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Molecular Docking Studies, Synthesis, Toxicological Evaluation using Brine Shrimp (Artemia salina L.) Model and Anti-inflammatory Activity of Some N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine Derivatives

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ABSTRACT

A series of new N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine derivatives were synthesized under microwave irradiation and evaluated for their anti-inflammatory activity and in-silico (molecular docking studies) to recognize the hypothetical binding motif of the title compounds using VLifeMDS software. The binding mode of the title compounds has been proposed based on the docking studies. They have interesting pharmacophore that display a broad spectrum of biological activity. The 1,3,4-thiadiazole scaffold is an interesting building block that has been used to synthesize a variety of useful bioactive compounds. The present studies widen the scope of the brine shrimp model that may prove quite helpful as a preliminary screen to determine toxic properties. In Brine shrimp lethality bioassay, compounds produced dose dependent cytotoxicity effect to brine shrimp nauplii. Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as the increase of vascular permeability, increase of protein denaturation, and membrane alteration. The pharmacological evaluation of 1,3,4-thiadiazole derivatives revealed that, among all the compounds screened compound code 3c were found to have promising anti-inflammatory activity.

Keywords: 1,3,4-thiadiazole, Molecular Docking, Brine Shrimp Lethality Assay, Anti-inflammatory Activity.

I. INTRODUCTION

Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1,3,4-thiadiazole (two nitrogen and one other heteroatom in a five-membered ring)[1]. The unique chemical properties and biological activity of 1,3,4-thiadiazoles make them as attractive targets for the medicinal chemists[2]. Inflammation is a complex defensive mechanism of the body to any noxious stimulus; this process may

vary from a localized to a generalized response characterized by the accumulation of fluids and leukocytes leading to edema and pain. Non-steroidal anti-inflammatory drugs are commonly used for the treatment of pain and inflammation associated with different diseases particularly rheumatoid arthritis, however their chronic use may cause GIT ulceration, bleeding and renal injury. Heterocyclic compounds nucleus are known to exhibit unique anti-inflammatory, antimicrobial and anticancer drugs and disease like breast cancer is the world's leading cause of cancer death so it is also need to develop potent molecule and So far, modification of the thiadiazole ring have proven highly effective with improved potency and lesser toxicity. Non-steroidal anti-inflammatory drugs (NSAIDs) represent a heterogeneous family of pharmacologically active compounds used to alleviate acute and chronic inflammation, pain and fever. A major mechanism of action of NSAIDs is lowering prostaglandin (PG) production through the inhibition of cyclo-oxygenase (COX) enzyme that catalyses the conversion of arachidonic acid into PG. Because PG has dual function; mediation of inflammation and cytoprotection in the stomach and intestine, long term usage of NSAIDs to relieve the symptoms of inflammation and pain always results in gastrointestinal (GI) disorders and renal toxicity. It is known that bacterial infections often produce pain and inflammation. In normal practice, chemotherapeutic, analgesic, and anti-inflammatory drugs are prescribed simultaneously which increases the risk for developing NSAIDs-related complications especially in the elderly, patients with a prior history of peptic ulcer disease and patients with impaired kidney functions. Hence, there is a pressing need for drugs having both antimicrobial and analgesic, anti-inflammatory activities with minimum adverse effects[3-4]. The ideology of green chemistry calls for the development of new chemical reactivities and reaction conditions that can potentially provide benefits for chemical synthesis in terms of resource and energy efficiency, product selectivity, operational simplicity and health and environmental safety[5]. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. Growth of green chemistry holds necessary potential for the reduction of by product, a reduction in the waste production and a lowering of energy cost[6-7]. Due to its ability to couple directly with reaction molecule and passing thermal conductivity leading to fast rise in the temperature microwave irradiation had used to improve many organic synthesis. Experiments have proved that microwave, in comparison with the Soxhlet extraction, use a lesser volume of solvent and sample and perform extraction at a much faster rate were previously reported for various plant extraction. Computational studies are the crucial steps in the drug designing. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor[8-14]. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations

