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# Identification of a 4-fluorobenzyl L-valinate amide benzoxaborole (**AN11736**) as a potential development candidate for the treatment of Animal African Trypanosomiasis (AAT)

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ABSTRACT

Novel L-valinate amide benzoxaboroles and analogues were designed and synthesized for a structure-activity-relationship (SAR) investigation to optimize the growth inhibitory activity against *Trypanosoma congolense* (*T. congolense*) and *Trypanosoma vivax* (*T. vivax*) parasites. The study identified 4-fluorobenzyl (1-hydroxy-7-methyl-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carbonyl)-L-valinate (**5**, **AN11736**), which showed $IC_{50}$ values of 0.15 nM against *T. congolense* and 1.3 nM against *T. vivax*, and demonstrated 100% efficacy with a single dose of 10 mg/kg against both *T. congolense* and *T. vivax* in mouse models of infection (IP dosing) and in the target animal, cattle, dosed intramuscularly. **AN11736** has been advanced to early development studies.


Animal African Trypanosomiasis (AAT) is a fatal, parasitic wasting disease of livestock and wild animals in Sub-Saharan Africa.[1] It is caused primarily by the two protozoan parasites *Trypanosoma congolense* (*T. congolense*) and *Trypanosoma vivax* (*T. vivax*), which are transmitted by tsetse flies.[1] AAT is responsible for 3 million cattle deaths annually and costs African livestock farmers approximately US$ 1–5 billion per year.[2] The current standard-of-care drugs, such as diminazene aceturate, isometamidium and homidium chloride, have been in use for several decades and are often ineffective with drug resistance becoming an increasing concern.[1] No new trypanocides have been approved for use in cattle for many years. Initial screening of the Anacor Pharmaceuticals library of novel boron-containing compounds identified an active compound (**1**, Fig. 1), which had an $IC_{50}$ = 5 nM against *T. congolense* and 69 nM against *T. vivax* while its enantiomer was much less active. A quick and simple modification on the amino acid side chain with an isopropyl group generated **2** (Fig. 1) with improved *in vitro* potency ($IC_{50}$ = 2 nM against both *T. congolense* and *T. vivax*). This encouraging result prompted us to investigate this chemical series further. We designed and synthesized a series of novel benzoxaboroles (**3**–**71**, Figs. 2–8) to optimize anti-parasitic activity, physicochemical and *in vitro* ADME properties, and the pharmacokinetic profile. Specifically, these molecules were designed to examine the effects of oxaborole 3-substituent variation (**3** vs **2**, Figs. 1 and 2), oxaborole 7-substituent variation (**4** vs **2**, Figs. 1 and 2; **5** vs **20**–**27**, Fig. 4), substituent changes on the benzyl group (**5**–**19**, Fig. 3), modification of the amino acid (**28**–**32**, Fig. 5), heteroaromatic methyl esters (**33**–**48**, Fig. 6), introduction of water-solubilizing scaffolds to the benzyl group (**49**–**54**, Fig. 7) and aliphatic esters (**55**–**71**, Fig. 8). Herein, we report the synthesis and antiparasitic activity against *T. congolense* and *T. vivax* of these novel compounds.

Compounds **1**–**71** were convergently synthesized from three building blocks: the left side alcohols (**72**), amino acid linkers

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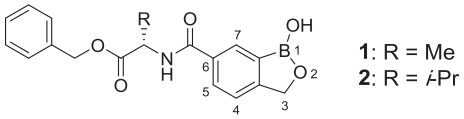



**Fig. 1.** Chemical structures of early hits (**1** and **2**).

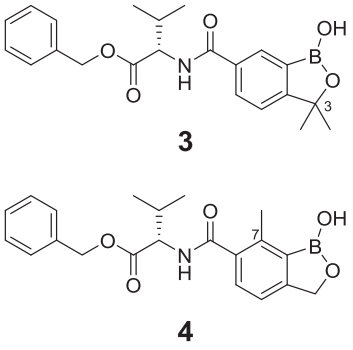
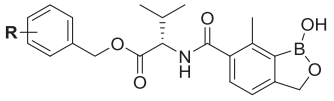
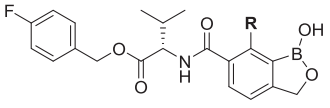



**Fig. 2.** Structures of benzoxaboroles with additional 3,3-$Me_2$ (**3**) or 7-Me (**4**) modification as compared to analog **2**.



