Res Chem Intermed (2018) 44:455–467
https://doi.org/10.1007/s11164-017-3113-2

Synthesis and molecular docking studies of novel 1,2,3-triazole ring-containing 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol derivatives as COX inhibitors

B. Sathish Kumar[1] · **P. V. Anantha Lakshmi**[1]

Received: 28 March 2017 / Accepted: 18 August 2017 / Published online: 2 September 2017

Abstract A series of novel 3-phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one derivatives **6a–j** were synthesized in click chemistry reaction conditions and evaluated in silico by docking studies to recognize their hypothetical binding motif with cyclooxygenase-1 and cyclooxygenase-2. All docked compounds exhibited good docking scores in the range from 208.357 to 161.285 as compared with 145.934 for indomethacin, and 168.763 to 147.904 as compared with 145.934 for ibuprofen. Among all the tested compounds, **6b** showed good docking score and good interactions with binding-site residues of the COX proteins.

Keywords Cyclooxygenase · Imidazole · 1,2,3-Triazole · Chalcone · Docking studies

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for treatment of pain and inflammation. NSAIDs act by blocking the cyclooxygenase (COX) enzyme and thus biosynthesis of prostaglandins (PGs) [1]. Cyclooxygenases (COXs) are the key enzymes in synthesis of prostaglandins, the main mediators of inflammation, pain, and increased body temperature (hyperpyrexia) [2]. NSAIDs block the COX enzymes and reduce prostaglandins throughout the body. As a consequence,

Electronic supplementary material The online version of this article (doi:10.1007/s11164-017-3113-2) contains supplementary material, which is available to authorized users.

✉ P. V. Anantha Lakshmi
pvanantha.ou@gmail.com

[1] Department of Chemistry, Osmania University, Hyderabad, Telangana 500007, India

ongoing inflammation, pain, and fever are reduced. However, NSAIDs have a number of adverse effects, mainly because of their inhibition of the constitutive isoform of COX. COX-1 and COX-2 are two isomeric forms of COX enzyme. Imidazoles, chalcones, and 1,2,3-triazoles are privileged heterocyclic structures present in various natural products and synthetic pharmaceuticals. Compounds containing imidazole moiety play an important role due to their biological activity. Imidazole derivatives have been found to exhibit diverse activities such as analgesic [3], antiinflammatory [4–7], antimicrobial [8–10], anticancer [11, 12], antitubercular [13], antiviral [14], anticonvulsant [15], and antidepressant [16] effects. Similarly, triazole derivatives occupy a unique position in heterocyclic chemistry due to their unique chemical and structural properties, receiving much attention over recent years and finding wide applications in medicinal chemistry [17]. The 1,2,3-triazole heterocyclic ring system shows significant biological activities, such as antiinflammatory [18], antibacterial [19], antiviral [20], anti-human immunodeficiency virus (HIV) [21], antidiabetic [22], DNA cleavage [23], and potassium channel activation [24] effects. On the other hand, chalcones represent an important group of natural products [25, 26]. Chalcones containing several functional groups exhibit a wide spectrum of biological activities, including antiinflammatory [27], antileishmanial [28], antimalarial [29], antitumor [30], and antibacterial [31] effects. Some known imidazole/chalcone derivatives (**1–4**) are shown in Fig. 1, while 1,2,3-triazole derivatives (**5–7**) reported as pharmacologically active agents are presented in Fig. 2.

The biological potency of imidazole, 1,2,3-triazole, and chalcone pharmacophores prompted us to synthesize the title compounds, hoping that their incorporation into a single structural entity could result in novel compounds. In the present study, we synthesized a series of novel 3-phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one derivatives **6a–j** and propose the molecular interactions and binding mode of these compounds with COX targets based on in silico molecular docking studies.

Results and discussion

Chemistry

We synthesized 1,2,3-triazole chalcone derivatives of 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol. All title compounds were synthesized using four different steps. In

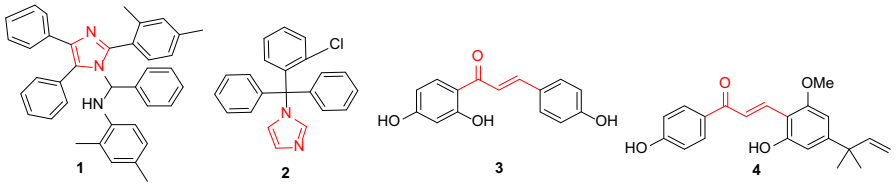


Fig. 1 Selected examples of imidazole/chalcone derivatives with pharmacological activity

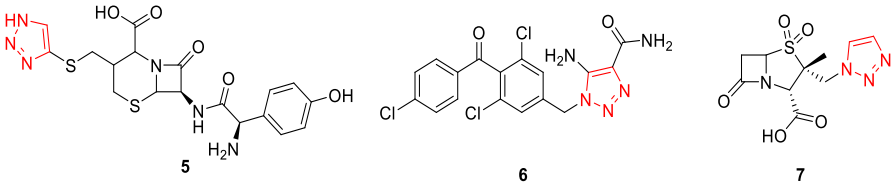
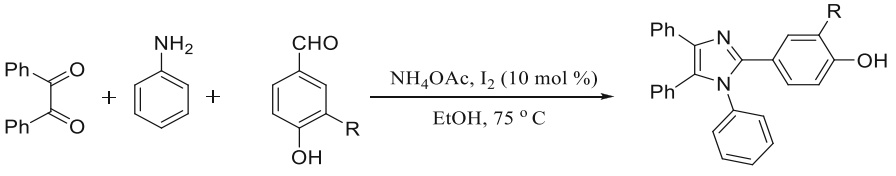


