Synthesis and Biological Activities of *cis* and *trans* 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-substitutedphenyl-1,3,2-dioxaphosphinan-2-yl)-4-cyano(ethoxycarbonyl)-1*H*-pyrazoles

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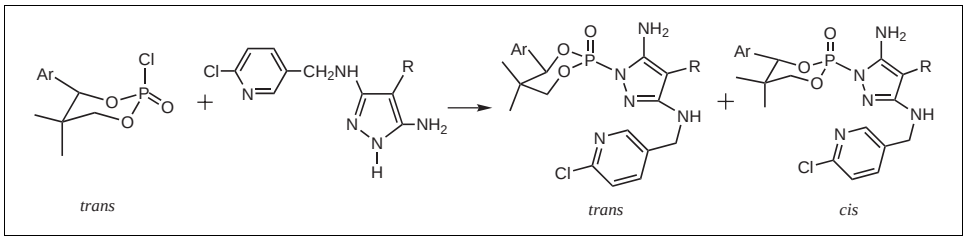

A series of novel title compounds have been designed and synthesized by a multi-step reaction, the stereochemistry of the reaction was investigated, the structures of all compounds prepared have been confirmed by ^{1}H NMR, IR, EI-MS spectroscopy and elemental analysis. The crystal structures of *cis* **6b** and *trans* **6b** were determined by single crystal X-ray diffraction. The results of preliminary bioassay indicate that some compounds possess a certain extent inhibition effect against aphides at the concentration of 250 ppm.

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Introduction.

5-Aminopyrazoles became of recent importance due to their wide biological and medicinal interest. Moreover, in recent years, 5-aminopyrazole derivatives have been extensively utilized as intermediates of fused pyrazoles of potential biological activities [1-5]. Insecticides which have the structure and mechanism similar to nicotine are called neonicotinoids [6]. Seven neonicotinoids, which have the pyridine-like moiety, have been commercialized and many SARs (structure-activity relationships) for these neonicotinoids have been reported [6,7]. The enantiomers of insecticidal alkaloids often behave differently in biochemical reactions process [8]. Nicotine is a typical example. Organic phosphorus heterocyclic compounds play an important role in pesticide science [9,10]. For example, 1,3,2-dioxaphosphinane compounds appear to be very important owing to their wide biological activities and stereochemistry [11,12]. So, it is very interesting to design novel biologically active compounds by bringing these three moieties into a molecular framework **6** with a view to study their additive effect on pesticidal properties. As a continuation of our search for new biological active compounds [13,14], herein, we designed and synthesized novel *cis* and *trans* title compounds. The synthetic routine is listed in Scheme 1. The preliminary insecticidal activities of prepared compounds are also reported.

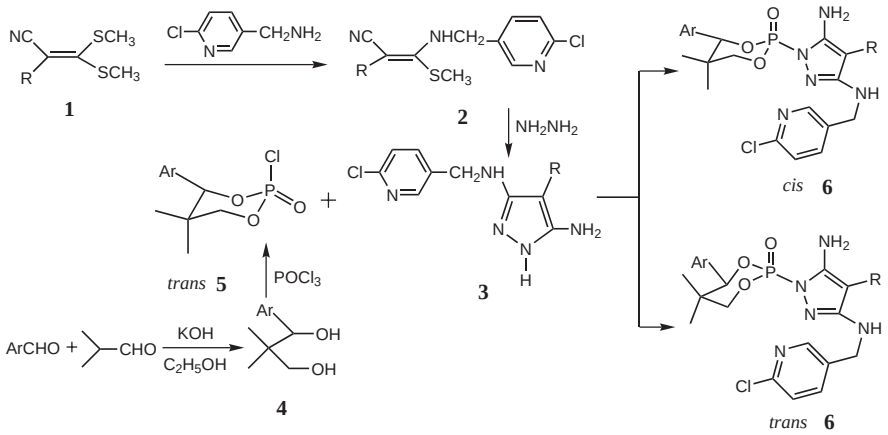
Results and Discussion.

