Sintesis dan aktivitas antitrombotik (Inhibisi Agregasi Platelet) turunan peptida Arg-Gli-Asp (RGD), NH2-Pen-Arg-Gli-Asp-Oksazol-Sis-NH2

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Abstrak

Agregasi platelet memainkan peranan di dalam mekanisme terjadinya penyakit-penyakit penyumbatan pembuluh darah seperti serangan "stroke" dan serangan jantung. Interaksi antara fibrinogen melalui untaian Arg-Gli-Asp (RGD) dengan reseptor platelet Glikoprotein IIb/IIIa merupakan tahap terpenting untuk terjadinya agregasi platelet. Interaksi ini dapat diinhibisi oleh peptida yang mengandung untaian RGD.

Peneliti terdahulu telah mensintesis peptida RGD siklis dengan untaian asam amino Siklo(1,5)Ac-Pen-Arg-Gli-Asp-Sis dan menguji aktivitas antitrombotiknya. Namun aktivitas antitrombotik peptida tersebut masih relatif rendah (ICsn 48 µM Plasma kaya platelet [PRP] darah manusia). Pada penelitian ini disintesis peptida RGD dengan untaian asam amino NH2-Per -Arg-Gli-Asp-Gksazol-Sis-NH2 melalui 6 tahapan reaksi. Adanya penambahan gugus oksazol pada peptida tersebut diharapkan dapat meningkatkan aktivitas antitrombotiknya.

Metode sintesis yang dipakai adalah metode sintesis fasa cair dengan aktivator DCCIHOBt (Dikloheksilkarbodiimidall-Hidroksibenzotriazol) dan proteksi Na-amino menggunakan metode t-Boc maupun Fmoc. Rendemen hasil sintesis setiap tahapan adalah 46 % hingga 81 %. Peptida hasiI sintesis diidentifikasi menggunakan Spektrofotorneter Infra Merah dan Spektrometer 'HNMR, serta dianalisis menggunakan Kromatografi Cair Kinerja Tinggi (KCKT). Peptida hasil sintesis diuji aktivitas antitrombotiknya secara in vitro menggunakan PRP darah manusia sehat dengan zat induser ADP dan bantuan alat agregometer. Hasil uji aktivitas antitrombotik memberikan harga IC50 41.4 p.M. <hr>Synthesis and Antithrombotic Activity (Inhibition of Platelet Aggregation) of Arg-Gly-Asp (Rgd) Peptide Derivative, NH2-Pen-Arg-Gly-Asp-Oxazole-Cys-NH2Platelet aggregation plays role in the mechanism of thrombosis disorders such as stroke and heart at-tack. The interaction between fibrinogen via Arg-Gly-Asp (RGD) sequence to the platelet Glycoprotein IIb/IIIa receptor is the most important step in the platelet aggregation formation. This interaction can be inhibited by RGD containing peptide.

In the previous study, the cyclic RGD has been synthesized, Cyclo(1,5)Ac-Pen-Arg-Gly-Asp-Cys and evaluating the antithrombotic activity. The antithrombotic activity of this peptide is relatively low (IC50 48 µM human blood Platelet Rich Plasma [PRP]). In the present study, we synthesized RGD containing peptide, NH2-Pen-Arg-Gly-Asp-Oxazole-Cys-N {2 in the 6 steps of reaction. The introducing of oxazole group into the peptide is expected to improve the antithrombotic activity.

The synthesis method is a liquid phase synthesis with the activator of DCCIHOBt (Dicyclohexylcarbodiimidell-Hydroxybenzotriazole) and Nu-amino protecting group using either t-Boc or Fmoc method. The yield of synthesis on each step is 46% - 81%. The identification of the peptide is

performed by using Spectrophotometry Infra Red and Spectrometry 1H NMR and also analyze using High Performance Liquid Chromatography (HPLC). The antithrombotic activity of the peptide were evaluated through in vitro test using PRP of healthy human blood with ADP as inducer agent, and aggregometer instrumentation. The result of antithrombotic activity test of the peptide is ICsa 41.4 M.M.