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Toward the development of chemoprevention agents. Part 1: Design, synthesis, and anti-inflammatory activities of a new class of 2,5-disubstituted-dioxacycloalkanes

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Abstract—A new class of 2,5-disubstituted-dioxacycloalkanes were designed and synthesized via stereoselective synthetic method as cancer chemoprevention agents. The anti-inflammatory activities of these compounds were tested using the xylene-induced mouse ear edema model. Some of these compounds exhibited comparable or better anti-inflammatory activities than that of aspirin suggesting that they can be further developed as potential anti-inflammatory drug lead compounds. In addition, treatment of these anti-inflammatory agents did not prolong tail bleeding time in mice. The structure/activity relationships were also analyzed among these compounds.

1. Introduction

Chemoprevention is a critical area of research in oncology. Chemoprevention refers to the use of non-toxic substances to delay, reverse or suppress multistage carcinogenesis.[1,2] Chemoprevention offers a unique scope to intervene in each stage of carcinogenesis by a wide variety of substances of either natural or synthetic origin. As inflammation is closely associated with tumorigenesis in many tumor types, substances with potent anti-inflammatory activities are anticipated to exert chemopreventive effects. Overwhelming evidence from non-experimental studies supports an association between long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and a substantially reduced risk for colorectal and other cancers.[3] NSAIDs could influence carcinogenesis through their cyclooxygenase inhibition, which seems to play an important role in cell transformation, tumor growth, and metastasis, but other mechanisms have been proposed.[4]

A strong interest has been focused on using NSAIDs as a chemopreventive strategy for colorectal cancer. NSAIDs possess several anti-cancer properties that confer a broad spectrum of chemo-preventive effects during different stages of colorectal tumorigenesis, inducing apoptosis, reducing angiogenesis, and inducing cell cycle arrest.[5] Traditional NSAIDs, such as aspirin, target both COX-1 and COX-2 and exhibit chemopreventive properties in epidemiological studies. However, the use of NSAIDs is often associated with side effects such as gastric bleeding. The chemoprevention agents are designed to give to huge numbers of people over long period of time, therefore, these agents must be of low toxicity, effective at low doses, and devoid of side effects.[5–8]

1,3-Dioxane derivatives have been reported recently having anti-inflammatory, anti-cancer, and reperfusion injury protection effects through their anti-proliferative and anti-inflammatory activities in human neutrophils and tumor cells.[9–12] Our laboratory has been investigating a new class of 2,5-disubstituted-1,3-dioxanes, some of which have shown to have anti-inflammatory properties greater than those of aspirin.[13–16] In contrast to classical, acidic NSAIDs, the new analogues of 1,3-dioxane are basic. To further improve the pharmacokinetic/pharmacodynamic and the therapeutic index of these 1,3-

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dioxane derivatives and, in this study, a new series of 2,5-disubstituted-dioxacycloalkanes were constructed using stereoselective synthesis. Chemoprevention trials require large numbers of subjects followed over many years and are therefore very expensive and difficult. In this study, we choose xylene-induced mouse ear edema model to evaluate the in vivo anti-inflammatory activities of these compounds. In addition, the cutaneous tail bleeding time in the rat was used for evaluation of the hemostatic effects of these newly synthetic compounds.

2. Results and discussion

2.1. Synthesis

We previously prepared 1,3-dioxacycle derivatives through the transacetalization of 1,1,3,3-tetramethoxypropane and aminodiols.[13–16] The main finding was the stereochemistry of ring formation is dependent on the structure of the aminodiol compounds. Based on this, new series of 2,5-disubstituted-dioxacycloalkanes were prepared, in this study, our strategy was to engage the pre-existing stereocenter of the chiral amino acids to direct the subsequent substituted benzaldehydes' acetalization reaction.

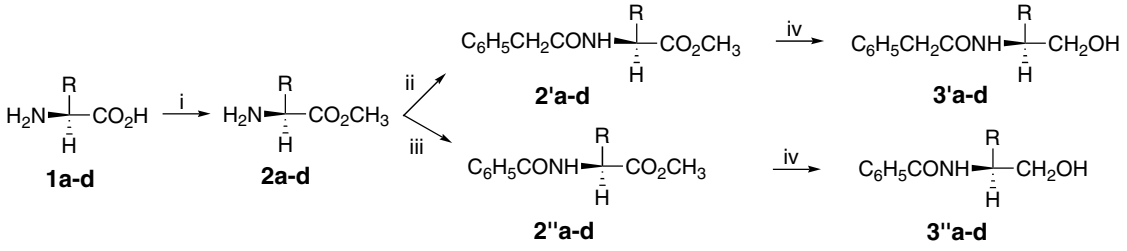
Using optically active amino acids as starting material, the chiral amino acids **1a**–**d** were easily converted to the corresponding methyl esters **2a**–**d** in the presence of thionyl chloride and methanol with high yields. After treating **2a**–**d** with phenylacetyl chloride or benzoyl chloride, followed by KBH_4 reduction, the corresponding phenylacetamidodiols **3′a**–**d** or benzoylacetamidodiols **3″a**–**d** were obtained in good yields. As a result, compounds **3′b**–**d** and **3″b**–**d** were enantiomerically pure (Scheme 1).

Subsequently, using *p*-toluenesulfonic acid as catalyst, 2-phenylacetamido-1,3-diols **3′a,b** or 2-benzoylacetamido-1,3-diols **3″a,b** were subjected to acetalization with benzaldehydes **4a**–**e**. As a result, (*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxan-5-yl)benzoylacetamides, **5a**–**j**, **5′a**–**j**, (*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxan-5-yl)phenylacetamides, **6a**–**j**, **6′a**–**j**, were obtained in good yield. Under this condition, the (*cis*)-*N*-(2-substitutedphenyl-1,3-dioxan-5-yl)amides were main products (Scheme 2).

Under the same condition, the acetalization of (E)-phenylvinyl aldehyde **4f** with 2-phenylacetamido-1,3-diols **3′a,b** or 2-benzoylacetamido-1,3-diols **3″a,b** stereoselectively provided a series of (*cis*)- and (*trans*)-isomers, namely, **7a**,**b**, **7′a**,**b**, **8a**,**b**, **8′a**,**b** (Scheme 3).

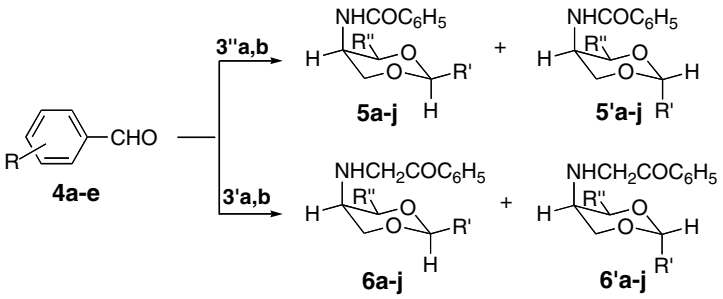
To investigate the impact of ring size on the stereoselectivity and the biological activity of 2,5-disubstituted-dioxacycloalkanes, the original 1,3-dioxane ring was expanded to seven- and eight- member ring (Scheme 4). Among the acetalization of benzaldehyde **4a**–**e** and 2-phenylacetamido-1,4-diol **3′c** or 2-benzoylacetamido-1,4-diol **3″c** only **4c**–**e** stereoselectively provided a series of isomers containing 7-membered dioxacycloalkanes, that is, (*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxacycloheptan-5-yl)phenylacetylamides **9c**–**e**, **9′c**–**e** and (*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxacycloheptan-5-yl)benzoylacetylamides **10c**–**e** and **10′c**–**e**. Under similar condition, among the acetalization of benzaldehyde **4a**–**e** and 2-phenylacetamido-1,5-diol **3′d** or 2-benzoylacetamido-1,5-diol **3″d**, only **4c**–**e** stereoselectively provided a series of isomers containing 8-membered dioxacycloalkanes [(*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxacyclooctan-5-yl)benzoylacetylamides **11c**–**e**, **11′c**–**e**, and (*cis*)- and (*trans*)-(2-substitutedphenyl-1,3-dioxacyclooctan-5-yl)phenylacetylamides **12c**–**e** and **12′c**–**e**] (Scheme 4).

An interesting feature of the new synthesis route is the stereoselectivity mediated through the substitutions on the ring. It is also worth noticing that the ratio between *cis*- and *trans*- products was dependent on the ring size formed during the acetalizations. These results suggest that the optically active amino acids may act as chiral auxiliaries for controlling the stereoselectivity during acetalization step.



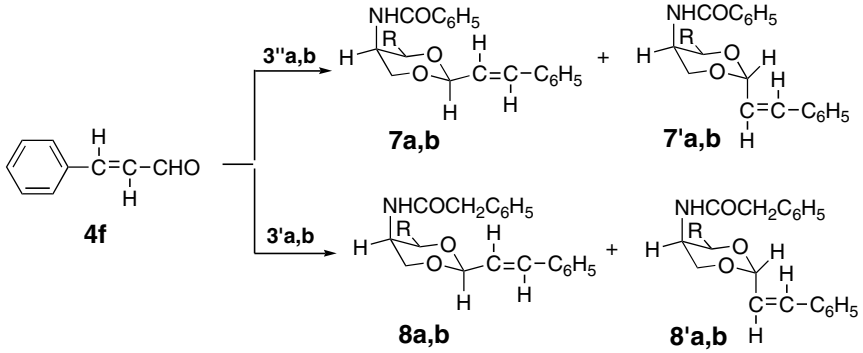
Compounds	R	Optical activity	Yield (%)	Compounds	R	Optical activity	Yield (%)
3′a	CH_2OH		91	**3″a**	CH_2OH		97
3′b	$CH(CH_3)OH$	$[\alpha]_D^{20}$=-32.5°(c=0.02, CH_3OH)	91	**3″b**	$CH(CH_3)OH$	$[\alpha]_D^{20}$=-30.0°(c=0.02, CH_3OH)	94
3′c	CH_2CH_2OH	$[\alpha]_D^{20}$=-28.4°(c=0.02, CH_3OH)	93	**3″c**	CH_2CH_2OH	$[\alpha]_D^{20}$=-26.0°(c=0.02, CH_3OH)	92
3′d	$CH_2CH_2CH_2OH$	$[\alpha]_D^{20}$=-23.3°(c=0.02, CH_3OH)	93	**3″d**	$CH_2CH_2CH_2OH$	$[\alpha]_D^{20}$=-21.0°(c=0.02, CH_3OH)	90

Scheme 1. Synthetic route to compounds **3′a**–**d** and **3″a**–**d**. Reagents and conditions: (i) $SOCl_2$/MEOH, 0 °C–rt; (ii) $C_6H_5CH_2COCl$/THF; (iii) C_6H_5COCl/THF; (iv) KBH_4/THF.



	R′	R″	Optical activity	Yield (%)		R′	R″	Optical activity	Yield (%)
5a	C_6H_5	H		69	**5′a**	C_6H_5	H		7
5b	4-CH_3-C_6H_4	H		65	**5′b**	4-CH_3-C_6H_4	H		8
5c	4-Cl-C_6H_4	H		70	**5′c**	4-Cl-C_6H_4	H		12
5d	4-NO_2-C_6H_4	H		70	**5′d**	4-NO_2-C_6H_4	H		10
5e	3-NO_2-C_6H_4	H		69	**5′e**	3-NO_2-C_6H_4	H		10
5f	C_6H_5	CH_3	$[\alpha]_D^{20}$=-13.5°(c=1.00, $CHCl_3$)	69	**5′f**	C_6H_5	CH_3	$[\alpha]_D^{20}$=14.7°(c=1.00, $CHCl_3$)	8
5g	4-CH_3-C_6H_4	CH_3	$[\alpha]_D^{20}$=-14.2°(c=1.00, $CHCl_3$)	65	**5′g**	4-CH_3-C_6H_4	CH_3	$[\alpha]_D^{20}$=12.7°(c=1.00, $CHCl_3$)	7
5h	4-Cl-C_6H_4	CH_3	$[\alpha]_D^{20}$=-13.1°(c=1.00, $CHCl_3$)	85	**5′h**	4-Cl-C_6H_4	CH_3	$[\alpha]_D^{20}$=10.9°(c=1.00, $CHCl_3$)	15
5i	4-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=-15.4°(c=0.02, $CHCl_3$)	85	**5′i**	4-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=28.5°(c=0.02, $CHCl_3$)	12
5j	3-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=-14.9°(c=1.00, $CHCl_3$)	84	**5′j**	3-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=12.7°(c=1.00, $CHCl_3$)	11
6a	C_6H_5	H		45	**6′a**	C_6H_5	H		8
6b	4-CH_3-C_6H_4	H		42	**6′b**	4-CH_3-C_6H_4	H		7
6c	4-Cl-C_6H_4	H		50	**6′c**	4-Cl-C_6H_4	H		10
6d	4-NO_2-C_6H_4	H		47	**6′d**	4-NO_2-C_6H_4	H		8
6e	3-NO_2-C_6H_4	H		45	**6′e**	3-NO_2-C_6H_4	H		8
6f	C_6H_5	CH_3	$[\alpha]_D^{20}$=-14.7°(c=1.00, $CHCl_3$)	35	**6′f**	C_6H_5	CH_3	$[\alpha]_D^{20}$=12.3°(c=1.00, $CHCl_3$)	6
6g	4-CH_3-C_6H_4	CH_3	$[\alpha]_D^{20}$=-13.6°(c=1.00, $CHCl_3$)	32	**6′g**	4-CH_3-C_6H_4	CH_3	$[\alpha]_D^{20}$=13.3°(c=1.00, $CHCl_3$)	5
6h	4-Cl-C_6H_4	CH_3	$[\alpha]_D^{20}$=-10.6°(c=1.00, $CHCl_3$)	40	**6′h**	4-Cl-C_6H_4	CH_3	$[\alpha]_D^{20}$=12.3°(c=1.00, $CHCl_3$)	8
6i	4-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=-13.8°(c=0.02, $CHCl_3$)	42	**6′i**	4-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=18.3°(c=0.02, $CHCl_3$)	7
6j	3-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=-12.8°(c=1.00, $CHCl_3$)	46	**6′j**	3-NO_2-C_6H_4	CH_3	$[\alpha]_D^{20}$=13.1°(c=1.00, $CHCl_3$)	8

Scheme 2. Synthetic route to compounds **5a**–**j**, **5′a**–**j**, **6a**–**j**, and **6′a**–**j**. Reagents and condition: $CHCl_3$/THF, rt, *p*-toluenesulfonic acid (catalyst), anhydrous Na_2SO_4. In **4a**: R = H; **4b**: R = 4-CH_3, **4c**: R = 4-Cl, **4d**: R = 4-NO_2, **4e**: R = 3-NO_2.

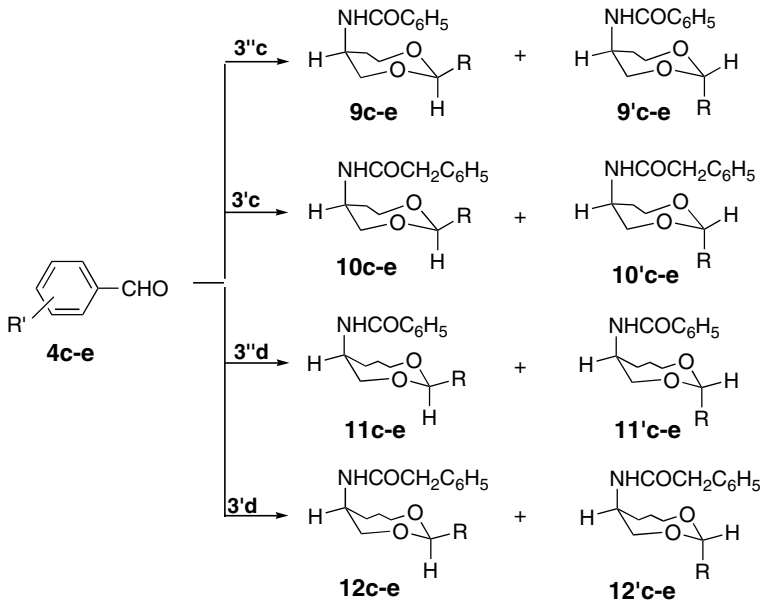


Compounds	R	Optical activity	Yield (%)	Compounds	R	Optical activity	Yield (%)
7a	H		71	**8a**	H		40
7′a	H		10	**8′a**	H		8
7b	CH_3	$[\alpha]_D^{20}$=24.1°(c=0.02, CH_3OH)	80	**8b**	CH_3	$[\alpha]_D^{20}$=22.3°(c=0.02, CH_3OH)	40
7′b	CH_3	$[\alpha]_D^{20}$=-18.2°(c=0.02, CH_3OH)	10	**8′b**	CH_3	$[\alpha]_D^{20}$=-16.9°(c=0.02, CH_3OH)	8

Scheme 3. Synthetic route to compounds **7a**,**b**, **7′a**,**b**, **8a**,**b**, **8′a**,**b**. Reagents and condition: $CHCl_3$, rt, 12 h, *p*-toluenesulfonic acid (catalyst), anhydrous Na_2SO_4.

2.2. Stereochemical assignment

To ensure correct structural assignment to these newly synthesized 2,5-disubstituted-dioxacycloalkanes, nuclear Overhauser effect (NOE) experiments were performed. The positive NOE effect was observed between the nitrogen proton at the 5-position and the phenyl proton at the 2-position for each of these compounds (**5a**–**e**, **6a**–**e**, **7a**, **8a**, **9c**–**e**, **10c**–**e**, **11c**–**e**, and **12c**–**e**). This further indicated that the substitutions at both the 2- and 5-positions of these compounds are in a *cis*-configuration. Two positive NOE signals were observed between the



	R	Optical activity	Yield (%)		R	Optical activity	Yield (%)
9c	4-Cl-C_6H_4	$[\alpha]_D^{20}$=13.7°(c=0.02, $CHCl_3$)	30	**9′c**	4-Cl-C_6H_4	$[\alpha]_D^{20}$=-15.0°(c=0.02, $CHCl_3$)	14
9d	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=16.8°(c=0.02, $CHCl_3$)	22	**9′d**	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=-15.6°(c=0.02, $CHCl_3$)	11
9e	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=13.7°(c=0.02, $CHCl_3$)	26	**9′e**	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=-12.8°(c=0.02, $CHCl_3$)	14
10c	4-Cl-C_6H_4	$[\alpha]_D^{20}$=19.2°(c=0.02, $CHCl_3$)	25	**10′c**	4-Cl-C_6H_4	$[\alpha]_D^{20}$=-16.4°(c=0.02, $CHCl_3$)	13
10d	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=21.0°(c=0.02, $CHCl_3$)	25	**10′d**	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=-19.3°(c=0.02, $CHCl_3$)	13
10e	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=17.9°(c=0.02, $CHCl_3$)	28	**10′e**	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=-14.8°(c=0.02, $CHCl_3$)	15
11c	4-Cl-C_6H_4	$[\alpha]_D^{20}$=16.0°(c=0.02, $CHCl_3$)	34	**11′c**	4-Cl-C_6H_4	$[\alpha]_D^{20}$=-13.4°(c=0.02, $CHCl_3$)	14
11d	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=20.0°(c=0.02, $CHCl_3$)	26	**11′d**	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=-18.0°(c=0.02, $CHCl_3$)	14
11e	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=17.2°(c=0.02, $CHCl_3$)	29	**11′e**	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=-13.7°(c=0.02, $CHCl_3$)	15
12c	4-Cl-C_6H_4	$[\alpha]_D^{20}$=17.6°(c=0.02, $CHCl_3$)	32	**12′c**	4-Cl-C_6H_4	$[\alpha]_D^{20}$=-14.3°(c=0.02, $CHCl_3$)	13
12d	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=18.2°(c=0.02, $CHCl_3$)	24	**12′d**	4-NO_2-C_6H_4	$[\alpha]_D^{20}$=-15.1°(c=0.02, $CHCl_3$)	12
12e	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=15.3°(c=0.02, $CHCl_3$)	28	**12′e**	3-NO_2-C_6H_4	$[\alpha]_D^{20}$=-11.7°(c=0.02, $CHCl_3$)	13

Scheme 4. Synthetic route to compounds **9c–e**, **10c–e**, **11c–e**, **12c–e** and **9′c–e**, **10′c–e**, **11′c–e**, **12′c–e**. Reagents and condition: $CHCl_3$, rt, *p*-toluenesulfonic acid (catalyst), anhydrous Na_2SO_4.

