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Molecular Docking Study, Synthesis and Anti-Inflammatory Activity of Novel Triazines

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ABSTRACT

Triazine derivatives were reported to show a wide range of biological activities. Hence, it was planned to perform docking studies, synthesize and screen these designed compounds for their *in vivo* anti-inflammatory activity. In order to study the interaction of ligands with the binding site of the enzyme, the triazine derivatives were docked on cyclooxygenase-2 (COX-2) enzyme using the drug design software *Maestro 9.5*, Schrodinger, USA. The series of 8 compounds showing good *Glide* score (G-score) was synthesized to form 4-anilinoquinoline triazines. The structures of the compounds were confirmed by IR, ^{1}H NMR and mass spectroscopy and the compounds were screened for anti-inflammatory activity by carrageenan- induced rat hind paw edema method, using Diclofenac as the standard. The G-scores of all the 8 compounds were closer to the scores displayed by the standard drugs, celecoxib and SC-558, there by suggesting that all the compounds interacted very well with the COX-2 enzyme. The *in vivo* anti-inflammatory activity results revealed that all the compounds displayed % inhibition of edema more than 90, which was better than that shown by the standard drug, Diclofenac. Amongst all the compounds, **3b** demonstrated the highest G-score as well as the highest anti-inflammatory activity. Hence, this compound may be explored as a potential lead molecule for further development.

Keywords: COX-2, 4-anilinoquinolines, triazines, docking, *Glide*, carrageenan- induced rathind paw edema.

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INTRODUCTION

Cyclooxygenases (COXs), which catalyze the first step in arachidonic acid metabolism [1], are the molecular targets of the non-steroidal anti-inflammatory drugs (NSAIDs) [2–4].Three isoforms of COX enzymes have been identified, namely, cyclooxygenase-1 (COX-1), a constitutive enzyme, cyclooxygenase-2 (COX-2), an isoform induced in response to a variety of pro-inflammatory stimuli,[5,6] and cyclooxygenase-3 (COX-3), present mainly in the cerebral cortex and human heart [7].While the anti-inflammatory effect of NSAIDs occurs as a result of COX-2 inhibition, inhibition of COX-1 isoform has led to many of the undesirable side effects including gastric irritation[8], renal [9-11]and hepatictoxicity[12]. Therefore, several new COX-2 selective targeted inhibitors, bypassing COX-1 enzymatic activity, were developed during the last two decades. These molecules, termed coxibs i.e., celecoxib [13], rofecoxib [14], valdecoxib [15]and etoricoxib[16] displayed reduced gastrointestinal side effects as compared to the traditional NSAIDs [17]. However, coxibs were recently pulled out from the market because of an increased risk of cardiovascular side effects [18]. Therefore, there is still existence of growing interest and challenge for the design and development of novel, highly safe and effective COX-2 inhibitors which lead to the reduced gastric and renal side effects as compared to the conventional NSAIDs. Since COX-2 enzyme is overexpressed in cancer, COX-2 inhibitors also display anticancer activity[19-23]. Triazine derivatives have been reported to possess a wide gamut of biological activities including anti-inflammatory[24], antifungal[25], anti-HIV[26], anticancer[27,28], antihypertensive[29], antimalarial[30,31], antibacterial[32], etc. Triazines have been extensively investigated for their enhanced COX-2 inhibitory activity [33,34]. Quinoline nucleus has also been proven to be a versatile heterocyclic moiety [35]. Many quinolines have been widely explored to target COX-2 enzyme for displaying their anti-inflammatory potential[36-38].Therefore, it was planned to perform docking studies and synthesize the combination of both triazine and quinoline moieties with a view to expect synergistic anti-inflammatory activity and improved efficacy compared to the traditional marketed NSAIDs. Docking studies on COX-2 enzyme were done prior to synthesis of triazine derivatives with a view to study the *in silico* interaction of the ligands with the enzyme, giving way to synthesis of only those best fit lead compounds which are proposed to exhibit improved anti-inflammatory activity by the mechanism of COX-2 inhibition.

