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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF α-AMINOPHOSPHONATE DERIVATIVES CONTAINING A PYRIDAZINE MOIETY

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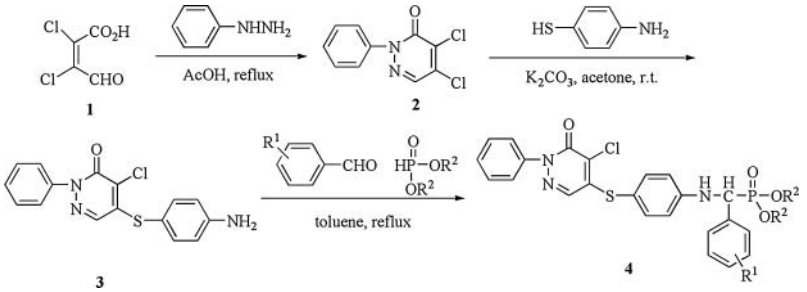
GRAPHICAL ABSTRACT



Abstract *The title compounds (**4**) were obtained by the reaction of 2-phenyl-4-chloro-5-(4-amin ophenyl)pyridazin-3(2H)-one, aldehydes, and* O,O′-dialkyl phosphite *under reflux conditions using dry toluene as a solvent.* The preliminary bioassays indicate *that the synthesized compounds have moderate to good against tobacco mosaic virus (TMV) activity. It was found that compound **4b** had a good inactivation effect in vivo against TMV, with an inhibition rate of 81.0%.*

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-Aminophosphonate derivatives; antiviral activity; pyridazine moiety; synthesis

INTRODUCTION

Pyridazine derivatives are known for their wide range of biological activities as insecticides,[1] fungicides,[2] plant virucides,[3] and as cardiotonics.[4] They also serve as important

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synthetic precursors to many active molecules due to the ease with which the four ring carbons can be functionalized. Another important class of compounds that belongs to the α-aminophosphonic acid group has been routinely employed as growth regulators,[5] fungicides,[6] plant virucides[7] and herbicides.[8] A great deal of research has been conducted in recent years on the development of suitable synthetic methodologies for biologically active α-aminophosphonates and their derivatives.[9–12] Among the various synthetic methods,[13] catalytic hydrophosphonylation of preformed imine by dialkyl phosphite is of particular interest, but this method suffers from lack of applicability to sensitive imines. To address the latter issue, and in our pursuit to prepare fluorinated heterocyclic α-aminophosphonates with potential antiviral activity against tobacco mosaic virus (TMV) in vivo, we had employed in situ–generated imine in a three-component, one-pot, Mannich-type reaction involving aldehyde, amine, and dialkyl phosphite.[14] In this article, we report the preparation of new pyridazin-3(2*H*)-one derivatives bearing α-aminophosphonate moiety and their subsequent evaluation as anti-TMV agents.

