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PEARLS

Polypharmacology of anthelmintics at host and parasite ion channels

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Introduction

An ideal anti-infective drug specifically, or at least selectively, engages a pathogen target. However, compared to viruses or bacteria, the genomes and proteomes of eukaryotic pathogens closely resemble those of their hosts. Many anti-infective chemotherapies have polypharmacology at both host and pathogen targets. Several drugs targeting human receptors have their origins as anti-parasitic drugs. For example, the dewormer phenothiazine gave rise to anti-histamine and anti-psychotic drug classes, and anti-protozoal quinazolines led to the development of quaalude tranquilizers. Anti-schistosomal chemotherapies are another illustration of this polypharmacology, and classes of compounds that kill schistosomes are derived from chemistry initially developed against host targets. While host receptor activity complicates lead development, it offers an advantage by leveraging a broader literature to deconvolute drug mechanisms.

1. How were the anti-schistosomal compounds praziquantel and meclonazepam discovered?

Schistosomiasis is a disease caused by infection with blood-dwelling parasitic flatworms. The current therapy, praziquantel, was discovered by Bayer/Merck and an experimental lead, meclonazepam, was discovered by Hoffmann-La Roche. Both originated by screening sedative libraries against parasites [1,2]. The rationale for why these libraries were chosen is not documented, but the connection between anti-parasitics and sedatives is not entirely arbitrary. Quaaludes have their origin in quinazoline anti-parasitic drugs [3]. Barbiturates also cause worms to release from the mesenteric vasculature and shift to the portal vein and liver. The anti-epilepsy drug and barbiturate derivative phenytoin has *in vivo* anti-schistosomal activity in mice [4]. The classes of compounds listed above are structurally similar. The core heterocyclic structures of meclonazepam (benzodiazepine), praziquantel (pyrazinoisoquinoline), and the experimental derivative N-benzamidoquinazolinone, BZQ (quinazoline, [5]), share a coupled ring with two nitrogens and a carbonyl group. These groups are also found in the ureic structure of barbiturates and phenytoin. Aligning these molecules' 3D conformers highlights this similarity; note the similar placement of nitrogens, carbonyl groups, and ring systems in Fig 1B.

2. Why do sedatives and related molecules have anthelmintic activity?

Several compounds in Fig 1A have sedative effects on humans. They also have anti-parasitic effects on schistosomes. Unfortunately, in the example of meclonazepam, these two effects manifest at the same dosing range [6]. Praziquantel, although derived from a weakly sedating chemical series [7], does not display dose-limiting sedation. Both compounds cause schistosome paralysis and tegument damage. In the case of praziquantel, this triggers detection by the host immune system and parasite clearance. However, the molecular targets that underpin these effects were unknown until recently.

Various classes of compounds with sedative effects act through $GABA_A$Rs [8–12], which are pentameric Ligand Gated Ion Channels (pLGICs) that mediate the flow of chloride ions. Schistosome genomes lack $GABA_A$R orthologs, and so sedative and anti-parasitic outcomes are not mediated by the same receptors [13]. Compounds in Fig 1A are privileged chemical scaffolds known to bind multiple biological targets. Some of the earliest work on praziquantel and meclonazepam speculated that they likely act directly on a mechanism transporting inorganic ions such as Ca^{2+} to cause parasite muscle contraction [14]. Voltage-gated Ca^{2+} (Ca_v) channels were initially hypothesized as targets. Co-expression of a schistosome accessory $Ca_v\beta$ subunit sensitizes a *mammalian* $Ca_v\alpha$ channel to praziquantel [15]. But it was never directly shown that praziquantel could cause Ca^{2+} influx through a *flatworm* $Ca_v\alpha$ channel. Rather, praziquantel and meclonazepam were later found to activate different members of the Voltage-Gated Ion Channel (VGIC) family, Transient Receptor Potential (TRP) channels [16–19]. These effects occur at concentrations that mirror the activity on worms *in vitro* (hundreds of nanomolar for praziquantel, and low micromolar for meclonazepam).

