Synthesis and Anti-platelet Activity of 3-phenyl-4(1H)-quinolones

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ABSTRACT: A series of substituted 3-phenyl-4(1H)-quinolones and their 4-alkoxy derivatives have been prepared and evaluated for antiplatelet activity. Among the series compound IVb 1 with 5-ethyl substituent and 4-methoxy group showed greater potency (IC50 = 13.29 µM) when compared to Aspirin (IC50 = 28.10 µM).

Introduction

Thrombin-mediated platelet activation and aggregation are critical for arterial thrombosis in unstable angina and myocardial infarction [Ruggeri et al., 2002]. Human platelet expresses two thrombin receptors PAR1, the principal receptor, and PAR4, which serves as an auxiliary factor to signal platelet activation [Covic et al., 2000]. Platelets play a central role in normal hemostasis and are key participants in pathologic thrombosis due to their capacity to adhere to injured blood vessels and to accumulate at the place of injury. Major stimuli able to induce platelet activation including shape change (into spiny spheres), secretion and aggregation include: collagen, thrombin, and adenosine diphosphate (ADP). These items can bind to fibrinogen, aggregate, and release the contents of their intracellular granules including ADP and serotonin; ADP and arachidonic acid (AA) metabolites act as endogenous platelet activators for thromboxane A2 (Tx A2), intensify the extent of platelet aggregation, and provide positive feedback. Platelet adhesion and activation is a normal physiological response to the accidental rupture of blood vessels, and when such activity is uncontrolled may cause thromboembolic artery occlusion, acute coronary syndrome, and ischemic stroke.

The process of platelet adhesion to extracellular matrix consists in binding to various glycoprotein (GP) receptors mediated by von Willebrand factor (vWF) and collagen [Eriksson et al., 2002]. Factor Xa is a trypsin-like serine protease situated at the convergence of the surface-activated intrinsic and factor-activated extrinsic coagulation pathways. The prothrombinase complex is formed by factor Xa on the phospholipid surface with factor Va and calcium; it catalyzes the proteolysis of prothrombin to thrombin (factor IIa).

Thrombin is the main, final enzyme in the phospholipids coagulation system that leads to fibrin formation. It provides positive and negative feedback regulatory signal in the normal hemostasis, while in pathological conditions factor Xa provides catalytic activation of thrombin. Thus, the inhibition factor Xa affects the coagulation but not the platelet function. Therefore, the inhibition factor Xa may provide a novel, effective antithrombotic drug that provides no risk of bleeding. Recently, the inhibition factor Xa has been intensely investigated in order to replace the existing therapies in the treatment or prevention of thromboembolic disorders [Huang et al., 2003]. Overall, looking at existing therapies and drugs, it can be argued that only some of the thrombotic disorders can be treated efficiently at this moment. Limitations originate from the mechanisms of action, pharmacokinetics, side effect profile and route of administration [Costi et al., 2005]. The current therapies necessitate the development of new, better and safer antithrombotic drugs with different modes of action.

Certain quinolin-2(1H)-one (carbostyril) derivatives have been proved to possess antiplatelet, anti-inflammatory, anti-ulcer, vasodilatory, and phosphodiesterase inhibitory activities [Tominaga et al 1984, Fujioka et al 1992]. Studies on quinolin-2(1H)-one skeleton revealed that the activity was influenced not only by the kind of peripheral side chains but also by the position, 5-substituted quinolin-2(1H)-one exhibited the most potent positive inotropic effect among their positional isomers [Tominaga et al., 1987]. The quinolin-2(1H)-one moiety is versatile and the inhibitory activity of quinolin-2(1H)-one α-methylene-cbutyrolactones against arachidonic acid (AA)-induced platelet aggregation decreases in the order 7-substituted > 6-substituted > 8-substituted. Huang et al., 1998 reported a series of phenyl-4-quinolone possessed aspirin like antiplatelet activity. Among all those compounds, 3-phenyl-4-quinolones (R3 =