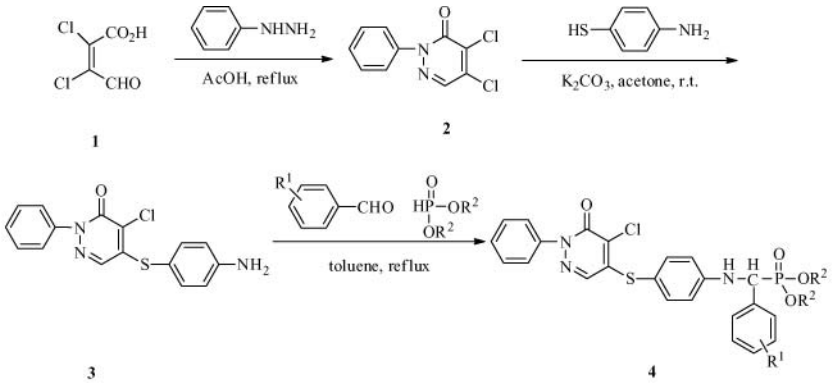
RESULTS AND DISSUSSION

4,5-Dichloro-2-phenyl-3-pyridazone was synthesized by following a published reaction of mucochloric acid with phenylhydrazine. The reaction of compound **2** with 4-aminothiophenol and anhydrous potassium carbonate in acetone then afforded 2-phenyl-4-chloro-5-(4-aminophenylthio) pyridazin-3(2*H*)-one **3**, which was finally reacted in a three-component reaction with different aldehydes and dialkyl phosphites to provide title α-aminophosphonates **4** (Scheme 1). Synthesis of **4** was executed in different solvents under varying conditions using Lewis acid catalysts, ionic liquids, microwave irradiation, and conventional heating. Under optimized conditions, the best result was obtained when the Mannich reaction was carried out for 7 h in dry toluene at its reflux temperature. The products **4a–l** were obtained in good to high chemical yield (51–79%).

The chemical structures of compounds **3** and **4a–l** were confirmed by their spectral data and elemental analysis. In the IR spectrum of **3**, the characteristic stretching frequency of N—H appeared at 3437–3342 cm^{-1}, whereas pyridazinone C&DBOND;O appeared at 1653 cm^{-1}. The chemical shifts in ^1H NMR spectrum showed a singlet at δ7.09 due to the presence of an amino group and a multiplet in the region δ 6.65–7.53 for aromatic protons. The products **4a–l** exhibited in their IR spectra the characteristic absorption bands at 3267–3300 cm^{-1} (N—H) and at 1660–1670 cm^{-1} (C=O). The ^1H NMR spectral data consisted of aromatic signals (δ 6.62–7.54) and chemical shifts near δ 4.72–4.78 appearing as a doublet of doublets due to the CH moiety adjacent to a phosphorus atom. The ^{31}P NMR spectral data showed the presence of a phosphorus atom and appeared around δ19.85–23.39 as singlets or doublets.

EXPERIMENTAL

The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr disks. ^1H, ^{13}C, ^{31}P, and ^{19}F NMR (solvent $CDCl_3$ or D_3CCOCD_3) spectra were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel.



1 2 3 4

Compound	R^1	R^2
4a	H	Et
4b	H	*n*-Pr
4c	H	*i*-Pr
4d	2-F	Et
4e	2-F	*n*-Pr
4f	2-F	*i*-Pr
4g	2-OCH_3	Et
4h	2-OCH_3	*n*-Pr
4i	2-OCH_3	*i*-Pr
4j	4-Cl	Et
4k	4-Cl	*n*-Pr
4l	4-Cl	*i*-Pr

Scheme 1 Synthetic route to title compounds **4**.

Dialkyl phosphites were prepared according to the method as described in the literature.[15] Compound **2** was prepared according to the procedure in the literature.[16] The antiviral activity assay and data for compounds **4a–l** can be found in the Supplemental Materials (available online).

2-Phenyl-4-chloro-5-(4-aminophenylthio)pyridazin-3(2*H*)-one 3

A mixture of **2** (0.96 g, 4 mmol), 4-aminothiophenol (0.5 g, 4 mmol), and anhydrous potassium carbonate (0.83 g, 6 mmol) in dry acetone (30 mL) was stirred for 2 h at room temperature. After cooling, the reaction mixture was filtered. The solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (V/V = 2:1) as the eluent to give the compound **3** (0.94 g, 71%), mp 164–166 °C; IR (ν cm^{-1}): 3437, 3342 (NH), 1653 (C=O), 1593, 1560, 1490; ^{1}H NMR (500 MHz, D_3CCOCD_3): δ 6.83–7.58 (m, 10H, Ar-H), 5.39 (s, 2H, NH_2); ^{13}C NMR (125 MHz, D_3CCOCD_3): δ 154.54, 151.58, 145.00, 141.85, 137.44, 132.40, 128.52, 128.12, 126.13, 125.55, 115.53, 109.94; Anal. Calcd. for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.48; H, 3.51; N, 12.58.

Preparation of Compound 4a–l

Compound **3** (0.20 g, 0.6 mmol) was first dissolved in dry toluene (10 mL). Aldehyde (0.6 mmol) and dialkyl phosphite (0.72 mmol) were added to the above solution, and then the mixture was refluxed for 7 h. The solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (V/V = 2:1) as the eluent to afford the corresponding pure α-aminophosphonates.

