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Access to modified peptides with heterocycle backbones using combinatorial chemistry

Applications of peptides in medicinal chemistry have several inherent limitations which can be resolved by use of peptide-like molecules. The cleavage of amide bond by proteases, low permeability, rapid metabolic processing, excretion and unwanted side effects are main restriction associated during peptide utilizations. Therefore, the development of new synthetic protocols to functionalized peptides is very important in view point of medicinal chemistry. Multicomponent reactions (MCRs) are an important and simple method in organic synthesis for the preparation of novel libraries of natural product-like compounds using naturally occurrence starting materials.

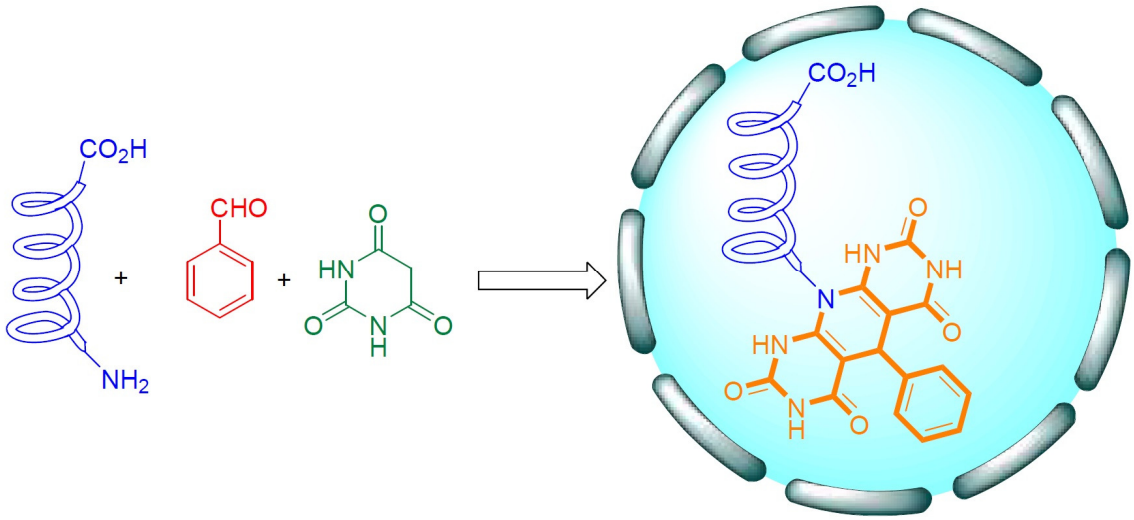
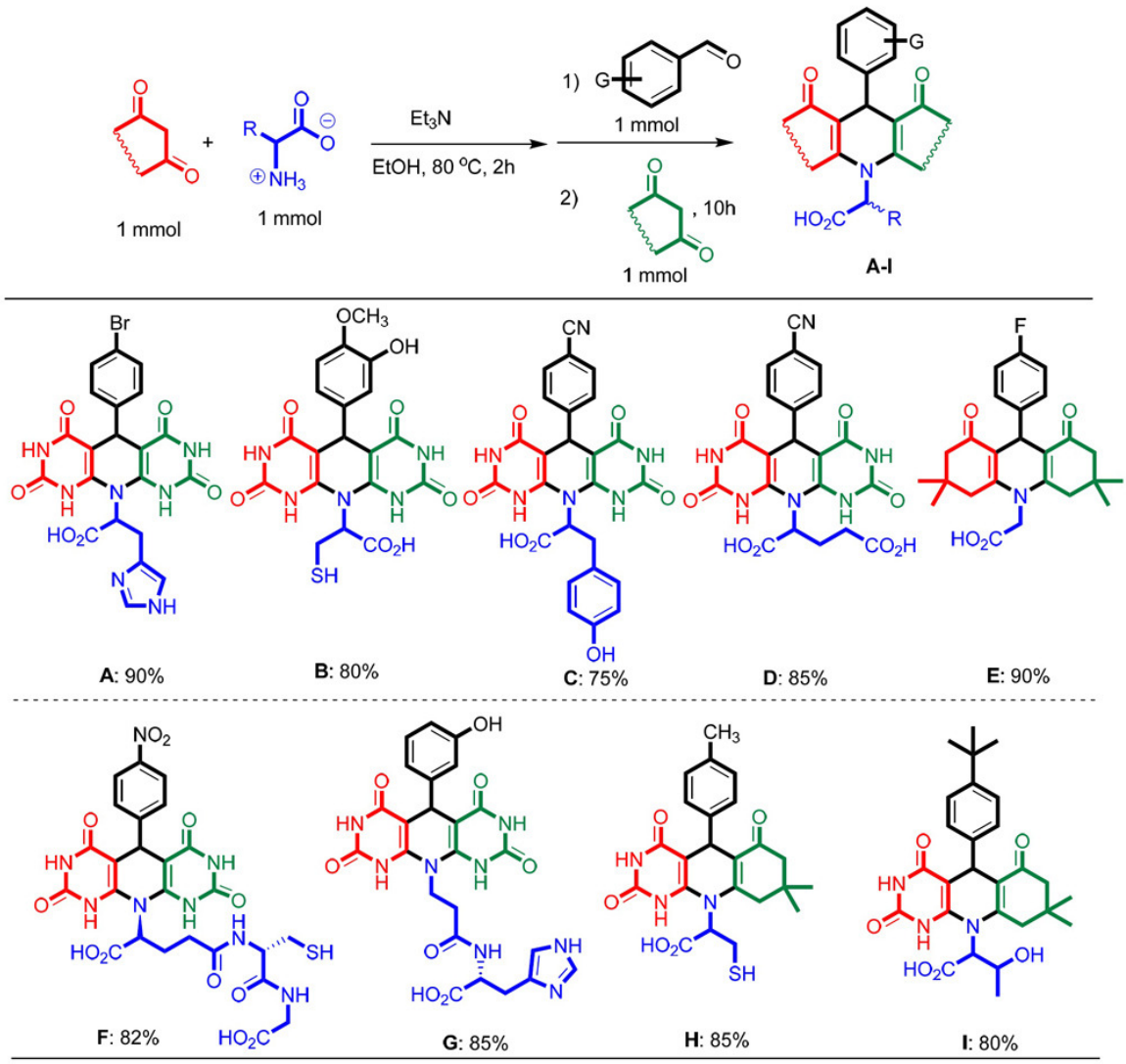


