Indian Journal of Chemistry
Vol. 47B, December 2008, pp. 1910-1914

An investigation leading to preparation of tetrahydro-quinazoline derivatives involving ureidoalkylation and α-amidoalkylation reactions

V K Pandey*, Mukesh, Anilesh Kumar & Noopur Trivedi

Department of Chemistry, University of Lucknow, Lucknow 226 007, India

E-mail: vinodkumarpandey@rediffmail.com

Received 11 October 2007; accepted (revised) 18 September 2008

Reaction of an aldehyde with excess equivalent of urea in ethanol affords alkylideno/arylideno-bis-ureas **1** which on condensation with *p*-aminophenol in acidic medium cyclised to 4-aralkyl-6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinazolines **2**. Reaction of **2** with arylamidoalcohols in concentrated H_2SO_4 results in 4-arylkyl-7-arylamido/imidoalkyl-6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinazolines **3**. Compounds **3** have been evaluated for their effect on central nervous system (CNS) and cardiovascular system (CVS).

Keywords: Ureidoalkylation, tetrahydroquinazolines, spontaneous motor activity

The chemistry of quinazoline compounds has been the subject of considerable interest though there had been only scattered reports of the investigation of the medicinal properties of such compounds. These are mainly compounds prepared as antimalarial drugs. The sedative hypnotic agent methaqualone[1,2] (2-methyl-3-(*o*-tolyl)-4-(3*H*)quinazolone) emerged as the most active of the series and till this date no superior anticonvulsant agent than this compound could be developed. Recently, interest in quinazolone chemistry has increased because of its association in cancer chemotherapy. All the studies were directed towards synthesizing quinazolines that had some resemblance to folic acid[3-10]. These compounds were evaluated for inhibition of the enzyme dihydrofolate reductase. The analogs were slightly more potent than methotrexate as inhibitors of dihydrofolate reductase in human leukemia cells[11,12]. Similar analogs were similarly found to be as active as methotrexate toward dihydrofolate reductase from rat liver and L1210 mouse leukemia[13]. The anticarcinogenic properties of tricycloquinazoline were studied in detail because of its possible formation from anthranilic acid derivatives in nature[14]. It possessed stronger activity towards mice (72%) than rats (27%). Its action resembled that of embedded plastic materials because it was recovered unmetabolized[15]. Several tetrahydroquinaozline analogs of folic acid were synthesized by Baker and his associates[16] as potential anticancer agents and the substance at 50 μg/mL gave 5% inhibition of *Streptococcus faecalis* on a flynnfolic acid medium containing 3 μg of folic acid. 4-Hydroxy and 8-nitro-4-chlorquinazolines have been incorporated into the nucleotide of vitamin B_{12}. These quinazoline vitamin analogs stimulated the growth of cobalamine requiring culture[17]. Quinazolones are also being extensively studied for their effects as diuretics. Thus, tetrahydro-quinazolinones are active as diuretics and their action is similar to that of thiazole. Their onset of action usually occurs within 1-2 hr and their peak diuretic effect is expressed within 3-6 hr[18].

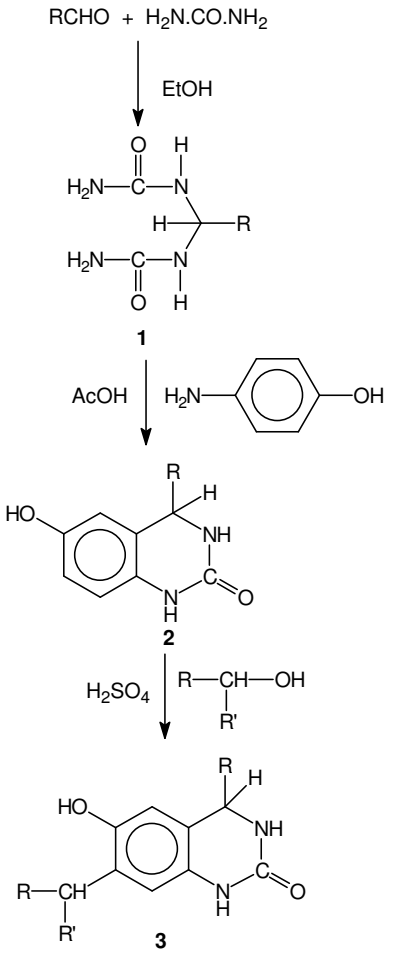
The wide spectrum biological activity of quinazolone derivatives and easy access of their synthesis led the authors to undertake the synthesis of some new quinazoline derivatives for studying their effects on cardiovascular system (CVS) and central nervous system (CNS) **(Scheme I)**.

