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A novel synthesis and herbicidal activity of fluorine-containing pyrazolo[3,4-*d*]pyrimidin-4-one derivatives

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Abstract

The 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-ones **6** have been successfully synthesized *via* a tandem aza-Wittig and annulation reactions of the corresponding iminophosphorances **4**, aromatic isocyanate, and substituted phenols **2** in 59–69% isolated yields using actonitrile as solvent. These novel compounds **6** could be oxidized to sulfones **7** by hydrogen peroxide in satisfactory yields (57–93%). Their structures were clearly verified by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS, Elemental analysis or X-ray diffraction crystallography). The results of preliminary bioassay indicated that these compounds possess herbicidal activity against the root of rape and barnyard grass.

Keywords: Pyrazolo[3,4-*d*]pyrimidin-4-one; Aza-Wittig reaction; Synthesis; Herbicide

1. Introduction

Pyrazolo[3,4-*d*]pyrimidin-4-one derivatives have extremely rich biological activities because of their structural similarity with purines [1]. They exhibit excellent antibacterial, antiphlogistic, and antitumor activities [2]. Accordingly, they are often employed in the treatment of erectile dysfunction in male animals [3]. Aryloxyphenoxypropionate (APP) derivatives have been found to be strong inhibitor of acetyl-coacarboxylase (ACCase) and used as a very important class of herbicides in the market [4]. In recent years, heterocycles were introduced to the structures of APP, which lead to the development of a new series of highly efficient herbicides. The heterocyclic units include whip, fenthiaprop-ethyl, quizalofop-ethyl, and two well-know fluorinated herbicides, fluazifop-butyl and heloxyfop-methyl [5].

It is well known that fluorine can affect the biological activity of compounds in a number of important ways. Therefore, fluorinated compounds in general and fluorinated heterocycles are the focus of many researches [6]. In the area of modern crop protection, fluoro agrochemicals are widely employed as herbicides, insecticides and fungicides [7]. Recently, aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds [8]. As part of our ongoing project aimed at investigating new herbicidal activity heterocycles [9], we have designed a series of novel fluorine-containing compounds which have both the skeletons of pyrazolo[3,4-*d*]pyrimidin-4-one and aryloxyphenoxypropionate (APP) based on biochemical rations. Herein, we would like to describe the use of a new annulation process (Scheme 1), the tandem aza-Wittig and cyclization reaction, to synthesize the title compounds, 6-(4-alkoxycarbonylalkoxy)-phenoxy-3-alkylthio(alkylsulfonyl)-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-ones **6** and **7**. The results of bioassay indicated that these title compounds possess herbicidal activity against the root of rape and barnyard grass.

2. Results and discussion

The iminophosphorane **4** [10], which was prepared by the reaction of 3-alkylthio-5-amino-4-ethoxycarbonyl-1-phenylpyrazole **3** [11] with triphenylphosphine and bromine using triethylamine as base in dichloromethane, reacted with 1 equivalent of aromatic isocyanate to afford carbodiimide **5**. The

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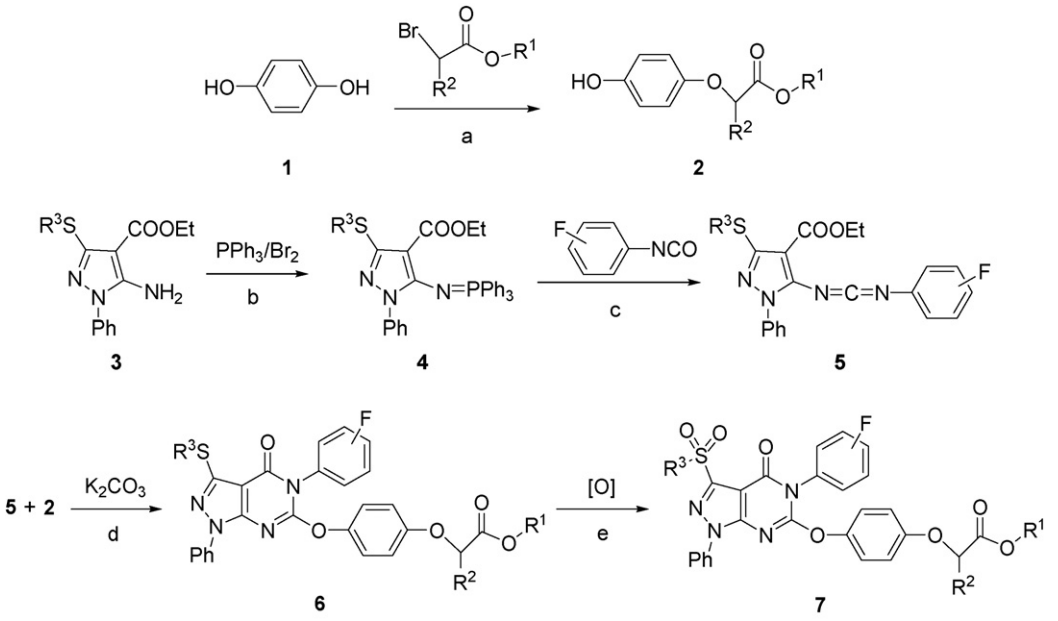
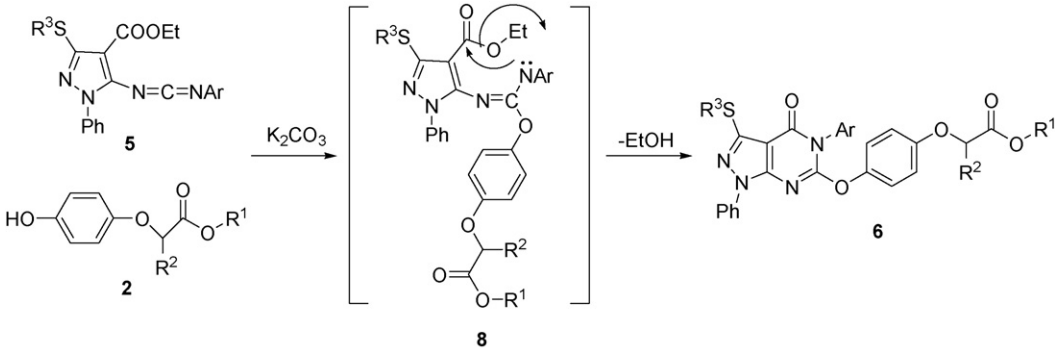
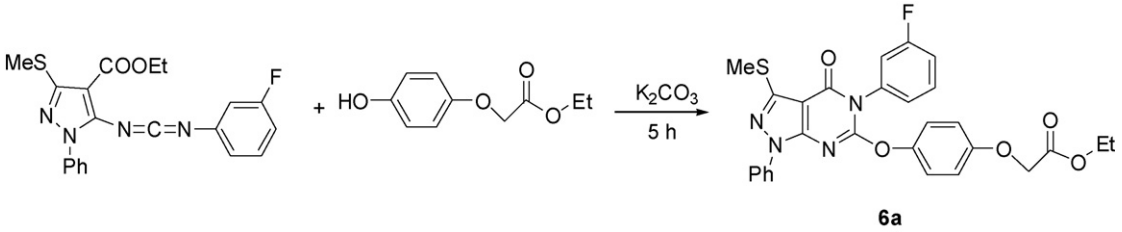


