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Phosphorus, Sulfur, and Silicon and the Related Elements

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SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME NEW 4-IMINO-3,5,7-TRISUBSTITUTED PYRIDO[2,3d]PYRIMIDINES AND THEIR RIBOFURANOSIDES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

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SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME NEW 4-IMINO-3,5,7-TRISUBSTITUTED PYRIDO[2,3-d]PYRIMIDINES AND THEIR RIBOFURANOSIDES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

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(Received April 22, 2003)

Some new nucleosides, viz. 4-imino-3,5,7-trisubstituted-1-(2',3',5'-tri-O-benzyl- β -D-ribofuranosyl)pyrido[2,3-d]pyrimidin/e-2(1H)-ones/ thiones(VII/VIII), have been synthesized by condensation of trimethylsilyl derivatives of 4-imino-3,5,7-trisubstituted pyrido[2,3d]pyrimidin/e-2(1H)-ones/thiones (III/IV) with β -D-ribofuranosyl-1-acetate-2,3,5-tribenzoate. Compounds III/IV have been synthesized by refluxing 2-amino-3-cyano-4,6-disubstituted pyridine (II) with substituted an arylisocyanate or an isothiocyanate respectively. The structure of all the synthesized compounds have been established by IR and ¹H NMR studies. These compounds have been screened for antimicrobial activities in order evaluate. The possibility of the derivatives to be used as potential chemotherapeutic agents.

Keywords: Antimicrobial activities; nucleosides; pyrido[2,3-*d*] primidines; spectral studies

The pyrido[2,3-*d*]pyrimidine derivatives have been well recognized and documented by a large number of patents, as chemotherapeutic agents, viz. antibacterial,^{1,2} anticancer,³⁻⁴ antiulcer,⁵ anticonvulsant,^{6,7} antihypertensive,⁸ antitumor,⁹ antifungal,^{10,11} antiAIDS,¹² antiherpes,¹³ antiviral,¹⁴ and antineuplastic.¹⁵ With a recent patent, e.g., Martin et al.¹⁶ have demostrated that pyrido[2,3-*d*]pyrimidines are active against P³⁸ kinase; Reinhard et al.¹⁷ have synthesized pyrido[2,3-*d*] pyrimidine derivatives as analogs of the antifolates methotrexate.

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The manifold of diverse pharmacological activities shown by pyrido[2,3-d]pyrimidines and our interest in this area^{18,19} led us to synthesize some new 4-imino-3,5,7-trisubstituted pyrido[2,3-d] pyrimidin/e-2-(1*H*)-ones/thions and their nucleosides, viz. 4-imino-3,5, 7-trisubstituted-1-(2',3',5'-tri-O-benzoyl- β -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2(1*H*)ones/thiones.

RESULTS AND DISCUSSION

2-Amino-3-cyano-4,6-disubstituted pyridines II were prepared via cyclisation²⁰ of chalcones I, on treatment with ammonium acetate in ethanol, via a Michael type condensation reaction. Compound II, on refluxing with phenyl isocyanate/isothiocyanate, afforded 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin/e-2(1*H*)-ones/thiones. Compound III/IV on treatment with hexamethyldisilazane in toluene, gave the corresponding trimethylsilyl derivatives V/VI, which, subsequently, on stirring with β -D-ribofuranose-1-acetate-2,3,5-tribenzoate in vacua, at 155–160°C for 10 h, afforded 4-imino-3,5,7-trisubstituted(2',3',5'-tri-O-benzoyl- β -D-ribofuranosyl)pyrido[2,3-*d*] pyrimidin/e-2(1*H*)-ones/thiones respectively (Scheme 1).

Characterization Data

The structure of synthesized compounds were well supported by their spectral data (Table I).

IR Spectra

In IR spectra bands due to the –CN and the –NH₂ groups in compound II appeared in the region 2230–2130 cm⁻¹, 3450–3315 cm⁻¹ respectively. Disappearance of –CN group and appearance of band due to >C=O group in the region 1750–1665 cm⁻¹ in compound (IIIa–d and VIIa–d) and >C=S groups in the region 1235–1200 cm⁻¹ in compounds (IVa–e and VIIIa–e) and observation of bands, due to >NH and >C=NH in the region 3410–3345 cm⁻¹ and 3230–3140 cm⁻¹, respectively, are supportive of their formation. Three characteristic bands of –NHCS moiety in the region 1560–1320 cm⁻¹ has also been observed in compound IVa, IVb, IVc, IVd, IVe and VIIIa, VIIIb, VIIIc, VIIId, VIIIe.

The absorption band, due to the >NH moiety in the region 3410– 3345 cm⁻¹ was found to be absent in compounds VII–VIII, suggesting that this was the site of ribosylation. The symmetric and asymmetric



SCHEME 1

stretching vibrations due of C–O–C linkage of the sugar moiety in compound VII–VIII has appeared in the region 1180 and 1020 cm⁻¹.

