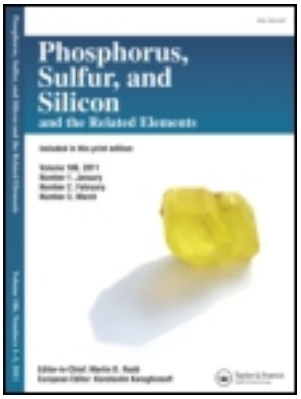

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Biological Evaluation of Novel Phosphonates Derivatives of As Potential Antitumor Agents

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PHOSPHONATES DERIVATIVES OF AS POTENTIAL ANTITUMOR AGENTS

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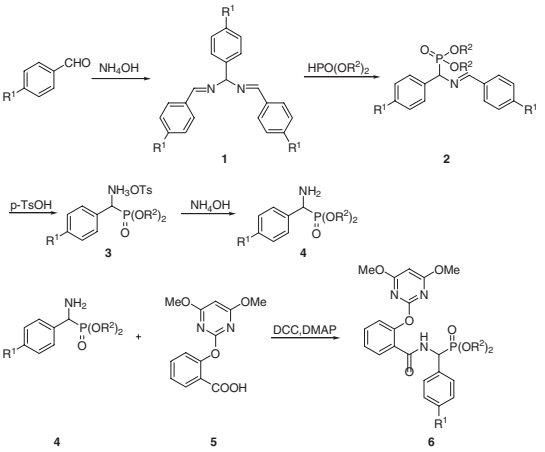
GRAPHICAL ABSTRACT



Abstract *A series of dialkyl [2-(4,6-dimethoxypyrimidin-2-yloxy)benzamido](aryl) methylphosphonates derivatives were designed and synthesized. All the new compounds were identified by elemental analysis, IR, ^{1}H NMR, ^{31}P NMR, and MS. Their antitumor activity against KB and CNE1 cells was examined. Some of the compounds showed potential antitumor activity, which provided some hints for further study of structure modification. In particular, the compounds **6i** and **6j** displayed more potent cytotoxic activities against KB in comparison with 5-FU.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Table S1]*

Keywords Phosphonate; pyrimidinylbenzoate; amide; antitumor activity

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INTRODUCTION

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] Recent studies on the biological evaluation of α-substituted phosphonates have revealed many compounds, with a wide range of biological effects, including herbicidal activity,[2,3] insecticidal activity,[4] antiviral activitity,[5–7] antifungal activity,[8] and antitumor agents.[9–11] A number of synthetic methods for the synthesis of α-aminoalkyl phosphonates also have been developed during the past years.[12–15] For these reasons, the synthesis of α-substituted phosphonates and their functionalized derivatives is an important objective.

At the same time, a variety of the reports with regard to the synthetic studies of the pyrimidine derivatives have been presented because they were documented to exhibit a wide range of biological activities.[16,17] Some pyrimidines have been reported as selective inhibitors of tyrosine phosphorylation by the epidermal growth-factor receptor (EGFR), and have become an important class of potential anticancer drugs.[18,19] The objective of this study was to design and synthesize novel α-substituted phosphonates by structural modification of pyrimidinylbenzoates.

RESULTS AND DISCUSSION

Chemistry

Dialkyl phosphites were obtained by the reported method,[20] and intermediates **4** were prepared according to the reported methods.[21] Compound **5** could be easily synthesized starting from methyl 2-hydroxybenzoate and 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (DMPS).[22]