can help to have good biological activity from any heterocyclic compound modification. Someday soon, you might be making your own medicines at home. That's because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series[15-23]. Toxicity of synthesized compounds using bioassay of brine shrimp lethality based on the ability to kill brine shrimps (Artemia salina nauplii). The assay is known to be a useful tool for either the preliminary evaluation of toxicity and have been used to detect fungal toxin, heavy metals, pesticides and dental cytotoxicity tests. The brine shrimp lethality assay (BSLA) was regularly used for primary screening as well as isolated compounds to control brine shrimp toxicity. The behavior also gives an indicator that the test materials may have cytotoxic properties. Brine shrimp bioassay for the lethality of synthetic compounds (Luo et al., 2000; Mclaughlin et al., 1998; Meyer et al., 1982) is a fast and systematic bioassay. By this process, the bioactivity and the pure compounds can be checked. In a basic zoological organism (brine nauplii) the system utilizes in-vivo lethality as a convenient control for screening and fractionation in the discovery of new bioactive natural products. Brine toxicity is closely correlated with cytotoxicity. Therefore, the cytotoxic fractionation and 3PS (P388) (in vivo murine leukaemia) active extracts using the brine lethality bioassay can be identified and then tracked (Alkofahi et al., 1988; Mclaughlin et al., 1998; Meyer et al., 1982). Brine shrimp assay has the benefits of being fast (24 hours), inexpensive, and easy (e.g., no aseptic techniques are required). This uses a large number of species effectively for statistical analysis, and requires no special facilities and a reasonably small sample size (2-20 mg or less). It also does not require animal serum, as is required for cytotoxicity. Therefore, although there are a number of anti-inflammatory drugs available in the market, there is a need to develop novel drugs with better safety profile[24-28].

II. MATERIALS AND METHODS

A. Molecular Docking Study:

Molecular docking study was performed using VLifeMDS 4.1 software on four N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine. VLifeMDS 4.1 software provided both rigid (no torsional flexibility for a protein as well as a ligand) and flexible (torsional flexibility to a ligand with a rigid protein) docking of the molecules. The target or receptor was either experimentally known or theoretically generated through knowledge-based protein modeling or homology modeling. The molecular docking tool has been developed to get a preferred geometry of interaction of ligand–receptor complexes having minimum interaction energy supported different scoring functions viz. only electrostatics, the sum of steric and electrostatic (parameters from the force field), and the dock score. This utility allowed us to screen a set of compounds for lead optimization. VLifeMDS uses to minimize the interaction energy between the ligand and receptor protein. The receptor of RNA-polymerase II carboxy-terminal domain (PDB code-3D9K) was obtained from protein data bank and water molecules in the crystal structure were deleted. The optimized receptor was then saved as mol file and used for docking simulation.

Ligand preparation

The 2D structures of the compounds were built and then converted into the 3D. The 3D structures were then energetically minimized up to the rms gradient of 0.01 using MMFF.

Identification of cavities

By using cavity determination option of software, cavities of enzyme were determined. The cavities in the receptor were mapped to assign an appropriate active site. The basic feature used to map the cavities were the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics. Hence, all the cavities that are present in receptor are identifed and ranked based on their size and hydrophobic surface area considering the dimensions and hydrophobic surface area, cavity with found to be the best void as an active site.

Scoring function

Distinction of good or bad docked conformation is based on scoring or fitness function. MDS uses fitness functions on only electrostatic and both steric and electrostatic interactions between receptor ligand as well as dock score scoring function. The dock score compute binding affinity of a given protein-ligand complex with known 3D structure[29-33].

B. Chemistry:

All chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased from Research and Merck laboratory, Mumbai. The melting points of synthesized compound were determined in open capillary tube method and are uncorrected. Thin layer chromatography was used confirmation of reaction and the purity of the intermediate and the final compounds by applying a single spot on TLC plate (silica gel G) using various solvents such as toluene, acetone, ethanol system. TLC plates were visualized under iodine chamber. IR spectra were recorded on FTIR. Chemical shift are reported in δ unit with respect to TMS as internal standard at diya lab, Airoli, Mumbai. Mass spectra were recorded on Pe sciex (model no. API 2000) software analyst 1.4.2 mode: Q1MS Q1/AUTO INJECTION from diya lab, airoli, Mumbai. 1,3,4-thiadiazole derivatives were synthesized by following procedure.

