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ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES OF NOVEL 2-THIOXO QUINAZOLINONYL CHALCONES

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ABSTRACT

A series of novel 2-thioxo quinazolinonyl chalcones were synthesized by the Claisen-Schmidt condensation reaction of 1-acetyl-2-thioxo quinazolin-4-(3*H*)-ones with benzaldehyde. The synthesized compounds were characterized by physical, elemental, IR, ^{1}H NMR and mass spectral data. Further, they were screened for *in vivo* analgesic and anti-inflammatory activities. Among them, the title compounds **3e**, **3f**, **3g**, **3k**, **3l**, **3q** and **3r** exhibited promising analgesic and anti inflammatory activities.

Key words: Thioxo quinazolinonyl chalcones, Analgesic activity, Egg white induced edema.

INTRODUCTION

Pain is a physiological response that alarms us about the danger. The process of nociception describes normal pain processing in response to noxious stimuli, which potentially damage physiological tissue(s). Three prominent categories of external noxious stimuli that can damage tissue(s); (i) mechanical (pressure, swelling, abscess, incision, tumor growth); (ii) thermal (burn, scald) and (iii) chemical (excitatory neurotransmitter, toxic substance, ischemia, and infection). Inflammation is a common defense mechanism in response to vascular tissue injury by infectious agents/antigens, chemical or physical damage initiating a series of events called inflammatory process[1,2]. It is usually associated with pain as a secondary process causing the release of chemical pain or inflammatory mediators[3] (histamine, serotonin, bradykinin, prostaglandins, potassium ions and substance P). The complex events and mediators involved in the inflammatory reactions can induce, maintain or aggravate many diseases[4]. Most of pharmacotherapies for inflammatory diseases are usually directed at modulation of various mediators involved in process of inflammation. Till date, non-steroidal anti-inflammatory drugs (NSAIDs) are preferred drugs in market for

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treatment of several inflammatory conditions like rheumatoid arthritis, osteoarthritis and musculoskeletal disorders etc. However, prolonged use of marketed NSAIDs can lead to nausea, fluid retention by acute or chronic renal failure, hypertension and precipitation of congestive heart failure (CHF), bleeding and gastric ulcers etc[5]. So, in order to get rid of above associated adverse drug reactions, synthesis of newer NSAIDs is the need of the hour (h). Therefore, the objective of the present study is synthesis of new chemical entities, followed by their screening for analgesic and anti-inflammatory activities.

Compounds with quinazolinone heterocyclic nucleus were found to possess broad spectrum of activities like antimicrobial[6], anthelmintic[7], analgesic and anti-inflammatory[8], antihypertensive[9], sedative and hypnotic[10], antidepressant[11] and anticancer activities[12]. However, only scanty work was done in synthesis of 3-aryl-2-thioxo quinazolin-4-(3*H*) ones. So, in the present work, we designed a scheme and synthesized 18 novel 2-thioxo quinazolinonyl chalcones. They were further characterized and screened for *in vivo* analgesic and anti-inflammatory activities.

EXPERIMENTAL

Melting points were determined by an open-end capillary tube method using electrically heated melting point apparatus. The respective values were expressed in ^{o}C and were uncorrected. Completion of the reaction and product formation were confirmed by running a thin layer chromatogram on silica gel and eluting with ethyl acetate and chloroform (3:7). The elemental analyses were performed using Carlo Erba-1108 elemental analyzer. IR spectra were recorded on a FTIR spectrophotometer Elmer 1600 series as KBr-disks. Proton NMR spectra were recorded on a FT-NMR spectrophotometer BRUCKER MX 400 MHz using TMS as internal standard. The mass spectrum of the compounds was recorded on Agilent 1100 series LC-MS.

