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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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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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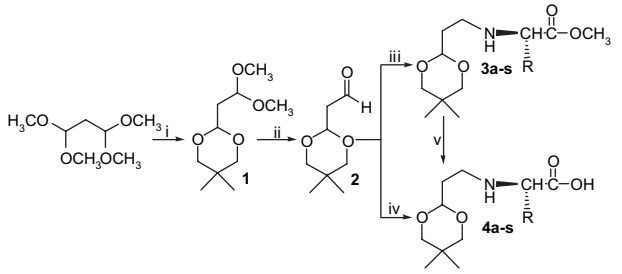


Scheme 1. The synthetic route of *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]-amino acids. Wherein **3a** and **4a** R = H, **3b** and **4b** R = CH_3, **3c** and **4c** R = $CH(CH_3)_2$, **3d** and **4d** R = $CH_2CH(CH_3)_2$, **3e** and **4e** R = $CH(CH_3)CH_2CH_3$, **3f** and **4f** R = $CH_2C_6H_5$, **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

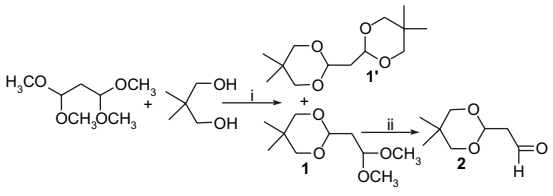
As illustrated in Scheme 1, both amino acids and their methylesters were used to react with 3-(5,5-dimethyl-1,3-dioxane-2-yl)propanal (**2**). In the presence of sodium hydroxide and anhydrous magnesium sulfate, HCl·L-Gly-OCH_3 was successively treated with half-fold excess of **2** and one-fold excess 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).

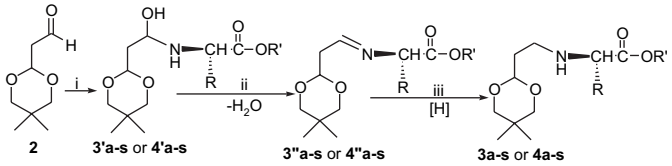
Table 2
Effect of procedure on the ratio of **1/1′**

Solvent	Catalyst	Temp. (°C)	Time (h)	Ratio of **1/1′**
THF	HCl (6 mol/L)	22	10	1:5
$CHCl_3$	HCl (6 mol/L)	22	10	1:3
Ether	HCl (6 mol/L)	22	10	1:6
Ethyl acetate	HCl (6 mol/L)	22	10	1:4
CH_2Cl_2	HCl (6 mol/L)	22	10	1.5:2
CH_2Cl_2	HCl (2 mol/L)	22	10	1:2
CH_2Cl_2	HCl (concentrated)	22	10	1:2
CH_2Cl_2	HCl (6 mol/L)	5	10	1:1
CH_2Cl_2	HCl (6 mol/L)	45	10	2:1
CH_2Cl_2	H_2SO_4 (6 mol/L)	22	10	1:4
CH_2Cl_2	H_2SO_4 (2 mol/L)	22	10	1:5
CH_2Cl_2	H_2SO_4 (concentrated)	22	10	1:4
CH_2Cl_2	H_2SO_4 (concentrated)	5	10	1:5
CH_2Cl_2	H_2SO_4 (concentrated)	45	10	1:9
CH_2Cl_2	H_3PO_4 (6 mol/L)	22	10	1:4
CH_2Cl_2	H_3PO_4 (2 mol/L)	22	10	1:4
CH_2Cl_2	H_3PO_4 (concentrated)	22	10	1:4
CH_2Cl_2	F_3CCO_2H (6 mol/L)	22	10	3:1
CH_2Cl_2	F_3CCO_2H (2 mol/L)	22	10	2:1
CH_2Cl_2	F_3CCO_2H (concentrated)	22	10	2:1
CH_2Cl_2	F_3CCO_2H (6 mol/L)	5	10	3:2
CH_2Cl_2	F_3CCO_2H (6 mol/L)	45	10	5:1
CH_2Cl_2	F_3CCO_2H (6 mol/L)	45	30	6:1
CH_2Cl_2	F_3CCO_2H (6 mol/L)	45	48	8:1

As depicted in Scheme 3, in the formation of both **3a–s** and **4a–s** from **2**, the key intermediate Schiff bases **3″a–s** or **4″a–s** resulted from the amino alcohols **3′a–s** or **4′a–s** via elimination of water were involved, which significantly depends on

Table 3
Effect of procedure on the yield of the partial hydrolysis of **1**

Solvent	Catalyst (mol/L)	Temp. (°C)	Time (h)	Yield (%)
Water	Oxalic acid (6)	22	6	43
CH_2ClCH_2Cl	Oxalic acid (6)	22	6	45
THF	Oxalic acid (6)	22	6	50
Aqueous CH_3CN (90%, v/v)	Oxalic acid (6)	22	6	65
Aqueous CH_3CN (90%, v/v)	Oxalic acid (6)	45	6	50
Aqueous CH_3CN (90%, v/v)	Oxalic acid (6)	5	6	70
Aqueous CH_3CN (90%, v/v)	Oxalic acid (2)	22	6	45
Water	HCl (6)	22	6	45
CH_2ClCH_2Cl	HCl (6)	22	6	43
THF	HCl (6)	22	6	50
Aqueous CH_3CN (90%, v/v)	HCl (6)	22	6	45
THF	HCl (2)	22	6	45
THF	HCl (6)	45	6	40
THF	HCl (6)	5	6	42
Water	F_3CCO_2H (6)	22	6	60
CH_2ClCH_2Cl	F_3CCO_2H (6)	22	6	62
THF	F_3CCO_2H (6)	22	6	55
Aqueous CH_3CN (90%, v/v)	F_3CCO_2H (6)	22	6	55
Aqueous CH_3CN (90%, v/v)	F_3CCO_2H (6)	22	6	50
Water	H_3PO_4 (6)	22	6	66
CH_2ClCH_2Cl	H_3PO_4 (6)	22	6	60
THF	H_3PO_4 (6)	22	6	62
Aqueous CH_3CN (90%, v/v)	H_3PO_4 (2)	22	6	50
Aqueous CH_3CN (90%, v/v)	H_3PO_4 (6)	45	6	90
Aqueous CH_3CN (90%, v/v)	H_3PO_4 (6)	45	8	80
Aqueous CH_3CN (90%, v/v)	H_3PO_4 (6)	45	10	76



Scheme 3. The steps included in the formation of **3a–s** or **4a–s** from **2** and amino acids or their methylesters. (i) Trifluoroacetic acid, amino acids or their methylesters; (ii) anhydrous $MgSO_4$; (iii) NaOH, $NaCNBH_3$ and methanol. For **3′a–s**, **3″a–s** and **3a–s** $R' = CH_3$ and the definition of R is the same as that in Scheme 1; for **4′a–s**, **4″a–s** and **4a–s** $R' = H$ and the definition of R is the same as that in Scheme 1.

the dehydrating agent. In the optimization of the elimination procedure, the condensation of **2** and glycine methylester was selected as the model reaction and carried out at three temperatures (22 °C, 35 °C, 45 °C), for which anhydrous $MgSO_4$, Na_2SO_4, Na_2CO_3 and molecular sieve were used as dehydrating agents, and the total yield of **3a** was examined as comparing criterion. The related data are listed in Table 4. The data indicated that when the elimination was carried out at 22 °C in methanol and anhydrous $MgSO_4$ was used as the dehydrating agent, **3a** was obtained in 80% total yield. If the elimination was carried out at 35 °C in methanol and anhydrous Na_2CO_3 was used as the dehydrating agent, the yield of **3a** was only 40%. Thus all eliminations were carried out at 22 °C in methanol and with anhydrous $MgSO_4$ as the dehydrating agent.

To determine if any racemization of the preexisting stereogenic center had occurred during the course of the synthesis, the HPLC analysis was used for determining the optical purity of **4a–s**. In the determination a Waters 600E instrument with UV detector (190–600 nm, at 275 nm) was used. The column Daicel Chiralpak AD-H (2.1 × 150 mm, 5 μm), the mobile phase consisted of isopropanol (A) and hexane (B), and 0.5 mL/min of LC flow rate were used. After 20 μL of the solution of **4a–s** in isopropanol (1.5 mM/L) was loaded, the column was eluted with the mobile phase. The gradient program was that after 2 min A was increased to 4% in 5 min, increased to 10% in 6 min and held for another 10 min. All the determinations gave only a single peak. These observations imply that no racemization of the preexisting stereogenic center occurred during the course of the synthesis.

