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RESEARCH ARTICLE

Synthesis and Herbicidal Evaluation of Aryloxyphenoxypropionate Derivatives Containing Purine Moiety

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Abstract: ***Background:*** A series of purinoxyphenoxypropionates were designed and synthesized by introducing 8-(trifluoromethyl)-9*H*-purine into the aryloxyphenoxypropionate backbone.

***Methods*:** The products were characterized by ^{1}H NMR and HRMS.

***Results and Conclusion*:** Preliminary bioassays indicated that most of the compounds exhibited good herbicidal activity at 200 mg/L.

Keywords: Purinoxyphenoxypropionates, herbicidal activity, ACCase, synthesis, antimycobacterial, antiviral.

1. INTRODUCTION

Acetyl-coenzyme A carboxylase (ACCase) is a key enzyme in fatty acid biosynthesis in both eukaryotes and prokaryotes [1, 2]. Aryloxyphenoxypropionate (APP) derivatives [3], such as diclofop-methyl, fenoxaprop-*p*-methyl, quizalofop-*p*-ethyl and haloxyfop-methyl (Fig. **1**), are strong inhibitors of ACCase and are a very important class of post-emergence herbicides used for the control of annual and perennial grasses in broadleaf crops.

From Fig. (**1**), recently discovered APP herbicides always contain different heterocycles motifs, such as pyridine, quizaline, benzoxazole and so on. In order to discover new bioactive compounds [4-14], especially new APP herbicides, the natural product purine was applied in this structure, because the purine possessed diverse activities including insecticidal [15], antimycobacterial [16], antiviral [17], anticancer [18]. Following our drug design strategies, the main structure phenoxypropionate was maintained, the heterocycle was replaced by purine. Here we described the synthesis and structural characterization of APP derivatives containing purine moiety, as well as the evaluation of their herbicidal activity against monocotyledonous and dicotyledonous plants.

2. EXPERIMENTAL

The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instrument Co., China) and were uncorrected. ^{1}H NMR spectra were recorded at 600 MHz using a Bruker AVANCE III HD spectrometer (Bruker Co., Switzerland) in $CDCl_3$ solution with TMS as the internal standard, and chemical shift values (δ) were given in parts per million (ppm). HRMS were recorded on an UPLC/Xevo G2-XS Q-TOF Waters mass spectrometer (Waters Corp., USA). Unless otherwise noted, all chemicals and reagents were commercially available and were used directly without further purification. All solvents were dried and redistilled before use.

2.1. Synthesis of 4,6-dichloropyrimidin-5-amine (1)

Iron powder (57.59 g, 1031.2 mmol) and saturated ammonium chloride solution (260.0 mL) were added to a solution of 4,6-dichloro-5-nitropyrimidine (100.02 g, 515.6 mmol) in 1200 mL of ethanol-water mixed solvent (5:1, v/v). The mixture was stirred and refluxed for 4 h. The insoluble materials were filtered off and washed with tetrahydrofuran. The filtrate was concentrated to 1/5 of its original volume under reduced pressure and extracted with ethyl acetate. The

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organic solution was washed with saturated salt water (3×300 mL), dried over anhydrous magnesium sulfate and evaporated under vacuum to get 4,6-dichloropyrimidin-5-amine (**1**) as pale yellow solid which was used without further purification. Yield 73.8%, m.p. 144-148°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.53 (s, 2H, NH_2), 8.23 (s, 1H, pyrimidine-H).

2.1.1. General Synthetic Procedure for 6-chloro-N^4-(substituted phenyl) pyrimidine-4, 5-diamine (2)

Compound **1** (11.48 g, 70.0 mmol) was added to a solution containing 190 mL of water, 30 mL of ethanol, 3 mL of concentrated hydrochloric acid and substituted phenyl amine (91.0 mmol). The solution was stirred and refluxed till the reaction finished (monitored by thin layer chromatography). The reaction mixture was cooled, neutralized with potassium carbonate and filtered. The residue was washed and recrystallized from a 1:2 water-methanol mixture to give the compounds **2a-2h**.