MATERIALS AND METHOD

The molecular docking studies of the triazine derivatives were performed using the drug design software *Maestro 9.5*, Schrodinger, USA. Compounds such as cyanuric chloride, various primary

and secondary amines, 4,7-dichloroquinoline (4,7-DCQ), dimethyl sulfoxide (DMSO), specially dried tetrahydrofuran (THF), ortho-phenylenediamine (OPD) and p-tolylsulfonic acid (p-TSA) were purchased from S. D. Fine Chemicals. Precoated silica gel GF_{254} plates, purchased from Merck, were used for TLC and spots were located by UV chamber. All the melting points were determined on Veego VMD melting point apparatus and are uncorrected. The IR spectra (KBr) of the compounds were determined on Spectrum RX-I FTIR spectrometer. ^{1}H NMR spectra of the compounds in $CDCl_3$ were recorded on Bruker Avance II 400 MHz NMR spectrometer. Mass spectra of all the compounds were recorded on Waters Micromass Q-TOF Micro.

Molecular docking

The crystal structure of the enzyme COX-2 complexed with SC-558 was obtained from Protein Data Bank (PDB code: 1CX2). The crystal structure was cleaned by deleting the water molecules and the cofactors. This was followed by adding hydrogen atoms in their standard geometry, adjusting the bond orders and formal charges. The crystal structure was then refined and the geometries were optimized with the OPLS_2005 force field using the standard protocol and parameters as included in *Glide*. The ligand structures were built, converted to 3D and were geometry minimized using the OPLS_2005 force field and to a gradient Root Mean Square Deviation (RMSD) below 0.01 kJ/Å.A receptor grid was generated at the radius of 20 Å from the centroid of the active site, which comprised of amino acid residues, namely, His90 Arg120, Tyr355, Tyr385, Arg513, Val523 and Ser530[39]. The ligand SC-558 was initially docked into the active site of the enzyme using the standard precision mode. During the docking procedure, the ligand was flexible, whereas the receptor was held rigid. The best docked pose was saved. The RMSD between the crystal structure and the docked pose was 0.1, thereby validating the docking protocol. After validation of the docking protocol, the structures of the ligands and the standards were docked on the active site of the enzyme using the standard precision mode. Table 1 shows the G-scores of the titled compounds, celecoxib and SC-558. Figure 1 shows the image of celecoxib interacting with the enzyme. Figure 2 shows the image of SC-558 interacting with the enzyme. Figure 3 shows the image of compound 3b interacting with the enzyme.

Synthesis of 4-anilinoquinoline triazines

The 4-anilinoquinoline triazines were synthesized in 3 steps:

Step 1: Synthesis of monosubstituted triazines (1)[40]

To an ice cold solution of cyanuric chloride (0.016 mol) and K_2CO_3 (0.032 mol), in dry tetrahydrofuran (THF) was added the solution of a desired amine (0.016 mol) in THF drop wise for 20 min and stirred at room temperature overnight. The reaction mixture was concentrated at room

temperature. Water was added to the resulting residue and the mixture was stirred properly and filtered. For all the synthesized compounds, the completion of the reaction was monitored by thin layer chromatography (TLC) on silica gel G coated plates. The solid products obtained were filtered and purified by recrystallization using ethanol.

