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# Synthesis, characterization, and investigation of the anti-inflammatory effect of 2,3-disubstituted quinazolin-4(1H)-one

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## Abstract

**Background:** Quinazolin-4(1H)-one nucleus has attracted the attention of medicinal chemists due to their clinical uses. Modification of quinazolinone ring for the development of pharmaceutical and clinical compound for its anti-inflammatory potential.

**Results:** In vitro anti-inflammatory activity of the synthesized compounds was performed by using egg albumin protein denaturation assay, while in vivo anti-inflammatory activity was performed by using carrageenan-induced rat paw edema and cotton pellet-induced granuloma pouch model.

In the present study, we synthesized a new series of 2,3-disubstituted quinazolin-4(1H)-one derivatives and evaluated their in vivo, in vitro anti-inflammatory effect. Their chemical structures are confirmed by FTIR, <sup>1</sup>HNMR, and mass spectrum. Among all the synthesized compounds, G1 and G3 exhibit the significant anti-inflammatory activity by inhibiting release of inflammatory mediators like prostaglandin, histamine, and serotonin. in both in vivo and in vitro models as compared to compound G2.

**Conclusion:** These synthesized compounds showed anti-inflammatory activity by inhibiting prostaglandins and COX enzymes. So, all test compounds may be used for both inflammation as well as inflammation-induced cancer therapy. Future various screening method related with inflammation and inflammation-induced cancer needs to be evaluated pre-clinically and clinically.

**Keywords:** Quinazolin-4(1H)-one, Anti-inflammatory, Carrageenan, Cotton pellet-induced granuloma

## 1 Background

Quinazolinone nucleus is an interesting molecule among the most important classes of an aromatic bicyclic compound with two nitrogen atoms in structure [1]. It consists of an aromatic benzo pyrimidine system made up of two fused six-member simple aromatic ring benzene and pyrimidine ring [2].

Recently, many efforts have been focused by researchers on the modification of quinazolinone ring for development of pharmaceutical and clinical compound. A brief survey

about biological importance of quinazolinone and their derivatives revealed that large number of publications began to appear after 1960s [3, 4]. Most of quinazolinone derivative which have been identified consist of wide range of antioxidant, antiviral, anticonvulsant, anti-inflammatory, antitubercular, antimicrobial, and analgesic activity [5]. Nowadays, quinazolin-4(1H)-one nucleus has attracted the attention of medicinal chemists due to their clinical uses.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain, and fever [6]. However, long-term clinical usage of NSAIDs is associated with significant side effects such as gastro-intestinal lesions,

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bleeding, and nephrotoxicity [7]; therefore, discovery of new safer anti-inflammatory agent presents a challenging goal.

SAR studies on quinazolinone ring system in various literatures suggest that substitution at positions 2 and 4 is very much important for better pharmacological activities [8]. The present work is to design novel substituted quinazolin-4-(1H)-one derivative and screened for their anti-inflammatory property.

## 2 Methods

### 2.1 Chemicals and apparatus

All the chemicals used were purchased from Alfa Aesar, Spectrochem Ltd and SD fine chemicals Ltd. Kandlakoya Village, Hyderabad, Telangana and Autonagar, Vanasthalipuram, Hayathnagar Mandal, Hyderabad, Telangana, India, respectively. Melting points of all the compounds were determined on an open capillary tube on super fit melting point apparatus.

The purity of all the final compounds was assessed by thin layer chromatography plates coated with silica Gel G (100–200 mesh size) to establish identity the reactants and products monitored in between reaction. Used petroleum ether:ethyl acetate:methanol 4:1:1 system as mobile phase. The spots were visualized by iodine vapor in iodine chamber and also using the UV-chamber. Solvents were distilled before use. Solvent extracts were dried over anhydrous sodium sulphate.

Infrared spectra were recorded using KBr on Shimadzu FTIR-Affinity spectrophotometer. Proton resonance magnetic spectra ( $^1\text{H}$ NMR) were recorded using BRUKER AVANCE II 400 NMR spectrometer, and chemical shifts were expressed in parts per million ( $\delta$  ppm), down field from TMS as an internal standard. Mass spectra were recorded using mass spectrometer; the spectra were recorded on WATER, Q-TOF MICROMASS (ESI-MS) instrument.

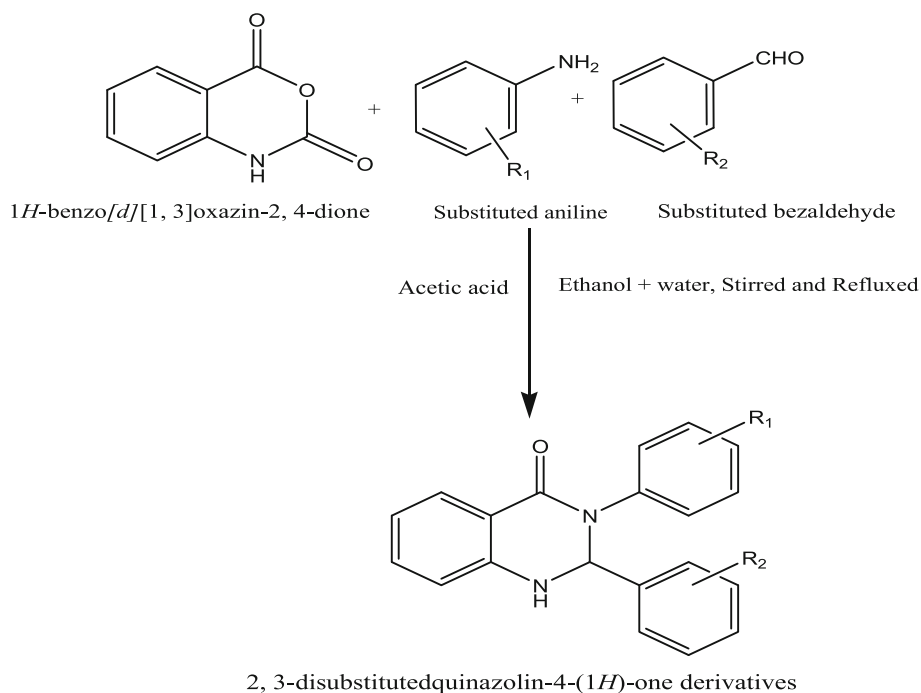
### 2.2 Experimental animal

Wistar rats weighing 150–250 g were procured from animal house of AISSMS College of Pharmacy, Pune, Maharashtra, India, ref. No. COP/PN/2017-18/91-3 on dates 6 October 2017 (IAEC No. CPCSEA/IAEC/OP-03/01-2 K17). Animals are provided with standard pallet diet and water ad libitum. Animals were placed in the cages 5 days prior to the experiment and ascertained the health status and were exposed to alternate 12 h light and dark cycles.

### 2.3 Experimental procedure

#### 2.3.1 Chemical synthesis and characterization

**2.3.1.1 General procedure for the synthesis of compounds** Isatoic anhydride (1 mmol) and substituted aniline (1.1 mmol) were mixed in a sufficient mixture of equal volumes of ethanol and water in a round bottom flask. Then, 5 ml of acetic acid was added to the mixture and stirred for approximately 20–30 min to dissolve the



**Fig. 1** Preparation of 2,3-disubstituted quinazolin-4(1H)-one derivative

reactants completely. Subsequently, substituted aldehyde (1 mmol) was added with condenser and refluxed for 1.5 h with continuous stirring. The reaction was monitored by thin layer chromatography using ethyl acetate and pet ether as the solvent system. After completion of the reaction, the content was poured into ice water. Solid mass or precipitate obtained was then filtered, washed with ice cold water, and recrystallized from hot ethanol to obtain pure 2,3-disubstituted quinazolin-4(1H)-one derivative. The melting points of compounds have been taken on open capillary tube and are uncorrected. All synthesized compounds were solid in nature and soluble in dimethyl sulfoxide solvent (Fig. 1) [9, 10]. The chemical structures, names, and abbreviations of the synthesized compounds are presented in Table 1.

### 2.3.2 Egg albumin protein denaturation

Egg albumin (0.2 ml), phosphate buffer saline of pH 6.4 (2.8 ml), and varying concentrations (50, 100, 150, 200, and 250 µg/ml) of test compounds of G1, G2, and G3 (2

ml) were used to prepare the reaction mixture (5 ml). The mixtures were incubated at 37 °C for 15 min and then heated at 70 °C for 5 min. After cooling, the absorbance was measured at 660 nm by using the vehicle as blank. Diclofenac sodium at 50, 100, 150, 200, and 250 µg/ml concentrations was used as reference standard [11].

