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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of novel diphenylthiazole derivatives as potential anti-inflammatory agents

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Abstract In the presented study, we synthesized a novel series of 18 diphenylthiazole derivatives and tested their anti-inflammatory properties. They showed significant anti-inflammatory properties in inflamed mice paws animal model. Docking-based analysis suggested that they act as COX enzyme inhibitors. The most potent compound **9e** is significantly more active in reducing inflamed animal paws compared to diclofenac. Accordingly, we believe these compounds are good leads for further development into potent anti-inflammatory drugs.

Keywords Diphenylthiazole · Anti-inflammatory · Docking · Inflamed animal paws

Introduction

Inflammation is a physiological reaction which involves cellular and biochemical responses that cause symptoms for common diseases and even an early phase for some serious ailments such as Alzheimer's disease, cancer, heart vascular diseases (Fitzgerald, 2004; Grosser *et al.*, 2006). Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketoprofen, ibuprofen and aceclofenac, which are currently in clinical use for the treatment of inflammatory disorders (Fitzgerald, 2004; Grosser *et al.*, 2006), are associated with major drawbacks related to gastrointestinal disorders such as dyspepsia, gastric ulcers and so forth. These side effects are due to the direct contact of their free carboxylic groups with the gastric mucosa and due to decreased production of prostaglandins in the GIT (Fries and Grosser, 2005; Sauzem *et al.*, 2008). In order to overcome these drawbacks, there is an urgent need to design and synthesize new anti-inflammatory agents with excellent anti-inflammatory response and minimal side effects.

Various diphenylthiazole derivatives have been successfully tested as anti-inflammatory agents (Carter *et al.*, 1999; Abdelazeem *et al.*, 2015), anti-prion agents (Heal *et al.*, 2007; Thompson *et al.*, 2010), monoamine transporter inhibitors (Enyedy *et al.*, 2002) and platelet aggregation inhibitors (Rynbrandt *et al.*, 1981). Accordingly, in response to the existing need for potent anti-inflammatory compounds devoid of the classical NSAIDs side effects combined with the interesting biological profiles of diphenylthiazole derivatives, we were prompted to undertake the synthesis of novel diphenylthiazole derivatives devoid of any carboxylic substituents (or any related bioisostere, e.g., sulfonamides (Carter *et al.*, 1999)) hoping to get improved anti-inflammatory activity and fewer side effects. In doing so, we have designed two scaffolds through tethering the diphenylthiazole skeleton, as a known anti-COXs pharmacophore, to various hydrophobic moieties using urea or amide linkers.

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Results and discussion

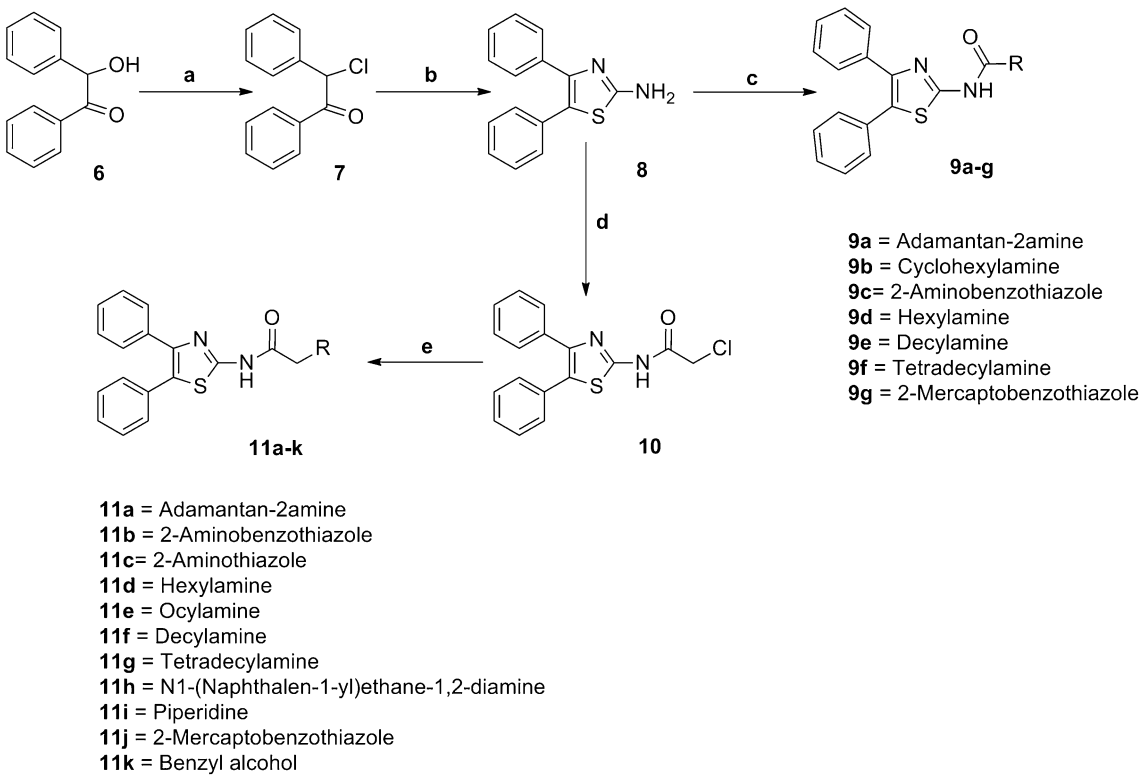
Chemistry

The synthesis of the novel diphenylthiazole derivatives was accomplished as depicted in Scheme 1. The starting material **8**, 4,5-diphenylthiazol-2-amine, was easily prepared by condensation of desyl chloride **7** with thiourea in absolute ethanol according to the reported method (Ren *et al.*, 2008). Subsequently, the amine **8** was reacted with *N,N*'-carbonyldiimidazole (CDI) in anhydrous tetrahydrofuran in the presence of triethylamine followed by addition of the appropriate amine, benzyl alcohol and benzo[*d*]thiazole-2-thiol and reflux for 6 h to afford the desired compounds **9a**–**g**. It should be mentioned that compounds **9b** and **9g** were reported as acyl CoA: cholesterol *O*-acyltransferase (ACAT) inhibitors which were prepared with a different procedure via reaction of the amine starting material **8** with the appropriate isocyanate in toluene (Romeo *et al.*, 1999). The reaction of chloroacetyl chloride with amine **8** in methylene chloride and triethylamine at 0 °C furnished the intermediate **10** which in turn was coupled with equimolar amount of various amines, benzyl alcohol and benzo[*d*]thiazole-2-thiol in DMF and potassium carbonate to afford the targeted compounds **11a**–**k**. All compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, ESI–MS and elemental analyses which were agreement with the calculated values.

In vivo anti-inflammatory activity and docking studies

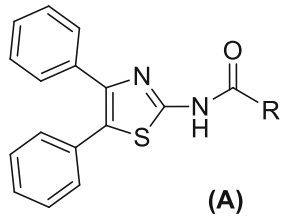
We tested the anti-inflammatory properties of the prepared compounds employing carrageenan-induced paw edema assay performed on male BALB/c mice. We recorded the observed reduction in the size of the inflamed paws upon administration of 60 mg/kg (body weight) oral dose of tested compounds 1 h before inflammation induction. Table 1 summarizes the in vivo anti-inflammatory results of our newly synthesized compounds, while Fig. 1 shows the anti-inflammatory results of two potent derivatives (**9e** and **11k**) compared to diclofenac-treated (oral dose of 60 mg/kg body weight) and untreated controls.

