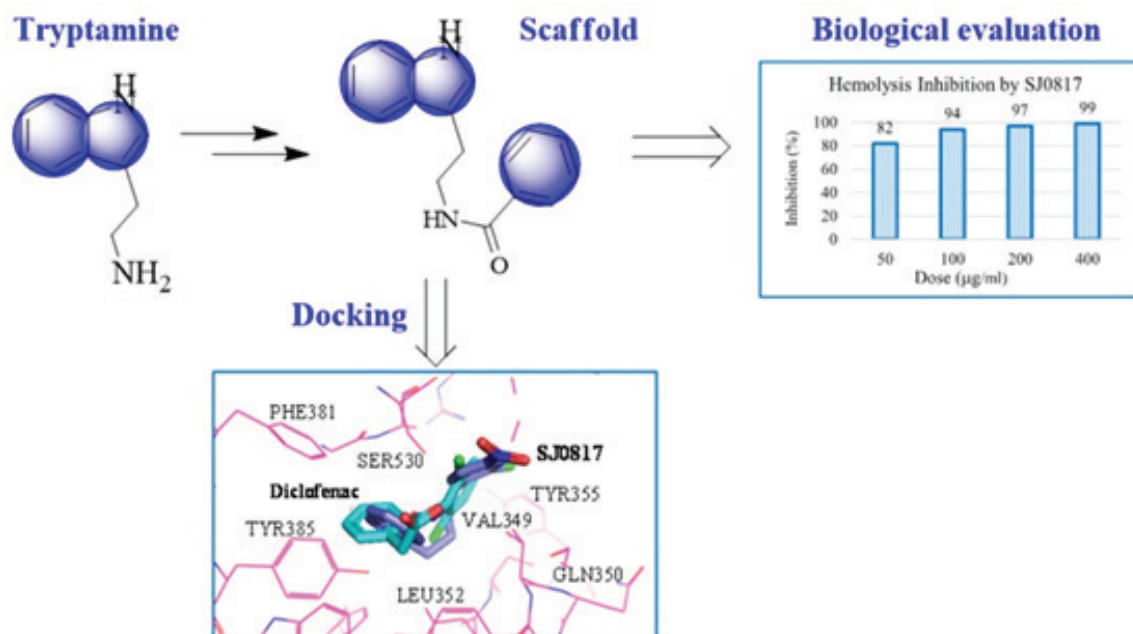


RESEARCH ARTICLE

Synthesis of Tryptaminamides for *In Vitro* Anti-inflammatory Activity and Subsequent *In Silico* Analysis

S. Bepary*, Md. M. Hossain, Md. T. Islam, S. R. Rony and Z. Alam Tareq



Highlights

- A novel series of tryptaminamide derivatives was synthesized using various nitro- and chloro-substituted benzoic acids.
- Synthesized amides were tested for *in vitro* anti-inflammatory potency
- *In silico* analysis was carried out by applying Autodock Vina
- Findings suggest tryptaminamides as a promising scaffold for the development of safer, potent anti-inflammatory agents.

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Synthesis of Tryptaminamides for *In Vitro* Anti-inflammatory Activity and Subsequent *In Silico* Analysis

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Abstract: Inflammation is a physiological response to tissue injury, characterized by redness, heat, swelling, and pain. Chronic, uncontrolled inflammation is associated with the development of diseases, such as Alzheimer's disease, arthritis, asthma, atherosclerosis, Crohn's disease, colitis, dermatitis, hepatitis, nephritis, etc. Conventional anti-inflammatory drugs are effective but often cause serious adverse effects, including gastrointestinal bleeding, ulceration, and perforation. In this study, a series of tryptaminamides was synthesized using derivatives of benzoic acid, including 2-chloro-5-nitrobenzoic acid, 4-nitrobenzoic acid, 2-chloro-4-nitrobenzoic acid, and 3-nitro-4-chlorobenzoic acid. Among the synthesized compounds, derivatives SJ0812, SJ0815, and SJ0817, containing both chloro and nitro-substituents, exhibited the highest *in vitro* anti-inflammatory activity, comparable to that of diclofenac. Subsequent *in silico* docking studies revealed additional binding pockets in the cyclooxygenase enzyme, suggesting opportunities for further structural optimization. These findings highlight the potential of tryptaminamide derivatives as a promising anti-inflammatory scaffold.

