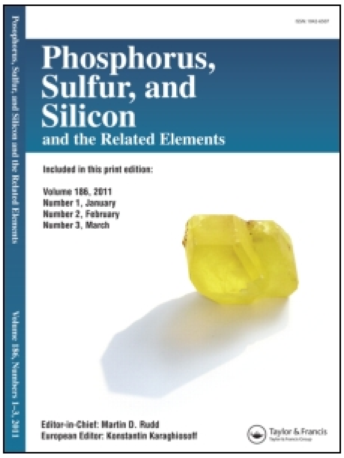


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Some Novel 4-Imino-3,5,7-Trisubstituted Pyrido[2,3-*d*]Pyrimidine-2(1*H*)-Thiones and Their Nucleosides as Potential Therapeutic Agents

Girwar Singh[a]; Gajendra Singh[a]; Ashok K. Yadav[a]; A. K. Mishra[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, (India)

To cite this Article Singh, Girwar , Singh, Gajendra , Yadav, Ashok K. and Mishra, A. K.(2000) 'Synthesis of Some Novel 4-Imino-3,5,7-Trisubstituted Pyrido[2,3-*d*]Pyrimidine-2(1*H*)-Thiones and Their Nucleosides as Potential Therapeutic Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 165: 1, 107 — 116
To link to this Article: DOI: 10.1080/10426500008076330
URL: http://dx.doi.org/10.1080/10426500008076330

Phosphorus, Sulfur and Silicon, 2000, Vol. 165, pp. 107-116
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF SOME NOVEL 4-IMINO-3,5,7-TRISUBSTITUTED PYRIDO[2,3-*d*]PYRIMIDINE-2(1*H*)-THIONES AND THEIR NUCLEOSIDES AS POTENTIAL THERAPEUTIC AGENTS

GIRWAR SINGH, GAJENDRA SINGH, ASHOK K. YADAV and A.K. MISHRA*

Department of Chemistry, University of Rajasthan, Jaipur-302004 (India)

(Received January 20, 2000; In final form May 07, 2000)

Some newer 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones were synthesized by the condensation of 2-amino-3-cyano-4,6-disubstituted pyridines with phenylisothiocyanate. The 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*)-thiones were synthesized by the condensation of trimethylsilyl derivatives of pyrido[2,3-*d*]pyrimidine with sugar namely β-*D*-ribofuranose 1-acetate-2,3,5-tribenzoate while 4-imino-3,5,7-trisubstituted-1-(2,3,5-tri-*O*-benzoyl-α-*D*-ribofuranosyl)pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones were prepared by condensing trimethylsilyl derivatives of pyrido[2,3-*d*]-pyrimidine with sugar in presence of $SnCl_4$. All the synthesized nucleosides and their precursors were characterized by spectral and elemental analysis data and have been screened for their antimicrobial activities.

Keywords: Pyrido[2,3-*d*]pyrimidines; nucleosides (α & β anomers); spectral data and antimicrobial activity

INTRODUCTION

Pyrido[2,3-*d*]pyrimidines were originally synthesized as compounds bearing structural kinship to many potent chemotherapeutic agents[1–2] like pteridine, aminopterin and methotrexate. Pyrido[2,3-*d*]pyrimidines have been reported to possess wide spectrum of biological activities such as diuretic[3], antimalerial[4], antiallergic[5], anticancer[6] antifungal[7], CNS depressant[8] and antiulcer[9] etc. Significant attention has been paid recently

* Corresponding Author.

for the synthesis of nucleosides of various heterocyclic bases as potential antiviral agents against Human Immunodeficiency Virus (HIV)[10–12]. Our interest in the area of pyrido[2,3-*d*]pyrimidines and in continuation of our earlier work[13] we wish to report here, the synthesis of some new 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones and their nucleosides (α & β anomers).

