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Original Article

Synthesis and Herbicidal Activity of Novel *P*-Menthane Derivatives Containing Sulfone Unit

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Abstract:
A series of novel *p*-menthane derivatives incorporating a sulfone unit were synthesized and evaluated for herbicidal activity under greenhouse conditions. Most of the compounds exhibited good post-emergence activity against *Echinochloa crusgalli*, *Digitaria sanguinalis*, and *Amaranthus retroflexus*, as well as good pre-emergence activity against *Digitaria sanguinalis*, and *Amaranthus retroflexus*. Notably, compound **4h** was identified as the most potent derivative, achieving an average control rate of 97.5% across the three weed species under both pre- and post-emergence applications, and displayed a more favorable crop safety profile than the reference herbicide diuron. Furthermore, compound **4i** showed herbicidal activity comparable to that of diuron, but with superior crop safety.

Keywords: *p*-menthane, sulfone, synthesis, herbicidal activity, crop safety

Introduction

The use of herbicides has been essential for ensuring agricultural productivity. However, the overreliance on conventional chemical herbicides, such as glyphosate, has resulted in ecotoxicological risks and the emergence of weed resistance, posing serious threats to the environment[1]. To address these challenges, there is an urgent need to develop novel, environmentally benign herbicides. Plant-derived herbicides, which are structurally based on natural products or their metabolites, offer distinct advantages, including novel modes of action, high target selectivity, and rapid environmental degradation. Consequently, they have emerged as a prominent research focus in recent years[2].

As a major constituent of natural turpentine, pinene can be converted into *p*-menthane skeleton through appropriate structural modifications[3,4]. More importantly, a series of studies have demonstrated that derivatives of *p*-menthane exhibited diverse biological activities, including herbicidal effects[5,6]. In 2018, Zhu and co-workers synthesized 1,8-*p*-menthanediamine and its heterocyclic Schiff base derivatives starting from 1,8-*p*-menthanediol. Pre-emergence herbicidal activity assays against *Lolium multiflorum* revealed that the heterocyclic Schiff base derivatives showed significantly higher activity[7]. In 2021, Zhang and colleagues synthesized *p*-menthane type secondary amine derivatives. Herbicidal activity evaluations against *Echinochloa crus-galli* indicated that several of these compounds exhibited herbicidal activity superior to that of the commercial herbicides diuron and glyphosate[8]. However, both of the above studies on herbicidal activity are limited exclusively to nitrogen-containing *p*-menthane derivatives. Therefore, to expand the structural diversity of the *p*-menthane family for the development of novel plant-derived herbicides, there remains a high demand for further investigation.

The sulfonyl group plays a crucial role in pesticide design, and its distinctive chemical properties render it a key structural motif for enhancing biological activity, optimizing physicochemical properties, and developing novel agrochemicals[9]. Guided by the pharmacophore fusion strategy and employing *p*-menthane as the lead structure, we herein report the design, synthesis, and herbicidal activity evaluation of *p*-menthane derivatives containing sulfone unit (Figure 1).

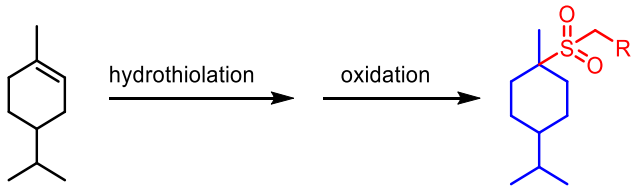


Figure 1. Synthesis of *p*-menthane derivatives containing sulfone unit

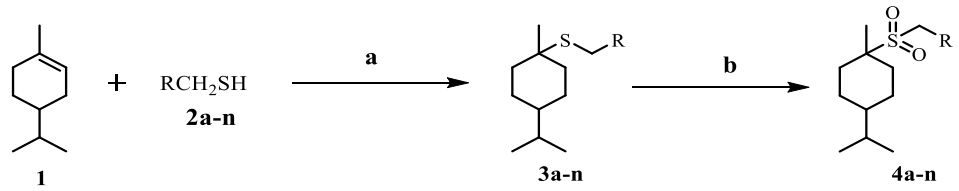
2. Materials and Methods

2.1. Materials and Instruments

All reagents and solvents were commercially available and used without further purification. Reactions were monitored by thin-layer chromatography. Column chromatography was performed using silica gel (300-400 mesh). The NMR spectra were recorded on a Bruker Avance 400 spectrometers at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ using TMS as an internal standard. High-resolution mass spectra were obtained with an AB Triple 5600 mass spectrometer by ESI on a TOF mass analyzer.

