Food Safety and Toxicology

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Turpentine derived secondary amines for sustainable crop protection: Synthesis, activity evaluation and QSAR study

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Abstract

In this study, we will report on the synthesis and application of efficient botanical agrochemicals from turpentine for sustainable crop protection. Two series of turpentine derived secondary amines were synthesized and identified by FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. The herbicidal activities against *Echinochloa crus-galli* were evaluated. The potential toxicity of the synthesized compounds was tested by MTT cytotoxicity analysis.

The effect of structure of the synthesized secondary amines and corresponding Schiff base compounds on their activities was investigated by Quantitative structure–activity relationship (QSAR) study. All target products were found to be low toxic, with similar or higher herbicidal activities than commercial herbicides diuron and Glyphosate. Results of QSAR study showed that a best four-descriptor QSAR model with r^2 of 0.880 and r_{loo}^2 of 0.818 was obtained. The four descriptors most relevant to the herbicidal activities are *the min valency of a N atom*, *the max total interaction for a C—H bond*, *the relative number of aromatic bonds*, and *the min partial charge (Q_{min})*.

Introduction

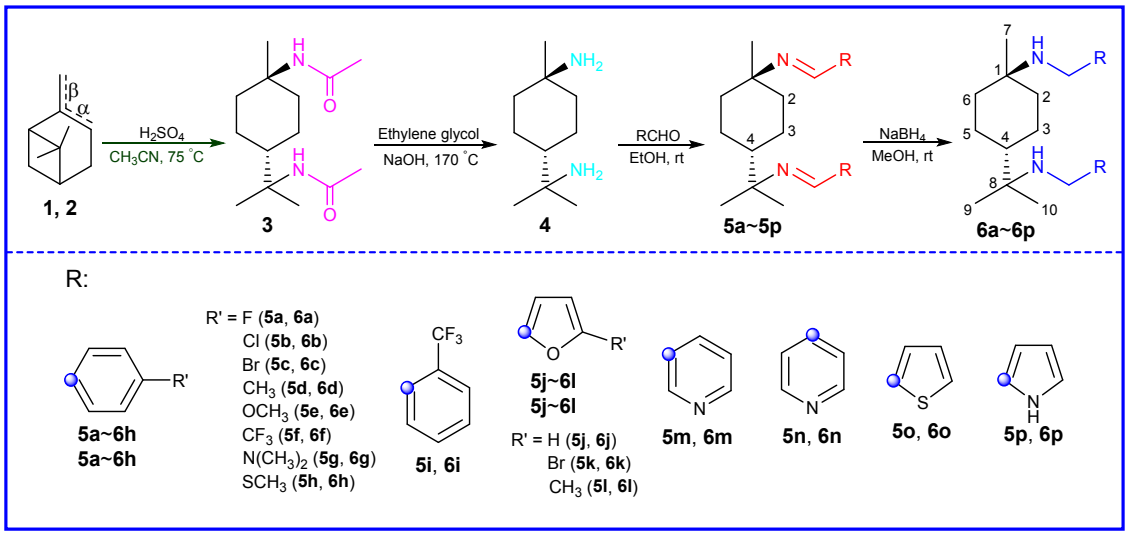
Weeds have a negative impact on food production due to the direct competition for nutrients, moisture, and light[1-3]. Yield losses caused by weeds in agriculture is greater than the reduction generated by disease, pests and insects[4-6]. In recent decades, synthetic herbicides have been the most reliable and economical weed control tools[7-8]. However, the application of synthetic herbicides accompanies increasing human health risk, environmental pollution and herbicidal resistance[9-11].

Therefore, the development for sustainable herbicides with high activity and low toxicity have attracted a lot of interests[10-14]. Relative to synthetic herbicides, most botanical herbicides extracted or derived from plants have received much more attention due to their lower toxicity and lower risk to mammals and ecological environments respectively[14-17].

Terpene is the most diverse group of secondary metabolic chemicals produced by plants, and represents the most abundant component in essential oils[3, 11, 17-20]. Mono- and sesquiterpenes can affect physiological processes in weeds and lead to the accumulation of

lipid globules in the cytoplasm or reduction in organelles[13]. This finding has attracted a lot of researchers to develop strategies for sustainable weed management[3, 11, 17-20].

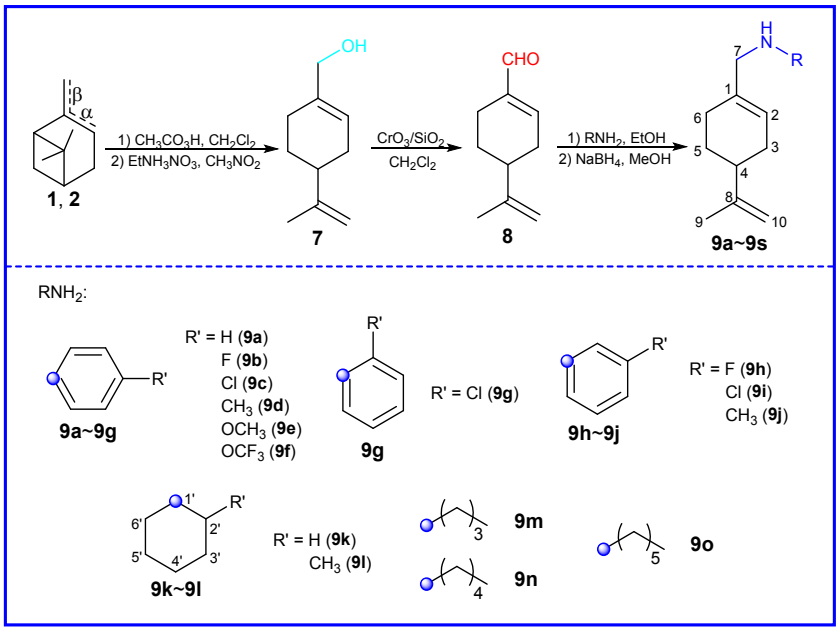
In our previous work, a series of monoterpene derivatives were synthesized and applied as herbicidal agrochemicals for weed management. Among them, *p*-menthane or *p*-menthene Schiff base compounds are found to possess low toxicity and high pre-emergence herbicidal activity against ryegrass[11, 18, 19]. However, there are some defects to the synthesis and application of Schiff base herbicides. The imine group (C=N) of Schiff base compounds are susceptible to hydrolysis and transamination by nucleophiles[21, 22]. It is difficult to separate and maintain the purified products since they decompose easily during column chromatography and eventually oxidize after prolonged storage.



