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Research Article

ENVIRONMENTALLY BENIGN SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-[3-(2-NAPHTHYL)[1,8]NAPHTHYRIDIN-2-YL]-3-(2-OXO-2*H*-3-CHROMENYL)-1*H*-4-PYRAZOLECARBALDEHYDES

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ABSTRACT

An efficient and convenient protocol for the transformation of 3-[2-(3-(2-naphthyl)[1,8]naphthyridin-2-yl)ethanhydrazonyl]-2*H*-2-chromoenones(hydrazones) **4** to 1-[3-(2-naphthyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazole carbalde- hydes **5** is achieved under microwave irradiation utilizing $POCl_3$-DMF over silica gel with high yields. The purity of the products is high. The process is environmentally benign and experimental procedure is very simple. The structural assignments to compounds **4** and **5** are based on their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The compounds **5** have been screened for their antibacterial activity.

Keywords: Pyrazolecarbaldehydes, 1,8-naphthyridine and 2*H*-2-chromenones.

1. INTRODUCTION

1,8- Napthyridines are novel class of heterocyclic compounds possessing a wide variety of biological activities[1-3] pyrazole derivatives have been reported to exhibit versatile biological action[4-6] The 2-H-2-chromenones occupy a prominent position in the realm of heterocyclic compounds[7-9]. Therefore, the synthesis of new representatives in these classes of heterocyclic compounds remained urgent. Microwave-assisted organic synthesis has emerged as a new lead in organic synthesis[10-12] The application of microwave (MW) heating under solvent-free reaction conditions[11] and on inorganic solid support[13] is a promising alternative to polluting reactions and has been a current field of interest. In view of this and in continuation of the interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives,[14-16] we report herein an efficient and convenient method for the synthesis of 1-[3-(2-naphthyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2H-3-chromenyl)-1H-4-pyrazolecarbaldehydes in solvent-free conditions under microwave irradiation using silica gel as solid support.

2. MATERIAL AND METHODS

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 brukar spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on a Shimadzu Lab Solutions . Microwave irradiation was carried out in a domestic microwave oven(LG MG 556P, 2450 MHz).

3. RESULTS AND DISCUSSIONS

1-[3(2-Naphthyl)[1,8]naphthyridin-2-yl] hydrazine **2** obtained by the hydrazinolysis of 2-chloro-3-(2-naphthyl)[1,8]naphthyridine **1** with hydrazine hydrate, on condensation with different 3-acetylcoumarins (3-acetyl-2*H*-2-chromenones) **3** in the presence of catalytic amount of DMF under MW irradiation afforded the corresponding 3-[2-(3-(2-naphthyl) [1,8]naphthyridin-2-yl)ethan-hydrazonyl]-2*H*-2-chromenones (hydrazones) **4** in excellent yields. The hydrazones **4** when subjected to the Vilsmeier-Haack reaction with $POCl_3$-DMF/SiO_2 under MW irradiation furnished the respective 1-[3-(2-naphthyl)[1,8]naphthyridn-2-yl]-3-(2-oxo-2*H*-chromenyl)-1*H*-4pyrazole carbaldehydes **5.** Reactions are not time consuming and the yields of the products are very good. The purity of the product is high.

