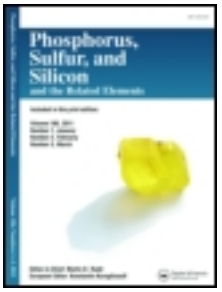

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SYNTHESIS OF NOVEL THIOXODERIVATIVES OF PYRIDO[2,3-d]PYRIMIDINES AND THEIR NUCLEOSIDES AS POSSIBLE ANTICANCER AGENTS

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SYNTHESIS OF NOVEL THIOXODERIVATIVES OF PYRIDO[2,3-d]PYRIMIDINES AND THEIR NUCLEOSIDES AS POSSIBLE ANTICANCER AGENTS

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Synthesis of some 2-thioxo-3,5,7-trisubstituted pyrido[2,3-d]pyrimidine-4(1H)-ones and corresponding nucleosides viz. 2-thioxo-3,5,7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]-pyrimidine-4 (1H)-ones is reported. The results of antimicrobial activities are also reported. The structures of the compounds have been established by elemental, IR and NMR analyses.

Key words: Thioxopyridopyrimidine, nucleoside, spectral studies and antimicrobial activity.

INTRODUCTION

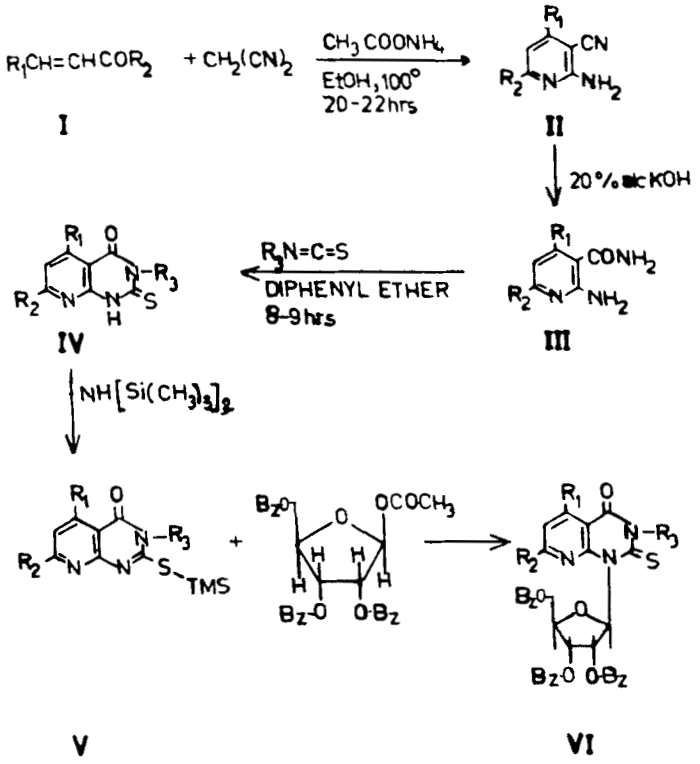
Pyridopyrimidine is a medicinally important nucleus, as it is a part of large number of anticancer drugs.[1–5] The oxo and dioxo derivatives of pyridopyrimidine have been reported to possess anticancer activity.[6] A recent report by Motoo *et al.* has suggested that dioxo derivatives of pyrido[2,3-d]pyrimidine are useful bases for the synthesis of anticancer nucleosides.[7] A pertinent literature survey revealed that nucleosides of thioxo derivatives of pyrido[2,3-d]pyrimidines have not been reported so far.

With the view that thioxo pyrido pyrimidine may modify the anticancer activity, it was thought worthwhile to undertake the synthesis of some 2-thioxo-3,5,7-trisubstitutedpyrido[2,3-d]pyrimidine-4(1H)ones (**IV**) and their nucleosides viz. 2-thioxo-3,5,7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-4(1H)-one (**IV**).