Biological activity

Compounds **3** were screened for their antihypertensive activity in Sprague Dowley rats of either sex weighing between 200-300 g at two different dose levels viz. 1.0 mg/kg and 5.0 mg/kg i.v. These compounds were also evaluated for their effects on central nervous system (CNS) involving albino mice of either sex weighing 18-20 g each. A qualitative structure activity relationship study reveals that nicotinamido substituted quinazolines are better antihypertensive agents than phthalimido, methyl-phthalimido and salicylamido substituted tetrahydro-quinazolines, since two such compounds having R″=nicotinamido caused a reduction in blood pressure at both the dose levels. Two compounds showed CNS stimulant activity and five compounds were found CNS depressants. The biological activity data are incorporated in **Tables I** and **II** respectively.

Experimental Section

The melting points of the synthesized compounds were determined in the open capillaries in the



Scheme 1

Toshniwal Electric Apparatus and the values reported are uncorrected. FT-IR spectra (ν_{max} or cm^{-1}) were recorded in KBr discs using a Perkin-Elmer spectrophotometer model 337 (USA). ^1H NMR spectra were taken on a Varian 60D instrument (USA) using $CDCl_3$ at 300 MHz. TMS was used as an internal standard. Purity of compounds was checked by TLC.

Alkylideno/arylideno-bis-ureas 1: Preparation of alkylideno/ arylideno-bis-ureas **1** is an example of ureidoalkylation reaction involving formation of new carbon-nitrogen bond. Thus, a mixture of an aliphatic/ aromatic aldehyde (0.02 mole) and urea (carbamide) (0.04 mole) in absolute ethanol (100 mL) was heated under reflux for 4 hr in such a manner that moist air did not pass into the reaction mixture. Ethanol was removed by distillation and the residual solid was washed with water. It was dried *in vacuo* and recrystallization from diluted methanol afforded analytically pure sample of ureidoalkylated product. Alkylideno/ arylideno-bis-ureas thus synthe-sized in this manner, are presented in **Table III**.

4-Aryl-6-hydroxy-2-oxo-1, 2, 3, 4-tetrahydroquinazolines 2: Synthesis of the target compounds **2** involves the cyclization step leading to the formation of quinazoline derivative. Alkylideno/ arylideno-bis-urea **1** (0.01 mole) and *p*-amino benzoic acid (0.01 mole) were dissolved in gl. acetic acid by stirring and heating slowly. The acidic solution was subsequently heated under reflux for 6 hr. The hot solution was cooled to RT and poured into ice-cold water (250 mL). On stirring vigorously for 0.5 hr, solidification started to occur which was completed on standing further for 0.5 hr. It was filtered off and washed successively with water (4 × 25 mL). The crude quinazoline derivative was dried under vacuum and recrystallized from diluted ethanol. The compounds of this type are presented in **Table III**.

Table I — Antihypertensive activity data of compounds **3a-i**

Compd	R	R′	R″	CVS Activity in rats (dose in mg/kg)			
				1.0 mg/kg		5.0 mg/kg	
				Fall in b.p. (mmHg)	Duration (in min)	Fall in b.p. (mmHg)	Duration (in min)
3a	Phenyl	Hydrogen	Phthalimido	↑ 10	Tr	12	Tr
3b	Phenyl	Phenyl	Salicylamido	↑18	Tr	N.A.	-
3c	*o*-Methoxyphenyl	Hydrogen	Phthalimido	N.A.	-	↑26	35
3d	Phenyl	Hydrogen	Methylphthalimido	N.A.	-	-	-
3e	*o*-Hydroxyphenyl	Hydrogen	Nicotinamido	25	Tr	40	Tr
3f	*o*-Hydroxyphenyl	Phenyl	Phthalimido	↑36	20	↑52	40
3g	*o*-Hydroxyphenyl	*o*-Hydroxyphenyl	Salicylamido	10	Tr	10	Tr
3h	Hydrogen	Phenyl	Nicotinamido	40	2	75	06
3i	*p*-Hydroxyphenyl	*o*-Hydroxyphenyl	Salicylamido	10	Tr	24	03

