

Synthesis and herbicidal activity of new substituted 2- and 4-pyrimidinyloxyphenoxypropionate derivatives

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Abstract

Aryloxyphenoxypropionates (APPs) are a class of herbicides targeting acetyl-CoA carboxylase (ACCase) in monocot chloroplast. The article presents the rational design and synthesis of a series of APPs with 2- and 4-pyrimidinyloxy moieties. The developed synthetic protocols are versatile and allow convenient functionalization of the phenoxypropionate core with various 2- or 4-pyrimidinyl moieties via the oxygen bridge by taking advantage of the reactivity difference between 2-methylsulfonyl and 4-chloro on the pyrimidine ring. Preliminary bioassay shows that most of title compounds have good herbicidal activities against rape and barnyard grass at 100 mg/L. Several compounds are more potent to inhibit the stalk growth of barnyard grass than the commercial herbicide cyhalofop.

Keywords: Aryloxyphenyloxypropionate, 2-methylsulfonylpyrimidine, 4-chloropyrimidine, synthesis, herbicidal activity

Introduction

Acetyl-CoA carboxylase (ACCase, EC 6.4.1.2) in plants is a key enzyme in *de novo* fatty acid biosynthesis, catalyzing the carboxylation of acetyl-CoA to malonyl-CoA.¹ There are two forms of ACCase in most plant families: the heteromeric form in plastids and the homomeric form in cytoplasm, with the exception of the grass family, including wheat and rice, which have the homomeric form in both cytosol and plastids.² The homomeric ACCase in grass plastids is the selective action target of aryloxyphenoxypropionate (APP) herbicides,³ which were introduced in the 1980s and have been extensively used worldwide to control a variety of grass weeds. The frequent use of this class of herbicides has resulted in an increasing resistance in many grass weeds.⁴ Developing new herbicides that inhibit both the susceptible and resistant forms of ACCase in grass weeds would have obvious commercial appeal.⁵

Some typical commercial APP herbicides (**I**: diclofop; **II**: cyhalofop; **III**: haloxyfop) are shown in Figure 1, which have the same phenoxypropionate portion, but different aryloxy rings. The structures of the yeast (*Saccharomyces cerevisiae*) ACCase carboxyl transfer (CT) domain in complexes with diclofop I and haloxyfop III have been solved by x-ray diffraction. The typical binding pattern revealed that the aryloxy groups were sandwiched between the side chains of two conserved amino acids Tyr-1738 and Phe-1956' in ACCase active site with obvious π - π interaction force.⁶ For higher plants, Delye and colleagues demonstrated the five residues Ile-1781 Trp-2027, Ile-2041, Asp-2078, and Gly-2096 in the active site of ACCase from *Alopecurus myosuroides* (black-grass) were involved in sensitivity to ACCase inhibitors, as demonstrated through a molecular, biological and biochemical approach combining with the three-dimensional modeling. Zhu and colleagues built the homology models of the ACCase CT domain from the sensitive and resistant foxtails and investigated the molecular mechanism of herbicide resistance and stereochemistry-activity relationships of APPs.⁷ The results indicated that not only the conserved residues for the π - π stacking but also the hydrogen binding environment were implicated in the binding modes of sensitive and resistant ACCase CT domains.

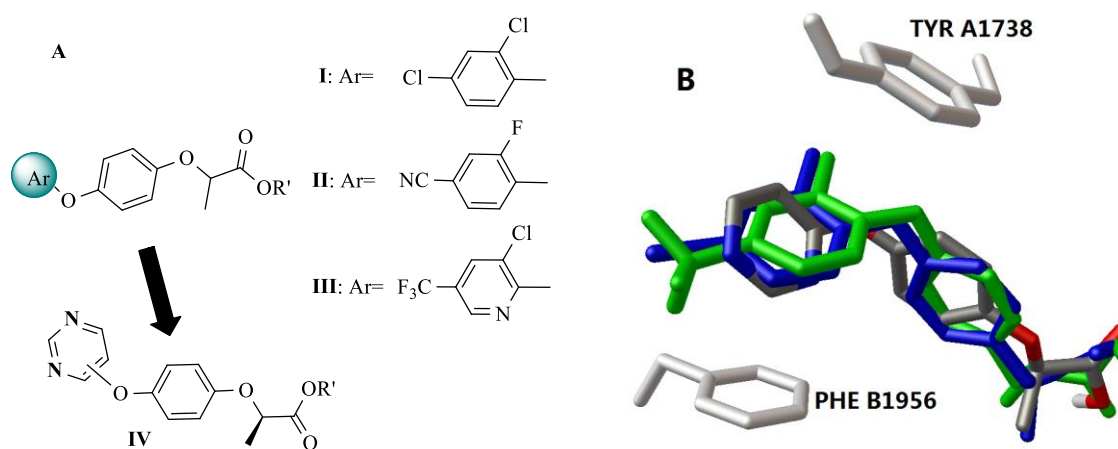


Figure 1. Strategy for the design of pyrimidinyloxyphenoxypropionates. A) Comparison in bioisosterism: **I**: diclofop; **II**: cyhalofop; **III**: haloxyfop; **IV**: Representative in this work; B Clustering of docked pyrimidinyl-4-oxyphenoxypropionic acid (IV, in atom color) with diclofop (in green) and haloxyfop (in blue) from crystal with the referred residues TYR A1738 and PHE B1956 in ACCase active site.

In our case, we intend to rationally design and synthesise new inhibitors targeting ACCase with the pyrimidinoxy group as the substituent of aryloxy portion in conventional APPs. The rational design was firstly considered according to the bioisosterism of pyrimidine ring with benzene and pyridine rings in diclofop I, cyhalofop II, and haloxyfop III, respectively (Figure 1A).⁸ Secondly, the pyrimidine ring is an extremely versatile building block for the manufacture of bioactive compounds such as herbicides,⁹ fungicides¹⁰ or insecticides¹¹ in the agrochemical

industry. However, there is limited literature disclosing the potential application of pyrimidinylphenoxypropionate compounds as herbicides.¹² Thirdly, molecular docking of our designed pyrimidinylphenoxypropionic acid (IV) into the active site of ACCase model results in the similar binding pattern as diclofop and haloxyfop in crystal⁶ (figure 1B) with comparable expected bioactivity. Moreover, since a subtle change of substituent on the aryloxy ring will produce a significant difference on the sensitivity to ACCase,¹³ the attempt to synthesize and identify new compounds that may target ACCase will be valuable for finding a solution against the resistance development in use of the herbicides.

Aimed at the ultimate goal, this work presents the synthesis of pyrimidinylphenoxypropionates and the preliminary bioassay on *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass). The developed synthetic protocols are versatile and allow convenient functionalization of the phenoxypropionate core with various 2- or 4-pyrimidinyl moieties via the oxygen bridge, by taking advantage of the reactivity difference between 2-methylsulfonyl and 4-chloro moieties on the pyrimidine ring (Scheme 3). Since the enantiomer with *R* configuration at α -position in the propionate portion is more sensitive than its *S* enantiomer,¹⁴ L-lactate is used as the chiral pool in synthesis of the desired products with *R* configuration. Meanwhile, the molecular structure of a representative compound has been characterized with X-ray diffraction.

Results and Discussion

Docking study

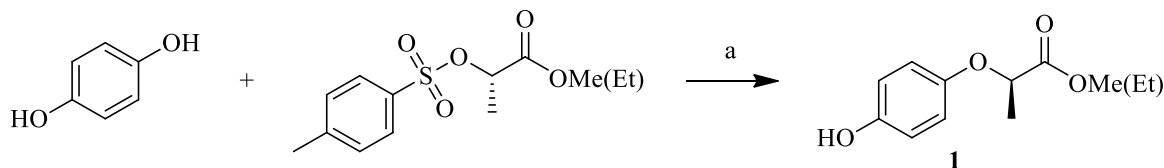
ACCase is a multidomain enzyme composed of three domains: biotin carboxylase, biotin carboxyl carrier protein, and carboxyltransferase, shorten as BC, BCCP, and CT domains respectively.¹⁵ The CT domain contains 800 residues and constitutes two subdomains with antisymmetric dimer arrangement, and the active site is located at the interface of the dimer. Two representative herbicides, haloxyfop and diclofop, bind to the active site and the binding mode with yeast ACCase has been resolved by X-ray diffraction.⁶ The main binding pattern is the aryloxy portions of the two inhibitors were sandwiched between the side chains of Tyr-1738 and Phe-1956' with similar orientation and showing π - π interactions. The amino acid sequences of this domain are highly conserved. For example, there is a sequence identity of 51% between the CT domains of foxtail and yeast ACCases⁷ and 55.3% between that of yeast and black-grass ACCases.³ These sequence identities imply the yeast CT domain is sufficient to achieve a satisfactory model.¹⁶ Therefore, the 3D structure of the yeast CT domain should be applicable to the high plant CT domains for molecular docking.

