

## Synthesis of phthalimide and naphthalimide derived Biginelli compounds and evaluation of their anti-inflammatory and anti-oxidant activities

Pradeep Ramesh Rao Totawar<sup>a</sup>, Ravi Varala<sup>b\*</sup>, Vijay Kotra<sup>c</sup> and Jitendra S. Pulle<sup>d</sup>

<sup>a</sup>Nagnath Arts, Commerce and Science College, Aundha Nagnath, Hingoli-431705, Maharashtra, India

<sup>b</sup>Scripts Pharma, Hyderabad-500 076, Telangana, India

<sup>c</sup>Faculty of Pharmacy, Quest International University, Ipoh 30250, Malaysia

<sup>d</sup>Shri Guru Buddhi Swami Mahavidyalaya, Purna, Parbhani-431511, Maharashtra, India

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### ABSTRACT

In the present work, synthesis of phthalimide and naphthalimide derived Biginelli compounds was performed. Allylation of phthalic & naphthalic anhydride, followed by ozonolysis resulted in the formation of *N*-phthalimido/naphthalimido acetaldehyde (**2** and **7**). These aldehydes were subjected to Biginelli reaction using urea/thiourea and divergent  $\beta$ -keto esters in the presence of sulfated tin oxide (5 mol%) as catalyst in ethanol reflux to produce the corresponding dihydropyrimidinone compounds (**5a-j** and **8a-h**). Additionally, both their antioxidant and anti-inflammatory functions were carried out. Compounds **5e**, **5f**, **5i**, and **5j** have shown potent to moderate potent activity for both antioxidant and anti-inflammatory activities when compared to standard. Compounds **8c** and **8g** have shown potent antioxidant and anti-inflammatory activities when compared to other compounds.

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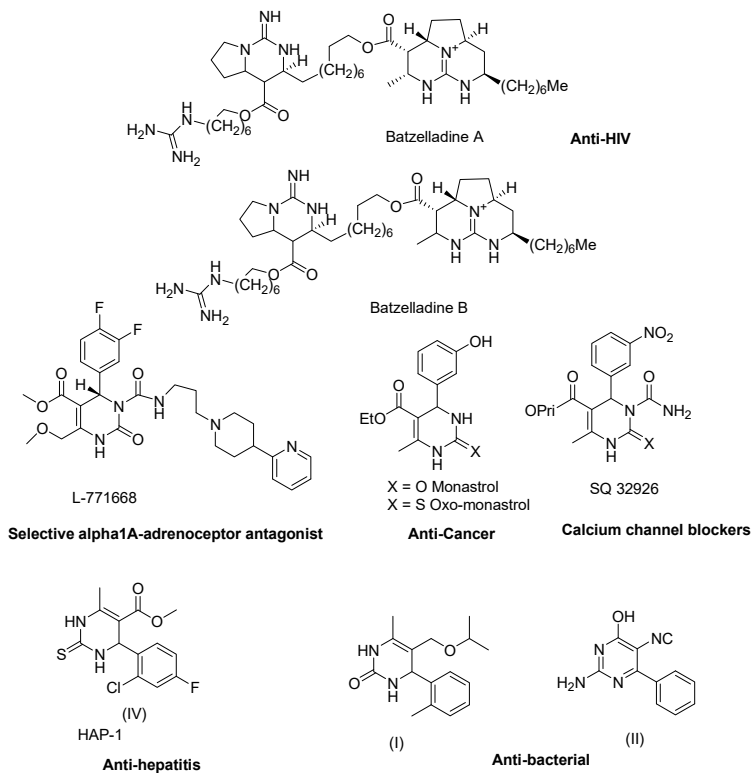
## 1. Introduction

