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Aryl sulfoxide scaffold useful as herbicide

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Abstract

The escalating demand for effective and sustainable weed management strategies, driven by urbanization expansion, is a critical challenge. Herbicides are pivotal tools in modern agriculture, addressing this challenge. Developing novel herbicides with enhanced efficacy and minimal environmental impact is crucial for food security and ecological balance. While numerous herbicides have been developed with varying availability over time and regions, there's a continuous need for innovation. In this study, we explored relatively understudied sulfoxide-containing herbicides and synthesized a smaller yet substantial sulfoxide scaffold for herbicide development. Through screening *Digitaria ciliaris* (Retz.) Koeler, *Amaranthus lividus* L., and *Solanum nigrum* L., we observed promising herbicidal efficacy, especially against Wild Amaranth. Encouraged by preliminary findings, we recognize the potential for refining the core structure. In summary, we fashioned a structurally simple sulfoxide scaffold showcasing discernible herbicidal impact on broadleaf weeds.

Keywords Herbicide, Pesticide, *Solanum nigrum* L., *Amaranthus lividus* L., Sulfoxide

Introduction

The escalating demand for effective and sustainable weed management strategies, driven by the continual expansion of urbanization, is a critical challenge to address [1]. Herbicides, pivotal tools in modern agriculture, play a central role in meeting this challenge [2]. The imperative to develop novel herbicides with heightened efficacy, minimal environmental impact, and straightforward synthesis has never been more pressing, ensuring the preservation of food security and ecological equilibrium [3].

In response to this imperative, recent years have witnessed dedicated endeavors to identify innovative herbicidal compounds capable of curbing the growth of formidable weed species (Scheme 1) [2, 4].

Notably, glyphosate and atrazine, while effective, exhibit toxic effects at elevated concentrations [5, 6], necessitating the pursuit of environmentally benign (selective) alternatives. This has prompted the exploration of novel chemical classes, including sulfur-containing compounds [7].

Sulfur can exist in various oxidation states (i.e., sulfide, sulfoxide, sulfone) [8]. Notably, the sulfone functional group (having a +6 oxidation state) is present in several herbicides, including pyrasulfotole, lancotrione, topramezone, and benzobicyclon (Scheme 2) [7, 9]. They have been proven to be effective; however, their synthesis is somewhat challenging, and thus, the preparation process could be costly.

In contrast to their sulfone counterparts, sulfoxide-containing herbicides remain relatively underexplored. This context gave rise to our research question: Can structurally simple sulfoxide-containing organic compounds harbor herbicidal potency? Addressing this question, we prepared a smaller yet suitably substantial sulfoxide scaffold (Scheme 3). This choice was made to not only mitigate volatility effectively but also to allow for structural flexibility, affording the potential for diversification. This central framework offers the opportunity for the introduction of diverse arenes and various nucleophiles at the terminal ethynyl position.