Synthesis and Structure Characterization of *cis* and *trans* **6**.

The reaction sequence of **6** is outlined in Scheme 1. The N, S-acetal **2** [15], which was prepared from dithioacetal **1** in the presence of 6-chloro-3-aminomethylpyridine, reacted with hydrazine to give 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1*H*-pyrazole **3** [16] in the refluxing ethanol. The synthesis of *trans* 2-chloro-1,3,2-dioxaphosphinane 2-oxide **5** [11] was proceeded from phosphoryl chloride and 1-aryl-2,2-dimethyl-1,3-propanediol **4** [17], which was prepared from aromatic aldehyde and isobutylraldehyde in the presence of potassium hydroxide in ethanol. The *trans* 2-chloro-1,3,2-dioxaphosphinane 2-oxide **5** was allowed to react with 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1*H*-pyrazole **3** in the presence of sodium hydroxide in acetonitrile at room temperature. The pure products of *cis* and *trans* **6** were separated from the reaction mixture by flash chromatography on silica gel and recrystallized from ethanol. In this case, phosphorylation of 1*H*-pyrazole **3** took place at N^1 position, instead of N^2 position, which can stem from the steric hindrance [18].

When we synthesized the title compounds with the substituted group R=COOEt, CN and Ar=Ph, 4-ClPh in the acetonitrile, both the two isomers can be obtained, *viz* **6a**, **6b**, **6f** and **6g**. The ratio of *cis* and *trans* isomers of **6a**, **6b**, **6f** and **6g** are 2.5:1, 1.5:1, 5:1 and 3:1, respectively (see table 1). The configuration of *trans* 1, 3, 2-dioxaphosphinane can be converted mostly in the acetonitrile by the attack of nucleophiles [19], namely, the main product has the *cis* configuration. In the synthesis of the

Scheme 1



title compounds, containing other substituted groups, we obtained one isomer of the product, *viz cis* **6**. According to the literatures, compounds **3** attack *trans* phosphoryl chloride from the opposed direction of the chlorine atom to form the configuration inversion product, which is the thermodynamic favored process [20].

isomers **6** from *cis* isomers **6** by the means of ^{1}H NMR, the chemical shift difference between the two methyl groups attached to the 1,3,2-dioxaphosphinane in *trans* **6** are larger than the values in *cis* **6**. For example, the chemical shift difference between the two methyl attached to the 1,3,2-dioxaphosphinane in *trans* **6a** is 0.35, while the value of *cis* **6a** is

Table 1
Physical Constants of *cis* and *trans* **6**

Compd.	R	Ar	Appearance	m.p. (°C)	Yield(%) [a]	configuration
6a	COOEt	Ph	White crystal	191.2-191.5	50	*cis*
6a	COOEt	Ph	White crystal	182.8-183.3	20	*trans*
6b	COOEt	4-ClPh	White crystal	179.7-180.3	39	*cis*
6b	COOEt	4-ClPh	White crystal	160.0-160.3	26	*trans*
6c	COOEt	2-ClPh	White crystal	197.7-198.3	46	*cis*
6d	COOEt	2,4-Cl_2Ph	White crystal	214.0-216.0	52	*cis*
6e	COOEt	4-CH_3Ph	White crystal	176.7-177.1	49	*cis*
6f	CN	Ph	White crystal	198.0-199.6	50	*cis*
6f	CN	Ph	White crystal	214.5-215.5	10	*trans*
6g	CN	4-ClPh	White crystal	233.8-235.0	45	*cis*
6g	CN	4-ClPh	White crystal	206.5-206.8	15	*trans*
6h	CN	2-ClPh	White crystal	220.3-222.3	45	*cis*
6i	CN	2,4-Cl_2Ph	White crystal	224.3-226.4	48	*cis*
6j	CN	4-CH_3Ph	White crystal	206.1-207.3	37	*cis*

[a] The isolated yield of the products of **6** based on flash chromatography on silica gel.