Fig. 2 Selected examples of 1,2,3-triazole derivatives with pharmacological activity

the first step, substituted 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol **1a**, **b** was prepared by stirring a mixture of benzil, aniline, 4-hydroxybenzaldehyde/4-hydroxy-3-methoxybenzaldehyde, ammonium acetate, and 10 mol% iodine in 5 ml ethanol at 75 °C for 1 h. In the second step, 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol **1a**, **b** was condensed with propargyl bromide in presence of K_2CO_3 in dimethylformamide (DMF) under reflux for 2 h to obtain corresponding propargyl products **2a**, **b**. In the next step, chalcone azides **5a–e** were synthesized by aldol condensation reaction of 1-(4-azidophenyl)ethan-1-one **3** with various substituted benzaldehydes **4a–e**. In the final step, intermediate **2a**, **b** was subjected to cycloaddition with chalcone azides **5a–e** under click chemistry reaction conditions in presence of copper(I) as catalyst in dry tetrahydrofuran (THF) for 12 h to obtain novel corresponding derivatives of 3-phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one **6a–j** in quantitative yields.

All title derivatives were characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR), infrared (IR), and electrospray ionization (ESI) mass spectroscopy (MS) analyses. The ^{1}H NMR signals appearing at δ 4.66 and 2.51 ppm confirm the *O*-propargylation of compound **2a**. All the triazole chalcone derivatives **6a–j** showed IR absorption bands from 3088 to 2971 cm^{-1}, corresponding to aromatic C–H stretching. Absorptions due to C=C, C=O, and C=N stretching were also observed at 1674 to 1670, 1711 to 1705, and 1244 to 1234 cm^{-1}, respectively. In ^{1}H NMR spectra, presence of singlet resonances at δ 5.30 to 5.22 ppm and 9.16 to 8.51 ppm were attributed to methylene protons attached to oxygen atom and proton of 1,2,3-triazole ring, respectively, whereas corresponding carbon resonances were observed in the ^{13}C NMR spectra at 60.94 to 60.01 and 123.3 to 122.5 ppm, respectively. All other protons and carbons resonated in expected regions.

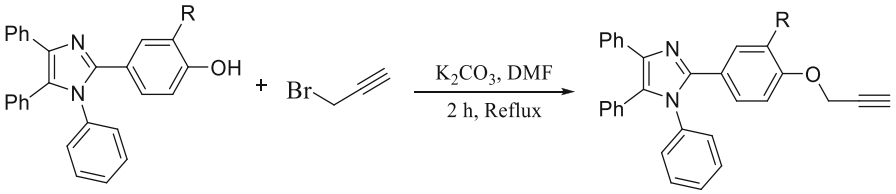
Step 1 Synthesis of 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol **1a**, **b**



1(a-b)

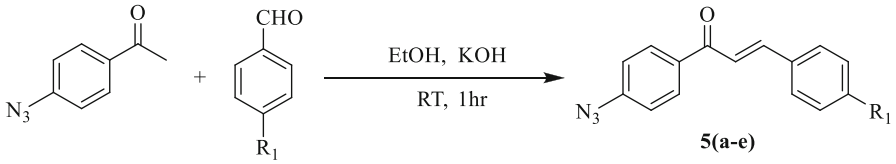
1a: R = H, **1b:** R = OCH_3

Step 2 Synthesis of 1,4,5-triphenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)-1*H*-imidazole **2a**, **b** (propargylation)



1(a-b) **2(a-b)**

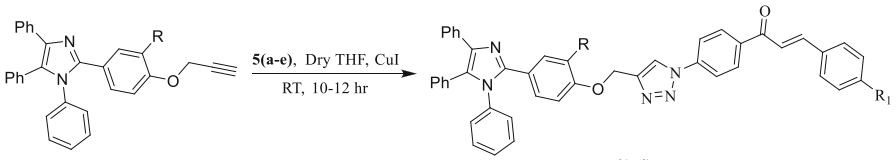
Step 3 Synthesis of azidochalcones **5a–e**



3 **4(a-e)** **5(a-e)**

5a: R_1= H, **5b:** R_1= NO_2, **5c:** R_1= Cl, **5d:** R_1= CH_3, **5e:** R_1= OCH_3

Step 4 Synthesis of 3-phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one derivatives **6a–j**



2(a-b) **6(a-j)**

6a: R= R_1= H,
6b: R= H, R_1= NO_2,
6c: R= H, R_1= Cl,
6d: R= H, R_1= CH_3,
6e: R= H, R_1= OCH_3,
6f: R= OCH_3, R_1= H,
6g: R= OCH_3, R_1= NO_2,
6h: R= OCH_3, R_1= Cl,
6i: R= OCH_3, R_1= CH_3,
6j: R= R_1= OCH_3