Careful evaluation of the structure–activity relationship in Table 1 shows that the structural requirements for potent anti-inflammatory bioactivities of urea-based analogs (**9a**–**g**) differ from those observed for the amide-based analogs (**11a**–**k**). For example, the urea derivative **9e** showed considerable anti-inflammatory reduction in inflamed mice paws compared to weak anti-inflammatory action for the

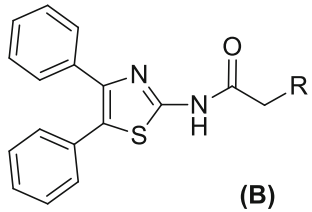


Scheme 1 [a]Reagents and reactions conditions: *a* $SOCl_2$, pyridine, 1 h; *b* thiourea, EtOH, reflux, 2 h; *c* CDI, appropriate amine or thiol, TEA, THF, reflux 6 h; *d* $ClCH_2COCl$, TEA, CH_2Cl_2, 0 °C, 5 h; *e* appropriate amine, alcohol or thiol, K_2CO_3, DMF, 60 °C, 3 h

Table 1 Edema thickness and inflammation reduction percent in response to oral administration of tested compounds compared to diclofenac and untreated control. Measurements were taken at 1, 2, 3 and 4 h post-administration



(A)



(B)

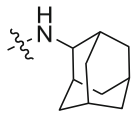
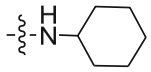
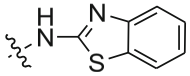
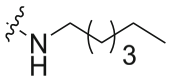
Compound[a]	Scaffold	R	1st h		2nd h		3rd h		4th h	
			Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%
9a	**A**		122.67 (±7.84)	4	108 (±11.82)	12.3	103.33 (±11.6)	9.2	94.33 (±4.63)	16.1
9b	**A**		122.5 (±5.58)	4.2	116.17 (±12.04)	5.7	110.67 (±8.59)	2.7	96.83 (±8.23)	13.9
9c	**A**		117.17 (±5.49)	8.3	121.67 (±10.65)	1.2	113.17 (±12.67)	0.5	99.5 (±16.37)	11.5
9d	**A**		126.17 (±12.29)	1.3	113.5 (±12.71)	7.9	110 (±12.57)	3.3	95.83 (±9.77)	14.8

Table 1 continued

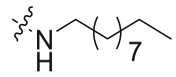
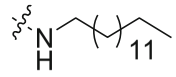
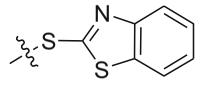
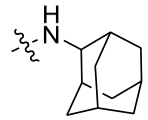
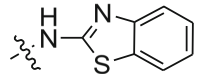
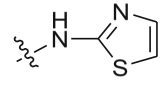
Compound[a]	Scaffold	R	1st h		2nd h		3rd h		4th h	
			Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%
9e	**A**		100.83** (±4.36)	21.1	96.33** (±3.78)	21.8	94.33* (±2.66)	17.1	89.83* (±3.54)	20.1
9f	**A**		108.67 (±10.33)	15	103.83 (±7.11)	15.7	96.67 (±3.88)	15	92* (±5.69)	18.2
9 g	**A**		113.5 (±11.33)	11.2	113.83 (±14.72)	7.6	106 (±16.3)	6.8	107.67 (±16.11)	4.2
11a	**B**		123.33 (±15.19)	3.5	118.5 (±18.14)	3.8	110.33** (±17.86)	3	92 (±9.94)	18.2
11b	**B**		114.83 (±10.13)	10.2	112 (±11.26)	9.1	106.83 (±10.09)	6.1	97.5 (±10.39)	13.3
11c	**B**		119.17 (±13.32)	6.8	122.17 (±11.3)	0.8	115.17 (±13.2)	−1.2	114.83 (±10.63)	−2.1

Table 1 continued

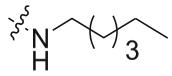
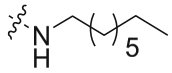
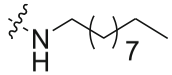
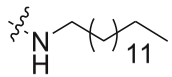
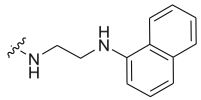
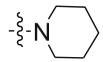
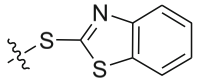
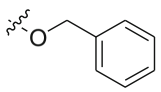
Compound[a]	Scaffold	R	1st h		2nd h		3rd h		4th h	
			Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%
11d	**B**		110.83 (±8.38)	13.3	107.33 (±6.62	12.9	102.17 (±3.6)	10.2	102 (±6.78)	9.3
11e	**B**		110.5 (±12.72)	13.6	103.17* (±8.4)	16.2	99.33 (±4.37)	12.7	102.5 (±4.85)	8.8
11f	**B**		117.83 (±18.15)	7.8	118.33 (±17.25)	3.9	116 (±18.58)	−2	109.5 (±19.12)	2.6
11 g	**B**		104.83** (±5.42)	18	103.5 (±6.38)	16	97.83 (±6.31)	14	97.67 (±5.75)	13.1
11 h	**B**		112.67 (±11.11)	11.9	108.67 (±5.01)	11.8	108.33 (±5.13)	4.8	100.33 (±6.12)	10.8
11i	**B**		122.83 (±13.09)	3.9	128.83 (±14.74)	−4.6	120.83 (±11.55)	-6.2	104.33 (±10.48)	7.2

Table 1 continued

Compound[a]	Scaffold	R	1st h		2nd h		3rd h		4th h	
			Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%	Edema Thickness[b] ($\times 10^{-3}$ mm) (±SD)	Inhibition%
11j	**B**		119.5 (±6.83)	6.5	114.33 (±9.48)	7.2	107.17 (±6.49)	5.8	105.5 (±4.97)	6.2
11 k	**B**		120.5 (±7.66)	5.7	111.67 (±4.23)	9.3	102.33 (±7.99)	10.1	98.83 (±8.66)	12.1
Diclofenac[c]	–	–	119.83 (±19.92)	6.3	118.22 (±16.24)	4	110.11 (±17.3)	3.2	99.72 (±16.15)	11.3
Control[d]	–	–	127.83 (±11.65)	–	123.17 (±12.78)	–	113.78 (±10.76)	–	112.44 (±13.08)	–

SD standard deviation

* $P < 0.05$, ** $P < 0.01$ as compared to control

[a] Dose of each compound is 60 mg/kg body weight

[b] Average measurements of six animals ($n = 6$)

[c] Diclofenac dose is 60 mg/kg body weight

[d] Untreated control

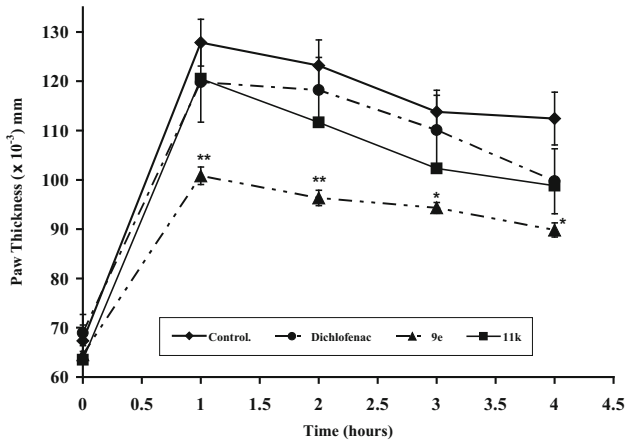


Fig. 1 Effects of **9e**, **11k**, diclofenac and untreated controls on paw edema induced by carrageenan in mice. Each value is represented as mean ± S.E.M. $*P < 0.05$, $**P < 0.01$ as compared to untreated control (one-way ANOVA)

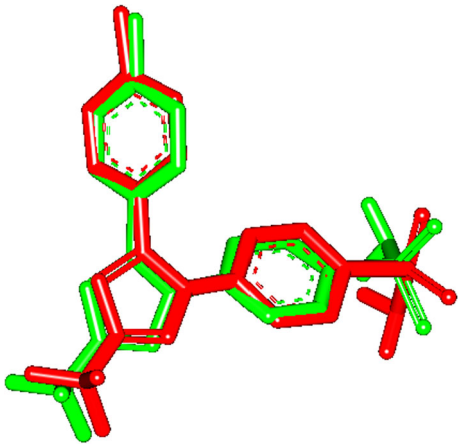


Fig. 2 Comparison between the docked pose of celecoxib (*red*) as produced by docking simulation and the crystallographic structure of this inhibitor within COX-1 (*green*, PDB code: 3KK6) (Color figure online)

corresponding amide-based analog **11f**. Similar trends can be seen by comparing the anti-inflammatory properties of **11d** versus **9d**, Table 1. These observations suggested that there could be two binding modes assumed by these compounds within the binding pocket(s) of certain inflammatory promoting enzyme(s), e.g., COX-1.

In an attempt to explain these observations, we docked two representatives, i.e., for urea and amide-based analogs, namely **9d** and **11k**, within the binding pocket of COX-1 enzyme (PDB code: 3KK6). We selected this particular crystallographic structure for COX-1 (i.e., 3KK6) because it includes celecoxib as co-crystallized ligand. Needless to say that celecoxib is potent selective COX-1 inhibitor, and should therefore appropriately imprint the binding pocket of COX-1 (i.e., by induced fit) in such away that gives better realistic docked poses for **9d** and **11k**.

