Synthesis and acaricidal activity of 4-pyrimidinyloxy- and 4-pyrimidinylaminoethylphenyl dioxolanes and oxime ethers

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Abstract: Novel types of mitochondrial respiration inhibitors at complex I, with emphasis on acaricidal activity, have been designed and prepared. The synthetic approach to these 4-pyrimidinylphenyl ethyl ethers and amines with a specific ketal or oxime function in the phenyl side chain is outlined. Bioassays demonstrate their high potential against important spider mites, like *Tetranychus urticae* and *Panonychus ulmi*. Structure–activity relationship studies and several biological parameters are discussed.

Keywords: acaricide; respiration inhibitor; NADH:ubiquinone oxidoreductase; quinazoline; pyrimidine; synthesis; SAN 1398 A

1 INTRODUCTION

The continuous search for new acaricides and insecticides, intensified by resistance problems and the need for new environmentally safe pesticides, has focused recently on inhibitors of the respiratory chain.[1,2] Several modern acaricides, which reached the market recently, such as fenazaquin,[3] tebufenpyrad,[4] fenpyroximate,[5] pyridaben[6] and pyrimidifen,[7] as well as the natural product rotenone, interrupt mitochondrial electron transport by inhibition of NADH:ubiquinone oxidoreductase (complex I).[8–12] Although several derivatives of fenazaquin (Fig 1; **I**) have been described already,[13,14] we found during the course of a research programme that substitution of fenazaquin's *tert*-butyl group by a dioxolane ring (general structure **II**) or an oxime function (general structure **III**) leads to new acaricides, which are highly effective against spider mites of major importance, like the two-spotted spider mite, *Tetranychus urticae* (Koch), and the European red mite, *Panonychus ulmi* (Koch). The new compounds display outstanding contact activity on mobile stages of the mites and in addition possess moderate ovicidal properties.

2 MATERIALS AND METHODS

2.1 Chemical synthesis

The quinazoline and pyrimidine derivatives 4-chloroquinazoline,[15] 4-chloro-5,6,7,8-tetrahydroquinazoline,[16] 4-chloro-5-methylthieno[2,3-*d*]pyrimidine,[17] 4-chloro-5-methoxy-6-methoxymethylpyrimidine[18] and 4,5-dichloro-6-ethylpyrimidine[19] were prepared according to literature procedures.

The synthetic pathways used to prepare the new dioxolanes and oxime ethers are shown in Fig 2. 2-Phenylethyl benzoate[20] (**1**) was transformed by Friedel–Crafts acylation[21] to the ketone **2**,[22,23] which served as a key intermediate. Ketalization and debenzoylation then gave dioxolanylphenethanols **4**. These were either converted to the corresponding amine **5** via a Mitsunobu reaction[24,25] or linked to an appropriate pyrimidine or quinazoline derivative to give 4-pyrimidinyloxyethyl phenyl dioxolanes such as **33**.

Representative procedures are given below.

2.1.1 2-(4-acetylphenyl)ethyl benzoate (2)

Anhydrous aluminum chloride (263 g, 1.98 mol) was suspended in dichloromethane (1800 ml). After cooling the mixture to 0 °C, acetyl chloride (81 g; 1.0 mol) and 2-phenylethyl benzoate[20] (**1**; 212 g; 0.94 mol) were added one after the other. The reaction mixture was stirred for 16 h at room temperature, and then poured into a mixture of crushed ice (500 ml) and concentrated hydrochloric acid (900 ml). After separation of the phases, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and aqueous potassium bicarbonate solution (100 g litre^{-1}), dried over magnesium

