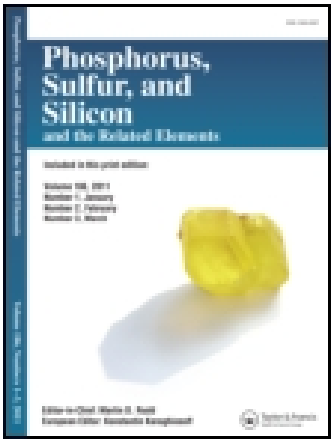

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Herbicidal Activity of O,O-Dialkyl(phenyl)-N-{1-[(6-chloropyridin-3-yl)methyl]-4-cyano-1H-1,2,3-triazol-5-yl}-1-amino-1-substitutedbenzyl-phosphonates

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SYNTHESIS AND HERBICIDAL ACTIVITY OF *O,O*-DIALKYL(PHENYL)-N-{1-[(6-CHLOROPYRIDIN-3-YL)METHYL]-4-CYANO-1*H*-1,2,3-TRIAZOL-5-YL}-1-AMINO-1-SUBSTITUTEDBENZYL-PHOSPHONATES

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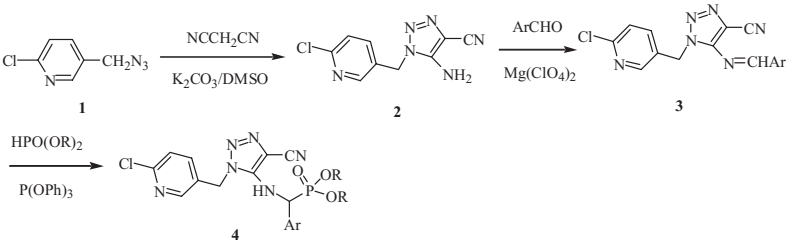
GRAPHICAL ABSTRACT



Abstract *A series of novel α-amino phosphonate derivatives containing both pyridine and 1,2,3-triazole moieties* ***4*** *were synthesized via a multi-step reaction. First, the condensation of 5-amino-1-[(6-chloropyridin-3-yl) methyl]-4-cyano-1H-1,2,3-triazole with various aromatic aldehydes in the presence of magnesium perchlorate afforded imines* ***3*** *in moderate yields; second, imines* ***3*** *reacted with dialkyl phosphites or triphenyl phosphite to give the title compounds* ***4*** *in moderate to good yields. Their structures were elucidated by spectroscopic data (IR,* ^{1}*H NMR,* ^{31}*P NMR, ESI-MS) and elemental analysis. The preliminary bioassay (in vitro) indicated that some of the title compounds* ***4*** *possessed moderate herbicidal activities against dicotyledonous plants (Brassica campestris L) at a concentration of 100 mg/L. However, compounds* ***4*** *did not exhibit herbicidal activities against Brassica campestris L at a concentration of 10 mg/L.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords α-Amino phosphonate; herbicidal activity; pyridine; triazole

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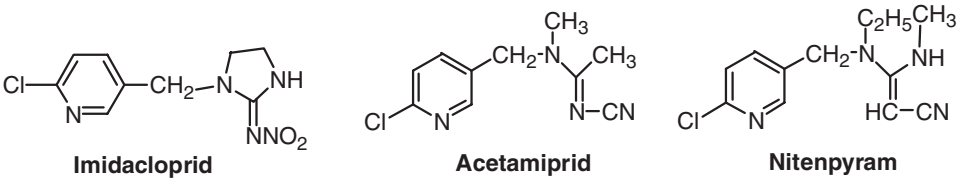


Figure 1 Structures of some commercial pyridine-containing pesticides.

