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Aminocarbazole alkaloid derivatives as potential modulators of p53mutants

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The tumor suppressor protein p53 is a major regulator of key cellular processes, including cell cycle arrest, apoptosis, DNA repair, stemness, invasion and migration. TP53 is the most commonly mutated gene in human cancer. In fact, over half of human cancers contain p53 mutations, particularly missense mutations, preferentially localized within the p53 DNA-binding domain. Mutant p53 is frequently associated with patient poor prognosis due to more aggressive tumor phenotypes, particularly increased proliferation, metastasis and resistance to therapy (REF). Heptaphylline is a carbazole alkaloid, isolated from *Clausena harmandiana* with promising antitumor effects. Herein, the semisynthesis of heptaphylline and two related secondary metabolites was performed for the purposes of enhancing their antitumor activity and improve physico-chemical properties. The molecular modifications were based on introduction of amine derivative moieties, which are present in some known p53 modulators. Reductive aminations using sodium triacetobohydride in acidic conditions were applied on three natural isolated carbaldehyde carbazole alkaloids to obtain a small library of amino derivatives. Both natural isolated carbazoles and amino derivatives were tested for their ability to inhibit tumor cell growth in human tumor cell lines expressing different forms of p53 (wild-type, mutants). Moreover, using a yeast-screening assay (REF), it was investigated the ability of heptaphylline to reactivate several mutant p53 forms with high prevalence in human cancer. Natural occuring carbazoles and the first series of amines investigated showed promising tumor cell growth inhibitory effects (GI_{50}<10μM). Also, some derivatives reestablished the wild-type-like activity to several mutant p53 in yeast, behaving as potential reactivators of mutant p53. These results suggest the discovery of a potential lead compound for the development of anticancer agents p53 modulators.

Biography

Solida Long is currently pursuing her PhD from University of Porto, Portugal, in Faculty of Pharmacy. She is a Lecturer from Bioengineering Department, Royal University of Phnom Penh, Cambodia.

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