Int. J. Chem. Sci. : 3 (1), 2005, 60–66

MICROBIAL STUDIES OF NEW AMIDES OF PYRIDOQUINOLONE

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ABSTRACT

Series of 6–hydroxy–4–oxo–pyrido [2,3–h]–3–[N–(substituted phenyl thiourido) carbonyl] quinoline (**3a–*l***) and 6–hydroxy–4–oxo–pyridol [2,3–h]–3–[N–(substituted phenylamino) carbonyl] quinoline (**4a–*l***) have been synthesised by the condensation of 6–hydroxy–4–oxo–pyrido [2,3–h] quinoline–3–carboxylic acid (**1**) with substituted aryl thioureas and aryl amines, respectively at C–3 position via 6–hydroxy–4–oxo–pyrido [2,3–h] quinoline–3–carbonyl chloride (**2**). The synthesized compounds have been characterized by elemental analysis, IR and ^{1}H NMR spectral data. Antibacterial and antifungal activity screening were carried out at two different concentrations with two gram positive and two gram negative bacteria for all the new compounds. The activity results of compounds (**3a–*l***) and (**4a–*l***) have been compared with each other. The compared results highlighted that the activity of substituted aryl amino compounds (**4a–*l***) are better than the substituted aryl thioureas (**3a–*l***).

Key words : Pyridoquinolone, Amide, Microbial.

INTRODUCTION

Quinolone and its various analogues have proved themselves to be one of the most effective therapeutic agents for the treatment of various infectious diseases. Durig the last few years almost all structural modifications of the quinolone nucleus have been made to C–6 fluorine substituted structures. However, the exact role of the C–6 fluorine has never been demonstrated. Recently, Ledoussal *et al.*[1] reported a series of non C–6 fluoroquinolones having antibacterial activities comparable to their C–6 fluoro analogs. More recently, Cacchetti *et al.*[2] found that good activity could still be obtained by replacing the C–6 fluorine atom with an amino group. Few other research workers also synthesized non C–6 fluoroquinolones derivatives and compared with fluro analogs.[3,4]

In our earlier paper, we reported the synthesis of 6–hydroxy–4–oxopyrido [2,3–h]–{N^4[substituted arylsulfanilamide] carbonyl} quinoline as potential antibacterial.[5] As a part of our continuing interest in synthesis of pyridoquinolones, we have shown a route for the

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synthesis of 6–hydroxy–4–oxo–pyridol [2,3–h]–3–[N–(substituted phenyl amino) carbonyl] quinoline (**4a–*l***). Antibacterial and antifungal activity screening were carried out at two different concentrations with two gram positive and two gram negative bacteria for all the synthesized compounds. The activity results of two series have been compared with each other.

RESULTS AND DISCUSSION

Minimum inhibitory concentration (MIC) for all the synthesized compounds have been tested against gram positive bacteria such as *S. aureus* and *B. subtilis* and gram negative such as *E. coli* and *P. aeruginosa* by cup plate method[6,7] using DMSO as a solvent. The solution of compounds at 100 µg/mL concentration was taken and compared with standard drug ciprofloxacin, ampicilline and amoxicilline.

From screening results, good activity was observed for gram positive bacteria in compounds (**3a,e,i**) (R = H, 4–OCH_3, 2–CH_3), (**4a,c,g,k**) (R = H, 4–Cl, 2–NO_2, 3–NO_2, 4–CH_3) respectively, and the remaining compounds were moderate to least active at 100 µg/mL concentration, while, at 200 µg/mL concentration, the good activity was observed in compounds (**3e,i**) (R = 4–OCH_3, 2–CH_3), (**4a,b,c,f**) (R = H, 3–Cl, 4–Cl, 2–NO_2) against gram positive bacteria respectively, and the remaining compounds were moderate to least active.

