Efficient synthesis of *N*-acylhydrazones in deep eutectic solvents: design of potential anticonvulsant agents and *in silico* study

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Keywords: Eco-friendly methodology, p-TSA, Lipinski parameters, Epileptic activity.

ABSTRACT

The use of eco-friendly solvents has been widely applied in the synthetic organic chemistry area, especially to substitute organic solvents which are toxic and volatile [1]. In this regard, Deep Eutectic Solvents (DES) have gained attention as a sustainable alternative compared to traditional organic solvents, besides having high purity and tunable viscosity and density [2]. In the field of medicinal chemistry, it is imperative to search for new drugs for epilepsy treatment, a neurologic disease that results in convulsive seizures caused by abnormal brain activity [3]. Current treatments for epilepsy are often less effective, frequently require combination with other therapies, can cause many adverse effects, and typically need to be used for extended periods. Thus, given the need for more selective drug candidates with fewer side effects, we present the synthesis of a new series of *N*-acyl-hydrazones with potential anticonvulsant activity, using DES-based green methodology as catalyst/solvent. In addition, an *in silico* study is provided to determine some insights about the oral bioavailability of the synthesized molecules. The reactions were performed in four different solvents, using choline chloride as the hydrogen bond acceptor and p-toluene sulfonic acid (*p*-TSA), urea (U), ethylene glycol (EG), or oxalic acid (OxA), as the hydrogen bond donor. These solvents were tested in a model reaction between isatin and benzhydrazide and the best reaction condition was extended for the other products. All compounds were characterized by Infrared and ^{1}H and ^{13}C Nuclear Magnetic Resonance. In addition, *in silico* studies were performed using the SwissADME online platform. Initially, the reaction conditions were performed with the model reaction, in the presence of 500 mg of each DES, and the reaction times varied between 1-120 minutes. The best reaction condition was achieved in ChCl:*p*-TSA, with complete conversion of the starting materials in only 1 minute and an excellent product yield of 95%. However, this solvent has the disadvantage of being very viscous (434 $mPa.s^{-1}$), which makes its handling difficult, when the reactions are performed at room temperature. To address this limitation, the addition of water to the eutectic solvent has proven to be a good option for the viscosity decrease without efficiency loss [4]. The reactions were performed in ChCl:*p*TSA:H_2O using different water contents (15, 35 e 50%), and in all cases the catalytic effect was maintained. Considering this similar behavior, we decided to use the condition with 50% water content to the other substrates, due to the smaller components amount used and easy handling, which provided the desired products in low reaction time (1-20 min) and good to excellent yields (72-96%). After the reaction, the DES was recovered and filtered with activated carbon, to be used in subsequent reactions. *In silico* parameters of the synthesized compounds indicated desirable characteristics for oral drugs, according to the Lipinski rule, since the rotational bonds and hydrogen acceptors/donors are within the established limits. The results showed cLogP between 1.98 and 3.72, molecular mass less than 500 g/mol, and adequate polar surface area, thus indicating good cell permeability. Furthermore, the results shown in the boiled-egg graph were significant, since of the 18 synthesized compounds, 14 presented good lipophilicity and adequate molecular size, showing potential to cross the blood-brain barrier. These characteristics suggest that therapeutic effects act directly on the central nervous system, like those needed for neurological diseases, such as epilepsy. On the other hand, compounds that present free amide nitrogen have characteristics for passive gastrointestinal absorption. Therefore, these molecules are relevant candidates for future studies on their biological activity. In addition, the reaction speed and the achievement of yields above 90% are highly relevant benefits from the point of view of green chemistry. The low toxicity and the possibility of reusing the solvent/catalyst without loss of catalytic activity at the end of the reactions demonstrate a sustainable resource.

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