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Synthesis and insecticidal activity of new substituted *N*-aryl-*N*′-benzoylthiourea compounds

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Abstract

Eight new substituted *N*-aryl-*N*′-benzoylthioureas have been synthesised by a facile and mild method with high yield at room temperature. The structures of all compounds were confirmed by ^{1}H NMR, mass and high resolution mass spectroscopy. The preliminary bioassay tests show that two of the compounds (**5b** and **5e**) exhibited a significant insecticidal activity on armyworm, *Leucania separata* Walker, at 500 mg l^{-1}.

Keywords: Benzoylthiourea; Synthesis; Insecticidal activity

1. Introduction

The chemistry of fluorine-containing compounds has been tremendously developed. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro organic compounds have been frequently applied to bio-related materials, medicines and agrochemicals [1]. Many fluorine-containing compounds exhibit significant agricultural activities, for example, insect growth regulating. In contrast to traditional pesticides, one of the mode of action for insect growth regulator (IGR) is to control the growth and development process of insects by interfering with chitin biosynthesis [2,3]. Much attention has been paid to IGR in recent 20 years because of their showing significant activity [4–7], especially for benzoyl(thio)urea derivatives [8–13].

In the last few years, we were pursuing investigations on the synthesis of containing fluorine insecticides, the introduction of fluorine atom often increases bioactivity of new compounds [14–16]. Among IGR, benzoylurea compounds were studied in more detail than benzoylthiourea [17]. In order to discover new leading compound with high insecticidal and low toxicity, we want to investigate continuously the effect of multi-fluorine atom introduced into benzoylthiourea. By a facile and convenient method, we synthesised some novel fluorine-containing substituted *N*-aryl-*N*′-benzoylthiourea and proceeded the preliminary bioassay tests. The preliminary bioassay tests show that some compounds (**5b** and **5e**) exhibit significant insecticidal activity on armyworm, *Leucania separata* Walker.

2. Results and discussion

2.1. Synthesis

Start from different benzoic acid (**1**), the key fluorine-containing benzoyl isothiocyanates (**3**) were synthesised through the reaction of benzoyl chloride (**2**) and powder ammonium thiocyanate. The final compounds (**5a–5h**) were obtained by the reaction of appropriate primary amine (**4**) and benzoyl isothiocyanates (**3**) (Fig. 1).

Unlike the reaction condition at the reflux of acetone reported in [8,13], this reaction is at room temperature, and the separation is convenient. The compounds' structure can be identified easily by molecular ion peak in MS spectra. All the structures are also confirmed by IR, ^{1}H NMR and HRMS.

In our compounds, significant long-range coupling is observed. Since F^{19} spin quantum number is $\frac{1}{2}$, the coupling

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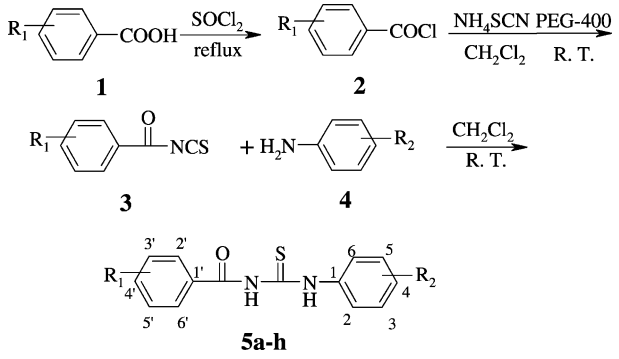


Fig. 1. The schematic representation of compounds **1**–**5**.