¹H NMR

The ¹H NMR spectra of compounds III and IV exhibit a multiplet in the region δ 6.66–8.12 due to aromatic protons. The >NH protons in compounds III and IV showed as a singlet at δ 8.09–8.26. In compound IIIa, IIb/IVa, IVb, and VIIa, VIIb/VIIIa, VIIIb the protons of the $-NH_2$ group appeared as a broad peak, in the region δ 3.88–4.52. In compound III/IV and VII/VIII protons of the >C=NH appeared δ 8.09–8.50, as a singlet. In the protons of the $-OCH_3$ group appeared a singlet between

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TABLE I The Physical Data and Spectral Data of 4-Imino-3,5,7-trisubstituted Pyrido[2,3-d]pyrimidines and Their Nucleoside

R		IH ₂ OCH ₃ CH ₃ OF		4.41 9.8	1.41 — 9.8 1.46 — — 9.8	4.41 - 9.8 4.46 9.8	4.41 - 9.8 4.46 9.8 	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4.41 - 9.8 4.46 9.8 	4.41 - 9.8 4.46 - 9.8 	4.41 - 9.8 1.46 - - 2.5 - - 4.52 3.70 9.98 4.53 3.65 - 3.90 - -	4.41 9.8 1.46 - 1.45 - 1.52 3.70 9.98 4.52 3.65 - 3.360 3.65 - 3.75 3.40 -	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4.41 - 9.8 4.46 - - 4.52 3.70 9.98 4.53 3.65 - 4.36 3.66 - 4.33 3.66 - 4.39 3.66 - 4.30 10.09 4.15 -	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
1 H NMR		-C=NH Ar-H Ar-NF		8.30 6.66-7.87 4.07-4.	8.30 6.66–7.87 4.07–4. 8.10 6.69–7.68 4.11–4.	8.30 6.66-7.87 4.07-4. 8.10 6.69-7.68 4.11-4. 8.09 6.87-8.12 —	8.30 6.66-7.87 4.07-4. 8.10 6.69-7.68 4.11-4. 8.09 6.87-8.12 8.31 6.67-7.87	8:30 6:66-7.87 4.07-4. 8:10 6:69-7.68 4.11-4. 8:09 6:87-8.12 8:31 6:67-7.87 8:25 7.0-7.80 4.21-4.	8.30 6.66-7.87 4.07-4. 8.10 6.69-7.68 4.11-4. 8.09 6.87-8.12 - 8.31 6.67-7.87 - 8.33 6.0-7.80 4.21-4. 8.35 6.0-7.80 4.21-4. 8.35 6.0-7.00 4.07-4.	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	8.30 6.66-7.87 4.07-4. 8.10 6.69-7.68 4.11-4. 8.10 6.69-7.68 4.11-4. 8.10 6.67-7.87 - 8.31 6.67-7.87 - 8.35 7.0-7.80 4.21-4. 8.35 6.9-8.00 4.07-4. 8.33 6.8-8.10 - 8.33 6.8-8.10 - 8.45 7.0-7.00 -	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{rrrr} 8.30 & 6.66-7.87 & 4.07-4.\\ 8.10 & 6.69-7.68 & 4.11-4.\\ 8.30 & 6.87-8.12 & \\ 6.87-7.81 & 6.67-7.81 & \\ 6.7-7.81 & 6.9-8.00 & 4.07-4.\\ 8.15 & 6.9-8.00 & 4.07-4.\\ 8.33 & 6.8-8.10 & \\ 8.33 & 6.8-8.10 & \\ 8.40 & 6.8-7.68 & \\ 8.40 & 6.8-7.68 & \\ 8.40 & 6.9-8.18 & \\ 8.40 & 6.9-8.18 & \\ 8.55 & 7.79-8.06 & 4.16-4.\\ 8.55 & 7.78-8.10 & \\ 8.56 & 7.78-8.10 & \\ 8.57 & 7.78-8.10 & \\ 8.58 & 6.79-8.05 & \\ 8.58 & 7.78-8.10 & \\ 8.58$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
m^{-1}		-C-O-C >NH >		- 8.20	8.20 8.15	8.20 8.15 8.10			8.20 8.15 8.15 8.10 8.25 8.25 8.20 8.20 8.20	8.20 8.15 8.15 8.15 8.15 8.20 8.23 8.20 8.20		8.20 8.15 8.15 8.10 8.25 8.25 8.26 8.20 8.21 8.20 8.22 8.22 8.23							- 8.20 - 8.15 - 8.15 8.16 - 8.25 - 8.26 - 8.26 - 8.26 - 8.26 - 8.26 - 8.26 - 1110-1065 - 1110-1065 - 1110-1065 - 1110-1020 - 11120-1020 - 1120-1080 - 1120-10	
IR (KBr) v_{max} cn		: >NH >C=O >C=S		3390 1680 -	3390 1680 — 3360 1665 —	3390 1680 3360 1665 3370 1700	3390 1680 3360 1665 3370 1700 3350 1685	3390 1680 3360 1665 3370 1700 3350 1685 3420 1220	3390 1680 3360 1665 3370 1700 3350 1685 3420 1220 3350 1220	3390 1680 3360 1665 3370 1700 3350 1685 3350 1685 3320 1685 3320 1220 3350 1235 3360 1235	3390 1680 3380 1665 3370 1700 3370 1700 3350 1685 3350 1220 3350 1235 3350 1210 3345 1210	3390 1680 3360 1665 3370 1700 3350 1855 3350 1825 3350 1220 3350 1235 3370 1235 3370 1226 3370 1225 3370 1225 3370 1225 33745 1226	33390 1680 - 33560 1665 - 3370 1765 - 3350 1665 - 3350 1700 - 3350 - 1220 3360 - 1235 3360 - 1235 3370 - 1225 3371 - 1225 3370 - 1226 3737 - 1226	3330 1680 - 3350 1665 - 3370 1665 - 3350 1665 - 3350 1700 - 3420 - 1220 3360 - 1235 3360 - 1225 3370 - 1225 3370 - 1225 3370 - 1226 3376 - 1225 3370 - 1226 3370 - 1226 3745 - 1226 - 1730 - - 