General procedure for the synthesis of methyl benzoate (1a)

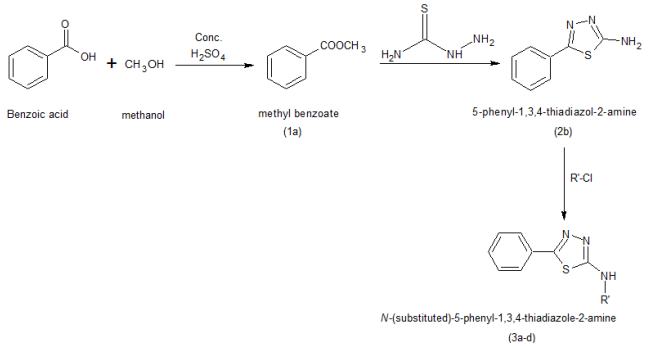
Methyl benzoate was synthesized by adding 0.1 mol of benzoic acid in 20 ml of methanol and reaction mixture was irradiated in microwave for 15 min at 340 watt. By adding few drops of H_2SO_4 as catalyst. After completion of reaction solid mass was formed and TLC was checked.

General procedure for synthesis of 5-phenyl-1,3,4 thiadiazole-2-amine (2b)

In the mixture of above methyl benzoate, thiosemicarbazide (0.1 mol) was added. The reaction mixture was irradiated in microwave for 20-30 min at 340 watt.

General procedure for synthesis of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine (3a-d)

In 5-phenyl-1,3,4 thiadiazole-2-amine, add (0.1mol) of substituted nitrobenzene and irradiate this mixture in microwave for 30min at 340 watt. After the completion of the reaction solid mass was formed and TLC was checked, and the product was recrystallized with methanol.



Scheme 1: Synthetic route for the preparation of the title compound (3a-d)

Analytical Data of the N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine

3a. N-(3-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 74%, m.p 138-140^{0}C, IR (KBr, cm-1): 1429.42 (C=N), 1584.18 (NO_2), 3258.31 (N-N str), 3604.52 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.57-3.64 (t, 3H, Ar-H), 4.21 (s, 1H, NH), 7.75-7.88 (m, 5H, Ar-H); mass m/z (M+) 298.4.

3b. N-(4-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 69%, m.p 147-149^{0}C, IR (KBr, cm-1): 1429.42 (C=N), 1549.23 (NO_2), 3243.12 (N-N str), 3615.35 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.49-3.52 (t, 3H, Ar-H), 4.38 (s, 1H, NH), 7.51-7.62 (m, 5H, Ar-H); mass m/z (M+) 298.3.

3c. N-(2,4-dinitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 88%, m.p 131-133^{0}C, IR (KBr, cm-1): 1428.99 (C=N), 3224.14 (N-N Str), 1558.82 (NO_2), 1H NMR (DMSO-d6, 400MHz) δ: 3.24-3.99 (d, 2H, Ar-H), 4.35 (s, 1H, NH), 7.29-7.83 (m, 5H, Ar-H); mass m/z (M+) 343.4.

3d. N-(2-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 82%; m.p. 122-124^{0}C; IR (KBr, cm-1): 1456.91(C=N), 1565.56 (NO_2), 3156.21 (N-N str), 3412.65 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.38-3.42 (t, 3H, Ar-H), 4.52 (s, 1H, NH), 7.34-7.41 (m, 5H, Ar-H); mass m/z (M+) 298.5.

C. Biological Evaluation:

i. Brine Shrimp Lethality Assay:

Brine shrimp lethality test has been used as a bioassay for a variety of toxic substances. A general bioassay that appears capable of detecting a broad spectrum of bioactivity, present in synthetic compounds, rather than more tedious and expensive *in-vitro* and *in-vivo* antitumor assays. Furthermore, it does not require animal serum as is needed for cytotoxicity.

Procedure:

Preparation of seawater

38 gm sea salt (without iodine) was weighed, dissolved in one liter of distilled water and filtered off to get clear solution.

