Synthesis of oxadiazole-2-oxide derivatives as potential drug candidates for schistosomiasis targeted on SjTGR

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Research

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Abstract

Background: Schistosomiasis is a chronic parasitic disease that affects millions of people's health worldwide. Since the increasing drug-resistant to praziquantel (PZQ), which is the primary drug for schistosomiasis, developing new drugs to treat schistosomiasis is crucial. Oxadiazole-2-oxides have been identified as a potential anti-schistosomiasis reagent targeted to thioredoxin glutathione reductase (TGR).

Methods: In this work, one of the oxadiazole-2-oxides derivatives furoxan was used as the lead compound to exploit series of novel furoxan derivatives for studying inhibitory activity against both recombinant Schistosoma japonicum TGR containing selenium (rSjTGR-Sec) and soluble worm antigen protein (SWAP) containing wild type Schistosoma japonicum TGR (wtSjTGR) to develop new leading compound for schistosomiasis. Thirty nine novel derivatives were prepared to test their activity to both two enzymes. The docking method was used to detect the bind sites between active molecule and SjTGR; The structure-activity relationship (SAR) of these novel furoxan derivatives was preliminarily analyzed.

Results: It was founded that several new derivatives such as compounds 6a-6d, 9ab, 9bd, 9be have a better activity to rSjTGR-Sec or SWAP containing wtSjTGR than furoxan. Interestingly, all intermediates bearing hydroxy (6a-6d) showed excellent inhibitory activity to both two enzymes. In particular, compound 6d with trifluoromethyl on pyridine ring has been found to have much higher inhibition to both rSjTGR-Sec (half-maximal inhibitory concentration, IC_{50}, 7.5nM) and SWAP containing wtSjTGR (IC_{50} 55.8nM) than furoxan. Additionally, the docking method revealed the matching sites between 6d and Schistosoma japonicum TGR (SjTGR), which theoretically lends support to the inhibitory activity of 6d.

Conclusion: The data obtained herein showed preliminarily that 6d with trifluoromethyl on pyridine ring could be a valuable leading compound for further study.

Background

Schistosomiasis is one of the most widely spread parasitic diseases in the world, as well as one of the main tropical endemic disease in Asia, Africa and South America [1]. It is estimated that there are approximately 779 million individuals around the world bearing the risk of schistosomes infection [2]. Schistosomiasis is caused by five species of the trematode flatworms, Schistosoma japonicum (S. japonicum), Schistosoma mansoni (S. mansoni), Schistosoma haematobium, Schistosoma mekongi and Schistosoma intercalatum. When a human body is infected, the worms will persist in the liver, hepatic portal system or the urinary tract system, leading to inflammation and obstructive disease [3]. In China, schistosomiasis is mainly caused by Schistosoma japonicum and more than 77 thousand people are infected [4].

The most effective drug for the treatment of schistosomiasis is PZQ (1), which has been extensively used since the 1980s [5] in the clinic without any back-up drugs. The overuse of praziquantel has caused and accelerated the emergence of drug resistance. Furthermore, PZQ is very effective against the adult forms of all schistosome species, but it is weak for juvenile forms of all schistosomes, which might be the
reason that PZQ can not cure schistosomiasis completely. Although R-PZQ was approved by the FDA as an orphan drug in 2018, it is also at risk of resistance and there still no relative drug against the migratory juvenile and sub-adult worms [6]. Therefore, it is very important and urgent to look for potential reagent to discover novel alternatives to PZQ for the treatment of schistosomiasis.

It has been proved that instead of separate thioredoxin reductase (TrxR) and glutathionereductase (GR) enzymes of mammalian hosts, a single multifunctional selenocysteine-containing flavoenzyme designated TGR in both S. mansoni TGR (SmTGR) and S. japonicum TGR (SjTGR) play a critical role in maintaining proper redox balance for parasite survival [1, 7] (Figure 1). The analysis showed that schistosome TGR is similar to mammalian TrxR and GR with amino acid sequence and domain structure distribution. The protein sequence contains the binding domain of nicotinamide adenine dinucleotide phosphate (NADPH) and flavin adenin dinucleotide (FAD), the transformation center between –SH and disulfide, and the dimer interface that in contact with pyridine nucleotide disulfide oxidoreductase. A carboxyl-terminal GCUG active site motif exists in the schistosome TGR that has the functions of both TR and GR. Moreover, schistosome TGR also has an additional extension of glutaredoxin (Grx) domain, it's made up of approximately 110 amino acids, with typical CPYC activity [7d, 8].

