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Microwave Assisted Synthesis, Characterization and Pharmacological Evaluation of Quinazolone Based Imidazole and Its Derivatives

Bhavna Kandpal and Jyotsna Meshram
Department of Chemistry, RashtrasantTukadojiMaharaj Nagpur University,
Nagpur Maharashtra, India.
bhavnakandpal21@gmail.com

Abstract::

A Series of N-(4,5-dihydro-2-(2-substitutedphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2phenylquinazoline-3(4H)-carboxamide **6(a-h)** were synthesized in good yield using microwave technique. The structures of the compounds obtained have been established on the basis of Spectral (IR, ^{1}H NMR and Mass) data. The present study also involves *in vivo* analgesic activity and *in vitro* antibacterial activity against few strains (gram positive and gram negative) of bacteria of synthesized compounds. Derivatives **6b**, **6d** and **6e** exhibit promising analgesic and antibacterial activity with reference to standard drug Ibuprofen and Ampicillin respectively.

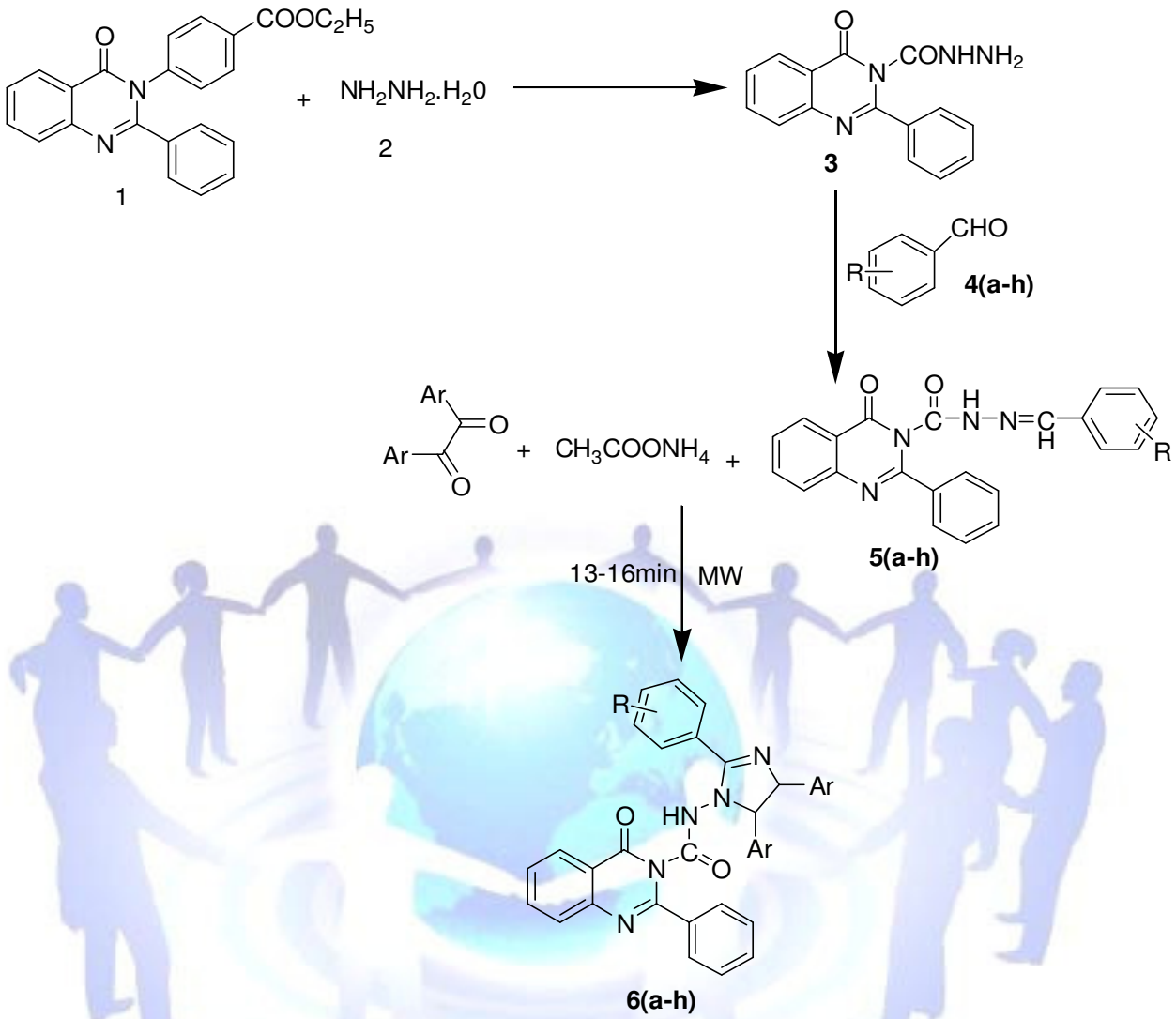
Keywords: Quinazolone, imidazole, analgesic, analgesic, antibacterial, gram positive and gram negative