For the docking of designed pyrimidinylphenoxypropionate, several steps were involved. 1) The model of CT domain was prepared by extracting water molecules and diclofop from the yeast CT complex (PDB code: 1UYT); 2) The active site was chosen as the docking center and the residues Tyr-1738 and Phe-1956' chosen as flexible; 3) Autodock 4.2 program with

MGLTools 1.5.2 interface software was used to perform and analyze the docking; 4) The most favorable docked conformation was used for visualization and prediction of the binding energy and bioactivity. The clustering of docked pyrimidinyloxyphenoxypropionic acid (IV) with diclofop and haloxyfop in crystal is shown in Figure 1B. The predicted binding energies of most favorable docked conformations were -6.36, -5.41 and -5.19 Kcal/mol, with respect to the three compounds, and all predicted inhibition constants were in the range of millimole. The key feature of pyrimidinyloxyphenoxypropionic acid in docking state is the pyrimidine ring sandwiched between the side chains of Tyr-1738 and Phe-1956', as the binding modes of diclofop and haloxyfop (Figure 1B). When the pyrimidine ring bears substituent(s), stronger binding with larger binding energy can be predicted. Thus the lead hit, pyrimidinyloxyphenoxypropionic acid, was chosen for the design and synthesis of series of substituted 2- and 4-pyrimidinyloxyphenoxypropionate derivatives in this paper.

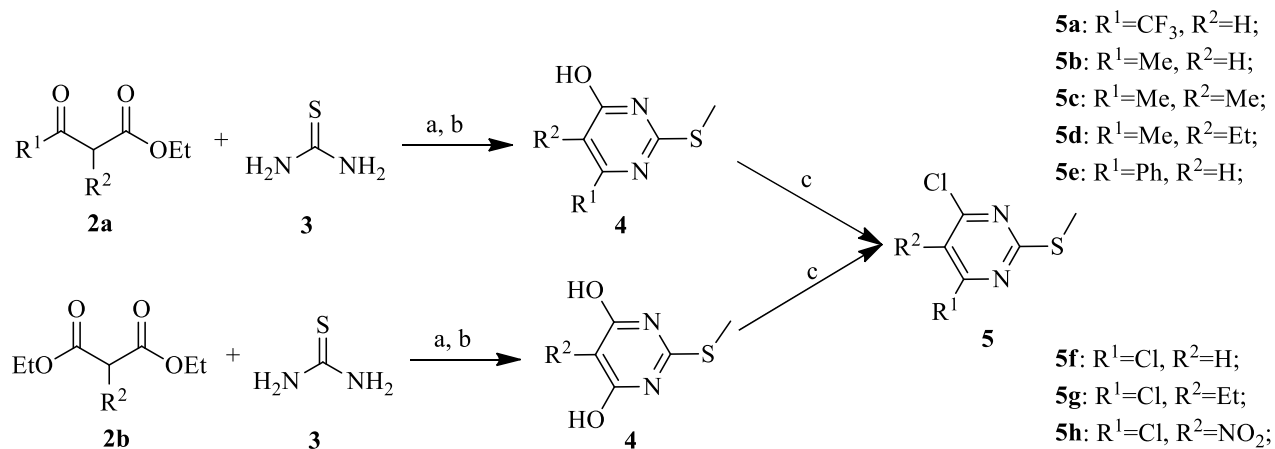
Chemistry

The design and synthesis of series of substituted 2- and 4-pyrimidinyloxy phenoxypropionate derivatives are outlined in Scheme 1-3. As shown in Scheme 1, hydroquinone was reacted with the chiral pool, methyl (*S*)-2-(tosyloxy)propanoate or ethyl (*S*)-2-(tosyloxy)propanoate, in the presence of sodium hydroxide, and (*R*)-2-(4-Hydroxy-phenoxy)-propionates **1** were produced.



Scheme 1. Reagents and conditions: (a) NaOH, MeOH, 40 °C; HCl acid.

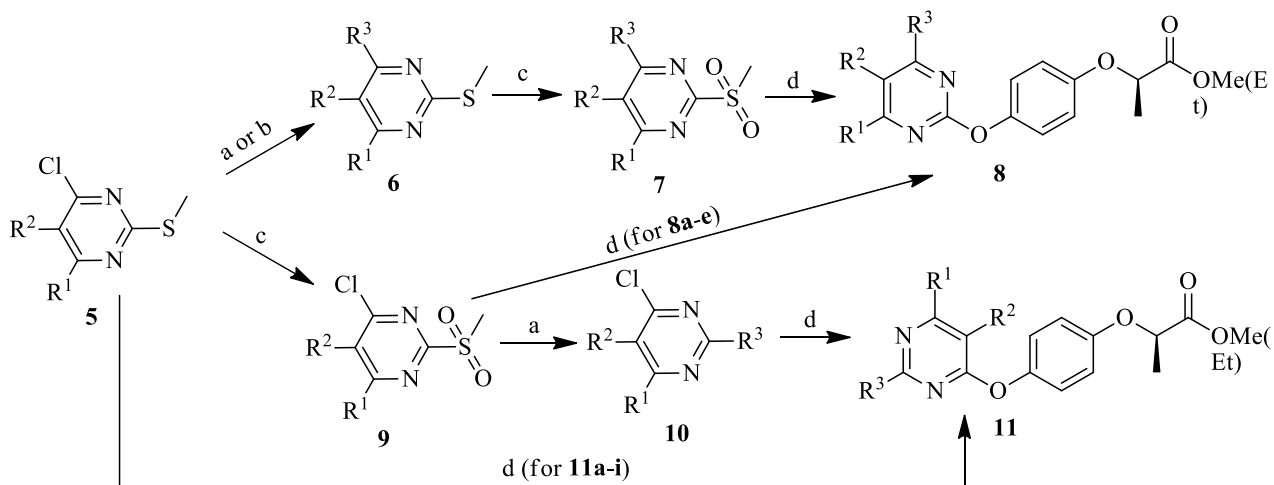
The condensation of 1,3-dicarbonyl derivatives **2** with thiourea **3** followed by the reaction with dimethyl sulfate to afford 2-methylthiopyrimidines **4**, which were converted to intermediates **5** by chlorination with POCl₃ (Scheme 2).



Scheme 2. Reagents and conditions: (a) NaOMe, MeOH, reflux; (b) SO₂(OMe)₂, NaOH, H₂O,

r.t.; HCl acid; (c) POCl₃, DMA, reflux.

The intermediates **5** could be further derivatized either to the 2-(methylthio)pyrimidines **6** by reacting with various alcohols or amines, or to the 4-chloro-2-(methylsulfonyl)pyrimidine derivatives **9** by oxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) in CH₂Cl₂ at room temperature. The 2-methylthiopyrimidines **6** were oxidized to the 2-methylsulfonylpyrimidines **7** with the similar oxidation conditions, whereas the 4-chloro-2-methylsulfonylpyrimidines **9** were converted to 2-alkoxy or 2-alkylamino-4-chloropyrimidines **10** by the similar substitution conditions. The intermediates **5**, **7**, **9** or **10** were reacted with the chiral pool (*R*)-2-(4-hydroxyphenoxy)propanoate **1** in the presence of K₂CO₃ in CH₃CN at refluxing condition to afford the title compounds **8a–m** and **11a–m** (Scheme 3).



