Polycyclic Aromatic Compounds

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New 1,2,3-Triazole-Tethered Chalcone Derivatives: Synthesis, Bioevaluation and Computational Study

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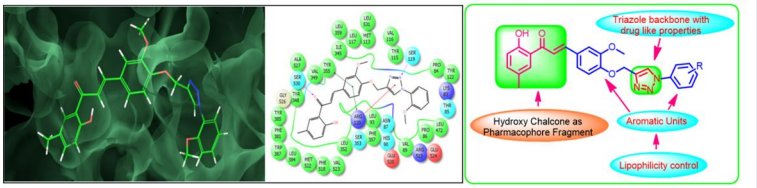
ABSTRACT

In search of new active molecules, a small focused library of novel 1,2,3-triazoles based chalcone derivatives has been efficiently prepared *via* the click chemistry approach. All the synthesized compounds were characterized with the help of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. The synthesized novel 1,2,3-triazoles based chalcone derivatives evaluated for their anti-inflammatory and antioxidant activity. Furthermore, molecular modeling study could support these outcomes by demonstrating very good binding affinities at the active site of the cyclooxygenase 2 (COX-2) iterating the potential of this scaffold for further optimization.

GRAPHICAL ABSTRACT



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Click chemistry; 1,2,3-triazoles; chalcone; anti-inflammatory; antioxidant

Introduction

Interest in chalcone scaffolds remains persistent due to their usefulness as diverse biological activities.[1–3] Some pharmacological activities attributed to chalcones and their synthetic analogues have been reported, such as antibacterial,[3] antifungal,[4] antioxidant,[5,6] antimalarial,[7–9] anticancer,[10–12] anti-HIV,[13] anti-inflammatory,[14,15] antimicrobial[16] and antileishmanial.[17,18]

1,2,3-Triazoles are a class of five membered nitrogen rich heterocycles received great attention due to their ease of synthesis by click reaction using copper as a catalyst as well as variety of pharmacological scope and biological properties.[19] In recent years, 1,2,3-triazole scaffold have

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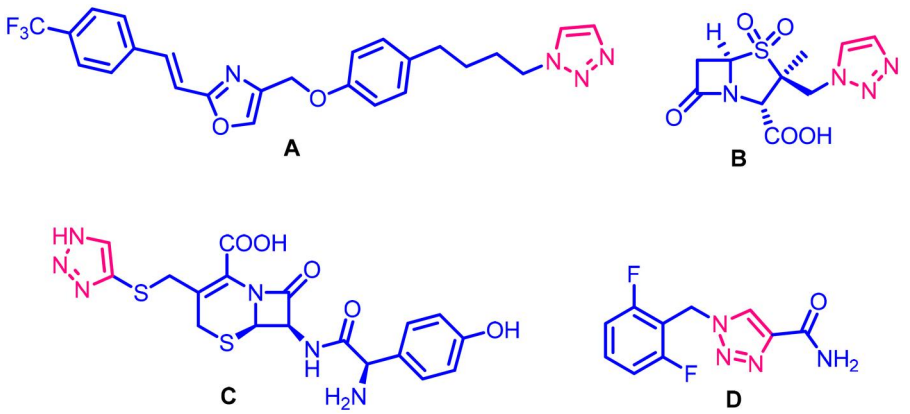


Figure 1. 1,2,3-Triazole containing drugs available in market.

received special attention in drug discovery because several drug molecules having 1,2,3-triazole group such as mubritinib (**A**), tazobactum (**B**), cefatrizine (**C**) and rufinamide (**D**) (Figure 1), which are used for the treatment of cancer and bacterial disease.

1,4-Disubstituted 1,2,3-triazoles have attracted great deal of attraction from the scientific community all over the world, because they endowed with various biological activities like antitubercular,[20] antiproliferative,[21,22] antimicrobial[23–25] and anticonvulsant.[26] In addition, triazole have been shows a significant anticancer activities.[27] In view of their widespread occurrence and enable to mimic different functional groups they have been used as a bioisostere for the synthesis of new active molecules.[28]

In last few years, molecular hybridization concept in drug design and development is used that fuze pharmacophoric moieties of different bioactivity to produce a new hybrid compound with improved biological activity, when compared to the parent drugs.[29] Nowadays the linker property of 1,2,3-triazole-hybrids having broad profile of activities. The linking of 1,2,3-triazole units with other pharmacophoric units leads to the hybrids with better biological activities than their parent. There are few reports in literature on 1,2,3-triazole bearing chalcone showed synergistic or additive pharmacological activities (Figure 2). For example, 1,2,3-triazole chalcone hybride exhibited antiproliferative **E** & **F**,[30] antioxidant **G**,[31] anticancer **H**,[32] antiplasmodial **I**,[33] antimicroabial, anticancer and antiplasmodial **J** & **K**,[34] antimicroabial **L**,[35] and antimalarial **M** & **N**36 activities.

Therefore, considering the significant feature of chalcone and triazoles, we have designed and synthesized series of novel 1,2,3-triazole tethered chalcone derivatives to enhance the anti-inflammatory and antioxidant properties (Figure 3).

Results and discussion

Chemistry

The synthesis of novel series of 1,2,3-triazole tethered chalcone (*E*)-3-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (**7a-l**) were summarized in the Scheme 1.[34] Initially, the propargylation of vanillin (**1**) was carried out by using propargyl bromide (**2**) at room temperature gives corresponding 3-methoxy-4-(prop-2-ynyloxy) benzaldehyde (**3**). In the next step, compound **3** was treated with 1-(2-hydroxy-5-methylphenyl)ethanone (**4**) in the presence of 10% potassium hydroxide solution in ethanol at room temperature gives (*E*)-1-(2-hydroxy-5-methylphenyl)-3-(3-methoxy-4-(prop-2-ynyloxy)phenyl)-prop-2-en-1-one (**5**). Finally, compound (**5**) reacted with aryl azides (**6a-l**) using $Cu(OAc)_2$ in *t*-BuOH:DMF:H_2O as a solvent to afford novel (*E*)-3-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-

