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SYNTHESIS AND BIOLOGICAL ASSESMENT OF QUINAZOLONE BASED AMIDE LINKAGE CONTAINING THIAZOLIDINONE AND THEIR DERIVATIVES

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ABSTRACT: A number of substituted quinazolones are well known for their pharmacological activities like anti-inflammatory, antibacterial and analgesic etc. The present work deals with synthesis of quinazolone based thiazolidinone in order to enhance the biological properties. A Series of (2-(substituted phenyl)-4-oxothiazolidin-3-yl) -4- (4-oxo-2-phenyl quinazolin-3(4H)-yl) benzamide **(6a-6h)** were synthesized in good yield. The structures of the compounds obtained have been established on the basis of Spectral (IR, ^{1}H NMR, ^{13}C NMR and Mass) data. The present study also involves *in vivo* anti- inflammatory activity and *in vitro* antibacterial activity against few strains (gram positive and gram negative) of bacteria of synthesized compounds. Derivatives **6a**, **6e** and **6g** exhibit promising anti-inflammatory and antibacterial activity with reference to standard drug Indomethacin and Ampicillin respectively.

INTRODUCTION: 4-Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. The nucleus is also known as wonder nucleus [1] because it gives out different derivatives with all different types of biological activities such as antitubercular [2], anti-microbial [3], anti-cancer [4], anticonvulsant [5], antihistaminic [6] etc. Quinazolones and their derivatives are versatile nitrogen containing heterocyclic compounds which have been known as a promising class of biologically active compounds and has broad spectrum medicinal values such as analgesic [7], anti-inflammatory [8], antibacterial [9], anti-fungal [10], anti-cancer [11] etc.

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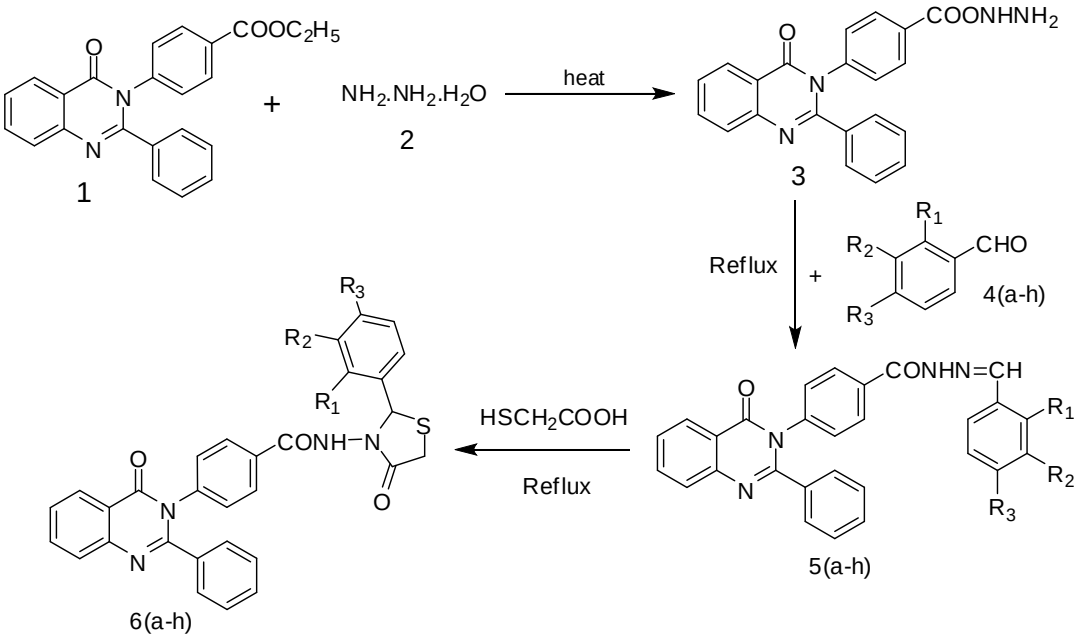
The stability and pharmacological properties of quinazolones has inspired us to synthesize quinazolone substituted amide linkage containing thiazolidinone and their derivatives with the objective to enhance the biological activities.

