Synthesis, structure and herbicidal activity of substituted phenyl pyrazole derivatives

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To search for novel Protox inhibitors, a series of phenyl and 1,4-benzoxazin-5-yl pyrazole derivatives were synthesised from 3-(4-chloro-2-fluoro-5-methoxyphenyl)-1-methyl-5-trifluoromethyl-1*H*-pyrazole or its halogen substituted derivatives, via a serial of reactions that included nitration, reduction, acetylation, ring closure, methylation, *etc.* The single crystal of 2-(N-acetylacetamido)-6-chloro-3-[4-chloro-5-(trifluoromethyl)-1-methyl-1*H*-pyrazol-3-yl]-4-fluorophenyl acetate was prepared, and its structure was determined by X-ray analysis. The preliminary bioassay test shows that some of the compounds have high bioactivity. Especially, even at a low dosage of 150 g hm^{-2}, 2-(N-acetylacetamido)-6-chloro-3-[4-chloro-5-(trifluoromethyl)-1-methyl-1*H*-pyrazol-3-yl]-4-fluorophenyl acetate exhibited high activity, the inhibiting rate for both of the weeds reached above 90%.

Keywords: Protox-inhibitor, pyrazoles, herbicidal activity, synthesis

Herbicides play an important role in agricultural practices. Protoporphyrinogen oxidase (Protox) is an enzyme in the chlorophyll biosynthetic pathway.[1] Herbicides inhibiting Protox are the ones of the most important class of herbicides. Their action mode is the inhibition of Protox, which causes the accumulation of protoporphyrin IX (Proto IX), which is involved in the light-dependent formation of singlet oxygen responsible for membrane peroxidation.[2] Most of Protox-inhibiting herbicides show high bioactivity and low toxicity. In the past 30 years, herbicides targeting Protox, which have been used commercially to control annual grasses and weeds in soybean, peanut, cotton, rice, and other crops, are developed rapidly.[3,4] Diphenyl ether (DPE) based herbicides are the first and widely used family of protox inhibitors and Nitrofen (Fig. 1) is the leading compound of this type.[5]

The bicyclic nature of diphenyl ethers is similar to the structure of half of protoporphyrinogen IX, which allows competitive inhibition of Protox located in the plastid by occupying the binding site for protoporphyrinogen IX.[6–8] Besides, many other chemical structures related to this family are reported such as phenyl heterocycles that include triazolinone, oxazolidone, pyrazole, phthalamide, *etc*.[9–12] Some samples of commercial Protox inhibitors are shown in Fig. 1.

As the development of Protox inhibitor, many benzoheterocyclic compounds have shown good herbicidal activity, which are effective at controlling grass and broadleaf weeds at low dosage.[13–16] Earlier work in our laboratory involved some pyrazole [17] and isoxazole [18] derivatives with high herbicidal activity. We now describe the synthesis of phenyl pyrazole analogues and some pyrazolyl benzoxazinone derivatives, whose preliminary bioassay showed some promising results.

Results and discussion

The synthesis of the compounds is described in the Schemes 1 and 2, and the yields were not optimised. The intermediates **3a–c** were synthesised from 3-(4-chloro-2-fluoro-5-methoxyphenyl)-1-methyl-5-trifluoromethyl-1*H*-pyrazole or its halogen substituted derivatives, via a two-step method including nitration and demethylation reaction (Scheme 1). The title compounds were obtained from compounds **3a–c** as shown in Scheme 2.

