Original Article
Bulletin of Pure and Applied Sciences.
Chemistry , Vol.42 C, No.1
January-June 2023: P.41-45

http://www.bpasjournals.com/chemistry
DOI: 10.48165/bpas.2023.42C.1.7
Print version ISSN 0970 4620
Online version ISSN 2320 320X

DNA recognitions of Benzimidazole based Bendamustine, Albendazole, and Mebendazole: a Molecular Docking Study

[1]Uzma Khan and [2]Souvik Sur*

Author Affiliations
[1]Department of Chemistry, Faculty of Engineering, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh 244001, India,
[2]Research and Development Center, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh 244001, India

***Corresponding Author**
Souvik Sur, Research and Development Center, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh 244001, India
E-mail: drsouvik.engineering@tmu.ac.in

Received on 25.02.2023, Revised on 03.05.2023, Approved on 11.05.2023, Accepted on 19.05.2023, Published on 20.06.2023

ABSTRACT
A few very well-known marketed drugs-Bendamustine, Albendazole, and Mebendazole are studied whether the drugs can bind with two different oligonucleotides or not. Molecular docking study was employed to find the capability of these drugs towards two entirely different DNA sequences. Due to the three-dimensional structures; those drugs are found to bind differentially with DNA duplexes. The other functional possibilities of known drugs with DNA recognitions might be helpful in drug repurposing purposes with the findings of present study.

Keywords: Benzimidazole, AT-rich DNA, GC-rich DNA, Molecular Docking

How to cite this article: Khan U. and Sur S. (2023). DNA recognitions of Benzimidazole based Bendamustine, Albendazole, and Mebendazole: a Molecular Docking Study. *Bulletin of Pure and Applied Sciences-Chemistry,* 42C (1), 41-45.

INTRODUCTION

Specific recognition of DNA sequences by small organic molecules is of importance both for the targeting of specific genes in a genome, and for chemotherapeutic purposes (Khan et al, 2012). The mechanistic views of few well known drugs which are widely used for medications in specific purposes are yet to be identified. Bendamustine belongs to a group of cancer medicines as alkylating agents which are based on benzimidazole moiety (Cheson & Rummel, 2009). Bendamustine injection is used to treat chronic lymphocytic leukemia and indolent B-cell non-Hodgkin's lymphoma in patients. It interferes with the growth of cancer cells, which are eventually destroyed by the body. Benzimidazole based other most important two well know drugs-albendazole and mebendazole are used in treatment of cancer as well as in parasitic infections (Chai, et al, 2021 and Bennett & Guyatt, 2000). Albendazole and mebendazole are most frequently prescribed for fungal infections and can also be used for intestinal tapeworm infections.

Since bendamustine, albendazole and mebendazole are marketed drugs, the oligonucleotide recognitions of these drugs can be an interesting finding. Hurley (2002) reported in literature that many anticancer drugs target DNA. Anti-tumour antibiotics tend to be more

specific in their interactions with DNA. Since no previous study was reported with the DNA recognition of bendamustine, albendazole and mebendazole (Figure 1), we have eager to know the possibilities of those drugs with DNA. Hoechst and other minor groove ligands specifically bind to AT/GC specific sequences (Pjura et al, 1987, Harshman et al, 1985 and Singh et al, 1992), where Hoechst is basically benzimidazole based molecule (Singh et al, 2013). The hexadecamers $d(GCGCGCGCGCGCGC)_2$ and $d(ATATATATATATAT)_2$ sequences are very prone to find whether the chosen drugs effectively bind to DNA strands or not. Therefore, systematic studies by designing analogues with improved sequence selectivity would facilitate a comprehensive understanding of drug–DNA interaction leading to the development of better drug designing.

In the present study, we have compared the sequence recognition properties of bendamustine, albendazole and mebendazole which is basically based on benzimidazoles moiety by means molecular docking approach. We also compare their binding scenario towards two completely different synthetic oligonucleotides. The findings from our study can open a window for drug repurposing purposes.