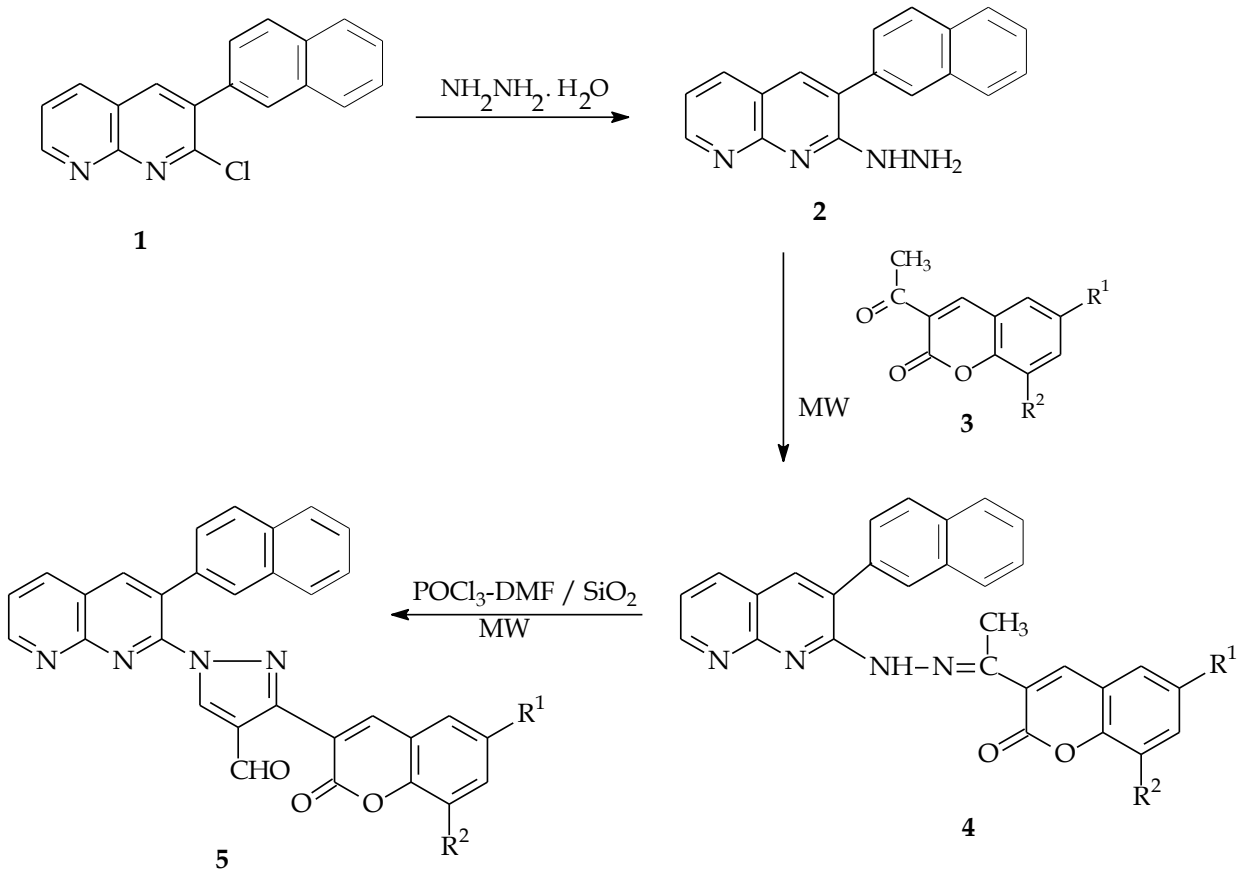
The experimental procedure is very simple. The process is environmentally benign.

The reaction proceeds to only 6-8% in 2.5 -4.0 min, when conducted under conventional conditions in an oil- bath preheated to 120 ^{o}C (measured immediately after MW irradiation)thus demonstrating the advantage of the MW heating method..

The structures of compounds **4** and **5** were determined by spectral (IR, ^{1}H NMR and MS) and analytical data.

The experimental simplicity, short reaction times, high yields and excellent purity and absence of solvent are the advantages of this method.

REACTION SCHEME



1 **2** **3** **4** **5**

	R¹	R²
a :	H	H
b :	H	OCH_3
c :	Cl	H
d :	Cl	Cl

	R¹	R²
e :	Br	H
f :	Br	Br
g :	NO_2	H
h :	5,6- Benzo	

4. Experimental Section

4.1. General procedure for the synthesis of 3-[2-(3-(2-naphthyl)[1,8]naphthyridin-2-yl)ethanhydrazonyl]-2*H*-2-chromenones (hydrazones), 4

A mixture of **1-[3-(2-naphthyl[1,8]napthyridine-2-yl]hydrazine 2** (0.01 mol), 3-acetylcoumarin **3** (0.01 mol) and DMF (5 drops) was exposed to microwave at 200 W intermittently at 10 sec intervals for the specified time (Table I). After completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **4 (**Table I).