Hatching of brine shrimp

Artemia salina leach (brine shrimp eggs) collected from pet shops was used as the test organism. Seawater was taken in the small tank, and shrimp eggs were moved to one side of the tank, and sealed on this side. The shrimp was allowed to hatch for two days and be matured like nauplii. Constant supply of oxygen was rendered during the process of hatching. The hatched shrimps are drawn to the light (phototaxis) and so egg shell-free nauplii from the illuminated portion of the tank was collected. The nauplii was taken by a pipette from the fish tank and filtered to improve visibility in fresh clear sea water and 10 nauplii was taken carefully by micropipette.

Preparation of test samples

In each experiment, 0.5mL of test compound of different concentration i.e (50, 100 and 150µg/mL) was added to brine solution and maintained at room temperature for 24hr under the light and surviving larvae were counted. Vehicle treated used as control for the test. Test solutions were used in sets of three tubes per dose. Replicas should be maintained to get

accurate results. The effectiveness or the concentration-mortality relationship of test compounds is usually expressed as a (IC_{50})[34-35].

ii. Anti-inflammatory Evaluation:

a. Protein denaturation using egg albumin

The mixture (5ml) consisted of 0.2ml of egg albumin (from fresh hen's egg), 2.8ml of phosphate buffered solution (PBS, pH 6.4) and 2ml of varying concentration of test samples so that final concentration become 50µg/ml and 100µg/ml. Similar volume of DMSO served as control. Then the mixtures were incubated at (37^0C ± 2) for 15 min. and then heated at 70^0C for 5min. After cooling, their absorbance was measured at 660nm (JASCO UV spectrophotometer) by using vehicle as blank and their viscosity was determined by using ostwald viscometer. Diclofenac at the final concentration of 50µg/ml and 100µg/ml was used as reference drug and treated similarly for determination of absorbance and viscosity. % inhibition of protein denaturation was calculated by using the following formula[36-39].

$$\% \text{ inhibition protein denaturation} = \frac{\text{Absorbance of control - Absorbance of test}}{\text{Absorbance of control}}$$

b. Protein denaturation using bovine serum albumin (BSA)

The reaction mixture was consisting of of test compound and G-max (50:50 ratio) at different concentrations and 1% of aqueous solution of bovine albumin. The samples were incubated at 37°C for 20 min and then heated at 57°C for 20 min. After cooling the samples, the absorbance of turbidity was measured at 660 nm[40].

% inhibition of protein denaturation was calculated by using following formula:

$$\% \text{ inhibition protein denaturation} = \frac{\text{Absorbance of control - Absorbance of test}}{\text{Absorbance of control}}$$

III. RESUTLS AND DISCUSSION

A. Molecular Docking Study:

Molecular docking study were subjected for the anti-inflammatory activity on receptor of RNA-polymerase II carboxy-terminal domain (PDB code-3D9K). The dock score of compounds code (3a-d) shown in the table and the minimum dock score for the compound code 3c is -37.39. The best pose obtained by docking results is reported where main interaction between ligand and receptor can be observed. All designed compound adopt a very similar conformation at binding pocket, showing hydrogen bond interaction with amino acid of ASN15B, aromatic interaction with amino acid TYR12B, PHE50B & Vander Waals binding with amino acid THR6A, GLN28A, TYR12B, ASN15B, LYS49B, PHE50B, LYS53B, CYS54B which shown by 2D representation diagram. Superimpose image of compound code 3c with receptor shown in Figure 3. The dock score of standard drug diclofenac was found to be -65.60.

