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Synthesis and evaluations of selective COX-2 inhibitory effects: benzo[*d*]thiazol analogs

Li-Ya He[a†], Shan-Shan Zhang[a†], Ding-Xin Peng[a], Li-Ping Guan[a*], Xi-Hong Wang [b*]

[a] *Food and Pharmacy College, Zhejiang Ocean University, Zhejiang, Zhoushan 316022, P. R. China*
[b] *Key Laboratory of Natural Resource of the Changbai Mountain and Functiaonal Molecules, Ministry of education, Yanbian University, Jilin Yanji 133000, China*

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ABSTRACT

A series of benzo[*d*]thiazole analogs were synthesized and evaluated for their anti-inflammatory and analgesic effects. Using an ear edema model, except for compounds **2k**, **2m-2q** and **3a**, other compounds showed the anti-inflammatory effects. Among them, compounds **2c**, **2d**, and **2g** showed the best anti-inflammatory activity (inhibition rate: 86.8 %, 90.7 % and 82.9 %, respectively). By the acetic acid-induced abdominal writhing test, except for compounds **2e**, **2l**, **2m**, **2o**, **2p** and **3a**, other compounds showed the analgesic effects with inhibition rate values of 51.9–100 % (**2a-2r**) and 68.6–100 % (**3a-3g**). Next, compounds **2c**, **2d**, **2g**, **3d**, **3f**, **3g** that displayed the excellent anti-inflammatory and analgesic activities were evaluated for their inhibitory effect against ovine COX-1 and COX-2. Compounds **2c**, **2d**, **2g**, **3d**, **3f**, **3g** were weak inhibitors of the COX-1 isozyme but exhibited the moderate COX-2 isozyme inhibitory effects IC_{50} from 0.28 to 0.77 μM and COX-2 selectivity indexes (SI: 18.6 to 7.2). This benzo[*d*]thiazole moiety will be proved to be of great significance for developing more potent COX-2 inhibitors.

Benzothiazoles are bicyclic heterocyclic aromatic hydrocarbon compounds that possess thiazole and phenyl rings including sulfur and nitrogen in their structures. Benzothiazole derivatives are an interesting core responsible for numerous types of biological effects and pharmacological properties including anticancer, antioxidant, anti-inflammatory, antibacterial, antiviral, analgesic, cycloxygenase and lipoxygenase inhibitory properties. [1-8]

The non-steroidal anti-inflammatory drugs are widely used therapeutics to treat the inflammation and pain from the various pathological disorders. The non-steroidal anti-inflammatory drugs affect by inhibiting cyclooxygenase enzymes, which catalyze prostaglandin biosynthesis through arachidonic acid. Cyclooxygenase enzymes-1 (COX-1) and cyclooxygenase enzymes-2 (COX-2) are two known cyclooxygenase isoform. But, the use of the non-steroidal anti-inflammatory drugs might lead to some side effect containing renal dysfunction, bleeding and pepticulcers, mainly non-selective or selective COX-1 inhibitors. [9,10] So, the interestingly selective inhibition of COX-2 over COX-1 is believed to reduce gastric ulceration side effect and identification of clinically useful non-steroidal analgesic and anti-inflammatory and drugs *via* selective inhibition of COX-2 is an ongoing goal in medicinal chemistry.[11,12] Therefore, the development and study of the efficient and new selective COX-2 inhibitory compounds is essential.

In addition to benzothiazole compounds have been reported to display the anti-inflammatory and analgesic effects, which is an important moiety in medicinal chemistry. Such as, compounds **I** displayed the anti-inflammatory activity with inhibition rate 78 %[13]. Compound **II** showed a good analgesic effect with IC_{50} for 3.70 mg[14]. In addition, Eleftheriou *et al*., also reported that a new series of benzisothiazole-2-ylimino-5-aryliden-4-thiazolidinones were also found to exhibit some COX-2 inhibitory activity (12.3-45.0 %) as shown Figure 1[16]. Among them, two compounds exhibited the highest potency and selectivity for COX-2 inhibitory activity introducting of two chloro groups.

