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Synthesis, Crystal Structure, and Herbicidal Activity of Pyrimidinyl Benzylamine Analogues Containing a Phosphonyl Group

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ABSTRACT: *A series of pyrimidinyl benzylamine analogues containing a phosphonyl group (***2***) was synthesized via the Mannich-type reactions of 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoaldehyde* **1***, aromatic amines, and dialkyl phosphites or triphenyl phosphite in the presence of* $Mg(ClO_4)_2$*. Their structures were characterized by spectroscopic data (infrared,* ^1H *NMR,* ^{31}P *NMR, and mass spectrometry) and elemental analyses, and compound* **2b** *was further determined by X-ray diffraction crystallography. The results of preliminary bioassays (in vitro) showed that most of title compounds* **2** *exhibited higher herbicidal activities against dicotyledonous weeds (Brassica campestris L.) than monocotyledonous weeds (Echinochloa crus-galli). Further bioassays (in vivo) indicated that some of* **2** *displayed as good herbicidal activity against amaranth pigweed (Amaranthus retroflexus) as the commercially available herbicide, Bispyribac-sodium, in both preemergence and postemergence treatments at the dose of 1.5 kg/ha.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:148–155, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20589

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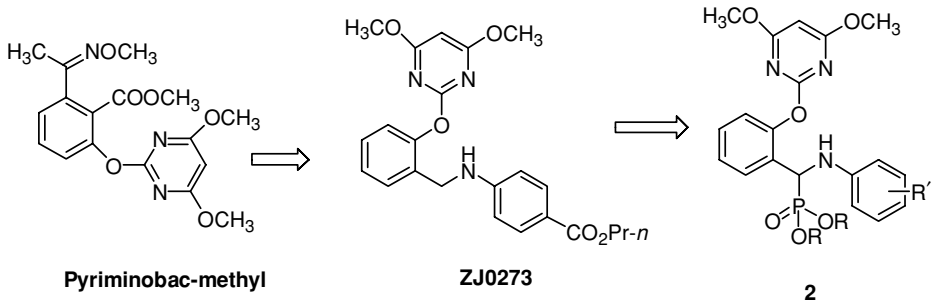
INTRODUCTION

Pyrimidinyl carboxylic acid derivatives are effective herbicides against barnyard grass in different growth stages including preemergence treatment; they also exhibit excellent safety on transplanted rice crops, animals, and fish. These herbicides, which are known as inhibitors of branched chain amino acid (acetolactate or acetohydroxyacid) synthase, have attracted considerable attention from the field of pesticide scientists [1–5]. To date, several pyrimidyl carboxylic acid derivatives, such as Pyriminobac-methyl, have been used as commercially herbicides. Furthermore, pyrimidyl benzylamine derivatives, for example, *N*-[4-(propanoxycarbonyl)phenyl]-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine (ZJ0273), have also been reported to show good herbicidal activities and have been commercialized in China as a prodrug herbicide [6]. Recently, α-amino phosphonic acid and their ester derivatives, as bioisosteres of natural amino acids, have received an increasing attention from the fields of medicinal chemistry and pesticide science because of their wide biological activities such as enzyme inhibitors, antibiotics, and haptens of catalytic antibodies, fungicides, herbicides, plant regulators, and plant virucides [7–13]. To find potent and selective herbicide lead structures, we have synthesized a series of novel pyrimidinyl benzylamine analogues containing a phosphonyl group (**2**) with structure similar to ZJ0273 (Scheme 1). These contain the skeleton of both pyrimidinyl benzylamine and α-amino phosphonate. We hypothesize that these compounds can be oxidized to pyrimidinyl carboxamides and further



SCHEME 1 Molecular designs of title compounds **2a–2r**.

hydrolyzed to its carboxylic acid derivatives in plant organisms, so they might also work as a prodrug of pyriminidyl carboxylic acid herbicides. In this paper, we reported the synthesis and their herbicidal activities of title compounds **2**.

EXPERIMENTAL

Instruments

^{1}H and ^{31}P NMR spectra were obtained on a Varian Mercury Plus-400 (400 MHz) or Varian Mercury Plus-600 (600 MHz) spectrometer at room temperature in $CDCl_3$, with tetramethylsilane and 85% H_3PO_4 as the internal and external standards, respectively; chemical shift values (δ) were in ppm. Elemental analyses were performed on a Germany Elementar Vario EL III elemental analyzer (Moselstraβe, Klotten, Germany). Mass spectra were obtained on a Finnigan TraceMS 2000 spectrometer (Hemel Hempstead, Hertfordshire, HP2 4TG, UK) at 70 eV by EI method or Applied Biosystems (Carlisle, Cumbria, CA6 4RD, UK) API 2000 LC/MS/MS (ESI-MS) spectrometer. The IR spectra were recorded on a Nicolet NEXUS470 spectrometer (Madison, WI 53711-4495, USA) as KBr pellets, with absorption given in cm^{-1}. X-ray diffraction was carried out on a Bruker Smart 1000 CCD diffractometer (Karlsruhe, Germany). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel GF254 plates. Column chromatographic purification was carried out with silica gel. Yields were not optimized. Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were dried and redistilled before use.

