Synthesis and Herbicidal Activity of Novel *N*-(2-Fluoro-5(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl)-2-phenoxyacetamide Derivatives

Wu, Daoxin[a](吴道新) Sun, Jiong[a](孙炯) Huang, Mingzhi*[,b](黄明智)
Mo, Hongbo[c](莫洪波) Wang, Xiaoguang[b](王晓光) Li, Hongwei[c](李宏伟)
Ren, Yeguo[b](任叶果) Hu, Zhibing[b](胡志彬)
He, Lian[b](何莲) Yin, Dulin[b](尹笃林)

[a] *School of Chemistry and Biological Engineering, Changsha University of Science and Technology, Changsha, Hunan 410114, China*
[b] *National Engineering Research Center for Agrochemicals, Hunan Research Institute of Chemical Industry, Changsha, Hunan 410007, China*
[c] *Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research* (*Ministry of Education of China*), *Hunan Normal University, Changsha, Hunan 410081, China*

Thirteen novel *N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)-2-phenoxy)acetamides were designed and synthesized utilizing 4-fluoro-aniline and ethyl 3-amino-4,4,4-trifluoro-but-2-enoate as starting materials. The chemical structures of all compounds were confirmed by ^{1}H NMR, IR, mass spectrum and elemental analyses. Subsequently, the herbicidal activities of the as-prepared compounds were evaluated in the greenhouse. Bioassay results indicated that most of compounds had better herbicidal activities against dicotyledonous weeds. Among all the tested compounds, compounds **4a**—**4i** showed good herbicidal activities at both pre-emergence and post-emergence treatment against two or three kinds of dicotyledonous weeds, such as *Abutilon theophrasti* Medic, *Amaranthus ascendens* L, and *Chenopodium album* L at the dosage of 75 g ai/ha.

Keywords synthesis design, 2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidine, *N*-phenyl-2-phenoxyacetamide, synthesis, herbicidal activity

Introduction

It is well known that uracil derivatives have important biological activities.[1] The uracil derivatives are more often used as antiphotosynthetic herbicides to control weeds in cotton, sugar beet, turnip, soya, pea, sunflower crop, vineyard, berry plantation, and orchard.[2] The uracil analog **1** discovered by the Hoffman-La Roche group in 1986,[3] which bears a highly functionalized phenyl group and a trifluoro methyl group at 4-position, is thought to be the first example of 6-membered cyclic imide with protoporhy rinogen oxidase (protox) inhibiting activity. Since then, structural modifications of 4-trifluoromethyluracils have been aggressively investigated. Among them, butafenacil **2**[4] and benzfendizone **3**[5] shown in Figure 1 have been developed as commercial herbicides. Butafenacil is used for the control of weeds including weeds grasses, such as *Abutilon theophrasti*, *Amaranthus retroflexus*, *Cassia obtusifolia*, *Chenopodium album*, *Chyrsanthemum segetum*, *Daturastramonium*, *Digitaria sanguinalis*, *Echinochloa crusgalli*, *Galium aparine*, *Matricaria chamomilla*, *Setariafaberii*, *Sinapis arvensis* and *Xanthium pennsylvanicum*, and diverse crops, such as cape, soya, cotton, rice, wheat and maize crops. Benzfendizone, when applied to post-emergence, provides control of dicotyledon weeds in orchards and no-till crop situations.[6]

The uracil-type herbicide has a substituted-pyrimidine-2,6-dione as common structural feature.[7] It has been recognized that the optimal substituent in pyrimidine-2,6-dione is trifluoromethyl group at 4-position, methyl at 3-position and multi-functionalized phenyl at 1-position. The trifluoromethyl group is the most favorable substituent, and enhances herbicidal activity markedly. The optimal substituent in the phenyl ring is halogen atoms like fluorine or chlorine at

* E-mail: huang-mz@163.com; Tel.: 0086-0731-85959096; Fax: 0086-0731-85959000
Received December 9, 2010; revised March 18, 2011; accepted July 17, 2011.
Project supported by the National Natural Science Foundation of China (No. 20872033), Hunan Provincial Natural Science Foundation of China (No. 07JJ1003) and Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education of China) (No. KLCBTCMR2008-14).

