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Design, Synthesis, and Antifeedant Activity Evaluation of 13/14-Arylthioether Matrine Derivatives

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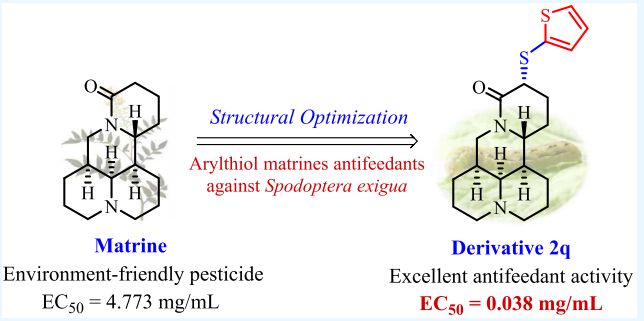
ABSTRACT: Introducing a sulfur atom into active agricultural molecules is an important strategy for pesticide development. Matrine, an environmentally friendly botanical pesticide, has the advantage of being easily degraded and has drawn attention in the agricultural field. To explore the novel matrine-type pesticides, in this study, we designed and synthesized 13/14-arylthioether matrine derivatives by introducing various aryl sulfide motifs into bioactive matrine. Most of the synthesized arylthioether matrines exhibited good antifeedant activity against *Spodoptera exigua*. Among them, compound **2q** showed the best antifeedant effect with an EC_{50} value of 0.038 mg/mL, which is approximately 125-fold more activity than matrine and reached the activity level of commercial standard azadirachtin A. Furthermore, compound **2q** exhibited an inhibitory effect on antifeedant-related enzyme carboxylesterase (CarE) from *S. exigua*. In short, the high activity of arylthioether matrines offers new insights into developing new antifeedants.



1. INTRODUCTION

Spodoptera exigua (Hübner) is a polyphagous pest that feeds on both foliage and fruit of host plants.[1] As a destructive secondary pest, it causes severe crop reduction and considerable economic losses worldwide.[2] The control of pest infestation currently relies on the use of chemical insecticides including antifeedants, repellants, and growth regulators. However, the long-term repeated use of chemical insecticides causes serious negative effects on the natural environment and human health, and even increases risks of insect resistance.[3−5] The plant-derived pesticides have the advantage of easy degradation and have become the source of inspiration for developing novel safe pesticides.[6,7] Structural modification of plant-derived agriculturally active compounds is an important method to improve their bioavailability or efficacy.[8,9] Pyrethroid insecticides (allethrin, permethrin, and fenvalerate)[10] and neonicotine insecticides (thiacloprid, imidacloprid, and thiamethoxam)[11] based on the structures of natural products have been developed and have great impact on crop protection.

Matrine is a naturally occurring quinolizidine alkaloid from the roots of *Sophora flavescens* (Leguminosae). Besides its use as a bioactive precursor for developing antineoplastic and antiviral agents,[12−14] matrine has promising agricultural properties, such as insecticidal, bacteriostatic, and acaricidal effects.[15] Matrine presents the advantage of being easily degraded and has been used as an environmentally friendly pesticide in China. However, when compared to chemical pesticides, the low activity of matrine limits its application when compared to the chemical pesticides.[15,16] Although the D-ring modification of matrine continues unabated in recent years, many studies mainly concentrate on its anticancer pharmacological activities,[17−19] and only a limited number of agriculture-related modifications are reported to find active agrochemicals. It has been found that the structural optimization at C-13 in the D-ring afforded a few potent bioactive compounds exhibiting good cytotoxic effects on Sf9 insect ovarian cells and insecticidal activities.[20,21] A series of 14 arylmatrine derivatives that had good insecticidal effects were synthesized *via* Pd-catalyzed one-pot reaction in our previous work.[22] The above structures indicate that various functional moieties at C-13 and C-14 positions might bring positive effects on agricultural activity and prove the feasibility of optimizing matrine through rational modification.

Sulfur-containing compounds play a significant role in the current applied crop protection research. Over one-third of agrochemicals contain at least one sulfur atom.[23,24] The common commercial examples include the dithiolane-class fungicide isoprothiolane,[25] the selective internal absorption-conducting triazine herbicide prometryn,[26] and the hydrox-

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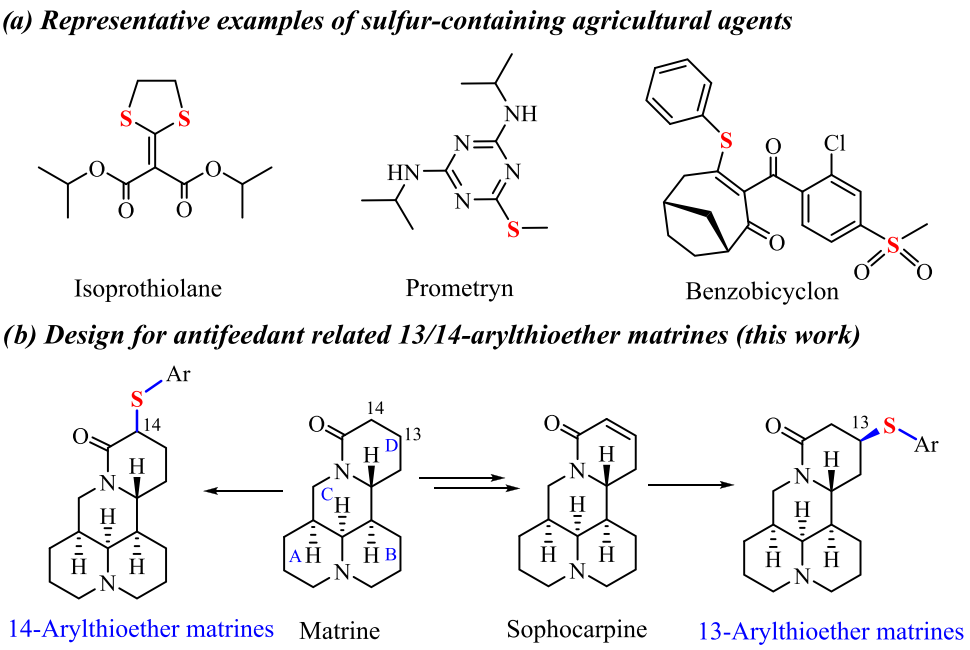
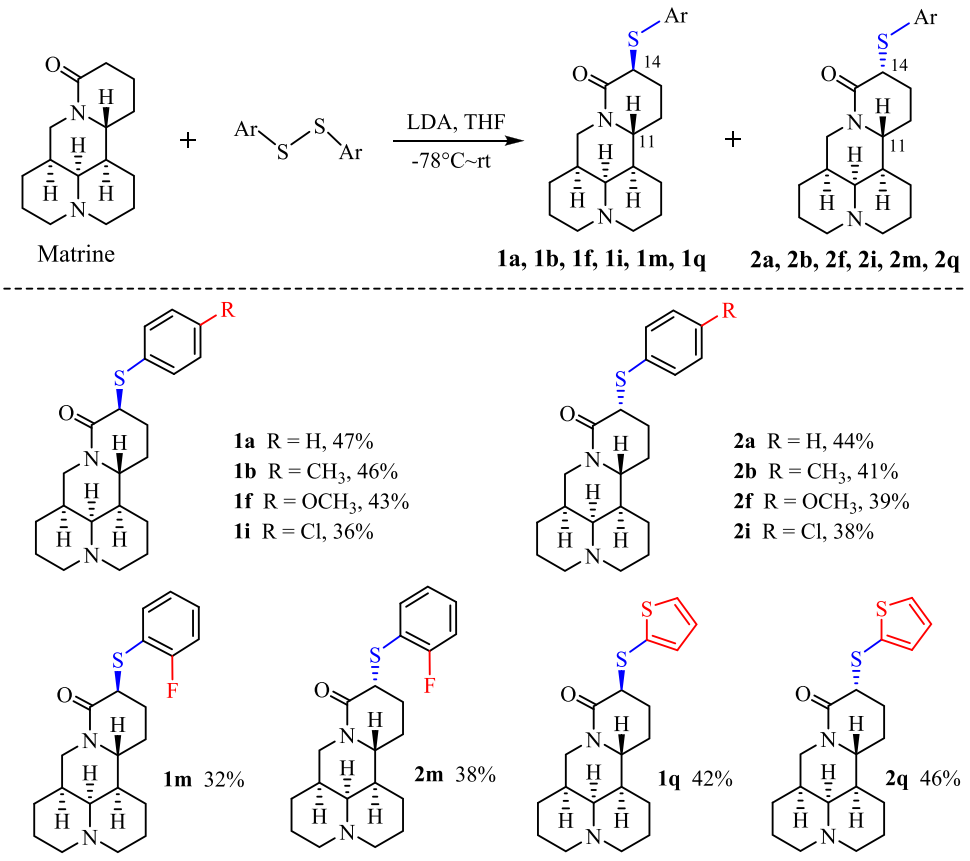


Figure 1. Representative sulfur-containing agricultural agents and synthetic strategy for arylthioether matrines.