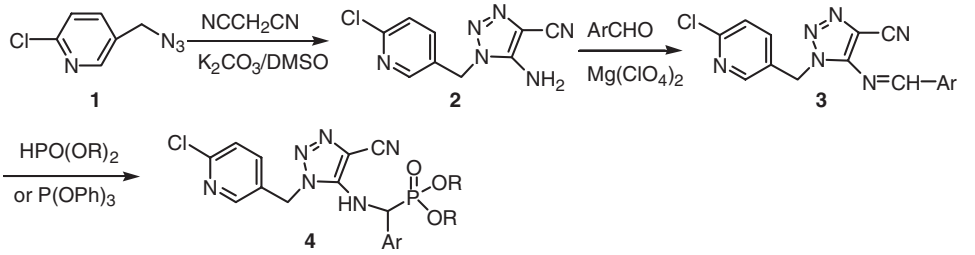
INTRODUCTION

α-Amino phosphonic acids and their ester derivatives, as bioisosteres of natural amino acids, are receiving increasing attention in medicinal chemistry and pesticide science, because some α-amino phosphonic acid derivatives have been found to exhibit a wide range of biological activities such as enzyme inhibition, antibiotics, and haptens of catalytic antibodies, fungicides, herbicides, plant regulators, and plant virucides [for example, antiviral agent against tobacco mosaic virus (TMV)].[1–7] For example, glyphosate is one of the best-selling herbicides in the world agrochemical market. Moreover, nitrogen heterocyclic compounds have played a major role in modern pesticide industry; it is reported that more than 85% of pesticides with high activity and low toxicity were nitrogen heterocyclic compounds. In the study of pharmaceuticals and agrochemicals, the introduction of pyridine into the parent compounds may improve their properties and biological activities, and many pyridine-containing compounds are known to possess a wide range of biological and pharmacological activities as well as low toxicity toward mammals.[8–11] Moreover, 5-(aminomethyl)-2-chloro-pyridine is an important pharmacophore in neonicotinoid insecticides, and many derivatives containing the pyridine nucleus have been commercialized as pesticides in plant protection (see Figure 1). Recently, click chemistry is a modular approach that uses only the most practical and reliable chemical transformations. Its applications are increasingly found in all aspects of drug discovery using bioconjugation reactions. It works well in conjunction with structure-based design and combinatorial chemistry techniques, and, through the choice of appropriate building blocks, can provide derivatives or mimics of "traditional" pharmacophores, drugs, and natural products.[12–15] However, the real power of click chemistry lies in its ability to generate novel structures that might not necessarily resemble known pharmacophores. The triazole products are more than just passive linkers; they readily associate with biological targets, through hydrogen bonding, and dipole interactions. Moreover, it is well known that many 1,2,3-triazole-related molecules play an important role in the development of agrochemicals such as insecticides, nematocides, acaricides, and plant growth regulators.[16–19] As a continuation of our research work—with an attempt to find novel biologically α-amino phosphonate derivatives containing nitrogen heterocycles,[20,21] a series of novel α-amino phosphonate derivatives containing both 1,2,3-triazole and pyridine moieties **4** were synthesized via a 1,2,3-triazole unit linking α-amino phosphonate and (6-chloropyridin-3-yl)methyl moieties. Their preliminary herbicidal activities were also evaluated in this article. The synthetic route is listed in Scheme 1.

RESULTS AND DISCUSSION

Synthesis and Structure Determination of Title Compounds 4

A series of novel α-amino phosphonate derivatives containing both pyridine and 1,2,3-triazole moieties **4** were synthesized via the multistep reactions; 2-chloro-5-(chloromethyl)-



R = Et, Ar = Ph (**4a**); R = Ph, Ar = Ph (**4b**); R = Et, Ar = 3,4-$Cl_2C_6H_3$ (**4c**); R = Ph, Ar = 3,4-$Cl_2C_6H_3$ (**4d**); R = Ph, Ar = 4-$NO_2C_6H_4$ (**4e**); R = Et, Ar = 4-$CH_3OC_6H_4$ (**4f**); R = CH_3, Ar = 3,4-$Cl_2C_6H_3$ (**4g**); R = Et, Ar = 4-ClC_6H_4 (**4h**); R = Ph, Ar = 4-ClC_6H_4 (**4i**).