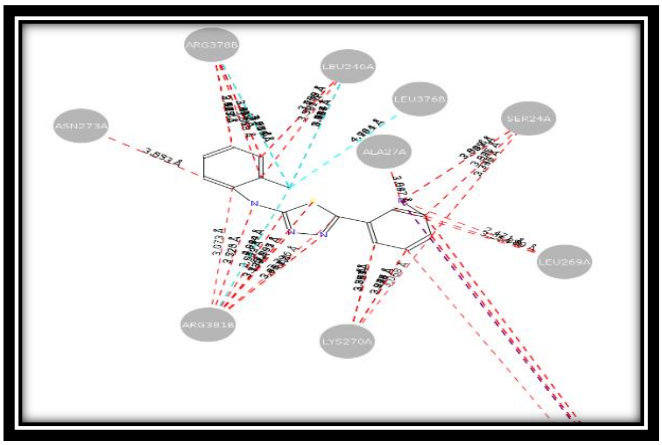


Fig 1: 2D representation of docking poses of compound code 3c

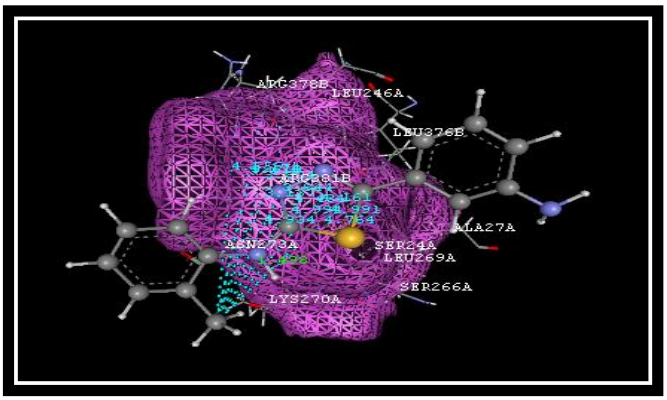


Fig 2: ligand 3c was shown in ball stick model

Fig 3: Superimpose image representation of docking poses of compound code 3c

Table 1: Anti-inflammatory activity results of molecular docking studies by using GRIP batch docking

Sr. no	Compound code	Docking score (Kcal/mol)
1	3a	-29.82
2	3b	-23.99
3	3c	-37.39
3	3c	-30.79
5	diclofenac	-65.60.

B. Chemistry:

The reported study was undertaken to synthesize methyl benzoate was synthesized by adding of benzoic acid in methanol and reaction mixture was irradiated in microwave for 15 min at 340 watts. By adding few drops of H_2SO_4 as catalyst. After completion of reaction solid mass was formed and TLC was checked. In next step mixture of methyl benzoate, thiosemicarbazide was added. The reaction mixture was irradiated in microwave for 20-30 min. at 340 watt. In 5-phenyl-1,3,4-thiadiazole-2-amine, add substituted nitrobenzene and irradiate this mixture in microwave for 30min at 340 watt. After the completion of the reaction solid mass was formed and further checked by TLC, and the product was recrystallized with methanol. The reaction sequence is shown in Scheme 1. Microwave assisted synthesis is faster, better and safer green chemistry approach for the traditional reactions. The time taken for the synthesis of 1,3,4-thiadiazole is drastically reduced by the microwave assisted synthesis. This technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis and highly accelerated rate of the reaction time with an improvement in yield and quality of product. The IR, NMR and mass spectra are fully consistent with the structure.

C. Biological Evaluation

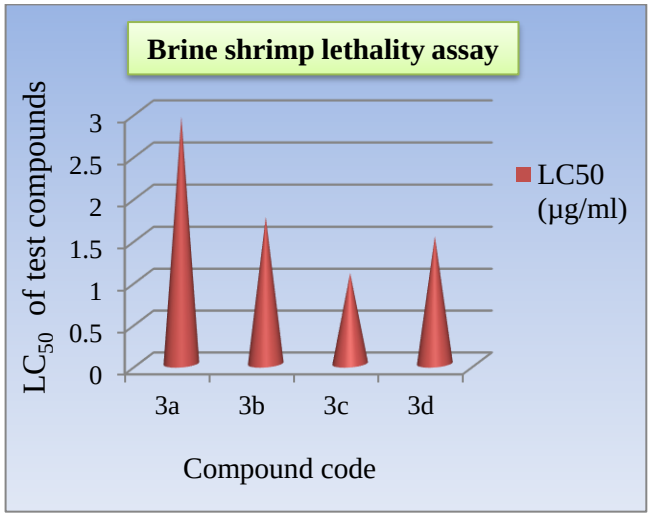
i. Brine Shrimp Lethality Assay:

