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Synthesis, Biological Evaluation, and Molecular Docking Studies of Novel 1,2,3-Triazole Derivatives as Potent Anti-Inflammatory Agents[1]

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Abstract—In the present study, a novel series of 1,2,3-triazole derivatives have been synthesized using click chemistry approach. The structures were confirmed by spectroscopic methods. The products were screened for their *in vivo* anti-inflammatory activity. The tested compounds **6a, 6f, 6g, 6i, 6j, 6n,** and **6p**, demonstrated potent anti-inflammatory activity compared to the reference drug ibuprofen. Molecular docking studies of these 1,2,3-triazole derivatives into the active site of human cyclooxygenase-2 (COX-2) (PDB code 4PH9) demonstrated good affinity for the enzyme and suggested binding properties similar to ibuprofen.

Keywords: 1,2,3-triazoles, click chemistry, anti-inflammatory, docking

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INTRODUCTION

Pharmacological effects of nonsteroidal anti-inflammatory drugs (NSAIDs) relate to the suppression of prostaglandin synthesis from arachidonic acid by inhibiting the membrane enzyme cyclooxygenases (COXs) [1] with a different degree of selectivity [2]. COX enzymes exist in two isoforms: COX-1 which is a housekeeping enzyme found in most of the cells and plays an important role in the protection of gastric mucosa, platelet aggregation and renal blood flow. COX-2 is an inducible isozyme significantly expressed during inflammation. Long term use of NSAIDs can lead to several adverse effects including gastro-intestinal (GI) ulcerations [3], cardiovascular toxicity [4], renal failure [5], and asthma [6]. These serious side effects are limiting the use of NSAIDs in common inflammation cases. Therefore, development of novel compounds with anti inflammatory activity and improved safety profile is of considerable importance.

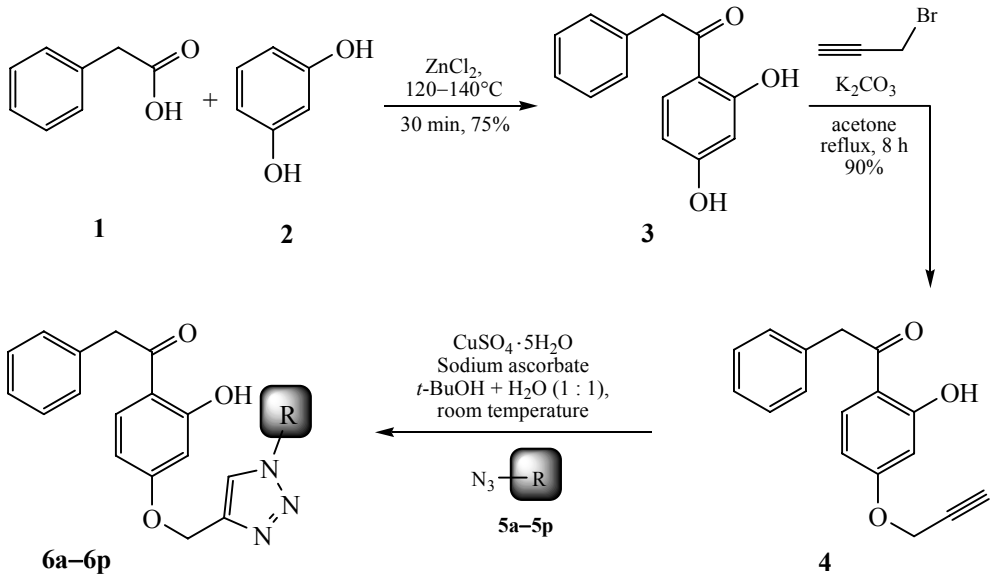
Among numerous applications in biology and medicine 1,2,3-triazoles demonstrate significan potential in synthetic accessibility by click chemistry [7], chemotherapy [8] and as anti-inflammatory agents [9]. 1,4-Disubstituted 1,2,3-triazoles obtained from copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions possess wide applications in synthetic organic [10], biological [11] and medicinal [12] chemistry. We hereby report synthetic approach to some novel 1,4-disubstituted 1,2,3-triazole derivatives by click chemistry. The synthesized compounds were screened for their in vivo anti-inflammatory activity. Docking studies were directed towards the active site of human COX-2 to predict the binding affinity and orientation of these novel triazole analogues **6a–6p**.

RESULTS AND DISCUSSION

General approach to synthesis of the target regioselective 1,4-disubstituted 1,2,3-triazoles was achieved by a 3-steps protocol (Scheme 1). Resorcinol **2** upon condensation with phenylacetic acid **1** in the presence of freshly fused $ZnCl_2$ produced 1-(2,4-dihydroxyphenyl)-2-phenylethanone (**3**). Selective *O*-alkylation of compound **3** was achieved by its refluxing with propargyl bromide and potassium carbonate to afford *para* alkylated compound **4** with 90% yield. Formation

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles.



of *para* alkylated product may be explained by mesomeric effect and steric factors: in compound **3** *ortho* hydroxy group is of lower nucleophilicity than *para* hydroxy group. ^{1}H NMR spectra demonstrated characteristic singlet at 12.91 ppm attributed to chelated phenolic hydrogen of *ortho* hydroxy group and two singlets at 4.73 (O–CH_2–, 2H) and 2.59 ppm (≡CH, 1H) that indicated O-propargylation with formation of 1-[2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl]-2-phenylethanone (**4**) as the major product. Various aliphatic and aromatic azides **5a–5p** (Fig. 1) were synthesized by utilizing literature protocols [13, 14].

