Design and synthesis of Hsp90 PROTAC degraders as potential anticancer agents

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Indroduction

Hsp90 (Heat Shock Protein 90) is a chaperon protein which plays role in protein folding and maintaining protein structures. It is overexpressed in cancer and stabilizes many oncoproteins and as such represents a good target for developing anticancer drugs. The majority of approved drugs today operate by *occupancy-driven pharmacology*. The PROTAC approach as a strategy in creating novel drugs utilizes *event-driven pharmacology* in which target proteins are degraded. In recent years it emerged as very attractive and conceptually novel approach in drug discovery and development. PROTACs are molecules with two warheads connected with a linker with general structure: Ligand$_{(protein\ of\ interest)}$-Linker-Ligand$_{(E3\ ligase)}$. One warhead binds the protein of interest (POI) and the other one binds E3 ligase, while the linker brings these two parts in close proximity permitting ubiquitination and subsequent degradation of the protein [1] (*Figure 1*). Two classes of compounds were studied: pyrrolopyrimidine and thienopyrimidine derivatives. Both classes of compounds were reported in the literature [2,3] and their structure is modified in order to investigate whether linker introduction deteriorate binding of those molecules to Hsp90 (*Figure 2*).

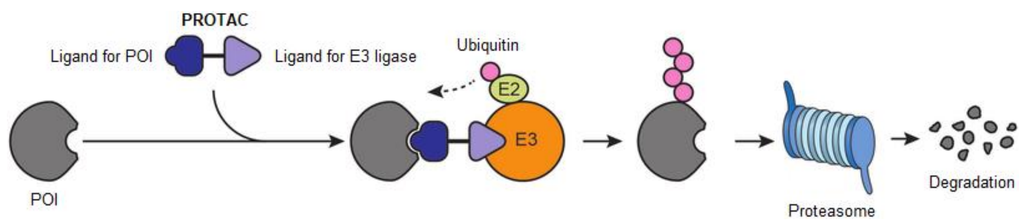

Figure 1. PROTAC-mediated POI degradation

Results and Discussion

Ligand$_{(Hsp90a)}$-Hsp90a interactions were examined using fluorescence polarization competition assay (*Figure 3*). IC_{50} values for compounds *TG-461* and *TG-518* are 0.229 μM and 0.525 μM, respectively.

Conclusion

Introduced linker does not deteriorate binding *TG-461* and *TG-518* to the Hsp90a. Thus, those compounds could be utilized for connecting with E3 recruiting elements using linkers in order to obtain complete PROTACs.

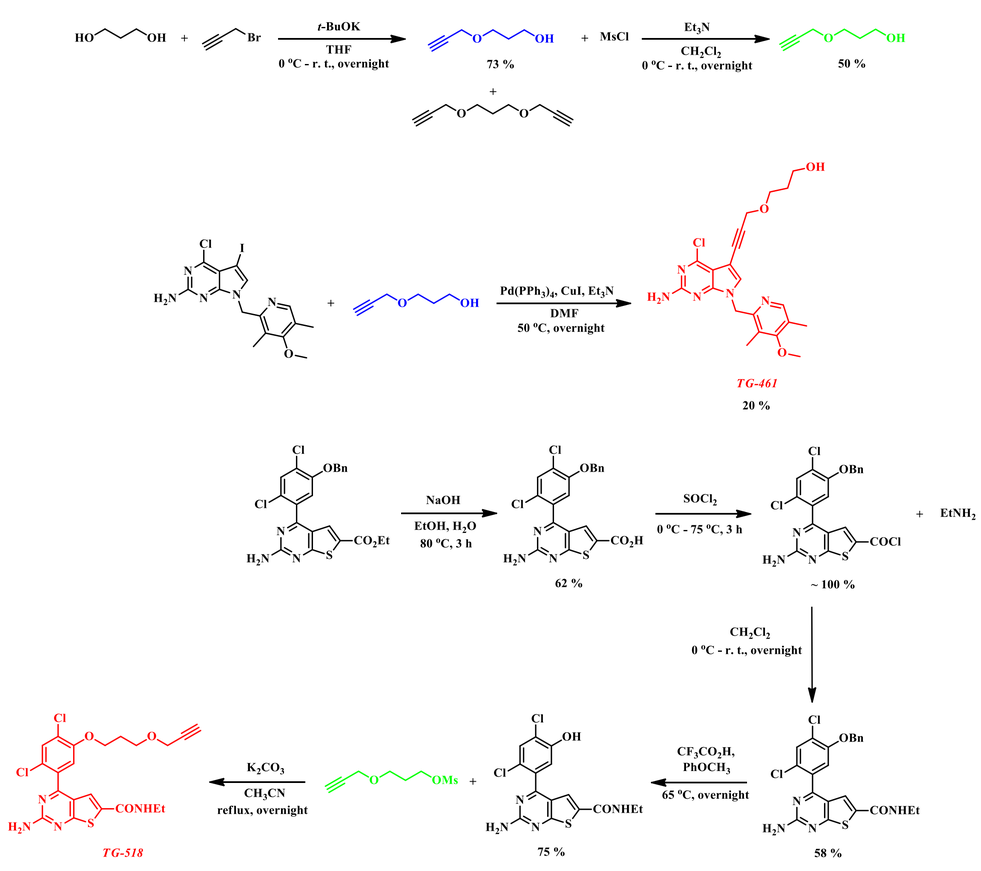

Figure 2. Synthetic routes for the Hsp90 ligands

References

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[3] Brough PA, Barril X, Borgognoni J, Chene P, Davies NG, Davis B, et al. Combining hit identification strategies: fragment-based and in silico approaches to orally active 2-aminothieno[2,3-d]pyrimidine inhibitors of the hsp90 molecular chaperone. *J. Med. Chem* 2009;52:4794−809.

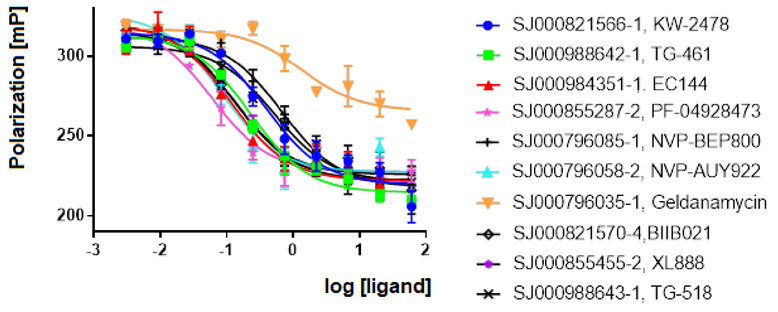

Figure 3. Florescence polarization competition assay

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