Scheme 1. Preparation of 14-Arylthioether Matrine Derivatives



yphenylpyruvate-inhibiting herbicide benzobicyclon (Figure 1a).[27] In light of this fact, introducing a sulfur atom might enhance the agricultural properties of the leading compound, which is an important strategy for designing new agrochemicals. Nevertheless, the modification of matrine by linking it with arylthioethers or arylthiols to construct matrine derivatives has been underexplored. As an extension to our continued studies on matrine-derived antifeedants,[22] a series of 13/14-thiolphenylmatrine derivatives were designed and synthesized (Figure 1b), with the goal of improving their antifeedant activity. Among these matrine-like compounds, derivative **2q** could be developed as a novel potent pesticide with excellent antifeedant properties against *S. exigua*. The

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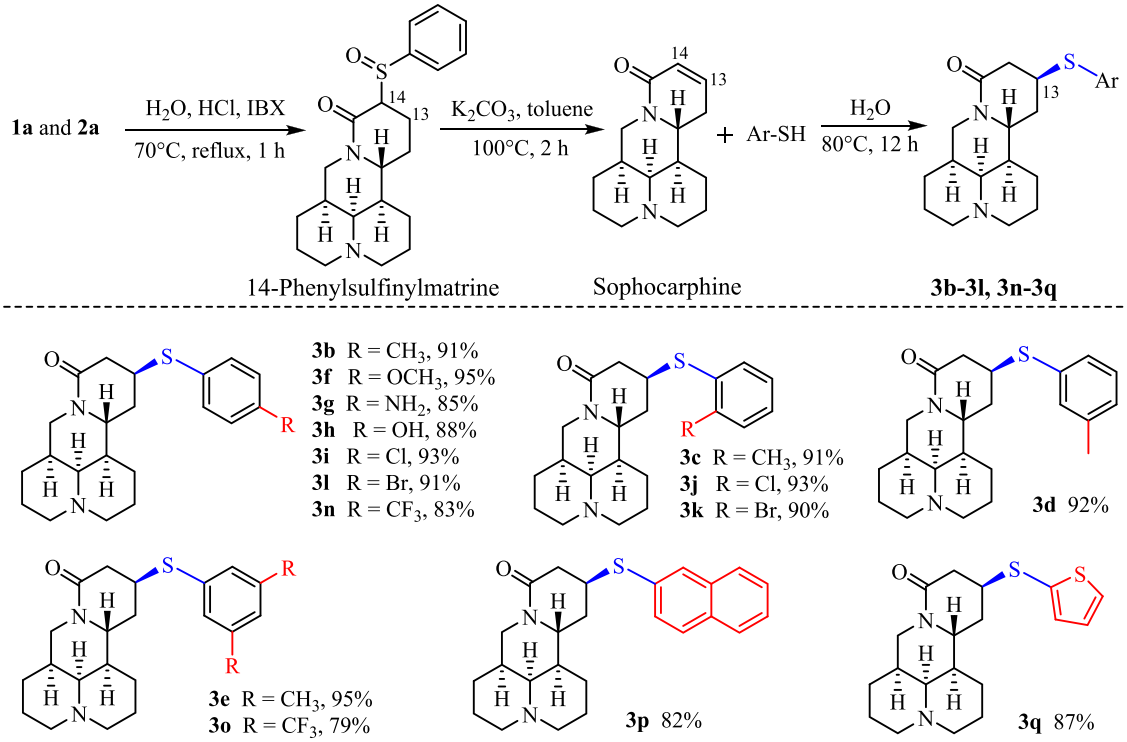
Scheme 2. Preparation of 13-Arylthio Matrine Derivatives



present study would provide new light for new matrine-type antifeedant development.

2. RESULTS AND DISCUSSION

2.1. Chemistry. 14-Arylthioether matrine derivatives were synthesized as shown in Scheme 1. Under the metal-free and environmentally friendly basic reaction conditions,[28] matrine was treated with deprotonating reagent lithium diisopropylamide (LDA) followed by reacting it with diphenyl sulfides to obtain 14-thiolphenylmatrines. Notably, the α-substitution of matrine with aryl sulfide is nonstereoselective, thus yielding an equimolar mixture of epimers in total yields of 70−91%. When diphenyl disulfide was employed as a substrate, a pair of 14-thiolphenylmatrine derivatives **1a** and **2a** were furnished in yields of 47 and 44%, respectively. Diaryl disulfides bearing electron-donating alkoxy (bis(4-methoxyphenyl)disulfide) or alkyl group (*p*-tolyl disulfide) participated in the nucleophilic substitution to result in desired derivatives **1f** and **2f**, and **1b** and **2b** in yield of 39−46%. Diaryl disulfides substituted with electron-withdrawing groups, such halogens (Cl, F), afforded the expected products **1i**/**2i** and **1m**/**2m** in 32−38% yield. Furthermore, the reaction worked quite well with heteroaryl sulfide, thereby generating matrine derivatives **1q** (42% yield) and **2q** (46% yield).

Products **1** and **2** possessing 14*S* and 14*R* configurations, respectively, can be directly separated by column chromatography on silica gel. The proton signal in the ^{1}H NMR spectra explained the configuration of C-14. According to the X-ray analysis reported in the literature,[29] the absolute configuration of parent compound matrine had been unquestionably confirmed as 5*S*,6*S*,7*R*,11*R*. When Hβ-11 and the aromatic ring from the C-14 substituent were located at the same orientation, the signal of Hβ-11 was relatively downfield due to the shielding effect; thereby, the configuration in the series of products **1** was established as 14*S*. In contrast, the signal of Hβ-11 was upfield in product **2** with a 14*R* configuration, in which Hβ-11 and the aromatic ring were located at opposite orientations.

The structure of the saturated D-ring in matrine is unfavorable for directly introducing groups into the C-13 position. Its analogue, sophocarpine, possessing an α,β-unsaturated ketone motif is convenient for the following structure derivatization. Hence, unseparated mixtures **1a** and **2a** were oxidized to 14-phenylsulfinylmatrine under the presence of 2-iodoxybenzoic acid (IBX). The intermediate 14-phenylsulfinylmatrine was further treated with potassium carbonate in refluxed toluene to provide sophocarpine in 75% yield (Scheme 2). The 13-thiolmatrine derivatives were further synthesized *via* the Michael addition reaction. Generally, the target products were obtained by reacting sophocarpine and different thiolphenols in the aqueous phase at 80 °C for 12 h. This easy-to-operate transformation under very mild reaction conditions avoided the use of strong alkaline and was compatible with all referred substrates. Whether functionalization groups with electron-withdrawing or electron-donating substituents were used, the reaction efficiencies were kept at an excellent level. Thiolphenols containing the active hydrogen, such as 4-aminobenzenethiol and 4-mercaptophenol, were tolerated and successfully afforded the related derivatives **3g** (85% yield) and **3h** (88% yield), respectively. Likewise, naphthalene-2-thiol participated in the reaction to afford **3p** in a relatively high yield of 82%. Thiophenethiol could also react with sophocarpine to give the corresponding product **3q** in 87% yield. Notably, the present nucleophilic addition reaction had the accurate stereoselectivity to provide 13-arylthiomatrines. To illustrate the structural information on 13-arylthiomatrines, the colorless crystal of **3h** was obtained by recrystallization in petroleum ether−CH_2Cl_2. The absolute configuration of 13-thiophenylmatrine derivatives was verified by single-crystal X-ray diffraction of compound **3h** (Figure 2).

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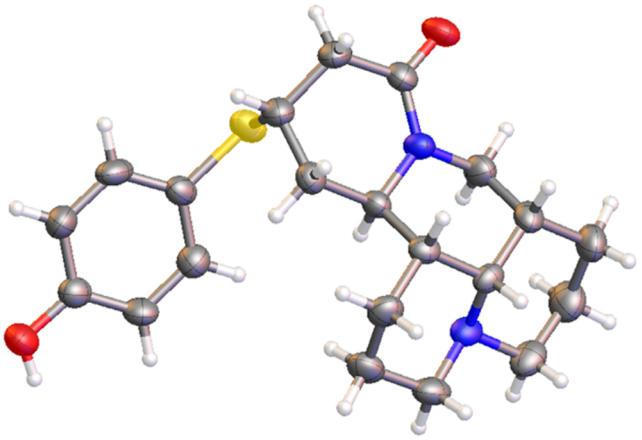


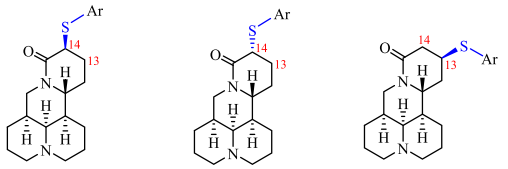
Figure 2. Crystal structure of compound **3h** (CCDC 2254603).

Detailed interpretation of the X-ray structure of **3h** suggested that H-11 and H-13 were adopted and located at the opposite orientation, and the absolute configuration was defined as 5*S*,6*S*,7*R*,11*R*,13*S*. All structures of 13/14-arylthiomatrines were characterized by NMR and high-resolution electron spray ionization mass spectrometry (HRESIMS).