How do the concentrations of compounds needed to achieve effects at targets in Fig 1 compare to levels achieved in human dosing? In the case of praziquantel, the EC_{50} at the TRP target is below the concentration encountered by worms *in vivo*. The C_{max} for the active R-enantiomer of praziquantel in pediatric school-age children is 1 μM [20], and levels of the R-trans-4-OH-PZQ metabolite (~10 μM) are also within the active range of this compound on the parasite TRP channel [21]. In the case of meclonazepam, a 1 mg dose has been shown to reach a C_{max} of ~30 nM [22]. Assuming linear scaling, a ~20 mg anti-schistosomal dose (assuming 70 kg body weight, [6]) would have a C_{max} of ~600 nM in systemic circulation. While this is below the concentration of meclonazepam that activates a schistosome TRP channel (~1 μM) and kills worms *in vitro* (~3 μM), schistosomes reside in the mesenteric vasculature, prior to first pass metabolism, and are likely exposed to concentrations of praziquantel and benzodiazepines as much as 10× higher than the systemic C_{max} [23,24].

While $GABA_A$Rs and VGICs are distinct ion channel classes, there is precedent for polypharmacology at these targets. Many compounds known to target $GABA_A$Rs also modulate VGICs—both parasite and mammalian TRPs [5,16–18,25], as well as Ca_v channels [15,26–28]. $GABA_A$Rs and VGICs are the focus of our discussion, given their relevance to anti-parasitic activity and host side effects, but it is noted these are