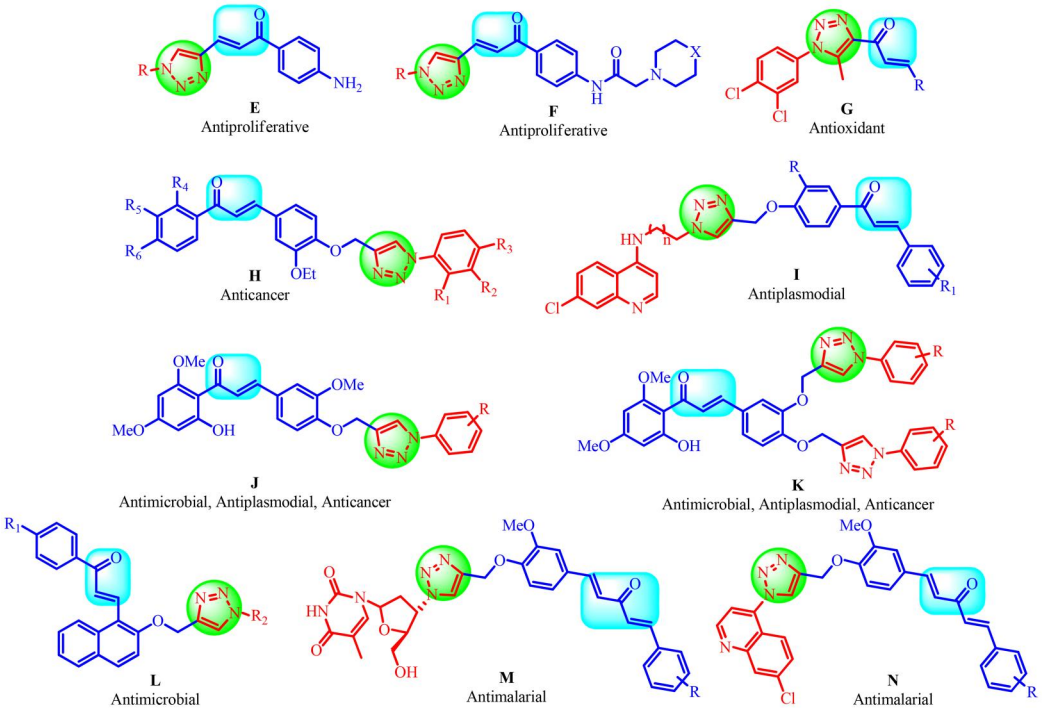


Figure 2. Reported 1,2,3-triazole bearing chalcone exhibited pharmacological activities.

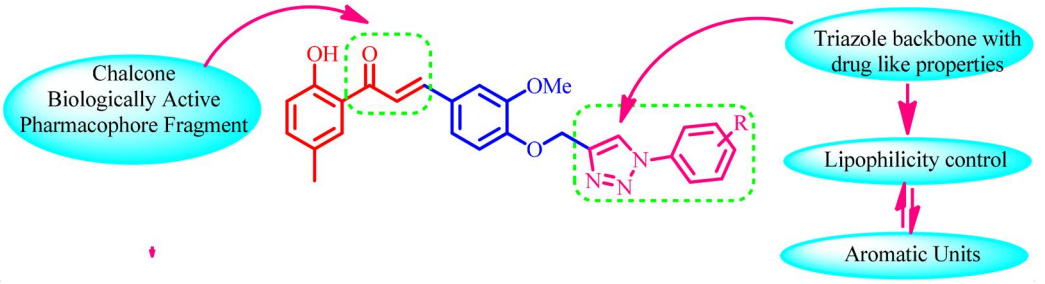
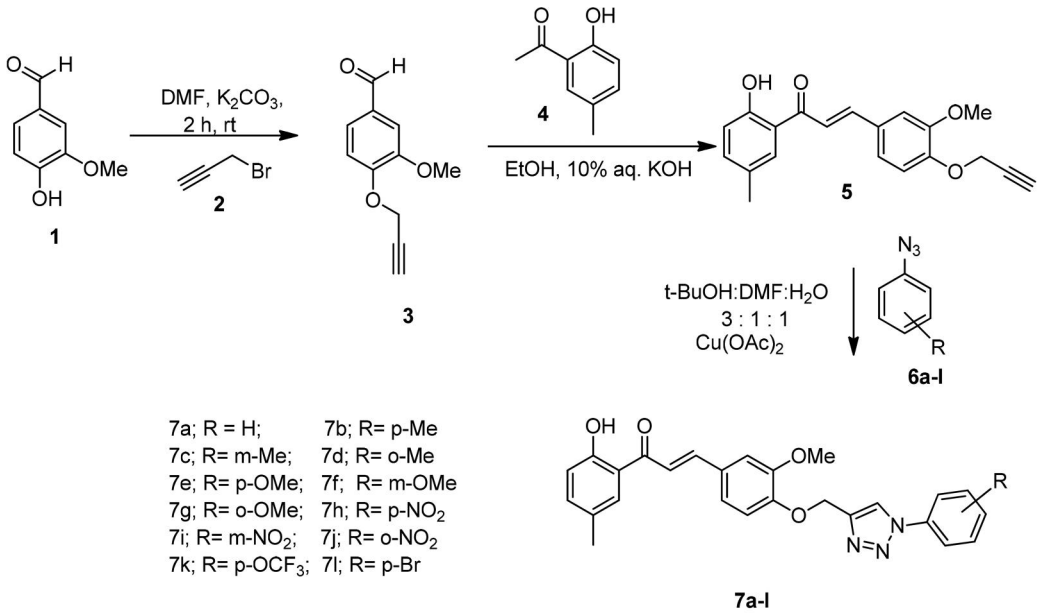


Figure 3. Designed series of novel 1,2,3-triazole tethered chalcone derivatives.

3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl) prop-2-en-1-one (**7a-l**) in good to excellent yield.

The structures of all the synthesized derivatives shown in Figure 4. The formation of compound (**5**) and (**7a-l**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. In the ^{1}H NMR spectrum of compound **7a**, the singlet for methyl and methylene group attached to the oxygen observed at δ 3.88 and 5.33 ppm, respectively. The singlet observed at δ 2.34 ppm confirms the presence of methyl group on benzene ring. The singlet peak observed at δ 8.96 ppm is for the triazolyl proton indicates the formation of traizole ring. In addition to this, the signal observed at δ 12.59 ppm indicates the presence of O-H proton of the phenolic group.

