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Research Article

Synthesis, Anti-Inflammatory, and Analgesic Activities of Derivatives of 4-Hydroxy-2-benzoxazolone

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Benzoxazolones are widely distributed in plants and are of increasing interest for a variety of pharmacological properties, such as detoxification, antibacterial, anti-inflammatory, and analgesic activities and tranquilizers (Michaelidou and Hadjipavlou-Litina, 2005; Doğruer et al., 1998). 4-Hydroxy-2-benzoxazolone (HBOA) is one of the major bioactive compounds in traditional Chinese herb drug *Acanthus ilicifolius* (Peng and Long, 2006) which has obvious anti-inflammatory and analgesic activities (Huo et al., 2004; Mani Senthil Kumar et al., 2008; Babu et al., 2001). In this research, we used 2-nitroresorcinol as starting material to prepare HBOA with a novel "one-pot-way." Derivatives of HBOA TC-2~TC-4 were obtained via electrophilic reagents and reacted with corresponding primary amines to afford Schiff Base derivatives TC-5~TC-10 for further study. Anti-inflammatory and analgesic activities of those derivatives were determined by using carrageenan-induced rat paw edema test. The analgesic activities of the derivatives were determined by the hot-plate test.

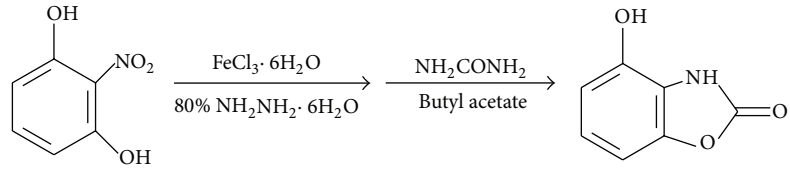
1. Introduction

In recent years, reports showed *Acanthus ilicifolius* has obvious anti-inflammatory, analgesic activities, and 4-hydroxy-2-benzoxazolone (HBOA) is one of the major bioactive benzoxazolones compounds [1]. According to modern medicinal theory, HBOA is a bioisosterism of Chlorzoxazone and has the possibility to be a kind of nonsteroidal anti-inflammatory drugs (NSAIDs). Since benzoxazolones are of bioactivities, many molecular modification and preliminary bioactivity evaluation studies have been performed [1–3]. Several useful compounds have been developed and evaluated for their analgesic properties, anti-inflammatory properties, and antifungal properties [4–7]. Nevertheless, most efforts focused on N-, 4-, 5-, or 6-substituted HBOA. Currently, 7-substituted benzoxazolone derivatives as well as their anti-inflammatory or analgesic properties have been scarcely reported. Therefore, we report the new method for synthesis of HBOA (Scheme 1), some new C-7 HBOA derivatives and their anti-inflammatory as well as analgesic activities.

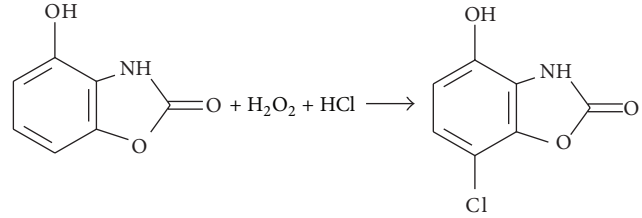
2. Experimental

Reagents and solvents used below were obtained from commercial sources. Melting points were measured by X4 micromelting point appearance. IR spectra were obtained with Perkin-Elmer Spectrum 100. The ^{1}H-NMR and ^{13}C-NMR spectra were run on a Bruker AVTCCE AV 600 MHz. The mass spectrum was obtained on a Waters AutoSpec Premier P776. Progress of the reaction was monitored by TLC using sheets precoated with UV fluorescent silica gel Merck 60F 254.

2.1. Preparation of HBOA. To a suspension of 4.0 g $FeCl_3 \cdot 6H_2O$ in 200 mL methanol, 9.0 g activated carbon was added and refluxed for 30 minutes. 31.0 g 2-nitroresorcinol (0.2 mol) was added and then 36 mL 80% hydrazine hydrate by drops was added in 2 hours. Keep stirring and refluxing for another 4 hours. We filtered all solution to another flask and dried all solvent under vacuum to yield dark syrup. 300 mL butyl acetate and 60.0 g (1 mol) urea were added to the syrup,



Scheme 1: Methodology for synthesis of HBOA.