The lethality of a test sample in a simple zoological organism such as the shrimp (*Artemia salina*) has been utilized in the Brine shrimp cytotoxicity test (BSCT). It is a very useful tool to screen a wide range of chemical compounds for their various bioactivities. It has been demonstrated that BSCT correlates reasonably well with cytotoxic and other biological properties. The brine shrimp bioassay has been established as a safe, practical and economic method for determination of bioactivities of synthetic

compound as well as plant products. The brine shrimp lethality bioassay also indicates antifungal effects, pesticidal effects, teratogenic effects, toxicity to environment and many more. Table 2 shows the lethality of different test sample to the brine shrimp nauplii. All the synthesized compounds (3a-d) were tested for cytotoxic activity by brine shrimp lethality assay. Among them compound code 3c and 3d showed a dose dependent cytotoxic activity at concentrations of (3c) 1.08µg/ml and (3d) 1.52µg/ml. The remaining compounds exhibited less activity when compared to the other compounds at various concentration levels. The degree of lethality is directly proportional to the concentration of the synthesized compounds.

Table 2: Brine shrimp lethality assay data of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine derivatives (3a-d)

Sr. no	Compound code	LC_{50} (µg/ml)
1	3a	2.94
2	3b	1.75
3	3c	1.08
4	3d	1.52



Graph 1: Brine shrimp lethality assay of synthesized compounds (3a-d)

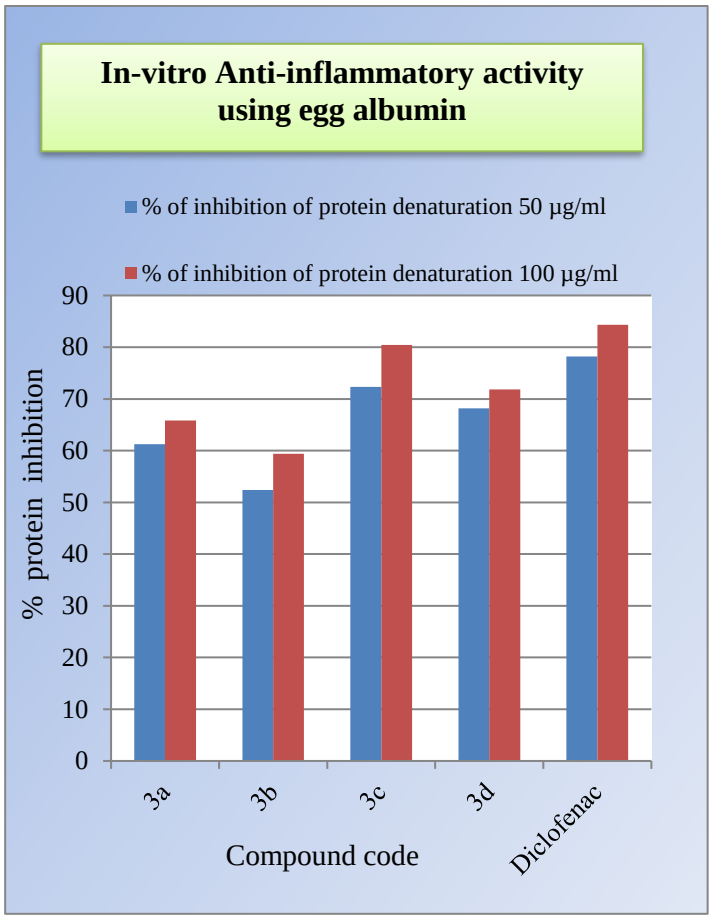
ii. Anti-inflammatory Evaluation:

a. Protein denaturation using egg albumin

In present study in-vitro results confirmed anti-inflammatory activity of new series of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine derivatives. As denaturation of proteins which is a well documented cause of inflammation. Several anti-inflammatory drugs shown dose dependent ability to inhibit thermally induced protein denaturation. Ability of 1,3,4-thiadiazole is to bring down thermal denaturation of protein is possibly a contributing factor for its anti-inflammatory activity. The data of our studies suggests that compound code 3c shows significant anti-inflammatory activity.

