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Discovery of a quinoline-based phenyl sulfone derivative as an antitrypanosomal agent

Huaisheng Zhang [a], Jasmine Collins [a], Rogers Nyamwihura [a], Shelbi Ware [a], Marcel Kaiser [b,c], Ifedayo Victor Ogungbe [a,*]

[a] Department of Chemistry, Jackson State University, Jackson, MS 39217, USA
[b] Department of Medical Parasitology & Infection Biology, Swiss Tropical and Public Health Institute, 4051 Basel, Switzerland
[c] University of Basel, Petersplatz 1, 4003 Basel, Switzerland

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ABSTRACT

A series of natural products-based phenyl sulfone derivative and their property-based analogues were investigated as potential growth inhibitors of *Trypanosoma brucei*. *Trypanosoma brucei* is a kinetoplastid protozoan parasite that causes trypanosomiasis. In this work, we found that nopol- and quinoline-based phenyl sulfone derivative were the most active and selective for *T. brucei*, and they were not reactive towards the active thiol of *T. brucei's* cysteine protease rhodesain. A thiol reactive variant of the quinoline-based phenyl sulfone was subsequently investigated and found to be a moderate inhibitor of rhodesain. The quinoline-based compound that is not reactive towards rhodesain can serve a template for phenotypic-based lead discovery while its thiol-active congener can serve as template for structure-based investigation of new antitrypanosomal agents.

Human African Trypanosomiasis (HAT), one of the neglected tropical diseases (NTDs), caused by protozoan *Trypanosoma brucei* is a declining public health problem on the African continent due to a gradual decrease in the number of reported cases in the past few years. It is most prevalent, at the moment, in the Democratic Republic of the Congo. Historically, the lack of adequate and rapid diagnostic tools as well as lack of effective, safe, and accessible medicines to treat HAT resulted in the death of hundreds of thousands of people. Despite the decrease in reported case, the lack of good network of primary healthcare facilities in most rural and remote places on the continent as well as the possibility of continuous transmission of the parasite from animal reservoirs to humans, make the disease a continuous threat to millions of people.[1–4] Discovery and development of effective oral drugs remains a key objective in combating the disease. In this regard, a promising drug candidate, nitroimidazole fexinidazole, is in the approval stages for the treatment of human African trypanosomiasis. It would be the first approved oral medicine to treat human African trypanosomiasis in several decades. Fexinidazole is also being investigated as a potential treatment for Chagas Disease.[5,6] Despite these recent gains, the drug development pipeline for HAT is sparse and there is need for continued investment and investigation into new chemical entities that can be developed as treatments and/or as prophylactic agents against the disease. Many plant-derived natural products have been reported as antiprotozoal agents. See review by Schmidt and colleagues.[7] In addition, natural products have been widely explored in anti-infective drug discovery. Most anti-infective agents are natural products-based/inspired.[8] However, due to the complexity and scarcity of most active agents, follow-up studies are usually difficult and rarely pursued in NTDs drug discovery.

The compounds described in this work were synthesized as outlined in Schemes 1 and 2. For compounds **5**–**25**, allyl phenyl sulfone (**1**) was reacted with bromine to obtain the 1,2-dibromide (**2**), in good yield (93%). This was followed by dehalogenation of the vicinal dibromide with sodium carbonate in diethyl ether to obtain (*E*)-((3-bromoprop-1-en-1-yl)sulfonyl)benzene (**3**). Compounds **4a**–**c** were obtained via etherification reaction between the appropriate 4-hydroxyphenylacetic acids and **3** in ethanol, using potassium hydroxide and sodium iodide. Compounds **4a**–**c** were then used to synthesize the corresponding amides (**5**–**10**) and esters (**11**–**25**) using CDI or DCC and DMAP as coupling reagents.[9–13] Detailed synthesis and compound characterization data are provided as Supporting Information.

* Corresponding author.
E-mail address: ifedayo.v.ogungbe@jsums.edu (I.V. Ogungbe).

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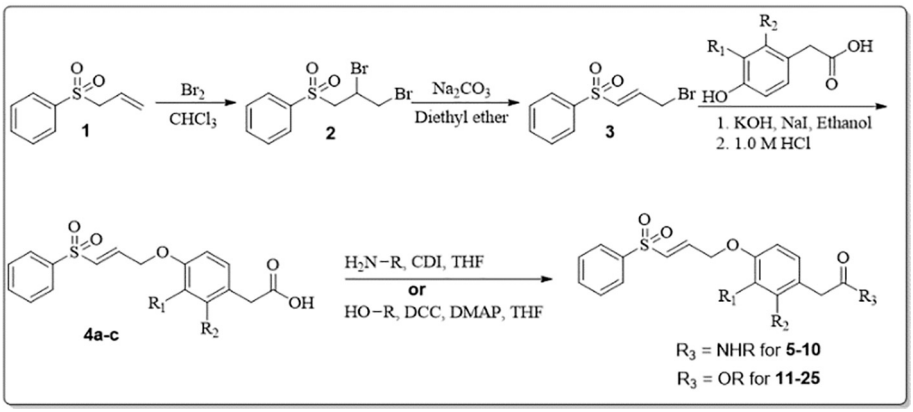
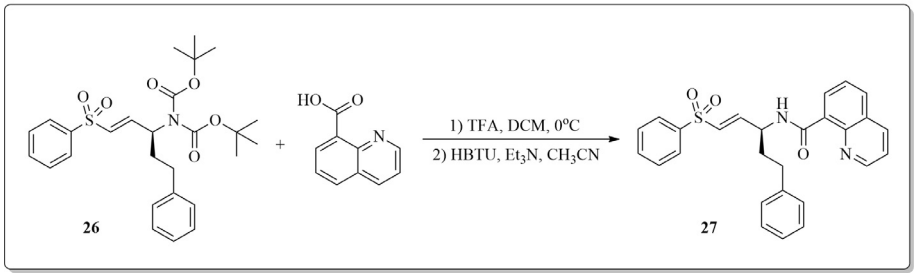
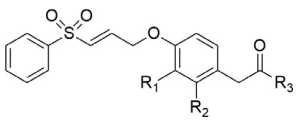


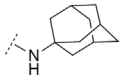
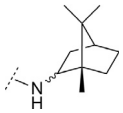
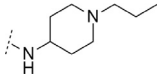
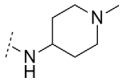
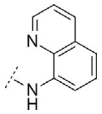
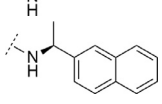
Scheme 1. Synthesis of target compounds **5**–**25**.



Scheme 2. Synthesis of target compound **27**.

Table 1
The antitrypanosomal activities of compounds **5**–**27**.



	R_1	R_2	R_3	*T. brucei* IC_{50}	Hep G2 IC_{50}
5	H	H		11.72 ± 0.83	>20
6	H	H		10.77 ± 0.31	>20
7	H	H		>20	>20
8	H	H		>20	>20
9	H	H		0.76 ± 0.11	>80
10	H	H		5.45 ± 0.20	>20