2.1.1.1. 6-chloro-N^4-(m-tolyl)pyrimidine-4,5-diamine (2a)

Brown solid, yield 69.3%, m.p. 155-157°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.53 (s, 2H, NH_2), 6.79 (s, 1H, NH), 6.95 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.24-7.25 (m, 1H, Ar-H), 7.32-7.33 (m, 2H, Ar-H), 8.18 (s, 1H, pyrimidine-H).

2.1.1.2. 6-chloro-N^4-(4-ethoxyphenyl)pyrimidine-4,5-diamine (2b)

Brown solid, yield 77.5%, m.p. 173-174°C; ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.0 Hz, 3H, CH_3), 3.49 (s, 2H, NH_2), 4.03 (q, *J* = 7.0 Hz, 2H, CH_2), 6.68 (s, 1H, NH), 6.91 (d, 2H, *J* = 8.9 Hz, Ar-H), 7.38 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.14 (s, 1H, pyrimidine-H).

2.1.1.3. 6-chloro-N^4-(3-isopropylphenyl)pyrimidine-4,5-diamine (2c)

Brown solid, yield 74.1%, m.p. 126-128°C; ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.26 (d, *J* = 6.9 Hz, 6H, $CH(\underline{CH_3})_2$), 2.88-2.95 (m, 1H, $\underline{CH}(CH_3)_2$), 3.58 (s, 2H, NH_2), 6.87 (s, 1H, NH), 7.00 (d, *J*=7.6 Hz, 1H, Ar-H), 7.20-7.31 (m, 2H, Ar-H), 7.41-7.43 (m, 1H, Ar-H), 8.17 (s, 1H, pyrimidine-H).

Other compounds **2** can be synthesized according to the similar procedure and can be used in the next reaction directly without further structure characterization.

2.1.2. General Synthetic Procedure for 6-chloro-9-(substituted phenyl)-8-(trifluoro-methyl) -9H-purine (3)

To a solution of compound **2** (15.0 mmol) in dry toluene (40.0 mL) was added trifluoroacetic acid (2.28 g, 30.0 mmol) and phosphorus oxychloride (4.2 mL, 45.0 mmol). The resulting mixture was stirred at room temperature for 0.5 h and then heated to reflux. After the reaction was completely finished, the reaction mixture was slowly and cautiously poured into 100 mL of ice/water, and the resulting mixture was basified with solid NaOH and $NaHCO_3$. The organic layer was then separated, washed with water, dried with anhydrous magnesium sulfate, and evaporated under vacuum to afford the compound **3a-3h**.

2.1.2.1. 6-chloro-9-(m-tolyl)-8-(trifluoromethyl)-9H-purine (3a)

Yellow solid, yield 74.1%, m.p. 78-79°C; ^{1}H NMR (600MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 7.22-7.23 (m, 2H, Ar-H), 7.45 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.51 (t, *J* = 8.1 Hz, 1H), 8.85 (s, 1H, pyrimidine-H).

2.1.2.2. 6-chloro-9-(4-ethoxyphenyl)-8-(trifluoromethyl)-9H-purine (3b)

Yellow viscous liquid, yield 74.1%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.48 (t, *J* = 7.0 Hz, 3H, CH_3), 4.13 (q, *J* = 7.0 Hz, 2H, CH_2), 7.08 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.84 (s, 1H, pyrimidine-H).

2.1.2.3. 6-chloro-9-(p-tolyl)-8-(trifluoromethyl)-9H-purine (3d)

Yellow solid, yield 74.1%, m.p. 78-80°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.50 (s, 3H, CH_3), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.84 (s, 1H, pyrimidine-H).

Other compounds **3** were synthesized using a similar experimental procedure and were used directly without further structure characterization in the next reaction.

2.1.3. General Procedure for the Synthesis of Target Compounds (4)

To a mixture of compound **3** (0.95 mmol) and potassium carbonate (0.26 g, 1.9 mmol) in dimethyl formamide (10 mL), appropriate alkyl 2-(4-hydroxyphenoxy)propanoate (1.14 mmol)was added while stirring. The reaction mixture was heated with stirring at 100°C for 7 h. After cooling the solution was poured into saturated brines (60 mL) and extracted with ethyl acetate (3×30mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was separated by flash chromatography (silica gel, 20:80 ethyl acetate/hexane) to afford the corresponding pure title compounds **4a-4o**.

