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V.O. Stadnichenko^{1,2}, A.O. Beshtynarska¹,
P.O. Borysko¹, O.S. Shyshlyk¹, G.M. Tolstanova²

¹ Enamine Ltd.

78, Winston Churchill Str., Kyiv, Ukraine, 02094

² Taras Shevchenko National University of Kyiv

64/13, Volodymyrska Str., Kyiv, Ukraine, 01601

stadal01@gmail.com, v.stadnichenko@enamine.net, vladyslav.stadnichenko@knu.ua

DISCOVERY OF QUINOLINE-TYPE CRBN LIGANDS AND THEIR APPLICATION IN THE PROTAC DEVELOPMENT

Background/Aim. The application of CRBN ligands in degrader design represents one of the most prominent approaches during the development and optimization of PROTACs [1]. This work aims to investigate the efficiency of synthesized CRBN:BRD4 PROTACs with quinoline-type binders as warheads targeting the CRBN E3 ligase. **Methods.** To evaluate ligand and bifunctional degrader binding to the CRBN protein, a TR-FRET assay was used. The ternary complex formation between the protein of interest (POI), PROTAC, and the E3 ligase was assessed using the developed TCF TR-FRET method [2]. **Results.** The quinoline-type compounds were selected during virtual screening and tested for their ability to bind CRBN in vitro. The 3 potent molecules demonstrated IC₅₀ values of 1.2 μ M, 2.4 μ M, and 3.5 μ M in the TR-FRET displacement assay. The set of 9 PROTAC degraders based on quinoline-type CRBN ligands was synthesized by Enamine's Chemistry Department. As a POI, the BRD4 enzyme was selected, and its well-known binder, JQ-1, serves as the warhead for the degrader design. The synthesized PROTACs have been tested in the binary TR-FRET assay, in which competitive binding to the CRBN/DDB1 complex was observed with the tested samples at 1.11 μ M ($n = 4$) and the Thalidomide-labeled probe. As a result, 2 out of 9 tested degraders bound the CRBN/DDB1 complex, with inhibition values >25% at the indicated concentration. Next, the 2 selected PROTACs were tested in dose-response for the ability to form a ternary complex between CRBN/DDB1 and BRD4 (BD1 domain) using the biochemical TCF TR-FRET assay. The known degrader dBET1 was used as an assay control. The EC₅₀ values for the 2 tested PROTACs were below 35 nM. Notably, PROTAC 1a demonstrated EC₅₀ and EC_{max} values lower than those of the reference compound dBET1: 14 nM vs 31 nM and 285 vs 370 nM, respectively. **Conclusions.** According to ternary complex formation analysis, the synthesized PROTAC 1a outperforms the glutarimide-based tool compound dBET1, suggesting that the quinoline moiety in the CRBN warhead represents a novel and potent approach for the PROTAC development.

Keywords: PROTAC, CRBN, ternary complex formation, dBET1.

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