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Novel synthesis and anti-inflammatory activities of 2,5-disubstituted-dioxacycloalkanes

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Abstract—A novel stereospecific synthetic route to obtain a series of 2,5-disubstituted-dioxacycloalkanes is reported. Using an in vivo inhibition assay by monitoring xylene-induced ear edema in mice, the structure–activity relationship of the dioxacycloalkane compounds was studied, and compounds possessing high anti-inflammatory activity were identified.

1. Introduction

There has been a long-standing interest in identifying novel targets for the rational development of anti-inflammatory drugs. Inhibitors that target proteins involved in signaling pathways have been developed and preliminary preclinical data suggest that they exhibit anti-inflammatory activity. Recent studies implicate protein kinase C (PKC) as another new target for the treatment of inflammatory disorders.[1–9] Some PKC inhibitors such as Stausporine, GF 1092203X, and Balanol analogs were confirmed to reduce a number of inflammatory processes that resulted from PKC activation by the topical application of phorbol myristate acetate to mouse ears.[1,6,7] In addition, 1,3-dioxane derivatives have been reported to possess PKC inhibitory activity and exert anti-inflammatory, anti-cancer, and reperfusion injury protection effects through their antiproliferative and anti-inflammatory activities in human neutrophils and tumor cells.[9]

We had previously described 1,3-dioxacycle derivatives that can be prepared through the transacetalation of 1,1,3,3-tetramethoxypropane and diols.[10,11] Our preliminary observations indicate that certain 1,3-dioxacycle compounds possess anti-inflammatory activities.[12] Encouraged by these finding, a novel series of 2,5-disubstituted-1,3-dioxacycloalkanes were subsequently prepared. Their corresponding structure–activity relationships were also characterized in the hope of obtaining additional compounds possessing better anti-inflammatory activities. During the preparation of 1,3-dioxacycle derivatives, the diol transacetalation process with 1,1,3,3-tetramethoxypropane was realized to afford a complex mixture of monocyclic and bicyclic acetals.[10,11] Consequently, to avert the tedious separation process for these isomeric mixtures, new methodologies have to be developed to prepare the 2,5-disubstituted-dioxacycloalkane compounds. Herein, we report a convenient and efficient method for the preparation of 2,5-substituted-dioxacycloalkanes via transacetalation using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO)[13] as catalyst under mild reaction conditions. With this improved synthetic approach, sufficient quantities of the 2,5-substituted-dioxacycloalkane compounds were readily prepared for animal testing, which subsequently enabled a more precise elucidation of their structure–activity relationship.

2. Results and discussion

Our previous results have demonstrated that it is possible to obtain 2,5-disubstituted-dioxacycloalkanes with

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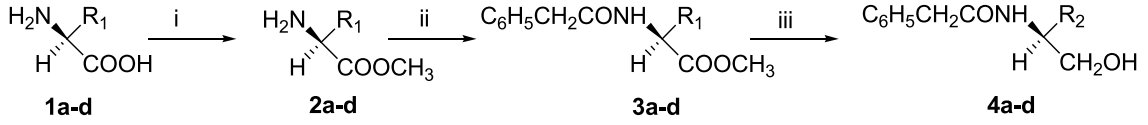
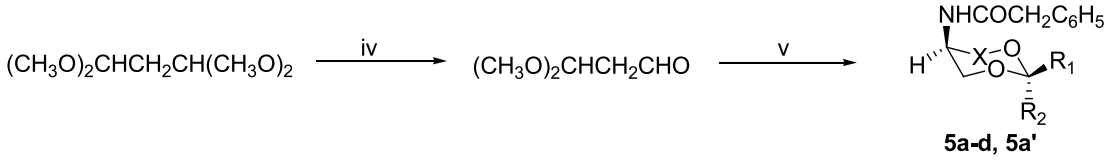
stereoselectivity through thermodynamic or kinetic control of the transacetalation.[10,11] Additionally, the stereochemistry of the ring formed in the transacetalation is also dependent on the structure of the amino-diol compounds.[10] Herein, we report an improved synthetic methodology toward the 2,5-disubstituted-dioxacycloalkanes. The amino-diols **4a**–**d**, which are key intermediates for the synthesis of 2,5-disubstituted-dioxacycloalkanes, were prepared according to previously reported methods.[10] Treatment of **4a**–**d** with 3,3-dimethoxypropanal using TABCO as catalyst provided the corresponding cyclic acetals **5a**–**d** in good to excellent yields. Compounds **5a**–**d** were then subjected to partial hydrolysis to afford cyclic aldehydes **6a**–**d** in quantitative yields. Further acetalizations were carried out with cyclic aldehydes as starting materials to provide stereospecific 2,5-disubstituted-dioxacycloalkanes **7a**–**d** (synthetic routes shown in Schemes 1–3). Upon comparing the anti-inflammatory effect of 2-(2,2-dimethoxyethyl)-5-benzoylamino-1,3-dioxane and 2-(2,2-dimethoxyethyl)-5-phenylacetamino-1,3-dioxane, it was observed that the latter exhibited better anti-inflammatory activity.[12] Therefore, the benzoylamide functionality was subsequently replaced with a phenylacetamide functionality. Using a previously described synthetic method,[10] the transacetalation of phenylacetaminodiols and equal amount of the 1,1,3,3-tetramethoxypropane gave a complex mixture of products comprised of both *cis*- and *trans*-2,5-disubstituted-1,3-dioxamonocycloalkane, and both *cis*- and *trans*-2,5-disubstituted-1,3-dioxabiscycloalkane. To enable stereospecific products, different reaction conditions and catalysts were investigated. It was observed that targeted stereospecific products could exclusively be achieved by using TABCO or trifluoroacetic acid (TFA) as catalyst under carefully chosen thermodynamic or kinetic control conditions. For example, the transacetalation of **4a**–**d** and 3,3-dimethoxypropanal at 50 °C using TABCO as catalyst exclusively gave the corresponding **5a**–**d**.