Table 3: Anti-inflammatory activity of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine derivatives (3a-d) measuring the percentage inhibition

Sr. no	Compound code	% inhibition of protein denaturation		Viscosity (cps)	
		50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1	3a	61.22	65.82	0.44	0.48
2	3b	52.41	59.41	0.40	0.43
3	3c	72.34	80.42	0.55	0.60
4	3d	68.15	71.84	0.46	0.49
5	Diclofenac	78.21	84.34	0.58	0.62



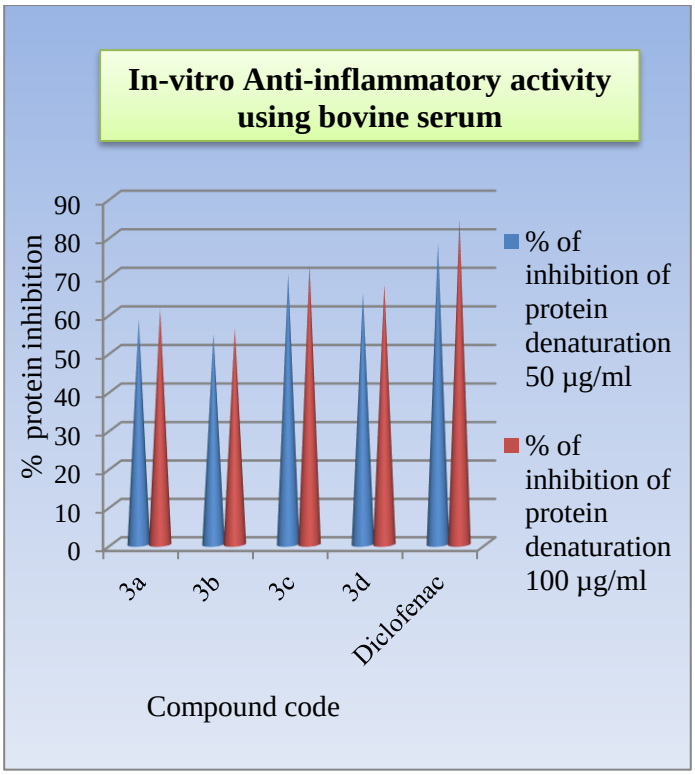
Graph 2: Anti-inflammatory activity of synthesized compounds (3a-d) using egg albumin

b. Protein denaturation using bovine serum albumin (BSA)

The autoantigen production in inflammation is due to denaturation of protein and several studies reveal that protein denaturation is one of the reasons for inflammation. Protein denaturation is a process in which proteins lose their tertiary structure and secondary structure by application of external stress or compound, such as strong acid or base, a concentrated inorganic salt, an organic solvent, or heat. Most biological proteins lose their biological function when denatured. The results suggests that compound code 3c shows significant anti-inflammatory activity.

Table 4: Anti-inflammatory activity of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine derivatives (3a-d) measuring the percentage inhibition

Sr. no	Compound code	% of inhibition of protein denaturation	
		50 µg/ml	100 µg/ml
1	3a	58.49	61.20
2	3b	54.72	56.12
3	3c	70.18	72.50
4	3d	65.32	67.45
5	Diclofenac	78.21	84.34



Graph 3: Anti-inflammatory activity of synthesized compounds (3a-d) using bovine serum

IV. CONCLUSION

In conclusion, molecular docking studies further help in understanding the various interactions between the ligands and enzyme active sites in detail and thereby help to design novel potent inhibitor. The docking experiments were carried out for all the synthesized compounds and compared the docking score with reference compound diclofenace for anti-inflammatory activity. Compounds code 3c showed higher binding score, which are further attributed to the anti-inflammatory activity of these compound. We have described an efficient and benign synthesis of 1,3,4-thiadiazole gives more yields and requires less time by microwave method. 1,3,4-thiadiazole is the key intermediate in the formation of these heterocyclic compounds. Toxicity of the prepared compounds was evaluated using artemia salina nauplii and cytotoxicity was inferred based on the same brine shrimp lethality assay. Although the brine shrimp lethality bioassay is an excellent choice to elementary toxicity investigations. All the synthesized compounds have been investigated for their anti-inflammatory activity. With our newly synthesized compounds, it is evident that compound code 3c have shown excellent anti-inflammatory activity. Accordingly, this novel class of new 1,3,4-thiadiazole derivatives reported from our laboratory, emerge as a valuable lead series with great potential to be used as anti-inflammatory agents, and as promising candidates for further efficacious evaluation.

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