Synthesis of 2-thioxo quinazolinonyl chalcones

Various novel 2-thioxo quinazolinones **(1a-r)** and their acetylated derivatives **(2a-r)** were synthesized as per methods described elsewhere[13,6]. Mixture of 0.01 mole of each **(2a-r)** compound [1-acetyl-3-(un)substituted phenyl-6-(un) substituted-2-thioxo-4(3*H*)-quinazolinones] and benzaldehyde in absolute ethanol (50 ml) containing 2% NaOH was refluxed for 8-12 h. Reaction mixture was concentrated and further allowed to stand at room temperature for 10 min. Later, the mixture was poured into a beaker containing ice cold water. The solid thus obtained was filtered, recrystallized from absolute ethanol to get the title compounds **(3a-r)**. The synthetic scheme is represented in **Scheme 1** and the characterization of the title compounds is shown in Table 1.

Table 1: Physical and spectral characterization data of synthesized compounds with their IDs

Id.	X	Y	Z	Mol. For & Mol. Wt	MP (°C)	% Yield	E. A (%): Calcd. (Found)			FTIR (ν cm^{-1})	^{1}H NMR (δ,ppm)
							C	H	N		
3a	H	H	H	$C_{23}H_{16}N_2OS$ (384)	130-2	26.7	71.87 (70.2)	4.16 (4.02)	7.29 (6.83)	1678.52 (-CO-CH=CH-), 1600.12 (-CH=CH-), 3146.53 (-CH of propene), 1516.87 (-CH=CH- of arom. ring), 3213.63 (Ar-CH-), 1211.32 (C=S)	6.87 (1H, d, -CO-CH=), 7.51 (1H, d, -CH-Ar), 7.06-8.32 (14H, m, Ar-H)
3b	H	Cl	H	$C_{23}H_{15}N_2O_2SCl$ (418.45)	190-2	40.6	65.95 (63.6)	3.58 (3.06)	6.69 (5.45)	1696.67 (-CO-CH=CH-), 1615.19 (-CH=CH-), 3016.62 (-CH of propene), 1545.91 (-CH=CH- of arom. ring), 3166.84 (Ar-CH-), 1232.51 (C=S)	6.81 (1H, d, -CO-CH=), 7.52 (1H, d, -CH-Ar), 7.16-8.26 (13H, m, Ar-H)
3c	H	Br	H	$C_{23}H_{15}N_2O_2SBr$ (463)	192-4	21.7	59.3 (59.0)	3.24 (3.08)	6.04 (5.91)	1713.64 (-CO-CH=CH-), 1618.93 (-CH=CH-), 3003.27 (-CH of propene), 1556.39 (-CH=CH- of arom. ring), 3184.25 (Ar-CH-), 1204.67 (C=S)	6.83 (1H, d, -CO-CH=), 7.48 (1H, d, -CH-Ar), 7.23-8.65 (13H, m, Ar-H)
3d	H	H	Cl	$C_{23}H_{15}N_2O_2SCl$ (418.45)	250-2	50.1	65.95 (64.5)	3.58 (3.22)	6.69 (6.42)	1677.72 (-CO-CH=CH-), 1648.16 (-CH=CH-), 3026.72 (-CH of propene), 1545.61 (-CH=CH- of arom. ring), 3296.812 (Ar-CH-), 1201.26 (C=S)	6.80 (1H, d, -CO-CH=), 7.46 (1H, d, -CH-Ar), 7.20-8.31 (13H, m, Ar-H)

