

## SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL THIAZOLE-PYRAZOLE INTEGRATED CHALCONES AS ANTIOXIDANT AND ANTI-INFLAMMATORY AGENTS

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## ABSTRACT

**Objective:** The objective of the present study was to synthesize the thiazole-pyrazole integrated chalcones and their *in vitro* antioxidant and anti-inflammatory evaluation.

**Methods:** The designed hybrid thiazole-pyrazole integrated chalcones (**3a-j**) were synthesized by Claisen-Schmidt reaction of substituted 1-(4-methyl-2-phenylthiazol-5-yl) ethanone and substituted pyrazole aldehyde in the presence of 10% NaOH in ethanol solvent under reflux condition. The chemical structures of synthesized compounds were confirmed by IR, <sup>1</sup>H nuclear magnetic resonance (NMR), <sup>13</sup>C NMR, and high-resolution mass spectra.

**Results:** All the title compounds were screened for their *in vitro* antioxidant and anti-inflammatory activity. The screening data indicated that tested compounds showed potent antioxidant activity with moderate anti-inflammatory potential.

**Conclusion:** Antioxidant screening data reveal that most of the synthesized compounds possess excellent 1,1-diphenyl-2-picrylhydrazyl and NO radical scavenging activity. Most of the compounds found to possess marked anti-inflammatory potential by effectively inhibiting the heat-induced albumin denaturation.

**Keywords:** Thiazole, Pyrazole, Chalcone, Antioxidant activity, Anti-inflammatory activity.

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## INTRODUCTION

Chalcones are richly present in nature, source of chalcone starting from ferns to higher plants and some of them are polyhydroxylated in the aryl nucleus [1,2]. Many synthetic methods are reported for the synthesis of chalcones such as Claisen-Schmidt reaction [3], Allan-Robinson condensation (synthesis of flavones through chalcones) [4], Suzuki coupling reaction [5], Ganguly's method (synthesis of flavones through chalcones) [6], Knoevenagel condensation [7], Mukaiyama-type aldol condensation [8], direct cross-coupling reaction [9], chalcone synthesis using boron trifluoride-etherate [10], sonochemical and microwave irradiation technique [11], and grinding technique [12]. The most widely used method is Claisen-Schmidt condensation of ketones and aldehydes.

The presence of thiazole and pyrazole nucleus in different organic structures leads to potent biological activities such as anticancer [13-14], antimicrobial [15-17], anti-inflammatory, and antioxidant [18], antidiabetic [19], and protein kinase inhibitor [20], literature survey reveals that so many of the natural and synthetic thiazole and pyrazole chalcones possess large number of pharmaceutical activities. Due to the importance and in continuation of our work on synthesis of biologically important molecules [21], here, we designed and synthesized various thiazole-pyrazole integrated chalcones (Scheme 1).

## EXPERIMENTAL SECTION

## Materials and methods

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. All the solvents were dried and distilled before use. The melting points were

determined in open capillary tube and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S Fourier-transform infrared spectrophotometer using potassium bromide. The <sup>1</sup>H nuclear magnetic resonance (NMR) was recorded in CDCl<sub>3</sub> using Bruker 400 MHz NMR spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane as an internal standard. Reactions were monitored using thin-layer chromatography (TLC) carried out on precoated aluminum plates. The visualization was achieved under ultraviolet light or staining with I<sub>2</sub>. Chromatographic separations were achieved on silica gel columns (Merck, 60-120 mesh) using gradient of hexane/ethyl acetate as eluent.

