Indian Journal of Chemistry
Vol. 37B, September 1998, pp. 894 - 898

Synthesis of indolo[2′,3′:5,6][1,2,4]triazino[4,3-*a*][1,8]- naphthyridines and 3′-(3-phenyl-1,8-naphthyridin-2-ylamino)spiro- [3*H*-3, 2′-thiazolidine]-2,4′(1*H*)-diones as potential antibacterial agents

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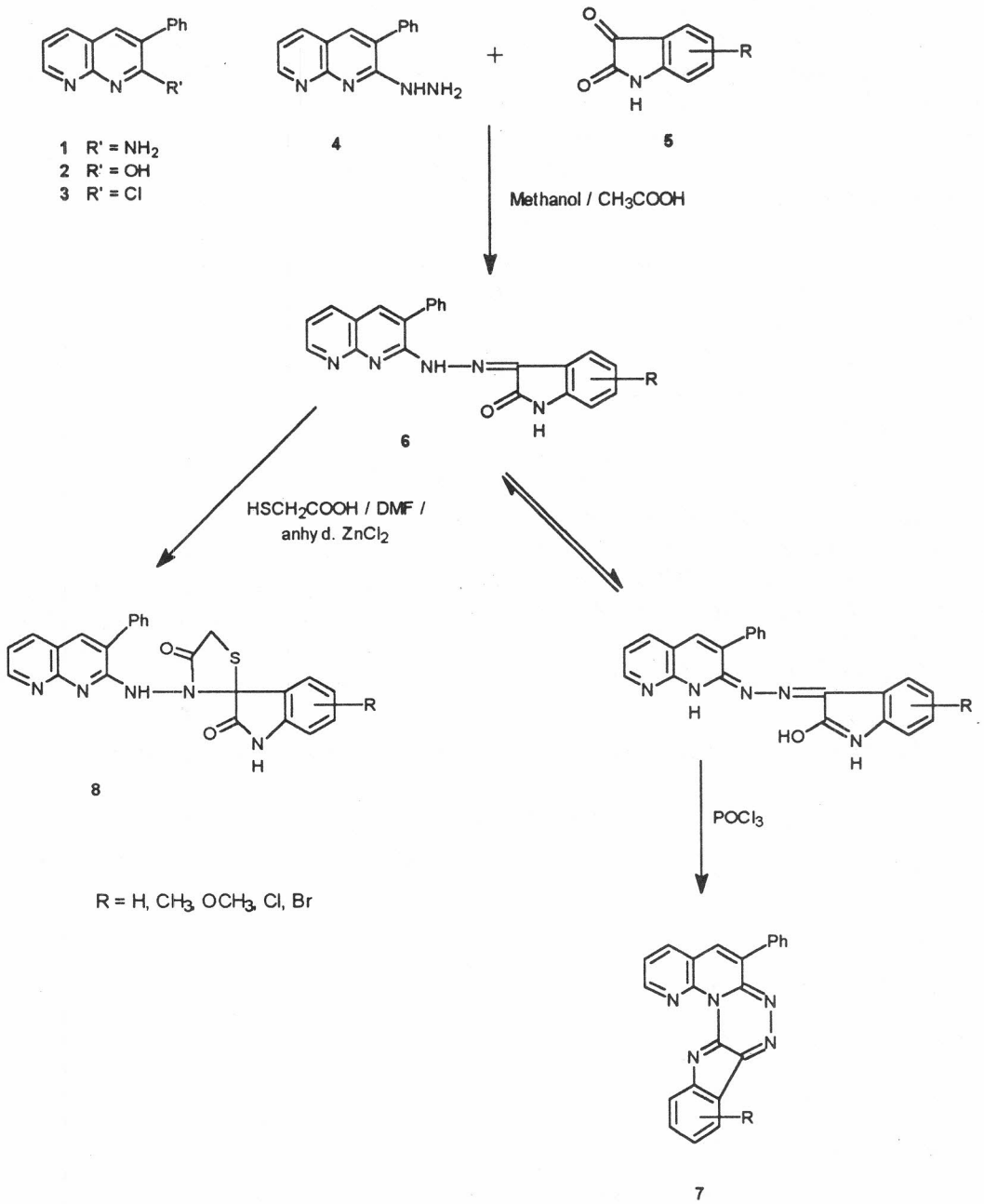
Received 1 August 1997; accepted (revised) 18 January 1998

