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Toward the development of chemoprevention agents (III): Synthesis and anti-inflammatory activities of a new class of 5-glycylamino-2-substituted-phenyl-1,3-dioxacycloalkanes

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Abstract—A new series of 5-glycylamino-2-substituted-phenyl-1,3-dioxacycloalkanes were designed and synthesized. The anti-inflammatory activities of these compounds were tested using the xylene-induced mouse ear edema model. Sixteen of these new compounds exhibited comparable or better anti-inflammatory activities than aspirin suggesting that they can be further developed as potential anti-inflammatory drug leads. In addition, treatment with these anti-inflammatory agents did not prolong tail bleeding time in mice. The structure/activity relationships were also analyzed among these compounds. Considering their good efficacy and safety profiles, some 5-glycylamino-2-substituted-phenyl-1,3-dioxacycloalkanes are worthy to be explored further in assessing the possible link between anti-inflammation and cancer prevention.

1. Introduction

Chronic injury or irritation by infectious or non-infectious processes may result in original inflammation, and an inflammatory response may subsequently lead to the recruitment of mast cells and leukocytes to the site of inflammation with release of free radicals, including reactive oxygen species (ROS).[1] Free radicals are known to be associated with cellular and genomic damage, in particular through acting on lipids and DNA, and thus contribute to tumorigenesis.[2–4] As a critical area in cancer chemoprevention, the use of non-toxic substances to delay, reverse or suppress multistage carcinogenesis offers a unique scope to intervene at different stages of tumorigenesis by a wide variety of substances of either natural or synthetic origins.[1,2]

Inflammation is a well-established cancer risk factor closely associated with tumorigenesis in many tumor types. Agents with potent anti-inflammatory activity will be considered as candidate chemopreventive drugs. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with a substantially reduced risk of developing colorectal as well as other types of cancer. This further supports the use of anti-inflammatory drugs as a chemopreventive strategy for cancer prevention.[5–8] Toward one of the related stages of colorectal tumorigenesis, including reducing angiogenesis and inducing cell cycle arrest and apoptosis, NSAIDs can be offered as individual chemopreventive agents.[5] Traditional NSAIDs, such as aspirin, usually target both COX-1 and COX-2 and exhibit chemopreventive properties. However, epidemiological studies associate the use of NSAIDs with side effects such as gastric bleeding. Having a low toxicity and being effective at low doses and devoid of side effects are clearly needs for the long-term use of chemopreventive agents.[9–12]

1,3-Dioxanes have been reported as having anti-inflammatory, anti-cancer, and reperfusion injury protection effects through their anti-proliferative and anti-inflammatory activities in human neutrophils and tumor cells.[13–16] Over the past decade, we have developed a series of new anti-inflammatory agents based on a 1,3-dioxane scaffold. Considering their anti-inflammatory

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potencies, basic properties, and lack of gastric bleeding risk, we have recently paid special attention to developing chemopreventive agents based on chemical structures with good anti-inflammatory activities, that is, 2-substitutedphenyl-5-amino-1,3-dioxacycloalkanes. Our previous structure–activity relationship studies indicated that the 5-amino group is responsible for the enhanced anti-inflammatory activities of these compounds.[17–20] It has been suggested that in 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives.[21] In particular, with certain non-alkyl substituents (e.g., F, NO_2, $SOCH_3$, NMe_3, etc.), the axial position is preferred.[16,22] In addition, the formation of hydrogen bonds between the protons of the 5-amino group and the 1,3-dioxygens further forces the 5-amino group to assume the axial orientation. However, the formed hydrogen bonds render the 5-amino functionally less flexible, which may affect its further interaction with the target. Toward this, our strategy is to introduce a small Gly residue to 5-amino group, thereby increasing molecular flexibility to further facilitate its interaction with the target (Fig. 1). Our preliminary studies suggest that these newly synthesized 2-substitutedphenyl-5-glycylamino-1,3-dioxanes not only fulfill the stereochemical requirements, but also have better biological activities compared to their parental compounds. Based on these preliminary findings, herein, we report the design, synthesis, and biological studies of this new series of 2-substitutedphenyl-5-glycylamino-1,3-dioxacycloalkanes. The in vivo anti-inflammatory activities of these compounds were evaluated using the xylene-induced mouse ear edema model. In addition, the bleeding risks of these newly synthesized compounds were also evaluated.

2. Results and discussion

2.1. Preparation of amino-diols *3a–c* via the reduction of methylesters of L-Ser, L-Thr, L-Asp, and L-Glu

The synthesis of the precursors, amino-diols **3a**–**c**, was straightforward. The synthetic route is presented in Scheme 1. Briefly, starting from L-amino acid, in the presence of $SOCl_2$ and methanol, L-Ser (**1a**), L-Thr (**1b**), and L-Asp (**1c**) were easily converted into their corresponding methylesters (**2a**–**c**) with 95% yield and subsequently subjected to reduction. The typical nucleophilic reactivity of $SOCl_2$ resulted in no chlorination of the primary hydroxyl groups of **1a**,**b**. After the treatment of **2a**–**c** with potassium borohydride, the 2-amino-1,3-diols (**3a**,**b**) and 2-amino-1,4-diol (**3c**) were obtained with 39–62% yields (Scheme 1). These amino-diols (**3a**–**c**) are important building blocks for the construction of the target compounds.

2.2. Preparation of 5-glycylamino-1,3-dioxanes via the stereospecific acetalization of amino-diols 3a,b and substituted benzaldehydes 4a–e

In our previous report, we have demonstrated that the anti-inflammatory activities of 2-phenyl-5-amino-1,3-dioxanes are stereochemically independent.[23] Based on this, we selected the thermodynamically stable (*cis*)-2-phenyl-5-amino-1,3-dioxanes **5a**–**e** and (*2S*,*4R*,*5R*)-2-phenyl-4-methyl-5-amino-1,3-dioxanes **5f**–**j** as the model compounds to perform the coupling reaction. The related reactions are presented in Scheme 2.

The preparation of (*cis*)-2-phenyl-5-amino-1,3-dioxanes **5a**–**e** was slightly modified based on our previously

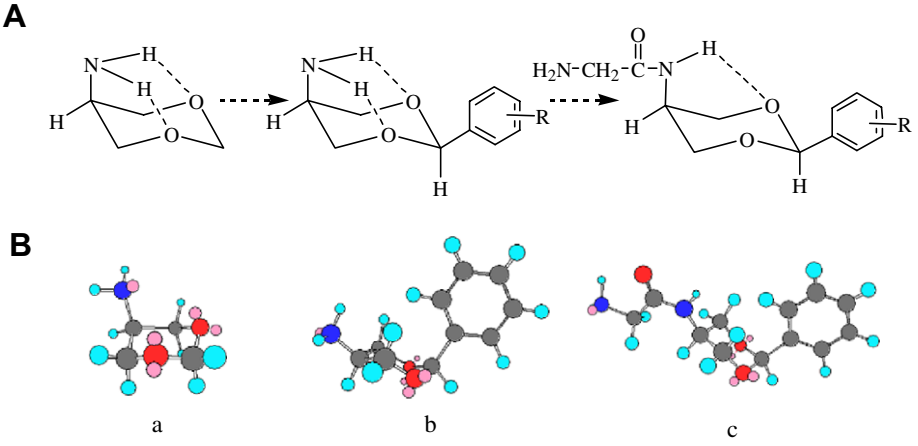
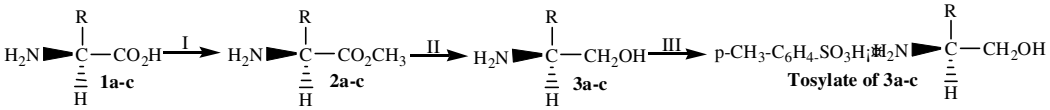
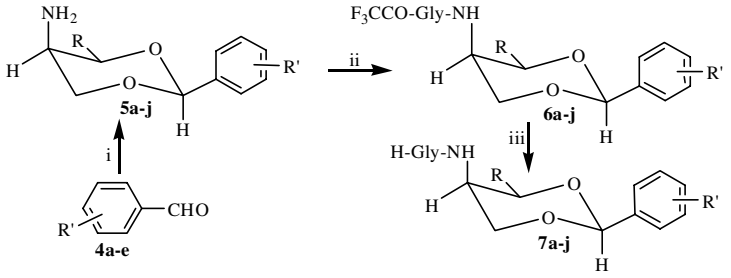


Figure 1. (A) The formed hydrogen bonds render the 5-amino functionally less flexible, which may affect its further interaction with the target. (B) The comparison of the energy minimized 3D structure: (a) energy minimized 3D structure of 5-amino-1,3-dioxacycloalkanes; (b) energy minimized 3D structure of 2-substitutedphenyl-5-amino-1,3-dioxane; (c) energy minimized 3D structure of 2-substitutedphenyl-5-glycylamino-1,3-dioxane.



