SYNTHESIS AND SAR OF 2-CARBOXYLIC ACID INDOLES AS INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1

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Plasminogen activator inhibitor-1 (PAI-1) is a member of the serine protease inhibitor (serpin) gene family and is the principal inhibitor of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA*) in vivo*. These serine proteinases convert plasminogen, an inactive zymogen, to the active enzyme plasmin, which digests fibrin clots by degrading insoluble fibrin molecules to small soluble fragments. In the acute setting, PAI-1 stored in platelet α-granules can be released upon platelet activation, resulting in significant local concentrations and the resistance of platelet-rich thrombi to lysis. In healthy individuals, PAI-1 expression is low, but it is elevated significantly in a number of diseases, including deep vein thrombosis, atherosclerosis, and type II diabetes. We have synthesized and evaluated a novel series of 2-carboxylic acid indole based inhibitors of PAI-1. Systematic modification of the N-1 position, the 5-position, and the 2-carboxylic acid of the indole scaffold resulted in the identification of several compounds that showed good potency against PAI-1. The design, synthesis and binding activity of 2-carboxylic acid indoles will be presented.