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Original article

Dihydropyrimidin-(2*H*)-ones obtained by ultrasound irradiation: a new class of potential antioxidant agents

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Abstract

An efficient and simple synthetic protocol for the Biginelli reaction has been developed for the preparation of several new dihydropyrimidinones, under ultrasound irradiation in the presence of NH_4Cl, in good yields and short reaction time. Some of the synthesized compounds were tested in vitro for their antioxidant activity. All of the selected compounds showed some antioxidant activity. Analogues compounds **3b** and **4b** exhibited a strong activity against lipid peroxidation induced by Fe + EDTA, while compounds **3b** and **3d** were the most potent in reducing ROS levels.

Keywords: Biginelli; Dihydropyrimidinones; Antioxidant; Reactive oxygen species; Pharmacological

1. Introduction

Dihydropyrimidinones (DHPMs) and their derivatives have attracted interest in medicinal chemistry, exhibiting pharmacological and therapeutic properties. The interest has shifted from DHPM calcium channel modulators [1] to other biologically active DHPM derivatives, e.g. α_{1a} adrenoceptor-selective antagonists, useful for the treatment of benign prostatic hyperplasia [2]. Moreover, the antihypertensive, antiviral, antibacterial and antitumoral activities have been described in [1,3]. In addition, several alkaloids containing the DHPMs core have been isolated from marine sources, which also exhibited interesting biological properties [4]. DHMP derivatives have clearly defined virus-inhibiting properties with respect to type 1 human immunodeficiency [5]. Although, during the last years extensive studies on the pharmacology of DHPMs have been reported in [3–5], the antioxidant activity of this ring system has never appeared in the literature. In the pathologic conditions an overproduction or scavenger diminution of the reactive oxygen species (ROS) can occur. In fact, ROS overproduction has been implicated in the installation and/or progression of a variety of human diseases, including diabetes and various neurodegenerative diseases [6]. Thus, the interest in natural and synthetic antioxidant compounds that could potentially retard the development of these diseases has grown considerably in the scientific community in the last decades.

The aim of this study was to evaluate the antioxidant potential of novel dihydropyrimidin-(2*H*)-ones. The procedure described herein provides an interesting protocol for the synthesis of novel dihydropyrimidin-(2*H*)-ones in good yields and operational simplicity. Importantly, all the dihydropyrimidin-(2*H*)-ones tested were pharmacologically active as antioxidant agents.

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2. Chemistry

The simple and direct method for the synthesis of DHPMs reported first by Biginelli in 1893 [7], involves a reaction in which three reactants come together in a single reaction vessel to form a new product that contains portions of all the components, a multicomponent reaction. The classical Biginelli reaction is a condensation reaction between an aldehyde, β-ketoester and urea under strongly acidic conditions. Usually, only low to moderates yields are obtained, in particular when substituted aromatic or aliphatic aldehydes are employed. In order to improve the efficiency of Biginelli reaction, many synthetic strategies involving combinations of Lewis acids and transition metal salts, e.g. BF_3–OEt_2 [8], montmorillonite (KSF) [9] polyphosphate esters [10] and reagents like $InCl_3$ [11], $InBr_3$, LiBr [12], TMSCl/NaI [13], $LaCl_3{\cdot}7H_2O$ [14], $CeCl_3{\cdot}7H_2O$ [15], $Mn(OAc)_3{\cdot}2H_2O$ [16], ammonium chloride (NH_4Cl) [17], which give better yields of DHPMs.

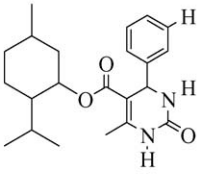
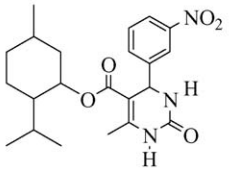
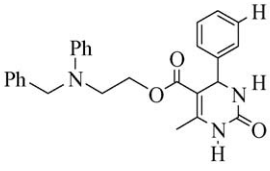
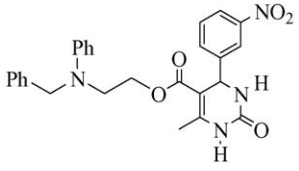
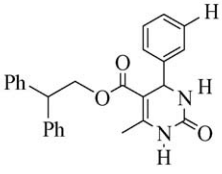
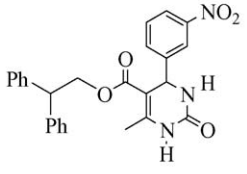
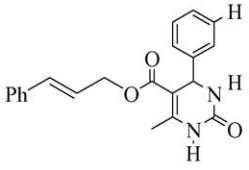
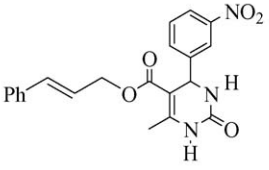
3. Result and discussion

A survey of literature shows that many organic reactions have been accelerated by ultrasound irradiation. Compared with traditional methods, this technique is more convenient and easily controlled [18].

Recently, we have developed a general method for the synthesis of 4-halo-3,5-dimethyl pyrazoles under ultrasound irradiation [19]. Stefani and Gatti [20] reported an efficient protocol for the synthesis of DHPMs by microwave irradiation in solvent free conditions. As part of our study searching on heterocyclic chemistry, we herein report the convenient synthesis of novel DHPMs by the one pot condensation of β-ketoesters **2** with appropriated aldehyde and urea, using ammonium chloride (NH_4Cl) as a mediator of the reaction. In the present study, the Biginelli-type cyclocondensation of a number of the four β-ketoesters **2** have been studied. The choice of ammonium chloride (NH_4Cl) was dictated by the inexpensive cost and the ability to promote the Biginelli reaction [17]. In our studies, we found that the methanol solvent reaction appropriated for these reactions gave the best results and in the absence of ammonium chloride no cyclocondensation occurred.

The cyclocondensation of β-ketoester **2** with aromatic aldehyde, urea, ammonium chloride (NH_4Cl 99.998%, *Merck Index* **12**, 537), in 15 ml of absolute methanol was irradiated in a water bath of an ultrasonic cleaner with a frequency of 40 kHz and a nominal power of 130 W, at 60 °C for the period as indicated in Table 1. The reaction flask was located in the

Table 1
The novel DHPMs **3**–**4**

Dihydropyrimidinones 3	Time (h)	Yields (%)[a]	Dihydropyrimidinones 4	Time (h)	Yields (%)[a]
 **3a**	5	65	 **4a**	3.5	65
 **3b**	2.5	80	 **4b**	3	90
 **3c**	3.5	75	 **4c**	3.5	73
 **3d**	3.5	75	 **4d**	3.5	70

[a] Yields of isolated products