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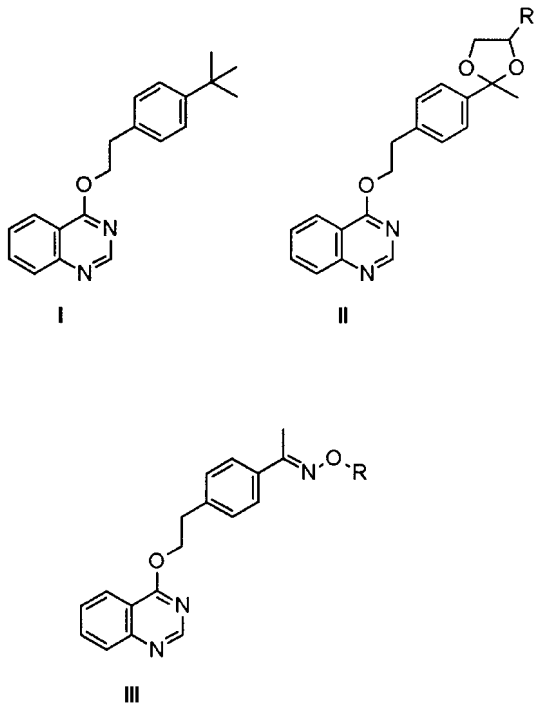


Figure 1. Structures of compounds discussed

sulfate and evaporated in vacuum. The residue was recrystallized from ethyl acetate + hexane. Yield: 165 g (0.62 mol, 66%), mp 90.5–91.5 °C. [^{1}H]NMR (deuterochloroform): δ = 8.04–7.35 (m, 9H), 4.56 (t, 2H), 3.15 (t, 2H), 2.60 (s, 3H).

*2.1.2 2-[4-(4-butyl-2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl benzoate (**3**)*

1,2-Hexanediol (11.8 g; 0.1 mol) and 4-toluenesulfonic acid monohydrate (0.5 g) were added to a solution of compound **2** (26.8 g; 0.1 mol) in toluene (200 ml). The resulting mixture was heated at reflux for 7 h using a Dean–Stark trap, then cooled and poured into a mixture of crushed ice, (100 ml) and aqueous potassium bicarbonate solution (100 g litre^{-1}; 100 ml). After separation of the phases, the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with aqueous potassium bicarbonate solution (100 g litre^{-1}) and water, dried over magnesium sulfate and evaporated in vacuum. Yield: 31.2 g (85 mmol, 85%). [^{1}H]NMR (deuterochloroform): δ = 8.05–7.22 (m, 9H), 4.54 (t, 2H), 4.15 (m, 1H), 3.87 (m, 2H), 3.09 (t, 2H), 1.71–1.25 (m, 9H), 0.96 (t, 3H).

*2.1.3 2-[4-(4-butyl-2-methyl-1,3-dioxolan-2-yl)phenyl]ethanol (**4**)*

Compound **3** (31.2 g; 85 mmol) was stirred in 150 ml of a solution of potassium hydroxide (100 g litre^{-1}) in methanol + water (80+20 by volume) for 2 h at room temperature. The mixture was concentrated in vacuum, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated in vacuum. Yield: 17.7 g (67 mmol, 79%). [^{1}H]NMR (deuterochloroform): δ = 7.42 (d, 2H), 7.20 (d, 2H), 4.15 (m, 1H), 3.93–3.80 (m, 4H), 2.87 (t, 2H), 1.69–1.22 (m, 9H), 0.95 (t, 3H).

*2.1.4 2-[4-(4-butyl-2-methyl-1,3-dioxolan-2-yl)phenyl]ethylamine (**5**)*

To a solution of compound **4** (9.5 g; 36 mmol), triphenylphosphine (10 g; 38 mmol) and phthalimide (5.9 g; 40 mmol) in tetrahydrofuran (400 ml), was added dropwise diethyl azodicarboxylate (7.3 g; 42 mmol). The reaction was stirred for 1 h at room temperature. The solvent was removed in vacuum and the residue dissolved in diethyl ether + hexane. The resulting precipitate was washed with the same mixture of solvents, the combined filtrate was evaporated in vacuum and the residue suspended in ethanol (40 ml). Methylamine solution (330 g litre^{-1} in ethanol; 40 ml) was added slowly. The reaction mixture was stirred for 3 h at room temperature, and then evaporated in vacuum. Yield: 6.8 g (26 mmol, 72%). [^{1}H]NMR (deuterochloroform): δ = 7.44 (d, 2H), 7.21 (d, 2H), 4.32 (m, 1H), 4.08 (t, 2H), 3.89–3.83 (m, 2H), 2.95 (t, 2H), 1.70 –1.27 (m, 9H), 0.96 (t, 3H).

