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Synthesis, biological evaluation of benzothiazole derivatives bearing a 1,3,4-oxadiazole moiety as potential anti-oxidant and anti-inflammatory agents

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ABSTRACT

Twenty benzothiazole derivatives bearing a 1,3,4-oxadiazole moiety were synthesized and evaluated for their anti-oxidant and anti-inflammatory activities. Among these compounds, **8h** and **8l** were appeared to have high radical scavenging efficacies as 0.05 ± 0.02 and 0.07 ± 0.03 mmol/L of IC_{50} values in $ABTS^{+\cdot}$ bioassay, respectively. In anti-inflammatory tests, compound **8h** displayed good activity with 57.35% inhibition after intraperitoneal administration, which was more potent than the reference drug (indomethacin). Molecular modeling studies were performed to investigate the binding mode of the representative compound **8h** into COX-2 enzyme. *In vitro* enzyme study implied that compound **8h** exerted its anti-inflammatory activity through COX-2 inhibition.

Oxidative stress and inflammation are closely related to the pathogenesis of various life-threatening human diseases, such as cancer, atherosclerosis, diabetes and its complications (i.e. diabetic nephropathy).[1–4] Mounting evidence indicates that oxidative stress and inflammation are inextricably intertwined, with complicated feedforward and feedback loops.[5–7] Consequently, development of novel and effective therapeutic drugs to prevent diseases caused by oxidative stress and inflammation is of great significance.[8,9] Benzothiazoles are fused bicyclic systems possessing diverse biological properties such as anti-inflammatory, antioxidant[10] and anticancer effects. In recent years, some benzothiazoles have found application in bioorganic and medicinal chemistry and in the development of clinical drugs such as pramipexole, lubeluzole, probenazole, ethoxazolamide, zopolrestat and bentaluron.[11] Moreover, it has long been known that compounds bearing 1,3,4-oxadiazole ring occupy a prominent place in medicinal chemistry due to its significant biological properties such as antimicrobial,[12] antioxidant[13] and anticancer.[14]

Heterocyclic chemistry has become one of the most important fields of research in pharmaceutical industry due to their many fold applications.[15] For example, Malhotra et al. reported that compound **A** displayed a potent antioxidant activity of up to 51.2% when used at a concentration of approximately 100 μg/mL. Their results show that oxadiazole pharmacophore results in hydrogen peroxide with potent scavenging activity.[16] Racané et al. reported that compound **B** exhibited good antioxidant activity.[17] Furthermore, benzoxazole moieties were observed a good template (compound **C**) for anti-inflammatory activity and p38α MAP kinase inhibition, which was found that isosteric replacement of sulphur atom in benzothiazole ring with oxygen atom showed reduced activity.[18] Fascinated by multifarious bioactivity of these heterocycles, we aimed to synthesize a compact system involving benzimidazole and oxadiazole (Fig. 1) entities conjugated with a hope to develop compounds possessing noteworthy pharmacological properties. Taking the aforementioned points into consideration, we designed and synthesized two series of compounds (**8a–o**, **10a–e**) (Fig. 2) using a hybrid strategy with compounds **A–C** as the lead compounds. These compounds were subsequently evaluated in terms of their anti-oxidant and anti-inflammatory activities. Antioxidant activity of these derivatives have been evaluated by DPPH (2,2′-diphenyl-1-picrylhydrazyl), hydroxyl radical ($OH^{\cdot}$) and ABTS (2,2′-Azino-bis-3-ethylbenzthia-zoline-6-sulfonic acid) radical scavenging assay. The anti-inflammatory activity was evaluated by an *in vivo* inhibition assay by monitoring xylene-induced ear edema in mice.

The synthetic procedure to obtain the final compounds is depicted in Scheme 1. Compounds **3a–k** were prepared using a previously