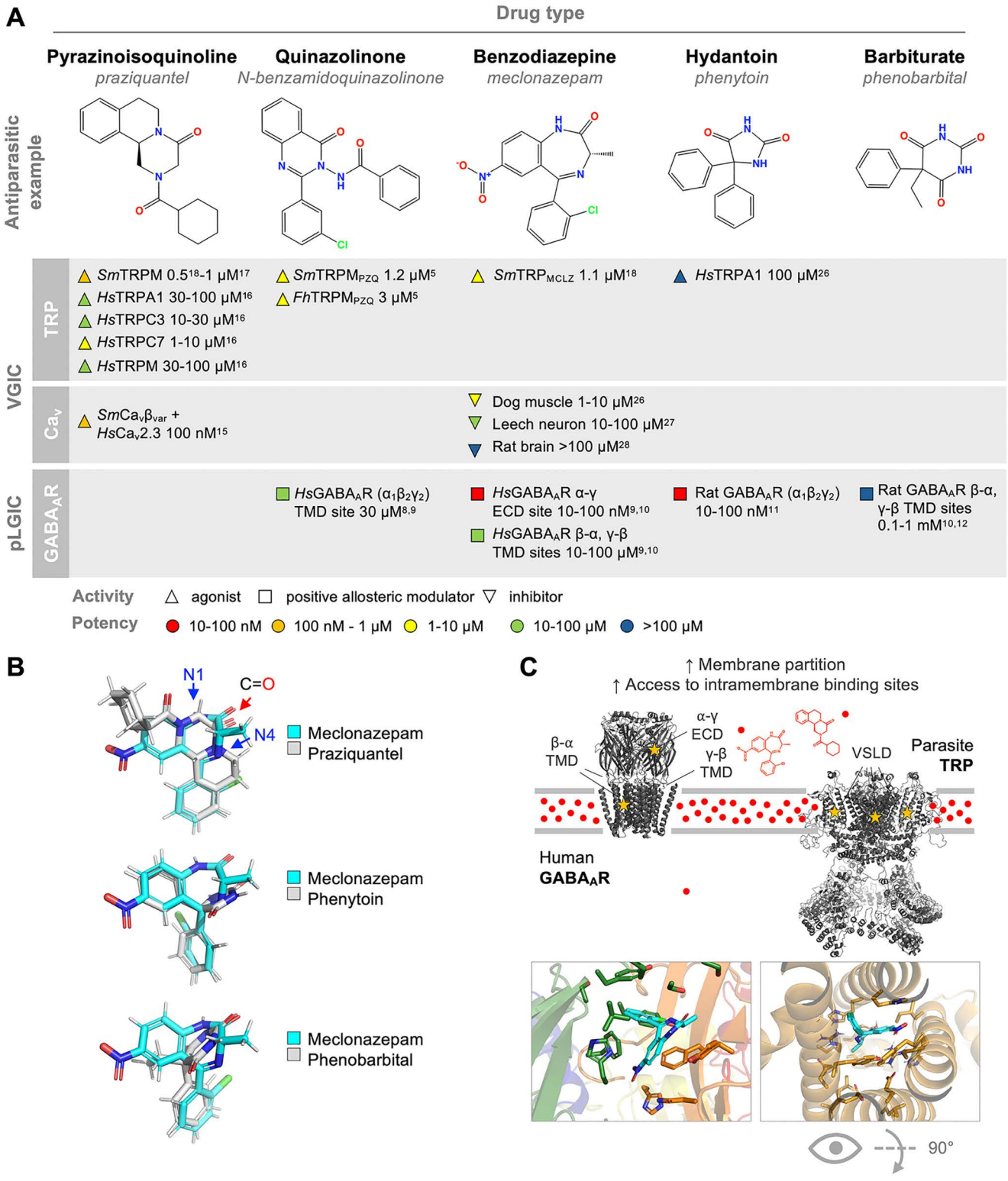

Fig 1. Anthelmintic pharmacophores have activity against both $GABA_AR$s and VGICs. A. Numerous structurally similar compounds with anti-schistosomal activity have actions on voltage-gated ion channel family members (e.g., Transient Receptor Potential (TRP) channels or voltage-gated Ca^{2+} (Ca_V) channels) and GABAergic pentameric ligand-gated ion channels ($GABA_AR$s). Selected examples of these interactions from literature

(reference number in superscript) and range of experimental drug concentration used in the assay are shown. △ = agonist, □ = positive allosteric modulator, ▽ = inhibitor, with fill color reflecting potency. *Hs* = human. *Sm* = *Schistosoma mansoni*. *Fh* = *Fasciola hepatica*. **B.** Small molecule alignment (BCL::MolAlign [50]) for meclonazepam (cyan) and several ligands from **(A)** (gray). 3D conformers show similar positioning of ring systems and heteroatoms; N1, N4 (blue arrows), and carbonyl group (red arrow) are annotated. **C.** Top—Drug binding sites for $GABA_AR$s (α1β2γ2 receptor structure PDB 6X3X [10]) and TRPs (no solved schistosome structure has been published, a homology model of schistosome Smp_333650 with *Drosophila* channel 5VKQ is shown). Visible sites given the channel orientation are starred. Drug binding sites include the $GABA_AR$ ECD between α and γ subunits, $GABA_AR$ TMD between β and α units (1/2 sites visible), $GABA_AR$ TMD between γ and β subunits (not starred, site positioned towards rear view of channel), and TRP VSLD (3/4 sites visible, one positioned in rear view of channel). Red symbols indicate partitioning of compounds into the plasma membrane. Bottom—Predicted binding pose of meclonazepam within the human $GABA_AR$ (left, ECD site between green γ2 and orange α1 subunits) and schistosome TRP VSLD (right) binding site [30]. Note, the schistosome TRP site is portrayed rotated 90 degrees, from above the channel, to provide a view unobstructed by helices S1–S4.

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not the only targets engaged by compounds in Fig 1. For example, binding and functional assays profiling other targets engaged by praziquantel and a meclonazepam derivative have been published [29,30].

3. Why would GABAergic sedatives act on parasite TRP channels?

Compounds such as the benzodiazepine meclonazepam target both $GABA_AR$s and TRPs, but act on different regions of these channels (Fig 1C). Benzodiazepines bind $GABA_AR$s at the extracellular interface of α-γ subunits and the interface of the transmembrane domains (TMDs) of β-α and γ-β subunits [31]. But benzodiazepines are predicted to bind parasite TRP channels within the voltage sensor-like domain (VSLD) [18], an intra-membrane region within each subunit that regulates channel gating. The predicted benzodiazepine binding sites of $GABA_AR$s and TRPs do not have obvious sequence or structural similarity. If the ligand binding sites of these two channel types are different, what explains their shared pharmacology? We can propose several possibilities.

