Synthesis and *in vivo* Anti-inflammatory Evaluation of Piperazine Derivatives Containing 1,4-Benzodioxan Moiety

Zhi-Ping Liu,^{†,1} Chang-Da Gong,^{†,2} Long-Yan Xie,² Xiu-Li Du,²
Yang Li² and Jie Qin^{*,2}

¹ School of Medical, Pingdingshan University, Pingdingshan 467000, P. R. China

² School of Life Sciences, Shandong University of Technology, Zibo 255049, P. R. China

* Corresponding author: E-mail: qinjietutu@163.com
Tel.: 0086-533-2780271; Fax: 0086-533-2781329

† These authors contributed equally to this work.

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Abstract

Six piperazine derivatives **6a–f** containing 1,4-benzodioxan moiety have been synthesized and characterized by ¹H NMR, ESI-MS and elemental analysis. The structure of **6d** was further confirmed by single crystal X-ray diffraction. All these novel compounds were screened for their *in vivo* anti-inflammatory activity employing classical *para*-xylene-induced mice ear-swelling model. The results revealed that most of the target compounds showed significant anti-inflammatory activities, especially compound **6a** with *ortho*-substituted methoxy group on the phenylpiperazine ring exhibited the best activity among the designed compounds.

Keywords: Piperazine; 1,4-benzodioxan; crystal structure; anti-inflammatory activity

1. Introduction

Inflammation, a biological process response to harmful stimuli or infection, has threatened human health seriously.^{1–3} Nonsteroidal anti-inflammatory drugs (NSAIDs) like diclofenac, indomethacin and naproxen are widely clinically used drugs for inflammatory disorders such as arthritis, peritendinitis and lupus erythematosus.^{4–7} However, long-term use of NSAIDs has been asso-

ciated with adverse side effects, including gastrointestinal ulceration, and even fatal internal bleeding.⁸ The stomach damage from NSAIDs is generally attributed to their acidic character as most of them are weak acids with pK_a values ranging from 3 to 5.^{8,9} Therefore, synthetic approaches based on design of non-acidic anti-inflammatory lead compounds have gained great interest nowadays.^{1,10–13}

Piperazine group, as a known pharmacophore, is part of many important alkaline heterocyclic compounds displaying a broad range of biological activities, *e.g.* antibacterial,¹⁴ anti-tumor,¹⁵ antidiabetic,¹⁶ and anti-psychiatry.¹⁷ Continuous efforts have also been made to prepare anti-inflammatory therapeutic agents containing piperazine scaffold. Li *et al.* reported a series of chalcone derivatives containing aryl-piperazine or aryl-sulfonyl-piperazine fragment and found compound **A** (Figure 1) as a potential anti-inflammatory agent.¹⁸ Silva *et al.* evaluated the anti-inflammatory effect of 4-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinecarboxylic acid ethyl ester (**B**, Figure 1) and the involvement of the serotonergic pathway.³ Mao

Figure 1. The structure of piperazine derivatives reported in previous literature sources.

et al. synthesized a series of piperazine substituted 3-aryl-5-furanyldihydropyrazole amide derivatives (C, Figure 1), the *in vitro* anti-inflammatory activity evaluation indicated that these compounds showed good inhibitory effect on the generation of inflammatory factor, NO.¹⁹ A series of piperazine analogues bearing pyridine or thiophene moieties have been synthesized by Kumar *et al.* (D, Figure 1), they also showed favorable anti-inflammatory efficacy.²⁰

Beyond that, it was reported that 1,4-benzodioxan afforded a new skeleton possessing anti-inflammatory activity.^{10,21,22} Potent anti-inflammatory activity of analogues containing 1,4-benzodioxan ring may be ascribed to the strong hydrogen-bonding interactions with amino acids in the active domain.¹⁰

of the synthesized molecules. Furthermore, the synthesized molecules have been subjected to *in vivo* anti-inflammatory evaluation.

