Journal of Applied Pharmaceutical Science
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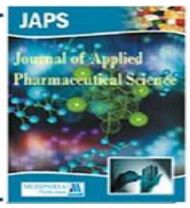


ISSN: 2231-3354
Received on: 31-05-2012
Revised on: 19-06-2012
Accepted on: 23-06-2012
**DOI:** 10.7324/JAPS.2012.2732

# Synthesis and biological evaluation of 2,4,5-triphenyl-1*H*-imidazole-1-yl Derivatives

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**ABSTRACT**

In the present investigation, our aim of synthesis is to find a molecule having multi drug treatment means the drug which resists the inflammation produce due to microbial infection. So, 2,4,5-triphenyl-1H-imidazole-1-yl derivatives were synthesized and tested for their anti-inflammatory activity in-vitro using Phenylbutazone as a reference drug and antimicrobial activity using clotrimazole and ciprofloxacin as a standard drug. Compound 6b was found to be the most potent derivative of the series.

**Keywords:** Triphenyl-Imidazole, Anti-inflammatory, Antimicrobial, Multidrug.

## INTRODUCTION

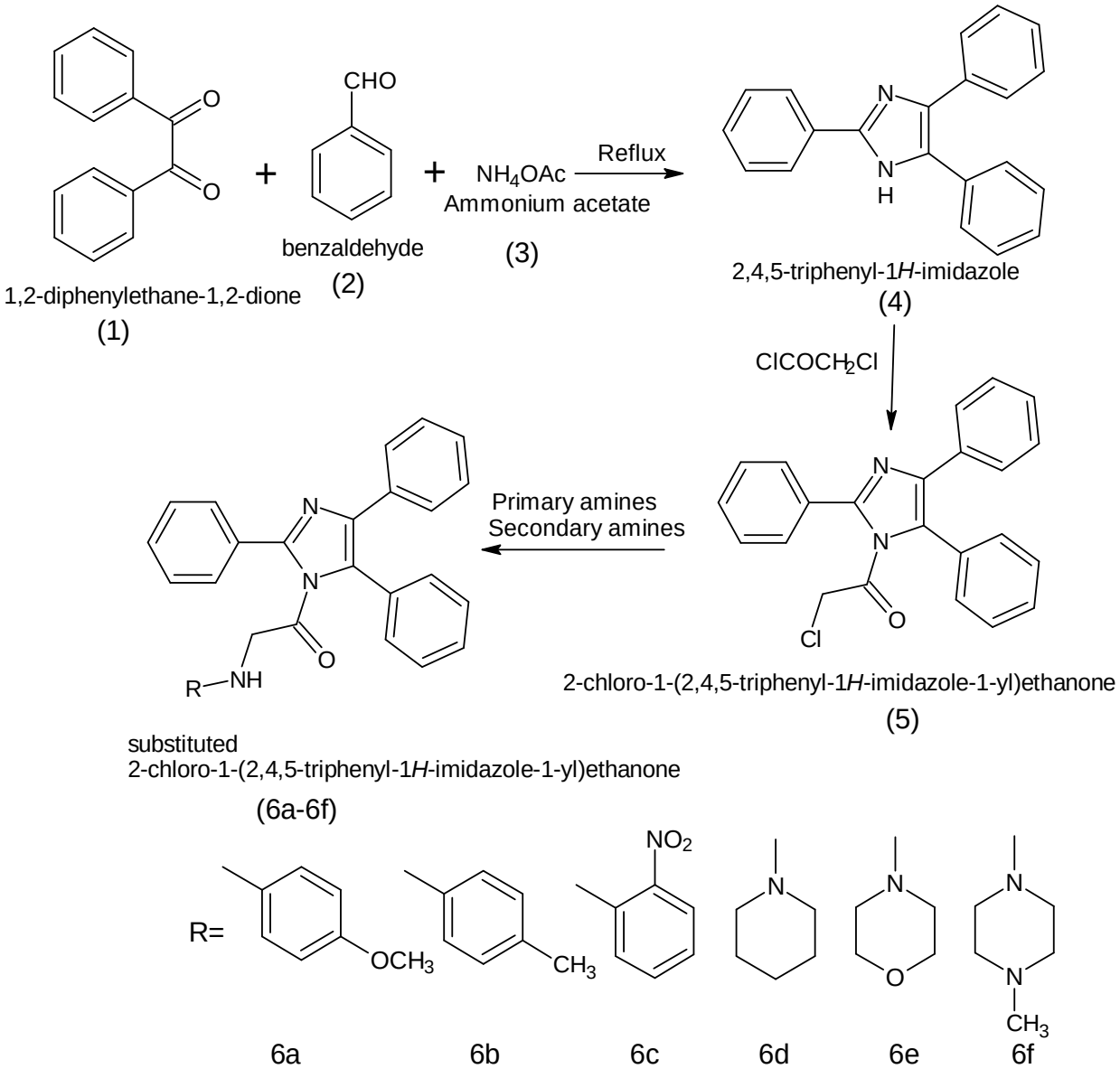
Multi drug treatment of inflammatory conditions associated with microbial infections posses a unique problem especially for patients with impaired liver or kidney functions. Hence, mono therapy with a drug having both anti-inflammatory and antimicrobial activities is highly desirable, both from the pharmacoeconomic as well as patient compliance points of view. Encouraged by these observations and in continuation of the research on the synthesis of five membered heterocyclic compounds. (Morrow et al, 2001, Rang et al, 2003, Lemke et al, 2008). Imidazole ring is bioisoster of pyrazole ring means both have 5 membered structures and 2 nitrogen and in particular some of pyrazole derivatives were in depth investigated as nonsteroidal anti inflammatory drugs (NSAIDs). The mechanism of action of this class of compounds is linked to the inhibition of cyclooxygenase COX-2. The presence of a pyrazole nucleus is a common feature in the chemical structure of several COX-2 inhibitors. Example-celecoxib. Imidazole derivatives are the important class of heterocyclic compounds that occur in many drugs like antibacterial, antifungal agents. Imidazole moiety plays a central role for their biological activity. Example-Azole class (Clotrimazole).