**5**: R = 4-F;
**6**: R = 4-Cl;
**7**: R = 3-F;
**8**: R = 3,4-diF;
**9**: R = 3,5-diF;
**10**: R = 3-$CF_3$;
**11**: R = 4-$CF_3$;
**12**: R = 3-$OCF_3$
**13**: R = 4-$OCF_3$;
**14**: R = 3-CN;
**15**: R = 4-CN;
**16**: R = 3-Cl-4-F;
**17**: R = 4-F-3-$CF_3$;
**18**: R = 3,4,5-triF;
**19**: R = 4-$SO_2CH_3$

**Fig. 3.** Structures of benzoxaboroles with variation of substituents on the benzyl ring (**5**–**19**) as compared to analog **4**.



**20**: R = H;
**21**: R = F;
**22**: R = $CHF_2$;
**23**: R = $CF_3$;
**24**: R = Et;
**25**: R = $Pr^n$;
**26**: R = $Pr^i$;
**27**: R = $Pr^c$

**Fig. 4.** Structures of benzoxaboroles with variation of 7-substituents on the benzene ring (**20**–**27**) as compared to analog **5**.

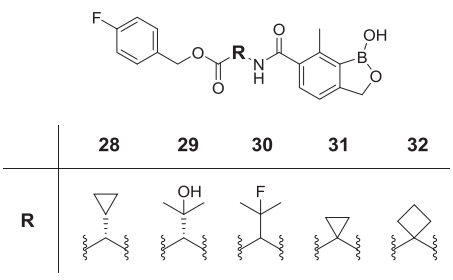



**Fig. 5.** Structures of benzoxaboroles with variation on the amino acid side chain (**28**–**32**) as compared to analog **5**.

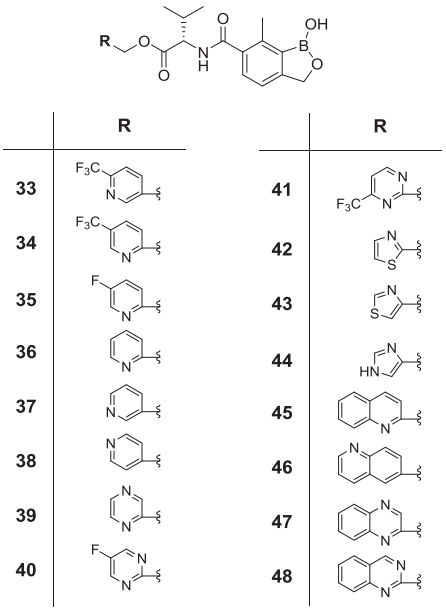



**Fig. 6.** Structures of benzoxaboroles with variation of the left side arylmethyl groups (**33**–**48**) as compared to analog **5**.

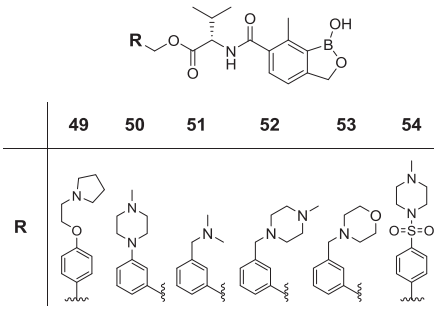



**Fig. 7.** Structures of benzoxaboroles with water-solubilizing scaffolds on the benzyl ring (**49**–**54**) as compared to analog **5**.

(**73**) and benzoxaborole 6-carboxylic acids (**76**).[3,4] The general synthetic route is shown in Scheme 1. Reaction of alcohols **72** with *N*-Boc protected amino acids **73** gave ester intermediates **74**, which were treated with dry hydrogen chloride to generate ester amine salts **75**. Condensation of these amine salts **75** with benzoxaborole 6-carboxylic acids **76** provided the final compounds **1**–**71**.

Scheme 2 illustrates the synthesis of 1-hydroxy-7-methyl-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carboxylic acid (**83**) as an example of key boron intermediates. Esterification of the acid **77** produced the ester **78**, which was formylated to yield **79**. Treatment of **79** with trifluoromethyl sulfonyl anhydride afforded the triflate compound **80**, which was converted to the pinacol boron intermediate **81**. Reduction of **81** and subsequent cyclization under aqueous acidic conditions generated the benzoxaborole ester **82**. Hydrolysis of the ester group in **82** afforded the acid **83**. The experimental procedures for the synthesis of **5** are described in the reference and note section.[5]

Activity of compounds **1**–**71** against *T. congolense* and *T. vivax* was determined using the whole cell assays as described [6] and their $IC_{50}$ values are summarized in Table 1.

Lead compound **2** exhibited an $IC_{50}$ of 2 nM against both *T. congolense* and *T. vivax*. The 3,3-dimethyl analog **3** was essentially inactive ($IC_{50}$ = 2580 nM against *T. c.* and 9190 nM against *T. v.*) but better activity was observed for the 7-methyl analog **4** ($IC_{50}$