Figure 1: Celecoxib docked on COX-2 enzyme

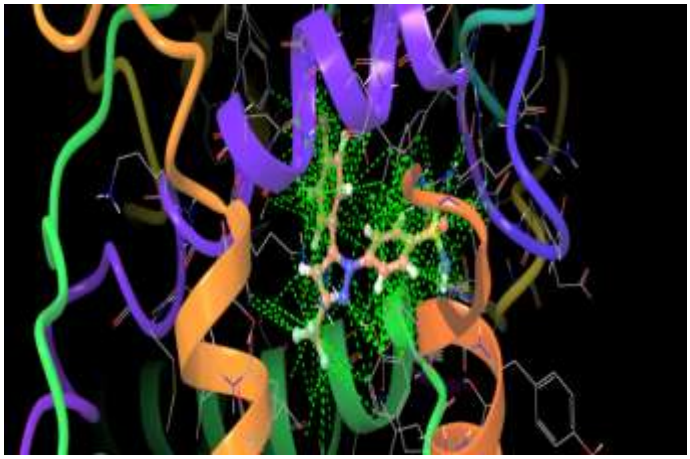

Figure 2: SC-558 docked on COX-2 enzyme

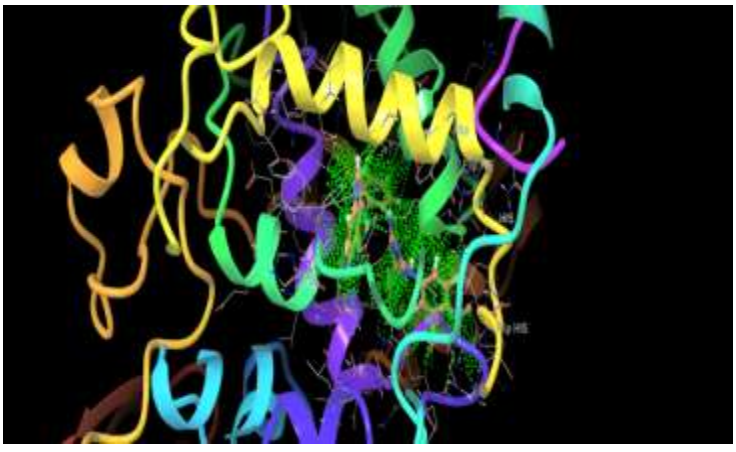

Figure 3: Compound 3b docked on COX-2 enzyme

Table 1: G-scores of the titled compounds

Sr no	Compound	G-score
1	3a	-9.45
2	3b	-9.76
3	3c	-9.12
4	3d	-9.23
5	3e	-9.34
6	3f	-9.25
7	3g	-9.31
8	3h	-9.26
10	Celecoxib	-10.02
11	SC-558	-9.08

Step 2: Synthesis of 4-anilinoquinolines (2) [40]

A solution of 4, 7-dichloroquinoline (0.050 mol) and OPD (0.050 mol) in absolute ethanol was refluxed for 3 h in presence of p-toluenesulfonic acid (TSA) as a catalyst. The precipitate of the product occurred during reflux. The precipitate was collected through filtration, washed with ethanol and dried to get the desired 4-anilinoquinoline with excellent yields.

Step 3: Synthesis of 4-anilinoquinoline triazines (3a-3h)

A reaction mixture of 4-anilinoquinoline (2) (0.002 mol), monosubstituted triazine (1) (0.002 mol) and K_2CO_3 (0.002 mol) in dimethyl sulfoxide (DMSO) was refluxed for 14 h. The reaction residue was dissolved in chloroform and the chloroform layer was washed with water and passed through anhydrous Na_2SO_4. The solution was concentrated to get the desired product. The product was recrystallized using 50% aqueous ethanol. The physical data of the titled compounds is demonstrated in **Table 2**. **Figure 4** shows the scheme for the synthesis of the compounds **3a-3h**. **Figure 5** shows the notation for protons (a-n) in general structure of the titled compounds **3a-3h**.