The targeted regioselective 1,4-disubstituted 1,2,3-triazole derivatives **6a–6p** were synthesized according to Huisgen's [2+3]-cycloaddition reaction [15] of 1-[2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl]-2-phenylethanone (**4**) with various aromatic and aliphatic azides **5a–5p**. In ^{1}H NMR spectra of the prducts the singlet recorded in the range of 7.53–8.21 ppm indicated the formation of 1,2,3-triazoles (Fig. 2).

Pharmacology. *In vivo anti-inflammatory activity.* The products **6a–6p** were screened for in vivo anti-inflammatory activity by using carrageenan-induced hind paw oedema model [16] of the oral dose of 10 mg/kg body weight and compared with the standard drug ibuprofen of the same oral dose. Anti-inflammatory activity was calculated at hourly intervals up to 6 h (Table 1). The differences of paw volumes

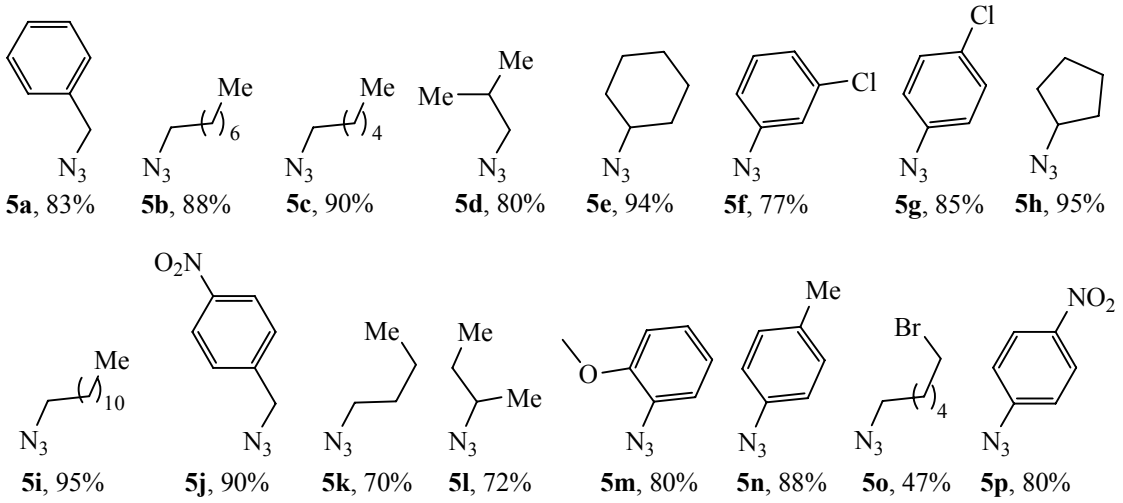


Fig. 1. Synthesized azides **5a–5p**.

