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Note

Synthesis and antibacterial activity of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles

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Condensation of 2-hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine **2** with different acetophenones in methanol containing a catalytic amount of glacial acetic acid affords the corresponding acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **3** in excellent yields. The hydrazones **3** when subjected to the Vilsmeier-Haack reaction with $POCl_3$-DMF gives 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles **4** in good yields. The structural assignments to compounds **3** and **4** are based on their elemental analyses and spectral data. Compounds **4** have been tested for their antibacterial activity.

Keywords: 2-Hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine, acetophenones, 1,8-naphthyridin-2-ylhydrazones, Vilsmeier-Haack reagent, 1,8-naphthyridinyl-pyrazoles.

1,8-Naphthyridines are an important class of heterocyclic compounds, several derivatives of which have been found to possess diverse types of biological activities including antibacterial[1], antihypertensive[2], antitumor[3] and anti-inflammatory[4]. Pyrazoles represent one of the most active classes of compounds possessing wide spectrum of biological activities[5-8]. In continuation of the earlier work[9-12] on synthesis of new 1,8-naphthyridine derivatives with potential biological activity, the present work involves the synthesis and antibacterial activity of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles.

The starting compound, 2-hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine **2** (ref. 13) required for the preparation of the target compounds, was obtained by the hydrazinolysis of 2-chloro-3-(3-chlorophenyl)-1,8-naphthyridine **1**. Compound **2** on condensation with different acetophenones in methanol in the presence of a catalytic amount of glacial acetic acid afforded the corresponding acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **3** in excellent yields. The hydrazones **3** on treatment with Vilsmeier-Haack reagent ($POCl_3$-DMF) furnished 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles **4** in good yields(**Scheme I,Table I**).

The structures of the compounds **3** and **4** have been confirmed on the basis of analytical and spectral (IR and ^{1}H NMR) data.

Antibacterial activity

All the title compounds **4** were screened *in vitro* for their antibacterial activity against the Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* using filter paper disc method of Vincent and Vincent[14] at 250 and 500 μg/disc concentrations. Gentamycin was used as standard for comparison. The results are given in **Table II.**

Experimental Section

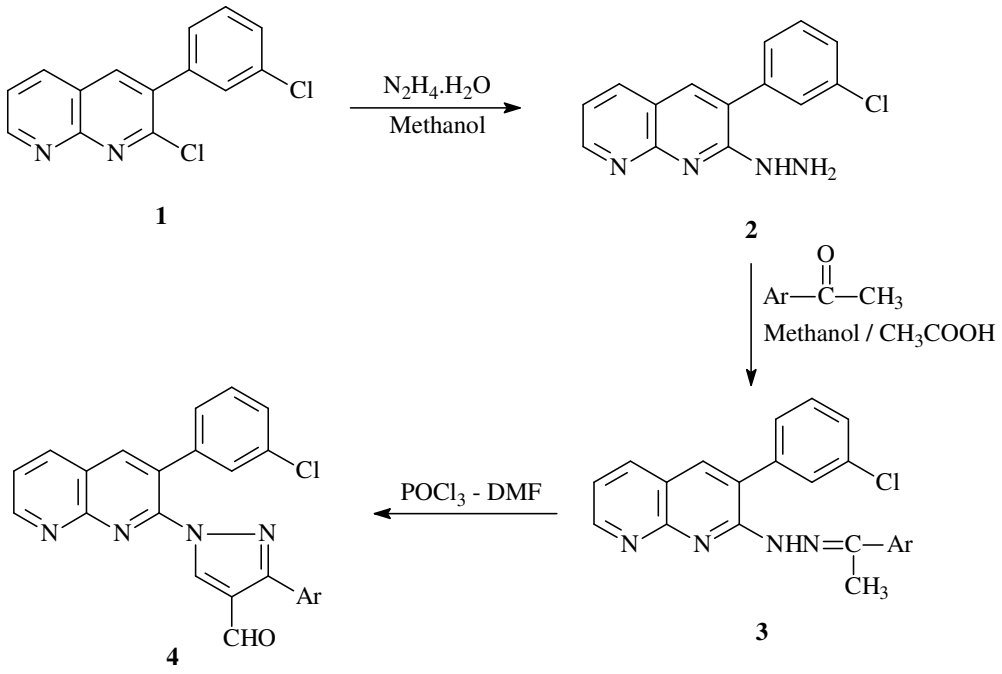
Melting points were recorded using Cintex melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC on silica gel G plates. IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard.

