

MICROWAVE ASSISTED SYNTHESIS OF SOME 2,4 DIHYDROXY 1,8-NAPHTHYRIDINES AND THEIR DERIVATIVES DEVOID OF SOLVENT AND CATALYST

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Abstract: Reaction of substituted 2-aminopyridines with diethylmalonates yields 2,4-dihydroxy-1,8-Naphthyridenes(1-18). The 6-chloro-2,4-dihydroxy-1,8-naphthyridene (5) when treated with different reagents varied substituted derivatives are produced. 6-chloro-2, 4-dihydroxy-1,8-naphthyridene(5) when treated with sodium azide offered 2,4-dihydroxy-1,8-naphthyridene-6-thiones (19-21). 6-azido-1,8-naphthyridine-2,4-diols(22-24) were obtained by reacting 5 with sodiumazide. The 6-hydrazinyl-1,8-naphthyridine-2,4-diols (25-27) and 2,4,6-trihydroxy-1,8-naphthyridenes (28-30) were produced by the reaction of 5 with hydrazine hydrate and acetic acid respectively.

Keywords: Naphthyridines, Thiazolidinones, Azitidinones.

Introduction

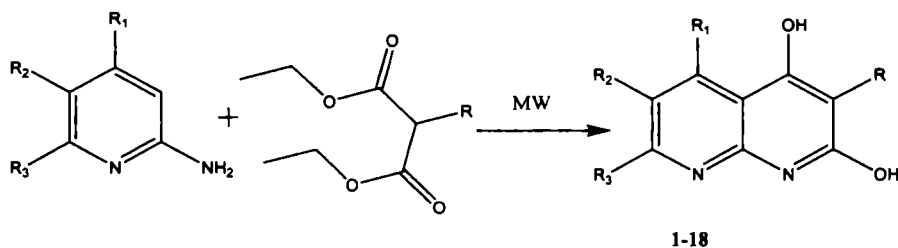
Naphthyridines attracted great attention of medical and synthetic chemists because of their versatile biological activity (1-6). Nalidixic acid, for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens (7). Naphthyridine derivatives react with adenosine receptors of sub types A₁ and A₂A (8). The major synthetic procedures to prepare 1,8-naphthyridenes from 2-aminopyridine with β -ketoesters (9). Keeping in mind the important properties of 1,8-naphthyridines, continuation of our earlier work on substituted 1,8-naphthyridines (10-14), we have synthesized a series of 2, 4-dihydroxy-1, 8-Naphthyridenes without using solvent and catalyst from 2-aminopyridine derivatives. The chloro group in 6-chloro-2,4-dihydroxy-1,8-naphthyridene(5) was investigated with various hetero nucleophiles of the various reagents available for the replacement of chlorine by Sulphur, Sodiamsulphide was found to be an efficient reagent affording nucleophilic substitution by sulphur and also providing scope for further reaction (15-19). In this paper we describe the synthesis and biological activity of some 1, 8-naphthyridene derivatives.

Results and Discussion

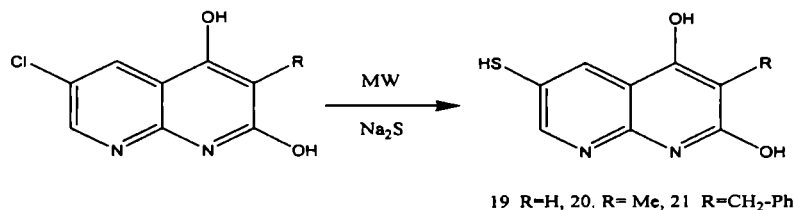
2-aminopyridine and diethylmalonate were irradiated in microwave oven at 400 watts to yield compound 1. The same procedure is extended to prepare compounds 2-18. The compound 5 is treated to give different compounds by the substitution of Cl group. In all cases the ¹HNMR spectra include characterization of naphthyridine ring system. The activity of compounds was determined using cup-plate agar diffusion method by measuring the inhibition zone in mm and the data is given in table 1. The characterization of the compounds is given in table 2.

Scheme 1

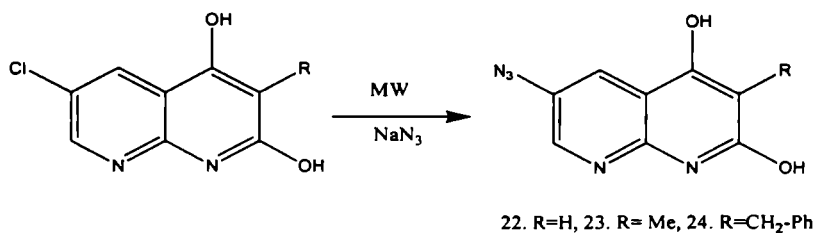
In conjunction with this work we report the synthesis of **1-18** by condensation of 2-aminopyridines and diethylmalonates in which compound **8** was identical in all aspects with an authentic sample previously prepared (**16**) by normal procedure. Here, we prepared no. of compounds by microwave reaction.

