Synthesis and insecticidal/acaricidal activity of novel 3-(2,4,6-trisubstituted phenyl)uracil derivatives†

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Abstract: A series of novel 3-(2,4,6-trisubstituted phenyl)uracil derivatives has been synthesised and assayed for insecticidal/acaricidal activity. The assay indicated certain requirements for optimal insecticidal activity, which can be summarised as follows: (a) the substituents on the phenyl ring should possess hydrophobicity and electron-withdrawing properties, and the sum of their volumes determines the level of activity; (b) the substituent at the 6-position on the uracil ring should also possess electron-withdrawing properties and hydrophobicity, together with the correct volume; (c) the 1-position on the uracil ring should be unsubstituted for activity against *Nephotettix cincticeps* and *Epilachna vigintioctopunctata*, but substituents with length C3 to C4 may be optimal for activity against *Tetranychus urticae*; (d) certain substituents at the 5-position of the uracil ring give activity against *E vigintioctopunctata* and *T urticae*, but not against *N cincticeps*; (e) a thiocarbonyl group at the 2-position of the uracil ring is less effective than a carbonyl group.

Of the compounds assayed, 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-trifluoromethyluracil showed high activity against all the species assayed.

Keywords: heterocyclic uracil; insecticidal activity; structure–activity relationships

1 INTRODUCTION

It is known that some uracil derivatives have biological activity, and typical examples of this can be found in the field of pharmaceuticals, such as 5-fluorouracil as a classic anti-tumour agent. However, in the field of agricultural chemicals, no compound of this class with insecticidal activity has, to our knowledge, been reported in the literature.

On the other hand, numerous heterocycles, such as pyrazole,[1,2] imidazole,[3] triazole,[4] triazolone[5] and pyrimidinone,[6] linked with a 2,4,6-trisubstituted benzene moiety have been reported in the literature or patents as being insecticidal. However, molecular design of the heterocyclic systems has tended to be focused mainly onto 5-membered rings, and only limited attention has been paid to 6-membered rings. With respect to substituents, most of the compounds reported in the literature possess electron-withdrawing groups or atoms such as halogen, haloalkyl or cyano on the phenyl ring, and studies appear to have been restricted to these. Detailed information on structure–activity relationships of the compounds has not been reported, although such data are of great interest. If the whole molecule fulfils the structural requirements for insecticidal activity shown by the reported compounds, further optimisation with other heterocycles in combination with a 2,4,6-trisubstituted benzene ring would bring new insecticidally active compounds.

In the course of our recent studies to find novel classes of insecticidal compounds relating to heterocycles possessing a multi-substituted aryl moiety,[1,7] we focused on 6-membered heterocyclic compounds. Amongst these compounds, a series of 3-(2,4,6-trisubstituted phenyl)uracil derivatives, which can be expressed by the general structure shown in Fig 1, were selected. Through synthesis and biological assay against *Hemiptera, Coleoptera* and *Tetranychus* spp, we have succeeded in finding novel 3-phenyluracil derivatives possessing insecticidal and acaricidal activity.

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Herein we report the synthesis of novel 3-(2,4,6-trisubstituted phenyl)uracil derivatives, and the insecticidal and acaricidal activities of these compounds, including detailed structure–activity relationships of the substituents on the molecule and LC_{50} values for representative compounds in the series.

2 EXPERIMENTAL

2.1 General

Melting points were measured with a Yanagimoto micro-melting point apparatus and were uncorrected. [1H]NMR spectra (60 MHz) were recorded in deuterochloroform unless otherwise indicated, with tetramethylsilane as internal standard, using a Hitachi R-1200 or JOEL PMX-60SI NMR spectrometer. Electron impact mass spectra were measured on a JOEL JMS AM-50.

2.2 Chemicals

Trisubstituted phenylisocyanate or phenylisothiocyanate derivatives were synthesised by an established route: reactions of trisubstituted aniline with trichloromethyl chloroformate, phosgene or thiophosgene. Ethyl trisubstituted phenylcarbamate derivatives were obtained from trisubstituted aniline and ethyl chloroformate.

Ethyl 3-amino-4,4,4-trifluoro-2-butenoate was obtained commercially or prepared from ethyl trifluoroacetoacetate and liquid ammonia. Ethyl 3-amino-5,5,5,4,4-pentafluoro-2-pentenoate and 2-amino-4-chloro-4,4-difluoro-2-butenoate were prepared from the corresponding ethyl perhalogenated acyl acetate and liquid ammonia in a similar manner. Ethyl 2-trifluoromethylpropionate was prepared from ethyl trifluoroacetate and ethyl propionate and was reacted with liquid ammonia to give ethyl 3-amino-2-methyl-4,4,4-trifluoro-2-butenoate. Ethyl 3-amino-2-cyano-4,4,4-trifluoro-2-butenoate was prepared by a Reformatski reaction from trifluoroacetonitrile and ethyl cyanoacetate.

