

Synthesis and Antimicrobial Activity of 2-(Aminoacid ester)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ⁵-benzoxazaphosphinin-2-thiones

M. Anil Kumar^a, K. Suresh Kumar^a, C. Devendranath Reddy^a, C. Naga Raju^a, C. Suresh Reddy^{a*} and P. Hari Krishna^b

^aDepartment of Chemistry, Sri Venkateswara University, Tirupati 517502, India.

^bDepartment of Plant Pathology, Sri Venkateswara Agricultural College, Angrau, Tirupati 517502, India.

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ABSTRACT

Synthesis of 2-(aminoacid ester)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ⁵-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-2H-1,3,2λ⁵-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, ¹H, ¹³C, ³¹P NMR and mass spectral data.

KEYWORDS

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

1. Introduction

Organophosphorus compounds¹ continue to receive widespread attention due to their ubiquity in biological systems² and their potential to serve as possible pharmaceuticals,³ agrochemicals⁴ 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-2H-1,3,2λ⁵-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-2H-1,3,2λ⁵-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

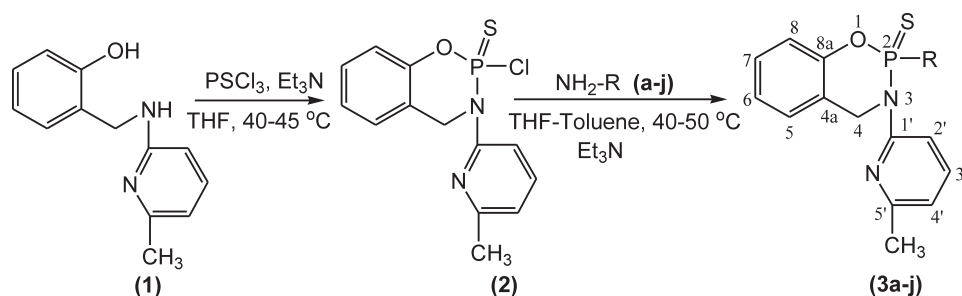
solvent were purified by column chromatography on silica gel. The synthetic and analytical data of title compounds **3a–j** are given in the experimental part.

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 ¹³C 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

* To whom correspondence should be addressed. E-mail: csrsvu@gmail.com



Compound	R	Compound	R
3a	HN-CH ₂ -COOCH ₃	3f	
3b	HN-CH ₂ -COOC ₂ H ₅	3g	
3c		3h	
3d		3i	
3e		3j	

Scheme 1

compounds did not possess 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. ¹H, ¹³C and ³¹P NMR spectra were recorded on Bruker 300 or AMX 400 MHz NMR spectrometers (Ettlingen, Germany) operating at 400 MHz for ¹H, 100 MHz for ¹³C and 161.89 MHz for ³¹P. NMR data were recorded in CDCl₃ and were referenced to TMS (¹H and ¹³C) and 85% H₃PO₄ (³¹P). 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-2H-1,3,2λ⁵-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-2H-1,3,2λ⁵-benzoxazaphosphinin-2-thione (2) was ascertained by TLC analysis run in a 3:7 mixture of ethyl acetate and hexane and the average R_f 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 amino acid 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 R_f 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			
	<i>Colletotrichum gloeosporioides</i>		<i>Sclerotium rolfsii</i>	
	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 ¹H NMR, ¹³C 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-1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminoacetate (3a)

Yield 87 %; viscous liquid. δ_H (400 MHz, CDCl₃) 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, -CH₂-), 4.90 (1H, dd, J 9.7, 14.6 Hz, -CH₂-), 4.08 (1H, brs, N-H), 3.83–3.73 (2H, m, N-CH₂-), 3.68 (3H, s, O-CH₃) and 2.48 ppm (3H, s, Ar-CH₃); δ_C (100 MHz, CDCl₃) 170.5 (d, ³J_{P,C} 10 Hz, C=O), 156.8 (C-5'), 153.3 (d, ²J_{P,C} 10 Hz, C-1'), 150.2 (d, ²J_{P,C} 11 Hz, C-8a), 137.7 (C-3'), 129.2 (C-5), 127.0 (C-7), 126.6 (d, ³J_{P,C} 7 Hz, C-4a), 124.6 (C-6), 118.8 (d, ³J_{P,C} 5 Hz, C-8), 117.5 (C-4'), 110.9 (C-2'), 52.4 (O-CH₃), 46.7 (-CH₂-), 43.6 (N-CH₂) and 24.3 ppm (Ar-CH₃); δ_P (CDCl₃) 60.92 ppm; ν_{max} (CHCl₃) 805 (P=S), 1744 (C=O) and 3328 cm⁻¹ (P-NH). HRMS calc. for C₁₆H₁₈N₃O₃PSNa: 386.0704; found: 386.0695 (M+Na).