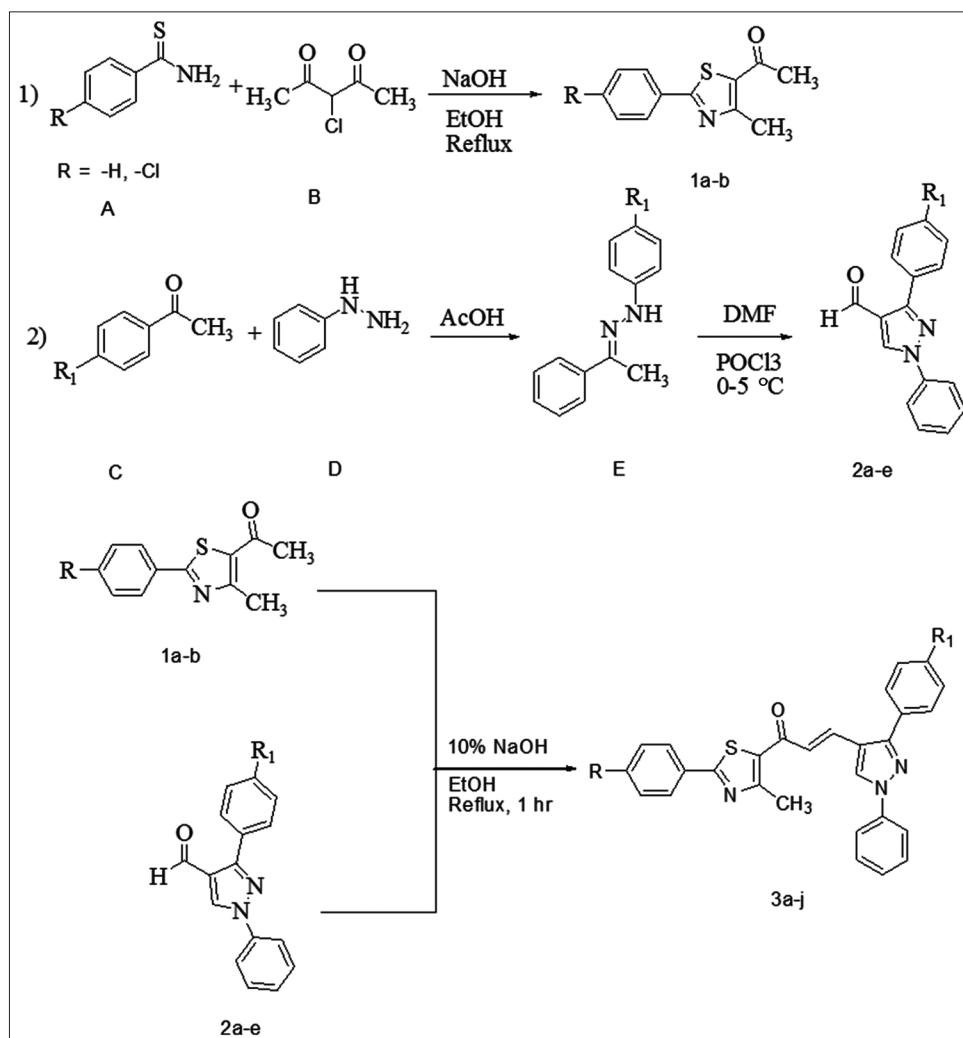
## General procedure for the preparation of thiazole-pyrazole integrated chalcones

Mixture of substituted 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (1 mmol) (**1a-b**) and substituted pyrazole aldehyde (1 mmol) (**2a-e**) was dissolved in 15 ml ethanol. To this reaction, mixture added freshly prepared 1 ml of 10% sodium hydroxide. The reaction mixture was refluxed at 80-90°C. The progress of reaction checked by TLC. After completion of the reaction (1 h), reaction mixture was poured in ice-cold water and stirred for 15 min. The obtained yellow-colored solid was filtered, washed with cold water, and dried. The crude product was recrystallized using ethanol to afford pure titled compound (**3a-j**).

## Spectral data of representative compound

(*E*)-1-(4-methyl-2-phenylthiazol-5-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl) prop-2-en-1-one (**3a**)

Yellow solid; 73%; M.P. 172-174°C; IR (KBr): 2922, 2852, 1742, 1650, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ=2.823 (s, 3H, Thy-CH<sub>3</sub>), 7.152



Where,

<b>3a</b> R <sub>1</sub> =H, R <sub>2</sub> =H	<b>3b</b> R <sub>1</sub> =H, R <sub>2</sub> =F	<b>3c</b> R <sub>1</sub> =H, R <sub>2</sub> =CH <sub>3</sub>
<b>3d</b> R <sub>1</sub> =H, R <sub>2</sub> =NO <sub>2</sub>	<b>3e</b> R <sub>1</sub> =H, R <sub>2</sub> =OCH <sub>3</sub>	<b>3f</b> R <sub>1</sub> =Cl, R <sub>2</sub> =H
<b>3g</b> R <sub>1</sub> =Cl, R <sub>2</sub> =F	<b>3h</b> R <sub>1</sub> =Cl, R <sub>2</sub> =CH <sub>3</sub>	<b>3i</b> R <sub>1</sub> =Cl, R <sub>2</sub> =NO <sub>2</sub>
<b>3j</b> R <sub>1</sub> =Cl, R <sub>2</sub> =OCH <sub>3</sub>		

