Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4 (2):699-706
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Study of synthesis of novel N,2-diphenylquinazolin-4-amine derivatives as an anti-inflammatory and analgesic agent

Bhushan R. Dravyakar[1*] and Pramod B. Khedekar[2]

[1]*Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road, Nagpur*
[2]*Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur*

ABSTRACT

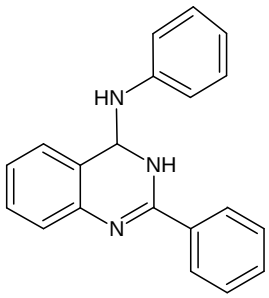
A series of substituted N,2-diphenylquinazolin-4-amines were synthesized by cyclization of methyl anthranilate and various substituted benzamide giving corresponding 2-phenylquinazolinone followed by replacement of ketonic oxygen with various aryl amino group via chlorination gateway to afford title compounds. The homogeneity and purity of compound was ascertained by Physical constant determination and chromatographic methods. The structure of the synthesized derivative was further confirmed by spectral (FTIR, NMR, MS) and elemental (C, H, N) analysis. These synthesized compounds were screened for anti-inflammatory and analgesic activities using, Rat paw edema method and Hot plate method respectively. All compounds showed average to better activity when compared with Diclofenac and Tramadol respectively as standard

Keywords: quinazoline, aniline, analgesic, anti-inflammatory, anticonvulsant activity.

INTRODUCTION:

Quinazoline is one of the most frequently reported heterocyclic compound in medicinal chemistry, which possess diverse biological activities like antineoplastic[1-3], anti-inflammatory, analgesic[4-8], antihistaminic[9], antihypertensive[10], cardiac stimulant activity[11], antimalarial[12], anticonvulsant[13-15], antimicrobial[16-18], etc. Aniline derivatives also exhibit some similar set of activities such as antimicrobial, analgesic, anti-inflammatory and anticonvulsant activity.[19, 20]

It has been showed that 2^{nd} and 4^{th} position of quinazoline plays a very crucial role in exhibiting pharmacological activity. In present investigation, we planned to target these positions for substitution of certain bulkier groups. As phenyl and aniline derivative gives good promising results earlier. Therefore later two moieties were substituted on respective 2^{nd} and 4^{th} positions. Quinazoline was prepared by condensation of methyl anthranilate and benzamides. The structures (**Figure-1**) were confirmed by IR H^1 NMR, mass spectra and elemental analysis. These compounds were screened for analgesic and anti-inflammatory activity using hot plate method and rat paw edema method respectively.



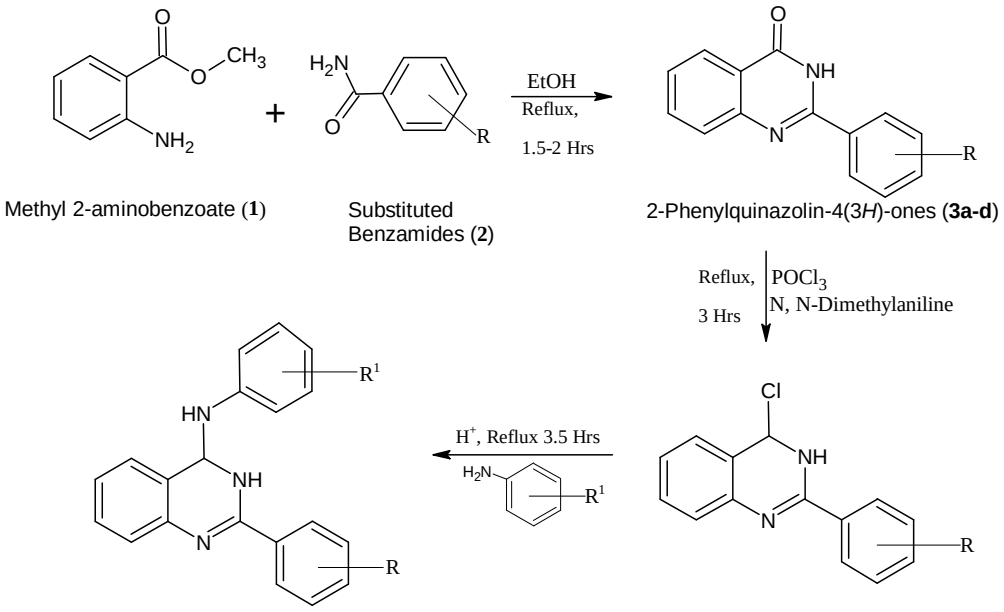
N,2-Diphenyl-3,4-dihydroquinazolin-4-amine derivative

