Discovering Novel Antitumor Agents via Untargeted Diversity-Oriented Synthesis (UnDOS): an integrated approach using IVS, bioinformatics, and omics for target deconvolution

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Diversity-Oriented Synthesis (DOS) has emerged as a powerful strategy in bioactive compound discovery, facilitating the generation of structurally diverse molecules that serve as essential chemical probes and promising therapeutic candidates across various fields, including oncology [a, b].
In this work, we present an Untargeted DOS (UnDOS) substrate-based strategy to discover novel antitumor agents and deconvolve their biological targets [c]. Using an *L*-amino acid as a common building block, we designed and synthesized a library of twenty small molecules featuring ten distinct privileged molecular scaffolds, which were phenotypically screened across a panel of human tumor cell lines. Among the synthesized library, compounds 31 and 63 were selected for further study due to their potent antiproliferative activity and selectivity against A-375 melanoma cells. To identify their binding partners and mechanism of action, we deployed an integrated workflow combining inverse virtual screening (IVS), bioinformatics, and multi-omics analyses. Targets were prioritized based on differential expression in A-375 cells versus non-tumorigenic HaCaT keratinocytes. Experimental validation confirmed measurable target interactions, identifying Transient Receptor Potential (TRP) channels and Bromodomain-containing Protein 4 (BRD4) as key mediators of activity. Cellular assays further demonstrated that both compounds induce pro-apoptotic pathways, protein misfolding, and oxidative stress.
Beyond identifying promising antitumor candidates, this study provides a versatile, broadly applicable target deconvolution framework applicable to a wide range of bioactive small molecules.

References

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Short bio:

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