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Co-crystallization Attempts of Paracetamol and Amikacin with Organic Boronic Acids

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ABSTRACT

The problems associated with low aqueous solubility and bioavailability are still not overcome by various active pharmaceutical ingredients. Recently, crystal engineering and pharmaceutical cocrystalization have been shown to be beneficial in enhancing pharmaceutical properties of compounds, even if their molecular structures remain unchanged. The objective of the study was to examine the possibility of utilizing certain specific organic boronic acids as co-formers in cocrystalization of the two most common APIs, namely, paracetamol, and amikacin, in search of new compounds that may have more applications in pharmaceutical use. Organic boronic acids were chosen as co-formers based on their distinctive capability to form strong directional hydrogen bonds via the $B(OH)_2$ group, creating a versatile tool to study new crystalline structures with APIs. The crystallization process was carried out with a mixture of phenylboronic acids and substituted phenylboronic acids in varying stoichiometric proportions and paracetamol and amikacin APIs. Slow solution evaporation was used as the basic method of crystallization. The resulting crystals were characterized by single-crystal analysis and thermal analysis regarding formation verification of cocrystals. It was found that despite the presence of various potential acceptor and donor sites in APIs and their predicted compatibility displayed by their structures concerning boronic acids, no new cocrystals could be prepared under various conditions tested throughout the study. The effect has created a method for isolating crystals from original APIs used over time. The obtained results indicate that the formation of pharmaceutical co-crystals with organic boronic acids is API-dependent and is not necessarily successful when favorable intermolecular interaction is expected. There is value in reporting negative results to improve understanding regarding principles for co-crystal designs and future crystal engineering.

KEYWORDS:
Pharmaceutical co-crystals; Co-crystallization; Crystal engineering; Hydrogen bonding; Solubility enhancement.

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1. Introduction

Organic boronic acids can be defined as oxygen-containing trivalent boron compounds in which the boron atom is covalently bonded with one alkyl, vinyl, or aryl group in a simple carbon and boron (σ C–B) covalent bond. The two valencies of boron remain occupied with hydroxyl groups, and these groups result in the acidic properties of the boronic acid compounds. Moderate Lewis acidity, chemical instability, and hydrogen-bonding properties altogether provide a unique combination in boronic acids and their aqueous solutions, making them promising reagents in contemporary chemistry. Although they were originally known for their applications in organic synthesis and their use in medicinal chemistry, they were also widely explored in the Suzuki-Miyaura cross-coupling reaction[1, 2] and as a basis for a glucose-based biosensor for diabetic diagnostics[3-6]. Based on these considerations, it might also be inferred that they can also be explored in pharmaceutical crystal engineering. Specifically, the $B(OH)_2$ moiety acts as a powerful and directional supramolecular synthon, offering a versatile platform for exploring unconventional hydrogen-bonding motifs with drug molecules.

Low aqueous solubility and bioavailability remain a major drawback for numerous APIs, resulting in a reduction in efficacy and irregular absorption[7, 8]. The advantage of crystal engineering has been realized in recent years as an effective strategy in the solid state with respect to improving the associated difficulties of APIs without modifying their chemical entity[9]. Of these methods, pharmaceutical co-crystallization has shown promise in enhancing solubility, related dissolution rates, and physicochemical properties of APIs[10]. Recent studies (2020–2023) have integrated high-throughput screening and computational prediction tools to accelerate the identification of viable co-formers[11-13].

Organic acids are some of the most frequently used co-formers in co-crystallization in pharmaceuticals because of their highly favorable and reliable hydrogen bond-donor properties[14]. Within this context, organoboronic acids are recently gaining attention as novel, alternative co-formers. Indeed, as revealed by experiments and previous investigations in this field as well as by our research, it was found that 4-halophenylboronic acids are able to co-crystallize successfully with various pharmaceutical molecules, such as acyclovir, caffeine, nitrofurazone, theophylline, and proline, under optimized solvent and stoichiometric conditions[15]. These results clearly confirm that boronic acids are able to act as efficient co-formers, although it seems to be system-dependent in many cases.

