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Synthesis and antibacterial activity of some novel spiro [3*H*-indole-3,5′-[1,3,4]oxadiazolo[3,2-*c*]thiazole]-2(1*H*)-ones and [1,3,4]oxadiazino[6,5-b]indoles containing 1,8-naphthyridine moiety

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Interaction of 2-phenyl-1,8-naphthyridine-3-carboxylic acid hydrazide **1** with different isatins **2** gives the corresponding isatin-β-(2-prenyl-1,8-naphthyridine-3-carbonylhydrazones) **3**. Cyclocondensation of **3** with mercaptoacetic acid in DMF in the presence of anhyd. $ZnCl_2$ affords 3′-(2-phenyl-1,8-naphthyridine-3-carbonylamino)spiro[3*H*-inole-3,2′-thiazolidine]-2,4′ (1*H*)-diones **4**, which on treatment with conc. H_2SO_4 undergo cyclodehydration to furnish the desired 2′-(2-phenyl-1,8-naphthyridin-3-yl) spiro[3*H*-indole-3,5′-[1,3,4]oxadiazolo[3,2-*c*]thiazole]-2(1*H*)-ones **5**. On the other hand, the hydrazones **3** on treatment with conc. H_2SO_4 leads to the formation of 2-(2-phenyl-1,8-naphthyridin-3-yl)-[1,3,4]oxadiazino[6,5-*b*]indoles **6**. The structures of the compounds **3-6** have been established on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and mass) data. The compounds **5** and **6** have been screened for their antibacterial activity.

Literature survey reveals that both 1,3,4-oxadiazoles[1,2] and thiazoles [3,4] are well known for their varied pharmacological and microbiological activities. Certain 1,8-naphthyridine derivatives are reported to be useful antibacterial[5,6] diuretic[7], antimalarial[8], anti-inflammatory[9] and antitumor[10] agents. The indole[11-13] and 1,3,4-oxadiazine[14] classes of heterocycles are of current interest due to their broad spectrum biological activity. Furthermore, in recent years chemistry on nitrogen bridged heterocycles has emerged as a frontier area of research in synthetic organic chemistry. Encouraged by these reports and in continuation of our interest in the chemistry of 1,8-naphthyridines[15-21], we report herein, the synthesis of a novel bridgehead nitrogen heterocyclic system containing a spiro-linkage, *viz.*, spiro[3*H*-indole-3,5′-[1,3,4]oxadiazolo-[3,2-*c*]oxadiazino[6,5-*b*]indoles containing 1,8-naphthyridine moiety. These compounds have been synthesized following the reaction sequence shown in **Scheme I**.

The starting compound, 2-phenyl-1,8-naphthyridine-3-carboxylic acid hydrazide **1** required for the preparation of the target compounds, was obtained by hydrazinolysis of ethyl 2-phenyl-1,8-naphthyridine-3-carboxylate[19], which in turn was prepared by the condensation of 2-aminonicotinaldehyde with ethyl benzoyl acetate in boiling methanol containing a catalytic amount of piperidine[19]. Compound **1** on reaction with different isatins **2** in methanol containing a catalytic amount of gl. acetic acid furnished the corresponding isatin-β-(2-phenyl-1,8-naphthyridine-3-carbonylhydrazones) **3** in very good yields. The hydrazones **3** on cyclocondensation with mercaptoacetic acid in refluxing DMF in the prescence of anhyd. $ZnCl_2$ afforded 3′-(2-phenyl-1,8-naphthyridine-3-carbonylamino)-spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **4**, which on cyclodehydration with conc. H_2SO_4 yielded 2′-(2-phenyl-1,8-napthyridin-3-yl)spiro[3*H*-indole-3,5′-[1,3,4]oxadiazolo-[3,2-*c*] thiazole]-2-(1*H*)-ones **5**.

