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Synthesis, characterization and biological evaluation of 3,4-dihydro quinazoline2(H)-one derivatives

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ABSTRACT

*A simple and general method has been developed for the synthesis of various 3,4-dihydro quinazolinone derivatives by the treatment of an aldehydes with excess equivalent of urea in ethanol affords Arylideno-bis-ureas **1** which on condensation with p-amino benzoic acid in acidic medium cyclised to 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolines **2**. Reaction of **2** with benzoylchloride in 10% NaOH results in 1-benzoyl 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolin-2(H)-one **3**. The structures of the compounds were characterized by elemental analysis, IR, 1H-NMR and 13C-NMR spectra. Compounds **3** have been evaluated for their analgesic and antibacterial activity.*

Keywords: Quinazoline, analgesic activity, antibacterial activity.

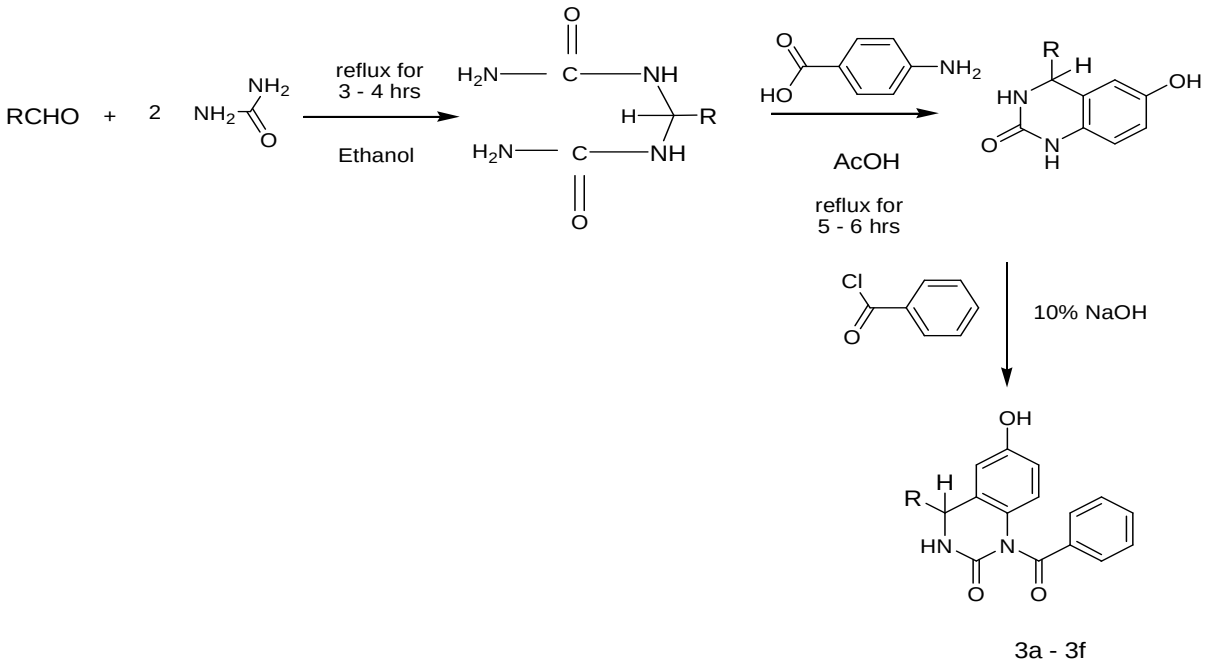
INTRODUCTION

Quinazolinones and their derivatives constitute an important class of heterocyclic Compounds. They occupy an important position in medicinal and pesticide chemistry, presenting a wide range of bioactivities. As medicines, many of them display antifungal [1], antimicrobial [2], anti-HIV [3], antitubercular [4], anticancer [5], anti-inflammatory [6], anticonvulsant [7], antidepressant [8],hypolipidemic [9], antiulcer [10], analgesic [11] or immunotropic activities [12] and are also known to act as thymidyalate synthase [13], poly(ADP-ribose) polymerase (PARP) [14], and

protein tyrosine kinase [15] inhibitors. As pesticides, they are used as insecticides [16], fungicides [17] and antiviral