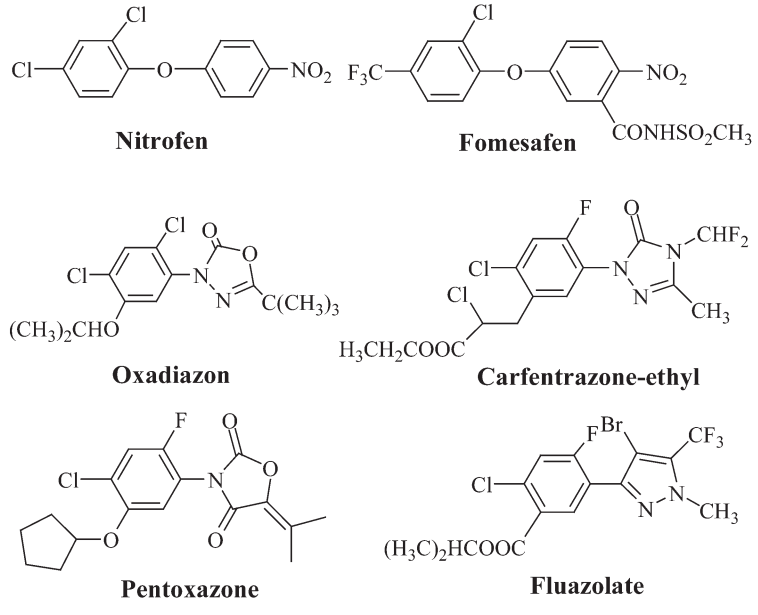

Fig. 1 Samples of commercial Protox inhibitors.

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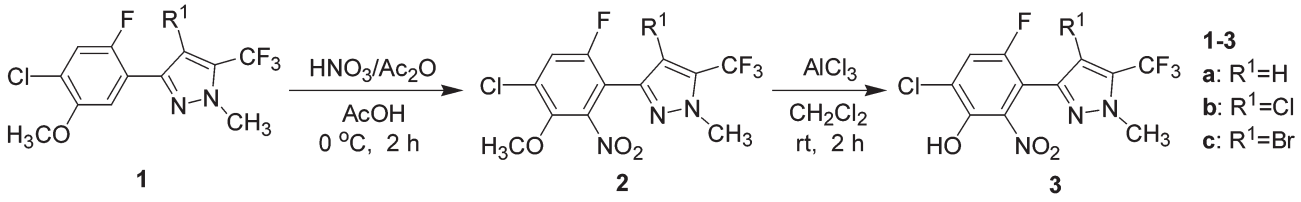
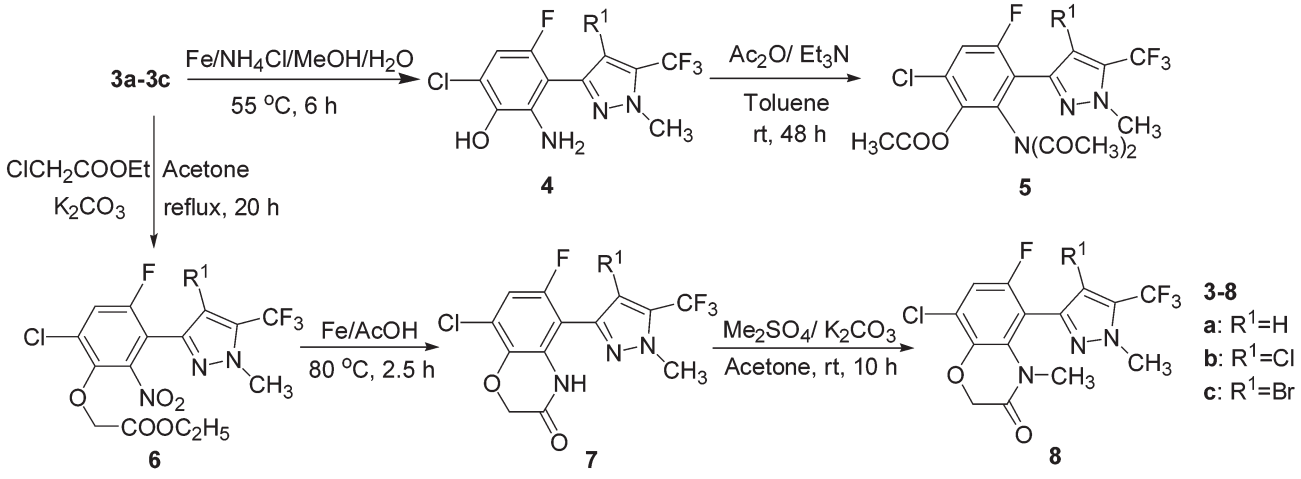


Scheme 1



Scheme 2

The synthesis of **4** is the key step, which involves reducing the nitro group to the amino group in a phenyl ring. Reduction of the nitro group by sodium sulfide or catalytic hydrogenation with Pd/C, Pt/C, and Ru/C gave poor selectivity. Finally, we found reduction of **3** with iron and saturated ammonium chloride gave a higher yield (86%) and selectivity. The product **4** is sensitive to air so the the reaction should be carried out under nitrogen, and the crude product was used directly in the next reaction without further purification.