Keywords: Anti-inflammatory; Molecular docking; Egg albumin; Human Red Blood Cells (HRBC); Tryptaminamides

INTRODUCTION

Inflammation is a complex biological adaptive response resulting from internal or external stimuli. These responses involve activation of various signaling pathways leading to the release of numerous inflammatory mediators (Yiu et al. 2018). The various immune cells related to inflammatory responses include macrophages, dendritic cells, mast cells, neutrophils, and lymphocytes (Akira et al., 2006). Acute inflammation is vital for the body's regular healing process as well as recovery processes. But if untreated, chronic inflammation may result in a variety of diseases, including cancer, cardiovascular diseases, and autoimmune disorders (Alur, 2023; Chaudhary et al., 2023; and Holub et al., 2024). Persisting stimuli may bring more damaging consequences (Junjie et al., 2024), leading to chronic diseases, like atherosclerosis, obesity, type-2 diabetes, inflammatory bowel diseases, asthma, neurodegenerative diseases, rheumatoid arthritis, and cancer (Hotamisligil, 2006; Hollingsworth et al., 1967; Robinson et al., 1992; Glass et al., 2010; Garrett et al., 2010; Fakhouri et al., 2010;

Mantovani et al., 2008; de Visser et al., 2006; de Martel et al., 2009).

There are studies that have reported the correlation between type-2 diabetes (Alshuweishi et al., 2024; Bosevski et al., 2015) and chronic obstructive pulmonary disease (Xu et al., 2024) with dysregulated or persistent inflammation. Obesity-related diseases have been reported to correlate with the elevated levels of various pro-inflammatory markers (Alshuweishi et al., 2024; Rajamanickam et al., 2024). Mild systemic inflammations have been reported to increase erythrocyte fragility, leading to increased chances of hemolysis. Genomic biomarkers have been reported to increase degranulation processes in primary human mast cells, thereby suggesting a contribution to diseases related to allergic responses (Tam et al., 2024).

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to be the most prescribed drugs in the world. It has been reported that every day, approximately 30 million people take NSAIDs around the world (Bhala et al., 2013; Caner et al., 2013). The existing anti-inflammatory therapies include the application of non-steroidal anti-inflammatory agents. Long-term therapy with these agents may cause gastrointestinal complications ranging from stomach irritation to life-threatening gastrointestinal ulceration and bleeding (Mellemkjaer et al., 2002), which can cause unexpected cardiovascular effects (Laurence et al., 2007) or renal injury (Tozkoparan et al., 2000). These side effects limit their use to treat inflammations. Thus, there is continuous research to investigate effective and safer drugs. While considering the specific drugs, indomethacin and diclofenac are the two potent agents commercially available for use in current clinical practices. Both of these compounds have acidic functions and thus play a crucial role in aggravating the gastrointestinal side effects. In this research, new molecules were designed to maintain structural similarity with these existing molecules (Figure 1).

As per the project proposal, some structural changes have been introduced to change the logP values to ensure altered tissue distribution. According to Lipinski's rule of five, lipophilicity is a crucial factor determining the

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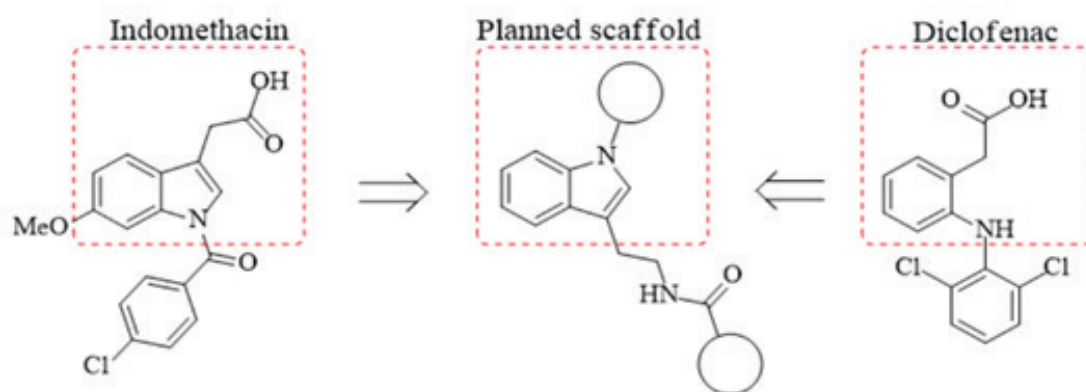