MATERIALS AND METHODS

Chemistry:

The chemicals used in the present work were AR grade and LR grade, purchased from Loba, Merck and Fisher scientific fine chemicals. The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The purified compounds were assigned for physical constant determination was carried out by open capillary method using LABHOSP melting point apparatus and recorded without correction. The structures were further confirmed by elemental(C,H,N) and spectral analysis like Infrared spectroscopy, Nuclear magnetic resonance spectroscopy and mass spectroscopy. The schematic representation of preparation of title compound was highlighted in **Scheme 1** and general procedures are as follows.

Scheme I: Schematic representation of *N*,2-Diphenyl-3,4-dihydroquinazolin-4-amine derivative preparation



General Procedure:

1. *Synthesis of 2-Phenylquinazoline-4(3H)-one derivative (**3a-d**)*:

A mixture of anthranilic acid (0.01 mol) with various benzamides (0.01 mol) was refluxed in ethanol for approx. 90 minutes and cooled. The resultant mixture was treated with aqueous solution of sodium bicarbonate in order to

dissolve the unreacted acid (ensure this complete dissolution by cessation of carbondioxide effervescence). The solid separated was washed with water, dried and recrystallised with ethanol as a white crystalline mass.

2. *Synthesis of 4-Chloro-2-Phenylquinazoline derivative* ***(4a-d)***:
The equimolar quantity of **3a-d,** N, N-dimethylaniline and phosphorous pentachloride were taken in dry benzene and refluxed in for 3 hrs. The reaction mixture was then cooled and filtered. The filtrate was diluted with benzene(30ml) then washed with 20% sodium hydroxide solution finally with water and dried over magnesium sulphate, the final organic layer get evaporated. The final product was recrystallized in heptane.

3. *Synthesis of N,2-Diphenylquinazolin-4-amine derivative* ***(5a-u)***:
A mixture of **4a-d** (0.5 mol) and substituted aniline was taken in 95% ethanol and refluxed for approx. 1.5 to 3.0 hrs. The reaction mixture was poured in a blend of 100 ml ice cold water with 20 ml of concentrated hydrochloric acid followed by vigorous continuous stirring gave pale white colored precipitate. Solvent methanol was used for recrystallization.

The physicochemical characterization, elemental and spectral analysis data was given below.

N,2-Diphenyl-3,4-dihydroquinazolin-4-amine (**5a**):
%Yield: 87; M.P.:151-152°C, $C_{20}H_{15}N_3$; Elemental analysis, *Calc.*: C(80.78%) H(5.08%) N(14.13%), *Obs.*: C(80.70%) H(4.99%) N(14.18%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.43-7.04 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzylidenimine); Mass (Mass (m/z)): [M]:297.

