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# Synthesis, molecular docking and anti-inflammatory potential of novel hydrazones of eugenol in tuberculosis treatment

Sachin H Rohane*[a], Vivekkumar K Redasani[a], Neeraj Kumar Fuloria[b] & Shivkanya Fuloria[b]

[a] YSPM YTC, Faculty of Pharmacy, Satara 415 011, Maharashtra, India

[b] Faculty of Pharmacy, AIMST University, Semeling, Bedong, Kedah 08100, Malaysia

E-mail: sachinrohane29@gmail.com

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The hydrazone derivatives of eugenol have been designed and synthesized *via* esterification, hydrazination and treatment with different aldehydes or ketones. All these compounds have been docked with 4COX and 3LN1 (COX-2 enzymes) using Schrodinger v7.4. The compounds have been characterized by IR, $^{1}$H NMR and LCMS. The compounds have been evaluated for their anti-inflammatory potential using *in vivo* carrageenan induced rat hind paw method and *in vitro* protein denaturation. The study reveals that most compounds have significant anti-inflammatory activity. Tested compounds as per literature prove that they show antitubercular activity. Among tested compounds, compounds **4**, **34**, **37** and **42** exhibit the highest anti-inflammatory activity. The present study shows that anti-inflammatory activity of the novel hydrazone derivatives of eugenol is strongly connected with the position of the substituent on aromatic aldehyde or ketone. As these compounds possess both the activities, therefore they may be useful in tuberculosis treatment.

**Keywords**: Hydrazone, Molecular docking, Anti-inflammatory activity

Hydrazones and their derivatives are one of the most important and pharmacologically rich therapeutic agents. These compounds have remarkable biological properties, such as anti-inflammatory, analgesic, anticonvulsant, anti-tubercular, antitumor, anti-HIV and antimicrobial activities[1,2]. The nitrogen in hydrazone is attached to hydrogen and these hydrazone is stable enough for synthesis. Nevertheless, in some cases, especially with simple alkyl group, they rapidly decompose or polymerizes unless there is at least one aryl group on nitrogen or the carbon[3]. When there is an aryl group the compounds are quite stable and these compound are called Schiff bases[4]. Cyclooxygenases (COX) or prostaglandin endoperoxide synthases are the key enzymes in the synthesis of prostaglandins, the main mediators of inflammation, pain, and increased body temperature (hyperpyrexia). The body produces two main isoforms of COX proteins, that is, cyclooxygenases-1 (COX-1) and cyclooxygenases-2 (COX-2). The COX-1 is involved in pain, causing blood clotting, and protecting the stomach, whereas COX-2 is involved in the pain by inflammation and plays a major role in prostaglandin biosynthesis in inflammatory cells and central nervous system[5,6]. Therefore, the development of new anti-inflammatory and analgesically active drugs with less ulcerogenic side effects is still a challenging target for the pharmaceutical scientist.

Drug discovery and development are complicated, time consuming and costly processes. They become more expensive when safety, efficacy and other issues are raised. *In silico* approach towards drug design plays a significant role in all stages of drug development from the initial lead design to final stage of clinical aspect of drug[7]. The present work is a continuation of research work carried out on hydrazone derivatives[8].

HDT is a new and promising conception in TB treatment. In this process, small molecules modulate host defence response, with or sometimes, without supportive antibiotics, to attain superior control of TB. Contrasting antibacterial, HDT agents work on host immunity and directly modulate immune functions. This helps to develop or avoid resistance *via M. tuberculosis* infection. Hence HDT shows potential therapy strategy to limit TB resistant strain cases and also for those individuals with accessible chronic, co-morbid circumstances for example HIV infection or diabetes.

So, by considering above objective, we thought to work on a lead which possesses anti-tubercular

activity and also modulates the host immunity response. This lead will control bacterial infection and also decrease the neutrophil dominated inflammation. Unlike antibacterial, HDT agent works by modulating individual defense functions; hence, progress of resistance is avoidable.

