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| Book Name: | [**Disease and Health: Research Developments**](https://www.bookpi.org/bookstore/product/disease-and-health-research-developments-vol-1/) |
| Manuscript Number: | **Ms\_BPR\_4679** |
| Title of the Manuscript: | **Targeting PD-1: A Computational Approach to Discover Small Molecule Inhibitors for Cancer Treatment** |
| Type of the Article | **Book Chapter** |

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| PART 1: Comments | | |
|  | Reviewer’s comment **Artificial Intelligence (AI) generated or assisted review comments are strictly prohibited during peer review.** | Author’s Feedback *(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.** | This manuscript addresses a highly significant topic at the intersection of cancer immunotherapy and drug discovery. Programmed cell death-1 (PD-1) is a pivotal immune checkpoint, and its blockade by monoclonal antibodies has revolutionized cancer treatment, yielding remarkable clinical success across many tumors​. However, antibody therapies have limitations such as high cost, intravenous delivery, and immune-related adverse effects, which motivates the search for small-molecule alternatives​. The study’s focus on discovering orally bioavailable PD-1 inhibitors is therefore timely and important, as small molecules could offer advantages in patient accessibility and safety. By leveraging a computational drug design pipeline to identify novel PD-1 inhibitors, the work contributes valuable insights and potential lead compounds to the field of cancer immunotherapy, addressing a known gap in the current therapeutic arsenal (since no small-molecule PD-1 inhibitors are yet clinically available). The integrated in silico approach showcased here can also serve as a model for accelerating drug discovery against other challenging protein–protein interaction targets. |  |
| **Is the title of the article suitable?**  **(If not please suggest an alternative title)** | The title of the manuscript is clear and accurately reflects its content. It explicitly mentions “Targeting PD-1” and “a Computational Approach to Discover Small Molecule Inhibitors for Cancer Treatment,” which encapsulates the study’s aim of using in silico methods to find PD-1 inhibitors as cancer therapeutics. This title prepares the reader for a paper about computational drug discovery in the context of PD-1 and immunotherapy, which is exactly what the study delivers. One minor suggestion for refinement could be to specify “in silico” or “computer-aided drug design” in the title for added clarity (e.g., “In Silico Discovery of Small-Molecule PD-1 Inhibitors for Cancer Immunotherapy”), but this may not be necessary. Overall, the current title is succinct and appropriate, successfully conveying the scope and significance of the work. |  |
| Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here. | The abstract is generally clear, informative, and provides a comprehensive overview of the study. It opens with context about the burden of cancer and the success of immune checkpoint inhibitors, then highlights the need for small-molecule alternatives and the value of computational methods. The authors succinctly describe their methodology – a workflow combining pharmacophore-based virtual screening, molecular docking, and ADMET prediction – and report key results, notably that 30 hit compounds were narrowed down to five promising candidates (identified by their ZINC database IDs) with the most favorable binding free energies. The abstract also mentions the potential of these compounds as starting points for designing safe and effective cancer immunotherapy drugs, and it notes that further optimization is necessary. This provides a balanced summary of both the achievements and the need for future work. One suggestion would be to ensure the abstract is tightly written and free of minor language issues (for instance, the phrase *“In the Silico Computational study”* could be corrected to *“In this in silico study”* for grammar clarity). |  |
| **Is the manuscript scientifically, correct? Please write here.** | The study appears to be scientifically sound and methodologically well structured. The authors follow a logical computer-aided drug design (CADD) workflow: starting with protein structure validation and binding-site identification, proceeding to pharmacophore query development and virtual screening, and then filtering hits via molecular docking and ADMET property predictions. Each step is grounded in established techniques or tools – for example, binding pockets on PD-1 were identified using multiple computational servers (DoGSiteScorer, FTSite, PrankWeb) to ensure robust pocket prediction​, and virtual screening was performed against the ZINC database using the ZincPharmer platform. The selection of top hits was based on docking Gibbs free energy (ΔG) values, a reasonable proxy for binding affinity, and the authors correctly interpret more negative ΔG values as indicating stronger predicted binding. The five lead compounds chosen for further analysis are clearly justified by these criteria. Moreover, the manuscript includes an interesting extension where the selected PD-1 binders were docked against CTLA-4, another checkpoint protein, to evaluate potential off-target or dual-target interactions​. This additional analysis adds depth to the study by addressing the specificity of the hits. All findings are presented with appropriate data (tables of docking scores, figures of binding sites, etc.), and the conclusions – that the identified compounds might serve as starting points for drug development, but require further optimization and experimental validation – are logically supported by the in silico results. One aspect to note is that, as with any computational study, the results are predictive: actual biological activity of these compounds remains to be confirmed experimentally. The authors acknowledge this by emphasizing the need for further evaluation. In summary, the scientific approach is rigorous and the data support the authors’ claims, making the study credible and valuable for the field. |  |
| **Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.**  **-** | The manuscript is supported by a robust list of references that appear to be both sufficient and up-to-date. |  |
| Is the language/English quality of the article suitable for scholarly communications? | The language quality of the manuscript is generally acceptable for scholarly communication, with clear technical descriptions and an academic tone maintained throughout. The manuscript is written in a formal and informative style, making it easy to follow the complex workflow and results. |  |
| Optional/General comments |  |  |

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| **PART 2:** | | |
|  | Reviewer’s comment | Author’s comment *(if agreed with the reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in detail)*  ***No significant ethical concerns are associated with this study, given its computational nature*** |  |

**Reviewer details:**

**Anirudh Mehta, Rutgers University, United States**