Integrated network pharmacology, molecular docking and biological validation revealed the inhibitory effect of a benzoxazinone derivative ZAK-I-57 in hepatocellular carcinoma

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Abstract:

Introduction: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide[1]. Although targeted therapies, such as sorafenib, have demonstrated improved survival benefits, they are modest[2]. Therefore, there is an urgent need to discover novel therapeutic agents for the treatment of HCC. Amidst this landscape, the development of novel therapeutic agent is crucial. This study investigated the therapeutic potential of benzoxazinone derivatives, which have emerged as promising candidates owing to their impressive efficacy and safety profiles.

Materials and Methods: This study explored the potential of benzoxazinone derivatives as innovative agents against HCC through a comprehensive approach integrating synthesis, network pharmacology, molecular docking, and extensive in vitro and in vivo evaluations. Derivatives were synthesized and characterized, followed by computational prediction of target interactions and mechanistic pathways. The anticancer activity of the compound was assessed using cell viability assays in HCC cell lines and western blotting to assess its impact on protein expression and antitumor efficacy in HCC xenografts derived from PLC/PRF/5 and patient-derived tumor xenograft (PDTX#1).

Results: ZAK-I-57 emerged as a standout compound, demonstrating optimal drug-likeness and pharmacokinetic properties that complied with ADMET standards. Molecular docking studies revealed strong affinities for key oncogenic targets, which were substantiated by western blotting assays showing the downregulation of the proliferative markers EGFR and c-MYC and upregulation of the apoptotic marker Bax. *In vitro* and in vivo evaluations confirmed ZAK-I-57's potent antitumor activity, significantly reduced tumor volume and weight, surpassed the performance of sorafenib, and maintained an excellent safety profile without notable systemic toxicity.

Conclusions: ZAK-I-57 presents a promising and innovative strategy for HCC treatment as demonstrated through network pharmacology, molecular docking, and both *in vitro* and *in vivo* assessments, supports its potential as a targeted therapeutic option for HCC (US-provisional patent (US63/657,193).

References:

1. Josep M. Llovet, *et al*. nature reviews clinical oncology, 2024. 21: 294-311.
2. Shikun Jiang, et al. Life Sciences, 2020.258:118252.