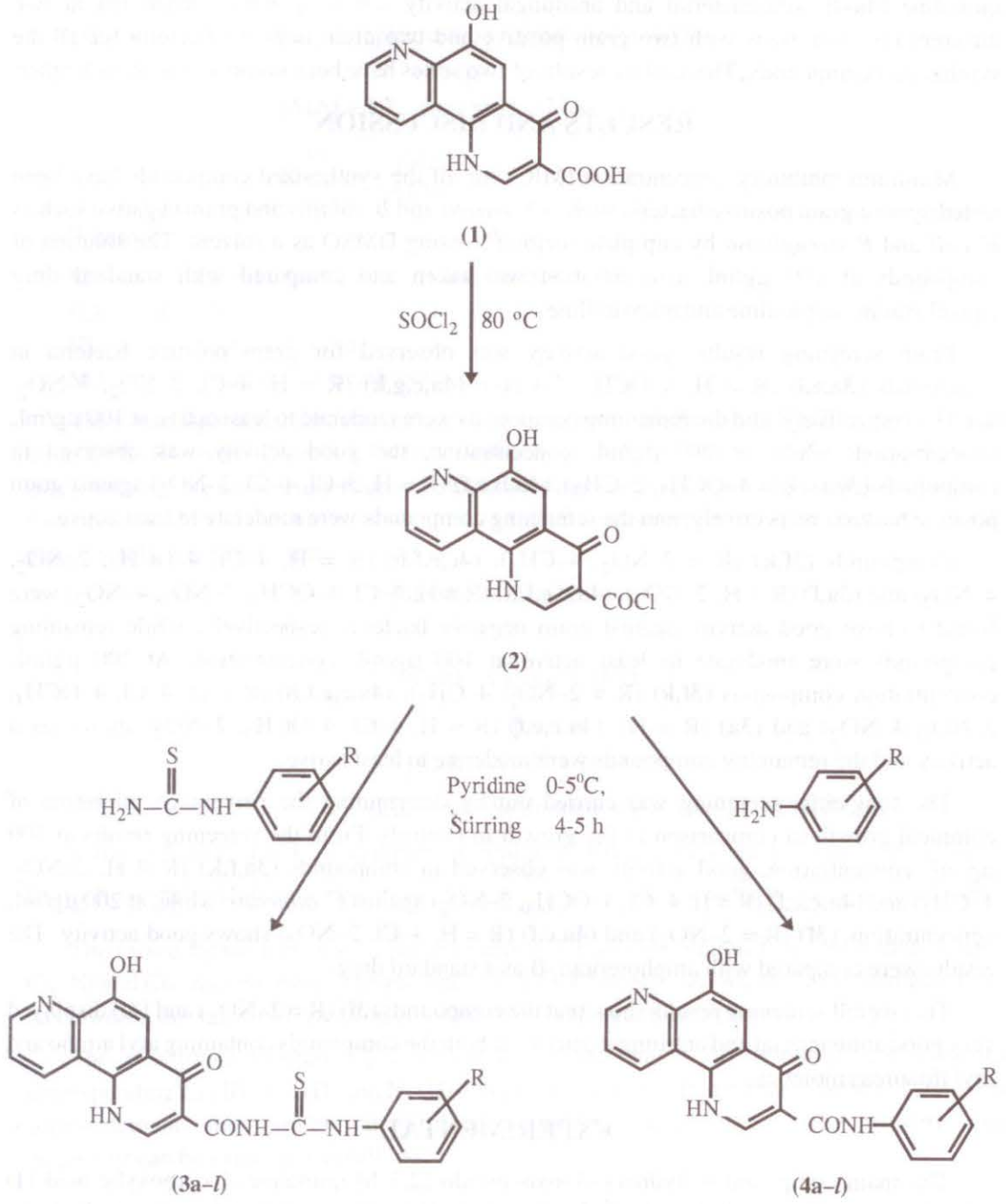
Compounds (**3f,k**) (R = 2–NO_2, 4–CH_3), (**4c,e,f,h**) (R = H, 4–Cl, 4–OCH_3, 2–NO_2, 4–NO_2) and (**3a,f**) (R = H, 2–NO_2), (**4a,c,e,f,h**) (R = H, 4–Cl, 4–OCH_3, 2–NO_2, 4–NO_2) were found to have good activity against gram negative bacteria, respectively, while remaining compounds were moderate to least active at 100 µg/mL concentration. At 200 µg/mL concentration compounds (**3f,k**) (R = 2–NO_2, 4–CH_3), (**4a,c,e,f,h**) (R = H, 4–Cl, 4–OCH_3, 2–NO_2, 4–NO_2) and (**3a**) (R = H), (**4a,c,e,f**) (R = H, 4–Cl, 4–OCH_3, 2–NO_2) shows good activity and the remaining compounds were moderate to least active.

