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Design, synthesis, and herbicidal activity of novel quaternary ammonium salt derivatives

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ABSTRACT

A series of novel quaternary ammonium salt derivatives were designed and synthesized by introducing the herbicide carboxylic acid into substituted aminoacetanilide compounds which derived from herbicides alachlor or acetochlor, using the intermediate derivatization methods in an attempt to obtain novel candidates for weed control. The herbicidal activity assays in greenhouse demonstrated that some of the title compounds exhibited good herbicidal activities against velvet leaf, youth-and-old age, barnyard grass, and foxtail. Especially, **III9** gave the best activity (EC_{50} (g a.i/ha): YOA 34.1, VEL 33.6, FOX 15.9, BYG 36.2). The field trials indicated that **III9** had better herbicidal activity than the commercial herbicide imazethapyr to control broadleaf weeds at 150 g a.i/ha. The present work demonstrated that the quaternary ammonium salt derivatives can be used as potential lead compounds for discovering novel herbicides with improved activity. **III9** itself is worthy of being further developed as an herbicidal candidate. Further syntheses, structure optimization studies, and field trials around **III9** are in progress.

1. Introduction

Herbicides, a major part of crop protection products, widely applied to major crops such as rice, corn and wheat, are playing an essential role by increasing both crop quality and yield [1]. Recently, the amide herbicides have been extensively used around the world, such as alachlor, acetochlor, butachlor and metolachlor. Most remarkable is that metolachlor and acetochlor ranked No. 5 and No. 8 with sales of $585 and $460 million U.S. dollars in 2014, respectively [2]. However, amide herbicides could damage succeeding crops and especially the crops in sandy soils with low organic matter [3]. While quaternary ammonium salt has lots of advantages, such as good emulsibility, excellent hydrophily, high ionic adsorbability and permeable diffusivity, due to its ionic structure [4]. Diquat and paraquat are famous herbicides of quaternary ammonium salt [5]. Consequently, enlightened by these characteristics of quaternary ammonium salt, some researchers have been paying much attention to search for novel agrochemicals concerning quaternary ammonium salt. For example, Dow AgroSciences introduced choline to traditional herbicide of 2,4-D to afford a new quaternary ammonium compound, compared with other 2,4-D amine or ester formulations, the new product not only keeps some advantages of 2,4-D, such as the same weed control efficacy and favorable environmental profile, but also gains new features of controlling stubborn grasses and resistant weeds with ultra-low volatility, minimized potential for drift, decreased odor and improved handling characteristics [6]. The above design concept, similar to the intermediate derivatization methods (IDM) which have been successfully used in design and optimization of new compounds [7–17], then stimulated our interest to bring quaternary ammonium salt into amide structures using IDM.

In this study, to discover novel compounds with higher herbicidal activity targeting control of unwanted plants, we designed and synthesized a series of quaternary ammonium salt derivatives containing substituted aminoacetanilide (Fig. 1 and Table 1) using alachlor, acetochlor as the parent structures by active compound derivatization method (ADM), one of three specifical approaches of IDM. The detailed syntheses, bioassay results, and structure-activity relationships of these compounds are discussed as follows.

2. Materials and methods

2.1. Chemical

All chemicals such as starting materials and reagents were commercially available (Sinopharm Chemical reagent Co. Ltd., Shanghai, China) and used without further purification except as indicated. Melting points were determined on a Büchi M-569 melting point apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^1H NMR spectra were recorded with a mercury 300 MHz spectrometer

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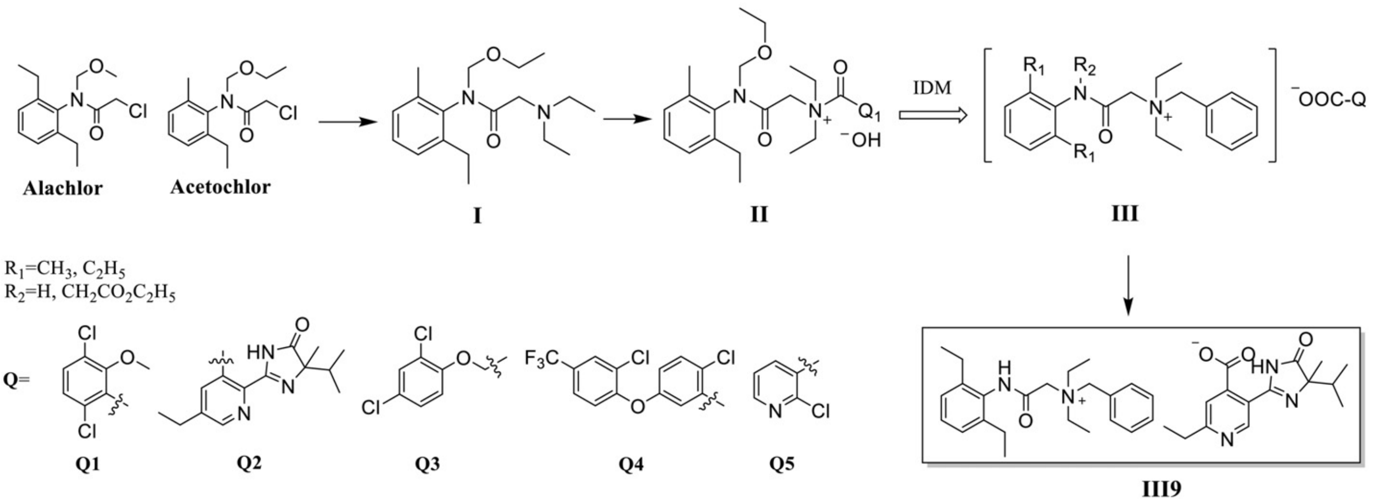


Fig. 1. Design of quaternary ammonium salt derivatives.

