ELSEVIER

Il Farmaco 57 (2002) 631–639

IL FARMACO

www.elsevier.com/locate/farmac

Synthesis of variously substituted 1,8-naphthyridine derivatives and evaluation of their antimycobacterial activity

Muwaffag Badawneh [a], Clementina Manera [b,*], Claudio Mori [b], Giuseppe Saccomanni [b], Pier Luigi Ferrarini [b]

[a] *Philadelphia University, PO Box 1101, Sweileh, Jordan*
[b] *Dipartimento di Scienze Farmaceutiche, Universitá di Pisa, via Bonanno 6, 56126 Pisa, Italy*

Received 13 October 2001; accepted 18 February 2002

Abstract

A series of 1,8-naphthyridine derivatives variously substituted in the 2, 3, 4 and 7 positions were synthesized for in vitro evaluation of antimycobacterial activity in accordance with an international program with the tuberculosis antimicrobial acquisition and coordinating facility (TAACF). Several compounds **4**, **8**, **12**, **14**, **19**, **29** and **30**, when tested at a concentration of 6.25 μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$, showed an interesting activity with % inhibition in the range 38–96%. The most effective substituent in position 2, 4 or 7 of the 1,8-naphthyridine nucleus seem to be the piperidinyl group.

Keywords: Tuberculostatic agents; 1,8-Naphthyridines; Morpholinyl; Piperazinyl; Piperidinyl

1. Introduction

Tuberculosis today can be considered one of the major problems for public health worldwide. In the last few years an unexpected return of this disease has taken place [1]. The World Health Organization has estimated that every year about eight million new cases of tuberculosis occur and about three million individuals die of this disease. This infection is present both in developing countries, where it is endemic, and in industrialized countries. Today the drugs used in the therapy of tuberculosis are still isoniazid, pyrazinamide, ethambutol, rifampin and streptomycin, generally used in combination [2]. However, the protracted use in time of these molecules represents the main cause of the outbreak of new resistant strains. For this reason, in the last few years, the search for new antitubercular agents has become very important. Among a large amount of molecules tested for this purpose the heterocyles benzofurane [3], benzothiazole [4,5], benzoisothiazole [6], benzimidazole [7–10], benzotriazole [11], triazolothiadiazole [12], isothiazolopyridines [13], quinoline [14–17], quinazoline [18–24] and quinoxaline [25].

In collaboration with an international program with the tuberculosis antimicrobial acquisition and coordinating facility (TAACF) we initiated a program of synthesis and antiinfective screening of a series of 1,8-naphthyridine derivatives structurally correlated to quinoline and phenyl-substituted quinazoline derivatives which possess tuberculostatic activity [14,15,18–20].

In a previous paper [26], we reported the preparation and the antimycobacterial activity of some 4-phenyl-1,8-naphthyridine derivatives variously substituted in positions 2 and 7 tested in vitro at a concentration of 12.5 μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$. Some of these compounds showed a marked activity with an inhibition $> 50\%$.

In this paper we describe the synthesis and biological results of some 1,8-naphthyridine derivatives substituted in positions 2, 3, 4 and 7 with some of the substituents present in the previous series [26] and with new substituents.

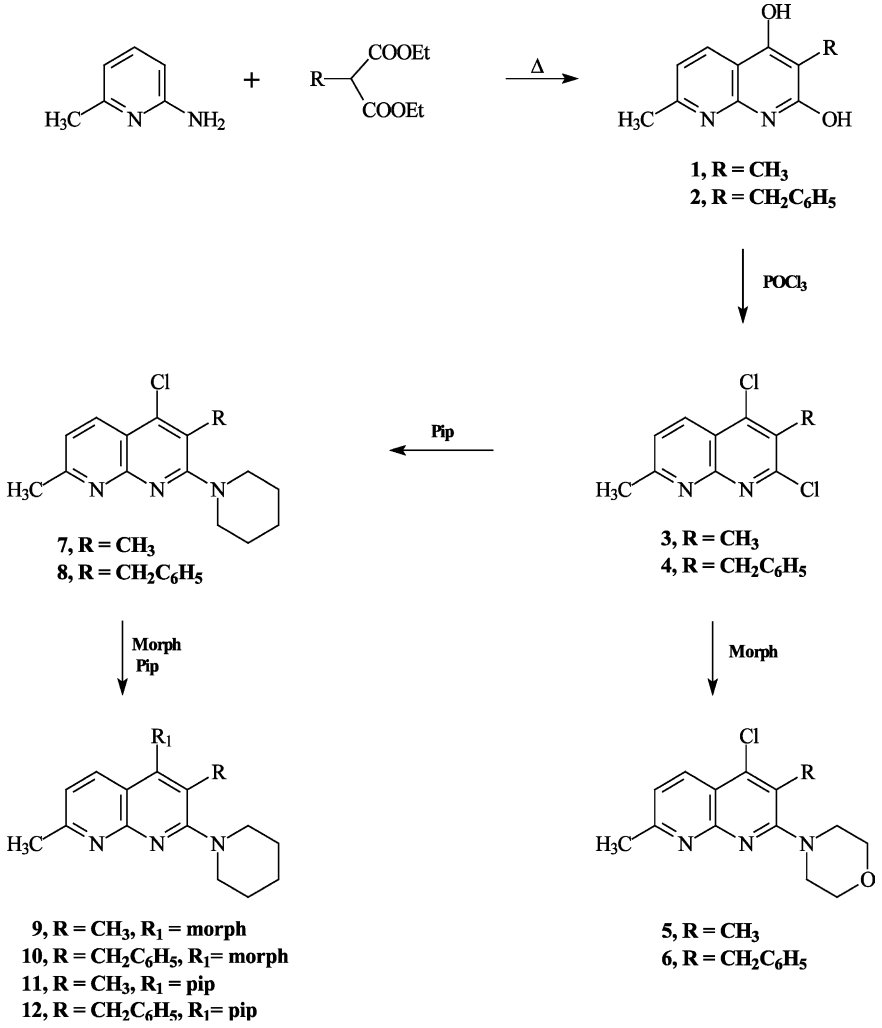
* Corresponding author
E-mail address: manera@farm.unipi.it (C. Manera).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01235-1