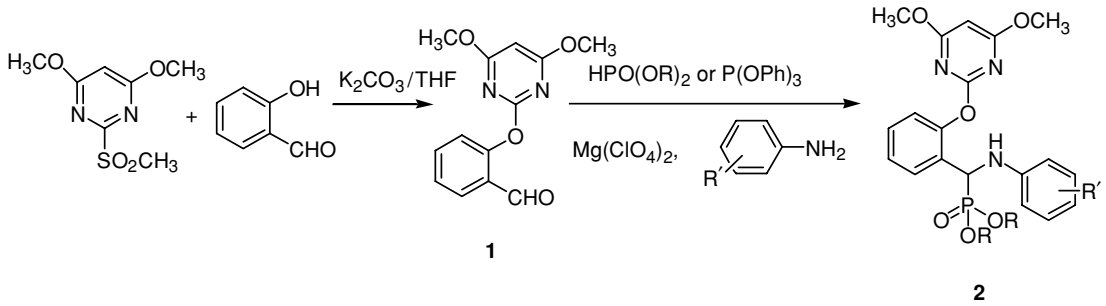
Synthesis of 2-(4,6-Dimethoxypyrimidin-2-yloxy)Benzoaldehyde **1**

A mixture of salicylaldehyde (1.22 g, 10 mmol), 4,6-dimethoxypyrimidin-2-yl-methyl sulfoxide (2.18 g, 10 mmol), and anhydrous potassium carbonate (2.07 g, 15 mmol) in dry tetrahydrofuran (15 mL) was stirred under reflux for 8 h. The solid was filtered off, and the liquid was poured into ice-cold water (20 mL). The crude product was collected by filtration. After recrystallization from ethanol/water (/1:1 v/v), a light yellow crystal was obtained (2.25 g), yield: 94%, mp: 61.5–62.5°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.85 (s, 6H, $2OCH_3$), 5.84 (s, 1H, pyrimidine-H), 7.22 (t, $J = 7.8$ Hz, 2H, ArH), 7.32 (t, $J = 8.0$ Hz, 1H, ArH), 7.60 (d, $J = 7.2$ Hz, 1H, ArH). Anal. Cacld. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.82; H, 4.51; N, 10.97.

General Procedures for the Synthesis of O,O′-Dialkyl (or Diphenyl)-[2-(4,6-Dimethoxypyrimidin-2-yloxy)phenyl] (Substituted Phenylamino) Methylphosphonates **2**

A mixture of 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoaldehyde **1** (0.78 g, 3 mmol), dialkyl phosphite or triphenyl phosphite (3 mmol), substituted phenylamine (3.3 mmol), and $Mg(ClO_4)_2$ (0.033 g, 0.15 mmol) in anhydrous acetonitrile (5 mL) was taken in a 25-mL flask, and the mixture was stirred at 50 to 60°C for 1 to 2 h (monitored by TLC). The solid was filtered off, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel, using petroleum ether and ethyl acetate (2:1 v/v) as the eluent, to give 2 white or yellow crystals in 41% to 87% yields (Scheme 2).

Data for **2a** (R = Me, R′ = H): yield, 78%; white crystals; mp 150–151°C; IR (KBr): ν 3312 (NH), 2958 (CH), 1604, 1497 (Ar), 1221, 1195 (P=O), 1171



SCHEME 2 Synthetic route of title compounds **2a–2r**.

(P—O—C), 1061 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 3.45 (d, $J = 10.2$ Hz, 3H, CH_3O), 3.79 (s, 6H, $2CH_3O$), 3.82 (d, $J = 10.8$ Hz, 3H, CH_3O), 5.26 (d, $J = 24.0$ Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 6.57 (d, $J = 6.4$ Hz, 2H, ArH), 6.65 (t, $J = 6.4$ Hz, 1H, ArH), 7.02 (t, $J = 6.4$ Hz, 2H, ArH), 7.21 (t, $J = 9.0$ Hz, 2H, ArH), 7.30 (t, $J = 7.8$ Hz, 1H, ArH), 7.65 (d, $J = 8.4$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.60; EI-MS: *m/z* 445 (M^+, 5.5), 337 (100), 335 (96.4), 304 (8.1), 197 (14.8), 196 (21.6), 77 (14.5). Anal. Cacld. for $C_{21}H_{24}N_3O_6P$: C, 56.63; H, 5.43; N, 9.43. Found: C, 56.40; H, 5.69; N, 9.12.

Data for **2b** (R = Et, R′ = H): yield, 73%; white crystals; mp 103–104.5°C; IR (KBr): ν 3305 (NH), 2986 (Ar—H), 1604, 1497 (Ar), 1362, 1223 (P=O), 1192, 1165 (P—O—C), 1056 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.06 (t, $J = 7.2$ Hz, 3H, CH_3), 1.29 (t, $J = 7.2$ Hz, 3H, CH_3), 3.69–3.73 (m, 1H, CH_2), 3.79 (s, 6H, $2CH_3O$), 3.90–3.94 (m, 1H, CH_2), 4.18–4.22 (m, 2H, CH_2), 5.22 (d, $J = 24.0$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.55 (d, $J = 7.8$ Hz, 2H, ArH), 6.64 (t, $J = 7.2$ Hz, 1H, ArH), 7.00 (t, $J = 7.2$ Hz, 2H, ArH), 7.18–7.21 (m, 2H, ArH), 7.28 (d, $J = 6.6$ Hz, 1H, ArH), 7.65 (d, $J = 7.2$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 23.27; EI-MS: *m/z* 473.5 (M^+, 3.7), 337 (100), 335 (94.5), 304 (6.2), 198 (64.7), 196 (49.9), 195 (21.6), 139 (9.5), 138 (13.6), 77 (25.5). Anal. Cacld. for $C_{23}H_{28}N_3O_6P$: C, 58.35; H, 5.96; N, 8.88. Found: C, 58.28; H, 6.14; N, 9.21.

