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

Leandro F. Pedrosa,[a] William P. de Macedo,[a] Antonia C. R. Furtado,[a] Guilherme P. Guedes,[a,b] Julio C. Borges,[a] Jackson A. L. C. Resende,[a] Maria G. F. Vaz,[a] Alice M. R. Bernardino[a] and Marcos C. de Souza[a]*

[a] *Instituto de Química, Universidade Federal Fluminense, 24020-141, Niterói, RJ, Brazil*
[b] *Instituto de Ciências Exatas - Departamento de Química, Universidade Federal Rural do Rio de Janeiro, 23070-200, Seropédica, RJ, Brazil*
E-mail: gqomarc@vm.uff.br

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.413

Abstract

Twelve new 1*H*-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, ^{1}H, ^{13}C and ^{31}P 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: 1*H*-Pyrazolo[3,4-*b*]pyridine, crystal structure, phosphoramidate, pyrazolopyridines

Introduction

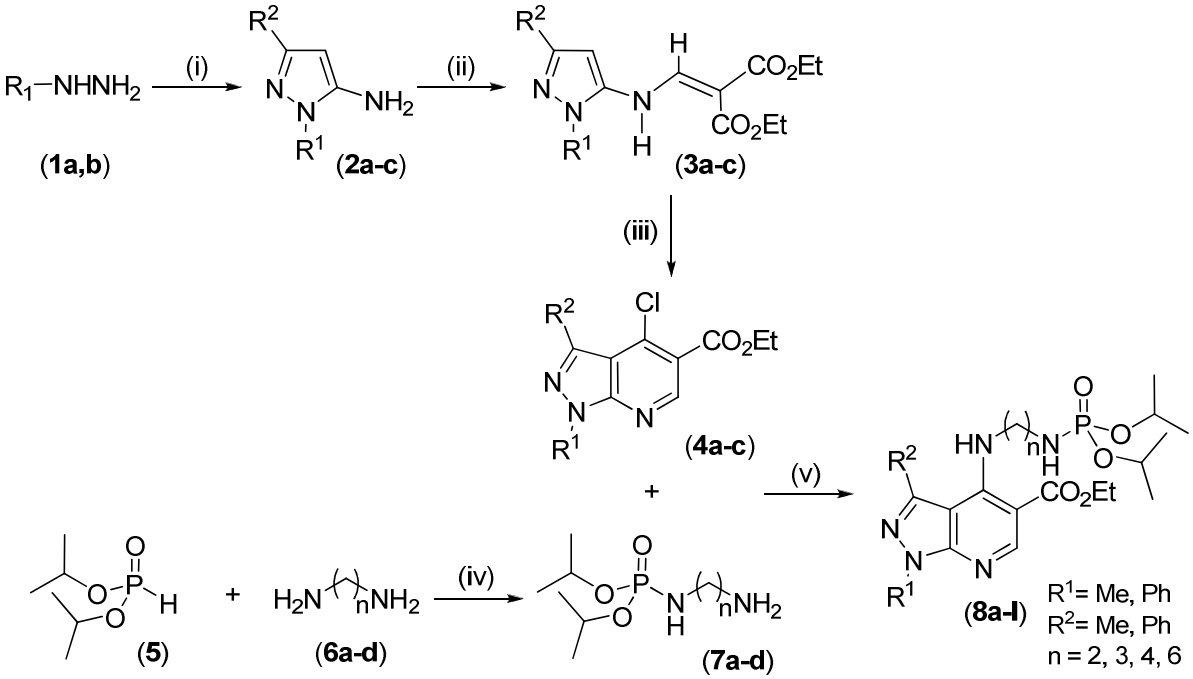
Fused heterocyclic containing pyrazolopyridine systems have been described associated with several biological and medicinal activities.[1-4] Substituted pyrazolo[3,4-*b*]pyridines represent a very important building block in organic synthesis and numerous studies have been reported due to their well-documented 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] antiviral[9] and antibacterial[10,11] 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] Introduction of a phosphoramidate group essentially changes the physical and chemical properties of the parent molecule, resulting in the

improvement of both polarization and intermolecular bonding characteristics.[19,20] Our particular interest in the synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates is use them 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 1*H*-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-1*H*-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 benzoyl-acetonitrile, followed by condensation of the intermediate 5-aminopyrazoles (**2a-c**) with diethyl ethoxymethylenemalonate and then by 'chlorocyclization' with $POCl_3$. Finally **4a-c** were purified by recrystallization from ethanol.[21-24]



Scheme 1. *Reagents and conditions*: (i) β-aminocrotononitrile or benzoylacetonitrile (ii) diethyl ethoxymethylenemalonate, ethanol, reflux, 2 h (iii) $POCl_3$, 110 ºC, 5 h, (iv) CCl_4, ethanol, T < 55 ºC, 10 min; (v) **7a-d**, THF, reflux, 9-12 h.

