

## The Synthesis and Biological Activities of *N*-(3-pyridylmethyl) *N'*-(trans-2-thio-4-substitutedphenyl)-5,5-dimethyl-1,3,2-dioxaphosphinane-2-yl)thioureas

De-Qing Shi  
Abudhaim Feras  
Y. Hamdan  
Yi Liu  
Xiao-Song Tan

Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, Hubei, P. R. China

*A series of novel title compounds were synthesized by the addition reaction of trans 2-isothiocyano-4-substitutedphenyl-5, 5-dimethyl-1,3,2-dioxaphosphinane 2-sulfide to 3-aminomethylpyridine or 2-chloro-5-amino methylpyridine. Their structures were confirmed by <sup>1</sup>H NMR, <sup>31</sup>P NMR, IR, MS, and elemental analyses. Results of preliminary bioassay showed that all new compounds possess good fungicidal activity and insecticidal activity to some extent.*

**Keywords** Biological activity; 1,3,2-dioxaphosphinane; substituted pyridine; synthesis; thiourea

### INTRODUCTION

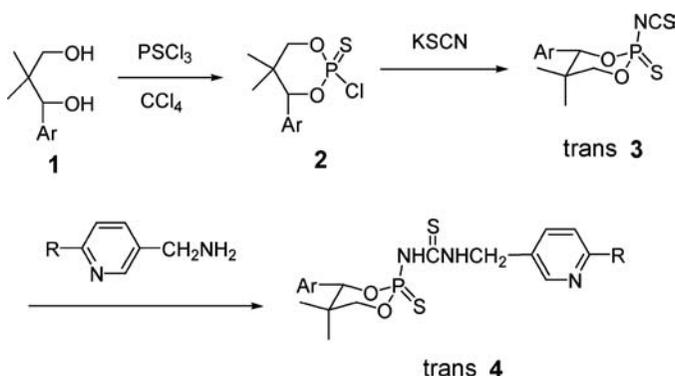
Neonicotinoid insecticides as nicotinic acetylcholine receptor inhibitors have attracted increasing attention because of their safety, low toxicity, and wide and high activities.<sup>1,2</sup> A lot of new insecticides, such as imidacloprid and acetamiprd, have been commercialized. It was found that most of the biological active nicotinic compounds contain the 3-aminomethylpyridine moiety.<sup>3</sup> Thiourea derivatives show wide biological activities, such as fungicidal, herbicidal, and insecticidal activities;

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Address correspondence to De-Qing Shi, Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, Hubei, 430079, P. R. China. E-mail: chshidq@yahoo.com.cn

however, because of their weak solubility and penetrate ability in an organism, phosphoryl thiourea derivatives have attracted many chemists' interest.<sup>4,5</sup> As a continuation of our research work, we designed and synthesized a number of novel asymmetric cyclophosphorylthiourea derivatives containing substituted pyridine. The synthetic route is shown in Scheme 1. Structures of the products were characterized by <sup>1</sup>H NMR, <sup>31</sup>P NMR, IR, MS, and elemental analyses. Results of the preliminary bioassay showed that the new compounds possess potential fungicidal activities and insecticidal activities to some extent.



SCHEME 1

## RESULTS AND DISCUSSION

### The Preparation of the Title Compounds 4

The title compounds **4** were synthesized by the multistep route outlined in Scheme 1.

Diols **1** react with  $\text{PSCl}_3$  in the presence of  $\text{CCl}_4$  as a solvent to obtain 2-chloro-4-substitutedphenyl-5, 5-dimethyl-1,3,2-dioxaphosphinane 2-sulfide **2**; the ratios of cis and trans isomers of compounds **2** are 1:1 approximatively,<sup>6</sup> **2** reacted with potassium thiocyanate to yield 2-isothiocyano-4-substitutedphenyl-5, 5-dimethyl-1,3,2-dioxaphosphinane 2-sulfide **3**, which are the mixture of cis and trans isomers. Trans isomers **3** can be obtained by fractional recrystallization with the mixture of ethyl ether and petroleum ether. The addition reaction of trans isomers **3** to 3-aminomethylpyridine or 2-chloro-5-aminomethylpyridine yield the trans target products **4**.

