RESEARCH ARTICLE

Synthesis of 1,8-Napthyridine derivatives and their evaluation as possible antiepileptic agents

Brijeshkunvar J Mishra*

Technocrats Institute of Technology- Pharmacy, Anand Nagar, Bhopal, Madhya Pradesh, India.

Received March 2017; Accepted April 2017

* Corresponding Author

Email: bjmishra08@gmail.com

ABSTRACT

Aminopropyloxy derivatives of 1,8-naphthyridines have been synthesized using the principle of Conrad-Limpach synthesis of quinolines. The hydroxy group at 2- position of the naphthyridine ring was converted to the corresponding epoxypropane ether derivative by etherification with epichlorhydrin. The epoxy ether was then aminated in presence of KOH with the corresponding amines to obtain the aminopropyloxy derivatives. The compounds were tested for anti convulsant action at dose of 150mg/Kg relative to diazepam (5mg/Kg) by prevention of PTZ-induced seizures in mice.

Keywords: Naphthyridine, anticonvulsant, Pentylenetetrazole, tonic clonic, aminopropyloxy

Introduction

Epilepsy has not received much attention for research in the past despite of its fatal effects. Although the disease is not having a higher potential as a fatal disease but the lack of any permanent treatment for the disease prompted to synthesize drugs that could be used for the treatment of the disease. Epilepsy, a ubiquitous disease characterized by recurrent seizures, inflicts more than sixty million people worldwide according to epidemiological studies. The majority of the anti epileptic drugs are in use since two decades and do not provide adequate control of the seizures in all patients. 1,8-naphthyridine derivatives have been reported to possess a variety of biological activities such as antibacterial (Bouzard et al., 1992), antimycobacterial (Ferrarini et al., 1998), antitumor (Zhang et al., 1999), anti-inflammatory (Takeshi et al., 1992), antiplatelet (Ferrarini et al., 2001), antisecretory (Scotese et al., 1987), antiallergic (Kuo et al., 1988), local anesthetic (Ferrarini et al., 1990) and benzodiazepine receptor activity (Settimo et al., 1994). Aryloxyaminopropanes are also reported to possess CNS depressant (Agrawal et al., 1990) and neuroleptic (Sur et al., 1980) activity. The hypothesis was to incorporate both 1,8-naphthyridine and aryloxyaminopropane moieties in a single molecule would increase the lipophilic property of the compounds and increase their ability to permeate through the blood-brain barrier thereby probably enhancing their anticonvulsant activity.

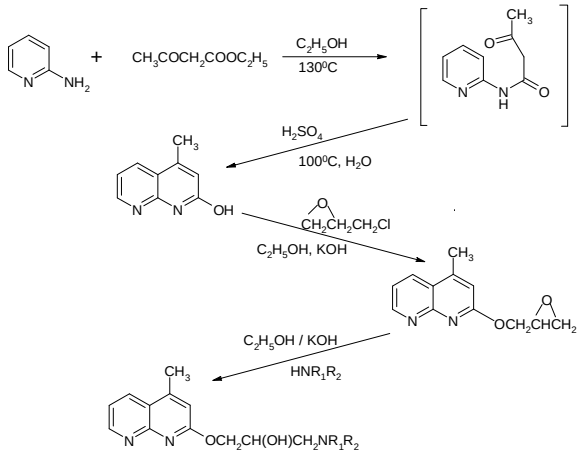
Materials and Methods

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr discs in Jasco FT-IR 470 plus spectrophotometer. ^{1}H NMR data has been recorded on a Bruker WM (300 MHz) NMR spectrometer using TMS as a reference compound (chemical shifts in δ, ppm) and mass spectra on a Joel-JMS-D300 spectrometer. The major chemicals were purchased from Aldrich Chemical Corporation. All other chemicals used were of analytical grade.

Five aryloxyaminopropane derivatives of 1,8-naphthyridines were synthesized utilizing the principle of Conrad-Limpach synthesis of quinolines.

