TMR

COMMENT

Natural Therapy Advances 2024;7(4):21. https://doi.org/10.53388/NTA2024021

Comment on "Flexible scaffold-based cheminformatics approach for polypharmacological drug design"

Jun Kang[1*]

[1]School of Life Sciences, Tianjin University, Tianjin 300072, China.

[*]**Correspondence to:** Jun Kang, School of Life Sciences, Tianjin University, No. 92 Weijin Road, Nankai District, Tianjin 300072, China. E-mail: jun.kang@tju.edu.cn.

Recently, a breakthrough article by Chen et al., "Flexible scaffold-based cheminformatics approach for polypharmacological drug design" was published in *Cell*. This work focuses on polypharmacological drugs (PPD) and innovatively proposes a flexible scaffold-based cheminformatics approach (FSCA) for drug design. The precursor drug molecule IHCH-7179, which possesses both 5-HT_{1A} receptor (5-HT_{1A}R) agonist and 5-HT_{2A} receptor (5-HT_{2A}R) antagonist activity, was successfully synthesized. IHCH-7179 molecule showed great potential for pharmacological effects in combating mental disorders and alleviating cognitive dysfunction in vivo [1].

For a long time, clinical drug development has focused on single-target therapies [2]. For diseases with complex pathogenesis, e.g. neurological and psychiatric disorders, including anxiety disorders, depression, and schizophrenia, due to the complex pathogenesis and involvement of multiple symptoms, single-target therapies are always not satisfied [3]. Therefore, the development of PPD is particularly important.

To overcome the limitations of single-target therapies, the design of PPD has attracted more attention. The 5-HT system is a pivotal neurotransmitter system in the human brain [4]. 5-HT_{1A}R is one of the most widely distributed 5-HT receptors, located on the soma and dendrites of 5-HT neurons [5]. 5-HT_{1A}R is closely related to depression and suicide [6]. Furthermore, 5-HT_{1A}R agonists mainly exert anti-anxiety effects by regulating 5-HT function, e.g. Buspirone and Tandospirone. In clinical practice, for severe refractory depression, the combination of 5-HT_{1A}R partial agonist Tandospirone could significantly promote the therapeutic efficacy of stress-induced anxiety-like behavior [7]. Combining D2 receptor antagonists or semi agonists with 5-HT_{1A}R agonists is one of the recent ideas for developing a new generation of antipsychotic drugs (including bifeprunox, aripiprazole, and SSR181505) [8], which can eliminate extrapyramidal adverse reaction, treat negative and positive symptoms, and cognitive impairment of schizophrenia.

The core concept of designing PPD is to predict pharmacological activity through combination patterns. Drugs targeting the serotonin receptor family typically consist of two pharmacophores: the first pharmacophore and the second pharmacophore. The first pharmacophore usually binds to the orthostatic binding pocket (OBP), while the second pharmacophore binds to the extended binding pocket (EBP). According to the published structures of serotonin receptor drug complexes, this study identified two common binding modes. Excitants such as Lysergic acid diethylamide (LSD) and ergotamine adopt a "stretching-up" binding posture, in which the four ring skeleton of the first pharmacophore presents an approximately planar configuration. While the second pharmacophore extends upward to the outer side of the membrane and binds to the shallow binding pocket (SBP). The antagonists such as lumateperone tend to adopt a "bending-down" binding mode, in which the four ring skeleton of the first pharmacophore presents a bent conformation at the intermediate connection, while the second pharmacophore extends downward to the deep binding pocket (DBP) of the transmembrane core region. Therefore, an ideal multi-target molecule performs a versatile conformation: a "stretching-up" binding posture in 5-HT_{1A}R to activate this type of receptor, and a "bending-down" binding posture in 5-HT_{2A}R to inhibit the activity of this type of receptor [1].

Drugs are usually composed of two or more pharmacophores. These pharmacophores bind to different receptor pockets, triggering receptor conformational changes and resulting in different pharmacological activities [9]. FSCA is based on target and skeleton structure information, targeting the clinical drug needs of diseases such as schizophrenia and dementia. The authors first selected multi ring skeletons with variable conformational features from the ChEMBL and Enamine compound libraries. Due to the presence of aromatic benzene ring structures in drugs targeting serotonin receptors, the identified variable conformation polycyclic skeleton should possess three characteristics. Firstly, the first ring, or the combination of the first and fourth rings is an aromatic ring; Secondly, the second non aromatic ring contains a sp^3 hybridized nitrogen atom. Thirdly, the third non aromatic ring contains a protonated, positively charged nitrogen atom, which facilitates the assembly and connection of the second pharmacophore, as well as anchoring with the conserved amino acid D3.32 of the amine receptor through salt bridge interaction; The C-N bond connecting the second and third rings exhibits conformational flexibility in the multi ring skeleton due to the reversible transformation property of the sp^3-sp^2 hybrid orbitals of nitrogen atoms [1].

According to the screened skeleton, the research group synthesized new flexible molecules. The molecules were connected by the identified 10 polycyclic frameworks with 4-fluorobenzene groups through a butanone-based linker. Subsequently, based on the previously analyzed structures of 5-HT_{1A}R (PDB ID: 7E2Z) and 5-HT_{2A}R (PDB ID: 7WC8), molecular docking screening was performed. 7 molecules could bind to the two proteins, and respectively adopted the binding modes of "stretching-up" and "bending-down". When binding to 5-HT_{1A}R, the multi ring skeleton presented a nearly planar conformation and binds to the OBP, while the 4-fluorobenzene group connected by the butanone linker extends upwards and binds to the open superficial pocket. When binding to 5-HT_{2A}R, the multi ring skeleton exhibited a bent conformation due to the close contraction of the transmembrane helix TM7, and the second extracellular loop ECL2. The collapse of the superficial pocket, and the influence of the hydrophobic interlayer environment composed of TM7 and ECL2 amino acid side chains. Due to the downward position of the nitrogen atom in the third ring of the connection, the 4-fluorobenzene group could only adopt a downward binding mode and bind to the DBP in the transmembrane core region [1].