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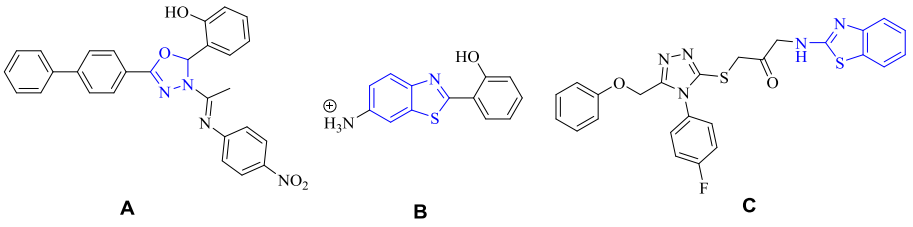
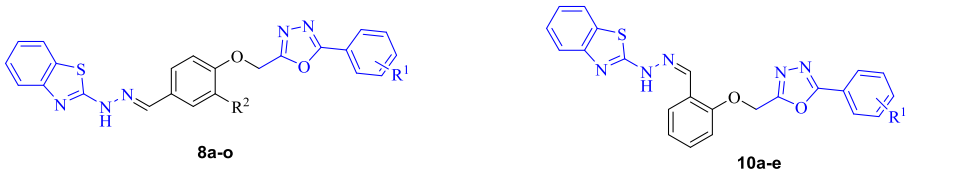
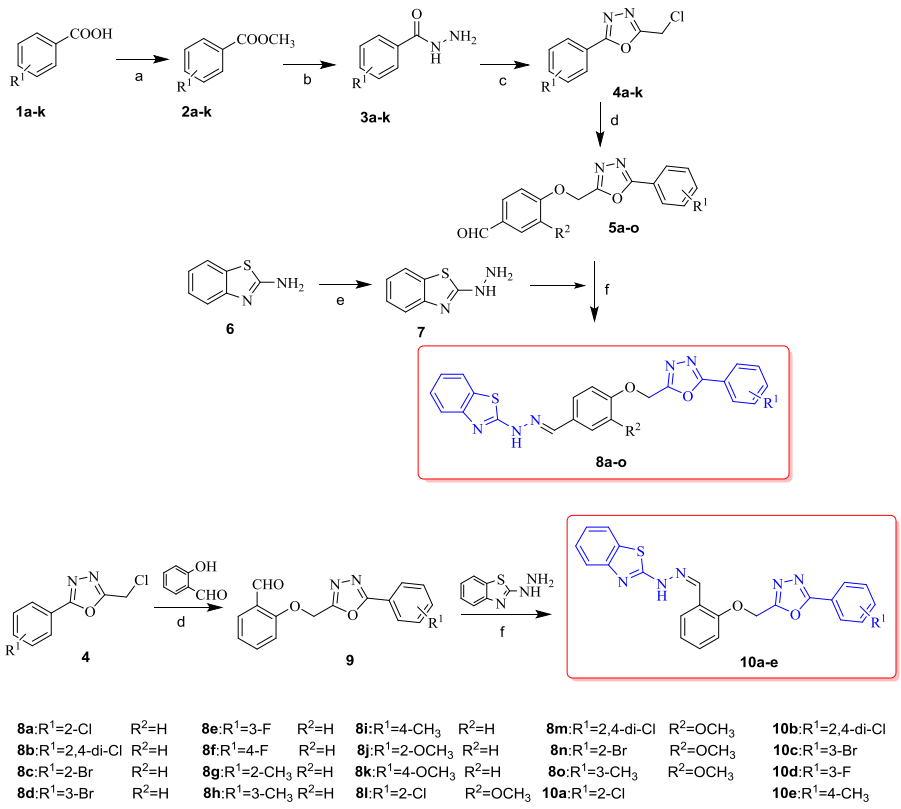


Fig. 1. Chemical structures of some reported compounds.



8a:R^1=2-Cl R^2=H; 8b:R^1=2,4-di-Cl R^2=H; 8c:R^1=2-Br R^2=H; 8d:R^1=3-Br R^2=H; 8e:R^1=3-F R^2=H; 8f:R^1=4-F R^2=H; 8g:R^1=2-CH_3 R^2=H; 8h:R^1=3-CH_3 R^2=H; 8i:R^1=4-CH_3 R^2=H; 8j:R^1=2-OCH_3 R^2=H; 8k:R^1=4-OCH_3 R^2=H; 8l:R^1=2-Cl R^2=OCH_3; 8m:R^1=2,4-di-Cl R^2=OCH_3; 8n:R^1=2-Br R^2=OCH_3; 8o:R^1=3-CH_3 R^2=OCH_3; 10a:R^1=2-Cl; 10b:R^1=2,4-di-Cl; 10c:R^1=3-Br; 10d:R^1=3-F; 10e:R^1=4-CH_3

Fig. 2. Design of target compounds based on the combination principles.



