**About**

Macrocycles, defined as rings of at least 12 heavy atoms, have garnered significant attention across various scientific fields, particularly in drug discovery [1]. Their appeal lies in their capacity to provide functional diversity and stereochemical complexity. This distinctive structural attribute empowers macrocycles to bind with high affinity and selectivity to ‘difficult to drug’ targets that are challenging to modulate with traditional small-molecule drugs or adhere to the Rule of Five (Ro5) [2-4]. Despite their size, macrocycles may still possess sufficient cell permeability and bioavailability, rendering them promising candidates for oral administration. While macrocyclic drugs were historically derived from natural sources, there is a growing inclination towards the de novo design of macrocycles as approved pharmaceuticals.[1] The rational design of potent, cell-permeable, orally available macrocyclic drugs poses numerous challenges, particularly concerning synthesis and conformational prediction [5-7].

The process of passive cell permeability involves several complex steps, including desolvation when the drug transitions from the extracellular aqueous environment to interacting with the negatively charged phospholipid head groups before penetrating the hydrophobic membrane interior. These steps are then reversed as the drug moves into the cytosol. Each of these processes is influenced to varying degrees by the molecular properties of the drug. For example, the compound's polarity, represented by its 3D polar surface area (PSA), significantly impacts the desolvation kinetics. The compound's size, approximated by the radius of gyration (Rgyr), affects the rate of diffusion across the membrane, while its lipophilicity (cLogP or cLogD) is crucial for the thermodynamics of permeation [6].

地图

描述已自动生成

1

22

33

44

55

66

77

88

99

1010

1111

PAMPA

(1) Garcia Jimenez, D.; Poongavanam, V.; Kihlberg, J. Macrocycles in drug discovery─ learning from the past for the future. *Journal of Medicinal Chemistry* **2023**, *66* (8), 5377-5396.

(2) Giordanetto, F.; Kihlberg, J. Macrocyclic drugs and clinical candidates: what can medicinal chemists learn from their properties? *Journal of medicinal chemistry* **2014**, *57* (2), 278-295.

(3) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews* **2012**, *64*, 4-17.

(4) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *Journal of medicinal chemistry* **2002**, *45* (12), 2615-2623.

(5) Sethio, D.; Poongavanam, V.; Xiong, R.; Tyagi, M.; Duy Vo, D.; Lindh, R.; Kihlberg, J. Simulation reveals the chameleonic behavior of macrocycles. *Journal of Chemical Information and Modeling* **2022**, *63* (1), 138-146.

(6) Over, B.; Matsson, P.; Tyrchan, C.; Artursson, P.; Doak, B. C.; Foley, M. A.; Hilgendorf, C.; Johnston, S. E.; Lee IV, M. D.; Lewis, R. J. Structural and conformational determinants of macrocycle cell permeability. *Nature Chemical Biology* **2016**, *12* (12), 1065-1074.

(7) Rossi Sebastiano, M.; Doak, B. C.; Backlund, M.; Poongavanam, V.; Over, B. r.; Ermondi, G.; Caron, G.; Matsson, P. r.; Kihlberg, J. Impact of dynamically exposed polarity on permeability and solubility of chameleonic drugs beyond the rule of 5. *Journal of medicinal chemistry* **2018**, *61* (9), 4189-4202.

(8) Poongavanam, V.; Atilaw, Y.; Ye, S.; Wieske, L. H.; Erdelyi, M.; Ermondi, G.; Caron, G.; Kihlberg, J. Predicting the permeability of macrocycles from conformational sampling–limitations of molecular flexibility. *Journal of Pharmaceutical Sciences* **2021**, *110* (1), 301-313.

(9) Poongavanam, V.; Wieske, L. H.; Peintner, S.; Erdélyi, M.; Kihlberg, J. Molecular chameleons in drug discovery. *Nature Reviews Chemistry* **2024**, *8* (1), 45-60.

(10) Rezai, T.; Bock, J. E.; Zhou, M. V.; Kalyanaraman, C.; Lokey, R. S.; Jacobson, M. P. Conformational flexibility, internal hydrogen bonding, and passive membrane permeability: successful in silico prediction of the relative permeabilities of cyclic peptides. *Journal of the American Chemical Society* **2006**, *128* (43), 14073-14080.

(11) Li, J.; Yanagisawa, K.; Sugita, M.; Fujie, T.; Ohue, M.; Akiyama, Y. CycPeptMPDB: A comprehensive database of membrane permeability of cyclic peptides. *Journal of Chemical Information and Modeling* **2023**, *63* (7), 2240-2250.