EASTERN MICHIGAN UNIVERSITY

Chemistry Department

M. S. Thesis Seminar

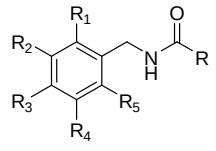
Darshani Weerakoon

(Cory Emal, advisor)

Tues., April 27th, 4:00 pm, Science Complex Rm 156

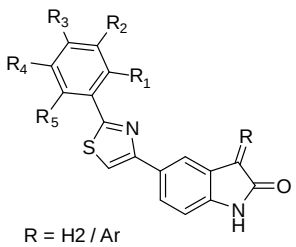
Design, Synthesis and Evaluation of Small Molecules as Inhibitors of Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor type-1 (PAI-1) is a member of the serine protease inhibitor (serpin) superfamily. Excessive levels of PAI-1 inhibit urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA), which is liable for the regulation of fibrinolysis as well as for the development of different pathological diseases like obesity, metabolic syndrome, tumor invasion and metastasis, and coronary heart disease. Currently, there is no Food and Drug Administration approved treatment for inactivating higher levels of PAI-1. Therefore, PAI-1 is considered an attractive drug target. Due to PAI-1's different structural conformations and multiple binding domains, development of PAI-1 inhibitors is a challenging situation. The most important challenge is to design and synthesize more potent molecule that could effectively inhibit PAI-1 than previously reported compounds. In this research study, according to the identified leading molecule, we describe the synthesis and evaluation of novel low molecular weight amides containing various moieties, including *para*-chlorobenzyl, polyphenols, oxindoles, or isatin-based units. By changing the substitution patterns of these compounds we will effectively change the potency of our inhibitors, and will be able to develop a structure-activity relationship that will allow us to design a more potent small molecule as a PAI-1 inhibitor.



R = Hydrazide
Alkyl / Aryl Hydrazide
Catechol

R1, R2, R3, R4, R5 = H / EWG



R = H2 / Ar

R1, R2, R3, R4, R5 = H / OH / EWG