Introduction:

Since the last decade of the twentieth century, protection of environment has been considered as one of the major issues by the chemical scientists and R and D experts [1]. The most significant way to fulfill this eco-requirement is to avoid or reduce the use of hazardous solvents and toxic chemicals and to develop new reactions which can minimize unnecessary formation of the by-products (wastes). Development of such methodologies can provide substantial contribution to green chemistry [2-3] and microwave is one of them.

Microwave- assisted rapid organic reactions constitute an emerging technology that makes experimentally and industrially important organic synthesis more effective and eco-friendly than conventional reactions [4] and synthesis of large class of heterocycles precede via microwave technology. Imidazoles and substituted imidazoles constitute an important class of pharmaceutical compounds which exhibit wide spectrum of biological activities [5-6].

Quinazolones and their derivatives are versatile nitrogen containing heterocyclic compounds which have been known as a promising class ofbiologically active compounds and has broad spectrum medicinal values such as analgesic [7] anti-inflammatory [8] antibacterial [9], anti-fungal [10], anti-cancer [11] etc. The stability and pharmacological properties of Quinazolones has inspired us to synthesize quinazolone substituted amide linkage containing imidazole and their derivatives with the objective to enhance the biological activities. In the present work a series of N-(4, 5-dihydro-2-(2-substitutedphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2phenylquinazoline-3(4H)-carboxamide **6(a-h)** were synthesized using microwave technique and all the synthesized derivatives were screened for their analgesic and antibacterial activity



Where **Ar**

6a= 2-C_6H_5OH; 6b= 4-C_6H_5OH; 6c= 2-C_6H_5Cl; 6d= 4-C_6H_5Cl; 6e= 2-$C_6H_5NO_2$; 6f=3-$C_6H_5NO_2$; 6g= 4- $C_6H_5OCH_3$; 6h=4- $C_6H_5N(CH_3)_2$

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. ^1H NMR spectra were recorded on Bruker-Advance (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 (Scheme: 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 (1 mol) and hydrazine hydrate (2mol) were refluxed for in absolute ethanol for 6 to 8 h. When the excess of alcohol was distilled off, the quinazolonehydrazides separated out as solid masses. These hydrazides were recrystallized from ethanol.

Synthesis of (Substituted benzylidene) -4- (4-oxo-2-phenylquinazolin-3(4H)-ylbenzohydrazide [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.

Synthesis of N-(4,5-dihydro-2-(2-substitutedphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo–2 phenylquinazoline -3(4H)-carboxamide [14]

A mixture of (Substitutedbenzylidene)-4-(4-oxo-2-phenylquinazolin-3(4H)-ylbenzohydrazide (0.01mol), benzil (0.01mol), ammonium acetate (0.01mol) was transferred into a dry mortar and was triturated to form a uniform mixture. The mixture was transferred into a 100 ml beaker and was microwave irradiation was carried out in 1000 W power for about 12-16 minutes. The completed and cooled reaction mixture was poured into 250 ml of water to remove excess of water and acetic acid, filtered and dried in a hot air oven. The crude product was washed with 20 ml benzene to remove any traces of unreacted benzil and products were purified by recrystallisation from chloroform.

