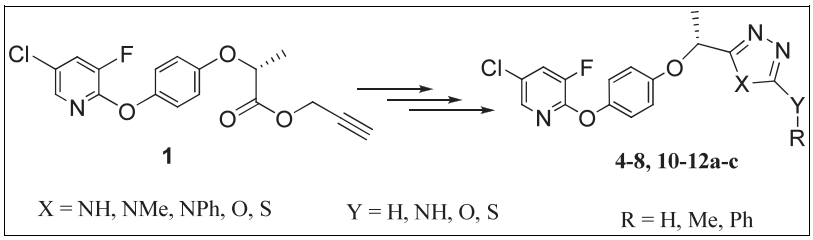
Synthesis, Characterization, and Herbicidal Activities of New 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, and 1,2,4-Triazoles Derivatives Bearing (*R*)-5-Chloro-3-fluoro-2-phenoxypyridine

Mehdi Kalhor[a]* and Akbar Dadras[b]

[a]Department of Chemistry, Payame Noor University, Tehran 19395–4697, Iran
[b]Industrial Pesticide Research Center, Alborz-Tehran, Iran
*E-mail: mekalhor@gmail.com

Received February 7, 2011
DOI 10.1002/jhet.950
Published online 20 March 2013 in Wiley Online Library (wileyonlinelibrary.com).



Synthesis of some novel 1,2,4-triazoles, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles bearing a (*R*) 5-(1-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl) unit, as a moiety of commercial herbicide, using their thiosemicarbazides in an alkaline, iodine and acidic media is reported, respectively. The structure of the synthesized compounds was characterized by IR, ^{1}H, ^{13}C NMR spectroscopic data, and elemental analyses. The herbicidal activities of synthesized compounds were evaluated against *Echinochloa cruss-galli*, *Avena fatua*, and *Sorgum halepense* weeds. Compounds **8** and **12a** showed potential herbicidal activity against gramineous weeds. Our results may provide some guidance for synthesis development of some novel oxa or thiadiazole and triazole-based herbicidal lead structures.

J. Heterocyclic Chem., **50**, 220 (2013).

INTRODUCTION

Until now, a variety of heterocyclic compounds containing nitrogen, oxygen, and sulfur atoms have significantly contributed too many current commercial drugs and agrochemicals. Among these heterocyclic compounds, 1,3,4-oxa and thiadiazoles possess a wide range of biological activities such as antitumor, antiviral, antimicrobial, anti-inflammatory, and antifungal [1–7]. Also, the biological activity of 1,2,4-triazoles including antidepressive, anti-inflammatory, antibacterial, antifungal, insecticidal, and antimicrobial properties [8–11], have been the subject of many literature reports in recent years. Furthermore, it has been reported that many compounds bearing these heterocyclic nucleus have a broad spectrum of potential herbicidal activities [12–15].

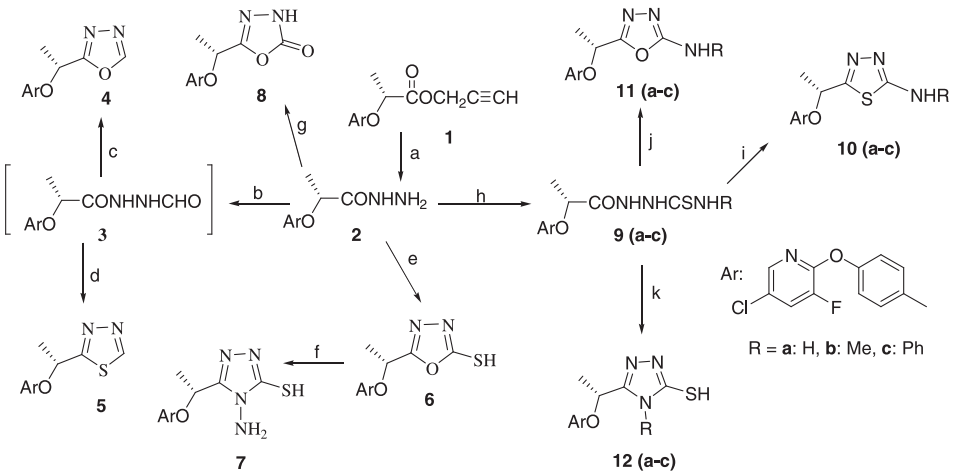
On the other hand, aryloxyphenoxypropionate herbicides (APPH) are known as interesting and highly effective class of herbicides in the international market over the past decade [16]. They are used effectively in a number of crops including soybeans and cereal grains, such as wheat, Barley and rice, to control grass weeds [17]. However, the continuous application of APPH has resulted in the evolution of resistant weeds [18]. In view of these highlights, the urgent synthetic development of herbicides with newer chemical structures is needed.

As part of ongoing studies on the synthesis and biological consideration of heterocycles [19–22], we wish to report the synthesis of new series of 5-membered heterocyclic titled compounds, bearing the (*R*)-5-(1-(4-(5-chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl) and their herbicidal activities.