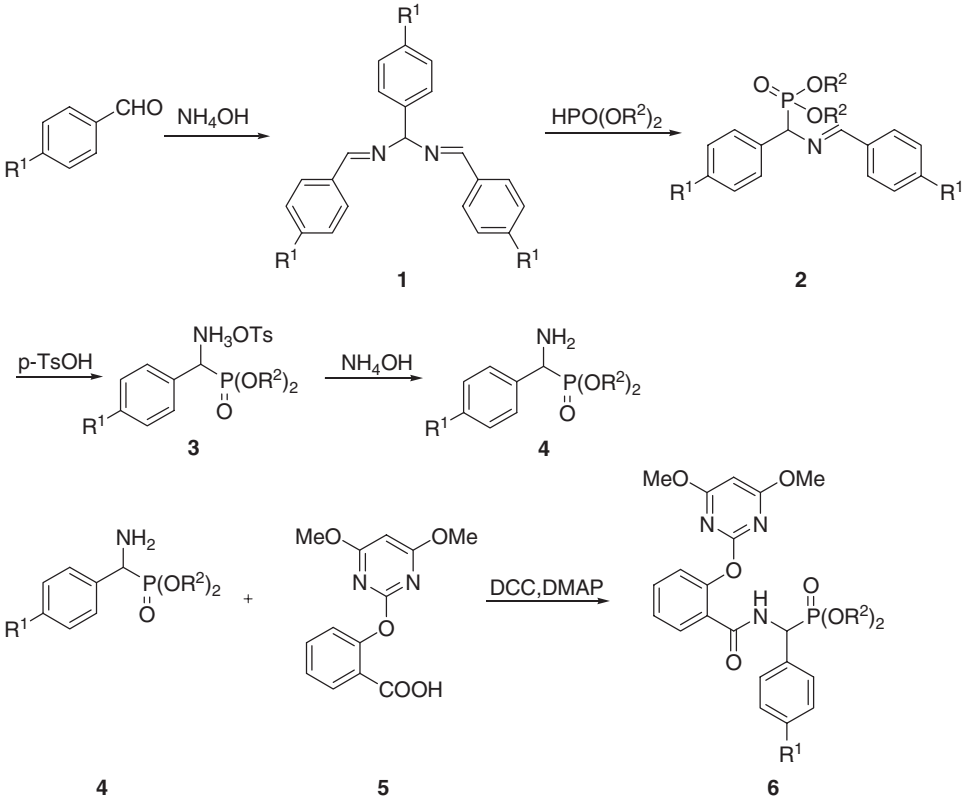
Subsequent reaction of compound **5** with substituted α-amino alkylphosphonates **4** in presence of DCC, and DMAP in CH_2Cl_2, lead to the formation of desired molecules in good yield. The synthetic pathway is outlined in Scheme 1, and the structures of **6a–j** are given in Table 1.

All of the reported compounds were purified over silica gel column and characterized spectroscopically.

The evidence for the formation of the compounds was obtained from ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra, which provide diagnostic tools for the positional elucidation

Table 1 The preparation of dialkyl [2-(4,6-dimethoxypyrimidin-2-yloxy)benzamido] (aryl) methylphosphonates **6a–j**

Compound	R^1	R^2	Yield (%)
6a	H	Me	69
6b	Me	Me	82
6c	Cl	Me	80
6d	H	Et	70
6e	OMe	Et	62
6f	Me	Et	82
6g	F	Et	70
6h	H	n-Bu	80
6i	Me	n-Bu	77
6j	OMe	n-Bu	75



6a: R^1 = H, R^2 = Me; **6b**: R^1 = Me, R^2 = Me;
6c: R^1 = Cl, R^2 = Me; **6d**: R^1 = H, R^2 = Et;
6e: R^1 = OMe, R^2 = Et; **6f**: R^1 = Me, R^2 = Et;
6g: R^1 = F, R^2 = Et; **6h**: R^1 = H, R^2 = n-Bu;
6i: R^1 = Me, R^2 = n-Bu; **6j**: R^1 = OMe, R^2 = n-Bu;

Scheme 1

of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The ^{1}H NMR spectrum of all the compounds showed singlet for one (NH) protons at δ (7.98–8.01), another singlet for one (pyrimidine-H) proton at δ (5.71–5.78) and a singlet for two (2 OCH_3) proton at δ (3.77–3.87). Thus, on the basis of the above data the products have been characterized as phosphonate derivatives.

^{13}C NMR spectra of the compounds were taken in $CDCl_3$ and the signal obtained further confirmed the proposed structures. The compounds showed a signal at (172.8–172.9) ppm due to (C=O) of phosphonate derivatives. All the compounds also showed a signal at (20.1–23.1) ppm due to (P=O) of phosphonate derivatives.