2.2. Biological Evaluation. *2.2.1. Antifeedant Activity against S. exigua and Structure–Activity Relationship (SAR) Analysis.* 12 14-arylthioether and 15 13-arylthioether matrine derivatives were evaluated for antifeedant activity against the third-instar larvae of *S. exigua* (Hübner) by means of the leaf-disk choice method. The commercial insecticide azadirachtin A was used as a positive control. According to our previous structure optimization work of matrine,[22] the initial concentration was chosen as 5 mg/mL. The primary results showed that most of synthesized derivatives have remarkable antifeedant activity against *S. exigua*. As shown in Table 1, for 14-arylthioether matrine derivatives, introducing a phenyl ring with an electron-withdrawing group (**1i**, **2i**, **1m**, and **2m**) had an obvious positive influence on the increase of activity when compared with the presence of the electron-donating group (**1a**, **2a**, **1b**, **2b**, **1f** and **2f**). The biological properties of molecule drugs are greatly affected by spatial configuration. For instance, the antifungal activity of (1*S*,2*R*)-bitertanol was 4.3–314.7 times higher than that of other stereoisomers against eight different pathogenic fungi.[30] Hence, the discussion of chiral pesticides at the stereoisomer level is of great benefit in understanding the structure–activity relationship (Figure 3). For the derivatives containing an electron-donating group in the benzene ring, the 14*S*-isomer (**1a**, **1b**, and **1f**) showed a preferable effect compared with the 14*R*-isomer (**2a**, **2b**, and **2f**). When halogens were introduced, the stereochemical change had different effects on the antifeedant activity of target compounds against *S. exigua*, *i.e.*, the activity of the 14*R*-isomer was better than that of the 14*S*-isomer. Furthermore, compounds **1q** and **2q** containing the heterocyclic thiophene substituent showed strongly improved activity compared to the parent compound matrine, indicating that the thiophene unit was the best group to improve antifeedant activity.

Among the 13-arylthio matrine derivatives, the antifeedant activity of compounds **3b–d**, which possessed a methyl substituent in the benzyl ring, showed moderate activities. The same trend was observed in compound **3e** which had two methyl groups, indicating that the introduction of methyl was unfavorable to the enhancement of antifeedant capacity.

Table 1. Antifeedant Activity of Matrine Derivatives against *S. exigua*[a]



1a, 1b, 1f, 1i, 1m, 1q **2a, 2b, 2f, 2i, 2m, 2q** **3b-3l, 3n-3q**

compound	Ar	configuration	FR (%)
1a	phenyl	14*S*	42.2 ± 2.1
1b	4-CH_3-phenyl	14*S*	43.8 ± 1.3
1f	4-OCH_3-phenyl	14*S*	54.5 ± 0.9
1i	4-Cl-phenyl	14*S*	73.2 ± 3.5
1m	2-F-phenyl	14*S*	70.5 ± 4.2
1q	thienyl	14*S*	90.2 ± 3.7
2a	phenyl	14*R*	31.4 ± 1.8
2b	4-CH_3-phenyl	14*R*	41.0 ± 0.6
2f	4-OCH_3-phenyl	14*R*	44.2 ± 2.2
2i	4-Cl-phenyl	14*R*	93.9 ± 2.5
2m	2-F-phenyl	14*R*	71.5 ± 1.8
2q	thienyl	14*R*	95.1 ± 1.7
3b	4-CH_3-phenyl	13*S*	68.8 ± 0.9
3c	2-CH_3-phenyl	13*S*	69.4 ± 1.3
3d	3-CH_3-phenyl	13*S*	70.4 ± 1.2
3e	3,5-di-CH_3-phenyl	13*S*	65.6 ± 1.9
3f	4-OCH_3-phenyl	13*S*	47.1 ± 3.0
3g	4-NH_2-phenyl	13*S*	52.8 ± 0.7
3h	4-OH-phenyl	13*S*	45.9 ± 1.1
3i	4-Cl-phenyl	13*S*	73.2 ± 1.9
3j	2-Cl-phenyl	13*S*	71.9 ± 2.3
3k	2-Br-phenyl	13*S*	59.5 ± 0.4
3l	4-Br-phenyl	13*S*	60.1 ± 2.4
3n	4-CF_3-phenyl	13*S*	57.9 ± 0.5
3o	3,5-di-CF_3-phenyl	13*S*	46.1 ± 3.2
3p	naphthyl	13*S*	62.0 ± 1.8
3q	thienyl	13*S*	51.8 ± 3.6
matrine			22.0 ± 5.2
azadirachtin A			95.3 ± 0.3

[a]Concentration at 5 mg/mL.

Furthermore, compounds **3f–h** which had methoxyl, amidogen, and hydroxy as aromatic substituents, respectively, were both inactive or gave extremely weak activity. A somewhat better antifeedant effect against *S. exigua* was achieved with halogen as the substituent. Among them, Cl-containing compounds **3i** and **3j** showed higher activity than Br- or F-containing derivatives (**3k–o**). In addition, the structural modification in different positions affected their bioactivity. For example, compounds **3q** and **3i** having sulfur-containing functional substitution at the C-14 position displayed relatively weak antifeedant activity. However, the corresponding C-13 analogues (**3q** and **3i**) exhibited satisfactory effects, demonstrating that the modification of the C-13 position could potentially yield benefits. In short, compounds **2i**, **1q**, and **2q** displayed excellent efficacy with an antifeedant ratio of over 90% at 5 mg/mL. In order to further evaluate the novel matrine-type pesticide, the EC_{50} was measured as shown in Table 2. The EC_{50} values of compounds **2i**, **1q**, and **2q** were 0.126, 0.215, and 0.038 mg/mL, respectively. Remarkably, derivative **2q** displayed the best antifeedant activity, which was 119-fold more activity than matrine (EC_{50} = 4.773 mg/mL),

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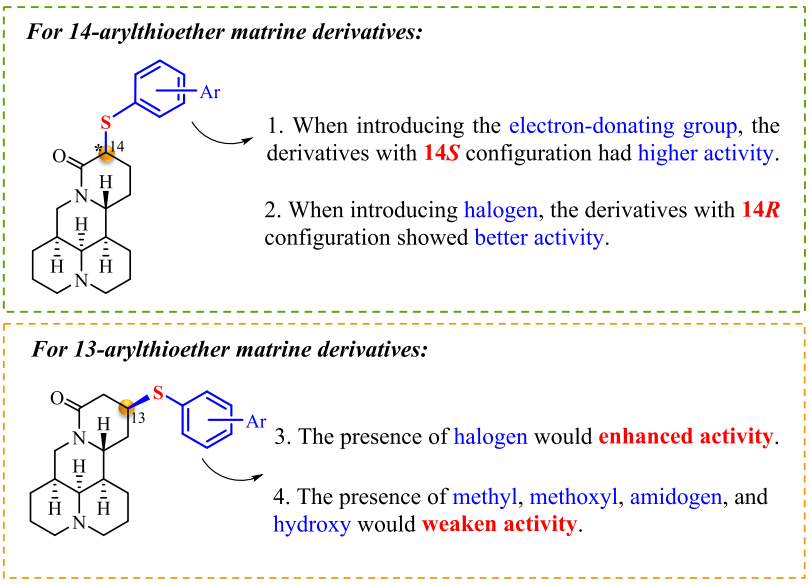

Figure 3. SARs of 13/14-arylthioether matrine derivatives on antifeedant activities.

Table 2. EC_{50} Values of Selected Compounds for Antifeedant Activity against *S. exigua*

compound	regression equation	EC_{50} (mg/mL)	95% confidence interval	R^2
2i	$y = 1.6x^3 + 0.97x^2 + 1.1x + 1.27$	0.126	0.038−0.226	0.992
1q	$y = 4.43x^3 - 2.86x^2 + 0.59x + 1.55$	0.215	0.001−0.547	0.998
2q	$y = 1.76x^3 + 0.7x^2 + 0.66x + 1.59$	0.038	0.003−0.118	0.999
matrine	$y = 2.46x^3 + 1.27x^2 + 0.48x + 1.5$	4.773	4.029−5.989	0.999
azadirachtin A	$y = -0.71x^3 - 0.98x^2 + 5.12x - 2.88$	0.040	0.004−0.120	0.998

Table 3. Enzyme Inhibitory Assay of Compound 2q at 5 mg/mL

	inhibition rate (%)			
compound	AChE	CarE	MFO	GSTs
2q	44.93 ± 0.09	95.99 ± 0.01	25.38 ± 0.23	40.18 ± 0.08
azadirachtin A	−21.73 ± 0.03	46.57 ± 0.06	38.43 ± 0.30	52.78 ± 0.04

and was comparable to that of commercial azadirachtin A (EC_{50} = 0.040 mg/mL). The above results demonstrated the great potential of sulfur-containing molecules for new leading compounds in the agricultural field.

