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Synthesis and antibacterial screening of *N*-[Naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl] spiroindoloazetidin-2-ones/thiazolidin-4-ones

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2-Amino-11-hydronaphtho[2,1:5,6]pyrano[4,3-*d*]thiazole **1a-d** on treatment with isatin affords naphtho[1,2-*b*]pyrano[3,4-*d*]thiazolo-8-yl(3-imino-2-oxo-1*H*-indole **2a-d** which on further reaction with chloroacetyl chloride and mercaptoacetic acid yields the corresponding *N*-[naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl]spiro-[3*H*-indole-(1*H*,2*H*)-3,4-(2*H*)-3-chloroazetidin-2,2-diones **3a-d** and *N*-[naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl]spiro-[3*H*-indole-(1*H*,2*H*)-3,2-(4*H*)-thiazolidine]-2,4-dione **4a-d**. All the compounds **2a-d**, **3a-d** and **4a-d** have been screened and found to possess considerable antibacterial activity.

Keywords: Naphthopyrans, azetidin-2-ones, thiazolidin-4-ones, 2-oxo-1*H*-indole, antibacterial activity

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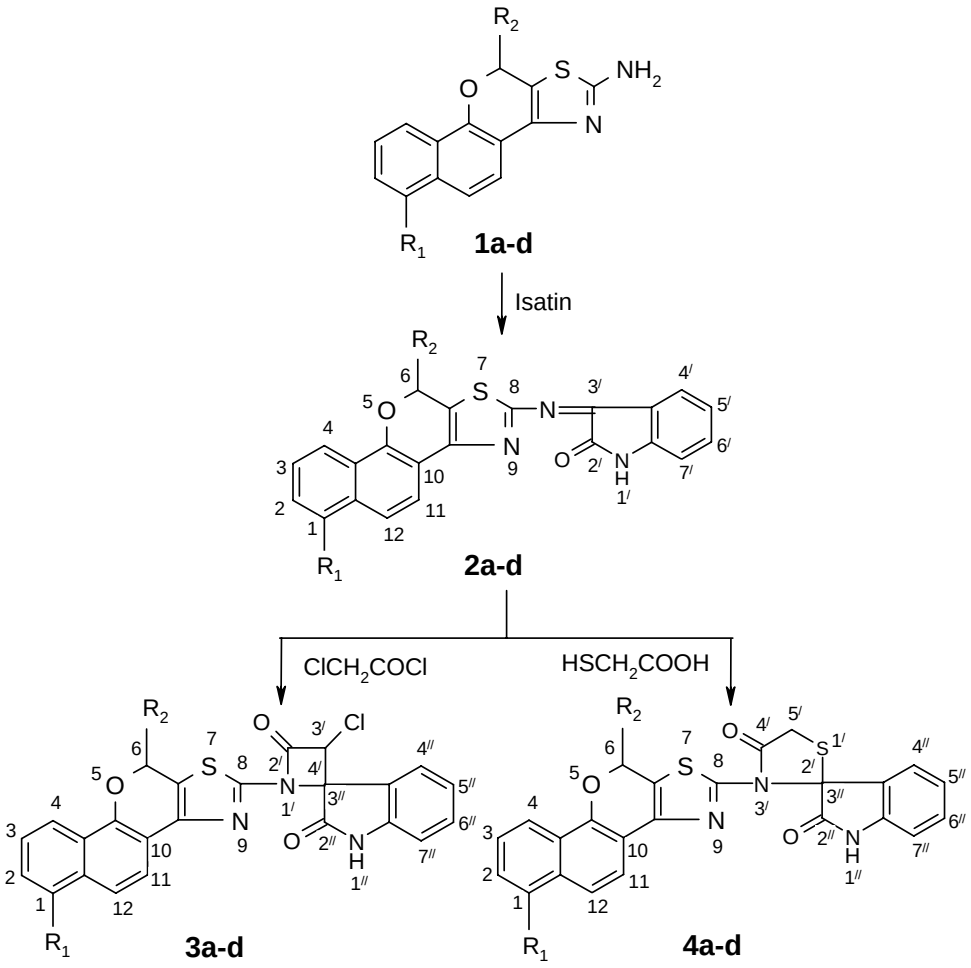
Naphthopyrans[1] are widely distributed in nature and are known to exhibit anti-hypertensive[2], antiallergic[3] and hair growth stimulant[4] activity. Moreover, pyranothiazole heterocycles possess herbicidal[5] activity. Various indole derivatives show a wide range of biochemical properties[6]. It has been reported[7] that if the indole ring is joined to other heterocyclic groups through a spiro-carbon atom, the resulting compounds show enhanced biological activity. The chemistry of azetidinones is of great importance because of the use of β-lactam derivatives for the treatment of tuberclosis[8]. 2-Azetidinones and its derivatives possess a variety of useful therapeutic properties[9-11] and interesting applications in the field of medicine[12-17]. Also, the thiazolidin-4-ones possess a wide range of pharmaceutical activity[18]. In view of the importance of the above compounds, it was planned to synthesize compounds in which the 2-amino-11-hydronaphtho[2,1:5,6]pyrano[4,3-*d*]thiazole[19] group is joined to the isatin, spiroindoloazetidin-2-one and spiroindolothiazolidin-4-one ring system *via* the N-atom of its free amino group. The resulting molecule was expected to be biologically active.