**Figure 1:** Redox pathways in mammals and S. mansoni.

The study of the anti-oxidative protection mechanism of S. mansoni indicated that schistosomes and mammalian hosts have obvious biochemical differences in the characteristics of reactive oxygen species (ROS) defense. The specificity of schistosomes in the ROS defense causes the biochemical differences of REDOX pathway between schistosomes and hosts (mammalian). Schistosome TGR is in a critical position in the REDOX pathway [9] and is inferred to be a potential target for new drug design.

In previous studies [1-2, 7], some oxadiazole-2-oxide analogues have been shown to inhibit SmTGR and SjTGR effectively, even had good worm killing activities in vivo. Importantly, unlike PZQ, some oxadiazole-2-oxides showed good juvenile and adult S. japonica killing activities in vitro [2]. Modifications around oxadiazole-2-oxide skeleton have demonstrated to be a valuable strategy for discovering potential antischistosomal agents. The application of bioisosteres is an effective strategy in drug design. The previous researchers mainly substituted on the benzene ring and changed in the CN moiety when designing the compound [1-2, 7], but did not pay attention to modification of benzene ring and other moieties in the furoxan structure with corresponding bioisosteres. Therefore, in this work, the strategy of the application of bioisosteres was exploited to design novel oxadiazole-2-oxide derivatives.

On the other hand, the prokaryotic expression system has been used extensively for protein expression due to its rapid growth rate, capacity for continuous fermentation, and relatively low cost. Due to the lack of the post-translational modifications of this expression system, the bioactivity, function, structure, solubility and so on will be affected to the expressed functional products. Although eukaryotic expression systems can resolve this problem, just like a two-edged sword, some disadvantages such as low yield, high demanding culture conditions and higher cost cannot be avoided totally [10]. Thus, the special SWAP containing wtSjTGR extracted from the host cells might be a better alternative target for studying
the bioactivity. It would reflect the actual situation in advance when Schistosoma japonicum is treated with chemical compounds. Therefore, the target compounds herein were also applied to test the inhibition activity on SWAP containing wtS/TGR besides rSjTGR-Sec.

In this work, two series of novel furoxan derivatives (7 and 9) are obtained through two ways, one is to replace the pheny moiety of furoxan with its bioisosteres pyridine or substituted pyridine, the other is to modify the cyano moiety into an ester or amine group. Besides, fluorine atom possesses a strong electron-withdrawing effect and high lipophilicity, appropriate introduction of fluorine atom into molecules can improve their biofunctions [11]. Therefore, several fluorine-containing derivatives were also intentionally synthesized. The target compounds (7 and 9) and their corresponding intermediates (6) were tested the inhibition activity on TrxR from rSjTGR-Sec and SWAP containing wtSjTGR respectively. Based on the result obtained, the SAR of these novel furoxan derivatives was preliminarily analyzed.

**Figure 2.** The structure of PZQ and furoxan and the general structure of compounds 6, 7 and 9.

**Methods**

**Reagent**

All chemical reagents involved in synthetic procedure were purchased commercially from J&K Chemicals. The chemical reagents used in activity measurement, such as DMSO, EDTA, DTNB, MTT, were purchased from Sigma-Aldrich Inc..

**Synthesis of Oxadiazole-2-oxide derivatives**

The synthesis of compounds 6a-d commenced with the synthesis of α, β-unsaturated esters (4a-d) from substituted nicotinaldehydes (3a-d) by wittig reaction [12]. Then compounds 4a-d were reducted using Diisobutylaluminum hydride (DIBAL-H) [13] to produce alcohols 5a-d. Subsequent sodium nitrate-mediated cyclization [13] gave oxadiazole-2-oxides (6a-d) (Scheme 1).