2. Experimental

2.1. Physical Measurements and Materials

Reagents and solvents used in this study were analytical grade and purchased commercially from Aladdin Industrial Corporation (China). ¹H NMR spectra were measured on a Bruker AM 500 spectrometer. Mass spectra were determined with an Autoflex II TM instrument for ESI-MS. Elemental analyses were performed on a Per-

Scheme 1. Synthetic route to 6a–f.

As mentioned above, it is a worthwhile goal to synthesize compounds containing piperazine and 1,4-benzodioxan rings utilizing molecular hybridization approach. The presence of the two bioactive skeletons in a single molecular frame may lead to potent derivatives possessing good anti-inflammatory activity.¹⁰ With this in mind, we have synthesized six compounds (6a–f) possessing piperazine and 1,4-benzodioxan moieties (Scheme 1). Spectral analyses using ESI mass spectrometry and ¹H NMR spectroscopy have been applied in order to affirm the structure

kin-Elmer model 2400 analyzer. The intermediate 5-(2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazole-2-thiol (4) was synthesized according to the literature method.^{23,24}

2.2. General Procedure for the Synthesis of Target Compounds 6a–f

To a solution of a substituted phenylpiperazines (6.0 mmol) in CH₂Cl₂ (30 mL) containing triethylamine (1

mL), chloroacetyl chloride (0.48 mL, 6.0 mmol) was added dropwise with stirring in ice water bath. Stirring was continued for 5 h and the reaction mixture was washed with 10% NaOH solution (2×5 mL). The organic layer was collected. After drying with anhydrous Na_2SO_4 , the solvent was removed in vacuo to yield the intermediate **5a–f**.

Oxadiazole derivative **4** (0.24 g, 1.0 mmol) and KOH (0.056 g, 1.0 mmol) dissolved in CH_3OH (20 mL) was treated with chloro derivatives **5a–f** (1.0 mmol). The mixture was stirred at room temperature about 4 h until the solid was precipitated. The solids **6a–f** were filtered and purified by recrystallization from MeOH.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(2-methoxyphenyl)piperazin-1-yl)ethanone (6a). White powder, 0.354 g, yield 75.5%, mp: 171.0–172.5 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.08 (t, 2H, CH_2), 3.13 (t, 2H, CH_2), 3.78 (t, 2H, CH_2), 3.86 (t, 2H, CH_2), 3.89 (s, 2H, OCH_3), 4.29–4.33 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.43 (s, 2H, SCH_2), 6.89–7.08 (m, 5H, ArH), 7.49–7.52 (m, 2H, ArH). ESI-MS: 959.33 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_5\text{S}$: C, 58.96; H, 5.16; N, 11.96. Found: C, 59.15; H, 5.13; N, 12.01%.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(3-methoxyphenyl)piperazin-1-yl)ethanone (6b). White powder, 0.367 g, yield 78.3%, mp: 158.1–159.4 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.16 (t, 2H, CH_2), 3.29 (t, 2H, CH_2), 3.81 (s, 5H, CH_2 , OCH_3), 3.88 (t, 2H, CH_2), 4.29–4.34 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.39 (s, 2H, SCH_2), 6.50–6.59 (m, 3H, ArH), 6.95 (d, 1H, ArH), 7.21 (t, 1H, ArH), 7.48–7.52 (m, 2H, ArH). ESI-MS: 491.33 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_5\text{S}$: C, 58.96; H, 5.16; N, 11.96. Found: C, 58.78; H, 5.14; N, 11.98%.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(4-methoxyphenyl)piperazin-1-yl)ethanone (6c). White powder, 0.358 g, yield 76.4%, mp: 194.2–196.3 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.07 (t, 2H, CH_2), 3.12 (t, 2H, CH_2), 3.75 (t, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.82 (t, 2H, CH_2), 4.29–4.34 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.41 (s, 2H, SCH_2), 6.84–6.96 (m, 5H, ArH), 7.48–7.52 (m, 2H, ArH). ESI-MS: 491.25 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_5\text{S}$: C, 58.96; H, 5.16; N, 11.96. Found: C, 59.20; H, 5.14; N, 11.99%.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(2-chlorophenyl)piperazin-1-yl)ethanone (6d). Yellow crystals suitable for X-ray diffraction were obtained from evaporation of a solution of **6d** in dichloromethane/methanol solution. Brown powder, 0.308 g, yield 65.2%, mp: 173.1–174.6 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.13 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), 3.81 (t, 2H, CH_2), 3.84 (t, 2H, CH_2), 4.31–4.35 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.44 (s, 2H, SCH_2), 6.97 (d, 2H, ArH), 7.04–7.06 (m, 2H, ArH), 7.41 (dd, 1H, ArH), 7.51–7.54 (m, 2H,