2.1.3.1. (S)-methyl 2-(4-((9-(m-tolyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy) Propanoate (4a)

Yellow viscous liquid, yield 74%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 2.47 (s, 3H, Ar-CH_3), 3.79 (s, 3H, OCH_3), 4.77 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.21 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.24-7.25 (m, 2H, Ar-H), 7.42 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.49 (t, *J* = 8.1 Hz, 1H, Ar-H), 8.58 (s, 1H, pyrimidine-H); HRMS calcd for $C_{23}H_{20}N_4O_4F_3$ ($[M + H]^+$) 473.1437, found 473.1426.

2.1.3.2. (S)-ethyl 2-(4-((9-(m-tolyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4b)

Yellow viscous liquid, yield 77%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.28 (t, 3H, $CH_2\underline{CH_3}$), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 2.47 (s, 3H, Ar-CH_3), 4.25 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.75 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.1

Hz, 2H, Ar-H), 7.21 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.24-7.25 (m, 2H, Ar-H), 7.42 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.49 (t, *J* = 8.1 Hz, 1H, Ar-H), 8.58 (s, 1H, pyrimidine-H); HRMS calcd for $C_{24}H_{22}N_4O_4F_3$ ([M + H]$^+$) 487.1593, found 487.1574.

2.1.3.3. (S)-methyl 2-(4-((9-(4-ethoxyphenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4c)

Yellow viscous liquid, yield 70%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.47 (t, *J* = 7.0 Hz, 3H, $CH_2\underline{CH_3}$), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 3.79 (s, 3H, OCH_3), 4.12 (q, *J* = 6.9 Hz, 2H, $\underline{CH_2}CH_3$), 4.77 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.96 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.21 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{24}H_{22}N_4O_5F_3$ ([M + H]$^+$) 503.1542, found 503.1553.

2.1.3.4. (S)-ethyl 2-(4-((9-(4-ethoxyphenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4d)

Yellow viscous liquid, yield 65%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.28 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.47 (t, *J* = 7.0 Hz, 3H, Ar-$OCH_2\underline{CH_3}$), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.12 (q, *J* = 7.0 Hz, 2H, Ar-$O\underline{CH_2}CH_3$), 4.25 (q, *J* = 7.1Hz, 2H, $\underline{CH_2}CH_3$), 4.75 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{25}H_{24}N_4O_5F_3$ ([M + H]$^+$) 517.1699, found 517.1719.

2.1.3.5. (S)-butyl 2-(4-((9-(4-ethoxyphenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4e)

Yellow viscous liquid, yield 68%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 0.90 (t, *J* = 7.4 Hz, 3H, $O(CH_2)_3\underline{CH_3}$), 1.31-1.37 (m, 2H, $O(CH_2)_2\underline{CH_2}CH_3$), 1.47 (t, *J* = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.58-1.60 (m, 2H, $OCH_2\underline{CH_2}CH_2CH_3$), 1.65 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.12 (q, *J* = 7.0 Hz, 2H, $O\underline{CH_2}CH_3$), 4.17-4.21 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$), 4.76 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.96 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.56 (s, 1H, pyrimidine-H); HRMS calcd for $C_{27}H_{28}N_4O_5F_3$ ([M + H]$^+$) 545.2012, found 545.1998.

2.1.3.6. (S)-butyl 2-(4-((9-(3-isopropylphenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4f)

Yellow viscous liquid, yield 73%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 0.89 (t, *J* = 7.1 Hz, 3H, $O(CH_2)_3\underline{CH_3}$), 1.27-1.31 (m, 8H, $CH(\underline{CH_3})_2$, $O(CH_2)_2\underline{CH_2}CH_3$), 1.60-1.64 (m, 5H, $OCH_2\underline{CH_2}CH_2CH_3$, $CH\underline{CH_3}$), 2.99-3.03 (m, 1H, $C\underline{H}(CH_3)_2$), 4.14-4.20 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$), 4.74 (q, 1H, *J* = 6.8 Hz, $\underline{CH}CH_3$), 6.94-6.98 (m, 2H, Ar-H), 7.17-7.26 (m, 4H, Ar-H), 7.44-7.51 (m, 2H, Ar-H), 8.58 (s, 1H, pyrimidine-H); HRMS calcd for $C_{28}H_{30}N_4O_4F_3$ ([M + H]$^+$) 543.2219, found 543.2244.

