**Evaluating hydrogen-bond propensity, hydrogen-bond coordination and hydrogen-bond energy as tools for predicting the outcome of attempted co-crystallizations**

Nandini Sarkar and Christer B. Aakeröy\*,

Department of Chemistry, Kansas State University, Manhattan, KS 66506-0401.Manhattan, KS 66506-0401.

\*aakeroy@ksu.edu

Table of Contents

[1. Nevirapine 2](#_Toc21458498)

[1.1. Hydrogen bond propensity (HBP) calculations 2](#_Toc21458499)

[1.2. Hydrogen bond coordination (HBC) calculations 2](#_Toc21458500)

[1.3. Hydrogen bond energy (HBE) calculations 3](#_Toc21458501)

[2. Diclofenac 4](#_Toc21458502)

[2.1. Hydrogen bond propensity (HBP) calculations 4](#_Toc21458503)

[2.2. Hydrogen bond coordination (HBC) calculations 4](#_Toc21458504)

[2.3. Hydrogen bond energy (HBE) calculations 6](#_Toc21458505)

# **1. Nevirapine**

## 1.1. Hydrogen bond propensity (HBP) calculations

|  |  |  |  |
| --- | --- | --- | --- |
| Co-formers | Homomeric interactions | Heteromeric interactions | =Hetero-Homo |
| Malonic acid | 0.43 | 0.49 | 0.06 |
| Glutaric acid | 0.37 | 0.48 | 0.11 |
| Benzoic acid | 0.29 | 0.39 | 0.1 |
| Maleic acid | 0.37 | 0.43 | 0.06 |
| Hippuric acid | 0.34 | 0.39 | 0.05 |
| 4-hydroxybenzoic acid | 0.28 | 0.43 | 0.15 |
| Cinnamic acid | 0.33 | 0.4 | 0.07 |
| Mandelic acid | 0.29 | 0.4 | 0.11 |
| Tartaric acid | 0.37 | 0.44 | 0.07 |
| Ferulic acid | 0.34 | 0.42 | 0.08 |
| Gallic acid | 0.27 | 0.44 | 0.17 |
| Citric acid | 0.32 | 0.44 | 0.12 |
| Urea | 0.98 | 0.93 | -0.05 |
| Oxalic acid | 0.25 | 0.28 | 0.03 |

## 1.2. Hydrogen bond coordination (HBC) calculations

Aromatic acids



|  |
| --- |
| Homomeric interactions (API--API) |
| Atom (D/A) | =0 | =1 | =2 | =3 |
| N4 (D) | 0.51 | 0.49 | 0.00 | 0.00 |
| N18 (A) | 0.90 | 0.09 | 0.01 | 0.00 |
| N9 (A) | 0.90 | 0.09 | 0.01 | 0.00 |
| O6 (A) | 0.29 | **0.67** | 0.04 | 0.00 |
| Homomeric interactions (co-former—co-former) |
| O29 (D) | 0.01 | **0.95** | 0.04 | 0.00 |
| O28 (A) | 0.45 | 0.51 | 0.03 | 0.00 |
| O29 (A) | 0.93 | 0.07 | 0.00 | 0.00 |

Aliphatic acids



|  |
| --- |
| Homomeric interactions (API--API) |
| Atom (D/A) | =0 | =1 | =2 | =3 |
| N4 (D) | 0.51 | 0.49 | 0.00 | 0.00 |
| N18 (A) | 0.91 | 0.08 | 0.01 | 0.00 |
| N9 (A) | 0.91 | 0.08 | 0.01 | 0.00 |
| O6 (A) | 0.32 | **0.64** | 0.03 | 0.00 |
| Homomeric interactions (co-former—co-former) |
| O27 (D) | 0.00 | **0.95** | 0.04 | 0.00 |
| O29 (D) | 0.00 | 0.95 | 0.04 | 0.00 |
| O26 (A) | 0.50 | 0.47 | 0.03 | 0.00 |
| O27 (A) | 0.93 | 0.07 | 0.00 | 0.00 |
| O28 (A) | 0.49 | 0.47 | 0.03 | 0.00 |
| O29 (A) | 0.91 | 0.07 | 0.03 | 0.00 |

