Synthesis and characterization of new 1H-pyrazolo[3,4-b]pyridine phosphoramidate derivatives


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Abstract
Twelve new 1H-pyrazolo[3,4-b]pyridine phosphoramidate derivatives were synthesized under mild conditions by nucleophilic aromatic substitution reaction of aminoalkylphosphoramidates over 4-Cl substituted pyrazolo[3,4-b]pyridine in good yields. The new compounds were characterized by IR, 1H, 13C and 31P NMR spectroscopy and HRMS. The crystal structure of one compound was solved by X-ray diffraction and showed a network of intermolecular interactions involving phosphoramidate groups.

Keywords: 1H-Pyrazolo[3,4-b]pyridine, crystal structure, phosphoramidate, pyrazolopyridines

Introduction

Fused heterocyclic containing pyrazolopyridine systems have been described associated with several biological and medicinal activities.1-4 Substituted pyrazolo[3,4-b]pyridines represent a very important building block in organic synthesis and numerous studies have been reported due to their well-documented biological activity.5-8 Several 4-substituted pyrazolo[3,4-b]pyridines have been obtained by our group through nucleophilic substitution of the 4-chloro precursor with variable nucleophiles and showed antileishmanial,5 antiviral9 and antibacterial10,11 promise.

It is known that coupling molecules with well-established pharmacological activities might be a good strategy to develop new significant products.12 In this context, heterocyclic linked to other biologically active molecules, like, e.g., phosphoramidates, can give rise to new derivatives with potential biological applications.13-18
improvement of both polarization and intermolecular bonding characteristics. Our particular interest in the synthesis of substituted 1H-pyrazolo[3,4-b]pyridine phosphoramidates is in chemotherapies for tropical diseases. In this work we report the first synthesis of pyrazolopyridine phosphoramidate derivatives as well as a discussion based on the X-ray diffraction of one representative derivative.

Results and Discussion

The syntheses of the new 1H-pyrazolo[3,4-b]pyridine phosphoramidates 8a-l were performed by nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-b]pyridines (4a-c) by aminoalkylphosphoramidates 7a-d (Scheme 1). The starting 4-chloro-1H-pyrazolo[3,4-b]pyridine derivatives 4a-c were available in our laboratory and could be easily prepared from condensation of appropriate hydrazine (1a,b) and β-aminocrotononitrile or benzoylacetonitrile, followed by condensation of the intermediate 5-aminopyrazoles (2a-c) with diethyl ethoxymethylenemalonate and then by ‘chlorocyclization’ with POCl₃. Finally 4a-c were purified by recrystallization from ethanol.

![Scheme 1](image)

Scheme 1. Reagents and conditions: (i) β-aminocrotononitrile or benzoylacetonitrile (ii) diethyl ethoxymethylenemalonate, ethanol, reflux, 2 h (iii) POCl₃, 110 °C, 5 h, (iv) CCl₄, ethanol, T < 55 °C, 10 min; (v) 7a-d, THF, reflux, 9-12 h.
The aminoalkylphosphoramidates 7a-d were synthesized from diisopropylphosphonate 5 and aliphatic diamines 6a-d.\textsuperscript{25,26} In order to guarantee monophosphorylation of the diamines, at least 2.5-fold excess of diamine in ethanol were used. Keeping alkaline pH and temperature below 55 °C is required to avoid bis-phosphorylation.

Nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-b]pyridines by amines has been used as a versatile route to new pyrazolopyridine derivatives.\textsuperscript{5,9,27-30} Thus, reaction of 4a-c with an excess (2 equiv.) of aminoalkylphosphoramidates 7a-d in refluxing THF for 9 to 12 h afforded the 1H-pyrazolo[3,4-b]pyridine phosphoramidates derivatives 8a-l in 52-98% yield (Table 1). The presence of an electron-withdrawing group (-CO$_2$Et) in 5-position of the substrate 4 and the excess of the nucleophilic agent 7 facilitate the reaction. The products were fully characterized by infrared, $^1$H, $^{13}$C, and $^{31}$P NMR spectroscopies and by high resolution mass spectrometry (HRMS).