*2.2.2. Antifeedant-Related Enzyme Inhibitory Effects of Compound **2q**.* Acetylcholinesterase (AChE) as a critical hydrolytic enzyme in the nervous system takes part in the equilibrate neural signal transaction through catalyzing of acetylcholine signal in the synaptic cleft. Enhanced AChE inhibition rate disrupts concordance of the neuromuscular activity and has substantial effects on behavior of insects. The metabolic detoxification enzymes including carboxylesterase (CarE), mixed-function oxidase (MFO), and glutathione *S*-transferases (GSTs) are associated with insecticide resistance, which protect insects from toxic compounds. It is generally accepted that these groups of enzymes are considered as vital target sites for the development of insecticides.[2,31] Therefore, the inhibitory activities of compound **2q** against AChE, CarE, MFO, and GSTs from *S. exigua* were further evaluated (Table 3). Notably, when larvae were treated with compound **2q** at a concentration of 5 mg/mL, **2q** presented potent CarE inhibitory activity with a percentage inhibition up to 95.99% compared to the positive control azadirachtin A (with a percentage inhibition of 46.57%). Furthermore, compound **2q** showed an extremely mild inhibitory effect against AChE and GSTs, with percent inhibition of 44.93 and 40.18%, respectively, but another enzyme MFO was not obviously inhibited at the same concentration. CarE may be the crucial target responsible for the excellent antifeedant activity against *S. exigua* of bioactive compound **2q**.

To clarify the binding interaction between the most promising antifeedant **2q** and CarE, the molecular docking study was carried out with CarE (PDB ID: 5TYJ) to reveal the possible binding sites and relevant binding energy. The molecular docking results showed that ligand **2q** bonds well with CarE (energy of −8.1 kcal/mol), which verified the *in vitro* enzyme inhibitory assay. As shown in Figure 4, the parent fraction of matrine analogue **2q** interacts with Met 308, Met 362, Leu 365, Arg 303, Lys 306, and Ile 358 through alkyl interactions. The thiophene heterocycle provided an amide−π stacked with Glu 294 and an alkyl interaction with Ile 139. The target ligand **2q** exhibited favorable interactions with CarE, which suggests that the modification of matrine could be potentially beneficial in enhancing activity.

3. CONCLUSIONS

Structure optimization of bioactive natural products has become an effective strategy for the development of new green pesticides. In the present study, 27 sulfur-containing matrine derivatives were designed and synthesized to explore

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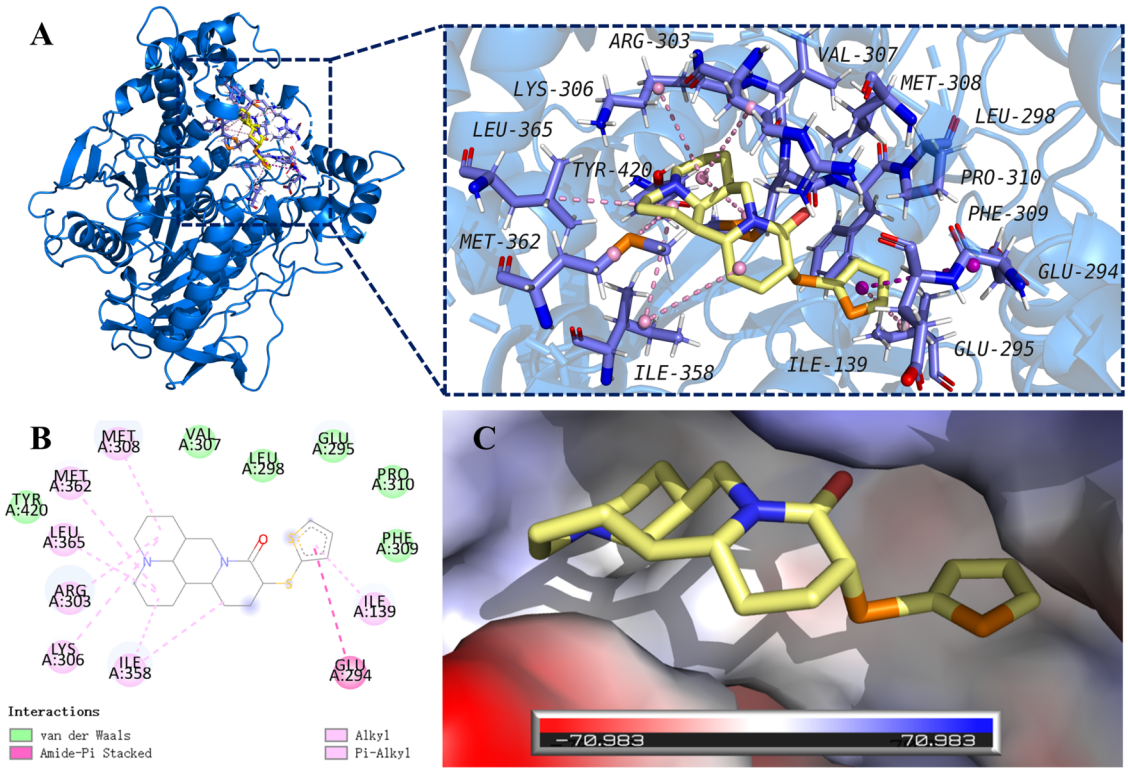

Figure 4. Molecular docking result of compound **2q** with CarE (PDB ID: 5TYJ). (A) Best docking posture of compound **2q** with CarE. (B) Residues of the active site involved in docking and types of bonds involved in docking. Alkyl and π−alkyl bonds are shown as light pink lines, and the amide−π bond is shown as a pink line. (C) The best docking posture of compound **2q** in the binding pocket. Carbon atoms of the ligand are represented as yellow sticks, nitrogen atoms as blue sticks, and sulfur atoms as yellow sticks.

the relationship between arylthioether substituents in matrine and antifeedant activity against *S. exigua*. Structure−activity relationship analysis indicated that the thiophene moiety was conducive to enhancing the antifeedant activity, and the modification of the C-13 position could potentially yield benefits in finding potential matrine-type antifeedant. Among them, compound **2q** (EC_{50} values of 0.038 mg/mL) showed excellent antifeedant effect against *S. exigua* with fold of 125 higher than that of parent compound matrine (EC_{50} = 4.773 mg/mL). Compared with commercial plant pesticide azadirachtin A, compound **2q** showed a similar potential, which is a promising lead compound for further matrine-type insecticide discovery. Furthermore, compound **2q** exhibited a potent inhibitory effect on the metabolic detoxification enzyme CarE. The above results might provide important guidance for the development and practical application of novel matrine-type pesticides.

4. MATERIALS AND METHODS

4.1. Chemistry. *4.1.1. General Information.* Matrine was purchased from Baoji Runyu Biotechnology Co., Ltd., with a purity of >98%. Unless otherwise specified, all reagents involved with this investigation were commercially available as analytical or chemical grades and were used directly without any purification. Reactions were carried out under an argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (GF 245) and visualized by UV irradiation (254 nm), spraying with Dragendorff's reagent, or staining with iodine. Column chromatography was carried out using silica gel H (Qingdao Sea Chemical Factory, Qingdao, People's Republic of China) under pressure. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on Bruker AV 400 and 600 nuclear magnetic resonance instruments. Chemical shifts were recorded in ppm relative to tetramethylsilane as the internal standard. HRESIMS spectra were recorded on a Waters Acquity UPLC/Xevo G2-S Q-Tof mass spectrometer.

4.1.2. General Preparation of 14-Arylthioether Matrine Derivatives. According to the reported method,[28] *n*-butyllithium (2.4 M in hexane, 0.73 mL) was dropwise added to a stirred solution of diisopropylamine (0.125 mL, 1.137 mmol) in tetrahydrofuran (THF) (1.7 mL) under an argon atmosphere at −78 °C. The mixture was stirred at −78 °C for 2 h followed by the addition of a solution of matrine (0.1 g, 0.4 mmol) in THF (0.5 mL) using a syringe pump. After the mixture was stirred for 30 min, the reaction temperature was increased to 25 °C within 10 min. After stirring for an additional 2 h at 25 °C, diphenyl sulfide (0.41 mmol) in THF (0.5 mL) was added. The reaction mixture was further stirred for 2 h at 25 °C before being quenched by adding saturated aqueous Na_2CO_3 (2 mL). The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. Then, the mixture was concentrated *in vacuo* and purified. The isomers were isolated by column chromatography on silica gel (eluent: CH_2Cl_2/CH_3OH from 80:1 to 60:1) to afford matrine derivatives (**1a**/**2a**, **1b**/**2b**, **1f**/**2f**, **1i**/**2i**, **1m**/**2m**, and **1q**/**2q**), with total yields of 70−91%.

*4.1.2.1. Compound **1a**.* White amorphous powder, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.30−7.23 (m, 3H), 4.40 (dd, J = 12.4, 4.4 Hz, 1H), 3.85 (br s, 1H), 3.78 (dd, J = 9.6, 5.2 Hz, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.80−2.77 (m, 2H), 2.22−2.17 (m, 1H), 2.08−2.04 (m, 2H),

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1.96−1.93 (m, 2H), 1.85 (d, J = 14.4 Hz, 1H), 1.76−1.66 (m, 5H), 1.60−1.50 (m, 2H), 1.48−1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 134.9, 132.7 × 2, 129.0 × 2, 127.4, 63.8, 57.3, 57.2, 53.5, 49.8, 43.0, 42.6, 35.6, 27.6, 26.5, 26.4, 25.2, 21.2, 20.8; HRESIMS (m/z) 357.2010 $[M + H]^+$ (calcd for $C_{21}H_{28}N_2OS$, 357.2001).