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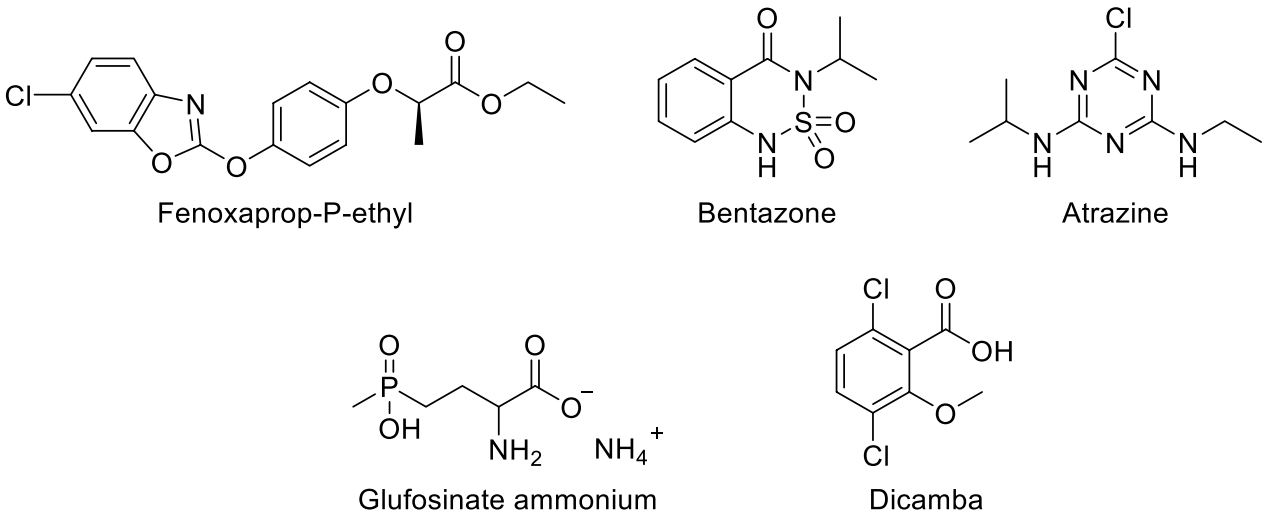