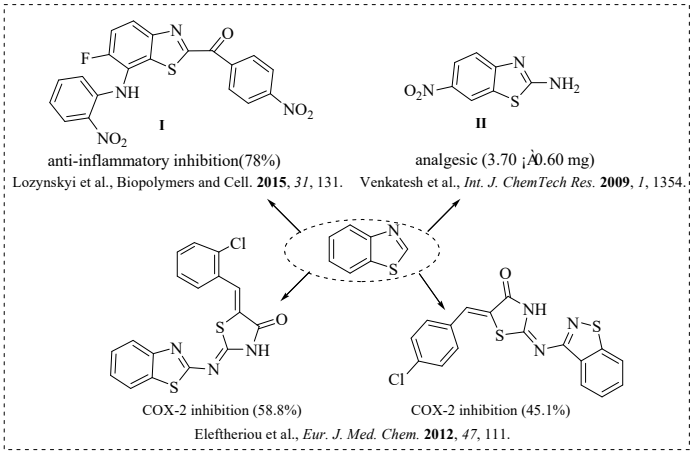


Figure 1. Benzothiazole analogs of reported anti-inflammatory, analgesic or as COX-2 inhibitors.

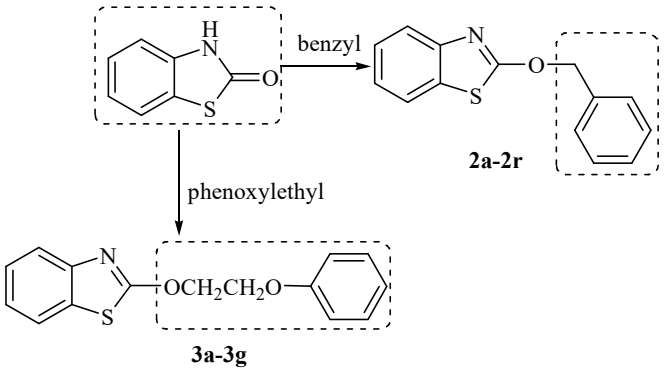
Selection of the fragments that can be used for the design of new chemicals with the required biological activity profile is a key stage in inhibitor of COX-2. Our research group has been studying with the chemical and biological properties of heterocyclic compounds. However, not many inhibition activity reports the inhibitor of COX-2 of benzo[*d*]thiazole and ethoxyl-benzo[*d*]thiazole analogs. Therefore the development with

E-mail: glp730@163.com (L.P.Guan); shwang@ybu.edu.cn(S.-H. Wang)

† These authors contributed equally to this work.
* Corresponding author. Tel.: +86-580-2555280.+86-433-2732207

essential.

Based on these results, as part of our groups search for the potential anti-inflammatory, analgesic and selective COX-2 inhibitory compounds with the chemical and biological properties of benzo [*d*]thiazol compounds, we synthesized eighteen benzyloxybenzo [*d*]thiazole (**2a-2r**) and seven phenoxylethoxylbenzo[*d*]thiazole analogs (**3a–3g**) (Figure 2), and evaluated their anti-inflammatory and analgesic effects *in vivo*. The COX-1 and COX-2 inhibition effects of selected compounds were also determined *in vitro.*