The percent inhibition of protein denaturation was calculated by following equation:

$$\% \text{ inhibition} = 100 \times [A_t/A_c - 1]$$

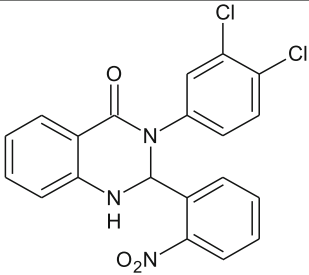
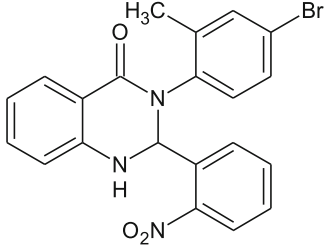
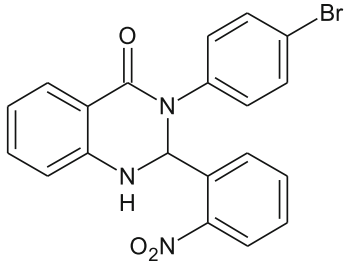
where  $A_t$  is the absorbance of test sample, and  $A_c$  is the absorbance of control.

### 2.3.3 Carrageenan-induced rat paw edema model

Acute anti-inflammatory activity was performed by using carrageenan-induced rat paw edema model [12]. Animals were divided into twelve groups ( $n = 6$ ), placed into different cages, and kept under standard conditions with free access to food and water.

Group 1 served as control received 1% CMC (carboxyl methyl cellulose). Group 2 served as positive

**Table 1** Chemical structures, names, and abbreviations of the synthesized compounds

Product	Name	Abbreviations
	3-(3,4-dichlorophenyl)-2-(2-nitrophenyl)- 2,3-dihydroquinazolin-4(1H)-one	<b>G1</b>
	3-(4-bromo-2-methylphenyl)-2-(2- nitrophenyl)-2,3-dihydroquinazolin-4(1H)- one	<b>G2</b>
	3-(4-bromophenyl)-2-(2-nitrophenyl)-2,3- dihydroquinazolin-4(1H)-one	<b>G3</b>

control received carrageenan. Group 3 served as standard received diclofenac sodium 20 mg/kg and suspended in 1% CMC [13]. Groups 4 to 12 were treated with test compounds G1, G2, and G3 with varying doses (5, 10, and 20 mg/kg), respectively. Edema was induced by injecting 0.1 ml of a 1% solution of carrageenan in saline into the sub plantar region of the right hind paw of the Wister rat [14]. The vehicle, test solutions, and diclofenac were administered 60 min prior to the injection of the phlogestic agent (carrageenan). The volume of paw edema was measured at 0, 1/2, 1, 2, 3, 4, 5, and 24 h after injection of carrageenan using plethysmometer [15]. The % inhibition in edema volume was calculated for each animal group using the following formula:

$$\% \text{inhibition} = \frac{\text{Mean paw of inflammation of control} - \text{Mean paw of inflammation of test}}{\text{Mean paw of inflammation of control}} \times 100$$

### 2.3.4 Cotton pellet-induced granuloma model

Sub-acute anti-inflammatory activity was assessed by cotton pellet-induced granuloma in rat. Animals were divided into eight groups ( $n = 6$ ) and kept under standard conditions with free access to food and water.

The rats were anesthetized under light ether anesthesia, and an incision was made in the lumbar region by curved scissors, a subcutaneous tunnel was made, and a sterilized cotton pellet ( $100 \pm 1$  mg) was inserted using blunted forceps. Group 1 served as control received 1% CMC. Group 2 served as standard

received diclofenac sodium 10 mg/kg [16]. Groups 3 to 8 received 10 and 20 mg/kg test compound (G1, G2, and G3) orally for seven consecutive days from the day of cotton pellet insertion. On the 8th day, under ether anesthesia cotton pellets were removed, dried, and weighed. The % inhibition was calculated by using the following formula [17]:

$$\% \text{ inhibition} = (1 - W_t/W_c) \times 100$$

where  $W_t$  is the weight of the cotton pellet of the test solution, and  $W_c$  is the weight of the cotton pellet of the control.

## 3 Results

### 3.1 Synthesis and spectral data

All the compounds were found to be soluble in dimethyl sulphoxide (DMSO). The mobile phase used for thin layer chromatography was petroleum ether:ethyl acetate:methanol.

#### 3.1.1 Synthesis of 3-(3,4-dichlorophenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1 h)-one

**3.1.1.1 Compound G1** The reaction provided 50% yield. TLC monitored by (pet ether, ethyl acetate, methanol) (4:1:1) and  $R_f$  value was (0.30). Recrystallized using hot ethanol and melting point found to be in the range of 201–205 °C.

IR (KBr):  $\nu$   $\text{cm}^{-1}$  3309 (N-H stretching), 3089 (C-H stretching), 1633 (C=O stretching), 1614 (C=C

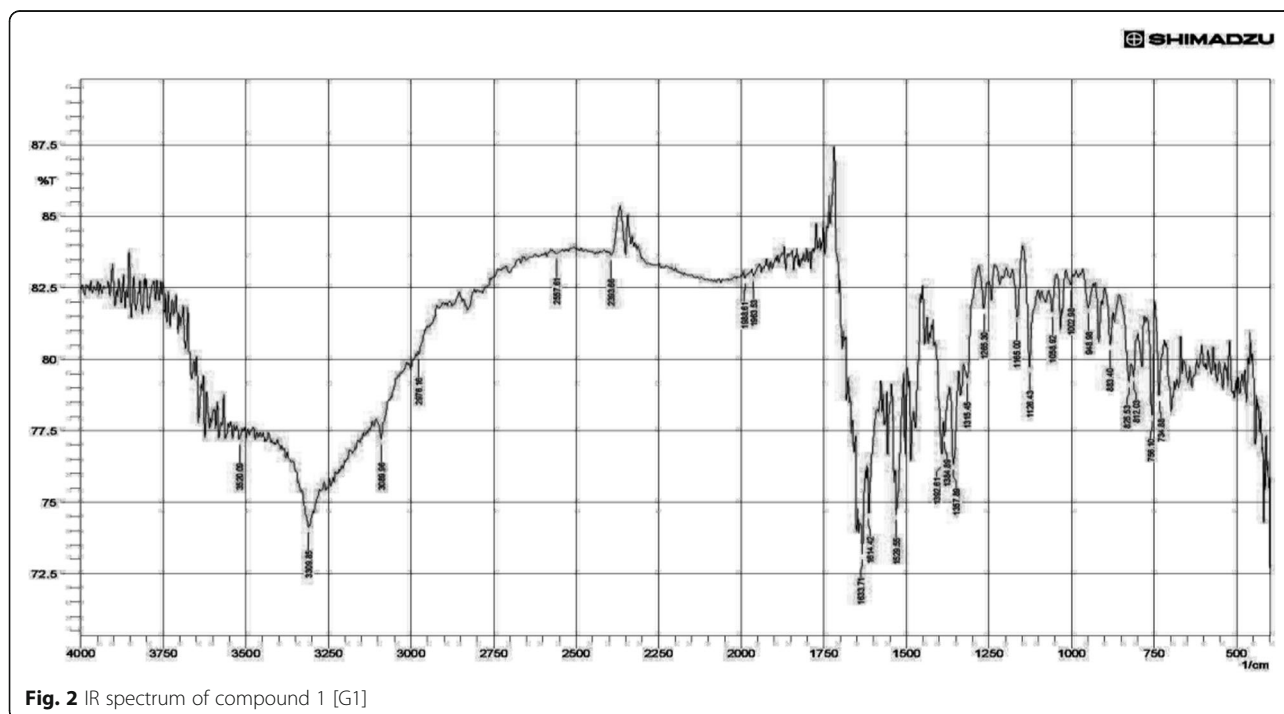


Fig. 2 IR spectrum of compound 1 [G1]