2.2 General Procedure for the Synthesis of Compounds **4a-n**

The compounds described in this paper were synthesized according to the following protocol (Figure 2).



Reagents and conditions: a) $B(C_6F_5)_2$, DCM, r.t.; b) *m*-CPBA, DCM, r.t..

R = Ph (**4a**); R = 4-CH_3-Ph (**4b**); R = 4-OCH_3-Ph (**4c**); R = 3-CH_3-Ph (**4d**); R = 4-F-Ph (**4e**); R = 4-Cl-Ph (**4f**); R = 3-F-Ph (**4g**); R = 3-Cl-Ph (**4h**); R = 3-Br-Ph (**4i**); R = 2-Cl-Ph (**4j**); R = 2-Br-Ph (**4k**); R = 4-CF_3-Ph (**4l**); R = 3-CF_3-Ph (**4m**); R = Cyclohexyl (**4n**)

Figure 2. Synthetic route of the target compounds 4a-n

4-isopropyl-1-methylcyclohex-1-ene **1** (2.76 g, 20 mmol), the substituted thiol **2** (20 mmol), and tris(pentafluorophenyl)borane (0.51 g, 1 mmol) were added to dichloromethane (20 mL). The mixture was stirred at room temperature for 12 h. After completion of the reaction, the solvent was evaporated under reduced pressure, and the residue was redissolved in *n*-hexane (40 mL). The resulting solution was filtered through a short silica gel column to remove insoluble impurities, and the filtrate was concentrated under reduced pressure to dryness, yielding the thioether **3**, which was used directly in the next oxidation step without further purification.

The thioether **3** was dissolved in dichloromethane (40 mL) and the solution was cooled to 0°C.

Then, *m*-chloroperoxybenzoic acid (*m*-CPBA, 6.91 g, 40 mmol) was added portionwise. The cooling bath was removed, and the mixture was stirred at room temperature until the thioether and sulfoxide intermediates were consumed. The reaction mixture was quenched with saturated aqueous sodium thiosulfate solution, extracted with dichloromethane, and the organic layer was washed with saturated aqueous sodium bicarbonate solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (20:1) as the eluent to afford the desired products **4**. The structures of all products were confirmed by $^1H/^{13}C$ NMR spectra and HRMS.

(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4a**). Light yellow oil (4.4 g, 75% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.37 (m, 4H), 7.35-7.31 (m, 1H), 4.34 (d, *J* 0.8 Hz, 2H), 1.95 (ddd, *J* 11.9, 7.9, 5.7 Hz, 2H), 1.82 (ddd, *J* 11.9, 8.1, 5.7 Hz, 2H), 1.69 (dt, *J* 6.8, 5.9 Hz, 1H), 1.58 (ddd, *J* 13.0, 8.1, 5.9 Hz, 2H), 1.47 (dt, *J* 13.4, 6.8 Hz, 1H), 1.41-1.34 (m, 5H), 0.87 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 131.3, 130.4, 129.2, 128.7, 62.3, 54.0, 43.1, 31.1, 30.4, 25.7, 20.0, 19.4; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{26}O_2S + H]^+$: 295.1727, found: 295.1728.

1-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)-4-methylbenzene (**4b**). Light yellow oil (4.8 g, 78% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29-7.27 (m, 2H), 7.12-7.09 (m, 2H), 4.34 (t, *J* 1.0 Hz, 2H), 2.33 (d, *J* 0.8 Hz, 3H), 1.68-1.62 (m, 4H), 1.57-1.50 (m, 4H), 1.42 (s, 3H), 1.37-1.30 (m, 2H), 0.90-0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.2, 130.0, 129.5, 128.6, 62.2, 53.8, 43.5, 32.2, 30.7, 26.0, 21.0, 20.1, 19.7; HRMS (ESI) *m/z*, calcd. for $[C_{18}H_{28}O_2S + H]^+$: 309.1883, found: 309.1885.