The aminoalkylphosphoramidates **7a-d** were synthesized from diisopropylphosphonate **5** and aliphatic diamines **6a-d**.[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.[5,9,27-30] Thus, reaction of **4a-c** with an excess (2 equiv.) of aminoalkyl-phosphoramidates **7a-d** in refluxing THF for 9 to 12 h afforded the 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates derivatives **8a-l** in 52-98% yield (Table 1). The presence of an electron-withdrawing group (-CO_2Et) 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. 1*H*-Pyrazolo[3,4-*b*]pyridine phosphoramidates **8a-l** prepared

Entry	Compd.	R^1	R^2	n	Mp (°C)	Yield[a] (%)
1	**8a**	Me	Me	2	125-126	80
2	**8b**	Me	Me	3	118-120	60
3	**8c**	Me	Me	4	42-44	81
4	**8d**	Me	Me	6	Oil	65
5	**8e**	Ph	Me	2	140-142	80
6	**8f**	Ph	Me	3	94-95	75
7	**8g**	Ph	Me	4	83-84	98
8	**8h**	Ph	Me	6	60-63	82
9	**8i**	Ph	Ph	2	Oil	54
10	**8j**	Ph	Ph	3	110-111	69
11	**8k**	Ph	Ph	4	Oil	53
12	**8l**	Ph	Ph	6	Oil	52

[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 $^3J_{HH}$ ~ 6.2 Hz and $^3J_{PH}$ ~ 7.5 Hz. The NH signal was detected as a broad triplet in the range 8.76-9.31 ppm with $^3J_{HH}$ ~ 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 $^3J_{HH}$ ~ 7.0 Hz and $^2J_{PH}$ ~ 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 $^{2}J_{PC}$ ~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 $^{3}J_{PC}$ ~5.2 Hz, but no coupling $^{2}J_{PC}$ was observed. The 1*H*-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.[31-34] Furthermore, infrared spectra exhibited strong absorptions for the P=O at 1269-1263 cm^{-1}, P-O around 990-978cm^{-1} and absorptions for the carbonyl group at 1680-1663 cm^{-1}. In the 3435-3199 cm^{-1} region, NH bands were observed.

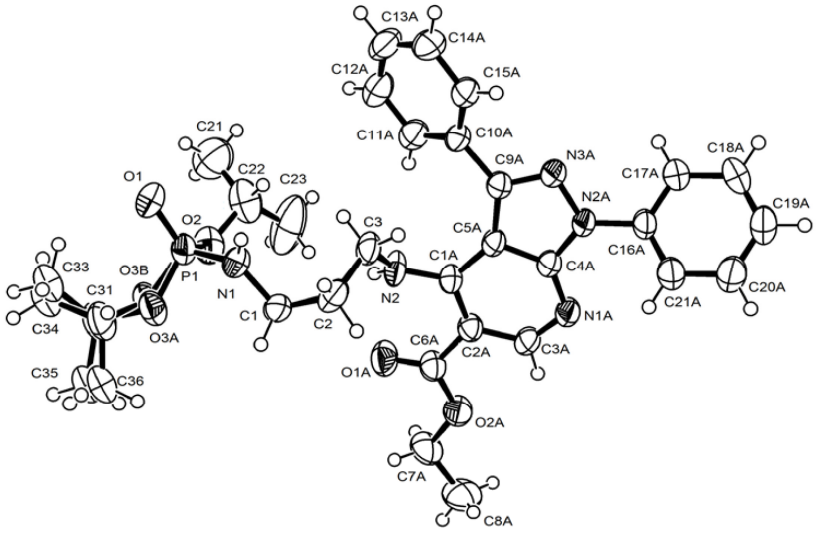


Figure 1. Ortep representation of the asymmetric unit of **8j**. Ellipsoids at 50% of probability.

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-1*H*-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-1*H*-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[34] (Table 2).