The structures of *cis* and *trans* **6** were deduced from their spectra data. In the ^{1}H NMR spectra of *cis* and *trans* **6**, the corresponding amino protons display a broad multiplicity. When R is ethoxycarbonyl group, its chemical shift is between 6.2-6.6 ppm while R is cyano group, the chemical shift of the corresponding amino protons are shifted downfield around 7.0-7.8 ppm due to the strong negative inductive effect. The two methylene protons of 1,3,2-dioxaphosphinane display doublet and multiplicity because of their different magnetic surrounding and coupling with each other or with the adjacent phosphorus atom. Interestingly, we can distinguish easily *trans* 0.27. Maybe the electronic and stereo effects play the major roles [14]. In addition, the EI-MS spectra of *cis* and *trans* **6** showed the anticipated molecular ion peaks, all the fragmentation ions are consistent with their structures and can be clearly assigned. The IR spectra of *cis* and *trans* **6** exhibited N-H, carbonyl, C=N and P=O absorptions.

Moreover, in order to confirm its structure and investigate its stereochemistry, two single crystal of *cis* **6b** and *trans* **6b** were obtained from absolute ethanol and their molecular structures were determined by X-ray diffraction (Figure 1, Figure 2) [21,22].

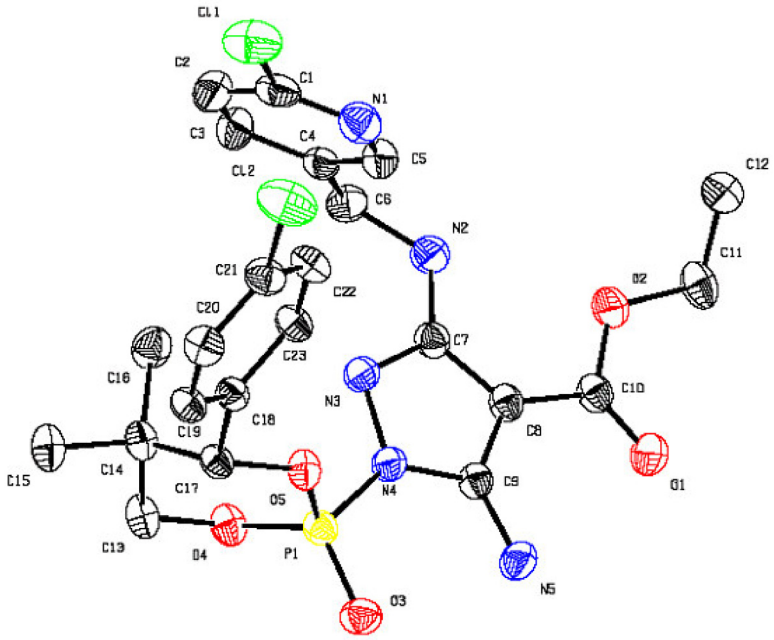


Figure 1. ORTEP Drawing of *cis* **6b**.

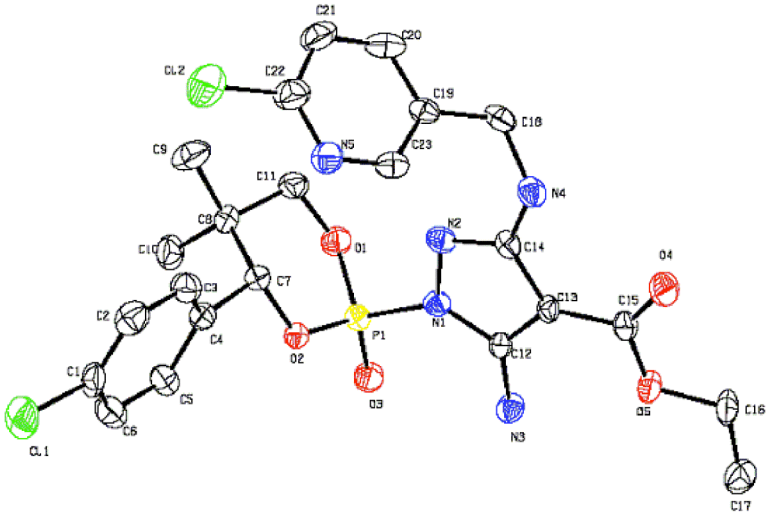


Figure 2. ORTEP Drawing of *trans* **6b**.