Table II — CNS activity data of compounds **3a-i**

Compd	R	R′	R″	Dose 1/5th of the ALD_{50} (mg/kg) i.p.		
				Death	SMA and reacting	Writhing
3a	Phenyl	Hydrogen	Phthalimido	0/5	↑	(–)
3b	Phenyl	Phenyl	Salicylamido	0/5	↑	(–)
3c	*o*-Methoxyphenyl	Hydrogen	Phthalimido	0/5	↓	(+)
3d	Phenyl	Hydrogen	Methylphthalimido	0/5	↓	(+)
3e	*o*-Hydroxyphenyl	Hydrogen	Nicotinamido	0/5	↓	(+)
3f	*o*-Hydroxyphenyl	Phenyl	Phthalimido	0/5	↓	(+)
3g	*o*-Hydroxyphenyl	*o*-Hydroxyphenyl	Salicylamido	0/5	↓	(+)
3h	Hydrogen	Phenyl	Nicotinamido	0/5	↓	(+)
3i	*p*-Hydroxyphenyl	*o*-Hydroxyphenyl	Salicylamido	0/5	↓	(+)

Table III — Characterisation data of compounds **1a-e**, **2a-e** and **3a-i**

Compd	R	R'	R"	m.p. (°C)	Yield (%)	Mol. formula	% N Found (Calcd)	IR (KBr) (ν_{max} in cm^{-1})	^1H NMR ($CDCl_3$) (δ, ppm)
1a	Phenyl	-	-	157-158	80	$C_9H_{12}N_4O_2$	26.61 (26.92)	1720 (CO), 3300 (NH), 3092 (Ar), 2920 (CH)	6.89-7.90 (m, 5H, ArH) 8.45 (brs, 6H, CONH), 3.58 (t, 1H, NCHN)
1b	*o*-Methoxyphenyl	-	-	180-181	75	$C_{10}H_{14}N_4O_3$	23.73 (23.52)	1725 (CO), 3345 (NH), 1125 (C–O–C), 3095 (Ar), 2930 (CH)	7.21-7.68 (m, 4H, ArH), 8.38 (brs, 6H, CONH), 3.67 (s, 3H, OCH_3), 3.72 (t, 1H, NCHN)
1c	*o*-Hydroxyphenyl	-	-	83-84	77	$C_9H_{12}N_4O_3$	25.23 (25.00)	1730 (CO), 3335 (NH), 3575 (OH), 3085 (Ar), 2935 (CH)	7.32-7.89 (m, 4H, ArH), 8.42 (brs, 6H, CONH), 4.72 (s, 1H, ArOH), (t, 1H, N–CH–N)
1d	Hydrogen	-	-	174-175	70	$C_3H_8N_4O_2$	42.27 (42.42)	1728 (CO), 3337 (NH) 2939 (CH)	8.48 (brs, 6H, CONH), 3.78 (t, 2H, NCH_2N)
1e	*p*-Hydroxyphenyl	-	-	182-183	69	$C_9H_{12}N_4O_3$	24.92 (25.00)	1732 (CO), 3340 (NH), 3580 (OH), 3075 (Ar), 2932 (CH)	7.32-7.86 (m, 4H, ArH), 8.52 (brs, 6H, CONH), 4.89 (s, 1H, ArOH), 3.82 (t, 1H, NCHN)
2a	Phenyl	-	-	159-160	70	$C_{14}H_{12}N_2O_2$	11.43 (11.66)	1750 (CO), 3310 (NH), 3020 (Ar), 2930 (CH)	7.1-7.6 (m, 8H, ArH), 8.32 (brs, 2H, CONH), 4.83 (s, 1H, ArOH), 4.61 (d, 1H, NCH)
2b	*o*-Methoxyphenyl	-	-	160-161	64	$C_{15}H_{14}N_2O_3$	10.52 (10.37)	3540 (OH), 1722 (CO), 3410 (NH) 3025 (Ar), 2925 (CH), 1130 (C–O–C)	6.9-7.5 (m, 7H, ArH), 8.4 (brs, 2H, CONH), 4.51 (s, 1H, ArOH), 3.85 (s, 3H, OCH3), 4.58 (d, 1H, NCH)
2c	*o*-Hydroxyphenyl	-	-	66-68	66	$C_{14}H_{12}O_3N_2$	10.51 (10.93)	3545 (OH), 1735 (CO), 3310 (NH), 3035 (Ar), 2895 (CH)	7.68-7. 98 (m, 7H, ArH), 8.2 (brs, 2H, CONH), 4.80 (s, 2H, ArOH), 4.32 (d, 1H, NCH)

Contd —

Table III — Characterisation data of compounds **1a-e**, **2a-e** and **3a-i** — *Contd*

