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Design and synthesis of sarolaner, a novel, once-a-month, oral isoxazoline for the control of fleas and ticks on dogs

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ABSTRACT

Over the last decade, the isoxazoline motif has become the intense focus of crop protection and animal health companies in their search for novel pesticides and ectoparasiticides. Herein we report the discovery of sarolaner, a proprietary, optimized-for-animal health use isoxazoline, for once-a-month oral treatment of flea and tick infestation on dogs.

The companion animal parasiticide market represents a major and rapidly growing segment in the animal health-industry, with an estimated value of approximately US $4.3 billion in 2013 (Source: Vetnosis). Ectoparasiticides, which control flea, tick, lice and mite infestations, are important to pet owners since they not only protect their pets against the direct impact of these parasites, but also may help to prevent the transmission of diseases by these parasites (*e.g.*, lyme disease).[1] The introduction of fipronil in 1994 generated a significant paradigm shift among ectoparasiticides, providing for the first time a highly effective and convenient *topical* monthly control method.[2] Significant market success resulted with annual global sales of Frontline® (Merial) and other animal health fipronil products reaching over US $800 million in 2012.[3] Consequently, over the last two decades, many animal health companies have dedicated significant efforts toward the development of novel and differentiated products, in specific, once-a-month, *orally* administered flea and tick agents for companion animals.[4] Much of this work has been based on leveraging the discovery efforts for new pesticides conducted by agrochemical companies. At the time that we embarked on our own active research in this arena, there were multiple reports in the patent literature of isoxazolines exhibiting insecticidal activity from such sources and representative examples of this class have recently entered the market for animal health use (Fig. 1).[5] Herein we report the discovery of sarolaner, a once-a-month, oral isoxazoline specifically optimized for the treatment of flea and tick infestation on dogs.

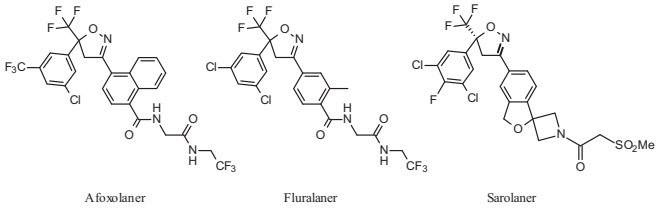

Figure 1. Ectoparasiticidal isoxazolies.

Our initial work in the area of isoxazolines culminated in the discovery of the novel isoxazoline azetidines with oral flea and tick activity in dogs.[6] The in vitro ectoparasiticidal data and oral dog pharmacokinetic (PK) profiles of two representative examples, **1** and **2**, synthesized in the course of that effort, are presented in Table 1.[7,8] With the understanding that plasma is the efficacious compartment, or at least an excellent surrogate for the efficacious compartment, an inspection of these data reveals that while **1**

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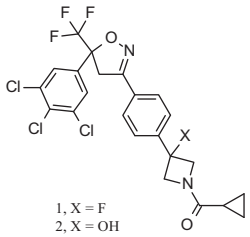
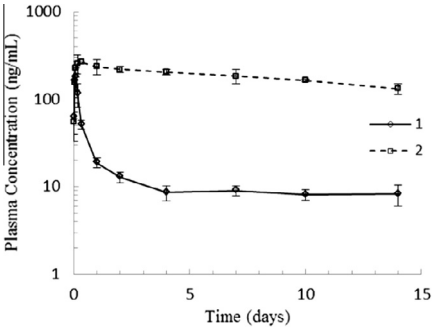
Table 1
In vitro ectoparasiticidal activities and oral dog PK profiles for representative isoxazoline azetidines **1** and **2**

Compound	Flea feed[a]	Soft Tick feed[a]		Computed properties[b]		
	LD_{80} (μg/mL)	ED_{50} (μg/mL)	LD_{100} (μg/mL)	M.W.	*A*log*P*	PSA
1	1	0.03	0.03	534	6.3	42
2	10	N.D.[c]	N.D.[c]	532	5.3	62





[a] Ref. 7.
[b] Pipeline pilot.
[c] Compounds inactive or weakly active in the flea feed assay were not progressed into the soft tick feed assay.