**Scheme 1: Synthesis of thiazole-pyrazole integrated chalcones**

(d, 1H, COCH=CH, J=15.2 Hz), 7.376–7.965 (m, 1H, Ar-H), 7.465–7.546 (m, 8H, Ar-H), 7.709–7.733 (m, 2H, Ar-H), 7.813–7.893 (m, 2H, Ar-H), 7.913 (d, 1H, COCH=CH, J=15.2 Hz), 7.995–8.019 (m, 2H, Ar-H), 8.36 (s, 1H, Pyr-H); high-resolution mass spectra (HRMS): m/z=448.1469 (M+1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>, δ in ppm): 18.64 (m, Thy-CH<sub>3</sub>), 117.92 (m, C), 119.44 (s, C), 123.95 (m, -CH), 126.90 (s, -CH), 127.04 (m, -CH), 127.37 (m, -CH), 128.81 (s, -CH), 128.86 (s, -CH), 129.12 (s, -CH), 129.60 (m, =CH), 131.15 (w, -CH), 131.26 (m, -CH), 132.21 (m, -CH), 132.89 (w, C), 135.00 (m, C), 139.35 (w, =CH), 154.05 (w, C), 160.28 (w, C), 169.03 (w, C), 182.29 (w, C=O).

*(E)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-methyl-2-phenylthiazol-5-yl)prop-2-en-1-one (3b)*

Yellow solid; 82%; M.P. 352–354°C; IR (KBr): 2922, 2852, 1747, 1650, 1215, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ=2.839 (s, 3H, Thy-CH<sub>3</sub>), 7.090 (d, 1H, COCH=CH, J=15.6 Hz), 7.196–7.240 (m, 2H, Ar-H), 7.383–7.402 (m, 1H, Ar-H), 7.481–7.543 (m, 5H, Ar-H), 7.682–7.718 (m, 2H, Ar-H), 7.800–7.883 (m, 2H, Ar-H and d, 1H, CO-CH=CH, J=15.2 Hz), 7.999–8.023 (m, 2H, Ar-H), 8.352 (s, 1H, Pyr-H); HRMS: m/z=466.1373 (M+1)

*(E)-1-(4-methyl-2-phenylthiazol-5-yl)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)prop-2-en-1-one (Compound 3c)*

Yellow solid; 70%; M.P. 204°C; IR (KBr): 3015, 2918, 1747, 1646, 755; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.447 (s, 3H, Ar-CH<sub>3</sub>), 2.821 (s, 3H, Thy-CH<sub>3</sub>), 7.092 (d, 1H, CO-CH=CH, J=15.6 Hz), 7.318–7.386 (m, 3H, Ar-H), 7.477–7.533 (m, 5H, Ar-H), 7.596–7.616 (d, 2H, Ar-H), 7.806–7.830 (m, 2H, Ar-H), 7.906 (d, 1H, CO-CH=CH, J=15.6 Hz), 7.997–8.021 (m, 2H, Ar-H), 8.344 (s, 1H, Pyr-H); HRMS: m/z=462.1628 (M+1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>, δ in ppm): 18.61 (m, Thy-CH<sub>3</sub>), 21.39 (m, Ar-CH<sub>3</sub>), 117.89 (m, C), 119.10 (w, C), 119.43 (s, -CH), 123.81 (m, -CH), 126.89 (s, -CH), 126.96 (s, -CH), 127.29 (s, -CH), 128.73 (s, -CH), 128.97 (s, -CH), 129.11 (s, -CH), 129.30 (s, -CH), 129.40 (s, -CH), 129.55 (m, -CH), 129.58 (s, =CH), 131.13 (s, -CH), 131.33 (m, C), 132.91 (m, C), 135.19 (m, C), 138.73 (m, C), 139.39 (m, =CH), 154.14 (w, C), 160.18 (m, C), 169.00 (m, C), 182.33 (m, C=O).