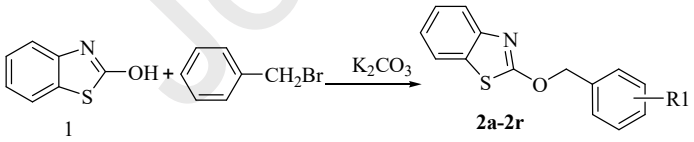


benzo[*d*]thiazol-2(3*H*)-one

Figure 2. The structures of benzo[*d*]thiazol analgesics **2a-2r** and **3a-3g**

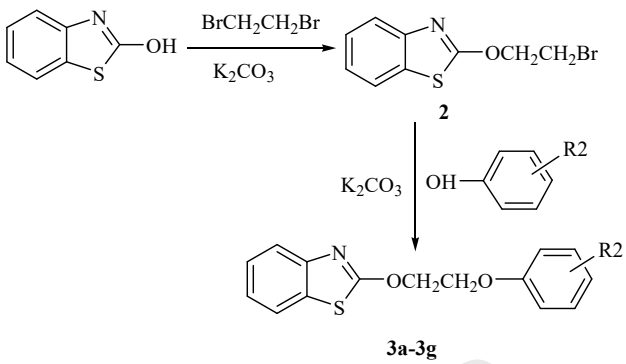
Compounds **2a–2r** and **3a–3g** were prepared as shown in Schemes 1. The commercially available benzo[*d*]thiazol-2-ol (**1**) is the starting material; compounds **2a–2r** is obtained through introduction of benzyl group by a one-step nucleophilic substitution reaction. Compounds **3a–3g** are obtained through a two-step reaction, the intermediate 2-(2-bromoethoxy) benzo[*d*] thiazole (**2**) is synthesized and underwent a nucleophilic substitution reaction with 1,2-dibromoethane, then the 2-(2-bromoethoxy)benzo[*d*]thiazole formed is reacted with substituted phenols.[17,18] The structures of Compounds **2a–2r** and **3a–3g** are determined by infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), carbon nuclear magnetic resonance (^{13}C-NMR) spectroscopy, and mass spectroscopy (MS).

The IR spectra of the synthesized derivatives **2a–2r** and **3a–3g** showed absorption bands at 1682–1686 cm^{-1} for the -C=N stretching vibration, 1250-1255 cm^{-1} for the C-O-C stretching vibration and 1050-1055 cm^{-1} for the C-S-C stretching vibration. The ^{1}H-NMR data confirmed the presence of an -CH_2Ph group as a singlet signal at 5.06-5.25 ppm. The ^{13}C-NMR spectra showed the appearance of a peak from 39.50–46.25 ppm for the -CH_2Ph group and 170.28–170.43 ppm for the C=N group. [19,20]



R1:

2a=H	**2b**=2-F	**2c**=3-F	**2d**=4-F
2e=2-Cl	**2f**=3-Cl	**2g**=4-Cl	**2h**=2-Br
2i=3-Br	**2j**=4-Br	**2k**=4-NO_2	**2l**=4-CN
2m=2-CF_3	**2n**=4-CF_3	**2o**=4-CH_3	**2p**=4-OCH_3
2q=3,5-$(CH_3)_2$	**2r**=3,5-$(OCH_3)_2$		



R2:

3a=H	**3b**=4-F	**3c**=4-Cl	**3d**=4-Br
3e=2,4-F_2	**3f**=2,4-Cl_2	**3g**=2,4-Br_2	

Scheme 1. The synthetic routes of compounds **2a–2r** .and **3a-3g**

Fragment can be selected for the design, synthesis and developing of the novel potent COX-2 inhibitors with a multiple mechanism of action[21]. Based on the results of fragment library analysis and taking into account the synthetic accessibility and SAR analysis of the designed thiazole derivatives. [22] Twenty-five benzo[*d*]thiazole derivatives and the reference drug indomethacin were evaluated for their anti-inflammatory activities using a xylene-induced ear edema model *in vivo*.[23] The percentage inhibition of the inflammation for benzo[*d*]thiazole derivatives was examined after 1 h of treatment with xylene. The anti-inflammatory activities of benzo[*d*]thiazole derivatives **2a-2r** and **3a-3g** (100 mg/kg) were comparable to indomethacin (100 mg/kg) (Table 1). 11 compounds **2a-2j** and **2l** displayed the anti-inflammatory effects administered intraperitoneally before the inflammatory agent xylene with ear inflammation values of 0.19 mg to 1.79 mg and the inhibition rate of the inflammation of 12.7 %–90.7 %. Nine compounds **2a-2d** and **2f-2j** exhibited good anti-inflammatory effects with inhibition values more than 65 %, which the part compounds was nearly equivalent to that of indomethacin (82.4 %). Except for compound **3a**, the rest compounds **3b-3g** exhibited the anti-inflammatory effect administered intraperitoneally before the inflammatory agent xylene with ear inflammation values from 0.11 mg to 0.90 mg and inhibition rate of inflammation of 56.1–94.6 %. Compounds **3d**, **3f**, and **3g** also showed the excellent anti-inflammatory effects with inhibition rate of inflammation of 94.6 %, 85,4 % and 87.3 %, respectively, which was nearly equivalent to that of indomethacin (82.4 %).