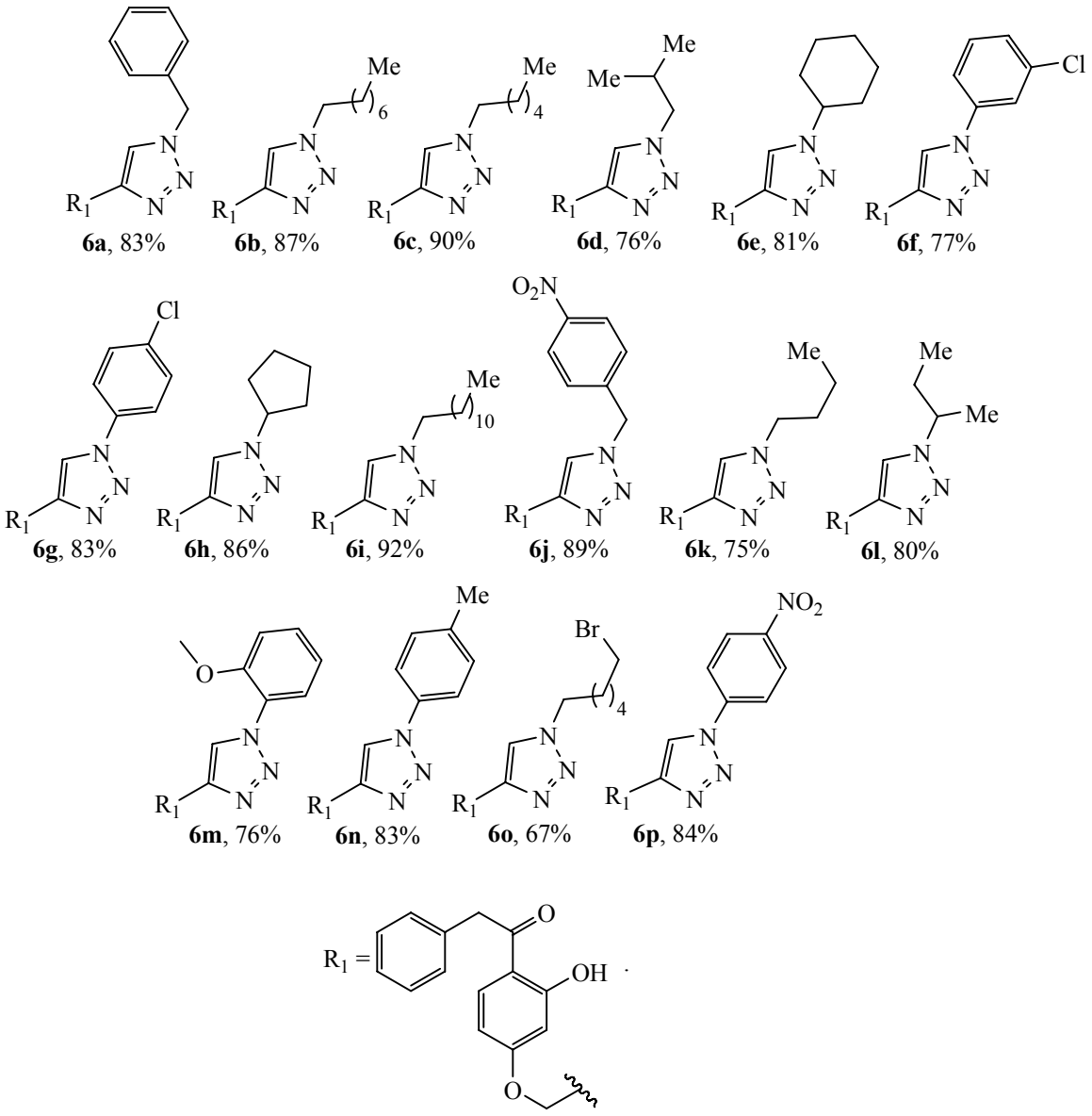


Fig. 2. Derivatives of target compound **6a–6p**.

were compared with the control group and the treated animals. Percentage inhibition was calculated as:

$$\text{Inhibition} = [(V_0 - V_t)/V_0] \times 100\%,$$

where V_0 is a volume of the paw control at time t, V_t is a volume of the paw of drug treated at time t.

Most of the test compounds demonstrated maximum activity at 4 h and then it decreased gradually over the following 2 h. All triazole derivatives **6a–6p** exhibited mild to strong anti-inflammatory activity compared to ibuprofen (Table 1). Compounds **6a, 6f, 6g, 6i, 6j, 6n,** and **6p** exhibited excellent anti-inflammatory activity. The compound **6j** which had *p*-nitrobenzyl group at the first position of triazole ring exhibited the most potent activity. Replacement of the benzyl group for an aryl group on triazole resulted in the decrease of activity. *para*-Substituted phenyl [NO_2 (**6p**) or Cl (**6g**) or Me (**6n**)] group at the first position of triazole influenced the activity making it more pronounced. Compounds **6b**, **6c, 6e,** and **6h** showed considerable inhibition of oedema (Table 1).

Molecular docking. Genetic optimization for ligand docking (GOLD) version 2.0 [17] was used for all synthesized compounds **6a–6p**. Those were docked

Table 1. In vivo anti-inflammatory activity of 1,2,3-triazoles **6a–6p**

Compound no.	Volume of edema[a] (mL) and % AI[b]					
	4 h		5 h		6 h	
	swelling	inhibition, %	swelling	inhibition, %	swelling	inhibition, %
6a	0.09±0.041[c]	93.43	0.11±0.054[c]	93.12	0.15±0.046[c]	92.06
6b	0.31±0.079[d]	77.37	0.39±0.017[d]	75.62	0.47±0.096[d]	75.13
6c	0.36±0.031	73.72	0.45±0.028	71.87	0.55±0.029	70.89
6d	0.71±0.056	48.17	0.88±0.063	45.00	0.86±0.032	54.49
6e	0.37±0.023	72.99	0.41±0.028	74.37	0.45±0.086	76.19
6f	0.11±0.091[c]	91.97	0.13±0.029[c]	90.51	0.18±0.081[c]	90.47
6g	0.17±0.039[c]	87.59	0.20±0.064[c]	87.50	0.24±0.056[c]	87.30
6h	0.39±0.032	71.53	0.47±0.051	70.62	0.63±0.074	66.66
6i	0.27±0.033[d]	80.29	0.33±0.036[d]	79.37	0.40±0.055[d]	78.83
6j	0.05±0.032[c]	96.35	0.07±0.045[c]	95.62	0.12±0.025[c]	93.65
6k	0.46±0.056	66.42	0.50±0.071	68.75	0.54±0.062	71.42
6l	0.64±0.072	53.28	0.78±0.045	51.25	0.73±0.043	61.37
6m	0.77±0.039	43.79	0.83±0.05	48.12	0.99±0.066	47.61
6n	0.23±0.067[d]	83.21	0.30±0.072[d]	81.25	0.36±0.042[d]	80.95
6o	0.66±0.072	51.82	0.78±0.045	51.25	0.78±0.062	58.73
6p	0.16±0.042[d]	88.32	0.20±0.038[d]	87.50	0.26±0.049[d]	86.24
Control (–)	1.37±0.012	–	1.60±0.019	–	1.89±0.009	–
Ibuprofen	0.06±0.027	95.62	0.07±0.027	95.62	0.10±0.021	94.70

[a] Values are expressed as mean ±SEM from six observations and Data is analyzed by one way ANOVA followed by Dunnett's "t" test.
[b] Values in parentheses. AI (%) is a percentage anti-inflammatory activity.
[c] Indicates $P < 0.001$.
[d] Indicates $P < 0.01$. Control (–) (0.1 mL of saline solution).

into the active site of COX-2 (PDB code 4PH9) (Table 2). Binding energies were calculated using ArgusLab [18] docking software (Table 2). Discovery studio visualizer has been utilized to visualize the binding conformations of these analogues **6a–6p** in the active site of 4PH9 protein.