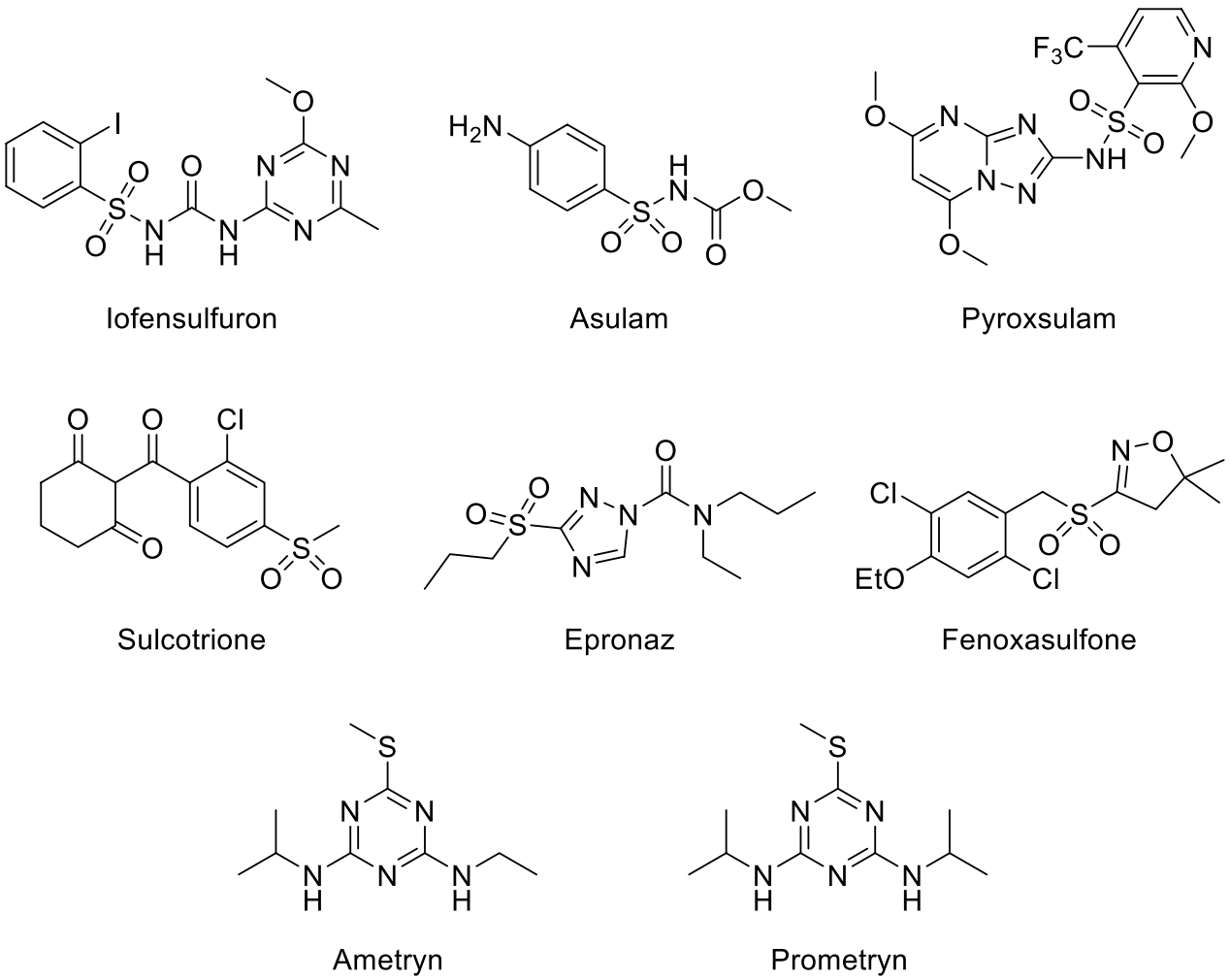
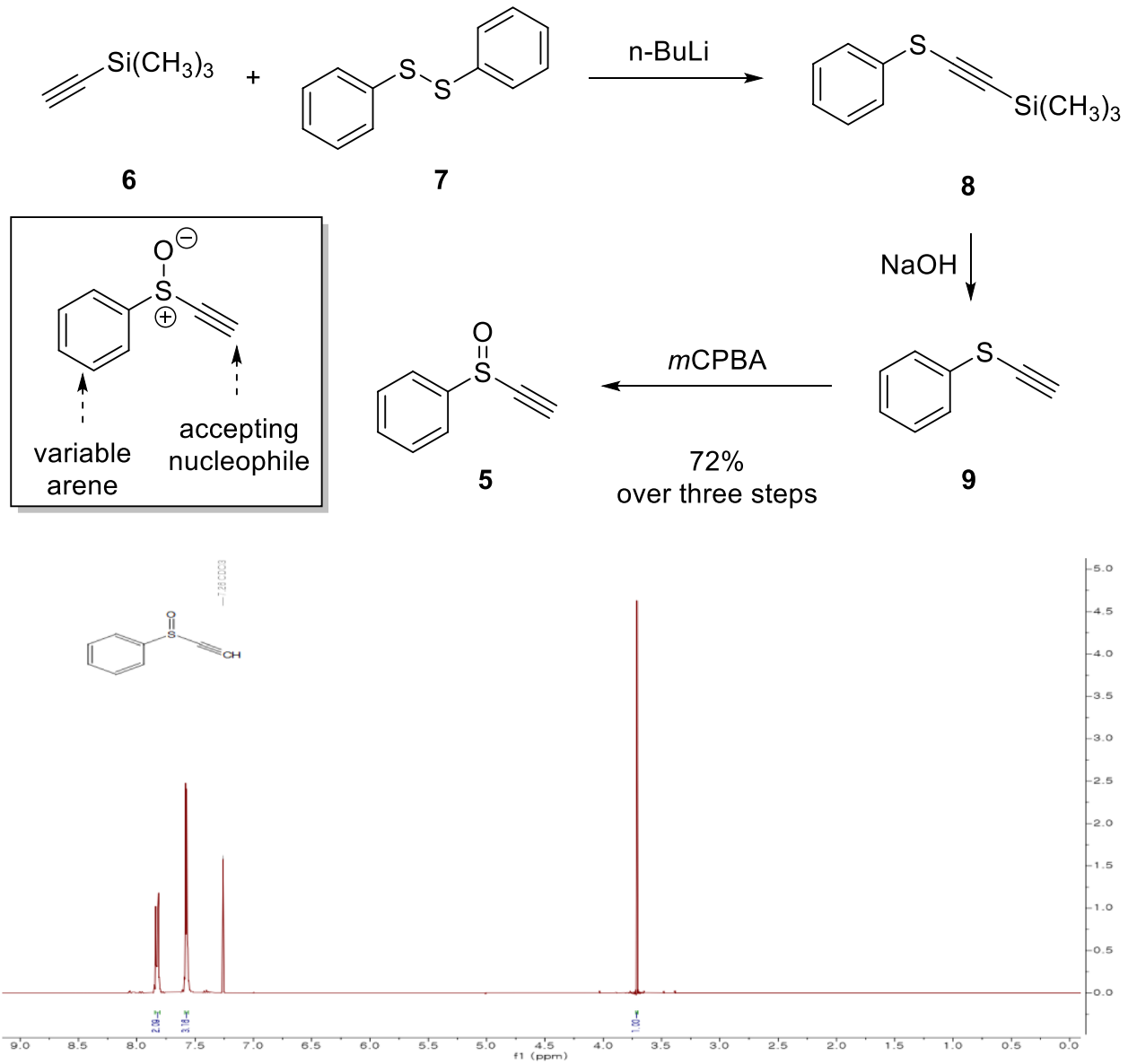