The spectral data of the synthesized derivatives is as follows:

N-(4,5-dihydro-2-(2-hydroxyphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2phenylquinazoline-3(4H)-carboxamide (6a)

IR KBr (cm^{-1})**:**1690(C=O), 1357(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 751(-OH),1675(CONH), 3325(-NH). **MS**: m/z 577(100%). **^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 5(s, 1H,-OH), 6.1(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.76-7.9(m, 22H, Aromatic). **Elemental analysis** (Calcd.): C: 74.85; H: 4.71; N: 12.12; (Found): C: 74.81; H: 4.68; N: 12.10%.

N-(4,5-dihydro-2-(4-hydroxyphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2phenylquinazoline-3(4H)-carboxamide(6b)

IR KBr (cm^{-1})**:**1688(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 750(-OH),1675(CONH), 3325(-NH). **MS**: m/z 577(100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 5(s,1H,-OH), 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.76-7.9(m, 22H, Aromatic). **Elemental analysis** (Calcd.): C: 74.85; H: 4.71; N: 12.12; (Found): C: 74.81; H: 4.68; N: 12.10%.

N-(2-(2-chlorophenyl)-4,5-dihydro-4,5-diphenylimidazol-1-yl)-4-oxo-2-phenyl quinazoline-3(4H)-carboxamide (6c)

IR KBr (cm^{-1})**:**1685(C=O), 1355(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH). **MS**: m/z 596(100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.76-7.9(m, 22H, Aromatic). **Elemental analysis** (Calcd.): C: 72.54; H: 4.40; N: 11.75; (Found): C: 72.51; H: 4.33; N: 11.72%.

N-(2-(4-chlorophenyl)-4,5-dihydro-4,5-diphenylimidazol-1-yl)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide(6d)

IR KBr (cm^{-1})**:**1688(C=O), 1356(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH). **MS**: m/z 596(100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.76-7.9(m, 22H, Aromatic). **Elemental analysis** (Calcd.): C: 72.54; H: 4.40; N: 11.75; (Found): C: 72.51; H: 4.33; N: 11.72%.

N-(4,5-dihydro-2-(2-nitrophenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide(6e)

IR KBr (cm^{-1})**:**1690(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH), 1550(-NO_2). **MS**: m/z 606(100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 7.08-8.22(m, 22H, Aromatic). **Elemental analysis** (Calcd.): C: 71.28; H: 4.32; N: 13.85; (Found): C: 71.24; H: 4.30; N: 13.81%.

N-(4,5-dihydro-2-(3-nitrophenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide (6f)

IR KBr (cm^{-1})**:**1685(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH), 1550(-NO_2). **MS**: m/z 606(100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 7.08-8.22(m, 22H, (Aromatic). **Elemental analysis** (Calcd.): C: 71.28; H: 4.32; N: 13.85; (Found): C: 71.24; H: 4.30; N: 13.81%.

N-(4,5-dihydro-2-(4-methoxyphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo-2-phenylquinazolin e-3(4H)-carboxamide(6g)

IR KBr (cm^{-1})**:** 1685(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH), 2830(-OCH_3). **MS**: m/z 591 (100%).**^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.80-7.51(m, 22H, Aromatic), 3.73(s, 3H,-OCH_3). **Elemental analysis** (Calcd.): C: 75.11; H: 4.94; N: 11.84; (Found): C: 75.09; H: 4.91; N: 11.81%.

N-(2-(4-(dimethylamino)phenyl)-4,5-dihydro-4,5-diphenylimidazol-1-yl)-4-oxophenyl quinazoline-3(4H)-carboxamide (6h)

IR KBr (cm^{-1})**:**1685(C=O), 1358(C–N stretch tertiary), 1610 (-C=N), 3038-3074 (Ar-CH), 1678(CONH), 3325(-NH). **MS** : m/z 604(100%). **^{1}H NMR** (400 MHz, DMSO-d_6 δ/ppm): 6.0(s, 1H,-NH), 4.3(s, 1H, CH-N), 6.6-7.9 (m, 23 H, Aromatic), 2.85(s, 6H,-$(CH_3)_2$). **Elemental analysis** (Calcd.): C: 75.48; H: 5.33; N: 13.90; (Found): C: 75.43; H: 5.31; N: 13.88 %.