Table 4
Effect of dehydrating agent on the yield of model compound **3a**

Dehydrating agent	Temp. (°C)	Yield (%)
Na_2CO_3	22	56
Na_2CO_3	35	40
Na_2CO_3	45	50
Na_2SO_4	22	70
Na_2SO_4	35	55
Na_2SO_4	45	60
$MgSO_4$	22	80
$MgSO_4$	35	73
$MgSO_4$	45	70
Molecular sieve	22	60
Molecular sieve	35	55
Molecular sieve	45	45

2.2. Xylene-induced ear edema

By use of a xylene-induced ear edema model the anti-inflammatory activities of **4a–s** were evaluated. The in vivo assay involves the test compounds being administrated orally by gavage in 0.5% carboxymethyl cellulose (CMC) suspension. Each compound was initially tested at a dose of 20 mg/kg. The observation explored that 17 compounds from **4a–s** showed significant inhibition against xylene-induced inflammation in mice as compared with the vehicle control (CMC alone, $p < 0.01$), suggesting that these compounds possess potent anti-inflammatory activity. It was especially noted that among **4a–s**, eight compounds exhibited an even higher anti-inflammatory activity than the standard reference drug aspirin ($p < 0.05$–0.01, cf. Fig. 1) (Fig. 2).

2.3. Dose-dependent anti-inflammatory activity

Three compounds (**4h**, **4n**, **4o**) with significant activity were administrated in a series of lower doses to obtain a detailed pharmacological activity profile. It was observed that the anti-inflammatory activity of **4h**, **4n** and **4o** was following dose-dependent manners (Figs. 3–5).

2.4. QSAR analysis

To perform a QSAR analysis on the anti-inflammatory activities of **4a–s**, 1664 different molecular parameters for each compound were generated from e-dragon webserver (http://www.vcclab.org/lab/edragon/). Then, the multiple linear regression method was employed to derive the QSAR equation of **4a–s**. In this study, the percentage of inhibition (*%Inhibition*) was considered as the *anti-inflammatory* activity of a molecule. As the number of compounds **4a–s** is 19, generally the optimum number of molecular descriptors used in the QSAR analysis should be not larger than four. To obtain an optimal QSAR equation, therefore, a genetic algorithm assisted descriptor selection procedure was applied to choose four parameters from all the obtained e-dragon descriptors. Finally, the following optimal QSAR equation in describing the anti-inflammatory effects of **4a–s** was determined:

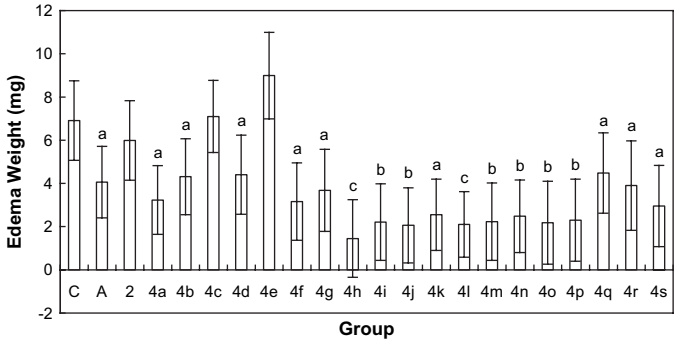


Fig. 1. Anti-inflammatory activity of **4a–s** against xylene-induced ear edema in mice; $n = 11$, C = CMC, A = aspirin. (a) Comparing with CMC group, $p < 0.01$; (b) comparing with CMC group, $p < 0.01$, and with aspirin group, $p < 0.05$; (c) comparing with CMC and aspirin groups, $p < 0.01$.

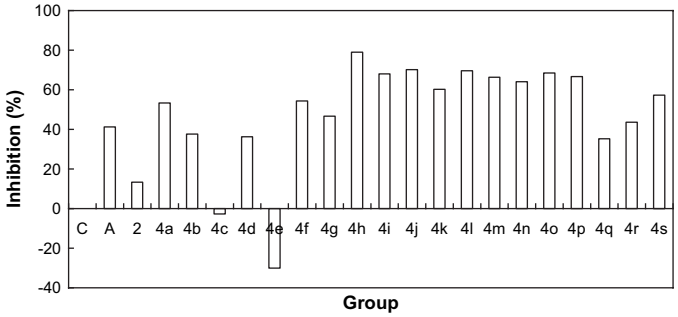


Fig. 2. Inflammatory inhibition of **4a–s** against xylene-induced ear edema in mice; $n = 11$, C = CMC, A = aspirin.

$$\%\text{Inhibition} = 339.3 - 27.8 \times \text{nCp} - 80.6 \times \text{Mor25e} - 28.2 \times \text{RDF040p} + 8.7 \times \text{RDF100u} \quad (1)$$

Where the regression coefficient (R) is 0.97. The nCp represents the number of terminal primary C(sp^3) within a molecule. The other three are 3D-descriptors. The Mor25e is group into the 3D-MoRSE descriptors [16], which are based on the idea of obtaining information from the 3D atomic coordinates by the transform used in electron diffraction studies for preparing theoretical scattering curves. Mor25e corresponds to signal 25, weighted by atomic Sanderson electronegativities. The RDF040p and RDF100u are classified into the RDF molecular descriptors, which were obtained by radial distribution functions centered on different interatomic distances (from 0.5 Å to 15.5 Å) [17]. The RDF molecular descriptors can be interpreted as the probability distribution of finding an atom in a spherical volume of certain radius. For RDF040p, the sphere radius is of 4.0 Å and atomic polarizability weights are used. For RDF100u, the sphere radius is of 10.0 Å and atomic weights are not used during its calculation.

To validate the established Eq. (1), the resubstitution, Leave-One-Out (LOO) and Leave-Two-Out (LTO) tests were carried out. To illustrate the predictive accuracy of the current QSAR model more explicitly, a parameter named absolute average error ($\overline{e}$) is defined as follows:

$$\overline{e} = \frac{\sum_{i=1}^{19} \left| \%\ \text{Inhibition}_{i,\text{measured}} - \%\ \text{Inhibition}_{i,\text{predicted}} \right|}{19} \quad (2)$$

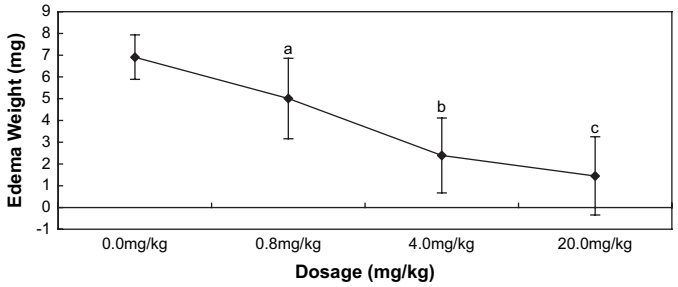


Fig. 3. Anti-inflammatory activity of **4h** at different doses against xylene-induced ear edema in mice; $n = 11$. (a) Comparing with 0.0 mg/kg (CMC) group, $p < 0.05$; (b) comparing with 0.8 mg/kg group, $p < 0.05$; (c) comparing with 4 mg/kg group, $p < 0.05$.

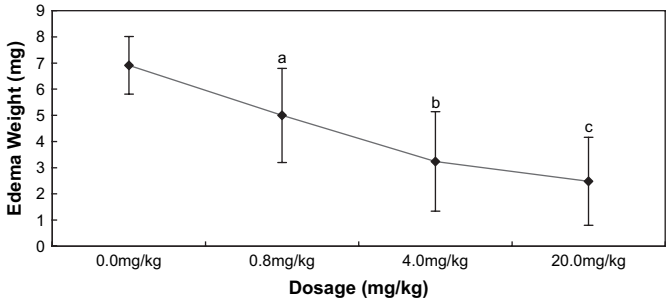


Fig. 4. Anti-inflammatory activity of **4n** at different doses against xylene-induced ear edema in mice. $n = 11$; (a) Comparing with 0.0 mg/kg (CMC) group, $p < 0.05$; (b) comparing with 0.8 mg/kg group, $p < 0.05$; (c) comparing with 4 mg/kg group, $p < 0.05$.

Where $\%\text{Inhibition}_{i,\text{measured}}$ and $\%\text{Inhibition}_{i,\text{predicted}}$ represent the measured and predicted values of inhibition effect for compound i, respectively. The resubstitution analysis gave an $\overline{e}$ value of 5.0, whereas the $\overline{e}$ values for the LOO and LTO tests were 6.8 and 7.0, implying a high predictive accuracy in the QSAR Eq. (1). The detailed results of the LOO test are further illustrated in Fig. 6.

