Classical intermolecular hydrogen bonding motifs of heterocyclic *rac*-2-amino-3-carbonitrile derivatives: Linking Hirshfeld surface analysis, ctDNA binding affinity and molecular docking

Sizwe J Zamisa[2], Precious Ngubane[1] Adesola Adeleke[1], Sreekantha B Jonnalagadda, Bernard Omondi [1,2],

[1] *School of Chemistry and Physics, University of KwaZulu-Natal, Private Bag X54001, Durban, 4000, South Africa*
[2] *School of Chemistry and Physics, University of KwaZulu-Natal, Private Bag X01, Pietermaritzburg, South Africa*
Corresponding author e-mail address: owaga@ukzn.ac.za

1. Introduction

DNA has become one of the primary targets in many drug design and discovery protocols based on its primary functions which include replication and transcription [1]. A malfunction of the two functions would lead to genome instability which may result in Down syndrome (trisomy 21) [2], diabetes [3] and human cancer [4]. DNA-targeted drugs aim to modulate the core DNA functions via various interactions which can be covalent or noncovalent [5]. Our interest is in the noncovalent interactions which include intercalation, electrostatic, and groove binding [6]. In this study, a set of derivatives of heterocyclic *rac*-2-amino-3-carbonitrile are used. The presence of polar functional groups can lead to various intermolecular interactions with DNA. These compounds also have chiral centers which are also known to influence interactions with DNA [7]. Working with compounds as racemic mixtures, correlation between the *in silico* and experimental DNA binding affinities can be tricky, and here we attempt to use crystal engineering approaches to link the two.

2. Results

Crystal structure analysis, show that different hydrogen bonding motifs are possible for the *rac*-2-amino-3-carbonitriles, chains and rings. Noncovalent interactions plots and molecular pairwise energy calculations were all used to determine the inherent properties of classical hydrogen bonding motifs with the rings having stronger molecular pairwise interactions compared to the chains. Hirshfeld surface analysis gave the contribution of reciprocal N…H and O…H contacts as 14.0-15.3% and 11.5-14.0% which were attributed to N—H…N and N—H…O hydrogen bonds, respectively. Investigations into the ctDNA binding ability of *rac*-2-amino-3-carbonitriles via a spectroscopic absorption technique revealed that all compounds have good ctDNA binding affinities with intrinsic binding constants (K_b) of 8.00 x 10^4 - 5.00 x 10^5 M^{-1}. Molecular docking studies were performed on each *R*- and *S*-enantiomer of the racemic compounds. Based on the calculated free energy change of the best docked pose, it was found that the compounds interact with B-DNA via a minor groove binding mode and that the docking of the *S*-enantiomers are more favourable than that of their enantiomeric counterparts for most compounds. The ratio of calculated free energy changes for the docking of the *R* enantiomer to that of the *S* enantiomer ($^{\Delta G_r}/_{\Delta G_s}$) including and the ratio of the contribution of reciprocal N…H contacts to that of reciprocal O…H contacts towards the Hirshfeld surface ($R_{(N...H):(O...H)}$) were found to correlate with experimental K_b values as shown in Figures 1 and 2, respectively.

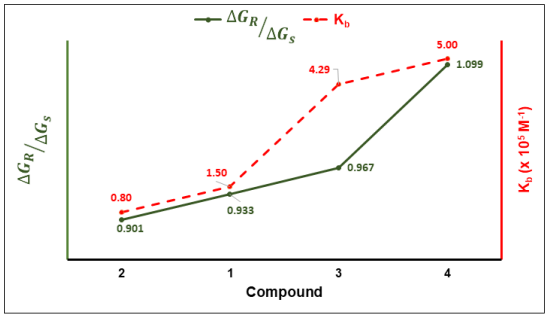

Fig. 1: Line graphs of K_b and $^{\Delta G_r}/_{\Delta G_s}$

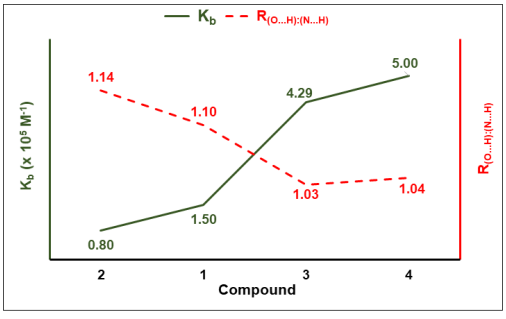

Fig. 2: Line graphs of experimental K_b and $R_{(N...H):(O...H)}$.

3. References

[1] M. K. Zeman and K. A. Cimprich, *Nat. Cell Biol.*. **16** (2014) 2-9.
[2] S. Rabinowicz, A. Lev, Y. N. Lee, D. Machnes-Maayan, U. Katz, A. Vardi, D. Mishali and R. Somech, *Pediatr. Res.*. **89** (2021) 102-109.
[3] A. A. Leontovich, R. V. Intine and M. P. Sarras, Jr., *J. Diabetes Res.* **2016** (2016) 2860780.
[4] N. Pillay, R. Brady, M. Dey, R. D. Morgan and S. S. Taylor, *Prog. Biophys. Mol. Biol.* **163** (2021) 160-170.
[5] K. Gurova, *Future Oncol* **5** (2009) 1685-1704.

[6] D. Sarkar, P. Das, S. Basak and N. Chattopadhyay, *J. Phys. Chem. B* **112** (2008) 9243-9249.
[7] X. Qu, J. O. Trent, I. Fokt, W. Priebe and J. B. Chaires, *Proc. Natl. Acad. Sci. U.S.A.* **97** (2000) 12032-12037.