ArH). ESI-MS: 495.17 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$: C, 55.87; H, 4.48; N, 11.85. Found: C, 56.09; H, 4.46; N, 11.90%.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(3-chlorophenyl)piperazin-1-yl)ethanone (6e). White powder, 0.376 g, yield 79.5%, mp: 191.8–193.1 °C. ^1H NMR (400 MHz, CDCl_3) δ 3.22 (t, 2H, CH_2), 3.34 (s, 2H, CH_2), 3.89 (s, 2H, CH_2), 3.84 (s, 2H, CH_2), 4.32–4.36 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.40 (s, 2H, SCH_2), 6.94–7.01 (m, 4H, ArH), 7.24 (t, 1H, ArH), 7.24 (m, 2H, ArH). ESI-MS: 495.25 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$: C, 55.87; H, 4.48; N, 11.85. Found: C, 56.03; H, 4.45; N, 11.91%.

2-(5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazol-2-ylthio)-1-(4-(4-chlorophenyl)piperazin-1-yl)ethanone (6f). White powder, 0.359 g, yield 76.1%, mp: 278.2–279.6 °C. ^1H NMR data for **6f** is unattainable because of its low solubility. ESI-MS: 495.25 ($[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$: C, 55.87; H, 4.48; N, 11.85. Found: C, 56.05; H, 4.46; N, 11.90%.

2. 3. Determination of Crystal Structure for **6d**

Crystal diffraction data for compound **6d** were collected on a Bruker SMART APEX CCD-based diffractometer (Mo K α radiation, $\lambda = 0.71073$ Å) at 298 K. Multi-scan absorption corrections were applied by SADABS.²⁵ The structures were solved by the directed method followed by

Table 1. Crystallographic data for **6d**.

6d	
Empirical formula	$\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$
M_r	472.94
crystalsyst	Monoclinic
Space group	$P2_1/c$
a (Å)	18.2038(19)
b (Å)	8.0092(8)
c (Å)	15.4024(16)
α (°)	90.00
β (°)	107.112(3)
γ (°)	90.00
V (Å ³)	2146.2(4)
Z	4
ρ_c (g cm ⁻³)	1.464
$F(000)$	984
T / K	298(2)
$\mu(\text{Mo-K}\alpha)/\text{mm}^{-1}$	0.314
Data / param. / restr.	5257 / 289 / 0
GOF (F^2)	1.037
R_1^a , wR_2 ($I > 2\sigma(I)$)	0.0634 / 0.1475
Large diff. peak / hole (e Å ⁻³)	0.514 / -0.482

$$^a R_1 = \Sigma ||F_o| - |F_c|| / \Sigma F_o, \quad ^b wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)]^{1/2}$$

Fourier syntheses. Structure refinement was performed by full-matrix least-squares procedures using SHELXL-97 program package.²⁶ Non-hydrogen atoms were refined using anisotropic thermal parameters. Hydrogen atoms were placed in their geometrically idealized positions and constrained to ride on their parent atoms. Details of crystallographic parameters, data collection, and refinements are summarized in Table 1. Relevant bond distances and bond angles are given in Table 2.