CH_3 at the 4-position, the phenyl proton at the 2-position, and the NH at the 5-position on the substitutions at 2-, 4-, and 5-positions of **5f–j**, **6f–j**, **7b**, and **8b**, respectively, indicating *cis*–configuration. In contrast, no positive NOE effect was observed between the substitutions at the 2- and 5-positions of compounds **5′a–e**, **6′a–e**, **7′a**, **8′a**, **9′c–e**, **10′c–e**, **11′c–e**, and **12′c–e**, indicating that the configuration of these compounds is a *trans*-configuration. The NOE difference experiment indicates that the substitutions at 2-, 4-, and 5-positions of **5′f–j**, **6′f–j**, **7′b**, **8′b** are in a *trans*-arrangement due to the absence of NOE signal.

2.3. Configuration conversion experiment

To further confirm the stereochemical nature of these compounds, configuration conversion experiment was carried out. When concentrated hydrochloric acid was employed as catalyst at 70 °C for 12 h, **5′a–j**, **6′a–j**, **7′a,b**, **8′a,b**, **9′c–e**, **10′c–e**, **11′c–e**, **12′c–e** were converted to **5a–j**, **6a–j**, **7a,b**, **8a,b**, **9c–e**, **10c–e**, **11c–e**, **12c–e**, respectively. With these conversions, **5′a–j**, **6′a–j**, **7′a,b**, **8′a,b**, **9′c–e**, **10′c–e**, **11′c–e**, **12′c–e** were confirmed to be kinetically controlled products, whereas **5a–j**, **6a–j**, **7a,b**, **8a,b**, **9c–e**, **10c–e**, **11c–e**, **12c–e** were thermodynamically stable products. This is a good example of demonstrating the possibility of isomer conversion from less thermodynamically stable compounds to more stable ones. This allows us to fine tune the desired stereospecificity by changing the experimental conditions such as reaction time, temperature, and catalyst.

2.4. In vivo anti-inflammatory activity and structure–activity relationship study[15,16]

The anti-inflammatory activities of newly synthesized compounds were evaluated using a xylene-induced ear edema model assay. Briefly, test compounds were administered orally in 0.5% carboxymethyl cellulose (CMC) suspension at a concentration of 20 mg/kg.

The starting compounds, N-substituted aminodiols, were first evaluated to confirm the necessity of 1,3-dioxane ring for anti-inflammatory activity (Table 1). Both compounds were ineffective suggesting that the rigid 1,3-dioxacycle ring is critical, consistent with our previously reported results.[15,16]

Next, we initiated the structure–activity relationship study using 1,3-dioxacycloalkane ring as a template

Table 1. Anti-inflammatory activities of N-substituted aminodiols **3′a–d**, **3″a–d** and aldehydes **4a–f** against xylene-induced ear edema in mice

Agents	Edema weight (X ± SD mg)
CMC	3.23 ± 0.74
3′a	3.88 ± 1.25
3′b	3.35 ± 0.87
3′c	3.44 ± 0.89
3′d	3.53 ± 0.82
Aspirin	1.85 ± 0.72
3″a	3.25 ± 0.73
3″b	3.32 ± 0.79
3″c	4.01 ± 1.35
3″d	3.38 ± 0.79
4a	3.45 ± 0.67
4b	3.72 ± 0.81
4c	3.80 ± 0.89
4d	3.39 ± 0.82
4e	3.50 ± 0.77
4f	3.40 ± 0.92

Dose of N-substituted aminodiols and aldehydes = 20mg/kg; dose of aspirin = 30 mg/kg; $n = 11$.

while exploring the influence of different modifications at 2-, 5-position and ring size. As evaluated using mice xylene-induced ear edema model, most of 2,5-disubstituted-1,3-dioxacycloalkanes exhibited well to moderate anti-inflammatory activities 2 h after administration at 20 mg/kg. As listed in Table 2, it was observed that most of compounds in the 6-membered ring series exhibited comparable or better potency (41–56% inhibition of inflammation) than the reference drug aspirin (aspirin: 41% inhibition of inflammation). Among these, compounds **5h**, **5i**, **6i**, **5′i**, **6′i** were the most potent anti-inflammatory agents in this series, achieving 55–57% inhibition of inflammation after 2-h treatment.

Upon comparing the anti-inflammatory effect of the benzoylamide series and the phenylacetamide ones, we noticed that the former exhibited better anti-inflammatory activity (i.e., **5b**: 48.0% vs **6b**: 36.5%; **5h**: 56.4% vs **6h**: 46.4%). It was also worthy noticing that the substitution on the phenyl ring is important for anti-inflammatory activity. It seemed the electron-withdrawing groups on the phenyl ring endowed the 2,5-disubstituted-dioxacycloalkanes with slightly better anti-inflammatory profiles (i.e., **5d**: 44.2%; **5e**: 42.9%; **5i**: 57.4%; **5j**: 42.0%; **5′d**: 48.7%; **5′e**: 45.2%; **5′h**: 47.1%; **5′i**: 55.4%; **5′j**: 46.8%; **6d**: 43.3%; **6e**: 41.3%; **6i**: 55.8%; **6j**: 47.1%; **6′d**: 44.6%; **6′e**: 42.6%; **6′i**: 55.1%; **6′j**: 46.5%). However, the chlorine substitution on the phenyl ring induced an ambiguous anti-inflammatory effect (**5c**: 28.5%; **6c**: 43.6%; **5h**: 56.4%; **6h**: 46.4%). In addition, carbon–carbon double bond insertion also decreased the anti-inflammatory profile (**5a**: 39.7%; **5f**: 43.9% vs **7a**: 35.6%; **7b**: 38.5%; **7′a**: 35.0%; **7′b**: 37.5%; **6a**: 38.5%; **6f**: 40.0% vs **8a**: 27.2%; **8b**: 32.1%; **8′a**: 29.5%; **8′b**: 33.3%).

To examine the importance of the spatial disposition, the anti-inflammatory activities of the *cis*- and *trans*- isomers were compared. The isomers of chiral compounds may express various biological activities. Nevertheless, in the case of 2,5-disubstituted-dioxacycloalkanes, only a few pair of the stereoisomers displayed distinguishable anti-inflammatory activities (**5b**: 48.0% vs **5′b**: 39.1%; **5c**: 28.5% vs **5′c**: 47.4%; **5h**: 56.4% vs **5′h**: 47.1%). Most of the *cis*- and *trans*- isomers exhibited the comparable anti-inflammatory activities (**5d**: 44.2% vs **5′d**: 48.7%; **5e**: 42.9% vs **5′e**: 45.2%; **5f**: 43.9% vs **5′f**: 43.9%; **5g**: 46.1% vs **5′g**: 44.9%; **5i**: 57.4% vs **5′i**: 55.4%; **5j**: 42.0% vs **5′j**: 46.8%; **6c**: 43.6% vs **6′c**: 42.0%; **6d**: 43.3% vs **6′d**: 44.6%; **6e**: 41.3% vs **6′e**: 42.6%; **6f**: 40.0% vs **6′f**: 41.3%; **6h**: 46.4% vs **6′h**: 46.1%; **6i**: 55.8% vs **6′i**: 55.1%; **6j**: 47.1% vs **6′j**: 46.5%). It seemed the stereochemical feature of these 2,5-disubstituted-dioxacycloalkanes has minimal impact on their biological activities.

In general, the ring size is an important parameter in the biological activity of cyclic compounds. In particular, it affects their transport, physicochemical, and biological properties. The efficacy of the 7-membered ring in a variety of drugs, for example, benzodiazapenes, is believed to be due to its modest degree of structural flexibility that permits receptor-induced fit, which might lead to improved biological profiles.[18] However, the anti-inflammatory activities of the compounds containing 7-, 8-membered dioxacycloalkanes were decreased over those of their corresponding 6-membered compounds (**5d**: 44.2% vs **10d**: 19.2%; **11d**: 20.5%; **5e**: 42.9% vs **10e**: 20.8%; **11e**: 19.9%; **5′d**: 48.7% vs **10′d**: 20.2%; **11′d**: 20.5%; **6c**: 43.6% vs **9c**: 23.7%; **12c**: 23.1%; **6d**: 43.3% vs **9d**: 18.9%; **12d**: 19.9%; **6e**: 41.3% vs **9e**: 20.1%; **12e**: 19.2%; **6′e**: 42.6% vs **9′e**: 21.2%; **12′e**: 19.9%). It appears that the stereochemical constraints of these compounds do not play important role in the biological profiles. We speculate that 7-, 8-membered dioxacycloalkanes may have unfavorable physicochemical properties (chemical stability, size, hydrophilicity, conformation) which needs further investigation.

2.5. Tail bleeding time measurements

The use of conventional NSAIDs is associated with a number of significant adverse events, including gastrointestinal (GI) bleeding, impaired platelet function, and prolonged bleeding time.[19,20] The clinical effects of NSAID-induced platelet dysfunction consist of an increased bleeding, prolonged surgical bleeding, and additive risk of significant or life-threatening bleeding in patients taking anticoagulants.[21] Both surgical and non-surgical studies have shown that conventional NSAIDs increase bleeding time and blood loss. To develop the safer anti-inflammatory agents, it is critical to evaluate if these newly synthetic agents have deleterious effect on normal hemostasis leading to bleeding complications. The cutaneous bleeding time model is the most common method used in animal experiments to investigate bleeding potential in humans.[19–27]

To evaluate the bleeding risk of the new anti-inflammatory agents, the tail bleeding time assays were performed on mice using previously reported method.[28] Male mice

Table 2. Anti-inflammatory activities of 2,5-disubstituted-dioxacycloalkanes against xylene-induced ear edema in mice

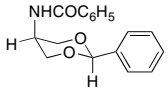
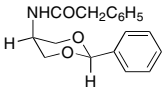
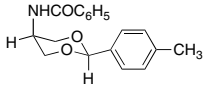
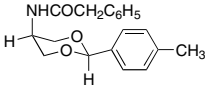
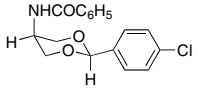
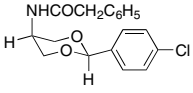
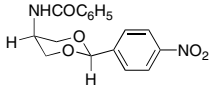
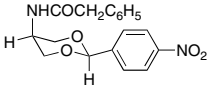
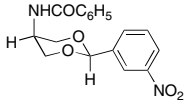
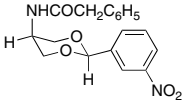
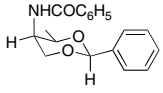
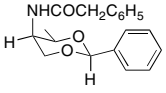
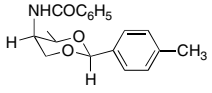
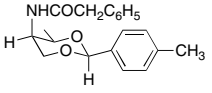
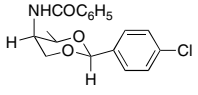
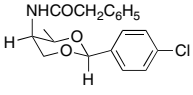
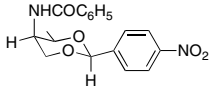
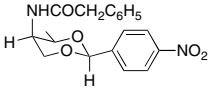
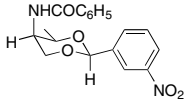
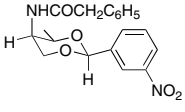
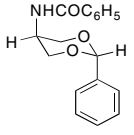
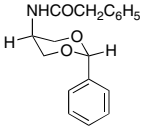
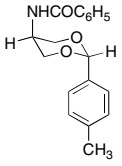
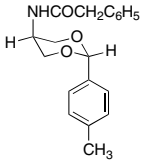
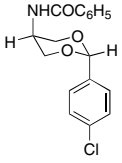
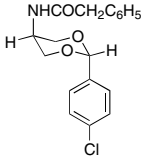
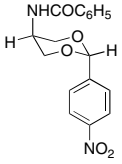
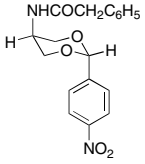
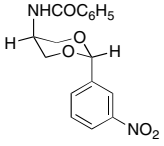
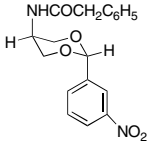
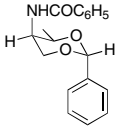
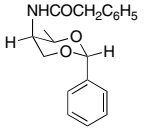
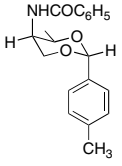
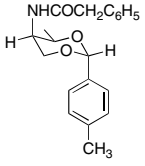
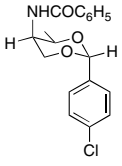
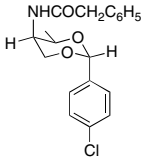
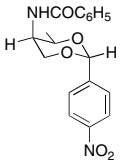
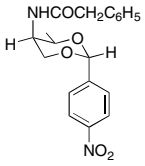
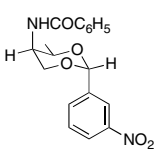
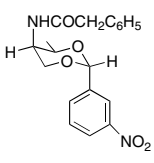
	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)	Agents	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)
CMC		3.12 ± 0.55		Aspirin		1.85 ± 0.72[b]	40.7
5a		1.88 ± 0.57[b]	39.7	**6a**		1.92 ± 0.71[b]	38.5
5b		1.62 ± 0.59[b]	48.0	**6b**		1.98 ± 0.78[b]	36.5
5c		2.23 ± 0.65[b]	28.5	**6c**		1.76 ± 0.75[b]	43.6
5d		1.74 ± 0.70[b]	44.2	**6d**		1.77 ± 0.71[a]	43.3
5e		1.78 ± 0.68[b]	42.9	**6e**		1.83 ± 0.69[b]	41.3
5f		1.75 ± 0.58[b]	43.9	**6f**		1.87 ± 0.65[b]	40.0
5g		1.68 ± 0.59[b]	46.1	**6g**		1.84 ± 0.66[b]	41.0
5h		1.36 ± 0.61[b]	56.4	**6h**		1.67 ± 0.61[b]	46.4
5i		1.33 ± 0.63[b]	57.4	**6i**		1.38 ± 0.63[b]	55.8
5j		1.81 ± 0.55[b]	42.0	**6j**		1.65 ± 0.59[b]	47.1
5′a		1.83 ± 0.59[b]	41.3	**6′a**		1.94 ± 0.76[b]	37.8

Table 2 (*continued*)

	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)	Agents	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)
5′b		1.90 ± 0.60[b]	39.1	**6′b**		2.01 ± 0.75[b]	35.6
5′c		1.64 ± 0.59[b]	47.4	**6′c**		1.81 ± 0.78[b]	42.0
5′d		1.60 ± 0.57[b]	48.7	**6′d**		1.73 ± 0.74[a]	44.6
5′e		1.71 ± 0.69[b]	45.2	**6′e**		1.79 ± 0.70[b]	42.6
5′f		1.75 ± 0.67[b]	43.9	**6′f**		1.83 ± 0.63[b]	41.3
5′g		1.72 ± 0.65[b]	44.9	**6′g**		1.80 ± 0.69[b]	42.3
5′h		1.65 ± 0.58[b]	47.1	**6′h**		1.68 ± 0.54[b]	46.1
5′i		1.39 ± 0.60[b]	55.4	**6′i**		1.40 ± 0.67[b]	55.1
5′j		1.66 ± 0.58[b]	46.8	**6′j**		1.67 ± 0.57[b]	46.5

(*continued on next page*)

Table 2 (*continued*)

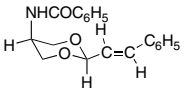
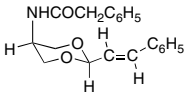
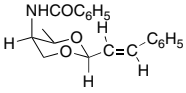
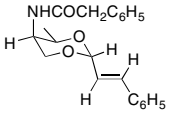
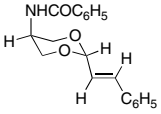
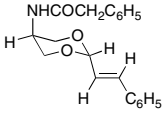
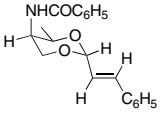
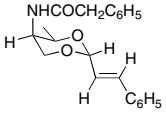
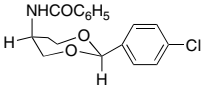
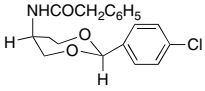
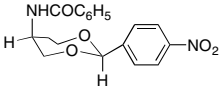
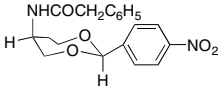
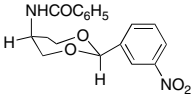
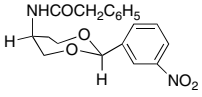
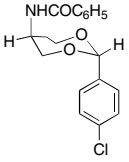
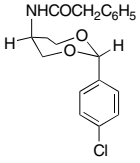
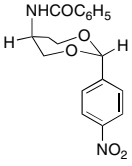
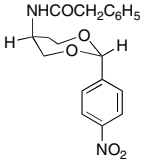
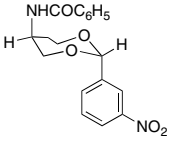
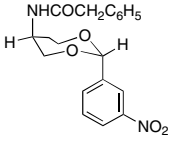
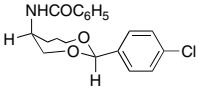
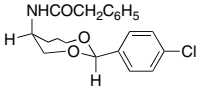
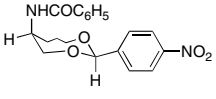
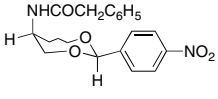
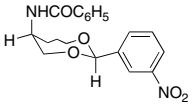
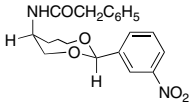
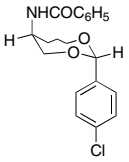
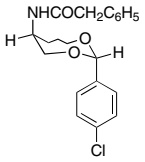
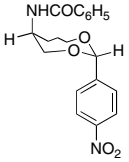
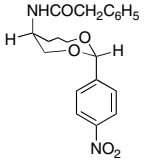
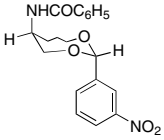
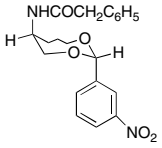
	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)	Agents	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)
7a		2.01 ± 0.53[b]	35.6	**8a**		2.27 ± 0.65[b]	27.2
7b		1.92 ± 0.54[b]	38.5	**8b**		2.12 ± 0.56[b]	32.1
7′a		2.03 ± 0.50[b]	35.0	**8′a**		2.20 ± 0.62[b]	29.5
7′b		1.95 ± 0.58[b]	37.5	**8′b**		2.08 ± 0.53[b]	33.3
9c		2.20 ± 0.55[b]	29.5	**10c**		2.38 ± 0.61[b]	23.7
9d		2.52 ± 0.51[b]	19.2	**10d**		2.53 ± 0.62[a]	18.9
9e		2.47 ± 0.56[a]	20.8	**10e**		2.49 ± 0.58[a]	20.1
9′c		2.24 ± 0.56[b]	28.2	**10′c**		2.36 ± 0.58[b]	24.4
9′d		2.49 ± 0.53[a]	20.2	**10′d**		2.51 ± 0.60[a]	19.6
9′e		2.44 ± 0.55[b]	21.8	**10′e**		2.46 ± 0.56[a]	21.2
11c		2.24 ± 0.53[b]	28.2	**12c**		2.40 ± 0.55[b]	23.1
11d		2.48 ± 0.52[a]	20.5	**12d**		2.50 ± 0.52[a]	19.9

Table 2 (*continued*)

	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)	Agents	Chemical structure	Edema weight (X ± SD mg)	Inhibition (%)
11e		2.50 ± 0.55[a]	19.9	**12e**		2.52 ± 0.56[a]	19.2
11′c		2.27 ± 0.55[b]	27.2	**12′c**		2.38 ± 0.54[b]	23.7
11′d		2.44 ± 0.54[b]	21.8	**12′d**		2.47 ± 0.55[a]	20.8
11′e		2.47 ± 0.54[a]	20.8	**12′e**		2.50 ± 0.53[a]	19.9

Dose of 2,5-disubstituted-1,3-dioxacycloalkanes = 20 mg/kg, dose of aspirin = 30 mg/kg; $n = 11$.
[a] Compare to control, $P < 0.05$.
[b] Compare to control, $P < 0.01$.

(18–22 g) were orally administered with the new anti-inflammatory agents. After the administration of 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. Baseline bleeding times were similar between treatment groups with an average of 113–121 s. Treatment with the new anti-inflammatory agents (**5a–j**, **5′a–j**, **6a–j**, **6′a–j**) at the high doses (200 mg/kg) did not significantly prolong bleeding time at any time point (30, 45, 60, 90 min) compared with NS (115–120 s) (Table 3).

3. Conclusion

The structure–activity relationship (SAR) data indicate that (i) the 1,3-dioxane ring is a suitable template to design a new class of anti-inflammatory compounds; (ii) good anti-inflammatory activity can be achieved by varying the electronic and steric properties at the 2- and 5- position substitution pattern.