N-(p-Chlorophenyl)-2-phenyl-3,4-dihydroquinazolin-4-amine (**5b**): % Yield: 82; M.P.:158-159°C; $C_{20}H_{14}ClN_3$; Elemental analysis, *Calc.*: C(72.40%) H(4.25%) Cl(10.69%) N(12.66%) *Obs.*: C(72.51%) H(4.29%)Cl(10.75%) N(12.78%); ^{1}HNMR ($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.37-7.05 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzyliden-imine); Mass (Mass (m/z)): [M+]:331

N-(p-Bromophenyl)-2-phenyl-3,4-dihydroquinazolin-4-amine (**5c**): % Yield: 78; M.P.:159-160°C; $C_{20}H_{14}BrN_3$; Elemental analysis, *Calc.*: C(63.84%) H(3.75%) Br(21.24%) N(11.17%), *Obs.* C(63.54%) H(3.85%) Br(21.22%) N(11.14%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzyliden-imine); Mass (Mass (m/z)): [M+]:375

4-[(2-Phenyl-3,4-dihydroquinazolin-4-yl)amino]phenol (**5d**):
% Yield: 65; M.P.:177-178°C; $C_{20}H_{15}N_3O$; Elemental analysis, *Calc.*: C(76.66%) H(4.82%) N(13.41%) O(5.11%), *Obs.*: C(76.80%) H(4.66%) N(13.51%) O(5.01%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.26-6.51 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzyliden-imine), 5.0(s, Ar C-OH); Mass (m/z): [M]:313

N-(p-Methoxyphenyl)-2-phenyl-3,4-dihydroquinazolin-4-amine (**5e**): % Yield: 79; M.P.:162-163°C; $C_{21}H_{17}N_3O$; Elemental analysis, *Calc.* C(77.04%) H(5.23%) N(12.84%) O(4.89%), Obs: C(77.24%) H(5.13%) N(12.73%) O(4.88%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzyliden-imine), 3.83 (s, Ar OCH_3); Mass (m/z): [M]:327

N-(o-Methylphenyl)-2-phenyl-3,4-dihydroquinazolin-4-amine **(5f):** % Yield: 82; M.P.:155-156°C; $C_{21}H_{17}N_3$; Elemental analysis, *Calc.*: C(81.00%)H(5.50%)N(13.49%), *Obs.*:C(82.02%)H(5.51%) N(13.84%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.31-6.85 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzylidenimine), 2.35 (s, Ar OCH_3); Mass(Mass (m/z)): [M]:311

N-(o,p-Dimethylphenyl)-2-phenyl-3,4-dihydroquinazolin-4-amine (**5g**): % Yield: 86; M.P.:163-165°C; $C_{22}H_{19}N_3$; Elemental analysis, *Calc.*: C(81.20%) H(5.89%) N(12.91%), *Obs.*: C(81.18%) H(5.92%) N(12.90%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.19-6.65 (t, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzylidenimine), 2.35 (d, Ar OCH_3); Mass (Mass (m/z)): [M]:325

2-(p-Methylphenyl)-N-phenyl-3,4-dihydroquinazolin-4-amine (**5h**): % Yield: 91; M.P.:152-154°C; $C_{21}H_{17}N_3$; Elemental analysis, *Calc.*: C(81.00%) H(5.50%) N(13.49%), *Obs.*: C(81.11%) H(5.56%) N(13.44%);

^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 6.58-7.50 (m, benzylidenimine), 2.35 (s, Ar OCH_3); Mass (m/z): [M]:311

N-(p-Chlorophenyl)-2-(4-methylphenyl)-3,4-dihydroquinazolin-4-amine (**5i**): %Yield:85; M.P.:182-183°C; $C_{21}H_{16}ClN_3$; Elemental analysis, C(72.93%) H(4.66%) Cl(10.25%) N(12.15%), *Obs.*: C(72.97%) H(4.70%) Cl(10.22%) N(12.14%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 7.29-7.62 (m, benzylidenimine), 3.83 (s, Ar OCH_3), Mass (m/z): [M]:345

N-(p-Bromophenyl)-2-(4-methylphenyl)-3,4-dihydroquinazolin-4-amine (**5j**): % Yield: 78; M.P.:168-169°C; $C_{21}H_{16}BrN_3$; Elemental analysis, *Calc.*: C(64.63%) H(4.13%) Br(20.47%) N(10.77%), *Obs.*: (64.73%) H(4.23%) Br(20.43%) N(10.81%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 7.09-7.50 (q, benzyliden-imine), 2.35 (s, Ar-CH_3); Mass (m/z): [M]:389