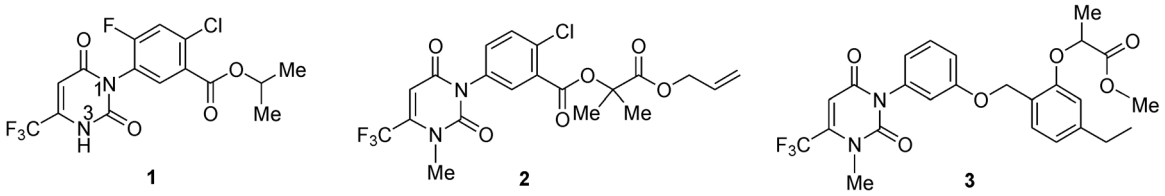


Figure 1 Typical protox inhibiting herbicides commercialized.

o-/*p*-position to uracil ring. It is interesting that the substituent at *m*-position of benzene ring often affects effectually the herbicidal activity and crop selectivity of uracil. Most of the modifications and optimizations have been focused on the substituent at *m*-position.[8] The typical uracils with *N*-modified phenyl ring systems are presented in Figure 2.[9-12]

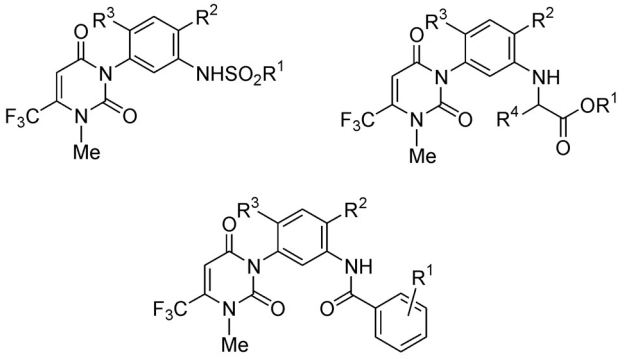


Figure 2 Typical uracils with *N*-modified phenyl ring systems.

The phenoxyacetic herbicides belong to synthetic auxins, which are widely used to control dicotyledon weeds in grass crops such as wheat, corn, sorghum, forages and turf grasses. One member of this group, 2,4-D,[13] is one of the first selective herbicides developed.

In our previous work, we introduced amide structure into uracil.[14-16] In order to find new lead compounds as potential agrochemicals, in the present paper novel *N*-(2-fluoro-5(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl)-2-phenoxy)acetamides (**4**) were designed and synthesized, which were combined by the active moieties of 4-trifluoromethyl-uracils and phenoxy carboxylic acids as depicted in Figure 3. Their chemical structures were characterized by ^{1}H NMR, IR, mass spectroscopy, and elemental analysis. Their herbicidal activities against dicotyledon weeds at pre- and post-emergence were determined in the greenhouse.

Experimental

Proton NMR spectra were obtained with a Varian INOVA300 spectrometer using tetramethylsilane (TMS) as internal standard and deuterochloroform as solvent. LC-mass spectra were recorded with an HP 1100 LC-MS (APCI) using positive ion scan mode. IR spectra were recorded in potassium bromide disks with a PE System 2000 FTIR spectrophotometer. Elemental analyses were carried out with a PE CHNS/O 2400 II elemental analyzer. Uncorrected melting points were taken on a WRS-1 melting point apparatus.

General procedure for the preparation of the 4a—4m

A mixture of 3.03 g (10.00 mmol) 3-(3-amino-4-fluorophenyl)-1-methyl-6-(trifluoromethyl)-pyrimidine-2,4(1*H*,3*H*)-dione (**10**) and 1.22 g (12.00 mmol) triethylamine in toluene (25 mL) was stirred, then measured 2-phenoxypropanoyl chloride or 2-phenoxyacetyl chloride (12 mmol) was added dropwise to the mixture at 0—5 ℃. The reaction was carried through at room temperature, and the end point of reaction was tested by TLC. The deposit was filtrated, and filtrate was poured into ice water (80 mL), and extracted with ethyl acetate (25 mL×3). The incorporated organic layer was washed sequentially with distilled water, saturated sodium bicarbonate solution

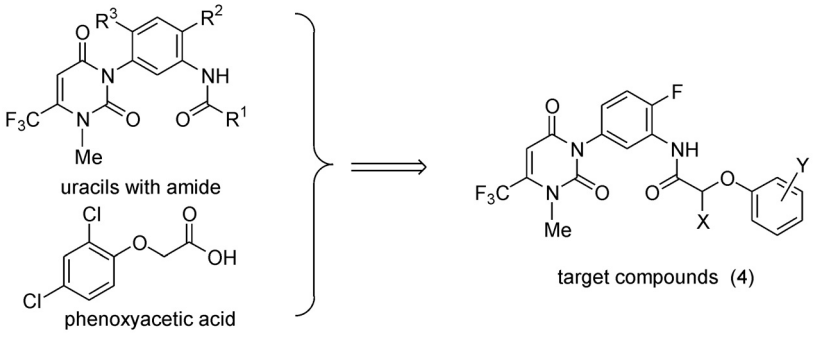


Figure 3 Design strategy for the target compounds.