2.1.3.7. (S)-ethyl 2-(4-((9-(p-tolyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4g)

Yellow viscous liquid, yield 76%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.28 (t, *J* = 7.1Hz, 3H, $CH_2\underline{CH_3}$), 1.64 (d, 3H, *J* = 6.8 Hz, $CH\underline{CH_3}$), 2.48 (s, 3H, Ar-CH_3), 4.25 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.75 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.33 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.56 (s, 1H, pyrimidine-H); HRMS calcd for $C_{24}H_{22}N_4O_4F_3$ ([M + H]$^+$) 487.1593, found 487.1619.

2.1.3.8. (S)-butyl 2-(4-((9-(p-tolyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4h)

Yellow viscous liquid, yield 74%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 0.91 (t, *J* =7.4Hz, 3H, $O(CH_2)_3\underline{CH_3}$), 1.32-1.36 (m, 2H, $O(CH_2)_2\underline{CH_2}CH_2CH_3$), 1.58-1.62 (m, 2H, $OCH_2\underline{CH_2}$ CH_2CH_3), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 2.48 (s, 3H, Ar-CH_3), 4.13-4.21 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$), 4.76 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.96 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.56 (s, 1H, pyrimidine-H); HRMS calcd for $C_{26}H_{26}N_4O_4F_3$ ([M + H]$^+$) 515.1906, found 515.1922.

2.1.3.9. (S)-methyl 2-(4-((9-(4-fluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4i)

Yellow viscous liquid, yield 80%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.65 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 3.79 (s, 3H, OCH_3), 4.77 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.21 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.44-7.47 (m, 2H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{22}H_{17}N_4O_4F_4$ ([M + H]$^+$) 477.1186, found 477.1196.

2.1.3.10. (S)-ethyl 2-(4-((9-(2-fluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4j)

Yellow viscous liquid, yield 82%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.27 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.25 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.75 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.22 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.36-7.41 (m, 2H, Ar-H), 7.48 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.62-7.66 (m, 1H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{23}H_{19}N_4O_4F_4$ ([M + H]$^+$) 491.1342, found 491.1338.

2.1.3.11. (S)-methyl 2-(4-((9-(3,4-difluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4k)

Yellow solid, yield 83%, m.p. 98-100^{o}C; ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.65 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 3.79 (s, 3H, OCH_3), 4.77 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.20 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.24-7.25 (m, 1H, Ar-H), 7.33-7.37 (m, 1H, Ar-H), 7.40-7.45 (m, 1H, Ar-H), 8.58 (s, 1H, pyrimidine-H); HRMS calcd for $C_{22}H_{16}N_4O_4F_5$ ([M + H]$^+$) 495.1092, found 495.1081.

2.1.3.12. (S)-ethyl 2-(4-((9-(3,4-difluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4l)

Yellow solid, yield 81%, m.p. 97-98^{o}C; ^{1}H NMR (600MHz, $CDCl_3$), δ: 1.28 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.64 (d, *J* = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.25 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.75 (q, *J* = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, *J* = 9.1

Hz, 2H, Ar-H), 7.20 (d, J = 9.1 Hz, 2H, Ar-H), 7.24-7.25 (m, 1H, Ar-H), 7.34-7.37 (m, 1H, Ar-H), 7.41-7.45 (m, 1H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{23}H_{18}N_4O_4F_5$ ([M + H]$^+$) 509.1248, found 509.1237.