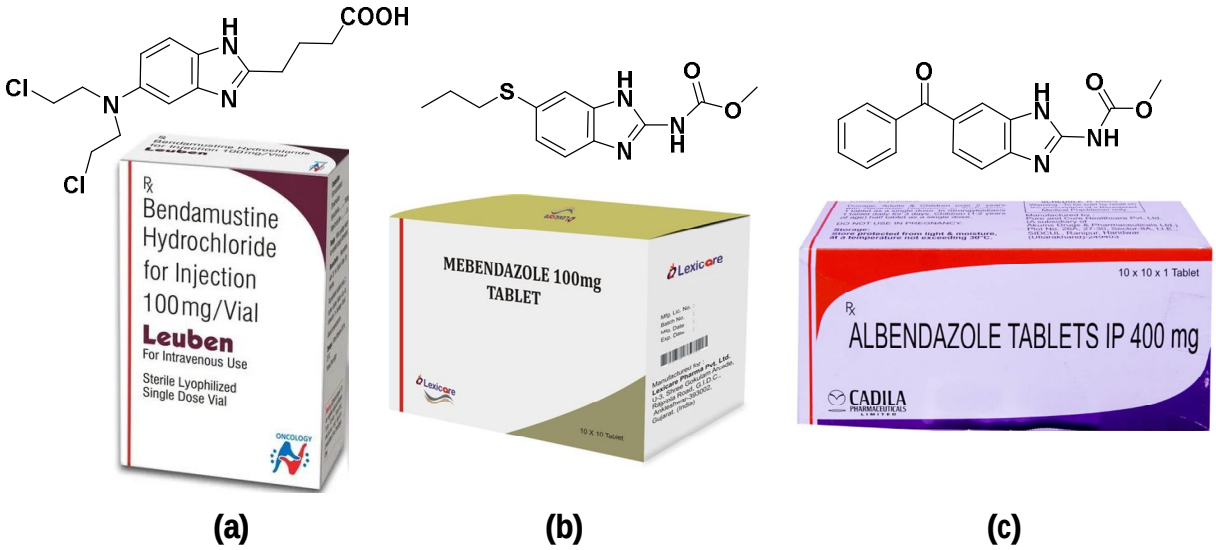


Figure 1: Chemical structures of (a) bendamustine, (b) albendazole and (c) mebendazole

EXPERIMENTAL PROCEDURE

For molecular docking experiment of bendamustine, albendazole and mebendazole with hexadecamers $d(GCGCGCGCGCGCGC)_2$ and $d(ATATATATATATAT)_2$ sequences, we have chosen AutoDock which is an excellent non-commercial docking program widely used (Huey et al, 2012 and Forli et al, 2016). Further, we employed a stochastic Lamarckian genetic algorithm for docking methodology and simultaneously minimizing its scoring function with better thermodynamic stability of the ligand bound to the DNA duplexes. We have used AutoDock Vina 4.2 for docking of chosen drugs i.e. bendamustine, albendazole and mebendazole. Intermediary steps, such as pdbqt files for DNA and ligands preparation and grid box creation were completed using Graphical User Interface program AutoDock Tools (ADT). We have manually added the polar hydrogens, Kollman charges to the targeted DNA sequences. The initial files of targeted DNA and drugs were saved in PDBQT format. AutoGrid was used for the preparation of the grid map using a grid box and the dimensions of the grid-box was set to $50 \times 50 \times 50$ xyz points with a spacing of 0.275 Å. The docking had been done in the grid box constituting minor and major

groove of DNA so that we can compare whether the drugs bind to major or minor groove.

Biovia Discovery Studio was used to analyze the obtained docked structures (Jejurikar et al, 2021 and Biovia, 2017). The nucleotides with close contact with all three analogues were labeled and those are called as the interactive residues. All the possible interactions which are present in each of the docked complex like H-bonding or other possible van der Waal interactions were checked and analyzed.

RESULT AND DISCUSSION

We have performed all the experiments using two target designed DNA sequences: $d(ATATATATATATATAT)_2$ and $d(GCGCGCGCGCGCGCGC)_2$. The molecular docking scores obtained from the most effective poses are tabulated in Table 1.

