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Synthesis and Antimicrobial Activity of 2-(Aminoacid ester)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thiones

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ABSTRACT

Synthesis of 2-(aminoacid ester)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thiones (3a–j) was accomplished through a two-step process. It involves the prior preparation of 2-chloro-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thione monochloride (2) and its subsequent reaction with the aminoacid ester hydrochlorides in dry tetrahydrofuran-toluene in the presence of triethylamine at various temperatures. These compounds were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data.

KEYWORDS

2-[(6-methyl-2-pyridyl) amino] methylphenol, 1,3,2-benzoxazaphosphinin-2-thione, antimicrobial activity.

1. Introduction

Organophosphorus compounds[1] continue to receive widespread attention due to their ubiquity in biological systems[2] and their potential to serve as possible pharmaceuticals,[3] agrochemicals[4] and chemical synthetic agents.[5] Phosphorus derivatives bearing an esterified aminoacid group on the phosphorus atom have been found to display useful anti-neoplastic properties.[6–9] The attachment of an aminoacid group to the phosphate moiety is expected to increase their cellular uptake and thus enhance their chemotherapeutic properties. In view of this we have synthesized new 6-membered heterocycles in which aminoacid esters are linked to the phosphorus atom. The antimicrobial activities of these compounds were studied and are reported below.

2. Results and Discussion

The synthesis of 2-(aminoacid ester)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thiones (**3a–j**) is accomplished in a two-step process. The synthetic route involves the condensation of 2-[(6-methyl-2-pyridyl)amino]methylphenol (**1**) with thiophosphoryl chloride in dry tetrahydrofuran in the presence of triethylamine at 40–45 °C to afford the corresponding intermediate 2-chloro-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thione (**2**).

In the second step the intermediate **2** was reacted with the respective aminoacid ester hydrochlorides in dry tetrahydrofuran-toluene in the presence of triethylamine to obtain the title compounds **3a–j** in good yields (Scheme 1). The second step of the reaction was completed at 40–50 °C with stirring for 3–5 h. The progress of the reaction was monitored by TLC analysis. Aliphatic aminoacid esters (**3a–e** and **i, j**) reacted with the thione monochloride (**2**) more readily than with the aromatic aminoacid esters (**3f–h**). The tetrahydrofuran-toluene mixture was found to be a good solvent system for the second step of the reaction. The crude products obtained after removing the solvent were purified by column chromatography on silica gel. The synthetic and analytical data of title compounds **3a–j** are given in the experimental part.

All the compounds **3a–j** exhibited absorption bands for P=S and P-NH in the regions 805–756 cm^{-1} and 3402–3145 cm^{-1}, respectively.[10] The aromatic protons of **3a–j** resonated as multiplets in the region δ 7.80–6.69 ppm. The C-4 methylene protons gave multiplets or triplets and pairs of doublets at δ 5.26–4.81 ppm, indicating their non-equivalence in the six-membered chair conformation of the benzoxazaphosphinine ring system.[11] These protons couple with phosphorus and the coupling constants differ by as much as 1 Hz. The ^{13}C NMR spectral data for **3a,c,e,f,i** and **j** are given in the experimental part. The endocyclic oxygen-bonded C-8a gave signals as doublets at δ 150.7–149.9 ppm. The C-4 methylene carbon chemical shifts appeared in the region δ 46.7–46.5 ppm. The methyl carbon, which is linked to the pyridine ring, resonated in the region δ 24.4–24.1 ppm. The chemical shift of the carbon atom α to the aminoacid ester group appeared at δ 43.6–60.5 ppm. The remaining carbon signals are observed in the expected regions.[11] Compounds **3a–j** show a phosphorus-31 resonance signal in the range of δ 58.95–62.14 ppm.[11,12] The high-resolution mass spectral data of **3a,e,i** and LCMS data of **3c,f,j** are provided in the experimental section.