General procedure for the synthesis of acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 3. A mixture of **2** (0.01 mole) and appropriate acetophenone (0.01 mole) in methanol (30 mL) containing a drop of glacial acetic acid was refluxed for 0.5 hr. The solid that separated out on cooling was filtered and recrystallized from methanol to afford **3** (**Table I**).

3a: IR (KBr): 3362 (NH), 1624 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) : δ 2.35 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.83 (m, 3H, C_4-H, C_5-H, C_6-H), 8.24 (m, 1H, C_7-H), 6.82 – 7.68 (m, 8H, Ar-H), 10.00 (s, 1H, NH).

3c: IR (KBr): 3355 (NH), 1623 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.74 (m, 1H, C_6-H), 7.82 (m, 2H, C_4-H, C_5-H), 8.28 (m, 1H, C_7-H), 6.95 – 7.60 (m, 8H, Ar-H), 10.05 (s, 1H, NH).

3d: IR (KBr): 3357 (NH), 1622 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) : δ 2.42 (s, 3H, CH_3), 7.78 (m, 3H,



Scheme I

Table I — Characterization data of compounds **3** and **4**

Compd	Ar	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
3a	*p*-$CH_3OC_6H_4$	140	92	$C_{23}H_{19}N_4OCl$	68.76 (68.57	4.77 4.72	13.99 13.91)
3b	*p*-$CH_3C_6H_4$	160	95	$C_{23}H_{19}N_4Cl$	71.59 (71.41	4.96 4.92	14.56 14.49)
3c	*p*-ClC_6H_4	190	94	$C_{22}H_{16}N_4Cl_2$	64.97 (64.86	3.97 3.93	13.82 13.76)
3d	*p*-BrC_6H_4	212	92	$C_{22}H_{16}N_4ClBr$	58.79 (58.60	3.60 3.55	12.50 12.43)
3e	*o*-HOC_6H_4	155	89	$C_{22}H_{17}N_4OCl$	67.78 (67.95	4.43 4.38	14.47 14.41)
3f	*p*-HOC_6H_4	258	90	$C_{22}H_{17}N_4OCl$	67.77 (67.95	4.44 4.38	14.49 14.41)
3g	*m*-$NO_2C_6H_4$	185	88	$C_{22}H_{16}N_5O_2Cl$	63.41 (63.23	3.88 3.83	16.84 16.77)
3h	*p*-$NO_2C_6H_4$	255	92	$C_{22}H_{16}N_5O_2Cl$	63.40 (63.23	3.89 3.83	16.83 16.77)
3i	C_6H_5	110	90	$C_{22}H_{17}N_4Cl$	71.04 (70.87	4.59 4.56	15.10 15.03)
3j	β-Naphthyl	88	90	$C_{26}H_{19}N_4Cl$	74.05 (73.85	5.00 4.50	13.32 13.25)
4a	*p*-$CH_3OC_6H_4$	>300	72	$C_{25}H_{17}N_4O_2Cl$	68.24 (68.10	3.90 3.86	12.78 12.71)
4b	*p*-$CH_3C_6H_4$	>300	80	$C_{25}H_{17}N_4OCl$	70.85 (70.67	4.04 4.00	13.26 13.19)
4c	*p*-ClC_6H_4	>300	78	$C_{24}H_{14}N_4Ocl_2$	64.90 (64.72	3.20 3.15	12.67 12.58)