The steps adapted in the synthesis of the derivatives are depicted in the scheme below (Scheme 1) adapted from the scheme already reported (Thomas et al., 2003).

1. Synthesis of 2-hydroxy-4-methyl-1, 8-naphthyridine.
2. Synthesis of 2-(2', 3'-epoxypropyloxy)-4-methyl-1, 8-naphthyridine.
3. Synthesis of 2-(3'-aminopropyloxy)-4-methyl-1, 8-naphthyridine.



Scheme 1: Synthetic route for naphthyridine derivatives

Synthesis of 2-hydroxy-4-methyl-1, 8-naphthyridine

To the mixture of ethylacetoacetate (0.1 moles) and amino pyridine (0.1 moles), 5 mL concentrated sulfuric acid was added. The reaction mixture was then refluxed at 135°C in an oil bath, with occasional stirring, until the completion of the reaction (approximately 5 hours). The reaction mixture was cooled to obtain the product, which was filtered, dried and *re-crystallized* from methanol-ether mixture. Completion of the reaction was monitored by TLC, yield 63%; m.p. 218-220°C; IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 785, 720 (Ar-H); ^1H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Synthesis of 2-(2', 3'-epoxypropyloxy)-4-methyl-1, 8-naphthyridine

To the 2-hydroxy-4-methyl-1,8-naphthyridine obtained from step 1 (0.1 moles), epichlorhydrin (0.1 moles) was added, in the presence of 10% alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether. The purity of product and completion of the reaction was monitored by TLC, yield 48%; m.p.228-230°C. IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^1H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

General method of synthesis of the amino propyloxy derivatives

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, an appropriate amine (0.1 moles), in the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product.

Synthesis of 1-diethylamino-3-(4-methyl-[1,8]naphthyridin-2-yloxy-propan-2-ol)

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, diethylamine (0.1 moles), in

the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product, NF 1, yield 74%; m.p.252-256°C.IR (KBr, cm^{-1}):3430 (O-H), 3320 (N-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^{1}H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Synthesis of 1-(4-methyl-[1,8]naphthyridin-2-yloxy)-3-phenylamino-propan-2-ol

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, aniline (0.1 moles), in the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product, NF 2, yield 76%; m.p.248-250°C. IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^{1}H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Synthesis of 1-(4-methyl-[1,8]naphthyridin-2-yloxy)-3-(pyridine-2-ylamino)-propan-ol

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, 2-aminopyridine (0.1 moles), in the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product, NF 3, yield 78%; m.p.260-264°C. IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^{1}H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Synthesis of N-[2-hydroxy-3-(4-methyl [1,8]naphthyridin-2-yloxy]-propyl] formamide

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, formamide (0.1 moles), in the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product, NF 4, yield 78%; m.p.256-260°C. IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^{1}H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Synthesis of 1-[2-hydroxy-3-(4-methyl-[1,8]naphthyridin-2-yloxy)-propyl]-piperidin 3-ol

To the 2-(2', 3'-epoxy-propyloxy)-4-methyl-1, 8-naphthyridine obtained from the step 2 (0.1 moles) was added, 3-hydroxy piperidine (0.1 moles), in the presence of alcoholic potassium hydroxide. The reaction mixture was refluxed until the completion of the reaction. On cooling, the product separated which was filtered, dried and *re-crystallized* from methanol-ether to give the corresponding final product, NF 5, yield 74%; m.p.258-262°C. IR (KBr, cm^{-1}):3430 (O-H), 1415 (C-H), 1238 (C-O), 1120 (C-O ether), 785, 720 (Ar-H); ^{1}H NMR (DMSO): δ 7.39 (s, 1H), 7.76 (s, 3H), 6.41-6.84 (d, 2H; 5, 6H), 3.87-4.14 (s, 1H; 2-OH), 3.32-3.86 (s, 3H; 7-CH_3), 6.4 (s, Ar-CH)

Anticonvulsant Testing

Pharmacological potential of the synthesized compounds was determined by the method of protection against pentylenetetrazole-induced convulsions (Vogel, 2002) in mice of body weight 18-22g. The number of protected animals in the treated groups was calculated as percentage of affected animals in the control group.