Cont…

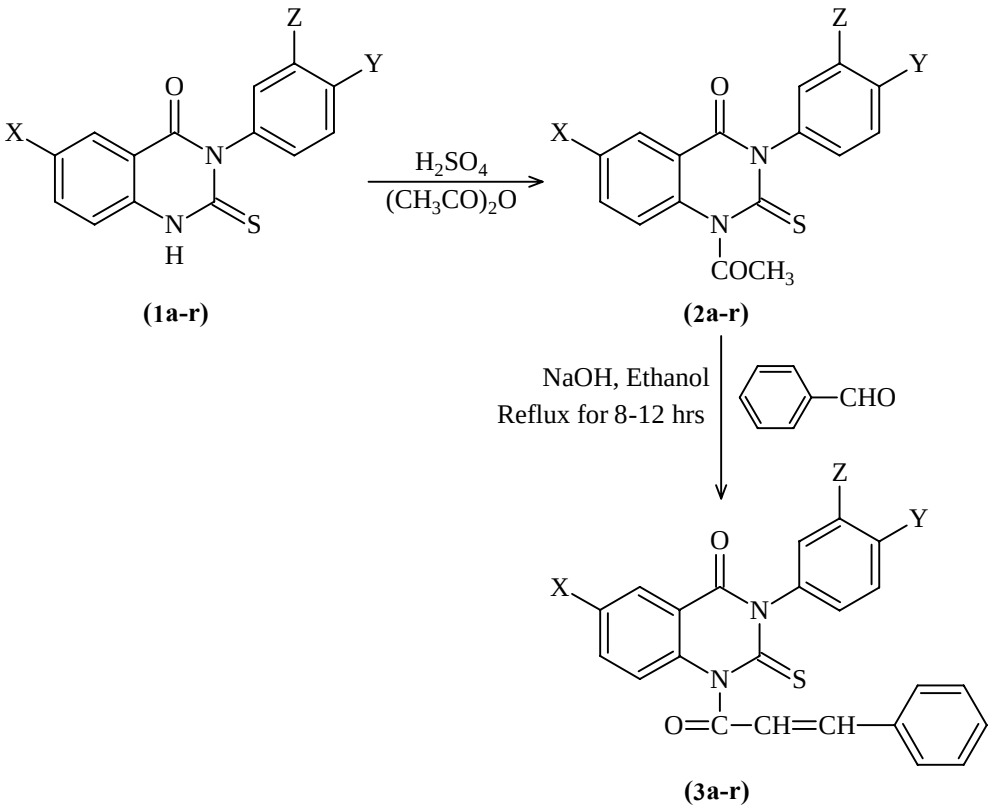
Id.	X	Y	Z	Mol. For & Mol. Wt	MP (°C)	% Yield	E. A (%): Calcd. (Found)			FTIR (ν cm^{-1})	^{1}H NMR (δ,ppm)
							C	H	N		
3e	H	F	H	$C_{23}H_{15}N_2O_2SF$ (402)	149-151	65.0	68.65 (66.5)	3.73 (3.51)	6.96 (5.87)	1656.80 (-CO-CH=CH-), 1610.46 (-CH=CH-), 3080.16 (-CH of propene), 1520.32 (-CH=CH- of arom. ring), 3108.62 (Ar-CH-), 1230.63 (C=S)	6.88 (1H, d, -CO-CH=), 7.52 (1H, d, -CH-Ar), 7.05-8.54 (13H, m, Ar-H)
3f	H	CH_3	H	$C_{24}H_{18}N_2O_2S$ (398)	166-8	67.3	69.34 (70.2)	4.52 (4.12)	7.03 (6.83)	1726.35 (-CO-CH=CH-), 1649.19 (-CH=CH-), 3028.34 (-CH of propene), 1514.17 (-CH=CH- of arom. ring), 3136.36 (Ar-CH-), 1271.13 (C=S)	6.90 (1H, d, -CO-CH=), 7.53 (1H, d, -CH-Ar), 7.18-8.18 (13H, m, Ar-H) 2.14 (3H, s, -CH_3)
3g	Br	H	H	$C_{23}H_{15}N_2O_2SBr$ (463)	148-150	56.5	59.62 (56.5)	3.24 (3.18)	6.04 (5.92)	1689.61 (-CO-CH=CH-), 1601.53 (-CH=CH-), 3158.73 (-CH of propene), 1509.81 (-CH=CH- of arom. ring), 3253.28 (Ar-CH-), 1206.57(C=S)	6.82 (1H, d, -CO-CH=), 7.44 (1H, d, -CH-Ar), 6.96-7.98 (13H, m, Ar-H)
3h	Br	Cl	H	$C_{23}H_{14}N_2O_2SBrCl$ (497.35)	152-4	47.3	55.49 (54.8)	2.81 (2.14)	5.62 (5.02)	1669.55 (-CO-CH=CH-), 1608.69 (-CH=CH-), 3304.17 (-CH of propene), 1537.32 (-CH=CH- of arom. ring), 3194.23 (Ar-CH-), 1261.49(C=S)	6.83 (1H, d, -CO-CH=), 7.49 (1H, d, -CH-Ar), 7.03-7.99 (12H, m, Ar-H)
3i	Br	Br	H	$C_{23}H_{14}N_2O_2SBr_2$ (542)	216-8	40.1	50.9 (49.2)	2.58 (2.28)	5.16 (5.07)	1674.12 (-CO-CH=CH-), 1605.15 (-CH=CH-), 3136.60 (-CH of propene), 1565.84 (-CH=CH- of arom. ring), 3270.41 (Ar-CH-), 1224.80 (C=S)	6.84 (1H, d, -CO-CH=), 7.46 (1H, d, -CH-Ar), 7.21-8.65 (12H, m, Ar-H)