2. Chemistry

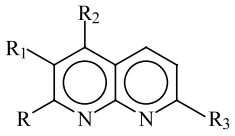
The 3-methyl- and 3-benzyl-2,4-dihydroxy-7-methyl-1,8-naphthyridines (**1** and **2**) were obtained from 2-amino-6-methylpyridine and diethyl methylmalonate or diethyl benzylmalonate, respectively by reflux in Dowtherm A. The reaction of **1** and **2** with phosphoryl chloride afforded the dichloro derivatives **3** and **4** which were allowed to react with morpholine or piperidine in toluene under reflux to give the corresponding 2-mono-substituted derivatives **5**, **6** and **7**, **8**, respectively because of the high reactivity of the chloro group in the 2 position [27]. When the 4-chloro derivatives **7** and **8** were treated with morpholine or piperidine in a sealed tube at 160 °C, the 2-piperidino-4-substituted derivatives **9**, **10** and **11**, **12**, respectively were obtained (Scheme 1, Tables 1 and 2).

The reaction of the 4-chloro-7-hydroxy-2-morpholino-1,8-naphthyridine (**13**) [27] with phosphoryl chloride afforded the dichloro derivative **14**, which by treatment with morpholine or piperidine in toluene at reflux afforded the corresponding derivatives **15** and **16** (Scheme 2, Tables 1 and 2). These compounds were allowed to react with morpholine or piperidine in a sealed tube at 160 °C to give the 4-substituted derivatives **17**–**19**. Under these conditions the 4-chloro derivative **13** was converted into the 4-morpholino and 4-piperidino derivatives **20** and **21**, respectively, which afforded the corresponding 2-chloro derivatives **22** and **23** by reaction with phosphoryl chloride. The 2-morpholino derivative **24** was obtained from **22** in analogous conditions, as reported above for compounds **16** (Scheme 2, Tables 1 and 2). The reaction of the 7-acetamido-2,4-dichloro-1,8-naphthyridine (**25**) [27] with morpholine or piperidine in toluene at reflux afforded the corresponding derivatives **26** and **27**, which by acid hydrolysis gave the 7-amino derivatives **28** [27] and **29**, respectively (Scheme 3, Tables 1 and 2). The 4-chloro derivative **29** was converted into the 4-piperidino derivative **30** by reaction with piperidine in a



Scheme 1. Synthetic route to variously substituted 3,7-dimethyl- and 3-benzyl-7-methyl-1,8-naphthyridine derivatives. Morph, morpholin-1-yl; Pip, piperidin-1-yl.

Table 1
Physical data of 1,8-napthyridine derivatives



Comp.	R	R_1	R_2	R_3	Crystallization solvent	M.p. (°C)	Yield (%)	Mass m/z	
								(M^+)	(Base)
1	OH	CH_3	OH	CH_3	EtOH	>300	53	190	190
2	OH	$C_6H_5CH_2$	OH	CH_3	EtOH	267–270	43	268	266
3	Cl	CH_3	Cl	CH_3	EtOH–H_2O	205–207	81	266	266
4	Cl	$C_6H_5CH_2$	Cl	CH_3	EtOH–H_2O	115–118	84	302	231
5	Morph	CH_3	Cl	CH_3	Petr. Ether 100–140°	128–131	88	277	157
6	Morph	$C_6H_5CH_2$	Cl	CH_3	Petr. Ether 100–140°	115–118	76	353	231
7	Pip	CH_3	Cl	CH_3	EtOH–H_2O	108–110	88	275	157
8	Pip	$C_6H_5CH_2$	Cl	CH_3	EtOH–H_2O	95–98	98	351	160
9	Pip	CH_3	Morph	CH_3	Toluene [a]	145–147	70	326	158
10	Pip	$C_6H_5CH_2$	Morph	CH_3	Toluene [a]	102–105	70	326	158
11	Pip	CH_3	Pip	CH_3	a	(oil)	10	324	241
12	Pip	$C_6H_5CH_2$	Pip	CH_3	Toluene [a]	118–120	10	400	316
14	Morph	H	Cl	Cl	EtOH–H_2O	200–205	66	283	163
15	Morph	H	Cl	Morph	Toluene	260–262	98	334	277
16	Morph	H	Cl	Pip	Benzene–Petr. Ether 40–60°	155–157	86	332	249
17	Morph	H	Morph	Morph	Toluene	250–253	84	385	328
18	Morph	H	Morph	Pip	Petr. Ether 100–140°	172–175	46	383	326
19	Morph	H	Pip	Pip	Petr. Ether 100–140°	197–200	49	381	41
20	Morph	H	Morph	OH	Petr. Ether 100–140°	268–270	34	316	316
21	Morph	H	Pip	OH	Toluene	247–250	50	314	314
22	Morph	H	Morph	Cl	Petr. Ether 100–140°	208–210	78	334	277
23	Morph	H	Pip	Cl	Petr. Ether 100–140°	145–148	85	332	275
24	Morph	H	Pip	Morph	Toluene	205–208	95	383	326
26	Morph	H	Cl	NHAc	Toluene	250–253	79	306	144
27	Pip	H	Cl	NHAc	Toluene	215–218	84	304	144
29	Pip	H	Cl	NH_2	Toluene	230–235	81	262	144
30	Pip	H	Pip	NH_2	Toluene	262–265	96	311	228
31	Morph	H	Morph	NH_2	Toluene	272–275	67	315	258
32	Morph	H	Pip	NH_2	Toluene	251–253	52	313	256
34	OH	C_6H_5	H	Cep	Toluene	224–226	77	378	250
35	OH	C_6H_5	H	Pipz	Benzene	235–237	82	306	250

Morph = Morpholinyl, Pip = Piperidinyl, Pipz = Piperazinyl, Cep = N–ethoxycarbonylpiperazinyl.
[a] Previously purified by flash chromatography [AcOEt–Petr. Ether (2:1)].

sealed tube at 160 °C. In analogous conditions compound **28**, by reaction with morpholine or piperidine, gave the 4-substituted derivatives **31** and **32** (Scheme 3, Tables 1 and 2).