We validated our docking settings by re-docking the co-crystallized inhibitor celecoxib, i.e., after being extracted from 3KK6, using the same docking settings intended for **9d** and **11k**. Figure 2 compares the docked pose of celecoxib with the corresponding experimental co-crystallized structure. Clearly from the figure, our docking settings closely reproduced the bound structure with RMSD value of 0.99 Å giving confidence in our docking experiment.

Figure 3 shows how **9d** and **11k** dock within COX-1. Obviously from the figure, the two compounds assume different binding modes within COX-1, which agrees with our previous suggestion.

Apparently, urea-based compounds, e.g., **9d**, assume a binding mode, shown in Fig. 3, in which the urea system is tightly hydrogen bonded to the side chains of **Tyr355**, **His90** and **Gln192**, while the diphenylthiazole groups are hydrophobically stacked within a hydrophobic pouch composed of the hydrophobic side chains of **Phe518**, **Met522**, **Trp387**, **Tyr385**, **Val349**, **Ala527** and **Leu531**. On the other hand, the hydrophobic hexyl chain of **9d** seems to protrude outside the binding pocket forming limited hydrophobic interactions with the aliphatic side chain of **Thr94** and **Ser516**.

This trend of interactions seems consistent among all urea-based structures including compounds having cyclic (cyclohexyl) and bicyclic (adamantane) hydrophobic aliphatic side chains, e.g., **9a** and **9b**. However, urea-based compounds with extended aliphatic side chains, i.e., **9f** and **9e**, apparently exhibit superior anti-inflammatory properties, probably because their hydrophobic character promotes their penetration across physiological membranes and binding into COX.

Interestingly, the urea derivatives **9g** and **9c** have mediocre anti-inflammatory properties. Apparently, the steric size of the benzothiazole ring in **9c** and **9g** seems to cause loss of the hydrogen bonding interaction connecting this group with the imidazole N of **His90**. In both compounds, weakened hydrogen bonding with **His90** explains their mediocre anti-inflammatory properties.

On the other hand, amide-based analogs seem to assume completely different poses within COX-1, as exemplified by **11k** shown in Fig. 3a, c. In these poses, the hydrophobic tails of these compounds tend to be deeply embedded inside a hydrophobic pocket comprised of **Pro86**, **Leu93** and **Ile89**. Clearly from Fig. 3c, both the amidic and alpha ether oxygen atoms of **11k** are hydrogen bonded to the guanidino side chain of **Arg120**. Analogous hydrogen bonding interaction is expected with other isosteric hydrogen bond acceptor groups (i.e., to the alpha ether in **11k**) at the same position (e.g., amine groups in **11a** and **11i**). On the other hand, the thiazole nitrogen of **11k**, and other amide-based analogs, seems to be hydrogen bonded to the phenolic hydroxy of **Tyr355**.

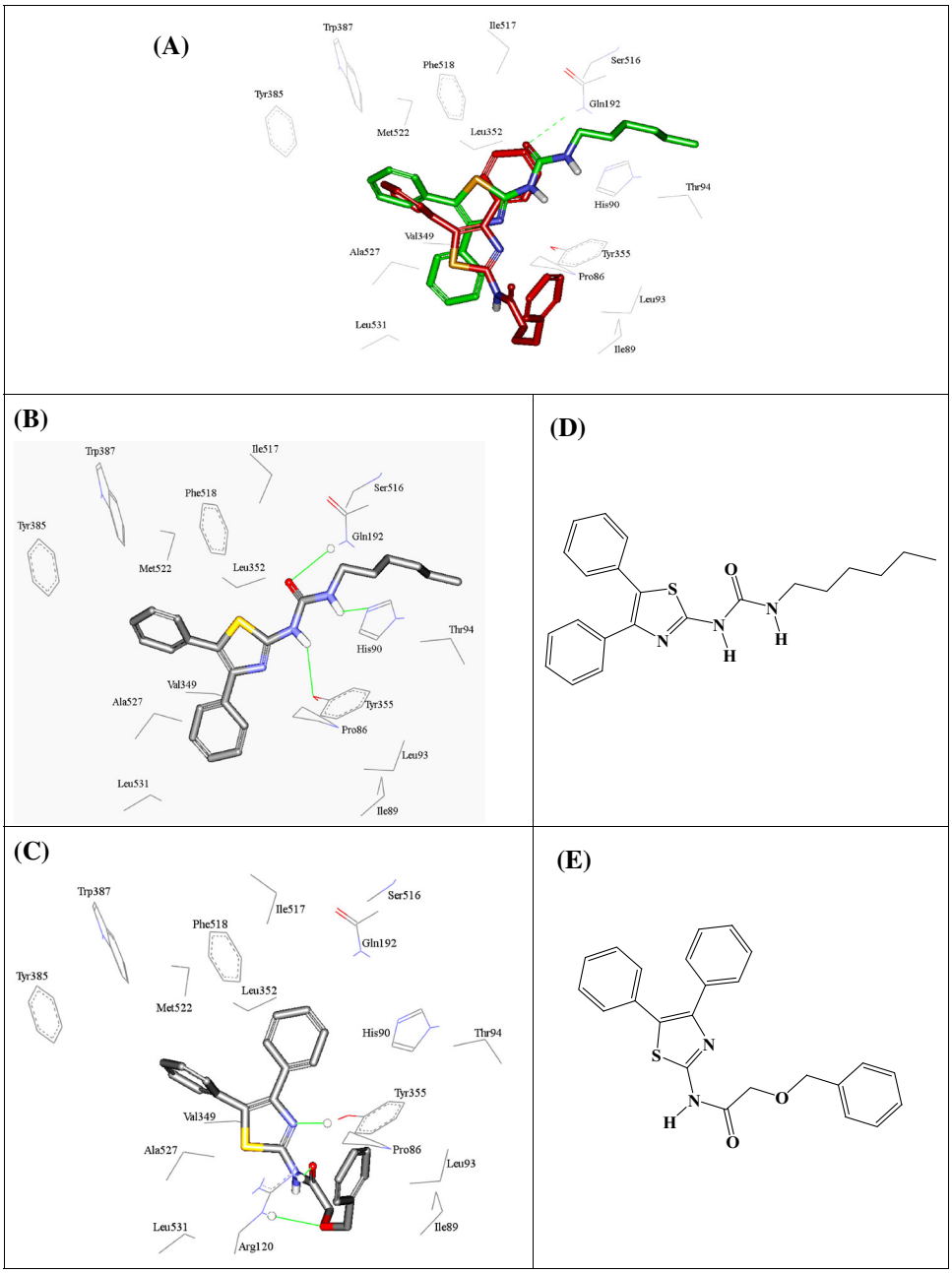


Fig. 3 **A** overlay of docked poses of **9d** (*green*) and **11 k** (*red*) within COX-1 enzyme (PDB code: 3KK6), **B** and **C** are the separate docked poses of **9d** and **11 m**, respectively, **D** and **E** are the chemical structures of **9d** and **11k**, respectively. *Green lines* in **B** and **C** represent hydrogen bonds (Color figure online)

Apparently, amide analogs with fairly large hydrophobic tails (e.g., **11f**) tend to sterically clash with the hydrophobic side chains of **Pro86**, **Leu93** and **Ile89**, which might explain their inferior bioactivities. However, amide analogs of larger hydrophobic chains (e.g., **11g** and **11h**) seem to have comparably enhanced anti-inflammatory properties because their hydrophobic character helps them to penetrate different physiological membranes and allow them to reach inflammatory sites more efficiently.

On the contrary, the hydrophilicity **11i**, which is related to its piperidine ring, renders the compound too hydrophilic and therefore less penetrant of inflammatory tissues causing the apparent weak anti-inflammatory potential of **11i**, i.e., compared to **11a** and **11k**.

Finally, **11b** and **11j** exhibited moderate anti-inflammatory properties, which seem to be related to their benzothiazole rings. The electron-withdrawing properties of benzothiazoles in these compounds should significantly reduce the electronic densities on the corresponding alpha heteroatoms (NH in **11b** and S in **11j**), which should undermine their hydrogen bond acceptor propensities with the guanidino side chain of **Arg120** leading to inferior ligand COX-1 affinities and therefore reduced anti-inflammatory properties. Unsurprisingly, these effects are

augmented in **11c**. The absence of the aromatic electronic density of the fused benzene ring in benzothiazole (i.e., **11b** and **11j**) renders simple thiazole (**11c**) rings significantly more electron withdrawing compared to benzothiazole, which should further reduce the hydrogen bonding acceptor tendency of the respective alpha NH in **11c** leading to the observed inferior anti-inflammatory properties of **11c** compared to **11b** and **11j**.