Data for **2c** (R = Et, R′ = 4-NO_2): yield, 51%; yellow crystals; mp 145–146°C; IR (KBr): ν 3308 (NH), 2982 (Ar—H), 1600, 1496 (Ar), 1225 (P=O), 1162 (P—O—C), 1050 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.06 (t, $J = 7.8$ Hz, 3H, CH_3), 1.30 (t, $J = 6.8$ Hz, 3H, CH_3), 3.68–3.73 (m, 1H, CH_2), 3.80 (s, 6H, $2CH_3O$), 3.91–3.95 (m, 1H, CH_2), 4.16–4.21 (m, 2H, CH_2), 5.25 (d, $J = 23.4$ Hz, 1H, PCH), 5.55 (s, 1H, NH), 5.80 (s, 1H, pyrimidine-H), 6.57 (d, $J = 9.0$ Hz, 2H, ArH), 7.24 (d, $J = 8.4$ Hz, 2H, ArH), 7.35 (t, $J = 8.4$ Hz, 1H, ArH), 7.60 (d, $J = 7.8$ Hz, 1H, ArH), 7.94 (d, $J = 8.4$ Hz, 2H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 24.36. Anal. Cacld. for $C_{23}H_{27}N_4O_8P$: C, 53.28; H, 5.25; N, 10.81. Found: C, 53.45; H, 5.47; N, 10.76.

Data for **2d** (R = Me, R′ = 4-NO_2): yield, 41%; yellow crystals; mp 175–176°C; IR (KBr): ν 3310 (NH), 2985 (Ar—H), 1606, 1492 (Ar), 1228 (P=O), 1152 (P—O—C), 1068 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 3.46 (d, $J = 9.6$ Hz, 3H, CH_3O), 3.82 (d, $J = 8.4$ Hz, 3H, CH_3O), 3.83 (s, 6H, $2CH_3O$), 5.30 (dd, $J = 24.0$ Hz, $J = 7.2$ Hz, 1H, PCH), 5.68 (s, 1H, NH), 5.81 (s, 1H, pyrimidine-H), 6.59 (d, $J = 7.8$ Hz, 2H, ArH), 7.24 (d, $J = 10.8$ Hz, 2H, ArH), 7.35 (d, $J = 7.2$ Hz, 1H, ArH), 7.62 (d, $J = 6.6$ Hz, 1H, ArH), 7.95 (d, $J = 7.8$ Hz, 2H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 23.64. Anal. Cacld. for $C_{21}H_{23}N_4O_8P$: C, 51.43; H, 4.73; N, 11.42. Found: C, 51.32; H, 4.90; N, 11.23.

Data for **2e** (R = Me, R′ = 4-Br): yield, 72%; white crystals; mp 138–139°C; IR (KBr): ν 3302 (NH), 2991 (Ar—H), 1608, 1502 (Ar), 1223 (P=O), 1165 (P—O—C), 1056 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 3.45 (d, $J = 10.8$ Hz, 3H, CH_3O), 3.80 (s, 6H, $2CH_3O$), 3.82 (d, $J = 11.4$ Hz, 3H, CH_3O), 5.19 (d, $J = 24.0$ Hz, 1H, PCH), 5.80 (s, 1H, pyrimidine-H), 6.45 (d, $J = 8.4$ Hz, 2H, ArH), 7.09 (d, $J = 9.6$ Hz, 2H, ArH), 7.21 (d, $J = 7.2$ Hz, 2H, ArH), 7.31 (d, $J = 7.8$ Hz, 1H, ArH), 7.61 (d, $J = 7.8$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.12; ESI-MS: *m/z* 546 ($M^+ + Na - 1$, 16), 524 (M^+, 100), 415 (21). Anal. Cacld. for $C_{21}H_{23}BrN_3O_6P$: C, 48.11; H, 4.42; N, 8.01. Found: C, 48.30; H, 4.45; N, 7.85.

Data for **2f** (R = Et, R′ = 4-Br): yield, 68%; white crystals; mp 117–118°C; IR (KBr): ν 3308 (NH), 2975 (Ar—H), 1598, 1514 (Ar), 1225 (P=O), 1160 (P—O—C), 1062 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.06 (t, $J = 7.2$ Hz, 3H, CH_3), 1.29 (t, $J = 7.2$ Hz, 3H, CH_3), 3.71–3.76 (m, 1H, CH_2), 3.79 (s, 6H, $2CH_3O$), 3.91–3.93 (m, 1H, CH_2), 4.19 (t, $J = 7.2$ Hz, 2H, CH_2), 5.15 (d, $J = 23.4$ Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.44 (d, $J = 8.4$ Hz, 2H, ArH), 7.07 (d, $J = 9.0$ Hz, 2H, ArH), 7.20 (d, $J = 8.4$ Hz, 2H, ArH), 7.29 (d, $J = 7.2$ Hz, 1H, ArH), 7.62

(d, $J = 7.2$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.06. Anal. Cacld. for $C_{23}H_{27}BrN_3O_6P$: C, 50.01; H, 4.93; N, 7.61. Found: C, 49.83; H, 4.69; N, 7.50.

Data for **2g** (R = Me, R′ = 4-CH_3O): yield, 63%; white crystals; mp 156–157°C; IR (KBr): ν 3302 (NH), 2978 (Ar—H), 1602, 1570 (Ar), 1356 (P=O), 1228 (P—O—C), 1060 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.46 (d, $J = 10.2$ Hz, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.78 (s, 6H, $2CH_3O$), 3.82 (d, $J = 10.8$ Hz, 3H, CH_3O), 5.20 (d, $J = 24.0$ Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 6.53 (d, $J = 7.8$ Hz, 2H, ArH), 6.59 (d, $J = 8.4$ Hz, 2H, ArH), 7.21 (d, $J = 8.4$ Hz, 2H, ArH), 7.28 (d, $J = 7.8$ Hz, 1H, ArH), 7.65 (d, $J = 7.8$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.35. Anal. Cacld. for $C_{22}H_{26}N_3O_7P$: C, 55.58; H, 5.51; N, 8.84. Found: C, 55.17; H, 5.54; N, 8.99.