4.1.2.2. Compound ***2a****.* White amorphous powder, 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.31−7.24 (m, 3H), 4.41 (dd, J = 12.4, 4.4 Hz, 1H), 3.91 (br s, 1H), 3.82−3.81 (m, 1H), 3.11 (t, J = 12.8 Hz, 1H), 2.85−2.80 (m, 2H), 2.07 (br s, 1H), 1.99−1.95 (m, 2H), 1.92−1.86 (m, 2H), 1.85−1.83 (m, 1H), 1.74−1.68 (m, 5H), 1.56−1.52 (m, 2H), 1.45−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 135.0, 132.3 × 2, 129.1 × 2, 127.5, 63.7, 57.3, 57.2, 53.4, 48.8, 43.6, 42.0, 35.3, 27.8, 26.5, 25.7, 23.1, 21.3, 20.9; HRESIMS (m/z) 357.2010 $[M + H]^+$ (calcd for $C_{21}H_{28}N_2OS$, 357.2001).

4.1.2.3. Compound ***1b****.* White amorphous powder, 46% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.86−3.82 (m, 1H), 3.75 (dd, J = 9.6, 5.4 Hz, 1H), 3.11 (t, J = 12.6 Hz, 1H), 2.82 (dd, J = 10.2 Hz, 1H), 2.78 (dd, J = 10.2 Hz, 1H), 2.32 (s, 3H), 2.21−2.16 (m, 1H), 2.08 (br s, 1H), 2.06−2.01 (m, 1H), 1.97−1.91 (m, 2H), 1.84 (d, J = 13.8 Hz, 1H), 1.74−1.66 (m, 5H), 1.59−1.57 (m, 1H), 1.52−1.49 (m, 1H), 1.45−1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 137.8, 133.6 × 2, 130.8, 129.8 × 2, 63.8, 57.3, 57.2, 53.5, 50.1, 42.9, 42.5, 35.5, 29.8, 27.8, 26.4, 26.3, 25.0, 21.3, 20.8; HRESIMS (m/z) 371.2148 $[M + H]^+$ (calcd for $C_{22}H_{31}N_2OS$, 371.2157).

4.1.2.4. Compound ***2b****.* White amorphous powder, 41% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.84 (br t, J = 3.6 Hz, 1H), 3.80−3.77 (m, 1H), 3.06 (t, J = 12.4 Hz, 1H), 2.81 (d, J = 10.2 Hz, 1H), 2.76 (d, J = 10.2 Hz, 1H), 2.31 (s, 3H), 2.06 (br s, 1H), 1.96−1.93 (m, 4H), 1.91−1.88 (m, 2H), 1.82 (br s, 1H), 1.71−1.65 (m, 3H), 1.59 (d, J = 13.2 Hz, 1H), 1.54−1.49 (m, 1H), 1.44−1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1678, 137.8, 133.0 × 2, 131.1, 129.9 × 2, 63.7, 57.3, 57.2, 53.3, 49.2, 43.5, 41.9, 35.3, 32.9, 30.2, 27.3, 25.4, 22.9, 21.2, 19.0; HRESIMS (m/z) 371.2148 $[M + H]^+$ (calcd for $C_{22}H_{31}N_2OS$, 371.2157).

4.1.2.5. Compound ***1f****.* White amorphous powder, 43% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.84−3.81 (m, 1H), 3.79 (s, 3H), 3.66 (dd, J = 9.0, 4.8 Hz, 1H), 3.06 (t, J = 12.6 Hz, 1H), 2.82 (d, J = 10.2 Hz, 1H), 2.77 (d, J = 10.2 Hz, 1H), 2.19−2.17 (m, 1H), 2.07 (br s, 1H), 2.01−1.90 (m, 3H), 1.83 (d, J = 15.0 Hz, 1H), 1.77−1.65 (m, 5H), 1.58−1.56 (m, 1H), 1.52−1.50 (m, 1H), 1.43−1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 159.9, 136.2 × 2, 124.6, 114.5 × 2, 63.8, 57.3, 57.2, 55.4, 53.5, 50.6, 42.9, 42.5, 35.5, 29.8, 27.8, 26.2, 25.0, 21.2, 20.8; HRESIMS (m/z) 387.2094 $[M + H]^+$ (calcd for $C_{22}H_{31}N_2O_2S$, 387.2106).

4.1.2.6. Compound ***2f****.* White amorphous powder, 39% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 4.39 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.81−3.74 (m, 2H), 3.06 (t, J = 13.2 Hz, 1H), 2.83 (d, J = 13.2 Hz, 1H), 2.76 (d, J = 13.2 Hz, 1H), 2.06 (br s, 1H), 1.97−1.89 (m, 6H), 1.72−1.66 (m, 4H), 1.62 (d, J = 15.6 Hz, 1H), 1.54−1.52 (m, 1H), 1.44−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.9, 135.8 × 2, 125.0, 114.7 × 2, 63.6, 57.3, 57.2, 55.5, 53.3, 50.0, 43.5, 41.9, 35.3, 29.8, 27.8, 26.4, 25.4, 21.3, 20.8; HRESIMS (m/z) 387.2094 $[M + H]^+$ (calcd for $C_{22}H_{31}N_2O_2S$, 387.2106).

4.1.2.7. Compound ***1i****.* White amorphous powder, 36% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46−7.45 (m, 2H), 7.26−7.24 (m, 2H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.88−3.84 (m, 1H), 3.75 (dd, J = 9.6, 4.8 Hz, 1H), 3.12 (t, J = 12.6 Hz, 1H), 2.83 (d, J = 10.8 Hz, 1H), 2.78 (d, J = 10.8 Hz, 1H), 2.20−2.18 (m, 1H), 2.10−2.07 (m, 2H), 1.97−1.92 (m, 2H), 1.84 (d, J = 14.4 Hz, 1H), 1.74−1.66 (m, 5H), 1.59−1.57 (m, 1H), 1.51−1.48 (m, 1H), 1.45−1.38 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 134.1 × 2, 133.6, 133.5, 129.1 × 2, 63.8, 57.3, 57.2, 53.5, 50.0, 43.1, 42.6, 35.6, 29.8, 27.8, 26.5, 25.3, 21.1, 20.8; HRESIMS (m/z) 392.1620 $[M + H]^+$ (calcd for $C_{21}H_{28}ClN_2OS$, 391.1611).

4.1.2.8. Compound ***2i****.* White amorphous powder, 38% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.27−7.26 (m, 2H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.85 (br t, J = 5.4 Hz, 1H), 3.83−3.81 (m, 1H), 3.09 (t, J = 8.4 Hz, 1H), 2.84 (d, J = 10.8 Hz, 1H), 2.79 (d, J = 10.8 Hz, 1H), 2.08 (br s, 1H), 2.01−1.95 (m, 4H), 1.91−1.89 (m, 1H), 1.83−1.66 (m, 5H), 1.62 (d, J = 12.6 Hz, 1H), 1.55−1.51 (m, 1H), 1.47−1.41 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 133.7, 133.6, 133.5 × 2, 129.2 × 2, 63.5, 57.3, 57.2, 53.4, 48.9, 43.7, 42.0, 35.4, 27.8, 26.4, 25.8, 23.1, 21.3, 20.9; HRESIMS (m/z) 392.1620 $[M + H]^+$ (calcd for $C_{21}H_{27}ClN_2OS$, 391.1611).

4.1.2.9. Compound ***1m****.* White amorphous powder, 32% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (td, J = 7.2, 1.8 Hz, 1H), 7.28−7.24 (m, 1H), 7.09−7.04 (m, 2H), 4.38 (dd, J = 13.2, 4.8 Hz, 1H), 3.96 (dd, J = 9.6, 4.8 Hz, 1H), 3.88−3.84 (m, 1H), 3.12 (t, J = 12.6 Hz, 1H), 2.83 (d, J = 10.8 Hz, 1H), 2.78 (d, J = 10.8 Hz, 1H), 2.22−2.19 (m, 1H), 2.10 (br t, J = 3.0 Hz, 1H), 2.03−1.98 (m, 1H), 1.95−1.93 (m, 2H), 1.84 (d, J = 14.4 Hz, 1H), 1.72−1.65 (m, 5H), 1.59−1.57 (m, 1H), 1.53−1.50 (m, 1H), 1.46−1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 163.9 (J = 245.0 Hz), 135.7, 129.8 (J = 8.0 Hz), 124.6 (J = 4.0 Hz), 121.6 (J = 18.0 Hz), 115.7 (J = 23.0 Hz), 63.7, 57.32, 57.29, 53.5, 48.6, 43.8, 42.5, 35.5, 29.8, 27.8, 26.4, 25.5, 21.3, 20.8; HRESIMS (m/z) 375.1911 $[M + H]^+$ (calcd for $C_{21}H_{28}FN_2OS$, 375.1906).