Experimental protocols: chemistry

Chemical reagents and solvents were obtained from commercial sources. Solvents are dried by standard methods when necessary. Melting points (m.p.) were uncorrected and were carried out by open capillary tube method using IA 9100MK-Digital Melting Point Apparatus. Microanalyses were measured at the Microanalytical Center, Faculty of Science, Cairo University. The proton magnetic resonance ^{1}H-NMR spectra were recorded on a Bruker APX400 spectrometer at 400 MHz in the specified solvent, chemical shifts were reported on the δ scale and were related to that of the solvent, and *J* values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker APX400 at 100 MHz at the Faculty of Pharmacy, Beni-Suef University. Mass spectra were recorded on Shimadzu Qp-2010 Plus, mass spectrometer, at 70 eV (EI) at the Microanalytical Center, Faculty of Science, Cairo University. Thin layer chromatography was done using Macherey–Nagel Alugram Sil G/UV254 silica gel plates and CH_2Cl_2:MeOH (9.5:0.5) as the eluting system.

2-chloro-1,2-diphenylethanone ***(7)*** (Ren *et al.*, 2008) Colorless crystals (EtOH): This compound was prepared from heating a mixture of benzoin (10 g, 47 mmol) and pyridine (5.7 ml) until a solution was obtained and then cooled in an ice bath until solid. The mass obtained was coarsely ground, and thionyl chloride (7.5 g, 63 mmol) was added slowly with vigorous stirring and cooling in an ice bath. After about an hour, water was added and the solid is coarsely ground, filtered and washed several times with water. The crude product was dried by suction and left overnight over calcium chloride until full dryness. The product was obtained as a white powder which was further recrystallized from ethanol to give colorless crystals of 2-chloro-1,2-diphenylethanone **7** (79 %).

4,5-diphenylthiazol-2-amine ***(8)*** (Ren *et al.*, 2008) Yellow crystals (EtOH): This compound was prepared from refluxing of a solution of 2-chloro-1,2-diphenylethanone, **7** (10 g, 41.5 mmol) in ethanol (40 ml) and thiourea (3.5 g, 45 mmol) for 2 h. The solvent was removed under vacuum, and the solid product was soaked in 100 mL of 30 % NaOH at 50 °C for 5 h. The crude product was filtered and washed with water to neutrality and then was recrystallized from 95 % ethanol. The product **8** was obtained as yellow crystals (75 %).

General procedure A *Synthesis of compounds* ***(9a–g)*** To a suspension of compound **8** (2 mmol) in THF (40 mL) was stirred at room temperature during addition of N,N′-carbonyldiimidazole (CDI, 3 mmol). The mixture was stirred for 2 h and treated with dropwise addition of various amines, alcohols or thiols (2.1 mmol) in anhydrous THF (10 mL). Then, the mixture was refluxed for more 6 h. The resulting reaction mixture was cooled to room temperature and distilled under reduced pressure. Water (50 mL) was added to remove excess CDI. The aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic extract was washed with water (30 mL) and brine (30 mL), respectively, and then dried with anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO_2) using hexane/ethylacetate (8: 2) as eluent to afford compounds **9a**–**g**.

1-(adamantan-2-yl)-3-(4,5-diphenylthiazol-2-yl)urea ***(9a)*** White solid (EtOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and adamantan-2-amine (2.1 mmol) according to general Procedure **A**. The product was obtained as a white solid. Yield 69 %, mp 209-210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53–1.59 (m, 2H), 1.70–1.85 (m, 10H), 1.06–2.09 (m, 2H), 3.81–3.92 (m, 1H), 7.15 (s, 1H, NH), 7.22–7.42 (m, 8H), 7.68–7.75 (m, 2H), 10.42 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 166.55 (C, C = O), 158.23 (C, C-2 thiazole ring), 153.40 (C, C-4 thiazole ring), 143.90 (C, C-5 thiazole ring), 136.75 (C, C-1 phenyl ring A), 129.63 (C, C-1 phenyl ring B), 129.39 (CH, C-2 and C-6 phenyl ring A), 129.33 (CH, C-3 and C-5 phenyl ring A), 128.75 (CH, C-2 and C-6 phenyl ring B), 128.64 (CH, C-3 and C-5 phenyl ring B), 122.10 (CH, C-4 phenyl ring A), 117.61 (CH, C-4 phenyl ring B), 56.19 (CH, C-2 adamantyl), 53.71 (CH, C-1 and C-3 adamantyl), 37.49 (CH_2, C-4 adamantyl), 37.17 (CH_2, C-6 adamantyl), 32.36 (CH, C-5 and C-7 adamantyl), 31.38 (CH_2, C-8 and C-10 adamantyl), 27.15 (CH, C-9 adamantyl). MS (EI) *m/z* 431.00 (M^{+2}). Anal. calcd for $C_{26}H_{27}N_3OS$: C, 72.69; H, 6.34; N, 9.78. Found: C, 72.34; H, 6.21; N, 9.85.

1-Cyclohexyl-3-(4,5-diphenylthiazol-2-yl)urea ***(9b)*** (Romeo *et al.*, 1999) White solid (EtOH): This compound was obtained from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and cyclohexyl amine (2.1 mmol) according to general Procedure **A.** The product was obtained as a white solid. Yield 67 %, mp 213–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17–1.52 (m, 5H), 1.64–1.83 (m, 5H), 3.33–3.56 (m, 1H), 6.52 (s, 1H, NH), 7.26–7.41 (m, 10H), 10.35 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 158.20 (C, C = O),

153.47 (C, C-2 thiazole ring), 143.89 (C, C-4 thiazole ring), 135.41 (C, C-5 thiazole ring), 132.73 (C, C-1 phenyl ring A), 129.62 (C, C-1 phenyl ring B), 129.32 (CH, C-2 and C-6 phenyl ring A), 128.77 (CH, C-3 and C-5 phenyl ring A), 128.63 (CH, C-2 and C-6 phenyl ring B), 128.11 (CH, C-3 and C-5 phenyl ring B), 127.95 (CH, C-4 phenyl ring A), 124.42 (CH, C-4 phenyl ring B), 48.50 (CH, C-1 cyclohexyl), 33.08 (CH_2, C-2 and C-6 cyclohexyl), 25.57 (CH_2, C-3 and C-5 cyclohexyl), 24.64 (CH_2, C-4 cyclohexyl). MS (EI) *m/z* 377.00 (M^+). Anal. calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.97; H, 6.32; N, 11.52.

1-(Benzo[d]thiazol-2-yl)-3-(4,5-diphenylthiazol-2-yl)urea ***(9c)*** White solid (EtOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and benzo[*d*]thiazol-2-amine (2.1 mmol) according to general Procedure **A**. The product was obtained as a white solid. Yield 63 %, mp 331–333 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (s, 1H, NH), 7.17–7.45 (m, 12H), 7.63 (d, $J = 7.93$ Hz, 1H), 7.90 (d, $J = 8.16$ Hz, 1H), 10.49 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 174.36 (C, C = O), 172.06 (C, C-2 benzothiazole), 158.22 (C, C-2 thiazole ring), 157.71 (C, C-4 thiazole ring), 149.89 (C, C-3*d* benzothiazole), 140.49 (C, C-5 thiazole ring), 130.57 (C, C-1*d* benzothiazole), 129.61 (C, C-1 phenyl ring A), 129.36 (C, C-1 phenyl ring B), 129.34 (CH, C-2 and C-6 phenyl ring A), 129.20 (CH, C-3 and C-5 phenyl ring A), 129.18 (CH, C-2 and C-6 phenyl ring B), 128.89 (CH, C-3 and C-5 phenyl ring B), 128.54 (CH, C-4 phenyl ring A), 128.52 (CH, C-4 phenyl ring B), 127.34 (CH, C-4 benzothiazole), 125.92 (CH, C-7 benzothiazole), 121.33 (CH, C-5 benzothiazole), 118.18 (CH, C-6 benzothiazole). MS (EI) *m/z* 428.00 (M^+). Anal. calcd for $C_{23}H_{16}N_4OS_2$: C, 64.46; H, 3.76; N, 13.07. Found: C, 64.61; H, 3.64; N, 13.15.