In conclusion, although cancer chemoprevention is possible for certain cancer types, drugs that have more acceptable side-effect profiles are desired compared to currently available NSAIDs. COX-2-specific inhibitors, which have an improved safety profile, as compared to traditional NSAIDs that inhibit both the COX-1 and COX-2 enzymes, seem to be well-suited drug candidates for cancer chemoprevention. The molecular and cellular mechanism study of these new compounds is currently under way.

4. Materials and methods

4.1. Experimental

All reactions were carried out under the inert atmosphere using nitrogen (1 bar) unless stated otherwise. 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 F254, 0.25 mm layer thickness, Germany) and HPLC (Waters, C18 column 4.6 × 150 mm, USA). NMR spectra were recorded at 300 MHz on a VXR-300 instrument or at 500 MHz on an Bruker Am-500 instrument in CDCl3 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). Statistical analysis was performed using One way ANOVA test with $p < 0.05$ as significant.

4.1.1. HCl·L-Ser-OCH$_3$ (2a). At 0 °C, thinly chloride was added dropwise to 50 ml of anhydrous methanol 3.75 ml (47.5 mmol). The solution was stirred at 0 °C for 30 min and 5.0 g (47.6 mmol) of L-Ser was added.

Table 3. Effect of 1,3-dioxacycloalkanes on the tail bleeding time (X ± SDs) of mice

Compound	Before drug administration	Post-drug administration			
		30 min	45 min	60 min	90 min
NS	118.0 ± 9.0	119.8 ± 8.0	119.7 ± 7.9	119.2 ± 8.1	118.9 ± 8.6
5a	114.4 ± 8.4	119.2 ± 8.5	118.8 ± 7.6	117.6 ± 8.0	118.7 ± 8.8
5b	115.2 ± 7.9	118.3 ± 8.1	119.0 ± 8.7	118.7 ± 7.9	118.4 ± 8.0
5c	115.3 ± 8.5	118.5 ± 8.4	118.9 ± 7.9	120.9 ± 8.6	119.4 ± 8.3
5d	122.3 ± 8.6	119.4 ± 8.7	118.7 ± 8.6	120.6 ± 8.7	119.4 ± 8.1
5e	117.6 ± 7.9	119.3 ± 8.7	118.2 ± 8.4	119.1 ± 8.6	120.2 ± 8.8
5g	113.4 ± 8.2	120.9 ± 9.0	121.0 ± 9.2	119.8 ± 8.7	118.7 ± 8.5
5h	117.9 ± 8.7	118.3 ± 7.9	118.9 ± 8.0	118.5 ± 8.1	118.7 ± 8.3
5i	117.3 ± 7.6	118.4 ± 8.6	119.2 ± 8.3	117.2 ± 8.0	118.9 ± 8.5
5j	118.2 ± 7.8	118.9 ± 7.6	119.2 ± 8.0	117.4 ± 8.5	118.3 ± 8.6
5′a	118.8 ± 7.9	119.3 ± 8.1	119.2 ± 8.5	119.7 ± 8.8	119.6 ± 8.0
5′b	119.1 ± 8.2	118.5 ± 8.0	119.2 ± 8.7	119.5 ± 8.9	117.8 ± 8.2
5′c	118.2 ± 8.0	119.0 ± 8.3	118.9 ± 8.5	118.7 ± 8.2	119.6 ± 8.7
5′d	120.3 ± 8.4	119.5 ± 8.7	117.7 ± 8.2	118.6 ± 8.0	118.9 ± 8.5
5′e	113.5 ± 8.3	118.8 ± 8.4	118.0 ± 7.7	118.4 ± 8.2	118.7 ± 8.6
5′f	115.5 ± 7.4	118.7 ± 8.2	118.9 ± 7.8	118.6 ± 8.2	118.9 ± 8.4
5′g	116.1 ± 8.4	120.4 ± 8.5	118.5 ± 8.2	118.9 ± 8.6	117.7 ± 7.6
5′h	114.8 ± 8.0	119.6 ± 8.7	118.6 ± 8.3	118.7 ± 8.2	118.6 ± 8.5
5′i	116.9 ± 7.6	117.8 ± 8.0	118.1 ± 8.1	118.8 ± 8.3	119.0 ± 8.7
5′j	113.0 ± 8.0	118.9 ± 8.3	118.2 ± 8.1	119.5 ± 8.6	118.2 ± 8.1
6a	115.2 ± 7.8	118.5 ± 8.0	119.3 ± 8.5	117.8 ± 8.0	118.9 ± 7.9
6b	116.5 ± 7.9	117.2 ± 7.8	118.6 ± 8.2	118.4 ± 8.1	119.2 ± 8.2
6c	117.6 ± 7.7	117.9 ± 8.0	119.2 ± 8.4	119.5 ± 8.3	118.4 ± 8.1
6d	119.5 ± 8.3	120.7 ± 8.9	120.2 ± 9.2	117.6 ± 8.3	117.7 ± 7.9
6e	114.9 ± 8.0	117.7 ± 7.9	118.5 ± 8.1	119.2 ± 8.8	118.6 ± 8.6
6f	118.2 ± 8.5	118.5 ± 8.1	119.0 ± 8.4	118.6 ± 8.1	117.9 ± 7.9
6g	116.5 ± 7.7	117.9 ± 7.8	118.6 ± 8.1	119.0 ± 8.4	118.5 ± 8.7
6h	119.7 ± 7.5	118.4 ± 7.6	119.6 ± 8.4	118.6 ± 8.4	119.0 ± 8.7
6i	116.7 ± 7.5	117.8 ± 8.0	118.5 ± 7.9	117.9 ± 7.6	117.2 ± 7.8
6j	120.5 ± 8.8	120.1 ± 8.5	118.7 ± 8.1	118.5 ± 8.3	118.6 ± 7.9
6′a	117.2 ± 7.8	118.5 ± 8.0	119.3 ± 8.5	117.8 ± 8.0	118.9 ± 7.9
6′b	119.5 ± 7.9	117.2 ± 7.8	118.6 ± 8.2	118.4 ± 8.1	119.2 ± 8.2
6′c	116.6 ± 7.7	117.9 ± 8.0	119.2 ± 8.4	119.5 ± 8.3	118.4 ± 8.1
6′d	119.5 ± 8.3	120.7 ± 8.9	120.2 ± 9.2	117.6 ± 8.3	117.7 ± 7.9
6′e	117.9 ± 8.0	117.7 ± 7.9	118.5 ± 8.1	119.2 ± 8.8	118.6 ± 8.6
6′f	119.2 ± 8.5	118.5 ± 8.1	119.0 ± 8.4	118.6 ± 8.1	117.9 ± 7.9
6′g	117.5 ± 7.7	117.9 ± 7.8	118.6 ± 8.1	119.0 ± 8.4	118.5 ± 8.7
6′h	118.7 ± 7.5	118.4 ± 7.6	119.6 ± 8.4	118.6 ± 8.4	119.0 ± 8.7
6′i	116.7 ± 7.5	117.8 ± 8.0	118.5 ± 7.9	117.9 ± 7.6	117.2 ± 7.8
6′j	120.5 ± 8.8	120.1 ± 8.5	118.7 ± 8.1	118.5 ± 8.3	118.6 ± 7.9

Dose = 200 mg/kg, $n = 10$.

The reaction mixture was stirred at room temperature for 24 h until TLC (CH_3Cl/CH_3OH, 9:1) indicated complete disappearance of L-Ser. The reaction mixture was evaporated under reduced pressure and the residue was triturated with petroleum ether repeatedly to provide 7304 mg (99%) of HCl·L-Ser-OCH_3 as a colorless powder (mp 161–162 °C) that was directly used for the next reaction.

4.1.2. HCl·L-Thr-OCH_3 (2b). Using the same procedure for the preparation of **2a**, starting from 4.998 g (47.5 mmol) of L-Thr, 7867 mg (98%) of HCl·L-Thr-OCH_3 was obtained as a colorless powder (mp 140–142 °C).

4.1.3. HCl·L-Asp-$(OCH_3)_2$ (2c). Using the same procedure for the preparation of **2a**, starting from 6.332 g (47.5 mmol) of L-Asp, 7.495 mg (98%) of HCl·L-Asp-$(OCH_3)_2$ was obtained as a colorless powder (mp 149–151 °C).

4.1.4. L-Glu-$(OCH_3)_2$ (2d). Using the same procedure for the preparation of **2a**, starting from 6.983 g (47.5 mmol) of L-Glu, 8146 mg (98%) of HCl·L-Glu-$(OCH_3)_2$ was obtained as a colorless powder (mp 136–138 °C).

4.1.5. *N*-Phenyl-L-Ser-OCH_3 (2′a). At 0 °C, 25 ml of saturated aqueous of sodium carbonate was added to the suspension of 1.0 g (6.4 mmol) of HCl·L-Ser-OCH_3 in 30 ml of THF. 1.106 ml (8.3 mmol) of phenylacetyl chloride was added upon stirring with pH adjustment to 8–9 by adding saturated aqueous of sodium carbonate. The reaction mixture was stirred at room temperature for 3 h until complete disappearance of L-Ser-OCH_3 as indicated by TLC (CH_3Cl/CH_3OH, 19:1). The reaction mixture was evaporated under reduced pressure and the residue was dissolved in 50 ml of ethyl acetate and washed with saturated aqueous of sodium bicarbonate (10 ml × 3), saturated aque-

ous of $KHSO_4$ (10 ml × 3), and saturated aqueous of NaCl (10 ml × 3). The solution was evaporated under reduced pressure and the residue was purified using chromatography (petroleum ether/ethyl acetate, 5:1). $C_6H_5CH_2CO$-L-Ser-OCH_3 (1140 mg with 75% yield) was obtained as a colorless powder (mp 77–79 °C).

4.1.6. *N*-Phenyl-L-Thr-OCH_3 (2′b). Using the same procedure for the preparation of **2′a**, starting from 1010 mg (6.0 mmol) of HCl·L-Thr-OCH_3, 1171 mg (77%) of *N*-phenyl-L-Thr-OCH_3 was obtained as a colorless powder (mp 90–92 °C).

4.1.7. *N*-Phenyl-L-Asp-(OCH_3) (2′c). Using the same procedure for the preparation of **2′a**, starting from 1182 mg (6.0 mmol) of HCl·L-Asp-$(OCH_3)_2$, 1345 mg (80%) of *N*-phenyl-L-Asp-$(OCH_3)_2$ was obtained as a colorless powder (mp 90–92 °C).

4.1.8. *N*-Phenyl-L-Glu-(OCH_3) (2′d). Using the same procedure for the preparation of **2′a**, starting from 1274 mg (6.0 mmol) of HCl·L-Glu-$(OCH_3)_2$, 1433 mg (81%) of *N*-phenyl-L-Glu-$(OCH_3)_2$ was obtained as a colorless powder (mp 111–113 °C).

4.1.9. *N*-Benzoyl-L-Ser-OCH_3 (2″a). Using the same procedure for the preparation of **2′a**, starting from 992 mg (6.4 mmol) of HCl·L-Ser-OCH_3 and 1162 mg (8.3 mmol) of benzoyl chloride, 1170 mg (82%) of *N*-benzoyl-L-Ser-OCH_3 was obtained as a colorless powder (mp 75–77 °C).

4.1.10. *N*-Benzoyl-L-Thr-OCH_3 (2″b). Using the same procedure for the preparation of **2′a**, starting from 1082 mg (6.4 mmol) of HCl·L-Thr-OCH_3, 1229 mg (81%) of *N*-benzoyl-L-Thr-OCH_3 was obtained as a colorless powder (mp 85–87 °C).

4.1.11. *N*-Benzoyl-L-Asp-(OCH_3) (2″c). Using the same procedure for the preparation of **2′a**, starting from 1261 mg (6.4 mmol) of HCl·L-Asp-$(OCH_3)_2$,1357 mg (80%) of *N*-benzoyl-L-Asp-$(OCH_3)_2$ was obtained as a colorless powder (mp 91–93 °C).

4.1.12. *N*-Benzoyl-L-Glu-(OCH_3) (2″d). Using the same procedure for the preparation of **2′a**, starting from 1350 mg (6.4 mmol) of HCl·L-Glu-$(OCH_3)_2$, 1446 mg (81%) of *N*-phenyl-L-Glu-$(OCH_3)_2$ was obtained as a colorless powder (mp 92–94 °C).

4.1.13. *N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]phenylacetamide (3′a). To the suspension of 200 mg (5.6 mmol) of KBH_4 in 10 ml of THF the solution of 238 mg (1.0 mmol) of *N*-Phenyl-L-Ser-OCH_3 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 **2′a**. The reaction mixture was adjusted to pH 10 with hydrochloric acid (2 mol/L) and evaporated under reduced pressure. The residue was purified by chromatography (CH_3Cl/CH_3OH, 19:1) to provide 190 mg (91%) of the title compound as a colorless powder. Mp 135–136 °C. IR (KBr) υ (cm^{-1}) = 3452, 3343, 3028, 3004, 2962, 2834, 1638, 1604, 1573, 1505, 1452, 721, 662. ^1H NMR (DMSO-d_6) δ (ppm) = 8.11 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 4.64 (broad, 2H), 3.95 (m, J = 6.0 Hz, 1H), 3.62 (s, 2H), 3.53 (d, J = 5.7 Hz, 4H). FAB-MS (m/z) 210 $[M+H]^+$.

4.1.14. (1*S*,2*R*)-*N*-[2-Hydroxy-1-(hydroxymethyl)propyl]phenylacetamide (3′b). Using the same procedure for the preparation of **3′a**, the title compound (203 mg with 91% yield) was obtained from 252 mg (1.0 mmol) of phenylacetyl-L-Thr-OCH_3 as a colorless powder. Mp 125–127 °C, IR (KBr) υ (cm^{-1}) = 3451, 3362, 3033, 3005, 2965, 2862, 1643, 1608, 1592, 1505, 1482, 712, 651. ^1H NMR (DMSO-d_6) δ (ppm) = 8.04 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 7.8 Hz, 1H), 4.24 (q, J = 6.0 Hz, 1H), 3.96 (m, J = 6.4 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 3.64 (s, 2H), 3.53 (s, 2H), 1.22 (d, J = 6.9 Hz, 3H). FAB-MS (m/z) 224 $[M+H]^+$. $[\alpha]_D^{20}$ − 32.5 (c 0.02, CH_3OH).

4.1.15. (1*S*)-*N*-[3-Hydroxy-1-(hydroxymethyl)propyl]-phenylacetamide (3′c). Using the same procedure for the preparation of **3′a**, the title compound (207 mg with 93% yield) was obtained from 252 mg (1.0 mmol) of phenylacetyl-L-Asp-$(OCH_3)_2$ as a colorless powder. Mp 132–134 °C. IR (KBr) υ (cm^{-1}) = 3415, 3344, 3023, 3006, 2964, 2833, 1632, 1602, 1585, 1506, 1463, 715, 651. ^1H NMR (DMSO-d_6) δ (ppm) = 8.03 (d, J = 5.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 4.75 (t, J = 3.9 Hz, 1H), 4.44 (t, J = 3.9 Hz, 1H), 4.06 (dq, J = 3.7 Hz, J = 2.5 Hz, 1H), 3.66 (s, 2H), 3.49 (s, 2H), 3.43 (t, J = 3.9 Hz, 1H), 3.40 (t, J = 3.9 Hz, 1H), 1.76 (dt, J = 4.7 Hz, J = 2.7 Hz,1H), 1.63 (dt, J = 5.6 Hz, J = 3.3 Hz, 1H) FAB-MS (m/z) 224 $[M+H]^+$. $[\alpha]_D^{20}$ − 28.4 (c 0.02, CH_3OH).

4.1.16. (1*S*)-*N*-[4-Hydroxy-1-(hydroxymethyl)butyl]-phenylacetamide (3′d). Using the same procedure for the preparation of **3′a**, the title compound (220 mg, 93% yield) was obtained from 266 mg (1.0 mmol) of phenylacetyl-L-Glu-$(OCH_3)_2$ as a colorless powder. Mp 102–104 °C, IR (KBr) υ (cm^{-1}) = 3425, 3345, 3033, 3004, 2952, 2841, 1636, 1604, 1587, 1505, 1442, 723, 662. ^1H NMR (DMSO-d_6) δ (ppm) = 8.06 (d, J = 4.9 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 4.67 (t, J = 3.9 Hz, 1H), 4.41 (t, J = 3.8 Hz, 1H), 3.96 (dq, J = 3.9 Hz, J = 2.4 Hz, 1H), 3.66 (s, 2H), 3.43 (t, J = 6.7 Hz, 1H), 3.38 (s, 2H), 3.35 (t, J = 6.6Hz, 1H), 1.68 (m, J = 4.8 Hz, 1H), 1.49 (m, J = 4.5 Hz, 1H), 1.45 (q, J = 3.6 Hz, 2H). FAB-MS (m/z) 238 $[M+H]^+$. $[\alpha]_D^{20}$ − 23.3 (c 0.02, CH_3OH).

4.1.17. *N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]benzoamide (3″a). Using the same procedure for the preparation of **3′a**, the title compound (189 mg, 97% yield) was obtained from 224 mg (1.0 mmol) of benzoyl-L-Ser-OCH_3 as a colorless powder. Mp 69–70 °C. IR (KBr) υ (cm^{-1}) = 3450, 3341, 3026, 3005, 2960, 2830, 1632,

1601, 1570, 1500, 1451, 723, 665. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.105 (s, 1H), 7.900 (d, J = 7.61 Hz, 2H), 7.514 (d, J = 7.53 Hz, 1H), 7.427 (t, J = 7.44 Hz, 2H), 3.853 (m, J = 6.21 Hz, 1H), 3.736 (d, J = 6.21 Hz, 2H), 2.006 (s, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm) = 166.950, 133.552, 130.994, 128.578, 127.227, 65.110, 54.592. FAB-MS (*m*/*z*) 196 $[M+H]^+$. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N 7.18. Found: C, 61.32; H, 6.56; N 7.30.

4.1.18. (1*S*,2*R*)-*N*-[2-Hydroxy-1-(hydroxymethyl)propyl]benzoamide (3″b). Using the same procedure for the preparation of **3′a**, the title compound (197 mg, 94% yield) was obtained from 238 mg (1.0 mmol) of benzoyl-L-Thr-OCH_3 as a colorless powder. Mp 75–77 °C, IR (KBr) υ (cm^{-1}) = 3448, 3355, 3031, 3007, 2962, 2860, 1645, 1606, 1590, 1503, 1480, 710, 653. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.012 (s, 1H), 7.946 (d, J = 7.51 Hz, 2H), 7.509 (t, J = 7.82 Hz, 1H), 7.435 (t, J = 7.60 Hz, 2H), 4.009 (m, J = 6.01 Hz, 1H), 3.792 (d, J = 6.27 Hz, 2H), 3.743 (q, J = 6.60 Hz, 1H), 2.113 (s, 2H), 1.222 (d, J = 6.01 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.561, 133.423, 131.850, 128.602, 127.284, 68.119, 62.613, 59.212, 17.873. FAB-MS (*m*/*z*) 210 $[M+H]^+$. $[\alpha]_D^{20}$ − 30.0 (*c* 0.02, CH_3OH). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N 6.69. Found: C, 63.25; H, 7.41; N 6.52.

4.1.19. (1*S*)-*N*-[3-Hydroxy-1-(hydroxymethyl)propyl]benzamide (3″c). Using the same procedure for the preparation of **3′a**, the title compound (192 mg, 92% yield) was obtained from 238 mg (1.0 mmol) of benzoyl-L-Asp-$(OCH_3)_2$ as a colorless powder. Mp 80–81 °C. IR (KBr) υ (cm^{-1}) = 3413, 3340, 3021, 3008, 2960, 2830, 1631, 1600, 1582, 1502, 1460, 712, 654. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.008 (s, 1H), 7.942 (d, J = 7.52 Hz, 2H), 7.505 (t, J = 7.46 Hz, 1H), 7.438 (t, J = 7.24 Hz, 2H), 3.794 (t, J = 3.93 Hz, 2H), 3.670 (t, J = 3.98 Hz, 1H), 3.525 (t, J = 3.73 Hz, 2H), 1.762 (dt, J = 4.73 Hz, J = 2.75 Hz, 2H), 2.007 (s, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.101, 133.498, 131.882, 128.597, 127.220, 69.003, 57.881, 47.692, 35.291. FAB-MS (*m*/*z*) 210 $[M+H]^+$. $[\alpha]_D^{20}$ − 26.0 (*c* 0.02, CH_3OH). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N 6.69. Found: C, 63.01; H, 7.06; N 6.75.