In the ^{13}C NMR spectrum of compound **7a**, the signals at δ 55.4 and 61.5 ppm indicates the presence of methyl and methylene carbons attached to the oxygen of the phenyl ring, respectively. The signal observed at δ 19.8 ppm indicates the methyl carbon attached to the benzene ring. Furthermore, the signal observed at δ 191.72 ppm indicates the presence of carbonyl carbon



Scheme 1. Synthesis of 1,2,3-triazole tethered chalcone derivatives **7a-l**.

present in chalcone functionality. For compound **7a**, the calculated mass for $[M]^+$ is 441.17, and in mass spectra the $[M+H]^+$ peak observed at 442.2.

Biological evaluation

Anti-inflammatory activity

All the newly synthesized 1,2,3-triazole-tethered chalcone derivatives were tested for *in vitro* anti-inflammatory activity in comparison with aspirin *via* HRBC membrane stabilization method. Anti-inflammatory agents control the biochemical processes involved during the inflammatory response by stabilizing the membranes of lysosomes.[37] The erythrocyte membrane is analogous to the lysosomal membrane, and its stabilization implies some samples may as well stabilize lysosomal membranes.[37] Stabilization of lysosomal membrane is important in limiting the inflammatory response by preventing the release of lysosomal constituents of activated neutrophils such as bactericidal enzymes and proteases, which cause further inflammation and damage on extracellular release.[37]

Among the synthesized compounds compound **7a** without any substituent on phenyl ring of the chalcone-triazole hybrid showed lesser % inhibition activity i.e. 16.96% (Table 1). Then, we introduced electron donating methyl group in phenyl ring, then it showed % inhibition activity sequence as *p*-Me (19.14%) > *o*-Me (18.20%) > *m*-Me (15.97%). Similarly, when methoxy group introduced on phenyl ring then % inhibition sequence was observed as *o*-OMe (28.95%) > *p*-OMe (28.78%) > *m*-OMe (27.75%). After electron donating group, we introduced electron withdrawing nitro group in phenyl ring, and the order of % inhibition was *m*-NO_2 (25.88%) > *o*-NO_2 (23.95%) > *p*-NO_2 (20.42%) (Figure 5).

% Inhibition of hemolysis activity

Most of the synthesized compounds exhibited equivalent % inhibition of hemolysis activity compared to standard drug Aspirin (Table 1). The % inhibition of hemolysis of the synthesized derivatives graphically shown in the Figure 6.

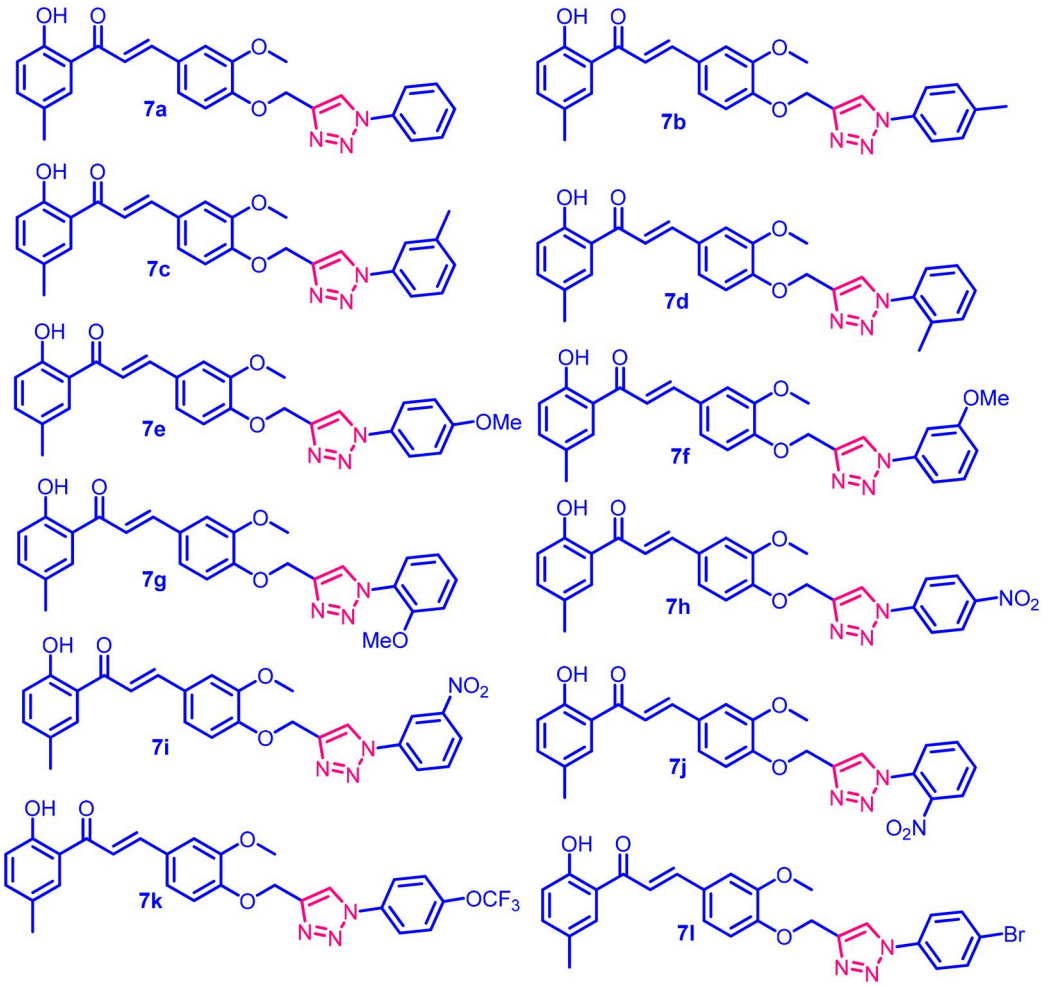


Figure 4. Structure of 1,2,3-triazole tethered chalcone derivatives **7a-l**.

DPPH anti-oxidant activity

Antioxidant activities of all the synthesized compounds were studied by using 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) method[38] with slight modifications. Ascorbic acid has been used as a standard drug. Among all the synthesized compounds, compound **7k** showed good antioxidant activity compared to the standard drug ascorbic acid.

Computational study

Molecular docking

Considering the promising levels of anti-inflammatory activity shown by the 1,2,3-triazoles based chalcone derivatives (**5**, **7a-l**), molecular docking study was performed to shed light onto the mechanistic and molecular basis of binding to Cyclooxygenase-2 (COX-2). In the absence of resource to perform enzyme-based assay, such *in silico* techniques provide a meaningful alternative to gauze the binding affinity of a bioactive molecule toward the target protein. It can also provide valuable insights into the type of thermodynamic interactions between the compounds

Table 1. % Inhibition of anti-inflammatory and hemolysis activity, IC_{50} values for antioxidant activity and molecular docking study data.