Figure 1: Design of the planned tryptaminamide scaffold based on structural features of the reference molecules, indomethacin and diclofenac.

bioavailability of any drug (Beata et al., 2023). It has been reported that the compound with logP higher than 5 has a lipophilicity value that results in higher tissue accumulation and rapid metabolic turnover. They will also have poor water solubility and strong plasma protein binding. These changes in cell permeability may influence gastrointestinal acidity, which could be beneficial for patients on long-term anti-inflammatory medication. At the same time, a different side-effect profile may emerge; if so, this new scaffold could still be considered for future development. The details of this project are presented in this report.

MATERIALS AND METHODS

Solvents, chemicals, and reagents

The necessary chemicals and reagents were taken from Sigma-Aldrich (USA) and TCI (Japan). The required solvents were taken from Duksan Pure Chemicals Co., Ltd, South Korea. and Daejung Chemical and Metal Co. Ltd. The planned amide derivatives were synthesized in the Medicinal Chemistry laboratory of the Department of Pharmacy. The purifications and separations were done by flash column chromatography using silica gel 45-100 μ , 200-400 mesh size).

Equipment used

A hot plate with a magnetic stirrer was used to run the reaction at various temperatures. The endpoint checking was performed by TLC using Sigma-Aldrich Glass plates of silica gel coated with fluorescent indicator F254. For usual evaporation, the RE100-Pro Digital Rotary Evaporator (DLab) was used. The characterization was done by ^1H NMR by Bruker 400 MHz in Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh. The ^1H NMR spectra were recorded employing DMSO- D_6 as solvent and TMS as the internal standard. Chemical shifts have been expressed in parts per million (ppm) values, and coupling constants have been expressed in hertz (Hz). Glass columns and a locally available positive air pump were used for flash column chromatography. Glass filters were used for necessary filtration work.

Synthesis of amides from tryptamine and benzoic acid derivatives

For amide coupling between tryptamine and derivatized

benzoic acids, the reported method (Hoque et al., 2021) was applied with minor modifications. The dried benzoic acids (1 mmol) were taken in a round-bottom flask, and dry dichloromethane was added. Oxalyl chloride (1.2 mmol) was added dropwise to the solution at room temperature with continuous stirring. After the subsequent addition of a catalytic amount of dimethylformamide, stirring was continued for an additional 1 hour during which the gas evolution ceased. Dry triethylamine (2.5 mmol) was added to the mixture using ice cooling. Tryptamine (1 mmol) was added, and stirring was continued for 2-6 hours. The solvent was removed *in vacuo* using by rotary evaporator. After the subsequent addition of ethyl acetate and water, the organic layer was collected. It was then washed with 1N NaOH solution and brine. The organic layer was then dried and evaporated under a rotary. The crude tryptaminamides thus obtained were purified by flash column chromatography. The structure of the pure product was confirmed by ^1H NMR spectroscopy.

Observing *in vitro* anti-inflammatory activity and RBC membrane stabilization

Preparation of red blood cell suspension

Fresh whole human blood (10 mL) was mixed with heparin in a centrifuge tube, and the mixture was centrifuged at 3000 rpm for 10 minutes. The residue was collected by removing the supernatant and subsequently washed with an equal volume of normal saline three times. The residual blood was reconstituted as a 10% v/v RBC suspension with normal saline for subsequent applications.

