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Synthesis, characterisation and antimicrobial activity of (5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2-yl) amino acid esters

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Abstract: Synthesis of a new series of (5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino acid esters (**3a**–**l**) was accomplished *via* a two step process, which involves the prior preparation of the monochloride intermediate (**2**) and its subsequent reaction with the amino acid esters in dry tetrahydrofuran in the presence of triethylamine at reflux temperature. The title compounds (**3a**–**l**) structures were established by analytical, IR, ^{1}H-, ^{13}C- and ^{31}P-NMR, and mass spectral data. They exhibited significant antibacterial and antifungal activity.

Keywords: dioxaphosphinane; 2-bromo-2-nitropropane-1,3-diol; amino acid ester hydrochlorides; antibacterial activity; antifungal activity.

INTRODUCTION

1,3,2-Dioxaphosphinanes are an important class of organophosphorus heterocycles, which continue to attract considerable interest due to their unique stereochemical features and diverse potential biological applications.[1–4] Compounds bearing an esterified amino acid group on the phosphorus atom have been found to display useful anti-neoplastic properties.[5–8] The phosphate moiety when attached to an amino acid group is expected to increase their cellular uptake and thus enhance their chemotherapeutic properties. In view of this, the synthesis of a new class of heterocyclic compounds was accomplished and their activity on bacteria and fungi was tested.

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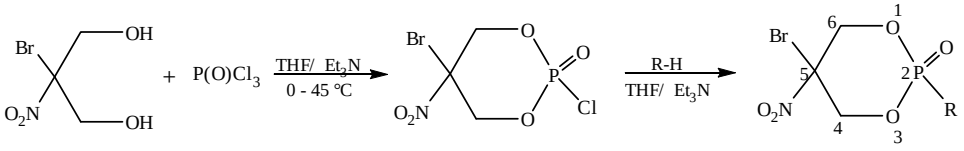
RESULTS AND DISCUSSION

Synthesis of (5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino acid esters (**3a**–**l**) was accomplished in a two-step process. The synthetic route (Scheme 1) involves the cyclization of equimolar quantities of 2-bromo-2-nitro-propane-1,3-diol (**1**) with phosphorus oxychloride in the presence of triethyl-amine in tetrahydrofuran (THF) to afford the corresponding monochloride (**2**). In the second step, the subsequent reaction of **2** with different amino acid ester hydrochlorides was realized at room temperature under stirring for 8–10 h to afford **3a**–**l**.



(1) **(2)** **(3a-l)**

Compound	R	Compound	R
3a	$-HN-CH_2-CO_2CH_3$	**3h**	$-NH-CH(COOCH_3)-CH_2-C_3H_3N_2$
3b	$-HN-CH(CH_3)-CO_2CH_3$	**3i**	$-NH-CH(COOCH_3)-CH_2-C_6H_5$
3c	$-HN-CH(CH_3)-CO_2C_2H_5$	**3j**	$-NH-CH(COOC_2H_5)-CH_2-C_6H_5$
3d	$-HN-CH(CH(CH_3)_2)-CO_2CH_3$	**3k**	$-HN-C_{10}H_6N(CO_2CH_3)$
3e	$-HN-CH(CO_2CH_3)-CH_2-CH_3$	**3l**	$-N-C_8H_5(CO_2Et)$
3f	$-HN-CH(CO_2Et)-CH_2-CH_3$		
3g	$-N-C_4H_6-CO_2CH_3$		

Scheme 1. Reaction route to the title compounds.