Table 1. Anti-inflammatory effects of compounds **2a-2r** and **3a-3g** *in vivo*

Compd	Anti-inflammatory activity				
	Edema mean ±SD (mg)	Inhibition rate %[a]		Edema mean ±SD (mg)	Inhibition rate %
2a	0.64±0.23**	68.8	**3a**	1.90±0.90	7.31
2b	0.52±0.19**	74.6	**3b**	0.56±0.32**	72.7
2c	**0.27±0.10*****	86.8	**3c**	0.69±0.22**	66.3
2d	**0.19±0.07*****	90.7	**3d**	**0.11±0.07*****	94.6
2e	1.75±0.64*	14,6	**3e**	0.90±0.17*	56.1
2f	0.41±0.24**	80.0	**3f**	**0.30±0.18*****	85.4
2g	**0.35±0.14*****	82.9	**3g**	**0.26±0.19*****	87.3
2h	0.50±0.26**	75.6			
2i	0.46±0.21**	77.6			
2j	0.45±0.18**	78.0			
2k	1.96±0.97	4.39			
2l	1.79±0.55*	12.7			

2m				
2n	1.80±0.86	12.2		
2o	2.01±0.76	1.95		
2p	2.00±0.75	2.43		
2q	2.04±0.83	0.50		
2r	1.14±0.50*	44.4		
Idm	0.36±0.23***	82.4	0.36±0.23***	82.4
control	2.05±0.40	—	2.05±0.40	—

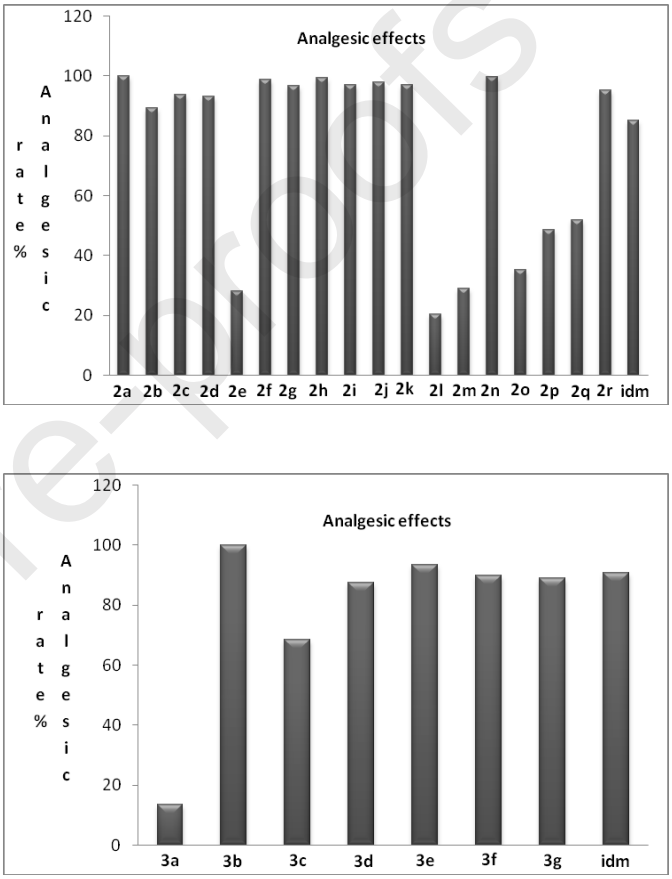
Idm: Indomethacin.