Scheme 1. Common herbicides being used in the field



Scheme 2. Selected examples of sulfur containing herbicides



Scheme 3. A general method for the synthesis of phenyl ethynyl sulfoxide (**5**) and its ^{1}H NMR spectrum measured in $CDCl_3$

To rapidly validate the concept, we proceeded to administer a foliar treatment using the sulfoxide compound in the screening of three weed species— *Digitaria ciliaris* (Retz.) Koeler, *Amaranthus lividus* L., and *Solanum nigrum* L. [10–12]. This approach provided valuable insights into the compound's potential as a pioneering herbicidal solution.

This study presents a discovery: a promising small chemical compound exhibiting promising herbicidal activity. Remarkably, this compound possesses a dual advantage—weed inhibition coupled with facile preparation and an environmentally benign nature.

Materials and methods

Preparation of target weeds

Germination rate investigation for 100 seeds of *Digitaria ciliaris* (Retz.) Koeler (collected in '95), *Amaranthus lividus* L. (collected in '99) and *Solanum nigrum* L. (purchased in '22), with a germination rate of 85% or higher. Confirmation of 15-day period under greenhouse conditions until the initial weed emergence stage. Seed sowing of 10 seeds per pot for each weed species 20 days prior to herbicide application. Implementation of foliar treatment on 2.5 ~ 3 leaf stage of emerging weeds.

Preparation and application of test samples

Each test sample was dissolved by adding 40 mg into 4 mL of DMSO to create a 1% solution. Calculation of treatment dosage per Pot: 0.154 mL/Pot × 12 (10 for weed emergence + 2 for excess) = Total 1.846 mL. Preparation of test sample for experimentation: Combine sample (1.846 mL) with distilled water or Tween® 80 (300 ppm) (10.154 mL) to make a total of 12 mL. Final prepared sample (1 mL) mixed with distilled water (2 mL), resulting in a total of 3 mL sprayed per Pot using a small sprayer (approximately 512.9 ppm of the herbicide, and 100 ppm of Tween® 80). Herbicide application was carried out in a Spray booth, ensuring even distribution within each Pot.

Efficacy evaluation

Post-emergence treatment, herbicidal efficacy symptoms on weeds were assessed using phytotoxicity observations, including leaf chlorosis, wilting, growth inhibition, and other noticeable symptoms. Comparison of herbicidal efficacy levels was conducted by comparing with commercial herbicides (fenoxaprop-p-ethyl EW as grass killer, bentazone SL as broad-leaf herbicide, glufosinate-ammonium SL as non-selective herbicide).

Biometric measurements

The number of shoots of each weed species in every Pot was counted. For each Pot, the above-ground portion of the weeds (excluding the roots) was sampled and weighed using a scale.

Calculation of herbicidal effect using biomass

$$\{1 - (\text{Biomass of Treated Group (g)} / \text{Biomass of Control Group (g)})\} \times 100 = \text{Herbicidal Efficacy (\%)}.$$

General information for the chemical synthesis

Unless otherwise noted, all reactions were carried out under Ar in flamed-dried glassware using anhydrous solvents. Anhydrous solvents were prepared by distillation over the indicated drying agents prior to use and were transferred under Ar: THF, Et_2O (Mg/anthracene), toluene (Na/K), CH_2Cl_2, MeOH (Mg); DMF and Et_3N were dried by an adsorption solvent purification system based on molecular sieves. Thin layer chromatography (TLC): Macherey–Nagel precoated plates (POLYGRAM®SIL/UV254). Flash chromatography: Merck silica gel 60 (40–63 μm) with technical grade solvents. NMR: Spectra were recorded on Bruker AV VIII 400 or 600 spectrometers in the solvents indicated. The solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$: $\delta_C = 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H = 7.26$ ppm; CD_3OD: $\delta_C = 49.0$ ppm; residual CHD_2OD in CD_3OD: $\delta_H = 3.31$ ppm; CD_2Cl_2: $\delta_C = 54.0$ ppm; residual $CHDCl_2$ in CD_2Cl_2: $\delta_H = 5.32$ ppm). FT-IR spectra were obtained on Thermo Scientific Nicolet 6700 and reported in frequency of the absorption (cm^{-1}). High resolution mass