Scheme 1 Synthesis route of the title compounds **4**.

pyridine reacted with sodium azide to generate 5-(azidomethyl)-2-chloro-pyridine **1**, which reacted with malononitrile in the presence of potassium carbonate to yield 5-amino-1-[(6-chloropyridin-3-yl)methyl]-4-cyano-1*H*-1,2,3-triazole **2**. When we choose the Mannich-type reaction of amine **2**, aromatic aldehydes, and dialkyl phosphites or triphenyl phosphite in the presence of magnesium perchlorate to synthesize the target compounds **4**—α-amino phosphonate derivatives containing both pyridine and 1,2,3-triazole moieties, only intermediate imines **3** were formed. Finally, imines **3** reacted with excess dialkyl phosphites or triphenyl phosphite to give **4** in moderate to good yields. Their structures were deduced from their spectral data (IR, ^{1}H NMR, ^{31}P NMR, ESI-MS) and elemental analysis. In the ^{1}H NMR spectra of **4**, the methine proton linking with the phosphonyl group was displayed as a doublet of doublets due to coupling with P and NH with coupling constants of 24 and 10 Hz, respectively. The methylene protons exhibited two doublets because of their different chemical surroundings and coupling with each other with a coupling constant of 16 Hz, while the NH proton appeared as a broad singlet with a variable chemical shift δ 6.0–7.0, in some cases, the NH signal peaks disappeared in ^{1}H NMR spectrum. For ^{31}P NMR spectra, all compounds displayed a singlet in the range δ 13–20. The IR spectra of compounds **4** showed the expected stretching absorption bands indicating the existence of the NH (3200–3300 cm^{-1}), C=N (~2230 cm^{-1}), P=O (~1225 cm^{-1}), P—O—C (~1025 cm^{-1}) moieties. The ESI-MS of compounds **4** revealed the existence of their strong molecular ion peaks, which were in accordance with the given structures of products **4**.

Herbicidal Activities

The herbicidal activity values of the title compounds **4** against *Brassica campestris L* (rape) and *Echinochloa crus-galli* (barnyard grass) have been investigated at dosages of 100 mg/L and 10 mg/L compared with the commercially available herbicide, glyphosate, according to the method described in the Supplemental Materials (available online).

CONCLUSION

In summary, we have synthesized a series of novel α-amino phosphonate derivatives containing both pyridine and 1,2,3-triazole moieties **4** via a multistep reaction. Finally,

imines **3** reacted with dialkyl phosphites or triphenyl phosphite to generate the title compounds **4** in moderate to good yields. The preliminary bioassay (in vitro) indicated that some of the title compounds **4** possessed moderate herbicidal activities against dicotyledonous plants (*Brassica campestris L*) at the concentration of 100 mg/L. However, compounds **4** did not exhibit herbicidal activities against *Brassica campestris L* at the concentration of 10 mg/L.

EXPERIMENTAL

Instruments

The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., Beijing, China) and were uncorrected. The IR spectra were recorded on a Nicolet NEXUS470 spectrometer as KBr pellets with absorption given in cm^{-1}. ^{1}H and ^{31}P NMR spectra were performed on a Varian Mercury Plus-400 (400 MHz) or Varian Mercury Plus-600 (600 MHz) spectrometer at room temperature in $CDCl_3$ with TMS and 85% H_3PO_4 as the internal and external standards, respectively. Mass spectra were measured on an Applied Biosystems API 2000 LC/MS/MS (ESI-MS) spectrometer. Elemental analysis was taken on a Vario EL III elemental analysis instrument. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were dried and redistilled before use. 5-(Azidomethyl)-2-chloro-pyridine **1** was prepared by the nucleophilic substitution of 2-chloro-5-(chloromethyl)-pyridine with sodium azide in refluxing ethanol in 95% yield according to the reported procedure.[22]

Synthesis of 5-Amino-1-[(6-chloropyridin-3-yl)methyl]-4-cyano-1*H*-1,2,3-triazole 2[23]

Compound **1** (8.4 g, 5 mmol), malononitrile (3.3 g, 5 mmol), and anhydrous potassium carbonate (20.7 g, 15 mmol) in DMSO (50 mL) were stirred at 40–50°C for 1 h (monitored by TLC). The mixture was poured into water (250 mL), and the solid was filtered, then washed with ethanol and ethyl ether, respectively. Compound **2** was obtained as a light yellow solid, yield: 90%; mp 215–217°C.