Data for **2h** (R = Et, R′ = 4-CH_3O): yield, 77%; white crystals; mp 129–130°C; IR (KBr): ν 3301 (NH), 2988 (Ar—H), 1608, 1568, 1515 (Ar), 1360 (P=O), 1223 (P—O—C), 1058 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.06 (t, $J = 6.6$ Hz, 3H, CH_3), 1.30 (t, $J = 7.2$ Hz, 3H, CH_3), 3.67 (s, 3H, CH_3O), 3.73–3.74 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.91–3.94 (m, 1H, CH_2), 4.20 (t, $J = 7.2$ Hz, 2H, CH_2), 5.16 (d, $J = 24.0$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.52 (d, $J = 8.4$ Hz, 2H, ArH), 6.58 (d, $J = 9.0$ Hz, 2H, ArH), 7.20 (d, $J = 8.4$ Hz, 2H, ArH), 7.28 (d, $J = 8.4$ Hz, 1H, ArH), 7.66 (d, $J = 6.6$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 24.86; EI-MS: *m/z* 504 (M^+, 14.0), 367 (76.9), 365 (100), 227 (73.6), 225 (56.0), 139 (19.5), 138 (14.5). Anal. Cacld. for $C_{24}H_{30}N_3O_7P$: C, 57.25; H, 6.01; N, 8.35. Found: C, 57.13; H, 6.17; N, 8.44.

Data for **2i** (R = Me, R′ = 2-Cl): yield, 57%; white crystals; mp 101–102°C; IR (KBr): ν 3305 (NH), 2992 (Ar—H), 1605, 1520 (Ar), 1356 (P=O), 1225 (P—O—C), 1062 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.50 (d, $J = 10.2$ Hz, 3H, CH_3O), 3.79 (s, 6H, $2CH_3O$), 3.83 (d, $J = 10.2$ Hz, 3H, CH_3O), 5.30 (d, $J = 23.6$ Hz, 1H, PCH), 5.78 (s, 1H, pyrimidine-H), 6.54–6.61 (m, 2H, ArH), 6.89 (t, $J = 7.8$ Hz, 1H, ArH), 7.19–7.25 (m, 3H, ArH), 7.32 (d, $J = 11.4$ Hz, 1H, ArH), 7.64 (d, $J = 11.4$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 24.86. Anal. Cacld. for $C_{21}H_{23}ClN_3O_6P$: C, 52.56; H, 4.83; N, 8.76. Found: C, 52.74; H, 5.02; N, 8.85.

Data for **2j** (R = Et, R′ = 2-Cl): yield, 75%; white crystals; mp 93–94°C; IR (KBr): ν 3307 (NH), 2991 (Ar—H), 1604, 1564, 1518 (Ar), 1362 (P=O), 1224 (P—O—C), 1055 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (t, $J = 7.6$ Hz, 3H, CH_3), 1.29 (t, $J = 7.6$ Hz, 3H, CH_3), 3.79 (s, 6H, $2CH_3O$), 3.81–4.04 (m, 2H, CH_2), 4.18–4.22 (m, 2H, CH_2), 5.25 (d, $J = 23.6$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.53–6.60 (m, 2H, ArH), 6.88 (t, $J = 7.6$ Hz, 1H, ArH), 7.18–7.23 (m, 3H, ArH), 7.29 (d, $J = 8.0$ Hz, 1H, ArH), 7.64 (d, $J = 8.0$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.18. Anal. Cacld. for $C_{23}H_{27}ClN_3O_6P$: C, 54.39; H, 5.36; N, 8.27. Found: C, 54.16; H, 5.48; N, 8.42.

Data for **2k** (R = Me, R′ = 3-Br): yield, 72%; white crystals; mp 154–155°C; IR (KBr): ν 3304 (NH), 2984 (Ar—H), 1607, 1572, 1516 (Ar), 1355 (P=O), 1224 (P—O—C), 1056 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.46 (d, $J = 10.2$ Hz, 3H, CH_3O), 3.79 (s, 6H, $2CH_3O$), 3.82 (d, $J = 10.2$ Hz, 3H, CH_3O), 5.22 (d, $J = 23.4$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.48 (d, $J = 6.8$ Hz, 1H, ArH), 6.67 (s, 1H, ArH), 6.76 (d, $J = 7.6$ Hz, 1H, ArH), 6.86 (t, $J = 7.4$ Hz, 1H, ArH), 7.21–7.25 (m, 2H, ArH), 7.32 (t, $J = 6.6$ Hz, 1H, ArH), 7.64 (d, $J = 7.2$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.20. Anal. Cacld. for $C_{21}H_{23}BrN_3O_6P$: C, 48.11; H, 4.42; N, 8.01. Found: C, 48.37; H, 4.51; N, 7.84.

Data for **2l** (R = Et, R′ = 3-Br): yield, 73%; white crystals; mp 115–116°C; IR (KBr): ν 3308 (NH), 2982 (Ar—H), 1612, 1581, 1519 (Ar), 1361 (P=O), 1226 (P—O—C), 1051 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, $J = 6.8$ Hz, 3H, CH_3), 1.30 (t, $J = 6.8$ Hz, 3H, CH_3), 3.70–3.79 (m, 1H, CH_2), 3.80 (s, 6H, $2CH_3O$), 3.85–3.92 (m, 1H, CH_2), 4.17–4.21 (m, 2H, CH_2), 5.18 (d, $J = 23.6$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.47 (d, $J = 6.0$ Hz, 1H, ArH), 6.66 (t, $J = 6.4$ Hz, 1H, ArH), 6.75 (d, $J = 6.8$ Hz, 1H, ArH), 6.85 (t, $J = 8.0$ Hz, 1H, ArH), 7.21–7.31 (m, 3H, ArH), 7.65 (d, $J = 7.6$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.36; ESI-MS: *m/z* 574 ($M^+ + Na - 1$, 8), 552 (M^+, 100), 413 (26). Anal. Cacld. for $C_{23}H_{27}BrN_3O_6P$: C, 50.01; H, 4.93; N, 7.61. Found: C, 50.25; H, 4.72; N, 7.80.