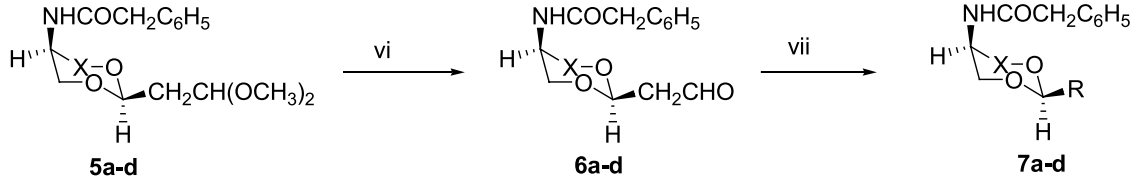
To ensure correct structural assignment to compounds **5a**–**d** and **7a**–**d**, nuclear Overhauser effect (NOE) difference experiments were performed. For each of these compounds analyzed, **5a**,**c**,**d** and **7a**,**b**, positive NOE effect were observed between the NH at the 5-position and the CH_2 at the 2-position, indicating that substitutions at both the 2- and 5-positions of these compounds are in a *syn*-arrangement. Similarly, a positive NOE effect was observed between the CH_3 at the 4-position and the CH_2 at the 2-position of compound **5b**, indicating that 2-dimethoxyethyl, 4-methyl and 5-phenylacetamino of **5b** are also in a *syn*-arrangement. For compound **7c**, two positive NOE signals were observed between the CH_3 at the 4-position and the CH_2 at the 2-position, and the NH at the 5-position, implying that the respective substitutions at 2-, 4- and 5-positions of **7c** on its



Scheme 1. Synthetic route to compounds **4a**–**d**. Reagents and conditions: (i) $SOCl_2$/MeOH, 0 °C to rt; (ii) phenylacetyl chloride, pH 8–9, rt; (iii) $NaBH_4$/THF, rt. In **1a**: L-Ser, $R_1 = CH_2OH$; **1b**: L-Thr, $R_1 = CH(CH_3)OH$; **1c**: L-Asp, $R_1 = CH_2COOH$; **1d**: L-Glu, $R_1 = CH_2CH_2COOH$. In **2a** and **3a**: $R_1 = CH_2OH$; **2b** and **3b**: $R_1 = CH(CH_3)OH$; **2c** and **3c**: $R_1 = CH_2COOCH_3$; **2d** and **3d**: $R_1 = CH_2CH_2COOCH_3$. In **4a**: $R_2 = CH_2OH$; **4b**: $R_2 = CH(CH_3)OH$; **4c**: $R_2 = CH_2CH_2OH$; **4d**: $R_2 = CH_2CH_2CH_2OH$.



Scheme 2. Synthetic route to compounds **5a**–**d** and **5a′**. Reagents and conditions: (iv): 6% orthophosphoric acid, rt; (v) For **5a**–**d**: TABCO (cat), diol **4a**–**d**, and $(EtO)_3CH$, 50 °C; for **5a′**: diol **4a**, TFA/$CHCl_3$, 15 °C, 4 h. In **5a**: $X = CH_2$, $R_1 = CH_2CH(OCH_3)_2$, $R_2 = H$; **5a′**: $X = CH_2$, $R_1 = H$, $R_2 = CH_2CH(OCH_3)_2$; **5b**: $X = (S)\text{-}CHCH_3$, $R_1 = CH_2CH(OCH_3)_2$, $R_2 = H$; **5c**: $X = CH_2CH_2$, $R_1 = CH_2CH(OCH_3)_2$, $R_2 = H$; **5d**: $X = CH_2CH_2CH_2$, $R_1 = CH_2CH(OCH_3)_2$, $R_2 = H$.



Scheme 3. Synthetic route to compounds **7a**–**d**. Reagents and conditions: (vi) oxalic acid, silica gel, $CHCl_3$, rt; (vii) TFA/$CHCl_3$, 50 °C. In **5a** and **6a**: $X = CH_2$; **5b** and **6b**: $X = (S)\text{-}CHCH_3$; **5c** and **6c**: $X = CH_2CH_2$; **5d** and **6d**: $X = CH_2CH_2CH_2$. In **7a**: $X = CH_2$, $R = CH_2CH(OCH_3)OC_2H_5$; **7b**: $X = CH_2$, R = 1,3-dioxapentan-2-yl-methylene; **7c**: X = (S)-$CHCH_3$, R = (2*S*,4*S*,5*S*)-4-methyl-5-phenylacetamino-1,3-dioxan-2-yl-methylene; **7d**: $X = CH_2CH_2$, R = (2*S*,5*S*)-5-phenylacetamino-1,3-dioxacyclooctan-2-yl-methylene.

two rings are in a *syn*-arrangement. On the basis of NOE experiment, **7d** was assigned as the *syn*-arrangement for the respective substitutions of 2-, 4- and 5-position on its hexacyclic ring and the *syn*-arrangement was also observed for both substitutions of 2- and 5-position on its heptacyclic ring. On the other hand, it was observed that **4a** was converted to **5a′** upon treatment with equal amount of 3,3-dimethoxypropanal using TFA as catalyst at 15 °C for 4 h. Under similar conditions, the acetalization of both **6b** and **4b** afforded **7c′** as the sole product. The NOE difference experiment showed that substitutions of 2- and 5-positions of **5a′** and **7c′** are in an *anti*-arrangement, because no NOE was observed between the NH at the 5-position and the CH_2 at the 2-position.