2. 4. *In vivo* Anti-Inflammatory Activities in Ear Edema

The animal studies were conducted according to the guideline issued by the State Food and Drug Administration (SFDA) of China. All experimental protocols were approved by the Animal Ethics Committee of Pingdingshan University. All efforts were made to minimize animal suffering. The anti-inflammatory activity was evaluated using *in vivo para*-xylene-induced mice ear-swelling model on Kunming mice,¹⁸ 35–40 days old and weighing 18–22 g, supplied by Jinan Pengyue Experimental Animal Breeding Company. Kunming mice were divided into eight groups of eight each. Group I, the control, comprised of animals treated with vehicle (0.5% CMC, 10 mL/kg), and groups II–VIII were dosage groups. Group II was treated with standard reference drug diclofenac (20 mg/kg), groups III–VIII were treated with target compounds **6a–f** (30 mg/kg), respectively. One hour later, ear swelling was induced by smearing 50 μ L *para*-xylene to each side of the right ears, the left ear served as a control. After 1 hour, the mice were sacrificed, and both ears at the same position were removed using a 6 mm diameter punch. Swelling degree and swelling inhibition were calculated according to the following formula:

Swelling degree (mg) = weight of right ear (mg) – weight of left ear (mg)

Swelling inhibition (%) = (average swelling degree of control group – average swelling degree of dosage group) / average swelling degree of control group $\times$ 100%

3. Results and Discussion

3. 1. Chemistry of Compounds **6a–f**

Appropriate 2-chloro-1-(4-phenylpiperazin-1-yl) ethanone derivatives **5** were reacted with 5-(2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)-1,3,4-oxadiazole-2-thiol **4** in CH₃OH/KOH solution *via* nucleophilic substitution reaction to furnish the respective target compounds **6a–f** (Scheme 1). The structures of **6a–f** were established by elemental and ¹H NMR and electrospray ionization mass spectrometry. In the ¹H NMR spectra of **6a–e**, the protons of the piperazin ring resonated as four triplets appearing at

δ 3.07–3.88 ppm. The multiplet corresponding to four protons characteristic of the –OCH₂CH₂– group was observed at δ 4.29–4.35 ppm. The –SCH₂– protons appeared as a sharp singlet around δ 4.39 ppm. The protons of the substituted phenyl ring resulted in the formation of the resonance signal at δ 6.94–7.54 ppm. The methoxy protons of **6a–c** appeared as a singlet at 3.78–3.89 ppm. The positive ion electrospray mass spectra of these compounds showed full abundance of the parent peak which corresponds to [M+Na]⁺ or [2M+Na]⁺.

3. 2. Crystal Structure

Table 2. Selected bond distances (Å) and angles (°) for **6d**.

C(1)–O(1)	1.439(3)	C(1)–C(2)	1.477(4)
C(2)–O(2)	1.431(3)	C(6)–C(9)	1.453(3)
C(9)–N(1)	1.280(3)	C(9)–O(3)	1.364(3)
N(1)–N(2)	1.417(3)	C(10)–N(2)	1.286(3)
C(10)–O(3)	1.353(3)	C(10)–S(1)	1.734(3)
C(11)–S(1)	1.805(3)	C(12)–N(3)	1.348(3)
O(1)–C(1)–C(2)	111.0(2)	O(2)–C(2)–C(1)	110.6(2)
C(3)–O(1)–C(1)	114.1(2)	C(8)–O(2)–C(2)	113.0(2)
N(1)–C(9)–C(6)	130.3(2)	N(2)–C(10)–S(1)	131.8(2)
C(10)–S(1)–C(11)	96.82(12)	N(3)–C(12)–C(11)	117.6(2)

Yellow crystals of **6d** suitable for X-ray structure analysis were obtained by slow evaporation of a mixture of dichloromethane and methanol. X-ray single-crystal diffraction reveals that compound **6d** crystallizes in monoclinic *P*₂₁/*c* space group. As shown in Figure 2, **6d** has a nonplanar chair-like conformation, the dihedral angle between 2-chlorobenzene ring and piperazine ring being 49.710(78)°; meanwhile the dihedral angle between 2-chlorobenzene ring and oxadiazole ring is 75.512(86)°. The piperazine ring in **6d** has a classical chair conformation.

