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Original Article

Synthesis, Anti-inflammatory and *in silico* Studies of few novel 1,2,4-Triazole Derived Schiff Base Compounds

Deepanshu Vishwakarma, Surya Prakash Gupta*

Rajiv Gandhi Institute of Pharmacy, Faculty of Pharmaceutical Science and Technology, AKS University, Satna, Madhya Pradesh, INDIA.

ABSTRACT

Background: Every year more than 1 billion prescriptions are written for all NSAIDs and yet the quest to develop new NSAIDs remains prominent. **Objectives:** The current investigation's goal was to synthesize and assess the anti-inflammatory potential of a few more recent 1,2,4-triazole derivatives. **Materials and Methods:** The synthesis of the 1,2,4-triazole compounds (SPG_{1-5}) was accomplished in three distinct steps involving formation of hydrazide of ibuprofen and followed by cyclization to 1,2,4-triazole nucleus and ultimately formation of Schiff's base in the final step. **Results:** Each compound was dark brown in color and were obtained in 65-71% yields and was insoluble in water and hexane whereas SPG_2 and SPG_3 were soluble in methanol and all compounds were soluble in chloroform. The compounds were evaluated for *in vitro* anti-inflammatory potential utilizing albumin denaturation and inhibition of protease action methods. With SPG4 having the best ability to produce the inhibition (62.44±2.889%) at a concentration of 500 g/mL, all the substances showed dosage-dependent inhibition of albumin denaturation. SPG4 was able to inhibit protease activity (46.63±3.211%) at 500 g/mL and the antiprotease efficacy was also dosage-dependent. **Conclusion:** It was evident that the triazole derivatives were able to display moderate anti-inflammatory action and could be optimized to develop lead molecule.

Keywords Triazole, Antiprotease, Anti-inflammatory, Albumin, *in silico*, *in vitro*.

Correspondence:
Dr. Surya Prakash Gupta
Professor and Director, Rajiv Gandhi Institute of Pharmacy, Faculty of Pharmaceutical Science and Technology, AKS University, Satna, Madhya Pradesh, INDIA.
Email: suryatony@yahoo.co.in

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INTRODUCTION

Nonsteroidal Anti-Inflammatory Medicines (NSAIDs) are a wide range of substances that are used to treat acute pain issues like headaches, postoperative pain and orthopaedic fractures as well as inflammatory, chronic and acute pain conditions like rheumatoid arthritis, osteoarthritis and gout. For all NSAIDs combined, more than 1 billion prescriptions are written annually. However, issues with Cardiovascular (CV) events and the possibility of major, perhaps fatal GI bleeding continue to be raised regarding the safety and tolerability of NSAIDs. It is generally known that there is a danger of significant NSAID-related adverse effects on the GI tract, cardiovascular system, kidneys and liver. In the last ten years, a PubMed search for the phrase "synthesis of anti-inflammatory agents" produced 83007 results.

The control of inflammation and pain is a growingly complicated medical issue. Primary care doctors must be able to offer therapeutic alternatives with good efficacy while posing the fewest safety and tolerability issues. NSAIDs are extensively used and very effective for treating pain. Concerns, however, still exist regarding the safety and tolerability of this class of medication.

In order to reduce the safety and tolerability concerns associated with the currently available NSAIDs while maintaining efficacy in managing inflammation and pain, it is necessary to create novel and effective NSAIDs.

Triazole, also referred to as pyrodiazole, belongs to the group of organic heterocyclic compounds with a five-member di-unsaturated ring structure consisting of two non-adjacent carbon atoms with three nitrogen atom.[1] Several clinically used drugs like Fluconazole (anti-fungal), Ribavirin (anti-viral), Anastrozole (anti-cancer), Alprazolam (CNS depressant), Rizatriptan (anti-migraine), Trazodone (anti-depressant) and Trapidil (anti-hypertensive) are found to contain triazoles.[2] A number of reports related to synthesis of various triazole derivatives with pharmacological potential has been found in the past decade.[3-7] 1,2,4-Triazoles are reportedly said to possess several pharmacological actions along with weak to good anti-inflammatory.[8,9] Hence in the present study it has been attempted to synthesize a few 1,2,4-triazole based compounds and assess their anti-inflammatory action.