The fungicidal screening was carried out by determining the percentage inhibition of colonical growth in comparison to the growth in controls. From the screening results at 100 µg/mL concentration, good activity was observed in compounds (**3a,f,k**) (R = H, 2–NO_2, 4–CH_3) and (**4a,c,e,f**) (R = H, 4–Cl, 4–OCH_3, 2–NO_2) against *C. albicans*, while, at 200 µg/mL concentration, (**3f**) (R = 2–NO_2) and (**4a,c,f**) (R = H, 4–Cl, 2–NO_2) shows good activity. The results were compared with amphotericin–B as a standard drug.

The overall screening results show that the compounds (**3f**) (R = 2–NO_2) and (**4f**) displayed very good antibacterial and antifungal activity in both the compounds containing aryl amino and aryl thioureas moieties.

EXPERIMENTAL

The main compound 6–hydroxy–4–oxo–pyrido [2,3–h] quinoline–3–carboxylic acid (**1**) was synthesized by reported method[8]. It was obtained by condensation of 5–amino–8–hydroxy


OH
N
O
HN
COOH
(1)
$SOCl_2$ 80 °C
OH
N
O
HN
COCl
(2)
S
H_2N—C—NH
R
Pyridine 0-5°C,
Stirring 4-5 h
H_2N
R
OH
N
O
HN
CONH—C—NH
S
R
(3a–l)
OH
N
O
HN
CONH
R
(4a–l)

quinoline with diethyl ethoxymethylene malonate (EMME), followed by cyclization and then acidic hydrolysis.

6–Hydroxy–4–oxo–pyridol[2,3–h] quinoline–3–carbonyl chloride (2)[9,10]

A mixture of 6–hydroxy–4–oxo–pyrido [2,3–h] quinoline–3–carboxylic acid (**1**) (1.28 g, 0.005 mole), 15 mL of thionyl chloride and 25 mL dry benzene was refluxed at 80°C about 4–5 h. The excess of thionyl chloride was removed by distillation with benzene. The obtained solid mass was 6–hydroxy–4–oxo–pyrido [2,3–h] quinoline–3–carbonyl chloride (**2**), which was directly used for the next step without further purification.

6–Hydroxy–4–oxo–pyrido [2,3–h]–3–[N–(p–methoxy phenylthiourido) carbonyl] quinoline (3e)[11,12]

A solution of compound (**2**) (1.37 g, 0.005 mole) in dry pyridine was added dropwise into a solution of p–methoxy phenyl thiourea (0.005 mole) in pyridine with constant stirring at 0–5°C and refluxed for 8 h. The whole content was poured into acidic crushed ice, the resultant solid mass was neutralized by $NaHCO_3$ (10%) solution. After neutralization, compound (**3e**) was precipitated, and washed with water. The purity of the compound was checked by TLC on silica gel plate using benzene : ethyl acetate. Yield 60%, m.p. 262°; IR (KBr): ν_{max} cm^{-1} : 1660 (amide–I); 1545 (amide–II); 1265 (amide–III); 1190 (C=S); 3400 (N–H); 1295 (C–N); 715 (N–H); 1680 (C=O); 3350 (–OH); 1225 (–OH); 1235 (C–O–C asym) and 1030 (C–O–C sym) ^1H NMR (DMSO) (0 ppm) 3.91 (3H, s, $-OCH_3$); 7.00–7.66 (4H, m, Ar–H); 7.9 (1H, q, C_5 H); 8.6 (1H, s, C_2 H); 8.8–10.1 (3H, m, pyrido); 9.20 (1H, s, –CONH–CS–); 9.65 (1H, s, –CSNH–Ar–) and 12.5 (1H, b, >NH).