Scheme 1. Synthesis of the title compounds **6** and **7**. Reagents and conditions: (a) R^1ONa, R^1OH, 0–35 °C, 6 h, yield 57–66%. (b) Et_3N, CH_2Cl_2, 0 °C for 30 min then 25 °C for 26 h, yield 84%. (c) CH_2Cl_2, rt, 2–5 h. (d) K_2CO_3, CH_3CN, reflux, 5 h, yield 59–69%. (e) $Na_2WO_4{\cdot}H_2O$, AcOH, 30% H_2O_2, 50 °C, 5 h, yield 57–93%.



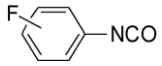
Scheme 2. The cyclization of carbodiimide **5** to synthesize the title compounds **6**.

Table 1
Optimization of the reaction conditions



Entry	Solvent	Temperature (°C)	Yield (%)
1	CH_3CN	80	65
2	CH_2Cl_2	40	11
3	Toluene	80	13
4	CH_3CN	25	20
5	CH_3CN	40	30

Table 2
Yields of compounds **6** and **7**

Compound		R^3	R^2	R^1	Yields of **6** (%)	Yields of **7** (%)
6a, **7a**	*m*-F–	Me	H	Et	65	72
6b, **7b**	*o*-F–	Me	H	Et	69	93
6c, **7c**	*p*-F–	Me	H	Et	69	69
6d, **7d**	*m*-F–	Me	Me	Et	65	82
6e, **7e**	*o*-F–	Me	Me	Et	61	88
6f, **7f**	*p*-F–	Me	Me	Et	63	85
6g, **7g**	*o*-F–	Me	Me	*n*-Pr	61	71
6h, **7h**	*p*-F–	Me	Me	*n*-Pr	62	62
6i, **7i**	*o*-F–	$PhCH_2$	Me	Me	59	57
6j, **7j**	*p*-F–	$PhCH_2$	Me	Me	66	88

reaction of 2-(4-hydroxyphenoxy)-carboxylate **2** [9,12] with **5** generated **6** in the presence of catalytic amount of potassium carbonate via guanidine intermediates **8**. This process can be rationalized in Scheme 2.

Optimization of the reaction conditions showed that better yield was obtained when polar solvent acetonitrile was used [13]. During the process, it is essential to control reaction temperature to in order to get good yields. A favourable temperature for the reaction was 80 °C (Table 1). Then, compound **6** were oxidized by hydrogen peroxide (H_2O_2) using sodium wolframate (Na_2WO_4) as the catalyst to give compounds **7** at about 40 °C. The results are summarized in Table 2.

