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Small changes for long term impact : optimization of structure kinetic properties : a case of CCR2 antagonists

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Stellingen
bij het proefschrift

Small Changes for Long Term Impact
Optimization of Structure Kinetic Properties:
A Case of CCR2 Antagonists

1. Despite the clinical failures, we remain cautiously optimistic that chemokine receptor antagonists can be of benefit in man. Their ultimate success, however, will depend on our ability to more clearly understand the role of chemokine receptors in driving the pathophysiology of complex autoimmune diseases than we currently do.

Pease J. and Horuk R. J. Med. Chem. 2012, 55, 9363–9392.

2. While it is clear that the balance of both preclinical and clinical data in rheumatoid arthritis no longer support the use of CCR2 antagonists or CCR2/5-dual antagonists for that indication, many other preclinical studies have suggested promising avenues for exploration in oncologic, neurologic, cardiovascular, metabolic, and fibrotic diseases. Thus, the emergence of a new generation of CCR2 antagonists appears well-timed.

Carter P. H. Expert Opin. Ther. Patents 2013, 23, 5, 549–568.

3. Building on the extensive knowledge generated by the earlier pioneers in this field [of chemokine receptors], there is reason to be optimistic that the next decade will see the identification and approval of many more drugs aimed at antagonizing chemokine receptors.

Pease J. and Horuk R. Expert Opin. Ther. Patents 2009, 19, 199–221.

4. Apparently, to be efficacious in treatment of CCR2-related diseases, high-affinity antagonism is not enough.

This thesis, chapters 3, 4 and 5.

5. The value of binding kinetics to drug discovery will be increased through an improved ability to identify optimal kinetic mechanisms and define kinetic structure activity relationships.

Swinney D. C., Curr Opin Drug Discov Devel. 2009, 12:31-39.

6. The combination of structure–affinity relationships and structure–kinetic relationships is “a must” for drug discovery in the 21st century.

This thesis, chapters 1 and 7.

7. To prolong residence time it is not enough to just increase a compound’s lipophilicity; a truly specific and tailored interaction must be generated between the ligand and its target.

This thesis, chapters 3, 4 and 5.

8. In a good drug every moiety has its own right location; you only need to find it, especially, when optimizing drug-target residence time.

This thesis, chapters 3, 4 and 5.

9. In life (the design of new drugs) desire (affinity) does not automatically mean long lasting relationships (long residence time).

This thesis, chapters 3, 4 and 5.

10. “Don't follow where the path may lead, go instead where there is no path and leave a trail.”

Ralph Waldo Emerson

11. “Continue hitting the wall with your head until you break through” – the only way how to succeed in obtaining a PhD.

12. “The chemistry must be respected.”

Walter White from “Breaking Bad” (season 3, episode 5).