Indian Journal of Heterocyclic Chemistry
Vol. 25, Oct.-Dec., 2015, pp. 101-104

EFFICIENT SYNTHESIS AND BIOLOGICAL PROPERTIES OF 6-ARYL-10-CHLORO-8-IODO-12*H*-[1,8] NAPHTHYRIDINO [2,1-*b*] QUINAZOLIN-12-ONES

K. Mogilaiah*, P. Koteswara Rao and A. Nageswara Rao
Department of Chemistry, Kakatiya University, Warangal-506 009
E-mail : mogilaiah_k@yahoo.co.in

Received 8 July 2015; Accepted 13 Nov. 2015

A simple and efficient, method for the synthesis of 6-aryl-10-chloro-8-iodo-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** by the cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with methyl 2-amino-5-chloro-3- iodobenzoate **2** in the presence of catalytic amount of DMF under microwave irradiation has been described. The yields are very good and purity is high. The structural assignments of compounds **3** were based on their elemental analyses and spectral (IR ^{1}H NMR and MS) data. Compounds **3** have been screened for their antibacterial and anti-inflammatory activities.

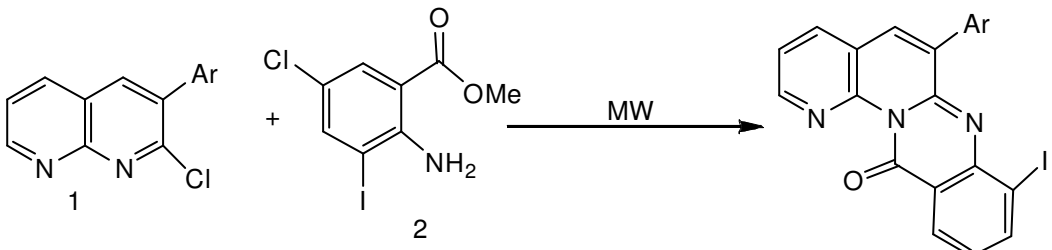
1,8-Naphthyridines are important biological agents and a significant amount of research activity has been directed towards this class. In particular, they are used as antibacterial[1], antiinflammatory[2] and antitumor[3] agents. Quinazolines have received great attention from synthetic and biological point of view[4-6]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and quinazoline might result in compounds with interesting biological activity. The microwave-induced organic reactions are becoming popular because of their simplicity and operational convenience[7-9]. Solvent-free microwave-assisted chemical reactions[8] are gaining importance due to the advantages and environmentally friendly processes they offer, as compared to conventional reactions. In view of this and in continuation of our interest in microwave-assisted organic transformations of 1,8-naphthyridine derivatives[10-12], we present herein, a simple and efficient method for the synthesis of 6-aryl-10-chloro-8-iodo-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** in solvent-free conditions under microwave irradiation and also evaluation of their antibacterial and anti-inflammatory properties.

Cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with methyl 2-amino-5-chloro-3-iodobenzoate **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded the corresponding 6-aryl-10-chloro-8-iodo-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** (Scheme-1), in very good yields (92-96%) with short reaction time (2.0-3.0 min). The products were obtained with a high degree of purity by this procedure. The process is environmentally friendly. The experimental procedure is very simple. It was observed that the neat mixtures of **1** and **2** did not reacted under microwave irradiation, but the reaction proceeds to completion within minutes on addition of few drops of high dielectric solvent such as DMF.

In a typical experimental procedure, equimolar quantities of 2-chloro-3-phenyl-1,8-naphthyridine **1**a, methyl 2-amino-5-chloro-3-iodobenzoate **2** and catalytic amount of DMF was exposed to microwave irradiation at 400 watts intermittently for 30 sec intervals for 2.5 min. The reaction mixture was cooled to RT, digested with cold water and filtered off. After usual work-up 10-chloro-8-iodo-6-phenyl 12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-one **3**a was obtained in 93% yield. The reaction is of general applicability and the various 6-aryl-10-chloro-8-iodo-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** synthesized are given in Table-1.

The reaction proceeds to only 6-8% in 2.0-3.0 min, when conducted under conventional conditions in an oil-bath preheated to 120^0 (measured immediately after microwave irradiation), thus demonstrating the advantage of the microwave heating method.

The structures of the compounds **3** were determined by spectral (IR, ^{1}H NMR and MS) and analytical data. The experimental simplicity, high yields, short reaction times, excellent purity and



	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$
d	2-Cl-C_6H_4
e	3-ClC_6H_4
f	4-ClC_6H_4
g	2-FC_6H_4

	Ar
h	3-FC_6H_4
i	4-FC_6H_4
j	3-BrC_6H_4
k	4-BrC_6H_4
l	2-$CF_3C_6H_4$
m	3-$CF_3C_6H_4$
n	4-$CF_3C_6H_4$
o	2-Naphthyl

