AN ELEGANT SYNTHESIS OF SOME NEW POTENTIAL BIOLOGICALLY ACTIVE PYRIDO[3,2-b][1,4]BENZOTHIAZINE DERIVATIVES AND THEIR NUCLEOSIDES BY PHASE TRANSFER CATALYSIS

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Abstract : 10*H*-7-Trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine, 10-acetyl-7-trifluoromethyl/ 9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine and 10*H*-7-trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine-5-oxide have been synthesized. The nucleosides viz., 10-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-7-trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine have been prepared by using phase transfer catalysis. Structural assignments were made on the basis of analytical and spectral data. All the synthesized compounds were screened for their antimicrobial activity.

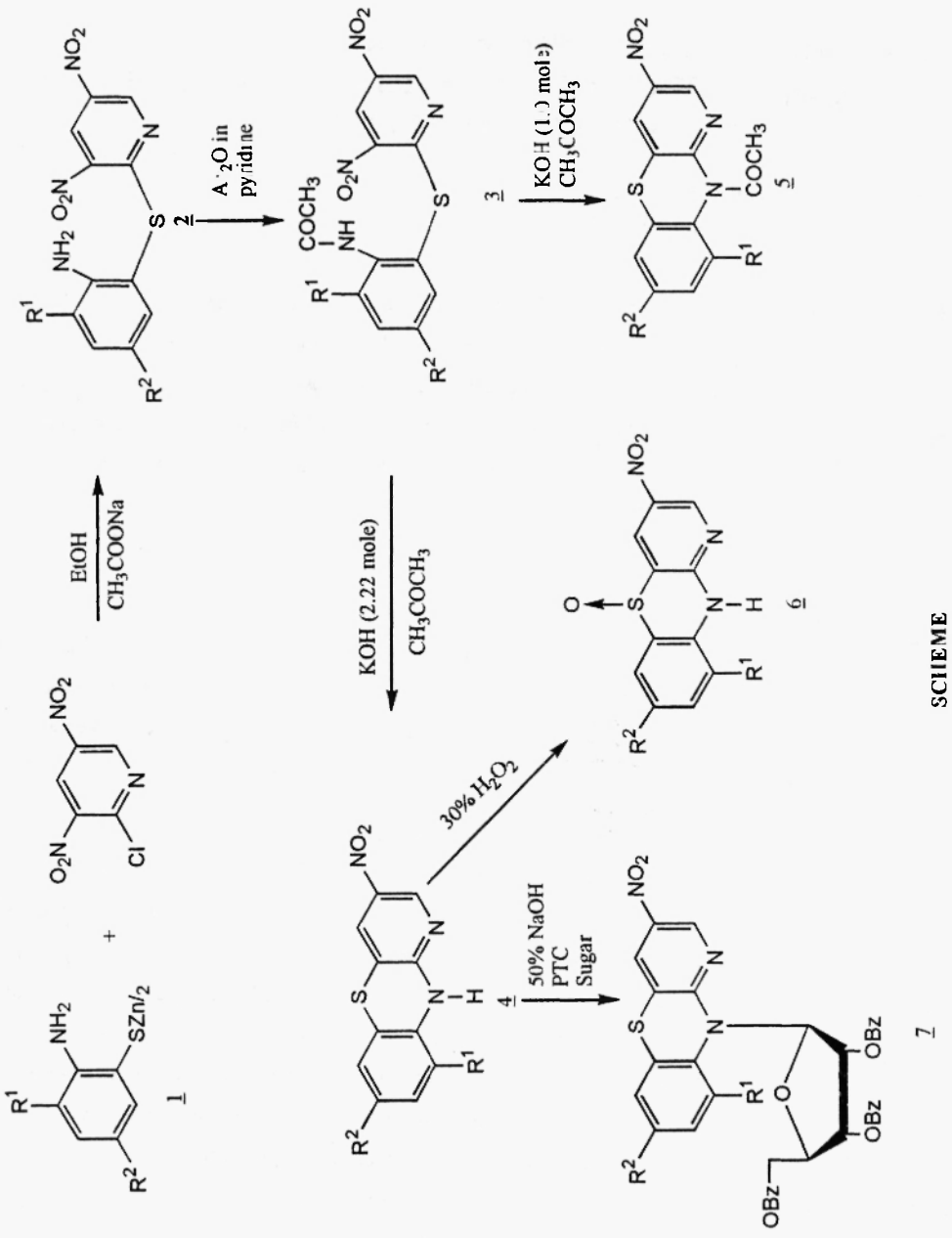
Introduction

Pyrido[3,2-b][1,4]benzothiazine are known to possess diverse biological activity such as antitumor (1), antileukemic (2), antiallergic (3), anticonvulsant (4), vermicidal (5) etc. Nucleosides of thiazine analogue were reported by Hernandez (6). A recent report by H. Luo et. al. (7) suggests that the nucleosides of phenothiazines demonstrate antihistaminic and antidepressant activity. A novel synthesis of some new pyrido[3,2-b][1,4]benzothiazine, 10 acetyl and 5 oxide derivatives and their nucleosides has been performed. The antimicrobial activities of the synthesized compounds have been reported.

Results and discussion

The condensation of zinc salt of 2-aminosubstituted benzenethiol 1 with 2-chloro-3,5-dinitropyridine in presence of anhydrous sodium acetate, in absolute ethanol, yielded 2-amino-substituted phenyl-2′-(3′,5′-dinitro)pyridyl sulphide 2. Compound 2 on treatment with acetic anhydride in pyridine gave 2-acetylamino substituted phenyl-2′-(3′,5′-dinitro)pyridyl sulphide 3, which was converted into 10*H*-substituted-3-nitro-pyrido[3,2-b][1,4]benzothiazine 4 and 10-acetyl-substituted-3-nitro-pyrido[3,2-b][1,4]benzothiazine 5 *via* smiles rearrangement (8) by treatment with 2.2 moles and 1.0 mole of potassium hydroxide, respectively, in