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Parasiticidal 2-alkoxy- and 2-aryloxyiminoalkyl trifluoromethanesulfonanilides

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Abstract—A series of novel 2-alkoxy- and 2-aryloxyiminoalkyl trifluoromethanesulfonanilide derivatives have shown significant in vitro parasiticidal activity against the ectoparasites *Ctenocephalides felis* and *Rhipicephalus sanguineus*. A number of these compounds also displayed significant in vitro endoparasite activity against the nematode *Haemonchus contortus*.

The cat flea, *Ctenocephalides felis*, and the brown dog tick, *Rhipicephalus sanguineus*, are prevalent nuisance ectoparasite species afflicting companion animals.[1,2] These pests cause blood loss anemia, allergic dermatitis, and are vectors for infectious pathogens.[3] Although the introduction of the topical insecticides fipronil, imidacloprid, and selamectin has revolutionized flea control on cats and dogs, of these, only fipronil and selamectin are known to be efficacious as acaricides. Moreover, since development of resistance to these parasiticides is a distinct possibility,[4] new agents to control fleas and ticks must continue to be discovered.

Trifluoromethanesulfonanilide (TFMS) derivatives **1** are reported to display potent insecticidal, acaricidal, and nematicidal properties.[5,6] For example, 4-chloro-2-methoxycarbonyl TFMS **1a** (amidoflumet) is under development for use against house dust mites,[5] whereas the 4-fluoroalkoxy TFMS compounds **1b**, **1c** control *Haemonchus contortus* in sheep at low dosages[6] (Fig. 1). Compounds containing the TFMS moiety are known to act as uncouplers of oxidative phosphorylation in mitochondria.[6]

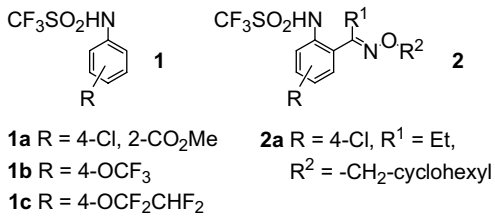

Figure 1.

As part of a program to discover new drugs to control important ectoparasites afflicting companion animals, a set of novel 2-alkoxyiminoalkyl TFMS compounds **2** were screened in a commercial, single-dose (1.26 μg/cm^2) cat flea assay.[7] An *O*-alkyloxime ether, 4-chloro-2-[1-(cyclohexylmethoxyimino)propyl] TFMS **2a**, gave 100% mortality in the cat flea assay, with a corresponding LC_{50} = 29 ng/cm^2 for *C. felis*. This compound subsequently gave 100% mortality in a single-dose (10 μg/tick) brown dog tick assay and an LD_{50} = 3.4 μg/tick for *R. sanguineus*,[7] demonstrating that the 2-alkoxyiminoalkyl TFMS template may deliver significant insecticidal and acaricidal activity. Furthermore, **2a** showed activity against the endoparasite *H. contortus*

Keywords: Trifluoromethanesulfonanilide; Oxime ether; Parasiticide; *Ctenocephalides felis* (cat flea); *Rhipicephalus sanguineus* (brown dog tick); *Haemonchus contortus*.
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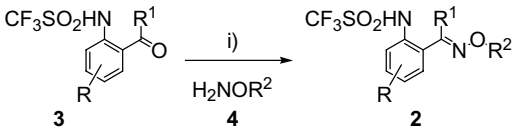


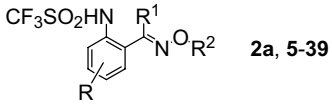
Scheme 1. Reagents: (i) *N*-(R^2O)phthalimide, $(CH_3)_2N(CH_2)_2NH_2$, EtOH then AcOH to pH 4 or $HCl{\cdot}H_2NOR^2$, NaOAc, EtOH.

(LD_{99} = 3 μM),[8] indicative of important broad-spectrum endectoparasiticidal activity.