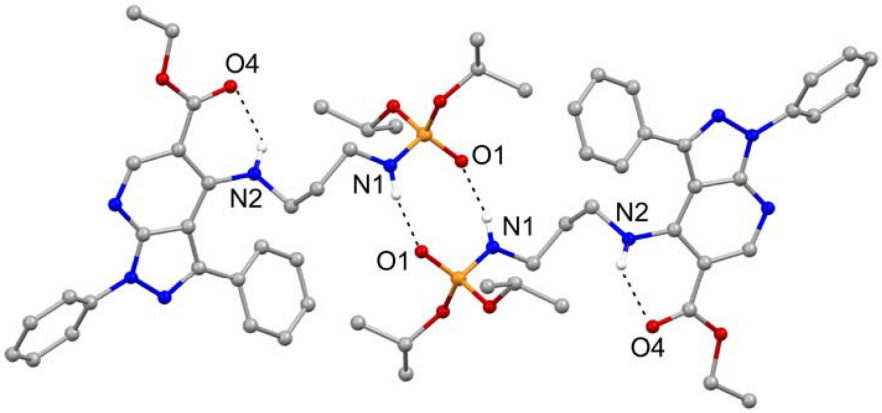


Figure 2. Hydrogen-bonding in compound **8j.**

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

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***
N2—H2···O4	0.86	2.27	2.715 (3)	112
N1—H1···O1^{i}	0.86	2.19	2.933 (3)	145

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-*b*]pyridine was successfully applied to aminoalkylphosphoramidates as the nucleophile. In this context, twelve new reported 1*H*-pyrazolo[3,4-*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}H, ^{13}C and ^{31}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% H_3PO_4 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 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates 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-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-ethylphosphoramidate (**8a**). Pale brown solid; yield 80%; mp 125-126 °C; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.25 and 1.28 (2d, 12H, $^3J_{(HH)}$ 6.4), 1.40 (t, 3H, $^3J_{(HH)}$ 6.9), 2.66 (s, 3H), 2.85 (dt, 1H, $^3J_{(HH)}$ 5.4 and 3.6), 3.28 (m, 2H), 3.74 (dt, 2H, $^3J_{(HH)}$ 6.0 and 5.4), 3.98 (s, 3H), 4.34 (q, 2H, $^3J_{(HH)}$ 6.9), 4.57 (dsep, 2H, $^3J_{(HH)}$ 6.3 and $^3J_{(PH)}$ 7.5), 8.86 (s, 1H), 9.24 (br t, 1H, $^3J_{(HH)}$ 5.0); ^{13}C NMR ($CDCl_3$): δ_C 14.16, 18.44, 23.61 (d, $^3J_{(PC)}$ 5.1), 33.55, 41.83, 49.69 (d, $^2J_{(PC)}$ 5.9), 60.41, 70.94 (d, $^2J_{(PC)}$ 5.9), 100.61, 103.08, 140.19, 152.33, 154.13, 154.93, 169.24; ^{31}P NMR ($CDCl_3$): δ_P 7.18 (s); HRMS (EI): *m*/*z* [M+H] calcd. for $C_{19}H_{32}N_5O_5P$: 441.21411. Found: 441.21400.

Diisopropyl 3-[5-(ethoxycarbonyl)-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-propylphosphoramidate (**8b**)**.** Pale brown solid; yield 60%; mp 118-120 °C; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.27 and 1.29 (2d, 12H, $^3J_{(HH)}$ 6.0), 1.38 (t, 3H, $^3J_{(HH)}$ 7.2), 1.94 (quin, 2H, $^3J_{(HH)}$ 6.6), 2.54 (dt, 1H, $^3J_{(HH)}$ 8.7 and 7.2), 2.67 (s, 3H), 3.06 (m, 2H), 3.69 (dt, 2H, $^3J_{(HH)}$ 6.6 and 5.0), 3.97 (s, 3H), 4.33 (q, 2H, $^3J_{(HH)}$ 7.2), 4.56 (dsep, 2H, $^3J_{(HH)}$ 6.0 and $^3J_{(PH)}$ 7.2), 8.86 (s, 1H), 9.31 (br t, 1H, $^3J_{(HH)}$ 3.9); ^{13}C NMR ($CDCl_3$): δ_C 14.15, 18.70, 23.63 (d, $^3J_{(PC)}$ 5.0), 32.32 (d, $^3J_{(PC)}$ 5.3), 33.44, 38.58, 45.32, 60.20, 70.63 (d, $^2J_{(PC)}$ 5.3), 99.93, 102.60, 140.21, 152.28, 154.13, 154.52, 169.24; ^{31}P NMR ($CDCl_3$): δ_P 7.40 (s); HRMS (EI): *m*/*z* [M+H] calcd. for $C_{20}H_{34}N_5O_5P$: 455.22976. Found: 455.22991.

Diisopropyl 4-[5-(ethoxycarbonyl)-1,3-dimethyl-1*H*-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); ^{1}H NMR ($CDCl_3$): 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 $^3J_{(PH)}$ 7.8), 8.86 (s, 1H), 9.33 (br t, 1H, $^3J_{(HH)}$ 3.9); ^{13}C NMR ($CDCl_3$): 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; ^{31}P NMR ($CDCl_3$): δ_P 7.40 (s); HRMS (EI): *m*/*z* [M+H] calcd. for $C_{21}H_{36}N_5O_5P$: 469.24541. Found: 469.24540.

