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MICROWAVE ASSISTED SYNTHESIS OF 4-AZETIDINONE DERIVATIVES OF 1, 8-NAPHTHYRIDINE

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ABSTRACT

2-Methyl-7-amino-1,8-naphthyridin-4-ol (**1**) reacts with different aldehydes to form 7-aminosubstituted-2-methyl-1,8-naphthyridin-4-ol derivatives (**2a-j**). These naphthyridines**2a-j** are cyclised to azetidinones (**3a-j**) by microwave irradiation of **2a-j** with chloroacetylchloride and a mild base to give 4-substituted-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-ones.

Keywords: Microwave, Tetrazole, 4-Azetidinone, 1,8-naphthyridine

INTRODUCTION

In current trend, research on of N-Heterocyclic compounds has been demanding since these derivatives show an extensive variety of activities.[1-9] Nalidixic acid possesses strong antibacterial activity, it is used for urinary tract infections treatment.[10] Derivatives of Naphthyridine reacts with adenosine receptors of associated types and A_2A A_1[11]. The mainmethodology[12] to set up 1,8-naphthyridenes from 2-aminopyridine with β-ketoesters is reported earlier. Keeping in mind the important properties of 1,8-Naphthyridines[13-16], we have synthesized a series of some naphthyridines. In the present communication, we report the synthesis of title compounds.

Compound (**1**) is prepared by Yudong Shen method [17] and converted into different derivatives. Tripti Singh et al., reported the synthesis of different azitidinone from aminopyridine[18] and Singh et al., from 2-amino-1,8-naphthyridine[19].Microwave heating refers to the use of electromagnetic waves ranges(0.01m to 1m) to generate heat. These lie in the region between I.R and radio wave. Microwave assisted Synthesis is measured to be advanced to other commercial methods. Microwave Assisted Organic Synthesis (MAOS), has come out as a new "lead" in organic synthesis. Synthesis through this process is simple, clean, fast, competent and economical.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Perkin-Elmer 383 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 400 MHz instrument. TMS is taken as internal Standard and chemical shifts are expressed δ ppm. The solvent used is DMSO-d_6. Mass spectrum was obtained on a Hewlett Packard mass spectrometer operating at 70ev.

4-ayl-3-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-ones (3a-e)

To compound **2a** in Dry THF, chloroacetyl chloride was added while stirring for 5 minutes. This reaction mixture was irradiated under microwave at 420 watts. The reaction crude was poured into ice cold water and extracted in ethanol.

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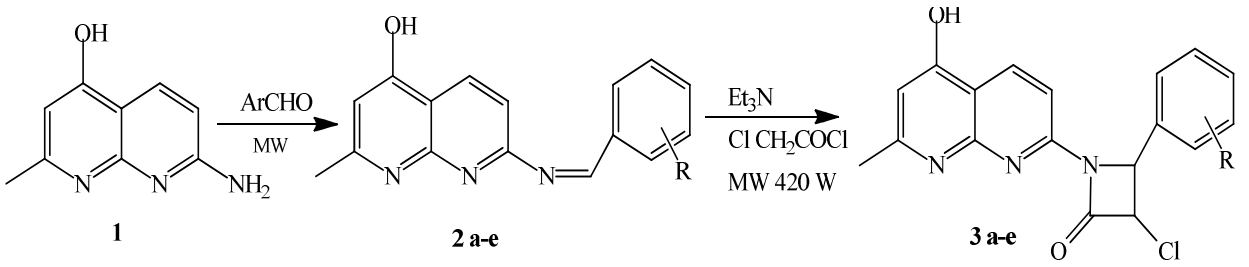
4-(3-fluorophenyl)-3-chloro--1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-one
^{1}H NMR in DMSO-d6: 2.41 (S, 3H), 4.92 (dd, 2H), 7.43 – 7.84 (m, 4H), 8.08 (d, 1H), 8.45 (d, 1H), 8.53 (d, 1H), 8.62(d, 1H), 9.11 (S, 1H), 12.11 (brs, 1H). MS: m/z 358 (m+1).

4-phenyl -3-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)- azetidin-2-one
^{1}H NMR in DMSO-d6 : 2.31 (S, 3H), 4.78 (dd, 2H), 7.40 – 7.84 (m, 5H), 8.10 (d, 1H), 8.45 (d, 1H), 9.01 (S, 1H), 12.10 (brs,1H). MS: m/z 340 (m+1).

4-(4-chlorophenyl)-3-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-one
^{1}H NMR in DMSO -d6: 2.41 (S, 3H), 4.92 (dd, 2H), 7.36 – 7.75 (m, 4H), 8.12 (d, 1H), 8.56 (d, 1H), 9.09 (S, IH), 12.08 (brs,1H). MS: m/z 374 (m+1).

4-(3-chlorophenyl)-3-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-one
^{1}H NMR in DMSO–d6 : 2.33 (S, 3H), 4.93 (dd, 2H), 7.38 – 7.65 (m, 4H), 8.08 (d, 1H), 8.55 (d, 1H), 9.07 (S, 1H), 12.08 (brs, 1H). MS: m/z 374 (m+1).

4-(2-chlorophenyl)-3-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-one
^{1}H NMR in DMSO –d6: 2.33 (S, 3H) 4.86 (dd, 2H) 7.36 – 7.66 (m, 4H), 8.10 (d-1H), 8.40 (d, 1H), 9.23 (S, 1H), 12.13 (brs, 1H). MS: m/z 374 (m+1).



1 **2 a-e** **3 a-e**

R = 3-fluorophenyl, phenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl
Scheme-1

RESULTS AND DISCUSSION

In the present study, microwave assisted synthesis for the derivatives of 1,8 napthyridines was investigated. 2-Methyl-7-amino-1,8-naphthyridin-4-ol (**1**) reacts with different aldehydes to form 7-amino substituted-2-methyl-1,8-naphthyridin-4-ol derivatives (**2a-j**). These Naphthyridines **2a-j** are cyclized to azetidinones (**3a-j**) by microwave irradiation of **2a-j** with Chlor-acetyl chloride and a mild base to give 4-substituted-chloro-1-(4-hydroxy-2-methyl-1,8-naphthyridin-7-yl)azetidin-2-ones. The reaction time in this microwave method is much lesser than commercial method. The yield of the product is also improved to the extent of 10% when compared to commercial methods.

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