To probe SAR associated with compound **2a**, a library of *O*-alkyloxime ether analogs **2** was prepared from the reaction of 2-keto TFMS precursors **3** with *O*-alkyloxyamines **4** (Scheme 1 and Table 1).[10,11]

As shown in Table 1, most *O*-alkyloxime ethers **2** displayed excellent activity against cat flea, although none were as potent as the commercial flea control drug fipronil. The best activity was obtained with an electron-withdrawing moiety on the TFMS ring (preferably R = 4-Cl), R^1 as a small alkyl group (methyl or ethyl), and R^2 as a small hydrophobic group.[12] For example, the *O*-(cyclopropylmethyl) derivative **11** gave an LC_{50} = 5 ng/cm^2. Significantly, most *O*-alkyloxime ethers highly active against *C. felis* were also similarly active against *R. sanguineus*, with some derivatives hav-

Table 1. Activity of compounds **2a**, **5–39** against *C. felis* (*C.f.*), *R. sanguineus* (*R.s.*), and *H. contortus* (*H.c*)[a]



2a, **5-39**

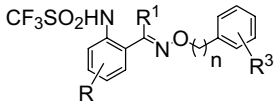
Compound	R	R^1	R^2	*C.f.* % Mortality[b]	*C.f.* LC_{50} (ng/cm^2)	*R.s.* % Mortality[b]	*R.s.* LD_{50} (μg/tick)	*H.c.* LD_{99} (μM)
2a	4-Cl	Et	–CH_2-cyclohexyl	100	29	100	3.4	7
5	4-Cl	Me	–CH_2-cyclohexyl	96		100		
6	4-Cl	*n*-Pr	-CH_2-cyclohexyl	70				11
7	4-Cl	Ph	-CH_2-cyclohexyl	8		52		
8	5-CF_3	Et	–CH_2-cyclohexyl	97		17		
9	4-Cl	Me	–CH_2-cyclopentyl	97	18	100	2.2	7.5
10	4-Cl	Et	–CH_2-cyclopentyl	97		90		
11	4-Cl	Me	–CH_2-cyclopropyl	100	5	100	1.0	
12	4-Cl	Et	–CH_2-cyclopropyl	100	8	100	1.2	36
13	4-Cl	Me	Cyclohexyl	100		100		
14	4-Cl	Et	Cyclohexyl	100		100	5.7	
15	4-Cl	*n*-Pr	Cyclohexyl	43				
16	4-Cl	Ph	Cyclohexyl	12		45		
17	5-CF_3	Me	Cyclohexyl	4				
18	4-Cl	Me	Cyclopentyl	100		100		
19	4-Cl	Et	Cyclopentyl	100	21	100	1.5	25
20	4-Cl	Me	Me	100		93		
21	4-Cl	Et	Me	100	15	95	0.89	16
22	4-Cl	Me	Et	100		85		>15
23	4-Br	Me	Et	100	11	100	1.2	>13
24	5-F	Me	Et	100		8		>15
25	6-OMe	Me	Et	45				>15
26	H	Me	Et	92		90		>16
27	4-Cl	Me	*i*-Pr	100		95		
28	4-Cl	Et	*i*-Pr	100		100		
29	4-Cl	Me	*t*-Bu	100	41	92	1.4	16
30	4-Cl	Et	*t*-Bu	100	43	90	1.5	
31	4-Cl	Me	–CH_2CF_3	100	6	82	0.94	18
32	4-Cl	Et	–CH_2CF_3	100		80		
33	4-Cl	Me	–$(CH_2)_2OMe$	100	12	100	0.71	
34	4-Cl	Et	–$(CH_2)_2OMe$	100		95		
35	4-Cl	Me	Allyl	100		100		
36	4-Cl	Et	Allyl	100	21	100	0.67	32
37	4-Cl	Me	Propargyl	100	11	100	0.99	
38	4-Cl	Et	Propargyl	100	27	100	0.86	20
39	4-Cl	Et	–CH_2-2′-thienyl	100	7	70	2.5	35
Fipronil					0.1–0.2			
Permethrin							0.14–0.22	
Ivermectin								0.006–0.007
Levamisole								0.71–1.3

[a] No entry indicates that the compound was not assayed.
[b] Measured at 24 h.

ing levels of dog tick activity comparable to the commercial ectoparasiticide permethrin: for example, compound **36** gave an LD_{50} = 0.67 μg/tick for *R. sanguineus*.