Starting from the 7-hydroxy-2-chloro-3-phenyl-1,8-naphthyridine (**33**) [28] by treatment with *N*-ethoxycarbonylpiperazin in a sealed tube at 160 °C was obtained the corresponding derivatives **34** which by alkaline hydrolysis gave the 7-piperazinyl derivative **35** (Scheme 4, Tables 1 and 2).

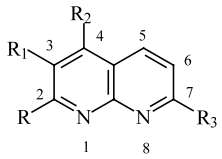
3. Pharmacology

All described compounds were tested in vitro for their antitubercular activity at the GWl Hansen's Disease Center (Colorado State University) within the TAACF screening program for the discovery of novel drugs for treatment of tuberculosis. The purpose of the screening program is to provide a resource whereby new experimental compounds can be tested for their capacity to inhibit the growth of *M. tuberculosis* $H_{37}Rv$ according to the method described by Collins and Franzblau [29].

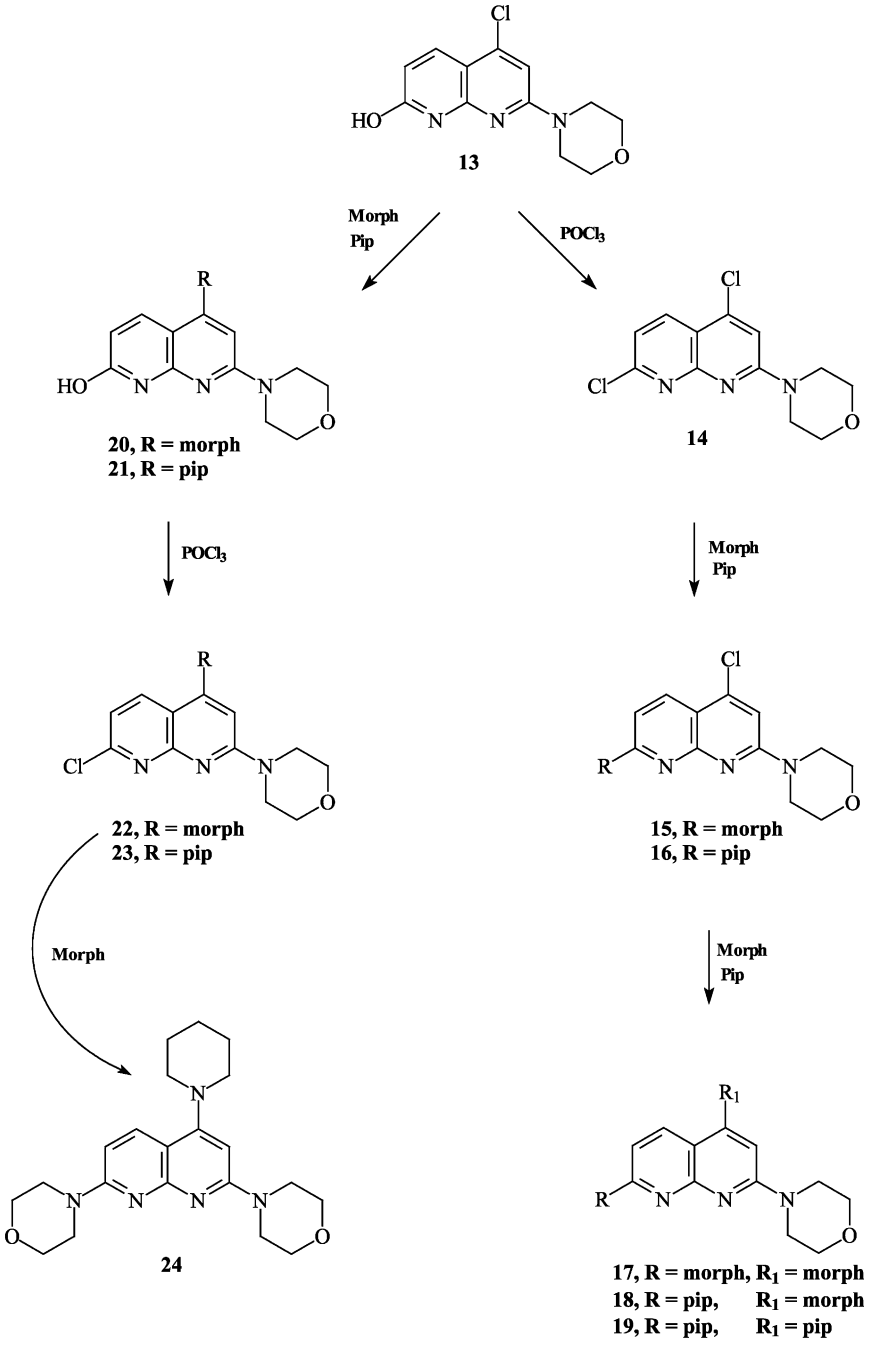
4. Results and discussion

Results of the in vitro evaluation of antitubercular activity of the tested compounds are reported in Table