## Materials and Methods

All chemicals, reagents and solvents were procured from Sigma-Aldrich and Merck Pvt. Ltd. The reactions were carried out in oven-dried glassware (120°C) under atmospheric conditions. The selected ten compounds from fifty-one *in silico* docked compounds were subjected to synthesis. The reactions and homogeneity of compounds were monitored by thin layer chromatography (TLC) over silica gel percolated plates using ethyl acetate, acetic acid and methanol (4:3:1, v/v) eluent mixture, and were visualized by UV irradiation. The synthesized compounds were purified using recrystallization. The melting points were determined using B-540 melting point apparatus using open capillaries and are uncorrected. The infrared spectra were recorded on a Shimadzu MIRacle-10, IRAffinity-1 in the range of 400 to 4000 $cm^{-1}$. The $^1H$ NMR spectra were recorded in $CDCl_3$ using Agilent VNMRS 400 instrument at 300 MHz with chemical shift 0-10. The chemical shifts are reported in δ (ppm) from 0-10 using tetramethylsilane (TMS) as internal standard. The mass spectra were obtained using LCMS6103 at *m/z* values: 0-500.

## Molecular docking

Ten compounds (Table 1) were docked in Small-Molecule Drug Discovery Suite of Schrodinger. All compounds were targeted on two enzymes such as 4-COX and 3LN1 involved in inflammation. Both the enzymes involved in COX-2 synthesis, and are an attractive target for the development of novel drugs against inflammation.

The structure of each compound was cleaned and optimized using Ligprep. The clean-up and optimization process included conversion of structures from 2D to 3D, addition of hydrogen atoms, generation of possible ionization state at the *p*H 7.0, generation of tautomers, generation of all combinations of stereoisomers, and energy minimization were confirmed. The low energy conformer of ligands was generated using OPLS3 force field. The energy data are given in Table 2.

Grid files represent the active site of enzyme that is searched when attempting to dock a ligand. Grids were generated by Receptor Grid Generation panel of Glide-v7.4. Grid excludes co-crystallized ligand and thus determines the position and size of the active site. The size of grid box was fixed so that ligand with size of </= 20 Å can be docked. The van der Waals radius scaling factor of 0.7 for atoms with a partial atomic charge (absolute value) less than 0.25 was used to soften the potential for non-polar parts of the receptor. The constraints were also defined as per various interactions visualized in PDB of co-crystalized ligands with respective enzyme. The rotatable groups like hydroxyl and thiol groups in enzymes were allowed to rotate.

The generated lower energy conformers of all ligands were docked into generated grid of active site of enzymes by XP precision of docking inside Glide-v7.4 [8,9].

## Synthesis

### Synthesis of ethyl aryloxy acetate, 2

A mixture of compound **1** (eugenol : 0.1mol), ethyl chloroacetate (0.1 mol) and anhyd. $K_2CO_3$ (0.15 mol) in dried acetone was refluxed for 12 h. Resultant mixture was distilled off and poured on to ice-cold water and stirred. Residue was extracted with ether and the extract was dried over anhyd. $Na_2SO_4$ to yield compound **2** (Scheme 1).

### Synthesis of ethylaryloxyacetyl hydrazine, 3

A mixture of compound **2** (0.05 mol) and hydrazine hydrate (0.075 mol) in ethanol was refluxed for 4 h and after distilling off the solvent, the residue was purified by recrystallization from methanol to yield compound **3**.

### Synthesis of hydrazones

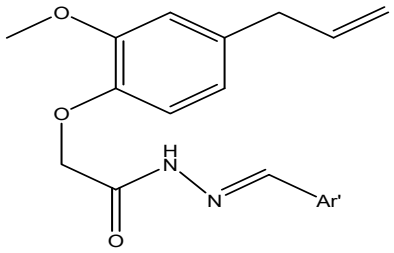
A mixture of compound **3** (0.01 mol) and 2,4-dihydroxy benzaldehyde (0.01 mol) was refluxed for 2 h using acetic acid. The crystals formed were washed with ice-cold water, dried and recrystallized from methanol to yield compound **1**. Following the same procedure using respective aldehydes / ketones, other compounds were synthesized[8].