To further confirm the stereochemical assignment of these compounds, configuration conversion experiment was carried out. When concentrated hydrochloric acid was employed as catalyst at 50 °C for 12 h, both **5a′** and **7c′** were converted to **5a** and **7c**, respectively. With these configuration conversions, **5a′** and **7c′** were confirmed to be kinetically controlled products, whereas **5a** and **7c** were thermodynamically stable products. This is an interesting example which shows the possibility for isomer conversion from the thermodynamically less stable compounds to the more stable ones. These results enable us to tune and acquire the desired stereospecificity by changing the experimental conditions, for example, reaction time, temperature, and catalyst.

All the 2,5-disubstituted-dioxacycloalkanes synthesized were evaluated for their anti-inflammatory activity by using a xylene-induced ear edema model assay.[14] Briefly, the in vivo assay involves the test compounds being administrated orally in 0.5% carboxymethyl cellulose (CMC) suspension. Each compound was initially tested at a concentration of 20 mg/kg. It was observed that seven of the tested compounds showed significant inhibition against xylene-induced inflammation in mice as compared with the control (Table 1), indicating that these compounds possess potent anti-inflammatory activity. It was especially noted that the most potent compound, **5a**, exhibited an even higher anti-inflammatory activity than the standard reference drug Aspirin. Subsequently, compounds with significant activity (namely **5a**, **5b**, **7a**, **7b**) were administrated in a series of lower concentration doses to enable a detailed pharmacological activity profile (Table 2).

Structure–activity relationship studies were also performed on a series of phenylacetaminodiols compounds to assess whether the presence of 1,3-dioxacycle rings is required for anti-inflammatory activity. Observations that both diol and 3,3-dimethoxypropanal were ineffective as anti-inflammatory compounds suggested that the rigid 1,3-dioxacycle ring should be retained. To examine the importance of the spatial disposition, two pairs of cyclic acetals with different stereochemistries were evaluated. Comparing compound **5a** with **5a′** and **7c** with **7c′**, their comparable anti-inflammatory activities indicated that stereochemical constraints of these 2,5-disubstituted-dioxacycloalkanes exhibited little or no effect toward their anti-inflammatory activities.

To investigate the effect of heterocyclic ring sizes, the anti-inflammatory activities of compounds **5a**–**d** and **7a**,**b** were compared. It was observed that the potencies of **5a**,**b** and **7a**,**b** are significantly higher than those of **5c**,**d** and **7c**. These observations indicate that the anti-inflammatory activity of 1,3-dioxane is more potent than either 1,3-dioxacycloheptane or 1,3-dioxacyclooctane,

Table 1. Anti-inflammatory activity of 1,3-dioxane derivatives against xylene-induced ear edema in mice

Agents	Anti-inflammatory activity	
	Edema weight (X ± SD mg)	Inhibition (%)
CMC	7.76 ± 1.55	N
Aspirin	4.17 ± 1.80[a]	46.3
DMPA	8.30 ± 1.87	N
4a	7.99 ± 2.09	N
4b	8.02 ± 2.04	N
4c	6.97 ± 1.99	10.2
4d	7.03 ± 1.78	9.4
5a	1.32 ± 1.13[a,d,e]	83.0
5a′	2.12 ± 1.34[a,d,e]	72.7
5b	2.76 ± 1.21[a,d,e]	64.4
5c	4.31 ± 1.46[a]	44.5
5d	4.10 ± 1.49[a]	47.2
6a	5.80 ± 1.56[b]	25.3
6b	5.86 ± 1.65[b]	24.5
6c	5.55 ± 1.98	28.5
6d	5.90 ± 1.75[c]	24.0
7a	3.41 ± 1.86[a,f]	56.0
7b	3.73 ± 1.33[a,f]	51.9
7c	5.23 ± 1.69[b]	32.6
7c′	5.11 ± 1.23[b]	34.1
7d	5.95 ± 1.95[c]	23.3

Dose = 20 mg/kg. DMPA = 3,3-dimethoxypropanal.
[a] Compared to CMC, DMPA, and **4a**–**d**, $p < 0.001$.
[b] Compared to CMC, $p < 0.01$.
[c] Compared to CMC, $p < 0.05$.
[d] Compared to Aspirin, $p < 0.05$.
[e] Compared to **5c**,**d** and **6a**–**d** and **7c**,**d**, $p < 0.05$.
[f] Compared to **7c**,**c′**,**d**, $p < 0.01$.

Table 2. Anti-inflammatory activity of **5a**,**b** and **7a**,**b** at different doses against xylene-induced ear edema in mice

Agents	Dose (mg/kg)	Edema weight (X ± SD mg)
5a	20	2.32 ± 1.13[a]
5b	20	2.76 ± 1.21[a]
7a	20	3.41 ± 1.86[a]
7b	20	3.73 ± 1.33[b]
5a	4	4.62 ± 1.09[c]
5b	4	4.95 ± 1.17[d]
7a	4	5.69 ± 1.21[d]
7b	4	5.44 ± 1.14[d]
5a	0.8	6.62 ± 1.21
5b	0.8	6.77 ± 1.19
7a	0.8	7.03 ± 1.26
7b	0.8	7.15 ± 1.33

[a] Compared to 4.0 mg/kg group, $p < 0.001$.
[b] Compared to 4.0 mg/kg group, $p < 0.01$.
[c] Compared to 0.8 mg/kg group, $p < 0.001$.
[d] Compared to 0.8 mg/kg group, $p < 0.01$.

suggesting that 2,5-disubstituted-1,3-dioxacycloalkane cannot be further maximized. In addition, based on the observations that **6a–d** exhibited a loss in their in vivo anti-inflammatory activity, we hypothesized the cyclic acetals **5a–d** do not exert their in vivo anti-inflammatory activities through hydrolytic conversion from **5a–d** to **6a–d**.