8a: R¹=CF₃, R²=H, R³=Cl;

8b: R¹=Me, R²=H, R³=Cl;

8c: R¹=Cl, R²=H, R³=Cl;

8d: R¹=Cl, R²=Et, R³=Cl;

8e: R¹=Cl, R²=NO₂, R³=Cl;

8f: R¹=CF₃, R²=H, R³=OMe;

8g: R¹=CF₃, R²=H, R³=OEt;

8h: R¹=CF₃, R²=H, R³=NHMe;

8i: R¹=CF₃, R²=H, R³=Me;

8j: R¹=Me, R²=H, R³=OMe;

8k: R¹=Me, R²=H, R³=NHMe;

8l: R¹=Cl, R²=NO₂, R³=OMe;

8m: R¹=OMe, R²=H, R³=OMe;

11a: R¹=CF₃, R²=H, R³=SMe;

11b: R¹=Me, R²=H, R³=SMe;

11c: R¹=Me, R²=Me, R³=SMe;

11d: R¹=Me, R²=Et, R³=SMe;

11e: R¹=OMe, R²=H, R³=SMe;

11f: R¹=NHMe, R²=H, R³=SMe;

11g: R¹=Cl, R²=H, R³=SMe;

11h: R¹=Cl, R²=NO₂, R³=SMe;

11i: R¹=Ph, R²=H, R³=SMe;

11j: R¹=Cl, R²=H, R³=OMe;

11k: R¹=OMe, R²=H, R³=OMe;

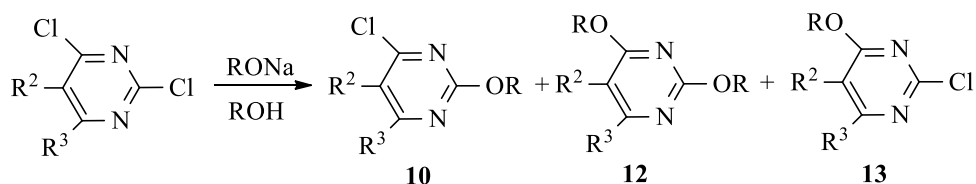
11l: R¹=OEt, R²=H, R³=OEt;

11m: R¹=Cl, R²=H, R³=NHMe;

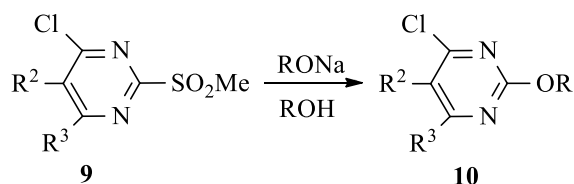
Scheme 3. The synthetic routes of the title compounds. Reagents and conditions: (a) R₃ONa, ROH, r.t.; (b) RNH₂, Et₃N, BuOH, reflux; (c) *m*-CPBA, CH₂Cl₂, r.t.; (d) (*R*)-methyl or ethyl 2-(4-hydroxyphenoxy)propanoate, K₂CO₃, CH₃CN, reflux;

In synthesis of the 4-chloropyrimidines **10**, we have tried a direct approach using 2,4-

dichloropyrimidine or its derivatives as the starting materials, because these compounds are commercially available and relatively cheap, and the nucleophilic substitution of chloro group on electron-deficient heterocycles is one of the most common methods to prepare the corresponding alkoxy or aryloxy derivatives. However, this straightforward approach suffered one major drawback: a mixture of **10**, **12** and **13** were obtained with **13** as the main product at the reactant ratio 1:1 (Scheme 4). This tendency provides a direct evidence that 2-chloro on pyrimidine has a relatively lower reactivity toward nucleophilic substitution than 4-chloro group. This approach cannot offer desired products with positions 2, 5 and 6 substituted while leaving the 4-chloro group intact. To overcome the problem, 2-methylsulfonyl were introduced to the position 2 on pyrimidine ring since it has a strong electron-withdrawing property that facilitates the nucleophilic substitution.¹⁷ Thus 2-methylsulfonylpyrimidine derivatives were reacted with various sodium alcoholates to afford 2-substituted-4-chloropyrimidine derivatives as shown in Scheme 5. The intermediate **10** can be readily reacted with (*R*)-2-(4-hydroxyphenoxy)propanoate **1** in the presence of K₂CO₃ in CH₃CN at refluxing condition to obtain the title compounds **11g-m** in good yields.



Scheme 4



Scheme 5

All of the title compounds **8** and **11** were confirmed by ¹H NMR, IR, MS and elemental analysis. The structure of one representative compound, Ethyl (*R*)-2-(4-(4,6-dimethoxypyrimidin-2-yloxy)phenoxy)propanoate **8m**, was further confirmed by single-crystal x-ray analysis (Figure 2). Complete crystallographic data for the structure of target compound **8m** reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as a CIF file (CCDC 775891). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

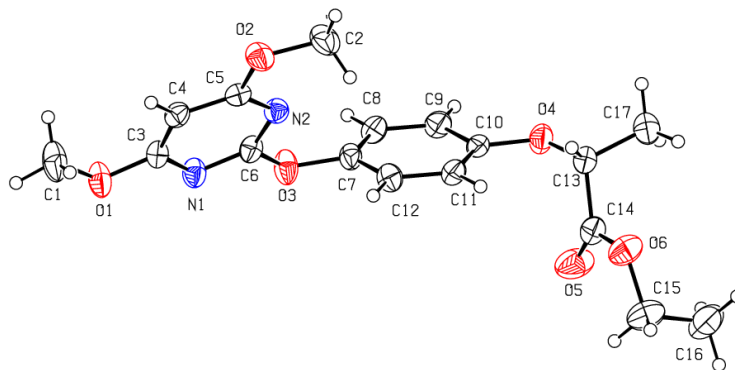


Figure 2. The crystal structure of compound **8m** obtained from single crystal X-ray analysis.

Herbicidal activities

The herbicidal activities of the synthesized compounds were tested in preliminary assays by using a reported procedure.¹⁸ As listed in table 1, most of the compounds showed notable herbicidal activities by inhibiting the root and stalk growth of not only monocotyledonous barnyard grass, but also dicotyledonous rape. For instance, **8f**, **8g**, **8m**, **11f**, **11h**, **11k** and **11m** showed inhibitory rates of >90% to the root growth of rape and inhibitory rates of >80% to the root growth of barnyard grass at concentration 100 mg/L. It is worth mentioning that most of the compounds were more potent to inhibit the stalk growth of barnyard grass with comparison to the commercial herbicide cyhalofop at concentration 10 mg/L. For example, **8a**, **8f**, **8h**, **11h**, **11k**, **11l** and **11m** showed inhibitory rates of >65% to the stalk growth of barnyard grass at concentration 10 mg/L, whereas the control showed only a low inhibitory capacity to the stalk growth. However, some of these compounds showed low selectivity and with the reduction of concentration to 10mg/L these compounds showed low inhibition rates to grass growth with comparison to the commercial herbicide cyhalofop. Meanwhile, of all the tested compounds, **8h**, **11k**, **11l** and **11m** to inhibit the growth of barnyard grass and **8m** to inhibit the growth of rape exhibited a relative selectivity in the test weeds at low concentration.

