Synthesis, characterization, Analgesics and Anti-inflammatory activity of Some 4,5,6,7-tetrahydrobenzothiophene Derivatives.

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Abstract
The synthesis, structure and biological activity of benzothiophene has been long focus of research interests in the field of Medicinal Chemistry. A number of benzothiophene derivatives have been reported to possess interesting biological activities such as Analgesic, Anti-inflammatory etc. In the present proposal, substituted Benzaldehyde was made to react with ketone to yield different Chalcones. Chalcones so prepared were further allowed to react with acetic anhydride to get tetrahydrobenzothiophene derivatives (4a-4m). All synthesized compound were characterized by IR, H¹-NMR and elemental Analysis. All the newly synthesized derivatives were screened for Analgesics and in-vitro anti-inflammatory activity by Inhibition of protein denaturation method using diclofenac as a standard.

Key Words
Tetrahydrobenzothiophenes, Anti-inflammatory, Analgesics.

Introduction
Benzothiophene have been shown to have a broad range of important biological activities including antibacterial, antimicrobial, analgesics, anti-inflammatory, antifungal etc. In order to synthesize active molecule of widely different composition such as combination of two heterocyclic framework to achieve good biological profile it was planned to synthesize some benzothiophene derivative containing 1,3,4 oxadiazole moiety. The synthesis of oxadiazole from benzothiophene was performed following steps shown in reaction scheme I. The required compound 1 has been prepared by reaction of cyclohexanone with ethylcyanoacetate using diethylamine by stirring the mixture for 30 min. The compound 2 was synthesized by reacting compound 1 with hydrazine hydrate reflux for 4 hrs in ethanol. The compound (3a-3m) was synthesized by reacting compound 2 with arylaldehydes in ethanol compound (3a-3m) on reaction with acetic anhydride gives compound (4a-4m). The homogeneity of all the synthesized compound was checked by TLC. The structures of synthesized compounds were assigned on basis of spectral data like IR, H¹-NMR spectral analysis. All the synthesized compounds were screened for biological activities like analgesic and invitro anti-inflammatory activities.

Materials and Methods
In this research work, the melting points of synthesized compounds were determined by open capillary tubes using paraffin bath and are uncorrected. Thin layer chromatography is among the most useful tools for following the progress of organic chemical reactions and for assaying the purity of organic compounds. To prepare TLC, clean and dry glass plates were taken. Uniform slurry of silica gel-G in water was prepared in ratio of 1:2. The plates were prepared manually by spread plate method. These were dried first at room temperature and then kept for activation at 110°C for 1 hour. However, Acetone: Benzene having proportion (1:1) was found suitable for most of the synthesized compounds. IR spectra were recorded on a JASCO FT-IR 4100 spectrophotometer, using KBr powder technique. The NMR spectra of the compounds were recorded on a Varian-NMR-mercury 300 MHz spectrophotometer from Pune University, in CDCl₃ using TMS as an internal standard.

Biological Investigation
The synthesized compounds were evaluated for analgesic and In-vitro anti-inflammatory activities. The standard and test compounds were administered i.p. and orally. The statistical analysis was done by using One way ANOVA followed by Dunnet test.

Analgesic activity
Male albino mice of weight range 20-25 gm were selected for study. They were grouped in different
comprising of 6 animals in each group. Before study
food was withdrawn but animal had free access to
water. Test compounds were administered orally at a
dose of 200 mg/kg body weight suspended in sterile
water for injection. Standard group received
Diclofenac at a dose of 25 mg/kg body weight
intraperitoneally at various pretreatment times prior
to acetic acid administration. The mice are placed
individually into glass beakers and after 30 minutes
administration of acetic acid, the mice are then
observed for a period of 10 minutes and the number
of writhes is recorded for each animal. For scoring
purposes, a writhes is indicated by stretching of the
abdomen with simultaneous stretching of at least one
hind limb. The formula for computing percent
protection. The results are presented in Table 2.

% Analgesic activity = (100 –n’/n) 100

Where n = Mean number of writhes of control group
n’ = Mean number of writhes of test group.