In silico molecular docking studies with cyclooxygenase-1 and cyclooxygenase-2

The molecular interaction of the title compounds was explored through molecular docking studies using Discovery Studio 2.1 software. The compounds were evaluated for their inhibitory effect on cyclooxygenase-1 (COX-1, PDB ID 2OYE) and cyclooxygenase-2 (COX-2, PDB ID 4PH9). For this study, crystallographic data for COX-1 and COX-2 were retrieved from the Protein Data Bank (http://www.rcsb.org). Retrieved crystal structures were cleaned, and hydrogen atoms added. All heteroatoms were removed before docking study, and the docking

energies (LibDock) of the title derivatives towards the antiinflammatory targets were explored. All compounds docked to the selected targets, and the docking results were compared with the standard control drugs indomethacin for COX-1 and ibuprofen for COX-2. The docking analysis of the synthesized compounds with COX-1 and COX-2 gave their docking scores and interaction patterns. All the docked compounds exhibited good docking scores in the range from 208.357 to 161.285 as compared with 145.934 for indomethacin (Table 1), and 168.763 to 147.904 as compared with 145.934 for ibuprofen (Table 2). Among all the compounds, **6b** showed good docking score of 208.357 and 168.763 as well as good interactions with binding-site residues of the target proteins COX-1 and COX-2, respectively. The docking pose of all the compounds revealed significant interaction with the active site of the respective targets. Moreover, potential hydrophobic contacts were found at the active site of the receptors. The significant docking score values imply that these compounds could represent potential leads for future non-steroidal antiinflammatory drugs (NSAIDs). The protein–ligand interaction of the compounds is visualized in Figs. 3 and 4.

Experimental

Chemistry

Melting points of all compounds were recorded on Cassia-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-C spectrometer using KBr optics. NMR spectra were recorded on Bruker Advance 400 MHz with tetramethylsilane (TMS) as internal standard; chemical shifts are expressed in δ ppm. Mass spectra were recorded on Hewlett Packard mass spectrometer operating at 70 eV. All reactions were monitored on silica gel precoated thin-layer chromatography (TLC) plates from Merck, and spots were visualized with ultraviolet (UV) light. Silica gel (100–200 mesh) used for column chromatography was procured from Merck.

*Synthesis of 4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenol (**1**)* Mixture of benzil (10 mmol), aniline (10 mmol), *p*-hydroxyaldehyde (10 mmol), ammonium acetate (10 mmol), and iodine (10 mol%) in 5 ml ethanol was stirred at 75 °C for 5 h. Reaction completion was monitored by TLC. After reaction completion, the reaction mixture was diluted with water (containing a small amount of $Na_2S_2O_3$). The solid imidazole products that separated out were filtered, washed with water, and dried. The crude products thus obtained were pure and subjected to further purification by column chromatography on silica gel (60–120 mesh size) using 25% ethylacetate in hexane as eluent to yield 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)phenol **1**.

*Synthesis of 1,4,5-triphenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)-1H-imidazole derivatives **2a**, **b*** 4-(1,4,5-Triphenyl-1*H*-imidazol-2-yl)phenol **1** (1.0 mol) along with 1.5 mol potassium carbonate was taken in dimethylformamide (DMF), and

Table 1 Docking score (LibDock) and ligand interaction data for compounds **6a–j** with active-site residues of cyclooxygenase-1 (PDB ID 2OYE)

Compound	LibDock score	Interacting atoms	Donor	Acceptor	H-bond distance (Å)
6a	183.644	P:ASN382:HD22—6a:N23	HD22	N23	2.020000
		P:ASN382:HD22—6a:N24	HD22	N24	1.528000
		6a:H74—P:ALA199:HB1	H74	HB	1.633000
		6a:H73—P:MET391:CE	H73	CE	1.903000
		6a:H73—P:MET391:HG1	H73	HG1	1.715000
6b	208.357	P:ASN382:HD22—6b:N24	HD22	N24	2.344000
		P:ASN382:HD21—6b:N24	HD21	N23	2.948000
		6b:H84—P:MET391:SD	H84	SD	2.039000
6c	169.693	P:MET391:HG2—6c:C42	HG2	C42	2.067000
		P:MET391:SD—6c:H75	SD	H75	2.201000
		P:MET391:HE2—6c:H70	HE2	H70	1.736000
6d	187.709	P:THR212:HN—6d:N5	HN	N5	1.540000
		P:ASN382:HD21—6d:O20	HD21	O20	2.216000
		6d:H72—P:MET391:SD	H72	SD	2.165000
		6d:C38—P:MET391:HG2	C38	HG2	2.101000
6e	198.695	P:THR212:HN—6e:N5	HN	N5	1.807000
		6e:H73—P:MET391:HB1	H73	HB1	1.745000
		6e:H57—P:VAL447:HG11	H57	HG11	1.785000
6f	180.295	P:ASN382:HD22—6f:N24	HD22	N24	2.368000
		P:ASN382:HD21—6f:N24	HD21	N24	2.353000
		6f:H75—P:ALA199:HB1	H75	HB1	1.798000
		6f:C19—P:VAL447:HG12	C19	HG12	2.197000
		6f:H62—P:VAL447:HG12	H62	HG12	1.570000
6g	161.285	6g:O35—P:ALA199:HA	O35	HA	1.496000
		6g:O57—P:MET391:HG2	O57	HG2	1.762000
		6g:H60—P:GLN203:OE1	H60	OE1	1.890000
6h	183.590	P:THR212:HG1—6h:N24	HG1	N24	1.448000
		P:THR212:HG1—6h:N23	HG1	N23	1.952000
6i	190.475	P:THR212:HG1—6i:N5	HG1	N5	2.521000
		P:ASN382:HD22—6i:O53	HD22	O53	1.950000
		P:ASN382:HD21—6i:O53	HD21	O53	2.369000
		P:MET391:HE2—6i:H71	HE2	H71	1.444000
		P:THR212:CB—6i:H77	CB	H77	1.956000
6j	194.448	P:ASN382:HD21—6j:O20	HD21	O20	2.467000
		P:THR212:HG1—6j:H89	HG1	H89	1.749000
		P:THR212:OG1—6j:H90	OG1	H90	2.042000
		6j:H72—P:MET391:CE	H72	CE	2.013000
		6j:H77—P:HIS388:CD2	H77	CD2	2.208000