Observation of stabilization against heat-induced hemolysis

Prevention of heat-induced hemolysis was analyzed by following the reported method (Mahmuda et al., 2020) with minor modifications. Isotonic buffer solution (5 mL each) was taken in centrifuge tubes containing 50, 100, 200, and 400 $\mu\text{g/mL}$ of test drugs, taking 6 sets for each concentration. Tubes having 5 mL of vehicle, no drug, were taken as a negative control. Diclofenac was applied as the reference standard. To each of the centrifuge tubes, there was added 0.05 mL of RBC suspension. After gentle mixing, one set of the various types of tubes was incubated at 54 $^{\circ}\text{C}$ for 20 minutes, and the remaining sets were maintained at 0- 4 $^{\circ}\text{C}$ for 20 minutes. Subsequently, the centrifuge tubes

were cooled, and the reaction mixtures were centrifuged at 3,000 rpm for 3 minutes. The supernatants were taken for measuring absorbance (OD) at 540 nm using an isotonic buffer solution as the blank. Analysis was done by the following two equations -

$$\text{Percentage of hemolysis} = \frac{(OD2-OD1) \times 100}{(OD3-OD1)} \quad (1)$$

Where,

OD1 = absorbance of test sample unheated;

OD2 = absorbance of the test sample heated;

OD3 = absorbance of the control sample heated.

$$\text{Percentage inhibition of hemolysis (\%)} = 100 - \text{hemolysis (\%)} \quad (2)$$

The tryptaminamides were used for the docking studies into the reported binding site of the cyclooxygenase-2 enzyme. The enzyme Protein Data Bank (PDB ID 1PXX) was collected from the internet (www.rcsb.org/structure/1PXX). The original PDB (Kiefer et al., 2003) was reported with reference drug diclofenac docked into the ligand binding site of cyclooxygenase-2 enzyme. The original PDB file was processed to get the separated ligand and receptor for the subsequent docking studies.

In silico analysis with the synthesized compounds

Preparation of the ligand file of the synthesized compounds

The compound structures were drawn using the ChemDraw software. The structures were first converted to the corresponding 3D structure by Chem 3D, and then they were subjected to energy minimization to get the most stable molecular form by using the same software. The structures were subsequently saved as the PDB files. The conversion of PDB format to PDBQT format was done by using the Autodock tools.

Docking of the ligand PDBQT in the receptor PDBQT file

The ligand PDBQT files were then docked into the receptor PDBQT by using the Autodock Vina software (Trott et al., 2010). The output PDBQT files were visualized by using PyMOL. The binding modes with the lowest energy were taken for interaction analysis.

RESULTS AND DISCUSSION

Synthesis of amides from tryptamine and benzoic acid derivatives

Reported similar method (Hoque et al., 2021) was tried for amide coupling between tryptamine and derivatized benzoic acids, as shown in Figure 2. Acids were successfully converted to the corresponding acyl chlorides by the acylating agent, oxalyl chloride. This intermediate was effectively coupled with tryptamine in the presence of TEA as the acid scavenger. However, the crude products obtained from these reactions were purified by flash column chromatography. The overall yields of the compounds ranged from 73-94%.

Characterization data of the synthesized compounds

N-(2-(1*H*-indol-3-yl)ethyl)-2-chloro-5-nitrobenzamide (**SJ-0812**): ¹H NMR (400 MHz, CDCl₃): δ 3.17 (t, *J* = 6.6 Hz, 2H), 3.88 (m, 2H), 6.20 (br s, 1H), 7.13-7.19 (m, 2H), 7.24 (m, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.09 (br s, 1H), 8.18 (m, 2H), 8.42 (m, 1H).

N-(2-(1*H*-indol-3-yl)ethyl)-4-nitrobenzamide (**SJ-0814**): ¹H NMR (400 MHz, CDCl₃): δ 3.15 (t, *J* = 6.5 Hz, 2H), 3.83-3.88 (m, 2H), 6.24 (br s, 1H), 7.11-7.12 (m, 1H), 7.14-7.18 (m, 2H), 7.27 (m, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.80-7.82 (m, 2H), 8.10 (br s, 1H), 8.23-8.25 (m, 2H).