In our present work, we have synthesized a series (2-(substituted phenyl)-4oxothiazolidin-3-yl)-4-(4-oxo-2-phenyl quinazoline -3(4H)-yl) benzamide **(6a-6h)** in good yield.

The synthesized ethyl 4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzoate **1** on reaction with hydrazine hydrate(2) gave 4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzohydrazide **3**, which on reaction with substituted benzaldehydes **4** in the presence of glacial acetic acid as a catalyst yielded (substituted benzylidene)-4- (4-oxo-2-phenylquinazolin-3(4H)-yl) benzohydrazide **5** which on further reaction with mercaptoacetic acid to synthesize (2-(substituted phenyl)-4oxothiazolidin-3-yl)-4-(4-oxo-2-phenyl quinazoline -3(4H)-yl) benzamide **(6a-6h)**.



Where R_1, R_2, R_3 = -OH, -Cl, $-OCH_3$, $-NO_2$, $-N(CH_3)_2$ etc.

SCHEME 1

MATERIALS AND METHODS: All reagents and solvents are of analytical grade and used directly. All melting points were determined by open tube capillaries method and are uncorrected. IR spectra (υ_{max} in cm^{-1}) were recorded on Schimadzu-IR Prestige 21 spectrophotometer using KBr technique. ^{1}H NMR spectra were recorded on Bruker-Avance (400 MHz), spectrophotometer using DMSO-d_6 solvent and TMS as internal standard. Mass spectra were recorded on Waters Micromass Q-T of micro spectrometer. TLC was carried out using Silica gel G procured from Merck. Solvent used was petroleum ether and ethyl acetate (7:3).

Synthetic protocol (Scheme1):

1. **Synthesis of 4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzohydrazide** [12]: A mixture of ethyl 4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzoate (1mol) and hydrazine hydrate (2mol) were refluxed for in absolute ethanol for 6 to 8 h. When the excess of alcohol was distilled off, the quinazolone hydrazides separated out as solid masses. These hydrazides were recrystallized from ethanol.

2. **Synthesis of (Substituted benzylidene) -4- (4-oxo-2-phenylquinazolin-3(4H)-ylbenzo hydrazide** [13]: A mixture of 4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzohydrazide (0.01mol) and substituted benzaldehyde (0.01mol) was refluxed in methanol(60.0 mL) in the presence of a catalytic amount of glacial acetic acid for 10 h. After reaction completion, the reaction mass was cooled to room temperature, and poured onto ice-cold water with vigorous string. The separated solid was filtered, washed with 5% sodium bisulfite solution to remove excess aldehyde and recrystallized from chloroform.

3. **Synthesis of (2-(substituted phenyl)-4oxothiazolidin-3-yl)-4-(4-oxo-2-phenyl quinazoline -3(4H)-yl) benzamide:** A solution of (Substituted benzylidene) -4- (4-oxo-2-phenylquinazolin-3(4H)-ylbenzohydrazide (0.01mol) in dry benzene (50 ml) and mercaptoacetic acid (0.012 mol) were refluxed for 12 hours. After completion of reaction, excess of benzene was distilled off and the resulting product was treated with 5% NaHCO3 solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from DMF.

