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Synthesis of 3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-arylazetidin-2-ones and 3-(2-Chloro-1,8-naphthyridine-7-yl)-2-arylthiazolidin-4-ones From 2-Amino-7-chloro-1,8-naphthyridine

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2-Amino-7-chloro-1,8-napthyridine (**1**) undergoes condensation with different aromatic aldehydes to form 2-arylideneamino-7-chloro-1,8-naphthyridines (**2-6**). These imines when treated with different reagents varied substituted derivatives are produced. Compounds **2-6** are converted to different dyes (**7-11**) by diazotization. Azetidinones (**12-16**) are obtained by the reaction of **2-6** and chloroacetylchloride in presence of triethylamine. Finally the imines are converted to thiazolidinones (**17-21**) by treating compounds with thioglycolic acid.

Key Words: Synthesis, Arylazetidinone, Arylthiazolidinone.

INTRODUCTION

In recent years, research on derivatives of 1,8-naphthyridine has been intensive because these compounds show a wide range of biological activities[1-9]. Nalidixic acid, for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens[10]. Naphthyridine derivatives react with adenosine receptors of sub types A_1 and A_2A[11]. The major synthetic procedures to prepare 1,8-naphthyridines from 2-aminopyridine are by making it to react with β-ketoesters[12]. Keeping in mind the important properties of 1,8-naphthyridines, in continuation of our earlier work on substituted 1,8-naphthyridines[13-16], we have synthesized a series of some dyes[7-11], azitidinones[12-16] and thiazolidinones[17]. Compound (**1**) is prepared by Yudong method[17] and converted into different derivatives. Singh *et al.*[18] reported the synthesis of different thiazolidinones and azitidinones from aminopyridine and Singh *et al.*[19], from 2-amino-1,8-naphthyridine. In present communication, the synthesis of 3-(2-chloro-1,8-naphthyridine-7-yl)-2-arylthiazolidin-4-ones and 3-chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-arylazetidin-2-ones from 2-amino-7-chloro-1,8-naphthyridine are reported.

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EXPERIMENTAL

Melting points were measured in a sulphuric acid bath and are uncorrected. The IR spectra were recorded on Brucher-IFS-66 FTIR instrument. 300 MHz NMR spectra were recorded using tetramethyl silane as an instrumental standard in DMSO-d_6. Chemical shifts were expressed in ppm. The elemental analyses (C, H, N) of these synthesized compounds was carried out. The purity of the compounds was checked by TLC and spots were visualized in iodine vapour.

Typical procedure for synthesis of 2-arylideneamino-7-chloro-1,8-naphthyridines: To a solution of 2-amino7-chloro-1,8-naphthyridine (0.01 mol) in ethanol (60n mL), aldehyde (0.01 mol) and a few drops of glacial acetic acid were added and the mixture refluxed for 10 h. It was then cooled, concentrated and poured into crushed ice and filtered. The solid thus obtained was purified by recrystallization from ethanol.

N'-(7-Chloro-1,8-naphthyridin-2-yl)-N-(phenylimino)benzamidine: To a solution of aniline (0.01 mol) in glacial acetic acid (10 mL), conc. HCl (3 mL) was added at 0-5 ºC. Then a solution of sodium nitrite (1 g in 5 mL water) was mixed to the above solution. The diazonium salt solution thus prepared was added drop-wise to a solution of 2-arylideneamino-7-chloro-1,8-naphthyridines (0.01 mol) in methanol (40 mL) with constant stirring at 0 °C. The reaction mixture was kept at room temperature for 1 d and then poured into crushed ice. The resulting solid was filtered and dried.

N'-(2-Chloro-1,8-naphthyridin-7-yl)-N-(phenylimino)benzamidine (7): IR (ν_{max}, cm^{-1}): 3012 (C-H arom.), 1612 (C=N), 1192 (C-N), 672 (C-Cl): ^{1}H NMR (DMSO-d_6) 7.12-7.45 (m, 10H) 7.52 (d, 1H, *J* = 8.23 Hz), 7.75 (d, 1H, *J* = 8.23 Hz), 7.98 (d, 1H, *J* = 8.23 Hz) 8.21 (d, 1H, *J* = 8.23 Hz).