Acetylation of **4** with acetic anhydride at ambient temperature resulted in the formation of **5**, a product of triacetylation. Because of high herbicidal activity of **5b**, we investigated it further by determining its crystal structure. This analysis revealed that **5b** was present. The structure of **5b** is shown in Fig. 2.

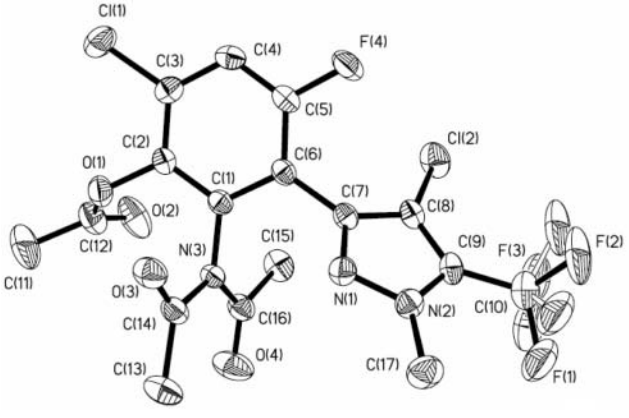


Fig. 2 ORTEP (ellipsoids at 30% probability) diagram of **5b** (Selected bond distances (Å): C(6)–C(7) 1.473(3), Cl(2)–C(8) 1.709(2), O(1)–C(2) 1.399(3), N(3)–C(1) 1.435(3), Cl(1)–C(3) 1.720(2), C(5)–F(4) 1.353(2), C(9)–C(10) 1.487(4); angles (deg): C(1)–C(6)–C(7) 121.1(2), C(7)–C(8)–Cl(2) 126.49(18), C(3)–C(2)–O(1) 119.3(2), C(2)–C(1)–N(3) 118.62(18)).

The herbicidal activity of the title compounds was determined with *Setaria viridis* and *Abutilon theophrasti,* and the results showed that some of the compounds had high bioactivity. **5b**, **5c**, **6b**, **6c**, **7b**, **7c**, **8b** and **8c** showed more than 80% inhibiting rate at the dosage of 600 g hm^{-2}. Especially, even at a low dosage of 150 g hm^{-2}, **5b** exhibited high activity, the inhibiting rate for both of the weeds reached above 90%. To further compare the activity of **5b** with commercial herbicide Fomesafen, they were tested at a lower concentration of 37.5 g hm^{-2}. **5b** showed 65% and 98% inhibition to *Setaria viridis* and *Abutilon theophrasti* respectively, while Fomesafen showed 40% and 65% inhibition to those two kinds of weeds. However, **5a, 6a, 7a** and **8a** were almost no activity against the testing weeds.

When no substituent on pyrazolyl position 4, there was no herbicidal activity nor low activity (**5a, 6a, 7a** and **8a**), but when a halogen (such as chlorine or bromine) is substituted on the pyrazole, most of them showed good herbicidal efficacy. Similar results have been reported by Meazza.[19] Their study on pyrroles showed that the halopyrrole nucleus was important for biological activity; if there was only hydrogen on the pyrrole the compounds were virtually inactive.

Experimental

All chemical reagents were commercially available and treated with standard methods before use. Melting points were taken on a Micro melting point apparatus (X-6, Beijing Tech Instrument Co. Ltd) and were uncorrected. ^{1}HNMR spectra were measured in deuterochloroform on a Varian VA400MHz spectrometer (Varian, USA) with TMS as an internal standard. Elemental analyses were performed on a Vario EL III (Elementar, German) elemental analysis instrumentation. Mass spectra were obtained with a HP1100 HPLC/Mass Selective Detector (HP, USA). IR spectra were recorded on a Nicolet-20DXB spectrometer.

1 was synthesised from 4-fluorophenol according to the existing methods.[20–22]

Preparation of **2a–c**

A mixed acid (27 mL, *V*(acetic anhydride): *V*(fuming nitric acid)= 2:1) was added dropwise to a solution of **1** (0.026 mol) in acetic acid

Table 1 Herbicidal activity of the title compounds[a]

Compd	*Setaria viridis*		*Abutilon theophrasti*	
	150[b]	600[b]	150[b]	600[b]
5a	0	0	0	0
5b	9	10	10	10
5c	7	8	10	10
6a	0	0	1	1
6b	1	1	10	10
6c	1	3	5	10
7a	0	0	1	1
7b	5	6	6	7
7c	1	3	3	6
8a	0	1	1	1
8b	3	8	9	10
8c	4	8	10	10
Fomesafen	9	10	9	10

[a] 0 = no activity and 10 = total kill.
[b] The usage dose of compounds (g a.i. hm^{-2}).