Condensation of 2-hydrazino-3-phenyl-1,8-naphthyridine **4** with different isatins **5** gives 2-(3-phenyl-1,8-naphthyridin-2-ylhydrazono)-2-indolinones **6**, which on cyclization with $POCl_3$ under reflux result in the formation of 7-phenylindolo[2′, 3′: 5, 6][1,2,4]triazino[4,3-*a*][1,8]naphthyridines **7**. The hydrazones **6** on treatment with mercaptoacetic acid in DMF in the presence of anhyd. $ZnCl_2$ afford 3′- (3-phenyl-1, 8-naphthyridin-2-ylamino)spiro [3*H*-indole-3, 2′ -thiazolidine]-2, 4′ (1*H*)-diones **8**. The structures of the compounds **6-8** have been established on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and mass) data and evaluated for their antibacterial activity.

The chemistry of 1,8-naphthyridine derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities[1] . Several of these derivatives are potent diuretic[2], potential antibacterial[3,4], antimalarial[5] and useful anti-inflammatory[6] agents. Various indole derivatives show a wide range of biological properties [7-10]. If the indole ring is joined to other heterocyclic systems through a spiro-carbon atom, the resulting compounds show an increased spectrum of biological activities. The 1,2,4-triazine[11] and 4-thiazolidinone[12,13] class of heterocycles are of current interest due to their potential pharmaceutical importance. Encouraged by these reports and in continuation of our work on the synthesis of 1,8-naphthyridines[14-20], we report herein, the synthesis of novel and hitherto unknown bridgehead nitrogen heterocyclic system namely indolo[2′,3′:5,6] [1,2,4]triazino[4,3-*a*] [1,8]naphthy- ridines and a new spiro heterocyclic system, spiro[3*H*-indole-3,2′-thiazolidine]-2,4′ (1*H*)-diones linked to the 1,8-naphthyridine nucleus through an NH linkage. Only a limited number of molecules where an NH group is linked to two heterocyclic moieties has been described in literature[21]. The synthetic route is outlined in Scheme I.

2-Amino-3-phenyl-1,8-naphthyridine **1**, obtained by the condensation of 2-aminonicotinaldehyde with phenylacetonitrile in boiling methanol containing a few drops of piperidine[22], on treatment with HNO_2 gave 2-hydroxy-3-phenyl-1,8-naphthyri-dine **2**[22]. Interaction of **2** with $POCl_3$ followed by the hydrazinolysis with refluxing hydrazine hydrate of the resultant 2-chloro-3-phenyl-1,8-naphthyridine **3** furnished the desired synthon, 2-hydrazino-3-phenyl-1,8-naphthyridine **4**[19]. Condensation of **4** with different isatins **5** in methanol containing a catalytic amount of gl. acetic acid afforded 2-(3-phenyl-1, 8-naphthyridin-2-ylhydrazono)-2-indolin-ones **6**. The structural assignments of these compounds were based on their elemental analyses and spectral data. The IR spectra of **6** exhibited absorption bands around 3185 (NH), 1720 (C=O) and 1615 cm^{-1} (C=N). The ^{1}H NMR spectrum of **6a** in DMSO-d_6 displayed two slightly broad singlets at δ 11.0 and 13.2 due to indole NH and NH protons, respectively. The protons at C-4, C-5, C-6 and C-7 on naphthyridine framework resonated separately as multiplets centred at δ 8.3, 8.6, 8.0 and 9.1, respectively. Aromatic protons appeared as a multiplet at δ 6.8-7.8. The mass spectrum of **6a** showed the molecular ion peak at m/z 365 (6%) together with a base peak at m/z 206 (100%); other prominent peaks appeared at m/z 337 (13.5%), 220 (43), 219 (62.7), 205 (55), 178