4.1.20. (1*S*)-*N*-[4-Hydroxy-1-(hydroxymethyl)butyl]benzamide (3″d). Using the same procedure for the preparation of **3′a**, the title compound (201 mg, 90% yield) was obtained from 252 mg (1.0 mmol) of benzoyl-L-Glu-$(OCH_3)_2$ as a colorless powder. Mp 92–94 °C. IR (KBr) υ (cm^{-1}) = 3422, 3343, 3035, 3008, 2950, 2843, 1634, 1602, 1585, 1503, 1446, 725, 660. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.007 (s, 1H), 7.943 (d, J = 7.42 Hz, 2H), 7.505 (d, J = 7.62 Hz, 1H), 7.428 (t, J = 7.43 Hz, 2H), 3.783 (d, J = 4.55 Hz, 2H), 3.679 (m, J = 4.55 Hz, 1H), 3.540 (t, J = 4.12 Hz, 2H), 2.008 (s, 2H), 1.674 (m, J = 4.50 Hz, 2H), 1.601 (t, J = 4.50 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm) = 165.681, 133.489, 131.886, 128.591, 127.282, 69.005, 63.291, 51.676, 28.391, 28.088. FAB-MS (*m*/*z*) 224 $[M+H]^+$. $[\alpha]_D^{20}$ − 21.0 (*c* 0.02, CH_3OH). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N 6.27. Found: C, 64.37; H, 7.80; N 6.40.

4.1.21. (*cis*)- and (*trans*)-(2-Phenyl-1,3-dioxan-5-yl)benzamide (5a and 5′a). The suspension of 418 mg (2.0 mmol) of 2-benzoylacetamido-1,3-diol (**3″a**), 276 mg (2.6 mmol) of benzaldehyde, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous Na_2SO_4, 50 ml of chloroform, and 4 ml of THF was stirred at room temperature overnight until the complete disappearance of **3″a** indicated by TLC ($CHCl_3$/CH_3OH, 20:1). The reaction mixture was 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 166 mg (69%) of **5a** and 17 mg (7%) of **5′a**.

Compound **5a**. Colorless powder. Mp 133–135 °C. IR (KBr): υ (cm^{-1}) = 3235, 1637, 1600, 1582, 1499, 1446, 763, 697. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.896 (d, J = 7.66 Hz, 2H), 7.804 (s, 1H), 7.623 (d, J = 7.00 Hz, 2H), 7.526 (t, J = 7.66 Hz, 1H), 7.512 (t, J = 7.00 Hz, 1H), 7.464 (t, J = 7.66 Hz, 2H), 7.440 (t, J = 7.00 Hz, 2H), 5.597 (s, 1H), 4.253 (d, J = 11.00 Hz, 2H), 4.234 (d, J = 10.04 Hz, 2H), 2.814 (m, J = 10.03 Hz, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.724, 138.614, 134.233, 132.755, 129.867, 128.987, 128.734, 127.937, 126.323, 102.452, 73.967, 46.403. EI-MS (*m*/*e*): 283 $[M]^+$. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N 4.94. Found: C, 72.20; H, 6.13; N 5.06.

Compound **5′a**. Colorless powder. Mp 146–148 °C. IR (KBr): υ (cm^{-1}) = 3236, 1635, 1603, 1580, 1501, 1443, 765, 695. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.994 (d, J = 7.63 Hz, 2H), 7.833 (s, 1H), 7.651 (d, J = 7.06 Hz, 2H), 7.554 (t, J = 7.63 Hz, 1H), 7.561 (t, J = 7.04 Hz, 1H), 7.634 (t, J = 7.63 Hz, 2H), 7.602 (t, J = 7.04 Hz, 2H), 5.711 (s, 1H), 4.512 (d, J = 10.47 Hz, 2H), 4.450 (d, J = 9.57 Hz, 2H), 2.986 (m, J = 9.55 Hz, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.989, 138.920, 134.566, 133.011, 130.230, 129.314, 129.008, 128.122, 126.523, 102.624, 74.168, 47.033. EI-MS (*m*/*e*): 283 $[M]^+$. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N 4.94. Found: C, 72.16; H, 6.09; N 5.10.

4.1.22. (*cis*)- and (*trans*)-2-[4′-Methylphenyl]-1,3-dioxan-5-yl]benzamide (5b and 5′b). Using the same procedure for the preparation of **5a** and **5′a**, from 166 (0.85 mmol) of **3″a** and 102 mg (0.85 mmol) of 4-methylbenzaldehyde, 164 mg (65%) of **5b** and 20 mg (8%) of **5′b** were obtained.

Compound **5b**. Colorless powder. Mp 134–136 °C. IR (KBr): υ (cm^{-1}) = 3238, 1652, 1603, 1580, 1501, 1452, 1382, 822, 763, 695. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.964 (d, J = 7.55 Hz, 2H), 7.804 (s, 1H), 7.526 (t, J = 7.55 Hz, 1H), 7.453 (t, J = 7.55 Hz, 2H), 7.472 (d, J = 7.80 Hz, 2H), 7.248 (d,

J = 7.80 Hz, 2H), 5.611 (s, 1H), 4.251 (d, J = 4.42 Hz, 2H), 4.114 (d, J = 4.36 Hz, 2H), 2.975 (m, J = 4.43 Hz, 1H), 2.365 (s, 3H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.722, 136.601, 133.482, 132.101, 130.112, 128.593, 127.224, 126.870, 103.115, 74.136, 46.131, 22.071. EI-MS (*m/e*): 297 $[M]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N 4.71. Found: C, 72.83; H, 6.52; N 4.85.

Compound **5′b**. Colorless powder. Mp 146–148 °C. IR (KBr): υ (cm^{-1}) = 3242, 1651, 1602, 1581, 1502, 1454, 1381, 821, 761, 695. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.982 (d, J = 7.54 Hz, 2H), 7.831 (s, 1H), 7.548 (t, J = 7.54 Hz, 1H), 7.475 (t, J = 7.54 Hz, 2H), 7.503 (d, J = 7.82 Hz, 2H), 7.271 (d, J = 7.82 Hz, 2H), 5.635 (s, 1H), 4.276 (d, J = 4.43 Hz, 2H), 4.127 (d, J = 4.37 Hz, 2H), 2.998 (m, J = 4.43 Hz, 1H), 2.382 (s, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.121, 136.690, 133.520, 132.152, 130.320, 128.704, 127.430, 127.113, 103.368, 74.316, 46.321, 22.314. EI-MS (*m/e*): 297 $[M]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N 4.71. Found: C, 72.83; H, 6.52; N 4.85.

4.1.23. (*cis*)- and (*trans*)-2-[4′-Chlorophenyl]-1,3-dioxan-5-yl]benzamide (5c and 5′c). Using the same procedure for the preparation of **5a** and **5′a**, from 166 (0.85 mmol) of **3″a** and 119 mg (0.85 mmol) of 4-chlorobenzaldehyde, 189 mg (70%) of **5c** and 33 mg (12%) of **5′c** were obtained.

Compound **5c**. Colorless powder, mp 168–170 °C. IR (KBr): υ (cm^{-1}) = 3240, 3019, 1654, 1629, 1600, 1582, 1500, 1454, 820, 769, 698. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.984 (d, J = 7.56 Hz, 2H), 7.762 (s, 1H), 7.631 (t, J = 7.56 Hz, 1H), 7.516 (d, J = 7.12 Hz, 2H), 7.438 (t, J = 7.56 Hz, 2H), 7.290 (d, J = 7.12 Hz, 2H), 5.611 (s, 1H), 4.304 (d, J = 3.76 Hz, 2H), 4.152 (d, J = 6.43 Hz, 2H), 2.923 (s, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.352, 137.691, 135.497, 133.252, 132.438, 129.524, 128.761, 128.487, 127.347, 102.194, 74.451, 46.867. EI-MS (*m/e*): 317 $[M]^+$. Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N 4.41. Found: C, 64.40; H, 5.15; N 4.30.

Compound **5′c**. Colorless powder, mp 133–135 °C. IR (KBr): υ (cm^{-1}) = 3242, 3017, 1656, 1627, 1603, 1580, 1504, 1452, 822, 771, 699. ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.997 (d, J = 7.55 Hz, 2H), 7.783 (s, 1H), 7.662 (t, J = 7.55 Hz, 1H), 7.540 (d, J = 7.14 Hz, 2H), 7.462 (t, J = 7.55 Hz, 2H), 7.320 (d, J = 7.14 Hz, 2H), 5.668 (s, 1H), 4.331 (d, J = 3.79 Hz, 2H), 4.176 (d, J = 6.40 Hz, 2H), 2.953 (s, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.564, 137.718, 135.734, 133.533, 132.682, 129.668, 128.876, 128.749, 127.743, 102.496, 74.868, 47.225. EI-MS (*m/e*): 317 $[M]^+$. Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N 4.41. Found: C, 64.38; H, 5.21; N 4.27.

4.1.24. (*cis*)- and (*trans*)-2-[4′-Nitrophenyl]-1,3-dioxan-5-yl]benzamide (5d and 5′d). Using the same procedure for the preparation of **5a** and **5′a**, from 166 (0.85 mmol) of **3″a** and 128 mg (0.85 mmol) of 4-nitrobenzaldehyde, 195 mg (70%) of **5d** and 28 mg (10%) of **5′d** were obtained.

Compound **5d**. Colorless powder, mp 220–224 °C. IR (KBr): υ (cm^{-1}) = 3278, 3015, 2920, 2860, 1656, 1620, 1605, 1580, 1525, 1450, 1352, 1192, 1070, 800, 719, 690. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.249 (d, J = 8.72 Hz, 2H), 7.869 (t, J = 6.9o Hz, 2H), 7.752 (d, J = 8.72 Hz, 2H), 7.557 (t, J = 6.64 Hz, 1H), 7.482 (t, J = 6.64 Hz, 2H), 7.110 (s, 1H), 5.667 (s, 1H), 4.310 (d, J = 7.01 Hz, 2H), 4.249 (d, J = 7.01 Hz, 2H), 3.679 (m, J = 6.88 Hz, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 170.547, 147.440, 143.302, 135.223, 129.784, 128.684, 128.500, 127.392, 123.424, 106.330, 73.906, 51.889. EI-MS (*m/e*) 328 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.30; H, 5.01; N, 8.48.

Compound **5′d**. Colorless powder, mp 120–122 °C. IR (KBr): υ (cm^{-1}) = 3275, 3020, 2905, 2858, 1649, 1625, 1600, 1590, 1528, 1435, 1354, 1188, 1075, 719, 690. ^{1}H NMR (DMSO-d_6) δ (ppm) = 8.258 (d, J = 9.3 Hz, 2H), 7.818 (d, J = 6.9 Hz, 2H), 7.694 (d, J = 9.0 Hz, 2H), 7.507 (t, J = 8.1 Hz, 1H), 7.458 (t, J = 7.5 Hz, 2H), 7.085 (s, 1H), 5.712 (s, 1H), 4.318 (t, J = 7.1 Hz, 2H), 4.262 (d, J = 7.2 Hz, 2H), 3.692 (t, J = 7.6 Hz, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = =40.101, 51.901, 73.954, 106.441, 123.004, 127.112, 128.440, 128.796, 129.112, 135.003, 143.101, 147.105, 170.120. EI-MS (*m/e*) 328 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.05; H, 4.79; N, 8.70.

4.1.25. (*cis*)- and (*trans*)-2-[3′-Nitrophenyl]-1,3-dioxan-5-yl]benzamide (5e and 5′e). Using the same procedure for the preparation of **5a** and **5′a**, from 166 mg (0.85 mmol) of **3″a** and 128 mg (0.85 mmol) of 3′-nitrobenzaldehyde, 195 mg (69%) of **5e** and 28 mg (10%) of **5′e** were obtained.

Compound **5e**. Mp 144–146 °C. IR (KBr): υ (cm^{-1}) = 3280, 3019, 2922, 2864, 1658, 1622, 1600, 1582, 1522, 1450, 1350, 1192, 1070, 860, 769, 742, 698. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.303 (s, 1H), 8.292 (d, J = 9.01 Hz, 1H), 8.011 (d, J = 7.53 Hz, 2H), 7.796 (s, 1H), 7.790 (d, J = 9.01 Hz, 1H), 7.626 (t, J = 7.53 Hz, 1H), 7.562 (t, J = 9.01 Hz, 1H), 7.531 (t, J = 7.53 Hz, 2H), 5.681 (s, 1H), 4.304 (d, J = 6.55 Hz, 2H), 4.220 (d, J = 6.34 Hz, 2H), 3.625 (m, J = 6.33 Hz, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR

(DMSO-d_6): δ (ppm) = 168.921, 148.964, 145.550, 133.435, 131.207, 128.684, 128.024, 127.241, 124.306, 101.124, 74.413, 46.323. EI-MS (*m/e*) 328 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.11; H, 4.80; N, 8.44.

Compound **5′e**. Mp 130–132 °C. IR (KBr): υ (cm^{-1}) = 3282, 3017, 2920, 2866, 1655, 1620, 1603, 1580, 1524, 1451, 1352, 1194, 1072, 861, 767, 745, 696. ^1H NMR ($CDCl_3$) δ (ppm) = 8.326 (s, 1H), 8.315 (d, J = 9.03 Hz, 1H), 8.046 (d, J = 7.55 Hz, 2H), 7.818 (s, 1H), 7.805 (d, J = 9.03 Hz, 1H), 7.647 (t, J = 7.55 Hz, 1H), 7.585 (t, J = 9.03 Hz, 1H), 7.553 (t, J = 7.55 Hz, 2H), 5.704 (s, 1H), 4.328 (d, J = 6.57 Hz, 2H), 4.251 (d, J = 6.36 Hz, 2H), 3.651 (m, J = 6.35 Hz, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.503, 149.536, 145.672, 133.864, 131.722, 129.006, 128.753, 127.823, 124.766, 101.843, 75.036, 46.975. EI-MS (*m/e*) 328 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.11; H, 4.80; N, 8.44.

4.1.26. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-(2-Phenyl-4-methyl-1,3-dioxan-5-yl)benzamide (5f and 5′f). Using the same procedure for the preparation of **5a** and **5′a**, from 100 mg (0.48 mmol) of **3″b** and 51 mg (0.85 mmol) of benzaldehyde, 98 mg (69%) of **5f** and 11 mg (8%) of **5′f** were obtained.

Compound **5f**. Colorless powder. Mp 125–127 °C. IR (KBr): υ (cm^{-1}) = 3285, 3013, 2925, 2864, 1652, 1622, 1601, 1582, 1382, 1192, 1070, 821. ^1H NMR ($CDCl_3$) δ (ppm) = 8.014 (s, 1H), 7.943 (d, J = 7.55 Hz, 2H), 7.660 (t, J = 7.55 Hz, 1H), 7.578 (t, J = 7.55 Hz, 2H), 7.572 (d, J = 6.72 Hz, 2H), 7.430 (t, J = 6.68 Hz, 1H), 7.396 (t, J = 6.67 Hz, 2H), 5.573 (s, 1H), 4.281 (m, J = 6.61 Hz, 1H), 4.220 (d, J = 4.52 Hz, 2H), 2.687 (t, J = 4.52 Hz, 1H), 1.337 (d, J = 4.50 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.546, 137.153, 133.517, 132.106, 128.757, 128.523, 127.472, 127.259, 126.865, 102.560, 74.868, 58.764, 18.611. EI-MS (*m/e*) 295 $[M]^+$. $[\alpha]_D^{20}$ − 13.5 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.53; H, 6.30; N, 4.90.

Compound **5′f**. Colorless powder. Mp 133–135 °C. IR (KBr): υ (cm^{-1}) = 3283, 3011, 2927, 2862, 1650, 1620, 1603, 1580, 1381, 1190, 1072, 824. ^1H NMR ($CDCl_3$) δ (ppm) = 8.232 (s, 1H), 8.024 (d, J = 7.60 Hz, 2H), 7.769 (t, J = 7.60 Hz, 1H), 7.728 (t, J = 7.60 Hz, 2H), 7.680 (d, J = 7.00 Hz, 2H), 7.593 (t, J = 7.00 Hz, 1H), 7.516 (t, J = 7.00 Hz, 2H), 5.734 (s, 1H), 4.441 (m, J = 6.70 Hz, 1H), 4.361 (d, J = 4.60 Hz, 2H), 2.867 (t, J = 4.60 Hz, 1H), 1.473 (d, J = 4.60 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.151, 137.936, 134.172, 132.915, 129.567, 129.223, 128.117, 127.961, 127.546, 103.156, 75.286, 59.431, 19.161. EI-MS (*m/e*) 295 $[M]^+$. $[\alpha]_D^{20}$ 14.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.89; H, 6.57; N, 4.52.

4.1.27. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Methylphenyl)-4-methyl-1,3-dioxan-5-yl]benzamide (5g and 5′g). Using the same procedure for the preparation of **5a** and **5′a**, from 100 mg (0.48 mmol) of **3″b** and 102 mg (0.85 mmol) of 4-methylbenzaldehyde, 96 mg (65%) of **5g** and 11 mg (7%) of **5′g** were obtained.

Compound **5g**. Colorless powder. Mp 152–154 °C. IR (KBr): υ (cm^{-1}) = 3278, 3022, 2902, 2856, 1645, 1622, 1602, 1593, 1436, 1384, 1186, 1072, 822, 739, 696. ^1H NMR ($CDCl_3$) δ (ppm) = 8.014 (s, 1H), 7.969 (d, J = 7.46 Hz, 2H), 7.540 (t, J = 7.46 Hz, 1H), 7.472 (d, J = 7.40 Hz, 2H), 7.435 (t, J = 7.46 Hz, 2H), 7.258 (d, J = 7.40 Hz, 2H), 5.612 (s, 1H), 4.240 (d, J = 4.50 Hz, 1H), 4.207 (d, J = 4.26 Hz, 1H), 4.138 (m, J = 6.00 Hz, 1H), 2.710 (m, J = 4.26 Hz, 1H), 2.403 (s, 3H), 1.313 (d, J = 6.00 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.147, 138.656, 135.466, 135.160, 134.132, 129.403, 129.004, 128.914, 127.912, 102.783, 76.867, 75.112, 50.224, 22.121, 18.659. EI-MS (*m/e*) 309 $[M]^+$. $[\alpha]_D^{20}$ − 14.2 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.47; H, 6.93; N, 4.32.

Compound **5′g**. Colorless powder. Mp 144–146 °C. IR (KBr): υ (cm^{-1}) = 3276, 3021, 2900, 2857, 1648, 1620, 1600, 1595, 1434, 1381, 1185, 1070, 820, 737, 698. ^1H NMR ($CDCl_3$) δ (ppm) = 8.124 (s, 1H), 8.010 (d, J = 7.52 Hz, 2H), 7.644 (t, J = 7.52 Hz, 1H), 7.621 (d, J = 7.50 Hz, 2H), 7.538 (t, J = 7.50 Hz, 2H), 7.412 (d, J = 7.50 Hz, 2H), 5.733 (s, 1H), 4.420 (d, J = 4.53 Hz, 1H), 4.318 (d, J = 4.30 Hz, 1H), 4.245 (m, J = 6.02 Hz, 1H), 2.844 (m, J = 4.30 Hz, 1H), 2.516 (s, 3H), 1.422 (d, J = 6.02 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.714, 139.121, 136.003, 135.542, 134.473, 129.922, 129.436, 129.114, 128.123, 103.535, 77.275, 75.536, 50.617, 22.685, 19.267. EI-MS (*m/e*) 309 $[M]^+$. $[\alpha]_D^{20}$ 12.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.11; H, 6.64; N, 4.68.

4.1.28. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Chlorophenyl)-4-methyl-1,3-dioxan-5-yl]benzamide (5h and 5′h). Using the same procedure for the preparation of **5a** and **5′a** from 100 mg (0.48 mmol) of **3″b** and 102 mg (0.85 mmol) of 4-chlorobenzaldehyde, 126 mg (85%) of **5h** and 22 mg (15%) of **5′h** were obtained.

Compound **5h**. Colorless powder. Mp 125–127 °C. IR (KBr): υ (cm^{-1}) = 3242, 3017, 1656, 1627, 1602, 1580, 1502, 1456, 823, 767, 699. ^1H NMR ($CDCl_3$) δ (ppm) = 8.104 (d, J = 7.46 Hz, 2H), 8.003 (s, 1H), 7.662 (t, J = 7.46 Hz, 1H), 7.501 (t, J = 7.46 Hz, 2H), 7.435 (t, J = 7.60 Hz, 2H), 7.414 (t, J = 7.60 Hz, 2H), 5.634 (s, 1H), 4.235 (m, J = 6.61 Hz, 1H), 4.217 (d, J = 5.44 Hz, 2H), 2.752 (m, J = 4.62 Hz, 1H), 1.371 (d, J = 6.61 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the

4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.367, 137.876, 135.223, 135.138, 133.114, 132.403, 129.664, 128.700, 127.488, 102.136, 77.103, 74.615, 50.155, 18.347. EI-MS (*m/e*) 330 $[M]^+$. $[\alpha]_D^{20}$ − 13.1 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.00; H, 5.61; N, 4.04.