4.1.1. Spectral data of the synthesized compounds (4a-h) 4a

IR (KBr): 3343 (NH), 1722 (lactone, C=O), 1614 (C=N), 1521 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.70 (s, 3H, CH_3), 7.88 (m, 2 H C_5-H, C_6-H), 8.05 (s, 1H, C_4-H,), 8.38 (m, 1H, C_7-H), 8.43 (s, 1H, C_4-H of coumarin), 7.03-7.82(m, 11H, Ar-H), 10.20 (s, 1H, NH); MS(ESI): *m/z* 457.35 $[M+H]^+$

4b

IR (KBr): 3347 (NH), 1723 (lactone, C=O), 1607 (C=N), 1524cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.72 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.90 (m, 2H, C_5 –H C_6-H), 8.10 (s, 1H, C_4-H,), 8.32 (m, 1H, C_7-H), 8.40 (s, 1H, C_4-H of coumarin), 7.00-7.75 (m, 10H, Ar-H), 10.18 (s, 1H, NH); MS(ESI): *m/z* 487.35 $[M+H]^+$

4c

IR (KBr): 3346 (NH), 1730 (lactone, C=O), 1618 (C=N), 1522 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.74 (s, 3H, CH3), 7.92(m, 2H, C_5-H C_6-H), 8.04 (s 1H, C_4-H,), 8.37 (m, 1H, C_7-H), 8.42 (s, 1H, C_4-H of coumarin), 7.20-7.64 (m, 10H, Ar-H), 10.20 (s, 1H, NH)); MS(ESI): *m/z* 491.35$[M+H]^+$

4d

IR (KBr): 3344 (NH), 1726 (lactone, C=O), , 1615 (C=N), 1530 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.75 (s, 3H, CH_3), 7.90 (m, 2H, C_5-H C_6-H), 8.07 (s, 1H, C_4-H,), 8.40 (m, 1H, C_7-H), 8.45 (s, 1H, C_4-H of coumarin), 7.18-7.66 (m, 9H, Ar-H), 10.22 (s, 1H, NH)); MS(ESI): *m/z* 525.30 $[M+H]^+$

4e

IR (KBr): 3353 (NH), 1728 (lactone, C=O),1621 (C=N), 1594 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.70 (s, 3H, CH_3), 7.86 (m, 2H, C_5-H C_6-H), 8.03 (s, 1H, C_4-H,), 8.38 (m, 1H, C_7-H), 8.40 (s, 1H, C_4-H of coumarin), 7.04-7.80 (m, 10H, Ar-H), 10.22 (s, 1H, NH); MS(ESI): *m/z* 535.25 $[M+H]^+$

4f

IR (KBr): 3345 (NH), 1723 (lactone, C=O), 1623 (C=N), 1598cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.76 (s, 3H, CH_3), 7.90(m, 2H, C_5-H C_6-H), 8.08 (s, 1H, C_4-H,), 8.40 (m, 1H, C_7-H), 8.58 (s, 1H, C_4-H of coumarin), 7.22-7.78 (m, 9H, Ar-H), 10.17 (s, 1H, NH); MS(ESI): *m/z* 613.20 $[M+H]^+$

4g

IR (KBr): 3340 (NH), 1725 (lactone, C=O), 1620 (C=N), 1592 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.73 (s, 3H, CH_3), 7.98 (m, 2H, C_5-H C_6-H), 8.10 (s, 1H, C_4-H,), 8.45 (m, 1H, C_{10}-H), 8.48 (s, 1H, C_4-H of coumarin), 7.20-7.75 (m, 10H, Ar-H), 10.20 (s, 1H, NH); MS(ESI): *m/z* 502.30 $[M+H]^+$

4h

IR (KBr): 3343 (NH), 1724 (lactone, C=O), 1619 (C=N), 1589 cm-1 (C=C); 1H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.75 (s, 3H, CH_3), 7.94 (m, 2H, C_5-H C_6-H), 8.09 (s, 1H, C_4-H,), 8.42 (m, 1H, C_{13}-H), 8.48 (s, 1H, C_4-H of coumarin), 7.15-7.82 (m, 13H, Ar-H), 10.22 (s, 1H, NH); MS(ESI): *m/z* 507.35 $[M+H]^+$