	Anti-inflammatory	Hemolysis	Antioxidant	Molecular Docking			
Cpd	(500 μg/mL)	(100 μg/mL)	(IC_{50} μg/mL)	Glide score	Glide energy (kcal/mol)	H-bonding (Å)	π-π /Cation-π stacking (Å)
3	28.27	26.88	886.19	−8.693	−46.563	Ser530 (1.806), Tyr355 (1.842)	Tyr387(2.171,1.623), Arg120(2.204)
7a	16.96	38.92	108.42	−7.822	−38.794	Ser530 (2.218), Ser519(2.517)	Tyr355(1.590), Arg120(1.739,4.574)
7b	19.14	35.17	315.48	−7.982	−40.189	Ser530(2.218)	Tyr355(1.874), Arg120(1.674, 3.362)/ Arg120(3.592)
7c	15.97	37.87	156.19	−7.525	−37.114	–	Tyr355(1.703, 1.637), Arg120(1.590, 5.308)/ Arg120(3.977)
7d	18.20	35.78	138.78	−7.845	−39.567	Ser530(2.087)	Arg120(1.790)/Arg120(4.348)
7e	28.78	26.36	117.46	−8.787	−48.644	Ser530(1.808)	Arg120(2.13, 3.756)/ Arg120(2.087)
7f	27.75	27.32	190.56	−8.589	−45.443	Ser530(1.776)	His90(4.801)
7g	28.95	26.18	234.34	−8.989	−49.291	Ser530 (2.196), Ser519(2.530)	Tyr355(1.573), Arg120(1.736)/Arg120(4.583)
7h	20.42	34.38	152.47	−8.095	−40.325	Ser530(1.862)	Arg120 (1.536, 4.801)/ Arg120 (4.053,4.984)
7i	25.88	29.32	720.00	−8.447	−44.248	Ser530(2.053, 2.081), Ser519(2.470)	Arg120(1.584)/Arg120(4.519)
7j	23.95	31.07	333.67	−8.136	−41.596	Ser530(1.923)	Arg120(1.442), Arg120(3.746, 4.145)
7k	25.79	29.41	79.03	−8.226	−42.713	Ser530(1.833)	Tyr355(1.855), Arg120(5.304)/Arg120(4.028)
7l	–	–	–	–	–	–	–
AP	86.11	37.18	–	–	–	–	–
AA	–	–	< 50	–	–	–	–

Cpd: Compound; AP: Aspirin; AA: Ascorbic Acid

and the active site amino acids to rationalize the obtained biological results and guide point mutations around scaffold to improve the binding affinity. COX-2 is known for a crucial role in converting arachidonic acid to prostaglandins (PG), which mediate the inflammation and pain.[39] Inhibition of COX-2 is paramount for the anti-inflammatory and analgesic function, making this target significant for the identification and optimization of novel anti-inflammatory and analgesic agents. Molecular docking study has been carried out using the standard protocol implemented in the GLIDE (Grid-based Ligand Docking with Energetics) module of the Schrödinger molecular modeling package (Please refer the supplementary material for detailed methodology).[40]

A perusal of the docked complexes of 1,2,3-triazoles based chalcone derivatives (**5**, **7a-l**) revealed that they could bind to the active site of COX-2 with good to excellent binding affinities engaging in multiple bonded and non-bonded interactions. Also a very good correlation was observed between their *in vitro* anti-inflammatory activity and the docking scores (Table 1). Further to identify the most significantly interacting residues and the nature of thermodynamic interactions governing the affinities of these molecules to COX-2, a detailed per-residue interaction analysis was carried which is elaborated for one of the most active analogue **7 g**.

A perusal of the lowest energy docked complex of **7g** (Figure 7) revealed that the molecule could bind to the active site of enzyme with high binding affinity (Glide docking score of −8.989; intermolecular binding energy of −49.291 kcal/mol) at co-ordinates close to the co-crystallized ligand. The molecule could snugly fit into the active site through a series of significant van der Waals interactions observed with Ser530(-1.558 kcal/mol), Ala527(-3.658 kcal/mol), Gly526(-2.225 kcal/mol), Val523(-3.387 kcal/mol), Met522(-1.727 kcal/mol), Phe518(-1.637 kcal/mol), Trp387(-1.3 kcal/mol), Tyr385(-1.712 kcal/mol), Phe381(-1.423 kcal/mol), Leu352(-2.432 kcal/mol) and Tyr348(-1.183 kcal/mol) residues *via* the 3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)-prop-2-en-1-one portion while the (4-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy) side chain attached to prop-2-en-1-one exhibited similar favorable interactions with Leu531(-2.074 kcal/mol), Glu524(-2.51 kcal/mol), Leu359(-1.86 kcal/mol), Ser353(-1.073 kcal/mol), Ile345(-1.034 kcal/mol), Leu123(-1.082 kcal/mol), Tyr122(-1.074 kcal/mol), Arg120(-1.084 kcal/mol), Ser119(-1.599 kcal/mol), Tyr115(-2.982 kcal/mol), Leu93(-1.154 kcal/mol), Val89(-2.938 kcal/mol) and Pro86(-1.621 kcal/mol) residues. While these van der Waals interactions were seen to the major driving force for mechanical interlocking of this molecule, its enhanced binding affinity is also attributed to significant electrostatic interactions with Ser530(-1.651 kcal/mol), Glu524(-1.728 kcal/mol), Glu520(-1.522 kcal/mol), Tyr385(-1.162 kcal/mol), Lys360(-1.068 kcal/mol), Tyr355(-1.961 kcal/mol), Arg120(-3.139 kcal/mol), Val116(-1.157 kcal/mol) and Tyr115(-1.404 kcal/mol) residues lining the active site. Furthermore, **7 g** was seen to be anchored at the active site through two very close hydrogen bonding interactions with Ser530(2.196 Å) and Ser519(2.530 Å) *via* the ketonic function (C=O) and triazole *N* respectively. Also, the compound was involved in a prominent π-π stacking interactions with Tyr355(1.573 Å), Arg120(1.736 Å) and cation-π interactions with Arg120(4.583). Such non-bonded interactions not serve as *anchor* but also guide the orientation of the ligand into the 3D space of active and further facilitate non-bonded interactions (van der Waals and electrostatic). Other molecules in the series (**5**, **7a-l**) also exhibited a very similar binding mode and associated thermodynamic interactions with active site residues speculating an identical mechanism of action (*Supporting Information*, Figure 1S-12S). Overall, the molecular docking study suggest that 1,2,3-triazole based chalcone possess good affinity toward COX-2 indicating that structural modifications around this scaffold can lead to compounds with improved binding affinity toward COX-2 and anti-inflammatory potency.