The structures of compounds **6** and **7** were deduced from their spectra data (IR, ^1H NMR, ^{13}C NMR, MS, Elemental analyses). **7b** was recrystallized by slow evaporation from CH_2Cl_2, which afforded single crystal that is analyzed by X-ray diffraction crystallography. The corresponding structure is shown in Fig. 1. X-ray structure analysis verified again the proposed structure, and showed that ring atoms in pyrazolo[3,4-*d*]pyrimidin-4-one moiety are essentially planar. The bond lengths of C(2)=N(4), C(3)=C(4), C(12)=N(1) are 1.311(3) Å, 1.381(3) Å, 1.289(3) Å, respectively, are longer than that of the typical C=N (1.28 Å) and C=C (1.34 Å), while the single bond lengths of C(4)–N(5), C(2)–C(3), C(3)–C(11), C(12)–N(2), C(4)–N(1), are 1.358(3) Å, 1.408(3) Å, 1.439(3) Å, 1.366(3) Å, 1.357(3) Å, respectively, are significantly shorter than the typical $C(sp^2)$=N (1.426 Å) and C–C (1.53 Å), showing a degree of delocalization.

The herbicidal activity of all compounds **6** and **7** against *Brassica napus* (rape) and *Echinochloa crus-galli* (barnyard grass) has been investigated at the dosage of 100 mg/L and 10 mg/L using known procedure [14] compared with distilled water and 2,4-dichlorophenoxy acetic acid (2,4-D), a commercially available herbicide. The results of bioassay showed that many of them exhibit good herbicidal activity when fluorine atom is introduced [9] (the inhibition rates are listed in Tables 3 and 4). It showed that the role of the fluorine position (*m*-, *p*-, *o*-) has not obvious influence on herbicidal activity, but it is worthy to note that the inhibition rates of **7** have gone up greatly when the sulfide group was oxidized to the sulfonyl group. Most of compounds **7** in the Table 4 exhibit good inhibition rates (80–98%) against the root of rape and barnyard grass at 100 mg/L. For example, **7a**, **7c**, **7d**, **7e**, **7f** showed >90% inhibitory rate to root of rape and barnyard grass. It is also interesting, that ethyl ester show higher herbicidal activity than the corresponding methyl ester and *n*-propyl ester in general. This may be due to the hydrolysis of the product [15]. The investigations on *R* and *S* isomers of products are going on further.

In summary, we have developed a novel approach to 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio(alkylsulfonyl)-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one derivatives via a tandem aza-Wittig and annulation reactions. The structures of the title compounds possess both the skeletons of pyrazolo[3,4-*d*]pyrimidin-4-one and aryloxyphenoxypropionate (APP). The biological evalution showed

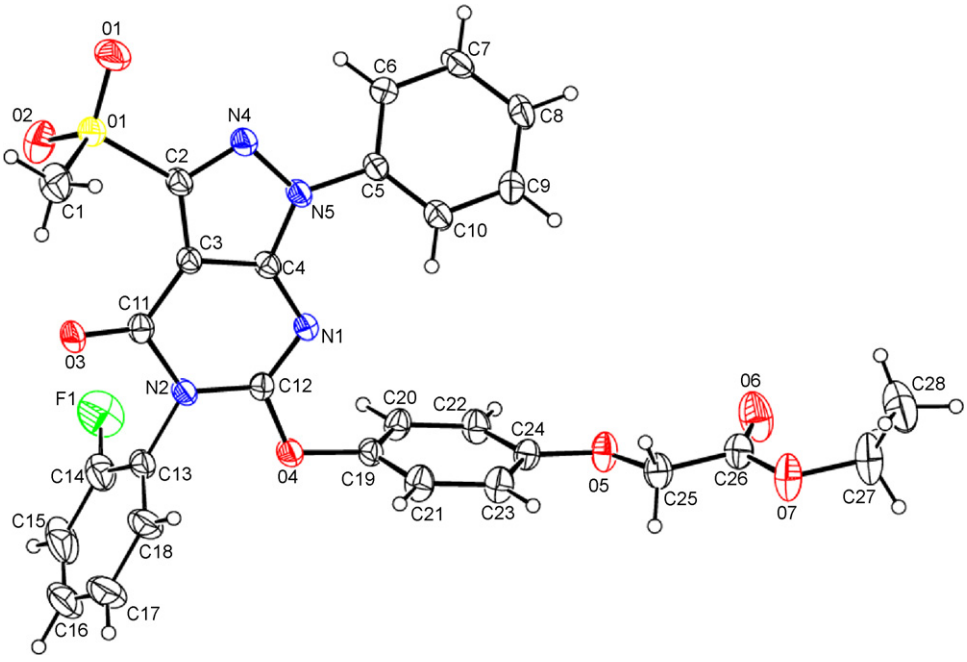
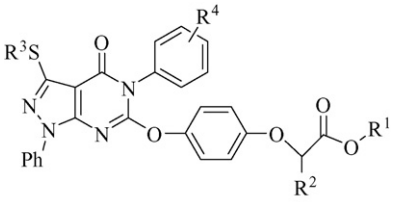


Fig. 1. View and atom labelling of **7b**.