Scheme 1. Synthesis route of *cis*-*p*-menthane type secondary amines

Previous studies showed that the NH groups in secondary amines are active sites of many pharmaceuticals and agrochemicals[23-25]. The design and synthesis of secondary amines is an area of growing interest. In previous reports, varieties of methods have been developed to synthesize secondary amines[26-28]. Nevertheless, traditional procedures are problematic because of harsh reaction conditions, low yields, and poor selectivity.

Selective hydrogenation of imine groups in Schiff bases using reducing agents is a very convenient and explicit route to prepare secondary amines. Through this procedure, secondary amines can be formed in mild conditions with high selectivity and yield[29-31]. In order to synthesize sustainable terpene derived botanical herbicides with higher activity, a novel and efficient method to prepare secondary amines from turpentine is reported in this paper (Scheme 1 and Scheme 2). The herbicidal activity of the obtained compounds against *Echinochloa crus-galli* was evaluated. The effect of structure on herbicidal activities of them was investigated by QSAR study.



Scheme 2. Synthesis route of *p*-menthene type secondary amine compounds

Experimental

Materials

cis-*p*-Menthane type Schiff base compounds (>98%) were synthesized and purified from turpentine according to our previous work[11, 19]. 4-(Methylthio) benzaldehyde (95%), *p*-anisaldehyde (98%), *p*-dimethylamino benzaldehyde (99%), 3-pyridine carboxaldehyde (98%), 4-pyridine carboxaldehyde (98%), pyrrole-2-carboxaldehyde (98%), 2-thiophene-

carboxaldehyde (98%), furfural (98%), aniline (99%), 4-fluoroaniline (98%), 4-chloroaniline (98%), 4-bromoaniline (99%), *p*-touidine (99%), *p*-anisidine (99%), 4-(trifluoromethoxy)aniline (98%), 2-chloroaniline (98%), 3-fluoroaniline (98%), 3-chloroaniline (99%), 3-toluidine (99%), cyclohexylamine (99%), 2-methylcyclohexylamine (98%, cis/trans mixture), *n*-butylamine (99%), amylamine (98%), n-hexylamine (99%), were comercial products from Aladdin Chemistry Co., LTD (Shanghai, China). *p*-Fluoro benzaldehyde (98%), *p*-chloro benzaldehyde (98%), *p*-bromo benzaldehyde (98%), *p*-methyl benzaldehyde (98%), *p*-methyl benzaldehyde (98%), 4-(trifluoromethyl) benzaldehyde (95%), 2-(trifluoromethyl) benzaldehyde (98%), 5-bromo-2-furaldehyde (98%) and 5-methyl-2-furaldehyde (98%) were obtained from Energy Chemical Co., Ltd (Shanghai, China). Perillaldehyde (98%) was purchased from Hunan Changsha kaimei flavor and fragrance Co., Ltd. Other reagents and solvents were commercial products used directly as received. *Echinochloa crus-galli* seeds were bought from Qingdao Dingsheng Seed Industry Co., Ltd (Qingdao, China).

Characterizations

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III HD 400 MHz spectrometer (Bruker, Germany) using DMSO-d_6 as the solvent and TMS as the internal standard. FT-IR spectra were determined by a Thermo Nicolet IS10 IR instrument (Thermo, USA). HRMS analysis were carried out on a Q-TOF6538 mass spectrometer (Agilent, USA). GC was performed on a Shimadzu GC-2014AF gas chromatography (Shimadzu, Japan). 0.25 mm i.d.×30 m quartz capillary column was applied for GC separation under the conditions as follows: holding for 2 min at 70 ℃, and raised to 100 ℃ at the rate of 3

℃/min and then raised to 270℃ at the rate of 10℃/min. Cytotoxicity assays were completed on a Winooski EL-X800 microplate reader (BioTek Instruments, lnc., USA).

Synthesis of *cis*-*p*-menthane type secondary amines

20 mmol *cis*-*p*-menthane type Schiff base was dissolved in a 250 mL round bottom flask containing 80 mL methanol. The system was cooled down to 0 ˚C in an ice water bath and then 50 mmol $NaBH_4$ total was added for three times over the course of 1 h. After the addition was complete, the mixture was stirred at room temperature for 0.5~1 h. After stirring, 5 mL cold distilled water was added to quench excess $NaBH_4$. The mixture was extracted with CH_2Cl_2 and washed with distilled water three times. The organic phase was collected, dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. A thick oil was obtained as the crude product and purified by recrystallization or column chromatography.

Synthesis of *p*-menthene type secondary amines

20 mmol perillaldehyde and 20 mmol corresponding amine were stirred in a 250 mL round bottom flask containing 80 mL methanol for 24 h. The system was cooled down to 0 ˚C and 50 mmol $NaBH_4$ total was added into the vigorously stirred solution for three times over the course of 1 h and reacted for another 0.5~1 h. The formed products were treated similar to that of *cis*-*p*-menthane type secondary amines and purified by column chromatograph.