Scheme 1. Preparation of the aminodiols **3a**–**c**. Reagents: (I) $SOCl_2$ and methanol; (II) potassium borohydride; (III) *p*-CH_3–C_6H_4–SO_3HIn **1a**–**3a** R = CH_2OH; **1b**–**3b** R = $CH(CH_3)OH$; **1c** R = CH_2CO_2H; **2c** R = $CH_2CO_2CH_3$; **3c** R = CH_2CH_2OH.



Scheme 2. The preparation of the target compounds **7a**–**j**. Reagents: (i) tosylate of **3c** and **3b**; (ii) DCC, HOBt, and anhydrous THF; (iii) solution of NaOH in alcohol. In **4a** R′ = H; **4b** R′ = 4-CH_3, **4c** R′ = 4-Cl, **4d** R′ = 4-NO_2, **4e** R′ = 3-NO_2; **5a**–**7a** R = R′ = H; **5b**–**7b** R′ = 4-CH_3, R = H; **5c**–**7c** R′ = 4-Cl, R = H; **5d**–**7d** R′ = 4-NO_2, R = H; **5e**–**7e** R′ = 3-NO_2, R = H; **5f**–**7f** R′ = 4-CH_3, R = CH_3; **5g**–**7g** R′ = 4-Cl, R = CH_3; **5h**–**7h** R′ = 4-NO_2, R = CH_3; **5i**–**7i** R′ = 4-NO_2, R = CH_3; **5j**–**7j** R′ = 3-NO_2, R = CH_3; the definitions of **3a**,**b** are the same as that of Scheme 1.

reported procedure.[23] The acetalization of the tosylate of 2-amido-1,3-diols **3a**,**b** and the substituted benzaldehydes **4a**–**e** stereospecifically provided **5a**–**j** with 88–96% yields. The stereospecificity of the acetalization is most likely due to the thermodynamic stability of the resulting acetalization products **5a**–**j**, and the stereospecificity favors the hydrogen bond formation between the 5-amino protons and the 1,3-dioxygens on the ring. It seems obvious that the equatorial orientation is a favorable conformation for the bulky 2-substitutedphenyl (Fig. 1).

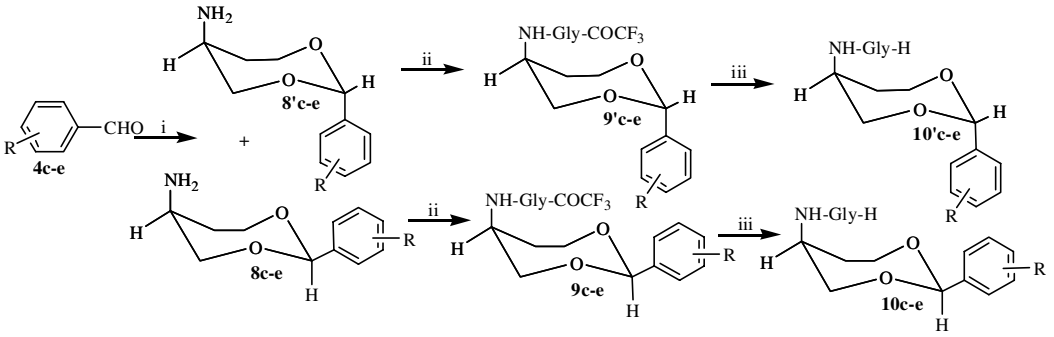
In the presence of 1-hydroxybenzotriazole hydrate (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC), F_3CCO-Gly-OH was coupled with **5a**–**e** to provide the intermediates (*cis*)-2-substitutedphenyl-5-trifluoroacetylglycyl-amino-1,3-dioxanes **6a**–**e**, which were then directly treated with a solution of NaOH in 10 mL of ethanol (80%) to remove the trifluoroacetyl groups. (*cis*)-2-Phenyl-5-glycylamino-1,3-dioxanes **7a**–**e** were then readily obtained with yields ranging from 85% to 90%.

Similarly, F_3CCO-Gly-OH was coupled with **5f**–**j** to give the intermediates (*2S*,*4R*,*5R*)-2-substitutedphenyl-4-methyl-5-trifluoroacetylglycyl-amino-1,3-dioxanes **6f**–**j**, which were also directly treated with a solution of NaOH in 10 mL of ethanol (80%) to remove the trifluoroacetyl groups. (*2S*,*4R*,*5R*)-2-Phenyl-4-methyl-5-glycylamino-1,3-dioxanes **7f**–**j** were easily obtained, and the yields ranged from 82% to 91%.

2.3. Preparation of 5-glycylamino-1,3-dioxaheptanes via the acetalization of amino-diol 3c and substituted benzaldehydes 4a–e

We have demonstrated previously good anti-inflammatory activities with 1,3-dioxanes > 1,3-dioxacycloalheptanes > 1,3-dioxacyclooctanes.[23] In order to further explore the stereochemical effect on biological activity after introducing the Gly residue, we selected (*2S*,*5S*)-2-substitutedphenyl-5-amino-1,3-dioxaheptanes **8c**–**e** and (*2R*,*5S*)-2-substitutedphenyl-5-amino-1,3-dioxaheptanes **8′c**–**e** as the model compounds to couple with H-Gly-OH. The related reactions are presented in Scheme 3.

The preparation of (*2S*,*5S*)-2-substitutedphenyl-5-amino-1,3-dioxaheptanes **8c**–**e** and (*2R*,*5S*)-2-substitutedphenyl-5-amino-1,3-dioxaheptanes **8′c**–**e** directly followed our previously reported procedure.[23] The acetalization of 2-amino-1,4-diol **3c** and substituted benzaldehydes **4c**–**e** stereoselectively provided (*2S*,*5S*)-isomers **8c**–**e** with 23–32% yield and (*2R*,*5S*)-isomers **8′c**–**e** with 15–22% yield. Compared with the six-membered ring, the seven-membered ring has higher molecular flexibility. The energy difference between the *cis*-isomers **8c**–**e** and the *trans*-isomers **8′c**–**e** was thereby minimized. It is worthwhile to mention that we attempted to carry out the acetalizations of 2-amino-1,4-diol **3c** and the substituted benzaldehydes **4a**,**b** under various conditions. However, no desired product was observed. It seems that not only the steric accessibility of the



Scheme 3. Preparation of 2-substitutedphenyl-5-glycylamino-1,3-dioxaheptanes **10** and **10′c**–**e**. Reagents: (i) tosylate of **3c** and **3b**; (ii) DCC, HOBt, and anhydrous THF; (iii) NaOH solution in alcohol. In **4c** R = 4-Cl, **4d** R = 4-NO_2, **4e** R = 3-NO_2; **8**–**10** and **8′**–**10′c** R = 4-Cl; **8**–**10** and **8′**–**10′d** R = 4-NO_2; **8**–**10** and **8′**–**10′e** R = 3-NO_2; the definition of **3c** is the same as that of Scheme 1.

5-amino group of amino-diol and carbonyl of benzaldehyde is one of the key factors, but the stability of the resulting products is also critical for the acetalizations of **3c** and **4a**,**b**. The electron densities of the phenyls in **4a**,**b** are relatively lower than that of the phenyls in **4c**–**e**, and thereby the stability of seven-membered rings is relatively lower than that of their corresponding six-membered rings. Thus, there was no product produced from the acetalizations of **3c** and **4a**,**b**.

Next, in the presence of HOBt and DCC, F_3CCO-Gly-OH was coupled with **8** and **8′c**–**e** to provide the intermediates (*2S*,*5S*)- and (*2R*,*5S*)-5-trifluoroacetyl-glycylamino-2-substitutedphenyl-1,3-dioxa-heptanes **9** and **9′c**–**e,** which were then directly treated with a solution of NaOH in 10 mL of ethanol (80%) to remove the trifluoroacetyl groups. (*2S*,*5S*)- And (*2R*,*5S*)-5-glycylamino-2-substitutedphenyl-1,3-dioxaheptanes **10** and **10′c**–**e** were obtained, and the yields ranged from 68% to 85%.

In summary, by use of these simple synthetic procedures, we have developed a new series of 2-substitutedphenyl-5-glycylamino-1,3-dioxacycloalkanes with good yields and high purities. This method can be easily scaled up to yield gram scale quantity of this new class of compounds, which could be advantageously applied to the preparation of amino acid-heterocyclic hybrids.

