LETTER TO EDITOR

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The Future of Innovative Drug Discovery: Integrating Dual Inhibition and Artificial Intelligence

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Dear Editor,

The field of drug discovery is on the brink of a profound transformation. Advances in technology and a deeper understanding of biological systems are driving unprecedented changes in how we discover and develop new medications. This editorial explores the future directions of innovative drug discovery research and its transformative potential.

Drug discovery is a long-term commitment characterized by "high risk and high reward." Traditionally, many companies and investors have preferred "low-hanging fruits" due to these challenges. Additionally, economic constraints have led to a reduction in robust industry-academia collaboration, which hampers the realization of the full scientific potential in innovative drug discovery and development. This highlights the urgent need for more strategic and rational approaches.

While significant successes have been achieved in some areas of treatment, failures persist. This calls for a reevaluation and transformation of current methodologies. Developing drugs that are affordable, effective, and have minimal side effects is becoming increasingly crucial. Expecting different outcomes from the same approaches is not scientifically valid. In tackling these hurdles, researchers continually explore various techniques and novel approaches, with a notable emphasis on computer-based methods. Notably, molecular docking and quantitative structure-activity relationship (QSAR) studies stand out as vital tools in this endeavor. Nonetheless, it's essential to acknowledge that while these techniques have made positive contributions to drug development, they are not without limitations. For instance, the relative nature of score functions in molecular docking and the challenges

associated with working on extensive datasets in QSAR studies are notable shortcomings. Consequently, the advancement of new methodologies is being vigorously pursued.

We are now in the era of big data. This is primarily due to the exponential growth in data generation, which now surpasses the cumulative data produced in all human history. In the past, acquiring data or information required substantial time and effort. However, in the contemporary world, data generation has become rapid and straightforward, resulting in the accumulation of massive datasets across various domains. The primary challenge lies in processing and translating this vast sea of data into actionable knowledge. Without this transformation, the abundance of data, often referred to as 'big data,' remains meaningless. Given the impracticality of relying solely on human cognition to achieve this, the concept of artificial intelligence (AI) has emerged—a form of computing capable of rapidly converting diverse data into meaningful knowledge. AI methods have been reported to be successful in QSARs, molecular property prediction, target prediction, virtual screening, ADMET, *de novo* drug design, and retrosynthetic design. Thanks to the opportunities offered by AI, significant advancements are being made in drug discovery processes.

Looking ahead, dual-target compounds will play a significant role in drug development. Dual-target compounds can provide more effective and broad-spectrum treatments by affecting multiple biological targets simultaneously. The development of dual inhibitors especially emerges as an effective strategy for advancing drug discovery for diseases with a multicausal nature (such as inflammation and cancer). A study, led by Guo et al., involved the design and synthesis of purine-based derivatives targeting JAK2 and BRD4(BD2) simultaneously. JAK2, a member of the JAK kinases family, plays a critical role in myeloproliferative neoplasms (MPNs), and its activation leads to enhanced NF-κB signaling. BRD4, on the other hand, is an epigenetic reader associated with histone acetylation. It regulates gene expression, including the c-Myc oncogene, and interacts with acetylated RelA of NF-κB. Interestingly, the combination of a JAK1/2 inhibitor (ruxolitinib) and a BRD4 inhibitor (JQ1) resulted in a further reduction of NF-κB activity. This suggests that targeting JAK2 and BRD4 with small molecules holds promise as a therapeutic strategy for MPNs. (Guo et al., 2023). These approaches, including dual-target compounds, hold promise for treating complex diseases like cancer and neurodegenerative disorders, offering new avenues for effective and safer therapies. (Masson et al., 2023).

In conclusion, the future of innovative drug discovery research is incredibly promising. With ongoing technological advancements and a collaborative approach, we are on the cusp of breakthroughs that could transform healthcare. By embracing these emerging technologies, we can develop revolutionary treatments that enhance patient outcomes and address pressing health challenges. Leveraging contemporary technologies such as artificial intelligence at the highest proficiency could elevate research to new dimensions. Combining this approach with dual-target compound development and artificial intelligence strategies could lead to more effective compounds in the future. Integrating different approaches could form the foundation of future innovative drug discovery research. It is an exciting era for researchers, clinicians, and patients alike, and the future holds remarkable potential for the evolution of drug discovery.

Best Regards.

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