Multi-component reactions (MCRs), which feature selectivity, excellent yields, quicker reaction times, atom economy, and environmental friendliness, are crucial tools in the arsenal of synthetic and medicinal chemists for the production of a wide range of new chemical entities (NCEs).<sup>1</sup> Traditional methodologies required multiple steps and rigorous workup procedures.<sup>2-4</sup> The Biginelli reaction is one of the MCRs, which produces 3,4-dihydropyrimidin-2(1*H*)-ones/thiones from the reaction of aldehydes, urea/thiourea and  $\beta$ -keto esters, with biological relevance,<sup>5-6</sup> such as calcium channel blockers, antihypertensive medicines, anti-inflammatory, anticancer, antiviral, and antibacterial, holds a prominent place among multi-component reactions (**Fig. 1**).<sup>7-13, 35</sup>

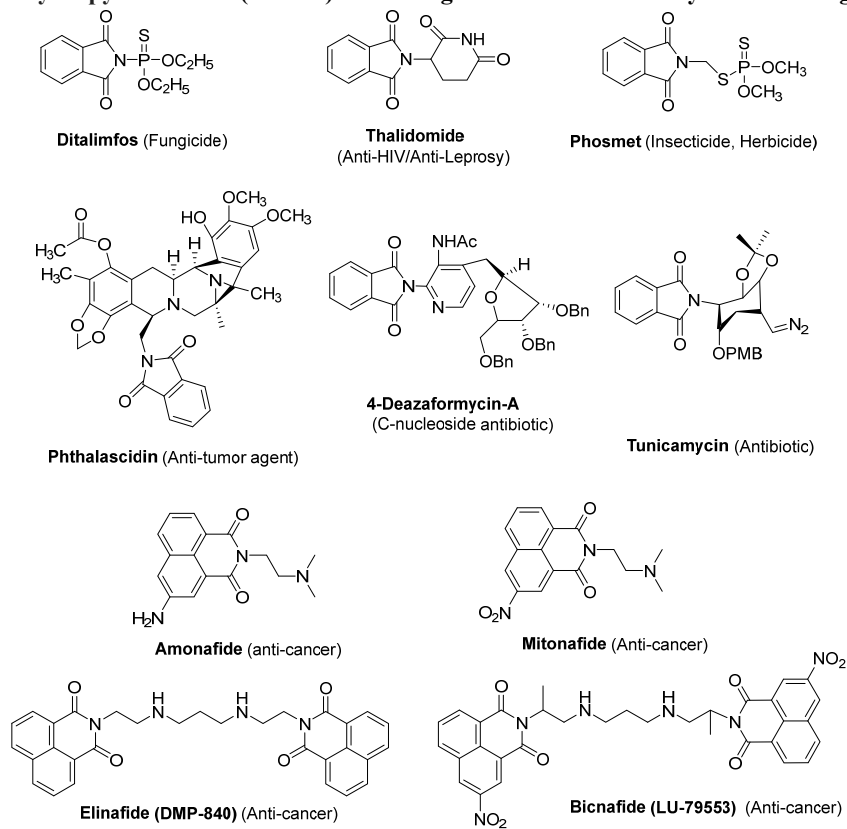
Tumor necrosis factor (TNF) inhibitors, analgesic, anticancer, anti-inflammatory, Ca channel blockers, antihypertensive, pesticide, insecticide, herbicide, and other biological actions have been linked to phthalimide derivatives (Figure 2).<sup>14-16</sup> The synthesis of phthalimide analogues is the subject of extensive study because of the wide range of applications they have in medicine. As the primary scaffold for numerous anticancer, anti-inflammatory, antidepressant, anti-protazoal, and antiviral medicines, among others, naphthalimides are a significant class of aromatic heterocycles with significant pharmacological relevance (**Fig. 2**).<sup>17-22</sup> Naphthalimide's tricyclic planar ring system is principally responsible for its intercalation with DNA to disrupt cellular processes, and the molecule's substitution pattern results in a number of other uses. The majority of them, including amonafide, have been dropped, nonetheless, due to their low therapeutic index

\* Corresponding author. Tel.: +91-9618286529  
E-mail address [ravivarala@gmail.com](mailto:ravivarala@gmail.com) (R. Varala)

and hemotoxicity. Numerous novel naphthalimide compounds have been created and synthesized in an effort to address these drawbacks and test them for improved efficacy.



