Indian Journal of Chemistry
Vol. 47B, May 2008, pp. 748-752

Synthesis of some new 10*H*-pyrido[3,2-*b*][1,4]benzothiazine and their ribofuranosides as possible chemotherapeutic agents

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Received 15 March 2007; accepted (revised) 13 February 2008

N-(2´,3´,5´-tri-O-*b*enzoyl-β-D-ribofuranosyl)-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitro pyrido[3,2-*b*][1,4]benzothiazine have been synthesized by the treatment of 10*H*-8-chloro-7-methyl/ 7,9-dimethyl/8-chloro-9-methyl-3-nitropyrido[3,2-*b*][1,4]benzothiazines-with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate in toluene. Compounds 10*H*-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitro pyrido[3,2-*b*][1,4]benzothiazine and 10-acetyl-8-chloro-7-methyl/7,9-dimethyl/ 8-chloro-9-methyl-3-nitro pyrido[3,2-*b*][1,4]benzothiazine-5-oxide have been synthesized. The structure of all the synthesized compounds have been established by elemental analysis, IR and ^{1}H NMR spectral data. All the synthesized heterocyclic compounds and their ribofuranosides have been screened for their antibacterial and antifungal activity.

Keywords: 10*H*-Pyrido[3,2-*b*][1,4]benzothiazine, ribofuranosides, IR, NMR spectra, antimicrobial activity

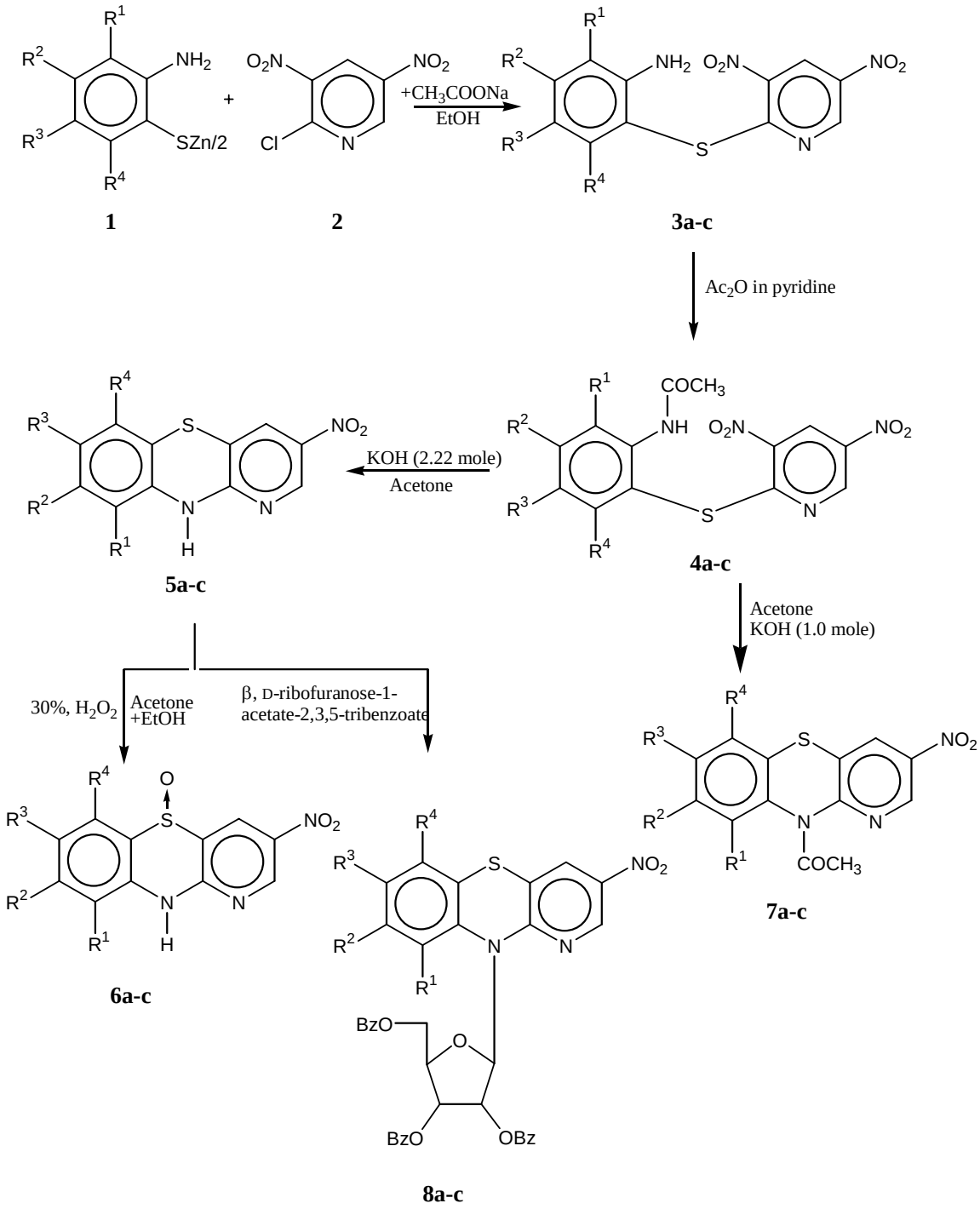
Perusal of the literature on pharmacological studies, reported for the 10*H*-pyrido[3,2-*b*][1,4]-*b*enzothiazines class of compounds, reveal that these compounds have immense chemotherapeutic importance as antitussive[1], antihypertensive[2], antitumor[3,4], analgesic[5], trypanocidal[6], antithyroid[7,8], anticonvulsant[9], antileukemic[10], antidepressant[11,12], antihistaminic[13], anesthetic[14], antiviral[15-17], sedative[18], antiallergic[19-21], antibacterial[22-24] and neuroleptic[25,26], *etc*. On account of variety of therapeutic applications, significant amount of work has been reported on the synthesis of 10*H*-pyrido[3,2-*b*][1,4]benzothiazines. In view of above and the interest in this area of research[27,28], it was thought workwhile to explore some new 10*H*-pyrido[3,2-*b*][1,4]benzothiazines and their ribofuranosides as potential chemotherapeutic agents.