From the literature survey, imidazole derivatives were found to be having diverse activity like anti-inflammatory (Amir et al, 2011, Puratchikody et al, 2007, Mader et al, 2008, Barta et al, 1998, Harsha et al, 2010) antimicrobial activity (Jain et al, 2010, Vijesh et al, 2011, Olender et al, 2009, Nagarapu et al, 2008, Yasodha et al, 2009, Ramachandran et al, 2011, Yadav et al, 2011, Hussain et al, 2009, Padmavathi et al, 2011) etc.

So the aim has been designed to synthesize 2,4,5-triphenyl-1*H*-imidazole-1-yl derivatives & to screen the diverse activity like anti-inflammatory, antifungal & antibacterial activity.

## MATERIALS AND METHOD

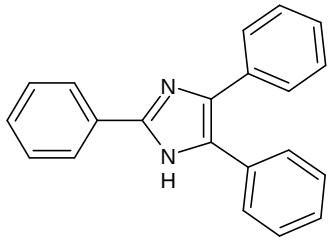
- The entire chemicals were supplied by S. D. Fine Chem. (Mumbai), Finar Chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai).
- Melting points were determined by open tube capillary method and were uncorrected.
- Purity of compounds was checked by thin layer chromatography (TLC) on silica gel-G in solvent system hexane-ethyl acetate (1:1) and the spots were located under iodine vapours and UV light.
- IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr.
- Mass spectra were obtained using 2010EV LCMS Shimadzu instrument.
- The $^{1}$H-NMR was recorded on Bruker advanced –II NMR-400MHz instruments using $CDCL_3$/DMSO-d6 as solvent and TMS (Tetra methyl silane) as internal standard, chemical shifts were expressed as δ values (ppm).




**Synthetic Pathway**

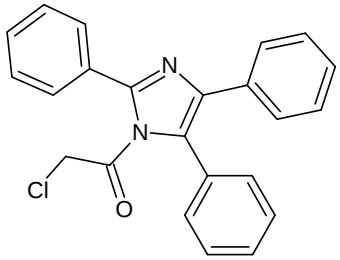
**Synthetic procedure of 2,4,5-triphenyl-1*H*-imidazole RADISZEWSKI SYNTHESIS**

Benzil (25mmol), benzaldehyde (25mmol) and ammonium acetate (130mmol) was dissolved in 100ml ethanoic acid (100%) in 250ml round bottom flask containing a magnetic stirrer bar and was heated at the mixture to reflux in oil bath for 1hr with stirring. After this time the mixture was cooled to room temperature and was filtered to remove precipitate which may be present. 500ml of water was added to filtrate and collected the precipitate by filtration with suction. Filtrate was neutralized with Ammonium Hydroxide and second crop of solid was collected. The two crop of solid was combined and recrystallized from aqueous ethanol. The yield and melting point of purified material was reported as below.




