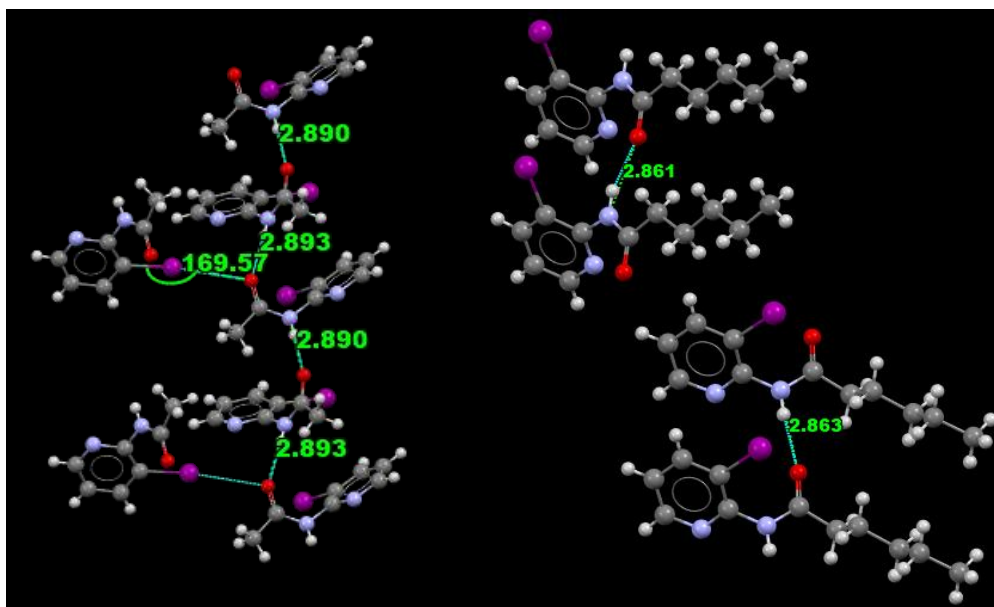


Figure 3.5. Different C=O groups observed in 3-iodo-methyl and 3-iodo-penyl.

In our previous study,⁵ we demonstrated that vibrational spectroscopy can be used as a diagnostic tool to distinguish the solid-state bonding modes (chain vs dimer) of amide derivatives of 2-aminopyridine. A clear separation was observed in the carbonyl stretching region, with chain motifs exhibiting lower C=O stretching frequencies (1670-1688 cm^{-1}) and dimer motifs showing higher frequencies (1697-1709 cm^{-1}). Specifically, the two ranges were distinct and non-overlapping for the two bonding modes. With only two outliers among the derivatives, an 86% (12/14) success rate was observed.

In the present study, we expanded the analysis by adding eight more molecules to the library and evaluated their solid-state bonding behavior using the same vibrational criteria. Introduction of a halogen atom on the aromatic backbone is expected to alter both the electronic environment and the steric nature of the pyridine ring. The MEP calculations showed that bromine and iodine substitution increase the acceptor potential of the amide carbonyl compared to the previously studied series. For other acceptor and donor sites, no clear trend was observed. IR data and crystallography revealed that all compounds formed chains via the carbonyl group, possibly due

to the greater influence of the acceptor site's electronegativity and sterics coming from the bigger halogen atoms.

Most importantly, this study revealed that the vibrational spectroscopic signatures of all eight newly synthesized compounds fell within the previously established IR trend. However, the lower band limit of the chains may need to be adjusted to 1655 cm^{-1} from 1670 cm^{-1} , as two chains obtained for the iodo analogs (3-iodo-propyl, 3-iodo-butyl) showed C=O stretching around 1656 cm^{-1} . When the results of both studies are combined, 20 out of 22 compounds (91%) fall within the defined range, giving clear support for the use of FTIR spectroscopy as a predictive and diagnostic tool for determining solid-state bonding modes in amide derivatives of 2-aminopyridine.

3.5 Conclusions

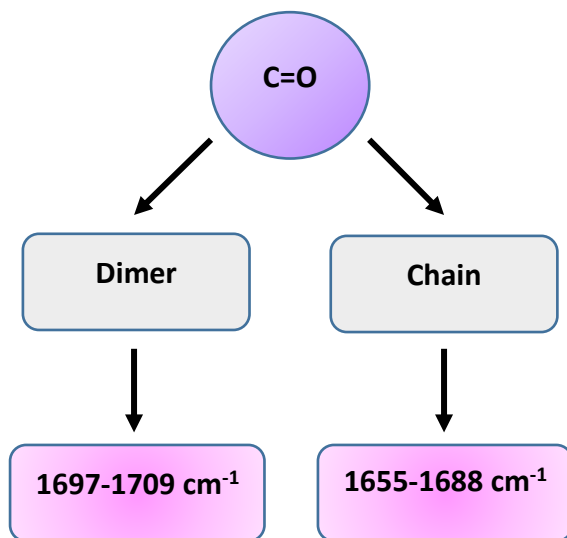


Figure 3.6. Schematic representation of the range of bands for dimers and chains.

This work demonstrates that FTIR spectroscopy can serve as a reliable diagnostic tool for identifying solid-state bonding modes in amide derivatives of 2-aminopyridine. Across two complementary series, distinct and non-overlapping carbonyl stretching frequency ranges were

observed for chain and dimer motifs, respectively (Figure 3.6). While a small number of exceptions were identified, the overall agreement remains high, and 20 of 22 (91%) appeared within the proposed range. Given the experimental challenges of growing single crystals, these findings highlight the potential of using FTIR spectroscopy as a predictive tool for solid-state analysis, as an alternative to SCXRD, and underscore the importance of expanding these studies to a broader range of molecules.

These two chapters showed that small functional changes in 2-aminopyridine derivatives can lead to two different types of homomeric interactions, chains and dimers. This observation sparked our curiosity about how these different homomeric preferences influence their ability to form heteromeric interactions. Will they engage in heteromeric interactions in a similar way, or will these structural differences lead to different interaction patterns? Or will they interact with other molecules with the same efficiency?

3.6 References

1. Borys Ośmiałowski; Kolehmainen, E.; Dobosz, R.; Ryszard Gawinecki; Kauppinen, R.; Arto Valkonen; Juha Koivukorpi; Rissanen, K. Self-Organization of 2-Acylaminopyridines in the Solid State and in Solution. *The Journal of Physical Chemistry A* **2010**, *114* (38), 10421–10426.
2. Amila Marie Abeysekera. *From Intermolecular Forces, via Crystal Engineering, to Mechanical Flexibility in the Organic Solid-State*; Ph.D. Dissertation, Kansas State University, 2021.
3. McQuade, D. T.; McKay, S. L.; Powell, D. R.; Gellman, S. H. Indifference to Hydrogen Bonding in a Family of Secondary Amides. *Journal of the American Chemical Society* **1997**, *119* (36), 8528–8532.
4. Kazim, M.; Siegler, M. A.; Lectka, T. Close Amide NH $\cdots$ F Hydrogen Bonding Interactions in 1,8-Disubstituted Naphthalenes. *The Journal of Organic Chemistry* **2020**, *85* (9), 6195–6200.
5. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers? *Crystal Growth & Design* **2025**, *25* (20).
6. Ma, C.-P.; Yao, L.; Ge, M.-F. Substituent Effects of Halopyridines. *Journal of Molecular Structure* **2008**, *881* (1-3), 123–131.

7. Sladek, V.; Punyain, K.; Ilčin, M.; Lukeš, V. Substitution Effect on the Intermolecular Halogen and Hydrogen Bonds of the σ -Bonded Fluorinated Pyridine $\cdots$ XY/HX Complexes (XY = F₂, Cl₂, ClF; HX = HF, HCl). *International Journal of Quantum Chemistry* **2014**, *114* (13), 869–878.
8. Abeysekera, A. M.; Sinha, A. S.; Aakeroy, C. B. The Impact of Halogen Substituents on the Synthesis and Structure of Co-Crystals of Pyridine Amides. *Molecules* **2021**, *26* (4), 1147.
9. Schwartz, T. M.; Burnett, M. E.; Green, K. N. Electronic Influence of Substitution on the Pyridine Ring within NNN Pincer-Type Molecules. *Dalton Transactions* **2020**, *49* (7), 2356–2363.
10. Kumar, P.; J. Mikko Rautiainen; Novotný, J.; Ward, J. S.; Marek, R.; Rissanen, K.; Rakesh Puttreddy. The Impact of *Ortho*-Substituents on Bonding in Silver(I) and Halogen(I) Complexes of 2-Mono- and 2,6-Disubstituted Pyridines: An In-Depth Experimental and Theoretical Study. *Chemistry - A European Journal* **2023**, *30* (13), e202303643–e202303643.
11. Carlsson, A.-C. C.; Mehmeti, K.; Uhrbom, M.; Karim, A.; Bedin, M.; Rakesh Puttreddy; Kleinmaier, R.; Neverov, A. A.; Bijan Nekoueishahraki; Jürgen Gräfenstein; Rissanen, K.; Máté Erdélyi. Substituent Effects on the [N–I–N]⁺ Halogen Bond. *Journal of the American Chemical Society* **2016**, *138* (31), 9853–9863.
12. Benassi, E.; Nurtay, L.; Fan, H. Para-Substituted Pyridines: Effects on the Interaction with 2-Perfluoropropyl Iodide and Vibrations. *Journal of Molecular Structure* **2022**, *1275*, 134632.
13. Bankiewicz, B.; Palusiak, M. Cooperation/Competition between Halogen Bonds and Hydrogen Bonds in Complexes of 2,6-Diaminopyridines and X-CY₃ (X = Cl, Br; Y = H, F). *Symmetry* **2021**, *13* (5), 766.
14. Vladimir Stilinović; Horvat, G.; Tomica Hrenar; Nemec, V.; Dominik Cinčić. Halogen and Hydrogen Bonding between (*N*-Halogeno)-Succinimides and Pyridine Derivatives in Solution, the Solid State and in Silico. *Chemistry - A European Journal* **2017**, *23* (22), 5244–5257.
15. Yu, S.; J. Mikko Rautiainen; Kumar, P.; Gentiluomo, L.; Ward, J. S.; Rissanen, K.; Rakesh Puttreddy. *Ortho*-Substituent Effects on Halogen Bond Geometry for N-Haloimide $\cdots$ 2-Substituted Pyridine Complexes. *Advanced Science* **2023**, *11* (6).
16. Aakeröy, C. B.; Spartz, C. L.; Dembowski, S.; Dwyre, S.; Desper, J. A Systematic Structural Study of Halogen Bonding *Versus* Hydrogen Bonding within Competitive Supramolecular Systems. *IUCrJ* **2015**, *2* (5), 498–510.
17. Borys Ośmiałowski; Kolehmainen, E.; Dobosz, R.; Ryszard Gawinecki; Kauppinen, R.; Arto Valkonen; Juha Koivukorpi; Rissanen, K. Self-Organization of 2-Acylaminopyridines in the Solid State and in Solution. *The Journal of Physical Chemistry A* **2010**, *114* (38), 10421–10426.
18. Rao, R. N.; Chanda, K. 2-Aminopyridine – an Unsung Hero in Drug Discovery. *Chemical Communications* **2022**, *58* (3), 343–382.

19. Kibou, Z.; Aissaoui, N.; Daoud, I.; Seijas, J. A.; Vázquez-Tato, M. P.; Klouche Khelil, N.; Choukchou-Braham, N. Efficient Synthesis of 2-Aminopyridine Derivatives: Antibacterial Activity Assessment and Molecular Docking Studies. *Molecules* **2022**, *27* (11), 3439.
20. Liu, Y.; Lu, L.; Zhou, H.; Xu, F.; Ma, C.; Huang, Z.; Xu, J.; Xu, S. Chemodivergent Synthesis of *N*-(Pyridin-2-Yl)Amides and 3-Bromoimidazo[1,2-*A*]Pyridines from α -Bromoketones and 2-Aminopyridines. *RSC Advances* **2019**, *9* (59), 34671–34676.
21. Bis, J. A.; McLaughlin, O. L.; Vishweshwar, P.; Zaworotko, M. J. Supramolecular Heterocatemers and Their Role in Cocrystal Design. *Crystal Growth & Design* **2006**, *6* (12), 2648–2650.
22. Mishra, A.; Gupta, R. Supramolecular Architectures with Pyridine-Amide Based Ligands: Discrete Molecular Assemblies and Their Applications. *Dalton Trans.* **2014**, *43* (21), 7668–7682.
23. Abate, C.; Savina Ferorelli; Niso, M.; Cesarea Lovicario; Infantino, V.; Paolo Convertini; Perrone, R.; Berardi, F. 2-Aminopyridine Derivatives as Potential σ_2 Receptor Antagonists. *ChemMedChem* **2012**, *7* (10), 1847–1857.
24. Saidahmatov, A.; Li, J.; Xu, S.; Hu, X.; Gao, X.; Kan, W.; Gao, L.; Li, C.; Shi, Y.; Sheng, L.; Wang, P.; Zhou, Y.; Liang, X.; Li, J.; Liu, H. Discovery of Novel 2-Aminopyridine-Based and 2-Aminopyrimidine-Based Derivatives as Potent CDK/HDAC Dual Inhibitors for the Treatment of Refractory Solid Tumors and Hematological Malignancies. *Journal of Medicinal Chemistry* **2024**, *67* (17), 15220–15245.
25. Khalid, T.; Malik, A.; Rasool, N.; Kanwal, A.; Nawaz, H.; Almas, I. Cracking the Code: The Clinical and Molecular Impact of Aminopyridines; a Review (2019–2024). *RSC Advances* **2025**, *15* (1), 688–711.
26. Kadirova, Sh. A.; Nuralieva, G. A.; Alieva, M. A.; Talipov, S. A.; Tilyakov, Z. G.; Parpiev, N. A. Synthesis and Crystal Structure of 2-Aminoacetyl-1,3,4-Thiadiazole. *Russian Journal of General Chemistry* **2005**, *75* (12), 1962–1964.

Chapter 4 - How do dimer and chain motifs of 2-aminopyridine derivatives influence cocrystal formation with carboxylic acids?

4.1 Introduction

In Chapters 2¹ and 3, we showed that 2-aminopyridine derivatives display two distinct homomeric bonding motifs in the solid state; dimers stabilized by N-H $\cdots$ N(py)/N(py) $\cdots$ H-N intermolecular hydrogen bonds, or N-H $\cdots$ O=C infinite chain-like interactions (Figure 4.1). These observations motivated us to explore whether these inherent structural features would also influence their ability to form cocrystals. As discussed in the general introduction, cocrystallization is a crystal engineering strategy that involves the formation of crystalline materials composed of two or more different and neutral molecular components in stoichiometric ratios, assembled through intermolecular interactions while still maintaining the precise intrinsic chemical identities of each component.²⁻⁶ Among the many intermolecular interactions involved in cocrystal formation, hydrogen bonding is particularly important for molecular recognition and for establishing new solid architectures.⁷⁻¹²

In this study, we aim to understand how the hydrogen-bonding motifs of 2-aminopyridine derivatives (*N*-(5-NO₂-pyridin-2-yl)acylamides and *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamides) affect their ability to form cocrystals with different coformers

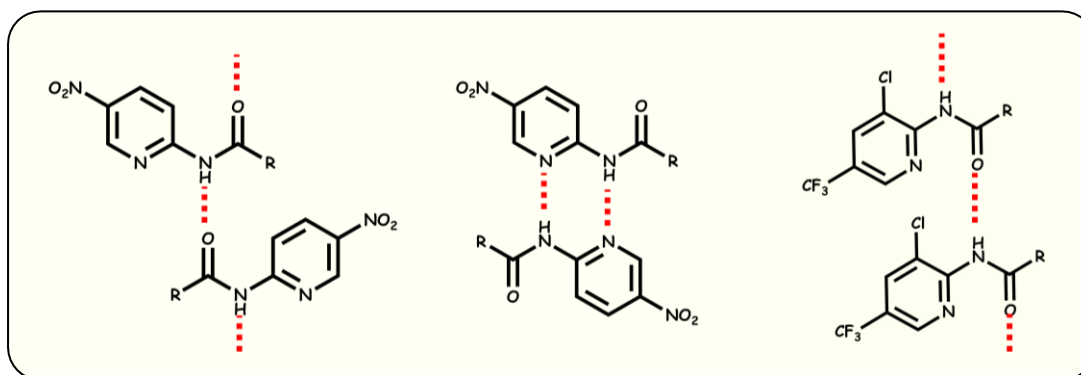


Figure 4.1. Interactions observed among target molecules.

To explore the influence of the nature of these structures on their ability to form cocrystals with various coformers, approximately 500 cocrystallization experiments were conducted involving 10 targets (Figure 4.2) and 50 different coformers. The study also addressed the influence of coformer strength (in terms of hydrogen-bond making abilities) on cocrystal formation. Finally, we attempt to identify any hydrogen-bond preferences among a series of postulated motifs, Figure 4.3.

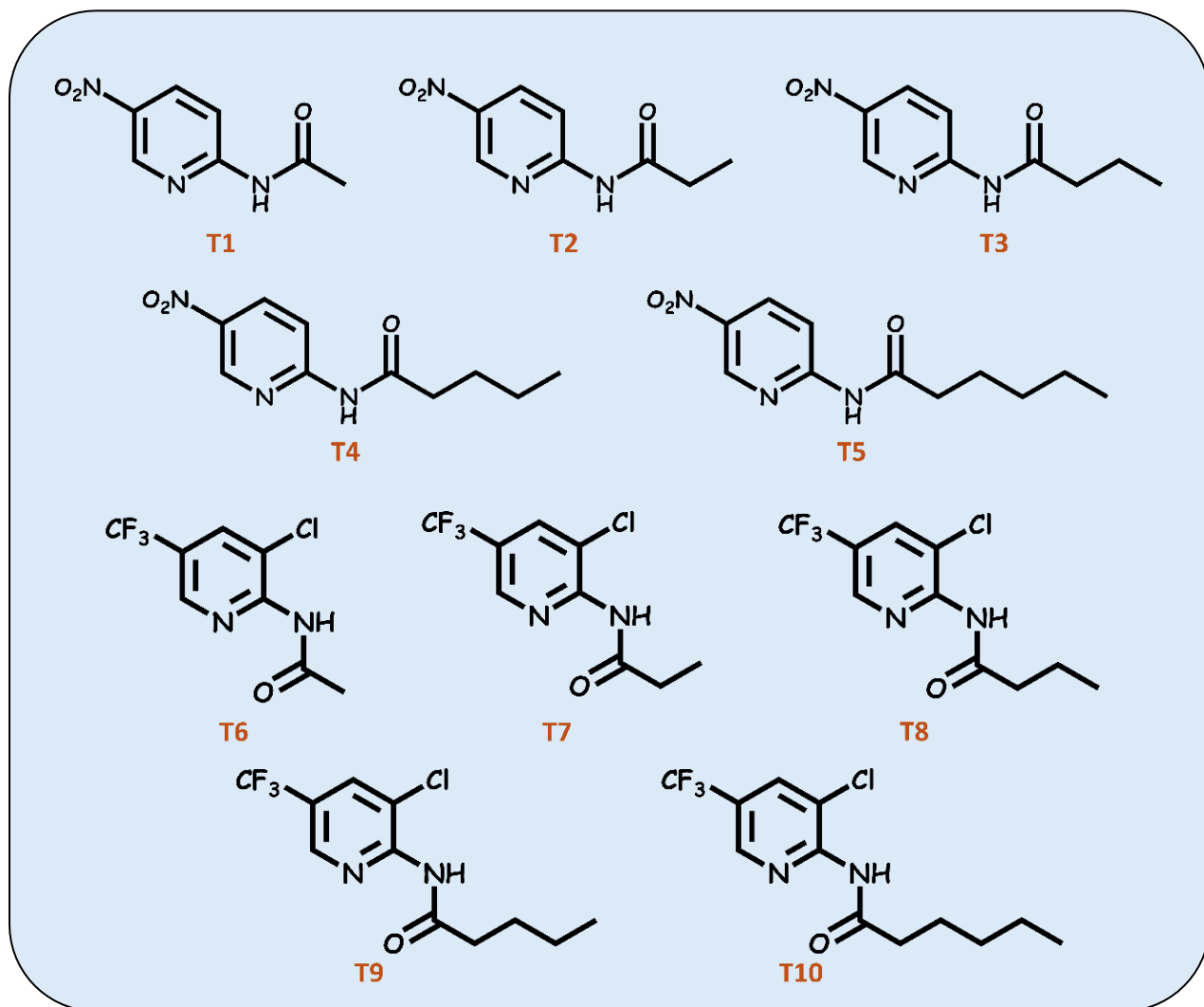


Figure 4.2. Target molecules used in this study.

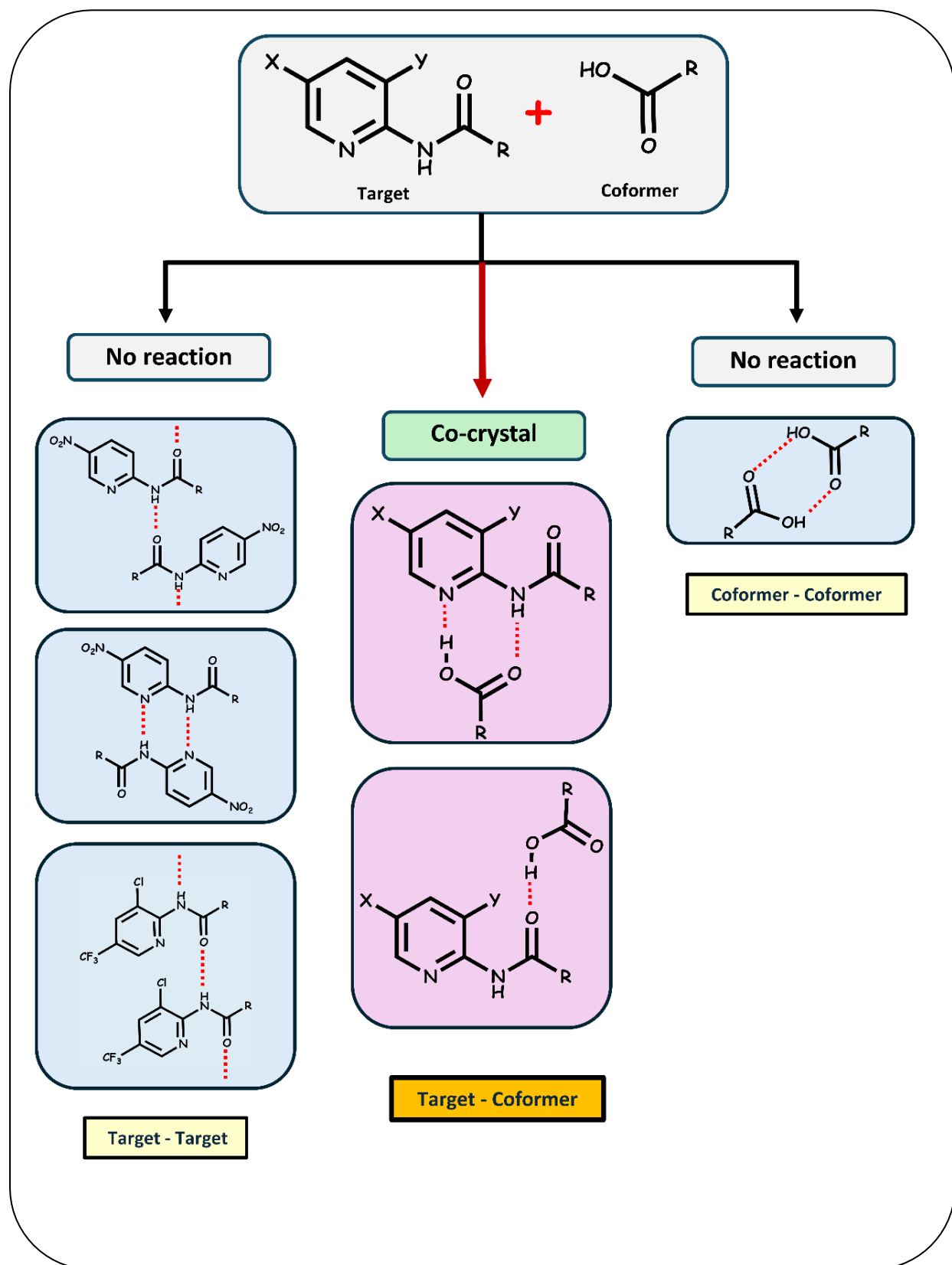


Figure 4.3. Possible outcomes of cocrystallization experiments.

4.2 Experimental section

4.2.1 Cocrystal screening with liquid-assisted grinding

All targets were synthesized as described in Chapter 2,¹ and all coformers and solvents were purchased from commercial sources and used without further purification. Cocrystal experiments with 50 carboxylic acids were conducted using liquid-assisted grinding (LAG) in the presence of methanol. A 1:1 or 2:1 molar ratio of the target compound and coformer was used for aromatic acids and aliphatic acids, respectively, and the resulting ground powders were characterized by FTIR spectroscopy. Aromatic acids were categorized into two groups (Table 4.1) based on the pKa values into strong acids and weak acids ($\text{pKa} \leq 4.15$ = strong acid). Approximately 500 cocrystallization experiments were performed. Broad absorption bands near 1850 cm^{-1} and 2450 cm^{-1} , characteristic of intermolecular $\text{O-H}\cdots\text{N}$ hydrogen bonds, indicated cocrystal formation. The IR spectra of the cocrystal screening experiments were recorded on a Nicolet 380 FTIR spectrometer using the attenuated total reflection (ATR) technique with a ZnSe crystal. Melting points were measured with a TA Instruments DSC Q20 differential scanning calorimeter. Single-crystal X-ray diffraction (SCXRD) data were collected on a Rigaku XtaLAB Synergy-S single-crystal X-ray diffractometer equipped with $\text{Cu K}\alpha$ radiation.

Table 4.1. Coformers used in this study

	Aromatic acids	Acid Code	pKa value
1	2,4-dinitrobenzoic acid	2,4-dNBA	1.43
2	Pentafluorobenzoic acid	PFBA	1.75
3	2-chloro-6-fluorobenzoic acid	2-Cl-6FIBA	2.04
4	2,4,6-trifluorobenzoic Acid	2,4,6-tFBA	2.28
5	5-bromo-2-chlorobenzoic acid	5-Br-2CIBA	2.49
6	2,3,4,5-tetrafluorobenzoic acid	2,3,4,5-tFBA	2.53
7	3,5-dinitrobenzoic acid	3,5-dNBA	2.82
8	2,6-difluorobenzoic acid	2,6-dFBA	2.85
9	4-nitrobenzoic acid	4-NBA	3.43
10	3-nitrobenzoic acid	3-NBA	3.46
11	4-cyanobenzoic acid	4-CBA	3.55

12	3-cyanobenzoic acid	3-CBA	3.60
13	3,4-dichlorobenzoic acid	3,4-dClBA	3.64
14	3-chlorobenzoic acid	3-ClBA	3.84
15	3-iodobenzoic acid	3-IBA	3.87
16	4-bromobenzoic acid	4-BBA	3.96
17	2,5-dimethylbenzoic acid	2,5-DMBA	3.99
18	Pentamethyl benzoic acid	PMBA	4.00
19	4-bromo-3-methylbenzoic acid	4-Br-3-MBA	4.04
20	4-fluorobenzoic acid	4-FBA	4.15
21	Benzoic acid	BA	4.20
22	m-toluic acid (3-methylBA)	m-TA	4.25
23	2,4-dimethoxybenzoic acid	2,4-dMxBA	4.36
24	4-methoxy benzoic acid	4-MxBA	4.50
25	Gallie Acid	GA	4.50
26	4-hydroxy-3-methoxybenzoic acid	4-H-3MxBA	4.53
27	4-hydroxybenzoic acid	4-HBA	4.57
28	3-dimethylaminobenzoic Acid	3-dMABA	4.76
29	3-aminobenzoic Acid	3-ABA	4.79
30	4-aminobenzoic Acid	4-ABA	4.87

	Aliphatic acids	Acid Code	pKa value
1	Oxalic acid	OA	1.25/4.28
2	L-aspartic acid	L-AA	1.99/3.90 /9.90
3	L-glutamic acid	L-GA	2.13/ 4.31 /9.67
4	4-imidazolecarboxylic acid	4-ICA	2.70
5	L-malonic acid	L-MIA	2.85/ 5.70
6	Fumaric acid	FA	3.02/4.38
7	Citric acid	CA	3.13 /4.76 /6.40
8	S- (+)-citramalic acid	CmA	3.35
9	D- (+)-malic acid	MA	3.40/5.05
10	Imidazole-4,5-dicarboxylic acid	I-4,5-dCA	3.60
11	Suberic acid	SubA	4.15
12	Succinic Acid	SucA	4.21 /5.64
13	Glutaric acid	GlA	4.32/ 5.42
14	Adipic acid	AA	4.41/5.41
15	Azelaic acid	AzA	4.55/5.50
16	Sebacic Acid	SebA	4.59 / 5.59
17	Crotonic acid	CrA	4.69
18	Pimelic acid	PiA	4.71/5.58
19	Palmitic acid	PalA	4.75
20	11-mercapto-undecanoic acid	MUA	4.95

4.2.2 Interaction energy calculations

Interaction energy (IE) calculations were performed only for target molecules explored in this study, using Spartan'14 Version 1.1.4. The target-target complex was first geometry-optimized using the DFT functional and the 6-311++G** triple-zeta basis set in vacuum. After geometry optimization, the atoms of one molecule of interest were 'frozen' using the 'freeze center' option, which is how Spartan distinguishes between two different molecules involved in an interaction energy calculation. After freezing one component, a single point energy calculation is carried out using the DFT functional and 6-311++G** triple zeta basis set in vacuum, with additional input 'INTERACTIONENERGY=BSSE' pasted into the options box, which not only calculates the interaction energy between the frozen and free molecules, but also applies counterpoise (CP) correction which accounts for the basis set superposition error (BSSE) associated with these calculations. Additional inputs 'MEM_STATIC=300' and 'SCFCYCLE=1000' were also employed to address the errors of the software running out of allocated temporary memory and the calculations requiring more iterative cycles than the preset to meet the convergence criterion.

4.3 Results

4.3.1 FTIR analysis of the ground samples

The results of the FTIR screening experiments are presented in Table 4.2 for strong aromatic acids, Table 4.3 for weak aromatic acids, and Table 4.4 for aliphatic acids ($\checkmark$ = positive, $\times$ = negative, $\dagger$ = submitted for SCXRD, * = crystal structure obtained).

Table 4.2. Results for strong aromatic acids

#	Coformer (Strong Aromatic Acids)	Targets									
		T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
1	2,4-dinitrobenzoic acid†	×	×	✓*	×	×	×	×	×	✓	✓
2	Pentafluorobenzoic acid	×	✓	✓	✓	✓	×	×	×	N/A	×
3	2-chloro-6-fluorobenzoic acid	×	✓	✓	×	×	×	✓	×	✓	✓
4	2,4,6-trifluorobenzoic Acid†	×	×	×	✓*	✓*	×	×	×	×	×
5	5-bromo-2-chlorobenzoic acid	×	×	✓	✓	✓	×	×	×	×	×
6	2,3,4,5-tetrafluorobenzoic acid†	×	×	✓*	✓*	✓*	×	×	×	×	✓
7	3,5-dinitrobenzoic acid†	×	✓*	✓*	✓*	✓*	×	×	×	×	×
8	2,6-difluorobenzoic acid	×	✓	✓	✓	✓	×	×	✓	×	✓
9	4-nitrobenzoic acid	×	×	✓	✓	✓	×	×	×	×	×
10	3-nitrobenzoic acid†	×	×	✓*	✓*	×	×	✓	✓	×	×
11	4-cyanobenzoic acid†	×	×	✓*	✓*	✓*	×	×	×	×	×
12	3-cyanobenzoic acid	✓	×	×	✓	✓	×	×	×	×	×
13	3,4-dichlorobenzoic acid†	✓	×	✓*	✓*	✓*	×	×	×	×	×
14	3-chlorobenzoic acid†	×	×	✓*	✓*	✓*	×	✓	×	×	×
15	3-iodobenzoic acid	✓	×	✓	✓	✓	×	✓	×	×	×
16	4-bromobenzoic acid	×	×	✓	✓	✓	×	×	×	×	×
17	2,5-dimethylbenzoic acid†	×	✓*	✓*	✓*	✓*	×	×	×	×	×
18	Pentamethyl benzoic acid	×	✓	✓	×	✓	×	×	×	×	×
19	4-bromo-3-methylbenzoic acid†	×	✓	✓*	✓*	×	×	×	×	×	×
20	4-fluorobenzoic acid†	×	×	✓*	×	×	×	×	×	×	×
# of positive cocrystals		3/20	7/20	18/20	16/20	15/20	0/20	4/20	2/20	2/19	4/20
% success rate		15%	35%	90%	80%	75%	0%	20%	10%	10.5%	20%
% total		(71/199)×100% = 35.68%									

Table 4.3. Results for weak aromatic acids

#	Coformer (Weak Aromatic Acids)	Targets									
		T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
1	Benzoic acid	×	×	✓	✓	✓	×	×	×	×	×
2	m-toluic acid (3-methylBA)†	×	×	✓*	✓*	×	×	×	×	×	×
3	2,4-dimethoxybenzoic acid	×	×	✓	✓	✓	×	×	×	×	×
4	4-methoxy benzoic acid†	×	×	✓*	✓*	✓	×	×	×	×	×
5	Gallic Acid	×	×	×	×	×	×	×	×	×	×
6	4-hydroxy-3-methoxybenzoic acid	×	×	✓	✓	✓	×	×	×	×	×
7	4-hydroxybenzoic acid	×	✓	✓	×	✓	×	×	×	×	×
8	3-dimethylaminobenzoic Acid†	×	✓ * 2 forms	✓*	✓*	✓*	×	×	✓	×	×
9	3-aminobenzoic Acid	×	×	✓	×	✓	×	×	×	×	×
10	4-aminobenzoic Acid†	×	✓ *	✓*	✓*	✓*	×	×	×	×	×
# of positive cocrystals		0/10	3/10	9/10	7/10	8/10	0/10	0/10	1/10	0/10	0/10
% success rate		0%	30%	90%	70%	80%	0%	0%	10%	0%	0%
% total		(28/100)×100% = 28%									

Table 4.4. Results for aliphatic acids

#	Coformer (Aliphatic Acids)	Targets									
		T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
1	Oxalic acid	✓	×	✓	×	✓	N/A	×	×	N/A	×
2	L-aspartic acid	✓	×	✓	×	×	N/A	×	×	N/A	×
3	L-glutamic acid	N/A	×	✓	×	×	N/A	×	×	N/A	×
4	4-imidazolecarboxylic acid	×	×	✓	✓	×	N/A	×	×	N/A	×
5	L-malonic acid	×	✓	✓	×	×	N/A	×	×	N/A	×
6	Fumaric acid	×	×	×	✓	✓	N/A	×	×	N/A	×
7	Citric acid	×	×	✓	✓	×	N/A	×	×	N/A	×
8	S- (+)-citramalic acid	×	✓	✓	×	×	N/A	×	×	N/A	×
9	D- (+)-malic acid	×	N/A	×	×	×	N/A	×	×	N/A	×
10	Imidazole-4,5-dicarboxylic acid	×	×	✓	✓	✓	N/A	×	×	N/A	×
11	Suberic acid	×	N/A	✓	×	×	N/A	×	×	N/A	×
12	Succinic Acid	×	N/A	✓	×	×	N/A	×	×	N/A	×
13	Glutaric acid	×	N/A	✓	✓	✓	N/A	×	×	N/A	×
14	Adipic acid	×	N/A	×	×	×	N/A	×	×	N/A	×
15	Azelaic acid	✓	×	✓	×	×	N/A	×	×	N/A	×
16	Sebacic Acid	×	N/A	✓	×	✓	N/A	×	×	N/A	×
17	Crotonic acid	×	×	✓	✓	×	N/A	×	×	N/A	×
18	Pimelic acid	×	N/A	✓	×	×	N/A	×	×	N/A	×
19	Palmitic	×	N/A	✓	×	×	N/A	×	×	N/A	×
20	11-mercapto-undecanoic acid	×	×	×	×	×	N/A	×	×	N/A	×
# of positive cocrystals		3/19	2/12	16/20	5/20	5/20	N/A	0/20	0/20	N/A	0/20
% success rate		15.79%	16.67%	80%	25%	25%	N/A	0%	0%	N/A	0%
% total		(31/151)×100% = 20.53%									

Based on the IR results, strong aromatic acids were most likely to form a cocrystal with the target, weak aromatic acids were less likely, and aliphatic acids were the least likely (Table 4.5).

Table 4.5. Influence of coformers

Influence of Coformers	
Acid type	Success rate/%
Strong aromatic acids	35.7%
Weak aromatic acids	28%
Aliphatic acids	20.5%

The influence of the targets showed that the highest cocrystal formation was observed for T3, T4, and T5, while the other targets exhibited comparatively lower cocrystal formations. Overall, the *N*-(5-NO₂-pyridin-2-yl)acylamides series resulted in 117 successful cocrystal formations out of

241 experiments, yielding a 48.6% success rate. The *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamides series yielded 13 positive results out of 209, resulting in a 6.2% success rate. Overall, this study yielded 130 positive results out of 450 grinding experiments, corresponding to a 28.9% success rate, as shown in Table 4.6. Among these, 66.0% of the cocrystal formations came from dimer motifs, and only 10.3% success came from chain motifs.

Table 4.6. Influence of targets

Influence of Targets										
Target	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Overall	6/49=	12/42=	43/50=	28/50=	28/50=	0/30=	4/50=	3/50=	2/29=	4/50=
Success/%	12.24%	28.57%	86%	56%	56%	0%	8%	6%	6.70%	8%
Success rate in each series	N-(5-NO ₂ -pyridin-2-yl)acylamides					N-(3-Cl-5-CF ₃ -pyridin-2-yl)acylamides				
	117/241=48.6%					13/209=6.2%				
Total % Success	130/450=28.9%									

4.3.2 Crystal growth

The ground mixtures that produced cocrystals were recrystallized from various solvents to obtain crystals suitable for single-crystal X-ray diffraction (SCXRD) analysis. However, since more than 100 samples formed crystals suitable for SCXRD, we only chose 15/50 coformers and submitted the cocrystals formed with those coformers only for SCXRD measurements to come up with a systematic explanation. Details of the crystallization solvents and resulting crystal characteristics are summarized in Table 4.7 and Appendix D for those crystals.

With those fifteen coformers, 50 positive cocrystals were formed, and 37 yielded crystals of sufficient quality for SCXRD measurements. All of them belonged to the *N*-(5-NO₂-pyridin-2-yl)acylamides series, while none of the *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamides formed suitable crystals for SCXRD.

Table 4.7. Solvents used for crystal growth and crystal descriptions

Cocrystal Code	Solvent	Melting Point (°C)	Color and Morphology
T2-3,5-dNBA	Methanol	182.38	Colorless, Irregular
T2-2,5-dMBA	Methanol	124.83,168.16	Colorless, Needle
T2-3-dMABA-form 1	Methanol	121.07	Light Orange, Plate
T2-3-dMABA-form 2	DCM	125.41	Orange, Plate
T2-4ABA	Ethyl acetate	154.46/153.40	Light yellow, Needle
T3-2,4-dNBA	Ethyl acetate	135.45	Colorless, prism
T3-2,3,4,5-tFBA	Methanol	115.28	Colorless, Plate
T3-3,5-dNBA	Ethyl Acetate	138.39	Colorless, Needle
T3-3NBA	Methanol	102.71	Colorless, Needle
T3-4CBA	Methanol	127.48	Colorless, Needle
T3-3,4-dCIBA	Methanol	132.58	Colorless, Plate
T3-3CIBA	Ethyl acetate	96.45	Colorless, Block
T3-2,5-dMBA	Methanol	113.87	Colorless, Plate
T3-4FBA	Methanol	92.43,105.30	Colorless, Needle
T3-m-TA	Methanol	95.25	Colorless, Plate
T3-4MxBA	Methanol	135.97	Colorless, Prism
T3-3-dMABA	Methanol	118.93/124.25	Orange, NA
T3-4ABA	Methanol	162.04	Yellow-Irregular
T4-2,4,6-tFBA	Methanol	101.95	Colorless, Needle
T4-2,3,4,5-tFBA	Methanol	109.06	Colorless, Needle
T4-3,5-dNBA	Methanol	137.27	Colorless, Needle
T4-3NBA	Methanol	111.47	Colorless, Needle
T4-4CBA	Methanol	126.22	Colorless, Needle
T4-3,4-dCIBA	Methanol	130.6	Colorless, Needle
T4-3CIBA	Methanol	111.07	Colorless, Plate
T4-2,5-dMBA	Methanol	141.31	Colorless, Needle
T4-4-Br-3-MBA	Methanol	-	Orange, Plate
T4-m-TA	Methanol	92.58/95.97	Colorless, Plate
T4-3-dMABA	Ethyl acetate	162.04	Orange, Plate
T4-2ABA	Methanol	143.19	Yellow, Plate
T5-2,4,6-tFBA	Methanol	110.36	Colorless, Needle
T5-2,3,4,5-tFBA	Methanol	111.66	Colorless, Needle
T5-3,5-dNBA	Methanol	-	Colorless, Needle
T5-4CBA	Methanol	110.78	Colorless, Needle
T5-3,4-dCIBA	Methanol	-	Colorless, Irregular
T5-3CIBA	Methanol	-	Colorless, Needle
T5-2,5-dMBA	Methanol	-	Colorless, Plate
T5-3-dMABA	Methanol	124.88	Orange, Plate
T5-2ABA	Methanol	122.38	Yellow, Needle

4.3.3 SCXRD analysis of cocrystals

Thirty-eight cocrystals, including one polymorph for T2-3dMABA, were successfully characterized by SCXRD. The most common primary interaction observed between the target and coformer was $\text{NH}\cdots\text{O}/\text{N}\cdots\text{OH}$ dimers in a 1:1 stoichiometry (Figure 4.4).

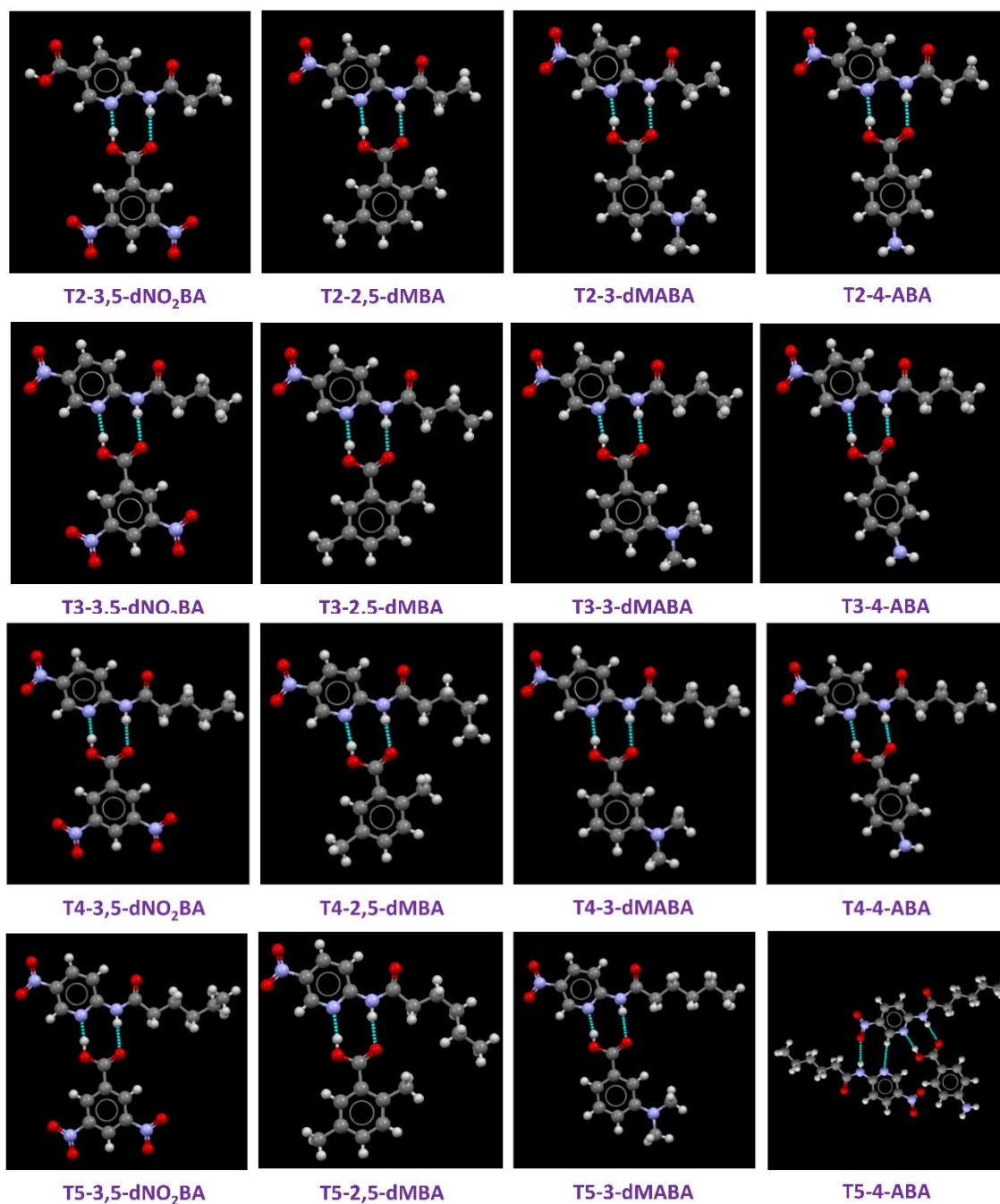


Figure 4.4. Some of the cocrystal structures of T2, T3, T4, and T5 targets.

4.3.4 Interaction energies of the targets

Table 4.8 summarizes interaction energy calculations among the target molecules. The calculations were performed using DFT/B3LYP/6-311++G ** basis set under vacuum, with BSSE correction, using Spartan 14 software.

Table 4.8. Interaction energy among target molecules

Compound	Interaction Energy/ kJ/mol
T1	-24.18
T2	-24.18
T3	-19.94
T4	-17.16
T6	-28.37
T7	-27.85
T8	-27.31
T9	-29.01

As mentioned, the target materials exhibited two types of primary hydrogen-bond motifs in the solid state; infinite chains and dimers. Analysis of the cocrystal structures indicated that target materials forming dimers were more likely to form cocrystals, while chain-forming target materials tended to form fewer cocrystals. Therefore, interaction energy calculations were performed for both chains and dimers to compare their relative strengths. The calculations revealed that individual chain interactions are relatively strong, whereas the interactions within dimers are individually weaker. These results indicate that chain-forming targets maintain strong bonding network that are difficult to disrupt as they form infinite chains, making them less favorable for cocrystal formation, while dimers are more adaptable for cocrystal formation (Figure 4.5).

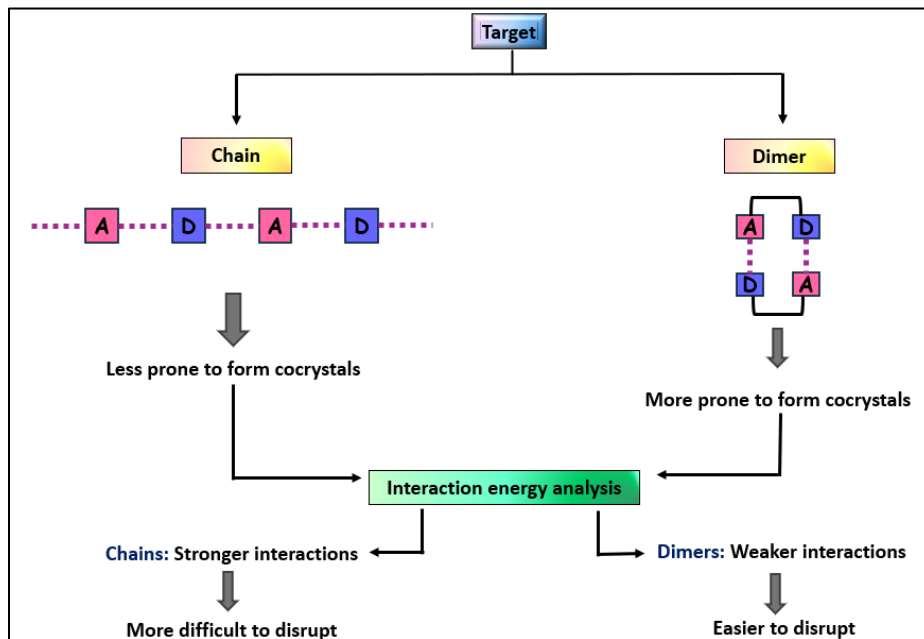


Figure 4.5. Bonding motifs and their influence on cocystal formation based on interaction energy calculations.

4.4 Discussion

130 of 450 attempted syntheses resulted in cocystals, 117 for the *N*-(5-NO₂-pyridin-2-yl)acylamides series and 13 for the *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamide series. The *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamide series was less prolific, which could be because of added steric interference, and also likely due to infinite chain motifs in these targets, which are difficult to break. In the *N*-(5-NO₂-pyridin-2-yl)acylamides series, the targets T1 and T2 also formed chains and exhibited fewer cocystals, whereas the majority of positive results came from targets T3, T4, and T5, which displayed dimeric homomeric interactions in the solid state (Figure 4.6).

Given the large number of positive results, SCXRD analysis was not performed for all cocystals formed with the 50 coformers, but for cocystals obtained with 15 selected coformers. Similar to

the overall IR analysis, the highest percentages of cocrystal formations within the selected 15 coformers (Table 4.9) were observed for T3, T4, and T5, with values of 93.33%, 86.67%, and 66.67%, respectively. In contrast, fewer positive results were obtained for T1, T2, and T6-T10.

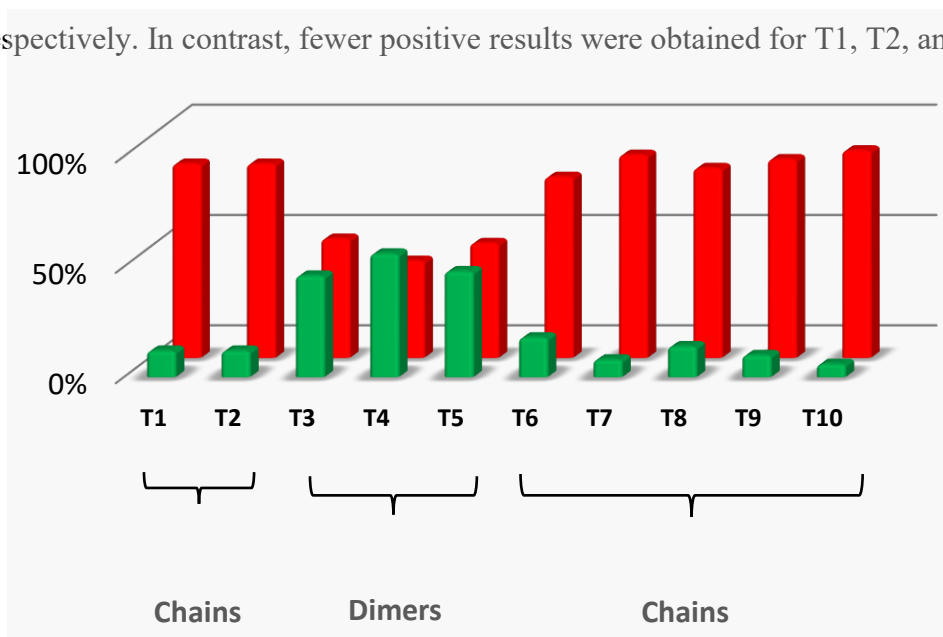


Figure 4.6. Influence of chain and dimer motifs on cocrystal formation.

Table 4.9. Selected coformers for SCXRD analysis

#	Coformer	Code
1	4-cyanobenzoic acid	4-CBA
2	3-nitrobenzoic acid	3-NBA
3	2,4-Dinitrobenzoic acid	2,4-dNBA
4	3,5-dinitrobenzoic acid	3,5-dNBA
5	4-fluorobenzoic acid	4-FBA
6	2,4,6-Trifluorobenzoic Acid	2,4,6-tFBA
7	2,3,4,5-tetrafluorobenzoic acid	2,3,4,5-tFBA
8	3-chlorobenzoic acid	3-CIBA
9	3,4-Dichlorobenzoic acid	3,4-dCIBA
10	4-Bromo-3-Methylbenzoic acid	4-Br-3-MBA
11	m-toluic acid (3-methylBA)	m-TA
12	2,5-dimethylbenzoic acid	2,5-DMBA
13	4-aminobenzoic Acid	4-ABA
14	3-dimethylaminobenzoic Acid	3-dMABA
15	4-methoxy benzoic acid	4-MxBA

The most common synthon observed between the target and coformer was $\text{NH}\cdots\text{O}/\text{N}\cdots\text{OH}$ 1:1 dimeric (Figure 4.7).

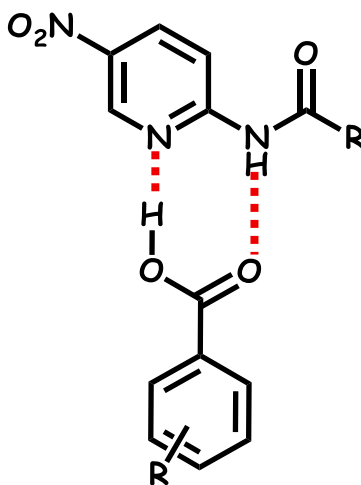


Figure 4.7. The most common synthon observed between the target and coformer.

After analyzing FTIR results and SCXRD results separately, targets that formed dimeric motifs themselves in their pure crystalline form exhibited a significantly higher tendency to form cocrystals than those that had chain motifs (Figure 4.8).

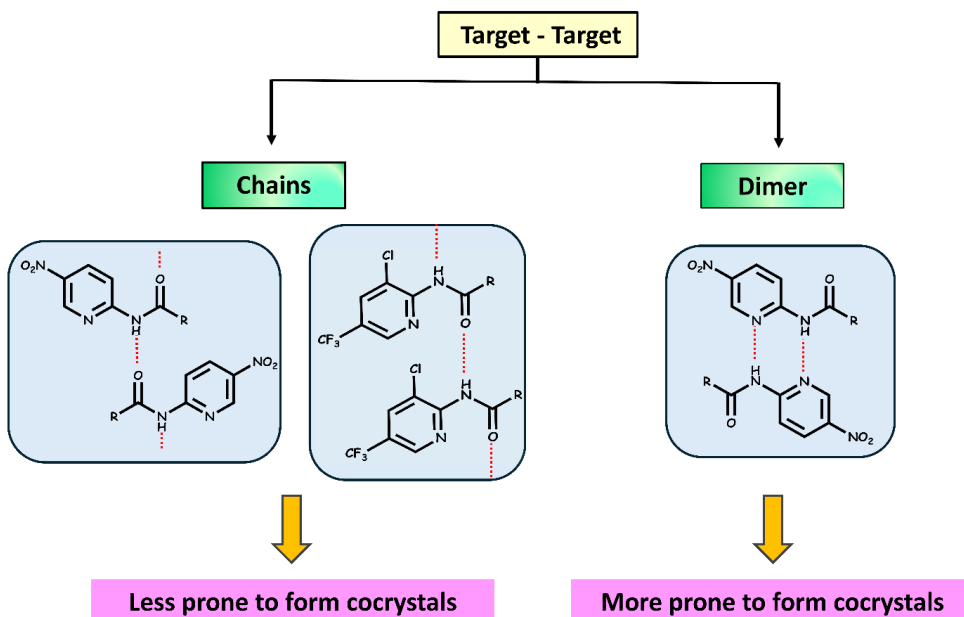


Figure 4.8. Influence of chain and dimer motifs on cocrystal formation.

Interaction energy calculations revealed that the dimeric associations were relatively weaker compared to the chain interactions, and this energetic difference likely facilitates the disruption of dimeric hydrogen bonds easily during cocrystallization, allowing the target molecule to more readily engage with coformers via new heteromeric interactions. In contrast, targets that form chains possess stronger, hydrogen-bond networks that may resist reorganization, resulting in fewer successful cocrystal formations.

The nature of the coformer also played a decisive role in cocrystal formation. Strong aromatic carboxylic acids exhibited the highest frequency of cocrystal formation, followed by weak aromatic acids, whereas aliphatic acids showed the lowest cocrystallization rate (Figure 4.9).

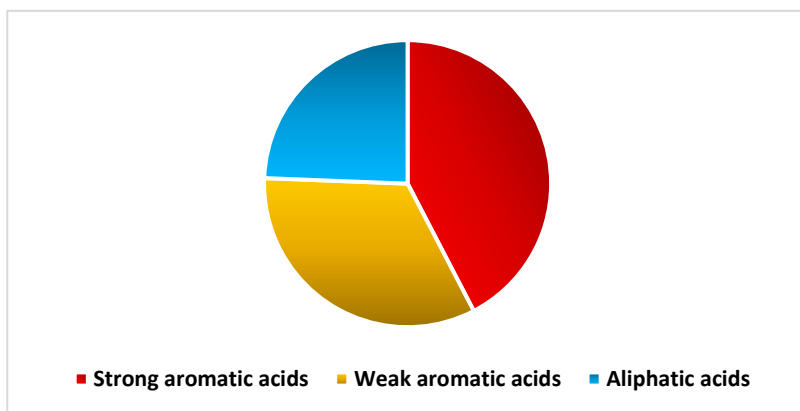


Figure 4.9. Influence of coformers.

4.5 Conclusions

Overall, the cocrystal screening revealed a strong dependence of cocrystal formation on both the supramolecular motifs of the targets and the nature of the coformers. The *N*-(5-NO₂-pyridin-2-yl)acylamide series showed significantly higher cocrystallization than the *N*-(3-Cl-5-CF₃-pyridin-2-yl)acylamide series, likely due to steric effects and the presence of chain-type self-assembly. Targets that formed dimeric motifs in their pure crystalline forms exhibited a greater tendency to form cocrystals, whereas chain-forming targets produced fewer cocrystals due to their stronger

and more extended hydrogen-bond networks (Figure 4.10). Interaction energy calculations supported this observation by showing that dimeric interactions are comparatively weaker, making them easier to disrupt. In addition, the nature of the coformer significantly influenced cocrystal formation, with strong aromatic carboxylic acids showing the highest success rates. Together, these results highlight the important roles of both target self-association and coformer strength (in terms of hydrogen-bond making abilities) in determining cocrystal formations.

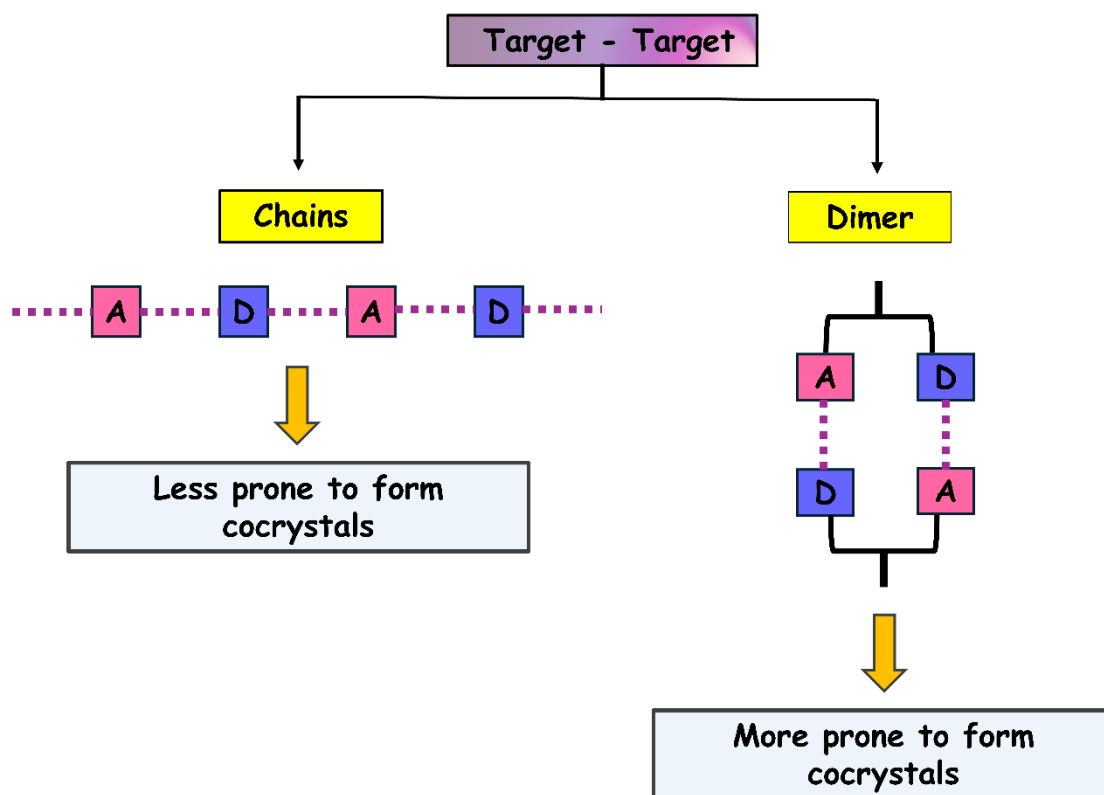


Figure 4.10. Key findings of the study.

Thus far, our studies have focused on relatively simple pyridine-based systems, examining their homomeric interactions and heteromeric interactions, raising the question of how added structural complexity might change their interactions and solid-state assemblies.

4.6 References

1. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers? *Crystal Growth & Design* **2025**, 25 (20).

2. Bolla, G.; Nangia, A. Pharmaceutical Cocrystals: Walking the Talk. *Chemical Communications* **2016**, 52 (54), 8342–8360.
3. Guo, M.; Sun, X.; Chen, J.; Cai, T. Pharmaceutical Cocrystals: A Review of Preparations, Physicochemical Properties and Applications. *Acta Pharmaceutica Sinica B* **2021**, 11 (8).
4. Kumar, S.; Nanda, A. Pharmaceutical Cocrystals: An Overview. *Indian Journal of Pharmaceutical Sciences* **2017**, 79 (6).
5. Karagianni, A.; Malamatar, M.; Kachrimanis, K. Pharmaceutical Cocrystals: New Solid Phase Modification Approaches for the Formulation of APIs. *Pharmaceutics* **2018**, 10 (1), 18.
6. Rodrigues, M.; Baptista, B.; Lopes, J. A.; Sarraguça, M. C. Pharmaceutical Cocrystallization Techniques. Advances and Challenges. *International Journal of Pharmaceutics* **2018**, 547 (1), 404–420.
7. Aakeröy, C. B.; Salmon, D. J. Building Co-Crystals with Molecular Sense and Supramolecular Sensibility. *CrystEngComm* **2005**, 7 (72), 439.
8. Hutchins, K. M. Functional Materials Based on Molecules with Hydrogen-Bonding Ability: Applications to Drug Co-Crystals and Polymer Complexes. *Royal Society Open Science* **2018**, 5 (6), 180564.
9. Devi, P.; Kakkar, S.; Vikas Budhwar; Choudhary, M.; Vikas Jogpal. Harnessing Hydrogen-Bonding: Advancements and Applications in Pharmaceutical Co-Crystallization. *Journal of Applied Pharmaceutical Research* **2025**, 13 (3), 45–64.
10. Venkatesan, P.; Flores-Manuel, F.; Sylvain Bernès; Cerón, M.; Pérez-Gutiérrez, E.; Subbiah Thamotharan; M. Judith Percino; Höpfl, H.; Sosa-Rivadeneira, M. V. Structural and Quantitative Analysis of Intermolecular Solid-State Interactions in Cocrystals Obtained from Nucleobases and Methylxanthines with Gallic Acid. *Journal of molecular structure* **2023**, 1280, 135074–135074.
11. Li, H.; Li, L.; Sun, J.; Han, J.; Yang, L.; Ren, X.; Tong, W. Construction and Preparation of the Novel ADN/CL-20 Cocrystal via Directional Hydrogen Bonding Design for Turning Hygroscopicity. *Inorganic Chemistry* **2024**, 63 (36), 16713–16725.
12. Zhang, L.; Jiang, S.-L.; Yu, Y.; Chen, J. Revealing Solid Properties of High-Energy-Density Molecular Cocrystals from the Cooperation of Hydrogen Bonding and Molecular Polarizability. *Scientific Reports* **2019**, 9 (1).

Chapter 5 - How molecular complexity governs the intermolecular interactions of amide-substituted 2-aminopyrimidine derivatives?

5.1 Introduction

The studies described so far focused on pyridine-based amide derivatives with one donor and two acceptor sites, providing relatively simple models for understanding supramolecular assembly. To explore how structural complexity affects supramolecular assembly, we introduced an additional acceptor site, so the system now contains one donor and three acceptor sites. This is particularly relevant to pharmaceutical drug molecules, which often contain multiple hydrogen-bond donors and acceptors distributed across complex scaffolds. Adding extra interaction sites, therefore, represents a step toward understanding such more complex molecular systems.

Hydrogen bonding is recognized as a crucial force for directing molecular organizations and self-assembly,¹⁻⁵ with extraordinary impacts on biological systems as well as in materials science. Halogen⁶⁻¹⁰ and chalcogen¹⁰⁻¹⁵ bonds also have the ability to organize individual molecular building blocks into supramolecular assemblies with precise metrics and configurations. Despite this understanding of intermolecular interactions, it can still be challenging to predict the bulk structural outcome involving molecules that present multiple interaction sites within a single framework.¹⁶⁻¹⁸ As a result, even relatively simple and rigid molecules can produce drastically different assemblies in the solid-state, which creates a considerable hurdle for supramolecular synthesis and bottom-up design of desirable architectures.¹⁹⁻²⁴

In this context, it has been shown that calculated molecular electrostatic potentials (MEP) can provide valuable insights when it comes to rationalizing preferred binding patterns of functional groups and small molecules.²⁵⁻²⁷ Often, the stronger hydrogen-bond acceptor sites (regions with large negative MEP) interact with the stronger hydrogen-bond donor sites (regions with large

positive MEP). However, this is not always the case, as systems with multiple donor and acceptor sites, sterics, and other environmental factors can result in alternative supramolecular assemblies. To further understand and rationalize these structural outcomes, we have conducted a systematic structural investigation of three distinct series of amide-substituted 2-aminopyrimidine derivatives that possess multiple donor and acceptor sites.

The 2-aminopyrimidine moiety is a significant component of numerous FDA-approved pharmaceutical drugs,²⁸⁻³¹ while the parent pyrimidine moiety ranks as the 10th most common aromatic moiety,³⁰ (Figure 5.1). Furthermore, this 2-aminopyrimidine moiety is associated with several important biological properties such as antitumor, antimicrobial, antiviral, antithrombotic, antiparasitic activity, *etc.*³²⁻³⁶

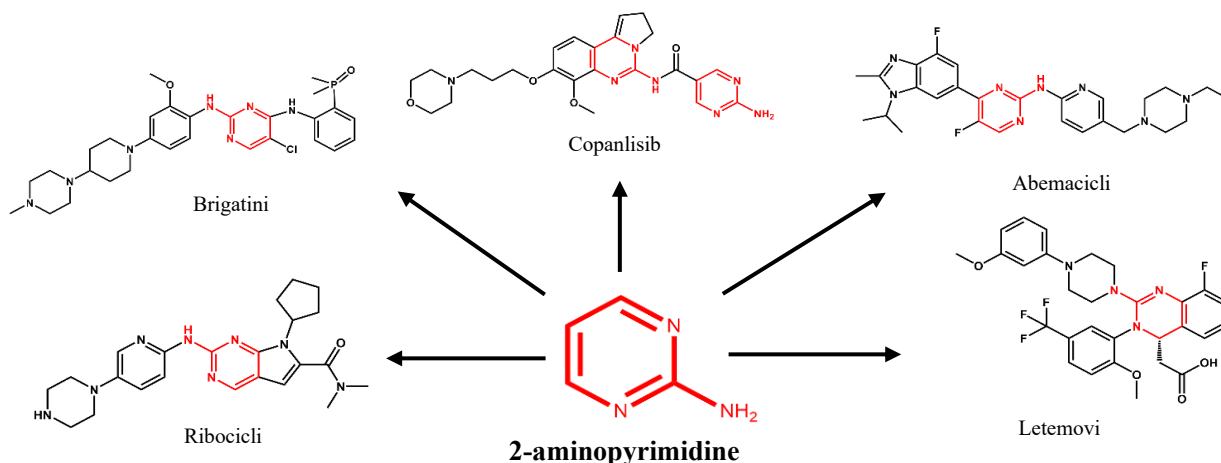


Figure 5.1. Some FDA-approved pharmaceutical drugs with 2-aminopyrimidine moieties.

In this study, we have synthesized and structurally characterized 21 molecules grouped into three series (**PM**, **Cl-PM**, and **Br-PM**) with different alkyl chain lengths, Figure 5.2. We examined the crystal structures of these derivatives, addressing several key questions, such as whether the length of the alkyl chain(-R) affects the supramolecular self-assembly and whether the chain's specific nature (having an odd or even number of carbon) impacts the crystal structures. Additionally, we

explore how these molecules adjust their behavior in the solid-state in the presence of an unequal number of hydrogen bond donors/acceptors. We also examine the balance between the structure-directing effects of hydrogen bonds and halogen bonds. Finally, we attempt to identify any motif-building hydrogen-bond preferences among a series of postulated motifs, Figure 5.3.

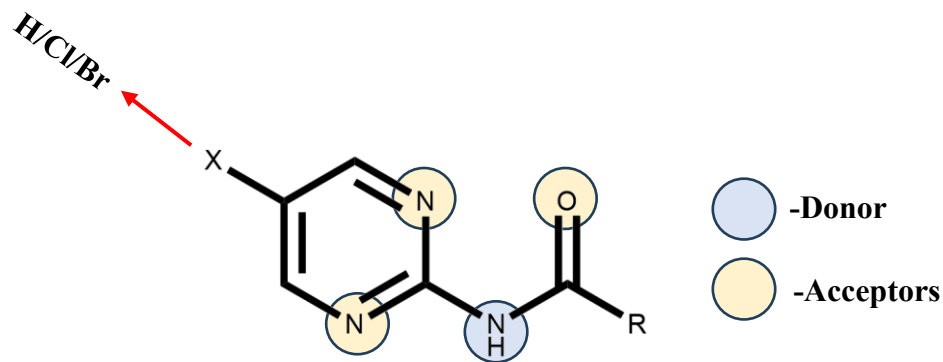


Figure 5.2. Potential hydrogen bond donor-acceptor sites.

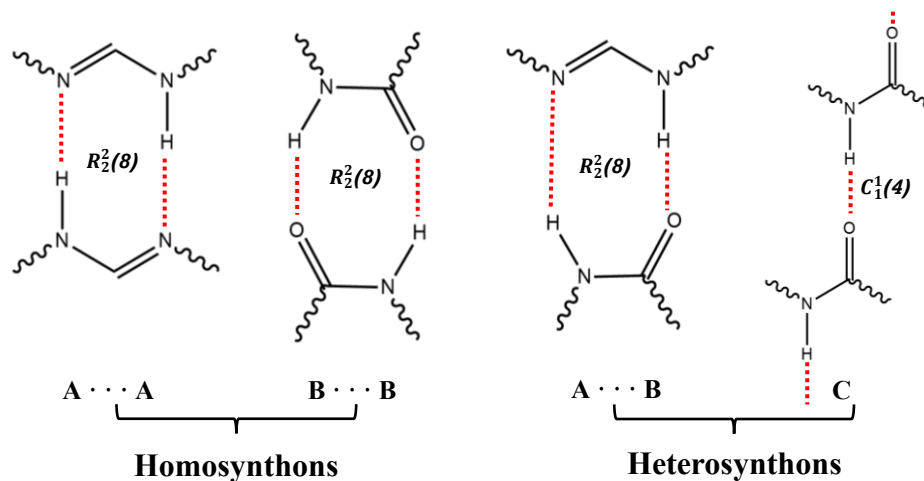


Figure 5.3. Postulated primary hydrogen bond motifs.

5.2 Experimental section

5.2.1 General

All precursors and solvents were purchased commercially and used without further purification.

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400Hz and 600Hz spectrometers.

Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra were recorded with a Nicolet 380 FTIR spectrometer using an attenuated total reflection (ATR) technique and ZnSe as the crystal.

All three series were synthesized according to an available literature procedure.³⁷

5.2.2 Syntheses of the PM Series

5.2.2.1 Synthesis of *N*-(pyrimidin-2-yl)acetamide (PM-methyl)

A solution of 2-aminopyrimidine (1.00 g, 11.00 mmol) in acetic anhydride (1.99 mL, 22.00 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 81.54%, Mp: 145-147 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.52 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.19 (s, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 169.48, 158.76, 158.17, 116.97, 25.08.

5.2.2.2 Synthesis of *N*-(pyrimidin-2-yl)propionamide (PM-ethyl)

A solution of 2-aminopyrimidine (1.00 g, 11.00 mmol) in propionic anhydride (2.68 mL, 22.00 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted using ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 82.39%, Mp: 126-128 °C. ¹H NMR (400 MHz, DMSO-d₆): 10.47 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.50(q, 2H), 1.05 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.83, 158.75, 158.21, 116.93, 30.14, 9.65.

5.2.2.3 Synthesis of *N*-(pyrimidin-2-yl)butyramide (PM-propyl)

A solution of 2-aminopyrimidine (0.50 g, 5.26 mmol) in butyric anhydride (1.66 mL, 10.52 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 81.84%, Mp: 102-104 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.48 (s, 1H), 8.64 (d, 2H), 7.16 (t, 1H), 2.46 (t, 2H), 1.59 (h, 2H), 0.91 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.88, 158.74, 158.17, 116.98, 38.73, 18.57, 14.07.

5.2.2.4 Synthesis of *N*-(pyrimidin-2-yl)pentanamide (PM-butyl)

A solution of 2-aminopyrimidine (0.50 g, 5.26 mmol) in pentanoic anhydride (2.11 mL, 10.52 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 76.37%, Mp: 106-108 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.48 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.48 (t, 2H), 1.53 (m, 2H), 1.31 (m, 2H), 0.89 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.02, 158.74, 158.17, 116.99, 36.53, 27.31, 22.23, 14.23.

5.2.2.5 Synthesis of *N*-(pyrimidin-2-yl)hexanamide (PM-pentyl)

A solution of 2-aminopyrimidine (0.50 g, 5.26 mmol) in hexanoic anhydride (2.43 mL, 10.52 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous

magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 86.53%, Mp: 110-112 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.48 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.47 (t, 2H), 1.57 (p, 2H), 1.29 (m, 2H), 0.86 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.02, 158.74, 158.18, 116.99, 36.78, 31.32, 24.85, 22.38, 14.33.

5.2.2.6 Synthesis of *N*-(pyrimidin-2-yl)heptanamide (PM-hexyl)

A solution of 2-aminopyrimidine (0.50 g, 5.26 mmol) in heptanoic anhydride (2.77 mL, 10.52 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 78.26%, Mp: 88-90 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.47 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.47 (t, 2H), 1.56 (p, 2H), 1.27 (m, 2H), 0.86 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.00, 158.74, 158.17, 116.99, 36.81, 31.51, 28.75, 25.12, 22.46, 14.39.

5.2.2.7 Synthesis of *N*-(pyrimidin-2-yl)octanamide (PM-heptyl)

A solution of 2-aminopyrimidine (0.50 g, 5.26 mmol) in octanoic anhydride (3.13 mL, 10.52 mmol) was stirred for 1.5 hrs at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted from ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 88.79%, Mp: 95-97 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.47 (s, 1H), 8.64 (d, 2H), 7.15 (t, 1H), 2.46 (t, 2H), 1.56 (p, 2H), 1.26 (m, 2H), 0.85 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.02, 158.74, 158.18, 116.99, 36.81, 31.64, 29.05, 28.95, 25.17, 22.53, 14.41.

5.3.2 Syntheses of the Cl-PM Series

5.2.3.1 Synthesis of *N*-(5-chloropyrimidin-2-yl)acetamide (Cl-PM-methyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in acetic anhydride (0.73 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 97.12%, Mp: 206-208 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.76 (s, 1H), 8.74 (s, 2H), 2.16 (s, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 169.22, 156.99, 156.44, 124.70, 25.02.

5.2.3.2 Synthesis of *N*-(5-chloropyrimidin-2-yl)propionamide (Cl-PM-ethyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in propionic anhydride (0.99 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 69.13%, Mp: 152-154 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.72 (s, 1H), 8.74 (s, 2H), 2.48 (q, 2H), 1.04 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 172.63, 156.96, 156.47, 124.59, 30.13, 9.55.

5.2.3.3 Synthesis of *N*-(5-chloropyrimidin-2-yl)butyramide (Cl-PM-propyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in butyric anhydride (1.26 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 46.49%, Mp: 104-106 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.72 (s, 1H), 8.74 (s, 2H), 2.44 (t, 2H), 1.58 (p, 2H), 0.90 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.71, 156.97, 156.42, 124.67, 38.70, 18.52, 14.03.

5.2.3.4 Synthesis of *N*-(5-chloropyrimidin-2-yl)pentanamide (Cl-PM-butyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in pentanoic anhydride (1.55 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 34.15%, Mp: 101-103 °C. ¹H NMR

(600 MHz, DMSO-d₆): δ 10.71 (s, 1H), 8.74 (s, 2H), 2.45 (t, 2H), 1.54 (p, 2H), 1.31 (h, 2H), 0.89 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.85, 156.97, 156.42, 124.68, 36.52, 27.23, 22.19, 14.21.

5.2.3.5 Synthesis of *N*-(5-chloropyrimidin-2-yl)hexanamide (Cl-PM-pentyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in hexanoic anhydride (1.79 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 47.05%, Mp: 93-98 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.70 (s, 1H), 8.74 (s, 2H), 2.44 (t, 2H), 1.54 (p, 2H), 1.27 (m, 4H), 0.86 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.85, 156.97, 156.43, 124.67, 36.77, 31.27, 24.78, 22.36, 14.32.

5.2.3.6 Synthesis of *N*-(5-chloropyrimidin-2-yl)heptanamide (Cl-PM-hexyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in heptanoic anhydride (2.03 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 30.11%, Mp: 82-85 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.70 (s, 1H), 8.74 (s, 2H), 2.44 (t, 2H), 1.54 (p, 2H), 1.27 (m, 6H), 0.85 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.83, 156.97, 156.43, 124.67, 36.80, 31.50, 28.72, 25.06, 22.45, 14.39.

5.2.3.7 Synthesis of *N*-(5-chloropyrimidin-2-yl)octanamide (Cl-PM-heptyl)

A solution of 2-amino-5-chloropyrimidine (0.50 g, 3.86 mmol) in octanoic anhydride (3.86 mL, 7.72 mmol) was stirred for 1.5 hrs at 160 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted using chloroform. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 28.28%,

Mp: 87-89 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.71 (s, 1H), 8.74 (s, 2H), 2.44 (t, 2H), 1.56 (p, 2H), 1.27 (m, 8H), 0.87 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.85, 156.97, 156.44, 124.67, 36.80, 31.62, 29.01, 28.93, 25.10, 22.52, 14.41.

5.2.4 Syntheses of the Br-PM Series

5.2.4.1 Synthesis of *N*-(5-bromopyrimidin-2-yl)acetamide (Br-PM-methyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in acetic anhydride (1.13 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 89.89%, Mp: 232-234 °C. ¹H NMR (600 MHz, DMSO-d₆): δ 10.73 (s, 1H), 8.80 (s, 2H), 2.17 (s, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 169.26, 159.07, 156.65, 113.31, 25.05.

5.2.4.2 Synthesis of *N*-(5-bromopyrimidin-2-yl)propionamide (Br-PM-ethyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in propionic anhydride (1.53 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 76.38%, Mp: 162-164 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (s, 1H), 8.79 (s, 2H), 2.47 (q, 2H), 1.05 (t, 3H). ¹³C NMR (600 MHz, DMSO-d₆): δ 172.66, 159.05, 156.68, 113.20, 30.16, 9.56.

5.2.4.3 Synthesis of *N*-(5-bromopyrimidin-2-yl)butyramide (Br-PM-propyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in butyric anhydride (1.96 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 79.45%, Mp: 136-138 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.79 (s, 2H), 2.43 (t, 2H), 1.57 (p, 2H), 0.90 (t, 3H). ¹³C NMR (600 MHz, DMSO-d₆): δ 173.54, 160.86, 158.45, 115.08, 40.53, 20.32, 15.85.

5.2.4.4 Synthesis of *N*-(5-bromopyrimidin-2-yl)pentanamide (Br-PM-butyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in pentanoic anhydride (2.40 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 66.52%, Mp: 116-118 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.79 (s, 2H), 2.45 (t, 2H), 1.54 (p, 2H), 1.31 (h, 2H), 0.89 (t, 3H). ¹³C NMR (600 MHz, DMSO-d₆): δ 173.69, 160.83, 158.41, 115.07, 38.33, 29.01, 13.98, 16.00.

5.2.4.5 Synthesis of *N*-(5-bromopyrimidin-2-yl)hexanamide (Br-PM-pentyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in hexanoic anhydride (2.77 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 76.67%, Mp: 105-107 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.79 (s, 2H), 2.44 (t, 2H), 1.55 (p, 2H), 1.28 (m, 4H), 0.85 (t, 3H). ¹³C NMR (600 MHz, DMSO-d₆): δ 173.70, 160.81, 158.40, 115.05, 38.57, 35.87, 33.04, 26.56, 24.15, 16.08.

5.2.4.6 Synthesis of *N*-(5-bromopyrimidin-2-yl)heptanamide (Br-PM-hexyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in heptanoic anhydride (3.16 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 65.12%, Mp: 109-111 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.79 (s, 2H), 2.44 (t, 2H), 1.55 (p, 2H), 1.28 (m, 6H), 0.86 (t, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 171.84, 159.05, 156.67, 113.27, 36.84, 31.51, 28.72, 25.06, 22.46, 14.40.

5.2.4.7 Synthesis of *N*-(5-bromopyrimidin-2-yl)octanamide (Br-PM-heptyl)

A solution of 2-amino-5-bromopyrimidine (1.00 g, 6.00 mmol) in octanoic anhydride (3.57 mL, 12.00 mmol) was stirred for 1.5 hrs at 150 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 87.94%, Mp: 98-100 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.68 (s, 1H), 8.79 (s, 2H), 2.44 (t, 2H), 1.55 (p, 2H), 1.26 (m, 8H), 0.85 (t, 3H). ¹³C NMR (400 MHz, DMSO-*d*₆): δ 171.83, 159.04, 156.67, 113.26, 36.83, 31.63, 29.02, 28.93, 25.10, 22.53, 14.41.