1-(4,5-Diphenylthiazol-2-yl)-3-hexylurea ***(9d)*** White solid (MeOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and hexylamine (2.1 mmol) according to general Procedure **A.** The product was obtained as a white solid. Yield 72 %, mp 164–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J = 6.36$ Hz, 3H, CH_3), 1.22–1.46 (m, 8H), 2.96 (t, $J = 4.12$, 2H), 6.54 (s, 1H, NH), 7.05 – 7.41 (m, 10H), 10.56 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 158.59 (C, C = O), 154.28 (C, C-2 thiazole ring), 143.88 (C, C-4 thiazole ring), 135.44 (C, C-5 thiazole ring), 132.77 (C, C-1 phenyl ring A), 129.58 (C, C-1 phenyl ring B), 129.27 (CH, C-2 and C-6 phenyl ring A), 128.76 (CH, C-3 and C-5 phenyl ring A), 128.58 (CH, C-2 and C-6 phenyl ring B), 128.04 (CH, C-3 and C-5 phenyl ring B), 127.90 (CH, C-4 phenyl ring A), 124.39 (CH, C-4 phenyl ring B), 51.50 (CH_2, C-1 hexyl), 31.54 (CH_2, C-2 hexyl), 30.50 (CH_2, C-3 hexyl), 26.54 (CH_2, C-4 hexyl), 22.57 (CH_2, C-5 hexyl), 14.32 (CH_2, C-6 hexyl). MS (EI) *m/z* 379.00 (M^+). Anal. calcd for $C_{22}H_{25}N_3OS$: C,69.62; H, 6.64; N, 11.07. Found: C, 69.79; H, 6.75; N, 10.95.

1-Decyl-3-(4,5-diphenylthiazol-2-yl)urea ***(9e)*** Yellow semisolid (MeOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and decan-1-amine (2.1 mmol) according to general Procedure **A**. The product was obtained as a yellow semisolid. Yield 68 %, mp 80–82 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, $J = 6.32$ Hz, 3H, CH_3), 1.18–1.51 (m, 16H), 3.12 (t, $J = 6.44$ Hz, 2H), 6.77 (s, 1H, NH), 7.20–7.40 (m, 10H), 8.08 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 158.42 (C, C = O), 154.36 (C, C-2 thiazole ring), 143.86 (C, C-4 thiazole ring), 135.43 (C, C-5 thiazole ring), 132.80 (C, C-1 phenyl ring A), 129.47 (C, C-1 phenyl ring B), 129.11 (CH, C-2 and C-6 phenyl ring A), 128.71 (CH, C-3 and C-5 phenyl ring A), 128.42 (CH, C-2 and C-6 phenyl ring B), 124.33 (CH, C-3 and C-5 phenyl ring B), 121.29 (CH, C-4 phenyl ring A), 116.88 (CH, C-4 phenyl ring B), 31.76 (CH_2, C-1 decyl), 31.74 (CH_2, C-2 decyl), 29.93 (CH_2, C-3 decyl), 29.49 (CH_2, C-4 decyl), 29.43 (CH_2, C-5 decyl), 29.19 (CH_2, C-6 decyl), 29.16 (CH_2, C-7 decyl), 26.72 (CH_2, C-8 decyl), 22.53 (CH_2, C-9 decyl), 14.14 (CH_2, C-10 decyl). MS (EI) *m/z* 435.00 (M^+). Anal. calcd for $C_{26}H_{33}N_3OS$: C, 71.69; H, 7.64; N, 9.65. Found: C, 71.84; H, 7.57; N, 9.49.

1-(4,5-Diphenylthiazol-2-yl)-3-tetradecylurea ***(9f)*** Yellow solid (MeOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and tetradecan-1-amine (2.1 mmol) according to general Procedure **A**. The product was obtained as a yellow solid. Yield 73 %, mp 64–65 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J = 4.18$ Hz, 3H, CH_3), 1.12–1.35 (m, 24H), 2.94 (t, $J = 8.13$ Hz, 2H), 6.52 (s, NH), 7.26–7.41 (m, 10H), 10.53 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 158.02 (C, C = O), 154.39 (C, C-2 thiazole ring), 129.68 (C, C-4 thiazole ring), 129.59 (C, C-5 thiazole ring), 129.35 (C, C-1 phenyl ring A), 129.29 (C, C-1 phenyl ring B), 128.90 (CH, C-2 and C-6 phenyl ring A), 128.77 (CH, C-3 and C-5 phenyl ring A), 128.65 (CH, C-2 and C-6 phenyl ring B), 128.60 (CH, C-3 and C-5 phenyl ring B), 128.35 (CH, C-4 phenyl ring A), 128.11 (CH, C-4 phenyl ring B), 31.76 (CH_2, C-1 tetradecyl), 29.91 (CH_2, C-2 tetradecyl), 29.51 (CH_2, C-3 tetradecyl), 29.50 (CH_2, C-4 tetradecyl), 29.48 (CH_2, C-5 tetradecyl), 29.44 (CH_2, C-6 tetradecyl), 29.17 (CH_2, C-7 tetradecyl), 29.14 (CH_2, C-8 tetradecyl), 29.11 (CH_2, C-9 tetradecyl), 26.69 (CH_2, C-10 tetradecyl), 22.55 (CH_2, C-11 tetradecyl), 15.14 (CH_2, C-12 tetradecyl), 14.81 (CH_2, C-13 tetradecyl), 14.38 (CH_2, C-14 tetradecyl). MS (EI) *m/z* 491.00 (M^+). Anal. calcd for $C_{30}H_{41}N_3OS$: C, 73.28; H, 8.40; N, 8.55. Found: C, 73.35; H, 8.34; N, 8.78.

S-benzo[d]thiazol-2-yl (4,5-diphenylthiazol-2-yl)carbamothioate ***(9g)*** Yellow crystals (EtOH): This compound was prepared from *4,5-diphenylthiazol-2-amine* ***8*** (2 mmol) and benzo[*d*]thiazole-2-thiol (2.1 mmol) according to general Procedure **A**. The product was obtained as a yellow crystal. Yield 71 %, mp 165–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28–7.73 (m, 14H), 7.95 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 167.74 (C, C = O), 163.70 (C, C-2 benzothiazole), 153.88 (C, C-2 thiazole ring), 132.06 (C, C-4 thiazole ring), 130.80 (C, C-3*d* benzothiazole), 130.77 (C, C-5 thiazole ring), 130.48 (C, C-1*d* benzothiazole), 130.15 (C, C-1 phenyl ring A), 129.95 (C, C-1 phenyl ring B), 129.83 (CH, C-2 and C-6 phenyl ring A), 129.74 (CH, C-3 and C-5 phenyl ring A), 129.66 (CH, C-2 and C-6 phenyl ring B), 129.51 (CH, C-3 and C-5 phenyl ring B), 129.29 (CH, C-4 phenyl ring A), 129.12 (CH, C-4 phenyl ring B), 126.69 (CH, C-4 benzothiazole), 122.11 (CH, C-7 benzothiazole), 122.09 (CH, C-5 benzothiazole), 118.94 (CH, C-6 benzothiazole). MS (EI) *m/z* 447.00 (M^{+2}). Anal. calcd for $C_{23}H_{15}N_3OS_3$: C, 62.00; H, 3.39; N, 9.43. Found: C, 62.32; H, 3.15; N, 9.64.

2-Chloro-N-(4,5-diphenylthiazol-2-yl)acetamide ***(10)*** Brown solid: This compound was synthesized from adding chloroacetyl chloride (2.9 g, 25.7 mmol) slowly to a solution of compound **8** (5 g, 19.8 mmol) and triethylamine (6 g, 59.5 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then for 5 h at room temperature. The organic layer was then separated and evaporated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2) using dichloromethane/methanol (9.5: 0.5) as eluent. The product **10** was obtained as brown solid. Yield 81 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.17 (s, 2H, CH_2), 7.28–7.46 (m, 10H), 12.09 (s, 1H, NH). MS (EI) *m/z* 328.05 (M^{+}).

General procedure B *Synthesis of compounds* ***(11a–k)*** Appropriate amine (3.3 mmol) and K_2CO_3 (9.9 mmol) were added, under mechanical stirring, to a solution of 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) in DMF (30 mL). The reaction mixture was heated at 60 °C for 3 h. After cooling, the mixture was poured onto H_2O (100 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine and dried. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column using methylene chloride/methanol (9.5:0.5) as eluent to give the final compounds **(11a–k)**.