Further, the hydrazones **3** on treatment with conc. H_2SO_4 at room temperature underwent cyclodehydration to afford 2-(2-phenyl-1,8-naphthyridin-3-yl)-[1,3,4]oxadiazino [6,5-*b*] indoles **6** (**Scheme I, Table I**).

The structural assignments to compounds **3** - **6** were based on their elemental analyses and spectral (IR, ^{1}H NMR and mass) data.

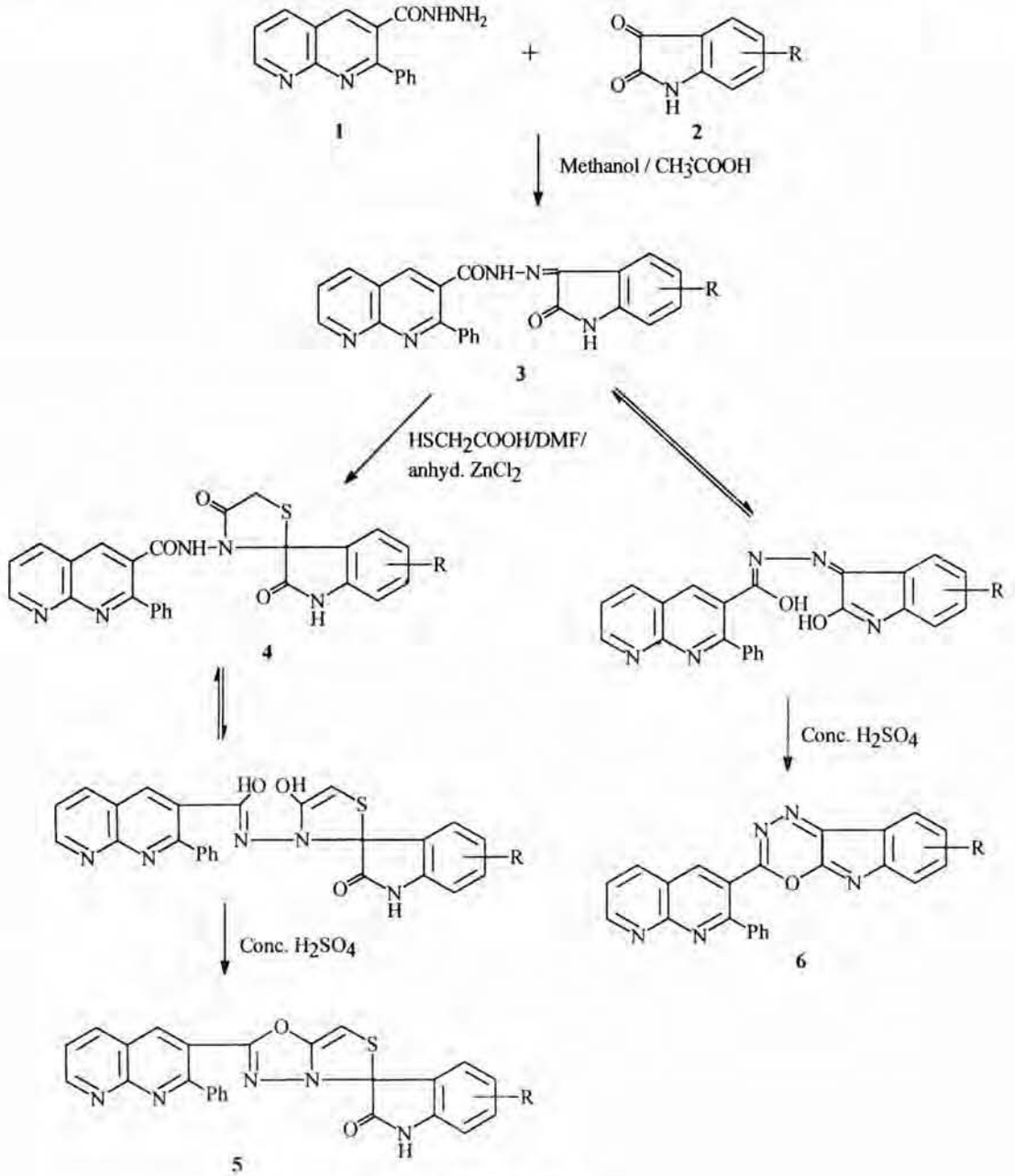
Antibacterial activity

The antibacterial activity of the compounds **5a-g** and **6a-g** was determined by filter paper disc method[22] against the following bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Bacillus mycoides* at 400 and 600 μg/disc concentrations using streptomycin as a standard drug at same concentration for comparison. The results are presented in **Table II**. The antibacterial activity data indicate that all the compounds are moderately to

highly active to the test bacteria at 600 μg/disc concentration. The activity of the compound depends upon the nature and position of the substituent at the indole moiety. Compounds **5b, 5e, 5f** and **6e** displayed promising antibacterial activity. Introduction of methoxyl group at indole moiety diminishes the activity of the compounds. Compound **5e** showed remarkable and comparable activity with that of standard drug streptomycin at the same concentration.

Experimental Section

General. Melting points were taken in open capillaries on a Cintex melting point apparatus and are uncorrected. Purity of the compounds were checked by TLC. IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a VG micromass 70 70 H instrument at 70 eV.



Scheme I

Table I—Characterization data of compounds **3 - 6**

Compd	R	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
3a	H	252	78	$C_{23}H_{15}N_5O_2$	70.38 (70.2	3.86 3.82	17.74 17.81)
3b	5-CH_3	230	90	$C_{24}H_{17}N_5O_2$	70.74 (70.76	4.21 4.18	17.32 17.20)