Crystals suitable for single-crystal X-ray diffraction were obtained for all 21 compounds through slow evaporation, Table 5.1. The PM-methyl crystal structure has been previously reported.¹⁸

Table 5.1. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color, Morphology
<i>N</i> -(pyrimidin-2-yl)acetamide	PM-methyl	Ethyl acetate	Colorless, plate
<i>N</i> -(pyrimidin-2-yl)propionamide	PM-ethyl	Ethyl acetate	Colorless, irregular
<i>N</i> -(pyrimidin-2-yl)butyramide	PM-propyl	Ethyl acetate	White, needle
<i>N</i> -(pyrimidin-2-yl)pentanamide	PM-butyl	Ethyl acetate	Colorless, irregular
<i>N</i> -(pyrimidin-2-yl)hexanamide	PM-pentyl	Ethyl acetate	Colorless, irregular
<i>N</i> -(pyrimidin-2-yl)heptanamide	PM-hexyl	Ethyl acetate	Colorless, needle
<i>N</i> -(pyrimidin-2-yl)octanamide	PM-heptyl	Ethyl acetate	Colorless, needle
<i>N</i> -(5-bromopyrimidin-2-yl)acetamide	Br-PM-methyl	Acetone + Methanol	Orange, plate
<i>N</i> -(5-bromopyrimidin-2-yl)propionamide	Br-PM-ethyl	Acetone + Methanol	Orange, prism
<i>N</i> -(5-bromopyrimidin-2-yl)butyramide	Br-PM-propyl	Acetone	Colorless, needle
<i>N</i> -(5-bromopyrimidin-2-yl)pentanamide	Br-PM-butyl	Acetonitrile	Colorless, block
<i>N</i> -(5-bromopyrimidin-2-yl)hexanamide - form 1	Br-PM-pentyl-Form 1	Acetonitrile	Colorless, plate
<i>N</i> -(5-bromopyrimidin-2-yl)hexanamide - form 2	Br-PM-pentyl-Form 2	Acetonitrile	Colorless, plate
<i>N</i> -(5-bromopyrimidin-2-yl)heptanamide	Br-PM-hexyl	Ethyl acetate	Colorless, needle
<i>N</i> -(5-bromopyrimidin-2-yl)octanamide	Br-PM-heptyl	Ethyl acetate	Colorless, needle

<i>N</i> -(5-chloropyrimidin-2-yl)acetamide	Br-PM-methyl	Ethyl acetate + Acetonitrile + Methanol	Colorless, irregular
<i>N</i> -(5-chloropyrimidin-2-yl)propionamide	Br-PM-ethyl	Methanol	Colorless, irregular
<i>N</i> -(5-chloropyrimidin-2-yl)butyramide	Br-PM-propyl	Chloroform	Colorless, plate
<i>N</i> -(5-chloropyrimidin-2-yl)pentanamide	Br-PM-butyl	Ethyl acetate	Colorless, block
<i>N</i> -(5-chloropyrimidin-2-yl)hexanamide	Br-PM-pentyl	Acetonitrile	Colorless, needle
<i>N</i> -(5-chloropyrimidin-2-yl)heptanamide	Br-PM-hexyl	Ethyl acetate	Colorless, plate
<i>N</i> -(5-chloropyrimidin-2-yl)octanamide	Br-PM-heptyl	Ethyl acetate	Colorless, needle

5.2.5 Molecular electrostatic potential calculations (MEP)

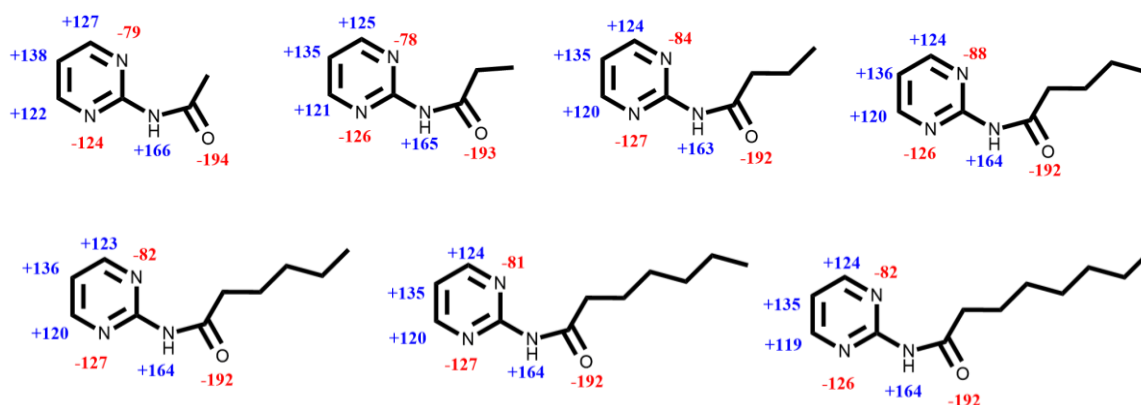
MEP surfaces were generated for all molecules explored in this study using Spartan'14 Version 1.1.4. The molecular skeleton was first loaded from a ChemDraw file, which was then geometry-optimized using DFT with the B3LYP functional and the 6-311++G** triple-zeta basis set in vacuum. On this optimized structure, the maxima and minima on the MEP surface (0.002 e/au isosurface) were determined using a positive point charge in the vacuum as a probe.

5.3 Results

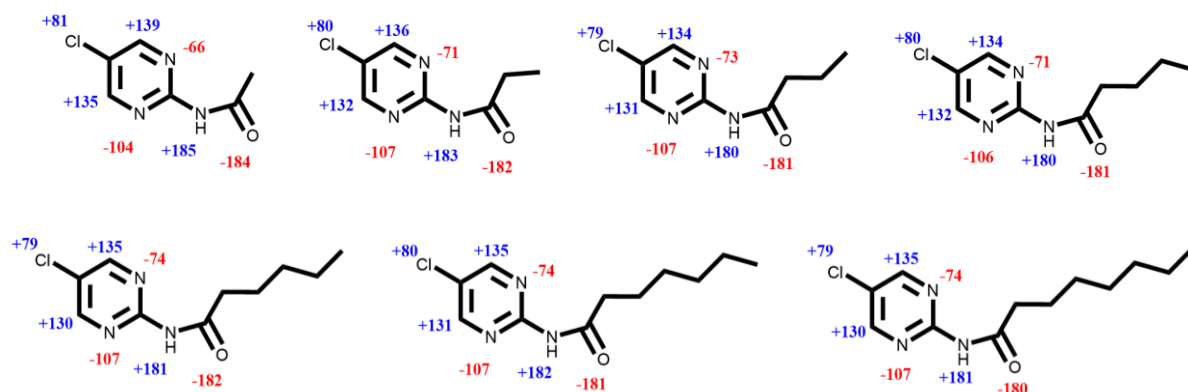
5.3.1 MEP values of the target materials

The calculated MEP values are shown in Figure 5.4.

5.3.1.1 MEP values of the PM Series



5.3.1.2 MEP values of the Cl-PM series



5.3.1.3 MEP values of the Br-PM series

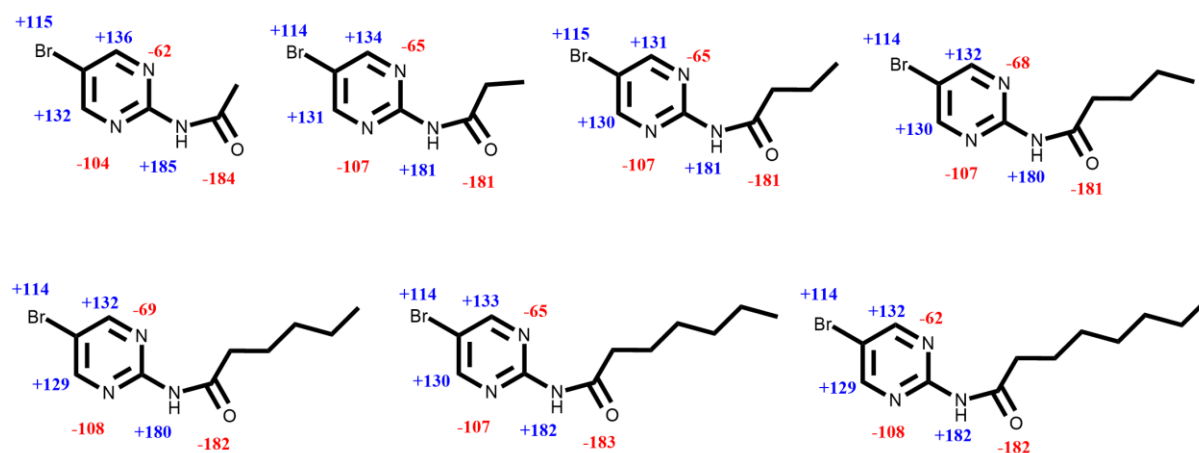


Figure 5.4. MEP values (kJ/mol) at the likely donor-acceptor sites in the 21 target compounds.

5.3.2 SCXRD analysis of the target materials

In each of the seven crystal structures from the PM series, the primary intermolecular interactions are four hydrogen bonds, C-H(py)⋯O=C / N(py)⋯H-N / N-H⋯N(py) / C=O⋯H-C(py), which produce tightly interlocked dimers, Figure 5.5.

In six of seven structures, there is an additional C-H(py)⋯O=C hydrogen bond, which serves to connect adjacent dimers (it is not present in the structure of **PM-propyl**). The only other

noteworthy hydrogen bonds (N(py)⋯H-C/ C-H⋯N(py)) appeared in the crystal structure of **PM-methyl**, which, interestingly, is the least sterically hindered molecule in this series.

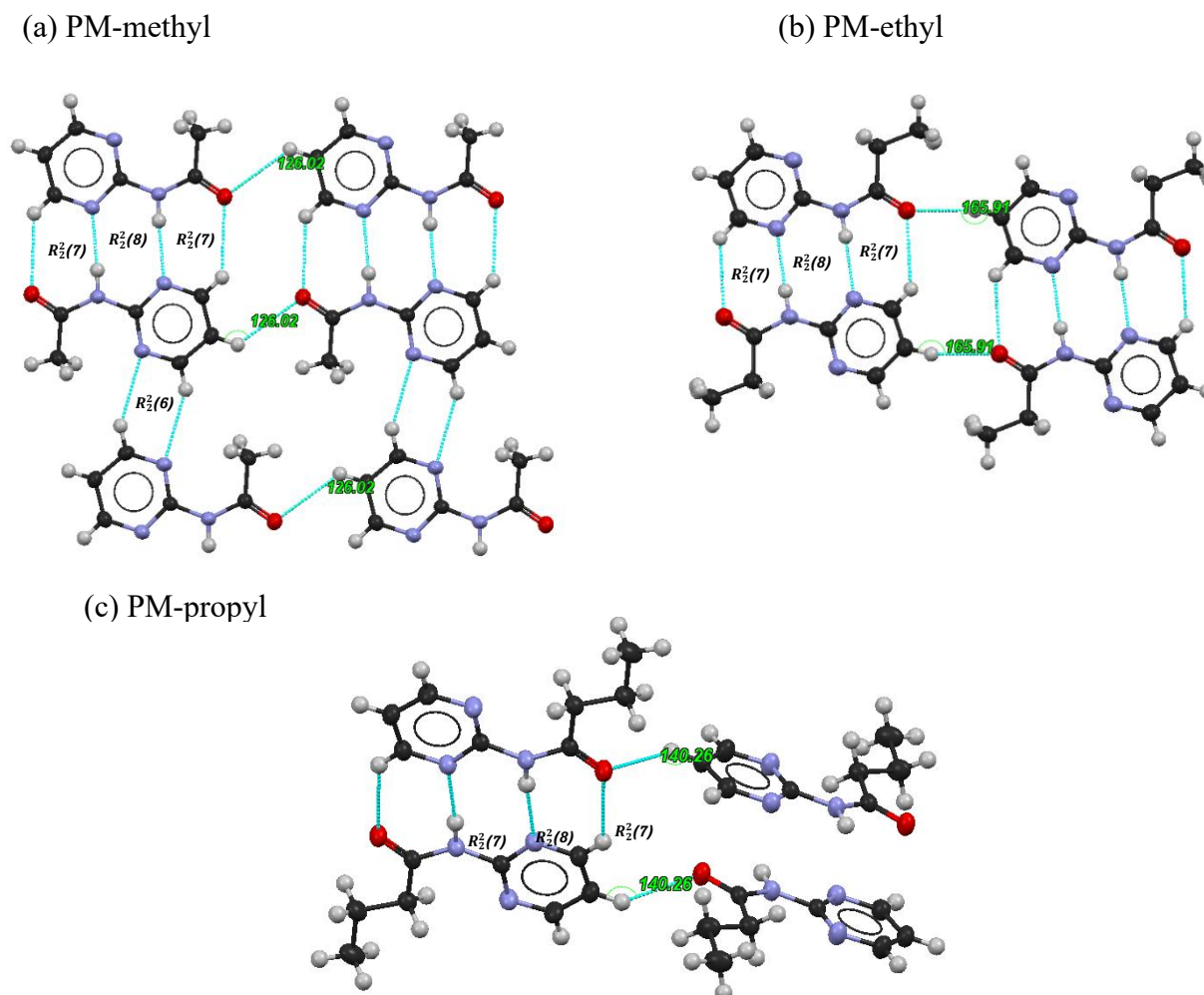
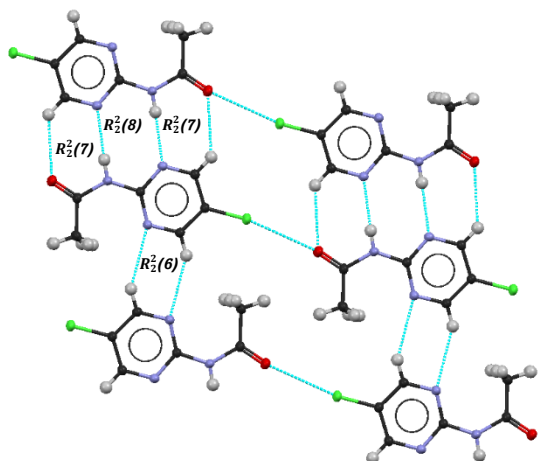


Figure 5.5. The intermolecular interactions in three different types of single crystal structures appeared in the PM series.

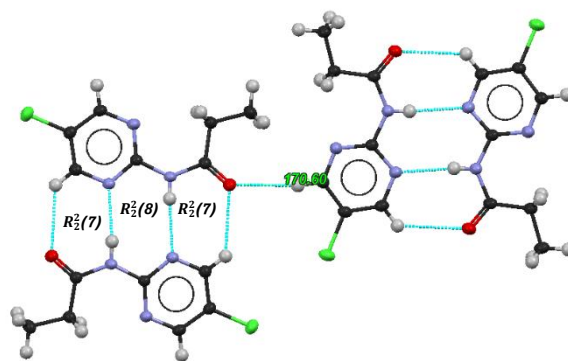
The dominant hydrogen bonds in the seven crystal structures of the Cl-PM series are shown in Figure 5.6. The addition of a halogen atom to the five-position has affected the supramolecular assembly compared to what was found in the PM-series. Five of the seven structures did display dimers created by four complementary hydrogen bonds, C-H(py)⋯O=C/ N(py)⋯H-N / N-

$\text{H}\cdots\text{N}(\text{py})$ / $\text{C}=\text{O}\cdots\text{H}-\text{C}(\text{py})$ similar to what was found in the corresponding members of the PM series. However, **Cl-PM-butyl** and **Cl-PM-heptyl** were completely different and instead presented $(\text{N}(\text{py})\cdots\text{H}-\text{C} / \text{N}-\text{H}\cdots\text{N}(\text{py}))/\text{C}=\text{O}\cdots\text{H}-\text{N}$ and $\text{C}=\text{O}\cdots\text{H}-\text{N}$ interactions, respectively. Two of the members in this series, **Cl-PM-methyl** and **Cl-PM-propyl**, also contained halogen bonds. All but one structure, **Cl-PM-ethyl**, comprised a $\text{C}-\text{H}(\text{py})\cdots\text{O}=\text{C}$ hydrogen bond. Finally, similar to what was noted in the PM-methyl structure, $(\text{N}(\text{py})\cdots\text{H}-\text{C} / \text{C}-\text{H}\cdots\text{N}(\text{py}))$ were present in the **Cl-PM-methyl** structure which has the least steric hindrance in this series.

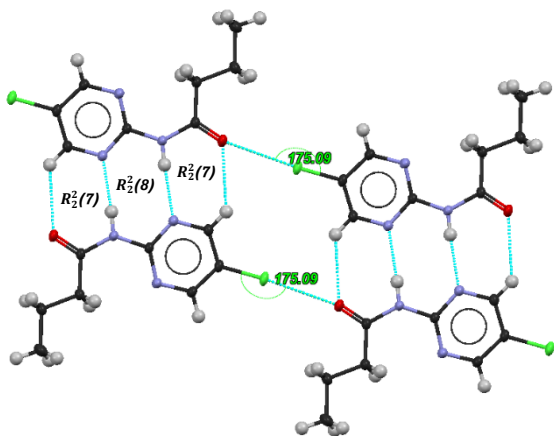
(a) Cl-PM-methyl



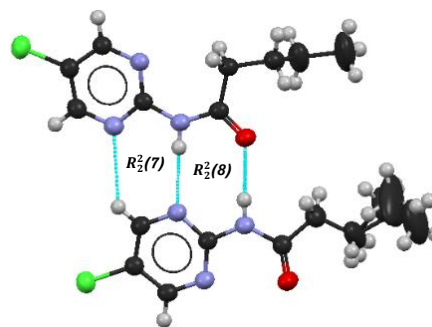
(b) Cl-PM-ethyl



(c) Cl-PM-propyl



(d) Cl-PM-butyl



(e) Cl-PM-heptyl

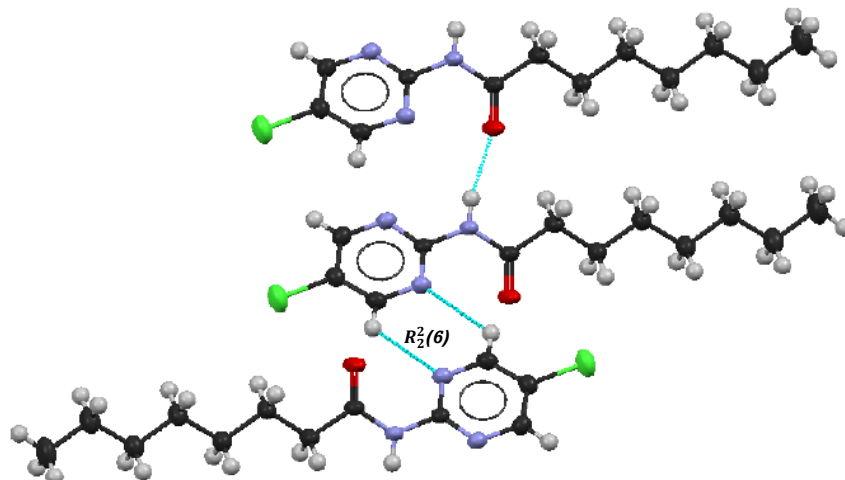


Figure 5.6. The intermolecular interactions in five different types of single crystal structures appeared in the Cl-PM series.

The Br-PM series was largely similar to the PM series, as all crystal structures contained the same dimers created by four intermolecular hydrogen bonds ($\text{C-H(py)} \cdots \text{O=C/N(py)} \cdots \text{H-N} / \text{N-H} \cdots \text{N(py)/C=O} \cdots \text{H-C(py)}$), Figure 5.7, similarly to what was found in the PM series. All but one structure, **Br-PM-ethyl**, also comprised a $\text{C-H(py)} \cdots \text{O=C}$ hydrogen bond as similar to Cl-PM-ethyl. Furthermore, two polymorphs of **Br-PM-pentyl** were obtained (Appendix E). Both were crystallized from acetonitrile and appeared as colorless plates in $P-1$ and $P2_1/c$ space groups, respectively. Similar to the PM-methyl and the Cl-PM-methyl structures, an additional hydrogen bond, ($\text{N(py)} \cdots \text{H-C} / \text{C-H} \cdots \text{N(py)}$), was present in **Br-PM-methyl**, again, the least sterically hindered member in the series.

The hydrogen and halogen bond angles and distances in the 22 crystal structures are given in Table 5.2.

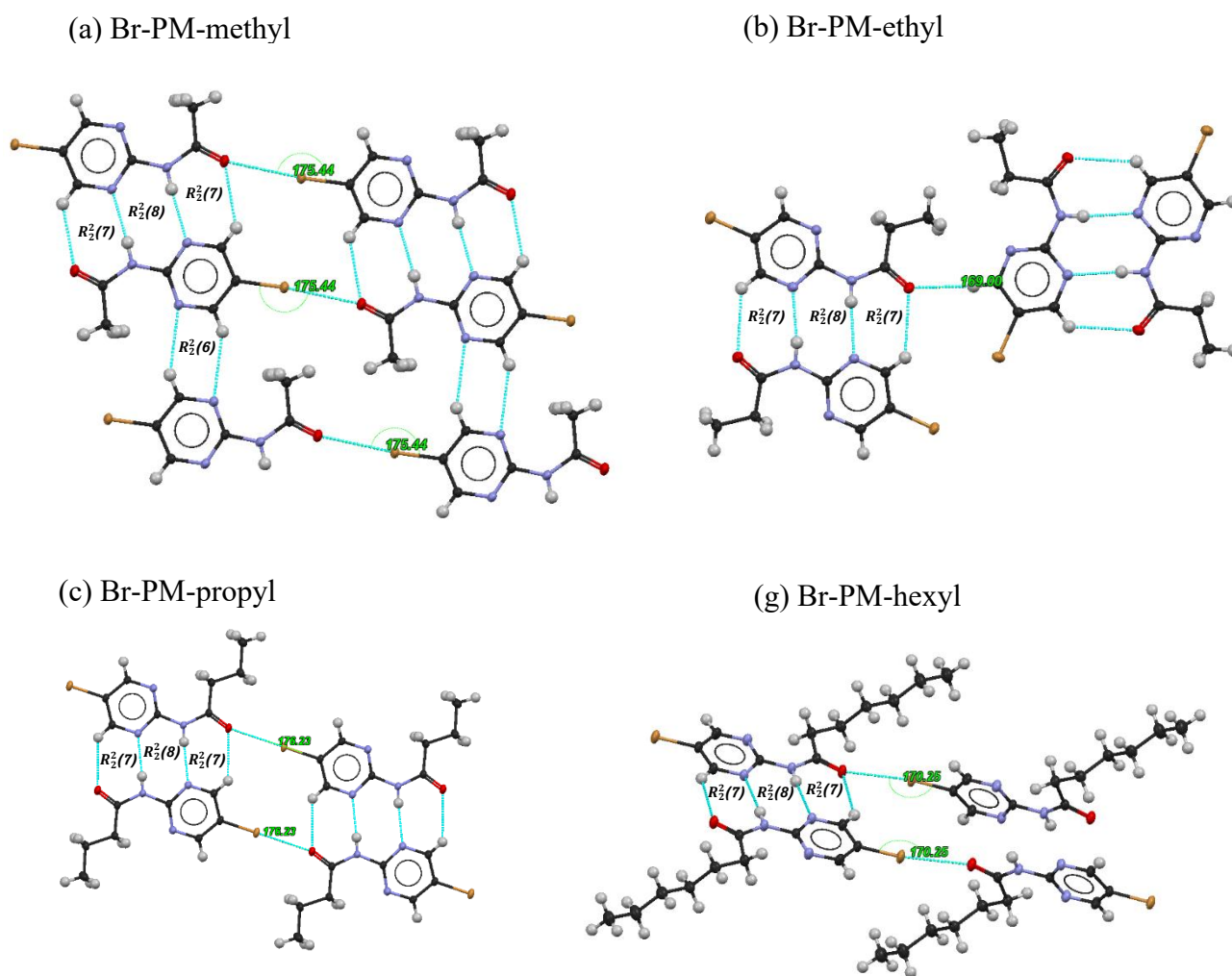


Figure 5.7. The intermolecular interactions in four different types of single crystal structures appeared in the Br-PM series.

In the crystal structures, hydrogen bond angles among the inter-dimers ranged from 126° to 166° , Table 5.2. In the chloro series, the halogen bond angles among inter-dimers ranged from 170° to 175° , and in the bromo series, from 168° to 177° , indicating that when halogen bonds are present, they tend to be more linear than hydrogen bonds.

Table 5.2. Inter-dimer hydrogen or halogen bond angles and distances

Alkyl chain	PM series (Hydrogen bond)		Cl-PM series (Halogen bond)		Br-PM series (Halogen bond)	
	C-X $\cdots$ O/ $^\circ$	X $\cdots$ O/ $\text{\AA}$	C-X $\cdots$ O/ $^\circ$	X $\cdots$ O/ $\text{\AA}$	C-X $\cdots$ O/ $^\circ$	X $\cdots$ O/ $\text{\AA}$

Methyl	126.02	3.348(2)	170.51	3.14998(4)	175.44	3.034(2)
Ethyl	165.91	3.226(4)	N/A	N/A	N/A	N/A
Propyl	140.26	3.184(16)	175.09	2.9322(9)	176.23	2.9105(13)
Butyl	155.68	3.4148(18)	N/A	N/A	172.06	2.8900(13)
Pentyl	156.77	3.2740(17)	N/A	N/A	176.32/172.11	2.9356(15)/2.9080(16)
Hexyl	154.71	3.294(2)	N/A	N/A	170.25	3.0090(14)
Heptyl	164.73	3.2784(17)	N/A	N/A	168.71	2.919(2)

5.4 Discussion

We initially hypothesized that these pyrimidine derivatives would potentially engage in four different types of synthons through $\text{N-H}\cdots\text{O}=\text{C}$ or $\text{N-H}\cdots\text{N}$ (py) hydrogen bonds, resulting in $\text{N-H}\cdots\text{N}/\text{N}\cdots\text{N-H}$, $\text{N-H}\cdots\text{O}=\text{C}/\text{C}=\text{O}\cdots\text{H-N}$ homo synthons, or $\text{N}\cdots\text{N-H}/\text{N-H}\cdots\text{O}=\text{C}$, $\text{N-H}\cdots\text{O}=\text{C}$ hetero synthons. However, in all three series, only the $\text{N-H}\cdots\text{N}/\text{N}\cdots\text{N-H}$ homo synthon was observed. In the final crystal structures, none of the compounds showed evidence of $C_1^1(4)$ chain formation. In contrast, additional hydrogen bonds involving aromatic protons were present, resulting in highly self-complementary dimers assembled via two different hydrogen bonds, Figure 5.8. The aromatic protons of these molecules do carry a relatively large positive charge due to the two heterocyclic nitrogen atoms, allowing them to act as reasonably effective hydrogen-bond donors. This could also explain how the system arranges itself in the presence of an unequal number of acceptors and donor sites. In these molecules, which contain one conventional donor and three acceptors, the aromatic protons can level that imbalance by providing effective hydrogen-bond donor sites.

In none of the three series did we observe any notable structural influences from variations in alkyl chain lengths. The increased steric bulk and molecular ‘greasiness’ did not alter the primary molecular recognition events that brought adjacent molecules together into tightly bound dimeric

units. Furthermore, the specific nature of the alkyl chain (odd or even number of carbons) also does not produce any notable changes in the crystal structures in this series (Figure 5.9).

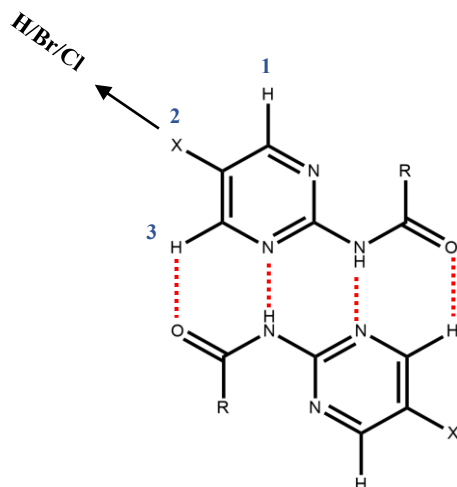


Figure 5.8. The primary intermolecular interactions in all the crystal structures.

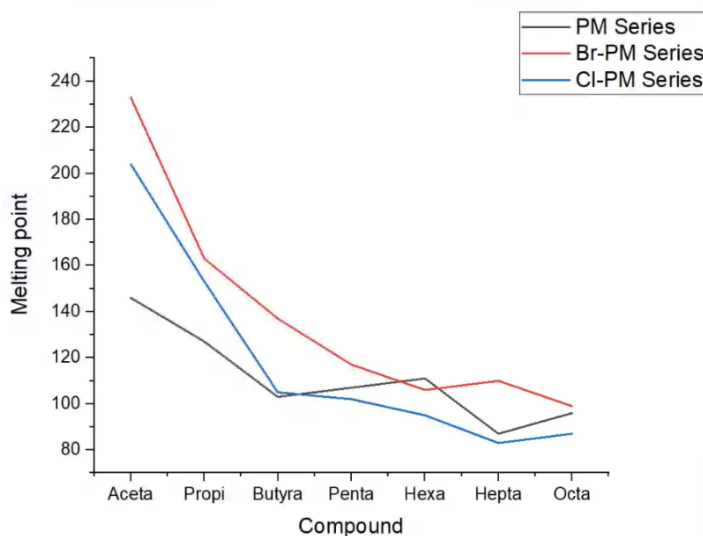


Figure 5.9. Thermal stability variation of three series.

Generally, an increase in molecular weight tends to enhance thermal stability due to increased van der Waals forces. However, as the alkyl chain length increases, the polarity of the molecule also decreases, making the material more hydrophobic (greasy), which can also reduce thermal stability. In our case, although molecular weight increases with the alkyl chain length, the

reduction in polarity seems to be the dominant factor, leading to a decrease in thermal stability. However, while chain length clearly affects thermal behavior, the odd or even nature of the alkyl chain shows no noticeable impact on thermal stability.

Compared to the PM series, the introduction of halogen atoms altered the MEP of the donor and the acceptor sites in the Br-PM series and Cl-PM series. The presence of electron-withdrawing groups decreases the electron density from donor sites, making them stronger donors. In contrast, the electron withdrawal from acceptor sites leads to decreased electron density, making them weaker acceptors. However, these changes in MEP did not significantly impact the supramolecular assembly, as the same primary interaction was retained in all crystal structures. However, our final observations suggest that hydrogen bonds can be replaced by halogen bonds without disrupting the overall self-assembly as long as the halogen bond donor is sufficiently strong.

To summarize, we synthesized three series of 2-aminopyrimidine derivatives: PM, Cl-PM, and Br-PM. Crystal structure determinations showed that in the PM series, adjacent dimers were further interconnected through a C-H $\cdots$ O hydrogen bond, and in the other two series, every inter-dimer link was provided by a near-linear halogen bond. In the PM series, all seven structures exhibited hydrogen bonding. In contrast, the chlorine series displayed only two halogen bonds, while in Br-PM, a Br $\cdots$ O halogen bond was present in seven of eight structures (including the polymorphs). This reflects the greater polarizability of the bromine atom, which enhances its ability to participate in structure-directing halogen bonds.

In crystal structures, among the inter-dimers, hydrogen bond angles ranged from 126° to 166°, while halogen bond angles varied from 170° to 175° in the chlorine series and 168° to 177° in the bromine series. These findings highlight that halogen bonds are more directional than hydrogen bonds. In hydrogen bonds, the charge is distributed across the entire hydrogen atom on the donor

site. In contrast, halogen bonds exhibit more directionality due to the specific alignment of the sigma hole along the p-orbital colinear with the covalent Cl/Br-C bond.

5.5 Conclusions

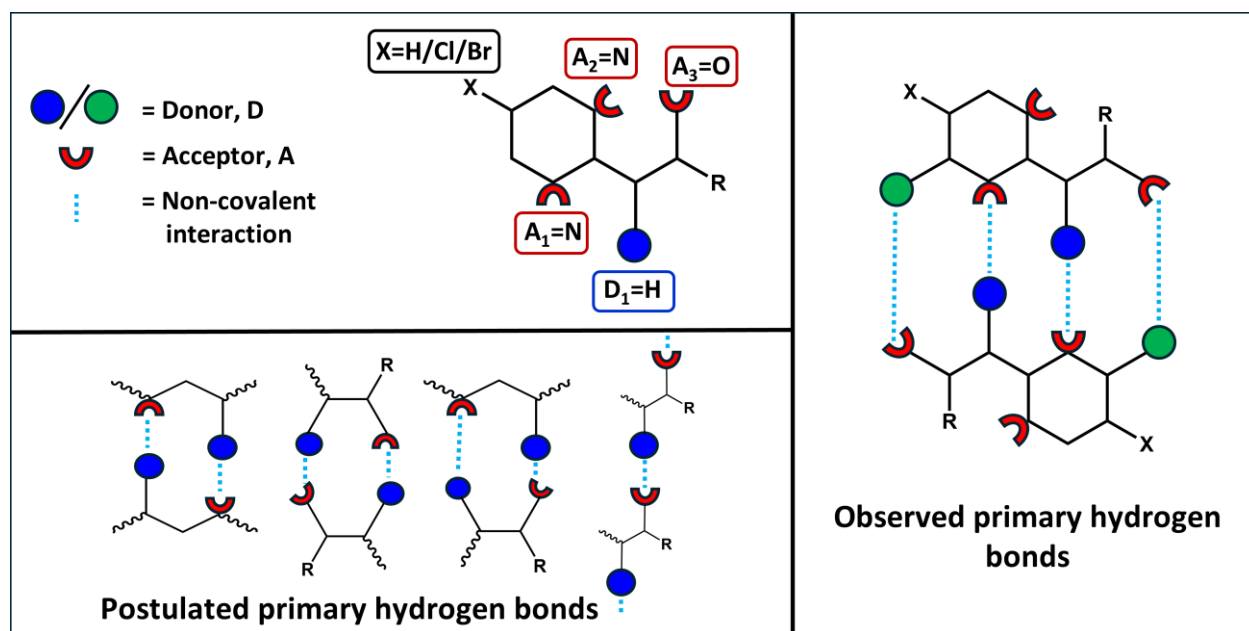


Figure 5.10. Key findings of the study.

This study was motivated by an ongoing need for systematic structural investigations of amide-substituted 2-aminopyrimidines to explore the influence and balance between hydrogen and halogen bonds in these crystal structures and as well as to understand how increasing molecular complexity affects these interactions, and to develop a reproducible method for supramolecular reactions. We investigated 21 amide derivatives of 2-aminopyrimidine, categorized into three different series (PM, Cl-PM, and Br-PM series) to explore the effect of alkyl chain length, nature, and halogen substitution on supramolecular assembly. Our findings revealed that steric effects, including the alkyl chain length and whether the chain contained an odd or even number of carbons, did not influence the final crystal structures (Figure 5.10).

We observed that the same primary bonding motifs remain mostly consistent across each series. Additionally, aromatic protons were found to act as hydrogen bond donors, helping to balance those systems with an unequal number of acceptors and donor sites. Moreover, we showed that hydrogen bonds can be replaced by halogen bonds without disrupting the overall crystal assembly if the halogen bond donor is sufficiently strong. This was mainly observed in the bromine series, where seven out of eight structures formed halogen bonds, compared to only two out of seven in the chlorine series.

Furthermore, it was noted that halogen bonds are more directional than hydrogen bonds. This was reflected in the crystal structures: hydrogen bond angles ranged from 126° to 166° in the PM series; chlorine halogen bonds ranged from 170° to 175°; and bromine halogen bonds ranged from 168° to 177°. Overall, these findings provide valuable insights into the role of halogen bonds in supramolecular assembly, demonstrating their potential as reliable alternatives to hydrogen bonding in crystal engineering.

Understanding the interplay between hydrogen and halogen bonds in molecules with moderate structural complexity expands the possibilities of designing new molecular structures with tailored noncovalent interactions. However, this study also raises an important question: how does increasing structural complexity influence supramolecular cocrystal assembly?

5.6 References

1. Sokolov, A. N.; MacGillivray, L. R. Supramolecular Ladders: Self-Assembly Fintium to Adfintium. *Crystal Growth & Design* **2006**, *6* (11), 2615–2624.
2. Ji, X.; Wang, J.; Wang, T.; Wang, N.; Li, X.; Huang, Y.; Huang, X.; Hao, H. Supramolecular Self-Assembly Process during Gelation and Crystallization of Cefradine. *Industrial & Engineering Chemistry Research* **2022**, *62* (1), 405–415.
3. Dergham, M.; Lin, S.; Geng, J. Supramolecular Self-Assembly in Living Cells. *Angewandte Chemie* **2022**, *61* (18).

4. Campos, M. T.; Pires, L. S.; Magalhães, F. D.; Oliveira, M. J.; Pinto, A. M. Self-Assembled Inorganic Nanomaterials for Biomedical Applications. *Nanoscale* **2025**, *17*, 5526–5570.
5. Nilabja Maity; Sharma, M. K.; Ghosh, S.; Huss-Hansen, M. K.; Roy, A.; Narayanan, R.; Matti Knaapila; Matsuda, W.; Seki, S.; Patil, S. Supramolecular Self-Assembly of Diketopyrrolopyrrole with Unprecedented Photoconductivity. *ACS Applied Electronic Materials* **2023**, *5* (9), 5093–5102.
6. Wang, H.; Bisoyi, H. K.; Urbas, A. M.; Bunning, T. J.; Li, Q. The Halogen Bond: An Emerging Supramolecular Tool in the Design of Functional Mesomorphic Materials. *Chemistry - A European Journal* **2018**, *25* (6), 1369–1378.
7. Varadwaj, P. R.; Marques, H. M.; Varadwaj, A.; Yamashita, K. π -Hole Halogen Bonds Are Sister Interactions to σ -Hole Halogen Bonds. *Crystal Growth & Design* **2024**, *24* (19), 7789–7807.
8. Meazza, L.; Foster, J. A.; Fucke, K.; Pierangelo Metrangolo; Resnati, G.; Steed, J. W. Halogen-Bonding-Triggered Supramolecular Gel Formation. *Nature Chemistry* **2012**, *5* (1), 42–47.
9. Scilabra, P.; Terraneo, G.; Resnati, G. The Chalcogen Bond in Crystalline Solids: A World Parallel to Halogen Bond. *Accounts of Chemical Research* **2019**, *52* (5), 1313–1324.
10. Aakeröy, C. B.; Fasulo, M.; Schultheiss, N.; Desper, J.; Moore, C. Structural Competition between Hydrogen Bonds and Halogen Bonds. *Journal of the American Chemical Society* **2007**, *129* (45),
11. Vogel, L.; Wonner, P.; Huber, S. M. Chalcogen Bonding: An Overview. *Angewandte Chemie International Edition* **2018**, *58* (7), 1880–1891.
12. Haberhauer, G.; Gleiter, R. The Nature of Strong Chalcogen Bonds Involving Chalcogen-Containing Heterocycles. *Angewandte Chemie International Edition* **2020**, *59* (47), 21236–21243.
13. Scheiner, S. Various Sorts of Chalcogen Bonds Formed by an Aromatic System. *The Journal of Physical Chemistry A* **2022**, *126* (25), 4025–4035.
14. Mahmudov, K. T.; Kopylovich, M. N.; Silva, M. F. C. G. da; Pombeiro, A. J. L. Chalcogen Bonding in Synthesis, Catalysis and Design of Materials. *Dalton Transactions* **2017**, *46* (31), 10121–10138.
15. Jia, S.; Ye, H.; You, L. Interplay between Chalcogen Bonds and Dynamic Covalent Bonds. *Organic Chemistry Frontiers* **2022**, *9* (15), 3966–3975.
16. F. Dean Toste; Sigman, M. S.; Miller, S. J. Pursuit of Noncovalent Interactions for Strategic Site-Selective Catalysis. *Accounts of Chemical Research* **2017**, *50* (3), 609–615.

17. Heleen Duijs; Kumar, M.; Dhiman, S.; Su, L. Harnessing Competitive Interactions to Regulate Supramolecular “Micelle-Droplet-Fiber” Transition and Reversibility in Water. *Journal of the American Chemical Society* **2024**, *146* (43).
18. Borys Ośmiałowski; Kolehmainen, E.; Satu Ikonen; Arto Valkonen; Kwiatkowski, A.; Grela, I.; Esa Haapaniemi. 2-Acylamino- and 2,4-Bis(Acylamino)Pyrimidines as Supramolecular Synthons Analyzed by Multiple Noncovalent Interactions. DFT, X-Ray Diffraction, and NMR Spectral Studies. *The Journal of Organic Chemistry* **2012**, *77* (21), 9609–9619.
19. Aragoni, M. C.; Cherchi, M. F.; Lippolis, V.; Pintus, A.; Podda, E.; Slawin, A. M. Z.; Woollins, J. D.; Arca, M. Self-Assembly of Supramolecular Architectures Driven by σ -Hole Interactions: A Halogen-Bonded 2D Network Based on a Diiminedibromido Gold(III) Complex and Tribromide Building Blocks. *Molecules* **2022**, *27* (19), 6289.
20. Bellavita, R.; Braccia, S.; Falanga, A.; Galdiero, S. An Overview of Supramolecular Platforms Boosting Drug Delivery. *Bioinorganic Chemistry and Applications* **2023**, *2023* (1), 1–15.
21. Wu, S.-T.; Long, L.-S.; Huang, R.-B.; Zheng, L.-S. PH-Dependent Assembly of Supramolecular Architectures from 0D to 2D Networks. *Crystal Growth & Design* **2007**, *7* (9), 1746–1752.
22. Caroprese, V.; Tekin, C.; Cencen, V.; Majid Mosayebi; Navid Asmari; Liverpool, T. B.; Woolfson, D. N.; Fantner, G. E.; Maartje M. C. Bastings. Interface Flexibility Controls the Nucleation and Growth of Supramolecular Networks. *Nature Chemistry* **2025**, *17* (3), 325–333.
23. Cameron, J. M.; Geoffroy Guillemot; Galambos, T.; Amin, S.; Hampson, E.; Kevin Mall Haidaraly; Newton, G. N.; Guillaume Izzet. Supramolecular Assemblies of Organo-Functionalised Hybrid Polyoxometalates: From Functional Building Blocks to Hierarchical Nanomaterials. *Chemical Society Reviews* **2022**, *51* (1), 293–328.
24. Eiji Yashima; Naoki Ousaka; Taura, D.; Shimomura, K.; Tomoyuki Ikai; Maeda, K. Supramolecular Helical Systems: Helical Assemblies of Small Molecules, Foldamers, and Polymers with Chiral Amplification and Their Functions. *Chemical Reviews* **2016**, *116* (22), 13752–13990.
25. Politzer, P.; Murray, J. S. Quantitative Analyses of Molecular Surface Electrostatic Potentials in Relation to Hydrogen Bonding and Co-Crystallization. *Crystal Growth & Design* **2015**, *15* (8), 3767–3774.
26. Spackman, M. A.; McKinnon, J. J.; Jayatilaka, D. Electrostatic Potentials Mapped on Hirshfeld Surfaces Provide Direct Insight into Intermolecular Interactions in Crystals. *CrystEngComm* **2008**, *10* (4).
27. Sandhu, B.; McLean, A.; Sinha, A. S.; Desper, J.; Sarjeant, A. A.; Vyas, S.; Reutzel-Edens, S. M.; Aakeröy, C. B. Evaluating Competing Intermolecular Interactions through Molecular Electrostatic Potentials and Hydrogen-Bond Propensities. *Crystal Growth & Design* **2017**, *18* (1), 466–478.

28. de la Torre, B.; Albericio, F. The Pharmaceutical Industry in 2017. An Analysis of FDA Drug Approvals from the Perspective of Molecules. *Molecules* **2018**, *23* (3), 533.
29. Baskar Nammalwar; Bunce, R. A. Recent Advances in Pyrimidine-Based Drugs. *Pharmaceuticals* **2024**, *17* (1), 104–104.
30. Yet, L. 2-Aminopyrimidines. *Privileged Structures in Drug Discovery* **2018**, 237–283.
31. Koroleva, E. V.; Gusak, K. N.; Ignatovich, Z. V. Synthesis and Applications of 2-Aminopyrimidine Derivatives as Key Intermediates in Chemical Synthesis of Biomolecules. *Russian Chemical Reviews* **2010**, *79* (8), 655–681.
32. Siddique, A.; Shaheen, S.; Iftikhar, A.; Faisal, A.; Rehman, H. M.; Shah, M.; Tahir, A.; Rashid, U. Bicyclic 2-Aminopyrimidine Derivatives as Potent VEGFR-2 Inhibitors and Apoptosis Inducers: Structure-Guided Design, Synthesis, Anticancer Assessment, and In-Silico Exploration. *European Journal of Medicinal Chemistry* **2025**, *293*, 117726.
33. Deng, W.; Chen, X.; Jiang, K.; Song, X.; Huang, M.; Tu, Z.-C.; Zhang, Z.; Lin, X.; Ortega, R.; Patterson, A. V.; Smaill, J. B.; Ding, K.; Chen, S.; Chen, Y.; Lu, X. Investigation of Covalent Warheads in the Design of 2-Aminopyrimidine-Based FGFR4 Inhibitors. *ACS Medicinal Chemistry Letters* **2021**, *12* (4), 647–652.
34. Xu, S.; Zhu, Y.; Meng, J.; Li, C.; Zhu, Z.; Wang, C.; Gu, Y.-C.; Han, L.; Wen, J.; Tong, M.; Shi, X.; Hou, Y.; Liu, Y.; Zhao, Y. 2-Aminopyrimidine Derivatives as Selective Dual Inhibitors of JAK2 and FLT3 for the Treatment of Acute Myeloid Leukemia. *Bioorganic Chemistry* **2023**, *134*, 106442.
35. Gerninghaus, J.; Rezart Zhubi; Kraemer, A.; Karim, M.; Tran; Joerger, A. C.; Schreiber, C.; Berger, L. M.; Benedict Tilman Berger; Theresa A.L. Ehret; Elson, L.; Lenz, C.; Saxena, K.; Mueller, S.; Shirit Einav; Knapp, S.; Hanke, T. Back-Pocket Optimization of 2-Aminopyrimidine-Based Macrocycles Leads to Potent Dual EPHA2/GAK Kinase Inhibitors with Antiviral Activity. *bioRxiv* **2024**, 67 (15).
36. Mo, C.; Zhang, Z.; Guise, C. P.; Li, X.; Luo, J.; Tu, Z.; Xu, Y.; Patterson, A. V.; Smaill, J. B.; Ren, X.; Lu, X.; Ding, K. 2-Aminopyrimidine Derivatives as New Selective Fibroblast Growth Factor Receptor 4 (FGFR4) Inhibitors. *ACS Medicinal Chemistry Letters* **2017**, *8* (5), 543–548.
37. Kadirova, Sh. A.; Nuralieva, G. A.; Alieva, M. A.; Talipov, S. A.; Tilyakov, Z. G.; Parpiev, N. A. Synthesis and Crystal Structure of 2-Aminoacetyl-1,3,4-Thiadiazole. *Russian Journal of General Chemistry* **2005**, *75* (12), 1962–1964.

Chapter 6 - Can the stoichiometry of cocrystals be controlled?

6.1 Introduction

The studies described in the previous chapters examined hydrogen-bonding preferences in nitrogen heterocyclic molecules and explored how these interactions influence the formation of cocrystals. These investigations highlighted the role of molecular recognition in directing supramolecular assembly in the solid state. Unlike covalent synthesis, where undesired products are often considered impurities or byproducts, supramolecular synthesis through cocrystallization offers unique opportunities. Different solid forms that arise from the same molecular components, such as cocrystals with different stoichiometries, can deliver distinct and meaningful products with unique structural and physicochemical properties. This aspect of supramolecular chemistry raises an important question: can the stoichiometry of cocrystals be controlled during their formation?

In the early days, cocrystal research primarily focused on selecting suitable coformers and supramolecular synthons to improve the reliability of synthesis.¹⁻⁷ However, subsequent studies⁸⁻¹³ revealed that stoichiometry can also be a critical design parameter for improving properties, as many compounds can form cocrystals with different stoichiometric ratios of targets-coformers.

Stoichiometric variation plays a significant role in determining crystal packing, hydrogen-bonding networks, and thermodynamic stability. For example, Rodríguez-Hornedo and coworkers demonstrated that cocrystal formation and the stability of the cocrystal depend strongly on how much coformer is dissolved in the solvent.¹⁴ They tested this with Carbamazepine (CBZ) and 4-aminobenzoic acid (4ABA) and discovered that at low 4ABA, the pure drug CBZ is most stable and it does not form any cocrystals, in intermediate levels of 4ABA, the cocrystal with 2:1 (CBZ:4ABA) is stable, and at higher 4ABA levels, the 1:1 cocrystal is the most stable. Additionally, this study also revealed that the solvent choice and composition are critical to

cocrystal design in solution-based cocrystallization. These findings highlight that cocrystal stoichiometry may be systematically controlled. Several experimental strategies have been developed to achieve intentional stoichiometric control. Leyssens and coworkers demonstrated that caffeine and maleic acid form either 1:1 or 2:1 cocrystals depending on their solubility in different solvents.¹⁵

The importance of stoichiometric control has also been explored in pharmaceutical cocrystals to determine whether changes in stoichiometric ratios affect material performance. Li and Matzger reported a dissolution study of three stoichiometrically different CBZ-4-ABA cocrystals (1:1, 2:1, and 4:1), each with distinct dissolution behavior. CBZ is a BCS class II anti-epileptic drug exhibiting low aqueous solubility and high permeability, and 4-ABA is a coformer with higher aqueous solubility than CBZ. This study revealed that stoichiometric control does not directly affect drug dissolution, but a weaker metastable cocrystal improves solubility because it shows a less dense crystal packing.⁸

In addition to solvent-based methods, mechanochemical methods have proven powerful for stoichiometric control of cocrystals.¹⁶ Jones and coworkers showed that grinding experiments with the same molecular components in different stoichiometries yield distinct cocrystal forms, and these forms can be interconverted by further mechanical treatment.¹⁷

Moving beyond batch synthesis, stoichiometric control has also been tested on larger-scale preparation. Kulkarni reported solvent-free continuous cocrystallization of caffeine and maleic acid, where precise control of composition enabled the selective production of either 1:1 or 2:1 cocrystals.¹⁸ Cocrystals with only 1:1 stoichiometry were obtained at 100 °C, and cocrystals with 1:2 stoichiometry were obtained at a higher temperature (110 °C). A mixture of 1:1 and 2:1 cocrystals was obtained at lower temperatures. This study shows that by selecting appropriate

target coformer ratios and temperature, the stoichiometry of the cocrystal can be controlled. These studies demonstrate that stoichiometric control in cocrystal synthesis is achievable, reproducible, and important, in both solvent-based and mechanochemical methods. Also, this should be regarded as a fundamental design parameter in crystal engineering and needs to be further studied.

In our study, we selected a target molecule (Figure 6.1) with multiple donor and acceptor sites that can undergo supramolecular reactions with suitable coformers (Figure 6.2). We wanted to establish whether we can deliberately control the stoichiometry of cocrystals through mechanochemical grinding and, if so, whether we can crystallize them in a suitable solvent while maintaining the same stoichiometry via slow evaporation. Additionally, we explored whether stoichiometric control can be related to the pKa of the coformer and how the pKa of our selected coformers relates to the MEPs of the donor and acceptor sites of the carboxylic group of coformers. Therefore, we selected coformers with varying acidities (the pKa values of the selected acids are listed in Table 6.1).¹⁹

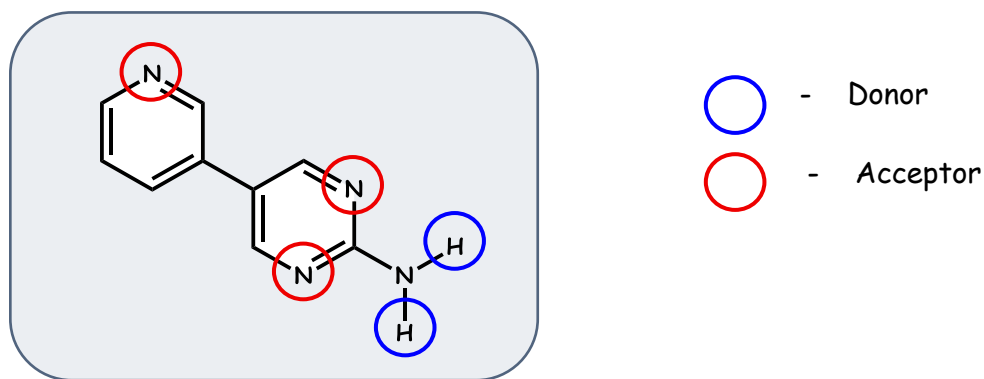


Figure 6.1. Chemical structure of the selected target, 5-(pyridin-3-yl) pyrimidin-2-amine.

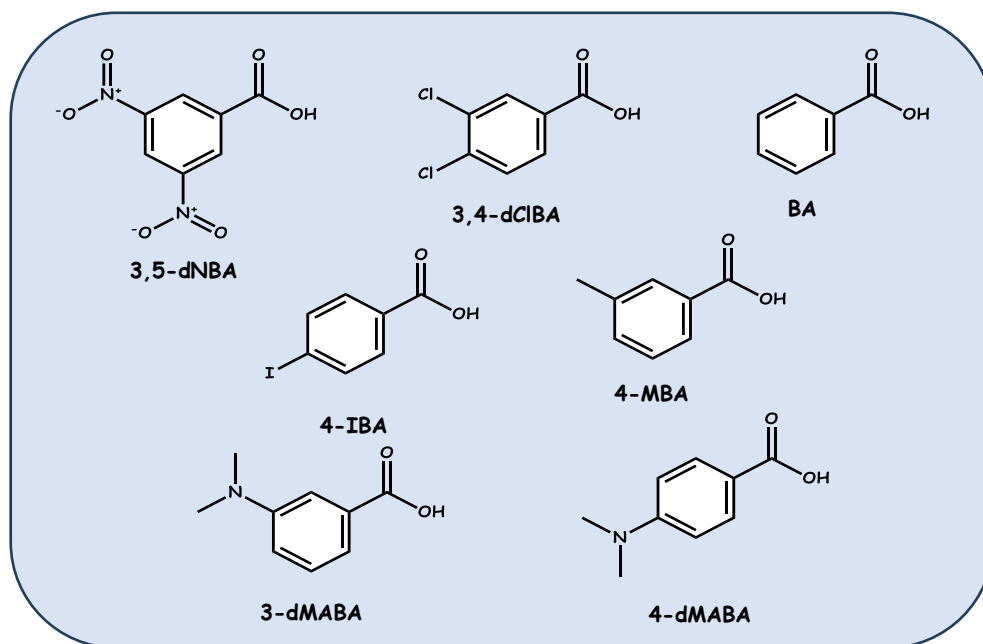


Figure 6.2. Chemical structures of selected coformers.

Table 6.1. pKa values of selected coformers

Coformer	Code	pKa
3,5-dinitrobenzoic acid	3,5-dNBA	2.83
3,4-dichlorobenzoic acid	3,4-dClBA	3.64
4-iodobenzoic acid	4-IBA	3.99
Benzoic acid	BA	4.19
3-methyl benzoic acid	3-MBA	4.27
3-dimethylamino benzoic acid	3-dMABA	4.76
4-dimethylamino BA	4-dMABA	5.20


Weaker acid

6.2 Experimental section

6.2.1 General

All precursors and solvents were purchased from commercial sources and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on Bruker 400 MHz spectrometers.

Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra were recorded using a Nicolet 380 FTIR spectrometer with attenuated total reflection (ATR) and a ZnSe crystal. Electrostatic potentials were calculated with the density functional B3LYP level of theory using the 6-311++G** basis set in vacuum, using Spartan'14 software.

6.2.2 Synthesis of the 5-(pyridin-3-yl) pyrimidin-2-amine (PM)

2-Amino-5-bromopyrimidine (3.83 g, 26.04 mmol), 3-pyridylboronic acid (3.20 g, 26.0 mmol), and sodium carbonate (2.80 g, 26.4 mmol) were added to a round-bottom flask (RB). Acetonitrile (75 mL) and water (75 mL) were added to the RB, and N₂ was bubbled through the mixture for 10 minutes. *Bis*(triphenylphosphine)palladium (II) dichloride (0.72g, 1.04 mmol) was added, and N₂ was bubbled for another five minutes. The apparatus was fitted with a condenser, and the mixture was heated under reflux at 80 °C under a N₂ atmosphere overnight. The product was purified through column chromatography. Yield 74.3 %, M.P: 191-193 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.86 (s, 1H), 8.64 (s, 2H), 8.52 (dd, J=4.9, 1.6 Hz, 1H), 8.04 (d, J=8.1 Hz, 1H), 7.45 (dd, J=8.0, 1H), 6.89 (s, 2H). ¹³C NMR (101 MHz, DMSO-d₆) δ 163.53, 156.67, 148.38, 146.66, 133.30, 131.51, 124.48, 119.68. The pure product was crystallized in ethyl acetate to obtain suitable crystals for SCXRD. Details of the crystallographic experiment are given in Appendix F.

6.2.3 Cocrystal screening by liquid-assisted grinding (LAG)

Liquid-assisted grinding was performed at 1:1 or 1:2 stoichiometric ratios of the target and coformers, with a few drops of methanol added. The IR spectra of the ground mixture and starting materials were compared to confirm the cocrystal formation, and the melting points were recorded. The ground mixtures identified as cocrystals were then allowed to slowly evaporate in suitable solvents for a few weeks to obtain crystals suitable for SCXRD.

6.3 Results

6.3.1 MEP values of the target molecule and cofomers

The calculated molecular electrostatic potentials (MEPs) of the target molecule and acceptor/donor sites of the carboxylic group of cofomers are shown in Figure 6.3 and Table 6.2.

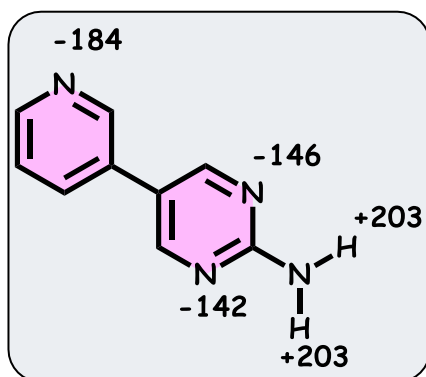


Figure 6.3. MEP values of the target/PM molecule. (kJ/mol).

Table 6.2. MEPs of the acceptor and donor sites of the carboxylic group of cofomers

 Weaker acid	Coformer	Acceptor MEP/kJ/mol	Donor MEP/kJ/mol
	3,5-dNBA	-108	+330
	3,4-dClBA	-142	+284
	4-IBA	-151	+275
	BA	-163	+259
	3-MBA	-168	+258
	3-dMABA	-179	+247
	4-dMABA	-193	+224

6.3.1.1 Correlations of coformer donor and acceptor MEPs with pKa values

The relationships between the donor and acceptor MEPs and the pKa values of the cofomers were plotted, and both show linear relationships (Figures 6.4 and 6.5).

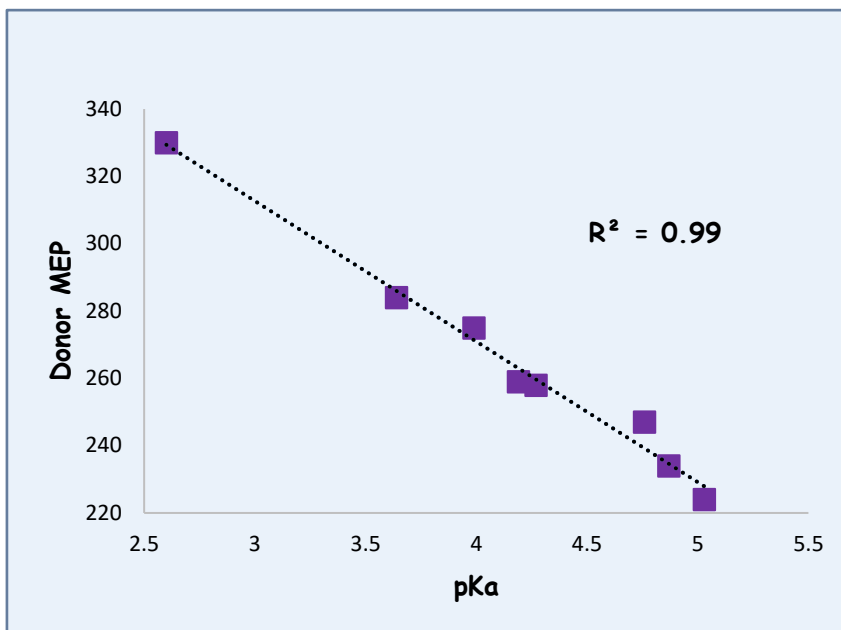


Figure 6.4. The relationship between the donor MEPs and the pKa values of the coformers.

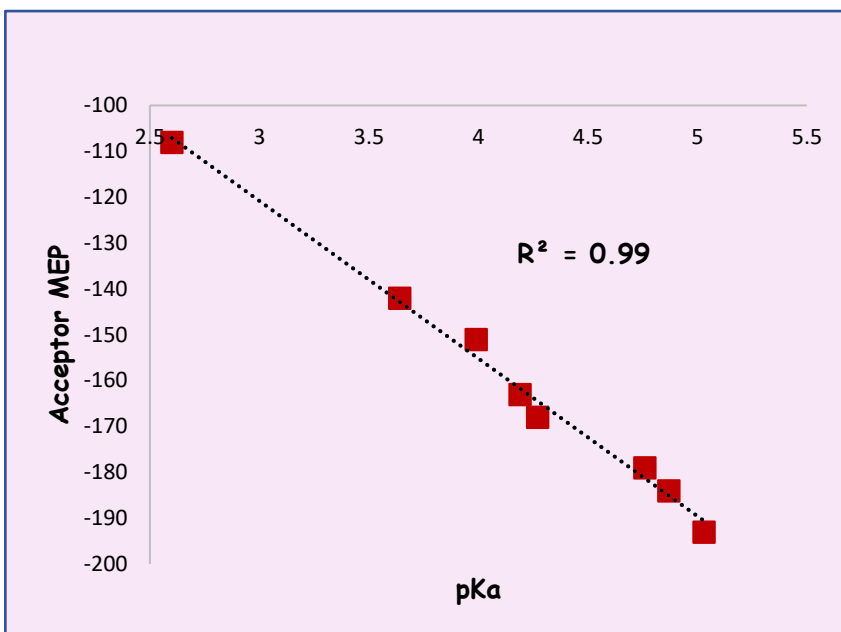


Figure 6.5. The relationship between the acceptor MEPs and the pKa values of the coformers.

6.3.2 FTIR evidence for cocrystal formation

The ground samples were first analyzed by FTIR to determine whether cocrystals had formed. The appearance of new peaks, the disappearance of pre-existing starting material peaks, or peak shifts

were considered as positive indicators of successful cocrystallization. Figure 6.6 shows the FTIR analysis of the target, PM with 3-MBA (1:1), provided to illustrate one of the analyses.

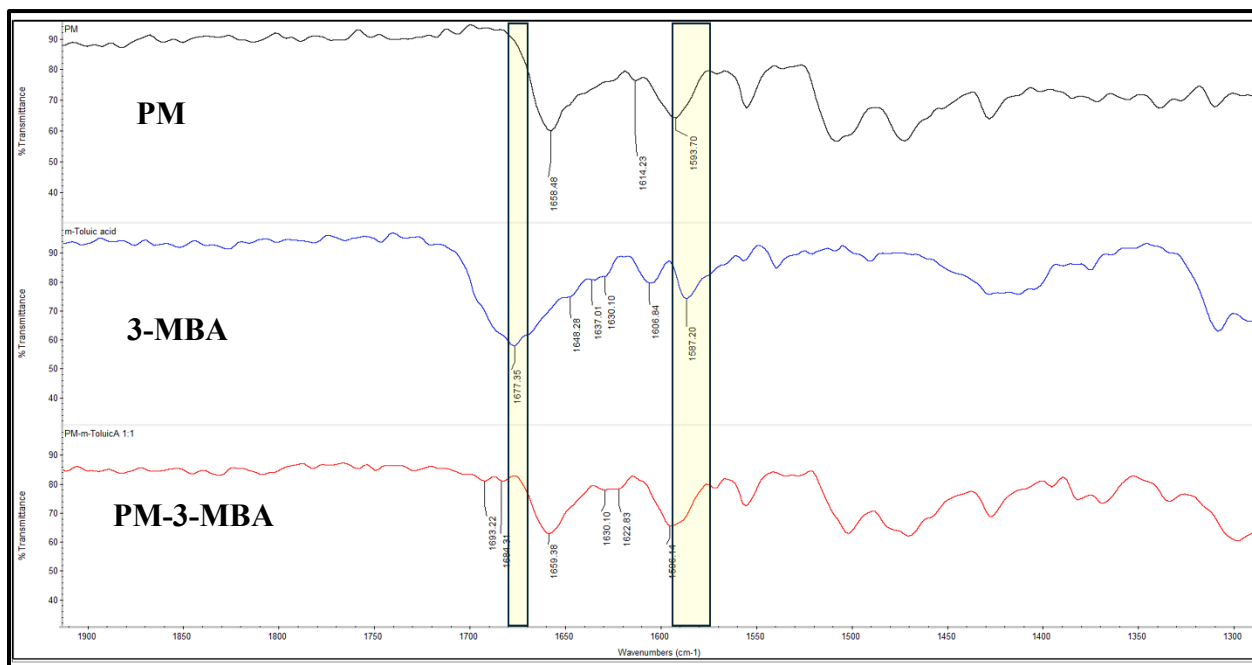


Figure 6.6. FTIR analysis of PM-3-MBA (1:1) ground sample with its starting materials.

If the FTIR spectrum of the 1:2 ground mixture exhibited new peaks, disappearance of pre-existing peaks, or peak shifts compared to the starting materials, and was also different from the spectrum of the 1:1 sample, it was considered evidence of a 1:2 cocrystal formation. All ground samples were analyzed in the same manner, and the resulting data are presented in Table 6.3.

All ground samples produced spectra different from those of their starting materials, and based on these spectra, all samples indicated positive cocrystallization (Table 6.4), although it was sometimes difficult to differentiate between 1:1 and 1:2 solid forms.

Table 6.3. IR frequencies of ground samples

Target N-H bending vibration = 1658 cm ⁻¹	Coformer C=O stretching/cm ⁻¹	1:1 sample/cm ⁻¹	1:2 sample/cm ⁻¹
Coformer			
3,5-dNBA	1698	1657	1658, 1682, 1698
3,4-dClBA	1673	1688,1666	1678,1653
4-IBA	1675	1692, 1667	1667
BA	1681/1670	1689, 1681, 1668,1656	1680,1663
3-MBA	1677	1659	1680
3-dMABA	1670	1676,1657	1685,1674,1662
4-dMABA	1667, 1600	1594, 1658	1659, 1593

Table 6.4. Summary of positive cocrystals based on IR analysis

Coformer	Cocrystal summary	
	1:1	1:2
3,5-dNBA	✓	✓
3,4-dClBA	✓	✓
4-IBA	✓	✓
BA	✓	✓
3-MBA	✓	✓
3-dMABA	✓	✓
4-dMABA	✓	✓

6.3.3 DSC analysis of cocrystals

Products were then analyzed by DSC to further confirm the formation of 1:1 and 1:2 solid forms in the 1:1 and 1:2 ground mixtures. Figure 6.7 shows the DSC analysis of PM and 3-MBA to illustrate how we use DSC to differentiate the formation of different solid forms in 1:1 and 1:2 stoichiometries.

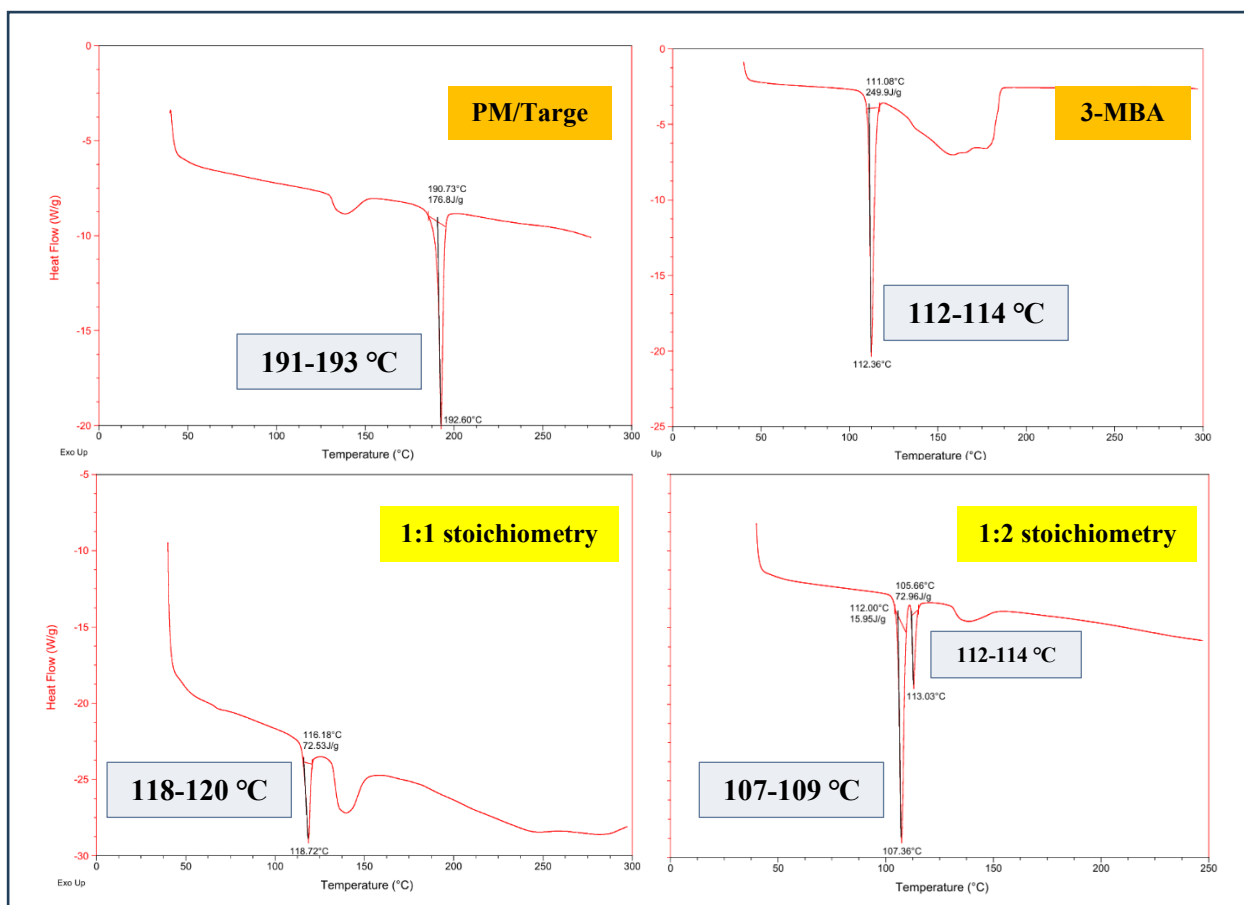


Figure 6.7. DSC analysis of PM-3-MBA (1:1 and 1:2) ground samples with their starting materials.

The target material's melting point is 191-193 °C, and the coformers' melting point is 112-114 °C. The 1:1 stoichiometric grinding mixture produced a product with a melting point of 118-120 °C, whereas the 1:2 stoichiometric grinding mixture yielded a product with a lower melting point of 107-109 °C, indicating the formation of two distinct solid forms in both ground samples. In the 1:2 sample, some unreacted acid is also present. In the same way, we analyzed all ground mixtures, and the melting points are given in Table 6.5.

Table 6.5. Melting points of ground mixtures

Target M.P. = 191-193 °C	Melting point/°C	1:1 ratio	1:2 ratio
Coformer			
3,5-dNBA	205-207	199-201	172-174
3,4-dClBA	204-206	163-164/178-181	178-181
4-IBA	270 -273	171-173/181-183	181-183
BA	121-125	122-124	123-125
3-MBA	112-114	118-120	107-109
3-dMABA	148-150	123-125	123-125
4-dMABA	241-243	156-158	154-157

Based on the DSC results, we were able to reach the following summary (Table 6.6).

Table 6.6. Summary of positive cocrystals based on DSC analysis

Coformer	1:1	1:2
3,5-dNBA	✓	✓
3,4-dClBA	✓	✓
4-IBA	✓	✓
BA	✓	✗
3-MBA	✓	✓
3-dMABA	✓	✗
4-dMABA	✓	✗

6.3.4 SCXRD analysis of target material (PM) and its cocrystals

6.3.4.1 Target material/PM

Crystals of the target material were obtained from ethyl acetate, and the asymmetric unit and the crystal structure, viewed along the crystallographic a-direction, are given in Figure 6.8. The crystals were grown as colorless, plate-shaped monoclinic crystals in the $P2_1$ space group. The asymmetric unit consisted of two target molecules, in which one interacts with the other via an -

N-C-N-H- binding moiety, forming N $\cdots$ H-N/N-H $\cdots$ N dimeric interactions. These interactions propagate to form infinite chains through these dimeric interactions. Notably, the pyridine nitrogen atom does not participate in any intermolecular interactions and remains available as a potential hydrogen-bond acceptor.

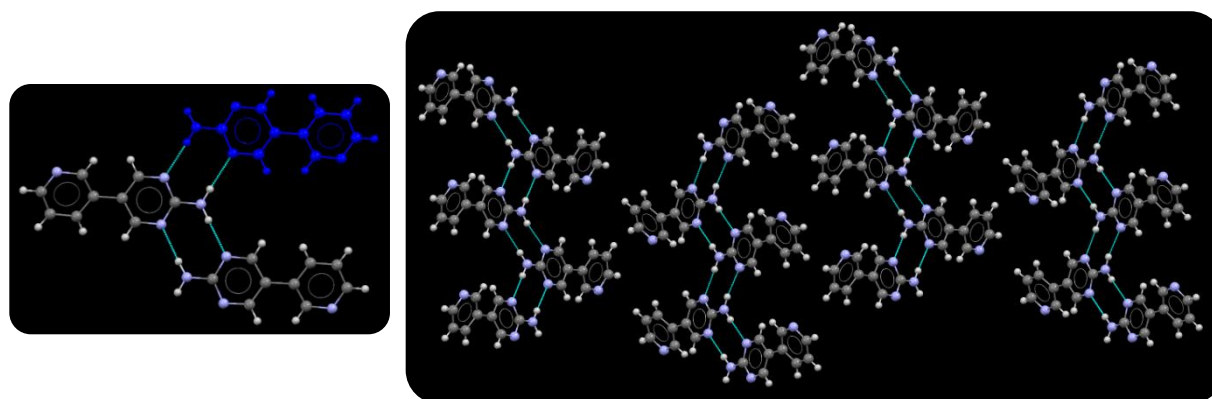


Figure 6.8. The asymmetric unit and a fragment of the crystal structure of 5-(pyridin-3-yl)pyrimidin-2-amine.

6.3.4.2 Cocrystals

After synthesis and analysis of powdered cocrystals, the cocrystals were crystallized from suitable solvents, yielding crystals as shown in Table 6.7. Details of crystallographic experiments are given in Appendix F.

Table 6.7. Solvents used for crystal growth and crystal descriptions

Compound	Solvent/s	Color and morphology
PM-3,5-dNBA (1:1)	Methanol	Colorless, plate
PM-3,4-dClBA (1:1)	Methanol	Colorless, needle
PM-4-IBA (1:1) - PI	Methanol + Ethyl acetate	Colorless, plate
PM-4-IBA (1:1) - PII	Methanol + Ethyl acetate	Colorless, irregular
PM-BA (1:1)	Methanol	Colorless, plate
PM-3-MBA (1:1)	Methanol	Colorless, plate
PM-3-MBA (1:2)	Methanol	Colorless, plate

PM-3-dMABA (1:1)	Methanol	Light yellow, plate
PM-3-dMABA (1:2)	Methanol	Light yellow, irregular

6.3.4.2.1 Crystal structure of PM-3,5-dNBA (1:1)

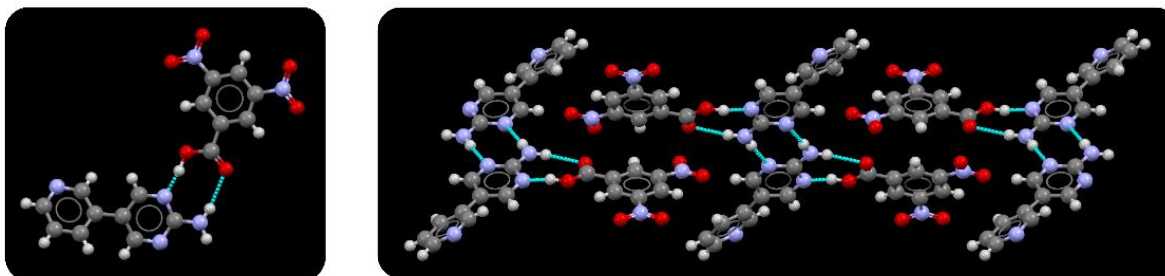


Figure 6.9. The asymmetric unit and a fragment of the crystal structure of PM-3,5-dNBA (1:1).

Crystallization from both the 1:1 and 1:2 ground mixtures yielded the same 1:1 stoichiometric cocrystal, although mechanochemical grinding produced products with both 1:1 and 1:2 stoichiometries. This preference may arise because the 1:1 cocrystal nucleates more readily in solution and continues to grow, suggesting it is the kinetic product. Once nucleation occurs, the solution crystallizes in the 1:1 form, even in the presence of excess coformer. In the crystal, PM displayed $\text{N-H}\cdots\text{O}=\text{C}/\text{O-H}\cdots\text{N}$ dimeric interactions with 3,5-dNBA, and the acceptor site on the pyridine ring was not involved in any intermolecular interaction (Figure 6.9).

6.3.4.2.2 Crystal structure of PM-3,4-dClBA (1:1)

Two slow evaporation crystallization experiments were carried out using 1:1 and 1:2 stoichiometric ratios. From the 1:1 solution sample, a 1:1 stoichiometric cocrystal was successfully obtained, whereas the 1:2 sample did not produce crystals suitable for SCXRD. However, mechanochemical grinding experiments indicated positive cocrystal formation for both stoichiometries. In the crystal structure, PM formed $\text{N-H}\cdots\text{O}=\text{C} / \text{O-H}\cdots\text{N}$ dimeric interactions

with 3,4-dClBA, similar to those observed in the PM-3,5-dNBA cocrystal. The acceptor site on the pyridine ring was not involved in any intermolecular interactions (Figure 6.10).

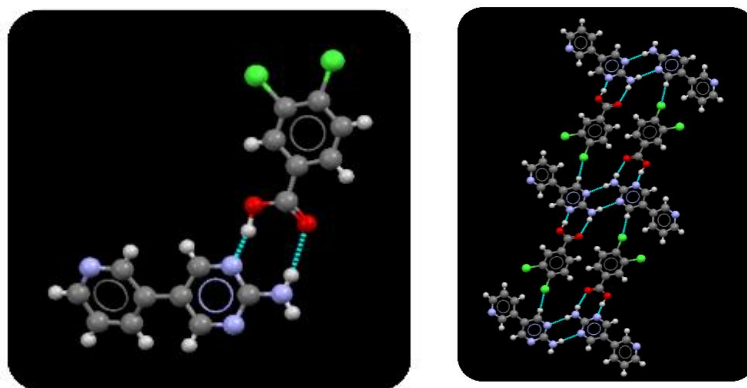


Figure 6.10. The asymmetric unit and a fragment of the crystal structure of PM-3,4-dClBA (1:1).

6.3.4.2.3 Crystal structures of PM-4-IBA (1:1)

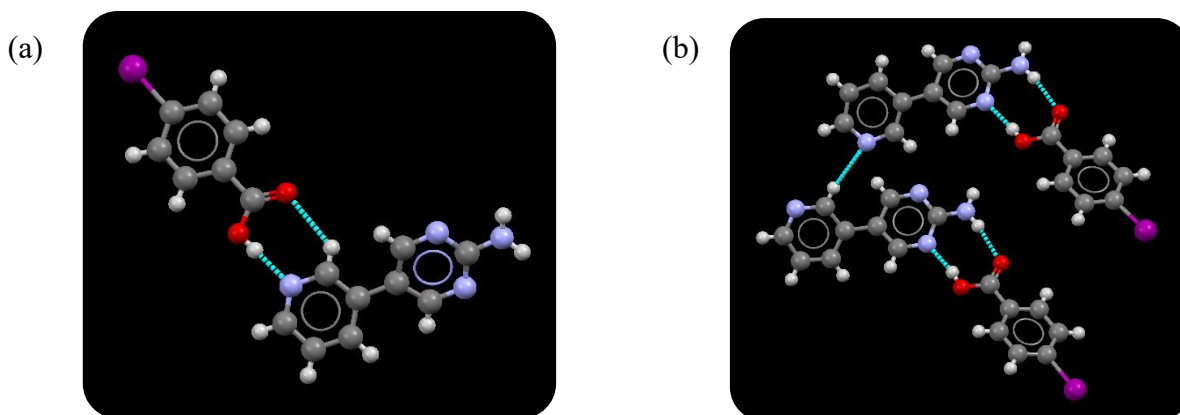


Figure 6.11. The asymmetric units of the crystal structures of (a) PM-4-IBA (1:1) form I, (b) PM-4-IBA (1:1) form II.

Crystal growth with 4-IBA by slow evaporation yielded two polymorphs with 1:1 stoichiometry in the $P2_1/c$ and $I2$ space groups. From the 1:1 mixture, a 1:1 cocrystal (polymorph I) was obtained. In contrast, slow evaporation of the 1:2 mixture produced the same 1:1 cocrystal (polymorph I)

along with an additional polymorph, which also exhibited a 1:1 stoichiometry. No 1:2 cocrystal was observed.