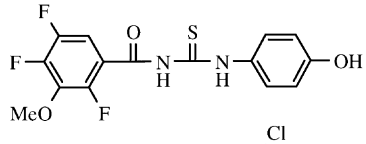
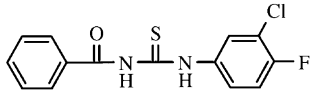
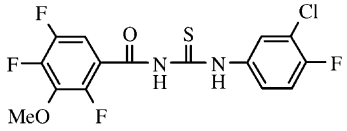
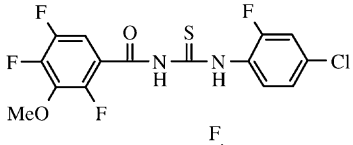
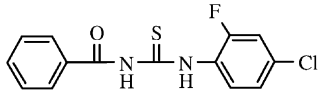
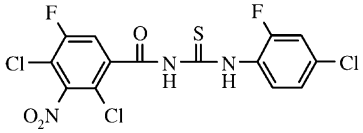
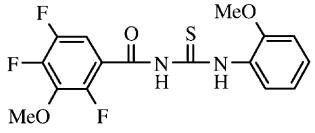
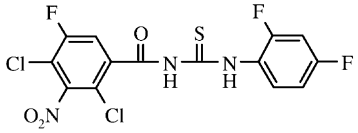
and split rule between fluorine and hydrogen is same as that of hydrogen and hydrogen. The *ortho* fluorine atom split hydrogen proton signal into doublet, the phenomenon is observed in all of our compounds. Even, many fluorine atoms exist in the same benzene ring, *meta* fluorine continually split the hydrogen proton signal into complicate spectra lines. For example, in benzoyl part of compound **5c**, three fluorine atoms and hydrogen atom coupled each other and hydrogen proton signal is split into octet, that is, a pattern of eight lines symmetrically distributed about the centre of the spectrum. The coupling constant between *ortho* fluorine atom and hydrogen is 11.7 Hz. The constant between *meta* fluorine and hydrogen $J_{F(m)–H}$ is 8.4 Hz. Similar ^{1}H NMR spectra are observed in compound **5a**, **5d** and **5h**.

2.2. Insecticidal activities

We examined the insecticide activity of *N*-aryl-*N*′-benzoylthiourea having a variety of substituents on the benzene ring. The insecticidal activity of compounds against armyworm (*Leucania separata* Walker) was measured according to the modified method described previously [14,18]. The result is shown in Table 1. Results are presented as mortality (%) determined at 500 mg l^{-1}.

Among the compounds, **5b** and **5e** possess significant biological activity, the mortality reaches to 100 and 80% in 48 h at 500 mg l^{-1}, respectively. The value LC_{50} of **5b** is 0.265 mM, which is much lower than that of *N*-(4-fluorophenyl)-*N*′-benzoylthiourea (36.5 mM), *N*-(4-chlorophenyl)-*N*′-benzoylthiourea (17.2 mM) [8], *N*-phenyl-*N*′-benzoylthiourea (>0.01%) [19]. For benzoylurea type IGR, in general, the introduction of F or Cl, especially 2,6-difluoro, to the benzoyl moiety, should increase bioactivity [17], the 4-Cl to the phenyl moiety produced the active structures than 4-F according to the literature [8]. In our case, only two compounds **5b** and **5e** without any groups on benzoyl moiety were the most active compounds. But, to our surprise, the function of introducing F to the benzoyl moiety is negative. It means that there might be some unknown factors to influence the role of fluorine. At the same time, we also found the death time of larvae of our compounds is much shorter than that of general benzoylurea type IGR. The later need 5–7 days. All these suggested that the mode of action of our compounds was different from benzoylurea type IGR and these compounds may be useful as leading compound for further structure–activity relationship studies. The study about the mode of action and the effect on bioactivity that the fluorinated position at phenyl moiety produces is in process.

Table 1
Mortality (%) of **5a**–**5h** against armyworms at 500 mg l^{-1}

Compound		Mortality (%)[a]
5a		20.0
5b		100.0 (LC_{50} = 0.265 mM)
5c		3.3
5d		10.0
5e		80.0 (LC_{50} = 0.406 mM)
5f		0.0
5g		6.7
5h		9.4

[a] The mortality (%) was determined by the number of live larvae in the treated bottles relative to that in the untreated controls after 48 h.