First, recent $GABA_AR$ and TRP structures show that drug binding sites are also occupied by lipids (reviewed in [32]). Lipids in the benzodiazepine $GABA_AR$ α-γ and α-β binding sites are displaced by drug [10]. Many lipid TRP agonists that bind near or within the VSLD have also been reported. Examples include phosphatidylinositol 4,5-bisphosphate, C3 [33], pregnenolone sulfate [34], testosterone [35], arachidonic acid, and fatty acids [36]. Solved structures for schistosome TRPs complexed with anthelmintics will be needed to determine whether these VSLD lipid binding sites are conserved in flatworm channels and if they overlap with anthelmintic binding sites. However, if similar lipids are involved in regulation of both $GABA_AR$ and TRP channels, this may explain polypharmacology across these classes.

Second, both the $GABA_AR$ TMD and TRP VSLD binding sites are situated within the plasma membrane and are accessible to compounds that partition into the lipid bilayer, in contrast to extracellular or cytosolic sites, which are accessible to aqueous-solubilized drugs [37]. Sedatives and anesthetics are known to intercalate into the plasma membrane, and their activity at TRP channels may relate to physicochemical properties that promote drug partitioning at high concentrations near the VSLD [38].

4. How does this inform future anti-schistosomal drug discovery?

Having identified the parasite targets of praziquantel and meclonazepam, we can now ask mechanistic questions regarding their pharmacological modulation and biological function. Schistosome TRPs have been expressed as homomeric channels *in vitro*, but we do not know whether subunits form homomeric or heteromeric assemblies *in vivo*. If different subunits interact, and each were targeted by unique ligands, might an admixture of compounds have even greater anti-parasitic effects? For example, heteromeric voltage-gated potassium (K_v) channels can be composed of subunits with distinct agonist binding sites, and co-administration of compounds has synergistic effects [39]. This approach may even address key limitations of praziquantel, such as lack of efficacy against juvenile, liver-stage worms.

Will all TRP agonists display anti-schistosomal activity? Chemotypes may vary in magnitude and duration of evoked Ca^{2+} influx, corresponding to differences in anti-parasitic efficacy. And as TRP channels are known multimodal sensors, it

is also important to consider whether *in vitro* assay conditions match *in vivo* conditions. For example, the chemical probe FPL-64176 is an agonist at the target of meclonazepam [18], but only causes paralysis of worms *in vitro* when worms are shifted from 37 °C to cooler temperatures (23 °C) [40]. This mirrors studies on TRP channels that show cooling potentiates chemical-evoked currents [41], or reciprocally that chemical treatment sensitizes cooling-evoked currents [42].

Possibly, variation in the ability of different stimuli to activate the channel is relevant to their normal biological function. Praziquantel and meclonazepam cause a massive, persistent, and non-desensitizing Ca^{2+} influx. But endogenous ligands may act on schistosome TRPs more subtly. For example, in other organisms TRP channels have sensory functions (taste sensing by human TRPM5 [36], *Brugia malayi* migration towards host-associated cues through OSM-9 [43]).

Finally, helminth TRPs may have unique features not found in mammalian orthologs. The schistosome benzodiazepine target, Smp_333650, clusters near the broader TRPM subfamily, although it is unusual in featuring N-terminal ankyrin domains. Along with other invertebrate TRPM-like channels (e.g., nematode 'TRPS' ced-11 [44]), these divergent clades merit further exploration to determine if they have atypical properties and pharmacology.

5. Broader relevance to anti-parasitic drug development

Several points raised above have parallels in chemotherapy of other parasites. Praziquantel and meclonazepam are inactive on *Fasciola* liver flukes, but target-based screens on TRPs are capable of identifying broad-spectrum ligands [5]. There is also precedent for roundworm anthelmintics that target TRPs and pLGICs. Diethylcarbamazine was discovered in the 1940s, as a derivative of the anthelmintic piperazine. While piperazine modulates $GABA_A$Rs, diethylcarbamazine is proposed to activate *Brugia* TRP channels (e.g., TRP-2, [45]). Ivermectin's mechanism shares some similarities with benzodiazepines and barbiturates discussed above, but it acts on different pLGICs, glutamate-gated chloride channels (GluCls). The ivermectin binding site overlaps with a phospholipid (1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoserine, POPS) binding site at the interface of two glc-1 TMDs [46]. Lipids often allosterically regulate channel activity, and both benzodiazepines and macrocyclic lactones bind similar lipid-occupied sites and display positive allosteric modulator (PAM) activity at their respective targets. It is unknown if the ivermectin binding site on other sensitive GluCls also binds lipids or what role these may play in channel regulation.