N'-(2-Chloro-1,8-naphthyridin-7-yl)-4-methoxy-N-(phenylimino)benzamidine (8): ^{1}H NMR (DMSO-d_6) 3.81 (S, 3H) 6.81 (d, 2H, *J* = 8.23 Hz), 7.20 (d, 2H, *J* = 8.23 Hz) 7.21-7.35 (m, 5H), 7.50 (d, 1H, *J* = 8.23 Hz), 7.74 (d, 1H, *J* = 8.23 Hz), 7.97 (d, 1H, *J* = 8.23 Hz), 8.20 (d, 1H, *J* = 8.23 Hz).

N'-(2-Chloro-1,8-naphthyridin-7-yl)-2-hydroxy-N-(phenylimino)benzamidine (9): ^{1}H NMR (DMSO-d_6) 6.81 (dd, 2H, *J* = 8.23 and 2.47 Hz), 7.21 (dd, 2H, *J* = 8.23, 2.47 Hz) 7.22-7.36 (m, 5H), 7.51 (d, 1H, *J* = 8.23 Hz), 7.75 (d, 1H, *J* = 8.23 Hz), 7.98 (d, 1H, *J* = 8.23 Hz), 8.21 (d, 1H, *J* = 8.23 Hz), 8.51 (brs, 1H).

N'-(2-Chloro-1,8-naphthyridin-7-yl)-4-hydroxy-N-(phenylimino)benzamidine (10): ^{1}H NMR (DMSO-d_6) 6.92 (d,2H), 7.12-7.35 (m, 7H), 7.52 (d, 1H, *J* = 8.23 Hz), 7.72 (d, 1H, J = 3.23 Hz), 7.96 (d, 1H, *J* = 8.23 Hz) 8.22 (d, 1H, *J* = 8.23 Hz).

N'-(2-Chloro-1,8-naphthyridin-7-yl)-3-hydroxy-4-methoxy-N-(phenylimino)benzamidine (11): ^{1}H NMR (DMSO-d_6) 3.78 (S, 3H), 6.81 (d, 1H, *J* = 8.23), 7.13-7.36 (m,7H) 7.51 (d, 1H, *J* = 8.23 Hz), 7.71 (d, 1H, *J* = 8.23 Hz), 7.95 (d, 1H, *J* = 8.23 Hz), 8.20 (d, 1H, *J* = 8.23 Hz) 8.48 (brs, 1H).

Synthesis of azetidin-2-ones: To a solution of 2-arylideneamino-7-chloro-1,8-naphthyridines (0.01 mol) in benzene (50 mL), chloroacetyl chloride (0.02 mol) and triethylamine (0.02 mol) were added drop-wise with constant stirring. The reaction mixture was then refluxed for 6 h and excess of benzene was distilled off. Resulting mixture was poured into crushed ice, filtered and the solid obtained was purified by recrystallization from ethanol.

3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-phenylazetidin-2-one (12): IR (ν_{max}, cm^{-1}): 3362 (N-H), 3038 (C-H arom.), 1742 (C=O), 1618 (C=N); ^{1}H NMR (DMSO-d_6) 5.28 (d, 1H, 4.94 Hz), 5.78 (d, 1H, 4.94 Hz) 7.12-7.21 (m, 5H), 7.51 (d, 1H, *J* = 8.23 Hz) 7.71 (d, 1H, *J* = 8.23 Hz), 7.95 (d, 1H, *J* = 8.23 Hz), 8.20 (d, 1H, *J* = 8.23 Hz).

3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-(4-methoxyphenyl)azetidin-2-one (13): ^{1}H NMR (DMSO-d_6) 3.78 (S, 8H), 5.24 (d, 1H, 4.94 Hz) 5.74 (d, 1H, 4.94), 6.81 (d, 2H, 7.98 Hz), 7.18 (d, 2H, 7.98 Hz), 7.50 (d, 1H, *J* = 8.23 Hz), 7.70 (d, 1H, *J* = 8.23 Hz), 7.95 (d, 1H, *J* = 8.23 Hz) 8.19 (d, 1H, *J* = 8.23 Hz).