2.1. Bioactivity

Susceptibility of test organisms to the title compounds (**3a–j**) was determined by employing the standard disc diffusion technique.[13] All the compounds (**3a–j**) were tested for their antifungal activity against the growth of *Colletotrichum gloeosporioides* and *Sclerotium rolfsii* along with the standard fungicide carbendazim at concentrations of 250 and 500 ppm (Table 1). Compounds **3a–j** were also screened for their antibacterial activity against the growth of *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Klebsiella pneumoniae* along with the standard gentamycin at concentrations of 100, 200 and 300 ppm (Table 2). The test

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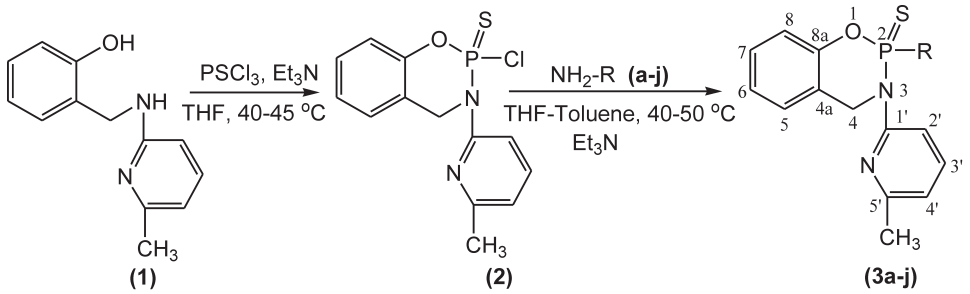

(1) (2) (3a-j)

Compound	R	Compound	R
3a	$HN-CH_2-COOCH_3$	**3f**	$NH-CH(COOCH_3)-CH_2$ (indole)
3b	$HN-CH_2-COOC_2H_5$	**3g**	$NH-CH(COOCH_3)-CH_2$ (imidazole)
3c	$HN-CH(COOCH_3)-CH_3$	**3h**	$NH-CH(COOCH_3)-CH_2-C_6H_5$
3d	$HN-CH(COOCH_3)-CH(CH_3)-CH_3$	**3i**	$COOCH_2C_6H_5$ (pyrrolidine)
3e	$NH-CH(COOC_2H_5)-CH_2-CH_2-CH_3$	**3j**	$COOCH_3$ (pyrrolidine)

Scheme 1

compounds did not posses significant antifungal or antibacterial activity.

3. Experimental

Melting points were recorded on Buchi R-535 (Flawil, Switzerland) apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer (Waltham, MA, USA) using KBr optics. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker 300 or AMX 400 MHz NMR spectrometers (Ettlingen, Germany) operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.89 MHz for ^{31}P. NMR data were recorded in $CDCl_3$ and were referenced to TMS (^{1}H and ^{13}C) and 85 % H_3PO_4 (^{31}P). Mass spectra were recorded on a Finnigan MAT 1020/Micro-Mass Q-Tof micro AMPS MAX 10/6A, Hz 60/50 system (Ringoes, NJ, USA) fitted with a built-in inlet system. Elemental analyses were performed using a Perkin Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India.

3.1. Synthesis of 2-Chloro-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thione (2)

A solution (0.002 mol) of thiophosphoryl chloride in 20 mL of dry THF was added dropwise over a period of 20 min to a stirred solution of 2-[(6-methyl-2-pyridyl)amino]methylphenol (**1**) (0.002 mol) and triethylamine (0.004 mol) in 25 mL of THF at 0–5 °C. After stirring for 3 h at 40–45 °C, formation of the intermediate, 2-chloro-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-thione (**2**) was ascertained by TLC analysis run in a 3:7 mixture of ethyl acetate and hexane and the average Rf value observed was 0.75. Triethylamine hydrochloride was removed by filtration. The filtrate was used for the next reaction step without further purification.

3.2. Typical Procedure for the Synthesis of 3a–j

To a stirred solution of aminoacid ester hydrochloride (0.002 mol) and triethylamine (0.004 mol) in dry toluene (10 mL) the intermediate monochloride (**2**), (0.002 mol) in dry tetrahydrofuran was added dropwise at 0 °C. After completion of the addition, the temperature of the reaction was raised to 40–50 °C and the reaction mixture was stirred for 3–5 h. After completion of the reaction, as indicated by TLC conducted in 3:7 mixture of ethyl acetate and hexane, an average Rf value of 0.60 was observed. The reaction mixture was filtered to remove solid triethylamine hydrochloride and the solvent was evaporated under reduced pressure to give the crude product. It was purified by column chromatography on silica gel (100–200 mesh,

Table 1 Antifungal activity of compounds **3a–j**.