Cont…

Id.	X	Y	Z	Mol. For & Mol. Wt	MP (°C)	% Yield	E. A (%): Calcd. (Found)			FTIR (ν cm^{-1})	^{1}H NMR (δ,ppm)
							C	H	N		
3j	Br	H	Cl	$C_{23}H_{14}N_2O_2SBrCl$ (497.35)	250-2	56.7	55.4 (52.6)	2.81 (2.17)	5.62 (5.05)	1663.17 (-CO-CH=CH-), 1620.01 (-CH=CH-), 3061.20 (-CH of propene), 1553.92 (-CH=CH- of arom. ring), 3175.51 (Ar-CH-), 1243.50 (C=S)	6.80 (1H, d, -CO-CH=), 7.49 (1H, d, -CH-Ar), 7.14-8.05 (12H, m, Ar-H)
3k	Br	F	H	$C_{23}H_{14}N_2O_2SBrF$ (481)	122-4	61.7	57.39 (55.8)	2.91 (2.13)	5.82 (4.96)	1666.60 (-CO-CH=CH-), 1619.16 (-CH=CH-), 3065.18 (-CH of propene), 1501.51 (-CH=CH- of arom. ring), 3201.99 (Ar-CH-), 1208.32 (C=S)	6.87 (1H, d, -CO-CH=), 7.55 (1H, d, -CH-Ar), 7.18-8.46 (12H, m, Ar-H)
3l	Br	CH_3	H	$C_{24}H_{17}N_2O_2SBr$ (477)	154-6	71.6	60.39 (60)	3.56 (3.48)	5.87 (5.18)	1666.55 (-CO-CH=CH-), 1627.97 (-CH=CH-), 3030.27 (-CH of propene), 1512.24 (-CH=CH- of arom. ring), 3190.37 (Ar-CH-), 1251.84 (C=S)	6.86 (1H, d, -CO-CH=), 7.56 (1H, d, -CH-Ar), 7.18-8.06 (12H, m, Ar-H) 2.33 (3H, s, -CH_3)
3m	I	H	H	$C_{23}H_{15}N_2O_2SI$ (510)	180-2	58.9	54.13 (52.7)	2.94 (2.52)	5.49 (4.47)	1676.76 (-CO-CH=CH-), 1607.42 (-CH=CH-), 3056.38 (-CH of propene), 1536.61 (-CH=CH- of arom. ring), 3321.73 (Ar-CH-), 1203.917 (C=S)	6.83 (1H, d, -CO-CH=), 7.42 (1H, d, -CH-Ar), 6.95-8.10 (13H, m, Ar-H)
3n	I	Cl	H	$C_{23}H_{14}N_2O_2SICl$ (544.35)	196-8	26.8	50.70 (49.9)	2.57 (2.18)	5.14 (5)	1687.71 (-CO-CH=CH-), 1653.05 (-CH=CH-), 3042.13 (-CH of propene), 1525.74 (-CH=CH- of arom. ring), 3201.91 (Ar-CH-), 1217.12 (C=S)	6.84 (1H, d, -CO-CH=), 7.46 (1H, d, -CH-Ar), 7.05-8.16 (12H, m, Ar-H)