The high activity against *C. felis* of compound **39**, an *O*-(2′-thienylmethyl) derivative (LC_{50} = 7 ng/cm^2), prompted the preparation of a set of isosteric *O*-benzyloxime ether analogs **40**–**62** from the reaction of 2-carbonyl TFMS precursors **3** with *O*-benzyloxyamines **4** (Scheme 1 and Table 2).[10,11] A number of these derivatives displayed high mortality in a single-dose cat flea assay, with some having LC_{50} values comparable to the best *O*-alkyloxime ether TFMS compounds. Good activity was observed for analogs where R^1 was a methyl or ethyl group,[13] and where the *O*-benzyl moiety contained at least one electron-withdrawing group: for example, compounds **40** and **45**. Two 5-trifluoromethyl TFMS derivatives, compounds **61** and **62**, were also

Table 2. Activity of compounds **40–80** against *C. felis* (*C.f.*), *R. sanguineus* (*R.s.*), and *H. contortus* (*H.c.*)[a]



40-80

Compound	R	R^1	*n*	R^3	*C.f.* % Mortality[b]	*C.f.* LC_{50} (ng/cm^2)	*R.s.* % Mortality[b]	*R.s.* LD_{50} (μg/tick)	*H.c.* LD_{99} (μM)
40	4-Cl	Et	1	4-Cl	100	12	83	2.5	1.7
41	4-Cl	Et	1	4-Br	78		58		1.8
42	4-Cl	Et	1	4-CF_3	98	17	90	2.7	0.84
43	4-Cl	Et	1	4-*t*-Bu	8[c]				6.9
44	4-Cl	Et	1	2-CF_3	96	36	31		2.7
45	4-Cl	Et	1	2,4-DiCF_3	100[c]	19	88		0.56
46	4-Cl	Et	1	2,4-DiCl	94[c]				0.84
47	4-Cl	Et	1	2,3-DiCl	63				0.63
48	4-Cl	Et	1	3,4-DiCl	100				1.3
49	4-Cl	Et	1	2,4-DiF	95[c]				7.2
50	4-Cl	Me	1	4-Cl	100		72		3
51	4-Cl	Me	1	2,4-DiCF_3	2[c]				0.22
52	4-Cl	*n*-Pr	1	4-CF_3	36[c]				3.2
53	4-Cl	*n*-Pr	1	2,4-DiCF_3	79[c]				2.5
54	4-Cl	*n*-Pr	1	2,4-DiCl	88				3.6
55	4-Cl	*i*-Pr	1	4-CF_3	12[c]				2.6
56	4-Cl	*i*-Pr	1	2,4-DiCF_3	10[c]				1.5
57	4-Cl	H	1	2,4-DiCF_3	10[c]				0.59
58	4-Cl	H	1	2,4-DiCl	12[c]				2
59	4-Cl	H	1	3,4-DiCl	42				1.4
60	4-Cl	Ph	1	2,4-DiCF_3	21[c]				3.1
61	5-CF_3	Me	1	4-Cl	100		27		
62	5-CF_3	Et	1	4-Cl	100		25		
63	4-Cl	Et	0	4-Cl	100	51	95		1
64	4-Cl	Et	0	4-F	100	35	92	1.5	3.5
65	4-Cl	Et	0	4-Br	78				3.7
66	4-Cl	Et	0	3-Cl	100				3.6
67	4-Cl	Et	0	3-CF_3	71				2
68	4-Cl	Et	0	3,4-Cl	99	6			1.9
69	5-CF_3	Et	0	4-Cl	100		17		
70	4-Cl	Me	0	4-Cl	90				1
71	4-Cl	Me	0	4-F	100	10	100	1.3	4.6
72	4-Cl	Me	0	4-Br	91				0.87
73	4-Cl	Me	0	3-Cl	100		47		3.8
74	4-Cl	Me	0	3-CF_3	96				0.83
75	4-Cl	Me	0	3,4-Cl	71				1.6
76	4-Cl	Me	0	H	6[c]				14
77	4-Cl	*n*-Pr	0	4-F	36				
78	4-Cl	*i*-Pr	0	4-Cl	100	71	65	1.7	11
79	4-Cl	*i*-Pr	0	4-F	100		42		
80	4-Cl	Ph	0	4-F	21				
Fipronil						0.1–0.2			
Permethrin								0.14	
Ivermectin									0.006–0.031
Levamisole									0.71–1.6

[a] No entry indicates that the compound was not assayed.
[b] Measured at 24 h.
[c] Measured at 8 h.

highly active against *C. felis*. Several *O*-benzyloxime ether derivatives were also active against *R. sanguineus*, although their levels of activity were generally less than the best *O*-alkyloxime ether TFMS compounds.