Pharmacological Activities:

Analgesic activities of synthesized derivatives (6a-6h) against standard drug ibuprofen

The experimental protocol for Analgesic 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). The paws of mice and rats are very sensitive to heat at temperatures which are not damaging the skin. The responses are jumping, withdrawal of the paws and licking of the paws. The hot plate, which is commercially available, consists of an electrically heated surface. The temperature is controlled for 55° to 56°C. This can be a copper plate or a heated glass surface. The animals are placed on the hot plate and the time until either licking or jumping occurs is recorded by a stop-watch [15]. Swiss albino rats weighing between 150-200g were used for evaluation of analgesic activity and were divided into different groups containing six animals in each group with 50% sex ratio. One group was served as a control containing 5% Tween-80 in distilled water, another group was administered with the standard drug Ibuprofen intraperitoneally at a dose of 10 mg/kg and remaining groups received test drug at a dose of 100mg/kg and 200mg/kg of the body weight, 15 min before the analgesic activity evaluation. The reaction time in seconds was noted for all the groups on Eddy's hot plates at 30, 60, 120 and 240 min.

Antibacterial activity of synthesized derivatives (6a-6h)

The synthesized derivatives **(6a-6h)** were screened for antibacterial activities in vitroagainst S. aureus, B. subtilis, E. coli and K. pneumonia 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 preparedby 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 (500µg /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°C for 24 to 48 hrs after which the plates were observed for zone of inhibition.

Result and Discussions:

Chemistry

The target compounds derivatives N-(4,5-dihydro-2-(2-substitutedphenyl)-4,5 diphenylimidazol-1-yl)-4-oxo–2phenylquinazoline-3(4H)-carboxamide **(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 65 to 76% of yield economy. The yields, melting

points and micro analytical data of the synthesized compounds are listed in **Table 1.**

The structures of the compounds **(6a-6h)** were deduced from their elemental analyses and their IR, ^{1}H 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 vibration were also recorded around 1559-1700 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 carbonyl stretching at 3325 cm^{-1} corresponds to C-NH bond formation which confirms the formation of imidazole ring.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 spectrashowed characteristic singlet at around 7.8 ppm for -CONH in the compounds. Presence of characteristic singlet around 4.0 ppm assigned to the protons attached to nitrogen confirms the formation of imidazole 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* analgesic activity**

The effect of compounds **6(a-h)** on white albino rats was evaluated at a dose of 100 mg/kg and 200 mg/kgusing hot plate methodat the time interval of 30, 60,120 and 240 minutes.. Results revealed that, all the synthesized compounds protected the rats from the pain induced by hot plate method and compounds shows significant analgesic activity against control at both the concentrations at 4th hour. However, the compounds were found to be more protective for rats against pain at 200 mg/kg than 100 mg/kg. Among the synthesized derivatives, compound **6b, 6d** and **6e** had shown the highest reaction time against hot plate treatment of rats at the dose of 100 mg/kg and 200 mg/kg respectively. All these synthesized derivatives which were found to exhibit good to moderate analgesic activity. Compounds **6b**, **6d** and **6e** are found to exhibit excellent analgesic activity while **6a** and **6c** exhibited good activity while remaining compounds exhibited moderate activity as compared to standard drug ibuprofen.

Pain is centrally modulated via a number of complex processes including opiate, dopaminergic descending noradrenergic and serotonergic systems [16-18].The analgesic effect produced by the tests and standards may be via central mechanisms involving these receptor systems or via peripheral mechanisms involved in the inhibition of prostaglandins, leukotrienes, and other endogenous substances that are key players in pain. The selective COX-2 inhibitor has high effective than the conventional NSAIDs and has low GI and high cardivascular side effects than to the conventional NSAIDs. According to our *in vivo* results described

in **Table 2** and **Table 3**, the synthesized derivatives act as effective painkillers at 4th hour and hence are found to be selective COX- 2 inhibitor.