3c	7-CH_3	216	86	$C_{24}H_{17}N_5O_2$	70.93 (70.76	4.22 4.18	17.31 17.20)
3d	3-OCH_3	238	83	$C_{24}H_{17}N_5O_3$	68.24 (68.09	4.08 4.02	16.48 16.55)
3e	5-Cl	226	88	$C_{23}H_{14}N_5O_2Cl$	64.82 (64.64	3.21 3.28	16.46 16.39)
3f	7-Cl	242	84	$C_{23}H_{14}N_5O_2Cl$	64.80 (64.64	3.23 3.28	16.45 16.39)
3g	5-Br	194	80	$C_{23}H_{14}N_5O_2Br$	8.33 (58.47	2.88 2.97	14.94 14.83)
4a	H	300	70	$C_{25}H_{17}N_5O_3S$	64.40 (64.24	3.68 3.64	14.91 14.99)
4b	5-CH_3	>300	80	$C_{26}H_{19}N_5O_3S$	64.72 (64.86	3.91 3.95	14.63 14.55)
4c	7-CH_3	>300	75	$C_{26}H_{19}N_5O_3S$	64.70 (64.86	3.90 3.95	14.65 14.55)
4d	5-OCH_3	>300	73	$C_{26}H_{19}N_5O_4S$	62.95 (62.78	3.76 3.82	14.14 14.08)
4e	5-Cl	>300	78	$C_{25}H_{16}N_5O_3SCl$	59.72 (59.88	3.13 3.19	13.83 13.97)
4f	7-Cl	>300	74	$C_{25}H_{16}N_5O_3SCl$	59.71 (59.85	3.15 3.19	13.81 13.97)
4g	5-Br	>300	72	$C_{25}H_{16}N_5O_3SBr$	54.80 (54.95	2.86 2.93	12.91 12.82)
5a	H	>300	50	$C_{25}H_{15}N_5O_2S$	66.75 (66.82	3.42 3.34	15.70 15.59)
5b	5-CH_3	>300	65	$C_{26}H_{17}N_5O_2S$	67.53 (67.39	3.62 3.67	15.23 15.12)
5c	7-CH_3	>300	60	$C_{26}H_{17}N_5O_2S$	67.55 (67.39	3.60 3.67	15.25 15.12)
5d	5-OCH_3	>300	58	$C_{26}H_{17}N_5O_3S$	65.32 (65.14	3.63 3.55	14.72 14.61)
5e	5-Cl	>300	63	$C_{25}H_{14}N_5O_2SCl$	62.32 (62.11	2.75 2.90	14.55 14.49)
5f	7-Cl	>300	61	$C_{25}H_{14}N_5O_2SCl$	62.34 (62.11	2.72 2.90	14.56 14.49)
5g	5-Br	>300	56	$C_{25}H_{14}N_5O_2SBr$	56.65 (56.82	2.61 2.65	13.40 13.26)
6a	H	258(d)	55	$C_{23}H_{13}N_5O$	73.78 (73.60	3.41 3.47	18.79 18.67)
6b	6-CH_3	274	70	$C_{24}H_{15}N_5O$	74.23 (74.04	3.82 3.86	17.80 17.99)
6c	8-CH_3	>300	66	$C_{24}H_{15}N_5O$	74.22 (74.04	3.80 3.86	17.82 17.99)
6d	6-OCH_3	>300	64	$C_{24}H_{15}N_5O_2$	71.24 (71.11	3.79 3.70	17.37 17.28)
6e	6-Cl	262	68	$C_{23}H_{12}N_5OCl$	67.60 (67.48	2.99 2.93	17.26 17.11)
6f	8-Cl	283	63	$C_{23}H_{12}N_5OCl$	67.62 (67.48	2.97 2.93	17.28 17.11)
6g	8-Br	247	65	$C_{23}H_{12}N_5OBr$	60.61 (60.79	2.61 2.64	15.54 15.42)