**Scheme 2**

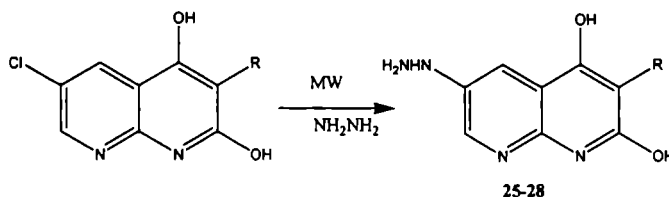
Preparation of **19-21** is followed by substitution of Cl group by SH group using sodiumsulphide in compound **5** by microwave reaction (**15**).

**Scheme 3**

In order to construct new derivative of naphthyridines **22, 23, 24** are obtained by the reaction of **5** and sodiumazide (**15**).

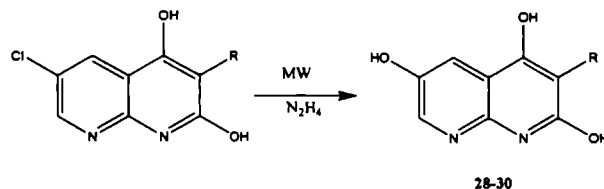
**Scheme 4**

The Cl group is next substituted by NH₂NH₂ group in compound **5** (**15**).



Scheme 5

Attention was next tuned to the substitution of Cl group by OH group in compound 5. The reaction was catalysed by acetic acid (15).

**Experimental Section**

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

General procedure for the preparation of 2,4-dihydroxy-1,8-naphthyridene derivatives (1-18) :

A mixture of 2-aminopyridine (9.0 m mole) and diethylmelonate (10 m mole) were ground well in a mortar to get homogeneous mixture. This mixture was irradiated in micro wave oven at 400 watts for 3-4 min. The reaction mixture was taken out, cooled and digested with water. The products were recrystallised from ethanol.

Formation of 2,4-dihydroxy-4,8-naphthyridene-6-thiones : (19-21)

Compound '5' (1 mole), sodium sulphide(1.5 m moles) were ground well to get lime powder and irradiated in microwave oven at 400 watts for 2 minutes. The reaction mixture was taken in to cold water and acidified with acetic acid. The solid obtained was filtered.

6-mercapto-1,8-naphthyridine-2,4-diol (19) IR: 3308.211 cm^{-1} (OH), 1620.723 cm^{-1} (C=N), 682.321 cm^{-1} (C-S); ^1H NMR (DMSO- d_6) 7.31 (S, 1H), 7.62 (S, 1H), 7.91 (S, 1H) 8.52 (brs, 2H), 11.82 (S, 1H).

6-mercapto-3-methyl-1,8-naphthyridine-2,4-diol (20) ^1H NMR (DMSO- d_6) 2.31 (S, 1H), 7.61 (S, 1H), 7.92 (S, 1H) 8.45 (brs, 2H), 11.78 (S, 1H).

3-benzyl-6-mercapto-1,8-naphthyridine-2,4-diol (21) ^1H NMR (DMSO- d_6) 4.24 (dd, 2H, J=12.08 Hz), 7.18-7.35 (M, 5H), 7.61 (S, 1H) 7.93 (S, 1H), 8.47 (brs, 2H) 11.77 (S, 1H).

Formation of 6-azido-1,8-naphthyridine-2,4-diols : (22-24)

Compound 5 (0.01mmole) a pinch of PTSA and sodium azide (0.01mmol) were taken in to a beaker and ground well to get powder. The contents are irradiated in micro oven at 400 watts for 3-4 min. The reaction mixture was washed with water and the solid obtained is purified by recrystallisation.

6-azido-1,8-naphthyridine-2,4-diol (22) IR: 3018.122 cm^{-1} (C-H aromatic), 2122.231 cm^{-1} (N_3), 1616.412 cm^{-1} (C=N); $^1\text{HNMR}$ (DMSO-d_6) 7.32 (s, 1H), 7.85 (s, 1H) 8.30 (s, 1H), 8.55 (brs, 2H).