acetone. Compound 4 on oxidation with H_2O_2 (30%) gave 10*H*-substituted 3-nitro-pyrido[3,2-b][1,4]benzothiazine-5-oxide 6. Compound 4 on stirring with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide (9) in a biphasic solvent viz; CH_2Cl_2-50% NaOH, in presence of tetrabutylammonium bromide as phase transfer catalyst (PTC) gave 10-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-substituted-3-nitro-pyrido[3,2-b][1,4]benzothiazine 7 in good yield (Scheme). The formation of 7 as an β-anomer in agreement with an earlier report (10).

The IR(KBr) spectra of compound 2 gave a distinct absorption band at 660-650 cm^{-1} due to C-S-C linkage. (This absorption band was also observed in compounds 3-7). Asymmetric and symmetric stretching vibrations of the primary amino group appeared in the region 3455-3445 cm^{-1}. Compound 3 showed absorption bands at 3110-3070 cm^{-1} and 1695-1685 cm^{-1} due to secondary amino group and carbonyl group respectively. The presence of >NH absorption at 3300-3260 cm^{-1} in compounds 4 and 6 indicated the free >NH at position 10. The absence of the >NH absorption in compound 5 and presence of absorption band at 1715-1695 cm^{-1} due to the carbonyl group confirms the structure of this compound. Absence of absorption band in the region 3300-3260 cm^{-1} due to >NH group in compound 7 indicates the attachment of sugar at this



SCHEME

position.

The ^{1}H NMR spectra of all the compounds showed a multiplet in the region δ 6.20-8.00 ppm due to phenyl protons. Spectra of compound 2 showed a broad singlet at δ 5.50-4.90 ppm due to NH_2 protons. The >NH proton in compounds 3,4, and 6 exhibited a peak at δ 8.10-8.54 ppm. Methoxy protons of the compounds (2c-7c) appeared as singlet at δ 3.52-3.60 ppm and ethoxy protons of the compounds (2b-7b) showed a triplet at δ 1.21-1.31 ppm alongwith a quartet at δ 3.91-4.21 ppm. The ^{1}H NMR spectra of 7 revealed the loss of signal due to the proton of the >NH group. This established that it is 10-substituted nucleoside. The other protons in compound 7 were found to be shifted slightly downfield as compared to 4 and sugar.

