

**CRYSTAL ENGINEERING OF MULTICOMPONENT SOLIDS
OF PHARMACEUTICALLY IMPORTANT MOLECULES
(OROTIC ACID, ISOOROTIC ACID, NSAIDS AND SULFA
DRUGS) WITH PYRIDINE AND AMINOPYRIDINE BASED
COFORMERS**

VINEET KUMAR



**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY DELHI
JANUARY 2018**

©Indian Institute of Technology Delhi (IITD), New Delhi, 2018

**CRYSTAL ENGINEERING OF MULTICOMPONENT SOLIDS
OF PHARMACEUTICALLY IMPORTANT MOLECULES
(OROTIC ACID, ISOOROTIC ACID, NSAIDS AND SULFA
DRUGS) WITH PYRIDINE AND AMINOPYRIDINE BASED
COFORMERS**

by

Vineet Kumar

Department of Chemistry

Submitted

*in fulfillment of the requirement of the degree of Doctor of philosophy
to the*



INDIAN INSTITUTE OF TECHNOLOGY DELHI

JANUARY 2018

CERTIFICATE

This is to certify that the thesis entitled, “**Crystal engineering of multicomponent solids of pharmaceutically important molecules (Orotic acid, isoorotic acid, NSAIDs and sulfa drugs) with pyridine and aminopyridine based coformers**” being submitted by **Mr. Vineet Kumar** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry, is a record of bonafide research work carried out by him. Mr. Vineet Kumar has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this dissertation have not been submitted, in part or full, to any other university or institute for award of any degree or diploma.

Dr. A. RAMANAN
Professor
Department of Chemistry
Indian Institute of Technology Delhi
New Delhi-110016

ACKNOWLEDGEMENTS

I express my deep sense of gratitude and profound thanks to my supervisor Prof. A. Ramanan. Throughout my Ph.D, he created a friendly research atmosphere for me, enlightened me with great ideas and patiently corrected my writing. It was really a lifetime experience for me to work with him. I wish to express my sincere thanks to Dr. Ram Thaimattam, for his valuable contribution, discussion and support throughout my Ph.D. work at IIT Delhi. I would like to thank the present and former heads of the Department of Chemistry and faculty members for their help and cooperation. I would also like to thank all the staff associated with the Department of Chemistry, IIT Delhi.

I am grateful to UGC, New Delhi, for providing fellowship support. I thank IIT Delhi and DST & SERB for providing instrumentation and other infrastructure facilities.

It gives me immense pleasure to thank my lab mates Dr. Shailesh Upreti, Dr. Monika Singh, Dr. Dinesh Kumar, Dr. Pramod Kumar Goswami, Manju, Balendra, Shailabh, Bharti, and Manisha for creating wonderful friendly atmosphere in the lab. The journey of research became easy with the support of Amit Singh, Gyandeshwar Rao, Bharat Chaubey, Satyendra Kumar, Jatinder Singh, Dharendra Yadav, Manu Dalela, Soumen Sinhababu, Chandan Jha, Mahendra, Arabinda, Gohil, Kasinath, Saurabh Gautam, Balvinder Singh, Sourav Sarkar and Sushma Yadav.

My Special thanks to Vedpal Arya and Chhayakanta Acharya, for their wonderful company and support. They made the stay memorable.

I am also grateful to my friend Rajive Mohan Sharma who has supported me along the way. I would like to thank my college friends Mohit Tyagi and Vikendra Dabash who helped me to cultivate patience and perseverance to endure challenges in life. The unconditional love and

blessings of my late grandfather, late grandmother, father and mother, my brother and sisters, my sweet nephew made me what I am today and I owe everything to them. Dedicating this thesis to them is a minor recognition to their boundless love and affection.

Vineet Kumar

ABSTRACT

Supramolecular chemistry or noncovalent chemistry concerns with the chemistry of intermolecular interactions which embraces different aspects of organic, inorganic and organometallic crystal chemistry. The impact is quite significant in the case of pharmaceutically important molecules as these undergo considerable changes during processing and formulation and thus influence its key solid state properties such as dissolution rate, bioavailability and stability. Crystal engineering focuses on intentional design of functional solids with desired physical and chemical properties. Crystal engineers commonly adopt supramolecular synthon approach to simplify the task of analyzing complex supramolecular architectures as well as to direct desired supermolecules. The supramolecular synthon concept can also be extended to coordination solids that include discrete complex based molecular solids to extended solids like coordination polymers and metal organic frameworks. A molecular solid nucleating from single or multicomponent system can result in a range of crystal forms such as cocrystal, salt-cocrystal and salt. These multiple crystal forms in turn, can exhibit polymorphism and/or undergo solvation/hydration. In the context of pharmaceutically active molecules, the multiple forms are gaining importance as functional materials as these can profoundly affect the physicochemical properties of industrially significant drug compounds.