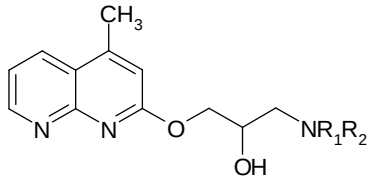
The anti-epileptic potential of the synthesized compounds is depicted in table 2.

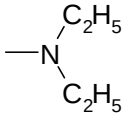
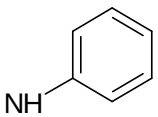
Results and Discussions

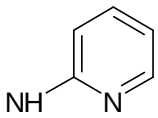
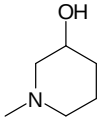
At low temperature the amine condenses with the ester at the keto group to give an anil, which catalyzes to naphthyridine-4-one on heating. On the other hand, at higher temperature, the initial product of the condensation is the anilide, which is formed by the condensation of the amine at the ester function. The anilide undergoes ring closure on heating, or in the presence of an acid, and on subsequent oxidation yields 2-hydroxy-4-methyl-1, 8- naphthyridine.

Characterization of the synthesized compounds was done by determining their melting points, UV absorption maxima, IR spectra, and ^{1}H NMR spectra. All the compounds were found to contain the shifts for epoxy, aromatic hydrogen and amine groups in the ^{1}H NMR spectra. The yield of all the synthesized compounds was found to be significant. The structural confirmation was done by the IR spectra which revealed the peaks for NH, C-O, aromatic CH, C-N for every compound.

Table 1: List of various synthesized derivatives of 1, 8-naphthyridine.



Compound Code	-- NR_1R_2	% Yield
NF-1		76
NF-2		74

NF-3		78
NF-4	NH_2	78
NF-5		74

The compounds were evaluated for the anticonvulsant activity at dose of 125mg/Kg and 250mg/Kg against convulsions induced by pentylenetetrazole. Prevention of seizures induced by PTZ and MES in laboratory animals is the most commonly used preliminary screening test for characterizing potential anticonvulsant drugs. The PTZ test represents a valid model for human generalized myoclonic and also absence seizures. Drugs that reduce T-type Ca^{2+} currents, such as ethosuximide can prevent seizures induced by PTZ. This type of seizures can also be prevented by drugs that enhance gamma amino butyric acid-type A (GABA-A) receptor-mediated inhibitory neurotransmission, such as benzodiazepines and phenobarbital. Furthermore, activation of *N*-methyl-daspartate receptor appears to be involved in the initiation and generalization of the PTZ-induced seizures. In this regard, drugs that block glutamatergic excitation mediated by NMDA receptor, such as felbamate, have anticonvulsant activity against PTZ-induced seizures. All the compounds exhibited significant anticonvulsant activity in dose dependent manner against the PTZ induced seizures. The order of the percent protection of the synthesized compounds was found to be NF-5 > NF-1 > NF-3 > NF-4 > NF-2. The compounds NF-5 and NF-1 in the dose of 250mg/Kg were found to be almost equipotent to diazepam (5mg/Kg).

Table 2: Anticonvulsant activity of the synthesized compounds

S. No.	Compound code	Dose (mg/Kg)	% Protection
1	NF-1	125	43.62
		250	89.27
2	NF-2	125	11.51
		250	26.30
3	NF-3	125	29.66
		250	61.03
4	NF-4	125	19.63
		250	34.35
5	NF-5	125	41.15
		250	94.20

It was found form the results of anticonvulsant activity that the compound with flexible amino substituent possessed better activity than that of

the compounds with rigid amino substituent, except NF-5. The exception of NF-5 led us to the conclusion that the aliphatic amino derivatives of the synthesized compounds were more potent as anticonvulsant in comparison to the aromatic amino derivatives.