The spectral data of the synthesized derivatives is as follows:

(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzamide (6a): IR KBr (cm^{-1})**:**1691(C=O), 1357(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 751(-

OH), 1675(CONH), 3325(-NH), 698(C-S). ^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 9.68(s, 1H, OH), 7.8(s, 1H, NH), 3.95 (s, 2H, CH_2S), 5.9(s, 1H, N-CH), 6.8- 8.13(m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ/ppm): 160.3(C=O), 136.1(C-N), 163.7(CONH), 168.8(N-C=O), 35.6(C-S), 51.1 (NCS), 153.7(C-OH), 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164,128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 127.6, 118.1, 153.7, 115.8, 128.5, 121.2, 128 (Aromatic). MS: m/z 534.15 (M^+, 100%).elemental analysis (calcd.): C= 67.40%, H=4.15%, N=10.48%, O=11.97%, S=6%; (found): C=67.36%, H =4.10%, N=10.44%, O=11.91%, S=5.98%.

(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzamide (6b): IR KBr (cm^{-1})**:**1688(C=O), 1354(C–N stretch tertiary), 1597 (-C=N), 3038-3074 (Ar-CH), 751(-OH), 1677(CONH), 3328(-NH), 705(C-S). ^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 9.43(s, 1H,-OH), 7.6(s, 1H, NH), 3.92(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 6.63-8.13(m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ / ppm): 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 57.3(NCS), 156.9(C-OH), 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164,128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 127.6, 115.8, 153.7, 115.8, 128.5, 121.2, 128 (Aromatic). MS: m/z 534.15 (M^+, 100%). Elemental analysis (calcd.): C= 67.40%, H=4.15%, N=10.48%, O=11.97%, S=6%; (found): C=67.36%, H=4.10%, N=10.44%, O=11.91%, S=5.98%.

(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6c): IR KBr (cm^{-1})**:**1691(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1550(-NO_2), 1678(CONH),3330(-NH),710(C-S).^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.6(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 7.35 - 8.13(m, 17H, Ar). MS: m/z 563.13 (M^+, 100%).^{13}C NMR (400 MHz, DMSO-d6, δ / ppm): 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 52.7(NCS), 149(C-NO_2), 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 127.6, 124.8, 128,134.7, 129.6, 133.4 (Aromatic). Elemental analysis (calcd.): C= 63.93%, H=3.76%, N=12.43%, O=14.19%, S=5.69%; (found): C=63.85%, H=3.73%, N=12.39%, O=14.17%, S=5.65%.

(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6d): IR KBr (cm^{-1})**:** 1691(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1550(-NO_2), 1678(CONH), 3330(-NH), 710(C-S).^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.8(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 7.52 - 8.13(m, 17H, Ar). MS: m/z 563.13 (M^+, 100%). ^{13}C NMR (400 MHz, DMSO-d6, δ / ppm): 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 56.3(NCS), 147.8(C-NO_2), 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 127.6, 124.8, 128,134.7, 129.6, 133.4 (Aromatic). Elemental analysis (calcd.): C=63.93%, H=3.76%, N=12.43%, O=14.19%, S=5.69%; (found: C=63.85%, H=3.73%, N=12.39%, O=14.17%, S=5.65%.

(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6e): IR KBr (cm^{-1})**:**1691(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 2832(-OCH_3), 1678(CONH), 3330(-NH), 710(C-S) .^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.8(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 3.83 (s, 3H,-OCH_3)7.52 -8.13(m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ/ppm): 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 57.3(NCS), 55.8(-OCH_3), 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 127.6, 159, 114.2, 129.7, 131.5, 129.7(Aromatic). MS: m/z 548.15 (M^+, 100%). Elemental analysis (calcd.): C= 67.87%, H=4.41%, N=10.21%, O=11.67%, S=5.84%; (found): C=67.85%, H=4.39%, N=10.19%, O=11.64%, S=5.81%.

(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6f): IR KBr (cm^{-1})**:**1691(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 735(C-Cl), 1678(CONH),3258(-NH),706(C-S) . ^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.8(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 7.52 - 8.13(m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ / ppm) 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 102.5(NCS), 134(C-Cl) 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 128.7, 128.5, 126.7, 130.1 (Aromatic). MS: m/z 552.10(M^+, 100%). Elemental analysis (calcd.): C= 65.15%, H=3.83%, Cl=6.41%, N=10.13%,

O=8.68%, S=5.80%; (found):C=65.11%, H=3.79%, Cl=6.39%, N=10.10%, O=8.65%, S=5.79% .