**Table 1. 1H-Pyrazolo[3,4-b]pyridine phosphoramidates 8a-l prepared**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd.</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>n</th>
<th>Mp (°C)</th>
<th>Yield\textsuperscript{a} (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>Me</td>
<td>Me</td>
<td>2</td>
<td>125-126</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>Me</td>
<td>Me</td>
<td>3</td>
<td>118-120</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td>Me</td>
<td>Me</td>
<td>4</td>
<td>42-44</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td>Me</td>
<td>Me</td>
<td>6</td>
<td>Oil</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>8e</td>
<td>Ph</td>
<td>Me</td>
<td>2</td>
<td>140-142</td>
<td>80</td>
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<tr>
<td>6</td>
<td>8f</td>
<td>Ph</td>
<td>Me</td>
<td>3</td>
<td>94-95</td>
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<tr>
<td>7</td>
<td>8g</td>
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<td>8h</td>
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<td>Me</td>
<td>6</td>
<td>60-63</td>
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<tr>
<td>9</td>
<td>8i</td>
<td>Ph</td>
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<td>10</td>
<td>8j</td>
<td>Ph</td>
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<td>3</td>
<td>110-111</td>
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<td>12</td>
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<td>Ph</td>
<td>6</td>
<td>Oil</td>
<td>52</td>
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</table>

\textsuperscript{a} Yields of pure, isolated products.

The $^1$H NMR spectra of compounds 8a-l showed a singlet in the range of 8.85-9.00 ppm attributable to the pyridine ring proton. The same spectra showed a quartet and triplet signals related to the ethyl ester group in the ranges 4.27-4.38 ppm and 1.38-1.41 ppm, respectively. The resonances of the isopropyl protons appeared as two doublets at 1.17-1.32 ppm and a doublet of septets around 4.56 ppm with $^3$J$_{HH}$ ~ 6.2 Hz and $^3$J$_{PH}$ ~ 7.5 Hz. The NH signal was detected as a broad triplet in the range 8.76-9.31 ppm with $^3$J$_{HH}$ ~ 5.1 Hz. On the other hand, NHP protons showed coupling with phosphorus and the neighbor methylene group, giving rise to a doublet of triplet around 2.80 ppm with $^3$J$_{HH}$ ~ 7.0 Hz and $^2$J$_{PH}$ ~ 9.0 Hz. In the aliphatic region, the unequivocal assignment of the signals for methylene protons was based on COSY correlations. The N-methyl protons signal of compounds 8a-d appeared as a singlet around 2.65-3.98 ppm and
the methyl protons signal for compounds 8a-h showed as a singlet at 2.76 ppm. Compounds 8e-l showed signals characteristic for aromatic protons of the phenyl groups around 7.27-8.21 ppm. Typically, the methyne carbon signal in β position to phosphorus appears as a doublet with $2J_{PC} \approx 5.2$ Hz around 70.8 ppm in $^{13}$C NMR spectroscopy. In all cases phosphorus and carbon in the aliphatic region showed coupling with $3J_{PC} \approx 5.2$ Hz, but no coupling $2J_{PC}$ was observed. The 1H-pyrazolo[3,4-b]pyridine phosphoramidates 8a-l showed in their decoupled $^{31}$P NMR spectra one signal in the region between 7.01-7.60 ppm, typical for phosphoramidates. Furthermore, infrared spectra exhibited strong absorptions for the P=O at 1269-1263 cm$^{-1}$, P-O around 990-978 cm$^{-1}$ and absorptions for the carbonyl group at 1680-1663 cm$^{-1}$. In the 3435-3199 cm$^{-1}$ region, NH bands were observed.

**Figure 1.** Ortep representation of the asymmetric unit of 8j. Ellipsoids at 50% of probability.

Single crystals of compound 8j suitable for X-ray diffraction were obtained by slow solvent evaporation at room temperature. The crystal data and structure refinement parameters for this compound are provided (See Supplementary Material, Table S1). The ORTEP representation of the asymmetric unit is shown in Figure 1. In this structure, the phosphoramidate group nitrogen atom is bonded to an aliphatic chain containing three carbon atoms, namely C1, C2 and C3. The bond lengths and angles are typical of phosphoramidate groups (Table S2). The 5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino moiety is linked to the alkyl skeleton through C3 atom. The torsion angle between the pyrazolo[3,4-b]pyridine plane and the phenyl group linked to N2A atom is 38.1º, while the torsion angle of the other phenyl groups linked to C9A atom is 30.5º. As consequence of the spatial arrangement of the phenyl groups, weak intermolecular interaction C-H···O, C-H···π e π···π stacking involving the 5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine moiety contributed to stabilize the crystal packing. Intramolecular hydrogen bonding between ester O4 oxygen and N2 amine atoms
was also observed. Furthermore, dimers of molecules raised due to the intermolecular hydrogen bonding involving the phosphoramidate O1 and N1 atoms (Figure 2), as previously reported for this compound class\textsuperscript{34} (Table 2).