2.3 Synthesis

Figure 2 depicts the general synthetic pathway to the 6-alkyl or 6-haloalkyl-3-(2,4,6-trisubstituted phenyl)-uracil derivatives extensively employed in this study, which were synthesised using a method reported in the literature.[8]

Thus, reactions of amino esters (**A**) with 2,4,6-trisubstituted phenyl isocyanates (**B**) or 2,4,6-trisubstituted phenyl carbamates (**B′**) in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF) afforded 3-(2,4,6-trisubstituted phenyl)-6-substituted uracils, and reactions with 2,4,6-trisubstituted phenyl thioisocyanate derivatives gave 3-(2,4,6-trisubstituted phenyl)-6-substituted-2-thiouracil derivatives. 5-Cyano-6-trifluoromethyluracil (**5d**) was prepared directly from ethyl 3-amino-2-cyano-4,4,4-trifluoro-2-butenoate (**A**, R′ = CN) with phenyl isocyanate. 5-Methyl-6-trifluoromethyluracil derivatives were prepared directly from ethyl 3-amino-2-methyl-4,4,4-trifluoro-2-butenoate in the same manner as above.

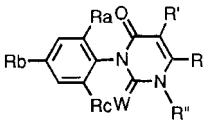
3-(2,4-Dinitro-6-trifluoromethylphenyl)-6-trifluoromethyluracil (**1s**) was alternatively synthesised via a cross-coupling reaction between 6-trifluoromethyluracil and 2,4-dinitro-6-trifluoromethylchlorobenzene as shown in Fig 3. Thus, 6-trifluoromethyluracil (**F**), prepared from ethyl trifluoroacetate (**C**) and *S*-methylthiourea (**D**) via 2-methylthio-4-trifluoromethyl-6(1*H*)pyrimidinone (**E**), was reacted with 2,4-dinitro-6-trifluoromethylchlorobenzene (**G**) in DMF in the presence of sodium hydride to give **1s**.

All substitutions except for the amino group at the 1-position on the uracil ring were carried out with the corresponding halides, such as alkyl halide or acetyl chloride, as shown in Fig 2. 1-Amino-3-(2,6-dichloro-4-trifluoromethylphenyl)-6-trifluoromethyluracil (**3k**) was obtained from the corresponding 1-unsubstituted uracil and 2,4-dinitrophenoxyamine in the presence of potassium carbonate in DMF.

3-(2,6-Dichloro-4-trifluoromethylphenyl) derivatives substituted with bromine (**4a**), or methylthio (**4e**) or methanesulfonyl (**4f**) groups at the 6-position were prepared by means of a substitution reaction on the uracil nucleus as depicted in Fig 4. Thus, bromination of 3-(2,6-dichloro-4-trifluoromethylphenyl)perhydropyrimidine-2,4,6-trione (**H**), which was prepared from 2,6-dichloro-4-trifluoromethylphenylurea (**I**) and malonyl dichloride (**J**), with phosphorus oxybromide in benzene gave 6-bromo-(2,6-dichloro-4-trifluoromethylphenyl)uracil (**4a**). The 6-bromo derivative was allowed to react with methylmercaptan sodium salt (MeSNa) to give 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-methylthiouracil (**4e**). Oxidation of **4e** to the corresponding sulfone (**4f**) was then easily accomplished using two equivalents of *m*-chloroperbenzoic acid (MCPBA) in methylene chloride at ambient temperature.

Halogenations of 5-unsubstituted uracil (**1a**) to the corresponding 5-chloro (**5b**) or 5-bromo (**5c**) derivatives were accomplished using *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in refluxing acetonitrile (Fig 5). Reactivity at the position was not sufficient to allow substitution with those agents at room temperature.

Typical syntheses for each pathway outlined in Figs



R : Me, CF_3, C_2F_5, Br. S(O)nMe
R' : H, Cl, Br, Me, CN
R" : alkyl, alkenyl, alkinyl, alkoxy, acyl, amino
W : O, S
Ra-c : halogen, alkyl, haloalkyl, haloalkoxy, CN, NO_2
n : 0-2

Figure 1. General structure of 3-(2,4,6-trisubsituted phenyl)uracil derivatives.

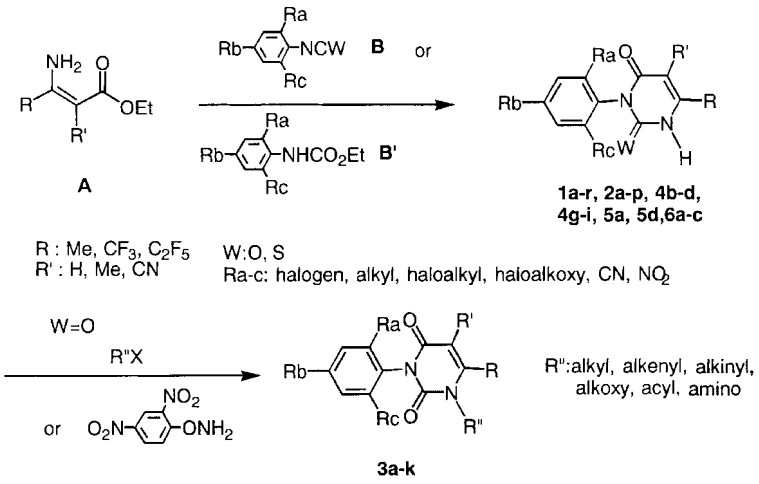


Figure 2. General synthetic pathway to 6-alkyl- or 6-haloalkyl-3-(2,4,6-trisubstituted phenyl)uracil derivatives.