As lipid interactions with ion channels become better understood, lipid-derived small molecules could also serve as leads for drug development. POPS binding at *C. elegans* glc-1 increases affinity of the channel for glutamate [46], and there is precedent for lipids as anti-parasitics. For instance, miltefosine activates trypanosome ion channels [47], while other alkylphospholipid analogs demonstrate *in vivo* efficacy against schistosomes [48].

Conclusions

Many anthelmintics were historically identified in phenotypic screens agnostic to drug targets, but were later found to act on ion channels. In the case of anti-schistosomal drugs, tranquilizer-like compounds were found to kill parasites—though via targets distinct from those causing human sedation. Why some compounds display polypharmacology at GABAergic and VGIC targets remains an open question. However, similarities in intra-membrane ligand binding sites may offer a partial explanation. Indeed, shortly after praziquantel's discovery, similarities were noted with the membrane-intercalating properties of anesthetics and tranquilizers [49]. More work is needed to understand gating mechanisms of these TRP channels, but allosteric sites such as the VSLD may present opportunities for parasite-selective chemotherapies. Although few new chemotypes have entered the anthelmintic pipeline, robust TRP functional assays and structural biology advances suggest these targets will yield promising leads.

Author contributions

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Funding acquisition: Mostafa Zamanian.

Investigation: John D. Chan, Mostafa Zamanian.

Methodology: Spencer S. Ericksen.

Visualization: John D. Chan, Spencer S. Ericksen.

Writing – original draft: John D. Chan.

Writing – review & editing: John D. Chan, Spencer S. Ericksen, Mostafa Zamanian.