N-(2-(1*H*-indol-3-yl)ethyl)-4-chloro-3-nitrobenzamide (**SJ-0815**): ¹H NMR (400 MHz, CDCl₃): δ 3.14 (t, *J* = 6.5 Hz, 2H), 3.83 (m, 2H), 6.22 (br s, 1H), 7.11 (m, 1H), 7.14-7.18 (m, 1H), 7.24-7.26 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.80-7.83 (m, 1H), 8.11 (m, 2H).

N-(2-(1*H*-indol-3-yl)ethyl)-2-chloro-4-nitrobenzamide (**SJ-0817**): ¹H NMR (400 MHz, CDCl₃): δ 3.14 (t, *J* = 6.5 Hz, 2H), 3.82-3.87 (m, 2H), 5.84 (br s, 1H), 7.13-7.16 (m, 2H), 7.21-7.25 (m, 1H), 7.32-7.40 (m, 2H), 7.56-7.58 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H), 8.08 (br s, 2H).

Biological evaluation of tryptamine derivatives

While considering the inhibition of hemolysis (Figure 3) by SJ0812, there was excellent inhibition of hemolysis. Even at doses of 50 µg/ml, there was 82% stabilization of the cell

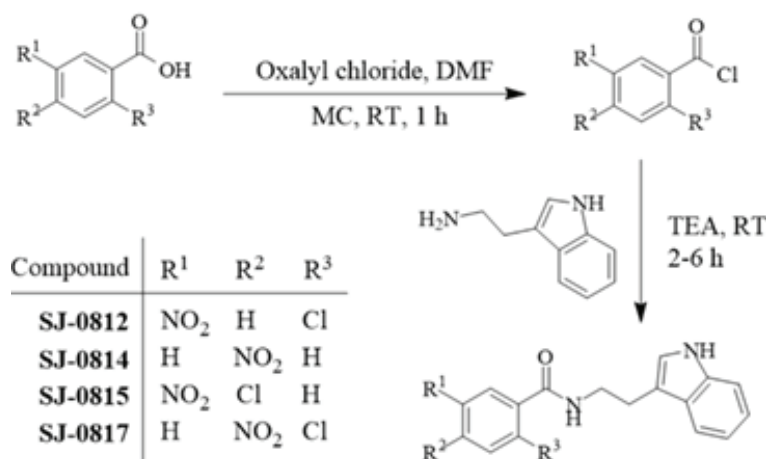


Figure 2: Coupling of tryptamine with derivatized benzoic acids

membrane. At 100, 200, and 400 $\mu\text{g/ml}$ doses, it offered 95%, 99% and 98% stabilization, respectively. Thus, there was dose-dependent stabilization from this synthesized compound.

Compound SJ0814 was found to have a potency slightly lower than that observed from SJ0812. While considering the inhibition of hemolysis by this amide, SJ0814, achieved 75% and 92% inhibition from 50 and 100 $\mu\text{g/ml}$ doses, respectively. While considering relatively higher doses, 200 and 400 $\mu\text{g/ml}$ doses showed 97% and 98% reductions of hemolysis, respectively. Thus, there were dose-dependent anti-inflammatory activities from this synthesized compound, SJ0814. Compound SJ0815 was found to have potency somewhat better than that observed from SJ0814. While considering the inhibition of hemolysis by this amide, SJ0815, there were 87% and 96% inhibitions achieved from 50 and 100 $\mu\text{g/ml}$ doses, respectively. Both the 100 and 200 $\mu\text{g/ml}$ doses offered 96% inhibition. A 400 $\mu\text{g/ml}$ dose also offered 98% reductions of hemolysis. Thus, there were also dose-dependent anti-inflammatory activities from this synthesized compound, SJ0815.

Compound SJ0817 was found to have potency similar to that of SJ0815. While observing the anti-inflammatory potential of this amide, there were 82% and 94% inhibitions achieved from 50 and 100 $\mu\text{g/ml}$ doses, respectively. Both the 200 and 400 $\mu\text{g/ml}$ doses offered nearly 100% inhibition in this study. There were also dose-dependent anti-inflammatory activities from this tryptaminamide, SJ0817. The activities obtained from the tryptaminamides were comparable with those observed from the standard, diclofenac, as shown in Figure 3.