2.4. In vivo anti-inflammatory assays of 2-substitutedphenyl-5-glycylamino-1,3-dioxacycloalkanes

To investigate the impact of Gly residue at the 5-amino group of 2-substitutedphenyl-5-amino-1,3-dioxacycloalk-anes on their in vivo biological activities, (*cis*)-2-substitutedphenyl-5-glycylamino-1,3-dioxanes (**7a**–**j**), (*2S*,*5S*)-2-substitutedphenyl-5-glycylamino-1,3-dioxaheptanes (**10c**–**e**), and (*2R*,*5S*)-2-substitutedphenyl-5-glycylamino-1,3-dioxaheptanes (**10′c**–**e**) were evaluated using a xylene-induced ear edema model assay. The test compounds were administer orally by gavage in 0.5% carboxymethyl cellulose (CMC) suspension. Each compound was tested at a dose of 20 mg/kg. It was observed that all of the tested compounds exhibited significant inhibition activity against xylene-induced inflammation in mice as compared with the CMC group, indicating that these compounds possess potent anti-inflammatory activities.

2.4.1. The introduction of a Gly residue at the 5-amino group led to enhanced anti-inflammatory activities in 2-substitutedphenyl-5-amino-1,3-dioxanes. The anti-inflammatory activities of 2-substitutedphenyl-5-glycylamino-1,3-dioxanes **7a**–**j** were tested using xylene-induced ear edema model. From Table 1, it was observed that the anti-inflammatory activities of all of the compounds **7a**–**j** (55–84%) were significantly higher ($P < 0.01$) than that of CMC. In order to investigate the impact of Gly residue on their anti-inflammatory activities, we compared the anti-inflammatory activities of 2-substitutedphenyl-5-amino-1,3-dioxanes **5a**–**j** (41–78%) with those of **7a**–**j**. It was noticed that the introduction of a Gly residue at the 5-amino group of **5a**–**j** indeed led to improved anti-inflammatory activities. In some cases, this tendency was significant, that is, when a Gly residue was introduced at the 5-amino group of **5c**, the anti-inflammatory activity was improved from 64% (**5c**) to 81% (**7c**) ($P < 0.01$). Similarly, in the case of **5h**, the anti-inflammatory activity was increased from 66% (**5h**) to 84% (**7h**) ($P < 0.01$).

Effective receptor interaction is dependent on the conformation assumed by the drug. The enhanced anti-inflammatory activity observed here might partially be due to the contribution of molecular flexibility resulting from the introduction of the Gly residue at the 5-amino group thereby leading to a favorable conformation assumed by 2-substitutedphenyl-5-glycylamino-1,3-dioxanes.

2.4.2. The introduction of a Gly residue at the 5-amino group led to significantly increased anti-inflammatory activities in 2-substitutedphenyl-5-amino-1,3-dioxaheptane. The anti-inflammatory activities of 2-substitutedphenyl-5-glycylamino-1,3-dioxanes **10c**–**e** and **10′c**–**e** were tested using xylene-induced ear edema model. From Table 2, it was observed that the inflammation inhibitions of **10c**–**e** (45–50%) and **10′c**–**e** (46–49%) are significantly ($P < 0.01$) higher than that of CMC. In addition, by com-

Table 1. Anti-inflammatory activities of 2-substitutedphenyl-5-glycylamino-1,3-dioxanes (**7a**–**j**) and 2-substitutedphenyl-5-amino-1,3-dioxanes (**5a**–**j**) against xylene-induced ear edema in mice

Agents	Edema weight ($X \pm$ SD mg)	Inhibition (%)	Agents	Edema weight ($X \pm$ SD mg)	Inhibition (%)
CMC[a]	3.12 ± 0.55		Aspirin	1.85 ± 0.72[b]	40.7
7a	1.45 ± 0.42[b]	55.1	**5a**	1.51 ± 0.53[b]	51.6
7b	1.41 ± 0.33[b]	54.8	**5b**	1.56 ± 0.21[b]	50.0
7c	0.58 ± 0.21[e]	81.4	**5c**	1.12 ± 0.57[c]	64.1
7d	1.11 ± 0.57[c]	64.4	**5d**	1.84 ± 0.73[b]	41.0
7e	1.24 ± 0.43[c]	60.3	**5e**	1.35 ± 0.50[b]	57.7
7f	1.40 ± 0.44[b]	55.1	**5f**	1.47 ± 0.50[b]	52.9
7g	1.35 ± 0.40[b]	56.7	**5g**	1.42 ± 0.35[b]	54.5
7h	0.51 ± 0.20[e]	83.7	**5h**	1.04 ± 0.29[d]	66.7
7i	0.56 ± 0.31[e]	82.1	**5i**	0.67 ± 0.52[d]	78.5
7j	1.16 ± 0.38[c]	62.8	**5j**	1.20 ± 0.42[c]	61.5

[a] CMC = vehicle, dose of **5a**–**j** and **7a**–**j** = 20 mg/kg, dose of aspirin = 30 mg/kg, $n = 11$.
[b] Compare to CMC $P < 0.01$.
[c] Compare to CMC $P < 0.01$, to aspirin $P < 0.05$.
[d] Compare to CMC and aspirin $P < 0.01$.
[e] Compare to CMC, aspirin, and **5a**–**h**,**j** $P < 0.01$.

Table 2. Anti-inflammatory activities of 2-substitutedphenyl-5-glycylamino-1,3-dioxaheptanes (**10** and **10′c–e**) and 2-substitutedphenyl-5-amino-1,3-dioxaheptanes (**8** and **8′c–e**) against xylene-induced ear edema in mice[a]

Agents	Edema weight ($X \pm$ SD mg)	Inhibition (%)	Agents ($X \pm$ SD mg)	Edema weight	Inhibition (%)
CMC	3.12 ± 0.55		Aspirin	1.85 ± 0.72[b]	
10c	1.60 ± 0.55[c]	48.7	**8c**	2.12 ± 0.56[b]	32.1
10d	1.56 ± 0.54[c]	50.0	**8d**	2.44 ± 0.53[b]	21.8
10e	1.71 ± 0.40[c]	45.2	**8e**	2.35 ± 0.52[b]	24.7
10′c	1.58 ± 0.56[c]	49.3	**8′c**	2.15 ± 0.53[b]	31.1
10′d	1.59 ± 0.51[c]	49.0	**8′d**	2.40 ± 0.55[b]	23.1
10′e	1.69 ± 0.53[c]	45.8	**8′e**	2.38 ± 0.55[b]	23.7

[a] CMC = vehicle, dose of **8** and **8′c–e** and **10** and **10′e–e** = 20 mg/kg, dose of aspirin = 30 mg/kg, $n = 11$.
[b] Compare to CMC $P < 0.01$.
[c] Compare to CMC $P < 0.01$, compare to aspirin $P < 0.05$.

parison of the anti-inflammatory activities between **10** and **10′c–e** and **8** and **8′c–e**, it was noticed that the introduction of a Gly residue at the 5-amino group of **8** and **8′c–e** resulted in a significant increase in anti-inflammatory activities. For instance, when a Gly residue was introduced into the 5-amino group, the inflammatory inhibition was increased from **8c–e** (22–32%) and **8′c–e** (24–31%) to **10c–e** (45–50%) and **10′c–e** (46–49%) ($P < 0.05$), respectively. Similarly, the enhanced anti-inflammatory activity observed here might also be partially due to the contribution of molecular flexibility resulting from the introduction of the Gly residue at the 5-amino group.

2.4.3. Dose-dependent anti-inflammatory activities. It was observed that the oral administration of compounds **7c**,**h**,**i**, and **10** and **10′c** at doses of 5.0, 10.0, and 20.0 mg/kg presents a dose-dependent anti-inflammatory response in the xylene-induced mouse ear edema test. At doses of 5.0, 10.0, and 20.0 mg/kg, the inflammatory inhibitions of **7c**,**h**,**i** were 31–35%, 61–64%, and 81–84%, respectively. The anti-inflammatory activities were significantly enhanced with the concentration increase. In the case of **10** and **10′c**, at doses of 5.0, 10.0, and 20.0 mg/kg, the inflammatory inhibition was about 16%, 32%, and 50%, respectively. A significant enhancement in their anti-inflammatory activities in compounds **10** and **10′c** with doses above 5.0 mg/kg was also observed. In comparison, the inflammatory inhibition of aspirin was 41% at a dose of 30 mg/kg. Furthermore, compounds **7c**,**h**,**i** exhibited higher anti-inflammatory activity than aspirin at a dose of 10.0 mg/kg. Clearly, compounds **7c**,**h**,**i**, and **10** and **10′c** exhibited a dose-dependent anti-inflammatory action (Table 3).