Chapter I provides a brief account of our literature survey on the crystal engineering of multicomponent solids and the motivation for the present work. Chapter II discusses the use of acid···pyridine synthon as a reliable tool to engineer new crystal forms of orotic and isoorotic acids with improved solubility. Thermodynamic stability of the keto form seems to dominate the crystallization of these two structural isomers. Fingerprint plots generated from Hirshfeld surface analysis provide further insights into the growth of these molecular solids. ΔpK_a rule appears to be

valid even in the presence of other competing weak interactions. Chapter III reports our attempts to cocrystallize three sulfa drugs viz. sulfamerazine, sulfamethazine and sulfamethoxazole with four coformers' viz. niflumic acid and flufenamic acid, 4-aminopyridine and piperazine. Although the molecular structures of smr, smx and smz are comparable, their propensities to form multiple solid forms with the four selected coformers were found to be significantly different. To understand this discrepancy, we investigated the structural chemistry of these solids by analyzing the interactions of key synthons present in single component SDs as well as those reported in the literature. The study revealed that recognition of the nature of key synthons occurring in single component SDs and the ability to break and form new synthons with coformers can be a viable strategy to design multicomponent solids based on sulfa drugs.

Chapter IV summarises a comparative structural feature of twelve new solids based on two nonsteroidal anti-inflammatory drugs, niflumic acid and mefenamic acid with amine and pyridine based coformers. A difference in pK_a of both the molecules with similar structural features enabled us to systematically understand the influence of ΔpK_a on the outcome of crystallization. The structural chemistry of all the solids is discussed on the basis of acid...pyridine synthon. Chapter V describes the synthesis and structural characterization of four new coordination solids of another drug molecule, flufenamic acid based on zinc and cobalt along with an auxiliary N-donor ligand. The trimeric cobalt analogues built of tetrahedral and octahedral units show weak antiferromagnetism at lower temperatures. The molecular Hirshfeld surface shape index and 2D fingerprint plots provided a quantitative mapping of intermolecular interactions observed in these solids. These complexes showed a higher affinity for BSA in comparison to free flufenamic acid. Chapter VI reports a brief summary of the results and conclusions derived from the present work along with a few directions for future work.

सार

इंटरमॉलिकुलर इंटरैक्शन के रसायन विज्ञान के साथ सुपरमौलेक्यूलर केमिस्ट्री या गैर-कॉन्ट्रैलेंट केमिस्ट्री चिंताओं जो कार्बनिक, अकार्बनिक और ऑर्गेनेटिकल क्रिस्टल केमिस्ट्री के विभिन्न पहलुओं को गले लगाती है। औषधि के महत्वपूर्ण अणुओं के मामले में प्रभाव काफी महत्वपूर्ण है क्योंकि इनके प्रसंस्करण और निर्माण के दौरान काफी बदलाव आते हैं और इस तरह विघटन दर, जैवउपलब्धता और स्थिरता जैसे महत्वपूर्ण ठोस गुणों को प्रभावित करते हैं। क्रिस्टल इंजीनियरिंग वांछित भौतिक और रासायनिक गुणों के साथ कार्यात्मक ठोस पदार्थों के जानबूझकर डिजाइन पर केंद्रित है। क्रिस्टल इंजीनियर आमतौर पर जटिल सुपरमौलेक्यूलर आर्किटेक्चर के विश्लेषण के कार्य को सरल बनाने के साथ-साथ वांछित वांछित सुपरमूलेक्यूलर को सरल बनाने के लिए सुप्रामोलेक्यूलर सिंथेन दृष्टिकोण को अपनाना चाहते हैं। सुप्रामोलेक्यूलर सिंथेन की अवधारणा को समन्वय के लिए भी बढ़ाया जा सकता है, जिसमें जटिल जटिल आधारित आणविक ठोस पदार्थ समन्वित पॉलिमर और धातु कार्बनिक फ्रेमवर्क जैसे विस्तारित ठोस होते हैं। सिंगल या मल्टीकॉम्पोनेंट सिस्टम से आणविक ठोस नाभिक परिणामस्वरूप क्रिस्टल, नमक-कॉक्रिस्टल और नमक जैसे क्रिस्टल रूपों का परिणाम हो सकता है। बदले में ये कई क्रिस्टल रूप, बहुरूपता प्रदर्शित कर सकते हैं और / या सल्वेशन / हाइड्रेशन से गुजर सकते हैं। औषधीय रूप से सक्रिय अणुओं के संदर्भ में, कई रूपों को कार्यात्मक सामग्री के रूप में महत्व प्राप्त होता है क्योंकि ये औद्योगिक रूप से महत्वपूर्ण दवाओं के यौगिकों के भौतिक गुणों को गंभीर रूप से प्रभावित कर सकते हैं।