*(E)-3-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-methyl-2-phenylthiazol-5-yl)prop-2-en-1-one (Compound 3e)*

Yellow solid; 80.50%; M.P. 176°C; IR (KBr): 2922, 2852, 1744, 1651, 1240, 757 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.830 (s, 3H, Ar-CH<sub>3</sub>),

3.884 (s, 3H, Ar-OCH<sub>3</sub>), 7.029–7.058 (m, 3H, Ar-H), 7.086 (d, 1H, CO-CH=CH, J=15.6 Hz), 7.344–7.528 (m, 5H, Ar-H), 7.637–7.659 (m, 2H, Ar-H), 7.799–7.823 (m, 2H, Ar-H), 7.896 (d, 1H, CO-CH=CH, J=15.6 Hz), 7.955–8.020 (m, 2H, Ar-H), 8.334 (s, 1H, Pyr-H); HRMS: m/z= 478.1576 (M+1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>, δ in ppm): 18.64 (m, Thy-CH<sub>3</sub>), 55.39 (m, Ar-OCH<sub>3</sub>), 114.32 (s, C), 117.76 (m, C), 119.39 (s, -CH), 123.75 (m, -CH), 124.67 (s, -CH), 126.90 (m, C), 126.94 (m, -CH), 127.27 (s, -CH), 129.12 (s, -CH), 129.58 (s, =CH), 130.11 (s, -CH), 131.14 (s, -CH), 131.27 (s, -CH), 132.89 (m, C), 135.22 (m, C), 139.38 (m, =CH), 153.89 (m, C), 160.15 (m, C), 160.24 (m, C), 168.99 (w, C), 182.31 (m, C=O).

(E)-1-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (Compound 3f)

Yellow solid; 67.00%; M.P. 186°C–188°C; IR (KBr): 3007, 2925, 1748, 1659, 755, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.804 (s, 3H, Thy-H), 7.081 (d, 1H, CO-CH=CH, J=15.2 Hz), 7.377–7.446 (m, 1H, Ar-H), 7.457–7.538 (m, 8H, Ar-H), 7.703–7.727 (m, 2H, Ar-H), 7.808–7.832 (m, 2H, Ar-H), 7.891–7.948 (m, 1H, Ar-H and d, 1H, CO-CH=CH, J=15.2 Hz), 8.351 (s, 1H, Pyr-H); HRMS: m/z=482.1087 (M+1)

(E)-1-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (Compound 3g)

Yellow Solid; Yield: 87.01%; M.P. 192°C; IR (KBr): 3048, 2927, 1749, 1653, 1209, 745, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.823 (s, 3H, Thy-CH<sub>3</sub>), 7.068 (d, 1H, CO-CH=CH, J=15.2 Hz), 7.194–7.238 (m, 3H, Ar-H), 7.385–7.403 (m, 1H, Ar-H), 7.445–7.467 (m, 2H, Ar-H), 7.503–7.542 (m, 2H, Ar-H), 7.676–7.711 (m, 2H, Ar-H), 7.795–7.882 (m, 1H, Ar-H and d, 1H, CO-CH=CH, J=15.6 Hz), 7.932–7.953 (m, 2H, Ar-H), 8.345 (s, 1H, Pyr-H); HRMS: m/z=500.0997 (M+1)

(E)-1-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)prop-2-en-1-one (Compound 3h)

Yellow Solid; Yield: 78.11%; M.P. 184°C; IR (KBr): 3121, 2919, 1751, 1656, 754, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.443 (s, 3H, Ar-CH<sub>3</sub>), 2.788 (s, 3H, Thy-CH<sub>3</sub>), 7.066 (d, 1H, CO-CH=CH, J=15.6 Hz), 7.312–7.384 (m, 3H, Ar-H), 7.427–7.464 (m, 3H, Ar-H), 7.489–7.529 (m, 2H, Ar-H), 7.588–7.608 (m, 2H, Ar-H), 7.800–7.880 (m, 2H, Ar-H), 7.913–7.952 (m, 1H, Ar-H and d, 1H, CO-CH=CH, J=15.2 Hz), 8.332 (s, 1H, Pyr-H); HRMS: m/z=496.1250 (M+). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>, δ in ppm): 18.56 (m, Thy-CH<sub>3</sub>), 21.39 (m, Ar-CH<sub>3</sub>), 117.83 (m, C), 119.41 (s, C), 123.59 (s, -CH), 126.98 (s, -CH), 127.32 (s, CH), 128.05 (s, -CH), 128.08 (s, -CH), 128.73 (s, -CH), 129.28 (s, -CH), 129.37 (s, -CH), 129.55 (s, -CH), 129.59 (s, =CH), 131.39 (s, -CH), 131.67 (m, C), 135.39 (m, C), 137.19 (m, C), 138.75 (m, C), 139.36 (m, =CH), 154.15 (m, C), 160.13 (m, C), 167.51 (m, C), 182.20 (m, C=O).

