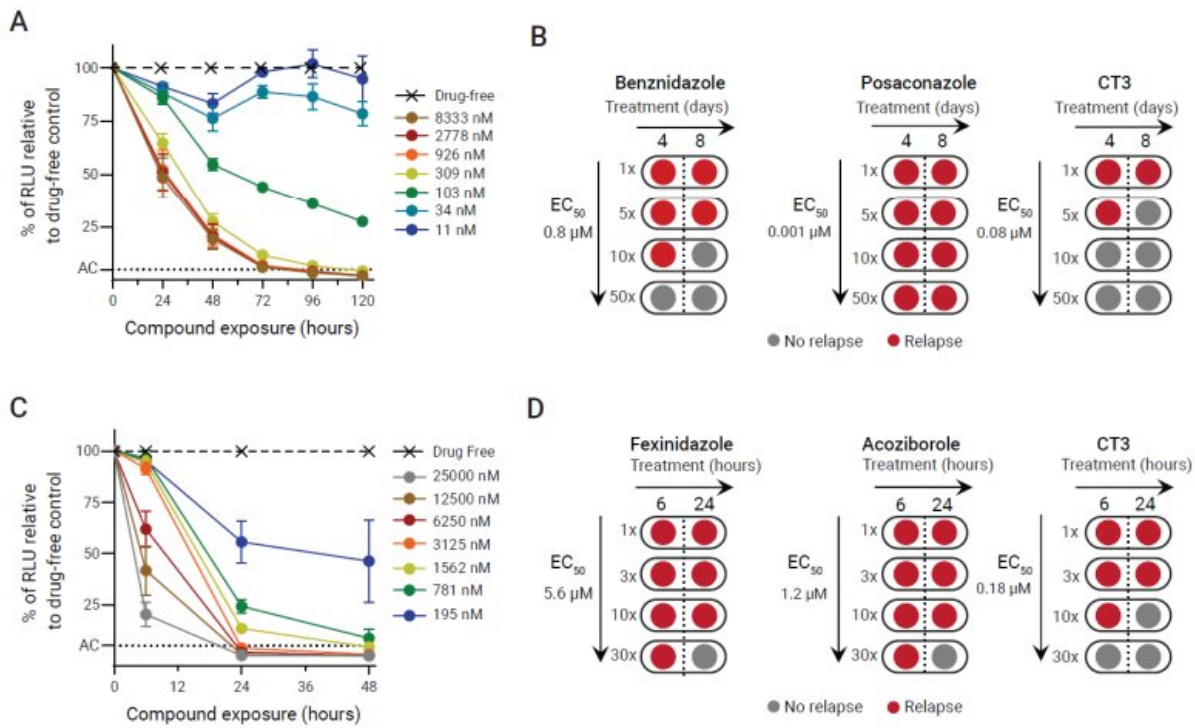


Potent new compound has breakthrough potential for parasitic sleeping sickness and Chagas treatment

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Experimental anti-parasitic properties of CT3. (A) Time to kill of CT3 of intracellular *T. cruzi* parasites. Data represent the mean \pm SEM of three independent biological replicates, where the rate of kill was calculated after comparing each treatment point to a drugfree control over 120 hours. An experimental curative benznidazole dose was used as an active control (AC). (B) Required absolute concentration (AC_{cure}) of CT3, benznidazole and posaconazole to achieve sterile cure of intracellular *T. cruzi* parasites after four and eight days of incubation. Data correspond to three independent in vitro

experiments, the absence of motile parasites by live microscopy after 25 days of monitoring was considered no relapse. (C) Time to kill analysis of CT3 against of bloodstream form of *T. b. brucei* parasites. The data represent the mean \pm SEM ($n=3$ independent biological replicates). With both parasites, note the concentration and time-dependent killing by CT3. (D) The absolute concentrations (AC_{cure}) required to achieve sterile cure under in vitro conditions of bloodstream form of *T. b. brucei* parasites with six and 24-hour incubation of CT3, acoziborole and fexinidazole. Luminescence relative units (RLU) of a curative concentration of melarsoprol were used as a threshold for determining the “no relapse” point in treated samples. Data correspond to 3 independent experiments. Credit: *Science* (2023). DOI: 10.1126/science.adh0614

Scientists have discovered a new class of compound that is potentially active against trypanosome parasites that cause human African trypanosomiasis (or sleeping sickness) and Chagas disease.

The findings—published in the journal *Science* and led by researchers at the University of Glasgow and Novartis Global Health (formerly Novartis Institutes for Tropical Diseases)—reveal potent compounds discovered for the two separate types of trypanosomiases, showing potential for development as new medicines for these diseases.

The study demonstrated that the compounds were able to cure a [mouse model](#) of sleeping sickness with just a single dose, and a short course of daily doses across five days cured Chagas disease in the same models.

African trypanosomiasis (or sleeping sickness) is a major killer disease that puts around 70 million people at risk in sub-Saharan African countries and is invariably fatal if untreated or inadequately treated. Meanwhile, around 7 million people are currently infected by Chagas disease, which can cause irreversible damage to the heart and digestive tract.

There are currently no drugs available that effectively cure Chagas disease; while for sleeping sickness, there have been some steps toward new therapies in recent years.

The researchers also show in the study exactly how the compounds, called cyanotriazoles (or CTs for short), kill parasites without adversely affecting host cells. These compounds selectively bind to a parasite enzyme (called topoisomerase II) that is essential for the replication and maintenance of DNA, which carries the genetic blueprint vital for life. By binding to and inhibiting this enzyme, the compounds introduce breaks into the DNA that are lethal to the [parasites](#).

The Glasgow group, led by Professor Mike Barrett from the Wellcome Center for Integrative Parasitology in the University's School of Infection & Immunity, made inroads into finding that mechanism of action using a technique known as metabolomics, through the Glasgow Polyomics facility, which showed how DNA was being degraded in the cells. Parasites resistant to the drugs had changed their topoisomerase protein structure such that they no longer bound the drug.

The Novartis team, led by Srinivasa Rao, worked out the three-dimensional structure of the trypanosome's topoisomerase, revealing how CTs bind to a particular part of the trypanosome's enzyme that is absent from the human version.

Mike Barrett, Professor of Biochemical Parasitology at the University of Glasgow, said, "Compounds with this degree of potency, working through a newly discovered mechanism, represent a major breakthrough. If they are proven to be safe in humans and retain the levels of activity seen in mice, they could offer the first effective therapy of Chagas disease which afflicts millions of people in Latin America."

More information: Srinivasa P. S. Rao et al, Cyanotriazoles are

selective topoisomerase II poisons that rapidly cure trypanosome infections, *Science* (2023). [DOI: 10.1126/science.adh0614](https://doi.org/10.1126/science.adh0614)

Provided by University of Glasgow

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