Data for **2m** (R = Me, R′ = 4-Cl): yield, 74%; white crystals; mp 142–143°C; IR (KBr): ν 3305 (NH), 2991 (Ar—H), 1604, 1566, 1519 (Ar), 1354 (P=O), 1220 (P—O—C), 1051 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.45 (d, $J = 10.8$ Hz, 3H, CH_3O), 3.79 (s, 6H, $2CH_3O$), 3.82 (d, $J = 10.8$ Hz, 3H, CH_3O), 5.19 (d, $J = 24.0$ Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.49 (d, $J = 8.4$ Hz, 2H, ArH), 6.95 (d, $J = 9.0$ Hz, 2H, ArH), 7.21 (d, $J = 7.8$ Hz, 2H, ArH), 7.31 (d, $J = 6.6$ Hz, 1H, ArH), 7.61 (d, $J = 6.6$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 243 MHz): δ 25.19. Anal. Cacld. for $C_{21}H_{23}ClN_3O_6P$: C, 52.56; H, 4.83; N, 8.76. Found: C, 52.68; H, 4.94; N, 8.97.

Data for **2n** (R = Et, R′ = 4-Cl): yield, 87%; white crystals; mp 119–121°C; IR (KBr): ν 3308 (NH), 2992 (Ar—H), 1603, 1569, 1520 (Ar), 1358 (P=O), 1222 (P—O—C), 1053 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, $J = 7.2$ Hz, 3H, CH_3), 1.30 (t, $J = 7.2$ Hz, 3H, CH_3), 3.70–3.77 (m, 1H, CH_2), 3.80 (s, 6H, $2CH_3O$), 3.82–3.93 (m, 1H, CH_2), 4.16–4.23

(m, 2H, CH_2), 5.16 (d, $J = 23.6$ Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.49 (d, $J = 7.2$ Hz, 2H, ArH), 6.94 (d, $J = 8.8$ Hz, 2H, ArH), 7.20–7.24 (d, $J = 6.8$ Hz, 2H, ArH), 7.30 (d, $J = 8.0$ Hz, 1H, ArH), 7.62 (d, $J = 8.0$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.54; ESI-MS: *m/z* 530 ($M^+ + Na - 1$, 11), 508 (M^+, 100), 369 (18). Anal. Cacld. for $C_{23}H_{27}ClN_3O_6P$: C, 54.39; H, 5.36; N, 8.27. Found: C, 54.13; H, 5.09; N, 7.91.

Data for **2o** (R = Me, R′ = 4-CF_3): yield, 84%; yellow crystals; mp 107–108°C; IR (KBr): ν 3307 (NH), 3001 (Ar—H), 1611, 1563, 1485 (Ar), 1361 (P=O), 1216 (P—O—C), 1064 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.46 (d, $J = 10.4$ Hz, 3H, CH_3O), 3.79 (s, 6H, $2CH_3O$), 3.82 (d, $J = 10.4$ Hz, 3H, CH_3O), 5.09 (s, 1H, NH), 5.27 (d, $J = 24.0$ Hz, 1H, PCH), 5.79 (s, 1H, pyrimidine-H), 6.60 (d, $J = 8.0$ Hz, 2H, ArH), 7.22–7.36 (m, 5H, ArH), 7.63 (d, $J = 8.0$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.68. Anal. Cacld. for $C_{22}H_{23}F_3N_3O_6P$: C, 51.47; H, 4.52; N, 8.18. Found: C, 51.25; H, 4.61; N, 8.39.

Data for **2p** (R = Et, R′ = 4-CF_3): yield, 87%; white crystals; mp 124–125°C; IR (KBr): ν 3305 (NH), 2996 (Ar—H), 1605, 1561, 1486 (Ar), 1357 (P=O), 1214 (P—O—C), 1060 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, $J = 7.2$ Hz, 3H, CH_3), 1.30 (t, $J = 7.2$ Hz, 3H, CH_3), 3.70–3.79 (m, 1H, CH_2), 3.81 (s, 6H, $2CH_3O$), 3.90–3.94 (m, 1H, CH_2), 4.19 (t, $J = 7.2$ Hz, 2H, CH_2), 5.08 (s, 1H, NH), 5.23 (d, 1H, $J = 23.2$ Hz, PCH), 5.78 (s, 1H, pyrimidine-H), 6.59 (d, $J = 8.4$ Hz, 2H, ArH), 7.20–7.32 (m, 5H, ArH), 7.64 (d, $J = 8.0$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 24.79; ESI-MS: *m/z* 541.6 (M^+, 100). Anal. Cacld. for $C_{24}H_{27}F_3N_3O_6P$: C, 53.24; H, 5.03; N, 7.76. Found: C, 53.37; H, 5.20; N, 7.86.

Data for **2q** (R = Ph, R′ = 4-CF_3): yield, 61%; white crystals; mp 153–154°C; IR (KBr): ν 3306 (NH), 3022 (Ar—H), 1609, 1569, 1487 (Ar), 1362 (P=O), 1217 (P—O—C), 1188, 1061 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 6H, $2CH_3O$), 5.21 (d, $J = 7.6$ Hz, 1H, NH), 5.72 (dd, $J = 8.8$ Hz, $J = 24.0$ Hz, 1H, PCH), 5.76 (s, 1H, pyrimidine-H), 6.65 (d, $J = 8.4$ Hz, 2H, ArH), 6.75 (d, $J = 8.4$ Hz, 2H, ArH), 7.03–7.37 (m, 13H, ArH), 7.71 (d, $J = 7.6$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.82; ESI-MS: *m/z* 659 ($M^+ + Na - 1$, 12), 637.6 (M^+, 87), 404 (100). Anal. Cacld. for $C_{32}H_{27}F_3N_3O_6P$: C, 60.29; H, 4.27; N, 6.59. Found: C, 60.13; H, 4.37; N, 6.73.