**Fig. 1. Dihydropyrimidinone (DHPM) containing various natural and synthetic analogues.**<sup>44-45</sup>



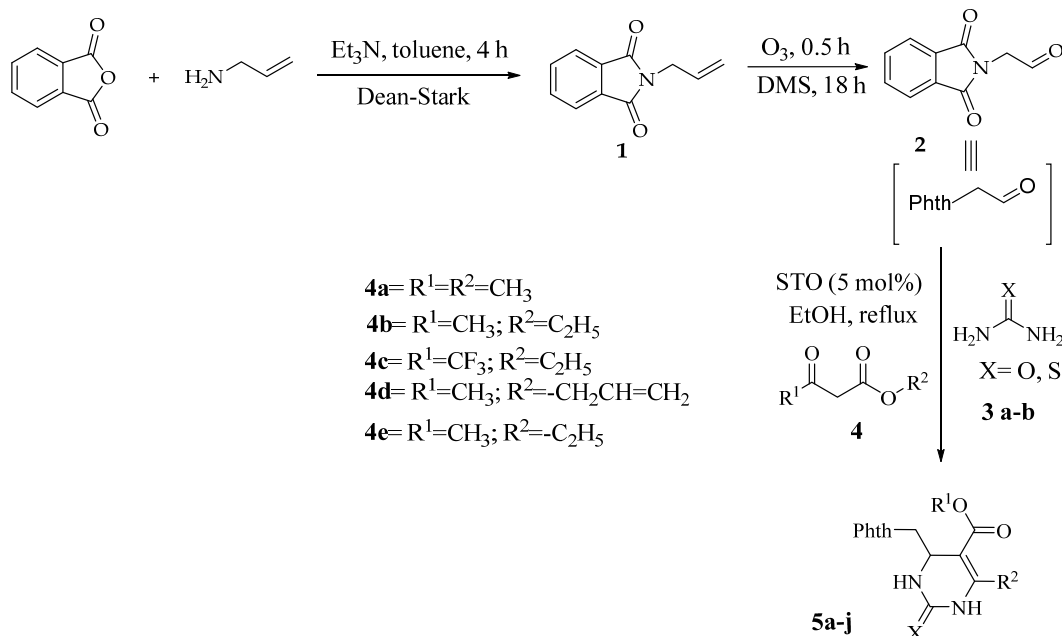
**Fig. 2. Representative biologically active phthalimide and naphthalimide analogues.**<sup>46-48</sup>

Sulfated tin oxide (hereafter referred to as STO) has received a lot of attention recently in the fields of catalysis and organic synthesis due to its high efficiency, low cost, greater stability, non-corrosive, reuse, and recyclability, as well as its large surface area.<sup>23</sup> As a result, they have been extensively used as a solid acid heterogeneous catalyst in a variety of synthetic transformations.<sup>24</sup>

The hybrid compounds (phthalimide/naphthalimide and dihydropyrimidinone) that contain these two essential heterocyclic scaffolds may exhibit significant or influential therapeutic potential. In keeping with our earlier findings on the chemistry of phthalimides and naphthalimides<sup>25-27</sup> and the synthesis of various dihydropyrimidinones,<sup>28-34</sup> a few hybrid analogues of *N*-naphthalaldehyde derived dihydropyrimidinones were prepared using straightforward chemistry and subjected to studies on their ability to reduce inflammation and fight free radicals.

## 2. Results and Discussion

As stated in the experimental procedure, initially, we generated *N*-phthalimido acetaldehyde (**2**) from ozonolysis of *N*-allyl phthalimide (**1**) based on our prior strategies (Scheme 1).<sup>25-27</sup> The spectral data of the two matched data from the literature.