Table II — Antibacterial activity results of the compounds **5** and **6**

Compd	Inhibition zone (in mm) against							
	E. coli at		*P. aeruginosa* at		*B. subtitis* at		*B. mycoides* at	
	400 µg/disc.	600 µg/disc.	400 µg/disc.	600 µg/disc.	400 µg/disc.	600 µg/disc.	400 µg/disc.	600 µg/disc.
5a	4.5	5.5	3.5	4.5	3.0	4.0	2.5	3.5
5b	7.5	8.5	6.5	8.0	5.5	7.0	4.5	5.5
5c	6.5	8.0	6.0	7.5	5.0	6.5	4.0	5.0
5d	3.5	5.0	2.5	3.5	2.0	3.5	2.5	3.5
5e	11.5	13.5	10.5	12.0	8.5	10.0	7.5	8.5
5f	9.5	10.5	8.5	10.0	7.0	9.0	7.0	8.0
5g	6.0	7.5	5.5	6.5	4.5	5.5	4.0	5.0
6a	3.5	4.5	2.5	3.5	2.0	3.0	1.5	2.5
6b	6.5	8.0	5.0	6.0	4.0	5.5	3.0	4.5
6c	5.5	6.5	4.0	5.5	3.5	4.0	2.5	3.5
6d	3.0	4.0	2.5	3.5	2.0	3.5	3.0	4.0
6e	10.0	11.5	8.5	10.0	7.0	8.5	6.5	8.0
6f	7.0	8.5	6.0	7.0	5.0	6.5	4.0	5.5
6g	5.0	6.5	4.5	5.5	3.0	4.5	2.5	3.5
Streptomycin	13.0	15.0	15.0	17.0	10.0	12.0	9.0	11.0

Isatin-β-(2-phenyl-1,8-naphthyridine-3-carbonyl-hydrazone) 3a. A mixture of **1** (0.01 mole) and **2** (R = H, 0.01 mole) in methanol (30 mL) in the presence of a catalytic amount of gl. acetic acid was heated under reflux for 30 min. The solid that separated on cooling was filtered, washed with cold methanol and recrystallized from methanol to give **3a**, yield 78%, m.p. 252°C; IR (KBr) : 3207 (NH), 1732 (indole C=O), 1665 (CONH), 1607 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) : δ 8.3 (m, 1H, C_4-H), 8.7 (m, 1H, C_5-H), 7.8 (m, 1H, C_6-H), 9.2 (m, 1H, C_7-H), 6.8-7.5 (m, 9H, Ar-H), 10.6 (s, 1H, CON*H*), 11.05 (s, 1H, indole NH); MS : m/z 393 (M^+, 5.6%), 365 (8), 248 (14), 233 (100), 206 (30), 205 (44), 178 (7), 102 (23.3), 91 (43.5), 75 (13.3).