In Scheme 2, compound 7 was readily prepared by esterification of alcohol 6a-d with various acyl chlorides using triethylamine and dimethylaminopyridine (DMAP) as base and catalyst respectively. The synthesis of target compounds 9 began with the treatment of compounds 6a-d with benzene sulfonyl chloride to generate unstable intermediates 8a-d, which were aminated in situ to afford various target amines 9. As a result, total 39 novel oxadiazole-2-oxide derivatives were synthesized and their structure were determined by NMR (nuclear magnetic resonance) and HRMS (high resolution mass spectrometer). The procedures for the preparation of compounds are detailed in Additional file 1

**Crystallography**

Normally, two isomers 6 and 6' were obtained (Scheme 1) and one of them was main product after cyclization. In order to confirm the conformation of main product, its crystal was selected and was measured on a SuperNova, Dual, Cu at zero, EosS2 diffractometer. The crystal was kept at 150 K during
data collection. Using Olex2, the structure was solved with the Superflip. Structure solution program using Charge Flipping and refined with the ShelXL. Refinement package used Least Squares minimisation.

**Preparation of the rSjTGR-Sec and the SWAP containing wtSjTGR**

The rSjTGR-Sec was expressed and harvested as described previously [7d, 15]. Most of rSjTGR-Sec was expressed in *E. coli* as a soluble His-tagged fusion protein when bacterial growth occurred at 24 °C. The rSjTGR-Sec was purified by His•Mag™ Agarose Beads according to manufacturer’s instructions. The concentration of purified rSjTGR-Sec was determined using a Bradford assay kit (Sangon, China), and the protein was identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and stored at 4 °C [16].

The soluble worm antigen protein (SWAP) containing wtSjTGR was prepared from adult schistosomes. The rabbits were infected with cercariae of *S. japonicum* by exposing their abdominal skin, were sacrificed at 42 day after infection to collect the adult schistosomes by perfusion. The worms were washed three times with phosphate buffered saline (PBS). After sufficient grinding of the adult schistosomes in PBS, suitable amount of benzoyl sulfonyl fluoride (PMSF) solution until its final concentration to 1 mM were added and the homogenate was centrifuged at 4°C, 12,000×g for 20 min[1, 7a]. The concentration of supernatant containing wtSjTGR was determined by Bradford assay kit (Sangon, China).

**Compounds Inhibition of rSjTGR-Sec and SWAP containing wtSjTGR**

The novel furoxan derivatives in the paper were dissolved in DMSO (dimethylsulfoxide) with the storage solution concentration of 64 millimoles per liter. The TrxR activities of SWAP containing wtSjTGR and rSjTGR-Sec was performed based on the methods described previously [17], and the inhibitory activities of the compounds against the TrxR activity of SWAP containing wtSjTGR and rSjTGR-Sec described in this paper were performed based on the method described previously [2]. The reaction was performed in 0.1 M potassium phosphate buffer (pH 7.0) containing 10 mM EDTA (Ethylene Diamine Tetraacetic Acid), 100 µM NADPH, 0.2 µg supernatant contained SWAP containing wtSjTGR or 0.6 µg rSjTGR-Sec and the compounds with different concentrations at 25°C in a final volume of 200 µL and initiated by adding 3 mM dithionitrobenzoic acid (DTNB). The increase of the absorbance at 412 nm was monitored, and the IC₅₀ values of the compounds were calculated by GraphPad Prism v6.0c software, and the results were reported in Table 1. All assays were done in triplicate.

**Docking study**

The crystal structure of SjTGR is a homodimer, and we retained chain B for docking studies [18]. The docking was conducted by AutoDock 4 and the results were displayed in Figure 4 and Figure 5. The results were further processed and displayed by PyMOL2.3.2. The hydrophobic effect between inhibitors and protein were analyzed by LigPlot+ v.2.1 and the result was showed in Figure 5.
Results And Discussion

Synthesis and Crystallography

Totally, thirty nine novel oxadiazole-2-oxide derivatives were synthesized following Scheme 1 and Scheme 2. The structures of these compounds were detailed in Table 1. During synthesis of the important intermediate 6, two isomers were inevitably formed when the oxadiazole-N-oxide ring was constructed by sodium nitrate-mediated cyclization. Gasco and co-workers reported [19] that intramolecular hydrogen bond played a crucial role on the formation of the main isomer during cyclization and could stabilize the structure of the isomer a (Scheme 3).