Biological Activities.

Compounds *cis* and *trans* **6** were tested for insecticidal activities against aphides at the concentration of 250 ppm according to a previously reported method [23]. The results of insecticidal activities did not show good toxic effect as our expectation (see Table 2). However, the isomers of *cis* and *trans* **6** have little distinction against the aphides. As we know, every neonicotinoid insecticide has two function sites, a cationic site and a hydrogen acceptor site, for

Table 2

Insecticidal activity of *cis* and *trans* **6** against aphides:
(250ppm, inhibitory rate %).

Cis **6a**	***Trans*** **6a**	***Cis*** **6b**	***Trans*** **6b**	***Cis*** **6c**	***Cis*** **6d**	***Cis*** **6e**	***Cis*** **6f**	***Trans*** **6f**	***Cis*** **6g**	***Trans*** **6g**	***Cis*** **6h**	***Cis*** **6i**	***Cis*** **6j**
18.4	25.6	40.9	36.8	0	21.2	38.2	24.2	44.4	29.3	0	0	23.3	16.7

binding to nicotinic acetylcholine receptors. The distance between the two acting nitrogen atoms of nicotine is 5.9 Å, other neonicotinoids also have approximately this distance between the two acting nitrogen atoms [6,7]. From the X-ray structures of *cis* **6b** (Figure 1) and *trans* **6b** (Figure 2) the nitrogen-nitrogen distance was determined to be 4.22 Å (N1-N2 in the *cis*) and 4.24 Å (N4-N5 in the *trans*) as compared to the value of nicotine compound. The shrunken distance of the two acting nitrogen atoms of *cis* and *trans* **6b** probably was caused by the strong intramolecular hydrogen bonds interactions [21,22]. Moreover, the larger steric hindrance maybe is an important fact of lower activities, which can prevent the nitrogen atom on the pyridine ring and the adjacent nitrogen atom from accessing the acting site of nicotinic acetylcholine receptors. Further studies directed toward the efficient nicotinic acetylcholine receptor pharmacophore are under investigation and will be reported in due course.

EXPERIMENTAL

Melting points were determined with a WRS-1B Digital melting point apparatus and are uncorrected. EI-MS spectra were measured on a Finnigan Trace Mass Spectrometer. IR spectra were recorded on a NICOLET NEXUS470 infrared Spectrometer. ^{1}H NMR spectra were taken on a Varian XL-400 Spectrometer. Elementary analyses were recorded on a Vario EL III elementary analysis instrument. X-ray diffraction analysis was performed on a BRUKER SMART 1000 CCD diffractometer. All of the solvents and materials were reagent grade and purified as required. N, S-acetal **2** [15], 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1*H*-pyrazole **3** [16], 1-aryl-2,2-dimethyl-1,3-propanediol **4** [17] and *trans* 2-chloro-1,3,2-dioxaphosphinane 2-oxide **5** [11] were prepared according to the corresponding literature methods.

General Procedure for the Preparation of *cis* and *trans* 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-substitutedphenyl-1,3,2-dioxaphosphinan-2-yl)-4-cyano (ethoxy-carbonyl)-1*H*-pyrazoles **6**.