References

Agrawal SK, Saxena AK, Jain PC, Anand N, Sur RN, Srimal RC, and Shawan BN (1990) Synthesis and structure activity relationship in aryloxyalkylamines. *Indian J Chem* **29B**: 80-84.

Bouzard D, Cesare PD, Essiz M, Jacquet J, Ledoussal B, Remuzon P, Kessler R, and Tomc JF (1992) Fluoronaphthyridines as antibacterial agents. 4. Synthesis and structure-activity relationships of 5-substituted-6-fluoro-7-(cycloamino)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. *J Med Chem* **35(3)**: 518-525.

Drug Discovery and Evaluation: Pharmacological Assays (Ed. H. G. Vogel), Springer-Verlag, Berlin Heidelberg (2002), pp. 385-593.

Ferrarini P, Manera C, Mori C, Badawneh M, and Saccomanni G (1998) Synthesis and evaluation of antimycobacterial activity of 4-phenyl-1,8-naphthtyridine derivatives *Farmaco* **53(12)**: 741-746.

Ferrarini P, Mori C, and Tellini N (1990) Synthesis and local anesthetic activity of (E)- and (Z)-diethylaminoethyl-iminoethers of 1,8-naphthyridine. *Farmaco* **45(3)**: 385-389.

Ferrarini PL, Badawneh M, Franconi F, Manera C, Miceli M, Mori C, and Saccomani G (2001) Synthesis and antiplatelet activity of some 2,7-di(N-cycloamino)-3-phenyl-1,8-naphthyridine derivatives. *Farmaco* **56(4)**: 311-318.

Kuo S, Tsai S, Li H, Wu C, Ishii K, and Nakamura H (1988) Studies on heterocyclic compounds. IX. Synthesis and antiallergic activity of furo [2,3-b] [1,8] naphthyridine-3,4 (2H, 9H)-diones, and 4H-furo [2,3-d] pyrido [1,2-alpha]-pyrimidine-3,4 (20-diones). *Chem Pharm Bull* **36(11)**: 4403-4407.

Scotese SA, Bauer R, and Bell S (1987) 2-Oxo-1,8-naphthyridine-3-carboxylic acid derivatives with potent gastric antisecretory properties *J Med Chem* **30(12)**: 2270-2277.

Settimo AD, Primofiore G, Settimo FD, Simorini F, Barili P, Senatore G, Martini C, and Luccacchini A (1994) Synthesis and benzodiazepine receptor activity of some 4,5-dihydro-1H-pyrazolo [4,3-c] [1,8] naphthyridine derivatives. *Drug Des Discov* **11(40)**: 307-328.

Sur RN, Shanker G, Rathore RSK, Chak IM, Agrawal SK, and Jain PC (1980) Pharmacological studies on 1-(p-aminophenoxy)-3-[N^1-(O-methoxypheynyl)-N^4-piperazinyl]propane dihydrochloride. *Indian J Exp Biol* **18**: 1190-1191.

Takeshi K, Fumio K, and Tadafumi T (1992) A novel synthesis and potent anti-inflammatory activity of 4-Hydroxy-2(1H)-oxo-1-phenyl-1,8-

naphthyridine-3-carboxamides, *J Med Chem* **35(6)**: 1130-1135.

Thomas LJ, Gangadhar R, Kishore SG, Ramchandran S, Saravanan M, and Sridhar SK (2003) Synthesis and pharmacological activities of 1,8-naphthyridine derivatives. *Indian Drugs* **40(6)**: 320-327.

Zhang SX, Bastow KF, Tachibana Y, Kuo SC, Hamel E, Mauger A, Narayana VL, and Lee KH (1999) Antitumor Agents. 196. Substituted 2-Thienyl-1,8-naphthyridin-4-ones: Their synthesis, cytotoxicity, and inhibition of Tubulin Polymerization 1. *J Med Chem* **42(20)**: 4081-4087.