Table 3
Herbicidal comparison with unfluorinated compounds



6

Compounds	R^1	R^2	R^3	R^4	Relative inhibition (root %/stalk %)			
					Rape		Barnyard grass	
					100 mg/L	10 mg/L	100 mg/L	10 mg/L
6a	Et	H	Me	*m*-F	78.4/48.7	46.1/25.6	95.6/62.1	60.9/55.2
6k	Et	H	Me	H	74.3/36.5	53.5/13.5	88.5/22.6	40.4/9.7
6l	Et	H	Me	*m*-Cl	65.3/21.1	35.6/17.3	80.8/32.3	59.6/19.4
6d	Et	Me	Me	*m*-F	93.1/73.1	59.4/32.7	88.5/25.8	75.0/0.0
6m	Et	Me	Me	*m*-Cl	85.1/55.8	70.3/30.8	82.7/22.6	73.1/12.9
6n	Et	Me	Me	*p*-Me	50.0/11.1	19.6/11.1	64.4/−31.6	53.3/10.5

that these compounds have good herbicidal activity and could be further developed as potential herbicides.

3. Experimental

3.1. Materials

All the solvent and materials are reagent grades and purified before use. 2-(4-Hydroxyphenoxy)-carboxylates **2** [9,12], 3-alkylthio-5-amino-4-ethoxycarbonyl-1-phenylpyrazole **3** [11], imimophosphoranes **4** [10] were prepared according to literature procedures.

Table 4
The herbicidal activity of compounds **6** and **7**

Compounds	Relative inhibition (root %/stalk %)			
	Rape		Barnyard grass	
	100 mg/L	10 mg/L	100 mg/L	10 mg/L
6a	78.4/48.7	46.1/25.6	95.6/62.1	60.9/55.2
6b	79.4/33.3	34.3/33.3	82.6/20.7	54.3/10.3
6c	81.2/42.3	47.5/15.4	90.4/19.4	59.6/−6.5
6d	93.1/73.1	59.4/32.7	88.5/25.8	75.0/0.0
6e	84.2/63.5	43.6/23.1	82.7/12.9	57.7/−6.4
6f	97.0/65.4	51.5/11.5	98.1/54.8	75.0/16.1
6g	25.5/10.6	10.0/19.1	61.9/16.1	33.3/9.7
6h	40.0/4.3	−10.0/−10.6	54.8/3.2	42.8/0.0
6i	56.7/68.1	5.5/8.5	78.6/74.2	42.8/29.0
6j	33.3/12.8	31.1/8.5	47.6/35.5	52.4/32.2
7a	98.0/84.6	44.1/7.7	97.8/75.9	78.3/51.7
7b	88.2/71.8	21.6/7.7	91.3/58.6	67.4/6.9
7c	97.1/64.1	46.1/7.7	93.5/62.1	67.4/−3.4
7d	97.1/74.4	45.1/30.8	93.5/51.7	69.6/20.7
7e	91.2/64.1	13.7/7.7	91.3/44.8	73.9/27.6
7f	97.1/82.5	50.0/30.8	95.6/72.5	74.1/58.0
7g	27.2/8.9	11.9/13.3	50.0/13.3	15.0/10.0
7h	83.7/42.2	17.4/6.7	87.5/10.0	37.5/0
7i	51.1/11.1	28.3/11.1	57.5/6.7	45.0/13.3
7j	79.3/40.0	27.2/6.7	75.0/13.3	57.5/−10.0
2,4-D	99.0/91.2	98.1/91.2	97.5/33.3	97.5/30.8

3.2. Measurements and instruments

IR was recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr film with absorption in cm^{-1}. ^1H NMR spectra were recorded on Mercury Plus-400 (400 MHz) spectrophotometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26). ^{13}C NMR spectra were recorded on Mercury Plus-400 (100 MHz) spectrophotometers with complete proton decoupling spectrophotometers ($CDCl_3$: 77.2). Mass spectra were measured on a Finnigan Trace MS spectrometer. Elementary analyses were taken on a Vario EL III elementary analysis instrument. X-ray diffraction crystallography was measured on Bruker Smart Apex Area CCD.

3.3. Preparation of 2-(4-hydroxyphenoxy)-carboxylates *2*

Compound **2** were prepared according to literature procedures [9,12]. Ethyl 2-(4-hydroxyphenoxy)-acetate was obtained after recrystallized with ether as white solid in 66% yield, mp 124–126 °C. Methyl-2-(4-hydroxyphenoxy)-propionate was got by distilling under reduced pressure in 62% yield as light yellow thick liquid, bp 165–167 °C/42 Pa, $M^+ = 196$; ethyl-2-(4-hydroxyphenoxy)-propionate was got in 59% yield, bp 135–138 °C/22 Pa, $M^+ = 210$; *n*-propyl-2-(4-hydroxyphenoxy)-propionate was got in 57% yield, bp 139–142 °C/38 Pa, $M^+ = 224$.

3.4. General procedure for the preparation of imimophosphoranes *4*

Imimophosphoranes **4** were prepared according to the reported procedures [10]. When R^3 is Me, a pale yellow crystal

in 84% yield was obtained, mp 192–194 °C, ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.70–7.16 (m, 20H), 3.61 (q, 2H, J = 7.2 Hz), 2.51 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz). When R^3 is benzyl, a pale yellow crystal in 86% yield was got, mp 86–87 °C, MS: (*m/z*) 613 (M^+), 614 (M^+ + 1), 615 (M^+ + 2).