Nevertheless, in spite of these encouraging cases, the relevance of organic boronic acids as co-formers has not been explored adequately in relation to a wide range of APIs with significant therapeutic value and applications in modern health care. Paracetamol and amikacin can be regarded as two of the widely prescribed pharmaceutical agents, and it has been suggested that their therapeutic efficacy could be hampered due to unfavorable conditions in their solid states, including solubility and bioavailability. Specifically, paracetamol exhibits limited compressibility and moderate aqueous solubility in high-dose forms, while amikacin, a highly polar aminoglycoside, suffers from significant hygroscopicity and limited membrane permeability[16, 17]. Though a significant number of formulation approaches have been explored in an attempt to improve the bioavailability of amikacin, including permeability and modern methods of drug delivery, much work has not been carried out based on its potential possibility of co-crystallization with a range of organic boronic compounds. Furthermore, reporting negative results is increasingly recognized as a significant contribution to pharmaceutical sciences, aiding the refinement of predictive models and preventing redundant experimental efforts[12]. Thus, this work proposes to assess the co-crystallization potentiality of paracetamol and amikacin with chosen organic boronic acids while shedding light on the underlying factors hindering co-crystallization and related aspects of disseminating negative results in the arena of pharmaceutical crystal engineering.

2. Materials and Methods.

Based on previously reported pharmaceutical co-crystals, structures available in the Cambridge Structural Database (CSD), and plausible hydrogen-bonding interactions predicted by crystal engineering principles, we carried out crystallization experiments using selected active pharmaceutical ingredients (APIs) and various organic boronic acids. X-ray structural analysis was employed as a primary method for the characterization of the obtained co-crystals.

2.1. Materials.

Paracetamol (of high purity, ≥99%) and amikacin sulfate (of high purity, ≥98%) were taken from the supplier, Sigma-Aldrich, without processing. The other organic boronic acids that acted as the co-forming materials were phenylboronic acid, 3-carboxyphenylboronic acid, 4-chlorophenylboronic acid, and 4-carboxyphenylboronic acid (of high purity). Methanol, ethanol, and distilled water of analytical grade (Merck) were used as solvents in all crystallization experiments. The solvents complied with the standards of the European Pharmacopoeia (Ph. Eur. Reagent Grade R)[18].

2.2. Crystallization experiments.

The crystallization experiments have been designed based upon the earlier reported pharmaceutical co-crystals, crystal structures documented in the Cambridge Structural Database (CSD), and predicted hydrogen bonding patterns based upon crystal engineering principles.

The active pharmaceutical ingredients and the boronic acids were prepared with 1:1 and 1:2 ratios. These mixtures were dissolved using appropriate solvents with constant stirring at room temperature until clear solutions were formed.

The co-crystallization attempts were done by the slow evaporation method, which ranks as one of the most popular methods used in the growth of small molecules[19]. Slow evaporation was specifically prioritized over high-throughput or mechanical methods, such as slurry conversion or grinding, to facilitate the growth of high-quality single crystals suitable for definitive structural characterization by SCXRD. The resultant solutions were then left to evaporate at a stable ambient temperature of 23 ± 2°C for 7 to 10 days. These conditions were maintained in order to keep the evaporation rate very slow and undisturbed, which might be necessary for the possible nucleation of co-crystalline phases. The control experiment aimed at crystallizing each API separately under similar conditions.

2.3. Methods.

Single crystal X-ray diffraction (SCXRD) was used, to check for the possibility of co-crystal formation. Differential scanning calorimetry (DSC) was used to look for thermal phenomena that would signal the

Table 1. Summary of experimental co-crystallization conditions and outcomes.

API	Co-former	Ratio (API:CF)	Solvent	Method	Outcome
Paracetamol	PBA, 3-CPBA, 4-CPBA, 4-ClPBA	1:1, 1:2	MeOH, EtOH	Slow Evap. (RT)	Starting Materials
Amikacin	PBA, 3-CPBA, 4-CPBA, 4-ClPBA	1:1, 1:2	H_2O, H_2O/ MeOH mixture	Slow Evap. (RT)	Starting Materials

Note: PBA: phenylboronic acid; 3-CPBA: 3-carboxyphenylboronic acid; 4-CPBA: 4-carboxyphenylboronic acid; 4-ClPBA: 4-chlorophenylboronic acid; MeOH: methanol; EtOH: ethanol; RT: room temperature.