8a:R^1=2-Cl R^2=H; 8b:R^1=2,4-di-Cl R^2=H; 8c:R^1=2-Br R^2=H; 8d:R^1=3-Br R^2=H; 8e:R^1=3-F R^2=H; 8f:R^1=4-F R^2=H; 8g:R^1=2-CH_3 R^2=H; 8h:R^1=3-CH_3 R^2=H; 8i:R^1=4-CH_3 R^2=H; 8j:R^1=2-OCH_3 R^2=H; 8k:R^1=4-OCH_3 R^2=H; 8l:R^1=2-Cl R^2=OCH_3; 8m:R^1=2,4-di-Cl R^2=OCH_3; 8n:R^1=2-Br R^2=OCH_3; 8o:R^1=3-CH_3 R^2=OCH_3; 10a:R^1=2-Cl; 10b:R^1=2,4-di-Cl; 10c:R^1=3-Br; 10d:R^1=3-F; 10e:R^1=4-CH_3

Scheme 1. Synthetic scheme for the synthesis of the target compounds. Reagents and conditions: (a) MeOH, H_2SO_4, 85–90%; (b) $NH_2NH_2{\cdot}H_2O$, 80–90%; (c) $POCl_3$, DMF, chloroacetic acid, 70–80%; (d) hydroxybenzaldehyde or vanillin, K_2CO_3, KI, acetone, reflux, 80–90%; (e) $NH_2NH_2{\cdot}H_2O$, $NH_2NH_2{\cdot}HCl$, ethylene glycol, 140 °C, 50–60%; (f) EtOH, AcOH, 60–80 °C, 60–80%.

described method.[19] Compounds **4a–k** were synthesized by refluxing an equimolar mixture of 2-hydroxyacetyl chloride with substituted benzohydrazide **3a–k** in phosphorous oxychloride. Intermediates **5** and **9** were prepared by the alkylation reactions of compound **4** with hydroxybenzaldehyde or vanillin, respectively. Intermediates **5** and **9** were then subjected to a condensation reaction with 2-hydrazinylbenzo[*d*]thiazole to provide the target compounds **8a–o** and **10a–e** in good yields. All new compounds showed excellent analytical and spectroscopic data, in good agreement with their structures (see Experimental Part).

This assay is mainly based on the electron transfer and reduction of the radical $ABTS^{+\cdot}$ cations, which may be more efficient than that of DPPH.[20] $ABTS^{+\cdot}$ generated by oxidation was determined by the commercial screening kit (Beyotime Institute of Biotechnology, Jiangsu, China). The color of the $ABTS^{+\cdot}$ solution changed due to the capacity of the antioxidant compounds to reduce the preformed radical. The

Table 1
Results of $ABTS^{+\cdot}$ antioxidant assay.

Compound	R^1	R^2	$ABTS^{+\cdot}$ IC_{50}(mmol/L) ± SD[a]
8a	2-Cl	H	0.45 ± 0.14
8b	2,4-di-Cl	H	0.51 ± 0.24
8c	2-Br	H	4.13 ± 0.16
8d	3-Br	H	0.23 ± 0.08
8e	3-F	H	0.29 ± 0.17
8f	4-F	H	2.29 ± 0.25
8g	2-CH_3	H	0.11 ± 0.05
8h	3-CH_3	H	0.05 ± 0.02
8i	4-CH_3	H	0.88 ± 0.20
8j	2-OCH_3	H	0.75 ± 0.22
8k	4-OCH_3	H	3.53 ± 0.14
8l	2-Cl	OCH_3	0.07 ± 0.03
8m	2,4-di-Cl	OCH_3	0.19 ± 0.07
8n	2-Br	OCH_3	1.28 ± 0.21
8o	3-CH_3	OCH_3	0.42 ± 0.25
10a	2-Cl	–	0.30 ± 0.16
10b	2,4-di-Cl	–	17.72 ± 0.13
10c	3-Br	–	1.71 ± 0.16
10d	3-F	–	0.39 ± 0.24
10e	4-CH_3	–	0.27 ± 0.17
Resveratrol[b]			1.42 ± 0.12

[a] SD is the standard deviation.
[b] Resveratrol as a positive control.

Table 2
Results of $DPPH^{\cdot}$ and $OH^{\cdot}$ antioxidant assay.