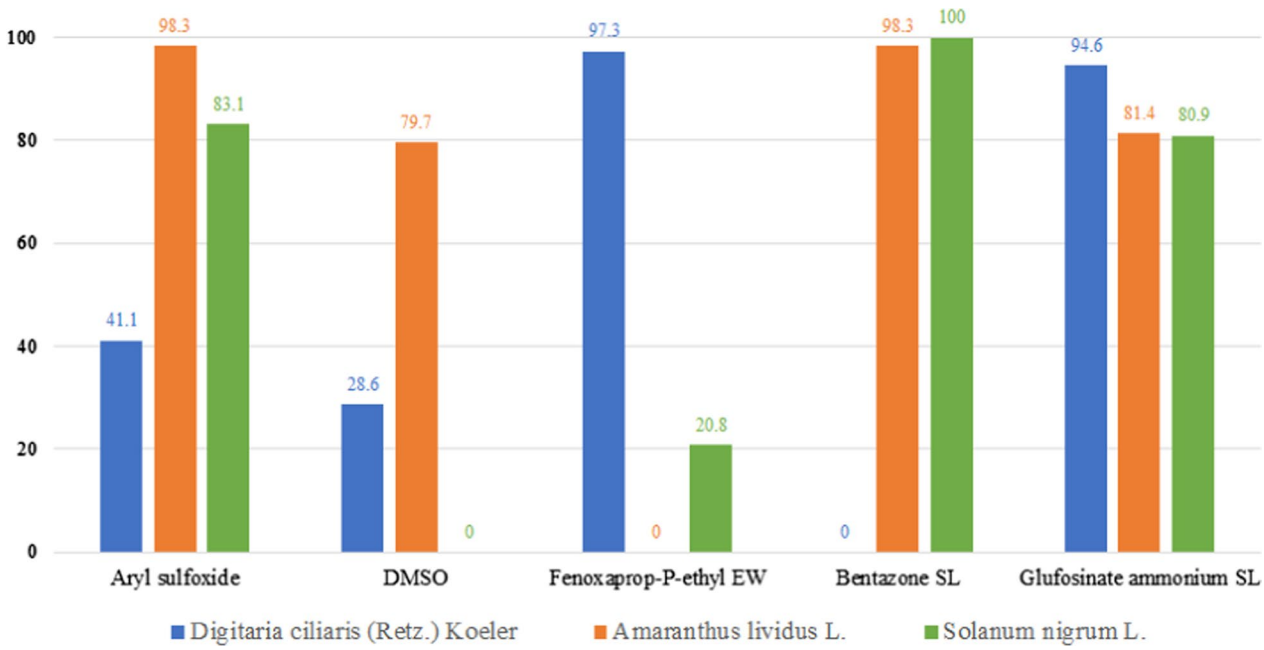


Fig. 1 Herbicide treatment on the three weeds. (control value up to 100%)

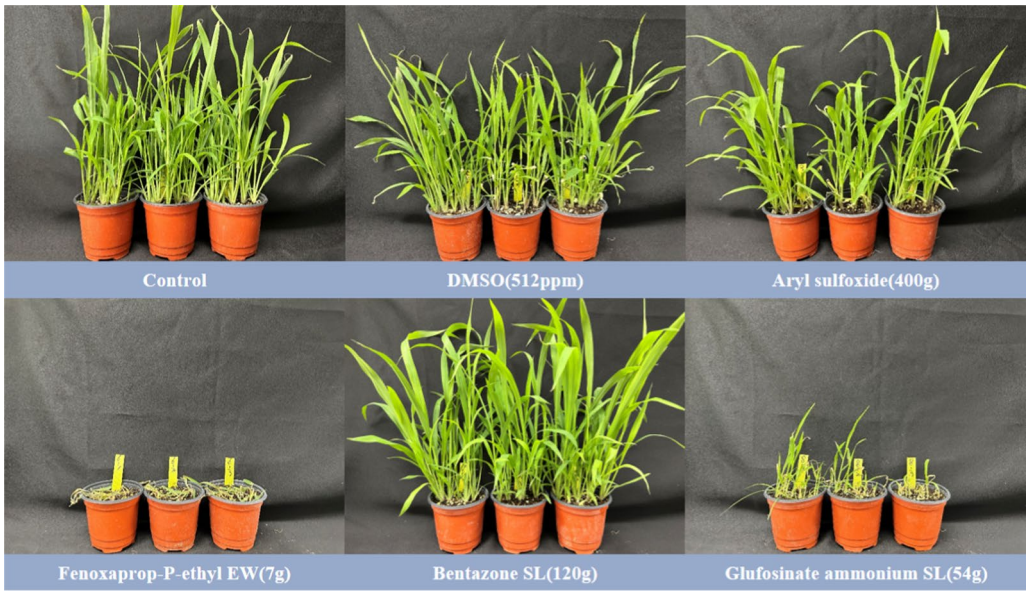


Fig. 2 Herbicidal effect of aryl sulfoxide by 400g a.i/10a on *Digitaria ciliaris (Retz.)* Koeler 15 days after application