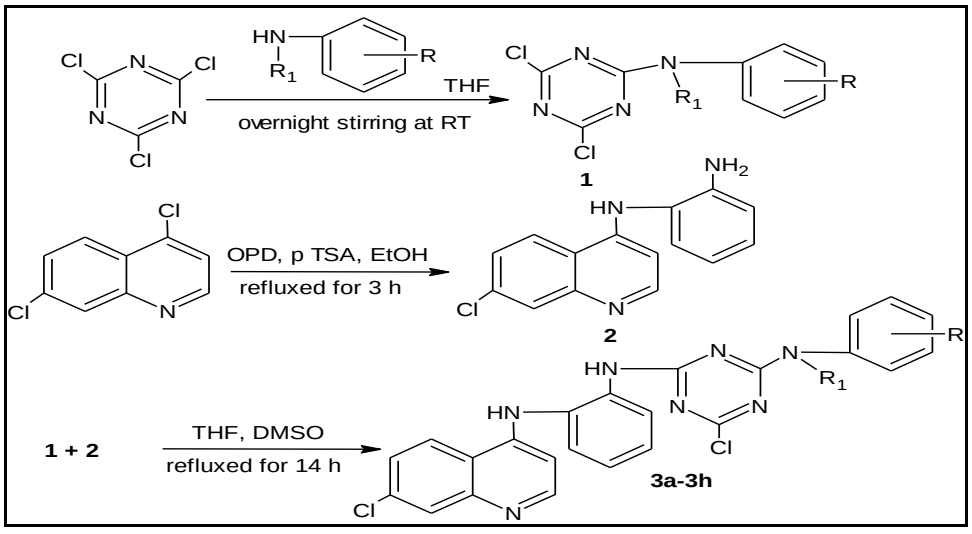

Figure 4: Scheme for the synthesis of compounds 3a-3h

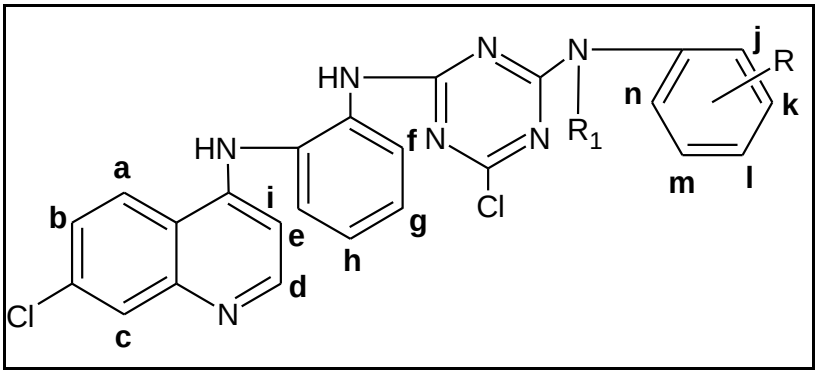

Figure 5: Notation for protons (a-n) in general structure of the titled compounds 3a-3h

Table 2: Physical data of the titled compounds

Compound	R	R_1	TLC (R_f)	Melting point (°C)	%Yield
3a	m-OCH_3	H	0.42	237	68
3b	m-NO_2	H	0.24	220	66
3c	o-NO_2	H	0.45	210	72
3d	p-OCH_3	H	0.39	244	76
3e	H	C_3H_7	0.46	254	71
3f	o-CH_3	H	0.35	232	65
3g	m-CH_3	H	0.42	215	69
3h	o-Cl	H	0.32	230	73

Spectral characterization of compounds 3a-3h

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3-methoxyphenyl)-1,3,5-triazine-2,4-diamine (3a): IRV_{max} (KBr)(cm^{-1}): 3336 (N-H str), 2972 (C-H str), 1572 (Ar C=C str), 746 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):8.57-8.59 (d, 1H, Ar, H_d), 8.43 (s, 1H, Ar, H_j), 8.32 (s, 1H, N-H), 7.99 (s, 1H, N-H), 7.87-7.89 (d, 1H, Ar, H_b), 7.78 (s, 1H, Ar, H_c), 7.47 (d, 1H, Ar, H_l), 7.38 (d, 1H, Ar, H_n), 6.92-7.15 (m, 1H, Ar, H_m), 6.82-6.85 (d, 1H, Ar, H_a), 6.73 (s, 1H, N-H), 6.66-6.76 (m, 2H, Ar, H_g,H_h), 6.31-6.33 (d, 2H, Ar H_f, H_i), 6.27-6.29 (d, 1H, Ar, H_e), 3.88 (s, 3H,OCH_3); MS: m/z 505 ($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine (3b): IR (KBr)V_{max} (cm^{-1}): 3390 (N-H str), 2923 (C-H str), 1609 (Ar C=C str), 797 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45-8.47 (d, 1H, Ar, H_l), 8.00 (s, 1H, Ar, H_j), 7.99 (s, 1H, N-H), 7.95 (s, 1H, N-H), 7.52 (d, 1H, Ar, H_b), 7.39-7.41 (d, 2H, Ar, H_i, H_f), 7.27 (s, 1H, Ar, H_c), 7.19 (d, 1H,Ar, H_d), 7.07 (d, 1H, Ar, H_n), 6.99-7.02 (d, 1H, Ar, H_a), 6.82-6.89(m, 1H, Ar, H_m), 6.71-6.77 (m, 2H, Ar, H_g, H_h)], 6.60 (s, 1H, N-H), 6.34-6.35 (d, 1H, Ar, H_e)]; MS: m/z 520 ($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(2-nitrophenyl)-1,3,5-triazine-2,4-diamine (3c): IR (KBr)V_{max} (cm^{-1}): 3370 (N-H str), 2954 (C-H str), 1604 (Ar C=C str), 783 (C-Cl

