Triazole-Based Compound as a Candidate To Develop Novel Medicines To Treat Toxoplasmosis

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This article reports anti-Toxoplasma gondii activity of 3-(thiophen-2-yl)-1,2,4-triazole-5-thione. The compound displayed significant and reproducible antiparasitic effects at nontoxic concentrations for the host cells, with an experimentally determined 50% inhibitory concentration (IC50) at least 30 times better than that of the known chemotherapeutic agent sulfadiazine. Purine nucleoside phosphorylase was defined as the probable target for anti-Toxoplasma activity of the tested compound. These results provide the foundation for future work to develop a new class of medicines to better treat toxoplasmosis.

Standard chemotherapy for the treatment of Toxoplasma infections relies on the inhibition of folate metabolism. The protocol recommends synergistic combination of diaminopyrimidines with sulfonamides, supplemented with folinic acid to mitigate the toxic effects of pyrimethamine on bone marrow. For patients with sensitivity to sulfonamides, macrolides and lincosamides are a second class of medications with anti-Toxoplasma activity. The third class of anti-Toxoplasma drugs, which are only occasionally used as a potential substitute, comprises electron transport inhibitors such as atovaquone (1). In all of these situations, drug resistance, high cost, limited efficacy, and side effects of these drugs often result in discontinuation of therapy (2–5). Therefore, new agents with better activity profiles and that are less expensive are needed. One possible class of drugs are s-triazole derivatives, and in this article, we present a newly found triazole-based candidate to develop novel medicines for more effective treatment of toxoplasmosis.

The search for agents that are potent and selective against Toxoplasma continues in several laboratories. Numerous inhibitors with activities in the nanomolar range with no appreciable in vitro toxicity to human cells have been identified. Examples are pyrimidines, oryzalidinones, berberines, tryptanthrines, thiocyanates, and bisphosphonates (6, 7). Our attention has been focused on the role of s-triazole series as potential new toxoplasmosis therapeutics. We found that 3-(thiophen-2-yl)-1,2,4-triazole-5-thione (compound 1) showed a potent and reproducible antiparasitic effect with no appreciable toxicity to human cells, while 4-ethyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4-triazole-5-thione (compound 2) was inactive.

The procedure for synthesis of 3-(thiophen-2-yl)-1,2,4-triazole-5-thione (compound 1) and 4-ethyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4-triazole-5-thione (compound 2) was inactive.

The procedure for synthesis of 3-(thiophen-2-yl)-1,2,4-triazole-5-thione (compound 1) and 4-ethyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4-triazole-5-thione (compound 2), the effects of tested compounds and sulfadiazine on the viability of L929 (ATCC no. CCL-1) and HeLa (ATCC no. CCL-2) cells, and inhibition of Toxoplasma (RH strain; ATCC no. 50174) growth were described elsewhere (8). The effect of tested compounds on the viability of L929 fibroblasts (percentage of viable cells) (Fig. 2) was measured using the MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] assay according to the international standard ISO 10993-5:2009(E). To calculate the reduction of cell viability compared to viability in the untreated blank, the following equation was used: % viability = 100 × (sample OD570/blank OD570), where sample OD570 is the mean value of the measured optical density at 570 nm of the tested samples and “blank OD570” is the mean value of the measured OD570 of the untreated cells. The 30% cytotoxicity concentration (CC50 [µg/ml]) represents the concentration of tested compounds that was required for a 30% cytotoxic effect of the tested compounds on L929 cells. Selectivity refers to the ratio of the CC50 value for L929 fibroblasts to the IC50 for T. gondii proliferation on the L929 host cells in the presence of 3-(thiophen-2-yl)-1,2,4-triazole-5-thione (compound 1) and sulfadiazine (and) with determined IC50s by 2 methods: incorporation of [3H]uracil (compound 1) and qRT-PCR (compound 2).

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The FlexX program was used as implemented in the LeadIT software package. The receptor for FlexX was prepared using the de-
ence is reversed, with strong binding of the inactive s-triazole (compound 2), which was in clear disagreement with experimental observations. Out of the chosen three proteins, the strongest binding is expected for 3AU9, and this enzyme seems to be the most probable target. The binding mode of the active ligand (compound 1) in its active site is illustrated in Fig. 3.

REFERENCES


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