Schistosomiasis is a neglected tropical disease prioritized by the World Health Organization (WHO), which is caused by the parasitic flatworm *Schistosoma* spp. with *S. mansoni*, *S. hematobium*, and *S. japonicum* being the most relevant species in human disease. More than 200 million people are estimated to suffer from this parasitic infection worldwide, whereby chronic infections do not only strongly affect human health and wellbeing, but can also lead to death. At the moment, morbidity control of schistosomiasis is achieved by preventive chemotherapy with the racemic drug praziquantel, consisting of the active enantiomer (R)-praziquantel (1) and the less active (S)-praziquantel (2) (Figure 1), which has been widely used over the past 40 years. Due to the risk for drug resistance and the need for more effective antischistosomals that target different stages of the parasite’s development, the identification of alternative or supplemental drugs is desired.

In the course of the search for potential new lead structures against schistosomiasis, cardenolides (cardiac glycosides) (3–5) were identified as lead structures during a prescreening in the herein presented study. Cardenolides are natural products based on a steroidal framework possessing (i) a β-configurated tertiary alcohol at C-14, (ii) an unsaturated lactone ring at C-17, and are (iii) often connected to a sugar fragment via the C-3 or the C-3 and C-4 (calotropin-like structures) to form cardiac glycosides (Figure 2). Typically, they are isolated from different plants such as the eponymous crown flower *Calotropis gigantean* but also foxglove, milkweed, and many others.4–6 Cardio glycosides have been known to mankind for over 2000 years and have been broadly applied, for example as arrow poison, homicidal or suicidal aids, and also as heart tonic.7 The cardiac activity is attributed to the inhibition of the sodium pump, Na⁺/K⁺ ATPase.8 Despite the toxicity of cardenolides and the resulting small therapeutic window, acetyldigitoxin (6a), digitoxin (6b), and digoxin (6c) have been successfully applied for the treatment of congestive heart failure for more than two centuries.9,10 In addition to their cardiotropic activity, antitumor effects of cardiac glycosides were already observed in the 1960s.11 During the last decades, the application of cardiac glycosides to treat cancer and other diseases was investigated.
more extensively.\textsuperscript{12–16} Although it has been observed that patients treated with cardiac glycosides had a lower cancer recurrence rate,\textsuperscript{17,18} the role of cardiac glycosides in cancer progression has not yet been elucidated. However, epidemiological\textsuperscript{19} as well as \textit{in vitro} and \textit{in vivo} studies strengthened the assumption that cardiac glycosides might be used as potent anticancer drugs in the future.\textsuperscript{20–24} The effective concentration at which an antitumor activity was shown was in a similar range as the concentration applied in therapeutic heart disease treatment.\textsuperscript{25,26} The broad application of cardenolides has already lead to their approval by the U.S. Food and Drug Administration (FDA), for instance acetyldigitoxin (Acylanid; (6a)) and digitoxin (Crystodigin (6b)), which are still used as cost-effective therapies in clinics for the treatment of traditional heart-related diseases in adults and children.\textsuperscript{27,28}

\section*{RESULTS AND DISCUSSION}

While searching for novel lead structures with an activity against \textit{S. mansoni}, cardenolides were identified coincidentally in a screen containing several cardenolides among other compound classes. A randomly selected set of 93 compounds (see Supporting Information, Table S1) including six cardenolides originating from a compound library of the Compound Platform (KIT, Germany) was used for the first evaluation (Scheme 1). Libraries of different compound classes are often used by the Molecule Archive of the KIT-Compound Platform to identify promising compound cores for novel applications.\textsuperscript{29}