RESULTS AND DISCUSSION

The general synthetic route for synthesis of target compounds is outlined in Scheme 1. The structure of synthesized compounds was established by means of their IR, ^{1}H NMR, ^{13}C NMR spectra, and elemental analyses. The ester **1** was synthesized according to the literature method [23], which then treated with 1.1 equivalents of hydrazine monohydrate to give acylhydrazine derivative **2**. The IR spectrum of acid hydrazide **2** showed the N-H stretching absorption near 3356, 3277 cm^{-1} and the C=O stretching one at 1677 cm^{-1}. Reaction of hydrazide **2** with excess amount of ethylorthoformiate in the presence of silica sulfuric acid (SSA) as a catalyst [24] afforded intermediate formylhydrazide **3**, which converted to oxadiazole **4** in refluxing ethylorthoformate. 1,3,4-Thiadiazole **5** was formed by reaction of intermediate **3** with P_2S_5 in xylene under reflux condition. In the IR spectra of the synthesized compounds **4** and **5**, the absence of NH groups associated with other spectroscopic data such as ^{1}H NMR, ^{13}C NMR, and elemental analysis are in support of the expected reactions. Oxadiazole 2-thiol, **6** was prepared *via* cyclization of compound **2** with

Scheme 1. Conditions: (a) N_2H_5OH, MeOH, 15 min, reflux; (b) $CH(OEt)_3$/SSA; (c) 21 h, Reflux; (d) P_2S_5, xylene, K_2CO_3, 12 h, reflux; (e) CS_2/NaOH, EtOH; (f) N_2H_5OH, BuOH; (g) triphosgene, THF, rt, 24 h; (h) R-NCS, EtOH, 4–8 h, reflux; (i) H_2SO_4, 0°C, 0.5 h; (j) I_2/KI, NaOH, 3–4 h; (k) 2N NaOH, 4 h, reflux.



carbon disulphide in the presence of potassium hydroxide in refluxing ethanol as previously reported methods [20]. Amino-1,2,4-triazole-3-thiol **7** was obtained by reaction of **6** and hydrazine hydrate. The absorption band observed at 3295–3193 cm^{-1} of the IR spectrum of **6** could be attributed to the NH_2 group. In the ^1H NMR spectrum of **7**, the resonance of NH_2 and SH groups was appeared as a singlet at 4.89 and 11.80 ppm, respectively, confirms the expected structure. Condensation of intermediate **2** with triphosgene in THF afforded the oxadiazole-2-one **8** according to the literature method [25]. Spectroscopic data of all synthesized compound were consistent with their structures.

The preparation of thiosemicarbazides **9a–c** was achieved by reaction of the corresponding substituted hydrazide **2** with ammonium, methyl or phenyl isothiocyanate [20]. The IR spectra of thiosemicarbazides **9a–c** showed characteristic absorption at 1138–1199, 1615–1691, and 3185–3420 cm^{-1} for the -C═S, C═O, and -NH stretching vibration, respectively. ^1H NMR spectra of **9a–c** showed singlet signals at 8.80–9.63 ppm due to the resonance of -NH-CS-NH and -CO-NH protons, respectively. The ^{13}C NMR spectrum of compound **9b** showed fourteen signals including a signal at 171.3 ppm for the -C═S and a signal at 180.2 ppm for the carbonyl carbon atom, which are in support of the expected structures.

Thiosemicarbazide derivatives **9a–c** underwent an intramolecular cyclization under basic, acidic or iodine conditions to produce 1,3,4-thiadiazoles **10a–c**, 1,3,4-oxadiazoles **11a–c**, and 1,2,4-triazole-3-thiols **12a–c** (Scheme 1). The IR spectra of **10a–c** showed absorption bands at 3412–3414 cm^{-1}, the characteristic of the NH group. Also in the ^1H NMR spectra of all 1,3,4-thiadiazoles, the singlet at 7.01 and 10.56–10.78 ppm was attributed to the resonance of the NH proton. The IR spectrum of oxadiazole **11b** showed absorption band at 1598 cm^{-1} due to C═N stretching vibration. The disappearance of CONH and CSNH signals of **11b** and also the appearance of the NH signal at 6.27 ppm confirm the formation of oxadiazole ring.

Triazole-3-thiols **12a–c** were obtained by refluxing the corresponding thiosemicarbazides in 2N NaOH solution, followed by acidification. The ^1H NMR spectra of compounds **12a–c** showed singlets at 12.65–12.85 ppm attributed to the resonance of the SH protons. All other required peaks were appeared at the exhibited region of the spectra.

Herbicidal activity and crop safety. Herbicidal activity against three weeds and crop safety of barley and wheat were evaluated for compounds **1**, as a reference, **4–8** and (**9–12a–c**) at 125 g a.i/ha application postemergence by previously reported method [26] that their results are summarized in Table 1. As shown in Table 1, all compounds showed good to excellent level of activity against all weeds tested without or with slight injury. The highest herbicidal activity was observed for compounds **8** and **12a**. Also, it was clarified that the activity of **12a** against *Avena fatua* was more potent without showing crop damage against Barley than that of clodinafop propargyl **1**, as a practical herbicide. Besides, it was considerable that 1,2,4-triazole structure have been useful for the improvement of herbicidal activity and crop selectivity.

In conclusion, we have described the synthesis of some novel 1,2,4-triazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles bearing a (*R*) 5-(1-(4-(5-chloro-3-fluoropyridin-2-yloxy) phenoxy)ethyl) unit, as a moiety of commercial herbicide, **2–8** and (**9–12a–c**) with good to high yields. We also evaluated their herbicidal activities against three weeds. Moreover, the present investigation demonstrated the compounds **8** and **12a** could be a practical herbicide that is ongoing in this regard.

Table 1

Herbicidal activities of compounds **1**, **4**–**8**, and (**9**–**12a**–**c**).

Compounds	Herbicidal activity (%)[a]			Damage (%)	
	Echinochloa crussgalli	*Avena fatua*	*Sorgum halepense*	Barley	Wheat
1[b]	100	85	80	35	0
4	90	80	60	10	0
5	80	65	60	5	0
6	85	75	55	10	0
7	75	60	40	0	0
8	100	85	70	0	0
10a	70	60	45	0	0
10b	80	70	50	5	0
10c	75	65	40	0	0
11a	90	80	60	10	0
11b	80	70	45	5	0
11c	85	75	45	5	0
12a	100	95	80	0	0
12b	85	65	60	0	0
12c	90	85	70	0	0

[a]Application: 125 g ha^{-1}, activity: 0 (no weed control or crop damage)–100 (complete killing of weed and crop).
[b]Clodinafop-propargyl as commercial herbicide.