Agents [18] such as TMV, CMV inhibitors. In light of the growing number of applications in recent years there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives. In our previous work in this area we reported that some of these compounds showed antifungal activities [17]. Nanda and his co-workers synthesized ten 3-(arylideneamino)-2-phenylquinazoline-4(3H)-ones, which were investigated for their antimicrobial activity against both Gram-positive (Staphylococcus aureus 6571 and Bacillus subtilis) and Gram negative bacteria (Escherichia coli K12 and Shigella dysenteriae 6) using a turbidometric assay method. It was found that the incorporation of the 3-arylideneamino substitutents enhanced the antibacterial activity of the quinazolone system [19].

SCHEME 1



EXPERIMENTAL SECTION

General

Melting points were determined in open capillary tubes on a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded for the compounds on Jasco FT/IR 5300 (KBr).The ^{1}H-NMR and ^{13}C-NMR (300.40 MHz) spectra were recorded on JEOL–AL 300 (Fourier Transform) instruments respectively. In proton nuclear magnetic resonance spectroscopy all exchangeable protons were confirmed by addition of D_2O. Chemical shifts are reported in ppm (δ) using tetra-methyl silane (TMS) as internal standard.

Synthesis of Arylideno-bis-ureas

A mixture of aldehydes (0.2 mol) and urea (0.4 mol) in absolute ethanol (100 ml) was heated under reflux for 4 hrs in such a manner that moisture air did not pass into the reaction mixture.

Ethanol was removed by distillation and the residual solid was washed with water. The crude product was dried in vacuo and recrystalization from dilute methanol.

Synthesis of 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolin-2(H)-one

A mixture of Arylideno-bis-ureas (0.2 mol) and p-amino benzoic acid (0.2 mol) were dissolved in glacial acetic acid (50 ml) by stirring and heating slowly. The acidic solution was subsequently heated under reflux for 5 hrs. The hot solution was cooled at room temperature and poured into ice-cold water (250 ml). On stirring vigorously for half an hour. It was filtered off and washed with water (3 × 25ml). The crude product was dried in vacuo and recrystallized from diluted ethanol.

Synthesis of 1-benzoyl 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolin-2(H)-one

To the iodine flask add 30ml of sodium hydroxide, 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolin-2(H)-one (0.02 mol) and followed by benzoyl chloride (0.02 mol). The flask was closed tightly and shaked well for 15 mins the crude crystal was out. The crude crystal was poured in 100ml of water and filter again the crystal was washed with water. The crude product was dried in vacuo and recrystallized from diluted ethanol.

1-benzoyl-6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3,4-dihydroquinazolin-2(H)-one

White solid, IR (cm-1): *v* 3032 (Qu-H, Ar-H), 2980 (Qu-CH3), 1678 (C=O), 1616, 1602, (C=N), 1568-1469 (C=C, benzene and quinazolinone rings), 772 (1,2-disubstituted benzene); 675 (Qu-Br), 1H-NMR: *δ* 2.57 (s, 3H, 2-Qu-C*H*3), 7.64-8.24 (m, 5H, Ar-*H*), 9.42 (s, 1H, Qu-=CH-Ar); 13CNMR:*δ* 172.3, 154.6, 153.3, 151.9, 143, 137.6, 136.4, 134, 132.2, 128.9, 128.5, 127.5, 127, 123.5, 122.0, 117.4, 114.1, 113.6, 113. 56.2, 52.2.