Pharmacology

The in vitro antitumor activity of the synthesized compounds against two cancer cell lines, including KB (oral carcinoma cell), and CNE1 (nasopharyngeal carcinoma cell) were assayed by MTT method. 5-FU was used as the reference drug. Experimental details and the table of activities (Table S1) are presented in the Supplemental Materials.

CONCLUSIONS

In conclusion, we have reported syntheses and biological activities of a series of dialkyl [2-(4,6-dimethoxypyrimidin-2-yloxy)benzamido] (aryl) methylphosphonates derivatives. The preliminary bioassay data showed that some of the synthesized compounds were potential antitumor activities. Further investigations on structural optimization and biological studies about these derivatives are still underway in our laboratory.

EXPERIMENTAL

Mass spectra were measured on a Finnigan Trace MS 2000 spectrometer. Infrared spectra were recorded in potassium bromide pellets with a Nicolet Avatar 360 FTIR spectrophotometer. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded in $CDCl_3$ solution at 600 MHz (^{1}H), 125 MHz (^{13}C) and 243 MHz (^{31}P) using tetramethysilane (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P) as internal standards with a Varian Mercury-Plus 600 spectrometer. Elemental analysis was performed with an Elementar Vario EL III elementary analyzer. Melting points (mp) were measured with an electrothermal mp apparatus and are uncorrected.

The General Synthetic Procedure for α-Aminoalkyl Phosphonates 4

The aldehyde (15 mmol) was added to ammonium hydroxide (30%, 15 mL) and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate was removed by filtration and dried. Dimethyl phosphite (6 mmol) was added to this solid and the resulting solution was stirred for about 2–5 h at 70 °C. p-Toluenesulfonic acid (6 mmol) in 50 mL. Tetrahydrofuran (THF) was added to the reaction mixture, which was stirred for 2 h at 0 °C. The precipitate was removed by filtration and washed with THF (20 mL). The precipitate was added to 15 mL aqueous ammonium hydroxide (10%) and stirred for 30 min at room temperature. Extraction with ether (100 mL), evaporation of the solvent, and chromatography on silica gel with EtOAc/n-hexane (4:1) gave the pure products as oils in 40–71% yields.

The General Synthetic Procedure for 2-(4,6-Dimethoxypyrimidin-2-Yloxy)Benzoic Acid 5

To 0.32 g (2.1 mmol) methyl 2-hydroxybenzoate and anhydrous K_2CO_3 0.59 g (4.2 mmol) in acetone (10 mL) was stirred at room temperature for 1 h. DMSP 0.49 g (2.25 mmol) was added. The reaction was continued for 18 h. Extraction with EtOAc (50 mL), evaporation of the solvent, and chromatography on silica gel with EtOAc/n-hexane (4:1) gave the pure products as white solid. After the solid was dissolved in acetone (20 mL), 2 mol/L NaOH was added, then stirred for another 2 h at room temperature, then 2 mol/L HCl was added, and the compound **5** was formed.

The General Synthetic Procedure for Dialkyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Benzamido](Aryl) Methylphosphonates 6a–j

A solution of compound **5** (1 mmol) in CH_2Cl_2 (10 mL) was stirred, followed by the addition of intermediate **4** (1 mmol), then the reaction system was cooled down to

0 °C, and then 1,3-dicyclohexylcarbodiimide (DCC) (1 mmol) and DMAP (0.1 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was reacted for about 10–24 h at 25 °C, then 1,3-dicyclohexylurea (DCU) was filtered off. The CH_2Cl_2 solvent was evaporated to the crude product, which was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (4:1) as an eluant to give the target compounds in yields of 62–82%.