(E)-1-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)-3-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (Compound 3j)

Yellow Solid; Yield: 76.32%; M.P. 176°C; IR (KBr): 3113, 2926, 1743, 1656, 1233, 754, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.813 (s, 3H, Thy-H), 3.885 (s, 3H, Ar-OCH<sub>3</sub>), 7.034–7.084 (m, 2H, Ar-H and d, 1H, CO-CH=CH, J=15.6 Hz), 7.365–7.383 (m, 1H, Ar-H), 7.437–7.459 (m, 2H, Ar-H), 7.489–7.529 (m, 2H, Ar-H), 7.631–7.655 (m, 2H, Ar-H), 7.795–7.819 (m, 2H, Ar-H), 7.895 (d, 1H, CO-CH=CH, J=15.2 Hz), 7.927–7.949 (m, 2H, Ar-H), 8.327 (s, 1H, Pyr-H); HRMS: m/z=512.1196 (M+).

## Biological activity

### In vitro anti-inflammatory activity by protein denaturation method

The reaction mixture (2.5 mL) consisted of 0.1 mL of egg albumin (from fresh hen's egg), 1.4 mL of phosphate-buffered saline (PBS, pH 6.4) and 1 mL of synthetic derivatives (1 mM). Similar volume of PBS served as control. Then, the mixtures were incubated at 37°C±2 in an incubator for 15 min and then heated at 70°C for 5 min. After cooling, their absorbance was measured at 660 nm using vehicle as blank. Diclofenac sodium at 1 mM was used as reference drug and treated similarly for the determination of absorbance. The percentage inhibition of protein

**Table 1: Anti-inflammatory and antioxidant activity of synthesized compound (3a-j)**

Compound No./Code	Anti-inflammatory activity % inhibition at 1 mM	Antioxidant activity % inhibition at 1 mM/mL			
		DPPH	H <sub>2</sub> O <sub>2</sub>	NO	SOR
3a	52	25.07	20.33	18.27	15.18
3b	58	25.58	21.78	51.90	22.47
3c	71	40.98	37.50	19.82	16.88
3d	45	32.72	23.96	23.80	20.25
3e	80	45.21	39.45	48.75	23.10
3f	62	39.87	25.66	26.40	15.54
3g	59	29.44	22.37	58.25	26.78
3h	74	41.69	35.81	22.57	18.05
3i	50	47.36	40.39	20.15	21.55
3j	86	48.05	43.60	55.12	25.90
Diclofenac sodium	90.21	-	-	-	-
Ascorbic acid	-	42.98	-	42.63	89.13
BHT	-	-	88.42	-	-

BHT: Butylated hydroxytoluene

denaturation was calculated using the following formula and results recorded in Table 1.

$$\% \text{ inhibition} = 100 \times (\text{Vt}/\text{Vc} - 1)$$

Where, Vt = absorbance of test sample and Vc = absorbance of control.

### 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activity

The molecule DPPH is characterized as a stable free radical by virtue of the delocalization of the spare electron over the molecule as a whole so that the molecule does not dimerize, as would be the case with most other free radicals. The delocalization of electron also gives progress to the deep violet color, characterized by an absorption band in ethanolic solution at about 517 nm. When a solution of DPPH is mixed with that of a substrate (AH) that can donate a hydrogen atom, then this gives rise to the reduced form with the loss of this violet color. To evaluate the antioxidant potential through free radical scavenging by the test samples, the change in optical density of DPPH radicals is monitored and results recorded in Table 1.

### Hydrogen peroxide scavenging (H<sub>2</sub>O<sub>2</sub>) activity

Human beings are exposed to H<sub>2</sub>O<sub>2</sub> indirectly through the environment nearly about 0.28 mg/kg/day with intake mostly from leaf crops. Hydrogen peroxide may enter the human body through inhalation of vapor or mist and through eye or skin contact. H<sub>2</sub>O<sub>2</sub> is rapidly decomposed into oxygen and water and this may produce hydroxyl radicals that can initiate lipid per oxidation and cause DNA damage in the body and results recorded in Table 1.

### Nitric oxide (NO) scavenging activity

NO is formed in biological tissues by specific NO synthases, which metabolizes arginine to citrulline with the formation of NO through a five electron oxidative reaction. The sodium nitroprusside is known to decompose in aqueous solution at physiological pH (7.2) producing NO. Under aerobic conditions, NO reacts with oxygen to produce stable products (nitrate and nitrite), the quantities of which can be determined using Griess reagent and results recorded in Table 1.