*2.1.5 4-[2-(benzoyloxy)ethyl]acetophenone oxime (**6**)*

Compound **2** (250 g, 0.93 mol) was suspended in ethanol (1100 ml). Hydroxylamine hydrochloride (97 g, 1.4 mol) and anhydrous sodium acetate (114 g; 1.4 mol) were added and the reaction stirred for 2 h at 60 °C. The mixture was cooled to room temperature, then poured on to crushed ice (500 ml) and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated in vacuum. Yield: 194 g (0.69 mol, 74%). [^{1}H]NMR (deuterochloroform): δ = 8.04–7.27 (m, 9H), 4.55 (t, 2H), 3.10 (t, 2H), 2.29 (s, 3H).

*2.1.6. O-(isopropyl)-4-[2-(benzoyloxy)ethyl]acetophenone oxime (**7**)*

Sodium hydride (0.7 g, 30 mmol) was suspended in *N*,*N*-dimethylformamide + tetrahydrofuran (1 + 1 by volume; 30 ml). A solution of compound **6** (7.0 g; 25 mmol) in *N*,*N*-dimethylformamide + tetrahydrofuran (1 + 1 by volume; 40 ml) was added dropwise. The mixture was stirred for 1 at room temperature, 2-chloropropane (2.0 g, 25 mmol) was added and the reaction stirred for a further 16 h at room temperature. The mixture was diluted with water and extracted with diethyl ether, the combined organic layers dried over magnesium sulfate and evaporated in vacuum. The residue was chromatographed on silica gel (hexane + diethyl ether, 1 + 1 by volume). Yield: 5.5 g (17 mmol, 67%). [^{1}H]NMR (deuterochloroform): δ = 8.04–7.24 (m, 9H), 4.55 (t, 2H), 4.42 (m, 1H), 3.11 (t, 2H), 2.23 (s, 3H), 1.33 (d, 3H), 1.30 (d, 3H).