Due to the physicochemical information embedded in the Mor25e, RDF040p and RDF100u descriptors is not intuitive, the established QSAR model may not be very informative to explain the molecular mechanism of anti-inflammatory effects of **4a–s**, although it has reached a high predictive accuracy. Further investigation is required to explore the possibility of the current QSAR model to screen the new derivatives of *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acid as potential anti-inflammatory agents.

3. Experimental section

3.1. Chemical synthesis

3.1.1. General

All the reactions were carried out under nitrogen (1 bar). ^{1}H (300 MHz and 500 MHz) and ^{13}C (75 MHz and 125 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers for solution in $CDCl_3$ with tetramethylsilane as internal standard. FAB/MS was determined on

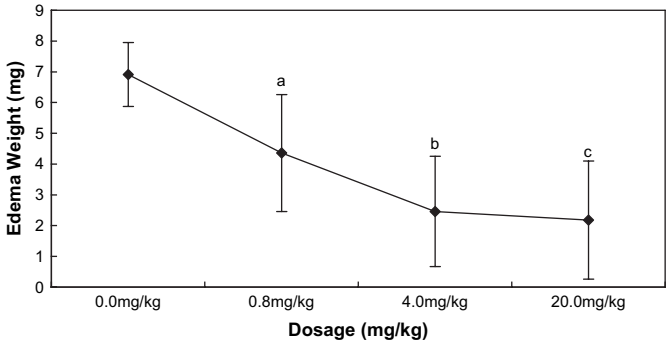


Fig. 5. Anti-inflammatory activity of **4o** at different doses against xylene-induced ear edema in mice. $n = 11$; a) Comparing with 0.0 mg/kg (CMC) group, $p < 0.05$; b) Comparing with 0.8 mg/kg group, $p < 0.05$; c) Comparing with 4 mg/kg group, $p < 0.05$.

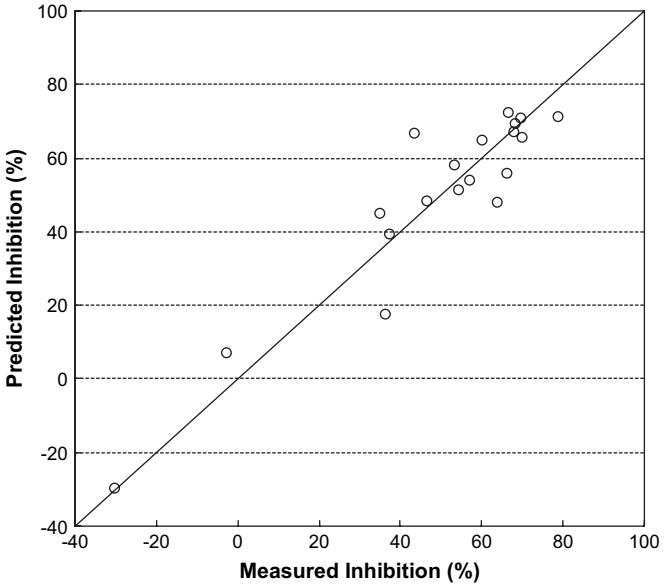


Fig. 6. Comparison of the predicted anti-inflammatory activities with the measured activities in the LOO test.

VG-ZAB-MS and TOF-MS was recorded on MDS SCIEX QSTAR. Optical rotations were determined on a Schmidt and Haensch Polartronic D instrument at 20 °C. All L-amino acids were purchased from China Biochemical Corp. TLC was made with Qingdao silica gel GF254. Chromatography was performed with Qingdao silica gel H60 or Sephadex-LH20. All solvents were distilled and dried before use by reference to literature procedures.

3.1.2. 2-(2,2-Dimethoxylethyl)-5,5-dimethyl-1,3-dioxane (*1*)

To the solution of 4.92 g (30.0 mmol) of 1,1,3,3-tetramethoxypropane, 0.78 g (7.5 mmol) of 2,2-dimethyl-1,3-propanediol in 25 mL of dichloromethane and 0.1 mL of trifluoroacetic acid (6 N) were added dropwise. The reaction mixture was stirred at 5 °C for 24 h and then additional 0.78 g (7.5 mmol) of 2,2-dimethyl-1,3-propanediol was added. The reaction mixture was stirred at 5 °C for another 24 h and TLC (petroleum ether/ethyl acetate, 15:1) indicated the complete disappearance of 2,2-dimethyl-1,3-propanediol. To the reaction mixture, 4.0 g of anhydrous sodium carbonate was added and stirred at room temperature for 2 h. After filtration and evaporation under reduced pressure, purification by chromatography (petroleum ether/ethyl acetate, 15:1) provided 4.89 g (80%) of the title compound as a colorless powder. ^{1}H NMR ($CDCl_3$): δ/ppm = 4.537 (t, $J = 6.0$ Hz, 1H), 4.488 (t, $J = 6.0$ Hz, 1H), 3.569 (d, $J = 11.1$ Hz, 2H), 3.405 (d, $J = 11.1$ Hz, 2H), 3.304 (s, 6H), 1.939 (m, $J = 6.0$ Hz, 2H), 1.161 (s, 3H), 1.089 (s, 3H).

3.1.3. 3-(5,5-Dimethyl-1,3-dioxane-2-yl)propanal (*2*)

The solution of 2.04 g (10.0 mmol) of 2-(2,2-dimethylethyl)-5,5-dimethyl-1,3-dioxane, 2 mL of H_3PO_4 (6 N), 50 mL of CH_3CN and 5 mL of water were stirred at 5 °C for 8 h, and TLC (petroleum ether/ethyl acetate, 15:1)

indicated the complete disappearance of 2-(2,2-dimethylethyl)-5,5-dimethyl-1,3-dioxane. The temperature of the reaction mixture was raised to 25 °C, diluted with 200 mL of water and extracted with dichloromethane (50 mL × 6). The collected dichloromethane phase was dried with anhydrous sodium sulfate. After filtration and evaporation under reduced pressure, purification by chromatography (petroleum ether/ether, 4:1) provided 1.43 g (90%) of the title compound as a colorless syrup. ESI-MS (*m/e*): 159 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ/ppm = 9.831 (s, 1H), 4.890 (t, J = 4.5 Hz, 1H), 3.683 (d, J = 11.1 Hz, 2H), 3.471 (d, J = 11.1 Hz, 2H), 2.717 (d, J = 4.5 Hz, 2H), 1.197 (s, 3H), 1.047 (s, 3H).

*3.1.4. General procedure for the preparation of N-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]amino acid methylesters (**3a–s**)*

The suspension of 1.0 mmol of amino acid methylester, 22 mg (0.55 mmol) of NaOH and 5 mL of methanol was stirred at room temperature for 10 min to form clean solution. After addition of 300 mg of anhydrous magnesium sulfate to the solution, 240 mg (1.52 mmol) of 3-(5,5-dimethyl-1,3-dioxane-2-yl)propanal (**2**) was added dropwise. After stirring at room temperature for 20 min, to the reaction mixture 126 mg (2.0 mmol) of $NaCNBH_3$ was added, stirred at room temperature for additional 6 h and TLC (petroleum/ether, 4:1) indicated complete disappearance of **2**. The reaction mixture was filtered and the filtrate was evaporated under vacuum to remove the solvent. The residue was purified by silica gel chromatography to give the title compound as a colorless powder.

*3.1.4.1. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]glycine methylesters (**3a**).* Yield: 185 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.86 (t, J = 4.8 Hz, 1H), 3.68 (d, J = 11.2 Hz, 2H), 3.67 (s, 3H), 3.49 (s, 2H), 3.47 (d, J = 11.2 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.13 (s, 1H), 1.90 (t, J = 6.5 Hz, 2H), 0.99 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 170.97, 102.32, 79.42, 52.47, 51.66, 38.94, 37.61, 32.87, 24.56, 23.19. EI/MS: 232 $[M+H]^+$. Anal. calcd for $C_{11}H_{21}NO_4$: C 57.12, H 9.15, N 6.06; found: C 57.00, H 9.25, N 6.21.

*3.1.4.2. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-alanine methylester (**3b**).* Yield: 201 mg (82%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.85 (t, J = 4.9 Hz, 1H), 3.67 (d, J = 11.1 Hz, 2H), 3.66 (s, 3H), 3.48 (q, J = 6.6 Hz, 1H), 3.46 (d, J = 11.1 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H), 2.13 (s, 1H), 1.66 (t, J = 6.6 Hz, 2H), 1.22 (d, J = 6.6 Hz, 3H), 0.99 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 170.96, 100.33, 79.42, 58.44, 51.66, 37.97, 36.51, 32.99, 24.56, 23.18, 22.11. ESI-MS (*m/e*): 246 $[M+H]^+$. Anal. calcd for $C_{12}H_{23}NO_4$: C 58.75, H 9.45, N 5.71; found: C 58.88, H 9.54, N 5.93.