Zinc mercaptide of 2-amino-4-chloro-5-methyl / 3,5-dimethyl / 4-chloro-3-methyl benzene thiols **1** and 2-chloro-3,5-dinitropyridine **2** were refluxed in ethyl alcohol in the presence of anhydrous sodium acetate to gave 2-amino-4-chloro-5-methyl/3,5-dimethyl/4-chloro-3-methyl phenyl-2´-(3´,5´-dinitro)pyridyl sulphides **3a-c**. Compound **3a-c** when reacted with acetic anhydride in the presence of pyridine afforded 2-acetylamino-4-chloro-5-methyl/3, 5-dimethyl/4-chloro-3-methyl phenyl-2´-(3´,5´-dinitro)pyridyl sulphide **4a-c**. Compound **4a-c** upon condensation with potassium hydroxide in 1:1 ratio afforded 10-acetyl-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitropyrido[3,2-*b*][1,4] benzothiazines **6a-c**. The same reaction in 1:2 molar ratio gave 10*H*-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitro pyrido[3,2-*b*][1,4] benzothiazines **5a-c**. Compound **5a-c** on treatment with hydrogen peroxide in ethanol-acetone fielded 10*H*-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitro pyrido[3,2-*b*] [1,4]benzothiazine-5-oxide **7a-c**. Compound **5a-c** on stirring with sugar *viz*. β-D-ribofuranose-1-acetate-2,3,5-tribenzoate in toluene at 155-60°C for 10-12 hr *in vacuo*, gave corresponding ribofuranosides **8a-c** (**Scheme I**).

Structure of all the synthesized compounds are well supported by spectroscopic and elemental analysis data (**Table I**).

The IR absorption band appeared between 670-650 cm^{-1} in compounds **5-8** due to C-S-C linkage. The carbonyl group absorbed at higher frequency 1710-1700 cm^{-1} in compounds **4** and **7**. Compounds **5** and **6** showed a band in the region 3300-3280 cm^{-1} due to >NH stretching vibrations. The sharp and strong absorption bands appeared between 1595-1580 and 1400-1370 cm^{-1} were due to asymmetric and symmetric stretching vibrations of $-NO_2$ group, respectively in compounds **5-8**.

In ^{1}H NMR spectra a singlet appeared at δ 3.52-3.55 due to $-COCH_3$ proton in compound **6**. The multiplet observed in the range at δ 6.30-8.82



1 **2** **3a-c** **4a-c** **5a-c** **6a-c** **7a-c** **8a-c**

Scheme I

corresponded to phenylic protons and protons of pyridine nucleus resonated in the region δ 8.20-8.90. A singlet appeared at δ 8.11-8.80 due to >NH group compounds **5** and **6**. The aromatic protons in ribofuranosides **8** appeared as a multiplet at δ 6.80-8.82. C_4'-H and $>CH_2$ protons of sugar moiety gave multiplet in the region δ 4.40-4.81, while C_2'-H and C_3'-H signals appeared in the region δ 5.35-5.95 as multiplet. The singlet at δ 6.45 is attributed to C_1'-H.