(25 mL) while maintaining the reaction solution at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h. The reaction solution was poured into water, filtered, and washed with water to give **2**.

3-(4-Chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (**2a**):[23] 83% yield; faint yellow solid after recrystallisation from ethanol; m.p. 94–96 °C; MS (API-ES, positive), *m/z*: 354 ([M+H]$^+$); ^{1}H NMR, *δ*: 7.37 (d, 1H, *J* = 9.6 Hz, Ph-*H*), 6.94 (d, 1H, *J* = 3.2 Hz, Pyr-*H*), 4.02 (s, 3H, Pyr-CH_3), 3.98 (s, 3H, OCH_3). Anal. Calcd for $C_{12}H_8ClF_4N_3O_3$ (353.7): C, 40.75; H, 2.28; N, 11.88. Found: C, 40.87; H, 2. 35; N, 11.67%.

4-Chloro-3-(4-chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (**2b**): Orange pasty matter and was used directly in the next reaction without purification; MS (API-ES, positive), *m/z*: 388 ([M+H]$^+$); ^{1}H NMR, *δ*: 7.42 (d, 1H, *J* = 7.6 Hz, Ph-*H*), 4.02 (s, 3H, Pyr-CH_3), 4.01 (s, 3H, OCH_3). Anal. Calcd for $C_{12}H_7Cl_2F_4N_3O_3$ (388.1): C, 37.14; H, 1.82; N, 10.83. Found: C, 36.87; H, 1.63; N, 10.67%.

4-Bromo-3-(4-chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (**2c**): Orange pasty matter that was used directly in the next reaction without purification; MS (API-ES, positive), *m/z*: 432 ([M+H]$^+$); ^{1}H NMR, *δ*: 7.42 (d, 1H, *J* = 7.6 Hz, Ph-*H*), 4.03 (s, 3H, Pyr-CH_3), 4.01 (s, 3H, OCH_3). Anal. Calcd for $C_{12}H_7BrClF_4N_3O_3$ (432.6): C, 33.32; H, 1.63; N, 9.71. Found: C, 32.99; H, 1.60; N, 9.62%.

Preparation of **3a–c**

A mixture of **2** (11 mmol), anhydrous aluminium chloride (27.7 mmol) and dichloromethane (70 mL) were stirred at ambient temperature for 2 h. The reaction solution was poured into icy hydrochloric acid and extracted with dichloromethane (20 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum.

6-Chloro-4-fluoro-3-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-nitrophenol (**3a**):[23] 100% yield; yellow powder. A sample suitable for analysis was obtained by recrystallisation from a mixture of petroleum ether and ethyl acetate (3:1 by volume); m.p. 94–97 °C; MS (API-ES, negative), *m/z*: 338 ([M–H]$^-$); ^{1}H NMR, *δ*: 9.75 (br, 1H, O*H*), 7.53 (d, 1H, *J* = 9.6 Hz, Ph-*H*), 6.95 (d, 1H, *J* = 3.2 Hz, Pyr-*H*), 4.01 (s, 3H, Pyr-CH_3). Anal. Calcd for $C_{11}H_6ClF_4N_3O_3$ (339.6): C, 38.90; H, 1.78; N, 12.37. Found: C, 38.84; H, 1.71; N, 12.42%.

6-Chloro-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4-fluoro-2-nitrophenol (**3b**): Light yellow powder that was used directly in the next reaction without purification. The yield of two steps was 82%. A sample suitable for analysis was obtained by recrystallisation with a mixture of petroleum ether and ethyl acetate (3:1 by volume); m.p. 85–87 °C; MS (API-ES, negative), *m/z*: 372 ([M–H]$^-$); ^{1}H NMR, *δ*: 9.52 (br, 1H, O*H*), 7.58 (d, 1H, *J* = 8.4 Hz, Ph-*H*), 4.03 (s, 3H, Pyr-CH_3). Anal. Calcd for $C_{11}H_5Cl_2F_4N_3O_3$ (374.1): C, 35.32; H, 1.35; N, 11.23. Found: C, 35.64; H, 1.43; N, 11.42%.