***O,O′*-Diethyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2H)-one]}(phenyl amino)-(phenyl)methylphosphonate (4a).** Mp 192–194 °C; yield 63%; IR (ν cm^{-1}): 3288 (NH), 2980, 1660 (C=O), 1593, 1519, 1490, 1234 (P=O), 1020 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65–7.53 (m, 15H, Ar-H), 5.21–5.25 (m, 1H, NH), 4.72 (dd, J = 24 Hz, 7.45 Hz, 1H, CH), 3.61–4.18 (m, 4H, $2OCH_2$), 1.30 (t, J = 7.15 Hz, 3H, CH_3), 1.09(t, J = 7.15 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.24, 16.28, 16.50, 16.55, 55.19, 56.38, 63.35, 63.39, 63.73, 63.79, 113.20, 115.05, 125.18, 127.34, 127.78, 127.82, 128.36, 128.43, 128.45, 128.78, 128.93, 133.16, 135.07, 137.42, 141.38, 144.78, 148.59, 148.71, 155.29; ^{31}P NMR (200 MHz, $CDCl_3$): δ 22.48; Anal. Calcd for $C_{27}H_{27}ClN_3O_4PS$: C, 58.32; H, 4.89; N, 7.56; Found: C, 58.08; H, 4.58; N, 7.27.

***O,O′*-Dipropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2H)-one]}(phenylamino)-(phenyl)methylphosphonate (4b).** Mp 196–199 °C; yield 58%; IR (ν cm^{-1}): 3292 (NH), 2968, 1664 (C=O), 1593, 1560, 1510, 1492, 1454, 1228 (P=O), 1004 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66–7.53 (m, 15H, Ar-H), 5.29–5.32 (m, 1H, NH), 4.74(dd, J = 24 Hz, 7.45 Hz, 1H, CH), 3.50–4.05 (m, 4H, $2OCH_2$), 1.64–1.71 (m, 2H, CH_2), 1.44–1.51 (m, 2H, CH_2), 0.91 (t, J = 7.45 Hz, 3H, CH_3), 0.78 (t, J = 7.45 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.94, 10.11, 23.74, 23.79, 23.95, 24.00, 68.79, 68.86, 69.02, 69.08, 112.97, 115.03, 125.19, 127.24, 127.82, 127.85, 128.37, 128.78, 128.90, 128.92, 133.18, 135.17, 137.40, 141.37, 144.86, 148.70, 148.80, 155.30; ^{31}P NMR (200 MHz, $CDCl_3$): δ 22.36; Anal. Calcd for $C_{29}H_{31}ClN_3O_4PS$: C, 59.64; H, 5.35; N, 7.19; Found: C, 59.68; H, 5.27; N, 7.38.

***O,O′*-Diisopropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(phenyl)methylphosphonate (4c).** Mp 182–184 °C; yield 57%; IR (ν cm^{-1}): 3278 (NH), 2978, 1662 (C=O), 1593, 1560, 1516, 1490, 1228(P=O), 999 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65–7.54(m, 15H, Ar-H), 5.23 (t, J = 8.3 Hz, 1H, NH), 4.66–4.72 (m, 2H, NCH+CH), 4.42–4.46 (m, 1H, CH), 1.33 (d, J = 6.3 Hz, 3H, CH_3), 1.25 (d, J = 6.3 Hz, 3H, CH_3), 1.24 (d, J = 6.3 Hz, 3H, CH_3), 0.90 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.19, 23.24, 23.93, 23.96, 24.24, 24.27, 24.32, 24.34, 55.59, 56.80, 72.16, 72.22, 72.65, 72.70, 112.89, 114.99, 125.20, 127.25, 127.96, 128.01, 128.27, 128.38, 128.79, 133.20, 135.41, 137.41, 141.37, 144.87, 148.83, 148.93, 155.31; ^{31}P NMR (200 MHz, $CDCl_3$): δ 20.67; Anal. Calcd for $C_{29}H_{31}ClN_3O_4PS$: C, 59.64; H, 5.35; N, 7.19; Found: C, 59.47; H, 5.17; N, 6.91.