Compound	R^1	R^2	$DPPH^{\cdot}$ IC_{50} (mmol/L) ± SD	$OH^{\cdot}$ IC_{50} (mmol/L) ± SD[a]
8h	3-CH_3	H	0.03 ± 0.01	292.55 ± 0.24
8l	2-Cl	OCH_3	0.05 ± 0.03	340.12 ± 0.17
Resveratrol[b]			0.99 ± 0.15	370.12 ± 0.21

[a] SD is the standard deviation.
[b] Resveratrol as a positive control.

inhibition of the superoxide production and the antioxidant activity were calculated from the percentage decrease in the absorbance. As indicated in Table 1, most of the synthesized compounds presented good antioxidant activity in comparison with the resveratrol, a natural product for affecting a wide range of intracellular mediators. Among these compounds, **8h** and **8l** seem to have high radical scavenging efficacy, IC_{50} values in $ABTS^{+\cdot}$ bioassay of 0.05 ± 0.02 and 0.07 ± 0.03 mmol/L, respectively. Table 2 shows that compounds **8h** and **8l** were also evaluated for their *in vitro* radical scavenging activity using the $DPPH^{\cdot}$ (1,1-diphenyl-2-picrylhydrazyl) radical as a reagent and hydroxyl radical ($OH^{\cdot}$) in the spectrophotometric test.[21] The resveratrol was taken as a standard drug.[22] Compounds **8h** and **8l** exhibited potent antioxidant activity with respective IC_{50} values of 0.03 ± 0.01 mmol/L and 0.05 ± 0.03 mmol/L in the $DPPH^{\cdot}$ assay, showing more potent antioxidant activity than the positive controls resveratrol (IC_{50} = 0.99 ± 0.15 mmol/L). The radical anion was then chemically or enzymatically converted into H_2O_2, which is then transformed into a highly reactive hydroxyl radical ($OH^{\cdot}$) in the presence of reduced transition metals. Compounds **8h** and **8l** also exhibited good antioxidant activity with the IC_{50} values of 292.55 ± 0.24 mmol/L and 340.12 ± 0.17 mmol/L in the $OH^{\cdot}$ assay, respectively. Those values conformed with the high performance observed in the $ABTS^{+\cdot}$ and $DPPH^{\cdot}$ assay.

Detailed structure-activity relationships (SAR) analysis on the benzothiazole and 1,3,4-oxadiazole moieties revealed several structural features that are crucial to maintaining the antioxidant activity. The presence of different substituents (R^1) on the phenyl ring of the 1,3,4-oxadiazole group was found to exert an appreciable influence on the observed effect on antioxidant activity, but no clear pattern could be found for the SAR. The derivatives **8b** (IC_{50} = 0.51 ± 0.24 mmol/L) and **10b** (IC_{50} = 17.72 ± 0.15 mmol/L), containing two Cl atoms, did not exhibit better antioxidant activity than derivatives with a single Cl atom. The 2-chlorinated derivative **10a** (IC_{50} = 0.30 ± 0.16 mmol/L) was more potent than the 2,4-dichlorated compound **10b**. The impact of the substituent position on the benzene ring on the efficacy was not predictable. For the derivatives bearing electron-donating substituents of the phenyl ring, it seems that the methyl group displays much more impact on the antioxidant activity than the methoxy group with an 4–8 fold increase in potency. The introduction of vanillin ring, which containing electron-withdrawing groups substituents (R^1) on the phenyl ring of the 1,3,4-oxadiazole group, improved the activity, as exemplified by a comparison of results for the compounds **8l–n** and **8a–c**. Furthermore, the position of the substituents (R^1) on the benzene ring of compounds **8g–i** had a pronounced effect on their activity, which varied according to the following orders: 3-CH_3 > 2-CH_3 > 4-CH_3 for the methyl-substituted compounds. This concept is also supported by our docking simulations described below. From these results, we focused on compound **8h** in subsequent studies. Further investigations are currently underway in our laboratory to modify and better understand these types of structure.

Oxidative stress has been demonstrated to be involved with the pathogenesis of Alzheimer's disease (AD).[23] Resveratrol, a native stilbene derivative with multiple activities has been advanced into phase II clinical trial for the treatment of AD due to its radical scavenging activity.[24] To further study the interaction mode and analyze the SAR profile of these derivatives for the amyloid precursor protein (PDB ID: 5BUO),[25] a molecular docking study was performed using the LibDock program in Discovery Studio 3.1. Enzyme structures were checked for missing atoms, bonds and contacts. Hydrogen atoms were added to the enzyme structure. Water molecules and bound ligands were manually deleted. The automated molecular docking program of MOE 2008.10 was used to dock compounds **8g**, **8h**, **8i** and **10e** on the active site of the amyloid precursor protein. The docking results for **resveratrol** are included as a reference. The result are shown in Fig. 3 and Table 3. Compound **8g** showed interaction with Met383 (4.03 Å), Gln454 (4.85 Å) and His436 (4.12 Å), respectively. Compound **8h** is bound into the active site, in which the benzothiazole ring formed a hydrogen bond with Gln454 (4.69 Å). The *m*-CH_3 atom of **8h** formed alkyl bond with Ala372 (4.39 Å) and the benzene ring of **8h** showed interaction with the backbone of Met383 (4.02 Å). Compound **8h** is bound into the active site, in which the 1,3,4-oxadiazole moiety formed a hydrogen bond with Lys447 (6.11 Å). Compound **8i** showed interaction with Met383 (4.00 Å) and Lys447 (5.76 Å), respectively. Moreover, Compound **10e** also had interactions with Lys447 (6.21 Å), His436 (5.58 Å) and His447 (6.21 Å), respectively. Especially, compound **8h** strongly bind to the target with a highest LibDock score of 106.12 among the examined compounds. These results therefore provide further evidence that the compound **8h** showed the greatest activity of these compounds, which are consistent with the results observed in the $ABTS^{+\cdot}$ assay.