### Superoxide radical (SOR) scavenging assay

SOR radical scavenging activity was carried out as per the reported method. The mixture consisting of 1 mL of nitro blue tetrazolium (NBT) solution (156 mM NBT in phosphate buffer, pH 7.4), 1 mL NADH solution (468 mM NADH in phosphate buffer, pH 7.4), and 1 mL of synthetic compound (1 mM) solution was mixed. The reaction was started by adding 1 mL of phenazinemethosulfate (PMS) solution (60 mM PMS in

phosphate buffer, pH 7.4) to the above mixture. The reaction mixture was incubated for 5 minutes at 25°C and the absorbance was measured at 560 nm against blank sample and compared with standards and percentage inhibition was calculated using the same formula as above. Decreased absorbance indicates increased SOR scavenging activity.

## RESULTS AND DISCUSSION

### Chemistry

Synthesis of thiazole-pyrazole integrated chalcones (**3a-j**) was achieved by Claisen-Schmidt reaction of substituted 1-(4-methyl-2-phenylthiazol-5-yl) ethanone and substituted pyrazole aldehyde in the presence of 10% NaOH in ethyl alcohol as a solvent under reflux condition. The synthesis of substituted pyrazole aldehydes was achieved as per the procedure reported in literature [22]. The chemical structures of synthesized compounds were confirmed by IR, <sup>1</sup>H NMR, and HRMS data.

### Biological evaluation

#### Anti-inflammatory activity

Denaturation of proteins is a well-established cause of inflammation. In the present work, the *in vitro* anti-inflammatory potential of synthesized thiazole-pyrazole integrated chalcones was evaluated against denaturation of egg albumin and the results are illustrated in Table 1. Most of the compounds were found to have significant anti-inflammatory properties. Compound **3j**, **3e**, **3h**, and **3c** exhibited significant inhibition of protein denaturation compared to the reference standard diclofenac sodium, a standard anti-inflammatory drug at 1 mM concentration; however, compound **3f**, **3g**, and **3b** showed good inhibition. On the other hand, all other compounds were also found to possess moderate inhibition of heat-induced egg albumin denaturation.

#### Antioxidant activity

Reactive oxygen species (ROS) and nitrogen species are responsible to the pathophysiology of anti-inflammatory conditions. Taking into the consideration of multifactorial character of oxidative stress which is involved in several pathological states, we have further evaluated antioxidant properties of synthesized compounds **3a-j** for their antioxidant potential against ROS such as DPPH, H<sub>2</sub>O<sub>2</sub>, NO, and SOR radicals compared to reference standard ascorbic acid and the results are listed in Table 1. All the synthesized compounds demonstrated good to moderate scavenging activity against DPPH and NO radicals, whereas moderate to weak activity against H<sub>2</sub>O<sub>2</sub> and SOR radicals. The antioxidant activity results revealed that the compounds **3j**, **3i**, **3e**, **3h**, and **3c** were found to possess significant inhibition of DPPH radical scavenging activity. On the other hand, all other compounds were found to be moderate scavengers of DPPH radical. Compound **3g**, **3j**, and **3b** exhibited significant inhibition of NO radicals compared to the standard drug ascorbic acid. However, remaining compounds were moderate NO radical scavengers compared to ascorbic acid. On the other hand, all the compounds were unveiled moderate to weak inhibition of peroxide (H<sub>2</sub>O<sub>2</sub>) and superoxide (SOR) radicals compared to reference drug butylated hydroxytoluene and ascorbic acid, respectively.

## CONCLUSION

All the newly synthesized compounds were confirmed by IR, <sup>1</sup>H NMR, and HRMS. *In vitro* antioxidant screening data of newly synthesized compounds revealed that most of the synthesized compounds possess excellent DPPH and NO radical scavenging activity. All the compounds found to possess marked anti-inflammatory potential by effectively inhibiting the heat-induced albumin denaturation. Further, bioassay, optimization, and structure-activity relationship of the title compounds are underway.

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## AUTHORS' CONTRIBUTIONS

Dnyaneshwar M Sirsat carried out experimental work, spectral characterization, biological evaluation, and wrote this article. Madhusudan T Bachute provided guidance for writing this article as well as provided guidance for crucial review and revision. Pradeep R Kate encouraged Dnyaneshwar M Sirsat to explore the finding of work.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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