RESULTS AND DISCUSSION

2-Amino-3-cyano-4,6-disubstitutedpyridine **II** were obtained from chalcones **I** with ammonium acetate in ethanol via a Michael type condensation. Compound **II**, when hydrolyzed with 20% alc.KOH solution, gave 2-amino-3-carboxamido-4,6-disubstitutedpyridines **III**.

Compounds **III** with appropriate arylisothiocyanates in diphenyl ether furnished **IV**. The arylisothiocyanates required for the reaction were synthesized by the usual methods. Compounds **IV** were treated with hexamethyl disilazane to give the corresponding trimethylsilyl derivatives **V** which when stirred with 2,3,5-tri-O-benzoyl-β-D-ribofuranose *in vacuo* at 155–160°C for 10 hrs gave the respective nucleosides **VI** (Scheme I).



SCHEME I

SPECTRAL STUDIES

The spectroscopic studies and elemental analyses (Table I) of the synthesized compounds are consistent with the proposed structures.

IR Spectra

The IR spectra of compound **II** showed a sharp peak in the region 2220–2110 cm^{-1} due to the —CN group.

Compounds **III** gave a band at 1685–1678 cm^{-1} due to >C═O in the —$CONH_2$ group with the disappearance of the —CN absorption band.

The stretching vibrations of the —NH group appeared as weak bands in the region 3440–3300 cm^{-1} and bending vibrations at 1520–1510 cm^{-1} in compounds **II** and **III**.

Compounds **IV** gave >C═O bands at 1720–1680 cm^{-1}, >C═S bands at 1200–1170 cm^{-1}, and three bands in the region 1585–1420 cm^{-1} due to a —NHCS moiety. Absorption due to a —NH group appeared at 3420–3375 cm^{-1} in **IV** which was not found in **VI**, confirming the ribosilation at this position.

TABLE I

Characterization data of compounds **IVa–f** and **VIa–f**

Comp No.	R_1	R_2	R_3	Molecular Formula	Yield %	M.P °C	Elemental analysis %Found (calculated) C	H	N	S
IV a	3,4-$(OCH_3)_2C_6H_3$	4-$NH_2C_6H_4$	4-$OC_2H_5C_6H_4$	$C_{29}H_{26}N_4O_4S$	84	>360*	66.49 (66.16)	4.96 (4.94)	10.60 (10.65)	6.05 (6.08)
IV b	"	"	4-$CH_3C_6H_4$	$C_{28}H_{24}N_4O_3S$	85	>348*	68.05 (67.74)	4.84 (4.83)	11.24 (11.29)	6.42 (6.45)
IV c	"	"	2-$OCH_3C_6H_4$	$C_{28}H_{24}N_4O_4S$	82	>360*	65.91 (65.63)	4.70 (4.69)	10.90 (10.94)	6.21 (6.25)
IV d	"	"	4-$OCH_3C_6H_4$	$C_{28}H_{24}N_4O_4S$	84	>344*	65.90 (65.63)	4.69 (4.69)	10.91 (10.94)	6.24 (6.25)
IV e	"	4-$OCH_3C_6H_4$	4-$OC_2H_5C_6H_4$	$C_{30}H_{27}N_3O_5S$	78	>360*	66.84 (66.54)	5.01 (4.99)	7.74 (7.76)	5.89 (5.91)
IV f	"	"	4-$OCH_3C_6H_4$	$C_{29}H_{25}N_3O_5S$	72	270	66.29 (66.03)	4.76 (4.74)	7.94 (7.97)	6.05 (6.07)
VI a	"	4-$NH_2C_6H_4$	4-$OC_2H_5C_6H_4$	$C_{55}H_{46}N_4O_{11}S$	70	145	68.33 (68.04)	4.75 (4.74)	5.74 (5.77)	3.29 (3.30)
VI b	"	"	4-$CH_3C_6H_4$	$C_{54}H_{44}N_4O_{10}S$	72	142	69.26 (68.94)	4.70 (4.68)	5.93 (5.96)	3.38 (3.40)
VI c	"	"	2-$OCH_3C_6H_4$	$C_{54}H_{44}N_4O_{11}S$	69	146	68.09 (67.78)	4.59 (4.60)	5.85 (5.86)	3.32 (3.35)
VI d	"	"	4-$OCH_3C_6H_4$	$C_{54}H_{44}N_4O_{11}S$	70	143	68.06 (67.78)	4.62 (4.60)	5.84 5.86)	3.33 (3.35)
VI e	"	4-$OCH_3C_6H_4$	4-$OC_2H_5C_6H_4$	$C_{56}H_{47}N_3O_{12}S$	69	139-40	68.49 (68.22)	4.78 (4.77)	4.24 (4.26)	3.24 (3.25)
VI f	"	"	4-$OCH_3C_6H_4$	$C_{55}H_{45}N_3O_{12}S$	70	135	68.26 (67.97)	4.65 (4.63)	4.31 (4.33)	3.21 (3.29)