Scheme 2: Methodology for synthesis of TC-2.

stirred at 90°C for 5 hours, and then cooled to room temperature. The crude HBOA was obtained by filtration and purified by recrystallization in 80% ethanol (yield 69.5%).

2.2. Preparation of TC-2. Compound TC-2 was prepared via chlorination reaction and TC-3 to TC-4 were prepared via Friedel-Crafts acylation on HBOA. To a solution of 1.51 g (0.01 mol) HBOA in 15 mL glacial acetic acid and 2 mL (0.024 mol) 37% HCl, 1.80 g (0.015 mol) H_2O_2 was added in 30 minutes by drops at 45°C, and then temperature was raised to 80°C and stirred for another 2 hours, cooled to room temperature, filtered, and washed with distilled water to obtain compound TC-2 (Scheme 2).

7-Chloro-4-hydroxy-2-benzoxazolone (TC-2). White solid (yield 61%), m.p. 226~228°C; FT-IR (KBr), υ: 3384 (OH), 3175 (NH), 1748 (C=O), 1625, 1562, 1492, 1467 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ: 11.90 (1H, s, N-H), 10.38 (1H, s, O-H), 7.07 (1H, d, J = 8.52 Hz, 6-ArH), 6.85 (1H, d, J = 8.52 Hz, 5-ArH). ^{13}C-NMR (DMSO-d6), δ154.1 (2-C), 143.4 (4-C), 138.0 (7a-C), 122.4 (6-C), 116.8 (7-C), 112.2 (3a-C), 103.1 (5-C), EI: m/z 185 (M^+, 100%).

2.3. Preparation of TC-3 to TC-4. To slurry of 1.51 g (0.01 mol) HBOA, 8.0 g (0.06 mol) $AlCl_3$ in 20 mL 1,2-dichloroethane, and 2 mL nitrobenzene, 0.04 mol acyl chloride was added by drops and stirred at rt. for 1 hour. Then temperature was raised to 80°C and stirred for another 4 hours. The reaction was quenched by cooling to rt. and pouring the slurry into 300 mL ice-cold water. Filtered and recrystallized with 90% ethanol to yield pure compounds TC-3 and TC-4 (Schemes 3 and 4).

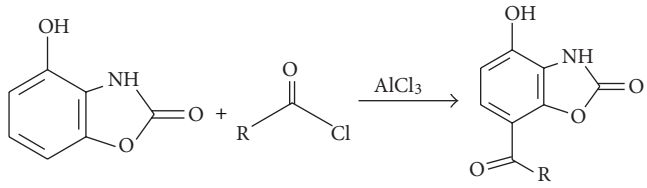
7-Acetyl-4-hydroxy-2-benzoxazolone (TC-3). White solid (68%), m.p. 226~228°C; FT-IR (KBr), υ: 3358 (OH), 2983, 2844, 1769 (C=O), 1702 (C=O), 1659, 1625, 1512, 1473, 1427, 1356, cm^{-1}; ^{1}H-NMR (DMSO-d6), δ: 11.88 (1H, s, N-H), 11.08 (1H, s, O-H), 7.46 (1H, d, J = 8.82 Hz, 6-ArH), 6.74 (1H, d, J = 8.82 Hz, 5-ArH), 2.65 (3H, s, $COCH_3^*$); ^{13}C-NMR (DMSO-d6), δ: 193.3 ($^*COCH_3$), 154.5 (2-C), 146.9 (4-C), 144.9 (7a-C), 123.7 (6-C), 118.7 (7-C), 113.6 (3a-C), 111.2 (5-C), 30.2 (CO^*CH_3). EI: m/z 193 (M^+, 78%).

7-Butyryl-4-hydroxy-2-benzoxazolone (TC-4). White solid (72%), m.p. 168~170; FT-IR (KBr), υ: 3138 (OH), 2964, 2933, 2901, 2875, 1777 (C=O), 1748 (C=O), 1659, 1632, 1494, 1472, 1376, 1237, 1156; ^{1}H-NMR (DMSO-d6), δ: 11.87 (1H, s, N-H), 10.05 (1H, s, O-H), 7.48 (1H, d, J = 8.82 Hz, 6-ArH), 6.75 (1H, d, J = 8.82 Hz, 5-ArH), 2.93 (2H, t, J = 7.14 Hz, $COCH_2{}^*CH_2CH_3$), 1.64 (2H, m, $COCH_2CH_2{}^*CH_3$), 0.93 (3H, t, J = 7.38 Hz, $COCH_2CH_2CH_3{}^*$); ^{13}C-NMR (DMSO-d6), δ: 195.7 ($^*COCH_2CH_2CH_3$), 154.5 (2-C), 146.7 (4-C), 144.7 (7a-C), 126.0 (6-C), 123.6 (7-C), 113.4 (3a-C), 111.3 (5-C), 43.6 ($CO^*CH_2CH_2CH_3$), 17.4 ($COCH_2{}^*CH_2CH_3$), 14.2 ($COCH_2CH_2{}^*CH_3$). EI: m/z 221 (M^+, 45%).