2–5 are described below; the yields were not optimised.

*2.3.1 3-(2,4,6-Trichlorophenyl)-6-trifluoromethyluracil (***1a***, General procedure for* ***1a–r, 2a–p, 4b–d, 4g–i, 5a, 5d*** *and* ***6a–c****)*

To a suspension of 3.53g (80mmol) of NaH in 70ml of DMF under ice-water cooling, a solution of 14.6g (80mmol) of ethyl 3-amino-4,4,4-trifluoro-2-butenoate in 30ml of DMF was added. After stirring for 30min, a solution of 14.6g (65.6mmol) of 2,4,6-trichlorophenylisocyanate in 70ml of DMF was added. The mixture was stirred for 2.5h at room temperature and for 0.5h at 80°C. The resulting mixture was poured onto ice-water, acidified with hydrochloric acid, and extracted with ethyl acetoacetate. The organic layer was washed with water and brine, and dried over sodium sulfate. After removal of the solvent, the residue was treated with isopropyl ether to obtain 18.9g of 3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil as a solid, yield 66%, mp: 224–227°C; *m/z* 358 (M^+); [^{1}H]NMR ($CDCl_3+CD_3OD$ δppm): 6.10 (1H, s), 7.38 (2H, s)

*2.3.2 3-(2,4-Dinitro-6-trifluoromethylphenyl)-6-trifluoromethyluracil (****1q****)*

To a solution of 1.0g (5.5mmol) of 6-trifluoromethyluracil in 10ml of DMF, 55% NaH was added under ice-water cooling and stirred for 0.5h at room temperature. 1.89g (7mmol) of 2,4-dinitro-6-trifluoromethylphenyl chloride was added to the mixture and stirred for 3h at room temperature. The resulting solution was poured onto ice-water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. After removal of the solvent, the residue remaining was treated with hexane to obtain 0.77g of 3-(2,4-dinitro-6-trifluoromethylphenyl)-6-trifluoromethyluracil, yield 34%, mp: 219–220.5°C; *m/z* 414 (M^+); [^{1}H]NMR ($CDCl_3+CD_3OD$, δppm): 6.10 (1H, s), 8.78 (1H, d, J=3Hz), 9.08 (1H, d, J=3Hz).

*2.3.3 3-(2,6-Dichloro-4-trifluoromethylphenyl)-6-methanesulfonyluracil (****4f****)*

A mixture of 0.5g (1.3mmol) of 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-methylthiouracil, 0.57g (3.3mmol) of MCPBA and 10ml of dichloromethane was stirred for 2h at room temperature. The reaction mixture was washed with water and dried over sodium sulfate. Removal of the solvent gave 0.17g of 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-methanesulfonyluracil as a white solid, yield 33%, mp: 219.0–222.0°C; [^{1}H]NMR (δppm): 3.20 (3H, s), 6.42 (1H, s), 7.63 (2H, s).

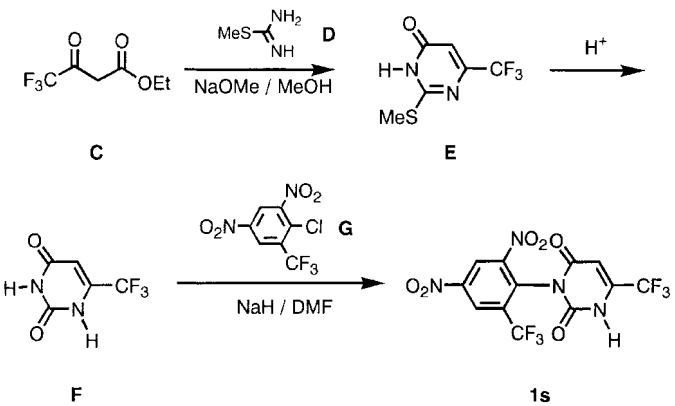


Figure 3. Synthesis of 3-(2,4-dinitro-6-trifluoromethylphenyl)-6-trifluoromethyluracil.

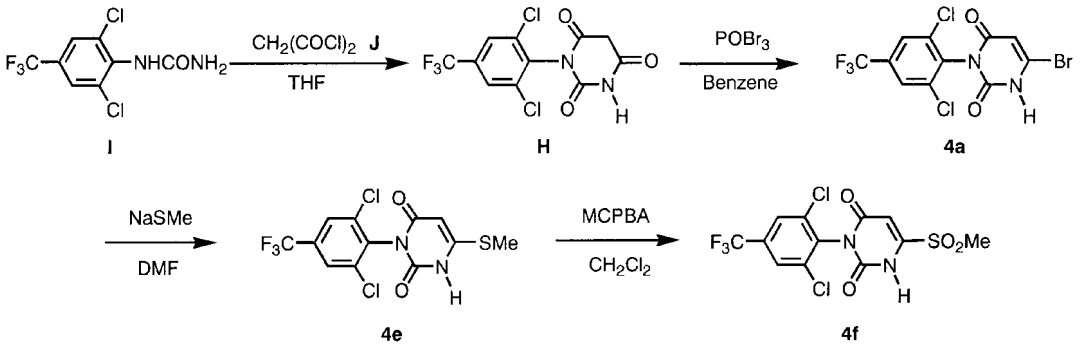


Figure 4. Synthetic scheme to 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-methansulfonyluracil.

