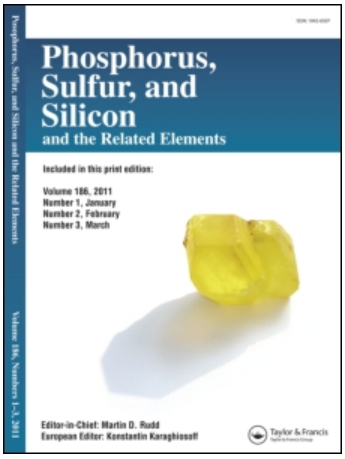

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SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME NEW 4-IMINO-3,5,7-TRISUBSTITUTED PYRIDO[2,3-*d*]PYRIMIDINES AND THEIR RIBOFURANOSIDES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

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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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*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(1*H*)-ones/thiones(VII/VIII), have been synthesized by condensation of trimethylsilyl derivatives of 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin/e-2(1*H*)-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 ^{1}H 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 P^{38} 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 cyclisation[20] 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).

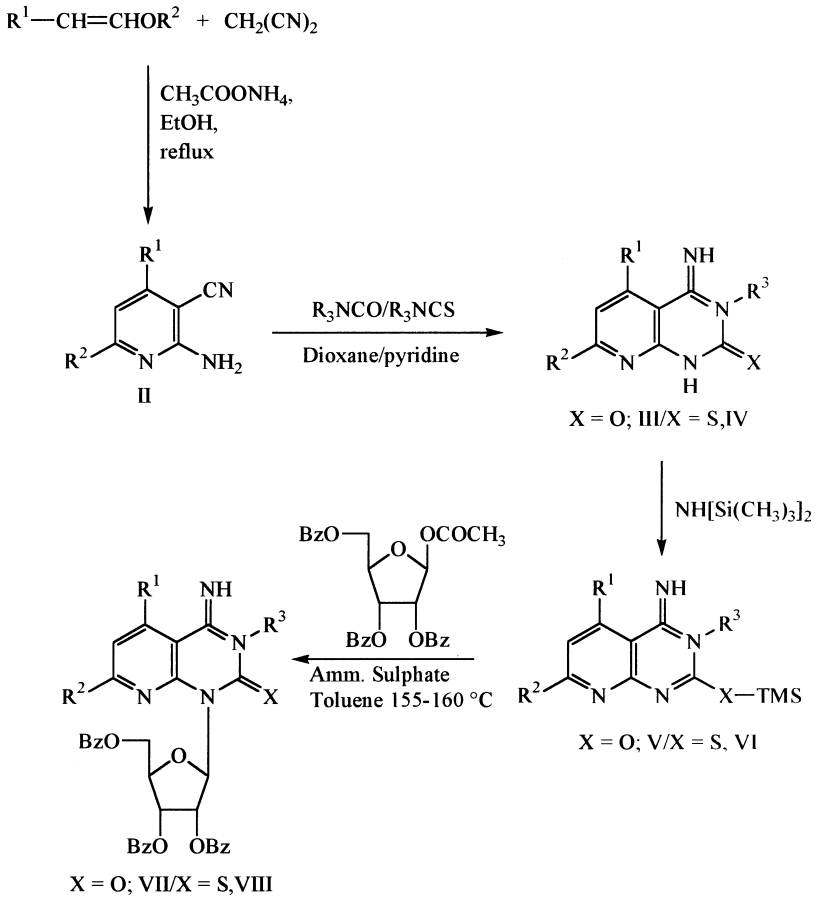
Characterization Data

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 —NH_2 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}.