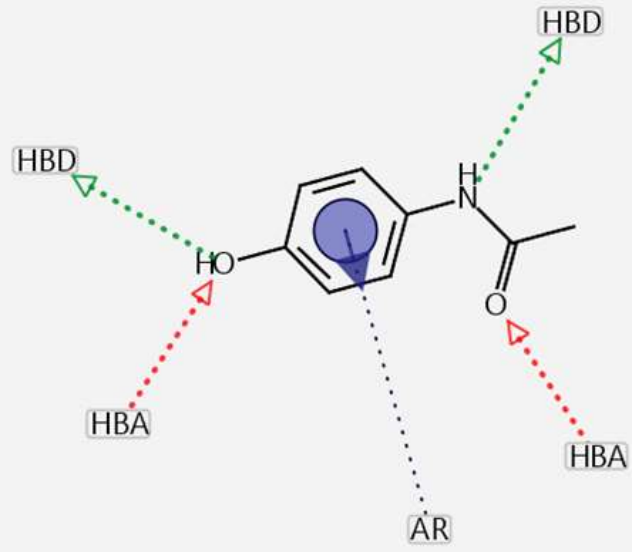


Figure 1. *Potential donor–acceptor interactions in the paracetamol molecule.*

existence of new crystalline forms. All the experiments were performed in triplicate to ensure their repeatability. Under the experimental conditions mentioned, no co-crystals of paracetamol/amikacin and the studied organic boronic acids could be isolated, as revealed by SCXRD and DSC analysis.

3. Results and Discussion.

A systematic screening for potential pharmaceutical co-crystals of paracetamol and amikacin with selected organic boronic acids was performed under various conditions, the results of which are summarized in Table 1**.**

3.1. Paracetamol.

Paracetamol was selected due to its widespread use and relevance in pharmaceutical applications. Two potential hydrogen-bonding interaction sites with organic boronic acids were considered (Fig.1), but only crystals of the starting material were obtained.

The search on the Cambridge Structural Database (CSD) yielded a large set of paracetamol crystal structures, including HUMJEE, HXACAN04, HXACAN08, and HXACAN29, to name a few. If the duplicates are considered, the number of records is nearly doubled. For example, HUMJEE is a monohydrate[20], while HXACAN04, HXACAN08, and HXACAN29 represent polymorphic forms crystallizing in the space groups $P2_1/a$ (or $P2_1/n$), $Pca2_1$, and Pbca, respectively[21-23]. Comparison of intermolecular interactions among these polymorphs shows conservation of classical hydrogen bonds, whereas the observed π-interactions (Fig. 2) correspond to three of the four interaction types predicted (Fig. 3).

3.2. Amikacin.

Considering the large number of potential hydrogen-bond donor and acceptor sites present in the amikacin molecule (Fig. 4), together with the availability of only a single reported crystal structure in the Cambridge Structural Database (GABFOE)[24], amikacin was selected as a particularly challenging