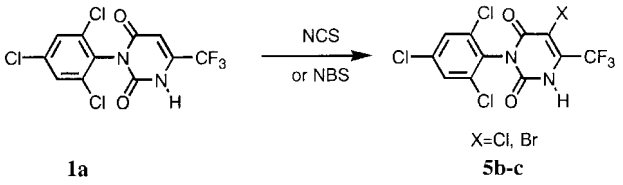


Figure 5. Halogenations at 5-position on the uracil nucleus.

*2.3.4 3-(2,6-Dichloro-4-trifluoromethylphenyl)-6-methylthiouracil (**4e**)*

A mixture of 1.62 g (4 mmol) of 6-bromo-3-(2,6-dichloro-4-trifluoromethylphenyl)uracil, 0.56 g (8 mmol) of methyl mercaptan sodium salt and 15 ml of DMF was stirred for 1.5 h at 90 °C. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over sodium sulfate. Removal of the solvent gave a crude solid, which was treated with hexane to give 0.68 g of 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-methylthiouracil as a white solid, yield 46%, mp: 219–222 °C; [^{1}H]NMR (δppm): 2.48 (s, 3H), 5.68 (s, 1H), 7.76 (s, 2H).

*2.3.5 6-Bromo-3-(2,6-dichloro-4-trifluoromethylphenyl)uracil (**4a**)*

A mixture of 3.4 g (10 mmol) of 3-(2,6-dichloro-4-trifluoromethylphenyl) perhydropyrimidine-2,4,6-trione, 14.3 g (50 mmol) of phosphorus oxybromide, 1.57 g (13 mmol) of dimethylaniline and 30 ml of benzene was stirred for 1.5 h at 75 °C. The reaction mixture was poured onto ice-water, washed with water and brine, and dried over sodium sulfate. Removal of the solvent gave a crude solid, which was treated with isopropyl ether to give 1.4 g of 6-bromo-3-(2,6-dichloro-4-trifluoromethylphenyl)uracil as a solid, yield 35%, mp: 259–260.5 °C; [^{1}H]NMR (δppm): 6.01 (1H, s), 7.77 (2H, s).

*2.3.6 1-Ethyl-3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil (**3a**)*

To a solution of 0.53 g (1.5 mmol) of 3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil in 5 ml of DMF, 0.09 g (2 mmol) of NaH was added and stirred for 1 h under ice-water cooling. A solution of 1.17 g (7.5 mmol) of ethyl iodide in 2 ml of DMF was added to the mixture and stirred for 5 h at 100 °C. The resulting mixture was poured onto ice-water and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent gave 0.20 g of 1-ethyl-3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil as a solid, yield 34%, mp: 136–137.5 °C; [^{1}H]NMR (δppm): 1.32 (3H, t, J=7.2 Hz), 3.95 (2H, q, J=7.2 Hz), 6.23 (1H, s), 7.33 (2H, s).

*2.3.7 5-Bromo-3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil (**5c**)*

A mixture of 3.6 g (10 mmol) of 3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil, 4.1 g (50 mmol) of sodium acetate, 6.4 g (40 mmol) of bromine and 30 ml of acetic acid was refluxed for 8 h. After removal of the solvent, the residue was dissolved in ethyl acetate and the solution was washed with water and brine. Removal of the solvent gave a crude product, which was washed with isopropyl ether to obtain 0.80 g of 5-bromo-3-(2,4,6-trichlorophenyl)-6-trifluoromethyluracil as a solid, yield 46%, mp: 222–225 °C; [^{1}H]NMR ($CDCl_3+CD_3OD$, δppm): 7.38 (2H, s).

2.4 Biological assays

Each compound was formulated as an emulsifable concentrate which was then diluted with water containing a surfactant to give AI concentrations of 500, 100 and 10 mg litre^{-1} to assess activity levels and to six concentrations for determinations of LC_{50} values.

2.4.1 Brown planthopper (Nilaparvata lugens Staol), Green rice leafhopper (Nephotettix cincticeps (Uhl), Small brown planthopper (Laodelphax striatellus (Fall))

Rice stems were immersed in each solution for 20 s. Each treated stem was put into a glass tube (2 cm diam × 10 cm high) with a small amount of water. After drying, seven third-instar nymphs or adults of *N cincticeps* were released into each tube, which was kept at 25 °C, 70% RH under long-day (16L/8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment, and two replications were made. A similar technique, with six concentrations, was used to determine LC_{50} values of selected compounds towards *N lugens*, *L striatellus*, and

susceptible and organophosphate-resistant strains of *N cincticeps*.

2.4.2 Twenty-eight-spotted lady beetle (Epilachna vigintioctopunctata F)

Tomato leaf cuts were immersed in the solutions for 20 s. Each treated leaf cut was placed in a Petri dish (3 cm diam) and seven third-instar larvae or adults of *E vigintioctopunctata* were released into each tube. Treated insects were kept at 25 °C, 70% RH under long-day (16L/8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment and two replications were made.