**Scheme 1.** Synthesis of Biginelli-phthalimide analogues.

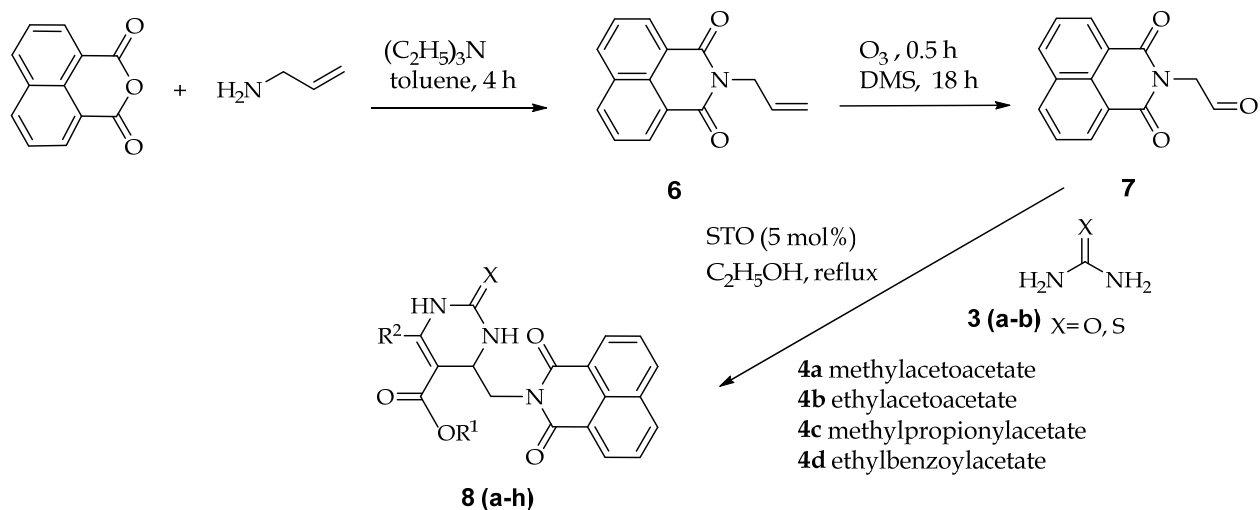
Divergent  $\beta$ -ketoesters (**4**, 1 equiv.), urea/thiourea (**3**, 1.5 equiv.), and *N*-phthalimido acetaldehyde (**2**) (1 equiv.) were allowed to react under reflux conditions with freshly made sulfated tin oxide (STO, 5 mol%) in ethanol (5 mL) as shown in Scheme 1. STO loading was increased to 10 mol% without appreciably changing the yield. Alcohol was discovered to be the preferred solvent for the synthesis of biginelli phthalimide analogues among the solvents examined, including acetonitrile, toluene, DMF, xylene, and CCl<sub>4</sub>. Different  $\beta$ -ketoesters were given the opportunity to react with thiourea/urea, and this resulted in a variety of products with good yields (83-97%) and quick (2-3.5 h) reaction periods (Table 1). There was enough spectral data to characterize every compound that was produced (see Supporting Information). Without losing its reactivity, the catalyst can be recycled and used at least four times (**5c**, 97%, 96%, 94%, and 94%, respectively).

**Table 1.** STO-Catalyzed synthesis of phthalimide derived Biginelli compounds.

Urea/Thiourea	1,3-diketones	Product	Time(h)	Yield(%) <sup>a</sup>
Urea	Methylacetoacetate	<b>5a</b>	2	90
Thiourea		<b>5b</b>	2.5	92
Urea	Ethylacetoacetate	<b>5c</b>	2	97
Thiourea		<b>5d</b>	2	94
Urea	Ethyl trifluoroacetoacetate	<b>5e</b>	3	83
Thiourea		<b>5f</b>	2.5	85
Urea	Allyl acetoacetate	<b>5g</b>	2.5	90
Thiourea		<b>5h</b>	2	93
Urea	Ethyl benzoylacetate	<b>5i</b>	3	91
Thiourea		<b>5j</b>	3.5	90