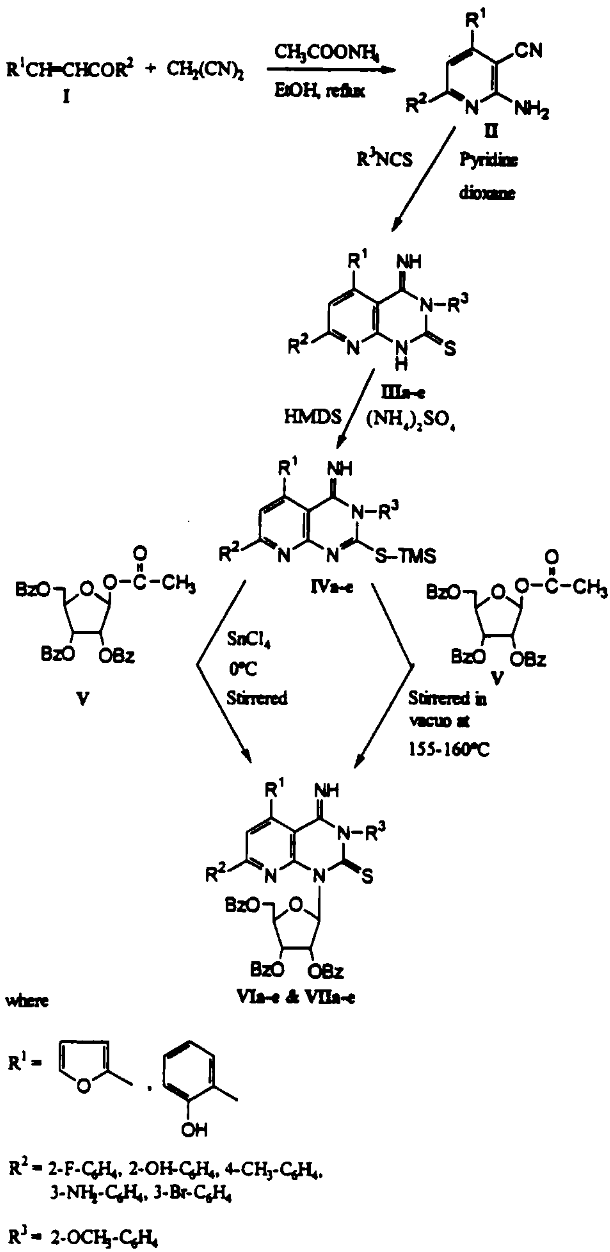
RESULTS AND DISCUSSION

4-Imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones **III** were synthesized by the condensation of 2-amino-3-cyano-4,6-disubstituted pyridines **II** with arylisothiocyanate in dioxane and pyridine. Compounds **II** were synthesized by condensing chalcones **I** with malononitrile in the presence of ammonium acetate through Michael type reaction. 4-Imino-3,5,7-trisubstituted-1-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl) pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones **VI** were prepared by the condensation of trimethylsilyl derivatives of pyrido[2,3-*d*]pyrimidine **IV** with sugar namely β-*D*-ribofuranose 1-acetate-2,3,5-tribenzoate **V** in vacuum at 155–160°C whereas, 4-imino-3,5,7-trisubstituted-1-(2,3,5-tri-*O*-benzoyl-α-*D*-ribofuranosyl)pyrido[2,3-*d*]-pyrimidine-2(1*H*)-thiones **VII** were synthesized by condensing compounds **IV** with sugar **V** in presence of $SnCl_4$ at 0°C in 1,2-dichloroethane.

The trimethylsilyl derivatives of pyrido[2,3-*d*]pyrimidines **IV**were synthesized by the reaction of pyrido[2,3-*d*]pyrimidines **III** with hexamethyldisilazane in presence of few crystals of ammonium sulphate. Formation of **VIa-e** (β-anomers) may be attributed due to SN^2-mechanism via neighbouring group participation and is in consonance with the earlier report. However, the formation of compounds **VIIa-e** (α-anomers) is perhaps due to coordination of $SnCl_4$ with -$OCOCH_3$ group of the sugar moiety and thus permitting condensation selectively. The reaction progress was monitored by TLC the products obtained were characterized by IR & ^{1}H NMR spectral data (Scheme 1).