***O,O′*-Diethyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenyl amino)-(2-fluorophenyl)methylphosphonate (4d).** Mp 206–208 °C; yield 66%; IR (ν cm^{-1}): 3298 (NH), 2978, 1668 (C=O), 1635, 1593, 1558, 1512, 1490, 1456, 1246 (P=O), 1026 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69–7.53 (m, 14H, Ar-H), 5.31–5.38 (m, 1H, NH), 5.15 (dd, J = 24 Hz, 8.6 Hz, 1H, CH), 3.68–4.26 (m, 4H, $2OCH_2$), 1.33 (t, J = 7.15 Hz, 3H, CH_3), 1.08 (t, J = 6.85 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.16, 16.21, 16.51, 16.56, 47.31, 48.52, 63.58, 63.63, 63.80, 63.86, 113.50, 114.79, 115.44, 115.62, 122.77, 122.88, 124.92, 125.19, 127.35, 128.38, 128.79, 130.05,

130.07, 130.12, 130.13, 133.15, 137.52, 141.36, 144.74, 148.18, 148.30, 155.30; ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.79 ($J = 4.6$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ –118.04; Anal. Calcd for $C_{27}H_{26}ClFN_3O_4PS$: C, 56.50; H, 4.57; N, 7.32; Found: C, 56.81; H, 4.21; N, 7.14.

***O,O′*-Dipropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(2-fluorophenyl)methylphosphonate (4e).** Mp 201–203 °C; yield 67%; IR (ν cm^{-1}): 3286 (NH), 2968, 1668 (C=O), 1595, 1560, 1512, 1490, 1456, 1228 (P=O), 1004 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67–7.52 (m, 14H, Ar-H), 5.32–5.35 (m, 1H, NH), 5.15 (dd, $J = 24.6$ Hz, 8.55 Hz, 1H, CH), 3.55–4.11 (m, 4H, $2OCH_2$), 1.41–1.72 (m, 4H, $2CH_2$), 0.91 (t, $J = 7.45$ Hz, 3H, CH_3), 0.75 (t, $J = 7.45$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.84, 10.09, 23.70, 23.74, 23.95, 24.00, 47.17, 48.41, 69.04, 69.10, 113.38, 114.78, 115.41, 115.58. 122.91, 123.02, 124.90, 125.19, 127.32, 128.37, 128.79, 130.02, 130.07, 133.16, 137.50, 141.36, 144.78, 148.26, 148.38, 155.30, 159.82, 161.73; ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.74 ($J = 4.6$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: -118.17; Anal. Calcd for $C_{29}H_{30}ClFN_3O_4PS$: C, 57.85; H, 5.02; N, 6.98; Found: C, 57.78; H, 5.02; N, 6.49.

***O,O′*-Diisopropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(2-fluorophenyl)methylphosphonate (4f).** Mp 228–230 °C; yield 59%; IR (ν cm^{-1}): 3284 (NH), 2978, 1668 (C=O), 1595, 1560, 1508, 1490, 1456, 1228 (P=O), 993 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68–7.51 (m, 14H, Ar-H), 5.23–5.38 (m, 1H, NH), 5.07 (dd, $J = 24.6$ Hz, $J = 8.6$Hz, H, CH), 4.77–4.80(m, 1H, CH), 4.41–4.45 (m, 1H, CH), 1.34 (d, $J = 6.3$ Hz, 3H, CH_3), 1.29 (d, $J = 6.3$ Hz, 3H, CH_3), 1.23 (d, $J = 6.3$ Hz, 3H, CH_3), 0.85 (d, $J = 6.3$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.05, 23.10, 23.96, 24.00, 24.26, 47.57, 48.80, 72.38, 72.44, 72.76, 72.82, 113.18, 114.71, 115.33, 115.51, 123.23, 123.34, 124.80, 125.20, 127.29, 128.38, 128.79, 129.85, 129.90, 133.18, 137.50, 141.37, 144.81, 148.44, 148.55, 155.30, 159.89, 161.91; ^{31}P NMR (200 MHz, $CDCl_3$): δ 19.99 ($J = 4.58$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -118.01; Anal. Calcd for $C_{29}H_{30}ClFN_3O_4PS$: C, 57.85; H, 5.02; N, 6.98; Found: C, 57.98; H, 5.24; N, 6.72.