*3.5. General procedure for the preparation of 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-ones **6a–6j***

To a solution of iminophosphorane **4** (2 mmol) in dry dichloromethane (25 mL), aromatic isocyanate (2 mmol) was added under nitrogen at room temperature. After the reaction mixture was stirred for 2–5 h, the solvent was removed under reduced pressure and then 25 mL anhydrous accetonitrile, 2.0 mmol 2-(4-hydroxyphenoxy)-carboxylates **2** and 0.05 g anhydrous potassium carbonate were added to the mixture. Stirring for another 5 h at refluxing, the mixture was cooled to room temperature and then filtered. The filtration was condensed under reduce pressure, and the residue was recrystallized with ethanol to give pure 6-(4-alkoxycarbonylalkoxy) phenoxy-3-alkylthio-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-ones **6a–6j**.

*3.5.1. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(3-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6a**)*

Spectral date are reference to [9c]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 14.3, 61.6, 66.0, 102.2, 115.5, 116.3, 116.6, 120.4, 122.7, 124.6, 126.3, 129.0, 130.7, 135.8, 138.7, 145.9, 147.6, 151.1, 154.1, 156.0, 157.3, 163.1, 168.7.

*3.5.2. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(2-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6b**)*

Spectral date are consistent with reference to [9c].

*3.5.3. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(4-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6c**)*

Spectral date are consistent with reference to [9c].

*3.5.4. 6-[4-(1-Ethoxycarbonylethoxy)]phenoxy-5-(3-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6d**)*

White crystals, mp 209–210 °C; yield, 65%; IR (KB) ν (cm^{-1}): 2991, 2928, 1743, 1704, 1600, 1575, 1549, 1502, 1349, 1195, 1134, 829, 779, 679; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, J = 8.4 Hz, Ar), 7.51 (q, 1H, J = 8.4 Hz, Ar), 7.33 (t, 2H, J = 8.0 Hz, Ar), 7.12–7.26 (m, 4H, Ar), 7.08 (d, 2H, J = 8.8 Hz, OC_6H_4O), 6.91 (d, 2H, J = 8.8 Hz, OC_6H_4O), 4.75 (q, 1H, J = 6.8 Hz, OCH), 4.22 (q, 2H, J = 7.2 Hz, OCH_2), 2.66 (s, 3H, SCH_3), 1.65 (d, 3H, J = 6.4 Hz, $\mathbf{CH_3}CH$), 1.24 (t, 3H, J = 7.2 Hz, $CH_2\mathbf{CH_3}$); EI-MS (70 eV, *m/z*): 560 (M^+), 562 (M^+ + 2); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_5S$: C, 62.13; H, 4.49; N, 9.99; Found: C, 62.32; H, 4.57; N, 10.02.

*3.5.5. 6-[4-(1-Ethoxycarbonylethoxy)]phenoxy-5-(2-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6e**)*

White crystals, mp 201–203 °C, yield, 61%; IR (KBr) ν (cm^{-1}): 2990, 2932, 1739, 1704, 1601, 1577, 1545, 1500, 1399, 1350, 1193, 1135, 1036, 896, 757; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, J = 8.0 Hz, Ar), 7.26–7.49 (m, 6H, Ar), 7.20 (t, 1H, J = 7.2 Hz, Ar), 7.10 (d, 2H, J = 8.8 Hz, OC_6H_4O), 6.91 (d, 2H, J = 8.8 Hz, OC_6H_4O), 4.75 (q, 1H, J = 6.8 Hz, OCH), 4.22 (q, 2H, J = 7.2 Hz, OCH_2), 2.68 (s, 3H, SCH_3), 1.65 (d, 3H, J = 6.4 Hz, $\mathbf{CH_3}CH$), 1.23 (t, 3H, J = 6.4 Hz, $CH_2\mathbf{CH_3}$); EI-MS (70 eV, *m/z*): 560 (M^+), 561 (M^+ + 1); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_5S$: C, 62.13; H, 4.49; N, 9.99; Found: C, 62.44; H, 4.38; N, 10.05.

*3.5.6. 6-[4-(1-Ethoxycarbonylethoxy)phenoxy-5-(4-fluorophenyl)-3-methylthio-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6f**)*

White crystals, mp 198–199 °C, yield, 63%; IR (KBr) ν (cm^{-1}): 2988, 2935, 1751, 1704, 1603, 1576, 1549, 1504, 1350, 1190, 1132, 1030, 896, 829, 758; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, J = 8.0 Hz, Ar), 7.18–7.36 (m, 7H, Ar), 7.07 (d, 2H, J = 9.2 Hz, OC_6H_4O), 6.90 (d, 2H, J = 8.8 Hz, OC_6H_4O), 4.75 (q, 1H, J = 6.8 Hz, OCH), 4.21 (q, 2H, J = 6.8 Hz, OCH_2), 2.64 (s, 3H, SCH_3), 1.65 (d, 3H, J = 7.2 Hz, $\mathbf{CH_3}CH$), 1.23 (t, 3H, J = 7.2 Hz, $CH_2\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 14.3, 18.6, 61.5, 73.3, 102.2, 115.9, 116.5, 116.7, 120.2, 122.6, 126.2, 128.9, 130.3, 130.4, 138.7, 145.8, 147.4, 151.1, 155.8, 156.2, 157.5, 161.6, 164.1, 171.9; EI-MS (70 eV, *m/z*): 560 (M^+), 561 (M^+ + 1); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_5S$: C, 62.13; H, 4.49; N, 9.99; Found: C, 61.86; H, 4.28; N, 9.76.