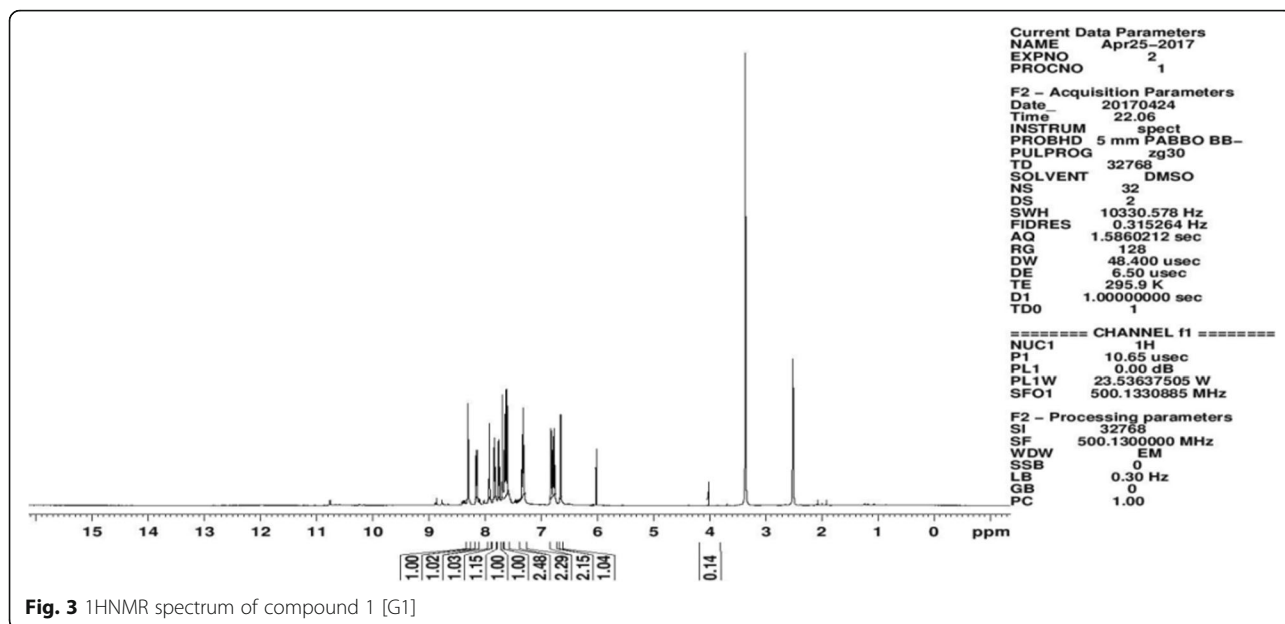


Fig. 3 <sup>1</sup>H NMR spectrum of compound 1 [G1]

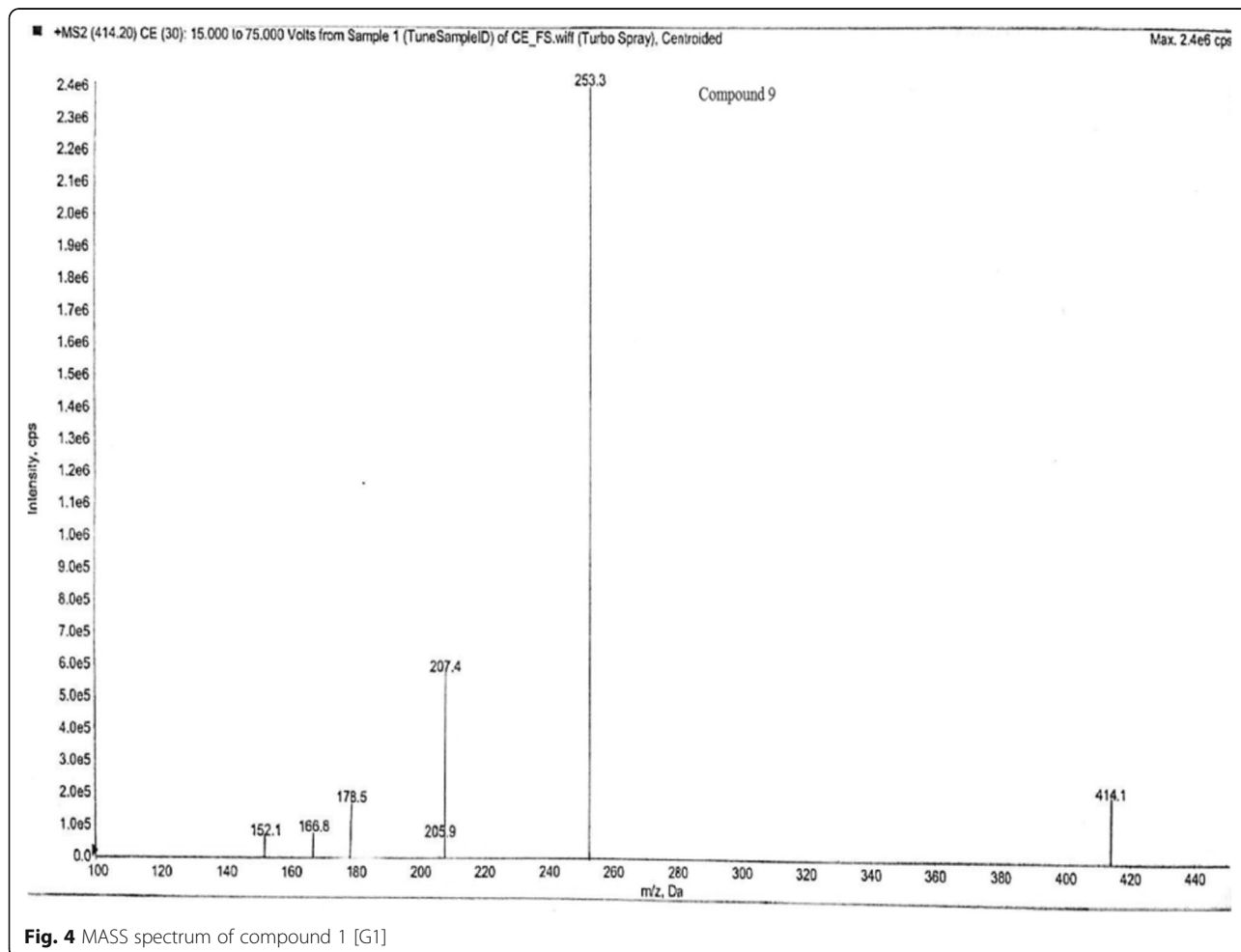
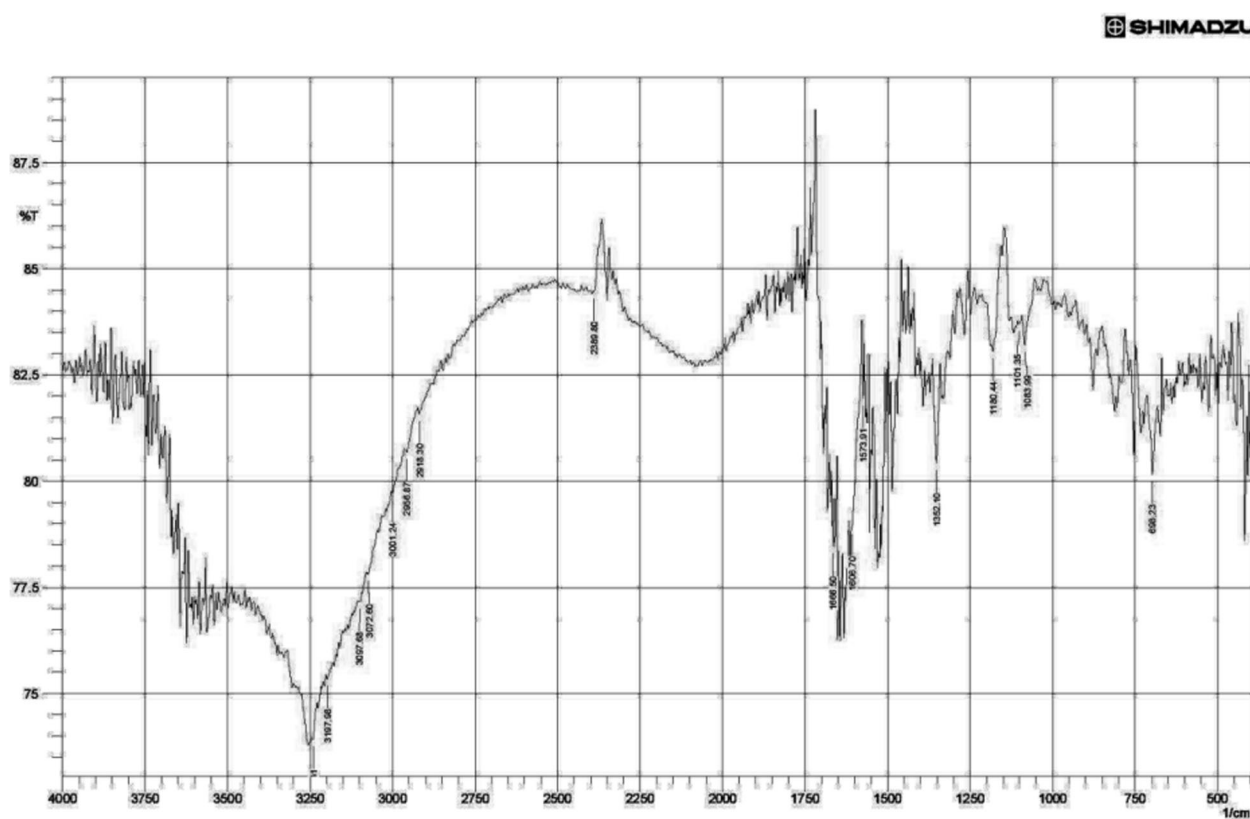
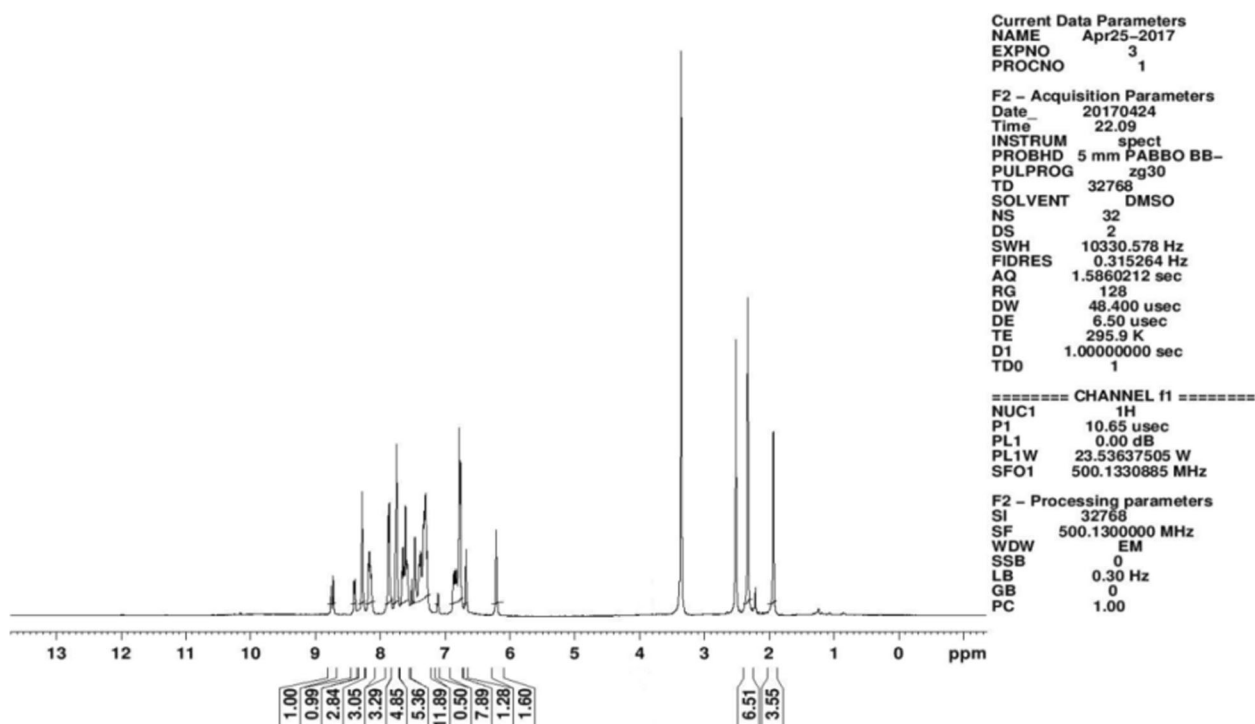