Other compounds in the series were prepared similarly and are listed in **Table I**.

3-(2-Phenyl-1,8-naphthyridine-3-carbonylamino)-spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-dione 4a. A mixture of **3a** (0.01 mole) and mercaptoacetic acid (0.01 mole) in DMF (30 mL) containing a pinch of anhyd. $ZnCl_2$ was heated under reflux for 6 hr. The reaction mixture was cooled and poured onto crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from DMF to afford **4a**, yield 70%, m.p. 300 °C; IR (KBr) : 3245 (NH), 1740 (thiazolidinone C=O), 1695 (indole C=O, and CONH), 1600 cm^{-1} (C=N); MS : m/z 467 (M^+, 6.4%), 425 (12.5), 248 (20), 233 (100), 219 (7.5%), 205 (68), 178 (32), 177 (16), 102 (52), 75 (18).

Other compounds in the series were prepared similarly and are lised in **Table I**.

2′-(2-Phenyl-1,8-naphthyridin-3-yl)spiro[3*H*-indole-3,5′-[1,3,4]oxadiazolo [3,2-*c*]thiazole]-2(1*H*)-one 5a. Compound **4a** (0.01 mole) was added slowly to conc. H_2SO_4 (10 mL) in the cold. The reaction mixture was kept for 6 hr at room temperature, poured onto crushed ice and neutralized with ammonia solution. The precipitate thus obtained was filtered, washed with water and recrystallized from DMF to furnish **5a**, yield 50%, m.p. >300°C; IR (KBr) : 3250 (NH) 1723 (C=O), 1605 (C=N), 1220 cm^{-1} (C-O-C); ^1H NMR (DMSO-d_6) : δ 8.2 (m, 1H, C_4-H), 8.6 (m, 1H, C_5-H), 7.85 (m, 1H, C_6-H), 9.1 (m, 1H, C_7-H), 6.9-7.6 (m, 10H, 9 ArH and C=CH-S), 11.2 (s, 1H, indole NH); MS : m/z 449 (M^+, 18%), 247 (29.6), 231 (70.4), 218 (37), 205 (100), 178 (12), 163 (8.5), 102 (25.9), 75 (18.5)

Other compounds in the series were prepared similarly and are listed in **Table I**.

2-(2-Phenyl-1,8-naphthyridin-3-yl)-[1,3,4]oxadiazino[6,5-*b*]indole 6a. Hydrazone **3a** (0.01 mole) was dissolved, with cooling, in conc. H_2SO_4 (10 mL). The reaction mixture stirred well, kept for 5 hr at room temperature, poured onto crushed ice and neutralized with ammonia solution. The resulting solid was filtered, washed thoroughly with water and recrystallized from methanol to obtain **6a**, yield 55%, m.p. 258°C (d); IR (KBr) : 1606 (C=N), 1216 cm^{-1} (C-O-C); ^1H NMR (DMSO-d_6) : δ 8.2 (m, 1H, C_4-H), 8.8 (m, 1H, C_5-H), 7.8 (m, 1H, C_6-H), 9.15 (m, 1H, C_7-H), 6.7 - 7.5 (m, 9H, Ar-H); MS : m/z 375 (M^+, 12%), 231 (100), 205 (18) 178 (9.5), 170 (15.6), 142 (26), 131 (43).

Other compounds in the series were prepared similarly and are listed in **Table I**.

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