*3.1.4.3. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-valine methylester (**3c**).* Yield: 238 mg (87%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.87 (t, J = 6.1 Hz, 1H), 3.68 (d, J = 10.4 Hz, 2H), 3.70 (s, 3H), 3.48 (m, J = 7.1 Hz, 1H), 3.47 (d, J = 10.4 Hz, 2H), 2.66 (t, J = 6.1 Hz, 2H), 2.38 (m, J = 7.1 Hz, 1H), 2.22 (s, 1H), 1.86 (t, J = 6.1 Hz, 2H), 1.01 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.99 (s, 3H), 0.62 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 171.73, 101.51, 79.40, 68.43, 39.33, 38.21, 33.22, 27.55, 24.57, 23.19, 17.40, 17.32. ESI-MS (*m/e*): 274 $[M+H]^+$. Anal. calcd for $C_{14}H_{27}NO_4$: C 61.51, H 9.96, N 5.12; found: C 61.66, H 9.83, N 5.31.

*3.1.4.4. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-leucine methylester (**3d**).* Yield: 227 mg (79%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.87 (t, J = 4.5 Hz, 1H), 3.69 (d, J = 10.6 Hz, 2H), 3.67 (s, 3H), 3.49 (t, J = 7.0 Hz, 1H), 3.47 (d, J = 10.6 Hz, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.11 (s, 1H), 1.86 (t, J = 6.0 Hz, 2H), 1.79 (m, J = 7.0 Hz, 1H), 1.62 (m, J = 7.0 Hz, 2H), 1.01 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 171.80, 102.11, 79.42, 59.69, 50.61, 41.22, 39.34, 38.84, 33.21, 27.10, 26.47, 26.46, 23.91, 23.32. ESI-MS (*m/e*): 288 $[M+H]^+$. Anal. calcd for $C_{15}H_{29}NO_4$: C 62.69, H 10.17, N 4.87; found: C 62.82, H 10.29, N 4.73.

*3.1.4.5. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-isoleucine methylester (**3e**).* Yield: 224 mg (78%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.87 (t, J = 4.6 Hz, 1H), 3.69 (d, J = 10.5 Hz, 2H), 3.63 (s, 3H), 3.49 (t, J = 7.1 Hz, 1H), 3.47 (d, J = 10.5 Hz, 2H), 2.67 (t, J = 6.2 Hz, 2H), 2.31 (m, J = 7.1 Hz, 1H), 2.21 (s, 1H), 1.86 (t, J = 6.2 Hz, 2H), 1.32 (m, J = 7.1 Hz, 2H), 1.02 (d, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.43, 102.31, 79.41, 69.55, 50.15, 41.20, 40.10, 33.38, 33.21, 27.29, 23.86, 23.32, 20.10, 17.36. ESI-MS (*m/e*): 288 $[M+H]^+$. Anal. calcd for $C_{15}H_{29}NO_4$: C 62.69, H 10.17, N 4.87; found: C 62.56, H 10.09, N 5.02.

*3.1.4.6. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-phenylalanine methylester (**3f**).* Yield: 273 mg (85%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 7.23 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 1H), 4.72 (t, J = 3.9 Hz, 1H), 3.92 (t, J = 6.5 Hz, 1H), 3.64 (s, 3H), 3.49 (d, J = 6.5 Hz, 2H), 3.33 (d, J = 6.5 Hz, 2H), 2.94 (m, J = 6.6 Hz, 2H), 2.75 (m, J = 4.2 Hz, 2H), 2.21 (s, 1H), 1.76 (m, J = 4.2 Hz, 2H), 0.99 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$): δ/ppm = 171.85, 137.33, 129.15, 128.35, 126.60, 100.89, 79.33, 63.15, 51.60, 40.07, 39.50, 38.25, 33.50, 22.85, 22.77. ESI-MS (*m/e*): 322 $[M+H]^+$. Anal. calcd for $C_{18}H_{27}NO_4$: C 67.26, H, 8.47, N 4.36; found: C 67.13, H 8.39, N 4.52.

*3.1.4.7. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-tyrosine methylester (**3g**).* Yield: 284 mg (79%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 7.20 (d, J = 7.2 Hz, 2H), 7.00 (d, J = 7.2 Hz, 2H), 5.18 (s, 1H), 4.78 (t, J = 4.1 Hz, 1H), 3.93 (t, J = 6.3 Hz, 1H), 3.69 (d, J = 10.2 Hz, 2H), 3.65 (s, 3H), 3.47 (d, J = 10.2 Hz, 2H), 2.95 (d, J = 6.3 Hz, 2H), 2.58 (t, J = 4.1 Hz, 2H), 2.21 (s, 1H), 1.76 (t, J = 4.1 Hz, 2H), 0.99

(s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$): δ/ppm = 172.65, 155.33, 135.34, 128.56, 116.82, 101.24, 79.29, 65.22, 50.39, 40.11, 39.55, 38.21, 33.52, 23.11, 22.87. ESI-MS (*m/e*): 361 $[M+H]^+$. Anal. calcd for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77; found: C 66.52, H 7.72, N 7.91.

*3.1.4.8. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-serine methylester (**3h**).* Yield: 204 mg (78%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.55 (t, J = 4.6 Hz, 1H), 3.81 (d, J = 6.6 Hz, 2H), 3.69 (d, J = 10.4 Hz, 2H), 3.65 (s, 3H), 3.47 (d, J = 10.4 Hz, 2H), 3.56 (t, J = 6.6 Hz, 1H), 2.68 (t, J = 4.6 Hz, 2H), 2.16 (s, 1H), 2.13 (s, 1H), 1.91 (t, J = 4.6 Hz, 2H), 0.97 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.30, 102.30, 79.40, 66.87, 64.33, 50.60, 40.95, 38.70, 33.60, 24.58, 23.18. ESI-MS (*m/e*): 262 $[M+H]^+$. Anal. calcd for $C_{12}H_{23}NO_5$: C 55.16, H 8.87, N 5.36; found: C 55.31, H 8.93, N 5.51.

*3.1.4.9. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-threonine methylester (**3i**).* Yield: 226 mg (82%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.64 (t, J = 4.7 Hz, 1H), 3.86 (m, J = 5.6 Hz, 1H), 3.69 (d, J = 10.0 Hz, 2H), 3.66 (s, 3H), 3.49 (d, J = 10.0 Hz, 2H), 3.47 (d, J = 5.6 Hz, 1H), 2.68 (t, J = 4.7 Hz, 2H), 2.16 (s, 1H), 2.13 (s, 1H), 1.93 (t, J = 4.7 Hz, 2H), 1.17 (d, J = 5.6 Hz, 3H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.41, 102.61, 79.42, 71.62, 68.76, 50.59, 40.78, 39.26, 32.25, 24.61, 23.15, 22.20. ESI-MS (*m/e*): 276 $[M+H]^+$. Anal. calcd for $C_{13}H_{25}NO_5$: C 56.71, H 9.15, N 5.09; found: C 56.86, H 9.24, N 5.27.

*3.1.4.10. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-aspartic acid dimethylester (**3j**).* Yield: 252 mg (83%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.70 (t, J = 4.7 Hz, 1H), 3.82 (t, J = 6.1 Hz, 1H), 3.69 (d, J = 10.1 Hz, 2H), 3.66 (s, 3H), 3.66 (s, 3H), 3.49 (d, J = 10.1 Hz, 2H), 2.58 (d, J = 6.1 Hz, 2H), 2.58 (t, J = 4.7 Hz, 2H), 2.16 (s, 1H), 1.93 (t, J = 4.7 Hz, 2H), 0.96 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.71, 176.21, 102.48, 79.32, 58.75, 50.58, 50.49, 41.12, 40.00, 39.64, 33.55, 24.53, 23.33. ESI-MS (*m/e*): 304 $[M+H]^+$. Anal. calcd for $C_{14}H_{25}NO_6$: C 55.43, H 8.31, N 4.62; found: C 55.58, H 8.20, N 4.77.