Invitro Anti-inflammatory activity
The standard drug Diclofenac and test compounds
were dissolved in minimum amount of dimethyl
formamide (DMF) and diluted with phosphate buffer
(0.2M, pH7.4). Final concentration of DMF in all
solution was less than 2.0%. Test solution (1ml)
containing different concentration of drug was mixed
with 1ml of 1%mM egg albumin solution in
phosphate buffer and incubated at 27 °C in BOD
incubator for 15 min. Denaturation was induced by
keeping the reaction mixture at 60 °C±1°C in water
bath for 10 min. After cooling the absorbance of
turbidity was measured at 660nm by UV-visible
spectrophotometer. Percent inhibition of protein
denaturation was calculated from control, where no
drug was added. The results are presented in Table 3.

% inhibition of denaturation = 100 × (1-A2/A1)

Where, A1 = Absorption of control sample
A2 = Absorption of test sample

Experimental
Route of synthesis
The synthesis of final compounds was carried out in
four steps,
Step I] Synthesis of 2amino 3carboxy 4,5,6,7-
tetrahydro benzothiophene,

To a mixture of cyclohexanone (0.2 mol),
ethylcyanoacetate (0.2mol) and sulphur (0.2 mol) in
ethanol (40 ml), diethylamine (0.2 mol) was added
drop wise with stirring. The 2-amino-3-carboxy-4,5,6,7-tetrahydrobenzothio
e crystals obtained were filtered, dried and recrystallized from ethanol.

Step II] Synthesis of 2-amino-4,5,6,7-
tetrahydrobenzothieno-3-carboxyhydrazide
2-Amino-3-carboxy-4,5,6,7 tetra hydro
benzothiophene (4.5 g, 0.002 mole) was dissolved
in absolute alcohol (20 ml). The solution was kept
under stirring magnetically. Hydrazine hydrate (10
ml, 99%) was added and the reaction mixture was
heated under reflux on a water bath for 4 hours. The
reaction mixture when cooled in ice water liberated
the carboxyhydrazide as colourless crystalline solid.
The product was collected by filtration and dried. It
was further purified by crystallization from ethanol.

Step III] Synthesis of 2-amino-3-(substituted
benzylidene carboxyhydrazide)-4,5,6,7-tetrahydro
benzothiophene, (3a-3m).
To a solution of 2-amino-4,5,6,7-
tetrahydrobenzothieno-3-carboxyhydrazide (1.05g.,
0.005 mole), in ethanol (12 ml), aromatic aldehyde
(0.005 mole) was added and the reaction mixture was
heated under reflux for 5 hours. The contents
were cooled and the solid separated was filtered, and
crystallized from suitable solvent.

Step IV] Synthesis of N-[3-(4-acetyl-5-substituted-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4,5,6,7-
tetrahydro-1-benzothiophen-2-y1]acetamide.(4a-
4m).
Compound 2-amino-3-(substituted benzylidene
carboxyhydrazide)-4,5,6,7 tetrahydrobenzothiophene
(0.353 g, 0.001 mol) and redistilled acetic anhydride
(10 mL) was heated under reflux for 5 h. The
reaction mixture was cooled, poured onto water and
allowed to stand at room temperature for 3 h. The
solid product formed was collected and recrystallized from petroleum ether/ethyl acetate
mixture as white crystals.

5.1.1: N-[3-(4-acetyl-5-(3,4,5trimethoxybenzene)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-
tetrahydro-1-benzothiophen-2-y1]acetamide.(4a)
IR (KBr) Vmax (cm⁻¹): 3247.54cm⁻¹ –NH, 3069cm⁻¹
Ar-CH, 2680cm⁻¹ N-CO, 2410cm⁻¹ NCOCH₃,
1369cm⁻¹ –CN, 1662.34 =C=O, 1253cm⁻¹ Ar-OCH₃,
887cm⁻¹ –C=S, 1H NMR (300MHz) (CDCl₃), d
(ppm) 11.3 (s,1H,NH), 7.25(s,1H, oxadiazole), 6.65
(s,1H,phenyl), 3.6 (s,9H,Ar-OCH$_3$), 2.7-2.8 (t,2H,-CH$_2$), 2.25 (s,3H,CO$_2$H), 1.85 (s,3H,CO$_2$H), 1.45 (m,8H,CH$_3$).