2.5. Tail bleeding time measurement

Conventional use of NSAIDs is usually associated with a number of significant adverse events, including gastrointestinal bleeding, impaired platelet function, and prolonged bleeding time. Clinical effects of NSAID-induced platelet dysfunction consist of increased bleeding, prolonged surgical bleeding and an additive risk of significant or life-threatening bleeding in patients. To develop safer anti-inflammatory agents, it is critical to evaluate these new synthetic agents for possible deleterious effects on normal hemostasis leading to bleeding complications. The cutaneous bleeding time model is the most common method used in animal experiments to deduce bleeding potential in humans.[24–32]

2-Substitutedphenyl-5-glycylamino-1,3-dioxanes **7a–j** and -1,3-dioxaheptanes **10** and **10′c–e** were orally administered at a 200 mg/kg dose to male mice (body weight 18–22 g). After 30, 45, 60, and 90 min, the mouse was placed in a tube holder with its tail protruding, and a 2-mm cut was made on the tail. Flowing blood was gently wiped away with a tissue every 30 s until bleeding ceased, and the time was recorded.

2.5.1. 5-Glycylamino-2-substitutedphenyl-1,3-dioxanes exhibited no bleeding effect. To explore the anti-inflammatory mechanism of these novel 5-glycylamino-2-substitutedphenyl-1,3-dioxanes, the tail bleeding time assays of **7a–j** were performed on mice using a literature method.[23] The observed bleeding time in mice at all time points tested (5–60 min) fell into a range of 118.8 ± 8.1–122.6 ± 9.0 s, which was equal to before administration (118.8 ± 7.7–122.0 ± 8.4 s) (Table 4). In each case, the

Table 3. Anti-inflammatory activities of **7c**,**h**,**i**, **10d**, and **10′d** at different doses against xylene-induced ear edema in mice[a]

Compound	Edema weight ($X \pm$ SD mg)	Inhibition (%)	Edema weight ($X \pm$ SD mg)	Inhibition (%)	Edema weight ($X \pm$ SD mg)	Inhibition (%)
Dose	5 mg/kg		10 mg/kg		20 mg/kg	
7c	2.15 ± 0.55	31.0	1.20 ± 0.22[d]	61.5	0.58 ± 0.21[b]	81.4
7h	1.95 ± 0.52	37.5	1.11 ± 0.20[d]	64.4	0.51 ± 0.20[b]	83.7
7i	2.02 ± 0.54	35.2	1.22 ± 0.26[d]	60.9	0.56 ± 0.31[b]	82.1
10c	2.62 ± 0.55	16.0	2.11 ± 0.54[e]	32.4	1.56 ± 0.54[c]	50.0
10′c	2.62 ± 0.54	16.0	2.12 ± 0.53[e]	32.0	1.59 ± 0.51[c]	49.0

[a] $N = 11$. Compare to 10 mg/kg group of the same compound $P < 0.01$.
[b] Compare to 10 mg/kg group of the same compound $P < 0.05$.
[c] Compare to 5 mg/kg group of the same compound $P < 0.01$.
[d] Compare to 5 mg/kg group of the same compound $P < 0.05$.

Table 4. Effect of 5-glycylamino-2-substitutedphenyl-1,3-dioxanes on the tail bleeding time (±SDs) of mice

Compound	Before administration	After administration			
		5 min	15 min	30 min	60 min
7a	119.5 ± 8.1	120.0 ± 8.0	120.2 ± 7.7	120.9 ± 8.2	120.5 ± 8.4
7b	120.0 ± 8.2	120.0 ± 8.2	120.3 ± 7.4	119.1 ± 8.1	120.3 ± 8.5
7c	118.8 ± 7.7	120.8 ± 8.3	120.6 ± 8.5	120.3 ± 7.7	120.0 ± 8.1
7d	119.7 ± 8.3	120.9 ± 8.0	120.4 ± 7.7	122.5 ± 8.3	121.0 ± 8.0
7e	122.0 ± 8.4	120.1 ± 8.2	120.2 ± 8.4	122.2 ± 8.4	121.2 ± 8.0
7f	120.1 ± 7.7	121.1 ± 8.4	119.8 ± 8.2	120.7 ± 8.2	121.8 ± 8.5
7g	121.0 ± 8.0	119.9 ± 8.3	122.6 ± 9.0	121.4 ± 8.3	120.3 ± 8.3
7h	121.5 ± 8.3	122.5 ± 8.7	120.5 ± 8.3	120.1 ± 8.0	120.4 ± 8.1
7i	118.8 ± 7.3	120.0 ± 7.6	121.0 ± 8.4	118.8 ± 8.1	120.5 ± 8.3
7j	119.7 ± 7.5	120.4 ± 8.3	120.8 ± 8.1	119.0 ± 8.3	119.9 ± 8.4

Dose = 200 mg/kg, $n = 10$; NS (normal saline) = vehicle.

Table 5. Effect of 5-glycylamino-2-substitutedphenyl-1,3-dioxaheptanes on the tail bleeding time (±SDs) of mice

Compound	Before administration	After administration			
		5 min	15 min	30 min	60 min
10c	119.3 ± 8.8	119.5 ± 8.2	120.4 ± 8.8	120.8 ± 8.1	120.1 ± 7.5
10d	119.6 ± 7.4	120.3 ± 7.6	123.0 ± 8.0	120.1 ± 8.7	119.3 ± 7.8
10e	118.6 ± 7.5	119.5 ± 7.7	119.5 ± 7.9	123.1 ± 8.8	119.6 ± 7.9
10′c	119.8 ± 7.8	121.1 ± 8.2	119.1 ± 8.6	120.0 ± 7.8	119.4 ± 7.5
10′d	118.5 ± 7.6	120.4 ± 7.9	120.7 ± 8.7	120.1 ± 7.5	119.2 ± 7.0
10′e	119.4 ± 7.8	121.0 ± 8.2	119.8 ± 8.4	120.2 ± 8.1	120.9 ± 8.3

Dose = 200 mg/kg, $n = 10$; NS (normal saline) = vehicle.

dose was 200 mg/kg body weight. This observation implied that at 10-fold anti-inflammatory dose the bleeding time of **7a**–**j** receiving mice was kept at a normal level and the introduction of Gly residue onto the 5-amino group of **5a**–**j** resulted in no bleeding risk.

2.5.2. 5-Glycylamino-2-substitutedphenyl-1,3-dioxaheptanes exhibited no bleeding effect. To explore the anti-inflammatory mechanism of these novel 5-glycylamino-2-substitutedphenyl-1,3-dioxaheptanes, the tail bleeding time assays of **10** and **10′c**–**e** were also performed on mice using a literature method.[23] The observed bleeding time in mice at all time points tested (5–60 min) fell into a range of 119.2 ± 7.0–123.1 ± 8.8 s, which was equal to before administration (118.5 ± 7.6–119.8 ± 7.8 s) (Table 5). In each case, the dose was 200 mg/kg body weight. This observation implied that, at 10-fold anti-inflammatory dose the bleeding time of **10** and **10′c**–**e** receiving mice was kept at a normal level and the introduction of Gly residue onto the 5-amino group of **8** and **8′c**–**e** resulted in no bleeding risk.

3. Conclusion

In this study, we have developed a series of new 2-substitutedphenyl-5-glycylamino-1,3-dioxacycloalkanes as potent anti-inflammatory agents. Sixteen of the newly synthesized compounds exhibit improved in vivo anti-inflammatory activities. In addition, these compounds did not prolong tail bleeding time even at high doses (200 mg/kg). Taken together, these newly synthesized compounds display a favorable pharmacological profile relative to the reference drug aspirin. Considering their efficacy and safety profiles, it would be worthwhile to work further in detail with these newly synthesized compounds in assessing the possible link between inflammatory inhibition and cancer prevention.

4. Experimental

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere (1 bar). Melting points are uncorrected. The agents used in this work were purchased from Sigma Chemical Co. (USA). Chromatography was performed on Qingdao silica gel H (Qingdao of China). The purities of the intermediates and the products were confirmed by TLC (Merck silica gel plates of type 60 F_{254}, 0.25 mm layer thickness, Germany) and HPLC (Waters, C_{18} column 4.6 × 150 mm, USA). NMR spectra were recorded at 300 MHz on a VXR-300 instrument or at 500 MHz on a Bruker Am-500 instrument in $CDCl_3$ with tetramethylsilane as internal standard. EI-MS was determined by Trace MS System (Thermo Finnigan, USA). Optical rotations were determined with a Schmidt+Haensch Polartromic D instrument (Germany). The statistical analysis of all the biological data was carried out by use of ANOVA test, $P < 0.05$ is considered significant.