SPECTRAL DATA

The proposed structure of the synthesized compounds are well supported by the spectral and elemental analysis data (Table. Ia, b).


R1CH=CHCOR2 + CH2(CN)2
I
CH3COONH4
EtOH, reflux
R1
CN
R2
N
NH2
II
R3NCS
Pyridine
dioxane
R1
NH
N-R3
R2
N
N
H
S
IIIa-e
HMDS
(NH4)2SO4
R1
NH
N-R3
R2
N
N
S-TMS
IVa-e
BzO
O
O-C-CH3
BzO
OBz
V
SnCl4
0°C
Stirred
Stirred in
vacuo at
155-160°C
R1
NH
N-R3
R2
N
N
S
BzO
O
BzO
OBz
VIa-e & VIIa-e
where
R1 =
O
OH
R2 = 2-F-C6H4, 2-OH-C6H4, 4-CH3-C6H4,
3-NH2-C6H4, 3-Br-C6H4
R3 = 2-OCH3-C6H4

SCHEME 1

TABLE Ia Characterization data of synthesized 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones III a-e

Comp. No.	R^1	R^2	R^3	*Molecular Formula*	*Yield %*	*M.P. °C*	*Elemental analysis calc. (Found) %*			
							C	*H*	*N*	*S*
IIIa	$-C_4H_3O$	$4-CH_3-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{25}H_{20}N_4O_2S$	72	79	68.18	4.54	12.73	7.27
							(68.22)	(4.59)	(12.68)	(7.24)
IIIb	$-C_4H_3O$	$2-OH-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{24}H_{18}N_4O_3S$	68	82	65.16	4.07	12.67	7.24
							(65.21)	(4.12)	(12.62)	(7.21)
IIIc	$-C_4H_3O$	$2-F-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{24}H_{17}N_4O_2FS$	81	85	64.86	3.83	12.61	7.21,
							(64.91)	(3 89)	(12 57)	(7.17)
IIId	$-C_4H_3O$	$3-Br.-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{24}H_{17}N_4O_2BrS$	68	93	57.03	3.36	11.09	6.34
							(56.98)	(3 39)	(11.04)	(6.29)
IIIe	$-C_6H_5O$	$3-NH_2-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{26}H_{20}N_5O_2S$	75	90–92	66.95	4.29	15.02	6.87
							(66.91)	(4 25)	(14.97)	(6.81)

TABLE Ib Characterization data of synthesized nucleosides of 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones VIa-e, VIIa-e

Comp. No.	R^1	R^2	R^3	*Molecular Formula*	*Yield %*	*M.P. °C*	*Elemental analysis calc. (Found) %*			
							C	*H*	*N*	*S*
VIa	$-C_4H_3O$	$4-CH_3.C_6H_4$	$2-OCH_3-C_6H_4$	$C_{51}H_{40}O_9N_4S$	82	191	69.23	4 52	6 33	3 62
							(69.29)	(4.56)	(6.27)	(3.58)
VIb	$-C_4H_3O$	$2-OH-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{38}O_{10}N_4S$	79	145	67.72	4.29	6 32	3.61
							(67.77)	(4 35)	(6.26)	(3.56)
VIc	$-C_4H_3O$	$2-F-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{37}O_9N_4FS$	81	148	67.57	4.17	6.31	3.60
							(67.62)	(4.23)	(6.28)	(3.55)
VId	$-C_4H_3O$	$3-Br-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{37}O_9N_4BrS$	76	156	63.22	3.90	5.90	3.37
							(63.27)	(3.97)	(5.85)	(3.32)
VIe	$-C_6H_5O$	$3-NH_2-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{52}H_{40}O_9N_5S$	78	215	68.57	4.39	7.69	3.52
							(68.63)	(4.44)	(7.62)	(3.45)
VIIa	$-C_4H_3O$	$4-CH_3.C_6H_4$	$2-OCH_3-C_6H_4$	$C_{51}H_{40}O_9N_4S$	72	230	69.23	4.52	6.33	3.62
							(69.28)	(4.55)	(6.26)	(3.57)
VIIb	$-C_4H_3O$	$2-OH-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{38}O_{10}N_4S$	68	245	67.72	4.29	6.32	3.61
							(67.76)	(4.34)	(6.25)	(3.55)
VIIc	$-C_4H_3O$	$2-F-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{37}O_9N_4FS$	71	250	67.57	4.17	6.31	3.60
							(67.61)	(4.22)	(6.27)	(3.55)
VIId	$-C_4H_3O$	$3-Br-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{50}H_{37}O_9N_4BrS$	69	235	63.22	3.90	5.90	3.37
							(63.26)	(3.96)	(5.84)	(3.31)
VIIe	$-C_6H_5O$	$3-NH_2-C_6H_4$	$2-OCH_3-C_6H_4$	$C_{52}H_{40}O_9N_5S$	73	280	68.57	4.39	7.69	3.52
							(68.62)	(4.45)	(7.63)	(3.44)