Diisopropyl 6-[5-(ethoxycarbonyl)-1,3-dimethyl-1*H*-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); ^{1}H NMR ($CDCl_3$): 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 $^3J_{(PH)}$ 7.5), 8.85 (s, 1H), 9.31 (br t, 1H, $^3J_{(HH)}$ 4.0); ^{13}C NMR ($CDCl_3$): 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; ^{31}P NMR ($CDCl_3$): δ_P 7.47 (s); HRMS (EI): *m*/*z* [M+H] calcd. for $C_{23}H_{40}N_5O_5P$: 497.27671. Found: 497.27680.

Diisopropyl 2-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl-amino]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); ^{1}H NMR ($CDCl_3$): 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), 2.87 (dt, 1H, $^3J_{(HH)}$ 9.0 and 6.8), 3.26 (m, 2H), 3.75 (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 $^3J_{(PH)}$ 9.0), 7.30 (t, 1H, $^3J_{(HH)}$ 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); ^{13}C NMR ($CDCl_3$): 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; ^{31}P NMR ($CDCl_3$): δ_P 7.23 (s); HRMS (EI): *m*/*z* [M+H] calcd. for $C_{24}H_{34}N_5O_5P$: 503.22976. Found: 503.22930.

Diisopropyl 3-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl-amino]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); ^{1}H NMR ($CDCl_3$): 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 $^3J_{(PH)}$ 7.5), 7.31 (t, 1H, $^3J_{(HH)}$ 7.5),

7.50 (t, 2H, $^{3}J_{(HH)}$ 7.5), 8.06 (d, 2H, $^{3}J_{(HH)}$ 8.6), 8.93 (s, 1H), 9.24 (br t, 1H, $^{3}J_{(HH)}$ 5.4); ^{13}C NMR ($CDCl_3$): δ_C 14.14, 18.71, 23.62 (d, $^{3}J_{(PC)}$ 4.4), 23,71, 32.56 (d, $^{2}J_{(PC)}$ 5.2), 38.67, 45.89, 60.47, 70.78 (d, $^{2}J_{(PC)}$ 5.6), 101.44, 104.44, 122.26, 126.19, 128.83, 138.73, 142.05, 152.67, 154.05, 154.64, 169.05; ^{31}P NMR ($CDCl_3$): δ_P 7.36 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{25}H_{36}N_5O_5P$: 517.24541. Found: 517.24540.

Diisopropyl 4-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]butylphosphoramidate (8g). Pale beige solid; yield 98%; mp 83-84 °C; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.29 and 1.31 (2d, 12H, $^{3}J_{(HH)}$ 6.3), 1.39 (t, 3H, $^{3}J_{(HH)}$ 7.2), 1.68 (m, 2H), 1.79 (m, 2H), 1.92 (br s, 1H), 2.52 (dt, 1H, $^{3}J_{(HH)}$ 8.9 and 6.3), 2.73 (s, 3H), 2.98 (m, 2H), 3.65 (dt, 2H, $^{3}J_{(HH)}$ 6.9 and 4.8), 4.34 (q, 2H, $^{3}J_{(HH)}$ 7.2), 4.58 (dsep, 2H, $^{3}J_{(HH)}$ 6.3 and $^{3}J_{(PH)}$ 7.5), 7.32 (t, 1H, $^{3}J_{(HH)}$ 7.3), 7.49 (t, 2H, $^{3}J_{(HH)}$ 7.5), 8.08 (d, 2H, $^{3}J_{(HH)}$ 8.5), 8.90 (s, 1H), 9.25 (br t, 1H, $^{3}J_{(HH)}$ 4.5); ^{13}C NMR ($CDCl_3$): δ_C 14.13, 18.66, 23.63 (d, $^{3}J_{(PC)}$ 4.9), 23.70 (d, $^{3}J_{(PC)}$ 4.3), 27.81, 28.80 (d, $^{2}J_{(PC)}$ 6.0), 40.92, 48.42, 60.43, 70.60 (d, $^{2}J_{(PC)}$ 5.8), 101.32, 104.38, 122.21, 126.14, 128.80, 138.73, 142.00, 152.68, 154.04, 154.60, 169.02; ^{31}P NMR ($CDCl_3$): δ_P 7.47 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{26}H_{38}N_5O_5P$: 531.26106. Found: 531.26110.