Antimicrobial Activity

All the synthesized heterocyclic compounds **5a-c** to **7a-c** and their ribofuranosides **8a-c** were screened for their antibacterial and antifungal activity following

Table I — Characterization data of compounds **5a-c, 6a-c, 7a-c** and **8a-c**

Compd	R^1	R^2	R^3	R^4	Yield %	m.p. (°C)	^{1}H NMR (δ, ppm from TMS)
5a	-H	-Cl	$-CH_3$	-H	68	213	6.89-8.53(4H, m, Ar-H), 8.80(1H, s, -NH), 2.18(3H, s, Ar-CH_3)
5b	$-CH_3$	-H	$-CH_3$	-H	65	203	6.70-8.62(4H, m, Ar-H), 8.11(1H, s, NH), 2.18(6H, s, Ar-CH_3)
5c	$-CH_3$	-Cl	-H	-H	71	237	6.83-8.56(4H, m, Ar-H), 8.70(1H, s, -NH), 2.20(3H, s, Ar-CH_3)
6a	-H	-Cl	$-CH_3$	-H	70	225	6.32-8.76(4H, m, Ar-H), 8.70(1H, s, NH), 1.98(3H, s, Ar-CH_3)
6b	$-CH_3$	-H	$-CH_3$	-H	66	179	6.18-8.59(4H, m, Ar-H), 8.65(1H, s, NH), 2.05(3H, s, Ar-CH_3)
6c	$-CH_3$	-Cl	-H	-H	69	245	6.40-8.82(4H, m, Ar-H), 8.71(1H, s, NH), 2.03(3H, s, Ar-CH_3)
7a	-H	-Cl	$-CH_3$	-H	67	226	6.30-8.74(4H, m, Ar-H), 3.47(3H, s, $COCH_3$), 2.12(3H, s, Ar-CH_3)
7b	$-CH_3$	-H	$-CH_3$	-H	62	169	6.60-8.72(4H, m, Ar-H), 3.54(3H, s, $COCH_3$), 2.13(6H, s, Ar-CH_3)
7c	$-CH_3$	-Cl	-H	-H	73	224	6.33-8.40(4H, m, Ar-H), 3.54(3H, s, $COCH_3$), 2.10(3H, s, Ar-CH_3)
8a	-H	-Cl	$-CH_3$	-H	67	248	6.85-8.75 (19H, m, Ar-H), 4.40-5.90 (6H, m, Sugar Moiety), 2.13 (6H, s, Ar-CH_3)
8b	$-CH_3$	-H	$-CH_3$	-H	64	182	6.80-8.70 (19H, m, Ar-H), 4.35-5.80 (6H, m, Sugar Moiety), 2.13 (6H, s, Ar-CH_3)
8c	$-CH_3$	-Cl	-H	-H	70	236	6.90-8.82 (19H, m, Ar-H), 4.40-5.95 (6H, m, Sugar Moiety), 2.14 (3H, s, Ar-CH_3)

the paper disc method of Varma and Nobles[29]. The concentration applied was 100 μg per disk streptomycin and mycostatin were used as reference compounds while testing antibacterial and antifungal activity, respectively (**Table II**).

Experimental Section

Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr disks on a Shimadzu FT-IR spectrometer and ^{1}H NMR spectra on Jeol AL-300 NMR spectrometer in $CDCl_3$/ DMSO-d_6 using TMS as an internal standard. The homogeneity of all the synthesized compounds were checked by TLC using silica gel as adsorbent and visualization was accomplished by UV light or iodine vapour in a chamber.

Synthesis of 2-amino-4-chloro5-methyl/3,5-dimethyl/4-chloro-3-methyl phenyl-2´-(3´-5´-dinitro)-pyridyl sulphides, 3a-c

A mixture of zinc mercaptide of substituted benzenethiol **1** (0.005 mole), 2-chloro-3,5-dinitropyridine **2** (0.01 mole) and anhydrous sodium acetate (0.025 mole) in absolute alcohol (1.5 mL) was refluxed for 4 hr on a water-bath. On cooling, a solid was obtained which was filtered, washed with water, dried and purified by recrystallization from ethyl alcohol.

Synthesis of 2-acetylamino-4-chloro-5-methyl/3,5-dimethyl/4-chloro-3-methyl phenyl-2´-(3´,5´-dinitro)pyridylsulphide, 4a-c

Compound **3** (0.005 mole) in pyridine (0.4 mL) and acetic anhydride (4.8 mL) were refluxed on a water-bath for 3 hr. The reaction contents were cooled to obtained the product. The mass was filtered, washed with water, dried and purified by recrystallization from benzene.