**Figure 2.** Hydrogen-bonding in compound 8j.

**Table 2.** Hydrogen-bond geometry for 8j (Å, °)

<table>
<thead>
<tr>
<th>D—H···A</th>
<th>D—H</th>
<th>H···A</th>
<th>D···A</th>
<th>D—H···A</th>
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<tbody>
<tr>
<td>N2—H2···O4</td>
<td>0.86</td>
<td>2.27</td>
<td>2.715 (3)</td>
<td>112</td>
</tr>
<tr>
<td>N1—H1···O1\textsuperscript{i}</td>
<td>0.86</td>
<td>2.19</td>
<td>2.933 (3)</td>
<td>145</td>
</tr>
</tbody>
</table>

Symmetry code: (i) \(-x+2, -y+1, -z\).

**Conclusions**

The methodology for nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-\textit{b}]pyridine was successfully applied to aminoalkylphosphoramidates as the nucleophile. In this context, twelve new reported 1\textit{H}-pyrazolo[3,4-\textit{b}]pyridine phosphoramidates were synthesized and characterized. The crystal data for a representative compound pointed out the formation of dimer due to the intermolecular hydrogen bonding involving the phosphoramidate O and N atoms.

**Experimental Section**

**General.** Analytical grade reagents and solvents were purchased from commercial sources and used without further purification. Melting points were obtained with a Fisher-Johns apparatus. \( ^1\text{H}, \, ^{13}\text{C} \) and \(^{31}\text{P}\) NMR spectra were recorded on a Varian UP-300 spectrometer at 299.95, 75.42
and 121.42 MHz, respectively, with TMS as internal standard or 85% H₃PO₄ as external standard. The chemical shifts (δ) are reported in ppm and the coupling constants (J) in hertz. TLC was carried out using silica gel F-254 Glass Plate (20 × 20 cm). Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. High resolution mass spectra (EI-70eV) were performed on a Varian MAT CH7 8500 direct inlet instrument. The Cl-substituted pyrazolo[3,4-b]pyridine (4a-c)²¹-²⁴ and aminoalkylphosphoramidates (7a-d)²⁵,²⁶ compounds were prepared as previously reported.

Typical procedure for preparation of 1H-pyrazolo[3,4-b]pyridine phosphoramidate derivatives (8a-l). Cl-substituted pyrazolo[3,4-b]pyridine (4a-c) (2.2 mmol) and the aminoalkylphosphoramidate (7a-d) (4.4 mmol) were dissolved in THF (10 mL) and the reaction mixture was heated at reflux until the disappearance of the starting 4 (9-12 h, monitored by TLC). The mixture was poured into ice and the resulting solid (except 8d,i,k,l) was filtered off, washed with distilled water and dried. Solids were recrystallized from ethanol/water (1:3). Compounds 8d,i,k,l were diluted with chloroform and washed with water (3 × 10 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure giving an oily product.