4.1. Preparation of amino acid methylesters (2a–c)

According to our previously reported procedure,[23] at 0 °C, to 50 mL of anhydrous methanol, 3.75 mL (47.5 mmol) of thionyl chloride was added dropwise. The solution was stirred at 0 °C for 30 min and then 47.6 mmol of L-Ser-OH, L-Thr-OH or L-Asp-OH was

added. The reaction mixture was stirred at room temperature for 24 h and TLC (CH_3Cl/CH_3OH, 9:1) indicated complete disappearance of L-Ser-OH, L-Thr-OH or L-Asp-OH. The reaction mixture was concentrated under reduced pressure and the residue was triturated with petroleum ether repeatedly to provide 7304 mg (99%) of HCl·L-Ser-OCH_3 (**2a**, colorless powder, mp 161–162 °C), 7867 mg (98%) of HCl·L-Thr-OCH_3 (**2b**, colorless powder, mp 140–142 °C) or HCl·L-Asp-$(OCH_3)_2$ (**2c**, colorless powder, mp 149–151 °C).

4.2. Preparation of aminodiols (3a–c)

According to the literature,[23] to the suspension of 200 mg (5.6 mmol) of KBH_4 in 10 mL of THF, the solution of 1.0 mmol of HCl·L-Ser-OCH_3, HCl·L-Thr-OCH_3 or HCl·L-Asp-$(OCH_3)_2$ in 20 mL of THF was added. The reaction mixture was stirred at room temperature for 24 h and TLC (C_2H_5OH/H_2O, 7:1) indicated complete disappearance of HCl·L-AA-OCH_3. At 0 °C, the reaction mixture was adjusted to pH 10 with hydrochloric acid (2 mol/L) and concentrated under reduced pressure. The residue was purified by chromatography (CH_3Cl/CH_3OH, 19:1) to offer 74 mg (62%) 2-aminopropane-1,3-diol hydrochloride (**3a**, colorless powder, mp 55–58 °C), 98 mg (58%) of (*2R,3R*)-2-aminobutane-1,3-diol hydrochloride [**3b**, colorless powder, mp 50–52 °C, $[\alpha]_D^{20}$ −4.0 (c = 4, H_2O)] or 55 mg (39%) of (*2S*)-2-aminobutane-1,4-diol hydrochloride [**3c**, yellow oil, $[\alpha]_D^{20}$ −13.5 (c = 4.0, H_2O)].

4.3. F_3CCO-Gly-OH

At 0 °C, 15.0 g (0.07 mol) of trifluoroacetic anhydride was added dropwise to the solution of 3.0 g (0.04 mol) of H-Gly-OH in 75 mL of anhydrous THF for 30 min. The reaction mixture was stirred at room temperature for 45 min and TLC ($CHCl_3$/MeOH, 10:1) indicated complete disappearance of H-Gly-OH. The reaction mixture was concentrated under reduced pressure and the residue was refluxed in 60 mL of mixed solvent of chloroform and petroleum (1:1) for 10 min, then cooled to room temperature. By filtration, 6.0 g (66%) of the title compound was obtained as a colorless powder, mp 117–118 °C.

4.4. Preparation of (*cis*)-5-amino-2-substitutedphenyl-1,3-dioxanes (5a–e)

According to the literature,[23] a mixture of 2.0 mmol of **3a**, 2.6 mmol of **4a**–**d** or **4e**, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous $NaSO_4$, 50 mL of chloroform, and 4 mL of THF was stirred at room temperature overnight until TLC ($CHCl_3/CH_3OH$, 20:1) indicated complete disappearance of **4a**–**d** or **4e**. The reaction mixture was then adjusted to pH 7 with sodium carbonate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel ($CHCl_3/CH_3OH$, 40:1) to provide the title compounds.

4.4.1. (*cis*)-(2-Phenyl-1,3-dioxan-5-yl)amine (5a). 315 mg (88%), colorless powder, mp 52–54 °C.

4.4.2. (*cis*)-[2-(4′-Methylphenyl)-1,3-dioxan-5-yl]amine (5b). 328 mg (85%), colorless powder, mp 55–56 °C.

4.4.3. (*cis*)-[2-(4′-Chlorophenyl)-1,3-dioxan-5-yl]amine (5c). 409 mg (96%), colorless powder, mp 76–78 °C.

4.4.4. (*cis*)-2-[4′-Nitrophenyl]-1,3-dioxan-5-yl]amine (5d). 419 mg (93%), colorless powder, mp 113–114 °C.

4.4.5. (*cis*)-2-[3′-Nitrophenyl]-1,3-dioxan-5-yl]amine (5e). 403 mg (93%), colorless powder, mp 50–52 °C.

4.5. Preparation of (*2S,4R,5R*)-(2-substitutedphenyl-4-methyl-1,3-dioxan-5-yl)amine (5f–j)

According to the literature,[23] a mixture of 2.0 mmol of **3b**, 2.6 mmol of **4a**–**d** or **4e**, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous $NaSO_4$, 50 mL of chloroform, and 4 mL of THF was stirred at room temperature overnight until TLC ($CHCl_3/CH_3OH$, 20:1) indicated complete disappearance of aminodiol. The reaction mixture was then adjusted to pH 7 with sodium carbonate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel ($CHCl_3/CH_3OH$, 40:1) to provide the title compounds.

4.5.1. (*2S,4R,5R*)-(2-Phenyl-4-methyl-1,3-dioxan-5-yl)amine (5f). 309 mg (80%), colorless powder, mp 48–50 °C, $[\alpha]_D^{20}$ −8.1 (c = 1.00, $CHCl_3$).

4.5.2. (*2S,4R,5R*)-2-[(4′-Methylphenyl)-4-methyl-1,3-dioxan-5-yl]amine (5g). 311 mg (75%), colorless powder, mp 63–64 °C, $[\alpha]_D^{20}$ −8.0 (c = 1.00, $CHCl_3$).

4.5.3. (*2S,4R,5R*)-2-[(4′-Chlorophenyl)-4-methyl-1,3-dioxan-5-yl]amine (5h). 386 mg (85%), colorless powder, mp 45–46 °C, $[\alpha]_D^{20}$ −8.0 (c = 1.00, $CHCl_3$).

4.5.4. (*2S,4R,5R*)-2-[(4′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]amine (5i). 419 mg (88%), colorless powder, mp 80–82 °C, $[\alpha]_D^{20}$ −8.3 (c = 1.00, $CHCl_3$).

4.5.5. (*2S,4R,5R*)-2-[(3′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]amine (5j). 433 mg (91%), colorless powder, mp 50–52 °C, $[\alpha]_D^{20}$ −8.1 (c = 1.00, $CHCl_3$).

4.6. Preparation of (*cis*)-2-substitutedphenyl-5-glycylamino-1,3-dioxanes (7a–e)

To a solution of 0.25 mmol of **5a**–**d** or **5e** in 10 mL of anhydrous THF at 0 °C, 426 mg (0.25 mmol) of F_3CCO-Gly-OH, 38 mg (0.28 mmol) of 1-hydroxybenzotriazole hydrate (HOBt), and 52 mg (0.25 mmol) of *N*,*N*′-dicyclohexylcarbodiimide (DCC) were added. The reaction mixture was stirred at 0 °C for 2 h, at room temperature for 10 h, and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **5a**–**d** or **5e.** Upon concentration under reduced pressure, the residue was dissolved in 20 mL of ethyl acetate. The solution was washed successively with saturated sodium bicarbonate, saturated sodium chloride, 5% kalium bisulfate, and again with saturated sodium chloride, and the organic

phase was dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the product was purified by silica column chromatography ($CHCl_3/CH_3OH$, 10:1) to provide the intermediates (*cis*)-5-trifluoroacetylglycylamino-2-substitutedphenyl-1,3-dioxanes **6a–d** or **6e.**

To a solution of 50 mg of NaOH in 10 mL of ethanol (80%), the obtained **6a–d** or **6e** was added. The reaction mixture was stirred at room temperature for 12 h and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **6a–d** or **6e**. Upon removal of ethanol, the residue was mixed with 2 mL of water and the solution was extracted with dichloromethane (3× 10 mL). The dichloromethane phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to provide (*cis*)-2-substitutedphenyl-5-glycylamino-1,3-dioxanes **7a–e**.

4.6.1. (*cis*)-2-Phenyl-5-glycylamino-1,3-dioxane (7a). Yield: 85%, colorless solids, mp 96–98 °C. IR(KBr): υ/cm^{-1} = 3249, 3183, 1692, 1644, 1632, 1605, 1576, 1504, 1455, 1053, 746, 695. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.209 (s,1H), 7.494 (d, J = 7.14 Hz, 2H), 7.390 (t, J = 7.51 Hz, 1H), 7.351 (t, J = 7.52 Hz, 2H), 5.579 (s, 1H), 4.165 (t, J = 2.20 Hz, 2H), 4.113 (d, J = 1.51 Hz, 2H), 3.644 (d, J = 4.80 Hz, 1H), 3.411 (s, 2H), 1.569 (s, 2H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.446, 137.848, 129.137, 128.345, 125.881, 101.774, 70.712, 44.742, 43.316. ESI-MS (*m*/*e*) 237 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.80; H, 7.00; N, 12.10.

