Is Praziquantel a lead compound for its amides and N-alkyl or aryl derivatives? – A molecular modeling insight at the binding site.

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Table S1. Database identifiers and taxonomic classification of TRP channel proteins used for phylogenetic and structural analyses in this study.

WormBase ParaSite	**NCBI protein ID**	**PDB ID**	**TRP Subfamily**	**Kingdom**	**Phylum**	**Class**	**Genus and species**
Smp 246790.1	---	---	$TRPM_{PZQ}$	Animalia	Platyhelminthes	Trematoda	*Schistosoma mansoni*
Smp_33365	---	---	$TRPM_{MCLZ}$	Animalia	Platyhelminthes	Trematoda	*Schistosoma mansoni*
---	**KAH8875111.1**	---	TRPM2	Animalia	Platyhelminthes	Trematoda	*Schistosoma japonicum*
---	**TNN21397.1**	---	TRPM3	Animalia	Platyhelminthes	Trematoda	*Schistosoma japonicum*
---	**XP_051068658.1**	---	TRPM2	Animalia	Platyhelminthes	Trematoda	*Schistosoma haematobium*
---	**GAA53128.1**	---	TRPM2	Animalia	Platyhelminthes	Trematoda	*Clonorchis sinensis*

---	**KAA3676789.1**	---	TRPM	Animalia	Platyhelminthes	Trematoda	*Paragonimus westermani*
---	**KAA0184185.1**	---	TRPM3	Animalia	Platyhelminthes	Trematoda	*Fasciolopsis buski*
---	**THD26109.1**	---	TRPM3	Animalia	Platyhelminthes	Trematoda	*Fasciola hepatica*
---	**TPP61073.1**	---	TRPM3	Animalia	Platyhelminthes	Trematoda	*Fasciola gigantica*
---	**OON13534.1**	---	TRP	Animalia	Platyhelminthes	Trematoda	*Opisthorchis viverrini*
---	**CDS17135.1**	---	TRP	Animalia	Platyhelminthes	Cestoda	*Echinococcus granulosus*
---	**CDS42162.1**	---	TRP	Animalia	Platyhelminthes	Cestoda	*Echinococcus multiloculari s*
---	**CDS27634.2**	---	TRP	Animalia	Platyhelminthes	Cestoda	*Hymenolepis microstoma*
---	---	**6NR3**	TRPM8	Animalia	Chordata	Aves	*Ficedula albicollis*
---	---	**8DDS**	TRPM3	Animalia	Chordata	Mammalia	*Mus musculus*
---	---	**6MIX**	TRPM2	Animalia	Chordata	Mammalia	*Homo sapiens*
---	---	**8SR8**	TRPM2 chanzyme	---	---	Choanoflagellatea	*Salpingoeca rosetta*