*3.5.7. 5-(2-Fluorophenyl)-3-methylthio-1-phenyl-6-[4-(1-propoxycarbonylethoxy)]phenoxy pyrazolo[3,4-d]pyrimidin-4-one (**6g**)*

White crystals, mp 185–187 °C; yield, 61%; IR (KBr) ν (cm^{-1}): 2988, 1743, 1702, 1601, 1576, 1500, 1398, 1190, 896, 757; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, J = 8.0 Hz, Ar), 7.20–7.46 (m, 7H, Ph), 7.09 (d, 2H, J = 9.2 Hz, OC_6H_4O), 6.91 (d, 2H, J = 9.2 Hz, OC_6H_4O), 4.76 (q, 1H, J = 7.2 Hz, CHC=O), 4.11 (t, 2H, J = 6.8 Hz, $O\mathbf{CH_2}Et$), 2.68 (s, 3H, SCH_3), 1.60–1.66 (m, 5H, $\mathbf{CH_3}CHO$ and $CH_2\mathbf{CH_2}CH_3$), 0.87 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4, 13.6, 18.7, 22.1, 67.1, 73.3, 102.2, 116.0, 116.6, 116.8, 120.4, 122.2, 122.7, 124.8, 126.3, 129.0, 130.6, 131.3, 138.7, 145.9, 147.6, 151.4, 155.9, 156.1, 156.8, 172.1; EI-MS (70 eV, *m/z*): 575 (M^+); Elemental Anal. Calcd. for $C_{30}H_{27}FN_4O_5S$: C, 62.71; H, 4.74; N, 9.75; Found: C, 62.93; H, 4.81; N, 9.92.

*3.5.8. 5-(4-Fluorophenyl)-3-methylthio-1-phenyl-6-[4-(1-propoxycarbonylethoxy)]phenoxy pyrazolo[3,4-d]pyrimidin-4-one (**6h**)*

White crystals, mp 188–189 °C; yield, 62%; IR (KBr) ν (cm^{-1}): 2971, 2930, 1752, 1702, 1603, 1576, 1505, 1349, 1132, 895, 830, 758; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, J = 7.6 Hz, Ar), 7.20–7.36 (m, 7H, Ph), 7.07 (dd, 2H,

J = 6.8 Hz and 2.8 Hz, OC_6H_4O), 6.91 (dd, 2H, J = 9.2 Hz and 2.8 Hz, OC_6H_4O), 4.76 (q, 1H, J = 6.8 Hz, CHC=O), 4.11 (t, 2H, J = 6.6 Hz, O**CH**$_2$Et), 2.68 (s, 3H, SCH_3), 1.60–1.66 (m, 5H, **CH**$_3$CHO and CH_2**CH**$_2$$CH_3$), 0.87 (t, 3H, J = 7.4 Hz, CH_3); EI-MS (70 eV, *m/z*): 575 (M^+); Elemental Anal. Calcd. for $C_{30}H_{27}FN_4O_5S$: C, 62.71; H, 4.74; N, 9.75; Found: C, 62.59; H, 4.65; N, 9.88.

*3.5.9. 3-Benzylsulfanyl-5-(2-fluorophenyl)-6-[4-(1-methoxycarbonylethoxy)]phenoxy-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**6i**)*

Spectral date are consistent with reference to [9a].

*3.5.10. 3-Benzylsulfanyl-5-(4-fluorophenyl)-6-[4-(1-methoxycarbonylethoxy)]phenoxy-1-phenylpyrazolo[3,4-d]pyrimidin-4-one e (**6j**)*

Spectral date are reference to [7a]; ^{13}C NMR (100MHz, $CDCl_3$):δ 18.7, 35.2, 52.5, 73.3, 102.5, 116.0, 116.6, 116.8, 120.4, 122.6, 126.3, 127.4, 128.5, 129.0, 129.4, 130.3, 130.4, 137.7, 138.7, 145.9, 146.3, 151.1, 155.8, 156.2, 157.5, 161.7, 164.1, 172.4.

*3.6. General procedure for the preparation of 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylsulfonyl-5-(fluoro-substituted)phenyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-ones **7a–7j***

To a 25 mL flask, 1.5 mmol **6** and 15 ml acetic acid were added at room temperature, and then 0.002 g (0.06 mmol) $Na_2WO_4{\cdot}H_2O$ was added with stirring. The reaction mixture was heated to 40 °C with vigorous stirring. To the reaction mixture, 0.51 g (4.5 mmol) 30% H_2O_2 was added slowly. After addition was completed, the mixture was heated to 50 °C and stirred for another 5 h. The reaction mixture was chilled to room temperature and dumped to a solution that was dispensed by 0.25 g Na_2SO_3 and 20 mL water. A lot of white solid was precipitated with stirring. Pure compounds **7** were obtained after recrystallization with ethanol.

