



## Original article

Synthesis and preliminary bioactivity assays of 3,4-dichloro-5-( $\omega$ -hydroxyalkylamino)-2(5H)-furanones

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## ABSTRACT

5-( $\omega$ -Hydroxyalkylamino) derivatives of mucochloric acids were synthesized through a facile substitution reaction of 3,4-dichloro-5-hydroxy-2(5H)-furanone (mucochloric acid) acetate or 5-methylcarbonate with an appropriate amino alcohol or aminodiol. The obtained products were characterized and screened for their antibacterial and antiprotozoal activities.

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## 1. Introduction

Mucochloric acid (3,4-Dichloro-5-hydroxy-2(5H)-furanone) (**1**) is a highly functionalized molecule, which can be used for several synthetic purposes [1–3]. The simple derivatives of mucochloric acid display interesting bioactivity. 5-Butoxy-3,4-dichloro-2(5H)-furanone is cytotoxic at 3  $\mu$ M concentration against MAC 13 and MAC 16 murine colon cancer cell lines [4]. Further improvements of the leading structure brought to 3,4-dichloro-5-(oxiran-2-ylmethoxy)-2(5H)-furanone derivatives showing cytotoxicity in nanomolar range on the same cancer cell lines [5]. A broad antibiotic activity against *Staphylococcus aureus* ATCC 25923 and other bacteria strains has been observed in the case of 4-amino-5-hydroxy-2(5H)-furanones [6].

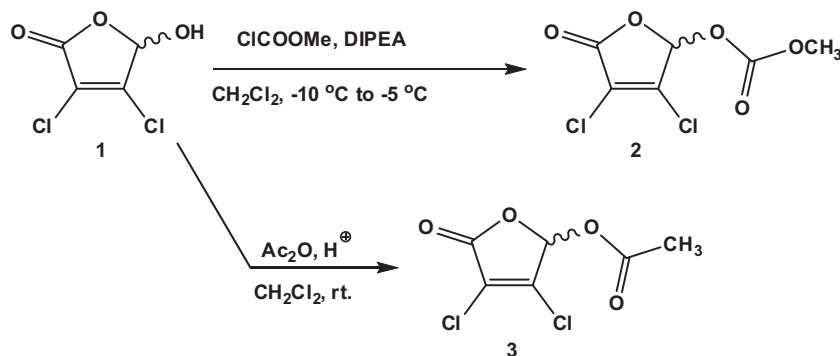
The 2(5H)-furanone moiety occurs in many natural products exhibiting various biological activities, namely antibiotic [7,8] cytotoxic [9–11] and antitumor [12]. As a part of our investigation for new antibacterial compounds we have considered the derivatives of 5-substituted mucochloric acid having the  $\omega$ -hydroxyalkylamino group on carbon C-5 of the 2(5H)-furanone ring. The desired compounds can be obtained conveniently by substitution of a good leaving group using the appropriate amino alcohols as nucleophiles.

The proposed structures would be similar to reported 4-N-alkylamino-3,4-dichloro-2(5H)-furanones showing moderate antibacterial activity [6]. On the other hand, presence of a hydroxyl group in the target molecules increases their hydrophilicity and, in the consequence, improves their bioavailability. Moreover, it opens a direct access towards further modifications, mainly by their conjugation with dipeptides and other molecules of biological importance.

Several attempts for the introduction of amino function into the molecule of mucochloric acid have been already described [13]. When the 5-hydroxy group of **1** was transformed into ether (alkoxy-), ester (benzoyl), carbamate or chloro group and treated subsequently with a double excess of an aromatic amine in polar aprotic solvent (DMSO, NMP), the substitution of chlorine on carbon C-4 occurs and the appropriate secondary amine was obtained in good yield of 80–91%. Similar results were obtained when aliphatic primary or secondary amines were applied. The reactions run according to tandem Michael addition-elimination mechanism [14–16]. When the same derivatives of mucochloric acid were treated with aniline in chloroform, derivatives of 1-aryl-3,4-dichloro-5-hydroxy-1,5-dihydro-2H-pyrrol-2-one were obtained [15]. Mucochloric acids reacted with amino group of natural nucleobases forming bicyclic systems or 3-amino-2-halopropenal derivatives [17,18]. Reductive amination of mucochloric acid furnishes  $\gamma$ -lactams. As the aminating agent substituted anilines, ethyl esters or amides of  $\alpha$ - and  $\beta$ -amino acids were employed [19,20]. Mucochloric acid treated with hydrazines or hydrazones

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Scheme 1.