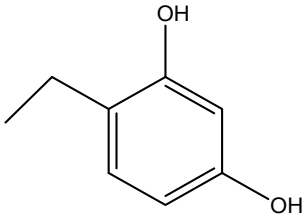
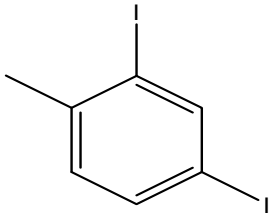
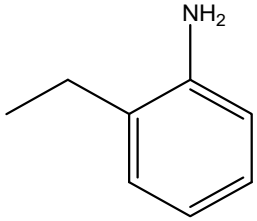
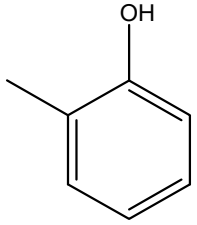
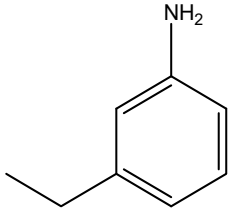
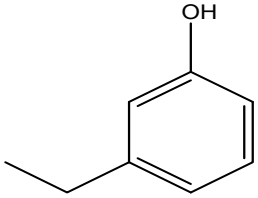
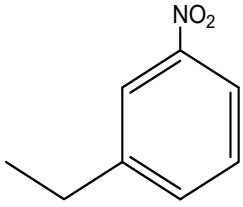
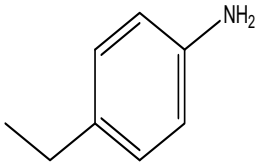
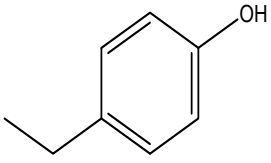
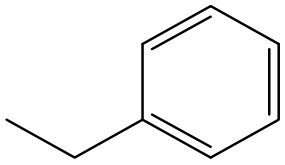
## Pharmacological Activity

### *In vivo* Anti-Inflammatory Activity

Animals were obtained from National Institute of Biosciences, Pune (Reg. No. 1091 /ABC/ 01 / CPCSEA). The present study was approved by Institutional Animal Ethics Committee (Reg. No. 1314/PO/Re/S/2009/CPCSEA) of Satara College of

Table 1 — List of compounds screened for molecular docking



| Compd | Ar′ | Compd | Ar′ |
|---|---|---|---|
| 1 |  | **2** |  |
| 3 |  | **4** |  |
| 5 |  | **6** |  |
| 7 |  | **8** |  |
| 9 |  | **10** |  |

Pharmacy, Satara Maharashtra, India. All animals were allowed free access to water and were kept on a constant standard diet. All procedures involving animals were carried out in accordance with the guidelines for the care and use of laboratory animals and were approved by the Ethics Committee of Satara College of Pharmacy, Satara. In carrageenan model Adult Wistar strain rats of male and female sex, weighing 150–200 g, were used for anti-inflammatory activity[10]. The animals were allowed food and water *ad libitum* except during the experiments. They were housed in wire- mesh cages at 25 ± 2°C, with 50±5% relative humidity and 12 h light/dark cycles. The animals were randomly allocated into groups and

fasted for 12–24 h before the experimental study and used for determining the anti-inflammatory activity. All test compounds and the reference drug were administered orally. The rats were divided into three groups (control, test compounds and standard drug) of six animals each. A freshly prepared suspension of 1% carrageenan, 0.1 mL was injected S.C. into the subplantar region of the right hind paw of each rat. The test compounds and standard drug Indomethacin[11–13] were administered orally at the dose of 10 mg/Kg to the animals of tested derivatives groups and the standard drug group, respectively, 1 h before the carrageenan injection. The paw weight of each rat was measured at 1, 2, 3 and 4 h intervals after carrageenan treatment with the help of a Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below.

% Inhibition of oedema = [(Dcontrol – Dtreated)/ Dcontrol]×100

where, Dcontrol = mean diameter of rats paw in controlled group, Dtreated = mean diameter of rats paw in test group.

Table 2 — Docking score of compounds

| Compd | Energy | 4COX XP GScore | 3LN1XP GScore |
|---|---|---|---|
| Indomethacine | 37.639404 | –10.739 | –6.157 |
| 1 | 35.16771 | –9.265 | –7.791 |
| 2 | 37.146057 | –8.442 | –6.428 |
| 3 | 37.631698 | –8.955 | –5.8 |
| 4 | 38.48256 | –9.066 | –6.2 |
| 5 | 38.717439 | –8.387 | –5.3 |
| 6 | 34.780646 | –8.813 | –6.43 |
| 7 | 40.730523 | –7.143 | –5.8 |
| 8 | 40.005803 | –9.093 | –6.7 |
| 9 | 40.785869 | –9.213 | –6.71 |
| 10 | 37.432105 | –9.028 | –5.7 |