3. 3. *In vivo* Anti-Inflammatory Activities

The anti-inflammatory activities of the synthesized piperazine derivatives **6a–f** were tested using *in vivo para*-xylene-induced mice ear-swelling model. All the target compounds were administered at a dose of 30 mg/kg and diclofenac (20 mg/kg) was used as the reference drugs. The results show that compounds **6a**, **6c**, **6d**, and **6f** exhibited significant anti-inflammatory activities (*p* < 0.01) (Table 3). In the present assay, compound **6a** bearing methoxy substituent at the *ortho* position of the phenyl piperazine showed the most effective anti-inflammatory activity; it was 1.3 times more active than diclofenac (inhibition values 68.02 vs. 52.03%). Preliminary structure–activity relationship analysis revealed that: (i) the substituent at different positions led to different activity, and the potency order was *ortho* > *para* > *meta*; (ii) in view of the comparison of

Figure 2. Molecular structure of **6d** (50% probability displacement ellipsoids), front and side views are presented.

the structures of compounds **6a** with **6d**, **6b** with **6e**, and **6c** with **6f**, the *in vivo* anti-inflammatory activities were **6a** > **6d**, **6b** > **6e**, and **6c** > **6f**. These results indicate that substitution at phenyl-piperazine with electron-donating methoxy group shows advantage over electron-withdrawing chlorine group at the same position, thus improving compound's anti-inflammatory activity. Meanwhile compared with the chalcone derivatives containing aryl-piperazine reported earlier, most of the compounds in the present assay were found to display enhanced *in vivo* anti-inflammatory activity.¹⁸

Table 3. Anti-inflammatory activities of the synthesized compounds **6a–f**.

Compound	Swelling degree (mg)	Inhibition (%)
6a	4.34 ± 0.24 ^a	68.02
6b	6.81 ± 0.54 ^a	49.82
6c	5.83 ± 0.74 ^a	57.04
6d	6.36 ± 0.45 ^a	59.15
6e	10.95 ± 0.31 ^a	19.31
6f	7.12 ± 1.03 ^a	52.47
Diclofenac	6.51 ± 0.95 ^a	52.03
Control	13.57 ± 1.09	—

^a Multiple comparison test $p < 0.01$ as compared to control

4. Conclusions

To sum up, a series of six piperazine derivatives **6a–f** containing 1,4-benzodioxan moiety were synthesized and screened primarily for *in vivo* anti-inflammatory activities potential in ear edema. The substituent at different posi-

tions led to different activity. Most of the synthetic compounds emerged as effective *in vivo* anti-inflammatory agents, demonstrating swelling inhibition even better than the reference control, diclofenac. Compound **6a** containing methoxy substituent at the *ortho* position of the phenyl piperazine displayed the most potent anti-inflammatory activity among the synthesized compounds. Our findings might provide information on developing potentially new and safe anti-inflammatory agents.

5. Supplementary Material

Crystallographic data (excluding structure factors) for the structural analysis have been deposited with the Cambridge Crystallographic Data Center as supplementary publication Nos. CCDC 1882249 (**6d**). Copies of the data can be obtained free of charge *via* www.ccdc.ac.uk/conts/retrieving.html (or from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: +44-1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

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Povzetek

Sintetizirali smo šest piperazinskih derivatov **6a–f**, ki vsebujejo 1,4-benzodioksanski fragment, ter jih karakterizirali z ¹H NMR, ESI-MS in elementno analizo. Strukturo produkta **6d** smo dodatno potrdili z rentgensko difrakcijsko analizo monokristala. Za vse nove spojine smo s pomočjo klasičnega *para*-ksilenskega testa otekanja ušes miši *in vivo* določili protivnetno aktivnost. Rezultati kažejo, da večina preiskovanih spojin izkazuje opazno protivnetno aktivnost, še posebej spojina **6a**, ki vsebuje *orto*-metoksi skupino na fenilpiperazinskem obroču, saj kaže najboljšo aktivnost izmed vseh pripravljenih spojin.