EXPERIMENTAL

All the solvents and materials are of reagent grade and purified as required. Melting points were determined using an electro thermal digital apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrophotometer (300 MHz) in $CDCl_3$ using Me_4Si as an internal standard. Chemical shifts are reported in ppm from TMS as the internal standard. Elemental analyses were performed on a Vario EL III elemental analyzer. The purity of all compounds was confirmed on silica gel coated aluminum plates (Merck). The ester **1** was synthesized as previously reported method [21, 23].

Synthesis of (*R*)-2-[4-(5-chloro-3-fluoro-pyridin-2-yloxy)-phenoxy]-propionic acid hydrazide (2). A mixture of compound **1** (3.5 g, 10 mmol) and hydrazine hydrate (98%) (1 g, 20 mmol) was refluxed in methanol (50 mL) for 15 min, and the reaction mixture was cooled and the precipitate obtained was filtered, washed with water, and dried. The product was crystallized from isopropanol to give white crystals **2**, Yield 94%, mp 150–152°C; IR (KBr): 3356, 3277 (N-H), 1677 (C═O), 1620, 1504 (C═N, C═C), 1197 (N-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.82 (s, 1Hpy.), 7.47 (d, J = 8.7 Hz, 1Hpy.), 7.05–6.89 (m , 4H, ph), 5.90 (s, 1H, NH), 5.25 (q, J = 6.5 Hz, 1H, H-chiral), 4.70 (br, 2H, NH_2), 1.55 (d, J = 6.5 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.7, 75.0, 116.3, 122.6, 125.1, 140.5, 145.1, 147.2, 148.6, 151.2, 154.1, 172.2 (C═O) ppm; Anal. Calcd. for $C_{14}H_{13}ClFN_3O_3$: C, 51.62; H, 4.02; N, 12.90. Found: C, 51.58; H, 4.03; N, 12.94.

Synthesis of (*R*)-5-chloro-3-fluoro-2-[4-(1-[1,3,4]oxadiazol-2-yl-ethoxy)-phenoxy]-pyridine (4). Acid hydrazide **2** (3.25 g, 10 mmol) and 0.02 g of SSA were refluxed in 30 mL of ethylorthoformate for 3 h affording intermediate formylhydrazide **3**. This reaction was refluxed for 21 h to obtain compound **4**. The product was isolated after cooling and recrystallized from toluene, Yield 86%, mp 98–100°C; IR (KBr): 3151, 3068 (C-H), 2936 (C-H), 1601, 1576, 1508, 1451 (C═N, C═C), 1298 (N-N), 1075 (N═C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.42 (s, 1H, oxadiazole), 7.77 (s , 1Hpy.), 7.43 (d, J = 8.7 Hz, 1Hpy.), 7.01–6.87 (m, 4H, ph), 5.60 (q, J = 6.5 Hz, 1H-chiral), 1.75 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 19.3, 67.5, 116.7, 122.4, 124.9, 140.0, 145.0, 147.3, 148.5, 151.1, 153.7, 154.2, 165.6; Anal. Calcd. for $C_{15}H_{11}ClFN_3O_3$: C, 53.66; H, 3.30; N, 12.52. Found: C, 53.54; H, 3.31; N, 12.55.

Synthesis of (*R*)-5-chloro-3-fluoro-2-[4-(1-[1,3,4]thiadiazol-2-yl-ethoxy)-phenoxy]-pyridine (5). To a solution of **3** (3.54 g, 10 mmol) in xylene (100 mL), phosphorous pentasulphide (2.22 g, 10 mmol) was added. The mixture was refluxed for 12 h, then filtered, washed with K_2CO_3 solution, and water. The solvent was evaporated and the residue was recrystallized from toluene/*n*-hexane, Yield 56%, mp 101–102°C; IR (KBr): 3056 (C-H), 1598, 1501, 1448, 1410 (C═N, C═C), 1084, 1029 (N═C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 9.06 (s, 1H, thiadiazole), 7.71 (s , $1H_{py.}$), 7.38 (d, J = 8.7 Hz, $1H_{py.}$), 7.00–6.89 (m, 4H, Ph), 5.78 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.71 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 22.7, 72.3, 116.6, 122.4, 124.9, 139.9, 145.0, 147.1, 148.5, 151.0, 152.8, 154.0, 172.8; Anal. Calcd. for $C_{15}H_{11}ClFN_3O_2S$: C, 51.21; H, 3.15; N, 11.94; S, 9.11. Found: C, 51.40; H, 3.14; N, 12.10; S, 9.14.

Synthesis of (*R*)-5-(1-(4-(5-chloro-3-fluoropyridin-2-yloxy) phenoxy)ethyl)-4-amino-4H-1,2,4-triazole-3-thiol (7). A mixture of compound **6** (1.83 g, 5 mmol) and hydrazine hydrate (98%) (1 g, 20 mmol) was refluxed in butanol (50 mL) for 6 h. After cooling, KOH (0.56 g, 10 mmol) was added to the reaction media and the formed precipitate was filtered. Then it was acidified with HCl (37%), washed with water and recrystallized from toluene, Yield 71%, mp 137–139°C; IR (KBr): 3295–3193 (N-H), 2752 (S-H), 1633, 1572, 1504, 1469, 1414 (C═N, C═C), 1234 (N-N), 1203 (C═S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 11.80 (br, 1H, SH), 7.86 (s, $1H_{py.}$), 7.52 (d, J = 8.7 Hz, $1H_{py.}$), 7.11–7.01 (m, 4H, ph), 5.54 (q, J = 6.5 Hz, 1H, H_{chiral}), 4.89 (s, 2H, NH_2), the SH and NH_2 protons disappeared on D_2O addition, 1.78 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 17.8, 69.0, 117.2, 122.5, 125.1, 140.0, 145.2, 147.4, 148.6, 151.1, 151.5, 154.18, 167.01; Anal. Calcd. for $C_{15}H_{13}ClFN_5O_2S$: C, 47.19; H, 3.43; N, 18.34; S, 8.40. Found: C, 47.26; H, 3.42; N, 18.29; S, 8.44.

