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SYNTHESIS AND PHARMACOKINETIC STUDY OF BIOACTIVE MORITA-BAYLIS-HILLMAN ADDUCTS

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ABSTRACT

Morita-Baylis-Hillman Adducts (MBHA) isatin derivatives represent an important class of compounds with a 3-hydroxy-2-oxindole core, that possesses a wide spectrum of biological activities, such as antiparasitic, antitumor, antimicrobial, and anti-inflammatory.[1] These polyfunctionalized compounds are obtained from an addition reaction between electrophilic species and different alkenes containing an electron-withdrawing group (Michael acceptor) and catalyzed by tertiary amines, such as DABCO, the most commonly used. However, obtaining MBHA requires a long reaction time and results in low product yields. In this context, the use of Deep Eutectic Solvents (DES) has emerged as an alternative media to substitute toxic and volatile organic solvents and improve the reaction conditions.[2] In the search for synthesis based on green chemistry principles, our research group presents herein the MBHA synthesis using choline chlorine-based-DES and the evaluation of the pharmacokinetic properties of the synthesized molecules. The adducts (IsaCN, CH_3IsaCN, CH_3IsaCO_2CH_3) were prepared using isatin and *N*-methylated derivatives, with methyl acrylate or acrylonitrile used as Michael acceptor, DABCO as catalyst, and DES (ChCl:U and ChCl:EG) as reaction solvent. The solvent based on ethylene glycol was used for the reaction having acrylonitrile as the acceptor, and ChCl:U for the reaction with methyl acrylate, to avoid parallel transesterification reaction. We observed an improvement in the reaction conditions, considering the lower reaction time and DABCO decrease from stoichiometric to catalytic amounts when compared with the traditional method.[2c] At the end of the reactions, the DES was recovered, recycled, and used for up to four cycles without loss of catalytic activity. The pharmacokinetic tests (*in vitro* tests of permeability through the gastrointestinal tract-GIT, blood-brain barrier-BBB, and microsomal metabolism)[3,4] were performed with the LASSBio-RJ research group. The fraction absorbed by the gastrointestinal tract was 29.68 and 45.82%, for IsaCN and CH_3IsaCN, respectively, presenting a great improvement with the insertion of methyl group. When the ester group was added to the compound CH_3IsaCO_2CH_3, the increase in the fraction absorbed was up to 10%, indicating that the presence of methyl and ester groups resulted in a permeability increase. On the other hand, the insertion of these same groups caused the BBB permeability reduction (IsaCN - 2.04×10^{-6}cm/s, CH_3IsaCN - 1.98×10^{-6}cm/s, CH_3IsaCO_2CH_3 - 1.97×10^{-6}cm/s.). All compounds evaluated presented a decreased pattern as the incubation was increased, results compatible with a metabolization process, indicating the occurrence of the hydrolysis process. In conclusion, we have developed a MBHA ecofriendly synthesis. In addition, from the *in vitro* tests, it was possible to observe that the insertion of groups such as methyl and ester favors permeability through the GIT, while disfavors permeability through the BBB.

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