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Note

Synthesis, antibacterial and antifungal activity of some new pyrido quinazolones

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Alkylideno/arylideno bis ureas **1** synthesized by ureido-alkylation in the presence of alcohols–which on treatment with *p*-aminobenzoic acid results in 4-aryl-6-carboxylato-1,2,3,4-tetra-hydroquinazolines **2**. Reaction of **2** with benzoin in presence of polyphosphoric acid yields 4-aryl-8,9-diphenyl-1,4 dihydro-3*H*, 7-oxo-1,3-diaza anthracene-2,6-dione **3**. Condensation of **3** with aromatic primary amine affords *N*-aryl-8,9-diphenyl (-2-oxo-pyrido [*g*]-4-aryl-2-oxo-1,3-dihydro quinazolines **4**. The new compound **4** has been screened for their antibacterial and antifungal activities.

Keywords: Tetrahydroquinazolines, calcium antagonists, alkylideno/aryldeno-bis-ureas, antibacterial, antifungal

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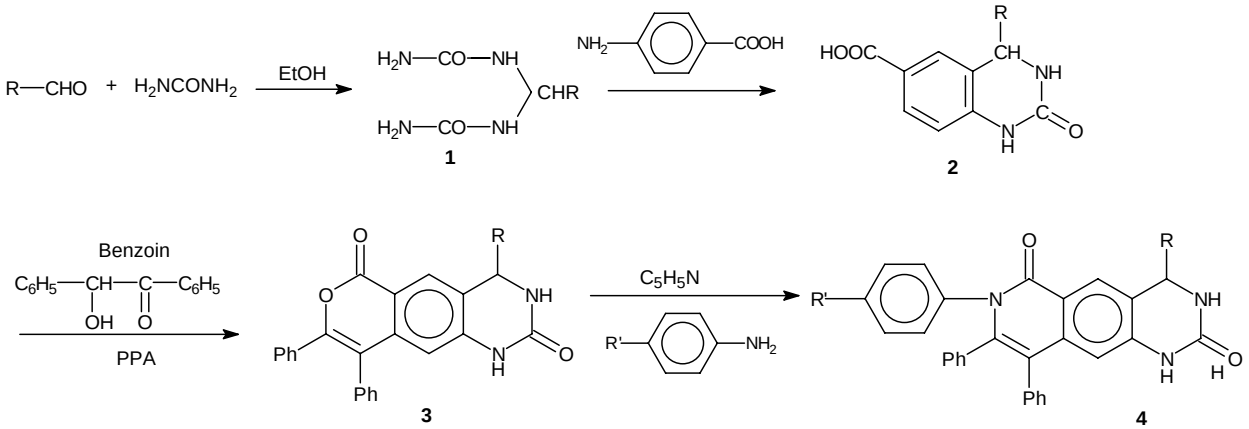
Pyrido derivatives constitute an important class of compounds possessing diverse type of biological properties including antibacterial, antidiabetic[1-6], antifungal[7] and antiarrhythmic[8]. In addition some pyridoderivatives are calcium antagonists and share the common property of interfering with the influx of extracellular calcium *via* the calcium L channel[9]. In addition, quinazolines/quinazolones are associated with various biological properties ranging from anti-convulsant[10] and antibacterial[11] to anti-diabetic[12]. Interest in quinazoline chemistry has increased recently because of their association with anticancer property[13]. The strategy adopted was the synthesis of quinazolone derivatives that has some resemblance to folic acid[14–16]. These compounds were mainly evaluated for inhibition of enzyme dihydrofolate reductase and were found inhibitors of dihydrofolate reductase in human leukaemia cells[17,18].