**Synthetic procedure of 2,4,5-triphenyl-1*H*-imidazole-1-carbonyl chloride**

Accurately weighed, (0.01mole) 2,4,5-triphenyl-1*H*-imidazole was dissolved in 20ml of acetone in conical flask. To this solution (0.02mol) of anhydrous potassium carbonate was added. A dropping funnel was fitted to the conical flask and in the dropping funnel a solution of (0.01mol) of chloro acetylchloride was taken. A very slow dropwise addition of chloroacetylchloride solution was done. The reaction mixture was stirred for 5-6 hours at cold condition. After 5-6 hours, excess of solvent and chloroacetyl chloride was removed by distillation under reduced pressure and the residue was washed with aqueous sodium bicarbonate (5%w/v, 30ml) and subsequently with cold water (50ml). The crude product was dried and on recrystallization from ethanol afforded white crystalline solid.




**Synthetic procedure of 2-(N-substituted)-1-(2,4,5-triphenyl-1*H*-imidazole-1-yl) ethanone**

In a conical flask, 2,4,5-triphenyl-1*H*-imidazole-1-carbonyl chloride (0.001 mole) was taken in acetone (10 ml) and p-Anisidine (0.001 mole) was added to it. To this mixture, (0.001mole) of anhydrous potassium carbonate was added. The solution was stirred for 4 h. The reaction mixture was poured onto crushed ice with constant stirring. The solution was neutralized with dil. HCl. The solid was filtered and washed with water. The product was recrystallized from acetone.

**Pharmacological Screening**

**Antiinflammatory activity (*in vitro*)**

All the synthesized compounds were screened for the *in vivo* anti-inflammatory activity by carrageenan induced rat paw edema method.

Method: Inhibition of carrageenan induced inflammation in rat paw
Animals used: Albino wistar rats
Number of animals used: 3
Dose of test compounds: 100 mg/kg
Dose of standard drug: 100 mg/kg (Phenylbutazone)
Route of administration: Oral (1% w/v Tween 80 suspension)
carrageenan suspension : Sub planter (0.1 ml of 1% w/v suspension in 0.9% saline solution)

**Method**

The method developed by Winter et al. was employed. Albino wistar rats of either sex (250- 300 g) were divided into various groups of three animals each. Animals were deprived of food for 12 h prior to experiment and only water was given *ad libitum.* First group was used as a control group and received 1 ml of 1% w/v Tween 80 suspension in saline, the second group received Tween 80 suspension of phenylbutazone (100 mg/kg) orally and the third group received Tween 80 suspension of test compounds at a dose of 100 mg/kg orally. One hour after the administration of the compounds, carrageenan suspension (0.1 ml of 1% w/v suspension in 0.9% saline solution) was injected into the sub planter region of left hind paw of animals. Immediately, the paw volume was measured using plethysmometer (initial paw volume, Vc). Thereafter, the paw volume was measured after 1 and 3 h after carrageenan administration. The difference between initial and subsequent readings gave the change in oedema volume for the corresponding time.

Oedema volume of control (Vc) and volume of treated (Vt) were used to calculate percentage (%) inhibition and (%) oedema volume by using following formula. (Winter et al, 1962)

Inhibition = $[1-(Vt/Vc)] \times 100$

% Oedema volume = $100 \times$ (Oedema volume after drug treatment/Initial volume)

**Antimicrobial activity**

In our current study, evaluation of antimicrobial activity was carried out by using filter disk method. The antifungal activity of all newly synthesized derivatives moiety were examined against *Candida albicans* and clotrimazole was used as a standard drug and response of microorganisms to the synthesized compounds has been measured with that of the standard drug ciprofloxacin and microorganisms were selected for the study was *Escherichia coli* (Gram –ve), *Bacillus subtilis* (+ve). Antifungal activity: 30g of the

medium was suspended in 1000ml of purified water. The mixture was allowed to boil till it forms a homogeneous solution. The medium was autoclaved at 121°C for 15minutes at 15psi. Media was cooled to the temperature of approximately 40°C temperature and microorganisms were inoculated to the media. 150ml was transfer to a Petri plates aseptically. Two such plates were prepared for each organism. Plates were allowed to cool for 20 minutes. Compounds were dissolved in DMSO and diluted in same to get concentration of 250µg/ml, 500µg/ml and 750µg/ml. Here both high and low strength disks were applied for each compound to be tested. The organism was reported as being sensitive if clear zone appears around both disks.