Product yields and elemental analysis, and IR, ^{1}H-, ^{13}C- and ^{31}P-NMR data of **3a**–**l** are given in Supplementary material. The spectral data agree with the proposed chemical structures for compounds **3a**–**l.** Characteristic absorption bands in IR spectra for the title compounds were observed in the regions 3418––3441, 1739–1748, 1554–1564, 1249–1258 and 552–563 cm^{-1} for N–H, C=O, NO_2, P=O and C–Br, respectively.[9]

In the ^{1}H-NMR spectra,[10] the aromatic protons of **3a**–**l** gave a multiplet at δ 6.1–8.4 ppm. The N–H protons appeared as a broad singlet signal at δ 8.02–8.75 ppm. The methoxy protons and methylene protons directly attached to the oxygen of ester moiety in compounds **3a**–**l** resonated in the range of δ 3.42–3.62 and 4.10–4.14 ppm, respectively. Similarly, the methyl functions in **3a**–**l** resonated in the region of δ 1.12–1.45 ppm. The ^{13}C-NMR spectra for **3a**, **b**, **c**, **e**, **f**, **j**, **k** and **l** showed carbon chemical shifts in the expected region.[10] The ^{31}P chemical shifts[11] were observed at δ 7.24–13.2 ppm for **3a**–**l** as a singlet. The mass spectra of compounds **3a**, **b**, **f**, **h**, **j** and **k** showed their respective molecular ion peak at the expected *m*/*z* mass value.

Antimicrobial activity

The compounds **3a–l** showed moderate activity against *Staphylococcus aureus* and *Escherichia coli*. The highlight is that the three compounds **3g, 3h** and **3j** were more effective (Table I).

TABLE I. Antibacterial activity of compounds **3a**–**j** (zone of inhibition, mm)

Compound	Concentration, ppm			
	100	50	100	50
	E. coli		*S. aureus*	
3a	8	6	8	5
3b	8	6	9	8
3c	9	7	9	7
3d	10	8	9	8
3e	10	8	9	7
3f	10	7	9	8
3g	11	8	10	7
3h	12	8	6	6
3i	10	7	9	6
3j	12	8	10	7
3k	10	8	9	7
3l	10	7	9	6
Penicillin	12	8	10	7

The results of the antifungal screening against *Aspergillus niger* and *Helminthosporium oryzae* are presented in Table II. It is gratifying to observe that the majority of the compounds (**3a**–**l**) exhibited higher antifungal activity against both tested fungal strains when compared with that of griseofulvin. The signi-

ficant results are that **3g** and **3h** exhibited higher activities than the standard griseofulvin against both the fungi.

Thus, a new group of compounds with very high antibacterial and fungicidal activity, higher than the presently used commercial bactericides and fungicides, have been discovered.

TABLE II. Antifunal activity of compounds **3a–j** (Zone of inhibition, mm)

Compound	Concentration, ppm			
	100	50	100	50
	A. niger		*H. oryzae*	
3a	8	6	8	7
3b	9	7	9	7
3c	9	8	8	7
3d	11	8	10	8
3e	10	8	10	7
3f	10	6	11	8
3g	13	7	9	5
3h	13	7	12	10
3i	9	8	10	8
3j	12	7	12	9
3k	10	8	10	7
3l	10	8	10	8
Griseofulvin	12	7	12	9

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The IR spectra (ν_{max} / cm^{-1}) were recorded as KBr pellets on a Perkin Elmer 1000 instrument. The ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded on a Varian AMX 400 MHz NMR spectrometer operating at 400 MHz for ^{1}H, 100.57 MHz for ^{13}C and 161.7 MHz for ^{31}P-NMR. All the compounds were dissolved in DMSO-d_6 and the chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85 % H_3PO_4 (^{31}P). The microanalyses data were obtained from the Central Drug Research Institute (CDRI), Lucknow, India.

*General procedure for the synthesis of (5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2--yl)amino acid esters (**3a–l**)*

Cyclization of equimolar quantities of 2-bromo-2-nitropropane-1,3-diol (**1**) with phosphorus oxychloride in the presence of triethylamine in THF afforded the corresponding monochloride (**2**). In the second step, reaction of **2** with different amino acid ester hydrochlorides at room temperature under stirring for 8–10 h afforded **3a**–**l**. Progress of the reaction was monitored by TLC analysis. The crude products obtained as residues after removal of the solvent on a rotary evaporator were purified by repeated washing with water to remove any residual triethylamine hydrochloride and then with cold methanol to remove the unreacted starting materials and other impurities. The crude title compounds (**3a**–**l**) were further purified by flash chromatography on silica gel, using hexane–ethyl acetate (8:2) as eluent. All of them were obtained in high yields (68–75 %).