Cytotoxicity Assays (MTT)

The potential cytotoxicity of the synthesized compounds was tested through the following procedure: The test compounds were dissolved with DMSO and diluted by complete medium. Dulbecco's modified Eagle's medium (DMEM) (containing 10% fetal

bovine serum (FBS) and 4 mmol/L L-glutamine) was used as the complete medium for BALB/c 3T3. Kaighn's Modification of Ham's F-12 containing 15% FBS was used as the complete medium for HUVEC to 10 μmol/L (The concentration of DMSO is lower than 0.1%). The BALB/c 3T3 or HUVEC were removed from ampoules preserved in liquid nitrogen and rapidly unfrozen in a 37 ˚C water bath. The cellular suspensions were transferred to culture flasks containing corresponding complete medium. The cultures were incubated at 37 ˚C in a humidified atmosphere of 5% CO_2 and 95% air. After 1–2 generations of reproduction, the cells were cultivated in a 96-well plate at a density of 3.5×10^3 cells per 100 μL complete medium for 24 h under the same culture conditions (37 ˚C, 5% CO_2 and 95% air). Afterwards, 100 μL test sample solution and 100 μL complete medium (as negative control) were added separately to the plate and incubated at 37 ˚C for 48 h. 20 μL 5 mg/mL MTT solution was added and allowed to incubate for a further 4 h. The supernatant was discarded. The formed crystals were dissolved by 0.15 mL DMSO and then the absorbance at a wavelength of 490 nm was recorded. At the end of incubation, the wells were treated by 20 μL of 5 mg/mL MTT solution. After further incubating for 4 h, the supernatants were discarded. The formazone crystals formed in living cells were dissolved in 150 μL of DMSO per well. The plates were shaken for 5 s and the absorbance was recorded at 490 nm using a microplate reader. The cytotoxicity was calculated according to equation 1:

$$y = \frac{X_2 - X_1}{X_2} \quad (1)$$

where y is the inhibition rate of cell growth, x_2 is the optical density (OD) value of the blank control group and x_1 is the OD value of experimental group.

Herbicidal activity evaluation

Echinochloa crus-galli was chosen as the test plant seeds for primary herbicide bioassay tests. The evaluation test was performed in a typical procedure: 10, 5.0, 2.5, 1.25, 0.625, 0.3125, 0.1563, 0.0781, 0.0391, 0.0195 and 0.0098 mmol test compounds were dissolved with 1.00 ml DMF and diluted with 1‰ aqueous solution of Tween-80 in 100 mL volumetric flasks to 10.0, 5.0, 2.5, 1.25, 0.625, 0.3125, 0.1563, 0.0781, 0.0391, 0.0195 and 0.0098 mmol/L respectively. The seeds were soaked in 28 ˚C water for 12 h and then transferred to moist gauze in a porcelain dish. Afterwards, the seeds were cultivated in dark at 30 ˚C until germination. 10 mL of the test solutions or blank control solution were added to a 9 cm diameter Petri dish lined with a piece of filter paper. Ten germinated seeds, similar in size, were added and cultivated in a climate-controlled growth chamber for 4 days at a temperature of 28±2 ˚C, light intensity of 5000 lx, relative humidity of 70~80% and day-night ratio of 16:8. The root and shoot length were measured and the growth inhibitory rates related to the control calculated according to the equation listed below:

$$y = \frac{X_0 - X_1}{X_0} \quad (2)$$

where y is the inhibition rates of the root or shoot growth, x_0 is the length of root or shoot for blank control samples, x_1 is the length of root or shoot treated by test samples.

Statistical analyses

The statistical regression equations of toxicity between the concentration of herbicides and the growth inhibitory rates of weeds were analyzed by DPS v 17.10[32] software at the variance analysis value no greater than 0.05. A proportional hazards model is proposed for the statistical analysis. The statistical results are obtained both for the estimation of the regression coefficient and the inhibition function. The median effect concentration (IC_{50})

and the concentration at the inhibition ratio of 90% (IC_{90}) were obtained from the parameters in the regression curves.

QSAR study

Geometry optimizations were conducted at B3LYP 6-31G(d) level using Gaussian software package, Gaussian 09[33], while structure visualization used GaussView 5[34]. Ampac 8.16 software[35] was used to convert the Gaussian output files into Ampac output files which were compatible structure forms for QSAR analysis with Codessa 2.7.10[36], as well as to calculate descriptors of the synthesized molecules. Molecular structures were transformed into a series of structure descriptors using Codessa 2.7.10 and QSAR models were established using the heuristic method according to reported references[37, 38]. A logarithmic function was used to transfer the distribution of the herbicidal activity values (Inhibitory medium concentration, IC_{50}, mg/L). The logarithm values of IC_{50} were arranged in ascending order and treated as the dependent variables of the QSAR model. The best QSAR model was determined by "breaking point" criterion (ΔR^2<0.02–0.04)[39]. Leave-one-out internal validation and three-fold internal validation were carried out to validate the stability of the QSAR model, and external validation were performed to validate the predictability of the QSAR model.