Data for **2r** (R = *n*-Bu, R′ = 4-CF_3): yield, 71%; yellow crystals; mp 71–72°C; IR (KBr): ν 3292 (NH), 2963 (Ar—H), 1599, 1567, 1469 (Ar), 1367 (P=O), 1228, 1194 (P—O—C), 1104, 1060 (C—O—C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.81 (t, $J = 7.6$ Hz, 3H, CH_3), 0.87 (t, $J = 7.6$ Hz, 3H, CH_3), 1.15–1.62 (m, 8H, $2CH_2CH_2$), 3.64–3.67 (m, 1H, CH_2), 3.78 (s, 6H, $2CH_3O$), 3.81–3.89 (m, 1H, CH_2), 4.09–4.14 (m, 2H, CH_2), 5.23 (d, $J = 23.6$ Hz, 1H, PCH), 5.77 (s, 1H, pyrimidine-H), 6.58 (d, $J = 8.4$ Hz, 2H, ArH), 7.20–7.24 (m, 4H, ArH), 7.30 (d, $J = 8.0$ Hz, 2H, ArH), 7.65 (d, $J = 8.0$ Hz, 1H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.16; ESI-MS: *m/z* 619 ($M^+ + Na - 1$, 11), 597.6 (M^+, 100), 404 (26). Anal. Cacld. for $C_{29}H_{35}F_3N_3O_6P$: C, 56.28; H, 5.90; N, 7.03. Found: C, 56.46; H, 5.81; N, 6.94.

Crystal Structure Determination

In the determination of the structure of the single crystal, X-ray intensity data were recorded on a Bruker SMART CCD area detector diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å). In the range $1.61° \leq \theta \leq 26.50°$, 10,172 independent reflections were obtained. Intensities were corrected for Lorentz and polarization effects and empirical absorption, and all data were corrected using the SADABS [14] program. The structure was solved by direct method using the SHELXS-97 program [15]. All of the nonhydrogen atoms were refined on $F2$ anisotropically by a full-matrix, least-squares method. The hydrogen atoms were located from the difference Fourier map, but their positions were not refined. The contributions of these hydrogen atoms were included in structure factor calculations. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0714P)^2 + 0.0000P]$, where $P = [(F_o)^2 + 2F_c^2]/3$. The maximum and minimum difference peaks and holes are 0.24 and –0.26 e Å^{-3}, respectively, $S = 0.89$, and $(\Delta/\sigma)_{max} = 0.00$. Atomic scattering factors and anomalous dispersion corrections were taken from the *International Table for X-ray Crystallography* [16]. X-ray diffraction indicated that the crystal ($C_{23}H_{28}N_3OP$, $M_r = 473.45$) is of triclinic, space group $P1$ with $a = 9.685(1)$ Å, $b = 16.366(2)$ Å, $c = 16.998(2)$ Å, $\alpha = 98.954(3)°$, $\beta = 101.436(3)°$, $\gamma = 104.859(2)°$, $V = 2491.0(6)$ Å^3, $Z = 4$, $D_c = 1.262$ g/cm^3, $F(000) = 1000$, μ(MoKα) = 0.152 mm^{-1}. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC No. 729200 (available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving/html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK).

Biological Assay

Herbicidal Activity (In Vitro). The herbicidal evaluation of compounds **2** was undertaken according to the previously reported method [17] and

TABLE 1 The Herbicidal Activities of Compounds **2a–2r** (In Vitro, % Inhibition)

	Brassica campestris		*Echinochloa crus-galli*	
Compound	*100 mg/L (Root/Stalk)*	*10 mg/L (Root/Stalk)*	*100 mg/L (Root/Stalk)*	*10 mg/L (Root/Stalk)*
2a	78.9/68.1	77.8/53.2	68.6/58.9	51.4/43.6
2b	84.4/76.6	43.3/31.9	37.1/51.3	20.0/51.3
2c	74.4/44.7	66.7/38.3	71.4/56.4	48.6/48.7
2d	64.4/48.9	53.3/40.4	65.7/46.2	48.6/43.6
2e	83.3/68.1	72.2/44.7	57.1/64.1	40.0/43.6
2f	74.4/68.1	68.9/57.4	60.0/61.5	37.1/41.0
2g	73.3/57.4	67.8/38.3	57.1/69.2	34.3/35.9
2h	78.9/51.1	73.3/46.8	51.4/64.1	37.1/48.7
2i	82.2/70.2	51.1/44.7	62.8/66.7	22.8/30.8
2j	65.5/63.8	45.5/46.8	48.6/56.4	22.8/38.5
2k	68.9/53.2	53.3/31.9	71.4/61.5	42.8/38.5
2l	68.9/51.1	43.3/36.2	37.1/48.7	5.7/30.8
2m	74.4/51.1	45.5/14.9	51.4/51.3	34.3/38.5
2n	77.8/51.1	57.8/21.3	37.1/33.3	31.4/20.5
2o	95.5/89.4	48.9/46.8	80.0/53.8	28.6/38.5
2p	93.3/80.8	64.4/48.9	74.3/53.8	34.3/30.8
2q	64.4/55.3	63.0/31.9	65.7/53.8	28.6/0
2r	64.4/55.3	54.4/38.3	65.7/41.0	45.7/35.9

carried out in the Laboratory of Biological Activities Test, College of Chemistry, Central China Normal University, Wuhan, People's Republic of China. The results are listed in Table 1.

Herbicidal Activity (In Vivo). The herbicidal activities of some of **2** were evaluated using the commercially available herbicide, Bispyribac-sodium, as the control drug according to a previously reported procedure [18,19].

Plant Material. Two dicotyledonous crops, rape (*Brassica campestris L.*) and amaranth pigweed (*Amaranthus retroflexus*), and two monocotyledonous crops, barnyard grass [*Echinochloa crus-galli*] and hairy crabgrass [*Digitaria sanguinalis* (L.) Scop.], were used to test the herbicidal activities of compounds. The seeds of amaranth pigweed were reproduced outdoors and stored at room temperature. Seeds of rape, barnyard grass, and hairy crabgrass were purchased from the Institute of Crop, Tianjin Agriculture Science Academy (Tianjin, China).