Compound **5a** also showed anti-inflammatory activity in the PMA (phorbol–myristate–acetate) induced mouse ear edema model,[12,15] which is a model of PKC-mediated acute inflammation. The in vivo anti-inflammatory effect of 2,5-disubstituted-dioxacycloalkanes most likely occurs via the inhibition of certain key enzymes involved in inflammation and/or cell signaling pathways, in which PKC is most likely the target protein. Experiments are currently underway to ascertain the protein target(s) of the dioxacycloalkane compounds, in which other possible protein targets may also include cyclooxygenase and lipoxygenase, and phosphoinositide 3-kinase. Identification and understanding the mechanism underlying the enzyme inhibition processes should prove beneficial for future treatment of inflammatory conditions.

In summary, a precise and efficient stereochemically controlled synthetic route to enable a series of 2,5-disubstituted-dioxacycloalkane compounds is presented. The dioxacycloalkane compounds possess dose-dependent in vivo anti-inflammatory properties, and it was found that both their ring sizes and substitutions at the 2-position have significant effects on their inhibitory properties.

3. Materials and methods

3.1. Experimental section

All reactions were carried out under nitrogen (1 bar). ^{1}H NMR spectra were recorded at 300 MHz on a VXR-300 instrument or at 500 MHz on an ARX-500 instrument in $CDCl_3$ with tetramethylsilane as the internal standard. IR spectra were recorded with a Perkin-Elmer 983 instrument and mass spectra with a ZAB-MS (70 eV) spectrometer. Chromatography was performed with Qingdao silica gel H. Optical rotations were determined on a Schmidt and Haensch Polartronic D instrument at 20 °C.

3.1.1. General procedure for phenylacetaminodiols 4a–d. L–Ser, L-Thr, L-Asp, or L-Glu were esterified to **2a–d** by methanol in 96–98 % yield and treated with phenylacetyl chloride to give **3a–d** in 75–81% yield.[10,11]

A solution of **3a–d** (4.5 mmol) in tetrahydrofuran (THF) (10 mL) was slowly added to a suspension of sodium borohydride (5.6 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 24 h until thin-layer of chromatography (TLC) ($CHCl_3$/CH_3OH, 30:1) indicated complete disappearance of **3a–d**. The reaction mixture was adjusted to pH 7 with hydrochloric acid (3%). After evaporation, the residue was dissolved in 50 mL of chloroform and washed with water (3×30 mL). The chloroform phase was dried with Na_2SO_4. After filtration and evaporation, **4a–d** were obtained as colorless crystals in 91–98% yields.

3.1.2. *N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]phenylacetamide (4a). Mp 135–136 °C. IR (KBr, cm^{-1}) *v*: 3452, 3343, 3028, 3004, 2962, 2834, 1638, 1604, 1573, 1505, 1452, 721, 662. ^{1}H NMR (DMSO-d_6 δ): 3.53 (d, J = 5.7 Hz, 4H), 3.62 (s, 2H), 3.95 (m, J = 6.0 Hz, 1H), 4.64 (br, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.64 (d, J = 7.5 Hz, 2H), 8.11 (d, J = 7.6 Hz, 1H). FAB-MS *m*/*z* (%): 210 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.12, H, 7.23, N, 6.70. Found: C, 63.35; H, 7.06; N, 6.59.

3.1.3. (1*S*,2*R*)-*N*-[2-Hydroxy-1-(hydroxymethyl)propyl]-phenylacetamide (4b). Mp 125–127 °C. IR (KBr, cm^{-1}) *v*: 3451, 3362, 3033, 3005, 2965, 2862, 1643, 1608, 1592, 1505, 1482, 712, 651. ^{1}H NMR (DMSO-d_6, δ): 1.22 (d, J = 6.9 Hz, 3H), 3.53 (s, 2H), 3.64 (s, 2H), 3.85 (d, J = 6.6 Hz, 2H), 3.96 (m, J = 6.4 Hz, 1H), 4.24 (q, J = 6.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 8.04 (d, J = 7.5 Hz, 1H). FAB-MS *m*/*z* (%): 224 $[M+H]^+$. $[\alpha]_D^{20}$ −32.5° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.50; H, 7.67; N, 6.27. Found: C, 64.62; H 7.56; N, 6.39.

3.1.4. (1*S*)-*N*-[3-Hydroxy-1-(hydroxymethyl)propyl]-phenylacetamide (4c). Mp 132–134 °C. IR (KBr, cm^{-1}) *v*: 3415, 3344, 3023, 3006, 2964, 2833, 1632, 1602, 1585, 1506, 1463, 715, 651. ^{1}H NMR (DMSO-d_6, δ): 1.63 (dt, J = 5.6 Hz, J = 3.3 Hz, 1H), 1.76 (dt, J = 4.7 Hz, J = 2.7 Hz, 1H), 3.40 (t, J = 3.9 Hz, 1H), 3.43 (t, J = 3.9 Hz, 1H), 3.49 (s, 2H), 3.66 (s, 2H), 4.06 (dq, J = 3.7 Hz, J = 2.5 Hz, 1H), 4.44 (t, J = 3.9 Hz, 1H), 4.75 (t, J = 3.9 Hz, 1H), 7.16 (t, J = 4.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 2H), 8.03 (d, J = 5.5 Hz, 1H). FAB-MS *m*/*z* (%): 224 $[M+H]^+$. $[\alpha]_D^{20}$ −28.4° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 64.50; H, 7.67; N, 6.27. Found: C, 64.32; H, 7.52; N, 6.43.

3.1.5. (1*S*)-*N*-[4-Hydroxy-1-(hydroxymethyl)butyl]phenylacetamide (4d). Mp 102–104 °C. IR (KBr, cm^{-1}) *v*: 3425, 3345, 3033, 3004, 2952, 2841, 1636, 1604, 1587, 1505, 1442, 723 662. ^{1}H NMR (DMSO-d_6, δ): 1.45 (q, J = 3.6 Hz, 2H), 1.49 (m, J = 4.5 Hz, 1H), 1.68 (m, J = 4.8 Hz, 1H), 3.35 (t, J = 6.6 Hz, 1H), 3.38 (s, 2H), 3.43 (t, J = 6.6 Hz, 1H), 3.66 (s, 2H), 3.96 (dq, J = 3.9 Hz, J = 2.4 Hz, 1H), 4.41 (t, J = 3.8 Hz, 1H), 4.67 (t, J = 3.9 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 8.06 (d, J = 4.9 Hz, 1H). FAB-MS *m*/*z* (%): 238 $[M+H]^+$. $[\alpha]_D^{20}$ −23.3° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.92; H, 8.26; N, 6.11.