Results and discussion

Synthesis and characterization of turpentine derived secondary amines

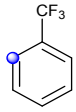
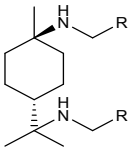
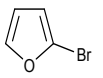
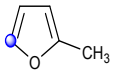
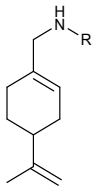
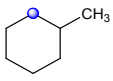
Compared with other methods of synthesis of secondary amines, the reduction of Schiff bases using $NaBH_4$ is one of the most feasible routes. However, Schiff base compounds are unstable and easily decompose in the column chromatography purification process. Several challenges were encountered in the preparation of turpentine derived secondary

amines. For *cis*-*p*-menthane type molecules, it is easy to obtain purified *cis*-*p*-menthane type Schiff bases through recrystallization[19]. The reduction of corresponding compounds with $NaBH_4$ leads to the formation of *cis*-*p*-menthane type secondary amines. However, *p*-menthene type Schiff bases prepared in our work are unstable and it is difficult to obtain *p*-menthene type Schiff bases through column chromatography or recrystallization processes. To resolve this problem, we directly reduced products formed by perillaldehyde and corresponding amines after they were stirred for 12 h in methanol at room temperature. Structures are confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS (seen in Supplementary Information). Yields of various secondary amine products were in the range of 63~98% (Table S1). Results indicated that this protocol is quite efficient for the synthesis of turpentine derived secondary amines.

Evaluation of Cytotoxicity

In order to investigate the potential cytotoxicity of the synthesized compounds on cells, BALB/c 3T3, which is recommended for cytotoxicity evaluation tests by European Union[40], was chosen in our investigation. Since HUVEC are vulnerable to turpentine, HUVEC are also used for MTT cytotoxicity analysis[41]. As it is listed in Table 1, the cytotoxicity analysis results showed that the inhibition rate of most compounds against BALB/c 3T3 and HUVEC was lower than 10% when the cells were treated with 10 μmol/L the DMSO solution of the synthesized compounds, which preliminarily indicated that they are not toxic to mammalian cells such as human and mouse cells.

213 Table 1. Cytotoxicity of turpentine derived secondary amines

Skeleton	R	inhibition rate (%) to BALB/c 3T3	inhibition rate (%) to HUVEC
	F	2.01	2.65
	Cl	5.64	4.88
	Br	10.64	11.98
	CH_3	7.00	2.40
	OCH_3	4.54	6.67
	CF_3	7.33	2.48
	$N(CH_3)_2$	4.09	6.93
	SCH_3	11.41	5.65
		4.59	5.27
		0.91	8.56
		2.57	8.03
		5.44	4.70
		0.08	9.22
		10.64	9.24
		8.04	4.96
		13.07	22.45
		7.11	4.03
		9.22	10.45
		12.60	14.34
		10.49	13.21
		2.67	0.78

Activity of turpentine derived secondary amines against *Echinochloa crus-galli*

Table 2. Inhibition efficacy of *cis*-*p*-menthane type secondary amines **6a**~**6p** and *p*-menthene type secondary amines **9k**~**9o** against shoot growth of *Echinochloa crus-galli*.

Compd.	10.00 [a]	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02
6a	/	/[b]	100.0	87.5	77.2	51.4	30.4	2.7	-[c]	/
6b	-[d]	65.9	33.1	21.4	11.4	21.7	4.7	-[c]	/	/
6c	/	/[b]	-[d]	65.3	50.3	30.6	6.9	-[c]	/	/
6d	/[b]	-[d]	94.2	84.3	45.8	24.7	16.9	2.9	-[c]	/
6e	-[d]	85.1	71.3	55.6	42.9	18.4	10.4	-[c]	/	/
6f	/[b]	-[d]	88.0	77.9	62.6	54.2	17.7	11.2	-[c]	/
6g	/[b]	-[d]	72.3	54.0	56.3	25.8	12.1	-[c]	/	/
6h	/[b]	-[d]	76.3	65.6	41.0	34.9	10.1	7.7	-[c]	/
6i	/[b]	-[d]	91.6	82.0	62.9	59.3	32.2	25.2	12.9	-[c]
6j	-[d]	95.3	63.3	23.8	7.7	5.4	-[c]	/	/	/
6k	/[b]	-[d]	82.4	76.8	41.2	32.9	19.7	20.4	-[c]	/
6l	-[d]	92.0	76.6	32.0	5.7	-[c]	/	/	/	/
6m	100.0	88.3	61.0	44.8	36.2	30.2	3.0	-[c]	/	/
6n	95.3	77.4	59.1	35.4	17.7	7.5	-[c]	/	/	/
6o	/[b]	-[d]	81.1	66.5	19.8	13.1	-[c]	/	/	/
6p	/[b]	-[d]	79.8	25.5	12.7	-[c]	/	/	/	/
9k	/[b]	100.0	80.3	69.4	62.7	46.5	21.8	17.8	15.0	-[c]
9l	/	/	/[b]	100.0	73.0	54.2	32.1	24.2	22.8	14.5
9m	/	/	/[b]	100.0	55.8	31.0	5.4	7.9	9.8	-[c]
9n	/	/	/[b]	100.0	73.4	43.4	13.9	9.8	-[c]	/
9o	/	/[b]	100.0	70.2	57.9	52.1	14.5	3.6	-[c]	/
Diuron	/	/[b]	-[d]	31.0	22.1	15.6	4.4	-[c]	/[b]	/
Glyphosate	/[b]	88.9	86.6	82.4	76.2	65.2	58.0	40.8	17.6	/[b]

Notes: [a] The data of this line are the concentration of different *p*-menthane type Schiff base derivatives solutions (mmol/L).

[b] The data at and higher or lower than this concentration were not determined.

[c] Have no inhibition activity at this concentration.

[d] The samples could not absolutely dissolved at and higher than this concentration.