Compound **5′h**. Colorless powder. Mp 120–122 °C. IR (KBr): υ (cm^{-1}) = 3240, 3015, 1655, 1625, 1600, 1582, 1505, 1454, 821, 768, 697. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.198 (d, *J* = 7.48 Hz, 2H), 8.114 (s, 1H), 7.826 (t, *J* = 7.48 Hz, 1H), 7.595 (t, *J* = 7.48 Hz, 2H), 7.566 (t, *J* = 7.62 Hz, 2H), 7.523 (t, *J* = 7.62 Hz, 2H), 5.810 (s, 1H), 4.456 (m, *J* = 6.60 Hz, 1H), 4.373 (d, *J* = 5.46 Hz, 2H), 2.912 (m, *J* = 4.64 Hz, 1H), 1.450 (d, *J* = 6.60 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.763, 138.165, 135.721, 135.524, 133.642, 132.933, 130.465, 129.535, 127.896, 102.643, 77.634, 75.155, 51.515, 19.432. EI-MS (*m/e*) 330 $[M]^+$. $[\alpha]_D^{20}$ 10.9 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.34; H, 5.59; N, 4.39.

4.1.29. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]benzamide (5i and 5′i). Using the same procedure for the preparation of **5a** and **5′a**, from 100 mg (0.48 mmol) of **3″b** and 73 mg (0.85 mmol) of 4-nitrobenzaldehyde, 139 mg (85%) of **5i** and 20 mg (12%) of **5′i** were obtained.

Compound **5i**. Colorless powder, mp 90–92 °C. IR (KBr): υ (cm^{-1}) = 3450, 3045, 2975, 2940, 2970, 1655, 1600, 1576, 1520, 1480, 1400, 1370, 1176, 1070, 741, 694. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.243 (d, *J* = 8.40 Hz, 2H), 7.939 (s, 1H), 7.848 (d, *J* = 7.40 Hz, 2H), 7.685 (t, *J* = 7.40 Hz, 1H), 7.486 (d, *J* = 8.40 Hz, 2H), 7.435 (t, *J* = 7.40 Hz, 2H), 5.787 (s, 1H), 4.639 (m, *J* = 3.94 Hz, 1H), 4.124 (d, *J* = 3.95 Hz, 2H), 3.697 (m, *J* = 4.02 Hz, 1H), 1.332 (d, *J* = 6.22 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 167.595, 147.511, 143.330, 133.484, 131.807, 128.669, 128.474, 127.344, 123.433, 103.212, 73.355, 56.898, 19.023. $[\alpha]_D^{20}$ − 15.4 (*c* 0.02, $CHCl_3$). EI-MS (*m/e*) 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.04; H, 5.23; N, 8.31.

Compound **5′i**. Colorless powder, mp 112–114 °C. IR (KBr): υ (cm^{-1}) = 3446, 3034, 2980, 2950, 2860, 1655, 1607, 1580, 1525, 1520, 1482, 1406, 1376, 1180, 1068, 790, 745, 690. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.295 (d, *J* = 8.52 Hz, 2H), 8.014 (s, 1H), 7.856 (t, *J* = 7.31 Hz, 2H), 7.695 (d, *J* = 8.52 Hz, 2H), 7.525 (t, *J* = 7.31 Hz, 1H), 7.481 (t, *J* = 7.31 Hz, 2H), 6.151 (s, 1H), 4.460 (m, *J* = 3.62 Hz, 1H), 4.260 (d, *J* = 2.75 Hz, 2H), 3.934 (m, *J* = 6.35 Hz, 1H), 1.368 (d, *J* = 6.3 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.114, 147.603, 143.514, 133.506, 132.002, 128.876, 128.555, 127.801, 123.565, 103.402, 73.581, 57.156, 19.226. $[\alpha]_D^{20}$ 28.5 (*c* 0.02, $CHCl_3$). EI-MS (*m/e*) 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.21; H, 5.41; N, 8.09.

4.1.30. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(3′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]benzamide (5j and 5′j). Using the same procedure for the preparation of **5a** and **5′a**, from 100 mg (0.48 mmol) of **3″b** and 73 mg (0.85 mmol) of 3-nitrobenzaldehyde, 137 mg (84%) of **5j** and 18 mg (11%) of **5′j** were obtained.

Compound **5j**. Colorless powder. Mp 140–142 °C. IR (KBr): υ (cm^{-1}) = 3281, 3017, 2925, 2862, 1656, 1620, 1602, 1580, 1525, 1453, 1381, 1352, 1190, 1071, 862, 767, 745, 699. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.281 (d, *J* = 8.40 Hz, 1H), 8.031 (s, 1H), 8.004 (s, 1H), 7.958 (d, *J* = 7.52 Hz, 2H), 7.914 (d, *J* = 7.86 Hz, 1H), 7.672 (t, *J* = 8.00 Hz, 1H), 7.543 (t, *J* = 7.52 Hz, 1H), 7.461 (t, *J* = 7.52 Hz, 2H), 5.713 (s, 1H), 4.235 (m, *J* = 4.32 Hz, 1H), 4.217 (d, *J* = 2.76 Hz, 2H), 2.744 (m, *J* = 3.14 Hz, 1H), 1.397 (d, *J* = 4.67 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.334, 149.271, 141.204, 133.652, 133.372, 132.151, 130.522, 128.773, 127.346, 124.827, 122.814, 100.178, 77.513, 75.276, 49.912, 18.864. EI-MS (*m/e*) 342 $[M]^+$. $[\alpha]_D^{20}$ − 14.9 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.27; H, 5.41; N, 8.27.

Compound **5′j**. Colorless powder. Mp 130–132 °C. IR (KBr): υ (cm^{-1}) = 3283, 3016, 2924, 2864, 1653, 1622, 1600, 1585, 1526, 1450, 1383, 1354, 1192, 1072, 863, 765, 747, 697. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.370 (d, *J* = 8.36 Hz, 1H), 8.133 (s, 1H), 8.012 (s, 1H), 7.987 (d, *J* = 7.50 Hz, 2H), 7.967 (d, *J* = 7.82 Hz, 1H), 7.782 (t, *J* = 7.92 Hz, 1H), 7.634 (t, *J* = 7.50 Hz, 1H), 7.516 (t, *J* = 7.50 Hz, 2H), 5.831 (s, 1H), 4.354 (m, *J* = 4.34 Hz, 1H), 4.318 (d, *J* = 2.78 Hz, 2H), 2.802 (m, *J* = 3.16 Hz, 1H), 1.415 (d, *J* = 4.65 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.878, 149.712, 141.625, 134.126, 133.743, 132.516, 131.121, 129.367, 127.863, 125.278, 123.418, 100.875, 78.135, 75.764, 50.988, 19.685. EI-MS (*m/e*) 342 $[M]^+$. $[\alpha]_D^{20}$ 12.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.05; H, 5.24; N, 8.06.

4.1.31. (*cis*)- and (*trans*)-(2-Phenyl-1,3-dioxan-5-yl)phenylacetamide (6a and 6′a). The suspension of 418 mg (2.0 mmol) of 2-phenylacetylaminopropane-1,3-diol(**3′a**), 276 mg (2.6 mmol) of benzaldehyde, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous Na_2SO_4, 50 ml of chloroform, and 4 ml of THF was stirred at room temperature overnight until the complete disappearance of **3″a** indicated by TLC ($CHCl_3$/CH_3OH, 20:1). The reaction mixture was 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 268 mg (45%) of **6a** and 48 mg (8%) of **6′a**.

Compound **6a**. Colorless powder, mp 150–152 °C. IR (KBr): υ (cm^{-1}) = 3239, 1631, 1602, 1581, 1498, 1449, 761,699. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.001 (s, 1H), 7.232 (d, J = 7.52 Hz, 2H), 7.221 (t, J = 7.47 Hz, 1H), 7.189 (t, J = 7.52 Hz, 2H), 7.171 (t, J = 7.37 Hz, 2H), 7.103 (t, J = 7.39 Hz, 1H), 7.083 (d, J = 7.37 Hz, 2H), 5.898 (s, 1H,), 4.070 (d, J = 4.41 Hz, 4H), 3.770 (d, J = 4.41 Hz, 1H), 3.644 (s, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.626, 136.967, 135.850, 129.841, 129.111, 128.393, 127.690, 127.644, 127.384, 105.978, 73.889, 51.867, 40.089. EI-MS (*m*/*e*): 297 $[M]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N 4.71. Found: C, 72.57; H, 6.58; N 4.75.

Compound **6′a**. Colorless powder, mp 194–195 °C. IR (KBr): υ (cm^{-1}) = 3237, 1651, 1603, 1581, 1500, 1452, 761, 699. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.004 (s, 1H), 7.302 (d, J = 7.54 Hz, 2H), 7.225 (t, J = 7.49 Hz, 1H), 7.192 (t, J = 7.54 Hz, 2H), 7.176 (t, J = 7.40 Hz, 2H), 7.110 (t, J = 7.41 Hz, 1H), 7.088 (d, J = 7.39 Hz, 2H), 5.902 (s, 1H,), 4.075 (d, J = 4.43 Hz, 4H), 3.774 (d, J = 4.43 Hz, 1H), 3.648 (s, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.932, 137.079, 136.165, 130.221, 129.323, 128.681, 127.897, 127.718, 127.431, 106.124, 74.132, 52.213, 40.304. EI-MS (*m*/*e*): 297 $[M]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N 4.71. Found: C, 72.87; H, 6.54; N 4.83.

4.1.32. (*cis*)- and (*trans*)-[2-(4′-Methylphenyl)-1,3-dioxan-5-yl]phenylacetamide (6b and 6′b). Using the same procedure for the preparation of **6a** and **6′a**, starting from 312 mg (2.6 mmol) of 4-methylbenzaldehyde, 261 mg (42%) of **6b** and 44 mg (7%) of **6′b** were obtained.

Compound **6b**. Colorless powder, mp 185–187 °C. IR (KBr): υ (cm^{-1}) = 3240, 1650, 1601, 1583, 1505, 1450, 1380, 820, 761,699. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) = 8.073 (s, 1H), 7.373 (d, J = 8.01 Hz, 2H), 7.281 (t, J = 7.81 Hz, 2H), 7.183 (d, J = 8.01 Hz, 2H), 7.081 (t, J = 7.81 Hz, 1H), 7.065 (t, J = 7.81 Hz, 2H), 5.981 (s, 1H), 4.108 (d, J = 11.05 Hz, 4H), 3.953 (d, J = 11.05 Hz, 1H), 3.572 (s, 2H), 2.314 (s, 3H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.564, 136.785, 135.901, 134.117, 129.794, 129.092, 128.976, 127.530, 127.407, 106.641, 73.882, 51.903, 40.080. EI-MS (*m*/*e*): 311 $[M]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N 4.50. Found: C, 73.15; H, 6.66; N 4.39.

Compound **6′b**. Colorless powder, mp 181–183 °C. IR (KBr):υ (cm^{-1}) = 3242, 1651, 1600, 1580, 1502, 1451, 1382, 822, 760, 695. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) = 8.203 (s, 1H), 7.376 (d, J = 8.12 Hz, 2H), 7.287 (t, J = 7.83 Hz, 2H), 7.188 (d, J = 8.12 Hz, 2H), 7.086 (t, J = 7.83 Hz, 1H), 7.069 (t, J = 7.83 Hz, 2H), 5.985 (s, 1H), 4.114 (d, J = 11.10 Hz, 4H), 3.960 (d, J = 11.10 Hz, 1H), 3.581 (s, 2H), 2.322 (s, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6) δ (ppm) = 167.737, 137.012, 136.021, 134.137, 129.820, 129.150, 129.027, 127.626, 127.415, 106.747, 74.631, 52.007, 40.100. EI-MS (*m*/*e*): 311 $[M]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N 4.50. Found: C, 73.37; H, 6.92; N 4.68.

4.1.33. (*cis*)- and (*trans*)-[2-(4′-Chlorophenyl)-1,3-dioxan-5-yl]phenylacetamide (6c and 6′c). Using the same procedure for the preparation of **6a** and **6′a**, from 365 mg (2.6 mmol) of 4-chlorobenzaldehyde, 331 mg (50%) of **6c** and 66 mg (10%) of **6′c** were obtained.

Compound **6c**. Colorless powder, mp 170–172 °C. IR (KBr): υ (cm^{-1}) = 3245, 3062, 1631, 1551, 1494,14571092, 829,705, 749. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.003 (s, 1H), 7.351 (d, J = 7.31 Hz, 2H), 7.153 (d, J = 7.22 Hz, 2H), 7.124 (d, J = 7.31 Hz, 2H), 7.071 (d, J = 7.22 Hz, 1H), 7.063 (d, J = 7.22 Hz, 2H), 5.457 (s, 1H), 4.061 (d, J = 4.61 Hz, 4H), 3.779 (m, J = 4.61 Hz, 1H), 3.449 (s, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 167.568, 135.879, 135.296, 132.897, 129.786, 129.203, 129.024, 128.792, 127.385, 105.994, 73.878, 51.882, 40.123. EI-MS (*m*/*e*): 345 $[M]^+$. Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N 4.05. Found: C, 66.17; H, 5.96; N 3.88.

Compound **6′c**. Colorless powder, mp 256–258 °C. IR (KBr): υ (cm^{-1}) = 3275, 3062, 1647, 1543, 1494, 1455, 1099, 814, 766,705. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.113 (s, 1H), 7.430 (d, J = 7.31 Hz, 2H), 7.381 (d, J = 7.22 Hz, 2H), 7.312 (d, J = 7.31 Hz, 2H), 7.285 (d, J = 7.22 Hz, 1H), 7.270 (d, J = 7.22 Hz, 2H), 5.489 (s, 1H), 4.121 (d, J = 4.61 Hz, 4H), 3.620 (m, J = 4.61 Hz, 1H), 3.369 (s, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 167.730, 136.357, 135.631, 133.112, 130.124, 129.657, 129.586, 129.132, 127.771, 106.021, 74.105, 52.044, 40.346. EI-MS (*m*/*e*): 345 $[M]^+$. Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N 4.05. Found: C, 65.80; H, 5.71; N 3.89.

4.1.34. (*cis*)- and (*trans*)-2-[4′-Nitrophenyl]-1,3-dioxan-5-yl]phenylacetamide (6d and 6′d). Using the same procedure for the preparation of **6a** and **6′a**, from 302 mg (2.0 mmol) of 4-nitrobenzaldehyde, 321 mg (47%) of **6d** and 58 mg (8%) of **6′d** were obtained.

Compound **6d**. Colorless powder, mp 201–203 °C. IR (KBr) 3266, 3018, 2917, 2854, 1659, 1617, 1602, 1575, 1543, 1457, 1191, 1065, 802, 724, 693 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm) = 8.123 (d, J = 9.21 Hz, 2H), 7.956 (s, 1H), 7.486 (t, J = 9.21 Hz, 2H), 7.142 (t, J = 6.91 Hz, 2H), 7.105 (t, J = 6.91 Hz, 1H), 7.057 (t, J = 6.91 Hz, 2H), 5.816 (s, 1H), 4.027 (d, J = 5.31 Hz, 4H), 3.768 (t, J = 5.37 Hz, 1H), 3.385 (s, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ

(ppm) = 167.541, 147.304, 142.982, 135.874, 129.784, 128.889, 128.422, 127.215, 105.813, 73.728, 51.869, 40.088. EI-MS (*m/e*): 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N 8.18. Found: C, 63.27; H, 5.41; N 8.07.

Compound **6′d**. Colorless powder, mp 107–109 °C. IR (KBr) 3271, 3023, 2920, 2856, 1654, 1622, 1558, 1546, 1542, 1437, 1186, 1071, 798, 715, 691 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm) = 8.126 (d, J = 9.32 Hz, 2H), 7.959 (s, 1H), 7.490 (t, J = 9.32 Hz, 2H), 7.149 (t, J = 6.95 Hz, 2H), 7.111 (t, J = 6.95 Hz, 1H), 7.063 (t, J = 6.95 Hz, 2H), 5.822 (s, 1H), 4.033 (d, J = 5.25 Hz, 4H), 3.791 (t, J = 5.27 Hz, 1H), 3.391 (s, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 167.721, 147.661, 143.143, 136.252, 130.004, 128.949, 128.615, 127.333, 106.036, 74.024, 52.362, 40.237. EI-MS (*m/e*): 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N 8.18. Found: C, 63.02; H, 5.18; N 8.32.

4.1.35. (*cis*)- and (*trans*)-2-[3′-Nitrophenyl]-1,3-dioxan-5-yl]phenylacetamide (6e and 6′e). Using the same procedure for the preparation of **6a** and **6′a**, from 302 mg (2.0 mmol) of 3-nitrobenzaldehyde, 195 mg (45%) of **6e** and 28 mg (8%) of **6′e** were obtained.

Compound **6e**. Mp 128–132 °C. IR (KBr) υ (cm^{-1}) = 3270, 3025, 2922, 2853, 1651, 1620, 1554, 1543, 1540, 1435, 1182, 1070, 860, 780, 715, 700, 691. ^1H NMR ($CDCl_3$) δ (ppm) = 8.360 (s, 1H), 8.611 (d, J = 9.00 Hz, 1H), 8.404 (d, J = 7.55 Hz, 2H), 8.216 (s, 1H), 7.928 (d, J = 9.00 Hz, 1H), 7.862 (t, J = 7.55 Hz, 1H), 7.764 (t, J = 9.00 Hz, 1H), 7.739 (t, J = 7.55 Hz, 2H), 5.818 (s, 1H), 4.740 (d, J = 6.58 Hz, 2H), 4.602 (d, J = 6.36 Hz, 2H), 3.952 (m, J = 6.35 Hz, 1H), 3.402 (s, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.812, 149.787, 146.605, 134.542, 132.323, 129.845, 128.943, 128.144, 125.363, 102.241, 75.530, 47.406, 40.138. EI-MS (*m/e*): 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N 8.18. Found: C, 63.22; H, 5.39; N 8.07.

Compound **6′e**. Mp 141–143 °C. IR (KBr) υ (cm^{-1}) = 3273, 3027, 2920, 2855, 1650, 1624, 1550, 1546, 1540, 1433, 1180, 1072, 862, 783, 712, 703, 690. ^1H NMR ($CDCl_3$) δ (ppm) = 8.460 (s, 1H), 8.702 (d, J = 9.00 Hz, 1H), 8.450 (d, J = 7.50 Hz, 2H), 8.304 (s, 1H), 7.985 (d, J = 9.00 Hz, 1H), 7.941 (t, J = 7.50 Hz, 1H), 7.856 (t, J = 9.00 Hz, 1H), 7.823 (t, J = 7.50 Hz, 2H), 5.920 (s, 1H), 4.882 (d, J = 6.55 Hz, 2H), 4.643 (d, J = 6.34 Hz, 2H), 3.967 (m, J = 6.33 Hz, 1H), 3.440 (s, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.933, 149.864, 146.927, 134.747, 132.651, 130.160, 129.351, 128.730, 125.646, 102.448, 75.967, 47.568, 40.561. EI-MS (*m/e*): 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N 8.18. Found: C, 63.22; H, 5.41; N 8.07.

4.1.36. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-(2-Phenyl-4-methyl-1,3-dioxan-5-yl)phenyl-acetamide (6f and 6′f). Using the same procedure for the preparation of **6a** and **6′a**, from 448 mg (2.0 mmol) of **3′b** and 212 mg (0.85 mmol) of benzaldehyde, 218 mg (35%) of **6f** and 37 mg (6%) of **6′f** were obtained.

Compound **6f**. Colorless powder. IR (KBr) υ (cm^{-1}) = 3273, 3030,, 1653, 1622, 1550, 1545, 1541, 1430, 1382, 1066, 739, 696. Mp 144–146 °C. ^1H NMR ($CDCl_3$) δ (ppm) = 8.123 (s, 1H), 8.343 (d, J = 7.56 Hz, 2H), 7.925 (t, J = 7.56 Hz, 1H), 7.856 (t, J = 7.56 Hz, 2H), 7.768 (d, J = 6.70 Hz, 2H), 7.685 (t, J = 6.66 Hz, 1H), 7.598 (t, J = 6.66 Hz, 2H), 5.936 (s, 1H), 4.726 (m, J = 6.64 Hz, 1H), 4.603 (d, J = 4.54 Hz, 2H), 3.392 (s, 2H), 2.989 (t, J = 4.54 Hz, 1H), 1.574 (d, J = 4.50 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.645, 138.351, 134.176, 133.363, 129.574, 129.328, 128.731, 128.196, 127.659, 103.607, 75.966, 59.653, 40.214, 19.540. EI-MS (*m/e*) 311 $[M]^+$. $[\alpha]_D^{20}$ − 14.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.40; H, 6.69; N, 4.64.