## 1.3. Hydrogen bond energy (HBE) calculations





|  |  |  |  |
| --- | --- | --- | --- |
| Co-formers | Homomeric interactions | Heteromeric interactions | =Hetero-HomoKJ/ mol |
| Malonic acid | 24.23 | 29.19 | 4.96 |
| Glutaric acid | 24.41 | 27.31 | 2.91 |
| Benzoic acid | 16.56 | 16.90 | 0.36 |
| Maleic acid | 18.69 | 21.56 | 2.87 |
| Hippuric acid | 30.91 | 33.09 | 2.18 |
| 4-hydroxybenzoic acid | 28.29 | 28.64 | 0.35 |
| Cinnamic acid | 17.95 | 17.93 | -0.02 |
| Mandelic acid | 20.56 | 24.50 | 3.94 |
| Tartaric acid | 21.34 | 39.4 | 18.06 |
| Ferulic acid | 21.97 | 27.00 | 5.03 |
| Gallic acid | 28.07 | 38.60 | 10.53 |
| Citric acid | 28.00 | 35.05 | 7.05 |
| Urea | 32.51 | 48.47 | 15.96 |
| Oxalic acid | 19.63 | 30.98 | 11.35 |

# **2. Diclofenac**

## 2.1. Hydrogen bond propensity (HBP) calculations

|  |  |  |  |
| --- | --- | --- | --- |
| Co-formers | Homomeric interactions | Heteromeric interactions | =Hetero-Homo |
| 3-aminopyridine | 0.87 | 0.64 | -0.23 |
| 2-aminopyridine | 0.69 | 0.82 | 0.13 |
| 2-amino-4,6-dimethylpyrimidine | 0.76 | 0.81 | 0.05 |
| 2-amino-4-chloro-6-methylpyrimidine | 0.82 | 0.82 | 0 |
| 3-hydroxypyridine | 0.73 | 0.75 | 0.02 |
| 2-amino-4-hydroxy-6-methylpyrimidine | 0.81 | 0.83 | 0.02 |
| 2-aminopyrimidine | 0.82 | 0.71 | -0.11 |
| 2-amino-5-chloropyridine | 0.69 | 0.81 | 0.12 |
| 4-chloro-2,6-diaminopyrimidine | 0.81 | 0.78 | -0.03 |
| 3,5-dimethylpyrazole | 0.36 | 0.3 | -0.06 |
| 2-chloropyrimidine | 0.51 | 0.55 | 0.04 |
| pyrazole | 0.56 | 0.53 | -0.03 |
| 3,5-dimethyl-4-chloropyrazole | 0.37 | 0.32 | -0.05 |
| 4-iodo-3,5-dimethylpyrazole | 0.41 | 0.32 | -0.09 |
| 2-amino-3,5-dibromopyridine | 0.73 | 0.82 | 0.09 |
| 4-bromopyraole | 0.52 | 0.45 | -0.07 |
| 4-iodopyrazole | 0.69 | 0.64 | -0.05 |

## 2.2. Hydrogen bond coordination (HBC) calculations

Pyridine group of co-formers



|  |
| --- |
| Homomeric interactions (API--API) |
| Atom (D/A) | =0 | =1 | =2 | =3 |
| N19 (D) | 0.43 | 0.56 | 0.00 | 0.00 |
| O9 (D) | 0.10 | **0.87** | 0.03 | 0.00 |
| N19 (A) | 1.0 | 0.00 | 0.00 | 0.00 |
| O11 (A) | 0.01 | 0.52 | 0.45 | 0.02 |
| O9 (A) | 0.93 | 0.07 | 0.00 | 0.00 |
| Homomeric interactions (co-former—co-former) |
| N8 (D) | 0.02 | **0.30** | 0.60 | 0.08 |
| N6 (A) | 0.03 | 0.81 | 0.16 | 0.00 |
| N8 (A) | 0.98 | 0.02 | 0.00 | 0.00 |

