

Discovery of *De Novo* Oxime-containing Flavonoids as Potent Anticancer Agent against Human Nasopharyngeal Carcinomas: Structure-Activity Relationship and Mechanism Studies

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Flavonoids and its derivatives are common components found in traditional Chinese medicine and food. Several studies indicated flavonoids could benefit in cancer prevention or therapy, but their structure-activity relationships (SAR) remain poorly defined. In order to further understand the SAR, a series of oxime-containing flavone derivatives were designed, synthesized and evaluated for their biological anti-cancer potential. The anti-proliferative ability of these compounds was measured by several human cancer cell lines from different origins including nasopharyngeal carcinoma, leukemia and lung carcinoma. Among over 30 different oxime-containing flavone derivatives, (*Z*)-6-[2-hydroxyimino-2-(4-methoxyphenyl ethoxy)]-2-phenyl-4*H*-1-benzopyran-4-one (WTC01) possessed most potent activity against human nasopharyngeal carcinoma cells growth with IC₅₀ of 400 nM. As determined by flow cytometry, WTC01 treatment results in an accumulation of human nasopharyngeal carcinoma NPC-TW01 and HONE-1 cells in G₂-M phase with time- and concentration-dependent manner before cell death. Furthermore, Annexin-V/propidium iodide (PI) binding assay, Hoechst 33258/PI double staining, and PARP cleavage indicates that cell death proceed through an apoptotic pathway. Interestingly, WTC01 also causes mitochondrial transmembrane potential loss and activation of caspase-9 and caspase-3 without noticeable activation of the caspase-8. These results suggest that the WTC01-mediated apoptotic signaling pathway depends on the mitochondria and caspase-9/-3 cascades. Further studies showed that WTC01 inhibits tubulin assembly through binding to the colchicine-binding site of tubulin, this data suggests that tubulin may serve as the cellular target for WTC01. Notably, the *in vivo* study showed that WTC01 exhibits good pharmacokinetic properties and completely inhibits the growth of NPC-TW01 xenograft tumor at *i.p.* doses of 25 and 50 mg/kg in nude mice. Taken together, these findings indicated that WTC01, a novel synthetic oxime-containing flavone, exhibits potent activity against cancer growth through the disruption of microtubule and has potential for management of nasopharyngeal malignancies.