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MATERIALS AND METHODS

Materials

Ibuprofen was purchased from Yarrow Pharmaceuticals. Hydrazine hydrate, carbon disulfide, aromatic aldehydes, ethanol, methanol, hexane, ethyl acetate and other reagents were procured from Loba, CDH, oxford, sigma and rankem. The glassware used during the study were of borosilicate grade and were cleaned using chromic acid cleaning mixture, rinsed with purified water and dried in hot air oven before use. Using an electrically heated melting point instrument, the melting point were observed using the open capillary technique and are uncorrected.

Synthesis of 1,2,4-triazoles

The multistep reaction scheme for synthesizing the target compounds was adapted from schemes reported by Kumari *et al.*,[6] Singh *et al.*[10] and Ledeti *et al.*[11] (Scheme 1).

Synthesis of 2-(4-isobutylphenyl)propanehydrazide from ibuprofen

In a round bottom flask, ibuprofen (0.05 mol), ethanol (75 mL) and concentrated sulfuric acid (0.5 mL) were refluxed for about 10 hr before being cooled to 5°C. By extracting with ether and separating the liquid product based on density from the reaction mixture, it was then purified. Hydrazine hydrate (0.10 mol) was added in the solution of the aforementioned product (0.05 mol) in absolute ethanol (30 mL) and refluxed for 6 hr. After cooling the solution, the separated solid precipitate was removed by filtration and recrystallized using ethanol.

Synthesis of 4-amino-5-(1-(4-isobutylphenyl) ethyl)-4H-1,2,4-triazole-3-thiol

The first step's hydrazide (0.05 mol) was dissolved in a potassium hydroxide (0.10 mol) in ethanol (30 mL) solution before being slowly mixed with (0.01 mol) carbon disulfide. The reaction mix was refluxed for 10-12 hr, allowed to cool at room temperature, followed by addition of hydrochloric acid to neutralise the resultant solution. To get the thione intermediate, the separated material was filtered, rinsed using ethanol, dried and recrystallized using ethanol. The thione intermediate and hydrazine hydrate were dissolved in 30 cc of ethanol and heated over reflux for 3 hr before being placed into ice. The 1,2,4-triazole-3-thiol was obtained by filtering, washing and recrystallizing the final product from the ethanol.

General method for synthesis of (Z)-4-(benzylideneamino)-5-(1-(4-isobutylphenyl) ethyl)-4H-1,2,4-triazole-3-thiol

Following the addition of a few drops of sulphuric acid, the reaction mixture of 1,2,4-triazole-3-thiol (0.01 mol) and different aromatic aldehydes (0.01 mol) in ethanol was allowed to heat under reflux conditions for the proper amount of time. By using thin layer chromatography, the reaction was tracked. After the reaction was finished, the result was placed onto ice and filtered, followed by a wash, before the solid contents were gathered and recrystallized using the ethanol.

(Z)-4-(benzylideneamino)-5-(1-(4-isobutylphenyl) ethyl)-4H-1,2,4-triazole-3-thiol, SPG_1

Color: Dark Yellow; IR (KBr, cm^{-1}): 3164 (aromatic C-H str.), 1595, 1505, 1399 (C=C ring str.), 1651 (C=N), 1013 (N-N), 689 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 8.10 (C-H, Imine), 7.21-7.23(Ar-H), 4.21 (C-H, methelene); 3.53 (S-H), 2.6 (C-H, methylene), 0.81 (C-H, methyl); ^{13}CNMR ($CDCl_3$, δ ppm): 150.77 (C-H, imine), 148.52, 145.02 (C-H, 1,2,4-triazole), 133.75 - 102.27 (C-H, benzene), 61.15-26.79 (C-H, aliphatic);Mass (m/e): 366.5; CHN (%): 70.41, 5.03, 15.35.

(Z)-4-((3-(1-(4-isobutylphenyl)ethyl)-5-mercapto-4H-1,2,4-triazol-4-ylimino)methyl)phenol, SPG_2