1-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)-4-methoxybenzene (**4c**). Yellow oil (4.9 g, 76% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 (dt, *J* 8.5, 1.1 Hz, 2H), 6.87-6.83 (m, 2H), 4.32 (t, *J* 1.2 Hz, 2H), 3.77 (s, 3H), 1.69-1.63 (m, 4H), 1.61-1.47 (m, 4H), 1.43 (s, 3H), 1.33-1.25 (m, 2H), 0.86 (d, *J* 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.7, 131.2, 124.1, 114.3, 61.4, 55.3, 53.1, 42.9, 31.3, 29.9, 25.7, 20.0, 19.6; HRMS (ESI) *m/z*, calcd. for $[C_{18}H_{28}O_3S + H]^+$: 325.1832, found: 325.1833.

1-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)-3-methylbenzene (**4d**). Light yellow oil (4.4 g, 72% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30-7.22 (m, 2H), 7.18 (dq, *J* 2.2, 1.2 Hz, 1H), 7.05-7.03 (m, 1H), 4.35 (t, *J* 0.9 Hz, 2H), 2.35 (t, *J* 0.7 Hz, 3H), 1.99-1.67 (m, 5H), 1.59-1.51 (m, 3H), 1.44-1.37 (m, 5H), 0.87 (d, *J* 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.8, 131.5, 130.2, 129.2, 128.0, 127.9, 62.5, 51.5, 43.3, 32.2, 30.8, 26.6, 21.1, 20.2, 19.8; HRMS (ESI) *m/z*, calcd. for $[C_{18}H_{28}O_2S + H]^+$: 309.1883, found: 309.1887.

1-fluoro-4-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4e**). Light yellow oil (4.7 g, 75% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28-7.25 (m, 2H), 7.07-7.02 (m, 2H), 4.33 (t, *J* 1.0 Hz, 2H), 1.97-1.86 (m, 4H), 1.62-1.48 (m, 4H), 1.41 (s, 3H), 1.34-1.27 (m, 2H), 0.89 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9 (d, *J* 252.1 Hz), 131.7 (d, *J* 8.1 Hz), 126.4 (d, *J* 3.1 Hz), 115.6 (d, *J* 20.0 Hz), 62.4, 53.6, 43.7, 32.2, 30.8, 26.2, 20.3, 19.5; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}FO_2S + H]^+$: 313.1633, found: 313.1635.

1-chloro-4-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4f**). White oil (5.1 g, 78% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36-7.28 (m, 4H), 4.35 (t, *J* 0.8 Hz, 2H), 1.98-1.87 (m, 4H), 1.63-1.55 (m, 4H), 1.42 (s, 3H), 1.36-1.29 (m, 2H), 0.87 (d, *J* 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.6,

131.3, 129.6, 129.2, 62.1, 54.2, 43.3, 32.0, 30.5, 26.3, 20.4, 19.8; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}ClO_2S + H]^+$: 329.1337, found: 329.1338.

1-fluoro-3-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4g**). Yellow oil (4.6 g, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (td, *J* 7.8, 4.9 Hz, 1H), 7.26-7.23 (m, 1H), 7.06-7.02 (m, 1H), 6.95 (m, 1H), 4.36 (t, *J* 1.2 Hz, 2H), 1.95-1.81 (m, 4H), 1.73-1.67 (m, 1H), 1.57-1.47 (m, 4H), 1.46-1.43 (m, 1H), 1.42 (s, 3H), 0.88 (d, *J* 6.6 Hz, 6H); 163.2 (d, *J* 251.1 Hz), 132.1 (d, *J* 8.2 Hz), 130.3 (d, *J* 8.1 Hz), 126.3 (d, *J* 3.3 Hz), 116.3 (d, *J* 20.1 Hz), 114.6 (d, *J* 19.6 Hz), 62.23, 54.0 (d, *J* 4.2 Hz), 44.5, 33.1, 32.6, 27.3, 21.5, 19.9; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}FO_2S + H]^+$: 313.1633, found: 313.1635.