## Structures and Configuration of the Intermediates 3 and Target Compounds 4

We easily can distinguish trans isomers **2** from cis isomers by the means of IR and  $^{31}\text{P}$  NMR. For IR, the stretching absorption band of the NCS group in trans isomers usually appears around  $1972\text{ cm}^{-1}$ , in contrast to about  $1965\text{ cm}^{-1}$  for a cis isomer. For  $^{31}\text{P}$  NMR spectra, the phosphorus signal of the cis isomer (45–48 ppm) is downfield relative to that of trans isomer (36–38 ppm), which can be due to the smaller O-P-O bond angle in cis isomers.<sup>7</sup>

Structures of target compounds **4** were confirmed by  $^1\text{H}$  NMR,  $^{31}\text{P}$  NMR, IR spectra, MS, and elemental analyses.

In  $^1\text{H}$  NMR spectra, the two methyl protons of 1,3,2-dioxaphosphinane appeared as two singlets, due to the two methyl groups lying in different magnetic environments. The two methylene protons of 1,3,2-dioxaphosphinane doublet and multiplicity because of their different magnetic surroundings and coupling with each other or with the adjacent phosphorus atom with the coupling constant of 10.6 Hz and 26 Hz, respectively; while the 4-position axial proton displayed singlets without coupling with the phosphorus atom. The protons of the methylene group linking with pyridine appears as multiple peaks. For  $^{31}\text{P}$  NMR spectra, the phosphorus atom of all compounds shows one set of a single peak, giving chemical shifts about 53 ppm, which is also consistent with the trans configuration of phosphorylthiourea.<sup>4</sup> IR spectra of all compounds showed normal stretching absorption bands, indicating the existence of the N-H ( $\sim 3150\text{ cm}^{-1}$ ), P=S ( $\sim 700\text{ cm}^{-1}$ ), P-O-C ( $\sim 1000\text{ cm}^{-1}$ ), C=S ( $\sim 1250\text{ cm}^{-1}$ ), and C=N ( $\sim 1500\text{ cm}^{-1}$ ) moiety. The EI mass spectra of compound **4** revealed the existence of the molecular ion peaks or anticipant fragmentation peaks, which were in good accordance with the given structures of products.

## Biological Activities

Preliminary bioassay results show that these title compounds possess moderate insecticidal and good fungicidal activities. For example, the death ratio of *Aphis glycine Matsumura* by compound **4b**, **4c**, and **4g** is, respectively, 76.7, 58.3, and 52.4% at the concentration of  $2.5 \times 10^{-4}$ , while the death ratio of *Tetranychus viennensis zacher* by compound **4a**, **4c**, and **4e** is, respectively, 41.9, 52.8, and 31.7% at the same concentration. The fungicidal activities of the target compounds are listed in Table I. Results show that these compounds are more effective to *Botrytis Cinerea* fungi than to other fungi. In the meantime, the compounds **4a** and **4i** are more effective to these fungi than other

**TABLE I Fungicidal Activities of Target Compounds 4 (The Plate Method, C = 50 ppm, Inhibition %)**

Fungi Kind	<i>Fusarium oxysporium</i>	<i>Rhizoctonia solani</i>	<i>Botrytis cinerea</i>	<i>Gibberella zeae</i>	<i>Botryosphaeria berengeriana</i>	<i>Bopolaris maydis</i>
<b>4a</b>	71.43	86.73	100	84.62	85.71	87.50
<b>4b</b>	57.14	79.59	100	57.69	64.29	50.00
<b>4c</b>	57.14	90.82	100	57.69	85.71	75.00
<b>4d</b>	61.90	73.47	84.21	69.23	78.57	75.00
<b>4e</b>	57.14	77.55	94.74	46.15	85.71	62.50
<b>4f</b>	61.90	85.71	100	61.54	85.71	62.50
<b>4g</b>	47.62	88.78	100	57.69	92.86	87.50
<b>4h</b>	61.90	92.86	100	76.92	78.57	93.75
<b>4i</b>	66.67	87.76	100	88.46	85.71	87.50
<b>4j</b>	23.81	83.67	100	46.15	71.43	62.50

compounds. Further structure and activity relationship studies are under way and will be reported in due course.