Fig. 3 Herbicidal effect of aryl sulfoxide by 400g a.i/10a on *Amaranthus lividus* L. 15 days after application

spectra (HRMS) were recorded on an AB SCIEX Q-TOF 5600 mass spectrometer. Optical rotation ($[\alpha]_D^{20}$ and $[\alpha]_D^{25}$): Krüss P8000-T, 10 cm/1 mL cell. Unless otherwise noted, all commercially available compounds (Acros, Aldrich, Alfa Aesar, TCI) were used as received. Melting points were determined on a A. KRÜSS OPTRONIC M3000.

Preparation of (ethynylsulfinyl)benzene (5)

To a stirred solution of crude ethynylsulfanyl-benzene **9**—carried out from compound **7** (17.0 mL, 11.7 g, 0.120 mol, 1.20 equiv.) without any purification—in CH_2Cl_2 (500 mL) was added *m*-chloroperbenzoic acid (70–75% w/w, 29.5 g, 0.120 mol, 1.20 equiv.) at 0 °C. After stirring at 0 °C for 24 h, the reaction was quenched

Fig. 4 Herbicidal effect of aryl sulfoxide by 400g a.i/10a on *Solanum nigrum* L. 15 days after application

with a saturated $NaHCO_3$ solution (100 mL). After phase separation, the aqueous phase was rinsed with Et_2O (3×100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc, 8:2) afforded (ethynylsulfinyl)benzene (10.8 g, 72% over three steps) as a brown oil. The spectral data were consistent with the reported one. Spectral characteristics were identical to those previously reported [14].

Results/discussion

Chemistry

The selection of sulfoxide 5 for this study was motivated by its structural flexibility. Retaining the sulfoxide core, the arene substituent can be readily interchanged with other arenes, while the alkyne substituent provides the opportunity to accommodate various nucleophiles. This strategic choice offers the potential for structural diversification and the exploration of a broader range of derivatives.

Preparation of phenyl ethynyl sulfoxide (**5**) was done following reported procedures. Treating ethynyl silane (**6**) with a strong base at low temperature generates a deprotonated terminal alkyne. Then, diphenyl disulfide was added to the reaction mixture slowly. Later, obtained sulfide **8** was desilylated under basic conditions to give ethynyl(phenyl)sulfane **9** [13]. Treating compound **9** with oxidant *m*CPBA afforded the desired (ethynylsulfinyl) benzene **5** [14] in 72% isolated yield.

These chemical steps were scalable and robust overall.

Biology

To evaluate the herbicidal efficacy of the newly discovered aryl sulfoxide with demonstrated herbicidal potential, we prepared pots with *Digitaria ciliaris* (Retz.) Koeler, *Amaranthus lividus* L., *Solanum nigrum* L. and conducted a comparative analysis by treating the three distinct weed species with three herbicides: fenoxaprop-P-ethyl EW, bentazone SL, and glufosinate ammonium SL, all known for their herbicidal properties [16]. Additionally, to serve as a comparative baseline, we included weeds treated solely with DMSO, as the substances were dissolved in DMSO prior to application (Figs. 1, 2, 3, 4). This approach enabled a comprehensive assessment of the herbicidal effects of the aryl sulfoxide compound.

While *Solanum nigrum L.* exhibited no discernible changes upon treatment with DMSO, *Digitaria ciliaris* (Retz.) Koeler showed a slight herbicidal effect (28.6%), and *Amaranthus lividus* L. displayed a significantly high herbicidal effect (79.7%) (Table 1). These results indicate that the DMSO solvent itself possesses herbicidal effects and underscore the significance of investigating the potential of the sulfoxide functional group [15].