2.4. Preparation of TC-5 to TC-10. Compounds TC-5 to TC-10 were prepared by reaction with corresponding primary amines to afford Schiff Base derivatives. To a solution of 0.01 mol starting material in 300 mL ethanol, 1.5 eq primary amine derivatives were added, refluxed for 3 hours, and then cooled to rt. and filtered and washed with distilled water to yield compounds TC-5~TC-10.

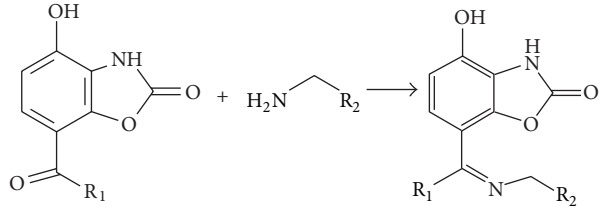
7-(1-(2-Hydroxyethylimino)ethyl)-4-hydroxy-2-benzoxazolone (TC-5). Yellow solid (91%), m.p. 270~271°C; FT-IR (KBr), υ: 3429 (O-H), 2963, 2873, 1757 (C=O), 1635, 1576, 1536, 1444, 1380, 1300, 1286, ^{1}H-NMR (DMSO-d6), δ: 16.80 (1H, s, N-H), 16.20 (1H, s, C_4-OH), 7.37 (1H, d, J = 9.0 Hz, 6-ArH), 6.46 (1H, d, J = 9.0 Hz, 5-ArH), 3.69 (7H, m), 3.43 (1H, s); ^{13}C-NMR (DMSO-d6), δ: 175.6 (C=N), 161.2 (2-C), 155.0 (4-C), 147.2 (7a-C), 125.0 (6-C), 121.2 (7-C), 113.0 (3a-C), 97.3 (5-C), 60.0 ($CN^*CH_2CH_2OH$), 48.2 ($CNCH_2{}^*CH_2OH$), 15.2 ($^*CH_3$). EI: m/z 236 (M^+, 100%).

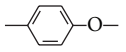
7-(1-(2-Hydroxyethylimino)butyl)-4-hydroxy-2-benzoxazolone (TC-6). Light yellow solid (45%), m.p. 255~257°C; FT-IR (KBr), υ: 3431 (O-H), 3323 (N-H), 3027 (=C-H), 2957,



TC-3 R = -CH_3
TC-4 R = -$CH_2CH_2CH_3$

Scheme 3: Methodology for synthesis of TC-3 and TC-4.



TC-5	R_1 = -CH_3	R_2 = -CH_2OH
TC-6	R_1 = -$CH_2CH_2CH_3$	R_2 = -CH_2OH
TC-7	R_1 = -$CH_2CH_2CH_3$	R_2 = -CH_2COOH
TC-8	R_1 = -$CH_2CH_2CH_3$	R_2 = -$CH(CH_3)COOH$
TC-9	R_1 = -$CH_2CH_2CH_3$	R_2 = -$CH_2(CH_2)_4COOH$
TC-10	R_1 = -$CH_2CH_2CH_3$	R_2 = 

Scheme 4: Methodology for synthesis of TC-3 and TC-4.

2863, 1751 (C=O), 1634, 1617, 1571, 1441, 1383, 1286, 1072, ^{1}H-NMR (DMSO-d6), δ: 16.84 (1H, s, N-H), 16.30 (1H, s, C_4-OH), 7.36 (1H, d, J = 9.0 Hz, 6-ArH), 6.47 (1H, d, J = 9.0 Hz, 5-ArH), 3.70 (4H, m), 3.51 (1H, s), 2.88 (2H, t, J = 2.28 Hz), 1.61 (2H, m), 1.04 (3H, d, J = 2.28 Hz); ^{13}C-NMR (600 MHz, DMSO), δ: 178.2 (*C=N), 161.6 (2-C), 155.0 (4-C), 147.1 (7a-C), 124.8 (6-C), 121.4 (7-C), 111.8 (3a-C), 97.5 (5-C), 60.1 (CN*CH_2CH_2OH), 47.9 (CNC$H_2^*CH_2OH$), 29.4 ($^*CH_2CH_2CH_3$), 22.0 ($CH_2{}^*CH_2CH_3$), 14.4 ($CH_2CH_2{}^*CH_3$). EI: m/z 264 (M^+, 100%).