**Diisopropyl 2-[5-(ethoxycarbonyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]-ethylphosphoramidate (8a).** Pale brown solid; yield 80%; mp 125-126 °C; IR (KBr, νmax, cm⁻¹): 3222 (m, νN-H), 2978 (m), 2933 (m), 1671(s, νC=O), 1586 (s), 1538 (m), 1434 (m), 1372 (w), 1339 (m), 1269 (m, νP=O), 1188 (m), 1108 (m), 978 (s, νP-O), 899 (w), 795 (w), 665 (w); ¹H NMR (CDCl₃): δH 1.25 and 1.28 (2d, 12H, 3JHH 6.4), 1.40 (t, 3H, 3JHH 6.9), 2.66 (s, 3H), 2.85 (dt, 1H, 3JHH 5.4 and 3.6), 3.28 (m, 2H), 3.74 (dt, 2H, 3JHH 6.0 and 5.4), 3.98 (s, 3H), 4.34 (q, 2H, 3JHH 6.9), 4.57 (dsep, 2H, 3JHH 6.3 and 3JPH 7.5), 8.86 (s, 1H), 9.24 (br t, 1H, 3JHH 5.0); ¹³C NMR (CDCl₃): δC 14.16, 18.44, 23.61 (d, 3JP 5.1), 33.55, 41.83, 49.69 (d, 2JP 5.9), 60.41, 70.94 (d, 2JP 5.3), 100.61, 103.08, 140.19, 152.33, 154.13, 154.93, 169.24; ³¹P NMR (CDCl₃): δP 7.18 (s); HRMS (EI): m/z [M+H] calcd. for C₁₉H₃₂N₅O₅P: 441.21411. Found: 441.21400.

**Diisopropyl 3-[5-(ethoxycarbonyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]-propylphosphoramidate (8b).** Pale brown solid; yield 60%; mp 118-120 °C; IR (KBr, νmax, cm⁻¹): 3213 (m, νN-H), 2976 (m), 2933 (m), 1663(s, νC=O), 1583 (s), 1536 (m), 1457 (m), 1372 (w), 1337 (m), 1264 (m, νP=O), 1228 (m), 1185 (m), 1115 (m), 978 (s, νP-O), 897 (w), 800 (w), 658 (w); ¹H NMR (CDCl₃): δH 1.27 and 1.29 (2d, 12H, 3JHH 6.0), 1.38 (t, 3H, 3JHH 7.2), 1.94 (quinn, 2H, 3JHH 6.6), 2.54 (dt, 1H, 3JHH 8.7 and 7.2), 2.67 (s, 3H), 3.06 (m, 2H), 3.69 (dt, 2H, 3JHH 6.6 and 5.0), 3.97 (s, 3H), 4.33 (q, 2H, 3JHH 7.2), 4.56 (dsep, 2H, 3JHH 6.0 and 3JPH 7.2), 8.86 (s, 1H), 9.31 (br t, 1H, 3JHH 3.9); ¹³C NMR (CDCl₃): δC 14.15, 18.44, 23.63 (d, 3JP 5.0), 32.32 (d, 3JP 5.3), 33.44, 38.58, 45.32, 60.20, 70.63 (d, 2JP 5.3), 99.93, 102.60, 140.19, 152.28, 154.13, 154.52, 169.24; ³¹P NMR (CDCl₃): δP 7.18 (s); HRMS (EI): m/z [M+H] calcd. for C₂₀H₃₄N₅O₅P: 455.22976. Found: 455.22991.
Diisopropyl 4-[5-(ethoxycarbonyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]butylphosphoramidate (8c). Beige solid; yield 81%; mp 42-44 °C; IR (KBr, ν_max, cm⁻¹): 3234 (m, νN-H), 2978 (m), 2934 (m), 1669 (s, νC=O), 1579 (s), 1536 (m), 1436 (m), 1373 (w), 1336 (m), 1263 (m, νP=O), 1187 (m), 1124 (m), 987 (s, νP-O), 896 (w), 799 (w), 753 (w), 665 (w); ¹H NMR (CDCl₃): δ_H 1.29 and 1.31 (2d, 12H, 3J(HH) 6.0 and 4.7), 1.39 (t, 3H, 3J(HH) 7.2), 1.71 (m, 7H), 2.49 (dt, 1H, 3J(HH) 7.8 and 7.5), 2.70 (s, 3H), 2.97 (m, 2H), 3.63 (dt, 2H, 3J(HH) 6.6 and 4.7), 3.97 (s, 3H), 4.33 (q, 2H, 3J(HH) 7.2), 4.59 (dsep, 2H, 3J(HH) 6.3 and 3J(PPH) 7.8), 8.86 (s, 1H), 9.33 (br t, 1H, 3J(HH) 3.9); ¹³C NMR (CDCl₃): δ_C 14.19, 18.68, 23.70 (d, 3J(PC) 6.1), 27.64, 28.87 (d, 3J(PC) 6.4), 33.50, 40.94, 47.95, 60.31, 70.62 (d, 2J(PC) 5.6), 99.94, 102.65, 140.23, 152.39, 154.19, 154.59, 169.29; ³¹P NMR (CDCl₃): δ_ρ 7.40 (s); HRMS (EI): m/z [M+H] calcd. for C₂₁H₃₆N₃O₃P: 469.24541. Found: 469.24540.