[a] % at 1 h of anti-inflammatory activity.

*p<0.05, ** p<0.01,*** p<0.001 compared with the PEG-400 (control) group

The structure activity relationship studies for the anti-inflammatory effects of eighteen analogs **2a-2r** and seven **3a–3g** shown in table 1 illustrated. Seventeen compounds reduced the ear inflammation and displayed the anti-inflammatory effects not only including the electron-donating substituents but also the electron-withdrawing substituents on the benzyloxy or phenoxyl-ethoxyl moiety. For compounds containing the electron-donating groups of -CH_3, -OCH_3, 3,5-$(CH_3)_2$ on the phenyl ring, do not show a good anti-inflammatory effects, only compound **2r** with 3,5-$(OCH_3)_2$ showed the anti-inflammatory activity. Among compounds possessing the electro-withdrawing substituents, fifteen compounds **2b-2j** and **3b-3g** with halogen atom substitution F (**2b**, **2c** and **2d**), Cl (**2e**, **2f** and **2g**), or Br (**2h**, **2i** and **2j**), resulted in the most anti-inflammatory effects when substituted at the *p*-position of the phenyl ring as demonstrated for compounds **2d**, **2g** and **2j**, with the best compound being **2d** with ear inflammation values 90.7 % for benzyloxybenzo[*d*] thiazole derivatives. Within **3b-3g** series, the excellent anti-inflammatory were observed when a halogen atom as electron-withdrawing groups was present. Compound **3d** exhibited the most effect with the bromine at *p*-position. Therefore, the substitution position of the halogen atom greatly influenced the anti-inflammatory effects. The order of activity for **2b-2j** derivatives containing substitutions on the phenyl ring was 4-F>2-F>3-F, 4-Cl>2-Cl>3-Cl, and 4-Br>2-Br> 3-Br. The order of activities for **3b-3d** compounds with substitutions on the phenyl ring was 4-Br>4-F>4-Cl and the order of activity for 2,4-disubstituted compounds **3e-3g** positions was 2,4-Br_2 2,4-Cl_2> 2,4-F_2. However, for compounds **2k-2n** with a trifluoromethyl (-CF_3), nitro (-NO_2) or cyano (-CN) groups on the phenyl ring do not display the anti-inflammatory activity. The replacement of less lipophilic nitro trifluoromethyl and cyano group substituent leads to a decrease effects. It may be no clear correlation between *in vivo* activity.

The analgesic effects of analogs **2a-2r** and seven **3a–3g** were evaluated by the acetic acid-induced abdominal writhing test and compared with indomethacin as the reference. Except for compounds **2e**, **2l**, **2m**, **2o**, **2p** and **3a**, other compounds displayed the analgesic effects a with activities inhibition rate values of 51.9–99.9 % (**2a-2r**) and 68.6–99.9 % (**3a-3g**) not only with the electron-donating substituents but also with the electron-withdrawing substituents on the phenyl ring at a dose of 100 mg/kg administered intraperitoneally (Figure 3). For four compounds including the electron-donor groups of -CH_3, -OCH_3, 3,5-$(CH_3)_2$, and 3,5-$(OCH_3)_2$ on the phenyl ring, the order of the analgesic effects was 3,5-$(OCH_3)_2$>3,5-$(CH_3)_2$>4-OCH_3>4-CH_3. Among compounds possessing electron-withdrawing substituents **2b-2j** series and **3b-3g** series, some with an halogen atom substituent group, F (**2b**, **2c** and **2d**), Cl (**2e**, **2f** and **2g**), or Br (**2h**, **2i** and **2j**), display the excellent analgesic effects specially when in the *m*-position of the phenyl ring as shown for series F (**2b**, **2c** and **2d**), Cl (**2e**, **2f** and **2g**), but at the *o*-position of the phenyl ring for compounds Br (**2h**, **2i** and **2j**). Thus, the position of the halogen atom substitution greatly also influenced the for compounds including substitutions on the phenyl ring was 3-F>4-F>2-F and 3-Cl>4-Cl>2-Cl. The order of effects observed for compounds containing a Br-substituent was 2-Br>4-Br>3-Br. For compounds **3b-3d** displayed the best analgesic effects was 4-F>4-Br>4-Cl, and the order of activity for 2,4-disubstituted compounds **3e-3g** positions was 2,4-F_2>2,4-Cl_2>2,4-Br_2. Compound **3b** with a 4- fluorine substituent showed the most analgesic effect with inhibition rate values of 99.9 %. For compounds **2k-2n** with a trifluoromethyl (-CF_3), nitro (-NO_2) or cyano (-CN) groups on the phenyl ring, compounds **2k** and **2n** displayed better analgesic activities with inhibition values of 97.0 % and 99.57 %. But compounds **2l** and **2m** did not show analgesic activities.