Table 1 continued

Compound	LibDock score	Interacting atoms	Donor	Acceptor	H-bond distance (Å)
Indomethacin	174.315	Indo:H26—P:ASN382:O	H26	O	1.763000
		P:ASN382:HD21—Indo:O5	HD21	O5	2.343000
		P:LEU295:HD23—Indo:H38	HD23	H38	1.792000
		P:HIS207:HE1—Indo:C9	HE1	C9	2.189000
		P:HIS207:HE1—Indo:N6	HE1	N6	1.944000

propargyl bromide (1.5 mol) in DMF was added to this solution. The reaction mixture was stirred (reflux) to afford crude 1,4,5-triphenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)-1*H*-imidazole. This crude residue was purified by column chromatography over silica gel (100–200 mesh) in 15% ethyl acetate in hexane to obtain compound **2** in pure state.

*1,4,5-Triphenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)-1H-imidazole (**2a**)* Yield 88%, m.p. 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 1H, CH), 4.66 (s, 2H, O–CH_2), 6.84 (d, $J = 8.8$ Hz, 2H, H-ph), 7.06–7.01 (m, 2H, H-ph), 7.13–7.10 (m, 2H, H-ph), 7.19 (s, 2H, H-ph), 7.28–7.21 (m, 7H, H-ph), 7.37 (d, $J = 8.8$ Hz, 2H, H-ph), 7.59 (d, $J = 7.2$ Hz, 2H, H-ph); ^{13}C NMR (400 MHz, $CDCl_3$): δ 55.7, 75.6, 78.3, 114.5, 124.1, 126.5, 127.3, 127.9, 128.2, 128.3, 128.5, 128.6, 129.0, 129.9, 130.2, 130.6, 130.7, 131.1, 134.6, 138.5, 146.6, 157.5; ESI–MS: *m/z* 427 (M + 1) observed for $C_{30}H_{22}N_2O$.

*Synthesis of 1-(4-azidophenyl)-3-phenylprop-2-en-1-one derivatives **5a–e*** Mixture of 1-(4-azidophenyl)ethan-1-one **3** (1.0 mmol) in 10 mL EtOH, KOH (1.0 mmol), and substituted benzaldehyde **4a–e** (1.0 mmol) was stirred at room temperature (RT) for 1 h. After dilution with water (100 mL), the resulting solid was filtered off, washed with water, and recrystallized from EtOH to obtain yellow compound **5a–e**.

*1-(4-Azidophenyl)-3-phenylprop-2-en-1-one (**5a**)* Yield 81%, m.p. 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.10 (m, 2H, H-ph), 7.46–7.40 (m, 3H, H-ph), 7.52 (d, $J = 15.7$ Hz, 1H, =CH), 7.65 (d, $J = 3.7$ Hz, 2H, H-ph), 7.83 (d, $J = 15.7$ Hz, 1H, =CH), 8.06 (d, $J = 8.7$ Hz, 2H, H-ph).

*Synthesis of 3-phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one derivatives **6a–j*** Intermediate, 1,4,5-triphenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)-1*H*-imidazole **2a**, **b** (3.0 mmol) was dissolved in dry THF (10 mL), and catalytic amount of copper iodide was added. To this, substituted 1-(4-azidophenyl)-3-phenylprop-2-en-1-one **5a–e** (3.0 mmol) in dry THF was added slowly while stirring at room temperature under nitrogen atmosphere. After 12 h (reaction progress monitored by TLC), the solvent was removed under reduced pressure and the residue diluted with distilled water and extracted thrice with ethyl acetate. The combined organic layers were dried over

Table 2 Docking score (LibDock) and ligand interaction data of compounds **6a–j** with active-site residues of cyclooxygenase-2 (PDB ID 4PH9)