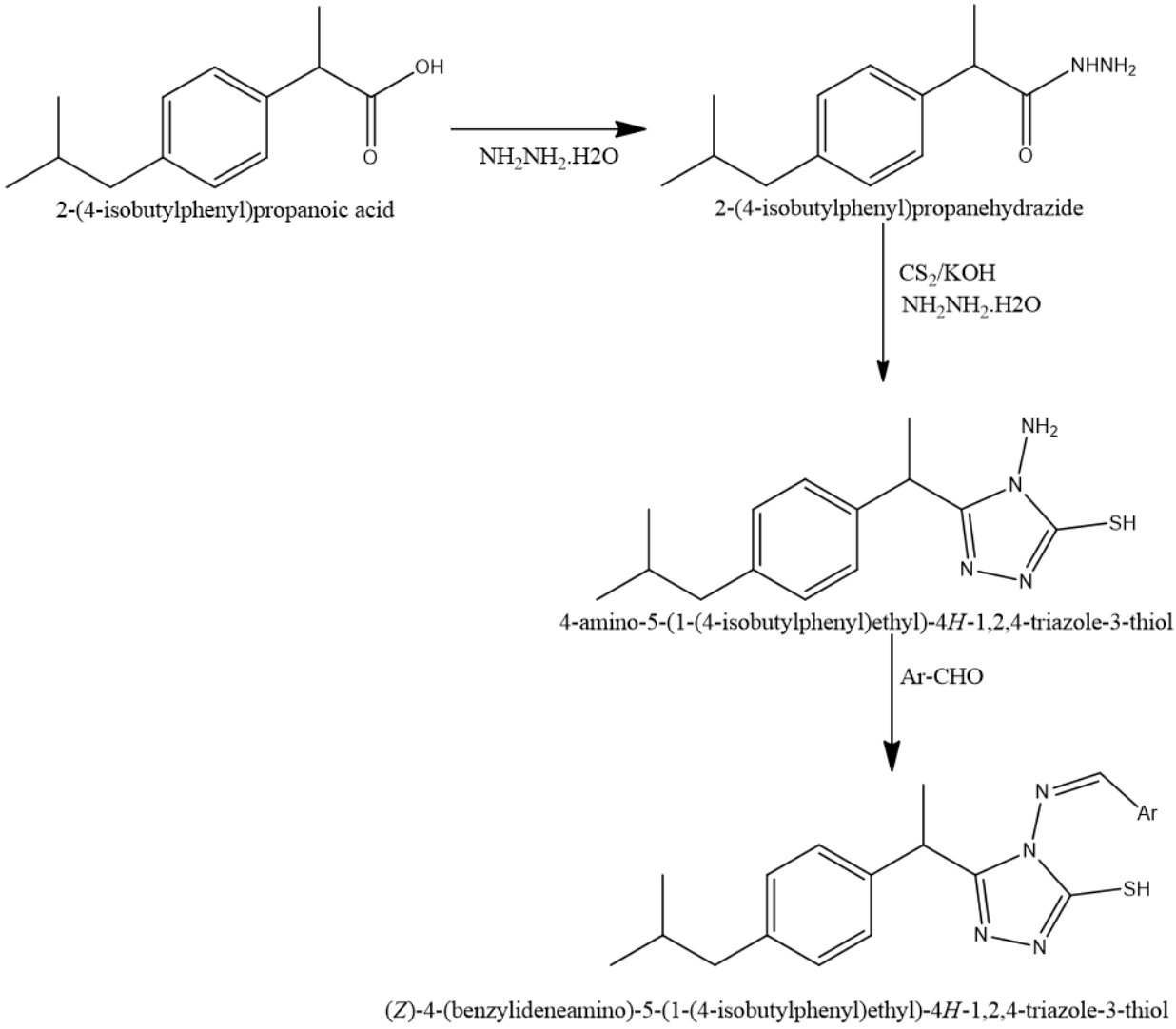
Color: Dark Yellow; IR (KBr, cm^{-1}): 3420 (Ar-OH), 3161 (aromatic C-H str.), 1657 (C=N), 1591, 1485, 1403 (C=C ring str.), 640 (C-S-C), 1063 (N-N); ^{1}H NMR ($CDCl_3$, δ ppm): 8.09 (C-H, Imine), 6.63-7.67 (Ar-H), 4.21 (C-H, methelene); 3.53 (S-H), 2.6 (C-H, methylene), 0.81 (C-H, methyl); ^{13}CNMR ($CDCl_3$, δ ppm): 150.23(C-H, imine), 148.18, 145.57 (C-H, 1,2,4-triazole), 133.53 - 102.19 (C-H, benzene), 61.28-23.26 (C-H, aliphatic);Mass (m/e): 381.6; CHN (%): 37.03, 5.95, 14.62.