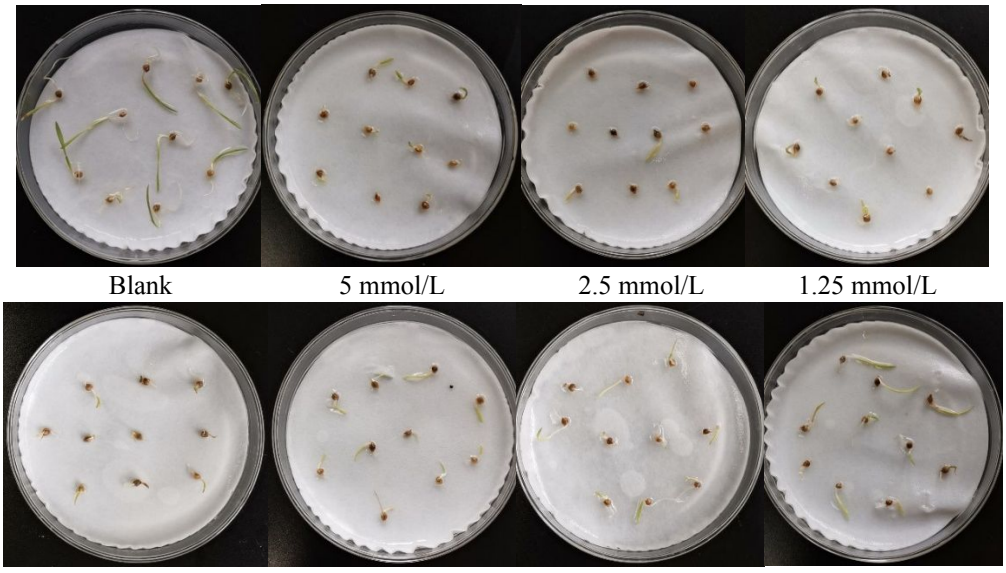


Fig. 1 Herbicidal activity of *cis*-*p*-menthane bis-5-bromo-2-furyl-amines **6k** against *Echinochloa crus-galli*.

The inhibition effects of turpentine derived secondary amines **6a**~**6p**, **9k**~**9o** and two of the most common commercial herbicides (glyphosate and diuron) against the growth of *Echinochloa crus-galli* were investigated and listed in Fig.1, Tables 2 and 3 (The raw data of 6k can be seen in Tables S2 and S3). Their toxicity regression equations and IC_{50} and IC_{90} values are listed in Table 4. It was found that most of the synthesized compounds **6a**~**6p** and **9k**~**9o** displayed apparent inhibition efficacy for both the root and the shoot growth of *Echinochloa crus-galli* (Tables 2 and 3). Similar to diuron and glyphosate, the synthesized compounds also showed higher inhibition activity against the root growth than the shoot growth of *Echinochloa crus-galli*. Compounds **6b**, **6c**, **6f**, **6h**, **6i** (Fig. 2, a), and **9k**~**9o** (Fig. 2, b) displayed similar or even higher activity against the root growth of *Echinochloa crus-galli* than diuron or glyphosate. It indicates that turpentine derived secondary amines are promising botanical agrochemicals for crop protection. It should be noted that the aromatic groups substituted *p*-menthene type secondary amines **9a**~**9j** showed almost no activity against the root growth of *Echinochloa crus-galli* and the

herbicidal activity of them against the shoot growth of *Echinochloa crus-galli* were also limited (Tables S4 and S5).

Table 3. Inhibition efficacy of *cis*-*p*-menthane type secondary amines **6a**~**6p** and *p*-menthene type secondary amines **9k**~**9o** against root growth of *Echinochloa crus-galli*.

Compd.	10.00 [a]	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02
6a	/	/	/[b]	100.0	97.6	94.0	34.1	22.8	-[c]	/[b]
6b	/	/	/[b]	100.0	93.1	92.8	76.1	22.7	22.8	-[c]
6c	/	/	/	/[b]	100.0	91.9	67.9	41.2	13.4	-[c]
6d	/	/	/[b]	100.0	98.8	88.7	61.2	4.8	-[c]	/[b]
6e	/	/[b]	100.0	98.4	93.3	52.0	35.9	-[c]	/[b]	/
6f	/	/	/[b]	100.0	96.5	93.6	85.8	49.3	33.7	-[c]
6g	/	/	/[b]	100.0	98.6	86.7	46.3	23.9	-[c]	/[b]
6h	/	/	/[b]	100.0	99.8	93.4	62.6	40.7	50.4	22.1
6i	/	/[b]	100.0	98.9	92.1	86.8	68.0	58.7	30.9	-[c]
6j	/[b]	100.0	97.9	83.1	64.4	33.9	10.1	6.2	-[c]	/[b]
6k	/	/	/[b]	100.0	70.7	38.6	19.8	9.4	-[c]	/[b]
6l	/	/[b]	100.0	92.1	58.0	0.9	-[c]	/[b]	/	/
6m	/	/[b]	100.0	86.6	82.7	69.6	34.8	27.9	-[c]	/[b]
6n	/[b]	100.0	98.7	92.4	76.1	60.6	52.4	31.1	-[c]	/[b]
6o	/	/[b]	100.0	90.9	52.7	35.5	12.1	-[c]	/[b]	/
6p	/	/[b]	100.0	99.2	91.7	67.3	21.2	19.3	-[c]	/[b]
9k	/	/[b]	100.0	92.7	92.0	75.7	61.1	54.7	53.4	46.3
9l	/	/	/[b]	100.0	96.7	76.9	66.4	47.3	45.2	35.7
9m	/	/	/[b]	100.0	94.7	75.1	58.8	55.0	53.8	37.4
9n	/	/	/[b]	100.0	96.3	81.7	61.0	57.5	42.7	42.5
9o	/	/	/[b]	100.0	94.8	91.2	78.7	60.6	48.4	44.0
Diuron	/	/[b]	-[d]	100.0	95.2	92.5	86.2	73.4	22.7	-[c]
Glyphosate	/[b]	/	/[b]	100.0	88.9	82.3	77.8	74.1	54.8	13.3

Notes: [a] The data of this line are the concentration of different *p*-menthane type Schiff base derivatives solutions (mmol/L).