Molecular binding pattern of ibuprofen with COX-2 (Fig. 3) revealed that it had hydrogen bonds with TYR356, ARG121, TRP388, TYR386, PHE519, VAL350, ALA528, LEU360, VAL117, LEU537 amino acids at the active site region. Among these amino acids TYR356 with bond distances 2.42, 5.21 Å and ARG121 with bond distances 3.01, 2.97 Å play an important role in formation of hydrogen bonds with COX-2 inhibitor. Compound **6j** formed hydrogen bonds with TYR356, ARG121, VAL89, VAL117, ILE92, LEU93, LEU360 amino acids. For **6j** ibuprophen like interactions with hydrogen bond distances viz. 3.00, 3.47 Å for ARG121 and 2.40, 2.63 Å for TYR356 were found (Fig. 4). Compound **6j** had high Gold fitness (67.63) and Chem scores (34.74) (Table 2).

EXPERIMENTAL

Commercially available reagents were used as supplied and some of those were distilled before use. All reactions were performed in oven dried glassware. All solvents were removed by evaporation at below 45°C under reduced pressure. Melting points were determined in open capillary tubes. IR spectra were recorded in KBr discs on an Infracold 337 Perkin-

Table 2. Gold fitness, Chem scores, and ArgusLabs binding energy values of 1,2,3-triazoles **6a–6p**

Comp. no.	GOLD scores		ArgusLabs Energies	
	gold fitness	chem score	Argus B.E, kcal/mol (elapsed time)	GA Dock B.E, kcal/mol (elapsed time)
6a	66.61	32.89	–14.02 (3)	–11.51 (14)
6b	61.00	30.64	–14.32 (5)	–11.80 (17)
6c	63.05	30.20	–12.84 (5)	–11.74 (41)
6d	57.87	29.65	–12.43 (4)	–7.78 (14)
6e	59.06	31.97	–13.94 (4)	–12.62 (16)
6f	60.41	33.37	–13.14 (3)	–13.91 (37)
6g	58.66	33.59	–13.02 (4)	–11.06 (14)
6h	57.03	30.76	–12.70 (3)	–11.21 (14)
6i	62.69	37.99	–12.39 (4)	–8.37 (20)
6j	67.63	34.74	–12.28 (3)	–12.44 (15)
6k	57.05	27.54	–12.23 (4)	–10.25 (14)
6l	49.83	30.53	–12.04 (4)	–9.01 (14)
6m	51.86	29.93	–12.27 (2)	–12.17 (15)
6n	55.88	33.01	–10.07 (2)	–14.47 (14)
6o	49.61	30.81	–11.58 (2)	–9.19 (14)
6p	58.02	32.54	–12.20 (2)	–10.93 (15)
Ibuprofen	41.29	30.59	–10.52 (3)	–10.11 (11)

Elmer spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AV 300 and 400 MHz spectrometer in $CDCl_3$ using TMS as the internal standard. TLC was carried out on aluminium sheets coated with silica gel 60 F_{254} (Merck, 1.05554) and visualized with UV light at 254 nm or alternatively by staining with aqueous basic potassium permanganate. Flash column chromatography was performed using silica gel (Merck, 60A, 100–200 mesh).

Synthesis of 1-(2,4-dihydroxyphenyl)-2-phenylethanone (3). Phenylacetic acid (3 g, 22.03 mmol) was added to freshly fused zinc chloride (3 g, 22.03 mmol) and heated to 120°C for 30 min followed by addition of resorcinol (2.42 g, 22.03 mmol). The reaction mixture was heated to 140°C for 30 min (TLC control), cooled down to room temperature, poured in to ice cold water (100 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 20% HCl (50 mL), saturated $NaHCO_3$ (25 mL) and brine (2 × 25 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate/pet ether eluent) to afford 1-(2,4-dihydroxyphenyl)-2-phenylethanone as off-white crystalline solid. Yield 76%, mp 112–117°C. ^{1}H NMR spectrum, δ, ppm: 12.70 s (1H), 7.77 d (J = 8.38 Hz, 1H), 7.39–7.33 m (2H), 7.31–7.27 m (3H), 6.42–6.37 m (2H), 4.24 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 165.9, 163.4, 134.9, 133.5, 130.0 (2C), 129.4 (2C), 127.8, 114.2, 108.9, 104.5, 46.1. LRMS: (ES^+) m/z = 229 [M + 1].

Synthesis of 1-[2-hydroxy-4-(prop-2-yn-1-yloxy)-phenyl]-2-phenylethanone (4). To a well stirred solution of compound **3** (3 g, 13.14 mmol) in dry acetone and K_2CO_3 (1.81 g, 13.14 mmol), propargyl bromide 80% in toluene (1.87 g, 15.77 mmol) was added drop wise and the reaction mixture was refluxed for about 6–8 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled down to room temperature and the excess of acetone was evaporated under reduced pressure. The residual mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL) and dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluent 5% ethyl acetate in pet ether) to afford the product **4** as light yellow solid. Yield 85%, mp 94–96°C. IR spectrum, ν, cm^{-1}: 3402 (C–OH), 3290 (≡C–H), 2136 (C≡C), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.70 s (1H), 7.82–7.78 m (1H), 7.39–7.33 m (2H), 7.32–7.27 m (3H), 6.55–6.50 m (2H), 4.73 s (2H), 4.24 s (2H), 2.59 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.0, 164.3, 134.9, 132.8, 130.0 (2C), 129.4 (2C), 127.8, 114.5, 108.9, 103.1, 78.4, 77.4, 57.1, 46.2. LRMS: (ES^+) m/z = 267 [M + 1], 289 [M + Na].