Antibacterial activity: All the Petri dishes were sterilized in oven at 160°C for 1 hour, Agar media, absorbent paper and test solutions were sterilized in autoclave at 121°C at 15psi then molten sterile agar was poured in sterile petridishes aseptically. The agar was allowed to cool and the bacterial suspension was poured into the petridishes aseptically. Placing the absorbent paper was absorbed with solutions of the compound in the petridishes aseptically. Incubated the petridishes at 37°C for antimicrobial for 24 hrs and observed the Zone of inhibition. (Anantnarayn et al, 1996, Pelczar *et al.*, 1986)

## RESULTS AND DISCUSSION

The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 10.44 to 76.11% inhibition of rat paw oedema volume after 4hr, whereas the standard drug phenylbutazone showed 85.07% inhibition of rat paw oedema volume after 4hr.

The compound 6b was found to be nearly equipotent to phenylbutazone which is used as standard drug. Compounds 10a, 6a, 10b, 6d have shown this activity but less potent than compound 6b and phenylbutazone. Compound 6c, 6e, 6f was found to be least potent among the series.

All the synthesized compounds were screened for their anti-fungal activity against *Candida albicans* and for anti-microbial activity against *B.subtilis* and *E.coli.*

Compounds 6c, 6d, 6e have shown good anti-fungal activity but less potent as compared to standard reference drug clotrimazole. Compounds 6a, 6b and 6f were found to be very least potent towards antifungal activity.

The antimicrobial activity was carried out against two microorganisms, *B.subtilis* and *E.coli*, and it was found that compounds 6b, 6c, 6d and 6e have shown good anti-bacterial activity as compared to standard drug ciprofloxacin. Compounds 6a and 6f were found to be very least potent towards antibacterial activity.

**Table. 1:** Analysis of compound (4).

| | |
|---|---|
| Molecular Formula | $C_{21}H_{16}N_2$ |
| Molecular Weight (g/mol) | 296.37 |
| Melting Point (°C) | 292-295 |
| Yield (%w/w) | 60 |
| TLC | Hexane: Ethyl acetate 7:3, Rf=0.60 |
| IR (υ, $cm^{-1}$) | 3152(>NH), 3058(Ar CH), 1686(>C=N), 1177(C-N) |
| Mass (m/e) | 296.8 (M+) |

**Table. 2:** Analysis of compound (5).

| | |
|---|---|
| Molecular Formula | $C_{23}H_{17}ClN_2O$ |
| Molecular Weight (g/mol) | 372.85 |
| Melting Point (°C) | 155-155 |
| Yield (%w/w) | 45 |
| TLC | Hexane: Ethyl acetate 7:3, Rf=0.50 |
| IR (υ, $cm^{-1}$) | 3051(ArCH), 1712(>C=O), 1650(>C=N), 1129(C-N), 771 (C-Cl) |
| Mass (m/e) | 372.9 (M+), 374 (M+2) |