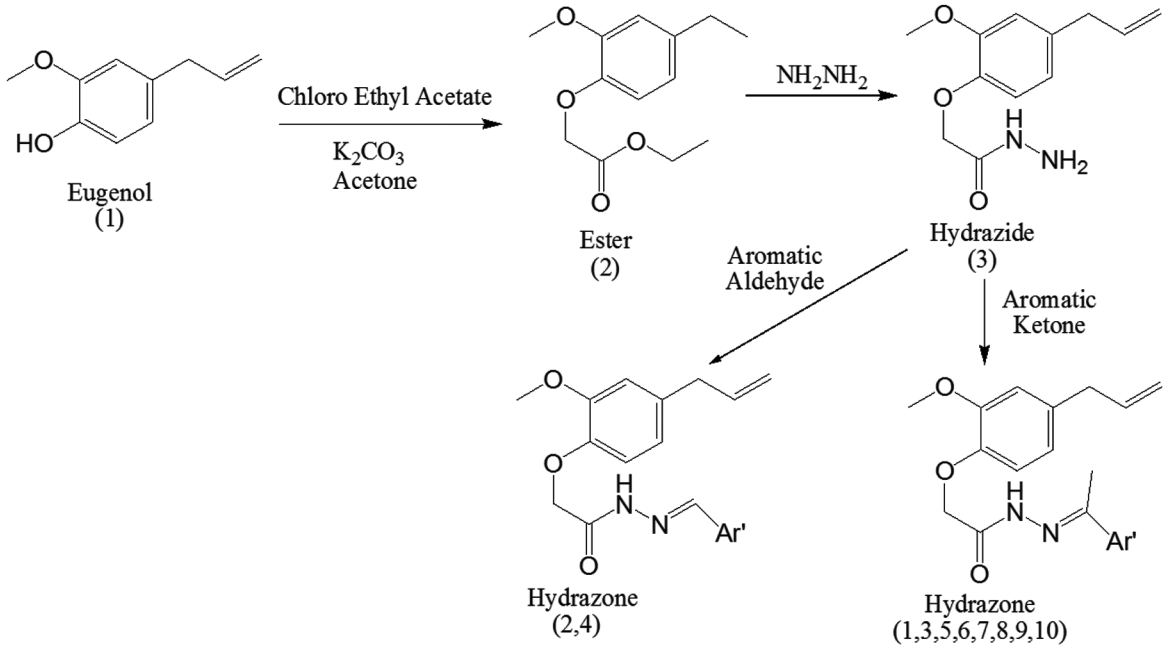
### *In vitro* anti-inflammatory activity

The synthesized compounds were screened for anti-inflammatory activity using inhibition of albumin denaturation technique[14–16] which was studied according to Mizushima and Kobayashi with slight modification. Test solution (1 mL) containing different concentrations of drug was mixed with 1 mL of 1 mM albumin solution in phosphate buffer and incubated at 27° ± 1°C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60° ± 1°C in waterbath for 10 min. After cooling, 2.5 mL of phosphate buffer was added to the above solutions, the turbidity was measured at 660 nm. Percentage of inhibition of denaturation was calculated from control where no drug was added. Indomethacin was used as the standard drug.

## Results and Discussion

### Molecular docking

The *in silico* study of all fifty-one compounds was performed using Small-Molecule Drug Discovery




Scheme 1 — Synthesis of novel hydrazones

Suite of Schrödinger. The compounds exhibited good docking score and predicted interaction with enzymes. The docking result of novel hydrazones against PDB:4COX revealed that the binding energies were in the range of –7.143 kcal/mol to –9.265 kcal/mol and for Indomethacin it was –10.7 kcal/mol. The docking result of novel hydrazone against PDB:3LN1 were found to be in the range of –5.8 kcal/mol to –7.791 kcal/mol and for Indomethacin it was –6.16 kcal/mol. The docking score of selected analogue were found near to reference drug. So it assured that analogue possess anti-inflammatory activity (Table 2). The molecules were tested for structure analysis by the visualization tool. The entire compounds protein-ligand complex showed H-bond with the active site residue ARG 120, SER 530, TYR 385, TRP 387 and MET522 of 4COX (Fig. 1) and HIE 75, TYR 341 and LEU338 of 3LN1 (Fig. 2).This interaction with the said proteins indicates that the hydrazone derivatives might be the best suited ligands possessing anti-inflammatory activity.