The *in vivo* anti-inflammatory activities of the synthesized compound **8h** was evaluated using the *in vivo para*-xylene-induced mice ear-swelling model. Dimethyl sulfoxide was used as the vehicle for the primary screening and the compound **8h** was administered at a dose of 100 mg/kg. Indomethacin (100 mg/kg) was used as reference drugs. As shown in Table 4, compound **8h** exhibited good anti-inflammatory activity at 100 mg/kg, measured as 57.35%, higher than the values for the reference drug indomethacin (43.62%). Furthermore, considering its promising anti-inflammatory activity, compound **8h** was chosen for further evaluation. A dose of 100 mg/kg was orally administered at

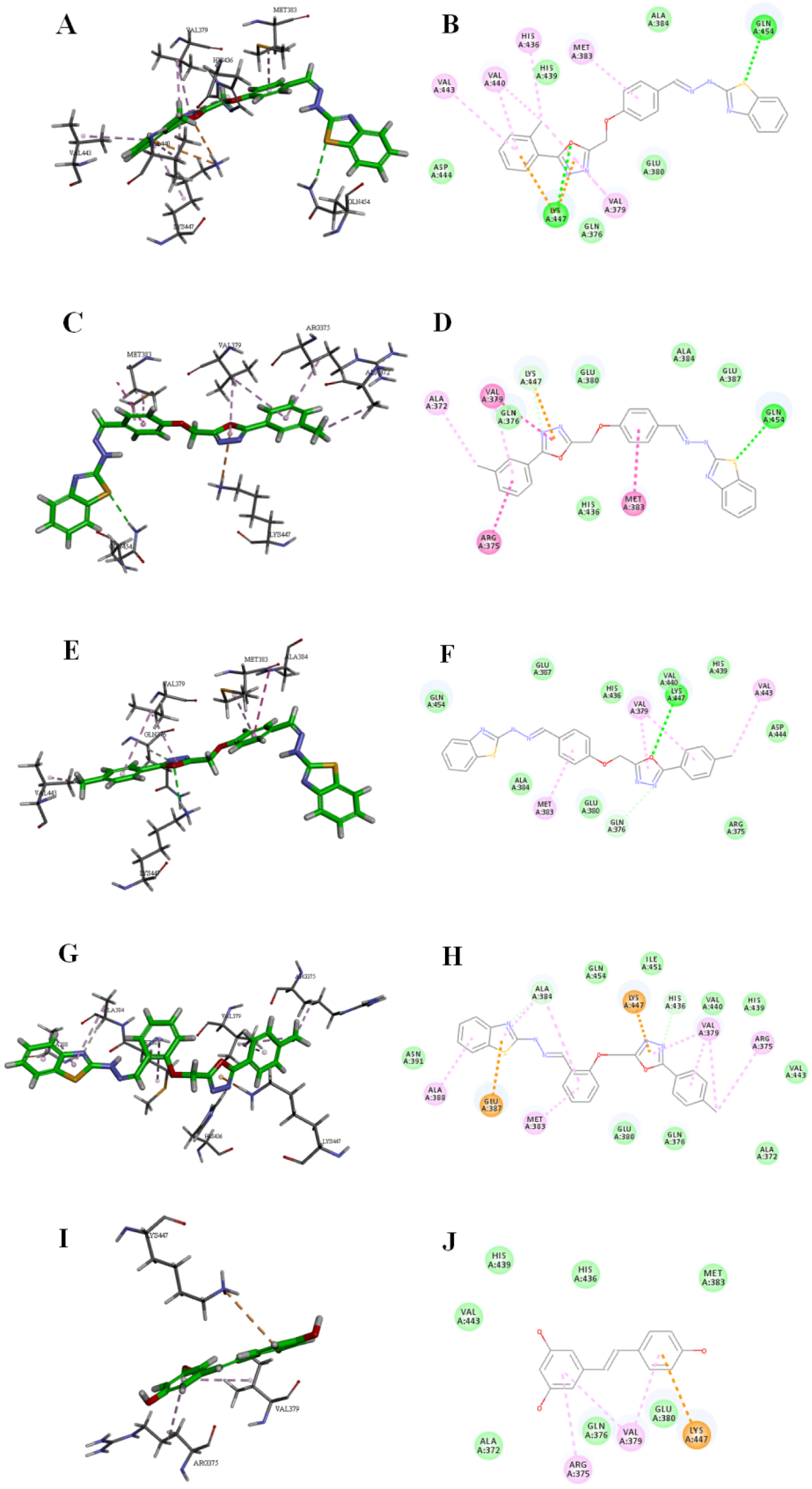


Fig. 3. The predicted binding mode of compounds **8g**, **8h**, **8i**, **10e** and **resveratrol** at the active site of the amyloid precursor protein (PDB ID: 5BUO). (A) Three-dimensional conformation of compound **8g** with 5BUO. (B) 2D interaction diagram of compound **8g** with 5BUO. (C) Three-dimensional conformation of compound **8h** with 5BUO. (D) 2D interaction diagram of compound **8h** with 5BUO. (E) Three-dimensional conformation of compound **8i** with 5BUO. (F) 2D interaction diagram of compound **8i** with 5BUO. (G) Three-dimensional conformation of compound **10e** with 5BUO. (H) 2D interaction diagram of compound **10e** with 5BUO. (I) Three-dimensional conformation of compound **resveratrol** with 5BUO. (J) 2D interaction diagram of compound **resveratrol** with 5BUO.

Table 3
The LibDock scores and docking interactions of compounds (**8g**, **8h**, **8i**, **10e** and **resveratrol**) with the amyloid precursor protein (PDB ID: 5BUO).

Compound	R^1	R^2	Interacting residues	LibDock score (k.cal/mol)
8g	2-CH_3	H	His436, Met383, Gln454	102.59
8h	3-CH_3	H	Met383, Gln454, Ala372, Lys447	106.12