6–Hydroxy–4–oxo–pyrido [2,3–h]–3–[N–(p–methoxy phenyl amino) carbonyl] quinoline (4e)[11,12]

A solution of compound (**2**) (1.37 g, 0.005 mole) in dry pyridine was added dropwise into a solution of p–methoxy aniline (0.005 mole) in pyridine with constant stirring at 0–5°C and refluxed for 8 h. The whole content was poured into acidic crushed ice; the resultant solid mass was neutralized by $NaHCO_3$ (10%) solution. After neutralization compound (**4e**) was precipitated, and washed with water. The purity of the compound was checked by TLC on silica gel plate using benzene : ethyl acetate. Yield 60%, m.p. 252°; IR (KBr): ν_{max} cm^{-1} : 1645 (amide–I); 1550 (amide–II); 1255 (amide–III); 3405 (N–H); 1280 (C–N); 710 (N–H); 1665 (C=O); 3320 (–OH); 1210 (–OH); 1230 (C–O–C asym); and 1020 (C–O–C sym); ^1H NMR (DMSO) (δ ppm); 3.91 (3H, s,$-OCH_3$); 7.00–7.66 (4H, m, Ar–H); 7.9 (1H, q, C_5 H); 8.6 (1H, s, C_2 H); 8.8–10.1 (3H,m, pyrido); 9.20 (1H, s, –CONH) and 12.5 (1H, b, >NH).

Table 1. Characterization data of 6–hydroxy–4–oxo–pyrido[2,3–h]–3–[N–(substituted phenyl thiourido/amino) carbonyl] quinoline (3a–*l*) and (4a–*l*)

No.	R	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analysis (%)			
					C		N	
					Calcd	Found	Calcd	Found
3a	H	$C_{20}H_{14}O_3N_4S$	284	65	61.53	61.45	14.35	14.28
3b	3–OH	$C_{20}H_{14}O_4N_4S$	270	60	59.11	59.05	13.79	13.76
3c	4–OH	$C_{20}H_{14}O_4N_4S$	290	58	59.11	59.07	13.79	13.71
3d	2–OCH_3	$C_{21}H_{16}O_4N_4S$	254	65	60.00	59.95	13.33	13.38
3e	4–OCH_3	$C_{21}H_{16}O_4N_4S$	262	60	60.00	59.94	13.33	13.27
3f	2–NO_2	$C_{20}H_{13}O_5N_5S$	284[d]	58	55.17	55.10	16.09	16.02
3g	3–NO_2	$C_{20}H_{13}O_5N_5S$	256	54	55.17	55.08	16.09	16.02
3h	4–NO_2	$C_{20}H_{13}O_5N_5S$	272	56	55.17	55.11	16.09	16.04
3i	2–CH_3	$C_{21}H_{16}O_3N_4S$	278	63	62.37	62.35	13.86	13.80
3j	3–CH_3	$C_{21}H_{16}O_3N_4S$	295	64	62.37	62.30	13.86	13.94
3k	4–CH_3	$C_{21}H_{16}O_3N_4S$	265	66	62.37	62.31	13.86	13.80
3l	3–Cl	$C_{20}H_{13}O_3N_4SCl$	285	65	56.53	56.47	13.19	13.12
4a	H	$C_{19}H_{13}O_3N_3$	274	62	68.88	68.81	12.68	12.61
4b	3–Cl	$C_{19}H_{12}O_3N_3Cl$	286	65	62.38	62.32	11.49	11.43
4c	4–Cl	$C_{19}H_{12}O_3N_3Cl$	262	55	62.38	62.33	11.49	11.40
4d	2–OCH_3	$C_{20}H_{15}O_4N_3$	296[d]	62	66.48	66.45	11.63	11.55
4e	4–OCH_3	$C_{20}H_{15}O_4N_3$	252	60	66.48	66.42	11.63	11.59
4f	2–NO_2	$C_{19}H_{12}O_5N_4$	240	54	60.63	60.55	14.89	14.85
4g	3–NO_2	$C_{19}H_{12}O_5N_4$	282	60	60.63	60.56	14.89	14.82
4h	4–NO_2	$C_{19}H_{12}O_5N_4$	254	65	60.63	60.55	14.89	14.82
4i	2–CH_3	$C_{20}H_{15}O_3N_3$	265	58	69.56	69.50	12.17	12.20
4j	3–CH_3	$C_{20}H_{15}O_3N_3$	285	55	69.56	69.48	12.17	12.13
4k	4–CH_3	$C_{20}H_{15}O_3N_3$	270	59	69.56	69.53	12.17	12.13
4l	2,5–di–CH_3	$C_{21}H_{17}O_3N_3$	292[d]	60	70.19	70.10	11.69	11.63