4.6.2. (*cis*)-2-(4′-Methylphenyl)-5-glycylamino-1,3-dioxane (7b). Yield: 90%, colorless solids, mp 105–108 °C. IR(KBr): υ/cm^{-1} = 3244, 3186, 1693, 1643, 1632, 1600, 1583, 1506, 1462, 1380, 1044, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.184 (s, 1H), 7.382 (d, J = 8.10 Hz, 2H), 7.191 (d, J = 7.80 Hz, 2H), 5.544 (s, 1H), 4.141 (d, J = 9.60 Hz, 2H), 4.030 (t, J = 6.00 Hz, 2H), 3.900 (s, 1H), 3.738 (d, J = 10.80 Hz, 1H), 3.407 (s, 1H), 2.354 (s, 3H), 1.614 (s, 2H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.455, 138.961, 135.071, 128.988, 125.744, 101.914, 70.679, 44.767, 43.341, 21.262. ESI-MS (*m*/*e*) 251 $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.14; H, 7.11; N, 11.44.

4.6.3. (*cis*)-2-(4′-Chlorophenyl)-5-glycylamino-1,3-dioxane (7c). Yield: 89%, colorless solids, mp 99–102 °C. IR(KBr): υ/cm^{-1} = 3254, 3186, 1690, 1639, 1603, 1584, 1505, 1383, 1455, 1047, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.188 (s, 1H), 7.427 (t, J = 7.40 Hz, 2H), 7.362 (t, J = 7.01 Hz, 2H), 5.550 (s, 1H), 4.153 (t, J = 6.50 Hz, 2H), 4.033 (d, J = 10.50 Hz, 2H), 3.898 (d, J = 5.10 Hz, 1H), 3.416 (s, 2H), 1.623 (s, 2H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.438, 136.364, 134.914, 128.494, 127.365, 100.925, 70.687, 44.709, 43.226. ESI-MS (*m*/*e*) 271 $[M+H]^+$. Anal. Calcd for $C_{12}H_{15}ClN_2O_3$: C, 53.24; H, 5.58; N, 10.35. Found: C, 53.00; H, 5.69; N, 10.11.

4.6.4. (*cis*)-2-(4′-Nitrophenyl)-5-glycylamino-1,3-dioxane (7d). Yield: 85%, light yellow solids, Mp128–131 °C. IR(KBr): υ/cm^{-1} = 3252, 3189, 1695, 1648, 1633, 1606, 1584, 1520, 1500, 1455, 1350, 1046, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.204 (d, J = 5.62 Hz, 2H), 8.064 (s, 1H), 7.635 (d, J = 8.50 Hz, 2H), 5.581 (d, J = 7.39 Hz, 1H), 4.168 (d, J = 10.20 Hz, 2H), 4.045 (d, J = 9.90 Hz, 2H), 3.847 (d, J = 5.10 Hz, 1H), 3.731 (d, J = 5.10 Hz, 1H), 3.459 (s, 1H), 1.982 (s, 2H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.446, 148.241, 144.194, 127.068, 123.475, 100.011, 70.786, 44.660, 43.226. ESI-MS (*m*/*e*) 282 $[M+H]^+$. Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.00; H, 5.50; N, 14.71.

4.6.5. (*cis*)-2-(3′-Nitrophenyl)-5-glycylamino-1,3-dioxane (7e). Yield: 90%, light yellow solids, mp 95–97 °C. IR(KBr): υ/cm^{-1} = 3245, 3180, 1692, 1640, 1605, 1583, 1522, 1503, 1456, 1352, 1045, 862, 775, 704. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.389 (s, 1H), 8.226 (d, J = 4.10 Hz, 2H), 7.826 (d, J = 7.80 Hz, 1H), 7.563 (t, J = 8.00 Hz, 1H), 5.635 (s, 1H), 4.184 (t, J = 12.60 Hz, 4H), 4.059 (d, J = 9.90 Hz, 2H), 3.476 (s, 1H), 2.418 (s, 2H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.018, 148.109, 139.744, 132.194, 129.293, 123.862, 121.307, 99.829, 70.670, 44.388, 43.267. ESI-MS (*m*/*e*) 282 $[M+H]^+$. Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.45; H, 5.22; N, 14.69.

4.7. Preparation of (*2S,4R,5R*)-2-substitutedphenyl-4-methyl-5-glycylamino-1,3-dioxanes (7f–j)

To a solution of 0.25 mmol of **5f–i** or **5j** in 10 mL of anhydrous THF at 0 °C, 426 mg (0.25 mmol) of F_3CCO-Gly-OH, 38 mg (0.28 mmol) of 1-hydroxybenzotriazole hydrate (HOBt), and 52 mg (0.25 mmol) of *N*,*N*′-dicyclohexylcarbodiimide (DCC) were added. The reaction mixture was stirred at 0 °C for 2 h, at room temperature for 10 h, and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **5f–i** or **5j**. Upon concentration under reduced pressure, the residue was dissolved in 20 mL of ethyl acetate. The solution was washed successively with saturated sodium bicarbonate, saturated sodium chloride, 5% kalium bisulfate, and saturated sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the product was purified by silica gel column chromatography ($CHCl_3/CH_3OH$, 10:1) to provide the intermediates (*cis*)-5-trifluoroacetylglycylamino-2-substitutedphenyl-1,3-dioxanes **6f–i** or **6j**.

To a solution of 50 mg of NaOH in 10 mL of ethanol (80%), the obtained **6f–i** or **6j** was added. The reaction mixture was stirred at room temperature for 12 h and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **6–i** or **6j**. Upon removal of ethanol, the residue was mixed with 2 mL of water and the solution was extracted with dichloromethane (3× 10 mL). The dichloromethane phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to provide (*cis*)-2-substitutedphenyl-5-glycylamino-1,3-dioxanes **7f–j**.

4.7.1. (*2S,4R,5R*)-2-Phenyl-4-methyl-5-glycylamino-1,3-dioxane (7f). Yield: 91%, light yellow oil. IR(KBr): υ/cm^{-1} = 3249, 3183, 1690, 1642, 1634, 1605, 1580, 1504,

1452, 1385, 1044, 744, 696. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.945 (s, 1H), 7.513 (q, J = 7.72 Hz, 2H), 7.386 (m, J = 7.68 Hz, 1H), 7.334 (t, J = 7.67 Hz, 2H), 5.573 (s, 1H), 4.167 (m, J = 4.70 Hz, 1H), 4.097 (t, J = 1.80 Hz, 2H), 3.927 (q, J = 11.60 Hz, 1H), 3.483 (s, 2H), 2.765 (s, 2H), 1.221 (d, J = 6.60 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.282, 137.914, 129.062, 128.321, 126.038, 101.725, 75.088, 71.503, 46.481, 44.207, 17.685. ESI-MS (*m*/*e*) 251 $[M+H]^+$. $[\alpha]_D^{20}$ −42.0 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.59; H, 7.40; N, 11.43.

4.7.2. (2*S*,4*R*,5*R*)-2-(4′-Methylphenyl)-4-methyl-5-glycylamino-1,3-dioxane (7g). Yield: 89%, light yellow oil. υ/cm^{-1} = 3253, 3186, 1691, 1644, 1637, 1605, 1580, 1504, 1452, 1385, 1044, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.959 (s, 1H), 7.338 (q, J = 8.10 Hz, 2H), 7.183 (d, J = 8.10 Hz, 2H), 5.552 (s, 1H), 4.146 (m, J = 4.00 Hz, 1H), 3.970 (d, J = 1.20 Hz, 2H), 3.938 (m, J = 1.50 Hz, 1H), 3.426 (s, 2H), 2.343 (s, 3H), 2.041 (s, 2H), 1.212 (d, J = 6.30 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.545, 138.804, 135.087, 128.906, 125.823, 101.708, 74.973, 71.445, 46.341, 44.511, 21.179, 17.644. ESI-MS (*m*/*e*) 265 $[M+H]^+$. $[\alpha]_D^{20}$ −34.0 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.40; H, 7.52; N, 10.83.

