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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ALKYL-2-{[3-(3'-CHLORO-4'-NITROPHENYL)-2-OXO-3,4-DIHYDRO-2*H*-1,3,2λ^5-BENZOXAZAPHOSPHININ-2-YL]AMINO} ALKANOATES

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ABSTRACT

Synthesis of alkyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazapho sphinin- 2-yl]amino} alkanoates (4a-j) were accomplished via a two-step process, involving the condensation of 2-[(3'-chloro-4'-nitrophenyl amino)methyl]phenol (1) with phosphorusoxychloride in the presence of triethylamine (TEA) in dry tetrahydrofuran (THF) to produce the corresponding monochloride intermediate (2), and subsequent reaction with the amino acid alkyl ester in dry THF in the presence of TEA at various temperatures. These compounds were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data and all them exhibited significant antibacterial and fungal activity.

KEYWORDS

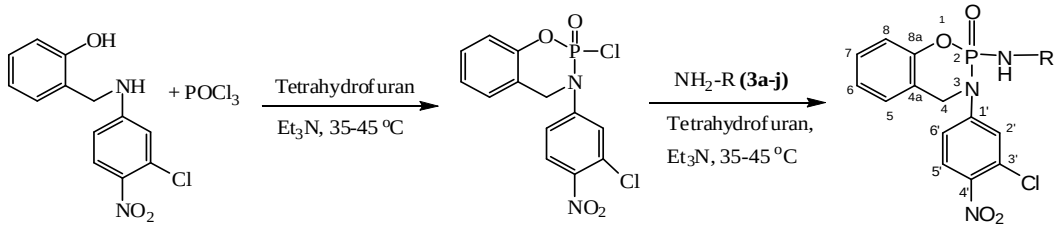
1,3,2-benzoxazaphosphinine, 2-[(3'-chloro-4'-nitrophenylamino)methyl] phenol, aminoacid ester, antimicrobial activity.

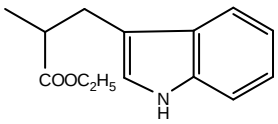
INTRODUCTION

Ubiquitous nature of organophosphorus compounds find extensive applications in the fields of agrochemicals[1], pharmaceuticals[2] and chemical synthesis[3]. Organo-phosphorus heterocyclic compounds bearing P-N functionality has shown significant medicinal and pesticidal activity[4-7], when linked with an aminoacid ester moiety helps to increase cellular uptake and enhance chemotherapeutic properties[8,9]. Simaltaneously aminoacid groups on phosphorus moiety possess useful anti-neoplastic properties[8-11]. In view of this, new six memberd Benzoxazaphosphinine heterocycles substituted with amino acids were synthesised and accomplished.

MATERIAL AND METHODS

All melting points were recorded on Buchi R-535 (Flawil, Switzerland) apparatus and are uncorrected. Elemental analyses were performed using a Perkin Elmer 2400 instrumentat the Central Drug Research Institute (CDRI), Lucknow, India. 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-AMX 400MHz NMR spectrometers (Ettlingen, Germany) operating at 400MHz for ^{1}H, 100MHz for ^{13}C and 161.89 MHz for ^{31}P. The compounds were dissolved in CD_3OD and chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85%H_3PO_4 (^{31}P). APCI mass spectra were recorded on LCMS-2010A Shimadzu instrument.



Compd.	R	Compd.	R
a	$-CH_2-COOCH_3$	f	$-CH(COOC_2H_5)-CH_2-CH_3$
b	$-CH_2-COOC_2H_5$	g	$-CH(COOC_2H_5)-CH_2-C_6H_5$
c	$-CH(COOCH_3)-CH_2-C_6H_5$	h	$-CH(COOC_2H_5)-CH_2-CH_2-CH_3$
d	$-CH(COOC_2H_5)-CH_3$	i	$-CH(COOC_2H_5)-CH(CH_3)-CH_3$
e	$-CH(COOC_2H_5)-CH_2-CH_2-SCH_3$	j	

