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Towards improved drug action : target binding kinetics and functional efficacy at the mGlu2 receptor

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Citation

Doornbos, M. L. J. (2018, September 12). *Towards improved drug action : target binding kinetics and functional efficacy at the mGlu2 receptor*. Retrieved from <https://hdl.handle.net/1887/65384>

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Issue Date: 2018-09-12

STELLINGEN

behorende bij het proefschrift

Towards improved drug action

Target binding kinetics and functional efficacy at the mGlu₂ receptor

1. Kinetic parameters should be assessed in the early phases of drug discovery to avoid overlooking promising drug candidates.
This thesis, chapters 3 and 4
2. Improved understanding of the structural, conformational and thermodynamic determinants of residence time is needed so that medicinal chemists can prospectively design this feature into a molecular series.
This thesis, chapter 4; Copeland RA. Nat Rev Drug Discov. 2016; 15: 87–95.
3. Covalent allosteric modulators are very useful tool compounds, and promising future medicines too.
This thesis, chapter 5
4. Label-free assays provide a powerful addition to existing traditional endpoint-assays.
This thesis, chapter 6
5. Understanding the modes of action for individual allosteric modulators is important since they vary between allosteric modulators and could influence *in vivo* pharmacological properties.
O'Brien et al. Mol. Pharm. 2018; 93: 526-540.
6. More advanced mathematical models are needed that incorporate residence time — along with pharmacokinetic parameters — to predict the required dose and dosing interval for humans that will provide the greatest opportunity for drug efficacy across a range of therapeutic areas.
Copeland RA. Nat Rev Drug Discov. 2016; 15: 87–95.
7. Label-free assays should be incorporated in clinical diagnostics, since they enable evaluation of drug potency using patient-derived cells, thereby contributing to precision medicine.
Hillger et al. Drug Discov. Today. 2017; 22: 1808-1815.
8. The general focus on publishing only positive results is wrong - it is useful and important to also publish well documented failures.
Pfeffer, C. & Olsen, B. R. J. Negat. Results Biomed. 2002; 1: 2.
9. Science is not just 'a matter of opinion'.
10. Research performed in collaborations provides stronger outcomes.
11. Simplicity is the hallmark of truth.
Herman Boerhaave
12. The pessimist complains about the wind; the optimist expects it to change; the realist adjusts the sails.