6-azido-3-methyl-1,8-naphthyridine-2,4-diol (23) $^1\text{HNMR}$ (DMSO-d_6) 2.312 (s, 3H), 7.84 (s, 1H) 8.28 (s, 1H), 8.48 (brs, 2H).

6-azido-3-benzyl-1,8-naphthyridine-2,4-diol (24) $^1\text{HNMR}$ (DMSO-d_6) 4.12 (dd, 2H, $J = 12.08$ Hz), 7.15-7.31 (m, 5H) 7.85 (s, 1H), 8.29 (s, 1H), 8.45 (brs, 2H).

Formation of 6-hydrazinyl-1,8-naphthyridine-2,4-diols (25-27)

To a solution of **5** (0.01mmol) and hydrazine hydrate(0.01mmole) and a pinch of sodium acetate are intimately mixed and irradiated in MW oven for 3-4 min. products obtained were washed with cold water and purified by recrystallisation.

6-hydrazinyl-1,8-naphthyridine-2,4-diol (25) IR: 3458.148 cm^{-1} (N-H), 3022.241 cm^{-1} (C-H aromatic), 1616.422 cm^{-1} (C=N); $^1\text{HNMR}$ (DMSO-d_6) 4.41 (brs, 3H), 7.28 (s, 1H), 7.58 (s, 1H), 8.21 (s, 1H) 8.32 (brs, 2H).

6-hydrazinyl-3-methyl-1,8-naphthyridine-2,4-diol (26) $^1\text{HNMR}$ (DMSO-d_6) 2.31 (s, 3H), 3.82 (brs, 3H), 7.29 (s, 1H), 8.22 (s, 1H) 8.38 (brs, 2H).

3-benzyl-6-hydrazinyl-1,8-naphthyridine-2,4-diol (27) $^1\text{HNMR}$ (DMSO-d_6) 3.75 (brs, 3H), 4.28 (dd, 2H, $J = 12.08$ Hz) 7.11-7.28 (m, 5H), 7.30 (s, 1H), 8.25 (s, 1H) 8.40 (brs, 2H).

Synthesis of 2,4,6-trihydroxy-1,8-naphthyridene (28-30)

Compound '**5**' (1m mole) and in 70% acetic and (10 ml) was heated under reflux for 4-6 hrs. The completion of reaction was checked by TLC upon cooling the reaction mixture a solid product precipitated out, which was filtered washed well with water.

1,8-naphthyridine-2,4,6-triol (28)) IR: 3310.235 cm^{-1} (O-H), 1618.124 cm^{-1} (C=N); $^1\text{HNMR}$ (DMSO-d_6) 7.28 (s, 1H), 7.62 (s, 1H), 7.98 (s, 1H) 8.30 (brs, 3H)

3-methyl-1,8-naphthyridine-2,4,6-triol (29) $^1\text{HNMR}$ (DMSO-d_6) 2.31 (s, 3H), 7.63 (s, 1H), 7.99 (s, 1H), 8.32 (brs, 3H)

3-benzyl-1,8-naphthyridine-2,4,6-triol (30) $^1\text{HNMR}$ (DMSO-d_6) 4.12 (dd, 2H, 12.08 Hz), 7.62 (s, 1H), 7.98 (s, 1H), 8.38 (brs, 3H), 7.12 – 7.32 (m, 5H).

Table 1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS AGAINST GRAM +VE
AND GRAM -VE BACTERIA

S.No.	Compound	<i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i>	<i>Bacillus cereus</i>	<i>Pseudomonas putida</i>	<i>Salmonella paratyphi A</i>	<i>Salmonella paratyphi B</i>
1.	1	1	3	1	-	4	1
2.	5	4	3	2	2	2	6
3.	11	5	3	2	1	2	6
4.	17	6	3	1	1	2	6
5.	19	6	5	3	6	2	-
6.	20	6	4	4	6	2	1
7.	21	7	5	5	6	1	2
8.	22	1.5	-	9	2	3	-
9.	23	2	-	9	3	4	-
10.	24	4	2	10	3	5	1
11.	25	9	2	1	5	5	1
12.	26	10	3	1	5	4	2
13.	27	12	4	2	7	7	1
14.	28	5	-	6	5	3	-
15.	29	5	1	7	7	4	1
16.	30	7	1	9	9	5	2

INHIBITION ZONE IN MM (- indicates no inhibitory activity)

Control inhibition zone (which indicates inhibition zone of solvent) was subtracted from inhibition zone of compounds which gives actual inhibition zone of compounds