Table 1. The herbicidal activities of title compounds

Compound	Inhibition rate/%			
	Rape (root/stalk)		Barnyard grass (root/stalk)	
	100 mg/L	10 mg/L	100 mg/L	10 mg/L
8a	91/39	47/29	79/68	62/66
8b	56/58	44/36	81/74	66/59
8c	74/65	42/63	66/27	17/27
8d	69/58	51/46	71/38	43/32
8e	81/58	70/36	88/70	72/56

Table 1. Continued

Compound	Inhibition rate/%			
	Rape (root/stalk)		Barnyard grass (root/stalk)	
	100 mg/L	10 mg/L	100 mg/L	10 mg/L
8f	93/51	42/24	89/57	64/67
8g	96/88	69/46	90/55	64/61
8h	56/42	32/15	82/65	70/68
8i	93/49	41/31	76/55	59/48
8j	46/43	41/35	79/72	69/64
8k	76/62	71/49	80/61	60/50
8l	89/58	69/45	77/67	70/58
8m	98/82	96 /72	87/59	48/9
11a	69/47	60/26	70/63	39/58
11b	72/56	44/24	89/37	70/30
11c	51/50	12/32	56/37	35/32
11d	53/50	30/43	70/63	54/43
11e	79/54	38/26	70/69	48/46
11f	90/70	52 /20	81/62	47/61
11g	62/48	55/41	71/46	60/39
11h	91/57	63/44	84/70	59/65
11i	81/58	70/36	88/70	72/56
11j	76/69	58/51	70/68	62/46
11k	98/86	47/52	91/71	78/77
11l	69/56	53/38	89/74	75/67
11m	98/84	48/40	94/81	72/75
Cyhalofop	77/46	27/39	95/66	95/37

In conclusion, a series of new aryloxyphenoxypropionate derivatives containing a pyrimidine ring were designed and synthesized. The developed synthetic protocols are versatile and allow convenient functionalization of the phenoxypropionate core with various 2- or 4-pyrimidinyl moieties via the oxygen bridge, by taking advantage of the reactivity difference between 2-methylsulfonyl and 4-chloro on the pyrimidine ring. The preliminary bioassay showed that most of the synthesized compounds had good herbicidal activities and were more potent to inhibit the

stalk growth of barnyard grass with comparison to the commercial APP herbicide cyhalofop at low concentration. Further investigation on the enzyme activity of these compounds toward both the herbicide-sensitive and resistant forms of ACCase is in progress in this laboratory.

Experimental Section

Docking study

The molecular docking was performed and analyzed with the Autodock 4.2 program and the MGLTools 1.5.2 interface software. The CT domain model structure of ACCase was rebuilt from the crystal structure of yeast CT complex (PDB code: 1UYT) by extracting water molecules and diclofop. The active site was chosen as the docking center and the side chains of Tyr-1738 and Phe-1956' as flexible. The lead hit pyrimidinyloxyphenoxypropionic acid (IV) and haloxyfop (III) were docked into the active site. The lowest predicted binding energies and inhibition constants were obtained. The most favorable docked conformations were used for visualization and prediction of the binding energy and bioactivity. Meanwhile, diclofop (I) in the crystal state of the yeast CT complex was replaced into the active site for comparing the conformations.

Chemistry

General. All solvents were redistilled before use. Melting points were taken on a Buchi B-545 melting point apparatus and are uncorrected. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1} . ^1H NMR spectra were recorded on a Mercury-Plus 400 or Mercury-Plus 600 spectrometer in CDCl_3 using TMS as an internal reference. MS were measured on a Finnigan Trace MS spectrometer, at 70 eV. Elemental analysis were taken on a Vario EL III elemental analyzer. The X-ray diffraction data were collected on a *BrukerSMART* AXS CCD diffractometer, $\text{MoK}\alpha$, $2\theta = 2.80\text{-}27.00^\circ$. Unless otherwise noted, all materials were commercially available and were used directly without further purification.

Synthesis of (*R*)-2-(4-hydroxyphenoxy)-propionate (1). The synthesis was performed according to the reported method¹⁹ with some modification. Briefly, to a vigorously stirred solution of hydroquinone (8.8 g, 80 mmol), sodium hydroxide (9.6 g, 240 mmol) in methanol (150 ml) at room temperature, (*S*)-2-(tosyloxy)propanoate (60 mmol) was added dropwise. After 24 h, the mixture was acidified with concentrated hydrochloric acid and heated at reflux for 2 h. The solvent was evaporated in vacuum and the residue was dissolved in 100 ml water, extracted with CH_2Cl_2 . The Organic layer was dried with Na_2SO_4 , the solvent was removed. The residue was purified by a silica gel column chromatography (petroleum ether-EtOAc) and give the corresponding **1** (*R*)-2-(4-hydroxyphenoxy)-propionate in high enantiomeric purity (>98% ee, by HPLC analysis).

Methyl (*R*)-2-(4-hydroxyphenoxy)propanoate. Yield 52%, brown solid, mp 62-64 °C (lit.²⁰ 64-67 °C).

Ethyl (*R*)-2-(4-hydroxyphenoxy)propanoate. Yield 66%, colourless prisms, mp 36-37 °C (lit.²⁰ 35 °C).

General procedure for the synthesis of 4-chloro-2-mercaptopyrimidines (**5**)

The synthesis was performed according to the reported method.^{21,22,23} A solution of thiourea **3** (3.8 g, 50 mmol), 1,3-dicarbonyl compound **2** (50 mmol) and sodium methoxide (6.5 g, 120 mmol) in methanol (100 mL) heated at reflux for 6 h. The solvents were evaporated, and H₂O (150 mL) was added. Dimethyl sulfate (6.3 g, 50 mmol) was added dropwise with vigorous stirring and the reaction was stirred for 24 h at room temperature. Then the mixture was neutralized with concentrated HCl and the precipitate was collected. The solid was dried in vacuum and used directly to react with POCl₃ (40 mL) in the presence of NEt₃ (5.05 g, 50 mmol) heated at 95-100 °C for 3 h. Solvents were removed at reduced pressure, and the residue was poured into ice water and extracted with diethyl ether. The organic phase was washed with aqueous NaHCO₃ and water, dried over Na₂SO₄. The solution was concentrated and the desired products **5** were obtained by recrystallization from the mixed solvent of EtOAc-petroleum ether.

4-Chloro-2-methylthio-6-trifluoromethylpyrimidine (5a). Yield 70%, white solid, mp 38-39 °C. ¹H NMR (600 MHz, CDCl₃), δ 2.55 (s, 3H, SCH₃), 6.66 (s, 1H, pyrimidine-H). MS (*m/z*, %): 228 (M⁺, 36), 193 (100), 124 (41). Anal. Calcd for C₆H₄ClF₃N₂S: C, 31.52; H, 1.76; N, 12.25%. Found: C, 31.74; H, 1.82; N, 11.97%.

4-Chloro-6-methyl-2-methylthiopyrimidine (5b). Yield 76%, white solid, mp 41-42 °C (lit.²⁴ mp 39-40 °C).

4-Chloro-5,6-dimethyl-2-methylthiopyrimidine (5c). Yield 78%, colourless prisms, mp 33-34 °C. ¹H NMR (600 MHz, CDCl₃), δ 2.46 (s, 3H, pyrimidine-CH₃), 2.56 (s, 3H, SCH₃), 2.68 (s, 3H, pyrimidine-CH₃). MS (*m/z*, %): 188 (M⁺, 52), 153 (66), 91 (78). Anal. Calcd for C₇H₉ClN₂S: C, 44.56; H, 4.81; N, 14.85%. Found: C, 44.25; H, 4.98; N, 14.69%.

4-Chloro-5-ethyl-6-methyl-2-methylthiopyrimidine (5d). Yield 72%, colourless prisms, mp 36-37 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.46 (t, 3H, *J* = 6.6 Hz, CH₂CH₃), 2.38 (s, 3H, pyrimidine-CH₃), 2.56 (s, 3H, SCH₃), 2.65 (q, 3H, *J* = 6.6 Hz, CH₂). MS (*m/z*, %): 202 (M⁺, 22), 167 (59), 120 (100). Anal. Calcd for C₈H₁₁ClN₂S: C, 47.40; H, 5.47; N, 13.82%. Found: C, 47.16; H, 5.62; N, 13.97%.

4-Chloro-2-methylthio-6-phenylpyrimidine (5e). Yield 75%, white solid, mp 37-38 °C (lit.²⁵ mp 35-36 °C).

4,6-Dichloro-2-methylthiopyrimidine (5f). Yield 72%, colourless prisms, mp 42-43 °C (lit.²⁶ mp 40-41 °C).

4,6-Dichloro-5-ethyl-2-methylthiopyrimidine (5g). Yield 78%, colourless prisms, mp 58-59 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.45 (t, 3H, *J* = 6.8 Hz, CH₂CH₃), 2.56 (s, 3H, SCH₃), 2.65 (q, 3H, *J* = 6.8 Hz, CH₂). MS (*m/z*, %): 223 (M⁺, 17), 187 (69), 123 (100). Anal. Calcd for C₇H₈Cl₂N₂S: C, 37.68; H, 3.61; N, 12.56%. Found: C, 37.84; H, 3.56; N, 12.71%.

4,6-Dichloro-2-(methylthio)-5-nitropyrimidine (5h). Yield 72%, pale yellow prisms, mp 56-57 °C (lit.²⁷ mp 61 °C).