*3.6.1. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(3-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7a**)*

Spectral date are reference to [9c]. ^{13}C NMR (100 MHz, $CDCl_3$):δ 14.3, 42.7, 61.7, 65.9, 100.9, 115.6, 116.3, 117.1, 121.8, 122.5, 124.4, 128.1, 129.2, 131.0, 135.8, 137.5, 145.6, 147.6, 151.8, 156.1, 156.3, 156.7, 163.6, 168.6.

*3.6.2. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(2-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7b**)*

Spectral date are consistent with reference to [9c].

*3.6.3. 6-(4-Ethoxycarbonylmethoxy)phenoxy-5-(4-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7c**)*

Spectral date are consistent with reference to [9c].

*3.6.4. 6-[4-(1-Ethoxycarbonylethoxy)]phenoxy-5-(3-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7d**)*

White crystals, mp 212–213 °C; yield 82%; IR (KBr) ν (cm^{-1}): 3118, 2990, 2928, 1720, 1600, 1579, 1558, 1502, 1327, 1197, 1134, 1095, 881, 770, 682, 571, 522; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 8.0 Hz, Ar), 7.56 (q, 1H, J = 6.4 Hz, Ar), 7.14–7.40 (m, 6H, Ar), 7.06 (d, 2H, J = 8.8 Hz, OC_6H_4O), 6.91 (d, 2H, J = 8.8 Hz, OC_6H_4O), 4.74 (q, 1H, J = 6.8 Hz, OCH), 4.21 (q, 2H, J = 7.2 Hz, OCH_2), 3.50 (s, 3H, S (O_2) CH_3), 1.65 (d, 3H, J = 6.4 Hz, **CH**$_3$CH), 1.24 (t, 3H, J = 7.2 Hz, CH_2**CH**$_3$); EI-MS (70 eV, *m/z*): 592 ($M^+ - 1$), 593 (M^+); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_7S$: C, 58.78; H, 4.25; N, 9.45; Found: C, 58.88; H, 4.23; N, 9.50.

*3.6.5. 6-[4-(1-Ethoxycarbonylethoxy)]phenoxy-5-(2-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7e**)*

White crystals, mp 233–235 °C, yield 88%; IR (KBr) ν (cm^{-1}): 3120, 2987, 2925, 1744, 1728, 1599, 1578, 1545, 1501, 1327, 1192, 1137, 1096, 905, 775, 696, 574, 523; ^{1}H NMR ($CDCl_3$, 400 MHz)δ 7.87 (d, 2H, J = 8.0 Hz, Ar), 7.27-7.47 (m, 7H, Ar), 7.08 (d, 2H, J = 9.2 Hz, OC_6H_4O), 6.91 (d, 2H, J = 9.2 Hz, OC_6H_4O), 4.75 (q, 1H, J = 6.4 Hz, OCH), 4.21 (q, 2H, J = 7.2 Hz, OCH_2), 3.51 (s, 3H, S (O_2) CH_3), 1.65 (d, 3H, J = 6.4 Hz, **CH**$_3$CH), 1.23 (t, 3H, J = 6.4 Hz, CH_2**CH**$_3$); EI-MS (70 eV, *m/z*): 592 ($M^+ - 1$), 593 (M^+); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_7S$: C, 58.78; H, 4.25; N, 9.45; Found: C, 58.82; H, 4.27; N, 9.51.

*3.6.6. 6-[4-(1-Ethoxycarbonylethoxy)]phenoxy-5-(4-fluorophenyl)-3-methylsulfonyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7f**)*

White crystals, mp 231–232 °C, yield 85%; IR (KBr) ν (cm^{-1}): 3117, 3006, 2925, 1749, 1720, 1605, 1577, 1546, 1504, 1328, 1201, 1137, 1098, 904, 775, 695, 560, 524; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 8.0 Hz, Ar), 7.24–7.40 (m, 7H, Ar), 7.05 (d, 2H, J = 9.2 Hz, OC_6H_4O), 6.90 (d, 2H, J = 9.2 Hz, OC_6H_4O), 4.74 (q, 1H, J = 6.4 Hz, OCH), 4.21 (q, 2H, J = 6.8 Hz, OCH_2), 3.50 (s, 3H, $S(O_2)CH_3$), 1.64 (d, 3H, J = 7.0 Hz, **CH**$_3$CH), 1.23 (t, 3H, J = 7.2 Hz, CH_2**CH**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$):δ 14.2, 18.6, 42.6, 61.6, 73.3, 100.9, 116.1, 116.9, 117.1, 121.7, 122.4, 128.0, 129.2, 130.2, 130.3, 137.6, 145.5, 147.6, 151.8, 156.0, 156.3, 156.9, 161.8, 164.3, 171.9; EI-MS (70 eV, *m/z*): 592 ($M^+ - 1$), 593 (M^+); Elemental Anal. Calcd. for $C_{29}H_{25}FN_4O_7S$: C, 58.78; H, 4.25; N, 9.45; Found: C, 58.85; H, 4.24; N, 9.53.