Compound **6′f**. Colorless powder. IR (KBr) υ (cm^{-1}) = 3274, 3032,, 1655, 1620, 1552, 1546, 1540, 1432, 1380, 1064, 735, 693. Mp 156–158 °C. ^1H NMR ($CDCl_3$) δ (ppm) = 8.350 (s, 1H), 8.401 (d, J = 7.62 Hz, 2H), 7.964 (t, J = 7.62 Hz, 1H), 7.924 (t, J = 7.62 Hz, 2H), 7.882 (d, J = 7.02 Hz, 2H), 7.759 (t, J = 7.02 Hz, 1H), 7.718 (t, J = 7.02 Hz, 2H), 5.964 (s, 1H), 4.746 (m, J = 6.72 Hz, 1H), 4.675 (d, J = 4.62 Hz, 2H), 3.406 (s, 2H), 3.008 (t, J = 4.62 Hz, 1H), 1.638 (d, J = 4.62 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 170.050, 138.954, 135.218, 133.862, 130.246, 129.876, 129.535, 128.627, 128.152, 103.755, 76.168, 60.134, 40.567, 19.784. EI-MS (*m/e*) 311 $[M]^+$. $[\alpha]_D^{20}$ 12.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.17; H, 6.89; N, 4.61.

4.1.37. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Methylphenyl)-4-methyl-1,3-dioxan-5-yl]phenyl-acetamide (6g and 6′g). Using the same procedure for the preparation of **6a** and **6′a** from 448 mg (2.0 mmol) of **3′b** and 240 mg (2.0 mmol) of 4-methylbenzaldehyde, 208 mg (32%) of **6g** and 33 mg (5%) of **6′g** were obtained.

Compound **6g**. Colorless powder. Mp 159–161 °C. IR (KBr) υ (cm^{-1}) = 3271, 3032, 1650, 1621, 1552, 1543, 1540, 1432, 1385, 1064, 820, 738, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 8.302 (s, 1H), 8.154 (d, J = 7.44 Hz, 2H), 7.891 (t, J = 7.44 Hz, 1H), 7.778 (d, J = 7.42 Hz, 2H), 7.717 (t, J = 7.44 Hz, 2H), 7.681 (d, J = 7.42 Hz, 2H), 5.864 (s, 1H), 4.631 (d, J = 4.52 Hz, 1H), 4.426 (d, J = 4.28 Hz, 1H), 4.386 (m, J = 5.84 Hz, 1H), 3.434 (s, 2H), 2.996 (m, J = 4.28 Hz, 1H), 2.567 (s, 3H), 1.502 (d, J = 5.84 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR

(DMSO-d_6): δ (ppm) = 169.274, 139.523, 136.412, 135.908, 135.122, 130.310, 129.849, 129.635, 128.825, 103.694, 77.759, 76.122, 51.341, 40.483, 23.812, 19.502. EI-MS (*m*/*e*) 325 $[M]^+$. $[\alpha]_D^{20}$ −13.6 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.74; H, 7.01; N, 4.18.

Compound **6′g**. Colorless powder. Mp 125–127 °C. IR (KBr) υ (cm^{-1}) = 3272, 3028,, 1654, 1620, 1552, 1546, 1543, 1431, 1380, 1068, 821, 737, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 8.344 (s, 1H), 8.179 (d, *J* = 7.50 Hz, 2H), 7.962 (t, *J* = 7.50 Hz, 1H), 7.868 (d, *J* = 7.52 Hz, 2H), 7.757 (t, *J* = 7.52 Hz, 2H), 7.708 (d, *J* = 7.52 Hz, 2H), 5.902 (s, 1H), 4.664 (d, *J* = 4.55 Hz, 1H), 4.601 (d, *J* = 4.34 Hz, 1H), 4.517 (m, *J* = 6.00 Hz, 1H), 3.505 (s, 2H), 3.014 (m, *J* = 4.32 Hz, 1H), 2.630 (s, 3H), 1.604 (d, *J* = 6.00 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.740, 139.880, 136.912, 136.341, 135.720, 130.843, 130.265, 130.772, 129.100, 104.213, 77.968, 76.633, 51.761, 40.807, 23.576, 19.784. EI-MS (*m*/*e*) 325 $[M]^+$. $[\alpha]_D^{20}$ 13.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.94; H, 7.20; N, 4.41.

4.1.38. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Chlorophenyl)-4-methyl-1,3-dioxan-5-yl]phenyl-acetamide (6h and 6′h). Using the same procedure for the preparation of **6a** and **6′a**, from 448 mg (2.0 mmol) of **3′b** and 280 mg (2.0 mmol) of 4-chlorobenzaldehyde, 276 mg (40%) of **6h** and 55 mg (8%) of **6′h** were obtained.

Compound **6h**. Colorless powder. IR (KBr) υ (cm^{-1}) = 3275, 3033, 1654, 1621, 1552, 1546, 1540, 1432, 1380, 1068, 822, 737, 694. Mp 137–139 °C. ^1H NMR ($CDCl_3$) δ (ppm) = 8.303 (d, *J* = 7.50 Hz, 2H), 8.211 (s, 1H), 7.997 (t, *J* = 7.50 Hz, 1H), 7.879 (t, *J* = 7.50 Hz, 2H), 7.750 (t, *J* = 7.62 Hz, 2H), 7.711 (t, *J* = 7.62 Hz, 2H), 5.841 (s, 1H), 4.530 (m, *J* = 6.60 Hz, 1H), 4.510 (d, *J* = 5.46 Hz, 2H), 3.451 (s, 2H), 2.976 (m, *J* = 4.64 Hz, 1H), 1.517 (d, *J* = 6.40 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.471, 138.795, 136.312, 136.181, 134.315, 133.320, 130.545, 129.614, 128.503, 103.224, 78.231, 75.526, 51.204, 40.097, 19.425. EI-MS (*m*/*e*) 345 $[M]^+$. $[\alpha]_D^{20}$ −10.6 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 66.08; H, 5.72; N, 4.12.

Compound **6′h**. Colorless powder. Mp 129–131 °C. IR (KBr) υ (cm^{-1}) = 3271, 3032, 1654, 1625, 1551, 1546, 1540, 1432, 1383, 1064, 823, 738, 697. ^1H NMR ($CDCl_3$) δ (ppm) = 8.387 (d, *J* = 7.50 Hz, 2H), 8.305 (s, 1H), 8.031 (t, *J* = 7.50 Hz, 1H), 7.899 (t, *J* = 7.50 Hz, 2H), 7.820 (t, *J* = 7.60 Hz, 2H), 7.806 (t, *J* = 7.60 Hz, 2H), 5.892 (s, 1H), 4.764 (m, *J* = 6.59 Hz, 1H), 4.631 (d, *J* = 5.48 Hz, 2H), 3.601 (s, 2H), 3.008 (m, *J* = 4.66 Hz, 1H), 1.785 (d, *J* = 6.45 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.676, 139.615, 136.748, 136.558, 134.753, 133.872, 130.981, 130.150, 128.957, 103.638, 78.654, 75.817, 52.007, 40.560, 19.748. EI-MS (*m*/*e*) 345 $[M]^+$. $[\alpha]_D^{20}$ 12.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.87; H, 5.74; N, 4.15.

4.1.39. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(4′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]phenyl-acetamide (6i and 6′i). Using the same procedure for the preparation of **6a** and **6′a**, from 448 mg (2.0 mmol) of **3′b** and 302 mg (2.0 mmol) of 4-nitrobenzaldehyde, 299 mg (42%) of **6i** and 50 mg (7%) of **6′i** were obtained.

Compound **6i**. Colorless powder, mp 127–129 °C. IR (KBr) υ (cm^{-1}) = 3450, 3045, 2975, 2940, 2970, 1655, 1600, 1576, 1520, 1480, 1400, 1370, 1176, 1070, 741, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 8.354 (d, *J* = 8.22 Hz, 2H), 8.196 (s, 1H), 8.025 (d, *J* = 7.46 Hz, 2H), 7.956 (t, *J* = 7.46 Hz, 1H), 7.795 (d, *J* = 8.22 Hz, 2H), 7.752 (t, *J* = 7.46 Hz, 2H), 5.873 (s, 1H), 4.831 (m, *J* = 3.96 Hz, 1H), 4.412 (d, *J* = 3.96 Hz, 2H), 3.905 (m, *J* = 4.10 Hz, 1H), 3.438 (s, 2H), 1.503 (d, *J* = 6.20 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 168.604, 148.537, 144.402, 134.510, 132.811, 129.591, 129.446, 128.429, 124.500, 104.304, 74.424, 57.887, 40.203, 19.346. $[\alpha]_D^{20}$ −13.8 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.11; H, 5.56; N, 7.78.

Compound **6′i**. Colorless powder, mp 120–122 °C. IR (KBr) υ (cm^{-1}) = 3446, 3034, 2980, 2950, 2860, 1655, 1607, 1580, 1525, 1520, 1482, 1406, 1376, 1180, 1068, 790, 745, 690. ^1H NMR ($CDCl_3$) δ (ppm) = 8.395 (d, *J* = 8.24 Hz, 2H), 8.230 (s, 1H), 8.150 (t, *J* = 7.34 Hz, 2H), 7.995 (d, *J* = 8.24 Hz, 2H), 7.853 (t, *J* = 7.34 Hz, 1H), 7.787 (t, *J* = 7.34 Hz, 2H), 5.963 (s, 1H), 4.866 (m, *J* = 3.65 Hz, 1H), 4.672 (d, *J* = 2.78 Hz, 2H), 3.987 (m, *J* = 6.32 Hz, 1H), 3.515 (s, 2H), 1.567 (d, *J* = 6.34 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.122, 148.637, 144.564, 134.750, 133.127, 129.868, 129.651, 128.821, 124.671, 104.523, 74.586, 58.120, 40.601, 19.664. $[\alpha]_D^{20}$ 18.3 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.94; H, 5.72; N, 7.90.

4.1.40. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(3′-Nitrophenyl)-4-methyl-1,3-dioxan-5-yl]phenylacetamide (6j and 6′j). Using the same procedure as that for preparation of **6a** and **6′a**, from 448 mg (2.0 mmol) of **3′b** and 302 mg (2.0 mmol) of 3-nitrobenzaldehyde, 315 mg (46%) of **6j** and 55 mg (8%) of **6′j** were obtained.

Compound **6j**. Colorless powder. Mp 147–149 °C. IR (KBr) υ (cm^{-1}) = 3273, 3027, 2925, 2854, 1653, 1622, 1550, 1545, 1540, 1432, 1382, 1185, 1072, 862, 781, 713, 702, 695. ^1H NMR ($CDCl_3$) δ (ppm) = 8.324 (d,

J = 8.42 Hz, 1H), 8.213 (s, 1H), 8.200 (d, J = 7.50 Hz, 2H), 8.112 (d, J = 8.01 Hz, 1H), 7.927 (t, J = 8.01 Hz, 2H), 7.831 (t, J = 7.54 Hz, 1H), 7.715 (t, J = 7.50 Hz, 2H), 5.764 (s, 1H), 4.530 (m, J = 4.34 Hz, 1H), 4.465 (d, J = 2.78 Hz, 2H), 3.427 (s, 2H), 2.913 (m, J = 3.16 Hz, 1H), 1.424 (d, J = 4.65 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.432, 150.126, 142.149, 134.726, 134.325, 133.144, 131.500, 129.745, 128.633, 125.782, 123.840, 101.226, 76.533, 76.163, 50.129, 40.113, 19.648. EI-MS (*m*/*e*) 356 $[M]^+$. $[\alpha]_D^{20}$ − 12.8 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.96; H, 5.56; N, 7.95.

Compound **6′j**. Colorless powder. Mp 140–142 °C. IR (KBr) υ (cm^{-1}) = 3271, 3025, 2928, 2852, 1655, 1621, 1552, 1546, 1541, 1434, 1381, 1187, 1070, 861, 782, 715, 704, 697. ^1H NMR ($CDCl_3$) δ (ppm) = 8.347 (d, J = 8.30 Hz, 1H), 8.221 (s, 1H), 8.219 (d, J = 7.52 Hz, 2H), 8.148 (d, J = 7.80 Hz, 1H), 7.984 (t, J = 7.90 Hz, 2H), 7.884 (t, J = 7.52 Hz, 1H), 7.761 (t, J = 7.52 Hz, 2H), 5.897 (s, 1H), 4.627 (m, J = 4.36 Hz, 1H), 4.582 (d, J = 2.76 Hz, 2H), 3.560 (s, 2H), 2.960 (m, J = 3.18 Hz, 1H), 1.466 (d, J = 4.64 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR (DMSO-d_6): δ (ppm) = 169.887, 150.723, 142.653, 135.160, 134.758, 133.559, 131.967, 130.335, 128.826, 126.186, 124.146, 101.857, 77.152, 76.745, 50.868, 40.691, 20.547. EI-MS (*m*/*e*) 356 $[M]^+$. $[\alpha]_D^{20}$ 13.1 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.13; H, 5.75; N, 7.95.

4.1.41. (*cis*)- and (*trans*)-[2-(*E*-Phenylvinyl)-1,3-dioxan-5-yl]benzamide (7a and 7′a). The suspension of 390 mg (2.0 mmol) of **3″a**, 343 mg (2.6 mmol) of *E*-phenylvinyl aldehyde, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous $NaSO_4$, and 50 ml of chloroform was stirred at room temperature for 12 h until the complete disappearance of **3″a** indicated by TLC ($CHCl_3$/CH_3OH, 20:1). The reaction mixture was then adjusted to pH 7 with $NaHCO_3$. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CHCl_3$/CH_3OH, 30:1) to provide 439 mg (71%) of **7a** and 62 mg (10%) of **7′a**.

Compound **7a**. Colorless powder, mp 119–121 °C. IR (KBr): υ (cm^{-1}) = 3250, 3191, 3030, 1673, 1646, 1639, 1455, 1047, 740, 695. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.024 (s, 1H), 7.844 (d, J = 6.66 Hz, 2H), 7.466 (t, J = 5.46 Hz, 1H), 7.409 (d, J = 6.66 Hz, 2H), 7.336 (t, J = 7.52 Hz, 2H), 7.287 (t, J = 6.081 Hz, 1H), 7.185 (d, J = 6.58 Hz, 2H), 6.814 (d, J = 16.20 Hz, 1H), 6.204 (d, J = 16.20 Hz, 1H), 5.526 (d, J = 3.32 Hz, 1H), 4.175 (d, J = 6.41 Hz, 4H), 4.032 (m, J = 6.51 Hz, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.584, 134.722, 133.387, 131.769, 128.586, 128.268, 127.653, 127.307, 126.941, 124.589, 74.365, 52.437. EI-MS (*m*/*e*) 309 $[M]^+$. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.64; H, 6.06; N, 4.61.

Compound **7′a**. Colorless powder, mp 115–117 °C. IR (KBr): υ (cm^{-1}) = 3251, 3190, 3032, 1675, 1645, 1637, 1456, 1044, 742, 697. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.01 (s, 1H), 7.772 (d, J = 7.51 Hz, 2H), 7.510 (t, J = 6.90 Hz, 1H), 7.451 (t, J = 8.70 Hz, 2H), 7.434 (d, J = 6.90 Hz, 2H), 7.338 (t, J = 6.00 Hz, 2H), 7.299 (d, J = 6.00 Hz, 1H), 6.823 (d, J = 16.20 Hz, 1H), 6.134 (d, J = 16.20 Hz, 1H), 5.124 (d, J = 4.32 Hz, 1H), 4.134 (d, J = 6.91 Hz, 4H), 3.688 (m, J = 6.51 Hz, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.304, 134.501, 133.120, 131.204, 128.316, 128.009, 127.312, 127.101, 126.515, 124.234, 74.073, 52.130. EI-MS (*m*/*e*) 309 $[M]^+$. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.86; H, 6.28; N, 4.65.

4.1.42. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(*E*-Phenylvinyl)-4-methyl-1,3-dioxan-5-yl]benzamide (7b and 7′b). Using the same procedure for the preparing **7a** and **7′a**, from 418 mg (2.0 mmol) of 2-benzoylamino-3-methyl-1,3-dibutanol (**3″b**), 517 mg (80%) of **7b** and 65 mg (10%) of **7′b** were obtained.

Compound **7b**. Colorless powder, mp 123–125 °C. IR (KBr): υ (cm^{-1}) = 3252, 3190, 3031, 1675, 1646, 1637, 1454, 1381, 1049, 740, 696. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.006 (s, 1H), 7.364 (d, J = 6.91 Hz, 2H), 7.297 (t, J = 6.00 Hz, 2H), 7.244 (t, J = 6.91 Hz, 1H), 7.238 (d, J = 6.91 Hz, 2H), 7.186 (t, J = 6.00 Hz, 2H), 7.015 (d, J = 6.00 Hz, 1H), 6.575 (d, J = 15.90 Hz, 1H), 6.366 (d, J = 15.90 Hz, 1H), 5.313 (d, J = 5.28 Hz, 1H), 4.346 (d, J = 5.71 Hz, 1H), 4.334 (d, J = 6.91 Hz, 2H), 3.878 (m, J = 6.61 Hz, 1H), 1.218 (d, J = 6.10 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.513, 134.768, 133.491, 131.842, 128.527, 128.183, 127.517, 127.047, 126.848, 126.207, 124.483, 105.438, 73.892, 73.751, 57.004, 18.625. $[\alpha]_D^{20}$ 24.1 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 323 $[M]^+$. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.40; H, 6.68; N, 4.19.

Compound **7′b**. Colorless powder. Mp.116–118 °C. IR (KBr): υ (cm^{-1}) = 3250, 3188, 3032, 1673, 1645, 1636, 1453, 1380, 1048, 741, 694. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.009 (s, 1H), 7.833 (d, J = 6.30 Hz, 2H), 7.507 (d, J = 6.60 Hz, 2H), 7.412 (t, J = 6.30 Hz, 2H), 7.295 (d, J = 6.60 Hz, 2H), 7.191 (t, J = 6.60 Hz, 1H), 7.024 (d, J = 6.30 Hz, 1H), 6.840 (d, J = 16.40 Hz, 1H), 6.242 (d, J = 16.40 Hz, 1H), 5.298 (d, J = 5.20 Hz, 1H), 4.305 (d, J = 6.50 Hz, 1H), 4.119 (m, J = 9.60 Hz, 2H), 3.641 (m, J = 6.30 Hz, 1H), 1.220 (d, J = 6.00 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.307, 134.381, 133.207, 131.502, 128.214,

128.001, 127.303, 126.988, 126.453, 126.003, 124.136, 105.143, 73.287, 73.175, 56.791, 18.256. $[\alpha]_D^{20}$ −18.2 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 323 $[M]^+$. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.18; H, 6.39; N, 4.45.

4.1.43. (*cis*)- and (*trans*)-[2-(*E*-Phenylvinyl)-1,3-dioxan-5-yl]phenylacetamide (8a and 8′a). The suspension of 418 mg (2.0 mmol) of **3′a**, 343 mg (2.6 mmol) of *E*-phenylvinyl aldehyde, 30 mg of tolylsulfonylic acid, 100 mg of anhydrous $NaSO_4$, and 50 ml of chloroform was stirred at room temperature for overnight until the complete disappearance of **3′a** indicated by TLC ($CHCl_3$/CH_3OH, 20:1). The reaction mixture then adjusted to pH 7 with $NaHCO_3$. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CHCl_3$/CH_3OH, 30:1) to provide 262 mg (40%) of **8a** and 52 mg (8%) of **8′a**.

Compound **8a**. Colorless powder, mp 135–136 °C. IR (KBr): υ (cm^{-1}) = 3248, 3189, 3032, 1675, 1644, 1637, 1458, 1049, 741, 694. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.02 (s, 1H), 7.33 (d, *J* = 7.66 Hz, 2H), 7.22 (t, *J* = 7.66 Hz, 2H), 7.16 (t, *J* = 7.66 Hz, 1H), 7.14 (t, *J* = 7.38 Hz, 2H), 7.10 (t, *J* = 7.38 Hz, 1H), 7.07 (d, *J* = 7.38 Hz, 2H), 6.73 (d, *J* = 16.20 Hz, 1H), 6.48 (dd, *J* = 16.20 Hz, *J* = 4.82 Hz, 1H), 5.14 (d, *J* = 4.82 Hz, 1H), 4.02 (d, *J* = 5.01 Hz, 4H), 3.78 (m, *J* = 5.01 Hz, 1H), 3.620 (s, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$):δ (ppm) = 169.884, 135.458, 134.820, 129.713, 128.794, 128.230, 127.524, 127.030, 126.883, 124.341, 105.927, 74.329, 52.007, 39.968. EI-MS (*m*/*e*) 323 $[M]^+$. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.16; H, 6.68; N, 4.17.