1-chloro-3-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4h**). Light yellow oil (5.2 g, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35-7.31 (m, 2H), 7.29-7.24 (m, 2H), 4.36 (t, *J* 0.9 Hz, 2H), 1.69-1.44 (m, 8H), 1.43 (s, 3H), 1.35-1.27 (m, 2H), 0.87 (d, *J* 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 134.7, 131.4, 130.4, 129.6, 129.1, 128.0, 62.5, 54.4, 43.6, 32.2, 30.6, 26.0, 20.2, 19.7; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}ClO_2S + H]^+$: 329.1337, found: 329.1340.

1-bromo-3-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4i**). Yellow oil (5.7 g, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48-7.46 (m, 1H), 7.37 (m, 2H), 7.23 (t, *J* 7.4 Hz, 1H), 4.35 (t, *J* 1.2 Hz, 2H), 1.92 (ddd, *J* 12.1, 8.0, 5.4 Hz, 2H), 1.77 (ddd, *J* 11.8, 7.7, 5.6 Hz, 2H), 1.65-1.43 (m, 6H), 1.40 (s, 3H), 0.86 (d, *J* 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.4, 132.0, 130.8, 130.5, 129.3, 123.1, 62.1, 48.7, 43.4, 32.0, 30.5, 25.5, 20.1, 19.8; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}BrO_2S + H]^+$: 373.0832, found: 373.0834.

1-chloro-2-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4j**). Light yellow oil (4.7 g, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36-7.33 (m, 2H), 7.30-7.23 (m, 2H), 4.44 (d, *J* 1.0 Hz, 2H), 1.97-1.93 (m, 2H), 1.84-1.80 (m, 2H), 1.75-1.70 (m, 1H), 1.59-1.41 (m, 8H), 0.88 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 134.9, 131.8, 131.6, 129.9, 129.0, 127.6, 61.3, 49.8, 42.5, 31.5, 29.4, 23.1, 20.0, 19.1; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}ClO_2S + H]^+$: 329.1337, found: 329.1339.

1-bromo-2-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)benzene (**4k**). Light yellow oil (5.3 g, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 (dd, *J* 7.5, 1.3 Hz, 1H), 7.34-7.24 (m, 3H), 4.45 (d, *J* 0.9 Hz, 2H), 1.96-1.80 (m, 4H), 1.74-1.69 (m, 1H), 1.60-1.38 (m, 8H), 0.86 (d, *J* 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.9, 132.8, 131.5, 129.1, 127.8, 126.5, 63.1, 55.0, 43.4, 32.1, 30.7, 25.9, 20.3, 19.5; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{25}BrO_2S + H]^+$: 373.0832, found: 373.0833.

1-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)-4-(trifluoromethyl)benzene (**4l**). Light yellow oil (5.4 g, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60-7.57 (m, 2H), 7.44 (dt, *J* 8.4, 1.2 Hz, 2H), 4.38 (t, *J* 1.0 Hz, 2H), 1.66-1.45 (m, 8H), 1.39 (s, 3H), 1.36-1.29 (m, 2H), 0.85 (d, *J* 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 131.1, 130.3 (d, *J* 2.1 Hz), 129.7 (q, *J* 32.0 Hz), 126.5 (q, *J* 4.1 Hz), 124.3 (q, *J* 268.1 Hz), 62.2, 54.4, 43.5, 32.0, 31.1, 26.2, 19.9, 19.6; HRMS (ESI) *m/z*, calcd. for $[C_{18}H_{25}F_3O_2S + H]^+$: 363.1601, found: 363.1603.

1-(((4-isopropyl-1-methylcyclohexyl)sulfonyl)methyl)-3-(trifluoromethyl)benzene (**4m**). Light yellow oil (5.1 g, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (m, 1H), 7.49 (dt, *J* 7.1, 2.0 Hz, 1H), 7.46-7.39 (m, 2H), 4.36 (t, *J* 0.9 Hz, 2H), 1.94 (ddd, *J* 12.0, 7.8, 5.8 Hz, 2H), 1.82 (ddd, *J* 11.9, 8.0, 5.5 Hz, 2H), 1.74-1.71 (m, 1H), 1.62-1.41 (m, 5H), 1.40 (s, 3H), 0.85 (d, *J* 6.6 Hz, 6H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm) 131.6 (q, *J* 32.1 Hz), 131.3, 130.16 (q, *J* 2.0 Hz), 129.5 (q, *J* 1.9 Hz), 127.4 (q, *J* 3.9 Hz), 125.0 (q, *J* 4.0 Hz), 122.9, 62.3, 53.2, 44.5, 32.3, 31.1, 26.2, 20.4, 19.3; HRMS (ESI) *m/z*, calcd. for $[C_{18}H_{25}F_3O_2S + H]^+$: 363.1601, found: 363.1605.

