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Synthesis and antibacterial activity of 1,3,4-oxadiazolyl-1,8-naphthyridines

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Condensation of (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)-acetic acid hydrazide **2** with different acetophenones yields the corresponding acetophenone (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)methylcarbonyl hydrazones **3**, which on treatment with acetic anhydride affords the respective 1-(4-acetyl-5-aryl-5-methyl-[1,3,4]oxadiazol-2-ylmethyl)-3-phenyl-1*H*-[1,8]naphthyridin-2-ones **4**. The structures of the compounds **3** and **4** have been confirmed on the basis of analytical and spectral data. The compounds **4** have been screened for their antibacterial activity.

Keywords: 1,8-Naphthyridinyl acetic acid hydrazide, acetophenones, condensation, 1,8-naphthyridinyl methylcarbonyl hydrazones acetic anhydride, cyclization, 1,3,4-oxadiazolyl-1, 8-naphthyridines

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1,3,4-Oxadiazoles constitute one of the most active class of compounds possessing diverse pharmacological and microbiological activity[1-4]. Literature survey reveals that various 1,8-naphthyridines have attracted considerable attention as they are also endowed with a wide range of biological activity[5-8]. In the light of these findings and in view of sustained interest in the synthesis of 1,8-naphthyridine derivatives[9-13], the synthesis of some new 1,3,4-oxadiazoles incorporating the 1,8-naphthyridine moiety *via* methylene bridge has been undertaken in order to assess their antibacterial profile.

Ethyl (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)-acetate **1**, obtained by the alkylation of 3-phenyl-1,8-naphthyridin-2(1*H*)-one with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3, on hydrazinolysis with refluxing hydrazine hydrate furnished the desired synthon, (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)acetic acid hydrazide **2** (Ref. 13). Compound **2** on condensation with different acetophenones in ethanol containing a catalytic amount of glacial acetic acid yielded the corresponding acetophenone (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)-methylcarbonylhydrazones **3** in excellent yields. Cyclization of **3** with an excess of acetic anhydride afforded 1-(4-acetyl-5-aryl-5-methyl-[1, 3, 4]oxadiazol-2-ylmethyl)-3-phenyl-1*H*-[1, 8]naphthyridin-2-ones **4** (**Scheme I**).

The structures of the compounds **3** and **4** were established by their elemental analyses and spectral (IR and ^{1}H NMR) data (**Table I**).

Antibacterial activity

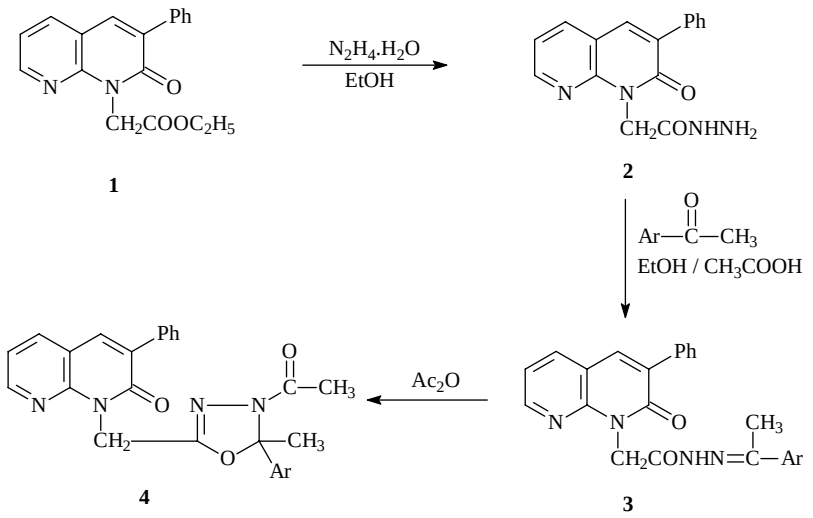
The antibacterial activity was assayed using filter paper disc method of Vincent and Vincent[14] by measuring the zone of inhibition in mm. All the title compounds **4** were screened *in vitro* for their antibacterial activity against the Gram-negative *Escherichia coli* and Gram-positive *Bacillus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

Experimental Section

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was determined by TLC. IR spectra were recorded in KBr pellet 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 preparation of acetophenone (2-oxo-3-phenyl-2*H*-[1,8]naphthyridin-1-yl)methyl-carbonyl hydrazone, 3a-h

A mixture of **2** (0.01 mole) and appropriate acetophenone (0.01 mole) in ethanol with a trace of



Scheme I

Table I – Physical and ^{1}H NMR spectral characterization data of compounds **3a-h** and **4a-h**