2-(adamantan-2-ylamino)-N-(4,5-diphenylthiazol-2-yl) acetamide ***(11a)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and adamantan-2-amine (0.5 g, 3.3 mmol) according to general Procedure **B**. The product was obtained as a brown solid. Yield 85 %, mp 109–110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38–1.45 (m, 2H), 1.61–1.80 (m, 10H), 1.97–2.10 (m, 2H), 3.00–3.09 (t, J = 6.74 Hz, 1H), 3.48 (s, 2H), 4.16 (s, 1H, NH), 7.10–7.63 (m, 10H), 7.95 (s, 1H, CONH). ^{13}C NMR (101 MHz, DMSO) δ 171.82 (C, C = O), 156.01 (C, C-2 thiazole ring), 144.27 (C, C-4 thiazole ring), 135.13 (C, C-5 thiazole ring), 132.35 (C, C-1 phenyl ring A), 129.70 (C, C-1 phenyl ring B), 129.37 (CH, C-2 and C-6 phenyl ring A), 128.90 (CH, C-3 and C-5 phenyl ring A), 128.69 (CH, C-2 and C-6 phenyl ring B), 128.36 (CH, C-3 and C-5 phenyl ring B), 128.14 (CH, C-4 phenyl ring A), 125.85 (CH, C-4 phenyl ring B), 61.41 (CH_2, CH_2NH), 49.86 (CH, C-2 adamantyl), 37.92 (CH, C-1 and C-3 adamantyl), 37.23 (CH_2, C-4 adamantyl), 31.96 (CH_2, C-6 adamantyl), 31.20 (CH, C-5 and C-7 adamantyl), 30.30 (CH_2, C-8 and C-10 adamantyl), 27.61 (CH, C-9 adamantyl). MS (EI) *m/z* 443.00 (M^{+}). Anal. calcd for $C_{27}H_{29}N_3OS$: C, 73.10; H, 6.59; N, 9.47. Found: C, 73.46; H, 6.35; N, 9.78.

2-(Benzo[d]thiazol-2-ylamino)-N-(4,5-diphenylthiazol-2-yl) acetamide ***(11b)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and benzo[*d*]thiazol-2-amine (3.3 mmol) according to general Procedure **B**. The product was obtained as a brown solid. Yield 68 %, mp 273–275 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 2H, CH_2), 4.25 (s, 1H, NH), 6.98–7.65 (m, 10H), 7.95 (s, 1H, NHCO). ^{13}C NMR (101 MHz, DMSO) δ 166.96 (C, C = O), 166.89 (C, C-2 benzothiazole), 162.92 (C, C-2 thiazole ring), 153.11 (C, C-4 thiazole ring), 131.28 (C, C-3*d* benzothiazole), 130.03 (C, C-5 thiazole ring), 129.99 (C, C-1*d* benzothiazole), 129.70 (C, C-1 phenyl ring A), 129.38 (C, C-1 phenyl ring B), 129.18 (CH, C-2 and C-6 phenyl ring A), 129.05 (CH, C-3 and C-5 phenyl ring A), 128.97 (CH, C-2 and C-6 phenyl ring B), 128.89 (CH, C-3 and C-5 phenyl ring B), 128.80 (CH, C-4 phenyl ring A), 128.74 (CH, C-4 phenyl ring B), 128.52 (CH, C-4 benzothiazole), 125.92 (CH, C-7 benzothiazole), 121.31 (CH, C-5 benzothiazole), 118.17 (CH, C-6 benzothiazole), 53.37 (CH_2, CH_2NH). MS (EI) *m/z* 442.00 (M^{+}). Anal. calcd for $C_{24}H_{18}N_4OS_2$: C, 65.13; H, 4.10; N, 12.66. Found: C, 65.36; H, 4.40; N, 12.46.

N-(4,5-diphenylthiazol-2-yl)-2-(thiazol-2-ylamino)acetamide ***(11c)*** Light brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and thiazol-2-amine (3.3 mmol) according to general Procedure **B**. The product was obtained as a light brown solid. Yield 63 %, mp 289–290 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 2H, CH_2), 4.72 (s, 1H, NH), 7.20–7.42 (m, 12H), 7.92 (s, 1H, NHCO). ^{13}C NMR (101 MHz, DMSO) δ 168.31 (C, C = O), 164.27 (C, C-2 thiazol-2-ylamino), 163.89 (C, C-2 thiazole ring), 154.45

(C, C-4 thiazole ring), 132.63 (C, C-4 thiazol-2-ylamino), 131.05 (C, C-5 thiazole ring), 130.72 (C, C-5 thiazol-2-ylamino), 130.31 (C, C-1 phenyl ring A), 130.23 (C, C-1 phenyl ring B), 130.08 (CH, C-2 and C-6 phenyl ring A), 129.86 (CH, C-3 and C-5 phenyl ring A), 129.69 (CH, C-2 and C-6 phenyl ring B), 127.26 (CH, C-3 and C-5 phenyl ring B), 122.68 (CH, C-4 phenyl ring A), 122.66 (CH, C-4 phenyl ring B), 54.71 (CH_2, CH_2NH). MS (EI) *m/z* 393.00 (M^+). Anal. calcd for $C_{20}H_{16}N_4OS_2$: C, 61.20; H, 4.11; N, 14.27 Found: C, 61.37; H, 4.18; N, 14.04

N-(4,5-diphenylthiazol-2-yl)-2-(hexylamino)acetamide ***(11d)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and hexylamine (3.3 mmol) according to general Procedure **B**. The product was obtained as a brown solid. Yield 58 %, mp 113–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.61 (t, $J = 6.53$ Hz, 3H, C$\underline{H_3}$), 0.95–1.06 (m, 6H), 1.13–1.18 (m, 2H), 2.28 (s, 1H, N$\underline{H}$), 2.65 (s, 2H), 2.85 (t, $J = 12.86$ Hz, 2H), 6.90–7.21 (m, 10H), 7.77 (s, 1H, CON$\underline{H}$). ^{13}C NMR (101 MHz, DMSO) δ 164.80 (C, C = O), 162.67 (C, C-2 thiazole ring), 135.82 (C, C-4 thiazole ring), 132.71 (C, C-5 thiazole ring), 129.92 (C, C-1 phenyl ring A), 129.81 (C, C-1 phenyl ring B), 129.64 (CH, C-2 and C-6 phenyl ring A), 129.30 (CH, C-3 and C-5 phenyl ring A), 128.88 (CH, C-2 and C-6 phenyl ring B), 128.57 (CH, C-3 and C-5 phenyl ring B), 128.32 (CH, C-4 phenyl ring A), 119.53 (CH, C-4 phenyl ring B), 37.53 (CH_2, CH_2NH), 36.13 (CH_2, C-1 hexyl), 31.41 (CH_2, C-2 hexyl), 29.44 (CH_2, C-3 hexyl), 26.50 (CH_2, C-4 hexyl), 22.51 (CH_2, C-5 hexyl), 14.21 (CH_2, C-6 hexyl). MS (EI) *m/z* 393.00 (M^+). Anal. calcd for $C_{23}H_{27}N_3OS$: C, 70.19; H,6.92; N, 10.68. Found: C, 70.3; H,6.74; N, 10.71

N-(4,5-diphenylthiazol-2-yl)-2-(octylamino)acetamide ***(11e)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and octylamine (3.3 mmol) according to general Procedure **B.** The product was obtained as a brown solid. Yield 65 %, mp 107–108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J = 6.46$ Hz, 3H), 1.23–1.39 (m, 12H), 2.50 (t, $J = 4.51$ Hz, 2H), 3.05 (d, $J = 8.32$ Hz, 2H), 3.50 (br s, 1H, N$\underline{H}$), 7.24–7.39 (m, 10H), 10.32 (s, 1H, CON$\underline{H}$). ^{13}C NMR (101 MHz, DMSO) δ 168.07 (C, C = O), 163.34 (C, C-2 thiazole ring), 144.30 (C, C-4 thiazole ring), 135.82 (C, C-5 thiazole ring), 133.14 (C, C-1 phenyl ring A), 130.03 (C, C-1 phenyl ring B), 129.73 (CH, C-2 and C-6 phenyl ring A), 129.18 (CH, C-3 and C-5 phenyl ring A), 129.04 (CH, C-2 and C-6 phenyl ring B), 128.51 (CH, C-3 and C-5 phenyl ring B), 128.36 (CH, C-4 phenyl ring A), 124.82 (CH, C-4 phenyl ring B), 37.50 (CH_2, CH_2NH), 36.18 (CH_2, C-1 octyl), 31.69 (CH_2, C-2 octyl), 31.15 (CH_2, C-3 octyl), 29.44 (CH_2, C-4 octyl), 29.11 (CH_2, C-5 octyl), 26.81 (CH_2, C-6 octyl), 22.54 (CH_2, C-7 octyl), 14.31 (CH_2, C-8 octyl). MS (EI) *m/z* 421.00 (M^+). Anal. calcd for $C_{25}H_{31}N_3OS$: C, 71.22; H, 7.10; N, 9.97. Found: C, 71.45; H, 7.19; N, 10.16