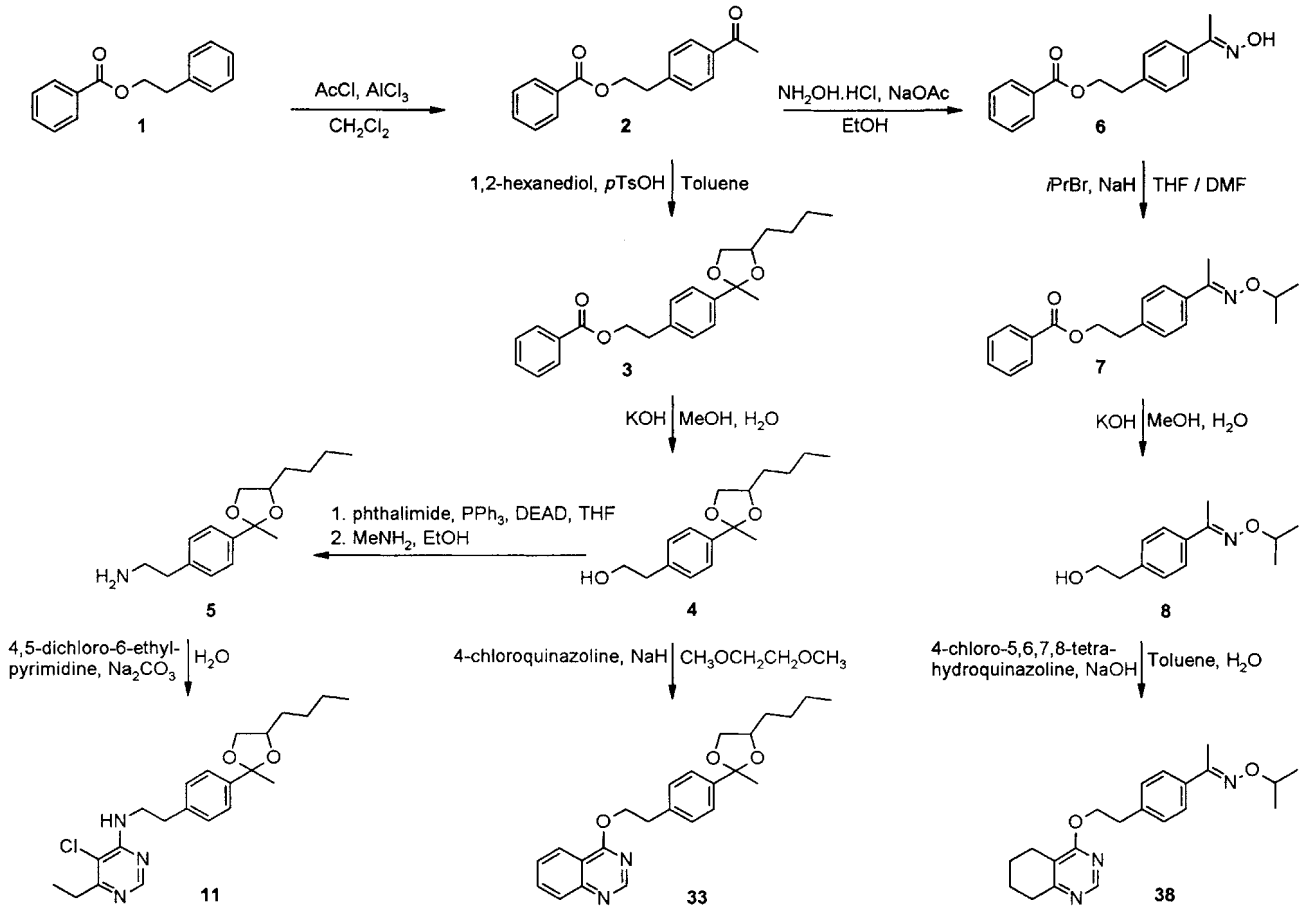


Figure 2. Synthetic routes to novel 4-pyrimidinyloxy- and 4-pyrimidinylamino-ethylphenyl dioxolanes and oxime ethers.

2.1.7. O-(isopropyl)-4-(2-hydroxyethyl)acetophenone oxime (8)

Compound **7** (5.0 g; 15 mmol) was stirred in a solution of potassium hydroxide (100 g litre^{-1}) in methanol + water (80 + 20 by volume) (100 ml) for 2 h at room temperature. The mixture was concentrated in vacuum, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated in vacuum. Yield: 2.7 g (12 mmol, 81%). [^{1}H]NMR (deuterochloroform): δ = 7.61 (d, 2H), 7.22 (d, 2H), 4.47 (q, 1H), 3.88 (t, 2H), 2.90 (t, 2H), 2.21 (s, 3H), 1.34 (d, 3H), 1.31 (d, 3H).

2.1.8 N-4-[2-[4-(4-butyl-2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl]-5-chloro-6-ethyl-pyrimidin-4-amine (11)

A mixture of compound **5** (2.1 g; 7.9 mmol), 4,5-dichloro-6-ethylpyrimidine[19] (1.8 g; 10 mmol) and sodium carbonate (2.4 g; 23 mmol) in water (40 ml) was heated to reflux for 3 h, then diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuum. The residue was chromatographed on silica gel (hexane + ethyl acetate, 1 + 1 by volume). Yield: 2.3 g (5.6 mmol, 71%). [^{1}H]NMR (deuterochloroform): δ = 8.42 (s, 1H), 7.43 (d, 2H), 7.19 (d, 2H), 5.44 (bs, 1H), 4.17 (m, 1H), 3.92–3.70 (m, 4H), 2.93 (t, 2H), 2.79 (q, 2H), 1.71–1.58 (m, 5H), 1.39 –1.21 (m, 7H), 0.91 (t, 3H).

