Design, Synthesis and Evaluation of New RGD-Peptidomimetics as Possible Antithrombotics – Part I

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ABSTRACT: New RGD-Peptidomimetics containing a rigid olefinic system in their backbone were designed and two such systems viz., 3-[(4-(2-aminoethyl carbamoyl) phenyl carbamoyl)methyl carbamoyl] acrylic acid methyl ester; 2-[(2-[3-(2-aminoethylcarbamoyl)-acryloylamino]-acetylaminobenzoylamino) propionic acid / substituted propionic acids were prepared by appropriate synthetic routes. All the new intermediates and final compounds were characterized with the help of their analytical and spectral data. These new molecules were evaluated for their possible antiplatelet activity by a standard method, ex vivo. Four of the new molecules (7, 14 a-c) were found to possess a potent antiplatelet activity comparable to that of aspirin, employed as a standard.

KEY WORDS : RGD-Peptidomimetics, Platelets, Antiplatelet, GP IIb/IIIa antagonists, Antithrombotics

Introduction

Thrombus is a clot formed inside the blood vessels. Platelets play a major role in thrombus formation and in the pathogenesis of thrombotic diseases such as acute myocardial infarction, unstable angina and cerebral thrombosis(Willerson et al.,1986;Fieschi et al.,1989; Nicol and Israels,2003). Platelets are activated by a wide variety of agonists(Coller ,1990) such as adenosine diphosphate (ADP), thrombin, collagen, serotonin, epinephrine, thromboxane A2 etc., resulting in platelet aggregation leading to clot formation. Current antithrombotic therapy employs agents that modify the platelet / endothelial cell arachidonate-prostaglandin system, such as prostacyclin analogues, cyclooxygenase inhibitors, thromboxane synthesis inhibitors and thromboxane receptor antagonists; and anticoagulants, such as heparin. Because of the involvement of several endogenous agonists in activating platelet function and aggregation, an inhibitor which acts against all agonists would represent a more efficacious antiplatelet agent than the currently available agonist-specific antiplatelet drugs.

Recently, a common pathway for all known agonists has been identified, namely the membrane protein, glycoprotein IIb/IIIa receptor complex (GP IIb / IIIa), mediating platelet aggregation(Phillips et al.,1991). The interaction of these receptors with adhesive glycoproteins present in subendothelium and in plasma allow attachment of platelets to damaged vessel surfaces or other platelets leading to thrombus. The development of a GP IIb/IIIa antagonist represents a promising new approach for antiplatelet activity.

The glycoprotein IIb/IIIa does not bind soluble proteins on unstimulated platelets, but GP IIb/IIIa in activated platelets is known to bind four soluble adhesive proteins, namely fibrinogen, Von Willebrand factor, fibronectin and vitronectin. The binding of fibrinogen and Von Willebrand factor to GP IIb/IIIa causes platelets to aggregate (Bennett and Vilaire.,1979).

The inhibitors of platelet aggregation by selectively blocking the association of fibrinogen-GP IIb/IIIa has formed the basis of an attractive antithrombotic strategy independent of various activation pathways without interfering the function of other receptors(Scarborough and Grelter.,2000;Phillips and Agir.,1977).

The binding of fibrinogen is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to adhesive proteins that bind GP IIb/IIIa(D’Souza et al.,1990;Mousa et al.,2001;Mousa and Bennett.,1996) Inhibition of GP IIb/IIIa with peptides containing the RGD sequence, or peptidomimetics based on the RGD sequence results in abolition of platelet aggregation and platelet thrombus formation (Coller et al.,1995).

The identification of the RGD sequence as a pharmacophore represented the first stage of the development of a peptide model for rational design(Ojima et al.,1995). The essential requirements to be a RGD-peptidomimetic are recognized, mostly such as: a basic terminal and an acidic terminal with a spacer of 13-16 atoms, the rigidity of the peptide backbone and in plasma allow attachment of platelets to damaged vessel surfaces or other platelets leading to thrombus. The development of a GP IIb/IIIa antagonist represents a promising new approach for antiplatelet activity.

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