(Z)-4-(4-chlorobenzylideneamino)-5-(1-(4-isobutylphenyl)ethyl)-4H-1,2,4-triazole-3-thiol, SPG_3

Color: Dark Yellow; IR (KBr, cm^{-1}): 3082 (aromatic C-H str.), 1597, 1520, 1412 (C=C ring str.), 1687 (C=N), 969 (Ar-Cl), 1054 (N-N), 673 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 8.14 (C-H, Imine), 7.29-7.63 (Ar-H), 4.21 (C-H, methelene); 3.53 (S-H), 2.6 (C-H, methylene), 0.81 (C-H, methyl); ^{13}CNMR ($CDCl_3$, δ ppm): 157.63 (C-H, imine), 147.25, 143.54 (C-H, 1,2,4-triazole), 135.75 - 101.19 (C-H, benzene), 61.15-26.79 (C-H, aliphatic);Mass (m/e): 399.1; CHN (%): 62.87, 5.82, 14.95.

(Z)-4-(4-nitrobenzylideneamino)-5-(1-(4-isobutylphenyl)ethyl)-4H-1,2,4-triazole-3-thiol, SPG_4

Color: Dark Yellow; IR (KBr, cm^{-1}): 3084 (aromatic C-H str.), 1683 (C=N), 1599, 1521, 1472 (C=C ring str.), 1341 (Ar-NO_2), 1049 (N-N), 663 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 8.06 (C-H, Imine), 7.24-7.64, Ar-H), 4.21 (C-H, methelene); 3.53 (S-H), 2.6 (C-H, methylene), 0.81 (C-H, methyl); ^{13}CNMR ($CDCl_3$, δ ppm): 151.53 (C-H, imine), 149.13, 144.81 (C-H, 1,2,4-triazole), 137.29 - 102.27 (C-H, benzene), 61.15-26.79 (C-H, aliphatic);Mass (m/e): 409.6; CHN (%): 62.01, 5.58, 17.21.



Scheme 1: Synthetic pathway for 4H-1,2,4-triazole-3-thiol compounds.

(Z)-4-(4-bromobenzylideneamino)-5-(1-(4-isobutylphenyl)ethyl)-4H-1,2,4-triazole-3-thiol, SPG_5

Color: Dark Yellow; IR (KBr, cm^{-1}): 3087 (aromatic C-H str.), 1688 (C=N), 1599, 1521, 1472 (C=C ring str.), 1344 (Ar-NO_2), 1053 (N-N), 665 (C-S); ^{1}H NMR ($CHCl_3$, δ ppm): 8.11 (C-H, Imine), 7.21-7.65 Ar-H), 4.21 (C-H, methelene); 3.53 (S-H), 2.6 (C-H, methylene), 0.81 (C-H, methyl); ^{13}CNMR ($CDCl_3$, δ ppm): 153.26 (C-H, imine), 148.52, 145.02 (C-H, 1,2,4-triazole), 135.26-102.27 (C-H, benzene), 61.15-26.79 (C-H, aliphatic);Mass (m/e): 443.1; CHN (%): 59.21, 4.26, 13.13.

Anti-inflammatory Study

Inhibition of albumin denaturation[14,15]

Each of the synthesized compounds was dispersed in DMSO before being properly diluted to provide solutions with strength of 100, 200, 300, 400 and 500 g/mL. For the test, 1% BSA solution in deionized water was made.

A total of 2000 mL of PBS, 2000 mL of BSA and 1000 mL of the SPG_{1-5} solutions were positioned in the reaction vessel. Pure water was utilised in the negative control vessels in place of the test solution, whereas the positive control vessels were filled with an ibuprofen solution (1 g/mL).

The reaction mixtures were heated for 5 min at 70°C after 15 min of incubation at 37°C. After the mixes had cooled to room temperature, each vessel's constituent absorbance was observed at 660 nm with the aid of a UV-visible spectrometer. The following formula was used to determine the % denaturation of albumin that was inhibited:

$$\% \text{ Denaturation inhibition} = (1\text{-}D/C) \times 100\%$$

Where C is the absorbance measurement without the sample (the negative control) and D is the absorbance value of the sample solution.