Compound	Zone of inhibition/mm [a]			
	Colletotrichum gloeosporioides		*Sclerotium rolfsii*	
	250 ppm	500 ppm	250 ppm	500 ppm
3a	1.8	0.5	1.0	–
3b	–	0.5	0.0	–
3c	2.3	1.0	–	–
3d	1.0	4.0	0.8	2.3
3e	2.8	–	5.5	1.75
3f	6.8	4.0	2.75	0.0
3g	5.3	0.0	0.0	6.8
3h	1.0	1.5	0.5	1.5
3i	3.5	0.8	0.0	4.5
3j	4.8	2.8	0.8	8.0
Carbendazim	19.0	19.5	19.0	9.25

[a] – indicates no activity.

ethyl acetate:hexane, 1:9) to afford the pure compound. The compounds thus obtained were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

3.3. Spectral Data

3.3.1. *Methyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro-*2H*-1,3,2λ^5-benzoxazaphosphinin-2-yl]aminoacetate* (**3a**)

Yield 87 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.47-7.13 (6H, m, Ar-H), 6.81 (1H, d, *J* 8 Hz, Ar-H), 5.21 (1H, t, *J* 15.6 Hz, -CH_2-), 4.90 (1H, dd, *J* 9.7, 14.6 Hz, -CH_2-), 4.08 (1H, brs, N-H), 3.83-3.73 (2H, m, N-CH_2-), 3.68 (3H, s, O-CH_3) and 2.48 ppm (3H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 170.5 (d, $^3J_{P\text{-}C}$ 10 Hz, C=O), 156.8 (C-5′), 153.3 (d, $^2J_{P\text{-}C}$ 10 Hz, C-1′), 150.2 (d, $^2J_{P\text{-}C}$ 11 Hz, C-8a), 137.7 (C-3′), 129.2 (C-5), 127.0 (C-7), 126.6 (d, $^3J_{P\text{-}C}$ 7 Hz, C-4a), 124.6 (C-6), 118.8 (d, $^3J_{P\text{-}C}$ 5 Hz, C-8), 117.5 (C-4′), 110.9 (C-2′), 52.4 (O-CH_3), 46.7 (-CH_2-), 43.6 (N-CH_2) and 24.3 ppm (Ar-CH_3); δ_P ($CDCl_3$) 60.92 ppm; ν_{max} ($CHCl_3$) 805 (P=S), 1744 (C=O) and 3328 cm^{-1} (P-NH). HRMS calc. for $C_{16}H_{18}N_3O_3PSNa$: 386.0704; found: 386.0695 (M+Na).

3.3.2. *Ethyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro-*2H*-1,3,2λ^5-benzoxazaphosphinin-2-yl]aminoacetate* (**3b**)

Yield 83 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.52–6.80 (7H, m, Ar-H), 5.25 (1H, t, *J* 15.4 Hz, -CH_2-), 4.87 (1H, dd, *J* 9.0, 14.8 Hz, -CH_2-), 4.14 (1H, brs, N-H), 3.80–3.71 (2H, m, N-CH_2-), 4.08 (2H, q, *J* 7.0 Hz, O-CH_2-), 2.46 (3H, s, Ar-CH_3) and 1.21 ppm (3H, t, *J* 7.0 Hz, O-CH_2-C*H*$_3$); δ_P ($CDCl_3$) 60.12 ppm; ν_{max} ($CHCl_3$) 764 (P=S), 1742 (C=O) and 3325 cm^{-1} (P-NH). Calc. for $C_{17}H_{20}N_3O_3PS$: C, 54.10; H, 5.34; N, 11.13 %; found: C, 54.14; H, 5.30; N, 11.09 %.

3.3.3. *Methyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro-*2H*-1,3,2λ^5-benzoxazaphosphinin-2-yl]aminopropanoate* (**3c**)

Yield 76 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.53–6.79 (7H, m, Ar-H), 5.26–4.87 (2H, m, -CH_2-), 4.16–4.07 (2H, m, N*H*-C*H*-CO), 3.69 (3H, s, O-CH_3), 2.49 (3H, s, Ar-CH_3) and 1.33 ppm (3H, d, *J* 6.7 Hz, NH-CH-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 173.6 (d, $^3J_{P\text{-}C}$ 9 Hz, C=O), 156.8 (C-5′), 153.3 (d, $^2J_{P\text{-}C}$ 10 Hz, C-1′), 150.1 (d, $^2J_{P\text{-}C}$ 11 Hz, C-8a), 137.5 (C-3′), 129.1(C-5), 127.0 (C-7), 126.6 (d, $^3J_{P\text{-}C}$ 7 Hz, C-4a), 124.6 (C-6), 118.7 (d, $^3J_{P\text{-}C}$ 5.5 Hz, C-8), 117.4 (C-4′), 111.2 (d, $^3J_{P\text{-}C}$ 2 Hz, C-2′), 52.4 (O-CH_3), 50.9 (d, $^2J_{P\text{-}C}$ 14.5 Hz, NH-CH), 46.6 (d, *J* 11.5 Hz, -CH_2-), 24.3 (Ar-CH_3) and 20.9 ppm (CH-CH_3); δ_P ($CDCl_3$) 61.95 ppm; ν_{max} ($CHCl_3$) 758 (P=S), 1741 (C=O) and 3315 (P-NH) cm^{-1}; *m/z* (LCMS) 378 (M+H); calc. for $C_{17}H_{20}N_3O_3PS$: C, 54.10; H, 5.34; N, 11.13 %; found: C, 54.13; H, 5.30; N, 11.17 %.