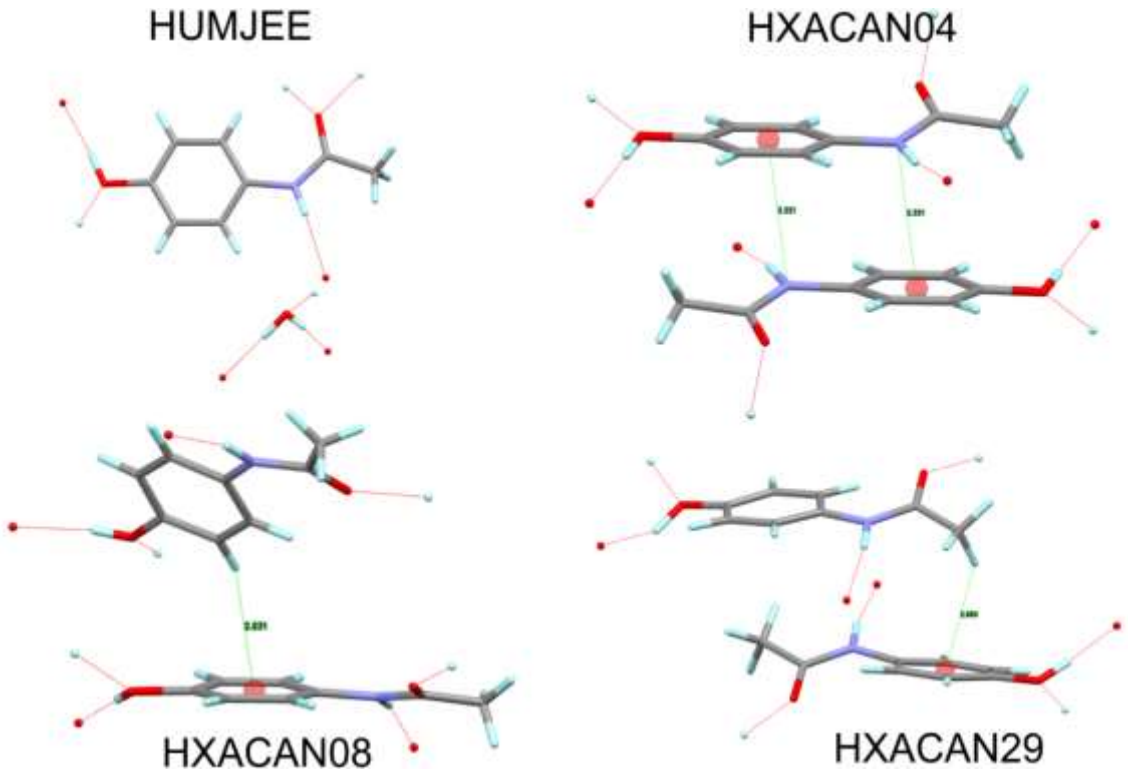


Figure 2. *Observed intermolecular interactions in the paracetamol molecule across the four polymorphic modifications.*

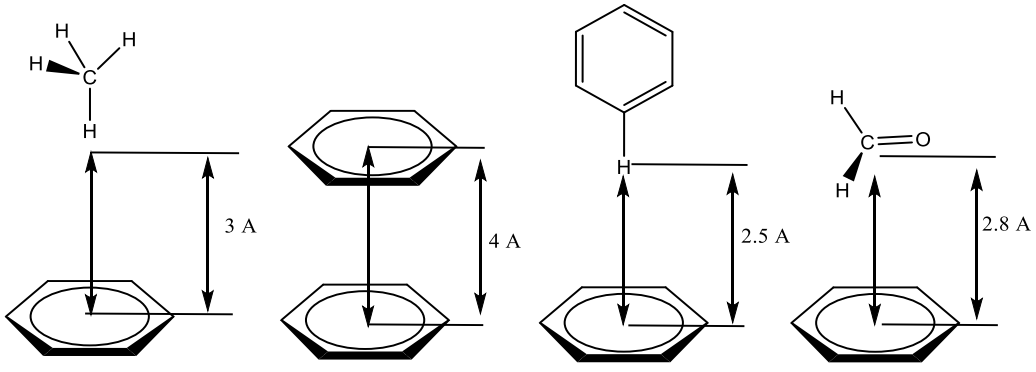


Figure 3. *Possible different geometries of weak C–H...π and π...π interactions.*

active pharmaceutical ingredient for co-crystallization studies. Although two plausible interaction motifs were predicted based on crystal engineering considerations, experimental crystallization attempts resulted exclusively in crystals of the starting material.

3.3. Organic boronic acids.

On the ground of known reproducibility of hydrogen bonding and other weak intermolecular interactions commonly observed in carboxylic acids, boronic acids and related organic fragments the plausible interaction patterns with the selected boronic acids were predicted (Fig. 5). The phenylboronic acid, 3-carboxyphenylboronic acid, 4-carboxyphenylboronic acid and 4-chlorophenylboronic acid were studied as co-formers. Among them the phenylboronic acid is one of the best known systems and its crystal structure has been described in the literature[25, 26]. In its solid state, it shows a number of expected weak interactions, such as CH…π.

3.4. Analysis of intermolecular interactions and co-crystallization challenges.

Despite the expected intermolecular interactions and dedicated attempts in terms of experimental screening, no new co-crystals could be isolated under the tested conditions for both paracetamol and amikacin. Several underlying factors likely contribute to these negative outcomes. Firstly, steric and electronic factors must be considered; the bulky phenyl rings of the organic boronic acids may impose significant steric hindrance, preventing the efficient molecular packing required for a stable heterosynthon with paracetamol or amikacin[12, 13].