1730 -	3390 1680 3380 1665 3370 1766 3370 1700 3350 1685 3350 1585 3350 1220 3350 1223 3350 1210 3356 1212 3357 1215 3356 1216 1710 1215 1773 1215 1773 1215 1773 1215 1773 1215	33390 1680 3350 1665 3370 1765 3350 1655 3350 1655 3350 1630 3350 1220 3350 1215 3350 1215 3370 1215 1730 1730 1730 1730 1730 1770 1770 1770	3330 1680 3350 1665 3370 1665 3370 1665 3350 1685 3350 1865 3350 1220 3350 1235 3370 1210 3371 1225 3370 1215 3371 1216 1710 1216 1710 1116 1710 1216	33390 1680 - 33560 1665 - 3370 1865 - 3350 1665 - 3350 1865 - 3350 1865 - 3430 1726 1226 3345 - 1225 3346 - 1210 3347 - 1225 3376 - 1225 3376 - 1225 3376 - 1210 - 1730 - - 1730 - - 1730 - - 1730 - - 1730 - - - 1746 - - 1760 - - 1200 - - 1200 - - - - - 1200 - - - -	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
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		Molecular formula		$C_{29}H_{23}CIN_5O_2$	$C_{29}H_{23}CIN_5O_2 \\ C_{25}H_{17}Cl_2N_5O$	$C_{25}H_{17}ClN_5O_2$ $C_{25}H_{17}Cl_2N_5O$ $C_{25}H_{15}Br_2ClN_4O$	C ₂₉ H ₂₃ CIN ₅ O ₂ C ₂₅ H ₁₇ Cl ₂ N ₅ O C ₂₅ H ₁₅ Br ₂ CIN ₄ O C ₂₅ H ₁₅ BrCl ₂ N ₄ O	$C_{25}H_{23}CIN_5O_2$ $C_{25}H_{17}Cl_2N_5O$ $C_{25}H_{15}Br_2CIN_4O$ $C_{25}H_{15}Br_2CIN_4O$ $C_{25}H_{15}BrCl_2N_4O$ $C_{30}H_{23}N_5O_2S$	C ₂₉ H ₂₃ CIN ₅ O ₂ C ₂₅ H ₁₇ Cl ₂ N ₅ O C ₂₅ H ₁₅ Br ₂ CIN ₄ O C ₂₅ H ₁₅ BrCl ₂ N ₄ O C ₃₆ H ₂₃ N ₅ O ₂ S C ₂₆ H ₂₀ CIN ₅ OS	$\begin{array}{c} C_{29}H_{23}CIN_5O_2\\ C_{25}H_{17}CI_2N_5O\\ C_{25}H_{15}Br_5CIN_4O\\ C_{25}H_{15}Br_5CIN_4O\\ C_{25}H_{15}Br_5CIN_4O\\ C_{20}H_{22}N_5O_2S\\ C_{26}H_{28}ON_5OS\\ C_{26}H_{18}Br_2N_4OS\\ C_{26}H_{18}Br_2N_4OS \end{array}$	C29H23CIN6O2 C25H17Cl2N6O C25H15BN5CIN4O C26H15BN5CIN4O C26H15BN5Q2S C36H23N6Q2S C26H36DN5 C26H36DN5 C36H38DN6QS C26H38BN5N4OS C26H38BN5N4OS	C29H33CIN502 C28H47018N60 C28H447018N50 C28H418P5CIN40 C39H33N502S C30H33N502S C28H38D2N40S 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C41.H23.BPCIN4.03 C41.H23.BPCIN4.03 C41.H23.BPCIN4.03 C41.H23.BPCIN4.03 C41.H23.BPCIN4.03 C41.H23.BPCIN2.03 C41.H23.BPCIN2.03 C41.H23.BPCIN2.03 C41.H23.BPCIN2.03 C41.H23.BPCIN2.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN3.03 C41.H23.BPCIN4.03 C41.H23.B	$\begin{array}{c} c_{23} H_{33} {\rm CIN}_{5} {\rm O}_{2} \\ c_{23} H_{17} {\rm Ob}_{16} {\rm No}_{10} \\ c_{24} H_{17} {\rm Ob}_{16} {\rm No}_{10} \\ c_{24} H_{18} {\rm Ber}_{10} {\rm No}_{10} \\ c_{26} H_{33} {\rm Nb}_{5} {\rm O}_{2} {\rm S} \\ c_{26} H_{33} {\rm Nb}_{5} {\rm O}_{2} {\rm S} \\ c_{26} H_{38} {\rm Nc}_{10} {\rm No}_{10} {\rm S} \\ c_{26} H_{18} {\rm Ber}_{11} {\rm A}_{10} {\rm S} \\ c_{26} H_{18} {\rm Ber}_{11} {\rm A}_{10} {\rm S} \\ c_{26} H_{18} {\rm Ber}_{11} {\rm A}_{10} {\rm S} \\ c_{26} H_{13} {\rm Ob}_{10} {\rm N}_{0} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{11} {\rm A}_{10} {\rm S} \\ c_{26} H_{13} {\rm Ob}_{10} {\rm N}_{0} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{11} {\rm A}_{10} {\rm S} \\ c_{26} H_{13} {\rm Ob}_{10} {\rm N}_{0} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{21} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{21} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{21} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} \\ c_{21} H_{38} {\rm Ber}_{10} {\rm O}_{10} {\rm N}_{10} {\rm O}_{10} {\rm O}_{10}$	C29.H23.CIN4.0.2 C29.H23.CIN4.0.2 C26.H17.015.N4.0 C26.H17.015.N4.0 C26.H13.BN2.CIN4.0 C30.H23.N4.0.5 C36.H3.BN2.N4.0S C36.H3.BNCIN4.0S C36.H3.BNCIN4.0S C36.H3.BNCIN4.0S C36.H3.BNCIN4.0S C36.H3.BNCIN4.09 C31.H3.BNCIN4.09 C32.H4.00 C31.H3.BNCIN4.09 C31.H3.BNCIN4.09 C32.H4.00 C31.H3.BNCIN4.09 C32.H4.00 C31.H3.BNCIN4.09 C32.H4.00 C32.H4	C29.H23CIN4.0.2 C21.H17015.N50 C21.H17015.N50 C21.H17015.N40 C21.H18.P12.N140 C30.H23.N50.28 C21.H3.B12.N140 C31.H3.B12.N140 C31.H3.B12.01N408 C31.H3.B12.01N4008 C31.H3.B12.01N4008 C31.H3.B12.01N4008 C31.H3.B12.01N408 C31.H3.B12	$\begin{array}{c} c_{23} H_{23} CIN_6 O_2 \\ c_{23} H_{15} B_{15} CIN_6 O \\ c_{23} H_{15} B_{15} CIN_4 O \\ c_{23} H_{15} B_{15} CIN_4 O \\ c_{24} H_{25} B_{15} N_6 O_2 \\ c_{26} H_{23} N_6 O_2 \\ c_{26} H_{13} B_{15} N_4 O \\ c_{26} H_{13} B_{15} N_4 O \\ c_{26} H_{13} B_{17} O_1 N_6 O \\ c_{26} H_{13} B_{17} O_1 N_6 O \\ c_{26} H_{13} B_{17} O_1 N_6 O \\ c_{26} H_{26} B_{17} O_1 O_1 O_6 O \\ c_{26} H_{26} B_{17} $