Synthesis of 5-(Arylmethyleneamino)-1-[(6-chloropyridin-3-yl)methyl]-4-cyano-1*H*-1,2,3-triazole*s* 3

Compound **2** (0.7g, 3 mmol), substituted benzaldehyde (3 mmol), magnesium perchlorate (0.03 g, 0.15 mmol) in toluene (20 mL), and DMSO (2 mL) were stirred under refluxing. The water formed was removed until no further water was formed or the reaction was complete as monitored by TLC. The mixture was concentrated under vacuum, and the crude product was purified by column chromatography on silica gel using a mixture of petroleum ether and acetone (4:1) as an eluent to give **3** as yellow solids in 69–83% yields, which can be used without further purification.

General Synthetic Procedures for *O,O*-Dialkyl(phenyl)-N-{1-[(6-chloropyridin-3-yl)methyl]-4-cyano-1*H*-1,2,3-triazol-5–yl}-1-amino-1-substitutedbenzyl Phosphonates 4

Compound 3 (1 mmol) and dimethyl phosphite, diethyl phosphite, or triphenyl phosphite (10 mmol) were stirred under reflux (90–160°C) for 3–12 h (monitored by TLC). The mixture was concentrated under vacuum, and the crude product was purified by column chromatography on silica gel using a mixture of petroleum ether and acetone (4:1) as an eluent to give **4** as white or yellow solids in 46–87% yields.

Data for 4a (R = Et, Ar = C_6H_5). Yield 81%, white solid, mp 154–156°C; IR (KBr): υ 3215 (N-H), 3024 (Ar), 2246 (CN), 1263 (P=O), 1042 (P−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.04 (t, $J = 7.2$ Hz, 3H, $CH_2\mathbf{CH_3}$), 1.30 (t, $J = 7.2$ Hz, 3H, $CH_2\mathbf{CH_3}$), 3.54–3.58 (m, 1H, OCH_2), 3.80–3.84 (m, 1H, OCH_2), 4.07–4.15 (m, 2H, OCH_2), 5.19 (dd, $J = 10.0$ Hz, $J = 23.2$ Hz, 1H, PCH), 5.42 (d, $J = 15.6$ Hz, 1H, CH_2), 5.48 (d, $J = 15.6$ Hz, 1H, CH_2), 6.75 (s, 1H, NH), 7.27–7.43 (m, 7H, ArH, PyH), 8.37 (s, 1H, PyH); ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 18.6; ESI-MS: *m/z* 498 (M+K-1, 12), 482 (M+Na-1, 59), 460 (M^+, 100). Anal. Calcd for $C_{20}H_{22}ClN_6O_3P$: C 52.12, H 4.81, N 18.24; found C 52.31, H 4.76, N 18.35.

Data for 4b (R = C_6H_5, Ar = C_6H_5). Yield 87%, light yellow crystals, mp 183–184°C; IR (KBr): υ 3262 (N-H), 3077 (ArH), 2232 (CN), 1584, 1488, 1455 (Ar), 1251 (P=O), 1158 (P−O−C), 952, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.09 (d, $J =$ 15.6 Hz, 1H, CH_2), 5.17 (d, $J = 15.6$ Hz, 1H, CH_2), 5.60 (dd, $J = 10.0$ Hz, $J = 24.2$ Hz, 1H, PCH), 6.42 (d, $J = 8.0$ Hz, 2H, ArH), 7.01–7.14 (m, 8H, ArH), 7.23–7.43 (m, 5H, ArH), 7.58 (d, $J = 7.6$ Hz, 2H, PyH), 7.95 (s, 1H, PyH); ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 243 MHz): δ 13.4; ESI-MS: *m/z* 578 (M+Na-1, 16), 556 (M^+, 100). Anal. Calcd for $C_{28}H_{22}ClN_6O_3P$: C 60.38, H 3.98, N 15.09; found C 60.10, H 3.91, N 15.24.