* Decomposed

^{1}H NMR Spectra

The ^{1}H NMR spectra for compounds **IV** gave aromatic protons at δ 6.9–7.9 ppm as multiplets. The absorption corresponding to integration of three protons each at δ 3.89–4.20 and δ 1.64 indicated the presence of —OCH_3 and —CH_3 groups, respectively.

The —NH_2 protons gave a broad peak at δ 3.55–3.58. A triplet at δ 1.28–1.30 with a quartet at δ 3.64–4.07, both having coupling constants of J = 6 Hz, due to —OCH_2CH_3 protons. The —NH proton appeared at δ 8.9–8.1 in compounds **IV**. The ^{1}H NMR spectra of **VI** revealed the loss of signal due to the proton of the —NH group.

This firmly established that **VI** are, in fact, the N-1-substituted nucleosides. The other protons in compounds **VI** were present, but slightly shifted downfield compared to the values given for compounds **IV**.

The protons of the sugar part in the nucleosides **VI** were found to be slightly shifted downfield with corresponding protons of the sugar.

ANTIMICROBIAL ACTIVITY

The compounds **IV** and nucleosides **VI** were screened for antimicrobial activity following the method of Bauer *et al.*[8] The concentration applied was 100 μg per disk. Streptomycin and Mycostatin were used as references while testing antibacterial and antifungal activity, respectively.

All compounds were found to be moderately active against various bacteria and fungi (Table II).

EXPERIMENTAL

All the mps were determined in open capillary tubes and were uncorrected. The IR spectra were recorded on a Perkin-Elmer-883 infrared spectrophotometer in KBr pellets. The ^{1}H NMR spectra were scanned in $CDCl_3$/DMSO-d_6 on an FX 90Q-JEOL spectrometer (90 MHz) using TMS as an internal standard.

Chemical shifts are expressed in δ values. The purity of compounds was checked by TLC using silica gel 'G' as adsorbent and visualization was accomplished by U.V. light or with iodine.

Chalcones (**I**) were synthesized by the usual methods.

Synthesis of 2-amino-3-cyano-4,6-disubstituted pyridine **II**: A mixture of an appropriate chalcone **I** (0.05 mole), malononitrile (0.05 mole), and ammonium acetate (0.4 mole) in ethanol (50 ml) was heated on a water bath for 20–22 hrs.

After cooling, the contents were poured onto crushed ice with constant stirring to obtain a solid mass, generally of yellow color with different shades.

This solid was washed with water and ethanol and then was recrystallized from DMF-EtOH or DMSO-EtOH mixture.

Synthesis of 2-amino-3-carboxamido-4,6-disubstituted pyridine **III**: 2-Amino-3-cyano-4,6-disubstitutedpyridine **II** (0.04 mole), KOH (0.7 mole), and ethanol (150 ml) were refluxed for 6–7 hrs. After boiling, the mixture was poured into excess of water. The solid thus obtained was washed with water and recrystallized from ethanol.