Diisopropyl 6-[5-(ethoxycarbonyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]hexylphosphoramidate (8h). Beige solid; yield 82%; mp 60-63 °C; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.30 and 1.32 (2d, 12H, $^{3}J_{(HH)}$ 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, $^{3}J_{(HH)}$ 6.6 and 5.0), 4.32 (q, 2H, $^{3}J_{(HH)}$ 7.2), 4.58 (dsep, 2H, $^{3}J_{(HH)}$ 6.1 and $^{3}J_{(PH)}$ 7.5), 7.30 (t, 1H, $^{3}J_{(HH)}$ 7.2), 7.49 (t, 2H, $^{3}J_{(HH)}$ 7.2), 8.05 (d, 2H, $^{3}J_{(HH)}$ 8.0), 8.93 (s, 1H), 9.24 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 14.18, 18.76, 23.73 (d, $^{3}J_{(PC)}$ 5.0), 26.24, 26.40, 31.44 (d, $^{2}J_{(PC)}$ 6.5), 41.23, 48.73, 60.52, 70.53 (d, $^{2}J_{(PC)}$ 5.0), 101.33, 104.41, 122.36, 126.32, 128.90, 138.65, 142.18, 154.73, 168.99; ^{31}P NMR ($CDCl_3$): δ_P 7.60 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{28}H_{42}N_5O_5P$: 559.29236. Found: 559.29230.

Diisopropyl 2-[5-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-ethylphosphoramidate (8i). Oil; yield 54%; IR (KBr, ν_{max}, 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, ν_{P-O}), 897 (w), 797 (w), 761 (w); ^{1}H NMR ($CDCl_3$): δ_H 1.17 and 1.23 (2d, 12H, $^{3}J_{(HH)}$ 6.4), 1.42 (t, 3H, $^{3}J_{(HH)}$ 7.2), 2.50 (dt, 1H, $^{3}J_{(HH)}$ 9.0 and 6.2), 2.78 (m, 2H), 2.90 (dt, 2H, $^{3}J_{(HH)}$ 8.9 and 6.0), 4.45 (q, 2H, $^{3}J_{(HH)}$ 7.2), 4.49 (dsep, 2H, $^{3}J_{(HH)}$ 6.3 and $^{3}J_{(PH)}$ 7.8), 7.33 (t, 1H, $^{3}J_{(HH)}$ 7.5), 7.51 (m, 5H), 7.69 (d, 2H, $^{3}J_{(HH)}$ 8.1), 8.17 (d, 2H, $^{3}J_{(HH)}$ 8.5), 8.85 (br t, 1H, $^{3}J_{(HH)}$ 5.7), 9.00 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 14.01, 23.43 (d, $^{3}J_{(PC)}$ 4.9), 41.70, 50.34 (d, $^{2}J_{(PC)}$ 5.2), 60.49, 70.58 (d, $^{2}J_{(PC)}$ 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; ^{31}P NMR ($CDCl_3$): δ_P 7.08 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{29}H_{36}N_5O_5P$: 565.24541. Found: 565.5400.

Diisopropyl 3-[5-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-propylphosphoramidate (8j). Pale beige solid; yield 69%; mp 110-111 °C; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.22 and 1.26 (2d, 12H, $^3J_{(HH)}$ 6.2), 1.41 (t, 3H, $^3J_{(HH)}$ 7.2), 1.49 (quin, 2H, $^3J_{(HH)}$ 6.0), 2.10 (dt, 1H, $^3J_{(HH)}$ 8.7 and 6.6), 2.79 (m, 2H), 4.37 (q, 2H, $^3J_{(HH)}$ 7.1), 4.48 (dsep, 2H, $^3J_{(HH)}$ 6.0 and $^3J_{(PH)}$ 7.5), 7.31 (t, 1H, $^3J_{(HH)}$ 7.3), 7.49 (m, 5H), 7.67 (d, 2H, $^3J_{(HH)}$ 8.0), 8.20 (d, 2H, $^3J_{(HH)}$ 8.6), 8.86 (br t, 1H, $^3J_{(HH)}$ 5.1), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 14.15, 23.61 (d, $^3J_{(PC)}$ 4.1), 32.41 (d, $^2J_{(PC)}$ 5.8), 46.43, 60.53, 70.57 (d, $^2J_{(PC)}$ 6.0), 102.73, 103.73, 122.38, 126.46, 128.44, 128.64, 128.84, 128.98, 134.97, 138.75, 146.84, 152.95, 154.04, 155.15, 168.71; ^{31}P NMR ($CDCl_3$): δ_P 7.12 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{30}H_{38}N_5O_5P$: 579.26106. Found: 579.26120.