## EXPERIMENTAL

<sup>1</sup>H NMR and <sup>31</sup>P NMR spectra were recorded with a Varian Mercury-Plus 400 spectrometer with TMS and 85% H<sub>3</sub>PO<sub>4</sub> as the internal and external reference, respectively, and DMSO-d<sub>6</sub> as the solvent, while mass spectra were obtained with a Finnigan Tracems2000 spectrometer using the EI method. IR spectra were measured by a Nicolet Nexus 470 spectrometer. Elemental analyses were performed with a Elementar Vario ELIII CHNSO elementary analyzer. Melting points were determined with a WRS-1B digital melting point apparatus, and the thermometer was uncorrected.

Reagents and solvents were available commercially and, purified according to conventional methods before use. Diols **1** were prepared according to references.<sup>10</sup> 2-chloro-5-aminomethylpyridine was obtained in the reported method.<sup>11</sup>

### 1. The Synthesis of 2-Chloro-4-Substitutedphenyl-5, 5-Dimethyl-1, 3,2-Dioxaphosphinane 2-Sulfide<sup>8</sup>

0.01 mol of diol **1**, 0.01 mol of PSCl<sub>3</sub>, and 20 mL of CCl<sub>4</sub> were added to a 50-mL three-necked reaction flask. The mixture was stirred under reflux for 4 h (monitored by TLC). The solvent was removed under reduced pressure, and the residue was dissolved in 25 ml CHCl<sub>3</sub>, washed with NaHCO<sub>3</sub> solution twice, and then washed with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After removing the solvent under

a reduced pressure; the crude product was obtained. The ratio of cis and trans isomer of products were determined by  $^1\text{H}$  NMR and  $^{31}\text{P}$  NMR.

## 2. General Procedure for the Synthesis of 2-Isothiocyano-4-substitutedphenyl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-Sulfide **3**<sup>4</sup>

12.5 mmol of compound **2** and 20 mL of anhydrous  $\text{CH}_3\text{CN}$  were added to a 50-mL three-necked flask. Twenty five mmol of KSCN was added under stirring, and the mixture was heated to 50–60°C for 20 h. The solid was filtered. After removing the solvent under reduced pressure, 30 mL of ethyl ether was added. The solid was filtered, and the filtrate was concentrated to obtain a crude product, which was fractional recrystallized with the mixture of ethyl ether and petroleum ether to give the pure trans compound **3**; yield: 36–64%.

## 3. General Procedure for the Synthesis of N-(3-pyridylmethyl) N'-(trans-2-thio-4-substitutedphenyl-5,5-dimethyl-1,3,2-dioxaphosphinane-2-yl) Thioureas **4**

Two mmol of trans compound **3** and 10 mL of anhydrous chloroform were added to a 50-mL flask. Two mmol of 3-aminomethylpyridine or 2-chloro-5-aminomethylpyridine in 10 mL of anhydrous chloroform was added dropwise to the reaction mixture. The reaction mixture was stirred at r.t. for 2–4 h (monitored by TLC). After removing the solvent, 20 mL of anhydrous ethyl ether was added; the solid formed was filtered and recrystallized by the mixture of ethanol and ethyl ether to give the pure compound **4**.

**4a** (Ar = phenyl, R = H): white solid, m.p. 168.3–168.7°, yield 78%;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 0.81 (s, 3H,  $\text{CH}_3$ ), 1.10 (s, 3H,  $\text{CH}_3$ ), 4.02 (dd, 1H,  $^2J_{\text{H-H}} = 11.2$  Hz,  $^3J_{\text{P-H}} = 26$  Hz,  $\text{CH}_2\text{OP}$ ), 4.38 (d, 1H,  $^2J_{\text{H-H}} = 10.0$  Hz,  $\text{CH}_2\text{OP}$ ), 4.82–4.86 (m, 2H,  $\text{NCH}_2$ ), 5.33 (s, 1H,  $\text{CH-Ar}$ ), 7.10–7.13 (m, 1H,  $\beta$ -H on pyridine), 7.26–7.40 (m, 6H,  $\text{Ar-H} + \text{NH}$ ), 7.57 (d, 1H,  $^3J_{\text{H-P}} = 7.6$  Hz,  $\gamma$ -H on pyridine), 8.11 (s, 1H,  $\alpha$ -H on pyridine), 8.47–8.50 (m, 1H,  $\alpha$ -H on pyridine), 8.53 (s, 1H,  $\text{NH}$ );  $^{31}\text{P}$  NMR (DMSO- $d_6$ )  $\delta$  = 53.06; Anal. calcd. For  $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_2\text{PS}_2$  (407): C, 53.07; H, 5.41; N, 10.32. Found: C, 53.44; H, 5.68; N, 10.03.