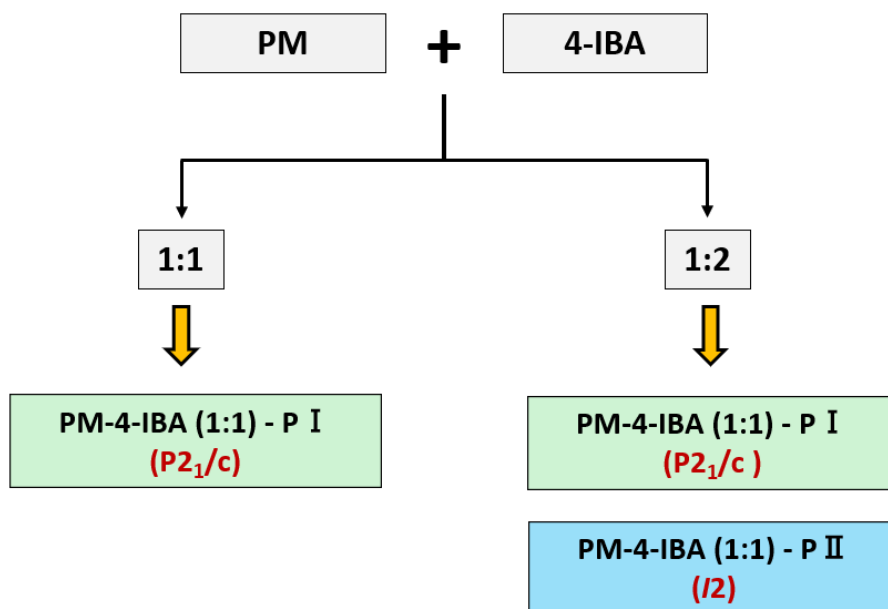


Figure 6.12. Schematic representation of cocrystal formation observed in the 1:1 and 1:2 slow evaporation samples.

The main difference between polymorphs was the location of the coformer interaction. In form I, the coformer interacted with the pyridine nitrogen atom on the second ring, which was not involved in the previously discussed cocrystals with 3,5-dNBA or 3,4-dClBA. In the asymmetric unit, there was only one target and one coformer molecule, and C-H $\cdots$ O=C/O-H $\cdots$ N dimeric interactions between target and coformer were discovered (Figure 6.11, (a)). The pre-existing homomeric interactions are not disturbed (Figure 6.12, (a)).

In contrast, in the second polymorph, the coformer interacted with the -N-C-N-H- binding site, replacing the target's homomeric interactions, forming N-H $\cdots$ O=C/O-H $\cdots$ N dimeric interactions (Figure 6.11, (b)). Within the asymmetric unit, there were two target molecules and two coformer molecules, all of which maintained a 1:1 stoichiometry.

6.3.4.2.4 Crystal structure of PM-BA (1:1)

Crystal growth by slow evaporation of the 1:1 solution produced a 1:1 stoichiometric cocrystal. Similarly, slow evaporation of the 1:2 solution also yielded the same 1:1 cocrystal, and no 1:2 cocrystal was observed. In the crystal structure, the target molecule and the coformer interact through the available pyridine nitrogen atom, forming $\text{C-H}\cdots\text{O}=\text{C}/\text{O-H}\cdots\text{N}$ dimeric interactions (Figure 6.13).

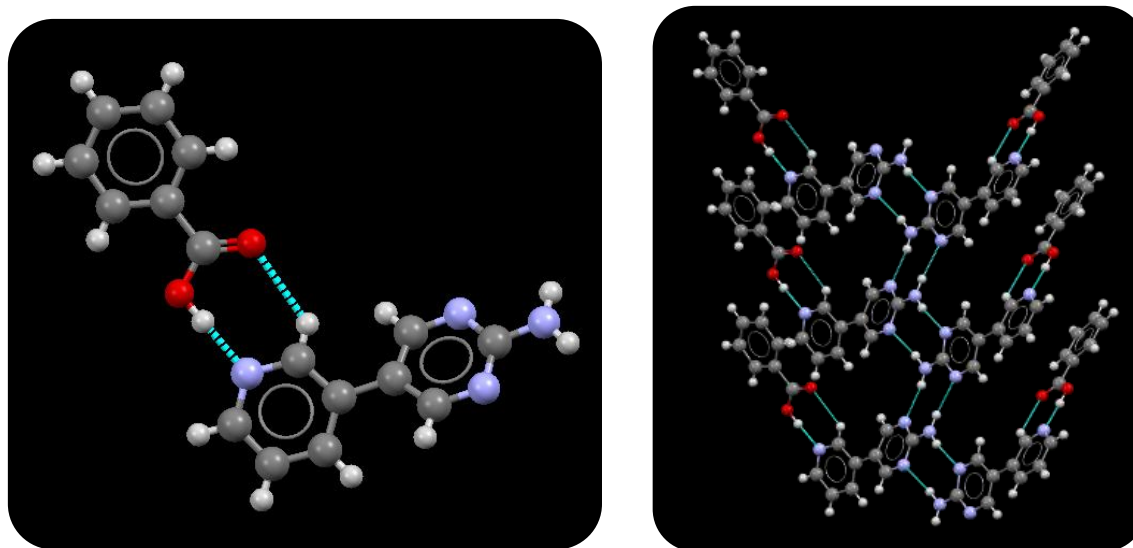


Figure 6.13. The asymmetric unit and a fragment of the crystal structure of PM-BA (1:1).

6.3.4.2.5 Crystal structures of PM-3-MBA (1:1) and PM-3-MBA (1:2)

Crystal growth with 3-MBA revealed the formation of both 1:1 and 1:2 cocrystals by slow evaporation. In the 1:1 stoichiometric form, the target molecule interacts with the coformer through the available pyridine nitrogen atom, forming $\text{O-H}\cdots\text{N}/\text{C-H}\cdots\text{O}=\text{C}$ dimeric interactions. In the 1:2 stoichiometric form, one target molecule interacts with two coformer molecules; one coformer engages the pyridine nitrogen atom by forming a single $\text{N}\cdots\text{H-O}$ interaction, and while the other coformer molecule interacts with the $-\text{N-C-N-H}-$ moiety, forming $\text{N-H}\cdots\text{O}=\text{C}/\text{O-H}\cdots\text{N}$ dimeric interactions. Although the pyridine nitrogen atom is involved in both structures, the way it interacts

differs slightly. In the 1:2 stoichiometric cocrystal, the coformer is flipped, interacting in the opposite direction, forming a single $\text{N}\cdots\text{H}-\text{O}$ interaction rather than an $\text{O}-\text{H}\cdots\text{N}/\text{C}-\text{H}\cdots\text{O}=\text{C}$ dimer (Figure 6.14).

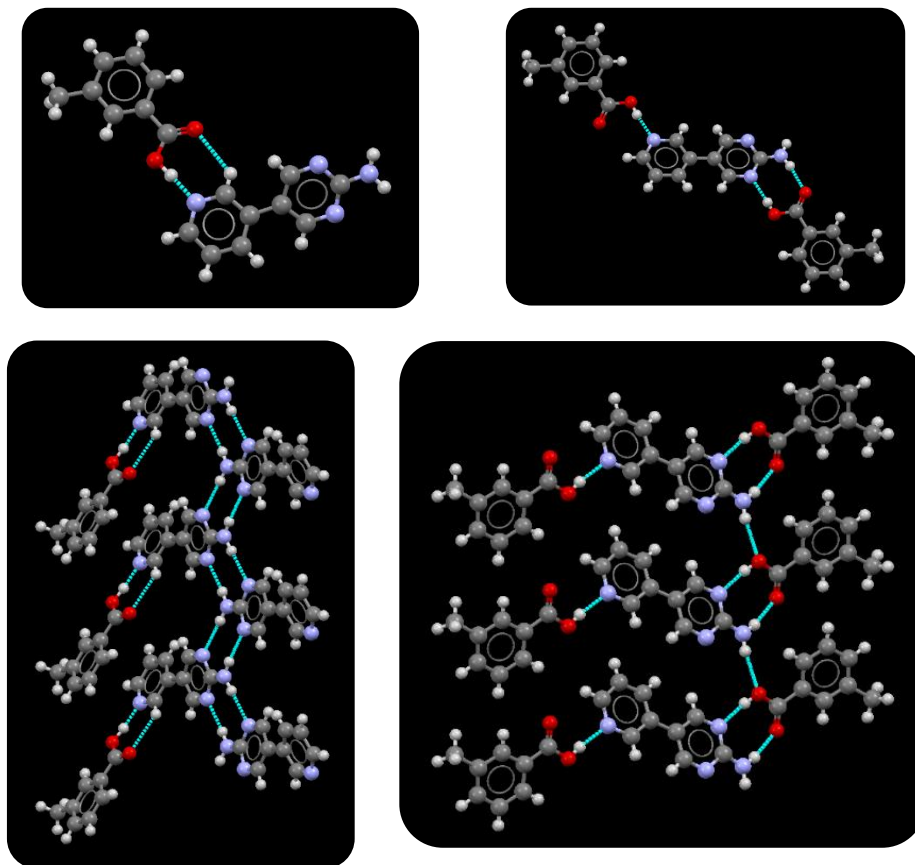


Figure 6.14. The asymmetric unit and fragments of the crystal structures of PM-3-MBA (1:1 and 1:2).

6.3.4.2.6 Crystal structures of PM-3-dMABA (1:1) and PM-3-dMABA (1:2)

The crystal structures of PM-3-dMABA exhibit the same interaction patterns as those of PM-3-MBA cocrystals and produced cocrystals in both 1:1 and 1:2 stoichiometric ratios. In the 1:1 cocrystal, the target molecule interacts through the available pyridine nitrogen atom, and in the 1:2 cocrystal, one coformer interacts with the pyridine nitrogen atom, while the second coformer interacts with the $-\text{N}-\text{C}-\text{N}-\text{H}-$ moiety. Similar to PM-3-MBA. in the 1:2 cocrystal, the coformer

molecule occupying the pyridine nitrogen atom is flipped compared to the 1:1 cocrystal, forming a single $\text{N}\cdots\text{H}-\text{O}$ interaction rather than an $\text{O}-\text{H}\cdots\text{N}/\text{C}-\text{H}\cdots\text{O}=\text{C}$ dimer (Figure 6.14).

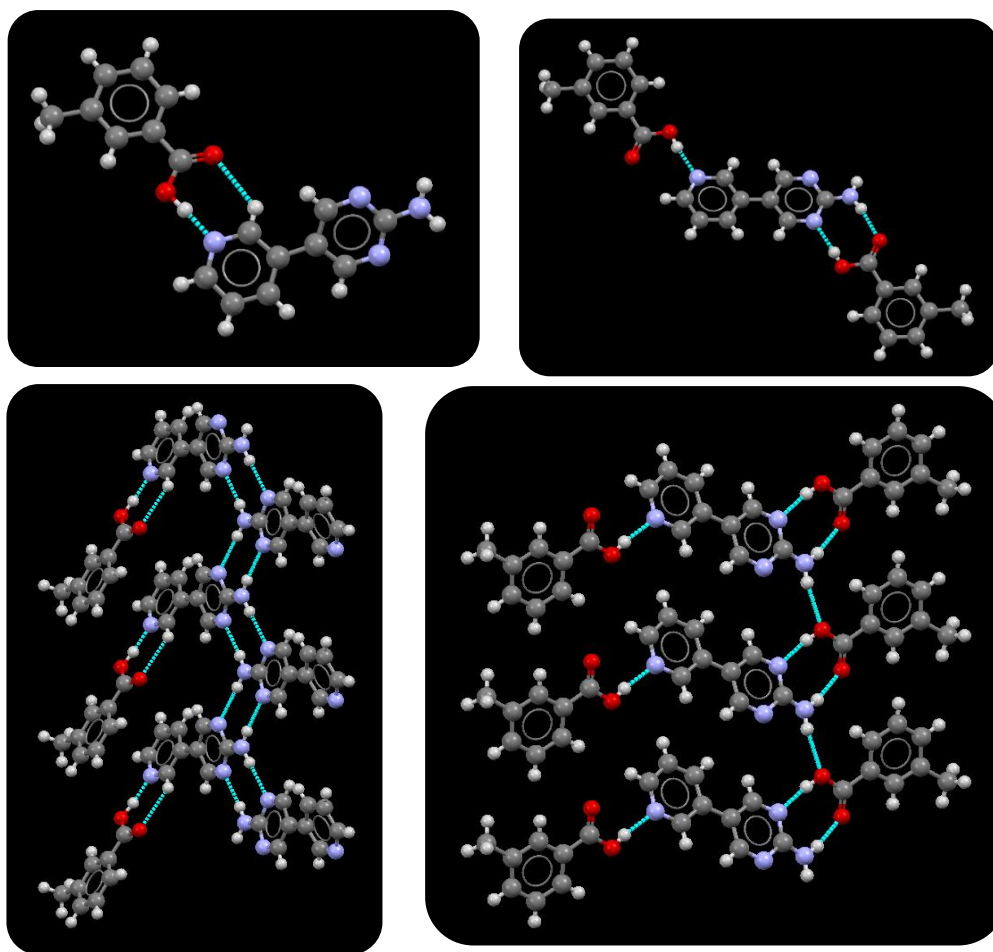


Figure 6.15. The asymmetric unit and fragments of the crystal structures of PM-3-dMABA (1:1 and PM-3-dMABA (1:2).

No crystals suitable for SCXRD were found for PM-4-dMABA in either 1:1 or 1:2 stoichiometric mixtures, although IR and DSC results suggested the formation of a cocrystal.

The summary of cocrystals that yielded suitable cocrystals is given in Table 6.8.

Table 6.8. Summary of cocrystal formation in solution

Cofomer	1:1	1:2
3,5-dNBA	✓	✗
3,4-dCIBA	✓	✗

4-IBA	✓	✗
BA	✓	✗
3-MBA	✓	✓
3-dMABA	✓	✓
4-dMABA	✗	✗

6.4 Discussion

In this study, we explored whether we could achieve stoichiometric control of cocrystals through mechanochemical grinding using a target with multiple donor and acceptor sites and selected coformers with different acidities. The target contains three potential acceptor sites and two donor sites (Figure 6.16(a)) and, overall, three possible binding sites (Figure 6.16(b)). The two N-H donor sites exhibit comparable ‘strengths’ or competitiveness, as indicated by molecular electrostatic potential (MEP) values. Among the acceptor sites, the pyridine nitrogen atom had the most negative MEP value, which suggests that it is the strongest acceptor. The two acceptor sites on the pyrimidine ring are slightly less negative, indicating a weaker acceptor strength relative to the pyridine nitrogen atom. The donor-acceptor MEP values of the carboxylic group of coformers vs the pK_a values of the coformers revealed a linear correlation between donor/acceptor strength and acidity.

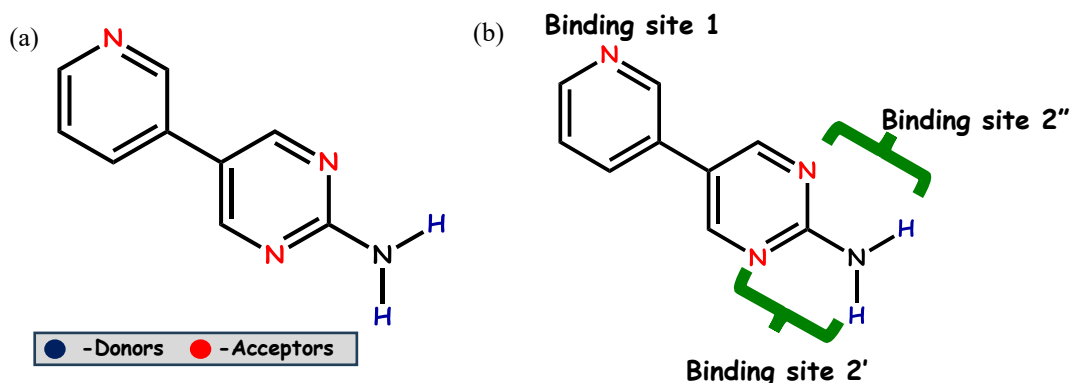


Figure 6.16. Two schematics showing (a) donor and acceptor sites of the target molecule, and (b) possible binding sites of the target molecule.

Solid-state grinding experiments indicated that cocrystals could form in both 1:1 and 1:2 stoichiometric ratios by systematically varying the coformer amount, as indicated by IR and DSC results. IR spectroscopy, however, provided limited clarity due to overlapping bands and multiple spectral shifts, which made it difficult to differentiate between the two stoichiometries. In contrast, melting point analysis confirmed the formation of distinct compounds, with separate melting points observed for the 1:1 and 1:2 mixtures.

Solution-based crystallization experiments yielded mixed results, unlike mechanochemical grinding, which depends on several factors, including solubility, solvation, and nucleation. Some combinations formed cocrystals consistent with the mechanochemical grinding, whereas others did not (Figure 6.17).

A mechanochemical grinding study by Jones and co-workers of 1:1 and 1:2 mixtures of nicotinamide and suberic acid reported that the 1:1 grinding mixture produced only the 1:1 cocrystal, whereas the 1:2 grinding mixture initially formed the 1:1 cocrystal but gradually converted to the 1:2 cocrystal upon extended grinding.¹⁷ This behavior suggested that grinding of 1:2 stoichiometry first produces the 1:1 kinetically favored product and then transforms into the thermodynamically more stable 1:2 form. However, the interconversion is relatively fast if the difference in stability between the two stoichiometric variations is not very significant.

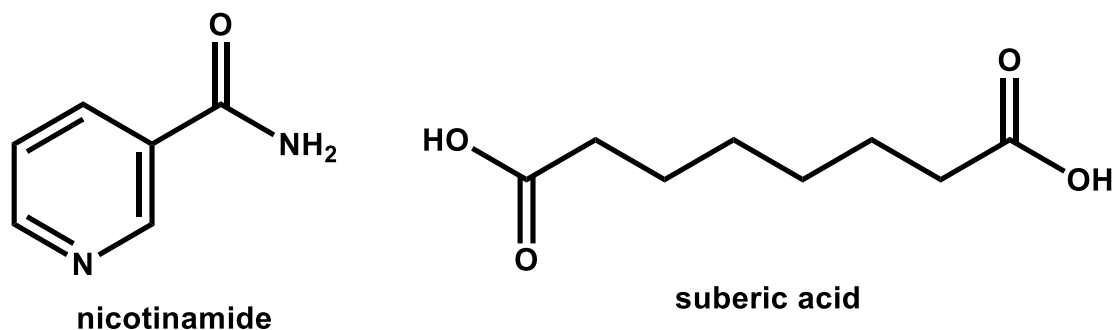


Figure 6.17. Schematic of nicotinamide and suberic acid.

In our study, mechanochemical grinding of a 1:1 mixture consistently yielded the 1:1 cocrystal, while 1:2 mixtures predominantly produced the 1:2 cocrystal under the same conditions. This observation suggests only a small difference in stability between the two heteromeric compounds. In contrast, slow evaporation from solvents, both in 1:1 and 1:2 grinding mixtures, predominantly yielded 1:1 cocrystals, further supporting the interpretation that the 1:1 form may be the kinetically favored product. Accessing the corresponding thermodynamic 1:2 cocrystal may therefore require alternative approaches, such as slurry experiments.²⁰ This behavior may also be interpreted in the context of Ostwald's rule of stages, which suggests that crystallization can proceed through metastable phases before reaching the most stable form.²¹ This can also be rationalized by the competition between supramolecular synthons of different strengths. The initial appearance of the 1:1 form likely results from the rapid establishment of the strongest available intermolecular interactions, followed by a transformation to the thermodynamically more stable 1:2 form. This would involve rearrangement of these interactions to produce the most stable packing arrangement.^{17,22} However, synthon energies were not included in the present study and will be explored in the future to investigate the relative stability of these compounds.

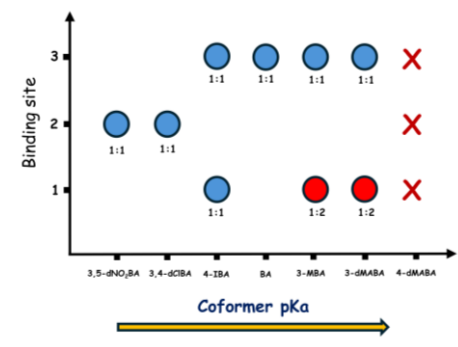


Figure 6.18. A summary of cocrystal stoichiometries obtained from slow evaporation.

A detailed analysis of single-crystal structures revealed that the hydrogen-bond capability of the coformer may also affect the crystallization outcome. The strongest acids, 3,5-dNBA and 3,4-

dClBA, formed exclusively 1:1 cocrystals, and both showed similar bonding patterns: heteromeric dimeric interactions with the pyrimidine sites, effectively disrupting pre-existing target-target interactions. The pyridine nitrogen atom, despite being a strong acceptor, remained unengaged, indicating that strong acids may favor the most stable two-point interactions over a single strong interaction. Intermediate acids, such as 4-IBA and BA, formed only 1:1 stoichiometry cocrystals, interacting primarily with the available pyridine nitrogen atom, which does not require breaking or replacing a pre-existing target-target motif. However, 4-IBA exhibited polymorphism, and in the second polymorph, the coformer interacted with the pyrimidine site, breaking pre-existing target interactions.

Weaker acids, such as 3-MBA and 3-dMABA, produced both 1:1 and 1:2 stoichiometries. In 1:1 complexes, the coformer interacts with the available pyridine nitrogen atom, requiring no competition or energy to break any target-target interactions. In 1:2 complexes, a second coformer molecule disrupted target-target interactions and engaged with the binding site 1. Very weak acids, such as 4-dMABA, failed to form cocrystals from solution (Figure 6.18).

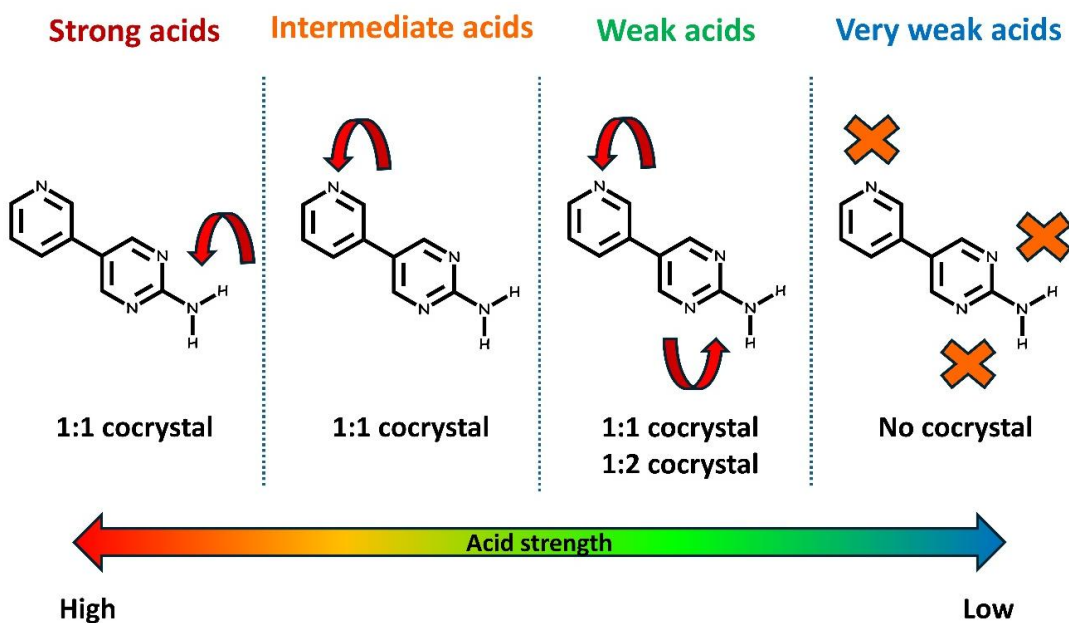


Figure 6.19. A schematic showing target binding sites of coformers with different strengths.

6.5 Conclusions

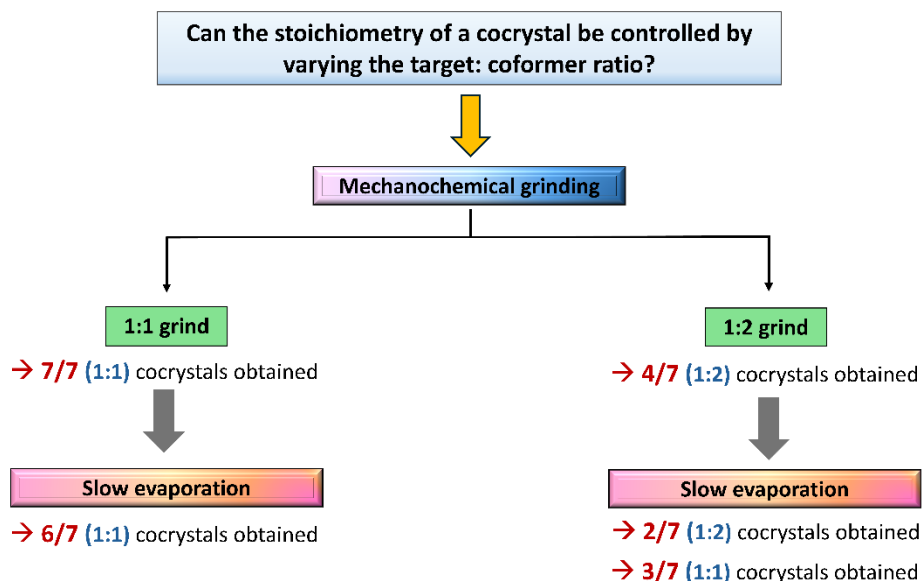


Figure 6.20. Roadmap of the key findings.

In this work, we have demonstrated that stoichiometric control in a cocystal can be achieved through mechanochemical grinding by adjusting the ratios of reactants. Crystal growth experiments further revealed that stoichiometric outcomes are strongly dependent on solubility, solvation, nucleation rates, and coformer strength, and in particular, the study suggests that the 1:1 stoichiometric cocystals may be the kinetic product. Strong coformers/acids preferentially formed stable 1:1 cocystals. In contrast, weaker acids formed both 1:1 and 1:2 stoichiometries. Very weak acids failed to form cocystals in solution, underscoring the importance of coformer strength. Mechanochemical grinding can be an effective strategy for controlling cocystal stoichiometry. However, our results also underscore that cocystal nucleation and crystallization outcomes reflect a balance between thermodynamic stability and kinetic accessibility.

6.6 References

1. Guo, M.; Sun, X.; Chen, J.; Cai, T. Pharmaceutical Cocystals: A Review of Preparations, Physicochemical Properties and Applications. *Acta Pharmaceutica Sinica B* **2021**, *11* (8).

2. Bolla, G.; Sarma, B.; Nangia, A. K. Crystal Engineering of Pharmaceutical Cocrystals in the Discovery and Development of Improved Drugs. *Chemical Reviews* **2022**, *122* (13), 11514–11603.
3. Rissanen, K. *Hot Topics in Crystal Engineering*; Elsevier, 2021.
4. Duggirala, N. K.; Perry, M. L.; Almarsson, Ö.; Zaworotko, M. J. Pharmaceutical Cocrystals: Along the Path to Improved Medicines. *Chemical Communications* **2016**, *52* (4), 640–655.
5. Singh, M.; Barua, H.; Vaskuri G.S. Sainaga Jyothi; Dhondale, M. R.; Nambiar, A. G.; Ashish Kumar Agrawal; Kumar, P.; Shastri, N. R.; Kumar, D. Cocrystals by Design: A Rational Coformer Selection Approach for Tackling the API Problems. *Pharmaceutics* **2023**, *15* (4), 1161–1161.
6. Saha, S.; Desiraju, G. R. Acid···Amide Supramolecular Synthon in Cocrystals: From Spectroscopic Detection to Property Engineering. *Journal of the American Chemical Society* **2018**, *140* (20), 6361–6373.
7. Friščić, T.; Jones, W. Cocrystal Architecture and Properties: Design and Building of Chiral and Racemic Structures by Solid–Solid Reactions. *Faraday Discussions* **2007**, *136*, 167.
8. Li, Z.; Matzger, A. J. Influence of Coformer Stoichiometric Ratio on Pharmaceutical Cocrystal Dissolution: Three Cocrystals of Carbamazepine/4-Aminobenzoic Acid. *Molecular Pharmaceutics* **2016**, *13* (3), 990–995.
9. Mishra, M.; Agrawal, S.; Bahadur, P.; Tiwari, S. Effect of Stoichiometry upon the Characteristics of Quercetin-Arginine Cocrystals Formulated through Solution Crystallization. *Drug Development and Industrial Pharmacy* **2024**, *50* (2), 163–172.
10. Dhibar, M.; Chakraborty, S.; Basak, S.; Pattanayak, P.; Chatterjee, T.; Ghosh, B.; Raafat, M.; Abourehab, M. A. S. Critical Analysis and Optimization of Stoichiometric Ratio of Drug-Coformer on Cocrystal Design: Molecular Docking, in Vitro and in Vivo Assessment. *Pharmaceutics* **2023**, *16* (2), 284.
11. Mohamad, K.; Hamizah Mohd Zaki; Nornizar Anuar; Mohammad Noor Jalil. Synthesis, Characterization and Morphological Study of Nicotinamide and *P*-Coumaric Acid Cocrystal. *Indonesian Journal of Chemistry* **2020**, *20* (3), 661–661.
12. Saikia, B.; Pathak, D.; Sarma, B. Variable Stoichiometry Cocrystals: Occurrence and Significance. *CrystEngComm* **2021**, *23* (26), 4583–4606.
13. Gao, J.; Zhai, H.; Hu, P.; Jiang, H. The Stoichiometry of TCNQ-Based Organic Charge-Transfer Cocrystals. *Crystals* **2020**, *10* (11), 993.
14. Jayasankar, A.; Reddy, L. S.; Bethune, S. J.; Rodríguez-Hornedo, N. Role of Cocrystal and Solution Chemistry on the Formation and Stability of Cocrystals with Different Stoichiometry. *Crystal Growth & Design* **2009**, *9* (2), 889–897.

15. Leyssens, T.; Springuel, G.; Montis, R.; Candoni, N.; Veesler, S. Importance of Solvent Selection for Stoichiometrically Diverse Cocrystal Systems: Caffeine/Maleic Acid 1:1 and 2:1 Cocrystals. *Crystal Growth & Design* **2012**, *12* (3), 1520–1530.
16. Friščić, T.; Jones, W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. *Crystal Growth & Design* **2009**, *9* (3), 1621–1637.
17. Karki, S.; Friščić, T.; Jones, W. Control and Interconversion of Cocrystal Stoichiometry in Grinding: Stepwise Mechanism for the Formation of a Hydrogen-Bonded Cocrystal. *CrystEngComm* **2009**, *11* (3), 470–481.
18. Kulkarni, C.; Wood, C.; Kelly, A. L.; Gough, T.; Blagden, N.; Paradkar, A. Stoichiometric Control of Co-Crystal Formation by Solvent Free Continuous Co-Crystallization (SFCC). *Crystal Growth & Design* **2015**, *15* (12), 5648–5651.
19. R. Williams, pKa data compiled by R. Williams. [Online accessed on]. <http://www.chem.wisc.edu/areas/organic/index-chem.htm>. 2011. [11/20/2025].
20. Haskins, M. M.; Zaworotko, M. J. Screening and Preparation of Cocrystals: A Comparative Study of Mechanochemistry vs Slurry Methods. *Crystal Growth & Design* **2021**, *21* (7), 4141–4150.
21. Burley, J. C.; Duer, M. J.; Stein, R. S.; Vrcelj, R. M. Enforcing Ostwald's Rule of Stages: Isolation of Paracetamol Forms III and II. *European Journal of Pharmaceutical Sciences* **2007**, *31* (5), 271–276.
22. Cinčić, D.; Friščić, T.; Jones, W. A Stepwise Mechanism for the Mechanochemical Synthesis of Halogen-Bonded Cocrystal Architectures. *Journal of the American Chemical Society* **2008**, *130* (24), 7524–7525.

Chapter 7 - Can the odd-even effect be used to dial in the structure-property relationship of acetylated 2-aminopyrazine derivatives?

7.1 Introduction

So far, our studies have focused on how structural features influence homomeric and heteromeric interactions in the solid state. Building on this understanding, the present chapter explores how structural control can be used to fine-tune physical properties of these materials.

The arrangement of molecules in the solid-state plays a crucial role in determining the physical properties of organic materials.¹⁻⁵ Even small variations in molecular structure can make a significant difference in packing, intermolecular interactions, and resulting physical properties.⁶⁻

¹⁰ Systematic variations in alkyl chain lengths within homologue series have been shown to display an odd-even effect, where compounds with even numbers of carbon atoms adopt more favorable alignments of terminal functional groups and thus more efficient intermolecular interactions.¹¹⁻¹⁴

Such molecules typically exhibit higher melting points than their odd-numbered counterparts, which often display conformational mismatches that disrupt optimal packing and reduce thermal stability. This effect has been extensively studied in *n*-alkanes, diols, dithiols, diamines, dicarboxylic acids, and *n*-alkyl carboxylic acids, demonstrating the importance of carbon chain length as a determinant of solid-state properties.¹⁵⁻²⁰ Across many organic materials, the odd-even effects have been used to engineer specific and tailor-made charge-transport²¹⁻²⁶, interfacial²⁷⁻³⁰, and thermal properties³¹⁻³⁵ of solid-state materials.

Taken together, these studies demonstrate that the number of carbon atoms in alkyl chains, especially the odd or even arrangement, is an important determinant of solid-state packing, affecting density and melting behavior, resulting from conformational strain and well-defined intermolecular interactions. Inspired by these results, we decided to explore if it would be possible

to covalently attach a range of odd-even alkyl chains onto an existing molecular scaffolding in order to impart specific thermal properties on the resulting compounds. In addition, we also wanted to establish if a decreasing degree of polarity on a molecular level could be translated into increased resistance to hygroscopicity on a macroscopic bulk level. We targeted a family of 2-aminopyrazine in the expectation that a commonly observed hydrogen-bonded dimer^{36,37} would provide the necessary core with considerable structural consistency,

7.2 Experimental section

7.2.1 General

All precursors and solvents were purchased from commercial sources and used without further purification. ¹H NMR spectra and ¹³C NMR spectra were recorded on a Bruker 400 MHz and 600 MHz spectrometers. Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter, and thermogravimetric analyses were conducted on a TA Instruments TGA Q50 instrument. IR spectra were recorded using a Nicolet 380 FTIR spectrometer with an attenuated total reflection (ATR) technique and a ZnSe crystal. PXRD patterns were collected using a Bruker X-ray powder diffractometer equipped with CuK_α radiation, operated at 30 kV and 15 mA. Single-crystal X-ray diffraction (SCXRD) data were collected on a Rigaku XtaLAB Synergy-S single-crystal X-ray diffractometer equipped with CuK_α radiation.

7.2.2 Synthesis of the PZ Series

The syntheses of N-(pyrazin-2-yl)alkylamides were carried out according to a literature procedure.³⁹

7.2.2.1 Synthesis of *N*-(pyrazin-2-yl)acetamide (PZ2)

A solution of 2-aminopyrazine (1.00 g, 11.0 mmol) in acetic anhydride (1.99 mL, 22.0 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The resulting precipitate was filtered off,

and the reaction contents were purified by column chromatography using a hexane/ethyl acetate (4:6) mixture as the eluant to isolate the pure product. Yield: 59.7 %, mp: 120-123 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 9.31 (s, 1H), 8.38 (dd, *J* = 3286.4, 2.6, 1.5 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 2.13 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 170.06, 149.27, 143.04, 139.99, 136.62, 24.12.

7.2.2.2 Synthesis of *N*-(pyrazin-2-yl)propionamide (PZ3)

A solution of 2-aminopyrazine (1.00 g, 11.0 mmol) in propionic anhydride (2.68 mL, 22.0 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water and dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 72.9 %, mp: 109-111 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.34 (s, 1H), 8.37 (dd, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 2.44 (q, *J* = 7.6 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 173.61, 149.35, 142.99, 139.87, 136.63, 29.51, 9.67.

7.2.2.3 Synthesis of *N*-(pyrazin-2-yl)butyramide (PZ4)

A solution of 2-aminopyrazine (1.00 g, 11.0 mmol) in butyric anhydride (3.32 mL, 22.0 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The resulting precipitate was filtered off, and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water and dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 61.5%, mp: 102-104 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.73 (s, 1H), 9.34 (s, 1H), 8.38 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.61 (h, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.84, 149.30, 143.04, 139.95, 136.66, 38.13, 18.69, 14.01.

7.2.2.4 Synthesis of *N*-(pyrazin-2-yl)pentanamide (PZ5)

A solution of 2-aminopyrazine (1.00 g, 11.0 mmol) in pentanoic anhydride (4.22 mL, 22.0 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water and dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 60.2%, mp: 87-90 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.73 (s, 1H), 9.34 (s, 1H), 8.38 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.58 (p, *J* = 7.5 Hz, 2H), 1.32 (h, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.95, 149.32, 143.03, 139.94, 136.66, 35.95, 27.36, 22.20, 14.19.

7.2.2.5 Synthesis of *N*-(pyrazin-2-yl)hexanamide (PZ6)

A solution of 2-aminopyrazine (1.00 g, 11.0 mmol) in hexanoic anhydride (4.86 mL, 22.0 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was filtered off, and the reaction contents were extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, and water and dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to isolate the pure product. Yield: 77.4% , mp: 95-98 °C. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 9.34 (s, 1H), 8.37 (d, *J* = 1.5 Hz, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.59 (p, *J* = 7.3 Hz, 2H), 1.30 - 1.25 (m, 4H), 0.86 (t, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.97, 149.31, 143.01, 139.92, 136.65, 36.20, 31.25, 24.92, 22.34, 14.28.

7.2.2.6 Synthesis of *N*-(pyrazin-2-yl)heptanamide (PZ7)

A solution of 2-aminopyrazine (0.50 g, 5.26 mmol) in heptanoic anhydride (2.77 mL, 10.52 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was washed

off with hexane to get the pure product. Yield: 71.6 %, mp: 91-93 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.34 (d, *J* = 1.5 Hz, 1H), 8.38 (dd, *J* = 1.9 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.59 (p, *J* = 7.2 Hz, 2H), 1.36 - 1.25 (m, 6H), 0.85 (t, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.92, 149.34, 143.00, 139.92, 136.68, 36.25, 31.47, 28.71, 25.20, 22.43, 14.38.

7.2.2.7 Synthesis of *N*-(pyrazin-2-yl)octanamide (PZ8)

A solution of 2-aminopyrazine (0.50 g, 5.26 mmol) in octanoic anhydride (3.13 mL, 10.52 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 75.9 %, mp: 99-101 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.34 (s, 1H), 8.38 (dd, *J* = 1.9 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.59 (p, *J* = 7.1 Hz, 2H), 1.33 - 1.22 (m, 8H), 0.85 (t, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.93, 149.34, 143.01, 139.93, 136.68, 36.25, 31.60, 29.01, 28.90, 25.24, 22.53, 14.40.

7.2.2.8 Synthesis of *N*-(pyrazin-2-yl)nonanamide (PZ9)

A solution of 2-aminopyrazine (1.00 g, 10.52 mmol) in octanoic anhydride (4.00 mL, 12.17 mmol) was stirred for 1.5 hours at 100 °C and then cooled to 0 °C. The precipitate that formed was washed off with hexane to get the pure product. Yield: 97.7%, mp: 95-99 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.34 (s, 1H), 8.37 (dd, *J* = 3.9 Hz, 1H), 8.33 (d, *J* = 2.5 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.58 (h, *J* = 6.3, 5.8 Hz, 3H), 1.25 (d, *J* = 11.3 Hz, 14H), 0.85 (t, *J* = 6.6 Hz, 4H).

Crystals suitable for single-crystal X-ray diffraction (SCXRD) of seven compounds out of eight were obtained by slow evaporation from a variety of solvents (Table 7.1). Suitable crystals of PZ9 could not be obtained, despite attempts with different solvents and solvent systems. Details of crystallographic experiments are given in Appendix G.

Table 7.1. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color, Morphology
<i>N</i> -(pyrazin-2-yl)acetamide	PZ2	Ethyl acetate	Colorless, plate
<i>N</i> -(pyrazin-2-yl)propionamide	PZ3	Ethyl acetate	Colorless, irregular
<i>N</i> -(pyrazin-2-yl)butyramide	PZ4	Ethyl acetate	Orange, prism
<i>N</i> -(pyrazin-2-yl)pentanamide	PZ5	Ethyl acetate	Orange, plate
<i>N</i> -(pyrazin-2-yl)hexanamide	PZ6	Ethyl acetate	Orange, irregular
<i>N</i> -(pyrazin-2-yl)heptanamide	PZ7	Acetonitrile	Colorless, plate
<i>N</i> -(pyrazin-2-yl)octanamide	PZ8	Acetonitrile	Colorless, plate
<i>N</i> -(pyrazin-2-yl)nonanamide	PZ9	-	-

7.2.3 Thermal Stability Analysis

The thermal stability of materials was analyzed using differential scanning calorimetry (DSC). Approximately 0.5-1.2 mg of each sample was accurately weighed and sealed in an aluminum pan. The measurements were carried out under a nitrogen atmosphere to prevent oxidation, and the samples were heated from 35 °C to 300 °C at a constant heating rate of 10°C/min. The corresponding thermograms were recorded, and the melting points were determined from the endothermic peak temperatures. All measurements were performed using the same instrument settings to ensure consistency and comparability among the samples.

7.2.4 Hygroscopicity Studies

Hygroscopicity studies were performed under controlled relative humidity (RH) conditions of 85% (using KCl) in a humidity chamber. A supersaturated salt solution was prepared to maintain constant humidity. Solid forms PZ2, PZ3, PZ4, and PZ5 were placed inside the chamber and

monitored over a defined period of time. Samples were analyzed weekly by thermogravimetric analysis (TGA).

7.3 Results

7.3.1 SCXRD analysis of target materials

The primary hydrogen bond patterns in the crystal structures of PZ2-PZ8 are displayed in Figure 7.1 (a-c), together with the relevant graph-sets notations.⁴⁰

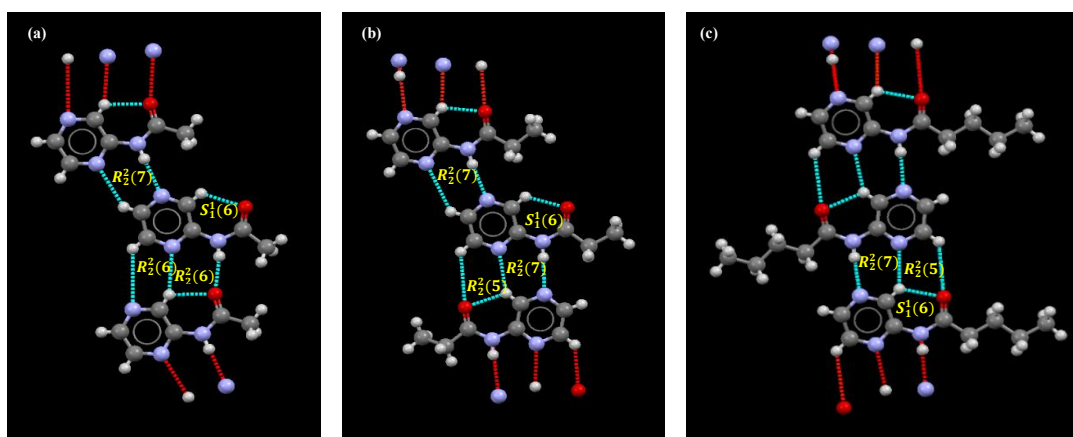


Figure 7.1. Primary hydrogen-bond interactions in the crystal structures of (a) PZ2, (b) PZ3, and (c) PZ5.

Compounds with an even number of carbon atoms in the alkyl chains adopt the packing arrangement shown in Figure 7.1(a), where all alkyl chains are oriented in the same direction, resulting in optimal packing. They displayed $\text{C-H(pz)} \cdots \text{N(pz)} / \text{N(pz)} \cdots \text{H-C(pz)} / \text{N-H} \cdots \text{C=O}$ primary hydrogen-bond interactions. In contrast, the odd-carbon compounds (PZ3 and PZ5) appear with their alkyl chains oriented in opposite directions (Figure 7.1(b) and 7.1 (c)). This leads to conformational mismatches that disrupt efficient packing. They displayed $\text{C-H(pz)} \cdots \text{O=C} / \text{N(pz)} \cdots \text{H-C(pz)} / \text{N-H} \cdots \text{N(pz)}$ primary interactions or $\text{N-H} \cdots \text{N(pz)} / \text{N(pz)} \cdots \text{H-C(pz)} / \text{C-}$

H $\cdots$ C=O interactions respectively. Notably, PZ7 is an exception, as it adopts the same packing arrangement as the even-carbon compounds.

In PZ2, PZ4, PZ6, PZ7, and PZ8 crystals, the alkyl chains and the aromatic rings were essentially segregated into different regions based on homomeric self-association. In PZ3 and PZ5, however, an aromatic ring of one molecule was more closely associated with the alkyl chain of a neighboring molecule.

7.3.2 Thermal stability of target materials

The melting points of each compound were determined (Table 7.2), and an overall decrease in melting temperature across the series was observed. However, compounds with an even number of carbon atoms consistently showed higher melting points than their odd-numbered analogues, suggesting enhanced thermal stability for the even-numbered series (Figure 7.2).

Table 7.2. Melting points and crystallographic densities.

Structure	T/K	D _{calc} /g cm ⁻³ (at T)	M.P./°C
PZ2 (C2)	294	1.365	134-136
PZ3 (C3)	210	1.337	107-110
PZ4 (C4)	210	1.310	109-112
PZ5 (C5)	210	1.221	87-90
PZ6 (C6)	210	1.224	95-98
PZ7 (C7)	210	1.189	91-93
PZ8 (C8)	210	1.209	99-102
PZ9 (C9)	-	-	88-96

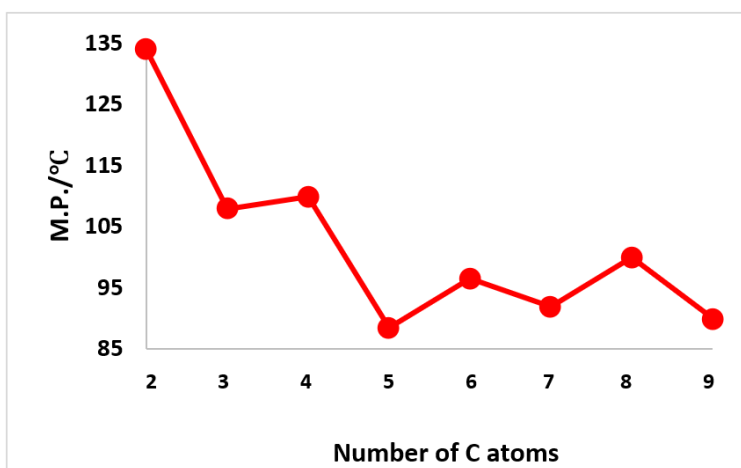


Figure 7.2. Melting point and crystal density for PZ2-PZ9.

7.3.3 Hygroscopicity of target materials

The TGA results showed that decreasing molecular ‘polarity’ enhances the resistance to hygroscopic behavior, with only PZ2 being hygroscopic in this series. PZ2 absorbs only 1 water molecule (11.2%) per PZ2 molecule, with this absorption remaining constant over time (Figure 7.3). Other compounds remained stable over time under the same conditions.

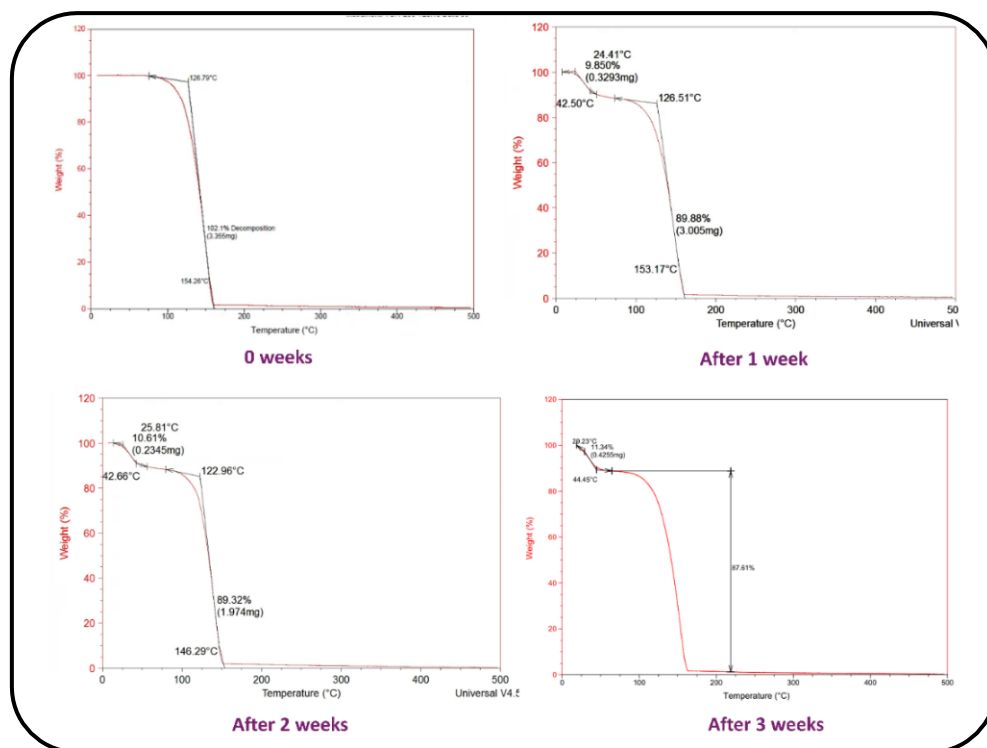


Figure 7.3. The TGA curves of PZ2 confirming the presence of water absorption.

7.4 Discussion

In this study, the effect of alkyl chain length, with emphasis on odd-even alternation, was investigated to understand its influence on the melting behavior of 2-aminopyrazine derivatives. Generally, an increase in molecular weight tends to enhance thermal stability by increasing the number of van der Waals interactions. However, as the alkyl chain length increases, the molecule's polarity simultaneously decreases, making the material more hydrophobic, thus potentially lowering its thermal stability. In our case, the reduced polarity appears to be the dominant factor, leading to a decrease in overall thermal stability up to PZ5. However, for longer chains (PZ6, PZ7, and PZ8), a slight increase in melting points was observed, suggesting that the effect of molecular weight begins to counterbalance the reduced polarity. These observations highlight the competing roles of molecular weight and polarity in determining the materials' thermal behavior.

Alongside this general trend, derivatives containing even-numbered alkyl chains consistently exhibit higher melting points than their odd-numbered counterparts, highlighting a clear odd-even effect on thermal stability. This odd-even alternation is further supported by crystal density data. Compounds with higher melting points are more dense, consistent with more efficient, compact crystal packing, whereas lower-melting-point derivatives show reduced densities, indicative of more open packing (Figure 7.4).

We also explored whether reduced molecular polarity could translate into enhanced resistance to hygroscopicity at the macroscopic level. Hygroscopicity tests revealed that only PZ2, with the shortest and most polar alkyl chain, exhibited significant water absorption, whereas none of the longer -chain derivatives showed any detectable moisture uptake under the same conditions. As alkyl chain length increases, materials become more hydrophobic, reducing their tendency to

interact with atmospheric moisture and thereby suppressing moisture uptake. These findings show a direct correlation between molecular-level polarity and macroscopic hygroscopicity.

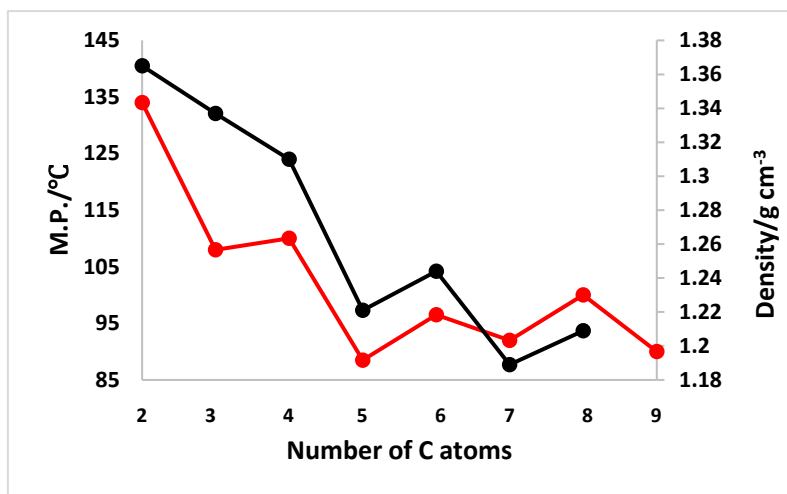


Figure 7.4. Melting point and crystal density for PZ2-PZ9 (red = melting point, black = density).

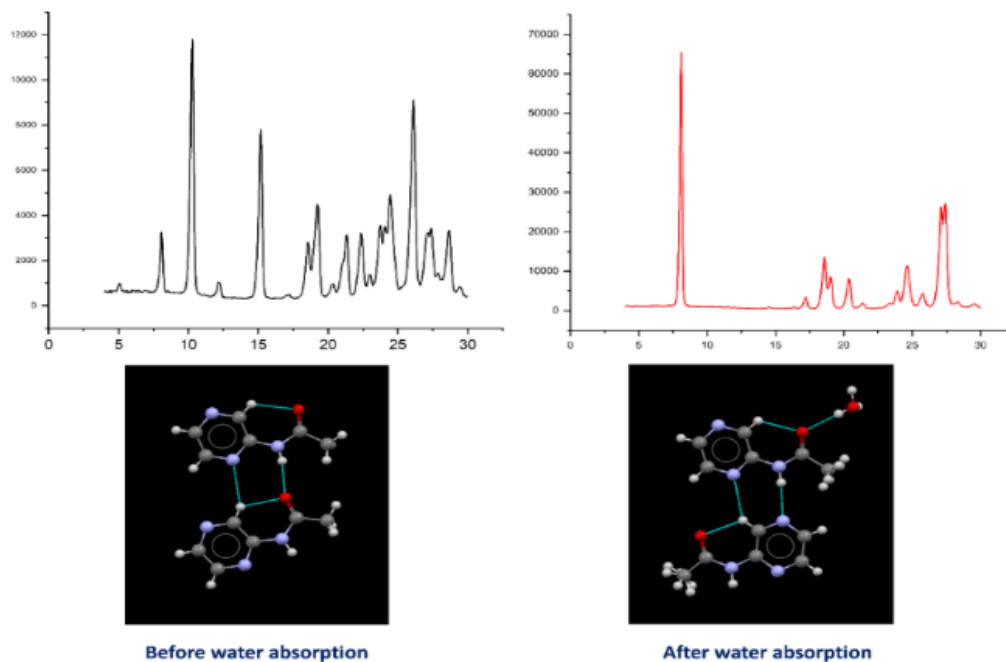


Figure 7.5. PXRD and SCXRD of PZ2.

Further testing was conducted on PZ2 to determine whether the observed moisture uptake is due to surface adsorption. PXRD analysis, followed by SCXRD, confirmed that it is not a surface

adsorption, as evidenced by changes in both the PXRD pattern and the crystal structure of PZ2 (Figure 7.5). Before water absorption, PZ2 crystallizes in the Pn space group, and after water absorption, it crystallizes in the $P2_1/c$ space group. The SCXRD further confirmed the adsorption of one water molecule over time.

Lastly, a family of 2-aminopyrazine derivatives was deliberately selected for this study with the expectation that the commonly observed N-H $\cdots$ N/N $\cdots$ H-N hydrogen-bond dimer (Figure 7.6, (a)) would provide the necessary core, thereby maintaining overall structural consistency across the series. However, none of the structures formed the anticipated dimer, yet mostly maintained the overall structural consistency through alternative intermolecular interactions. The aromatic protons in these compounds have a relatively high positive charge due to the presence of two nitrogen atoms in the ring, which promotes alternative hydrogen bonds⁴¹ and alters the expected interaction patterns. However, the structures remained largely constant across the series (Figure 6, (b)), except for two compounds with odd-numbered alkyl chains (Figure 7.6, (c) and (d)).

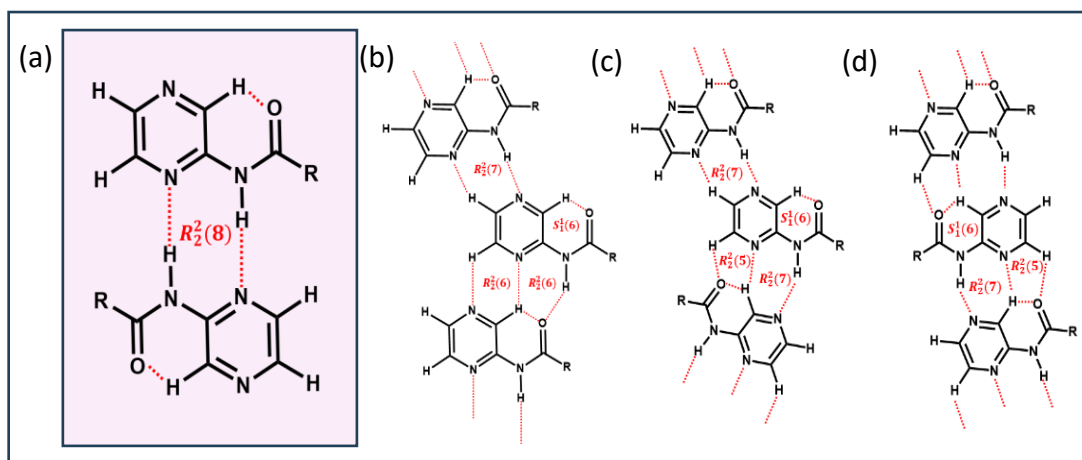


Figure 7.6. (a) The anticipated hydrogen bonding pattern and (b), (c), (d) observed hydrogen bonding patterns.

7.5 Conclusions

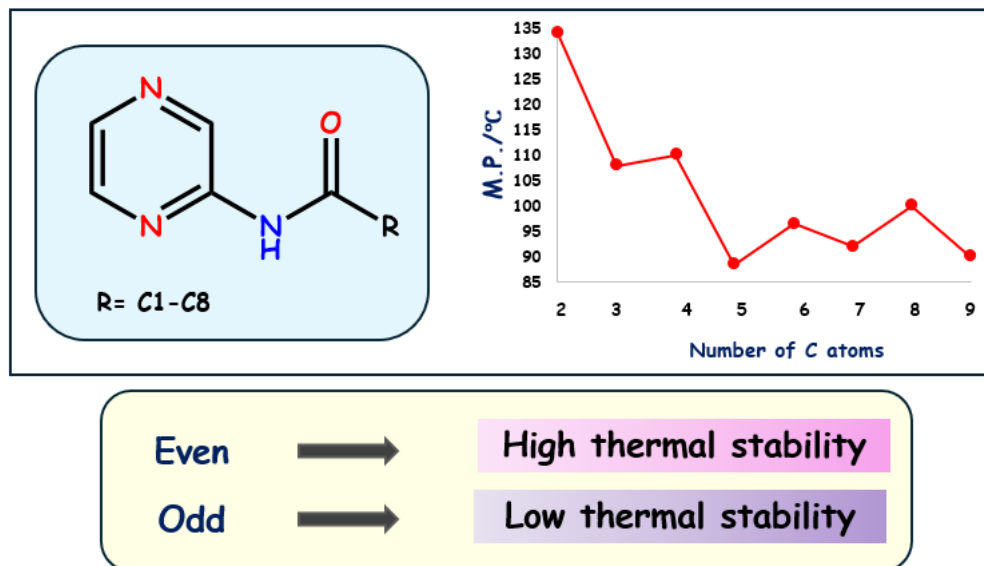


Figure 7.7. Key findings of the study.

In conclusion, this study systematically investigated the influence of the odd-even effect on the thermal behavior of 2-aminopyrazine derivatives, and the results confirmed that it plays a dominant role in governing thermal properties. Even-numbered derivatives exhibited higher melting points and densities, reflecting more efficient crystal packing, whereas odd-numbered derivatives exhibited poor packing and reduced thermal stabilities. In contrast, hygroscopicity tests reveal that decreasing molecular polarity can increase macroscopic resistance to hygroscopicity, with only PZ2 being hygroscopic. Interestingly, increasing the alkyl chain length by just one carbon atom was sufficient to prevent water absorption, indicating that even a small structural modification can significantly influence bulk properties. Finally, although the anticipated N-H $\cdots$ N/N $\cdots$ H-N dimer was not observed, the series maintained the overall structural consistency through alternative interactions, showing the adaptability of the hydrogen-bond network. Collectively, these findings highlight that subtle variations in alkyl chains provide a powerful strategy to alter solid-state arrangements and, consequently, macroscopic properties.

7.6 References

1. Varghese S, Das S. Role of Molecular Packing in Determining Solid-State Optical Properties of π -Conjugated Materials. *The journal of physical chemistry letters*. 2011 Mar 29;2(8):863–73.
2. Li Q, Li Z. Molecular Packing: Another Key Point for the Performance of Organic and Polymeric Optoelectronic Materials. *Accounts of Chemical Research*. 2020 Apr 3;53(4):962–73.
3. Zhang H, Zhang Z, Ye K, Zhang J, Wang Y. Organic Crystals with Tunable Emission Colors Based on a Single Organic Molecule and Different Molecular Packing Structures. *Advanced Materials*. 2006 Sep 18;18(18):2369–72.
4. Jones W. An Appreciation of Organic Solid-State Chemistry and Challenges in the Field of “Molecules, Materials, Medicines.” *Israel Journal of Chemistry*. 2016 Nov 9;57(1-2):117–23.
5. Azzaya Khasbaatar, Xu Z, Lee JH, Campillo-Alvarado G, Hwang C, Onusaitis BN, et al. From Solution to Thin Film: Molecular Assembly of π -Conjugated Systems and Impact on (Opto)electronic Properties. *Chemical reviews*. 2023 Jun 5;123(13):8395–487.
6. Desiraju GR, Gavezzotti A. Crystal structures of polynuclear aromatic hydrocarbons. Classification, rationalization and prediction from molecular structure. *Acta Cryst*. 1989 Oct 1;45(5):473–82.
7. Gavezzotti A, Filippini G. Polymorphic Forms of Organic Crystals at Room Conditions: Thermodynamic and Structural Implications. *Journal of the American Chemical Society*. 1995 Dec 1;117(49):12299–305.
8. Dou JH, Zheng YQ, Yao ZF, Yu ZA, Lei T, Shen X, et al. Fine-Tuning of Crystal Packing and Charge Transport Properties of BDOPV Derivatives through Fluorine Substitution. *Journal of the American Chemical Society*. 2015 Dec 9;137(50):15947–56.
9. Maleki F, Thorley KJ, Iqbal HF, Vong D, Maitra T, Petty A, et al. Design Rules to Optimize the Intermolecular and Long-Range Packing of Organic Semiconductor Crystals. *Chemistry of Materials*. 2024 May 5;36(9):4794–805.
10. Monika, Verma A, Tiwari MK, Show B, Saha S. Modulation of Weak Interactions in Structural Isomers: Positional Isomeric Effects on Crystal Packing and Physical Properties and Solid-State Thin-Film Fabrication. *ACS Omega*. 2019 Dec 30;5(1):448–59.
11. An X-ray investigation of normal paraffins near their melting points. *Proceedings of the Royal Society of London*. 1932 Dec 1;138(836):514–30.
12. D. Bond A. On the crystal structures and melting point alternation of the n -alkyl carboxylic acids. *New Journal of Chemistry*. 2004;28(1):104–14.

13. Thalladi VR, Nüsse M, Boese R. The Melting Point Alternation in α,ω -Alkanedicarboxylic Acids. *Journal of the American Chemical Society*. 2000 Sep 8;122(38):9227–36.
14. Bunn CW. The crystal structure of long-chain normal paraffin hydrocarbons. The “shape” of the . *Trans Faraday Soc*. 1939;35(0):482–91.
15. Flory PJ, Vrij A. Melting Points of Linear-Chain Homologs. The Normal Paraffin Hydrocarbons. *Journal of the American Chemical Society*. 1963 Nov;85(22):3548–53.
16. Broadhurst MG. An analysis of the solid phase behavior of the normal paraffins. *Journal of research of the National Bureau of Standards*. 1962 May 1;66A(3):241–1.
17. Desiraju Gautam R. Crystal Engineering: A Holistic View. *Angewandte Chemie International Edition*. 2007 Nov 12;46(44):8342–56.
18. Burnett EK, Ai Q, Cherniawski BP, Parkin SR, Risko C, Briseno AL. Even–Odd Alkyl Chain-Length Alternation Regulates Oligothiophene Crystal Structure. *Chemistry of Materials*. 2019 Jul 22;31(17):6900–7.
19. Tomislav Balić, Marija Paurević, Počkaj M, Medvidović-Kosanović M, Goman D, Aleksandar Széchenyi, et al. Influence of Aliphatic Chain Length on Structural, Thermal and Electrochemical Properties of n-alkylene Benzyl Alcohols: A Study of the Odd–Even Effect. *Molecules*. 2022 Jun 12;27(12):3781–1.
20. Tong L, Yang J, Yang Y, Liu Z, Fang M, Li Z. Odd–Even Effect in Charge Transfer Complexes through the Regulation of the Alkyl Chain. *ACS Materials Letters*. 2024 Jun 4;6(7):2748–56.
21. Wang S, Mandal M, Zhang H, Breiby DW, Yildiz O, Ling Z, et al. Odd–Even Alkyl Chain Effects on the Structure and Charge Carrier Transport of Two-Dimensional Sn-Based Perovskite Semiconductors. *Journal of the American Chemical Society*. 2024 Jul 2;146(28):19128–36.
22. Choghaei M, Schiffer M, Tyagi V, Righetto M, Du J, Buchmüller M, et al. Odd-even effects in lead-iodide-based Ruddlesden–Popper 2D perovskites. *Journal of Materials Chemistry A*. 2025;13(24):18935–47.
23. Roche GH, Bruckner G, Dumitrescu DG, Moreau JJE, van der Lee A, Wantz G, et al. Structural Odd–Even Effect Impacting the Dimensionality of Transport in BTBT- C_n OH Organic Field Effect Transistors. *Advanced Electronic Materials*. 2021 Sep 27;8(1).
24. Park W, Kwon M, Lee DH, Yoo S, Yang W, Park JS, et al. Odd–Even Effects of Linear Alkyl-Based Organic Spacers for Efficient Charge Transport in Two-Dimensional Dion–Jacobson Tin Perovskites. *Journal of the American Chemical Society*. 2025 May 16;147(21):17926–35.
25. Stoliar P, Rajendra Kshirsagar, Massi M, Annibale P, Albonetti C, de M, et al. Charge Injection Across Self-Assembly Monolayers in Organic Field-Effect Transistors: Odd–Even Effects. *Journal of the American Chemical Society*. 2007 May 1;129(20):6477–84.

26. Baghbanzadeh M, Simeone FC, Bowers CM, Liao KC, Thuo M, Baghbanzadeh M, et al. Odd–Even Effects in Charge Transport across *n*-Alkanethiolate-Based SAMs. *Journal of the American Chemical Society*. 2014 Nov 20;136(48):16919–25.
27. Fadwa Ben Amara, Dionne ER, Kassir S, Pellerin C, Badia A. Molecular Origin of the Odd–Even Effect of Macroscopic Properties of *n*-Alkanethiolate Self-Assembled Monolayers: Bulk or Interface?. *Journal of the American Chemical Society*. 2020 Jun 29;142(30):13051–61.
28. Chen J, Wang Z, Oyola-Reynoso S, Gathiaka SM, Thuo M. Limits to the Effect of Substrate Roughness or Smoothness on the Odd–Even Effect in Wetting Properties of *n*-Alkanethiolate Monolayers. *Langmuir*. 2015 Jun 19;31(25):7047–54.
29. Piotr Cyganik, Terfort A, Zharnikov M. Odd-even effects in the structure and properties of aryl-substituted aliphatic self-assembled monolayers. *Nano Research*. 2023 Dec 1;17(5):4231–43.
30. Tao F, Bernasek SL. Understanding Odd–Even Effects in Organic Self-Assembled Monolayers. *Chemical Reviews*. 2007 Apr 18;107(5):1408–53.
31. Cegielka DM, Bodek Ł, Zharnikov M, Cyganik P. Odd–Even Effects in the Structure and Thermal Stability of Carboxylic Acid Anchored Monolayers on Naturally Oxidized Aluminum Surface. *The Journal of Physical Chemistry Letters*. 2025 Mar 25;16(13):3343–50.
32. Guangxin Lv, Shen C, Shan N, Jensen E, Li X, Evans CM, et al. Odd–even effect on the thermal conductivity of liquid crystalline epoxy resins. *Proceedings of the National Academy of Sciences*. 2022 Nov 7;119(46).
33. Kahwaji S, White MA. Organic Phase Change Materials for Thermal Energy Storage: Influence of Molecular Structure on Properties. *Molecules*. 2021 Nov 2;26(21):6635.
34. Ramin L, Jabbarzadeh A. Odd–Even Effects on the Structure, Stability, and Phase Transition of Alkanethiol Self-Assembled Monolayers. *Langmuir*. 2011 Jul 13;27(16):9748–59.
35. Park S, Kim E, Choi Y, Jang J, Kwak K, Cho M, et al. Thermoresponse of Odd-Even Effect in *n*-Alkanethiolate Self-Assembled Monolayers on Gold Substrates**. *Chemistry - A European Journal*. 2022 Dec 22;29(15).
36. Wu R, Bernhard Brutschy. Infrared Depletion Spectroscopy and Structure of the 2-Aminopyridine Dimer. *The Journal of Physical Chemistry A*. 2004 Sep 8;108(45):9715–20.
37. Ottiger P, Frey JA, Frey HM, Leutwyler S. Jet-Cooled 2-Aminopyridine Dimer: Conformers and Infrared Vibrational Spectra. *The Journal of Physical Chemistry A*. 2009 Apr 9;113(18):5280–8.
38. Kadirova ShA, Nuralieva GA, Alieva MA, Talipov SA, Tilyakov ZG, Parpiev NA. Synthesis and Crystal Structure of 2-Aminoacetyl-1,3,4-thiadiazole. *Russian Journal of General Chemistry*. 2005 Dec;75(12):1962–4.

39. Kadirova, Sh. A.; Nuralieva, G. A.; Alieva, M. A.; Talipov, S. A.; Tilyakov, Z. G.; Parpiev, N. A. Synthesis and Crystal Structure of 2-Aminoacetyl-1,3,4-Thiadiazole. *Russian Journal of General Chemistry* **2005**, 75 (12), 1962–1964.
40. Etter MC. Encoding and decoding hydrogen-bond patterns of organic compounds. *Accounts of Chemical Research*. 1990 Apr 1;23(4):120–6.
41. Marasinghe AA, Averkiev BB, Aakeröy CB. Examining intermolecular interactions in crystal structures of amide-substituted 2-aminopyrimidine derivatives. *CrystEngComm*. 2025;27.

Chapter 8 - Analogue of favipiravir and its cocrystals: Insights into structure-property relationships

8.1 Introduction

Building on our previous study of pyrazine-based backbones, the present study focuses on a pharmaceutical molecule containing this backbone. Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide) is a broad-spectrum antiviral drug that was approved in Japan in 2004 for influenza treatment and that received additional interest during the 2019 coronavirus outbreak as a potential COVID-19 therapeutic agent. The drug acts as a prodrug that is intracellularly converted into its ribofuranosyl-5'-triphosphate form, which inhibits viral RNA polymerase, thereby suppressing viral replication (Figure 8.1).¹⁻⁴

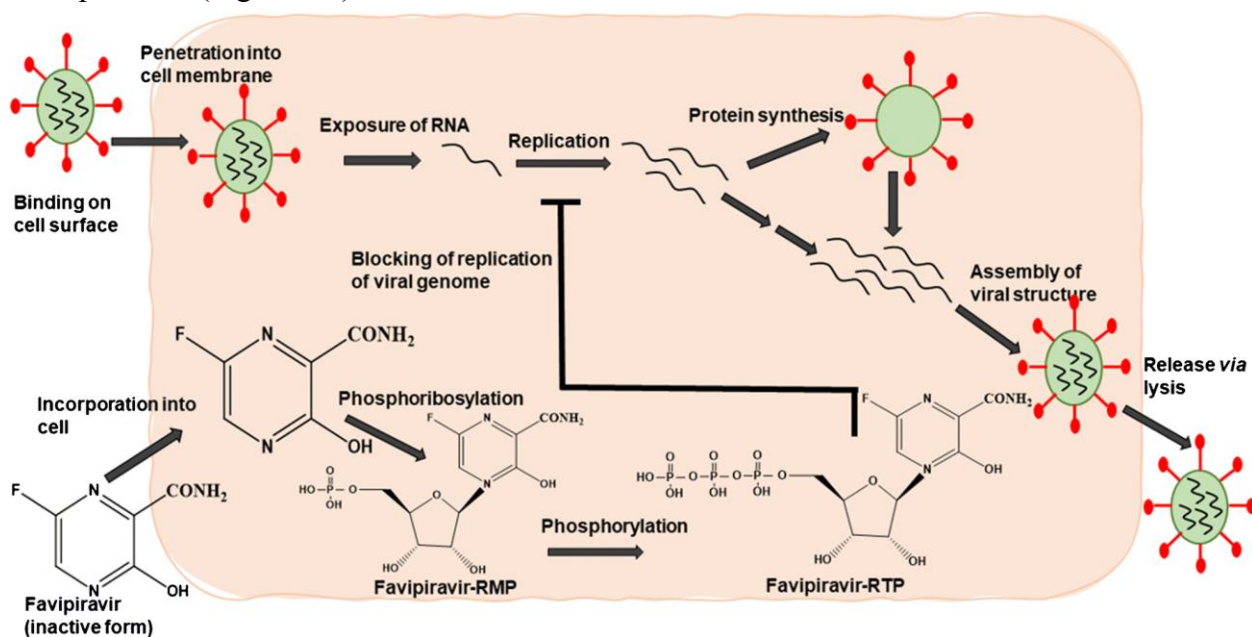


Figure 8.1. The mechanism of action of favipiravir.

Despite its promising antiviral activity, favipiravir exhibits several limitations associated with its physical properties, including relatively low aqueous solubility (8.7 mg/mL), high permeability (1.09×10^{-5} – 1.35×10^{-5} cm/s), and poor tabletability.⁵⁻⁸ One of the key structural features of

favipiravir is its ability to undergo keto-enol tautomerism (Figure 8.2) and rotamerism, which makes it conformationally flexible resulting in different physical forms.⁹⁻¹² To date, two crystalline forms of this drug have been identified, and this has also been a challenge in drug development.^{13,14} Favipiravir is generally considered a BCS class II drug,¹⁵ but reported classifications vary across different studies, and this is not yet an FDA-approved drug.^{5,16}

As pharmaceutical cocrystallization has emerged as an effective crystal engineering approach to improve the solid-state properties of active pharmaceutical ingredients (APIs), several studies have reported cocrystals of favipiravir, as it has multiple hydrogen-bond donors and acceptors, making it a suitable candidate for cocrystallization.^{6, 17-19} This has led to notable improvements in solubility and dissolution behavior of favipiravir, underscoring the importance of this strategy for improving physical properties.

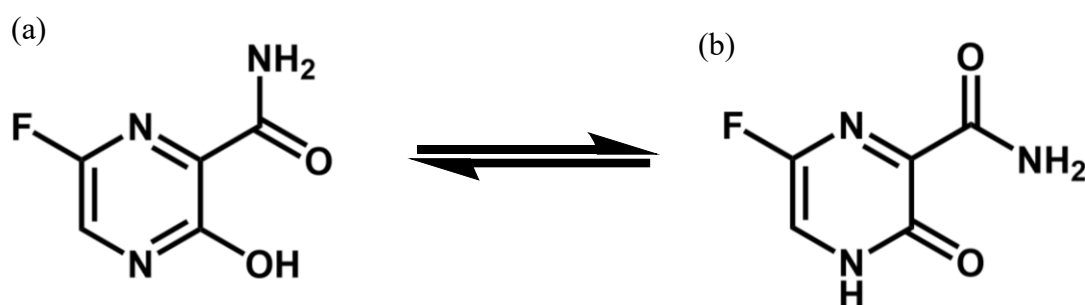


Figure 8.2. The enol (a) and keto (b) isomers of favipiravir.

To investigate the structural landscape resulting from a specific atom-atom substitution we have synthesized an iodo analogue of favipiravir and its cocrystals with the same coformers previously used for favipiravir.^{6, 17-19} Systematic variations in molecular structure are widely employed in crystal engineering, as they help understand how small structural changes affect material properties. Changing the halogen atom from fluorine to iodine can modulate steric effects, and polarizability, thereby directly influencing crystal packing and lattice stability. Studying the iodo

analogue of favipiravir will therefore provide a broader understanding of how halogen atoms affect solid-state organization.

With this in mind, we decided to examine the structural landscape of the iodo derivative of favipiravir (Figure 8.3) to establish whether it forms cocrystals with the same coformers (Figure 8.4) previously^{6, 17-19} used for favipiravir. Furthermore, we wanted to evaluate how halogen-atom substitution influences the physicochemical properties of the resulting cocrystals compared to those of favipiravir.

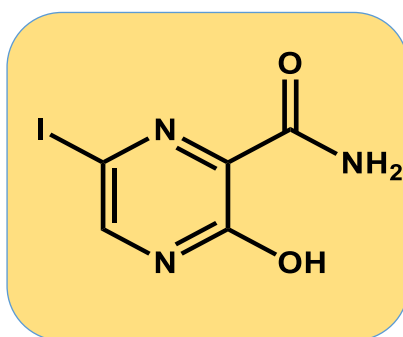


Figure 8.3. Chemical structure of the iodo analogue of favipiravir (2-hydroxy-5-iodobenzamide).

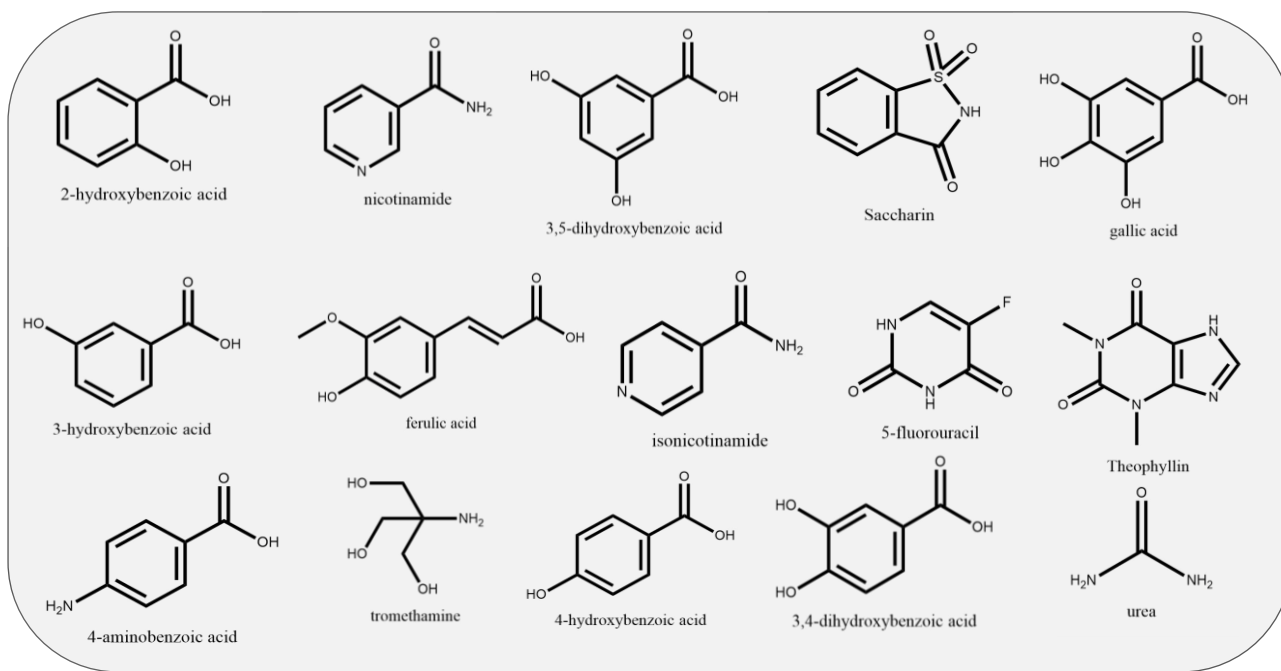


Figure 8.4. Coformers used for the cocrystallization studies.

8.2 Experimental section

8.2.1 General

All precursors and solvents were purchased from commercial sources and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra were recorded using a Nicolet 380 FTIR spectrometer with attenuated total reflection (ATR) and a ZnSe crystal. Single-crystal X-ray diffraction (SCXRD) data were collected on a Rigaku XtaLAB Synergy-S single-crystal X-ray diffractometer equipped with Cu K α radiation. PXRD patterns were collected using a Bruker X-ray powder diffractometer equipped with Cu K α radiation, operated at 30 kV and 15 mA. Electrostatic potentials were calculated with the density functional B3LYP level of theory using the 6-311++G** basis set in vacuum, using Spartan'14 software.

8.2.2 Synthesis

8.2.2.1 Synthesis of 2-hydroxy-5-iodobenzamide (I-Fav)

2-Hydroxybenzamide (1.00g, 7.30 mmol) was dissolved in DMF, and *N*-iodosuccinimide (2.62 g, 12.00 mmol) was added and allowed to react for six hours at 80 °C. The reaction mixture was diluted with water, resulting in a pale brown precipitate. The precipitate was then filtered and washed with sufficient $\text{Na}_2\text{S}_2\text{O}_3$ solution to remove excess *N*-iodosuccinimide from the crude, then washed with water to obtain a yellowish-orange-colored precipitate. Yield = 42.9%. M.P. 217-219 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 12.46 (s, 1H), 8.64 (s, 1H), 7.61 (s, 1H), 5.87 (s, 1H). ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 169.43, 161.69, 152.18, 135.15, 100.66.

8.2.2.2 Cocrystal synthesis by liquid-assisted grinding (LAG)

Liquid-assisted grinding was performed on a 1:1 stoichiometric mixture of 2-hydroxy-5-iodobenzamide and each coformers in the presence of 1 or 2 drops of methanol. The ground mixtures were analyzed by PXRD to confirm the formation of new crystalline phases and by IR spectroscopy and DSC to further confirm the cocrystal formation. The positive ground mixtures were then slowly evaporated using suitable solvents for a few weeks to obtain crystals suitable for SCXRD.