Notes: idm: Indomethacin

Figure 3. Analgesic effect of the designed compounds **2a-2r** and **3a-3g**

Traditional non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen or indomethacin, mainly non-selective or selective COX-1inhibitors, was associated with renal disorders, gastrointestinal problems and bleeding diathesis.[25-27] The gastrointestinal irritation, bleeding, and ulceration side effects of the classical non-steroidal anti-inflammatory drugs are attributed to their selectivity for COX-1 versus COX-2. Therefore, the development of novel selective COX-2 inhibitors through medicinal chemistry approaches is essential.[28,29] So, in this present study, we select six compounds **2c**, **2d**, **2g**, **3d**, **3f**, **3g** that showed the excellent anti-inflammatory and analgesic activities were evaluated for their inhibitory effect against ovine COX-1 and COX-2 (Table 2). The results exhibited that three compounds including a benzyloxybenzo[*d*]thiazole moiety were weak inhibitors of the COX-1 isozyme but showed moderate COX-2 isozyme inhibitory effects (IC_{50} from 0.28 μM to 0.77 μM) and COX-2 selectivity indexes (SI: 18.6 to 7.2). Furthermore, three compounds containing phenoxylethoxylbenzo[*d*]thiazole moiety

were moderate COX-2 isozyme inhibitory effects (IC_{50}: from 0.27 μM to 0.41 μM) and COX-2 selectivity indexes (SI: 19.7 to 10.4). Additionally, the activity of compound **2c** (IC_{50}=0.28 μM, SI=18.6) was more similar to inhibitors of the COX-2 isozyme than the reference drug celecoxib (IC_{50} =0.27 μM, SI=19.7). The results indicated that the molecular hybridization of benzo[*d*] thiazole pharmacophore of the COX-2 inhibitors was a useful building block to produce effective hybrid scaffolds with improved analgesic and anti-inflammatory effect potential.

Table 2. COX-1/COX-2 enzyme inhibition assay *in vitro*

Compounds	COX-1, IC_{50}(μM) [a]	COX-2, IC_{50}(μM)	COX-2, SI [b]
2c	5.22±0.10	0.28±0.12	18.6
2d	6.20±0.15	0.37±0.19	16.8
2g	5.55±0.20	0.77±0.29	7.2
3d	5.32±0.26	0.50±0.08	10.6
3f	4.28±0.18	0.41±0.26	10.4
3g	5.08±0.14	0.36±0.03	14.1
Celecoxib	5.33±0.11	0.27±0.07	19.7

[a] IC_{50} value is the compound concentration required to produce 50% inhibition of COX-1 or COX-2 for means of three determinations and deviation from the mean is <10% of the mean value.