प्रथम अध्याय में बहुक्रियावादी ठोस पदार्थों के क्रिस्टल इंजीनियरी पर हमारे साहित्य सर्वेक्षण का संक्षिप्त विवरण और वर्तमान कार्य के लिए प्रेरणा प्रदान करता है। अध्याय II में एसिड ... पायराइडिन सिंथेन के उपयोग के बारे में चर्चा की गयी है, जो एक विश्वसनीय उपकरण के रूप में विकसित किया गया है ताकि बेहतर विलेयता के साथ ऑरोटिक और ईज़ूरोटिक एसिड के नए क्रिस्टल रूपों को इंजीनियर किया जा सके। केटो प्रपत्र के थर्मोडायनेमिक स्थिरता इन दो संरचनात्मक आइसोमर्स के क्रिस्टलीकरण पर हावी हैं। हिर्शफेल्ड सतह विश्लेषण से उत्पन्न फिंगरप्रिंट भूखंड इन आणविक ठोस पदार्थों के विकास में और अंतर्दृष्टि प्रदान करते हैं। अन्य प्रतियोगी कमजोर इंटरैक्शन की उपस्थिति में भी पीकेए के नियम मान्य हैं। अध्याय III में तीन सल्फा दवाओं को संसाधित करने के हमारे प्रयासों की जानकारी है सल्फामेराज़ीन, सुल्फामेथाज़ीन और सल्फामैथॉक्सीज़ोल, चार कॉफ़र्मर्स के साथ। निफ़्ल्यूमिक एसिड और फ़्लूफ़ैनेमिक एसिड, 4-एमिनोपीरीडिन और पिपराज़ीन। हालांकि smr, smx और smz के आणविक संरचना तुलनीय हैं, चार चयनित कोफ़ोर्मर्स के साथ कई ठोस रूपों बनाने के लिए उनके propensities काफी अलग पाए गए थे। इस विसंगति को समझने के लिए, हमने इन घटकों के संरचनात्मक रसायन विज्ञान की जांच की, जो एक एकल घटक एसडी में मौजूद प्रमुख संश्लेषणों के साथ-साथ साहित्य में रिपोर्ट किए गए संवादों का विश्लेषण करते हैं। अध्ययन से पता चला है कि एकल घटक एसडी में होने वाले प्रमुख संवेदकों की प्रकृति की मान्यता और कोफ़ोर्मर्स के साथ नए सिन्थेन को तोड़ने की क्षमता सल्फा दवाओं के आधार पर मल्टीकॉम्पोनेंट ठोस डिजाइन करने के लिए एक व्यवहार्य रणनीति हो सकती है।

चतुर्थ अध्याय में दो नॉनटैरोएडियल एंटी-इन्फ़्लेमेट्री ड्रग्स, नीफ़्ल्यूमिक एसिड और मेफ़ेनैमिक एसिड के आधार पर आमीन और पायराइडिन आधारित कोफ़ॉर्मर्स के आधार पर बारह नए ठोस पदार्थों की एक तुलनात्मक संरचनात्मक सुविधा का सार है। समान संरचनात्मक सुविधाओं के साथ दोनों

अणुओं के पीकेए में अंतर, क्रिस्टलीकरण के परिणाम पर Δ पीकेए के प्रभाव को व्यवस्थित रूप से समझने में सक्षम है। सभी ठोस पदार्थों के संरचनात्मक रसायन विज्ञान की चर्चा एसिड ... पायरिडिन सिंथेन के आधार पर की जाती है। अध्याय V में संश्लेषण और संरचनात्मक लक्षण वर्णन किया गया है जो एक अन्य दवा अणु के चार नए समन्वय ठोस, जस्ता और कोबाल्ट के आधार पर फ्लूफेनैमिक एसिड और सहायक एन-दाता लैगंद के साथ। टेट्राहेड्रल और अक्टाइड्रल इकाइयों के बने ट्राइमेरिक कोबाल्ट एनालाॅग्स कम तापमान पर कमजोर एंटीफोरोमनेटिविटी दिखाते हैं। आणविक हिरशफेल्ड सतह आकार सूचकांक और 2 डी फिंगरप्रिंट भूखंडों में इन ठोस पदार्थों में मनाया जाने वाला इंटरमॉलिकुलर इंटरैक्शन का एक मात्रात्मक मानचित्रण प्रदान किया गया था। इन कॉम्प्लेक्सों में मुफ्त फ्लुफाइनैमिक एसिड की तुलना में बीएसए के लिए एक उच्च संबंध दिखाई दिया। अध्याय छठी भविष्य के काम के लिए कुछ दिशा-निर्देशों के साथ-साथ वर्तमान कार्य से प्राप्त परिणामों और निष्कर्षों का एक संक्षिप्त सारांश प्रस्तुत करता है।