4.2. General procedure for the synthesis of 1-[3-(2-naphthyl][1,8]naphthyridin-2-yl)-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes, 5

To the Vilsmeier-Haack reagent (0.03 mol) at 0-5°C, compound **4** (0.01 mol) was added portion wise. After the addition was complete, the reaction flask was kept at RT for 5 min and silica gel (3 g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in microwave oven at 400 W intermittently at 30 sec intervals for the specified time (Table 1). on completion of reaction as indicated by TLC the reaction mixture was cooled, treated with chilled water and filtered. The solid obtained by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from methanol to furnish **5** (**Table 1**).

4.2.1. Spectral data of the synthesized compounds (5a-h):

5a

IR (KBr): 1726 (lactone, C=O),1680 (aldehyde C=O) 1612 (C=N), 1567 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.95 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.38 (m, 1H, C_7-H of naphthyridine), 8.48 (s, 1H, C_4-H of coumarin), 7.10-7.65 (m, 12H, CH of pyrazole, 11 Ar-H), 9.70 (s, 1H, CHO); MS(ESI): *m/z* 495.30 $[M+H]^+$

5b

IR (KBr): 1722 (lactone, C=O),1669 (aldehyde C=O) 1612 (C=N), 1580cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 3.92 (s, 3H, OCH3), 7.90 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.35 (m, 1H, C_7-H of naphthyridine), 8.50 (s, 1H, C_4-H of coumarin), 7.00-7.68 (m, 11H, CH of pyrazole, 10Ar-H), 9.72 (s, 1H, CHO); MS(ESI): *m/z* 525.35 $[M+H]^+$

5c

IR (KBr): 1731 (lactone, C=O), 1673(aldehyde C=O) 1610 (C=N), 1566 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.93 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.36 (m, 1H, C_7-H of

naphthyridine), 8.40 (s, 1H, C_4-H of coumarin), 7.12-7.60 (m, 11H, CH of pyrazole, 10 Ar-H), 9.70 (s, 1H, CHO); MS(ESI): *m/z* 529.35$[M+H]^+$

5d

IR (KBr): 1730 (lactone, C=O), 1675 (aldehyde, C=O), 1607 (C=N), 1572cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.92 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.43 (s, 1H, C_4-H of coumarin), 7.15-7.64 (m, 10H, CH of pyrazole, 9 Ar-H), 9.75 (s, 1H, CHO); MS(ESI): *m/z* 563.35 $[M+H]^+$

5e

IR (KBr): 1731 (lactone, C=O) 1672 (aldehyde C=O),1606 (C=N), 1567 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.95 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.38 (m, 1H, C_7-H of naphthyridine), 8.44 (s, 1H, C_4-H of coumarin), 7.10 – 7.78 (m, 11H, CH of pyrazole, 10 Ar-H), 9.73 (s, 1H, CHO); MS(ESI): *m/z* 573.20 $[M+H]^+$

5f

IR (KBr): 1732 (lactone, C=O), 1670 (aldehyde C=O) 1605 (C=N), 1559 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.93 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.42 (s, 1H, C_4-H of coumarin), 7.12-7.76 (m, 10 H, CH of pyrazole, 9Ar-H), 9.76 (s, 1H, CHO); MS(ESI): *m/z* 651.25 $[M+H]^+$

5g

IR (KBr): 1730 (lactone, C=O), 1682 (aldehyde C=O) 1610 (C=N), 1562 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 7.98 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.45 (m, 1H, C_7-H of naphthyridine), 8.48 (s, 1H, C_4-H of coumarin), 7.10-7.66 (m, 11H, CH of pyrazole, 10 Ar-H), 9.74 (s, 1H, CHO); MS(ESI): *m/z* 540.30 $[M+H]^+$

5h

IR (KBr): 1723 (lactone, C=O), 1669 (aldehyde C=O) 1617 (C=N), 1560 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) : δ 8.00 (m, 3H, C_4-H, C_5-H C_6-H of naphthyridine), 8.43 (m, 1H, C_7-H of naphthyridine), 8.45 (s, 1H, C_4-H of coumarin), 7.20-7.70 (m, 14H, CH of pyrazole, 13 Ar-H), 9.78 (s, 1H, CHO); MS(ESI): *m/z* 545.35 $[M+H]^+$.