2.1.9 4-[2-[4-(4-butyl-2-methyl-1,3-dioxolan-2-yl)phenyl]ethoxy]quinazoline (33)

Sodium hydride (1.6 g, 65 mmol) was suspended in 1,2-dimethoxyethane (50 ml) and cooled to 0 °C. A solution of compound **4** (14.3 g; 54 mmol) in 1,2-dimethoxyethane (100 ml) was added dropwise. The reaction was stirred for 1 h at room temperature and cooled again to 0 °C, then 4-chloroquinazoline[15] (9.7 g; 59 mmol) added in portions. The mixture was stirred for 16 h at room temperature, cooled to 0 °C, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated in vacuum. The residue was chromatographed on silica gel (hexane + ether; 8 + 2 by volume). Yield: 17.3 g (44 mmol, 82%). [^{1}H]NMR (deuterochloroform): δ = 8.80 (s, 1H), 8.18–7.31 (m, 8H), 4.79 (t, 2H), 4.18 (m, 1H), 3.86 (m, 2H), 3.21 (t, 2H), 1.74–1.20 (m, 9H), 0.90 (t, 3H).

2.1.10 O-(isopropyl)-4-[2-(5,6,7,8-tetrahydroquinazolin-4-yloxy)ethyl]acetophenone oxime (38)

To a solution of compound **8** (85 g; 0.38 mol) in toluene (500 ml) were added successively aqueous

sodium hydroxide (300 g litre^{-1}; 250 ml) benzyltriethylammonium chloride (5.0 g; 22 mmol) and 4-chloro-5,6,7,8-tetrahydroquinazoline[16] (70 g; 0.42 mol) in portions. The mixture was stirred for 5 h at room temperature, then extracted with diethyl ether and washed with water. The organic layer was dried over magnesium sulfate and evaporated in vacuum. The residue was chromatographed on silica gel (hexane + ethyl acetate; 7 + 3 by volume). Yield: 120 g (0.34 mol, 90%). [^{1}H]NMR (deuterochloroform): δ = 8.49 (s, 1H), 7.60 (d, 2H), 7.26 (d, 2H), 4.57 (t, 2H), 4.46 (q, 1H), 3.10 (t, 2H), 2.79 (t, 2H), 2.52 (t, 2H), 2.21 (s, 3H), 1.88–1.73 (m, 4H), 1.35 (d, 3H), 1.30 (d, 3H).

2.2 Formulations and standards

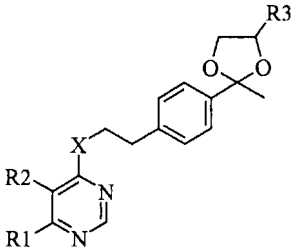
The test compounds were applied as 100 g litre^{-1} emulsifiable concentrates in *N,N*-dimethyl formamide + xylene, using Atlox 4851B as surfactant. Fenazaquin and tebufenpyrad (both > 95%) were used similarly as standards. Commercial hexythiazox 100 g kg^{-1} WP (Trevi 10WP) and fenpyroximate 500 g litre^{-1} SC (Kiron 50SC) were used as standards in field tests.

2.3 Biological assays

2.3.1 Acaricidal assays on two-spotted spider mite, Tetranychus urticae (Koch)

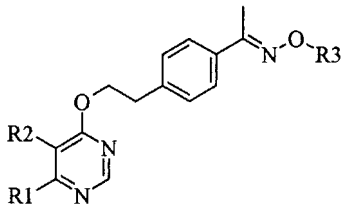
For these biological assays, conducted in the labora-

Table 1. Acaricidal activity against *Tetranychus urticae* of 4-pyrimidinyloxy- and 4-pyrimidinylaminoethylphenyl dioxolanes