4.7.3. (2*S*,4*R*,5*R*)-2-(4′-Chlorophenyl)-4-methyl-5-glycylamino-1,3-dioxane (7h). Yield: 82%, light yellow oil. IR(KBr): υ/cm^{-1} = 3255, 3186, 1690, 1644, 1633, 1604, 1580, 1505, 1386, 1454, 1045, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 7.905 (d, J = 9.30 Hz, 1H), 7.389 (m, J = 10.10 Hz, 2H), 7.324 (m, J = 8.01 Hz, 2H), 5.502 (s, 1H), 4.095 (q, J = 11.10 Hz, 1H), 4.022 (q, J = 11.70 Hz, 2H), 3.923 (d, J = 11.9 Hz, 1H), 3.604 (s, 2H), 1.210 (s, 2H), 1.144 (d, J = 6.30 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ/ppm = 170.831, 136.422, 134.832, 128.469, 127.661, 100.909, 75.137, 71.445, 46.547, 44.605, 17.636. ESI-MS (*m*/*e*) 285 $[M+H]^+$. $[\alpha]_D^{20}$ −36.0 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.62; H, 6.19; N, 9.57.

4.7.4. (2*S*,4*R*,5*R*)-2-(4′-Nitrophenyl)-4-methyl-5-glycylamino-1,3-dioxane (7i). Yield: 82%, light yellow solids, mp 136–140 °C. IR(KBr): υ/cm^{-1} = 3252, 3184, 1691, 1645, 1634, 1604, 1585, 1527, 1502, 1454, 1386, 1354, 1044, 820. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.205 (d, J = 8.70 Hz, 2H), 7.939 (d, J = 9.00 Hz, 1H), 7.646 (q, J = 7.30 Hz, 2H), 6.117 (s, 1H), 4.197 (m, J = 3.90 Hz, 1H), 4.024 (q, J = 10.50 Hz, 2H), 3.894 (d, J = 4.50 Hz, 2H), 3.470 (s, 1H), 2.331 (s, 2H), 1.223 (d, J = 6.30 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.282, 148.208, 144.268, 127.192, 123.475, 100.019, 75.401, 71.668, 46.267, 44.363, 17.611. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ −34.0 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.65; H, 5.99; N, 14.46.

4.7.5. (2*S*,4*R*,5*R*)-2-(3′-Nitrophenyl)-4-methyl-5-glycylamino-1,3-dioxane (7j). Yield: 85%, light yellow solids, mp 78–81 °C. IR(KBr): υ/cm^{-1} = 3249, 3186, 1645, 1637, 1601, 1582, 1522, 1502, 1458, 1381, 1351, 1048, 743, 699. ^{1}H NMR ($CDCl_3$): δ/ppm = 8.396 (s, 1H), 8.220 (d, J = 7.50 Hz, 1H), 7.990 (d, J = 9.60 Hz, 1H), 7.842 (q, J = 7.80 Hz, 1H), 7.549 (q, J = 7.60 Hz, 1H), 5.671 (s, 1H), 4.224 (t, J = 6.90 Hz, 1H), 4.070 (m, J = 5.20 Hz, 2H), 3.941 (d, J = 5.40 Hz, 1H), 3.494 (s, 2H), 2.330 (s, 2H), 1.256 (d, J = 6.30 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ/ppm = 172.858, 148.150, 139.851, 132.260, 129.293, 123.845, 121.389, 99.854, 75.393, 71.659, 46.201, 44.643, 17.611. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ −34.1 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.67; H, 5.93; N, 14.51.

4.8. Preparation of (2*S*,5*S*)- and (2*R*,5*S*)-(2-substituted-phenyl-1,3-dioxaheptan-5-yl)-amine (8c–e) and (8′c–e)

According to the literature,[23] the suspension of 102 mg (0.72 mmol) of **3c** (tosylate), 0.72 mmol of **4c**, **4d** or **4e**, 10 mg of tolylsulfonylic acid, 30 mg of anhydrous $NaSO_4$, 20 mL of chloroform, and 4 mL of THF was stirred at 50 °C for 12 h and TLC ($CHCl_3$/CH_3OH, 20:1) indicated complete disappearance of **3c**. The reaction mixture was cooled to 20 °C and adjusted to pH 7 with sodium carbonate. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to provide the title compound.

4.8.1. (2*S*,5*S*)-2-(4′-Chlorophenyl-1,3-dioxaheptan-5-yl)amine (8c). 49 mg (30%), colorless powder, mp 48–49 °C, $[\alpha]_D^{20}$ 8.0 (c = 1.00, $CHCl_3$).

4.8.2. (2*R*,5*S*)-2-(4′-Chlorophenyl-1,3-dioxaheptan-5-yl)amine (8′c). 35 mg (21%), colorless powder, mp 56–57 °C, $[\alpha]_D^{20}$ −6.0 (c = 1.00, $CHCl_3$).

4.8.3. (2*S*,5*S*)-2-(4′-Nitrophenyl-1,3-dioxaheptan-5-yl)amine (8d). 39 mg (23%), colorless powder, mp 76–78 °C, $[\alpha]_D^{20}$ 8.0 (c = 1.00, $CHCl_3$).

4.8.4. (2*R*,5*S*)-2-(4′-Nitrophenyl-1,3-dioxaheptan-5-yl)amine (8′d). 26 mg (15%), colorless powder, mp 61–63 °C, $[\alpha]_D^{20}$ −16.0 (c = 1.00, $CHCl_3$).

4.8.5. (2*S*,5*S*)-[2-(3′-Nitrophenyl)-1,3-dioxaheptan-5-yl]amine (8e). 55 mg (32%), colorless powder, mp 68–70 °C, $[\alpha]_D^{20}$ 12.0 (c = 1.00, $CHCl_3$).

4.8.6. (2*R*,5*S*)-[2-(3′-Nitrophenyl)-1,3-dioxaheptan-5-yl]amine (8′e). 38 mg (22%), colorless powder, mp 65–67 °C, $[\alpha]_D^{20}$ −6.0 (c = 1.00, $CHCl_3$).

4.9. Preparation of (2*S*,5*S*)- and (2*R*,5*S*)-2-substitutedphenyl-5-glycylamino-1,3-dioxa-heptanes (10) and (10′c–e)

To a solution of 0.25 mmol of **8c** and **8′c**, **8d** and **8′d** or **8e** and **8′e** in 10 mL of anhydrous THF at 0 °C, 426 mg (0.25 mmol) of F_3CCO-Gly-OH, 38 mg (0.28 mmol) of HOBt, and 52 mg (0.25 mmol) of DCC were added. The reaction mixture was stirred at 0 °C for 2 h, at room temperature for 10 h, and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **8c** and **8′c**, **8d** and **8′d** or **8e** and **8′e**. Upon concentration under

reduced pressure, the residue was dissolved in 20 mL of ethyl acetate. The solution was washed successively with saturated sodium bicarbonate, saturated sodium chloride, 5% kalium bisulfate, and saturated sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the product was purified by silica gel column chromatography ($CHCl_3/CH_3OH$, 10:1) to provide the intermediates (*2S*,*5S*)- and (*2R*,*5S*)-2-substitutedphenyl-5-trifluoroacetyl-glycylamino-1,3-dioxa-heptanes **9c** and **9′c**, **9d** and **9′d** or **9e** and **9′e**.

To a solution of 50 mg of NaOH in 10 mL of ethanol (80%), the obtained **9c** and **9′c**, **9d** and **9′d** or **9e** and **9′e** were added. The reaction mixture was stirred at room temperature for 12 h and TLC ($CHCl_3$/MeOH = 10:1) indicated complete disappearance of **9c** and **9′c**, **9d** and **9′d** or **9e** and **9′e**. Upon removal of ethanol, the residue was mixed with 2 mL of water and the solution was extracted with dichloromethane (3× 10 mL). The dichloromethane phase was dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure to provide (*2S*,*5S*)- and (*2R*,*5S*)-2-substitutedphenyl-5-glycylamino-1,3-dioxaheptanes **10** and **10′c**–**e**.

4.9.1. (*2S*,*5S*)-2-(4′-Chlorophenyl)-5-glycylamino-1,3-dioxaheptanes (10c). Yield: 73%, light yellow solids, mp 120–124°C. IR(KBr): υ/cm^{-1} = 3342, 3041, 2964, 2911, 2841, 1692, 1641, 1602, 1554, 1460, 1372, 1171, 1055, 823, 745, 694. ^1H NMR ($CDCl_3$): δ/ppm = 7.850 (s, 1H), 7.424 (d, *J* = 8.01 Hz, 2H), 7.338 (d, *J* = 8.01 Hz, 2H), 5.744 (s, 1H), 4.202 (s, 1H), 3.966 (d, *J* = 12.00 Hz, 1H), 3.843 (d, *J* = 11.50 Hz, 2H), 3.541 (t, *J* = 5.80 Hz, 1H), 3.393 (s, 2H), 1.951 (t, *J* = 12.00 Hz, 1H), 1.855 (d, *J* = 14.50 Hz, 1H), 1.548 (s, 2H). ^{13}C NMR ($CDCl_3$): δ/ppm = 172.017, 137.604, 134.285, 128.357, 127.801, 99.597, 64.420, 62.383, 46.942, 44.860, 35.537. ESI-MS (*m*/*e*) 285 $[M+H]^+$. $[\alpha]_D^{20}$ 36.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.60; H, 6.14; N, 9.61.

