To bind or not to bind, that is an important question! : Development of covalent probes for adenosine receptors

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STELLINGEN

Behorend bij het proefschrift

To bind or not to bind, that is an important question! Development of covalent probes for adenosine receptors

1. The increasing number of covalent drugs with market approval demonstrates their prevalence and pharmacological advantages over a reversible mechanism of action. *Bauer, RA. Drug Discov. Today*, **2015**; *20*(9), 1061–1073.

2. The use of covalent ligands to modify receptors has facilitated the studies to investigate a receptor's structural biology, molecular pharmacology and drug design. *Schwalbe, T., Huebner, H., & Gmeiner, P. Bioorg. Med. Chem.* ***2019****; 27(13), 2959–2971*.

3. Sulfonyl fluoride electrophiles have become important chemical biology and molecular pharmacology tools to probe target binding sites and investigate functionally important amino acid residues. *Narayanan, A., & Jones, L. H. Chem. Sci.* ***2015****; 6(5), 2650–2659*.

4. Activity-Based Protein Profiling (ABPP) emerged as a chemical proteomic strategy that utilizes a small molecule's covalent binding to a target protein to facilitate target validation and profile drug-target interactions. *Cravatt, B. F., Wright, A. T., & Kozarich, J. W., Annu. Rev. Biochem.* ***2008****; 77(1), 383–414.*

5. Covalent ligands that bind to receptors irreversibly serve as powerful tools to profile receptor's pharmacological effects. *This thesis, chapter 3,4 and 5*

6. Small changes will make a big difference-both on ligands and receptors. *This thesis, chapter 3, 4 and 6*

7. A structure-based approach developed for a compound library based on an existing pharmacophore facilitates the ration design of covalent ligands. *This thesis, chapter 4*

8. Functionalized probes enable the assessment of receptor subtype distribution and hold promise as biomarkers in translation drug discovery. *This thesis, chapter 6*

9. The role of a talented chemist is similar to that of an excellent chef. Both have the power to make food molecules dance with the receptors on your tongue.

10. We shouldn't overlook the power of irreversibility in our life, and in science as well.

11. "If you think you are too small to make a difference, try sleeping with a mosquito."- Dalai Lama

12. You can't always get what you want. Unless you form a covalent relationship with it.