***O,O′*-Diethyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenyl amino)-(2-methoxyphenyl)methylphosphonate (4g).** Mp 205–207 °C; yield 79%; IR (ν cm^{-1}): 3280 (NH), 2980, 1664 (C=O), 1635, 1593, 1558, 1514, 1490, 1458, 1246 (P=O), 1026 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67–7.53 (m, 14H, Ar-H), 5.36–5.42 (m, 2H, NCH+NH), 3.56–4.22 (m, 7H, $2OCH_2$+OCH_3), 1.32 (t, $J = 7.45$ Hz, 3H, CH_3), 1.02 (t, $J = 7.45$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.19, 16.24, 16.55, 16.60, 47.08, 48.31, 55.87, 63.16, 63.21, 63.59, 63.64, 110.61, 112.53, 114.77, 121.25, 123.60, 125.19, 127.12, 128.16, 128.36, 128.78, 129.50, 133.25, 137.40, 141.36, 145.03, 148.69, 148.80, 155.32, 157.18, 157.23; ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.39; Anal. Calcd for $C_{28}H_{29}ClN_3O_5PS$: C, 57.39; H, 4.99; N, 7.17; Found: C, 57.68; H, 5.01; N, 7.00.

***O,O′*-Dipropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(2-methoxyphenyl)methylphosphonate (4h).** Mp 193–195 °C; yield 72%; IR (ν cm^{-1}): 3296 (NH), 2966, 1670 (C=O), 1635, 1593, 1560, 1519, 1490, 1456, 1230 (P=O), 997 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67–7.53 (m, 14H, Ar-H), 5.37–5.43 (m, 1H, NCH+NH), 3.43–4.10 (m, 7H, $2OCH_2$+OCH_3), 1.36–1.73 (m, 4H, $2CH_2$), 0.92 (t, $J = 7.45$ Hz, 3H, CH_3), 0.73 (t, $J = 7.45$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.88, 10.14, 23.69, 23.73, 23.96, 24.01, 47.00, 48.23, 55.81, 68.60, 68.66,

68.86, 68.92, 110.55, 112.49, 114.74, 121.24, 123.71, 125.19, 127.12, 128.20, 128.24, 128.36, 128.78, 129.45, 133.24, 137.40, 137.40, 141.37, 145.03, 148.70, 148.81, 155.32, 157.11, 157.16; ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.35; Anal. Calcd for $C_{30}H_{33}ClN_3O_5PS$: C, 58.68; H, 5.42; N, 6.84; Found: C, 58.71; H, 5.22; N, 6.82.

***O,O′*-Diisopropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(2-methoxyphenyl)methylphosphonate (4i).** Mp 222–224 °C; yield 51%; IR (ν cm^{-1}): 3300 (NH), 2976, 1664 (C=O), 1595, 1560, 1519, 1490, 1458, 1228 (P=O), 1002 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67–7.53(m, 14H, Ar-H), 5.29–5.35 (m, 1H, NCH+NH), 4.74–4.80 (m, 1H, OCH), 4.34–4.40 (m, 1H, OCH), 3.93 (s, 3H, OCH_3), 1.34 (d, J = 6.3 Hz, 3H, CH_3), 1.28 (d, J = 6.3 Hz, 3H, CH_3), 1.21 (d, J = 6.3 Hz, 6H, $2CH_3$), 0.76 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.92, 22.97, 23.99, 24.03, 24.25, 24.28, 24.39, 24.41, 47.39, 48.63, 55.78, 71.83, 71.88, 72.37, 72.43, 110.57, 112.36, 114.70, 121.19, 124.13, 125.20, 127.14, 128.17, 128.21, 128.34, 128.78, 129.28, 133.25, 137.39, 141.39, 145.04, 148.87, 148.97, 155.32, 157.28; ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.78; Anal. Calcd for $C_{30}H_{33}ClN_3O_5PS$: C, 58.68; H, 5.42; N, 6.84; Found: C, 58.85; H, 5.12; N, 6.60.