4-{[2-(4-Methylphenyl)-3,4-dihydroquinazolin-4-yl]amino} phenol (**5k**): % Yield: 93; M.P.:164-165°C; $C_{21}H_{17}N_3O$; Elemental analysis, *Calc.*: C(77.04%) H(5.23%) N(12.84%) O(4.89%) *Obs.*: C(77.24%) H(5.27%) N(12.89%) O(4.83%), ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.26-6.51 (q, Ar-H of 2-Phenyl), 7.09-7.50 (q, benzyliden-imine), 2.35 (s, Ar-CH_3), 5.0 (s, Ar-OH), Mass (m/z): [M]:327

N-(p-Methoxyphenyl)-2-(p-methylphenyl)-3,4-dihydroquinazolin-4-amine (**5l**): % Yield: 88; M.P.:155-156°C; $C_{22}H_{19}N_3O$; Elemental analysis, *Calc.*: C(77.40%) H(5.61%) N(12.31%) O(4.69%), *Obs.*: C(77.45%) H(5.66%) N(12.27%) O(4.74%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.329-6.55 (q, Ar-H of 2-Phenyl), 7.09-7.50 (q, benzylidenimine), 2.35 (s, Ar-CH_3), 3.73 (s, Ar-CH_3); Mass (m/z): [M]:341

N-(o-Methylphenyl)-2-(p-methylphenyl)-3,4-dihydroquinazolin-4-amine (**5m**): % Yield: 81; M.P.:152-153°C; $C_{22}H_{19}N_3$; Elemental analysis, *Calc.*: C(81.20%) H(5.89%) N(12.91%), *Obs.*: C(81.28%) H(5.85%) N(12.86%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.19-6.65 (q, Ar-H of 2-Phenyl), 7.09-7.50 (q, benzylidenimine), 2.35 (t, Ar-CH_3); Mass (m/z): [M]:325

N-(o,p-Dimethylphenyl)-2-(p-methylphenyl)-3,4-dihydro-quina-zolin-4-amine (**5n**): % Yield: 87; M.P.:168-170°C; $C_{23}H_{21}N_3$; Elemental analysis, *Calc.*: C(81.38%) H(6.24%) N(12.38%), *Obs.*: C(81.35%) H(6.27%) N(12.41%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.19-6.65 (q, Ar-H of 2-Phenyl), 7.09-7.50 (q, benzylidenimine), 6.58 (t, Ar-CH_3); Mass (m/z): [M]:339

2-(p-Bromophenyl)-N-phenyl-3,4-dihydroquinazolin-4-amine (**5o**): % Yield: 76; M.P.:171-173°C; $C_{20}H_{14}BrN_3$; Elemental analysis, *Calc.*: C(63.84%) H(3.75%) Br(21.24%) N (11.17%), *Obs.*: C (63.89%) H (3.71%) Br (21.27%) N(11.18%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.37-7.05 (q, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzylidenimine), 6.58 (s, C-N-); Mass (m/z): [M]:376

2-(p-Bromophenyl)-N-(p-chlorophenyl)-3,4-dihydroquinazolin-4-amine (**5p**) % Yield: 74; M.P.:187-189°C; $C_{20}H_{13}BrClN_3$; Elemental analysis, *Calc.*: C(58.49%) H(3.19%) Br(19.46%) Cl(8.63%) N(10.23%), *Obs.*: C(58.51%) H(3.17%) Br(19.49%) Cl(8.59%) N(10.25%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.37-7.05 (q, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzylidenimine); Mass (m/z): [M^+]:410