2.1.3.13. (S)-butyl 2-(4-((9-(3,4-difluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4m)

Yellow viscous liquid, yield 86%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3H, $O(CH_2)_3\underline{CH_3}$), 1.30-1.36 (m, 2H, $O(CH_2)_2\underline{CH_2}CH_3$), 1.62-1.63 (m, 2H, $OCH_2\underline{CH_2}CH_2CH_3$), 1.64 (d, J = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.15-4.22 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$), 4.76 (q, J = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, J = 9.1 Hz, 2H, Ar-H), 7.19 (d, J = 9.1 Hz, 2H, Ar-H), 7.24-7.25 (m, 1H, Ar-H), 7.34-7.37(m, 1H, Ar-H), 7.40-7.45 (m, 1H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{25}H_{22}N_4O_4F_5$ ([M + H]$^+$) 537.1561, found 537.1536.

2.1.3.14. (S)-methyl 2-(4-((9-(2,4-difluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4n)

Yellow viscous liquid, yield 81%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.65 (d, J = 6.8Hz, 3H, $CH\underline{CH_3}$), 3.79 (s, 3H, OCH_3), 4.78 (q, J = 6.8Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, J = 9.1Hz, 2H, Ar-H), 7.12-7.16 (m, 2H, Ar-H), 7.21 (d, J = 9.1 Hz, 2H, Ar-H), 7.47-7.50 (m, 1H, Ar-H), 8.57(s, 1H, pyrimidine-H); HRMS calcd for $C_{22}H_{16}N_4O_4F_5$ ([M + H]$^+$) 495.1092, found 495.1081.

2.1.3.15. (S)-ethyl 2-(4-((9-(2,4-difluorophenyl)-8-(trifluoromethyl)-9H-purin-6-yl)oxy)phenoxy)propanoate (4o)

Yellow viscous liquid, yield 84%, ^{1}H NMR (600MHz, $CDCl_3$) δ: 1.28 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.65 (d, J = 6.8 Hz, 3H, $CH\underline{CH_3}$), 4.25 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.75 (q, J = 6.8 Hz, 1H, $\underline{CH}CH_3$), 6.97 (d, J = 9.1 Hz, 2H, Ar-H),

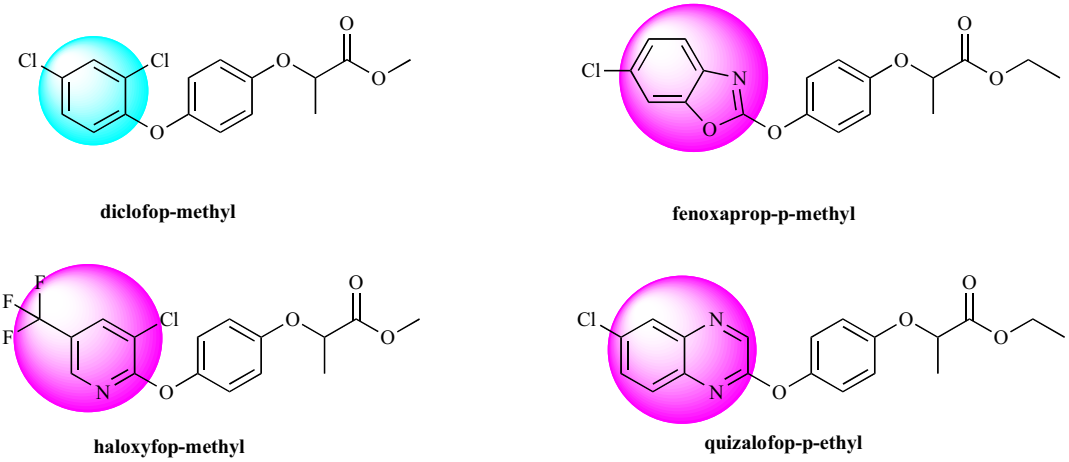
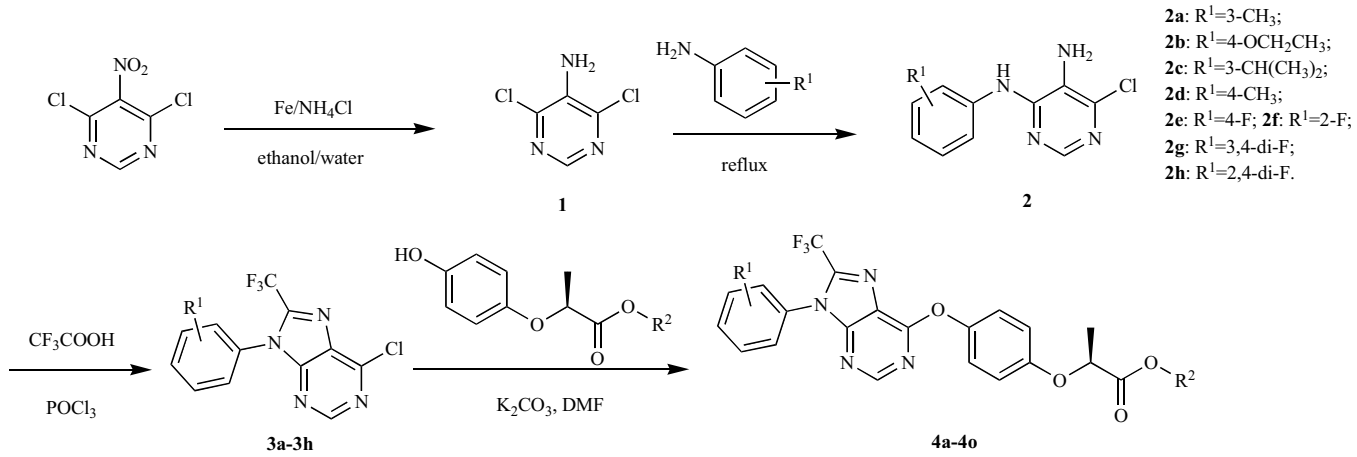