With this intention, the 2-Amino-11-hydronaphtho[2,1:5,6]pyrano(4,3-*d*)thiazole **1a-d** was condensed with isatin to afford Naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl(3-imino-2-oxo)-1*H*-indole **2a-d**. The IR spectrum of **2a-d** showed bands around 3441 for the N-H stretching, 3050 for C-H stretching and 1700 cm^{-1} for the carbonyl group, *etc*. Its ^{1}H NMR spectrum indicated a singlet at δ 12.92 for the >NH of the indole ring, which was D_2O exchangeable. Compounds **2a-d** on treatment with chloroacetyl chloride and mercaptoacetic acid yielded the N-[naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl]spiro-3*H*-indole-(1*H*,2*H*)-3,4-(2*H*)-3-chloroazetidin-2,2-diones **3a-d** and N-[naphtho[1, 2-*b*]pyrano[3, 4-*d*]thiazol-8-yl]spiro-(3*H*-indole-(1*H*,2*H*)-3,2-(4*H*)-thiazolidine)-2,4-diones **4a-d**, respectively, (**Scheme I**). Compounds **3a-d** gave positive Beilsteins green flame test and Lassaignes sodium fusion test for the presence of chlorine.

Antibacterial activity

All the synthesized compounds **2a-d**, **3a-d** and **4a-d** were screened for their antibacterial activity against *S. aureus*, *S. pyogenes*, *S. albus* and *E. coli* according to the standard procedure (**Table I**). The minimum inhibitory concentration (MIC) was determined using tube dilution method according to standard procedure[20]. DMF was used as a solvent and blank. Ciprofloxacin (MIC: 5 μg/mL) was used as the antibacterial standard. The observation of the data (**Table I**) reveals that the compound **2b** was more effective against *S. pyogenes* at a concentration of



1a-4a: R_1= -H, R_2= -H

1b-4b: R_1= -H, R_2= -Br

1c-4c: R_1= -H, R_2= -OH

1d-4d: R_1= -CH_3, R_2= -OH

Scheme I

9 μg/mL compared to the other members of the same series. On the other hand, compound **3b** was more active against *S. albus* at a concentration of 8 μg/mL and **4b** against *E. coli* at a concentration of 11 μg/mL. All other compounds of the same series exhibited significant to moderate antibacterial activity.

Experimental Section

Melting points were determined in open capillaries on Thomas Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 400 (400 MHz) instrument using TMS as an internal standard and DMSO-d_6 as solvent. Chemical shifts are given in δ (ppm) and coupling constants *J* in Hz. Mass spectra were recorded on a Shimadzu GC-MS instrument. Elemental analysis (C, H, N) was performed on a Perkin-Elmer 240 analyzer and all values are within ±0.4% of theoretical unless otherwise specified. All products were purified by recrystallisation from ethanol.

General procedure for the synthesis of naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl(3-imino-2-oxo)-1*H*-indole (2a-d, Table II). To the solution **1a-d** (0.01 mole) in ethanol (25 mL) was added isatin (0.01 mole, 1.47 g) and catalytic amount of glacial acetic acid (3-4 drops), and the reaction mixture refluxed on a water-bath for 3 hr. The mixture was then cooled and poured onto crushed ice-water. The product separated was filtered, dried and purified by recrystallisation from ethanol.

Table I — Antibacterial activity data (MIC μg/mL) of compounds **2a-d** to **4a-d**

Compd	Antibacterial activity			
	S. aureus	*S. pyogenes*	*S. albus*	*E. coli*
2a	40	35	67	88
2b	12	09	21	20
2c	60	55	98	90
2d	68	71	82	112
3a	110	84	43	52
3b	10	17	08	20
3c	58	79	81	63
3d	93	44	38	53
4a	127	99	54	61
4b	13	16	29	11
4c	32	74	81	40
4d	56	69	90	101
Ciprofloxacin	5	5	5	5

General procedure for the synthesis of *N*-[naphtho[1, 2-*b*]pyrano[3, 4-*d*]thiazol-8-yl]spiro-[3*H*-indole-(1*H*, 2*H*)-3, 4-(2*H*)-3-chloroazetidine]-2,2-diones (3a-d, Table II). A mixture of compounds **2a-d** (0.01 mole) and chloroacetyl chloride (0.02 mole) in 1,4-dioxane (20 mL) in the presence of catalytic amount of triethylamine was stirred for 6 hr. The reaction mixture was later poured onto crushed ice-water. The product separated was filtered, washed, dried and purified by recrystallisation from dichloromethane.