N,2-Bis(p-bromophenyl)-3,4-dihydroquinazolin-4-amine (**5q**):
% Yield: 82; M.P.:184-185°C; $C_{20}H_{13}Br_2N_3$; Elemental analysis, *Calc.*: C(52.78%) H(2.88%) Br(35.11%) N(9.23%) *Obs.*: C(52.73%) H(2.93%) Br(35.15%) N(9.27%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.32-7.21 (q, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzyliden-imine); Mass (m/z): [M]:455

4-{[2-(4-Bromophenyl)-3,4-dihydroquinazolin-4-yl]amino}phenol (**5r**): % Yield: 74; M.P.:178-180°C; $C_{20}H_{14}BrN_3O$; Elemental analysis, Cal.: C(61.24%) H(3.60%) Br(20.37%) N(10.71%) O(4.08%), *Obs.*: C(61.28%)

H(3.58%) Br(20.35%) N(10.73%) O(4.12%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.26-6.51 (q, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzylidenimine), 5.0(s, Ar -OH); Mass (m/z): [M]: 392.

2-(p-Bromophenyl)-N-(p-methoxyphenyl)-3,4-dihydroquinazolin-4-amine (**5s**) % Yield: 77; M.P.:181-182°C; $C_{21}H_{16}BrN_3O$; Elemental analysis, *Calc.*: C(62.08%) H(3.97%) Br(19.67%) N(10.34%) O(3.94%), *Obs.*: C(62.13%) H(3.93%) Br(19.65%) N(10.37%) O(3.91%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (q, Ar C-NH), 6.32-6.55 (q, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzylidenimine), 2.35 (s, Ar -CH_3); Mass (m/z): [M]:405

2-(p-Bromophenyl)-N-(o-methylphenyl)-3,4-dihydroquinazolin-4-amine (**5t**): % Yield: 80; M.P.:176-178°C; $C_{21}H_{16}BrN_3$; Elemental analysis, *Calc.*: C(64.63%) H(4.13%) Br(20.47%) N(10.77%), *Obs.*: C(64.68%) H(4.16%) Br(20.44%) N(10.77%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.31-6.84 (t, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzyliden-imine), 2.35 (s, Ar -CH_3); Mass (m/z): [M]:390

2-(p-Bromophenyl)-N-(o,p-dimethylphenyl)-3,4-dihydro-quina-zolin-4-amine (**5u**): % Yield: 93; M.P.:179-181°C; $C_{22}H_{18}BrN_3$; Elemental analysis, *Calc.*: C(65.36%) H(4.49%) Br(19.76%) N(10.39%), *Obs.*: C(65.38%) H(4.52%) Br(19.72%) N(10.35%); ^{1}HNMR($CDCl_3$) δppm: 7.1(q, Ar-H of quinazoline), 2.0(s, sec. NH), 5.04 (s, methine), 4.0 (s, Ar C-NH), 6.19-6.65 (t, Ar-H of 2-Phenyl), 7.46-7.51 (q, benzyliden-imine), 2.35 (d, Ar -CH_3); Mass (m/z): [M]:403

Pharmacology:
We have investigated anti-inflammatory and analgesic activity of *N,2-diphenylquinazolin-4-amine* derivatives by carrageenan induced rat paw edema test and Hot Plate method using Diclofenac and Tramadol as a standard respectively. The compound were suspended in 1% aqueous Carboxyl Methyl Cellulose solution and administered orally to experimental animal.

Anti inflammatory activity [21]:
Carrageenan induced Rat Paw Edema Method:
Rats were divided in groups of six animals each. A mark was made on both the hind paws just below the tibio-tarsal junction so that each time the paw could be dipped in the mercury column of plethysmograph up to the mark to ensure constant paw volume. To each group, except the control group, test compounds were administered orally in a dose level 50 mg/kg. The control group received an equivalent amount of vehicle only. One group received Diclofenac (50 mg/kg). After one hour, carrageenan (0.1 mL, 1% w/v solution in saline) was injected into the sub plantar tissue of the left hind paw of control and Diclofenac-treated group as well. The same volume of saline solution was injected into that of the right hind paw to serve as reference non-inflamed paw for comparison. The initial paw volume was measured immediately after injection. The difference in paw volume, 3h after carrageenan injection, was measured in control, standard, and treated groups. The percent reduction in paw volume was calculated from the equation % anti-inflammatory = [(n – n')/n] 6100, where n was the average difference in thickness between the left and the right hind paw of control group and n' was that of the test group of rats.