Table 2
^{1}H-NMR chemical shifts (δ ppm/TMS)



Comp.	H_3 (s)	H_5 (d)	H_6 (d)	 (m)	(m)	Others	Solv.
1	---	8.07	7.03	----	----	1.97 (s, 3-CH_3); 2.49 (s, 7-CH_3); 11.30 (brs, OH)	DMSO
2	---	8.16	7.09	----	----	2.50 (s, 7-CH_3); 3.89 (s, CH_2); 7.21 (m, Ph); 11.63 (brs, OH); 10.59 (brs, OH)	DMSO
3	---	8.44	7.65	----	----	2.61 (s, 3-CH_3); 2.71 (s, 7-CH_3)	DMSO
4	---	8.50	7.66	----	----	2.73 (s, 7-CH_3); 4.45 (s, CH_2) ; 7.21 (m, Ph)	DMSO
5	---	8.26	7.34	----	3.79 ; 3.33	2.44 (s, 3-CH_3); 2.63 (s, 7-CH_3)	DMSO
6	---	8.30	7.40	----	3.69 ; 3.18	2.66 (s, 7-CH_3); 4.31 (s, CH_2) ; 7.16 (m, Ph)	DMSO
7	---	8.22	7.32	3.17 ; 1.66	----	2.41 (s, 3-CH_3); 2.62 (s, 7-CH_3)	DMSO
8	---	8.26	7.35	3.20 ; 1.64	----	2.63 (s, 7-CH_3); 4.28 (s, CH_2); 7.18 (m, Ph)	DMSO
9	---	8.18	7.05	3.25 ; 1.68	3.90 ; 3.30	2.33 (s, 3-CH_3); 2.69 (s, 7-CH_3)	$CDCl_3$
10	---	8.17	6.88	3.26 ; 1.58	3.54 ; 2.89	2.58 (s, 7-CH_3); 4.13 (s, CH_2); 7.10 (m, Ph)	$CDCl_3$
11	---	8.13	7.01	3.24 ; 1.69	----	2.28 (s, 3-CH_3); 2.68 (s, 7-CH_3)	$CDCl_3$
12	---	8.06	6.85	3.30 ; 1.55	----	2.69 (s, 7-CH_3); 4.13 (s, CH_2); 7.08 (m, Ph)	$CDCl_3$
14	7.02	8.17	7.17	----	3.79	----	$CDCl_3$
15	6.71	8.10	6.65	----	3.78	----	$CDCl_3$
16	6.63	7.95	6.70	3.74 ; 1.67	3.74	----	$CDCl_3$
17	6.09	7.85	6.56	----	3.75 ; 3.10	----	DMSO
18	6.05	7.78	6.59	3.75 ; 1.65	3.90 ; 3.10	----	$CDCl_3$
19	6.03	7.78	6.58	3.75 ; 1.64	3.72 ; 3.07	----	$CDCl_3$
20	5.93	7.65	6.29	----	3.88 ; 3.08	9.30 (brs, OH)	$CDCl_3$
21	5.90	7.61	6.28	3.60 ; 1.71	3.75 ; 3.03	9.25 (brs, OH)	$CDCl_3$
22	6.05	7.85	7.08	----	3.79 ; 3.10	----	$CDCl_3$
23	6.27	7.96	7.03	3.78 ; 1.74	3.78 ; 3.03	----	$CDCl_3$
24	6.06	7.85	6.56	3.76 ; 1.78	3.76 ; 3.05	----	$CDCl_3$
26	6.88	8.24	8.10	----	3.72	2.21 (s, CH_3); 9.40 (brs, AcNH)	$CDCl_3$
27	7.32	8.20	8.01	3.71 ; 1.61	----	2.10 (s, CH_3); 10.84 (brs, AcNH)	DMSO
29	7.10	8.05	6.70	3.72 ; 1.55	----	4.90 (brs, NH_2)	DMSO
30	6.13	7.63	6.33	3.58 ; 2.92 ; 1.58	----	4.85 (brs, NH_2)	DMSO
31	6.11	7.81	6.73	----	3.91 ; 3.09	4.81 (brs, NH_2)	DMSO
32	6.16	7.68	6.40	3.36 ; 1.64	3.62 ; 3.01	6.31 (brs, NH_2)	DMSO
34	----	7.84	6.76	----	3.67	1.21 (t, CH_3); 4.09 (q, CH_2); 7.34 (m, Ph); 7.72 (m, Ph); 7.92 (s, H_4); 11.76 (brs, OH)	DMSO
35	---	7.80	6.72	----	3.60 ; 2.76	7.34 (m, Ph); 7.78 (m, Ph); 7.89 (s, H_4); 11.60 (brs, OH)	DMSO



Scheme 2. Synthetic route to variously substituted 2-(morpholin-1-yl)-1,8-naphthyridine derivatives. Morph, morpholin-1-yl; Pip, piperidin-1-yl.