3-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-6-chloro-4-fluoro-2-nitrophenol (**3c**): Yellow powder that was used directly in the next reaction without purification. The yield of two steps was 83%. A sample suitable for analysis was obtained by recrystallisation from a mixture of petroleum ether and ethyl acetate (3:1); m.p. 86–89 °C; MS (API-ES, negative), *m/z*: 416 ([M–H]$^-$); ^{1}H NMR, *δ*: 9.83 (br, 1H, O*H*), 7.58 (d, 1H, *J* = 8.4 Hz, Ph-*H*), 4.04 (s, 3H, Pyr-CH_3). Anal. Calcd for $C_{11}H_5BrClF_4N_3O_3$ (418.5): C, 31.57; H, 1.20; N, 10.04. Found: C, 31.69; H, 1.23; N, 10.25%.

Preparation of **4a–c**

Under nitrogen a mixture of **3** (10.9 mmol), iron (0.068 mol), a solution of saturated ammonium chloride (120 mL) and methanol (80 mL) were stirred at 55 °C for 6 h. Then methanol was removed under vacuum. The reaction solution was filtered and the filtrate was extracted with ethyl acetate (40 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum.

2-Amino-6-chloro-4-fluoro-3-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)phenol (**4a**):[23] 86% yield; brown solid that was used directly in the next reaction without purification.

2-Amino-6-chloro-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4-fluorophenol (**4b**): 95% yield of crude product; brown paste that was used directly in the next reaction without purification.

2-Amino-3-(4-bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-6-chloro-4-fluorophenol (**4c**): 90% yield of crude product; brown paste that was used directly in the next reaction without purification.

Preparation of **5a–c**

A mixture of **4** (2.1 mmol), acetic anhydride (10.6 mmol), triethylamine (0.2 mL) and toluene (30 mL) was stirred at ambient temperature for 48 h. The reaction solution was poured into water and extracted with toluene (10 mL × 3). The combined organic layer was washed with a solution of 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography with petroleum ether:acetone (6:1 by volume) as eluent.

2-(N-Acetylacetamido)-6-chloro-4-fluoro-3-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)phenyl acetate (**5a**): 52% yield; light yellow powder; m.p. 125–127 °C; MS (API-ES, positive), *m/z*: 436 ([M+H]$^+$), 458 ([M+Na]$^+$), 474 ([M+K]$^+$); ^{1}H NMR, *δ*: 7.42 (d, 1H, *J* = 10.0 Hz, Ph-*H*), 6.95 (s, 1H, Pyr-*H*), 3.99 (s, 3H, Pyr-CH_3); 2.33 (s, 3H, OCOCH_3); 2.26 (s, 6H, N(COCH_3)$_2$); IR (KBr), *v*: 1767, 1722 cm^{-1}. Anal. Calcd for $C_{17}H_{14}ClF_4N_3O_4$ (435.8): C, 46.86; H, 3.24; N, 9.64. Found: C, 47.07; H, 3.21; N, 9.55%.

2-(N-Acetylacetamido)-6-chloro-3-(4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-4-fluorophenyl acetate (**5b**): 44% yield; white powder; m.p. 119–120 °C; MS (API-ES, positive), *m/z*: 470 ([M+H]$^+$), 492 ([M+Na]$^+$); ^{1}H NMR, *δ*: 7.44 (d, 1H, *J* = 8.5 Hz, Ph-*H*), 4.00 (s, 3H, Pyr-CH_3); 2.32 (s, 3H, OCOCH_3); 2.23 (s, 6H, N(COCH_3)$_2$); IR (KBr), *v*: 1770, 1724 cm^{-1}; Anal. Calcd for $C_{17}H_{13}Cl_2F_4N_3O_4$ (470.2): C, 43.42; H, 2.79; N, 8.94. Found: C, 43.51; H, 2.73; N, 8.94%.