#### Synthesis and characterization of synthesized compounds

The ten hydrazone compounds were selected for synthesis based on their *in silico* docking results. The derivatives were synthesized by condensation of arylhydrazide with various aromatic aldehydes or ketones using ethanol. Physical data including melting point and percentage practical yield of all synthesized compounds (Table 3) and characterization data are mentioned below. In the IR spectra, all hydrazone derivatives displayed characteristic band from 1700-1650 $cm^{-1}$ attributed to C=O stretching vibration. The N-H stretching vibration of the compounds exhibited a band around 3150 $cm^{-1}$. The stretching bands for C=C and C=N groups were observed at 1610-1490 $cm^{-1}$. In general, the IR stretching frequencies for –OH groups varied for the compounds **1**, **4**, **6** and **9** in the region 3200-3650 $cm^{-1}$. In the $^{1}H$ NMR spectra of all the compounds, the aromatic and aliphatic protons were observed at the specified δ (ppm) scale. Aromatic protons were observed around δ 6.15-7.78. Synthesized hydrazones displayed characteristic NMR signals for –OH, –NH, –CH=N- protons as coupled peaks at δ 4.90-5.10, 7.10-6.90 and 3.35-2.53 respectively. This characterization data revealed the confirmation of successful synthesis of selected derivatives of hydrazones.

## Pharmacological Activity

#### *In vivo* Anti-Inflammatory Activity

*In vivo* activity was carried out at a dose of 10 mg/kg by carrageenan induced paw edema method. Carrageenan is a strong chemical that functions in stimulating the release of inflammatory and pro-inflammatory mediators, including bradykinin, histamine, tachykinins, reactive oxygen, and nitrogen species. Typical signs of inflammation