1-benzoyl 6-hydroxy-4-phenoxy-3,4-dihydroquinazolin-2(H)-one

White solid, , IR (cm-1): *v* 3030 (Qu-H, Ar-H), 1678 (C=O), 1605, 1585 (C=N), 1517, 1470 (C=C,benzene and quinazolinone rings), 881, 829 (1,2,4-trisubstituted benzene), 675 (Qu-Br), 1H-NMR: *δ* 2.57 (s, 3H, 2-Qu-C*H*3), 7.64-8.24 (m, 5H, Ar-*H*), 9.42 (s, 1H, Qu-N=CH-Ar); 13C-NMR: *δ* 172.4, 163.2, 158.2 154.1, 146.6, 136.4, 135.1, 130.1. 129.9, 129.8, 129.6, 128.9, 128.8, 127.3, 127.0, 121.6, 117.4, 109.1, 65.2, 49.9.

1-benzoyl 6--hydroxy-4-(1H indol-3-yl)-3,4-dihydroquinazolin-2(H)-one

White solid, IR (cm-1): *v* 3061 (Qu-H, Ar-H), 1688 (C=O), 1605, 1587 (C=N), 1575-1468 (C=C, benzene and quinazolinone rings), 868, 827 (1,2,4-trisubstituted benzene); 675 (Qu-Br), 1HNMR:*δ* 2.55 (s, 3H, 2-Qu-CH3), 7.60-8.24 (m, 6H, Ar-H, Qu-H), 9.39 (s, 1H, Qu-N=CH-Ar); 13CNMR:*δ* 172.4, 164.0, 160.5, 157.3, 154.8, 145.7. 147.0, 138.6, 137.8, 130.5, 129.8, 129.7, 129.4, 129.3, 129.0, 123.3, 119.3,113.5, 72.2, 52.8.

1-benzoyl 6-hydroxy-4-(3-nitrophenyl)-3,4-dihydroquinazolin-2(H)-one

White solid, IR (cm-1): *v* 3066 (Qu-H, Ar-H), 1678 (C=O), 1597 (C=N), 1579-1443 (C=C,benzene and quinazolinone rings), 781, 710 (1,2,3-trisubstituted benzene), 675 (Qu-Br); 1H-NMR: *δ*2.50 (s, 3H, 2-Qu-CH3), 7.45-8.95 (m, 6H, Ar-H, Qu-H), 9.37 (s, 1H, Qu-N=CH-Ar); 13C-NMR: *δ*172.5, 165.9, 158.6, 155.0, 154.6, 145.7, 141.2, 138.0, 135.0, 133.7, 130.2, 129.7, 129.4, 129.3, 123.4,120.1, 119.4, 104.6, 65.1, 53.4.

1-benzoyl 6-hydroxy-4-p-tolyl-3,4-dihydroquinazolin-2(H)-one
White solid, IR (cm-1): *v* 3030 (Qu-H, Ar-H), 1678 (C=O), 1605, 1585 (C=N), 1517, 1470 (C=C,benzene and quinazolinone rings), 881, 829 (1,2,4-trisubstituted benzene), 675 (Qu-Br), 1H-NMR: *δ*2.50 (s, 3H, 2-Qu-C*H*3), 7.61-8.23 (m, 6H, Qu-H, Ar-*H*), 9.02 (s, 1H, Qu-N=CH-Ar); 13C-NMR: *δ*171.3, 167.6, 160.0, 158.6, 156.9, 154.8, 151.3, 145.8, 142.0, 137.9, 129.8, 129.1, 127.5, 123.1, 119.3, 119.0, 117.5, 102.8, 65.2, 51.5.

1-benzoyl-4-(3,4-dimethoxyphenyl)- 6-hydroxy-3,4-dihydroquinazolin-2(H)-one
White solid, IR (cm-1): *v* 3076 (Qu-H, Ar-H), 1682 (C=O), 1610, 1599 (C=N), 1568-1447(C=C, benzene and quinazolinone rings), 1529, 1348 (Ar-NO2), 880, 833 (1,2,4-trisubstituted benzene),675 (Qu-Br); 1H-NMR: *δ* 2.59 (s, 3H, 2-Qu-CH3), 7.62-8.87 (m, 6H, Ar-H, Qu-H), 9.55 (s, 1H, Qu-N=CH-Ar); 13C-NMR: *δ* 171.1, 163.0, 155.7, 154.7, 147.4, 145.4, 141.5, 140.1, 137.9, 132.6, 129.8, 129.4,123.4, 128.4, 122.9, 119.6, 115.1, 109.5, 104.1, 73.2, 65.2, 52.7.