(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6g): IR KBr (cm^{-1})**:**1691(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 735(C-Cl), 1678(CONH),3258(-NH),706(C-S) . ^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.8(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 7.17-8.13(m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ / ppm) 160.6(C=O), 163.7(CONH), 136.1(C-N) 168.8(N-C=O), 35.6(C-S), 102.5 (NCS), 132.7(C-Cl) 126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 128.7, 128.5, 126.7, 130.1 (Aromatic). MS: m/z 552.10(M^+, 100%). Elemental analysis (calcd.): C= 65.15%, H=3.83%, Cl=6.41%, N=10.13%, O=8.68%, S=5.80%; (found): C=65.11%, H= 3.79%, Cl=6.39%, N=10.10%, O=8.65%, S=5.79%.

(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl) benzamide (6h): IR KBr (cm^{-1})**:**1685(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3258(-NH), 710(C-S). ^{1}H NMR (400 MHz, DMSOd_6) δ/ppm: 7.8(s, 1H,-NH), 3.95(s, 2H, CH_2S), 5.92(s, 1H, N-CH), 3.06 (s, 6H, N $(CH_3)_2$), 7.05-8.13 (m, 17H, Ar). ^{13}C NMR (400 MHz, DMSO-d6, δ / ppm) 160.6(C=O), 163.7 (CONH), 136.1(C-N) 168.8 (N-C=O), 35.6(C-S), 102.5(NCS), 149.5(C- N $(CH_3)_2$), 40.2 (CH_3)126.6, 127.3, 133.4, 126.7, 148.7, 120.8, 164, 128.6, 128.2, 128.8, 130.1, 124.5, 124.5, 129.6, 112.8, 127.4, 128.7 (Aromatic). MS: m/z 561.18(M^+, 100%). Elemental analysis (calcd.): C=68.43%, H=4.85%, N=12.47%, O=8.55%, S=5.71 %; (found): C=68.41% H=4.83%, N=12.45% O=8.52%, S=5.74%.

Pharmacological Activities:

1. **Anti-inflammatory activity of synthesized derivatives (6a-6h) against carrageenan induced paw edema in rats:** The experimental protocol for Anti-inflammatory activity was approved by Institutional Animal Ethical Committee (IAEC) as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment Government of India (536/ 02/ CPCSEA) (SPCP/2013/595/1). Synthesized compounds were screened *in vivo* for anti-inflammatory activity using rat paw edema model of Winter *et al* [14] where inflammation is induced by injecting carrageenan in hind paw of Wistar albino rats.

   Rats weighing around 150-200 g were used for the present study and divided into different groups containing six animals in each group with 50% sex ratio. One Group served as a control containing 5% Tween-80 in distilled water and another group received Indomethacin as a standard drug at a dose of 10 mg/kg and the remaining groups received test drugs at a dose of 150and 250mg/kg of body weight.

   One hour after the oral administration of synthesized compounds, reference drug, an injection of freshly prepared 0.1ml carrageenan (1% carrageenan in 0.9% NaCl) was injected into the left hind limb of each rat under the subplantar aponeurosis. Measurement of paw volume was done by means of volume displacement technique using *Plethysmometer*[15]. Paw volume was recorded at the interval of 0, 1, 2, 3 and 4 hours and Percentage inhibition is calculated using the formula:

$$\% \text{ inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

   Where Vt= Increase in paw volume in treated group, Vc= Increase in paw volume in control

   All the results were expressed as mean ± S.E.M and compared with Student't' test. The data were statistically analyzed by one –way analysis of variance (ANOVA) and $P<0.05$ were considered as significant.