Antimicrobial activity

All the synthesized compounds were evaluated for their antimicrobial activities at a conc. of 100 μg/disc in agar media using paper disk method of J.C. Gould et al. (11). Streptomycin and mycostatin were used as the reference compounds in antibacterial and antifungal activites, respectively. All the tested compounds were found to be moderately active against various bacteria and fungi, table-2.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a NICOLET MEGNA FT-IR 550 spectrometer and ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 on a FX 90Q Jeol spectrophotometer at 90 MHz using TMS as the internal standard. The purity of the compounds was checked by TLC using silica gel 'G' as adsorbent and visualization was accomplished by U.V. light or iodine.

Synthesis of 2-amino-5-trifluoromethyl/-3-ethoxy/-3-methoxy phenyl-2 -(3 ,5 -dinitro) pyridyl sulphide 2.

A mixture of zinc mercaptide of a substituted 2-aminobenzenethiol 1 (0.005 mole) and 2-chloro-3,5-dinitropyridine (0.01 mole), anhydrous sodium acetate (0.025 mole) and absolute ethanol (15 ml) was refluxed for 4 hr on a water bath. The solid obtained on cooling was collected by filtration, washed with water, dried and recrystallized from ethanol.

Synthesis of 2-acetylamino-5-trifluoromethyl/-3-ethoxy/-3-methoxy phenyl-2'(3',5'-dinitro) pyridyl sulphide 3.

A solution of 2-aminosubstituted phenyl pyridyl sulphide 2 (0.005 mole) in pyridine (0.4 ml) and acetic anhydride (4.8 ml) was heated over water bath for 2 hr. The solid, separated on cooling, was filtered, washed with water, dried and recrystallized from isopropanol.

Synthesis of 10*H*-7-trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine 4a-c. *via* Smiles rearrangement.

To a refluxing solution of 3 (0.005 mole) in acetone (6.5 ml), potassium hydroxide (0.6 g) was added in small portions and refluxing continued for further 3 hr. Acetone was then distilled off and water (7.0 ml) was added to the residue. The product thus obtained was collected by filtration, washed well with water and recrystallized from benzene.

Synthesis of 10-acetyl-7-trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine 5a-c. *via* Smiles rearrangement.

To a stirred, ethanolic solution of potassium hydroxide (0.28g), acetone (10 ml) was added under nitrogen atmosphere. This was followed by the addition of 3 (0.005 mole) and rapid reduction, by distillation of the solvent to half of its original volume (5 ml). An equal volume of water (5 ml) was added to obtain a yellow solid product, which was

collected by filtration, washed with water dried and recrystallized from isopropanol.

Synthesis of 10*H*-7-trifluoromethyl/-9-ethoxy/-9-methoxy-3-nitro-pyrido[3,2-b][1,4]benzothiazine-5-oxide 6a-c.

Substituted 10*H*-pyrido[3,2-b][1,4]benzothiazine 4 (0.002 mole) was dissolved in a hot solution of ethanol (7.5 ml) and acetone (15 ml). To this, hydrogen peroxide (0.002 mole or 0.2 ml of 30% w/v) was added and the reaction contents were heated under reflux for 3 hr. The colour of the solution darkened during refluxing. The solvent was removed by distillation, and the residue was recrystallized from ethanol.

Synthesis of 10-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-trifluoromethyl/-9-ethoxy/-9-methoxy)-3-nitro-pyrido[3,2-b][1,4]benzothiazine 7a-c.

A mixture of 4 (0.002 mole) and tetrabutylammonium bromide (0.0002 mole) in dichloromethane (5 ml) was stirred at room temperature. 50% Aqueous NaOH (10 ml) was added dropwise in this mixture and stirred for 30 min. To it a solution of 2,3,5-tri-*O*-benzoyl-β-D- ribofuranosyl bromide (0.002 mole) in small volume of dichloromethane was gradually poured in three-four instalments. The reaction mixture was again stirred for 3hr.

After completion of the reaction, dichloromethane (50 ml) and water (50 ml) was added and shaken in a separatory funnel. The layers were separated and the organic layer was washed twice with water (25 ml). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed by distillation. The residue was chromatographed on a silica gel column with solvent (CH_2Cl_2 : EtOAc, 95 : 5). Distillation of the solvent from main zone yielded a solid, which on recrystallization from methanol gave 7a-c. Physical data of 4-7 are recorded in Table-1.