2-(Decylamino)-N-(4,5-diphenylthiazol-2-yl)acetamide ***(11f)*** Yellow solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and decylamine (3.3 mmol) according to general Procedure **B**. The product was obtained as a yellow solid. Yield 69 %, mp 165–167 °C. 1H NMR (400 MHz, DMSO-d6) δ 0.84 (t, J = 4.35 Hz, 3H, C$\underline{H_3}$), 1.13–1.41 (m, 16H), 3.06 (t, $J = 6.53$ Hz, 2H), 3.36 (s, 2H), 3.45 (s, 1H, N$\underline{H}$), 7.14–7.43 (m, 10H), 7.98 (s, 1H, CON$\underline{H}$). ^{13}C NMR (101 MHz, DMSO) δ 161.29 (C, C = O), 149.68 (C, C-2 thiazole ring), 140.07 (C, C-4 thiazole ring), 130.36 (C, C-5 thiazole ring), 129.71 (C, C-1 phenyl ring A), 129.38 (C, C-1 phenyl ring B), 129.15 (CH, C-2 and C-6 phenyl ring A), 128.90 (CH, C-3 and C-5 phenyl ring A), 128.72 (CH, C-2 and C-6 phenyl ring B), 128.49 (CH, C-3 and C-5 phenyl ring B), 127.47 (CH, C-4 phenyl ring A), 113.02 (CH, C-4 phenyl ring B), 62.30 (CH_2, CH_2NH), 50.18 (CH_2, C-1 decyl), 35.06 (CH_2, C-2 decyl), 31.77 (CH_2, C-3 decyl), 29.47 (CH_2, C-4 decyl), 29.42 (CH_2, C-5 decyl), 29.20 (CH_2, C-6 decyl), 29.19 (CH_2, C-7 decyl), 26.81 (CH_2, C-8 decyl), 22.57 (CH_2, C-9 decyl), 14.43 (CH_2, C-10 decyl). MS (EI) *m/z* 449.00 (M^+). Anal. calcd for $C_{27}H_{35}N_3OS$: C, 72.12; H, 7.85; N, 9.35. Found: C, 72.32; H, 7.57; N, 9.14.

N-(4,5-diphenylthiazol-2-yl)-2-(tetradecylamino)acetamide ***(11g)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and tetradecylamine (3.3 mmol) according to general Procedure **B**. The product was obtained as a brown solid. Yield 73 %, mp 149–150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, $J = 7.59$ Hz, 3H), 1.04–1.41 (m, 26H), 3.44 (s, 2H, C$\underline{H_2}$), 3.88 (s, 1H, N$\underline{H}$), 7.13–7.43 (m, 10H), 7.98 (s, 1H, CON$\underline{H}$). ^{13}C NMR (101 MHz, DMSO) δ 166.55 (C, C = O), 161.85 (C, C-2 thiazole ring), 147.15 (C, C-4 thiazole ring), 129.70 (C, C-5 thiazole ring), 129.38 (C, C-1 phenyl ring A), 129.25 (C, C-1 phenyl ring B), 129.14 (CH, C-2 and C-6 phenyl ring A), 128.91 (CH, C-3 and C-5 phenyl ring A), 128.87 (CH, C-2 and C-6 phenyl ring B), 128.75 (CH, C-3 and C-5 phenyl ring B), 124.32 (CH, C-4 phenyl ring A), 117.31 (CH, C-4 phenyl ring B), 62.76 (CH_2, CH_2NH), 55.11 (CH_2, C-1 tetradecyl), 31.76 (CH_2, C-1 tetradecyl), 29.52 (CH_2, C-2 tetradecyl), 29.50 (CH_2, C-3 tetradecyl), 29.47 (CH_2, C-4 tetradecyl), 29.42 (CH_2, C-5 tetradecyl), 29.40 (CH_2, C-6 tetradecyl), 29.38 (CH_2, C-7 tetradecyl), 29.18 (CH_2, C-8 tetradecyl), 29.16 (CH_2, C-9 tetradecyl), 29.15 (CH_2, C-10 tetradecyl) (CH_2, C-11 tetradecyl), 29.13 (CH_2, C-12 tetradecyl),

22.56 (CH_2, C-13 tetradecyl), 14.40 (CH_2, C-14 tetradecyl). MS (EI) *m/z* 505.00 (M^+). Anal. calcd for $C_{31}H_{43}N_3OS$: C, 73.62; H, 8.57; N, 8.31. Found: C, 73.48; H, 8.63; N, 8.69

N-(4,5-diphenylthiazol-2-yl)-2-((2-(naphthalen-1-ylamino) ethyl)amino)acetamide ***(11h)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and N^1-(naphthalen-1-yl)ethane-1,2-diamine (3.3 mmol) according to general Procedure **B.** The product was obtained as a brown solid. Yield 66 %, mp 100–101 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 1H, NH), 2.94 (t, $J = 6.09$ Hz, 2H), 3.31 (t, $J = 7.61$ Hz, 2H), 4.51 (s, 2H), 4.73 (s, 1H, NH), 7.08–7.12 (m, 3H), 7.19–7.42 (m, 14H), 8.14 (s, 1H, CONH). ^{13}C NMR (101 MHz, DMSO) δ 171.52 (C, C = O), 166.59 (C, C-2 thiazole ring), 162.77 (C, C-4 thiazole ring), 156.03 (C, C-5 thiazole ring), 144.62 (C, C-1 naphthyl), 144.28 (CH, C-2 naphthyl), 135.14 (C, C-8*a* naphthyl), 134.50 (C, C-1 phenyl ring A), 132.36 (C, C-1 phenyl ring B), 129.74 (CH, C-2 and C-6 phenyl ring A), 129.39 (CH, C-3 and C-5 phenyl ring A), 128.92 (CH, C-2 and C-6 phenyl ring B), 128.71 (CH, C-3 and C-5 phenyl ring B), 128.49 (CH, C-4 phenyl ring A), 128.41 (C, C-3 naphthyl), 127.29 (C, C-4*a* naphthyl), 126.04 (C, C-4 naphthyl), 124.39 (C, C-5 naphthyl), 123.56 (C, C-8 naphthyl), 122.03 (C, C-7 naphthyl), 115.93 (C, C-6 naphthyl), 103.47 (CH, C-4 phenyl ring B), 52.04 (CH_2, $NHCH_2CO$), 47.87 (CH_2, Ar-$NHCH_2CH_2NH$), 43.65 (CH_2, Ar-$NHCH_2CH_2NH$). MS (EI) *m/z* 479.00 (M^+). Anal. calcd for $C_{29}H_{26}N_4OS$: C, 72.78; H, 5.48; N, 11.71. Found: C, 72.58; H, 5.64; N, 11.90

N-(4,5-diphenylthiazol-2-yl)-2-(piperidin-1-yl)acetamide ***(11i)*** Light brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and piperidine (3.3 mmol) according to general Procedure **B**. The product was obtained as a light brown solid. Yield 61 %, mp 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41–1.57 (m, 6H), 2.55 (s, 4H), 3.29 (s, 2H), 7.32–7.45 (m, 10H), 7.98 (S, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ 169.56 (C, C = O), 162.86 (C, C-2 thiazole ring), 155.80 (C, C-4 thiazole ring), 135.07 (C, C-5 thiazole ring), 132.26 (C, C-1 phenyl ring A), 129.71 (C, C-1 phenyl ring B), 129.40 (CH, C-2 and C-6 phenyl ring A), 128.89 (CH, C-3 and C-5 phenyl ring A), 128.72 (CH, C-2 and C-6 phenyl ring B), 128.43 (CH, C-3 and C-5 phenyl ring B), 128.20 (CH, C-4 phenyl ring A), 125.93 (CH, C-4 phenyl ring B), 61.44 (CH_2, CH_2 NH), 54.26 (CH_2, C-1 and C-5 piperidine), 25.93 (CH_2, C-2 and C-4 piperidine), 23.95 (CH_2, C-3 piperidine). MS (EI) *m/z* 377.00 (M^+). Anal. calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 70.32; H, 6.50; N, 11.35.