8i	4-CH_3	H	Met383, Lys447	101.73
10e	4-CH_3	–	Glu387, His436, Lys447	102.04
Resveratrol			Lys447	81.97

Table 4
Anti-inflammatory activities of compounds **8h** and Indometacin following i.p. administration.

	Dose (mg/kg)	Number of mice	Edema mean ± S.D. (mg)	Inhibition rate (%)
DMSO	100	5	8.70 ± 0.90	–
Indometacin	100	5	5.15 ± 0.05**	43.62
8h	100	5	0.80 ± 0.01***	57.35

$^{**}p < 0.01$, $^{***}p < 0.001$ compared with a vehicle group.
– No anti-inflammatory activity.

Table 5
Anti-inflammatory activity of compound **8h** administered orally at different times before xylene application.

Time (h)	Dose (mg/kg)	Number of mice	Inhibition rate (%)	
			8h	Indometacin
1	100	5	50.56*	25.29*
2	100	5	54.25**	52.34**
3	100	5	49.68*	46.09*
4	100	5	47.87	30.38
5	100	5	42.50	19.18
24	100	5	37.71	12.51

$^{*}0.01 < p < 0.05$ compared with vehicle group, $^{**}p < 0.01$ compared with vehicle group.

Table 6
Anti-inflammatory activity of compound **8h** administered orally at different doses.

Time (h)	Dose (mg/kg)	Number of mice	Inhibition rate (%)	
			8h	Indometacin
2	100	5	59.44**	58.28**
2	50	5	54.72**	25.85*
2	25	5	44.98	19.05*

$^{*}p < 0.05$, $^{**}p < 0.01$ compared with vehicle group.

different time intervals (1, 2, 3, 4, 5 and 24 h) for xylene application. As indicated in Table 5, the activity of compound **8h** showed a regular increase as the time interval lengthened until reaching a peak at 2 h (54.25%). Compound **8h** displayed slightly higher activity than indomethacin (52.34%). The effect of the dosage on the activity of compound **8h** was also evaluated at concentrations of 25, 50 and 100 mg/kg at 2 h after oral administration as shown in Table 6. At a higher dose of 100 mg/kg, compound **8h** showed the highest anti-inflammatory activity (59.44%), which was equipotent to the positive controls indomethacin (58.28%).

