

# Boron-based drugs as antiprotozoals

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## Purpose of review

Boron-based drugs represent a new class of molecules that have been found to exhibit attractive properties and activities against a number of protozoans causative of neglected tropical diseases.

## Recent findings

This review highlights recent advances in discovery of potential treatments for human African trypanosomiasis, malaria and Chagas disease from a class of boron-containing drugs, the benzoxaboroles.

## Summary

Research at several biotechnology companies, sponsored by product development partners (PDPs), has been successful in identifying a novel class of boron-based drugs, the benzoxaboroles, as potential treatments for neglected tropical diseases. This work was based, in part, on the earlier observation of antifungal, antibacterial and anti-inflammatory activities of the benzoxaboroles. The unique properties of boron, namely its ability to reversibly interact with biochemical targets through an empty p-orbital, are important to the success of these new drug candidates. Physicochemical and pharmacokinetic properties of the boron-based compounds are consistent with features required for oral absorption, metabolic stability and low toxicity – all important for progression of this class to clinical trials.

## Keywords

benzoxaboroles, Chagas disease, human African trypanosomiasis, malaria, neglected tropical diseases

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## Introduction

Infectious diseases caused by protozoan parasites represent a significant area of unmet medical need, particularly in the developing world [1–3]. Many of the drugs available to treat these infections are of limited efficacy or exhibit toxicity that precludes widespread use [4–6]. Primarily due to the economic realities of the geographical distribution of these diseases, little drug discovery effort has been applied in this area, limiting the potential for development of new effective treatments. Over the past several years, through collaborations between product-development partnerships, biotechnology companies and academic researchers, a class of boron-containing compounds, the benzoxaboroles, has been discovered to exhibit interesting activity against important protozoan pathogens including *Trypanosoma brucei*, *Plasmodium falciparum* and *Trypanosoma cruzi*.

Boron-containing compounds have received increasing attention over the past several years as potential drugs. This interest is predicated to a large degree on the unique electronic properties of boron, which allow it to act as a transition-state mimetic for the tetrahedral intermediate

of peptide bond cleavage observed in proteolytic enzymes [7–9]. In addition to the boronic acids explored by numerous researchers, the benzoxaboroles, a class of compounds wherein the boron atom is incorporated into a heteroaromatic ring system, have provided a number of interesting anti-inflammatory, antifungal and antibacterial drug candidates [10,11,12,13]. Evaluation of the benzoxaboroles for antiparasitic activity followed the strategy outlined in Fig. 1. More specifically, screening of the Anacor Pharmaceuticals benzoxaborole library in whole cell assays (*T. brucei*, *P. falciparum* and *T. cruzi*) identified a number of interesting sub-classes of benzoxaboroles (A–E) which were then further characterized and optimized as described below.

## Human African trypanosomiasis

Human African trypanosomiasis (HAT, African sleeping sickness), caused by the kinetoplastid parasite *T. brucei*, is endemic across sub-Saharan Africa, affects over 10 000 people each year, and is fatal if left untreated [14–16]. Existing treatments for this disease, particularly when parasites have invaded the brain (stage 2), are inadequate due to toxicity and ineffectiveness [17,18]. Screening

the benzoxaborole library against *T. brucei* resulted in identification of a number of attractive starting points (e.g. 1–3) for a drug discovery program as depicted in Fig. 2 [19\*].

Initially evaluated at the Sandler Center of the University of California, San Francisco at a single concentration of 1  $\mu\text{mol/l}$ , complete dose response curves were generated on a subset of hits by SCYNEXIS, affording 45 compounds with an  $\text{IC}_{50}$  below 500 nmol/l and eight compounds with an  $\text{IC}_{50}$  below 100 nmol/l. Evaluation of in-vitro (absorption, distribution, metabolism, excretion) properties (metabolic stability, permeability, solubility and lipophilicity) suggested the majority of these compounds were suitable for further optimization, and work was initiated on several sub-series of compounds, most notably the benzoxaborole-6-carboxamides (3–5) [20]. Expansion of SAR (structure-activity relationships) around the carboxamide series revealed that benzamides with electron-withdrawing substituents such as chloro or trifluoromethyl at the ortho position, and a fluoro substituent at the para position, such as in SCYX-6759 (5), were particularly interesting in terms of both antiparasitic potency and pharmacokinetic properties [20]. The only limitation of SCYX-6759 and close analogs was the observation that brain levels (in mice) of these compounds dropped to sub-therapeutic concentrations within 6–12 h following a single oral dose of 50 mg/kg, which demanded twice-daily (b.i.d.) dosing in a mouse model of stage 2 HAT [20]. In this model, mice were infected with *T. b.*

