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DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL IMATINIB AND NILOTINIB ANALOGUES EXPRESSING ENHANCED ANTIPLATELET AND ANTICANCER ACTIVITIES

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Introduction. Platelet activation, is a key factor in the thrombotic events in patients with cancer. Tyrosine kinase inhibitors (TKIs), such as imatinib and nilotinib, are widely used in cancer therapy and, in addition to their anti-tumour properties, they express antiplatelet activities (*Pantazi D., et al. DDDT. 2019;13:4225*). Structural optimisation of these drugs may increase their antiplatelet and anti-cancer activities and may offer potential therapeutic benefit.

Aim. We designed and synthesized novel imatinib and nilotinib analogues and evaluated their effects on tumor cell proliferation as well as their antiplatelet activity, in vitro.

Materials and Methods. A series of structurally optimized imatinib and nilotinib analogues were synthesized and their structural properties were analyzed by means of density functional theory calculations. Platelet aggregation assays in platelet-rich plasma (PRP) in vitro, were performed using human platelets prepared form peripheral blood of healthy volunteers. Platelets were activated with adenosine diphosphate (ADP), thrombin-activated peptide-6 (TRAP-6) or arachidonic acid (AA). Cancer cell proliferation was assessed in HepG2 cells, in culture, by measuring cell viability and growth. Analyses of the relationship between structure and activity of the synthetic imatinib and nilotinib analogues was performed as we have previously described (*Pechlivani et al. Pharmaceuticals, 2024;17:349*).

Results. The synthetic imatinib and nilotinib analogues exhibited significantly increased inhibitory potency towards platelet aggregation as compared with parent compounds, especially when AA was used as a platelet agonist. Importantly, the nilotinib analogues also expressed more potent inhibitory effect on HepG2 cell proliferation. DFT and structural analyses indicate that specific functional group placement, electronic distribution and hydrogen bond interactions contribute to the improved activities of the synthetic molecules. These findings highlight the critical molecular features of the synthetic molecules responsible for the expression of dual antiplatelet and anti-cancer effects.

Conclusions. Targeted structural modifications of imatinib and nilotinib can yield analogues with potent antiplatelet activity while retaining or enhancing their anticancer properties. These results support the development of synthetic molecules for possible therapeutic applications in treating cancer and preventing thrombosis.