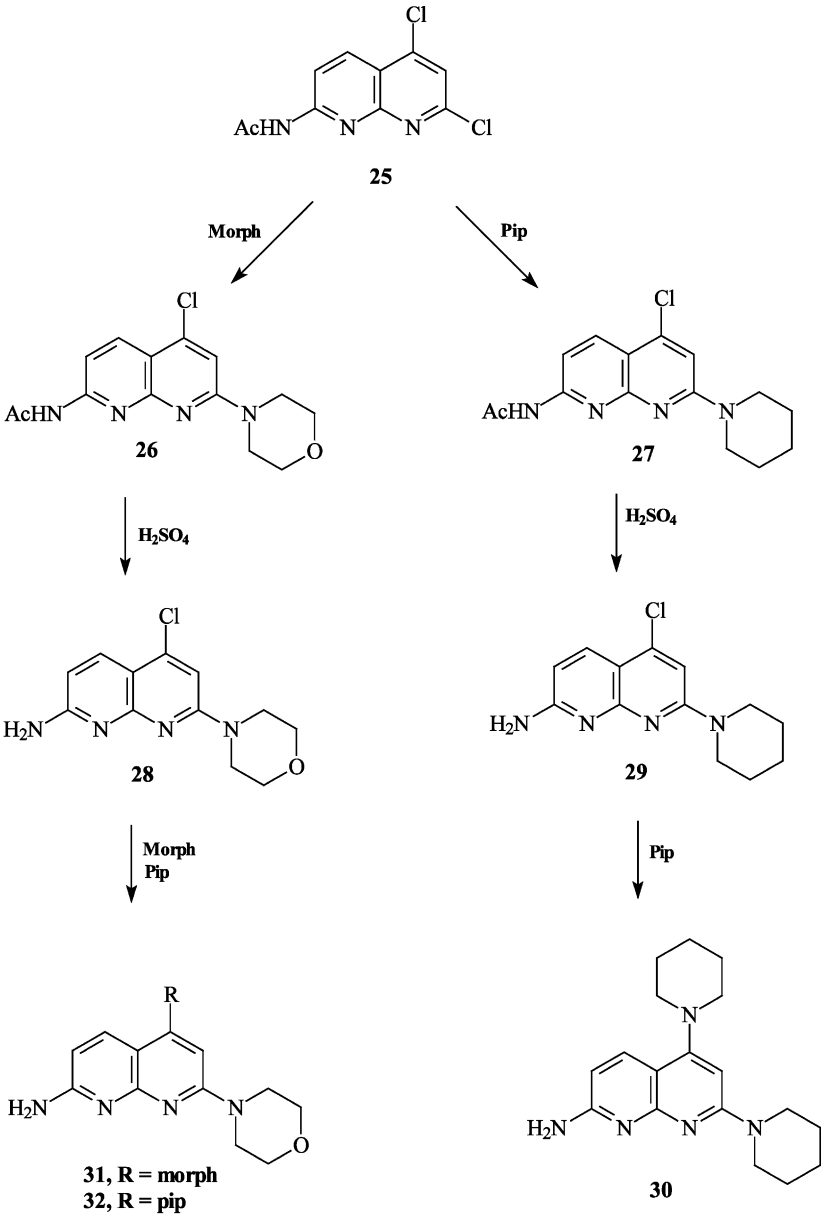
3 and they show an interesting activity for several compounds. Compounds **4**, **8**, **12**, **14**, **19**, **29** and **30** exhibited a growth inhibition against *M. tuberculosis* $H_{37}Rv$ at a concentration of 6.25 μg/ml in the range 38–96%. These data were compared with those of rifampicin, as reference drug, that showed an inhibition activity of 98% at a concentration of 0.25 μg/ml.

In spite of the restricted number of compounds tested in this study, some preliminary consideration of structure–activity relationships can be put forward.

Before all, the biological results indicate that 1,8-naphthyridine derivatives reported in this study exhibited a greater antimycobacterial activity than that of 4-phenyl-naphthyridine derivatives tested at concentration of 12.5 μg/ml [26].

From analysis of biological results reported in Table 3, the 3-benzyl derivatives **4**, **6**, **8** and **10** are more active than the corresponding 3-methyl derivatives **3**, **5**, **7** and **9**, consequently it can be deduced that the benzyl group in the position 3 of the heterocyclic ring seem to be more effective than the methyl group in the same position.

Furthermore, the comparison of compounds **6** (20%) versus **8** (41%), **10** (20%) versus **12** (96%), **19** (43%)



Scheme 3. Synthetic route to variously substituted 7-acetamido- and 7-amino-1,8-naphthyridine derivatives. Morph, morpholin-1-yl; Pip, piperidin-1-yl.

versus **24** (11%) and **30** (72%) versus **31** (0%) and **32** (6%) clearly indicate that the morpholino group either in the position 2, 4 or 7 of the heterocyclic ring cause a decrease of activity.

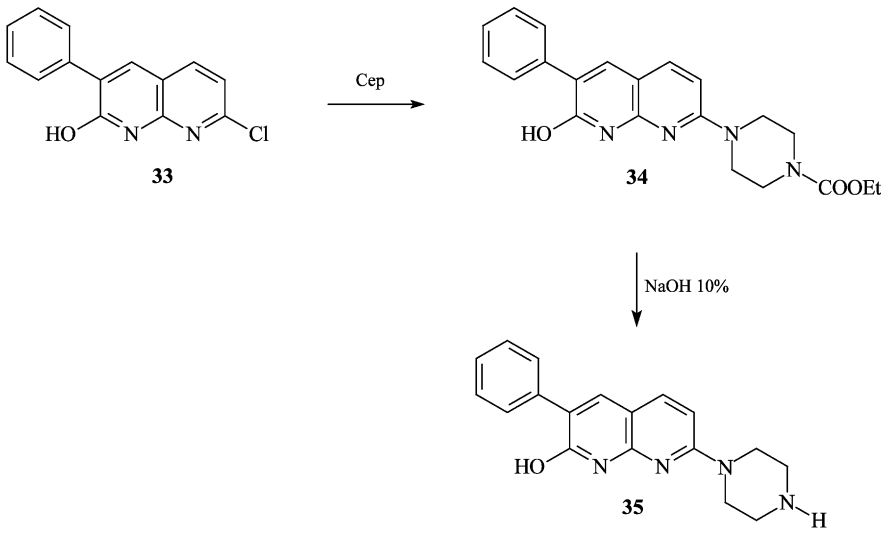
When a hydroxy group was introduced into position 2, 4 or 7 of the 1,8-naphthyridine nucleus, inactive compounds (**1**, **2**, **13**, **20** and **21**) were obtained, as also reported in a previous paper for the analogous 4-phenyl derivatives [26].