In continuation of our research work on the designing and synthesis of biologically active compounds the present communication, deals with the synthesis of *N*-aryl-8,9-diphenyl-(-2-oxo-pyrido [*g*]-4-aryl-2-oxo-1,3-dihydroquinazolines (**Scheme I, Table I**). The antibacterial and antifungal activities are shown in **Tables II** and **III**

Biological Activity

All the seven compounds **4a-g** were screened for their antibacterial activity against three bacterial strains *viz.*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumoniae*[18] (**Table II**). These compounds were also evaluated for their antifungal activity against two fungi *viz.*, *Aspergillus flavus* and *Aspergillus niger* at four concentration levels *viz.* 10, 20, 50 and 100 μg/mL involving disc diffusion method[19] **(Table III)**. Two compounds *viz.* **4c** and **4f** displayed high antibacterial activity against *Pseudomonas aeruginosa* while one compound **4d** showed high activity against *Klebsiella pneumomoniae.* All the compounds were found to exhibit high antifungal activity at 100 μg/mL (80-95%) but at lower concentration level (10 μg/mL)



Scheme 1

Table I — Characterization data of *N*-Aryl-8,9-diphenyl-2-oxopyrido [*g*] 4-aryl-2-oxo-1,3-dihydro-quinazolines

Compd	R	R ′	m.p. °C	Yield (%)	Mol. formula	% N		^{1}H NMR
						Found	Calcd	
1a	Phenyl	–	178	65	$C_9H_{12}N_4O_2$	26.52	26.92	6.0 (s, 2H, –NH_2), 6.98 (t, 1H, –CH), 7.09-7.20 (m, 5H, Ar-H)
1b	Hydrogen	–	169	70	$C_3H_8N_4O_2$	42.15	42.42	6.01 (s, 2H, –NH_2), 6.8 (t, 2H, –CH_2)
2a	Phenyl	–	284	60	$C_{15}H_{12}N_2O_3$	10.20	10.45	6.0 (s, 1H, –NH), 6.3 (d, 1H, –NH), 7.2-7.8 (m, 8H, Ar-H), 6.4 (d, 1H, –CH)
2b	Hydrogen	–	249	67	$C_9H_8N_2O_3$	14.33	14.58	4.12 (d, 2H, –CH_2), 6.13 (s, 1H, NH), 6.01 (t, 1H, NH), 7.30-7.80 (m, 3H, Ar-H)
3a	Phenyl	–	145	53	$C_{29}H_{20}N_2O_3$	5.99	6.31	4.40 (d, 2H, -CH_2), 6.14 (s, 1H, -NH), 6.3 (d, 1H, NH), 7.10-7.9 (m, 11H, Ar-H)
3b	Hydrogen	–	136	59	$C_{23}H_{16}N_2O_3$	7.31	7.61	6.0 (d, 1H, -CH), 6.11 (s, 1H, -NH), 6.29 (d, 1H, –NH), 7.09-7.90 (m, 17H, Ar-H)
4a	Phenyl	Hydrogen	128	45	$C_{35}H_{25}N_3O_2$	7.89	8.09	6.9-7.9 (m, 22H, Ar-H), 6.01 (s, 1H, -NH), 6.10 (d, 1H, -NH)
4b	Phenyl	Chloro	140	42	$C_{35}H_{24}N_3O_2Cl$	7.37	7.59	6.0 (s, 1H, NH), 6.09 (d, 1H, NH), 7.10-7.89 (m, 21H, Ar-H)
4c	Phenyl	Methoxy	170	40	$C_{36}H_{27}N_3O_3$	7.34	7.65	3.70 (s, 3H, -OCH_3), 6.0 (S, 1H, -NH), 6.0 (s, 1H, –NH), 6.19 (d, 1H, –NH), 6.99-7.81 (m, 21H, Ar-H)
4d	Phenyl	Methyl	130	40	$C_{36}H_{27}N_3O_2$	7.39	7.83	2.40 (s, 3H, –CH_3), 5.98 (s, 1H, NH), 6.9 (d, 1H, –NH), 7.10-7.79 (m, 21H, Ar-H)
4e	Hydrogen	Hydrogen	220	38	$C_{29}H_{21}N_3O_2$	9.29	9.48	4.30 (d, -2H, -CH_2), 6.03 (s, 1H, NH), 6.11 (d, 1H, NH), 7.11-7.67 (m, 17H, Ar-H)
4f	Hydrogen	Chloro	194	49	$C_{29}H_{20}N_3O_2Cl$	8.50	8.79	4.38 (d, 2H, CH_2), 6.03 (s, 1H, NH), 6.09 (d, 1H, –NH), 7.11-7.70 (m, 16H, –Ar-H)
4g	Hydrogen	Methoxy	186	40	$C_{30}H_{23}N_3O_3$	8.41	8.88	3.74 (s, 3H, –OCH_3), 4.32 (d, 2H, –CH_2), 6.6 (s, 1H, -NH), 6.9 (d, 1H, –NH), 7.10-7.90 (m, 16H, Ar-H)