Compound	LibDock score	Interacting atoms	Donor	Acceptor	H-bond distance (Å)
6a	151.374	A:LYS83:HZ1—6a:N23	HZ1	N23	2.123000
		6a:H76—A:PRO84:CG	H76	CG	2.092000
		6a:H76—A:PRO84:CG	H76	CG	2.092000
6b	168.763	A:LYS83:HZ1—6b:N24	HZ1	N24	2.182000
		A:LYS83:HZ1—6b:N23	HZ1	N23	2.116000
		A:VAL117:CG2—6b:H57	CG2	H57	2.149000
6c	165.327	A:LYS83:HZ1—6c:N23	HZ1	N23	1.840000
		A:LYS83:HZ1—6c:N24	HZ1	N24	2.342000
		6c:C22—A:LYS83:HZ1	C22	HZ1	2.124000
		6c:H73—A:TYR116:CD1	H73	CD1	1.923000
6d	166.671	A:LYS83:HZ1—6d:N23	HZ1	N23	2.265000
		A:LYS83:HZ1—6d:N24	HZ1	N24	2.487000
		6d:H57—A:VAL117:CG2	H57	CG2	1.855000
6e	155.597	A:LYS83:HZ1—6e:N24	HZ1	N24	2.116000
		A:LYS83:HZ1—6e:N23	HZ1	N23	1.853000
		A:TYR116:CD1—6e:H75	CD1	H75	2.186000
		A:VAL117:CG2—6e:H58	CG2	H58	2.115000
6f	147.904	A:LYS83:HZ1—6f:N24	HZ1	N24	2.311000
		A:LYS83:HZ1—6f:N23	HZ1	N23	1.852000
		6f:C22—A:LYS83:HZ1	C22	HZ1	1.878000
6g	150.416	A:TYR116:HH—6g:N5	HH	N5	2.115000
		6g:H63—A:SER120:OG	H63	OG	1.809000
		6g:H79—A:TYR116:HH	H79	HH	1.349000
		6g:H69—A:TYR116:CD2	H69	CD2	1.885000
6h	152.342	6h:H78—A:LYS83:CA	H78	CA	2.036000
		6h:H75—A:LEU473:CA	H75	CA	1.972000
		6h:H75—A:SER472:O	H75	O	1.808000
6i	157.998	A:LYS83:HZ1—6i:N24	HZ1	N24	2.351000
		A:LYS83:HZ1—6i:N23	HZ1	N23	2.221000
		6i:C22—A:LYS83:HZ1	C22	HZ1	2.172000
		6i:C44—A:ILE92:CG2	C44	CG2	2.449000
6j	160.589	A:TYR116:HH—6j:N5	HH	N5	2.494000
		6j:H82—A:TYR116:HH	H82	HH	1.727000
		6j:H59—A:LEU473:CG	H59	CG	2.182000
		6j:H86—A:SER472:OG	H86	OG	1.961000
		6j:H62—A:SER120:OG	H62	OG	1.989000
Ibuprofen	145.934	Ibr:H16—A:SER122:N	H16	N	1.830000
		Ibr:H32—A:LEU473:CD2	H32	CD2	1.914000
		Ibr:H23—A:VAL117:CG2	H23	CG2	2.068000

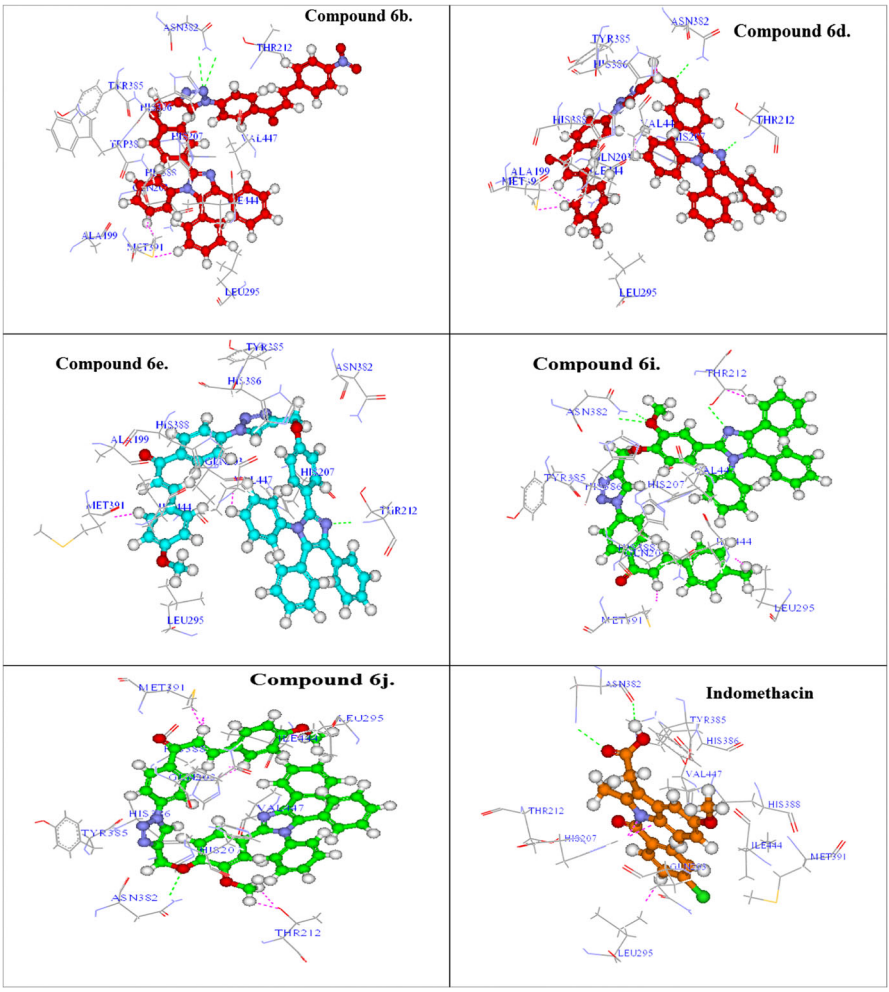


Fig. 3 Receptor–ligand hydrogen bonds (*green*) and bumps (*pink*) of compounds **6b**, **d**, **e**, **i**, **j**, and indomethacin with active-site residues of cyclooxygenase-1 (PDB ID 2OYE). (Color figure online)

anhydrous Na_2SO_4 and concentrated to obtain the product. The crude product was purified by column chromatography with 25% ethyl acetate in hexane.