4.1.2.10. Compound ***2m****.* White amorphous powder, 38% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (td, J = 7.8, 1.8 Hz, 1H), 7.28−7.24 (m, 1H), 7.11 (td, J = 7.2, 1.2 Hz, 1H), 7.07−7.04 (m, 1H), 4.36 (dd, J = 12.6, 4.2 Hz, 1H), 3.95−3.94 (m, 1H), 3.82−3.82 (m, 1H), 3.07 (t, J = 12.6 Hz, 1H), 2.83 (d, J = 12.6 Hz, 1H), 2.78 (d, J = 12.6 Hz, 1H), 2.08 (s, 1H), 1.97−1.92 (m, 5H), 1.90−1.87 (m, 2H), 1.77−1.70 (m, 3H), 1.67 (d, J = 15.0 Hz, 1H), 1.63 (d, J = 12.6 Hz, 1H), 1.52−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 162.5 (J = 245.0 Hz), 135.2, 129.9 (J = 8.0 Hz), 124.6 (J = 4.0 Hz), 121.4 (J = 18.0 Hz), 115.8 (J = 23.0 Hz), 63.7, 57.3, 57.2, 53.3, 47.7, 43.5, 41.9, 35.3, 27.7, 26.3, 25.5, 23.0, 21.1, 20.8; HRESIMS (m/z) 375.1911 $[M + H]^+$ (calcd for $C_{21}H_{28}FN_2OS$, 375.1906).

4.1.2.11. Compound ***1q****.* White amorphous powder, 42% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (dd, J = 5.4, 1.2 Hz, 1H), 7.21 (dd, J = 3.6, 1.2 Hz, 1H), 6.98 (dd, J = 5.4, 1.2 Hz, 1H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 3.82−3.78 (m, 1H), 3.66 (dd, J = 10.2, 5.4 Hz, 1H), 3.09 (t, J = 12.6 Hz, 1H), 2.82 (d, J = 10.8 Hz, 1H), 2.77 (d, J = 10.8 Hz, 1H), 2.22−2.17 (m, 1H), 2.06 (br s, 1H), 2.05−2.01 (m, 1H), 1.97−1.91 (m, 2H), 1.83 (d, J = 13.8 Hz, 1H), 1.76−1.66 (m, 5H), 1.61−1.56 (m, 1H), 1.53−1.50 (m, 1H), 1.44−1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 136.1, 132.1, 130.8, 127.6, 63.7, 57.3, 57.3, 53.5, 52.0, 43.3, 42.4, 35.4, 27.8, 26.4, 26.3, 25.6, 21.1,

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20.8; HRESIMS (m/z) 363.1568 [M + H]$^+$ (calcd for $C_{19}H_{27}N_2OS_2$, 363.1565).

4.1.2.12. Compound ***2q***. White amorphous powder, 46% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (dd, J = 5.4, 1.2 Hz, 1H), 7.24 (dd, J = 3.6, 1.2 Hz, 1H), 6.99 (dd, J = 5.4, 1.2 Hz, 1H), 4.37 (dd, J = 13.2, 4.2 Hz, 1H), 3.81−3.80 (m, 1H), 3.77−3.76 (m, 1H), 3.06 (t, J = 12.0 Hz, 1H), 2.83 (d, J = 10.2 Hz, 1H), 2.78 (d, J = 10.2 Hz, 1H), 2.06 (s, 1H), 1.99−1.96 (m, 1H), 1.94−1.89 (m, 3H), 1.71−1.67 (m, 5H), 1.60 (d, J = 12.8 Hz, 1H), 1.54−1.49 (m, 1H), 1.44−1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 136.1, 132.1, 130.9, 127.8, 63.7, 57.3, 57.2, 53.3, 51.6, 43.2, 42.1, 35.4, 27.8, 26.4, 24.9, 22.6, 21.2, 20.8; HRESIMS (m/z) 363.1568 [M + H]$^+$ (calcd for $C_{19}H_{27}N_2OS_2$, 363.1565).

4.1.3. General Preparation of 13-Arylthioether Matrine Derivatives. A mixture of **1a** and **2a** (1.2 g, 3.35 mmol) was added to the solution of concentrated HCl (0.4 mL, 4.8 mmol) in H_2O (60 mL). After compounds **1a** and **2a** completely disappeared, IBX (2.8 g, 10 mmol) was added. The suspension was refluxed at 70 °C for 1 h. Then, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was filtered through filter paper to remove precipitate. The filtrate was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 14-pheylsulfinylmatrine. 14-Pheylsulfinylmatrine was used without further purification. K_2CO_3 (0.530 g, 3.32 mmol) was added to a stirred solution of 14-pheylsulfinylmatrine in toluene, and the reaction mixture was refluxed at 100 °C for 2 h. After the mixture cooled to room temperature, the reaction solution was added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel to give sophocarpine (0.62 g, 75% yield) as a white solid.

A solution of sophocarpine (0.03 g, 0.12 mmol) and various substituted phenyl thiols (0.180 mmol, 1.5 equiv) in 1 mL of H_2O was refluxed at 80 °C for 12 h. The resulting mixture was then extracted with EtOAc. The combined organic extracts were dried in Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was further purified by column chromatography on silica gel (eluent: CH_2Cl_2/CH_3OH from 90:1 to 60:1), affording 13-arylthio matrine derivatives (**3b**−**l** and **3n**−**q**) in 79−95% yields.

4.1.3.1. Compound ***3b***. White amorphous powder, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.36 (d, J = 12.8 Hz, 1H), 4.08−4.07 (m, 1H), 3.45 (s, 1H), 3.12 (t, J = 10.0 Hz, 1H), 2.81 (t, J = 13.6 Hz, 2H), 2.68−2.64 (m, 1H), 2.47−2.43 (m, 1H), 2.33 (s, 3H), 2.11 (s, 1H), 1.98−1.94 (m, 3H), 1.77−1.63 (m, 7H), 1.53−1.50 (m, 2H), 1.45−1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 138.2, 133.9 × 2, 130.0 × 2, 129.5, 64.0, 57.3 × 2, 51.2, 42.2, 42.0, 39.4, 38.3, 35.8, 31.1, 27.8, 26.7, 21.2 × 2, 20.8; HRESIMS (m/z) 371.2165[M + H]$^+$ (calcd for $C_{22}H_{31}N_2OS$, 371.2157).

4.1.3.2. Compound ***3c***. White amorphous powder, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.2, 2.0 Hz, 1H), 7.22−7.18 (m, 1H), 7.17−7.13 (m, 2H), 4.38 (dd, J = 12.4, 4.0 Hz, 1H), 4.11−4.06 (m, 1H), 3.53−3.52 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.81 (t, J = 13.6 Hz, 2H), 2.68 (dd, J = 17.2, 4.8 Hz, 1H), 2.49 (dd, J = 17.2, 4.8 Hz, 1H), 2.42 (3H, s), 2.11−2.04 (m, 2H), 1.98−1.91 (m, 3H), 1.77−1.66 (m, 5H), 1.58−1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 140.6, 132.9, 130.7, 127.8, 126.6 × 2, 64.0, 57.3 × 2, 51.3, 42.3, 42.0, 38.3 × 2, 35.7, 31.3, 27.8, 26.6, 21.3, 21.0, 20.7; HRESIMS (m/z) 371.2139 [M + H]$^+$ (calcd for $C_{22}H_{31}N_2OS$, 371.2157).

4.1.3.3. Compound ***3d***. White amorphous powder, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.23 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 4.33 (dd, J = 12.8, 4.4 Hz, 1H), 4.09−4.06 (m, 1H), 3.53−3.52 (m, 1H), 3.11 (t, J = 12.8 Hz, 1H), 2.80 (t, J = 14.4 Hz, 2H), 2.67 (dd, J = 17.2, 5.2 Hz, 1H), 2.44 (dd, J = 17.2, 5.2 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 1H), 2.04−1.90 (m, 5H), 1.77−1.65 (m, 4H), 1.58−1.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 139.0, 133.8, 133.0, 130.2, 129.0, 128.7, 64.0, 57.3 × 2, 51.2, 42.2, 42.0, 38.9, 38.3, 35.8, 31.1, 27.8, 26.6, 21.4, 21.2, 20.7; HRESIMS (m/z) 371.2170 [M + H]$^+$ (calcd for $C_{22}H_{31}N_2OS$, 371.2157).

4.1.3.4. Compound ***3e***. White amorphous powder, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.09 (m, 3H), 4.35 (dd, J = 12.6, 4.4 Hz, 1H), 4.12−4.06 (m, 1H), 3.33−3.31 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.81 (t, J = 13.6 Hz, 2H), 2.56 (dd, J = 16.0, 4.4 Hz, 1H), 2.51 (s, 6H), 2.39 (dd, J = 16.0, 4.4 Hz, 1H), 2.12−2.06 (m, 2H), 1.97−1.84 (m, 3H), 1.78−1.65 (m, 5H), 1.58−1.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 143.4 × 2, 131.7, 128.7, 128.4 × 2, 63.9, 57.3 × 2, 51.3, 42.5, 41.9, 39.0, 38.6, 35.7, 31.6, 27.8, 26.6, 22.3 × 2, 21.3, 20.7; HRESIMS (m/z) 385.2325 [M + H]$^+$ (calcd for $C_{23}H_{33}N_2OS$, 385.2314).