***In silico* analysis for the binding pattern**

Docking analysis was done by using the Autodock Vina software published by The Scripps Research Institute.

Based on the observations from the biological evaluations, the most potent compound, SJ0817, was taken for this *in silico* investigation. A comparison was made of the orientation of SJ0817 with that of diclofenac. Among the various modes found, the orientation having the lowest energy was considered for detailed studies. As shown in Figure 4, the synthesized compound, SJ0817, was taking the position comparable to that of standard diclofenac as reported earlier. The most vital roles were played by the residues like ARG120, PHE381, TYR385, TRP387, LEU352, TYR355, VAL349, SER530, VAL344, etc. The orientation has been shown in two different views here.

The biological activity revealed that the synthesized tryptamine derivatives have good potential as anti-inflammatory agents, since all of the synthesized compounds have very high inhibitory activity against hemolysis. So, the orientation of SJ0817 has been analyzed to find out the necessary modifications to be made in the future. As shown in Figure 5, the indole NH is close to a gap G1, being in the vicinity of non-polar PHE518 and TRP387 residues on one side and polar GLY526 residue on the other side. Thus, there seems to be scope to derivatize this indole NH for further exploration in this regard. Again, the benzamide moiety took a site surrounded by LEU359, VAL116, LEU117, and ILE345. As per observation from this docking, these non-polar moieties created a gap, G2, close to the benzene ring of SJ0817. Thus, additional groups can be thought for this position. Further substituents can be better considered to observe the structure-activity relationship.

The biological activity, along with the docking results, has further been analyzed by applying the LigPlot⁺ (Raghvendra et al., 2023) to observe the possible hydrogen bonds with the binding pocket of the receptor (Figure 6).

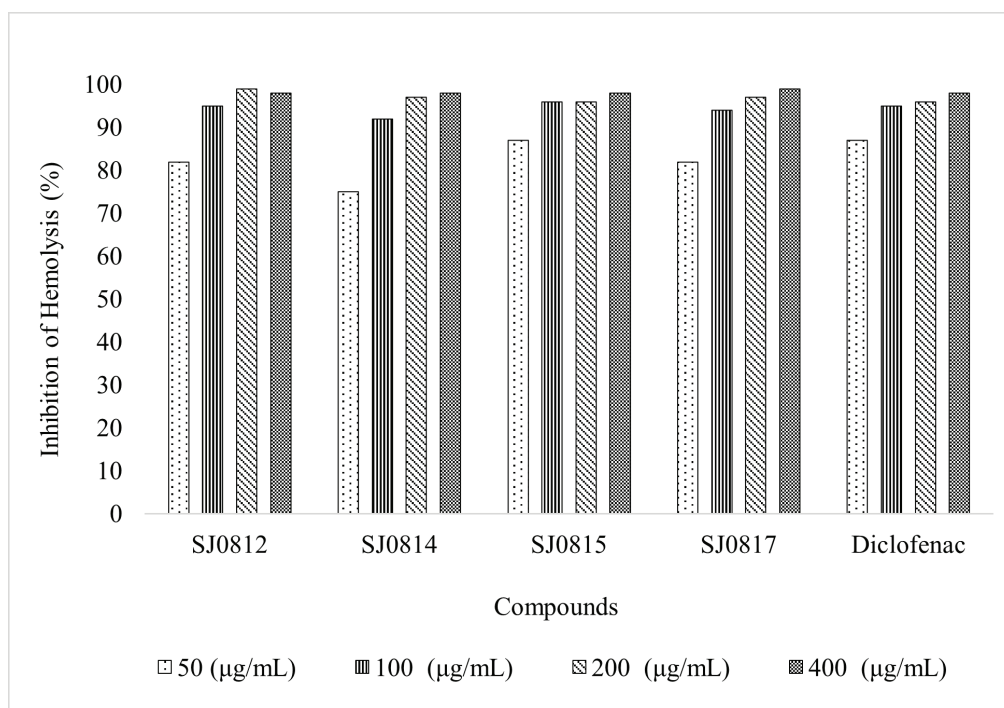


Figure 3: Inhibition (%) of hemolysis by the synthesized compounds (SJ0812, SJ0814, SJ0815, SJ0817) and diclofenac at various doses

