Drug Discovery & Development

Synthesis Of Novel Cereblon E3 Ligase Ligands, Compounds Formed Thereby, and Pharmaceutical Compositions Containing Them

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The Invention

UW-Madison researchers developed a novel class of molecules that bind cereblon (CRBN), a ubiquitin ligase. These molecules may be used in the development of PROTAC therapeutics. The researchers started with a molecule known to bind to CRBN with poor affinity. In silico modeling suggested conformational changes in the molecule could address the poor binding, so they added functional groups to the ring impacting the conformation of the molecule. Some substitutions destroyed binding to the enzyme while others improved binding. Using this structure-activity study, the researchers created small libraries of bi- and tri-substituted molecules. Various substituents were installed at the ortho, meta, and para positions of the phenyl group in PDHUs and compared with the parent compound for relative binding affinity. Interestingly, an analogue with an ortho hydroxyl substituent almost completely lost the binding affinity, while analogues with a meta and para hydroxy group enhanced the binding to 57% and 38%, respectively. Methyl-, ethyl- and chloro-substituents on the ortho-position improved the binding to 35%, 29% and 36% from the original 20% of the parent compound. A compound with a methoxy substituent on the ortho-position decreased the binding, while placing the MeO on the meta-position improved the binding to 33%. Compounds bearing longer substituents on the meta-position further improved the binding to 56% and 44%, respectively. Substituents on the para-positions were also tolerated, though they did not improve the binding as much as those on the meta-positions. The inventors used this structure-activity data to design the next generation molecules they plan to make in the next 12 months.

Additional Information

For More Information About the Inventors

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Tech Fields

- Drug Discovery & Development : Drug production & design

For current licensing status, please contact Rafael Diaz at rdiaz@warf.org or 608-960-9847