2.4.3 Two-spotted spider mite (Tetranychus urticae Koch)

Newly hatched larvae of *T urticae* on kidney bean leaf discs (prepared by the Rothamsted method) were sprayed with the solutions of the chemicals via a 'Rotary Spray Tower' to give a standard deposit of 2.5 ml cm^{-2}. Treated mites were kept at 25 °C, 70% RH under long-day (16L/8D) conditions. Mortality was observed six days later. Thirty to forty larvae were used for each treatment and two replications were made.

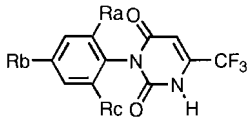
3 RESULTS AND DISCUSSION

Table 1 contains data on a series of 3-(2,4,6-trisubstituted phenyl)uracil analogues in which the 2- and 6-positions on the phenyl group were substituted with various electron-withdrawing groups and atoms. Emphasis was placed primarily on variations of the substituent at the 4-position, with the 2- and 6-positions fixed as chlorine atoms (**1a–f**).

A chlorine atom as an electron-withdrawing substituent at the 4-position on the phenyl ring (**1a**) gave activity against *N cincticeps* (NC), but activities against the other two species, *E vigintioctopunctata* (EV) and *T urticae* (TU) were rather low. As the substituent was increased in size, the spectrum of activity tended to expand. Replacement of chlorine at the 4-position with bromine (**1b**) or trifluoromethyl (**1c**) gave activity against EV, and that against NC increased to the 10 mg $litre^{-1}$ level. A pentafluoroethyl group (**1d**) gave broad-spectrum activity, including TU, and a trifluoromethoxy group (**1e**) gave the highest ratings against all the three species assayed. Introduction of a nitro group (**1f**), a hydrophilic electron-withdrawing group, at the 4-position on the phenyl ring reduced the overall activity.

Replacement of the chlorine atom at the 6-position of the phenyl ring, as in **1c**, with a bromine atom (**1g**) increased the insecticidal activity compared to the 2,6-dichloro analogue. In the series of 2,6-dibromo derivatives (**1h–m**), however, the activities of the compounds containing trifluoromethyl (**1h**) or trifluoromethoxy (**1i**) groups at the 4-position, which had high ratings in the 2,6-dichlorophenyl derivatives, were somewhat lower. However, a 4-bromo-derivative, 2,4,6-tribromophenyluracil (**1j**), gave the highest ratings against all the three species. The introduction of a fluorine atom (**1k**), as the smallest halogen, reduced activity.

Table 1. Biological activity of 3-(2,4,6-trisubstituted phenyl)-6-trifluoromethyluracil derivatives



					Activity rating[a]		
Compound	*Ra*	*Rb*	*Rc*	*mp (°C)*	*NC*	*EV*	*TU*
1a	Cl	Cl	Cl	224–227	2	1	1
1b	Cl	Br	Cl	241–243	2	2	1
1c	Cl	CF_3	Cl	248–250	3	2	1
1d	Cl	C_2F_5	Cl	300<	2	2	1
1e	Cl	OCF_3	Cl	247–220.5	3	3	3
1f	Cl	NO_2	Cl	221–224	2	1	2
1g	Cl	CF_3	Br	206–208.5	3	2	3
1h	Br	CF_3	Br	220–223	3	2	2
1i	Br	OCF_3	Br	205–208	2	2	1
1j	Br	Br	Br	240–241	2	2	3
1k	Br	F	Br	229–231	2	1	2
1l	Br	i-Pr	Br	237.5–241	1	1	1
1m	Br	c-hex	Br	264–266	1	1	1
1n	F	Br	F	213–215.5	2	1	1
1o	F	F	F	178–181	1	2	2
1p	Cl	CF_3	NO_2	172–174	2	2	2
1q	NO_2	NO_2	CF_3	219–220.5	1	1	1

[a] Lc_{95} (mg $litre^{-1}$); >500: 1, 500–100: 2, 100–10: 3.

The introduction of alkyl groups at the 4-position on the phenyl ring, while not leading to complete inactivation, showed a tendency to reduce activity (**1l–m**). The trifluoromethyl group has been recognised as showing similar size effects to the isopropyl group.[9] However, the introduction of an isopropyl group (**1l**) as an alternative to the trifluoromethyl group at the 4-position drastically reduced overall activity compared to those of trifluoromethyl analogues. This suggests that the substituent at the 4-position on the phenyl ring should possess electron-withdrawing properties.

The introduction of a fluorine atom at both the 2- and 6-position (**1n**) tended to reduce activity compared to **1j**, which suggests that proper volume or bulkiness is needed at these positions to provide high insecticidal activity. Further substitution of a fluorine atom at the 4-position led to a further decline in activity (**1o**).

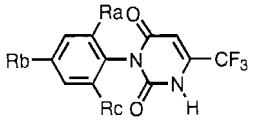
The substitution of a nitro group at the *ortho*-position on the phenyl ring reduced or completely eliminated activity. (**1p–q**).

From all the results shown in Table 1, it is concluded that the substituent at the 4-position should have electron-withdrawing and hydrophobic properties, together with the correct volume. The order of activity was $OCF_3 > CF_3 \geq C_2F_5$.

Although some compounds gave high activity against TU, structure–activity relationships were not clear.