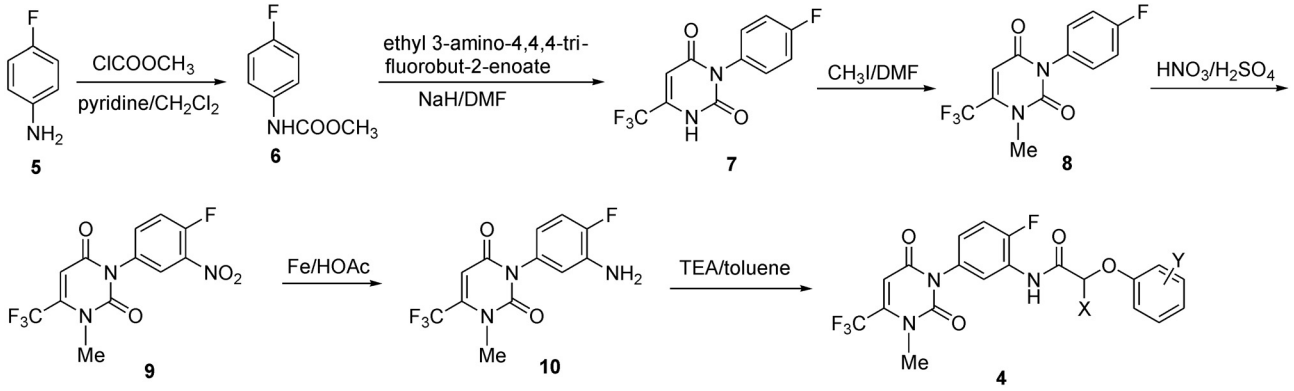


Figure 4 General synthetic route for the target compounds **4**.

and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using 4∶1 petroleum ether (b.p. 60—90 ℃)/ethyl acetate as the eluent to yield target compounds **4a**—**4m** as white solid or yellow solid.