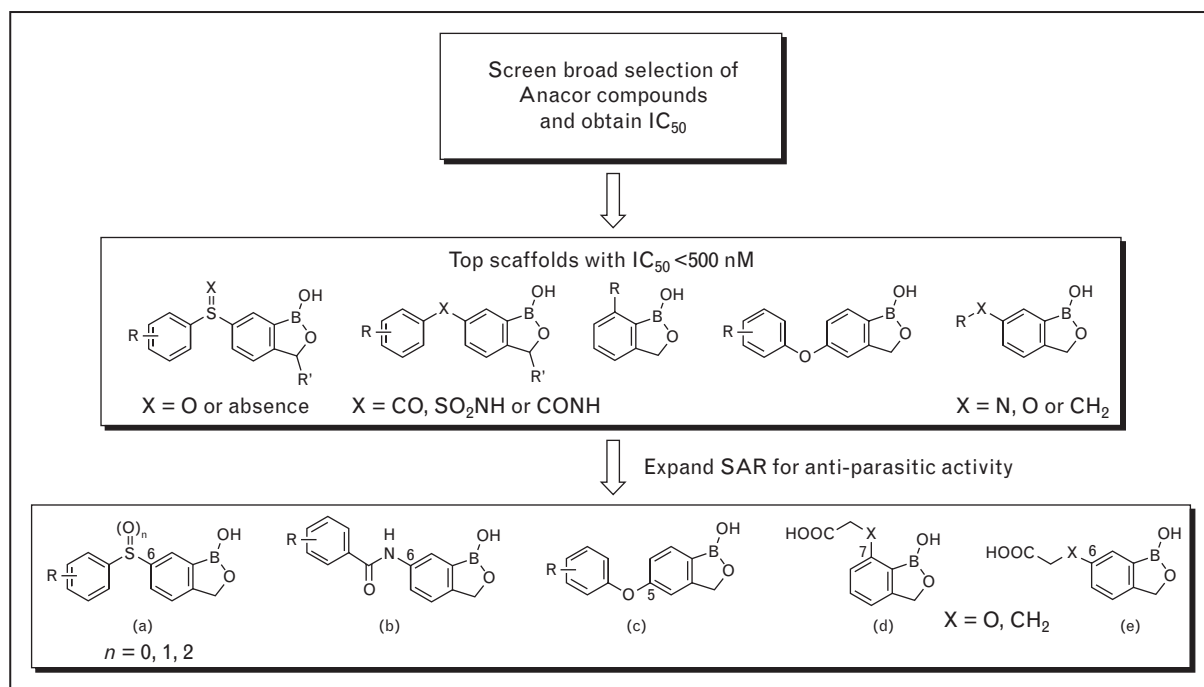
### Key points

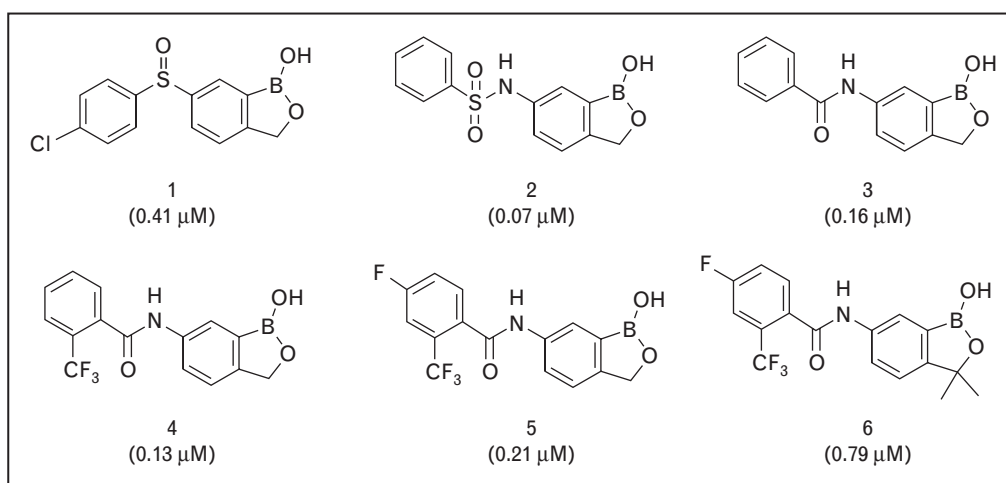
- Due to the unique properties of boron which facilitate reversible interactions with biochemical targets, incorporation of this element into drug candidate molecules has provided interesting lead molecules as antiparasitics.
- In human African trypanosomiasis, an orally active benzoxaborole 6-carboxamide has been identified which is curative in an animal model of stage 2 (CNS) disease.
- A benzoxaborole 7-propionic acid with excellent in-vitro activity against *Plasmodium falciparum* has been discovered and has progressed to in-vivo malaria models.
- Benzoxaboroles have shown promise as potential treatments for Chagas disease, though further optimization is required to realize cures in a stringent in-vivo model of this disease.