A solution of 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1*H*-pyrazole **3** (4 mmol) in anhydrous acetonitrile (20 mL) and sodium hydroxide powder (5mmol) was added to a 50 mL three-necked flask, after vigorously stirring for 5 minutes, the solution of *trans* 2-chloro-1,3,2-dioxaphosphinane 2-oxide **5** (4.5 mmol) in anhydrous acetonitrile (10 mL) was added dropwise while cooling in an ice-bath. After the addition was finished, the mixture was stirred at room temperature until the reaction finished (monitored by thin lay chromatography). The workup involved stripping of the solvent followed by an addition of water and extraction of the product mixture into chloroform, after phase separation, drying over anhydrous sodium sulphate, filtration and evaporation, the crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate(3:1---1:1,V/V) as the eluent, giving a white solid, the physical data of the title compounds 6 were listed in **Table 1**.

cis Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphinan-2-yl)-1*H*-pyrazole-4-carboxylate (**6a**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.35 (t, 3H, *J*=7.3 Hz, CH_2CH_3), 4.00 (dd, $^2J_{H-H}$=11.2 Hz, $^2J_{P-H}$=20.4 Hz, 1H, CH_2OP), 4.30 (q, *J*=6.4 Hz, 2H, CH_2CH_3), 4.45 (d, *J*=6.8 Hz, 2H, CH_2NH), 4.48 (d, $^2J_{H-H}$=10.8 Hz, 1H, CH_2OP), 5.48 (s, 1H, CH_2Ar), 6.40~6.64 (b, 2H, NH_2), 7.18~7.36 (m, 7H, CH_2NH, Ar-H, ß-H on pyridine), 7.73 (d, 1H, γ-H on pyridine, *J*=6.8 Hz), 8.42 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{23}H_{27}ClN_5O_5P$: C, 53.13; H, 5.23; N, 13.47. Found: C, 53.14; H, 5.12; N, 13.50.

trans Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphinan-2-yl)-1*H*-pyrazole-4-carboxylate **6a**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.71 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.35 (t, 3H, *J*=7.2 Hz, CH_2CH_3), 4.01 (dd, $^2J_{H-H}$=11.6 Hz, $^2J_{P-H}$=20.8 Hz, 1H, CH_2OP), 4.31 (q, *J*=6.8 Hz, 2H, CH_2CH_3), 4.46 (d, *J*=7.2 Hz, 2H, CH_2NH), 4.73 (d, $^2J_{H-H}$=10.4 Hz, 1H, CH_2OP), 5.54 (s, 1H, CH_2Ar), 6.20~6.40 (b, 2H, NH_2), 7.16~7.37 (m, 7H, CH_2NH, Ar-H, β-H on pyridine), 7.73 (d, *J*= 6.4Hz 1H, γ-H on pyridine, *J*=6.8Hz), 8.44 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{23}H_{27}ClN_5O_5P$: C, 53.13; H, 5.23; N, 13.47. Found: C, 53.45; H, 5.24; N, 13.47.

cis Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-1*H*-pyrazole-4-carboxylate (**6b**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.35 (t, *J*=7.6 Hz, 3H, CH_2CH_3), 4.08 (dd, $^2J_{H-H}$=11.6 Hz, $^3J_{P-H}$=20.8 Hz, 1H, CH_2OP), 4.34 (q, *J*=6.8 Hz, 2H, CH_2CH_3), 4.49 (d, *J*=7.2 Hz, 2H, CH_2NH), 4.53 (d, $^2J_{H-H}$=10.8 Hz, 1H, CH_2OP), 5.44 (s, 1H, *CH*-Ar), 6.40~6.66 (b, 2H, NH_2), 7.11~7.35 (m, 6H, CH_2NH, Ar-H, β-H on pyridine), 7.72 (d, *J*=7.6 Hz, 1H, γ-H on pyridine), 8.41 (s, 1H, α-H on pyridine); IR (KBr) (υ_{max}/cm^{-1}) 3455, 3350, 1687, 1582, 1258, 1054, 999; MS (m/z, %): 556 (M+2, 90), 553 (M+1, 48), 554 (M+, 100), 295 (11), 125 (21), 67 (9), 55 (33).