3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-(2-hydroxyphenyl)azetidin-2-one (14): ^{1}H NMR (DMSO-d_6) 5.26 (d, 1H, 4.94 Hz), 5.76 (d, 1H, 4.94 Hz), 6.82 (dd 2H, *J* = 8.23, 2.47 Hz), 7.24 (dd, 2H, *J* = 8.23, 2.47 Hz), 7.52 (d 1h, *J* = 8.23, 2.47 Hz), 7.52 (d1, H, *J* = 8.23 Hz), 7.74 (d, 1H, *J* = 8.23 Hz), 7.96 (d1H, *J* = 8.23 Hz), 8.22 (d, 1H, *J* = 8.23 Hz), 8.61 (brs, 1H).

3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-(4-chlorophenyl)azetidin-2-one (15): ^{1}H NMR (DMSO-d_6); 5.25 (d, 1H, 4.94 Hz), 5.75 (d1H, 4.94 Hz), 6.91 (d, 2H 8.23 Hz), 7.22 (d, 2H *J* = 8.23 7.52 (d, 1H, *J* = 8.23 Hz), 7.73 (d, 1H, *J* = 8.23 Hz), 7.96 (d,1H, *J* = 8.23), 8.21 (d, 1H, *J* = 8.23 Hz).

3-Chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-(3-hydroxy-4-methoxyphenyl)azetidin-2-one (16): ^{1}H NMR (DMSO-d_6); 3.76 (S, 3H) 5.27 (d, 1H, 4.94 Hz), 5.74 (d, 1H, 4.94 Hz), 6.82 (d, 1H, *J* = 8.23 Hz), 7.18 (d, 1H, *J* = 8.23 Hz), 7.29 (S, 1H), 7.51 (d, 1H, *J* = 8.23 Hz), 7.72 (d, 1H, *J* = 8.23 Hz), 7.94 (d1H, *J* = 8.23 Hz), 8.21 (d, 1H, *J* = 8.23 Hz), 8.48 (brs, 1H).

Synthesis of thiozolidinones: To a solution of 2-arylideneamino-7-chloro-1,8-naphthyridines in absolute ethanol (60 mL) (0.01 mol) thioglycolic acid (0.01 mol) and anhydrous zinc chloride (2 g) were refluxed for 8 h, concentrated, cooled and poured into crushed ice and then filtered. The solid obtained was purified by recrystallization.

3-(2-Chloro-1,8-naphthyridin-7-yl)-2-phenylthiazolidin-4-one (17): IR (ν_{max}, cm^{-1}): 3031 (C-H arom.), 1682 (C=O), 1610 (C=N), 1174 (C-N), 682 (C-S-C); ^{1}H NMR (DMSO-d_6) 3.52 (dd, 2H, *J* = 18.94 Hz), 6.56 (S, 1H), 7.12-7.44 (m, 5H), 7.51 (d, 1H), *J* = 8.23 Hz 7.74 (d, 1H, 8.23 Hz), 7.96 (d, 1H, *J* = 8.23 Hz), 8.22 (d, 1H, 8.23 Hz).

3-(2-Chloro-1,8-naphthyridin-7-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (18): ^{1}H NMR (DMSO-d_6) 3.79 (S, 3H) 3.51 (dd, 2H, *J* = 18.94 Hz), 6.55 (S, 1H) 6.82 (d 2H, *J* = 8.23 Hz), 7.21 (d, 2H, *J* = 8.23 Hz), 7.52 (d, 1H, *J* = 8.23 Hz), 7.72 (d, 1H, J = 8.23 Hz), 7.98 (d, 1H, J = 8.23 Hz), 8.21 (d, 1H, J = 8.23 Hz).