*brucei* TREU 667, a strain of the parasite known to establish a low-level brain penetrant infection [21].

This limitation was addressed through modification of the C(3) position of the benzoxaborole core, specifically through addition of a gem-dimethyl substitution as in SCYX-7158 (6). Whereas intrinsic potency of the gem-dimethyl analogs was generally lower than C(3) unsubstituted analogs, brain levels were maintained at therapeutic concentrations for close to 24 h, allowing

**Figure 1** Schematic representation of screening strategy for identification of boron-based antiparasitic compounds



**Figure 2** Chemical structures of benzoxaborole compounds along with their in-vitro IC<sub>50</sub> results (μmol/l) against *Trypanosoma brucei*

Experimental procedures for the in-vitro assays are described in [19,20].

demonstration of efficacy in the CNS mouse model following once-daily oral dosing at 12.5 mg/kg [22<sup>\*\*</sup>]. On the basis of these efforts, SCYX-7158 was progressed to preclinical toxicology and safety pharmacology studies. Results of these studies have supported submission of a clinical trials application for this compound; phase 1 trials are anticipated in 2012.

## Malaria

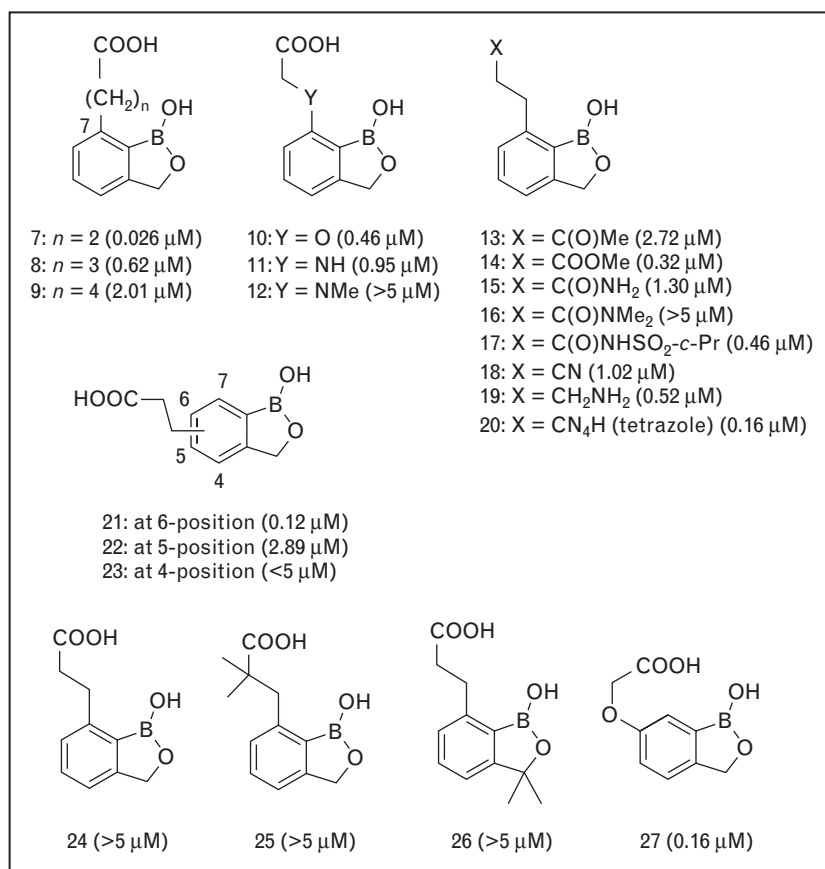
The urgent need for new antimalarial drugs [23] coupled with our success in phenotypic screening of boron-containing compounds against bacteria, fungi and trypanosomes, prompted us to initiate a whole cell screening campaign against the malaria parasite *P. falciparum* [24<sup>\*</sup>]. A set of 1034 boron-containing compounds was screened against W2-strain (multidrug resistant) *P. falciparum* at 10 μmol/l, and activities of hits were titrated. IC<sub>50</sub> values were below 1 μmol/l for 32 compounds, below 500 nmol/l for 21 compounds, and below 100 nmol/l for two compounds. Grouping the screened compounds by structural similarity identified five chemical scaffolds that were analyzed further for their overall properties. Analysis of each of these scaffold families for in-vitro potency, cytotoxicity, uniformity of SAR, and drug-like property predictors [25,26] led to selection of two closely related series (D and E) that were selected for lead optimization (Fig. 1).