Antiprotease action method[16,17]

For the test, 0.12 mg of trypsin, 2 mL of 20 mM pH 7.0 Tris-HCl buffer and 2 mL of test sample at various strengths (100-500 g/mL) were combined to create the reaction component. 2 mL of a 0.8% w/v aqueous solution of casein was added after the reaction component had been kept for incubation at 37°C for 5 min. Additionally, the incubation of the reaction component was carried out for 20 min. 4 mL of 70% perchloric acid was flown down to the mixture to halt the process. After centrifuging the turbid suspension produced by the reaction, the supernatant was collected and the absorbance was observed at 210 nm using buffer as a blank. The following formula was used to compute the protease inhibitory activity's % inhibition:

Percentage inhibition = (Abs control-Abs Sample) × 100/ Abs control

Statistical Analysis

The results of each experiment were obtained in triplicate and they are shown as mean along with the standard deviation. Using Graph Pad Instat software, a one-way ANOVA was used to analyse the differences between the experimental groups, followed by a Dunnet's multiple comparison test.

RESULTS AND DISCUSSION

Chemistry

The triazoles represent a class of heterocyclic compounds with vivid variety of pharmacological potential. The synthesis of the 1,2,4-triazole compounds (SPG_{1-5}) was accomplished in three distinct steps involving formation of hydrazide of ibuprofen and followed by cyclization to 1,2,4-triazole nucleus and ultimately formation of Schiff's base in the final step. The physicochemical characteristics were evaluated and the spectral characters of the compounds were studied.[18,19]

The Schiff's base formation occurs via nucleophilic attack of the amine nitrogen to the electrophilic carbonyl carbon of the aldehyde. This leaves the nitrogen deprotonated, with the NH electrons pushing the away the oxygen atom from the carbonyl group leading to the formation of an imine bond (C=N). A molecule of water is being displaced during this process.

The melting point and yield of the synthesized Schiff bases is presented in Table 1. The yield of the compounds was calculated on the basis of the dry weight of the final product and the theoretical yield that could be obtained for the reaction. The retention factor value (R_f) was calculated as the ratio of the distance travelled by the sample to the distance travelled by the solvent in the selected solvent system for TLC. All the synthesized compounds were soluble in methanol and chloroform.

All the synthesized Schiff bases compounds exhibited stretching and bending peaks of the functional groups present. N-N (1000-1100 cm^{-1}), C-S (600-700 cm^{-1}), aromatic C-H (3000-3200 cm^{-1}) were found in the compounds. The vibrations of O-H (3300-3500 cm^{-1}), C-O (1670-1340 cm^{-1}), C-N stretching