2. **Antibacterial activity of synthesized derivatives (6a-6h):** The synthesized derivatives **(6a-6h)** were screened for antibacterial activities in vitro against S. aureus, B. subtilis, E. coli and K. pneumoniae using well diffusion method .The Ampicillin and Streptomycin were used as standard drugs and ethanol was used as negative control. In this technique Petri dishes of agar medium plate were prepared by pouring melted agar inoculated with above mentioned strains of

bacteria. After the agar settled, wells were made in the agar Petri dishes. Solutions of standard (1mg/ml) and test samples (500 µg /ml) were prepared using ethanol as a solvent in sterile cotton plugged tubes. Sample size for all the compound and standard was fixed at 0.1 ml. The wells of agar Petri dishes were impregnated with standard and test compounds in the sterile condition. All the nutrient agar plates were incubated at 37^{o}C for 24 to 48 hrs after which the plates were observed for zone of inhibition.

RESULT AND DISCUSSION

Chemistry: The target compounds (2-(substituted phenyl)-4oxothiazolidin-3-yl)-4-(4-oxo-2-phenyl quinazoline -3(4H)-yl) benzamide derivatives **(6a-6h)** were synthesized by three step synthetic protocol highlighted in **scheme1.**Reaction progress was duly monitored by TLC and the products were isolated by simple and usual work up with 53 to 76% of yield economy. The yields, melting points and micro analytical data of the synthesized compounds are listed in **Table 1.**

TABLE1: CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS (6a-6h)

Compounds	R_1	R_2	R_3	M P (^{o}C)	Yield (%)	Mol. formula	Mol. Wt
1a	-OH	H	H	186	69	$C_{30}H_{22}N_4O_4S$	534.14
1b	H	H	-OH	182	62	$C_{30}H_{22}N_4O_4S$	534.14
1c	$-NO_2$	H	H	173	71	$C_{30}H_{21}N_5O_5S$	563.13
1d	H	$-NO_2$	H	169	53	$C_{30}H_{21}N_5O_5S$	563.13
1e	H	H	$-OCH_3$	188	76	$C_{31}H_{24}N_4O_4S$	548.15
1f	-Cl	H	H	153	58	$C_{30}H_{21}ClN_4O_3S$	552.10
1g	H	H	-Cl	151	67	$C_{30}H_{21}ClN_4O_3S$	552.10
1h	H	H	$-N(CH_3)_2$	128	65	$C_{32}H_{27}N_5O_3S$	561.18

The structures of the compounds **(6a-6h)** were deduced from their elemental analyses and their IR, ^{1}H, ^{13}C NMR and mass spectral data. The solid state IR spectra of these compounds reveal a characteristic aromatic stretching at around 3038-3074 cm^{-1}. Sharp carbonyl stretching vibrations were also recorded around1559-1700 cm^{-1}. The stretching vibrations for amide group (CONH) are recorded at around 1665-1680cm^{-1}.Spectra also cleared the information regarding the frequency ranging between 1525-1650 cm^{-1} and 1335-1350 cm^{-1} which corresponds to the presence of (-C=N) and (C–N stretch tertiary) respectively.

The ^{1}H NMR spectra were recorded in DMSO-d6 at room temperature using TMS as internal standard. The NMR data of all compounds reveal multiplets peak between 7.35 and 8.13 owing to the presence of aromatic protons. The spectra showed characteristic singlet at around 7.8 ppm for -CONH in the compounds.

Presence of characteristic singlet around 3.95 ppm assigned to the protons attached to sulphur confirms the formation of thiazolidinone ring. All other peaks in the IR and NMR spectra are in well agreement with the contents of functionalities in the synthesized molecules.

The mass spectra of these compounds displayed a molecular ion peak at appropriate m/z values, which were corresponding well with the respected molecular formulas. All the compounds have given the satisfactory elemental analysis.

