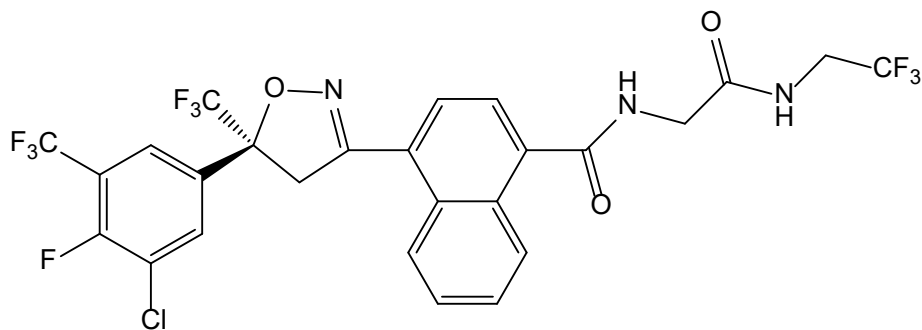


Efficacy example:

Example 53: Efficacy of Injectable Formulation Against *Rhipicephalus (Boophilus) microplus* ticks.

The efficacy of long-acting injectable compositions of the invention comprising the compound of formula (S)-Ie against *Rhipicephalus microplus* ticks on cattle was determined against an untreated control group.



(S)-Ie

The compound of formula (S)-Ie was formulated in an injectable composition at a concentration of 10% (w/v) in a carrier as listed below:

Formulation 3: 90 % w/v Miglyol 812 (medium chain triglycerides)

Formulation 5: 8% (w/v) ethanol, Q.S. with polyethylene glycol 400.

The compound (S)-Ie was dosed at 0.6 mg/kg body weight. Six healthy head of cattle were used in each study group. Cattle in Group 6 were untreated (control). Cattle in Groups 2, 3, 4, 5 and 6 were treated on Day 0 subcutaneously with injectable compositions comprising (S)-Ie. Groups 3 and 5 received Formulation 3 and Formulation 5, respectively.

On days -45, -43, -40, -38, -36, -33, -31, -29, -26, -24, -22, -19, -17, -15, -12, -10, -8, -5, -3 and -1, each animal was infested with a minimum of **5,000** viable tick larvae.

From day zero until the end of the study, animals were individually infested with approximately 5,000 tick larvae ***twice a week*** and, from days 1 to 105, engorged ticks dropping from each animal (each day) during the previous 24 hours were collected and counted for all groups.

Note: The above infestation challenge schedule is significantly more frequent than in Example 51 (specification: page 215-218) in the patent application as filed (i.e. twice a week challenges in the instant example as compare to day 7 then every 14 days in Example 51). In the previous study, Example 51: “several weeks before treatment, cattle were infested three times a week with approximately 2500 *Rhipicephalus microplus* larvae to establish ongoing infestations. Each animal was challenged by infestation with approximately 5000 *R. microplus* larvae on **Days 7 and 21 and every 14 days** thereafter. Ticks dropping from each animal in the previous 24 hours were collected daily and counted from Day 1 until the end of the study. The cattle in study Groups 3, 5 and 6 were not infested further when the efficacy of the treatment dropped significantly.” [emphasis added] Example 51 also differs from the instant study by the pre-infestation protocol used to establish ongoing infestations (2500 *R. microplus* larvae in Example 51 versus 5000 in the instant case), as well as the dose (0.5 mg/kg in Example 51 versus 0.6 mg/kg in the instant example).

Tables 3A, 3B and 3C below show the total tick count % efficacy of injectable compositions comprising compound of the invention (S)-Ie) against *R. microplus* for selected days through Day 105 post treatment compared with the untreated control group and the comparison isoxazoline compounds. As evidenced from the data in Tables 3A, 3B and 3C below, the compositions comprising the compound (S)-Ie of the invention in Miglyol 812 as well as in ethanol/PEG400 dosed at 0.6 mg/kg, provide surprising and unexpected efficacy against *Rhipicephalus microplus* ticks for an extended period of time. The superior efficacy of compound (S)-Ie against *R. microplus* ticks in Miglyol 812 and ethanol/PEG400 is unexpected and unpredictable.

Table 3A: Tick Count Efficacy Against *Rhipicephalus microplus*

Treatment Group	Average % Efficacy (Tick Count)						
	Day	Day	Day	Day	Day	Day	Day
	5	10	15	20	25	30	35
Formulation 3¹	98	100	100	100	100	100	100
Formulation 5²	97	100	100	100	100	100	100

1. Formulation 3: 10% w/v ((S)-Ie), 90% w/v Miglyol 812 (medium chain triglycerides)

2. Formulation 5: 10% w/v ((S)-Ie), 8% w/v ethanol, QS PEG 400

Table 3B: Tick Count Efficacy Against *Rhipicephalus microplus*

Treatment Group	Average % Efficacy (Tick Count)						
	Day	Day	Day	Day	Day	Day	Day
	40	45	50	65	70	75	80
Formulation 3¹	100	100	100	100	100	100	96
Formulation 5²	100	100	100	100	100	100	84

1. Formulation 3: 10% w/v ((S)-Ie), 90% w/v Miglyol 812 (medium chain triglycerides)

2. Formulation 5: 10% w/v ((S)-Ie), 8% w/v ethanol, QS PEG 400

Table 3C: Tick Count Efficacy against *Rhipicephalus microplus*

Treatment Group	Average % Efficacy (Tick Count)			
	Day	Day	Day	Day
	90	95	100	105
Formulation 3¹	87	78	73	49
Formulation 5²	70	71	59	33

1. Formulation 3: 10% w/v ((S)-Ie), 90% w/v Miglyol 812

2. Formulation 5: 10% w/v ((S)-Ie), 8% w/v ethanol, QS PEG 400