Compound **8′a**. Colorless powder, mp 150–152 °C. IR (KBr): υ (cm^{-1}) = 3247, 3188, 3030, 1673, 1645, 1638, 1456, 1047, 743, 695. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.00 (s, 1H), 7.28 (d, *J* = 7.42 Hz, 2H), 7.18 (t, *J* = 7.42 Hz, 2H), 7.12 (t, *J* = 7.42 Hz, 1H), 7.10 (t, *J* = 7.34 Hz, 2H), 7.08 (t, *J* = 7.34 Hz, 1H), 7.04 (d, *J* = 7.34 Hz, 2H), 6.76 (d, *J* = 11.54 Hz, 1H), 5.72 (dd, *J* = 11.54 Hz, *J* = 7.32 Hz, 1H), 5.24 (d, *J* = 4.82 Hz, 1H), 3.96 (d, *J* = 5.01 Hz, 4H), 3.88 (m, *J* = 5.01 Hz, 1H), 3.660 (s, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.267, 135.124, 134.463, 129.506, 128.373, 128.007, 127.307, 126.994, 126.356, 124.107, 105.612, 74.007, 51.981, 39.634. EI-MS (*m*/*e*) 323 $[M]^+$. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.70; N, 4.20.

4.1.44. (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-[2-(*E*-phenylvinyl)-4-methyl-1,3-dioxan-5-yl] phenylacetyl amide (8b and 8′b). Using the same procedure for preparing **8a** and **8′a**, from 446 mg (2.0 mmol) of **3′b**, 270 mg (40%) of **8b** and 52 mg (8%) of **8′b** were obtained.

Compound **8b**. Colorless powder, mp 125–127 °C. IR (KBr): υ (cm^{-1}) = 3249, 3187, 3034, 1673, 1645, 1635, 1456, 1382, 1048, 742, 695. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.88 (s, 1H), 7.29 (d, *J* = 7.47 Hz, 2H), 7.24 (t, *J* = 7.47 Hz, 2H), 7.16 (t, *J* = 7.33 Hz, 2H), 7.14 (t, *J* = 7.47 Hz, 1H), 7.08 (t, *J* = 7.33 Hz, 1H), 7.05 (d, *J* = 7.33 Hz, 2H), 6.63 (d, *J* = 12.12 Hz, 1H), 6.25 (dd, *J* = 12.12 Hz, *J* = 6.00 Hz, 1H), 5.23 (d, *J* = 6.00 Hz, 1H), 4.42 (m, *J* = 4.65 Hz, 1H), 4.02 (d, *J* = 4.65 Hz, 2H), 3.72 (m, *J* = 4.65 Hz, 1H), 3.421 (s, 2H), 1.22 (d, *J* = 4.88 Hz, 3H). In NOESY experiment, NOEs between the CH_3 at the 4-position and the proton of phenyl at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.874, 135.462, 134.847, 129.661, 128.973, 128.214, 127.651, 127.332, 126.957, 124.351, 104.979, 73.910, 73.801, 56.517, 18.769. EI-MS (*m*/*e*): 337 [M]. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.61; H, 6.71; N, 4.28.

Compound **8′b**. Colorless powder, mp 141–143 °C. IR (KBr): υ (cm^{-1}) = 3251, 3190, 3031, 1675, 1642, 1633, 1457, 1381, 1049, 740, 696. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.86 (s, 1H), 7.26 (d, *J* = 7.45 Hz, 2H), 7.20 (t, *J* = 7.45 Hz, 2H), 7.12 (t, *J* = 7.31 Hz, 2H), 7.10 (t, *J* = 7.45 Hz, 1H), 7.06 (t, *J* = 7.31 Hz, 1H), 7.02 (d, *J* = 7.31 Hz, 2H), 6.61 (d, *J* = 12.38 Hz, 1H), 6.22 (dd, *J* = 12.38 Hz, *J* = 6.12 Hz, 1H), 5.27 (d, *J* = 6.12 Hz, 1H), 4.46 (m, *J* = 4.88 Hz, 1H), 4.06 (d, *J* = 4.88 Hz, 2H), 3.78 (m, *J* = 4.61 Hz, 1H), 3.460 (s, 2H), 1.24 (d, *J* = 4.88 Hz, 3H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.212, 135.170, 134.230, 129.241, 128.537, 128.009, 127.307, 127.112, 126.535, 124.107, 104.651, 73.682, 73.531, 56.304, 18.447. EI-MS (*m*/*e*): 337 [M]. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.87; H, 6.96; N, 4.05.

4.1.45. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Chlorophenyl-1,3-dioxaheptan-5-yl)phenyl-acetamide (9c and 9′c). Using the same procedure for preparing **8a** and **8′a**, from 161 mg (0.72 mmol) of **3′c** and 105 mg (0.72 mmol) of 4-chlorobenzaldehyde, 77 mg (30%) of **9c** and 36 mg (14%) of **9′c** were obtained.

Compound **9c**. Colorless powder, mp 132–134 °C. IR (KBr): υ (cm^{-1}) = 3325, 3042, 2963, 2918, 2841, 1640, 1600, 1555, 1460, 1372, 1172, 1050, 822, 745, 693. ^1H NMR ($CDCl_3$) δ (ppm) = 7.376 (s, 1H), 7.199 (d, *J* = 7.50 Hz, 2H), 7.138 (t, *J* = 7.54 Hz, 2H), 7.127 (d, *J* = 7.50 Hz, 2H), 7.068 (d, *J* = 7.50 Hz, 1H), 7.045 (d, *J* = 7.50 Hz, 2H), 5.542 (s, 1H), 4.017 (m, *J* = 4.34 Hz, 1H), 3.588 (d, *J* = 4.34 Hz, 2H), 3.468 (s, 2H), 3.371 (t, *J* = 4.34 Hz, 2H), 1.671 (m, *J* = 4.34 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.778, 135.879, 135.346, 132.884, 129.901, 129.008, 128.976, 128.796, 127.572, 104.724, 69.329, 58.271, 45.078, 33.073. EI-MS (*m*/*e*) 345 $[M]^+$. $[\alpha]_D^{20}$ 13.7 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.87; H, 5.69; N, 4.12.

Compound **9′c**. Colorless powder, mp 139–141 °C. IR (KBr): υ (cm^{-1}) = 3322, 3041, 2966, 2916, 2843, 1641, 1602, 1552, 1450, 1376, 1162, 1053, 820, 742, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 7.763 (s, 1H), 7.343 (d, *J* = 7.52 Hz, 2H), 7.218 (t, *J* = 7.56 Hz, 2H), 7.271 (d, *J* = 7.52 Hz, 2H), 7.186 (d, *J* = 7.52 Hz, 1H), 7.097 (d, *J* = 7.52 Hz, 2H), 5.597 (s, 1H), 4.265 (m, *J* = 4.36 Hz, 1H), 3.659 (d, *J* = 4.36 Hz, 2H), 3.497 (s, 2H), 3.412 (t, *J* = 4.36 Hz, 2H), 1.761 (m, *J* = 4.36 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.957, 135.998, 135.634, 133.017, 129.986, 129.367, 129.048, 128.967, 127.891, 105.034, 69.591, 58.720, 45.565, 33.472.EI-MS (*m*/*e*) 345 $[M]^+$. $[\alpha]_D^{20}$ −15.0 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.89; H, 5.79; N, 4.02.

4.1.46. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Nitrophenyl-1,3-dioxaheptan-5-yl)phenylacetamide (9d and 9′d). Using the same procedure for preparing **8a** and **8′a**, from 161 mg (0.72 mmol) of **3′c** and 108 mg (0.72 mmol) of 4-nitrobenzaldehyde, 56 mg (22%) of **9d** and 28 mg (11%) of **9′d** were obtained.

Compound **9d**. Colorless powder, mp 125–127 °C. IR (KBr): υ (cm^{-1}) = 3315, 3046, 2973, 2915, 2854, 1646, 1603, 1564, 1521, 1464, 1370, 1351, 1175, 1051, 821, 742, 695. ^1H NMR ($CDCl_3$) δ (ppm) = 8.141 (d, *J* = 9.21 Hz, 2H), 7.803 (s, 1H), 7.454 (d, *J* = 9.21 Hz, 2H), 7.137 (t, *J* = 7.52 Hz, 2H), 7.072 (t, *J* = 7.52 Hz, 1H), 7.062 (t, *J* = 7.52 Hz, 2H), 5.477 (s, 1H), 3.908 (m, *J* = 3.64 Hz, 1H), 3.587 (d, *J* = 3.64 Hz, 2H), 3.471 (s, 2H), 3.377 (t, *J* = 3.67 Hz, 2H), 1.678 (m, *J* = 3.66 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 169.898, 147.452, 143.268, 135.945, 130.121, 129.017, 128.422, 127.376, 123.521, 104.153, 69.310, 58.212, 45.016, 33.063. $[\alpha]_D^{20}$ 16.8 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.17; H, 5.54; N, 7.73.

Compound **9′d**. Colorless powder, mp 129–131 °C. IR (KBr): υ (cm^{-1}) = 3310, 3051, 2960, 2910, 2845, 1640, 1602, 1520, 1456, 1370, 1351, 1165, 1050, 820, 738, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm) = 8.305 (d, *J* = 9.24 Hz, 2H), 7.875 (s, 1H), 7.674 (d, *J* = 9.24 Hz, 2H), 7.378 (t, *J* = 7.55 Hz, 2H), 7.279 (t, *J* = 7.55 Hz, 1H), 7.260 (t, *J* = 7.55 Hz, 2H), 5.774 (s, 1H), 3.957 (m, *J* = 3.65 Hz, 1H), 3.875 (d, *J* = 3.65 Hz, 2H), 3.737 (t, *J* = 3.65 Hz, 2H), 3.490 (s, 2H), 1.892 (m, *J* = 3.68 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.235, 147.824, 143.863, 136.007, 130.652, 129.712, 128.837, 127.736, 124.007, 104.637, 69.727, 58.807, 45.612, 33.715. $[\alpha]_D^{20}$ −15.6 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.15; H, 5.70; N, 7.93.

4.1.47. (2*S*,5*S*)- and (2*R*,5*S*)-2-(3′-Nitrophenyl-1,3-dioxaheptan-5-yl)phenylacetamide (9e and 9′e). Using the same procedure for the preparation of **8a** and **8′a**, from 161 mg (0.72 mmol) of **3′c** and 108 mg (0.72 mmol) of 3-nitrobenzaldehyde, 67 mg (26%) of **9e** and 36 mg (14%) of **9′e** were obtained.

Compound **9e**. Colorless powder, mp 127–129 °C. IR (KBr): υ (cm^{-1}) = 3316, 3032, 2967, 2922, 2852, 1646, 1610, 1560, 1525, 1465, 1369, 1351, 1164, 1048, 861, 776, 745, 692. ^1H NMR ($CDCl_3$) δ (ppm) = 8.119 (s, 1H), 8.114 (d, *J* = 9.10 Hz, 1H), 8.004 (s, 1H), 7.577 (t, *J* = 9.10 Hz, 1H), 7.427 (d, *J* = 9.10 Hz, 1H), 7.147 (t, *J* = 7.52 Hz, 2H), 7.074 (t, *J* = 7.52 Hz, 1H), 7.059 (t, *J* = 7.52 Hz, 2H), 5.481 (s, 1H), 3.911 (m, *J* = 3.74 Hz, 1H), 3.561 (d, *J* = 3.74 Hz, 2H), 3.464 (s, 2H), 3.337 (t, *J* = 3.65 Hz, 2H), 1.681 (m, *J* = 3.65 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.512, 148.367, 138.087, 135.873, 133.654, 129.768, 129.314, 129.104, 128.961, 127.472, 122.647, 103.167, 69.394, 58.271, 45.137, 40.807, 33.096. $[\alpha]_D^{20}$ 13.7 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.90; H, 5.56; N, 7.95.

Compound **9′e**. Colorless powder, mp 135–137 °C. IR (KBr): υ (cm^{-1}) = 3328, 3030, 2961, 2914, 2842, 1642, 1603, 1554, 1456, 1375, 1166, 1049, 861, 772, 741, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 8.327 (s, 1H), 8.241 (d, *J* = 9.12 Hz, 1H), 8.009 (s, 1H), 7.752 (t, *J* = 9.12 Hz, 1H), 7.724 (d, *J* = 9.12 Hz, 1H), 7.471 (t, *J* = 7.54 Hz, 2H), 7.145 (t, *J* = 7.54 Hz, 1H), 7.097 (t, *J* = 7.54 Hz, 2H), 5.520 (s, 1H), 3.957 (m, *J* = 3.76 Hz, 1H), 3.607 (d, *J* = 3.76 Hz, 2H), 3.471 (s, 2H), 3.473 (t, *J* = 3.66 Hz, 2H), 1.773 (m, *J* = 3.66 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.769, 148.673, 138.768, 136.386, 133.892, 130.127, 129.761, 129.567, 129.154, 127.768, 122.957, 103.761, 69.834, 58.726, 45.738, 41.087, 33.692. $[\alpha]_D^{20}$ −12.8 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.00; H, 5.69; N, 8.00.

4.1.48. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4-Chlorophenyl-1,3-dioxaheptan-5-yl)benzamide (10c and 10′c). Using the same procedure for the preparation of **8a** and **8′a**, from 150 mg (0.72 mmol) of **3″c** and 101 mg (0.72 mmol) of 4-chlorobenzaldehyde, 57 mg (25%) of **10c** and 30 mg (13%) of **10′c** were obtained.

Compound **10c**. Colorless powder, mp 129–131 °C. IR (KBr): υ (cm^{-1}) = 3315, 3046, 2967, 2915, 2844, 1642, 1603, 1560, 1528, 1462, 1375, 1174, 1052, 821, 743, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 7.949 (d, *J* = 8.72 Hz, 2H), 7.514 (t, *J* = 8.72 Hz, 1H), 7.437 (d, *J* = 8.72 Hz, 2H), 7.379 (s, 1H), 7.212 (d, *J* = 7.51 Hz, 2H), 7.127 (d, *J* = 7.51 Hz, 2H), 5.794 (s, 1H), 4.112 (d, *J* = 4.32 Hz, 4H), 3.764 (d, *J* = 4.32 Hz, 1H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 166.712, 135.432, 135.301, 132.878, 131.907, 129.072, 128.768, 128.569, 127.257, 105.642, 73.878, 52.341. $[\alpha]_D^{20}$ 19.2 (*c* 0.02, $CHCl_3$). EI-MS (*m*/*e*) 331$[M]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 64.98; H, 5.32; N, 4.40.

Compound **10′c**. Colorless powder, mp 134–136 °C. IR (KBr): υ (cm^{-1}) = 3318, 3050, 2964, 2912, 2840, 1644, 1600, 1525, 1452, 1373, 1160, 1050, 822, 744, 695. ^1H NMR ($CDCl_3$) δ (ppm) = 7.981 (d, J = 8.74 Hz, 2H), 7.589 (t, J = 8.74 Hz, 1H), 7.472 (d, J = 8.74 Hz, 2H), 7.431 (s, 1H), 7.522 (d, J = 7.53 Hz, 2H), 7.353 (d, J = 7.53 Hz, 2H), 5.806 (s, 1H), 4.221 (d, J = 4.36 Hz, 4H), 3.946 (d, J = 4.36 Hz, 1H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.013, 135.868, 135.912, 133.172, 132.314, 129.642, 129.140, 128.895, 127.735, 106.117, 74.115, 52.517. $[\alpha]_D^{20}$ − 16.4 (c 0.02, $CHCl_3$). EI-MS (*m/e*) 331 $[M]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.33; H, 5.59; N, 4.04.

4.1.49. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4-Nitrophenyl-1,3-dioxaheptan-5-yl)benzamide (10d and 10′d). Using the same procedure for the preparation of **8a** and 8′**a**, from 150 mg (0.72 mmol) of **3″c** and 108 mg (0.72 mmol) of 4-nitrobenzaldehyde, 62 mg (25%) of **10d** and 32 mg (13%) of **10′d** were obtained.

Compound **10d**. Colorless powder, mp 121–123 °C. IR (KBr): υ (cm^{-1}) = 3301, 3040, 2970, 2920, 2850, 1645, 1609, 1562, 1525, 1460, 1372, 1351, 1170, 1048, 823, 740, 692. ^1H NMR ($CDCl_3$) δ (ppm) = 8.223 (d, J = 9.0 Hz, 2H), 7.892 (d, J = 7.5 Hz, 2H), 7.767 (s, 1H), 7.534 (t, J = 7.5 Hz, 1H), 7.465 (d, J = 9.0 Hz, 2H), 7.377 (t, J = 7.5 Hz, 2H), 5.789 (s, 1H), 4.512 (m, J = 3.2 Hz, 1H), 4.064 (d, J = 3.2 Hz, 2H), 3.360 (t, J = 3.0 Hz, 2H), 1.740 (m, J = 3.6 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.608, 145.602, 145.511, 133.499, 131.876, 129.178, 128.611, 127.302, 123.255, 104.235, 69.001, 58.022, 49.116, 32.336. $[\alpha]_D^{20}$ 21.0 (c 0.02, $CHCl_3$). FAB-MS (*m/e*) 342 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.26; H, 5.43; N, 8.06.

Compound **10′d**. Colorless powder, mp 124–126 °C. IR (KBr): υ (cm^{-1}) = 3310, 3051, 2960, 2910, 2845, 1640, 1602, 1520, 1456, 1370, 1350, 1165, 1050, 822, 739, 694. ^1H NMR ($CDCl_3$) δ (ppm) = 8.228 (d, J = 8.1 Hz, 2H), 8.003 (s, 1H), 7.815 (d, J = 7.8 Hz, 2H), 7.673 (d, J = 7.8 Hz, 1H), 7.525 (t, J = 8.1 Hz, 2H), 7.457 (t, J = 7.8 Hz, 2H), 5.531 (s, 1H), 3.934 (m, J = 3.3 Hz, 1H), 3.697 (d, J = 3.3 Hz, 2H), 3.379 (t, J = 4.1 Hz, 2H), 1.725 (m, J = 4.0 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 168.331, 146.117, 145.880, 133.781, 132.070, 129.351, 129.006, 127.881, 123.704, 104.221, 68.541, 58.308, 49.414, 32.597. $[\alpha]_D^{20}$ − 19.3 (c 0.02, $CHCl_3$). FAB-MS (*m/e*) 342 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.07; H, 5.19; N, 8.30.

4.1.50. (2*S*,5*S*)- and (2*R*,5*S*)-2-(3′-Nitrophenyl-1,3-dioxaheptan-5-yl)benzamide (10e and 10′e). Using the same procedure for the preparation of **8a** and **8′a**, from 150 mg (0.72 mmol) of **3″c** and 108 mg (0.72 mmol) of 3-nitrobenzaldehyde, 69 mg (28%) of **10e** and 37 mg (15%) of **10′e** were obtained.

Compound **10e**. Colorless powder, mp 114–116 °C. IR (KBr): υ (cm^{-1}) = 3300, 3037, 2963, 2927, 2854, 1648, 1612, 1564, 1522, 1463, 1356, 1167, 1051, 860, 741, 695. ^1H NMR ($CDCl_3$) δ (ppm) = 8.124 (s, 1H), 8.117 (d, J = 9.12 Hz, 1H), 8.007 (s, 1H), 7.907 (d, J = 7.54 Hz, 2H), 7.572 (t, J = 9.07 Hz, 1H), 7.504 (t, J = 7.54 Hz, 1H), 7.454 (d, J = 9.07 Hz, 1H), 7.437 (t, J = 7.54 Hz, 2H), 5.478 (s, 1H), 3.907 (m, J = 3.72 Hz, 1H), 3.644 (d, J = 3.72 Hz, 2H), 3.364 (t, J = 3.60 Hz, 2H), 1.718 (m, J = 3.62 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.521, 148.402, 138.004, 133.687, 133.515, 131.811, 129.278, 128.542, 127.274, 122.348, 103.146, 69.343, 58.107, 45.371, 33.004. $[\alpha]_D^{20}$ 17.9 (c 0.02, $CHCl_3$). EI-MS (*m/e*) 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.07; H, 5.19; N, 8.30.