Secondly, competitive crystallization kinetics and solvent effects play a decisive role. In our experiments using methanol and ethanol, the strong self-association of boronic acids via $B(OH)_2$ homosynthons (dimers) appears to be thermodynamically more favorable than the formation of co-crystal lattices. This is further complicated by the robust lattice energy of the pure APIs, which outcompetes the

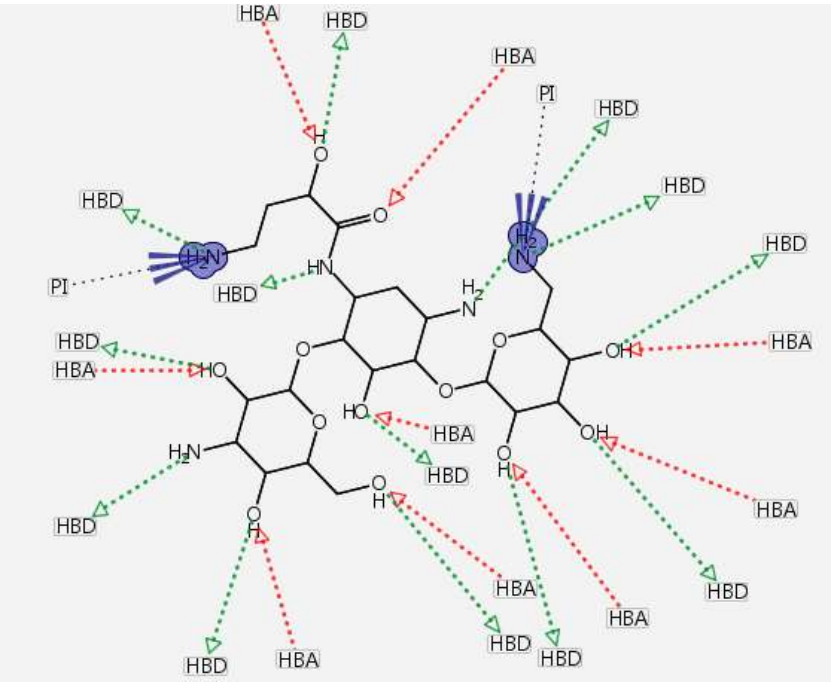
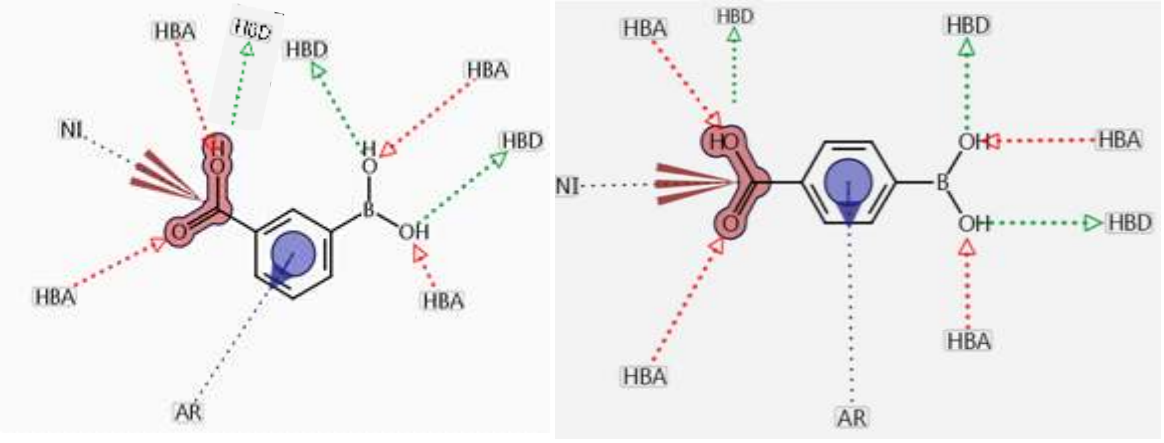
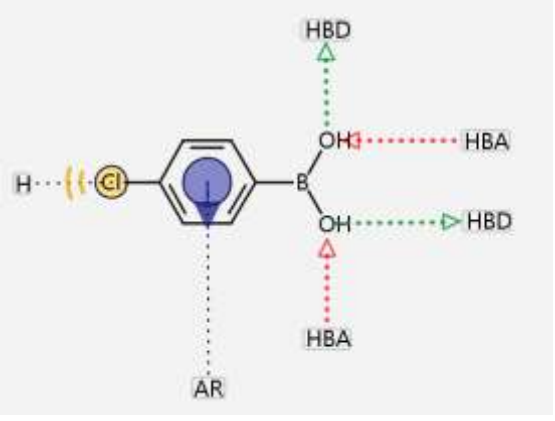