To examine the effects of substituents with electron-donating properties at the 2- and 6-position on the phenyl ring, some alkyl groups were introduced. The results are shown in Table 2. Substitution of one methyl group at the 6-position of **1a**, as in **2a–b**, slightly reduced the insecticidal activity against NC compared to that of 2,6-dichlorophenyl derivatives, but led to some activity against EV and TU. Introducing a cyano group at the 4-position, as an electron-withdrawing group, led to complete loss of activity (**2c**). Introduction of methyl groups at both 2- and 6-position slightly reduced activity (**2d–m**). In a series of 2,6-dimethylphenyl analogues, substitution at the 4-position with a trifluoromethoxy group (**2f**) produced relatively high insecticidal activity, as was also observed in the 2,6-dihalogen derivatives (Table 1). Some insecticidal activity was retained on the introduction of the electron-withdrawing methylsulfinyl group (**2k**), but this was reduced on replacement by methanesulfonyl (**21**), and an ethoxycarbonyl group at the 4-position led to complete inactivation (**2m**). It is considered that the length and/or volume of the substituent at the 4-position may contribute to optimal activity in addition to the properties found in the compounds listed in Table 1. An electron-donating group at the 4-position, as in **2g, 2i** and **2j**, led to a reduction in activity, as had been found with the 2,6-dihalogeno derivatives (Table 1)

Table 2. Biological activity of 3-(2,4,6-trisubstituted phenyl)-6-trifluoromethyluracil derivatives with the electron-donating substituents at 2- and 6-positions on the phenyl ring



					Activity rating[a]		
Compound	*Ra*	*Rb*	*Rc*	*mp (°C)*	*NC*	*EV*	*TU*
2a	Cl	Cl	Me	217–219	2	2	2
2b	Cl	Br	Me	220–224	1	2	1
2c	Cl	CN	Me	287–289	1	1	1
2d	Me	Br	Me	242.5–243.5	2	2	1
2e	Me	I	Me	272–275.5	1	2	2
2f	Me	OCF_3	Me	277–279	3	2	2
2g	Me	Me	Me	218–220	1	1	1
2h	Me	CN	Me	273–276	1	1	1
2i	Me	OMe	Me	183–185	1	1	1
2j	Me	SMe	Me	273–276	1	1	1
2k	Me	SOMe	Me	262–264	2	2	1
2l	Me	SO_2 Me	Me	300<	1	1	1
2m	Me	CO_2 Et	Me	264–268	1	1	1
2n	Et	Br	Et	179.5–181	2	2	1
2o	Me	Br	i-Pr	241–242.5	1	2	1
2p	i-Pr	Br	i-Pr	176–180	1	2	1

[a] See Table 1.

Elongation or enlargement of the methyl group at the 2- and/or 6-position to ethyl or isopropyl, as in **2n–p**, retained activity, but no clear tendencies were observed.

Considering the results shown in Tables 1 and 2, while the 2- and 6-position on the phenyl ring do not necessarily have to be substituted with electron-withdrawing groups, such electronic properties at these positions firmly improve the insecticidal activity. As to size, small and compact substituents at the 2- and 6-position are favourable to biological activity. The substituent at the 4-position on the phenyl ring should be hydrophobic with electron-withdrawing properties as well as suitable size or shape.

Comparing the compounds which gave the highest ratings for all the species, such as **1e,1g** and **1j**, the sum of the volumes of the substituents on the phenyl ring is almost identical. This result indicates that the volume of the phenyl moiety in the whole molecule may be responsible for optimal activity. The effects of the electron-withdrawing substituents on the phenyl ring suggest that the electronic properties at the 3-position on the uracil ring may influence interaction with a receptor in the insect body system.

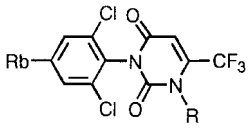
In order to examine the effects of substituents at the 1-position of the uracil ring, a variety of groups were introduced. The results are shown in Table 3.

Substituents at the 1-position on the uracil ring tended to reduce or completely eliminate activity against NC, although some activity was retained against EV and TU (**3a–k**). Introducing substituents which were assumed to be degradable in the insect body, such as acetyl (**3b**) or ethoxymethyl (**3h**) gave biological activity against all species. Other groups which were not considered to be easily degradable led to complete inactivation against NC and EV. However, the presence of an amino group, which is also not considered to be easily degradable, gave compounds (eg **3k**) showing activity against these two species. Some compounds possessing slightly longer groups, C3 to C4, as in **3e, 3f, 3g** and **3i**, showed activity against TU. Against NC and EV, it was suggested that the hydrogen atom on the nitrogen at the 1-position on the uracil ring seemed to have a specific role in making the properties of the molecule suitable for activity, which could be postulated as hydrogen bonding between the molecule and a receptor. The hydrogen atoms on the amino group may play a role as hydrogen bonding donors in place of the hydrogen atom on the uracil ring nitrogen. Against TU, structural requirements seem to be different from those required for NC and EV, and the proper length of the substituent, which should not be easily degradable, would appear to be important in some cases.

Table 4 contains data on a series of uracil analogues in which the 6-position has been substituted with various groups to examine the effects of combinations of such substituents with those on the phenyl ring.