3.1.6. 3,3-Dimethoxypropanal. Aqueous orthophosphoric acid (1 mL, 6%) was added to 1,1,3,3-tetramethoxypropane (2.0 g, 12.2 mmol), and the mixture was stirred at rt for 40 h until TLC (petroleum ether/ether, 2:1) indicated the complete consumption of 1,1,3,

3-tetramethoxypropane. Ether (30 ml) was added to the above mixture, and the solution neutralized with sodium carbonate and filtered. The filtrate was subsequently concentrated and the residue was purified with flash chromatography (petroleum ether/ether, 2:1) to give 850 mg (60%) of the title compound as a colorless syrup. IR (KBr, cm^{-1}) *v*: 3000, 2944, 2839, 1735, 1622, 1453, 1391, 1144, 935. ^1H NMR (DMSO-d_6, δ): 2.76 (dd, $J = 7.6$ and 7.3 Hz, 2H), 3.42 (s, 6H), 4.69 (t, $J = 7.3$ Hz, 1H), 9.75 (t, $J = 7.6$ Hz, 1H).

3.1.7. (*cis*)-*N*-[2-(2,2-Dimethoxyethyl)-1,3-dioxan-5-yl]phenylacetamide (5a). To a solution of 3,3-dimethoxypropanal (94 mg, 0.5 mmol), triethyl orthoformate (0.5 mmol) and **4a** (105 mg, 0.5 mmol) in acetonitrile (10 mL), 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) (0.005 mmol) was added. The reaction mixture was stirred at 50 °C until TLC indicated the completion of the reaction, and then neutralized with sodium carbonate. The product was extracted with ethyl acetate (3×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated, purified with flash chromatography ($CHCl_3/CH_3OH$, 30:1) to give 135 mg (yield 86%) of the title compound as a colorless powder. Mp 139–141 °C. IR (KBr, cm^{-1}) *v*: 3264, 3060, 2920, 2852, 1620, 1601, 1569, 1540, 1446, 1380, 1360, 1189, 1074, 721, 696. ^1H NMR (DMSO-d_6, δ): 1.96 (t, $J = 7.9$ Hz, 2H), 3.36 (s, 6H), 3.64 (s, 2H), 4.06 (d, $J = 12.4$ Hz, 4H), 4.12 (m, $J = 9.5$ Hz, 1H), 4.55 (t, $J = 6.3$ Hz, 1H), 4.77 (d, $J = 6.3$ Hz, 1H), 7.08 (d, $J = 9.4$ Hz, 1H), 7.23 (t, $J = 9.1$ Hz, 2H), 7.51 (d, $J = 9.1$ Hz, 1H), 7.70 (d, $J = 9.1$ Hz, 2H). FAB-MS *m*/*z* (%) 310 $[M+H]^+$. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.30; H, 7.30; N, 4.62.

3.1.8. [(2*S*,4*R*,5*R*)-*N*-2-(2,2-Dimethoxyethyl)-4-methyl-1,3-dioxan-5-yl]phenylacetamide (5b). A similar procedure was used as that for the preparation of **5a**, starting from **4b** (112 mg, 0.5 mmol), the title compound (130 mg, yield 80%) was obtained as colorless syrup. IR (KBr, cm^{-1}) *v*: 3432, 3051, 2970, 2930, 2865, 1660, 1593, 1570, 1475, 1406, 1375, 1355 1178, 1065, 710, 690. ^1H NMR (DMSO-d_6, δ): 1.21 (d, $J = 8.1$ Hz, 3H), 1.98 (t, $J = 5.1$ Hz, 2H), 3.35 (s, 6 H), 3.66 (s, 2H), 3.96 (d, $J = 9.7$ Hz, 1H), 3.99 (q, $J = 5.4$ Hz, 1H), 4.04 (d, $J = 14.1$ Hz, 1H), 4.14 (dt, $J = 5.5$ Hz, $J = 1.5$ Hz, 1H), 4.62 (t, $J = 5.3$ Hz, 1H), 4.75 (d, $J = 5.3$ Hz, 1H), 6.82 (d, $J = 10.1$ Hz, 1H), 7.15 (t, $J = 7.4$ Hz, 2H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 2H). FAB-MS *m*/*z* (%): 324 $[M+H]^+$. $[\alpha]_D^{20}$ −23.0° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.32; H, 7.96; N, 4.13.

3.1.9. [(2*R*,5*S*)-*N*-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]phenylacetamide (5c). A similar procedure was used as that for the preparation of **5a**, starting from **4c** (112 mg, 0.5 mmol), the title compound (138 mg, yield 85%) was obtained as a colorless powder. Mp 117–119 °C. IR (KBr, cm^{-1}) *v*: 3308, 3052, 2970, 2929, 2858, 1642, 1602, 1565, 1451, 1380, 1189, 1084, 722, 692. ^1H NMR (DMSO-d_6, δ): 1.90 (q, $J = 5.2$ Hz, 2H), 1.94 (t, $J = 5.3$ Hz, 2H), 3.37 (s, 6H), 3.63 (dd, $J = 6.75.0$ Hz, 2H), 3.66 (s, 2H), 3.94 (d, $J = 7.2$ Hz, 1H), 4.08 (d, $J = 7.2$ Hz, 1 H), 4.32 (dt, $J = 5.8$ 2.7 Hz, 1H), 4.55 (t, $J = 5.6$ Hz, 1H), 4.85 (t, $J = 4.3$ Hz, 1 H), 6.91 (d, $J = 5.5$ Hz, 1H), 7.17 (t, $J = 7.4$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.50 (d, $J = 7.4$ Hz, 2H). FAB-MS *m*/*z* (%): 324 $[M+H]^+$. $[\alpha]_D^{20}$ −11.0° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.01; H, 7.66; N, 4.49.