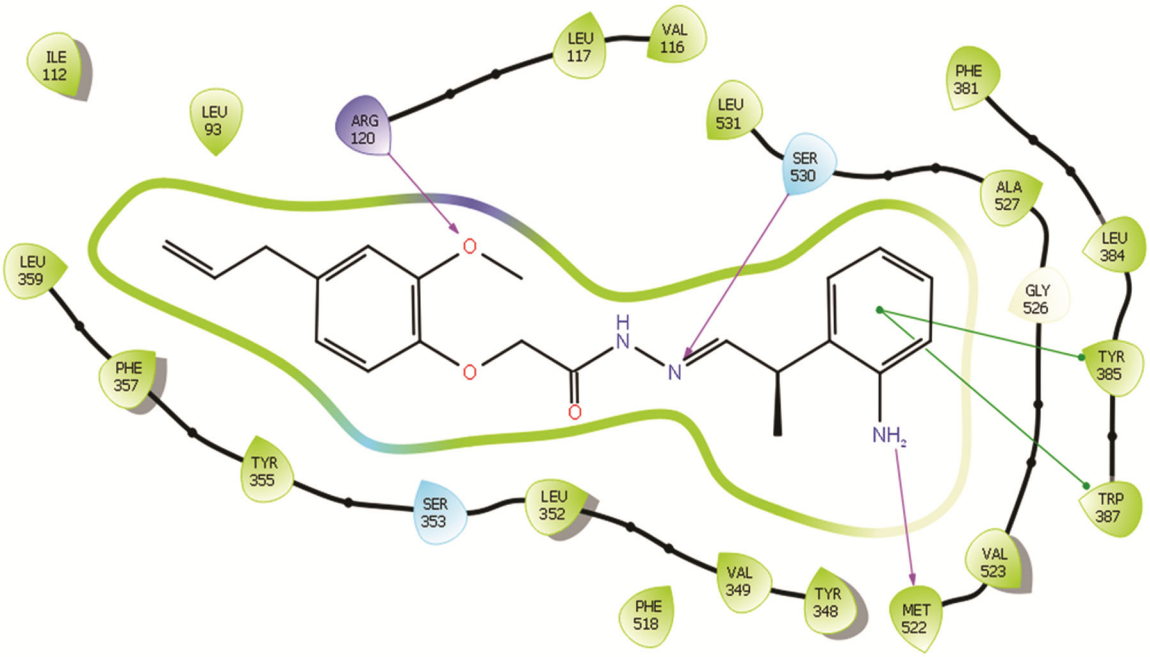



Fig. 1 — Molecular docking of compound on PDB: 4COX

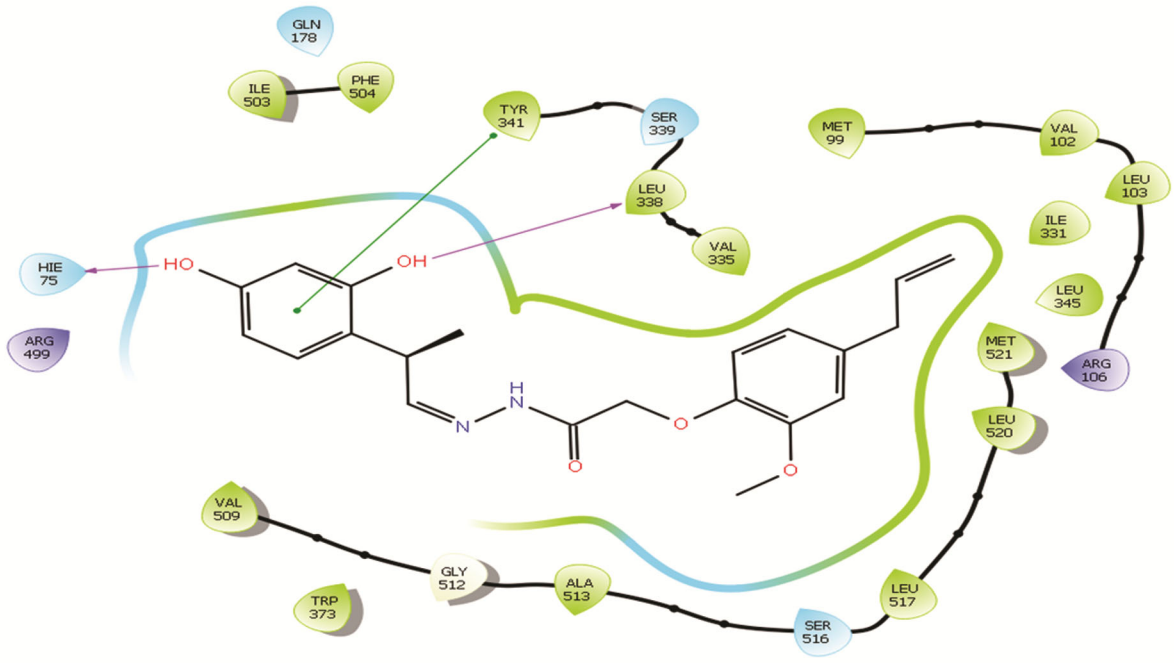



Fig. 2 — Molecular docking of compound on PDB: 3LN1

Table 3 — Physical characteristics of synthesized hydrazones

| Compd | Mol. Formula | Mol. Weight | m.p. (°C) | Yield (%) |
|---|---|---|---|---|
| 1 | $C_{20}H_{22}N_2O_5$ | 370.15 | 220-221 | 73.1 |
| 2 | $C_{19}H_{18}I_2N_2O_3$ | 576.18 | 235-236 | 62 |
| 3 | $C_{20}H_{23}N_3O_3$ | 353.17 | 191-192 | 84.4 |
| 4 | $C_{19}H_{20}N_2O_4$ | 340.37 | 229-230 | 88.1 |
| 5 | $C_{20}H_{23}N_3O_3$ | 353.17 | 190-191 | 59.1 |
| 6 | $C_{20}H_{22}N_2O_4$ | 354.16 | 217-218 | 74.1 |
| 7 | $C_{20}H_{21}N_3O_5$ | 383.42 | 235-236 | 60.1 |
| 8 | $C_{20}H_{23}N_3O_3$ | 353.17 | 190-191 | 72.1 |
| 9 | $C_{20}H_{22}N_2O_4$ | 354.16 | 219-220 | 76.8 |
| 10 | $C_{20}H_{22}N_2O_3$ | 338.16 | 184-185 | 65.5 |

include edema, hyperalgesia, and erythema, which develop immediately following the treatment of carrageenan. From the data, it was revealed that all tested compounds significantly reduced carrageenan induced edema (Table 4). Among the tested compounds, compounds **1**, **5** and **8** may be considered as potent anti-inflammatory agents and comparable with standard anti-inflammatory drug, Indomethacin and near to other standard drugs like Ibuprofen[11] and Diclofenac sodium[17]. The derivatives with hydroxyl aldehyde or ketone substitution exhibited substantial activity. The molecular docking was performed on designed compounds to check whether compounds possessed anti-inflammatory activity. The hypothesis has been proposed that compounds should possess the activity. Molecular docking was checked against two COX-2 enzymes PDB *i.e.* 4COX and 3LN1 for anti-inflammatory activity. The docking result of novel hydrazone revealed that the binding energies were in the range of –5.952 kcal/mol to –9.265 kcal/mol. This interaction with the said proteins indicates that the hydrazone derivatives might be the best suited ligands possessing anti-inflammatory activity. When these synthesized compounds were tested for *in vitro* as well as *in vivo* activity, they were found to have good anti-inflammatory activity.