The superior anti-inflammatory activity of the target compound led us to study the molecular docking with the COX-2 enzyme to rationalize the observed anti-inflammatory activity and elucidate a possible mechanism of action of these compounds. To gain insight into the interaction between **8h** and COX-2 enzyme, a docking simulation was performed using COX-2 (PDB ID: 4COX).[26] Enzyme structures were checked for missing atoms, bonds and contacts. Hydrogen atoms were added to the enzyme structure. Water molecules and bound ligands were manually deleted. The docking results for indomethacin are included as a reference. Fig. 4 shows the preferred coordination modes of **8h** and **indomethacin** with COX-2 protein. Compound **8h** is bound into the active site, in which the 1,3,4-oxadiazole moiety formed a hydrogen bond with Lys343 (2.03 Å) and His283 (4.55 Å). Compound **8h** is bound into the active site where the benzene ring at the position of the 1,3,4-oxadiazole moiety shows interaction with Glu284 (2.78 Å) and His285 (4.16 Å). In comparison, **indomethacin** is bound into the active site where the indole ring group shows interaction with His283 (4.96 Å). The Cl atom of **indomethacin** formed alkyl bond with His285 (3.35 Å) and the benzene ring of **indomethacin** formed hydrogen bond with the backbone of Glu284 (2.50 Å). Otherwise, Fig. 4c and f present the enzyme surface model, which revealed that compound **8h** was well inserted into the active pocket of COX-2, comparably indicating its activity is more potent activity than indomethacin's. Furthermore, compound **8h** presented with better anti-inflammatory activity and showed higher docking scores (145.52 k.cal/mol) than indomethacin (86.76 k.cal/mol). Summarizing, these results suggested that the anti-inflammatory activity of compound **8h** might be bound to the COX-2 protein.

According to the docking study, the inhibitory effect on COX-2 produced by compound **8h** represents a possible mechanism of action for its anti-inflammatory activity. To verify our hypothesis, we measured the effect of compound **8h** and standard drugs (**indomethacin** and **celecoxib**) on COX-2 using the ELISA assay. The result is shown in Fig. 5. The activity of compound **8h** was more similar to inhibitor of the COX-2 enzyme than the reference drug **celecoxib**. Additionally, at concentrations of 10 μmol/L, compound **8h** decreased COX-2 activity by 35% when compared with the negative control. Hence, the compound reported herein is a promising starting points for the development of an inhibitor of COX-2.

In conclusion, two series of benzothiazole derivatives bearing a 1,3,4-oxadiazole moiety were synthesized and evaluated for their antioxidant and anti-inflammatory activity. Compounds **8h** and **8l** exhibited potent antioxidant activity, which showed more potent than the positive controls resveratrol. The *in vivo* anti-inflammatory investigation revealed that compound **8h** inhibited the progress of inflammation better than indomethacin at the same dosage. The binding mode of the optimal compound **8h** was rationalized by molecular docking. Furthermore, the activity of compound **8h** was more similar in magnitude to inhibitors of the COX-2 enzyme than the reference drug **celecoxib**. These results suggested that **8h** might be a promising lead to develop novel anti-oxidant and anti-inflammatory agents, thus preventing oxidative stress and inflammation-induced diseases.

Declaration of Competing Interest

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.