Table of contents

CERTIFICATE	i
ACKNOWLEDGEMENTS	iii
ABSTRACT	v
Table of contents	vii
List of Figures	xi
List of Tables	xix
Abbreviations	xxi
Chapter I	
Introduction	1
I.1 Supramolecular Chemistry	3
I.2 Noncovalent interactions	5
I.3 Supramolecular synthon	8
I.4 Crystal engineering	10
I.5 Cambridge Structural Database (CSD)	11
I.6 Acid···pyridine synthon	12
I.7 Sulfonamide···coformer synthon	16
I.8 Multicomponent crystals	19
I.9 Pharmaceutical salt	25
I.10 Pharmaceutical cocrystal	27
I.11 Salt vs cocrystal	28
I.12 Solvates and hydrates	29
I.13 Polymorphism	31
I.14 Impact of cocrystals on various physical properties	31
I.15 Bioavailability improvement via coordination complex formation	34
I.16 Motivation for present work	35
References:	40

Chapter II

Multicomponent solids of uracil derivatives: orotic and isoorotic acids	57
II.1 Introduction	60
II.2 Experimental section	61
II.3 X-ray structure determination	64
II.4 Other physical measurements.....	67
II.5 Results and discussion.....	67
II.6 Crystal structures of OA based solids	72
II.7 Crystal Structures of IOA based solids	83
II.8 Hirshfeld surface analysis	89
II.9 Solubility- hydrogen bonding correlation	95
II.10 Impact of ΔpK_a on solid forms	98
II.11 Conclusion.....	99
References:.....	100

Chapter III

Structural landscape of multicomponent solids based on sulfa drugs	103
III.1 Introduction.....	106
III.2 Experimental Section	108
III.3 X-ray structure determination	111
III.4 Cambridge crystallographic database search	114
III.5 Computational details	114
III.6 Other physical measurements	114
III.7 Results and discussion	115
III.8 SD-SD synthon	126
III.9 SD-Coformer synthons	129
III.10 Conclusion	145
References:.....	147

Chapter IV

Multicomponent solids of niflumic and mefenamic acid

based on acid-pyridine synthon	151
IV.1 Introduction	154
IV.2 Design of Nif and Mef based solids using supramolecular synthon approach.....	156
IV.3 Experimental Section	157
IV.4 X-ray structure determination	158
IV.5 Results and discussion.....	167
IV.6 Crystal structure of bipyridine based solids	169
IV.7 Crystal structures of aminopyridine based solids	174
IV.8 Crystal structures of piperazine based solids	181
IV.8 Hirshfeld surface analysis	182
IV.9 Effect of <i>pKa</i> on solid forms	190
IV.10 Conformational Flexibility	192
IV.11 Solubility studies	194
IV.13 Conclusion.....	195
References:	196

Chapter V

Synthesis, crystal structures and binding studies of NSAIDs based metal complexes. 199

V.1 Introduction	202
V.2 Experimental Section.....	204
V.3 Other physical measurements	205
V.4 X-ray crystallography	205
V.5 Results and discussion.....	207
V.6 Hirshfeld surface analysis of 30-33	218
V.7 FTIR spectroscopy.....	221
V.8 Thermal stability.....	222
V.9 Binding of bovine serum albumin with the coordination complexes	223
V.10 Magnetic Properties.....	225
V.11 Conclusion	228

References:.....	229
CHAPTER VI	
Summary, Conclusions and Future directions.....	233
Appendix I	
Rietveld refinement of PXRD patterns of solids 1 - 33.....	236
Appendix II	
DSC thermogram for solid 1-29.....	249
Appendix III	
UV spectra for solubility studies of solids reported.....	266
Academic Resume of the Author	281

List of Figures

Figure I.1 Frequency of occurrence for different synthons by CSD Conquest 1.17; 2016...	12
Figure I.2 PAS solids based on the acid...pyridine synthon.....	14
Figure I.3 ASA solids based on the ring motif, $R_4^4(12)$	15
Figure I.4 DIC solids based on the acid...pyridine synthon.....	16
Figure I.5 Sulfonamide group involved in several drug molecules.....	17
Figure I.6 Types of two point recognition in sulfonamide...acid synthon.....	18
Figure I.7 Four types of interactions observed for sulfonamide...pyridine synthon.....	19
Figure I.8 Multiple crystal forms of a molecule.....	21
Figure I.9 Statistical tendency of the propensity of the salts and non-salts to occur in different forms (Adapted from reference 99).....	24
Figure I.10 Relative occurrence of AB (cocrystal) and A^+B^- (salt) as a function of calculated ΔpK_a . (Adapted from references 125).....	29
Figure I.11 Relative occurrence of AB and A^+B^- as a function of calculated ΔpK_a . (Adapted from references 183).....	35
Figure II.1 (a) In the 2:1 salt 1 , head to head orotate dimers are bonded sidewise to form zig- zag tapes which are further interlinked by $bpeeH_2^{2+}$ cations via N-H...O bonds resulting in a layer. (b) Layers are stacked one over the other through N-H... π and C-H... π	73
Figure II.2 (a) In the 1:1 salt 2 , a polar tape of alternating OA^- and $bpeH^+$ are connected by synthons VII and VIII wherein all the carboxylate groups are pointed in one direction. These tapes stack to generate a layer and two such layers stack to generate a double layer connected by C-H...O where all the tapes are oriented in same direction. (b) Alternate stacking of the double layers in such a way that tapes in adjacent double layers are perpendicularly oriented, which are interlinked by C-H...O. There is no acid...acid (amidic) linkage in 2	75