Fig. 4 MASS spectrum of compound 1 [G1]

**Fig. 5** IR spectrum of compound 2 [G2]**Fig. 6** <sup>1</sup>H NMR spectrum of compound 2 [G2]



stretching), 1529 (NO<sub>2</sub> stretching), 1126 (C-N stretching), 825 (C-Cl stretching) (Fig. 2).

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δppm 8.295 (s, 1H, N-H), 8.155-8.152 (quartet, J = 7.6 Hz, 6.4 Hz, 1.2 Hz, 1H, Ar-H), 7.820 (s, 1H, Ar-H), 7.742 (s, 1H, Ar-H), 7.650 (s, 1H, Ar-H), 7.598 (s, 1H, Ar-H), 7.328 (s, 1H, Ar-H), 7.318-7.314 (d, J = 1.6 Hz, 2H, Ar-H), 6.782 (s, 1H, C-H), 6.767 (s, 1H, Ar-H), 6.650-6.645 (d, J = 2 Hz, 2H, Ar-H) (Fig. 3).

Mass spectrum shows the formation of molecular ion peak at *m/z* = 414.1 (C<sub>21</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>-414.24) (Fig. 4).

### 3.1.2 Synthesis of 3-(4-bromo-2-methylphenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4-(1H)-one

**3.1.2.1 Compound G2** The reaction provided 76.99% yield. The TLC monitored by (pet ether 3:3 n-Hexane) and *R<sub>f</sub>* value was (0.28). Recrystallized using hot ethanol and melting point found to be in the range of 230–231 °C.

IR (KBr): ν cm<sup>-1</sup> 3197 (N-H stretching), 3097 (C-H stretching), 3001 (Ar-H stretching), 1666 (C=C stretching), 1373 (CH<sub>3</sub> stretching), 1352 (NO<sub>2</sub> stretching), 1180 (C-N stretching), 698 (C-Br stretching) (Fig. 5).

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δppm 8.275 (s, 1H, Ar-H), 7.872-7.857 (d, J = 6 Hz, 2H, Ar-H), 7.742 (s, 1H, Ar-H), 7.460 (s, 1H, Ar-H), 7.328 (s, 2H, Ar-H), 7.272 (s, 1H, Ar-H), 6.773-6.751 (d, J = 8.8 Hz, 2H, Ar-H), 6.671 (s, 1H, Ar-H), 6.206 (s, 1H, C-H), 2.321 (s, 3H, CH<sub>3</sub>) (Fig. 6).

MS: Mass spectrum shows the formation of molecular ion peak at *m/z* = 439.5 (C<sub>21</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>3</sub>-438.27) (Fig. 7).

### 3.1.3 Synthesis of 3-(4-bromophenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4-(1H)-one

**3.1.3.1 Compound G3** The reaction provided 39.26% yield. The TLC monitored by (pet ether 3:2 n-hexane) and *R<sub>f</sub>* value was (0.55). Recrystallized using hot ethanol and melting point found to be in the range of 227–228 °C.

IR (KBr): ν cm<sup>-1</sup> 3331 (N-H stretching), 3089 (C-H stretching), 3082 (Ar-H stretching), 1768 (C=O stretching), 1614 (C=C stretching), 1519 (NO<sub>2</sub> stretching), 1176 (C-N stretching), 717 (C-Br stretching) (Fig. 8).

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>) δppm 8.277-8.273 (triplet, J = 1.6 Hz, 1.2 Hz, 1H, N-H), 8.139 (s, 1H, Ar-H), 7.739-7.736 (d, J = 1.2 Hz, 1H, Ar-H), 7.633 (s, 1H,

