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Extended Abstract

Strategies to Discover p53 Activators and a p73 Activator for Neuroblastoma †

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In our quest to discover antitumor agents with novel mechanisms of action, our strategy concerned multiple molecular modifications in a chemical core. As the xanthone molecule can be considered as a privileged structure, particularly in this field of chemotherapics [1], a library of xanthones was built, with several compounds showing promising cell growth inhibitory activity [2]. To disclose the mechanism of action of the most potent derivatives, in silico and in HTS screening approaches were employed [3].

Following this, our group identified LEM1 as αv inhibitor of the p53–MDM2 interaction [4]. In tumors with impaired p53 signaling, like neuroblastoma (NBL), one of the most common childhood solid cancers, TAp73-activating agents arise as a promising therapeutic strategy, alternative to p53 activation, to suppress tumor growth and chemoresistance [5]. In the present work, we unveil the discovery of LEM2, a small molecule with a xanthone scaffold, as a new activator of TAp73 with antitumor activity, alone and in combination with conventional chemotherapeutics, in NBL [4].

The results showed a potent TAp73-dependent cytotoxic activity of LEM2, superior to that of nutlin-3a (a known TAp73 activator), through induction of cell cycle arrest and apoptosis and upregulation of TAp73 target genes, in NBL cells. Additionally, LEM2 sensitized these cells to the effect of doxorubicin or cisplatin. In conclusion, the potent antitumor activity of LEM2 towards primary patient-derived NBL cells, both alone and in combination with conventional chemotherapeutics, may predict promising clinical applications in NBL therapy.

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