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

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SUMMARY

This thesis starts with a brief description of the evolution of drug discovery from the "trial and error experiments" to the complex "rational drug design" transforming development of new drugs into the multi-disciplinary field as we know it today (**chapter 1**). However, despite all the developments and gained knowledge, it is still very difficult to develop effective and safe drugs. Recently, a paradigm shift has been proposed that instead of structure–affinity relationship (SAR) based drug discovery one should use both SAR and structure–kinetic relationships (SKR). This could result in the next evolutionary jump of drug discovery and development. To test this rationale a G protein-coupled receptor (GPCR) family member – chemotactic chemokine receptor 2 (CCR2) was chosen as the target of interest. At the time of beginning of this thesis the literature already described a "graveyard" of failed CCR2 ligands whose development was based on SAR only. However, several chemical structures showed potential to improve their binding kinetics especially when an indane moiety was incorporated (described in this thesis).

The indane (2,3-dihydro-1*H*-indene) ring system *per se* is an appealing scaffold for biologically active compounds and is reviewed in **chapter 2**. It provides a wide range of possibilities to incorporate specific substituents in different directionalities, thus being an attractive template structure for medicinal chemists. Notably, many indane-based compounds are being used in the clinic to treat various diseases, such as indinavir, an HIV-1 protease inhibitor, indantadol, a potent MAO-inhibitor, the amine uptake inhibitor indatraline, and the ultra–long–acting β-adrenoceptor agonist indacaterol. Given the diversity of targets these drugs act on, one could argue that the indane ring system is a privileged substructure, just like indole, the nitrogen atom containing unsaturated version of it.

Chapter 3 describes the development of a competition association assay for CCR2 and the primary investigation on the relation of the structure of the ligand and its receptor residence time [i.e. SKR] next to a traditional SAR. This approach resulted in the discovery of a new 5-

bromo-indane derivative with high affinity (3.6 nM) as CCR2 antagonist with a residence time of 135 min.

Chapter 4 contains the report on our findings on both SAR and SKR studies for a series of 3-((inden-1-yl)amino)-1-isopropyl-cyclopentane-1-carboxamides as CCR2 antagonists. SAR studies showed that this class of compounds tolerates a vast diversity of substituents on the indenyl ring with only small changes in affinity. However, the SKR is affected greatly by minor modifications of the structure. The combination of SAR and SKR in the hit-to-lead process resulted in the discovery of a new high–affinity and long–residence–time CCR2 antagonist (K_i = 2.4 nM; RT = 714 min).

In **chapter 5** we report new findings on the SAR and SKR of the reference compound MK-0483, its diastereomers, and structural analogues of it as CCR2 antagonists. On the "right–hand" side of the molecules the 7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline group generally yields better affinity and longer drug–target residence time (RT). On the "left–hand" side SAR of the phenyl ring suggests that lipophilic hydrogen bond accepting substituents on the 3-position are favourable. However, SKR suggests that a lipophilic group with a certain size is desired (e.g. 3-Br, 3-*i*Pr). Alternatively a shielded hydrogen bond can also prolong the residence time; this was most prominently observed in MK-0483 itself (K_i = 1.2 nM, RT = 724 min).

Next to the SKR studies outlined above, we also developed a novel *N*-(2-oxo-2-(piperidin-4-ylamino)ethyl)-3-(trifluoromethyl)benzamide series of human CCR2 chemokine receptor antagonists described in **chapter 6**. With a pharmacophore model based on known CCR2 antagonists a new core scaffold was designed, analogues of it synthesized and SAR studies derived yielding a new high affinity CCR2 antagonist *N*-(2-((1-(4-(3-methoxyphenyl)cyclohexyl)piperidin-4-yl)amino)-2-oxoethyl)-3-(trifluoromethyl)benzamide.

Finally, general conclusions about the research described in this thesis are outlined. This is also supplemented with future erspectives of CCR2 antagonists based upon the knowledge and results obtained from this work (**chapter 7)**.