Scheme I

(10.4),. 147 (52), 119 (88), 92 (59.7), 91 (17.9) and 64 (25).92

The hydrazones **6** on cyclization with $POCl_3$ furnished 7-phenylindolo[2′,3′: 5,6][1,2,4]triazino [4,3-*a*][1,8] naphthyridines **7** in moderate yields. The absence of bands due to NH and C=O stretchings in the IR spectra of **7** suggested the cyclization of **6** to **7**. The ^{1}H NMR spectrum of **7a** in DMSO-d_6 showed multiplets centred at δ 8.2, 8.5, 7.9 and 8.9 assignable to C-8, C-9, C-10 and C-11 protons, respectively. The aromatic cluster accounting for nine protons appeared at δ 6.8-7.7. The structures of **7** were further substantiated by their mass spectra. Compound **7a** in its mass spectrum exhibited the molecular ion peak at m/z 347 (7.5%). The base peak appeared at m/z 205 (100%) and the other characteristic peaks appeared at m/z 320 (17.9%), 179 (5), 171 (37), 144 (68.7), 142 (25), 128 (88), 102 (15) and 77 (43).

The cyclocondensation of **6** with mercapto-acetic acid in refluxing DMF in the presence of a pinch of anhyd. $ZnCl_2$ afforded the desired 3′-(3-phenyl-1,

8-naphthyridin-2-ylamino)- spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **8** in good yields. The structures of these compounds were in conformity with their elemental analyses and spectral characteristics. The IR spectra of **8** showed absorption bands around 1735 (thiazolidinone C=O), 1690 (indole C=O), 2800 (CH_2) and 3350 cm^{-1} (NH) indicating the transformation of **6** into a spiro system **8.** The ^1H NMR spectrum of **8a** in DMSO-d_6 showed the presence of methylene protons by exhibiting a singlet at δ 3.6. The proton of bridged NH was found to resonate at δ 12.5 and the proton of indole NH at δ 10.5. The protons at C-4, C-5, C-6 and C-7 on naphthyridine framework were observed separately as multiplets centered at δ 8.1, 8.8, 7.8 and 9.0, respectively. The remaining nine aromatic protons appeared as a multiplet at δ 6.8-7.6. The mass spectrum of **8a** displayed the molecular ion peak at m/z 439 (15%) along with a base peak at m/z 220 (100%). Other important peaks were observed at m/z 397 (18.4%), 307 (12), 205 (45), 179 (32.7), 163 (25), 132 (35.6), 119 (14), 105 (28), 91 (65) and 77 (22).

Antibacterial activity

All the componds reported in Table I were tested for their antibacterial activity against the bacteria *Escherichia coli, pseudomonas aeruginosa, Bacillus subtilis* and *Bacillus mycoides* following the filter paper disc technique[23] at 400 and 600 μg/disc concentrations. Streptomycin was used as a standard drug for comparison. The results are given in Table II. All the compounds were active against both the gram-negative and gram-positive bacteria at the concentration of 400 μg/disc. However, the degree of inhibition varied both with the test compound as well as with the bacterium. Compounds **6e, 7a, 7f, 8b** and **8c** exhibited high inhibition, whereas **6c, 7b, 7c, 8a** and **8f** were moderately active. Rest of the compounds displayed weak antibacterial activity. From the screening results it was observed that compounds **7** and **8** are more active than their parent hydrazones **6.**

Experimental Section

General. All melting points are uncorrected. Purity of the compounds was checked by TLC. IR spectra (KBr) were recorded 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