1-((cyclohexylmethyl)sulfonyl)-4-isopropyl-1-methylcyclohexane (**4n**). White oil (4.1 g, 68%); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.12 (d, *J* 6.1 Hz, 2H), 2.11 (m, 1H), 1.88 (ddd, *J* 12.0, 7.9, 5.6 Hz, 2H), 1.79 (ddd, *J* 11.9, 8.0, 5.8 Hz, 2H), 1.69 (m, 1H), 1.60-1.48 (m, 6H), 1.48-1.39 (m, 9H), 1.38 (s, 3H), 0.88 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 61.2, 54.1, 43.5, 35.2, 32.2, 30.6, 30.1, 26.6, 26.0, 25.5, 20.1, 19.6; HRMS (ESI) *m/z*, calcd. for $[C_{17}H_{32}O_2S + H]^+$: 301.2196, found: 301.2197.

2.3 Herbicidal activity Test

Following literature procedures [10], test compounds were dissolved in DMSO (1.0% stock) and diluted with 0.1% Tween-80 to the required concentrations. Post-emergence herbicidal activity against Echinochloa crusgalli, Digitaria sanguinalis, and Amaranthus retroflexus was evaluated. Weed seeds were sown in pots (8.0 cm inner diameter) filled with soil, covered with 0.2~0.5 cm of soil, and grown at 25 ± 8 °C in a greenhouse. At the two-leaf stage, seedlings were sprayed with the compound solutions at 750 g a.i./ha. Untreated and solvent (DMSO+Tween-80) controls were included, with Diuron (750 g a.i./ha) as the positive control. Herbicidal activity was visually assessed 21 days after treatment.

2.4 Crop safety assay

According to the procedures in the literature[11], the safety of the test compound on six common crop species (wheat, rice, maize, peanut, soybean, and cucumber) were evaluated using foliar spray application. Seeds were sown in plastic pots (9 cm in diameter) and placed in a greenhouse with temperatures ranging from 15 to 30 °C. When the plants reached a height of 4-9 cm, the test compound was applied at a dosage of 750 g a.i./ha using a foliar spray method. At 14 days after treatment, the extent of phytotoxicity as assessed for each crop species, with comparisons made against untreated control plants.

3. Results and Discussion

3.1 Chemistry

As illustrated in Scheme 2, the target compounds 6 were synthesized via a two-step sequence involving Lewis acid-mediated hydrothiolation followed by selective oxidation of the resulting thioethers. In the hydrothiolation step, conventional Lewis acids such as $SnCl_4$, $AlCl_3$, $TiCl_4$, and $Sc(OTf)_3$ were initially evaluated, however, all of them exhibited low catalytic efficiency for this transformation. Inspired by the work of Stephan and co-workers[12], we subsequently investigated a series of carbon-, boron-, and phosphorus-based Lewis acid catalysts. Among these, $B(C_6F_5)_3$ proved to be the most effective, affording the thioether intermediates **3** in good yields. For the selective oxidation of thioethers **3**, a variety of oxidants including H_2O_2, Oxone, *m*-CPBA, NaClO, and $KMnO_4$ were explored. Notably, *m*-CPBA displayed the highest reactivity under the conditions examined.