Table II — Antibacterial activity data of *N*-aryl-8,9-diphenyl-2-oxo-pyrido [*g*] 4-aryl-2-oxo-1,3-dihydroquinazolines

Compd	R	R'	Ampicilin (Control)	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Klebsiella pneumoniae*
4a	Phenyl	Hydrogen	14.83 mm	>10 mm	>10 mm	>6 mm
4b	Phenyl	Chloro	14.83 mm	>10 mm	>10 mm	>10 mm
4c	Phenyl	Methoxy	14.83 mm	>14 mm	>6 mm	>10 mm
4d	Phenyl	Methyl	14.83 mm	>6 mm	>10 mm	>14 mm
4e	Hydrogen	Hydrogen	14.83 mm	>10 mm	>6 mm	>6 mm
4f	Hydrogen	Chloro	14.83 mm	>14 mm	>6 mm	>6 mm
4g	Hydrogen	Methoxy	14.83 mm	>10 mm	>6 mm	>6 mm

only two compounds *viz.*, **4c** and **4g**, showed high activity against *Aspergillus flavus*.

Results and Discussion

All the synthesized compound have been characterized by elemental analysis, IR and ^{1}H NMR spectral studies. In the IR spectrum of **4g** a peak at 3474 cm^{-1} (N-H str.) along with a peak at 1530 cm^{-1} (N-H bending) and a peak at 1660 cm^{-1} (due to lactam >C=O) appeared. The ^{1}H NMR spectrum compound **4c (Table I)** showed signals at δ 3.74 due to –OCH_3 proton at δ 6.65 due to NH proton and at δ 6.9-7.9 due to aromatic proton.

Experimental Section

The melting point of compound were determined in open glass capillaries in Toshniwal melting point apparatus and recorded value are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr on Perkin-Elmer 157 spectrophotometer in region ν_{max} 4000-400 cm^{-1} and ^{1}H NMR spectra in DMSO-d_6 on a DRX (200 MHz) and DRX (300 MHz) NMR

Table III — Antifungal activity data of *N*-aryl-8,9-diphenyl-2-oxopyrido [*g*] 4-aryl-2-oxo-1,3-dihydro-quinazolines

Compd	R	R'	Concentration (μg/mL)	*A. flavus*		*A. niger*	
				Colony diameter	Inhibition (%)	Colony diameter	Inhibition (%)
4a	Phenyl	Hydrogen	10	1.4	53.3	0.8	60
			20	1.2	60.0	0.5	75
			50	0.8	73.3	0.2	90
			100	0.4	86.7	0.1	95
4b	Phenyl	Chloro	10	1.2	60	1.0	50
			20	0.7	76	0.6	70
			50	0.5	83.3	0.4	80
			100	0.2	93.3	0.2	90
4c	Phenyl	Methoxy	10	0.8	73.3	1.5	25
			20	0.6	80	0.6	70
			50	0.2	93.3	0.5	75
			100	0.1	96.6	0.3	85
4d	Phenyl	Methyl	10	1.2	60	1.3	35
			20	1.0	66.66	1.1	45
			50	0.4	86.6	0.9	55
			100	0.2	93.3	0.6	70
4e	Hydrogen	Hydrogen	10	1.1	63.3	1.0	50
			20	0.8	73.3	0.8	60
			50	0.7	76.6	0.6	70
			100	0.4	86.6	0.3	85
4f	Hydrogen	Chloro	10	1.2	60	1.1	45
			20	0.9	70	0.9	55
			50	0.7	76.6	0.7	65
			100	0.3	90	0.3	85
4g	Hydrogen	Methoxy	10	1.0	66.6	0.9	55
			20	0.9	70	0.8	60
			50	0.5	83.3	0.5	75
			100	0.2	93.3	0.2	90
	Control	–	–	3	–	2	–