2-(1-(4-Hydroxy-2-benzoxazolone-7-yl)butylide-neamino)acetic Acid (TC-7). White solid (56%), m.p. 80~182°C; FT-IR (KBr), v: 3333 (O-H), 3138 (N-H), 2969, 2880, 1740 (C=O), 1721 (C=O), 1625, 1593, 1509, 1425, 1370, 1228, 1057; ^{1}H-NMR (DMSO-d6), δ: 13.45 (1H, s, COO-H), 11.68 (1H, s, N-H), 8.24 (1H, s, O-H), 7.64 (1H, d, J = 9.0 Hz, 6-ArH), 6.45 (1H, d, J = 9.0 Hz, 5-ArH), 3.85 (2H, s, CNCH_2^*COOH), 2.95 (2H, t, J = 7.38 Hz, $CH_2{}^*CH_2CH_3$), 1.66 (2H, m, $CH_2CH_2{}^*CH_3$), 0.95 (3H, t, J = 7.38 Hz, $CH_2CH_2CH_3{}^*$); ^{13}C-NMR (DMSO-d6)δ: 177.6 (*COOH), 172.1 (*C=N), 158.0 (2-C), 156.6 (4-C), 147.1 (7a-C), 128.0 (6-C), 115.1 (7-C), 112.7 (3a-C), 110.1 (5-C), 60.1 (CN*CH_2COOH), 42.2 ($^*CH_2CH_2CH_3$), 18.3 ($CH_2{}^*CH_2CH_3$), 14.1 ($CH_2CH_2{}^*CH_3$). EI: m/z 278 (M^+, 12%).

2-(1-(4-Hydroxy-2-benzoxazolone-7-yl)butylide-neamino)propanoic Acid (TC-8). White solid (56%), m.p. 144~146°C; FT-IR (KBr), v: 3352 (O-H), 2966, 2937, 2876, 1721 (C=O), 1702 (C=O), 1642, 1605, 1512, 1456, 1383, 1232, 1067, 802; ^{1}H-NMR (DMSO-d6), δ: 13.49 (1H, s, COO-H), 13.16 (1H, s, N-H), 8.14 (1H, s, O-H), 7.63 (1H, d, J = 9.0 Hz, 6-ArH), 6.45 (1H, d, J = 9.0 Hz, 5-ArH), 4.19 (1H, q, J = 7.2 Hz, CNCH*(CH_3)COOH), 2.96 (2H, t, J = 3.66 Hz, $CH_2{}^*CH_2CH_3$), 1.65 (2H, m, $CH_2CH_2{}^*CH_3$), 1.33 (3H, d, J = 2.88 Hz, CNCH($CH_3{}^*$)COOH), 0.95 (3H, t, J = 3.60 Hz, $CH_2CH_2CH_3{}^*$); ^{13}C-NMR (600 MHz, DMSO), δ: 195.6 (*COOH), 176.7 (*C=N), 154.5 (2-C), 146.7 (4-C), 144.7 (7a-C), 126.0 (6-C), 123.5 (7-C), 113.4 (3a-C), 105.5 (5-C), 60.6 (CN*$CH(CH_3)$COOH), 43.5 ($^*CH_2CH_2CH_3$), 30.0 ($CH_2{}^*CH_2CH_3$), 17.5 (CNCH($^*CH_3$)COOH), 14.2 ($CH_2CH_2{}^*CH_3$). m/z 292 (M^+, 40%).