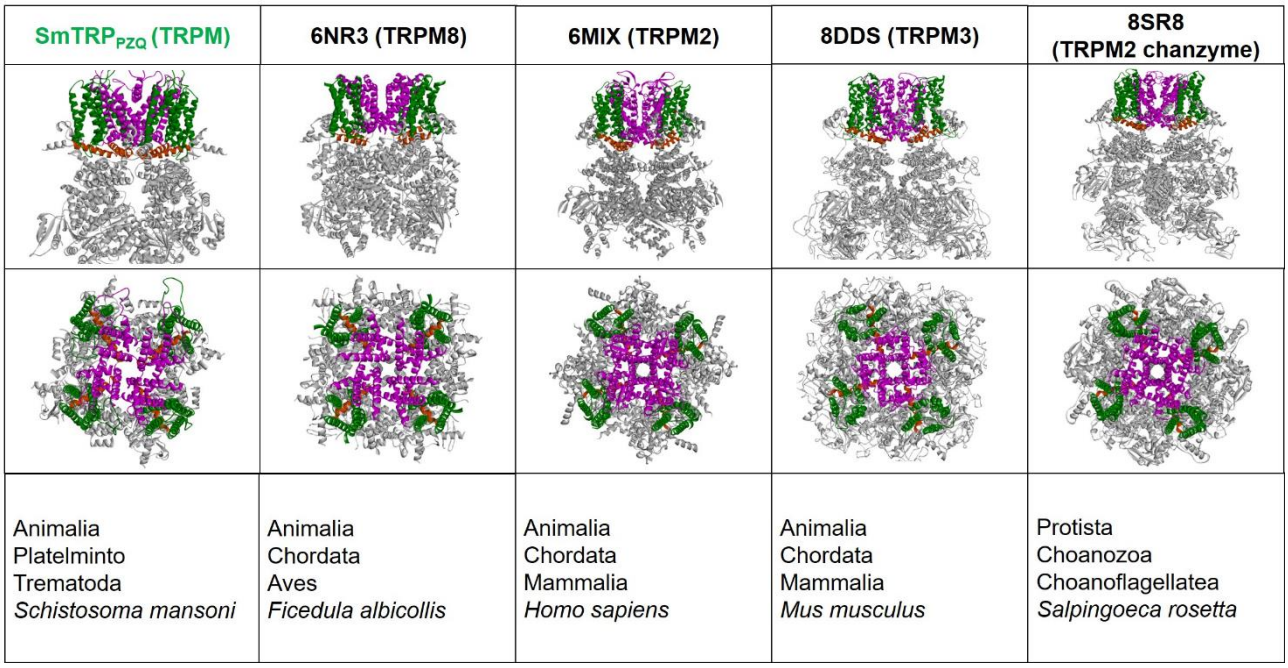

Fig. S1 Comparative scheme of TRPM channels from different species. First column: homology model of Sm.TRPM$_{PZQ}$ (Smp_246790). Other columns: crystallographic structures (PDB codes; TRPM type in first line; taxonomy in last line). All share a common transmembrane core: green, VSLD; purple, pore domain; gray, variable intracellular región

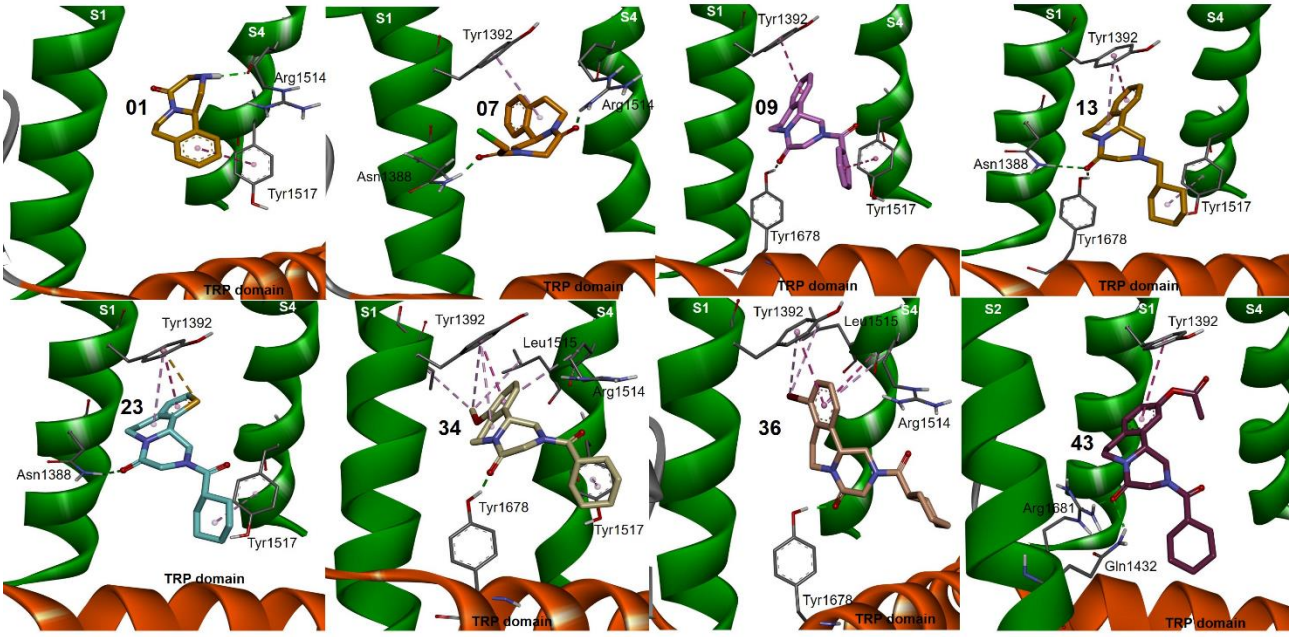

Fig. S2 Interactions of Sm.TRPM$_{PZQ}$ with PZQ derivatives. Image showing the chemical interactions of the analyzed derivatives

Annotation:

We did not search for artificial intelligence (AI) solutions before 20th of May 2026. The following section is a copy of t**he answer generated by Google AI:**

Why Praziquantel lacks me-too derivatives in the commercial pharmaceutical NTD *market?*

Why is PZQ not a lead compound for its derivatives?