Table I — Physical data of compounds **6, 7** and **8**

Compd	R	m.p. °C	Yield (%)	Mol. formula (M^+)	Found (%) (Calcd)		
					C	H	N
6a	H	220	75	$C_{22}H_{15}N_5O$ (365)	72.52 (72.33	4.15 4.11	19.26 19.18)
6b	5-CH_3	242	84	$C_{23}H_{17}N_5O$	72.68 (72.82	4.56 4.49	18.58 18.47)
6c	7-CH_3	260	78	$C_{23}H_{17}N_5O$	72.65 (72.82	4.57 4.49	18.56 18.47)
6d	5-OCH_3	254	83	$C_{23}H_{17}N_5O_2$	69.72 (69.87	4.35 4.30	17.85 17.72)
6e	5-Cl	248	86	$C_{22}H_{14}N_5O$ Cl	66.26 (66.17	3.66 3.51	17.65 17.54)
6f	7-Cl	235	82	$C_{22}H_{14}N_5O$ Cl	66.27 (66.17	3.64 3.51	17.67 17.54)
6g	5-Br	258	80	$C_{22}H_{14}N_5O$ Br	59.60 (59.46	3.18 3.15	15.85 15.77)
7a	H	265	55	$C_{22}H_{13}N_5$ (347)	76.16 (76.08	3.84 3.75	20.26 20.17)
7b	1-CH_3	256	60	$C_{23}H_{15}N_5$	76.68 (76.45	4.25 4.16	19.34 19.39)
7c	3-CH_3	272	64	$C_{23}H_{15}N_5$	76.65 (76.45	4.23 4.16	19.33 19.39)
7d	3-OCH_3	268	56	$C_{23}H_{15}N_5O$	73.36 (73.21	3.91 3.98	18.65 18.57)
7e	1-Cl	280 (d)	62	$C_{22}H_{12}N_5$ Cl	69.36 (69.29	3.26 3.15	18.46 18.37)

—contd.

Table I — Physical data of compounds **6, 7** and **8** (*—contd.*)

Compd	R	m.p. °C	Yield (%)	Mol. formula (M^+)	Found (%) (Calcd)		
					C	H	N
7f	3-Cl	290	65	$C_{22}H_{12}N_5Cl$	69.38	3.25	18.48
					(69.29	3.15	18.37)
7g	3-Br	285	58	$C_{22}H_{12}N_5Br$	61.82	2.90	16.55
					(61.97	2.82	16.43)
8a	H	296	72	$C_{24}H_{17}N_5O_2S$	65.76	3.95	15.82
				(439)	(65.60	3.87	15.95)
8b	5-CH_3	264	76	$C_{25}H_{19}N_5O_2S$	66.37	4.12	15.54
					(66.23	4.19	15.45)
8c	7-CH_3	283 (d)	70	$C_{25}H_{19}N_5O_2S$	66.35	4.14	15.57
					(66.23	4.19	15.45)
8d	5-OCH_3	273	75	$C_{25}H_{19}N_5O_3S$	63.83	4.15	14.81
					(63.97	4.05	14.93)
8e	5-Cl	285 (d)	78	$C_{24}H_{16}N_5O_2SCl$	60.74	3.30	14.74
					(60.89	3.38	14.80)
8f	7-Cl	258 (d)	74	$C_{24}H_{16}N_5O_2SCl$	60.73	3.32	14.72
					(60.89	3.38	14.80)
8g	5-Br	278	73	$C_{24}H_{16}N_5O_2SBr$	55.75	3.02	13.65
					(55.60	3.09	13.51)