(Scheme)

Synthesis of intermediate (2):-

A solution of phosphorusoxychloride (0.002 mole) in 20mL of dry tetrahydrofuran (THF) were added dropwise to a stirred solution of 2-[(3'-chloro-4'-nitrophenylamino)methyl]phenol (1) (0.002 mole) and triethylamine (TEA) (0.004 mole) in 20 mL of dry THF at 0-5 ^{0}C over a period of 30 min. After stirring for 4-5 h at 35-45°C, formation of the intermediate (2) was ascertained by TLC analysis in 7:3 mixtures of hexane and ethyl acetate. Triethylamine hydrochloride was removed by filtration. The filtrate was used for the next step without further purification.

Typical procedure for the synthesis of (4a-j):-

To a stirred solution of aminoacid ester hydrochloride (0.002 mole) and TEA (0.004 mole) in dry THF (10 mL) the intermediate monochloride (2), (0.002 mole) in dry THF was added dropwise at 0°C. After completion of the addition, the temperature of the reaction was raised to 35-45°C and the reaction mixture was stirred for 4-5 h. After completion of the reaction, as indicated by TLC conducted in 7:3 mixture of hexane and ethyl acetate, 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, hexane: ethyl acetate, 9:1) to afford the pure compound. The compounds thus obtained were characterized by IR, ^{1}H, ^{13}C, and ^{31}P NMR, and mass spectroscopy.

Physical, analytical and spectral data for the compounds (4a-j):-

Methyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino} acetate (4a):

m.p.171-173ºC, Yield was found to be 77%; IR (KBr): 3408(-NH), 1751(C=O), 1227 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.67-6.81 (m, 7H, Ar-H), 4.52 (brs, 1H, NH), 4.47-4.23 (m, 2H, -CH_2-), 3.96 (s, 3H, O-CH_3), 3.61(s, 2H, N-CH_2); ^{13}C NMR (CD_3OD): δ 152.3 (C=O), 150.2 (d, $^2J_{P-C}$ = 11 Hz, C-8a), 146.6 (C-1'), 130.4 (C-4'), 129.6 (C-3'), 129.2 (C-4a), 128.6 (C-7), 128.1 (C-5), 124.6 (C-5'), 121.2 (C-6), 118.0 (C-2'), 116.0 (C-8), 108.9 (C-6'), 51.6 (O-CH_3), 45.3 (C-4), 44.1 (-CH_2-), 44.0 (N-CH_2); ^{31}P NMR (CD_3OD): δ 6.75; LCMS: *m/z* 411(M^+), 413 (M+2). *Anal*. Calcd. for $C_{16}H_{15}ClN_3O_6P$: C, 46.67; H, 3.67; N,10.21. Found: C, 46.60; H, 3.54; N, 9.98.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino} acetate, (4b):

m.p.186-188ºC, Yield was found to be 79%; IR (KBr): 3374 (-NH), 1736 (C=O), 1238 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.85-6.89 (m, 7H, Ar-H), 4.46 (brs, 1H, NH), 4.45-4.17 (m, 2H, -CH_2-), 3.69 (s, 2H, N-CH_2), 4.13-3.98 (m, 2H O-CH_2), 2.14 (s, 3H, -CH_3); ^{13}C NMR (CD_3OD): δ 163.3 (C=O), 149.8 (d, $^2J_{P-C}$ 10 Hz, C-8a), 146.2 (C-1'), 130.5 (C-4'), 128.9 (C-3'), 128.8 (C-4a), 128.4 (C-7), 126.7 (C-5), 124.9 (C-5'), 122.2 (C-6), 116.5 (C-2'), 112.0 (C-8), 108.5 (C-6'), 60.5 (-OCH_2-), 46.7 (C-4), 45.3 (-CH_2-), 42.6 (N-CH_2-), 18.8 (-CH_3); ^{31}P NMR (CD_3OD): δ 9.27; LCMS: m/z 425 (M^+), 427 (M+2). *Anal*. Calcd. for $C_{17}H_{17}ClN_3O_6P$: C, 47.96; H, 4.02; N, 9.87. Found: C, 46.96; H, 3.99; N, 9.59.

Methyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}-3-phenylpropanoate, (4c):

m.p.204-206ºC, Yield was found to be 69%; IR (KBr): 3412 (-NH), 1743 (C=O), 1231 (P=O)cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.48-7.08 (m, 12H, Ar-H), 4.54 (brs, 1H, NH), 4.51-4.24 (m, 2H, -CH_2-), 3.72-3.63 (m, 1H, N-CH-), 3.74 (s, 3H O-CH_3), 3.46-2.95 (m, 2H, -CH_2-); ^{31}P NMR (CD_3OD): δ 9.16; LCMS: m/z 501, 503 (M+2). *Anal*. Calcd. for $C_{23}H_{21}ClN_3O_6P$: C, 55.04; H, 4.22; N, 8.37. Found C, 54.89; H, 4.14; N, 8.25.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}-propanoate, (4d):

m.p.189-191ºC, Yield was found to be 71%; IR (KBr): 3361(-NH), 1731 (C=O), 1218 (P=O)cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.49-7.02 (m, 7H, Ar-H), 5.03 (brs, 1H, NH), 4.38-4.19 (m, 2H, -CH_2-), 3.76-3.64 (m, 1H, N-CH-), 3.62-3.51 (m, 2H O-CH_2-), 1.22 (m, 3H, O-CH_2-CH_3), 1.02 (s, 3H, O-CH_3); ^{13}C NMR (CD_3OD): δ 153.4 (C=O), 150.3 (d, $^2J_{P-C}$ 10 Hz, C-8a), 143.3 (C-1'), 132.7 (C-4'), 128.7 (C-3'), 128.6 (C-4a), 127.6 (C-7), 127.2 (C-5), 123.5 (C-5'), 121.4 (C-6), 113.8 (C-2'), 113.3 (C-8), 110.4 (C-6'), 50.6 (-OCH_2-), 45.1 (-CH_2-), 44.6 (C-4), 44.4 (N-CH-), 19.2 (-CH-), 14.2 (-CH_2-). ^{31}P NMR (CD_3OD): δ 6.02; LCMS: m/z 439, 441 (M+2). *Anal*. Calcd. for $C_{18}H_{19}ClN_3O_6P$: C, 49.16; H, 4.35; N, 9.55. Found C, 49.97; H, 4.19; N, 9.45.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}-4-(methylsulfanyl)butanoate, (4e):

m.p.203-205ºC, Yield was found to be 74%; IR (KBr): 3394 (-NH), 1729 (C=O), 1224 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.51-6.84 (m, 7H, Ar-H), 4.47 (brs, 1H, NH), 4.49-4.21 (m, 2H, -CH_2-), 4.58-4.53 (m, 1H, N-CH-), 3.94-3.88 (m, 2H O-CH_2-), 2.45-2.28 (m, 4H, -CH_2-CH_2-)1.28 (m, 3H, -CH_3), 1.99(s, 3H, SCH_3); ^{31}P NMR (CD_3OD): δ 5.66; LCMS: m/z 499 (M^+), 501 (M+2). *Anal*. Calcd. for $C_{20}H_{23}ClN_3O_6PS$: C, 48.05; H, 4.64; N, 8.41. Found: C, 47.89; H, 4.55; N, 8.39.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino} butanoate, (4f):

m.p.187-189ºC, Yield was found to be 73%; IR (KBr): 3369 (-NH), 1727 (C=O), 1221 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.53-6.54 (m, 7H, Ar-H), 4.35 (brs, 1H, NH), 4.27-4.02 (m, 2H, -CH_2-), 3.38-3.12 (m, 1H, N-CH-), 3.75-3.47 (m, 2H O-CH_2-CH_3), 1.38 (m, 3H, O-CH_2-CH_3), 3.02-2.21(m, 2H, -CH-CH_2-), 1.79-1.36 (t, 3H, -CH-CH_2-CH_3); ^{31}P NMR (CD_3OD): δ 7.08;

LCMS: m/z 439, 404 (M+2). *Anal*. Calcd. for $C_{19}H_{21}ClN_3O_6P$: C, 49.16; H, 4.35; N, 9.55. Found: C, 48.15; H, 4.25; N, 9.24.