Structures D and E are benzoxaboroles containing a side-chain carboxyl moiety substituted at either the 6- or 7-position. SAR studies for lead structures D and E focused on understanding the importance of the carboxyl group, the side-chain length, the side-chain atoms and

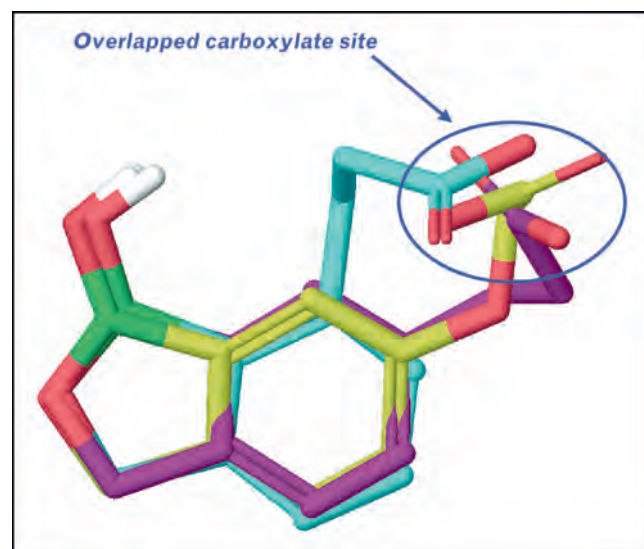
positional isomers of the carboxyl function around the ring. The set of analogs synthesized for this evaluation is shown in Fig. 3 along with their IC<sub>50</sub> values vs. *P. falciparum*.

As seen from the in-vitro data, compound 7, which contains a carboxyethyl side chain attached at the 7-position of the benzoxaborole nucleus, showed the highest antimalarial potency with an IC<sub>50</sub> of 26 nmol/l. Lengthening the side chain in 7 or moving it to adjacent ring positions reduced antimalarial activity, with the 6-position analog 21 showing the second best potency (IC<sub>50</sub> = 120 nmol/l). The excellent potency of 7 was also reduced by alterations to the side-chain terminal functional group as seen by compounds 13–20, with the acidic tetrazole analog 20 being the best in this set of compounds with an IC<sub>50</sub> of 160 nmol/l. Likewise, replacement of the side-chain benzylic methylene group in 7 with different heteroatoms also reduced activity (compounds 10–12). Finally, expanding the ring size of the oxaborole ring to a 6-membered ring (24) led to inactivity as did introduction of gem-di-methyls on the side chain (25) or on the oxaborole ring (26). Pharmacophore alignment analysis of compounds 7, 21 and 27 suggests that this series of compounds probably share a common binding motif which includes a carboxylate site, as depicted in Fig. 4. Compounds missing the carboxylate group, such as 13 and 18, or compounds with mis-aligned carboxylate group, such as compounds 22 and 23, all have much weaker activity (>1 μmol/l).

