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Microwave-assisted Solvent-free Synthesis and Antibacterial Activity of 6-Aryl-8-(4-methoxyphenyl)-8,11-dihydropyrazolo[3',4':4,5]pyrimido[1,2-*a*][1,8] naphthyridin-11-ones

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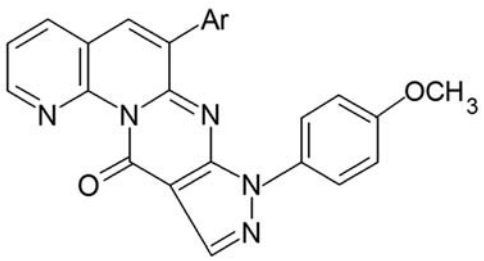
ABSTRACT A simple and efficient method for the synthesis of 6-aryl-8-(4-methoxyphenyl)-8,11-dihydropyrazolo[3',4':4,5]pyrimido[1,2-*a*][1,8]naphthyridin-11-ones **3** by the cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with 5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylic acid **2** in the presence of a catalytic amount of DMF in solvent-free conditions under microwave irradiation has been described. The reaction proceeds efficiently in high yields and a state of excellent purity. The structures of compounds **3** are assigned on the basis of their spectral (IR,^{1}H nuclear magnetic resonance and MS) and analytical data. The compounds **3** have been evaluated for their antibacterial activity.



3

KEYWORDS 1,8-Naphthyridine, Pyrazole, Pyrimidine, Microwave irradiation, Antibacterial activity.

INTRODUCTION

1,8-Naphthyridines have received great attention from the synthetic and biological point of view.[1,2] Various biological activities are associated with pyrazole ring system.[3,4] The pyrimidine moiety is an important pharmacophoric element in medicinal chemistry.[5,6] Therefore, it was envisaged that chemical entities with 1,8-naphthyridine, pyrazole, and pyrimidine might result in compounds with interesting biological activity.

The MW induced organic reactions are becoming popular because of their simplicity and operational convenience.[7-9] Solvent-free MW assisted chemical reactions[8] are gaining importance due to the advantages and environmentally friendly process they offer, as compared to conventional reactions. In view of these observations, we report herein an efficient and convenient method for the synthesis of 6-aryl-8-(4-methoxyphenyl)-8,11-dihydropyrazolo[3',4':4,5]pyrimido[1,2-*a*][1,8] naphthyridin-11-ones in solvent-free conditions under microwave irradiation.

RESULTS AND DISCUSSION

Chemistry

Cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylic

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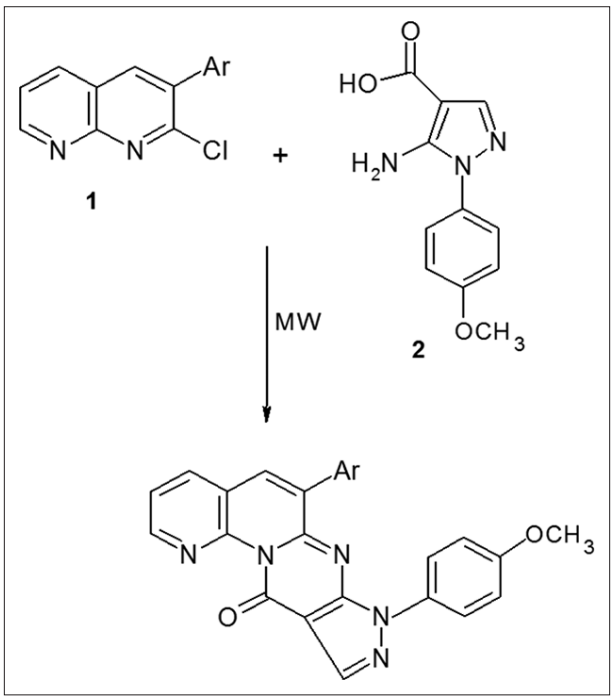
acid **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded 6-aryl-8- (4-methoxyphenyl)-8,11-dihydropyrazolo-[3',4':4,5] pyrimido [1,2-*a*] [1,8]naphthyridin-11-ones **3** [**Scheme 1**] in very good yields. It was observed that mixture of **1** and **2** reacted under MW irradiation and the reaction proceeds to completion within minutes on addition of few drops of a high dielectric solvent such as DMF.