*3-Phenyl-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (**6a**)* Yield 82%, m.p. 213–215 °C; IR spectrum, ν, cm^{-1}: 1233, 1672, 1716, 2971; ^1H NMR (400 MHz, DMSO-d_6): δ 5.22 (s, 2H, O–CH_2), 6.95 (t, $J = 7.5$ Hz, 2H, H-ph), 7.31 (d, $J = 7.4$ Hz, 2H, H-ph), 7.48–7.74 (m, 8H, =CH, H-ph), 7.81–7.96 (m, 4H, =CH, H-ph), 8.15–8.31 (m, 8H, H-ph), 8.75–8.83 (m, 4H, H-ph), 8.90 (dd, $J = 7.5$, 1.4 Hz, 2H, H-ph), 8.98 (s, 1H, =CH of triazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.94, 114.38, 119.84, 123.08, 123.30, 126.33, 128.09, 128.30, 128.32, 128.39, 128.47, 128.50, 128.74,

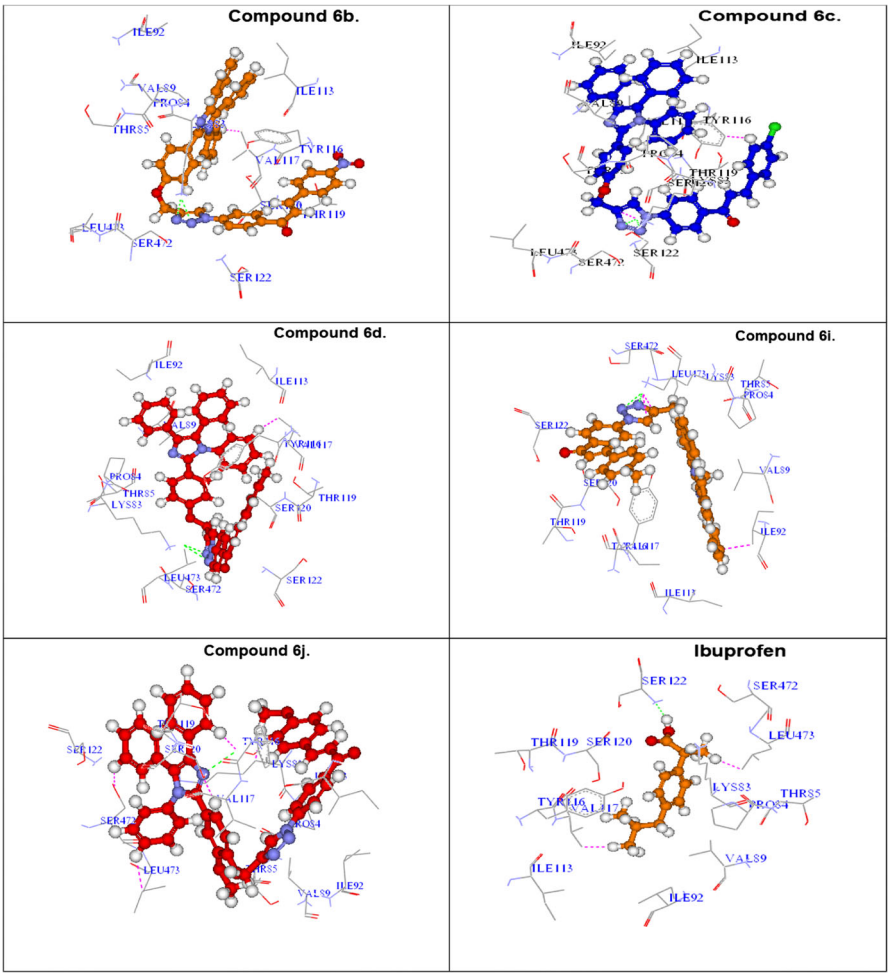


Fig. 4 Receptor–ligand hydrogen bonds (*green*) and bumps (*pink*) of compounds **6b**, **c**, **d**, **i**, **j**, and ibuprofen with active-site residues of cyclooxygenase-2 (PDB ID 4PH9). (Color figure online)

129.12, 129.68, 130.03, 130.17, 130.20, 1230.46, 131.09, 134.45, 136.45, 136.74, 139.50, 140.01, 145.06, 149.94, 150.03, 157.93, 196.89; ESI–MS: *m/z* 676 (M + 1) observed for $C_{45}H_{33}N_5O_2$.