Compd	Ar	m.p. °C	Yield (%)	Mol. formula (Mol. wt)	Found (%) Cacld C	H	N	^{1}H NMR ($CDCl_3$) (δ, ppm)
3a	C_6H_5	264	85	$C_{24}H_{20}N_4O_2$ (396)	72.98 (72.72	5.09 5.05	14.20 14.14)	2.22 (s, 3H, CH_3), 5.92 (s, 2H, CH_2), 7.80 (m, 2H, C_4-H, C_6-H), 7.93 (m, 1H, C_4-H), 8.55 (m, 1H, C_7-H), 8.80 (s, 1H, CONH), 7.11-7.50 (m, 10H, Ar-H)
3b	*p*-$CH_3C_6H_4$	250	94	$C_{25}H_{22}N_4O_2$ (410)	73.35 (73.17	5.31 5.36	13.73 13.65)	2.20 (s, 3H, CH_3), 2.30 (s, 3H, N=C-CH_3), 5.85 (s, 2H, CH_2), 7.85 (m, 2H, C_4-H, C_6-H), 8.00 (m, 1H, C_5-H), 8.63 (m, 1H, C_7-H), 9.02 (s, 1H, CONH), 7.02-7.48 (m, 9H, Ar-H)
3c	*p*-$CH_3OC_6H_4$	230	90	$C_{25}H_{22}N_4O_3$ (426)	70.60 (70.42	5.20 5.16	13.22 13.14)	2.28 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.82 (s, 2H, CH_2), 7.78 (m, 2H, C_4-H, C_6-H), 7.97 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 9.12 (s, 1H, CONH), 7.15-7.52 (m, 9H, Ar-H)
3d	*p*-ClC_6H_4	260	92	$C_{24}H_{19}N_4O_2Cl$ (430.5)	66.73 (66.90	4.46 4.41	13.09 13.01)	2.23 (s, 3H, CH_3), 5.85 (s, 2H, CH_2), 7.80 (m, 2H, C_4-H, C_6-H), 7.95 (m, 1H, C_5-H), 8.52 (m, 1H, C_7-H), 9.05 (s, 1H, CONH), 7.05-7.50 (m, 9H, Ar-H)
3e	*p*-BrC_6H_4	210	89	$C_{24}H_{19}N_4O_2Br$ (474)	60.99 (60.76	4.05 4.01	11.88 11.81)	2.22 (s, 3H, CH_3), 5.90 (s, 2H, CH_2), 7.82 (m, 2H, C_4-H, C_6-H), 7.89 (m, 1H, C_5-H), 8.56 (m, 1H, C_7-H), 9.00 (s, 1H, CONH), 7.12-7.47 (m, 9H, Ar-H)
3f	*m*-$NO_2C_6H_4$	205	88	$C_{24}H_{19}N_5O_4$ (441)	65.48 (65.31	4.36 4.31	15.95 15.87)	2.27 (s, 3H, CH_3), 5.93 (s, 2H, CH_2), 7.88 (m, 2H, C_4-H, C_6-H), 8.12 (m, 1H, C_5-H), 8.70 (m, 1H, C_7-H), 9.12 (s, 1H, CONH), 7.15-7.49 (m, 9H, Ar-H)
3g	*p*-$NO_2C_6H_4$	200	90	$C_{24}H_{19}N_5O_4$ (441)	65.49 (65.31	4.35 4.31	15.94 15.87)	2.25 (s, 3H, CH_3), 5.94 (s, 2H, CH_2), 7.92 (m, 2H, C_4-H, C_6-H), 8.20 (m, 1H, C_5-H), 8.87 (m, 1H, C_7-H), 9.20 (s, 1H, CONH), 7.12-7.47 (m, 9H, Ar-H)

(Contd)

Table I – Physical and ^{1}H NMR spectral characterization data of compounds **3a-h** and **4a-h**—*Contd*