For our case, two isomers 6 and 6' were obtained (Scheme 1) and one of them was the main product after cyclization. To confirm the position of N-oxide moiety, is the main product 6 or 6'? The crystal of the main product was obtained. It was interesting that the X-ray confirmed that the main product had a similar conformation with the isomer a in Scheme 3, and specifically, the main product was 6a (Scheme 1). The crystal structure showed that there were two independent molecules in an asymmetric unit (Figure 3a). One molecule's nitrogen atom was labeled with N1, N2 and N3, and the other molecule's nitrogen atom was labeled with N4, N5 and N6. However, intermolecular hydrogen bonds instead of intramolecular hydrogen bonds were found in the crystal of 6a. The molecular labeled N1, N2 and N3 of nitrogen atoms formed a hydrogen bonds helix chain (Figure 3b), in addition, the molecular labeled N4, N5 and N6 of nitrogen atoms formed a hydrogen bonds zigzag chain (Figure 3c). This result also indicated that after the pyridine replaced the benzene, the intramolecular hydrogen bond showed in Scheme 3 might not be necessary for the formation of main isomer 6a-d.

Figure 3: (a) Crystal structure of 6a; (b) Hydrogen bond helix chain formed by molecules labeled N1, N2 and N3 of nitrogen atoms; (c) Hydrogen bond zigzag chain formed by molecules labeled N4, N5 and N6 of nitrogen atoms.

Activity assessments of TGR

With furoxan as the positive control, oxadiazole-2-oxides (6, 7, 9) were evaluated for their inhibitory activities against both rSjTGR-Sec and SWAP containing wtSjTGR under different concentrations (Table 1). As shown in Table 1, all intermediates bearing hydroxy (6a-6d) showed better inhibitory activity against both two enzymes than furoxan. The pyridine ring in the structure of compound 6a had a stronger electron withdraw effect on the oxadiazole-2-oxide ring than compound 6b, and 6a (IC\textsubscript{50} 70nM of SWAP containing wtSjTGR, IC\textsubscript{50} 36nM of rSjTGR-Sec) had better inhibitory activity on both two enzymes than 6b (IC\textsubscript{50} 0.14\mu M of SWAP containing wtSjTGR, IC\textsubscript{50} 0.39\mu M of rSjTGR-Sec). Compared with 6b, the electron-donating methoxy group at the ortho position of pyridine (like compound 6c) decreased the inhibitory activity (6c, IC\textsubscript{50} 1.1\mu M of SWAP containing wtSjTGR, IC\textsubscript{50} 2.4\mu M of rSjTGR-Sec). Notably, electron-withdrawing group trifluoromethyl made 6d exhibited excellent inhibitory effect (IC\textsubscript{50} 7.5nM of
SWAP containing wtSjTGR, IC₅₀ 55.8nM of rSjTGR-Sec). These data indicated that the electron-withdrawing substituents very possibly provided potency enhancements of activity.

To further investigate the relationship between the structure and bioactivity, modification of hydroxyl group into the ester group and amine, respectively afforded compounds 7 and 9. It was found that the ester group could not effectively improve the inhibitory effect, except the ethyl ester (7ca), chloracetyl ester (7ae, 7be), benzoyl ester (7af, 7cf) and acryloyl ester (7bj) exhibited inhibitory effects similar to furoxan. Only 7ca (IC₅₀ 34.77µM of SWAP containing wtSjTGR) showed inhibitory effect against SWAP containing wtSjTGR, but not as good as furoxan. Among chloracetyl esters, maybe is because the pyridine ring of 7ae had a stronger electron-withdrawing effect, 7ae (IC₅₀ 4.23µM of SWAP containing wtSjTGR) had a slight advantage over 7be (IC₅₀ 16.40µM of SWAP containing wtSjTGR, IC₅₀ 14.82µM of rSjTGR-Sec). However, 7ae did not show an effective inhibitory effect on rSjTGR-Sec. As for phenyl derivatives, 7af (IC₅₀ 8.87µM of SWAP containing wtSjTGR, IC₅₀ 3.23µM of rSjTGR-Sec) and 7cf (IC₅₀ 12.51µM of SWAP containing wtSjTGR) did not differ significantly in inhibiting SWAP containing wtSjTGR, but 7cf did not show an inhibitory effect on rSjTGR-Sec. Among acrylate compounds, only 7bj showed inhibitory activity against SWAP containing wtSjTGR (IC₅₀ 5.80µM).