3.3.4. *Methyl 3-methyl-2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro-*2H*-1,3,2λ^5-benzoxazaphosphinin-2-yl]aminobutanoate* (**3d**)

Yield 81 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.50–6.75 (7H, m, Ar-H), 5.20–4.89 (2H, m, -CH_2-), 4.02–3.94 (1H, m, NH-C*H*-CO), 3.72 (3H, s, O-CH_3), 2.48 (3H, s, Ar-CH_3), 1.55–1.45 (1H, m, -C*H*-(CH_3)$_2$) and 1.12 ppm (6H, d, *J* 6.8 Hz, -CH-(C*H*$_3$)$_2$); δ_P ($CDCl_3$) 58.95 ppm; ν_{max} ($CHCl_3$) 760 (P=S), 1740 (C=O) and 3329 cm^{-1} (P-NH). Calc. for $C_{19}H_{24}N_3O_3PS$: C, 56.29; H, 5.97; N, 10.36 %; found: C, 56.24; H, 5.93; N, 10.30 %.

Table 2 Antibacterial activity of compounds **3a–j**.

Compound	Zone of inhibition/mm [a]											
	Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Klebsiella pneumoniae*		
	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm
3a	–	1.2	3.4	–	–	2.0	–	–	–	–	–	–
3b	–	–	–	–	–	2	–	–	–	–	–	2.0
3c	4.0	6.2	7.4	2.5	3.0	5.5	2.8	4.0	5.2	–	3.4	4.0
3d	2.0	3.4	5.0	–	2.0	4.2	3.2	4.2	6.0	1.5	3.2	5.0
3e	–	2.0	4.3	–	3.0	4.0	2.5	3.0	4.0	–	–	–
3f	9.2	12.0	14.5	8.0	11.5	15.0	10.0	12.0	15.3	8.0	13.2	16.0
3g	11.3	14.5	17.0	–	1.8	4.2	–	–	2.0	–	3.2	5.3
3h	4.5	5.0	7.0	–	3.0	5.0	2.0	4.5	5.0	–	2.3	5.2
3i	8.0	11.2	13.0	–	–	–	–	–	–	–	–	–
3j	4.2	6.2	8.0	–	2.0	4.2	–	–	2.0	–	–	2.0
Gentamycin	19.0			19.0			20.0			18.0		

[a] – indicates no activity.

3.3.5. *Ethyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminopentanoate* (**3e**)

Yield 71 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.43–7.01 (6H, m, Ar-H), 6.74 (1H, d, *J* 7.2 Hz, Ar-H) 5.21–5.11 (1H, m, -CH_2-), 4.92–4.81 (1H, m, -CH_2-), 4.12–4.01 (3H, m, O-CH_2 and N*H*), 3.92–3.81 (1H, m, NH-C*H*-CO), 2.43 (3H, s, Ar-CH_3), 1.59–1.41 (2H, m, CH_2-CH_2-CH_3), 1.16 (3H, t, *J* 7.8 Hz, OCH_2-CH_3), 1.11–1.05 (2H, m, CH_2-CH_2-CH_3) and 0.80 ppm (3H, t, *J* 6.8 Hz, CH_2-CH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 172.7 (d, $^3J_{P\text{-}C}$ 8 Hz, C=O), 156.7 (C-5′), 153.4 (d, $^2J_{P\text{-}C}$ 10 Hz, C-1′), 150.1 (d, $^2J_{P\text{-}C}$ 11 Hz, C-8a), 137.4 (C-3′), 129.1 (C-5), 127.1 (C-7), 126.6 (d, $^3J_{P\text{-}C}$ 7 Hz, C-4a), 124.6 (C-6), 118.7 (d, $^3J_{P\text{-}C}$ 6 Hz, C-8), 117.3 (C-4′), 111.3 (d, $^3J_{P\text{-}C}$ 2 Hz, C-2′), 61.3 (O-CH_2), 55.2 (NH-C*H*-CO), 46.7 (d, *J* 7 Hz, -CH_2-), 36.5 (d, *J* 5 Hz, CH_2-CH_2-CH_3), 24.3 (Ar-CH_3), 18.1 (CH_2-CH_2-CH_3), 14.1 (O-CH_2-CH_3) and 13.6 ppm (CH_2-CH_2-CH_3); δ_P ($CDCl_3$) 60.43 ppm; ν_{max} ($CHCl_3$) 805 (P=S), 1735 (C=O) and 3310 cm^{-1} (P-NH); HRMS calc. for $C_{20}H_{26}N_3O_3PSNa$: 442.1330; found: 442.1312 (M+Na).

