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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of novel pyrethriods containing eugenol moiety

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Abstract A novel series of pyrethriods was designed and synthesized by connecting various eugenol derivatives to either a chrysanthematic acid or 2-(4-chlorophenyl)-3-methylbutanoic acid. The insecticidal activity of target compounds has been evaluated by an immersion method on the fourth instar larvae of *Culex pipens quinquefasciatus*. The results revealed that the larvae were sensitive to synthesized compounds. Varying substituents in both acid moiety and eugenol group resulted in new compounds that exhibited different contact toxicity. Compound **3a** showed the highest activity and is currently under further investigation.

Keywords Pyrethriod · Eugenol derivatives · Synthesis · Synergy · Insecticidal activity

Introduction

Insecticides with the structure of pyrethrins are neuropoisons and broad-spectrum, which hold some promises in vector control. They are highly toxic to target organisms, biodegradable in nature, and less toxic to mammals (Fakoorziba *et al.*, 2009; Sukumaran *et al.*, 2005; Katsuda, 1999). However, due to the excessive use of pyrethriods during the past 20 years, incidences in resistance to all classes of existing insecticides have made vector control more and more difficult. Therefore, there is an urgent need to develop novel insecticides in order to combat resistance (Tewary *et al.*, 2006).

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Two strategies can be used to develop novel pyrethriods. One is to improve the efficacy of existing natural substances such as from allethrin to prallethrin, and the other is to improve their stability to make them more photostable just like resmethrin.

To address the insecticide resistance, there has been mounting interest to combine the use of pyrethriods with other substances in order to exploit the synergistic effects. For example, it is well-established that piperonyl butoxide (PBO) can be effectively used together with other synthetic pyrethriods, due to its ability to inhibit the monooxygenases as detoxifying enzymes. We noticed that molecules based on eugenol are structurally similar to PBO (Fakoorziba *et al.*, 2009; Pap *et al.*, 2001; Enan, 2001; Steven, 2001). Moreover, eugenol itself is a repellent against mosquitoes, and its derivatives have pronounced in medicinal properties, such as antibacterial, fungicidal, antiviral, antioxidant, antitumor, and anaesthetic (Mastelic *et al.*, 2008; Ogata *et al.*, 2005; Chaieb *et al.*, 2007; Park *et al.*, 2000).

Here we report the synthesis of a novel class of compounds which combine eugenol derivative to either a chrysanthematic acid or 2-(4-chlorophenyl)-3-methylbutanoic acid moiety. We think that the combination of the two moieties could result in functional synergy that leads to target molecules with interesting insecticidal properties. Since eugenol is widely available from natural sources, this could make the synthesis of hybrid molecules economical.

Results and discussion

Chemistry

The activities of target molecules depended on the synergy between the eugenol with different substituents and the

acidic moiety. In order to improve stability and minimize oxidation of target molecules in the screening tests, the eugenolic hydroxyl was protected by either an ethyl or an acetyl group. The double bond was kept intact as it could provide the product with antioxidant properties.

The synthetic route was outlined in Scheme 1.

In the reaction processes, the conditions had a significant influence on the selectivity. The main product and reaction time would depend greatly on a correct solvent. In the case of acetylation, the acetic anhydride was also used as a solvent and the reaction was terminated shortly in order to avoid acetylation toward the Friedel–Crafts reaction. The subsequent radical brominations were carried out in CCl_4 to afford the desired bromides **2a** and **2b**. If a polar solvent was used, the bromination would occur on the benzene ring instead of the allylic position. During the esterifications, the bromides **2a** and **2b** were added dropwise to the reaction media in order to avoid undesired [1 + 1] cyclization. Besides, a basic medium would benefit the esterification more than an aroylation in side reaction.

Bioactivity

The synthesized compounds (**3a**–**4b**) were tested against the 4th instar larvae to evaluate their contact toxicities. After a 24 h exposure, all compounds showed activities, which varied according to the substituent on the eugenol group as well as on acidic moiety. Table 1 showed the results of contact toxicities.

The activity was showing in a decreasing order from **3a**, **3b**, **4a**, to **4b**. Compound **3a** showed the highest contact mortality after 24 h in the immersion test (Itoh *et al.*, 1986). The higher activity of **3a** and **3b** over **4a** and **4b** could be attributed to higher volatility and permeability of the chrysanthematic acid ester than the 2-(4-chlorophenyl)-3-methylbutanoic acid ester. Also we noticed the *O*-ethylation at the eugenol (**3a** and **4a)** has resulted in higher insecticidal activity over the *O*-acetylation (**3b** and **4b**). Indeed, the acetylation has led to a considerable loss of activity (Tewary *et al.*, 2006). This fact could be attributed to the electron-donor of an alkyl.