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Table 1 : Characterization data of the synthesized compounds

Compd.	R^1	R^2	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analyses found (calc.) %		
						C	H	N
4a	H	CF_3	$C_{12}H_6F_3N_3O_2S$	280-282	67	46.20 (46.0)	1.22 (1.91)	13.12 (13.14)
4b	OC_2H_5	H	$C_{13}H_{11}N_3O_3S$	302-304	65	53.93 (53.90)	3.84 (3.80)	14.51 (14.53)
4c	OCH_3	H	$C_{12}H_9N_3O_3S$	325-327	63	52.39 (52.36)	3.29 (3.27)	15.24 (15.27)
5a	H	CF_3	$C_{14}H_8F_3N_3O_3S$	208-210	64	46.20 (46.19)	2.29 (2.25)	11.75 (11.80)
5b	OC_2H_5	H	$C_{15}H_{13}N_3O_4S$	200-202	60	54.39 (54.38)	3.95 (3.92)	12.61 (12.68)
5c	OCH_3	H	$C_{14}H_{11}N_3O_4S$	233-235	61	53.12 (52.99)	3.49 (3.47)	13.21 (13.24)
6a	H	CF_3	$C_{12}H_6F_3N_3O_3S$	320-322	68	43.79 (43.77)	1.85 (1.82)	12.73 (12.76)
6b	OC_2H_5	H	$C_{13}H_{11}N_3O_4S$	335-337	71	51.18 (51.14)	3.65 (3.60)	13.72 (13.77)
6c	OCH_3	H	$C_{12}H_9N_3O_4S$	318-320	73	49.51 (49.48)	3.12 (3.09)	14.41 (14.43)
7a	H	CF_3	$C_{31}H_{23}F_3N_3O_9S$	158-160	65	60.28 (60.23)	3.48 (3.43)	5.52 (5.54)
7b	OC_2H_5	H	$C_{31}H_{31}N_3O_{10}S$	141-143	61	63.89 (63.84)	4.27 (4.22)	5.71 (5.72)
7c	OCH_3	H	$C_{38}H_{27}N_3O_{10}S$	195-197	64	63.43 (63.42)	4.05 (4.03)	5.80 (5.84)

Table 2 : Antimicrobial activity of the synthesized compounds zone of growth inhibition (mm) (activity index)*

Compd.	Escherichia coli (gram + ve)	Staphylococcus aureus (gram - ve)	Aspergillus niger	Aspergillus flavus	Curvularia lunata	Fusarium oxysporium
4a	13.5 (1.23)	13.9 (1.26)	11.6 (1.45)	13.5 (1.69)	11.7 (1.58)	12.5 (1.56)
4b	11.9 (1.08)	11.5 (1.05)	10.6 (1.33)	12.5 (1.56)	12.6 (1.48)	12.0 (1.50)
4c	12.2 (1.11)	11.0 (1.00)	9.4 (1.17)	11.9 (1.49)	12.5 (1.50)	12.0 (1.50)
5a	13.0 (1.18)	13.5 (1.23)	10.9 (1.36)	14.4 (1.80)	12.0 (1.54)	12.5 (1.56)
5b	12.0 (1.09)	11.2 (1.02)	10.6 (1.33)	10.8 (1.35)	11.9 (1.49)	11.5 (1.44)
5c	12.5 (1.14)	11.5 (1.05)	10.8 (1.35)	11.0 (1.38)	12.3 (1.50)	12.0 (1.50)
6a	13.2 (1.20)	13.5 (1.23)	14.2 (1.78)	13.0 (1.62)	10.4 (1.36)	11.6 (1.45)
6b	12.4 (1.13)	12.0 (1.09)	9.9 (1.24)	9.9 (1.24)	10.7 (1.34)	11.5 (1.44)
6c	12.5 (1.14)	11.9 (1.08)	10.5 (1.31)	10.0 (1.25)	10.9 (1.30)	11.8 (1.48)
7a	13.5 (1.23)	13.8 (1.25)	10.6 (1.33)	12.5 (1.56)	12.0 (1.5)	11.0 (1.38)
7b	12.6 (1.15)	11.8 (1.07)	11.2 (1.40)	10.8 (1.35)	11.3 (1.41)	11.0 (1.38)
7c	12.3 (1.12)	12.5 (1.14)	11.2 (1.40)	11.0 (1.38)	11.7 (1.46)	11.0 (1.38)

Values is parentheses represent activity index : $\frac{\text{Inhibition area of the sample}}{\text{Inhibition area of the standard}}$