2-(2,4-Dichlorophenoxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl) propanamide (4a) Yellow solid, yield 85%, m.p. 292.8 — 293.5 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.96 (s, 1H, NH), 8.42 (q, J=2.3 Hz, 1H, ArH), 7.45 (d, J=2.7 Hz, 1H, ArH), 7.20—7.24 (m, 2H, ArH), 6.89—6.98 (m, 2H, ArH), 6.36 (s, 1H, =CH), 4.82 (q, J=5.3 Hz, 1H, CH), 3.53 (s, 3H, NCH_3), 1.68 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) v: 1728, 1685 (C=O), 3400 (N—H) cm^{-1}; LC-MS (positive ion) m/z (%): 520 [(M+1)$^+$, 100]. Anal. calcd for $C_{21}H_{15}Cl_2F_4N_3O_4$: C 48.48, H 2.91, N 8.08; found C 48.39, H 2.97, N 8.17.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl)-2-(2-methoxyphenoxy)propanamide (4b)** Yellow solid, yield 89%, m.p. 66.5—67.0 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.47 (s, 1H, NH), 8.44 (q, J=1.5 Hz, 1H, ArH), 7.19—7.26 (m, 1H, ArH), 6.88—7.06 (m, 5H, ArH), 6.35 (s, 1H, =CH), 4.71 (q, J=1.5 Hz, 1H, CH), 3.90 (s, 3H, OCH_3), 3.53 (s, 3H, NCH_3), 1.68 (d, J=6.9 Hz, 3H, $CHCH_3$); IR (KBr) v: 1732, 1688 (C=0), 3345 (N—H) cm^{-1}; LC-MS (positive ion) m/z (%): 482 [(M+1)$^+$, 100]. Anal. calcd for $C_{22}H_{19}F_4N_3O_5$: C 56.89, H 3.98, N 8.73; found C 56.95, H,3.87, N 8.64.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)-2-(*m*-tolyloxy)propanamide (4c)** Yellow solid, yield 89%, m.p. 115.8—116.5 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.65 (s, 1H, NH), 8.40—8.43 (m, 1H, ArH), 7.01—7.25 (m, 3H, ArH), 6.85—6.91 (m, 3H, ArH), 6.36 (s, 1H, =CH), 4.75 (q, J=5.3 Hz, 1H, CH), 3.54 (s, 3H, NCH_3), 2.35 (s, 3H, $ArCH_3$), 1.63 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) v: 1731, 1692 (C=O), 3345 (N—H) cm^{-1}; LC-MS (positive ion) m/z (%): 466 [(M+1)$^+$, 100]. Anal. calcd for $C_{22}H_{19}F_4N_3O_4$: C 56.78, H 4.11, N 9.03; found C 56.81, H 4.15, N 9.07.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)-2-(*p*-tolyloxy)propanamide (4d)** White solid, yield 88%, m.p. 131.5—132.3 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.65 (s, 1H, NH), 8.40—8.43 (m, 1H, ArH), 7.25—7.77 (m, 2H, ArH), 6.75—6.94 (m, 4H, ArH), 6.36 (s, 1H, =CH), 4.79 (q, J=5.3 Hz, 1H, CH), 3.54 (s, 3H, NCH_3), 2.30 (s, 3H, $ArCH_3$), 1.63 (d, J=6.9 Hz, 3H, $CHCH_3$); IR (KBr) v: 1732, 1689 (C=O), 3392 (N—H) cm^{-1}; LC-MS (positive ion) m/z (%): 466 [(M+1)$^+$, 100]. Anal. calcd for $C_{22}H_{19}F_4N_3O_4$: C 56.78, H 4.11, N 9.03; found C 56.69, H 4.16, N 9.08.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl)-2-(3-fluorophenoxy)propanamide (4e)** White solid, yield 85%, m.p. 105.5 — 106.2 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.53 (s, 1H, NH), 8.95 (dd, J=2.7, 2.9 Hz, 1H, ArH), 7.30 (d, J=6.9 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 7.20—7.24 (m, 1H, ArH), 6.91—6.96 (m, 1H, ArH), 6.69—6.79 (m, 3H, ArH), 6.36 (s, 1H, =CH), 4.79 (q, J=5.3 Hz, 1H, CH), 3.54 (s, 3H, NCH_3), 1.65 (d, J=6.9 Hz, 3H, $CHCH_3$); IR (KBr) v: 1730, 1685 (C=O), 3415 (N—H); LC-MS (positive ion) m/z (%): 470 [(M+1)$^+$, 100] cm^{-1}. Anal. calcd for $C_{21}H_{16}F_5N_3O_4$: C 53.74, H 3.44, N 8.95; found C 53.79, H 3.39, N 8.89.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydro-pyrimidin-1(6*H*)-yl)phenyl)-2-phenoxypropanamide (4f)** Yellow solid, yield 87%, m.p. 136.1—136.8 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.65 (s, 1H, NH), 8.42 (q, J=2.3 Hz, 1H, ArH), 7.33 (t, J=1.8 Hz, 2H, ArH), 7.20—7.26 (m, 1H, ArH), 7.05 (t, J=1.5 Hz, 1H, ArH), 6.90—6.95 (m, 3H, ArH), 6.37 (s, 1H, =CH), 4.80 (q, J=5.3 Hz, 1H, CH), 3.55 (s, 3H, NCH_3), 1.65 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) v: 1731, 1682 (C=O), 3376 (N—H) cm^{-1}; LC-MS (positive ion) m/z (%): 452 [(M+1)$^+$, 100]. Anal. calcd for $C_{21}H_{17}F_4N_3O_4$: C 55.88, H 3.80, N 9.31; found C 55.79, H 3.85, N 9.40.

2-(4-Chloro-3-methylphenoxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)propanamide (4g) Yellow solid, yield 86%, m.p. 70.3—71.2 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.57 (d, J=1.8 Hz, 1H, NH), 8.40 (q, J=2.3 Hz, 1H, ArH), 7.24—7.28 (m, 1H, ArH), 7.18—7.22 (m, 1H, ArH), 6.90—6.96 (m, 1H, ArH), 6.85 (d, J=3.0 Hz, ArH), 6.73—6.77 (m, 1H, ArH), 6.36 (s, 1H, =CH), 4.74 (q, J=5.3 Hz, 1H, CH), 3.54 (d, J=1.2 Hz, 3H, NH_3), 2.36 (s, 3H, $ArCH_3$), 1.62 (d, J=6.9 Hz, 3H, $CHCH_3$); IR (KBr) ν: 1731, 1691 (C=O), 3412 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 500 [(M+1)$^+$, 100]. Anal. calcd for $C_{22}H_{18}ClF_4N_3O_4$: C 52.86, H 3.63, N 8.41; found C 52.80, H 3.67, N 8.30.