3.2 Herbicide activity

The greenhouse herbicidal activity results of the target compounds were presented in Table 1. At a dosage of 750 g a.i./ha, compounds **4e-k** exhibited excellent pre- and post-emergence activity against *Digitaria sanguinalis* and *Amaranthus retroflexus*, as well as outstanding post-emergence activity against *Echinochloa crusgalli*. Notably, compounds **4g-i** displayed post-emergence inhibition rates exceeding 90% against all three weed species. In particular, compound **4h** achieved pre-emergence inhibition rates above 90%. Furthermore, compounds **4g-i** showed relatively high mean pre- and post-

emergence inhibition rates against the three weeds, ranging from 87.5% to 97.8%. It was worth noting that compound **4h** exhibited the highest average herbicidal activity in both pre- and post-emergence assays, a performance comparable to that of the reference herbicide Diuron.

Table 1. Herbicide activity of the compounds 4a-n.

Compound	Post-emergent herbicidal activity [a] / %			Pre-emergent herbicidal activity [a] / %		
	Echinochloa crusgalli	*Digitaria sanguinalis*	*Amaranthus retroflexus*	*Echinochloa crusgalli*	*Digitaria sanguinalis*	*Amaranthus retroflexus*
4a	70	70	70	45	70	75
4b	70	75	75	50	70	80
4c	75	70	70	50	70	80
4d	70	70	85	45	70	75
4e	80	80	90	70	80	90
4f	85	85	90	75	80	95
4g	90	90	90	80	85	90
4h	100	95	100	90	100	100
4i	90	90	90	80	85	90
4j	85	80	90	70	85	90
4k	80	80	90	70	85	90
4l	75	70	80	60	70	80
4m	70	70	75	60	70	75
4n	55	60	60	30	65	70
Diuron [b]	100	100	100	90	95	100

[a] Compounds and positive control were tested at 750 g a.i./ha; [b] Diuron was used as positive control.

Given the promising herbicidal activity of these sulfone-containing p-menthane derivatives, the structure-activity relationship (SAR) of the R group was further explored. When R was a phenyl ring, both the electronic properties and substitution pattern significantly influenced the herbicidal activity. Notably, the introduction of halogen substituents onto the phenyl ring (R) was more beneficial than electron-donating groups (e.g., Me and MeO), particularly in terms of pre-emergent activity against *Echinochloa crusgalli* and *Digitaria sanguinalis*. As shown in Table 2, compounds **4e-k**, bearing halogen substituents, exhibited enhanced activities. Furthermore, the position of the halogen substituent on the phenyl ring also played a critical role. For instance, compound **4h**, with a *meta*-chloro group, showed higher activity than the *para*-chloro analogue **4f** and *ortho*-chloro analogue **4j**. Among the *para*-halogenated analogues (**4g-i**), chlorinated compound **4h** exhibited the highest herbicidal activity. It should be noted that the introduction of the trifluoromethyl group did not lead to an enhancement of the herbicidal activity of the compounds. When the aryl group was replaced by a cyclohexyl group (**4n**), the corresponding herbicidal activity decreased markedly.

3.3 Crop Safety

As shown in Table 3, the tested compound **4h** exhibited no phytotoxic effects on wheat, rice and peanut. It caused mild phytotoxicity on corn and soybean, with growth inhibition rates ranging from 10% to 29%. In contrast, severe inhibition was observed on cucumber and radish, where the growth inhibition rates fell between 50% and 69%. Notably, the overall crop safety profile of compound **4h** was superior to that of the positive control across all tested crops. These results indicate that compound **4h** possessed a favorable

selectivity for certain crop species, while displaying acceptable or negligible effects on others.

Table 3. Crop safety assessment of 4h on different crops.

Compound	Injury rate [a] / %						
	wheat	rice	corn	peanut	soybean	cucumber	radish
4h	G	G	F	G	F	D	D
Diuron [b]	A	A	A	B	B	A	A

[a] Rating of fresh weight inhibition rate relative to blank control group[13]: A. 100%; B. 99%-90%; C. 89%-70%; D. 69%-50%; E. 49%-30%; F. 29%-10%; G. 0-10%.

4. Conclusions

In summary, fourteen *p*-menthane derivatives containing sulfone fragments were synthesized and screened for herbicidal activity. Most of the synthesized compounds demonstrated potent activity against *Echinochloa crusgalli*, *Digitaria sanguinalis*, and *Amaranthus retroflexus*. In particular, compound **4h** exhibited excellent herbicidal capacity and a crop safety profile, underscoring its promising potential for further agricultural application.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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