2-(Benzo[d]thiazol-2-ylthio)-N-(4,5-diphenylthiazol-2-yl) acetamide ***(11j)*** Light brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and benzo[*d*]thiazole-2-thiol (3.3 mmol) according to general Procedure **B**. The product was obtained as a light brown solid. Yield 63 %, mp 99-100 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.48 (s, 2H), 7.27 – 7.47 (m, 10H), 7.81 (d, $J = 8.10$ Hz, 2H), 7.93 (s, 1H, NH), 8.00 (d, $J = 7.99$ Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.77 (C, C = O), 166.19 (C, C-2 benzothiazole), 152.89 (C, C-2 thiazole ring), 144.38 (C, C-4 thiazole ring), 135.23 (C, C-3*d* benzothiazole), 135.06 (C, C-5 thiazole ring), 132.21 (C, C-1*d* benzothiazole), 129.69 (C, C-1 phenyl ring A), 129.41 (C, C-1 phenyl ring B), 128.89 (CH, C-2 and C-6 phenyl ring A), 128.77 (CH, C-3 and C-5 phenyl ring A), 128.45 (CH, C-2 and C-6 phenyl ring B), 128.25 (CH, C-3 and C-5 phenyl ring B), 126.94 (CH, C-4 phenyl ring A), 126.07 (CH, C-4 phenyl ring B), 125.10 (CH, C-4 benzothiazole), 122.34 (CH, C-7 benzothiazole), 121.61 (CH, C-5 benzothiazole), 116.07 (CH, C-6 benzothiazole), 36.82 (CH_2, CH_2S). MS (EI) *m/z* 460.00 (M^+). Anal. calcd for $C_{24}H_{17}N_3OS_3$: C, 62.72; H, 3.73; N, 9.14. Found: C, 62.50; H, 3.91; N, 9.44.

2-(Benzyloxy)-N-(4,5-diphenylthiazol-2-yl)acetamide ***(11k)*** Brown solid: This compound was prepared from 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide **10** (1 g, 3.3 mmol) and benzyl alcohol (3.3 mmol) according to general Procedure **B**. The product was obtained as a brown solid. Yield 57 %, mp 278–280 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.20 (s, 2H), 5.17 (s, 2H), 7.21–7.43 (m, 15H), 7.95 (s, 1H, CONH). ^{13}C NMR (101 MHz, DMSO) δ 169.41 (C, C = O), 162.77 (C, C-2 thiazole ring), 149.03 (C, C-4 thiazole ring), 145.04 (C, C-5 thiazole ring), 139.65 (C, C-1 benzyloxy), 129.74 (C, C-1 phenyl ring A), 129.45 (C, C-1 phenyl ring B), 129.41 (CH, C-2 and C-6 phenyl ring A), 129.23 (CH, C-3 and C-5 phenyl ring A), 128.98 (CH, C-2 and C-6 phenyl ring B), 128.90 (CH, C-3 and C-5 phenyl ring B), 128.52 (CH, C-2 and C-6 benzyloxy), 128.48 (CH, C-3 and C-5 benzyloxy), 127.05 (CH, C-4 phenyl ring A), 126.86 (CH, C-4 phenyl ring B), 123.66 (CH, C-4 benzyloxy), 63.32 (CH_2, $COCH_2$), 56.20 (CH_2, OCH_2). MS (EI) *m/z* 401.00 (M^+). Anal. calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99. Found: C, 72.12; H, 5.15; N, 7.20.

In vivo anti-inflammatory assay: measurement of paw edema

1. Animals
   Male BALB/c mice (28–30 g) were housed in a controlled environment and provided with standard rodent chow and water. Six mice including three males and

three females were used to test each compound, as a control or for diclofenac as positive control.

2. Carrageenan-induced paw edema assay
   Animal groups ($n = 6$ per particular treatment) received orally 60 mg/kg (body weight) dose of the tested compounds, diclofenac or vehicle (untreated controls). One hour later, test animals received 30 µl of carrageenan (1 % W/V in saline) s.c. on the plantar surface of the left hind paw. The development of paw edema was assessed by measuring paw-thickness changes at 0 (immediately), 1, 2, 3 and 4 h after carrageenan injection using electronic digital caliper (Moilanen *et al.*, 2012; Posadas *et al.*, 2004). The right hind paw served as a reference of non-inflamed paw for qualitative comparison. Results are expressed as paw thickness (mm) and percent thickness reduction compared to control (Inhibition percent) as in Table 1.

Docking studies

Preparation of COX-1 crystal structure: The 3D coordinates of COX-1 were retrieved from the Protein Data Bank (COX-1 PDB code: 3KK6, resolution: 2.75 Å). Hydrogen atoms were added to the protein utilizing DS 2.0 templates for protein residues. Gasteiger–Marsili charges were assigned to the protein atoms as implemented within DS 2.0 (Gasteiger and Marsili, 1980).

The protein structure was utilized in subsequent docking experiments without energy minimization. Docking experiment was conducted employing LigandFit docking engine. There are two steps implemented in the LigandFit process (Taha and AlDamen, 2005).

1. Defining the location(s) of potential binding site (Discovery Studio version 2.5 (DS 2.5) User Manual; Accelrys Inc: San Diego, CA, 2009; Gehlhaar *et al.*, 1995; Venkatachalam *et al.*, 2003). In the current docking experiments, the binding site was generated from the cocrystallized ligand (PDB codes: 3KK6) within the targeted protein.
2. Docking the ligands in the binding site (Discovery Studio version 2.5 (DS 2.5) User Manual; Accelrys Inc: San Diego, CA, 2009.; Gehlhaar *et al.*, 1995; Venkatachalam *et al.*, 2003). In LigandFit, docking is composed of few substeps: (1) conformational search of flexible ligands employing Monte Carlo randomized process. (2) Pose/conformation selection based on shape similarity with the binding site. (3) Candidate conformers/poses exhibiting low shape discrepancy are further enrolled in calculation of the dock energies. (4) Each docked conformation/pose is further fitted into the binding pocket through a number of rigid-body minimization iterations. (5) Docked conformers/poses that have docking energies below certain user-defined threshold are subsequently clustered according to their RMS similarities. Representative conformers/poses are then selected, further energy-minimized within the binding site, and saved for subsequent scoring.

In first case, all synthesized compounds in their unionized forms were docked into the binding site in the presence of explicit water molecules. The following docking configurations were employed:

- Monte Carlo search parameters were number of trials = 30,000 and search step for torsions with polar hydrogens = 30.0°.
- The RMS threshold for ligand-to-binding site shape match was set to 2.0 Å employing a maximum of 2.0 binding site partitions.
- Interaction energy parameters: The interaction energies were assessed employing CFF force field (version 1.02) with a non-bonded cutoff distance of 10.0 Å and distance dependent dielectric. An energy grid extending 3.0 Å from the binding site was implemented. The interaction energy was estimated by a trilinear interpolation value using soft potential energy approximations (Discovery Studio version 2.5 (DS 2.5) User Manual; Accelrys Inc: San Diego, CA, 2009.; Venkatachalam *et al.*, 2003).
- Rigid-body ligand minimization parameters: 40 steps of steepest descend followed by 80 BFGS minimization iterations were applied to every orientation of the docked ligand. High-ranking docked conformers/poses were scored using six scoring functions: Jain (Jain, 1996; Krammer *et al.*, 2005; Venkatachalam *et al.*, 2003), LigScore1, LigScore2 (Krammer *et al.*, 2005; Venkatachalam *et al.*, 2003), PLP1 (Gehlhaar *et al.*, 1995), PLP2 and PMF (Muegge, 2001; Muegge and Martin, 1999). LigScore1 and LigScore2 scores were calculated employing CFF force field (version 1.02) and using grid-based energies with a grid extension of 7.5 Å across the binding site. PMF scores were calculated employing cutoff distances of 12.0 Å for carbon–carbon interactions and other atomic interactions, while PMF04 scores were calculated employing cutoff values of 6.0 and 9.0 Å for carbon–carbon interactions and other atomic interactions, respectively.

Conclusions

In the presented study, we synthesized several diphenylthiazole derivatives linked to hydrophobic fragments via amide or urea tethers. Our compounds showed significant anti-inflammatory properties in inflamed mice

paws animal model, docking-based analysis suggests they primarily inhibit COX. The most potent compound (**9e**) exhibited superior anti-inflammatory properties compared to diclofenac. These results need further investigations to study the mechanism of action in vitro, and we are planning to publish the full biological results in a future communication.

Compliance with ethical standards

Conflict of interest None of the authors of the above manuscript has declared any conflict of interest.

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