Figure II.3 In the 2:1 salt hydrate **3**, orotate ions form separate chains linked by synthon III. (b) The chains stacks laterally mediated through water molecule with a separation of 3.2 Å to form an anionic layer. (c)The anionic layers are interlinked by *bppH*⁺ ions through N–H···O hydrogen bonds generating channels along [001].....77

Figure II.4 In the 1:1 salt **4**, the dimer formed through synthon IV aggregates into a tetramer through synthon X. (b) The tetramers align perpendicular to each other forming a sheet square-type arrangement in a brick wall fashion. (c) The arrangement of the sheets show a three-fold interpenetration.....78

Figure II.5 Crystal structure of 1:1:1 salt-cocrystal **5**. (a) A dimer formed between OA and OA[−] through synthon IV extends into a chain like in **1**. The chains are further connected through synthon II generating infinite zig-zag anionic sheets. However, the sheet formed in **5** is different (refer Figure 1b) as the smaller *4apH*⁺ facilitates the packing of the chains through N–H···O and O–H···O.....80

Figure II.6 In the 1:1 salt **6**, (a) OA[−] anions are linked through synthon III forming a zig-zag tape. The OA[−] moieties are inclined by about 42° in the tapes. (b) Lateral stacking of these tapes separated by about 3.5 Å generate an OA[−] layer. These layers are inter linked by *4apH*⁺ cations via N–H···O to generate the crystal structure.....82

Figure II.7 (a) The acid···pyridine···acid trimers forming a chain through synthon XII in **7**. (b) The adjacent chains cross-sect each other at an angle of 32.35° through N–H···O.....83

Figure II.8 Acid···pyridine···acid trimers interact through synthon XII forming a chain in **8**. (b) Adjacent sheets are further connected through synthon V forming the 3D hydrogen bonded network.....85

Figure II.9 (a) Acid···base dimer interact through synthons XII and XIII extending into 1D chains in **9**; the chains are linked to each other through acid···acid interaction (N–H···O) forming sheets. The sheets are further stabilized through C–H···π.....86

Figure II.10 (a) A pair of acid···base dimer interacts through synthon XV forming a discrete nonlinear tetramer in **10**. (b) The tetramers are connected through water molecules generating a step-like structure.....88

Figure II.11 (a and d) Structural environment of OA and IOA monohydrates have been shown through Hirshfeld surface. (b-f) Fingerprint plots of both the solids for all interaction, resolution of plot in O···H/H···O interactions. The presence of two spikes are characteristic of carboxylic acid.....90

Figure II.12 (a-c) Fingerprint plot of OA in solid **1** $(\text{OA})_2^-(\text{bpeeH})^{+2}$, plot resolved in O···H/H···O and N···H/H···N interactions respectively. (d-f) Fingerprint plot of IOA in solid **7** $(\text{IOA})_2\cdot\text{bpee}$, all interaction, resolution of plot in O···H/ H···O and N···H/H···N interactions respectively.....91

Figure II.13 (a-c) Fingerprint plot of OA in solid **2** $(\text{OA})^-(\text{bpeH})^+$ (b) and (c) plot resolved in O···H/ H···O and N···H/H···N interactions respectively. (d) Fingerprint plot of solid **8** $(\text{IOA})_2(\text{bpe})$ all interaction (e) O···H/ H···O and (f) and N···H/H···N interactions.....92

Figure II.14 (a- f) Fingerprint plot of both OA and OA⁻ in solid **3** $(\text{OA})_2\cdot\text{bppH}_2^{2+}\cdot 2\text{H}_2\text{O}$ which is again resolved in O···H/ H···O and N···H/H···N interactions respectively. (g-h) Fingerprint plot of IOA in solid **9** $(\text{IOA})\cdot(\text{bpp})$ all interaction, O···H/ H···O and N···H/H···N interactions.....93

Figure II.15 (a) Fingerprint plot of both OA and OA⁻ in solid **5** $(\text{OA})\cdot(\text{OA})^-(\text{4apH})^+$ (b)/(e) and (c)/(f) resolved in O···H/ H···O and N···H/H···N interactions respectively. (g) Fingerprint plot of OA⁻ in solid **6** $(\text{OA})^-(\text{4apH})^+$ all interaction (h) O···H/ H···O and (i) and N···H/H···N interactions. (i) Fingerprint plot of IOA in solid **10** $(\text{IOA})^-(\text{4apH})^+\cdot 3\text{H}_2\text{O}$ and plot is resolved in O···H/ H···O and N···H/H···N (k), (j) respectively.....94