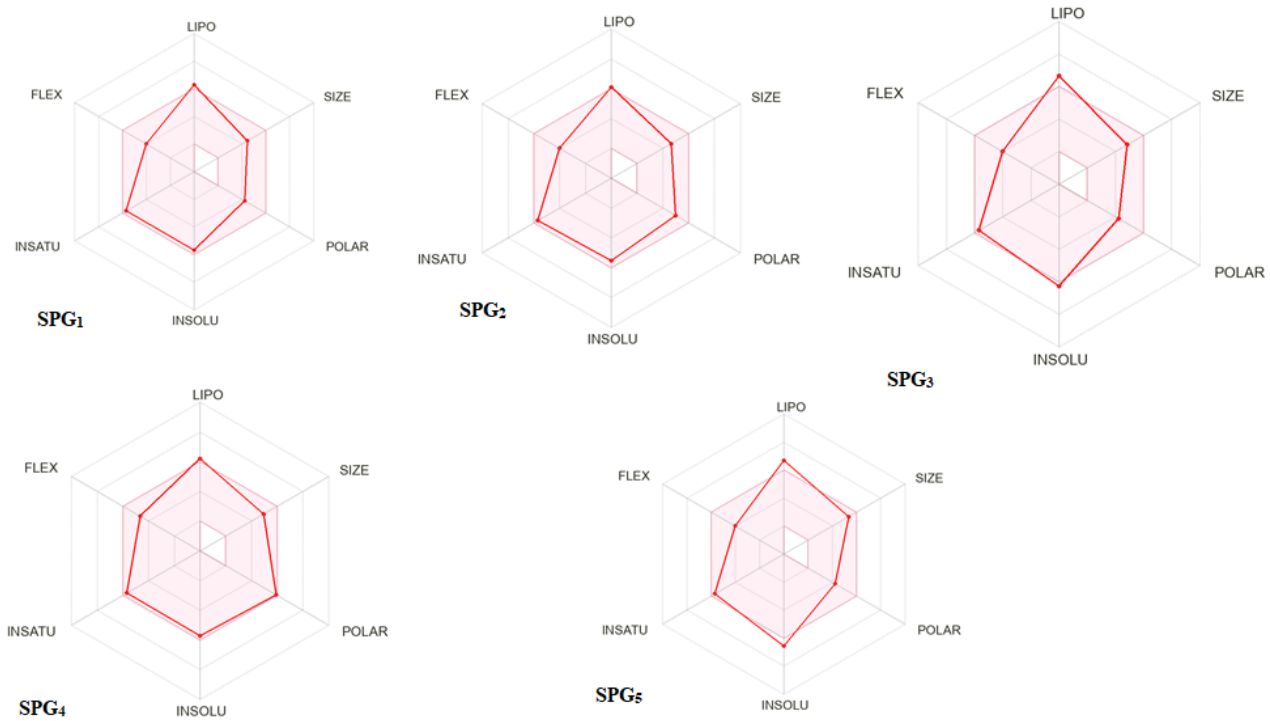


Figure 1: Bioavailability radar for SPG_{1-5}.

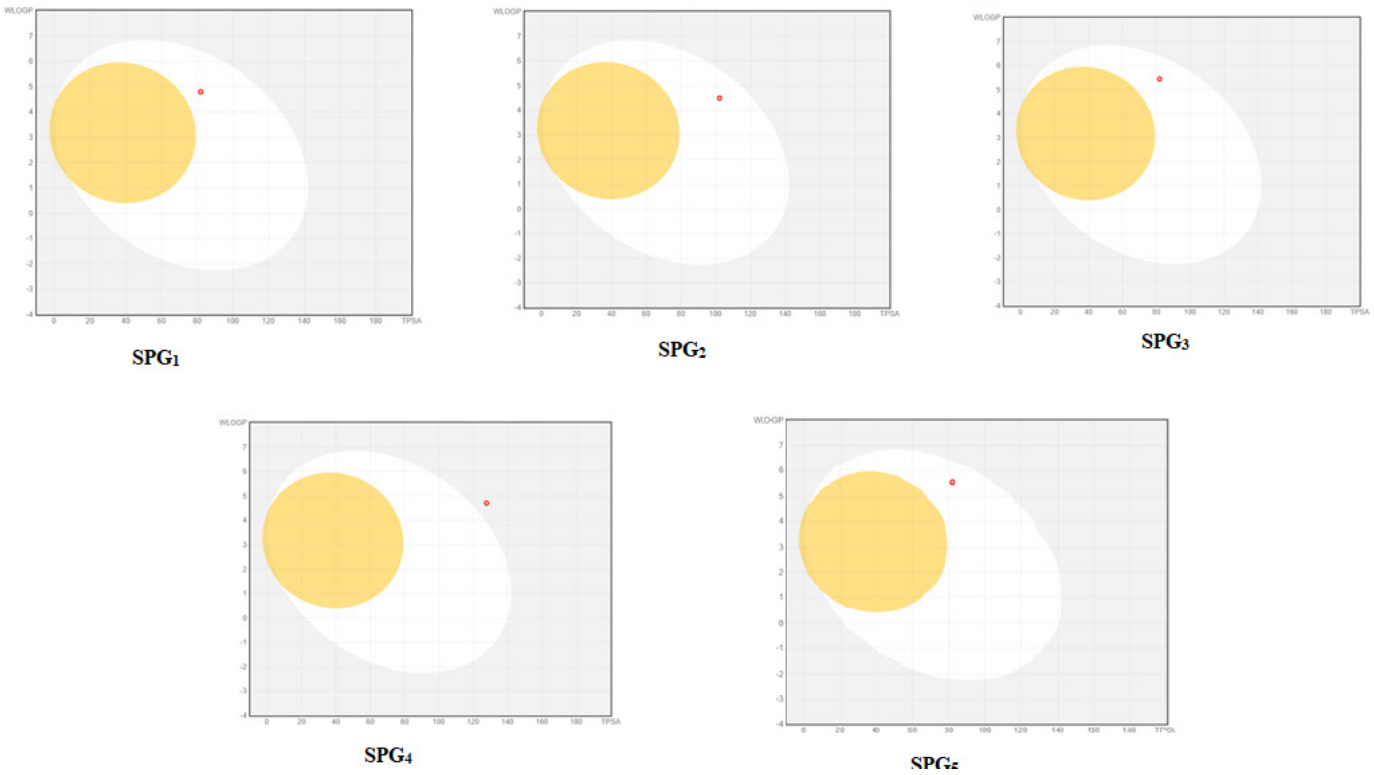
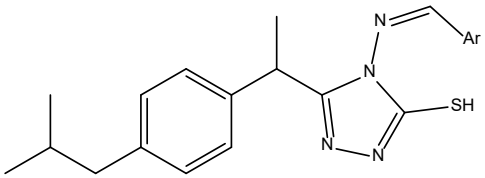


Figure 2: BOILED-Egg for SPG_{1-5}.