3.3.6. *Methyl 3-(1*H-*3-indolyl)-2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]amino-propanoate* (**3f**)

Yield 87 %; solid, m.p 125–127 °C. δ_H (400 MHz, $CDCl_3$) 8.00 (1H, brs NH), 7.45–6.74 (12H, m, Ar-H), 5.19–4.87 (2H, m, -CH_2-), 4.54–4.30 (1H, m, NH-C*H*-CO), 4.10 (1H, brs, NH), 3.23–2.98 (2H, m, C-CH_2-C), 3.54 (3H, s, O-CH_3) and 2.47 ppm (3H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 172.3 (d, $^3J_{P\text{-}C}$ 8 Hz, C=O), 156.5 (C-5′), 153.0 (d, $^2J_{P\text{-}C}$ 10 Hz, C-1′), 149.9 (d, $^2J_{P\text{-}C}$ 10.5 Hz, C-8a), 137.3 (C-3′), 137.2, 135.8 (indole bridged carbons), 129.0 (C-5), 127.1 (C-7), 126.9 (CH-pyrrole), 126.6 (d, $^3J_{P\text{-}C}$ 7.5 Hz, C-4a), 124.5 (C-6), 123.1, 122.9, 121.8, 119.2, 118.2 (d, *J* 6 Hz, C-8), 117.3 (C-4′), 111.1 (C-2′), 108.9 (C-pyrrole), 55.6 (O-CH_3), 52.0 (d, *J* 5.5 Hz, NH-C*H*-CO), 46.5 (d, *J* 6.5 Hz, -CH_2), 30.0 (CH_2-indole) and 24.1 ppm (Ar-CH_3); δ_P ($CDCl_3$) 62.06 ppm; ν_{max} (KBr) 756 (P=S), 1740 (C=O) and 3380 cm^{-1} (P-NH); *m/z* (LCMS) 494 (M+H); calc. for $C_{25}H_{25}N_4O_3PS$: C, 60.97; H, 5.12; N, 11.38 %; found: C, 60.93; H, 5.09; N, 11.42 %.

3.3.7. *Methyl 3-(1*H-*5-imidazolyl)-2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminopropanoate* (**3g**)

Yield 83 %; solid, m.p 75–78 °C. δ_H (300 MHz, $CDCl_3$) 8.25 (1H, brs NH), 7.80–6.73 (9H, m, Ar-H), 5.12–4.86 (3H, m, -CH_2- and NH-C*H*), 4.45 (1H, brs, NH), 3.61 (3H, s, O-CH_3), 3.11–2.91 (2H, m, NH-CH-CH_2) and 2.45 ppm (3H, s, Ar-CH_3); δ_P ($CDCl_3$) 61.92 ppm; ν_{max} (KBr) 799 (P=S), 1742 (C=O) and 3145 cm^{-1} (P-NH). Calc. for $C_{20}H_{22}N_5O_3PS$: C, 54.17; H, 5.00; N, 15.79 %; found: C, 54.12; H, 5.05; N, 15.75 %.

3.3.8. *Methyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]amino-3-phenylpropanoate* (**3h**)

Yield 78 %; semi-solid. δ_H (300 MHz, $CDCl_3$) 7.50–6.70 (12H, m, Ar-H), 5.25–4.87 (2H, m, -CH_2-), 4.25–4.18 (1H, m, NH-C*H*-CO), 4.10 (1H, brs, NH), 3.68 (3H, s, O-CH_3), 3.11–3.02 (2H, m, CH_2-Ph) and 2.48 ppm (3H, s, Ar-CH_3); δ_P ($CDCl_3$) 62.14 ppm; ν_{max} ($CHCl_3$) 762 (P=S), 1744 (C=O) and 3328 cm^{-1} (P-NH). Calc. for $C_{23}H_{24}N_3O_3PS$: C, 60.92; H, 5.33; N, 9.27 %; found: C, 60.88; H, 5.29; N, 9.22 %.