The influence of the amino group, in position 7 of the heterocyclic ring on the antimycobacterial activity is not clear at this time; in fact the 7-amino derivative **29** and **30** showed an inhibition activity of 38 and 72%, respectively, whereas the 7-amino derivatives, **31** and **32** possessed a very poor activity. More probably the inactivity of these last compounds is due to the presence of the morpholinyl group on the heterocyclic ring.

However, on the basis of the biological results, it is interesting to point out that the most effective substituent in the positions 2, 4 or 7 of the 1,8-naphthyridine nucleus seem to be the piperidinyl group.

Furthermore, the above data of biological activity and those previous reported [26] seem to show that a balance between both lipophilic and electronegative effects is necessary to determine an appreciable antimycobacterial activity.

In the light of the above results we can conclude that



Scheme 4. Synthetic route to substituted 2-hydroxy-3-phenyl-1,8-naphthyridine derivatives. Cep, *N*-ethoxycarbonylpiperazin-1-yl; Pipz, piperazin-1-yl.

the 1,8-naphthyridine ring appears to be a useful substrate for antitubercular agents.

5. Experimental

5.1. Chemistry

All compounds were routinely checked for their structure by IR and ^{1}H NMR spectroscopy. M.p.s were determined on a Köfler hot-stage apparatus and are uncorrected. The IR spectra were measured with a Genesis Series FTIR ATI Mattson. The ^{1}H NMR spectra were determined in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard, on a Varian CFT-20 NMR spectrometer. Analytical TLC was carried out on Merck 0.2 mm precoated silica gel glass plates (60 F-254) and location of spots was detected by illumination with a UV lamp. Elemental analyses of all compounds synthesized for C, H and N were within $\pm 0.4\%$ of theoretical values and were performed by our analytical laboratory.

5.1.1. General procedure for the preparation of 2,4-dihydroxy-1,8-naphthyridine derivatives **1** and **2**

A mixture of 2-amino-6-methylpyridine (9.0 mmol) and diethyl benzylmalonate or diethyl methylmalonate (10.0 mmol) in 10 ml of Dowtherm A was refluxed for 15 min. The solution was allowed to rest at r.t. and after 24 h the precipitate formed was collected by filtration and washed with petroleum ether to obtain the title compounds (Tables 1 and 2).

5.1.2. General procedure for the preparation of mono- and dichloro-1,8-naphthyridine derivatives **3**, **4**, **14**, **22** and **23**

A mixture of 5 mmol of the appropriate hydroxy-1,8-naphthyridine **1**, **2**, **13** [27], **20** or **21** $POCl_3$ (10 ml for **13**, **20** and **21** or 15 ml for **1** and **2**) was heated at 90 °C for 40 min. After cooling, the solution obtained was treated with ice and water and then alkalinized with concd. NH_4OH (pH $\cong$ 8). The solid was collected by filtration, washed with water and purified by crystallization to give the title compounds (Tables 1 and 2).

5.1.3. General procedure for the preparation of (morpholin-1-yl)-**5**, **6**, **15**, **24** and **26** and (piperidin-1-yl)-**7**, **8**, **16** and **27**-1,8-naphthyridine derivatives.

A mixture of 2 mmol of appropriate chloro-1,8-naphthyridine **3**, **4**, **14**, **23** or **25** and 5 mmol of morpholine or piperidine in 20 ml of $C_6H_5CH_3$ was refluxed for 6 h. The solvent was evaporated to dryness in vacuo and the residue was treated with water, filtered and purified by crystallization to give the title compounds. Only the compound **26** was purified by flash chromatography (Tables 1 and 2).

5.1.4. 7-Amino-4-chloro-2-(morpholin-1-yl) (**28**) [27] and 7-amino-4-chloro-2-(piperidin-1-yl)-1,8-naphthyridine (**29**)

A solution of 5.0 mmol of the 7-acetamido-4-chloro-1,8-naphthyridine **26** or **27** in 20 ml of 10% H_2SO_4 was refluxed for 2 h and then, after cooling, the pH was adjusted to 9 with concd. NH_4OH. The solid was separated by filtration and purified by crystallization (Tables 1 and 2).

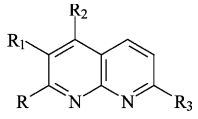
*5.1.5. General procedure for the preparation of (morpholin-1-yl)- **9**, **10**, **17**, **18**, **20** and **31**, (piperidin-1-yl)- **11**, **12**, **19**, **21**, **30** and **32** and (N-ethoxycarbonylpiperazin-1-yl)- **34** -1,8-naphthyridine derivatives*

A mixture of 5 mmol of appropriate 4-chloro-1,8-naphthyridine (**7**, **8**, **13**, **15**, **16**, **28**, **29**) or 7-hydroxy-2-chloro-3-phenyl-1,8-naphthyridine (**33**) and 20 mmol of appropriate amine was kept for 16 h in a sealed tube, at 160 °C. After cooling, the crude residue was treated with water and the solid obtained was collected by filtration, washed with water, and purified by crystallization or by flash chromatography (Tables 1 and 2).

*5.1.6. 2-methoxy-3-phenyl-7-(piperazin-1-yl)-1,8-naphthyridine (**35**)*

A solution of 1 mmol of the 7-carbethoxypiperazinyl derivative **34** in 25 ml of EtOH and 25 ml of 10% aq. NaOH was refluxed for 16 h and then concentrated in vacuo to a small volume. The pH of the solution was adjusted to 8–9 with 10% HCl and the solution was extracted twice with $CHCl_3$: the combined extracts were dried (magnesium sulfate) and evaporated to dryness in vacuo to obtain the piperazin-1-yl derivative **35**, which was purified by crystallization (Tables 1 and 2).