Analgesic activity [21]**:**
Hot Plate method:
Swiss albino mice of either sex were divided into twenty one different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 h prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 2% v/v solution of Tween 80 was given by oral route and after o min and 90 min behavioral changes count. The jumping and paw liking was noted o min, 90 min. The percentage inhibition in analgesic activity was evaluated using the following formula.

%inhibition = 1- [latency before treatment/latency after treatment]x 100

Table-1: Anti-inflammatory activity and gastric ulceration of compounds 5a-u

Comp.	Ulcer Index	Swelling in thickness [x 10^{-2}mm][a] (% inhibition)	
		2 Hrs	3.5 Hrs
5a	0/6	12.4±1.02(40.39)	13.0±1.24(40.88)
5b	0/6	15.3±1.54(49.84)	16.4±1.68(51.57)
5c	0/6	13.6±2.12(44.30)	14.1±1.47(44.34)
5d	0/6	16.1±1.8 (52.44)	20.7± 2.1 (63.11)
5e	0/6	9.40±0.1 (30.62)	13.5±1.4 (41.16)
5f	0/6	15.6± 1.2 (50.81)	19.8± 1.8 (60.37)
5g	0/6	13.9±2.4 (45.28)	16.7±1.2 (50.91)
5h	1/6	11.9±1.2 (38.76)	12.6±0.7 (38.41)
5i	0/6	20.2±1.4 (65.80)	22.6±1.5 (68.90)
5j	0/6	12.7±1.8 (41.37)	14.3±2.1 (43.60)
5k	1/6	13.6±2.8 (44.30)	17.1±2.1 (52.13)
5l	0/6	11.5±2.1 (37.46)	16.2±1.4 (49.39)
5m	0/6	10.2±1.5 (33.22)	13.1± 2.0 (39.94)
5n	0/6	13.3±1.5 (43.32)	12.4±1.6 (37.80)
5o	0/6	11.7±0.7 (38.11)	14.2±4.5 (43.29)
5p	0/6	12.5±0.2 (40.72)	12.9±2.4 (39.33)
5q	0/6	20.5±3.5 (66.78)	21.1±2.0 (64.33)
5r	1/6	8.6±1.7 (28.01)	12.1±2.3 (36.89)
5s	0/6	10.1±0.5 (32.90)	13.1±1.4 (39.94)
5t	0/6	13.4±2.4 (43..65)	13.7±4.0 (41.77)
5u	0/6	12.5±2.3 (40.72)	13.4±2.1 (40.85)
Control	0/6	30.7 ± 0.96	31.8 ± 1.1
Standard	1/6	16.2± 1.2 (52.77)	21.4±1.4 (65.24)

Note:Number of animals used, n=6, Dose 50 mg/Kg body weight, inhibition %=[1-(Vt/Vc) × 100] where Vt is mean relative change in paw volume in test animals ND Vc is mean relative change in control group. All the test compounds are significant at P < 0.001 from the control. (Two way ANOVA followed by Bonferroni post test) [a] mean±SD.