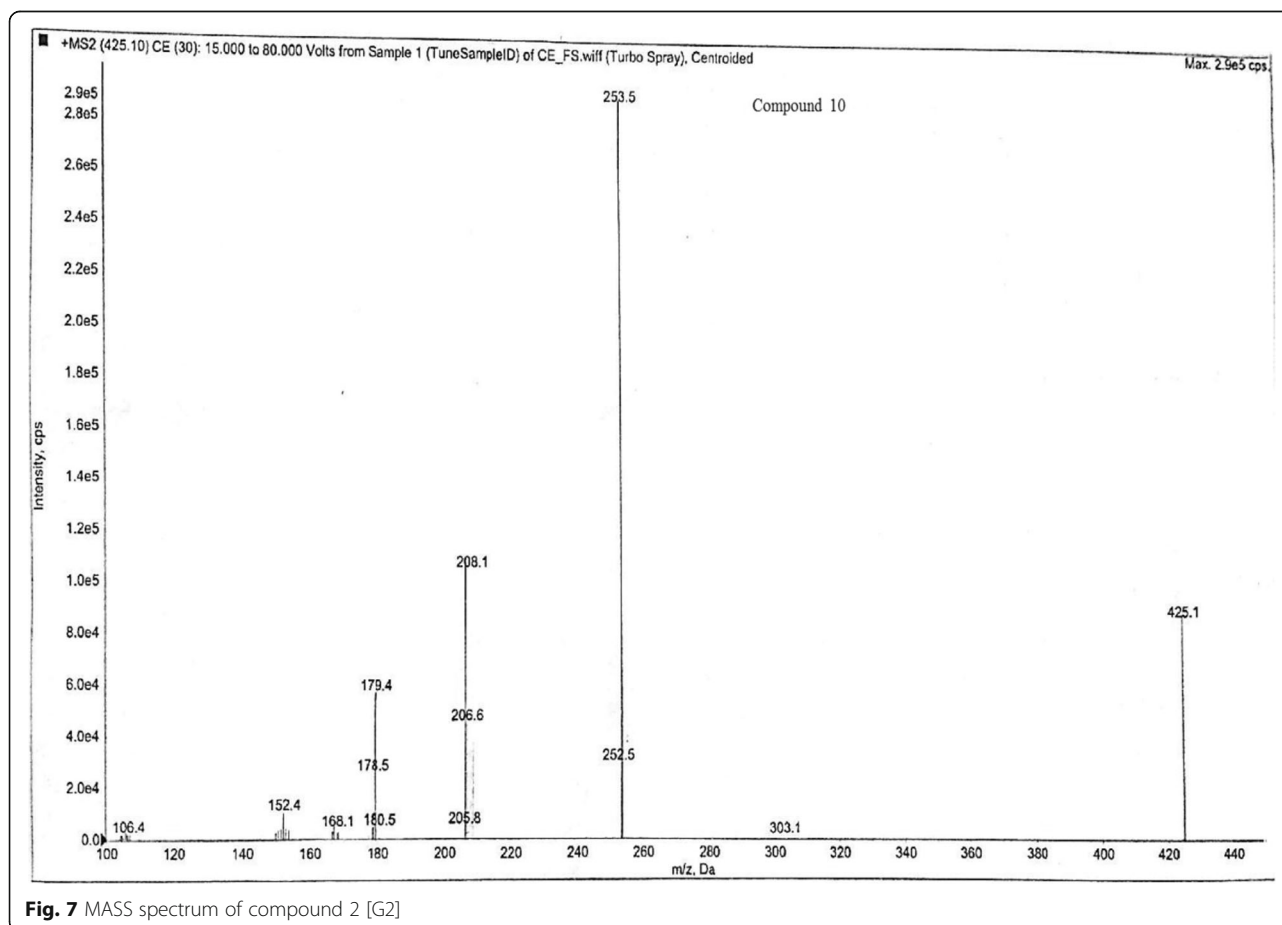


Fig. 7 MASS spectrum of compound 2 [G2]

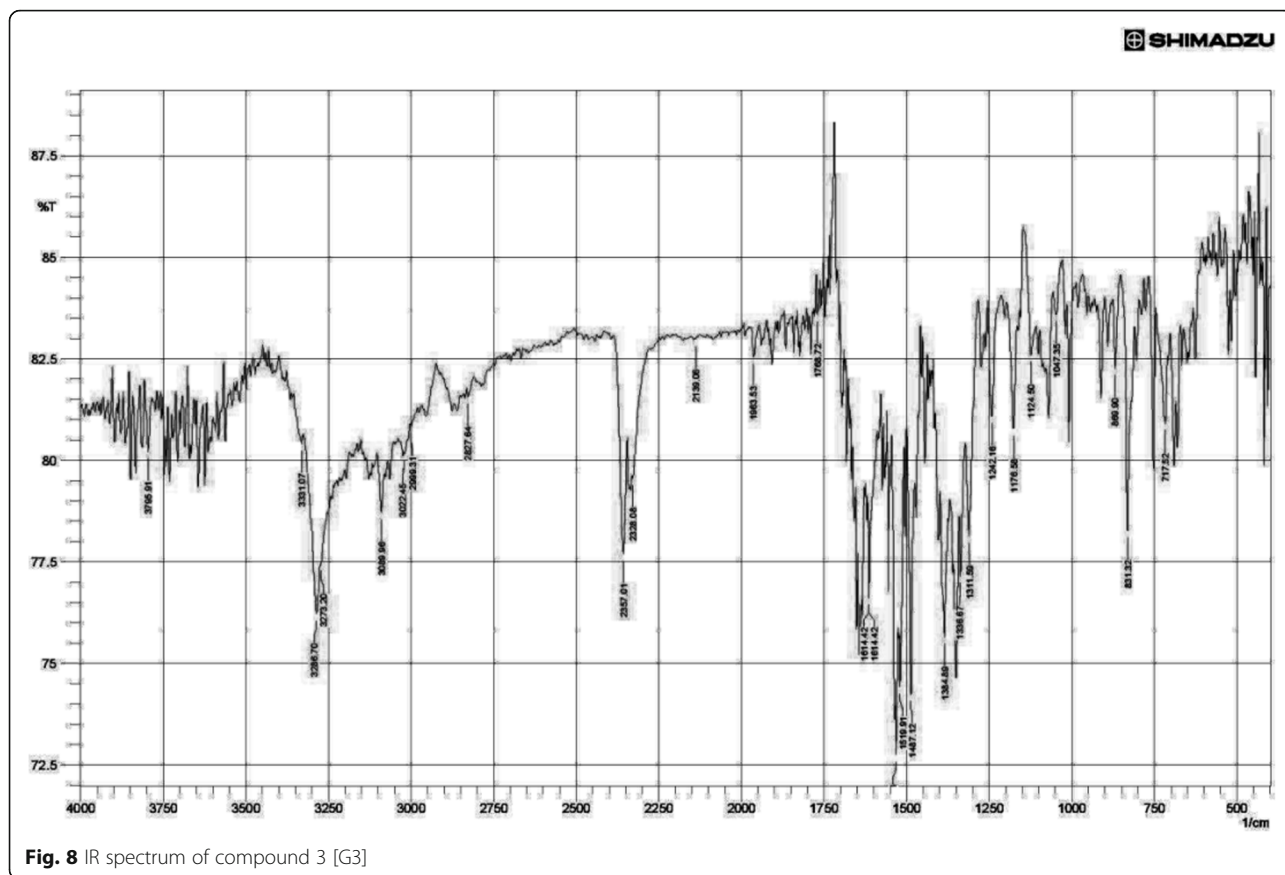


Fig. 8 IR spectrum of compound 3 [G3]

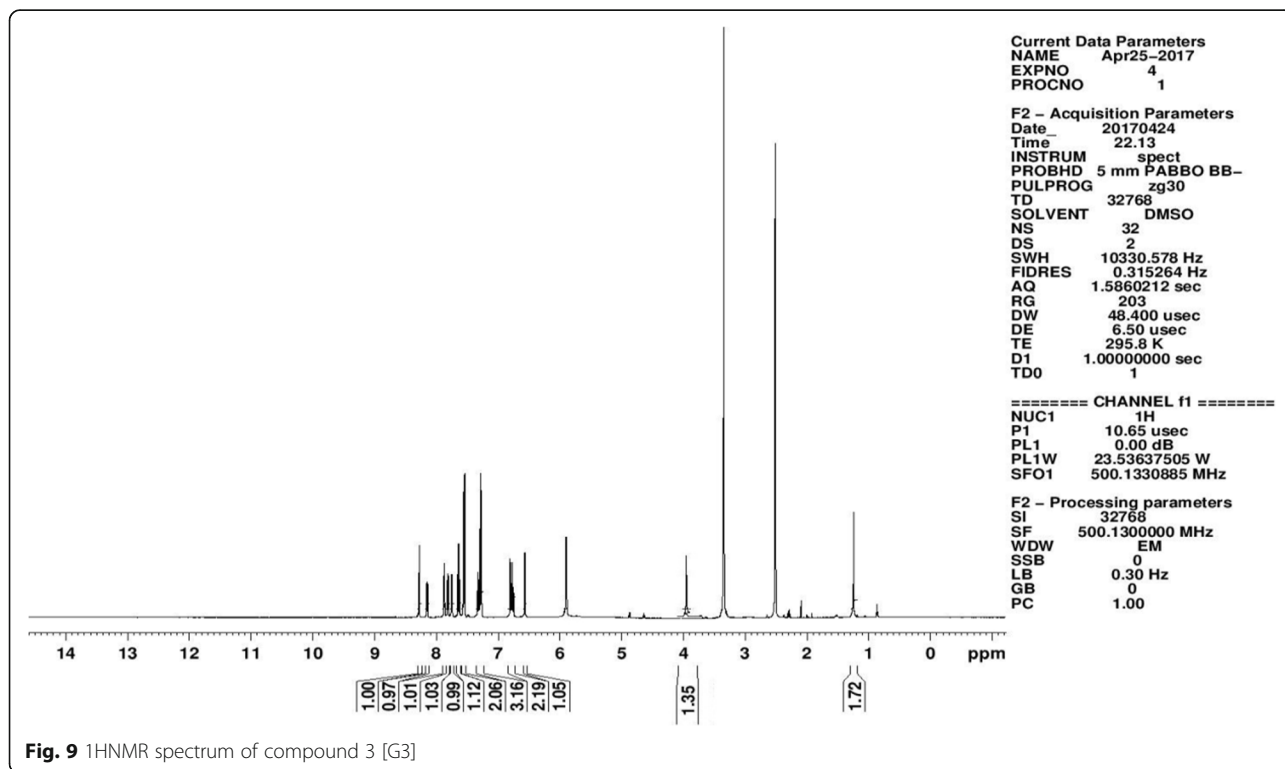


Fig. 9 <sup>1</sup>H NMR spectrum of compound 3 [G3]