Figure 4. *Potential donor–acceptor interactions in the amikacin molecule.*



a) 3-carboxyphenylboronic acid b) 4-carboxyphenylboronic acid



c) 4-chlorophenylboronic acid

Figure 5. *Representation of potential interactions in the organoboron acids used.*

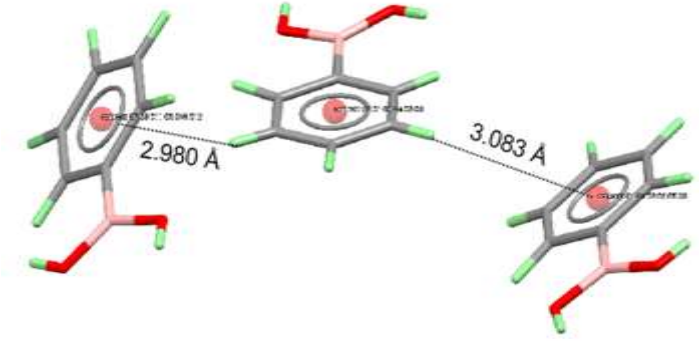


Figure 6. *Observed CH…π weak interactions in phenylboronic acid.*

potential energy gain from a new co-crystal phase under slow evaporation conditions[11, 13]. While 3-carboxyphenylboronic acid has been shown to successfully co-crystallize with theophylline via robust O–H...O and N–H...N hydrogen-bonded layers[27], the structural complexity and specific hydrogen-bonding topology of paracetamol and amikacin likely present a higher thermodynamic barrier to such assembly.

Future research could explore alternative approaches, such as liquid-assisted grinding or slurry methods in different solvent systems, to overcome these kinetic barriers[12]. Additionally, molecular modeling and hydrogen bond propensity analysis could be utilized in future screenings to better rationalize the selection of co-formers[11].

These observations prove that the application of organic boronic acids as co-formers in pharmaceutical co-crystal formation is strongly dependent on specific systems and that it is generally not possible to predict in advance the application prospects of boronic acids as co-formers in co-crystal formation. The present study serves to illustrate the limitations in terms of boronic acids as co-formers and also underlines the value of negative screening studies.

4. Conclusion.

Organic boronic acids were explored as co-formers for co-crystallization with paracetamol and amikacin by a strategy combining solid-state analysis with crystallization experiments. Although numerous hydrogen-bond donor and acceptor sites are available and favorable interaction motifs are considered, no new co-crystalline phases have been obtained. These results point out the challenges in certain active pharmaceutical ingredients to form co-crystals with organic boronic acids and prove that favorable interaction models do not necessarily lead to co-crystallization.

The reporting of such negative results provides value to the scientific community by establishing the empirical boundaries of boronic acid-based co-crystallization and thereby eliminating the need for wasteful and possibly redundant experimental screening efforts. Additionally, the results of this study hold the potential to be used as essential data to improve the development of computational models and machine learning models.

Future research directions include the study of more complex ternary systems or the use of alternative crystallization techniques such as liquid-assisted grinding, which may help bypass the kinetic issues observed in the study. Additionally, the use of the above-described techniques of molecular modeling and hydrogen bond propensity analysis has the potential to provide a rationalized approach to the selection of co-formers of difficult-to-crystallize APIs such as paracetamol and amikacin.

References:

1. Miyaura N., Suzuki A. Stereoselective synthesis of arylated (E)-alkenylboronates via the palladium-catalyzed cross-coupling reaction of (E)-1-alkenylboronates with aryl halides. *Chem. Commun.* 19, 866-867, 1979.
2. Miyaura N., Yamada K., Suzuki A. A new stereospecific synthesis of unsymmetrical (E, E)-1,3-dienes by the palladium-catalyzed reaction of (E)-1-alkenylboronates with (E)-1-alkenyl halides. *Tetrahedron Lett.* 20, 3437-3440, 1979.
3. Tong A.J., Yamauchi A., Hayashita T., Teramae N. Boronic acid-fluorophore conjugates with high sensitivity and selectivity for glucose in water at physiological pH. *Anal. Chem.* 73, 1530-1536, 2001.
4. Camara J.N., Suri J.T., Cappuccio F.E., Wessling R.A., Singaram B. Boronic acid-based glucose sensors. *Tetrahedron Lett.* 43, 1139-1141, 2002.
5. Zenkl G., Klimant I. Optical sensors for the detection of D-glucose based on fluorescence quenching. *Sens. Actuators B Chem.* 139, 125-131, 2009.