2-(2,4-Dichlorophenoxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)acetamide (4h) Yellow solid, yield 78%, m.p. 185.1—186.3 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.01 (s, 1H, NH), 8.43 (q, J=3.0 Hz, 1H, ArH), 7.46 (d, J=2.4 Hz, 1H, ArH), 7.25—7.29 (m, 1H, ArH), 7.24 (d, J=2.7 Hz, 1H, ArH), 6.86—6.99 (m, 1H, ArH), 6.87 (d, J=9.0 Hz, 1H, ArH), 6.36 (s, 1H, =CH), 4.63 (s, 2H, CH_2), 3.54 (s, 3H, NCH_3); IR (KBr) ν: 1733, 1681 (C=O), 3391 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 506 [(M+1)$^+$, 100]. Anal. calcd for $C_{21}H_{15}Cl_2F_4N_3O_4$: C 44.48, H 2.91, N 8.08; found C 44.51, H 2.89, N 8.01.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)-2-(4-(methylthio)phenoxy)propanamide (4i)** Yellow solid, yield 82%, 38.8—40.9 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.01 (s, 1H, NH), 8.44 (q, J=1.5 Hz, 1H, ArH), 7.19—7.26 (m, 1H, ArH), 6.70—7.06 (m, 5H, ArH), 6.36 (s, 1H, =CH), 4.66 (q, J=9.0 Hz, 1H, CH), 3.87 (s, 3H, SCH_3), 3.57 (s, 3H, NCH_3), 1.63 (d, J=6.9 Hz, 3H, $CHCH_3$); IR (KBr) ν: 1732, 1687 (C=O), 3357 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 498 [(M+1)$^+$, 100]. Anal. calcd for $C_{22}H_{19}F_4N_3O_4S$: C 53.12, H 3.85, N 8.45; found C 53.07, H 3.95, N 8.52.

2-(2-Fluoro-4-nitrophenoxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)propanamide (4j) Yellow solid, yield 81%, m.p. 166.8 — 167.1 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.13 (s, 1H, NH), 8.38 (q, J=3.0 Hz, 1H, ArH), 7.74—7.78 (m, 1H, ArH), 7.33—7.37 (m, 1H, ArH), 7.21—7.25 (m, 1H, ArH); 7.07—7.11 (m, 1H, ArH), 6.93—6.99 (m, 1H, ArH), 6.36 (s, 1H, =CH), 4.99 (q, J=5.3 Hz, 1H, CH), 3.53 (s, 3H, NCH_3), 1.71 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) ν: 1728, 1687 (C=O), 3372 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 515 [(M+1)$^+$, 100]. Anal. calcd for $C_{21}H_{15}F_5N_4O_6$: C 49.04, H 2.94, N 10.89; found C 48.96, H 2.98, N 10.93.

2-(Biphenyl-4-yloxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)propanamide (4k) Yellow solid, yield 90%, m.p. 97.4—98.7 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.65 (s, 1H, NH), 8.43 (q, J=2.3 Hz, 1H, ArH), 7.52—7.57 (m, 1H, ArH), 7.39—7.45 (m, 1H, ArH), 7.29—7.35 (m, 1H, ArH), 7.18—7.25 (m, 1H, ArH), 7.02—7.07 (m, 1H, ArH), 6.90—6.95 (m, 1H, ArH), 6.36 (s, 1H, =CH), 4.84 (q, J=5.3 Hz, 1H, CH), 3.54 (s, 3H, NCH_3), 1.67 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) ν: 1731, 1687 (C=O), 3410 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 528 [(M+1)$^+$, 100]. Anal. calcd for $C_{27}H_{21}F_4N_3O_4$: C 61.48, H 4.01, N 7.97; found C 61.59, H 4.09, N 7.91.