In summary, the carboxylic acid containing benzoxaborole 7 was found to exhibit excellent in-vitro potency against *P. falciparum*. SAR for this series of compounds was

**Figure 3** Chemical structures of benzoxaborole compounds along with their in-vitro IC<sub>50</sub> results (μmol/l) against *Plasmodium falciparum*

Experimental procedure for the in-vitro assay is described in [24]. Reproduced with permission from [24].

**Figure 4** Superposition of low energy conformers of compounds 7 (cyan), 21 (purple) and 27 (yellow)

narrow, and to date, all structural modifications either reduced or eliminated activity. Ongoing work, including pharmacokinetic, efficacy and safety studies will be reported in future publications.

### Chagas disease

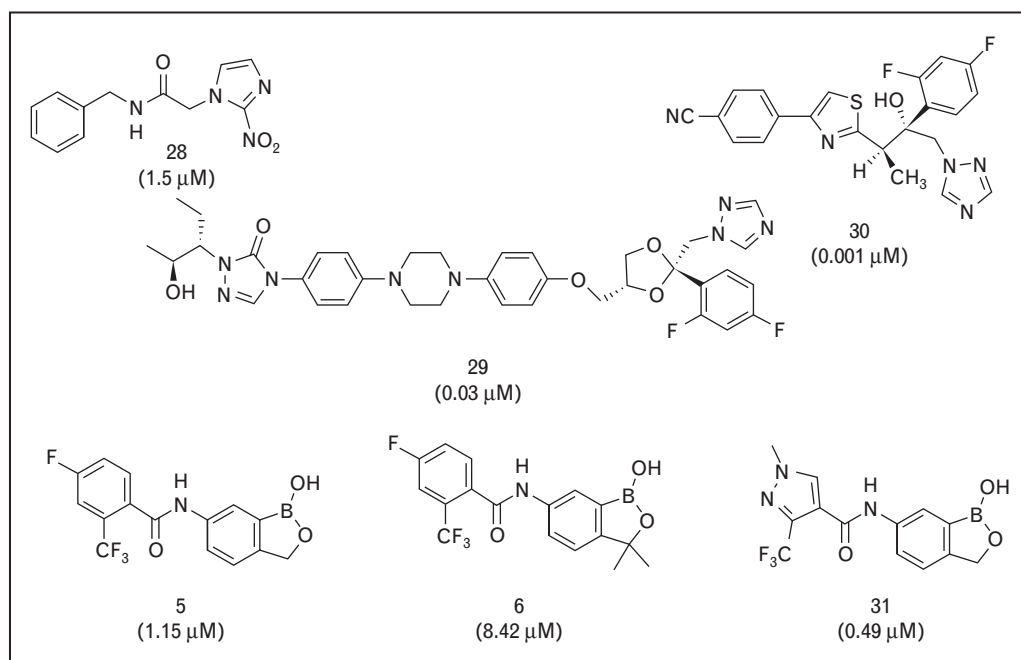
The challenge in the development of new drugs to treat Chagas disease lies in demonstrating efficacy in the chronic form of the disease, a difficult condition to model in preclinical settings and an equally difficult task to monitor in clinical trials to obtain proof of cure. The causative parasitic agent *T. cruzi* invades the muscle cells of the heart and/or the gastrointestinal tract, causing extensive damage to these organs over time [27,28]. Other tissues and organs are also affected as the disease progresses through an acute and then indeterminate phase, presenting as a chronic illness some 10–15 years later. The current standard of care, benznidazole (28), a nitroimidazole originally thought to mediate parasite killing by inducing oxidative stress [29], but now proposed to undergo enzyme-mediated activation by

nitroreductases within the parasite [30–32], is not efficacious in patients with chronic disease and can cause undesirable side-effects in adults, ranging from gastrointestinal discomfort to neuropathy, leading to poor patient compliance over the 60-day treatment regime. Newer agents, posaconazole (29) and ravuconazole (30), shown in Fig. 5, target inhibition of sterol biosynthesis by binding to *T. cruzi* CYP51, an enzyme required to demethylate the sterol core [33,34]. These agents are the first to enter clinical trials for the treatment of Chagas disease in over 40 years. Concern regarding the potential for development of resistance to azole-based therapies suggests there is a need for new agents acting via different mechanisms in this field.