					LC_{95} (mg litre^{-1})		
					Contact		Ovicidal
Compound No	R_1	R_2	R_3	X	2–3 days	8–10 days	6 days
9	C_2H_5	Cl	$CH_2OCH_2CH{=}CH_2$	NH	1	2	>400
10	—CH=CH—CH=CH—		$CH_2OCH_2C(CH_3){=}CH_2$	O	0.3	2	119
11	C_2H_5	Cl	$CH_2CH_2CH_2CH_3$	NH	2	3	16
12	—CH=CH—CH=CH—		CH_2OCH_2CCH	O	3	3	>400
13	—S— CH—$C(CH_3)$—		$CH_2SCH_2CH_3$	O	6	4	>400
14	—CH=CH—CH=CH—		$CH_2OCH_2C(Cl){=}CH_2$	O	2	5	84
15	—S— CH—$C(CH_3)$—		$CH_2OCH_2CH{=}CH_2$	O	3	5	34
16	CH_2OCH_3	OCH_3	$CH_2SCH_2CH_3$	O	3	5	23
17	—CH_2—CH_2—CH_2—CH_2—		$CH_2OCH_2CH{=}CH_2$	NH	8	8	>400
18	—CH=CH—CH=CH—		$CH_2OCH_2CH{=}CH_2$	O	20	9	37
19	CH_2OCH_3	OCH_3	$CH_2OCH_2CH{=}CH_2$	O	3	10	37
20	CH_2OCH_3	OCH_3	CH_2SCH_3	O	8	10	12
21	CH_2OCH_3	OCH_3	$CH_2OCH(CH_3)_2$	O	5	11	150
22	—CH_2—CH_2—CH_2—CH_2—		$CH_2OCH_2CH_2OCH_3$	O	20	11	100
23	—S—CH—$C(CH_3)$—		$CH_2CH_2CH_2CH_3$	O	29	11	13
24	—CH=CH—CH=CH—		CH_2OCH_3	O	7	12	4
25	—S—CH—$C(CH_3)$—		CH_2SCH_3	O	10	12	>400
26	—CH=CH—CH=CH—		C_6H_5	O	19	12	105
27	—S—CH—CH—		$CH_2OCH_2CH{=}CH_2$	O	1	13	29
28	—CH_2—CH_2—CH_2—CH_2—		CH_2OCH_2CCH	O	7	13	16
29	—CH_2—CH_2—CH_2—CH_2—		$CH_2CH_2CH_2CH_3$	NH	5	14	>400
30	—CH=CH—CH=CH—		$CH_2OCH_2C_6H_5$	O	19	14	>400
31	—CH=CH—CH=CH—		$CH_2O(4{-}Cl{-}C_6H_5)$	O	36	15	47
32	—CH=CH—CH=CH—		$CH_2OCH_2CH{=}CHCH_3$	O	49	17	>400
33	—CH=CH—CH=CH—		$CH_2CH_2CH_2CH_3$	O	26	18	80
34	—CH_2—CH_2—CH_2—CH_2—		$CH_2OCH(CH_3)_2$	O	7	22	12
35	—CH=CH—CH=CH—		CH_2Cl	O	23	22	42
36	—CH_2—CH_2—CH_2—CH_2—		$CH_2OCH_2CH{=}CH_2$	O	43	32	20
	Tebufenpyrad				11	11	17
	Hexythiazox				>500	13	14
	Fenazaquin				74	74	173

Table 2. Acaricidal activity against *Tetranychus urticae* of 4-pyrimidinyloxy-ethylphenyl oxime ethers



				LC_{95}(mg litre^{-1})		
				Contact		Ovicidal
Compound no	R1	R2	R3	2–3 days	8–10 days	6 days
37	—CH=CH—CH=CH—		$CH_2CH_2OCH_3$	9	9	25
38	—CH_2—CH_2—CH_2—CH_2—		$CH(CH_3)_2$	13	11	124
39	CH_2OCH_3	OCH_3	$CH_2CH_2OCH_3$	13	14	284
40	—CH_2—CH_2—CH_2—CH_2—		CH_2SCH_3	9	15	37
41	—CH=CH—CH=CH—		CH_2OCH_3	17	15	>400
42	—CH_2—CH_2—CH_2—CH_2—		CH_2OCH_3	19	15	76
43	—CH_2—CH_2—CH_2—CH_2—		$CH_2CH_2OCH_3$	13	20	56
44	—CH_2—CH_2—CH_2—CH_2—		$CH_2CH=CH_2$	46	21	80
45	—CH=CH—CH=CH—		$CH_2C(Cl)=CH_2$	40	22	69
46	—CH=CH—CH=CH—		$CH_2C(CH_3)=CH_2$	60	22	58
47	—CH_2—CH_2—CH_2—CH_2—		$CH_2C(CH_3)=CH_2$	50	43	369
	Tebufenpyrad			11	11	17
	Hexythiazox			>500	13	14
	Fenazaquin			74	74	173

tory, a susceptible laboratory strain reared at Sandoz Agro was used.