***In-vivo* anti-inflammatory activity:** The anti-inflammatory activity of synthesized compounds **(6a-6h)** was studied using carrageenan induced rat paw edema model at the concentration of 150 mg/kg and 250mg/kg of body weight. Edema was reduced by test compounds in a dose dependent manner till the end of the fourth hour.

In carrageenan administered animals, the severe swelling was reached at one hour which increases slightly upto third hour and then it remains constant till fourth hour.

The group treated by standard drug (Indomethacin) showed decreased paw edema significantly throughout the period of study. The swelling was almost completely reduced during the fourth hour in Indomethacin treated rats. The percentage inhibition is calculated with respect to control group and the results were given in **Table 2** and **Table 3**

TABLE 2: PERCENTAGE INHIBITION OF COMPOUNDS (150mg/kg) AGAINST CARRAGEENAN INDUCED PAW EDEMA IN RATS

S. No.	Compounds	Increase in Paw volume (ml) (at different time intervals)					Percentage inhibition
		0h	1h	2h	3h	4h	
1	Control	0.26±0.003	0.88±0.01	0.87±0.01	0.87±0.01	0.87±0.01	-
2	6a	0.25±0.003	0.75±0.001	0.67±0.003	0.54±0.01	0.45±0.01*	48.27
3	6b	0.25±0.003	0.80±0.01	0.73±0.01	0.64±0.003	0.59±0.01	32.18
4	6c	0.25±0.003	0.82±0.01	0.76±0.001	0.70±0.007	0.65±0.003*	25.28
5	6d	0.25±0.003	0.79±0.007	0.68±0.001	0.57±0.005	0.54±0.003	37.54
6	6e	0.25±0.003	0.78±0.001	0.64±0.001	0.55±0.007	0.51±0.01*	41.37
7	6f	0.25±0.003	0.80±0.001	0.77±0.005	0.64±0.001	0.61±0.003*	29.88
8	6g	0.25±0.003	0.73±0.003	0.64±0.001	0.50±0.003	0.43±0.001*	51.57
9	6h	0.25±0.003	0.90±0.003	0.82±0.002	0.71±0.001	0.76±0.003	20.00
10	Standard	0.23±0.009	0.16±0.007	0.11±0.008	0.09±0.008	0.08±0.007*	91.6

∗ P<0.05 against control at fourth hour. Results were expressed as mean ± S.E.M for n=6 rats in each group. The data were statistically analyzed by one way analysis of variance (ANOVA) and compared with Student't' test

TABLE 3: PERCENTAGE INHIBITION OF COMPOUNDS (250mg/kg) AGAINST CARRAGEENAN INDUCED PAW EDEMA IN RATS

S. No.	Compounds	Increase in Paw volume (ml) (at different time intervals)					Percentage inhibition
		0h	1h	2h	3h	4h	
1	Control	0.25±0.003	0.88±0.01	0.87±0.01	0.87±0.01	0.87±0.001	-
2	6a	0.25±0.003	0.48±0.001	0.40±0.03	0.31 ±0.09	0.25±0.001*	71.26
3	6b	0.25±0.003	0.50±0.01	0.41±0.007	0.37±0.01	0.32±0.01	62.31
4	6c	0.25±0.003	0.54±0.002	0.51±0.01	0.47±0.01	0.41±0.01*	56.84
5	6d	0.25±0.003	0.51±0.01	0.45±0.001	0.38±0.003	0.33±0.01*	62.06
6	6e	0.25±0.003	0.49±0.01	0.42±0.009	0.33±0.002	0.27±0.009	68.96
7	6f	0.25±0.003	0.56±0.01	0.50±0.002	0.46±0.001	0.38±0.004*	60.00
8	6g	0.25±0.003	0.43±0.01	0.37±0.001	0.25±0.001	0.23±0.001	73.56
9	6h	0.25±0.003	0.62±0.01	0.50±0.01	0.42±0.001	0.49±0.01*	48.42
10	Standard	0.23±0.009	0.16±0.007	0.11±0.008	0.09±0.008	0.08±0.007*	91.6

