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ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 8–18
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]amino acids: Their synthesis, anti-inflammatory evaluation and QSAR analysis

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Received 16 November 2006; received in revised form 2 March 2007; accepted 8 March 2007
Available online 4 April 2007

Abstract

Developing novel anti-inflammatory drugs is increasingly important in modern pharmaceutical industry. In this work, the reactions of both amino acids and their methylesters with 3-(5,5-dimethyl-1,3-dioxane-2-yl)propanal (**2**) were performed to either directly provide the goal products *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acids (**4a**–**s**) in 9–65% yields or provide the intermediates *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acid methylesters (**3a**–**s**) in 78–87% yields. The saponification of **3a**–**s** provided **4a**–**s** in 80–89% yields. Using a xylene-induced ear edema model, the anti-inflammatory activities of these newly synthesized anti-inflammatory agents were evaluated. The results indicated that comparing to the vehicle control 17 out of **4a**–**s** significantly inhibited the development of inflammation in mice ($p < 0.01$). In particular, eight out of **4a**–**s** exhibited an even higher anti-inflammatory activity than the standard reference drug aspirin ($p < 0.05$–0.01). A QSAR analysis was performed by use of the molecular descriptors generated from e-dragon software. The predictive accuracy of the established QSAR model implies that it may be promising for screening the new derivatives of 2-position amino acid substituted 1,3-dioxanes as potential anti-inflammatory agents.

Keywords: Anti-inflammatory drug; Chemical synthesis; Amino acid; 1,3-Dioxane; QSAR

1. Introduction

Inflammation is known not only as a symptom of great deal of common diseases but also as an early phase of some serious diseases such as cancer [1–3], heart vascular diseases [4–6] and Alzheimer's dementia [7–9]. Thus the discovery of novel anti-inflammatory drugs has been attracting a lot of interests. As promising anti-inflammatory agents substituted 1,3-dioxanes were prepared in some laboratories [10–14]. Though the structure modifications and SAR analysis of the reported 1,3-dioxane anti-inflammatory agents explored the importance for both 2- and 5-position substitutions, the diversity was still poor. For instance, the 2-position substituents were mainly alkyls, and the 5-position substituents were mainly alkylaminos and amidos, which were inherently resulted from the simplicity of the aldehyde and the 1,3-diol commonly used in the synthetic reactions [10,13,14].

It is well known that amino acids are usually used as pharmacokinetic group in drug development. To increase the substitution diversity and improve pharmacokinetics, in the present paper a synthetic route of new 1,3-dioxanes, *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acids, was established and 19 new compounds were accordingly prepared (see Scheme 1). Moreover, the anti-inflammatory activities

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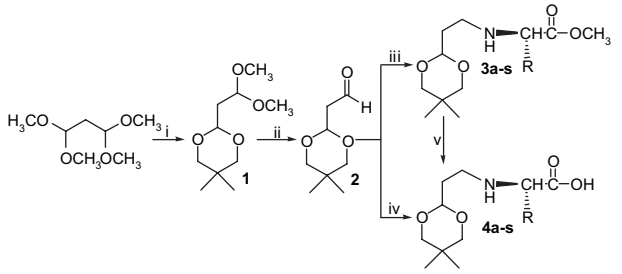
doi:10.1016/j.ejmech.2007.03.015



Scheme 1. The synthetic route of *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]-amino acids. Wherein **3a** and **4a** R = H, **3b** and **4b** R = CH_3, **3c** and **4c** R = $CH(CH_3)_2$, **3d** and **4d** R = $CH_2CH(CH_3)_2$, **3e** and **4e** R = $CH(CH_3)CH_2CH_3$, **3f** and **4f** R = $CH_2C_6H_5$, **3g** and **4g** R = $CH_2C_6H_4$-OH-*p*, **3h** and **4h** R = CH_2OH, **3i** and **4i** R = $CH(OH)CH_3$, **3j** R = $CH_2CO_2CH_3$, **4j** R = CH_2CO_2H, **3k** R = $CH_2CH_2CO_2CH_3$, **4k** R = $CH_2CH_2CO_2H$, **3l** and **4l** R = indole-5-yl-CH_2, **3m** and **4m** R = $CH_2CH_2SCH_3$, **3n** and **4n** R = $CH_2CH_2CH_2NHC(NH)NH_2$, **3o** and **4o** R_1 = CH_2CONH_2, **3p** and **4p** R = $CH_2CH_2CONH_2$, **3q** and **4q** R = imidazole-4-yl-CH_2, **3r** R = $CH_2CH_2CH_2CH_2NHCBz$, **4r** R = $CH_2CH_2CH_2CH_2NH_2$, **3s** and **4s** R = cyclobutylamine-2-yl. (i) 2,2-Dimethyl-1,3-propanediol, dichloromethane and trifluoroacetic acid; (ii) H_3PO_4 (6 N), aqueous CH_3CN (90%, v/v); (iii) amino acid methylester, NaOH, $NaCNBH_3$ and methanol; (iv) amino acid, NaOH, $NaCNBH_3$ and methanol; (v) NaOH and methanol.

of 19 *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acids were evaluated using xylene-induced ear edema. Finally, the QSAR analysis was also performed.