[b] The data at and higher or lower than this concentration were not determined.

[c] Have no inhibition activity at this concentration.

[d] The samples could not absolutely dissolved at and higher than this concentration.

The IC_{50} and IC_{90} values analyzed by DPS v 17.10 software showed that the herbicidal activity of *cis*-*p*-menthane type secondary amines were influenced by the electronic characteristic of the substituted groups. Introduction of electron-withdrawing substituents at the phenyl ring such as CF_3, F, Cl and Br is beneficial to the herbicidal activity, whereas electron-donating group substituted compounds **6d** and **6e** gave less potent derivatives. According to the difference between substituents on the phenyl ring, IC_{50} values of **6a**~**6p** against the root growth of *Echinochloa crus-galli* follows a sequence of CF_3 > Br > Cl > F = $N(CH_3)_2$ > CH_3 > OCH_3. It is almost in consistent with the electron withdrawing properties of the substituents. For aromatic heterocyclic compounds, the influence of the substituents on the activity of them also follow the rule of phenyl ring compounds. And furthermore, the hydrogenated *cis*-*p*-menthane type Schiff base compounds substituted with N aromatic rings are more active than that with O or S rings. We presumed that this phenomenon was caused by the water-solubility of their heterocycle rings[19]. For pyrrole, furan or thiophene rings, a pair of lone pair electrons in N, O or S atoms participated in the formation of aromatic rings. The formation of hydrogen bond of N, O and S atoms in aqueous solutions are greatly weakened. However, the NH groups in pyrrole rings can also form hydrogen bonds with H_2O. Thus, the water solubility and herbicidal activity of **6m**, **6n** and **6p** are higher than **6j**~**6l** and **6o**.

269 Table 4. Toxicity regression equations, IC_{50} and IC_{90} values of *cis*-*p*-menthane type secondary amines
270 **6a**~**6p** and *p*-menthene type secondary amines **9k**~**9o** against *Echinochloa crus-galli*.

Compd.	Shoot			Root		
	toxicity regression equation	IC_{50} (mmol/L)	IC_{90} (mmol/L)	toxicity regression equation	IC_{50} (mmol/L)	IC_{90} (mmol/L)
6a	y=7.1061+3.8282x r=0.9194	0.2817	0.6090	y=8.8042+4.6102x r=0.9539	0.1496	0.2837
6b	y=4.3133+1.1267x r=0.8959	4.0692	>20	y=8.4445+3.4334x r=0.9133	0.0993	0.2344
6c	y=5.3265+2.0413x r=0.9763	0.6919	2.9367	y=9.8121+4.5963x r=0.9260	0.0898	0.1706
6d	y=5.6240+2.2599x r=0.9887	0.5295	1.9541	y=8.9853+5.0831x r=0.9803	0.1644	0.2938
6e	y=4.9834+1.5381x r=0.9953	1.0252	6.9821	y=7.5354+4.2576x r=0.9528	0.2538	0.5076
6f	y=5.6188+1.6380x r=0.9817	0.4190	2.5386	y=8.5508+3.1361x r=0.9176	0.0738	0.1890
6g	y=5.0960+1.4196x r=0.9583	0.8558	6.8406	y=8.8019+4.5541x r=0.9621	0.1463	0.2796
6h	y=5.1686+1.5091x r=0.9840	0.7732	5.4633	y=8.6150+2.9404x r=0.9282	0.0590	0.1608
6i	y=5.7738+1.3629x r=0.9919	0.2706	2.3581	y=7.7231+2.5604x r=0.9190	0.0864	0.2735
6j	y=4.3856+2.7669x r=0.9654	1.6674	4.8441	y=6.4016+3.2753x r=0.9432	0.3733	0.9190
6k	y=5.3497+1.3065x r=0.9528	0.5400	5.1676	y=7.9717+4.6595x r=0.8711	0.2303	0.4338
6l	y=4.1864+3.3718x r=0.9938	1.7430	4.1820	y=6.4771+7.7423x r=0.9828	0.6445	0.9435
6m	y=5.2284+2.9295x r=0.8725	0.8357	2.2882	y=7.2036+3.1182x r=0.8643	0.1965	0.5062
6n	y=4.4878+2.0133x r=0.9950	1.7963	7.7789	y=6.8471+2.6071x r=0.9122	0.1957	0.6069
6o	y=4.9640+2.4199x r=0.9687	1.0348	3.5030	y=6.9246+4.6661x r=0.9150	0.3869	0.7281
6p	y=4.3604+3.2807x r=0.9590	1.5666	3.8512	y=7.6055+3.7867x r=0.9586	0.2051	0.4471
9k	y=6.2592+2.1910x r=0.8261	0.2663	1.0238	y=7.3312+1.8495x r=0.8135	0.0549	0.2707
9l	y=7.4680+2.5740x r=0.7937	0.1100	0.3460	y=8.0546+2.4702x r=0.8518	0.0580	0.1915
9m	y=7.3744+3.5355x r=0.7933	0.2130	0.4908	y=7.9301+2.3204x r=0.8185	0.0546	0.1948
9n	y=8.0151+4.7490x r=0.8804	0.2318	0.4315	y=8.0466+2.3993x r=0.8434	0.0537	0.1838
9o	y=6.7971+3.6928x r=0.8749	0.3261	0.7251	y=8.1651+2.3573x r=0.8612	0.0454	0.1588
Diuron	y=4.4608+1.2865x r=0.9645	2.6249	>20	y=8.5162+3.0574x r=0.9007	0.0708	0.1858
Glyphosate	y=5.7656+0.9600x r=0.9658	0.1594	3.4470	y=8.0724+2.4699x r=0.8500	0.0570	0.1883

Even the herbicidal selectivity and the safety of turpentine derived secondary amines **6a**~**6p** and **9k**~**9o** are not included in this paper, *N*-(4-fluorobenzyl)-4-isopropyl-1-methylcyclohex-3-enamine, which is a typical secondary amine compound derived from turpentine, was found to be a broad-spectrum and safety herbicide in our previous work[42], indicating that turpentine derived secondary amines could be developed as potential herbicides for weed control.