General procedure for 1,4-disubstituted 1,2,3-triazole analogues 6a–6p. Propargyl derivative (**4**) (100 mg, 0.375 mmol) was dissolved in 5 mL of aqueous *t*-BuOH (50%). $CuSO_4 \cdot 5H_2O$ (5 mol %), sodium ascorbate (10 mol %) and azide (0.45 mmol) were added to the solution. The reaction mixture was stirred for 1 h at room temperature. Upon completion of the process the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL).

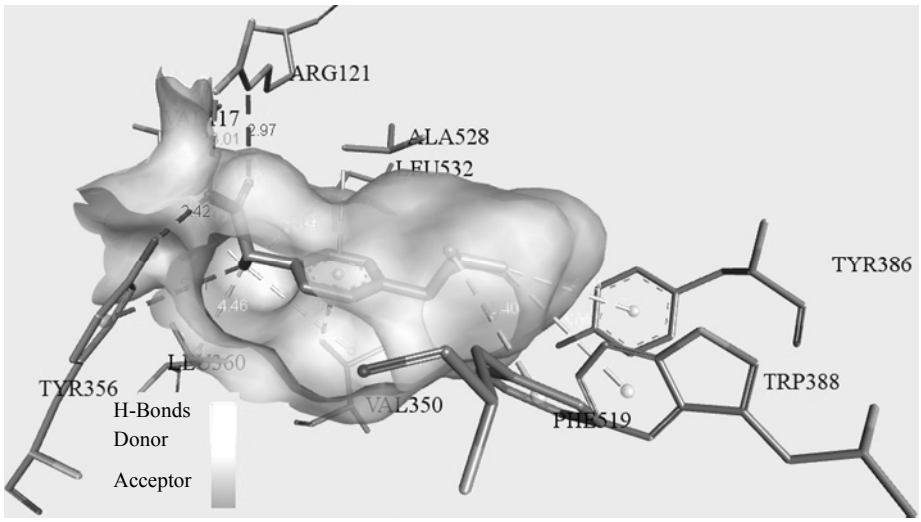


Fig. 3. Docking pose of ibuprofen into the COX-2 (4PH9) active site. Hydrogen bonds are shown in dotted lines.

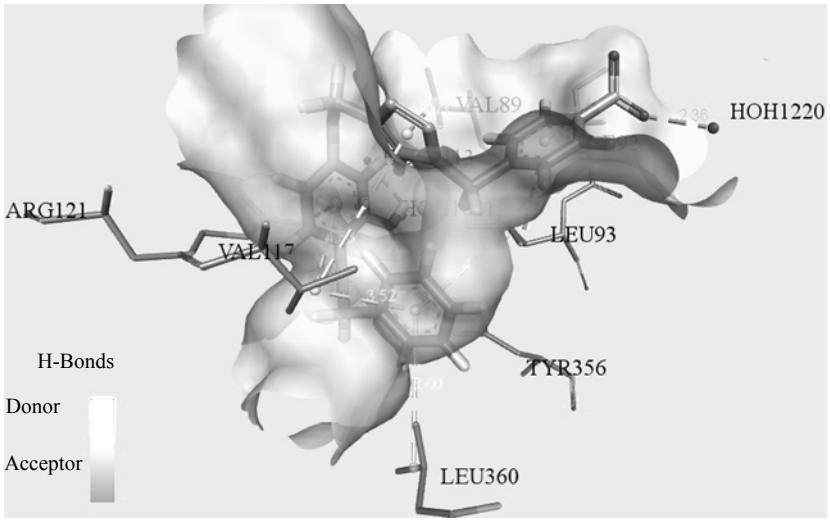


Fig. 4. Docking pose of compound **6j** into the COX-2 (4PH9) active site. Hydrogen bonds are shown in dotted lines.

The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluent ethyl acetate in pet ether) to afford the corresponding 1,4-disubstituted 1,2,3-triazole analogues.

1-{4-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6a). Yield 83%, white solid, mp 127–129°C. IR spectrum, ν, cm^{-1}: 3442 (C–OH), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.66 s (1H), 7.77–7.75 m (1H), 7.53 s (1H), 7.38–7.25 m (10H), 6.51–6.48 m (2H), 5.54 s (2H), 5.19 s (2H), 4.21 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 166.2, 165.3, 144.2, 135.4, 135.3, 133.3, 130.5 (2C), 130.3 (2C), 130.0, 129.8 (2C), 129.2 (2C), 128.2, 124.2, 114.8, 109.3, 103.5, 63.99, 56.2, 46.9. LRMS: (ES^+) *m/z* = 422 [*M* + Na].

1-{2-Hydroxy-4-[(1-octyl-1*H*-1,2,3-triazol-4-yl)-methoxy]phenyl}-2-phenylethanone (6b). Yield 87%, white solid, mp 89–90°C. IR spectrum, ν, cm^{-1}: 3436 (C–OH), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.67 s (1H), 7.79–7.76 m (1H), 7.60 s (1H), 7.37–7.26 m (5H), 6.54–6.50 m (2H), 5.22 s (2H), 4.35 t (*J* = 5.6 Hz, 2H), 4.22 s (2H), 1.94–1.86 m (2H), 1.33–1.25 m (10 H), 0.87 t (*J* = 5.3 Hz, 3H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.0, 165.1, 143.4, 134.9, 132.9, 130.0 (2C), 129.4 (2C), 127.7, 123.5, 114.3, 108.7, 103.0, 63.3, 51.7, 46.1, 32.5 (2C), 31.6, 27.5, 23.8 (2C), 15.4. LRMS: (ES^+) *m/z* = 422 [*M* + 1], 444 [*M* + Na].