Diisopropyl 6-[5-(ethoxycarbonyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]hexylphosphoramidate (8d). Oil; yield 65%; IR (KBr, ν_max, cm⁻¹): 3233 (m, νN-H), 2977 (m), 2934 (m), 1670(s, νC=O), 1580 (s), 1536 (m), 1437 (m), 1373 (w), 1337 (m), 1263 (m, νP=O), 1181 (m), 1124 (m), 985 (s, νP-O), 896 (w), 799 (w), 665 (w); ¹H NMR (CDCl₃): δ_H 1.30 and 1.32 (2d, 12H, 3J(HH) 6.3), 1.47 (m, 11H), 1.70 (quin, 2H, 3J(HH) 6.1), 2.64 (m, 6H), 2.86 (m, 2H), 3.60 (dt, 2H, 3J(HH) 6.6 and 5.1), 3.95 (s, 3H), 4.37 (q, 2H, 3J(HH) 7.1), 4.60 (dsep, 2H, 3J(HH) 6.0 and 3J(PPH) 7.5), 8.85 (s, 1H), 9.31 (br t, 1H, 3J(HH) 4.0); ¹³C NMR (CDCl₃): δ_C 13.97, 18.49, 23.46 (d, 3J(PC) 4.5), 25.99, 26.13, 30.15, 31.19 (d, 3J(PC) 6.6), 33.21, 40.96, 47.94, 60.01, 70.15 (d, 2J(PC) 5.5), 99.53, 102.27, 139.97, 152.08, 153.87, 154.25, 168.99; ³¹P NMR (CDCl₃): δ_ρ 7.47 (s); HRMS (EI): m/z [M+H] calcd. for C₂₁H₃₆N₃O₃P: 497.27671. Found: 497.27680.

Diisopropyl 2-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]ethylphosphoramidate (8e). Pale brown solid; yield 80%; mp 140-142 °C; IR (KBr, ν_max, cm⁻¹): 3202 (m, νN-H), 2979 (m), 2931 (m), 1675(s, νC=O), 1599 (s), 1508 (m), 1438 (m), 1373 (w), 1345 (m), 1268 (m, νP=O), 1235 (s), 1129 (m), 1108 (m), 989 (s, νP-O), 897 (w), 797 (w), 665 (w); ¹H NMR (CDCl₃): δ_H 1.25 and 1.28 (2d, 12H, 3J(HH) 6.3), 1.40 (t, 3H, 3J(HH) 6.9), 2.75 (s, 3H), 2.83 (dt, 1H, 3J(HH) 9.0 and 6.8), 3.26 (m, 2H), 3.67 (dt, 2H, 3J(HH) 9.0 and 6.3), 4.32 (q, 2H, 3J(HH) 6.9), 4.58 (dsep, 2H, 3J(HH) 6.3 and 3J(PPH) 6.9), 7.03 (s, 3J(PPH) 6.3), 7.49 (m, 2H), 8.09 (d, 2H, 3J(HH) 8.6), 8.87 (s, 1H), 9.10 (br t, 1H, 3J(HH) 4.8); ¹³C NMR (CDCl₃): δ_C 14.10, 18.33, 23.59 (d, 3J(PC) 4.9), 41.95, 50.19 (d, 2J(PC) 4.4), 60.52, 70.90 (d, 2J(PC) 5.7), 102.06, 104.92, 122.10, 126.13, 128.80, 138.70, 141.97, 152.63, 153.94, 154.98, 168.95; ³¹P NMR (CDCl₃): δ_ρ 7.23 (s); HRMS (EI): m/z [M+H] calcd. for C₂₃H₄₄N₅O₅P: 503.22976. Found: 503.22930.