<sup>a</sup>Isolated yield

We expanded this approach to include the synthesis of Biginelli compounds produced from naphthalimides because the outcomes from phthalimide hybrid analogues intrigued us. According to the experimental protocol, *N*-allyl naphthalimide (**6**) was ozonolyzed to produce *N*-naphthalimido acetaldehyde (**7**).<sup>17</sup> The spectral data of **7** corresponded to data from the literature. Aldehyde **7** was dissolved in ethanol, and then excess urea/thiourea (**3a-b**) and  $\alpha,\beta$ -ketoesters (**4a-d**) were added to the resultant solution. The reaction was accelerated by STO (5 mol%) in ethanol, and when it was conducted out under reflux conditions, the required products (**8a-h**) were produced in yields that ranged from moderate to good (78-94%) (**Scheme 2**).



- 8a** (93%) R<sup>1</sup>=CH<sub>3</sub>; R<sup>2</sup>=CH<sub>3</sub>; X=O      **8e** (87%) R<sup>1</sup>=C<sub>2</sub>H<sub>5</sub>; R<sup>2</sup>=CH<sub>3</sub>; X=O)  
**8b** (90%) R<sup>1</sup>=CH<sub>3</sub>; R<sup>2</sup>=CH<sub>3</sub>; X=S)      **8f** (78%) R<sup>1</sup>=C<sub>2</sub>H<sub>5</sub>; R<sup>2</sup>=CH<sub>3</sub>; X=S)  
**8c** (89%) R<sup>1</sup>=CH<sub>3</sub>; R<sup>2</sup>=C<sub>2</sub>H<sub>5</sub>; X=O)      **8g** (82%) R<sup>1</sup>=C<sub>2</sub>H<sub>5</sub>; R<sup>2</sup>=Ph; X=O)  
**8d** (94%) R<sup>1</sup>=CH<sub>3</sub>; R<sup>2</sup>=C<sub>2</sub>H<sub>5</sub>; X=S)      **8h** (91%) R<sup>1</sup>=C<sub>2</sub>H<sub>5</sub>; R<sup>2</sup>=Ph; X=S)

**Scheme 2.** Synthesis of Biginelli-naphthalimide analogues.

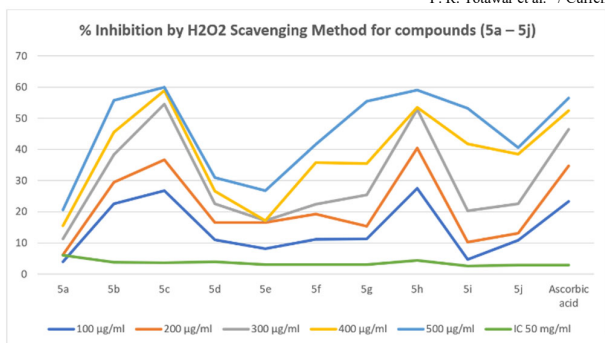
## Biological activities

### Antioxidant activity:

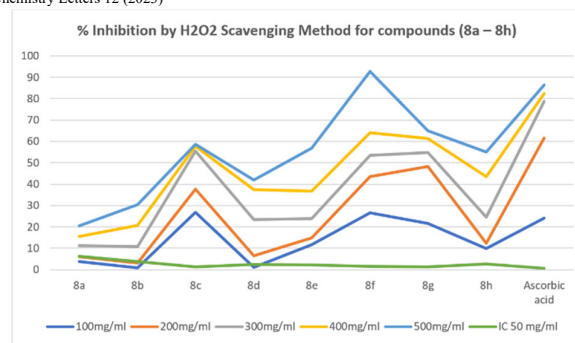
All of the compounds in the title displayed antioxidant activity by scavenging hydrogen peroxide.<sup>36</sup> Compound **5i** has demonstrated greater activity when compared to standard among the compounds tested for antioxidant activity. Following compound **5j**, which shown strong action, were compounds **5e** and **5f**, which displayed moderate activity (**Table 2** and **Fig. 3**). Compounds **8c** and **8g** from the compounds (**8a-h**) have demonstrated potent action when compared to other compounds activity (**Table 3** and **Fig. 4**).