2-(N-Acetylacetamido)-3-(4-bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-6-chloro-4-fluorophenyl acetate (**5c**): 51% yield; white solid; m.p. 134–137 °C; MS (API-ES, positive), *m/z*: 514 ([M+H]$^+$), 536 ([M+Na]$^+$); ^{1}H NMR, *δ*: 7.44 (d, 1H, *J* = 8.4 Hz, Ph-*H*), 4.02 (s, 3H, Pyr-CH_3); 2.32 (s, 3H, OCOCH_3), 2.23 (s, 6H, N(COCH_3)$_2$); IR (KBr), *v*: 1780, 1727 cm^{-1}. Anal. Calcd for $C_{17}H_{13}BrClF_4N_3O_4$ (514.7): C, 39.67; H, 2.55; N, 8.16. Found: C, 39.50; H, 2.63; N, 8.32%.

Preparation of **6a–c**

A mixture of **3** (2.4 mmol), anhydrous potassium carbonate (5 mmol), ethyl chloroacetate (3.3 mmol) and acetone (5 mL) was refluxed for 20 h. The reaction solution was poured into water and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by silica gel chromatography with petroleum ether:ethyl acetate (3:1 by volume) as eluent.

Ethyl 2-(6-chloro-4-fluoro-3-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-2-nitrophenoxy)acetate (**6a**): 82% yield; white solid; m.p. 102–103 °C; MS (API-ES, positive), *m/z*: 426 ([M+H]$^+$), 448 ([M+Na]$^+$); ^{1}H NMR, *δ*: 7.39 (d, 1H, *J* = 9.6 Hz, Ph-*H*), 6.94 (d, 1H, *J* = 3.2 Hz, Pyr-*H*), 4.70 (s, 2H, OCH_2COO), 4.31 (q, 2H, *J* = 7.2 Hz, OCH_2CH$_3$), 4.01 (s, 3H, Pyr-CH_3),1.33 (t, 3H, *J* = 7.2 Hz, OCH$_2$CH_3); IR (KBr), *v*: 1749, 1545, 1271 cm^{-1}. Anal. Calcd for $C_{15}H_{12}ClF_4N_3O_5$ (425.7): C, 42.32; H, 2.84; N, 9.87. Found: C, 42.71; H, 2.90; N, 9.93%.

Ethyl 2-(6-chloro-3-(4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-4-fluoro-2-nitrophenoxy)acetate (**6b**): 76% yield; white

solid; m.p. 79–80 °C; MS (API-ES, positive), *m/z*: 460 ([M+H]$^+$), 482 ([M+Na]$^+$); ^{1}H NMR, δ: 7.45 (d, 1H, J = 8.4 Hz, Ph-*H*), 4.74 (s, 2H, OCH_2COO), 4.29 (q, 2H, J = 7.2 Hz, OCH_2CH$_3$), 4.02 (s, 3H, Pyr-CH_3), 1.32 (t, 3H, J = 7.2 Hz, OCH$_2$CH_3); IR (KBr), *v*: 1766, 1548, 1272 cm^{-1}. Anal. Calcd for $C_{15}H_{11}Cl_2F_4N_3O_5$ (460.2): C, 39.15; H, 2.41; N, 9.13. Found: C, 39.51; H, 2.46; N, 8.98%.

Ethyl 2-(3-(4-bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-6-chloro-4-fluoro-2-nitrophenoxy)acetate (**6c**): 75% yield; white solid; m.p. 78–80 °C; MS (API-ES, positive), *m/z*: 504 ([M+H]$^+$), 526 ([M+Na]$^+$); ^{1}H NMR, δ: 7.44 (d, 1H, J = 8.4 Hz, Ph-*H*), 4.74 (s, 2H, OCH_2COO), 4.29 (q, 2H, J = 7.2 Hz, COOCH_2CH$_3$), 4.04 (s, 3H, Pyr-CH_3), 1.32 (t, 3H, J = 7.2 Hz, COOCH$_2$CH_3); IR (KBr), *v*: 1763, 1555, 1271 cm^{-1}. Anal. Calcd for $C_{15}H_{11}BrClF_4N_3O_5$ (504.6): C, 35.70; H, 2.20; N, 8.33. Found: C, 35.35; H, 2.35; N, 8.57%.

Preparation of **7a–7c**

A mixture of **6** (1 mmol) and iron powder (10 mmol) in acetic acid (15 mL) was heated to 80 °C for 2.5 h under nitrogen atmosphere. The mixture was cooled and filtered. The filtrate was diluted with water and extracted with ethyl acetate (20 mL × 3). The ethyl acetate extracts were washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, concentrated under vacuum, and recrystallised from alcohol to give **7**.