Synthesis of (*R*)-5-(1-(4-(5-chloro-3-fluoropyridin-2-yloxy) phenoxy)ethyl)-1,3,4-oxadiazol-2(3*H*)-one (8). To a solution of the acid hydrazide **2** (3.25 g, 10 mmol) in 50 mL of THF was added a solution of triphosgene (2.2 g, 7.5 mmol) in 50 mL of tert-butyl methyl ether. After stirring for 24 h at room temperature, 50 mL of 5% Na_2CO_3 solution was added to the reaction mixture; the organic layer was washed with 5% $NaHCO_3$ solution, brine and dried over Na_2SO_4. Post-removal of the solvent, the residue was recrystallized from isopropanol to give **8**, Yield 90%, mp 132–134° C; IR (KBr): 3249 (N-H), 1769 (C═O), 1620, 1506 (C═N, C═C), 1205 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 9.60 (s, 1H, NH.), the NH proton disappeared on D_2O addition, 7.89 (s, $1H_{py.}$), 7.53 (d, J = 8.7 Hz, $1H_{py.}$), 7.13–7.03 (m, 4H, ph), 5.21 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.75 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.7, 68.9, 117.5, 122.8, 125.4, 140.5, 146.3, 148.0, 148.5, 151.7, 154.6, 155.2, 156.9; Anal. Calcd. for $C_{15}H_{11}ClFN_3O_4$: C, 51.22; H, 3.15; N, 11.95. Found: C, 51.28; H, 3.16; N, 11.91.

General procedure for synthesis of the Thiosemicarbazides (9a-c). Acid hydrazide **2** (3.25g, 0.01 mol) was suspended in 50 mL of absolute ethanol and 0.011 mol of ammonium thiocyanate and 0.011 mol HCl 37% or 0.011 mol of methyl, phenyl isothiocyanate was added. The reactions was refluxed

for 4–8 h and monitored by TLC using the system of mobile phase ethyl acetate/hexane 1:1. The solids obtained were filtered and washed with water and recrystallized from toluene.

(R)-1-(2-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy) propanoyl) thiosemicarbazide (9a). Yield 65%, mp 184–186°C, IR (KBr): 3318 (NH_2), 3291, 3185 (N-H), 1692 (C=O), 1615, 1505, 1451 (C=N, C=C), 1238 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 9.63 (s, 1H, NH), 8.82 (s, 1H, NH), 7.87 (s, $1H_{py.}$), 7.51 (d, J = 8.7 Hz, $1H_{py.}$), 7.02–7.10 (m, 4H, ph), 6.74 (s, 2H, NH_2), 4.82 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.65 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.5, 75.1, 116.8, 122.6, 125.1, 140.1, 145.2, 147.5, 148.3, 151.2, 153.9, 170.4 (C=S), 179.2 (C=O); Anal. Calcd. for $C_{15}H_{14}ClFN_4O_3S$: C, 46.82; H, 3.67; N, 14.56; S, 8.33. Found: C, 47.00; H, 3.69; N, 14.51; S, 8.31.

(R)-1-(2-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy) propanoyl)-4-methyl thiosemicarbazide (9b). Yield 92%, mp 152–154°C, IR (KBr): 3420, (NH_2), 3318, 3185 (NH), 2997, 2940, 1691 (C=O), 1565, 1506, 1449, 1413 (C=N, C=C), 1291 (N&&bond;;N), 1238 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 9.36 (s, 1H, NH), 8.80 (s, 1H, NH), 7.84 (s, $1H_{py.}$), 7.50 (d, J = 8.7 Hz, $1H_{py.}$), 7.10–6.93 (m, 4H, ph), 6.72 (s, 1H, NHMe), the NH protons disappeared on D_2O addition, 4.85 (q, J = 6.5 Hz, 1H, H_{chiral}), 3.02 (s, 3H, NCH_3), 1.67 (J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.3, 31.5, 74.7, 116.6, 122.7, 125.2, 140.0, 145.2, 147.5, 148.3, 151.2, 153.8, 171.3 (C=S), 180.2 (C=O); Anal. Calcd. for $C_{16}H_{16}ClFN_4O_3S$: C, 48.18; H, 4.04; N, 14.05; S, 8.04. Found: C, 47.99; H, 4.04; N, 14.10; S, 8.07.

(R)-1-(2-(4-(5-Chloro-3-fluoropyridin-2-yloxy) phenoxy) propanoyl)-4-phenyl thiosemicarbazide (9c). Yield 94%, mp 138–140°C, IR (KBr): 3420, 3374, 3297 (N-H), 3060, 2940, 1685 (C=O), 1506, 1450, 1412 (C=N, C=C), 1239 (N-N), 1199 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 9.79 (s, 1H, NH), 9.32 (s, 1H, NH), 9.02 (s, 1H, NH), 7.80 (s, $1H_{py.}$), 7.50 (d, J = 8.7 Hz, $1H_{py.}$), 7.40–6.97 (m, 9H, ph), 4.81 (q, J = 6.5 Hz, $1H_{chiral}$), 1.60 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.3, 74.7, 116.8, 122.5, 124.3, 125.1, 126.1, 128.9, 137.5, 140.0, 145.1, 147.4, 148.6, 151.1, 154.0, 170.3 (C=S), 179.8 (C=O); Anal. Calcd. for $C_{21}H_{18}ClFN_4O_3S$: C, 54.72; H, 3.94; N, 12.16; S, 6.96. Found: C, 54.79; H, 3.93; N, 12.13; S, 6.96.