6-(1-(4-Hydroxy-2-benzoxazolone-7-yl)butylide-neamino) hexanoic Acid (TC-9). Light yellow solid (44%), m.p. 138.5~140°C; FT-IR (KBr), v: 3368 (O-H), 2962, 2943, 2874, 1732 (C=O), 1707 (C=O), 1637, 1606, 1517, 1465, 1375, 1088, 798; ^{1}H-NMR (DMSO-d6), δ: 13.51 (1H, s, COO-H), 12.06 (1H, s, N-H), 7.96 (1H, s, O-H), 7.61 (1H, d, J = 9.0 Hz, 6-ArH), 6.43 (1H, d, J = 9.0 Hz, 5-ArH), 3.11 (2H, t, J = 6.84 Hz, CNC$H_2^*CH_2CH_2CH_2CH_2$COOH), 2.96 (2H, m,

$CNCH_2CH_2CH_2CH_2CH_2{}^*COOH$), 2.21 (2H, t, J = 7.38 Hz, $CH_2{}^*CH_2CH_3$), 1.64 (2H, m, $CNCH_2CH_2{}^*CH_2CH_2CH_2COOH$), 1.52 (2H, m, $CNCH_2CH_2CH_2CH_2{}^*CH_2COOH$), 1.45 (2H, m, $CNCH_2CH_2CH_2{}^*CH_2CH_2COOH$), 1.31 (2H, m, $CH_2CH_2{}^*CH_3$), 0.93 (3H, t, J = 7.38 Hz, $CH_2CH_2CH_3{}^*$); ^{13}C-NMR (DMSO-d6), δ: 174.9 (*COOH), 172.3 (*C=N), 158.1 (2-C), 156.0 (4-C), 155.7 (7a-C), 127.5 (6-C), 115.5 (7-C), 112.5 (3a-C), 110.4 (5-C), 59.4 ($CN^*CH_2CH_2CH_2CH_2CH_2COOH$), 47.7 ($CNCH_2CH_2CH_2CH_2{}^*CH_2COOH$), 34.1 ($^*CH_2CH_2CH_3$), 29.6 ($CNCH_2{}^*CH_2CH_2CH_2CH_2COOH$), 26.4 ($CNCH_2CH_2CH_2{}^*CH_2CH_2COOH$), 24.7 ($CNCH_2CH_2{}^*CH_2CH_2CH_2COOH$), 18.3 ($CH_2{}^*CH_2CH_3$), 14.1 ($CH_2CH_2{}^*CH_3$). m/z 334 (M^+, 32%).

7-(1-(4-Methoxyphenylimino)butyl)-4-hydroxy-2-benzoxazolone (TC-10). Light yellow solid (52%), m.p. 206~207°C; FT-IR (KBr), υ: 3438 (O-H), 2972, 2876, 2836, 1778 (C=O), 1631, 1608, 1570, 1510, 1442, 1376, 1071, 1034 ($\nu_s(C_{7a}\text{-O-}C_2)$, 850; ^{1}H-NMR (DMSO-d6), δ: 12.09 (1H, s, N-H), 11.85 (1H, s, O-H), 7.54 (1H, d, J = 8.76 Hz, 6-ArH), 7.08 (2H, d, J = 8.94 Hz, 3′,5′-ArH), 6.82 (1H, d, J = 8.76 Hz, 5-ArH), 6.51 (2H, d, J = 8.94 Hz, 2′,6′-ArH), 3.79 (3H, s, $OCH_3{}^*$), 2.74 (2H, t, J = 5.76 Hz, $CH_2{}^*CH_2CH_3$), 1.58 (2H, m, $CH_2CH_2{}^*CH_3$), 0.83 (3H, t, J = 7.38 Hz, $CH_2CH_2CH_3{}^*$); ^{13}C-NMR (DMSO-d6), δ: 177.4 (*C=N), 157.6 (1′-C_{Ar}), 154.9 (2-C), 151.2 (4-C), 146.9 (7a-C), 137.2 (4′-C_{Ar}), 124.5 (6-C), 123.6 (3′,5′-C_{Ar}), 119.6 (7-C), 115.0 (2′,6′-C_{Ar}), 113.4 (3a-C), 100.5 (5-C), 55.8 (O^*CH_3), 31.1 ($^*CH_2CH_2CH_3$), 22.6 ($CH_2{}^*CH_2CH_3$), 14.4 ($CH_2CH_2{}^*CH_3$) m/z: 326 (M^+, 38%).