In the first place, effects of the combination of the substituents at the 6-position on the uracil ring and the

Table 3. Biological activity of 1-substituted phenyl-6-trifluoromethyluracil derivatives



Compound	R	Rb	mp (°C)	Activity rating[a] NC	EV	TU
1a	H	Cl	224–227	2	1	1
3a	Et	Cl	136–137.5	1	1	1
3b	COMe	Cl	117–120	2	2	2
3c	CH_2 CN	Cl	173–175	1	1	1
3d	CH_2 Ph	Cl	127–129	1	1	1
3e	n-Pr	Cl	oil	1	2	2
3f	CH_2 CH=CH_2	Cl	104–105	1	2	1
3g	CH_2 C≡CH	Cl	131–132	1	2	2
3h	CH_2 OEt	Cl	H	2	2	3
3i	n-Bu	Cl	106–107	1	1	2
1c	H	CF_3	248–250	3	2	1
3j	Me	CF_3	145–148	1	1	1
3k	NH_2	CF_3	198–201	2	2	1

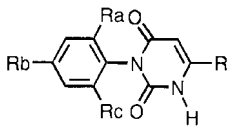
[a] See Table 1.

4-position on the phenyl ring were examined using 3-(2,6-dichloro-4-trifluoromethylphenyl)uracil derivatives and 3-(2,4,6-trichlorophenyl)uracil derivatives (**1c,4a–i**). In the series of 2,6-dichloro-4-trifluoromethylphenyl derivatives (**1a,1c, 4a–f**), replacement of the trifluoromethyl group (**1c**) at the 6-position on the uracil ring with a bromine atom (**4a**), whose Van der Waals volume is close to that of the trifluoromethyl group, resulted in a decrease in activity. Replacing one atom of the trifluoromethyl group with a chlorine atom slightly increased activity against TU (**4b**). Elongation of the chain from trifluoromethyl to pentafluoroethyl (**4c**) increased the activities against EV and TU. A methyl group (**4d**), as an electron-donating group, led to complete inactivity. A methylthio (**4e**) or methanesulfonyl group (**4f**) instead of the trifluoromethyl group also drastically reduced activity.

Similar variations in activity were observed in 2,4,6-trichlorophenyluracil derivatives with different substituents at the 6-position of the uracil ring (**1a, 4g–i**), but these were favourable compared to those found with the 2,6-dichloro-4-trifluoromethyl analogues. Replacement of one fluorine atom to give a chlorodifluoromethyl group (**4g**) or elongation to pentafluoroethyl (**4h**) provided broad-spectrum activity and the latter compound gave the highest ratings against EV and TU. However, a heptafluoropropyl group (**4i**) produced a slight decrease in insecticidal activity compared with the pentafluoroethyl group. The *tert*-butyl group is one of the common constituents in insecticidally and acaricidally active compounds,[10] and is the substituent on the 1,3,4-oxadiazole-5-one derivatives reported as giving favourable activity in our previous paper.[7] However, it was not effective in this uracil system, as the *tert*-butyl analogue (**4j**) was inactive in comparison with the trifluoromethyl derivative (**1j**).

Considering the results obtained here, an electron-withdrawing group with the correct shape and hydrophobicity at the 6-position of the uracil ring and a trifluoromethyl group or halogen atom at the 4-position on the phenyl ring were required for the development of optimal insecticidal activity, and subtle changes in the properties of the substituents affect the latter. In both cases, a pentafluoroethyl group at the 6-position led to relatively high potency.

Table 5 shows the effects of the substituent at the 5-position on the uracil ring. Substituents at this position

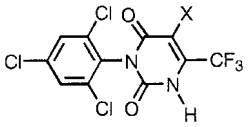


Compound	R	Ra	Rb	Rc	mp (°C)	Activity rating[a] NC	EV	TU
1c	CF_3	Cl	CF_3	Cl	248–250	3	2	1
4a	Br	Cl	CF_3	Cl	259–260.5	1	1	1
4b	CF_2 Cl	Cl	CF_3	Cl	236–239	2	2	2
4c	CF_3 CF_2	Cl	CF_3	Cl	207–209	3	2	2
4d	Me	Cl	CF_3	Cl	246–248	1	1	1
4e	MeS	Cl	CF_3	Cl	219–222	1	1	1
4f	$MeSO_2$	Cl	CF_3	Cl	219–220	1	1	1
1a	CF_3	Cl	Cl	Cl	224–227	2	1	1
4g	CF_2 Cl	Cl	Cl	Cl	268–270	3	2	2
4h	CF_3 CF_2	Cl	Cl	Cl	236–239	3	3	2
4i	CF_3 CF_2 CF_2	Cl	Cl	Cl	203–207	3	2	1
1j	CF_3	Br	Br	Br	240–241	2	2	3
4j	t-Bu	Br	Br	Br	286–289	1	1	1

Table 4. Biological activity of 3-(2,4,6-trisubstituted phenyl)-6-substituted uracil derivatives

[a] See Table 1.

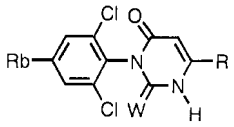
Table 5. Biological activity of 3-(2,4,6-trichloro phenyl)-5-substituted 6-trifluoromethyluracil derivatives



			Activity rating[a]		
Compound	X	mp (°C)	NC	EV	TU
1a	H	224–227	2	1	1
5a	Me	222–225	1	2	2
5b	Cl	238–239.5	1	2	1
5c	Br	219–222	2	3	2
5d	CN	Solid	1	1	1

[a] See Table 1.