Figure II.16 Solubility of OA based solids. Solid **5** is the most soluble OA based multicomponent solids.....95

Figure II.17 Solubility of IOA based solids. Solid **10** is the most soluble IOA based multicomponent solids.....96

Figure II.18 Solubility and % O···H interaction correlation between bipyridine and amino pyridine coformer based solids of OA and IOA respectively.....	97
Figure III.1 Primary aggregation of SD and coformer in the solids 11-18	117
Figure III.2 Aggregation of <i>smr</i> and <i>4ap</i> in solid 1 , anion-cation pair stack one over the other forming 1D ladder which further extends through N–H···N along the second dimension.....	119
Figure III.3 Aggregation of the symmetry independent components in solid 12 . The <i>smr</i> and <i>pip</i> molecules aggregate into two different linear tapes: Tape 1 (left) and tape 2 (right) interact through two distinct $R_4^4(18)$ motifs based on N–H ⁺ ···O and N–H ⁺ ···N [–]	120
Figure III.4 Crystal packing of the solid 13 . <i>smx1</i> , <i>4ap1</i> and the water aggregate to form a linear chain connected through the $R_4^4(16)$ and $R_4^4(12)$ (left). These chains are interlinked through N–H _{<i>smx1</i>-aniline} ···O _{<i>smx2</i>} and N ⁺ –H _{<i>4-ap1</i>} ···N _{<i>smx2</i>-oxazole} , forming sheets (right).....	121
Figure III.5 Aggregation of <i>smx</i> and <i>pip</i> molecules into linear chains in the solid 14 through $R_4^4(12)$ motif involving N ⁺ –H···N [–] and N ⁺ –H···O. Notice that the N ⁺ –H···N and N ⁺ –H···O are along the equatorial and axial directions of the <i>pip</i> cation. Compare this with tape 1 of Fig. III.2.....	122
Figure III.6 In 15 and 16 , the molecules <i>smz</i> and <i>nif/ffa</i> forming a cavity. Similar units are stacked one over the other along <i>b</i> -axis on the <i>bc</i> -plane through N–H···O forming a 3D crystal structure.....	123
Figure III.7 Two distinct <i>smz</i> – <i>4ap</i> pairs (red and cyan) interlink through N–H···O and N–H···N forming a tape in solid 17	124
Figure III.8 Aggregation of <i>smz</i> and <i>pip</i> molecules into linear chains in the solid 18 through $R_4^4(18)$ motif involving N ⁺ –H···N [–] and N ⁺ –H···O. Note that the N ⁺ –H···N and N ⁺ –H···O are along the axial and equatorial directions of the <i>pip</i> cation. The aggregation of the components is similar to that observed in tape 2 of solid 12 . The other variations can be seen in Fig. 2 (tape 1) and Fig. 4.....	125

Figure IV.1 Nif- <i>bpe</i> -Nif trimers are connected through C-H $\cdots$ N (synthon VII) and C-H $\cdots$ F forming a planar sheet.....	170
Figure IV.2 In 20 and 20a , Nif- <i>bpee</i> -Nif trimers are connected through C-H $\cdots$ N and C-H $\cdots$ F forming a planar sheet.....	171
Figure IV.3 (a) In 21 , Nif- <i>bpp</i> -Nif trimers are connected through C-H $\cdots$ F with other trimers forming a planar sheet. (b) Different sheets are again connected via other C-H $\cdots$ F interactions.....	172
Figure IV.4 (a) Mef- <i>bpe</i> -Mef trimers are connected through C-H $\cdots$ π with other trimers in both the planes in 25 . (b) Isostructural 26 show the same types of interaction with Mef- <i>bpee</i> -Mef trimers.....	173
Figure IV.5 (a) Nif- <i>bpp</i> dimers connected through C-H $\cdots$ N with the other dimer forming a planar sheet in 27 . (b) Planar sheets are stacked one over the other via C-H $\cdots$ π and C-H $\cdots$ N.....	174
Figure IV.6 (a) Nif- <i>2ap</i> dimers are connected through N-H $\cdots$ O with other dimers to form a 1D Chain in 22 . (b) The chains are interconnected via C-H $\cdots$ F in the other two planes forming a 3D network.....	176
Figure IV.7 (a) Nif- <i>2ap</i> dimers connected through N-H $\cdots$ O with other dimers to form a tetramer in 22a . (b) Tetramers are stacked one over the other through C-H $\cdots$ π interaction and cross-sects each other via C-H $\cdots$ F interaction.....	177
Figure IV.8 (a) In 23 , Nif- <i>4ap</i> dimers are connected through N-H $\cdots$ O with other dimers forming a 1D Chain. (b) The chains are interconnected in perpendicular fashion via C-H $\cdots$ F and C-H $\cdots$ O interaction.....	178
Figure IV.9 (a) In 28 , Mef- <i>2ap</i> dimers are connected through N-H $\cdots$ O with other dimers forming column via N-H $\cdots$ O. These columns form 3D network by interacting with other columns via C-H $\cdots$ π	179