				4	H4	6H4 6H4 6H4	ਸ਼ੋ ਸ਼ੋ ਸ਼ੋ ਸ਼ੋ	CGH CGH CGH H3CGH	C6H4 C6H4 C6H4 C6H4 C6H4 H3C6H4 H3C6H4	-Сен. -Сен. -Сен. -Сен. -Сен. Л.,Сен. Л.,Сен. Л.,Сен.	-C6H4 -C6H4 -C6H4 -C6H4 -C6H4 3H3C6H4 3H3C6H4 3H3C6H4 3H3C6H4 3H3C6H4	1-C ₆ H ₄ 1-C ₆ H ₄ 1-C ₆ H ₄ 1-C ₆ H ₄ 1-C ₆ H ₄ CH ₅ C ₆ H ₄ CH ₅ C ₆ H ₄ CH ₅ C ₆ H ₄ H ₃ C ₆ H ₄	-C6H1 -C6H1 -C6H1 -C6H1 -C6H1 -C6H1 -C6H1 -C6H1 CH3 C6H1 H3 C6H1 C6H1 C6H1	-C6,H4 -C6,H4 -C6,H4 -C6,H4 -C6,H4 CH3,C6,H4 CH3,C6,H4 CH3,C6,H4 H3,C6,H4 H3,C6,H4 H3,C6,H4 C6,H4 C6,H4 C6,H4	1-C6H4 1-C6H4 1-C6H4 1-C6H4 1-C6H4 CH3C6H4 CH3C6H4 CH3C6H4 H3C6H4 H3C6H4 H3C6H4 H3C6H4 IC6H4 IC6H4 IC6H4 IC6H4	С.6.Н. С.6.Н. С.6.Н. С.6.Н. ЭН3С6.Н. ЭН3С6.Н. 3.С.6.Н. 3.С.6.Н. С.6.Н. С.6.Н. С.6.Н. С.6.Н. С.6.Н.	-C6H4 -C6H4 -C6H4 -C6H4 -C6H4 -C6H4 -C6H4 -C6H4 -3-C6H4 -5-C6H4 -C	-Се,Н, -Се,Н, -Се,Н, -Се,Н, -Се,Н, -Се,Н, ССВ, Се, Н, В, С6,Н, В, С6,Н, В, С6,Н, В, С6,Н,	-C6H1 -C6H1	-C6H4 -C6H4
		${ m R}_3$		3-Cl-C ₆ H	3-C1-C ₆ 3-C1-C ₆	3-CI-C 3-CI-C 3-CI-C	3-CI-(3-CI-(3-CI-(3-CI-(3-Cl-6 3-Cl-6 3-Cl-6 3-Cl-6 2-OC	3-Cl- 3-Cl- 3-Cl- 3-Cl- 2-OC 2-OC	3-CJ 3-CJ 2-OC 2-OC 2-OC 2-OC	3-CI 3-CI 3-CI 2-O(2-O(2-O(2-O(2-O(3-C 3-C 3-C 2-0 2-0 2-0 2-0 2-0 4-C	20000 20000 20000 20000 20000 20000 20000 20000	3-CO 2-CO 2-CO 2-CO 2-CO 2-CO 2-CO 2-CO 2	2000 2000 2000 2000 2000 2000 2000 200	3-CC 2-000 2-CC 2-000 2-CC 2-000 2-CC 2-CC	3-CI 2-CI 2-CI 2-CI 2-CI 2-CI 2-CI 2-CI 2	2-0 2-0 2-0 2-0 2-0 2-0 2-0 2-0 2-0 2-0		2.00 2.00 2.00 2.00 2.00 2.00 2.00 2.00
		$ m R_2$ $ m R_3$		4-NH ₂ C ₆ H ₄ 3-Cl-C ₆ H	4-NH ₂ C ₆ H ₄ 3-Cl-C ₆ 4-NH ₂ C ₆ H ₄ 3-Cl-C ₆	4-NH ₂ C ₆ H ₄ 3-Cl-C 4-NH ₂ C ₆ H ₄ 3-Cl-C 4-BrC ₆ H ₄ 3-Cl-C	4-NH ₂ C ₆ H ₄ 3-Cl-(4-NH ₂ C ₆ H ₄ 3-Cl-(4-BrC ₆ H ₄ 3-Cl-(4-BrC ₆ H ₄ 3-Cl-(4-BrC ₆ H ₄ 3-Cl-(4-NH ₂ C ₆ H ₄ 3-Cl- 4-NH ₂ C ₆ H ₄ 3-Cl- 4-BrC ₆ H ₄ 3-Cl- 4-BrC ₆ H ₄ 3-Cl- 4-BrC ₆ H ₄ 3-Cl- 4-BrC ₆ H ₄ 2-Cl-	4-NH ₂ C ₆ H ₄ 3-CI- 4-NH ₂ C ₆ H ₄ 3-CI- 4-BrC ₆ H ₄ 3-CI- 4-BrC ₆ H ₄ 3-CI- 4-BrC ₆ H ₄ 3-CI- 5 4-NH ₂ C ₆ H ₄ 2-OC 4-NH ₂ C ₆ H ₄ 2-OC	4-NH ₂ C ₆ H ₄ 3-C1 4-NH ₂ C ₆ H ₄ 3-C1 4-BrC ₆ H ₄ 3-C1 4-BrC ₆ H ₄ 3-C1 4-BrC ₆ H ₄ 3-C1 5 4-NH ₂ C ₆ H ₄ 2-O1 4-NH ₂ C ₆ H ₄ 2-O1 4-BrC ₆ H ₄ 2-O1	$\begin{array}{l} 4\text{-}\mathrm{NH}_2\mathrm{G}\mathrm{H}_4 \ \ 3\text{-}\mathrm{Ci}\\ 4\text{-}\mathrm{NH}_2\mathrm{G}\mathrm{G}\mathrm{H}_4 \ \ 3\text{-}\mathrm{Ci}\\ 4\text{-}\mathrm{Br}\mathrm{G}\mathrm{e}\mathrm{H}_4 \ \ 3\text{-}\mathrm{Ci}\\ 4\text{-}\mathrm{Br}\mathrm{G}\mathrm{e}\mathrm{H}_4 \ \ 3\text{-}\mathrm{Ci}\\ 4\text{-}\mathrm{H}\mathrm{S}\mathrm{G}\mathrm{G}\mathrm{H}_4 \ \ 2\text{-}\mathrm{Oi}\\ 4\text{-}\mathrm{H}\mathrm{H}_2\mathrm{G}\mathrm{H}_4 \ \ 2\text{-}\mathrm{Oi}\\ 4\text{-}\mathrm{H}\mathrm{C}\mathrm{e}\mathrm{H}_4 \ \ 2\text{-}\mathrm{Oi}\\ 4\text{-}\mathrm{Br}\mathrm{G}\mathrm{e}\mathrm{H}_4 \ \ 2\text{-}\mathrm{Oi}\\ 4\text{-}\mathrm{Oi}\ 2\text{-}\mathrm{Oi}\ 2\text{-}Oi$	$\begin{array}{rcrc} 4\text{-}\mathrm{NH}_2\mathrm{C}\mathrm{6}\mathrm{H}_4 & 3\text{-}\mathrm{C}\\ 4\text{-}\mathrm{NH}_2\mathrm{C}\mathrm{6}\mathrm{H}_4 & 3\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{C}\mathrm{6}\mathrm{H}_4 & 3\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{C}\mathrm{6}\mathrm{H}_4 & 3\text{-}\mathrm{C}\\ 4\text{-}\mathrm{NH}_2\mathrm{C}\mathrm{H}_4 & 2\text{-}\mathrm{O}\\ 4\text{-}\mathrm{NH}_2\mathrm{C}\mathrm{6}\mathrm{H}_4 & 2\text{-}\mathrm{O}\\ 