4-(2-aminophenyl)-1-benzoyl-6-hydroxy-3,4-dihydroquinazolin-2(1H)-one
White solid, yield 70%; m.p.207~208 °C; IR (cm-1): *v* 3061 (quinazolinone-H, Ar-H), 1684 (C=O), 1603, 1587 (C=N), 1551-1445(C=C, benzene and quinazolinone rings), 764, 696 (1,2,3-trisubstituted benzene), 768.0, 690.5(monosubstituted benzene); 1H-NMR: *δ* 7.42-8.28 (m, 13H, quinazolinone-H and Ar-H), 9.48 (s, 1H,N=CH); 13C-NMR: *δ* 171.3, 166.1, 164.4, 157.8, 153.0, 146.1, 134.9, 134.6, 133.9, 130.2, 129.9, 129.7, 127.8, 127.6, 127.1, 126.8, 121.0, 118, 112.3, 102.5, 53.1.

1-benzoyl-4-(3-chloro-4-nitrophenyl)-6-hydroxy-3,4-dihydroquinazolin-2(1H)-one
White solid, yield 78%; m.p. 179-180.3 °C; IR (cm-1): *v* 3055 (quinazolinone-H, Ar-H), 1680 (C=O), 1607, 1587 (C=N), 1566-1472(C=C, benzene and quinazolinone rings), 770, 690 (1,2,3-trisubstituted benzene), 766, 690(monosubstituted benzene); 1H-NMR: *δ* 7.43-8.28 (m, 12H, quinazolinone-H and Ar-H), 9.37 (s, 1H,N=CH); 13C-NMR: *δ* 173.1, 166.1, 158.1, 153.8, 146.7, 135.3, 135.0, 133.4, 130.2, 130.1, 130.0, 129.3, 128.3,128.1, 127.8, 127.5, 121.8, 118.4, 113.1, 74.3, 52.6.

1-benzoyl-4-(2-chlorophenyl)-6-hydroxy-3,4-dihydroquinazolin-2(1H)-one
White needles, yield 69%; m.p.137.6~139.6 °C; IR (cm-1): *v* 3057 (quinazolinone-H, Ar-H), 1678 (C=O), 1603, 1591 (C=N), 1566-1445 (C=C, benzene and quinazolinone rings), 881, 830 (1,2,4-trisubstituted benzene), 770, 692 (monosubstituted benzene); 1H-NMR *δ*: 7.45-8.25 (m, 13H, quinazolinone-H and Ar-H), 9.11 (s, 1H,N=CH); 13C-NMR *δ*: 170.0, 161.7, 158.3, 156.3, 153.6, 151.4, 147.2, 146.7, 135.4 , 134.9 , 130.6, 130.0, 128.2, 127.8 , 127.3, 126.9, 126.6, 121.5, 120.6, 119.0, 117.3, 51.8.

1-benzoyl-6-hydroxy-4-(4-methoxyphenyl)-3,4-dihydroquinazolin-2(1H)-one
White solid, yield 89%; m.p.203~204 °C; IR (cm-1) *v*: 3080 (ArH), 1678 (C=O), 1611, 1597 (C=N), 1570-1447 (C=C, benzene,quinazolinone and pyridine rings), 839 (1,4-disubstituted benzene), 825, 726 (4-subsituted pyridine); 1H-NMR: *δ* 7.36-7.82 (m, 8H, Ar-H, Qu-H), 8.27 (d, 2H, 3-Py-H, *J* = 5 Hz), 8.70 (d, 2H, 2-Py-H, *J* = 5 Hz), 9.11 (s, 1H, Qu-N=CH-Ar); 13C-NMR: *δ* 171.7, 68.1, 166.0, 164.0, 158.2, 151.8, 150.0, 146.5, 142.6, 135.4, 131.7, 129.4, 128.3 , 127.4, 124.3, 121.9, 117.1, 113.6, 105.2, 103.3, 75.3, 51.4.