3.3.2. Ethyl 2-[3-(6-methyl-2-pyridyl)-2-thioxo-3,4-dihydro-2H-1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminoacetate (3b)

Yield 83 %; viscous liquid. δ_H (400 MHz, CDCl₃) 7.52–6.80 (7H, m, Ar-H), 5.25 (1H, t, J 15.4 Hz, -CH₂-), 4.87 (1H, dd, J 9.0, 14.8 Hz, -CH₂-), 4.14 (1H, brs, N-H), 3.80–3.71 (2H, m, N-CH₂-), 4.08 (2H, q, J 7.0 Hz, O-CH₂-), 2.46 (3H, s, Ar-CH₃) and 1.21 ppm (3H, t, J 7.0 Hz, O-CH₂-CH₃); δ_P (CDCl₃) 60.12 ppm; ν_{max} (CHCl₃) 764 (P=S), 1742 (C=O) and 3325 cm⁻¹ (P-NH). Calc. for

C₁₇H₂₀N₃O₃PS: 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-1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminopropanoate (3c)

Yield 76 %; viscous liquid. δ_H (400 MHz, CDCl₃) 7.53–6.79 (7H, m, Ar-H), 5.26–4.87 (2H, m, -CH₂-), 4.16–4.07 (2H, m, NH-CH-CO), 3.69 (3H, s, O-CH₃), 2.49 (3H, s, Ar-CH₃) and 1.33 ppm (3H, d, J 6.7 Hz, NH-CH-CH₃); δ_C (100 MHz, CDCl₃) 173.6 (d, ³J_{P,C} 9 Hz, C=O), 156.8 (C-5'), 153.3 (d, ²J_{P,C} 10 Hz, C-1'), 150.1 (d, ²J_{P,C} 11 Hz, C-8a), 137.5 (C-3'), 129.1 (C-5), 127.0 (C-7), 126.6 (d, ³J_{P,C} 7 Hz, C-4a), 124.6 (C-6), 118.7 (d, ³J_{P,C} 5.5 Hz, C-8), 117.4 (C-4'), 111.2 (d, ³J_{P,C} 2 Hz, C-2'), 52.4 (O-CH₃), 50.9 (d, ²J_{P,C} 14.5 Hz, NH-CH), 46.6 (d, J 11.5 Hz, -CH₂-), 24.3 (Ar-CH₃) and 20.9 ppm (CH-CH₃); δ_P (CDCl₃) 61.95 ppm; ν_{max} (CHCl₃) 758 (P=S), 1741 (C=O) and 3315 (P-NH) cm⁻¹; m/z (LCMS) 378 (M+H); calc. for C₁₇H₂₀N₃O₃PS: 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-1,3,2λ⁵-benzoxazaphosphinin-2-yl]aminobutanoate (3d)

