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Isatin come on the stage of CDK4/6 inhibitor

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Abstract: Cyclin-dependent kinase (CDK) 4/6 inhibitors have significantly improved the prognosis for patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer, including those with metastatic or advanced breast cancer (mBC/ABC). Recent research has focused on developing CDK4/6 inhibitors with diverse structural frameworks, including isatin-based compounds. Isatin and its derivatives have shown promise in inhibiting CDK4/6, with potential efficacy against breast cancer cell lines. Studies have also indicated that isatinyl-2-aminobenzoylhydrazone (ISABH) complexes, particularly those with transition metals like nickel (Ni-ISABH), exhibit strong binding affinities to CDK6 and fulfill key pharmacokinetic criteria.

Keywords: CDK4/6 inhibitor, cancer, metastasis, breast cancer

The deregulation of the cyclin D1-CDK4/6-Rb signaling cascade, which drives uncontrolled cell proliferation, is a hallmark of breast cancer. Cyclin D-CDK4/6 activity, resulting from cyclin D overexpression, CDK4/6 mutations or amplifications, and the loss of cyclin D-CDK4/6 negative regulators, leads to Rb hyperphosphorylation and, consequently, uncontrolled cell proliferation. Therefore, targeting CDK4/6 is crucial in anticancer therapy [1].

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved three CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—for the treatment of HR+/HER2- advanced or metastatic breast cancer (ABC/mBC) [2]. These orally administered compounds share similar structures and effectively bind to the ATP-binding pocket of CDK4 and CDK6, preventing Rb phosphorylation and halting the cell cycle. Palbociclib and ribociclib exhibit comparable affinity for CDK4 and CDK6, whereas abemaciclib has been shown to be more selective for CDK4 than CDK6 in vitro, with additional activity against CDK9 [1].

The development of CDK4/6 inhibitors has significantly altered the therapeutic management of HR+ breast cancer. However, continued research is essential to develop new therapeutic strategies that can prevent or overcome clinical resistance, thereby optimizing treatment outcomes. Among the promising areas of research are natural substances like quercetin [3] and isatin-containing compounds.

The potential of isatinyl-2-aminobenzoylhydrazone (ISABH) and its complexes with transition metals as CDK6 inhibitors has been investigated in silico [4]. This study demonstrated that isatin-derived compounds exhibit potential against breast cancer cell lines, such as MCF-7 and MDA-MB-231. Additionally, the authors reported that these isatin derivatives could inhibit not only CDK6 but also CDK2, CDK4, and CDK9. The literature reviewed by the authors also supports the use of transition metal complexes as active substances in inorganic-based medicines, illustrating the application of bioinorganic chemistry to a range of diseases, including antibacterial and anticancer therapies.

Nusantoro and Fadlan's (2021) research revealed that the ISABH complex with nickel (Ni-ISABH) demonstrated the highest binding affinity (-9.4 kcal/mol) among the tested transition metal complexes and ISABH. Ni-ISABH binds to the active site of CDK6 and interacts with the amino acid residues Glu99 and Asp104 through hydrogen bonding. Furthermore, Ni-ISABH meets the absorption, distribution, metabolism, excretion, and toxicity (ADMET) criteria according to Lipinski's rule, suggesting that it is a viable CDK6 inhibitor in silico [4].

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