1-benzoyl-6-hydroxy-4-(2-nitrophenyl)-3,4-dihydroquinazolin-2(1H)-one
White solid, yield 74%; m.p.184~186 °C; IR (cm-1): *v* 3060 (quinazolinone-H, Ar-H), 1670 (C=O), 1603, 1590 (C=N), 1564, 1445 (C=C, benzene and quinazolinone rings), 903 (1,3-disubstituted benzene), 766, 696 (mono- substituted benzene); 1H-NMR: δ 5.60 (s, 2H,), 7.38-8.19 (m, 13H, quinazolinone-H and Ar-H), 9.40 (s, 1H, N=CH); 13C-NMR: δ 172.3, 165.2, 161.0, 158.4, 157.8, 153.0, 146.1, 134.9, 134.6 133.9, 130.2, 129.9, 129.7, 127.8, 127.6, 127.1, 126.8, 121.0, 109.4, 53.5.

1-benzoyl-6-hydroxy-4-phenyl-3,4-dihydroquinazolin-2(1H)-one
White solid, yield 72%; m.p.179.4~181.0 °C; IR (cm-1): *v* 3061 (quinazolinone-H, Ar-H), 1672 (C=O), 1605, 1591 (C=N), 1564-1445 (C=C, benzene and quinazolinone rings), 843 (1,4-disubstituted benzene), 766, 696 (monosubstituted benzene); 1H-NMR: δ 5.68 (s, 2H), 7.42-8.28 (m, 14H, quinazolinone-H and Ar-H),9.48 (s, 1H, N=CH);^{13}C-NMR: δ 175.2, 166.1, 160.0, 158.1, 153.8, 146.7, 135.3, 135.0, 133.4, 130.2, 130.1, 130.0, 129.3, 128.3,128.1, 127.8, 127.5, 121.8, 114.9, 104.1, 53.1.

Anti bacterial activity
All the compound (3a-3f) was screened (dose 500 µg/ml for their antibacterial activities against the gram –ve bacteria Escherichia coil & Pseudomonas aeruginosa and gram +ve bacteria Bacillus Subtillis & Staphylococcus Aureus using standard antibiotic drug as a control. The biological activities of these compounds have been evaluated by using disc diffusion method. Dimethyl formamide was used as a solvent. Activities were determined by using the cultivated Disc and the inhibition zones were measured in mm and results are shown in table (2). The compound in the concentration of 500µg/ml was not found to antibacterial activity against Escherichia coil & Salmonella typhi respectively. The compound in the concentration of 500µg/ml was found to posses good antibacterial activity against Bacillus Subtillis & Staphylococcus Aureus respectively

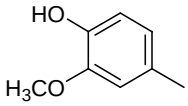
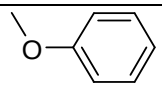
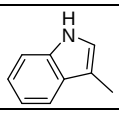
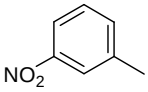
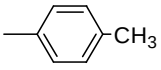
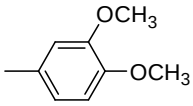
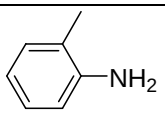
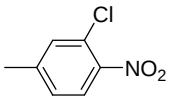
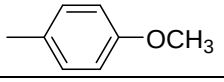
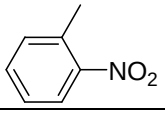
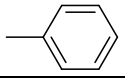
Analgesic activity
In this present study the analgesic activity of synthesized compounds were evaluated by Complete Freund's adjuvant method. Male Sprague Dawley rats (180–220 g) were used in this study. Animals were randomly distributed into 6 groups according to body weight. Each group consisted of 8 rats. G1 served as Normal Control. G2 was administered with FCA; G3 was administered with Diclofenac at 30 mg/kg while G4, G5 and G6 were given synthesized compounds 100mg/kg between respectively. Dose Volume was fixed at 5 ml/kg. 40µl of Fruends complete adjuvant emulsion was injected at a concentration of 1 mg/ml intraplantarly (i.pl.) into the left hind paw of rat. The animals were left after FCA injections for evaluation after 24 hrs. Paw withdrawal response was evaluated 24hrs after administration of FCA using Randall Sellito Analgesiometer. The model of inflammatory nociception was adapted from Randall and Selitto (1957). A cutoff of 150 g was used to avoid tissue damage or injury.