IR

IR spectra of compounds **II** showed a sharp band in the region 2230–2210 cm^{-1}, indicating the presence of -C≡N group. The stretching and bending vibrations due to – NH_2 group was appeared in the region 3450–3310 cm^{-1} and 1525–1500 cm^{-1} respectively. Disappearance of band due to -C≡N and appearance of new bands due to >C=S, >C=NH, and >NH in the region 1220–1185, 3190–3160, and 3140–3110 cm^{-1} respectively, indicated the formation of compounds **III** from compounds **II**. The absence of band due to >NH stretching vibrations in the spectra of compounds **VI** & **VII** indicated the site of ribosylation by substitution of hydrogen atom of >NH group. In compounds **VI** & **VII**, bands due to carbonyl group and C-O-C linkage were appeared at 1750–1725 cm^{-1} and 1170–1050 cm^{-1}, respectively.

^{1}HNMR

All the synthesized compounds gave a complex multiplet for aromatic protons in the region of δ 7.0–7.9 ppm. The imino protons in compounds **III**, **VI** & **VII**appeared as singlet at δ 8.9–9.1 ppm while the >NH proton showed their presence in compounds **III** at δ 8.1–8.3 ppm. Peaks due to $-CH_3$, $-OCH_3$, & $-NH_2$ protons were appeared in the region δ 2.1–2.3, δ 3.76–3.99 & δ 5.20–5.41 ppm, respectively while peak due to -OH proton was found to be merged with Ar-H wherever it present. Absence of peak due to >NH proton in compounds **VI** & **VII** confirm the ribosylation at this position & formation nucleosides. In compounds **VI** $C_{1'}$-H i.e. anomeric proton appeared as singlet at δ 6.40 ppm (It should appear as doublet with J = 2–3 Hz but at 90 MHz it appeared as singlet) confirm the β configuration while it appeared as doublet at δ 6.52 ppm with J = 8Hz in compounds **VII** confirm the α configuration.

ANTIMICROBIAL ACTIVITY

Synthesized pyrido[2,3-*d*]pyrimidines and their nucleosides were evaluated for their antibacterial and antifungal activity following the method Bauer *et. al*[14], using streptomycin in antibacterial and mycostatin in antifungal activity, as the reference compounds. All the synthesized compounds showed moderate to good activity against the organisms viz. *Escherichia coli* (gram negative bacteria), *Staphylococcus aureus* (gram positive bacteria) *Aspergillus niger, Aspergillus flavus*, and *Fusarium oxysporium* (fungi). The results have been tabulated in the form of activity indices. A close look on activity indices indicated that nucleosides showed better activity than their precursor. Further, it was also observed thus α-anomer showed better activity than β-anomer in most of the cases (table II).