Cont…

Id.	X	Y	Z	Mol. For & Mol. Wt	MP (°C)	% Yield	E. A (%): Calcd. (Found) C	H	N	FTIR (ν cm^{-1})	^{1}H NMR (δ,ppm)
3o	I	Br	H	$C_{23}H_{14}N_2O_2SIBr$ (589)	216-8	66.7	46.87 (45.1)	2.37 (2.23)	4.75 (3.96)	1661.50 (-CO-CH=CH-), 1607.42 (-CH=CH-), 3029.58 (-CH of propene), 1515.30 (-CH=CH- of arom. ring), 3236.95 (Ar-CH-), 1211.89(C=S)	6.85 (1H, d, -CO-CH=), 7.51 (1H, d, -CH-Ar), 7.24-8.57 (12H, m, Ar-H)
3p	I	H	Cl	$C_{23}H_{14}N_2O_2SICl$ (544.35)	270-2	69.2	50.70 (49.8)	2.57 (2.36)	5.14 (4.93)	1716.35 (-CO-CH=CH-), 1663.40 (-CH=CH-), 3059.37 (-CH of propene), 1484.15 (-CH=CH- of arom. ring), 3236.66 (Ar-CH-), 1209.41 (C=S)	6.78 (1H, d, -CO-CH=), 7.42 (1H, d, -CH-Ar), 7.00-8.16 (12H, m, Ar-H)
3q	I	F	H	$C_{23}H_{14}N_2O_2SIF$ (528)	140-2	56.2	52.28 (50.2)	2.65 (2.15)	5.30 (5.18)	1667.59 (-CO-CH=CH-), 1610.45 (-CH=CH-), 3106.65 (-CH of propene), 1507.07 (-CH=CH- of arom. ring), 3237.30 (Ar-CH-), 1264.28(C=S)	6.79 (1H, d, -CO-CH=), 7.48 (1H, d, -CH-Ar), 6.95-8.56 (12H, m, Ar-H)
3r	I	CH_3	H	$C_{24}H_{17}N_2O_2S$ I (524)	190-2	80.4	54.97 (53.9)	3.24 (3.06)	5.34 (4.72)	1660.47 (-CO-CH=CH-), 1649.19 (-CH=CH-), 3023.69 (-CH of propene), 1508.70 (-CH=CH- of arom. ring), 3136.36 (Ar-CH-), 1208.76 (C=S)	6.86 (1H, d, -CO-CH=), 7.53 (1H, d, -CH-Ar), 7.14-8.21 (12H, m, Ar-H) 2.26 (3H, s, $-CH_3$)



Scheme 1: Synthesis of Novel 2-thioxo quinazolinonyl Chalcones

Pharmacology

Animal experiments were conducted in accordance with the principles of laboratory animal care NIH guidelines. The study protocol was approved by the Institutional Animal Ethical Committee of Chalapathi Institute of Pharmaceutical Sciences, Guntur, India. Swiss albino mice (20-25 g) and Wister albino rats (180-220 g) were used for *in vivo* studies. All the animals were inbreed, housed in polypropylene cages under controlled environmental conditions of 25 ± 1^{o}C, 45-55% relative humidity (RH) and a 12 hrs light/12 hrs dark cycle. Experimental animals had free access to standard rodent pellets and water *ad libitum* unless stated elsewhere during experimentation.

Analgesic activity

*In vivo a*nalgesic activity of the synthesized compounds was performed by Eddy's hot plate method[14]. Swiss albino mice of either sex weighing about 20-25 g were used for this experiment. All the animals were fasted for 6 hrs before starting experiment. Animals

were divided into three groups (n=6 per each group), (i) Group I-Std. Pentazocine (30 mg/Kg) in 1% v/v Tween 80 solution; (ii) Group II - Vehicle (1% v/v Tween-80) and (iii) Group III-test compounds (5 mg/Kg solubilised in 1% v/v Tween 80) dose. Group III animals were further divided into different subgroups for checking the analgesic activity of all test compounds. Animals were placed on a hot plate maintained at constant temperature of 55±0.5^{o}C immediately after intraperitoneal (i.p.) administration of test compounds. Latency to exhibit the nociceptive response such as licking paws or jumping was recorded by a stop watch. A saturation cut-off time of 15 sec was selected to avoid tissue damage to the paws.