Figure IV.10 (a) In **28**, Mef—H₂O—Mef tetramers are formed via synthon II and further connected through N—H···O with each other tetramer forming columns. (b) These columns form 3D network by interacting with others via C—H··· π and π ··· π interactions.....180

Figure IV.11 (a) In **24**, Nif—*pip*—Nif trimer formed via synthon VIII are connected forming a linear tape. (b) Interaction of tapes through C—H···F led to porous columns on the *bc* plane.....181

Figure IV.12 Mef—*pip*—Mef trimers in (Mef)²⁺(*pip*)²⁻·2H₂O formed via synthon VIII are connected via water molecules forming a linear tape..... 182

Figure IV.13 (a and e) Structural environment of Nif, Mef I and Mef II have been shown through Hirshfeld surface analysis. (b-d) Resolved fingerprint plots of Nif crystal structure interactions in O···H/H···O, C···H/H···C and F···H/H···F interactions. (f-g, and i-j) Resolved fingerprint plots of both forms of Mef in O···H/H···O and C···H/H···C interactions. The presence of the two spikes is characteristic of the carboxylic acid dimer in all the solids.....183

Figure IV.14 (a-h) Resolved fingerprint plots of Nif I and Nif II of solid **19** in O···H/H···O, N···H/H···N, C···H/H···C and F···H/H···F interactions respectively. (i-p) Resolved fingerprint plots of Nif of solid **20** and in O···H/ H···O and N···H/H···N interactions respectively.....184

Figure IV.15 (a-f) Resolved fingerprint plots of Mef of solid **25** and **26** in O···H/ H···O, N···H/H···N and C···H/ H···C interactions respectively.....185

Figure IV.16 (a-d) Resolved fingerprint plots of Nif of solid **21** in O···H/ H···O, N···H/H···N, C···H/ H···C and F···H/ H···F interactions respectively. (e-g) Resolved fingerprint plots of Mef of solid **27** in O···H/ H···O, N···H/H···N and C···H/ H···C interactions respectively.....186

Figure IV.17 (a-l) Resolved fingerprint plots of Nif in **22**, and Nif I & Nif II in **22a** in O···H/ H···O, N···H/H···N, C···H/ H···C and F···H/ H···F interactions respectively. (m-o)

Resolved fingerprint plots of **28** in O···H/ H···O, N···H/H···N and C···H/ H···C interactions respectively.....187

Figure IV.18 (a-d) Resolved fingerprint plots of Nif in **23** in O···H/ H···O, N···H/H···N, C···H/ H···C and F···H/ H···F interactions respectively. (e-g) Resolved fingerprint plots of Mef in **29** in O···H/ H···O, N···H/H···N and C···H/ H···C interactions respectively.....188

Figure IV.19 (a-d) Resolved fingerprint plots of Nif of solid **24** in O···H/ H···O, N···H/H···N, C···H/ H···C and F···H/ H···F interactions respectively. (e-g) Resolved fingerprint plots of Mef of (Mef⁻)₂·pip²⁺·2H₂O in O···H/ H···O, N···H/H···N and C···H/ H···C interactions respectively.....189

Figure IV.20 (a) Molecular overlay diagrams of Nif in salts/cocrystals. Color codes: Light blue – Nif, Red – **19**, Orange – **20**, Yellow – **20a**, Green – **21**, Cyan – **22**, Blue – **22a**, Purple – **23**, Magenta – **24**. (b) Molecular overlay diagrams of Mef molecule in salts/cocrystals. Color codes: Light blue – Mef I, Green – Mef II, Red – **25**, Orange – **26**, Yellow – **27**, Cyan – **28**, Blue – **29**, Purple – **30**.....193

Figure IV.21 Solubility of Nif based multicomponent solids.....194

Figure IV.22 Solubility of Mef based multicomponent solids.....195

Figure V.1 (a) The molecular trinuclear cobalt complex in **30**. (b) Tetrahedral and octahedral coordination around cobalt metal (ligand parts were omitted for clarity).....208

Figure V.2 Supramolecular aggregation of the trinuclear cobalt complex in **30** via C–H···F and Type 1 F···F interactions. The amino groups are projected towards the empty channel.....209

Figure V.3 The molecular complex unit in **32** is identical to **30** and **31** except for the ligand.....210