under acidic conditions is transformed into appropriate 3(2*H*)-pyridazinone derivatives [20]. The reactions of mucochloric acid with simple formamides and acetamides in the presence of catalytic amount of sulphuric acid gave products of chlorine atom on carbon C-4 substitution [6]. The 4,5 bis-aziridinyl derivative of mucochloric acid was obtained by the treatment of 3,4,5-trichloromuco acid with aziridine in the presence of triethylamine [5]. According to these indications, we have assumed that the same effect could be obtained when at 5-position of 2(5*H*)-furanone ring a good leaving group would be presented. The reaction of mucochloric acid with amino alcohols with the purpose to introduce  $\omega$ -hydroxyalkyl linkers at the 2(5*H*)-furanone ring is of a particular interest due to the possibility of further modifications of these side chains. It is intriguing that according to our knowledge any attempts of such investigation were reported in the past.

## 2. Results and discussion

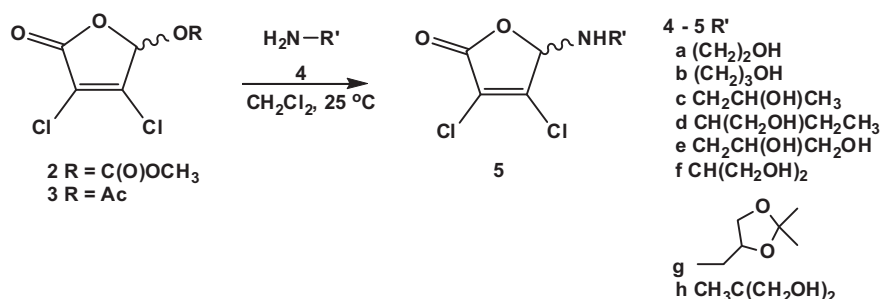
### 2.1. Chemistry

As the first step, mucochloric acid (**1**) was transformed into its derivatives containing labile group at carbon C-5. Thus, **1** was treated with methyl chloroformate in the presence of diisopropylethylamine and the appropriate carbonate **2** was obtained in good yield. Treatment of **1** with acetic anhydride under acidic conditions gave 5-acetoxy-3,4-dichloro-2(5*H*)-furanone (**3**) in satisfactory yield (Scheme 1). Subsequently, the obtained derivatives of mucochloric acid were subjected to the agency of amino alcohols applied as the *N*-centered nucleophiles in the substitution reaction. In a standard procedure the mucochloric acid derivative **2** or **3** (1 equiv.) was treated with 2 equiv. of the suitable amino alcohol **4a–h** in dichloromethane at room temperature (Scheme 2). TLC indicated the total consumption of substrate after 0.5–2 h.

The excess of amino alcohol was removed from the post-reaction mixture by evaporation under diminished pressure and the products were isolated using column chromatography. The yields of products **5a–g** vary in the range of 17%–58% for acetates and 24–76% in the case of carbonates used as starting materials. Several factors affect the yield of substitution products. It seems that the leaving group evokes the major effect on reaction efficiency. In the all performed experiments the highest yield was obtained when 3,4-dichloro-5-methoxycarbonyloxy-2(5*H*)-furanone **2** was used as a starting material (Entry 1–7). The second factor is the structure of the attacking amino alcohol. When the aminodiols were applied, the yield of substitution products dramatically decreased (Entry 5, 6). Similar effect can be ascribed to the steric hindrance around the amino group in **4**. Thus, the reagent having amino group attached to primary carbon atom gave the highest yield of substitution product **5** in comparison with reactant possessing amino group at secondary carbon atom (Entry 5, 6). In the case of 2-amino-2-methylpropane-1,3-diol (**4h**) reaction does not occur (Table 1).

We investigated also the influence of reaction medium on the efficacy of substitution. The reactions of **2** with 1-amino-2-propanol (**4c**) (in molar ratio **3:4c** = 1:2) were performed in different solvents. In non polar solvents the obtained yields were satisfactory, 46% and 64% for the reaction in toluene and dichloromethane, respectively. Addition of methanol to dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 1:1, v/v) decreased yield of **5c** to 38%. When methanol in the mixture with CH<sub>2</sub>Cl<sub>2</sub> was replaced by aprotic DMF (the same volume ratio, 1:1) the yield of **5c** slightly increased to 47%. But in both last experiments the appearance of color unidentified substances was observed. When the reaction was carried out in the solution of DMF, DMSO and *N*-methyl-2-pyrrolidone (NMP), the expected product of substitution reaction **5** was not detected. Instead of it – a tar composed of inseparable substances was observed.

It should be noticed that apart from **4g**, in all of the cases amino alcohols possessing free hydroxyl groups were applied what



Scheme 2.

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