RESULTS AND DISCUSSION

Chemistry
The target compounds were prepared by using the reaction sequence in **Scheme 1**. A series of novel Quinazoline derivatives were synthesized by reaction of an aldehydes with excess

equivalent of urea in ethanol affords Arylideno-bis-ureas which on condensation with *p*-aminophenol in acidic medium cyclised to 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolines. Reaction of with benzoylchloride in 10% NaOH results in 1-benzoyl 4-aryl-6-hydroxy-2-oxo-3,4-dihydroquinazolin-2(H)-one. The homogenity of the compounds was monitored by thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualized by iodine vapour.
The compounds were identified by IR, ^{1}H-NMR and ^{13}C NMR. The physical data of compounds were presented in Table 1

TABLE: 1: Characterization data for compounds 3a – 3l

Compound code	R	Molecular Formula	Molecular Weight	Melting Point ºC	Rf Value	Percentage Yield %
3a		$C_{22}H_{18}N_2O_5$	390	216	0.95	66
3b		$C_{21}H_{16}N_2O_4$	360	209	0.87	68
3c		$C_{23}H_{17}N_3O_3$	383	190	0.96	67
3d		$C_{21}H_{15}N_3O_5$	389	180	0.89	60
3e		$C_{22}H_{18}N_2O_3$	358	197	0.91	62
3f		$C_{23}H_{20}N_2O_5$	404	203	0.99	71
3g		$C_{21}H_{17}N_3O_3$	359	185	0.85	63
3h		$C_{21}H_{14}ClN_3O_5$	423	184	0.86	64
3i		$C_{21}H_{15}N_2ClO_3$	378	189	0.86	70
3j		$C_{22}H_{18}N_2O_4$	374	172	0.89	75
3k		$C_{21}H_{15}N_3O_5$	389	185	0.88	65
3l		$C_{21}H_{16}N_2O_3$	344	182	0.92	63

Anti bacterial activity

The results are given in table (3) Synthesized compounds were evaluated for their antibacterial activity by disc diffusion method. At 500 µg/mL, the title compounds exhibited weak activities against Bacillus subtilis and Staphylococcus aureus which are lower than that of a ciprofloxacin standard. Among the compound were found to be resistant to Pseudomonas aeruginosa and Escherichia coil.

Table – 2: Antibacterial activity of the compounds 3a – 3l

S. NO.	COMPOUND CODE	DIAMETER OF ZONE OF HIHIBITION (IN MM)			
		Bacillus subtilis	***Staphylococcus aureus***	***Pseudomonas aeruginosa***	***Escherichia coil***
		500 µg/disc	**500 µg/disc**	**500 µg/disc**	**500 µg/disc**
1	3a	11	10	-	-
2	3b	13	11	-	-
3	3c	12	11	-	-
4	3d	13	13	-	-
5	3e	15	10	-	-
6	3f	13	14	-	-
7	3g	15	12	-	-
8	3h	09	13	-	-
9	3i	11	15	-	-
10	3j	13	11	-	-
11	3k	15	14	-	-
12	3l	11	13	-	-
13	Standard (Ciprofloxacin) 5 µg/disc	28	31	31	30