4.1.3.5. Compound ***3f***. White amorphous powder, 95% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 4.35 (d, J = 12.0 Hz, 1H), 4.07−4.06 (m, 1H), 3.80 (s, 3H), 3.35 (br s, 1H), 3.13 (t, J = 13.2 Hz, 1H), 2.84 (d, J = 12.0 Hz, 1H), 2.78 (d, J = 12.0 Hz, 1H), 2.64 (dd, J = 18.0, 7.2 Hz, 1H), 2.45 (dd, J = 18.0, 7.2 Hz, 1H), 2.11 (s, 1H), 1.97−1.92 (m, 4H), 1.75−1.65 (m, 5H), 1.52−1.50 (m, 2H), 1.44−1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.1, 136.5 × 2, 123.3, 114.8 × 2, 64.0, 57.3 × 2, 55.5, 51.2, 42.1, 42.0, 39.8, 38.2, 35.7, 31.0, 27.8, 26.6, 21.2, 20.7; HRESIMS (m/z) 387.2100 [M + H]$^+$ (calcd for $C_{22}H_{31}N_2O_2S$, 387.2106).

4.1.3.6. Compound ***3g***. White amorphous powder, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.25 (m, 2H), 6.61−6.59 (m, 2H), 4.34 (dd, J = 12.4, 4.4 Hz, 1H), 4.08−4.05 (m, 1H), 3.80 (br s, 2H), 3.27−3.26 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.84 (t, J = 15.6 Hz, 2H), 2.64 (dd, J = 17.2, 4.8 Hz, 1H), 2.44 (dd, J = 17.2, 4.8 Hz, 1H), 2.10 (s, 1H), 1.97−1.88 (m, 5H), 1.75−1.63 (m, 4H), 1.52−1.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 147.2, 136.8 × 2, 119.8, 115.1 × 2, 64.0, 57.3 × 2, 51.2, 42.0, 39.9, 38.2, 35.8, 34.9, 30.9, 27.8, 26.6, 21.2, 20.7; HRESIMS (m/z) 372.2065 [M + H]$^+$ (calcd for $C_{21}H_{30}N_3OS$, 372.2110).

4.1.3.7. Compound ***3h***. White amorphous powder, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.39 (dd, J = 12.8, 4.4 Hz, 1H), 4.13−4.06 (m, 1H), 3.38−3.36 (m, 1H), 3.23 (t, J = 12.4 Hz, 1H), 2.88−2.80 (m, 2H), 2.54 (dd, J = 22.0, 4.8 Hz, 1H), 2.46 (dd, J = 22.0, 4.8 Hz, 1H), 2.17−2.11 (m, 2H), 1.99−1.96 (m, 2H), 1.89−1.80 (m, 2H), 1.73−1.63 (m, 4H), 1.56−1.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 158.2, 137.0 × 2, 121.1, 116.6 × 2, 63.7, 57.3 × 2, 51.1, 42.9, 42.0, 40.0, 37.5, 35.6, 31.4, 27.8, 26.5, 21.2, 20.7; HRESIMS (m/z) 373.1942 [M + H]$^+$ (calcd for $C_{21}H_{29}N_2O_2S$, 373.1950).

4.1.3.8. Compound ***3i***. White amorphous powder, 93% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 7.8 Hz, 2H),

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7.31 (d, J = 7.8 Hz, 2H), 4.35 (dd, J = 12.6, 4.8 Hz, 1H), 4.08−4.06 (m, 1H), 3.54 (q, J = 7.2 Hz, 1H), 3.14 (t, J = 12.6 Hz, 1H), 2.83 (d, J = 11.4 Hz, 1H), 2.78 (d, J = 11.4 Hz, 1H), 2.69 (dd, J = 17.4, 4.8 Hz, 1H), 2.48 (dd, J = 17.4, 4.8 Hz, 1H), 2.11 (s, 1H), 2.05−2.00 (m, 1H), 1.97−1.89 (m, 3H), 1.74−1.66 (m, 4H), 1.60−1.38 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 134.5 × 2, 134.2, 132.0, 129.4 × 2, 63.9, 57.3 × 2, 51.1, 42.3, 42.0, 39.5, 38.2, 35.8, 31.2, 27.9, 26.7, 21.3, 20.8; HRESIMS (m/z) 391.1635 $[M + H]^+$ (calcd for $C_{21}H_{28}ClN_2OS$, 391.1611).

4.1.3.9. Compound ***3j***. White amorphous powder, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 5.6, 3.2 Hz, 1H), 7.73−7.41 (m, 1H), 7.22−7.20 (m, 2H), 4.37 (dd, J = 12.4, 4.4 Hz, 1H), 4.12−4.08 (m, 1H), 3.71−3.70 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.84 (t, J = 13.6 Hz, 2H), 2.66 (dd, J = 17.2, 6.8 Hz, 1H), 2.51 (dd, J = 17.2, 6.8 Hz, 1H), 2.12−2.04 (m, 2H), 1.98−1.92 (m, 3H), 1.80−1.65 (m, 5H), 1.58−1.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 137.2, 134.1, 132.6, 130.3, 129.0, 127.4, 63.9, 57.3 × 2, 51.2, 42.3, 42.0, 38.2, 37.7, 35.7, 31.1, 27.8, 26.6, 21.2, 20.7; HRESIMS (m/z) 391.1635 $[M + H]^+$ (calcd for $C_{21}H_{28}ClN_2OS$, 391.1611).

4.1.3.10. Compound ***3k***. White amorphous powder, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.6, 1.2 Hz, 1H), 7.44 (dd, J = 8.0, 1.6 Hz, 1H), 7.28 (td, J = 8.0, 2.0 Hz, 1H), 7.11 (td, J = 8.0, 2.0 Hz, 1H), 4.38 (dd, J = 12.8, 4.4 Hz, 1H), 4.11−4.08 (m, 1H), 3.71−3.69 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.80 (t, J = 14.4 Hz, 2H), 2.72 (dd, J = 16.4, 4.4 Hz, 1H), 2.46 (dd, J = 16.4, 4.4 Hz, 1H), 2.12−2.06 (m, 2H), 1.99−1.92 (m, 3H), 1.83−1.65 (m, 5H), 1.58−1.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 134.7, 133.6 × 2, 129.0, 128.0 × 2, 63.9, 57.3 × 2, 51.2, 42.3, 42.0, 38.2, 38.0, 35.7, 31.0, 27.7, 26.5, 21.1, 20.6; HRESIMS (m/z) 435.1119 $[M + H]^+$ (calcd for $C_{21}H_{28}BrN_2OS$, 435.1106).

4.1.3.11. Compound ***3l***. White amorphous powder, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.30−7.28 (m, 2H), 4.36 (dd, J = 12.8, 4.4 Hz, 1H), 4.06 (br s, 1H), 3.52−3.50 (m, 1H), 3.11 (t, J = 12.0 Hz, 1H), 2.80 (t, J = 14.4 Hz, 2H), 2.68 (dd, J = 17.2, 4.8 Hz, 1H), 2.43 (dd, J = 17.2, 4.8 Hz, 1H), 2.11 (s, 1H), 2.02−1.87 (m, 5H), 1.74−1.65 (m, 4H), 1.53−1.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.5, 132.2 × 2, 129.3 × 2, 122.0, 63.8, 57.2 × 2, 50.9, 42.2, 41.8, 39.1, 38.0, 35.6, 31.0, 27.7, 26.5, 21.1, 20.6; HRESIMS (m/z) 435.1117 $[M + H]^+$ (calcd for $C_{21}H_{28}BrN_2OS$, 435.1106).

4.1.3.12. Compound ***3n***. White amorphous powder, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 4.38 (dd, J = 12.8, 4.4 Hz, 1H), 4.08 (s, 1H), 3.71−3.67 (m, 1H), 3.13 (t, J = 12.4 Hz, 1H), 2.81 (br s, 2H), 2.70 (dd, J = 17.2, 4.8 Hz, 1H), 2.53 (dd, J = 17.2, 4.8 Hz, 1H), 2.13−2.06 (m, 2H), 1.97−1.91 (m, 3H), 1.84 (s, 1H), 1.77−1.66 (m, 4H), 1.55−1.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 139.1, 131.3 × 2, 129.5 (J = 33 Hz), 126.0 × 2 (J = 3 Hz), 122.7 (J = 270 Hz), 63.9, 57.3 × 2, 51.0, 42.4, 41.9, 38.4, 38.1, 35.7, 31.2, 27.8, 26.6, 21.2, 20.7; HRESIMS (m/z) 425.1830 $[M + H]^+$ (calcd for $C_{22}H_{28}F_3N_2OS$, 425.1874).

4.1.3.13. Compound ***3o***. White amorphous powder, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.72 (s, 1H), 4.38 (dd, J = 12.8, 4.4 Hz, 1H), 4.26−4.07 (m, 1H), 3.75−3.73 (m, 1H), 3.14 (t, J = 12.4 Hz, 1H), 2.84−2.81 (m, 2H), 2.73 (dd, J = 16.8, 4.4 Hz, 1H), 2.54 (dd, J = 16.8, 4.4 Hz, 1H), 2.43−2.14 (m, 1H), 2.10−2.05 (m, 1H), 2.00−1.92 (m, 3H), 1.74−1.66 (m, 5H), 1.57−1.41 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 138.0, 132.5 × 2 (J = 33 Hz), 131.0 × 2 (J = 3 Hz), 122.1 (J = 271.5 Hz), 121.0 (J = 3 HZ), 63.8, 57.4, 57.3, 51.0, 42.4, 42.0, 39.1, 38.0, 35.7, 31.2, 27.9, 26.6, 21.3, 20.7; HRESIMS (m/z) 493.1704 $[M + H]^+$ (calcd for $C_{23}H_{27}F_6N_2OS$, 493.1748).