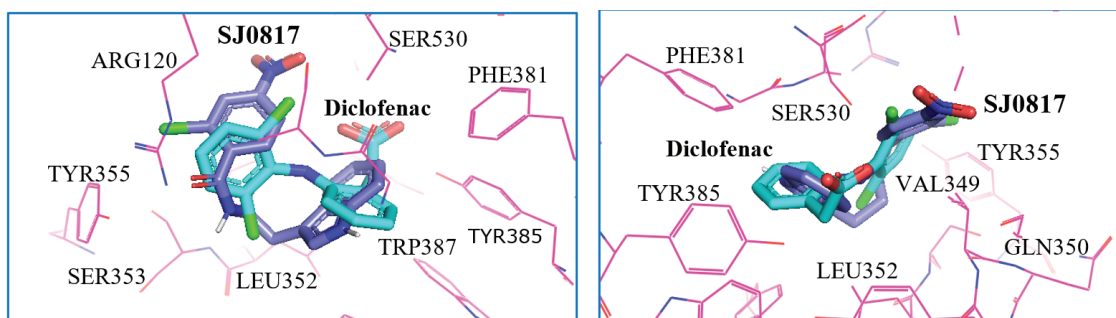


Figure 4: Orientation of SJ0817 and diclofenac in the binding site of the COX enzyme (Two views)

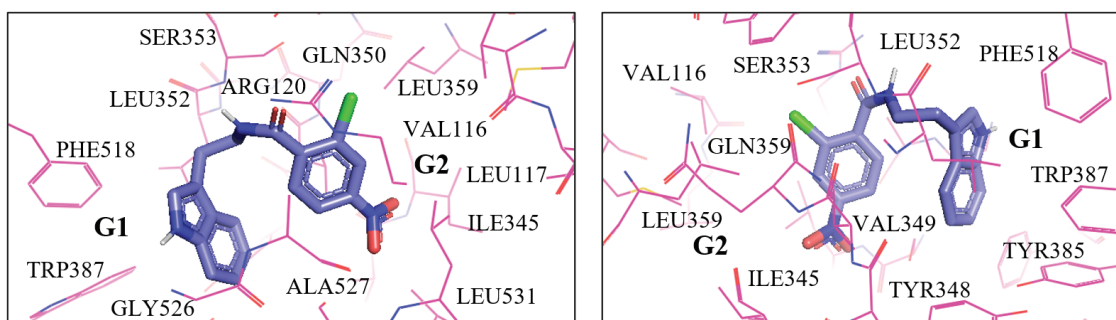


Figure 5: Important residues for binding SJ0817 in the binding site of the COX enzyme