Antimicrobial activity

The antimicrobial activities[12] of **3a**–**l** were tested against the growth of *S. aureus* (ATCC 25923) (gram +ve) and *E. coli* (ATCC 25922) (gram –ve) by the disc diffusion method at two concentrations (100 and 50 ppm) on 6 mm diameter discs.

They were also screened for antifungal activity against *A. niger* (ATCC 16404) and *H. oryzae* (ATCC 11000) species along with the standard fungicide griseofulvin by the disc diffusion method at two different concentrations (100 and 50 ppm) on the same disc size.

SUPPLEMENTARY MATERIAL

The analytical and spectral data of the title compounds are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И АНТИМИКРОБНА АКТИВНОСТ ЕСТАРА (5-БРОМ-5-НИТРО-2-ОКСИДО-1,3,2-ДИОКСАФОСФИНАН-2-ИЛ)-АМИНО-КИСЕЛИНА

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Остварена је синтеза естара (5-бром-5-нитро-2-оксидо-1,3,2-диоксафосфинан-2-ил)-амино-киселина у два реакциона корака. У првом је извршена синтеза монохлоридног интермедијера (**2**), а у следећем реакција интермедијера са естрима амино-киселина, у сувом тетрахидрофурану у присуству триетиламина на температури кључања. Структура деривата (**3a**–**l**) је утврђена аналитичким и спектралним методама (IC, NMR (^{1}H, ^{13}C и ^{31}P) и масена спектрометрија). Испитивањем антимикробне активности добијених деривата утврђено је да показују значајно добру антибактеријску и антифунгалну активност.

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REFERENCES

1. a) A. M. Polozov, A. V. Khotinen, E. N. Klimovitskii, *Phosphorus, Sulfur Silicon Relat. Elem.* **109** (1996) 581; b) D. Bouchu, *Phosphorus, Sulfur Silicon Relat. Elem.* **15** (1983) 33; c) R. L. Shao, G. F. Yang, W. S. Miao, *Chem. J. Chin. Univ.* **16** (1995) 391
2. a) R. S. Edmundson, O. Johnson, D. W. Jones, *Phosphorus, Sulfur Silicon Relat. Elem.* **46** (1989) 61; b) R. S. Edmundson, O. Johnson, D. W. Jones, T. J. King, *J. Chem. Soc. Perkin Trans. 2* (1985) 69; c) O. Johnson, D. W. Jones, R. S. Edmundson, *Acta Crystallogr. Sect. C* **45** (1989) 142
3. J. A. Mosbo, J. G. Verkade, *J. Am. Chem. Soc.* **95** (1973) 204
4. a) C. Meier, *Angew. Chem., Int. Ed. Engl.* **35** (1996) 70; b) M. Sasaki, K. Moriguchi, K. Yanagi, *Agric. Biol. Chem.* **52** (1988) 159
5. C. McGuigan, P. Narashiman, *Synthesis* (1993) 311
6. K. G. Devine, C. McGuigan, T. J. O'Connor, S. R. Nicholis, D. Kinchington, *AIDS* **4** (1990) 371

7. P. J. Cox, *Biochem. Pharmacol.* **28** (1979) 2045
8. M. Szekerke, *Cancer Treatment Rep.* **60** (1976) 347
9. P. Vasu Govardhana Reddy, Y. Hari Babu, C. Suresh Reddy, *J. Heterocycl. Chem.* **40** (2003) 535
10. M. Veera Narayana Reddy, A. Bala Krishna, C. Suresh Reddy, *Eur. J. Med. Chem.* **45** (2010) 1828
11. M. Anil Kumar, K. Suresh Kumar, C. Devendranath Reddy, C. Naga Raju, C. Suresh Reddy, P. Hari Krishna, *S. Afr. J. Chem*. **62** (2009) 26
12. D. V. Mangte, S. P. Deshmukh, D. D. Bhokare, A. Arti Deshpande, *Indian J. Pharm. Sci.* **69** (2007) 295.