General procedure for the synthesis of *N*-[naphtho[1,2-*b*]pyrano[3,4-*d*]thiazol-8-yl]spiro-[3*H*-indole-(1*H*, 2*H*)-3, 2-(4*H*)-thiazolidine]-2, 4-diones (4a-d, Table II). Compound **2a-d** (0.01 mole) and mercaptoacetic acid (0.01 mole, 1.84 g) were refluxed in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (25 mL) for 6 hr. The mixture was then cooled and poured onto crushed ice-

Table II— Characterization data of compounds **2a-d** to **4a-d**

Compd	Mol. formula	m.p. °C	Yield (%)	MS m/z	^{1}H NMR (DMSO-d_6)
2a	$C_{22}H_{13}N_3O_2S$	183	82	M^+383	^{1}H NMR: δ 5.60 (s, 2H, C_6 >CH_2), 6.90-8.00 (m, 10H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
2b	$C_{22}H_{12}N_3O_2SBr$	164	72	M^+462	^{1}H NMR: δ 5.62 (s, 2H, C_6 >CH_2), 6.90-7.90 (m, 9H, Ar-H), 11.02 (s, 1H, >N-H, D_2O exchangeable).
2c	$C_{22}H_{13}N_4O_2S$	178	80	M^+399	^{1}H NMR: δ 5.42 (s, 1H, -OH, D_2O exchangeable), 5.62 (s, 2H, C_6 >CH_2), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
2d	$C_{23}H_{15}N_4O_2S$	179	81	M^+413	^{1}H NMR: δ 1.22 (d, 3H, C_6 –CH_3), 4.68 (q, 1H, C_6-H), 5.48 (s, 1H, -OH, D_2O exchangeable), 6.88-7.90 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
3a	$C_{24}H_{14}N_3O_3SCl$	199	62	M^+459	^{1}H NMR: δ 3.20 (s, 1H, >CHCl), 5.60 (s, 2H, C_6 >CH_2), 6.90-8.00 (m, 10H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
3b	$C_{24}H_{13}N_3O_3SBrCl$	190	72	M^+538	^{1}H NMR: δ 3.22 (s, 1H, >CHCl), 5.62 (s, 2H, C_6 >CH_2), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
3c	$C_{24}H_{14}N_3O_4SCl$,	201	77	M^+475	^{1}H NMR: δ 3.22 (s, 1H, >CHCl), 5.42 (s, 1H, -OH, D_2O exchangeable), 5.62 (s, 2H, C_6 >CH_2), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
3d	$C_{25}H_{16}N_3O_4SCl$,	186	68	M^+489	^{1}H NMR: δ 1.22 (d, 3H, C_6 –CH_3), 4.68 (q, 1H, C_6-H), 3.22 (s, 1H, >CHCl), 5.42 (s, 1H, -OH, D_2O exchangeable), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
4a	$C_{24}H_{15}N_3O_3S_2$	211	82	M^+425	^{1}H NMR: δ 3.60 (s, 2H, -S-CH_2-), 5.62 (s, 2H, C_6 >CH_2), 6.90-8.10 (m, 10H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
4b	$C_{24}H_{14}N_3O_3S_2$	196	73	M^+504	^{1}H NMR: δ 3.62 (s, 2H, -S-CH_2-), 5.60 (s, 2H, C_6 >CH_2), 6.90-8.10 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
4c	$C_{24}H_{15}N_3O_4S_2$,	171	69	M^+441	^{1}H NMR: δ 3.62 (s, 2H, -S-CH_2-), 5.40 (s, 1H, -OH, D_2O exchangeable), 5.62 (s, 2H, C_6 >CH_2), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).
4d	$C_{25}H_{17}N_3O_4S_2$	188	80	M^+455	^{1}H NMR: δ 1.22 (d, 3H, C_6 –CH_3), 3.60 (s, 2H, -S-CH_2-), 4.68 (q, 1H, C_6-H), 5.42 (s, 1H, -OH, D_2O exchangeable), 5.62 (s, 2H, C_6 >CH_2), 6.90-7.98 (m, 9H, Ar-H), 11.00 (s, 1H, >N-H, D_2O exchangeable).

water. The product separated was filtered, dried and purified by recrystallisation from ethanol.

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