Compd	R	R'	R"	m.p. (°C)	Yield (%)	Mol. formula	% N Found (Calcd)	IR (KBr) (ν_{max} in cm^{-1})	^1H NMR ($CDCl_3$) (δ, ppm)
2d	Hydrogen	-	-	175-176	72	$C_8H_8N_2O_2$	17.28 (17.07)	1740 (CO), 3330 (NH), 2910 (CH), 3540 (OH), 3037 (Ar)	7.25-7.58 (m, 3H, ArH), 8.33 (brs, 2H, CONH), 4.79 (s, 1H, ArOH), 4.46 (d, 2H, NCH_2)
2e	*p*-hydroxyphenyl	-	-	185-186	68	$C_{14}H_{12}N_2O_3$	10.58 (10.93)	3550 (OH), 1732 (CO), 3320 (NH), 3020 (Ar), 2928 (CH)	7.68-7.98 (m, 7H, ArH), 8.45 (brs, 2H, CONH), 4.81 (s, 2H, ArOH), 4.38 (d, 1H, NCH)
3a	phenyl	Hydrogen	Phthalimido	205-206	54	$C_{23}H_{17}N_3O_4$	10.31 (10.52)	3610 (OH), 1730 (CO), 3300 (NH), 2930 (CH), 3025 (Ar)	7.25-7.58 (m, 16H, ArH), 4.74 (s, 2H, ArOH), 8.21 (brs, 2H, CONH), 4.50 (d, 1H, NCH_2)
3b	Phenyl	Phenyl	Salicylamido	210-211	60	$C_{28}H_{23}N_3O_4$	9.32 (9.03)	3605 (OH), 1720 (CO), 3340 (NH), 3030 (Ar), 2938 (CH)	7.62-7.80 (m, 1H, ArH), 4.74 (s, 2H, ArOH), 8.24 (brs, 3H, CONH), 4.60 (d, 1H, NCH), 8.23 (s, 1H, NH)
3c	*o*-Methoxyphenyl	Hydrogen	Phthalimido	220-221	56	$C_{24}H_{19}N_3O_5$	9.51 (9.79)	3620 (OH), 1735 (CO), 3350 (NH), 3032 (Ar), 2940 (CH), 1130 (C–O–C)	7.20-7.94 (m, 10H, ArH), 8.4 (brs, 2H, CONH), 4.73 (s, 1H, ArOH), 3.75 (s, 2H, NCH_2)
3d	Phenyl	Hydrogen	Methyl-phthalimido	225-226	55	$C_{24}H_{19}N_3O_4$	10.42 (10.16)	3580 (OH), 1740 (CO), 3342 (NH), 3035 (Ar), 2945 (CH)	7.15-7.54 (m, 11H, ArH), 8.32 (brs, 2H, CONH), 3.52 (s, 2H, N–CH_2), 4.73 (s, 1H, ArOH)
3e	*o*-Hydroxyphenyl	Hydrogen	Nicotinamido	107-110	53	$C_{21}H_{18}N_4O_4$	14.10 (14.35)	3585 (OH), 1633 (CH), 1740 (CO), 3350 (NH), 3040 (Ar), 2940 (CH)	6.90-7.88 (m, 10H, ArH), 8.19 (brs, 3H, CONH), 4.76 (s, 2H, ArOH), 3.78 (s, 2H, NCH_2).
3f	*o*-Hydroxyphenyl	Phenyl	Phthalimido	>300	57	$C_{29}H_{21}N_3O_5$	8.22 (8.55)	3545 (OH), 1735 (CO), 3400 (NH), 3025 (Ar), 2930 (CH)	7.35-7.95 (m, 15H, ArH), 3.69 (s, 1H, NCH), 4.83 (s, 2H, ArOH), 8.52 (brs, 2H, CONH)
3g	*o*-Hydroxyphenyl	*o*-Hydroxy phenyl	Salicylamido	79-81	59	$C_{28}H_{23}N_3O_6$	8.21 (8.45)	3555 (OH), 1740 (CO), 3410 (NH), 3030 (Ar), 2932 (CH)	6.90-7.56 (m, 14H, ArH), 4.51 (s, 4H, ArOH), 8.52 (brs, 3H, CONH), 3.79 (s, 1H, NCH).

