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Design, Syntheses, and Conformational Study of Angiogenesis Inhibitors

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Since anti-angiogenesis could lead to the suppression of tumor growth, angiogenesis inhibitors have received particular attention for their therapeutic potential. In this study, two angiogenic inhibitors using the bioactive sequence from the kringle 5, AK1(KLYDY), AK2(KLWDF) were designed and synthesized. We have investigated their solution structures using NMR spectroscopy and their activities as angiogenesis inhibitors. AK2 has an intramolecular hydrogen bond between the side chain amino proton of Lys1 and the carboxyl oxygen of Asp4 with a N···O distance of 3.34 Å, while AK1 shows more flexible structures than AK2. Indole ring in Trp is much bigger than the phenyl ring in Tyr and may have good face-to-edge interaction enforcing more rigid and constrained conformational features of AK2. Because of this relatively stable structure, Trp3 in AK2 may have better hydrophobic interaction with Phe5 than Tyr3 in AK1 if two adjacent aromatic groups are located in hydrophobic pocket of receptor. Since AK2 shows the similar anti-angiogenic activities to AK1, we also were able to confirm that the activity of AK1 is irrelevant to the Tyr phosphorylation. More rigid drug with higher activities can be provided by the mimetic approaches. For the further development of the angiogenesis inhibitors, these conformational studies on our lead peptides will be helpful in design of peptidomimetics.