Diisopropyl 3-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]propylphosphoramidate (8f). Beige solid; yield 75%; mp 94-95 °C; IR (KBr, ν_max, cm⁻¹): 3199 (m, νN-H), 2978 (m), 2930 (m), 1679 (s, νC=O), 1583 (s), 1526 (m), 1444 (m), 1371 (w), 1273 (m), 1228 (m, νP=O), 1153 (m), 1109 (m), 979 (s, νP-O), 897 (w), 799 (w), 690 (w); ¹H NMR (CDCl₃): δ_H 1.27 and 1.29 (2d, 12H, 3J(HH) 6.0), 1.39 (t, 3H, 3J(HH) 7.2), 1.95 (quin, 2H, 3J(HH) 6.6), 2.58 (dt, 1H, 3J(HH) 8.9 and 6.0), 2.76 (s, 3H), 3.07 (m, 2H), 3.72 (dt, 2H, 3J(HH) 6.9 and 4.8), 4.35 (q, 2H, 3J(HH) 7.2), 4.57 (dsep, 2H, 3J(HH) 6.0 and 3J(PPH) 7.5), 7.31 (t, 1H, 3J(HH) 7.5),
Diisopropyl 4-[[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1H-pyrazol-3-yl]-N-(pyridin-4-yl)amido]butylphosphoramidate (8g). Pale beige solid; yield 98%; mp 83-84 °C; IR (KBr, νmax, cm⁻¹): 3202 (m, νN-H), 2980 (m), 2931 (m), 1675 (s, νC=O), 1599 (s), 1508 (m), 1438 (m), 1373 (w), 1268 (m, νP=O), 1339 (m), 1235 (m), 1129 (m), 989 (s, νP=O), 761 (w); ¹H NMR (CDCl₃): δH 1.29 and 1.31 (2d, 12H, ³J(HH) 6.3), 1.39 (t, 3H, ³J(HH) 7.2), 1.68 (m, 2H), 1.79 (m, 2H), 1.92 (br s, 1H), 2.52 (dt, 1H, ³J(HH) 8.9 and 6.3), 2.73 (s, 3H), 2.98 (m, 2H), 3.65 (dt, 2H, ³J(HH) 6.9 and 4.8), 4.34 (q, 2H, ³J(HH) 7.2), 4.58 (dsep, 2H, ³J(HH) 6.3 and ³J(PH) 7.5), 7.32 (t, 1H, ³J(HH) 7.3), 7.49 (t, 2H, ³J(HH) 7.5), 8.08 (d, 2H, ³J(HH) 8.5), 8.90 (s, 1H), 9.25 (br t, 1H, ³J(HH) 4.5); ¹³C NMR (CDCl₃): δC 14.13, 18.66, 23.63 (d, ³J(PC) 4.9), 23.70 (d, ³J(PC) 4.3), 27.81, 28.80 (d, ³J(PC) 6.0), 40.92, 48.42, 60.43, 70.60 (d, ³J(PC) 5.8), 101.32, 104.38, 122.21, 126.14, 128.80, 138.73, 142.00, 152.68, 154.04, 154.60, 169.02; ³¹P NMR (CDCl₃): δP 7.47 (s); HRMS (EI): m/z [M+H] calcd. for C₂₉H₃₆N₅O₆P: 517.24541. Found: 517.24540.

Diisopropyl 6-[[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1H-pyrazol-3-yl]-N-(pyridin-4-yl)amido]hexylphosphoramidate (8h). Beige solid; yield 82%; mp 60-63 °C; IR (KBr, νmax, cm⁻¹): 3228 (m, νN-H), 2979 (m), 2933 (m), 1677 (s, νC=O), 1596 (s), 1508 (m), 1433 (m), 1374 (w), 1340 (m), 1264 (m, νP=O), 1229 (s), 1130 (m), 1109 (m), 981 (s, νP=O), 895 (w), 796 (w), 750 (w); ¹H NMR (CDCl₃): δH 1.30 and 1.32 (2d, 12H, ³J(HH) 6.3), 1.45 (m, 9H), 1.76 (m, 2H), 2.47 (m, 1H), 2.75 (s, 3H), 2.81 (m, 2H). 3.62 (dt, 2H, ³J(HH) 6.6 and 5.0), 4.32 (q, 2H, ³J(HH) 7.2), 4.58 (dsep, 2H, ³J(HH) 6.1 and ³J(PH) 7.5), 7.30 (t, 1H, ³J(HH) 7.2), 7.49 (t, 2H, ³J(HH) 7.2), 8.05 (d, 2H, ³J(HH) 8.0), 8.93 (s, 1H), 9.24 (br s, 1H); ¹³C NMR (CDCl₃): δC 14.18, 18.76, 23.73 (d, ³J(PC) 5.0), 26.24, 26.40, 31.44 (d, ³J(PC) 6.5), 41.23, 48.73, 60.52, 70.53 (d, ³J(PC) 5.0), 101.33, 104.41, 122.36, 126.32, 128.90, 138.65, 142.18, 154.73, 168.99; ³¹P NMR (CDCl₃): δP 7.60 (s); HRMS (EI): m/z [M+H] calcd. for C₂₈H₃₄N₅O₅P: 531.26106. Found: 531.26110.