4\text{-}\mathrm{Br}\mathrm{C}\mathrm{6}\mathrm{H}_4 & 2\text{-}\mathrm{O}\\ 4\text{-}\mathrm{Br}\mathrm{C}\mathrm{6}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{B}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{H}_4 & 4\text{-}\mathrm{C}\\ 4\text{-}\mathrm{Br}\mathrm{B}\mathrm{B}\mathrm{C}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}\mathrm{B}B$	$\begin{array}{c} 4\cdot NH_2 C_6 H_4 \ 3\cdot C_1 \\ 4\cdot NH_2 C_6 H_4 \ 3\cdot C_1 \\ 4\cdot Br C_6 H_4 \ 3\cdot C_1 \\ 4\cdot Br C_6 H_4 \ 3\cdot C_1 \\ 1\cdot 4\cdot NH_2 C_6 H_4 \ 2\cdot O_1 \\ 4\cdot Br C_6 H_4 \ 3\cdot C_1 \\ 4\cdot Sr C_6 H_4 \ 3\cdot C_1 \\ 5\cdot 4\cdot NH_2 C_6 H_4 \ 3\cdot NH_2 \\ 5\cdot 4\cdot NH_2 C_6 H_4 \ 3\cdot NH_2 \\ 5\cdot 4\cdot NH_2 \ NH_2$	$\begin{array}{c} 4\cdot NH_2 C_6 H_4 \ 3\cdot C_1 \\ 4\cdot NH_2 C_6 H_4 \ 3\cdot C_1 \\ 4\cdot Br C_6 H_4 \ 2\cdot O_1 \\ 4\cdot Br C_6 H_4 \ 2\cdot O_1 \\ 4\cdot Br C_6 H_4 \ 2\cdot O_1 \\ 4\cdot Br C_6 H_4 \ 4\cdot C_1 \\ 4\cdot Br C_6 H_4 \ 3\cdot C_1 \\ 4\cdot NH_2 C_1 \\ 4\cdot NH_2 C_1 \\ 4\cdot NH_2 \\ 5\cdot NH$	4.NH ₂ C ₆ H ₄ 3.C 4.NH ₂ C ₆ H ₄ 3.C 4.NH ₂ C ₆ H ₄ 3.C 4.BNC ₆ H ₄ 3.C 4.BNC ₆ H ₄ 3.C 4.BNC ₆ H ₄ 2.O 4.NH ₂ C ₆ H ₄ 2.O 4.BNC ₆ H ₄ 2.O 4.BNC ₆ H ₄ 3.C 4.BNC ₆ H ₄ 3.C 4.NH ₂ C ₆ H ₄ 3.C	4.NH ₂ C ₆ H ₄ 3.C1 4.NH ₂ C ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 2.C0 4.NH ₂ C ₆ H ₄ 2.C0 4.BNC ₆ H ₄ 2.C0 4.BNC ₆ H ₄ 2.C0 4.BNC ₆ H ₄ 4.C1 4.BNC ₆ H ₄ 4.C1 4.BNC ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1	$\begin{array}{c} 4 \cdot NH_2 C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot NH_2 C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot Br C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot Br C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot Br C_6 H_1 & 2 \cdot O(1 \\ 4 \cdot Br C_6 H_1 & 2 \cdot O(1 \\ 4 \cdot Br C_6 H_1 & 2 \cdot O(1 \\ 4 \cdot Br C_6 H_1 & 2 \cdot O(1 \\ 4 \cdot Br C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot Br C_6 H_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C F_1 & 3 \cdot C_1 \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr S_C \\ 4 \cdot Hr S_C & 4 \cdot Hr \\ 4 \cdot Hr S_C & 4 \cdot Hr \\ 4 \cdot Hr \\ 4 \cdot Hr $	$\begin{array}{c} 4\cdot NH_2 G_6H_4 \ 3\cdot C_1 \\ 4\cdot NH_2 G_6H_4 \ 3\cdot C_1 \\ 4\cdot Br G_6H_4 \ 3\cdot C_1 \\ 4\cdot Br G_6H_4 \ 3\cdot C_1 \\ 4\cdot Br G_6H_4 \ 2\cdot O_1 \\ 4\cdot Br G_6H_4 \ 3\cdot C_1 \\ 5\cdot Br G_6H_4 \ 3\cdot C$	4.NH ₂ C ₆ H ₄ 3.C1 4.NH ₂ C ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 2.00 4.BNC ₆ H ₄ 2.01 4.NH ₂ C ₆ H ₄ 3.C1 4.BNC ₆ H ₄ 3.C1 4.B	$\begin{array}{c} 4.NH_{2}G_{6}H_{4} \ 3.Cl \\ 4.NH_{2}G_{6}H_{3} \ 3.Cl \\ 4.NH_{2}G_{6}H_{3} \ 3.Cl \\ 4.BNG_{6}H_{4} \ 3.Cl \\ 4.BNG_{6}H_{4} \ 2.Ol \\ 4.NH_{2}G_{6}H_{4} \ 2.Ol \\ 4.NH_{2}G_{6}H_{4} \ 2.Ol \\ 4.BNG_{6}H_{4} \ 2.Ol \\ 4.BNG_{6}H_{4} \ 3.Cl \\ 4.BNG_{6}H_{6} \ 3.Cl \\ 4.BNG_{6} \ 3.Cl \ 3.Cl \\ 4.BNG_{6} \ 3.Cl \ 3.Cl \\$
		d. R_1 R_2 R_3	$2-OHC_6H_6$ $4-NH_2C_6H_4$ $3-Cl-C_6H_4$		3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl-C ₆	$3-ClC_6H_4$ $4-NH_2C_6H_4$ $3-Cl-C$ $3-BrC_6H_4$ $4-BrC_6H_4$ $3-Cl-C$	3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl-(3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl-(4-ClC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl-(3-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-CI- 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-CI- 4-CIC ₆ H ₄ 4-BrC ₆ H ₄ 3-CI- 2-OHC ₁₀ H ₆ 4-NH ₂ C ₆ H ₄ 2-OC	$\begin{array}{rcl} 3\text{-}ClC_6H_4 & 4\text{-}NH_2C_6H_4 & 3\text{-}Cl\\ 3\text{-}BrC_6H_4 & 4\text{-}BrC_6H_4 & 3\text{-}Cl\\ 4\text{-}ClC_6H_4 & 4\text{-}BrC_6H_4 & 3\text{-}Cl\\ 2\text{-}OlC_10H_4 & 4\text{-}NH_2C_6H_4 & 2\text{-}Cl\\ 2\text{-}OlC_10H_6 & 