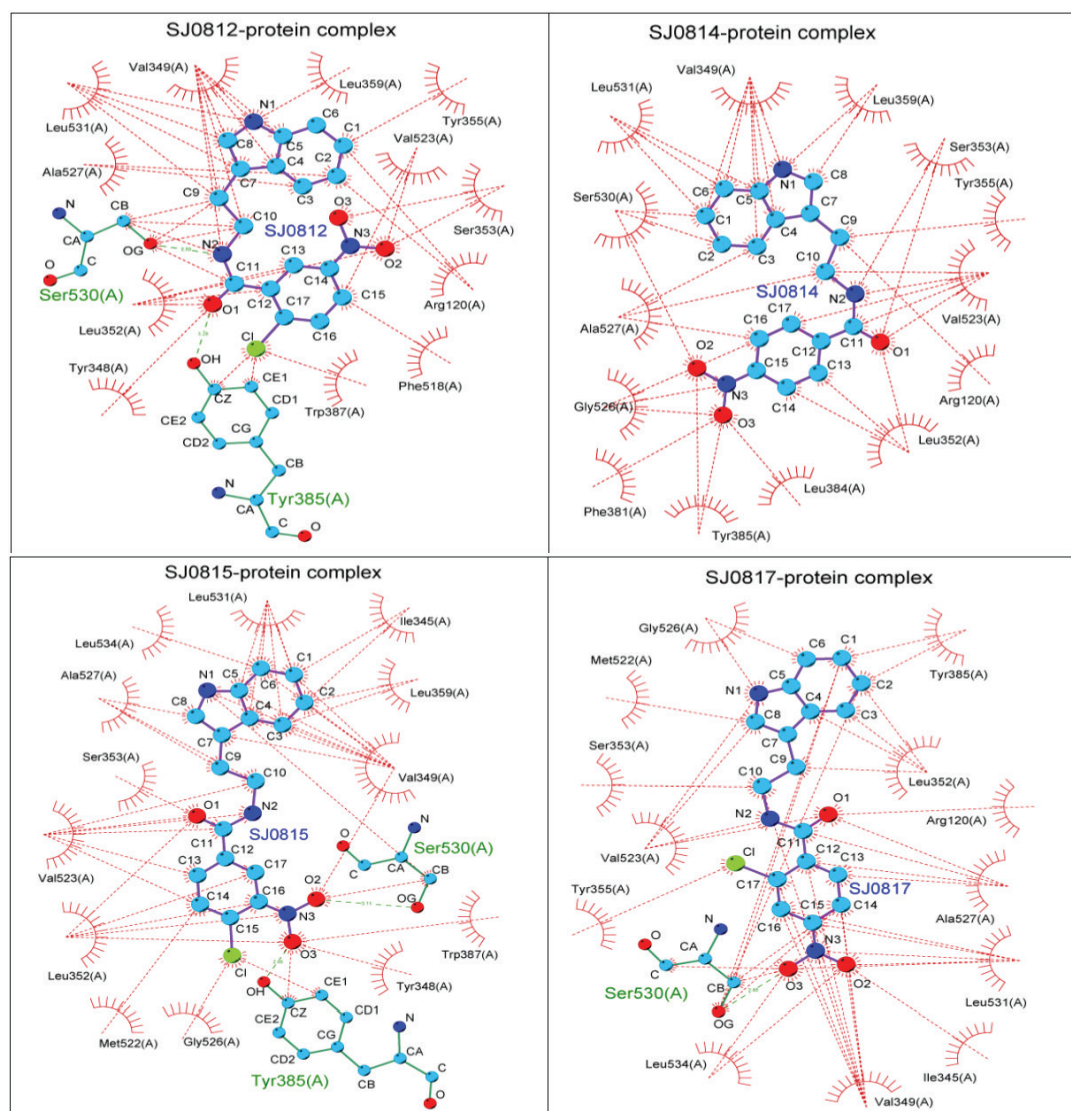


Figure 6: LigPlots obtained from the docking results of the synthesized compounds

As shown in Figure 6, compound SJ0812 has the potential for forming a hydrogen bond with SER530 and TYR385; however, compound SJ0814 does not have the potential for this option. This may result in the comparatively reduced anti-inflammatory potential compared to the former. Similarly, compound SJ0815 shows hydrogen bonding with SER530 and TYR385, whereas compound SJ0817 shows a hydrogen bond with only SER530 residue. These compounds were also relatively more potent than SJ0814, as shown in Figure 3.

CONCLUSIONS

The tryptaminamides exhibit promising potency in inhibiting hemolysis, indicating the strong membrane-stabilizing potential of this novel scaffold. This property is particularly relevant for chronic inflammatory disorders, as mast cell stabilization is a key strategy for preventing long-term inflammation. Furthermore, since this scaffold is an amide rather than the corresponding acid, its successful development could provide a better-tolerated option for long-term management of inflammatory conditions. Therefore, further studies are warranted to derivatize this scaffold and conduct a comprehensive structure–activity relationship (SAR) analysis of this pharmacophore.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Conceptualization and design of the project: **S.B.**; Synthesis, workup, and purification: **S.B.**, **M.M.H.**; Biological data collection, data processing: **M.M.H.**, **M.T.I.**, **Z.A.T.**; Characterization: **S.B.**, **S.R.R.**; Preparation of Manuscript: **S.B.** All of the authors read and approved the final version of the manuscript.

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