Ethyl-3-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}proponoate, (4g):

m.p.188-190ºC, Yield was found to be 77%; IR (KBr): 3402 (-NH), 1748 (C=O), 1234 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.95-6.65 (m, 12H, Ar-H), 4.55 (brs, 1H, NH), 4.32-4.20 (m, 2H, -CH_2-), 3.98-3.62 (m, 1H, -CH-), 3.55-3.20 (t, 2H, -OCH_2-CH_3), 3.37-3.25 (d, 2H -CH_2-), 1.38 -1.12 (d, 3H, -OCH_2-CH_3); ^{31}P NMR (CD_3OD): δ 8.16; LCMS: m/z 515 (M^+), 517 (M+2). *Anal*. Calcd. for $C_{24}H_{23}ClN_3O_6P$: C, 55.88; H, 4.49; N, 8.15. Found: C, 55.15; H, 4.25; N, 7.94.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino} pentanoate, (4h):

m.p.202-204ºC, Yield was found to be 73%; IR (KBr): 3388 (-NH), 1739 (C=O), 1217 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.48-6.83 (m, 7H, Ar-H), 4.30 (brs, 1H, NH), 4.25-4.12 (m, 2H, -CH_2-), 3.38-3.12 (m, 1H, N-CH-), 3.76-3.46 (m, 2H, O-CH_2-), 1.79-1.72 (m, 2H, -CH-CH_2-),1.38 (m, 3H, O-CH_2-CH_3), 1.79-1.36 (t, 3H, -CH-CH2-CH_3); ^{31}P NMR (CD_3OD): δ 7.39; LCMS: m/z 467 (M^+), 469 (M+2). *Anal*. Calcd. for $C_{20}H_{23}ClN_3O_6P$: C, 51.35; H, 4.96; N, 8.98. Found: C, 51.04; H, 4.55; N, 8.94.

Methyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}-3-methylbutanoate, (4i):

Solid, m.p.176-178ºC, Yield was found to be 77%; IR (KBr): 3372 (-NH), 1732 (C=O), 1211 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.67-7.07 (m, 7H, Ar-H), 4.41 (brs, 1H, NH), 4.26-4.20 (m, 2H, -CH_2-),4.02-3.98 (m, 1H, N-CH-), 3.54 (s, 3H, O-CH_3), 1.42-1.32 (m,1H, -CH), 1.17 (d, 6H, -CH_3); ^{31}P NMR (CD_3OD): δ 6.62; LCMS: m/z 453, 455 (M+2). *Anal*. Calcd. for $C_{19}H_{21}ClN_3O_6P$: C, 50.29; H, 4.66; N, 9.26. Found: C, 50.10; H, 4.55; N, 9.14.

Ethyl-2-{[3-(3'-chloro-4'-nitrophenyl)-2-oxo-3,4-dihydro-2H-1,3,2λ^5-benzoxaza-phosphinin-2-yl] amino}-2-(1H-3-indolyl)acetate, (4j):

m.p.121-123ºC, Yield was found to be 77%; IR (KBr): 3417 (-NH), 1754 (C=O), 1242 (P=O) cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.98(brs, 1H, NH), 7.57-6.98 (m, 12H, Ar-H), 4.51 (brs, 1H, NH), 4.32-4.16 (m, 2H, -CH_2-), 4.63-4.51 (m, 1H, N-C<u>H</u>-), 3.96-3.85 (m, 2H, O-CH_2-CH_3), 1.62-1.54 (m, 2H, -CH_2-),1.17 (t, 3H, O-CH_2-CH_3); ^{31}P NMR (CD_3OD): δ 10.15;LCMS: m/z 570 (M^+), 572 (M+2). *Anal*. Calcd. for $C_{27}H_{26}ClN_4O_6P$: C, 57.00; H, 4.61; N, 9.85 Found: C, 56.94; H, 4.56; N, 9.81.