str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.52-8.57 (d, 1H, Ar, H_d), 8.21 (d, 1H, Ar, H_k), 7.98 (s, 1H, N-H), 7.91 (s, 1H, N-H), 7.72-7.84 (m, 2H, Ar, H_l, H_m)], 7.59-7.61 (d, 2H, Ar, H_i, H_f)], 7.37 (s, 1H, Ar H_c), 7.29 (d, 1H,Ar, H_b), 7.20-7.25 (d, 1H, Ar, H_n), 7.13-7.16 (d, 1H, Ar,H_a), 6.91-6.99 (m, 2H, Ar, H_g, H_h), 6.80 (s, 1H, N-H), 6.44-6.46 (d, 1H, Ar, H_e); MS: m/z 520 ($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (3d): IRV_{max} (KBr)(cm^{-1}): 3330 (N-H str), 2862(C-H str), 1564 (Ar C=C str), 748 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):8.65-8.69 (d, 1H, Ar, H_d), 8.48-8.52 (d, 1H, Ar, H_a), 8.45 (s, 1H, N-H), 8.29 (s, 1H, N-H), 7.97-8.03 (d, 1H,Ar, H_b), 7.89 (s, 1H, Ar, H_c), 7.78-7.81 (dd, 2H, Ar, H_j, H_k), 7.52-7.57(dd, 2H, Ar, H_m, H_n), 6.93 (s, 1H, N-H), 6.76-6.86 (m, 2H, Ar, H_g, H_h), 6.41-6.43 (d, 2H, Ar, H_f, H_i), 6.37-6.39 (d, 1H, Ar, H_e), 3.69 (s, 3H,OCH_3); MS: m/z 505 ($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-propyl-N^4-phenyl-1,3,5-triazine-2,4-diamine (3e): IR (KBr)V_{max}(cm^{-1}): 3376 (N-H str), 2957 (C-H str), 1570 (Ar C=C str), 753 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H, N-H), 7.64-7.66 (d, 1H, Ar, H_d), 7.55-7.56 (d, 1H, Ar, H_a), 7.53 (s, 1H, N-H), 7.50-7.51 (d, 1H,Ar, H_b), 7.41-7.48 (m, 2H, Ar, H_k, H_m), 7.38-7.37 (d, 2H, Ar, H_j, H_n), 7.34-7.35 (d, 2H, Ar, H_i, H_f), 7.30 (s, 1H, Ar, H_c), 7.24-7.29 (m, 1H, Ar, H_l), 6.99-7.22 (m, 2H, Ar, H_g, H_h), 6.89-6.91 (d, 1H, Ar, H_e), 3.95-4.00 (t, 2H, N-CH_2), 3.16 (sextet, 2H, CH_2), 2.62 (t, 3H, CH_3); MS: m/z 517($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(2-methylphenyl)-1,3,5-triazine-2,4-diamine (3f): IRV_{max} (KBr)(cm^{-1}): 3350 (N-H str), 2857(C-H str), 1587 (Ar C=C str), 758 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73-8.75 (d, 1H, Ar H_d), 8.69-8.72 (d, 1H, Ar, H_a), 8.43 (s, 1H, N-H), 8.12 (s, 1H, N-H), 8.00-8.04 (d, 1H,Ar, H_b), 7.92 (s, 1H, Ar, H_c), 7.87 (d, 1H, Ar, H_k), 7.58 (m, 1H, Ar, H_l), 7.35-7.41(m, 1H, Ar, H_m), 7.26-7.28(d, 1H, Ar, H_n), 7.06 (s, 1H, N-H), 6.83-6.89 (m, 2H, Ar, H_g, H_h), 6.53-6.56 (d, 2H, Ar, H_f, H_i), 6.23-6.25 (d, 1H, Ar,H_e), 2.07 (s, 3H, CH_3); MS: m/z 489($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3-methylphenyl)-1,3,5-triazine-2,4-diamine (3g): IRV_{max} (KBr)(cm^{-1}): 3349 (N-H str), 2961(C-H str), 1583 (Ar C=C str), 756 (C-Cl str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.64-8.69 (d, 1H, Ar, H_d), 8.59-8.62 (d, 1H, Ar, H_a), 8.47 (s, 1H, N-H), 8.19 (s, 1H, N-H), 7.98-8.03 (d, 1H,Ar, H_b), 7.85 (s, 1H, Ar, H_c), 7.69 (s, 1H, Ar, H_j), 7.43 (d, 1H, Ar, H_l), 7.12-7.23(m, 1H, Ar, H_m), 7.07-7.09(d, 1H, Ar, H_n), 6.93 (s, 1H, N-H), 6.75-6.82 (m, 2H, Ar, H_g, H_h), 6.31-6.33 (d, 2H, Ar, H_f, H_i), 6.27-6.29 (d, 1H, Ar, H_e), 2.12 (s, 3H, CH_3); MS: m/z 489($M+H^+$).

