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Development of Small Molecules Targeting Procaspase-8 at the DISC

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Pharmacological targeting *via* small molecule-based chemical probes has recently acquired attention as a valuable tool to dissect molecular mechanisms. Induction of extrinsic apoptosis *via* CD95/Fas and TRAIL-R1/2 is initiated by the formation of the Death-Inducing Signaling Complex (DISC). Procaspase-8 activation at the DISC is a central event triggering extrinsic apoptosis. Procaspase-8 activation takes place at the death effector domain (DED) filaments that are formed at the DISC. Hence, targeting the DED filaments is essential to gain insight into DISC control and pharmacological targeting of extrinsic apoptosis. In this study we developed the group of chemical probes that were designed *in silico* to target procaspase-8 at the DED filaments. This was followed by their experimental validation via cell viability assays and selection of the most effective compounds. Taken together, our study describes a development of new chemical compounds that are constructed to target procaspase-8 and extrinsic apoptosis.

Keywords: procaspase-8, small molecules, DED, DISC, apoptosis, caspase activation, DR