SCHEME-1

Table-1
Physical data of compounds **3**

Compd	Ar	Reaction time (min)	M.P. (^{0}C)	Yield (%)
3a	C_6H_5	2.5	178	93
3b	4-$CH_3C_6H_4$	3.0	210	95
3c	4-$CH_3OC_6H_4$	3.0	165	93
3d	2-Cl-C_6H_4	2.5	218	94
3e	3-ClC_6H_4	2.0	228	92
3f	4-ClC_6H_4	2.5	221	96
3g	2-FC_6H_4	2.5	232	93
3h	3-FC_6H_4	3.0	205	92
3i	4-FC_6H_4	3.0	238	95
3j	3-BrC_6H_4	2.5	224	92
3k	4-BrC_6H_4	3.0	168	94
3l	2-$CF_3C_6H_4$	2.5	213	93
3m	3-$CF_3C_6H_4$	2.0	226	92
3n	4-$CF_3C_6H_4$	3.0	208	95
3o	2-Naphthyl	3.0	143	94

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

absence of solvent are the advantages of this method and thus, the method is environmentally benign.

Antibacterial activity

All the title compounds **3** were evaluated for their antibacterial activity against Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* using filter paper disc method of Vincent and Vincent[13] at 250 and 500 μg/disc concentrations. Gentamycin was used as standard for comparison. Compounds **3**b, **3**d, **3**f, **3**i and **3**n showed promising antibacterial activity.

Anti-inflammatory activity

All the title compounds **3** were tested for their anti-inflammatory activity by applying carrageenan-induced rat paw edema method[14], using Diclofenac sodium as reference drug for comparison. Compounds **3**b, **3**f, **3**i and **3**n exhibited significant anti-inflammatory activity at 4th hr.

Experimental

Melting points were determined on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked by precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a Shimadzu FTIR-8400S spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on a VG170708H 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 methyl 2-amino-5-chloro-3-iodobenzoate **2** was purchased from Aldrich Chemical Company.

6-Aryl-10-chloro-8-iodo-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones : General procedure

A mixture of 3-aryl-2-chloro-1,8-naphthyridine **1** (0.01 mol), methyl 2-amino-5-chloro-3-iodobenzoate **2** (0.01 mol) and DMF (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 30 sec intervals for the specified time (Table-1). On completion of reaction as indicated by TLC, the reaction mixture was allowed to attain RT and digested with cold water. The separated solid was filtered, washed with water and purified by recrystallization from methanol to furnish **3** (Table-1).

Spectral data

3a : IR (KBr): 1651 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): δ 7.72 (m, 2H, C_2-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.83 (s, 1H, C_{11}-H), 7.96 (m, 1H, C_4-H), 8.72 (m, 1H, C_2-H), 7.15-7.62 (m, 5H, ArH); MS (ESI): m/z 484 $[M+H]^+$.

3b : IR (KBr): 1655 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 7.62 (m, 2H, C_3-H, C_5-H), 7.72 (s, 1H, C_{10}-H), 7.80 (s, 1H, C_{11}-H), 7.90 (m, 1H, C_4-H), 8.65 (m, 1H, C_2-H), 7.12-7.35 (m, 4H, ArH); MS (ESI): m/z 498 $[M+H]^+$.

3c: IR (KBr): 1663 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H, OCH_3), 7.65 (m, 2H, C_3-H, C_5-H), 7.74 (s, 1H, C_{10}-H), 7.82 (s, 1H, C_{11}-H), 7.95 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 6.75-7.22 (m, 4H, ArH); MS (ESI): m/z 514 $[M+H]^+$.

3d: IR (KBr): 1653 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$): 7.68 (m, 2H, C_3-H, C_5-H), 7.78 (s, 1H, C_{10}-H), 7.84 (s, 1H, C_{11}-H), 7.93 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.16-7.43 (m, 4H, ArH); MS (ESI): m/z 518 $[M+H]^+$.

3e: IR (KBr): 1658 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): 7.66 (m, 2H, C_3-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.86 (s, 1H, C_{11}-H), 7.97 (m, 1H, C_4-H), 8.68 (m, 1H, C_2-H), 7.15-7.45 (m, 4H, ArH); MS (ESI): m/z 518 $[M+H]^+$.

3f: IR (KBr): 1673 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.62 (m, 2H, C_3-H, C_5-H), 7.75 (s, 1H, C_{10}-H), 7.85 (s, 1H, C_{11}-H), 7.95 (m, 1H, C_4-H), 8.63 (m, 1H, C_2-H), 7.18-7.40 (m, 4H, ArH); MS (ESI): 518 $[M+H]^+$.

3g: IR (KBr): 1672 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$): 7.67 (m, 2H, C_3-H, C_5-H), 7.78 (s, 1H, C_{10}-H), 7.83 (s, 1H, C_{11}-H), 7.92 (m, 1H, C_4-H), 8.58 (m, 1H, C_2-H), 7.08-7.32 (m, 4H, ArH); MS (ESI): m/z 502 $[M+H]^+$.

3h: IR (KBr): 1669 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): 7.75 (m, 2H, C_3-H, C_5-H), 7.82 (s, 1H, C_{10}-H), 7.87 (s, 1H, C_{11}-H), 7.96 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.20-7.55 (m, 4H, ArH); MS (ESI): m/z 502 $[M+H]^+$.