[b] SI: selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

In conclusion, 25 benzo[*d*]thiazole compounds bearing a benzyloxy or phenoxylethoxyl moiety were designed, synthesized and evaluated for their anti-inflammatory and analgesic activities. The results indicated that 18 compounds displayed the anti-inflammatory effects, 20 compounds showed the analgesic. Among them, compounds **2d** and **3d** exhibited the most anti-inflammatory with inhibition of inflammation of 90.7 % and 94.6 %. Next, compounds **2c**, **2d**, **2g**, **3d**, **3f**, **3g** that displayed the excellent anti-inflammatory and analgesic activities were evaluated for their inhibitory effect against ovine COX-1 and COX-2, compounds **2c**, **2d**, **2g**, **3d**, **3f**, **3g** were weak inhibitors of the COX-1 isozyme but showed moderate COX-2 isozyme inhibitory activities IC_{50} from 0.28 μM to 0.77 μM) and COX-2 selectivity indexes (SI: 18.6 to 7.2). Hence, these compounds reported herein are promising starting points for the development of an inhibitor of COX-2.

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19. A stirred solution of benzothiazolone (3.0 mmol), anhydrous K_2CO_3 (3.0 mmol) and 5 mL DMF were placed to round-bottomed flask, the reaction solution was mixed for 1 hour at 60 °C, after that, 1.2 mmol 4-fluorobrominated benzyl was placed slowly to the reaction solution. The reaction solution was refluxed for five h, the reaction process was determined by TLC. The filtrate was cleaned through acetone. The removal of solution by vacuum distillation, the crude products was purified with MeOH. The yield, melting point, and spectral data of each compound are given as below.

mp: 89.4-89.9°C. IR (KBr) cm^{-1}: 2924, 1684, 1252, 1054. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.11 (s, 2H, -CH_2Ph), 6.94-7.21 (m, 4H, -C_6H_4), 7.23-7.45 (m, 4H, -C_6H_4). ^{13}C-NMR ($CDCl_3$, 75 MHz): 45.52, 111.09, 115.72, 116.01,122.67, 122.73, 123.38, 126.39, 128.93, 129.04,130.98, 136.79 ,160.74,

20. A stirred solution of benzothiazolone (3.0 mmol), anhydrous K_2CO_3 (3.0 mmol) and 5 mL DMF were added a round-bottomed flasks, the reaction solution was stirred for 1 hour at 60 °C, and, 2-(2-bromoethoxy)benzo[*d*]thiazole (3.0 mmol) was slowly added the reaction solution, after the completion of the reaction (monitored by TLC), then added 10 mL the mixture of NaOH and 4-bromophenols. The reaction solution was refluxed for 5 hours. Filtered 10% HCl was washed through water. The crude product was recrystallized with methanol.

    2-[2-(4-bromophenoxyl)ethoxyl]benzo[*d*]thiazole (**3d**). Yield: 40.11%, mp: 83.8-85.0°C. IR (KBr) cm^{-1}: 2924, 1684, 1252, 1054. ^{1}H-NMR($CDCl_3$, 300 MHz): 4.26 (t, 2H, -CH_2), 4.34 (t, 2H, -CH_2), 6.68-6.70 (m, 4H, -C_6H_4), 7.16-7.43 (m, 4H, -C_6H_4). ^{13}C-NMR ($CDCl_3$, 75 MHz): 42.27, 65.61, 109.85, 111.22, 113.52, 116.18, 117.25, 122.59, 122.70, 123.28, 126.29, 132.32, 137.38, 157.19, 170.34. ESI-MS calcd for $C_{15}H_{13Br}NO_2S^+$ ([M+H]$^+$): 349.98; found: 350.05.

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$I]^+$): 260.05; found: 260.00.

Declaration of interests

☑The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Synthesis and evaluations of selective COX-2 inhibitory effects: benzo[*d*]thiazol analogs

Li-Ya He[a†], Shan-Shan Zhang[a†], Ding-Xin Peng[a], Li-Ping Guan[a*], Xi-Hong Wang [b*]