3.1.10. [(2*R*,5*S*)-*N*-2-(2,2-Dimethoxyethyl)-1,3-dioxacyclooctan-5-yl]phenylacetamide (5d). A similar procedure was used as that for the preparation of **5a**, starting from **4d** (119 mg, 0.5 mmol), the title compound (123 mg, yield 76%) was obtained as a colorless powder. Mp 125–127 °C. IR (KBr, cm^{-1}) *v*: 3460, 3051, 2952, 2891, 2822, 1651, 1602, 1593, 1508, 1455, 1372, 1192, 1085, 762, 688. ^1H NMR (DMSO-d_6, δ): 1.78 (m, $J = 5.2$ Hz, 4H), 1.93 (dd, $J = 6.2$ Hz, $J = 4.9$ Hz, 2H), 3.30 (s, 3H), 3.32 (s, 3H), 3.52 (d, $J = 7.2$ Hz, 1H), 3.65 (s, 2H), 3.88 (d, $J = 7.2$ Hz, 1H), 4.31 (dt, $J = 5.6$ Hz, $J = 2.4$ Hz, 1H), 4.48 (t, $J = 6.1$ Hz, 1H), 4.55 (m, $J = 4.8$ Hz, 2H), 6.64 (t, $J = 9.3$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 2H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 7.2$ Hz, 2 H). FAB-MS *m*/*z* (%): 338 $[M+H]^+$. $[\alpha]_D^{20}$ −14.5° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07 N, 4.15. Found: C, 63.98; H, 7.99; N, 4.26.

3.1.11. (*trans*)-*N*-[2-(2,2-Dimethoxyethyl)-1,3-dioxan-5-yl]phenylamide (5a′). To a solution of **4a** (105 mg, 0.5 mmol) and 3,3-dimethoxypropanal (94 mg, 0.5 mmol) in 10 mL of chloroform, 20 mg of trifluoroacetic acid was added. The reaction mixture was stirred at 15 °C for 4 h, and then neutralized with sodium carbonate. The residue was purified by flash chromatography (CH_3Cl/CH_3OH, 30:1) to give 143 mg (yield 92%) of the title compound as colorless powder. Mp. 122–124 °C. IR (KBr, cm^{-1}) *v*: 3287, 3055, 2962, 2931, 2852, 1638, 1604, 1549, 1456, 1405, 1382, 1191, 1086, 707, 682. ^1H NMR (DMSO-d_6, δ): 1.96 (t, $J = 5.3$ Hz, 2H), 3.37 (s, 6H), 3.45 (d, $J = 11.2$ Hz, 4H), 3.65 (s, 2H), 4.45 (m, $J = 3.9$ Hz, 1H), 4.53 (t, $J = 7.8$ Hz, 1H), 4.56 (t, $J = 7.8$ Hz, 1H), 5.64 (d, $J = 7.8$ Hz, 1H), 5.72 (d, $J = 7.8$ Hz, 1H), 7.19 (t, $J = 9.1$ Hz, 2H), 7.43 (d, $J = 9.1$ Hz, 1H), 7.71 (d, $J = 9.1$ Hz, 2H). FAB-MS *m*/*z* (%): 310 $[M+H]^+$. $[\alpha]_D^{20}$ −16.4° (*c* 0.02, CH_3OH). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.01; H, 7.55; N, 4.40.

3.1.12. [(*cis*)-*N*-(2-Carbonylmethyl-1,3-dioxan-5-yl)]-phenylamide (6a). To a mixture of **5a** (309 mg, 1.0 mmol) and 30 mg of silica gel in chloroform (20 mL), 30 mg of oxalic acid was added. The reaction mixture was stirred at 45 °C for 40 h, and then neutralized with sodium carbonate, filtered, and concentrated. The crude product was purified with flash chromatography ($CHCl_3/CH_3OH$, 50:1) to give 225 mg (yield 85%) of the title compound as colorless syrup. IR (KBr, cm^{-1}) *v*: 3304, 3021, 2961, 2922, 2855, 1762, 1631, 1604, 1570, 1543, 1448, 1200, 1067, 727, 692. ^1H NMR (DMSO-d_6, δ): 2.77 (d, $J = 3.8$ Hz, 2H), 3.64 (s, 2H), 4.28 (d, $J = 5.6$ Hz, 2H), 4.33 (d, $J = 6.5$ Hz, 2H), 4.46 (m, $J = 3.8$ Hz, 1H), 4.95 (t, $J = 4.8$ Hz, 1 H), 5.98 (d,

J = 7.5 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 7.2 Hz, 2H), 9.81 (t, J = 2.5 Hz, 1H). FAB-MS m/z (%): 264 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.99; H, 6.70; N, 5.50.

3.1.13. (2*S*,4*S*,5*R*)-[*N*-(2-Carbonylmethyl)-4-methyl-1,3-dioxan-5-yl]phenylacetamide (6b). Similar procedure was used as that for the preparation of **6a**. Starting from **5b** (323 mg, 1.0 mmol), 227 mg (yield 82%) of the title compound was obtained as colorless syrup. IR (KBr, cm^{-1}) v: 3442, 3059, 2968, 2939, 2862, 1758, 1648, 1602, 1573, 1480, 1415, 1381, 1174, 1062, 716, 694. ^1H NMR (DMSO-d_6, δ): 1.28 (d, J = 6.1 Hz, 3H), 2.82 (d, J = 3.7 Hz, 2H), 3.66 (s, 2H), 4.03 (d, J = 10.4 Hz, 1H), 4.07 (d, J = 10.4 Hz, 1H), 4.14 (m, J = 10.7 Hz, 1H), 4.15 (t, J = 8.5 Hz, 1H), 5.25 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 6.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 9.84 (t, J = 2.6 Hz, 1H). FAB-MS m/z (%): 278 $[M+H]^+$. $[\alpha]_D^{20}$ −26.2° (c 0.02, CH_3OH). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.78; H, 6.82; N 5.20.