***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**.

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 **6b**, **6d** and **6e** were found to be potent antibacterial agents against all the tested strains of bacteria, **6a** and **6c** were moderately active, **6f** and **6g** is slightly active while **6h** is inactive against all strains of bacteria.

Table. 1- Physical data of synthesized derivatives 6(a-h)

Compounds	Ar	M P (°C)	Yield (%)	Mol. formula	Mol. wt
6a	2-OHC_6H_4	185	64	$C_{36}H_{27}N_5O_3$	577
6b	4-OHC_6H_4	189	71	$C_{36}H_{27}N_5O_3$	577
6c	2-ClC_6H_4	173	77	$C_{36}H_{26}ClN_5O_2$	596
6d	4-ClC_6H_4	145	78	$C_{36}H_{26}ClN_5O_2$	596
6e	2-$NO_2C_6H_4$	171	61	$C_{36}H_{26}N_6O_4$	606
6f	3-$NO_2C_6H_4$	168	79	$C_{36}H_{26}N_6O_4$	606
6g	4-$OCH_3C_6H_4$	197	73	$C_{37}H_{29}N_5O_3$	591
6h	4-$N(CH_3)_2C_6H_4$	182	76	$C_{28}H_{32}N_6O_2$	604

Table. 2- Reaction time in seconds at a dose (100 mg/kg) against pain induced by hot plate method

S. No	Compound	Reaction time in seconds at time (minutes) (mean ± sem)			
		30	60	120	240
1	Control	0.78±0.004	0.76±0.005	0.76±0.004	0.76±0.003
2	standard	0.86±0.001	2.95±0.003	4.86±0.001	4.91±0.001*
3	6a	0.80±0.007	1.79±0.001	1.84±0.006	2.89±0.003
4	6b	0.82±0.004	1.82±0.05	2.88±0.009	3.38±0.001
5	6c	0.82±0.001	1.76±0.003	1.82±0.005	2.94±0.007*
6	6d	0.81±0.003	1.93±0.001	2.89±0.009	3.54±0.001
7	6e	0.80±0.002	1.46±0.01	1.91±0.001	3.01±0.007
8	6f	0.78±0.001	1.41±0.003	1.96±0.004	2.84±0.01*
9	6g	0.79±0.002	1.51±0.003	1.83±0.001	2.73±0.001*
10	6h	0.81±0.004	1.31±0.004	1.72±0.001	2.07±0.007*

∗P<0.05 against the control at the 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- Reaction time in seconds at a dose (200 mg/kg) against pain induced by hot plate method

S. No	Compound	Reaction time in seconds at time (minutes) (mean ± sem)			
		30	60	120	240
1	Control	0.78±0.004	0.76±0.05	0.76±0.004	0.76±0.007
2	standard	0.86±0.001	2.95±0.009	4.86±0.001	4.91±0.007
3	6a	0.81±0.007	2.04±0.01	2.97±0.006	3.28±0.004*
4	6b	0.82±0.004	2.34±0.01	3.56±0.003	3.89±0.001
5	6c	0.82±0.07	1.81±0.004	2.91±0.005	3.24±0.001
6	6d	0.81±0.003	2.32±0.02	3.17±0.001	3.94±0.02
7	6e	0.80±0.002	1.77±0.01	2.97±0.007	3.77±0.001*
8	6f	0.78±0.001	1.43±0.005	2.52±0.006	2.89±0.002
9	6g	0.79±0.005	1.67±0.003	2.39±0.09	2.76±0.009
10	6h	0.81±0.007	1.94±0.006	2.21±0.01	2.38±0.001

∗P<0.05 against the control at the 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. 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	+	+	++	-
6d	++	+++	++	++
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).

Conclusion:

N-(4,5-dihydro-2-(2-substitutedphenyl)-4,5-diphenylimidazol-1-yl)-4-oxo–2phenyl quinazoline-3(4H)-carboxamide 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 (ibuprofen) at a dose of 200mg/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 as painkillers (analgesic) and for bacterial infections.

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