A moderate amount of mealie leaves, which were treated with the test solution dissolving the compound, was placed on moistened filter paper in three broad bottles. Each bottle was infested with 10 s-instar larvae of the southern armyworm. The number of live larvae was observed in 48 h.

3. Experimental

Melting points were obtained with an electrothermal digital apparatus made in Beijing and are uncorrected.

The infrared (IR) spectra were recorded on a Nicolet 470 infrared Fourier transform spectrometer using potassium bromide pellets. The proton nuclear magnetic resonance (^{1}H NMR, 500 MHz) spectra were recorded on Bruker WP-500SY spectrometers with CD_3Cl as the solvent and TMS as internal standard. High resolution mass spectra were obtained on MicroMass GCT CA 055 spectrometers. Analytical thin-layer chromatography (TLC) was carried out on precoated plated (silica gel 60 F_{254}), and spots were visualised with ultraviolet light. All chemicals or reagents were purchased from standard commercial suppliers.

3.1. General procedure

Fluorine-containing benzoic acid (10 mmol) and thionyl chloride (20–50 mmol) were refluxed for 5 h, thionyl chloride was removed under reduced pressure. Benzoyl chloride was used in next reaction without purification. Powered ammonium thiocyanate (15 mmol), appropriate benzoyl chloride (10 mmol), PEG-400 (0.18 g, 3% with respect to ammonium thiocyanate) and methylene dichloride (25 ml) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at room temperature for 1 h or so, then appropriate amine (10 mmol) was added, and the mixture was stirred for 8–12 h. The mixture was filtered off to remove inorganic salts and the filtrate was concentrated under reduced pressure. The resulting solid was recrystallised from anhydrous ethanol to give respond as benzolylthiourea.

3.1.1. Syntheses of N-(4-hydroxylphenyl)-N′-(2,4,5-trifluoro-3-methoxylbenzoyl)thiourea (**5a**)

Yield 78%, mp 182–83 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 4.09 (s, 3H, –OCH_3), 5.15 (s, 1H, –OH), 6.85 (d, 2H, $J = 6.8$ Hz, H-3, H-5), 7.49 (d, 2H, $J = 6.8$ Hz, H-2, H-6), 7.58 (o, 1H, $J_{F(o)-H} = 11.7$ Hz, $J_{F(m)-H} = 8.4$ Hz, H-6′), 9.49 (d, 1H, $J = 14.0$ Hz, C=SNH), 12.13 (s, 1H, C=ONH). IR (KBr): $v = 3300$, 3240, 1680, 1540, 1500, 1470, 1440, 1370, 1230, 1210, 1190, 1160, 1100, 1050, 720 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 357 ($M^+ + 1$) (4.74), 356 (M^+) (27.39), 205 ($C_8H_6F_3NO_2$) (19.71), 189 ($C_8H_4F_3O_2$) (100.00), 161 ($C_7H_4F_3O$) (10.39), 151 (C_7H_5NOS) (69.54), 146 (C_6HF_3O) (8.46), 109 (C_6H_7NO) (6.85), HRMS Calcd. for $C_{15}H_{11}F_3N_2O_3S$ 356.0442. Found: 356.0430.

3.1.2. Syntheses of N-(3-chloro-4-fluorophenyl)-N′-benzoylthiourea (**5b**)

Yield 92.2%, mp 152–153 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 7.19 (t, 1H, $J = 8.6$, H-5), 7.57 (m, 3H, H-3′, H-5′, H-6), 7.68 (t, 1H, H-4′), 7.89 (m, 3H, H-2, H-2′, H-6′), 9.12 (s, 1H, C=SNH), 12.58 (s, 1H, C=ONH). IR (KBr): $v = 3125$ (NH), 3000, 2950, 2800 (C–H), 1660, 1620, 1570, 1530, 1490, 1350, 1260, 1160, 870, 810, 690 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 308 ($M^+ + 2$) (6.42), 308 (M^+) (18.59), 273 ($M^+ - Cl$) (6.14), 187 (C_7H_4ClFNS) (55.24), 145 (C_6H_5ClFN) (6.07), 121 ($C_6H_5CONH_2$) (9.02), 105 ($C_6H_5C{=}O$) (100.00), 77 (C_6H_5) (67.83), HRMS Calcd. for $C_{14}H_{10}ClFN_2OS$ 308.0186. Found: 308.0189.