Pyrimidine group of co-formers



|  |
| --- |
| Homomeric interactions (API--API) |
| Atom (D/A) | =0 | =1 | =2 | =3 |
| N20 (D) | 0.38 | 0.61 | 0.01 | 0.00 |
| O10 (D) | 0.04 | **0.93** | 0.03 | 0.00 |
| N20 (A) | 1.0 | 0.00 | 0.00 | 0.00 |
| O10 (A) | 0.95 | 0.05 | 0.00 | 0.02 |
| O12 (A) | 0.08 | 0.73 | 0.18 | 0.01 |
| Homomeric interactions (co-former—co-former) |
| N9 (D) | 0.01 | **0.19** | 0.73 | 0.07 |
| N6 (A) | 0.17 | 0.79 | 0.03 | 0.00 |
| N9 (A) | 0.98 | 0.02 | 0.03 | 0.00 |
| N2 (A) | 0.16 | 0.80 | 0.03 | 0.00 |

Pyrazole group of co-formers



|  |
| --- |
| Homomeric interactions (API--API) |
| Atom (D/A) | =0 | =1 | =2 | =3 |
| N19 (D) | 0.41 | 0.58 | 0.01 | 0.00 |
| O9 (D) | 0.09 | **0.88** | 0.03 | 0.00 |
| N19 (A) | 1.0 | 0.00 | 0.00 | 0.00 |
| O11 (A) | 0.01 | 0.56 | 0.41 | 0.02 |
| O9 (A) | 0.93 | 0.07 | 0.00 | 0.00 |
| Homomeric interactions (co-former—co-former) |
| N1 (D) | 0.01 | **0.82** | 0.16 | 0.00 |
| N2 (A) | 0.09 | 0.91 | 0.00 | 0.00 |

## 2.3. Hydrogen bond energy (HBE) calculations

|  |  |  |  |
| --- | --- | --- | --- |
| Co-formers | Homomeric interactions | Heteromeric interactions | =Hetero-HomoKJ/ mol |
| 3-aminopyridine | 19.73 | 22.07 | 2.34 |
| 2-aminopyridine | 16.18 | 17.57 | 1.39 |
| 2-amino-4,6-dimethylpyrimidine | 18.35 | 18.37 | 0.02 |
| 2-amino-4-chloro-6-methylpyrimidine | 17.60 | 17.60 | 0.00 |
| 3-hydroxypyridine | 21.41 | 21.10 | -0.31 |
| 2-amino-4-hydroxy-6-methylpyrimidine | 19.95 | 19.97 | 0.027 |
| 2-aminopyrimidine | 18.29 | 18.28 | -0.01 |
| 2-amino-5-chloropyridine | 14.50 | 15.20 | 0.70 |
| 4-chloro-2,6-diaminopyrimidine | 20.13 | 19.40 | -0.72 |
| 3,5-dimethylpyrazole | 20.67 | 21.83 | 1.17 |
| 2-chloropyrimidine | 14.50 | 15.20 | 0.70 |
| pyrazole | 19.75 | 20.12 | 0.37 |
| 3,5-dimethyl-4-chloropyrazole | 20.67 | 21.83 | 1.17 |
| 4-iodo-3,5-dimethylpyrazole | 20.67 | 21.83 | 1.17 |
| 2-amino-3,5-dibromopyridine | 12.15 | 12.74 | 0.59 |
| 4-bromopyraole | 19.75 | 20.12 | 0.37 |
| 4-iodopyrazole | 19.75 | 20.12 | 0.37 |