Anal. Calcd. For $C_{23}H_{26}Cl_2N_5O_5P$: C, 49.83; H, 4.73; N, 12.63. Found: C, 49.96; H, 4.77; N, 12.57.

trans Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-1*H*-pyrazole-4-carboxylate (**6b**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.70 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.35 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 4.00 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.4 Hz, 1H, CH_2OP), 4.28 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.47 (d, *J*=6.8 Hz, 2H, CH_2NH), 4.72 (d, $^2J_{H-H}$=11.2 Hz, 1H, CH_2OP), 5.48 (s, 1H, *CH*-Ar), 6.40~6.66 (b, 2H, NH_2), 7.11~7.35 (m, 6H, CH_2NH, Ar-H, β-H on pyridine), 7.72 (d, *J*=8.0 Hz, 1H, γ-H on pyridine), 8.41 (s, 1H, α-H on pyridine); IR (KBr) (υ_{max}/cm^{-1}) 3473, 3357, 1689, 1582, 1281, 1037, 998; MS (m/z, %): 556 (M+2, 76), 553 (M+1, 51), 554 (M+, 100), 295(3), 125 (15), 67(6), 55(42).

Anal. Calcd. For $C_{23}H_{26}Cl_2N_5O_5P$: C, 49.83; H, 4.73; N, 12.63. Found: C, 50.12; H, 4.75; N, 12.75.

cis Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(2-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-1*H*-pyrazole-4-carboxylate (**6c**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.35(t, *J*=7.6 Hz, 3H, CH_2CH_3), 4.12 (dd, $^2J_{H-H}$=11.6 Hz, $^3J_{P-H}$=20.0 Hz, 1H, CH_2OP), 4.31 (q, *J*=6.4 Hz, 2H, CH_2CH_3),

4.45 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.55 (d, $^2J_{H-H}$=10.4 Hz, 1H, *CH*$_2$OP), 6.08 (s, 1H, *CH*-Ar), 6.50~6.80 (b, 2H, NH$_2$), 7.26~7.42 (m, 6H, CH$_2$*NH*, Ar-H, β-H on pyridine), 7.73 (d, *J*=7.6 Hz, 1H, γ- H on pyridine), 8.43 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{23}H_{26}Cl_2N_5O_5P$: C, 49.83; H, 4.73; N, 12.63. Found: C, 50.04; H, 4.54; N, 12.62.

cis Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(2,4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-1*H*-pyrazole-4-carboxylate (**6d**).

^{1}H NMR ($CDCl_3$, 400 MHz): 0.97 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$), 1.35 (t, *J*=7.2 Hz, 3H, CH$_2$*CH*$_3$), 4.06~4.15 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.4 Hz, 1H, *CH*$_2$OP), 4.34 (q, *J*=7.2 Hz, 2H, *CH*$_2$CH$_3$), 4.44 (d, *J*=7.2 Hz, 2H, *CH*$_2$NH), 4.55 (d, $^2J_{H-H}$=10.8 Hz, 1H, *CH*$_2$OP), 6.01 (s, 1H, *CH*-Ar), 6.40~6.62 (b, 2H, NH$_2$), 7.26~7.40 (m, 5H, CH$_2$*NH*, Ar-H, β- H on pyridine), 7.72 (d, *J*=8.0 Hz, 1H, γ- H on pyridine), 8.43 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{23}H_{25}Cl_3N_5O_5P$: C, 46.92; H, 4.28; N, 11.89. Found: C, 47.12; H, 4.29; N, 11.88.

cis Ethyl 5-amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-methylphenyl)-1,3,2-dioxaphosphinan-2-yl]-1*H*-pyrazole-4-carboxylate (**6e**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (s, 3H, CH$_3$), 1.22 (s, 3H, CH$_3$), 1.35 (t, *J*=7.6Hz, 3H, CH$_2$*CH*$_3$), 2.35 (s, 3H, *CH*$_3$-Ar), 3.99 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.8 Hz, 1H, *CH*$_2$OP), 4.33 (q, *J*=6.4 Hz, 2H, *CH*$_2$CH$_3$), 4.43 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.71 (d, $^2J_{H-H}$=10.8 Hz, 1H, *CH*$_2$OP), 5.51 (s, 1H, *CH*-Ar), 6.20~6.42 (b, 2H, NH$_2$), 7.06~7.31 (m, 6H, CH$_2$*NH*, Ar-H, β- H on pyridine), 7.72 (d, *J*=6.8 Hz, 1H, γ- H on pyridine), 8.43 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{24}H_{29}ClN_5O_5P$: C, 53.99; H, 5.47; N, 13.12. Found: C, 54.12; H, 5.24; N, 13.18.