3.1.14. (2*R*,5*S*)-[*N*-(2-Carbonylmethyl)-1,3-dioxacycloheptan-5-yl]phenylacetamide (6c). Similar procedure was used as that for the preparation of **6a**. Starting from **5c** (323 mg, 1.0 mmol), 209 mg (yield 75%) of the title compound was obtained as colorless syrup. IR (KBr, cm^{-1}) v: 3441, 3056, 2969, 2941, 2860, 1761, 1644, 1605, 1575, 1482, 1418, 1380, 1172, 1064, 717, 692 . ^1H NMR (DMSO-d_6, δ): 1.87 (q, J = 5.5 Hz, 2H), 1.94 (t, J = 5.5 Hz, 2H), 3.61 (dd, J = 6.5 5.2 Hz, 2H), 3.65 (s, 2H), 3.96 (d, J = 7.4 Hz, 1H), 4.11 (d, J = 7.5 Hz, 1H), 4.34 (dt, J = 5.9 2.5 Hz, 1 H), 4.57 (t, J = 5.8 Hz, 1H), 6.03 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 4.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 7.5 Hz, 2H), 9.81 (t, J = 2.7 Hz, 1 H). FAB-MS m/z (%): 278 $[M+H]^+$. $[\alpha]_D^{20}$ −14.5° (c 0.02, CH_3OH). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.12; H, 7.10; N, 4.98.

3.1.15. (2*R*,5*S*)-[*N*-(2-Carbonylmethyl)-1,3-dioxacyclooctan-5-yl]phenylacetamide (6d). Similar procedure was used as that for the preparation of **6a**. Starting from **5d** (337 mg, 1.0 mmol), 207 mg (yield 71%) of the title compound was obtained as a colorless syrup. IR (KBr, cm^{-1}) v: 3444, 3058, 2966, 2942, 2865, 1760, 1641, 1602, 1577, 1480, 1415, 1382, 1170, 1062, 715, 690. ^1H NMR (DMSO-d_6, δ): 1.82 (m, J = 5.4 Hz, 4H), 1.94 (dd, J = 6.4 4.5 Hz, 2H), 3.54 (d, J = 7.4 Hz, 1H), 3.64 (s, 2H), 3.92 (d, J = 7.4 Hz, 1H), 4.33 (dt, J = 5.8 2.7 Hz, 1H), 4.46 (t, J = 6.2 Hz, 1H), 4.56 (m, J = 4.9 Hz, 2H), 6.65 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 2H), 9.77 (t, J = 2.8 Hz, 1H). FAB-MS m/z (%): 292 $[M+H]^+$. $[\alpha]_D^{20}$ −17.1° (c 0.02, CH_3OH). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found C, 65.87; H, 7.40; N, 4.96.

3.1.16. (*cis*)-[*N*-2-(2-Ethoxy-2-methoxyethyl)-1,3-dioxan-5-yl]phenylacetamide (7a). To a solution of **6a** (263 mg, 1.0 mmol) in methanol (32 mg, 1.0 mmol) and ethanol (46 mg, 1.0 mmol), 20 mg of trifluoroacetic acid in 10 mL of chloroform was added. The reaction mixture was stirred at 50 °C for 8 h, and then neutralized with sodium carbonate, filtered, concentrated. The residue was purified by flash chromatography ($CHCl_3/CH_3OH$, 30:1) to give 289 mg (yield 89%) of the title compound as colorless powder. Mp 136–138 °C. IR (KBr, cm^{-1}) v: 3262, 3058, 2918, 2850, 1622, 1603, 1564, 1542, 1443, 1384, 1361, 1187, 1070, 722, 694. ^1H NMR (DMSO-d_6, δ): 1.76 (t, J = 4.9 Hz, 2 H), 1.99 (t, J = 7.8 Hz, 2H), 3.33 (q, J = 4.9 Hz, 2H), 3.36 (s, 3H), 3.66 (s, 2H), 4.03 (d, J = 12.1 Hz, 4H), 4.14 (m, J = 9.2 Hz, 1H), 4.53 (t, J = 6.5 Hz, 1H), 4.75 (d, J = 6.5 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 7.21 (t, J = 9.0 Hz, 2H), 7.49 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 2H). FAB-MS m/z (%): 324 $[M+H]^+$. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.01; H, 7.66; N, 4.51.

3.1.17. (*cis*)-[*N*-2-(1,3-Dioxolan-2-yl)methyl-1,3-dioxan-5-yl]phenylacetamide (7b). A similar procedure was used as that for the preparation of **7a**. Starting from **6b** (263 mg, 1.0 mmol) and glycol (62 mg, 1.0 mmol), 268 mg (yield 87%) of the title compound was obtained as colorless powder. Mp 127–129 °C. IR (KBr, cm^{-1}) v: 3320, 3038, 2948, 2841, 1636, 1601, 1504, 1447, 1459, 1189, 1078, 737, 699. ^1H NMR (DMSO-d_6, δ): 2.07 (t, J = 6.1 Hz, 2H), 3.66 (s, 2H), 3.86 (t, J = 5.9 Hz, 2H), 4.01 (t, J = 6.0 Hz, 2H), 4.08 (d, J = 8.1 Hz, 4H), 4.10 (m, J = 8.0 Hz, 1H), 4.83 (t, J = 6.3 Hz, 1H), 5.00 (t, J = 6.3 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.9 Hz, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 7.3 Hz, 2H). FAB-MS m/z (%): 308 $[M+H]^+$. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.70; H, 6.99; N, 4.72.