***N*-(2-Fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)-2-(4-nitrophenoxy)acetamide (4l)** White solid, yield 75%, m.p. 199.3—199.8 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.59 (s, 1H, NH), 8.38—8.42 (m, 1H, ArH) , 8.30—8.27 (m, 2H, ArH), 6.79—6.29 (m, 4H, ArH), 6.37 (s, 1H, =CH), 4.72 (s, 2H, CH_2), 3.54 (s, 3H, NCH_3); IR (KBr) ν: 1727, 3413 (C=O), 3413 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 483 [(M + 1)$^+$, 100]. Anal. calcd for $C_{20}H_{14}F_4N_4O_6$: C 49.80, H 2.93, N 11.62; found C 42.97, H 2.89, N 11.71.

2-(5-Fluoro-2,4-dinitrophenoxy)-*N*-(2-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl)phenyl)propanamide (4m) Yellow solid, yield 74%, m.p. 202.7 — 203.7 ℃ [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.03 (s, 1H, NH), 8.95 (d, J=7.8 Hz, 1H, ArH), 8.35 (s, 1H, ArH), 7.26 (d, J=5.7 Hz, 1H, ArH), 6.96—7.04 (m, 2H, ArH), 6.36 (s, 1H, =CH), 5.10 (q, J=4.5 Hz, 1H, CH), 3.55 (s, 3H, NCH_3), 1.79 (d, J=6.6 Hz, 3H, $CHCH_3$); IR (KBr) ν: 1731, 1696 (C=O), 3387 (N—H) cm^{-1}; LC-MS (positive ion) *m*/*z* (%): 560 [(M+1)$^+$, 100]. Anal. calcd for $C_{21}H_{14}F_5N_5O_8$: C 45.09, H 2.52, N 12.59; found C 44.93, H 2.46, N 12.65.

Syntheses of target compounds

The starting material 4-fluoroaniline (**5**) was treated with methyl chloroformate to give ethyl 4-fluorophenylcarbamate (**6**), which was followed by incorporation with ethyl 3-amino-4,4,4-trifluorobut-2-enoate to provide 3-(4-fluorophenyl)-6-(trifluoromethyl)pyrimidine-2,4-(1*H*,3*H*)-dione (**7**). Compound **7** and iodomethane were treated with potassium carbonate in DMF to yield 3-(4-fluorophenyl)-1-methyl-6-(trifluorometheyl)pyrimidine-2,4(1*H*,3*H*)-dione (**8**), which was followed by nitration reaction using the mixture of HNO_3 and H_2SO_4 to form 3-(4-fluorophenyl-3-nitrophenyl)-1-methyl-6-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**9**). Hydrogenation reaction of compound **9** using iron powders as reducing reagent formed 3-(3-amino-4-fluorophenyl)-1-methyl-6-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**10**). The detail synthesis processes for intermediates **6**—**10** were modified on the basis of the literature.[14] Their melting points were listed as fol-

lows: **6**, m.p. 54.8—56.0 ℃; **8**, m.p. 129.1—129.9 ℃; **9**, m.p. 168.9—170.0 ℃; **10**, m.p. 165.9—167.6 ℃. Reaction of intermediate **10** with an appropriate 2-phenoxypropanoyl chloride or 2-phenoxyacetyl chloride in the presence of triethylamine results in the target compounds **4**.

The as-synthesized compounds **4** were characterized by IR, ^{1}H NMR, mass spectra and elemental analyses. All spectra and data were consistent with the assigned structures. The IR spectra of compounds showed N—H and C=O stretching bands at *ca.* 3412 and 1700 cm^{-1}, respectively.

General procedure for the biological activity of the 4a—4m

Test compounds were formulated as 100 g/L emulsified concentrates by using *N*,*N*-dimethylformamide as solvent and TW-80 as emulsification reagent. The stock solutions were diluted with water to the required concentration and applied to pot-grown plants in a greenhouse. The soil used was a clay soil with pH of 6.5, 1.7% of organic matter, 37.5% of clay particles, and CEC of 12.9 cmol/kg. The rate of application (grams of active ingredient (ai) per hectare) was calculated by the total amount of active ingredient in the formulation divided by the surface area of the pot.