*3.1.4.11. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-glutamic acid dimethylester (**3k**).* Yield: 254 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.52 (t, J = 4.3 Hz, 1H), 3.69 (d, J = 10.1 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 3H), 3.49 (d, J = 10.1 Hz, 2H), 3.44 (t, J = 5.6 Hz, 1H), 2.88 (t, J = 4.3 Hz, 2H), 2.34 (t, J = 5.6 Hz, 2H), 2.13 (s, 1H), 1.92 (t, J = 5.6 Hz, 2H), 1.82 (t, J = 4.3 Hz, 2H), 0.97 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.77, 172.32, 99.56, 79.31, 63.58, 50.61, 50.34, 40.22, 39.65, 33.85, 30.36, 29.10, 24.50, 23.47. ESI-MS (*m/e*): 318 $[M+H]^+$. Anal. calcd for $C_{15}H_{27}NO_6$: C 56.77, H 8.57, N 4.41; found: C 56.89, H 8.66, N 4.58.

*3.1.4.12. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-tryptophan methylester (**3l**).* Yield: 292 mg (81%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 8.91 (s, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.94 (s, 1H), 4.61 (t, J = 4.6 Hz, 1H), 3.91 (t, J = 5.8 Hz, 1H), 3.69 (d, J = 10.0 Hz, 2H), 3.66 (s, 3H), 3.49 (d, J = 10.0 Hz, 2H), 2.91 (d, J = 5.8 Hz, 2H), 2.64 (t, J = 4.6 Hz, 2H), 2.13 (s, 1H), 1.86 (t, J = 4.6 Hz, 2H), 0.97 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.31, 136.35, 131.66, 122.51, 121.78, 120.45, 119.60, 112.09, 111.01, 101.51, 79.43, 65.72, 50.58, 40.24, 39.63, 33.79, 31.10, 24.52, 23.45. ESI-MS (*m/e*): 361 $[M+H]^+$. Anal. calcd for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77; found: C 66.79, H 7.74, N 7.59.

*3.1.4.13. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-methionine methylester (**3m**).* Yield: 241 mg (79%). ESI-MS (*m/e*): 306 $[M+H]^+$. ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.65 (t, J = 4.5 Hz, 1H), 3.70 (d, J = 10.0 Hz, 2H), 3.65 (s, 3H), 3.57 (t, J = 5.8 Hz, 1H), 3.50 (d, J = 10.0 Hz, 2H), 2.66 (t, J = 4.5 Hz, 2H), 2.47 (t, J = 5.8 Hz, 2H), 2.12 (s, 1H), 2.01 (t, J = 5.8 Hz, 2H), 2.11 (s, 3H), 1.87 (t, J = 4.5 Hz, 2H), 0.96 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.12, 101.00, 79.37, 63.08, 50.40, 40.28, 39.50, 33.81, 33.16, 30.49, 24.48, 23.52, 17.50. ESI-MS (*m/e*): 306 $[M+H]^+$. Anal. calcd for $C_{14}H_{27}NO_4S$: C 55.05, H 8.91, N 4.59; found: C 55.22, H 8.80, N 4.73.

*3.1.4.14. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-arginine methylester (**3n**).* Yield: 261 mg (79%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 8.74 (s, 2H), 8.71 (s, 1H), 6.51 (s, 1H), 4.64 (t, J = 4.8 Hz, 1H), 3.70 (d, J = 10.0 Hz, 2H), 3.66 (s, 3H), 3.56 (t, J = 5.6 Hz, 1H), 3.51 (d, J = 10.0 Hz, 2H), 2.82 (t, J = 5.6 Hz, 2H), 2.64 (t, J = 4.8 Hz, 2H), 2.14 s, 1H), 1.63 (m, J = 5.6 Hz, 2H), 1.88 (t, J = 4.8 Hz, 2H), 1.53 (m, J = 5.6 Hz, 2H), 0.90 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.07, 162.60, 101.11, 78.83, 63.75, 50.44, 41.48, 40.32, 39.54, 33.68, 29.24, 27.12, 24.42, 23.55. ESI-MS (*m/e*): 331 $[M+H]^+$. Anal. calcd for $C_{15}H_{30}N_4O_4$: C 54.52, H 9.15, N 16.96; found: C 54.37, H 9.07, N 17.11.

*3.1.4.15. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-asparagine methylester (**3o**).* Yield: 236 mg (82%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 6.22 (s, 2H), 4.65 (t, J = 4.5 Hz, 1H), 3.78 (t, J = 5.7 Hz, 1H), 3.62 (s, 3H), 3.50 (d, J = 10.0 Hz, 2H), 3.48 (d, J = 10.0 Hz, 2H), 2.80 (t, J = 4.5 Hz, 2H), 2.74 (d, J = 5.7 Hz, 2H), 2.14 (s, 1H), 1.89 (t, J = 4.5 Hz, 2H), 0.98 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.71, 172.60, 102.68, 79.37, 61.48, 50.37, 41.18, 40.27, 36.34, 32.11, 24.33, 23.28. ESI-MS (*m/e*): 289 $[M+H]^+$. Anal. calcd for $C_{13}H_{24}N_2O_5$: C 54.15, H 8.39, N 9.72; found: C 54.30, H 8.27, N 9.56.

*3.1.4.16. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-glutamine methylester (**3p**).* Yield: 257 mg (85%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 6.22 (s, 2H), 4.67

(t, $J = 4.7$ Hz, 1H), 3.64 (s, 3H), 3.60 (t, $J = 5.6$ Hz, 1H), 3.51 (d, $J = 10.0$ Hz, 2H), 3.48 (d, $J = 10.0$ Hz, 2H), 2.79 (t, $J = 4.7$ Hz, 2H), 2.23 (d, $J = 5.6$ Hz, 2H), 2.14 (s, 1H), 1.89 (d, $J = 5.6$ Hz, 2H), 1.89 (t, $J = 4.7$ Hz, 2H), 0.98 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 175.48, 172.10, 102.31, 79.07, 62.98, 50.37, 41.22, 40.36, 33.01, 31.49, 27.20, 24.39, 23.31. ESI-MS (*m/e*): 303 $[M + H]^+$. Anal. calcd for $C_{14}H_{26}N_2O_5$: C 55.61, H 8.67, N 9.26; found: C 55.45, H 8.55, N 9.10.

*3.1.4.17. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-hiatidine methylester (**3q**).* Yield: 249 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 12.31 (s, 1H), 8.65 (s, 1H), 7.37 (s, 1H), 4.67 (t, $J = 4.6$ Hz, 1H), 3.86 (t, $J = 4.3$ Hz, 1H), 3.62 (s, 3H), 3.55 (d, $J = 10.0$ Hz, 2H), 3.50 (d, $J = 10.0$ Hz, 2H), 3.25 (t, $J = 4.3$ Hz, 2H), 2.29 (d, $J = 5.3$ Hz, 2H), 2.14 (s, 1H), 1.92 (d, $J = 5.3$ Hz, 2H), 0.98 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.30, 135.59, 134.64, 122.47, 101.02, 79.34, 64.93, 50.39, 41.36, 40.40, 33.33, 31.47, 24.57, 23.19. ESI-MS (*m/e*): 312 $[M + H]^+$. Anal. calcd for $C_{15}H_{25}N_3O_4$: C 57.86, H 8.09, N 13.49; found: C 58.01, H 8.20, N 13.33.

*3.1.4.18. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-benzyllysine methylester (**3r**).* Yield: 349 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.71 (s, 1H), 8.45 (s, 2H), 7.87 (d, $J = 7.0$ Hz, 2H), 7.34 (t, $J = 7.0$ Hz, 2H), 6.95 (t, $J = 7.0$ Hz, 1H), 4.671 (t, $J = 4.6$ Hz, 1H), 3.62 (t, $J = 5.5$ Hz, 1H), 3.62 (s, 3H), 3.54 (d, $J = 10.0$ Hz, 2H), 3.49 (d, $J = 10.0$ Hz, 2H), 2.86 (t, $J = 4.8$ Hz, 2H), 2.76 (t, $J = 4.6$ Hz, 2H), 2.14 (s, 1H), 1.96 (t, $J = 4.8$ Hz, 2H), 1.86 (m, $J = 4.8$ Hz, 2H), 1.89 (t, $J = 4.6$ Hz, 2H), 1.60 (m, $J = 4.8$ Hz, 2H), 0.98 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.25, 158.35, 141.07, 129.02, 127.50, 126.97, 101.76, 79.00, 70.11, 63.77, 50.33, 49.11, 41.44, 40.27, 34.57, 33.22, 31.49, 22.55, 24.30, 23.46. ESI-MS (*m/e*): 437 $[M + H]^+$. Anal. calcd for $C_{23}H_{36}N_2O_6$: C 63.28, H 8.31, N 6.42; found: C 63.44, H 8.43, N 6.59.