4\text{-}NH_2C_6H_4 & 2\text{-}OC\\ 3\text{-}ClC_6H_4 & 4\text{-}NH_2C_6H_4 & 2\text{-}OC\\ \end{array}$	3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 2-OHC ₁₀ H ₄ 4-BrC ₆ H ₄ 2-Cl 3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-OC 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 2-OC 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 2-OC	3-ClC ₆ H ₁ 4-NH ₂ C ₆ H ₁ 3-Cl 3-BrC ₆ H ₁ 4-BrC ₆ H ₁ 3-Cl 3-ClC ₆ H ₁ 4-BrC ₆ H ₁ 3-Cl 2-ClC ₆ H ₁ 4-BrC ₆ H ₁ 2-Cl 3-ClC ₆ H ₁ 4-NH ₂ C ₆ H ₁ 2-Ol 3-BrC ₆ H ₁ 4-BrC ₆ H ₁ 2-Ol 3-BrC ₆ H ₁ 4-BrC ₆ H ₁ 2-Ol 4-ClC ₆ H ₁ 4-BrC ₆ H ₁ 2-Ol	3-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-C 3-B ₆ C ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-C 3-B ₇ C ₆ H ₄ 4-B ₇ C ₆ H ₄ 3-C 4-CIC ₆ H ₄ 4-B ₇ C ₆ H ₄ 2-O 3-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-O 3-B ₇ C ₆ H ₄ 4-B ₇ C ₆ H ₄ 2-O 3-B ₇ C ₆ H ₄ 4-B ₇ C ₆ H ₄ 2-O 2-CIC ₆ H ₄ 4-B ₇ C ₆ H ₄ 4-D 2-CIC ₆ H ₄ 4-B ₇ C ₆ H ₄ 4-D	3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 2-OHC ₀ H ₄ 4-BrC ₆ H ₄ 2-O 3-ClC ₆ H ₄ 4-BrC ₆ H ₄ 2-O 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 2-O 3-BrC ₆ H ₄ 4-BrC ₆ H ₄ 2-O 2-ClC ₆ H ₄ 4-BrC ₆ H ₄ 2-O 2-ClC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 2-ClC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl 2-ClC ₆ H ₄ 4-BrC ₆ H ₄ 3-Cl	$\begin{array}{llllllllllllllllllllllllllllllllllll$	3-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-C 3-SIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-C 4-CIC ₆ H ₄ 4-BHC ₆ H ₄ 3-C 2-OHC ₁₀ H ₆ 4-NH ₂ C ₆ H ₄ 2-O 3-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-O 3-SIC ₆ H ₄ 4-BHC ₆ H ₄ 2-O 4-CIC ₆ H ₄ 4-BHC ₆ H ₄ 2-O 2-CIC ₆ H ₄ 4-BHC ₆ H ₄ 2-O 2-CIC ₆ H ₄ 4-BHC ₆ H ₄ 3-C 2-CIC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-C	3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 4-ClC ₆ H ₄ 4-BhC ₆ H ₄ 3-Cl 2-OHC ₁₀ H ₆ 4-NH ₂ C ₆ H ₄ 2-Cl 3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-Ol 3-BhC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-Ol 4-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-Ol 2-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 2-Ol 2-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BhC ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BhC ₆ H ₄ 3-Cl 3-BrC ₆ H ₄ 4-BhC ₆ H ₄ 3-Cl	3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-BrG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-BrG ₆ H ₄ 4-BrG ₆ H ₄ 3-CI 2-OHC ₀ H ₄ 4-BrG ₆ H ₄ 3-CI 2-OHC ₀ H ₄ 4-BrG ₆ H ₄ 2-OI 3-CIG ₆ H ₄ 4-BrG ₆ H ₄ 2-OI 3-BrG ₆ H ₄ 4-BrG ₆ H ₄ 2-OI 2-CIG ₆ H ₄ 4-BrG ₆ H ₄ 2-OI 2-CIG ₆ H ₄ 4-BrG ₆ H ₄ 3-CI 3-BrG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-BrG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-BrG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI 3-CIG ₆ H ₄ 4-NH ₂ G ₆ H ₄ 3-CI	$\begin{array}{llllllllllllllllllllllllllllllllllll$	2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 3-CI 3-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 3-CI 4-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 3-CI 2-OHC ₁₀ H ₆ 4-NH2.C ₆ H ₄ 2-OI 2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-OI 2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 3-CI 2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-OI 2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-CI 2-CIC ₆ H ₄ 4-NH2.C ₆ H ₄ 2-CI 2-BrC ₆ H ₄ 2-DCI 2-BrC ₆ H ₆	3-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 4-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 4-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 4-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 2-CIC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 3-CI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI 3-BrC ₆ H ₄ 4-NH ₅ C ₆ H ₄ 2-OI