3.3.9. *Benzyl 1-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]-2-pyrrolidinecarboxylate* (**3i**)

Yield 77 %; semi-solid. δ_H (400 MHz, $CDCl_3$) 7.42–6.99 (11H, m, Ar-H), 6.69 (1H, d, *J* 8 Hz, Ar-H), 5.22–4.95 (4H, m, O-CH_2Ph and -CH_2-), 4.38–4.30 (1H, m, N-C*H*-), 3.45–3.28 (2H, m, N-CH_2), 2.40 (3H, s, Ar-CH_3) and 1.90–1.70 ppm (4H, m, -CH_2-CH_2-); δ_C (100 MHz, $CDCl_3$) 173.1 (C=O), 156.5 (C-5′), 153.3 (d, $^2J_{P\text{-}C}$ 10 Hz, C-1′), 150.7 (d, $^2J_{P\text{-}C}$ 10 Hz, C-8a), 137.7 (C-3′), 135.6 (C-1″), 129.1 (C-5), 128.5 (C-3″ and C-5″), 128.2 (C-4″), 128.1 (C-2″ and C-6″), 127.1 (C-7), 126.7 (d, $^3J_{P\text{-}C}$ 7 Hz, C-4a), 124.5 (C-6), 118.7 (d, $^3J_{P\text{-}C}$ 5 Hz, C-8), 117.1 (C-4′), 110.8 (C-2′), 66.8 (O-CH_2-Ph), 60.5 (d, $^2J_{P\text{-}C}$ 6 Hz , N-CH-CO), 49.5 (d, $^2J_{P\text{-}C}$ 3 Hz, N-CH_2), 46.6 (-CH_2-), 31.9, 29.7 (-CH_2-CH_2-) and 24.4 ppm (Ar-CH_3); δ_P ($CDCl_3$) 59.70 ppm; ν_{max} ($CHCl_3$) 803 (P=S), 1449 and 1744 cm^{-1} (C=O); HRMS calc. for $C_{25}H_{26}N_3O_3PSNa$: 502.1330; found: 502.1310 (M+Na).

3.3.10. *Methyl 1-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro*-2H-*1,3,2λ⁵-benzoxazaphosphinin-2-yl]-2-pyrrolidinecarboxylate* (**3j**)

Yield 82 %; viscous liquid. δ_H (400 MHz, $CDCl_3$) 7.54–6.79 (7H, m, Ar-H), 5.23–4.88 (2H, m, -CH_2-), 4.47–4.36 (1H, m, N-C*H*-) 3.74 (3H, s, OCH_3), 3.52–3.30 (2H, m, N-CH_2-), 2.49 (3H, s, Ar-CH_3) and 2.05–1.68 ppm (4H, m, -CH_2-CH_2-); δ_C (100 MHz, $CDCl_3$) 173.7 (C=O), 156.5 (C-5′), 153.3 (d, $^2J_{P\text{-}C}$ 10.5 Hz, C-1′), 150.7 (d, $^2J_{P\text{-}C}$ 11 Hz, C-8a), 137.6 (C-3′), 129.1 (C-5), 127.0 (C-7), 126.6 (d, $^3J_{P\text{-}C}$ 7 Hz, C-4a), 124.6 (C-6), 118.6 (d, $^3J_{P\text{-}C}$ 10 Hz, C-8), 117.2 (C-4′), 110.9 (d, $^3J_{P\text{-}C}$ 2 Hz, C-2′), 60.4 (d, $^2J_{P\text{-}C}$ 6.5 Hz, N-CH-CO), 52.0 (OCH_3), 46.6, (-CH_2-), 42.2 (N-CH_2), 31.9, 29.6 (-CH_2-CH_2-) and 24.4 ppm (Ar-CH_3); δ_P ($CDCl_3$) 58.96 ppm; ν_{max} ($CHCl_3$) 757 (P=S), 1745 (C=O) and 3402 cm^{-1} (P-NH); *m/z* (LCMS): 404 (M+H); calc. for $C_{19}H_{22}N_3O_3PS$: C, 56.57; H, 5.50; N, 10.42 %; found: C, 56.62; H, 5.56; N, 10.37 %.

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