Synthesis of 10*H*-8-chloro-7-methyl/7,9-dimethyl/8-chloro-9-methyl-3-nitropyrido [3,2-b][1,4]-benzothiazines, 5a-c

To a stirred mixture of compound **4** (0.005 mole) in acetone (6.5 mL), potassium hydroxide (0.62 g) was added and the reaction mass was refluxed for 3 hr. Acetone was distilled off and water (7.0 mL) was added to the residue. The product, thus obtained, was collected by filtration, washed with water, dried and purified by recrystallization from benzene.

Synthesis of 10-acetyl-8-chloro-7-methyl / 7,9-dimethyl / 8-chloro-9-methyl-3-nitro pyrido [3,2-b] [1,4] benzothiazine, 7a-c

To a stirred ethanolic solution of potassium hydroxide (0.28 g), acetone (10 mL) was added under inert atmosphere, followed by addition of compound **4** (0.05 mole). It was heated on a waterbath, until the original volume was reduced to half (5 mL), and then water (5 mL) was added. The yellow solid product thus obtained was collected by filtration, which was then washed with water, dried and purified by recrystallization from isopropanol.

Synthesis of 10*H*-8-chloro-7-methyl / 7,9-dimethyl / 8-chloro-9-methyl-3-nitro pyrido[3,2-*b*][1,4] benzothiazine-5-oxide, 6a-c

To a solution of 10*H*-substituted-3-nitro-pyrido [3,2-*b*][1,4] benzothiazine **6** (0.002 mole) in warm

Table II — Antiminobial activity of synthesized 10*H*-pyrido [3, 2-*b*] [1,4] benzothiazine and their ribofuranosides: zone of growth inhibition (mm)
(Activity index)*

Compd	Bacteria		Fungi	
	Escherichia coli (Gram negative)	Staphylococcus Aureus (Gram positive)	Aspergillus Niger	Aspergillus Flavus
5a	8.5 (0.86)	8.6 (0.87)	9.2 (0.85)	9.7 (0.89)
5b	8.2 (0.83)	8.2 (0.83)	9.0 (0.83)	8.9 (0.82)
5c	9.5 (0.96)	8.4 (0.85)	8.9 (0.82)	10.3 (0.95)
6a	8.7 (0.88)	8.9 (0.90)	8.8 (0.81)	9.7 (0.89)
6b	8.5 (0.84)	7.9 (0.60)	8.5 (0.78)	8.9 (0.82)
6c	8.9 (0.90)	8.7 (0.80)	8.8 (0.81)	9.6 (0.88)
7a	8.4 (0.85)	7.9 (0.80)	9.1 (0.84)	9.6 (0.88)
7b	7.9 (0.80)	7.8 (0.79)	8.6 (0.79)	8.5 (0.78)
7c	8.9 (0.90)	8.3 (0.84)	9.4 (0.87)	9.7 (0.89)
8a	9.1 (0.92)	9.7 (0.98)	10.2 (0.94)	11.3 (1.04)
8b	8.8 (0.89)	9.2 (0.93)	9.9 (0.91)	10.6 (0.98)
8c	9.4 (0.95)	9.8 (1.00)	10.3 (0.95)	11.1 (1.02)

Activity index* = Inhibition area of sample/inhibition area of standard.
Values in parentheses represent activity index.

solution of ethanol (7.5 mL), acetone (15 mL), H_2O_2 (30%) (0.0021 mole) was added and mixture was refluxed for 3 hr. The colour of the solution darkened during the refluxing. The solvent was removed by distillation and the product was purified by recrystallization from ethanol.

Synthesis of N-(2´-3´-5´-tri-O-*b*enzoyl-β-D-) rebo-furanosyl-8-chloro-7-methyl /7,9-dimethyl/8-chloro-9-methyl-3-nitropyrido[3, 2-*b*][1, 4]benzothiazines, 8a-c

To a solution of **5** (0.002 mole) in minimum toluene, β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (0.002 mole) was added and the contents were refluxed under stirring on a oil-bath at 155-60°C, *in vacuo* for 15 min. The *vacuo* was removed and the reaction mixture was protected from moisture by fitting a guard tube, stirring was further continued for 10 hr and vacuum was applied for 10 min, at intervals of 1 hr. The viscous mass thus produced was dissolved in methanol, boiled for 10 min and cooled to RT. The reaction mixture was filtered and the methanol was removed by distillation under reduced pressure. The viscous residue thus obtained was dissolved in ether, filtered, concentrated and kept in fridge overnight to get crystalline ribofuranosides.

Acknowledgement

Authors are grateful to the Head, Chemistry Department, University of Rajasthan, Jaipur for providing laboratory facilities.

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