 b Three characteristic bands of –NHCS moiety in the region 1560–1320 cm⁻¹ also have been observed in compounds IVa, IVb, IVc, IVd, IVe and VIIIa, VIIIb, VIIIc, VIIId, VIIIe.

 δ 3.60–3.90 in compounds IVa, IVb, IVc, IVd/VIIIa, VIIIb, VIIIc, VIIId; and the protons of the –CH₃ groups were observed between singlet at δ 3.40–3.70 in compounds IVe, VIIIe. In the NMR spectra of ribofuranosides VII and VIII, a multiplet due to aromatic protons appeared at δ 6.69–8.20. The peak due to >NH moiety was found to be absent, indicating the site of attachment of the sugar, while, a singlet due to the –OH protons in compounds IIIa, IVa, VIIa, VIIIa was noticed in the region at δ 9.80–10.09.

Antimicrobial Screening

All the synthesized compounds were screened for their antibacterial and antifungal activities at the conc. of 100 μ g/disc, using streptomycin and mycostatin, respectively, as the reference compounds. The test organism used included *Escherichia coli* (gram negative bacteria), *Staphylococcus aureus* (gram positive bacteria), *Aspergillus flavus, Aspergillus niger*, and *Fusarium oxysporium* (Fungi). The disc diffusion method developed by Varma et al.²¹ has been followed. The results have been tabulated (Table II) in the form of inhibition zones and activity indices. Although, all the compounds show moderate to fairly good activities, a closer look on the activity indices reveals that the ribofuranosides are better antimicrobial agents than their bases.

EXPERIMENTAL SECTION

Melting point of all the synthesized compounds were determined in open capillary tube and are uncorrected. IR spectra were recorded on NICOLET MEGNA FT-IR 550 spectrometer and ¹H NMR spectra on a JEOL FX 90Q spectrophotometer using TMS as internal standard (chemical shifts in δ , ppm). The purity of compounds was checked by elemental analysis and also by TLC using silica gel "G," as adsorbent and visualization was accomplished by UV light /Iodine.

Synthesis of 2-Amino-3-cyano-4,6-disubstituted Pyridine II

A chalcone (0.05 mmol), malononitrile (0.05 mmol), and ammonium acetate (0.4 mmol) in ethanol (150 ml) was refluxed on a water bath for 20–22 h and then the contents were poured onto crushed ice with constant shaking. The solid, thus obtained, was washed with water several times, and finally with ethanol. Recrystallization from ethanol to gave²² II.