(Varian, Palo Alto, CA) with deuterochloroform or deuterium oxide as the solvent and tetramethylsilane (TMS) as the internal standard.

An overview synthesis of quaternary ammonium salt derivatives was shown in Scheme 1.

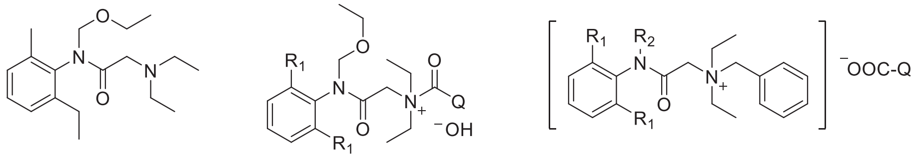
*2.1.1. Synthesis of 2-(diethylamino)-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (**I**)*

To a solution of acetochlor (50 g, 0.19 mol) in acetonitrile (400 mL) was added potassium carbonate (39.3 g, 0.285 mol), followed by addition dropwise of diethylamine (13.5 g, 0.19 mol) at room temperature. The reaction mixture was refluxed for 4 h, cooled to room temperature. The mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure to give intermediate **I** as a yellow oil (42 g) with yield of 72.4%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) = 0.83–0.88 (3H, m, N—CH_2—CH_3), 1.12–1.21 (6H, m, O—CH_2—CH_3, benzyl-CH_2—CH_3), 2.12 (3H, s, benzyl-CH_3), 2.46–2.53 (6H, m, benzyl-CH_2—CH_3, N—CH_2—CH_3), 2.77 (2H, s, CO—CH_2), 3.66 (2H, q, OCH_2—CH_3), 4.91 (2H, s, OCH_2—N), 7.13–7.21 (3H, m, benzyl-H).

*2.1.2. Synthesis of quaternary ammonium hydroxide compound (**II**) [18]*

Dicamba acide (0.72 g, 3.3 mmol) (**Q1**) was added to the solution of 2-(diethylamino)-*N*-(ethoxymethyl)-*N*-(2-ethyl-6-methylphenyl) acetamide (**I**) (1 g, 3.3 mmol) in THF (30 mL). The mixture was stirred over night at room temperature. The solvent was removed under reduced pressure to achieve intermediate **II** as a yellow oil (1.5 g) with yield of 83.3%. ^{1}H NMR (300 MHz, D_2O) δ_H (ppm) = 1.17–1.22 (6H, m, CH_2—CH_3), 1.37 (6H, m, N—CH_2—CH_3), 2.11 (3H, s, benzyl-CH_3), 2.58 (2H, q, benzyl-CH_2—CH_3), 3.53 (4H, q, N—CH_2), 3.67 (2H, q, O—CH_2—CH_3), 3.82 (3H, s, O—CH_3), 4.22 (2H, s, N—CH_2—CO), 5.98 (2H, s, N—CH_2—O), 6.98 (1H, m, benzyl-H), 7.17 (2H, m, benzyl-H), 7.22 (2H, m, benzyl-H).

Table 1
Herbicidal activity of synthesized compounds in greenhouse.



I **II** **III**

Compd.	R_1	R_2	Q	YOA post- EC$_{50}$ g a.i/ha	YOA post- 95% d[a]	VEL post- EC$_{50}$ g a.i/ha	VEL post- 95% d	FOX post- EC$_{50}$ g a.i/ha	FOX post- 95% d	BYG post- EC$_{50}$ g a.i/ha	BYG post- 95% d
I	CH_3	–	–	>1000	/[b]	>1000	/	>1000	/	>1000	/
II	CH_3	–	Q1	62.7	44.2–89.0	264.3	183.4–380.9	800.3	557.5–1109.1	960.6	647.4–1425.5
III1	CH_3	$CH_2CO_2C_2H_5$	Q2	170.4	138.6–209.6	338.0	253.1–451.4	398.8	337.9–470.7	362.0	310.0–422.7
III2	CH_3	$CH_2CO_2C_2H_5$	Q3	77.6	65.2–92.2	70.4	58.2–85.3	>1000	/	>1000	/
III3	CH_3	H	Q1	48.8	28.5–83.7	130.0	106.3–159.0	960.6	647.4–1425.5	>1000	/
III4	CH_3	H	Q2	105.0	49.0–129.6	355.7	278.0–451.9	260.7	186.3–364.9	>1000	/
III5	CH_3	H	Q3	96.7	80.9–115.6	253.8	188.7–341.6	890.2	632.3–1253.3	>1000	/
III6	CH_3	H	Q4	165.6	138.8–197.8	223.4	182.3–273.8	483.8	341.5–685.3	899.0	634.2–1274.4
III7	CH_3	H	Q5	>1000	/	>1000	/	>1000	/	>1000	/
III8	C_2H_5	H	Q1	45.6	38.1–54.6	67.0	58.3–77.0	358.8	245.4–524.6	453.6	376.3–546.7
III9	C_2H_5	H	Q2	31.4	25. 6–38.5	33.6	27.4–40.8	15.9	10.7–23.6	36.2	30.2–43.4
III10	C_2H_5	H	Q3	180.4	141.9–229.4	137.9	115.2–165.2	>1000	/	899.0	634.2–1274.4
III11	C_2H_5	H	Q4	52.6	45.7–60.5	219.0	186.3–257.5	252.6	227.4–280.6	770.9	572.3–1038.5
III12	C_2H_5	H	Q5	>1000	/	>1000	/	>1000	/	>1000	/

[a] Confidence limit.

[b] The value could not be measured accurately.