1-{4-[(1-Hexyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6c). Yield 90%, white solid, mp 86–88°C. IR spectrum, ν, cm^{-1}: 3430

(C–OH), 1663 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.67 s (1H), 7.79–7.76 m (1H), 7.60 s (1H), 7.37–7.27 m (5H), 6.54–6.50 m (2H), 5.25 s (2H), 4.35 t (*J* = 7.1 Hz, 2H), 4.22 s (2H), 1.94–1.87 m (2H), 1.36–1.25 m (8H), 0.87 t (*J* = 6.9 Hz, 3H). ^{13}C NMR spectrum, δ_C, ppm: 202.1, 165.6, 164.7, 142.9, 134.3, 132.2, 129.3 (2C), 128.7 (2C), 127.1, 122.7, 113.5, 107.9, 102.2, 62.1, 50.5, 44.8, 31.1, 30.2, 26.1, 22.4, 13.9. LRMS: (ES$^+$) *m/z* = 394 [*M* + 1].

1-{2-Hydroxy-4-[(1-isobutyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-2-phenylethanone (6d). Yield 76%, white solid, mp 96–98°C. IR spectrum, ν, cm^{-1}: 3431 (C–OH), 1666 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.68 s (1H), 7.80–7.78 m (1H), 7.60 s (1H), 7.38–7.28 m (5H), 6.56–6.53 m (2H), 5.25 s (2H), 4.24 s (2H), 4.19 d (*J* = 7.23 Hz, 2H), 2.27–2.22 m (1H), 0.98 d (*J* = 6.70 Hz, 6H). ^{13}C NMR spectrum, δ_C, ppm: 202.1, 165.6, 164.7, 142.8, 134.3, 132.2, 129.3 (2C), 128.7 (2C), 127.1, 123.2, 113.6, 107.9, 102.2, 62.2, 57.7, 44.8, 29.7, 19.8 (2C). LRMS: (ES$^+$) *m/z* = 366 [*M* + 1].

1-{4-[(1-Cyclohexyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6e). Yield 81%, white solid, mp 106–108°C. IR spectrum, ν, cm^{-1}: 3443 (C–OH), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.66 s (1H), 7.79–7.76 m (1H), 7.62 s (1H), 7.37–7.26 m (5H), 6.56–6.52 m (2H), 5.21 s (2H), 4.50–4.41 m (1H), 4.22 s (2H), 2.25–2.20 m (2H), 1.96–1.91 m (2H), 1.79–1.72 m (3H), 1.53–1.40 m (2H), 1.34–1.26 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.3, 165.4, 143.4, 135.3, 133.3, 130.4 (2C), 129.8 (2C), 128.2, 121.8, 114.9, 109.2, 103.6, 64.2, 62.2, 47.0, 35.8 (2C), 27.5 (2C), 27.4. LRMS: (ES$^+$) *m/z* = 392 [*M* + 1], 414 [*M* + Na].

1-{4-[(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]-2-hydroxyphenyl}-2-phenylethanone (6f). Yield 77%, white solid, mp 160°C. IR spectrum, ν, cm^{-1}: 3446 (C–OH), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.69 s (1H), 8.06 s (1H), 7.78–7.64 m (3H), 7.55–7.05 m (7H), 6.55 s (2H), 5.30 s (2H), 4.22 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.1, 165.6, 164.4, 144.1, 137.6, 135.7, 134.2, 132.3, 130.9, 129.3 (2C), 129.1, 128.7 (2C), 127.1, 121.0, 120.8, 118.6, 113.7, 107.8, 102.2, 62.0, 44.9. LRMS: (ES$^+$) *m/z* = 419.9 [*M* + 1].

1-{4-[(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]-2-hydroxyphenyl}-2-phenylethanone (6g). Yield 83%, white solid, mp 176°C. IR spectrum, ν, cm^{-1}: 3447 (C–OH), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.69 s (1H), 8.05 s (1H), 7.78–7.66 m (3H), 7.49 d (*J* = 6.7 Hz, 2H), 7.39–7.19 m (5H), 6.54 s (2H), 5.28 s (2H), 4.21 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.1, 165.6, 164.4, 144.0, 135.3, 134.8, 134.2, 132.3, 130.0 (2C), 129.3 (2C), 128.7 (2C), 127.1, 121.7 (2C), 121.0, 113.7, 107.8, 102.2, 61.9, 44.9. LRMS: (ES$^+$) *m/z* = 420 [*M* + 1].

1-{4-[(1-Cyclopentyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6h). Yield 86%, white solid, mp 115°C. IR spectrum, ν, cm^{-1}: 3445 (C–OH), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.68 s (1H), 7.80–7.76 m (1H), 7.62 s (1H), 7.38–7.32 m (2H), 7.31–7.26 m (3H), 6.55–6.52 m (2H), 5.21 s (2H), 4.98–4.90 m (1H), 4.22 s (2H), 2.33–2.23 m (2H), 2.11–2.01 m (2H), 1.97–1.86 m (2H), 1.83–1.71 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 166.3, 165.4, 143.5, 135.3, 133.3, 130.4, 129.8, 128.2, 122.8, 114.8, 109.2, 103.6, 64.1, 63.9, 46.9, 35.6 (2C), 26.4 (2C). LRMS: (ES$^+$) *m/z* = 378 [*M* + 1].