Table –3: Analgesic activity of the compounds 3a – 3l

S.No	Treatment	Dose	Mean Paw Withdrawal Threshold (gms)
1	Normal Control	0.5% of CMC	127.1± 11.74
2	FCA Control	40 µl (1 mg/ml)	74 ± 8.053
3	Diclofenac	30 mg/kg	124.3 ± 7.626
4	3a	100mg/kg	116.1± 5.22
5	3b	100mg/kg	85.57± 3.035
6	3c	100mg/kg	131 ±2.405
7	3d	100mg/kg	124.7 ± 2.49
8	3e	100mg/kg	87.71± 3.778
9	3f	100mg/kg	81.37 ± 2.289
10	3g	100mg/kg	111.1± 2.52
11	3h	100mg/kg	92.57± 3.035
12	3i	100mg/kg	131 ±2.405
13	3j	100mg/kg	114.7 ± 2.91
14	3k	100mg/kg	107.71± 2.75
15	3l	100mg/kg	91.37 ± 4.58

P<0.001 by Dunnet's't' test (multiple comparison test) compared with control. Values are expressed in mean ± SEM (n = 15)

Analgesic activity

The results are given in table (3) Synthesized compounds were evaluated for their analgesic activity by Complete Freund's adjuvant method. Diclofenac was used as standard. Among the compound 3a, 3c, 3d, 3g, 3i, 3j & 3k displayed good analgesic activity.

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REFERENCES

[1] A Spinks & W S Waung ; In Progress in Medicinal Chemistry edited by G P Ellis & G B West, Vol. III, Butterworths, Washington, **1963**; 261.
[2] J B Hynes ; J M Buck ; D'Souza L & Freisheim J H; *J MedChem*, 18, **1975**, 1191.
[3] J M Fukunga ; C Hansch & E E Steller, *J Med Chem*, 19, **1976**, 605.
[4] J B Hynes; D E Easen; C M Garreti; K E Shares & J H Friesheim, *J Med Chem*, 20, **1977**, 588.
[5] A Rosowshy ; J L Marini; M E Nadal & E J Modest, *J Med Chem*, 13, **1970**, 822.
[6] A M Albrecht ; D J Hutchinson ; F K Pearce & W J Suling , *Mol Pharmacol*, 6, **1970**, 323.
[7] F I Carroll ; B Berrang & C P Linn , Chem Ind, London, **1975**; 477.
[8] J Davoll,British Patent, 41**, 1968**; 1,735, 898; Chem Abstr, 70, **1969**; 47487.
[9] Dawoli J & Johason A M, J Chem Soc, 1970, 997.
[10] D G Johns ; R L Capizzi ; A Nahas ; A R Cashmore & J R Bertiono, *Biochem Pharmacol*, 19, 1970, 1528.
[11] United States Pharmacopeia Dispensing Information (USPDI). 7th Edn., Vol. 1, Diuretics, Eastan P A, Mack Printing, **1987**;796.
[12] K.D.Tripathi, Essentials of Medical Pharmacology, 5th edition, **2003**.
[13] Roger Walker, Clinical Pharmacy and Therapeutics, 3rd edition, 584.
[14] Wesley; G.Clark; D Craig Brater; Alice, Jhonson, R.Goth's Medical Pharmacology, Mosby year book, Inc., Missouri, **1991**, 3rd edition, 628-636.
[15] Satoskar; R.S.Bhandrakar and Ainapure, S.P. Pharmacology and Pharmacotherapeutics, 16th edition, Popular Prakashan, Mumbai, 611-683.
[16] J.G Hardman; L.E Limbid; and Gilman,. The Pharmacological basis of therapeutics, **,** 10th edition, McGraw Hill, New York, **2001;** 1143 -1170.
[17] Jane, N.Delgado and William. Wilson and Giswold's textbook of organic medicinal and pharmaceutical chemistry., 9th edition, **1998** ;235.
[18] Hitchcock, C.A.*Biochem. soc.* Trans., **1991**, 19:782.
[19] W. Gold. Antibiotics Annual, *New York Medical Encyclopedia*, **1956**.