Table 3
Antimycobacterial in vitro activity of the tested compounds expressed as % inhibition of *M. tuberculosis* $H_{37}Rv$ at a concentration of 6.25 μg/ml



Comp.	R	R_1	R_2	R_3	% Inhibition
1	OH	CH_3	OH	CH_3	0
2	OH	$C_6H_5CH_2$	OH	CH_3	0
3	Cl	CH_3	Cl	CH_3	1
4	Cl	$C_6H_5CH_2$	Cl	CH_3	55
5	Morph	CH_3	Cl	CH_3	0
6	Morph	$C_6H_5CH_2$	Cl	CH_3	20
7	Pip	CH_3	Cl	CH_3	17
8	Pip	$C_6H_5CH_2$	Cl	CH_3	41
9	Pip	CH_3	Morph	CH_3	11
10	Pip	$C_6H_5CH_2$	Morph	CH_3	20
12	Pip	$C_6H_5CH_2$	Pip	CH_3	96
13 [27]	Morph	H	Cl	OH	2
14	Morph	H	Cl	Cl	38
15	Morph	H	Cl	Morph	0
16	Morph	H	Cl	Pip	27
17	Morph	H	Morph	Morph	11
18	Morph	H	Morph	Pip	0
19	Morph	H	Pip	Pip	43
20	Morph	H	Morph	OH	9
21	Morph	H	Pip	OH	0
22	Morph	H	Morph	Cl	1
23	Morph	H	Pip	Cl	8
24	Morph	H	Pip	Morph	11
27	Pip	H	Cl	AcNH	8
29	Pip	H	Cl	NH_2	38
30	Pip	H	Pip	NH_2	72
31	Morph	H	Morph	NH_2	0
32	Morph	H	Pip	NH_2	6
34	OH	C_6H_5	H	Cep	16
35	OH	C_6H_5	H	Pipz	11
RMP					98

5.2. Pharmacology

Primary screening was conducted at 6.25 μg/ml against the virulent strain *M. tuberculosis* $H_{37}Rv$ *M. tuberculosis* was grown in BACTEC 12B medium containing radiolabelled substrate [29]. Labelled CO_2 produced was detected and quantified by the automatic BACTEC 460-radiometric system. Compounds effecting $\leq 96\%$ inhibition in the primary screening (MIC > 6.25 μg/ml) were not evaluated further. The standard compound used in this primary assay was rifampicin (MIC = 0.25 μg/ml).

Acknowledgements

The in vitro evaluation of the antituberculosis activity was carried out in the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) at the National Institute of Allergy and Infectious Disease, Southern Research Institute, GWL Hansen's Disease Center and Colorado State University, USA; we thank J.A. Maddry, Ph.D. for his collaboration.

References

[1] N.E. Billo, Global aspects of tuberculosis, in: P.R.J. Gangadharam, P.A. Jenkins (Eds.), Mycobacteria II Chemotherapy, Chapman & Hall, New York, 1998, pp. 1–14.
[2] N. Lounis, B. Ji, C. Truffot-Pernot, J. Grosset, Which aminoglycoside or fluoroquinolone is more active against Mycobacterium tuberculosis in mice, Antimicrob. Agents Chemother. 41 (1997) 607–610.
[3] A.N. Grinev, V.M. Lyubchanskaya, G.Y. Uretskaya, T.F. Vlasova, G.N. Pershin, N.S. Bogdanova, I.S. Nikolaeva, V.V. Peters, T.A. Guskova, Synthesis and study of the biological activity of aminomethyl derivatives of 4-hydroxybenzofuran, Khim-Farm. Zh. 11 (1977) 78–81 (Chem. Abstr. 87 (1977) 68053w).
[4] K. Waisser, J. Kunes, Z. Odlerova, Antitubeculotics. Part LIX. Correlation of structural parameters with antituberculotic activity in a group of 2-benzamidobenzothiazoles, Collect. Czech. Chem. Commun. 56 (1991) 2978–2985.
[5] E. Sidoova, Z. Odlerova, K Waisser, 6-Cinnamylideneamino-2-*n*-hexylthiobenzothiazole and its preparation as an antimycobacterial, Czech. CS 275, p. 212, (Chem. Abstr. 119 (1993) 271151y).
[6] G. Ambrosoli, M.P. Ciuti, M.G. Menozzi, M.R. Mingiardi, Attivitá antitubercolare di benzisotiazolin-3-tioni e di 3-iminobenzo-1,2-ditioli, Boll. Chim. Farm. 109 (1970) 251–258.
[7] B. Milczararska, J. Sawlewicz, J.W. Manowska, Reactions of cyanomethylbenzimidazoles. Part III. Reaction of cyanomethylbenzimidazoles with isocyanates and isothiocyanates, Pol. J.