In silico ADME prediction

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. A computational study of all the

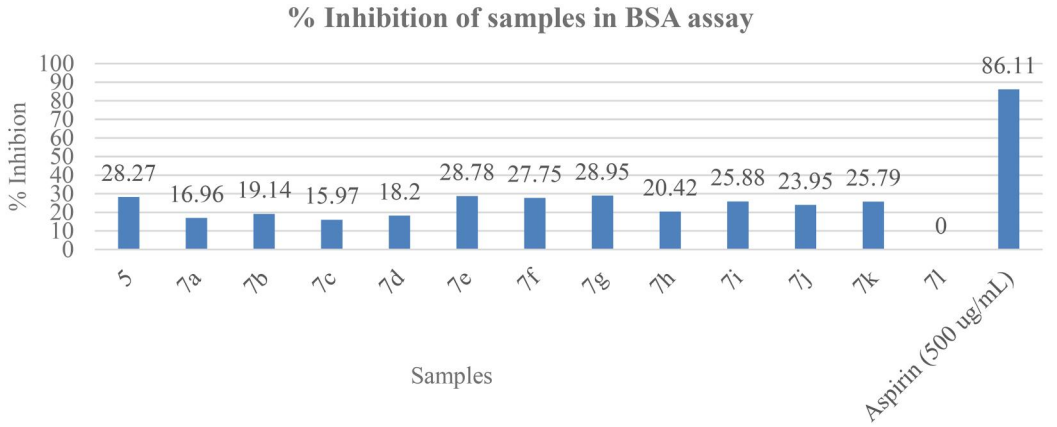


Figure 5. Graph for the percent inhibition of compounds *in vitro* anti-inflammatory activity.

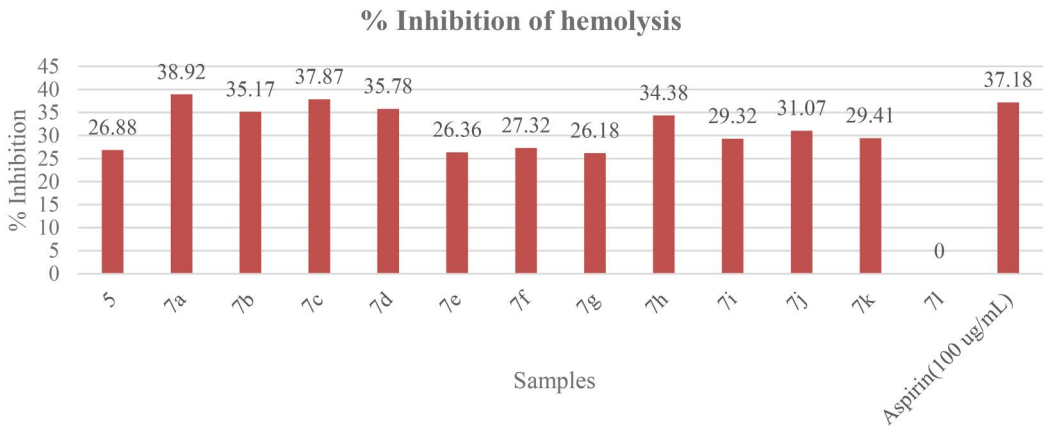


Figure 6. Graph for the % inhibition of hemolysis.

synthesized compounds was performed for the prediction of ADME properties and the value obtained is presented in Table 2. It is observed that compounds exhibited a good % ABS (% absorption) ranging from 63.35 to 79.16%.

Furthermore, except compound **7k** and **7l**, none of the synthesized derivatives violates Lipinski's rule of five (miLog $p \leq 5$). A molecule likely to be developed as an orally active drug candidate should not show more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) $\leq$ 5, molecular weight $\leq$ 500, number of hydrogen bond acceptors $\leq$ 10 and number of hydrogen bond donors $\leq$ 5.[41] The larger the value of the drug-likeness model score, the higher is also the probability that the particular molecule will be active. Except compound **7k** & **7l**, remaining all the tested compounds followed the criteria for orally active drugs and therefore, these compounds may have a good potential for eventual development as oral agents.

Experimental

All solvents and reagents were purchased commercially and used as supplied. The purity of compounds were checked by TLC and visualized under UV light. Melting points of compounds were determined in open capillaries and are uncorrected. IR spectra were recorded on FT-IR spectrophotometer. NMR spectra were recorded by using Bruker Advance neo 500 spectrophotometer

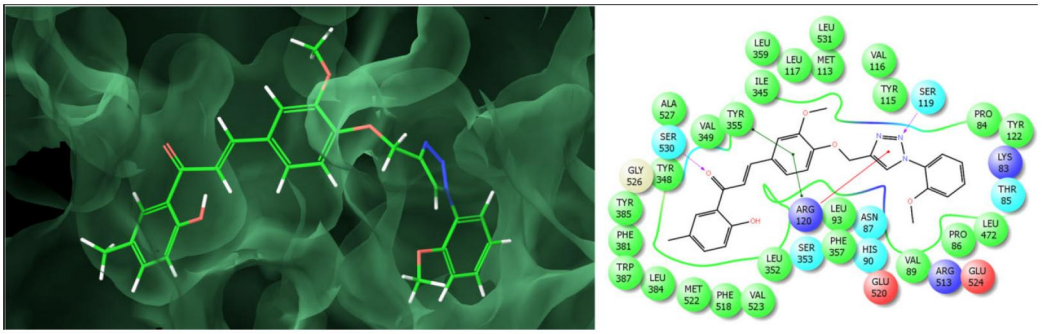


Figure 7. Binding mode of **7 g** at the active site of COX-2 (on right side: the pink, green and red lines represent the hydrogen bonding, π-π stacking and cation-pi interactions respectively).

(500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), DMSO-d*6* as solvent and TMS as an internal standard. Chemical shift values are expressed as ppm units and coupling constant values are in hertz. Mass spectra were obtained on Waters, Q-TOF micromass (ESI-MS) mass spectrometer.