5.1.2: N-[3-(4-acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4b)
IR (KBr) Vmax (cm$^{-1}$), 3247.54 cm$^{-1}$–NH, 3069 cm$^{-1}$ Ar-CH, 2680 cm$^{-1}$ N-CO, 2410 cm$^{-1}$ NCOCH$_3$, 1610 –C=O, 1355 cm$^{-1}$ –CN, 1251 cm$^{-1}$ Ar-OCH$_3$, 885 cm$^{-1}$ –C=S.

5.1.3: N-[3-(4-acetyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4c)
IR (KBr) Vmax (cm$^{-1}$), 3522 cm$^{-1}$ Ar-CH, 3248 cm$^{-1}$ –NH, 2676 cm$^{-1}$ NCO(stretching), 2414 cm$^{-1}$ NCOCH$_3$, 1622 –C=O, 1260 cm$^{-1}$ –C-N, 881 cm$^{-1}$ –C=S.

5.1.4: N-[3-(4-acetyl-5-4-(dimethylaniline)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4d)
IR (KBr) Vmax (cm$^{-1}$), 3524 cm$^{-1}$ Ar-CH, 3242 cm$^{-1}$ –NH, 2985 cm$^{-1}$ Ar-CH$_2$, 2672 cm$^{-1}$ NCO(stretching), 2413 cm$^{-1}$ NCOCH$_3$, 1262 cm$^{-1}$ C-N, 885 cm$^{-1}$ –C=S.

5.1.5: N-[3-(4-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4e)
IR (KBr) Vmax (cm$^{-1}$), 3277.24 cm$^{-1}$ Ar-OH, 3124 cm$^{-1}$ –NH, 2854 cm$^{-1}$ Ar-CH, 2423 cm$^{-1}$ NCOCH$_3$, 1614.23 –C=O, 1112.45 cm$^{-1}$ C-N, 912-885 cm$^{-1}$ –C=S.

5.1.6: N-[3-(4-acetyl-5-(3-nitrobenzene)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4f)
IR (KBr) Vmax (cm$^{-1}$), 3243.14 cm$^{-1}$ –NH, 3146 cm$^{-1}$ Ar-CH, 2542 cm$^{-1}$ N-CO, 2311 cm$^{-1}$ NCOCH$_3$, 1632 –C=O, 1361-1531 cm$^{-1}$ Ar–NO$_2$, 1306 cm$^{-1}$–CN, 808 cm$^{-1}$ –C=S.

5.1.7: N-[3-(4-acetyl-5-(2-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4g)
IR (KBr) Vmax (cm$^{-1}$), 3327.32 cm$^{-1}$ Ar-OH, 3248 cm$^{-1}$ –NH, 2939 cm$^{-1}$ Ar-CH, 2413 cm$^{-1}$ NCOCH$_3$, 1660.77 –C=O, 1147.68 cm$^{-1}$ C-N, 956-885 cm$^{-1}$ –C=S, 1H NMR (300MHz) (CDCl$_3$), δ (ppm) 11.25 (s,1H,NH), 7.4 (d,1H,phenyl), 7.3 (s,1H, oxadiazole), 7.0 (d,1H,phenyl), 6.85 (t,1H,phenyl), 4.4 (s,1H,Ar-OH), 2.7-2.8 (t,2H,-CH$_2$), 2.3 (s,3H,CO$_2$H)$_3$, 1.85 (s,3H,CO$_2$H)$_3$, 1.4 (m,8H,CH$_3$).

5.1.8: N-[3-(4-acetyl-5-(4-nitrobenzene)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4h)
IR (KBr) Vmax (cm$^{-1}$), 3247.54 cm$^{-1}$–NH, 3085 cm$^{-1}$ Ar-CH, 2660 cm$^{-1}$ N-CO, 2410 cm$^{-1}$ NCOCH$_3$, 1531.2 –C=O, 1316-1442 cm$^{-1}$ Ar–NO$_2$, 1203 cm$^{-1}$–CN, 887 cm$^{-1}$ –C=S.

5.1.9: N-[3-(4-acetyl-5-benzyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4i)
IR (KBr) Vmax (cm$^{-1}$), 3428 cm$^{-1}$ Ar-CH, 3248 cm$^{-1}$ –NH, 2676 cm$^{-1}$ NCO(stretching), 2410 cm$^{-1}$ NCOCH$_3$, 1639 –C=O, 1265 cm$^{-1}$ C-N, 884 cm$^{-1}$ –C=S.