3.1.3. Syntheses of N-(3-chloro-4-fluorophenyl) -N′-(2,4,5-trifluoro-3-methoxylbenzoyl)thiourea (**5c**)

Yield 64%, mp 162–163 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 4.09 (s, 3H, –OCH_3), 7.17 (t, 1H, $J_{56} = 8.6$, $J_{45} = 8.8$ Hz, H-5), 7.51 (m, 1H, H-6), 7.59 (o, 1H, $J_{F(o)-H} = 11.7$ Hz, $J_{F(m)-H} = 8.4$ Hz, H-6′), 7.84 (dd, 1H, $J_{24} = 6.5$ Hz, $J_{26} = 2.7$ Hz, H-2), 9.53 (d, 1H, $J = 14.5$ Hz, C=SNH), 12.29 (s, 1H, C=ONH). IR (KBr): $v = 3400$, 1680, 1550, 1500, 1460, 1370, 1270, 1200, 1100, 1040, 870, 830, 780, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 392 (M^+) (17.35), 205 ($C_8H_6F_3NO_2$) (19.45), 189 ($C_8H_4F_3O_2$) (100.00), 161 ($C_7H_4F_3O$) (20.00), 129 (C_6H_3ClF) (18.51), 92 (C_6H_6N) (14.36). HRMS Calcd. for $C_{15}H_9ClF_4N_2O_2S$ 392.0009. Found: 392.0016.

3.1.4. Syntheses of N-(2-fluoro-4-chlorophenyl)-N′-(2,4,5-trifluoro-3-methoxybenzoyl)thiourea (**5d**)

Yield 83.3%, mp 155–56 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 4.09 (s, 3H, –OCH_3), 7.19 (m, 2H, H-3, H-5), 7.63 (o, 1H, $J_{F(o)-H} = 11.7$ Hz, $J_{F(m)-H} = 8.4$ Hz, H-6′), 8.41 (t, 1H, $J_{56} = 8.6$ Hz, $J_{26} = 8.1$ Hz, H-6), 9.57 (d, 1H, $J = 14.5$ Hz, C=SNH), 12.44 (s, 1H, C=ONH). IR (KBr): $v = 3050$, 1680, 1600, 1540, 1510, 1470, 1370, 1220, 1150, 1100, 1050, 910, 820, 780, 760, 600 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 392 (M^+) (29.37), 205 ($C_8H_6F_3NO_2$) (18.13), 189 ($C_8H_4F_3O_2$) (100.00), 161 ($C_7H_4F_3O$) (13.51), 146 (C_6HF_3O) (11.68). HRMS Calcd. for $C_{15}H_9ClF_4N_2O_2S$ 392.0009. Found: 392.0013.

3.1.5. Syntheses of N-(2-fluoro-4-chlorophenyl)-N′-benzoylthiourea (**5e**)

Yield 91.9%, mp 133–134 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 7.15 (m, 1H, H-3, H-5), 7.49 (t, 2H, $J_{6'5'} = J_{2'3'} = 8.0$ Hz, H-3′, H-5′), 7.61 (t, 1H, $J = 7.4$ Hz, H-4′), 7.85 (d, 2H, $J_{5'6'} = J_{3'2'} = 8.0$ Hz, H-2′, H-6′), 8.34 (t, 1H, $J_{56} = 8.6$ Hz, $J_{26} = 8.2$ Hz, H-6), 9.11 (s, 1H, C=SNH), 12.64 (s, 1H, C=ONH). IR (KBr): $v = 3240$, 1680, 1600, 1550, 1530, 1350, 1260, 1210, 1150, 880, 800, 690 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 308 (M^+) (4.74), 273 ($M^+ - Cl$) (6.14), 186 (C_7H_3ClFNS) (83.11), 145 (C_6H_5ClFN) (9.23), 121 ($C_6H_5CONH_2$) (8.20), 105 ($C_6H_5C{=}O$) (100.00), 77 (C_6H_5) (32.56), HRMS Calcd. for $C_{14}H_{10}ClFN_2OS$ 308.0186. Found: 308.0189.