***O,O′*-Diethyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(4-chlorophenyl)methylphosphonate (4j).** Mp 206–208 °C; yield 58%; IR (ν cm^{-1}): 3282 (NH), 2983, 1662 (C=O), 1593, 1521, 1489, 1234 (P=O), 1016 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62–7.53 (m, 14H, Ar-H), 5.24–4.27 (m, 1H, NH), 4.70 (dd, J = 24 Hz, 6.85 Hz, 1H, NCH), 3.71–4.81 (m, 4H, $2OCH_2$), 1.15 (t, J = 6.9 Hz, 3H, CH_3), 1.30 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.32, 16.37, 16.52, 16.57, 54.61, 55.83, 63.57, 63.62, 63.80, 63.84, 113.56, 115.04, 125.18, 127.39, 128.41, 128.81, 129. 09, 129.12, 129.16, 133.15, 133.72, 134.29, 137.48, 141.34, 144.70, 148.33, 148.45, 155.30; ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.80; Anal. Calcd for $C_{27}H_{26}Cl_2N_3O_4PS$: C, 54.92; H, 4.44; N, 7.12; Found: C, 55.07; H, 4.44; N, 7.08.

***O,O′*-Dipropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(4-chlorophenyl phenyl)methylphosphonate (4k).** Mp 156–158 °C; yield 67%; IR (ν cm^{-1}): 3288 (NH), 2970, 1666 (C=O), 1593, 1516, 1489, 1232 (P=O), 999 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63–7.53 (m, 14H, Ar-H), 5.20–4.39 (m, 1H, NH), 4.70 (dd, J = 24 Hz, 6.85 Hz, 1H, NCH), 3.60–4.08 (m, 4H, $2OCH_2$), 1.49–1.56 (m, 4H, $2CH_2$), 0.91 (t, J = 7.45 Hz, 3H, CH_3), 0.81 (t, J = 7.45 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.96, 10.09, 23.80, 23.84, 23.95, 24.00, 54.57, 55.78, 68.98, 69.05, 69.12, 113.50, 115.02, 125.18, 127.37, 128.40, 128.80, 129.13, 133.14, 133.86, 134.25, 137.47, 141.35, 144.71, 148.39, 148.49, 155.29; ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.70; Anal. Calcd for $C_{29}H_{30}Cl_2N_3O_4PS$: C, 56.31; H, 4.89; N, 6.79; Found: C, 56.39; H, 4.52; N, 6.49.

***O,O′*-Diisopropyl-4{[(2-phenyl-4-chloro-5-thio)pyridazin-3(2*H*)-one]}(phenylamino)-(4-chlorophenyl phenyl)methylphosphonate (4l).** Mp 198–200 °C; yield 63%; IR (ν cm^{-1}): 3267 (NH), 2978, 1664 (C=O), 1593, 1516, 1489, 1234 (P=O), 993 (P-O-C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62–7.53 (m, 14H, Ar-H), 5.21–5.22 (m, 1H, NH), 4.48–4.74 (m, 3H, NCH+2CH), 1.33 (d, J = 6.3 Hz, 3H, CH_3), 1.28 (d, J = 6.3 Hz, 3H, CH_3), 1.24 (d, J = 6.3 Hz, 3H, CH_3), 0.98 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.40, 23.44, 23.93, 23.96, 24.26, 55.08, 56.29, 72.42, 72.48, 72.66, 72.72, 113.31, 114.98, 125.19, 127.34, 128.40, 128.80, 128.96, 129.25, 129.29, 133.16, 134.07, 134.15, 137.46, 141.35, 144.76, 148.59, 148.70, 155.30; ^{31}P NMR (200 MHz, $CDCl_3$): δ 19.85; Anal. Calcd for $C_{29}H_{30}Cl_2N_3O_4PS$: C, 56.31; H, 4.89; N, 6.79; Found: C, 56.18; H, 4.72; N, 6.67.

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