5.1.10: N-[3-(4-acetyl-5-(4-chlorobenzene)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4j)
IR (KBr) Vmax (cm$^{-1}$), 3524 cm$^{-1}$ Ar-CH, 3244 cm$^{-1}$ –NH, 2672 cm$^{-1}$ NCO(stretching), 2413 cm$^{-1}$ NCOCH$_3$, 1601 –C=O, 1262 cm$^{-1}$ C-N, 885 cm$^{-1}$ –C=S, 715 cm$^{-1}$–C=Cl.

5.1.11: N-[3-(4-acetyl-5-(3-chlorobenzene)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4k)
IR (KBr) Vmax (cm$^{-1}$), 3425 cm$^{-1}$ Ar-CH, 3214 cm$^{-1}$ –NH, 2654 cm$^{-1}$ NCO(stretching), 2454 cm$^{-1}$ NCOCH$_3$, 1718 –C=O, 1345 cm$^{-1}$ C-N, 798 cm$^{-1}$ –C=S, 744 cm$^{-1}$–C=Cl.

5.1.12: N-[3-(4-acetyl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4l)
IR (KBr) Vmax (cm$^{-1}$), 3598 cm$^{-1}$ Ar-CH, 3247.54 cm$^{-1}$–NH, 2981 cm$^{-1}$-CH$_3$, 2676 cm$^{-1}$ NCO(stretching), 2410 cm$^{-1}$ NCOCH$_3$, 1535.06 –C=O, 1263 cm$^{-1}$ C-N, 890 cm$^{-1}$ –C=S.

5.1.13: N-[3-(4-acetyl-5-ethyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]acetamide.(4m)
IR (KBr) Vmax (cm$^{-1}$), 3544 cm$^{-1}$ Ar-CH, 3254.34 cm$^{-1}$–NH, 2885 cm$^{-1}$ CH$_2$-CH$_2$, 2616 cm$^{-1}$ NCO(stretching), 2410 cm$^{-1}$ NCOCH$_3$, 1619 –C=O, 1252 cm$^{-1}$ C-N, 877 cm$^{-1}$ –C=S.

**Result and Discussion**

Pharmacological Screening

All the synthesized compounds were subjected to analgesic activity at a 200 mg/kg; body weight dose using acetic acid induced writhing method in mice. All the synthesized compounds showed significant analgesic activity as compared to the standard Diclofenac. All the synthesized compounds were subjected to In vitro anti-inflammatory activity by using inhibition of albumin denaturation technique.

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The synthesized compounds have different concentration, the absorbance was measured and calculate the percentage inhibition and IC\textsubscript{50} value. The results for evaluation of analgesic and invitro anti-inflammatory activity are presented in table 2 and 3 respectively. Compounds 4e, 4h and 4j exhibited excellent analgesic activity with percent protection 49.17, 54.58 and 61.17 respectively as compared to standard. Amongst all synthesized compounds could inhibit the denaturation of albumin in comparison with standard. The standard drug Diclofenac exhibited IC\textsubscript{50} value are 242.28 ppm. Amongst all synthesized compounds 4e, 4h and 4j exhibited excellent anti-inflammatory activity with IC\textsubscript{50} 282.10, 186.94 and 295.80 ppm respectively as compared to standard.

**Conclusion**

Substituted benzothiophene derivatives was synthesized and to screen the synthesized compounds for analgesic and in-vitro anti-inflammatory activity. The compounds planned for synthesis were prepared under available laboratory conditions and purity of the compounds were checked by melting point and Rf value and structural confirmation is done by IR and \textsuperscript{1}HNMR data. Amongst all synthesized compounds 4e, 4h and 4j exhibited significant analgesic activity with percent protection 49.17, 54.58 and 61.17 respectively as compared to standard and the standard drug diclofenac exhibited IC\textsubscript{50} value are 242.28 ppm. Amongst all synthesized compounds 4e, 4h and 4j exhibited significant anti-inflammatory activity with IC\textsubscript{50} 282.10, 186.94 and 295.80 ppm respectively as compared to standard.