8.3 Results

8.3.1 FTIR and DSC analysis of I-Fav

I-Fav exhibited possible different forms, as indicated by the IR spectrum (Figure 8.5) and the DSC (Figure 8.6). The IR spectrum suggests the presence of both enol and keto forms in the solid state, as evidenced by three C=O stretching vibrations, and DSC shows two peaks, indicating different solid forms.

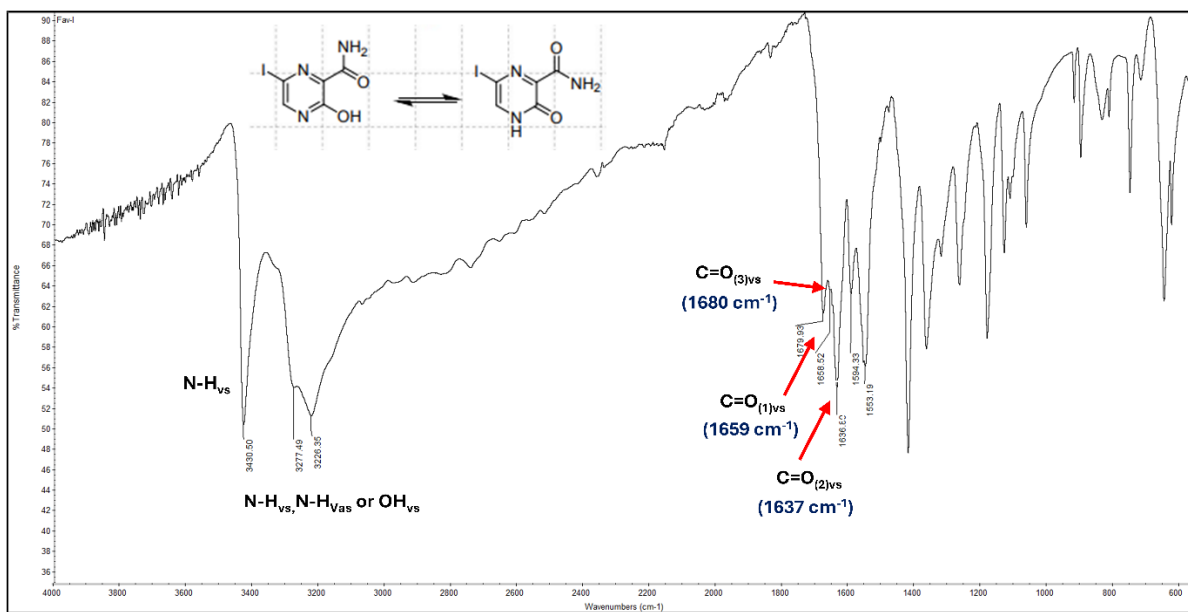


Figure 8.5. IR spectrum of the ground mixture.

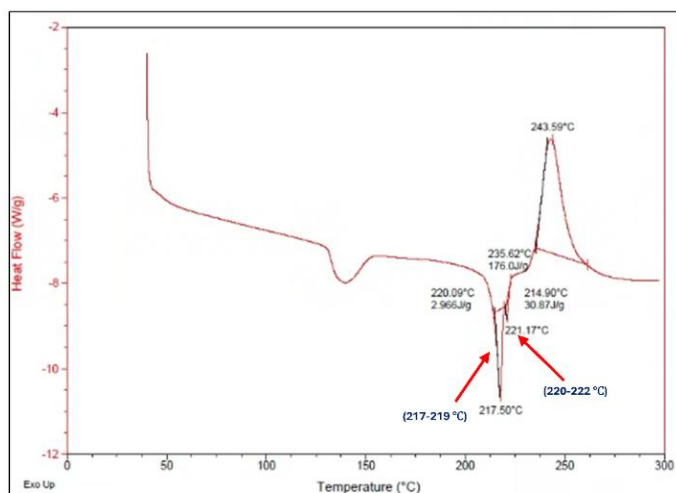


Figure 8.6. DSC of the ground mixture.

8.3.2 SCXRD analysis of I-Fav

The powdered sample was allowed to crystallize under various conditions to identify possible forms. The solvents/conditions used for crystal growth and crystal descriptions are listed in Table 8.1. Details of crystallographic experiments are given in Table 8.2 and Appendix H. The primary hydrogen bonds present are displayed in Figure 8.7.

Table 8.1. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point/ °C
2-hydroxy-5-iodobenzamide- Form I	I-Fav -I	Dimethylformamide	Orange, needle	207-209
2-hydroxy-5-iodobenzamide- Form II	I-Fav -II	Methanol + Ethanol +Ethyl acetate	Orange, plate	221-223
2-hydroxy-5-iodobenzamide- Form III	I-Fav -III	Methanol	Yellow, needle	218-220
2-hydroxy-5-iodobenzamide- Form IV	I-Fav -IV	Heat/No solvent	Colorless, plate	220-222

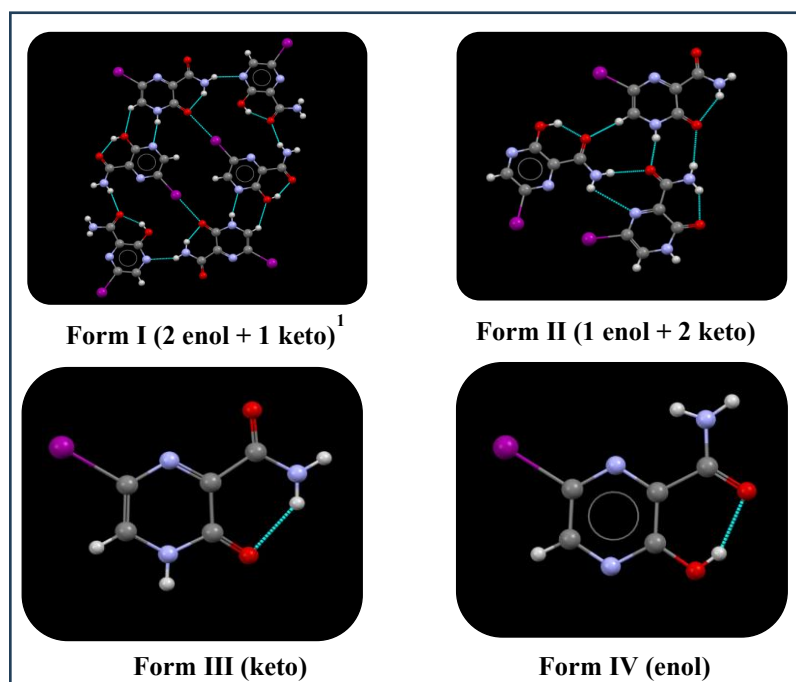


Figure 8.7. Forms of I-Fav.

Table 8.2. Some crystallographic parameters and enol/keto ratios of four forms

Compound	Enol: Keto ratio	Space group	a/Å	b/Å	c/Å	Z: Z'
I-Fav-I	2:1	$P 2_1/n$	7.94473(4)	23.04677(9)	24.66163(10)	24: 6
I-Fav-II	1:2	$P 2_1/c$	12.6611(3)	5.01590(10)	35.2516(8)	12 : 3
I-Fav-III	0:1	$F d d 2$	29.8381(10)	22.6885(7)	4.33819(18)	16 : 1
I-Fav-IV	1:0	$P 2_1$	4.4914(2)	5.1753(2)	16.4120(6)	2: 1

Form I of I-Fav was previously reported by Romero and coworkers in 2023 ⁹, and we recrystallized it from DMF and reanalyzed it, obtaining improved cell parameters. In this structure, molecules are connected in a 2:1 enol-to-keto stoichiometric ratio, and there are six molecules in the asymmetric unit. The molecules display a combination of intra- and intermolecular interactions, as shown in Figure 8.8(a).

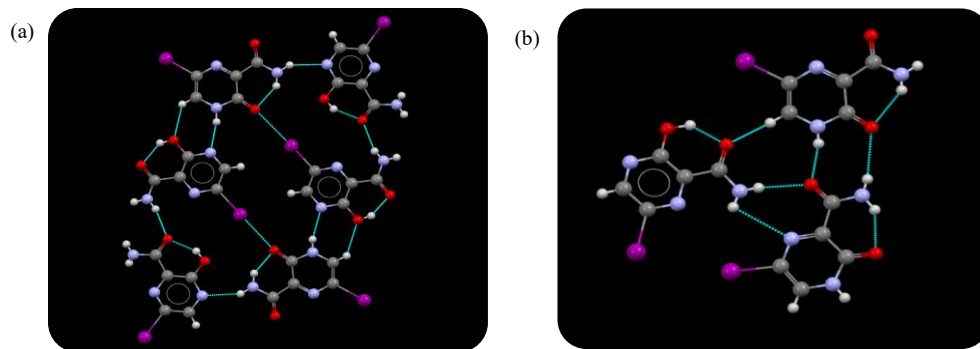


Figure 8.8. Form I and Form II of I-Fav with labels.

Form II was obtained as orange plates from a methanol-ethanol-ethyl acetate mixture (Figure 8.8, (b)) and displayed a 1:2 enol to keto ratio with three independent molecules in the asymmetric unit. In contrast to form I, no halogen bonds were observed in this structure.

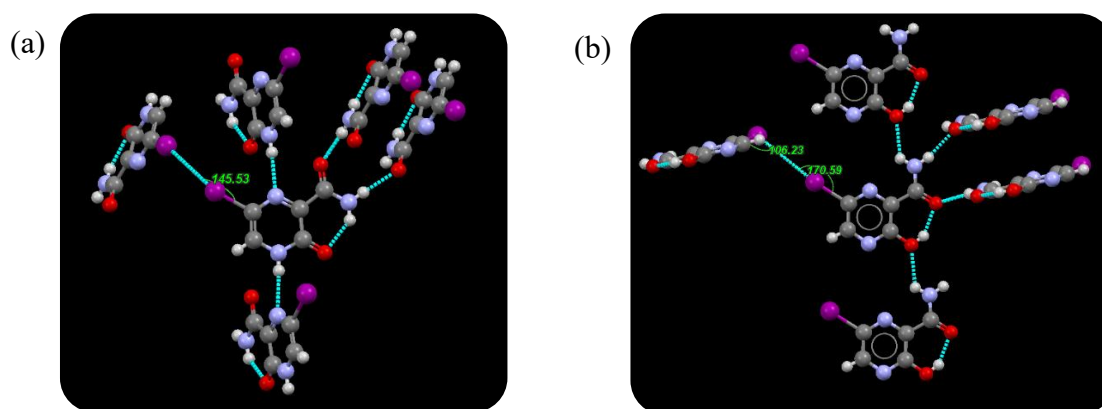


Figure 8.9. Form III and Form IV of I-Fav with labels.

Form III was obtained from methanol by slow evaporation and contains only the keto form. The asymmetric unit contains one independent molecule. The crystal structure also displays type I halogen bonds (Figure 8.9 (a)). Form IV (Figure 8.9 (b)) was obtained by melting the material and slowly cooling it, and it consisted solely of the enol form. The asymmetric unit also consisted of one independent molecule. An intramolecular hydrogen bond was observed, and the structure is further stabilized by several intermolecular interactions, including type II halogen bonds.

8.3.3 Cocrystallization results of I-Fav

Building on our understanding of the I-Fav structural landscape, we next explored its ability to form cocrystals. The resulting grinding experiments were analyzed by PXRD and FTIR. PXRD was used to detect the formation of different crystalline phases, and the appearance of new peaks or the disappearance of peaks from the starting materials indicated the formation of new crystalline phases; a conclusive sign of cocrystallization. Figure 8.10 shows the cocrystallization of theophylline and I-Fav, with a distinct PXRD pattern compared to the two starting materials.

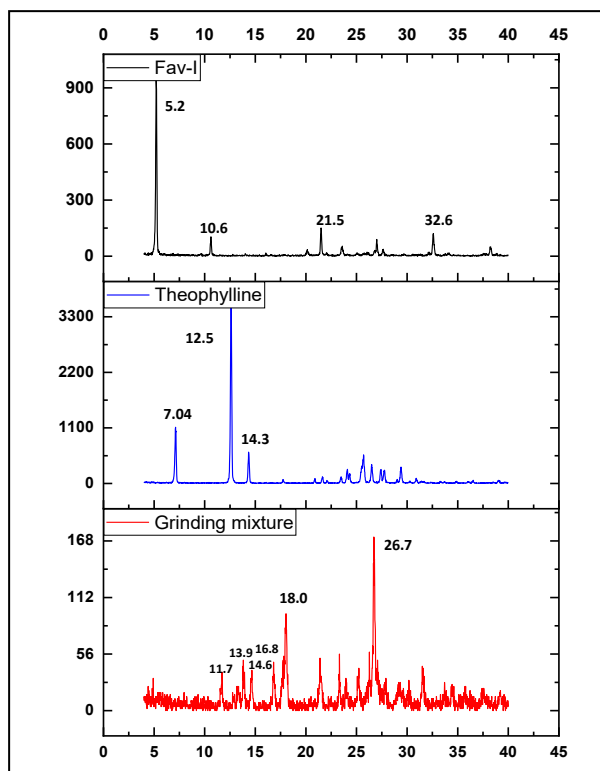


Figure 8.10. PXRD patterns of I-Fav -Theo and its starting materials.

Some experiments yielded PXRD patterns that made it difficult to determine whether positive cocrystallization had occurred based solely on PXRD data. Therefore, FTIR was employed to further characterize all ground mixtures. Figure 8.11 shows a comparison of the FTIR spectra of

theophylline, I-Fav, and the ground mixture thereof. In the FTIR analysis, we compared the amide carbonyl and NH₂ stretching bands, along with theophylline carbonyl bands, to those of the ground mixtures. We found that many of the vibrational signatures of the starting material had completely shifted, and no residual starting material bands remained, indicating successful cocrystal formation.

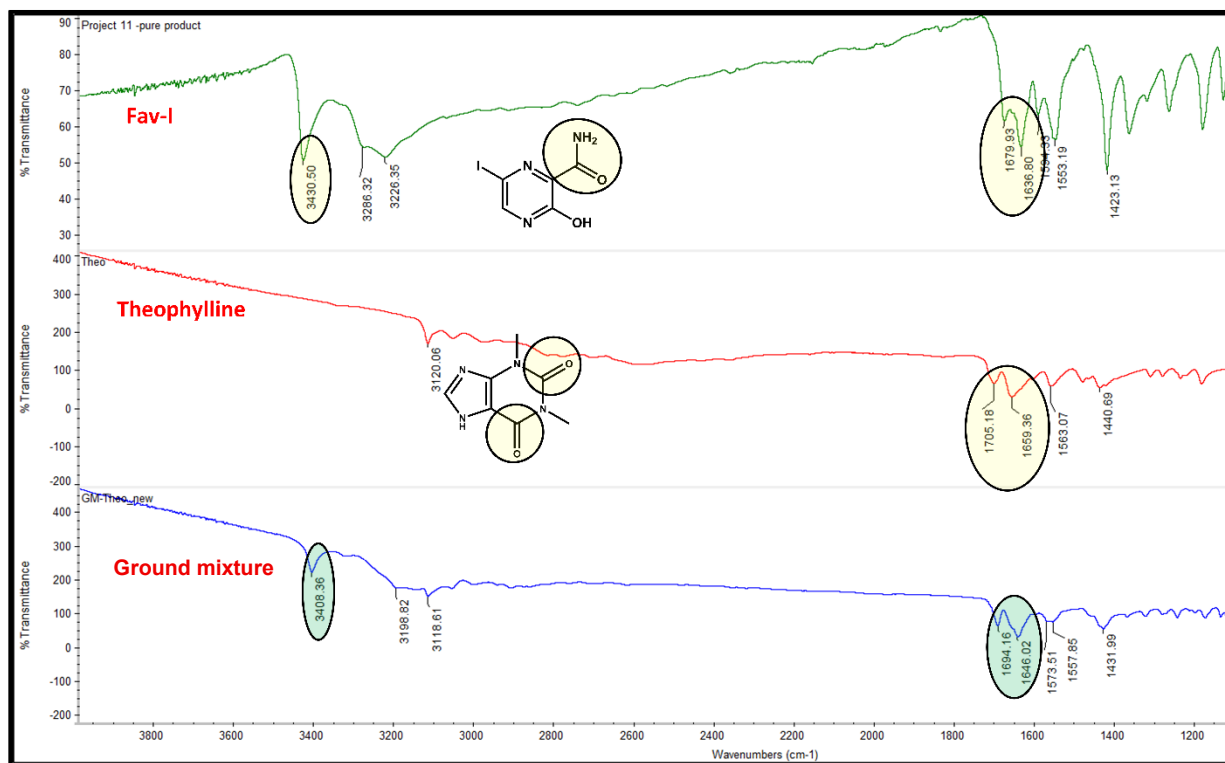


Figure 8.11. IR spectra of I-Fav-Theo ground mixture and its starting materials.

Based on the IR analyses, all ground mixtures showed evidence of cocrystal formation, Table 8.3.

Table 8.3. Summary of grinding experiments

	Coformer	PXRD	IR
1	5-fluorouracil	√	√
2	Saccharin	√	√
3	Theophylline	√	√
4	Tromethamine	√	√

5	4-aminobenzoic acid	√	√
6	Nicotinamide	X	√
7	Isonicotinamide	√	√
8	Urea	X	√
9	Ferulic acid	X	√
10	3-hydrobenzoic acid	√	√
11	4-hydrobenzoic acid	X	√
12	3,5-dihydrobenzoic acid	X	√
13	Gallic acid	√	√
14	3,4-dihydrobenzoic acid	√	√
15	2-hydrobenzoic acid	√	√
	Success rate	66.67%	100%

According to literature,¹⁸ favipiravir and 2HBA did not form cocrystals, and gallic acid and 3,4-dHBA formed hydrates.^{17,18} Based on our IR results, all ground mixtures indicate positive cocrystallization; however, it is not possible to confirm, conclusively, whether the compounds were hydrates or cocrystals.

8.3.4 SCXRD results of cocrystals

Slow evaporation was employed for single-crystal growth, and only three cocrystals suitable for SCXRD were obtained, probably due to the polarity/solubility mismatch between the coformer and the I-Fav. The solvents used for crystal growth and crystal descriptions for the resultant cocrystals are listed in Table 8.4, and the details of crystallographic experiments are given in Appendix H.

Table 8.4. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point/ °C
2-hydroxy-5-iodobenzamide + Theophylline	I-Fav -Theo	Methanol	Colorless, prism	224-226
2-hydroxy-5-iodobenzamide + Tromethamine	I-Fav -Tro	Methanol	Colorless, needle	141-144
2-hydroxy-5-iodobenzamide + 5-fluorouracil	I-Fav -5-flu	Methanol	Colorless, needle	204-206

All three crystals of cocrystals were grown from methanol and form 1:1 stoichiometric solids (Figure 8.12 (a)). I-Fav adopts the enol form in two of the three cocrystals, while the I-Fav -Tro cocrystal exhibits the keto form. These cocrystals were stabilized by several intra- and intermolecular interactions. Upon close examination, these structures were found to be further stabilized by halogen bonds (Appendix I). However, all structures crystallized differently compared to those previously reported for favipiravir cocrystals ^{6,17-19} (Figure 8.13), which indicates that the F $\rightarrow$ I atom-atom substitution has a considerable effect on specific intermolecular interactions as well as on overall crystal packing.

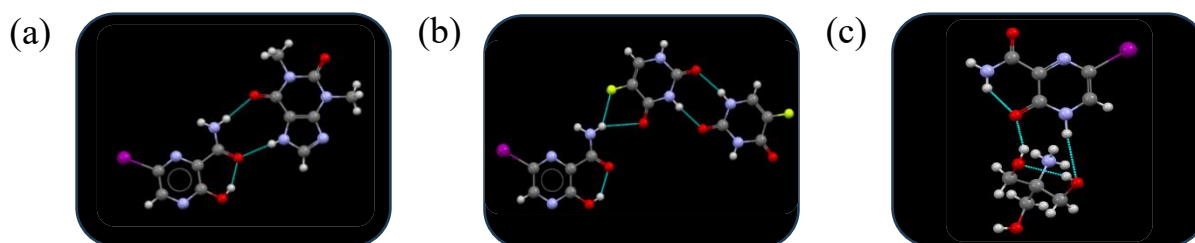


Figure 8.12. Asymmetric units of (a) I-Fav-Theo cocrystal, (b) I-Fav-5-flu cocrystal, and (c) I-Fav-Tro cocrystal.

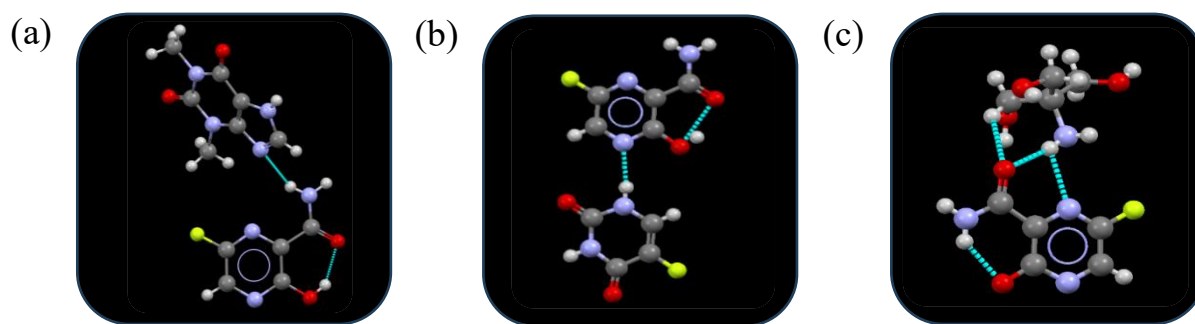


Figure 8.13. Asymmetric unit of (a) Fav-Theo cocrystal, (b) Fav-5-flu cocrystal, and (c) Fav-Tro cocrystal.

8.3.5 Thermal stability of cocrystals

Thermal stabilities were also determined, and most of the I-Fav cocrystals displayed improved properties compared to the favipiravir cocrystals.^{6,17-19} However, melting points have been reported only for nine favipiravir cocrystals. Therefore, the comparison was limited to these nine cocrystals and their corresponding iodo analogues (Figure 8.14). Among these nine cocrystals, six showed higher melting points compared to the corresponding favipiravir cocrystals, while the remaining three cocrystals exhibited lower thermal stability.

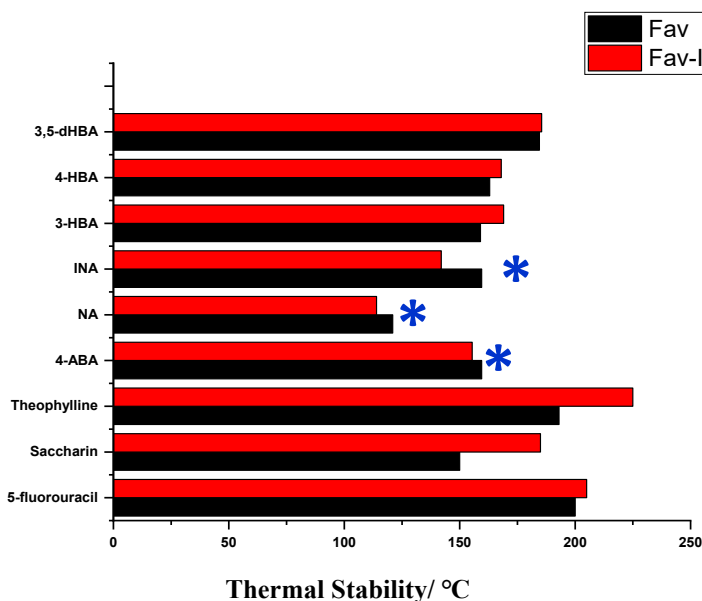


Figure 8.14. Thermal stability comparison of I-Fav and Fav cocrystals (* = outliers).

8.4 Discussion

The primary goal of this study was to explore how fluorine-to-iodine substitution affects the solid-state organization of the iodo analogue of favipiravir compared to favipiravir. The successful isolation of multiple forms of the iodine derivative reveals an expanded crystal form diversity compared to favipiravir, which has been reported to exhibit only two forms (Figure 8.15).¹³

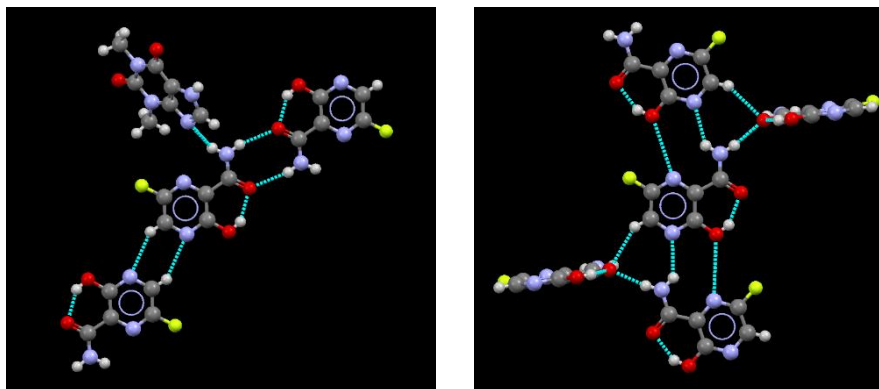


Figure 8.15. Two reported forms of favipiravir.

This behavior can be explained by the influence of the substituent at the 6-position (Figure 8.16) on the keto-enol equilibrium, as well as by the polarity of the surrounding environment. In general, the enol form is preferred in apolar media, whereas the keto form is stabilized in polar solvents.⁹ Therefore, by controlling solvent polarity, mixtures of enol and keto tautomers can be obtained. As the I-Fav crystallized into different forms in different environments, the effect of solvent polarity is clearly evident.

In contrast, both reported forms of favipiravir exist in the enol form, whereas the iodo analogue exhibits both keto and enol tautomers. This observation may be explained by the fact that keto tautomerism becomes increasingly favored with decreasing electronegativity of the substituent at the 6-position, following the trend $H \gg I \approx Br > Cl \geq F$.⁹ The electronegativity of the 6-substituent alters the ring's overall dipole moment and charge distribution. When the substituent is strongly electron-withdrawing, such as F, the keto form becomes less stable. Among the halogen atoms, Br and I promote greater keto character than F or Cl, which may lead to mixtures of keto and enol forms in both the solid state and in solution.

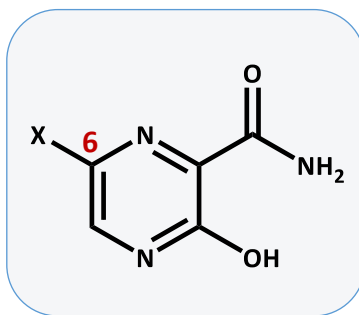


Figure 8.16. General structure of favipiravir analogues with the 6-position labeled.

There is no clear evidence regarding the precise impact of iodine substitution on cocrystal formation. For favipiravir, fourteen out of fifteen experiments have shown positive results, including twelve cocrystals and two hydrates, while only one system did not form a cocrystal. However, the iodo analogue showed positive results with all coformers; however, there is still insufficient structural data to definitively determine whether all the obtained phases are cocrystals or hydrates. Nevertheless, PXRD, DSC, and IR analyses suggest the formation of new crystalline phases.

Notably, thermal stability analysis of the iodo analogue cocrystals revealed markedly higher melting points than those of favipiravir itself (67%). This can be attributed to the presence of the heavier iodine atom. In halogen-substituted compounds, the incorporation of bulkier halogens with higher molecular weights, such as iodine, often enhances lattice stability.^{20,21} Additionally, the presence of iodine may increase melting points by promoting more intermolecular interactions, including halogen bonds. Similar improvements in thermal stability for halogenated compounds compared to their non-halogenated analogues have been widely reported in the literature.²⁰⁻²² However, halogen substitution alone does not fully determine thermal stability, and the overall supramolecular packing within the crystal lattice also plays a significant role. Therefore, the

observed increase in melting points for most of the I-Fav cocrystals likely arises from a combination of the larger iodine atom and favorable crystal packing interactions.

Properties such as solubility, dissolution behavior, and permeability remain to be investigated to determine whether the observed structural changes translate into improved drug performance. In addition, the impact of iodine on drug toxicity and overall safety must be carefully evaluated to assess its suitability for pharmaceutical applications. Nevertheless, these findings establish a solid foundation for future studies and demonstrate that halogen substitution combined with cocrystallization is a promising strategy for overcoming solid-state limitations.

8.5 Conclusions

Table 8.5. Summary of key findings of the study

Compound	Tautomer (s)	Crystal forms	Cocrystal formation	Thermal stability
Favipiravir	Enol only	2	12/15	Lower thermal stability
Favipiravir iodo analogue	Keto+ Enol	4	15/15	Higher thermal stability

This study demonstrates that iodine substitution of favipiravir expands the crystal form diversity and introduces both keto and enol tautomers, in contrast to favipiravir, which crystallizes only in the enol form. Iodo analogue cocrystals generally exhibit higher thermal stability, likely due to the heavier iodine atom and the increased number of intermolecular interactions (Table 8.5). Overall, these findings highlight that iodine substitution, combined with cocrystallization, is a promising approach to modulate solid-state properties, providing a foundation for further studies on properties such as solubility, permeability, and bioavailability, which are known limitations of favipiravir.

8.6 References

1. Furuta, Y.; Gowen, B. B.; Takahashi, K.; Shiraki, K.; Smee, D. F.; Barnard, D. L. Favipiravir (T-705), a Novel Viral RNA Polymerase Inhibitor. *Antiviral Research* 2013, *100* (2), 446–454.
2. Delang, L.; Abdelnabi, R.; Neyts, J. Favipiravir as a Potential Countermeasure against Neglected and Emerging RNA Viruses. *Antiviral Research* 2018, *153*, 85–94.
3. Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X. Structure of Mpro from COVID-19 Virus and Discovery of Its Inhibitors. *Nature* 2020, *582* (7811), 289–293.
4. Sood, S.; Bhatia, G. K.; Seth, P.; Kumar, P.; Kaur, J.; Gupta, V.; Punia, S.; Tuli, H. S. Efficacy and Safety of New and Emerging Drugs for COVID-19: Favipiravir and Dexamethasone. *Current Pharmacology Reports* **2021**, *7* (2), 49–54.
5. Selin Seda TİMUR; Meltem ATAŞOĞLU; Yalçın ÖNER; Tutku Ceren KARABULUT; Hakan EROĞLU. In Vitro Studies for BCS Classification of an Antiviral Agent, Favipiravir. *Journal of Research in Pharmacy* **2021**, *25*(6) (25(6)), 944–952.
6. Wang, X.; Wang, L.; Yao, C.; Xie, G.; Song, S.; Li, H.; Qu, Y.; Tao, X. Novel Formulations of the Antiviral Drug Favipiravir: Improving Permeability and Tabletability. *Crystal Growth & Design* **2021**, *21* (7), 3807–3817.
7. Favipiravir. go.drugbank.com. <https://go.drugbank.com/drugs/DB12466>. (Accessed, 10.02. 2025)
8. Gupta, S.; Omar, T.; Zhou, Q.; Scicolone, J.; Callegari, G.; Dubey, A.; Muzzio, F. High-Dose Modified-Release Formulation of a Poorly Soluble Drug via Twin-Screw Melt Coating and Granulation. *International Journal of Pharmaceutics* **2025**, *670*, 125090.
9. Romero, A. H.; Fuentes, G.; Suescun, L.; Piro, O.; Echeverría, G.; Gotopo, L.; Pezaroglo, H.; Guzmán Álvarez; Cabrera, G.; Cerecetto, H.; Couto, M. Tautomerism and Rotamerism of Favipiravir and Halogenated Analogues in Solution and in the Solid State. *The Journal of Organic Chemistry* **2023**, *88* (15), 10735–10752.
10. Umar, Y. Theoretical Studies of the Rotational and Tautomeric States, Electronic and Spectroscopic Properties of Favipiravir and Its Structural Analogues: A Potential Drug for the Treatment of COVID-19. *Journal of Taibah University for Science* **2020**, *14* (1), 1613–1625.
11. Deneva, V.; Slavova, S.; Kumanova, A.; Vassilev, N.; Nedeltcheva-Antonova, D.; Antonov, L. Favipiravir—Tautomeric and Complexation Properties in Solution. *Pharmaceutics* **2022**, *16* (1), 45–45.
12. Assis, L. C.; de Castro, A. A.; de Jesus, J. P. A.; da Cunha, E. F. F.; Nepovimova, E.; Krejcar, O.; Kuca, K.; Ramalho, T. C.; La Porta, F. de A. Theoretical Insights into the Effect of Halogenated Substituent on the Electronic Structure and Spectroscopic Properties of the

Favipiravir Tautomeric Forms and Its Implications for the Treatment of COVID-19. *RSC Advances* **2021**, *11* (56), 35228–35244.

13. Goloveshkin, A. S.; Korlyukov, A. A.; Вологжанина, А. В. Novel Polymorph of Favipiravir-an Antiviral Medication. *Pharmaceutics* **2021**, *13* (2), 139–139.
14. Babashkina, M. G.; Frontera, A.; Кертман, А. В.; Yasemin Saygideğer Kont; S. Murugavel; Safin, D. A. Favipiravir: Insight into the Crystal Structure, Hirshfeld Surface Analysis and Computational Study. *Journal of the Iranian Chemical Society* **2021**, *19* (1), 85–94.
15. Sajadian, S. A.; Ardestani, N. S.; Esfandiari, N.; Askarizadeh, M.; Jouyban, A. Solubility of Favipiravir (as an Anti-COVID-19) in Supercritical Carbon Dioxide: An Experimental Analysis and Thermodynamic Modeling. *The Journal of Supercritical Fluids* **2022**, *183*, 105539.
16. Gattani, V.; Dawre, S. Development of Favipiravir Loaded PLGA Nanoparticles Entrapped in In-Situ Gel for Treatment of Covid-19 via Nasal Route. *Journal of Drug Delivery Science and Technology* **2022**, *79*, 104082.
17. Deka, P.; Gogoi, D.; Althubeiti, K.; Rao, D. R.; Thakuria, R. Mechano-synthesis, Characterization, and Physicochemical Property Investigation of a Favipiravir Cocrystal with Theophylline and GRAS Coformers. *Crystal Growth & Design* **2021**, *21* (8), 4417–4425.
18. Li, H.; Wang, L.; Xie, G.; Yao, C.; Song, S.; Qu, Y.; Han, P.; Wang, H.; Sun, Y.; Wu, H.; Tao, X. Cocrystals of Favipiravir: Improved Physicochemical Properties and Solution Stability Study. *Crystal Growth & Design* **2023**, *23* (12), 8656–8669.
19. Li, H.; Wang, L.; Ye, X.; Yao, C.; Song, S.; Qu, Y.; Jiang, J.; Wang, H.; Han, P.; Liu, Y.; Tao, X. Efficient Screening of Pharmaceutical Cocrystals by Microspacing In-Air Sublimation. *Journal of the American Chemical Society* **2024**, *146* (17), 11592–11598.
20. Mirocki, A.; Lopresti, M. Impact of Halogen Substituent Nature and Position on the Structural and Energetic Properties of Carbamazepine Cocrystals with Meta-Halobenzoic Acids: A Two-Pathway Synthesis Study. *ChemPlusChem* **2025**, *90* (11).
21. Benito, M.; Frontera, A.; Elies Molins. Cocrystallization of Antifungal Compounds Mediated by Halogen Bonding. *Crystal growth & design* **2023**, *23* (4), 2932–2940.
22. Nanubolu, J. B.; Ravikumar, K. Correlating the Melting Point Alteration with the Supramolecular Structure in Aripiprazole Drug Cocrystals. *CrystEngComm* **2016**, *18* (6), 1024–1038.

Chapter 9 - Can we modulate some photophysical properties of cocrystals?

9.1 Introduction

We previously explored how systematic modifications of molecular structure influence physical properties of bulk materials such as thermal stabilities and hygroscopicity. Building on these, the present chapter focuses on modulating the photophysical properties of cocrystals, examining how structural features can be leveraged to control properties.

Key characteristics of solid-state materials, such as thermal stability¹⁻⁴, aqueous solubility⁵⁻⁷, mechanical flexibility⁸⁻¹², and manufacturability¹³⁻¹⁴, determine performance and effectiveness when transitioning from fundamental research to applications and devices. The molecular building blocks of a crystalline material also impact its bulk properties, and the relative orientation of these building blocks with respect to each other can make a dramatic difference in physical properties. With this in mind, a range of bottom-up strategies has been employed to control solid-state assembly through the deliberate use of directional intermolecular forces.¹⁵⁻²²

Recently, cocrystallization has emerged as an effective way to tune photophysical properties of solid-state materials. In 2020, Zeng and coworkers reported the color tuning of an active pharmaceutical ingredient via cocrystallization, presenting metronidazole and pyrogallol cocrystals as a case study.²³ In this study, the cocrystal showed an increased dissolution rate compared to the drug itself, and the results suggested that the cocrystal strategy may be used to tune the color of pharmaceutical drugs, which might help drug formulation development. A study by Wang and coworkers developed a color-tunable up-conversion emission switch in which two different electron donors with the same acceptor molecule yield distinct red and yellow emissions, providing a good example of controlling cocrystal-to-cocrystal transformation. ²⁴ MacGillivray

and coworkers reported a red zwitterionic cocrystal of acetaminophen and 2,4-pyridinedicarboxylic acid, and despite both parent materials being colorless, the cocrystal exhibited a red color, due to reduced π - π gap as determined using density functional theory calculations.²⁵ Together, these studies suggest that cocrystallization can be a powerful approach to modulate photophysical properties of solid-state materials.

Inspired by such studies, we explored the possibility of fine-tuning photophysical properties in a series of cocrystals by making very specific changes to the nature of the coformers, whilst keeping the overall crystal structures as consistent as possible. We also examined the relative importance of competing factors in solid-state assembly such as hydrogen bonding and ‘sterics’ by increasing the chain length of our target material systematically, to maintain considerable control of the main structural parameters and metrics in these solids. With these two goals in mind, we synthesized nine cocrystals using five different acceptor molecules (targets) and two different donor molecules (coformers). The molecules are classified as ‘donors’ and ‘acceptors’ based on the role they are most likely to play in a charge-transfer scenario. Here, we chose 3-dimethylaminobenzoic acid (3DMABA), and 4-aminobenzoic acid (4ABA) as donors with different electron-donating capacities and (*N*-(5-nitropyridin-2-yl)acetamide (T1), *N*-(5-nitropyridin-2-yl)propionamide (T2), *N*-(5-nitropyridin-2-yl)butyramide (T3), *N*-(5-nitropyridin-2-yl)pentanamide (T4), and *N*-(5-nitropyridin-2-yl)hexanamide (T5) as acceptors to set up a group of cocrystals (Figure 9.1).

The choice of coformers was deliberate, and we expected the carboxylic acid functionality of the donors to form robust R_2^2 (8) dimeric hydrogen-bonding (Figure 9.2) with the pyridine and amide nitrogen atom of the acceptors; this heterosynthon is well established in the literature.²⁶⁻²⁸ We intended for this to promote a certain amount of structural consistency across the series of cocrystals. If overall structural control was achieved, we hypothesized that it would be possible to

make deliberate changes to the photophysical behavior of these materials simply by referencing the calculated HOMO-LUMO gap of donor-acceptor pairs of molecules.

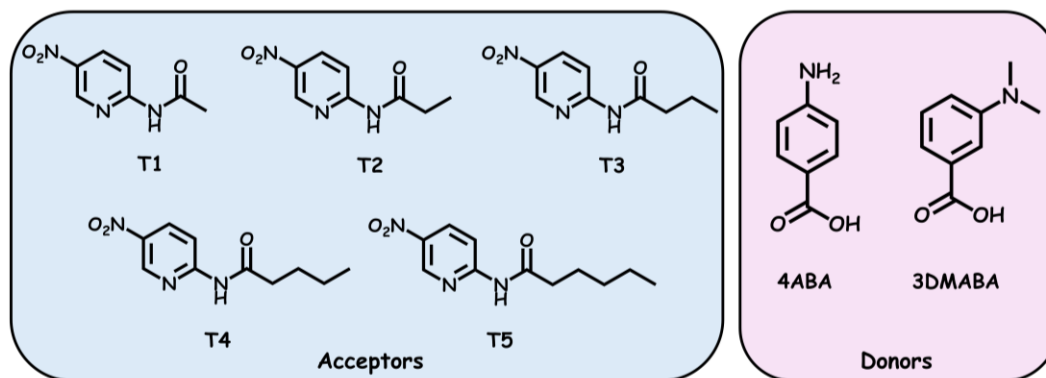


Figure 9.1. Chemical structures of donor and acceptor molecules.

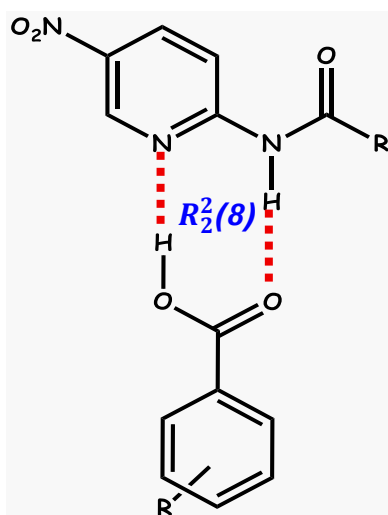


Figure 9.2. Anticipated $R_2^2(8)$ dimeric hydrogen-bonding motif.

9.2 Experimental section

9.2.1 General

All acceptor molecules were synthesized and purified in our laboratory.²⁹ Other precursors and solvents were purchased from commercial sources and used without further purification. Melting points were recorded on a TA Instruments DSC Q20 differential scanning calorimeter. IR spectra

were recorded with a Nicolet 380 FTIR spectrometer using an attenuated total reflection (ATR) technique with a ZnSe crystal. Single-crystal X-ray diffraction (SCXRD) data were collected on a Rigaku XtaLAB Synergy-S single-crystal X-ray diffractometer equipped with Cu K α radiation. PXRD patterns were collected using a Bruker X-ray powder diffractometer equipped with CuK α radiation, operated at 30 kV and 15 mA. Diffuse reflectance absorbance data were measured using a Cary 500 UV-Vis-NIR spectrophotometer. HOMO-LUMO calculations were done with density functional B3LYP level of theory using 6-311++G** basis set in vacuum, using Spartan'14 software.³⁰

9.2.2 Preparation of the cocrystals

Liquid-assisted grinding was performed with equimolar amounts of donor and acceptor in the presence of one or two drops of methanol. In each case, the FTIR spectrum of the ground mixture was compared to those of the pure starting materials to confirm cocrystal formation. A solution of the ground mixture in a suitable solvent was then allowed to evaporate slowly for about one week to allow crystal formation. No cocrystals incorporating T1 were formed; on the other hand, two polymorphs of T2-3DMABA cocrystals were formed. Details concerning these cocrystals formed by this procedure are presented in Table 9.1.

Table 9.1. Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point/°C
N-(5-nitropyridin-2-yl)propionamide +3DMABA-Polymorph I	T2-3DMABA-PI	Methanol	Light orange, plate	121-123 °C
N-(5-nitropyridin-2-yl)propionamide +3DMABA-Polymorph II	T2-3DMABA-PII	Dichloromethane	Orange, plate	125-127 °C
N-(5-nitropyridin-2-yl)butyramide + 3DMABA	T3-3DMABA	Methanol	Reddish orange, irregular block	123-125 °C
N-(5-nitropyridin-2-yl)pentanamide +3DMABA	T4-3DMABA	Methanol	Orange, irregular block	140-142 °C
N-(5-nitropyridin-2-yl)hexanamide +3DMABA	T5-3DMABA	Methanol	Orange, plate	123-125 °C

N-(5-nitropyridin-2-yl)propionamide +4ABA	T2-4ABA	Ethyl acetate	Light yellow, needle	154-156 °C.
N-(5-nitropyridin-2-yl)butyramide + 4ABA	T3-4ABA	Methanol	Yellow, irregular	161-164 °C
N-(5-nitropyridin-2-yl)pentanamide +4ABA	T4-4ABA	Methanol	Yellow, plate	141-144 °C
N-(5-nitropyridin-2-yl)hexanamide +4ABA	T5-4ABA	Methanol	Light yellow, needle	121-123 °C

Selected crystallographic data are summarized in Table 9.2, while complete experimental details are given in Appendix I. The structures were solved with the ShelXT 2018/2³¹ structure solution program using the intrinsic phasing solution method, and Olex2³² was used as the graphical interface. The model was refined with version 2018/3 of ShelXL 2018/3³³ using Least Squares minimization.

Table 9.2. Crystallographic data

Structure	Space group	Z, Z'	<i>a</i> /Å	<i>b</i> /Å	<i>c</i> /Å	<i>U</i> _{cell} /Å ³	T/K	<i>D</i> _{calc} /g cm ⁻³ (at T)
T2-3DMABA-PI	<i>P2₁/n</i>	4,1	16.7360(4)	4.91439(11)	21.9254(5)	1784.68(7)	200.00(10)	1.341
T2-3DMABA-PII	<i>C2/c</i>	8,1	24.8829(8)	6.1032(2)	23.3288(12)	3484.7(2)	295.0(4)	1.374
T3-3DMABA	<i>P</i> -1	2,1	6.21761(15)	12.5048(2)	12.7578(4)	945.96(4)	200.0(1)	1.314
T4-3DMABA	<i>P</i> -1	2,1	6.35274(15)	12.46903(18)	12.9378(3)	966.16(4)	200(2)	1.335
T5-3DMABA	<i>P</i> -1	2,1	6.42159(9)	12.65205(14)	13.02701(17)	992.29(2)	200.00(10)	1.347
T2-4ABA	<i>P2₁/n</i>	4,1	12.5882(2)	5.17490(7)	23.3666(4)	1521.34(4)	200.00(10)	1.451
T3-4ABA	<i>P</i> -1	2,1	5.8059(4)	11.8005(10)	12.9057(16)	823.35(14)	200.00(10)	1.397
T4-4ABA	<i>P</i> -1	2,1	6.15171(12)	12.3495(4)	12.6749(4)	892.97(4)	295.9(3)	1.340
T5-4ABA	<i>P2₁/n</i>	4,1	20.1578(5)	4.90086(14)	32.5043(9)	3210.75(15)	297(1)	1.265

9.2.3 Solid-state replacement studies

Solid-state replacement experiments were carried out to evaluate the possibility of coformer exchange in the pre-formed cocrystals. The isolated cocrystal was mixed with the second, and potentially disruptive, coformer in two different stoichiometric ratios (1:0.5 and 1:1 relative to the original coformer composition), and the mixtures were subjected to liquid-assisted grinding

(LAG). The resulting products were analyzed by PXRD and compared with PXRD patterns of the starting cocrystals and the corresponding starting materials to determine whether coformer exchange had occurred.

9.3 Results

9.3.1 Physical appearance

All starting targets and coformers in this study appeared as white or off-white powders. However, striking color changes occurred during the grinding studies, as depicted in Figure 9.3. It should be noted that none of the grinding experiments with T1 produced any cocrystals, based on our IR analysis, and neither of the ground mixtures of T1 gave any notable color changes.



Figure 9.3. Physical appearance of starting materials: T3, 3DMABA, 4ABA, and their ground mixtures.

All cocrystals that were formed with T2-T5 displayed distinctly different physical appearances (Figure 9.4) compared to their respective starting materials.

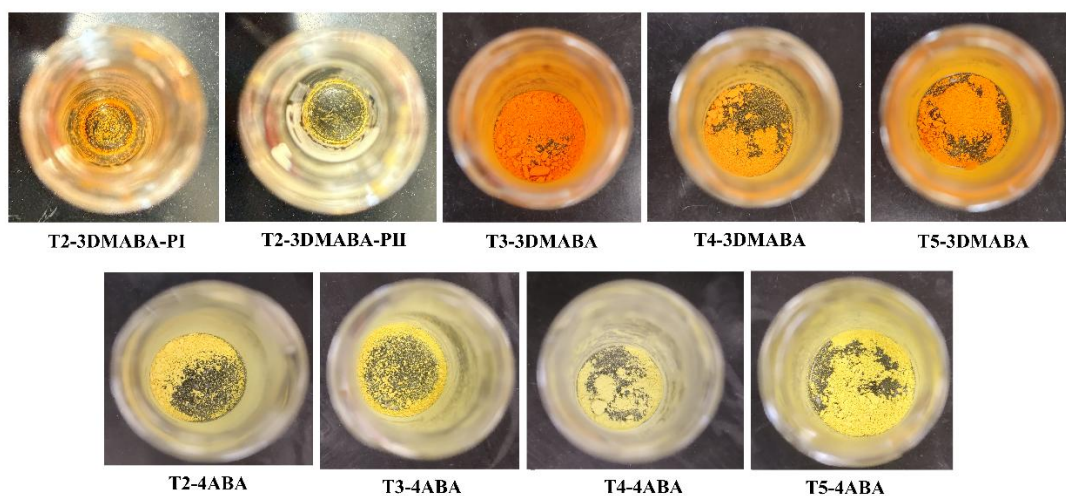


Figure 9.4. Physical appearance of resultant ground mixtures.

9.3.2 Infrared spectra (IR) analysis

To confirm the formation of cocrystals, the IR spectra of acceptors, donors, and ground mixtures were analyzed. The characteristic peaks of all five acceptors, two donors, and ground mixtures are given in Table 9.3.

Table 9.3. IR frequencies of acceptors, donors and ground mixtures.

		Coformer	
		3DMABA	4ABA
Target	IR stretch/cm ⁻¹	1670	1660
T1	1685/1669	1678/1670	1672/1662/1656
T2	1682	1705, 1672	1707, 1672
T3	1695	1712, 1675	1706, 1675
T4	1697	1714, 1679	1715, 1674
T5	1697	1712, 1679	1695, 1686

In the IR spectrum of each cocrystal, the characteristic peaks have shifted significantly from their original positions. However, for the T1 acceptor with both 3DMABA and 4ABA, the signature coformer bands remained in the same place, indicating no cocrystal formation.

In the 3DMABA coformer, the C=O stretch is observed at 1670 cm^{-1} , while in the 4ABA coformer it is located at 1660 cm^{-1} . The C=O modes of the four ground mixtures, T2-3DMABA, T3-3DMABA, T4-3DMABA, and T5-3DMABA, corresponding to the 3DMABA donor, exhibit a blue shift, at $1672, 1675, 1679$, and 1679 cm^{-1} , respectively. In these four mixtures, the C=O band accountable for acceptors, T2, T3, T4, and T5, are also blue shifted to $1705, 1712, 1714$, and 1712 cm^{-1} , respectively.

As with the ground mixtures of the 3DMABA coformer, the four mixtures of the 4ABA coformer exhibit a blue shift for donor C=O, at $1672, 1675, 1674$, and 1686 cm^{-1} , respectively. In these four cocrystals, the C=O peaks accountable for targets T2, T3, and T4 are also blue shifted to $1707, 1706$, and 1715 cm^{-1} , respectively, except the C=O band for T5. For T5-4ABA, the C=O mode belonging to T5 is red-shifted to 1695 cm^{-1} , confirming the formation of a different type of cocrystal.

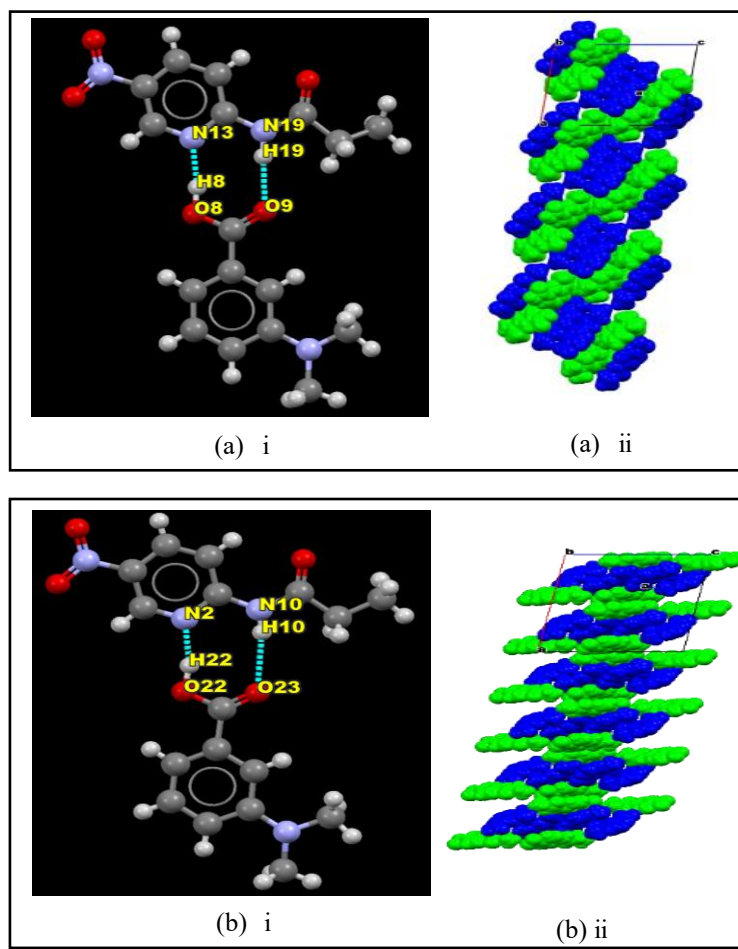
In summary, significant shifts of the position of the C=O stretching modes were taken as evidence for cocrystal formation.

9.3.3 Crystal structure analysis (SCXRD)

We obtained crystals suitable for single-crystal X-ray diffraction for nine cocrystals (T2-3DMABA-PI, T2-3DMABA-PII, T3-3DMABA, T4-3DMABA, T5-3DMABA, and T2-4ABA, T3-4ABA, T4-4ABA, T5-4ABA). In all but one compound, there is a 1:1 stoichiometric ratio of the donor and acceptor molecules. The one exception is T5-4ABA, where the donor: acceptor ratio is 1:2. In addition, T2-3DMABA produced two polymorphs, crystallized from methanol and dichloromethane, respectively, Table 9.1.

The polymorphs of T2 belonged to $P2_1/n$ and $C2/c$ space groups in the monoclinic system. The T3-3DMABA, T4-3DMABA, and T5-3DMABA cocrystals exhibit a similar packing arrangement to each other, all in the triclinic, $P-1$ space group, Figure 9.5.

All donor and acceptor molecules in the cocrystals are stacked in a slipped face-to-face arrangement, facilitating charge-transfer between neighboring π clouds. Charge-transfer is indicated by relatively short interplanar distances (3.171 Å for T2-3DMABA-PI, 3.324 Å for T2-3DMABA-P1I, 3.337 Å for T3-3DMABA, 3.345 Å for T4-3DMABA, and 3.299 Å for T5-3DMABA (Appendix I) leading to colored compounds. The donor and acceptor of each cocrystal are interconnected through $C=O\cdots H-N$ and $O-H\cdots N(py)$ hydrogen bonds (Figure 9.5 (a) i, (b) i, and (c) i).



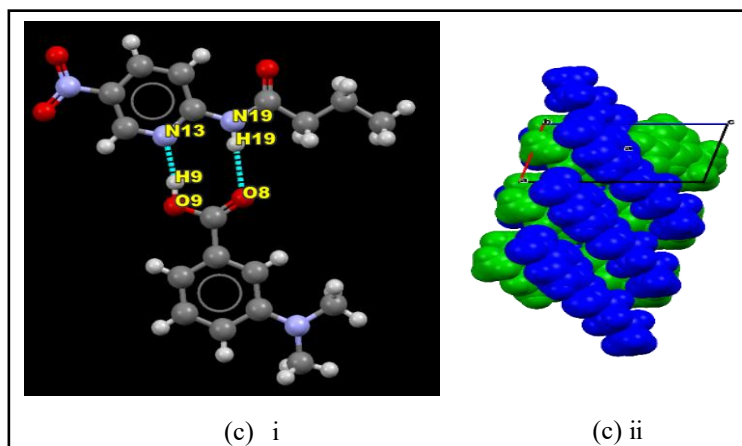


Figure 9.5. (a) i. Asymmetric unit of T2-3DMABA-PI, (a) ii. $\pi\cdots\pi$ stacking, (b) i. Asymmetric unit of T2-3DMABA-PII, (b) ii. $\pi\cdots\pi$ stacking, (c) i. Asymmetric unit of T3-3DMABA, (c) ii. $\pi\cdots\pi$ stacking (blue = donor, green = acceptor).

In the series with 4ABA coformer, the cocrystals belonged to two different space groups, $P2_1/n$ and $P-1$. T2-4ABA and T5-4ABA belong to the $P2_1/n$ space group in the monoclinic system, and T3-4ABA and T4-4ABA belong to the $P-1$ space group in the triclinic system. In each case, acceptor and donor appear in a 1:1 stoichiometric ratio except for the one with the T5 target, where they interact in a 2:1 acceptor: donor ratio, Figure 9.6 (c). Although T2-4ABA and T5-4ABA belong to the same space group, the packing arrangement is different since the molar ratios are different. In the first three cocrystals, the layers are weakly connected with a face-to-face pattern leading to charge-transfer interaction, but the last one was completely different (interlayer distances: 3.237 Å for T2-4ABA, 3.175 Å for T3-4ABA, 3.277 Å for T4-4ABA, and 3.355 Å for T5-4ABA (Appendix I).

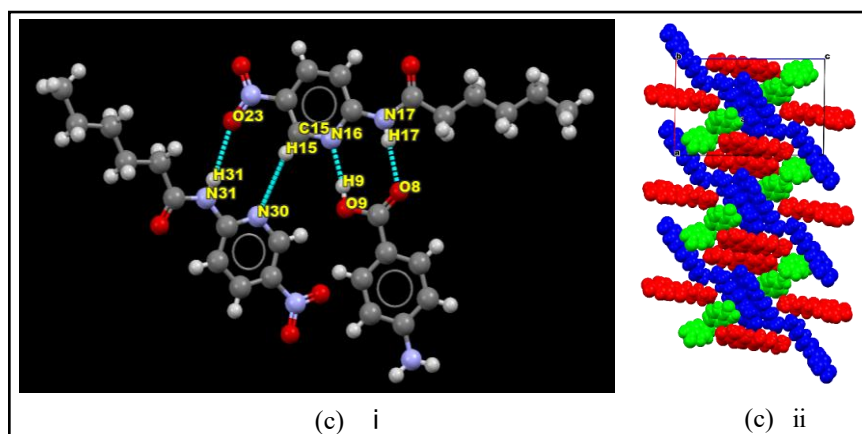
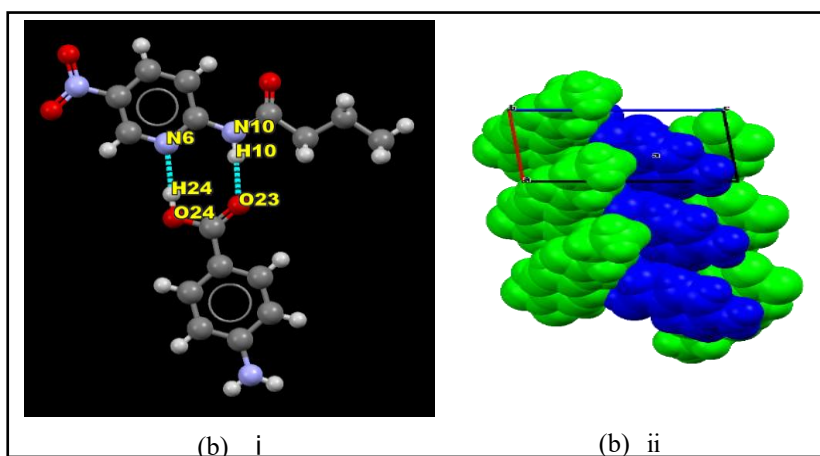
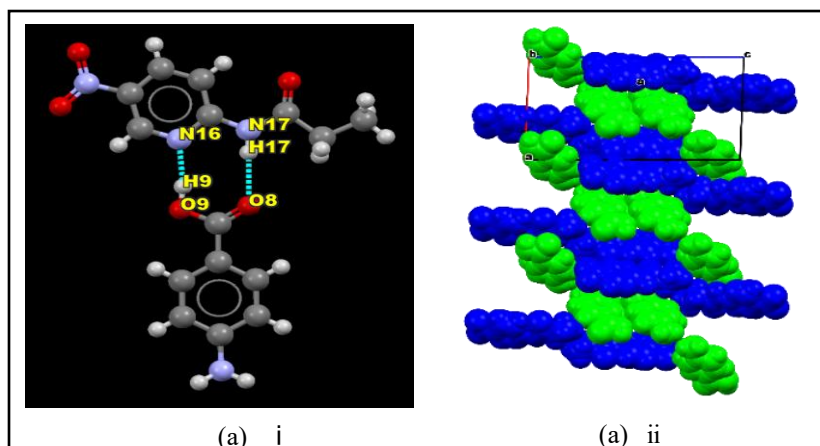


Figure 9.6. (a) i. Asymmetric unit of T2-4ABA, (a) ii. $\pi\cdots\pi$ stacking (blue = donor, green = acceptor), (b) i. Asymmetric unit of T3-4ABA-P1I, (b) ii. $\pi\cdots\pi$ stacking (green = donor, blue/red = acceptors), (c) i. Asymmetric unit of T5-4ABA, (c) ii. Charge-transfer structure.

9.3.4 Powder X-ray diffraction (PXRD) analysis

To establish phase purity of the cocrystals, the PXRD patterns of the acceptor, donors, and ground mixtures were analyzed. The simulated PXRD patterns of the nine cocrystals were generated using Mercury⁶³ and compared with the experimental PXRD patterns of the ground mixtures (Appendix I). The powder patterns of the cocrystals are different from those of the individual donors and acceptors, suggesting the formation of new crystalline phases. Furthermore, the diffraction peak positions in the experimental PXRD patterns of the six cocrystals (T3-3DMABA, T4-3DMABA, T5-3DMABA, T2-4ABA, T3-4ABA, and T4-4ABA) and the simulated PXRD patterns are consistent with each other, without the presence of additional peaks, underscoring that these powders are structurally homogenous. However, the simulated and experimental powder patterns of T2-3DMABA and T5-4ABA are different and also unrelated to their donor and acceptor PXRD patterns, respectively, indicating possible polymorphism (which was separately confirmed for T2-3DMABA in our single-crystal X-ray studies).

9.3.5 HOMO-LUMO calculations

Frontier molecular orbital theory can provide valuable insights into the photophysical properties of charge-transfer compounds. To explore whether it is possible to correlate the observed photophysical properties of these cocrystals with the calculated HOMO-LUMO energy gap, we carried out the relevant DFT calculations at the B3LYP/6-311++G** level of theory in vacuum using Spartan to determine the energy levels of donors and acceptors separately, as well as for the heteromeric donor-acceptor pairs. (Figures 9.7 and 9.8). Donor and acceptor molecules display wide HOMO-LUMO gaps with values of 4.2 eV for 3DMABA, 4.9 eV for 4ABA, and 4.5 eV for all four target molecules. When the cocrystals are formed, the HOMO-LUMO gaps are narrowed. The energy gap values [$E_{\text{LUMO}} - E_{\text{HOMO}}$] of T2-3DMABA, T3-3DMABA, T4-3DMABA, T5-

3DMABA, T2-4ABA, T3-4ABA, T4-4ABA, and T5-4ABA are 2.6 eV, 2.5 eV, 2.5 eV, 2.5 eV, 3.3 eV, 3.3 eV, 3.3 eV, 3.5 eV, and 3.1 eV, respectively. This narrowing facilitates the charge-transfer between donor and acceptor molecules. As shown in Figures 7 and 8, the HOMOs of the four cocrystals are located on the corresponding donors, and the LUMOs are distributed on the acceptors. It further confirms that the charge-transfer transitions take place from donors to acceptors. Moreover, the colors of the materials aligned effectively with the resultant energy gaps.

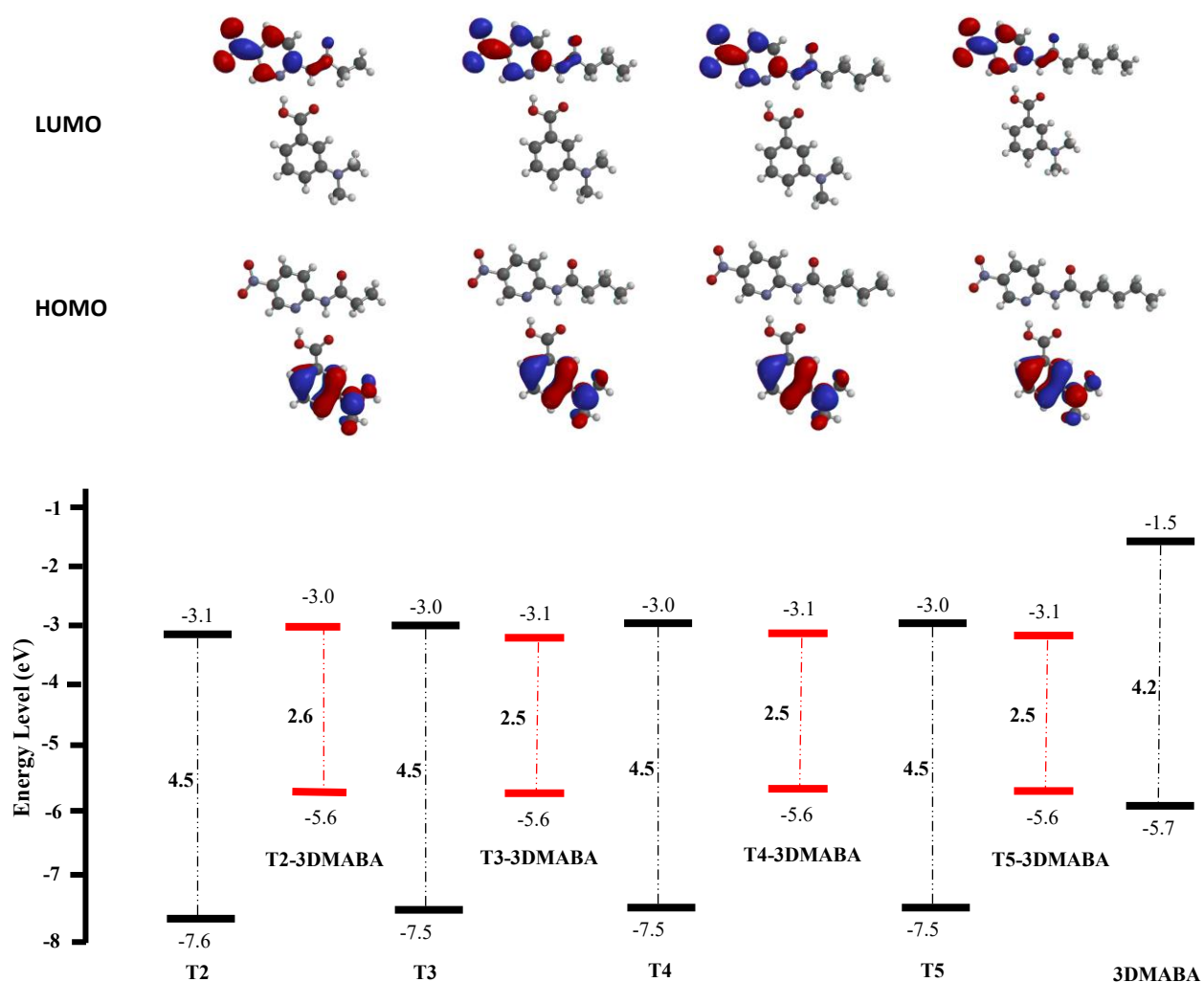


Figure 9.7. HOMO and LUMO energy level diagrams of 3DMABA cocrystals and their starting materials.

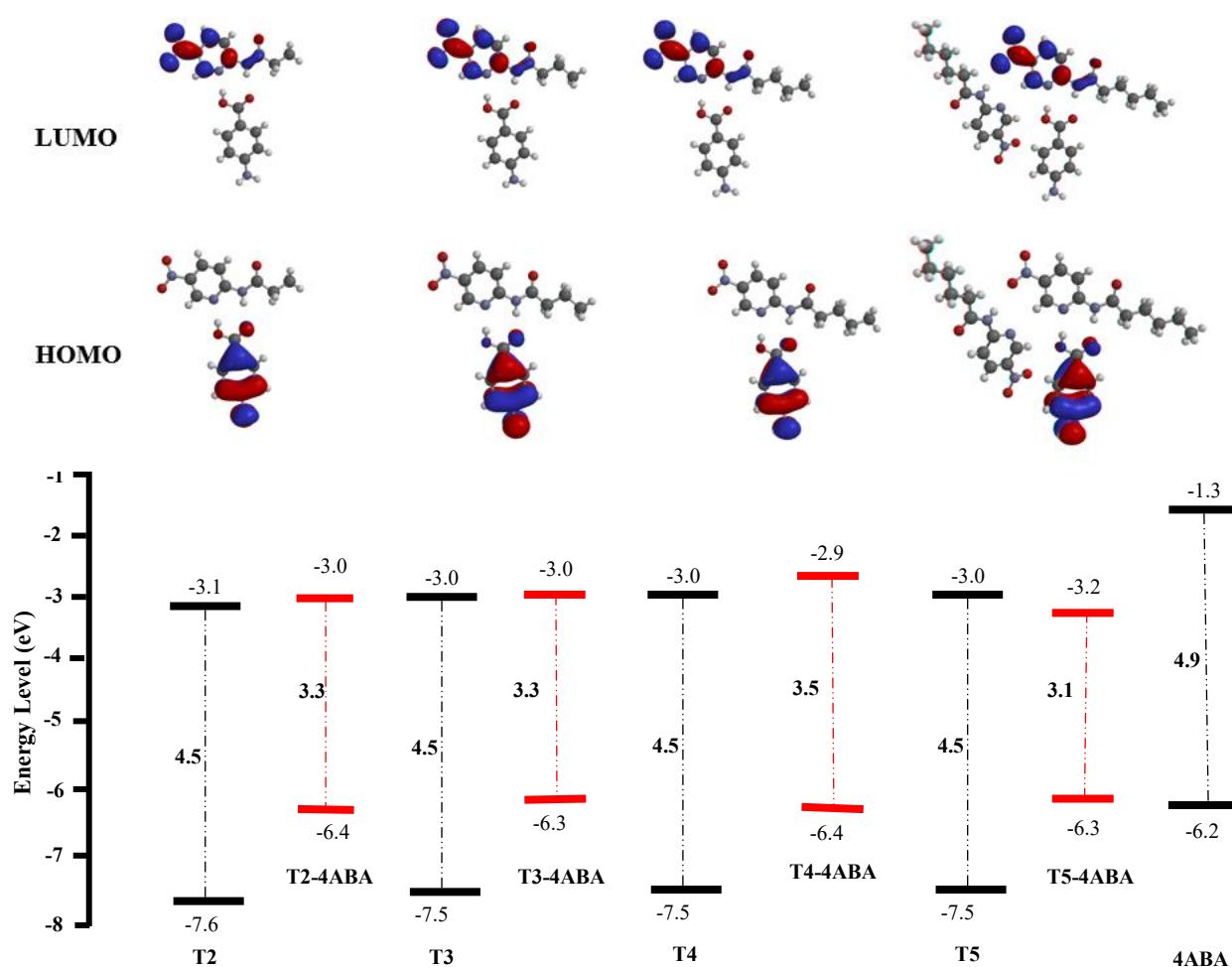


Figure 9.8. HOMO and LUMO energy level diagrams of 4ABA cocrystals and their starting materials.

9.3.5 Charge transfer character

The optical properties and electronic transitions for T3-3DMABA and T3-4ABA were further investigated using TD-DFT calculations at the B3LYP/6-31G level of theory in vacuum using Gaussian. The calculated electronic absorption spectrum of T3-3DMABA exhibits two low-energy transitions at 679 nm (S1) and 676 nm (S2), and each is composed of multiple electronic transitions. The oscillator strengths of these transitions are 0.0064 a.u. and 0.0343 a.u.,

respectively. Therefore, it can be concluded that this absorption peak is dominated by the excitation at 676 nm.

Similarly, the electronic absorption spectrum of T3-4ABA was calculated at the same level of theory. Two low-energy transitions were observed at 487 nm (S1) and 486 nm (S2), with oscillator strengths of 0.0028 a.u. and 0.0029 a.u., respectively. Since the oscillator strengths are nearly identical, both transitions contribute similarly to the absorption spectrum. Analysis of the molecular orbital contributions shows that the first excited state (S1, 487 nm) arises from a combination of HOMO $\rightarrow$ LUMO+1 and HOMO-1 $\rightarrow$ LUMO transitions, while the second excited state (S2, 486 nm) involves HOMO-1 $\rightarrow$ LUMO+1 and HOMO $\rightarrow$ LUMO+1 transitions. These results indicate that both states have comparable transition probabilities, leading to similar intensities in the calculated spectrum. The transitions and their contributions are given in Table 9.4 and Figure 9.9.

Table 9.4. Calculated electronic absorption parameters

Compound	Excitation energy/eV	Excited state	Oscillator strength (a.u)	Transitions	Weight
T3-3DMABA	1.8255 (679 nm)	1	0.0064	HOMO-1 $\rightarrow$ LUMO	21.03%
				HOMO-1 $\rightarrow$ LUMO+1	3.83%
				HOMO $\rightarrow$ LUMO	22.08%
				HOMO $\rightarrow$ LUMO+1	2.95%
	1.8334 (676 nm)	2	0.0343	HOMO-1 $\rightarrow$ LUMO	0.04%
				HOMO-1 $\rightarrow$ LUMO+1	19.75%
				HOMO $\rightarrow$ LUMO	2.7%
				HOMO $\rightarrow$ LUMO+1	23.36%
T3-4ABA	2.5461 (487 nm)	1	0.0028	HOMO-1 $\rightarrow$ LUMO	19.72%
				HOMO $\rightarrow$ LUMO	30.12%
	2.5522 (486 nm)	2	0.0029	HOMO-1 $\rightarrow$ LUMO+1	21.76%
				HOMO $\rightarrow$ LUMO+1	28.08%

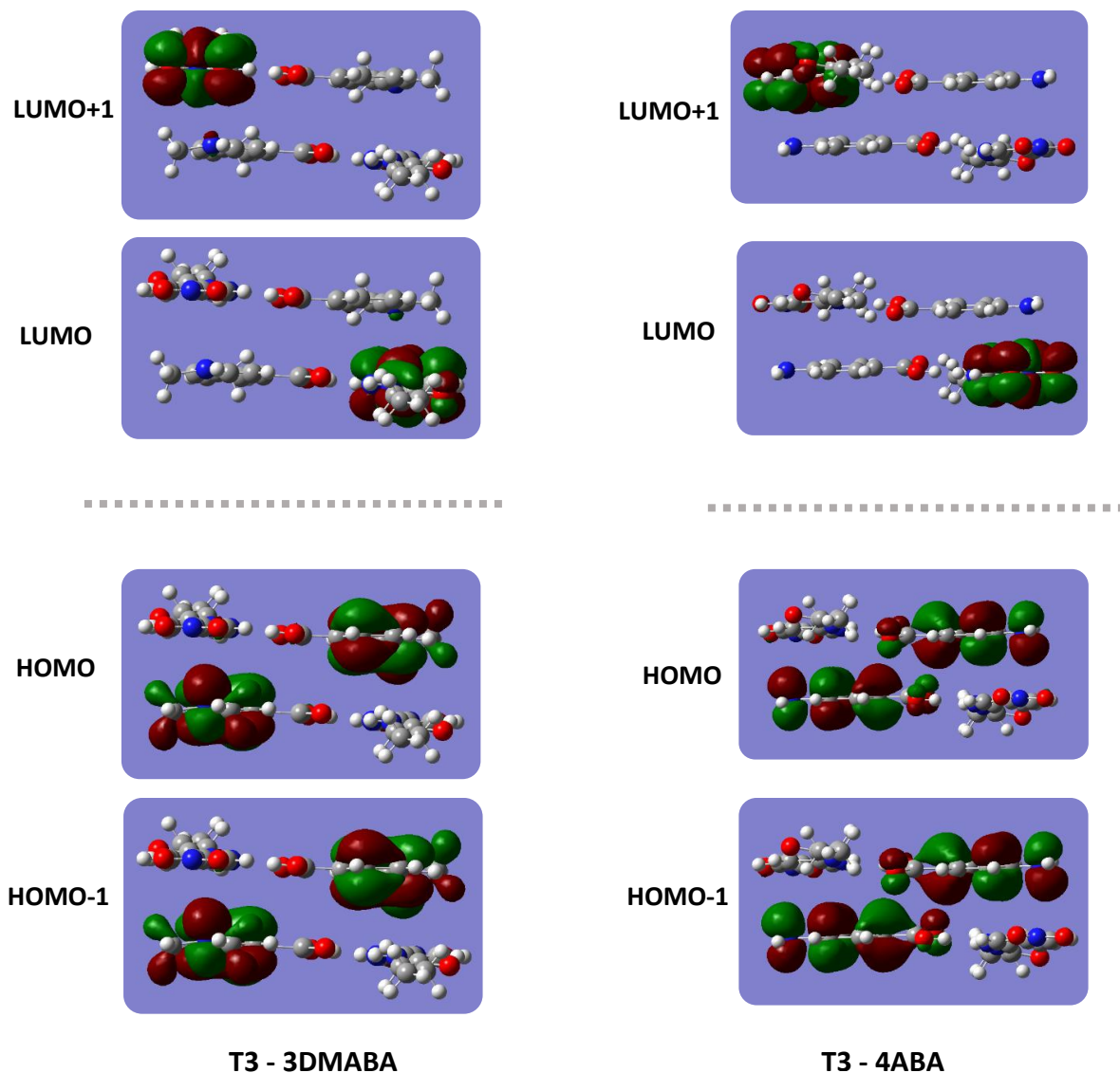


Figure 9.9. Molecular orbitals contributing to the transitions.

9.3.6 Photophysical properties

9.3.6.1 Solid-state UV absorption

Solid-state UV absorption spectra of the acceptors, donors, and cocrystals were obtained to investigate the photophysical properties of the cocrystals (Figure 9.10 and Appendix I). Acceptor molecules exhibit absorption peaks in the range of 300-420 nm, while 3DMABA shows the absorption around 350-450 nm, and 4ABA has a strong absorption within 325-350 nm. In

particular, the absorption peaks of cocrystals with 3DMABA cofomers exhibit a wide range of absorbance within 400-600 nm, and the cocrystal with 4ABA cofomer shows a broad range of absorbance within 400-500 nm. The absorption peaks of the acceptor and the donor molecules can be attributed to $\pi \rightarrow \pi^*$ transitions. Moreover, the absorption bands of all nine cocrystals display broadening and red-shift, indicating the occurrence of charge-transfer between the acceptor and the donor molecules within the cocrystals.

The absorbance wavelengths of these materials are more readily related to the observed colors of each material, respectively. The cocrystals with 3DMABA absorb mostly below 600 nm, and they appear red/orange to the naked eye. Similarly, cocrystals with 4ABA are yellow, and they all absorb below 500 nm, which is consistent with expectations.

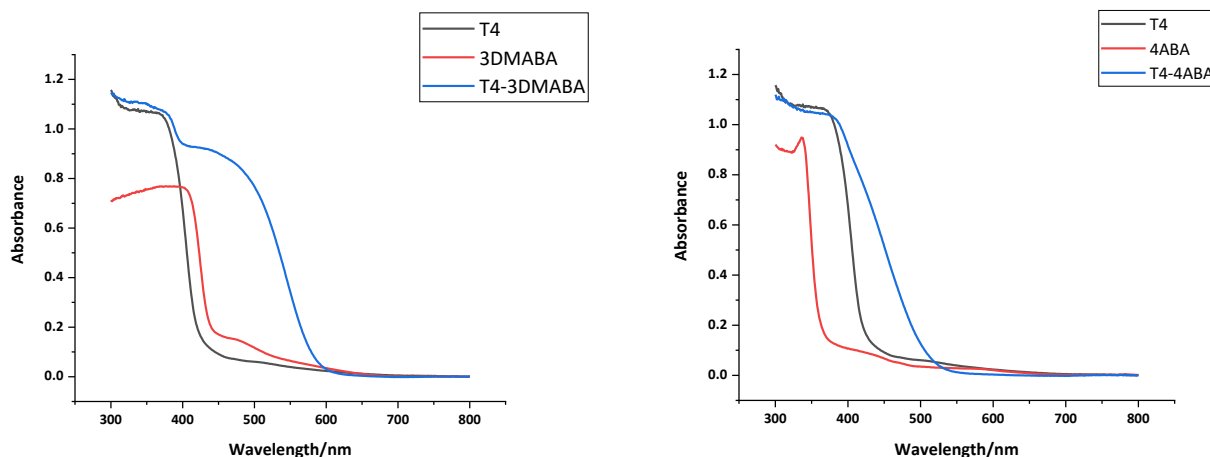


Figure 9.10. Solid-state UV-Visible spectra comparison of (a) T4-3DMABA cocrystal with its parent materials and (b) T4-4ABA cocrystal with its parent materials.

9.3.6.2 Photoluminescence studies

Photoluminescence (PL) spectra were collected using a Jobin-Yvon Fluoromax-2 with a xenon arc lamp source and photon-counting detection electronics. Although several compounds exhibited photoluminescence, the observed color did not originate from their emission. Instead, visible color

arises solely from their absorption characteristics in the UV-visible range. The corresponding photoluminescence data are provided in Appendix I.

9.3.7 Solid-state replacement studies

The PXRD patterns of the ground products showed no significant differences from those of the parent cocrystal (Appendix I). All characteristic peaks of the original cocrystal and the second coformer were retained, and no new peaks corresponding to a new phase were observed. These results indicate that solid-state replacement has not occurred under the given conditions, even at a 1:1 stoichiometric ratio. This indicated that the initially formed cocrystal is thermodynamically stable and resistant to coformer replacement at least under the experimental conditions that we explored.

9.4 Discussion

The present study demonstrates that systematic modification of target molecules and the use of different coformers can provide an effective strategy for tuning photophysical properties of cocrystals. In this work, nine charge-transfer cocrystals were synthesized and all of them exhibited distinct visible color changes during LAG, suggesting the formation of charge-transfer cocrystals. IR spectroscopy further confirmed the formation of new cocrystals through characteristic shifts in vibrational bands relative to the starting materials, and DSC revealed new melting points for each compound.