*3.1.4.19. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-proline methylester (**3s**).* Yield: 349 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 4.86 (t, $J = 4.6$ Hz, 1H), 3.67 (d, $J = 11.1$ Hz, 2H), 3.62 (s, 3H), 3.46 (d, $J = 11.1$ Hz, 2H), 3.42 (t, $J = 5.5$ Hz, 1H), 2.65 (t, $J = 4.6$ Hz, 2H), 2.31 (t, $J = 5.5$ Hz, 2H), 1.87 (q, $J = 4.6$ Hz, 2H), 1.82 (q, $J = 5.5$ Hz, 2H), 1.65 (m, $J = 5.5$ Hz, 2H), 0.98 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 172.42, 102.30, 79.36, 67.13, 50.38, 49.11, 39.88, 37.61, 32.72, 27.89, 25.63, 24.55, 23.19. ESI-MS (*m/e*): 272 $[M + H]^+$. Anal. calcd for $C_{14}H_{25}NO_4$: C 61.97, H 9.29, N 5.16; found: C 62.13, H 9.41, N 5.33.

*3.1.5. General procedure for the preparation of N-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]-amino acids (**4a–s**) via the saponification of **3a–s***

At 0 °C, to the solution of 1.00 mmol of **3a–s** in 4 mL of methanol and 4 mL of water, 180 mg (4.54 mmol) of NaOH was added. The reaction mixture was stirred at 0 °C for 100 min and TLC (chloroform/methanol, 30:1) indicated the completion of the reaction. The reaction mixture was adjusted to pH 2 with hydrochloric acid (2 mol/L). Upon evaporation, the residue was dissolved in 50 mL of chloroform. The organic phase was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. After filtration, the title compounds were obtained as colorless powder upon evaporation under reduced pressure and purified with flash chromatography ($CHCl_3/CH_3OH$, 30:1).

*3.1.5.1. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]glycine (**4a**).* Yield: 191 mg (88%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.87 (s, 1H), 4.87 (t, $J = 4.7$ Hz, 1H), 3.68 (d, $J = 11.0$ Hz, 2H), 3.49 (s, 2H), 3.47 (d, $J = 11.0$ Hz, 2H), 2.67 (t, $J = 6.6$ Hz, 2H), 2.51 (s, 1H), 1.90 (t, $J = 6.6$ Hz, 2H), 0.99 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 174.50, 102.33, 79.38, 55.10, 39.00, 37.63, 32.74, 24.56, 23.19. EI/MS (*m/e*): 218 $[M + H]^+$. $[\alpha]_D^{20} = -41.4$ ($c = 0.1$, DMSO). Anal. calcd for $C_{10}H_{19}NO_4$: C 55.28, H 8.81, N 6.45; found: C 55.39, H 8.90, N 6.30.

*3.1.5.2. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-alanine (**4b**).* Yield: 206 mg (89%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.86 (s, 1H), 4.87 (t, $J = 4.6$ Hz, 1H), 3.68 (d, $J = 11.0$ Hz, 2H), 3.66 (q, $J = 7.2$ Hz, 1H), 3.47 (d, $J = 11.0$ Hz, 2H), 2.79 (t, $J = 6.0$ Hz, 2H), 2.13 (s, 1H), 1.69 (t, $J = 6.0$ Hz, 2H), 1.13 (d, $J = 7.2$ Hz, 3H), 1.00 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (BHSC-300, DMSO-d_6): δ/ppm = 177.37, 100.56, 79.44, 60.50, 38.37, 37.26, 33.00, 24.58, 23.19, 22.47. ESI-MS (*m/e*): 232 $[M + H]^+$. $[\alpha]_D^{20} = -72.0$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{11}H_{21}NO_4$: C 57.12, H 9.15, N 6.06; found: C 57.00, H 9.07, N 6.21.

*3.1.5.3. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-valine (**4c**).* Yield: 225 mg (87%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.73 (s, 1H), 4.87 (t, $J = 6.0$ Hz, 1H), 3.69 (d, $J = 10.9$ Hz, 2H), 3.49 (m, $J = 7.0$ Hz, 1H), 3.47 (d, $J = 10.9$ Hz, 2H), 2.66 (t, $J = 6.0$ Hz, 2H), 2.38 (m, $J = 7.0$ Hz, 1H), 2.23 (s, 1H), 1.87 (t, $J = 6.0$ Hz, 2H), 1.01 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 7.0$ Hz, 3H), 1.00 (s, 3H), 0.63 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.37, 102.36, 79.41, 70.61, 39.36, 38.85, 37.22, 27.57, 24.57, 23.19, 17.40, 17.32. ESI-MS (*m/e*): 260 $[M + H]^+$. $[\alpha]_D^{20} = 4.0$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{13}H_{25}NO_4$: C 60.21, H 9.72, N 5.40; found: C 60.07, H 9.60, N 5.57.

*3.1.5.4. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-leucine (**4d**).* Yield: 240 mg (88%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.70 (s, 1H), 4.88 (t, $J = 4.6$ Hz, 1H), 3.70 (d, $J = 10.7$ Hz, 2H), 3.49 (t, $J = 7.2$ Hz, 1H), 3.48 (d, $J = 10.7$ Hz, 2H), 2.67 (t, $J = 6.2$ Hz, 2H), 2.11 (s, 1H), 1.87 (t, $J = 6.2$ Hz, 2H), 1.79 (m, $J = 7.2$ Hz, 1H), 1.62 (m, $J = 7.2$ Hz, 2H), 1.02 (d, $J = 7.2$ Hz, 3H), 1.01 (d, $J = 7.2$ Hz, 3H), 0.99 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.41, 102.37, 79.42, 60.62, 41.23, 39.36, 38.86, 33.22, 27.11, 26.50, 26.47, 23.92, 23.33. ESI-MS (*m/e*): 274

$[M+H]^+$. $[\alpha]_D^{20} = -53.0$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{14}H_{27}NO_4$: C 61.51, H 9.96, N 5.12; found: C 61.38, H 9.82, N 5.29.

*3.1.5.5. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-isoleucine (**4e**).* Yield: 240 mg (88%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.71 (s, 1H), 4.87 (t, $J = 4.5$ Hz, 1H), 3.70 (d, $J = 10.9$ Hz, 2H), 3.49 (t, $J = 7.0$ Hz, 1H), 3.48 (d, $J = 10.9$ Hz, 2H), 2.671 (t, $J = 6.0$ Hz, 2H), 2.315 (m, $J = 7.0$ Hz, 1H), 2.210 (s, 1H), 1.864 (t, $J = 6.0$ Hz, 2H), 1.325 (m, $J = 7.0$ Hz, 2H), 1.02 (d, $J = 7.0$ Hz, 3H), 1.02 (t, $J = 7.0$ Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.42, 102.35, 79.41, 69.56, 41.21, 40.11, 33.40, 33.21, 27.30, 23.87, 23.32, 20.11, 17.37. ESI-MS (*m/e*): 274 $[M+H]^+$. $[\alpha]_D^{20} = -47.0$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{14}H_{27}NO_4$: C 61.51, H 9.96, N 5.12; found: C 61.64, H 10.05, N 5.01.

*3.1.5.6. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-phenylalanine (**4f**).* Yield: 255 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.70 (s, 1H), 7.24 (t, $J = 7.6$ Hz, 2H), 7.20 (d, $J = 7.6$ Hz, 2H), 7.01 (t, $J = 7.6$ Hz, 1H), 4.82 (t, $J = 4.2$ Hz, 1H), 3.93 (t, $J = 6.6$ Hz, 1H), 3.70 (d, $J = 10.9$ Hz, 2H), 3.48 (d, $J = 10.9$ Hz, 2H), 2.98 (d, $J = 6.6$ Hz, 2H), 2.75 (t, $J = 4.2$ Hz, 2H), 2.21 (s, 1H), 1.76 (t, $J = 4.2$ Hz, 2H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$): δ/ppm = 176.85, 137.33, 129.15, 128.35, 126.60, 100.89, 79.33, 63.15, 40.07, 39.50, 38.25, 33.50, 22.85, 22.77. ESI-MS (*m/e*): 308 $[M+H]^+$. $[\alpha]_D^{20} = -8.3$ ($c = 0.1$, DMSO). Anal. calcd for $C_{17}H_{25}NO_4$: C 66.43, H 8.20, N 4.56; found: C 66.29, H 8.13, N 4.72.