Anti-inflammatory activity

Egg-albumin induced rat paw edema method[15] was adopted for screening the anti-inflammatory activity of the synthesized compounds. Wister Albino rats of either sex weighing about 180-220 g were used for the study. The paw edema was induced in the plantar region of the rat right hind paw. They were fasted for 6 hrs and deprived of water only during the experiment. The water deprivation was to ensure uniform hydration and to minimize variability in edematous response. Animals were divided into three groups (n=6 per each group), (i) Group I - Std. Diclofenac sodium (20 mg/Kg); (ii) Group II - Vehicle (0.2 mL of 1% v/v Tween 80) and (iii) Group III - test compounds (10 mg/Kg solubilised in 1% v/v Tween 80). Group - III animals were further divided into different subgroups for checking the anti-inflammatory activity of all test compounds. All the synthesized compounds were administered intra-peritoneally 30 min before the intra dermal injection of the phlogistic agent (0.1 mL of fresh undiluted egg albumin) in the plantar region of the right hind paw. Paw volume was measured by mercury displacement method using a plethysmograph at 0 min and 1 h, 2 hrs and 3 hrs after egg-albumin injection. Anti-inflammatory activity of all test compounds at each time of observation was calculated as percent inhibition of edema in the animals treated with substances under test, in comparison to the vehicle-treated animals. The percentage inhibition of edema is calculated using the formula :

$$\% \text{ inhibition} = [(V_0 - V_t)\ V_0] \times 100$$

Where V_t is volume of edema at corresponding time; V_0 is the volume of edema of control rats at the same time.

RESULTS AND DISCUSSION

Analgesic activity

The mean basal reaction time and reaction time after 30 min of drug administration of compounds **(3a-r)** and standard drug (Pentazocine) were recorded and are shown in

Fig. 1. Generally various methods like tail flick method, tail immersion method, eddy's hot plate method, paw-pressure method are reported in literature for performing analgesic activity. Of these, eddy's hot plate method is one of the widely used method. After 30 min of administration, compounds **3e**, **3f**, **3**g, **3k**, **3l**, **3q** and **3r** showed significant analgesic activity as observed in reaction time (sec), when compared to control.

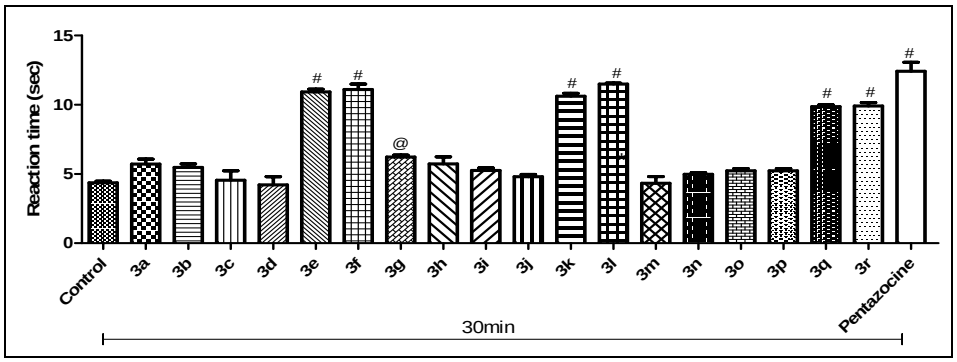


Fig. 1: Analgesic activity of 2-thioxo quinazolinonyl chalcones. Results are expressed as Mean ± SEM (n=6). Statistical analysis of data was carried out by one-way analysis of variance followed by the *Dunnets post hoc comparison test;* $^{@}P < 0.01$ and $^{\#}P < 0.001$

Anti-inflammatory activity

The edema volumes and % edema inhibition data of all compounds and standard (Diclofenac sodium) after 1 h of administration was recorded and represented in Fig. 2 and Fig. 3.