Synthesis of 2-thioxo-3,5,7-trisubstituted pyrido [2,3-d]pyrimidin-4(1H)-one **IV**: A mixture of 2-amino-3-carboxamido-4,6-disubstitutedpyridine **III** (0.001 mole) and the appropriate arylisothiocyanate (0.001 mole) was refluxed in diphenyl ether (15 ml) for 8–9 hrs.

The reaction mixture, after cooling, was added to cold ethanol, and the separated solid was filtered, washed with ethanol, and recrystallized from a DMF-ethanol mixture or glacial acetic acid.

TABLE II

Antimicrobial activity of compounds **IVa–f** and **VIa–f** zone of growth inhibition (mm) (activity index)

	Escherichia coli (gram +ve)	*Staphylococcus aurius* (gram -ve)	*Aspergillus niger*	*Aspergillus flavous*	*Curvularia lunata*	*Fusarium moniliformae*
IV a	8.2 (1.03)	8.7 (1.04)	8.4 (1.02)	8.0 (1.00)	7.7 (1.03)	8.0 (1.03)
IV b	8.5 (1.06)	8.5 (1.01)	8.1 (0.99)	8.0 (1.00)	7.8 (1.04)	8.0 (0.98)
IV c	8.4 (1.05)	8.7 (1.04)	8.0 (0.98)	8.2 (1.03)	7.6 (1.01)	8.3 (1.01)
IV d	8.4 (1.05)	8.4 (1.00)	8.2 (1.00)	7.8 (0.98)	7.2 (0.96)	8.0 (0.98)
IV e	7.5 (0.94)	8.0 (0.95)	7.5 (0.91)	7.6 (0.95)	7.0 (0.93)	8.1 (0.92)
IV f	7.8 (0.98)	7.9 (0.94)	7.9 (0.96)	7.9 (0.99)	7.0 (0.93)	7.8 (0.95)
VI a	8.4 (1.05)	8.8 (1.05)	8.4 (1.02)	8.2 (1.03)	7.7 (1.03)	8.2 (1.00)
VI b	8.6 (1.07)	8.6 (1.02)	8.2 (1.00)	8.0 (1.00)	7.9 (1.05)	8.1 (0.99)
VI c	8.5 (1.06)	8.7 (1.04)	8.2 (1.00)	8.2 (1.03)	7.8 (1.04)	8.4 (1.02)
VI d	8.6 (1.07)	8.5 (1.01)	8.1 (0.99)	7.7 (0.96)	7.1 (0.95)	8.2 (1.00)
VI e	7.7 (0.96)	8.2 (0.98)	7.7 (0.94)	7.7 (0.96)	7.2 (0.96)	8.1 (0.99)
VI f	7.9 (0.99)	8.0 (0.95)	8.0 (0.98)	8.0 (1.00)	7.1 (0.95)	7.9 (0.96)

• Activity index = Inhibition area of the sample / Inhibition area of the standard.

Synthesis of 2-thioxo-3,5,7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-4-(1H)-one **VI**: To a concentrated solution of 2-thioxo-3,5,7-trisubstitutedpyrido-[2,3-d]pyrimidine **IV** (0.002 mole) in toluene was added hexamethyl disilazane (0.0124 mole) together with few crystals of ammonium sulphate. After 4 hrs at reflux, the remaining clear colored solution was filtered.

The solvent was removed under vacuo at 100°C. A sugar (2,3,5-tri-O-benzoyl-β-D-ribofuranose) (0.002 mole) was added to the above pasty mixture, and the mixture was stirred at 155–160°C under vacuum for 15 minutes in absence of moisture. The reaction mixture was stirred for 10 hrs; during the reaction period the vacuum was regularly applied for five minutes at the end of every hour. The melt was boiled in methanol for 10 minutes, cooled, and filtered. The filtrate was evaporated to dryness. The viscous residue was dissolved in diphenyl ether from which crystals of the nucleosides were obtained.

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