Strategy for synthesis of enantiomerically pure xanthones - amino acid derivatives

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Xanthone derivatives can exhibit a variety of physiological/pharmacological activities, depending on the nature and position of the substituents in the dibenzo-γ-pyrone scaffold.[1] The ability of chiral derivatives of xanthones with potential pharmacological associated properties and enantioselectivity have been described.[2]

Nowadays, chiral pharmaceuticals represent 40–50% of the market and the preferential approval drives towards the use of enantiomerically pure form in therapeutics.[3] Based on the past experience a new small library of promising chiral xanthones - amino acid derivatives, for further biological activity evaluation, was synthesized. Both enantiomers of the amino esters from valine, phenylglycine, alanine and leucine were bonded to carboxylated xanthones using *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent. Mild alkali conditions were used to hydrolyse the esters in order to obtain the chiral amino acid derivatives.

The structures of all the compounds were elucidated by ^{1}H and ^{13}C NMR, IR and MS. The enantiomeric excess was evaluated by liquid chromatography using the chiral stationary phase (Lux 3 µm cellulose) and diode array detector.

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1. Pinto, M.M.M., *et al. Curr. Med. Chem*. 2005, 12, 2517.
2. Fernandes, C., et al. Bioorg Med Chem. 2014, 22(3), 1049.
3. Tiritan, M. E., Ribeiro, A. R., Fernandes, C., Pinto, M. M. M. (2016). Chiral pharmaceuticals 1-28. Kirk-Othmer Encyclopedia of Chemical Technology. Edited by Wiley online Library.DOI: 10.1002/0471238961.1608011823092009.a01.pub2