### Physicochemical Parameters of 2-(N-substituted)-1-(2,4,5-triphenyl-1*H*-imidazole-1-yl) ethanone

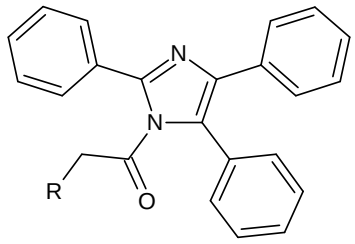



**Table. 3:** Analysis of 2-(N-substituted)-1-(2,4,5-triphenyl-1*H*-imidazole-1-yl) ethanone.

| Compound Code | R | Molecular formula | Molecular weight | M.P. (□C) | % Yield |
|---|---|---|---|---|---|
| 6a | $-C_6H_5(P\text{-}OCH_3)$ | $C_{30}H_{25}N_3O_2$ | 459.54 | 120-125 | 35 |
| 6b | $-C_6H_5(P\text{-}CH_3)$ | $C_{30}H_{25}N_3O$ | 443.20 | 130-133 | 25 |
| 6c | $-C_6H_5(O\text{-}NO_2)$ | $C_{29}H_{22}N_4O_3$ | 474.51 | 110-115 | 40 |
| 6d | $-NC_5H_{10}$ | $C_{28}H_{27}N_3O$ | 421.53 | 130-135 | 30 |
| 6e | $-NC_4H_8O$ | $C_{27}H_{25}N_3O_2$ | 423.51 | 115-118 | 25 |
| 6f | $-NC_4H_8(N\text{-}CH_3)$ | $C_{28}H_{28}N_4O$ | 436.55 | 100-105 | 35 |

**Table 4:** Spectral characteristics of 2-(N-substituted)-1-(2,4,5-triphenyl-1*H*-imidazole-1-yl) ethanone.

| Compound Code | IR (υ, $cm^{-1}$) | MASS (m/e) | $^1$H NMR (δ ppm) |
|---|---|---|---|
| 6a | 3390 (>NH), 3074 (Ar CH), 1654 (>C=O), 1643 (>C=N), 1234 (-C-O), 1033 (C-N) | 460.3($M^+$) | 7.91-6.63 (m, 19**H**, ArH), 3.74 (s, 2H, N-C**H**$_2$), 3.41 (s, 3H, O-C**H**$_3$) |
| 6b | 3174 (-NH), 3055 (ArCH), 1672 (>C=O), 1650 (>C=N), 1072 (C-N) | 443.9($M^+$) | ---- |
| 6c | 3185 (-NH), 3132 (Ar CH), 1660 (>C=N), 1676 (>C=O), 1485 (-$NO_2$), 1250 (C-N) | 422.0($M^+$) | ---- |
| 6d | 3058 (ArCH), 1662 (>C=O), 1644 (>C=N), 1105 (C-N) | 475.0($M^+$) | ---- |
| 6e | 3051 (Ar CH), 1690 (C=N), 1650 (C=O), 1321 (C-O), 1129 (C-N) | 423.0($M^-$) | ---- |
| 6f | 3078 (ArCH), 1680 (>C=N), 1661 (>C=O), 1126 (C-N) | ----- | 8.11-7.36 (m, 15H, Ar**H**), 3.27 (s, 2H, N-C**H**$_2$), 2.56 (m, 8H, C**H**$_2$), 2.13 (s, 3H, N-C**H**$_3$) |

**Table. 5:** Screening of Anti-inflammatory activity in Albino mice (by rat paw oedema method).

| Compound Code | Inhibition of inflammation (mm) | | | | | % inhibition | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0hr | 1hr | 2hr | 3hr | 4hr | 1hr | 2hr | 3hr | 4hr |
| Control | 0.67 ± 0.03 | 0.67 ± 0.02 | 0.67 ± 0.01 | 0.67 ± 0.03 | 0.67 ± 0.02 | --- | --- | ---- | --- |
| Standard (Phenylbutazone) | 0.67 ± 0.02 | 0.48 ± 0.03 | 0.26 ± 0.01 | 0.18 ± 0.02 | 0.10 ± 0.03 | 28.35 | 61.19 | 73.13 | 85.07 |
| 6a | 0.67 ± 0.03 | 0.55 ± 0.02 | 0.48 ± 0.03 | 0.30 ± 0.01 | 0.21 ± 0.03 | 17.19 | 28.35 | 55.22 | 68.65 |
| 6b | 0.68 ± 0.02 | 0.48 ± 0.02 | 0.40 ± 0.03 | 0.28 ± 0.01 | 0.16 ± 0.03 | 28.35 | 40.29 | 58.20 | 76.11 |
| 6c | 0.67 ± 0.01 | 0.66 ± 0.03 | 0.63 ± 0.03 | 0.62 ± 0.02 | 0.60 ± 0.02 | 1.492 | 5.970 | 7.462 | 10.44 |
| 6d | 0.68 ± 0.03 | 0.56 ± 0.02 | 0.48 ± 0.02 | 0.35 ± 0.03 | 0.26 ± 0.03 | 16.41 | 28.35 | 47.76 | 61.19 |
| 6e | 0.68 ± 0.01 | 0.60 ± 0.03 | 0.55 ± 0.01 | 0.48 ± 0.01 | 0.35 ± 0.03 | 10.44 | 17.19 | 28.35 | 47.76 |
| 6f | 0.68 ± 0.02 | 0.59 ± 0.03 | 0.50 ± 0.01 | 0.43 ± 0.03 | 0.33 ± 0.01 | 11.94 | 25.37 | 35.82 | 50.74 |