The 93 randomly selected compounds were tested for their ability to reduce the viability of NTS (newly transformed schistosomula) of \textit{S. mansoni} at a concentration of 10 \textmu M (Supporting Information, Table S1). Altogether, seven compounds were able to kill all NTS (viability reduction = 100%), of which four of these compounds were cardenolides. To our knowledge, cardenolide-containing traditional medicines have not been used in the treatment of infectious diseases. Moreover, the activity of cardenolides has not yet been tested against schistosomes to date. On a broader view, a handful of studies have reported the activity of steroids against \textit{S. mansoni} in laboratory studies. For example, the diuretic spironolactone revealed an \textit{in vitro} activity of 7.2 \textmu M against \textit{S. mansoni} \textit{in vitro} and moderate \textit{in vivo} activity.\textsuperscript{30} Arylmethylaminosteroids with excellent antimalarial activity also affected \textit{S. mansoni} \textit{in vitro}.\textsuperscript{31}

Encouraged by these positive results for cardenolide-type compounds in the prescreen, a set of 73 cardenolides was collected. Out of the 73 compounds, 61 were naturally occurring compounds that have been isolated from \textit{Calotropis gigantea} and \textit{Asclepias} spp\textsuperscript{32–37} and consist of different cardenolides without a sugar unit (compounds type 3, Figure 3), with one (compounds type 4 and 5, Figure 3), or with three to four sugar units (compounds type 6, Figure 3). The sugar part is either monolinked or double-linked at C-3 (and C-2).
An additional 12 steroidal compounds were synthesized to complement additional chemical motifs. The 12 synthetic aglycons were inspired by the core structure of bufadienolide cardiac glycosides, cardenolide-resembling compounds bearing other cycles than the butenolide at position C-17 of the steroid core (e.g., pyridine or substituted arenes), yet lacking the sugar part of typical cardenolides (for a list of the aglycon derivatives, please see Supporting Information, Table S3). The 73 cardenolide-type compounds were tested with respect to the potential to affect the mortality of NTS and adult *S. mansoni* (Table S3, Supporting Information).

Altogether, 20 compounds were found to affect NTS after an exposure time of 72 h at a concentration of 10 μM with a viability reduction of at least 80%. These compounds were then chosen for further investigations with respect to their ability to reduce the viability of adult *S. mansoni* (Scheme 1, decision 1). For seven compounds, all belonging to compound type 5 (Figure 3, Table 1), a reduction of the viability of adult *S. mansoni* of at least 80% at concentrations of 1 μM was observed. These compounds were chosen for concentration dependent studies on adult *S. mansoni* (Scheme 1, decision 2). The determined IC_{50} values revealed that all compounds are active in the nanomolar range (below 400 nM). Therefore, all seven cardenolides were used for further studies (Scheme 1, decision 3 and Figure 4). In comparison, the known anthelmintic praziquantel has an IC_{50} value of 100 nM against adult *S. mansoni* and an IC_{50} value of 2.2 μM against NTS.

To assess cytotoxic effects of the identified compounds, they were subjected to a cytotoxicity assay on L6 rat myoblast cells (Table 1). Calactin 3′ acetate was toxic to L6 cells at nanomolar concentrations, the remaining six compounds were found to be toxic in the low micromolar range (IC_{50} = 1−9 μM). To determine the therapeutic index of the active substances, the IC_{50} values of these compounds in adult *S. mansoni* and L6 cells were compared. Two compounds (5c, 5j) had a therapeutic index between 0 and 19; three compounds (5a, 5aa, 5f) had an index of 20 and higher, and two additional compounds (5g and 5z) had an index of 50 and higher. Hence, these two compounds, namely gomphoside monoacetate (5g) and uscharin (5z), were considered the most promising compounds in this study for the treatment of larval and adult *S. mansoni* species in vitro as they showed a comparable activity as the known drug praziquantel. A full list of all activities can be found in the Supporting Information Table S4.