Table 1 Bioassay of contact activity against the 4th instar larvae of *Culex pipens quinquefasciatus*

Time[b] Mortality[a] Comps	1 (h)	4 (h)	12 (h)	24 (h)
Blank test	0	0	0	5
3a	15	22	40	97
3b	10	25	34	88
4a	10	23	42	96
4b	14	25	47	85
Allethrin	12	20	33	85
Fenvalerate	10	18	40	88

[a] Abbort's formula was used to calculate percent corrected mortality

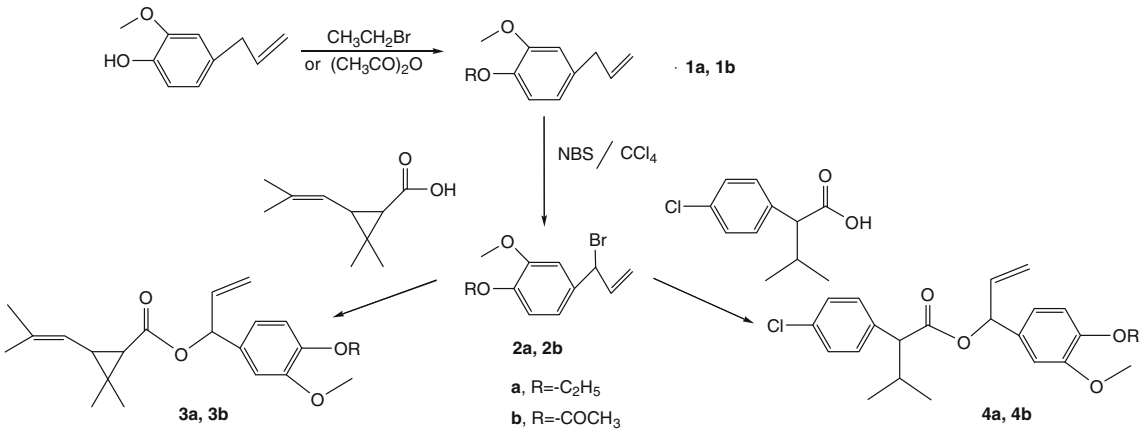
[b] Contact time (h)

Experimental

General

Melting points were determined on a XSP-1 micro-melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer. Chemical shifts were given with TMS as an internal reference. Elemental analyses were carried out on a Carlo Erba 1106 analyzer. The results of these assays are shown in Tables 2 and 3.

All reagents and solvents were of commercially available unless otherwise stated. The fourth instar larvae of *Culex pipens quinquefasciatus* were used for the test insect.



Scheme 1 Synthetic route of target molecules

Chemistry

4-Allyl-2-methoxylphenetole (Haworth, 1936) ***1a***

To a well-stirred solution of eugenol (5.41 g, 33 mmol), C_2H_5OH (10 ml) and H_2O (10 ml), 30% NaOH (3.1 ml) was added dropwise at room temperature. Once the mixture was warmed to 60°C, C_2H_5Br (7.30 g, 67 mmol) in ethanol (10 ml) was added slowly. Then a stir was kept at 60°C for 20 h. After cooled and separated, the organic phase was washed with H_2O, 10% NaOH and H_2O in turn. After dried and concentrated, the resulting mixture was separated over a silica column with the hexane/EtOAc (80/20, v/v). A brown resinous semisolid **1a** (5.8 g, yield 92%) was obtained in M.p. 37–38°C.

4-Allyl-2-methoxyphenyl acetate (Sato et al., 2007) ***1b***

A mixture of eugenol (0.98 g, 6 mmol), acetyl oxide (2.04 g, 20 mmol) and CH_3COOH (2 ml) was refluxed 1.5 h. Then it was cooled to the room temperature. A mixture of H_2O and ice was added under stirring. The organic layer was separated and then was washed with H_2O, 10% NaOH and H_2O in order. After dried and concentrated, the resulting mixture was separated over a silica column with the hexane/EtOAc (80/20, v/v). A brown resinous semisolid **1b** (1.2 g, yield 97%) was obtained in M.p. 30–31°C.

4-(1-Bromoallyl)-1-ethoxy-2-methoxybenzene ***2a****,*
4-(1-Bromoallyl)-2-methoxyphenyl acetate ***2b***

Being shone under a lamp (200 W), a mixture of **1a** (1.15 g, 6 mmol) or **1b** (1.23 g, 6 mmol) and *N*-bromosuccinimide (1.06 g, 9 mmol) in CCl_4 (30 ml) was refluxed for 25 h. After filtrated, the filtrate was evaporated to dryness. The crude product **2a** (1.31 g, yield 81%) or **2b** (1.30 g, yield 76%) was obtained and directly transferred to the next step to avoid being hydrolyzed in air.