— Contd

Table I — Characterization data of compounds **3** and **4**— *Contd*

Compd	Ar	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
4d	*p*-BrC_6H_4	>300	71	$C_{24}H_{14}N_4OClBr$	59.14 (58.96	2.92 2.87	11.52 11.46)
4e	*o*-HOC_6H_4	>300	67	$C_{24}H_{15}N_4O_2Cl$	67.73 (67.53	3.56 3.51	13.19 13.13)
4f	*p*-HOC_6H_4	>300	70	$C_{24}H_{15}N_4O_2Cl$	67.71 (67.53	3.57 3.51	13.18 13.13)
4g	*m*-$NO_2C_6H_4$	>300	65	$C_{24}H_{14}N_5O_3Cl$	63.41 (63.23	3.12 3.07	15.42 15.37)
4h	*p*-$NO_2C_6H_4$	>300	68	$C_{24}H_{14}N_5O_3Cl$	63.42 (63.23	3.11 3.07	15.44 15.37)
4i	C_6H_5	>300	70	$C_{24}H_{15}N_4OCl$	70.32 (70.16	3.69 3.65	13.70 13.64)
4j	β-Naphthyl	>300	66	$C_{28}H_{17}N_4Cl$	75.77 (75.59	3.87 3.82	12.68 12.60)

Table II – Antibacterial activity data of compounds **4**

Compd	Inhibition zone in mm			
	E. coli at		*B. subtilis* at	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
4a	5.5	8.0	4.0	8.5
4b	8.0	12.5	6.0	9.5
4c	9.5	15.0	7.5	10.0
4d	7.5	9.0	4.0	6.0
4e	5.0	7.0	3.5	5.5
4f	6.5	10.0	4.5	7.5
4g	4.5	7.5	3.5	5.0
4h	5.5	8.0	4.0	6.0
4i	6.0	9.5	4.5	6.5
4j	6.5	9.0	5.0	7.0
Gentamycin	12	22	8	15

C_4-H, C_5-H, C_6-H), 8.30 (m, 1H, C_7-H), 6.95 – 7.65 (m, 8H, Ar-H), 10.05 (s, 1H, NH).

3h: IR (KBr): 3360 (NH), 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.46 (s, 3H, CH_3), 8.20 (m, 3H, C_4-H, C_5-H, C_6-H), 8.40 (m, 1H, C_7-H), 7.08 – 7.90 (m, 8H, Ar-H), 10.30 (s, 1H, NH).

3i: IR (KBr): 3354 (NH), 1617 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, CH_3), 8.20 (m, 3H, C_4-H, C_5-H, C_6-H), 8.32 (m, 1H, C_7-H), 6.92 – 7.83 (m, 11H, Ar-H), 10.15 (s, 1H, NH).

General procedure for the synthesis of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 4. To the Vilsmeier-Haack reagent prepared from DMF (10 mL) and $POCl_3$ (1.1 mL, 0.012 mole), hydrazone **3** (0.01 mole) was added and the reaction mixure stirred at 60-65°C for 3 hr and then poured into ice-cold water. The solid that separated on neutralization with $NaHCO_3$ was filtered, washed with water and recrystallized from methanol to give **4** (**Table I**).

4a: IR (KBr): 1671 (C=O), 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 8.10 (m, 1H, C_6-H), 8.22 (s, 1H, C_4-H), 8.40 (m, 1H, C_5-H), 8.75 (m, 1H, C_7-H), 6.80 – 7.95 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

4c: IR (KBr): 1678 (C=O), 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.02 (m, 1H, C_6-H), 8.15 (s, 1H, C_4-H), 8.30 (m, 1H, C_5-H), 8.72 (m, 1H, C_7-H), 7.15 – 7.80 (m, 9H, CH of pyrazole, 8Ar-H), 9.66 (s, 1H, CHO).

4d: IR (KBr): 1684 (C=O), 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.15 (m, 1H, C_6-H), 8.40 (m, 2H, C_4-H, C_5-H), 8.70 (m, 1H, C_7-H), 7.15 – 7.90 (m, 9H, CH of pyrazole, 8Ar-H), 9.62 (s, 1H, CHO).

4h: IR (KBr): 1674 (C=O), 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.00 (m, 1H, C_6-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.60 (m, 1H, C_7-H), 7.22 – 7.88 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

4j: IR (KBr): 1678 (C=O), 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.15 (m, 1H, C_6-H), 8.40 (m, 2H, C_4-H, C_5-H), 8.70 (m, 1H, C_7-H), 7.20 – 7.98 (m, 12H, CH of pyrazole, 11Ar-H), 9.63 (s, 1H, CHO).

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