Fig. 1. A schematic representing the functionalization of peptides through a multicomponent reaction.

Consequently, design of a synthetic approach to use peptides in MCRs results in the production of new peptide-like compounds, which maybe help us to resolve peptide application limitations and open up a new direction on further application of these compounds. As well, by use of amino acids as unites of peptides in MCRs, it is possible to synthesize new functionalized amino acids which can be used in synthesize of desired peptides. Encouraged by our previous work, we anticipated that amino acids and peptides might also be good participants in MCR reactions as amine component. To our delight, a variety of amino acids and peptides could be efficiently undergone in a MCR containing β-dicarbonyl compound and aldehydes, furnishing heterocyclic functionalized amino acids and peptides under mild reaction conditions (Fig. 1). An optimized condition was found to convert different amino acids and peptides to corresponding pyrimidine-fused heterocycles in excellent to good isolated yields (Scheme 1).



Scheme 1. Synthesis of amino acid and peptide functionalized heterocycles.

The generality of this protocol was highlighted using a range of amino acids including histidine (**A**), cysteine (**B**), tyrosine (**C**), glutamic acid (**D**) and glycine (**E**). Furthermore, glutathione (**F**) and L-carnosine (**G**) peptides were also worked well with this MCR. Interestingly, it is possible to conduct a four-component reaction using different β-dicarbonyl compound, affording different heterocyclic backbone. For example using barbituric acid and dimedone, acridine derivatives incorporating amino acid moieties were synthesized (**H** and **I**).

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Publication

Amino acids and peptides as reactants in multicomponent reactions: modification of peptides with heterocycle backbones through combinatorial chemistry.
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