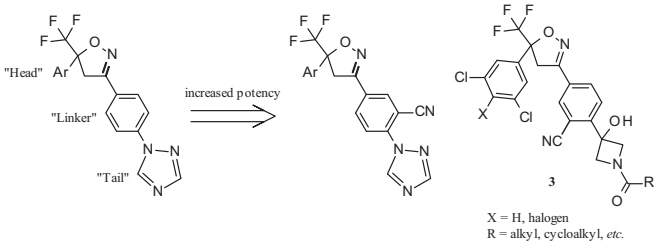


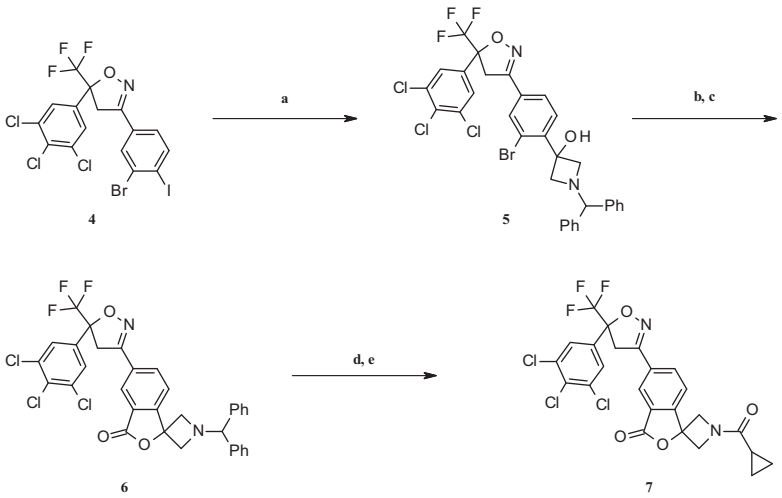
Figure 2. Hypothesized potency optimization of **2** through placement of a CN group.

exhibits superior in vitro flea and tick potency, **2** affords a superior dog PK profile due to its higher systemic plasma concentrations.[9] The challenge in front of us was to incorporate both of these features in a single molecule; thus, we intended to modulate the structure of **2** to improve in vitro potency (flea feed LD_{80} <1 μg/mL; soft tick feed ED_{50} <0.1 μg/mL) while maintaining its dog PK profile.

Previous reports in the patent literature demonstrated the superior ability of an *ortho* substitution in the linker aryl ring of an isoxazoline to improve insecticidal potency. Thus, the placement of a cyano substituent *ortho* to the triazole ring (Fig. 2) was shown to drastically improve insecticidal potency.[10] From this, we postulated that we could enhance the in vitro potency of **2**, while maintaining its favorable PK profile, by placing a cyano substituent *ortho* to the azetidine attachment on the linker phenyl as shown in the generic structure **3**.

Attempted synthesis of a representative analog of the generic structure **3** started with the bromoiodo arene intermediate **4** (Scheme 1).[11] In situ Grignard generation, followed by the addition of the azetidinone building block led to hydroxyazetidine **5**. Somewhat unexpectedly, cyanation of **5**, in place of affording the intended cyano substituted hydroxyazetidine **3**, led to the cyclized lactone **6**, presumably arising from facile intramolecular attack of the hydroxyl on the cyano functional group and hydrolysis of the intermediate oxoamidine.

Opportunistic synthesis and in vitro testing of amide **7** revealed it to possess promising insecticidal potency (cf. **2**); even more



Scheme 1. Reagents and conditions: (a) *i*PrMgCl, THF, azetidinone, −40 °C to −10 °C, 52%; (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, microwave, 150 °C; (c) H_2O, 70 °C, 58% (steps b–c); (d) chloroethyl chloroformate, DCM-acetonitrile, MeOH, reflux, 71%; (e) *c*-PrCOCl, TEA, DCM, 46%.