Diisopropyl 2-[[5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazol-3-yl]-N-(pyridin-4-yl)amido]ethylphosphoramidate (8i). Oil; yield 54%; IR (KBr, νmax, cm⁻¹): 3202 (m, νN-H), 2980 (m), 2931 (m), 1675 (s, νC=O), 1599 (s), 1508 (m), 1438 (m), 1373 (w), 1345 (w), 1269 (m, νP=O), 1235 (s), 1129 (m), 1108 (m), 989 (s, νP=O), 897 (w), 797 (w), 761 (w); ¹H NMR (CDCl₃): δH 1.17 and 1.23 (2d, 12H, ³J(HH) 6.4), 1.42 (t, 3H, ³J(HH) 7.2), 2.50 (dt, 1H, ³J(HH) 9.0 and 6.2), 2.78 (m, 2H), 2.90 (dt, 2H, ³J(HH) 8.9 and 6.0), 4.45 (q, 2H, ³J(HH) 7.2), 4.49 (dsep, 2H, ³J(HH) 6.3 and ³J(PH) 7.8), 7.33 (t, 1H, ³J(HH) 7.5), 7.51 (m, 5H), 7.69 (d, 2H, ³J(HH) 8.1), 8.17 (d, 2H, ³J(HH) 8.5), 8.85 (br t, 1H, ³J(HH) 5.7), 9.00 (s, 1H); ¹³C NMR (CDCl₃): δC 14.01, 23.43 (d, ³J(PC) 4.9), 41.70, 50.34 (d, ³J(PC) 5.2), 60.49, 70.58 (d, ³J(PC) 5.8), 103.15, 103.72, 122.16, 126.31, 128.35, 128.51, 128.65, 128.71, 134.37, 138.62, 146.62, 152.77, 153.94, 155.26, 168.51; ³¹P NMR (CDCl₃): δP 7.08 (s); HRMS (EI): m/z [M+H] calcd. for C₂₉H₃₆N₅O₅P: 565.24541. Found: 565.5400.
Diisopropyl 3-[5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]-propylphosphoramidate (8j). Pale beige solid; yield 69%; mp 110-111 °C; IR (KBr, νmax, cm⁻¹): 3230 (m, νN-H), 2978 (m), 2935 (m), 1679 (s, νC=O), 1568 (s), 1504 (m), 1457 (m), 1372 (w), 1338 (m), 1265 (m, νP=O), 1231 (s), 1168 (m), 1100 (m), 985 (s, νP-O), 896 (w), 756 (w), 708 (w); ¹H NMR (CDCl₃): δH 1.22 and 1.26 (2d, 12H, 3J(HH) 6.2), 1.41 (t, 3H, 3J(HP) 7.2), 1.49 (quin, 2H, 3J(HP) 6.0), 2.10 (dt, 1H, 3J(HP) 8.7 and 6.6), 2.79 (m, 2H), 4.37 (q, 2H, 3J(HP) 7.1), 4.48 (dsep, 2H, 3J(HP) 6.0 and 3J(HP) 7.5), 7.31 (t, 1H, 3J(HP) 7.3), 7.49 (m, 5H), 7.67 (d, 2H, 3J(HP) 8.0), 8.20 (d, 2H, 3J(HP) 8.6), 8.86 (br t, 1H, 3J(HP) 5.1), 8.98 (s, 1H); ¹³C NMR (CDCl₃): δC 14.15, 23.61 (d, 3J(HP) 4.1), 32.41 (d, 3J(HP) 5.8), 46.43, 60.33, 70.75 (d, 3J(HP) 6.0), 102.73, 103.73, 122.38, 126.46, 128.44, 128.84, 128.98, 134.97, 138.75, 146.84, 152.95, 154.04, 155.15, 168.71; ³¹P NMR (CDCl₃): δP 7.12 (s); HRMS (EI): m/z [M+H] calcd. for C₃₀H₃₈N₅O₅P: 579.26106. Found: 579.26120.