Data for 4c (R = Et, Ar = 3,4-$Cl_2C_6H_3$). Yield 80%, white solid, mp 183–185°C; IR (KBr): υ 3212 (N-H), 3070, 2980 (Ar), 2229 (CN), 1594, 1461, 1396, 1336 (Ar), 1238 (P=O), 1023 (P−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14 (t, $J = 7.2$ Hz, 3H, $CH_2\mathbf{CH_3}$), 1.26 (t, $J = 7.2$ Hz, 3H, $CH_2\mathbf{CH_3}$), 3.69–3.75 (m, 1H, OCH_2), 3.90–3.96 (m, 1H, OCH_2), 4.04–4.08 (m, 2H, OCH_2), 5.12 (dd, $J = 9.2$ Hz, $J = 23.8$ Hz, 1H, PCH), 5.48 (d, $J = 16.0$ Hz, 1H, CH_2), 5.57 (d, $J = 16.0$ Hz, 1H, CH_2), 6.43 (s, 1H, NH), 7.23–7.50 (m, 4H, ArH, PyH), 7.51 (d, $J = 8.4$ Hz, 1H, PyH), 8.46 (s, 1H, PyH); ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 18.6; ESI-MS: *m/z* 551 (M+Na, 5), 529 (M+1, 100). Anal. Calcd for $C_{20}H_{20}ClN_6O_3P$: C 45.35, H 3.81, N 15.86; found C 45.17, H 3.92, N 15.93.

Data for 4d (R = C_6H_5, Ar = 3,4-$Cl_2C_6H_3$). Yield 77%, light yellow solid, mp 193–195°C; IR (KBr): υ 3215 (N-H), 2986 (Ar), 2231 (CN), 1597, 1465, 1354 (Ar), 1235 (P=O), 1028 (P−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.06 (d, $J = 15.2$ Hz, 1H, CH_2), 5.19 (d, $J = 15.6$ Hz, 1H, CH_2), 5.53 (dd, $J = 10.0$ Hz, $J = 24.2$ Hz, 1H, PCH), 6.65 (s, 1H, NH), 6.74 (d, $J = 7.6$ Hz, 2H, PyH), 7.03 (d, $J = 7.2$ Hz, 2H, ArH), 7.13–7.40 (m, 10H, ArH), 7.55 (s, 1H, PyH), 8.21 (s, 1H, ArH); ^{31}P $\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 19.4; ESI-MS: *m/z* 647 (M+Na, 12), 626.5 (M+2, 81), 624.6 (M^+, 100), 403 (35), 327 (42), 274 (51). Anal. Calcd for $C_{28}H_{20}Cl_3N_6O_3P$: C 53.74, H 3.22, N 13.43; found C 53.68, H 3.15, N 13.50.

Data for 4e (R = C_6H_5, Ar = 4-$NO_2C_6H_4$). Yield 46%, white solid, mp 210–211°C; IR (KBr): υ 3210 (N-H), 2995 (Ar), 2237 (CN), 1591, 1464, 1352 (Ar), 1238 (P=O), 1040 (P−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.09 (d, $J = 15.6$ Hz, 1H, CH_2), 5.17 (d, $J = 15.6$ Hz, 1H, CH_2), 5.97 (dd, $J = 9.6$ Hz, $J = 23.6$ Hz, 1H, PCH),

6.28 (s, 1H, NH), 6.65 (d, J = 8.4 Hz, 2H, PyH), 7.09 (d, J = 8.0 Hz, 2H, ArH), 7.16 (d, J = 8.0 Hz, 2H, ArH), 7.19–7.43 (m, 10H, ArH), 8.11 (s, 1H, PyH); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, 162 MHz): δ 20.2; ESI-MS: *m/z* 622 (M+Na-1, 69), 601 (M^+, 100). Anal. Calcd for $C_{28}H_{21}ClN_7O_5P$: C 55.87, H 3.52, N 16.29; found C 55.98, H 3.31, N 16.50.

Data for 4f (R = Et, Ar = 4-MeOC$_6$H$_4$). Yield 62%, white solid, mp 169–170°C; IR (KBr): υ 3218 (N-H), 2991 (Ar), 2238 (CN), 1591, 1455, 1380 (Ar), 1235 (P=O), 1037 (P−O−C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.04 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.30 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 3.50–3.52 (m, 1H, OCH_2), 3.78 (s, 3H, OCH_3), 3.80–3.84 (m, 1H, OCH_2), 4.06–4.12 (m, 2H, OCH_2), 5.06 (dd, J = 9.0 Hz, J = 23.1 Hz, 1H, PCH), 5.42 (d, J = 16.2 Hz, 1H, CH_2), 5.51 (d, J = 16.2 Hz, 1H, CH_2), 6.00 (s, 1H, NH), 6.82 (d, J = 8.0 Hz, 2H, ArH), 7.24 (d, J = 8.4 Hz, 2H, ArH), 7.31 (d, J = 8.4 Hz, 1H, PyH), 7.48 (d, J = 8.0 Hz, 1H, PyH), 8.42 (s, 1H, PyH); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, 243 MHz): δ 20.6; ESI-MS: *m/z* 512 (M+Na-1, 18), 490 (M^+, 52), 257 (100). Anal. Calcd for $C_{21}H_{24}ClN_6O_4P$: C 51.38, H 4.93, N 17.12; found C 51.53, H 4.99, N 17.35.