*3.1.5.7. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-tyrosine (**4g**).* Yield: 258 mg (80%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.76 (s, 1H), 7.21 (d, $J = 7.2$ Hz, 2H), 7.00 (d, $J = 7.2$ Hz, 2H), 5.18 (s, 1H), 4.78 (t, $J = 4.0$ Hz, 1H), 3.93 (t, $J = 6.4$ Hz, 1H), 3.70 (d, $J = 10.7$ Hz, 2H), 3.48 (d, $J = 10.7$ Hz, 2H), 2.96 (d, $J = 6.4$ Hz, 2H), 2.58 (t, $J = 4.0$ Hz, 2H), 2.22 (s, 1H), 1.77 (t, $J = 4.0$ Hz, 2H), 0.99 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$): δ/ppm = 176.65, 155.34, 135.34, 128.56, 116.83, 101.25, 79.30, 65.23, 40.11, 39.56, 38.21, 33.52, 23.12, 22.88. ESI-MS (*m/e*): 324 $[M+H]^+$. $[\alpha]_D^{20} = -50.6$ ($c = 0.2$, DMSO). Anal. calcd for $C_{17}H_{25}NO_5$: C 63.14, H 7.79, N 4.33; found: C 63.01, H 7.68, N 4.50.

*3.1.5.8. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-serine (**4h**).* Yield: 215 mg (87%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.71 (s, 1H), 4.55 (t, $J = 4.5$ Hz, 1H), 3.81 (d, $J = 6.5$ Hz, 2H), 3.69 (d, $J = 10.8$ Hz, 2H), 3.47 (d, $J = 10.8$ Hz, 2H), 3.56 (t, $J = 6.5$ Hz, 1H), 2.69 (t, $J = 4.5$ Hz, 2H), 2.17 (s, 1H), 2.14 (s, 1H), 1.92 (t, $J = 4.5$ Hz, 2H), 0.98 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 174.16, 102.526, 79.42, 66.91, 64.34, 40.96, 38.72, 33.61, 24.59, 23.18. ESI-MS (*m/e*): 248 $[M+H]^+$. $[\alpha]_D^{20} = 14.3$ ($c = 0.1$, DMSO). Anal. calcd for $C_{11}H_{21}NO_5$: C 53.43, H 8.56, N 5.66; found: C 53.30, H 8.44, N 5.79.

*3.1.5.9. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-threonine (**4i**).* Yield: 214 mg (82%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.67 (s, 1H), 4.64 (t, $J = 4.8$ Hz, 1H), 3.86 (m, $J = 5.8$ Hz, 1H), 3.69 (d, $J = 10.2$ Hz, 2H), 3.50 (d, $J = 10.2$ Hz, 2H), 3.47 (d, $J = 5.8$ Hz, 1H), 2.68 (t, $J = 4.8$ Hz, 2H), 2.16 (s, 1H), 2.13 (s, 1H), 1.94 (t, $J = 4.8$ Hz, 2H), 1.18 (d, $J = 5.8$ Hz, 3H), 1.00 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.01, 102.63, 79.43, 71.63, 68.77, 40.79, 39.27, 32.26, 24.62, 23.16, 22.20. ESI-MS (*m/e*): 262 $[M+H]^+$. $[\alpha]_D^{20} = -77.3$ ($c = 0.1$, DMSO). Anal. calcd for $C_{12}H_{23}NO_5$: C 55.16, H 8.87, N 5.36; found: C 55.30, H 8.98, N 5.51.

*3.1.5.10. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-aspartic acid (**4j**).* Yield: 226 mg (82%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.88 (s, 1H), 10.82 (s, 1H), 4.71 (t, $J = 4.6$ Hz, 1H), 3.83 (t, $J = 6.0$ Hz, 1H), 3.70 (d, $J = 10.0$ Hz, 2H), 3.50 (d, $J = 10.0$ Hz, 2H), 2.59 (d, $J = 6.0$ Hz, 2H), 2.58 (t, $J = 4.6$ Hz, 2H), 2.17 (s, 1H), 1.94 (t, $J = 4.6$ Hz, 2H), 1.00 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.78, 176.24, 102.51, 79.34, 58.79, 41.12, 40.02, 39.64, 33.56, 24.55, 23.35. ESI-MS (*m/e*): 276 $[M+H]^+$. $[\alpha]_D^{20} = -78.3$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{12}H_{21}NO_6$: C 52.35, H 7.69, N 5.09; found: C 52.21, H 7.58, N 5.26.

*3.1.5.11. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-glutamic acid (**4k**).* Yield: 243 mg (84%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.77 (s, 1H), 10.70 (s, 1H), 4.53 (t, $J = 4.2$ Hz, 1H), 3.69 (d, $J = 10.0$ Hz, 2H), 3.49 (d, $J = 10.0$ Hz, 2H), 3.44 (t, $J = 5.7$ Hz, 1H), 2.89 (t, $J = 4.2$ Hz, 2H), 2.34 (t, $J = 5.7$ Hz, 2H), 2.13 (s, 1H), 1.93 (t, $J = 5.7$ Hz, 2H), 1.83 (t, $J = 4.2$ Hz, 2H), 0.97 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.77, 176.32, 99.57, 79.32, 63.60, 40.22, 39.65, 33.86, 30.41, 27.11, 24.51, 23.47. ESI-MS (*m/e*): 290 $[M+H]^+$. $[\alpha]_D^{20} = 62.7$ ($c = 0.1$, CH_3Cl). Anal. calcd for $C_{13}H_{23}NO_6$: C 53.97, H 8.08, N 4.84; found: C 53.83, H 8.00, N 4.99.

*3.1.5.12. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-tryptophan (**4l**).* Yield: 295 mg (85%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.74 (s, 1H), 8.92 (s, 1H), 7.22 (d, $J = 7.2$ Hz, 1H), 7.20 (t, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.10 (t, $J = 7.2$ Hz, 1H), 6.96 (s, 1H), 4.62 (t, $J = 4.5$ Hz, 1H), 3.92 (t, $J = 5.9$ Hz, 1H), 3.69 (d, $J = 10.2$ Hz, 2H), 3.50 (d, $J = 10.2$ Hz, 2H), 2.92 (d, $J = 5.9$ Hz, 2H), 2.64 (t, $J = 4.5$ Hz, 2H), 2.14 (s, 1H), 1.86 (t, $J = 4.5$ Hz, 2H), 0.97 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.112, 136.35, 131.70, 122.52, 121.80, 120.50, 119.610, 112.10, 111.02, 101.53, 79.44, 65.72, 40.25, 39.64, 33.80, 31.11, 24.52, 23.45. ESI-MS (*m/e*): 347 $[M+H]^+$. $[\alpha]_D^{20} = 26.3$ ($c = 0.1$, DMSO). Anal. calcd for $C_{19}H_{26}N_2O_4$: C 65.87, H 7.56, N 8.09; found: C 65.73, H 7.44, N 8.23.

*3.1.5.13. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-methionine (**4m**).* Yield: 230 mg (79%). ^{1}H NMR (BHSC-300,

DMSO-d_6): δ/ppm = 10.67 (s, 1H), 4.65 (t, J = 4.6 Hz, 1H), 3.70 (d, J = 10.1 Hz, 2H), 3.57 (t, J = 5.9 Hz, 1H), 3.51 (d, J = 10.1 Hz, 2H), 2.67 (t, J = 4.6 Hz, 2H), 2.48 (t, J = 5.9 Hz, 2H), 2.13 (s, 1H), 2.02 (t, J = 5.9 Hz, 2H), 2.11 (s, 3H), 1.87 (t, J = 4.6 Hz, 2H), 0.97 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.01, 101.07, 79.38, 63.10, 40.30, 39.51, 33.83, 33.16, 30.51, 24.48, 23.53, 17.51. ESI-MS (*m/e*): 292 $[M+H]^+$. $[\alpha]_D^{20} = -77.3$ (c = 0.1, CH_3Cl). Anal. calcd for $C_{13}H_{25}NO_4S$: C 53.58, H 8.65, N 4.81; found: C 53.44, H 8.57, N 4.96.

*3.1.5.14. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-arginine (**4n**).* Yield: 256 mg (81%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.68 (s, 1H), 8.76 (s, 2H), 8.72 (s, 1H), 6.52 (s, 1H), 4.65 (t, J = 4.7 Hz, 1H), 3.71 (d, J = 10.2 Hz, 2H), 3.56 (t, J = 5.7 Hz, 1H), 3.52 (d, J = 10.2 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H), 2.65 (t, J = 4.7 Hz, 2H), 2.15 (s, 1H), 1.64 (m, J = 5.7 Hz, 2H), 1.88 (t, J = 4.7 Hz, 2H), 1.54 (m, J = 5.7 Hz, 2H), 0.91 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 176.14, 162.85, 101.13, 78.85, 63.78, 41.51, 40.34, 39.56, 33.69, 29.24, 27.13, 24.43, 23.56. ESI-MS (*m/e*): 317 $[M+H]^+$. $[\alpha]_D^{20} = -106.0$ (c = 0.1, DMSO). Anal. calcd for $C_{14}H_{28}N_4O_4$: C 53.15, H 8.92, N 17.71; found: C 53.34, H 9.03, N 17.57.