Determination of herbicidal activity against dicotyledonous weeds and monocotyledonous weeds

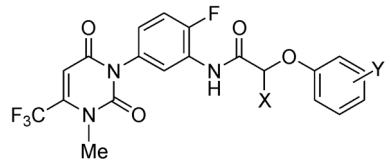
Plastic pots (9-cm diameter) were filled with soil to a depth of 6 cm. Approximately 20 seeds of *A. theophrasti*, *C. album*, *A. ascendens*, *D. sanguinalis*, *E. crus-galli*, and *S. viridis* were sown in the soil at the depth of 5-mm and grown at 22—25 ℃ in a greenhouse. The diluted formulation test solutions were applied to pre-emergence for 24 h after weeds were sown. For the post-emergence treatment, dicotyledonous weeds were treated at the 2-leaf stage and monocotyledonous weeds were treated at the 1-leaf stage. The pre- and post-emergence application rates were 75 g of ai/ha. Untreated seedlings were used as the control group while the solvent (*N*,*N*-dimethylformamide)-treated seedlings were used as the solvent control group. Each treatment was conducted in triplicate. After cultivation for 15 d, the herbicidal activities on test weeds were evaluated by comparing visually the weed growth inhibition of all test treatments with untreated controls, calculated as the average of the triplicates, and rated on the basis of percentage of weed growth inhibition using the following rating system: good (++), >80%; fair (+), 50%—80%; poor (−), <50%.

Result and discussion

Herbicidal activity

As shown in Table 1, most of the as-prepared compounds have good herbicidal activities against dicotyledonous weeds tested at the dosage of 75 g ai/ha. Among the all tested compounds, compounds **4a**—**4i** showed good herbicidal activities at both pre-emergence

Table 1 Comparison among synthesized chemicals on the weed control activity



No	X	Y	Pre-emergence activity (75 g ai/ha)						Post-emergence activity (75 g ai/ha)					
			AT[a]	CA	AA	DS	EC	SV	AT	CA	AA	DS	EC	SV
4a	CH_3	2-Cl, 4-Cl	++[b]	++	++	−	−	−	++	++	++	−	−	−
4b	CH_3	2-OCH_3	++	++	++	−	−	−	++	++	++	++	+	++
4c	CH_3	3-CH_3	++	++	++	−	−	−	++	++	++	−	−	−
4d	CH_3	4-CH_3	++	++	++	−	−	−	+	++	++	−	−	−
4e	CH_3	3-F	++	++	++	−	−	−	++	++	++	−	−	−
4f	CH_3	H	++	++	++	−	−	−	++	++	++	−	−	−
4g	CH_3	3-CH_3, 4-Cl	++	++	++	−	−	−	++	++	++	−	−	−
4h	H	2-Cl, 4-Cl	+	++	++	−	−	−	++	++	++	−	−	−
4i	CH_3	4-SCH_3	+	++	++	−	−	−	++	++	++	−	−	−
4j	H	2-F, 4-NO_2,	++	++	++	−	−	−	−	−	−	−	−	−
4k	CH_3	4-Ph	+	+	+	−	−	−	+	+	++	−	−	−
4l	H	4-NO_2	−	−	−	−	−	−	−	−	−	−	−	−
4m	CH_3	5-F, 2-NO_2, 4-NO_2	−	−	−	−	−	−	−	−	−	−	−	−

[a] AT for *Abutilon theophrasti* Medic; CA for *Chenopodium album* L.; AA for *Amaranthus ascendens* L.; DS for *Digitaria sanguinalis* L.; EC for *Echinochloa crus-galli* L.; SV for *Setaria viridis* L. [b] Rating system for the growth inhibition percentage: ++ for>80%; + for 50%—80%; − for <50%.

and post-emergence treatment against two or three kinds of dicotyledonous weeds, such as *Abutilon theophrasti* Medic, *A. ascendens*, and *C. album*. Compound **4j** exhibits almost the same activities at pre-emergence treatments against three kinds of dicotyledonous weeds. Compound **4k** has close herbicidal activities at both pre-emergence and post-emergence treatments against three kinds of dicotyledonous weeds. But compounds **4l** and **4m** have poor activities at the conditions tested, at either pre- or post-emergency. Furthermore, all test compounds, except compound **4b**, showed lower or no herbicidal activities at both pre-emergence and at post-emergence treatments against monocotyledon weeds *D. sanguinalis*, *E. crus-galli*, and *S. viridis*. The result is demonstrated that the combination of the active moieties between 4-trifluoromethyluracil and phenoxy carboxylic acid has continually held their activities against dicotyledonous weeds, but has not good herbicidal efficacy against monocotyledon weeds. The test data indicate that we did not get the new compounds with brand spectrum herbicidal activity on dicotyledonous weeds and monocotyledon weeds.