	Bact	teria	Fungl						
Compd. no.	E. Coli	St. oureus	A. Niger	A. Flavus	F. Oxysporium				
IIIa	7.9 (0.96)	7.9 (0.90)	8.9 (1.10)	9.0 (1.03)	9.5 (1.04)				
IIIb	8.0 (0.98)	8.3(0.99)	9.2(1.13)	9.4 (1.08)	9.6 (1.05)				
IIIc	8.3 (1.01)	8.4(0.95)	9.0 (1.11)	9.2(1.06)	9.3 (1.02)				
IIId	8.4 (1.02)	8.5(0.97)	9.4 (1.16)	9.6 (1.10)	9.8 (1.08)				
IVa	8.1 (0.99)	8.2(0.93)	9.1 (1.12)	9.3 (1.07)	9.6 (1.05)				
IVb	8.2(1.00)	8.6 (0.98)	9.4 (1.16)	9.5 (1.09)	9.7 (1.07)				
IVc	8.5 (1.04)	8.4(0.95)	9.3(1.15)	9.8 (1.13)	9.5 (1.04)				
IVd	8.6 (1.07)	8.9 (1.01)	9.9 (1.22)	9.9 (1.14)	9.9 (1.09)				
IVe	8.7 (1.06)	8.7 (0.99)	9.8 (1.21)	9.7 (1.11)	10.2(1.12)				
VIIa	8.8 (1.07)	9.2 (1.05)	9.6 (1.19)	9.9 (1.14)	9.9 (1.09)				
VIIb	9.1 (1.11)	8.9 (1.01)	10.1(1.25)	10.1 (1.16)	10.2(1.12)				
VIIc	9.9 (1.21)	9.3 (1.06)	9.9 (1.22)	9.8 (1.13)	10.1 (1.11)				
VIId	10.0(1.22)	9.9 (1.1)	10.4 (1.28)	10.6 (1.22)	10.5(1.15)				
VIIIa	9.8 (1.20)	9.5(1.07)	10.2(1.26)	9.6 (1.10)	9.8 (1.08)				
VIIIb	10.1(1.23)	9.4 (1.07)	10.5 (1.30)	9.9 (1.14)	10.2(1.12)				
VIIIc	10.3(1.26)	10.0 (1.14)	10.0 (1.29)	10.1 (1.16)	10.5(1.15)				
VIIId	10.9(1.33)	10.3(1.17)	11.2 (1.38)	10.5(1.21)	11.1(1.22)				
VIIIe	10.6(1.29)	10.2(1.16)	11.1(1.37)	10.3(1.18)	10.6 (1.16)				

TABLE II Results of Antimicrobial Study of 4-Imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin/e-2(1*H*)-ones/thiones and Their Ribofuraosides Zone of Growth Inhibition (mm) (activity index)^{*a*}

^{*a*}(Activity index) = Inhibition zone of the sample/inhibition zone of the standard.

Following 2-amino-3-cyano-4,6-disubstituted pyrimidines were synthesized:

- IIa 2-amino-3-cyano-4-(2-hydroxynaphthaldehyde)-6-(4-aminophenyl) pyridine: m.p. 135°C; yield 60%
- IIb 2-amino-3-cyano-4-(3-chlorophenyl)-6-(4-aminophenyl)pyridine: m.p. 105°C; yield 82%
- IIc 2-amino-3-cyano-4-(3-bromophenyl)-6-(4-bromophenyl)pyridine: m.p. 110°C; yield 77%
- IId 2-amino-3-cyano-4-(4-chlorophenyl)-6-(4-bromophenyl)pyridine: m.p. 112°C; yield 70%
- IIe 2-amino-3-cyano-4-(2-chlorophenyl)-6-(4-bromophenyl)pyridine: m.p. 120°C; yield 75%

Preparation of 4-Imino-3,5,7-trisubstituted Pyrido[2,3-*d*]pyrimidine-2(1*H*)-Ones III

A mixture of II (0.01 mmol), an arylisocyanate (0.01 mmol), dioxane (18.0 ml), and pyridine (2.0 ml) was refluxed at 150°C for about 18–20 h.

After cooling, the contents of the flask were poured onto crushed ice with constant stirring. The yellow solid mass, thus obtained, was washed with water. The dried crude product, so obtained, was recrystallized for DMF-ethanol (1:10).

Synthesis of 4-Imino-3,5,7-trisubstituted Pyrido[2,3-*d*]pyrimidines-2(1*H*)-thiones IV

Compounds of II (0.01 mmol), appropriate aryl isothiocyanate (0.01 mmol), dioxane (15.0 ml), and pyridine (2.0 ml), were refluxed at 150° C for about 18–20 h. After cooling, the contents of the flask were poured onto crushed ice with constant stirring. The yellow solid mass, thus obtained, was washed with water. The dried crude product was recrystallized form DMF-ethanol (1:10).

Synthesis of 4-Imino-3,5,7-trisubstituted-1-(2',3',5'-tri-O-benzoyl- β -D-ribofuranosyl)pyrido[2,3-*d*]pyrimidin/e-2 (1*H*)-ones VII/Thiones VIII

Compounds III, IV (0.002 mmol) were refluxed with hexamethyl disilazane (0.0124 mmol) containing few crystals of ammonium sulphate, in toluene (30 ml) for 4 h. The coloured solution, thus obtained, was filtered and the solvent was removed in vacuo at 100°C. To this, β -D-ribofuranose-1-acetate-2,3,5-tribenzoate (0.02 mmol) was added and then stirred at 155–160°C, under vaccuum, for 15 min in the absence of moisture. The reaction contain was stirred for 10 h. During the reaction period, the vaccuum was regularly applied for 5 min, at the end of each hour. The melt so obtained was boiled in methanol for 10 min, cooled, and filtered. The viscous mass of ribofuranoside, so obtained, was crystallized with diethyl ether.

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