4.9.2. (*2R*,*5S*)-2-(4′-Chlorophenyl)-5-glycylamino-1,3-dioxaheptanes (10′c). Yield: 75%, colorless solids, mp 107–109°C. IR(KBr): υ/cm^{-1} = 3340, 3042, 2965, 2913, 2843, 1690, 1643, 1605, 1552, 1461, 1373, 1172, 1053, 825, 742, 691. ^1H NMR ($CDCl_3$): δ/ppm = 7.791 (d, *J* = 6.00, 1H), 7.450 (d, *J* = 8.50 Hz, 2H), 7.347 (d, *J* = 8.00 Hz, 2H), 5.720 (s, 1H), 4.299 (m, *J* = 2.90 Hz, 1H), 3.932 (m, *J* = 6.70 Hz, 2H), 3.718 (m, *J* = 4.70 Hz, 2H), 3.350 (d, *J* = 2.50 Hz, 2H), 2.026 (m, *J* = 4.60 Hz, 1H), 1.820 (q, *J* = 4.70 Hz, 1 H), 1.482 (s, 2H). ^{13}C NMR ($CDCl_3$): δ/ppm = 171.956, 137.726, 134.163, 128.304, 127.686, 100.054, 68.204, 60.445, 47.232, 44.692, 35.209. ESI-MS (*m*/*e*) 285 $[M+H]^+$. $[\alpha]_D^{20}$ −38.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.63; H, 6.12; N, 9.60.

4.9.3. (*2S*,*5S*)-2-(4′-Nitrophenyl)-5-glycylamino-1,3-dioxaheptanes (10d). Yield: 68%, light yellow solids, mp 135–138 °C. IR(KBr): υ/cm^{-1} = 3343, 3045, 2972, 2915, 2853, 1690, 1645, 1603, 1563, 1524, 1460, 1370, 1354, 1173, 1054, 825, 744, 691. ^1H NMR ($CDCl_3$): δ/ppm = 8.227 (d, *J* = 9.00 Hz, 2H), 7.882 (d, *J* = 7.50 Hz, 1H), 7.681 (d, *J* = 8.50 Hz, 2H), 5.819 (s, 1H), 4.202 (q, *J* = 4.00 Hz, 1H), 3.991 (m, *J* = 4.00 Hz, 2H), 3.875 (m, *J* = 5.10 Hz, 1H), 3.610 (m, *J* = 2.60 Hz, 1H), 3.403 (s, 2H), 1.976 (m, *J* = 4.70 Hz, 1H), 1.883 (m, *J* = 2.40 Hz, 1H), 1.557 (s, 2H). ^{13}C NMR ($CDCl_3$): δ/ppm = 172.063, 147.979, 145.927, 127.480, 123.406, 99.124, 64.924, 62.589, 46.904, 44.821, 35.438. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ 35.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.65; H, 5.94; N, 14.00.

4.9.4. (*2R*,*5S*)-2-(4′-Nitrophenyl)-5-glycylamino-1,3-dioxaheptanes (10′d). Yield: 79%, light yellow oil. IR(KBr): υ/cm^{-1} = 3332, 3034, 2961, 2913, 2845, 1690, 1641, 1602, 1526, 1455, 1372, 1352, 1164, 1045, 824, 743, 695. ^1H NMR ($CDCl_3$): δ/ppm = 8.234 (d, *J* = 9.00 Hz, 2H), 7.805 (d, *J* = 6.54 Hz, 1H), 7.700 (d, *J* = 9.00 Hz, 2H), 5.796 (s, 1H), 4.307 (m, *J* = 2.20 Hz, 1H), 3.994 (m, *J* = 4.70 Hz, 1H), 3.924 (m, *J* = 2.40 Hz, 1H), 3.785 (m, *J* = 4.40 Hz, 2H), 3.354 (d, *J* = 3.50 Hz, 2H), 2.054 (m, *J* = 4.40 Hz, 1H), 1.848 (m, *J* = 2.60 Hz, 1H), 1.552 (s, 2H). ^{13}C NMR ($CDCl_3$): δ/ppm = 172.017, 147.979, 146.064, 127.427, 123.437, 99.650, 68.562, 60.972, 47.240, 44.699, 35.217. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ −39.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 53.11; H, 5.68; N, 14.46.

4.9.5. (*2S*,*5S*)-2-(3′-Nitrophenyl)-5-glycylamino-1,3-dioxaheptanes (10e). Yield: 79%, light yellow oil. IR(KBr): υ/cm^{-1} = 3324, 3043, 2960, 2921, 2852, 1693, 1640, 1616, 1554, 1523, 1460, 1366, 1355, 1162, 1054, 862, 770, 745, 693. ^1H NMR ($CDCl_3$): δ/ppm = 8.364 (s, 1H), 8.192 (d, *J* = 7.50 Hz, 1H), 7.927 (d, *J* = 8.50 Hz, 1H), 7.829 (t, *J* = 7.50 Hz, 1H), 7.550 (d, *J* = 8.30 Hz, 1H), 5.819 (s, 1H), 4.203 (q, *J* = 3.80 Hz, 1H), 3.997 (m, *J* = 3.90 Hz, 1H), 3.897 (t, *J* = 10.30 Hz, 1H), 3.839 (d, *J* = 3.50 Hz, 1H), 3.619 (t, *J* = 3.50 Hz, 1H), 3.450 (s, 2H), 2.140 (s, 2H), 1.977 (m, *J* = 5.00 Hz, 1H), 1.888 (d, *J* = 14.50 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ/ppm = 172.025, 148.261, 141.326, 132.561, 129.242, 123.399, 121.713, 98.933, 64.771, 62.620, 46.912, 44.814, 35.430. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ 20.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.67; H, 5.91; N, 14.01.

4.9.6. (*2R*,*5S*)-2-(3′-Nitrophenyl)-5-glycylamino-1,3-dioxaheptanes (10′e). Yield: 85%, light yellow oil. IR(KBr): υ/cm^{-1} = 3322, 3031, 2966, 2914, 2842, 1690, 1643, 1604, 1556, 1520, 1456, 1374, 1355, 1163, 1052, 864, 770, 735, 696. ^1H NMR ($CDCl_3$): δ/ppm = 8.409 (s, 1H), 8.190 (d, *J* = 7.42 Hz, 1H), 7.905 (d, *J* = 8.50 Hz, 1H), 7.824 (d, *J* = 7.50 Hz, 1H), 7.556 (t, *J* = 8.00 Hz, 1H), 5.879 (s, 1H), 4.301 (d, *J* = 3.50 Hz, 1H), 3.952 (m, *J* = 5.90 Hz, 2H), 3.759 (m, *J* = 4.10 Hz, 2H), 3.408 (d, *J* = 4.00 Hz, 2H), 2.354 (s, 2H), 2.042 (m, *J* = 4.50 Hz, 1H), 1.850 (t, *J* = 6.80 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ/ppm = 171.529, 148.238, 141.388, 132.675, 129.281, 123.406, 121.560, 99.436, 68.379, 60.918, 47.408, 44.371, 35.079. ESI-MS (*m*/*e*) 296 $[M+H]^+$. $[\alpha]_D^{20}$ −24.0 (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.64; H, 5.93; N, 14.48.

4.10. In vivo anti-inflammatory assay

4.10.1. Animals. Male Kunming mice (about 25 g) were inbred and grown in the animal room at the College of Pharmacy, Peking University. The animal room was maintained at 23 ± 2 °C with a 12 h light/dark cycle. Food and tap water were supplied ad libitum. The ethical guidelines described in the NIH Guide for Care and Use of Laboratory Animals were followed throughout the experiments.

4.10.2. Xylene-induced ear edema. Male Kunming mice were randomly divided into three groups of 12 mice, namely the test group, vehicle control group, and positive control group. The mice in vehicle control group were administer orally a suspension of Aspirin in CMC at a dosage of 30 mg/kg, while the mice in the test group were administer orally a suspension of **7a**–**j**, **10c**–**e** or **10′c**–**e** in CMC at a dosage of 20 mg/kg. 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, mice were sacrificed 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.

4.11. Tail bleeding time measurement

The new anti-inflammatory agents were orally administered to male mice (body weight 18–22 g). After administration at 30, 45, 60, and 90 min, a mouse was placed in a tube holder with its tail protruding, and a 2-mm cut was made on the tail. Flowing blood was gently wiped away with a tissue every 30 s until bleeding ceased and the time was recorded.

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