*3.6.7. 5-(2-Fluorophenyl)-3-methylsulfonyl-1-phenyl-6-[4-(1-propoxycarbonylethoxy)]phenoxy pyrazolo[3,4-d]pyrimidin-4-one (**7g**)*

White crystals, mp 172–176 °C; yield, 71%; IR (KBr) ν (cm^{-1}): 3120, 2971, 1732, 1599, 1578, 1550, 1501, 1196, 1137, 1038, 903, 761, 574, 519; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, J = 8.0 Hz, Ar), 7.24–7.39 (m, 8H, Ar), 7.06 (d, 2H, J = 8.8 Hz, OC_6H_4O), 6.91 (d, 2H, J = 9.2 Hz, OC_6H_4O), 4.75 (q, 1H, J = 6.8 Hz, CHC=O), 4.11 (t, 2H, J = 7.6 Hz,

O**CH**$_2$CH$_2$CH$_3$), 3.50 (s, 3H, S(O$_2$)CH$_3$), 1.60–1.66 (m, 5H, OCH**CH**$_3$ and OCH$_2$**CH**$_2$CH$_3$), 0.87 (t, 3H, J = 7.6 Hz, OCH$_2$CH$_2$**CH**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 10.4, 18.7, 22.1, 42.7, 67.1, 73.3, 100.8, 116.1, 116.6, 116.8, 121.1, 122.5, 125.1, 128.1, 129.2, 130.4, 131.7, 137.6, 145.6, 146.6, 147.7, 152.0, 155.6, 156.1, 156.8, 172.0; EI-MS (70 eV, *m/z*): 606 ($M^+ - 1$), 607 (M^+); Elemental Anal. Calcd. for $C_{30}H_{27}FN_4O_7S$: C, 59.40; H, 4.49; N, 9.24; Found: C, 59.51; H, 4.54; N, 9.18.

3.6.8. 5-(4-Fluorophenyl)-3-methylsulfonyl-1-phenyl-6-[4-(1-propoxycarbonylethoxy)]phenoxy pyrazolo[3,4-d]pyrimidin-4-one (**7h**)

White crystals, mp 211–213 °C; yield, 62%; IR (KBr) ν (cm^{-1}): 3979, 2969, 2919, 1721, 1605, 1579, 1558, 1504, 1194, 1137, 1093, 1034, 902, 763, 558, 521; ^{1}H NMR (CDCl$_3$, 400MHz) δ 7.88 (d, 2H, J = 8.0 Hz, Ar), 7.24–7.39 (m, 8H, Ar), 7.05 (d, 2H, J = 8.8 Hz, OC$_6$H$_4$O), 6.90 (d, 2H, J = 8.8 Hz, OC$_6$H$_4$O), 4.75 (q, 1H, J = 6.8 Hz, CHC=O), 4.11 (t, 2H, J = 7.6 Hz, O**CH**$_2$CH$_2$CH$_3$), 3.50 (s, 3H, S(O$_2$)CH$_3$), 1.59–1.66 (m, 5H, OCH**CH**$_3$ and OCH$_2$**CH**$_2$CH$_3$), 0.87 (t, 3H, J = 7.6 Hz, OCH$_2$CH$_2$**CH**$_3$); EI-MS (70 eV, *m/z*): 606 ($M^+ - 1$), 607 (M^+); Elemental Anal. Calcd. for $C_{30}H_{27}FN_4O_7S$: C, 59.40; H, 4.49; N, 9.24; Found: C, 59.52; H, 4.56; N, 9.20.

3.6.9. 3-Benzylsulfonyl-5-(2-fluorophenyl)-6-[4-(1-methoxycarbonylethoxy)]phenoxy-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7i**)

Spectral date are consistent with reference to [9a].

3.6.10. 3-Benzylsulfonyl-5-(4-fluorophenyl)-6-[4-(1-methoxycarbonylethoxy)]phenoxy-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (**7j**)

Spectral date are reference to [7a]; ^{13}C NMR (100 MHz, CDCl$_3$): δ 18.7, 52.5, 60.5, 73.2, 101.3, 116.1, 116.9, 117.2, 121.7, 122.5, 126.7, 128.0, 128.9, 129.2, 129.8, 130.2, 130.3, 131.5, 137.6, 145.6, 146.6, 151.8, 156.0, 156.4, 156.9, 161.9, 164.4, 172.3.

3.7. Herbicidal testing

Herbicidal testing of the newly synthesized compounds **6** and **7** was carried out in a plant growth room. Temperature 23 ± 1 °C, RH 60 ± 5%, light intensity 10 Klux, photoperiod 8 h/day. Twenty seeds of each one of weed species including rape and barnyard grass were chosen for testing. Seedlings were grown in the test plate of 9 cm diameter containing two pieces of filter paper and 9 mL solution of the tested compound (100 mg/L and 10 mg/L, respectively). Distilled water and 2,4-dichlorophenoxyl acetic acid (2,4-D), a commercially available herbicide in the market, were used as comparison compound. The herbicidal activity was assessed as the inhibition rate in comparison with the distilled water. The herbicidal rating score based on visual observation. Range from 0% to 100%, 0% means no effect, 100% means complete killing.

3.8. Crystal structure determination

Single crystal X-ray diffraction data for **7b** at 292 K on a Bruker Smart Apex Area CCD equipped with Mo Kα radiation (λ = 0.71073 Å). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-604929. Copies of the data can be obtained, free of charge, on application to CCDC, Cambridge, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

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