4.1.3.14. Compound ***3p***. White amorphous powder, 82% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.81−7.76 (m, 3H), 7.50−7.47 (m, 3H), 4.38 (dd, J = 12.6, 4.2 Hz, 1H), 4.14−4.10 (m, 1H), 3.68−3.66 (m, 1H), 3.14 (t, J = 12.6 Hz, 1H), 2.83−2.78 (m, 2H), 2.73 (dd, J = 17.4, 5.4 Hz, 1H), 2.56 (dd, J = 17.4, 5.4 Hz, 1H), 2.11 (s, 1H), 2.09−2.05 (m, 1H), 1.97−1.92 (m, 3H), 1.75−1.67 (m, 5H), 1.57−1.50 (m, 3H), 1.42−1.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 133.8, 132.7, 131.9, 130.9, 130.1, 128.8, 127.8, 127.5, 126.8, 126.5, 64.0, 57.4, 57.3, 51.2, 42.3, 42.0, 39.0, 38.3, 35.8, 31.3, 27.9, 26.7, 21.3, 20.8; HRESIMS (m/z) 407.2163 $[M + H]^+$ (calcd for $C_{25}H_{31}N_2OS$, 407.2157).

4.1.3.15. Compound ***3q***. White amorphous powder, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 5.2, 1.2 Hz, 1H), 7.17−7.16 (m, 1H), 7.01−6.98 (m, 1H), 4.35 (dd, J = 12.8, 4.4 Hz, 1H), 4.11−4.08 (m, 1H), 3.32−3.30 (m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.84−2.77 (m, 2H), 2.64 (dd, J = 17.6, 4.4 Hz, 1H), 2.50 (dd, J = 17.6, 4.4 Hz, 1H), 2.11 (s, 1H), 2.01−1.91 (m, 4H), 1.77−1.63 (m, 5H), 1.49−1.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 136.6, 136.2, 130.9, 127.9, 64.0, 57.3 × 2, 51.1, 42.1, 41.6, 37.9, 35.8, 34.8, 30.8, 27.8, 26.6, 21.2, 20.8; HRESIMS (m/z) 363.1557 $[M + H]^+$ (calcd for $C_{19}H_{27}N_2OS_2$, 363.1565).

4.1.4. X-ray Crystallographic Analysis of Compound ***3h***. Colorless crystals of compound **3h** were recrystallized from petroleum ether/CH_2Cl_2 (about 5:1, v/v) at room temperature. X-ray data were collected on an Oxford Xcalibur Eos diffractometer with Mo Kα radiation (λ = 0.710 73 Å). Each structure was solved by direct methods using SHELXL-97, and all atoms were refined anisotropically using full-matrix least-squares difference Fourier techniques. Crystallographic data for the structure of **3h** have been deposited with the Cambridge Crystallographic Data Centre as supporting publication CCDC 2254603, respectively. Copies of these data can be obtained, free of charge, on application to the CCDC *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, U.K., fax: +441223 336033, email: deposit@ccdc.cam.ac.uk).

4.1.4.1. Crystallographic Data of Compound ***3h***. $C_{21}H_{28}N_2O_2S$, mass (M) = 372.51, monoclinic, a = 6.9783(5) Å, b = 16.0059(11) Å, c = 8.6756(8) Å, α = 90°, β = 91.027°, γ = 90°, V = 968.86(13) Å^3, Z = 2, T = 293.15 K, μ (Mo Kα) = 0.185 mm^{-1}, F (000) = 400.0, D_{calc} = 1.277 g/cm^3. A total of 4232 reflections were measured (6.37° ≤ 2θ ≤ 52.734°), containing 3389 unique reflections (R_{int} = 0.0217, R_{sigma} = 0.0551), which were used in all calculations. The final R_1 was 0.0493 ($I > 2\sigma(I)$) and wR_2 was 0.1162 (all data). The goodness of fit on F^2 was 1.065. Flack parameter = 0.05(7).

4.2. *In Vivo* Antifeedant Activity Assay. *S. exigua* (Hübner) used in this work was purchased from Henan Jiyuan Baiyun Industry Co., Ltd., P. R. China. The culture was continuously maintained on cabbage foliage at room temperature (24 ± 1 °C), 65 ± 5% relative humidity, and a photoperiod of 16:8 (L/D) in the laboratory.

The antifeedant activity of the synthesized compounds was estimated by the no-choice leaf-disk method.[32,33] The tested compounds were dissolved in acetone and then diluted to different concentration gradients with a 10% acetone−water

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solution (containing 0.2% Tween-80). Azadirachtin A was used as a positive control. Leaf disks of 5 cm diameter were punched from fresh leaves of *Brassica oleracea* using a borer. Then, treated leaf disks were painted with 20 μL of each dilution, and control leaf discs were treated with the same amount of an acetone−water solution. The treated leaf discs were allowed to dry at 38 °C in a drying oven for 6−8 h. After drying, one treated and one control disc were added to the same Petri dishes (150 mm in diameter), with wet filter paper at the bottom. Groups of five healthy third-instar larvae were selected and weighed to determine the average weight of each group (450 ± 50 mg). Larvae were starved 6 h prior to each bioassay and then were placed at the center of the Petri dish. After 24 h, larvae were removed from the Petri dish, and the cumulative consumptions of leaf area were measured by the coordinate paper chip method. Each treatment was replicated at least three times. The food reduction (FR) in each disk was determined using the equation: FR = (CK − T)/CK × 100% (CK is the control leaf disk area eaten; T is the treated leaf disk area eaten). Compounds with FR > 90% were tested in a dose−response experiment to calculate their EC_{50} value (the effective dose for 50% feeding reduction) and SD value using software Origin 2019.

4.3. Antifeedant-Related Enzyme Inhibitory Assay of Compound 2q. The test of antifeedant-related enzyme inhibitory effects was conducted according to the previous reports.[32] Similar-sized third-instar larvae of *S. exigua* were weighed, and 9 volumes of normal saline were added. The samples were centrifuged at 12 000 rpm for 20 min at 4 °C. 100 μL of supernatant was collected and dissolved in 0.1 M phosphate-buffered saline (PBS, pH 7.5) as the subsequent enzyme solution. The test compound **2q** and positive control (azadirachtin A) were dissolved in dimethyl sulfoxide (DMSO) and diluted with PBS to the tested concentration.

4.3.1. AChE Inhibitory Effect. 140 μL of PBS (0.1 M, pH 8.0), 10 μL of test compound solution, and 10 μL of diluted enzyme solution were mixed and incubated at 30 °C for 20 min. Then, 10 μL of 0.01 M acetylthiocholine iodide was added and incubated at 37 °C. After 20 min, 10 μL of 5,5′-dithiobis(2-nitrobenzoic acid) (0.01 M) was added to terminate the reaction. The absorbance was measured at 405 nm.

4.3.2. CarE Inhibitory Effect. 50 μL of diluted enzyme solution and 50 μL of test compound solution were mixed and incubated for 20 min; 50 μL of 0.01 M α-naphthylacetate was then added and incubated. After 20 min, 50 μL of diazoblue lauryl sulfate solution was added and the reaction was terminated. Absorbance was measured at 600 nm.

4.3.3. MFO Inhibitory Effect. 50 μL of diluted enzyme solution and 50 μL of test compound solution were mixed and incubated for 20 min. Then, 50 μL of 0.05 M paranitroanisole was added and incubated for another 20 min. The reaction was terminated with 40 μL of 0.01 M HCl. The absorbance was measured at 405 nm.

4.3.4. GSTs Inhibitory Effect. First, 50 μL of diluted enzyme solution and 50 μL of test compound solution were mixed and incubated for 20 min. Then, 50 μL of glutathione (0.01 M) and 50 μL of 1-chloro-2,4-dinitrobenzene (0.01 M) were added, and the absorbance was measured at 340 nm. Percentage inhibition (%) = $[(A_b - A_s)/A_b] \times 100\%$; A_b and A_S are the absorbances of the blank control and sample group, respectively.

4.4. Molecular Docking Analysis. Ligand−protein docking was performed using Autodock Vina 1.2.4, predicating the best ligand bonding pose of the ligand. The search space was defined by a 100 × 100 × 100 Å^3 box with a 0.592 Å spacing, with the center at X: 22.645; Y: 9.344; Z: −25.364, which encompassed the entire active site cavity of the CarE model. Docking simulation results were evaluated in terms of the total estimated binding energy. A CarE model was retrieved from the Protein Data Bank (https://www.rcsb.org/). The structural figures were drawn in PyMOL v 2.5.2.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05568.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

Single crystal diffraction of **3h** (CCDC 2254603) (CIF)

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Notes

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