General procedure for the synthesis of 2-methylsulfonylpyrimidines (9)

The synthesis was performed according to the reported method.¹⁸ 2-methylthiopyrimidine **5** or **6** (10 mmol) was dissolved in dichloromethane (20 mL) and a solution of *m*-CPBA (25 mmol) in CH₂Cl₂ (40 mL) was added dropwise at room temperature. After stirring for 10 h, the reaction mixture was washed sequentially with saturated NaHSO₃, saturated Na₂CO₃, brine, and dried over anhydrous MgSO₄. Concentration in vacuum gave 2-methylsulfonylpyrimidine **9**.

4-Chloro-2-methylsulfonyl-6-trifluoromethylpyrimidine (9a). Yield 81%, pale yellow prisms, mp 81-82 °C. ¹H NMR (600 MHz, CDCl₃), δ 3.34 (s, 3H, SO₂CH₃), 6.67 (s, 1H, pyrimidine-H). MS (*m/z*, %): 260 (M⁺, 28), 181 (62), 146 (100). Anal. Calcd for C₆H₄ClF₃N₂O₂S: C, 27.65; H, 1.55; N, 10.75%. Found: C, 27.93; H, 1.58; N, 11.02%.

4-Chloro-6-methyl-2-methylsulfonylpyrimidine (9b). Yield 81%, colourless prisms, mp 244-245 °C. ¹H NMR (600 MHz, CDCl₃), δ 2.43 (s, 3H, pyrimidine-CH₃), 3.38 (s, 3H, SO₂CH₃), 6.72 (s, 1H, pyrimidine-H). MS (*m/z*, %): 206 (M⁺, 11), 171 (46), 127 (45), 92 (100). Anal. Calcd for C₆H₇ClN₂O₂S: C, 34.87; H, 3.41; N, 13.56%. Found: C, 34.90; H, 3.76; N, 13.45%.

4-Chloro-5,6-dimethyl-2-methylsulfonylpyrimidine (9c). Yield 85%, white solid, mp 185-186 °C. ¹H NMR (600 MHz, CDCl₃), δ 2.46 (s, 3H, pyrimidine-CH₃), 2.67 (s, 3H, CH₃), 3.34 (s, 3H, SO₂CH₃). MS (*m/z*, %): 220 (M⁺, 19), 185 (59), 141 (100), 106 (74). Anal. Calcd for C₇H₉ClN₂O₂S: C, 38.10; H, 4.11; N, 12.69%. Found: C, 38.23; H, 4.21; N, 12.56%.

4-Chloro-5-ethyl-6-methyl-2-methylsulfonylpyrimidine (9d). Yield 80%, colourless prisms, mp 171-172 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.42 (t, 3H, *J* = 6.8 Hz, CH₂CH₃), 2.38 (s, 3H, pyrimidine-CH₃), 2.68 (q, 3H, *J* = 6.8 Hz, CH₂), 3.38 (s, 3H, SO₂CH₃). MS (*m/z*, %): 234 (M⁺, 24), 199 (62), 155 (100), 120 (46). Anal. Calcd for C₈H₁₁ClN₂O₂S: C, 40.94; H, 4.72; N, 11.94%. Found: C, 40.82; H, 4.66; N, 12.31%.

4-Chloro-2-methylsulfonyl-6-phenylpyrimidine (9e). Yield 82%, white solid, mp 149-150 °C. ¹H NMR (600 MHz, CDCl₃), δ 3.34 (s, 3H, SO₂CH₃), 6.80 (s, 1H, pyrimidine-H), 7.80-7.42 (m, 5H, ArH). MS (*m/z*, %): 269 (M⁺, 32), 233 (52), 189 (65), 154 (100). Anal. Calcd for C₁₁H₉ClN₂O₂S: C, 49.17; H, 3.38; N, 10.42%. Found: C, 49.38; H, 3.24; N, 10.16%.

4,6-Dichloro-2-methylsulfonylpyrimidine (9f). Yield 80%, colourless prisms, mp 132-133 °C, (lit.²⁸ mp 154-156 °C).

4,6-Dichloro-5-ethyl-2-methylsulfonylpyrimidine (9g). Yield 85%, colourless prisms, mp 124-125 °C. ¹H NMR (600 MHz, CDCl₃), δ 2.68 (t, 2H, *J* = 6.8 Hz, CH₂), 3.38 (s, 3H, SO₂CH₃), 1.62 (q, 3H, *J* = 6.8 Hz, CH₃). MS (*m/z*, %): 255 (M⁺, 25), 219 (61), 184 (56), 140 (100). Anal. Calcd for C₇H₈Cl₂N₂O₂S: C, 32.95; H, 3.16; N, 10.98%. Found: C, 32.69; H, 3.26; N, 11.05%.

4,6-Dichloro-2-methylsulfonyl-5-nitropyrimidine (9h). Yield 81%, pale yellow prisms, mp 76-77 °C. ¹H NMR (600 MHz, CDCl₃), δ 3.35 (s, 3H, SO₂CH₃). MS (*m/z*, %): 272 (M⁺, 16), 236 (63), 200 (100), 122 (76). Anal. Calcd for C₅H₃Cl₂N₃O₄S: C, 22.07; H, 1.11; N, 15.44%. Found: C, 22.39; H, 1.16; N, 15.27%.

General procedure for the synthesis of (R)-2-(4-(pyrimidin-2-yloxy)phenoxy)propanoates (8) and (R)-2-(2-(pyrimidin-4-yloxy)phenoxy)propanoates (11)

The synthesis was performed according to the reported method²⁹ with some modification. Briefly, a solution of (R)-2-(4-hydroxy-phenoxy)-propanoate **1** (10 mmol), anhydrous K₂CO₃ (2.5 equiv, 25 mmol) in CH₃CN (50 ml) was stirred at room temperature for 0.5 h. After another 0.5 h of reflux, the solution of 4-chloropyrimidine **5**, **10** (10 mmol) or 2-methylsulfonyl pyrimidine **7**, **9** (10 mmol) in CH₃CN (20 ml) was added dropwise and the mixture heated at reflux for another 4 h. After evaporation of the solvent, water was added and the mixture was extracted with ethyl acetate and the organic phase was dried over MgSO₄. The products **8** or **11** were purification by flash chromatography on silica gel.

Methyl (R)-2-(4-(4-chloro-6-trifluoromethylpyrimidin-2-yloxy)phenoxy)propanoate (8a). Yield 65%, white solid, mp 98-100 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.63 (d, 3H, *J* = 6.6 Hz, CHCH₃) 3.79 (s, 3H, OCH₃), 4.74 (q, *J* = 6.6 Hz, 1H, CH), 6.47 (1H, s, pyrimidine-H), 6.89 (d, *J* = 7.2 Hz, 2H, ArH), 7.06 (d, *J* = 7.8 Hz, 2H, ArH), IR (KBr) ν: 1743, 1678, 1504, 1352, 1211 cm⁻¹. MS (*m/z*, %): 376 (M⁺, 21), 376 (34), 341 (28). Anal. Calcd for C₁₅H₁₂ClF₃N₂O₄: C, 47.82; H, 3.21; N, 7.44%. Found: C, 48.13; H, 3.19; N, 7.80%.

Methyl (R)-2-(4-(4-chloro-6-methylpyrimidin-2-yloxy)phenoxy)propanoate (8b). Yield 45%, white solid, mp 39-40 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.63 (d, *J* = 6.8 Hz, 3H, CHCH₃), 2.54 (s, 3H, pyrimidine-CH₃), 3.77 (s, 3H, OCH₃), 4.75 (q, *J* = 6.8 Hz, 1H, CH), 6.28 (s, 1H, pyrimidine-H), 6.89 (d, *J* = 9.0 Hz, 2H, ArH), 7.12 (d, *J* = 9.0 Hz, 2H, ArH). IR (KBr) ν: 3438, 1757, 1599, 1206 cm⁻¹. MS (*m/z*, %): 322 (M⁺, 65), 287 (100), 235 (50). Anal. Calcd for C₁₅H₁₅ClN₂O₄: C, 55.82; H, 4.68; N, 8.68%. Found: C, 55.76; H, 4.71; N, 8.95%.