*3-(4-Nitrophenyl)-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (**6b**)* Yield 87%, m.p. 210–213 °C; IR spectrum, *v*, cm^{-1}: 1224, 1672, 1715, 3087; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 2H, O–CH_2), 7.00 (d, $J = 8.8$ Hz, 2H, H-ph), 7.12–7.27 (m, 7H, H-ph), 7.28–7.31 (m, 3H, =CH, H-ph), 7.31–7.38 (m, 8H, H-ph), 7.48 (d, $J = 7.4$ Hz, 2H, H-ph), 7.81 (d, $J = 6.9$ Hz, 2H, H-ph), 7.98 (d, $J = 11.8$ Hz, 1H, =CH), 8.24 (d, $J = 9.1$ Hz, 2H, H-ph), 8.47 (d, $J = 9.1$ Hz, 2H, H-ph), 9.16 (s, 1H, =CH of triazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.51, 114.38, 119.73, 122.61,

123.10, 123.30, 126.30, 128.09, 128.26, 128.30, 128.40, 128.53, 128.69, 128.70, 128.74, 129.12, 129.68, 130.20, 130.46, 131.09, 134.45, 136.45, 136.74, 139.51, 140.00, 144.83, 145.03, 149.34, 149.51, 150.03, 157.89, 195.01; ESI–MS: *m/z* 721 (M + 1) observed for $C_{45}H_{32}N_6O_4$.

*3-(4-Chlorophenyl)-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (**6c**)* Yield 85%, m.p. 200–202 °C; IR spectrum, *v*, cm^{-1}: 1244, 1672, 1709, 3088; ^1H NMR (400 MHz, DMSO-d_6): δ 5.24 (s, 2H, O–CH_2), 7.01 (d, $J = 8.7$ Hz, 2H, H-ph), 7.16–7.26 (m, 9H, H-ph), 7.27–7.30 (m, 3H, =CH, H-ph), 7.31–7.36 (m, 5H, H-ph), 7.50 (d, $J = 7.5$ Hz, 2H, H-ph), 7.61 (d, $J = 11.7$ Hz, 1H, =CH), 8.09 (d, $J = 8.6$ Hz, 2H, H-ph), 8.17 (d, $J = 8.6$ Hz, 2H, H-ph), 8.31–8.46 (m, 3H, H-ph), 9.08 (s, 1H, =CH of triazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.61, 114.40, 119.81, 122.61, 123.08, 123.30, 126.33, 128.10, 128.26, 128.30, 128.40, 128.53, 128.69, 128.70, 128.75, 129.12, 129.70, 130.21, 130.45, 131.10, 134.49, 134.51, 136.45, 136.76, 139.61, 140.03, 144.83, 149.35, 149.53, 150.03, 157.90, 195.20; ESI–MS: *m/z* 710 (M + 1) observed for $C_{45}H_{32}ClN_5O_2$.

*3-(p-Tolyl)-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (**6d**)* Yield 81%, m.p. 206–209 °C; IR spectrum, *v*, cm^{-1}: 1238, 1670, 1705, 3072; ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 5.27 (s, 2H, O–CH_2), 7.11–7.36 (m, 5H, =CH and H-ph), 7.36–7.53 (m, 3H, =CH, H-ph), 7.56 (d, $J = 7.9$ Hz, 2H, H-ph), 7.58–7.85 (m, 10H, =CH, H-ph), 7.92–8.06 (m, 3H, H-ph), 8.18 (d, $J = 6.2$ Hz, 2H, H-ph), 8.31 (d, $J = 7.8$ Hz, 2H, H-ph), 8.50 (d, $J = 7.9$ Hz, 2H, H-ph), 8.66 (s, 1H, =CH of triazole); ESI–MS: *m/z* 690 (M + 1) observed for $C_{46}H_{35}N_5O_2$.

*3-(4-Methoxyphenyl)-1-(4-(4-((4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phen- yl)prop-2-en-1-one (**6e**)* Yield 80%, m.p. 200–202 °C; IR spectrum, *v*, cm^{-1}: 1244, 1672, 1709, 2977; ^1H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 3H, OCH_3), 5.30 (s, 2H, O–CH_2), 7.09 (d, $J = 9.7$ Hz, 2H, H-ph), 7.20 (d, $J = 7.5$ Hz, 2H, H-ph), 7.29–7.40 (m, 3H, =CH, H-ph), 7.49 (d, $J = 8.1$ Hz, 2H, H-ph), 7.55–7.80 (m, 7H, =CH, H-ph), 7.81–7.99 (m, 5H, H-ph), 8.00–8.15 (m, 4H, H-ph), 8.20 (d, $J = 8.9$ Hz, 2H, H-ph), 8.45 (d, $J = 8.2$ Hz, 2H, H-ph), 9.09 (s, 1H, =CH of triazole); ESI–MS: *m/z* 706 (M + 1) observed for $C_{46}H_{35}N_5O_3$.

*1-(4-(4-((2-Methoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-3-phenyl prop-2-en-1-one (**6f**)* Yield 80%, m.p. 210–212 °C; IR spectrum, *v*, cm^{-1}: 1243, 1672, 1710, 2985; ^1H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 5.25 (s, 2H, O–CH_2), 7.00 (d, $J = 7.5$ Hz, 1H, =CH), 7.07–7.24 (m, 4H, H-ph), 7.30–7.46 (m, 12H, H-ph), 7.53–7.62 (m, 5H, H-ph), 7.85 (d, $J = 7.4$ Hz, 2H, H-ph), 7.92 (dd, $J = 7.3$, 1.4 Hz, 2H, H-ph), 8.05 (d, $J = 7.5$ Hz, 2H, H-ph), 8.29 (d, $J = 13.2$ Hz, 1H, =CH), 8.91 (s, 1H, =CH of triazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.04, 60.01, 113.71, 114.12, 119.13, 122.09, 122.50, 125.33, 127.08, 127.30, 127.32, 127.38, 127.45, 127.50, 127.81, 128.15, 128.71, 129.03, 129.14, 129.20, 129.46, 130.09, 133.45, 135.12, 135.53, 138.62,

139.14, 144.63, 149.01, 149.53, 150.13, 158.01, 196.58; ESI–MS: *m/z* 706 (M + 1) observed for $C_{46}H_{35}N_5O_3$.