3i : IR (KBr): 1673 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): 7.72 (m, 2H, C_3-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.85 (s, 1H, C_{11}-H), 7.98 (m, 1H, C_4-H), 8.65 (m, 1H, C_2-H), 7.15-7.48 (m, 4H, ArH); MS (ESI): m/z 502 $[M+H]^+$.

3j: IR (KBr): 1671 (C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$): 7.76 (m, 2H, C_3-H, C_5-H), 7.84 (s, 1H, C_{10}-H), 7.90 (s, 1H, C_{11}-H), 8.00 (m, 1H, C_4-H), 8.64 (m, 1H, C_2-H), 7.20-7.57 (m, 4H, ArH); MS (ESI): m/z 562 $[M+H]^+$.

3k: IR (KBr): 1658 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): 7.74 (m, 2H, C_2-H, C_5-H), 7.88 (s, 1H, C_{10}-H), 7.93 (s, 1H, C_{11}-H), 8.03 (m, 1H, C_4-H), 8.70 (m, 1H, C_2-H), 7.16-7.50 (m, 4h, ArH); MS (ESI): m/z 562 $[M+H]^+$.

3l: IR (KBr): 1670 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.70 (m, 2H, C_3-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.95 (s, 1H, C_{11}-H), 8.00 (m, 1H, C_4-H), 8.66 (m, 1H, C_2-H), 7.18-7.74 (m, 4H, ArH); MS (ESI): m/z 552 $[M+H]^+$.

3m: IR (KBr): 1663 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): 7.65 (m, 2H, C_3-H, C_5-H), 7.76 (s, 1H, C_{10}-H), 7.90 (s, 1H, C_{11}-H), 8.02 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.20-7.58 (m, 4H, ArH); MS (ESI): m/z 552 $[M+H]^+$.

3n: IR (KBr): 1672 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): 7.68 (m, 2H, C_3-H, C_5-H), 7.78 (s, 1H, C_{10}-H), 7.86 (s, 1H, C_{11}-H), 7.98 (m, 1H, C_4-H), 8.72 (m, 1H, C_2-H), 7.16-7.45 (m, 4H, ArH); MS (ESI): m/z 552 $[M+H]^+$.

3o : IR (KBr): 1659 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H, C_3-H, C_5-H), 8.25 (s, 1H, C_{10}-H), 8.30 (s, 1H, C_{11}-H), 8.20 (m, 1H, C_4-H), 8.58 (m, 1H, C_2-H), 7.22-7.68 (m, 7H, ArH); MS (ESI): m/z 534 $[M+H]^+$.

Acknowledgement

The authors are thankful to the Director, IICT, Hyderabad for providing ^{1}H NMR and mass spectra. Two of them (PKR and ANR) are grateful to CSIR, New Delhi for the award of Senior Research Fellowships.

References

1. C.Y. Hong, Y.K. Kim, J.H. Chang, S.H. Kim, H. Choi, D.H. Nam, Y.Z. Kim and J.H. Kwak, *J. Med. Chem.,* **40** (1997), 3584.
2. G. Roma, M.D. Bracci, G. Grassi, D. Piras, V. Ballabeni, M. Tognolini, S. Bertoni and E. Barocelli, *Eur. J. Med. Chem.,* **45** (2010), 352.
3. C. Manera, G. Saccomanni, B. Adinolfi, V. Benetti, A. Ligresti, M.G. Cascio, T. Tuccinardi, V. Luccheri, A. Martinelli, P. Nieri, E. Masini, V.D. Marzo and P.L. Ferrarini, *J. Med. Chem.,* **52** (2009), 3644.
4. T.P. Tran, E.L. Ellsworth, M.A. Stier, J.M. Domagala, H.D.H. Showalter, S.J. Gracheck, M.A. Shapiro, T.E. Joannides and R. Singh, *Bioorg. Med. Chem. Lett.,* **14** (2004), 4405.
5. J. He, X. Wang, X. Zhao, Y. Liang, H. He and L. Fu, *Eur. J. Med. Chem.,* **54** (2012), 925.
6. A. Sharma, V. Luxami and K. Paul, *Bioorg. Med. Chem. Lett.,* **23** (2013), 3288.
7. S. Caddick, *Tetrahedron,* **51** (1995), 10403.
8. A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis* (1998), 121.
9. P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, **57** (2001), 9225.
10. K. Mogilaiah, D. Praveena and A. Aara, *Indian J. Heterocyclic Chem.,* **23** (2014), 261.
11. K. Mogilaiah, P. K. Rao and A.N. Rao, *Indian J. Heterocyclic Chem.,* **24** (2014), 153.
12. K. Mogilaiah, D. Praveena, S. Jyothi and A.N. Rao, *Indian J. Heterocyclic Chem.,* **24** (2015), 315.
13. J.C. Vincent and H.W. Vincent, *Proc. Soc. Exptl. Biol. Med.,* **55** (1944), 162.
14. C.A. Winter, E.A. Risely and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.,* **111** (1962), 544.

3348/2015