References

1. Groll E. Praziquantel. Adv Pharmacol Chemother. 1984;20:219–38.
2. Stohler HR. Ro 11-3128, a novel schistosomicidal compound. In: Proceedings of the 10th International Congress of Chemotherapy; 1978. p. 147–8.
3. Jang CS, Fu FY, Wang CY, Huang KC, Lu G, Chou TC. Ch'ang Shan, a Chinese antimalarial herb. Science. 1946;103(2663):59. https://doi.org/10.1126/science.103.2663.59-b PMID: 17835430
4. Luttermoser GW. Results of laboratory screening tests of compounds for possible schistosomecidal agents. I. Rhodanines and hydantoins. Am J Trop Med Hyg. 1954;40:33.
5. Sprague DJ, Park S-K, Gramberg S, Bauer L, Rohr CM, Chulkov EG, et al. Target-based discovery of a broad-spectrum flukicide. Nat Struct Mol Biol. 2024;31(9):1386–93. https://doi.org/10.1038/s41594-024-01298-3 PMID: 38714890
6. Baard AP, Sommers DK, Honiball PJ, Fourie ED, du Toit LE. Preliminary results in human schistosomiasis with Ro 11-3128. S Afr Med J. 1979;55(16):617–8. PMID: 380021
7. Thesing J, Seitz G, Pohlke R, Sommer S, Muller-Calgan H, Gotz M. 1, 2, 3, 6, 7, 11b-hexahydro-4h-pyrazino-2, 1-a-isoquinolines. US Patent. 3393195A; 1968.
8. Hammer H, Bader BM, Ehnert C, Bundgaard C, Bunch L, Hoestgaard-Jensen K, et al. A multifaceted GABAA receptor modulator: functional properties and mechanism of action of the sedative-hypnotic and recreational drug methaqualone (Quaalude). Mol Pharmacol. 2015;88(2):401–20. https://doi.org/10.1124/mol.115.099291 PMID: 26056160
9. Chojnacka W, Teng J, Kim JJ, Jensen AA, Hibbs RE. Structural insights into GABAA receptor potentiation by Quaalude. Nat Commun. 2024;15(1):5244. https://doi.org/10.1038/s41467-024-49471-y PMID: 38898000
10. Kim JJ, Gharpure A, Teng J, Zhuang Y, Howard RJ, Zhu S, et al. Shared structural mechanisms of general anaesthetics and benzodiazepines. Nature. 2020;585(7824):303–8. https://doi.org/10.1038/s41586-020-2654-5 PMID: 32879488
11. Granger P, Biton B, Faure C, Vige X, Depoortere H, Graham D, et al. Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. Mol Pharmacol. 1995;47(6):1189–96. https://doi.org/10.1016/s0026-895x(25)08760-7 PMID: 7603459
12. Rho JM, Donevan SD, Rogawski MA. Direct activation of GABAA receptors by barbiturates in cultured rat hippocampal neurons. J Physiol. 1996;497 (Pt 2)(Pt 2):509–22. https://doi.org/10.1113/jphysiol.1996.sp021784 PMID: 8961191
13. Johnson H, VanHooreweghe M, Satori JA, Chan JD. Schistosomes contain divergent ligand-gated ion channels with an atypical Cys-loop motif. MicroPubl Biol. 2023;2023:10.17912/micropub.biology.000694. https://doi.org/10.17912/micropub.biology.000694 PMID: 36713055
14. Pax R, Bennett JL, Fetterer R. A benzodiazepine derivative and praziquantel: effects on musculature of *Schistosoma mansoni* and *Schistosoma japonicum*. Naunyn Schmiedebergs Arch Pharmacol. 1978;304(3):309–15. https://doi.org/10.1007/BF00507974 PMID: 714190
15. Kohn AB, Anderson PA, Roberts-Misterly JM, Greenberg RM. Schistosome calcium channel beta subunits. Unusual modulatory effects and potential role in the action of the antischistosomal drug praziquantel. J Biol Chem. 2001;276(40):36873–6. https://doi.org/10.1074/jbc.C100273200 PMID: 11500482
16. Gunaratne GS, Yahya NA, Dosa PI, Marchant JS. Activation of host transient receptor potential (TRP) channels by praziquantel stereoisomers. PLoS Negl Trop Dis. 2018;12(4):e0006420. https://doi.org/10.1371/journal.pntd.0006420 PMID: 29668703
17. Park S-K, Gunaratne GS, Chulkov EG, Moehring F, McCusker P, Dosa PI, et al. The anthelmintic drug praziquantel activates a schistosome transient receptor potential channel. J Biol Chem. 2019;294(49):18873–80. https://doi.org/10.1074/jbc.AC119.011093 PMID: 31653697
18. Park S-K, Sprague DJ, Rohr CM, Chulkov EG, Petrow I, Kumar S, et al. The anthelmintic meclonazepam activates a schistosome transient receptor potential channel. J Biol Chem. 2024;300(1):105528. https://doi.org/10.1016/j.jbc.2023.105528 PMID: 38043794
19. Sprague DJ, Rohr CM, Marchant JS. TRP drop, TRP drop: a steady patter of anti-schistosomal target illumination. Front Parasitol. 2024;3:1349623. https://doi.org/10.3389/fpara.2024.1349623 PMID: 39817176
20. Kovač J, Meister I, Neodo A, Panic G, Coulibaly JT, Falcoz C, et al. Pharmacokinetics of praziquantel in *Schistosoma mansoni*- and *Schistosoma haematobium*-infected school- and preschool-aged children. Antimicrob Agents Chemother. 2018;62(8):e02253-17. https://doi.org/10.1128/AAC.02253-17 PMID: 29866859