Compound **10′e**. Colorless powder, mp 117–119 °C. IR (KBr): υ (cm^{-1}) = 3307, 3034, 2964, 2919, 2849, 1645, 1609, 1557, 1522, 1459, 1351, 1162, 1051, 862, 739, 692. ^1H NMR ($CDCl_3$) δ (ppm) = 8.301 (s, 1H), 8.245 (d, J = 9.14 Hz, 1H), 8.017 (s, 1H), 7.933 (d, J = 7.57 Hz, 2H), 7.684 (t, J = 9.14 Hz, 1H), 7.584 (t, J = 7.57 Hz, 1H), 7.497 (d, J = 9.14 Hz, 1H), 7.460 (t, J = 7.57 Hz, 2H), 5.521 (s, 1H), 3.967 (m, J = 3.75 Hz, 1H), 3.687 (d, J = 3.75 Hz, 2H), 3.390 (t, J = 3.65 Hz, 2H), 1.731 (m, J = 3.66 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 168.057, 148.914, 138.537, 134.172, 133.700, 132.113, 129.644, 128.772, 127.901, 122.843, 103.643, 69.671, 58.710, 45.713, 33.410. $[\alpha]_D^{20}$ − 14.8 (c 0.02, $CHCl_3$). FAB-MS (*m/e*) 342 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.25; H, 5.41; N, 8.08.

4.1.51. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Chlorophenyl-1,3-dioxaoctan-5-yl)benzamide (11c and 11′c). Using the same procedure for the preparation of **8a** and **8′a** from 106 mg (0.47 mmol) of **3″d** and 66 mg (0.47 mmol) of 4-chlorobenzaldehyde, 55 mg (34%) of **11c** and 23 mg (14%) of **11′c** were obtained.

Compound **11c**. Colorless powder, mp 113–115 °C. IR (KBr): υ (cm^{-1}) = 3316, 3035, 2934, 2853, 1655, 1633, 1600, 1584, 1502, 1454, 1382, 1195, 1050, 821, 741, 693 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm) = 7.613 (d, J = 7.51 Hz, 2H), 8.010 (s, 1H), 7.241 (t, J = 7.60 Hz, 1H), 7.131 (t, J = 7.60 Hz, 2H), 7.117 (d, J = 7.20 Hz, 2H), 7.044 (t, J = 7.20 Hz, 2H), 5.341 (s, 1H), 3.631 (m, J = 6.21 Hz, 1H), 3.520 (d, J = 6.51 Hz, 2H), 3.223 (t, J = 6.00 Hz, 2H), 1.507 (m, J = 6.01 Hz, 2H), 1.422 (m, J = 6.01 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.103, 135.210, 133.324, 132.767, 131.813, 129.003, 128.732, 128.303, 127.412, 104.251, 69.114, 63.317, 49.251, 28.430,

25.369. EI-MS (*m/e*) 345 $[M]^+$. $[\alpha]_D^{20}$ 16.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 66.07; H, 5.96; N, 4.17.

Compound **11′c**. Colorless powder, mp 118–120 °C. IR (KBr): υ (cm^{-1}) = 3322, 3041, 2930, 2850, 1654, 1628, 1607, 1584, 1505, 1452, 1380, 1187, 1049, 823, 742, 701. ^1H NMR ($CDCl_3$) δ (ppm) = 7.952 (d, *J* = 7.62 Hz, 2H), 8.024 (s, 1H), 7.524 (t, *J* = 7.62 Hz, 1H), 7.437 (t, *J* = 7.62 Hz, 2H), 7.207 (d, *J* = 7.22 Hz, 2H), 7.130 (t, *J* = 7.22 Hz, 2H), 5.515 (s, 1H), 3.926 (m, *J* = 6.32 Hz, 1H), 3.773 (d, *J* = 6.91 Hz, 2H), 3.403 (t, *J* = 6.01 Hz, 2H), 1.796 (m, *J* = 6.11 Hz, 2H), 1.481 (m, *J* = 6.11 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.848, 135.541, 133.803, 133.114, 132.055, 129.520, 129.132, 128.883, 127.905, 104.852, 69.867, 63.880, 49.947, 29.034, 26.143. EI-MS (*m/e*) 345 $[M]^+$. $[\alpha]_D^{20} = -13.4$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.86; H, 5.74; N, 4.13.

4.1.52. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Nitrophenyl-1,3-dioxaoctan-5-yl)benzamide (11d and 11′d). Using the same procedure for the preparation of **8a** and **8′a**, from 106 mg (0.47 mmol) of **3″d** and 72 mg (0.47 mmol) of 4-nitrobenzaldehyde, 44 mg (26%) of **11d** and 23 mg (14%) of **11′d** were obtained.

Compound **11d**. Colorless powder, mp 133–135 °C. IR (KBr): υ (cm^{-1}) = 3310, 3050, 2930, 2850, 1650, 1630, 1605, 1580, 1525, 1450, 1386, 1350, 1190, 1050, 821, 738, 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm) = 8.156 (d, *J* = 9.02 Hz, 2H), 8.014 (s, 1H), 7.631 (d, *J* = 9.02 Hz, 2H), 7.601 (t, *J* = 7.54 Hz, 1H), 7.437 (t, *J* = 7.54 Hz, 2H), 7.408 (t, *J* = 7.54 Hz, 2H), 5.834 (s, 1H), 4.303 (m, *J* = 6.91 Hz, 1H), 3.963 (d, *J* = 6.91 Hz, 2H), 3.955 (d, *J* = 6.91 Hz, 2H), 1.821 (m, *J* = 6.12 Hz, 2H), 1.794 (m, *J* = 6.12 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.814, 145.506, 145.345, 133.512, 132.237, 129.042, 128.651, 127.342, 123.401, 105.061, 69.371, 63.501, 29.320, 25.4533. EI-MS (*m/e*) 356 $[M]^+$. $[\alpha]_D^{20}$ 20.0 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.17; H, 5.76; N, 7.77.

Compound **11′d**. Colorless powder, mp 116–118 °C. IR (KBr): υ (cm^{-1}) = 3318, 3060, 2950, 2860, 1660, 1625, 1610, 1590, 1520, 1460, 1383, 1351, 1119, 1090, 819, 738, 692. ^1H NMR ($CDCl_3$) δ (ppm) = 8.193 (d, *J* = 8.7 Hz, 2H), 8.022 (s, 1H), 7.906 (d, *J* = 7.2 Hz, 2H), 7.517 (t, *J* = 7.5 Hz, 1H), 7.450 (t, *J* = 8.7 Hz, 2H), 7.435 (t, *J* = 7.2 Hz, 2H), 5.520 (s, 1H), 3.902 (m, *J* = 6.3 Hz, 1H), 3.771 (d, *J* = 6.9 Hz, 2H), 3.316 (t, *J* = 6.7 Hz, 2H), 1.498 (m, *J* = 6.1 Hz, 2H), 1.403 (m, *J* = 6.1 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.222, 145.343, 145.126, 133.220, 132.001, 128.885, 128.201, 127.040, 123.111, 104.890, 69.105, 63.212, 28.881, 25.003. $[\alpha]_D^{20}$ −18.0 (*c* 0.02, $CHCl_3$). EI-MS (*m/e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.87; H, 5.52; N, 7.71.

4.1.53. (2*S*,5*S*)- and (2*R*,5*S*)-2-(3′-Nitrophenyl-1,3-dioxaoctan-5-yl)benzamide (11e and 11′e). Using the same procedure for the preparation of **8a** and **8′a**, from 106 mg (0.47 mmol) of **3″d** and 72 mg (0.47 mmol) of 3-nitrobenzaldehyde, 49 mg (29%) of **11e** and 25 mg (15%) of **11′e** were obtained.

Compound **11e**. Colorless powder, mp 124–126 °C. IR (KBr): υ (cm^{-1}) = 3322, 3045, 2921, 2844, 1642, 1621, 1603, 1586, 1524, 1456, 1384, 1349, 1190, 1075, 861, 768, 699. ^1H NMR ($CDCl_3$) δ (ppm) = 8.127 (s, 1H), 8.121 (d, *J* = 9.04 Hz, 1H), 8.011 (s, 1H), 7.931 (d, *J* = 7.49 Hz, 2H), 7.591 (d, *J* = 9.04 Hz, 1H), 7.523 (t, *J* = 7.49 Hz, 1H), 7.448 (t, *J* = 9.04 Hz, 1H), 7.421 (t, *J* = 7.49 Hz, 2H), 5.479 (s, 1H), 3.917 (m, *J* = 6.55 Hz, 1H), 3.624 (d, *J* = 6.55 Hz, 2H), 3.361 (t, *J* = 6.37 Hz, 2H), 1.549 (m, *J* = 6.12 Hz, 2H), 1.458 (m, *J* = 6.12 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.522, 148.223, 138.014, 133.701, 133.432, 130.994, 129.240, 128.611, 127.320, 122.661, 103.427, 69.708, 63.579, 49.447, 28.694, 25.867. $[\alpha]_D^{20}$ 17.2 (*c* 1.00, $CHCl_3$). EI-MS (*m/e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.17; H, 5.78; N, 7.94.

Compound **11′e**. Colorless powder, mp 127–129 °C. IR (KBr): υ (cm^{-1}) = 3315, 3042, 2926, 2847, 1648, 1625, 1601, 1582, 1524, 1453, 1381, 1349, 1194, 1072, 863, 765, 702. ^1H NMR ($CDCl_3$) δ (ppm) = 8.361 (s, 1H), 8.320 (d, *J* = 9.03 Hz, 1H), 8.014 (s, 1H), 7.967 (d, *J* = 7.52 Hz, 2H), 7.633 (d, *J* = 9.03 Hz, 1H), 7.600 (t, *J* = 7.52 Hz, 1H), 7.584 (t, *J* = 9.03 Hz, 1H), 7.488 (t, *J* = 7.52 Hz, 2H), 5.694 (s, 1H), 3.973 (m, *J* = 6.54 Hz, 1H), 3.647 (d, *J* = 6.54 Hz, 2H), 3.450 (t, *J* = 6.35 Hz, 2H), 1.598 (m, *J* = 6.10 Hz, 2H), 1.466 (m, *J* = 6.10 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 167.940, 148.653, 138.824, 133.789, 133.661, 131.073, 129.547, 129.034, 127.651, 123.046, 103.763, 70.124, 63.795, 50.106, 29.323, 26.401. $[\alpha]_D^{20}$ −13.7 (*c* 1.00, $CHCl_3$). EI-MS (*m/e*) 356 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.17; H, 5.78; N, 7.94.

4.1.54. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Chlorophenyl-1,3-dioxaoctan-5-yl)phenylacetamide (12c and 12′c). Using the same procedure for the preparation of **8a** and **8′a**, from 111 mg (0.47 mmol) of **3′d** and 66 mg (0.47 mmol) of 4-chlorobenzaldehyde, 54 mg (32%) of **12c** and 22 mg (13%) of **12′c** were obtained.

Compound **12c**. Colorless powder, mp 120–122 °C. IR (KBr): υ (cm^{-1}) = 3324, 3030, 2931, 2850, 1651, 1630, 1602, 1581, 1504, 1450, 1385, 1191, 1048, 818, 743, 692. ^1H NMR ($CDCl_3$) δ (ppm) = 8.004 (s, 1H), 7.127 (d, *J* = 7.50 Hz, 2H), 7.057 (t, *J* = 7.20 Hz, 2H), 7.030 (d, *J* = 7.50 Hz, 2H), 7.011 (d,

J = 7.20 Hz, 1H), 7.005 (d, J = 7.20 Hz, 2H), 5.412 (s, 1H), 3.613 (m, J = 6.01 Hz, 1H), 3.470 (s, 2H), 3.302 (d, J = 6.00 Hz, 2H), 3.113 (t, J = 6.00 Hz, 2H), 1.500 (m, J = 6.00 Hz, 2H), 1.422 (m, J = 6.00 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.102, 135.623, 134.801, 132.644, 129.157, 129.002, 128.637, 128.305, 127.502, 104.163, 69.337, 63.654, 49.104, 28.307, 25.424. EI-MS (*m/e*) 359 $[M]^+$. $[\alpha]_D^{20}$ 17.6 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.63; H, 6.07; N, 4.01.

Compound **12′c**. Colorless powder, mp 130–132 °C. IR (KBr): υ (cm^{-1}) = 3314, 3035, 2937, 2854, 1651, 1622, 1600, 1584, 1507, 1458, 1377, 1182, 1047, 820, 744, 692. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.019 (s, 1H), 7.295 (d, J = 7.51 Hz, 2H), 7.167 (t, J = 7.32 Hz, 2H), 7.131 (d, J = 7.51 Hz, 2H), 7.087 (d, J = 7.32 Hz, 1H), 7.069 (d, J = 7.32 Hz, 2H), 5.531 (s, 1H), 3.937 (m, J = 6.20 Hz, 1H), 3.668 (d, J = 6.01 Hz, 2H), 3.476 (s, 2H), 3.434 (t, J = 6.01 Hz, 2H), 1.686 (m, J = 6.00 Hz, 2H), 1.487 (m, J = 6.00 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.887, 136.324, 135.479, 133.160, 130.057, 129.561, 129.323, 129.045, 127.802, 104.791, 70.112, 64.030, 49.637, 29.121, 26.332. EI-MS (*m/e*) 359 $[M]^+$. $[\alpha]_D^{20}$ − 14.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.67; H, 6.22; N, 3.78.

4.1.55. (2*S*,5*S*)- and (2*R*,5*S*)-2-(4′-Nitrophenyl-1,3-dioxaoctan-5-yl)phenylacetamide (12d and 12′d). Using the same procedure for the preparation of **8a** and **8′a**, from 111 mg (0.47 mmol) of **3′d** and 72 mg (0.47 mmol) of 4-nitrobenzaldehyde, 42 mg (24%) of **12d** and 21 mg (12%) of **12′d** were obtained.

Compound **12d**. Colorless powder, mp 136–138 °C. IR (KBr): υ (cm^{-1}) = 3321, 3043, 2919, 2837, 1644, 1627, 1600, 1575, 1520, 1456, 1351, 1194, 1048, 821, 742, 693. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.120 (d, J = 8.94 Hz, 2H), 8.010 (s, 1H), 7.443 (d, J = 8.94 Hz, 2H), 7.130 (t, J = 7.30 Hz, 2H), 7.069 (t, J = 7.30 Hz, 1H), 7.059 (d, J = 7.30 Hz, 2H), 5.397 (s, 1H), 3.914 (m, J = 5.39 Hz, 1H), 3.585 (d, J = 5.42 Hz, 2H), 3.464 (s, 2H), 3.364 (t, J = 5.24 Hz, 2H), 1.505 (m, J = 5.12 Hz, 2H), 1.454 (m, J = 5.12 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.671, 147.413, 143.112, 135.903, 129.812, 128.914, 128.701, 127.516, 123.482, 104.316, 69.727, 63.591, 40.007, 28.767, 25.989. EI-MS (*m/e*) 370 $[M]^+$. $[\alpha]_D^{20}$ 18.2 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.78; H, 5.81; N, 7.77.

Compound **12′d**. Colorless powder, mp 150–152 °C. IR (KBr): υ (cm^{-1}) = 3326, 3047, 2939, 2845, 1665, 1629, 1613, 1581, 1522, 1462, 1347, 1190, 1050, 822, 739, 694. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.181 (d, J = 9.00 Hz, 2H), 8.015 (s, 1H), 7.953 (d, J = 9.00 Hz, 2H), 7.543 (t, J = 7.51 Hz, 2H), 7.457 (t, J = 7.51 Hz, 1H), 7.212 (d, J = 7.51 Hz, 2H), 5.726 (s, 1H), 3.981 (m, J = 5.44 Hz, 1H), 3.713 (d, J = 5.44 Hz, 2H), 3.561 (t, J = 5.26 Hz, 2H), 3.469 (s, 2H), 1.570 (m, J = 5.14 Hz, 2H), 1.487 (m, J = 5.14 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 171.142, 147.901, 143.561, 136.304, 130.104, 129.215, 129.003, 128.104, 123.781, 104.671, 70.121, 64.114, 40.557, 29.146, 26.371. EI-MS (*m/e*) 370 $[M]^+$. $[\alpha]_D^{20}$ − 15.1 (*c* 0.02, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 65.04; H, 6.03; N, 7.42.

4.1.56. (2*S*,5*S*)- and (2*R*,5*S*)-2-(3′-Nitrophenyl-1,3-dioxaoctan-5-yl)phenylacetamide (12e and 12′e). Using the same procedure for the preparation of **8a** and **8′a**, from 111 mg (0.47 mmol) of **3′d** and 72 mg (0.47 mmol) of 3-nitrobenzaldehyde, 49 mg (28%) of **12e** and 23 mg (13%) of **12′e** were obtained.

Compound **12e**. Colorless powder, mp 131–133 °C. IR (KBr): υ (cm^{-1}) = 3335, 3032, 2915, 2836, 1647, 1611, 1600, 1582, 1524, 1452, 1388, 1352, 1194, 1052, 860, 773, 699. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.114 (s, 1H), 8.105 (d, J = 8.91 Hz, 1H), 8.012 (s, 1H), 7.563 (d, J = 8.91 Hz, 1H), 7.463 (d, J = 8.90 Hz, 1H), 7.138 (t, J = 7.32 Hz, 2H), 7.058 (t, J = 7.32 Hz, 1H), 7.046 (t, J = 7.32 Hz, 2H), 5.473 (s, 1H), 3.912 (m, J = 6.20 Hz, 1H), 3.582 (d, J = 6.20 Hz, 2H), 3.459 (s, 2H), 3.364 (t, J = 6.20 Hz, 2H), 1.610 (m, J = 6.20 Hz, 2H), 1.461 (m, J = 6.15 Hz, 2H). In the NOE experiment, a positive NOE was observed between the NH-functionality at the 5-position and the proton of the phenyl at the 2-position. ^{13}C NMR ($CDCl_3$): δ (ppm) = 170.452, 148.305, 138.087, 135.892, 133.614, 130.025, 129.303, 128.964, 127.432, 122.686, 103.489, 69.760, 63.599, 49.103, 40.085, 28.682, 25.968. EI-MS (*m/e*) 370 $[M]^+$. $[\alpha]_D^{20}$ 15.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.76; H, 6.11; N, 7.67.

Compound **12′e**. Colorless powder, mp 138–140 °C. IR (KBr): υ (cm^{-1}) = 3331, 3037, 2915, 2835, 1639, 1622, 1600, 1576, 1524, 1446, 1385, 1351, 1196, 1051, 859, 771, 701. ^{1}H NMR ($CDCl_3$) δ (ppm) = 8.162 (s, 1H), 8.210 (d, J = 8.93 Hz, 1H), 8.021 (s, 1H), 7.661 (d, J = 8.93 Hz, 1H), 7.593 (d, J = 8.93 Hz, 1H), 7.380 (t, J = 7.34 Hz, 2H), 7.254 (t, J = 7.34 Hz, 1H), 7.163 (t, J = 7.34 Hz, 2H), 5.741 (s, 1H), 3.974 (m, J = 6.22 Hz, 1H), 3.825 (d, J = 6.22 Hz, 2H), 3.630 (t, J = 6.22 Hz, 2H), 3.472 (s, 2H), 1.676 (m, J = 6.22 Hz, 2H), 1.516 (m, J = 6.13 Hz, 2H). In the NOE experiment no NOE was observed. ^{13}C NMR ($CDCl_3$): δ (ppm) = 171.234, 148.956, 138.706, 136.289, 134.015, 130.657, 129.813, 129.464, 127.861, 123.045, 103.947, 70.013, 64.131, 49.738, 40.812, 29.134, 26.320. EI-MS (*m/e*) 370 $[M]^+$. $[\alpha]_D^{20}$ − 11.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.74; H, 5.87; N, 7.71.

4.2. In vivo anti-inflammatory assay

4.2.1. Animals. Male Kunming mice (about 25 g) were inbred and grown in the animal laboratory at the college of Pharmacy, Peking University. The animal facility was

maintained at 23 ± 2 °C with a 12 h light/dark cycle. The ethical guidelines described in the NIH guide for care and use of Laboratory Animals were followed.

4.2.2. Xylene-induced ear edema.[15–18] 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 administered orally with a suspension of Aspirin in CMC at a dosage of 20 mg/kg, and a concentration of 0.3 mg/ml, and the mice in the test group were administered orally a suspension of 1,3-dioxacycloalkane 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 used as control. Two hours after xylene application, the 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.

4.3. Tail bleeding time measurement

The new anti-inflammatory agents were orally administered to male mice (body weight 18–22 g). After the administration of 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 until it stopped was gently wiped away with a tissue every 30 s until bleeding ceased and the time recorded.

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