In vivo, combined with in vitro experiments confirmed the multifunctional activity of the newly synthesized molecule. Both the 3- and 4-ring skeleton drugs, IHCH-7162 and IHCH-7179, exhibited dual activity as 5-HT_{1A}R agonists and 5-HT_{2A}R antagonists. Among them, IHCH-7179 adopted a binding mode of "stretching-up" and "bending-down" in 5-HT_{1A}R and 5-HT_{2A}R, respectively. Subsequent structural analysis revealed that the drug binding pocket of dopamine D2 receptor shares structural characteristics similar to 5-HT_{1A}R. Therefore, the multi-target molecules showed dopamine D2 receptor agonist activity, avoiding cognitive deterioration caused by long-term inhibition of dopamine D2 receptor by existing drugs. In the mouse model of mental disorders, IHCH-7179 exhibited excellent antipsychotic symptoms. It effectively inhibited the shaking head twitch response (HTR) induced by LSD in mice and alleviated the pre pulse inhibition disorder (PPI) induced by LSD. IHCH-7179 also

showed significant improvement in the manic hyperactive symptoms induced by MK-801. In the APP/PS1 mouse model of Alzheimer's disease, IHCH-7179 can partially improve cognitive symptoms, which is of great significance for the treatment of Alzheimer's disease. These results indicated that IHCH-7179 may become a potential multi-target, multifunctional drug with the potential to treat various mental illnesses and cognitive impairments [1].

In summary, this study proposes a clever drug design approach, by screening pharmacophores with variable conformational features to adapt to different receptor pockets, diverse binding modes are generated, thereby achieving multi-target and multi efficacy pharmacological activity. This is a highly innovative work that provides new ideas for the development of next-generation multi-target molecules.

References

1. Chen Z, Yu J, Wang H, et al. Flexible scaffold-based cheminformatics approach for polypharmacological drug design. *Cell.* 2024;187(9):2194–2208.e22. Available at: http://doi.org/10.1016/j.cell.2024.02.034
2. Duan XP, Qin BD, Jiao XD, et al. New clinical trial design in precision medicine: discovery, development and direction. *Signal Transduct Target Ther.* 2024;9(1):57. Available at: http://doi.org/10.1038/s41392-024-01760-0
3. Scangos KW, State MW, Miller AH, et al. New and emerging approaches to treat psychiatric disorders. *Nat Med.* 2023;29(2):317–333. Available at: http://doi.org/10.1038/s41591-022-02197-0
4. Jocham G, Ullsperger M. Neuropharmacology of performance monitoring. *Neurosci Biobehav Rev.* 2009;33(1):48–60. Available at: http://doi.org/10.1016/j.neubiorev.2008.08.011
5. Wang J, Mei Y, Zhang X, et al. Aberrant serotonergic signaling contributes to the hyperexcitability of CA1 pyramidal neurons in a mouse model of Alzheimer's disease. *Cell Rep.* 2023;42(3):112152. Available at: http://doi.org/10.1016/j.celrep.2023.112152
6. Rahn KA, Cao YJ, Hendrix CW, et al. The role of 5-HT1A receptors in mediating acute negative effects of antidepressants: implications in pediatric depression. *Transl Psychiatry.* 2015;5(5):e563. Available at: http://doi.org/10.1038/tp.2015.57
7. Zhan TT, Dong ZY, Yi LS, et al. Tandospirone prevents stress-induced anxiety-like behavior and visceral hypersensitivity by suppressing theta oscillation enhancement *via* 5-HT_{1A} receptors in the anterior cingulate cortex in rats. *Front Cell Neurosci.* 2022;16:922750. Available at: http://doi.org/10.3389/fncel.2022.922750
8. Newman-Tancredi A, Kleven MS. Comparative pharmacology of antipsychotics possessing combined dopamine D2 and serotonin 5-HT1A receptor properties. *Psychopharmacology (Berl).* 2011;216(4):451–473. Available at: http://doi.org/10.1007/s00213-011-2247-y
9. Watanabe N, Shinozaki Y, Ogiwara S, et al. Diphenyl-tetrazol-propanamide Derivatives Act as Dual-Specific Antagonists of Platelet CLEC-2 and Glycoprotein VI. *Thromb Haemost.* 2024;124(3):203–222. Available at: http://doi.org/10.1055/a-2211-5202

Competing interests

The author declares no conflicts of interest.

Abbreviations

PPD, polypharmacological drugs; 5-HT_{1A}RH, 5-HT_{1A} receptor; 5-HT_{2A}R, 5-HT_{2A} receptor; LSD, Lysergic acid diethylamide.

Citation

Kang J. Comment on "Flexible scaffold-based cheminformatics approach for polypharmacological drug design". *Nat Ther Adv.* 2024;7(4):21. doi: 10.53388/NTA2024021.

Executive editor: Xin-Yue Zhang.

Received: 12 August 2024, **Accepted:** 20 November 2024, **Available online:** 27 November 2024.