Addendum: A cellular chemical probe targeting the chromodomains of Polycomb repressive complex 1

Jacob I Stuckey, Bradley M Dickson, Nancy Cheng, Yanli Liu, Jacqueline L Norris, Stephanie H Cholensky, Wolfram Tempel, Su Qin, Katherine G Huber, Cari Sagum, Karynne Black, Fengling Li, Xi-Ping Huang, Bryan L Roth, Brandi M Baughman, Guillermo Senisterra, Samantha G Pattenden, Masoud Vedadi, Peter J Brown, Mark TBedford, Jinrong Min, Cheryl H Arrowsmith, Lindsey I James and Stephen V Frye

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In our original Article, we reported the discovery of a chemical probe for the CBX domains of Polycomb repressive complex 1 (PRC1). In subsequent studies undertaken in our laboratories by Kelsey Lamb (Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA), we have observed that our modular synthetic approach detailed in this article leads to epimerization at the alanine position. In the reported synthesis in the original paper, the amide coupling of tripeptide intermediate **13** to tripeptide intermediate **7** for the formation of final product UNC3866 (or for the formation of UNC4219, the amide coupling of tripeptide intermediate **13** to tripeptide intermediate **10**) resulted in approximately 40% epimerization at the alanine side chain by NMR. The linear approach outlined in the revised protocol in the Supplementary Note avoids this problem by utilizing a synthetic route in which each amide coupling is performed on the N-Boc-protected amino acid, a method known to diminish epimerization, as validated in our studies by NMR spectra. We note that UNC3866 was originally synthesized using the linear route, despite the modular synthesis reported in the original Supplementary Note, and therefore biological data reported for this compound were not affected. While UNC4219, UNC4007 and UNC4195 were synthesized using the modular route, resynthesis of compounds by the linear route validated that all data obtained using these compounds were unaffected by alanine epimerization. Based on these observations, we provide an alternative synthetic route in this Addendum that avoids alanine epimerization. The protocols have been updated in the Supplementary Note to this Addendum.

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