Table 6. Biological activity of 2-thiocarbonyl-3-(2,4,6-trisubstituted phenyl)uracil derivatives



					Activity rating[a]		
Compound	R	Rb	W	mp (°C)	NC	EV	TU
6a	CF_3	Cl	S	208–210	1	3	1
6b	CF_3	CF_3	S	205–207	1	1	1
6c	CF_2Cl	Cl	S	208–214	1	2	1
1a	CF_3	Cl	O	224–227	2	1	1
1c	CF_3	CF_3	O	248–250	3	2	1
4g	CF_2Cl	Cl	O	268–270	3	2	2

[a] See Table 1.

resulted in a reduction in activity against NC, but the compounds were effective against EV (**5a–c**). A bromine atom gave a particularly high rating against the latter (**5c**). The presence of a cyano group at the 5-position (**5d**) resulted in a loss of activity. These results can be construed as showing that the substituent at this position must be hydrophobic.

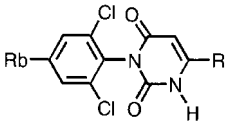
Table 6 shows the uracil derivatives on which the ring carbonyl at the 2-position on the uracil ring was replaced by a thiocarbonyl group. This resulted in a complete loss of activity against NC (**6a–c**), and, although mortalities were shown against EV and TU, effects of structure changes were not clear.

To assess in detail the insecticidal potential and spectrum against Hemiptera species and EV as a representative of Coleoptera, compounds **1c,1e** and **4c** were selected from the compounds showing highest activities. Assays were conducted against *N lugens* (NL), *L striatellus* (LS), NC and EV, and the results in terms of LC_{50} values are shown in Table 7. It is interesting to note that most of the compounds listed in that table possessed insecticidal activity not only against larvae but also against adults of *Hempitera;* in particular, **1c** was effective against all species tested. It is also interesting to note that activity relationships against larvae and adults of LS are very different from those against NC. **1c** was much more active against adult LS than against adult NC, but slightly less active against the larvae of LS than against those of NC.

Uracil compounds were found to be effective against organophosphate-resistant NC, which clearly shows that there is no cross-resistance against that chemistry. The difference in activity between the resistant and the susceptible strains of NC is negligible, with LC_{50} values for **1c** against larvae of 6.5 and 6.0 mg litre^{-1}, respectively. Activities against adults were much less than against larvae.

Compound **1c** was the most active of those tested against EV, with an LC_{50} value of 5 mg litre^{-1}. The most active compound against NL was **4c** with an LC_{50} value of 4.3 mg litre^{-1}, only one-quarter of that of the conventional pyrethroid insecticide, trebon.

In conclusion, a series of 3-(2,4,6-trisubstituted phenyl)uracil derivatives has been synthesised and assayed for insecticidal and acaricidal activity; detailed structure–activity relationships against *N cincticeps, E vigintioctopunctata* and *T urticae* have been elucidated. The requirements for optimal insecticidal activity can



			LC_{50} (mg litre^{-1})								
			NL[a]		LS		R-NC		S-NC		EV
	R	Rb	Larvae	Adult	Larvae	Adult	Larvae	Adult	Larvae	Adult	Larvae
1c	CF_3	CF_3	6.0	7.7	10.9	5.5	6.5	117	6.0	124	5.0
1e	CF_3	OCF_3	24.2	145	67.0	36.3	6.8	>333	18.8	>333	19.5
4c	C_2F_5	CF_3	4.3	14.1	11.8	16.4	6.8	>333	32.9	>333	26.2
	Trebon		18.5	10.1	–	1.7	2.1	1.0	1.0	0.9	–

Table 7. LC_{50} values of selected 3-trisubstituted phenyluracil derivatives

[a] NL: *N lugens;* LS: *L striatellus;* NC: *N cincticeps;* EV: *E vigintioctopunctata;* R: Resistant strain; S: Susceptible strain.

be summarised as follows: (a) the substituents on the phenyl ring should be hydrophobic and have electron-withdrawing properties; the sum of their volumes controls the level of activity. Chlorine, trifluoromethyl or trifluoromethoxy substituents were found to be particularly favourable. (b) The substituent at the 6-position on the uracil ring should also have electron-withdrawing properties, hydrophobicity and the correct volume. (c) Optimal activity against *N cincticeps* and *E vigintioctopunctata* is obtained when there is no substituent at the 1-position of the uracil ring, but a substituent with length C3 to C4 at this position may be optimal against *T urticae*. (d) A substituent at the 5-position of the uracil ring increases activity against *E vigintioctopunctata* and *T urticae*, but not against *N cincticeps*. (e) A thiocarbonyl group at the 2-position of the uracil ring was less effective than a carbonyl group. Insecticidal properties were confirmed not only with larvae but also with adults of the species assayed; of the compounds assayed, 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-trifluoromethyluracil (**1c**) showed high activity against all the species, and 3-(2,6-dichloro-4-trifluoromethylphenyl)-6-pentafluoroethyluracil (**4c**) also showed good insecticidal properties. Its LC_{50} value against larvae of *N lugens*, 4.3 mg litre^{-1}, was the highest activity recorded.

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