*3.1.5.15. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-asparagine (**4o**).* Yield: 233 mg (85%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.74 (s, 1H), 6.22 (s, 2H), 4.66 (t, J = 4.6 Hz, 1H), 3.78 (t, J = 5.6 Hz, 1H), 3.50 (d, J = 10.2 Hz, 2H), 3.49 (d, J = 10.2 Hz, 2H), 2.81 (t, J = 4.6 Hz, 2H), 2.75 (d, J = 5.6 Hz, 2H), 2.14 (s, 1H), 1.90 (t, J = 4.6 Hz, 2H), 0.99 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.02, 175.54, 102.69, 79.38, 61.49, 41.19, 40.28, 36.35, 32.12, 24.34, 23.29. ESI-MS (*m/e*): 275 $[M+H]^+$. $[\alpha]_D^{20} = -60.6$ (c = 0.1, CH_3Cl). Anal. calcd for $C_{12}H_{22}N_2O_5$: C 52.54, H 8.08, N 10.21; found: C 52.71, H 8.19, N 10.38.

*3.1.5.16. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-glutamine (**4p**).* Yield: 248 mg (86%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.72 (s, 1H), 6.23 (s, 2H), 4.67 (t, J = 4.8 Hz, 1H), 3.60 (t, J = 5.5 Hz, 1H), 3.52 (d, J = 10.2 Hz, 2H), 3.49 (d, J = 10.2 Hz, 2H), 2.80 (t, J = 4.8 Hz, 2H), 2.23 (d, J = 5.5 Hz, 2H), 2.15 (s, 1H), 1.90 (d, J = 5.5 Hz, 2H), 1.90 (t, J = 4.8 Hz, 2H), 0.98 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.35, 175.49, 102.34, 79.08, 62.98, 41.22, 40.37, 33.02, 31.50, 27.21, 24.40, 23.32. ESI-MS (*m/e*): 289 $[M+H]^+$. $[\alpha]_D^{20} = -123.3$ (c = 0.1, CH_3Cl). Anal. calcd for $C_{13}H_{24}N_2O_5$: C 54.15, H 8.39, N 9.72; found: C 54.00, H 8.31, N 9.58.

*3.1.5.17. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-histidine (**4q**).* Yield: 259 mg (87%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 12.34 (s, 1H), 10.77 (s, 1H), 8.66 (s, 1H), 7.38 (s, 1H), 4.67 (t, J = 4.5 Hz, 1H), 3.87 (t, J = 4.2 Hz, 1H), 3.56 (d, J = 10.2 Hz, 2H), 3.50 (d, J = 10.2 Hz, 2H), 3.25 (t, J = 4.2 Hz, 2H), 2.30 (d, J = 5.2 Hz, 2H), 2.14 (s, 1H), 1.92 (d, J = 5.2 Hz, 2H), 0.99 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.40, 135.60, 134.65, 122.48, 101.03, 79.34, 64.94, 41.36, 40.40, 33.34, 31.48, 24.58, 23.19. ESI-MS (*m/e*): 298 $[M+H]^+$. $[\alpha]_D^{20} = 53.1$ (c = 0.1, DMSO). Anal. calcd for $C_{14}H_{23}N_3O_4$: C 56.55, H 7.80, N 14.13; found: C 56.41, H 7.71, N 14.29.

*3.1.5.18. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl)ethyl]-L-proline (**4s**).* Yield: 218 mg (85%). ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.85 (s, 1H), 4.86 (t, J = 4.7 Hz, 1H), 3.68 (d, J = 11.0 Hz, 2H), 3.46 (d, J = 11.0 Hz, 2H), 3.43 (t, J = 5.6 Hz, 1H), 2.66 (t, J = 4.7 Hz, 2H), 2.32 (t, J = 5.6 Hz, 2H), 1.87 (q, J = 4.7 Hz, 2H), 1.83 (q, J = 5.6 Hz, 2H), 1.65 (m, J = 5.6 Hz, 2H), 0.99 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.43, 102.32, 79.37, 67.13, 49.12, 39.88, 37.61, 32.73, 27.90, 25.64, 24.56, 23.19. ESI-MS (*m/e*): 258 $[M+H]^+$. $[\alpha]_D^{20} = -16.0$ (c = 0.1, CH_3Cl). Anal. calcd for $C_{13}H_{23}NO_4$:C 60.68, H 9.01, N 5.44; found: C 60.52, H 9.10, N 5.30.

*3.1.6. N-[2-(5,5-Dimethyl-1,3-dioxane-2-yl) ethyl]-L-lysine (**4r**)*

To the solution of 436 mg (1.00 mmol) of *N*-[2-(5,5-dimethyl-1,3-dioxane-2-yl)ethyl]-L-benzyllysine methylester in 10 mL of trifluoroacetic acid, 4 mL of $CF_3COOH-CF_3SO_3H$ and 4 mL of phenyl methyl ether were added. The reaction mixture was stirred at 0 °C for 2 h and evaporation under reduced pressure. The residue was treated with 100 mL of ether, the formed powder was purified by Sephadex G10 column (distilled water) and 246 mg (yield 85%) of the title compound was obtained as colorless powder. ^{1}H NMR (BHSC-300, DMSO-d_6): δ/ppm = 10.71 (s, 1H), 8.45 (s, 2H), 4.68 (t, J = 4.7 Hz, 1H), 3.63 (t, J = 5.6 Hz, 1H), 3.55 (d, J = 10.1 Hz, 2H), 3.50 (d, J = 10.1 Hz, 2H), 2.87 (t, J = 4.9 Hz, 2H), 2.77 (t, J = 4.7 Hz, 2H), 2.15 (s, 1H), 1.96 (t, J = 4.9 Hz, 2H), 1.86 (m, J = 4.9 Hz, 2H), 1.89 (t, J = 4.7 Hz, 2H), 1.61 (m, J = 4.9 Hz, 2H), 0.99 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (D_2O): δ/ppm = 177.11, 101.78, 79.14, 63.78, 49.91, 41.45, 40.27, 34.58, 33.23, 31.49, 22.55, 24.31, 23.46. ESI-MS (*m/e*): 289 $[M+H]^+$. $[\alpha]_D^{20} = -132.0$ (c = 0.1, DMSO). Anal. calcd for $C_{14}H_{28}N_2O_4$: C 58.31, H 9.79, N 9.71; found: C 58.48, H 9.90, N 9.56.

*3.1.7. General procedure for the preparation of **4a–s** via the condensation of **2** and amino acids*

The mixture of 1.0 mmol of amino acid and 1.1 mmol of NaOH was dissolved in 5 mL of methanol by stirring at room temperature for 10 min and then 300 mg of anhydrous magnesium sulfate was added. To the suspension, 3.0 mmol of **2** was added dropwise. After stirring at room temperature for 20 min, to the reaction mixture 2.5 mmol of $NaCNBH_3$ was added, stirred at room temperature for additional 8 h and TLC (petroleum/ether, 4:1) indicated complete disappearance of **2**. The reaction mixture was filtered and the filtrate was evaporated under vacuum to remove the solvent. The residue was purified by silica gel chromatography to provide the title compound as a colorless powder.

3.2. Xylene-induced ear edema

Male ICR mice were randomly divided into three groups of 11 mice, namely the test group, vehicle control group, and positive control group. The mice in vehicle control group were administrated orally CMC, the mice in positive control group were administrated orally a suspension of aspirin in CMC at a dosage of 20 mg/kg, and a concentration of 0.3 mg/mL, while the mice in the test group were administrated orally a suspension of **4a–s** in CMC at a dosage of 20 mg/kg, 4.0 mg/kg, 0.8 mg/kg, and a concentration of 2.0 mg/mL, 0.4 mg/mL, 0.08 mg/mL. Thirty minutes later, 0.03 mL of xylene was applied to both the anterior and posterior surfaces of the right ear. The left ear was considered as control. Two hours after xylene application, the mice were killed and both ears were removed. Using a cork borer with a diameter of 7 mm, several circular sections were taken and weighed. The increase in weight caused by the irritant was measured through subtracting the weight of the untreated left ear section from that of the treated right ear section. The statistical analysis of the data was carried out by use of ANOVA test, $p < 0.05$ is considered significant.

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