3. Result and Discussion

3.1. Biological Testing

3.1.1. Analgesic Activity. Analgesic activity was examined by using the hot-plate test protocol [8, 9]. 120 Webster mice of both sexes weighing 18–22 g were used for study. All animals were fed diet in pellets following standard good laboratory practices. Mice were divided into 12 groups. All of the compounds and the reference drug were suspended in 0.5% carboxymethyl cellulose (CMC) solution. The first group as negative control received 5% CMC solution and the second group received aspirin (g) as a reference drug, while the other groups received the 10 test compounds. Mice were dropped gently in a dry glass beaker of 1 dm^3 capacity maintained at 50.5–55°C. Normal reaction time in seconds for all mice was determined at time intervals of 30, 60, and 90 minutes; this is the interval extending from the instant the mouse reaches the hot beaker till the animal licks its feet or jumps out of the beaker (dose 10 mg/kg). The relative potencies to aspirin (g) were then determined (Table 1). Mice were maintained under 12 h light/dark cycles with controlled temperature (28°C).

HBOA and TC-3, TC-5, TC-7, TC-8, and TC-9 exhibited more petent analgesic than aspirin. Compounds TC-3, TC-8, and TC-9 showed around twice the activity of aspirin after 90 minutes.

Table 1: Analgesic activities of test compounds.

Comp. number	Comparative analgesic potency to aspirin after time in minutes		
	30 min	60 min	90 min
HBOA	1.16 ± 0.03	1.88 ± 0.09	1.10 ± 0.16
TC-2	0.70 ± 0.09	1.55 ± 0.12	0.55 ± 0.08
TC-3	0.37 ± 0.07	1.88 ± 0.13	2.14 ± 0.14
TC-4	0.35 ± 0.03	0.80 ± 0.07	0.87 ± 0.13
TC-5	0.91 ± 0.05	1.12 ± 0.08	1.45 ± 0.15
TC-6	0.15 ± 0.04	0.45 ± 0.09	0.56 ± 0.09
TC-7	1.01 ± 0.06	1.20 ± 0.12	1.35 ± 0.13
TC-8	0.68 ± 0.07	0.88 ± 0.11	1.98 ± 0.14
TC-9	0.60 ± 0.05	0.91 ± 0.10	1.81 ± 0.21
TC-10	0.98 ± 0.08	0.40 ± 0.7	0.31 ± 0.08
Aspirin	1.00	1.00	1.00

All results were significantly different from the standard and normal control. Value at P = 0.05.

Table 2: Anti-inflammatory of test compounds.

Comp. number	Increase in edema (mL) ± SEM	% protection	Activity relative to aspirin
Control	1.06 ± 0.04	0.0	0.0
HBOA	0.82 ± 0.03	22.5	54
TC-2	0.64 ± 0.03	39.6	95
TC-3	0.48 ± 0.03	54.7	131
TC-4	0.73 ± 0.03	31.1	75
TC-5	0.57 ± 0.03	46.2	111
TC-6	0.85 ± 0.03	19.8	48
TC-7	0.73 ± 0.03	31.1	75
TC-8	0.46 ± 0.03	56.6	136
TC-9	0.78 ± 0.03	26.4	64
TC-10	0.95 ± 0.03	10.4	25
Aspirin	0.62 ± 0.03	41.5	100

All results were significantly different from the standard and normal control. Value at P = 0.05.

3.1.2. Anti-Inflammatory Activity. Anti-inflammatory activity was examined by using carrageenan-induced rat paw edema test [10]. Seventy-two adult Sprague-Dawley rats, weighing 150–180 g, were used. All animals were fed diet in pellets following standard good laboratory practices. The animals were randomly divided into 12 groups of six animals each. All of the compounds and the reference drug were suspended in 0.5% carboxymethyl cellulose (CMC) solution. The standard drug aspirin and the test compounds were given at a dose of 20 mg/kg. After one hour of the administration of the compounds and standard drug, 0.1 mL of 1% carrageenan solution in saline was injected into the subplantar region of the right hind paw of each rat. The right hind paw volume was measured after 3 h of carrageenan treatment by means of plethysmometer.

The test compounds showed anti-inflammatory activity ranging from 10.4% to 56.6%, whereas the standard drug aspirin showed 41.5% inhibition of edema after three hours. Compounds TC-3, TC-5, and TC-8 showed more potent anti-inflammatory activity than aspirin (Table 2).

3.2. Chemistry. In this research, we synthesized compounds TC-2 to TC-10, and their bioactivities were tested by carrageenan-induced rat paw edema and hot-plate test methods. The results show that compounds HBOA and TC-3, TC-5, TC-7, TC-8, and TC-9 are active as analgesic and compounds TC-3, TC-5, and TC-8 are active as anti-inflammatory agent, while the other compounds are poorly active towards the tested organisms.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Tieyu Chen and Guangjin Zheng have equally contributed to this work.

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