Antimicrobial activity

Antimicrobial and antifungal activity of all the title compounds (4a-j) were tested against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram -ve) bacteria and fungi by disc diffusion method two different concentrations (200, 400 ppm)[12]. Penicillin and Griseofulvin were taking as a references. All the compounds showed moderate activity against both the bacteria and fungi shown in Table 1 and Table 2.

Table-1: Antibacterial activity of compounds (4a-j) (µg/disc)

Compound	Zone of inhibition (%)			
	Staphylococcus aureus		*Escherchia coli*	
	200 µg/disc	400 µg/disc	200 µg/disc	400 µg/disc
a	14	17	15	19
b	13	16	13	17
c	16	19	14	15
d	18	20	17	21
e	14	16	10	14
f	17	18	16	13
g	16	17	15	15
h	12	14	13	14
i	10	11	10	11
j	14	13	12	16
Penicillin	20	25	20	25

Table-2: Antifungal activity of compounds (4a-j) (µg/disc)

Compound	Zone of inhibition (%)			
	Staphylococcus aureus		*Escherchia coli*	
	200 µg/disc	400 µg/disc	200 µg/disc	400 µg/disc
a	18	22	20	25
b	21	24	22	26
c	20	21	19	19
d	22	25	24	23
e	20	22	21	22
f	19	18	16	18
g	18	16	15	16
h	17	15	18	19
i	16	16	17	18
j	10	11	16	15
Griseofulvin	25	30	25	30

RESULTS AND DISCUSSION

Synthesis of title compounds (4a-j) involves cyclo condensation of 2-[(3'-chloro-4'-nitrophenyl amino)methyl] phenol (1) with phosphorusoxychloride in dry THF in the presence of TEA at 35-45°C to afford the corresponding monochloride intermediate (2). Further step the intermediate (2) was reacted with the respective aminoacid ester hydrochlorides (3a-j) in dry THF in the presence of TEA afforded title compounds (4a-j) in good yields **(Scheme)**. The second step of the reaction was completed at 35-45°C with stirring for 4-5 h. The progress of the reaction was monitored by TLC analysis. Aliphatic aminoacid esters **4a, 4b, 4d-f, 4h** and **4i** reacted with the monochloride (2) more readily than with the aromatic aminoacid esters **4c, 4g** and **4j**. The crude products obtained after removing the solvent were purified by column chromatography on silica gel using ethyl acetate:hexane mixture a eluent. The title compounds (4a-j) were characterized by elemental analysis, IR, ^{1}H, ^{13}C and ^{31}P NMR and mass spectral data[13].

All the title compounds (4a-j) exhibited absorption bands for P-NH, C=O and P=O in the regions of 3417-3361, 1754-1727 and 1242-1211cm^{-1} respectively[13]. The aromatic protons of (4a-j) resonated as multiplets in the region δ 7.95-6.54. The C-4 methylene protons resonated as multiplets at δ 4.51-4.17, indicating their non-equivalence in the six membered chair conformation of the benzoxazaphosphinine ring system[13-15].

The ^{13}C NMR spectral data for **4a, 4b** and **d** are given in the experimental part. The endocyclic oxygen-bonded C-8a gave signals as doublets at δ 150.3–149.8. The C-4 methylene carbon chemical shifts appeared in the region δ 46.7-44.6. The chemical shift of the carbon atom α to the amino acid ester group appeared at δ 44.4-42.6. The remaining carbon signals are observed in the expected regions[13,14]. Compounds (4a-j) show a phosphorus-31 resonance signal in the range of δ 10.04-6.05 ppm[14].

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