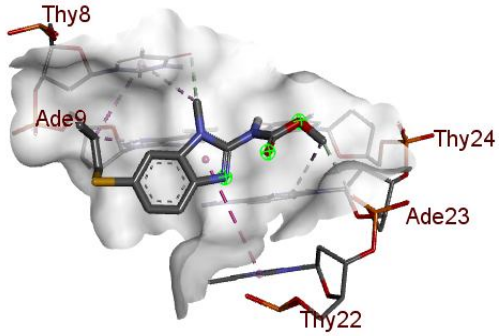
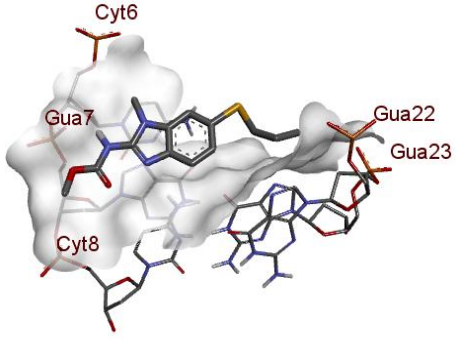
Table 1: Docking Scores calculated

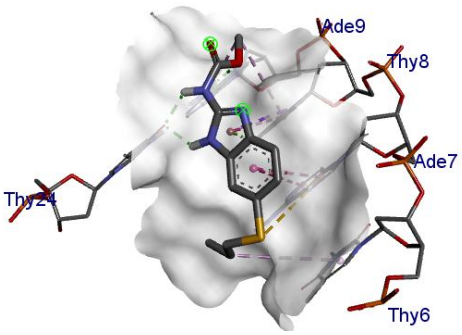
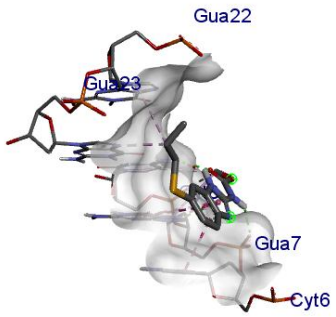
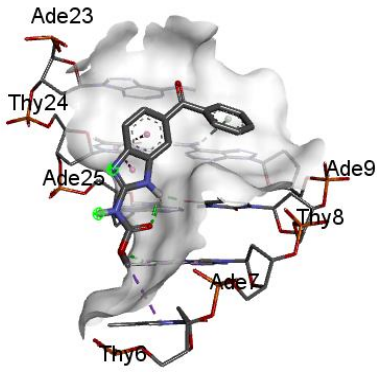
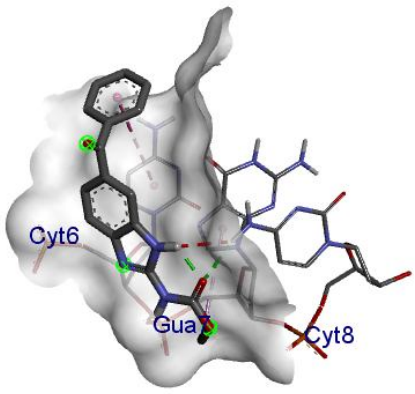
Ligand	Docking score with $d(ATATATATATATATAT)_2$	Docking score with $d(GCGCGCGCGCGCGCGC)_2$
Bendamustine	-4.35	-3.22
Albendazole	-5.11	-4.06
Mebendazole	-6.79	-4.83

*Scores were obtained as binding free energies in kcal mol^{-1}

The interactive residues i.e. nucleotides were found in case of $d(ATATATATATATATAT)_2$ are present in minor groove of DNA duplex for albendazole and mebendazole whereas bendamustine was found to bind in major groove because of their 3D structures and acceptor site availabilities in the groove pocket. On the other hand, all three drugs exclusively bound to the major groove with $d(GCGCGCGCGCGCGCGC)_2$, the nucleotides are found in major grove of DNA duplex. All the found residues are mentioned in Table 2. The corresponding docking scores reflect their binding scenario in each DNA-drug complex.