1. *Staphylococcus aureus* – coccus ,gram +ve,causes toxic shock syndrome(TSS).
2. *Klebsiella pneumoniae* –rod shape or bacilli,gram-ve,causes pneumonia
3. *Bacillus cereus* – rod ,gram +ve,causes food borne diseases
4. *Pseudomonas putida* – rod,gram –ve
5. *Salmonella paratyphi A* – rod,gram-ve,causes typhoid
6. *Salmonella paratyphi B* – rod,gram –ve,causes typhoid

Perusal of the above table reveals that the derivatives having chlorine as substituent is more toxic than simple dihydroxy compound to all six bacteria. Among the chloro group compounds, the compound which has methyl group and benzyl group slight more toxic than 5-chloro, 2,4-dihydroxy 1,8-Naphthyridine. Azido substituent has shown toxicity to bacteria except *Salmonella paratyphi B* and *Klebsiella pneumoniae*. Thio and hydroxyl substituted derivatives are also more toxic towards all bacteria. The compounds which have hydrazine substituent have shown versatile toxicity to all bacteria.

Table 2
Characterization table of 2,4-Dihydroxy 1,8 – Naphthyridines

Comnd	R	R ₁	R ₂	R ₃	M.Formula	M.P °C	Mass (M+1)
1.	H	H	H	H	C ₈ H ₆ N ₂ O	268-270	163
2.	H	H	H	Me	C ₈ H ₇ N ₃ O	>300	177
3.	H	H	H	NH ₂	C ₉ H ₈ N ₂ O	278-280	178
4.	H	H	Me	H	C ₉ H ₈ N ₂ O	265-268	177
5.	H	H	Cl	H	C ₉ H ₈ N ₂ O	267-270	197
6.	H	Me	H	H	C ₈ H ₅ ClN ₂ O	270-272	177
7.	Me	H	H	H	C ₉ H ₈ N ₂ O ₂	270-272	177
8.	Me	H	H	Me	C ₁₀ H ₁₀ N ₂ O ₂	>300	191
9.	Me	H	H	NH ₂	C ₉ H ₇ N ₂ O ₂ Cl	>300	192
10.	Me	H	Me	H	C ₁₀ H ₁₀ N ₂ O ₂	>300	191
11.	Me	H	Cl	H	C ₁₅ H ₁₂ N ₂ O ₂	290-292	211
12.	Me	Me	H	H	C ₁₆ H ₁₄ N ₂ O ₂	>300	191
13.	CH ₂ Ph	H	H	H	C ₁₅ H ₁₃ N ₃ O ₂	260-263	253
14.	CH ₂ Ph	H	H	Me	C ₁₆ H ₁₄ N ₂ O ₂	267-270	268
15.	CH ₂ Ph	H	H	NH ₂	C ₁₆ H ₁₁ N ₂ O ₂ Cl	258-262	269
16.	CH ₂ Ph	H	Me	H	C ₁₆ H ₁₄ N ₂ O ₂	266-268	268
17.	CH ₂ Ph	H	Cl	H	C ₆ H ₁₁ N ₂ O ₂ Cl	272-274	289.5
18.	CH ₂ Ph	Me	H	H	C ₁₆ H ₁₄ N ₂ O ₂	266-268	2.68
19.	H	-	-	-	C ₈ H ₆ N ₂ O ₂ S	256-258	195
20.	Me	-	-	-	C ₉ H ₈ N ₂ O ₂ S	260-262	209
21.	CH ₂ Ph	-	-	-	C ₁₅ H ₁₂ N ₂ O ₂ S	261-263	285
22.	H	-	-	-	C ₈ H ₅ N ₃ O ₂	258-260	204
23.	Me	-	-	-	C ₉ H ₇ N ₃ O ₂	262-264	218.5
24.	CH ₂ Ph	-	-	-	C ₁₅ H ₁₄ N ₅ O ₂	262-264	294.1
25.	H	-	-	-	C ₈ H ₈ N ₄ O ₂	256-258	193.2
26.	Me	-	-	-	C ₉ H ₁₀ N ₄ O ₂	258-260	207.1
27.	CH ₂ Ph	-	-	-	C ₁₅ H ₁₄ N ₄ O ₂	254-256	283.3
28.	H	-	-	-	C ₈ H ₆ N ₂ O ₃	264-268	179.1
29.	Me	-	-	-	C ₉ H ₈ N ₂ O ₃	268-271	193.2
30.	CH ₂ Ph	-	-	-	C ₁₅ H ₁₁ N ₂ O ₃	269-272	269.1

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