Table 1: Characterization of compounds 4 and 5

Compd	Reaction Time (min)	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Cacld)		
					C	H	N
4a	0.25	195	96	$C_{29}H_{20}N_4O_2$	76.42 (76.30)	4.44 4.42	12.31 (12.27)
4b	0. 5	179	98	$C_{30}H_{22}N_4O_3$	74.17 (74.06)	4.57 4.56	11.57 (11.52)
4c	0.25	208	97	$C_{29}H_{19}ClN_4O_2$	71.08 (70.95	3.92 3.90	11.44 (11.41)
4d	0.5	215	96	$C_{29}H_{18}Cl_2N_4O_2$	66.42 (66.30)	3.47 3.45	10.70 (10.66)
4e	0.25	192	96	$C_{29}H_{19}BrN_4O_2$	65.17 (65.06)	3.60 3.58	10.50 (10.46)
4f	0.5	187	95	$C_{29}H_{18}Br_2N_4O_2$	56.83 (56.70)	2.96 2.95	9.15 (9.12)
4g	0. 5	198	96	$C_{29}H_{19}N_5O_4$	69.57 (69.45)	3.83 3.82	14.01 (13.97)
4h	0.5	221	96	$C_{33}H_{22}N_4O_2$	78.38 (78.25)	4.40 4.38	11.09 (11.06)
5a	2.5	152	86	$C_{31}H_{18}N_4O_3$	75.40 (75.29)	3.68 3.67	11.36 (11.33)
5b	3.0	170	87	$C_{32}H_{20}N_4O_4$	73.39 (73.27)	3.85 3.84	10.72 (10.68)
5c	3.5	112	86	$C_{31}H_{17}ClN_4O_3$	70.51 (70.39)	3.26 3.24	10.63 (10.59)
5d	4.0	134	85	$C_{31}H_{16}Cl_2N_4O_3$	60.20 (60.09)	2.87 2.86	9.98 (9.94)
5e	3.5	110	86	$C_{31}H_{17}BrN_4O_3$	65.05 (64.93)	3.91 2.99	9.81 (9.77)
5f	4.0	119	84	$C_{27}H_{13}Br_2N_4O_3$	57.20 (57.08)	2.49 2.47	8.62 (8.59)
5g	3.5	148	84	$C_{31}H_{17}N_5O_5$	69.13 (69.01)	3.20 3.18	13.01 (12.98)
5h	3.5	104	86	$C_{35}H_{20}N_4O_3$	77.32 (77.20)	3.72 3.70	10.33 (10.29)

5. Antibacterial activity

All the title compounds **5** were evaluated for their antibacterial activity against the Gram-negative Escherichia coli and Gram-positive *Bacillus subtilis* using filter paper disc method of Vincent and Vincent method[17] at 250 and 500 µg/disc concentrations. Gentamycin was used as standard for comparison. The results are given in Table 2. Compounds 5b, 5c and 5d showed promising antibacterial activity.

Table 2: Antibacterial activity results of the compounds 5

Compd	Inhibition zone (in mm)			
	E. coli at		*B. subtilis* at	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
5a	8.0	10.5	5.5	9.0
5b	10.0	12.5	6.5	9.0
5c	11.0	18.5	7.0	12.0
5d	10.0	13.5	6.0	10.5
5e	8.5	10.5	5.5	8.5
5f	8.0	9.5	5.0	7.5
5g	6.0	8.0	4.5	6.5
5h	7.0	9.0	6.0	10.0
Gentamycin	12.0	22.0	8.0	15.0

6. CONCLUSION

In summary, we have developed an efficient strategy for the synthesis of -[3-(2-naphthyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazole carbaldehydes. This method provides the desired products under operationally simple and convenient conditions with good yields. This approach involves a simple experimental procedure with broad substrate scope and is sustainable to wide range of functionalities. All the desired products showed very promising antibacterial activity against the standards.

7. ACKNOWLEDGMENTS

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