Contd —

Table III — Characterisation data of compounds **1a-e**, **2a-e** and **3a-i** — *Contd*

Compd	R	R'	R"	m.p. (°C)	Yield (%)	Mol. formula	% N Found (Calcd)	IR (KBr) (ν_{max} in cm^{-1})	^1H NMR ($CDCl_3$) (δ, ppm)
3h	Hydrogen	Phenyl	Nicotinamido	110-111	52	$C_{21}H_{18}N_4O_3$	14.86 (14.97)	1660 (CN), 3610 (OH), 3360 (NH), 1735 (CO), 3035 (Ar), 2938 (CH)	7.61-7.90 (m, 11H), ArH), 8.61 (brs, 3H, CONH), 4.51 (s, 1H, NCH), 4.71 (s, 1H, ArOH).
3i	*p*-Hydroxyphenyl	*o*-Hydroxy phenyl	Salicylamido	140-141	55	$C_{28}H_{23}N_3O_6$	8.69 (8.45)	3535 (OH), 3345 (NH), 1750 (CO), 3035 (Ar), 2930 (CH).	6.85-7.91 (m, 14H, ArH), 8.57 (brs, 3H, CONH), 4.69 (s, 4H, ArOH), 4.32 (s, 1H, NCH).

4-Aryl-7-arylamido/imidoalkyl-6-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinazolines 3: The preparation of **3** involves the C-amidoalkylation reaction *ortho* to the hydroxyl function. Thus, a mixture of 4-aryl-6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinazoline **2** (0.005 mole) and an amido/ imidoalcohol (0.005 mole) was dissolved in concentrated sulphuric acid carefully by stirring at RT. While dissolving, the contents were cooled. The acidic solution was stirred for 1 hr at RT and left under refrigeration for 24 hr. Subsequently, it was poured into ice-cold water carefully and stirred vigorously. A solid separated out which was allowed to settle down. It was filtered off and washed with water to remove any sulphonated product. The crude compound after drying *in vacuo* was subjected to recrystallization from ethanol. The quinazoline derivatives synthesized in this experimental way are recorded in **Table III** alongwith their characterization data.

Acknowledgement

The authors express their sincere thanks to the Head, Department of Chemistry, Lucknow University, Lucknow for providing necessary laboratory facilities. Thanks are also due to the Director, CDRI, Lucknow for providing elemental, spectral and biological activity data.

References

1 Soulariac A & Gottesmann C, *Life Sci*, 6, **1967**, 1229.
2 Spinks A & Waung W S, in *Progress in Medicinal Chemistry* edited by G P Ellis & G B West, Vol. III, (Butterworths, Washington) **1963**, p. 261.
3 Hynes J B, Buck J M, D'Souza L & Freisheim J H, *J Med Chem*, 18, **1975**, 1191.
4 Fukunga J M, Hansch C & Steller E E, *J Med Chem*, 19, **1976**, 605.
5 Hynes J B, Easen D E, Garreti C M, Shares K E & Friesheim J H, *J Med Chem*, 20, **1977**, 588.
6 Rosowshy A, Marini J L, Nadal M E & Modest E J, *J Med Chem*, 13, **1970**, 822.
7 Albrecht A M, Hutchinson D J, Pearce F K & Suling W J, *Mol Pharmacol*, 6, **1970**, 323.
8 Carroll F I, Berrang B & Linn C P, *Chem Ind*, (London), **1975**, 477.
9 Davoll J, *British Patent*, 41, **1968**, 1,735, 898; *Chem Abstr*, 70, **1969**, 47487.
10 Dawoli J & Johason A M, *J Chem Soc*, **1970**, 997.
11 Johns D G, Capizzi R L, Nahas A, Cashmore A R & Bertiono J R, *Biochem Pharmacol*, 19, **1970**, 1528.
12 Hutchinson D J, *Cancer Chemother Pep*, 52, **1968**, 697.
13 Richer W E & McCormac J J, *J Med Chem*, 17, **1974**, 943.
14 Cooper F C & Partridge M W, *J Chem Soc*, **1954**, 3429.
15 Baldwin R W, Cunninghan C J & Pastridge M W, *Brit J Cancer*, 13, **1959**, 94.
16 Baker B R, Kochler R, Goodman L & Graw J D, *J Amer Chem Soc*, 80, **1958**, 5779; *Chem Abstr*, 26, **1961**, 1156.
17 Perlman D & Barett J M, *Can J Microbiol*, 4, **1958**, 9.
18 United States Pharmacopeia Dispensing Information (USPDI). 7th Edn., Vol. 1, *Diuretics*, Eastan P A, Mack Printing, **1987**, 796.