Table 2. Antimicrobial data of 6–hydroxy–4–oxo–pyrido [2,3–h]–3–[N–(substituted phenyl thiourido/amino) carbonyl] quinoline (3a–*l*) and (4a–*l*)

Code No.	Antibacterial activity (Zone of inhibition in mm.), 100/200 μg/mL				Antifungal activity (Zone of inhibition of mm.), 100/200 μg/mL
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
3a	10/12	9/11	8/11	10/14	5/7
3b	7/10	9/14	7/9	7/9	1/4
3c	7/10	10/14	8/11	6/10	1/3
3d	6/7	4/7	–/4	8/10	–/2
3e	10/14	9/12	9/13	8/11	3/6
3f	9/12	9/13	10/14	10/11	4/8
3g	6/10	8/10	5/9	5/9	2/5
3h	6/8	–/4	6/10	6/8	–/3
3i	10/14	9/11	8/10	8/10	3/7
3j	–/4	6/9	4/6	2/4	–/2
3k	7/10	10/14	10/14	8/11	4/7
3*l*	4/4	6/7	5/5	–/–	2/–
4a	10/15	12/16	11/15	10/14	5/8
4b	8/12	9/14	8/13	9/12	3/7
4c	11/15	11/15	12/16	11/15	5/9
4d	–/4	5/9	5/8	6/8	–/–
4e	10/16	9/11	10/16	11/16	4/7
4f	10/13	11/14	12/15	12/14	5/8
4g	8/14	10/13	9/13	8/13	3/6
4h	12/15	8/10	11/14	11/13	3/5
4i	6/13	9/12	–/10	4/10	–/3
4j	–/–	5/5	6/6	6/6	–/–
4k	7/9	11/13	8/9	7/8	2/3
4*l*	9/13	8/10	9/12	9/11	1/3
Standard drugs					
Ciprofloxacin					**Amphotericin–B**
	15/25	17/28	17/29	16/26	9/19
Ampicilline					
	15/28	17/30	18/30	18/31	
Amoxicilline					
	13/24	16/29	16/28	15/27	

Similarly all the compounds were prepared by same method using various substituted aryl thioureas and substituted aryl amines.

The characterization and activity data of final compounds (**3a–*l***) and (**4a–*l***) were described in Tables 1 and 2.

ACKNOWLEDGEMENT

The authors are thankful to the Head, Department of Chemistry and the Head, Bioscience Department, Veer Narmad South Gujarat University, Surat for laboratory and antibacterial screening. We also thank CDRI, Lucknow for elemental and ^{1}H NMR spectral analyses.

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Accepted : 22.11.04