No. of animals used in each Group (n) = 3, Values are expressed as Mean±SEM
Dose of test compound = 100mg/kg, Dose of Phenylbutazone = 100mg/kg
Anti-inflammatory activity of the test compounds were compared with reference to standard drug. Data were analysed by student's t-test for n=9; p=0.000186

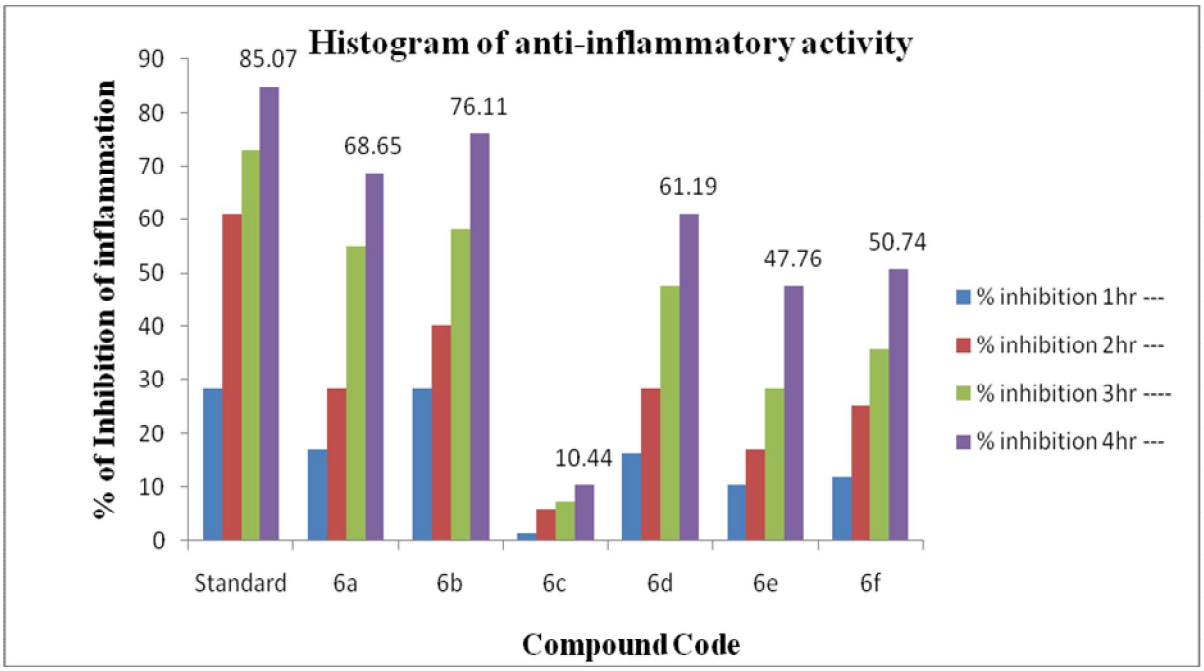
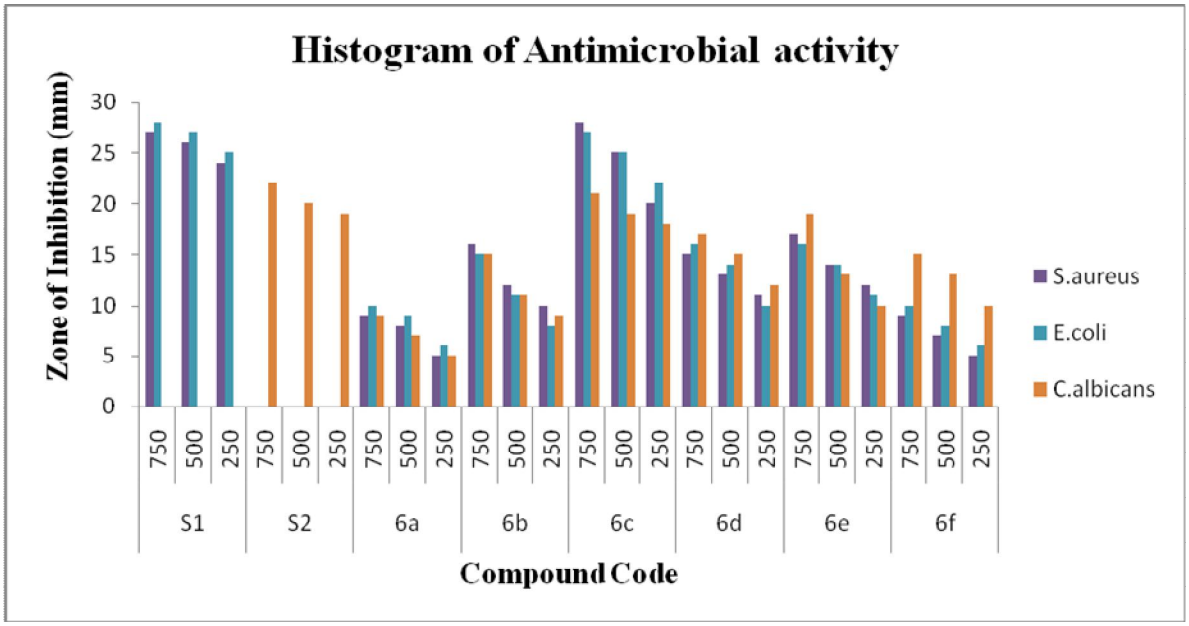