Crystallographic data were obtained, providing detailed insight into their supramolecular assembly. Structural analyses revealed that most cocrystals adopt a 1:1 donor-acceptor stoichiometry, except for T5-4ABA, which forms a 2:1 acceptor-to-donor ratio. Nevertheless, across the nine synthesized cocrystals, the $R_2^2(8)$ hydrogen-bond motif was persistent, indicating that the primary supramolecular synthon remains robust despite variations in targets and

coformers. The retention of this motif also demonstrates that the expected hydrogen-bonding interactions between the target and coformer functional groups direct the crystal packing and maintain structural consistency across the series. Further, they showed that they are packed in a slipped face-to-face arrangement, in which acceptor aromatic rings interact with donor aromatic rings through charge transfer interactions. PXRD analyses further confirmed the homogeneity of the synthesized materials. The PXRD patterns of the ground samples aligned well with those simulated from the crystal structures and were absent from the remaining starting materials.

Theoretical calculations provide additional insight into these structures. The calculated HOMO-LUMO energy gaps for the donor-acceptor pairs fall within the visible range, supporting the formation of charge-transfer interactions. In particular, the relatively smaller energy gaps calculated for the 3DMABA cocrystals and slightly larger gaps obtained for the 4ABA cocrystals agreed with the observed colors. Theoretical calculations also indicated that the HOMO is localized on the donor molecule, while the LUMO is localized on the acceptor molecule, as expected for these charge-transfer cocrystals. Additionally, calculations of the charge-transfer character further support the presence of donor-to-acceptor electronic transitions,

The solid-state UV-visible absorption spectra provide further experimental evidence for these charge-transfer interactions. The broadening and red-shift of absorption bands in the solid state are characteristic of intermolecular π - π interactions between donor and acceptor molecules. These spectral changes support the conclusion that the observed colors originate primarily from donor-acceptor π - π charge-transfer interactions. Photoluminescence studies showed that only some cocrystals are photoluminescent. Importantly, the observed colors of the cocrystals arise mainly from absorption rather than emission processes.

Finally, solid-state replacement experiments indicate that no coformer exchange occurs within the cocrystals, demonstrating the stability of pre-existing cocrystals.

Overall, the results demonstrate that coformer selection provides an effective way of modulating the photophysical properties of charge-transfer cocrystals without significantly altering their fundamental structural motifs. The correlation between calculated HOMO-LUMO gaps and experimentally observed colors indicates that theoretical predictions can serve as a tool for pre-determining cocrystals with targeted photophysical properties.

9.5 Conclusions

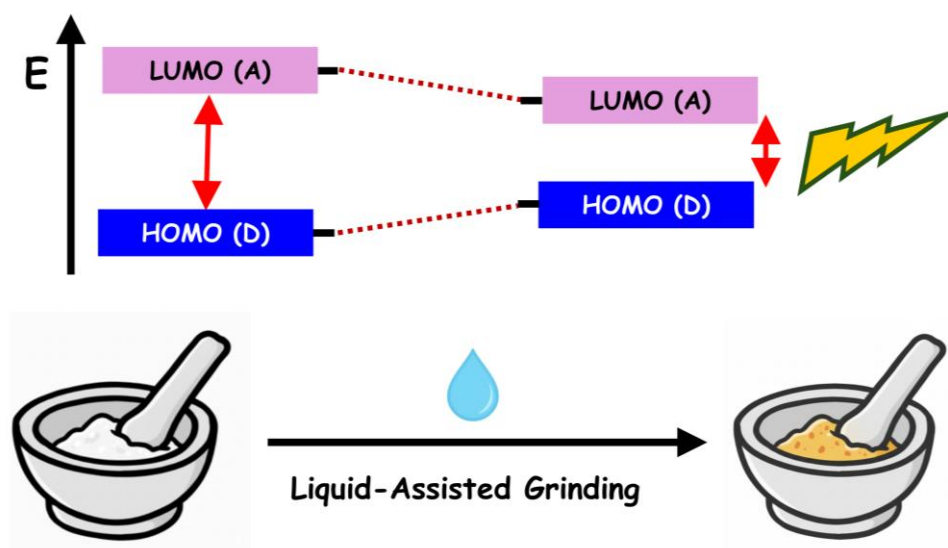


Figure 9.10. Summary of findings of the study.

In summary, nine cocrystals were successfully synthesized and fully characterized. By deliberately selecting coformers and systematically modifying the targets, we were able to maintain structural consistency across all cocrystals while preserving the $R_2^2(8)$ hydrogen-bonded motif. The crystal structure analysis reveals that the donor and acceptor molecules in each cocrystal are combined in a 1:1 stoichiometric ratio, except for T5-4ABA, which has a 2:1 acceptor: donor ratio. This

demonstrates that competing intermolecular forces, such as sterics and hydrogen bonding, do not significantly restrict control over solid-state structural parameters.

All cocrystals exhibited color changes during liquid-assisted grinding. These cocrystals have small HOMO-LUMO gaps (2.6 eV for T2-3DMABA-PI; 2.5 eV for T3-3DMABA, T4-3DMABA, and T5-3DMABA; 3.3 eV for T2-4ABA and T3-4ABA; 3.5 eV for T4-4ABA; and 3.1 eV for T5-4ABA), which facilitates charge-transfer and serves as a rationale for their observed colors. This indicates that calculated HOMO-LUMO gaps of donor-acceptor pairs can be used to guide the design of functional cocrystals with desired colors.

In solid-state UV-visible spectra, the absorption bands of all cocrystals display considerable broadening and red shift, indicating the occurrence of charge-transfer between the acceptor and the donor molecules within the cocrystals. Photoluminescence studies showed that only some compounds are photoluminescent; however, the observed colors arise solely from UV-visible absorption.

Overall, this study shows that systematic coformer selection enables modulation of photophysical properties and establishes a predictive strategy for the rational design of functional cocrystal systems

9.6 References

1. Barra, G.; Guadagno, L.; Raimondo, M.; M. Gabriella Santonicola; Toto, E.; Stefano Vecchio Cipriotti. A Comprehensive Review on the Thermal Stability Assessment of Polymers and Composites for Aeronautics and Space Applications. *Polymers* **2023**, *15* (18), 3786–3786.
2. Rahban, M.; Zolghadri, S.; Salehi, N.; Ahmad, F.; Haertlé, T.; Rezaei-Ghaleh, N.; Sawyer, L.; Saboury, A. A. Thermal Stability Enhancement: Fundamental Concepts of Protein Engineering Strategies to Manipulate the Flexible Structure. *International Journal of Biological Macromolecules* **2022**, *214*, 642–654.
3. Svärd, M.; Ahuja, D.; Rasmuson, Å. C. Calorimetric Determination of Cocrystal Thermodynamic Stability: Sulfamethazine–Salicylic Acid Case Study. *Crystal Growth & Design* **2020**, *20* (7), 4243–4251.

4. Clarke, H. D.; Arora, K. K.; Bass, H. M.; Padmini Kavuru; Tien Teng Ong; Twarita Pujari; Wojtas, Ł.; Zaworotko, M. J. Structure–Stability Relationships in Cocrystal Hydrates: Does the Promiscuity of Water Make Crystalline Hydrates the Nemesis of Crystal Engineering? *Crystal Growth & Design* **2010**, *10* (5), 2152–2167.
5. Oja, M.; Sild, S.; Piir, G.; Maran, U. Intrinsic Aqueous Solubility: Mechanistically Transparent Data-Driven Modeling of Drug Substances. *Pharmaceutics* **2022**, *14* (10), 2248.
6. Izuren, A.; Bakhtiar, M. T.; Rahim, S. A.; Adam, F.; Danial, W. H.; Mohd. Solid-State Modification Strategies for Alpha-Mangostin Solubility Enhancement: A Review on Recent Progress. *Journal of Pharmacy* **2025**, *5* (1), 170–185.
7. Wang, M.; Zhang, H.; Li, X.; Zhu, B.; Ren, G.-B.; Qi, M.-H.; Li, Z.; Xu, X. Cocrystal Strategy for Modulating Solubility, Dissolution, and Biological Activity of Triflumezopyrim: Preparation, Characterization, and Theoretical Calculations. *Crystal Growth & Design* **2025**, *25* (16), 6636–6655.
8. Wu, W.; Wei, Z.; Wang, J.; Shang, J.; Wang, M.; Chi, S.-S.; Wang, Q.; Du, L.; Zhang, T.; Zheng, Z.; Deng, Y. Enabling High-Energy Flexible Solid-State Lithium Ion Batteries at Room Temperature. *Chemical Engineering Journal* **2021**, *424*, 130335.
9. Wang, Z.; Han, W.; Shi, R.; Han, X.; Zheng, Y.; Xu, J.; Bu, X.-H. Mechanoresponsive Flexible Crystals. *JACS Au* **2024**, *4* (2), 279–300.
10. Chen, K.; Wu, W.; Zhao, H.; Wei, Y.; Zhu, S.; Huang, X.; Wang, N.; Wang, T.; Hao, H. Designing Dynamic Crystals with Multiple Flexibilities through a Cocrystal Strategy for Flexible Photo-Controlled Switches. *Crystal Growth & Design* **2023**, *23* (12), 8637–8645.
11. Wei, G.; Chen, P.; Wu, J.; Liang, Y.; Li, J.; Huang, H.; Lan, Z.; Liang, X.; Zhou, W.; Qing, P.; Tang, S. Recent Progress of Flexible Solid-State Supercapacitors: Electrodes, Electrolytes and Practical Application. *ChemPhysChem* **2024**, *26* (4), e202400957–e202400957.
12. Mohammad, A.; Köhler, T.; Biswas, S.; Stöcker, H.; Meyer, D. C. A Flexible Solid-State Ionic Polymer Electrolyte for Application in Aluminum Batteries. *ACS Applied Energy Materials* **2023**, *6* (5), 2914–2923.
13. Agne, M. T.; Böger, T.; Bernges, T.; Zeier, W. G. Importance of Thermal Transport for the Design of Solid-State Battery Materials. *PRX Energy* **2022**, *1* (3), 031002_1–031002_11.
14. Aakeröy, C. B.; Desper, J.; Fasulo, M.; Hussain, I.; Levin, B.; Schultheiss, N. Ten Years of Co-Crystal Synthesis; the Good, the Bad, and the Ugly. *CrystEngComm* **2008**, *10* (12), 1816.
15. Liu, Y.; Wang, L.; Zhao, L.; Zhang, Y.; Li, Z.-T.; Huang, F. Multiple Hydrogen Bonding Driven Supramolecular Architectures and Their Biomedical Applications. *Chemical Society Reviews* **2024**, *53* (3), 1592–1623.
16. Steiner, T. The Hydrogen Bond in the Solid State. *Angewandte Chemie International Edition* **2002**, *41* (1), 48–76.

17. Ichiro Hisaki; Suzuki, Y.; Gomez, E.; Ji, Q.; Norimitsu Tohnai; Nakamura, T.; Abderrazzak Douhal. Acid Responsive Hydrogen-Bonded Organic Frameworks. *Journal of the American Chemical Society* **2019**, *141* (5), 2111–2121.
18. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Examining Intermolecular Interactions in Crystal Structures of Amide-Substituted 2-Aminopyrimidine Derivatives. *CrystEngComm* **2025**, *27* (43), 7000–7011.
19. Wang, H.; Bisoyi, H. K.; Urbas, A. M.; Bunning, T. J.; Li, Q. The Halogen Bond: An Emerging Supramolecular Tool in the Design of Functional Mesomorphic Materials. *Chemistry - A European Journal* **2018**, *25* (6), 1369–1378.
20. Meazza, L.; Foster, J. A.; Fucke, K.; Pierangelo Metrangolo; Resnati, G.; Steed, J. W. Halogen-Bonding-Triggered Supramolecular Gel Formation. *Nature Chemistry* **2012**, *5* (1), 42–47.
21. Scilabra, P.; Terraneo, G.; Resnati, G. The Chalcogen Bond in Crystalline Solids: A World Parallel to Halogen Bond. *Accounts of Chemical Research* **2019**, *52* (5), 1313–1324.
22. Vogel, L.; Wonner, P.; Huber, S. M. Chalcogen Bonding: An Overview. *Angewandte Chemie International Edition* **2018**, *58* (7), 1880–1891.
23. Zheng, K.; Gao, S.; Chen, M.; Li, A.; Wu, W.; Qian, S.; Pang, Q. Color Tuning of an Active Pharmaceutical Ingredient through Cocrystallization: A Case Study of a Metronidazole–Pyrogallol Cocrystal. *CrystEngComm* **2020**, *22* (8), 1404–1413.
24. Wang, Y.; Wu, H.; Jones, L. O.; Mosquera, M. A.; Stern, C. L.; Schatz, G. C.; Stoddart, J. F. Color-Tunable Upconversion-Emission Switch Based on Cocrystal-To-Cocrystal Transformation. *Journal of the American Chemical Society* **2023**, *145* (3), 1855–1865.
25. John R.G. Sander; Dejan-Krešimir Bučar; Henry, R. F.; Baltrusaitis, J.; Geoff G.Z. Zhang; Macgillivray, L. R. A Red Zwitterionic Co-Crystal of Acetaminophen and 2,4-Pyridinedicarboxylic Acid. *Journal of pharmaceutical sciences* **2010**, *99* (9), 3676–3683.
26. Abeysekera, A. M.; Sinha, A. S.; Aakeroy, C. B. The Impact of Halogen Substituents on the Synthesis and Structure of Co-Crystals of Pyridine Amides. *Molecules* **2021**, *26* (4), 1147.
27. Bis, J. A.; Zaworotko, M. J. The 2-Aminopyridinium-Carboxylate Supramolecular Heterosynthon: A Robust Motif for Generation of Multiple-Component Crystals. *Crystal Growth & Design* **2005**, *5* (3), 1169–1179.
28. Hemamalini, M.; Loh, W.-S.; Quah, C. K.; Fun, H.-K. Investigation of Supramolecular Synthons and Structural Characterisation of Aminopyridine-Carboxylic Acid Derivatives. *Chemistry Central Journal* **2014**, *8* (1).
29. Marasinghe, A. A.; Averkiev, B. B.; Aakeröy, C. B. Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers? *Crystal Growth & Design* **2025**, *25* (20), 8703–8711.

30. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *Journal of Applied Crystallography* **2009**, 42 (2), 339–341.
31. Usón, I.; Sheldrick, G. M. An Introduction to Experimental Phasing of Macromolecules Illustrated BySHELX; New Autotracing Features. *Acta Crystallographica Section D Structural Biology* **2018**, 74 (2), 106–116.
32. Sheldrick, G. M. SHELXT– Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallographica Section A Foundations and Advances* **2015**, 71 (1), 3–8.
33. Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. Mercury 4.0: From Visualization to Analysis, Design and Prediction. *Journal of Applied Crystallography* **2020**, 53 (1), 226–235.

Chapter 10 - Future work

In Chapter 2, we systematically investigated how alkyl chain length influences the formation of chain- and dimer-bonding intermolecular structural features in 2-aminopyridine derivatives. However, we did not examine how bulky aromatic groups attached to the amide group may affect chain and dimer motif formation, even though two of our compounds contained phenyl rings. This would be very interesting to explore because it is well known that aromatic pi-pi interactions are capable of providing considerable structural influence.

In Chapter 6, we described how we successfully identified cocrystals of the PM (5-(pyridin-3-yl)pyrimidin-2-amine) molecule with selected coformers in 1:1 and 1:2 stoichiometric ratios. However, further investigations are required to better understand (i) the true mechanisms governing their formation and (ii) to identify robust methods for synthesizing the thermodynamically stable product (Figure 10.1).

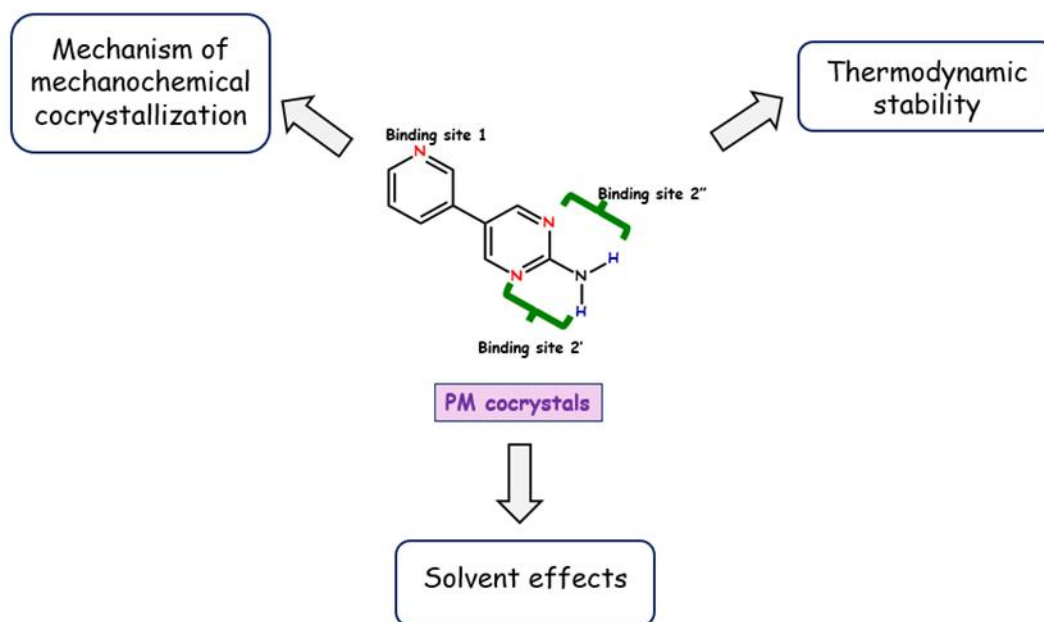


Figure 10.1. Schematic of planned future work for Chapter 6.

The intrinsic mechanism of mechanochemical cocrystallizations needs to be explored further by monitoring the formation of the cocrystal as a function of time during the grinding experiment.^{1,2} In such experiments, grinding will be paused at short time intervals, and the resulting solid phases will be analyzed by PXRD. The experiment will be carried out for longer periods than usual grinding experiments (up to 60 minutes) to determine if the product converts from intermediate phases to the thermodynamic product. Such experiments would provide a better understanding of whether cocrystal formation follows a stepwise mechanism involving kinetically favored intermediates that transform into thermodynamically more stable phases later. In addition, since we obtained the kinetic product predominantly in the crystal growth in solution, slurry experiments will be performed to identify the thermodynamically stable product.³⁻⁶

The choice of solvent is also an important factor for solution-based crystal growth, as it can influence solubility, hydrogen bonding, and nucleation conditions. Moreover, the temperature used for solution-based cocrystallization can also have a significant impact, as it alters the solvent evaporation rate, which, in turn, affects the cocrystal formation. There are many examples illustrating how a specific solvent or solvent mixture can selectively direct the formation of cocrystals with particular stoichiometries.⁷⁻⁹ For example, cyanuric acid and 4,4'-bipyridine form a 2:1 cocrystal when crystallized from methanol, whereas a 1:1 cocrystal is obtained in an aqueous medium. Blagden et al. showed that when a 2:1 stoichiometric ratio of benzoic acid and isonicotinamide was allowed to form cocrystals in a water-ethanol solvent system, they resulted in two different cocrystals based on the solvent composition.⁷ A 2:1 cocrystal was obtained in a higher water content, whereas a 1:1 cocrystal was obtained with a higher ethanol content (Figure 10. 2). Although solvent effects are clearly important, they were not systematically investigated in this work and will be addressed in future studies.

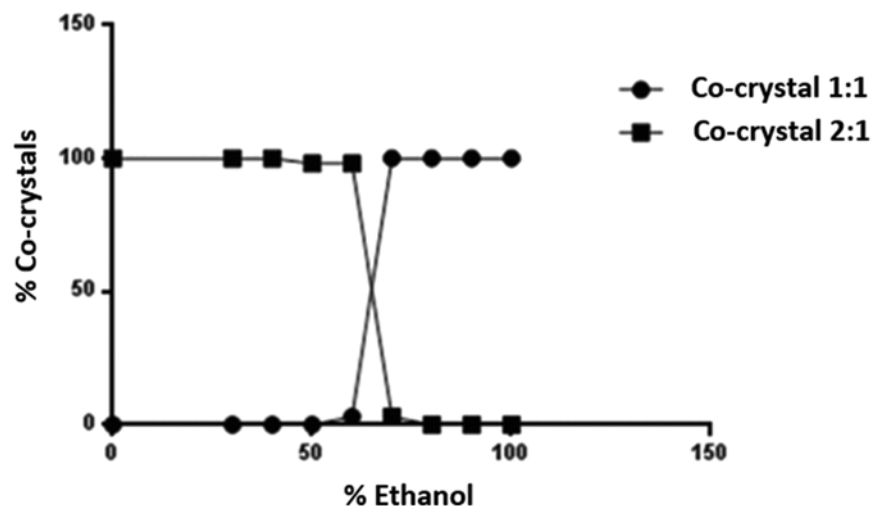


Figure 10.2. Comparison of the growth of (1:1) and (2:1) cocrystals of benzoic acid and isonicotinamide in different solvent compositions. ⁷

In chapter 8, an iodo analogue of favipiravir and its cocrystals were synthesized. Since the study primarily focused on fundamental structural analysis and potential improvements in solid-state properties through cocrystallization, a pharmacological evaluation was not performed. In the future, we plan to conduct pharmacological studies to assess the biological activity and medicinal potential of this analogue. Second, the work described in this thesis focused only on the thermal stability of the obtained cocrystals, although we initially intended to investigate several other properties. Future work will therefore examine solubility and dissolution behavior. ¹⁰⁻¹⁴ Finally, not all cocrystals yielded crystals suitable for structural analysis, primarily due to the incompatibility of solvents with the I-Fav and coformers (Figure 10.3). To overcome these limitations, alternative methods for synthesizing cocrystals will be explored, such as melt mixing and sublimation. ¹⁵⁻¹⁹

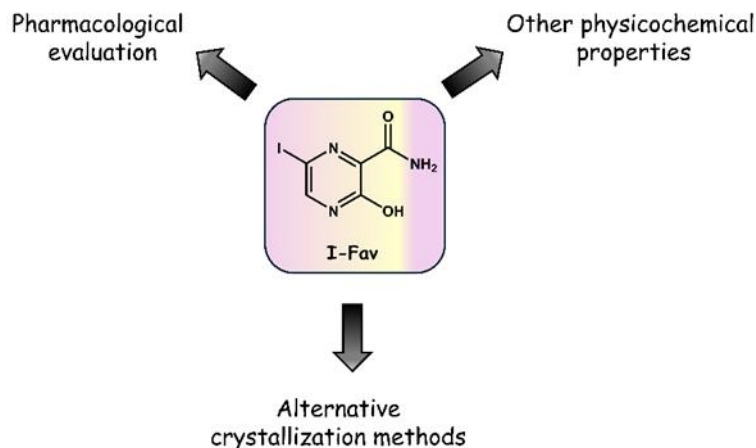


Figure 10.3. Schematic of planned future work for Chapter 8.

10.1 References

1. Karki, S.; Friščić, T.; Jones, W. Control and Interconversion of Cocrystal Stoichiometry in Grinding: Stepwise Mechanism for the Formation of a Hydrogen-Bonded Cocrystal. *CrystEngComm* **2009**, *11* (3), 470–481.
2. Cinčić, D.; Friščić, T.; Jones, W. A Stepwise Mechanism for the Mechanochemical Synthesis of Halogen-Bonded Cocrystal Architectures. *Journal of the American Chemical Society* **2008**, *130* (24), 7524–7525.
3. Haskins, M. M.; Zaworotko, M. J. Screening and Preparation of Cocrystals: A Comparative Study of Mechanochemistry vs Slurry Methods. *Crystal Growth & Design* **2021**, *21* (7), 4141–4150.
4. Zhang, S.; Chen, H.; Rasmuson, Åke. C. Thermodynamics and Crystallization of a Theophylline–Salicylic Acid Cocrystal. *CrystEngComm* **2015**, *17* (22), 4125–4135.
5. Takata, N.; Shiraki, K.; Takano, R.; Hayashi, Y.; Terada, K. Cocrystal Screening of Stanolone and Mestanolone Using Slurry Crystallization. *Crystal Growth & Design* **2008**, *8* (8), 3032–3037.
6. Ahuja, D.; Ramisetty, K. A.; Sumanth, P. K.; Crowley, C. M.; Lusi, M.; Rasmuson, Å. C. Microwave Assisted Slurry Conversion Crystallization for Manufacturing of New Co-Crystals of Sulfamethazine and Sulfamerazine. *CrystEngComm* **2020**, *22* (8), 1381–1394.
7. Munshi, T.; Redha, B.; Feeder, N.; Meenan, P.; Blagden, N. Impact of Mixed Solvent on Co-Crystal Solubility, Ternary Phase Diagram, and Crystallization Scale Up. *Crystal Growth & Design* **2016**, *16* (4), 1817–1823.
8. Saikia, B.; Pathak, D.; Sarma, B. Variable Stoichiometry Cocrystals: Occurrence and Significance. *CrystEngComm* **2021**, *23* (26), 4583–4606.

9. Seaton, C. C.; Parkin, A.; Wilson, C. C.; Blagden, N. Controlling the Formation of Benzoic Acid: Isonicotinamide Molecular Complexes. *Crystal Growth & Design* **2008**, *9* (1), 47–56.
10. Good, D. J.; Rodríguez-Hornedo, N. Solubility Advantage of Pharmaceutical Cocrystals. *Crystal Growth & Design* **2009**, *9* (5), 2252–2264.
11. Shayanfar, A.; Asadpour-Zeynali, K.; Jouyban, A. Solubility and Dissolution Rate of a Carbamazepine–Cinnamic Acid Cocrystal. *Journal of Molecular Liquids* **2013**, *187*, 171–176.
12. Naureen, F.; Shah, Y.; Shahnaz; Khuda, F. Determination of Saturated Solubility of Mirtazapine Using UV Visible Spectrophotometer. *Pharmaceutical Communications* **2024**, *3* (01), 27–34.
13. Kumar, L.; Suhas, B.; Pai, G. K.; Verma, R. Determination of Saturated Solubility of Naproxen Using UV Visible Spectrophotometer. *Research Journal of Pharmacy and Technology* **2015**, *8* (7), 825.
14. Al-Kazemi, R.; Al-Basarah, Y.; Nada, A. Dissolution Enhancement of Atorvastatin Calcium by Cocrystallization. *Advanced Pharmaceutical Bulletin* **2019**, *9* (4), 559–570.
15. Barmapalexis, P.; Karagianni, A.; Nikolakakis, I.; Kachrimanis, K. Preparation of Pharmaceutical Cocrystal Formulations via Melt Mixing Technique: A Thermodynamic Perspective. *European Journal of Pharmaceutics and Biopharmaceutics* **2018**, *131*, 130–140.
16. Chen, A.; Cai, P.; Luo, M.; Guo, M.; Cai, T. Melt Crystallization of Celecoxib–Carbamazepine Cocrystals with the Synchronized Release of Drugs. *Pharmaceutical Research* **2022**, *40* (2), 567–577.
17. Yan, Y.; Chen, J.-M.; Lu, T.-B. Thermodynamics and Preliminary Pharmaceutical Characterization of a Melatonin–Pimelic Acid Cocrystal Prepared by a Melt Crystallization Method. *CrystEngComm* **2015**, *17* (3), 612–620.
18. Li, A.; Li, S.; Wang, J.; Chen, Y.; Lu, M. Pterostilbene–Nicotinamide Cocrystal: A Case Report of Single Cocrystals Grown from Melt Microdroplets. *Crystal Growth & Design* **2022**, *23* (1).
19. Ou, X.; Li, X.; Rong, H.; Yu, L.; Lu, M. A General Method for Cultivating Single Crystals from Melt Microdroplets. *Chemical Communications* **2020**, *56* (69), 9950–9953.

Appendix A - Additional information for Chapter 1

3/3/26, 4:58 PM

RightsLink Printable License

AMERICAN CHEMICAL SOCIETY LICENSE TERMS AND CONDITIONS

Mar 03, 2026

This Agreement between Aloka. A. Marasinghe ("You") and American Chemical Society ("American Chemical Society") consists of your license details and the terms and conditions provided by American Chemical Society and Copyright Clearance Center.

License Number	6221570118651
License date	Mar 03, 2026
Licensed Content Publisher	American Chemical Society
Licensed Content Publication	Journal of the American Chemical Society
Licensed Content Title	The Melting Point Alternation in α,ω -Alkanedicarboxylic Acids
Licensed Content Author	Venkat R. Thalladi, Markus Nüsse, Roland Boese
Licensed Content Date	Sep 1, 2000
Licensed Content Volume	122
Licensed Content Issue	38
Volume number	122
Issue number	38
Type of Use	Thesis/Dissertation

<https://s100.copyright.com/AppDispatchServlet>

1/4

Figure A.1. Copyright permission for Chapter 1, Figure 1.1.

ELSEVIER LICENSE
TERMS AND CONDITIONS

Mar 04, 2026

This Agreement between Aloka A. Marasinghe ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number	6221990516143
License date	Mar 04, 2026
Licensed Content Publisher	Elsevier
Licensed Content Publication	Elsevier Books
Licensed Content Title	Comprehensive Supramolecular Chemistry II
Licensed Content Author	R. Thakuria, T.S. Thakur
Licensed Content Date	Jan 1, 2017
Licensed Content Pages	27
Start Page	283
End Page	309
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1

Figure A.2. Copyright permission for Chapter 1, Figure 1.4.

AMERICAN CHEMICAL SOCIETY LICENSE
TERMS AND CONDITIONS

Mar 20, 2026

This Agreement between Aloka A. Marasinghe ("You") and American Chemical Society ("American Chemical Society") consists of your license details and the terms and conditions provided by American Chemical Society and Copyright Clearance Center.

License Number	6233240582976
License date	Mar 20, 2026
Licensed Content Publisher	American Chemical Society
Licensed Content Publication	Crystal Growth and Design
Licensed Content Title	"Triply Activated" Phenyl 3-Iodopropiolates: Halogen-Bond Donors with Remarkable σ -Hole Potentials
Licensed Content Author	Vinu V. Panikkattu, Adam S. Huber, Abhijeet S. Sinha, et al
Licensed Content Date	Mar 1, 2022
Licensed Content Volume	22
Licensed Content Issue	3
Volume number	22
Issue number	3
Type of Use	Thesis/Dissertation

Figure A.3. Copyright permission for Chapter 1, Figure 1.9.

AMERICAN CHEMICAL SOCIETY LICENSE
TERMS AND CONDITIONS

Mar 20, 2026

This Agreement between Aloka A. Marasinghe ("You") and American Chemical Society ("American Chemical Society") consists of your license details and the terms and conditions provided by American Chemical Society and Copyright Clearance Center.

License Number	6233240891893
License date	Mar 20, 2026
Licensed Content Publisher	American Chemical Society
Licensed Content Publication	Crystal Growth and Design
Licensed Content Title	Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration
Licensed Content Author	Andrew V. Trask, W. D. Samuel Motherwell, William Jones
Licensed Content Date	May 1, 2005
Licensed Content Volume	5
Licensed Content Issue	3
Volume number	5
Issue number	3
Type of Use	Thesis/Dissertation

Figure A.4. Copyright permission for Chapter 1, Figure 1.15.



Marketplace

This is a License Agreement between Aloka A. Marasinghe ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the Marketplace Permissions General Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the Marketplace Permissions General Terms and Conditions below.

Order Date	20-Mar-2026	Type of Use	Republish in a
Order License ID	1711393-1	Publisher	thesis/dissertation
ISSN	1466-8033	Portion	ROYAL SOCIETY OF CHEMISTRY Image/photo/illustration

LICENSED CONTENT

Publication Title	CrystEngComm	Publication Type	e-Journal
Article Title	Role of hydrogen bonding in cocrystals and coamorphous solids: indapamide as a case study	Start Page	2043
		End Page	2048
		Issue	13
		Volume	21
Author / Editor	Royal Society of Chemistry (Great Britain)	URL	http://www.rsc.org/Publishing/Journals/ce/index.asp
Date	01/01/1999		
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		
Rightsholder	Royal Society of Chemistry		

REQUEST DETAILS

Portion Type	Image/photo/illustration	Distribution	Worldwide
Number of Images / Photos / Illustrations	2	Translation	Original language of publication
Format (select all that apply)	Print, Electronic	Copies for the Disabled?	No
Who Will Republish the Content?	Academic institution	Minor Editing Privileges?	No
Duration of Use	Life of current edition	Incidental Promotional Use?	No
Lifetime Unit Quantity	Up to 499	Currency	USD
Rights Requested	Main product		

NEW WORK DETAILS

Figure A.5. Copyright permission for Chapter 1, Figure 1.16 and 1.17.



Marketplace

This is a License Agreement between Aloka A. Marasinghe ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the Marketplace Permissions General Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the Marketplace Permissions General Terms and Conditions below.

Order Date	20-Mar-2026	Type of Use	Republish in a thesis/dissertation
Order License ID	1711378-1	Publisher	ROYAL SOCIETY OF CHEMISTRY
ISSN	1466-8033	Portion	Image/photo/illustration

LICENSED CONTENT

Publication Title	CrystEngComm	Rightsholder	Royal Society of Chemistry
Article Title	Building co-crystals with molecular sense and supramolecular sensibility	Publication Type	e-Journal
Author / Editor	Royal Society of Chemistry (Great Britain)	Start Page	439
Date	01/01/1999	Issue	72
Language	English	Volume	7
Country	United Kingdom of Great Britain and Northern Ireland	URL	http://www.rsc.org/Publishing/journals/ce/index.asp

REQUEST DETAILS

Portion Type	Image/photo/illustration	Distribution	Worldwide
Number of Images / Photos / Illustrations	1	Translation	Original language of publication
Format (select all that apply)	Print, Electronic	Copies for the Disabled?	No
Who Will Republish the Content?	Academic institution	Minor Editing Privileges?	No
Duration of Use	Life of current edition	Incidental Promotional Use?	No
Lifetime Unit Quantity	Up to 499	Currency	USD
Rights Requested	Main product		

NEW WORK DETAILS

Title	Dissertation-From Intermolecular Forces to Physical Properties via Crystal Engineering - Introduction	Institution Name	Kansas State University
Instructor Name	Aloka A. Marasinghe	Expected Presentation Date	2026-03-26

Figure A.6. Copyright permission for Chapter 1, Figure 1.18.



Marketplace

This is a License Agreement between Aloka A. Marasinghe ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the Marketplace Permissions General Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the Marketplace Permissions General Terms and Conditions below.

Order Date	20-Mar-2026	Type of Use	Republish in a thesis/dissertation
Order License ID	1711391-1	Publisher	ROYAL SOCIETY OF CHEMISTRY
ISSN	1466-8033	Portion	Image/photo/illustration

LICENSED CONTENT

Publication Title	CrystEngComm	Rightsholder	Royal Society of Chemistry
Article Title	The quest for a molecular capsule assembled via halogen bonds	Publication Type	e-Journal
Author / Editor	Royal Society of Chemistry (Great Britain)	Start Page	6366
Date	01/01/1999	Issue	20
Language	English	Volume	14
Country	United Kingdom of Great Britain and Northern Ireland	URL	http://www.rsc.org/ Publishing/Journals/ce/index.asp

REQUEST DETAILS

Portion Type	Image/photo/illustration	Distribution	Worldwide
Number of Images / Photos / Illustrations	2	Translation	Original language of publication
Format (select all that apply)	Print, Electronic	Copies for the Disabled?	No
Who Will Republish the Content?	Academic institution	Minor Editing Privileges?	No
Duration of Use	Life of current edition	Incidental Promotional Use?	No
Lifetime Unit Quantity	Up to 499	Currency	USD
Rights Requested	Main product		

NEW WORK DETAILS

Title	Dissertation-From Intermolecular Forces to Physical Properties via Crystal Engineering - Introduction	Institution Name	Kansas State University
Instructor Name	Aloka A. Marasinghe	Expected Presentation Date	2026-03-26

Figure A.7. Copyright permission for Chapter 1, Figure 1.22 and 1.23.

ELSEVIER LICENSE
TERMS AND CONDITIONS

Mar 02, 2026

This Agreement between Aloka A. Marasinghe ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number	6220821279451
License date	Mar 02, 2026
Licensed Content Publisher	Elsevier
Licensed Content Publication	Dyes and Pigments
Licensed Content Title	Deep insight into the charge-transfer cocrystals: Decreasing structural overlap induced bathochromically shift emission
Licensed Content Author	Yue Shen, Jia-wang Hou, Yun-ting Liu, Xiao-han Wan, Meng-yu Bai, Xin-dong Jiang, Wen-long Duan, Feng Yan
Licensed Content Date	Jul 1, 2023
Licensed Content Volume	215
Licensed Content Issue	n/a
Licensed Content Pages	1
Start Page	111277

Figure A.8. Copyright permission for Chapter 1, Figure 1.24.

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS

Mar 04, 2026

This Agreement between Aloka A. Marasinghe ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	6222000775956
License date	Mar 04, 2026
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Pharmaceutical Research
Licensed Content Title	Indomethacin–Saccharin Cocrystal: Design, Synthesis and Preliminary Pharmaceutical Characterization
Licensed Content Author	Srinivas Basavoju et al
Licensed Content Date	Aug 17, 2007
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	4

Figure A.9. Copyright permission for Chapter 1, Figure 1.25.

**Marketplace**

This is a License Agreement between Aloka A. Marasinghe ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the Marketplace Permissions General Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the Marketplace Permissions General Terms and Conditions below.

Order Date	04-Mar-2026	Type of Use	Republish in a thesis/dissertation
Order License ID	1706059-1	Publisher	ROYAL SOCIETY OF CHEMISTRY
ISSN	1466-8033	Portion	Image/photo/illustration

LICENSED CONTENT

Publication Title	CrystEngComm	Publication Type	e-Journal
Article Title	Novel Crystal Forms of Entresto: A Supramolecular Complex of Trisodium Sacubitril Valsartan Hemipentahydrate	Start Page	7387
		End Page	7393
		Issue	42
		Volume	24
Author / Editor	Royal Society of Chemistry (Great Britain)	URL	http://www.rsc.org/Publishing/journals/ce/index.asp
Date	01/01/1999		
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		
Rightsholder	Royal Society of Chemistry		

REQUEST DETAILS

Portion Type	Image/photo/illustration	Distribution	Worldwide
Number of Images / Photos / Illustrations	2	Translation	Original language of publication
Format (select all that apply)	Print, Electronic	Copies for the Disabled?	No
Who Will Republish the Content?	Academic institution	Minor Editing Privileges?	No
Duration of Use	Life of current edition	Incidental Promotional Use?	No
Lifetime Unit Quantity	Up to 499	Currency	USD
Rights Requested	Main product		

NEW WORK DETAILS

Figure A.10. Copyright permission for Chapter 1, Figure 1.26.

Appendix B - Additional information for Chapter 2

2/12/26, 2:46 PM

RightsLink Printable License

AMERICAN CHEMICAL SOCIETY LICENSE TERMS AND CONDITIONS

Feb 12, 2026

This Agreement between Aloka A. Marasinghe ("You") and American Chemical Society ("American Chemical Society") consists of your license details and the terms and conditions provided by American Chemical Society and Copyright Clearance Center.

License Number	6206660146594
License date	Feb 12, 2026
Licensed Content Publisher	American Chemical Society
Licensed Content Publication	Crystal Growth and Design
Licensed Content Title	Structural Landscape of 2-Aminopyridine Derivatives: Chains or Dimers?
Licensed Content Author	Aloka A. Marasinghe, Boris B. Averkiev, Christer B. Aakeröy
Licensed Content Date	Oct 1, 2025
Licensed Content Volume	25
Licensed Content Issue	20
Volume number	25
Issue number	20
Type of Use	Thesis/Dissertation
Requestor type	Author (original work)
Format	Print and Electronic

<https://s100.copyright.com/AppDispatchServlet>

1/4

Figure B.1. Copyright permission for Chapter 2.

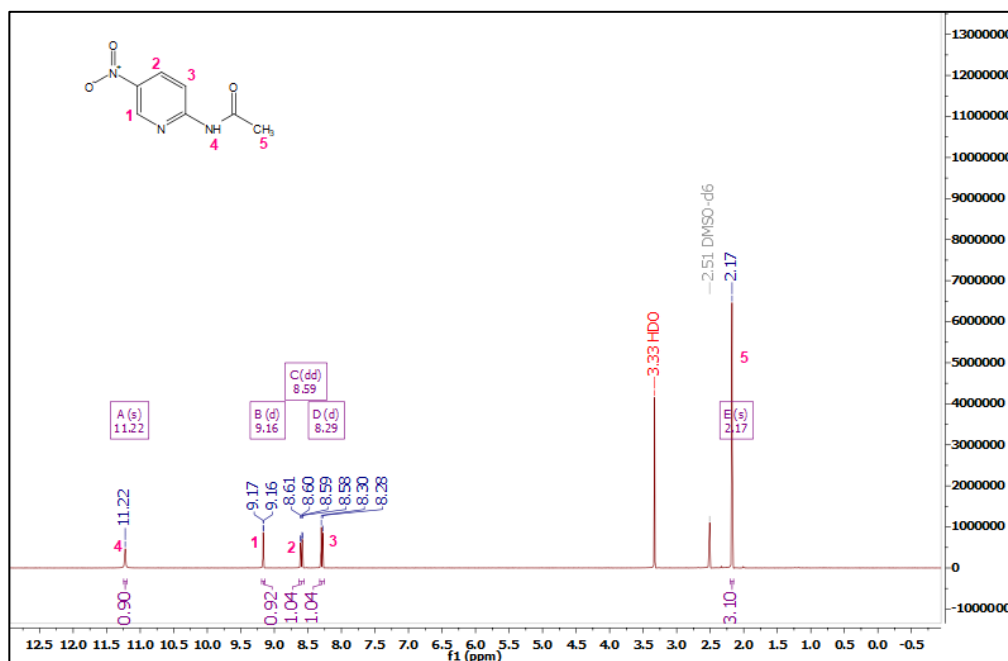


Figure B.2. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)acetamide (NO₂-methyl).

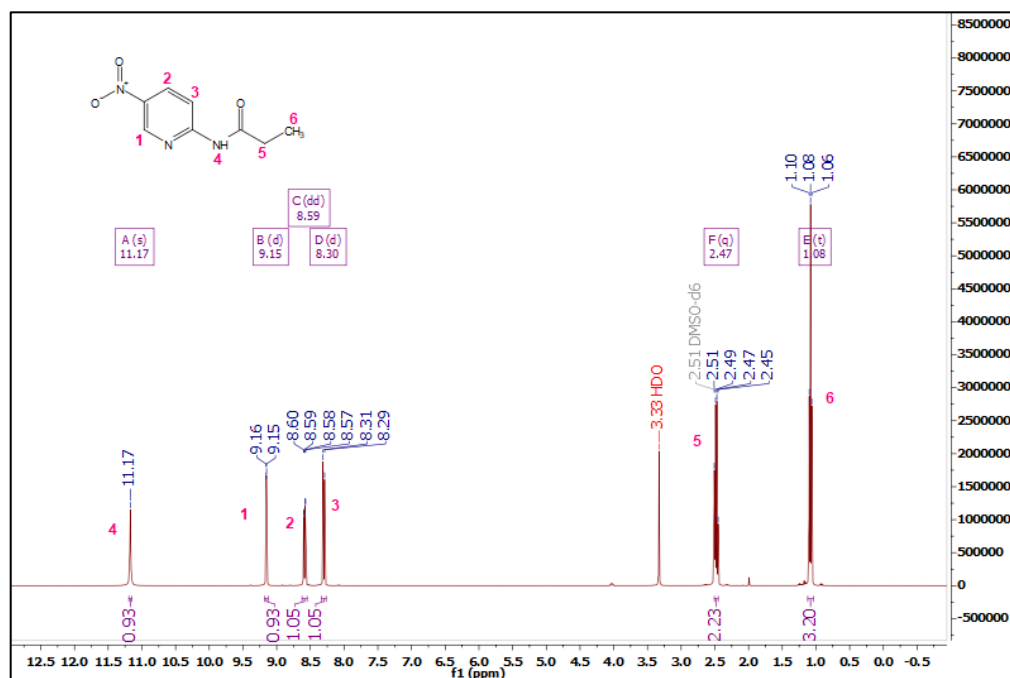


Figure B.3. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)propionamide (NO₂-ethyl).

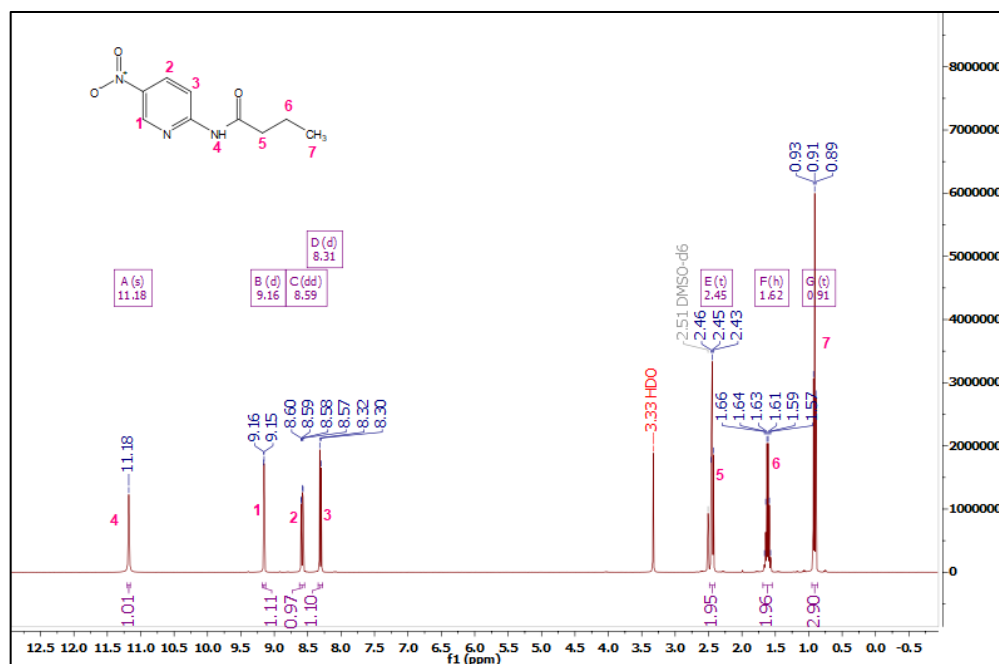


Figure B.4. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)butyramide (NO₂-propyl).

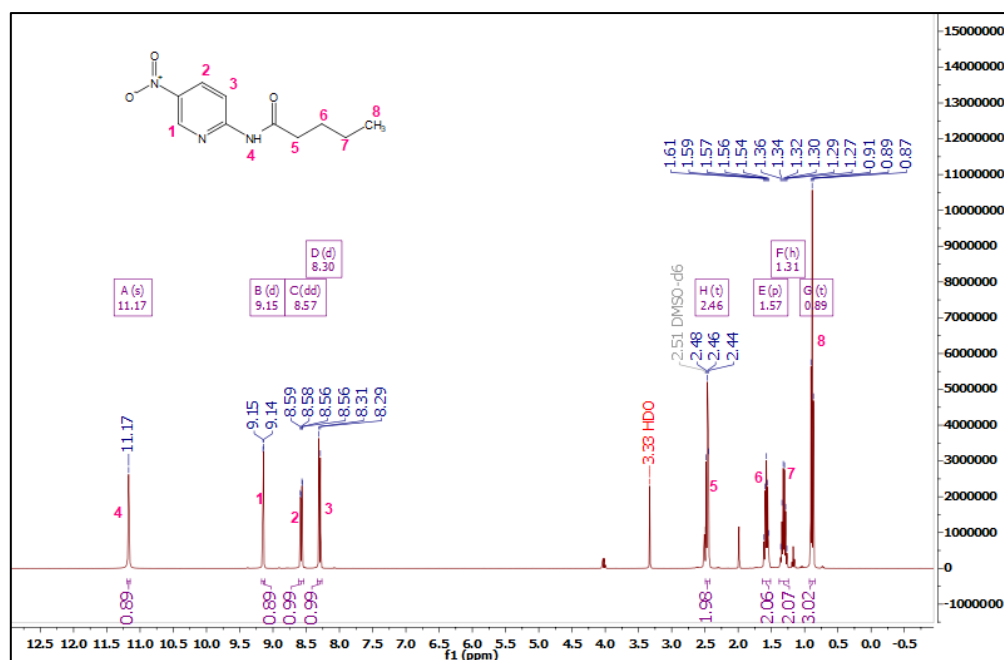


Figure B.5. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)pentanamide (NO₂-butyl).

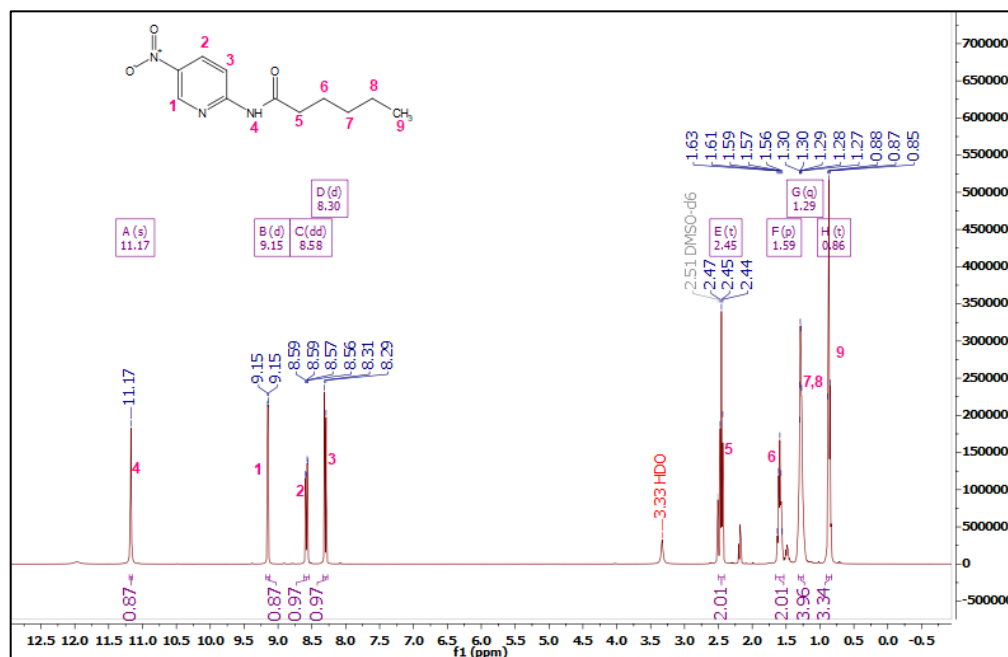


Figure B.6. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)hexanamide (NO_2 -pentyl).

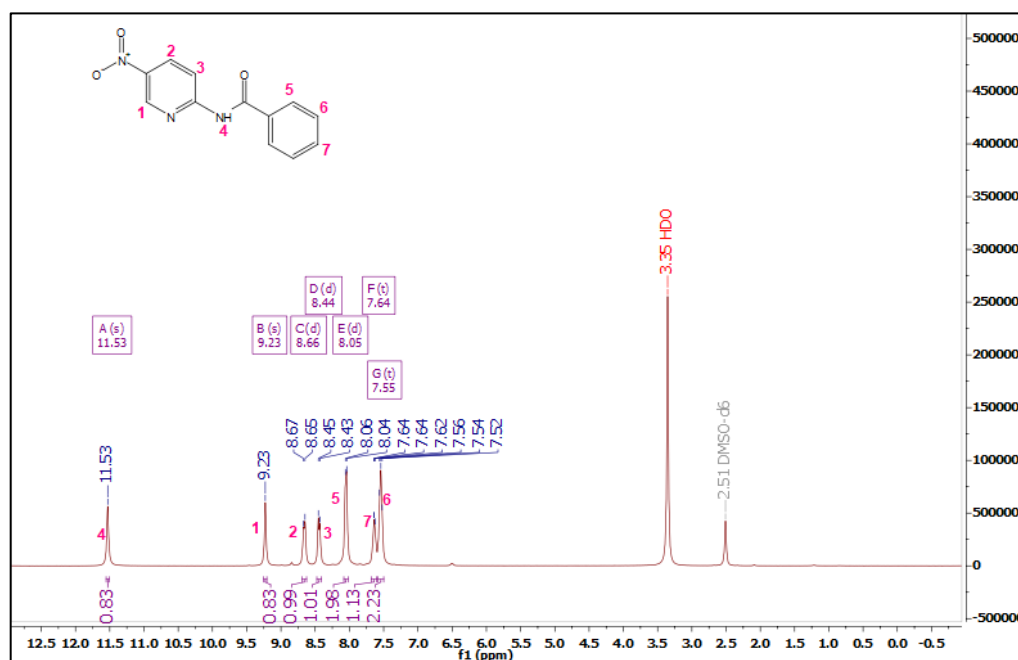


Figure B.7. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(5-nitropyridin-2-yl)benzamide (NO_2 -phenyl).

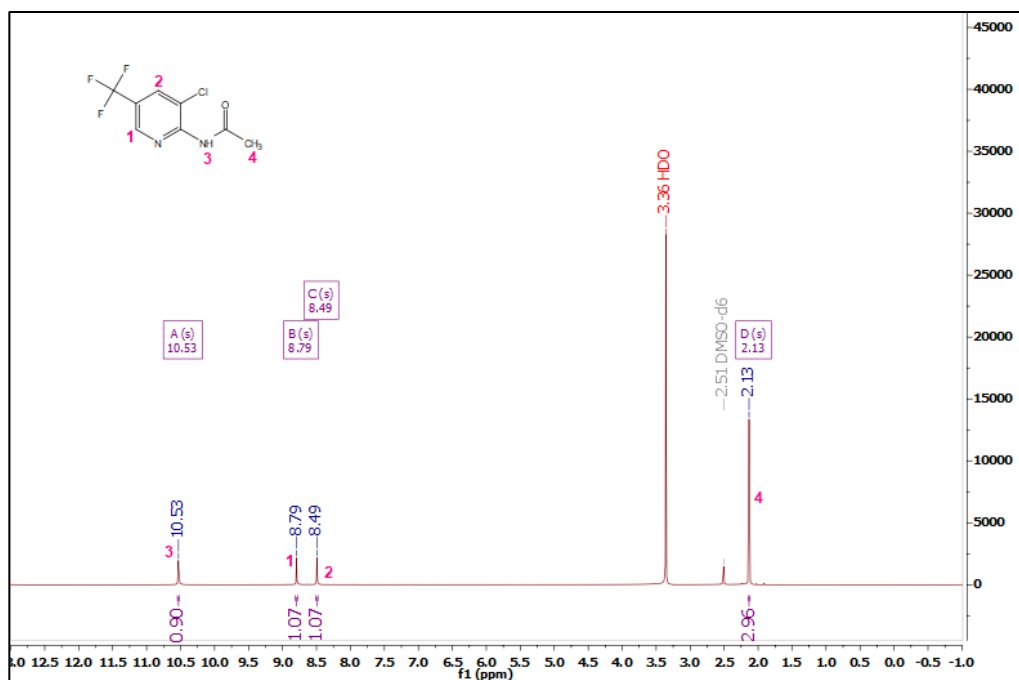


Figure B.8. ^1H NMR (600 MHz, DMSO- d_6) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)acetamide (Cl- CF_3 -methyl).

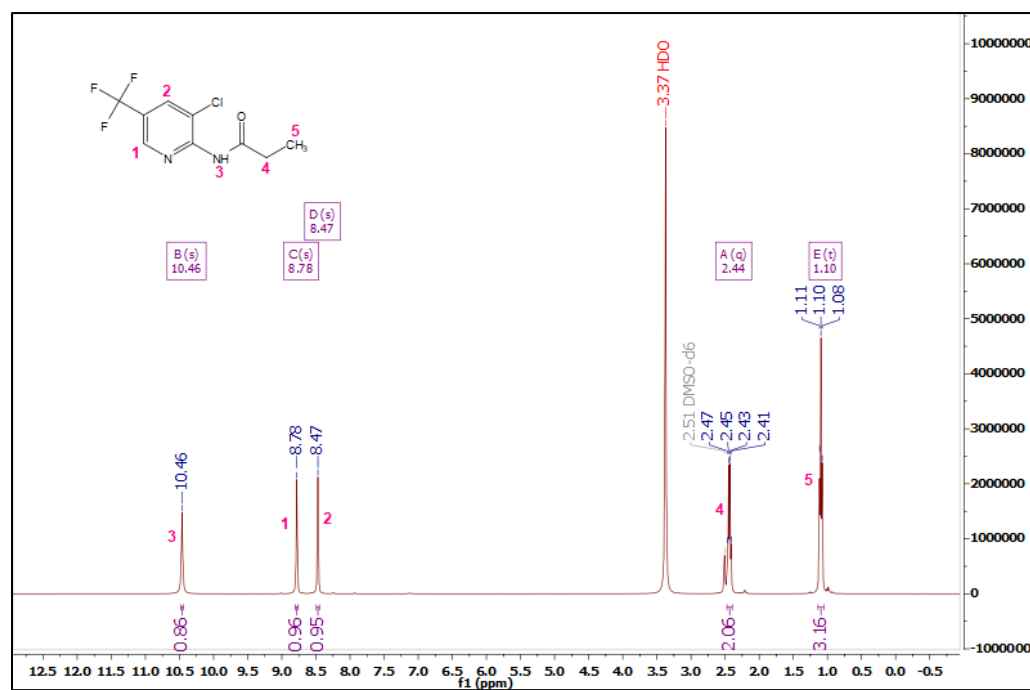


Figure B.9. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)propionamide (Cl- CF_3 -ethyl).

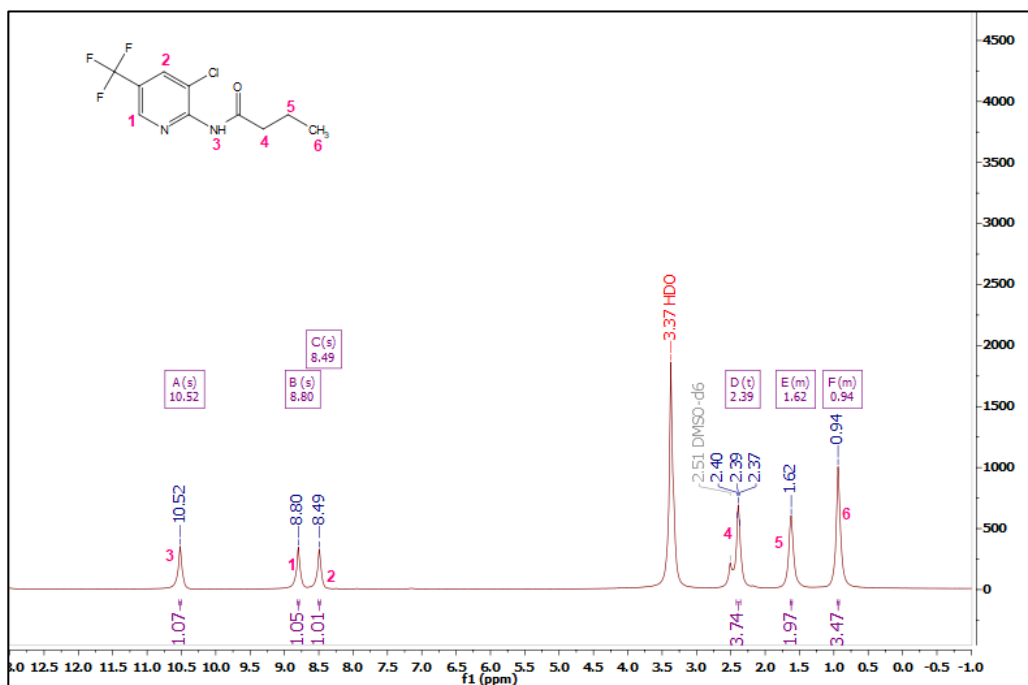


Figure B.10. ^1H NMR (600 MHz, DMSO- d_6) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)butyramide (Cl- CF_3 -propyl).

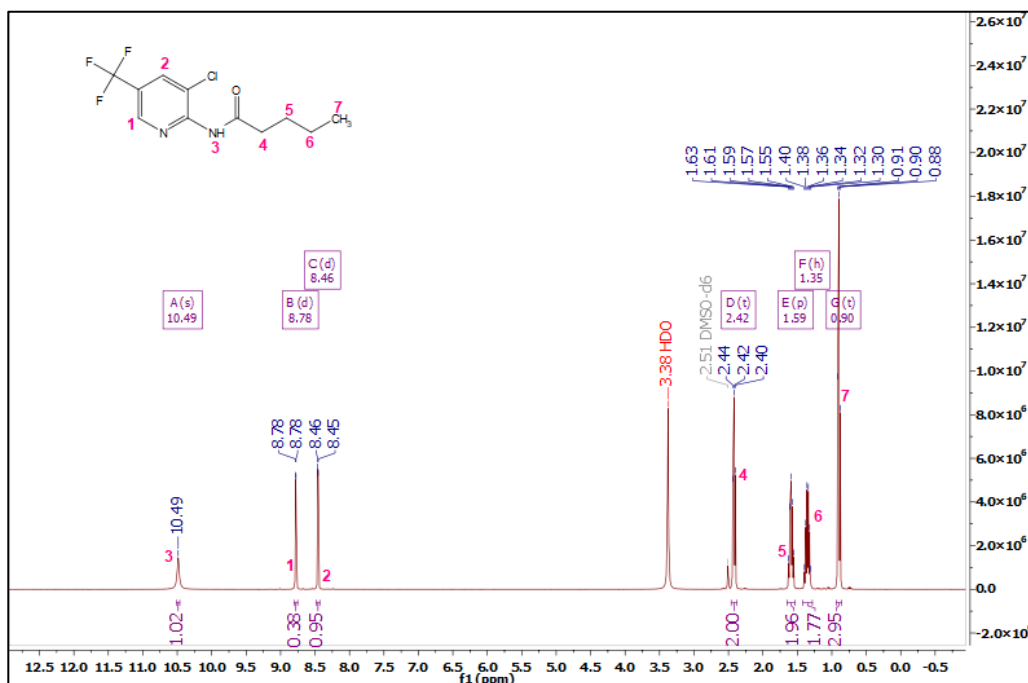


Figure B.11. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)pentanamide (Cl- CF_3 -butyl).

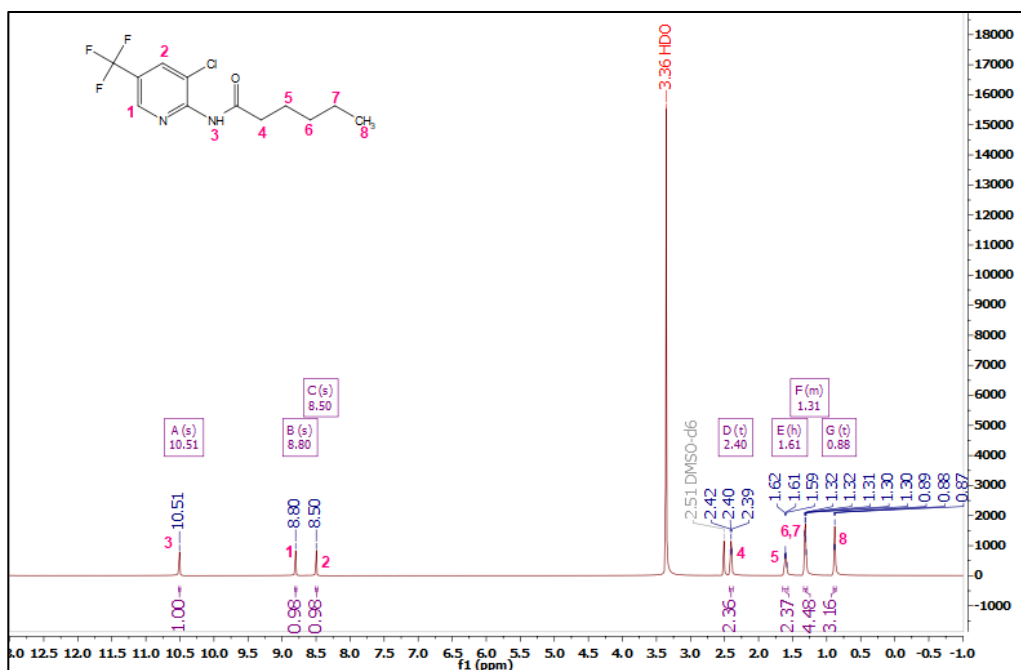


Figure B.12. ¹H NMR (600 MHz, DMSO-d₆) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)hexanamide (Cl-CF₃-pentyl).

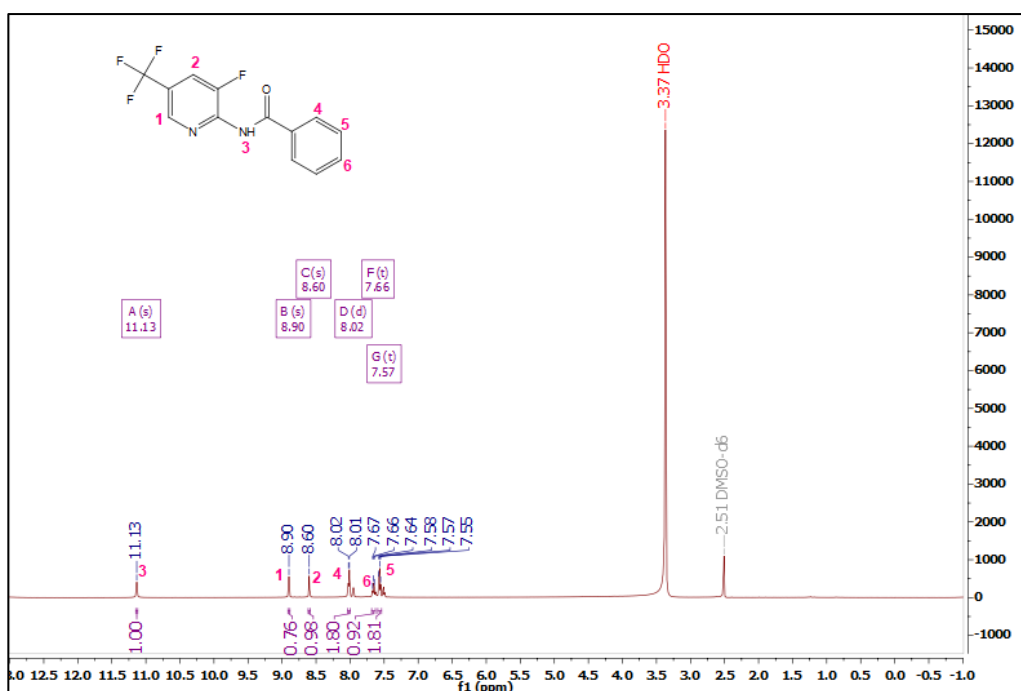


Figure B.13. ¹H NMR (400 MHz, DMSO-d₆) spectrum of N-(3-chloro-5-trifluoromethylpyridin-2-yl)benzamide (Cl-CF₃-phenyl).

Table B.1. Crystallographic information for the NO₂ series crystal structures

Code	NO ₂ -methyl-polymorph I	NO ₂ -methyl-polymorph II	NO ₂ -ethyl
Formula	C ₇ H ₇ N ₃ O ₃	C ₇ H ₇ N ₃ O ₃	C ₈ H ₉ N ₃ O ₃
<i>D</i> calc./ g cm ⁻³	1.506	1.493	1.462
m/mm ⁻¹	1.034	1.025	0.973
Formula Weight	181.16	181.16	195.18
Colour	colourless	colourless	colourless
Shape	prism	irregular	prism
Size/mm ³	0.12×0.05×0.03	0.15×0.10×0.09	0.12×0.05×0.03
<i>T</i> /K	220.00(10)	210.00(10)	210.00(10)
Crystal System	triclinic	triclinic	monoclinic
Space Group	<i>P</i> -1	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	7.2283(2)	8.02943(18)	4.50892(10)
<i>b</i> /Å	9.7152(2)	8.12347(16)	21.7772(5)
<i>c</i> /Å	11.6501(3)	13.3252(3)	9.21050(16)
α /°	91.812(2)	87.5332(16)	90
β /°	91.105(2)	74.8204(18)	101.4070(19)
γ /°	102.238(2)	73.9913(19)	90
<i>V</i> /Å ³	798.85(3)	805.90(3)	886.53(3)
<i>Z</i>	4	4	4
<i>Z</i> '	2	2	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> min/°	3.797	3.438	4.06
<i>Q</i> max/°	77.575	79.744	77.599
Measured Refl.	6216	5931	8830
Independent Refl.	6216	5931	1864
Reflections with <i>I</i> > 2(<i>I</i>)	5569	5474	1712
<i>R</i> _{int}	-	-	0.0183
Parameters	246	246	133
Restraints	0	0	0
Largest Peak	0.208	0.180	0.208
Deepest Hole	-0.23	-0.240	-0.158
GooF	1.047	1.064	1.032
<i>wR</i> ₂ (all data)	0.1146	0.1197	0.1008
<i>wR</i> ₂	0.1119	0.1176	0.0991
<i>R</i> _{<i>I</i>} (all data)	0.0417	0.0424	0.0376
<i>R</i> _{<i>I</i>}	0.0384	0.0405	0.0355

Code	NO ₂ -propyl-polymorph I	NO ₂ -propyl-polymorph II	NO ₂ -butyl
Formula	C ₉ H ₁₁ N ₃ O ₃	C ₉ H ₁₁ N ₃ O ₃	C ₁₀ H ₁₃ N ₃ O ₃
<i>D</i> calc./ g cm ⁻³	1.403	1.429	1.362
m/mm ⁻¹	0.907	0.925	0.859
Formula Weight	209.21	209.21	223.23
Colour	colourless	colourless	colourless
Shape	irregular	plate	plate
Size/mm ³	0.07×0.04×0.02	0.40×0.07×0.02	0.21×0.05×0.01

<i>T</i> /K	210.00(10)	200.00(10)	150.00(10)
Crystal System	monoclinic	orthorhombic	monoclinic
Space Group	<i>P</i> 2 ₁ / <i>c</i>	<i>Pnma</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	9.0227(3)	10.14871(17)	5.6933(2)
<i>b</i> /Å	18.8967(6)	6.59742(12)	9.1087(4)
<i>c</i> /Å	5.8106(2)	14.5221(3)	21.0588(11)
α /°	90	90	90
β /°	90.335(3)	90	94.456(4)
γ /°	90	90	90
<i>V</i> /Å ³	990.68(5)	972.33(3)	1088.78(8)
<i>Z</i>	4	4	4
<i>Z'</i>	1	0.5	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	4.68	5.317	5.293
<i>Q</i> _{max} /°	76.942	79.406	78.785
Measured Refl.	7138	4395	8282
Independent Refl.	2034	1119	2196
Reflections with <i>I</i> > 2(<i>I</i>)	1488	1022	1696
<i>R</i> _{int}	0.0338	0.0197	0.0498
Parameters	142	96	150
Restraints	0	0	0
Largest Peak	0.132	0.148	0.244
Deepest Hole	-0.139	-0.206	-0.282
GooF	1.025	1.064	1.078
<i>wR</i> ₂ (all data)	0.1142	0.0973	0.1631
<i>wR</i> ₂	0.1019	0.0940	0.1748
<i>R</i> _I (all data)	0.0606	0.0375	0.0710
<i>R</i> _I	0.0407	0.0348	0.0557

Code	NO ₂ -pentyl	NO ₂ -phenyl
Formula	C ₁₁ H ₁₅ N ₃ O ₃	C ₁₂ H ₉ N ₃ O ₃
<i>D</i> _{calc.} / g cm ⁻³	1.328	1.484
m/mm ⁻¹	0.819	0.924
Formula Weight	237.26	243.22
Colour	colourless	colourless
Shape	plate	plate
Size/mm ³	0.19×0.05×0.01	0.09×0.04×0.01
<i>T</i> /K	150.00(10)	294.9(8)
Crystal System	triclinic	triclinic
Space Group	<i>P</i> -1	<i>P</i> -1
<i>a</i> /Å	5.6262(5)	5.7530(5)
<i>b</i> /Å	9.0985(6)	7.2811(6)
<i>c</i> /Å	12.0319(9)	13.4868(10)
α /°	105.347(6)	101.345(6)
β /°	91.822(7)	100.260(7)
γ /°	90.524(6)	90.498(7)
<i>V</i> /Å ³	593.55(8)	544.48(7)
<i>Z</i>	2	2

Z'	1	1
Wavelength/Å	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α
$Q_{min}/^{\circ}$	3.812	6.206
$Q_{max}/^{\circ}$	79.499	78.56
Measured Refl.	6768	5701
Independent Refl.	2397	2111
Reflections with $I > 2(I)$	1969	1621
R_{int}	0.0428	0.0409
Parameters	159	167
Restraints	0	0
Largest Peak	0.222	0.438
Deepest Hole	-0.281	-0.28
GooF	1.102	1.071
wR_2 (all data)	0.1757	0.2067
wR_2	0.1677	0.1906
R_I (all data)	0.0666	0.0802
R_I	0.0566	0.0669

Table B.2. Crystallographic information for the Cl-CF₃ series crystal structures

Code	Cl-CF ₃ -methyl	Cl-CF ₃ -ethyl	Cl-CF ₃ -propyl
Formula	C ₈ H ₆ ClF ₃ N ₂ O	C ₉ H ₈ ClF ₃ N ₂ O	C ₁₀ H ₁₀ ClF ₃ N ₂ O
$D_{calc.}/\text{g cm}^{-3}$	1.71	1.607	1.069
m/mm^{-1}	0.432	3.524	1.563
Formula Weight	238.6	252.62	266.65
Colour	light yellow	colourless	colourless
Shape	needle	needle	needle
Size/mm ³	0.11×0.03×0.02	0.26 × 0.03 × 0.02	0.237 × 0.018 × 0.007
T/K	149.99(10)	210.00(10)	210.00(10)
Crystal System	triclinic	monoclinic	triclinic
Space Group	$P-1$	$P2_1/n$	$P-1$
$a/\text{Å}$	4.7910(5)	4.83435(8)	4.80254(13)
$b/\text{Å}$	9.8561(8)	13.2158(3)	11.8213(3)
$c/\text{Å}$	10.7070(10)	16.3556(4)	20.7088(7)
$\alpha/^{\circ}$	109.061(8)	90	75.468(3)
$\beta/^{\circ}$	99.810(8)	92.4297(19)	88.852(2)
$\gamma/^{\circ}$	96.389(8)	90	84.664(2)
$V/\text{Å}^3$	463.27(8)	1044.02(4)	1133.13(6)
Z	2	4	4
Z'	1	-	-
Wavelength/Å	0.71073	1.54184	1.54184
Radiation type	Mo K _α	Cu K _α	Cu K _α
$Q_{min}/^{\circ}$	2.441	8.606	4.408
$Q_{max}/^{\circ}$	31.34	155.862	155.962
Measured Refl.	5565	15854	17349
Independent Refl.	2416	2195	4699

Reflections with I >2(I)	1604	2195	4699
R_{int}	0.049	0.0406	0.0439
Parameters	141	173	310
Restraints	0	51	0
Largest Peak	0.451	0.26	0.45
Deepest Hole	-0.354	-0.25	-0.41
GooF	0.992	1.114	
wR_2 (all data)	0.1236	0.1073	0.1448
wR_2	0.1097	0.1051	0.1364
R_I (all data)	0.0899	$R_1 = 0.0442$	0.0702
R_I	0.0507	0.0405	0.0536

Code	Cl-CF ₃ -butyl	Cl-CF ₃ -pentyl	Cl-CF ₃ -phenyl
Formula	C ₁₁ H ₁₂ ClF ₃ N ₂ O	C ₁₂ H ₁₄ ClF ₃ N ₂ O	C ₁₃ H ₈ ClF ₃ N ₂ O
$D_{calc.}/g\text{ cm}^{-3}$	1.555	1.455	1.563
m/mm^{-1}	3.131	2.816	2.993
Formula Weight	280.68	294.7	300.66
Colour	colourless	colourless	colourless
Shape	needle	needle	needle
Size/mm ³	0.316 × 0.027 × 0.016	0.30×0.02×0.01	0.09×0.03×0.02
T/K	140.02(10)	210.00(10)	295.2(3)
Crystal System	triclinic	triclinic	monoclinic
Space Group	$P-1$	$P-1$	$P2_1/n$
$a/\text{\AA}$	4.76716(12)	4.7818(3)	10.0203(3)
$b/\text{\AA}$	11.4387(4)	10.7147(8)	4.93051(15)
$c/\text{\AA}$	12.4307(3)	13.4436(7)	25.9237(9)
$\alpha/^\circ$	116.059(3)	91.830(5)	90
$\beta/^\circ$	99.003(3)	93.648(5)	94.134(3)
$\gamma/^\circ$	90.330(2)	101.535(5)	90
$V/\text{\AA}^3$	599.31(3)	672.80(7)	1277.43(7)
Z	2	2	4
Z'	-	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K _{α}	Cu K _{α}	Cu K _{α}
$Q_{min}/^\circ$	8.044	3.298	3.419
$Q_{max}/^\circ$	155.97	72.044	80.017
Measured Refl.	10083	7010	9232
Independent Refl.	2482	2535	2650
Reflections with I >2(I)	2482	2146	2146
R_{int}	0.0401	0.0554	0.0351
Parameters	211	173	213
Restraints	0	0	0
Largest Peak	0.45	0.666	0.248
Deepest Hole	-0.30	-0.53	-0.225
GooF	1.05	1.072	1.081
wR_2 (all data)	0.1022	0.1828	0.1294
wR_2	0.1002	0.176	0.1208

R_I (all data)	0.0412	0.0769	0.0573
R_I	0.0381	0.0684	0.0454

Appendix C - Additional information for Chapter 3

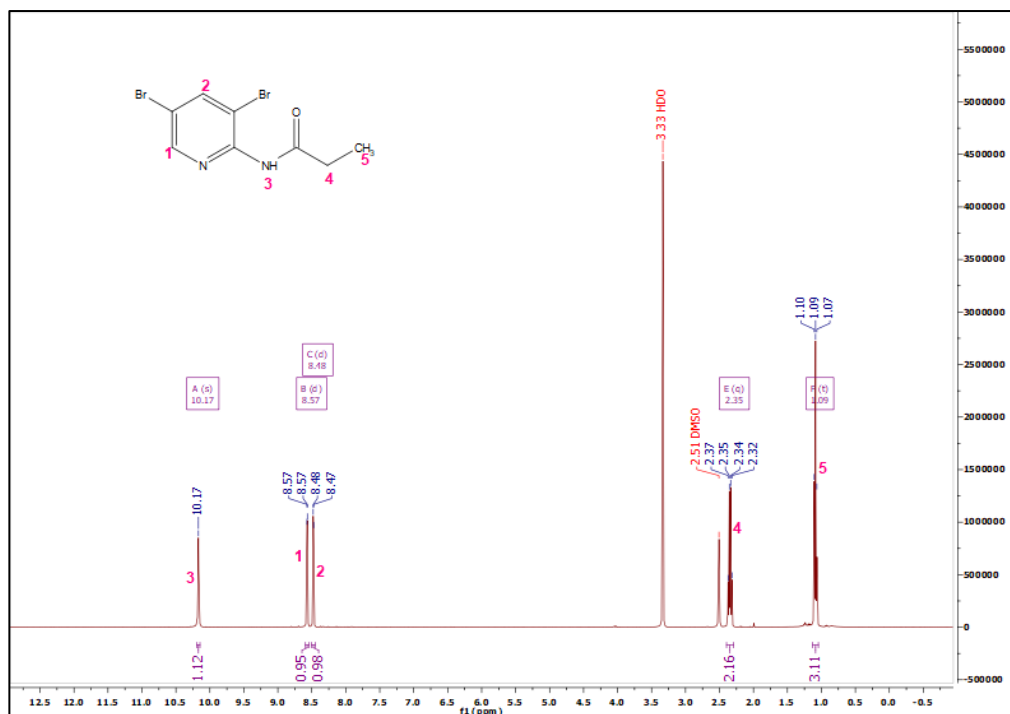


Figure C.1. ¹H NMR (400 MHz, DMSO-d₆) spectrum of N-(3,5-dibromopyridin-2-yl)propionamide (3,5-diBr-ethyl).

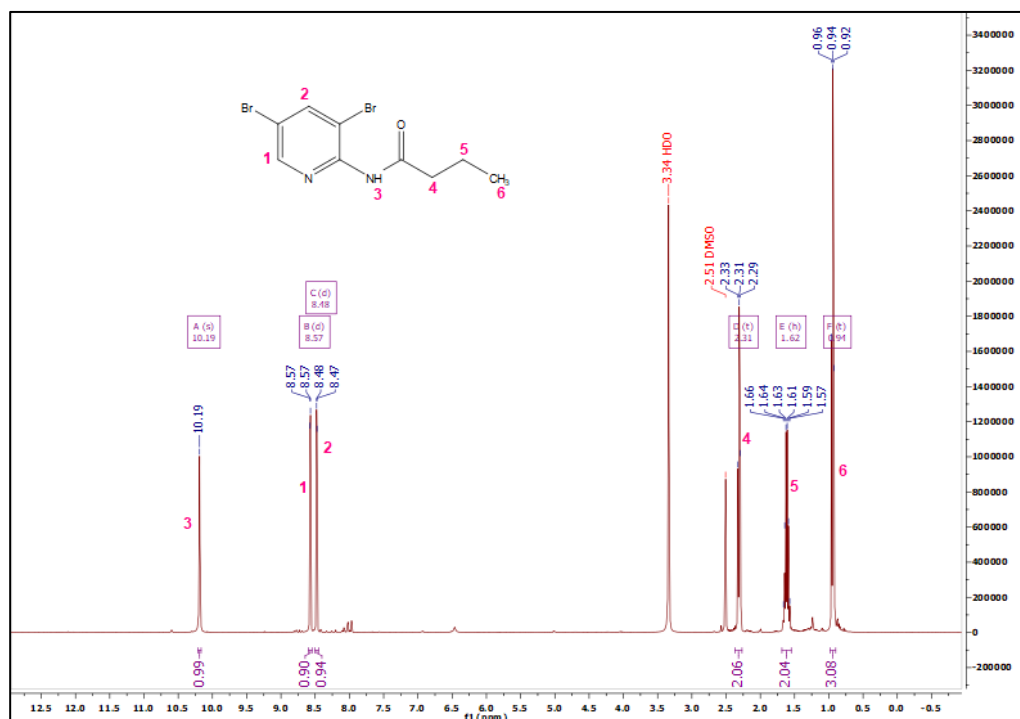


Figure C.2. ¹H NMR (400 MHz, DMSO-d₆) spectrum of N-(3,5-dibromopyridin-2-yl)butyramide (3,5-diBr-propyl).