Treatment. The emulsions of purified compounds were prepared by dissolving them in *N*,*N*-dimethylformamide (100 μL) with the addition of a little Tween 20 and proper water. There were three replicates for each treatment. The mixture of the same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was used as the control.

Preemergence Treatment. Sandy clay (100 g) in a plastic box (11 cm × 7.5 cm × 6 cm) was moistened with water. Fifteen sprouting seeds of the weed under test were planted in fine earth (0.6-cm depth) in the glasshouse and sprayed with the test compound solution.

Postemergence Treatment. Seedlings (one leaf and one stem) of the weed were sprayed with the test compounds at the same rate as that used in the preemergence test. For both methods, the fresh weights were determined 21 days later and the percentage inhibition relative to the controls was calculated. The herbicidal activity is summarized in Table 2.

RESULTS AND DISCUSSION

Synthesis

Salicylaldehyde reacted with 4,6-dimethoxypyrimidin-2-yl-methylsulfone in the presence of potassium carbonate to generate 2-(4,6-dimethoxypyrimidin-2-yloxy)benzoaldehyde **1** in a high yield. Target compounds **2** were synthesized via the Mannich-type reactions of **1**, aromatic amines, and dialkyl phosphites or triphenyl phosphite in the presence of $Mg(ClO_4)_2$ in moderate to good yields. It was found that $Mg(ClO_4)_2$ can reduce the reaction time and improve the yields of products **2** greatly. The structures of target compounds **2** were confirmed from their spectroscopic data (infrared, ^{1}H NMR, ^{31}P NMR, EI-MS, or ESI-MS) and

TABLE 2 The Herbicidal Activities of Some of **2** (In Vivo, 1.5 kg/ha, % Inhibition)

	Preemergence Treatment				*Postemergence Treatment*			
Compound	*Brassica campestris*	*Amaranthus retroflexus*	*Echinochloa crus-galli*	*Digitaria sanguinalis*	*Brassica campestris*	*Amaranthus retroflexus*	*Echinochloa crus-galli*	*Digitaria sanguinalis*
2b	61.6	100	87.9	90.3	87	100	90.7	62.0
2o	36.4	81.8	33.7	33.7	25.3	54.7	24.9	23.2
2p	62.3	51.1	6.0	5.0	9.3	39.8	18.6	10.0
Bispyribac-sodium	99.9	100	95.5	96.7	100	100	100	100

elemental analyses. In addition, the crystal structure of compound **2b** was further determined by X-ray single-crystal diffraction analyses. As shown in Fig. 1, the dihedral angels between pyrimidine and phenyl [C(7)—C(9)—C(11)] rings, pyrimidine and phenyl [C(15)—C(17)—C(19)] rings, two phenyl rings are 89.28, 25.43, and 68.55°, respectively. In addition, some intra- and intermolecular hydrogen bonds were observed, such as N(3)—H(3A)···O(4) [2.15(2) Å, 164.9 (2)°], C(11)—H(11)···N(3) [2.59 Å, 100°], C(13)—H(13)···O(1)[2.45 Å, 102°], C(15)—H(15)···O(12) [2.57 Å, 138°], C(20)—H(23B)···O(3) [2.59 Å, 157°], C(23)—H(23B)···O(3) [2.59 Å, 132°], in crystal **2b**.

Herbicidal Activities

The preliminary herbicidal activity (in vitro) of compounds **2** against *B. campestris L.* (rape) and *Echinochloa crus-galli* (barnyard grass) has been investigated at the dosages of 100 and 10 mg/L, respectively. The results indicated that some of **2** possessed good herbicidal activities against dicotyledonous plants (*B. campestris L.*) at the concentration of 100 mg/L. For example, compounds **2o** and **2p** possessed 95.5% and 93.3% inhibitory activities against the root of *B. campestris L.* and 89.4% and 80.8% against the stalk at the concentration of 100 mg/L, respectively. Further bioassays (in vivo) indicated that some compounds of **2** exhibited as good

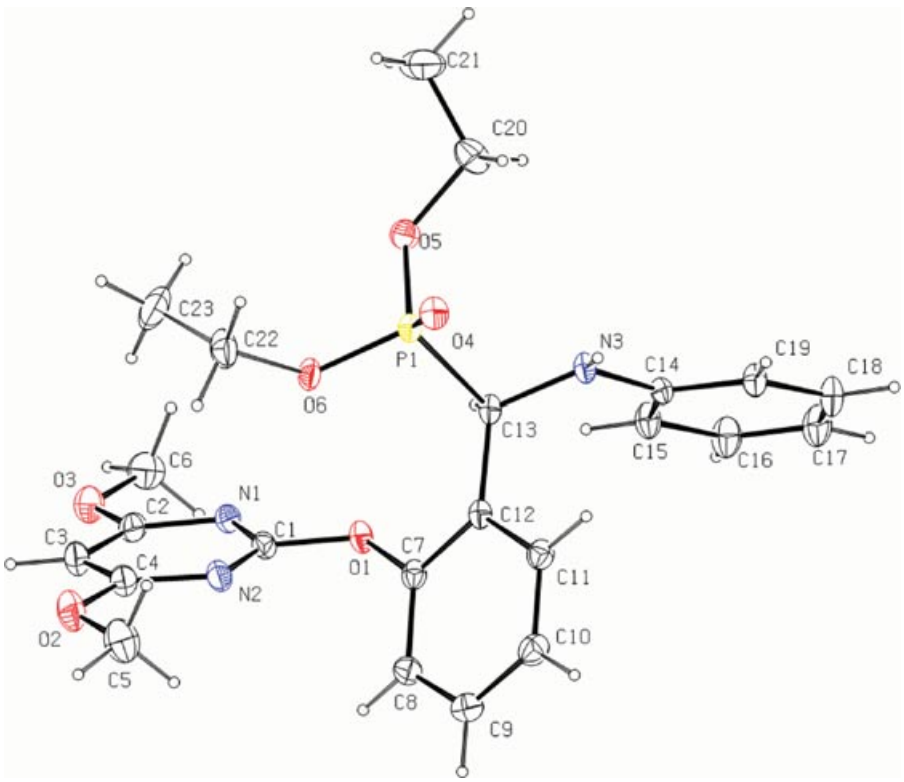


FIGURE 1 Molecular structure of compound **2b**.