Some amine derivatives (9aa, 9ab, 9bd, 9be, 9da) showed inhibitory activity, among which 9bd had an inhibitory effect against SWAP containing wtSjTGR at the nanomolar level (IC₅₀ = 42nM). Compared with phenyl amino derivative 9aa, 9ba, 9ca and 9da, the pyridine with strong electron-withdrawing ability improved the activity, such as, compounds 9aa (IC₅₀ 21.57µM to SWAP containing wtSjTGR) and 9da (IC₅₀ 11.62µM to SWAP containing wtSjTGR, IC₅₀ 3.73µM to rSjTGR-Sec) showed better inhibition effect than 9ba (IC₅₀>50µM) and 9ca (IC₅₀>50µM). Similar to phenyl amino derivatives, 4-trifluoromethoxyphenyl amino derivative 9ab (IC₅₀ 0.62µM to SWAP containing wtSjTGR, IC₅₀ 1.52µM to rSjTGR-Sec) showed better inhibitory effect than 9bb (IC₅₀>50µM both to SWAP containing wtSjTGR and rSjTGR-Sec). However, among piperazine substituted derivatives (9ac, 9ad and 9bd), 9bd exhibited good inhibitory activity against SWAP containing wtSjTGR (IC₅₀ 0.042µM). Interestingly, compound 9be is an intermediate of a synthetic target molecule, but it displayed much better inhibitory effects (IC₅₀ 0.63µM to SWAP containing wtSjTGR, IC₅₀ 0.22µM to rSjTGR-Sec) than furoxan. Perhaps the sulfamide or Si-O-N moieties in molecule 9be has some influence on enzyme inhibition ability, this result might provide a new direction for more compounds design.

Docking studies

To rationalize the obtained bioactivity data and to understand how the synthesized inhibitors interact with schistosomal proteins, the selected compounds with high activity 6d, 7af and 9ab were docked to the available crystal structure of SjTGR (thioredoxin glutathione reductase from Schistosoma japonicum, PDB ID:4LA1). The crystal structure of SjTGR is a homodimer, and we retained chain B for docking studies. The results were displayed in Figure 4 and Figure 5.
Compound 6d formed four hydrogen bonds with Asp433, Ser117 and Thr153, and a π-cation interaction with Arg393(Figure 4a) and two strong hydrogen bonds existed between the hydroxyl moiety of 6d and SjTGR. These results could explain the highest activity of 6d. Compound 7af formed two hydrogen bonds with Cys154 and Asp433, and a π-cation interaction with Arg393(Figure 4b), while the pyridine ring and oxadiazole ring didn’t form any type of interactions with the residues of Arg393. Compound 9ab formed one hydrogen bond with Ser276, a π-cation interaction with Arg393 and a π-π stacking interaction with Tyr296. It’s noticed that the oxadiazole ring participated in the formation of chemical bonds, to constitute more interaction bonds. The distance between the oxadiazole ring and other ring -shaped conjugated structures should be taken into consideration. After superimposing three compounds (6d,7af and 9ab) together (Figure 4d), each of them formed one π-cation interaction with Arg393, therefore, Arg393 was speculated to play a role of anchor during the binding process.