In a typical case, a mixture of 2-chloro-3-phenyl-1,8-naphthyridine **1a,** 5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylic acid **2** and DMF (5 drops) was subjected to MW irradiation at 400 watts intermittently at 30sec intervals for 3.5 min. The reaction mixture was allowed to cool to RT and treated with cold water. After work-up 6-phenyl-8- (4-methoxyphenyl)-8,11-dihydropyrazolo-[3',4':4,5] pyrimido[1,2-*a*][1,8] naphthyridin-11-one **3a** was obtained in 93% yield. The reaction is of general applicability and the different pyrazolo-[3',4':4,5] pyrimido[1,2-*a*][1,8]naphthyridin-11-ones **3** synthesized are presented in **Scheme 1**.

The reaction proceeds only to a minor extent (6–10% in 3.5–4.0 min) when conducted under conventional conditions in an oil bath preheated to 120°C (temperature measured at the end of the exposure during MW experiment), thus demonstrating the advantage of the MW heating method.

The structural assignments of the compounds **3** are based on their elemental analyses and spectral (IR,^{1}H nuclear magnetic resonance [NMR] and MS) data. The simple operation, short reaction times, high yields, and excellent purity of the products are notable advantages of this method.



Scheme 1
Ar - a: C_6H_5, b: 4-$CH_3OC_6H_4$, c: 2-ClC_6H_4, d: 3-ClC_6H_4, e: 4-ClC_6H_4, f: 2-F C_6H_4, g: 3-F C_6H_4, h: 4-F C_6H_4, i: 3-CF_3 C_6H_4, j: 4-CF_3 C_6H_4

Antibacterial activity

All the title compounds **3** were tested for their antibacterial activity against Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* using filter paper disc technique of Vincent and Vincent[10] at 250 and 500 µg/disc concentrations. Gentamycin was used as a standard for comparison. The results are presented in **Table 1**. Compounds **3e** and **3h** showed promising antibacterial activity.

EXPERIMENTAL

Melting points were measured on a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was inferred from thin layer chromatography (TLC) on silica gel-G plates (Merck, 60F-254). IR spectra (KBr) were recorded on a Perkin-Elmer Fourier transform-infrared spectrophotometer.^{1}H NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on a VG 170708H spectrometer. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Microwave irradiation was carried out in a domestic microwave oven (LG MG 556P, 2450 MHz). The 5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole- 4-carboxylic acid **2** was purchased from Aldrich Chemical Company.

Synthesis of 6-aryl-8-(4-methoxyphenyl)-8,11-dihydropyrazolo-[3',4':4,5]pyrimido[1,2-*a*] [1,8] naphthyridin-11-ones 3: General procedure

A mixture of 3-aryl-2-chloro-1,8-naphthyridine **1 (**0.01 mol), 5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylic acid **2 (**0.01 mol) and DMF (5 drops) was subjected to MW irradiation at 400 watts intermittently at 30 s intervals for the period indicated in **Table 2**. On completion of the reaction (monitored by TLC), the reaction mixture was cooled and treated with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to give **3** [**Table 2**].

Spectral data

- **3**a: IR(KBr) cm^{-1}: 1656(C=O),1606(C=N); ^{1}H NMR($CDCl_3$): δ 3.86(s,3H,OCH_3), 7.80 (m, 2H, C_3-H, C_5-H), 7.86 (s, 1H, C_{10}-H), 8.00 (m, 1H, C_4-H), 8.75 (m, 1H, C_2-H), 7.18-7.42 (m, 9H, Ar-H); MS(ESI):m/z 420 $[M+H]^+$.
- **3**b: IR(KBr): 1665(C=O), 1605(C=N); ^{1}H NMR($CDCl_3$): δ 3.85(s,6H,2×OCH_3), 7.78 (m, 2H, C_3-H, C_5-H), 8.02 (s, 1H, C_{10}-H), 8.15 (m, 1H, C_4-H), 8.58 (m, 1H, C_2-H), 7.00–7.22 (m, 8H, Ar-H); MS(ESI):m/z 450 $[M+H]^+$.
- **3**c: IR(KBr): 1662 (C=O), 1606 (C=N);^{1}H NMR($CDCl_3$): δ 3.84 (s,3H,OCH_3), 7.76 (m, 2H, C_3-H, C_5-H), 7.96 (s, 1H, C_{10}-H), 8.06 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.20–7.52 (m, 8H, Ar-H); MS(ESI): m/z 454 $[M+H]^+$.
- **3**d: IR(KBr): 1667 (C=O), 1608 (C=N);^{1}H NMR($CDCl_3$): δ 3.86(s,3H,OCH_3), 7.80 (m, 2H, C_3-H, C_5-H), 7.98 (s, 1H, C_{10}-H), 8.30 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.22–7.56 (m, 8H, Ar-H); MS(ESI):m/z 454 $[M+H]^+$.