21. Park S-K, Friedrich L, Yahya NA, Rohr CM, Chulkov EG, Maillard D, et al. Mechanism of praziquantel action at a parasitic flatworm ion channel. Sci Transl Med. 2021;13(625):eabj5832. https://doi.org/10.1126/scitranslmed.abj5832 PMID: 34936384
22. Coassolo P, Aubert C, Cano JP. Plasma determination of 3-methylclonazepam by capillary gas chromatography. J Chromatogr. 1985;338(2):347–55. https://doi.org/10.1016/0378-4347(85)80105-5 PMID: 3998022
23. Xiao SH, You JQ, Guo HF. Plasma pharmacokinetics and therapeutic efficacy of praziquantel and 4-hydroxypraziquantel in *Schistosoma japonicum*-infected rabbits after oral, rectal, and intramuscular administration. Am J Trop Med Hyg. 1992;46(5):582–8. https://doi.org/10.4269/ajtmh.1992.46.582 PMID: 1599052
24. Ochs HR, Greenblatt DJ, Eichelkraut W, Bakker C, Göbel R, Hahn N. Hepatic vs. gastrointestinal presystemic extraction of oral midazolam and flurazepam. J Pharmacol Exp Ther. 1987;243(3):852–6. https://doi.org/10.1016/s0022-3565(25)39300-6 PMID: 3694534
25. López-González MJ, Luis E, Fajardo O, Meseguer V, Gers-Barlag K, Niñerola S, et al. TRPA1 channels mediate human gingival fibroblast response to phenytoin. J Dent Res. 2017;96(7):832–9. https://doi.org/10.1177/0022034517695518 PMID: 28571526
26. Yamakage M, Matsuzaki T, Tsujiguchi N, Honma Y, Namiki A. Inhibitory effects of diazepam and midazolam on Ca2+ and K+ channels in canine tracheal smooth muscle cells. Anesthesiology. 1999;90(1):197–207. https://doi.org/10.1097/00000542-199901000-00026 PMID: 9915329
27. Johansen J, Taft WC, Yang J, Kleinhaus AL, DeLorenzo RJ. Inhibition of Ca2+ conductance in identified leech neurons by benzodiazepines. Proc Natl Acad Sci U S A. 1985;82(11):3935–9. https://doi.org/10.1073/pnas.82.11.3935 PMID: 3858853
28. Taft WC, DeLorenzo RJ. Micromolar-affinity benzodiazepine receptors regulate voltage-sensitive calcium channels in nerve terminal preparations. Proc Natl Acad Sci U S A. 1984;81(10):3118–22. https://doi.org/10.1073/pnas.81.10.3118 PMID: 6328498
29. Chan JD, Cupit PM, Gunaratne GS, McCorvy JD, Yang Y, Stoltz K, et al. The anthelmintic praziquantel is a human serotoninergic G-protein-coupled receptor ligand. Nat Commun. 2017;8(1):1910. https://doi.org/10.1038/s41467-017-02084-0 PMID: 29208933
30. Mian MY, Sharmin D, Mondal P, Belayet JB, Hossain MM, McCusker P, et al. Development of non-sedating benzodiazepines with in vivo antischistosomal activity. Antimicrob Agents Chemother. 2024;68(9):e0036924. https://doi.org/10.1128/aac.00369-24 PMID: 39136467
31. Masiulis S, Desai R, Uchański T, Serna Martin I, Laverty D, Karia D, et al. GABAA receptor signalling mechanisms revealed by structural pharmacology. Nature. 2019;565(7740):454–9. https://doi.org/10.1038/s41586-018-0832-5 PMID: 30602790
32. Cheng WWL, Arcario MJ, Petroff JT 2nd. Druggable lipid binding sites in pentameric ligand-gated ion channels and transient receptor potential channels. Front Physiol. 2022;12:798102. https://doi.org/10.3389/fphys.2021.798102 PMID: 35069257
33. Yin Y, Zhang F, Feng S, Butay KJ, Borgnia MJ, Im W, et al. Activation mechanism of the mouse cold-sensing TRPM8 channel by cooling agonist and PIP2. Science. 2022;378(6616):eadd1268. https://doi.org/10.1126/science.add1268 PMID: 36227998
34. Yin Y, Park C-G, Feng S, Guan Z, Lee H-J, Zhang F, et al. Molecular basis of neurosteroid and anticonvulsant regulation of TRPM3. Nat Struct Mol Biol. 2025;32(5):828–40. https://doi.org/10.1038/s41594-024-01463-8 PMID: 39809942