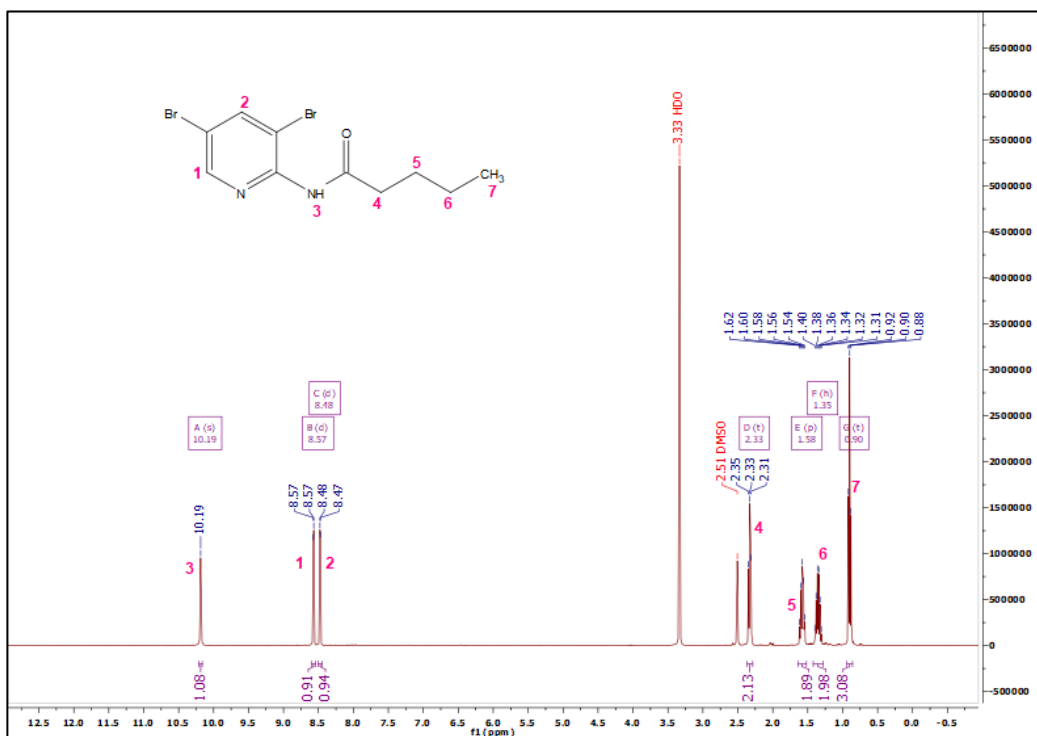


Figure C.3. ¹H NMR (400 MHz, DMSO-d₆) spectrum of N-(3,5-dibromopyridin-2-yl)pentanamide (3,5-diBr-butyl).

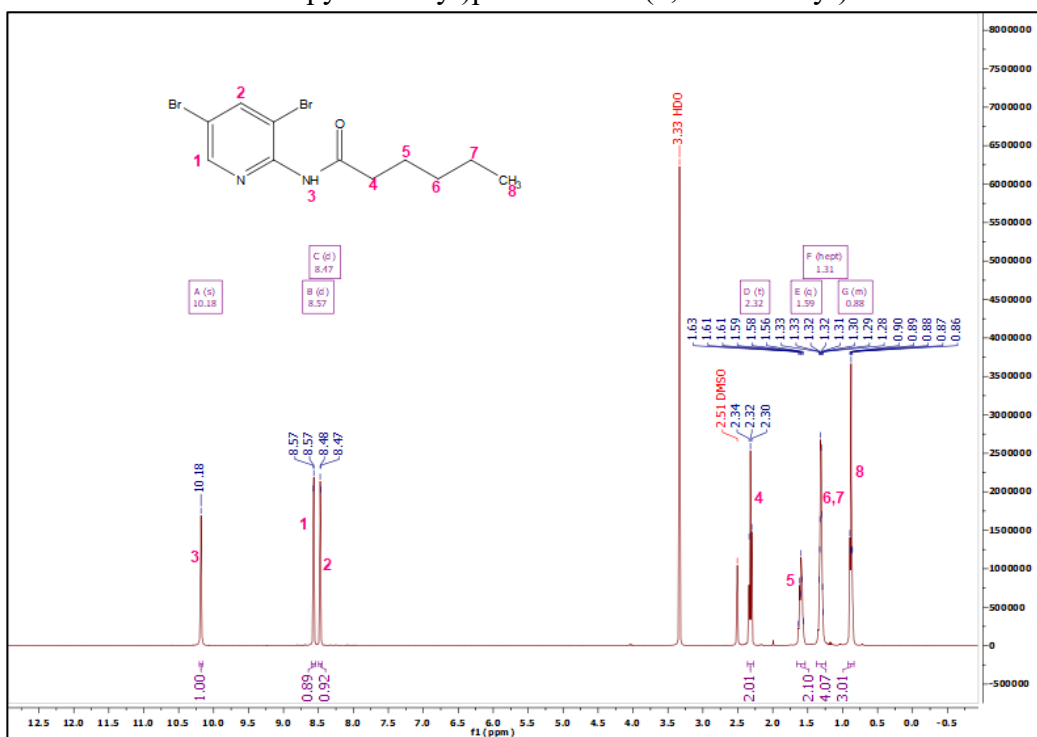


Figure C.4. ¹H NMR (400 MHz, DMSO-d₆) spectrum of N-(3,5-dibromopyridin-2-yl)hexanamide (3,5-diBr-pentyl).

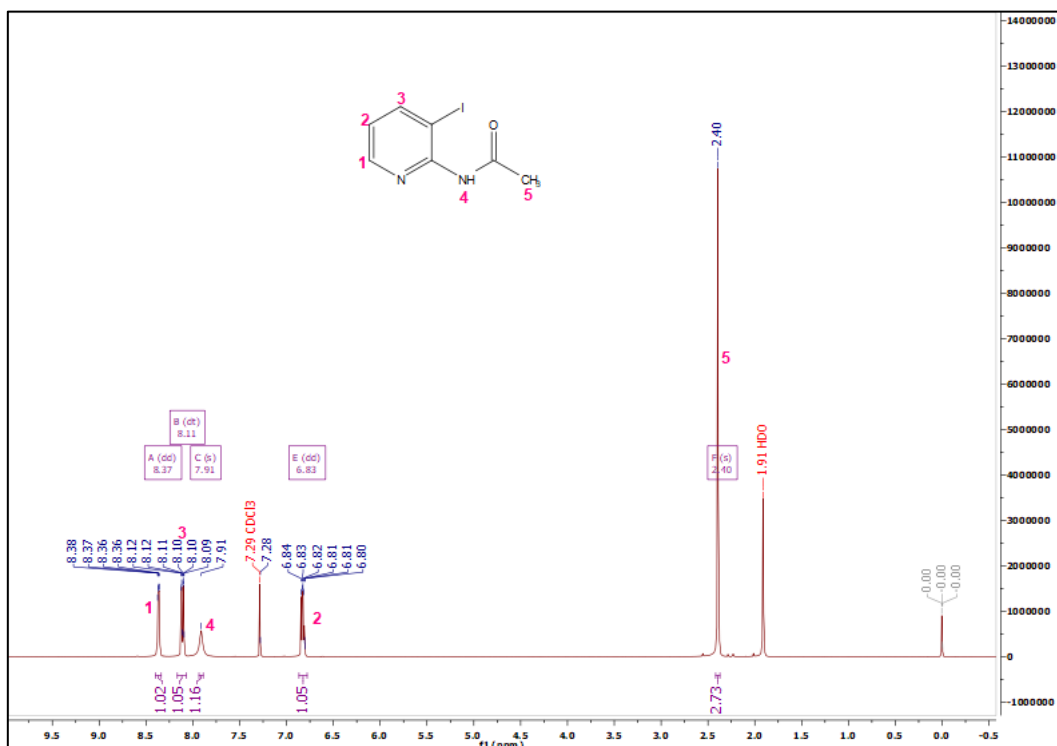


Figure C.5. ¹H NMR (400 MHz, Chloroform-*d*) spectrum of N-(3-iodopyridin-2-yl)acetamide (3-iodo-methyl).

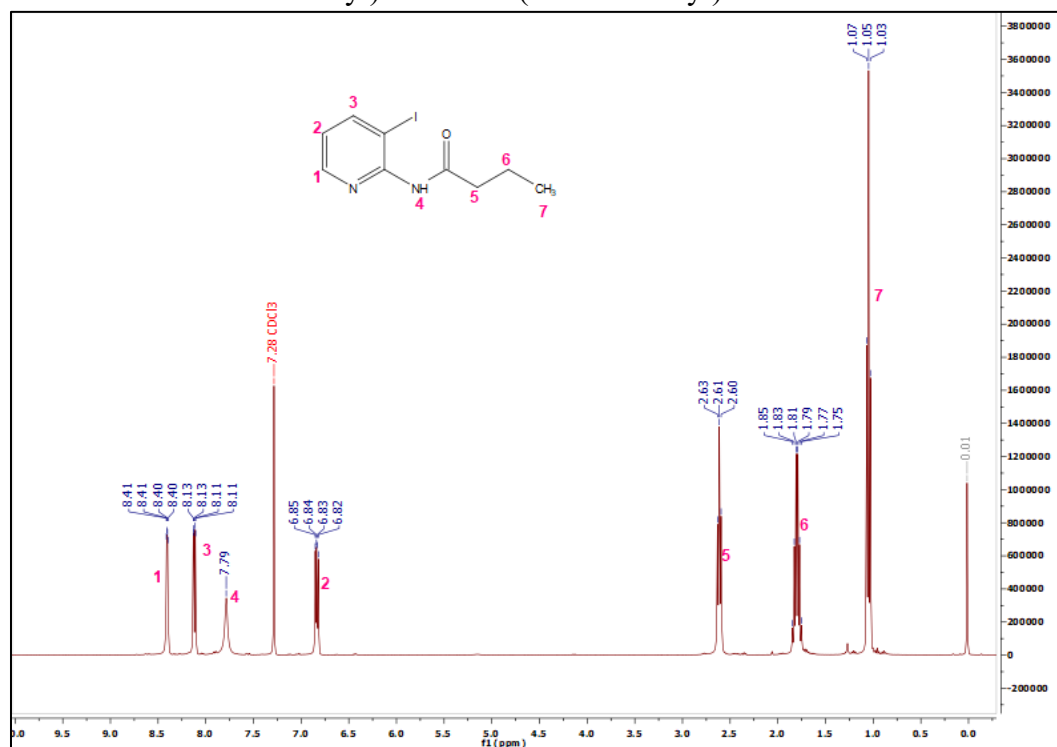


Figure C.6. ¹H NMR (400 MHz, Chloroform-*d*) spectrum of N-(3-iodopyridin-2-yl)butyramide (3-iodo-propyl).

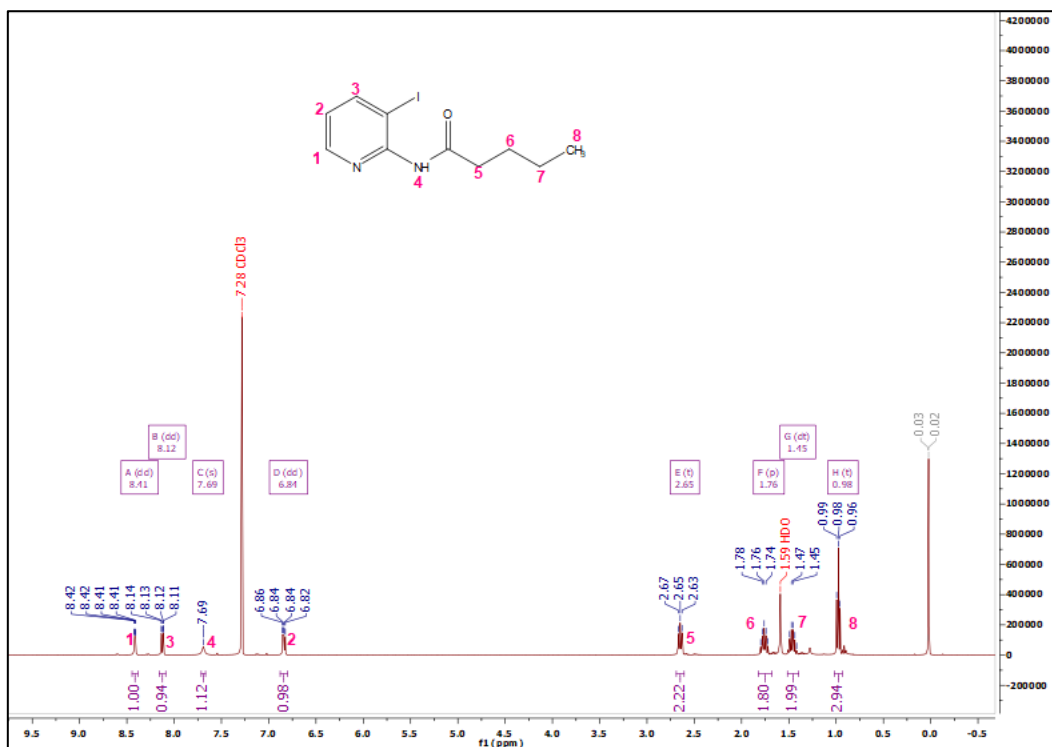


Figure C.7. ^1H NMR (400 MHz, Chloroform- d) spectrum of N-(3-iodopyridin-2-yl)pentanamide (3-iodo-butyl).

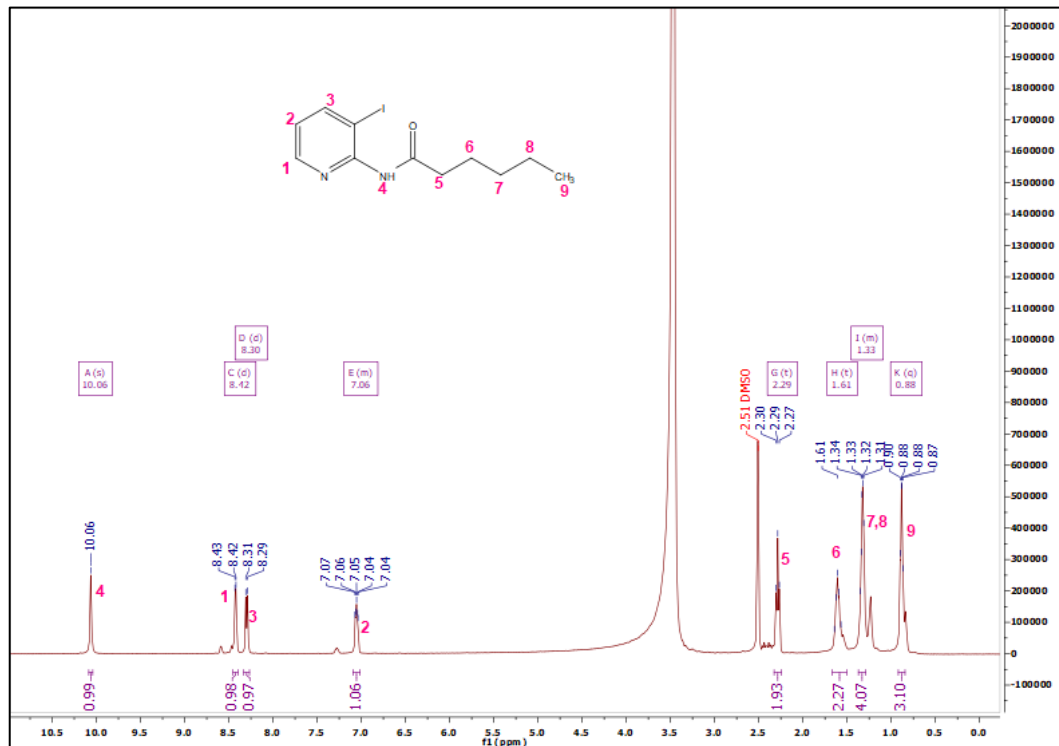


Figure C.8. ^1H NMR (400 MHz, DMSO- d_6) spectrum of N-(3-iodopyridin-2-yl)hexanamide (3-iodo-pentyl).

Table C.1. Crystallographic information for the 3,5-dibromo series crystal structures

Compound	3,5-dibromo - ethyl	3,5-dibromo - propyl	3,5-dibromo - butyl	3,5-dibromo - pentyl
Formula	C ₈ H ₈ Br ₂ N ₂ O	C ₉ H ₁₀ Br ₂ N ₂ O	C ₁₀ H ₁₂ Br ₂ N ₂ O	C ₁₁ H ₁₄ Br ₂ N ₂ O
<i>D</i> _{calc.} / g cm ⁻³	1.999	1.916	1.891	1.791
μ/mm ⁻¹	9.761	8.983	8.525	6.228
Formula Weight	307.98	322.01	336.04	350.06
Colour	colourless	colourless	yellow	colourless
Shape	needle	needle	needle	needle
Size/mm ³	0.10×0.02×0.01	0.06×0.01×0.01	0.16×0.01×0.01	0.30×0.03×0.02
<i>T</i> /K	293(2)	210.00(10)	150.00(10)	210.00(10)
Crystal System	monoclinic	monoclinic	triclinic	triclinic
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> -1
<i>a</i> /Å	4.84170(10)	4.7566(3)	4.7731(2)	4.78153(14)
<i>b</i> /Å	13.4406(3)	10.6612(9)	10.7402(9)	10.6651(4)
<i>c</i> /Å	15.7310(4)	22.1111(17)	11.9625(4)	13.0948(4)
α/°	90	90	86.751(5)	87.547(3)
β/°	91.397(2)	95.514(6)	80.682(4)	85.773(3)
γ/°	90	90	77.296(6)	77.114(3)
<i>V</i> /Å ³	1023.40(4)	1116.09(15)	590.20(6)	648.95(4)
<i>Z</i>	4	4	2	2
<i>Z'</i>	1	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	0.71073
Radiation type	Cu K _α	Cu K _α	Cu K _α	Mo K _α
θ _{min} /°	4.327	4.017	3.745	2.472
θ _{max} /°	79.783	68.221	79.544	31.211
Measured Refl.	8185	6365	4783	8388
Independent Refl.	2183	2034	4783	3448
Reflections with <i>I</i> > 2(<i>I</i>)	1861	1482	4217	2870
<i>R</i> _{int}	0.0310	0.0545	.	0.0254
Parameters	123	128	126	150
Restraints	0	0	0	0
Largest Peak	0.998	1.219	1.276	1.01
Deepest Hole	-0.823	-0.567	-0.722	-0.465
GooF	1.059	1.012	1.161	1.07
<i>wR</i> ₂ (all data)	0.0964	0.1351	0.1674	0.0819
<i>wR</i> ₂	0.0923	0.1231	0.1633	0.0788
<i>R</i> _{<i>I</i>} (all data)	0.0396	0.0749	0.068	0.0464
<i>R</i> _{<i>I</i>}	0.0339	0.0524	0.0602	0.0347

Table C.2. Crystallographic information for the 3-iodo series crystal structures

Code	3-iodo-methyl	3-iodo-propyl	3-iodo-butyl	3-iodo-pentyl
Formula	C ₇ H ₇ IN ₂ O	C ₉ H ₁₁ IN ₂ O	C ₁₀ H ₁₃ IN ₂ O	C ₁₁ H ₁₅ IN ₂ O
<i>D</i> _{calc.} / g cm ⁻³	1.977	1.800	1.720	1.633
μ/mm ⁻¹	28.161	2.957	21.209	19.277
Formula Weight	262.05	290.10	304.12	318.15
Colour	colourless	pale green	dark yellow	colourless
Shape	needle	plate	needle	needle

Size/mm ³	0.13×0.02×0.01	0.15×0.03×0.02	0.24×0.03×0.03	0.14×0.01×0.01
<i>T</i> /K	292.9(4)	150.00(10)	210.00(10)	210.00(10)
Crystal System	monoclinic	monoclinic	monoclinic	triclinic
Space Group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1
<i>a</i> /Å	14.9733(7)	4.74032(19)	4.78780(8)	4.7428(3)
<i>b</i> /Å	8.9699(4)	25.5787(10)	28.2733(4)	14.1658(11)
<i>c</i> /Å	14.2975(6)	8.8861(3)	8.74078(12)	19.6495(10)
α /°	90	90	90	95.841(6)
β /°	113.511(5)	96.641(3)	97.0817(14)	96.730 (5)
γ /°	90	90	90	96.501(5)
<i>V</i> /Å ³	1760.86(14)	1070.23(7)	1174.19(3)	1293.74 (14)
<i>Z</i>	8	4	4	4
<i>Z</i> '	2	1	1	2
Wavelength/Å	1.54184	0.71073	1.54184	1.54184
Radiation type	Cu K α	Mo K α	Cu K α	Cu K α
θ_{min} /°	3.219	2.441	3.126	2.280
θ_{max} /°	80.506	33.620	79.620	68.229
Measured Refl.	26003	14773	8800	13402
Independent Refl.	3841	3653	2486	4689
Reflections with <i>I</i> > 2(<i>I</i>)	3339	2841	2271	2886
<i>R</i> _{int}	0.0466	0.0325	0.0395	0.0726
Parameters	209	119	132	273
Restraints	0	0	0	6
Largest Peak	1.358	1.658	0.659	1.181
Deepest Hole	-1.408	-1.007	-0.887	-0.770
GooF	1.069	1.094	1.085	1.024
<i>wR</i> ₂ (all data)	0.0967	0.1153	0.0987	0.1667
<i>wR</i> ₂	0.0933	0.1104	0.0970	0.1460
<i>R</i> _{<i>I</i>} (all data)	0.0435	0.0617	0.0367	0.1013
<i>R</i> _{<i>I</i>}	0.0377	0.0457	0.0344	0.0562

Appendix D - Additional information for Chapter 4

Table D.1. Crystallographic information for the T2 series cocrystal structures

Code	T2-2,5-dMBA	T2-3,5-dNO ₂	T2-3dMABA-form 1
Formula	C ₁₇ H ₁₉ N ₃ O ₅	C ₁₆ H ₁₃ N ₄ O ₉	C ₁₇ H ₂₀ N ₄ O ₅
<i>D</i> _{calc.} / g cm ⁻³	1.333	1.573	1.341
m/mm ⁻¹	0.832	1.14	0.841
Formula Weight	345.35	405.3	360.37
Colour	colourless	colourless	light orange
Shape	needle	irregular	plate
Size/mm ³	0.09×0.03×0.03	0.28×0.15×0.12	0.28×0.04×0.00
<i>T</i> /K	210.00(10)	210.00(10)	200.00(10)
Crystal System	monoclinic	triclinic	monoclinic
Space Group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	13.1917(2)	8.81977(15)	16.7360(4)
<i>b</i> /Å	4.89126(9)	10.68818(19)	4.91439(11)
<i>c</i> /Å	26.7523(5)	10.9514(2)	21.9254(5)
<i>a</i> °	90	64.773(2)	90
<i>b</i> °	94.4801(18)	69.1624(18)	98.240(2)
<i>g</i> °	90	71.3907(16)	90
<i>V</i> /Å ³	1720.89(6)	855.52(3)	1784.68(7)
<i>Z</i>	4	2	4
<i>Z'</i>	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	3.314	4.618	3.116
<i>Q</i> _{max} /°	79.873	79.857	80.512
Measured Refl.	12252	14064	13114
Independent Refl.	3590	3692	3662
Reflections with <i>I</i> > 2(<i>I</i>)	2982	3252	2689
<i>R</i> _{int}	0.0304	0.0291	0.0341
Parameters	237	314	247
Restraints	0	4	0
Largest Peak	0.202	0.58	0.208
Deepest Hole	-0.211	-0.333	-0.224
GooF	1.055	1.073	1.039
<i>wR</i> ₂ (all data)	0.1277	0.1474	0.1508
<i>wR</i> ₂	0.1215	0.1424	0.1331
<i>R</i> _{<i>I</i>} (all data)	0.0571	0.0531	0.0674
<i>R</i> _{<i>I</i>}	0.0475	0.0491	0.0493

Code	T2-3dMABA-form 2	T2-4ABA
Formula	C ₁₇ H ₂₀ N ₄ O ₅	C ₁₅ H ₁₆ N ₄ O ₅
<i>D</i> _{calc.} / g cm ⁻³	1.374	1.451
m/mm ⁻¹	0.862	0.939
Formula Weight	360.37	332.32
Colour	orange	light yellow
Shape	plate	needle

Size/mm ³	0.13×0.06×0.02	0.29×0.01×0.01
<i>T</i> /K	295.0(4)	200.00(10)
Crystal System	monoclinic	monoclinic
Space Group	<i>C2/c</i>	<i>P2₁/n</i>
<i>a</i> /Å	24.8829(8)	12.5882(2)
<i>b</i> /Å	6.1032(2)	5.17490(7)
<i>c</i> /Å	23.3288(12)	23.3666(4)
<i>a</i> /°	90	90
<i>b</i> /°	100.391(4)	91.8814(16)
<i>g</i> /°	90	90
<i>V</i> /Å ³	3484.7(2)	1521.34(4)
<i>Z</i>	8	4
<i>Z'</i>	1	1
Wavelength/Å	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	3.612	3.785
<i>Q</i> _{max} /°	80.128	79.786
Measured Refl.	11779	11401
Independent Refl.	3650	3225
Reflections with <i>I</i> > 2(<i>I</i>)	2357	2645
<i>R</i> _{int}	0.0429	0.0326
Parameters	246	234
Restraints	0	0
Largest Peak	0.207	0.187
Deepest Hole	-0.201	-0.258
GooF	1.048	1.084
<i>wR</i> ₂ (all data)	0.2083	0.1091
<i>wR</i> ₂	0.1849	0.1044
<i>R</i> _I (all data)	0.0938	0.0554
<i>R</i> _I	0.0655	0.0443

Table D.2 Crystallographic information for the T3 series cocrystal structures

Code	T3-2,3,4,5-fl	T3-2,4-dNO ₂	T3-2,5-diCH ₃
Formula	C ₁₆ H ₁₃ F ₄ N ₃ O ₅	C ₁₆ H ₁₅ N ₅ O ₉	C ₁₈ H ₂₁ N ₃ O ₅
<i>D</i> _{calc} / g cm ⁻³	1.541	1.519	1.312
m/mm ⁻¹	1.26	1.096	0.807
Formula Weight	403.29	421.33	359.38
Colour	colourless	colourless	colourless
Shape	plate	prism	plate
Size/mm ³	0.12×0.06×0.02	0.14×0.05×0.03	0.30×0.04×0.02
<i>T</i> /K	210.00(10)	210.00(10)	200.00(10)
Crystal System	triclinic	orthorhombic	triclinic
Space Group	<i>P</i> -1	<i>P2₁2₁2₁</i>	<i>P</i> -1
<i>a</i> /Å	4.86180(10)	5.22919(16)	4.90830(8)
<i>b</i> /Å	11.3550(2)	14.0294(5)	13.0781(2)
<i>c</i> /Å	15.9165(4)	25.1119(7)	14.3839(3)
<i>a</i> /°	91.323(2)	90	86.9579(16)
<i>b</i> /°	96.255(2)	90	83.9364(16)

$g/^\circ$	95.250(2)	90	82.4135(13)
$V/\text{\AA}^3$	869.30(3)	1842.26(10)	909.40(3)
Z	2	4	2
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K_α	Cu K_α	Cu K_α
$Q_{min}/^\circ$	2.794	3.52	3.092
$Q_{max}/^\circ$	79.918	80.057	79.961
Measured Refl.	13977	13546	20107
Independent Refl.	3736	3952	3893
Reflections with $I > 2(I)$	3065	3648	3429
R_{int}	0.0228	0.0499	0.0295
Parameters	262	280	247
Restraints	0	0	0
Largest Peak	0.332	0.2000	0.215
Deepest Hole	-0.239	-0.278	-0.159
GooF	1.079	1.051	1.03
wR_2 (all data)	0.1274	0.1165	0.1196
wR_2	0.1206	0.1143	0.1159
R_1 (all data)	0.0501	0.0460	0.0467
R_1	0.0424	0.0428	0.0417

Code	T3-3,4-dCl	T3-3,5-dNO ₂	T3-3-Cl
Formula	C ₁₆ H ₁₅ Cl ₂ N ₃ O ₅	C ₁₆ H ₁₅ N ₃ O ₉	C ₁₆ H ₁₆ ClN ₃ O ₅
$D_{calc.}/\text{g cm}^{-3}$	1.488	1.502	1.453
m/mm^{-1}	3.576	1.084	2.326
Formula Weight	400.21	421.33	365.77
Colour	colourless	colourless	colourless
Shape	plate	needle	block
Size/ mm^3	0.13×0.07×0.02	0.12×0.04×0.03	0.18×0.06×0.04
T/K	210.00(10)	210.00(10)	210.00(10)
Crystal System	triclinic	monoclinic	triclinic
Space Group	$P-1$	$P2_1/n$	$P-1$
$a/\text{\AA}$	4.87480(10)	8.26213(12)	6.0859(2)
$b/\text{\AA}$	12.0211(3)	6.01994(10)	7.6444(2)
$c/\text{\AA}$	15.5775(4)	37.4638(4)	18.2137(5)
$a/^\circ$	93.197(2)	90	99.188(2)
$b/^\circ$	90.063(2)	90.3432(12)	90.396(2)
$g/^\circ$	101.531(2)	90	91.061(2)
$V/\text{\AA}^3$	892.96(4)	1863.33(5)	836.30(4)
Z	2	4	2
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K_α	Cu K_α	Cu K_α
$Q_{min}/^\circ$	2.841	2.359	2.458
$Q_{max}/^\circ$	72.138	80.032	79.863
Measured Refl.	11834	19473	10711
Independent Refl.	3482	4043	3486

Reflections with I > 2(I)	2920	3506	3006
R_{int}	0.0366	0.0289	0.029
Parameters	244	281	235
Restraints	0	0	0
Largest Peak	0.26	0.228	0.535
Deepest Hole	-0.333	-0.179	-0.271
GooF	1.059	1.039	1.055
wR_2 (all data)	0.1418	0.1058	0.1314
wR_2	0.1307	0.1014	0.126
R_I (all data)	0.0461	0.0458	0.0515
R_I	0.0381	0.0394	0.0453

Code	T3-3-diCH ₃ N	T3-3-NO ₂	T3-4-CN	T3-4-fl
Formula	C ₁₈ H ₂₂ N ₄ O ₅	C ₁₆ H ₁₆ N ₄ O ₇	C ₁₇ H ₁₆ N ₄ O ₅	C ₁₆ H ₁₆ FN ₃ O ₅
<i>D</i> calc./ g cm ⁻³	1.314	1.43	1.342	1.437
m/mm ⁻¹	0.813	0.977	0.851	0.988
Formula Weight	374.39	376.33	356.34	349.32
Colour	orange	colourless	colourless	colourless
Shape	?	needle	needle	needle
Size/mm ³	0.33×0.08×0.02	0.27×0.02×0.02	0.28×0.04×0.03	0.33×0.04×0.03
<i>T</i> /K	200.0(1)	210.00(10)	210.00(10)	210.00(10)
Crystal System	triclinic	triclinic	monoclinic	monoclinic
Space Group	<i>P</i> -1	<i>P</i> -1	<i>P</i> ₂ /c	<i>P</i> ₂ /c
<i>a</i> /Å	6.21761(15)	4.99171(9)	4.83063(6)	7.59530(10)
<i>b</i> /Å	12.5048(2)	11.5069(3)	31.9978(5)	14.04110(10)
<i>c</i> /Å	12.7578(4)	30.9609(6)	11.58214(19)	30.4154(3)
<i>a</i> /°	79.345(2)	88.0014(18)	90	90
<i>b</i> /°	78.280(3)	87.1547(16)	99.9929(13)	95.4890(10)
<i>g</i> /°	80.4467(17)	79.9953(18)	90	90
<i>V</i> /Å ³	945.96(4)	1748.55(7)	1763.09(5)	3228.82(6)
<i>Z</i>	2	4	4	8
<i>Z</i> '	1	2	1	2
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> min/°	3.582	3.902	2.762	2.919
<i>Q</i> max/°	80.089	80.038	79.506	79.899
Measured Refl.	17956	20113	17575	32800
Independent Refl.	4064	7154	3761	6984
Reflections with I > 2(I)	3741	5526	3030	5862
R_{int}	0.0236	0.0387	0.0399	0.0328
Parameters	255	505	244	463
Restraints	0	0	0	0
Largest Peak	0.163	0.21	0.227	0.236
Deepest Hole	-0.263	-0.229	-0.202	-0.199
GooF	1.103	1.057	1.053	1.038
wR_2 (all data)	0.1092	0.1435	0.1729	0.1187
wR_2	0.1073	0.1342	0.1646	0.1134

R_I (all data)	0.0402	0.0614	0.0657	0.0481
R_I	0.0375	0.0474	0.0575	0.0404

Code	T3-NH ₂	T3-4OCH ₃	T3-3-CH ₃
Formula	C ₁₆ H ₁₈ N ₄ O ₅	C ₁₇ H ₁₉ N ₃ O ₆	C ₁₇ H ₁₉ N ₃ O ₅
$D_{calc.}/\text{g cm}^{-3}$	1.397	1.381	1.382
m/mm^{-1}	0.89	0.894	0.863
Formula Weight	346.34	361.35	345.35
Colour	yellow	colourless	colourless
Shape	irregular	prism	plate
Size/ mm^3	0.16×0.12×0.11	0.30×0.13×0.07	0.33×0.16×0.04
T/K	200.00(10)	200.00(10)	200.00(10)
Crystal System	triclinic	monoclinic	monoclinic
Space Group	$P\bar{1}$	$P2_1/n$	$P2_1/n$
$a/\text{\AA}$	5.8059(4)	13.0517(3)	7.65985(9)
$b/\text{\AA}$	11.8005(10)	5.04275(8)	6.09444(6)
$c/\text{\AA}$	12.9057(16)	26.4711(5)	35.6251(4)
a°	73.991(9)	90	90
b°	78.882(9)	93.9326(18)	93.5547(10)
g°	78.277(7)	90	90
$V/\text{\AA}^3$	823.35(14)	1738.13(5)	1659.87(3)
Z	2	4	4
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α
$Q_{min}/^\circ$	3.601	3.68	2.485
$Q_{max}/^\circ$	81.117	79.808	79.824
Measured Refl.	11962	14179	13173
Independent Refl.	3406	3693	3582
Reflections with $I > 2(I)$	2923	3251	3299
R_{int}	0.0349	0.0305	0.0218
Parameters	243	245	237
Restraints	0	0	0
Largest Peak	0.239	0.241	0.257
Deepest Hole	-0.259	-0.173	-0.185
GooF	1.057	1.040	1.088
wR_2 (all data)	0.1498	0.1248	0.0999
wR_2	0.1439	0.1201	0.0974
R_I (all data)	0.0555	0.0505	0.0374
R_I	0.0495	0.0448	0.0349

Table D.3 Crystallographic information for the T4 series cocrystal structures

Code	T4-2,3,4,5-fl	T4-2,4,6-fl	T4-2,5-diCH ₃
Formula	C ₁₇ H ₁₅ F ₄ N ₃ O ₅	C ₂₇ H ₂₉ F ₃ N ₆ O ₈	C ₁₉ H ₂₃ N ₃ O ₅
$D_{calc.}/\text{g cm}^{-3}$	1.548	1.411	1.299
m/mm^{-1}	1.244	1.011	0.788
Formula Weight	417.32	622.56	373.4
Colour	colourless	colourless	colourless

Shape	needle	needle	needle
Size/mm ³	0.30×0.02×0.01	0.35×0.02×0.01	0.23×0.02×0.02
<i>T</i> /K	200.00(10)	210.00(10)	200.00(10)
Crystal System	triclinic	triclinic	monoclinic
Space Group	<i>P</i> -1	<i>P</i> -1	<i>C</i> 2/ <i>c</i>
<i>a</i> /Å	5.06721(10)	4.90321(17)	25.2079(8)
<i>b</i> /Å	13.7011(4)	18.1251(9)	4.97601(13)
<i>c</i> /Å	14.0676(4)	18.4556(10)	30.9158(10)
<i>a</i> °	68.244(3)	116.531(5)	90
<i>b</i> °	81.177(2)	91.841(4)	100.155(3)
<i>g</i> °	84.523(2)	91.214(3)	90
<i>V</i> /Å ³	895.56(4)	1465.53(14)	3817.2(2)
<i>Z</i>	2	2	8
<i>Z'</i>	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	3.411	2.679	2.904
<i>Q</i> _{max} /°	80.259	78.853	79.901
Measured Refl.	11198	16255	13678
Independent Refl.	3713	5734	4043
Reflections with <i>I</i> > 2(<i>I</i>)	2903	3500	2912
<i>R</i> _{int}	0.0324	0.0464	0.0544
Parameters	272	411	274
Restraints	0	0	24
Largest Peak	0.264	0.26	0.238
Deepest Hole	-0.249	-0.265	-0.206
GooF	1.063	1.039	1.031
<i>wR</i> ₂ (all data)	0.117	0.1971	0.1341
<i>wR</i> ₂	0.1103	0.1699	0.1197
<i>R</i> ₁ (all data)	0.0587	0.0962	0.0744
<i>R</i> ₁	0.0446	0.0615	0.0503

Code	T4-3,4-diCl	T4-3,5-diNO₂	T4-3-Cl
Formula	C ₁₇ H ₁₇ Cl ₂ N ₃ O ₅	C ₁₇ H ₁₇ N ₅ O ₉	C ₁₇ H ₁₈ ClN ₃ O ₅
<i>D</i> _{calc.} / g cm ⁻³	1.464	1.488	1.415
m/mm ⁻¹	3.418	1.058	2.204
Formula Weight	414.23	435.35	379.79
Colour	colourless	colourless	colourless
Shape	needle	needle	plate
Size/mm ³	0.40×0.04×0.03	0.19×0.02×0.01	0.15×0.07×0.01
<i>T</i> /K	200.00(10)	200.00(10)	200.00(10)
Crystal System	triclinic	monoclinic	triclinic
Space Group	<i>P</i> -1	<i>C</i> 2/ <i>c</i>	<i>P</i> -1
<i>a</i> /Å	4.87001(7)	27.9184(7)	5.04078(10)
<i>b</i> /Å	12.6656(3)	5.97470(13)	13.4518(3)
<i>c</i> /Å	15.4607(3)	23.4620(6)	13.4964(3)
<i>a</i> °	89.3955(17)	90	99.1349(19)
<i>b</i> °	86.8021(14)	96.710(2)	93.0157(18)
<i>g</i> °	80.6742(15)	90	98.4318(18)

$V/\text{\AA}^3$	939.57(3)	3886.76(16)	891.08(3)
Z	2	8	2
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K_{α}	Cu K_{α}	Cu K_{α}
$Q_{min}/^{\circ}$	2.863	3.188	3.327
$Q_{max}/^{\circ}$	80.004	78	79.553
Measured Refl.	11172	11754	10341
Independent Refl.	3880	3935	3574
Reflections with $I > 2(I)$	11172	3024	3136
R_{int}	0.0305	0.0349	0.0311
Parameters	253	289	244
Restraints	0	0	0
Largest Peak	0.302	0.159	0.367
Deepest Hole	-0.24	-0.177	-0.243
GooF	1.101	1.079	1.062
wR_2 (all data)	0.1129	0.1177	0.1269
wR_2	0.1095	0.1108	0.1222
R_I (all data)	0.0423	0.0632	0.0482
R_I	0.0383	0.0458	0.043

Code	T4-3-diCH ₃ N	T4-3-NO ₂	T4-4-Br-3-CH ₃
Formula	C ₁₉ H ₂₄ N ₄ O ₅	C ₁₇ H ₁₈ N ₄ O ₇	C ₁₈ H ₂₀ BrN ₃ O ₅
$D_{calc.}/\text{g cm}^{-3}$	1.335	1.425	1.531
m/mm^{-1}	0.815	0.958	3.255
Formula Weight	388.42	390.35	438.28
Colour	None	colourless	pale orange
Shape	?	needle	plate
Size/ mm^3	0.19×0.14×0.06	0.24×0.03×0.02	0.21×0.17×0.05
T/K	200(2)	200.00(10)	200.00(10)
Crystal System	triclinic	triclinic	monoclinic
Space Group	$P-1$	$P-1$	$P2_1/n$
$a/\text{\AA}$	6.35274(15)	4.96088(8)	6.15336(7)
$b/\text{\AA}$	12.46903(18)	12.0470(2)	15.39939(16)
$c/\text{\AA}$	12.9378(3)	31.3015(6)	20.0693(2)
$a/^{\circ}$	97.3653(16)	98.5918(15)	90
$b/^{\circ}$	103.862(2)	91.4079(14)	91.2821(10)
$g/^{\circ}$	99.5009(15)	99.9270(14)	90
$V/\text{\AA}^3$	966.16(4)	1819.57(5)	1901.25(3)
Z	2	4	4
Z'	1	2	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K_{α}	Cu K_{α}	Cu K_{α}
$Q_{min}/^{\circ}$	3.574	2.859	3.618
$Q_{max}/^{\circ}$	80.154	79.986	80.046
Measured Refl.	37103	26926	17620
Independent Refl.	4176	7726	4097
Reflections with $I > 2(I)$	3858	5891	3760
R_{int}	0.0285	0.0336	0.0401

Parameters	264	523	254
Restraints	0	0	0
Largest Peak	0.259	0.448	0.627
Deepest Hole	-0.231	-0.279	0.329
GooF	1.083	1.064	1.076
wR_2 (all data)	0.1162	0.1567	0.1023
wR_2	0.1136	0.1446	0.1002
R_I (all data)	0.0412	0.0668	0.0388
R_I	0.039	0.0518	0.0367

Code	T4-CN	T4-4-NH ₂	T4-3-CH ₃
Formula	C ₁₈ H ₁₈ N ₄ O ₅	C ₁₇ H ₂₀ N ₄ O ₅	C ₁₈ H ₂₁ N ₃ O ₅
$D_{calc.}/\text{g cm}^{-3}$	1.345	1.34	1.306
m/mm^{-1}	0.84	0.841	0.804
Formula Weight	370.36	360.37	359.38
Colour	colourless	yellow	colourless
Shape	needle	plate	plate
Size/mm ³	0.30×0.03×0.03	0.15×0.11×0.03	0.20×0.06×0.02
T/K	200.00(10)	295.9(3)	200.00(10)
Crystal System	monoclinic	triclinic	monoclinic
Space Group	$P2_1/c$	$P-1$	$P2_1/n$
$a/\text{\AA}$	4.85817(7)	6.15171(12)	16.7193(2)
$b/\text{\AA}$	29.7628(5)	12.3495(4)	5.16327(6)
$c/\text{\AA}$	12.8236(2)	12.6749(4)	21.1736(3)
a°	90	73.875(3)	90
b°	99.4174(13)	79.965(2)	91.1948(12)
g°	90	76.405(2)	90
$V/\text{\AA}^3$	1829.21(5)	892.97(4)	1827.44(4)
Z	4	2	4
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α
$Q_{min}/^\circ$	2.969	3.655	3.335
$Q_{max}/^\circ$	79.804	80.078	79.928
Measured Refl.	13434	14844	12341
Independent Refl.	3821	3854	3783
Reflections with $I > 2(I)$	3298	3482	3253
R_{int}	0.0264	0.0174	0.0266
Parameters	253	252	245
Restraints	0	1	0
Largest Peak	0.251	0.144	0.166
Deepest Hole	-0.191	-0.188	-0.182
GooF	1.08	1.078	1.028
wR_2 (all data)	0.1145	0.1287	0.1108
wR_2	0.1099	0.1253	0.1054
R_I (all data)	0.0483	0.0453	0.0469
R_I	0.0417	0.0426	0.0396

Table D.4. Crystallographic information for the T5 series cocrystal structures

Code	T5-3-Cl	T5-3diMABA	T5-4ABA
Formula	C ₁₈ H ₂₀ ClN ₃ O ₅	C ₂₀ H ₂₆ N ₄ O ₅	C ₂₉ H ₃₇ N ₇ O ₈
Dcalc./ g cm ⁻³	1.422	1.347	1.265
m/mm ⁻¹	2.155	0.812	0.782
Formula Weight	393.82	402.45	611.65
Colour	colourless	orange	light yellow
Shape	needle	plate	needle
Size/mm ³	0.16×0.03×0.02	0.16×0.12×0.04	0.10×0.02×0.02
T/K	150.00(10)	200.00(10)	297(1)
Crystal System	monoclinic	triclinic	monoclinic
Space Group	P2 ₁ /c	P-1	P2 ₁ /n
a/Å	5.01440(10)	6.42159(9)	20.1578(5)
b/Å	13.3931(2)	12.65205(14)	4.90086(14)
c/Å	27.4515(3)	13.02701(17)	32.5043(9)
a/°	90	76.6124(10)	90
b/°	93.8960(10)	75.8298(12)	90.875(2)
g/°	90	80.7872(10)	90
V/Å ³	1839.34(5)	992.29(2)	3210.75(15)
Z	4	2	4
Z'	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
Qmin/°	3.227	3.572	2.562
Qmax/°	79.945	79.934	78.442
Measured Refl.	16634	20759	24768
Independent Refl.	3975	4253	6488
Reflections with I > 2(I)	3595	3980	3585
R _{int}	0.0413	0.0187	0.0376
Parameters	253	273	423
Restraints	0	0	0
Largest Peak	0.321	0.283	0.202
Deepest Hole	-0.236	-0.294	-0.193
GooF	1.045	1.081	1.018
wR ₂ (all data)	0.0993	0.1156	0.1726
wR ₂	0.0966	0.114	0.1407
R ₁ (all data)	0.0423	0.0408	0.0994
R ₁	0.0378	0.0391	0.0538

Code	T5-2,3,4,5-fl	T5-2,4,6-fl	T5-2,5-diCH ₃
Formula	C ₁₈ H ₁₇ F ₄ N ₃ O ₅	C ₂₉ H ₃₃ F ₃ N ₆ O ₈	C ₂₀ H ₂₅ N ₃ O ₅
Dcalc./ g cm ⁻³	1.468	1.398	1.295
m/mm ⁻¹	1.16	0.982	0.776
Formula Weight	431.35	650.61	387.43
Colour	colourless	colourless	colourless
Shape	needle	needle	plate
Size/mm ³	0.28×0.02×0.01	0.15×0.01×0.01	0.26×0.07×0.02
T/K	200.00(10)	210.00(10)	150.0(5)
Crystal System	triclinic	triclinic	triclinic

Space Group	<i>P</i> -1	<i>P</i> -1	<i>P</i> -1
<i>a</i> /Å	4.78918(9)	4.8840(2)	4.89908(8)
<i>b</i> /Å	12.2190(3)	18.0690(7)	13.15204(19)
<i>c</i> /Å	17.2979(4)	19.1787(8)	15.9892(2)
<i>a</i> °	101.369(2)	66.110(4)	77.1583(12)
<i>b</i> °	94.0816(18)	87.807(4)	84.7462(11)
<i>g</i> °	98.7096(19)	88.165(3)	82.4882(12)
<i>V</i> /Å ³	975.60(4)	1546.11(12)	993.76(3)
<i>Z</i>	2	2	2
<i>Z'</i>	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	2.62	2.839	2.84
<i>Q</i> _{max} /°	79.759	78.547	79.82
Measured Refl.	11382	17802	26448
Independent Refl.	4060	6007	4176
Reflections with <i>I</i> > 2(<i>I</i>)	3161	3555	3842
<i>R</i> _{int}	0.0242	0.0553	0.0258
Parameters	280	429	264
Restraints	0	0	0
Largest Peak	0.286	0.294	0.233
Deepest Hole	-0.206	-0.262	-0.214
GooF	1.041	1.028	1.058
<i>wR</i> ₂ (all data)	0.1397	0.2204	0.1041
<i>wR</i> ₂	0.131	0.1858	0.1022
<i>R</i> _I (all data)	0.0626	0.1139	0.0399
<i>R</i> _I	0.049	0.0695	0.0372

Code	T5-3,4-dCl	T5-3,5-dNO ₂	T5-4CN
Formula	C ₁₈ H ₁₉ Cl ₂ N ₃ O ₅	C ₁₈ H ₁₉ N ₅ O ₉	C ₁₉ H ₂₀ N ₄ O ₅
<i>D</i> _{calc.} / g cm ⁻³	1.429	1.507	1.308
m/mm ⁻¹	3.246	1.057	0.806
Formula Weight	428.26	449.38	384.39
Colour	colourless	colourless	colourless
Shape	irregular	needle	needle
Size/mm ³	0.09×0.08×0.05	0.40×0.03×0.01	0.40×0.04×0.01
<i>T</i> /K	200.00(10)	150.00(10)	200.00(10)
Crystal System	triclinic	monoclinic	triclinic
Space Group	<i>P</i> -1	<i>I</i> 2/ <i>a</i>	<i>P</i> -1
<i>a</i> /Å	9.0768(3)	27.6487(7)	4.88505(8)
<i>b</i> /Å	9.0837(3)	5.17999(9)	11.1351(2)
<i>c</i> /Å	12.6868(5)	30.2938(8)	18.4476(3)
<i>a</i> °	105.164(3)	90	101.5273(15)
<i>b</i> °	98.256(3)	114.085(3)	90.6641(13)
<i>g</i> °	92.782(3)	90	96.4956(14)
<i>V</i> /Å ³	995.09(6)	3960.96(19)	976.32(3)
<i>Z</i>	2	8	2
<i>Z'</i>	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184

Radiation type	Cu K _α	Cu K _α	Cu K _α
$Q_{min}/^\circ$	3.658	3.196	2.446
$Q_{max}/^\circ$	80.017	79.608	79.841
Measured Refl.	13025	14558	11075
Independent Refl.	4152	4207	4077
Reflections with $I > 2(I)$	3347	3443	3338
R_{int}	0.0483	0.05	0.0195
Parameters	273	298	291
Restraints	2	0	6
Largest Peak	0.481	0.232	0.148
Deepest Hole	-0.429	-0.234	-0.161
GooF	1.036	1.045	1.082
wR_2 (all data)	0.1513	0.1086	0.1288
wR_2	0.1412	0.1016	0.123
R_I (all data)	0.0635	0.0509	0.0515
R_I	0.0521	0.0408	0.0425

Table D.5. Hydrogen bond distances of crystal structures

Co-crystal Code	N-H...O	D...A/Å	N...H-O	A...D/Å
T2-3,5-dNBA	N7-H7...O23	2.9097(16)	N2...H22-O22	2.6472(15)
T2-2,5-dMBA	N7-H7...O23	2.864(2)	N2...H22-O22	2.7266(18)
T2-3-dMABA-form 1	N19-H19...O9	2.876(2)	N13...H8-O8	2.701(2)
T2-3-dMABA-form 2	N10-H10...N23	3.058(3)	N2...H22-O22	2.671
T2-4ABA	N17-H17...O8	2.909(2)	N16...H9-O9	2.700(2)
T3-2,4-dNBA	N7-H7...O27	2.916(3)	N1...H26-O26	2.654(3)
T3-2,3,4,5-tFBA	N10-H10...O23	2.9235(14)	N1...H24-O24	2.6700(14)
T3-3,5-dNBA	N22-H22...O11	2.8560(16)	N16...H12-O12	2.6903(15)
T3-3NBA	N19-H19...O9	2.8700(19)	N18...H8-O8	2.7263(19)
T3-4CBA	N10-H10...O24	2.900(2)	N2...H23-O23	2.678(2)
T3-3,4-dCIBA	N11-H11...O23	2.936(2)	N2...H24-O24	2.677(2)
T3-3CIBA	N17-H17...O10	2.9327(18)	N11...H9-O9	2.6841(18)
T3-2,5-dMBA	N18-H18...O8	2.8275(14)	N12...H9-O9	2.7371(13)
T3-4FBA	N27-H27...O9	2.9403(13)	N21...H8-O8	2.6787(13)
T3-m-TA	N17-H17...O9	2.9466(13)	N11...H8-O8	2.6897(11)
T3-4MxBA	N18-H18...O8	2.8410(15)	N12...H9-O9	2.7161(15)
T3-3-dMABA	N19-H19...O8	2.9079(12)	N13...H9-O9	2.6671(12)
T3-4ABA	N10-H10...O23	2.7800(18)	N6...H24-O24	2.7912(17)
T4-2,4,6-tFBA	N10-H10...O3	2.818(3)	N3...H2-O2	2.734(3)
T4-2,3,4,5-tFBA	N7-H7...O28	2.919(2)	N1...H29-O29	2.687(2)
T4-3,5-dNBA	N7-H7...O30	2.841(3)	N1...H31-O31	2.636(3)
T4-3NBA	N31-H31...O8	2.891(2)	N25...H9-O9	2.693(2)
T4-4CBA	N18-H18...O9	2.9185(15)	N12...H8-O8	2.6521(15)

T4-3,4-dCIBA	N18-H18···O10	2.8993(17)	N17···H11-O11	2.6724(15)
T4-3CIBA	N17-H17···O9	2.9477(19)	N11···H10-O10	2.6606(19)
T4-2,5-dMBA	N7-H7···O24	2.830(2)	N6···H25-O25	2.730(2)
T4-4-Br-3-MBA	N18-H18···O9	2.905(2)	N12···H10-O10	2.706(2)
T4-m-TA	N17-H17···O9	2.8919(14)	N11···H8-O8	2.6915(15)
T4-3-dMABA	N19-H19···O8	2.9115(13)	N18···H9-O9	2.6769(13)
T4-2ABA	N17-H17···O8	2.7887(14)	N11···H9-O9	2.8284(12)
T5-2,4,6-tFBA	N10-H10···O3	2.819(4)	N3···H2-O2	2.746(4)
T5-2,3,4,5-tFBA	N20-H20···O12	2.9016(18)	N19···H13-O13	2.6653(19)
T5-3,5-dNBA	N22-H22···O11	2.8309(17)	N16···H12-O12	2.6683(15)
T5-4CBA	N21-H21···O9	2.8775(16)	N12···H8-O8	2.7094(16)
T5-3,4-dCIBA	N18-H18···O11	2.920(3)	N12···H10-O10	2.673(3)
T5-3CIBA	N17-H17···O9	2.9344(16)	N16···H10-O10	2.6897(16)
T5-2,5-dMBA	N18-H18···O8	2.8091(13)	N12···H9-O9	2.7504(12)
T5-3-dMABA	N19-H19···O8	2.9928(14)	N18···H9-O9	2.6629(13)
T5-2ABA	N17-H17···O8	2.828(3)	N16···H9-O9	2.747(2)

Appendix E - Additional information for Chapter 5

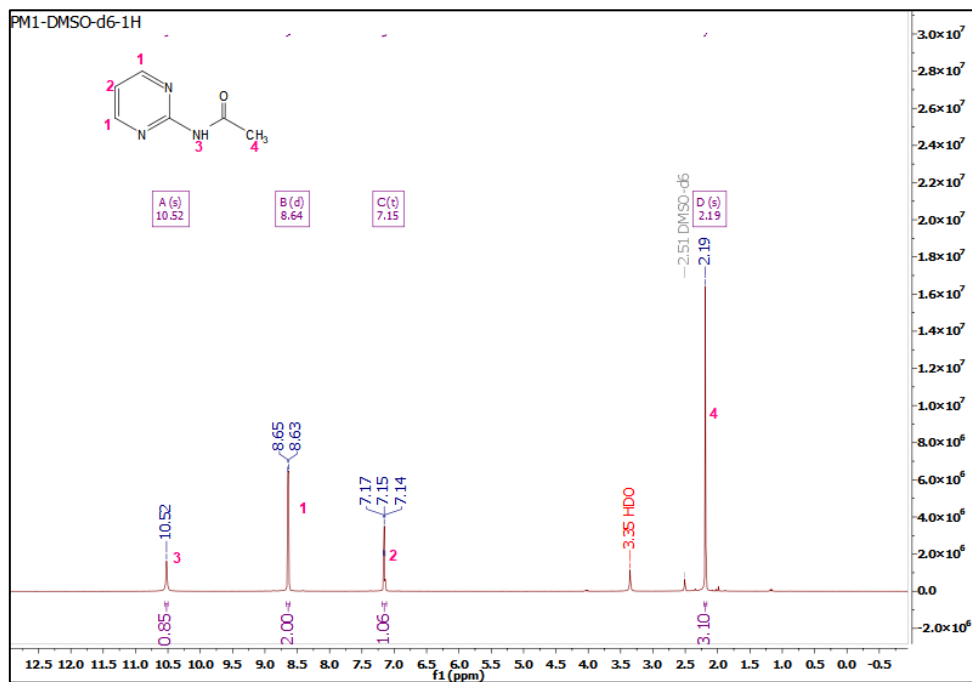


Figure E.1. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(pyrimidin-2-yl)acetamide (PM-methyl).

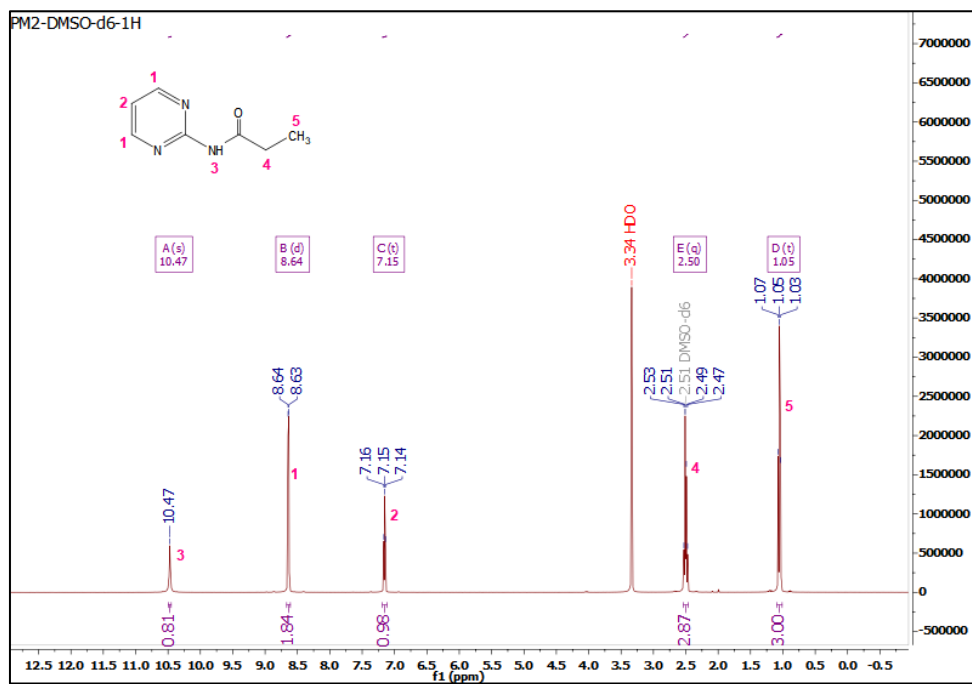


Figure E.2. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(pyrimidin-2-yl)propionamide (PM-ethyl).

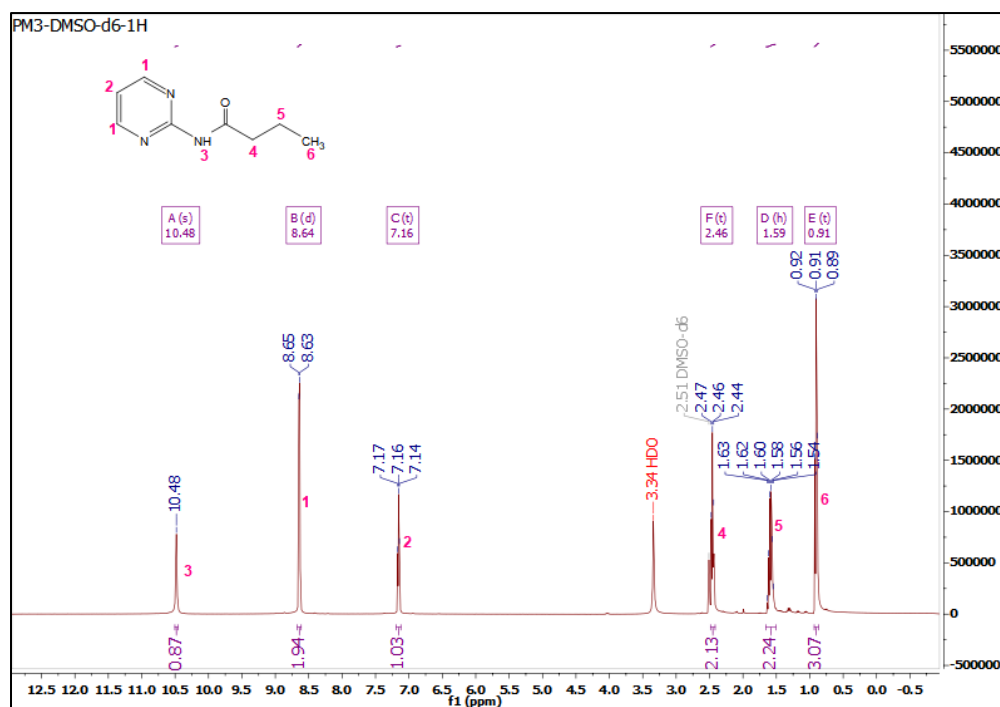


Figure E.3. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrimidin-2-yl)butyramide (PM-propyl).

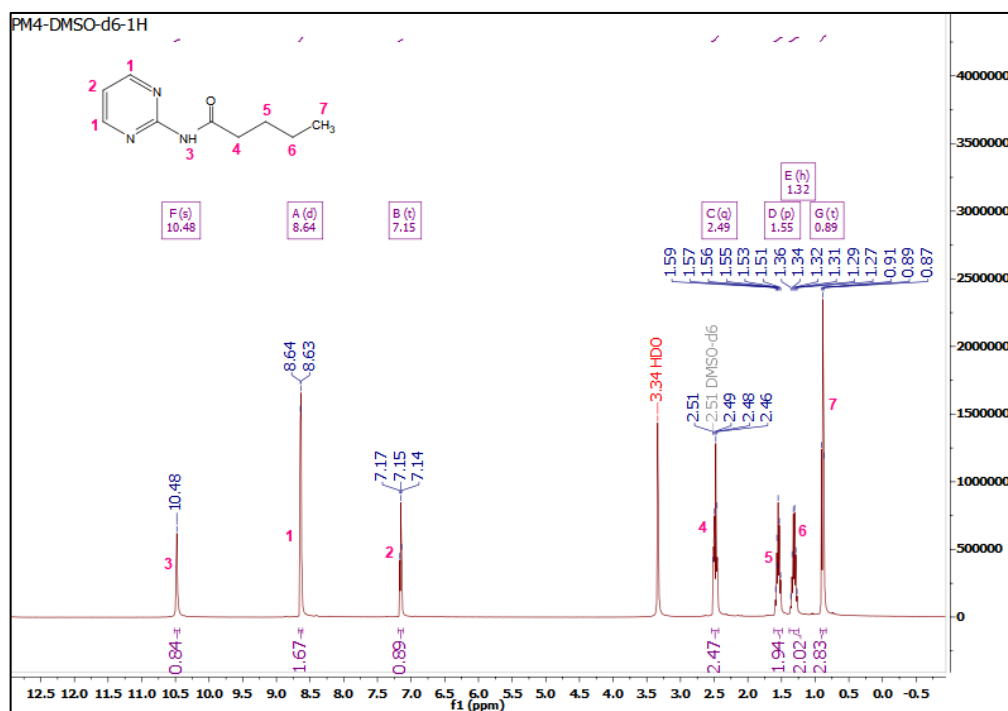


Figure E.4. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrimidin-2-yl)pentanamide (PM-butyl).

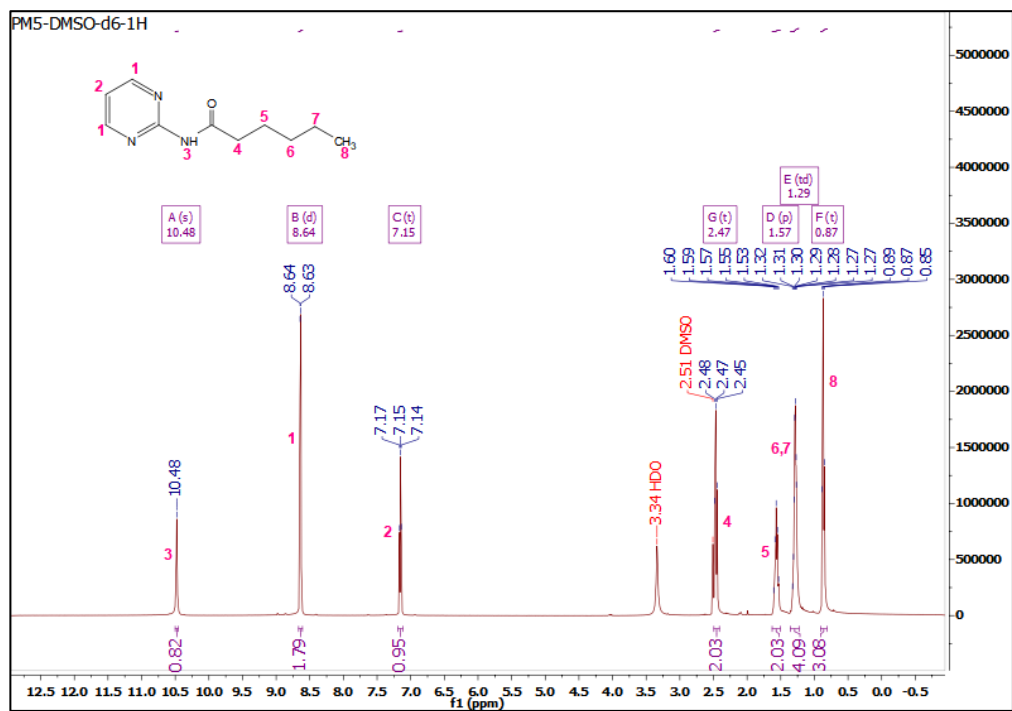


Figure E.5. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrimidin-2-yl)hexanamide (PM-pentyl).

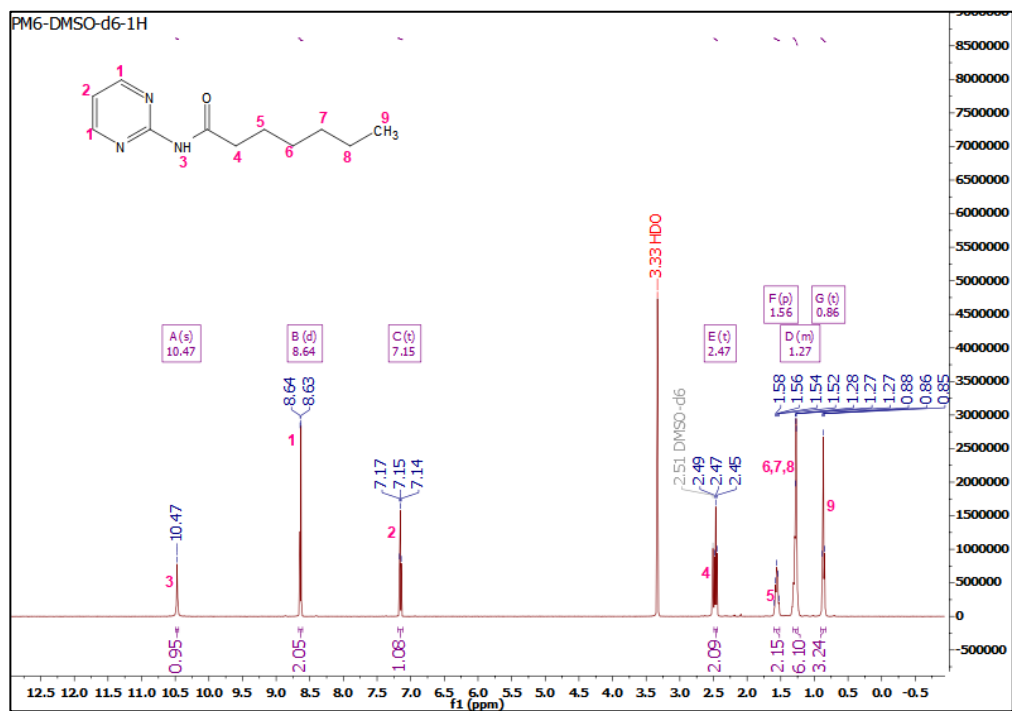


Figure E.6. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrimidin-2-yl)heptanamide (PM-hexyl).

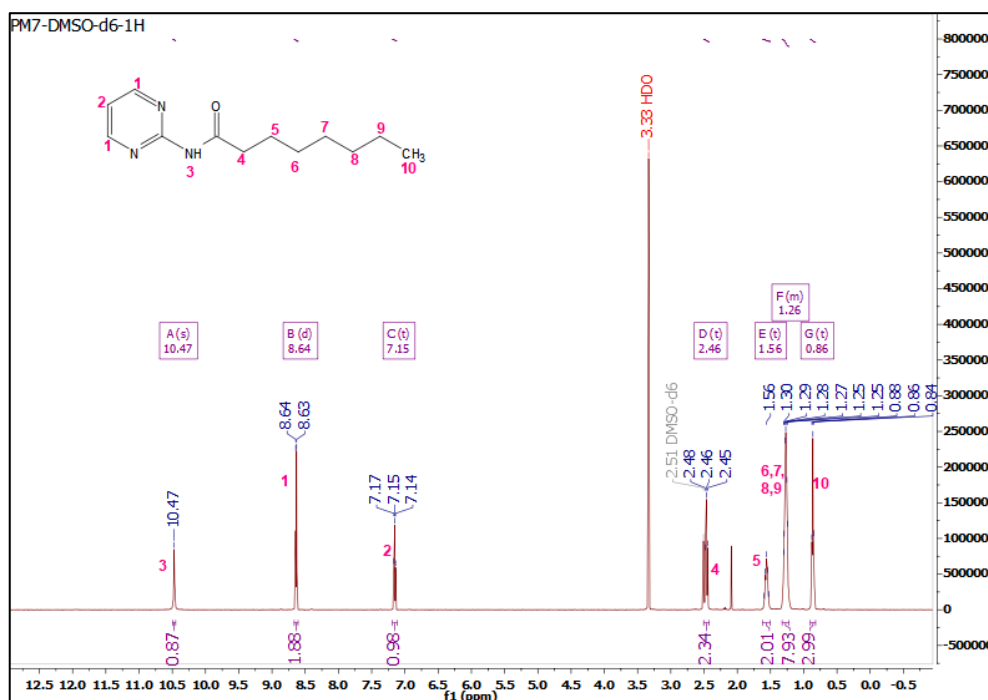


Figure E.7. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrimidin-2-yl)octanamide (PM-heptyl).

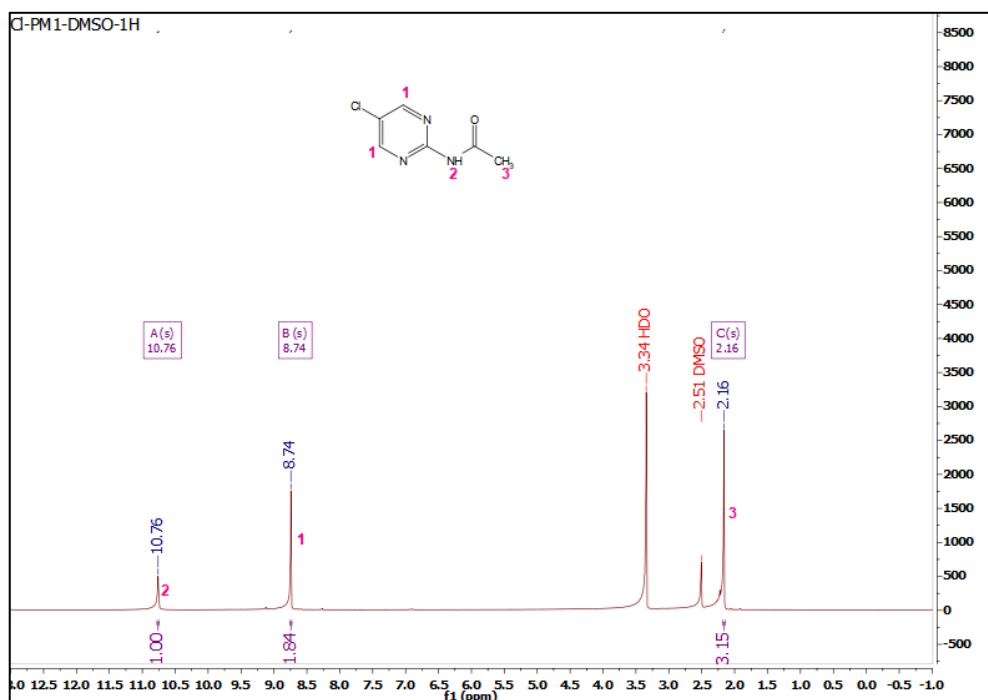


Figure E.8. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-chloropyrimidin-2-yl)acetamide (Cl-PM-methyl).

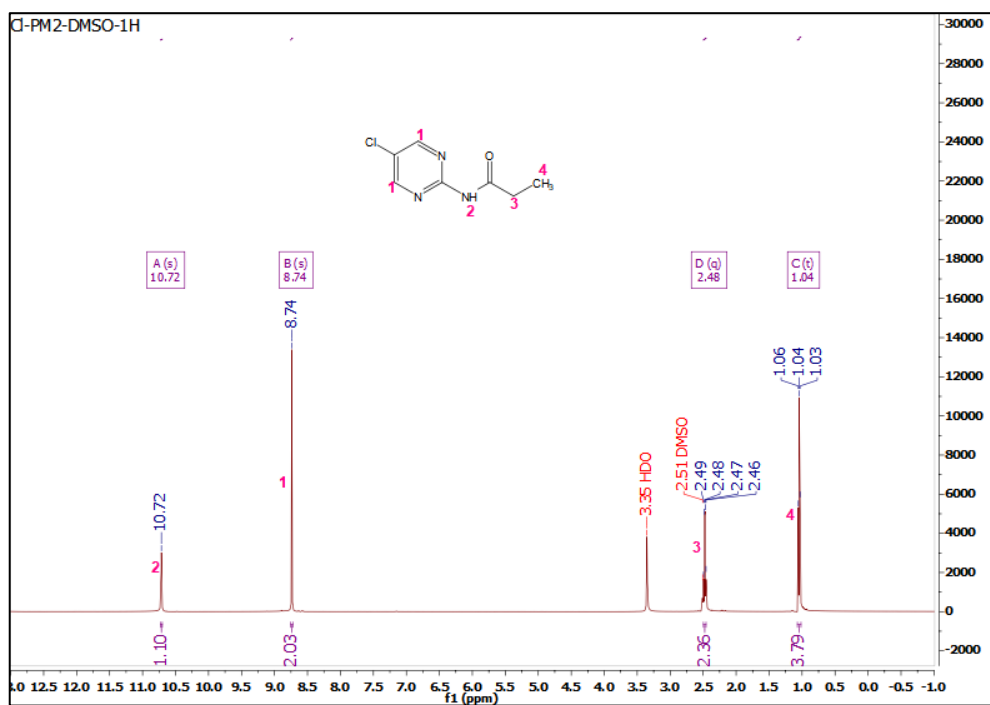


Figure E.9. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-chloropyrimidin-2-yl)propionamide (Cl-PM-ethyl).

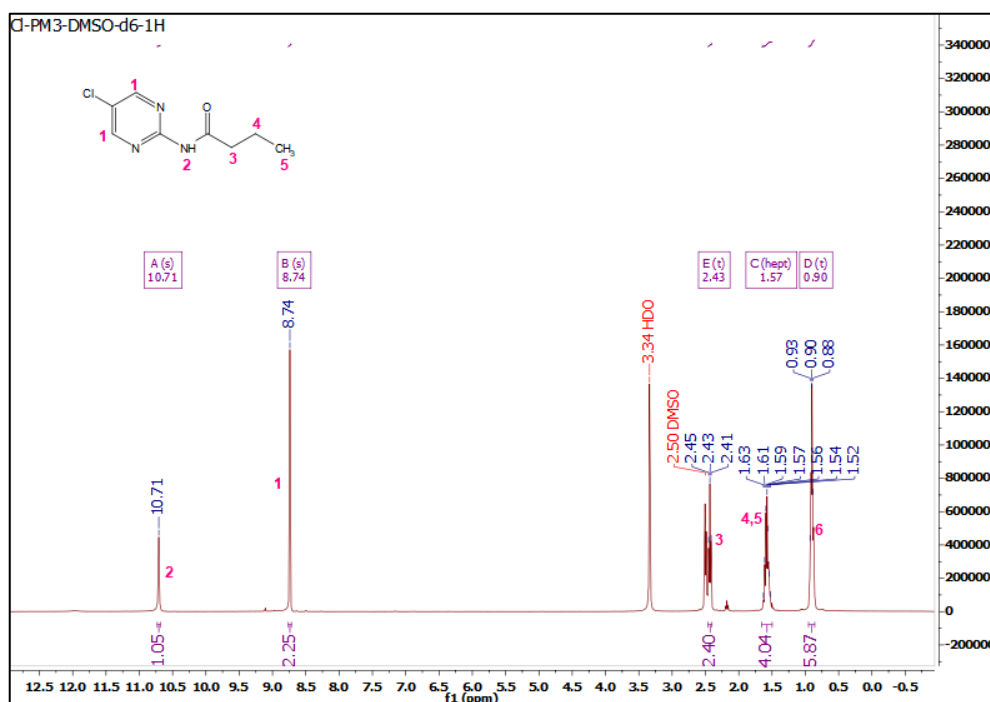
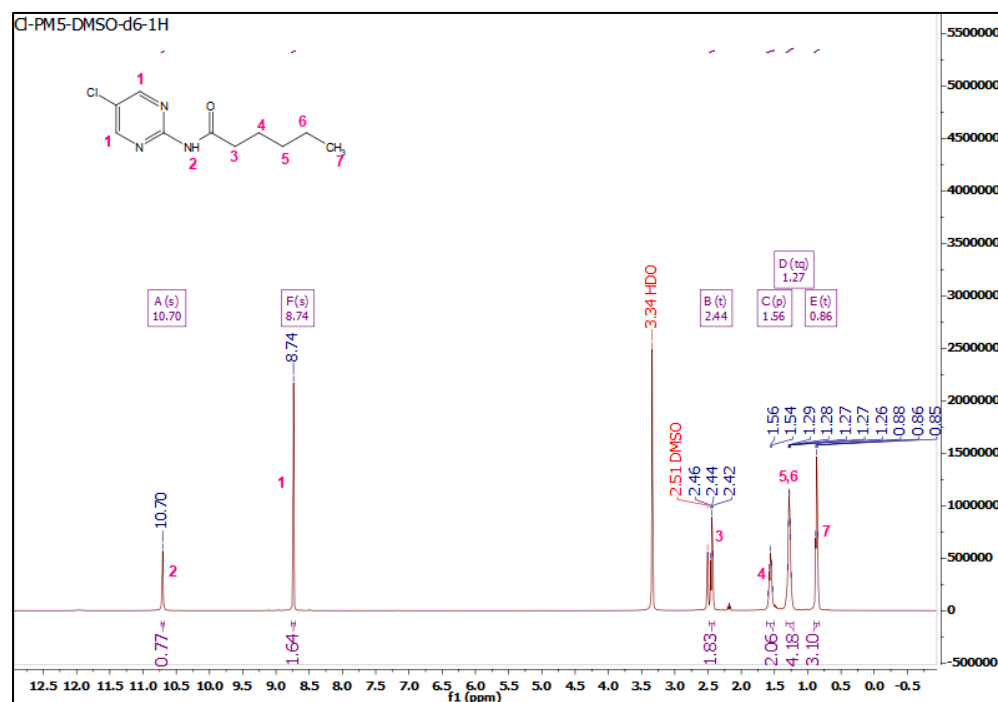
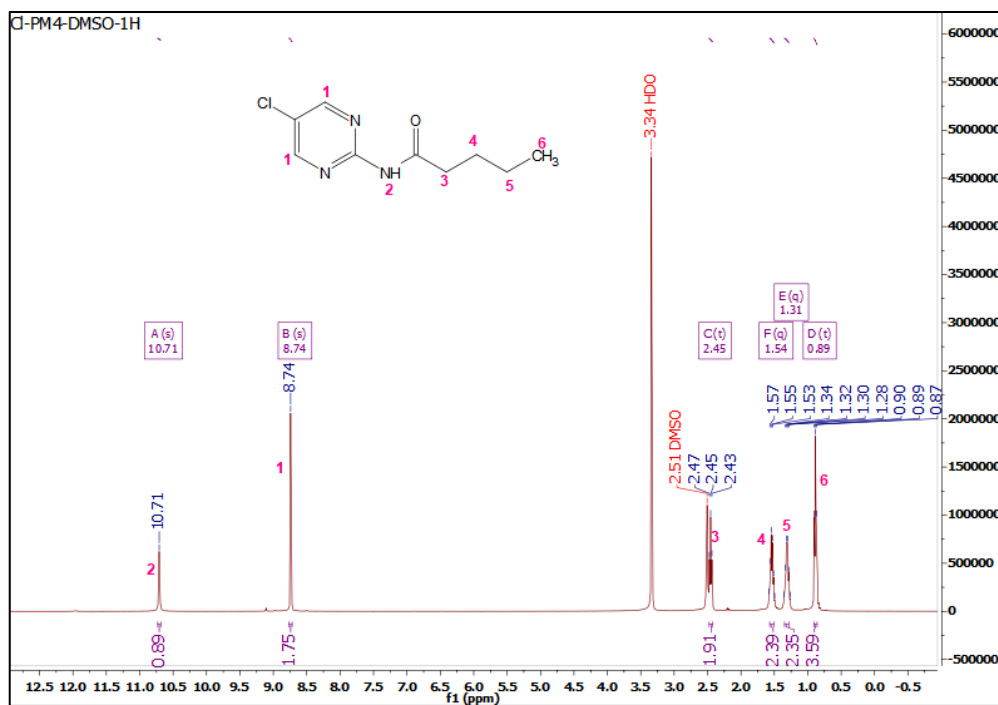


Figure E.10. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-chloropyrimidin-2-yl)butyramide (Cl-PM3-propyl).