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AI Overview

Praziquantel lacks "me-too" derivatives because of its highly specific mechanism—binding to a flatworm-specific ion channel—and the stringent, unprofitable market for neglected tropical diseases. Modifying its structure usually disrupts its efficacy, and there is no financial incentive for pharmaceutical companies to develop similar alternatives. [1, 2]

1. Unique Target and Strict Structure-Activity Relationship (SAR)

Praziquantel acts specifically on a flatworm-specific transient receptor potential (TRP) ion channel (TRPMPZQ). It requires a delicate steric and electronic balance to enter and disrupt the parasite's calcium regulation. Research has shown that even slight structural modifications to the prazino-isoquinoline core often result in a severe loss of potency, meaning chemical analogs are either too toxic or ineffective. [1, 2, 3, 4, 5]

2. The Neglected Tropical Disease (NTD) Market

Schistosomiasis and other parasitic worm infections primarily affect rural, impoverished populations in developing regions. Because the ability-to-pay of these consumers is exceptionally low, praziquantel is manufactured and distributed at a very low cost (often around US \(\$0.20\) to treat a child). Consequently, major pharmaceutical companies do not see a return on investment that would justify the massive costs of preclinical research, clinical trials, and regulatory approval for a me-too drug. [1, 2, 3, 4]

3. The Path Forward: Reformulation Rather Than Derivatives

Because designing new chemical entities is economically unviable, scientific and global health efforts focus instead on improving praziquantel itself: [1, 2]

- Enantiomeric Purity: Praziquantel is sold as a racemic mixture of two enantiomers. Only the \(R(-)\) enantiomer drives the anti-parasitic effects, while the \(S(+)\) enantiomer contributes to the drug's bitter taste and side

effects. Efforts are directed toward producing the pure active enantiomer, which improves tolerability without requiring a new drug class.

- Pediatric Formulations: Organizations like Drugs for Neglected Diseases initiative (DNDi) have historically invested in dispersible, child-friendly formulations of praziquantel rather than structurally altered derivatives. [1, 2, 3, 4, 5]

While new drug classes targeting different pathways are being researched to combat potential drug resistance, they are completely novel mechanisms (like the antimalarial drug artemether) rather than praziquantel me-too derivatives.

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AND

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AI Overview

N-benzamidoquinazolinone (BZQ) is a groundbreaking, first-in-class, broad-spectrum flukicide designed to overcome the natural insensitivity of Fasciola parasites to praziquantel (PZQ). By effectively activating the TRPMPZQ ion channel, BZQ successfully paralyzes a wide range of flatworm parasites.

How BZQ Bypasses PZQ Inactivity

- The Target Protein: PZQ achieves its antiparasitic effects by acting as an agonist on a transient receptor potential (TRP) ion channel (TRPMPZQ).
- The Genetic Hurdle: Schistosoma species have an asparagine residue in their TRPMPZQ binding pocket that permits PZQ binding. However, Fasciola species have a single amino acid substitution (a threonine instead of asparagine), which prevents PZQ from activating the channel.
- The *BZQ Solution*: BZQ is specifically optimized to bind within the unique voltage-sensor-like domain (VSLD) cavity of the Fasciola ion channel. This precise molecular fit allows BZQ to successfully trigger the channel's activation, making it highly effective against Fasciola species.

Why BZQ is a Promising Broad-Spectrum Option

- Broad Spectrum Efficacy: By triggering TRPMPZQ channels across various parasites, BZQ acts as a "universal activator".

- Comparable Schistosome Action: In addition to its efficacy against Fasciola, BZQ retains antischistosomal activity against Schistosoma mansoni that is comparable to PZQ itself.

- Destructive Impact: Studies have shown BZQ induces rapid, protracted paralysis and structural damage to the protective teguments of liver flukes.

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