Synthesis and structural proof of novel oxazolo[5,4-d]pyrimidine derivatives as potential VEGFR2 inhibitors. *In vitro* study of their anticancer activity

Autorzy

Aleksandra Sochacka-Ćwikła

Andrzej Regiec

Żaneta Czyżnikowska

Urszula Śliwińska-Hill

Anna Kwiecień

Benita Wiatrak

Agnieszka Rusak

Klaudia Krawczyńska

Monika Mrozowska

Sylwia Borska

Katarzyna Ratajczak

Anna Pyra

Marcin Mączyński

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Streszczenie

The present study aimed to design and synthesize novel 6-*N*-benzyloxazolo[5,4-*d*]pyrimidin-7(6*H*)-imines **3a-j** as possible inhibitors of the vascular endothelial growth factor receptor 2 (VEGFR2). The structures of newly synthesized compounds were confirmed via spectral and crystallographic data. NOESY spectroscopy was very useful in distinguishing between 6-*N*-benzyl-7(6*H*)-imine **3a** and isomeric 7-*N*-benzyl-7-amine **4a**, obtained by Dimroth rearrangement. Molecular docking at the VEGFR2 active site was performed, indicating that 7(6*H*)-imines should have a similar binding mode as type II VEGFR2 inhibitors. All derivatives were preliminary evaluated for *in vitro* cytotoxic activity against four human cancer cell lines, including lung cancer (A549), colorectal cancer (HT-29), melanoma (A375), breast cancer (MCF7), using tivozanib as a reference drug, and some of them were subjected to VEGFR2 inhibition, anti-angiogenic activity, and human serum albumin (HSA) binding assays. Only 6-*N*-2,4-dimethoxybenzyl derivative **3h** appeared to be as active as tivozanib against all tested anticancer cell lines but equally toxic to healthy normal human dermal fibroblasts (NHDF). Derivatives **3f** (6-*N*-2-methybenzyl) and **3b** (6-*N*-4-methylbenzyl) have revealed slightly worse activity than **3h**. They were cytotoxic agents comparable to tivozanib against three anticancer lines, but only **3b** showed no cytotoxicity against NHDF. Both **3b** and **3h** proved to be effective VEGFR2 inhibitors with IC_{50} values comparable to that of tivozanib. Notably, **4a** did not actually show an anticancer effect against the tested cancer lines, in contrast to isomeric **3a**. In an angiogenesis assay, **3f** and **3h** significantly suppressed the tube formation ability of human dermal microvascular endothelial cells (HMEC-1), indicating their anti-angiogenic potential. The interactions between these compounds and HSA appeared to occur at two specific binding sites.

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