QSAR study on the herbicidal activity

To further study the relationship between the molecular structure parameters and the herbicidal activity of turpentine derived Schiff bases and secondary amines, thirty three compounds of **5a**~**5p**, **6a**~**6p** and **9k**~**9o** were selected to build QSAR models to investigate the relationship between the structure and their herbicidal activities (The herbicidal activity of **5a**~**5p** against the root growth of *Echinochloa crus-galli* and their toxicity regression equations, IC_{50} and IC_{90} values are summarized in Tables S6 and S7). Two substituted *cis*-*p*-menthane type compounds (four compounds) and one substituted *p*-menthene type compound were selected randomly as external validation database to validate the predictability of the obtained optimal QSAR model (In this work **5k**~**5l**, **6k**~**6l** and **9k** were selected as the validation compounds). More than 500 molecular descriptors are calculated by Ampac 8.16 and Codessa 2.7.10. A series of QSAR models with different number of descriptors were obtained by heuristic method encoded in Codessa 2.7.10. The squared correlation coefficient (R^2) of QSAR models with different numbers of descriptors were summarized in Table 5. According to the "breaking point" criterion, the QSAR model with four descriptors was selected as the best model.

Table 5. R^2 of QSAR models with different number of descriptors

Number of descriptor	R^2	R_{n+1}^2-R_n^2
1	0.507	0.19
2	0.697	0.135
3	0.832	0.048
4	0.880	0.038
5	0.918	0.01
6	0.928	0.022
7	0.950	-

Details of this four-descriptor QSAR model are listed in Table 6 and the regression coefficients of descriptors (X) are calculated by the heuristic regression algorithm. Based on these data, the best QSAR model can be written as a linear regression equation: lg (IC_{50}) = −45.198 + 7.880 × (Min valency of a N atom) + 1.556 × (Max total interaction for a C—H bond) + 2.325 × (Relative number of aromatic bonds) − 4.757 × (Min partial charge (Qmin)); N = 33, R^2 = 0.880, F = 51.446, s^2 = 0.027. N represents the number of samples, R^2 represents the squared value of the correlation coefficient of the model, F represents the Fisher test value, and s^2 represents the variance of the model.

Table 6. Details of this four-descriptor QSAR model

No.	Regression coefficient (X)	Standard error (ΔX)	t-test	Descriptors
0	-45.198	4.483	-10.082	Intercept
1	7.880	1.062	7.420	Min valency of a N atom
2	1.556	0.252	6.175	Max total interaction for a C-H bond
3	2.325	0.386	6.021	Relative number of aromatic bonds
4	-4.757	1.206	-3.946	Min partial charge (Qmin)

Fig. 3 gives the comparison between experimental values ($lgIC_{50}$) and predicted values ($logIC_{50}$) from QSAR model listed in Table 6. It demonstrates satisfactory linear relationship (R^2 = 0.880) and the regression equation is statistically significant. Both

Leave-one-out internal validation and three-fold internal validation are performed to validate the stability of the obtained optimal QSAR model, and the results are listed in Table 7. As shown in Table 7, the R^2 of Leave-one-out internal validation calculated directly by the Codessa is 0.818. The R^2, $R_{training}^2$, and R_{test}^2 of the optimal QSAR model are 0.880, 0.867, and 0.890, respectively. Thus, there are little differences between these correlation coefficients, indicating that the QSAR model is of good stability.

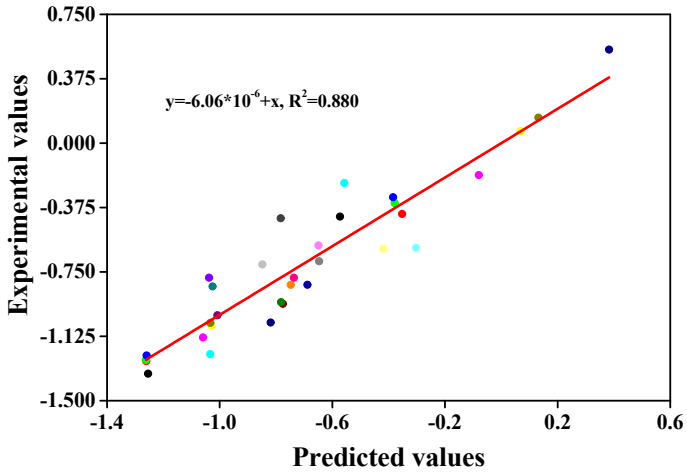


Fig. 3 Comparison of the experimental values ($lgIC_{50}$) and predicted values ($logIC_{50}$) based on QSAR model data set.

Table 7. internal validation of QSAR model.

R^2	R_{loo}^2	Training Set	N	R^2(fit)	Test Set	N	R^2(fit)
0.880	0.818	A+B	22	0.889	C	11	0.897
		B+C	22	0.834	A	11	0.927
		A+C	22	0.879	B	11	0.847
		Average	-	0.867	Average	-	0.890

The external validation results of the obtained optimal QSAR model were illustrated in Fig. 4. The results showed the small difference between the experimental values ($lgIC_{50}$) and predicted values ($lgIC_{50}$) of the external data set exhibited small difference and excellent linear relationship (R^2=0.937), proving that the QSAR model have good predictive ability.