**4b** (Ar = 3-fluorophenyl, R = H): white solid, m.p. 151.9–152.1°C, yield 62%;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 0.79 (s, 3H,  $\text{CH}_3$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 4.05 (dd, 1H,  $^2J_{\text{H-H}} = 10.4$  Hz,  $^3J_{\text{P-H}} = 26$  Hz,  $\text{CH}_2\text{OP}$ ), 4.38 (d, 1H,  $^2J_{\text{H-H}} = 10.4$  Hz,  $\text{CH}_2\text{OP}$ ), 4.67–4.75 (m, 2H,  $\text{NCH}_2$ ), 5.57 (s, 1H,  $\text{CH-Ar}$ ), 7.12–7.36 (m, 4H,  $\text{Ar-H} + \beta$ -H on pyridine), 7.44–7.50 (m, 1H,  $\text{Ar-H}$ ),

7.70 (d, 1H,  $^3J_{\text{H-P}} = 7.6$  Hz,  $\gamma$ -H on pyridine), 8.45–8.47 (m, 1H,  $\alpha$ -H on pyridine), 8.53 (s, 2H,  $\alpha$ -H on pyridine + NH), 9.71 (s, 1H, NH);  $^{31}\text{P}$  NMR (DMSO- $d_6$ )  $\delta = 52.92$ ; MS,  $m/z$  (%) 425 ( $M^+$ , 0.2), 262 (8.1), 162 (22.4), 147 (44.5), 145 (45.0), 132 (60.5), 123 (53.0), 114 (36.5), 108 (100), 94 (47.6), 78 (54.4), 62. (47.1), 54 (64.5), 38 (95.0); Anal. calcd. for  $\text{C}_{18}\text{H}_{21}\text{FN}_3\text{O}_2\text{PS}_2$  (425): C, 50.82; H, 4.94; N, 9.88. Found: C, 50.77; H, 5.20; N, 10.15.

**4c** (Ar = 4-nitrophenyl, R = H): pale yellow solid, m.p. 147.7–148.2°C, yield 34.7%;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 0.77$  (s, 3H,  $\text{CH}_3$ ), 0.92 (s, 3H,  $\text{CH}_3$ ), 4.30 (dd, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $^3J_{\text{P-H}} = 25.6$  Hz,  $\text{CH}_2\text{OP}$ ), 4.46–4.76 (m, 3H,  $\text{NCH}_2 + \text{CH}_2\text{OP}$ ), 5.58 (s, 1H,  $\text{CH-Ar}$ ), 7.36–7.60 (m, 4H, Ar-H), 7.73–7.75 (d, 1H,  $^3J_{\text{H-P}} = 8.0$  Hz,  $\beta$ -H on pyridine), 7.91–7.93 (d, 1H,  $^3J_{\text{H-P}} = 6.5$  Hz,  $\gamma$ -H on pyridine), 8.22–8.32 (m, 2H,  $\alpha$ -H on pyridine + NH), 8.46 (s, 1H,  $\alpha$ -H on pyridine), 9.61 (s, 1H, NH);  $^{31}\text{P}$  NMR (DMSO- $d_6$ )  $\delta = 53.08$ ; Anal. calcd. for  $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_4\text{PS}_2$  (452): C, 47.79; H, 4.65; N, 12.39. Found: C, 47.51; H, 4.88; N, 12.50.