Figure V.4 Supramolecular aggregation of the trinuclear cobalt complex in **32** through C–H···F and Type 1 F···F interactions. The amino groups are projected towards the empty channel and remain silent.....211

Figure V.5 Molecular Hirshfeld surface shape index for the solids (a) 30 , (b) 31 , (c) 32 and (d) 33	219
Figure V.6 Resolved fingerprint plots for the solids (a-d) 30 , (e-h) 31 , (i-l) 32 and (m-p) 33 in F···F, C···H, F···H and H···H interactions.....	220
Figure V.7 FTIR spectra of the solids 30 to 33 in the range 1000-2000 cm ⁻¹	221
Figure V.8 TG curves for the solids 30-33	223
Figure V.9 A comparison of the binding affinity of solids 30-33 and <i>ffa</i> for BSA.....	225
Figure V.10 $\chi_{\text{M}}T$ versus T plots of solids 30 and 32	227

List of Tables

Table I.1 Selected noncovalent interactions. (Adapted from reference 4).....	6
Table I.2 Properties of Hydrogen bonds. (Adapted from reference 2).....	7
Table I.3 Variation of important physical and chemical properties which can be different for crystal forms and solvates of the same substance (Adapted from reference 89).	25
Table I.4 % occurrence of functional group in APIs.....	38
Table II.1 Crystallization condition employed for the synthesis of 1-10	63
Table II.2 Crystal structure data and structural refinement of solids 1 to 10	65
Table II.3 A schematic representation of the synthons observed between acid:acid and acid:coformer of the solids 1-10	69
Table II.4 Dominant aggregates observed in the solids 1-10	70
Table II.5 The outcome of solids by <i>pKa</i> difference in between OA, IOA and cofomers...	99
Table III.1 Crystallization condition used for the preparation of sulfa drug based solids identified in the present study and their physical properties.....	109
Table III.2 A combinatorial methodology as applied in the present study to screen for multicomponent solids of SDs with various cofomers.....	110
Table III.3 Crystal structure data and structure refinement of the solids 11 to 18	112
Table III.4 ΔpK_a values of SD based solids forms reported in the present study.....	116
Table III.5 Key hydrogen bond D...A distances found in solids 11 - 18	126
Table III.6 Occurrences of SD–SDs synthons and multicomponent solids based on SDs deposited in the CSD.....	128
Table III.7 The energies for the formation of synthons as shown in Table III.8.....	131

Table III.8 Synthons considered for the calculation of energies as listed in Table 6.....	132
Table III.9 Occurrences of various SD-coformer synthons in the previously reported multicomponent solid forms of SDs with distinct organic cofomers.....	134
Table III.10 Occurrences of various SD-coformer synthons in the previously reported SD based solids and those reported in the present study(red colored), and the type of SD-SD synthons present in the input SDs. Various possible SD-coformer synthons are shown in Table 1 and Scheme 1.	136
Table III.11 Classification of the previously reported SD based solids with various cofomers that do not fit in Table S1 and those with various solvents based on whether or not the cofomer/solvent disrupt the key SD-SD synthon present in the input SD. The reported salts with strong organic and inorganic acids shown in the last column are not considered in the analysis.....	140
Table IV.1 Different types of cofomer and combinations used in this study.....	159
Table IV.2 Crystal data and structure refinement of the solids 19 - 29	163
Table IV.3 Physical properties of solids identified in the present study.....	166
Table IV.4 The outcome of solids by <i>pKa</i> difference in between Nif, Mef and cofomers.....	191
Table IV.5 Torsion angles of Nif and Mef in the free state and in salt/cocrystal form.....	193
Table V.1 Crystal structure data and structure refinement of the solids 30 to 33	206
Table V.2 Selected bond lengths and angles for solids 30 - 33	212
Table V.3 Zinc carboxylate bridged complex reported in the literature having the same coordination mode as in solids 30 - 33	217
Table V.4 Selected stretching vibrations of carboxylato in the solids 30 - 33	222
Table V.5 Magnetic properties of linear, trimeric cobalt clusters.....	228

Abbreviations

1. BCS = Biopharmaceutics classification system
2. OA = Orotic acid
3. IOA = Isoorotic acid
4. *bpee* = 1,2-Bis(4-pyridyl)ethylene
5. *bpe* = 1,2-Bis(4-pyridyl)ethane
6. *bpp* = 1,3-Di(4-pyridyl)propane
7. *2ap* = 2-Amino pyridine
8. *4ap* = 4-Amino pyridine
9. *pip* = Piprazine
10. SDs = Sulfa drugs
11. *smr* = Sulfamerazine
12. *smz* = Sulfamethazine
13. *smx* = Sulfamethoxazole
14. *sdz* = Sulfadiazine
15. *Nif* = Niflumic acid
16. *Mef* = Mefenamic acid
17. *ffa* = Flufenamic acid