Ethyl (R)-2-(4-(4,6-dichloropyrimidin-2-yloxy)phenoxy)propanoate (8c). Yield 58%, colourless needles, mp 64-65 °C. ¹H NMR (400 MHz, CDCl₃), δ 1.27 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 1.64 (d, *J* = 4.9 Hz, 3H, CHCH₃), 4.24 (q, *J* = 4.9 Hz, 2H, CH₂), 4.74 (q, *J* = 6.8 Hz, 1H, CH), 6.80 (s, 1H, pyrimidine-H), 6.91 (d, *J* = 9.2 Hz, 2H, ArH), 7.11 (d, *J* = 8.8 Hz, 2H, ArH). IR (KBr) ν: 3116, 2922, 1747, 1265, 1240, 1190, 771 cm⁻¹. MS (*m/z*, %): 356 (M⁺, 25), 321 (26), 310 (100), 283 (24), 237 (69). Anal. Calcd for C₁₅H₁₄Cl₂N₂O₄: C, 50.44; H, 3.95; N, 7.84%. Found: C, 50.05; H, 3.81; N, 7.98%.

Ethyl (R)-2-(4-(4,6-dichloro-5-ethylpyrimidin-2-yloxy)phenoxy)propanoate (8d). Yield 65%, white solid, mp 43-44 °C. ¹H NMR (400 MHz, CDCl₃), δ 1.19 (t, *J* = 7.6 Hz, 3H, pyrimidine-CH₂CH₃), 1.27 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.63 (d, *J* = 4.9 Hz, 3H, CHCH₃), 2.84 (q, *J* = 7.6 Hz, 2H, pyrimidine-CH₂CH₃), 4.23 (q, *J* = 4.9 Hz, 2H, OCH₂CH₃), 4.73 (q, *J* = 6.8 Hz, 1H, CH), 6.90 (d, *J* = 8.8 Hz, 2H, ArH), 7.08 (d, *J* = 8.8 Hz, 2H, ArH). IR (KBr) ν: 2981, 1753, 1398, 1191, 820 cm⁻¹. MS (*m/z*, %): 384 (M⁺, 100), 349 (62), 249 (23). Anal. Calcd for C₁₇H₁₈Cl₂N₂O₄: C, 53.00; H, 4.71; N, 7.27%. Found: C, 53.28; H, 4.96; N, 7.10%.

Methyl (R)-2-(4-(4,6-dichloro-5-nitropyrimidin-2-yloxy)phenoxy)propanoate (8e). Yield 50%, pale yellow prisms, mp 80-81 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.64 (d, *J* = 6.6 Hz, 3H, CHCH₃), 3.94 (s, 3H, OCH₃), 4.75 (q, *J* = 6.6 Hz, 1H, CH), 6.90 (d, *J* = 9.0 Hz, 2H, ArH), 7.08

(d, $J = 9.0$ Hz, 2H, ArH); IR (KBr) ν : 3442, 1740, 1581, 1195 cm^{-1} . MS (m/z , %): 388 (M^+ , 76), 301 (84), 192 (65). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_6$: C, 43.32; H, 2.86; N, 10.83%. Found: C, 43.80; H, 2.94; N, 11.15%.

Methyl (R)-2-(4-(4-methoxy-6-trifluoromethylpyrimidin-2-yloxy)phenoxy)propanoate (8f). Yield 67%, white solid, mp 137-138 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.64 (d, $J = 6.6$ Hz, 3H, CHCH_3), 3.79 (s, 3H, OCH_3), 3.90 (s, 3H, pyrimidine- OCH_3), 4.77 (q, $J = 6.6$ Hz, 1H, CH), 6.76 (s, 1H, pyrimidine-H), 6.90 (d, $J = 7.8$ Hz, 2H, ArH), 7.13 (d, $J = 7.8$ Hz, 2H, ArH). IR (KBr) ν : 1758, 1611, 1504, 1370, 1294 cm^{-1} . MS (m/z , %): 372 (M^+ , 12), 284 (12), 216 (10). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_5$: C, 51.62; H, 4.06; N, 7.52%. Found: C, 52.05; H, 4.27; N, 7.98%.

Methyl (R)-2-(4-(4-ethoxy-6-trifluoromethylpyrimidin-2-yloxy)phenoxy)propanoate (8g). Yield 70%, white solid, mp 140-141 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.33 (t, $J = 6.8$ Hz, 3H, CH_2CH_3), 1.64 (d, $J = 6.8$ Hz, 3H, CHCH_3), 3.78 (s, 3H, OCH_3), 4.32 (q, $J = 7.0$ Hz, 2H, CH_2CH_3), 4.77 (q, $J = 6.8$ Hz, 1H, CH), 6.76 (s, 1H, pyrimidine-H), 6.90 (d, $J = 7.2$ Hz, 2H, ArH), 7.11 (d, $J = 7.2$ Hz, 2H, ArH); IR (KBr) ν : 1759, 1605, 1504, 1375, 1201 cm^{-1} . MS (m/z , %): 386 (M^+ , 10), 321 (13), 228 (22). Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_5$: C, 52.85; H, 4.44; N, 7.25%. Found: C, 52.60; H, 4.36; N, 7.53%.

Methyl (R)-2-(4-(4-methylamino-6-trifluoromethylpyrimidin-2-yloxy)phenoxy)propanoate (8h). Yield 55%, white solid, mp 95-97 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.63 (d, $J = 6.8$ Hz, 3H, CHCH_3), 2.93 (d, $J = 4.2$ Hz, 3H, NHCH_3), 3.78 (s, 3H, OCH_3), 4.75 (q, $J = 6.8$ Hz, 1H, CH), 5.35 (s, 1H, NH), 6.38 (s, 1H, pyrimidine-H), 6.87 (d, $J = 8.4$ Hz, 2H, ArH), 7.10 (d, $J = 8.4$ Hz, 2H, ArH). IR (KBr) ν : 1745, 1619, 1506, 1370, 1185 cm^{-1} . MS (m/z , %): 371 (M^+ , 10), 282 (34). Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_5$: C, 51.75; H, 4.34; N, 11.32%. Found: C, 52.89; H, 4.29; N, 11.49%.

Methyl (R)-2-(4-(4-methyl-6-trifluoromethylpyrimidin-2-yloxy)phenoxy)propanoate (8i). Yield 49%, slight yellow solid, mp 40-41 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.63 (d, $J = 6.6$ Hz, 3H, CHCH_3), 3.79 (s, 3H, pyrimidine- CH_3), 3.78 (s, 3H, OCH_3), 4.77 (q, $J = 6.6$ Hz, 1H, CH), 6.90 (d, $J = 7.2$ Hz, 2H, ArH), 7.12 (d, $J = 7.2$ Hz, 2H, ArH), 7.21 (s, 1H, pyrimidine-H). IR (KBr) ν : 1757, 1600, 1504, 1367, 1200 cm^{-1} . MS (m/z , %): 356 (M^+ , 21), 346 (34), 311 (28); Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4$: C, 53.94; H, 4.24; N, 7.86%. Found: C, 53.78; H, 4.49; N, 7.98%.

Methyl (R)-2-(4-(4-methoxy-6-methylpyrimidin-2-yloxy)phenoxy)propanoate (8j). Yield 70%, colourless needles, mp 43-44 °C. ^1H NMR (400 MHz, CDCl_3), δ 1.63 (d, $J = 6.8$ Hz, 3H, CHCH_3), 3.77 (s, 3H, OCH_3), 3.88 (s, 3H, pyrimidine- OCH_3), 4.75 (q, $J = 6.8$ Hz, 1H, CH), 6.47 (s, 1H, pyrimidine-H), 6.89 (d, $J = 9.2$ Hz, 2H, ArH), 7.10 (d, $J = 8.8$ Hz, 2H, ArH). IR (KBr) ν : 3438, 1757, 1599, 1504, 1352 cm^{-1} . MS (m/z , %): 318 (M^+ , 21), 231 (70), 195 (66). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5$: C, 60.37; H, 5.70; N, 8.80%. Found: C, 6.75; H, 5.42; N, 8.92%.