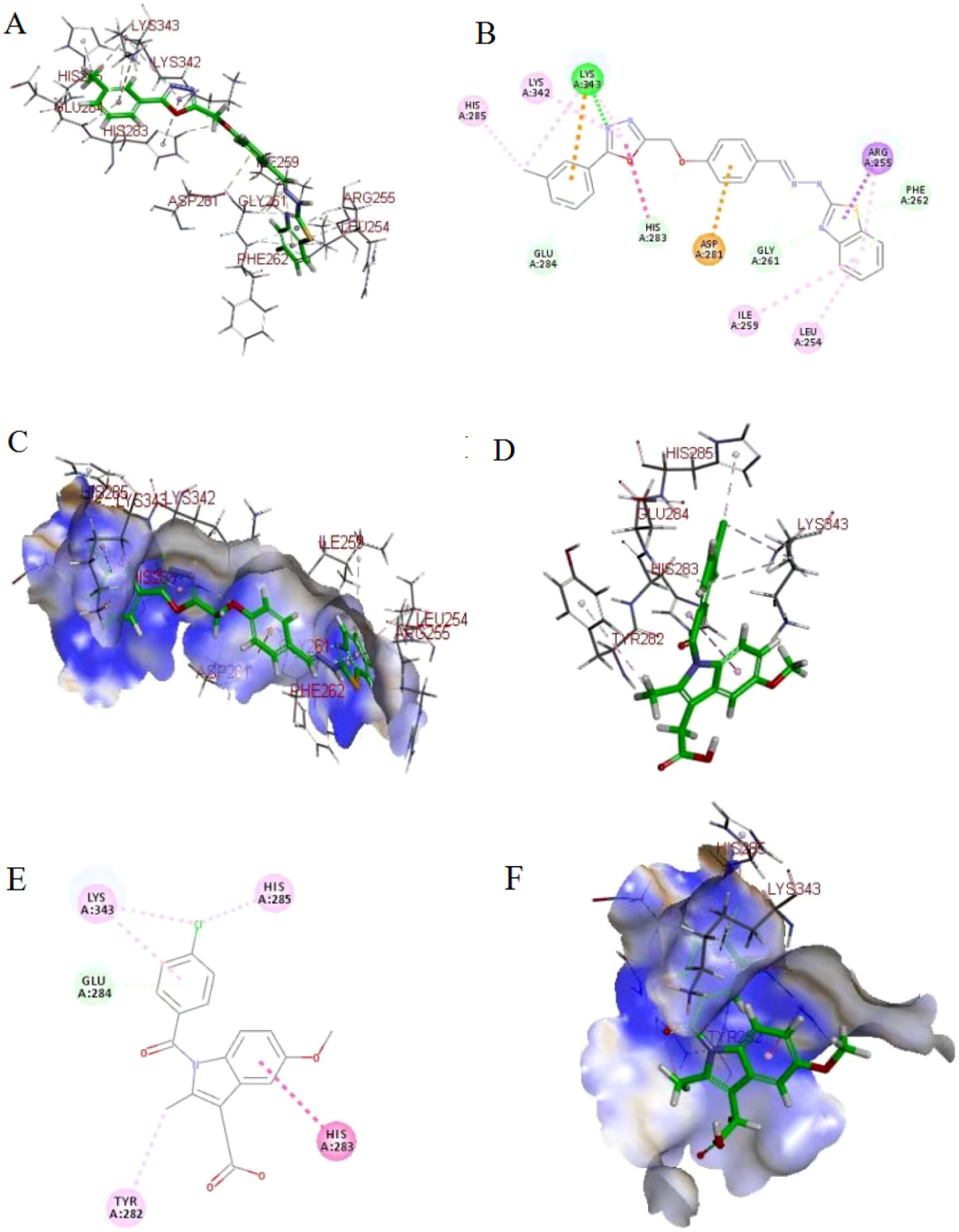


Fig. 4. The predicted binding mode of compound **8h** and **indomethacin** at the active site of the COX-2 enzyme. (A) Three-dimensional conformation of compound **8h** docked in COX-2 complex. (B) 2D interaction diagram of compound **8h** at the active site of COX-2. (C) Docked conformation of the most active compound **8h** in COX-2. (D) Three-dimensional conformation of compound **indomethacin** docked in COX-2 complex. (E) 2D interaction diagram of **indomethacin** at the active site of COX-2. (F) Docked conformation of **indomethacin** in COX-2.

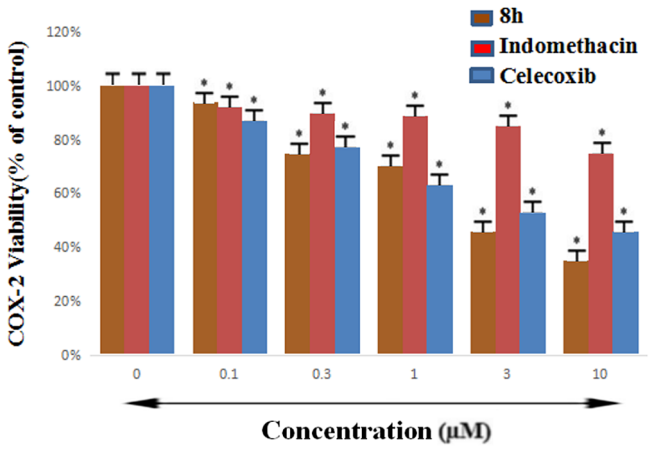


Fig. 5. Inhibition of COX-2 activities of compounds **8h**, **indomethacin** and **celecoxib**. Data are represented as the mean ± standard deviation of three independent experiments. *$p < 0.05$, significant with respect to the control.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127237.

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