2.3.1.1 Contact activity

Bush bean plants (*Phaseolus vulgaris* L), two-leaf stage, were infested with approximately 30 mites two days before treatment. A mixed population (eggs, nymphs and adults) was treated in an application tunnel (spray volume 1000 litre ha^{-1}; four nozzles). Three replicates per concentration, five concentrations (100, 25, 6.25, 1.6, 0.4 mg AI litre^{-1}) per test series per test compound were used. The treated plants were kept at 25 °C and 50% RH. in a climatic chamber with 16 h light. Rapid contact activity was evaluated after two or three days. Slow contact activity was recorded eight or ten days after treatment. Relative reduction of the mite population was calculated according to Abbott.[26] LC_{95} values were estimated using logit analysis.[27]

2.3.1.2 Ovicidal activity

A glue ring (diameter 2 cm) was placed on the upper side of a leaf from a bush bean plant, two-leaf stage. Five to seven adult females were placed inside the glue ring area and were allowed to lay eggs. The females were removed after 24 h and the eggs were sprayed with four different concentrations (100, 25, 6.25, 1.6 mg AI litre^{-1}) using three replicates per concentration per test series. The treated plants were kept in a climatic chamber at 25 °C, 50% RH and 16 h light. After six days the percentage of unhatched eggs was recorded. LC_{95} values were calculated using logit analysis.[27]

2.3.2 Acaricidal assay on European red mite, Panonychus ulmi (Koch)

Direct contact activity of selected compounds on *Panonychus ulmi* (Koch), European red mite, was measured in the laboratory. Apple leaf discs (diameter: 35 mm) infested with 10 adult mites or L4 larvae were treated with the test compounds using a spray Potter tower (2 ml per treatment). Three replicates per concentration, four concentrations (30, 6, 1.25 and 0.25 mg litre^{-1}) per test compound were used. The treated leaf discs were stored in a climatic chamber at 25 °C, 50% RH and 16 h light. Mortality (%) was recorded after two to three days to calculate the LC_{95} values (logit analysis).[27]

2.3.3 Toxicity to honey bee (Apis mellifera L)

Each test honey bee was treated individually by applying 1 µl test solution (in acetone) ventrally on the thorax (topical application). Five different test concentrations were used (20, 15, 10, 5, 2.5 µg AI per bee). Ten bees per replicate and three replicates per concentration per compound were performed. A test period of three days was used to record dead and affected bees. Parathion-ethyl was used as standard of known toxicity.

2.3.4 Field trials

Field trials and small plot garden trials on apples were conducted in the years 1994 and 1995 in the South of France and in Switzerland. Test compounds were formulated as 100 g litre ECs. Doses of 5 g, 7.5 g and 10 g AI hl^{-1} were applied as a high-volume spray to

Table 3. Acaricidal activity against *Panonychus ulmi*, bee toxicity and field results of 4-pyrimidinyloxy- and 4-pyrimidinylaminoethylphenyl dioxolanes and oxime ethers

	Contact							
	P ulmi	*Honeybees*	*Field trials*					
	2–3 days	*2 days*	*11 days*	*21 days*	*10 days*	*24 days*	*11 days*	*21 days*
No.	LC_{95} (mg litre^{-1})	LD_{50} (μg per litre)	% efficacy at 5g AI hl^{-1}		% efficacy at 7.5g AI hl^{-1}		% efficacy at 10g AI hl^{-1}	
10	23	–	54	90	–	–	56	90
14	4.5	–	57	90	–	–	59	100
15	4	–	60	100	–	–	74	95
18	12	3	73	81	44	97	75	88
19	2	–	79	71	–	–	90	100
33	10	13/48	90	100	60	100	96	100
36	32	8	–	–	69	76	–	–
42	27	3	–	–	55	90	–	–
46	43	7	–	–	70	66	–	–
47	64	6	–	–	54	67	–	–
Fenazaquin	14	10	42	95	81	100	60	95
Tebufenpyrad	–	5	88	98	–	–	96	98
Fenpyroximate	–	–	88	99	–	–	–	–
Parathion-ethyl[a]	–	0.13	–	–	–	–	–	–