Ar-H), 7.556-7.552 (d,  $J = 1.6$  Hz, 1H, Ar-H), 7.542-7.539 (d,  $J = 1.2$  Hz, 2H, Ar-H), 7.318-7.316 (d,  $J = 0.8$  Hz, 2H, Ar-H), 7.283-7.279 (d,  $J = 1.6$  Hz, 1H, Ar-H), 7.270-7.266 (d,  $J = 1.6$  Hz, 1H, Ar-H), 6.805 (s, 1H, Ar-H), 6.761 (s, 1H, Ar-H), 6.565-6.559 (d,  $J = 2.4$  Hz, 1H, C-H) (Fig. 9).

MS: Mass spectrum shows the formation of molecular ion peak at  $m/z = 425.1$  ( $C_{20}H_{14}BrN_3O_3$ -424.24) (Fig. 10).

## 3.2 Pharmacological methods for screening of synthesized compounds

### 3.2.1 In vitro anti-inflammatory activity

**3.2.1.1 Egg albumin protein denaturation** Table 2 presents G1, G2, and G3 that showed significant inhibition of protein denaturation, i.e., 40%, 41.66%, and 49.16%, respectively, at 250  $\mu$ g/kg, which were comparable to that of the diclofenac-treated group (70%).

### 3.2.2 Anti-inflammatory activity

**3.2.2.1 Carrageenan-induced rat paw edema** Figure 11 presents percent inhibition in the anti-inflammatory activity of compound G1, G2, and G3 and was evaluated in carrageenan-induced rat paw edema model. The results of the study indicated, oral administration of compounds G1, G2, and G3 significantly ( $p < 0.01$ ) decreased the carrageenan-induced rat paw edema volume after 2 h of carrageenan injection. The results of the study were comparable to that of diclofenac-treated animals (Table 3).

**3.2.2.2 Cotton-pellet induced granuloma** Groups treated with test compounds G1, G2, and G3 showed significant reduction in the weight of the cotton pellet when compared with the control group. Among these test compounds, G3 at a dose of 20 mg/kg showed about 50.68% inhibition in granuloma weight, which is comparable to that of diclofenac (54.20%) (Table 4).

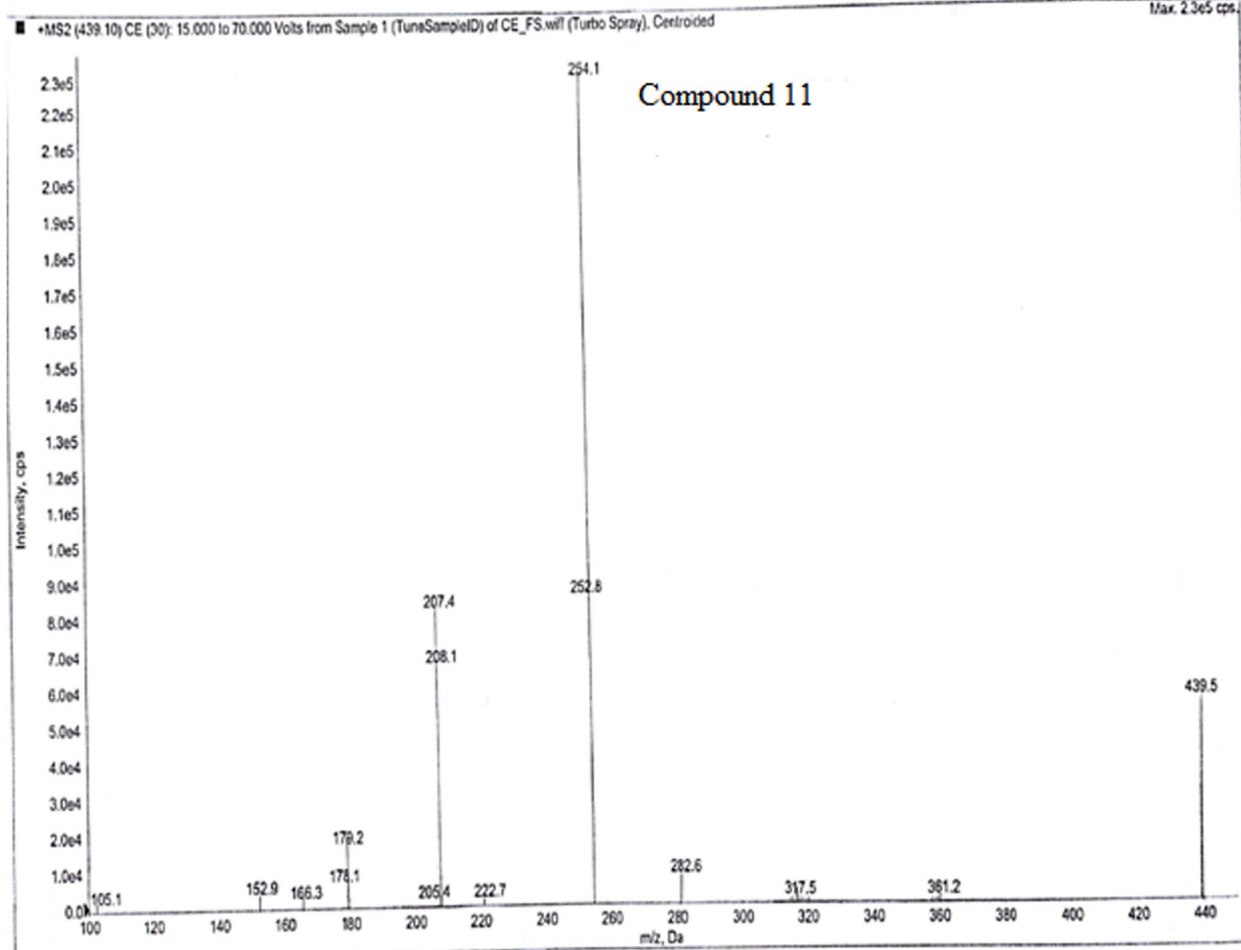


Fig. 10 MASS spectrum of compound 3 [G3]

**Table 2** Effect of test compounds on egg albumin protein denaturation

Design of treatment	Concentration ( $\mu\text{g/ml}$ )	Mean $\pm$ SEM	% inhibition
<b>Group-I (control)</b>	–	$1.2 \pm 0.059$	–
<b>Group-II (diclo)</b>	50	$0.55 \pm 0.015^*$	54.16
	100	$0.49 \pm 0.040^{**}$	59.16
	150	$0.42 \pm 0.033^{**}$	65.00
	200	$0.40 \pm 0.080^{**}$	66.66
	250	$0.36 \pm 0.032^{**}$	70.00
<b>Group-III (G1)</b>	50	$0.78 \pm 0.047$	35.00
	100	$0.78 \pm 0.048^*$	35.00
	150	$0.78 \pm 0.047^*$	35.00
	200	$0.72 \pm 0.006^{**}$	40.00
	250	$0.71 \pm 0.002^{**}$	40.00
<b>Group-IV (G2)</b>	50	$0.71 \pm 0.002$	40.83
	100	$0.71 \pm 0.008$	40.83
	150	$0.71 \pm 0.009^*$	40.83
	200	$0.70 \pm 0.008^*$	41.66
	250	$0.70 \pm 0.006^{**}$	41.66
<b>Group-V (G3)</b>	50	$0.82 \pm 0.014$	31.66
	100	$0.80 \pm 0.011^*$	33.33
	150	$0.75 \pm 0.003^*$	37.50
	200	$0.73 \pm 0.009^{**}$	39.00
	250	$0.61 \pm 0.004^{**}$	49.16