Methyl (R)-2-(4-(4-methyl-6-methylaminopyrimidin-2-yloxy)phenoxy)propanoate (8k). Yield 65%, white solid, mp 90-91 °C. ^1H NMR (400 MHz, CDCl_3), δ 1.63 (d, $J = 6.8$ Hz, 3H, CHCH_3), 2.89 (d, $J = 4.8$ Hz, 3H, NHCH_3), 3.78 (s, 3H, OCH_3), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 5.44 (s, 1H, NH), 6.07 (s, 1H, pyrimidine-H), 6.86 (d, $J = 9.2$ Hz, 2H, ArH), 7.08 (d, $J = 8.8$ Hz,

2H, ArH). IR (KBr) ν : 3283, 1753, 1581, 1503, 1352 cm^{-1} . MS (m/z , %): 337(M^+ , 31), 299 (100), 138 (21). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_4$: C, 60.56; H, 6.03; N, 13.24%. Found: C, 60.32; H, 6.32; N, 12.87%.

Methyl (R)-2-(4-(4-chloro-6-methoxy-5-nitropyrimidin-2-yloxy)phenoxy)propanoate (8l). Yield 54%, colourless prisms, mp 92-93 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.63 (d, $J = 6.6$ Hz, 3H, CHCH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, pyrimidine- OCH_3), 4.75 (q, $J = 6.6$ Hz, 1H, CH), 6.90 (d, $J = 9.0$ Hz, 2H, ArH), 7.08 (d, $J = 9.0$ Hz, 2H, ArH). IR (KBr) ν : 3430, 1750, 1576, 1218 cm^{-1} . MS (m/z , %): 383 (M^+ , 62), 296 (96), 204 (38). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_7$: C, 46.95; H, 3.68; N, 10.95%. Found: C, 46.65; H, 3.49; N, 10.63%.

Ethyl (R)-2-(4-(4,6-dimethoxypyrimidin-2-yloxy)phenoxy)propanoate (8m). Yield 67%, white solid, mp 77-78 °C. ^1H NMR (400 MHz, CDCl_3), δ 1.26 (t, $J = 7.2$ Hz, 3H, CH_3), 1.63 (d, $J = 8.0$ Hz, 3H, CHCH_3), 3.83 (s, 6H, pyrimidine- OCH_3), 4.23 (q, $J = 3.5$ Hz, 2H, CH_2), 4.73 (q, $J = 6.8$ Hz, 1H, CH), 5.77 (s, 1H, pyrimidine-H), 6.88 (d, $J = 8.8$ Hz, 2H, ArH), 7.11 (d, $J = 8.8$ Hz, 2H, ArH). IR (KBr) ν : 2987, 1746, 1502, 1195 cm^{-1} . MS (m/z , %): 348 (M^+ , 100), 246(98), 375 (18). Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_6$: C, 58.61; H, 5.79; N, 8.04%. Found: C, 58.42; H, 5.68; N, 8.15%.

Methyl (R)-2-(4-(2-methylthio-6-trifluoromethylpyrimidin-4-yloxy)phenoxy)propanoate (11a). Yield 75%, white solid, mp 101-102 °C. ^1H NMR (600 MHz, CDCl_3), δ 1.65 (d, $J = 6.6$ Hz, 3H, CHCH_3), 2.40 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 4.77 (q, $J = 6.8$ Hz, 1H, CH), 6.79 (s, 1H, pyrimidine-H), 6.93 (d, $J = 9.0$ Hz, 2H, ArH), 7.06 (d, $J = 9.0$ Hz, 2H, ArH). IR (KBr) ν : 1750, 1586, 1507, 1405, 1281, 1190 cm^{-1} . MS (m/z , %): 388 (M^+ , 36), 284 (43), 209 (78); Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4\text{S}$: C, 49.48; H, 3.89; N, 7.21%. Found: C, 49.12; H, 4.01; N, 7.46%.

Ethyl (R)-2-(4-(6-methyl-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11b). Yield 79%, white solid, mp 83-84 °C. ^1H NMR (400 MHz CDCl_3), δ 1.27 (t, $J = 6.3$ Hz, 3H, CH_2CH_3), 1.64 (d, $J = 6.8$ Hz, 3H, CHCH_3), 2.38 (s, 3H, ArCH_3), 2.40 (s, 3H, SCH_3), 4.24 (q, $J = 6.3$ Hz, 2H, CH_2), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 6.26 (s, 1H, pyrimidine-H), 6.90 (d, $J = 8.8$ Hz, 2H, ArH), 7.05 (d, $J = 8.8$ Hz, 2H, ArH). IR (KBr) ν : 1747, 1196, 1276, 1250, 759 cm^{-1} . MS (m/z , %): 348 (M^+ , 41), 301 (42), 300 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 58.60; H, 5.79; N, 8.04%. Found: C, 58.27; H, 5.83; N, 8.10%.

Ethyl (R)-2-(4-(5,6-dimethyl-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11c). Yield 86%, colourless needles, mp 73-75 °C. ^1H NMR (CDCl_3 , 400 MHz), δ 1.26 (t, $J = .2$ Hz, 3H, CH_2CH_3), 1.63 (d, $J = 6.8$ Hz, 3H, CHCH_3), 2.20 (s, 3H, pyrimidine- CH_3), 2.46 (s, 3H, pyrimidine- CH_3), 4.22 (q, $J = 7.2$ Hz, 2H, CH_2), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 6.89 (d, $J = 9.2$ Hz, 2H, ArH), 7.03 (d, $J = 9.2$ Hz, 2H, ArH). IR (KBr) ν : 1753, 1196, 1296, 1206 cm^{-1} . MS (m/z , %): 362 (M^+ , 100), 315 (94), 289 (55), 260 (49). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: C, 59.65; H, 6.12; N, 7.73%. Found: C, 59.49; H, 6.07; N, 7.80%.

Ethyl (R)-2-(4-(5-ethyl-6-methyl-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11d). Yield 74%, colourless needles, mp 53-54 °C. ^1H NMR (400 MHz, CDCl_3), δ 1.19 (t, $J = 7.5$ Hz, 3H, pyrimidine- CH_2CH_3), 1.26 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.63 (d, $J = 6.8$ Hz, 3H, CHCH_3), 2.22 (s, 3H, ArCH_3), 2.45 (s, 3H, SCH_3), 2.68 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 4.22 (q, $J = 7.2$ Hz,

2H, OCH₂CH₃), 4.74 (q, *J* = 6.8 Hz, 1H, CH), 6.89 (d, *J* = 8.8 Hz, 2H, ArH), 7.04 (d, *J* = 8.8 Hz, 2H, ArH). IR (KBr) ν : 1753, 1503, 1372, 1196 cm⁻¹. MS (*m/z*, %): 376 (M⁺, 100), 329 (62), 207 (54), 101 (48). Anal. Calcd for C₁₉H₂₄N₂O₄S: C, 60.62; H, 6.43; N, 7.44%. Found: C, 60.48; H, 6.36; N, 7.37%.

Methyl (R)-2-(4-(6-methoxy-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11e). Yield 72%, white solid, mp 82-84 °C. ¹H NMR (400 MHz, CDCl₃), δ 1.64 (d, *J* = 7.2 Hz, 3H, CHCH₃), 2.44 (s, 3H, SCH₃), 3.78 (s, 3H, OCH₃), 3.93 (s, 6H, pyrimidine-OCH₃), 4.75 (q, *J* = 7.2 Hz, 1H, CH), 5.66 (s, 1H, pyrimidine-H), 6.88 (d, *J* = 8.8 Hz, 2H, ArH), 7.04 (d, *J* = 8.8 Hz, 2H, ArH). IR (KBr) ν : 3453, 1753, 1576, 1204 cm⁻¹. MS (*m/z*, %): 350 (M⁺, 41), 303 (100), 215 (10); Anal. Calcd for C₁₆H₁₅F₃N₂O₄S: C, 54.85; H, 5.18; N, 7.99%. Found: C, 54.92; H, 5.06; N, 8.09%.