Table-2: Analgesic activity of compound 5a-u

Comp.	Maean Latency [a]		% Inhibition
	0 Hrs	5 Hrs	
5a	1.57±0.56	3.48±0.15	54.88±0.53
5b	1.77±0.43	2.32±0.19	23.70±0.89
5c	1.28±0.28	1.90±0.23	32.63±0.19
5d	2.61±0.75	4.90±0.79	46.50±0.24
5e	1.68±0.36	3.10±0.83	48.63±0.51
5f	1.86±0.52	2.90±0.19	35.86±0.85
5g	2.89±0.15	3.34±0.23	14.24±0.46
5h	1.49±0.46	2.80±0.27	36.00±0.75
5i	1.15±0.24	2.50±0.57	54.00±0.68
5j	2.32±0.16	2.97±0.69	21.88±0.43
5k	1.72±0.38	2.70±0.81	36.26±0.29
5l	2.15±0.84	3.2±0.74	31.87±0.47
5m	1.57±0.56	3.48±0.15	54.48±0.53
5n	1.77±0.43	3.32±0.19	46.68±0.89
5o	1.28±0.28	2.5±0.23	48.80±0.19
5p	2.61±0.75	4.90±0.79	55.91±0.24
5q	1.68±0.36	2.10±0.83	20.00±0.51
5r	1.86±0.52	3.90±0.19	52.30±0.85
5s	2.89±0.15	5.34±0.23	45.88±0.46
5t	1.49±0.46	2.80±0.27	46.78±0.75
5u	1.15±0.24	1.50±0.57	23.33±0.68
Control	3.68±0.61	6.18±0.21	39.76
Standard	2.51±0.93	7.17±0.34	64.99±0.25

Note: Number of animals used, n=6, Dose 50 mg/Kg body weight, inhibition %=[1-(latency before treatment/latency after treatment) × 100]. All the test compounds are significant at P < 0.001 from the control. (Two way ANOVA followed by Bonferroni post test) [a] mean ±SD.

RESULTS AND DISCUSSION

A series of *N,2-diphenylquinazolin-4-amine* derivatives, were synthesized using simple synthetic route **(Scheme I)**. It involves cyclization reaction between methyl anthranilate and various benzamides to form a corresponding quinazolinones followed by chlorination and amination at 4-position of basic ring afford a title. All compounds synthesized are obtained in crystalline form and with good practical yield. The purity and homogeneity of compounds synthesized were determined by sharp melting points and TLC method. The chemical structures were confirmed by FTIR, NMR, and Mass spectrum. All derivatives showed a broad absorbance band at about 1310-1650 cm^{-1} associated with stretching vibrations of bonded aromatic C-N, C=N, and N-H, indicating presence of three nitrogen containing group in the structure. The compound also explain a strong absorbance band at 1420 cm^{-1} of –O-H stretching vibration, absorbance at 800 cm^{-1} stretching vibration indicating present of Cl group, 530 cm^{-1}stretching vibration indicating present of Br group. NMR of compounds showed sharp peak at 6-7.80 ppm, indicating present of aromatic hydrogen at different places of structure and also showed a peak for sec. NH at 2.0 ppm, 5.0-6.04 for methine group, In MS spectra of the synthesized N, 2-diarylquinazolin-4-amines molecular peaks are weak (less than 10%). Instead, peaks M-1, M-2 and M-3 are intensive, the latter often being main ones. The peaks mentioned probably arise from a molecular radical-cation by departures of hydrogen atoms. They can leave from the positions 1, 2 or 3 of the hetero-ring. There were also observed peaks probably identical with the molecular peaks and fragmentation routes of the corresponding N, 2-diarylquinazolin-4-amines. These results support an assumption that, in contrast to a liquid phase, in a gas phase both tautomeric forms of title compounds are present.

Preliminary pharmacological screening includes approximate toxicity testing (LD_{50}) on both rats as per the OECD guidelines for selecting the dose. The LD_{50} of all the derivatives was found >200mg/kg. The anti-inflammatory activity of test compounds was performed on the Albino rats of SD and Wister strain. The anti-inflammatory activity of compounds was done by using of Carageenan Induced Rat Paw Method. The test compounds (5-d,f,i,k,l and q) showed significant peripheral activity when compared with the standard drug Diclofenac sodium. The title compounds (5-a,d,e,i,m,n,o,p,r and t) exhibits nice results about analgesic activity too when performed on Swiss Albino Mice. This observation suggests that N, 2-diarylquinazolin-4-amines are possessing peripheral as well as central activity which is less frequently observed that same compound having both activities.