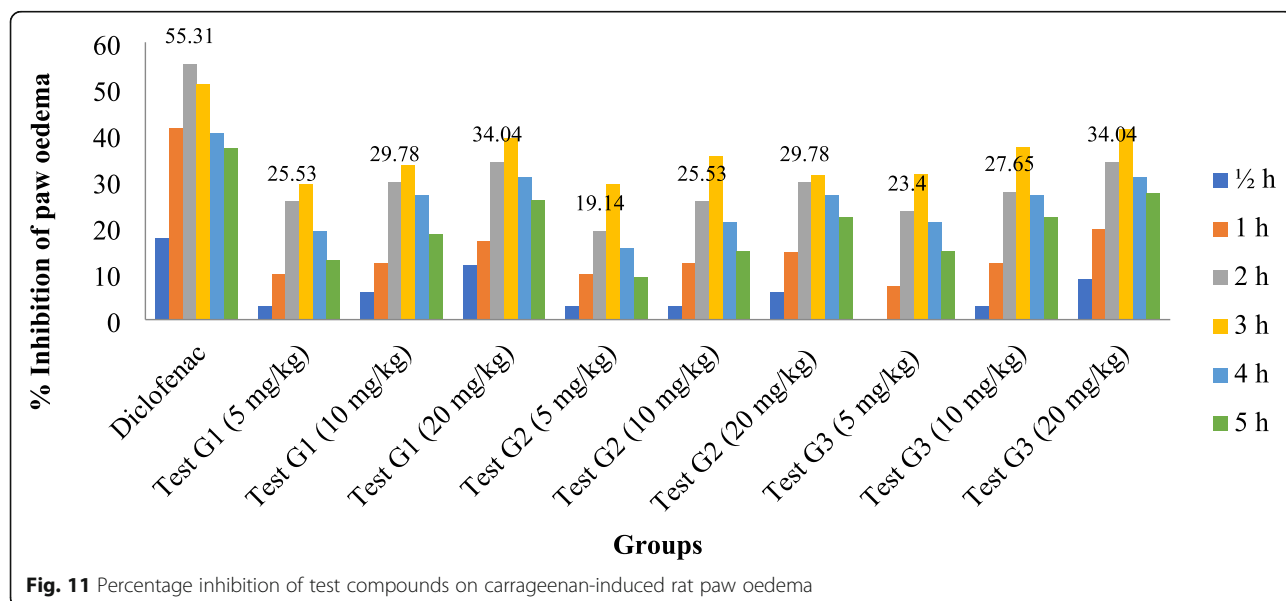
Values are expressed as mean  $\pm$  SEM ( $n = 6$ ) and ANOVA followed by Dunnett's test

\* $p < 0.05$ , \*\* $p < 0.001$  when compared with control

#### 4 Discussion

Heat-induced denaturation of egg albumin proteins is as effective as native proteins in provoking delayed hypersensitivity like sickness and glomerulo-nephritis [18]. Moreover, it was already proved that conventional NSAIDs do

not act only by the inhibition of endogenous prostaglandin production by blocking the COX enzyme but also by prevention of denaturation of proteins [19]. From the result obtained in the present study, the quinazolinone derivatives showed considerable anti-inflammatory activity by



**Fig. 11** Percentage inhibition of test compounds on carrageenan-induced rat paw oedema

**Table 3** Effect of test compounds on carrageenan induced rat paw edema

Groups	Paw volume (ml)							
	0 h	½ h	1 h	2 h	3 h	4 h	5 h	24 h
<b>Control</b>	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
<b>Positive control</b>	0.30 ± 0.017	0.34 ± 0.010	0.41 ± 0.014	0.47 ± 0.016	0.51 ± 0.014	0.52 ± 0.014	0.54 ± 0.010	0.26 ± 0.008
<b>Diclofenac</b> (20 mg/kg)	0.28 ± 0.008	0.28 ± 0.008*	0.24 ± 0.016**	0.21 ± 0.012**	0.25 ± 0.013**	0.31 ± 0.014**	0.34 ± 0.020**	0.23 ± 0.018
<b>Test G1</b> (5 mg/kg)	0.30 ± 0.008	0.33 ± 0.008	0.37 ± 0.016	0.35 ± 0.012	0.36 ± 0.020	0.42 ± 0.016	0.47 ± 0.017	0.25 ± 0.008
<b>Test G1</b> (10 mg/kg)	0.30 ± 0.008	0.32 ± 0.008	0.36 ± 0.015	0.33 ± 0.015*	0.34 ± 0.020**	0.38 ± 0.016*	0.44 ± 0.015	0.26 ± 0.008
<b>Test G1</b> (20 mg/kg)	0.30 ± 0.008	0.30 ± 0.013	0.34 ± 0.023*	0.31 ± 0.014**	0.31 ± 0.016**	0.36 ± 0.017**	0.40 ± 0.016**	0.26 ± 0.012
<b>Test G2</b> (5 mg/kg)	0.30 ± 0.010	0.33 ± 0.011	0.37 ± 0.007	0.38 ± 0.012	0.36 ± 0.016	0.44 ± 0.036	0.49 ± 0.040	0.28 ± 0.008
<b>Test G2</b> (10 mg/kg)	0.30 ± 0.010	0.33 ± 0.013	0.36 ± 0.009	0.35 ± 0.012*	0.33 ± 0.016**	0.41 ± 0.036*	0.46 ± 0.020	0.30 ± 0.008
<b>Test G2</b> (20 mg/kg)	0.31 ± 0.010	0.32 ± 0.011	0.35 ± 0.007*	0.33 ± 0.012*	0.35 ± 0.016**	0.38 ± 0.036**	0.42 ± 0.040*	0.29 ± 0.008
<b>Test G3</b> (5 mg/kg)	0.29 ± 0.008	0.34 ± 0.013	0.38 ± 0.023	0.36 ± 0.014	0.35 ± 0.016	0.41 ± 0.017	0.46 ± 0.016	0.26 ± 0.012
<b>Test G3</b> (10 mg/kg)	0.30 ± 0.008	0.33 ± 0.012	0.36 ± 0.024	0.34 ± 0.015*	0.32 ± 0.016**	0.38 ± 0.019**	0.42 ± 0.014*	0.25 ± 0.012
<b>Test G3</b> (20 mg/kg)	0.32 ± 0.008	0.31 ± 0.013	0.33 ± 0.023*	0.31 ± 0.014**	0.30 ± 0.016**	0.36 ± 0.017**	0.49 ± 0.016**	0.27 ± 0.012

Values are expressed as mean ± SEM (n = 6) and ANOVA followed by Dunnett's test

\*p < 0.05, \*\*p < 0.001 when compared with the control group

inhibiting the denaturation of proteins, and its effect was comparable to that of diclofenac (Table 2).

The present findings exhibited a concentration-dependent inhibition of protein denaturation by quinazolinone derivatives (G1, G2, and G3) throughout the concentration range. Diclofenac sodium (at the concentration range of 50–250 µg/ml) was used as reference drug exhibited concentration-dependent inhibition of protein denaturation; however, the effect of diclofenac was found to be more significant (70% at 250 µg/ml) as compared to synthesized compounds. Among these, G2 and G3 showed prominent inhibition of protein denaturation 41.66% and 49.16% at 250 µg/ml concentration, respectively.

Carrageenan, a muco-polysaccharide, is a most commonly and well-studied phlogistic agent, producing edema in 3 h [20]. In the present study, quinazolinone derivative showed promising anti-inflammatory activity; this may be due to reduction in prostaglandin synthesis via COX inhibition [21]. In the present study, quinazolinone derivatives,

i.e., G1, G2, and G3, showed dose-dependent inhibition of the second phase of carrageenan-induced rat paw edema, suggesting the inhibition of prostaglandins release [22]. Among all test compounds, G3 showed more significant inhibition as compared to G1 and G2 (G3 > G1 > G2). This suggests that the possible mechanism of the anti-inflammatory action of the test compounds may be due to reduction in pro-inflammatory mediators like prostaglandins, histamine, and serotonin [5].

The cotton pellet-induced granuloma pouch method is widely used to assess the transudative and proliferative components of chronic inflammation [23]. In the present study, G3 at a dose of 10 mg/kg showed significant reduction in the cotton pellet weight 50.68% when compared with control, whereas animals treated with diclofenac depicted significant reduction in cotton pellet weight (54.20%). Newly synthesized compound of 2,3-disubstituted quinazolin-4(1H)-one derivatives may possess prominent anti-inflammatory action with minimum side effect over conventional quinazolinone derivative.