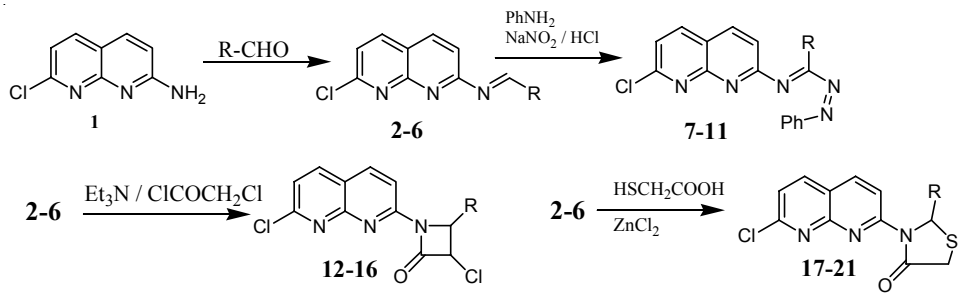
3-(2-Chloro-1,8-naphthyridin-7-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one (19): ^{1}H NMR (DMSO-d_6) 3.52 (dd, 2H, *J* = 18.94 Hz), 6.57 (S, 1H), 6.83 (d, 2H, *J* = 8.23 Hz; 2.47 Hz), 7.22 (d, 2H, *J* = 8.2 3 Hz), 7.52 (d, 1H, *J* = 8.23 Hz), 7.76 (d, 1H, *J* = 8.23 Hz), 7.96 (d, 1H, *J* = 8.23 Hz), 8.22 (d, 1H, *J* = 8.23 Hz) 8.51 (brs, 1H).

3-(2-Chloro-1,8-naphthyridin-7-yl)-2-(4-chlorophenyl)thiazolidin-4-one (20): ^{1}H NMR (DMSO-d_6) 3.33 (dd, 2H, *J* = 18.94 Hz), 6.53 (S, 1H), 6.93 (d, 2H, *J* = 8.23 Hz), 7.18 (d, 2H, *J* = 8.23 Hz), 7.54 (d, 1H, *J* = 8.2 3 Hz), 7.74 (d, 1H, *J* = 8.23 Hz), 7.94 (d, 1H, *J* = 8.23 Hz), 8.22 (d,1H, *J* = 8.23 Hz).

3-(2-Chloro-1,8-naphthyridin-7-yl)-2-(3-hydroxy-4-methoxyphenyl)-thiazolidin-4-one (21): ^{1}H NMR (DMSO-d_6) 3.35 (dd, 2H, *J* = 18.94 Hz), 3.78 (S, 3H), 6.54 (S, 1H), 6.83 (d, 2H, *J* = 8.23 Hz), 7.10 (d, 1H *J* = 8.23Hz), 7.29 (s, 1H), 7.53 (d, 2H, *J* = 8.23Hz), 7.74 (d, 1H, *J* = 8.2 3 Hz), 7.94 (d, 1H, *J* = 8.23 Hz), 8.22 (d, 1H, *J* = 8.23 Hz), 8.46 (brs, 1H).

RESULTS AND DISCUSSION

The synthetic pathway of compounds is shown in **Scheme-I**. 2-Amino-7-chloro-1,8-naphthyridine (**1**) is prepared from 2-aminopyridine and malic acid. Compound **1** was reacted with various aromatic aldehydes separately, resulted in the formation of arylideneimino-7-chloro-1,8-naphthyridines (**2-6**). Compounds **2-6** were treated with aniline and sodium nitrite in the presence of conc. HCl to yield formazans (**7-11**). Furthermore compounds **2-6** on cyclization with triethylamine/chloroacetyl chloride and thioglycolicacid gave 3-chloro-1-(2-chloro-1,8-naphthy-ridin-7-yl)-4-arylazetidin-2-ones (**12-16**) and 3-(2-chloro-1,8-naphthyridine-7-yl)-2-arylthiazolidin-4-ones (**17-21**), respectively. The analytical and physical data are presented in Table-1.