O, O-Dimethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (Phenyl)Methylphosphonate (6a)

White solid, mp 146.1∼147.8 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 3.54 (d, 3H, $J = 10.8$ Hz, OCH_3), 3.65 (d, 3H, $J = 10.8$ Hz, OCH_3), 3.78 (s, 6H, OCH_3), 5.72 (q, 1H, $J =$ 9.6 Hz, CH), 5.77 (s, 1H, CH), 7.20∼7.52 (m, 8H, Ph-H), 7.85 (d, 1H, $J = 6.0$ Hz, Ph-H), 8.01 (d, 1H, $J = 6.6$ Hz, NH); ^{13}C NMR ($CDCl_3$, TMS, 125 MHz): 49.9 ($J_{c,p} = 126.5$ Hz), 53.5 ($J_{c,p} = 21.0$ Hz), 54.3, 85.5, 123.2, 126.0, 127.3, 127.8, 127.9, 128.1, 128.6, 131.1, 132.4, 134.5, 150.1, 163.4, 164.4, 172.9; ^{31}P NMR ($CDCl_3$): 22.7; IR (KBr,υ/cm^{-1}): 3261 (N-H), 1669 (C=O), 1224 (P=O); MS (EI): m/z 473 (9), 363 (34), 298 (29), 258 (100), 103 (30), 68 (54); anal. calcd. For C, 55.81; H, 5.11; N, 8.88. Found: C, 55.47; H, 5.47; N, 8.72%.

O, O-Dimethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (p-Tolyl)Methylphosphonate (6b)

White solid, mp 137.7∼139.2 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 2.30 (s, 3H, CH_3), 3.55 (d, 3H, $J = 10.8$ Hz, OCH_3), 3.65 (d, 3H, $J = 10.8$ Hz, OCH_3), 3.79 (s, 6H, OCH_3), 5.69 (q, 1H, $J = 9.6$ Hz, CH), 5.76 (s, 1H, CH), 7.06∼7.51 (m, 7H, Ph-H), 7.80 (d, 1H, $J = 7.2$ Hz, Ph-H), 8.00 (d, 1H, $J = 7.8$ Hz, NH); ^{31}P NMR ($CDCl_3$): 23.1; IR (KBr,υ/cm^{-1}): 3248 (N-H), 1662 (C=O), 1217 (P=O); MS (EI): m/z 487 (9), 259 (100), 231 (21), 139 (25); anal. calcd. For C, 56.67; H, 5.38; N, 8.62. Found: C, 56.98; H, 5.74; N, 8.36%.

O, O-Dimethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (4-Chlorophenyl)Methylphosphonate (6c)

White solid, m.p. 122.1∼123.9 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 3.58 (d, 3H, J = 10.8 Hz, OCH_3), 3.66 (d, 3H, J = 10.8 Hz, OCH_3), 3.79 (s, 6H, OCH_3), 5.68 (q, 1H, J = 9.0 Hz, CH), 5.78 (s, 1H, CH), 7.20∼7.53 (m, 7H, Ph-H), 7.79 (d, 1H, J = 6.6 Hz, Ph-H), 8.01 (d, 1H, J = 7.8 Hz, NH); ^{31}P NMR ($CDCl_3$): 22.7; IR (KBr,υ/cm^{-1}): 3259 (N-H), 1669 (C=O), 1221 (P=O); MS (EI): m/z 507 (1), 139 (20), 108 (100), 79 (13); anal. calcd. For C, 52.03; H, 4.56; N, 8.27. Found: C, 52.33; H, 4.88; N, 8.11%.

O, O-Diethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (Phenyl)Methylphosphonate (6d)

White solid, mp 151.9∼152.7 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 1.11 (t, 3H, $J = 6.6$ Hz, CH_3), 1.23 (t, 3H, $J = 6.6$ Hz, CH_3), 3.78 (s, 6H, OCH_3), 3.94∼4.05 (m, 4H, OCH_2), 5.69 (q, 1H, $J = 9.6$ Hz, CH), 5.75 (s, 1H, CH), 7.19∼7.51 (m, 8H, Ph-H), 7.87 (m, 1H, Ph-H), 8.01 (d, 1H, $J = 6.0$ Hz, NH); ^{31}P NMR ($CDCl_3$): 20.2; IR (KBr,υ/cm^{-1}): 3239

(N-H), 1671 (C=O), 1238 (P=O); MS (EI): m/z 501 (10), 364 (16), 258 (100), 103 (15), 77 (7); anal. calcd. For C, 57.48; H, 5.63; N, 8.38. Found: C, 57.64; H, 5.33; N, 8.30%.