![Figure 3. Structural motifs of the naturally occurring calotropin-like cardenolides of type 3−7 used in this study.](https://www.acsinfecdis.org/doi/10.1021/acsinfecdis.0c00175)

![Figure 4. Structural motifs of the naturally occurring calotropin-like cardenolides of type 5 affecting NTS and adult *Schistosoma mansoni*.](https://www.acsinfecdis.org/doi/10.1021/acsinfecdis.0c00175)

Table 1. Activities of Seven Selected Compounds of Type 5

| no. | R^1 | R^2 | R^3 | 1 μM | 0.1 μM | IC_{50} (nM) | IC_{50} (L6)/IC_{50} (adult) |
|-----|-----|-----|-----|------|--------|-------------|---------------------------|
| 5a  | CHO | H   | H   | 97   | 22.9   | 371         | 20.0                      |
| 5c  | CH_3 | H   | Ac  | 84   | 29     | 223         | 4.6                       |
| 5f  | CH_3 | H   | H   | 94   | 24.4   | 196         | 38.9                      |
| 5j  | CHO | H   | Ac  | 90   | 26.5   | 335         | 0.03                      |
| 5g  | CH_3 | H   | Ac  | 99   | 24.4   | 138         | 68                        |
| 5aa | CHO | H   |     | 98   | 31.3   | 137         | 20.0                      |
| 5z  | CHO | H   |     | 100  | 51     | 76          | 81.5                      |

aEffect on NTS at a concentration of 10 μM was 100% after 72 h treatment for all compounds except for 5ad (effect: 90%). bEffect on adult worms after 72 h. cIC_{50} (L6)/IC_{50} (adult).
against schistosomes in vitro (LC_{50} values of 0.1–0.4 μM) are in the range of other disease indications; e.g., cancer cell viability is inhibited by digitoxin at a range of 10–100 nM.44 As worms are exposed before the first pass through the liver, the therapeutic concentration is expected to be within the therapeutic window. In vivo, a low worm burden reduction of 38 and 0% was observed for gomphoside monoacetate (5g) and uscharin (5z), respectively (Table 2). A hepatic shift could be observed in mice treated with gomphoside monoacetate, with many dead and live worms observed in the liver, confirming the antischistosomal activity of the compound 5g. However, a higher dose than 10 mg/kg was not tested given the fact that one mouse was found dead 3 h after treatment.

## CONCLUSION

In conclusion, two lead compounds (5g, 5z) were identified with good in vitro activity against both NTS and adult Schistosoma, suggesting their potential as drug candidates for the treatment of schistosomiasis. The activity of both compounds gomphoside monoacetate (5g) and uscharin (5z) was found to be comparable to that of the known therapeutic praziquantel. A preliminary in vivo study of 5g showed a slight worm reduction of 38% in the mouse model. The reason for the low in vivo activity cannot be explained as cardiac glycosides have favorable pharmacokinetic properties.45 However, uscharin (5z) is predicted to be a substrate of the gastrointestinal P-glycoprotein (P-gp), which is responsible for the active efflux of xenobiotics back into the intestinal lumen.46 Possibly, a combined treatment with a known P-gp inhibitor such as quinidine might then improve uscharin uptake and increase its distribution and efficacy.47 In further studies, ADME studies and structure–activity relationship studies will be performed to improve the in vitro activity of the two presented lead structures with respect to enhanced drug tolerance. These studies will be pivotal as these compounds have a narrow safety margin. Moreover, it might be interesting to study the mechanism of action of the drugs against schistosomes. As mentioned cardiac glycosides are allosteric inhibitors of Na+/K⁺-ATPase.8 However, differences exists between the (Na⁺ + K⁺) ATPase of S. mansoni and that of the human host.38 Therefore, it remains to be elucidated if the mechanism of action is related to the inhibition of the pump. The anticancer activity of the cardiac glycoside cerberin revealed an inhibition of P13K/AKT/mTOR signaling depleting polo-like kinase 1 (PLK-1), c-Myc, and STAT-3 expression as well as increasing the generation of reactive oxygen species.49 The latter seem to play a role in the antischistosomal activity of the artemisinins and synthetic peroxides.50