^{1}H NMR

The ^{1}H 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

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

								IR (KBr) ν_{max} cm^{-1}				^1H NMR						
Compd.	R_1	R_2	R_3	Molecular formula	M.W.	Yield %	m.p.°C	>NH	>C=O	>C=S	—C—O—C	>NH	>C=NH	Ar—H	Ar—NH_2	—OCH_3	—CH_3	—OH
IIIa	2-OHC_6H_6	4-$NH_2C_6H_4$	3-Cl-C_6H_4	$C_{29}H_{23}ClN_5O_2$	491.5	76	90	3390	1680	—	—	8.20	8.30	6.66–7.87	4.07–4.41	—	—	9.8
IIIb	3-ClC_6H_4	4-$NH_2C_6H_4$	3-Cl-C_6H_4	$C_{25}H_{17}Cl_2N_5O$	459	78	85	3360	1665	—	—	8.15	8.10	6.69–7.68	4.11–4.46	—	—	—
IIIc	3-BrC_6H_4	4-BrC_6H_4	3-Cl-C_6H_4	$C_{25}H_{15}Br_2ClN_4O$	582.5	75	70	3370	1700	—	—	8.10	8.09	6.87–8.12	—	—	—	—
IIId	4-ClC_6H_4	4-BrC_6H_4	3-Cl-C_6H_4	$C_{25}H_{15}BrCl_2N_4O$	537	79	90	3350	1685	—	—	8.25	8.31	6.67–7.87	—	—	—	—
IVa	2-$OHC_{10}H_6$	4-$NH_2C_6H_4$	2-$OCH_3C_6H_4$	$C_{30}H_{23}N_5O_2S$	517	70	69	3420	—	1220	—	8.20	8.25	7.0–7.80	4.21–4.52	3.70		9.98
IVb	3-ClC_6H_4	4-$NH_2C_6H_4$	2-$OCH_3C_6H_4$	$C_{26}H_{20}ClN_5OS$	485.5	72	110	3350	—	1235	—	8.09	8.15	6.9–8.00	4.07–4.36	3.65		—
IVc	3-BrC_6H_4	4-BrC_6H_4	2-$OCH_3C_6H_4$	$C_{26}H_{18}Br_2N_4OS$	594	82	65	3360	—	1210	—	8.21	8.39	6.8–8.10	—	3.60		—
IVd	4-ClC_6H_4	4-BrC_6H_4	2-$OCH_3C_6H_4$	$C_{26}H_{18}BrClN_4OS$	549.5	85	80	3345	—	1225	—	8.26	8.45	7.0–7.09	—	3.90		—
IVe	2-ClC_6H_4	4-BrC_6H_4	4-$CH_3C_6H_4$	$C_{26}H_{18}BrClN_4S$	533.5	72	95	3370	—	1215	—	8.25	8.40	6.8–7.68	—	3.75	3.40	—
VIIa	2-$OHC_{10}H_6$	4-$NH_2C_6H_4$	3-ClC_6H_4	$C_{55}H_{40}ClN_5O_9$	949.5	70	85	—	1730	—	1080–1030	—	8.30	7.11–8.06	4.03–4.39	—	—	10.09
VIIb	3-ClC_6H_4	4-$NH_2C_6H_4$	3-ClC_6H_4	$C_{51}H_{37}Cl_2N_5O_8$	917	65	70	—	1710	—	1110–1065	—	8.40	6.95–8.18	3.88–4.15	—	—	—
VIIc	3-BrC_6H_4	4-BrC_6H_4	3-ClC_6H_4	$C_{51}H_{35}Br_2ClN_4O_8$	1026.5	75	72	—	1745	—	1100–1030	—	8.46	7.03–8.03	—	—	—	—
VIId	4-ClC_6H_4	4-BrC_6H_4	3-ClC_6H_4	$C_{51}H_{35}BrCl_2N_4O_8$	981	78	80	—	1750	—	1090–1020	—	8.50	7.78–8.10	—	—	—	—
VIIIa	2-$OHC_{10}H_6$	4-$NH_2C_6H_4$	2-$OCH_3C_6H_4$	$C_{56}H_{43}N_5O_9S$	961	70	62	—	—	1200	1135–1070	—	8.37	7.11–8.20	4.14–4.45	3.82		10.02
VIIIb	3-ClC_6H_4	4-$NH_2C_6H_4$	2-$OCH_3C_6H_4$	$C_{52}H_{40}ClN_5O_8S$	929.5	76	75	—	—	1215	1180–1080	—	8.35	6.79–8.05	4.16–4.50	3.88		—
VIIIc	3-BrC_6H_4	4-BrC_6H_4	2-$OCH_3C_6H_4$	$C_{52}H_{38}Br_2N_4O_8S$	1038	62	90	—	—	1205	1120–1050	—	8.20	6.69–8.18	—	3.91		—
VIIId	4-ClC_6H_4	4-BrC_6H_4	2-$OCH_3C_6H_4$	$C_{52}H_{38}BrClN_4O_8S$	993.5	85	93	—	—	1225	1140–1070	—	8.20	6.78–8.10	—	3.80		—
VIIIe	2-ClC_6H_4	4-BrC_6H_4	4-$CH_3C_6H_4$	$C_{52}H_{38}BrClN_4O_7S$	977.5	82	95	—	—	1235	1130–1040	—	8.31	6.79–8.03	—	4.13	3.70	—

[a] All the compounds gave satisfactory elemental analysis (C, H and N within ±0.13% of theoretical value).