Pharmacol. Pharm. 28 (1976) 521–528 (Chem. Abstr. 87 (1977) 5865s).
[8] L. Bukowski, Synthesis and some reactions of 2-cyanomethylimidazol[4,5-*b*]pyridine. Tuberculostatic investigations of obtained compounds, Pol. J. Pharmacol. Pharm. 38 (1986) 91–98 (Chem. Abstr. 106 (1987) 176258m).
[9] P.R. Kagthara, N.S. Shah, R.K. Doshi, H.H. Parekh, Synthesis of some arylamides, sulfonamides and 5-oxoimidazolones as novel bioactive compounds derived from benzimidazole, Heterocycl. Commun. 4 (1998) 561–566.
[10] S.V. Kokitkar, N.P. Shetgiri, Synthesis, spectral studies and biological activity of 4′-oxothiazolidinyl benzimidazoles, J. Chem. Res., Synop. 7 (2000) 336–338.
[11] P. Sanna, A. Carta, M.E.R. Nikookar, Synthesis and antitubercular activity of 3-aryl substituted-2-1H(2H9-benzotriazol-1(2)-yl)acrylonitriles, Eur. J. Med. Chem. 35 (2000) 535–543.
[12] R.H. Udupi, P. Purushottmachar, A.R. Bhat, Studies on antitubercular agents: synthesis of 4-pyridoyl-3-substituted-1,2,4-triazolo[3,4-*b*[1,3,4]thiadiazolidines, Indian J. Heterocycl. Chem. 9 (2000) 287–290.
[13] W. Malinka, M. Sieklucka-Dziuba, G. Rajtar, W. Zgodzinski, Z. Kleinrok, Synthesis and preliminary screening of derivatives of -(4-arylpiperazin-1-yalkyl-3-oxoisothiazolo[5,4-*b*]pyridines as CNS and antimycobacterial agents, Pharmazie 55 (2000) 416–425 (Chem. Abstr. 133 (2000) 222643).
[14] T. Haruaki, S. Katsumasa, S. Hajime, I. Yoshifumi, Antimicobacterial activity of a newly synthesized fluoroquinolone, Y-26611, Kekkaku 67 (1992) 515–520 (Chem. Abstr. 119 (1993) 266305x).
[15] P.K. Desai, P. Desai, D. Machhi, C.M. Desai, D. Patel, Quinoline derivatives as antitubercular/antibacterial agents, Indian J. Chem., Sect. B 35 (1996) 871–873 (Chem. Abstr. 125 (1996) 221530).
[16] B.Y. Zhao, R. Pine, J. Domagala, K. Drlica, Fluroquinolone action against clinical isolates of Mycobacterium tuberculosis: effects of a C-8-methoxyl group on survival in liquid media and in human macrophages, Antimicrob. Agents Chemother. 43 (1999) 661–666 (Chem. Abstr. 130 (1999) 322845).
[17] S.P. Oza, A.K. Parikh, A.r. Parikh, 5-Imidazolinone: 4-arylidene-1-(*N*-methyl-2′(1*H*)-quinolon-4′-ylthioacetamido)-2-phenyl-5-oxoimidazolines, J. Inst. Chem. 71 (1999) 54–55 (Chem. Abstr. 132 (2000) 265150).
[18] P.B. Trivedi, N.K. Undavia, M.A. Dave, K.N. Bhatt, N.C. Desai, Synthesis and antimicrobial activity of some heterocyclic compounds, Indian J. Chem., Sect. B 32 (1993) 497–500 (Chem. Abstr. 119 (1993) 49341b).
[19] B.B.R. Shah, J.J. Bhatt, H.H. Patel, N.K. Undavia, P.B. Trivedi, N.C. Desai, Synthesis of 2,3-disubstituted-3,1-quinazolin-4(4*H*)-ones as potential anticancer and anti-HIV agents, Indian J. Chem., Sect. B 34 (1995) 201–208 (Chem. Abstr. 123 (1995) 33013t).
[20] M. Khalifa, S. El-Basil, K.M. Youssef, Synthesis of some quinazolone derivatives with tuberculostatic activity, Zagazig J. Pharm. Sci. 4 (1995) 287–293 (Chem. Abstr. 124 (1996) 86925).
[21] R.H. Udupi, B. Ramesh, A.R. Bhat, Synthesis and biological activity of some quinazolinone derivatives, Indian J. Hetrocycl. Chem. 8 (1999) 301–304 (Chem. Abstr. 131 (1999) 271850).
[22] P.Y. Shirodkar, M.M. Vartak, Synthesis biological and qsar evaluation of Mannich bases of 6-nitro-quinazolones, Indian J. Hetrocycl. Chem. 9 (2000) 239–240 (Chem. Abstr. 133 (2000) 135284).
[23] A.R. Bhat, G. Shenoy, K. Mohan, Synthesis and biological activities of Mannich bases of 7-nitro-2-methyl-4(3*H*)-quinazolinone, Indian J. Hetrocycl. Chem. 9 (2000) 319–320 (Chem. Abstr. 134 (2001) 271850).
[24] K. Waisser, H. Dostal, L. Kubicova, K. Kolar, Antituberculous derivatives of quinazoline, Ceska. Slov. Farm. 49 (2000) 113–118 (Chem. Abstr. 132 (2000) 342690).
[25] J. Kunes, M. Spulak, K. Waisser, M. Slosarek, J. Janota, Quinaxoline derivatives as potential antituberculotic agents, Pharmazie 55 (2000) 858–859 (Chem. Abstr. 134 (2001) 128391).
[26] P.L. Ferrarini, C. Manera, C. Mori, M. Badawneh, G. Saccomanni, Synthesis and evaluation of antimycobacterial activity of 4-phenyl-1,8-naphthyridine derivatives, II Farmaco 53 (1998) 741–746.
[27] P.L. Ferrarini, C. Mori, M. Badawneh, C. Manera, A. Martinelli, M. Miceli, F. Romagnoli, G. Saccomanni, Unusual nitration of substituted 7-amino-1,8-napthyridine in the synthesis of compounds with antiplatelet activity, J. Heterocycl. Chem. 34 (1997) 1501–1510.
[28] S. Carboni, A. Da Settimo, P.L. Ferrarini, P.L. Ciantelli, Investigation of some tetrazole derivatives of 1,8-Naphthiridines, J. Heterocycl. Chem. 7 (1970) 1037–1043.
[29] L.A. Collins, S.G. Franzblau, Microplate alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium, Antimicrob. Agents Chemother. 42 (1997) 1004–1009.