When the solution of aryl sulfoxide dissolved in DMSO was applied, a noticeable increase in herbicidal efficacy (between 10 and 20%) was observed for both *Digitaria ciliaris* (Retz.) Koeler and *Amaranthus lividus* L., compared to the treatment with DMSO alone. Notably, *Amaranthus lividus* L. displayed a remarkable

Table 1 Herbicidal efficacies of treatments sulfoxide **5** and comparison with commercial herbicides[a,b,c,d]

Treatments	10a per a.i	*Digitaria ciliaris* (Retz.) Koeler			*Amaranthus lividus L*			Solanum *nigrum* L		
		Number of plants	Fresh weight	Control value	Number of plants	Fresh weight	Control value	Number of plants	Fresh weight	Control value
Ary1 sulfoxide (5)	400 g	7.3	6.6	41.1	4.3	0.1	98.3	7.3	3.1	83.1
DMSO	512 ppm	9.0	8.0	28.6	6.3	1.2	79.7	8.7	18.6	0
Fenoxaprop-P-ethyl EW	7 g	6.0	0.3	97.3	7.0	7.2	0	8.7	14.5	20.8
Bentazone SL	120g	8.0	11.5	0	1.7	0.1	98.3	0.0	0.0	100
Glufosinate ammonium SL	54 g	7.0	0.6	94.6	3.3	1.1	81.4	3.7	3.5	80.9
Control	–	8.3	11.2	–	6.7	5.9	–	8.0	18.3	–

[a] Weight measured 15 days after the herbicide treatment, [b] Number of plants in a Pot [c] Fresh weight (g/Pot), [d] Control value (%)

herbicidal rate of 98.3%, nearly eradicating the species. In the case of *Solanum nigrum* L., the herbicidal rate significantly increased to 83.1%, demonstrating a clear enhancement.

The effectiveness of aryl sulfoxide stands out when compared to fenoxaprop-P-ethyl. Fenoxaprop-P-ethyl exhibits relatively high herbicidal potency against *Digitaria ciliaris* (Retz.) Koeler. However, its efficacy against *Solanum nigrum* L. is notably lower than that of aryl sulfoxide. Particularly concerning *Amaranthus lividus* L., the application of fenoxaprop-P-ethyl yielded no herbicidal effect at all. indicating inferior results compared to the treatment even with DMSO alone.

While bentazone demonstrated remarkably high herbicidal rates (98.3% for *Amaranthus lividus* L. and 100% for *Solanum nigrum* L.), it exhibited no herbicidal effect on *Digitaria ciliaris* (Retz.) Koeler. Glufosinate ammonium displayed positive activity across all three weeds species. However, in the case of *Amaranthus lividus* L., aryl sulfoxide exhibited superior activity compared to glufosinate ammonium.

Comparing the characteristics of the weeds, *Digitaria ciliaris* (Retz.) Koeler is known as a grass weed, whereas *Amaranthus lividus* L. and *Solanum nigrum* L. are broadleaf weeds. As a result, these two weed types exhibit similar trends in response to herbicide treatments. Unlike fenoxaprop-P-ethyl, known for its effectiveness against grass weeds, both aryl sulfoxide and bentazone show stronger effectiveness against broadleaf weeds. Remarkably, aryl sulfoxide demonstrates moderate efficacy against both grass and broadleaf weeds, potentially positioning it as a more competitive herbicide option.

In conclusion, we have developed an adaptable sulfoxide scaffold with potential utility as a herbicide through a concise four-step synthesis. This structural framework offers the advantage of ease in diversification, equipped with suitable sites for further derivatization. In contrast to available commercial herbicides, this compound exhibited substantial herbicidal activity against broadleaf weeds such as *Amaranthus lividus* L. and *Solanum nigrum* L. Ongoing synthetic endeavors to produce sulfoxide derivatives featuring the core structure are underway, and comprehensive results of herbicidal screening tests will be revealed in the near future.

Abbreviations

Ar	Argon
DAA	Days after anthesis
DMSO	Dimethyl sulfoxide
NMR	Nuclear magnetic resonance
THF	Tetrahydrofuran

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Author contributions
All authors equally contributed to the study conception and design. HK synthesized and characterized materials. IH and SR prepared and carried out the biological assays. YK and KH prepared the manuscript.

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Availability of data and material
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
All authors declare no conflict of interest.

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16. The three herbicides (fenoxaprop-P-ethyl EW 7%, bentazone SL 40%, and glufosinate ammonium SL 18%) as products were provided by SUNGBO Chemicals

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