Table 1: Physicochemical data of SPG_{1-5}.



Compound	Ar	Molecular Formula	Rf value	Yield (%)	Melting Point (°C)
SPG_1	Benzaldehyde	$C_{21}H_{24}N_4S$	0.57	69.3	220-223
SPG_2	4-hydroxy benzaldehyde	$C_{21}H_{24}N_4OS$	0.53	65.2	210-212
SPG_3	4-chloro benzaldehyde	$C_{21}H_{23}ClN_4S$	0.61	70.1	208-211
SPG_4	4-nitro benzaldehyde	$C_{21}H_{23}N_5O_2S$	0.66	69.7	192-194
SPG_5	4-bromo benzaldehyde	$C_{21}H_{23}BrN_4S$	0.62	70.1	196-199

(1215-1260 cm^{-1}) and C-Cl and C-Br (820-850 cm^{-1}) were also found in the compounds having these functional groups.

The ^{1}HNMR spectra of the compounds displayed chemical shift in region of 6.6-7.9 corresponding to aromatic CH and 8.1-8.2 corresponding to the imine hydrogen (N=CH) in all the compounds. The chemical shifts corresponding to the protons of thiol (S-H), methyl and methylene were also present in all the compounds. The mass spectra of the compounds were found to contain peaks due to fragmentation of the molecules. All the compounds presented a distinct and prominent molecular ion peak along with isotopic peaks.

Anti-inflammatory action

The anti-inflammatory action of the synthesized Schiff bases was assessed using two of the well-established *in vitro* methods viz., antiprotease activity and inhibition of albumin denaturation. The results are presented in Tables 2 and 3 respectively.

Protein denaturation has a strong link to the onset of inflammation and can cause a number of inflammatory disorders, including arthritis. It has been suggested that tissue damage may result from denaturing the proteins that make up cells or intercellular material. As a result, the test compounds' capacity to prevent protein denaturation indicates that they have a clear potential for anti-inflammatory effect.

Table 2: Inhibition of albumin denaturation by SPG_{1-5}.

Treatment	Inhibition of albumin denaturation (%)					
	100 µg/mL	200 µg/mL	300 µg/mL	400 µg/mL	500 µg/mL	10 µg/mL
SPG1	5.5±0.291	11.1±1.156	21.3±1.194	29.5±2.167	37.1±3.869	ND
SPG2	4.19±1.163	9.24±1.196	17.06±1.695	21.37±2.068	29.06±3.162	ND
SPG3	9.01±1.659	19.18±2.617	30.68±3.415	42.11±3.306	51.33±4.219***	ND
SPG4	13.31±2.165	23.35±2.314	33.21±3.182	50.27±3.092	62.44±2.889***	ND
SPG5	9.22±2.002	13.97±2.099	24.51±2.228	34.29±2.069	41.48±3.754	ND
Ibuprofen	ND	ND	ND	ND	ND	51.63±4.316***

ND-Not Determined; n=5; Values are Mean±SD, p<0.001.

Table 3: Percent inhibition of protease action by SPG_{1-5}.

Treatment	Inhibition of Protease Activity (%)					
	10 µg/mL	100 µg/mL	200 µg/mL	300 µg/mL	400 µg/mL	500 µg/mL
Ibuprofen	51.53±2.086***	ND	ND	ND	ND	ND
SPG1	ND	4.18±0.911	7.14±0.833	11.57±1.011	19.91±1.633	23.35±2.033
SPG2	ND	3.85±0.899	7.01±1.033	10.43±1.066	14.08±1.066	19.18±1.523
SPG3	ND	6.36±1.333	13.44±0.933	18.11±2.066	22.51±1.333	33.29±3.011
SPG4	ND	8.83±1.033	15.04±1.168	20.98±2.011	33.72±2.333	46.63±3.211***
SPG5	ND	5.04±0.933	8.77±0.666	13.54±1.033	18.82±2.011	26.37±2.988

ND-Not Determined; n=5; Values are Mean±SD, p<0.001.