**References**

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![Scheme 1]

**Table no 1: Physical data of synthesized compounds.**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>% yield</th>
<th>Melting point</th>
<th>Rf value</th>
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<tr>
<td>4a</td>
<td>3,4,5(0CH3)3C6H2-</td>
<td>C23H27N3O3S</td>
<td>473</td>
<td>70</td>
<td>50-53</td>
<td>0.45</td>
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<tr>
<td>4b</td>
<td>p-OCH3-C6H4-</td>
<td>C21H23N3O3S</td>
<td>413</td>
<td>55</td>
<td>55-56</td>
<td>0.62</td>
</tr>
<tr>
<td>4c</td>
<td>-C6H5</td>
<td>C20H21N3O3S</td>
<td>383</td>
<td>79</td>
<td>75-78</td>
<td>0.80</td>
</tr>
<tr>
<td>4d</td>
<td>N-(CH3)2-C6H4-</td>
<td>C22H23N3O3S</td>
<td>428</td>
<td>20</td>
<td>105-106</td>
<td>0.48</td>
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<tr>
<td>4e</td>
<td>p-OH-C6H4-</td>
<td>C20H23N3O3S</td>
<td>401</td>
<td>69.13</td>
<td>98-100</td>
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<td>4f</td>
<td>m-NO2-C6H4-</td>
<td>C20H23N3O3S</td>
<td>430</td>
<td>64</td>
<td>60-62</td>
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<tr>
<td>4g</td>
<td>o-OH-C6H4-</td>
<td>C20H23N3O3S</td>
<td>401</td>
<td>68</td>
<td>95-98</td>
<td>0.72</td>
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<tr>
<td>4h</td>
<td>p-NO2-C6H4-</td>
<td>C20H23N3O3S</td>
<td>430</td>
<td>51</td>
<td>108-110</td>
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<tr>
<td>4i</td>
<td>-CH=CH-C6H4-</td>
<td>C21H23N3O3S</td>
<td>397</td>
<td>58</td>
<td>45-46</td>
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<tr>
<td>4j</td>
<td>p-Cl-C6H4-</td>
<td>C20H22ClN3O3S</td>
<td>419</td>
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<td>335</td>
<td>69.33</td>
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<td>0.48</td>
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Table 2: Analgesic activity of N-[3-(4-acetyl-5-substituted-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-
tetrahydro-1- benzothiophen-2-yl]acetamide.

<table>
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<tr>
<th>Group</th>
<th>Dose</th>
<th>No. of writhes ± SEM</th>
<th>Percentage Inhibition</th>
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<tr>
<td>Control</td>
<td>0.1ml/10g</td>
<td>42.05±0.50</td>
<td>-</td>
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<tr>
<td>Standard</td>
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<td>8.6±0.42**</td>
<td>79.78</td>
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<tr>
<td>4a</td>
<td>200mg/kg</td>
<td>26.9±2.08**</td>
<td>36.94</td>
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<tr>
<td>4b</td>
<td>200mg/kg</td>
<td>23.85±1.5**</td>
<td>43.88</td>
</tr>
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<td>4c</td>
<td>200mg/kg</td>
<td>29.1±1.73**</td>
<td>31.78</td>
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<tr>
<td>4d</td>
<td>200mg/kg</td>
<td>27.2±2.08**</td>
<td>36.24</td>
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<td>4e</td>
<td>200mg/kg</td>
<td>21.6±1.2**</td>
<td>49.17</td>
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<td>4f</td>
<td>200mg/kg</td>
<td>27.60±1.000**</td>
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<td>45.14</td>
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<td>4h</td>
<td>200mg/kg</td>
<td>19.32±0.97**</td>
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<tr>
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<td>200mg/kg</td>
<td>29.3±1.856**</td>
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<td>4j</td>
<td>200mg/kg</td>
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<td>4m</td>
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<td>22.83±1.80**</td>
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**p<0.01, * p<0.05,  NS Non signifiant, n=6 ; Data expressed as Mean ± SEM; Data was analyzed by one-
way ANOVA followed by Dunnett’s test.

Table 3: Anti-inflammatory data of N-[3-(4-acetyl-5-substituted-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4,5,6,7-
tetrahydro-1- benzothiophen-2-yl]acetamide.

<table>
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<th>Conc.(µg/ml)</th>
<th>25</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
<th>Ic50(ppm)</th>
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<tbody>
<tr>
<td>Standard</td>
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<td>29</td>
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<td>32</td>
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<td>40</td>
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