[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 $-CH_3$ 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 μg/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 ^{1}H 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 gave[22] II.

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]

	Bacteria		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)

[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.

REFERENCES

[1] A. Gupta, A. K. Sharma, and L. Prakash, *Heterocyclic Chem.*, **3,** 117 (1993).
[2] L. F. Kuyper, J. M. Garvey, D. P. Baccanari, J. N. Chompness, D. K. Stammers, and C. R. Beddell, *Bioorg. Med. Chem.*, **4,** 593 (1996).
[3] T. Bar, P. Zimmermann, R. Boer, V. Gekeler, W. Isc, H. Boss, and W. R. Olrich, PCT Int Appl. WO 97, 19, 946 (Cl. 107D 471/04) June 5, 1997, CHAPPl. 95/3, 322, November 24, 1995; *Chem. Abstr.*, **127,** 81463 (1997).
[4] A. K. Sharma, Swati, A. K. Yadav, and L. Prakash, *Phosphosrus, Sulfur, Silicon*, **112,** 109 (1996).
[5] T. H. Brown, R. J. Ife, and C. A. Leach, Eur. Pat. Appl. EP 404, 355 (Cl C07 D 471/04), December 27, 1990; G. B. Appl. 89/12, 336, May 30, 1989, 14 pp; *Chem Abstr.*, **114,** 164273 (1991).

[6] H. Sladowska, *Formaco*, **48,** 77 (1993).
[7] R. M. Shafik, N. H. Eshba, H. Nabil, M. M. El-Semary, and F. M. Abdelkreem, *Alexandra J. Pharm. Sci.*, **9,** 55, (1995); *Chem. Abstr.*, **123,** 1332611 (1995).
[8] A. Monge, V. M. Merino, and M. C. S. Martin, Span. ES 2, 009, 217 (Cl. CO7 D 471/04), September 16, 1989, Appl. 8, 701, 988, July 7, 1987; 6 pp; *Chem. Abstr.*, **114,** 164275 (1991).
[9] K. Tomita, K. Chiba, S. Kashimot, K. Shibamori, and Y. Tsuziki, PCT Int. Appl. WO 95, 35, 559 (Cl. CO7D 417/04), December 21, 1995, Jpn. Appl. 94/156; 578; June 14, 1994, 103 pp; *Chem. Abstr.*, **124,** 289559 (1996).
[10] G. Singh, Swati, A. K. Mishra, and L. Prakash, *J. Indian. Chem.*, **37B,** 517 (1998).
[11] G. Singh, G. Singh, A. K. Yadav, and A. K. Mishra, *Phosphorus, Sulfur, and Silicon*, **165,** 107 (2000).
[12] T. H. Bowlin, Eur. Pat. Appl. EP, 472, 181 (Cl.A61K31/70), August 26, 1992, U.S. Appl. 517,042, August 22, 1990, 28 pp.; *Chem.,Abstr.*, **117,** 70267 (1992).
[13] I. Verheggen, A. V. Aerschot, R. Snoeck, et al., *J. Med. Chem.*, **36,** 2033 (1993).
[14] R. Pratap and V. N. Yarovenkom, *Nucleosides, Nucleotides, and Nuclic Acid*, **19,** 845, (2000); *Chem. Abstr.*, **133,** 193394 (2000).
[15] C. Whi-Gun, C. K. C. Thomas, and C. Ching-jer, *Tetrahedron*, **54,** 8661 (1998).
[16] J. J. Chen, J. P. Dunn, D. M. Goldstein, and C. M. Stahl (*F. Hoff-mann-La Roche Ag. Switz.*). PCT Int. Appl. WO 2002, 064594 **A2** 207 pp. (2002).
[17] F. Schonfeld and R. Troschutz, *Heterocycles*, **55,** 1679 (2001).
[18] N. Kumar, G. Singh, and A. K. Yadav, *Heteroatom Chem.*, **12,** 52 (2001).
[19] H. Agarwal, Swati, A. K. Yadav, and L. Prakash, *Phosphorus, Sulfur, Silicon*, **141,** 159 (1998).
[20] B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *Vogels Text Book of Practical Organic Chemistry* (Longman Group Ltd., London, 1980) p. 796.
[21] R. S. Varma and W. L. Nobles, *J. Pharm. Sci.*, **112,** 61 (1972).
[22] A. Sakweai and H. Midornikawa, *Bull. Chem. Soc. Japan*, **41,** 430 (1968).