Table 4: Bioavailability features of SPG_{1-5}.

Property	SPG_1	SPG_2	SPG_3	SPG_4	SPG_5
Log P	4.81	4.36	5.8	4.03	5.35
H-bond acceptors	03	04	03	05	03
H-bond donors	00	01	0	00	00
Drug likeliness	Yes, 1 violation	Yes, 0 violation	Yes, 1 violation	Yes, 0 violation	Yes, 1 violation

According to other reports, leukocyte proteases play a substantial role in the progression of tissue damage throughout inflammatory reactions and protease inhibitors may offer a significant degree of protection. Thus, the fact that test substances reduce protease activity indicates their function as anti-inflammatory agents.

The primary scaffold present in all the compounds was identical to the structure of NSAID ibuprofen, as it was utilized as the starting reagent for preparation of the molecules. This was envisioned to be helpful in obtaining anti-inflammatory action in the compounds. All of the Schiff base derivatives presented dose-dependent inhibition in albumin denaturation, with SPG4 having the strongest ability to do so at a concentration of 500 g/mL (62.442.889%). SPG4 was able to decrease the activity of proteases by 46.633.211% at 500 g/mL due to the dose dependence of the antiprotease action. The type of substitution on the aromatic ring attached to the imine carbon played vital role in the activity of the compounds. It was evident from the results that the higher the electron withdrawing ability of the substitution attached on this ring, the better was the anti-inflammatory activity of the compound. The order of activity was SPG_4>SPG_3>SPG_5>SPG_1>SPG_2.

In silico study

The pharmacokinetic features affect drug likeliness and oral bioavailability of molecules. Some important features predicted using SwissADME online program are presented in the Table 4.

The bioavailability radar and BOILED-Egg for the synthesized compounds is presented in Figures 1 and 2.

The colored zone in the pharmacokinetic radar depicts the suitable physicochemical space for oral bioavailability of the molecules. It was predicted from the *in silico* study that all the molecules possessed oral bioavailability and were suitable to be drug like with either 0 or 1 violation from the Lipinski's rule of five for drug likeliness.

Any point located in the yolk of the BOILED-Egg are considered to be molecules that might be passively permeated through the blood brain barrier. On the other hand any point located in the

yolk of the BOILED-Egg are considered to be molecules that might be passively absorbed by the gastrointestinal tract whereas point outside the Egg represents that the molecule is neither absorbed nor brain penetrant.[20] Figures 1 and 2 reveal that all the synthesized molecule were having sufficient oral bioavailability and neither of them possessed the ability to cross the blood brain barrier.

CONCLUSION

The objective of the present investigation was to develop newer anti-inflammatory molecules based on 1,2,4-triazole moiety. The compounds possessed sufficient oral bioavailability to be drug like. The anti-inflammatory action was affected by the electron withdrawing tendency of the substituents. To conclude, it was evident that the presence of triazole nucleus along the isobutylphenyl and imine substitution was able to display moderate anti-inflammatory action and could be optimized to develop lead molecule.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

^{1}H-NMR: Proton Nuclear Magnetic Resonance; **BSA:** Bovine Serum Albumin; **IR:** Infra red; **R_f:** Retention factor; **PBS:** Phosphate buffer saline.

SUMMARY

Nonsteroidal anti-inflammatory medicines (NSAIDs) are widely used to treat acute pain issues, including headaches, postoperative pain, and osteopaedic fractures. However, concerns about cardiovascular events and potential fatal gastrointestinal bleeding persist. To reduce safety and tolerability concerns, novel and effective NSAIDs are needed. Triazoles, also known as pyrodiazole, are organic heterocyclic compounds with a five-membered di-unsaturated ring structure. Several clinically used drugs contain triazoles, and a study has attempted to synthesize 1,2,4-triazole-based compounds and evaluate their anti-inflammatory activity.

The multistep reaction scheme for synthesizing the target compounds was adapted from previous studies. The first step involved refluxing ibuprofen with ethanol and concentrated sulfuric acid, then adding hydrazine hydrate and carbon disulfide to the reaction mixture. The second step involved dissolved hydrazide in potassium hydroxide and carbon disulfide, refluxing for 10-12 hours, and then neutralizing the result. The resulting compounds were then analyzed for their anti-inflammatory activity. This study aims to provide therapeutic alternatives with good efficacy while minimizing safety and tolerability concerns.

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