spectrometer using TMS as internal standard (Chemical shift in δ, ppm).

Alkylideno/arylideno bis ureas 1. A mixture of an aldehyde (0.01 mole) and urea (0.2 mole) in ethanol was heated under reflux 4 h. Subsequently, ethanol was distilled off and residual thick oily material was cooled to 0°C. It solidified in about 1 h. After washing initially with 1% NaOH solution and finally with cold water, the resultant solid was filtered. The crude material was dried at 100°C and recrystallized from diluted ethanol. Alkylideno/arylideno bis-ureas thus synthesized are recorded in **Table I**.

4-Aryl-6-carboxylato-1,2,3,4–tetrahydroquinazolines 2. Alkylideno/arylideno-bis-urea **1** (0.06 mole) and *p*-aminobenzoic acid (0.06 mole) were mixed together and heated at 145-150°C for 4 hr. A clear liquid was obtained on heating which on cooling to RT solidified. It was treated with diluted HCl (50 mL) and stirred very well. After filtering off the solid, it was washed with water several times and treated with an aqueous solution of sodium-bicarbonate (10%). Vigorous effervescence as a result of evolution of carbon dioxide occurred which subsided on adding more solution of sodium bicarbonate. When the effervescence completely ceased the solid was filtered off. This solid was rejected and the filtrate was acidified with diluted hydrochloric acid. On complete neutralization, a solid separated out which was filtered off and washed with water. It was dried at 100°C and recrystallized from glacial acetic acid. The compounds of this category are recorded in **Table I** along with their characterization data.

4-Aryl-8,9-diphenyl-1,4-dihydro-3*H*-7-oxa-1,3-diazaanthracene-2,6-dianes 3. A mixture of 4-aryl-6-carboxylato-1,2,3,4-tetrahydroquinazoline **2** (0.02 mole) and benzoin (desyl alcohol) (0.02 mole) in polyphosphoric acid (10 mL) was heated at 100°C for 5 h. During heating, the contents were occasionally stirred. Subsequently, the reaction mixture was poured into ice cold water (100 mL) and left as such for 1 h. A solid separated out, which was filtered off

and washed initially with 10% aqueous sodium bicarbonate solution (50 mL) and finally with water (2×25 mL). The solid thus obtained, was dried under vacuum and recrystallized from methanol. The compound thus synthesized are recorded in **Table I**.

N-Aryl-8,9-diphenyl (-2-oxo-pyrido-[g]-4-aryl-2-oxo-1,3-dihydro-quinazolines 4. The titled compounds 4 were synthesized by heating under reflux a mixture of 4-aryl-8,9-diphenyl-1,4-dihydro-3*H*-7-oxa-1,3-diazanthracene-2,5,6-dione 3 (0.01 mole) and aromatic primary amine (0.02) in anhydrous pyridine (30 mL) for 6 h. The solution was cooled to RT and acidified with dil. HCl (50 mL). A solid separated out which was filtered off and washed with water successively (4 × 25 mL). It was air dried and recrystallized from diluted ethanol. The compounds of this category are present in **Table I** along with their data for characterization.

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