35. Asuthkar S, Demirkhanyan L, Sun X, Elustondo PA, Krishnan V, Baskaran P, et al. The TRPM8 protein is a testosterone receptor: II. Functional evidence for an ionotropic effect of testosterone on TRPM8. J Biol Chem. 2015;290(5):2670–88. https://doi.org/10.1074/jbc.M114.610873 PMID: 25480785
36. Liu P, Shah BP, Croasdell S, Gilbertson TA. Transient receptor potential channel type M5 is essential for fat taste. J Neurosci. 2011;31(23):8634–42. https://doi.org/10.1523/JNEUROSCI.6273-10.2011 PMID: 21653867
37. Payandeh J, Volgraf M. Ligand binding at the protein-lipid interface: strategic considerations for drug design. Nat Rev Drug Discov. 2021;20(9):710–22. https://doi.org/10.1038/s41573-021-00240-2 PMID: 34257432
38. Perillo MA, García DA, Arce A. Partitioning of 1,4-benzodiazepines into natural membranes. Mol Membr Biol. 1995;12(2):217–24. https://doi.org/10.3109/09687689509027510 PMID: 7795712
39. Manville RW, Abbott GW. Ancient and modern anticonvulsants act synergistically in a KCNQ potassium channel binding pocket. Nat Commun. 2018;9(1):3845. https://doi.org/10.1038/s41467-018-06339-2 PMID: 30242262
40. McCusker P, Chan JD. Anti-schistosomal action of the calcium channel agonist FPL-64176. Int J Parasitol Drugs Drug Resist. 2019;11:30–8. https://doi.org/10.1016/j.ijpddr.2019.08.006 PMID: 31561039
41. del Camino D, Murphy S, Heiry M, Barrett LB, Earley TJ, Cook CA, et al. TRPA1 contributes to cold hypersensitivity. J Neurosci. 2010;30(45):15165–74. https://doi.org/10.1523/JNEUROSCI.2580-10.2010 PMID: 21068322
42. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, et al. A TRP channel that senses cold stimuli and menthol. Cell. 2002;108(5):705–15. https://doi.org/10.1016/s0092-8674(02)00652-9 PMID: 11893340
43. Wheeler NJ, Heimark ZW, Airs PM, Mann A, Bartholomay LC, Zamanian M. Genetic and functional diversification of chemosensory pathway receptors in mosquito-borne filarial nematodes. PLoS Biol. 2020;18(6):e3000723. https://doi.org/10.1371/journal.pbio.3000723 PMID: 32511224
44. Himmel NJ, Gray TR, Cox DN. Phylogenetics identifies two eumetazoan TRPM clades and an eighth TRP family, TRP soromelastatin (TRPS). Mol Biol Evol. 2020;37(7):2034–44. https://doi.org/10.1093/molbev/msaa065 PMID: 32159767
45. Williams PDE, Kashyap SS, Robertson AP, Martin RJ. Diethylcarbamazine elicits calcium signals by activation of *Brugia malayi* TRP-2b channels heterologously expressed in HEK293 cells. Res Sq. 2025;:rs.3.rs-7359086. https://doi.org/10.21203/rs.3.rs-7359086/v1 PMID: 40964010
46. Althoff T, Hibbs RE, Banerjee S, Gouaux E. X-ray structures of GluCl in apo states reveal a gating mechanism of Cys-loop receptors. Nature. 2014;512(7514):333–7. https://doi.org/10.1038/nature13669 PMID: 25143115

47. Rodriguez-Duran J, Pinto-Martinez A, Castillo C, Benaim G. Identification and electrophysiological properties of a sphingosine-dependent plasma membrane Ca2+ channel in *Trypanosoma cruzi*. FEBS J. 2019;286: 3909–3925.

48. Yepes E, Varela-M RE, López-Abán J, Dakir EH, Mollinedo F, Muro A. In vitro and in vivo anti-schistosomal activity of the alkylphospholipid analog edelfosine. PLoS One. 2014;9(10):e109431. https://doi.org/10.1371/journal.pone.0109431 PMID: 25302497

49. Andrews P. Praziquantel: mechanisms of anti-schistosomal activity. Pharmacol Ther. 1985;29(1):129–56. https://doi.org/10.1016/0163-7258(85)90020-8 PMID: 3914644

50. Brown BP, Mendenhall J, Meiler J. BCL::MolAlign: three-dimensional small molecule alignment for pharmacophore mapping. J Chem Inf Model. 2019;59(2):689–701. https://doi.org/10.1021/acs.jcim.9b00020 PMID: 30707580