Diisopropyl 4-[5-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-butylphosphoramidate (8k). Oil; yield 53%; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.25 (m, 16H), 1.41 (t, 3H, $^3J_{(HH)}$ 7.2), 2.65 (m, 6H), 2.85 (m, 2H), 4.36 (q, 2H, $^3J_{(HH)}$ 7.1), 4.54 (dsep, 2H, $^3J_{(HH)}$ 6.3 and $^3J_{(PH)}$ 7.5), 7.30 (t, 1H, $^3J_{(HH)}$ 7.0), 7.52 (m, 5H), 7.70 (d, 2H, $^3J_{(HH)}$ 8.0), 8.21 (d, 2H, $^3J_{(HH)}$ 8.6), 8.79 (br t, 1H, $^3J_{(HH)}$ 5.4), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 14.05, 23.56 (d, $^3J_{(PC)}$ 4.1), 27.68, 28.45 (d, $^2J_{(PC)}$ 4.1), 40.56, 40.84, 48.81, 60.38, 70.38 (d, $^2J_{(PC)}$ 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; ^{31}P NMR ($CDCl_3$): δ_P 7.51 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{31}H_{40}N_5O_5P$: 593.65356. Found: 593.65438.

Diisopropyl 6-[5-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-hexylphosphoramidate (8l). Oil; yield 52%; IR (KBr, ν_{max}, 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); ^{1}H NMR ($CDCl_3$): δ_H 1.19 and 1.25 (2d, 12H, $^3J_{(HH)}$ 6.0), 1.27 (m, 2H), 1.39 (t, 3H, $^3J_{(HH)}$ 7.1), 2.47 (dt, 1H, $^3J_{(HH)}$ 9.0 and 7.8), 2.79 (m, 2H), 2.88 (dt, 2H, $^3J_{(HH)}$ 8.6 and 5.6), 4.37 (q, 2H, $^3J_{(HH)}$ 6.9), 4.48 (dsep, 2H, $^3J_{(HH)}$ 6.0 and $^3J_{(PH)}$ 7.5), 7.31 (t, 1H, $^3J_{(HH)}$ 7.5), 7.49 (m, 5H), 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); ^{13}C NMR ($CDCl_3$): δ_C 14.16, 23.59 (d, $^3J_{(PC)}$ 4.4), 29.57, 41.87, 50.49, 50.55, 60.68, 70.77 (d, $^2J_{(PC)}$ 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; ^{31}P NMR ($CDCl_3$): δ_P 7.01 (s); HRMS (EI): *m/z* [M+H] calcd. for $C_{33}H_{44}N_5O_5P$: 621.30801. Found: 621.30754.

Acknowledgements

We thank FAPERJ, CNPq and CAPES for financial support and the LDRX-UFF for data collection of compound **8j**.

References

1. El-Borai, M. A.; Rizk, H. F.; Beltagy, D. M.; El-Deeb, I. Y. *Eur. J. Med. Chem.* **2013**, *66*, 415-422. http://dx.doi.org/10.1016/j.ejmech.2013.04.043 PMid:23831694
2. Wenglowsky, S.; Ahrendt, K. A.; Buckmelter, A. J.; Feng, B.; Gloor, S. L.; Gradl, S.; Grina, J.; Hansen, J. D.; Laird, E. R.; Lunghofer, P.; Mathieu, S.; Moreno, D.; Newhouse, B.; Ren, L.; Risom, T.; Rudolph, J.; Seo, J.; Sturgis, H. L.; Voegtli, W. C.; Wen, Z. *Bioorg. Med. Chem. Lett.* **2011**, *21* (18), 5533-5537. http://dx.doi.org/10.1016/j.bmcl.2011.06.097 PMid:21802293
3. Qin, J.; Zhou, W.; Huang, X.; Dhondi, P.; Palani, A.; Aslanian, R.; Zhu, Z.; Greenlee, W.; Cohen-Williams, M.; Jones, N.; Hyde, L.; Zhang, L. *ACS Med. Chem. Lett.* **2011**, *2* (6), 471-476.
4. Patel, J. B.; Meiners, B. A.; Salama, A. I.; Malick, J. B.; U'Prichard, D. C.; Giles, R. E.; Goldberg, M. E.; Bare, T. M. *Pharmacol. Biochem. Be.* **1988**, *29* (4), 775-779. http://dx.doi.org/10.1016/0091-3057(88)90205-5
5. Mello, H.; Echevarria, A.; Bernardino, A. M.; Canto-Cavalheiro, M.; Leon, L. L. *J. Med. Chem.* **2004**, *47*, 5427-5432. http://dx.doi.org/10.1021/jm0401006 PMid:15481980
6. Ochiai, H.; Ishida, A.; Ohtani, T.; Kusumi, K.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Nakaia, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 4089-4100. http://dx.doi.org/10.1016/j.bmc.2004.05.032 PMid:15246087
7. Dyck, B.; Grigoriadis, D. E.; Gross, R. S.; Guo, Z.; Haddach, M.; Marinkovic, D.; McCarthy, J. R.; Moorjani, M.; Regan, C. F.; Saunders, J.; Schwaebe, M. K.; Szabo, T.; Williams, J. P.; Zhang, X.; Bozigian, H.; Chen, T. K. *J. Med. Chem.* **2005** *48* (12), 4100-4110. http://dx.doi.org/10.1021/jm050070m PMid:15943483
8. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61,* 4439-4449. http://dx.doi.org/10.1021/jo960316i
9. Bernardino, A. M. R.; Castro, H. C.; Frugulhetti, I. C. P. P.; Loureiro, N. I. V.; Azevedo, A. R.; Pinheiro, L. C. S.; Souza, T. M. L.; Giongo, V.; Passamani, F.; Magalhães, U. O.; Albuquerque, M. G.; Cabral, L. M.; Rodrigues, C. R. *Bioorg. Med. Chem.* **2008**, *16* (1), 313-321. http://dx.doi.org/10.1016/j.bmc.2007.09.032 PMid:17937990
10. Bernardino, A. M. R.; Azevedo, A. R.; Pinheiro, L. C. S.; Borges, J. C.; Carvalho, V. L.; Miranda, M. D.; Meneses, M. D. F.; Nascimento, M.; Ferreira, D.; Rebello, M. A.; Silva, V. A. G. G.; Frugulhetti, I. C. P. P.; *Med. Chem. Res.* **2007**,*16*, 352-369.