**4d** (Ar = 4-chlorophenyl, R = H): white solid, m.p. 165.5–166.1°C, yield 39.5%;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 0.74$  (s, 3H,  $\text{CH}_3$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 4.05 (dd, 1H,  $^2J_{\text{H-H}} = 11.2$  Hz,  $^3J_{\text{P-H}} = 25.6$  Hz,  $\text{CH}_2\text{OP}$ ), 4.42 (d, 1H,  $^2J_{\text{H-H}} = 10.4$  Hz,  $\text{CH}_2\text{OP}$ ), 4.69–4.75 (m, 2H,  $\text{NCH}_2$ ), 5.55 (s, 1H,  $\text{CH-Ar}$ ), 7.34 (d, 2H,  $^3J_{\text{H-H}} = 8.4$  Hz, Ar-H), 7.49 (d, 2H,  $^3J_{\text{H-H}} = 8.0$  Hz, Ar-H), 7.70 (d, 1H,  $^3J_{\text{H-H}} = 7.2$  Hz,  $\beta$ -H on pyridine), 8.46 (d, 2H,  $^3J_{\text{H-H}} = 4.8$  Hz,  $\alpha$ -H,  $\gamma$ -H on pyridine), 8.53 (s, 1H,  $\alpha$ -H on pyridine), 9.67 (s, 1H, NH);  $^{31}\text{P}$  NMR (DMSO- $d_6$ )  $\delta = 53.01$ ; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) 3260 (N-H), 1509 (C=N), 653 (P=S), 1013 and 982 (P–O–C), 1266 (C=S); MS,  $m/z$  (%) 443 ( $M + 2$ , 4), 441 ( $M^+$ , 7.6), 335 (17), 333 (41.8), 280 (31.3), 278 (67.3), 142 (19.9), 138 (26.9), 136 (25.8), 124 (16.4), 110 (19.6), 89 (22.8), 78 (34.2), 62 (28.3), 55 (45.0), 40 (100), 38 (86.8); Anal. calcd. for  $\text{C}_{18}\text{H}_{21}\text{ClN}_3\text{O}_2\text{PS}_2$  (441.5): C, 48.92; H, 4.76; N, 9.51. Found: C, 48.81; H, 4.54; N, 9.25.

**4e** (Ar = 2-chlorophenyl, R = H): pale yellow solid, m.p. 140.3–141.7°C, yield 44%;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 0.76$  (s, 3H,  $\text{CH}_3$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 4.10 (dd, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $^3J_{\text{P-H}} = 26.2$  Hz,  $\text{CH}_2\text{OP}$ ), 4.53 (d, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $\text{CH}_2\text{OP}$ ), 4.85 (s, 2H,  $\text{NCH}_2$ ), 5.95 (s, 1H,  $\text{CH-Ar}$ ), 7.35–7.50 (m, 5H, Ar-H +  $\beta$ -H on pyridine), 8.23 (m, 1H,  $^3J_{\text{H-H}} = 6.2$  Hz,  $\gamma$ -H on pyridine), 8.67–8.75 (m, 2H,  $\alpha$ -H on pyridine), 8.99 (s, 1H, NH), 10.17 (s, 1H, NH); IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) 3178 (N-H), 1509 (C=N), 672 (P=S), 1035 and 987 (P–O–C), 1218 (C=S); MS,  $m/z$  (%) 443 ( $M + 2$ , 1.9), 441 ( $M^+$ , 2.5), 382 (7.7), 298 (12.2), 142 (18.0), 138 (23.3), 114 (34.7), 95 (19.4), 89 (21.7), 78 (19.6), 75 (18.3), 62 (46.3), 54 (66.9), 40 (100); Anal. calcd. for  $\text{C}_{18}\text{H}_{21}\text{ClN}_3\text{O}_2\text{PS}_2$  (441.5): C, 48.92; H, 4.76; N, 9.51. Found: C, 48.67; H, 4.98; N, 9.73.

