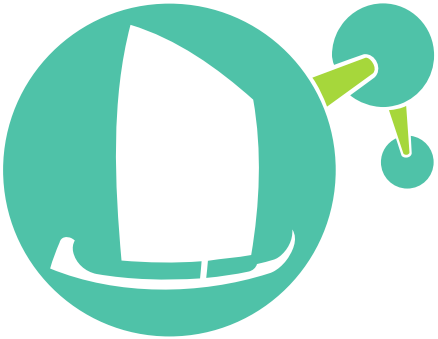

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Design, synthesis and biological evaluation of cysteine protease inhibitors

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Cysteine proteases are proteolytic enzymes involved in the degradation of proteins. Considering their sequence homology three structurally different groups are formed: papain-like (clan CA), ICE-like (clan CD) and picornain-like (clan PA(C)) [1]. The great majority of cysteine proteases belong to the first two clans, being of particular interest for this work, parasite cysteine proteases which belong to clan CA. Cysteine proteases are implicated in several disease processes, such as inflammatory and immunological disorders [2], playing also a key role in some parasites life cycle, like falcipain from the parasite, *Plasmodium falciparum*, the causative agent of malaria [3]. *Plasmodium falciparum*, expresses four cysteine proteases from clan CA, known as falcipains, being falcipain-2 and 3 of particular interest as therapeutic targets given their importance to the parasite life cycle [3]. Several cysteine proteases inhibitors have been developed, taking in consideration the recognition sequence of peptide substrates and different warheads have been tested, like, diazo ketones. This class is very interesting since it inhibits irreversibly, cysteine proteases, by alkylation of the active site thiol group. Besides the irreversible inhibition mechanism , these compounds also present a very high specificity for cysteine proteases, although they are also able to inhibit serine proteases but in a much slower pace [4]. Bearing these facts in mind, several compounds carrying the diazo moiety were synthesized (Figure 1) [5,6], and their activity against falcipain-2 was evaluated by Prof. Philip Rosenthal in the USA.

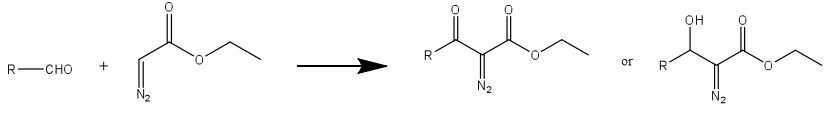

Fig. 1. Generic scheme for the synthesis of diazo moiety bearing compounds (R = alkyl, aryl, peptidyl)

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