6-Chloro-N^2-(2-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(2-chlorophenyl)-1,3,5-triazine-2,4-diamine (3h): IRV_{max} (KBr)(cm^{-1}): 3225 (N-H str), 2874(C-H str), 1568 (Ar C=C str), 762 (C-Cl

str); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72-8.76 (d, 1H, Ar, H_b), 8.51 (d, 1H, Ar, H_k), 8.28 (s, 1H, N-H), 8.01 (s, 1H, N-H), 7.82-7.94 (m, 2H, Ar, H_l, H_m), 7.69-7.71 (d, 2H, Ar, H_i, H_f), 7.47 (s, 1H, Ar, H_c), 7.39 (d, 1H,Ar, H_d), 7.30-7.35 (d, 1H, Ar, H_n), 7.23-7.26 (d, 1H, Ar,H_a), 6.95-7.09 [m, 2H, Ar, H_g, H_h), 6.84 (s, 1H, N-H), 6.54-6.56 (d, 1H, Ar, H_e); MS: m/z 513($M+H^+$).

Acute oral toxicity

Acute oral toxicity studies were performed as per the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, Test No. 423, 2008. The protocol of the work was approved by the Institutional Animal Ethics Committee (IAEC) (CUSCP/IAEC/19/2013). Before experimentation, the mice were divided into a control group and test groups, each group consisting of six mice. The control group received orally a single dose of 10 ml/kg body weight of a control, i. e. 1% w/v sodium carboxymethyl cellulose (Na CMC) suspension. The test compounds, at the dose levels of 500, 1000 and 2000 mg/kg body weight of a mouse, were administered orally to the mice present in the test groups. After the administration of the test compounds, mice were observed for a period of 14 days for the changes in the skin, fur, eyes, behavioral pattern and mortality.

***In vivo* anti-inflammatory activity**

Carrageenan induced rat hind paw edema method[41]

The rats were fasted for 24 h and divided into a negative control group (vehicle), a positive control group (diclofenac) and 8 test groups (synthesized compounds), each group consisting of six animals. The negative control group received 1 ml of 1% Na CMC, the positive control group received 30 mg/kg body weight of diclofenac in 1% Na CMC and the test groups received 200 mg/kg body weight of the synthesized compounds suspended in 1% Na CMC. The rats were dosed orally, 1 h prior to 0.1 ml sterile carrageenan (1% solution) injection in the sub plantar region of the right hind paw. Carrageenan caused visible redness and pronounced swelling in the rat paw. The paw was marked with ink at the level of the lateral malleolus. The paw volume was measured plethysmographically, immediately after the carrageenan injection and again at 1, 2, 3 and 4 h after carrageenan challenge of oral administration of the test compounds.