Methyl (R)-2-(4-(6-methylamino-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11f). Yield 70%, white solid, mp 85-86 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.63 (d, *J* = 6.8 Hz, 3H, CHCH₃), 2.38 (s, 3H, SCH₃), 3.78 (s, 3H, OCH₃), 3.95 (d, *J* = 4.8 Hz, 3H, NHCH₃), 4.74 (q, *J* = 6.8 Hz, 1H, CH), 5.05 (s, 1H, NH), 5.29 (s, 1H, ArH), 6.89 (d, *J* = 9.0 Hz, 2H, ArH), 7.05 (d, *J* = 9.0 Hz, 2H, ArH). IR (KBr) ν : 3273, 1751, 1584, 1209 cm⁻¹. MS (*m/z*, %): 349 (M⁺, 55), 262 (65), 195 (100). Anal. Calcd for C₁₆H₁₉N₃O₄S: C, 55.00; H, 5.48; N, 12.03%. Found: C, 55.32; H, 5.39; N, 12.25%.

Ethyl (R)-2-(4-(6-chloro-2-methylthiopyrimidin-4-yloxy)phenoxy)propanoate (11g). Yield 72%, white solid, mp 60-61 °C. ¹H NMR (400 MHz, CDCl₃), δ 1.27 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 1.64 (d, *J* = 6.4 Hz, 3H, CHCH₃), 2.35 (s, 3H, pyrimidine-CH₃), 2.39 (s, 3H, SCH₃), 4.24 (q, *J* = 3.2 Hz, 2H, CH₂), 4.74 (q, *J* = 6.8 Hz, 1H, CH), 6.44 (s, 1H, pyrimidine-H), 6.91 (d, *J* = 9.2 Hz, 2H, ArH), 7.04 (d, *J* = 9.2 Hz, 2H, ArH). IR (KBr) ν : 2994, 1741, 1503, 1192 cm⁻¹. MS (*m/z*, %): 368 (M⁺, 35), 266 (100), 109 (47). Anal. Calcd for C₁₆H₁₇ClN₂O₄S: C, 52.10; H, 4.65; N, 7.60%. Found: C, 52.34; H, 4.32; N, 7.43%.

Methyl (R)-2-(4-(6-chloro-2-methylthio-5-nitropyrimidin-4-yloxy)phenoxy)propanoate (11h). Yield 78%, colourless needles, mp 107-108 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.65 (d, *J* = 6.6 Hz, 3H, CHCH₃), 2.35 (s, 3H, SCH₃), 3.78 (s, 3H, OCH₃), 4.77 (q, *J* = 6.8 Hz, 1H, CH), 6.91 (2 d, *J* = 9.0 Hz, H, ArH), 7.08 (d, *J* = 8.4 Hz, 2H, ArH). IR (KBr) ν : 3437, 1741, 1548, 1187 cm⁻¹. MS (*m/z*, %): 399 (M⁺, 42), 364 (36), 32 (78). Anal. Calcd for C₁₅H₁₄ClN₃O₆S: C, 45.06; H, 3.53; N, 10.51%. Found: C, 45.31; H, 3.56; N, 10.81%.

Ethyl (R)-2-(4-(2-methylthio-6-phenylpyrimidin-4-yloxy)phenoxy)propanoate (11i). Yield 79%, white solid, mp 91-93 °C. ¹H NMR (400 MHz, CDCl₃), δ 1.27 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.65 (d, *J* = 6.8 Hz, 3H, CHCH₃), 2.48 (s, 3H, SCH₃), 4.25 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 4.75 (q, *J* = 6.8 Hz, 1H, CH), 6.82 (s, 1H, pyrimidine-H), 6.92 (d, *J* = 8.8 Hz, 2H, ArH), 7.10 (d, *J* = 8.8 Hz, 2H, ArH), 8.02-7.48 (m, 5H, ArH). IR (KBr) ν : 1761, 1184, 1263, 1205 cm⁻¹. MS (*m/z*, %): 410 (M⁺, 67), 363 (100), 207 (34.05), 128 (88.77). Anal. Calcd for C₂₂H₂₂N₂O₄S: C, 64.37; H, 5.40; N, 6.82%. Found: C, 64.49; H, 5.36; N, 6.90%.

Methyl (R)-2-(4-(6-chloro-2-methoxy-pyrimidin-4-yloxy)phenoxy)propanoate (11j). Yield 78%, colourless needles, mp 81-82 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.63 (d, *J* = 6.8 Hz, 3H,

CHCH₃), 3.78 (s, 3H, OCH₃), 3.91 (s, 3H, pyrimidine-OCH₃), 4.75 (q, $J = 6.8$ Hz, 1H, CH), 6.45 (s, 1H, pyrimidine-H), 6.90 (d, $J = 7.8$ Hz, 2H, ArH), 7.05 (d, $J = 7.8$ Hz, 2H, ArH). IR (KBr) ν : 3445, 1735, 1572, 1201 cm⁻¹. MS (m/z , %): 338 (M⁺, 72), 216 (82), 159 (60). Anal. Calcd for C₁₅H₁₅ClN₂O₅: C, 53.19; H, 4.46; N, 8.27%. Found: C, 53.40; H, 4.38; N, 8.39%.

Methyl (R)-2-(4-(2,6-dimethoxypyrimidin-4-yloxy)phenoxy)propanoate (11k). Yield: 70%, white solid, mp 40-41 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.63 (d, $J = 6.8$ Hz, 3H, CHCH₃), 3.78 (s, 3H, OCH₃), 3.90 (s, 3H, pyrimidine-OCH₃), 3.95 (s, 3H, pyrimidine-OCH₃), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 5.64 (s, 1H, pyrimidine-H), 6.89 (d, $J = 9.0$ Hz, 2H, ArH), 7.05 (d, $J = 9.0$ Hz, 2H, ArH); IR (KBr) ν : 3441, 1736, 1591, 1207 cm⁻¹. MS (m/z , %): 334 (M⁺, 64), 247 (100), 155 (58). Anal. Calcd for C₁₆H₁₈N₂O₆: C, 57.48; H, 5.43; N, 8.38%. Found: C, 57.65; H, 5.46; N, 8.22%.

Methyl (R)-2-(4-(2,6-diethoxypyrimidin-4-yloxy)phenoxy)propanoate (11l). Yield 70%, white solid, mp 54-56 °C. ¹H NMR (600 MHz, CDCl₃), δ 1.34 (t, $J = 6.9$ Hz, 3H, CH₃), 1.37 (t, $J = 6.9$ Hz, 3H, CH₃), 1.63 (d, $J = 6.8$ Hz, 3H, CHCH₃), 3.75 (s, 3H, OCH₃), 4.32 (q, $J = 6.9$ Hz, 2H, CH₂), 4.37 (q, $J = 6.9$ Hz, 2H, CH₂), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 5.59 (s, 1H, pyrimidine-H), 6.90 (d, $J = 9.0$ Hz, 2H, ArH), 7.04 (d, $J = 9.0$ Hz, 2H, ArH). IR (KBr) ν : 3400, 1743, 1609, 1202 cm⁻¹. MS (m/z , %): 362 (M⁺, 70), 275 (95), 195 (86). Anal. Calcd for C₁₈H₂₂N₂O₆: C, 59.66; H, 6.12; N, 7.73%. Found: C, 59.82; H, 6.33; N, 7.92%.

Methyl (R)-2-(4-(6-chloro-2-methylaminopyrimidin-4-yloxy)phenoxy)propanoate (11m). Yield 72%, white solid, mp 90-91 °C. ¹H NMR (400 MHz CDCl₃), δ 1.63 (d, $J = 6.8$ Hz, 3H, CHCH₃), 2.89 (d, $J = 4.8$ Hz, 3H, NHCH₃), 3.78 (s, 3H, OCH₃), 4.74 (q, $J = 6.8$ Hz, 1H, CH), 5.44 (s, 1H, NH), 6.07 (s, 1H, pyrimidine-H), 6.86 (d, $J = 9.2$ Hz, 2H, ArH), 7.08 (d, $J = 8.8$ Hz, 2H, ArH). IR (KBr) ν : 3426, 1752, 1618, 1194 cm⁻¹. MS (m/z , %): 337 (M⁺, 42), 302 (65), 180 (79). Anal. Calcd for C₁₅H₁₆ClN₃O₄: C, 53.34; H, 4.77; N, 12.44%. Found: C, 53.60; H, 4.58; N, 12.44%.

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