### *In vitro* anti-inflammatory activity

Denaturation of proteins is a well-documented cause of inflammation. All aldehyde or ketone derivatives of hydrazone have shown dose dependent ability to thermally induced protein denaturation. As a part of the investigation on the mechanism of the anti-inflammatory activity, ability of hydrazone derivatives to inhibit protein denaturation was studied. All synthesized compounds were effective in inhibiting heat induced albumin denaturation at different concentrations (Table 5) and compounds **1**, **5** and **8** showed significant activity.

### Spectroscopic characterization data of newly synthesized hydrazone derivatives

**1**: IR: 1653 (CO of CONH), 1568 (N-H Bending), 1213 (C-O) 3288 $cm^{-1}$ (C-OH); $^1$H NMR: δ 18.36 (N=C-$CH_3$), 110, 130, 147, 150 (C-H Aromatic ring), 159 (C-OH), 174 (N=C), 179 (C=O); $^{13}$C NMR: δ 8.60 (O=C-N-H), 6.15, 6.40, 6.54, 6.78 (C-H Aromatic ring), 3.75 ($CH_3O$), 1.22 (N=C-CH3); MS: *m/z* 370.1

Table 4 — Anti-inflammatory effects of the tested compounds and Indomethacin

| Compd | % change from baseline | | | |
|---|---|---|---|---|
| | 1 h | 2 h | 3 h | 4 h |
| Control | 33.47±6.32 | 42.70±1.99 | 49.82±2.99 | 52.07±2.97 |
| Indomethacin | 13.79±4.51* | 27.97±2.56 | 19.00±3.03* | 25.02±1.70* |
| **1** | 7.58±0.51* | 18.20±2.67* | 24.79±3.32* | 30.19±3.5* |
| **2** | 13.62±1.78* | 21.95±4.04* | 27.39±3.60* | 32.32±5.41* |
| **3** | 21.55±3.47 | 27.71±2.91 | 25.56±4.38* | 30.19±4.67* |
| **4** | 14.48±3.57* | 19.67±5.76* | 22.31±4.35* | 30.41±3.90* |
| **5** | 15.00±4.81* | 21.68±3.56* | 21.60±2.66* | 25.47±2.85* |
| **6** | 21.20±3.15 | 27.97±2.93 | 29.27±2.55* | 28.95±3.60* |
| **7** | 14.31±3.54* | 20.74±4.94* | 23.37±3.40* | 28.84±3.15* |
| **8** | 14.31±4.33* | 21.68±3.56* | 21.84±2.53* | 25.92±2.59* |
| **9** | 15.86±4.49* | 19.27±5.57* | 22.90±4.40* | 26.93±3.18* |
| **10** | 14.31±3.51* | 21.55±3.16* | 21.72±2.37* | 25.25±2.24* |

Note: Data represent the mean ± standard error of the mean (n = 6). Values represent the mean ± S.E. of six animals for each group. * $p< 0.05$: statistically significant from control. (One way ANOVA followed by Tukey test).

Table 5 — Screening of *In-vitro* anti-inflammatory activity

| Compd | Absorbance value (Mean + SE) | Inhibition of denaturation (%) |
|---|---|---|
| Control | 0.098 + 0.009 | – |
| 1 | 0.187 + 0.002 | 90.81 |
| 2 | 0.162 + 0.007 | 65.30 |
| 3 | 0.161 + 0.005 | 64.28 |
| 4 | 0.162 + 0.003 | 65.37 |
| 5 | 0.183 + 0.004 | 86.73 |
| 6 | 0.176+ 0.004 | 79.93 |
| 7 | 0.170 + 0.002 | 73.80 |
| 8 | 0.178 + 0.005 | 81.63 |
| 9 | 0.170 + 0.003 | 73.80 |
| 10 | 0.164 + 0.002 | 68.02 |
| Indomethacin | 0.170 + 0.002 | 73.80 |

**2**: IR: 1674 (CO of CONH), 1595 (N-H Bending), 1273 (C-O) 758 $cm^{-1}$ (C-I); $^1$H NMR: δ 8.60 (O=C-N-H), 8.10(N=CH), 6.33, 6.40, 6.51, 6.55 (C-H Aromatic ring), 3.73($CH_3O$); MS: *m/z* 575

**3**: IR: 1662 (CO of CONH), 1525 (N-H Bending), 1384 (C-O) 3253, 3286 $cm^{-1}$ (C-$NH_2$); $^1$H NMR: δ 8.80 (O=C-N-H), 6.33, 6.40, 6.51, 6.87 (C-H Aromatic ring), 3.72($CH_3O$), 1.21(N=C-CH3); MS: *m/z*, 353.3