http://dx.doi.org/10.1007/s00044-007-9035-6
11. Leal, B.; Afonso, I. D. F.; Rodrigues, C. R.; Abreu, P. A.; Garrett, R.; Pinheiro, L. C. S.; Azevedo, A. R.; Borges, J. C.; Vegi, P. F.; Santos, C. U. C. C.; da Silveira, F. C. A.; Cabral, L. C. M.; Frugulhetti, I. C. P. P.; Bernardino, A. M. R.; Santos, D. O.; Castro, H. C. *Bioorg. Med. Chem.* **2008**, *16* (17), 8196-8204.
http://dx.doi.org/10.1016/j.bmc.2008.07.035
PMid:18701299
12. Barreiro, E. J.; Fraga, C. A. M. *Química Medicinal: As Bases Moleculares da Ação dos Fármacos*, 2ª Ed., Artmed, Porto Alegre, 2008, p. 343, 536.
13. Cheng, C. M.; Liu, X. H.; Li, Y. M.; Ma, Y.; Tan, B.; Wan, R.; Zhao, Y. F. *Orig. Life Evol. Biosph.* **2004**, *34*, 455-464.
http://dx.doi.org/10.1023/B:ORIG.0000043122.97856.79
14. Quin, L. D. *A guide to organophosphorus chemistry*, John Wiley & Sons Inc: New York, 2000, p. 2, 375.
15. Garrido-Hernandez, H.; Moon, K. D.; Geahlen, R. L.; Borch, R. F. *J. Med. Chem.* **2006**, *49* (11), 3368-3376.
http://dx.doi.org/10.1021/jm060142p
PMid:16722656 PMCid:PMC2505179
16. Voorde, J. V.; Liekens, S.; McGuigan, C.; Murziani, P. G. S.; Slusarczyk, M.; Balzarini, J.; *Biochem. Pharmacol.* **2011**, *82* (5), 441-452.
http://dx.doi.org/10.1016/j.bcp.2011.05.024
PMid:21658373
17. Wu, L. Y.; Anderson, M. O.; Toriyabe, Y.; Maung, J.; Tajon, T. Y.; Kazak, C.; Moser, M.; Berkman, J.; Campbell, C. E.; *Bioorg. Med. Chem.* **2007**, *15* (23), 7434-7443.
http://dx.doi.org/10.1016/j.bmc.2007.07.028
PMid:17869524
PMCid:PMC2065856
18. Torres, T. S.; de Macedo, W. P.; Pedrosa, L. F.; de Souza, M. C. B. V.; Ferreira, V. F.; Cunha, A. C.; Fogel, T.; Santos, F. D.; Marques, I. P.; Paixão, I. C. D. P.; Souza, M. C. *Lett. Org. Chem.* **2008**, *5*, 644-650.
http://dx.doi.org/10.2174/157017808786857615
19. Erion, M. D.; Reddy, K. R.; Boyer, S. H.; Matelich, M. C.; Gomez-Galeno, J.; Lemus, R. H.; Ugarkar, B. G.; Colby, T. J.; Schanzer, J.; Van Poelje, P. D. *J. Am. Chem. Soc.* **2004**, *126*, 5154-5163.
http://dx.doi.org/10.1021/ja031818y
PMid:15099098
20. Lehsten, D. M.; Baehr, D. N.; Lobl, T. J.; Vaino, A. R. *Org. Process. Res. Dev.* **2002**, *6*, 819-822.
http://dx.doi.org/10.1021/op025562c