O, O-Diethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (4-Methoxyphenyl)Methylphosphonate (6e)

White solid, mp 124.9∼126.7 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 1.12 (t, 3H, J = 7.2 Hz, CH_3), 1.25 (t, 3H, J = 7.2 Hz, CH_3), 3.78 (s, 9H, OCH_3), 3.94∼4.06 (m, 4H, OCH_2), 5.62 (q, 1H, J = 11.4 Hz, CH), 5.73 (s, 1H, CH), 6.76∼7.75 (m, 8H, Ph-H), 7.99 (d, 1H, J = 6.0 Hz, NH); ^{13}C NMR ($CDCl_3$, TMS, 125 MHz): 16.2 ($J_{c,p}$ = 19.1 Hz), 49.6 ($J_{c,p}$ = 128.3 Hz), 54.2, 55.1, 62.9 ($J_{c,p}$ = 21.0 Hz), 85.3, 113.8, 123.0, 125.8, 126.8, 127.6, 129.2, 130.8, 132.2, 150.0, 152.2, 163.3, 164.4, 172.7; ^{31}P NMR ($CDCl_3$): 20.4; IR (KBr,υ/cm^{-1}): 3238 (N-H), 1666 (C=O), 1250 (P=O); MS (EI): m/z 531 (14), 259 (100), 133 (16), 91 (8); anal. calcd. For C, 56.49; H, 5.69; N, 7.91. Found: C, 56.78; H, 5.22; N, 7.57%.

O, O-Diethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (p-Tolyl)Methylphosphonate (6f)

White solid, mp 125.3∼126.7 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 1.12 (t, 3H, J = 6.6 Hz, CH_3), 1.23 (t, 3H, J = 6.6 Hz, CH_3), 2.30 (s, 3H, CH_3), 3.80 (s, 6H, OCH_3), 3.81∼4.05 (m, 4H, OCH_2), 5.65 (q, 1H, J = 9.6 Hz, CH), 5.74 (s, 1H, CH), 7.03∼7.50 (m, 7H, Ph-H), 7.77 (d, 1H, J = 7.2 Hz, Ph-H), 8.00 (d, 1H, J = 7.8 Hz, NH); ^{31}P NMR ($CDCl_3$): 21.0; IR (KBr,υ/cm^{-1}): 3249 (N-H), 1662 (C=O), 1221 (P=O); MS (EI): m/z 515 (8), 259 (70), 258 (100), 119 (17); anal. calcd. For C, 58.25; H, 5.87; N, 8.15. Found: C, 58.58; H, 5.71; N, 7.90%.

O, O-Diethyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (4-Fluorophenyl)Methylphosphonate (6g)

White solid, mp 128.8∼130.3 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 1.13 (t, 3H, J = 7.2 Hz, CH_3), 1.23 (t, 3H, J = 7.2 Hz, CH_3), 3.78 (s, 6H, OCH_3), 3.85∼4.05 (m, 4H, OCH_2), 5.65 (q, 1H, J = 9.0 Hz, CH), 5.76 (s, 1H, CH), 6.92∼7.52 (m, 7H, Ph-H), 7.79 (d, 1H, J = 6.0 Hz, Ph-H), 8.00 (d, 1H, J = 7.2 Hz, NH); ^{31}P NMR ($CDCl_3$): 21.1; IR (KBr,υ/cm^{-1}): 3245 (N-H), 1673 (C=O), 1235 (P=O); MS (EI): m/z 519 (6), 381 (14), 258 (100), 230 (5); anal. calcd. For C, 55.49; H, 5.24; N, 8.09. Found: C, 55.68; H, 5.50; N, 8.03%.