Yield 81 %; viscous liquid. δ_H (400 MHz, CDCl₃) 7.50–6.75 (7H, m, Ar-H), 5.20–4.89 (2H, m, -CH₂-), 4.02–3.94 (1H, m, NH-CH-CO), 3.72 (3H, s, O-CH₃), 2.48 (3H, s, Ar-CH₃), 1.55–1.45 (1H, m, -CH-(CH₃)₂) and 1.12 ppm (6H, d, J 6.8 Hz, -CH-(CH₃)₂); δ_P (CDCl₃) 58.95 ppm; ν_{max} (CHCl₃) 760 (P=S), 1740 (C=O) and 3329 cm⁻¹ (P-NH). Calc. for C₁₉H₂₄N₃O₃PS: 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											
	<i>Staphylococcus aureus</i>			<i>Bacillus subtilis</i>			<i>Escherichia coli</i>			<i>Klebsiella pneumoniae</i>		
	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, CDCl₃) 7.43–7.01 (6H, m, Ar-H), 6.74 (1H, d, *J* 7.2 Hz, Ar-H) 5.21–5.11 (1H, m, -CH₂-), 4.92–4.81 (1H, m, -CH₂-), 4.12–4.01 (3H, m, O-CH₂ and NH), 3.92–3.81 (1H, m, NH-CH-CO), 2.43 (3H, s, Ar-CH₃), 1.59–1.41 (2H, m, CH₂-CH₂-CH₃), 1.16 (3H, t, *J* 7.8 Hz, OCH₂-CH₃), 1.11–1.05 (2H, m, CH₂-CH₂-CH₃) and 0.80 ppm (3H, t, *J* 6.8 Hz, CH₂-CH₂-CH₃); δ_{C} (100 MHz, CDCl₃) 172.7 (d, ³*J*_{P-C} 8 Hz, C=O), 156.7 (C-5'), 153.4 (d, ²*J*_{P-C} 10 Hz, C-1'), 150.1 (d, ³*J*_{P-C} 11 Hz, C-8a), 137.4 (C-3'), 129.1 (C-5), 127.1 (C-7), 126.6 (d, ³*J*_{P-C} 7 Hz, C-4a), 124.6 (C-6), 118.7 (d, ³*J*_{P-C} 6 Hz, C-8), 117.3 (C-4'), 111.3 (d, ³*J*_{P-C} 2 Hz, C-2'), 61.3 (O-CH₂), 55.2 (NH-CH-CO), 46.7 (d, *J* 7 Hz, -CH₂-), 36.5 (d, *J* 5 Hz, CH₂-CH₂-CH₃), 24.3 (Ar-CH₃), 18.1 (CH₂-CH₂-CH₃), 14.1 (O-CH₂-CH₃) and 13.6 ppm (CH₂-CH₂-CH₃); δ_{P} (CDCl₃) 60.43 ppm; ν_{max} (CHCl₃) 805 (P=S), 1735 (C=O) and 3310 cm⁻¹ (P-NH); HRMS calc. for C₂₀H₂₆N₃O₃PSNa: 442.1330; found: 442.1312 (M+Na).

3.3.6. Methyl 3-(1H-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, CDCl₃) 8.00 (1H, brs NH), 7.45–6.74 (12H, m, Ar-H), 5.19–4.87 (2H, m, -CH₂-), 4.54–4.30 (1H, m, NH-CH-CO), 4.10 (1H, brs, NH), 3.23–2.98 (2H, m, C-CH₂-C), 3.54 (3H, s, O-CH₃) and 2.47 ppm (3H, s, Ar-CH₃); δ_{C} (100 MHz, CDCl₃) 172.3 (d, ³*J*_{P-C} 8 Hz, C=O), 156.5 (C-5'), 153.0 (d, ²*J*_{P-C} 10 Hz, C-1'), 149.9 (d, ²*J*_{P-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, ³*J*_{P-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-CH₃), 52.0 (d, *J* 5.5 Hz, NH-CH-CO), 46.5 (d, *J* 6.5 Hz, -CH₂), 30.0 (CH₂-indole) and 24.1 ppm (Ar-CH₃); δ_{P} (CDCl₃) 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 C₂₅H₂₅N₄O₃PS: C, 60.97; H, 5.12; N, 11.38 %; found: C, 60.93; H, 5.09; N, 11.42 %.