cis 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphinan-2-yl)-4-cyano-1*H*-pyrazole (**6f**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0.82 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$), 4.16 (dd, $^2J_{H-H}$=11.6 Hz, $^3J_{P-H}$=20.8 Hz, 1H, *CH*$_2$OP), 4.40 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.69 (d, $^2J_{H-H}$=10.8 Hz, 1H, *CH*$_2$OP), 5.83 (s, 1H, *CH*-Ar), 7.06 7.54 (m, 9H, NH$_2$, CH$_2$*NH*, Ar-H, β--H on Pyridine), 7.86 (d, *J*=7.2 Hz, 1H, γ- H on pyridine), 8.48 (s, 1H, α-H on pyridine); MS (m/z, %): 475 (M+2, 15), 474 (M+1, 9), 473 (M+, 38), 247 (8), 145 (27), 126 (100), 117 (60), 91(93), 77(40).

Anal. Calcd. For $C_{21}H_{22}ClN_6O_3P$: C, 53.33; H, 4.69; N, 17.77. Found: C, 53.57; H, 4.58; N, 17.76.

trans 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-(5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphinan-2-yl)-4-cyano-1*H*-pyrazole (**6f**).

^{1}H NMR(DMSO-d6, 400 MHz): δ 0.67 (s, 3H, CH$_3$), 0.95 (s, 3H, CH$_3$), 4.21 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.4 Hz, 1H, *CH*$_2$OP), 4.39 (d, *J*=6.4 Hz, 2H, *CH*$_2$NH), 4.81 (d, $^2J_{H-H}$=11.2 Hz, 1H, *CH*$_2$OP), 5.40 (s, 1H, *CH*-Ar), 7.09 7.52 (m, 9H, NH$_2$, CH$_2$*NH*, Ar-H, β--H on pyridine), 7.86 (d, *J*=6.8 Hz, 1H, γ- H on pyridine), 8.48 (s, 1H, α-H on pyridine); MS (m/z, %): 475 (M+2, 12), 474 (M+1, 8), 473 (M+, 27), 247 (9), 145 (21), 126 (100), 117 (42), 91 (68), 77 (32).

Anal. Calcd. For $C_{21}H_{22}ClN_6O_3P$: C, 53.33; H, 4.69; N, 17.77. Found: C, 53.26; H, 4.59; N, 17.73.

cis 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-4-cyano-1*H*-pyrazole (**6g**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0. 0.74 (s, 3H, CH$_3$), 0.91 (s, 3H, CH$_3$), 4.17 (dd, $^2J_{H-H}$=11.6 Hz, $^3J_{P-H}$=20.8 Hz, 1H, *CH*$_2$OP), 4.33 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.52 (d, $^2J_{H-H}$ =10.4 Hz, 1H, *CH*$_2$OP), 5.78 (s, 1H, *CH*-Ar), 7.08~7.53 (m, 8H, NH$_2$, CH$_2$*NH*, Ar-H, β--H on pyridine), 7.79 (d, *J*=7.6 Hz, 1H, γ- H on pyridine), 8.34 (s, 1H, α-H on pyridine); IR(KBr) (υ_{max}/cm^{-1}) 3380, 3337, 2216, 1587, 1268, 1046, 996.