3.1.18. *N*,*N*′-Methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisphenyl-acetamide (7c). A similar procedure was used as that for the preparation of **7a**. Starting from **6b** (277 mg, 1.0 mmol) and **4b** (223 mg, 1.0 mmol), 398 mg (yield 85%) of the title compound was obtained as colorless powder. Mp 122–124 °C. IR (KBr, cm^{-1}) v: 3545, 3409, 3060, 2969, 2920, 2852, 1648, 1625, 1597, 1526, 1481, 1417, 1380, 1354, 1180, 1063, 719, 691. ^1H NMR (DMSO-d_6, δ): 1.25 (d, J = 6.7 Hz, 6H), 2.07 (t, J = 6.1 Hz, 4H), 3.65 (s, 2H), 3.94 (d, J = 7.2 Hz, 2H), 4.09 (d, J = 12.0 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.11 (dt, J = 8.8 Hz, J = 2.5 Hz, 2H), 4.84 (t, J = 6.2 Hz, 2H), 6.78 (d, J = 6.1 Hz, 2H), 7.44 (t, J = 8.9 Hz, 4H), 7.51 (t, J = 8.3 Hz, 2H), 7.81 (d, J = 8.4 Hz, 4 H). FAB-MS m/z (%): 469 $[M+H]^+$. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.67; H, 6.70; N, 5.79.

3.1.19. *N*,*N*′-Methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl]-[(2′*S*,5′*R*)-1,3-dioxacyclo-octan-2,5-diyl]bisphenyl-acetamide (7d). A similar procedure was used as that for the preparation of **7a.** Starting from **6c** (277 mg, 1.0 mmol) and **4c** (223 mg, 1.0 mmol), 393 mg (yield 84%) of the title compound was obtained as a colorless powder. Mp 132–134 °C. IR (KBr, cm^{-1}) v: 3552, 3448, 3058, 2973, 2908, 2849, 1652, 1628, 1602, 1527, 1478, 1401, 1373, 1178, 1060, 728, 685. ^1H NMR (DMSO-d_6, δ): 1.24 (d, J = 6.5 Hz, 3H), 1.98 (m, J = 5.5 Hz,

2H), 2.05 (t, $J = 7.5$ Hz, 2H), 3.65 (s, 2H), 3.95 (d, $J = 12.5$ Hz, $J = 3.2$ Hz, 2H), 3.75 (d, 1H), 3.92 (d, $J = 8.2$ Hz, 2H), 3.95 (d, $J = 12.5$ 3.2 Hz, 2H), 4.15 (d, $J = 10.5$ Hz, 2H), 4.27 (m, $J = 5.9$ Hz, 1H), 4.47 (m, $J = 5.9$ Hz, 1H), 4.84 (t, $J = 4.8$ Hz, 1H), 4.97 (t, $J = 9.2$ Hz, 1H), 6.78 (d, $J = 6.7$ Hz, 1H), 6.83 (d, $J = 6.6$ Hz, 1H), 7.44 (t, $J = 7.3$ Hz, 2H), 7.48 (t, $J = 7.3$ Hz, 2H), 7.78 (d, $J = 7.4$ Hz, 2H), 7.83 (d, $J = 7.3$ Hz, 2H). FAB-MS: m/z (%) = 469 $[M+H]^+$. $[\alpha]_D^{20}$ −17.2° (c 0.02, CH_3OH). Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.46; H, 6.99; N, 6.11.

3.1.20. *N*,*N*′-Methylenebis[(2*S*,4*R*,5*R*)/(2*S*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisphenyl-acetamide (7c′). To a solution of **6b** (277 mg, 1.0 mmol), and **4b** (223 mg, 1.0 mmol) in 10 mL of chloroform, 20 mg of trifluoroacetic acid was added. The reaction mixture was stirred at 15 °C for 4 h, and then neutralized with sodium carbonate, filtered, concentrated. The residue was subjected to flash chromatography ($CHCl_3/CH_3OH$, 30:1) to give 389 mg (yield 83%) of the title compound as colorless powder. Mp 158–160 °C. IR (KBr, cm^{-1}) v: 3551, 3406, 3052, 2974, 2907, 2862, 1652, 1632, 1601, 1533, 1484, 1402, 1371, 1366, 1185, 1058, 728, 702. ^1H NMR (DMSO-d_6, δ): 1.23 (d, $J = 6.5$ Hz, 3H), 1.28 (d, $J = 6.7$ Hz, 3H), 2.07 (t, $J = 6.1$ Hz, 2H), 3.66 (s, 2H), 3.98 (d, $J = 7.2$ Hz, 2 H), 4.06 (d, $J = 12.0$ Hz, 2H), 4.09 (dt, $J = 8.2$ 2.4 Hz, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 4.80 (t, $J = 6.0$ Hz, 2H), 4.82 (t, $J = 6.0$ Hz, 2H), 6.76 (d, $J = 6.1$ Hz, 2H), 7.45 (t, $J = 7.5$ Hz, 4H), 7.52 (t, $J = 7.6$ Hz, 2H), 7.84 (d, $J = 7.4$ Hz, 4H). FAB-MS m/z (%): 469 $[M+H]^+$. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.80; H, 6.99; N, 5.81.

3.2. In vivo anti-inflammatory assay

3.2.1. 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 was followed throughout the experiments.

3.2.2. Xylene-induced ear edema.[14] 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 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 orally administrated a suspension of 1,3-dioxacycloalkane in CMC at a dosage of 20, 4.0, and 0.8 mg/kg, and a concentration of 2.0, 0.4, and 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. Inhibition percentage was expressed as a reduction in weight with respect to the control group.

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