**Table 2.** Antioxidant activity of synthesized compounds by hydrogen peroxide scavenging method.

Compound	% inhibition by H <sub>2</sub> O <sub>2</sub> scavenging method					IC 50
	Concentrations (µg/ml)					
	100 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml	500 µg/ml	
<b>5a</b>	3.9	6.2	11.29	15.53	20.55	6.1
<b>5b</b>	22.6	29.5	38.4	45.5	55.8	3.85
<b>5c</b>	26.8	36.7	54.5	58.9	59.95	3.67
<b>5d</b>	10.98	16.48	22.54	26.56	30.9	3.88
<b>5e</b>	8.1	16.52	17.21	17.22	26.81	3.00
<b>5f</b>	11.1	19.3	22.43	35.7	41.6	3.02
<b>5g</b>	11.23	15.36	25.45	35.43	55.5	3.09
<b>5h</b>	27.5	40.5	52.95	53.47	59	4.35
<b>5i</b>	4.7	10.30	20.34	41.71	53.13	2.53
<b>5j</b>	10.78	13.07	22.61	38.55	40.63	2.90
Ascorbic acid	23.3	34.78	46.45	52.45	56.46	2.88



**Fig. 3.** % Inhibition by H<sub>2</sub>O<sub>2</sub> scavenging method for compounds **5a-j**



**Fig. 4.** % Inhibition by H<sub>2</sub>O<sub>2</sub> Scavenging Method for compounds **(8a-h)**

**Table 3.** % inhibition by H<sub>2</sub>O<sub>2</sub> scavenging method Concentrations (µg/ml).

Compound	% inhibition by H <sub>2</sub> O <sub>2</sub> scavenging method Concentrations (µg/ml)					IC 50 µg/ml
	100 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml	500 µg/ml	
<b>8a</b>	3.8	6.1	11.34	15.49	20.58	6.2
<b>8b</b>	0.76	3.17	10.73	20.75	30.34	3.74
<b>8c</b>	26.79	37.67	55.38	57.82	58.64	1.36
<b>8d</b>	0.99	6.52	23.45	37.34	41.89	2.48
<b>8e</b>	11.67	14.75	23.98	36.83	56.86	2.27
<b>8f</b>	26.49	43.49	53.44	64.12	92.67	1.62
<b>8g</b>	21.62	48.32	54.76	61.43	64.93	1.39
<b>8h</b>	9.82	12.46	24.48	43.62	54.92	2.69
<b>Ascorbic acid</b>	24.2	61.64	78.62	82.26	86.43	0.64

### Anti-inflammatory activity

Using a carrageenan-induced acute paw oedema method in rats, all of the title compounds were evaluated for their ability to reduce inflammation.<sup>37</sup> Compounds **5e**, **5f**, **5i**, and **5j** among them have significantly reduced paw oedema (**Table 4**, **Fig. 5**). The compound **5i** showed highest protection of 81.67 %, followed by compounds **5j**, **5e** and **5f** (80.35, 80.26 and 79.37 % respectively). According to the aforementioned findings, molecules with ethyl benzoyl and ethyl trifluoro groups exhibit more activity than those without these groups. Paw oedema has been significantly reduced by compound **8c** and compound **8g** having ethyl and phenyl substituents, respectively (**Table 5**, **Fig. 6**).

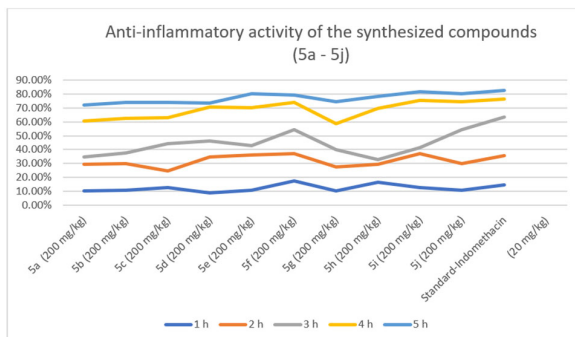
**Table 4.** Anti-inflammatory activity of the phthalimide derived Biginelli compounds.