Fig. (1). The representative aryloxphenoxypionate herbicides.



2a: R^1=3-CH_3; **2b**: R^1=4-OCH_2CH_3; **2c**: R^1=3-$CH(CH_3)_2$; **2d**: R^1=4-CH_3; **2e**: R^1=4-F; **2f**: R^1=2-F; **2g**: R^1=3,4-di-F; **2h**: R^1=2,4-di-F.

4a: R^1=3-CH_3, R^2=CH_3; **4b**: R^1=3-CH_3, R^2=CH_2CH_3; **4c**: R^1=4-OCH_2CH_3, R^2=CH_3; **4d**: R^1=4-OCH_2CH_3, R^2=CH_2CH_3; **4e**: R^1=4-OCH_2CH_3, R^2=$(CH_2)_3CH_3$; **4f**: R^1=3-$CH(CH_3)_2$, R^2=$(CH_2)_3CH_3$; **4g**: R^1=4-CH_3, R^2=CH_2CH_3; **4h**: R^1=4-CH_3, R^2=$(CH_2)_3CH_3$; **4i**: R^1=4-F, R^2=CH_3; **4j**: R^1=2-F, R^2=CH_2CH_3; **4k**: R^1=3,4-di-F, R^2=CH_3; **4l**: R^1=3,4-di-F, R^2=CH_2CH_3; **4m**: R^1=3,4-di-F, R^2=$(CH_2)_3CH_3$; **4n**: R^1=2,4-di-F, R^2=CH_3; **4o**: R^1=2,4-di-F, R^2=CH_2CH_3.

Scheme 1. The synthetic route of title compounds.

Table 1. Herbicidal activity (growth inhibition, %) of title compounds at 200mg/L concentration.

Compound	*Triticum aestivum*	*Sorghum bicolor*	*Echinochloa crus-galli*	*Cucumis sativus*	*Brassica campestris*	*Raphanus sativus*
	Root/Stalk	Root/Stalk	Root/Stalk	Root/Stalk	Root/Stalk	Root/Stalk
4a	20/30	30/40	30/0	20/0	50/40	25/0
4b	0/0	50/0	30/45	0/55	0/45	45/0
4c	100/85	100/95	100/100	100/90	100/100	100/100
4d	100/95	100/90	100/100	100/100	100/85	100/100
4e	100/100	100/85	100/100	100/100	100/100	95/100
4f	70/60	55/65	70/80	85/65	75/70	80/60
4g	100/100	100/100	100/100	85/100	100/100	100/95
4h	100/95	100/95	100/100	100/100	100/100	100/100
4i	100/100	100/100	100/100	100/100	100/100	100/100
4j	70/50	65/45	70/65	70/50	0/65	0/0
4k	100/100	100/100	100/100	100/100	100/100	100/100
4l	100/100	100/100	100/100	100/100	100/100	100/100
4m	100/100	100/95	100/100	100/100	100/100	100/100
4n	0/0	0/0	0/0	0/0	0/0	0/0
4o	0/0	0/0	0/0	0/0	0/0	0/0
Pyribambenz propyl	95/95	100/90	100/95	95/90	100/100	100/90