21. Mello, H.; Carvalho, M. G.; Echevarria, A.; Bernardino, A. M. R.; Silva, E. F.; *Quim. Nova* **1999**, *22*, 26-30.
http://dx.doi.org/10.1590/S0100-40421999000100006
22. Taylor, E. C.; Hart, K.; *J. Am. Chem. Soc*. **1959**, *81*, 2456-2464.
http://dx.doi.org/10.1021/ja01519a045
23. Höhn, H.; Denzel, T.; Janssen, W.; *J. Heterocycl. Chem*. **1972**, *9*, 235-253.
http://dx.doi.org/10.1002/jhet.5570090212
24. Lynch, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F.; *Can. J. Chem.* **1988**, *66*, 420-428.
http://dx.doi.org/10.1139/v88-074
25. Souza, M. C.; Macedo, W. P.; Torres, T. S.; Pedrosa, L. F.; Alt, H. G. *Phosphorus Sulfur* **2006**, *181*, 1885-1893.
http://dx.doi.org/10.1080/10426500500543776
26. Pedrosa, L. F. *ChemSpider SyntheticPages* 2011, http://cssp.chemspider.com/491 (accessed Aug 13, 2013).
27. Matthews, T. P.; Klair, S.; Burns, S.; Boxall, K.; Cherry, M.; Fisher, M.; Westwood, I. M.; Walton, M. I.; McHardy, T.; Cheung, K.-M. J.; Van Montfort, R.; Williams, D.; Aherne, G. W.; Garrett, M. D.; Reader, J.; Collins, I. *J. Med. Chem.* **2009**, *52*, 4810-4819.
http://dx.doi.org/10.1021/jm900314j
PMid:19572549
28. Schenone, S.; Bruno, O.; Bondavalli, F.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Manetti, F.; Morbidelli, L.; Trincavelli, L.; Martini, C.; Lucacchini, A. *Eur. J. Med. Chem.* **2004**, *39*, 153-160.
http://dx.doi.org/10.1016/j.ejmech.2003.11.007
PMid:14987824
29. Ochiai, H.; Ishida, A.; Ohtani, T.; Kusumi, K.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 4089-4100.
http://dx.doi.org/10.1016/j.bmc.2004.05.032
PMid:15246087
30. Hamblin, J. N.; Angell, T. D. R.; Ballantine, S. P.; Cook, C. M.; Cooper, A. W. J.; Dawson, J.; Delves, C. J.; Jones, P. S.; Lindvall, M.; Lucas, F. S.; Mitchell, C. J.; Neu, M. Y.; Ranshaw, L. E.; Solanke, Y. E.; Somers, D. O.; Wiseman, J. O. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4237-4241.
http://dx.doi.org/10.1016/j.bmcl.2008.05.052
PMid:18539455
31. Pedrosa, L. F.; Souza, M. C.; Faustino, M. A. F.; Neves, M. G. P. M. S.; Silva, A. M. S.; Tomé, A. C.; Ferreira, V. F.; Cavaleiro, J. A. S. *Aust. J. Chem.* **2011**, *64*, 939-944.
http://dx.doi.org/10.1071/CH11013
32. Santos, V. M. R.; Donnici, C. L.; DaCosta, J. B. N.; Caixeiro, J. M. R. *Quim. Nova* **2007**, *30*, 159-170.
http://dx.doi.org/10.1590/S0100-40422007000100028

33. Santos, V. M. R.; DaCosta, J. B. N.; Sant'Anna, C. M. R.; Oliveira, M. C. C. *Phosphorus Sulfur* **2004**, *179*, 173-184. http://dx.doi.org/10.1080/10426500490257122
34. Pedrosa, L. F.; Macedo, W. P.; Furtado, A. C. R.; Guedes, G. P.; Pinheiro, L. C. S.; Resende, J. A. L. C.; Vaz, M. G. F.; Bernadino, A. M. R.; Souza, M. C. *Synth. Commun.* **2013**, *43*, 3373-3386. http://dx.doi.org/10.1080/00397911.2013.786092