Compound	1 h	2 h	3 h	4 h	5 h
Control	0.33±0.02	0.59±0.01	0.63±0.02	0.73±0.02	0.85±0.01
<b>5a</b> (200 mg/kg)	0.29±0.01 (10.42%)	0.55±0.03 (29.48%)	0.37±0.02 (34.63%)	0.29±0.03* (60.78%)	0.22±0.01** (72.18%)
<b>5b</b> (200 mg/kg)	0.29±0.04 (10.64%)	0.55±0.04 (29.86%)	0.43±0.04 (37.62%)	0.28±0.03* (62.44%)	0.19±0.03** (74.04%)
<b>5c</b> (200 mg/kg)	0.28±0.04 (12.64%)	0.56±0.04 (24.38%)	0.39±0.03 (44.37%)	0.29±0.04* (62.84%)	0.18±0.04** (74.22%)
<b>5d</b> (200 mg/kg)	0.31±0.03 (08.92%)	0.53±0.01 (34.82%)	0.34±0.04 (46.28%)	0.26±0.02 (70.64%)	0.20±0.01** (73.84%)
<b>5e</b> (200 mg/kg)	0.29±0.03 (10.56%)	0.52±0.04 (36.10%)	0.38±0.02 (43.10%)	0.26±0.01** (70.42%)	0.17±0.04*** (80.26%)
<b>5f</b> (200 mg/kg)	0.25±0.02 (17.32%)	0.53±0.04 (36.86%)	0.33±0.03 (54.54%)	0.24±0.01 (74.22%)	0.18±0.02 (79.37%)
<b>5g</b> (200 mg/kg)	0.25±0.04 (10.34%)	0.55±0.02 (27.38%)	0.40±0.01 (40.16%)	0.30±0.02* (58.62%)	0.18±0.04** (74.52%)
<b>5h</b> (200 mg/kg)	0.26±0.03 (16.28%)	0.54±0.04 (29.64%)	0.36±0.02 (32.88%)	0.26±0.01 (69.86%)	0.17±0.02 (78.46%)
<b>5i</b> (200 mg/kg)	0.28±0.04 (12.64%)	0.52±0.04 (36.87%)	0.34±0.01 (41.48%)	0.25±0.01** (75.29%)	0.16±0.03*** (81.67%)
<b>5j</b> (200 mg/kg)	0.29±0.02 (10.46%)	0.54±0.04 (29.86%)	0.36±0.03 (54.24%)	0.25±0.04** (74.64%)	0.15±0.04*** (80.35%)
Indomethacin (20 mg/kg)	0.26±0.02 (14.44%)	0.54±0.01 (35.83%)	0.32±0.01* (63.28%)	0.24±0.03*** (76.59%)	0.15±0.02*** (82.94%)

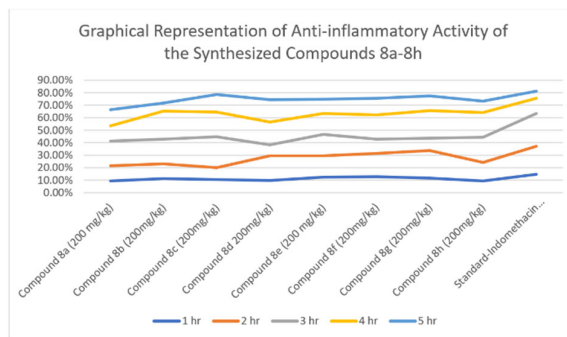
All values are mean ± SEM values using 6 animals in each group.

Significant differences with respect to control group was evaluated by ANOVA, Dunnett's 't' test .

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.