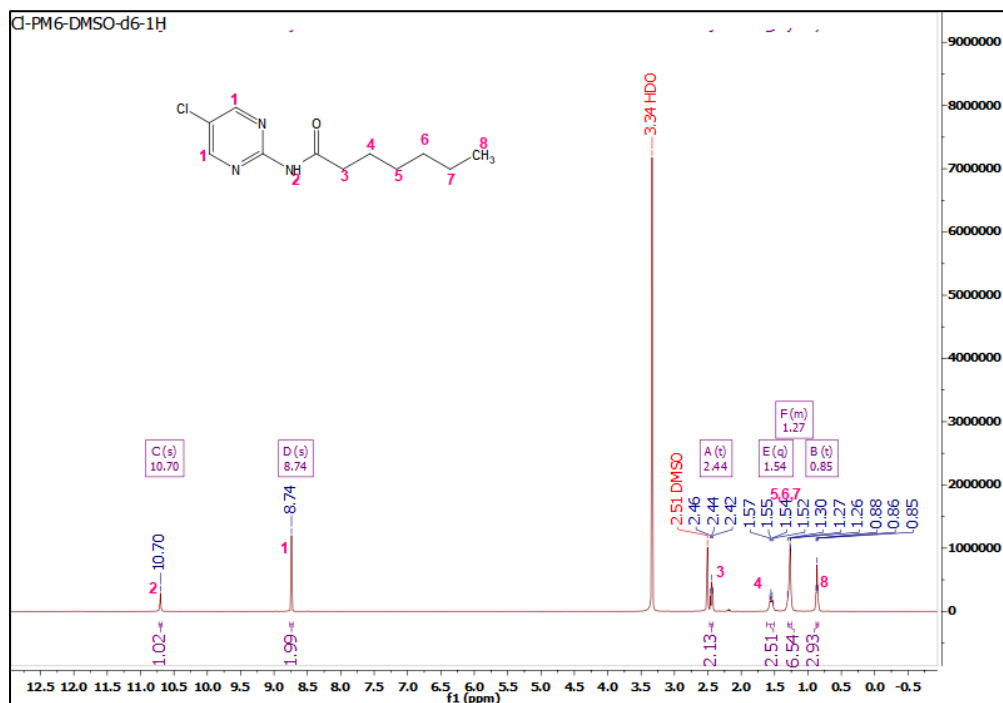


Figure E.13. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-chloropyrimidin-2-yl)heptanamide (Cl-PM-hexyl).

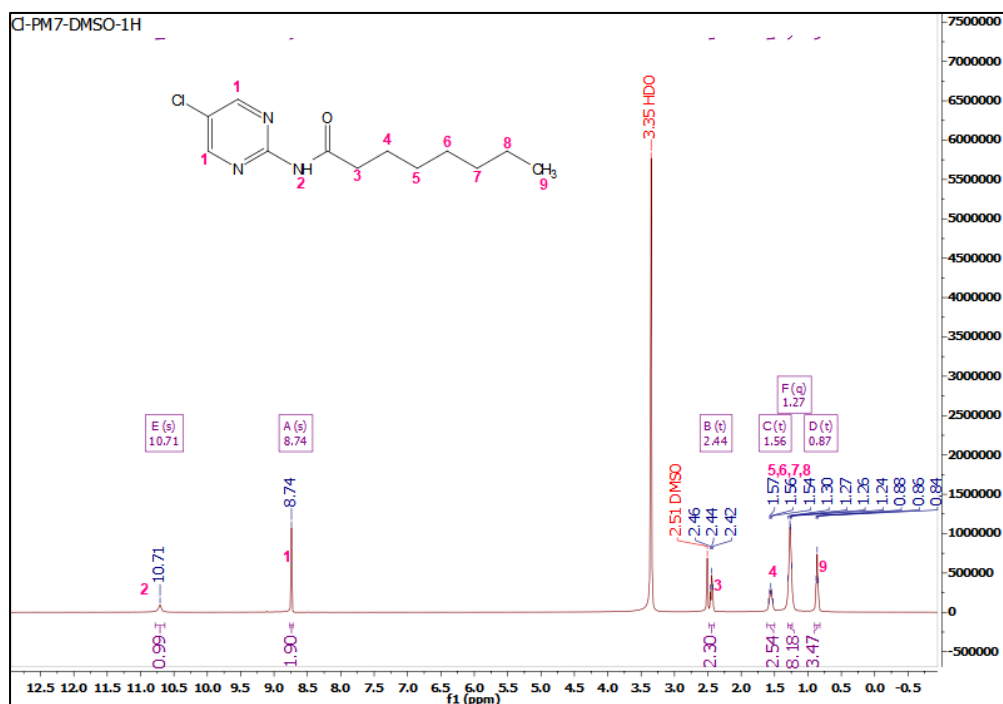


Figure E.14. ¹H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-chloropyrimidin-2-yl)octanamide (Cl-PM-heptyl).

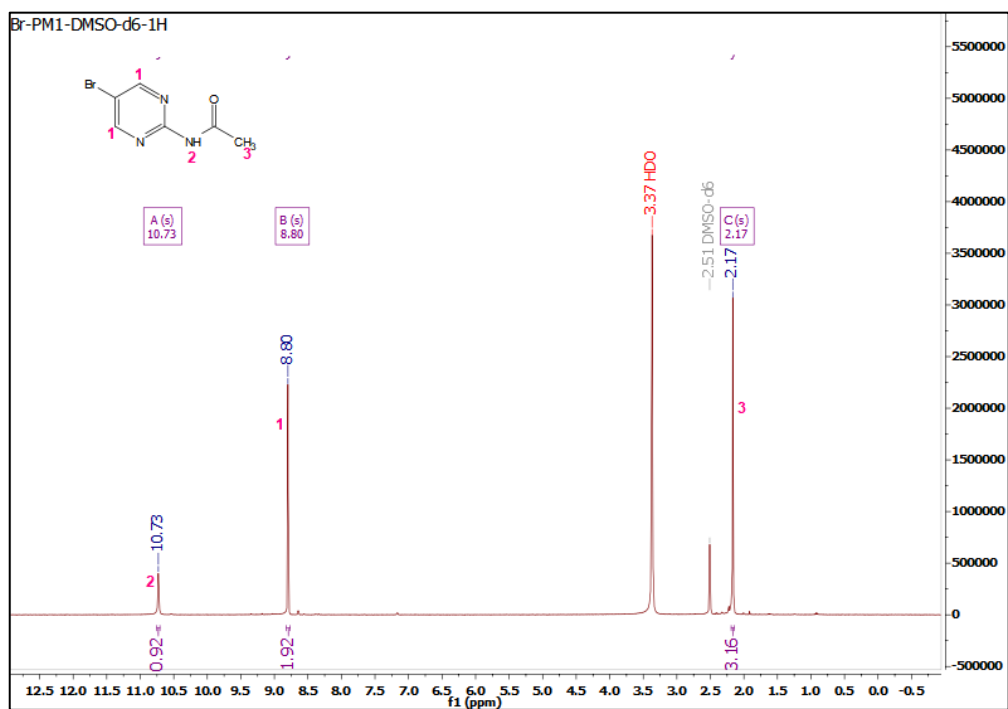


Figure E.15. ^1H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-bromopyrimidin-2-yl)acetamide (Br-PM-methyl).

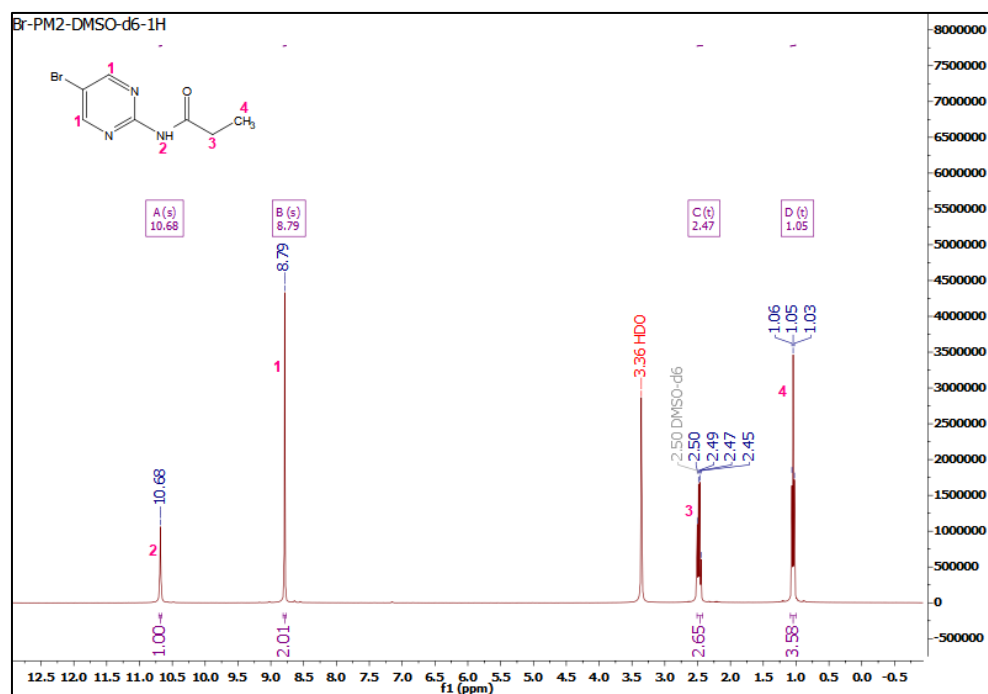


Figure E.16. ^1H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(5-bromopyrimidin-2-yl)propionamide (Br-PM-ethyl).

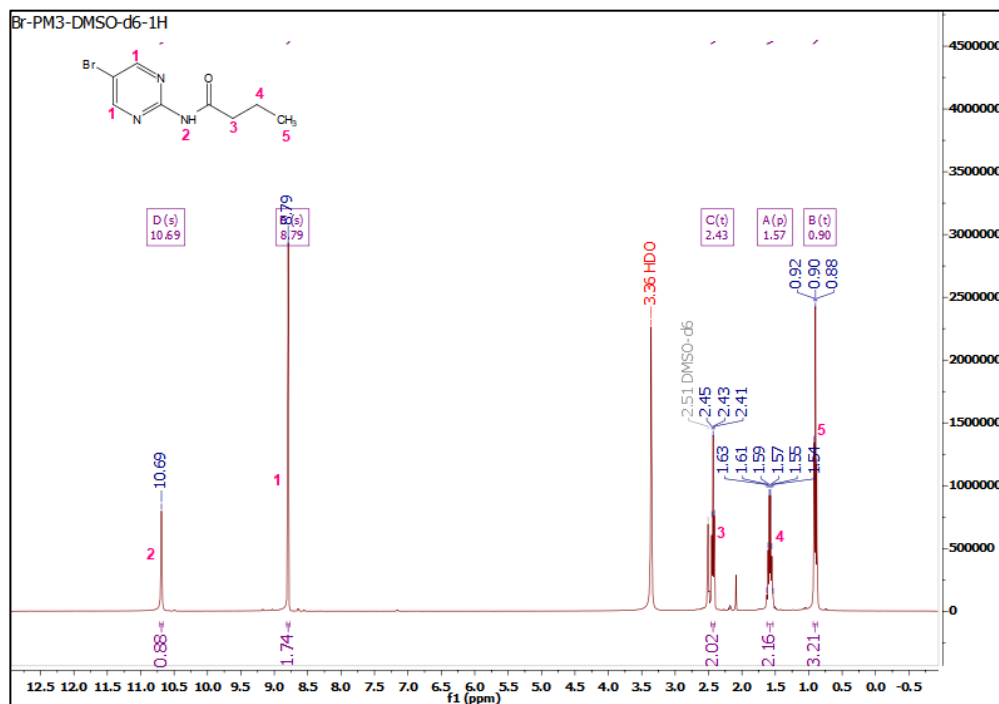


Figure E.17. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-bromopyrimidin-2-yl)butyramide (Br-PM-propyl).

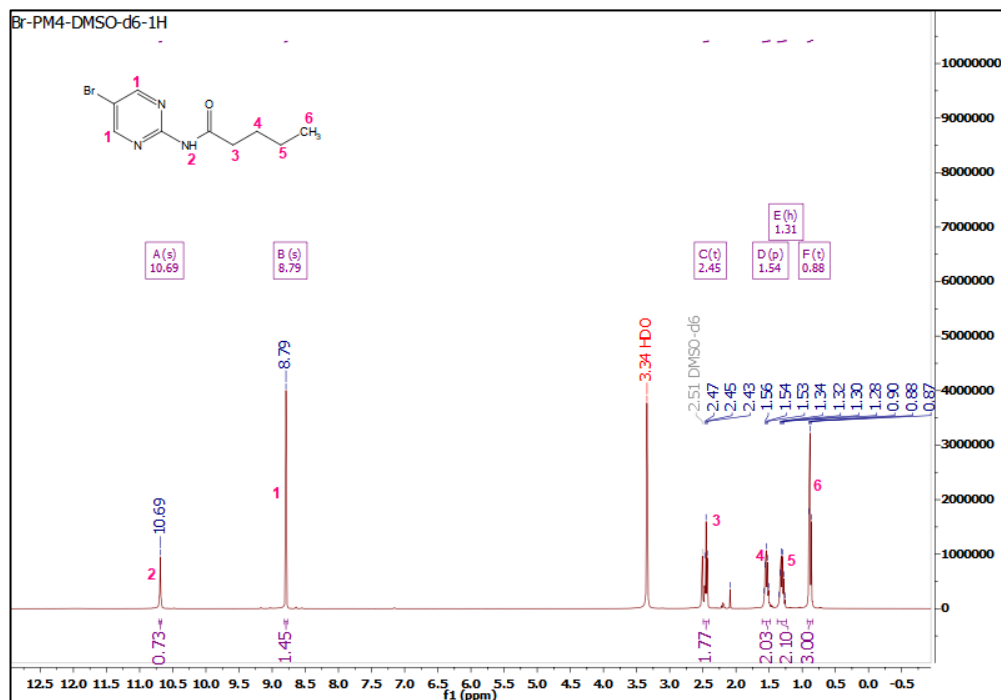


Figure E.18. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-bromopyrimidin-2-yl)pentanamide (Br-PM-butyl).

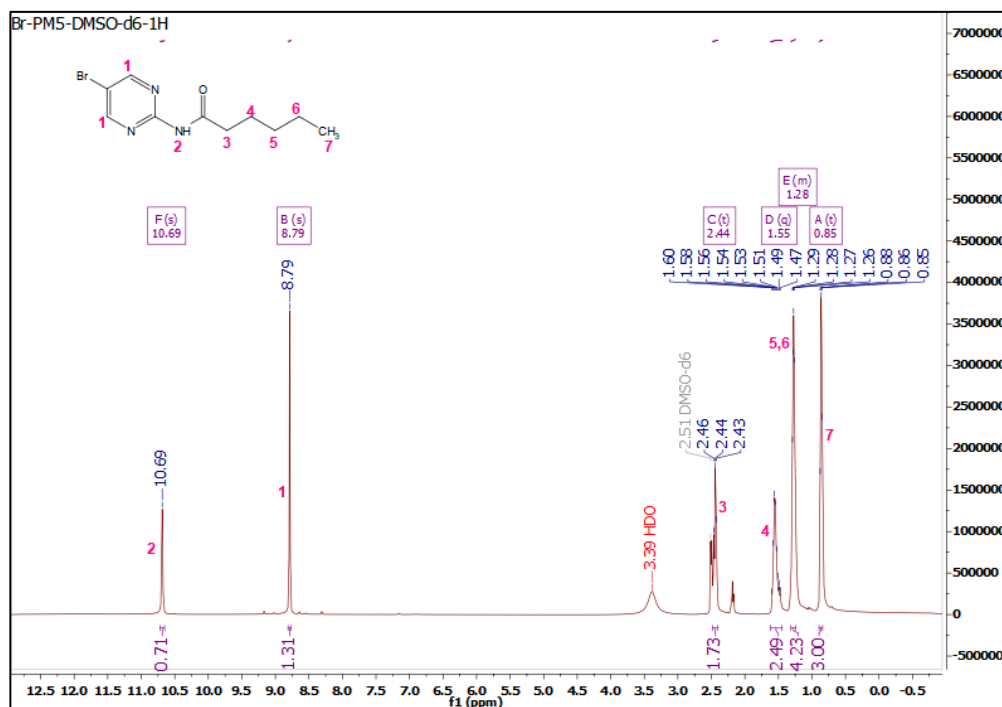


Figure E.19. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-bromopyrimidin-2-yl)hexanamide (Br-PM-pentyl).

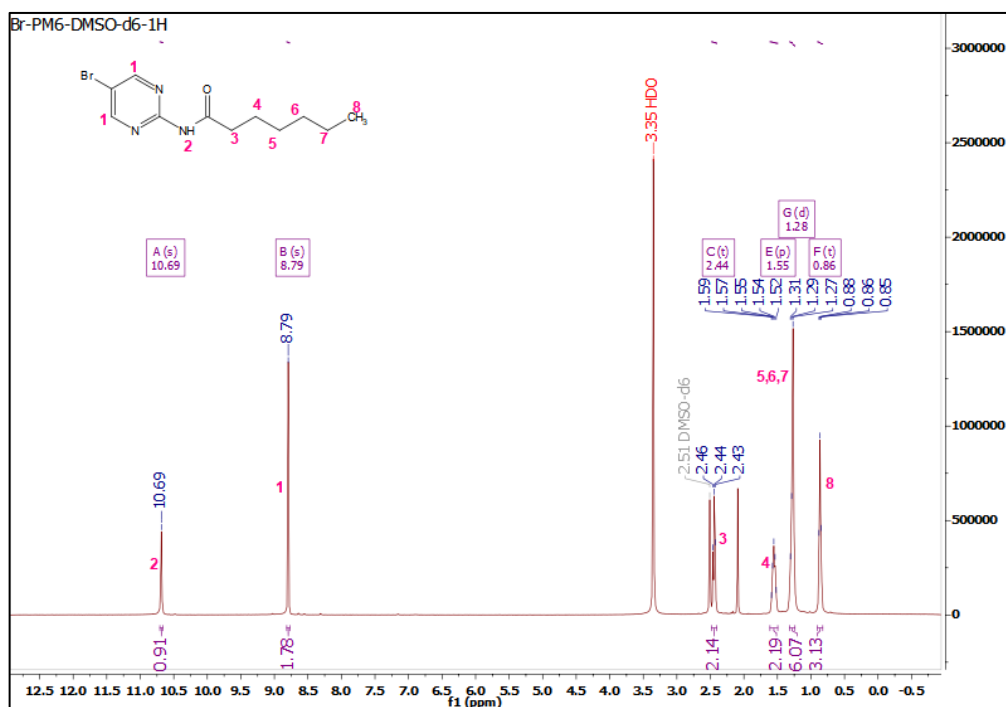


Figure E.20. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-bromopyrimidin-2-yl)heptanamide (Br-PM-hexyl).

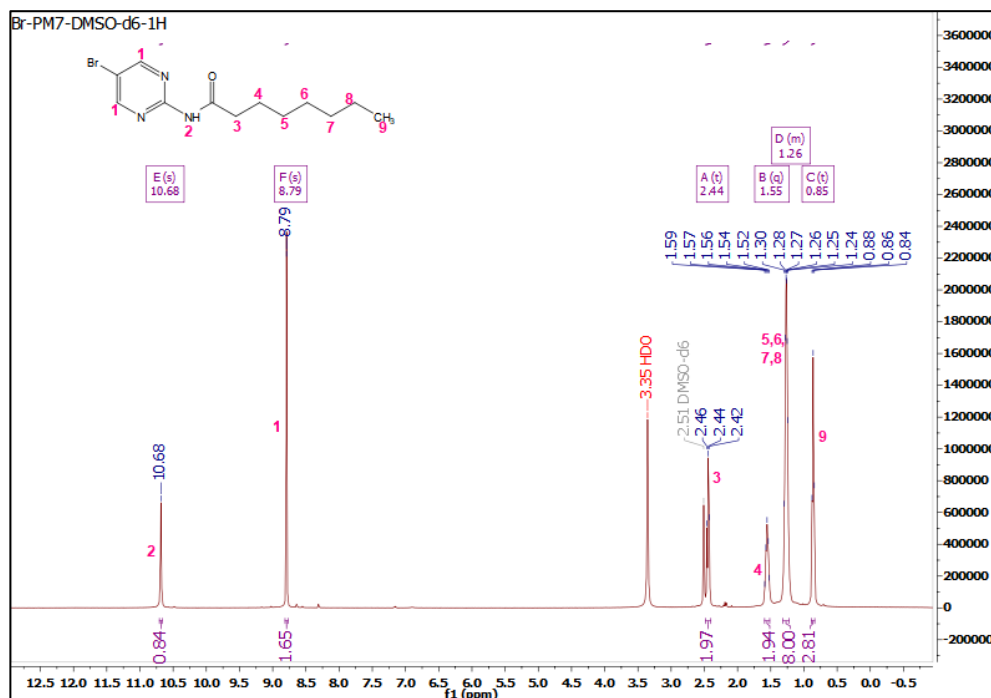


Figure E.21. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(5-bromopyrimidin-2-yl)octanamide (Br-PM-heptyl).

Table E.1. Crystallographic information for the PM series crystal structures

Compound	PM-methyl	PM-ethyl	PM-propyl	PM-butyl
Formula	$\text{C}_6\text{H}_7\text{N}_3\text{O}$	$\text{C}_7\text{H}_9\text{N}_3\text{O}$	$\text{C}_8\text{H}_{11}\text{N}_3\text{O}$	$\text{C}_9\text{H}_{13}\text{N}_3\text{O}$
$D_{\text{calc.}}/\text{g cm}^{-3}$	1.398	1.307	1.273	1.235
m/mm^{-1}	0.839	0.759	0.719	0.681
Formula Weight	137.15	151.17	165.2	179.22
Colour	colourless	colourless	white	colourless
Shape	plate	irregular	needle	irregular
Size/ mm^3	$0.16 \times 0.08 \times 0.02$	$0.19 \times 0.13 \times 0.08$	$0.15 \times 0.02 \times 0.01$	$0.16 \times 0.10 \times 0.03$
T/K	294.28(10)	294.20(10)	294.1(2)	294.25(10)
Crystal System	triclinic	monoclinic	monoclinic	monoclinic
Space Group	$P-1$	$I2/m$	$I2/a$	$I2/a$
$a/\text{\AA}$	5.7366(4)	9.4300(16)	17.7106(5)	14.1135(5)
$b/\text{\AA}$	7.7844(5)	6.8202(14)	5.3994(2)	9.5709(3)
$c/\text{\AA}$	8.2021(5)	12.068(2)	18.1317(5)	15.7423(5)
$\alpha/^\circ$	69.903(6)	90	90	90
$\beta/^\circ$	79.695(5)	98.060(16)	96.210(3)	114.958(4)
$\gamma/^\circ$	71.797(6)	90	90	90
$V/\text{\AA}^3$	325.71(4)	768.5(2)	1723.69(10)	1927.87(13)

<i>Z</i>	2	4	8	8
<i>Z'</i>	1	0.5	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	5.763	5.589	4.907	5.565
<i>Q</i> _{max} /°	79.647	68.219	79.933	79.922
Measured Refl.	4241	4507	8395	11115
Independent Refl.	1387	756	1876	2088
Reflections with <i>I</i> > 2(<i>I</i>)	1194	563	1576	1677
<i>R</i> _{int}	0.029	0.0599	0.0284	0.0322
Parameters	96	71	115	123
Restraints	0	0	0	0
Largest Peak	0.209	0.349	0.133	0.128
Deepest Hole	-0.144	-0.201	-0.117	-0.190
GooF	1.078	1.045	1.062	1.080
<i>wR</i> ₂ (all data)	0.131	0.1980	0.1074	0.1360
<i>wR</i> ₂	0.1266	0.1712	0.1030	0.1278
<i>R</i> _{<i>I</i>} (all data)	0.0478	0.0775	0.0437	0.0519
<i>R</i> _{<i>I</i>}	0.0438	0.0615	0.0364	0.0441

Compound	PM-pentyl	PM-hexyl	PM-heptyl
Formula	C ₁₀ H ₁₅ N ₃ O	C ₁₁ H ₁₇ N ₃ O	C ₁₂ H ₁₉ N ₃ O
<i>D</i> _{calc.} / g cm ⁻³	1.215	1.202	1.185
<i>m</i> /mm ⁻¹	0.656	0.637	0.617
Formula Weight	193.25	207.27	221.3
Colour	colourless	colourless	colourless
Shape	irregular	needle	needle
Size/mm ³	0.26×0.14×0.10	0.18×0.02×0.02	0.32×0.02×0.02
<i>T</i> /K	292.66(13)	210.00(10)	210.00(10)
Crystal System	triclinic	triclinic	monoclinic
Space Group	<i>P</i> -1	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	5.48770(10)	5.4040(3)	9.4878(2)
<i>b</i> /Å	9.4348(3)	9.4516(4)	5.36366(9)
<i>c</i> /Å	10.5745(3)	11.8359(3)	24.6068(5)
<i>α</i> /°	86.598(2)	86.634(3)	90
<i>β</i> /°	83.945(2)	78.835(3)	97.8206(19)
<i>γ</i> /°	76.146(2)	74.900(4)	90
<i>V</i> /Å ³	528.28(2)	572.59(4)	1240.58(4)
<i>Z</i>	2	2	4
<i>Z'</i>	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> _{min} /°	4.207	3.807	3.626
<i>Q</i> _{max} /°	79.941	79.132	79.614
Measured Refl.	8131	6602	7258

Independent Refl.	2263	2366	2554
Reflections with $I > 2(I)$	1952	2059	2153
R_{int}	0.0306	0.0216	0.0341
Parameters	132	141	150
Restraints	0	0	0
Largest Peak	0.167	0.215	0.141
Deepest Hole	-0.197	-0.175	-0.252
GooF	1.059	1.074	1.052
wR_2 (all data)	0.136	0.1361	0.1166
wR_2	0.1312	0.1306	0.1108
R_I (all data)	0.0475	0.0544	0.0493
R_I	0.0438	0.0474	0.0417

Table E.2. Crystallographic information for the Cl-PM series crystal structures

Compound	Cl-PM-methyl	Cl-PM-ethyl	Cl-PM-propyl	Cl-PM-butyl
Formula	$C_6H_6ClN_3O$	$C_7H_8ClN_3O$	$C_8H_{10}ClN_3O$	$C_9H_{12}ClN_3O$
$D_{calc}/g\ cm^{-3}$	1.596	1.475	1.403	1.308
m/mm^{-1}	4.261	3.683	3.297	2.905
Formula Weight	171.59	185.61	199.64	213.67
Colour	colourless	colourless	colourless	colourless
Shape	irregular	irregular	plate	block
Size/ mm^3	$0.16 \times 0.14 \times 0.08$	$0.14 \times 0.12 \times 0.08$	$0.23 \times 0.06 \times 0.03$	$0.17 \times 0.10 \times 0.10$
T/K	210.00(10)	210.00(10)	210.00(10)	240.00(10)
Crystal System	orthorhombic	triclinic	triclinic	monoclinic
Space Group	$Cccm$	$P-1$	$P-1$	$P2_1/c$
$a/\text{\AA}$	11.52290(10)	11.72860(10)	4.48170(10)	8.51521(9)
$b/\text{\AA}$	18.7942(3)	12.73070(10)	8.33370(10)	26.9519(2)
$c/\text{\AA}$	6.59400(10)	13.53730(10)	12.9705(2)	9.59636(7)
a°	90	116.5720(10)	89.4260(10)	90
b°	90	103.2490(10)	87.8120(10)	99.8219(9)
g°	90	99.7370(10)	77.4270(10)	90
$V/\text{\AA}^3$	1428.02(3)	1671.82(3)	472.475(14)	2170.09(3)
Z	8	8	2	8
Z'	0.5	4	1	2
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K_α	Cu K_α	Cu K_α	Cu K_α
Q_{min}°	4.501	3.891	3.41	3.28
Q_{max}°	79.885	79.923	79.932	79.955
Measured Refl.	3405	37773	10560	27544
Independent Refl.	854	7231	2039	4696

Reflections with $I > 2(I)$	808	6691	1983	4264
R_{int}	0.0210	0.0219	0.0263	0.0274
Parameters	71	453	124	283
Restraints	0	0	0	4
Largest Peak	0.308	0.260	0.314	0.199
Deepest Hole	-0.381	-0.506	-0.235	-0.228
GooF	1.147	1.091	1.103	1.047
wR_2 (all data)	0.1020	0.0961	0.0821	0.1325
wR_2	0.1004	0.0945	0.0817	0.1302
R_I (all data)	0.0397	0.0343	0.0306	0.0495
R_I	0.0387	0.0326	0.0301	0.0466

Compound	Cl-PM-pentyl	Cl-PM-hexyl	Cl-PM-heptyl
Formula	C ₁₀ H ₁₄ ClN ₃ O	C ₁₁ H ₁₆ ClN ₃ O	C ₁₂ H ₁₈ ClN ₃ O
$D_{calc.}/g\ cm^{-3}$	1.333	1.289	1.261
m/mm^{-1}	2.811	2.588	2.42
Formula Weight	227.69	241.72	255.74
Colour	colourless	colourless	colourless
Shape	needle	plate	needle
Size/ mm^3	0.12×0.03×0.01	0.25×0.07×0.01	0.21×0.02×0.02
T/K	210.00(10)	210.00(10)	210.00(10)
Crystal System	monoclinic	monoclinic	triclinic
Space Group	$P2_1/n$	$P2_1/c$	$P-1$
$a/\text{\AA}$	11.8655(2)	14.1859(2)	4.79170(10)
$b/\text{\AA}$	4.92610(8)	4.43507(5)	7.8274(2)
$c/\text{\AA}$	20.0131(3)	20.7479(4)	18.7292(4)
a°	90	90	98.463(2)
b°	104.1198(16)	107.3484(18)	97.059(2)
g°	90	90	100.985(2)
$V/\text{\AA}^3$	1134.44(3)	1245.98(4)	673.80(3)
Z	4	4	2
Z'	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K _a	Cu K _a	Cu K _a
$Q_{min}/^\circ$	3.959	3.264	2.414
$Q_{max}/^\circ$	80.012	79.725	80.04
Measured Refl.	8403	10186	10790
Independent Refl.	2430	2692	2900
Reflections with $I > 2(I)$	2201	2455	2627
R_{int}	0.0214	0.0270	0.0299
Parameters	141	150	159
Restraints	0	0	0
Largest Peak	0.199	0.184	0.251
Deepest Hole	-0.232	-0.177	-0.263
GooF	1.050	1.052	1.063
wR_2 (all data)	0.0902	0.0918	0.101
wR_2	0.0879	0.0891	0.0989
R_I (all data)	0.0349	0.0350	0.0408

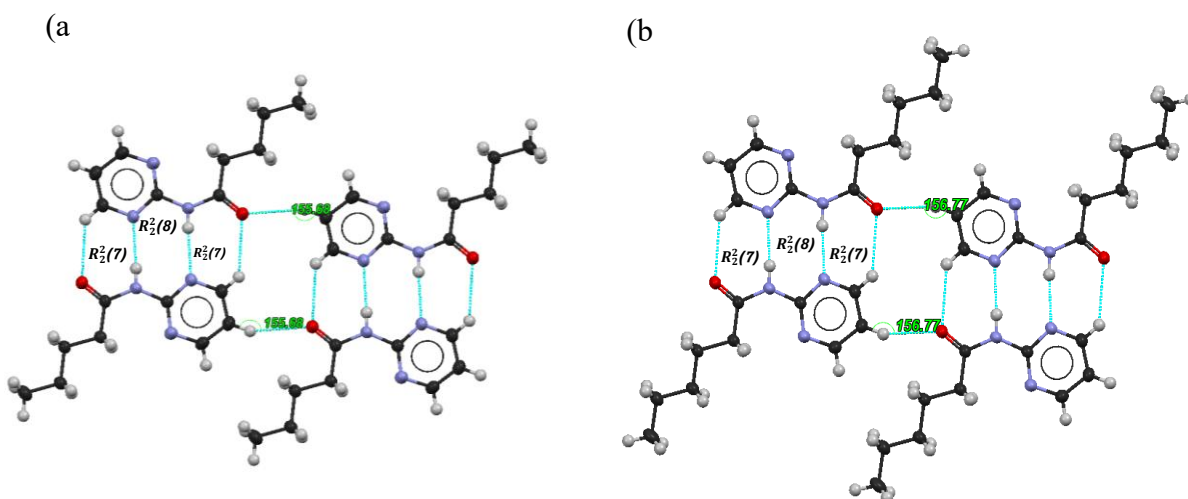
R_I	0.0319	0.0322	0.0374
-------	--------	--------	--------

Table E.3. Crystallographic information for the Br-PM series crystal structures

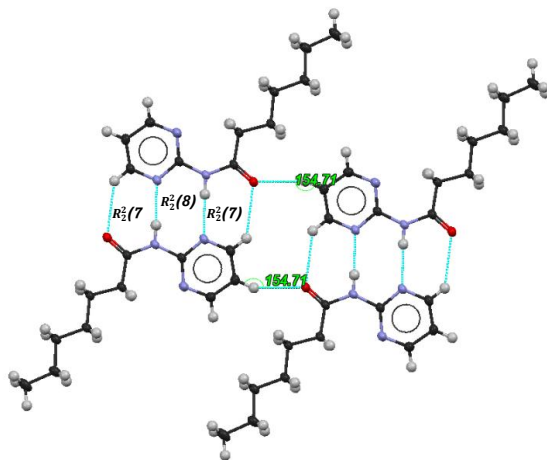
Compound	Br-PM-methyl	Br-PM-ethyl	Br-PM-propyl	Br-PM-butyl
Formula	C ₆ H ₆ BrN ₃ O	C ₇ H ₈ BrN ₃ O	C ₈ H ₁₀ BrN ₃ O	C ₉ H ₁₂ BrN ₃ O
<i>D</i> calc./ g cm ⁻³	1.936	1.797	1.659	1.594
m/mm ⁻¹	7.106	6.235	5.465	4.999
Formula Weight	216.05	230.07	244.1	258.13
Colour	orange	orange	colourless	colourless
Shape	plate	prism	needle	block
Size/mm ³	0.15×0.08×0.03	0.06×0.03×0.03	0.21×0.03×0.01	0.15×0.10×0.04
<i>T</i> /K	210.00(10)	210.00(10)	210.00(10)	210.00(10)
Crystal System	orthorhombic	triclinic	triclinic	triclinic
Space Group	<i>Cccm</i>	<i>P</i> -1	<i>P</i> -1	<i>P</i> -1
<i>a</i> /Å	11.8524(2)	11.91357(16)	4.59547(11)	8.16640(10)
<i>b</i> /Å	18.7728(2)	12.78923(14)	8.48559(18)	10.95870(10)
<i>c</i> /Å	6.66220(10)	13.5543(2)	12.8938(4)	13.4268(2)
<i>a</i> °	90	116.3584(13)	89.593(2)	70.2550(10)
<i>b</i> °	90	103.3625(12)	87.432(2)	73.2710(10)
<i>g</i> °	90	100.5427(10)	76.571(2)	78.2360(10)
<i>V</i> /Å ³	1482.36(4)	1701.06(4)	488.56(2)	1075.49(2)
<i>Z</i>	8	8	2	4
<i>Z'</i>	0.5	4	1	2
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α	Cu K _α
<i>Q</i> min/°	4.412	3.893	3.431	3.601
<i>Q</i> max/°	79.935	79.992	79.319	80.023
Measured Refl.	4747	38605	10411	20918
Independent Refl.	890	7366	2074	4659
Reflections with <i>I</i> >2(<i>I</i>)	863	6792	1978	4406
<i>R</i> _{int}	0.0291	0.0285	0.0342	0.0228
Parameters	71	453	123	263
Restraints	0	0	0	0
Largest Peak	0.459	0.654	0.286	0.322
Deepest Hole	-0.473	-0.973	-0.536	-0.657
GooF	1.143	1.059	1.111	1.05
<i>wR</i> ₂ (all data)	0.0723	0.0713	0.0662	0.064
<i>wR</i> ₂	0.0718	0.0700	0.0657	0.0633
<i>R</i> _I (all data)	0.0264	0.0277	0.025	0.0243
<i>R</i> _I	0.0259	0.0257	0.0241	0.0232

Compound	Br-PM-pentyl-From 1	Br-PM-pentyl-From 2	Br-PM-hexyl	Br-PM-heptyl
Formula	C ₁₀ H ₁₄ BrN ₃ O	C ₁₀ H ₁₄ BrN ₃ O	C ₁₁ H ₁₆ BrN ₃ O	C ₁₂ H ₁₈ N ₃ OBr
<i>D</i> calc./ g cm ⁻³	1.539	1.537	1.527	1.427
m/mm ⁻¹	4.607	4.601	4.378	3.926
Formula Weight	272.15	272.15	286.18	300.2
Colour	colourless	colourless	colourless	colourless

Shape	plate	plate	needle	needle
Size/mm ³	0.22×0.12×0.01	0.15×0.09×0.02	0.28×0.02×0.02	0.14×0.01×0.01
<i>T</i> /K	210.00(10)	210.00(10)	210.00(10)	210.00(10)
Crystal System	monoclinic	triclinic	monoclinic	triclinic
Space Group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> -1
<i>a</i> /Å	26.6210(2)	4.22728(7)	11.27079(12)	5.4649(2)
<i>b</i> /Å	10.98102(12)	9.25178(15)	5.29124(5)	10.9705(4)
<i>c</i> /Å	8.05210(6)	15.5113(2)	21.5186(2)	12.1885(4)
<i>a</i> /°	90	83.8025(13)	90	92.709(3)
<i>b</i> /°	93.5054(7)	88.2380(13)	104.0832(10)	102.343(3)
<i>g</i> /°	90	77.2224(13)	90	100.682(3)
<i>V</i> /Å ³	2349.43(4)	588.148(16)	1244.72(2)	698.59(4)
<i>Z</i>	8	2	4	2
<i>Z</i> '	2	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α	CuK _α
<i>Q</i> min/°	3.327	2.866	4.083	3.728
<i>Q</i> max/°	79.925	79.969	79.855	79.976
Measured Refl.	28790	8938	14677	8672
Independent Refl.	5067	2536	2713	2908
Reflections with <i>I</i> >2(<i>I</i>)	4631	2499	2476	2558
<i>R</i> _{int}	0.0344	0.0185	0.0329	0.0530
Parameters	319	141	150	159
Restraints	8	0	0	0
Largest Peak	0.622	0.449	0.574	0.800
Deepest Hole	-0.483	-0.443	-0.538	-0.537
GooF	1.090	1.076	1.082	1.033
<i>wR</i> ₂ (all data)	0.0904	0.0616	0.0767	0.1050
<i>wR</i> ₂	0.0884	0.0614	0.0744	0.1018
<i>R</i> ₁ (all data)	0.0331	0.0237	0.0315	0.0472
<i>R</i> ₁	0.0307	0.0235	0.0287	0.0407



(c)



(d)

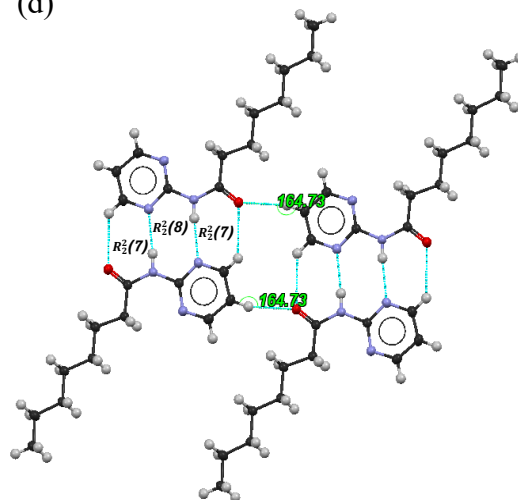
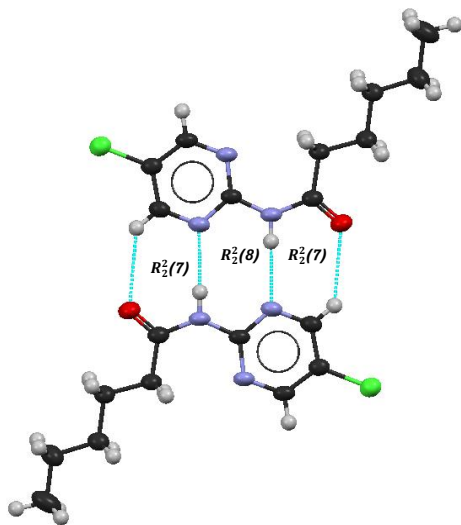


Figure E.22. Interactions seen in single crystal structures of the PM series: (a) PM4, (b) PM5, (c) PM6, and (d) PM7.

(a)



(b)

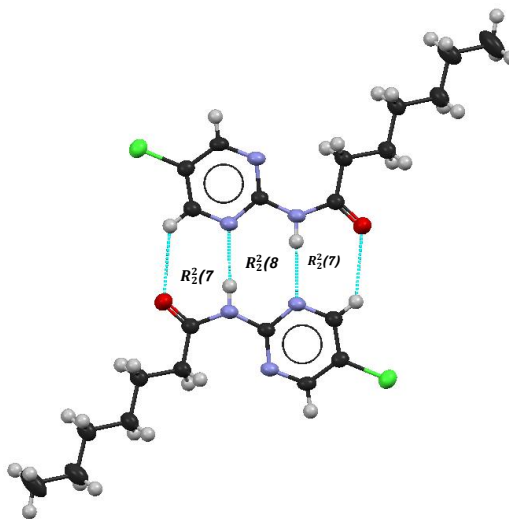


Figure E.13. Interactions seen in single crystal structures of the Cl-PM series: (a) Cl-PM5, and (d) Cl-PM6.

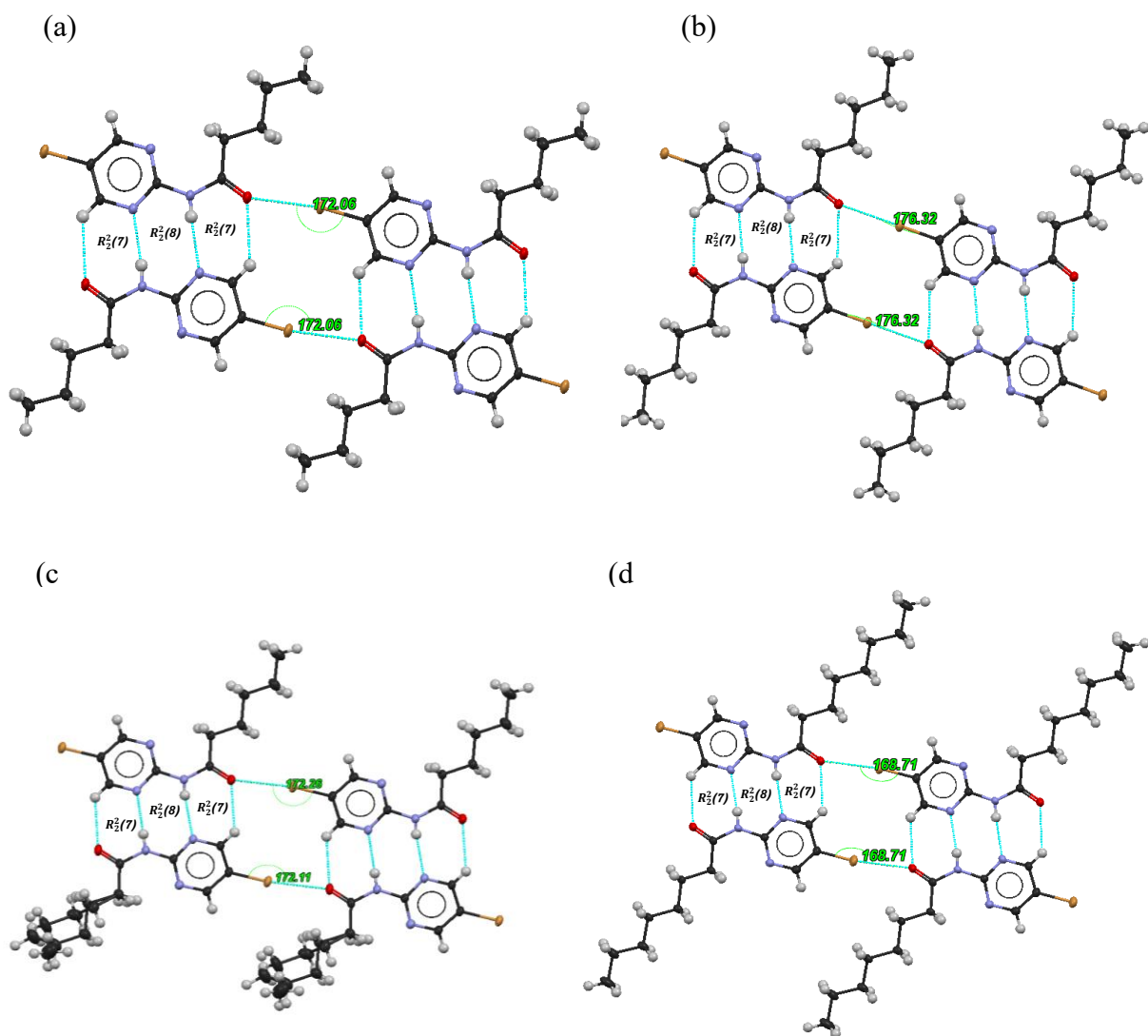


Figure E.24. Interactions seen in single crystal structures of the Br-PM series: (a) Br-PM4, (b) Br-PM5-form 1, (c) Br-PM5-form 2, and (d) Br-PM7.

Appendix F - Additional information for Chapter 6

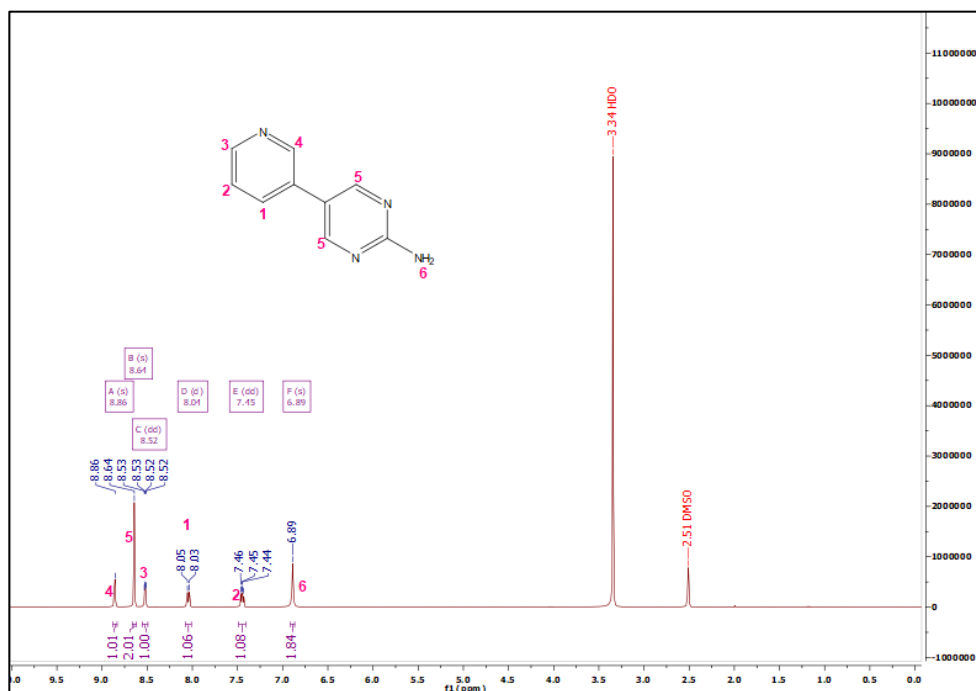


Figure F.F.1. ¹H NMR (400 MHz, DMSO-d₆) spectrum of 5-(pyridin-3-yl)pyrimidin-2-amine.

Table F.1. Crystallographic information for the cocrystal structures

Compound	PM	PM-3,5-dNBA (1:1)	PM-3,4-dCIBA (1:1)	PM-BA (1:1)
Formula	C ₉ H ₈ N ₄	C ₁₆ H ₁₂ N ₆ O ₆	C ₁₆ H ₁₂ Cl ₂ N ₄ O ₂	C ₁₆ H ₁₄ N ₄ O ₂
<i>D</i> _{calc.} / g cm ⁻³	1.308	1.550	1.543	1.305
μ/mm ⁻¹	0.689	1.047	3.897	0.734
Formula Weight	172.19	384.32	363.20	294.31
Colour	colourless	colourless	colourless	colourless
Shape	plate	plate	needle	plate
Size/mm ³	0.29×0.17×0.05	0.19×0.04×0.01	0.15×0.01×0.01	0.20×0.10×0.03
<i>T</i> /K	210.00(10)	210.00(10)	210.00(10)	180.00(10)
Crystal System	monoclinic	monoclinic	monoclinic	orthorhombic
Space Group	<i>P</i> 2 ₁	<i>P</i> 2 ₁ / <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>Pbca</i>
<i>a</i> /Å	5.25350(10)	9.50838(9)	29.1141(6)	7.45278(17)
<i>b</i> /Å	25.9979(4)	5.91447(5)	3.80603(9)	10.9671(2)
<i>c</i> /Å	6.47550(10)	29.3138(3)	29.2700(7)	36.6461(8)
α/°	90	90	90	90
β/°	98.7220(10)	92.7103(8)	105.455(2)	90
γ/°	90	90	90	90
<i>V</i> /Å ³	874.20(3)	1646.68(3)	3126.10(13)	2995.28(11)
<i>Z</i>	4	4	8	8
<i>Z</i> '	2	1	1	1

Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α	Cu K α
$\theta_{min}/^\circ$	3.400	3.018	3.133	2.411
$\theta_{max}/^\circ$	79.477	79.864	79.947	74.493
Measured Refl.	13876	17700	9214	11746
Independent Refl.	3682	3594	3248	3045
Reflections with I > 2(I)	3460	3243	2580	2614
R_{int}	0.0265	0.0181	0.0371	0.0385
Parameters	251	265	229	211
Restraints	1	1	0	0
Largest Peak	0.141	0.170	0.417	0.387
Deepest Hole	-0.227	-0.227	-0.0334	-0.260
GooF	1.051	1.070	1.030	1.100
wR_2 (all data)	0.1125	0.0962	0.1269	0.2172
wR_2	0.1109	0.0932	0.01186	0.2120
R_I (all data)	0.0399	0.0378	0.0589	0.0770
R_I	0.0383	0.0344	0.0452	0.0709

Compound	PM-4-iodoBA (1:1) - PI	PM-4-iodoBA (1:1) - PII	PM-3-MBA (1:1)	PM-3-MBA (1:2)
Formula	C ₁₆ H ₁₃ IN ₄ O ₂	C ₁₆ H ₁₃ IN ₄ O ₂	C ₁₇ H ₁₆ N ₄ O ₂	C ₂₅ H ₂₄ N ₄ O ₄
$D_{calc.}/\text{g cm}^{-3}$	1.719	1.791	1.305	1.361
μ/mm^{-1}	15.627	16.285	0.723	0.786
Formula Weight	420.20	420.20	308.34	444.48
Colour	colourless	colourless	colourless	colourless
Shape	plate	irregular	plate	plate
Size/mm ³	0.06×0.02×0.01	0.06×0.01×0.01	0.10×0.06×0.02	0.20×0.13×0.02
T/K	210.00(10)	210.00(10)	180.00(10)	130.02(10)
Crystal System	monoclinic	monoclinic	monoclinic	monoclinic
Space Group	$P2_1/c$	$I2$	$P2_1/c$	Pn
$a/\text{\AA}$	20.5182(4)	18.8853(6)	19.8414(10)	11.62320(16)
$b/\text{\AA}$	7.53674(14)	6.51749(16)	7.6330(4)	6.47182(8)
$c/\text{\AA}$	10.5929(2)	25.8679(7)	10.5342(4)	14.70109(16)
$\alpha/^\circ$	90	90	90	90.0
$\beta/^\circ$	97.502(2)	101.787(3)	100.341(5)	101.3167(12)
$\gamma/^\circ$	90	90	90	90.0
$V/\text{\AA}^3$	1624.07(6)	3116.81(15)	1569.49(13)	1084.36(2)
Z	4	8	4	2
Z'	1	2	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α	Cu K α
$\theta_{min}/^\circ$	2.172	2.656	4.531	4.448
$\theta_{max}/^\circ$	80.555	69.884	80.218	79.804
Measured Refl.	14176	22750	4974	18922
Independent Refl.	3512	5806	4974	3829
Reflections with I > 2(I)	2935	5131	3934	3448
R_{int}	0.0380	0.0565	.	0.0326

Parameters	220	417	222	302
Restraints	0	1	0	2
Largest Peak	0.649	1.037	0.169	0.828
Deepest Hole	-1.110	-1.091	-0.192	-0.243
GooF	1.053	1.051	1.058	1.102
wR_2 (all data)	0.0788	0.1053	0.1458	0.1460
wR_2	0.0745	0.1004	0.1358	0.1361
R_I (all data)	0.0451	0.0478	0.0624	0.0562
R_I	0.0353	0.0407	0.0493	0.0501

Code	PM-3-dMABA (1:1)	PM-3-dMABA (1:2)	4-dMABA-PIV
Formula	C ₁₈ H ₁₉ N ₅ O ₂	C ₂₇ H ₃₀ N ₆ O ₄	C ₉ H ₁₁ NO ₂
$D_{calc.}/\text{g cm}^{-3}$	1.301	1.346	1.300
μ/mm^{-1}	0.721	0.758	0.757
Formula Weight	337.38	502.57	165.19
Colour	light yellow	light yellow	colourless
Shape	plate	irregular	plate
Size/mm ³	0.22×0.16×0.03	0.04×0.04×0.03	0.06×0.03×0.01
T/K	180.00(10)	180.00(10)	210.00(10)
Crystal System	monoclinic	monoclinic	monoclinic
Space Group	$P2_1/c$	Pn	$P2_1/n$
$a/\text{\AA}$	21.0362(5)	13.5450(3)	7.7127(3)
$b/\text{\AA}$	7.46761(15)	6.79712(13)	10.5159(5)
$c/\text{\AA}$	11.3318(2)	14.2479(3)	20.8144(9)
$\alpha/^\circ$	90	90	90
$\beta/^\circ$	104.699(2)	109.009(3)	90.315(4)
$\gamma/^\circ$	90	90	90
$V/\text{\AA}^3$	1721.85(7)	1240.23(5)	1688.15(12)
Z	4	2	8
Z'	1	1	2
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α
$\theta_{min}/^\circ$	2.171	3.912	4.248
$\theta_{max}/^\circ$	79.962	80.117	70.020
Measured Refl.	15667	26617	12902
Independent Refl.	3702	5042	3166
Reflections with $I > 2(I)$	3137	4045	2007
R_{int}	0.0248	0.0355	0.0476
Parameters	240	340	239
Restraints	0	99	4
Largest Peak	0.217	0.591	0.158
Deepest Hole	-0.237	-0.318	-0.207
GooF	1.052	1.071	1.016
wR_2 (all data)	0.1141	0.2250	0.1607
wR_2	0.1083	0.2061	0.1388
R_I (all data)	0.0471	0.0879	0.0878
R_I	0.0406	0.0731	0.0539

Appendix G - Additional information for Chapter 7

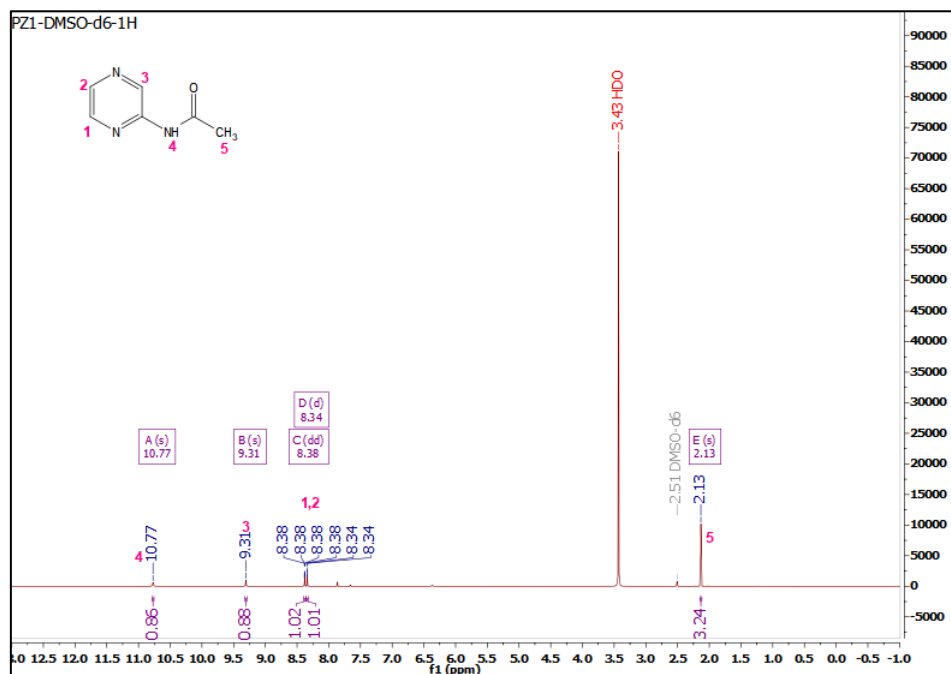


Figure G.1. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrazin-2-yl)acetamide (PZ-methyl).

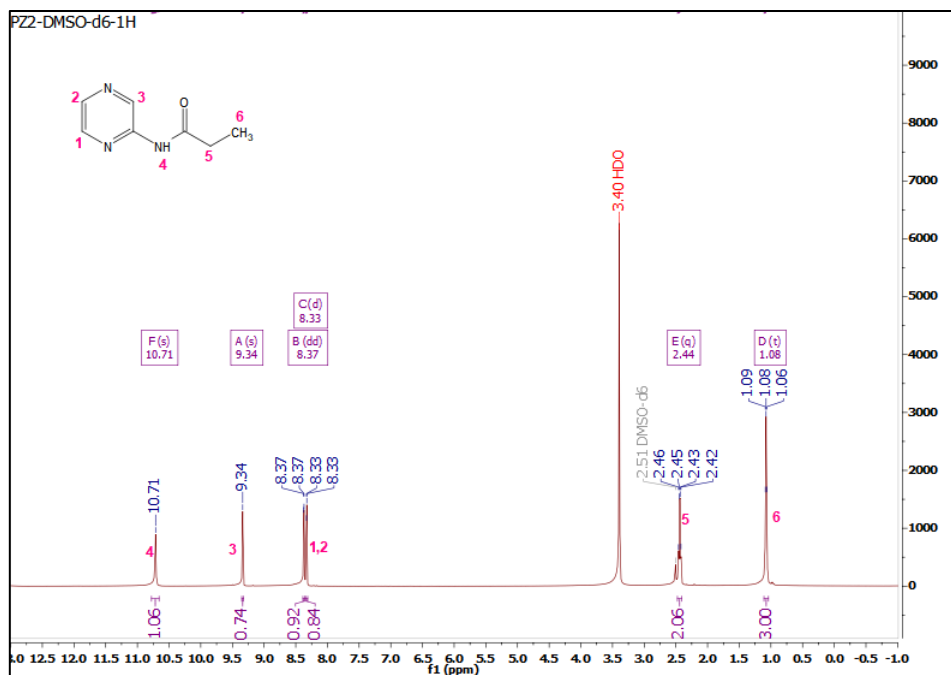


Figure G.2. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrazin-2-yl)propionamide (PZ-ethyl).

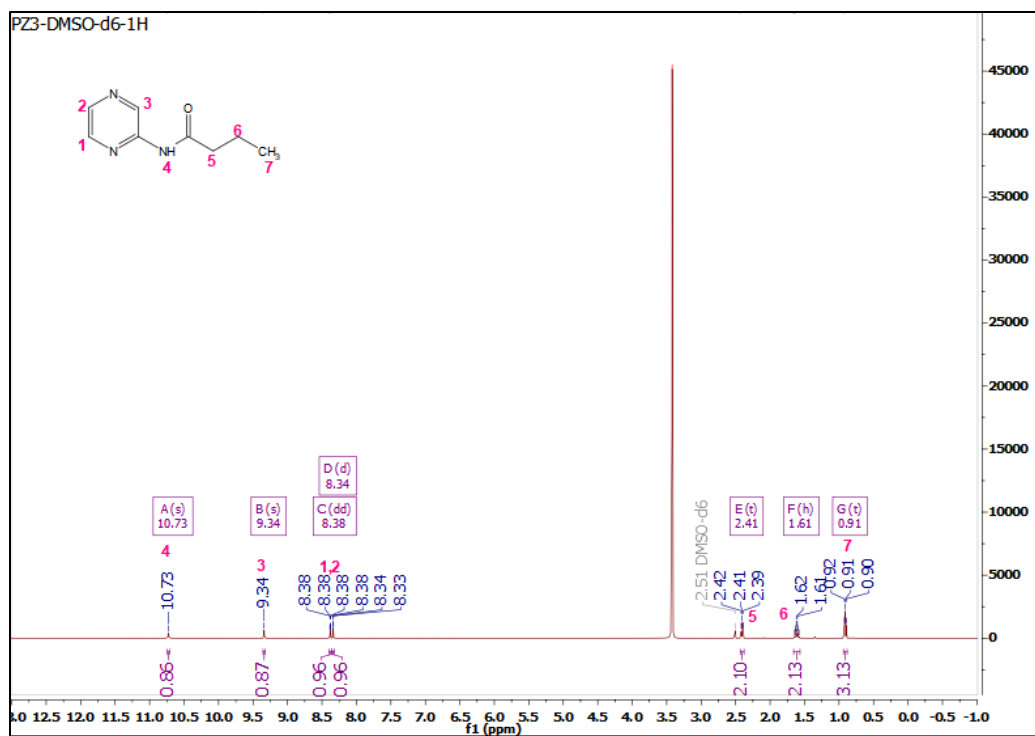


Figure G.3. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrazin-2-yl)butyramide (PZ-propyl).

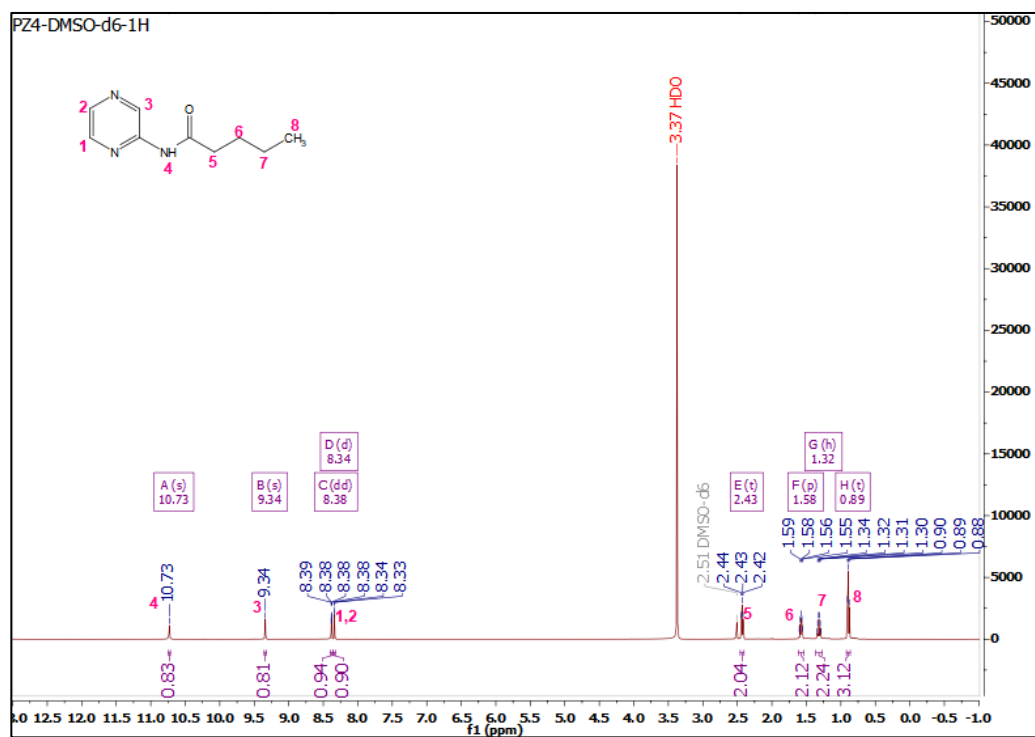


Figure G.4. ^1H NMR (400 MHz, DMSO- d_6) spectrum of *N*-(pyrazin-2-yl)pentanamide (PZ-butyl).

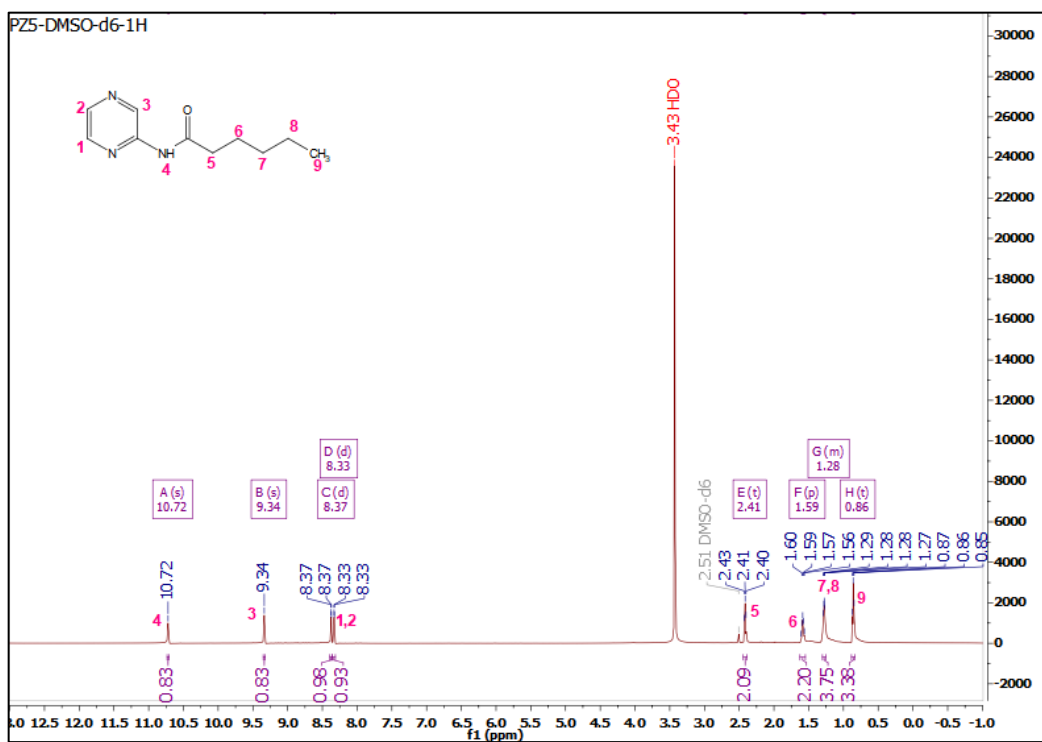


Figure G.5. ^1H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(pyrazin-2-yl)hexanamide (PZ-pentyl).

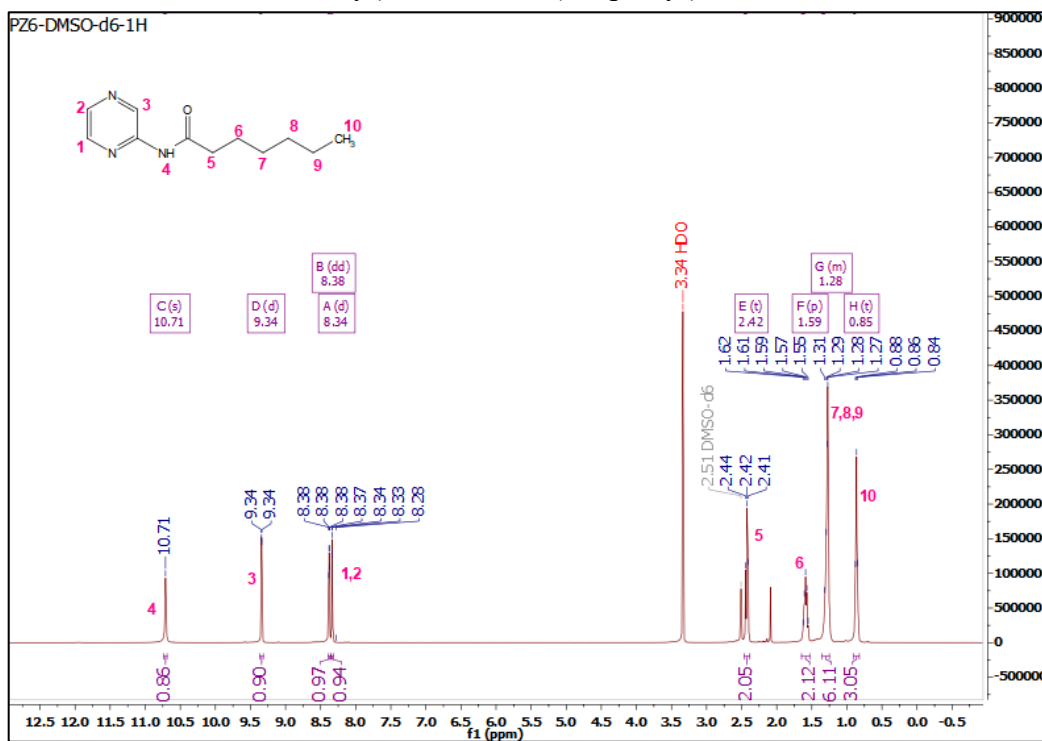


Figure G.6. ^1H NMR (400 MHz, DMSO-d₆) spectrum of *N*-(pyrazin-2-yl)heptanamide (PZ-hexyl).

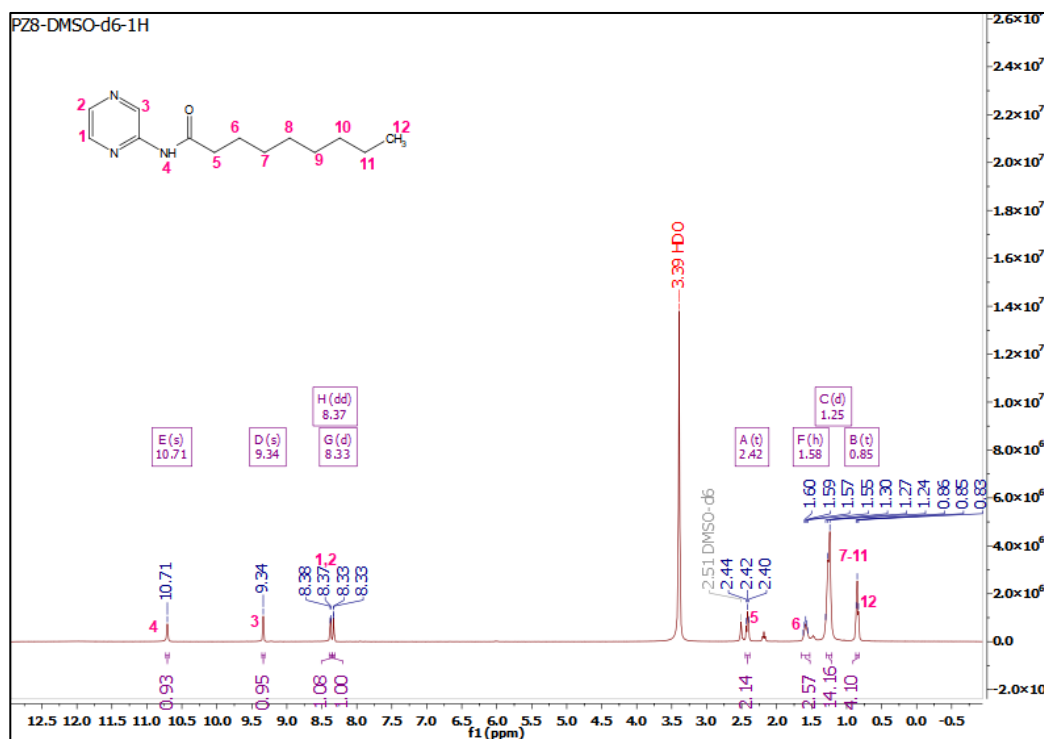
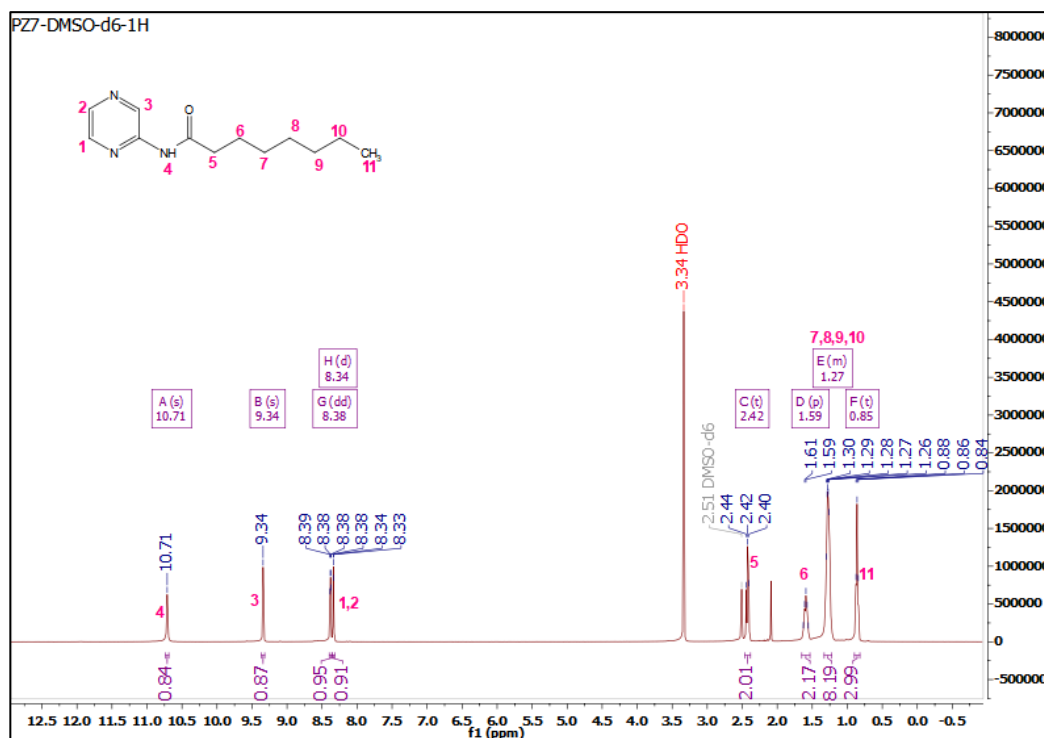


Table G.1. Crystallographic information for the PZ series crystal structures

Code	PZ-methyl	PZ-ethyl	PZ-propyl	PZ-butyl
Formula	C ₆ H ₇ N ₃ O	C ₇ H ₉ N ₃ O	C ₈ H ₁₁ N ₃ O	C ₉ H ₁₃ N ₃ O
$D_{\text{calc.}} / \text{g cm}^{-3}$	1.365	1.337	1.310	1.221
μ / mm^{-1}	0.819	0.777	0.740	0.673
Formula Weight	137.15	151.17	165.20	179.22
Colour	colourless	colourless	orange	orange
Shape	plate	irregular	prism	plate
Size/mm ³	0.38×0.15×0.06	0.04×0.04×0.03	0.14×0.12×0.05	0.24×0.15×0.02
T/K	294.0(1)	209.99(10)	210.00(10)	210.00(10)
Crystal System	monoclinic	triclinic	monoclinic	monoclinic
Space Group	Pn	$P-1$	$P2_1/n$	$P2_1/c$
$a/\text{\AA}$	5.0284(3)	8.4791(3)	5.37130(10)	9.2186(2)
$b/\text{\AA}$	16.8737(10)	11.1074(4)	41.8856(7)	10.7160(2)
$c/\text{\AA}$	8.1771(5)	13.0709(4)	7.80350(10)	9.8745(3)
α°	90	68.526(3)	90	90
β°	105.825(6)	81.176(3)	107.456(2)	91.112(2)
γ°	90	81.630(3)	90	90
$V/\text{\AA}^3$	667.51(7)	1126.66(7)	1674.78(5)	975.28(4)
Z	4	6	8	4
Z'	2	3	2	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
Q_{min}°	2.619	3.656	2.110	4.798
Q_{max}°	80.179	80.192	79.130	79.898
Measured Refl.	9528	13484	11592	6688
Independent Refl.	2029	4546	3514	2045
Reflections with $I > 2(I)$	1747	3368	2979	1779
R_{int}	0.0381	0.0309	0.0267	0.0186
Parameters	191	333	227	123
Restraints	2	22	0	0
Largest Peak	0.122	0.303	0.145	0.149
Deepest Hole	-0.154	-0.238	-0.187	-0.197
GooF	1.093	1.029	1.064	1.062
wR_2 (all data)	0.1132	0.1545	0.1056	0.1167
wR_2	0.1015	0.1393	0.1011	0.1128
R_I (all data)	0.0443	0.0700	0.0440	0.0464
R_I	0.0381	0.0521	0.0376	0.0409

Code	PZ-pentyl	PZ-hexyl	PZ-heptyl
Formula	C ₁₀ H ₁₅ N ₃ O	C ₁₁ H ₁₇ N ₃ O	C ₁₂ H ₁₉ N ₃ O
$D_{\text{calc.}} / \text{g cm}^{-3}$	1.244	1.189	1.209
μ / mm^{-1}	0.672	0.630	0.630
Formula Weight	193.25	207.27	221.30
Colour	orange	colourless	colourless
Shape	irregular	plate	plate
Size/mm ³	0.08×0.03×0.02	0.17×0.09×0.02	0.18×0.03×0.01

<i>T</i> /K	210.00(10)	210.00(10)	210.00(10)
Crystal System	monoclinic	monoclinic	monoclinic
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	5.42753(14)	5.4058(3)	5.42822(13)
<i>b</i> /Å	50.8181(9)	56.9212(19)	59.6267(13)
<i>c</i> /Å	7.80542(16)	7.8356(4)	7.82621(19)
α /°	90	90	90
β /°	106.618(3)	106.135(5)	106.227(3)
γ /°	90	90	90
<i>V</i> /Å ³	2062.94(8)	2316.1(2)	2432.17(10)
<i>Z</i>	8	8	8
<i>Z'</i>	2	2	2
Wavelength/Å	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α
<i>Q</i> _{min} /°	3.479	3.105	2.964
<i>Q</i> _{max} /°	74.657	67.284	75.957
Measured Refl.	11926	8645	14975
Independent Refl.	3973	8645	4802
Reflections with <i>I</i> > 2(<i>I</i>)	3017	8006	3621
<i>R</i> _{int}	0.0310	-	0.0347
Parameters	263	274	299
Restraints	0	0	0
Largest Peak	0.137	0.472	0.184
Deepest Hole	-0.208	-0.389	-0.221
GooF	1.019	1.048	1.033
<i>wR</i> ₂ (all data)	0.1302	0.2933	0.1227
<i>wR</i> ₂	0.1198	0.2897	0.1131
<i>R</i> _{<i>I</i>} (all data)	0.0620	0.0965	0.0609
<i>R</i> _{<i>I</i>}	0.0460	0.0930	0.0444

Appendix H - Additional information for Chapter 8

3/4/26, 2:27 PM

RightsLink Printable License

SPRINGER NATURE LICENSE TERMS AND CONDITIONS

Mar 04, 2026

This Agreement between Aloka A. Marasinghe ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	6222080350277
License date	Mar 04, 2026
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Current Pharmacology Reports
Licensed Content Title	Efficacy and Safety of New and Emerging Drugs for COVID-19: Favipiravir and Dexamethasone
Licensed Content Author	Shivani Sood et al
Licensed Content Date	Feb 18, 2021
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1

<https://s100.copyright.com/AppDispatchServlet>

1/7

Figure H.1. Copyright license for Chapter 8, Figure 8.1.

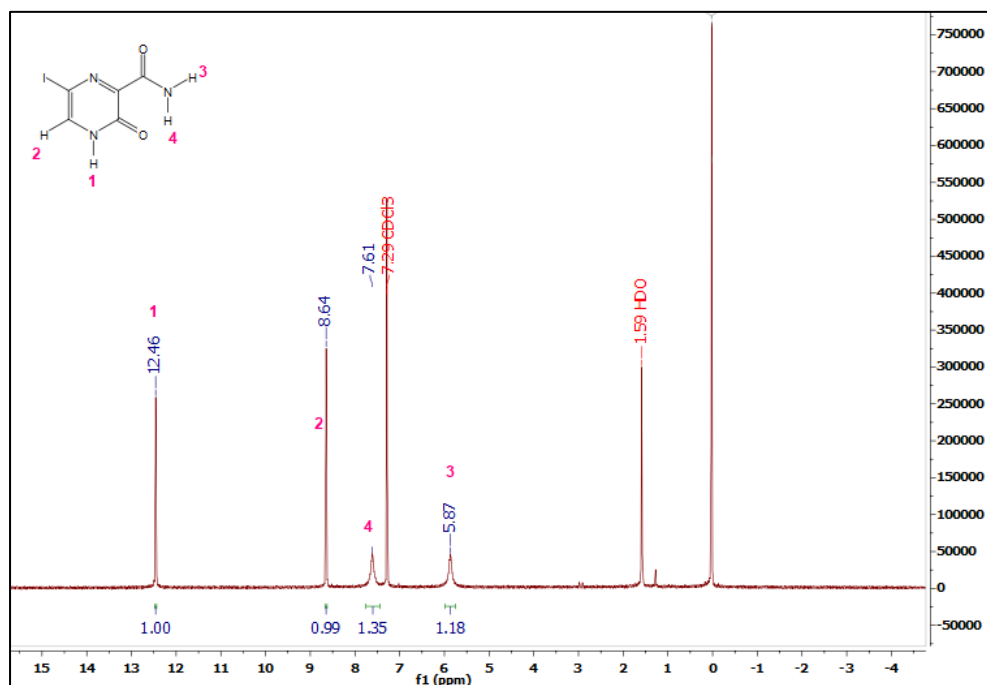


Figure H.2. ^1H NMR (400 MHz, DMSO- d_6) spectrum of 2-hydroxy-5-iodobenzamide.