General procedure for synthesis of the 1,3,4-thiadiazoles (10a–c). The thiosemicarbazides **9a–c** (10 mmol) was added slowly to a concentrated sulfuric acid (5 mL), which was stirred and kept at 0°C. The reaction mixture was stirred in ice bath for 0.5 h. It was then poured into ice-water and neutralized with concentrated aqueous ammonia. The precipitate was filtered, washed with water, dried and recrystallized from ethanol to give pure **10a–c**.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-1,3,4-thiadiazol-2-amine (10a). Yield 64%, mp 177–178°C, IR (KBr): 3412–3279 (NH), 3105 (C-H), 1617, 1504, 1450, 1413 (C=N, C=C), 1239 (N-N), 1202 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.97 (s, $1H_{py.}$), 7.85 (d, J = 8.7 Hz, $1H_{py.}$), 7.49–7.28 (m, 4H, ph), 7.01–6.50 (br, 2H, NH_2), the NH and NH_2 protons disappeared on D_2O addition, 5.50 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.74 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 22.2, 72.3, 116.7, 122.3, 124.9, 140.0, 147.1, 151.1, 153.8, 154.1, 163.2, 169.4, 173.8; Anal. Calcd. for $C_{15}H_{12}ClFN_4O_2S$: C, 49.12; H, 3.30; N, 15.27; S, 8.74. Found: C, 49.24; H, 3.32; N, 15.33; S, 8.76.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-N-methyl-1,3,4-thiadiazol-2-amine (10b). Yield 67%, mp 155–158°C, IR (KBr): 3414 (N-H), 3067 (C-H), 1640, 1575, 1505, 1455, 1410 (C=N, C=C), 1236 (N-N), 1202 (C-N), 1034 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 10.78 (s, 1H, NH), 7.83 (s, $1H_{py.}$), 7.49 (d, J = 8.7 Hz, $1H_{py.}$), 7.2–6.92 (m, 4H, ph), 5.48 (q, J = 6.5 Hz, 1H, H_{chiral}), 3.36 (s, 3H, NCH_3), 1.81 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 21.4, 33.4, 72.0, 116.7, 122.6, 125.1, 140.1, 145.1, 147.8, 148.6, 151.0, 153.3, 160.0, 167.0; Anal. Calcd. for $C_{16}H_{14}ClFN_4O_2S$: C, 50.46; H, 3.71; N, 14.71; S, 8.42. Found: C, 50.28; H, 3.72; N, 14.68; S, 8.45.

5-((R)-1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-N-phenyl-1,3,4-thiadiazol-2-amine (10c). Yield 81%, mp 118–120°C, IR (KBr): 3412, 3280 (N-H), 3059 (C-H), 1602, 1552, 1503, 1448 (C=N, C=C), 1199 (C-N), 1061 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 10.56 (s, 1H, NH), the NH proton disappeared on D_2O addition, 7.85 (s, $1H_{py.}$), 7.48 (d, J = 8.7 Hz, $1H_{py.}$), 7.3–6.75 (m, 9H, ph), 5.55 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.69 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 21.9, 72.2, 116.6, 119.5, 122.4, 125.0, 127.6, 129.8, 139.1, 140.0, 145.1, 147.3, 147.5, 151.1, 153.8, 160.6, 168.1; Anal. Calcd. for $C_{21}H_{16}ClFN_4O_2S$: C, 56.95; H, 3.64; N, 12.65; S, 7.24. Found: C, 57.10; H, 3.64; N, 12.60; S, 7.22.

General procedure for synthesis of the 1,3,4-oxadiazoles (11a–c). To a cooled and well-stirred solution of thiosemicarbazides **9a–c** (2 mmol) in ethanol (50 mL) was added a solution of 5 N NaOH (1 mL). To this clear solution, a solution of 5% KI/I_2 was added until a permanent tinge color of iodine persisted at room temperature. The reaction mixture was refluxed for 3–4 h. The result was concentrated and cooled to room temperature to give the solid product, which was filtered, air dried, and recrystallized from ethanol.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-1,3,4-oxadiazol-2-amine (11a). Yield 68%, 177–178°C, IR (KBr): 3415–3314 (N-H), 3118 (C-H), 1650, 1613, 1505, 1455 (C=N, C=C), 1204 (C-N), 1037 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.80 (s, $1H_{py.}$), 7.61 (d, J = 8.7 Hz, $1H_{py.}$), 7.28–7.04 (m, 4H, ph), 6.50 (br, 2H, NH_2), 5.40 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.95 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.9, 67.6, 116.8, 122.4, 125.0, 140.0, 147.1, 151.1, 153.8, 154.2, 163.2, 169.4, 173.8; Anal. Calcd. $C_{15}H_{12}ClFN_4O_3$: C, 51.37; H, 3.45; N, 15.97. Found: C, 51.20; H, 3.47; N, 15.87.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-N-methyl-1,3,4-oxadiazol-2-amine (11b). Yield 72%, mp 168–169°C, IR (KBr): 3414 (N-H), 3067 (C-H), 1632, 1598, 1504, 1448 (C=N, C=C), 1199 (C-N), 1090 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.81 (s, $1H_{py.}$), 7.47 (d, J = 8.7 Hz, $1H_{py.}$), 7.2–7.00 (m, 4H, ph), 6.27 (s, 1H, NH), the NH proton disappeared on D_2O addition, 5.39 (q, J = 6.5 Hz, 1H, H_{chiral}), 2.95 (s, 3H, NCH_3), 1.71 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 19.1, 67.7, 116.6, 122.3, 125.0, 140.0, 145.1, 147.1, 148.6, 151.2, 154.4, 159.0, 164.6; Anal. Calcd. for $C_{16}H_{14}ClFN_4O_3$: C, 52.68; H, 3.87; N, 15.36. Found: C, 52.59; H, 3.86; N, 15.33.