6. Wu X., Li H., Vilaivan T., James T.D. Selective sensing of saccharides using a boronic acid based fluorescent sensor. *Chem. Commun.* 1, 52-54, 2007.
7. Childs S.L., Zalelle N.R., Stahly G.P., Stahly B.C. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. *CrystEngComm* 6, 266-271, 2004.
8. Bolla G., Nangia A. Pharmaceutical cocrystals: walking the line between academic curiosity and industrial necessity. *Chem. Commun.* 52, 8342-8360, 2016.
9. Almarsson Ö., Zaworotko M.J. Crystal engineering of the pharmaceutical solid state. *Chem. Commun.* 17, 1889-1896, 2004.
10. Childs S.L., Stahly G.P., Park A. The non-equivalence of solvates and cocrystals. *J. Am. Chem. Soc.* 129, 6996-6997, 2007.
11. Seyedhi S., et al. Computational Screening of Coformers for Pharmaceutical Co-crystals: Recent Advancements. *Cryst. Growth Des.* 22, 2500-2515, 2022.
12. Mura P. Analytical techniques for the solid-state characterization of pharmaceutical cocrystals. *J. Pharm. Biomed. Anal.* 113030, 2020.
13. Yan Y., et al. Machine learning in pharmaceutical cocrystals: Predictability and insights. *Int. J. Pharm.* 642, 123163, 2023.
14. Aakerøy C.B., Forbes S., Desper J. Using supramolecular synthesis to drive the formation of pharmaceutical cocrystals. *CrystEngComm* 12, 22-24, 2010.
15. Dyulgerov V., Sbirkova-Dimitrova H., Iliev K., Shivachev B. The co-crystallization of 4-halophenylboronic acid with aciclovir, caffeine, nitrofurazone, theophylline, and proline in function of weak interactions. *Crystals* 13, 468, 2023.
16. Savjani K.T., Gajjar A.K., Savjani J.K. Drug solubility: Importance and enhancement techniques. *ISRN Pharm.* 195727, 2012.
17. Sweetman S. (2011). *Martindale: The Complete Drug Reference* 37th ed. London, Pharmaceutical Press.
18. European Pharmacopoeia (Ph. Eur.) [online]. 11th Edition. Strasbourg, France; Council of Europe, 2022 [cited 16 February 2026]. Available from Internet: www.edqm.eu.
19. Brittain H.G. (2009). *Polymorphism in Pharmaceutical Solids* 2nd ed. New York, Informa Healthcare, pp. 1-20.
20. Parkin S., Barr G., Dong W., Faber J.S., Simpson J., Wilson C.C., et al. Monohydrate of paracetamol. *Acta Crystallogr. B* 58, 134-141, 2002.
21. Naumov P., Jovanovski G., Drew M.G.B., Ng S.W. Polymorphism of paracetamol. *J. Mol. Struct.* 455, 45-53, 1998.
22. Nichols G., Frampton C.S. Physicochemical characterization of the orthorhombic polymorph of paracetamol crystallizing in the space group $Pca2_1$. *J. Pharm. Sci.* 87, 684-693, 1998.
23. Perrin M.A., Neumann M.A., Elmaleh H., Zaske L. Crystal structure determination of paracetamol form III from powder X-ray diffraction data. *Chem. Commun.* 25, 3129-3131, 2009.
24. Bau R., Tsyba I. Crystal structure of amikacin. *J. Am. Chem. Soc.* 121, 11215-11219, 1999.
25. Rettig S.J., Trotter J. Crystal structure of phenylboronic acid, C6H5B(OH)2. *Can. J. Chem.* 55, 3071-3075, 1977.
26. Cyrański M.K., Dobrzańska L., Połomska-Buczek M., Krygowski T.K. Phenylboronic acid: Experimental and theoretical study on the aromaticity of the ring and on the OHO hydrogen bonds. *J. Mol. Struct.* 874, 185-191, 2008.
27. Dyulgerov V., Nikolova R.P., Dimova L.T., Shivachev B.L. 3-Carboxyphenylboronic acid–theophylline (1/1). *Acta Crystallogr. Sect. E: Struct. Rep. Online* 68, o2250, 2012.