Diisopropyl 4-[5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]-butylphosphoramidate (8k). Oil; yield 53%; IR (KBr, νmax, cm⁻¹): 3240 (m, νN-H), 2977 (m), 2932 (m), 1674 (s, νC=O), 1573 (s), 1501 (m), 1462 (m), 1373 (w), 1337 (m), 1262 (m, νP=O), 1175 (m), 1106 (m), 989 (s, νP=O), 895 (w), 776 (w), 699 (w); ¹H NMR (CDCl₃): δH 1.25 (m, 16H), 1.41 (t, 3H, 3J(HP) 7.2), 2.65 (m, 6H), 2.85 (m, 2H), 4.36 (q, 2H, 3J(HP) 7.1), 4.54 (dsep, 2H, 3J(HP) 6.3 and 3J(HP) 7.5), 7.30 (t, 1H, 3J(HP) 7.0), 7.52 (m, 5H), 7.70 (d, 2H, 3J(HP) 8.0), 8.21 (d, 2H, 3J(HP) 8.6), 8.79 (br t, 1H, 3J(HP) 5.4), 8.98 (s, 1H); ¹³C NMR (CDCl₃): δC 14.05, 23.56 (d, 3J(HP) 4.1), 27.68, 28.45 (d, 2J(HP) 4.1), 40.56, 40.84, 48.81, 60.38, 70.38 (d, 2J(HP) 5.5), 102.46, 103.55, 122.23, 126.29, 128.27, 128.45, 128.72, 128.81, 134.84, 138.69, 146.85, 152.84, 153.94, 155.04, 168.59; ³¹P NMR (CDCl₃): δP 7.51 (s); HRMS (EI): m/z [M+H] calcd. for C₃₁H₃₆N₅O₅P: 593.65356. Found: 593.65438.

Diisopropyl 6-[5-(ethoxycarbonyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-ylamino]-hexylphosphoramidate (8l). Oil; yield 52%; IR (KBr, νmax, cm⁻¹): 3243 (m, νN-H), 2977 (m), 2930 (m), 1680 (s, νC=O), 1573 (s), 1502 (m), 1453 (m), 1373 (m), 1267 (m, νP=O), 1177 (m), 1107 (m), 990 (s, νP=O), 896 (w), 776 (w), 699 (w); ¹H NMR (CDCl₃): δH 1.19 and 1.25 (2d, 12H, 3J(HP) 6.0), 1.27 (m, 2H), 1.39 (t, 3H, 3J(HP) 7.1), 2.47 (dt, 1H, 3J(HP) 9.0 and 7.8), 2.79 (m, 2H), 2.88 (dt, 2H, 3J(HP) 8.6 and 5.6), 4.37 (q, 2H, 3J(HP) 6.9), 4.48 (dsep, 2H, 3J(HP) 6.0 and 3J(HH) 7.5), 7.31 (t, 1H, 3J(HH) 7.5), 7.49 (m, 6H), 7.75 (d, 2H, 3J(HH) 8.0), 8.20 (d, 2H, 3J(HH) 8.6), 8.90 (br t, 1H, 3J(HH) 5.6), 9.00 (s, 1H); ¹³C NMR (CDCl₃): δC 14.16, 23.59 (d, 3J(HP) 4.4), 29.57, 41.87, 50.49, 50.55, 60.68, 70.77 (d, 2J(HP) 5.3), 103.30, 103.88, 122.40, 126.54, 128.52, 128.69, 128.82, 128.89, 134.52, 138.73, 146.80, 152.92, 155.45, 168.71; ³¹P NMR (CDCl₃): δP 7.01 (s); HRMS (EI): m/z [M+H] calcd. for C₃₃H₄₄N₅O₅P: 621.30801. Found: 621.30754.

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