3.1.6. Syntheses of N-(2-fluoro-4-chlorophenyl)-N′-(2,4-dichloro-3-nitro-5-fluorobenzoyl)thiourea (**5f**)

Yield 74.9%, mp 220–221 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 7.16 (m, 1H, H-3, H-5), 7.68 (d, 1H, $J = 7.8$ Hz, H-6′), 8.31 (t, 1H, $J_{56} = 8.6$ Hz, $J_{26} = 8.2$ Hz, H-6), 9.18 (s, 1H, C=SNH), 12.02 (s, 1H, C=ONH). IR (KBr): $v = 3200$, 3050, 1690, 1590, 1560, 1540, 1450, 1400, 1350, 1230, 1160, 890, 800, 720 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 439 (M^+) (1.16), 408 ($M^+ + 4$-Cl)

(10.64), 406 ($M^+ + 2$-Cl) (80.12), 404 ($M^+ - Cl$) (100), 238 ($C_6H^{37}Cl_2FNO_2C{=}O$) (47.62), 236 ($C_6H^{35}Cl_2FNO_2{-}C{=}O$) (88.82), 188 ($C_7H_4ClFNS$) (6.55), 187 ($C_6H_3ClFN{=}C{=}S$) (80.12), 145 ($C_6H_5ClFN$) (11.86), 131 ($C_6H_3{}^{37}ClF$) (2.34), 129 ($C_6H_3{}^{35}ClF$) (6.47), HRMS Calcd. for $C_{14}H_6Cl_3F_2N_3O_3S$ 438.9164. Found: 438.9169.

*3.1.7. Syntheses of N-(2-methoxyphenyl)-N′-(2,4,5-trifluoro-3-methoxylbenzoyl)thiourea (**5g**)*

Yield 86.0%, mp 142–143 °C. MS (EI, 70 eV): *m*/*z* (%): 370 (M^+) (11.53), 205 ($C_8H_6F_3NO_2$) (22.90), 189 ($C_8H_4F_3O_2$) (100.00), 165 (C_8H_7NOS) (32.10), 146 (C_6HF_3O) (9.24), 122 (C_7H_8NO) (15.18). HRMS Calcd. for $C_{16}H_{13}F_3N_2O_3S$ 370.0599. Found: 370.0599.

*3.1.8. Syntheses of N-(2,4-difluorophenyl)-N′-(2,4-dichloro-3-nitro-5-fluorolbenzoyl)thiourea (**5h**)*

Yield 52.2%, mp 191–192 °C. ^{1}H NMR (CD_3Cl, 500 MHz): δ 7.12 (m, 1H, H-3, H-5), 7.67 (d, 1H, $J = 7.8$ Hz, H-6′), 8.29 (m, 1H, H-6), 9.18 (s, 1H, C=SNH), 12.01 (s, 1H, C=ONH). IR (KBr): $\nu = 3200, 3050, 1690, 1610, 1560, 1450, 1400, 1230, 1170, 970, 860, 800, 720\ cm^{-1}$. MS (EI, 70 eV): *m*/*z* (%): 424 (M^+) (3.12), 391($M^+ + 2$-Cl) (78.34), 389 ($M^+ - Cl$) (100), 238 ($C_6H^{37}Cl_2FNO_2C{=}O$) (43.48), 236 ($C_6H^{35}Cl_2FNO_2{-}C{=}O$) (88.90), 171 ($C_6H_3F_2N{=}C{=}S$) (80.12), 129 ($C_6H_5F_2N$) (11.86), 113 ($C_6H_3F_2$) (2.34). HRMS Calcd. for $C_{14}H_6Cl_2F_3N_3O_3S$ 424.1869. Found: 424.1870.

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