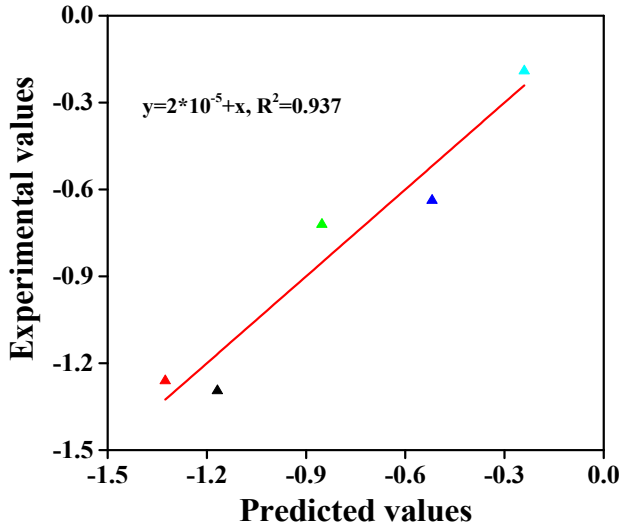


Fig. 4 Comparison of the experimental values ($lgIC_{50}$) and predicted values ($lgIC_{50}$) based on external data set.

According to the Codessa's Reference Manual[43, 44], the descriptors used to construct the optimal QSAR model can be explained as follows. The first descriptor, *Min valency of an N atom*, relates to the strength of intramolecular bonding interactions and characterizes the stability of the described molecules, their conformational flexibility, and other valency-related properties. The second descriptor, *Max total interaction for a C—H bond*, is quantum mechanical energy-related descriptor. It characterizes the maximum total interaction energy of the C—H bond of the described molecules. The third descriptor, *Relative number of aromatic bonds,* is a constitutional descriptor. It is related to the size of conjugate system, reflecting the stability of a molecule. The fourth descriptor, *Min partial charge* (Q_{min}), is an electrostatic descriptor and counts the charge distribution of the described molecules. When the regression coefficient of the descriptor is positive, it indicates that the value of the descriptor is positively related to $lgIC_{50}$ value, and vice versa. As shown in Table 6, the first three descriptors are positively related to the $lgIC_{50}$ value of the derivative, whereas the fourth descriptor is negatively related to the $lgIC_{50}$ value of the

derivative. Since the smaller the $lgIC_{50}$ value, the higher the herbicidal activity of the derivative, we speculate that larger chemical valence of N atom, smaller partial charge, lower interaction energy of the C—H bond, and less aromatic bonds are beneficial to improve the herbicidal activity of turpentine derived Schiff bases and secondary amines.

Supporting Information

Complete characterization data and herbicidal activity study details. This material is available free of charge via the Internet at http://pubs.acs.org.

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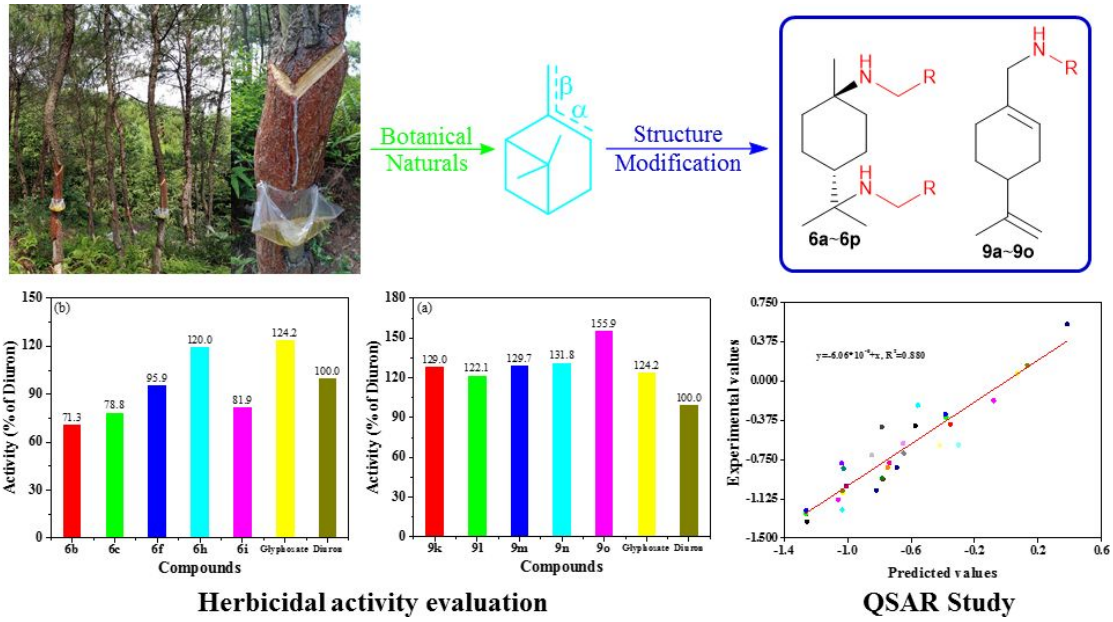
TOC Graphic


Botanical
Naturals
Structure
Modification
6a~6p
9a~9o
(b)
Activity (% of Diuron)
71.3
78.8
95.9
120.0
81.9
124.2
100.0
6b
6c
6f
6h
6i
Glyphosate
Diuron
Compounds
(a)
129.0
122.1
129.7
131.8
155.9
124.2
100.0
9k
9l
9m
9n
9o
Experimental values
Predicted values
Herbicidal activity evaluation
QSAR Study