Table 1: Antibacterial activity data of compounds 3

Compound	Inhibition zone (in mm)			
	E. coli at		*B. subtilis* at	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
3a	9.0	14.0	7.5	11.0
3b	10.0	18.0	7.5	12.0
3c	9.5	16.5	7.0	11.5
3d	9.0	14.5	6.5	10.5
3e	11.0	21.0	7.5	14.5
3f	9.0	14.5	7.0	12.5
3g	8.5	12.5	6.5	11.0
3h	11.0	20.5	7.5	13.5
3i	8.5	13.5	6.5	11.5
3j	10.5	19.0	7.0	13.0
Gentamycin	12.0	22.0	8.0	15.0

Table 2: Physical data of compounds 3

Compounds	Ar	Reaction time (min)	M.P (°C)	Yield (%)
3a	C_6H_5	3.5	242	93
3b	4-$CH_3OC_6H_4$	4.0	256	95
3c	2-ClC_6H_4	3.5	270	93
3d	3-ClC_6H_4	3.5	288	92
3e	4-ClC_6H_4	4.0	282	96
3f	2-FC_6H_4	3.5	240	93
3g	3-FC_6H_4	4.0	252	92
3h	4-FC_6H_4	4.0	278	95
3i	3-$CF_3C_6H_4$	4.0	260	92
3j	4-$CF_3C_6H_4$	4.0	285	94

All the compounds gave satisfactory C, H, N elemental analyses

- **3**e: IR(KBr): 1676 (C=O), 1604 (C=N);^{1}H NMR($CDCl_3$): δ 3.85(s,3H,OCH_3), 7.72 (m, 2H, C_3-H, C_5-H), 7.84 (s, 1H, C_{10}-H), 8.00 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.20–7.48 (m, 8H, Ar-H); MS(ESI):m/z 454 $[M+H]^+$.
- **3**f: IR(KBr): 1672 (C=O), 1608 (C=N);^{1}H NMR($CDCl_3$): δ 3.84(s,3H,OCH_3), 7.65 (m, 2H, C_3-H, C_5-H), 7.88 (s, 1H, C_{10}-H), 8.00 (m, 1H, C_4-H), 8.66 (m, 1H, C_2-H), 7.15–7.40 (m, 8H, Ar-H); MS(ESI):m/z 438 $[M+H]^+$.
- **3**g: IR(KBr): 1670 (C=O), 1606 (C=N);^{1}H NMR($CDCl_3$): δ 3.86 (s,3H,OCH_3), 7.56 (m, 2H, C_3-H, C_5-H), 7.88 (s, 1H, C_{10}-H), 7.98 (m, 1H, C_4-H), 8.64 (m, 1H, C_2-H), 7.10–7.42 (m, 8H, Ar-H); MS(ESI):m/z 438 $[M+H]^+$.
- **3**h: IR(KBr): 1670 (C=O), 1605 (C=N);^{1}H NMR($CDCl_3$): δ 3.85(s,3H,OCH_3), 7.75 (m, 2H, C_3-H, C_5-H), 7.84 (s, 1H, C_{10}-H), 7.96 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.12–7.24 (m, 8H, Ar-H); MS(ESI):m/z 438 $[M+H]^+$.
- **3**i: IR(KBr): 1664 (C=O), 1607 (C=N);^{1}H NMR($CDCl_3$): δ 3.86(s,3H,OCH_3), 7.90 (m, 2H, C_3-H, C_5-H), 8.00 (s, 1H, C_{10}-H), 8.08 (m, 1H, C_4-H), 8.72 (m, 1H, C_2-H), 7.18–7.52 (m, 8H, Ar-H); MS(ESI):m/z 488 $[M+H]^+$.
- **3**j: IR(KBr): 1660 (C=O), 1605 (C=N);^{1}H NMR($CDCl_3$): δ 3.84(s,3H,OCH_3), 7.87 (m, 2H, C_3-H, C_5-H), 7.92 (s, 1H, C_{10}-H), 8.05 (m, 1H, C_4-H), 8.68 (m, 1H, C_2-H), 7.20–7.62 (m, 8H, Ar-H); MS(ESI):m/z 488 $[M+H]^+$.

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