**4**: IR: 1653 (CO of CONH), 1573 (N-H Bending), 1292 (C-O) 3431 $cm^{-1}$ (C-OH); $^1$H NMR: δ 8.60 (O=C-N-H), 8.11(N=CH), 6.33, 6.40, 7.10, 7.44 (C-H Aromatic ring), 3.75($CH_3O$); MS: *m/z* 339.1

**5**: IR: 1658 (CO of CONH), 1589 (N-H Bending), 1317 (C-O) 3361, 3460 $cm^{-1}$ (C-$NH_2$); $^1$H NMR: δ 8.60 (O=C-N-H), 6.33, 6.40, 6.68, 7.04 (C-H Aromatic ring), 3.71 ($CH_3O$) 1.20 (N=C-$CH_3$); MS: *m/z* 353

**6**: IR: 1651 (CO of CONH), 1570 (N-H Bending), 1292 (C-O) 3410 $cm^{-1}$ (C-OH); $^1$H NMR: δ 8.60 (O=C-N-H), 6.31, 6.42, 6.68, 7.04 (C-H Aromatic ring), 4.25 (C-$NH_2$), 3.75 ($CH_3O$), 1.20 (N=C-$CH_3$); MS: *m/z*, 353.2

**7**: IR: 1680 (CO of CONH), 1519 (N-H Bending), 1242 (C-O) 1342 $cm^{-1}$ (C-$NO_2$); $^1$H NMR: δ 8.60 (O=C-N-H), 6.34, 6.51, 7.47, 7.51 (C-H Aromatic ring), 3.75 ($CH_3O$), 1.20 (N=C-$CH_3$); MS: *m/z* 383.2

**8**: IR: 1660 (CO of CONH), 1523 (N-H Bending), 1381 (C-O) 3251, 3288 $cm^{-1}$ (C-$NH_2$); $^1$H NMR: δ 8.61 (O=C-N-H), 6.32, 6.47, 6.87, 6.90 (C-H Aromatic ring), 4.00 (C-$NH_2$), 3.74 ($CH_3O$), 1.20 (N=C-$CH_3$); MS: *m/z* 353.1

**9**: IR: 1653 (CO of CONH), 1568 (N-H Bending), 1273 (C-O) 3288 $cm^{-1}$ (C-OH); $^1$H NMR: δ 8.61 (O=C-N-H), 6.32, 6.40, 6.54, 6.95 (C-H Aromatic ring), 3.77 ($CH_3O$), 1.20 (N=C-$CH_3$); MS: *m/z* 353.8

**10**: IR: 1680 (CO of CONH), 1556 (N-H Bending), 1278 (C-O) $cm^{-1}$; $^1$H NMR: δ 8.60 (O=C-N-H), 6.34, 6.40, 7.12, 7.21 (C-H Aromatic ring), 3.73 ($CH_3O$), 1.20 (N=C-$CH_3$); MS: *m/z* 336.2

## Conclusion

A novel series of hydrazone derivatives were synthesized by using conventional methods and all compounds were characterized by physical and spectral data. The synthesized compounds were evaluated for *in vivo* and *in vitro* anti-inflammatory activity. Results revealed that most of the compounds have significant anti-inflammatory

activity. Among the tested compounds, compound **4**, **34** and **42** exhibited the highest anti-inflammatory activity. Furthermore, to help understand the interactions between the ligands and enzyme active sites, the molecular docking studies were carried out for all the synthesized compounds toward active site of COX-2 enzymes and compared the docking score with references drug Indomethacin. All the compounds exhibited good docking score which are agreed and supported the anti-inflammatory activity of these compounds. Molecular docking results along with the biological data suggested that the tested compounds have the potential as valuable leads for anti-inflammatory activity.

Hydrazone derivatives of eugenol possess both activitiesy *i.e.* anti-inflammatory and antimycobacterial by acting on two different enzymes COX-2 and inhA resp. The anti-inflammatory activity modulates the host immune response and decreases the inflammation in lungs and antimycobacterial activity controls the bacterial infection and ultimately saves the lung from damage. This is the best way to improve TB treatment. This lead will control bacterial infection and also decrease the neutrophil dominated inflammation. Unlike other antibacterials, these agents also work by modulating individual defense functions; hence, progress of resistance is avoidable.

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