∗ P<0.05 against control at fourth hour. Results were expressed as mean ± S.E.M for n=6 rats in each group. The data were statistically analyzed by one way analysis of variance (ANOVA) and compared with Student't' test

Results reveal that, the synthesized compounds shows moderate to excellent anti-inflammatory activity in comparison to standard drug Indomethacin at both the concentration after 4hours. However, the compounds were found to be more protective towards carrageenan at the concentration of 250mg/kg than 150mg/kg. Among the synthesized derivatives, the compound **6a**, **6e** and **6g** are found to be potent anti-inflammatory agents, compounds **6b**, **6d, 6f** showed moderate activity while compounds **6c** and **6h** showed poor anti-inflammatory results.

Carrageenan-induced paw edema as an *in vivo* model of inflammation has been frequently used to assess the anti-edematous effects, which is known to be sensitive to cyclooxygenase (COX) inhibitors and has been used to evaluate the effects of NSAID. Development of edema in the paw of the rat after the injection of carrageenan involves three phases by several inflammatory mediators released in an ordinary sequence. An initial phase during the first 1.5 h is caused by the release of histamine and serotonin, the second phase is mediated by Bradykinin-like substances from 1.5 to 2.5 h. The treatment with the COX-1 inhibitor could reduce the first and second phases of paw edema.

Finally, COX-2 is up-regulated only in the third phase, the mediator of which is suspected to be prostaglandins, proteases and lysozymes occur from 2.5 to 6 h after carrageenan injection [16]. As our synthesized drugs were also found to be effective against carrageenan after 4 hours, which means that they inhibit edema in third phase and thus inhibit cyclooxygenase (COX-2) pathway of inflammation.

***In-vitro* antibacterial activity:** The antibacterial activities of compounds **(6a-6h)** have been carried out using some strains of bacteria using well diffusion method. Ampicillin and streptomycin were taken as a standard drug. The compounds were tested against two strains of each of gram positive and gram negative bacteria. The interpreted results were given in **Table 4**.

TABLE 4: ANTIBACTERIAL ACTIVITY OF COMPOUNDS (6a-6h)

Compounds	Gram Positive Bacteria		Gram Negative Bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumonia*
6a	++	+	+++	+++
6b	++	-	+	+
6c	-	+	++	-
5d	++	-	+	+
6e	++	++	++	+++
6f	+	-	-	-
6g	+++	+	+++	++
6h	-	-	+	-
Ampicillin	+++	++	+++	++
Streptomycin	+++	+++	+++	+++

Key to symbols: inactive = - (inhibition zone < 5 mm); slightly active = + (inhibition zone 5-10 mm); moderately active = + + (inhibition zone 10-15 mm); highly active = + + + (inhibition zone > 15 mm).

The screening results of antibacterial activity suggested that the compounds **(6a-6h)** showed moderate to excellent antibacterial activity at the concentration of 500μg/ml. Compounds **6a**, **6e** and **6g** were found to be potent antibacterial agents against all the tested strains of bacteria, **6b** and **6d** were moderately active, **6f** is slightly active only against *S. aureus* while **6h** is inactive against all strains of bacteria.

CONCLUSION: (2-(substitutedphenyl)-4-oxo thiazolidin-3-yl)-4-(4-oxo-2-phenylquinazoline-3(4H)-yl) benzamide derivatives were synthesized in good yield. All the compounds were characterized on the basis of elemental and spectral data. These compounds showed poor to excellent anti-inflammatory activity in comparison to reference drug (Indomethacin) at a dose of 250mg/kg. These compounds were also found to be potent antibacterial agents at a concentration of 500 μg /ml against gram positive and gram negative strains of bacteria in comparison to reference drug (Ampicillin and Streptomycin). Thus, the target compound and its derivatives can be used as potent drugs for bacterial infections and inflammations.

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