**Figure 4:** In (a), (b) and (c), the protein (SjTGR) is shown as ribbons, the synthesized inhibitors are shown in orange sticks, and the residues that can interact with inhibitors are shown as green sticks. (a) Compound 6d forms a π-cation interaction (red dashed line) with Arg393 and hydrogen bonds (yellow dashed lines) with Ser117, Thr153 and Asp433. (b) Compound 7af forms a π-cation interaction with Arg393 and hydrogen bonds with Cys154, and Asp433. (c) Compound 9ab forms a π-cation interaction with Arg393, a π-π stacking interaction (blue dashed line) with Tyr296, and a hydrogen bond with Ser276. (d) Superposition of docking poses of compounds 6d (blue), 7af (purple), 9ab (green) in the binding pocket of *S. japonicum* TGR.

On the other hand, the hydrophobic effect was showed by red arcs with spokes radiating toward the atoms involved (Figure 5). The numbers of the residues that had hydrophobic contacts with the inhibitors were associated negatively with the enzyme inhibitory activities. Among three compounds (6d,7af and 9ab) compound 7af had the most of hydrophobic contacting residues and it had the lowest activity, compound 6d had the least of hydrophobic contacting residues and it exhibited the highest activity.

**Figure 5:** LigPlot+ generated two-dimensional schematic overview of molecular interactions between SjTGR and compound 6d, 7af and 9ab. Hydrogen bonds are indicated by green dashed lines with corresponding distances between the atoms given in Å. Hydrophobic contacts are shown by red arcs with spokes radiating toward the atoms involved.

**Conclusions**

Using furoxan as the leading compound, series of novel esters and amine derivatives have been synthesized by modifying the cyano moiety into an ester or amine group and replacing phenyl moiety with its bioisosteres pyridine or substituted pyridine. Moreover, the structure of the key intermediate for target compounds was confirmed by crystallography method. The inhibitory activity of all title compounds and key intermediates were evaluated against the TrxR activity of both rSjTGR-Sec and SWAP containing wtSjTGR for the first time. Several new derivatives, 6a-d, 9ab, 9bd, 9be have a better activity to rSjTGR-Sec or SWAP containing wtSjTGR than furoxan. The SAR of these novel furoxan derivatives was preliminarily
analyzed. Pyridine ring with strong electron-withdrawing ability might be beneficial to enhance the inhibitory effect. Docking studies have shown that hydroxyl moiety can form two strong hydrogen bonds with SjTGR, which is of great help to enhance the inhibitory activity of compounds. Compound 6d with trifluoromethyl on pyridine ring has the highest activity and is a good SjTGR inhibitor and could be potent antischistosomal agents.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Data supporting the conclusions of this article are included within the article and its additional file.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

DS, YH and GL designed the experiments and drafted the manuscript. GL, HC and WZ prepared and identified the compound. QG and SL performed the biological experiments and conducted the data analysis.

CF performed the docking study. GL, QG and CF drafted the initial version of the manuscript. DS, YH and GL drafted the final version of the manuscript. All authors read and approved the final manuscript.

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Not applicable.

**Abbreviations**
PZQ: praziquantel; TGR: thioredoxin glutathione reductase; SjTGR: Schistosoma japonicum TGR; SmTGR: Schistosoma mansoni TGR; rSjTGR-Sec: recombinant Schistosoma japonicum TGR containing selenium; SWAP: soluble worm antigen; wtSjTGR: wild type SjTGR; SAR: structure-activity relationship; TrxR: thioredoxin reductase; GR: glutathione reductase; NADPH: nicotinamide adenine dinucleotide phosphate; FAD: flavin adenine dinucleotide; ROS: reactive oxygen species; NMR: nuclear magnetic resonance; HRMS: high resolution mass spectrometer; SDS-PAGE: sodium dodecyl sulfate polyacrylamide gel electrophoresis; PBS: phosphate buffered saline; DMSO: dimethyl sulfoxide; EDTA: ethylene diamine tetraacetic acid; DTNB: dithionitrobenzoic acid; DIBAL-H: Diisobutylaluminum hydride; DMAP: dimethylaminopyridine; PMSF: benzoyl sulfonyl fluoride.

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Tables

Due to technical limitations, Table 1 is only available as a download in the supplementary files section.