5-((R)-1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-N-phenyl-1,3,4-oxadiazol-2-amine (11c). Yield 74%, mp 121–124°C, IR (KBr): 3413, 3317 (N-H), 3067 (C-H), 1622, 1573, 1504, 1452 (C=N, C=C), 1205 (C-N), 1078 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 9.59 (s, 1H, NH), 7.85 (s, $1H_{py.}$), 7.51 (d, J = 8.7 Hz, $1H_{py.}$), 7.46–7.00 (m, 9H, ph), 5.49 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.81 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 19.1, 67.8, 116.9, 117.7, 122.4, 125.0, 125.1, 129.3, 137.8, 140.1, 145.2, 147.3, 147.4, 151.3, 154.5,

159.4, 161.0; Anal. Calcd. for $C_{21}H_{16}ClFN_4O_3$: C, 59.09; H, 3.78; N, 13.13. Found: C, 59.27; H, 3.80; N, 13.24.

General procedure for synthesis of the 1,2,4-triazoles (12a-c). A solution of 10 mmol thiosemicarbazide **9a-c** in 2*N* sodium hydroxide (25 mL) was heated under reflux for 4 h. After cooling to room temperature, diluted hydrochloric acid for neutralizing was added. The precipitate was filtered and washed several times with water. The compounds were recrystallized from toluene/*n*-hexane.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-4H-1,2,4-triazole-3-thiol (12a). Yield 55%, mp 176–178°C; IR (KBr): 3412, 3233 (N-H), 2529 (S-H), 1615, 1505, 1449 (C═N, C═C), 1200 (C═S), 846 (C-S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 12.75 (s, 1H, SH.), 10.36 (s, 1H, NH), the SH and NH protons disappeared on D_2O addition, 7.81 (s, $1H_{py.}$), 7.46 (d, J = 8.7 Hz, $1H_{py.}$), 7.02–6.96 (m, 4H, ph), 5.25 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.70 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 19.1, 68.2, 116.5, 122.2, 124.9, 139.8, 145.6, 146.8, 147.9, 151.3, 153.6, 161.5, 170.5; Anal. Calcd. for $C_{15}H_{12}ClFN_4O_2S$: C, 49.12; H, 3.30; N, 15.27; S, 8.74. Found: C, 48.94; H, 3.32; N, 15.32; S, 8.70.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-4-methyl-4H-1,2,4-triazole-3-thiol (12b). Yield 76%, mp 120–125°C; IR (KBr): 3413 (NH), 3099, 2935 (C-H), 2752 (SH), 1598, 1574, 1504, 1448, (C═N, C═C), 1233 (N-N), 1198 (C═S), 732 (C-S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 12.85 (br, 1H, SH), 7.85 (s, $1H_{py.}$), 7.48 (d, J = 8.7 Hz, $1H_{py.}$), 7.24–7.06 (m, 4H, ph), 5.50 (q, J = 6.5 Hz, 1H, H_{chiral}), 3.66 (s, 3H, NCH_3), 1.76 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.2, 31.3, 68.5, 116.4, 122.6, 125.1, 140.1, 145.1, 147.5, 148.6, 151.1, 151.5, 153.6, 168.0; Anal. Calcd. for $C_{16}H_{14}ClFN_4O_2S$: C, 50.46; H, 3.71; N, 14.71; S, 8.42. Found: C, 50.60; H, 3.71; N, 14.69; S, 8.43.

(R)-5-(1-(4-(5-Chloro-3-fluoropyridin-2-yloxy)phenoxy)ethyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (12c). Yield 94%, mp 169–171°C, IR (KBr): 3413 (N-H), 3100, 2920 (C-H), 1615, 1598, 1503, 1447 (C═N, C═C), 1235 (N-N), 1199 (C═S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 12.65 (br, 1H, SH), 7.85 (s, $1H_{py.}$), 7.48 (d, J = 8.7 Hz, $1H_{py.}$), 7.3–6.75 (m, 9H, ph), 5.21 (q, J = 6.5 Hz, 1H, H_{chiral}), 1.63 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 17.9, 68.4, 117.1, 122.3, 125.1, 128.2, 129.6, 130.2, 133.0, 140.1, 140.2, 145.1, 147.5, 148.6, 151.1, 151.5, 153.6; Anal. Calcd. for $C_{21}H_16ClFN_4O_2S$: C, 56.95; H, 3.64; N, 12.65; S, 7.24. Found: C, 56.82; H, 3.63; N, 12.68; S, 7.26.

Herbicidal testing. The herbicidal activities of new cyclic compounds **4–8** and **9–12a–c** were evaluated for post-emergence inhibitory effect against *Echinochloa cruss-galli* (*Ech*), *Avena fatua* (*Ave*), and *Sorgum halepense* (*Sor*) weeds using known procedure [21, 26]. For these tests, an emulsion concentrate at EC 8% was formulated by mixing eight parts of the active ingredients (a.i.), 14 parts of blended emulsifiers MS and FF_4 (trade name), 10 parts of cyclohexanone, 30 parts of pine oil and added sunflower oil up to 100 mL. Herbicidal testing was carried out at the three- to four-leaf stage by a sprayer at the rate of 125 g a.i/ha with a spelling volume of 1000 L ha^{-1}. All the treatments were replicated three times in a completely randomized design. Three weeks after the treatment, weed control and crop damage were calculated as the inhibition percent by making a biomass reduction comparison between samples treated with each compound and a sample treated with distilled water (Table 1). Range %0 means no effect and %100 means complete killing (eq. 1).

$$\%\text{Herbicidal activity} = W_b = W_t/W_b\tilde{n}100 \qquad (1)$$

W_b = biomass of blank; W_t = biomass of treated

Acknowledgments. The authors express their deep gratitude to Department of Chemistry, Payame Noor University for providing financial support and also thank the Industrial Pesticide Research Center for the evaluating of herbicidal activities.