**4f** (Ar = phenyl, R = Cl): yellow solid, m.p. 153.6–155.3°C, yield 72%;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  = 0.74 (s, 3H,  $\text{CH}_3$ ), 0.98 (s, 3H,  $\text{CH}_3$ ), 4.05 (dd, 1H,  $^3J_{\text{H-P}} = 10.6$  Hz,  $^2J_{\text{H-H}} = 26$  Hz,  $\text{CH}_2\text{OP}$ ), 4.41 (d, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $\text{CH}_2\text{OP}$ ), 4.70–4.74 (m, 2H,  $\text{NCH}_2$ ), 5.55 (s, 1H, CH-Ar), 7.31 (d, 1H,  $^3J_{\text{H-H}} = 7.2$  Hz,  $\gamma$ -H on pyridine), 7.37–7.47 (m, 5H, Ar-H), 7.76 (d, 1H,  $^3J_{\text{H-H}} = 6.0$  Hz,  $\beta$ -H on pyridine), 8.36 (s, 1H,  $\alpha$ -H on pyridine), 8.48 (s, 1H, NH), 9.74 (d, 1H,  $^3J_{\text{H-H}} = 10.0$  Hz, NH);  $^{31}\text{PNMR}$  (DMSO- $d_6$ )  $\delta$  = 52.96; Anal. calcd. for  $\text{C}_{18}\text{H}_{21}\text{ClN}_3\text{O}_2\text{PS}_2$  (441.5): C, 48.92; H, 4.76; N, 9.51. Found: C, 49.24; H, 4.93; N, 9.39.

**4g** (Ar = 3-fluorophenyl, R = Cl): white solid, m.p. 136.2–137.0°C, yield 86%;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  = 0.77 (s, 3H,  $\text{CH}_3$ ), 0.97 (s, 3H,  $\text{CH}_3$ ), 4.01–4.10 (dd, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $^3J_{\text{P-H}} = 25.6$  Hz,  $\text{CH}_2\text{OP}$ ), 4.41 (d, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $\text{CH}_2\text{OP}$ ), 4.65–4.78 (m, 2H,  $\text{NCH}_2$ ), 5.55 (s, 1H, CH-Ar), 7.12–7.25 (m, 3H, Ar-H), 7.45–7.50 (m, 1H, Ar-H), 7.64 (d, 1H,  $^3J_{\text{H-H}} = 8.0$  Hz,  $\gamma$ -H on pyridine), 7.97 (d, 1H,  $^3J_{\text{H-H}} = 10.0$  Hz,  $\beta$ -H on pyridine), 8.58 (s, 1H,  $\alpha$ -H on pyridine), 8.59 (s, 1H, NH), 9.85 (s, 1H, NH);  $^{31}\text{P NMR}$  (DMSO- $d_6$ )  $\delta$  = 52.94; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) 3133 (N-H), 1459 (C=N), 696 (P=S), 1020 and 981 (P-O-C), 1173 (C=S); MS,  $m/z$  (%) 459.2 ( $\text{M}^+$ , 0.9), 317 (44.5), 261 (100), 161 (40.5), 145 (22.8), 134 (27.8), 113 (24.7), 108 (32.7), 94 (17.8), 78 (15.3), 54 (29.0), 40 (62.3); Anal. calcd. for  $\text{C}_{18}\text{H}_{20}\text{ClFN}_3\text{O}_2\text{PS}_2$  (459.5): C, 47.01; H, 4.35; N, 9.14. Found: C, 46.87; H, 4.23; N, 9.41.

**4h** (Ar = 4-methylphenyl, R = Cl): white solid, m.p. 141.9–143.1°C, yield 30%;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  = 0.72 (s, 3H,  $\text{CH}_3$ ), 0.97 (s, 3H,  $\text{CH}_3$ ), 2.32 (s, 3H,  $\text{CH}_3$ -Ar), 4.04 (dd, 1H,  $^2J_{\text{H-H}} = 10.4$  Hz,  $^3J_{\text{P-H}} = 26.2$  Hz,  $\text{CH}_2\text{OP}$ ), 4.39 (d, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $\text{CH}_2\text{OP}$ ), 4.69–4.74 (m, 2H,  $\text{NCH}_2$ ), 5.46 (s, 1H, CH-Ar), 7.18–7.23 (m, 4H, Ar-H), 7.45 (d, 1H,  $^3J_{\text{H-H}} = 8.0$  Hz,  $\gamma$ -H on pyridine), 7.77 (d, 1H,  $^3J_{\text{H-H}} = 6.0$  Hz,  $\beta$ -H on pyridine), 8.35 (s, 1H,  $\alpha$ -H on pyridine), 8.48 (d, 1H,  $^3J_{\text{H-H}} = 8.4$  Hz, NH), 9.72 (s, 1H, NH);  $^{31}\text{PNMR}$  (DMSO- $d_6$ )  $\delta$  = 53.01; MS,  $m/z$  (%) 422 (1.8), 382 (5.0), 376 (15.5), 294 (100), 283 (10.4), 256 (45.7), 134 (14.6), 104 (30.4), 90 (35.8), 76 (32.6), 62 (31.2); Anal. calcd. for  $\text{C}_{19}\text{H}_{23}\text{ClN}_3\text{O}_2\text{PS}_2$  (455.5): C, 50.05; H, 5.05; N, 9.22. Found: C, 49.96; H, 4.81; N, 9.18.