Table H.1. Crystallographic information for the Fav-I polymorphic crystal structures

Compound	Fav-IA-I	Fav-IA-II	Fav-IA-III	Fav-IA-IV
Formula	$\text{C}_5\text{H}_4\text{IN}_3\text{O}_2$	$\text{C}_5\text{H}_4\text{IN}_3\text{O}_2$	$\text{C}_5\text{H}_4\text{IN}_3\text{O}_2$	$\text{C}_5\text{H}_4\text{IN}_3\text{O}_2$
$D_{\text{calc.}}/\text{g cm}^{-3}$	2.339	2.373	2.404	2.308
μ/mm^{-1}	4.206	4.268	4.324	4.151
Formula Weight	265.01	265.01	265.01	265.01
Colour	orange	orange	yellow	colourless
Shape	needle	plate	needle	plate
Size/ mm^3	$0.15 \times 0.03 \times 0.02$	$0.18 \times 0.06 \times 0.02$	$0.17 \times 0.02 \times 0.01$	$0.27 \times 0.12 \times 0.01$
T/K	293.0(4)	294(1)	294.6(5)	293.0(2)
Crystal System	monoclinic	monoclinic	orthorhombic	monoclinic
Space Group	$P2_1/n$	$P2_1/c$	$Fdd2$	$P2_1$
$a/\text{\AA}$	7.9475(2)	12.6611(3)	29.8234(12)	4.4914(2)
$b/\text{\AA}$	23.0470(4)	5.01590(10)	22.6528(8)	5.1753(2)
$c/\text{\AA}$	24.6638(5)	35.2516(8)	4.33493(18)	16.4120(6)
$\alpha/^\circ$	90	90	90	90
$\beta/^\circ$	91.396(2)	96.282(2)	90	91.809(4)
$\gamma/^\circ$	90	90	90	90
$V/\text{\AA}^3$	4516.21(17)	2225.27(9)	2928.60(19)	381.30(3)
Z	24	12	16	2
Z'	6	3	1	1
Wavelength/ $\text{\AA}$	0.71073	0.71073	0.71073	0.71073
Radiation type	Mo K_α	Mo K_α	Mo K_α	Mo K_α
$\theta_{\text{min}}/^\circ$	2.419	2.325	2.258	2.483
$\theta_{\text{max}}/^\circ$	37.703	38.019	38.019	35.622

Measured Refl.	77441	44905	8767	11637
Independent Refl.	21993	11444	3314	3072
Reflections with I > 2(I)	12658	7747	2605	2100
R_{int}	0.0266	0.0317	0.0203	0.0403
Parameters	667	334	116	112
Restraints	34	0	1	3
Largest Peak	1.128	0.679	0.684	0.976
Deepest Hole	-0.876	-1.321	-0.366	-0.385
GooF	1.005	1.034	1.046	0.976
wR_2 (all data)	0.0866	0.0827	0.0615	0.0806
wR_2	0.0742	0.0755	0.0579	0.0745
R_I (all data)	0.0787	0.0545	0.0436	0.0591
R_I	0.0351	0.0317	0.0289	0.0349

Table H.2. Crystallographic information for the Fav-I cocrystal structures

Code	Fav-IA-5-Flu	Fav-IA-Theo	Fav-IA-Tro
Formula	C ₁₃ H ₁₀ F ₂ IN ₇ O ₆	C ₁₂ H ₁₂ IN ₇ O ₄	C ₉ H ₁₅ IN ₄ O ₅
$D_{calc.}/\text{g cm}^{-3}$	2.036	1.931	1.976
μ/mm^{-1}	15.385	2.127	19.638
Formula Weight	525.18	445.19	386.15
Colour	colourless	colourless	colourless
Shape	needle	prism	needle
Size/mm ³	0.07×0.01×0.01	0.11×0.02×0.01	0.18×0.01×0.01
T/K	293.1(6)	294.4(6)	293.1(4)
Crystal System	monoclinic	monoclinic	orthorhombic
Space Group	$P2_1/m$	$P2_1/c$	$Pbca$
$a/\text{\AA}$	6.9340(6)	7.6772(3)	20.3705(9)
$b/\text{\AA}$	6.3637(12)	14.7736(7)	7.2574(5)
$c/\text{\AA}$	19.6295(19)	13.5049(6)	35.1223(14)
α°	90	90	90
β°	98.451(10)	90.596(4)	90
γ°	90	90	90
$V/\text{\AA}^3$	856.8(2)	1531.65(12)	5192.4(5)
Z	2	4	16
Z'	0.5	1	2
Wavelength/ $\text{\AA}$	1.54184	0.71073	1.54184
Radiation type	Cu K α	Mo K α	Cu K α
$\theta_{min}/^\circ$	2.276	2.653	3.323
$\theta_{max}/^\circ$	68.133	35.679	80.614
Measured Refl.	5642	25925	23545
Independent Refl.	1686	6455	5515
Reflections with I > 2(I)	1089	4783	3605
R_{int}	0.0648	0.0296	0.0583
Parameters	175	243	351
Restraints	6	0	1
Largest Peak	1.846	0.659	2.408

Deepest Hole	-1.331	-0.532	-2.013
GooF	1.036	1.049	1.052
wR_2 (all data)	0.2306	0.0802	0.2281
wR_2	0.2034	0.0746	0.2037
R_I (all data)	0.1168	0.0472	0.1073
R_I	0.0802	0.0299	0.0741

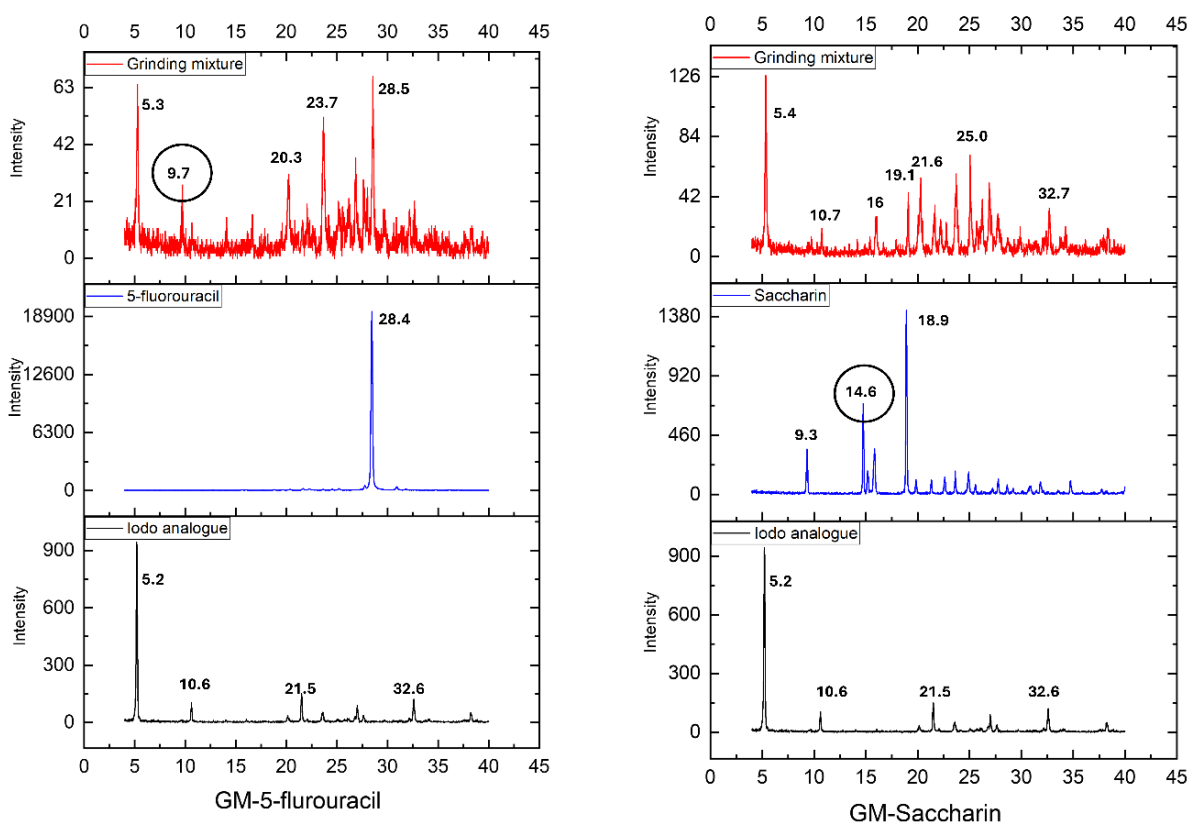


Figure H.3. PXRD analysis of Fav-IA-5-fluorouracil and Fav-IA-Saccharin ground samples and their starting materials.

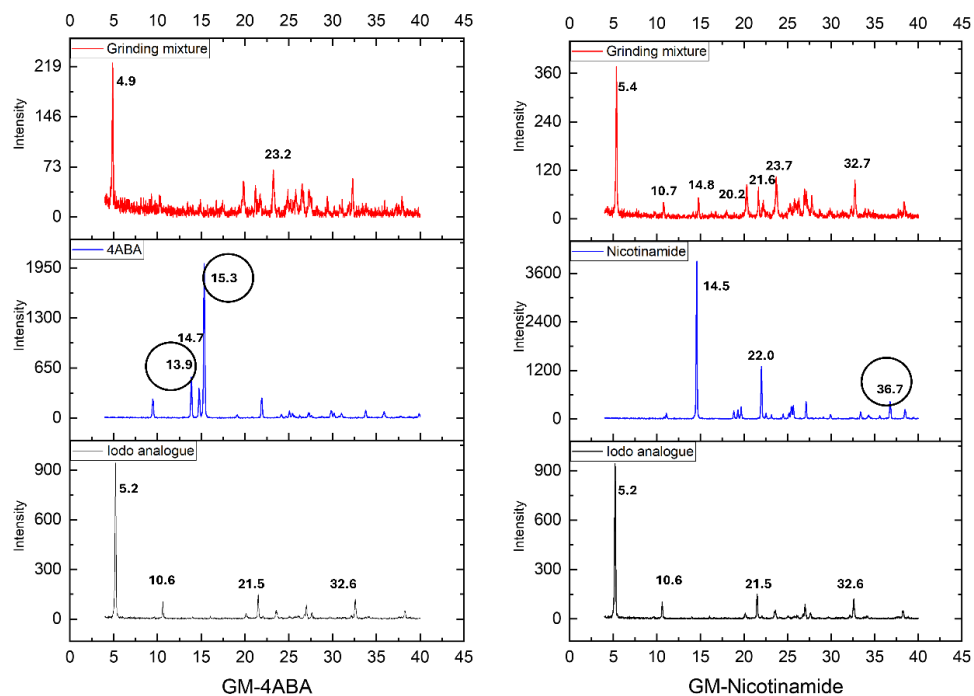


Figure H.4. PXRD analysis of Fav-IA-4-ABA and Fav-IA-Nicotinamide ground samples and their starting materials.

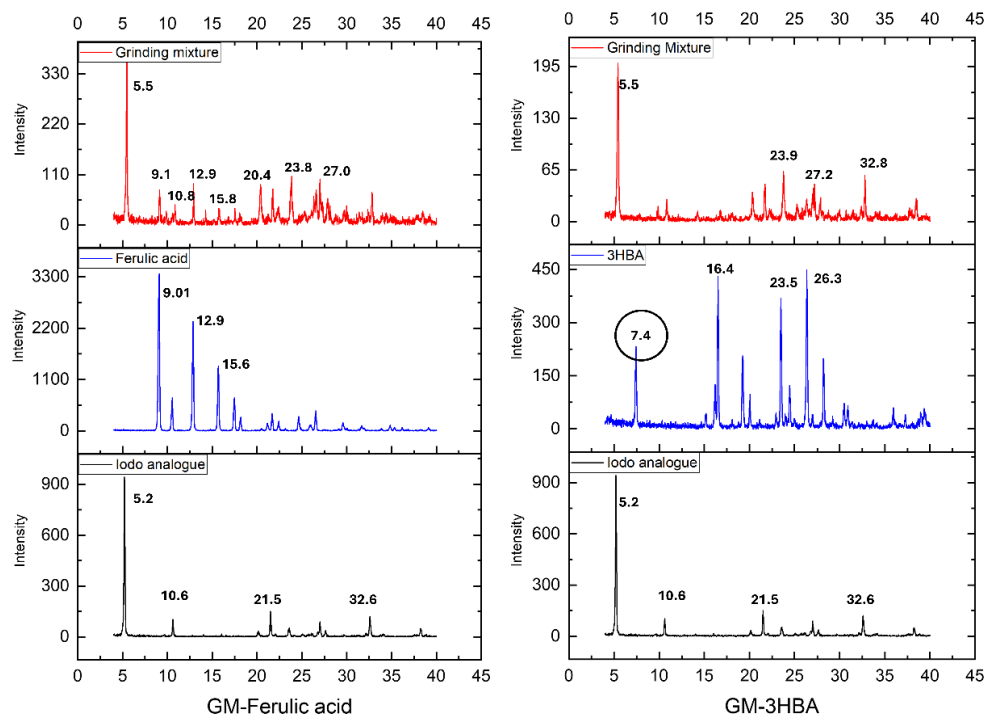


Figure H.5. PXRD analysis of Fav-IA-FerulicA and Fav-IA-3HBA ground samples and their starting materials.

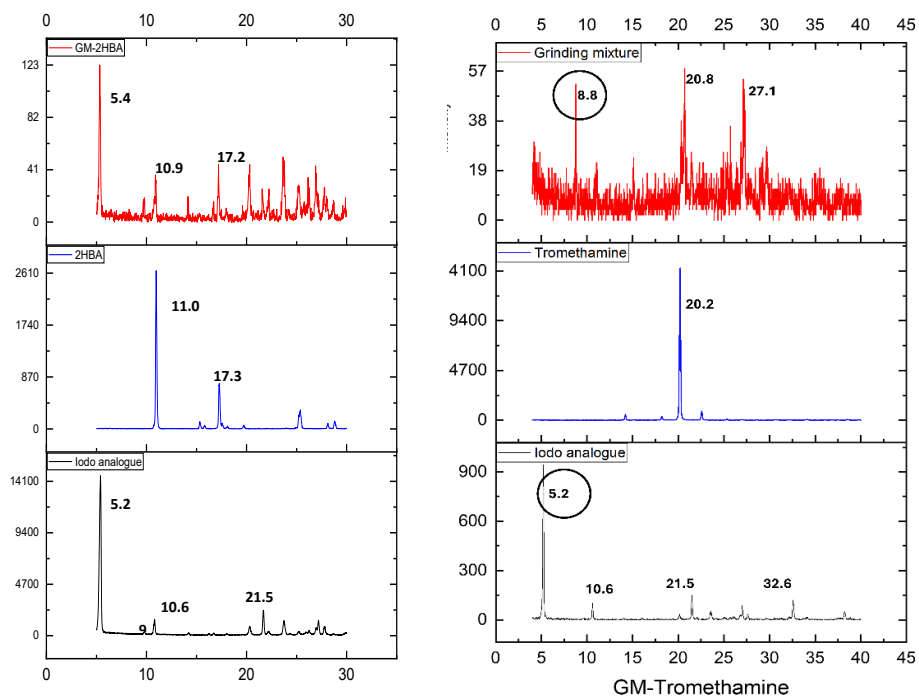


Figure H.6. PXRD analysis of Fav-IA-2-HBA and Fav-IA-Tromethamine ground samples and their starting materials.

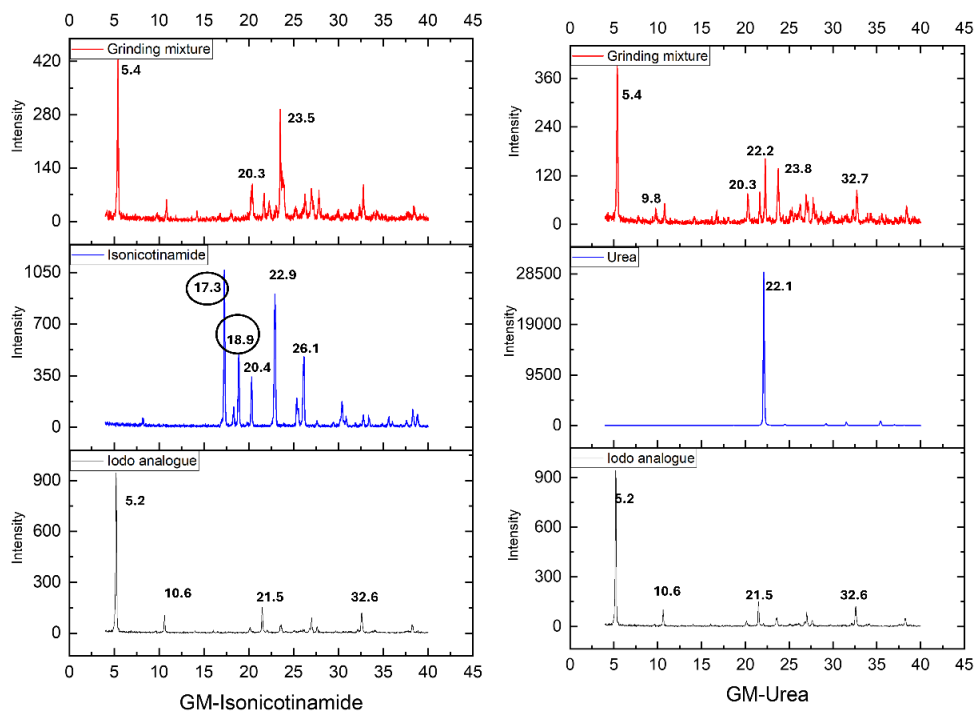


Figure H.7. PXRD analysis of Fav-IA-Isonicotinamide and Fav-IA-Urea ground samples and their starting materials.

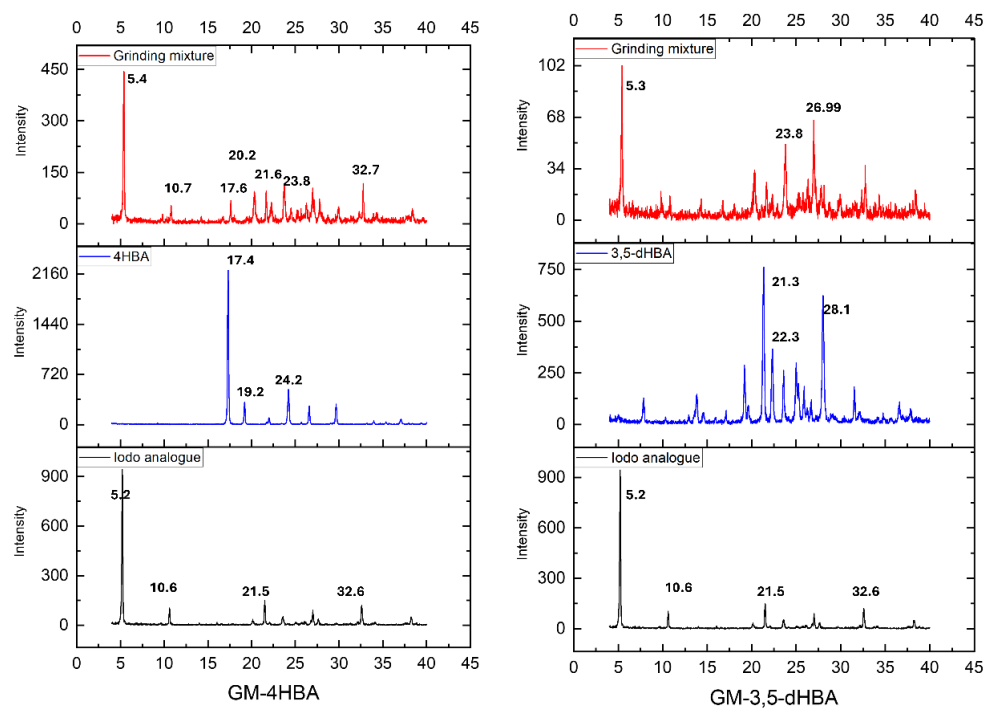


Figure H.8. PXRD analysis of Fav-IA-4-HBA and Fav-IA-3,5-dHBA ground samples and their starting materials.

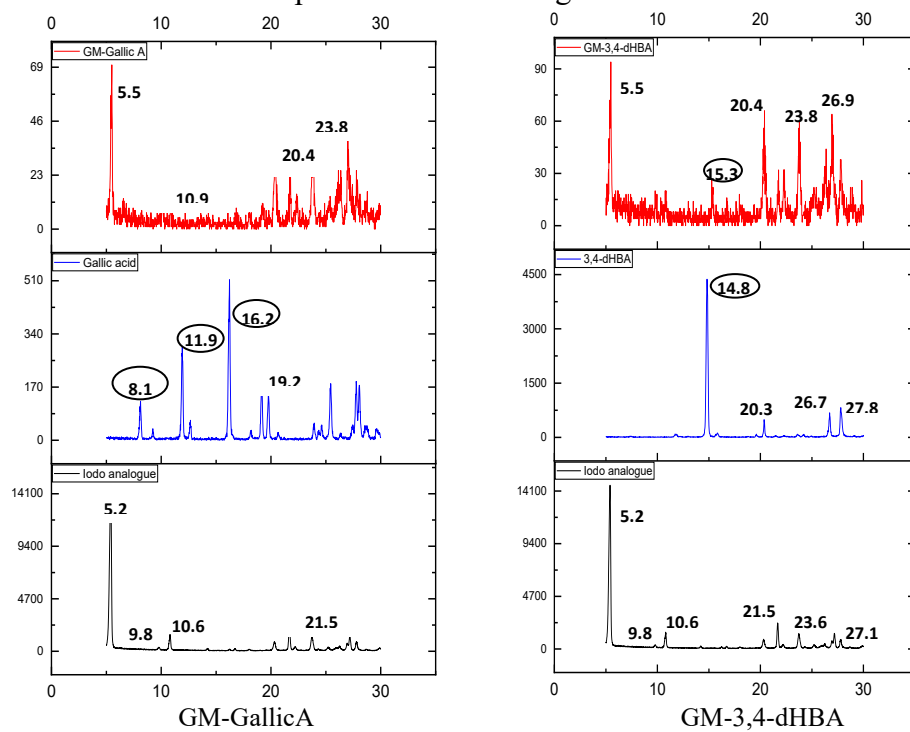


Figure H.9. PXRD analysis of Fav-IA-GallicA and Fav-IA-3,4-dHBA ground samples and their starting materials.

Table H.3. Thermal stabilities of Fav and I-Fav cocrystals.

Thermal stabilities/°C			
#	Coformer	Fav cocrystals ^{5,6}	Fav-IA cocrystals
1	5-fluorouracil	*	204-206
2	Saccharin	*	179-181 / 184-186
3	Theophylline	197.3	224-226
4	Tromethamine	-	141-144
5	4-aminoBA	159.5	154-156
6	Nicotinamide	120-122	113-115
7	Isonicotinamide	158.6-160.6	134-136
8	Urea	-	123-125
9	Ferulic acid	172.7	150-153
10	3-HBA	159.25	161-163/168-170
11	4-HBA	163.65	167-169
12	3,5-dHBA	188.25	181-183
13	Gallic acid	179.9 (hydrate)	196-198
14	3,4-diHBA	183.85 (hydrate)	155-158
15	2HBA	N/A	141-143/146-149

Appendix I - Additional information for Chapter 9

Table I.1. Crystallographic information for the 3DMABA cocrystal structures

Cocrystal	T2-3DMABA-PI	T2-3DMABA-PII	T3-3DMABA	T4-3DMABA	T5-3DMABA
Formula	C ₁₇ H ₂₀ N ₄ O ₅	C ₁₇ H ₂₀ N ₄ O ₅	C ₁₈ H ₂₂ N ₄ O ₅	C ₁₉ H ₂₄ N ₄ O ₅	C ₂₀ H ₂₆ N ₄ O ₅
<i>D</i> calc./ g cm ⁻³	1.341	1.374	1.314	1.335	1.347
μ /mm ⁻¹	0.841	0.862	0.813	0.815	0.812
Formula Weight	360.37	360.37	374.39	388.42	402.45
Colour	light orange	orange	orange	Orange	orange
Shape	plate	plate	plate	plate	plate
Size/mm ³	0.28×0.04×0.00	0.13×0.06×0.02	0.33×0.08×0.02	0.19×0.14×0.06	0.16×0.12×0.04
<i>T</i> /K	200.00(10)	295.0(4)	200.0(1)	200(2)	200.00(10)
Crystal System	monoclinic	monoclinic	triclinic	triclinic	triclinic
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> -1	<i>P</i> -1	<i>P</i> -1
<i>a</i> /Å	16.7360(4)	24.8829(8)	6.21761(15)	6.35274(15)	6.42159(9)
<i>b</i> /Å	4.91439(11)	6.1032(2)	12.5048(4)	12.46903(18)	12.65205(14)
<i>c</i> /Å	21.9254(5)	23.3288(12)	12.7578(4)	12.9378(3)	13.02701(17)
α /°	90	90	79.345(2)	97.3653(16)	76.6124(10)
β /°	98.240(2)	100.391(4)	78.280(3)	103.862(2)	75.8298(12)
γ /°	90	90	80.4467(17)	99.5009(15)	80.7872(10)
<i>V</i> /Å ³	1784.68(7)	3484.7(2)	945.96(4)	966.16(4)	992.29(2)
<i>Z</i>	4	8	2	2	2
<i>Z'</i>	1	1	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α	Cu K α	Cu K α
θ min/°	3.116	3.612	3.582	3.574	3.572
θ max/°	80.512	80.128	80.089	80.154	79.934
Measured Refl.	13114	11779	17956	37103	20759
Independent Refl.	3662	3650	4064	4176	4253

Table I.2. Crystallographic information for the 4ABA cocrystal structures

Cocrystal	T2-4ABA	T3-4ABA	T4-4ABA	T5-4ABA
Formula	C ₁₅ H ₁₆ N ₄ O ₅	C ₁₆ H ₁₈ N ₄ O ₅	C ₁₇ H ₂₀ N ₄ O ₅	C ₂₉ H ₃₇ N ₇ O ₈
<i>D</i> calc./ g cm ⁻³	1.451	1.397	1.340	1.265

μ/mm^{-1}	0.939	0.890	0.841	0.782
Formula Weight	332.32	346.34	360.37	611.65
Colour	light yellow	yellow	yellow	light yellow
Shape	needle	irregular	plate	needle
Size/ mm^3	$0.29 \times 0.01 \times 0.01$	$0.16 \times 0.12 \times 0.11$	$0.15 \times 0.11 \times 0.03$	$0.10 \times 0.02 \times 0.02$
T/K	200.00(10)	200.00(10)	295.9(3)	297(1)
Crystal System	monoclinic	triclinic	triclinic	monoclinic
Space Group	$P2_1/n$	$P-1$	$P-1$	$P2_1/n$
$a/\text{\AA}$	12.5882(2)	5.8059(4)	6.15171(12)	20.1578(5)
$b/\text{\AA}$	5.17490(7)	11.8005(10)	12.3495(4)	4.90086(14)
$c/\text{\AA}$	23.3666(4)	12.9057(16)	12.6749(4)	32.5043(9)
α°	90	73.991(9)	73.875(3)	90
β°	91.8814(16)	78.882(9)	79.965(2)	90.875(2)
γ°	90	78.277(7)	76.405(2)	90
$V/\text{\AA}^3$	1521.34(4)	823.35(14)	892.97(4)	3210.75(15)
Z	4	2	2	4
Z'	1	1	1	1
Wavelength/ $\text{\AA}$	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
$\theta_{\min}^\circ$	3.785	3.601	3.655	2.562
$\theta_{\max}^\circ$	79.786	81.117	80.078	78.442
Measured Refl.	11401	11962	14844	24768
Independent Refl.	3225	3406	3854	6488

Interplanar distances of cocrystals

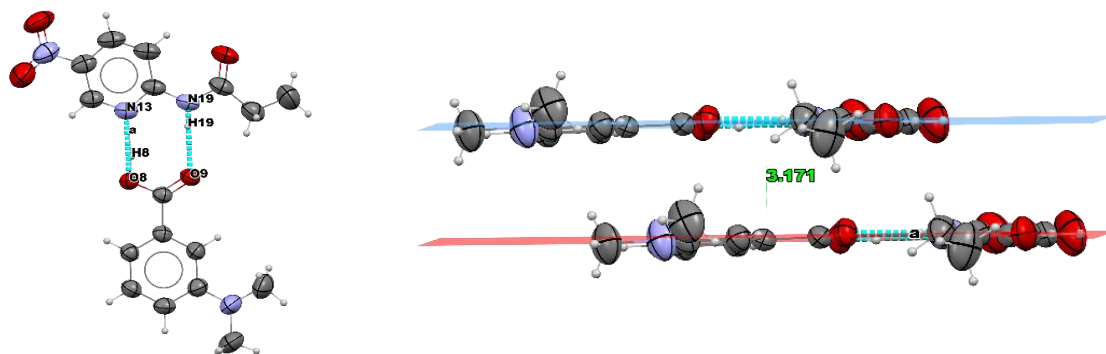


Figure I.1. Interplanar distances of T2-3DMABA-PI.

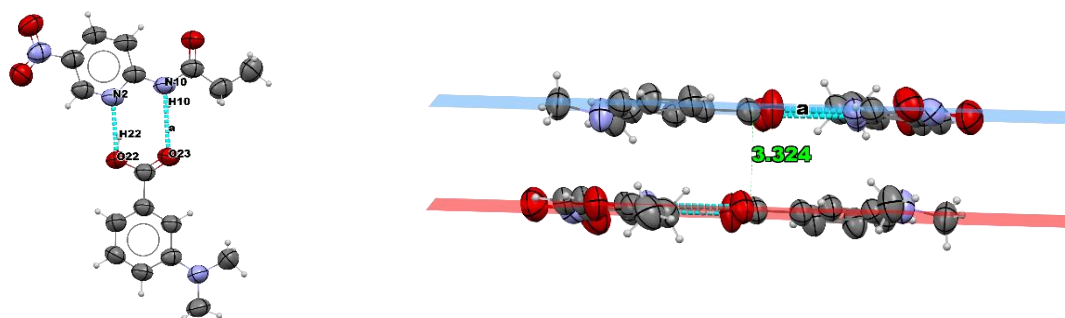


Figure I.2. Interplanar distances of T2-3DMABA - PII.

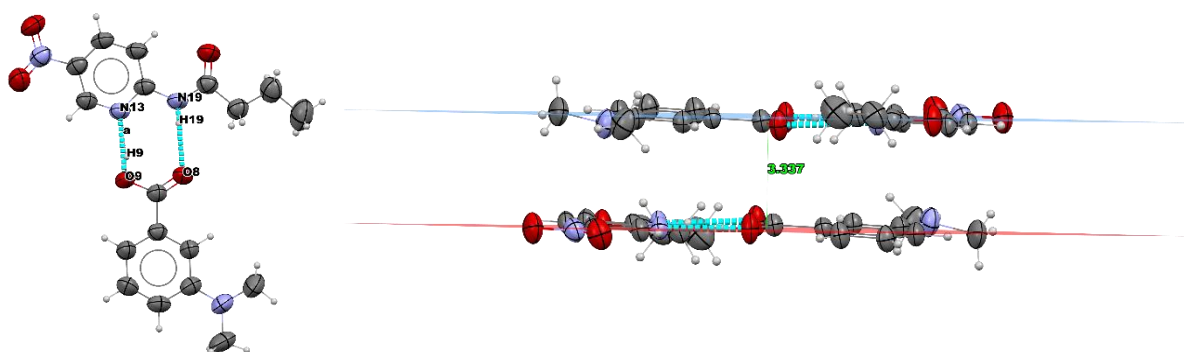


Figure I.3. Interplanar distances of T3-3DMABA.

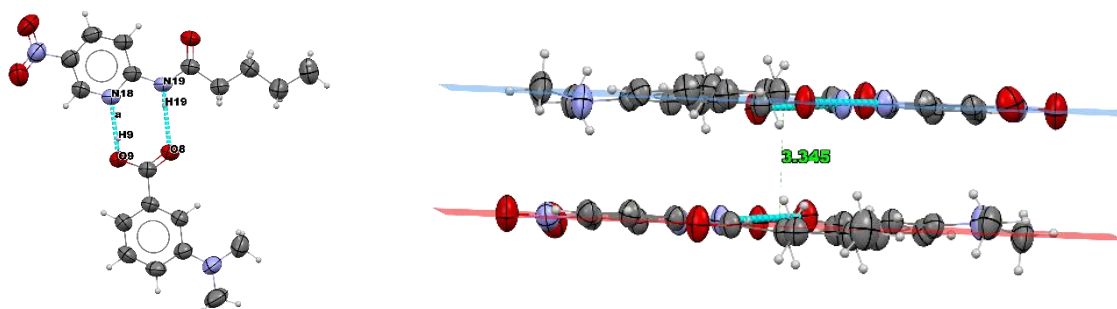


Figure I.4. Interplanar distances of T4-3DMABA.

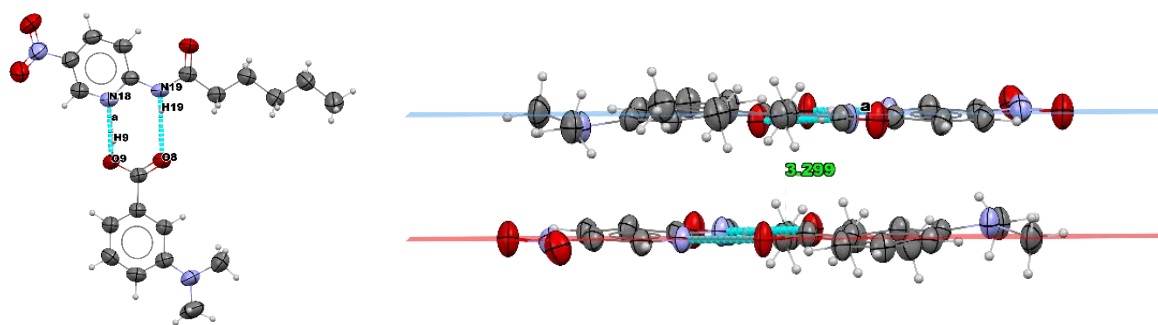


Figure I.5. Interplanar distances of T5-3DMABA.

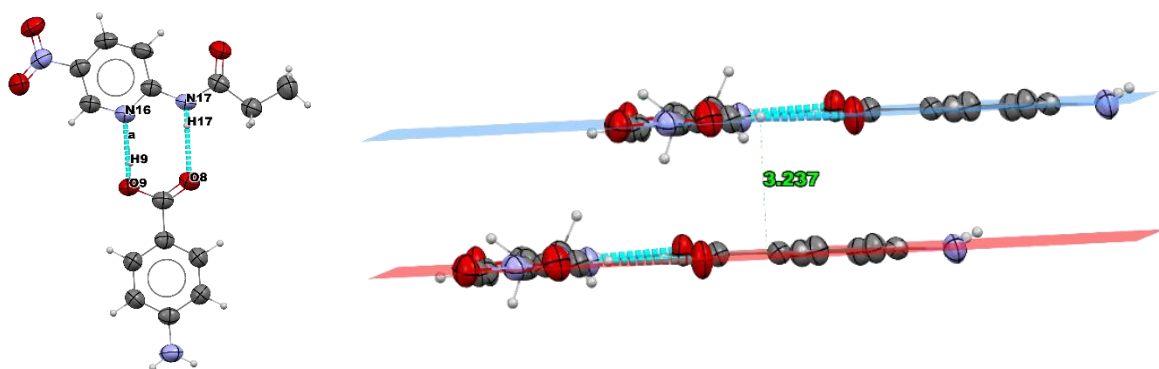


Figure I.6. Interplanar distances of T2-4ABA.

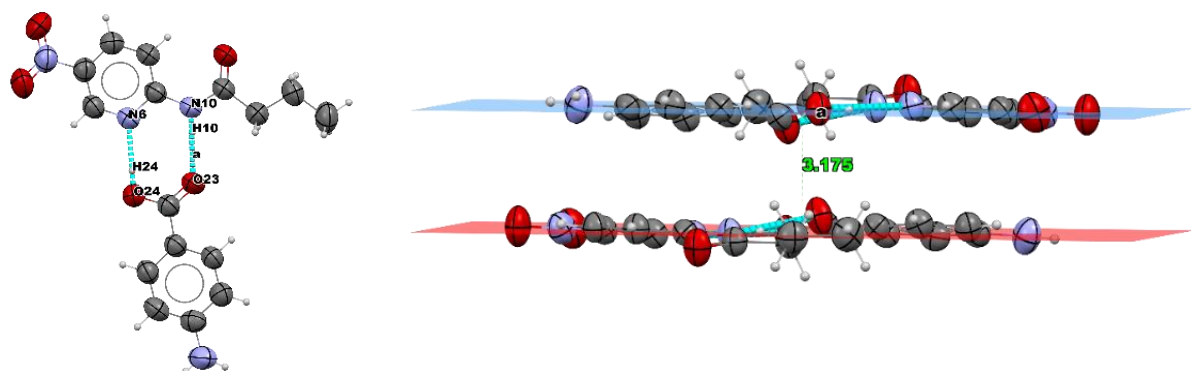


Figure I.7. Interplanar distances of T3-4ABA.

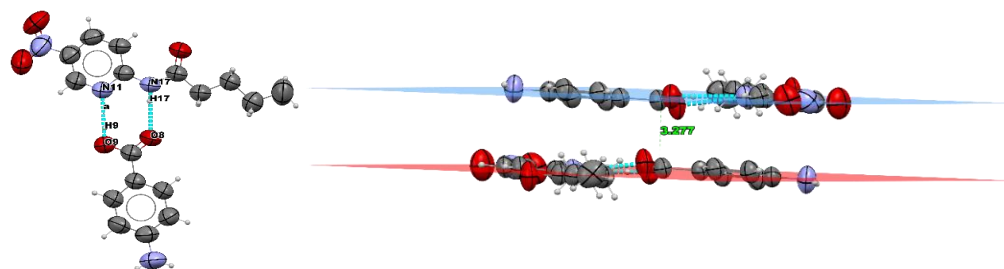


Figure I.8. Interplanar distances of T4-4ABA.

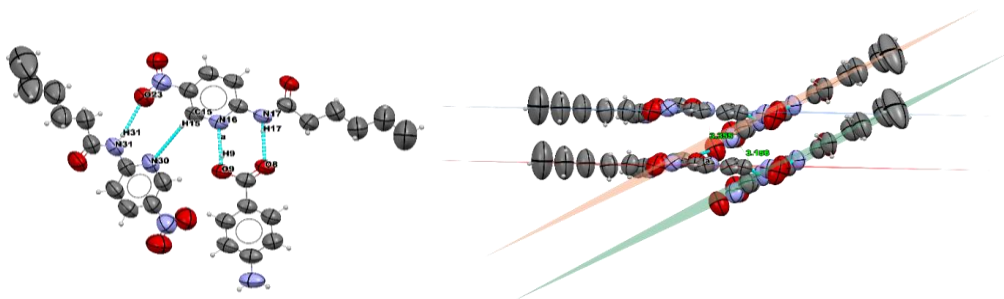


Figure I.9. Interplanar distances of T5-4ABA.

PXRD patterns of ground mixtures

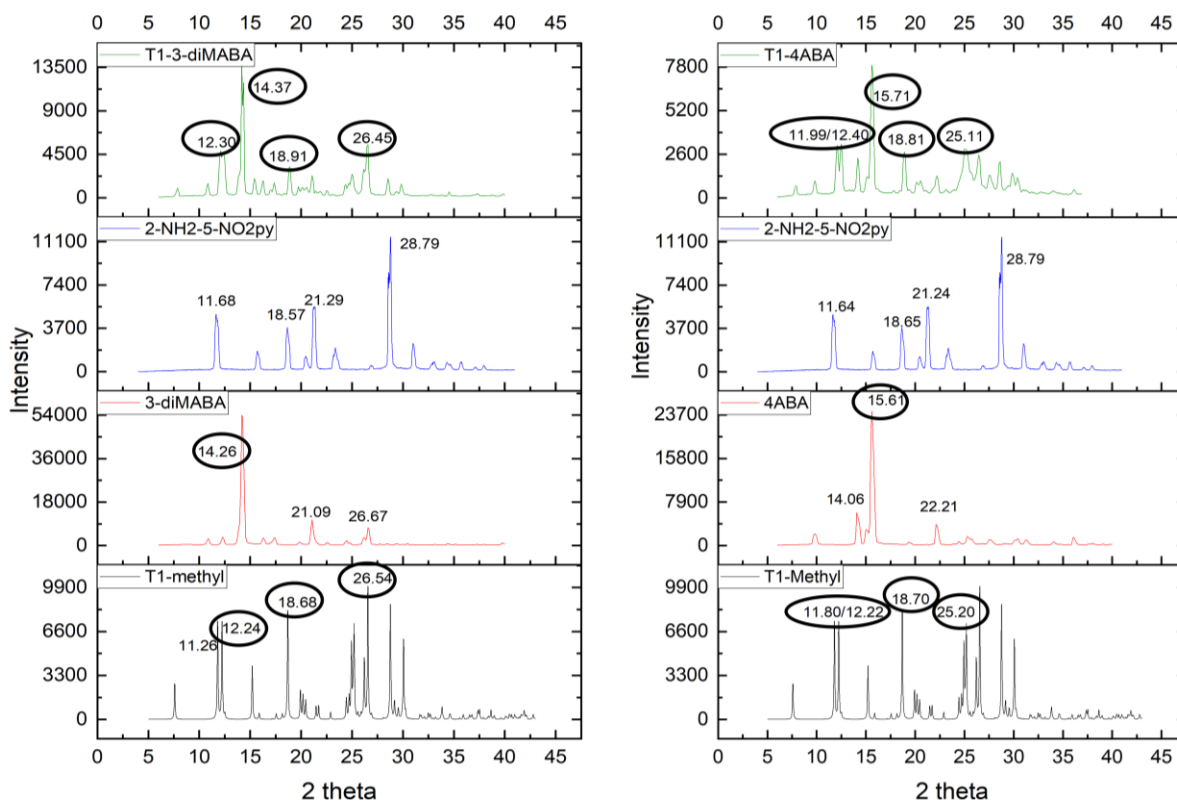


Figure I.10. Two negative results for T1-3DMABA and T1-4ABA.

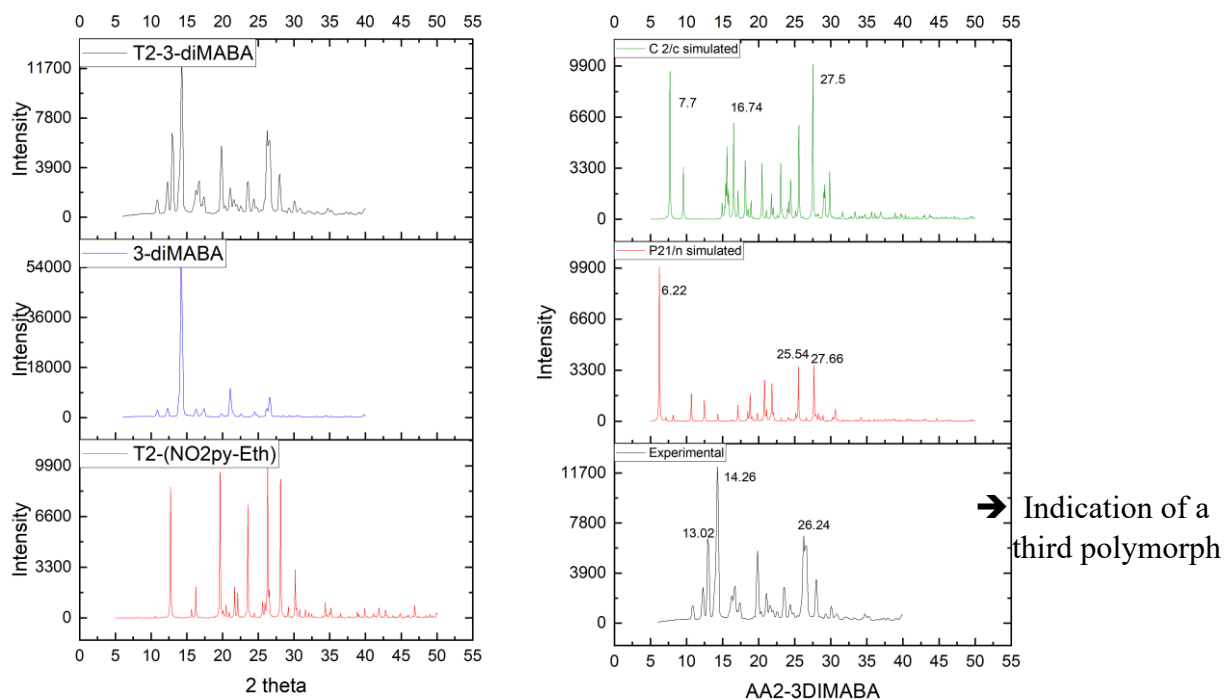


Figure I.11. PXRD of T2-3DMABA.

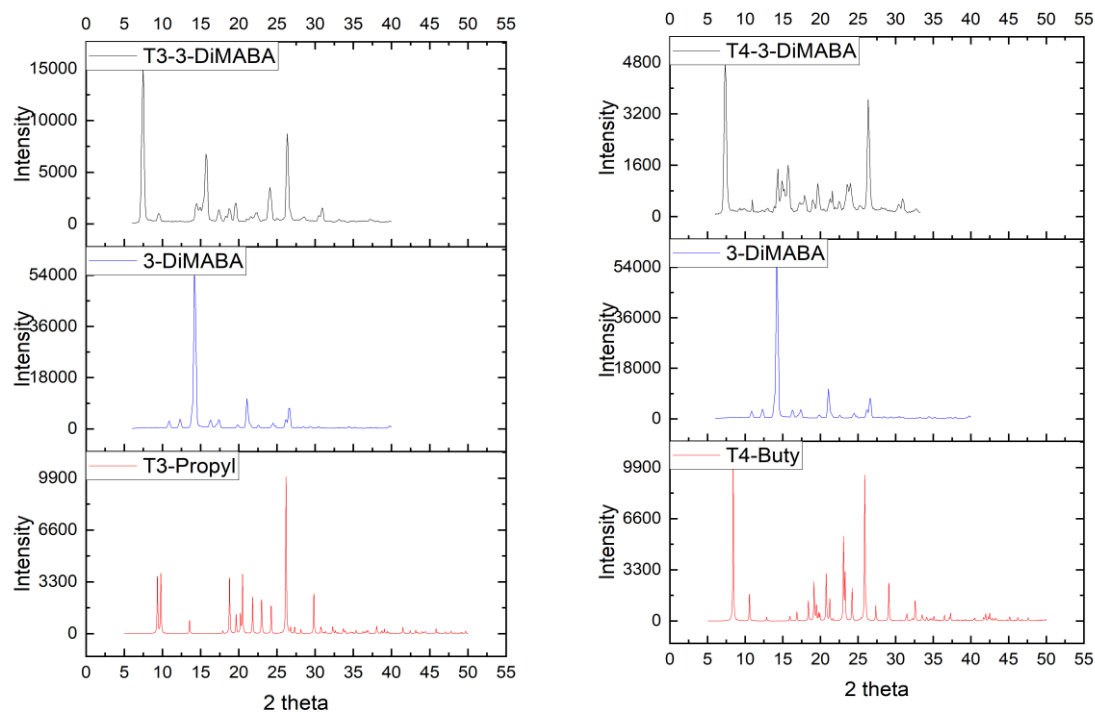


Figure I.12. PXRD of T3-3DMABA and T4-3DMABA.

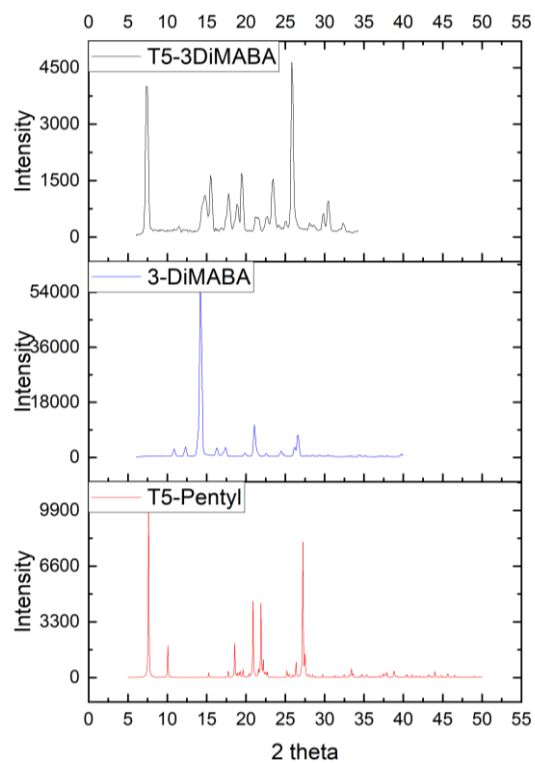
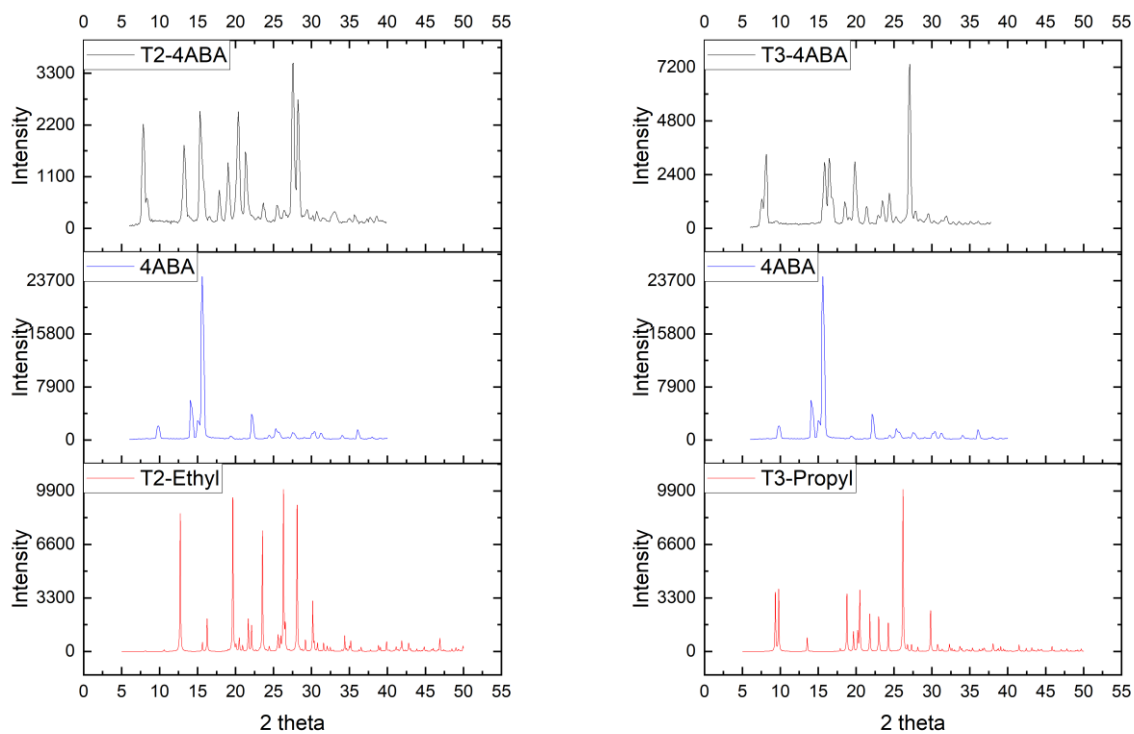


Figure I.13. PXRD of T5-3DMABA.



Appendix Figure I.14. PXRD of T2-4ABA and T3-4ABA.

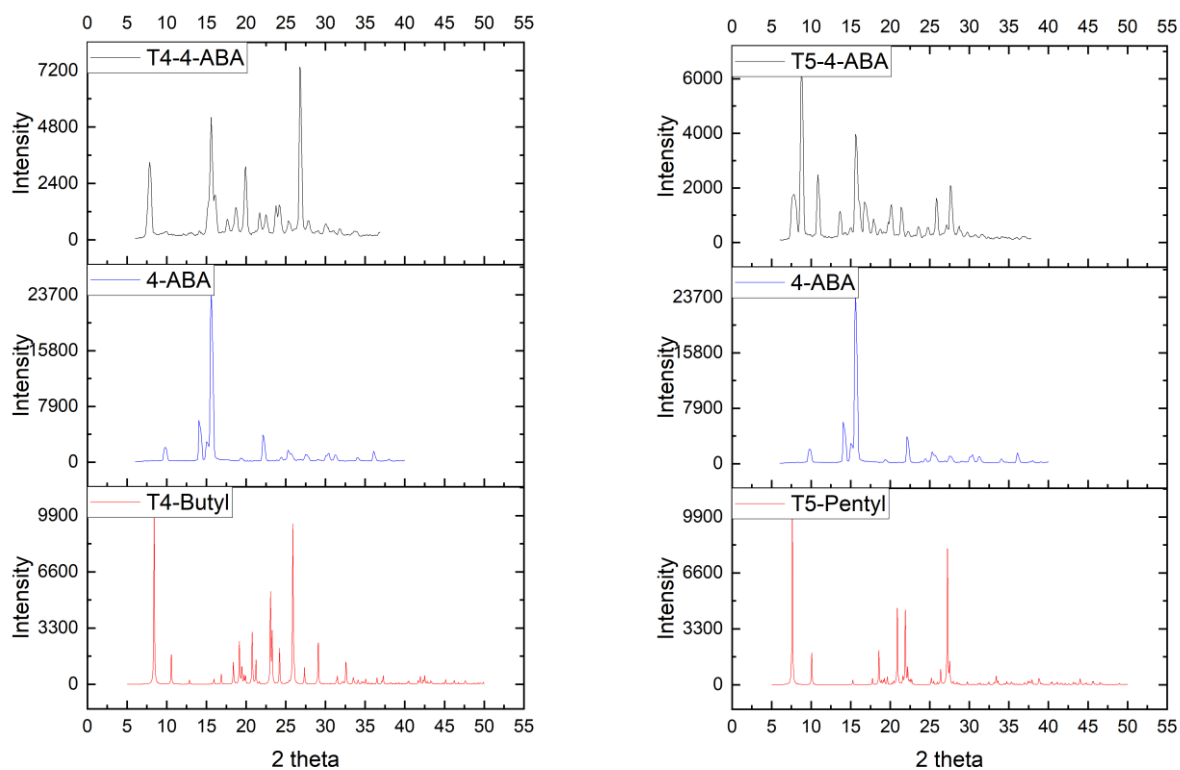


Figure I.15. PXRD of T4-4ABA and T5-4ABA.

Solid-state UV-visible spectra

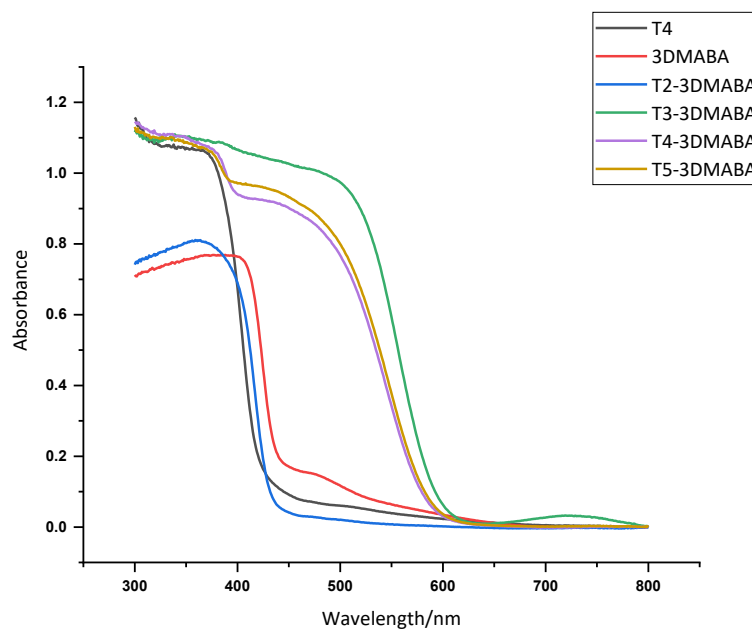


Figure I.16. Solid-state UV-vis spectra for 3DMABA cocrystals.

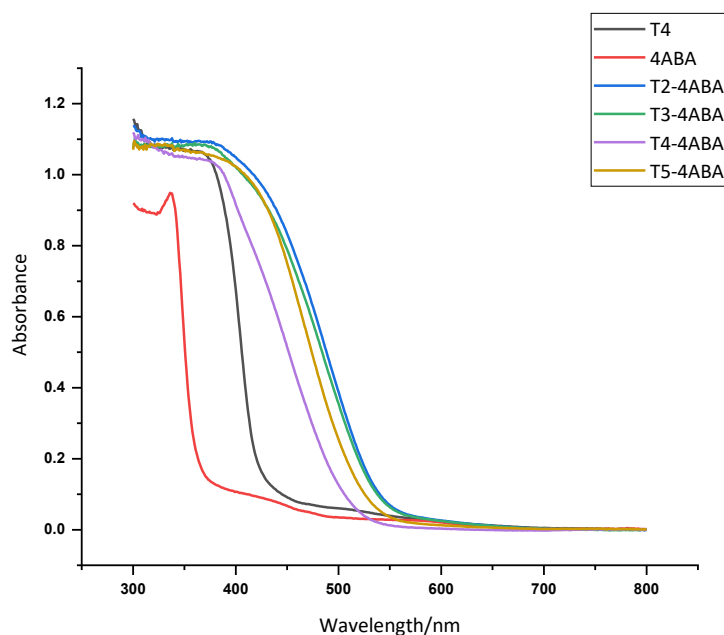
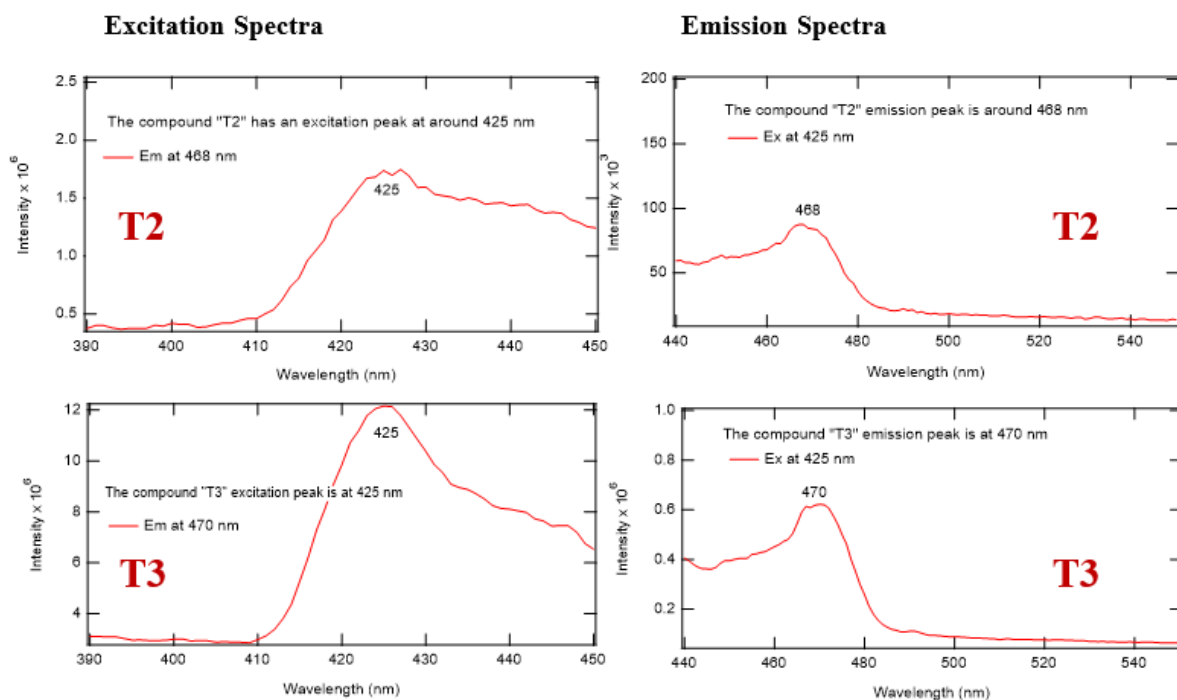


Figure I.17. Solid-state UV-vis spectra for 4ABA cocrystals.

Photoluminescence studies



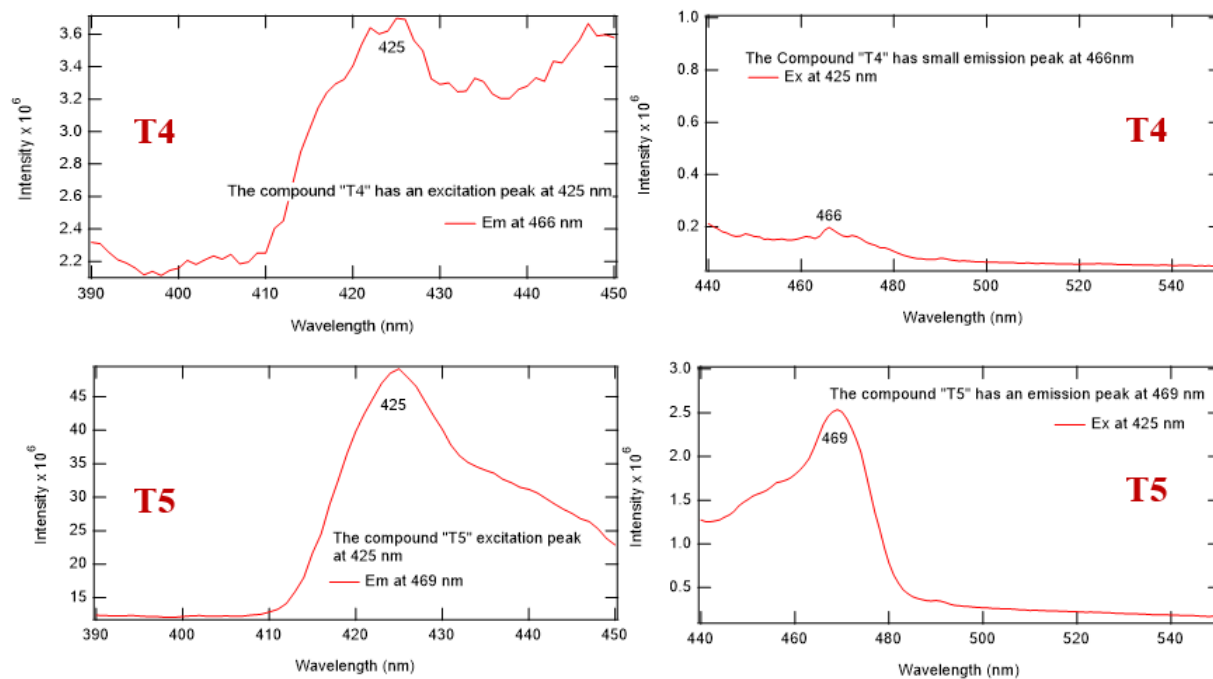


Figure I.18. Photoluminescence spectra of targets.

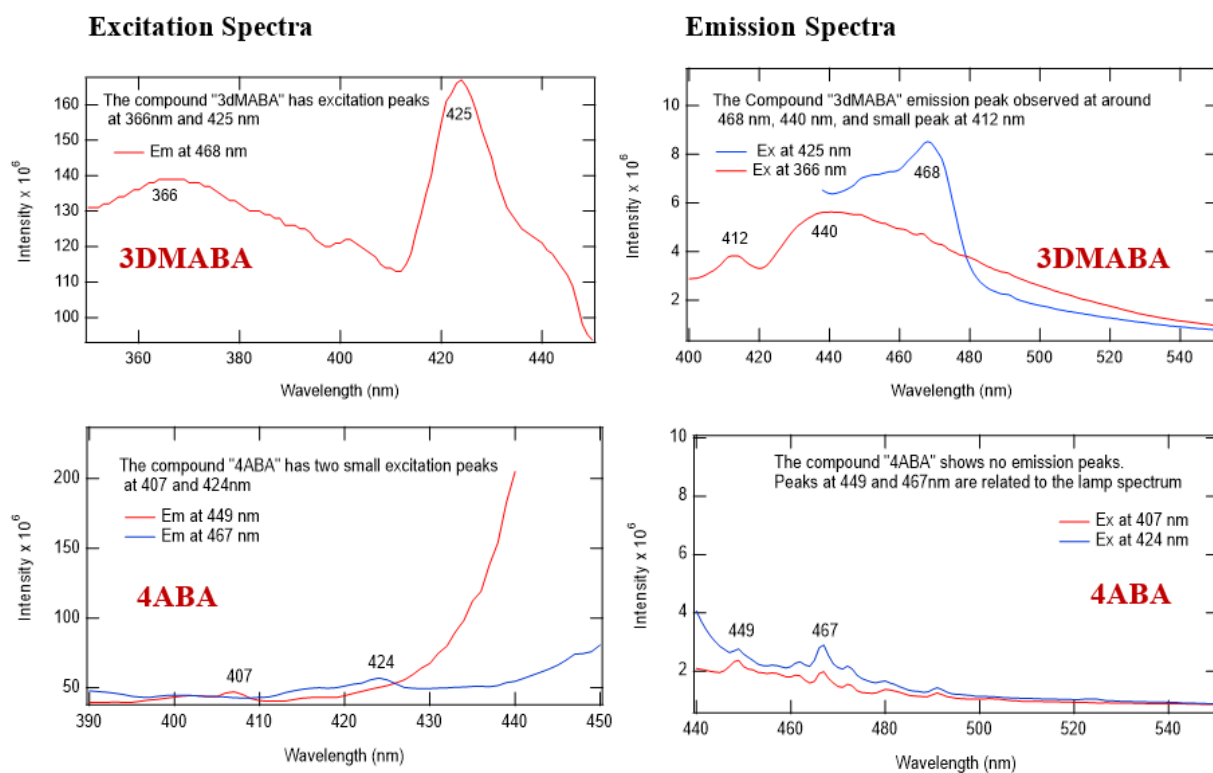


Figure I.19. Photoluminescence spectra of cofomers.

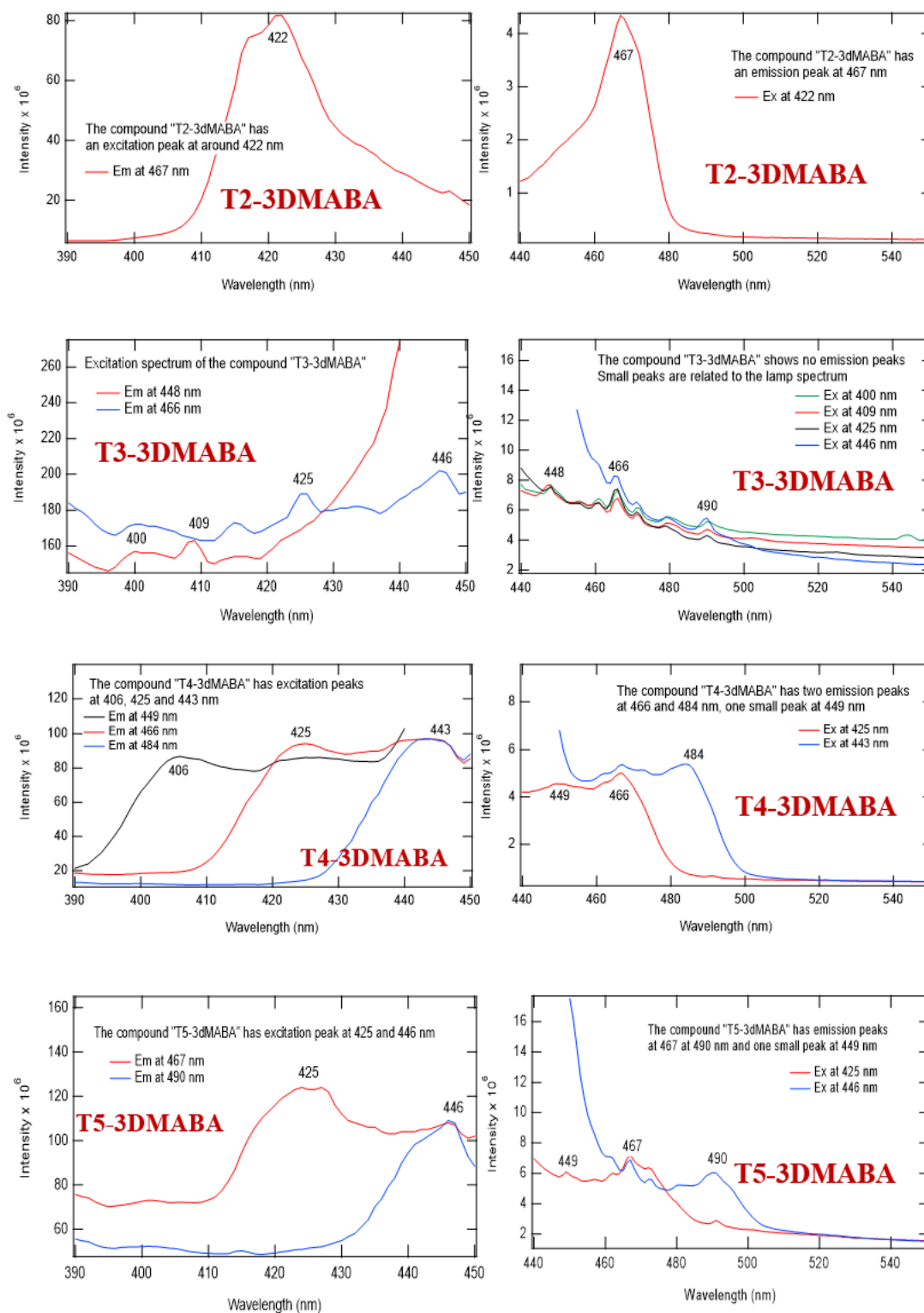


Figure I.20. Photoluminescence spectra of 3DMABA cocrystals.

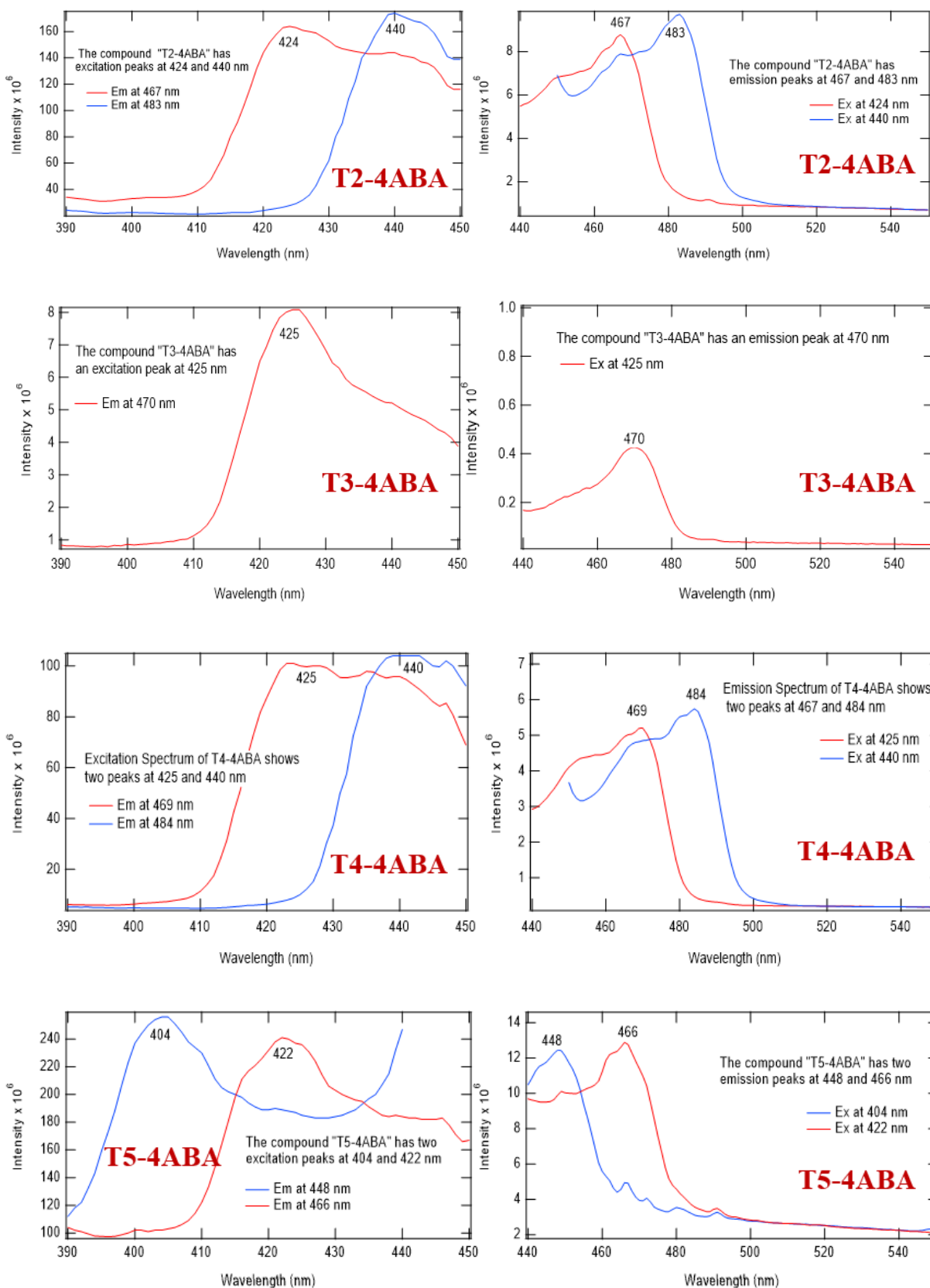


Figure I.21. Photoluminescence spectra of 4ABA cocrystals.

Solid-state replacement studies

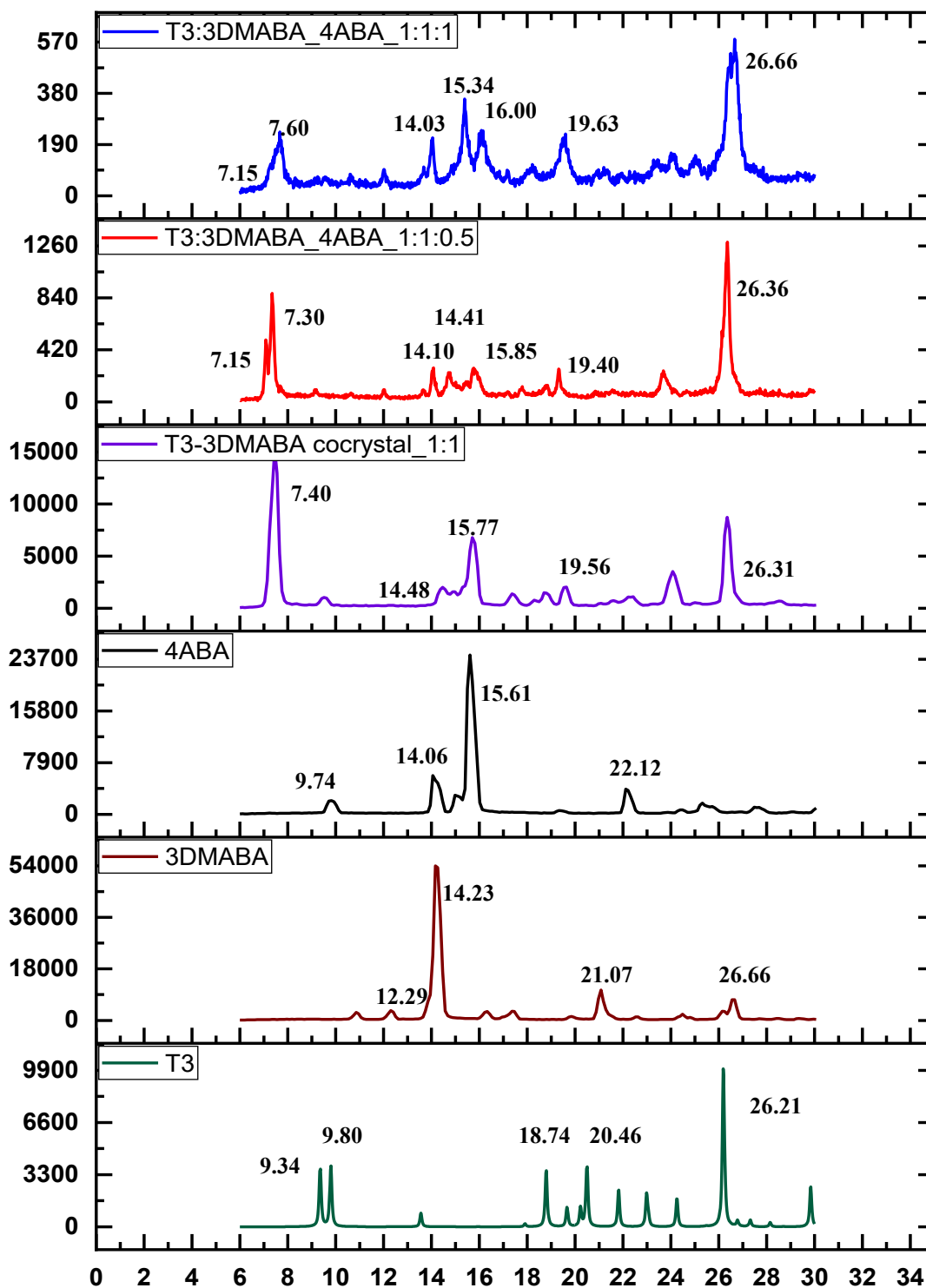


Figure I.22. Solid-state replacement study of T3-3DMABA cocrystal.

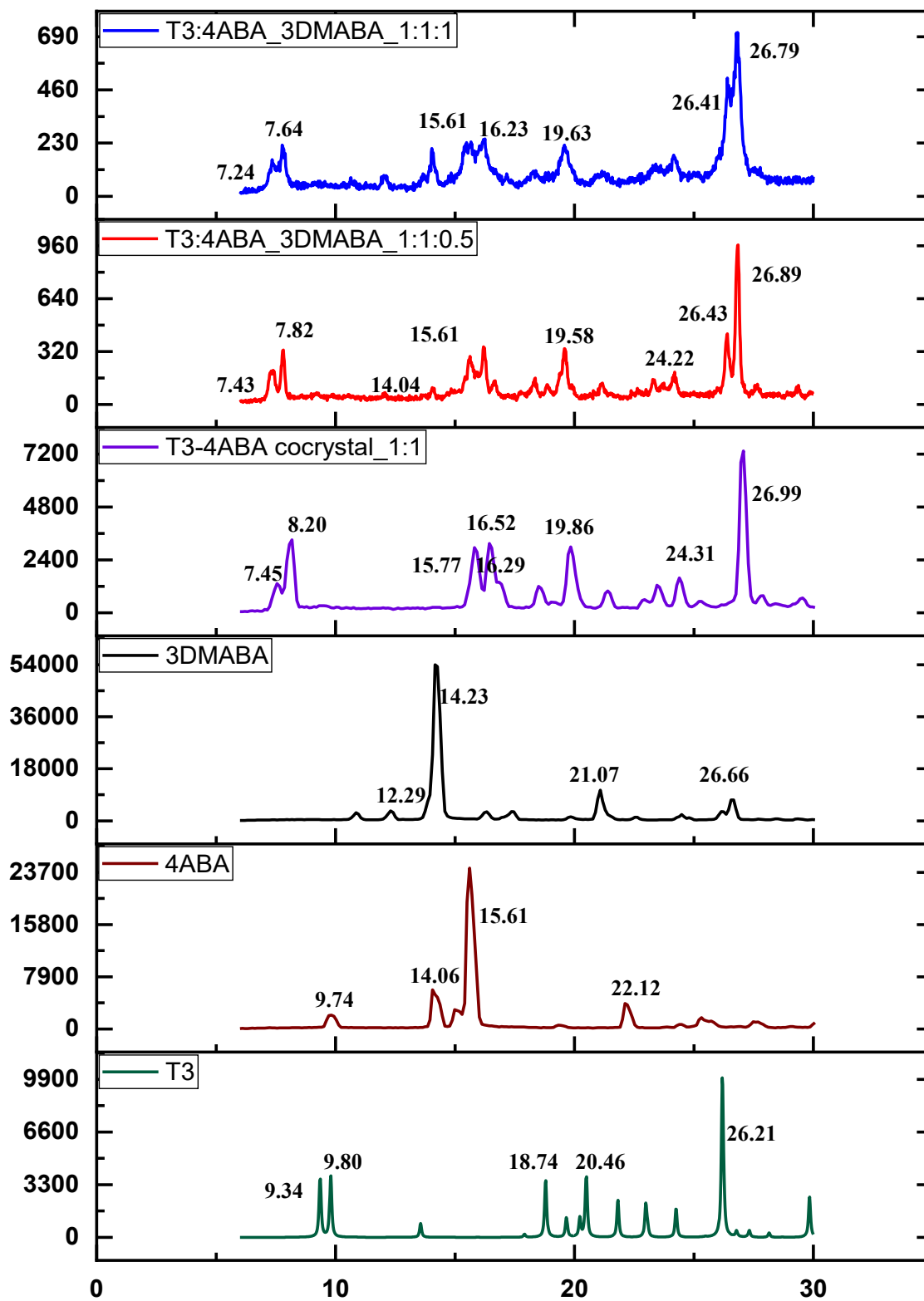


Figure I.23. Solid-state replacement study of T3-4ABA cocrystal.

Appendix J - Additional information for Chapter 10

3/20/26, 2:41 PM

RightsLink Printable License

AMERICAN CHEMICAL SOCIETY LICENSE TERMS AND CONDITIONS

Mar 20, 2026

This Agreement between Aloka A. Marasinghe ("You") and American Chemical Society ("American Chemical Society") consists of your license details and the terms and conditions provided by American Chemical Society and Copyright Clearance Center.

License Number	6233230099905
License date	Mar 20, 2026
Licensed Content Publisher	American Chemical Society
Licensed Content Publication	Crystal Growth and Design
Licensed Content Title	Impact of Mixed Solvent on Co-Crystal Solubility, Ternary Phase Diagram, and Crystallization Scale Up
Licensed Content Author	Tasnim Munshi, Batul Redha, Neil Feeder, et al
Licensed Content Date	Apr 1, 2016
Licensed Content Volume	16
Licensed Content Issue	4
Volume number	16
Issue number	4
Type of Use	Thesis/Dissertation

<https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=53a37c9a-fffa-4133-be16-0c7d6600742b>

1/4

Figure J.1. Copyright license for Chapter 8, Figure 10.2.