Water-soluble fasciolicidal compounds derived from benzimidazole

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Technology description

BRIEF DESCRIPTION OF THE TECHNOLOGY

A group of researchers from the National Autonomous University of Mexico invented two novel compounds that may be useful for treating fascioliasis in cattle.

POTENTIAL APPLICATIONS, BENEFITS AND USES OF THE TECHNOLOGY

Phosphatriclaben is a highly water soluble phosphate salt prodrug of triclabendazole. Aqueous solubility and stability, hydrolysis by alkaline phosphatase, and in vivo fasciolicidal activity in sheep were evaluated. The aqueous solubility of phosphatriclaben at pH 7 was 88,000-fold that of triclabendazole. Phosphatriclaben showed certain aqueous stability (>95% after 26 h) at pH 7, making it a candidate for developing pharmaceutical compositions in the form of solutions that can easily be hydrolyzed by the enzyme alkaline phosphatase (t = 13.6 s) to liberate the precursor compound. An aqueous solution of phosphatriclaben administered intramuscularly to sheep at concentrations of 4, 6 and 8 mg/kg showed a fasciolicidal efficiency of 96.5%, 98.4% and 99.2%, respectively. Also, phosphatriclaben reduced 100% the excretion of eggs at any of these concentrations.

Alpha-pro is a water soluble phosphonooxymethyl prodrug of a compound named “alpha” which had been created and characterized by the same group of researchers. Alpha-pro improved the aqueous solubility of its precursor compound by 50,000 times and it is stable at neutral pH. This prodrug showed faciolicidal activity when evaluated in vitro against excystedFasciola hepatica. A preliminary in vivo evaluation of alpha-pro was carried out via oral, intramuscular and subcutaneous administration in sheep artificially infected withF. hepatica metacercariae. At an intramuscular dose of 4 mg/kg, the activity of alpha-pro was similar to that of compound alpha at an oral dose of 15 mg/kg. Accordingly, a dose significantly lower of any of these prodrugs may achieve a therapeutic efficacy equivalent to the efficacy achieved with a 12 mg/kg dose of triclabendazole, which may be translated in savings of the quantity of active pharmaceutical ingredient (API) necessary to treat fascioliasis in cattle. Hence, it is expected that by reducing the dose of API, the content of residual API in feces, urine and milk, and environment pollution, will be reduced proportionally.

Phosphatriclaben or alpha-pro may not cause irritation or adverse effects at the moment of its administration or thereafter, and may be administered to a herd of cattle easily, rapidly and practically, consequently the operational risks associated with its use may be reduced in comparison with oral drugs.

Because alpha-pro is a novel experimental compound, it has not generated resistance anywhere; accordingly it may represent a viable alternative for controlling fascioliasis in cattle.

TECHNOLOGY READINESS LEVEL (TRL)

The above mentioned studies provide evidence of the water solubility and fasciolicidal activity of phosphatriclaben or alpha-pro. The researchers are working in the development of a composition for each compound and they have performed some of the experiments necessary to test its biological activity. Accordingly, a TRL of 3 or 4 is estimated.

MARKET INFORMATION

The infection of domestic ruminant species withFasciolaspp. causes economic losses higher than 3 billion USD per year in the worldwide cattle production, with more than 600 million infected animals [1] . In Mexico, estimated economic losses because of liver flukeare equivalent to US$130.91 million [2] . The presence of fascioliasis has been diagnosed in 29 (out of 32) States of Mexico and its prevalence is as diverse as follows:

Prevalence	73 - 100%	31 - 70%	2.0 - 21.5%	< 2.0%	NA
States of Mexico	Hidalgo Tabasco Mexico Michoacan Veracruz	Guanajuato Tlaxcala Morelos Puebla Jalisco Durango Aguascalientes Oaxaca	Sonora Chiapas Chihuahua Coahuila Tamaulipas Zacatecas San Luis Potosi	Baja California Yucatan Quintana Roo	Mexico City Campeche Guerrero Colima Nayarit Sinaloa Nuevo Leon Queretaro

Although there is a number of fasciolicides in the market, only triclabendazole shows efficacy against all evolutionary stages of the parasite. However, the overuse and inadequate dosing are generating the phenomenon of resistance of the parasite. Accordingly, it is necessary to implement new strategies for controlling fascioliasis effectively.

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