**Fig. 1:** Histogram of Anti-inflammatory Activity.

**Table. 6:** Antimicrobial Activity.

| Compound Code | Concentration (μg/ml) | Zone of inhibition(mm) | | |
|---|---|---|---|---|
| | | Gram +ve | Gram –ve | Fungi |
| | | *S.aureus* | *E.coli* | *C.albicans* |
| Ciprofloxacin | 750 | 27 | 28 | - |
| | 500 | 26 | 27 | - |
| | 250 | 24 | 25 | - |
| Clotrimazole | 750 | - | - | 22 |
| | 500 | - | - | 20 |
| | 250 | - | - | 19 |
| 6a | 750 | 9 | 10 | 9 |
| | 500 | 8 | 9 | 7 |
| | 250 | 5 | 6 | 5 |
| 6b | 750 | 16 | 15 | 15 |
| | 500 | 12 | 11 | 11 |
| | 250 | 10 | 8 | 9 |
| 6c | 750 | 26 | 25 | 21 |
| | 500 | 24 | 23 | 19 |
| | 250 | 20 | 19 | 18 |
| 6d | 750 | 15 | 16 | 17 |
| | 500 | 13 | 14 | 15 |
| | 250 | 11 | 10 | 12 |
| 6e | 750 | 17 | 13 | 19 |
| | 500 | 14 | 11 | 13 |
| | 250 | 12 | 9 | 10 |
| 6f | 750 | 9 | 10 | 15 |
| | 500 | 7 | 8 | 13 |
| | 250 | 5 | 6 | 10 |




S1= Ciprofloxacin as a standard
S2= Clotrimazole as a standard
**Fig. 2:** Histogram of Antibacterial and Antifungal activity.

## CONCLUSION

All the synthesized compounds were characterized by IR and some of by Mass and $^{1}$H-NMR spectroscopy. When increases in aromaticity while substitution showed decrease in activity. Results of substituted compounds containing electron donating groups like methyl and methoxy functional group are showed more active than electron withdrawing nitro functional group. From the obtained results, we can conclude that compound 6b will be the better candidate. In future study, further investigation on the mechanism of action of some of our compound may reveal new compounds with potent anti-inflammatory action and antimicrobial Activity.

## ACKNOWLEDGEMENT

The author Shailesh P. Zala is thankful to the project guide Assoc. Prof. Dr. Badmanaban R., co-guide Prof. Dr. D. J. Sen. and principal and head of department Dr. C. N. Patel and thankful to the all staff members of Shri Sarvajanik Pharmacy College, Mehsana, Gujarat to fulfil the project successfully. I expand my thanks to CPCSEA committee for providing animal facilities and approval of my project. Also thankful to the Quality Assurance Department of Shri Sarvajanik Pharmacy College, Mehsana for UV and IR spectral data, Oxygen Healthcare, Ahmedabad for Mass spectral data and CSMCRI, Bhavnagar and NIPER, Punjab University, Mohali for NMR spectral datas.

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