EXPERIMENTAL

Melting point of all the synthesized compounds were determined in open capillary tube and are uncorrected. The IR spectra were determined in KBr disc on a NICOLET MEGNA FT-IR 550 spectrometer and ^{1}HNMR spectra in $CDCl_3$/DMSO-d_6 on a FX 90Q JEOL type spectrophotometer using TMS as internal standard (chemical shift in δ ppm). The purity of compounds were checked by TLC using silica gel "G" as adsorbent and visualization was accomplished by UV light or iodine.

Chalcones were synthesized by reported methods[15].

Synthesis of 2-amino-3-cyano-4,6-disubstituted pyridines II

A mixture of appropriate chalcones **I** (0.05 mole), malononitrile (0.05 mole) and ammonium acetate (0.4 mole) in ethanol (50 ml) was refluxed on a water-bath for 20–22 hrs, cooled and poured onto crushed ice with constant striring. The solid thus obtained was washed with water and cold ethanol and recrystallized from ethanol.

Synthesis of 4-imino-3,5,7-trisubstituted pyrido [2,3-*d*]pyrimidine -2(1*H*)-thiones III

Compounds **II** (0.01 mole), appropriate arylisothiocyanate (0.01 mole), dioxane (15ml) and pyridine (2.0 ml) was refluxed at 150°C at 20–22 hrs. After cooling, the contents of flask were poured onto crushed ice with constant stirring. The solid mass thus obtained was washed with water, aqueous sodium bicarbonate 5% (W/V) and finally with water. The dried crude mass was recrystallized from glacial acetic acid.

TABLE II Antimicrobial activity of pyrido[2,3-*d*]pyrimidines and their nucleosides

Test organism	*Inhibition Zone (mm)*														
	IIIa	*IIIb*	*IIIc*	*IIId*	*IIIe*	*VIa*	*VIb*	*VIc*	*VId*	*VIe*	*VIIa*	*VIIb*	*VIIc*	*VIId*	*VIIe*
Gram negative bacteria	14.0	13.0	14.5	15.0	14.5	16.0	17.0	18.0	19.0	19.5	20.5	17.5	18.5	19.0	20.0
E. coli	(0.96)	(0.95)	(1.0)	(1.02)	(1.0)	(1.04)	(1.08)	(1.10)	(1.12)	(1.14)	(1.17)	(1.09)	(1.11)	(1.12)	(1.15)
Gram positive bacteria	20.0	19.0	21.0	19.5	22.0	23.0	25.0	27.0	22.0	26.0	28.0	22.5	25.0	27.0	27.5
S. aureus	(0.99)	(0.97)	(1.0)	(0.98)	(1.02)	(1.05)	(1.12)	(1.16)	(1.02)	(1.14)	(1.20)	(1.03)	(1.12)	(1.16)	(1.18)
Fungi															
Aspergillus niger	9.9	9.6	9.7	10.2	9.9	11.6	12.5	11.7	12.5	12.0	10.0	11.5	12.0	11.5	12.0
	(1.02)	(0.98)	(1.0)	(1.05)	(1.02)	(1.19)	(1.28)	(1.21)	(1.28)	(1.24)	(1.03)	(1.17)	(1.26)	(1.17)	(1.24)
Aspergillus flavus	9.6	9.7	9.9	10.3	9.6	10.7	11.7	11.5	12.5	11.0	12.0	11.5	11.0	12.4	11.7
	(0.97)	(0.98)	(1.0)	(1.04)	(0.97)	(1.09)	(1.19)	(1.17)	(1.26)	(1.13)	(1.22)	(1.16)	(1.13)	(1.25)	(1.19)
Fusarium oxysporium	9.2	10.3	9.6	10.5	10.0	12.5	12.6	11.2	11.4	12.0	13.0	12.5	12.4	11.5	12.0
	(0.94)	(1.05)	(0.98)	(1.07)	(1.02)	(1.27)	(1.28)	(1.14)	(1.16)	(1.22)	(1.31)	(1.27)	(1.25)	(1.18)	(1.22)

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

Synthesis of 4-imino-3,5,7-trisubstituted-1-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl) pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones VI

Synthesized compounds **III** (0.02 mole) were refluxed with HMDS (hexamethyldisilazane) (0.0124 mole) alongwith a few crystals of ammonium sulphate in toluene (30 ml) for 8 hrs under anhydrous condition. The coloured solution thus obtained was filtered and the solvent was removed under vacuum at 100°C. The sugar viz. β-*D*-ribofuranose 1-acetate-2,3,5-tribenzoate (0.02 mole) was added to the above pasty mixture and it 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 solid mass of nucleosides **VI** thus obtained was recrystallized from diethyl ether.