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

Yield 83 %; solid, m.p 75–78 °C. δ_{H} (300 MHz, CDCl₃) 8.25 (1H, brs NH), 7.80–6.73 (9H, m, Ar-H), 5.12–4.86 (3H, m, -CH₂- and NH-CH), 4.45 (1H, brs, NH), 3.61 (3H, s, O-CH₃), 3.11–2.91 (2H, m, NH-CH-CH₂) and 2.45 ppm (3H, s, Ar-CH₃); δ_{P} (CDCl₃) 61.92 ppm; ν_{max} (KBr) 799 (P=S), 1742 (C=O) and 3145 cm⁻¹ (P-NH). Calc. for C₂₀H₂₂N₅O₃PS: 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, CDCl₃) 7.50–6.70 (12H, m, Ar-H), 5.25–4.87 (2H, m, -CH₂-), 4.25–4.18 (1H, m, NH-CH-CO), 4.10 (1H, brs, NH), 3.68 (3H, s, O-CH₃), 3.11–3.02 (2H, m, CH₂-Ph) and 2.48 ppm (3H, s, Ar-CH₃); δ_{P} (CDCl₃) 62.14 ppm; ν_{max} (CHCl₃) 762 (P=S), 1744 (C=O) and 3328 cm⁻¹ (P-NH). Calc. for C₂₃H₂₄N₃O₃PS: 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, CDCl₃) 7.42–6.99 (11H, m, Ar-H), 6.69 (1H, d, *J* 8 Hz, Ar-H), 5.22–4.95 (4H, m, O-CH₂Ph and -CH₂-), 4.38–4.30 (1H, m, N-CH-), 3.45–3.28 (2H, m, N-CH₂), 2.40 (3H, s, Ar-CH₃) and 1.90–1.70 ppm (4H, m, -CH₂-CH₂-); δ_{C}

(100 MHz, CDCl₃) 173.1 (C=O), 156.5 (C-5'), 153.3 (d, ²*J*_{P-C} 10 Hz, C-1'), 150.7 (d, ²*J*_{P-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, ³*J*_{P-C} 7 Hz, C-4a), 124.5 (C-6), 118.7 (d, ³*J*_{P-C} 5 Hz, C-8), 117.1 (C-4'), 110.8 (C-2'), 66.8 (O-CH₂-Ph), 60.5 (d, ²*J*_{P-C} 6 Hz, N-CH-CO), 49.5 (d, ²*J*_{P-C} 3 Hz, N-CH₂), 46.6 (-CH₂-), 31.9, 29.7 (-CH₂-CH₂-) and 24.4 ppm (Ar-CH₃); δ_{P} (CDCl₃) 59.70 ppm; ν_{max} (CHCl₃) 803 (P=S), 1449 and 1744 cm⁻¹ (C=O); HRMS calc. for C₂₅H₂₆N₃O₃PSNa: 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, CDCl₃) 7.54–6.79 (7H, m, Ar-H), 5.23–4.88 (2H, m, -CH₂-), 4.47–4.36 (1H, m, N-CH-) 3.74 (3H, s, OCH₃), 3.52–3.30 (2H, m, N-CH₂-), 2.49 (3H, s, Ar-CH₃) and 2.05–1.68 ppm (4H, m, -CH₂-CH₂-); δ_{C} (100 MHz, CDCl₃) 173.7 (C=O), 156.5 (C-5'), 153.3 (d, ²*J*_{P-C} 10.5 Hz, C-1'), 150.7 (d, ²*J*_{P-C} 11 Hz, C-8a), 137.6 (C-3'), 129.1 (C-5), 127.0 (C-7), 126.6 (d, ³*J*_{P-C} 7 Hz, C-4a), 124.6 (C-6), 118.6 (d, ³*J*_{P-C} 10 Hz, C-8), 117.2 (C-4'), 110.9 (d, ³*J*_{P-C} 2 Hz, C-2'), 60.4 (d, ²*J*_{P-C} 6.5 Hz, N-CH-CO), 52.0 (OCH₃), 46.6, (-CH₂-), 42.2 (N-CH₂), 31.9, 29.6 (-CH₂-CH₂-) and 24.4 ppm (Ar-CH₃); δ_{P} (CDCl₃) 58.96 ppm; ν_{max} (CHCl₃) 757 (P=S), 1745 (C=O) and 3402 cm⁻¹ (P-NH); *m/z* (LCMS): 404 (M+H); calc. for C₁₉H₂₂N₃O₃PS: C, 56.57; H, 5.50; N, 10.42 %; found: C, 56.62; H, 5.56; N, 10.37 %.

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