CONCLUSION

The synthesis of new *N,2-diphenylquinazolin-4-amine* derivatives are prepared from one the common, easy but effective method giving moderate to good practical yields. Both spectral and elemental analysis provides enough evidences about the structures of the title compounds. Furthermore the compounds are active against both analgesia and inflammation suggests their central and peripheral activities. Therefore, it increases the scope and importance of title compound to further explore its diversified activities.

REFERENCES

[1] S. Mhaske, N. Argade, *Tetrahedron*, **2006**, 62 9787.
[2] M. P. Chandrika, T. Yakaiah, A. Raghuramarao, B. Narasaiah, Chakrareddy N, Shridhar V. *European J. Med Chem*. **2008**, 43, 846.
[3] M. Abdulrahman, G. Sami, A. Hassan, A Alaa, *European J of Med Chem*. **2009**, 44: 2379.
[4] H. Cottam, H. Shih, L. Tehrani, D. Wasson, D. Carson, *J. Med. Chem.* **1996**, 39 2.
[5] M. Mosaad, K, Mohsen, K. Emad, A. Nageh, N. Salwa, *Acta Pol Pharma n Drug Res*, **2009**, 66, 5, 487.
[6] F Oma, E Kassem, H Ibrahem, M Kamel, *Acta Pol Pharm n Drug Res*, **2008**, 65, 1, 11.
[7] A. Mohammad, T. Davood, B. Abbas, *J Pharm Pharmaceut Sci*. **2005**, 8, 3, 419.
[8] E. Limbird, P. Molinoff, R Ruddon, A. Gilman, Basics of Pharmacology, McGrawHill, New-York, **1997**, 17, 537.
[9] M. Mohsen, Y. Mohhmad, A. Khairy., S. Abbas, *European J. Med. Chem.* **2010**, 45, 3365.
[10] V. Alagarsamy, S. Murugesan, *Chem. Pharm. Bull.*, **2007**, 55, 1, 76.
[11] R. LeMahieu, M.Carson, W. Nason, D. Parrish, A. Welton, H. Baruth, B. Yaremko, *J. Med. Chem.*, **1983**, 26, 420.
[12] G. Kinsella, I. Rozas, G. Watson, *J. Med. Chem*. **2006**, 49, 501.
[13] M. Bolognesi, G. Marucci, P.Angeli, M. Buccioni, A. Minarini, M. Rosini, V. Tumiatti, C. Melchiorre, *J. Med. Chem*. **2001**, 44 362.

[14] V. Alagarsamy, V. Muthukumar, N. Pavalarani, P. Vasanthanathan, and R. Revathi, *Biol. Pharm. Bull.*, **2003,** 26, 4,557.
[15] S. Kashaw, V. Kashaw, P. Mishra, N. Jain, J. Stable. *European J Med Chem.*, **2009**; 44, 4335.
[16] T. Singh, S. Sharma, V. Srivastava & A. Kumar, *Indian J. of Chem.*, **2006,** 45B, 2558.
[17] S. Nanda, A. Ganguli and R. Chakraborty, *Molecules*, **2007,** 12, 2413.
[18] J. Kunes, J. Bazant, M. Pour, K. Waisser, M. Slosarek, *Il Farmaco*, **2000**, 55, 725.
[19] A. Nagar, L. Rathi, N. Chugh, V. Pise, Bendale, *Der Pharma Chemica*, **2010**, 2, 3, 37.
[20] O. Bhusnure, Y. Vibhute, B. Poul, A. Rathod, *Int. J. of Pharma World Res.* **2011**, 2, 1, 45.
[21] H. Vogel, F. Vogel, W. Vogel, J. Sandow, *Drug Dis and Eval Pharmacol Assay.*, **2005**, 2, 759, 772.