A number of *O*-benzyloxime ether TFMS compounds also displayed excellent activity against *H. contortus* when screened in a high-throughput *H. contortus* larval development assay.[8] Many derivatives showed levels of activity comparable to the commercial endoparasiticide drug levamisole, although none was as potent as ivermectin. Good activity was obtained for ketoxime ethers where R^1 was a methyl or ethyl group and R^3 consisted of at least one electron-withdrawing group: for example, compounds **42** and **51**. Aldoxime ethers such as compound **57** were also highly active in the nematode assay. It is apparent from SAR that the optimal *O*-benzyl moiety for activity against *H. contortus* was the 2,4-bis(trifluoromethyl)benzyl group. Significantly, the most active *O*-benzyloxime derivative (compound **51**, LD_{99} = 0.22 μM) maintained activity against resistant strains of *H. contortus*: LD_{99} = 0.53 μM for the benzimidazole- and levamisole-resistant Lawes strain and LD_{99} = 0.53 μM for the avermectin-resistant CAVR strain. Furthermore, compound **51** was active against the McMaster strains of *Ostertagia circumcinta*, LD_{99} = 1.1 μM, and *Trichostrongylus colubriformis*, LD_{99} = 2.2 μM.

To further probe SAR associated with the 2-alkoxyiminoalkyl TFMS template, the *O*-benzyl moiety was replaced with an *O*-aryl unit. This structural change eliminates a potential site of metabolic and/or chemical degradation. Thus, a set of *O*-aryloxime ethers **63**–**80** were prepared from the reaction of a 2-keto TFMS **3** with an *O*-aryloxyamine **4** (Scheme 1 and Table 2).[10,11] A number of these derivatives gave high mortality in a cat flea assay, with some displaying levels of activity comparable to the best *O*-alkyloxime ether TFMS compounds. The most active derivatives had R^1 as a methyl, ethyl or *i*-propyl group, and R^3 as a mono- or di-halo substituent: for example, compounds **68**, **71**, and **78**. Several *O*-aryloxime ether derivatives were also highly active in the dog tick assay, although these compounds had LD_{50} values significantly greater than permethrin. In some cases an *O*-aryloxime ether derivative was highly active against both ectoparasites: for example, compound **71** (LC_{50} = 10 ng/cm^2 for *C. felis*, and LD_{50} = 1.3 μg/tick for *R. sanguineus*). In contrast, a 5-trifluoromethyl TFMS derivative (compound **69**) highly active against *C. felis* was inactive against dog tick. Many *O*-aryloxime ether derivatives also displayed good activity when screened in a *H. contortus* larval assay: for example, compound **74** (LD_{99} = 0.83 μM).

In summary, a number of novel 2-alkoxy- and 2-aryloxyiminoalkyl TFMS derivatives displayed excellent in vitro activity against *C. felis* and *R. sanguineus*. The best balance of activity against these ectoparasites was generally exhibited by *O*-alkyloxime ether derivatives. Furthermore, *O*-benzyl- and *O*-aryloxime ether TFMS derivatives often displayed high in vitro activity against the endoparasite *H. contortus*. The best endectoparasiticidal activity was shown by *O*-benzyl- and *O*-aryloxime ether derivatives such as compounds **42** and **64**, respectively. Further research to explore the parasiticidal activity associated with the 2-alkoxy- and 2-aryloxyiminoalkyl TFMS template is ongoing.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.10.090.

References and notes

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7. *C. felis* and *R. sanguineus* assays were conducted by the Centre for Entomological Research and Insecticide Technology, UNSW, Randwick, NSW, Australia, or by Agrisearch Services Pty. Ltd, 50 Leewood Drive, Orange, NSW, Australia. Representative in vitro *C. felis* and *R. sanguineus* single-dose assays and LC_{50}/LD_{50} measurement protocols are described in Supplementary data.
8. Nematocide assays were conducted by Microbial Screening Technologies Pty. Ltd, Smithfield, NSW, Australia. *H. contortus* LD_{99} values were determined using the larval development assay described in Ref. 9.
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11. Representative procedures describing the preparation of 2-alkoxy- and 2-aryloxyiminoalkyl TFMS compounds, and *O*-alkyl-, *O*-benzyl-, and *O*-aryloxyamines are given in Supplementary data.
12. Mitochondrial uncoupling activity is primarily a function of acidity (pK_a) and lipophilicity ($\log P$), see: Terada, H. *Biochim. Biophys. Acta* **1981**, *639*, 225.
13. The low *C. felis* mortality observed for compound **51** probably reflects measurement of mortality at 8 h rather than 24 h.