### METHODS

#### Cytotoxicity Studies on Rat Skeletal Myoblast L6 Cells.

Rat skeletal myoblast L6 cells were seeded in 96-well plates (2 × 103 cells/well) (BD Falcon, United States) using RPMI 1640 medium supplemented with 10% iFCS and 1.7 μM l-glutamine. Following adhesion of the cells for 24 h at 37 °C and 5% CO₂, the IC_{50} of test compounds was determined using concentrations of 0.12, 0.37, 1.11, 3.33, 10, 30, and 90 μM. Podophyllotoxin served as positive control. Seventy hours postincubation, 10 μL of resazurin dye (Sigma) was added, and the plates were incubated for another 2 h. The plates were then read using a SpectraMax M2 (Molecular Devices) plate reader with an excitation wavelength of 530 nm and emission wavelength of 590 nm.

#### Preparation of NTS.

_S. mansoni_ cercariae were harvested from infected snails and mechanically transformed to NTS. A NTS suspension at a concentration of 100 NTS per 50 μL was prepared using Medium 199 (Invitrogen, Carlsbad, CA) supplemented with 5% inactivated fetal calf serum (iFCS) and 100 U/mL penicillin and 100 mg/mL streptomycin (Invitrogen). NTS were incubated with 10 μM of the drugs for 72 h at 37 °C, 5% CO₂. Compounds were tested at least in triplicate, and the highest concentration of DMSO served as control. NTS were evaluated by microscopic readout (Carl Zeiss, Germany, magnification 80X) using a viability scale scoring death, changes in motility, viability, and morphological alterations. For the IC_{50} determination assays, drug concentrations used started with the concentration used from the single concentration screen and followed a 3-fold dilution series for a total of 5 concentrations. All viability scores were averaged across replicates and normalized to the average viability scores of the control wells. To calculate IC_{50} values, viability scores were converted into effect scores which were entered, along with the drug concentrations, into the IC_{50} calculating software, CompuSyn2 (ComboSyn Inc., 2007).

#### Ethical Considerations and Animals.

Animal studies were carried out in accordance with Swiss national and cantonal regulations on animal welfare at the Swiss Tropical and Public Health Institute (Basel, Switzerland (permission no. 2070)). Female mice (NMRI strain; age 3 weeks; weight ca. 20–22 g) were purchased from Charles River, Germany. Mice were kept under environmentally controlled conditions (temperature ∼25 °C; humidity ∼70%; 12 h light and 12 h dark cycle) with free access to water and rodent diet and acclimatized for 1 week before infection.

#### Preparation of Adult _S. mansoni_.

Adult schistosomes were removed by picking from the hepatic portal system and mesenteric veins of mice which had been infected with 100 _S. mansoni_ cercariae 49 days earlier. The worms were washed with PBS (pH 7.4) and kept in RPMI 1640 culture medium supplemented with penicillin and streptomycin and 5% heat-inactivated fetal calf serum at 37 °C in an atmosphere of 5%
CO₂ until use. Worms were incubated in flat bottom 24-well plates (BD, Falcon) in the presence of 1 and 10 μM of the test compounds for 72 h. Two wells served as negative controls with culture medium and 1% DMSO. Phenotypes were monitored daily scoring motility, viability and morphological alterations under an inverse microscope (Carl Zeiss, Germany, magnification 80X), using the same viability scale mentioned above. For the IC₅₀ determination assays drug concentrations used started at 1 μM and followed a 3-fold dilution series. IC₅₀ values were computed using CompuSyn2 (CompoSyn Inc., 2007).

**In Vivo Studies.** Mice were infected as described above by subcutaneously injecting approximately 100 S. mansoni cercariae. Single oral doses of 10 mg/kg of the two compounds were administered to groups of four mice 49 days (adult infection) postinfection, respectively. Untreated mice served as controls. Mice were euthanized using CO₂ 21 days after treatment; worms were picked, sexed, and counted, and the worm burden reduction was calculated.

### ASSOCIATED CONTENT

**Supporting Information**
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsinfecdis.0c00175.

S1: results of the prescreen; S2: synthesis of the steroidal aglycons; S3: synthesis of voruscharin (PDF)

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