The benzoxaborole scaffold presents an exciting opportunity for the development of a novel therapy for Chagas disease. As described above, benzoxaboroles have demonstrated activity against other protozoan parasites such as *P. falciparum* and *T. brucei*, and we have leveraged the output of the existing HAT drug discovery consortium, screening diversity sets of oxaborole-containing compounds against *T. cruzi* to identify a novel Chagas lead series. The in-vitro inhibitory activity of ca. 1000 compounds screened against *T. cruzi* in a whole cell assay ranged from 0.5 to greater than 10  $\mu\text{mol/l}$ , with clear structure activity relationship trends noted. The majority of the compounds of interest ( $\text{IC}_{50} \sim 1 \mu\text{mol/l}$ ) were based on the 6-amido oxaborole scaffold successfully

elaborated for the HAT effort. HAT preclinical candidate SCYX-7158 (6) was less active than SCYX-6759 (5), which lacks the gem-dimethyl group on the borole ring ( $\text{IC}_{50} = 8.42$  and  $1.15 \mu\text{mol/l}$ , respectively, Fig. 5). Compound 5 was profiled as a benchmark compound in a mouse model of acute *T. cruzi* infection. Following a sub-lethal dose of parasites, mice were treated with 10 mg/kg orally once daily for 5 days resulting in 100% inhibition of bloodstream parasitemia. Given this high level of activity at low dose and short treatment period, 5 was profiled in a more stringent chronic model which tests the ability of compounds to clear parasites from deep tissue reservoirs. In this model, drug treatment is followed by 10 days of monitoring for the return of parasitemia and monitoring is continued through three rounds of immunosuppression (using cyclophosphamide) and recovery [36]. Mice treated with 5 saw a rebound of parasitemia prior to the final round of immunosuppression. Higher drug doses and longer treatment times did not improve this outcome. Although this is a particularly stringent in-vivo model, other agents, for example posaconazole, have demonstrated a cure. Subsequent lead optimization work undertaken by the Chagas consortium has identified new analogs with improved in-vitro potency ( $\text{IC}_{50}$  0.2–0.5  $\mu\text{mol/l}$ ) and good pharmacokinetic profiles. Typically, these newer, more potent analogs such as 31 have shorter half-lives than 5, yet the in-vivo outcome in the *T. cruzi* mouse models was the same – 100% inhibition of bloodstream parasitemia in the acute

Figure 5 Chemical structures of compounds along with their in-vitro  $\text{IC}_{50}$  results ( $\mu\text{mol/l}$ ) against *Trypanosoma cruzi*



Experimental procedure for the in-vitro assay is described in [35].

model and parasite rebound after immunosuppression in the chronic model. With little known about the biology of *T. cruzi* and no specific mode of action identified for oxaborole-containing molecules, the development of these agents proceeds empirically. Regardless, 5 and its congeners present an exciting opportunity to find a novel therapy. There are no other boron-based drugs or preclinical molecules reported in the literature as having activity against *T. cruzi*.

## Conclusion

Boron-containing compounds such as the benzoxaboroles from Anacor Pharmaceuticals represent an interesting class of potential antiparasitic drug candidates. Building on the known antibacterial, antifungal and anti-inflammatory properties of this class, screening of benzoxaboroles in whole cell antiparasitic assays followed by optimization of physicochemical and pharmacokinetic properties have resulted in identification of several potential preclinical candidates. Whereas not yet fully explored for each new drug candidate, the general safety and toxicological profiles of the benzoxaboroles which have progressed to clinical trials for anti-bacterial [37] and anti-inflammatory applications are encouraging [38,39,40]. The most advanced antiparasitic application of the benzoxaboroles is opposite *T. brucei*, in which a clinical candidate (SCYX-7158, 6) has been identified. Benzoxaboroles with in-vivo activity against both *P. falciparum* and *T. cruzi* have been identified, and lead compounds for these applications are currently being characterized. In conclusion, the application of boron-containing compounds as treatments for parasitic infections appears to hold promise, but is still at a relatively early stage of development.

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## Conflicts of interest

The following organizations have provided funding for the work described in this review: The Drugs for Neglected Diseases initiative and Medicines for Malaria Ventures (Anacor Oxaboroles, MMV 09/0030).

R.T.J. is an employee of SCYNEXIS Inc.; J.J.P. is an employee of Anacor Pharmaceuticals Inc.; and M.K. is an employee of Epicem Pty Ltd. The authors declare no competing financial interests.

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