Novel 3-(2-Oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoates from Dimethyl-2-oxoglutarate and Test of Their Biological Activity

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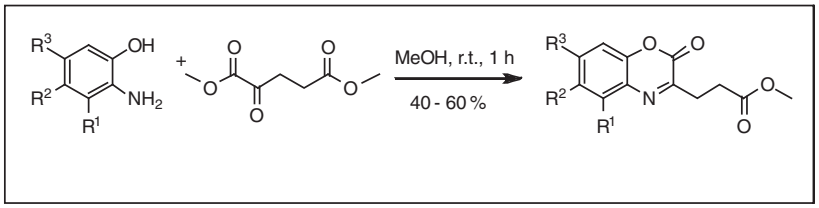

Five novel 3-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoates were synthesized under mild conditions from 2-aminophenols and dimethyl-2-oxoglutarate. Biological assays of these 1,4-benzoxazinones were conducted with three bacterial strains and one yeast. All compounds were active against a *Candida albicans* ATCC 10231, whereas only methyl 3-(6-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoate showed a general moderate activity against the bacterial strains tested.

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INTRODUCTION

This article was inspired by two conceptually different areas of our research. On the one hand, 2-oxoglutaric acid, well known as a part of the citric acid cycle, is—in accordance to the *White biotechnology for green chemistry* concept—a 2-oxocarboxylic acid [1] now accessible in large quantities by fermentation of paraffines, glycerol, ethanol, glucose, or sunflower oil. Hence, 2-oxoglutaric acid is on its way from a laboratory chemical to a biotechnologically manufactured industrial product [2–4]. Earlier, we reported on the synthesis of heterocycles based on this building block [5]. On the other hand, naturally occurring 2*H*-1,4-benzoxazin-3(4*H*)-ones from cereal plants are well known for their high biological activity as intrinsic resistance factors of these plants [6]. From this perspective, 1,4-benzoxazines are of general interest for biological testing. The versatility of related 1,4-benzoxazin-2-ones is similarly linked to their potential pharmacological uses [7–9] and their photochemical activity [10–13]. For example, 1,4-benzoxazin-2-ones prepared from *o*-aminophenols and methyl acylpyruvates show significant antimicrobial activities against *Staphylococcus aureus* and *Escherichia coli*. Common strategies that have been employed for their synthesis are the reaction of substituted 2-aminophenols with 2-oxoesters [14–17], alkyl propiolates [18], or β-nitroacrylates [19].

Here, we report a facile synthesis of novel 3-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoates from 2-aminophenols and dimethyl-2-oxoglutarate and results of their antimicrobial and antifungal testing.

RESULTS AND DISCUSSION

Synthesis of 3-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoates 3a–e. Dimethyl-2-oxoglutarate **2** (Scheme 1) was prepared in a high yield (85%) by esterification of 2-oxoglutaric acid with methanol according to the procedure formerly reported [20]. As shown in Scheme 1, the reaction of dimethyl-2-oxoglutarate with an equimolar amount of 2-aminophenol **1a**, 2-amino-5-methylphenol **1b**, 2-amino-4-methylphenol **1c**, 2-amino-3-methylphenol **1d**, and 2-amino-4-chlorophenol **1e** afforded the corresponding 3-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)propanoates **3a–e** in good yields under very mild conditions. All novel compounds **3a–e** obtained have been characterized by spectroscopic data and elemental analysis as shown in the Experimental section. The commercial availability of 2-aminophenols **1a–e** was the reason for the pattern of substituents described here. Heterocycles **3a–e** have not been reported yet.

Antimicrobial activity of compounds 3a–e. Biological activity of the products (**3a–e**) in form of DMSO solutions was assessed against fungus and yeast by the method of discs, also known as Bauer-Kirby method as described in the Biological Assay section. The biological strains studied were *S. aureus* ATCC 6538 (gram-positive bacteria), *E. coli* ATCC 10536 and *Proteus vulgaris* ATCC 6896 (gram-negative bacteria), and *Candida albicans* ATCC 10231 (yeast). A blank test was performed with DMSO, and the result was negative, that is, no aureola was formed indicating no inhibition of microbial growth. The