Evaluation

Decrease in the paw volume from 0 to 4th h was calculated as the per cent inhibition of edema by the following equation:

Per cent inhibition of edema = 100 x [1 – (A – X)/(B – Y)]

where,

A - Mean paw volume of rats in the test group after carrageenan injection

B - Mean paw volume of rats in the control group after carrageenan injection

X - Mean paw volume of rats in the test group before carrageenan injection

Y - Mean paw volume of rats in the control group before carrageenan injection

Statistical analysis

The results were expressed as MEAN±SEM and were analyzed using one way analysis of variance (ANOVA). The probability of 0.001 or less was considered statistically significant. Table 3 shows the results of % inhibition of edema of all the synthesized compounds and diclofenac after 4h.

Table 3: Per cent inhibition of edema of the titled compounds after 4 h

Sr. no.	Compound	% Inhibition of edema (Mean±SEM)
1	3a	93.33±0.882
2	3b	97.00±0.577
3	3c	91.00±1.155
4	3d	91.33±0.882
5	3e	94.33±0.882
6	3f	91.00±0.577
7	3g	94.00±0.577
8	3h	92.00±1.155
9	Diclofenac	90.00±0.577
10	Negative control	19.33±0.333

RESULTS AND DISCUSSION

Molecular docking

Celecoxib and SC-558 were used as the standards for docking as they are selective COX-2 inhibitors. The active site of COX-2 is divided into 3 important regions[42] the first being a hydrophobic pocket defined by Tyr385, Trp387, Phe518, Ala201, Tyr248 and Leu352, the second region being the entrance of the active site lined with the hydrophilic residues Arg120, Glu524, Tyr355 and the third is a side pocket lined by His90 Arg513 and Val523. In case of the selective COX-2 inhibitors such as SC-558, the phenyl ring was in the close vicinity of the hydrophobic pocket and the phenyl sulfonamide group occupied the side pocket and showed binding with Leu352, Ser353. An interaction with Arg513 has also been identified as an important residue in the binding of selective COX-2 inhibitors according to the site-directed mutagenesis data. The docking results revealed that the G-scores of all 8 compounds were found to be more than -9.10, which were closer to the scores of the standards, thereby proving that all the synthesized compounds interacted very well with COX-2 enzyme. Compound **3b** demonstrated the highest G-score amongst all the other test compounds. The compounds, on docking on the active site, formed hydrogen bonds with mostly Tyr355 and Arg120. Good vdw interaction of the compounds was

observed with all the amino acids present in all the 3pockets of the enzymes; therefore, the G-score values were good.

Chemistry

After docking a series of triazine derivatives on COX-2 enzyme, those compounds displaying G-score more than that shown by the standard were successfully synthesized using inexpensive reactants and were produced with good yields of more than 60%. The structures of the compounds were characterized and confirmed by IR, ^{1}H NMR and mass spectroscopy.

Acute oral toxicity

From the toxicity studies, the data revealed that all the synthesized compounds were confirmed to be non-toxic up to2000 mg/kg dose level and were well tolerated by the experimental animals. Therefore, the dose selected and fixed for pharmacological evaluation was 1/10th of 2000 mg/kgi.e. 200 mg/kg.

***In vivo* anti-inflammatory activity**

Since celecoxib has been banned for use and withdrawn from the market, diclofenac was used as the standard drug for *in vivo* anti-inflammatory activity. The compounds were tested at 200 mg/kg dose and the results were compared with that of diclofenac as the standard drug. The *in vivo* anti-inflammatory activity results revealed that all the compounds displayed % inhibition of edema more than 90, which is better than that shown by diclofenac. Amongst all the compounds, compound **3b** demonstrated the highest anti-inflammatory activity.

CONCLUSION

Compounds displaying good G-score also exhibited anti-inflammatory activity better than that shown by the standard drug, diclofenac. Good G-score interpreted that the mechanism of action of the titled compounds can be the inhibition of COX-2 enzyme. Amongst all the compounds, the compound **3b** demonstrated the highest G-score as well as the highest anti-inflammatory activity. Hence, this compound may be explored as a potential lead molecule for further development. Relating the structures to the pharmacological activity, it can be proposed that the triazines attached to mono substituted arylamines bearing nitro, methoxy and alkyl functional groups displayed increased anti-inflammatory activity.

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