**Table 4** Influence of derivatives on cotton pellet granuloma pouch method

Group	Group dose	Granuloma dry weight (mg)	% inhibition
<b>Control</b>	1% CMC	46.34 ± 0.32	–
<b>Diclofenac</b>	10	21.72 ± 0.30**	<b>54.20</b>
<b>G1</b>	10	36.47 ± 0.26*	23.18
	20	29.44 ± 0.28*	44.25
<b>G2</b>	10	35.17 ± 0.50*	25.84
	20	31.35 ± 0.53*	33.90
<b>G3</b>	10	30.00 ± 0.58*	47.29
	20	23.39 ± 0.24**	<b>50.68</b>

\*p < 0.05, \*\*p < 0.001 when compared with control

## 5 Conclusion

A series of new 2,3-disubstituted quinazolin-4(1H)-one derivatives (G1, G2, and G3) were synthesized as well as characterized for their structure elucidation and screened for its anti-inflammatory (in vivo and in vitro).

Among these synthesized compounds, G1 and G3 exhibit more significant anti-inflammatory activity in both in vivo and in vitro models.

In future, this antagonism between inflammation and immunity also affects the outcome of cancer treatment and needs to be considered when designing new therapeutic approaches.

## Abbreviations

CMC: Carboxyl methyl cellulose; G1-3: (3,4-Dichlorophenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one; G2-3: (4-Bromo-2-methylphenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one; G3-3: (4-Bromophenyl)-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one

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## Authors' contributions

AK contributed in the preparation of study design along with the manuscript writing.

VN contributed in the interpretation of data and manuscript writing.

BG contributed in conducting animal experimentation, interpretation of data, and manuscript writing. All authors have read and approved the final manuscript for publication.

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## Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Ethics approval and consent to participate

This study was approved by the ethical committee of AISSMS College of Pharmacy, Pune.

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## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## References

- Mehta S, Kumar S, Marwaha RK, Narasimhan B, Ramasamy K, Lim SM, Shah S, Mani V. (2019) Synthesis, molecular docking and biological potentials of new 2-(4-(2-chloroacetyl) piperazin-1-yl)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)acetamide derivatives. *BMC Chem.* 113 doi:<https://doi.org/10.1186/s13065-019-0629-0>.
- Li HQ, Li DD, Lu X, Xu YY, Zhu HL (2012) Design and synthesis of 4, 6-substituted-(diaphenylamino)s as potent EGFR inhibitors with antitumor activity *Bioorg Med Chem.* (20):317–323. <https://doi.org/10.1016/j.bmc.2011.10.085>
- Kamel MM, Zagahary WA, Al-Wabli RI, Anwar MM (2016) Synthetic approaches and potential bioactivity of different functionalized and quinazolinone scaffolds. *Egypt Pharmaceut J* 15(3):98. <https://doi.org/10.4103/1687-4315.197580>
- Faraj FL, Zahedifard M, Paydar M, Looi CY, Abdul Majid N, Ali HM, Abdulla MA (2014) Synthesis, characterization, and anticancer activity of new derivatives against MCF-7 cells. *Sci World J.* 1–15. <https://doi.org/10.1155/2014/212096>
- Asif M (2014) Chemical characteristics, synthetic methods, and biological potential of and quinazolinone derivatives. *Int J Med Chem.* <https://doi.org/10.1155/2014/395637>
- Wongrakpanich S, Wongrakpanich A, Melhado K, & Rangaswami J. (2018) A comprehensive review of non-steroidal anti inflammatory drug use in the elderly. *Agi and Dis.* 9(1):143. doi:<https://doi.org/10.14336/ad.2017.0306>
- Wood RC III, Wyatt JE, Bullins KW, Hanley AV, Hanley GA, Denham JW, Panus PC (2013) Hariforoosh S. Effects of rebamipide on nephrotoxicity associated with selected NSAIDs in rats. *Eur. J. Pharmacol.* 720(1-3):138–146. <https://doi.org/10.1016/j.ejphar.2013.10.035>
- Jafari E, Khajouei MR, Hassanzadeh F, Hakimelahi GH, Khodarahmi GA. (2016) Quinazolinone and derivatives: recent structures with potent antimicrobial and cytotoxic activities. *Res Pharm Sci.* 11(1):1–14. PMID: 27051427.
- Razavi N, Akhlaghinia B (2016) Hydroxyapatite nanoparticles (HAP NPs): a green and efficient heterogeneous catalyst for three-component one-pot synthesis of 2, 3-dihydroquinazolin-4 (1 H)-one derivatives in aqueous media. *New J Chem.* 40(1):447–457. <https://doi.org/10.1039/C5NJ02123E>
- Magyar Á, Hell Z (2016) One-pot three-component synthesis of 2, 3-Dihydroquinazolin-4 (1H)-ones in the presence of a molecular sieve supported lanthanum catalyst. *Catal Lett.* 146(6):1153–1162. <https://doi.org/10.1007/s10562-016-1734-5>
- Chandra S, Chatterjee P, Dey P, Bhattacharya S (2012) Evaluation of anti-inflammatory effect of ashwagandha: a preliminary study in vitro. *Phcog J.* 4(29):4. <https://doi.org/10.5530/pj.2012.29.7>
- Amdekar S, Roy P, Singh V, Kumar A, Singh R, Sharma P (2012) Anti-inflammatory activity of lactobacillus carrageenan-induced paw edema in male Wistar rats. *Int J Inflamm.* 1–6. <https://doi.org/10.1155/2012/752015>
- Sheorey RV, Thangathiruppathy A, Alagarsamy V (2013) Synthesis, analgesic and anti-inflammatory activities of 3-ethyl-2-substituted amino-3H-quinazolin-4-ones. *Trop J Pharm Res.* 12(4):583–589
- Padhy BM, Kumar VL (2005) Inhibition of Calotropis procera latex-induced inflammatory hyperalgesia by oxytocin and melatonin. *Mediators Inflamm.* (6):360-5. <https://doi.org/10.1155/MI.2005.360>
- Kshirsagar AD, Panchal PV, Harle UN, Nanda RK, Shaikh HM (2014) Anti-inflammatory and antiarthritic activity of anthraquinone derivatives in rodents. *J Inflamm, Int.* 12 pages. <https://doi.org/10.1155/2014/690596>
- Shakya AK, Kaur A, Al-Najjar BO, Naik RR (2016) Molecular modeling, synthesis, characterization and pharmacological evaluation of benzo[d]oxazole derivatives as non-steroidal anti-inflammatory agents. *Saudi Pharm J.* 24(5):616–624. <https://doi.org/10.1016/j.jsps.2015.03.018>
- Opie EL (1962) On the relation of necrosis and inflammation to denaturation of proteins. *J Exp Med.* 115:597–608. <https://doi.org/10.1084/jem.115.3.597>
- Gudipati R, Anreddy RN, Manda S (2011) Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1, 3, 4-oxadiazole-2-yl) phenylimino} indolin-2-one derivatives. *Saudi Pharm J* 19(3):153–158. <https://doi.org/10.1016/j.jsps.2011.03.002>
- Ashok P, Koti BC, Thippeswamy AH, Tikare VP, Dabadi P, Viswanathaswamy AH. (2010) Evaluation of antiinflammatory activity of Centrathurum anthelminticum (L) Kuntze seed. *Indian J Pharm. Sci* 72(6):697. Doi:10.4103%2F0250-474X.84577
- Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A, Ghorbanzadeh B. (2015) A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. *Indian J Pharmacol.* 47(3):292. doi: 10.4103%2F0253-7613.157127.
- Robinson DR (1983) Prostaglandins and the mechanism of action of anti-inflammatory drugs. *Am J Med.* 75(4):26–31. [https://doi.org/10.1016/0002-9343\(83\)90325-x](https://doi.org/10.1016/0002-9343(83)90325-x)
- Akindele AJ, Oladimeji-Salami JA, Usuwah BA (2015) Antinociceptive and anti-inflammatory activities of Telfairia occidentalis hydroethanolic leaf extract (Cucurbitaceae). *J Med Food.* 18(10):1157–1163. <https://doi.org/10.1089/jmf.2014.0146>
- Patil KR, Mahajan UB, Unger BS, Goyal SN, Belemkar S, Surana SJ, Ojha S, Patil CR. (2019) Animal models of inflammation for screening of anti-inflammatory drugs: implications for the discovery and development of phytopharmaceuticals. *Int J Mol Sci.* 20(18):4367. doi: 10.3390/ijms20184367.

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