O, O-Di-n-Butyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (Phenyl)Methylphosphonate (6h)

White solid, mp 72.3∼74.1 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 0.79∼0.89 (m, 6H, CH_3), 1.18∼1.56 (m, 8H, CH_2), 3.87 (s, 6H, OCH_3), 3.71∼3.98 (m, 4H, OCH_2), 5.68 (q, 1H, J = 9.0 Hz, CH), 5.73 (s, 1H, CH), 7.19∼7.49 (m, 8H, Ph-H), 7.83 (d, 1H, J = 5.4 Hz, Ph-H), 8.01 (d, 1H, J = 6.6 Hz, NH); ^{13}C NMR ($CDCl_3$, TMS, 125 MHz): 13.5, 18.5 ($J_{c,p}$=9.5 Hz), 32.4 ($J_{c,p}$ = 23.0 Hz), 50.2 ($J_{c,p}$=126.5 Hz), 54.3, 66.7 ($J_{c,p}$ = 19.3 Hz), 85.5, 123.1, 125.9, 127.4, 127.9, 128.0, 128.4, 131.1, 132.2, 135.0, 150.1, 163.3, 164.4, 172.8; ^{31}P NMR ($CDCl_3$): 20.1; IR (KBr, υ/cm^{-1}): 3238 (N-H), 1664 (C=O), 1243 (P=O);

MS (EI): m/z 557 (7), 259 (100), 139 (11), 82 (12); anal. calcd. For C, 60.31; H, 6.51; N 7.54. Found: C, 60.52; H, 6.23; N, 7.36%.

O, O-Di-n-Butyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (p-Tolyl)Methylphosphonate (6i)

White solid, mp 90.3∼91.5 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 0.79∼0.88 (m, 6H, CH_3), 1.18∼1.57 (m, 8H, CH_2), 2.30 (s, 3H, CH_3), 3.77 (s, 6H, OCH_3), 3.71∼3.98 (m, 4H, OCH_2), 5.66 (q, 1H, $J = 11.2$ Hz, CH), 5.72 (s, 1H, CH), 7.02∼7.49 (m, 7H, Ph-H), 7.76 (d, 1H, $J = 6.4$ Hz, Ph-H), 7.99 (d, 1H, $J = 7.6$ Hz, NH); ^{13}C NMR ($CDCl_3$, TMS, 125 MHz): 13.5, 18.5 ($J_{c,p} = 9.6$ Hz), 21.1, 32.4 ($J_{c,p} = 24.9$ Hz), 50.0 ($J_{c,p} = 128.5$ Hz), 54.2, 66.6 ($J_{c,p} = 19.1$ Hz), 85.5, 123.1, 125.9, 127.5, 127.9, 129.2, 131.0, 131.9, 132.2, 137.6, 150.0, 163.3, 164.3, 172.8; ^{31}P NMR ($CDCl_3$): 21.0; IR (KBr,υ/cm^{-1}): 3271 (N-H), 1669 (C=O), 1225 (P=O); MS (EI): m/z 571 (10), 259 (100), 139 (11), 82 (11); anal. calcd. For C, 60.94; H, 6.70; N, 7.35. Found: C, 61.09; H, 6.50; N, 7.15%.

O, O-Di-n-Butyl [2-(4,6-Dimethoxypyrimidin-2-Yloxy)Phenoxyamino] (4-Methoxyphenyl)Methylphosphonate (6j)

White solid, mp 86.5∼87.3 °C; ^{1}H NMR ($CDCl_3$, TMS, 600 MHz): 0.79∼0.89 (m, 6H, CH_3), 1.18∼1.58 (m, 8H, CH_2), 3.77 (s, 9H, OCH_3), 3.71∼3.99 (m, 4H, OCH_2), 5.63 (q, 1H, $J = 10.0$ Hz, CH), 5.71 (s, 1H, CH), 6.76 (d, 2H, $J = 8.4$ Hz, Ph-H), 7.17∼7.51 (m, 5H, Ph-H), 7.70 (d, 1H, $J = 6.4$ Hz, Ph-H), 7.98 (d, 1H, $J = 6.4$ Hz, NH); ^{31}P NMR ($CDCl_3$): 20.4; IR (KBr, υ/cm^{-1}): 3239 (N-H), 1664 (C=O), 1244 (P=O); MS (EI): m/z 587 (51), 260 (78), 133 (100), 121 (40); anal. calcd. For C, 59.28; H, 6.52; N, 7.15. Found: C, 59.76; H, 6.31; N, 6.83%.

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