**4i** (Ar = 4-chlorophenyl, R = Cl): yellow solid, m.p. 150.4–151.1°C, yield 43%;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  = 0.74 (s, 3H,  $\text{CH}_3$ ), 0.96 (s, 3H,  $\text{CH}_3$ ), 4.07 (dd, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $^3J_{\text{P-H}} = 25.6$  Hz,  $\text{CH}_2\text{OP}$ ), 4.39 (d, 1H,  $^2J_{\text{H-H}} = 10.8$  Hz,  $\text{CH}_2\text{OP}$ ), 4.69–4.75 (m, 2H,  $\text{NCH}_2$ ), 5.53 (s, 1H, CH-Ar), 7.34 (d, 2H,  $^3J_{\text{H-H}} = 8.4$  Hz, Ar-H), 7.46–7.51 (m, 3H, Ar-H +  $\gamma$ -H on pyridine), 7.77 (d, 1H,  $^3J_{\text{H-H}} = 8.4$  Hz,  $\beta$ -H on pyridine), 8.36 (s, 1H,  $\alpha$ -H on pyridine), 8.50 (s, 1H, NH), 9.76 (d, 1H,  $^3J_{\text{H-H}} = 11.2$  Hz, NH); Anal. calcd. for  $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}_2\text{PS}_2$  (476): C, 45.38; H, 4.20; N, 8.82. Found: C, 45.55; H, 4.11; N, 9.07.

**4j** (Ar = 2, 4-dichlorophenyl, R = Cl): white solid, m.p. 124.6–125.3°C, yield 45%;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  = 0.75 (s, 3H,  $\text{CH}_3$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 4.10 (dd, 1H,  $^2J_{\text{H-H}} = 10.6$  Hz,  $^3J_{\text{P-H}} = 26$  Hz,  $\text{CH}_2\text{OP}$ ), 4.35–4.37 (m, 1H,  $\text{CH}_2\text{OP}$ ), 4.72 (d, 2H,  $^3J_{\text{H-H}} = 6.0$  Hz,  $\text{NCH}_2$ ), 5.36 (s, 1H,  $\text{CH-Ar}$ ), 7.38–7.75 (m, 3H,  $\text{Ar-H}$ ), 7.96 (d, 1H,  $^3J_{\text{H-H}} = 9.2$  Hz,  $\gamma\text{-H}$  on pyridine), 8.08 (d, 1H,  $^3J_{\text{H-H}} = 10.4$  Hz,  $\beta\text{-H}$  on pyridine), 8.32 (s, 1H,  $\alpha\text{-H}$  on pyridine), 8.50 (s, 1H,  $\text{NH}$ ), 9.62 (s, 1H,  $\text{NH}$ );  $\text{MS}$ ,  $m/z$  (%) 427 (6.1), 227 (4.3), 165 (2.6), 154 (15.0), 130 (8.5), 128 (9.7), 119 (10.2), 106 (9.0), 90 (100), 63 (10.4), 39 (81.0);  $\text{Anal. calcd. for C}_{18}\text{H}_{19}\text{Cl}_3\text{N}_3\text{O}_2\text{PS}_2$  (510.5): C, 42.31; H, 3.72; N, 8.23. Found: C, 42.19; H, 3.90; N, 8.54.

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