8-Chloro-6-fluoro-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-2H-1,4-benzoxazin-3(4H)-one (**7a**): 78% yield; white solid; m.p. 163–165 °C; MS (API-ES, positive), *m/z*: 350 ([M+H]$^+$), 372 ([M+Na]$^+$); ^{1}H NMR, δ: 11.03 (br, 1H, N*H*), 7.15 (d, 1H, J = 4.4 Hz, Pyr-*H*), 6.91 (d, 1H, J = 11.2 Hz, Ph-*H*), 4.69 (s, 2H, OCH_2CO), 4.11 (s, 3H, Pyr-CH_3); IR (KBr), *v*: 1690 cm^{-1}. Anal. Calcd for $C_{13}H_8ClF_4N_3O_2$ (349.7): C, 44.65; H, 2.31; N, 12.02. Found: C, 44.85; H, 2.43; N, 11.98%.

8-Chloro-5-(4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-6-fluoro-2H-1,4-benzoxazin-3(4H)-one (**7b**):[21] 69% yield; white solid; m.p. 143–144 °C; MS (API-ES, positive), *m/z*: 384 ([M+H]$^+$); ^{1}H NMR, δ: 8.62 (br, 1H, N*H*), 6.95 (d, 1H, J = 9.2 Hz, Ph-*H*), 4.67 (s, 2H, OCH_2CO), 4.10 (s, 3H, Pyr-CH_3); IR (KBr), *v*: 1701 cm^{-1}. Anal. Calcd for $C_{13}H_7Cl_2F_4N_3O_2$ (384.1): C, 40.65; H, 1.84; N, 10.94. Found: C, 40.72; H, 2.03; N, 11.01%.

5-(4-Bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-8-chloro-6-fluoro-2H-1,4-benzoxazin-3(4H)-one (**7c**): 89% yield; white solid; m.p. 150–151 °C; MS (API-ES, positive), *m/z*: 428 ([M+H]$^+$), 450 ([M+Na]$^+$); ^{1}H NMR, δ: 8.52 (br, 1H, N*H*), 6.95 (d, 1H, J = 8.8 Hz, Ph-*H*), 4.68 (s, 2H, OCH_2CO), 4.12 (s, 3H, Pyr-CH_3); IR (KBr), *v*: 1702 cm^{-1}. Anal. Calcd for $C_{13}H_7BrClF_4N_3O_2$ (428.6): C, 36.43; H, 1.65; N, 9.80. Found: C, 36.65; H, 1.58; N, 10.02%.

Preparation of **8a–c**

A mixture of compound **7** (1 mmol), anhydrous potassium carbonate (5 mmol), Me_2SO_4 (1.5 mmol) and acetone (5 mL) was stirred at ambient temperature for 10 h. The reaction solution was poured into water and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was purified by silica gel chromatography with petroleum ether:ethyl acetate (3:1 by volume) as eluent.

8-Chloro-6-fluoro-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-4-methyl-2H-1,4-benzoxazin-3(4H)-one (**8a**): 59% yield; white solid after recrystallisation from alcohol; m.p. 162–164 °C; MS (API-ES, positive), *m/z*: 364 ([M+H]$^+$), 386 ([M+Na]$^+$); ^{1}H NMR, δ: 7.00 (d, 1H, J = 9.2 Hz, Ph-*H*), 6.81 (s, 1H, Pyr-*H*), 4.66 (s, 2H, OCH_2CO), 4.05 (s, 3H, Pyr-CH_3), 2.78 (s, 3H, CON-CH_3); IR (KBr), *v*: 1690 cm^{-1}. Anal. Calcd for $C_{14}H_{10}ClF_4N_3O_2$ (363.7): C, 46.23; H, 2.77; N, 11.55. Found: C, 46.60; H, 2.58; N, 11.38%.