1-{4-[(1-Dodecyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6i). Yield 92%, white solid, mp 80°C. IR spectrum, ν, cm^{-1}: 3448 (C–OH), 1673 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.68 s (1H), 7.80–7.76 m (1H), 7.61 s (1H), 7.37–7.32 m (2H), 7.28–7.26 m (3H), 6.53–6.51 m (2H), 5.22 s (2H), 4.36 t (*J* = 7.3 Hz, 2H), 4.22 s (2H), 1.96–1.87 m (2H), 1.30–1.22 m (18H), 0.88 t (*J* = 6.81 Hz, 3H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.3, 165.3, 143.8, 135.3, 133.3, 130.4 (2C), 129.8 (2C), 128.2, 123.9, 114.8, 109.2, 103.6, 64.1, 52.5, 47.0, 34.2, 32.5, 32.0, 31.9 (2C), 31.8, 31.7, 31.3, 28.8, 25.1, 16.6. LRMS: (ES$^+$) *m/z* = 478 [*M* + 1].

1-{2-Hydroxy-4-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy)phenyl}-2-phenylethanone (6j). Yield 89%, light yellow solid, mp 160°C. IR spectrum, ν, cm^{-1}: 3431 (C–OH), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.68 s (1H), 8.29–8.23 m (2H), 7.82–7.77 m (1H), 7.65 s (1H), 7.44 d (*J* = 8.65 Hz, 2H), 7.36 m (2H), 7.30 m (3H), 6.55–6.50 m (2H), 5.69 s (2H), 5.26 s (2H), 4.25 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.0, 164.8, 148.7, 144.6, 141.8, 134.8, 132.9, 130.0 (2C), 129.4 (2C), 129.3 (2C), 127.8, 125.1 (2C), 123.7, 114.4, 108.6, 103.0, 63.2, 54.4, 46.2. LRMS: (ES$^+$) *m/z* = 445 [*M* + 1].

1-{4-[(1-Butyl-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6k). Yield 75%, white solid, mp 84–86°C. IR spectrum, ν, cm^{-1}: 3429 (C–OH), 1658 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.69 s (1H), 7.83–7.77 m (1H), 7.63 s (1H), 7.40–

7.34 m (2H), 7.32–7.28 m (3H), 6.58–6.53 m (2H), 5.26 s (2H), 4.40 t (*J* = 7.23 Hz, 2H), 4.25 s (2H), 1.99–1.89 m (2H), 1.46–1.34 m (2H), 1.00 t (*J* = 7.33 Hz, 3H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 166.2, 165.4, 143.7, 135.3, 133.3, 130.4 (2C), 129.8 (2C), 128.2, 124.0, 114.8, 109.2, 103.6, 64.0, 52.5, 46.9, 34.4, 22.1, 15.9. LRMS: (ES$^+$) *m/z* = 388 [*M* + Na].

1-{4-[(1-(*sec*-Butyl)-1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone (6l). Yield 80%, white solid, mp 72°C. IR spectrum, ν, cm^{-1}: 3431 (C–OH), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.69 s (1H), 7.82–7.74 m (1H), 7.61 s (1H), 7.40–7.25 m (5H), 6.58–6.49 m (2H), 5.19 s (2H), 4.66–4.53 m (1H), 4.22 s (2H), 1.96–1.82 m (2H), 1.57 d (*J* = 6.63 Hz, 3H), 0.86 t (*J* = 7.16 H z, 3H). ^{13}C NMR spectrum, δ_C, ppm: 202.0, 165.6, 164.7, 142.7, 134.3, 132.2, 129.3 (2C), 128.7 (2C), 127.1, 120.8, 113.5, 107.9, 102.1, 62.3, 59.1, 44.8, 30.3, 20.9, 10.4. LRMS: (ES$^+$) *m/z* = 366 [*M* + 1].

1-{2-Hydroxy-4-[(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-2-phenylethanone (6m). Yield 76%, white solid, mp 136–138°C. IR spectrum, ν, cm^{-1}: 3435 (C–OH), 1667 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.71 s (1H), 8.21 s (1H), 7.78 d (*J* = 9.14 Hz, 2H), 7.46–7.39 m (1H), 7.36–7.30 m (2H), 7.29–7.23 m (3H), 7.13–7.04 m (2H), 6.59–6.52 m (2H), 5.29 s (2H), 4.21 s (2H), 3.87 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 202.1, 165.6, 164.7, 151.0, 142.2, 134.3, 132.2, 130.3, 129.3 (2C), 128.7 (2C), 127.1, 126.0, 125.4, 125.3, 121.2, 113.6, 112.2, 108.0, 102.2, 62.1, 56.0, 44.9. LRMS: (ES$^+$) *m/z* = 416 [*M* + 1].

1-{2-Hydroxy-4-[(1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-2-phenylethanone (6n). Yield 83%, mp 148°C. IR spectrum, ν, cm^{-1}: 3440 (C–OH), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.69 s (1H), 8.06–8.01 m (1H), 7.82–7.77 m (1H), 7.61 d (*J* = 7.91 Hz, 2H), 7.39–7.27 m (7H), 6.56 m (2H), 5.31 s (2H), 4.23 s (2H), 2.43 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 166.3, 165.2, 144.5, 140.1, 135.3, 133.3, 131.4 (2C), 130.9, 130.4 (2C), 129.8 (2C), 128.2, 122.3, 121.7 (2C), 115.0, 109.2, 103.7, 64.0, 47.0, 23.5. LRMS: (ES$^+$) *m/z* = 400 [*M* + 1].