(d) = decompose

Table II — Antibacterial screening results of the compounds **6, 7** and **8**

Compd	Inhibition zone (in mm) against							
	E.coli at		*P.aeruginosa* at		*B.subtilis* at		*B.mycoides* at	
	400µg/disc	600 µg/disc	400µg/disc	600 µg/disc	400 µg/disc	600 µg/disc	400 µg/disc	600 µg/disc
6a	2.0	3.0	1.5	2.5	1.5	2.0	1.0	1.5
6b	1.5	2.5	1.0	2.0	1.0	1.5	2.0	3.0
6c	2.5	3.5	3.0	4.0	3.5	5.5	2.0	3.5
6d	2.0	3.5	1.5	2.0	2.0	2.5	1.5	2.0
6e	5.0	6.5	4.5	5.5	5.0	6.0	4.5	5.5
6f	2.0	3.5	2.5	3.0	2.5	3.0	2.5	3.5
6g	1.5	2.0	2.0	2.5	1.5	2.5	2.0	2.5
7a	6.0	7.0	7.0	7.5	7.5	8.5	5.0	6.5
7b	3.0	4.0	3.5	5.0	3.0	4.5	2.0	2.5
7c	3.5	4.5	3.0	4.0	2.5	3.0	2.5	3.5
7d	2.5	3.5	1.5	2.0	2.0	3.0	1.5	2.0
7e	2.0	2.5	2.5	3.5	2.5	3.0	2.0	3.0
7f	6.5	8.0	6.0	7.5	7.5	8.5	6.5	7.5
7g	2.5	3.5	2.5	3.0	2.0	3.5	2.5	3.5
8a	4.5	6.0	5.0	6.5	4.0	5.5	4.5	5.5
8b	6.5	7.5	5.5	6.5	6.0	7.5	8.0	8.5
8c	7.5	8.5	8.5	9.0	8.0	9.5	7.5	8.5
8d	3.0	4.0	3.5	4.0	2.5	3.5	2.0	3.5
8e	3.5	4.5	3.0	4.0	3.5	4.0	2.5	3.5
8f	4.0	5.5	4.5	5.5	3.5	4.5	4.0	5.0
8g	2.0	2.5	2.5	3.5	2.0	3.0	2.5	3.5
Strepto-mycin	13.0	15.0	15.0	17.0	10.0	12.0	9.0	11.0

mass spectra on a VG micromass 7070 H instrument at 70 eV. Compounds **5** were prepared by the procedure described by Marvel and Heirs [24].

3-(3-phenyl-1,8-naphthyridin-2-ylhydrazono) -2-indolinones 6: General procedure. A mixture of **4** (0.01 mole) and **5** (0.01 mole) was refluxed in methanol (30 mL) in the presence of a catalytic amount of gl. acetic acid for 3 hr and cooled. The solid that separated was filtered and recrystallized from methanol to give **6** (Table I).

7-Phenyl-indolo[2′3′ : 5,6] [1,2,4]triazino [4,3-*a*] [1,8]naphthyridines 7 : General procedure. A mixture of **6** (0.01 mole) and $POCl_3$ (10 mL) was refluxed in an oil-bath at 130^0 for 5 hr. The reaction mixture was cooled to room temperature, poured onto crushed ice and neutralized with Na_2CO_3. The solid thus obtained, was filtered,

washed well with water and recrystallized from methanol to afforded 7 (Table I).

3′-(3-Phenyl-1, 8-naphthyridin-2-ylamino)spiro-[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones 8: General procedure. An equimolar mixture of 6 (0.01 mole) and mercaptoacetic acid (0.01 mole) in DMF (25 mL) containing a pinch of anhyd. $ZnCl_2$ was refluxed for 5 hr, cooled and poured onto crushed ice. The precipitate thus obtained was filtered, washed with water and recrystallized from DMF to furnish **8** (Table I).

Acknowledgement

The authors wish to thank Prof N Satyanarayana, Principal, University Arts & Science College, Kakatiya University, Warangal for providing necessary facilities and the Director, IICT, Hyderabad for ^{1}H NMR and mass spectra. One of them (R B R) thanks CSIR, New Delhi, for the award of a senior research fellowship.

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