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One-pot synthesis of some new fluoro dipeptides from fluorinated isoxazoline derivatives using solid-phase ball-milling technique

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ABSTRACT Solid-phase peptide synthesis (SPPS) of some new fluorinated dipeptides using a mechanochemical procedure from fluorinated-isoxazoline derivatives has been reported. Unlike dicyclohexylcarbodiimide, we have successfully employed 2-chloro-4,6-dimethoxy-1,3,5-triazine as a coupling reagent in the presence of ethyl acetate as a liquid additive during the coupling reaction. This solvent-free procedure showed a remarkably faster reaction rate and enhanced workup process, as well as yields of the reported dipeptides. This could be due to the fact that the development of *N,N*-dicyclo hexylurea (insoluble byproduct) can be easily avoided in the absence of dicyclohexylcarbodiimide (DCC), which is usually responsible for the purification of the synthesized peptides, and consequently, yields are lower. Moreover, using DCC as a coupling reagent makes the synthetic procedure tedious as well. Synthesis of these reported fluoro-dipeptides has also been compared. Preliminary studies have shown that a few dipeptides exhibit anticancer activities.