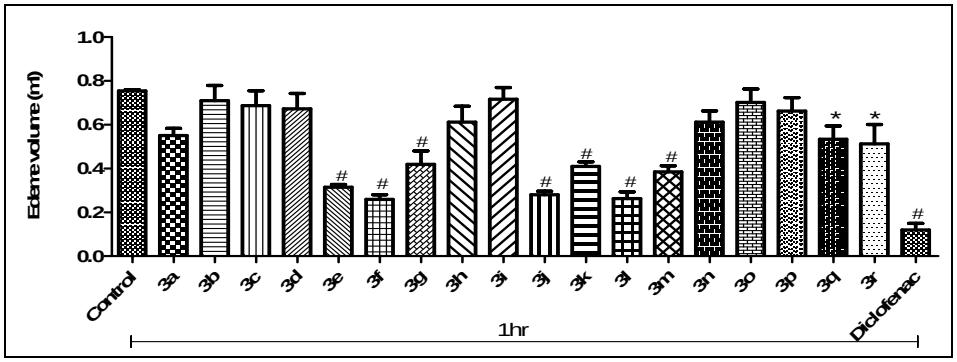


Fig. 2: Anti-inflammatory activity of 2-thioxo quinazolinonyl chalcones. Results are expressed as Mean ± SEM (n=6). Statistical analysis of data was carried out by one-way analysis of variance followed by the *Dunnets post hoc comparison test;* $^{*}P < 0.05$, and $^{\#}P < 0.001$

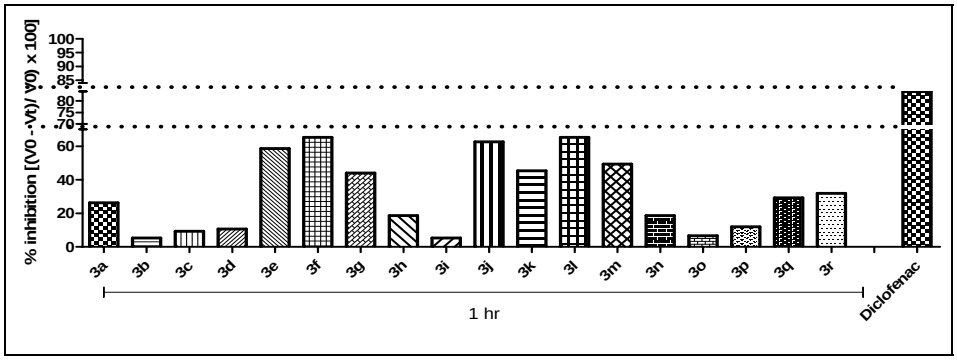


Fig. 3: % inhibition $[(V_0-V_t)/V_0 \times 100]$ data of 2-thioxo quinazolinonyl chalcones in anti- inflammatory activity

Previous studies showed that extent of inflammation induced by egg albumin are similar to that produced by carrageenine[16,17]. Edema formation due to egg albumin in the rat paw is a biphasic event. The early phase edema which begins immediately after the administration of the irritant and lasting up to 2 hrs is probably due to the release of histamine and serotonin; while the later phase edema, starting from 3 hrs and continuing till 5 hrs is induced by bradykinin, protease, prostaglandins and lysosome[18]. Subcutaneous injection of egg albumin into the rat paw produces edema resulting from plasma extravasation, increased tissue water and plasma protein exudation along with neutrophil extravasation[19].

All the compounds **(3a-r)** at a dose of 10 mg/Kg body weight exhibited anti-inflammatory activity. However, compounds **3e**, **3f**, **3g**, **3j**, **3k**, **3l**, **3m**, **3q** and **3r** exhibited significant ($^{*}P < 0.05$, $^{@}P < 0.01$ and $^{\#}P < 0.001$) edema inhibition in comparison with control.

CONCLUSION

In our present investigation, substitution at 1st position of the quinazolinone ring was found to be beneficial like other positions. The observed analgesic and anti-inflammatory activities might be due to the inhibition of the neurotransmitters release. As all the synthesized compounds contains 2-propen-1-one moiety and 2-thioxo quinazolinone nucleus, it seems that the halogenated aryl groups and halogens at 6th and 3rd position of the thioxoquinazolinone nucleus respectively might be responsible for observed activities. Interestingly, compounds, which showed good analgesic activity also showed good anti-inflammatory activities. In future, further studies like establishment of structure activity relationship (QSAR) might be necessary for studying mechanism of action.

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