Compd	Ar	m.p. °C	Yield (%)	Mol. formula (Mol. wt)	Found (%) Cacld C	H	N	^{1}H NMR ($CDCl_3$) (δ, ppm)
3h	β-Naphthyl	262	87	$C_{28}H_{22}N_4O_2$ (446)	75.53 (75.34	4.98 4.93	12.62 12.56)	2.23 (s, 3H, CH_3), 5.92 (s, 2H, CH_2), 7.82 (m, 2H, C_4-H, C_6-H), 7.90 (m, 1H, C_5-H), 8.56 (m, 1H, C_7-H), 8.85 (s, 1H, CONH), 7.08-7.51 (m, 12H, Ar-H)
4a	C_6H_5	>300	60	$C_{26}H_{22}N_4O_3$ (438)	71.41 (71.23	5.06 5.02	12.72 12.79)	2.20 (s, 3H, CH_3), 2.35 (s, 3H, $COCH_3$), 5.43 (s, 2H, CH_2), 7.69 (m, 2H, C_4-H, C_6-H), 7.96 (m, 1H, C_5-H), 8.51 (m, 1H, C_7-H), 7.16-7.57 (m, 10H, Ar-H)
4b	*p*-$CH_3C_6H_4$	>300	70	$C_{27}H_{24}N_4O_3$ (452)	71.87 (71.68	5.35 5.31	12.47 12.39)	2.18 (s, 3H, CH_3, 2.22 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 5.52 (s, 2H, CH_2), 7.76 (m, 2H, C_4-H, C_6-H), 7.93 (m, 1H, C_5-H), 8.38 (m, 1H, C_7-H), 7.08-7.52 (m, 9H, Ar-H)
4c	*p*-$CH_3OC_6H_4$	>300	64	$C_{27}H_{24}N_4O_4$ (468)	69.39 (69.23	5.18 5.13	11.91 11.97)	2.20 (s, 3H, CH_3), 2.38 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 5.48 (s, 2H, CH_2), 7.80 (m, 2H, C_4-H, C_6-H), 8.05 (m, 1H, C_5-H), 8.56 (m, 1H, C_7-H), 7.05-7.43 (m, 9H, Ar-H)
4d	*p*-ClC_6H_4	>300	68	$C_{26}H_{21}N_4O_3Cl$ (472.5)	66.21 (66.03	4.49 4.44	11.92 11.85)	2.18 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 5.54 (s, 2H, CH_2), 7.76 (m, 2H, C_4-H, C_6-H), 7.98 (m, 1H, C_5-H), 8.57 (m, 1H, C_7-H), 7.08-7.53 (m, 9H, Ar-H)
4e	*p*-BrC_6H_4	>300	62	$C_{26}H_{21}N_4O_3Br$ (516)	60.66 (60.47	4.02 4.07	10.93 10.85)	2.16 (s, 3H, CH_3), 2.38 (s, 3H, $COCH_3$), 5.56 (s, 2H, CH_2), 7.79 (m, 2H, C_4-H, C_6-H), 8.15 (m, 1H, C_7-H), 8.60 (m, 1H, C_7-H), 7.10-7.49 (m, 9H, Ar-H)
4f	*m*-$NO_2C_6H_4$	>300	61	$C_{26}H_{21}N_5O_5$ (483)	64.89 (64.60	4.40 4.35	14.57 14.49)	2.18 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 5.58 (s, 2H, CH_2), 7.83 (m, 2H, C_4-H, C_6-H), 8.23 (m, 1H, C_5-H), 8.85 (m, 1H, C_7-H), 7.10-7.47 (m, 9H, Ar-H)
4g	*p*-$NO_2C_6H_4$	>300	63	$C_{26}H_{21}N_5O_5$ (483)	64.87 (64.60	4.41 4.35	14.56 14.49)	2.17 (s, 3H, CH_3), 2.45 (s, 3H, $COCH_3$), 5.57 (s, 2H, CH_2), 7.86 (m, 2H, C_4-H, C_6-H), 8.36 (m, 1H, C_5-H), 8.92 (m, 1H, C_7-H), 7.15 – 7.54 (m, 9H, Ar-H)
4h	β-Naphthyl	>300	62	$C_{30}H_{24}N_4O_3$ (488)	73.95 (73.77	4.96 4.92	11.56 11.48)	2.19 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 7.90 (m, 2H, C_4-H, C_6-H), 8.02 (m, 1H, C_5-H), 8.65 (m, 1H, C_7-H), 7.12-7.49 (m, 12H, Ar-H)

glacial acetic acid was refluxed for 2 h. The solid that separated out on cooling was filtered and purified by recrystallization from ethanol to afford **3a-h**. The characterization data of compounds **3a-h** are given in **Table I**.

General procedure for the preparation of 1-(4-acetyl-5-aryl-5-methyl-[1, 3, 4]oxadiazol-2-yl-methyl)-3-phenyl-1*H*-[1,8]naphthyridin-2-one, 4a-h

A mixture of **3a** (0.01 mole) and an excess of acetic anhydride (15 mL) was refluxed for 3 h. The excessive acetic anhydride was distilled off and the residue was poured into ice-cold water. The solid that

Table II — Antibacterial screening results of compounds **4a-h**

Compd	Inhibition zone in mm			
	E. coli at		*B. subtilis* at	
	250 μg/ disc	500 μg/ disc	250 μg/ disc	500 μg/ disc
4a	2.0	3.5	1.5	2.5
4b	3.5	5.0	2.0	3.5
4c	2.5	4.0	1.0	2.0
4d	5.0	7.5	3.5	5.5
4e	3.0	4.0	1.5	3.0
4f	2.0	3.0	1.0	2.5
4g	3.0	4.5	2.5	4.0
4h	1.5	2.5	1.0	2.0
Gentamycin	12	22	8	15

separated was filtered, washed with water and purified by recrystallization from ethanol to afford **4a-h**. The characterization data of compounds **4a-h** are given in **Table I**.

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