Synthesis of 4-imino-3,5,7-trisubstituted-1-(2,3,5-tri-*O*-benzoyl-α-*D*-ribofuranosyl) pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones VII

Compounds **III** (0.01 mole) was refluxed with HMDS (60 ml) alongwith a few crystals of ammonium sulphate in toluene (20 ml) for 8 hrs under anhydrous condition. The coloured solution thus obtained was filtered and the solvent was removed in under vacuum at 100°C. The above pasty mass was dissolved in anhydrous 1,2-dichloroethane (40 ml) and a solution of sugar (β-*D*-ribofuranose 1-acetate-2,3,5-tribenzoate) (0.011 mole) in dry 1,2- dichloroethane (5ml) was added with stirring. The mixture was cooled to 0°C and a solution of $SnCl_4$(1.6 ml) was added dropwise with stirring and the completion of reaction was judged by TLC (2,3 hrs.) and then poured onto saturated $NaHCO_3$ solution. It was extracted with chloroform, dried over anhydrous $MgSO_4$ and filtered to get compounds **VII**. It was recrystallized from EtOH.

Acknowledgements

Authors are thankful to the Head, Chemistry Department, University of Rajasthan, Jaipur, for providing laboratory facilities. One of the author (Dr. Gajendra Singh) is thankful to CSIR, New Delhi for financial assistance.

References

1. W.L.F. Armarego, Advan, *Heterocyclic Chem.*, **1**, 253 (1953).
2. W. Pfleiderer, Angew *Chem. Intern. Ed.*, **3**, 114 (1964).
3. A.A. Santill, D.H. Kim, *J. Med. Chem.*, **15**, 442 (1972).
4. J. Dovolli, J. Kalrke and E.F. Elslarger, *J. Med. Chem.*, **15**, 837 (1972).
5. L.R. Bennett, C.J. Blankley, R.W. Fleming, R.D. Smith and D.K. Tessonann, *J. Med. Chem.*, **24**, 382 (1981).
6. D.W. Fry, R.C. Jackson, *Cancer Meta. Staris. Rev.*, **5** **(3)**, 251 (1987); *Chem. Abstr.*, **107**, 7 (1987).
7. R. Sharma, R.D. Goyal, L. Prakash, *Indian J. Chem.*, Sect. B. **31B(10)**, 493 (1996).
8. F. Herold, *Acta Pol Pharm.*, **42(3)**, 263 (1985); *Chem. Abstr.*, **106**, 156390 (1987).
9. D.E. Beallic, R. Crossley, K.H. Dikinson, G.M. Dover; *J. Med. Chemo-chim. Ther.*, **18(3)**, 277 (1983).
10. E.S.H. El Ashry, Y.El Kilany, *Adv. Heterocycl. Chem.*, **67**, 391 (1996).
11. H. Mitsuya, S. Broder, *Proc. Natl. Acad. Sci. USA*, **83**, 1911 (1986).
12. S.B. Pai, S.H. Liu, Y.L. Zhu, C.K. Chu, Y.C. Cheng. *Antimicrob. Agents Chemother*, **40**, 380 (1996).
13. G. Singh, Swati, A.K. Mishra, L. Prakash, *Indian J. Chem.*, **37B**, 517 (1998).
14. A.W. Bauer, W.M.M. Kibby, J.C. Sherins and M.Turck, *Am. J. Clin. Path*, **45**, 493 (1996).
15. Vogel's Text book of Practical organic chemistry, Longman Group Ltd., London, p. 796 (1980).