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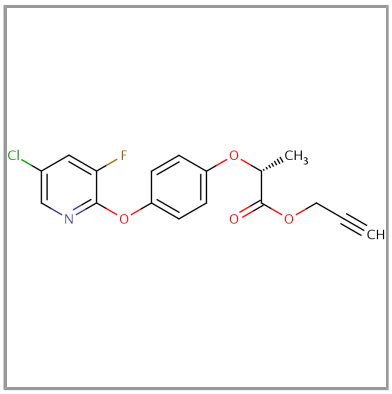

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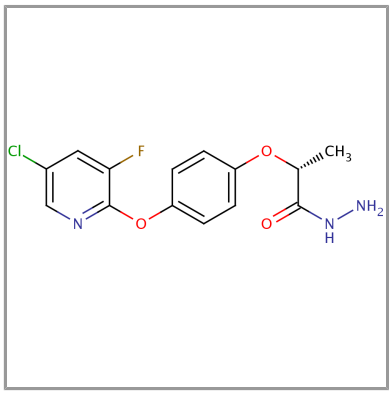

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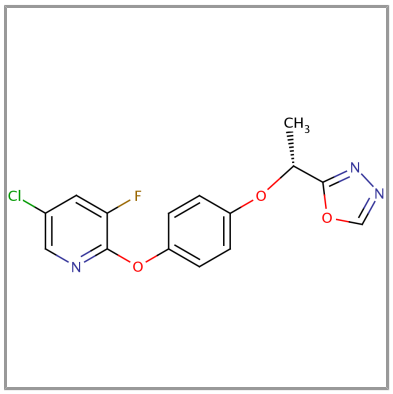

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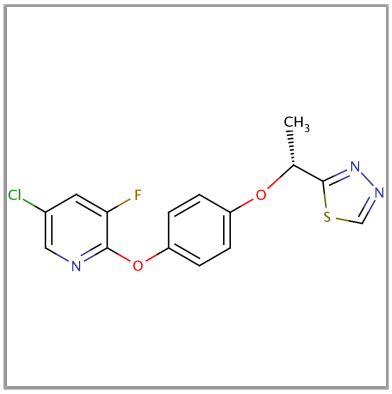

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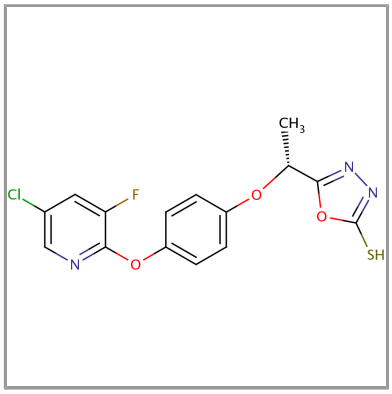

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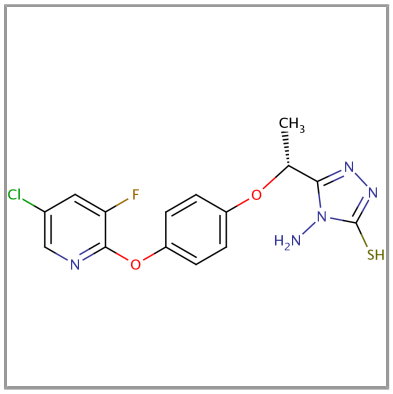

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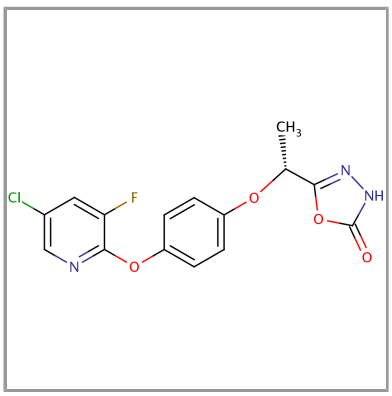

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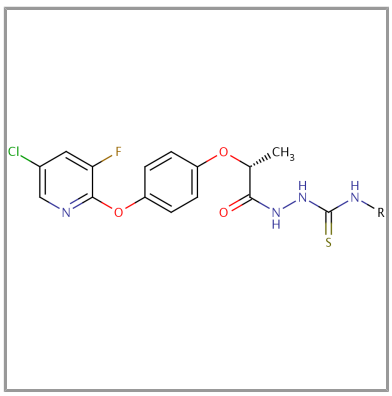

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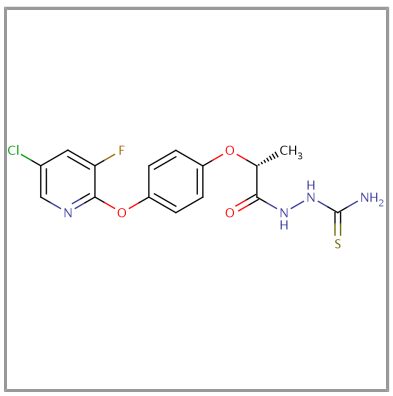