**Fig. 5.** Anti-inflammatory activity of the synthesized compounds (**5a-j**)



**Fig. 6.** Anti-inflammatory Activity of the Synthesized Compounds **8a-h**

**Table 5.** Anti-inflammatory activity of the synthesized compounds **8a-h**

Group	1 h	2 h	3 h	4 h	5 h
Control 1% Water (1 ml/kg)	0.32±0.01	0.58±0.02	0.61±0.02	0.74±0.01	0.83±0.02
<b>8a</b> (200 mg/kg)	0.27±0.02 (9.37%)	0.43±0.01 (21.62%)	0.31±0.02 (41.34%)	0.22±0.03 (53.32%)	0.21±0.02 (66.38%)
<b>8b</b> (200 mg/kg)	0.21±0.02 (11.34%)	0.42±0.02 (22.96%)	0.32±0.02 (42.86%)	0.23±0.01 (65.29%)	0.18±0.04** (71.64%)
<b>8c</b> (200 mg/kg)	0.45±0.02 (10.53%)	0.48±0.03 (20.19%)	0.29±0.02 (44.67%)	0.24±0.02 (64.53%)	0.17±0.02* (78.42%)
<b>8d</b> (200 mg/kg)	0.26±0.01 (09.64%)	0.46±0.02 (29.64%)	0.34±0.03 (38.39%)	0.24±0.02 (56.53%)	0.16±0.01** (74.28%)
<b>8e</b> (200 mg/kg)	0.28±0.02 (12.32%)	0.48±0.03 (29.68%)	0.32±0.02 (46.56%)	0.26±0.01 (63.46%)	0.16±0.02** (74.84%)
<b>8f</b> (200 mg/kg)	0.23±0.03 (12.65%)	0.49±0.03 (31.46%)	0.31±0.02 (42.67%)	0.27±0.02 (62.24%)	0.15±0.03** (75.52%)
<b>8g</b> (200 mg/kg)	0.25±0.01 (11.75%)	0.46±0.03 (33.63%)	0.32±0.02 (43.46%)	0.25±0.03 (65.63%)	0.17±0.01* (77.22%)
<b>8h</b> (200 mg/kg)	0.27±0.02 (9.43%)	0.46±0.01 (24.24%)	0.33±0.02 (44.43%)	0.26±0.04 (64.26%)	0.18±0.03** (73.04%)
Indomethacin (20 mg/kg)	0.26±0.01 (14.67%)	0.52±0.02 (37.26%)	0.31±0.01** (63.39%)	0.24±0.03*** (75.47%)	0.14±0.02*** (81%)

All values are mean ± SEM values using 6 animals in each group.

Significant differences with respect to control group was evaluated by ANOVA, Dunnett's 't' test.

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

### Acute oral toxicity

On the basis of the guidelines for the produced compounds **8a-h**, acute oral toxicity was conducted. Following administration of 200 mg/kg body weight for all the compounds, no harmful effects were seen. Therefore, additional anti-inflammatory action was performed at a dose of 100 mg/kg body weight, which was deemed safe because no deaths were noticed.

### 3. Conclusions

In this study, authors have presented a low-cost, environmentally friendly method for producing phthalimido and naphthalimido-dihydropyrimidine hybrid analogues by reacting *N*-naphthalimido acetaldehyde, divergent β-keto esters with urea/thio-urea under reflux conditions in ethanol with 5 mol% sulfated tin oxide (STO) as a Lewis acid catalyst. The results of screening synthetic compounds for their antioxidant and anti-inflammatory properties are performed. When compared to standards, compounds **5e**, **5f**, **5i**, and **5j** have demonstrated powerful to moderately potent efficacy for both antioxidant and anti-inflammatory properties. According to the aforementioned findings, molecules with ethyl benzoyl and ethyl trifluoro groups exhibited more activity than those without these groups. When compared to other compounds, compounds **8c** and **8g** with ethyl and phenyl substituents have demonstrated strong antioxidant and anti-inflammatory effects.

### Acknowledgements

Dr. RV thanks Dr. Ch. V. Rajasekhar, Scrips Pharma for his continued support and encouragement.

### 4. Experimental

Please refer to Supporting Information

This paper ensures that applied sciences are very important in nature due to their various uses as reported before.<sup>38-43</sup>

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