General procedure for the synthesis of (E)-1-(2-hydroxy-5-methylphenyl)-3-(3-methoxy-4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one (5)

In a round bottom flask (RBF), mixture of 3-methoxy 4-(prop-2ynloxy)benzaldehyde (**3**) (10 mmol) and 1-(2-hydroxy-5-methyl phenyl) ethanone (**4**) (10 mmol) were stirred with 10% ethanolic KOH for 48 h at room temperature. Progress of the reaction was monitored by thin layer chromatography (TLC) on silica coated aluminum plate by using ethyl acetate: hexane as a solvent system. TLC plate was visualized by ultraviolet light. After completion of the reaction, mixture were poured on to ice-cold water with stirring. Then these reaction mixtures were acidified with con. hydrochloric acid (HCl). Solid product obtained was filtered off, washed with water and crystallized in hot ethanol to obtain pure product.

General procedure for the synthesis of (E)-3-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7a-l)[34]

In RBF, (*E*)-1-(2-hydroxy-5-methylphenyl)-3-(3-methoxy-4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one (**5**) (0.5 mmol) was dissolved in *t*-BuOH:DMF:H_2O (3:1:2, 12 ml) mixture of solvent with constant stirring. In this reaction mixture, Copper diacetate (20 mol %) was added and stirred further 10-15 min. After that (0.5 mmol) of an aryl azide (**6a-l**) was added and stirred for next 24-30 h. Progress of the reaction was monitored by using TLC. After the completion of the reaction, ice cold water was added to the reaction mixture and allowed to stir for further 25-30 min. Obtained solid was filtered off, dried in air and crystallized with ethanol (95%) to obtain pure product (**7a-l**).

(E)-1-(2-Hydroxy-5-methylphenyl)-3-(3-methoxy-4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one (5)

Yield: 64%; Yellow solid; mp: 180-182 °C; IR cm^{-1}: 1633, 1504, 1252; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 12.55 (s, 1H), 8.06 (s, 1H), 7.93 (d, $J = 15.4$ Hz, 1H), 7.82 (d, $J = 15.4$ Hz, 1H), 7.57 (s, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 7.38 (d, $J = 8.3$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H), 6.90 (d,

Table 2. Pharmacokinetic parameters were important for good oral bioavailability and its drug-likeness model score.

Cpd Rule	% ABS –	TPSA (A^2) –	n-ROTB –	MV –	MW < 500	miLog *P* ≤ 5	n-ON < 10	n-OHNH < 5	Lipinski violation ≤ 1	Drug likeness model score
7a	79.16	86.48	8	397.63	441.49	4.85	7	1	0	0.32
7b	79.16	86.48	8	414.20	455.51	5.29	7	1	1	0.14
7c	79.16	86.48	8	414.20	455.51	5.48	7	1	1	0.19
7d	79.16	86.48	8	414.20	455.51	5.46	7	1	1	0.15
7e	75.98	95.72	9	423.18	471.51	4.90	8	1	0	0.18
7f	75.98	95.72	9	423.18	471.51	5.09	8	1	1	0.20
7g	75.98	95.72	9	423.18	471.51	4.90	8	1	0	0.08
7h	63.35	132.31	9	420.97	486.48	4.80	10	1	0	0.20
7i	63.35	132.31	9	420.97	486.48	4.99	10	1	0	0.22
7j	63.35	132.31	9	420.97	486.48	4.97	10	1	0	0.10
7k	75.98	95.72	10	437.92	525.48	5.82	8	1	2	0.06
7l	79.16	86.48	8	415.52	520.38	5.66	7	1	2	0.15

Cpd: Compound, % ABS: Percentage Absorption, TPSA: Topological Polar Surface Area, n-ROTB: Number of Rotatable Bonds, MV: Molecular Volume, MW: Molecular Weight, milogP: Logarithm of Partition Coefficient of Compound Between n-Octanol and Water, n-ON Acceptors: Number of Hydrogen Bond Acceptors, n-OHNH Donors: Number of Hydrogen Bonds Donors.

$J = 8.4$ Hz, 1H), 4.89 (d, $J = 1.8$ Hz, 2H), 3.89 (s, 3H), 3.61 (s, 1H), 2.34 (s, 3H); 13 C NMR ^{13}C NMR (125 MHz, DMSO-d6) δ ppm 193.43, 159.95, 149.21, 149.10, 145.08, 137.00, 130.12, 128.09, 127.71, 123.49, 120.03, 119.36, 117.42, 113.39, 111.77, 78.79, 78.50, 55.90, 55.78, 19.91; MS (ESI-MS): m/z 319.13 $(M + H)^+$.

(E)-3-(4-((1-Phenyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7a)

Yield: 90%; mp: 188-200 °C; IR cm^{-1}: 1639, 1504, 1253, 3151; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.59 (s, 1H), 8.96 (s, 1H), 8.08 (s, 1H), 6.8-8.0 (m, 12H), 5.33 (s, 2H), 3.88 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 191.72, 159.10, 148.97, 150.08, 147.40, 136.94, 136.43, 132.00, 130.22, 129.77, 128.61, 125.69, 123.09, 122.90, 120.12, 120.04, 120.01, 118.96, 117.74, 113.42, 110.73, 61.54, 55.44, 19.83; MS (ESI-MS): m/z 442.2 $(M + H)^+$.

(E)-3-(4-((1-p-Tolyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7b)

Yield: 91%; mp: 196-198 °C; IR cm^{-1}: 1633, 1514, 1250, 3143; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.58 (s, 1H), 8.92 (s, 1H), 8.07 (s, 1H), 7.93 (d, $J = 15.2$ Hz, 1H), 7.88-7.74 (m, 3H), 7.57 (s, 1H), 7.50 (d, $J = 6.8$ Hz, 1H), 7.46-7.35 (m, 3H), 7.32 (d, $J = 7.4$ Hz, 1H), 6.90 (d, $J = 7.9$ Hz, 1H), 5.31 (s, 2H), 3.87 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.44, 159.96, 150.10, 149.11, 145.21, 143.19, 138.31, 137.00, 134.18, 130.12, 127.76, 127.71, 123.85, 122.97, 120.03, 119.93, 119.92, 119.15, 117.42, 113.12, 111.68, 61.44, 55.71, 20.45, 19.91; MS (ESI-MS): m/z 456.2 $(M + H)^+$.