Structure-activity relationship study

Some interesting structure-activity relationship still can be drawn from the data in Table 1. Firstly, the optimal substituent (Y) on the phenyl ring of phenoxy carboxylic acid moiety is hydrogen atom or other electron-donating group, such as halogen atom, methoxy, methyl, methylthio. When the electron-withdrawing group, such as nitro or phenyl, is introduced into the position, the herbicidal activities of the corresponding compounds decrease. For example, compounds **4a**—**4i** show higher herbicidal activities than compounds **4j**—**4m**. Secondly, the influence of the substituent's position on the phenyl ring of phenoxy carboxylic acid moiety on herbicidal activities is not obvious or can not be concluded on the basis of the data given. For example, compound **4c** (3-CH_3) and **4d** (4-CH_3) exhibit similar activities. Thirdly, it is also not obvious whether introducing the methyl group on the X-position can enhance the herbicidal activities of corresponding compounds. The activities between **4a** (X＝CH_3) and **4h** (X＝H) have not remarkable difference. Finally, the influence of fluorine atom on herbicidal activities is obvious. The herbicidal activities of fluorine-substituted compounds are better than the non-fluorine-containing ones. For example, compound **4j** (Y＝2-F, 4-NO_2) exhibits better herbicidal activities than **4l** (Y＝4-NO_2).

References

1 Fustero, S.; Sanzcervera, J. F.; Mérida, S.; Román, R.; Villanova, S.; de Arellano, C. R. *J. Fluorine Chem.* **2008**, *129*, 836.

2 Pozharskii, A. F.; Soldatenkov, A. T.; Katrizky, A. R. *Heterocycles in Life and Society*: *An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine, and Agriculture*, John Wiley and Sons, New York, **1997**.

3 Wenger, J.; Winternitz, P. *EP 195346*, **1986** [*Chem. Abstr.* **1987**, *106*, 50241] (in German).

4 Sting, A. R.; Siegrist, U. E.; Baumeister, P. F. *DE 19741411*, **1998** [*Chem. Abstr.* **1998**, *128*, 243878] (in German).

5 Sehgel, S.; Theodoridis, G. *Trip Report*: *The 30th Northeast Regional Meeting of the American Chemical Society*, Durham, New Hampshire, June 24—27, **2001**.

6 Theodoridis, G.; Bahr, J. T.; Hotzman, F. W.; Sehgel, S.; Suarez, D. P. *Crop Prot.* **2000**, *19*, 533.

7 Fustero, S.; Sanz-Cervera, J. F.; Piera, J.; Sánchez-Roselló, M.; Chiva, G.; Simón-Fuentes, A. *J. Fluorine Chem.* **2004**, *125*, 621.

8 Boger, P.; Wakabayashi, K. *Peroxidizing Herbicides*, Springer, Berlin, **1999**, pp. 53—56.

9 Sato, J.; Fukuda, K.; Itoh, K.; Urawa, K. S.; Yono, T. N.; Omiya, S. W. *US 5154755*, **1992** [*Chem. Abstr.* **1993**, *118*, 191761].

10 Kawamura, Y.; Funabashi-shi, C. K.; Satow, J.; Fukuda, K.; Yoshiki-gun, Y. K.; Itoh, K.; Kita, H. *EP 496595*, **1992** [*Chem. Abstr.* **1992**, *117*, 191497].

11 Enomoto, M.; Nishinomiya, H.; Takamuya, S.; Takarazuka, H.; Toyonaka, O.; Shojima, S.; Nagano, E. *EP 540023*, **1993** [*Chem. Abstr.* **1993**, *119*, 139259] (in German).

12 Andvee, R.; Drewes, M. W.; Dollinger, M.; Stantel, H. J. *DE 19523640*, **1997** [*Chem. Abstr.* **1997**, *126*, 117988] (in German).

13 Aydın, H.; Özdemir, N.; Uzunören, N. *Forensic Sci. Int.* **2005**, *153*, 53.

14 Huang, M.; Li, H.; Pang, H.; Zhang, Q.; Ren, Y.; Yin, D. *Chin. J. Org. Chem.* **2008**, *28*, 1433.

15 Huang, M.; Zhang, Q.; Ren, Y.; Lei, M.; Huang, L.; Ren, J.; Yang, G. *Chin. J. Org. Chem.* **2006**, *26*, 1539.

16 Huang, M.; Chen, Z.; Pang, H.; Li, H.; Zhang, Q.; Lei, M.; Xu, M. *Agrochemicals* **2008**, *47*, 333 (in Chinese).

(E1012095 Cheng, F.)