Table 2: Docking pose with interactive residues

Drug	Docking pose with interactive residues* in $d(ATATATATATATATAT)_2$	Docking pose with interactive residues* in $d(GCGCGCGCGCGCGCGC)_2$
Bendamustine	 Residues: T8, A9, T22, A23, A24	 Residues: G7, C8, C6, G22, G23

Albendazole	 Residues: T8, A9, T24, T6, A7	 Residues: G7, C8, C21, G22, C23
Mebendazole	 Residues: A23, A9, T24, A25, T8, A7, T6	 Residues: G7, C8, C21, G22, C23

*A=Adenine, T=Thymine, G=Guanine, C=Cytosine

The docked analogues were shown from their best docking complexes. The three-dimensional structures after docking were analyzed and the interactive nucleotide residues were identified. In most of the cases with AT-rich DNA track, the binding of drug moieties came from both side of the DNA strands whereas with GC-track mostly ineffective binding of drugs were observed. The docking score here proportionately increases with the increased number of neighbor nucleotide residues in each case. The types of interactions like van der Waal and pi-pi interactions are also found among the docked structures which were found to be actual reflections of their docking scores.

CONCLUSION

From the present study, we have found that bendamustine, albendazole and mebendazole bind differentially with AT and GC-rich DNA sequences. Due to the three dimensional structures the drugs preferentially bind to the minor as well as major grooves of DNA. With $d(ATATATATATATATAT)_2$ sequence, albendazole and mebendazole bind more tightly as compared to bendamustine, the calculated docking scores support the observation in this regard. But with GC-rich DNA sequence-$d(GCGCGCGCGCGCGCGC)_2$, the drugs were found ineffectively bound in the grooves. Further confirmation can be made from structural analysis through molecular dynamics in future.

Acknowledgement:
UK is thankful to Teerthanker Mahaveer University, Moradabad for financial assistance and facility available for her research work. SS is also thankful to the facility provided by Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India and granting seed money for the completion of this project via ref. TMU/R.O./2020-21/Seed money /002 dated 19/06/2021.

REFERENCES

1. Bennett, A., & Guyatt, H. (2000). Reducing intestinal nematode infection: efficacy of albendazole and mebendazole. *Parasitology Today*, *16*(2), 71-77.
2. Biovia, D. S. (2017). BIOVIA discovery studio visualizer. *Softw. Version*, *20*, 779.
3. Chai, J. Y., Jung, B. K., & Hong, S. J. (2021). Albendazole and mebendazole as anti-parasitic and anti-cancer agents: an update. *The Korean Journal of Parasitology*, *59*(3), 189.
4. Cheson, B. D., & Rummel, M. J. (2009). Bendamustine: rebirth of an old drug. *Journal of Clinical Oncology*, *27*(9), 1492-1501.
5. Forli, S., Huey, R., Pique, M. E., Sanner, M. F., Goodsell, D. S., & Olson, A. J. (2016). Computational protein–ligand docking and virtual drug screening with the Auto Dock suite. *Nature protocols*, *11*(5), 905-919.
6. Hurley, L. H. (2002). DNA and its associated processes as targets for cancer therapy. *Nature Reviews Cancer*, *2*(3), 188-200.
7. Harshman, K. D., & Dervan, P. B. (1985). Molecular recognition of B-DNA by Hoechst 33258. *Nucleic acids research*, *13*(13), 4825-4835.
8. Huey, R., Morris, G. M., & Forli, S. (2012). Using Auto Dock 4 and Auto Dock vina with Auto Dock Tools: a tutorial. *The Scripps Research Institute Molecular Graphics Laboratory*, *10550*(92037), 1000.
9. Jejurikar, B. L., & Rohane, S. H. (2021). Drug designing in discovery studio.
10. Khan, G. S., Shah, A., & Barker, D. (2012). Chemistry of DNA minor groove binding agents. *Journal of photochemistry and photobiology B: Biology*, *115*, 105-118.
11. Pjura, P. E., Grzeskowiak, K., & Dickerson, R. E. (1987). Binding of Hoechst 33258 to the minor groove of B-DNA. *Journal of Molecular Biology*, *197*(2), 257-271.
12. Singh, M. P., Joseph, T., Kumar, S., Bathini, Y., & Lown, J. W. (1992). Synthesis and sequence-specific DNA binding of a topoisomerase inhibitory analog of Hoechst 33258 designed for altered base and sequence recognition. *Chemical research in toxicology*, *5*(5), 597-607.
13. Singh, M., Sur, S., Rastogi, G. K., Jayaram, B., & Tandon, V. (2013). Bi and tri-substituted phenyl rings containing bisbenzimidazoles bind differentially with DNA duplexes: a biophysical and molecular simulation study. *Molecular Bio Systems*, *9*(10), 2541-2553.