[a] Toxic standard for bee toxicity studies.

run-off (three replicates per compound per concentration). Twenty-five leaves were collected randomly from each tree 10 to 11 days and 21 to 24 days after treatment. Relative reduction of the mite population was calculated according to Abbott.[26]

3 RESULTS AND DISCUSSION

As shown in Tables 1 and 2, the tested compounds displayed superior contact activity in comparison to the standards tebufenpyrad, hexythiazox and fenazaquin, whereas ovicidal activity was poor in many cases. A few compounds, for example **11, 20, 33, 38** and **46** showed an interesting translaminar activity (not shown in table). The persistence was overall within the range of the standards.

The basic molecular skeleton represented in the general formula of Tables 1 and 2 is necessary to reach this level of activity. The large assortment of cyclic and acyclic variations of R1 and R2 suggests that these pyrimidine substituents are easily exchangeable. However, the replacement of the chlorine atom in compounds **9** and **11** by a cyano group or the introduction of a substituent into the 2-position of the pyrimidine ring leads to completely inactive compounds. In our experience, the combination R1 = C_2H_5, R2 = Cl and X = NH results in very active acaricides, which also, unfortunately, show high mammalian toxicity. In comparison with these amines, the employment of an oxygen atom in the linker between the pyrimidine and phenyl rings has a positive influence on bee toxicity without reducing activity against spider mites. In the cases of the ketals and the oxime ethers, R3 is preferably a linear lipophilic substituent with three to five chain atoms.

A statistically significant correlation was observed between contact activity values on *T. urticae* (LC_{95} 8–10 days) and on *P. ulmi* (LC_{95} 2–3 days) with compounds **10, 14, 15, 18, 19, 33, 36, 42, 46** and **47** ($r = 0.83$; $df = 8$; $P < 0.01$),[28] which is not the case for fenazaquin.

Small plot garden trials and field trials in apple orchards on *P ulmi* were conducted with compounds **10, 14, 15, 18, 19, 33, 36, 42, 46** and **47** (Table 3). In these trials, the best compound, SAN 1398 A (**33**), was at least as effective as the standards fenazaquin, tebufenpyrad and fenpyroximate at the same application rate (5–10 g AI hl^{-1}). On the beneficial predatory mite *Typhlodromus pyri* (Scheut), compound **33** had a better selectivity than fenazaquin (30% mite reduction versus 51%). Therefore **33** can be categorized as 'low toxicity to predatory mites'. In comparison with fenazaquin and tebufenpyrad, this interesting acaricide displayed also the lowest toxicity (contact activity) on worker honey bees. According to the EPPO guideline 170 (1993),[29] **33** can be considered as 'low risk to honey bees'. Moreover, this compound gave good control of *Varroa jacobsoni* (Oud), an important ectoparasitic mite of the honey bee.

4 CONCLUSION

Two new subclasses of substituted 4-hydroxy- and 4-aminopyrimidines and -quinazolines have been discovered which possess a remarkable profile of acaricidal activity and favourable ecotoxicological properties. The best compound, SAN 1398 A (**33**), performed as well as the common standard acaricides for the control of *Panonychus ulmi* under standard field conditions. Due to its relative safeness to honey bees

and the predatory mite *Typhlodromus pyri*, **33** is an excellent candidate for integrated pest control. A further interesting feature of **33** might be its useful activity against *Varroa jacobsoni*, an ectoparasite of the honey bee, especially since *Varroa* has been reported to be increasingly resistant to tau-fluvalinate (Apistan®) in Europe.[30]

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