herbicidal activity against *A. retroflexus* as the commercially available herbicide, Bispyribac-sodium, at a dose of 1.5 kg/ha. For example, compound **2b** showed 100% inhibition against amaranth pigweed (*A. retroflexus*) in both preemergence and postemergence treatments at the dose of 1.5 kg/ha and compound **2o** exhibited 81.8% inhibition against amaranth pigweed (*A. retroflexus*) in preemergence treatments at the same concentration.

CONCLUSIONS

We synthesized a series of pyrimidinyl benzylamine analogs containing a phosphonyl group (**2**) via the Mannich-type reaction. The results of preliminary bioassays showed that some of **2** displayed good herbicidal activity against the root of *B. campestris L.* at the concentration of 100 mg/L. Further bioassays (in vivo) indicated that some of **2** exhibited as good herbicidal activity against amaranth pigweed (*A. retroflexus*) as the commercially available herbicide, Bispyribac-sodium, in both preemergence and postemergence treatments at the dose of 1.5 kg/ha.

REFERENCES

[1] Hirai, K.; Uchida, A.; Ohno, R. In Herbicide Classes in Development: Mode of Action, Targets, Genetic Engineering, Chemistry, Boger, P.; Wakabayashi, K.; Hirai, K. (Eds.); Springer-Verlag: Berlin, Heidelberg, 2002; pp. 179–278.
[2] Shimizu, T. J. Pestic Sci 1997, 22, 254–257.
[3] Tamaru, M.; Inoue, J.; Hanai, R. J Agric Food Chem 1997, 45, 2777–2783.
[4] Tamaru, M.; Takehi, T.; Masuyama, N. Pestic Sci 1996, 47, 327–335.
[5] Tomlin, C. D. S. The Pesticide Manual, A World Compendium, 14th ed.; British Crop Production Council, Hampshire, GU34 2QD, UK, 2006; p. 911.
[6] (a) Lv, L.; Chen, J.; Wu, J.; Ling, W.; Mao, L. S.; Li, M. Z.; Cai, X.; Peng, W. L.; Wu, Y.; Wu, S. G.; Wang, H. J.; Wang, G. C.; Cui, H.; Han, S. D.; Qiu, W. L.; Wang, Y. H. US Patent 6,800,590 B2, 2004; (b) Lv, L.; Wu, J.; Chen, J.; Ling, W.; Peng, W. L.; Mao, L. S.; Wang, G. C.; Li, M. Z. ZL Patent 0,0130,735.5, 2003; (c) Wu, J.; Cheng, J.; Lu, L. J Agric Food Chem 2006, 54(16), 5954–5957.
[7] Kuhkar, V. P.; Hudson, H. R. (Eds.). Synthesis of α-Aminoalkanephosphonic and α-Aminophosphinic Acids; Wiley: Chichester, UK, 2000.
[8] Palacios, F.; Alonso, C.; de los Santos, J. M. Chem Rev 2005, 105, 899–931.
[9] Gioia, P. L.; Chuah, P. H.; Sclapari, T. WO Patent 2,007,054,540, 2007.
[10] Kafarski, P.; Lejczak, B. Curr Med Chem Anti-Cancer Agents 2001, 1, 301–312.
[11] Lintunen, T.; Yli-Kauhaluoma, J. T. Bioorg Med Chem Lett 2000, 10, 1749–1750.
[12] Kafarski, P.; Lejczak, B. Phosphorus Sulfur 1991, 63, 193–215.
[13] Chen, M. H.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Cai, X. J.; Hu, D. Y.; Xue, W.; Zeng, S. J Agric Food Chem 2009, 57, 1383–1388.
[14] Sheldrick, G. M. Program for Empirical Absorption Correction of Area Detector Data; University of Göttingen: Germany, 1996.
[15] Sheldrick, G. M. SHELXTL V5.1, Software Reference Manual; Bruker AXS: Madison, WI, 1997.
[16] Wilson, A. J. International Table for X-ray Crystallography; Kluwer: Dordrecht, the Netherlands, 1992; Vol. C, Tables 6.1.1.4 (pp. 500–502) and 4.2.6.8 (pp. 219–222).
[17] (a) Chen, X. B.; Shi, D. Q.; Zhu, X. F. Chin J Chem 2007, 25, 1854–1858; (b) Liu, H.; Wang, H. Q.; Ding, M. W.; Liu, Z. J.; Xiao, W. J. J Fluoro Chem 2006, 127, 1584–1590.
[18] (a) Chen, X. B.; Shi, D. Q. Chin J Org Chem 2009, 29, 1096–1099; (b) Liu, Y.; Cai, B.; Li, Y.; Song, H.; Huang, R.; Wang, Q. J Agric Food Chem 2007, 55, 3011–3017.
[19] (a) Wang, Q.; Sun, H.; Cao, H.; Cheng, M.; Huang, R. J Agric Food Chem 2003, 51, 5030–5035; (b) Liu, Y. X.; Wei, D. G.; Zhu, Y. R.; Liu, S. H.; Zhang, Y. L.; Zhao, Q. Q.; Cai, B. L.; Li, Y. H.; Song, H. B.; Liu, Y.; Wang, Y.; Huang, R. Q.; Wang, Q. M. J Agric Food Chem 2008, 56, 204–212.