(E)-3-(4-((1-m-Tolyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7c)

Yield: 93%; mp: 194-196 °C; IR cm^{-1}: 1635,1506,1250, 3151; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.60 (s, 1H), 8.94 (s, 1H), 8.07 (s, 1H), 7.93 (d, $J = 12.1$ Hz, 1H), 7.84 (d, $J = 13.7$ Hz, 1H), 7.79-7.26 (m, 8H), 6.90 (d, $J = 4.7$ Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.44, 160.02, 150.10, 149.14, 145.20, 143.25, 139.54, 136.99, 136.38, 130.12, 129.54, 129.23, 127.79, 127.69, 123.85, 123.00, 120.45, 120.01, 119.12, 117.43, 117.11, 113.12, 111.67, 61.44, 55.69, 20.76, 19.90; MS (ESI-MS): m/z 456.2 $(M + H)^+$.

(E)-3-(4-((1-o-Tolyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7d)

Yield: 90%; mp: 192-194 °C; IR cm^{-1}: 1635, 1504, 1248, 3138; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.58 (s, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 7.92 (s, 1H), 7.85 (s, 1H), 7.58 (s, 1H), 7.32-4.49 (m, 7H), 6.90 (s, 1H), 5.32 (s, 2H), 3.87 (s, 3H), 2.31 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.45, 159.97, 150.14, 149.18, 145.22, 142.28, 137.00, 136.05, 132.90, 131.25, 130.13, 129.74, 127.80, 127.71, 126.89, 126.43, 125.89, 123.85, 120.04, 119.16, 117.43, 113.29, 111.71, 61.46, 55.71, 19.91, 17.28; MS (ESI-MS): m/z 456.2 $(M+H)^{+}$.

(E)-3-(4-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7e)

Yield: 92%; mp: 238-240 °C; IR cm^{-1}: 1635, 1516, 1252; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.57 (s, 1H), 8.84 (s, 1H), 8.13-6.76 (m, 12H), 5.22 (s, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 191.73, 159.22, 148.95, 147.42, 145.22, 143.43, 136.95, 131.96, 130.23, 129.85, 127.74, 125.68, 123.85, 122.86, 121.70, 120.12, 118.96, 117.74, 114.76, 113.38, 110.74, 61.56, 55.70, 55.43, 19.83; MS (ESI-MS): m/z 472.2 $(M+H)^{+}$.

(E)-3-(4-((1-(3-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7f)

Yield: 88%; mp: 230-230 °C; IR cm^{-1}: 1637, 1506, 1250, 3145; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.63 (s, 1H), 8.99 (s, 1H), 8.06 (s, 1H), 7.93 (d, $J=14.5$ Hz, 1H), 7.84 (d, $J=14.6$ Hz, 1H), 7.61-7.27 (m, 8H), 7.05 (s, 1H), 6.89 (d, $J=6.9$ Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.40, 160.04, 150.06, 149.11, 145.16, 137.43, 136.95, 130.63, 130.09, 127.79, 127.64, 123.80, 123.16, 119.94, 119.05, 117.39, 114.28, 113.07, 111.93, 111.61, 105.64, 61.43, 55.64, 55.40, 19.87; MS (ESI-MS): m/z 472.2 $(M+H)^{+}$.

(E)-3-(4-((1-(2-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7 g)

Yield: 90%; mp: 224-226 °C; IR cm^{-1}: 1637, 1506, 1248, 3132; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.60 (s, 1H), 8.61 (s, 1H), 8.07 (s, 1H), 7.92 (s, 1H), 7.84 (d, $J=12.9$ Hz, 1H), 7.64 (s, 1H), 7.60-6.84 (m, 8H), 5.31 (s, 2H), 3.86 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.45, 160.02, 151.50, 150.20, 149.11, 145.25, 141.98, 136.99, 130.67, 130.13, 127.71, 126.83, 125.64, 125.48, 123.89, 120.76, 120.02, 119.08, 117.43, 113.07, 112.87, 111.61, 61.35, 55.97, 55.68, 19.91; MS (ESI-MS): m/z 323.1 $(M+H)^{+}$.

(E)-3-(4-((1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7h)

Yield: 86%; mp: 248-250 °C; IR cm^{-1}: 1637, 1506, 1519, 1338, 1252; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.56 (s, 1H), 9.20 (s, 1H), 8.47 (d, $J=8.0$ Hz, 2H), 8.26 (d, $J=8.3$ Hz, 2H), 8.07 (s, 1H), 7.93 (d, $J=15.4$ Hz, 1H), 7.83 (d, $J=15.3$ Hz, 1H), 7.59 (s, 1H), 7.50 (d, $J=7.4$ Hz, 1H), δ 7.39 (d, $J=7.8$ Hz, 1H), 7.22 (d, $J=9.4$ Hz, 1H).6.90 (d, $J=8.3$ Hz, 1H), 5.36 (s, 2H), 3.88 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 191.72, 159.93, 148.99, 147.31, 146.66, 145.16, 144.35, 140.66, 136.96, 132.13, 130.23, 127.71, 125.68, 125.45, 123.36, 120.63, 120.59, 120.12, 117.75, 113.53, 110.77, 61.47, 55.74, 19.91; MS (ESI-MS): m/z 487.2 $(M+H)^{+}$.

(E)-3-(4-((1-(3-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7i)

Yield: 86%; mp: 224-226 °C; IR cm^{-1}: 1639, 1568, 1506, 1531, 1346, 1255, 1313, 3153; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.56 (s, 1H), 9.22 (s, 1H), 8.76 (s, 1H), 8.43 (d, $J = 7.5$ Hz, 1H), 8.34 (d, $J = 7.7$ Hz, 1H), 8.06 (s, 1H), 7.98-7.88 (m, 2H), 7.83 (d, $J = 15.4$ Hz, 1H), 7.58 (s, 1H), 7.49 (s, 1H), 7.38 (d, $J = 8.2$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 1H), 5.35 (s, 2H), 3.88 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.42, 159.95, 150.01, 149.13, 148.40, 145.16, 143.76, 137.00, 131.43, 130.12, 127.85, 127.71, 126.08, 123.83, 123.58, 123.10, 120.02, 119.20, 117.42, 114.79, 113.21, 111.70, 61.37, 55.74, 19.91; MS (ESI-MS): m/z 487.2 $(M + H)^{+}$.