8-chloro-5-(4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-6-fluoro-4-methyl-2H-1,4-benzoxazin-3(4H)-one (**8b**): 78% yield; white pasty matter after purification by silica gel chromatography with petroleum ether:ethyl acetate (3:1 by volume) as eluent; MS (API-ES, positive), *m/z*: 398 ([M+H]$^+$); ^{1}H NMR, δ: 7.02 (d, 1H, J = 9.2 Hz, Ph-*H*), 4.67 (br, 2H, OCH_2CO), 4.08 (s, 3H, Pyr-CH_3), 2.75 (s, 3H, CON-CH_3); IR (KBr), *v*: 1697 cm^{-1}. Anal. Calcd for $C_{14}H_9Cl_2F_4N_3O_2$ (398.1): C, 42.23; H, 2.28; N, 10.55. Found: C, 41.97; H, 2.08; N, 10.71%.

5-(4-bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-8-chloro-6-fluoro-4-methyl-2H-1,4-benzoxazin-3(4H)-one (**8c**): 80% yield; white pasty matter after purification by silica gel chromatography with petroleum ether:ethyl acetate (3:1 by volume) as eluent; MS (API-ES, positive), *m/z*: 442 ([M+H]$^+$); ^{1}H NMR, δ: 7.01 (d, 1H, J = 8.8 Hz, Ph-*H*), 4.6–4.7 (m, 2H, OCH_2CO), 4.11 (s, 3H, Pyr-CH_3), 2.74 (s, 3H, CON-CH_3); IR (KBr), *v*: 1695 cm^{-1}. Anal. Calcd for $C_{14}H_9BrClF_4N_3O_2$ (442.6): C, 37.99; H, 2.05; N, 9.49. Found: C, 37.67; H, 1.89; N, 9.56%.

Crystal structure determination

Saturated solution of **5b** in EtOAc was covered with n-hexane, and stood in air at room temperature to give single crystals. The data were obtained on a Bruker SMART APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Empirical absorption corrections were performed using the SADABS program.[24] Structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2 using Shelx97.[25] All of the non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were generated and refined in ideal positions. Crystallographic parameters of **5b**: empirical formula: $C_{17}H_{13}Cl_2F_4N_3O_4$; formula weight: 470.20; crystal system: Monoclinic; space group: *P*2(1)/*n*; a = 10.210(5) Å, b = 9.442(5) Å, c = 21.312(10) Å; β = 100.407(6) deg.; V = 2020.7(17) Å^3; Z = 4; DCalcd = 1.546 g cm^{-3}; T = 273(2) K; μ = 0.387 mm^{-1}; F(000) = 952; θ: 1.94 to 25.25 deg; limiting indices: $-12 \le h \le 10$, $-11 \le k \le 11$, $-20 \le l \le 25$; Reflns collected/unique: 10015 / 3665 [$R(int)$ = 0.0661]; $GOF(F^2)$: 1.056; R^1/wR^2 [I>2sigma(I)] = 0.0417/0.0892, R_1/wR_2 (all data) = 0.0648/0.0944; Largest diff. peak and hole: 0.278 and –0.270 e A^{-3}. The crystal structure of **5b** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number is CCDC 782092.

Herbicidal activity test

The target plants for the test were *Setaria viridis* (Linn.) and *Abutilon theophrasti* Medic. A solution of the new compounds dissolved in a small amount of acetone was diluted with boiled tap water containing 0.1% Tween 80. Weeds (*Setaria viridis* (Linn.) and *Abutilon theophrasti Medic.*, two or three leaf stage) which grow well and have the same leaf stage were selected, and were spray treated with an atomiser at a rate of 600 L hm^{-2}. Then the weeds were aeration-dried and were cultured at room temperature. Weeds treated with water were the contol test. The herbicidal activity of the compounds was determined after 10 days of treatment. Evaluations were based on a percentage scale of 0–10 in which 0 = no activity and 10 = total kill.

Conclusions

A series of phenyl and 1,4-benzoxazin-5-yl pyrazole derivatives were synthesised from 3-(4-chloro-2-fluoro-5-methoxyphenyl)-1-methyl-5-trifluoromethyl-1*H*-pyrazole or its halogen substituted derivatives, via a series of reactions that included nitration, reduction, acetylation, ring closure, methylation, *etc.*. The single crystal of 2-(*N*-acetylacetamido)-6-chloro-3-(4-chloro-5-(trifluoro-methyl)-1-methyl-1*H*-pyrazol-3-yl)-4-fluorophenyl acetate was prepared, and its structure was determined by X-ray analysis. The preliminary bioassay test showed that some of the compounds had high bioactivity.

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