7.12-7.16 (m, 2H, Ar-H), 7.21 (d, J = 9.1 Hz, 2H, Ar-H), 7.47-7.50 (m, 1H, Ar-H), 8.57 (s, 1H, pyrimidine-H); HRMS calcd for $C_{23}H_{18}N_4O_4F_5$ ($[M + H]^+$) 509.1248, found 509.1283.

3. RESULTS AND DISCUSSION

3.1. Synthesis

The synthetic route of the title compounds is outlined in Scheme **1**. The intermediate 4,6-dichloropyrimidin-5-amine (**1**) was prepared from 4,6-dichloro-5-nitropyrimidine by reduction using iron powder. Compound **1**, in an aqueous ethanol solution containing a small amount of hydrochloric acid, was coupled with a diverse set of anilines giving rise to diaminopyrimidine intermediates (**2**) which were cyclized with trifluoroacetic acid to give the corresponding substituted purines (**3**) according to the literatures [19, 20]. The series **4** compounds were synthesized by condensation reaction of the series **3** compounds with the appropriate 2-(4-hydroxyphenoxy)propanoate according to the reported method [21].

3.2. Spectra

The title compounds were identified by ^{1}H NMR and HRMS. The HRMS showed an ion of M+H, which was consistent with the calculated masses of the compounds. In the ^{1}H NMR spectra of **4a-4o,** quartet at δ 4.74-4.78 ppm was assignable to the methyne protons, and doublet at δ 1.64-1.65 ppm corresponded to the methyl protons, and the protons in the purine appeared as characteristic singlet signal at δ 8.56-8.58 ppm.

4. HERBICIDAL ACTIVITY

Preliminary herbicidal activity of compounds **4a-4o** was evaluated against monocotyledonous (*Triticum aestivum*, *Sorghum bicolor*, *Echinochloa crus-galli*) and dicotyledonous (*Cucumis sativus*, *Brassica campestris*, *Raphanus sativus*) plants, respectively according to the reported procedure [22, 23]. Pyribambenz propyl was used as positive control. All test compounds were dissolved in DMF with the Tween-80 as emulsifying reagent, then diluted with water to 200mg/L and applied to the plants which were cultivated in culture dish. The inhibition of root and stem growth was evaluated 7 days after treatment. As listed in Table **1**, most of the compounds displayed excellent herbicidal activity against all test plants. Particularly. Nine compounds (**4c-4e**, **4g-4i**, **4k-4m**) in particular exhibited 85%-100% herbicidal activity at 200 mg/L. The structure-activity relationship is as follows: Compounds **4a, 4b**, **4f**, **4j** exhibited much lower herbicidal activity than compounds **4c-4e** and **4g-4i**, which indicated that substitution at the ortho-position or meta-position instead of para-position of the phenyl ring will lead to a decrease in herbicidal activity. Compounds **4k-4m** showed similar herbicidal activity, which indicated that different alkyl groups will not affect the activity. Meanwhile, comparing our previous work, when the CH_3 of purine was

replaced to CF_3, the herbicidal activity was increased. The halo Cl on the benzene ring decrease the herbicidal activity. In this paper, we applied the halo F to the benzene ring, the herbicidal activity is higher than that of Cl.

CONCLUSION

In summary, a series of APP derivatives containing purine were synthesized, and their structures were confirmed by ^{1}H NMR and HRMS. Bioassays indicated that some of the title compounds exhibited better herbicidal activity against monocotyledonous and dicotyledonous plants.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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