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Abstract

Design and Synthesis of Cysteine Protease Inhibitors †

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We have been preparing new dipeptidyl inhibitors against parasitic cysteine proteases cruzain (related to Chagas disease) and rhodesain (related to Sleeping Sickness disease), and against human cathepsins. Inhibitors display new warheads embedded into a dipeptidic framework. Dipeptidyl epoxyesters [1] and Dipeptidyl enoates [2] are highly potent irreversible inhibitors of cruzain and rhodesain. We also prepared an oxidized version of well-known Vinylsulfones (Epoxysulfones [3]) as inhibitors of human cathepsins. Recently, we have reported the synthesis of Dipeptidyl nitroalkenes [4] as a new type of highly potent covalent reversible inhibitors of cysteine proteases exhibiting certain selectivity for the parasitic cysteine proteases rhodesain and cruzain.

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