1-(4-(4-((2-Methoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one ***(6g)*** Yield 86%, m.p. 196–198 °C; IR spectrum, *v*, cm^{-1}: 1236, 1672, 1711, 2975; ^1H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H, OCH_3), 5.23 (s, 2H, O–CH_2), 7.01 (d, $J = 8.7$ Hz, 2H, H-ph), 7.16–7.26 (m, 7H, H-ph), 7.30 (d, $J = 7.9$ Hz, 2H, H-ph), 7.32–7.38 (m, 7H, H-ph), 7.50 (d, $J = 7.5$ Hz, 2H, H-ph), 8.09 (d, $J = 8.6$ Hz, 2H, H-ph), 8.17 (d, $J = 8.6$ Hz, 2H, H-ph), 8.49 (d, $J = 11.6$ Hz, 1H, =CH), 8.56 (d, $J = 9.6$ Hz, 1H, =CH), 8.86 (d, $J = 7.9$ Hz, 2H, H-ph), 9.03 (s, 1H, =CH of triazole); ESI–MS: *m/z* 751 (M + 1) observed for $C_{46}H_{34}N_6O_5$.

3-(4-Chlorophenyl)-1-(4-(4-((2-methoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one ***(6h)*** Yield 81%, m.p. 205–207 °C; IR spectrum, *v*, cm^{-1}: 1241, 1671, 1712, 3093; ^1H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 5.23 (s, 2H, O–CH_2), 7.00 (d, J = 8.0 Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H, =CH), 7.27 (d, $J = 7.3$ Hz, 2H, H-ph), 7.46–7.53 (m, 9H, H-ph), 7.54–7.68 (m, 10H, H-ph), 7.77 (d, $J = 7.3$ Hz, 2H, H-ph), 8.03 (d, $J = 8.7$ Hz, 2H, H-ph), 8.10 (d, $J = 11.7$ Hz, 1H, =CH), 8.54 (s, 1H, =CH of triazole); ESI–MS: *m/z* 440 (M + 1) observed for $C_{46}H_{34}ClN_5O_3$.

1-(4-(4-((2-Methoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-3-(p-tolyl)prop-2-en-1-one ***(6i)*** Yield 76%, m.p. 180–183 °C; IR spectrum, *v*, cm^{-1}: 1241, 1671, 1712, 3093; ^1H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 3.75 (s, 3H, OCH_3), 5.24 (s, 2H, O–CH_2), 7.00 (d, $J = 7.7$ Hz, 1H, =CH), 7.08 (d, $J = 7.7$ Hz, 2H, H-ph), 7.17–7.24 (m, 3H, H-ph), 7.25–7.43 (m, 10H, H-ph), 7.49–7.59 (m, 5H, H-ph), 7.75 (d, $J = 7.4$ Hz, 2H, H-ph), 7.84 (dd, $J = 7.3$ Hz, 1.4 Hz, 2H, H-ph), 7.95 (d, $J = 7.7$ Hz, 2H, H-ph), 8.20 (d, $J = 11.9$ Hz, 1H, =CH), 8.51 (s, 1H, =CH of triazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.10, 54.96, 60.91, 113.43, 114.08, 119.91, 120.60, 122.95, 123.37, 123.50, 125.78, 126.91, 127.70, 128.20, 128.41, 128.55, 128.80, 129.10, 129.20, 129.70, 131.70, 132.57, 133.56, 133.98, 135.20, 138.50, 139.40, 139.50, 142.15, 144.71, 147.90, 149.46, 150.46, 150.13, 157.95, 196.90; ESI–MS: *m/z* 720 (M + 1) observed for $C_{47}H_{37}N_5O_3$.

1-(4-(4-((2-Methoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one ***(6j)*** Yield 82%, m.p. 196–197 °C; IR spectrum, *v*, cm^{-1}: 1222, 1670, 1711, 2982; ^1H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.29 (s, 2H, O–CH_2), 7.05 (d, $J = 9.7$ Hz, 1H, =CH), 7.14 (d, $J = 7.5$ Hz, 2H, H-ph), 7.33–7.27 (m, 3H, H-ph), 7.44 (d, $J = 9.1$ Hz, 1H, =CH), 7.73–7.50 (m, 8H, H-ph), 7.94–7.75 (m, 5H, H-ph), 8.09–7.95 (m, 4H, H-ph), 8.14 (d, $J = 8.9$ Hz, 2H, H-ph), 8.39 (d, $J = 8.2$ Hz, 2H, H-ph), 8.99 (s, 1H, =CH of triazole); ESI–MS: *m/z* 736 (M + 1) observed for $C_{47}H_{37}N_5O_4$.

Acknowledgements We thank the DST-FIST Program of India (SR/FST/CSI-213/2010) for financial support. B.S.K. is grateful to UGC-New Delhi, India for granting a junior research fellowship. We also thank the Director of CFRD-OU, Hyderabad for providing spectral analysis facilities.

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