(E)-3-(4-((1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7j)

Yield: 84%; mp: 210-212 °C; IR cm^{-1}: 1635, 1506, 1531, 1344, 1250; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.58 (s, 1H), 8.87 (s, 1H), 8.24 (d, $J = 6.0$ Hz, 1H), 8.08 (s, 1H), 7.97-7.86 (m, 5H), 7.59 (s, 1H), 7.51 (s, 1H), 7.39 (d, $J = 6.9$ Hz, 1H), 7.33 (s, 1H), 6.91 (d, $J = 6.9$ Hz, 1H), 5.35 (s, 2H), 3.89 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.44, 159.95, 150.07, 149.12, 145.19, 143.91, 142.99, 136.99, 134.29, 131.13, 130.12, 128.90, 127.84, 127.71, 127.52, 126.17, 125.42, 123.81, 120.01, 119.18, 117.41, 113.24, 111.72, 61.30, 55.70, 19.89.

(E)-3-(4-((1-(4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxy phenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7k)

Yield: 84%; mp: 214-216 °C; IR cm^{-1}: 1633, 1506, 1250; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.57 (s, 1H), 9.03 (s, 1H), 8.00-8.15 (m, 3H), 7.93 (d, $J = 13.7$ Hz, 1H), 7.83 (d, $J = 13.6$ Hz, 1H), 7.61 (m, 3H), 7.50(s,1H), 7.39 (s, 1H), 7.32 (s, 1H), 6.91 (s, 1H), 5.33 (s, 2H), 3.88 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.44, 159.97, 150.05, 149.14, 147.83, 145.19, 143.53, 136.99, 135.27, 130.13, 127.83, 123.83, 123.37, 122.47, 122.07, 120.91, 120.03, 119.19, 118.86, 117.42, 113.18, 111.69, 61.38, 55.70, 19.89.; MS (ESI-MS): m/z 526.2 $(M + H)^{+}$.

(E)-3-(4-((1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (7 l)

Yield: 89%; mp: 220-222 °C; IR cm^{-1}: 1633, 1510, 1250; ^{1}H NMR (500 MHz, DMSO) δ ppm 12.58 (s, 1H), 9.03 (s, 1H), 7.73 – 8.00 (m, 11H), 6.89 (s, 1H), 5.31 (s, 2H), 3.86 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ ppm 193.47, 160.06, 150.06, 149.23, 145.32, 145.15, 143.49, 137.50, 136.99, 131.67, 131.40, 130.13, 127.84, 123.83, 123.23, 122.58, 119.95, 119.10, 117.44, 113.13, 111.64, 61.37, 55.71, 19.89; MS (ESI-MS): m/z 520.2 $(M + H)^{+}$.

Experimental procedure for biological activity

Anti-inflammatory activity

The anti-inflammatory activity of all the synthesized compounds were carried out by Heat induced hemolysis and protein denaturation assay methods with slight modifications.37a,b Protein denaturation assay was carried out with slight modification in the procedure37c using bovine serum albumin (BSA) as protein and the standard drug Aspirin. Each 1 mL of Aspirin at concentrations 100, 200, 400, 500, and 600 μg/ml and synthetic compounds (500 and 1000 µg/

mL) were was allowed to homogenized separately with 1 mL of aqueous solution of BSA (5%) and incubated for 15 min at 27 °C. The mixture of distilled water and BSA was used as the control. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 min at 70 °C. The denaturation of all samples was carried out. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 660 nm by measuring extent of turbidity in terms of per cent inhibition in each sample tube. Each test was conducted thrice and mean of the readings were recorded. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = (\text{absorbance of control} - \text{absorbance of sample})/(\text{absorbance of control}) \times 100$$

Heat induced hemolysis

Blood from the healthy human volunteer were collected. Blood samples were mixed with Phosphate buffer solution (PBS) of pH 7.4 and centrifuged at 3000 rpm for 5 min. The packed cells were washed with PBS and a 10% Human RBC suspension was prepared. Samples were prepared In PEG-water solution. Aspirin was used as standard of concentration 25, 50 and 100 µg/mL. Reaction mixtures consisted of 1 mL test sample, 0.5 mL of Human RBC suspension, and 1.5 mL 0.9% saline solution. It was incubated at 37 °C for 30 min and centrifuged at 3000 rpm. The hemoglobin content of the supernatant solution was measured spectrophotometrically at a 560 nm wavelength using shimadzu 1800 UV-Visible spectrophotometer. Aspirin that used as a standard and a control was made by substituting the test samples with saline solution. The percentage of HRBC membrane stabilization was calculated using equation:

$$\%\ \text{Inhibition of hemolysis} = (1 - \text{Abs sample}/\text{Abs control})\ \text{x}\ 100.$$

Antioxidant activity

Free radical scavenging capacity of samples were carried out using 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) method with slight modifications.[38] Briefly, 10 mM solution of DPPH was prepared in Ethanol as the working solution. Different concentrations of standard (100 µL, 10-50ug/mL) and test solutions, absolute ethanol and DPPH working solution (1600 µL) were placed in a cuvette maintaining 3000 µL as total volume. Solutions was kept in absence of light and incubated for 15 min in dark place at room temperature. The absorbance of all samples was measured using an UV-Vis spectrophotometer (Shimadzu 1800) at 517 nm in triplicate. Ascorbic acid was used as positive control. The per cent inhibition was calculated by following equation.

$$(\%\ \text{inhibition of DPPH} = (A_0 - A_s/A_0)\ \text{x}100).$$

This value was taken as percent scavenging, where A_0 is the absorbance of DPPH solution and A_s is the absorbance of DPPH in presence of sample. All the tests were performed in triplicate.

In silico ADME

In this study, we calculated molecular volume (MV), molecular weight (MW), logarithm of the partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five[42] using Molinspiration online property calculation toolkit.[43] Absorption (% ABS) was calculated by: % ABS = 109-(0.345 × TPSA).[44] Drug-likeness model score (a collective property of physico-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software.[45]

Conclusion

In conclusion, in search of new active molecules, a small focused library of 1,2,3-triazoles based chalcone derivatives has been efficiently prepared *via* the click chemistry approach. All the synthesized compounds were characterized with the help of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. Several derivatives were exhibited anti-inflammatory and antioxidant activity compared to the standard drug. Furthermore, molecular modeling study could support these outcomes by demonstrating very good binding affinities at the active site of the cyclooxygenase 2 (COX-2) iterating the potential of this scaffold for further optimization. Moreover, the synthesized compounds were found to possess good antioxidant profile as well.

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Disclosure statement

The authors declare no conflict of interest, financial or otherwise.

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