Data for 4g (R = CH$_3$, Ar = 3,4-Cl$_2$C$_6$H$_3$). Yield 67%, white solid, mp 175–176°C; IR (KBr): υ 3212 (N-H), 2995 (Ar), 2241 (CN), 1585, 1452, 1376 (Ar), 1236 (P=O), 1042 (P−O−C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.54 (d, J = 10.8 Hz, 3H, OCH_3), 3.76 (d, J = 10.8 Hz, 3H, OCH_3), 5.14 (dd, J = 9.0 Hz, J = 24.0 Hz, 1H, PCH), 5.47 (d, J = 16.2 Hz, 1H, CH_2), 5.56 (d, J = 15.6 Hz, 1H, CH_2), 6.36 (s, 1H, NH), 7.22 (d, J = 7.6 Hz, 1H, PyH), 7.35 (d, J = 8.4 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.44 (d, J = 8.4 Hz, 1H, ArH), 7.50 (d, J = 7.6 Hz, 1H, PyH), 8.44 (s, 1H, PyH); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, 243 MHz): δ 20.3; ESI-MS: *m/z* 522 (M+Na-1, 12), 500 (M^+, 100). Anal. Calcd for $C_{18}H_{16}Cl_3N_6O_3P$: C 43.09, H 3.21, N 16.75; found C 42.94, H 3.07, N 16.90.

Data for 4h (R = Et, Ar = 4-ClC$_6$H$_4$). Yield 72%, white solid, mp 176–178°C; IR (KBr): υ 3241 (N-H), 3070, 2987 (Ar), 2227 (CN), 1591, 1492, 1459, 1340 (Ar), 1228 (P=O), 1019 (P−O−C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.09 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.28 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 3.61–3.63 (m, 1H, OCH_2), 3.85–3.88 (m, 1H, OCH_2), 4.05–4.12 (m, 2H, OCH_2), 5.13 (dd, J = 9.6 Hz, J = 23.7 Hz, 1H, PCH), 5.46 (d, J = 15.6 Hz, 1H, CH_2), 5.53 (d, J = 15.6 Hz, 1H, CH_2), 6.53 (s, 1H, NH), 7.27–7.33 (m, 5H, ArH, PyH), 7.48 (d, J = 7.6 Hz, 1H, PyH), 8.42 (s, 1H, PyH); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, 243 MHz): δ 19.3; ESI-MS: *m/z* 532 (M+K-1, 38), 516 (M+Na-1, 8), 494 (M^+, 100). Anal. Calcd for $C_{20}H_{21}Cl_2N_6O_3P$: C 48.50, H 4.27, N 16.97; found C 48.27, H 4.34, N 16.76.

Data for 4i (R = C$_6$H$_5$, Ar = 4-ClC$_6$H$_4$). Yield 84%, white solid, mp 110–112°C; IR (KBr): υ 3242 (N-H), 2986 (Ar), 2225 (CN), 1588, 1461, 1345 (Ar), 1231 (P=O), 1024 (P−O−C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.98 (s, 2H, CH_2), 5.49 (dd, J = 9.6 Hz, J = 24.6 Hz, 1H, PCH), 6.63 (d, J = 8.4 Hz, 2H, ArH), 6.98 (s, 1H, NH), 7.02–7.33 (m, 12H, PyH, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 8.04 (s, 1H, PyH); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, 243 MHz): δ 19.7; ESI-MS: *m/z* 612 (M+Na-1, 35), 590 (M^+, 100). Anal. Calcd for $C_{28}H_{21}Cl_2N_6O_3P$: C 56.87, H 3.58, N 14.21; found C 56.93, H 3.47, N 14.39.

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