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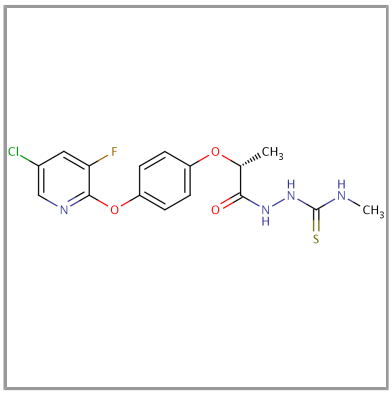

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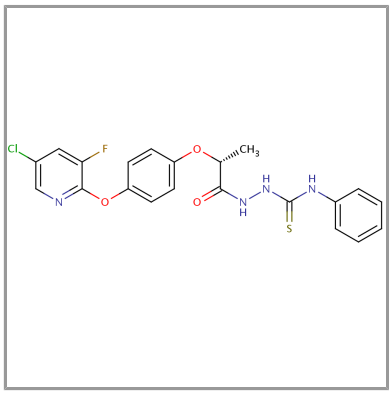

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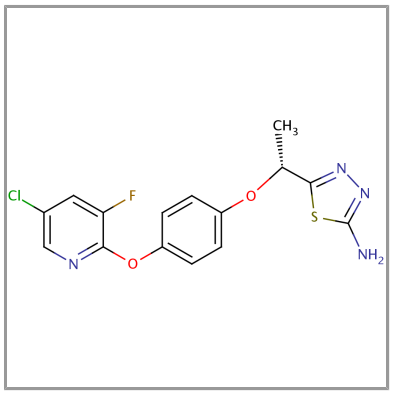

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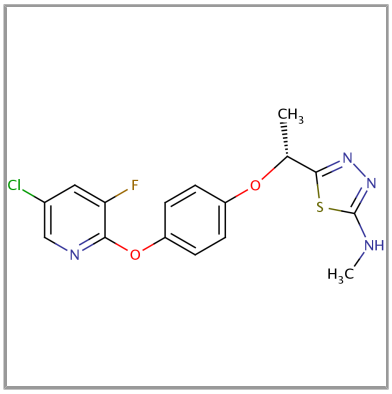

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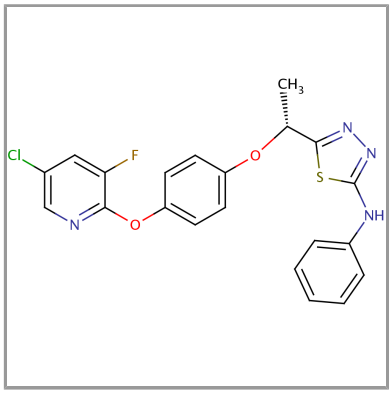

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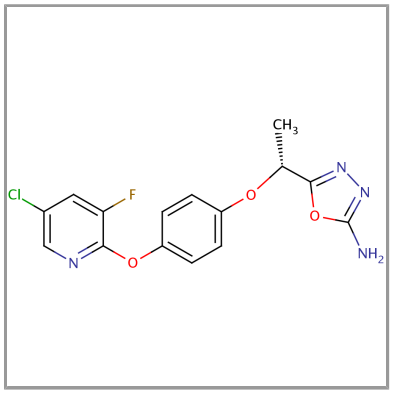

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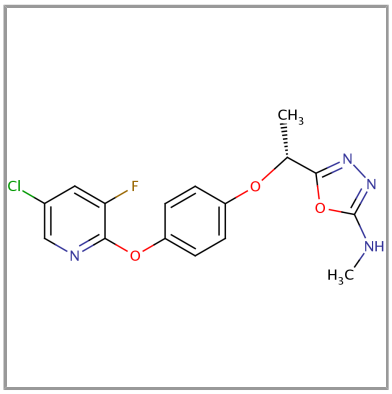

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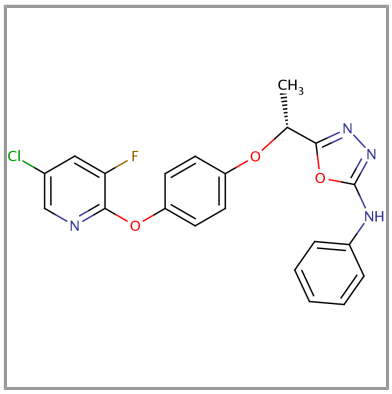

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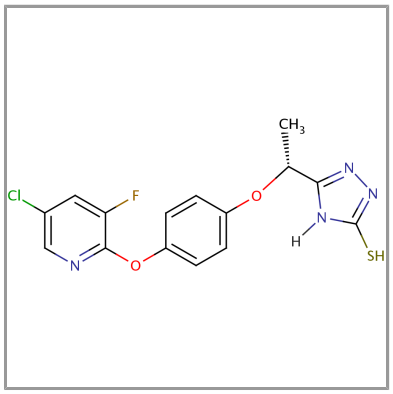

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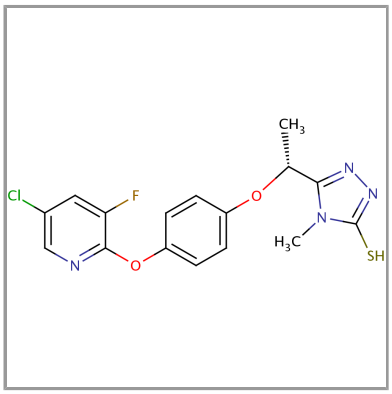

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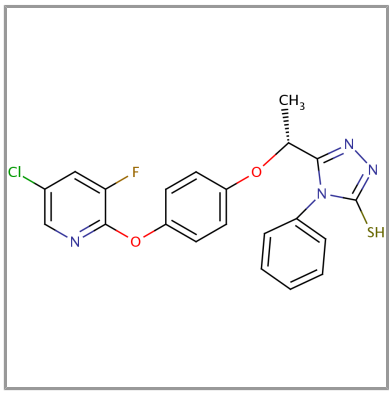

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