1-{4-[(1-(6-Bromohexyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]-2-hydroxyphenyl}-2-phenylethanone (6o). Yield 67%, white solid, mp 113–115°C. IR spectrum, ν, cm^{-1}: 3448 (C–OH), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.68 s (1H), 7.81–7.77 m (1H), 7.62 s (1H), 7.38–7.33 m (2H), 7.29 t (*J* = 3.33 Hz, 2H), 7.28 s (1H), 6.57–6.52 m (2H), 5.23 d (*J* = 8.36 Hz, 2H), 4.39 t (*J* = 7.15 Hz, 2H), 4.24 s (2H), 3.28 t (*J* = 6.77 Hz, 2H), 1.99–1.93 m (2H), 1.64–1.57 m (2H), 1.42 m (4H). ^{13}C NMR spectrum, δ_C, ppm: 202.3, 166.1, 165.7, 143.5, 135.1, 133.2, 130.5 (2C), 129.9 (2C), 127.9, 124.1, 114.8, 108.9, 103.2, 63.5, 51.9, 46.8, 37.5, 35.2, 31.1, 27.4, 26.3. LRMS: (ES$^+$) *m/z* = 472 [*M* + 1].

1-{2-Hydroxy-4-[(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-2-phenylethanone (6p). Yield 84%, yellow solid, mp 158–160°C. IR spectrum, ν, cm^{-1}: 3449 (C–OH), 1677=O). ^{1}H NMR spectrum, δ, ppm: 12.70 s (1H), 8.46–8.42 m (2H), 8.18 s (1H), 8.00 d (*J* = 8.50 Hz, 2H), 7.39–7.32 m (4H), 7.29–7.27 m (2H), 6.56–6.54 m (2H), 5.34 s (2H), 4.23 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 202.2, 166.6, 165.7, 148.3, 144.1, 142.8, 134.4, 132.5, 130.3 (2C), 128.6 (2C), 126.1, 124.5 (2C), 122.7, 121.1 (2C), 113.5, 107.9, 102.2. LRMS: (ES$^+$) *m/z* = 431 [*M* + 1], 453 [*M* + Na].

Biological evaluation. *Animals.* Albino rats of Wistar strain male sex, weighing 150–250 g were purchased from National Institute of Nutrition, Hyderabad, India, and housed under standard environmental conditions (temperature: 24 ± 1°C, light/dark cycle: 10/14 h). The rats were fed with standard pellet diet (Amrut laboratory animal feed, Maharashtra, India) and water *ad libitum*. Animals were acclimatized to laboratory conditions at least 1 week prior to conducting the experiments according to the guide lines of CPCSEA–New Delhi, (Registration no. 915/ac/05/CPCSEA).

In vivo anti-inflammatory activity. The synthesized compounds assessed for their anti-inflammatory activity using carrageenan-induced rat paw edema method. Male Wistar rats (150–250 g) were fasted with access of water at least 24 h prior to the experiments and divided randomly into groups (control, standard and the test groups) of five rats each. The rat paw edema was induced by subcutaneous injection of 0.1 mL of 1% freshly prepared saline solution of carrageenan into the right hind paw of rats. The standard drug ibuprofen (10 mg/kg body weight) was given orally as a positive control. The control group was administered orally with 0.9% of 0.1 mL of saline solution only. The test groups were administered orally with the synthesized compounds at the equimolar dosage of the standard drug, 1 h before the administration of carrageenan. The paw volumes were measured using plethysmometer at interval of 1 h.

Molecular modelling. Hyperchem 8.0, Swiss Protein Data Base Viewer (SPDBV) 3.7 [19] version, GOLD Version 2.0, ArgusLabs 4.0.1 and Discovery studio visualiser 4.1 docking programs were used to determine the interactions, affinities, binding energies and selectivity of compounds **6a–6p**. Ligands energy minimization was carried out by using Hyper chem. 8.0 version. The protein-ligand interactions between COX-2 (PDB code 4PH9) and target molecules **6a–6p** were prepared for docking studies by adding hydrogen atoms, removing water molecules, co-crystallized inhibitors and refined by using the Deep View/ SPDBV. Basic amines were protonated and acidic carboxyl groups were de-protonated prior to charge calculation. Then successful docking has been performed using GOLD 2.0. GOLD was used to evaluate gold fitness function and Chem score. ArgusLab 4.0.1 docking software used here to visualize the binding conformations and to calculate the binding energies of the analogues **6a–6p**. Discovery studio visualizer has been utilized to visualize the best binding poses of the final target analogues **6a–6p** within the active site of 4PH9 protein.

CONCLUSIONS

A group of novel 1-{4-[(1*H*-1,2,3-triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone derivatives **6a–6p** were synthesized using click chemistry and characterized by spectroscopic methods. All synthesized compounds demonstrated anti-inflammatory activity. The products **6a, 6f, 6g, 6i, 6j, 6n,** and **6p** exhibited excellent activity. Various substituents at the first position of triazole ring demonstrated considerable influence on anti-inflammatory activity. Most of biological experimental data were correlated with docking results and revealed that the molecules that exhibited high Gold fitness scores demonstrated good Chem scores. Molecular binding interactions of an *in silico* data demonstrated that **6j** had high specificity towards the COX-2 binding site and could be a potent anti-inflammatory compound.

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