2. Results and discussion

2.1. Chemical synthesis

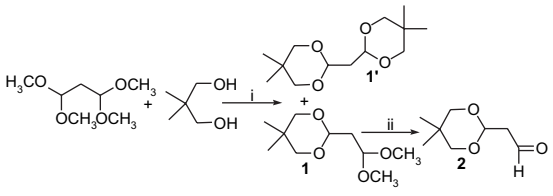
As illustrated in Scheme 1, both amino acids and their methylesters were used to react with 3-(5,5-dimethyl-1,3-dioxane-2-yl)propanal (**2**). In the presence of sodium hydroxide and anhydrous magnesium sulfate, HCl·L-Gly-OCH_3 was successively treated with half-fold excess of **2** and one-fold excess of $NaCNBH_3$ to provide *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl) ethyl]amino acid methylesters (**3a–s**) in 78–87% yields. At 0 °C, **3a–s** were treated by a solution of sodium hydroxide in a 1:1 mixture of methanol and water (2 mol/L), *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acids (**4a–s**) were smoothly formed in 80–89% yields. Though **4a–s** can be directly formed via the reactions of amino acids, **2** and $NaCNBH_3$, two-fold excess of **2** and one-and-a-half-fold excess of $NaCNBH_3$ had to be used, only yields less than 65% were obtained, which were significantly lower than the total yields through **3a–s** to **4a–s**. The data are listed in Table 1.

As we knew, the transacetalization of 1,1,3,3-tetramethoxypropane and 2,2-dimethyl-1,3-propanediol depicted in Scheme 2 usually gave both monocyclic derivative 2-(2,2-dimethoxylethyl)-5,5-dimethyl-1,3-dioxane (**1**) and dicyclic derivative bis(5,5-dimethyl-1,3-dioxane-2-yl)-methane (**1′**), and **1′** was the preferential product [15]. However, the ratio of **1/1′** can be regulated through optimizing the procedure by appropriately selecting the reaction solvent, catalyst, temperature and time. To optimize the procedure, four acids (H_2SO_4, HCl, H_3PO_4, F_3CCO_2H) of three concentrations (concentrated, 6 N, 2 N), five solvents, three temperatures (45 °C, 22 °C, 5 °C) and three times (10 h, 30 h, 48 h) were used in the present study. The related data are listed in Table 2. The data indicate that when the reaction was carried out in CH_2Cl_2 at 5 °C for 48 h and 6 N trifluoroacetic acid was used as the catalyst, the highest ratio of **1/1′** (8:1) was observed. If the reaction was carried out in CH_2Cl_2 at 45 °C for 10 h and concentrated H_2SO_4 was used as the catalyst, the lowest ratio of **1/1′** (1:9) was observed.

Table 1
Yields (%) of **3a–s** (from **2**) and **4a–s** (directly from **2** or from **3a–s** via **2**)

From **2**		From **2**		From **3a–s**		From **3a–s** via **2**	
3a	80	**4a**	61	**4a**	88	**4a**	70
3b	82	**4b**	13	**4b**	89	**4b**	73
3c	87	**4c**	37	**4c**	87	**4c**	76
3d	79	**4d**	40	**4d**	88	**4d**	70
3e	78	**4e**	48	**4e**	88	**4e**	69
3f	85	**4f**	65	**4f**	80	**4f**	68
3g	79	**4g**	60	**4g**	80	**4g**	63
3h	78	**4h**	27	**4h**	87	**4h**	68
3i	82	**4i**	12	**4i**	82	**4i**	67
3j	83	**4j**	12	**4j**	82	**4j**	68
3k	80	**4k**	30	**4k**	84	**4k**	67
3l	81	**4l**	42	**4l**	85	**4l**	69
3m	79	**4m**	9	**4m**	79	**4m**	62
3n	79	**4n**	16	**4n**	81	**4n**	64
3o	82	**4o**	17	**4o**	85	**4o**	70
3p	85	**4p**	15	**4p**	86	**4p**	73
3q	80	**4q**	65	**4q**	87	**4q**	70
3r	80	**4r**	65	**4r**	85	**4r**	68
3s	80	**4s**	10	**4s**	85	**4s**	68

In our previous paper **2** was obtained via a partial hydrolysis of **1**, in which the mixture of oxalic acid and silica gel was used as the catalyst, a 1:1 mixture of 1,2-dichloroethane and tetrahydrofuran was used as the solvent, and the reaction was carried out at 60–100 °C for 6–60 h [15]. In order to lower the temperature of the partial hydrolysis of **1** (cf. Scheme 2), here four acids (oxalic acid, HCl, H_3PO_4, F_3CCO_2H) of two concentrations (6 N, 2 N), three temperatures (45 °C, 22 °C, 5 °C), four solvents (water, 1,2-dichloroethane, tetrahydrofuran, aqueous CH_3CN), and three times (6 h, 8 h, 10 h) were used. The related data are listed in Table 3. The data indicate that when the partial hydrolysis was carried out in aqueous CH_3CN (90%, v/v), with H_3PO_4 (6 N) as the catalyst and at 5 °C for 6 h, **1** was converted into **2** in the highest yield (90%). If the partial hydrolysis was carried out in tetrahydrofuran, with 6 N HCl as the catalyst and at 45 °C for 6 h, the yield of **2** was the lowest (40%).



Scheme 2. Compound **1** was firstly formed via the transacetalization of 1,1,3,3-tetramethoxypropane and 2,2-dimethyl-1,3-propanediol, and then partially hydrolyzed to **2**. (i) Dichloromethane and hydrochloric acid; (ii) H_3PO_4 (6 N), aqueous CH_3CN (90%, v/v).