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Imidazo[1,2-*b*]pyridazines targeting *Tg*CDPK1 as new anti-*Toxoplasma gondii* chemotherapeutic treatments

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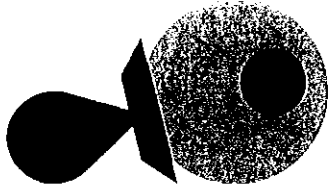
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Toxoplasmosis is responsible of non negligible numbers of uveitis, encephalitis cases, and congenital infections characterized by neurologic damages and abortion. The therapeutic arsenal of toxoplasmosis (a combination of a 2,4-diaminopyrimidine with a sulfonamide drug) targets folate metabolism and consequently induces bone marrow depression requiring administration of folinic acid. Furthermore, its controversial efficacy supports the need of more specific medicines with less toxicity. In this context, the *Toxoplasma gondii* calcium-dependent protein kinase 1 (*Tg*CDPK1) is a promising parasite target. This enzyme without homologue in mammals plays a central role in regulating motility, host cell invasion, and egress of the parasite. Interestingly, the rare small glycine "gatekeeper" at the ATP-binding site renders the adjacent hydrophobic pocket accessible to selective inhibitors. We have designed and synthesized twenty imidazo[1,2-*b*]pyridazines compounds targeting *Tg*CDPK1 (Moine et al. 2015; Eur. J. Med. Chem.). Seven molecules were able to inhibit the *Tg*CDPK1 activity with IC₅₀ < 1 μM and to inhibit the growth of *T. gondii* parasites *in vitro* with higher efficiency than pyrimethamine (EC₅₀ < 1 μM). Three imidazo[1,2-*b*]pyridazine hydrochloride salts have been tested in a model of acute toxoplasmosis. Parasite burdens were strongly diminished (> 90% reduction) in the lungs and brain of mice infected with *T. gondii* and treated with each of the three compounds. Levels of hepatic and renal markers did not vary, suggesting no short-term toxicity of these inhibitors (Moine et al. in revision). The ability of our imidazo[1,2-*b*]pyridazines to block transplacental passage of parasites will be next evaluated in a model of congenital toxoplasmosis.

Keywords: Toxoplasmosis, CDPK1, *in vivo*

*Speaker



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