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Design of selective inhibitors for human immunoproteasomes

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Stellingen
Behorende bij het proefschrift

Design of selective inhibitors for human immunoproteasomes

1. The continuous use of the flawed proteasome inhibitor MG-132 as the benchmark proves that old habits die hard.
2. Reporting a compound as selective inhibitor for one or more proteasomal active sites without determining its selectivity or potency for the remaining proteasomal active sites is disingenuous. Lee, M. *et al. J. Med. Chem.* **2019**, *62*, 4444-4455.
3. The current definition of a “blockbuster drug” reflects its annual sales, while the definition should reflect the drug’s positive impact on society and societal health.
4. Inhibitors that block, next to all three immunoproteasome active sites, in part also some constitutive active sites are preferable over truly immunoproteasome-selective ones for the treatment of multiple myeloma. Besse, A. *et al. Cell Chem. Bio.* **2019**, *26*, 340-351. de Bruin, G. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 4199-4203.
5. Not being able to accurately predict the disparities in inhibition profiles of minor modifications at the P3 position shows that we still do not fully understand the intricate interaction between the proteasome inhibitor and each catalytically active proteasome subunit. This thesis, chapter 2.
6. The thought that an inhibitor is not worth synthesizing or testing because crystallographic analysis dictates it will not fit should be discouraged. This thesis, chapter 3.

7. The diastereoselective epoxidation of the alkene using vanadyl acetylacetonate and tert-butyl hydroperoxide, as used by de Bruin, while elegant, is not strictly speaking synthetically efficient. This thesis chapters 2, 3, 4 and 5. de Bruin, G., Chemical tools to monitor and quantify human proteasome activities. Thesis, Leiden University, **2016**.
8. Determining chemical designs by what is available instead of what is optimal, yields creative but not always successful inhibitors. This Thesis, chapter 4.
9. The University of Leiden should allot more resources to Technology Transfer officers to actively participate in initial developmental stages of patentable ideas in order to valorize said ideas into a potentially valuable product and/or service for society.
10. Knowledge transfer in the form of teaching is an integral part of doctoral research and it should be evaluated as such.

Patrick Mark Dekker
Leiden, 28 November 2024