Table 2 Yields and characterization of target compounds

Compound	Yield[a] (%)	M.p. (°C)	Formula	Elemental analysis (%)[b]	
				C	H
3a	63	yel. lq.	$C_{22}H_{30}O_4$	73.45 (73.71)	8.51 (8.44)
3b	65	yel. lq.	$C_{22}H_{28}O_5$	71.21 (70.94)	7.83 (7.58)
4a	67	142–143	$C_{23}H_{27}ClO_4$	68.84 (68.56)	6.80 (6.75)
4b	72	150–151	$C_{23}H_{25}ClO_5$	66.40 (66.26)	5.83 (6.04)

[a] Yield of isolated pure products

[b] The data in parentheses are calculated values

3-Methoxyl-4-ethoxylphenyl-1-propenyl-3-yl-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate ***3a****,*
3-Methoxyl-4-ethoxylphenyl-1-propenyl-3-yl-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate ***3b***

A mixture of NaOH (0.96 g, 24 mmol) and 2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid (4.03 g, 24 mmol) in H_2O (20 ml) was stirred at the room temperature for 3 h. **2a** (6.51 g, 24 mmol) or **2b** (6.84 g, 24 mmol) in CCl_4 (15 ml) was added dropwise and refluxed for 15 h. The organic layer was extracted by ether, washed with H_2O, and then dried. After the solvent was removed, the crude product was purified over a silica column with THF/petroleum ether (1/20, v/v).

3a: A yellow liquid was obtained (5.42 g, 63%).
3b: A yellow liquid was obtained (6.08 g, 68%).

1-(4-Ethoxy-3-methoxyphenyl)allyl 2-(4-chlorophenyl)-3-methylbutanoate ***4a****, 1-(4-Acetoxy-3-methoxyphenyl)allyl 2-(4-chlorophenyl)-3-methylbutanoate* ***4b***

A mixture of 2-(4-chlorophenyl)-3-methylbutanoic acid (5.10 g, 24 mmol) and NaOH (0.96 g, 24 mmol) in H_2O (20 ml) was stirred at a room temperature for 3 h. Then **2a** (6.51 g, 24 mmol) or **2b** (6.84 g, 24 mmol) in CCl_4 (15 ml) was added dropwise and refluxed for 15 h. The organic layer was extracted by ether and washed with H_2O, then was dried. After the solvent was removed, the crude product was purified over a silica column with THF/petroleum ether (1/10, v/v).

4a: White crystals were obtained (6.48 g, 67%), M.p. 142–143°C.
4b: White crystals were obtained (7.20 g, 72%), M.p. 150–151°C.

Contact toxicity

The contact toxicity tests were conducted in the standard immersion method (Itoh *et al.*, 1986). These compounds were diluted with acetone at a concentration of 0.025 mg/ml. Tests were carried out by exposing the 20 early fourth instar larvae to a mixture of H_2O (200 ml) and the corresponding solution of insecticide (1 ml) in a 250 ml glass beaker. The dead and moribund larvae were recorded after 24 h of exposure. The larvae were considered to be moribund if they failed to flex their head to siphon, when stimulated. All the tests were carried out at a room temperature of 25 ± 2°C at a relative humidity of 70 ± 10% and 16:8 h (light:dark).