Scheme-I

The derivatives having methoxy as substituent were more toxic than simple hydroxy compound and chloro compound to all 6 bacteria mentioned in Table-2. Among all compounds, the dyes were slight more toxic than thiazolidinones and aziditazones. Thiazolidinones and azetidinones derivatives are also toxic towards all bacteria. The compounds which have methoxy substituent have shown versatile toxicity to all bacteria (Table-2).

TABLE-1
ANALYTICAL DATA OF 2,4-DIHYDROXY 1,8-NAPHTHYRIDINES

Compd.	R	m.f.	m.p. (ºC)	Yield (%)	Mass (M+1)
2	Phenyl	$C_{15}H_{10}N_3Cl$	220-223	66	267.06
3	*p*-Methoxyphenyl	$C_{16}H_{12}N_3OCl$	221-224	64	298.07
4	*o*-Hydoxy phenyl	$C_{15}H_{10}N_3OCl$	218-220	70	284.05
5	*p*-Chloro phenyl	$C_{15}H_9N_3Cl_2$	216-218	72	302.01
6	*m*-Hydroxy, *p*-Methoxy phenyl	$C_{16}H_{12}N_3O_2Cl$	222-225	69	314.06
7	Phenyl	$C_{21}H_{14}N_5Cl$	224-226	68	372.09
8	*p*-Methoxyphenyl	$C_{22}H_{16}N_5OCl$	221-223	72	402.10
9	*o*-Hydoxy phenyl	$C_{21}H_{14}N_5OCl$	220-223	70	388.09
10	*p*-Chloro phenyl	$C_{21}H_{13}N_5Cl_2$	222-225	75	406.05
11	*m*-Hydroxy, *p*-Methoxy phenyl	$C_{22}H_{16}N_5O_2Cl$	221-223	69	418.10
12	Phenyl	$C_{17}H_{11}N_3OCl_2$	217-219	65	344.19
13	*p*-Methoxyphenyl	$C_{18}H_{13}N_3O_2Cl_2$	218-221	82	374.04
14	*o*-Hydoxy phenyl	$C_{17}H_{11}N_3O_2Cl_2$	223-226	78	360.20
15	*p*-Chloro phenyl	$C_{17}H_{10}N_3OCl_3$	223-225	70	378.60
16	*m*-Hydroxy, *p*-Methoxy phenyl	$C_{18}H_{13}N_3O_3Cl_2$	224-226	68	390.00
17	Phenyl	$C_{17}H_{12}N_3OSCl$	218-221	65	342.00
18	*p*-Methoxyphenyl	$C_{18}H_{14}N_3O_2SCl$	220-223	76	372.00
19	*o*-Hydoxy phenyl	$C_{17}H_{12}N_3O_2SCl$	222-224	65	358.00
20	*p*-Chloro phenyl	$C_{17}H_{11}N_3OSCl_2$	221-224	66	376.30
21	*m*-Hydroxy, *p*-Methoxy phenyl	$C_{18}H_{14}N_3O_3SCl$	225-227	62	388.00

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS AGAINST
GRAM POSITIVE AND GRAM NEGATIVE BACTERIA

Compd.	SA	KP	BC	PN	SPA	SPB
7	4	3	7	1	1	2
8	19	15	12	17	9	8
9	10	11	8	9	5	4
10	18	15	11	15	7	9
11	20	17	12	16	8	9
12	9	6	18	1	-	1
13	10	9	10	5	-	1
14	5	4	6	5	1	2
15	8	7	7	6	1	1
16	12	11	13	7	2	3
17	6	4	1	1	1	2
18	10	9	8	4	3	2
19	8	5	2	3	1	2
20	10	8	6	4	2	3
21	12	11	15	9	2	4
Control (Methanol)	1	3	1	-	4	1

SA = *Staphylococcus aureus*; KP = *Klebsiella pneumoniae*; BC = *Bacillus cereus*;
PP = *Pseudomonas putida*; SPA = *Salmonella paratyphi* A; SPB = *Salmonella paratyphi* B;
Inhibition zone in mm (- indicates no inhibitory activity).

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