Anal. Calcd. For $C_{21}H_{21}Cl_2N_6O_3P$: C, 49.72; H, 4.17; N, 16.57. Found: C, 49.91; H, 4.06; N, 16.58.

trans 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-4-cyano-1*H*-pyrazole (**6g**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0.69 (s, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$), 4.20 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.0 Hz, 1H, *CH*$_2$OP), 4.34 (d, *J*=6.4 Hz, 2H, *CH*$_2$NH), 4.58 (d, $^2J_{H-H}$=11.2 Hz, 1H, *CH*$_2$OP), 5.44 (s, 1H, *CH*-Ar), 7.09~7.53 (m, 8H, NH$_2$, CH$_2$*NH*, Ar-H, β--H on pyridine), 7.85 (d, *J*=7.2 Hz, 1H, γ- H on pyridine), 8.48 (s, 1H, α-H on pyridine); IR(KBr) (υ_{max}/cm^{-1}) 3440, 3333, 2205, 1583, 1273, 1058, 997.

Anal. Calcd. For $C_{21}H_{21}C_{l2}N_6O_3P$: C, 49.72; H, 4.17; N, 16.57. Found: C, 49.68; H, 4.12; N, 16.60.

cis 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(2-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-4-cyano-1*H*-pyrazole (**6h**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0.83 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 4.13 (dd, $^2J_{H-H}$=11.6 Hz, $^3J_{P-H}$=20.8 Hz, 1H, *CH*$_2$OP), 4.34 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.52 (d, $^2J_{H-H}$ =10.8 Hz, 1H, *CH*$_2$OP), 6.42 (s, 1H, *CH*-Ar), 7.11~7.53 (m, 8H, NH$_2$, CH$_2$*NH*, Ar-H, β- H on pyridine), 7.82 (d, *J*=7.6 Hz, 1H, γ- H on pyridine), 8.37 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{21}H_{21}Cl_2N_6O_3P$: C, 49.72; H, 4.17; N, 16.57. Found: C, 49.51; H, 4.13; N, 16.42.

cis 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(2,4-chlorophenyl)-1,3,2-dioxaphosphinan-2-yl]-4-cyano-1*H*-pyrazole (**6i**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 00.83 (s, 3H, CH$_3$), 0.98 (s, 3H, CH$_3$), 4.16 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.8 Hz, 1H, *CH*$_2$OP), 4.37 (d, *J*=6.8 Hz, 2H, *CH*$_2$NH), 4.71 (d, $^2J_{H-H}$=10.8 Hz, 1H, *CH*$_2$OP), 6.06 (s, 1H, *CH*-Ar), 7.09~7.53 (m, 7H, NH$_2$, CH$_2$*NH*, Ar-H, β- H on pyridine), 7.82 (d, *J*=8.0 Hz, 1H, γ- H on pyridine), 8.37 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{21}H_{20}Cl_3N_6O_3P$: C, 46.56; H, 3.72; N, 15.51. Found: C, 46.72; H, 3.64; N, 15.62.

cis 5-Amino-3-[(6-chloro-3-pyridyl)methyl]amino-1-[5,5-dimethyl-2-oxo-4-(4-methylphenyl)-1,3,2-dioxaphosphinan-2-yl]-4-cyano-1*H*-pyrazole (**6j**).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0.73 (s, 3H, CH$_3$), 0.94 (s, 3H, CH$_3$), 4.15 (dd, $^2J_{H-H}$=11.2 Hz, $^3J_{P-H}$=20.4 Hz, 1H, *CH*$_2$OP), 4.33 (d, *J*=7.2 Hz, 2H, *CH*$_2$NH), 4.52 (d, $^2J_{H-H}$ =10.8 Hz, 1H, *CH*$_2$OP), 5.68 (s, 1H, *CH*-Ar), 7.01~7.49 (m, 8H, NH$_2$, CH$_2$*NH*, Ar-H, β-H on pyridine), 7.80 (d, *J*=5.6 Hz, 1H, γ- H on pyridine), 8.33 (s, 1H, α-H on pyridine).

Anal. Calcd. For $C_{22}H_{24}ClN_6O_3P$: C, 54.27; H, 4.97; N, 17.26. Found: C, 54.45; H, 4.77; N, 17.35.

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