Table 3 Characterization of target compounds

Compound	^{1}H NMR	^{13}C NMR	UV (CH_3OH) λ_{max}
3a	($CDCl_3$, 600 MHz) δ: 1.133–1.301 (m, 7H, $C(CH_3)_2$, O=C–CH), 1.455–1.482 (t, 3H, OCH_2–CH_3), 1.630–1.776 (m, 7H, CH–CH, $=C(CH_3)_2$), 3.418–3.472 (m, 1H, $=CH_{2a}$), 3.707–3.774 (m, 1H, $=CH_{2b}$), 3.900 (s, 3H, OCH_3), 4.087–4.126 (quad, 2H, OCH_2), 4.555–4.602 (m, 1H, $(CH_3)_2C=CH$), 4.855–4.937 (m, 1H, Ph–CH), 6.118–6.164 (m, 1H, $CH_2=CH$), 6.845–6.863 (d, 1H, Ph–H), 7.018–7.037 (d, 2H, Ph–H)	($CDCl_3$, 400 MHz) δ: 14.89 (OCH_2–CH_3), 18.49, 20.60 (2C, $=C(CH_3)_2$), 22.21, 25.57 (2C, $C(CH_3)_2$), 33.28 ($(CH_3)_2C$), 34.62 (=CH–CH), 54.08 (O=C–CH), 55.97 (OCH_3), 64.25 (OCH_2), 74.15 (Ph–CH), 111.18, 111.87, 120.35, 135.24, 148.77, 169.69 (6C, Ph), 117.84 ($=CH_2$), 120.75 ($(CH_3)_2C=CH$), 127.60 ($(CH_3)_2C=$), 135.93 ($CH_2=CH$), 171.06 (C=O)	203 nm (Abs 0.384), 238 nm (0.140), 280 nm (0.070)
3b	($CDCl_3$, 600 MHz) δ: 1.061–1.201 (m, 7H, $C(CH_3)_2$, O=C–CH), 1.530–1.716 (m, 7H, CH–CH, $=C(CH_3)_2$), 3.418–3.472 (m, 1H, $=CH_{2a}$), 3.707–3.774 (m, 1H, $=CH_{2b}$), 3.190 (s, 3H, O=C–CH_3), 3.890 (s, 3H, OCH_3), 4.540–4.502 (m, 1H, $(CH_3)_2C=CH$),4.955–5.137 (m, 1H, Ph–CH), 6.138–6.184 (m, 1H, $CH_2=CH$), 6.675–6.893 (d, 1H, Ph–H), 6.728–6.897 (d, 2H, Ph–H)	($CDCl_3$, 400 MHz) δ: 18.49, 20.60 (2C, $=C(CH_3)_2$), 22.21, 25.90 (2C, $C(CH_3)_2$), 33.34 ($(CH_3)_2C$), 34.63 (=CH–CH), 54.12 (O=C–CH), 55.98 (OCH_3), 74.44 (Ph–CH), 111.18, 111.90, 120.41 (3C, Ph), 117.88 ($=CH_2$), 120.39 ($(CH_3)_2C=CH$), 127.60 ($(CH_3)_2C=$), 135.29 (CH–Ph), 135.86 ($CH_2=CH$), 148.74, 148.88 (2C, O–Ph), 169.72 (CH_3–C=O), 171.06 (C=O)	210 nm (Abs 1.600), 280 nm (0.150)
4a	($CDCl_3$, 400 MHz) δ: 0.722–0.749, 0.988–1.004 (dd, 6H, $CH(CH_3)_2$), 1.465–1.499 (t, 3H, CH_2–CH_3), 2.371–2.387 (m, 1H, $(CH_3)_2CH$),3.225–3.252 (d, 1H, O=C–CH), 3.343–3.391 (t, 1H, $=CH_{2a}$), 3.625–3.652 (t, 1H, $=CH_{2b}$), 3.820 (s, 3H, OCH_3), 4.085–4.138 (quad, 2H, OCH_2), 4.471–4.481 (m, 1H, OCH), 6.080–6.092 (s, 1H, =CH–), 6.823–6.843, 6.947–6.968 (dd, 2H, OPh–H), 6.905 (s, 1H, OAr–H), 7.248–7.329 (d, 4H, ClPh–H)	($CDCl_3$, 400 MHz) δ: 14.78 (OCH_2–CH_3), 20.15, 21.46 (2C, $CH(CH_3)_2$), 31.73 ($(CH_3)_2CH$), 32.20 (OCH_3), 53.47 (O=C–CH), 55.87 (OCH_2), 59.54 (O–CH), 64.24, 74.79, 110.89, 120.33, 136.22, 148.84 (6C, O–Ph), 77.04 ($=CH_2$), 127.03 (=CH), 111.79, 133.35 (2C, Cl–Ph), 128.73 (2C, Cl–Ph), 130.02 (2C, Cl–Ph), 171.73 (O=C)	232 nm (Abs 0.963), 275 nm (0.544), 315 nm (0.340)
4b	($CDCl_3$, 400 MHz) δ: 2.317 (s, 6H, $CH(CH_3)_2$), 3.861 (s, 7H, $(CH_3)_2CH$, OCH_3, O=C–CH_3), 3.887–3.899 (d, 1H, ClPh–CH), 4.209–4.219 (d, 1H, $=CH_{2a}$), 4.237–4.248 (d, 1H, $=CH_{2b}$), 4.675–4.719 (m, 1H, OPh–CH), 5.297 (s, 1H, =CH–), 5.319 (s, 1H, OPh–H), 7.008–7.045 (m, 6H, Ph–H)	($CDCl_3$, 400 MHz) δ: 20.68 (2C, $(CH_3)_2$), 30.93 (O=C–CH_3), 37.69 (2C, $(CH_3)_2CH$, OCH_3), 53.48 (2C, OPh–CH, ClPh–CH), 54.62 (2C, $CH=CH_2$), 56.02 (3C, Cl–C, 2(CH–Ph)), 112.58, 120.68 (4C, Cl–Ph), 122.84 (3C, O–Ph), 136.90, 140.25 (2C, O–C), 151.05 (CH_3–C=O), 168.68 (C=O)	205 nm (Abs 0.510), 283 nm (0.078)

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