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Re: Habilitation thesis review for Dr Russell Richard Anthony Kitson

To whom it may concern,

This report relates to the habilitation thesis of Dr Russell Richard Anthony Kitson, submitted to Charles University, Department of Organic and Bioorganic Chemistry, Faculty of Pharmacy, in partial fulfilment of the requirements for the title and degree of Docent. In addition to the thesis, I have also checked the Turnitin check report (by Pavel Obdrzalek) and I am fully satisfied that the thesis is an original work produced by Dr Kitson.

The abstract clearly articulates the work develop Hsp90 inhibitors and the importance of this topic. Clear acknowledgement of which aspects of the work are the candidate's own, which were done in direct conjunction with others, and which were performed by collaborators is noted.

In lieu of an introduction, a perspective review article co-authored by Kitson is included as chapter 1. As first author of this manuscript, which has just one other author (Moody) I can be very confident that Kitson played a lead role in the writing of this review, and hence the usage of this perspective review article as the introduction is entirely appropriate. The review summarises extremely well synthetic research activities for targeting Heat Shock protein 90 (Hsp90) with molecules from the geldanamycin and radicicol families and provides a very good biological overview. The writing, presentation, and level of scholarship of the review are all excellent. A detailed an authoritative coverage of the topic is provided, which I note has been cited 48 times (based on citation metrics given on the ASC website linked to the original article, January 2024), attesting to its importance to the research community. I also noted no errors of significant omissions in the review. The review details the importance of the benzoquinone ansamycin geldanamycin and the resorcylic acid macrolactone radicicol in drug discovery programs. It also describes ways in which novel methodologies have been developed by synthetic organic chemists to make these synthetic challenging compounds, along with analogues. As such, Kitson demonstrates high-level, deep knowledge of medicinal chemistry and synthetic organic chemistry in the review, comfortably meeting the standard expected to justify appointment as Associate Professor.

Chapter 2 is a commentary on the submitted research work, focused on research done in Nottingham and Warwick (2010-2022). The work is subdivided into two categories: 1) work based on the geldanamycin natural product, which is the largest body of work; 2) work based on the radicicol natural product. In the geldanamycin work, 19 substituted derivatives were designed and examined via various analytical methods, and complementary cross-coupling approaches for their synthesis developed. The derivatives were shown to be potent Hsp90 inhibitors outperform the parent compounds in some aspects of the cancer and Parkinson's studies. They are also less toxic, which gives the substrates significant potential for use as therapeutics. The radicicol analogues work is less developed in comparison, but also shows much promise, with good Hsp90 binding observed, albeit with an enthalpic penalty observed compared to the parent compound. Following the commentary, seven primary literature research publications in high quality journals are presented in the thesis all of which have come from this research; this represents an outstanding body of novel and highly important research. Kitson is first and/or corresponding author on 5/7 of these papers, including the manuscript *Nature Chem.* **2013**, (5), 307-314, which is arguably the most impressive contribution of them all. These manuscripts

clearly demonstrate high academic standards and are a major contribution to the chemical and medicinal literature, comfortably meeting/exceeding the standard expected to justify appointment as Associate Professor.

In summary, Kitson has produced an outstanding habilitation thesis. In my opinion, he very clearly meets the standard expected to justify appointment as Associate Professor. The thesis clearly evidences that he is a highly skilled and knowledgeable scientist, with great expertise in synthetic organic chemistry, medicinal chemistry and various associated methods and techniques. Also, although it is not part of my remit to assess Dr Kitson's teaching experience, I note that much of the research described in the thesis was during predominantly-teaching focused positions, attesting to his skill at combining teaching and research very successfully. Kitson has an excellent reputation within the UK for his abilities as an innovative and outstanding and passionate teacher of chemistry – I have no doubt that if the habilitation committee decide to grant Dr Kitson the academic title of Associate Professor ("Docent"), he will be an enormous asset to Charles University.

Dr William P Unsworth, DPhil, MChem, MRSC
(Associate Professor)