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Research paper

Structure-guided design of novel *Trypanosoma brucei* Methionyl-tRNA synthetase inhibitors

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ABSTRACT

A screening hit **1** against *Trypanosoma brucei* methionyl-tRNA synthetase was optimized using a structure-guided approach. The optimization led to the identification of two novel series of potent inhibitors, the cyclic linker and linear linker series. Compounds of both series were potent in a *T. brucei* growth inhibition assay while showing low toxicity to mammalian cells. The best compound of each series, **16** and **31**, exhibited EC_{50}s of 39 and 22 nM, respectively. Compounds **16** and **31** also exhibited promising PK properties after oral dosing in mice. Moreover, compound **31** had moderately good brain permeability, with a brain/plasma ratio of 0.27 at 60 min after IP injection. This study provides new lead compounds for arriving at new treatments of human African trypanosomiasis (HAT).

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1. Introduction

Human African trypanosomiasis (HAT) is a parasitic disease caused by the protozoan *Trypanosoma brucei* [1,2]. The disease is endemic in regions of sub-Saharan Africa, causing infection risk to 70 million people [3,4]. Without treatment, the disease is invariably fatal. Current treatment for HAT includes suramin, pentamidine, melarsoprol, eflornithine, or a combination of nifurtimox and eflornithine [2,5]. These drugs have many shortcomings, including high toxicity and/or require administration by injection [6]. Thus, there is urgent need for the development of new therapeutics that are effective, safe, easy to administer, and affordable.

Methionyl-tRNA synthetase (MetRS) of *T. brucei* (*Tb*MetRS) plays an essential role in protein translation, providing the methionine charged tRNAs needed for biosynthesis of protein peptide chains [7]. It has been shown that *Tb*MetRS is an attractive drug target for the development of a new HAT treatment [8,9]. However, some previously reported inhibitors have drawbacks. For example, the aminoquinolone-based analogues of inhibitors that target bacterial MetRS [10,11] have poor PK profiles and poor membrane permeability despite potent *in vitro* activity against *T. brucei* parasites [8]. Urea-based inhibitors have improved pharmacokinetic characteristics and membrane permeability, but their potency against the parasites is suboptimal [9]. As part of our continued effort to discover novel MetRS inhibitors, a high-throughput screen of the NIH Molecular Libraries Small Molecule Repository was performed with *Tb*MetRS [12], leading to the discovery of compound **1**. In this paper we report the structure-guided optimization of **1** that resulted in novel *Tb*MetRS inhibitors with good potency, high selectivity, promising PK properties as well as brain permeability.

2. Results and discussion

2.1. Molecular design

Compound **1** (Fig. 1E) was identified as a weak inhibitor of *Tb*MetRS in a high-throughput orthogonal screening [12], showing

Abbreviations: AP, auxiliary pocket; CNS, central nervous system; EMP, enlarged methionine pocket; HAT, human African trypanosomiasis; MetRS, methionyl-tRNA synthetase; SAR, structure-activity relationship.

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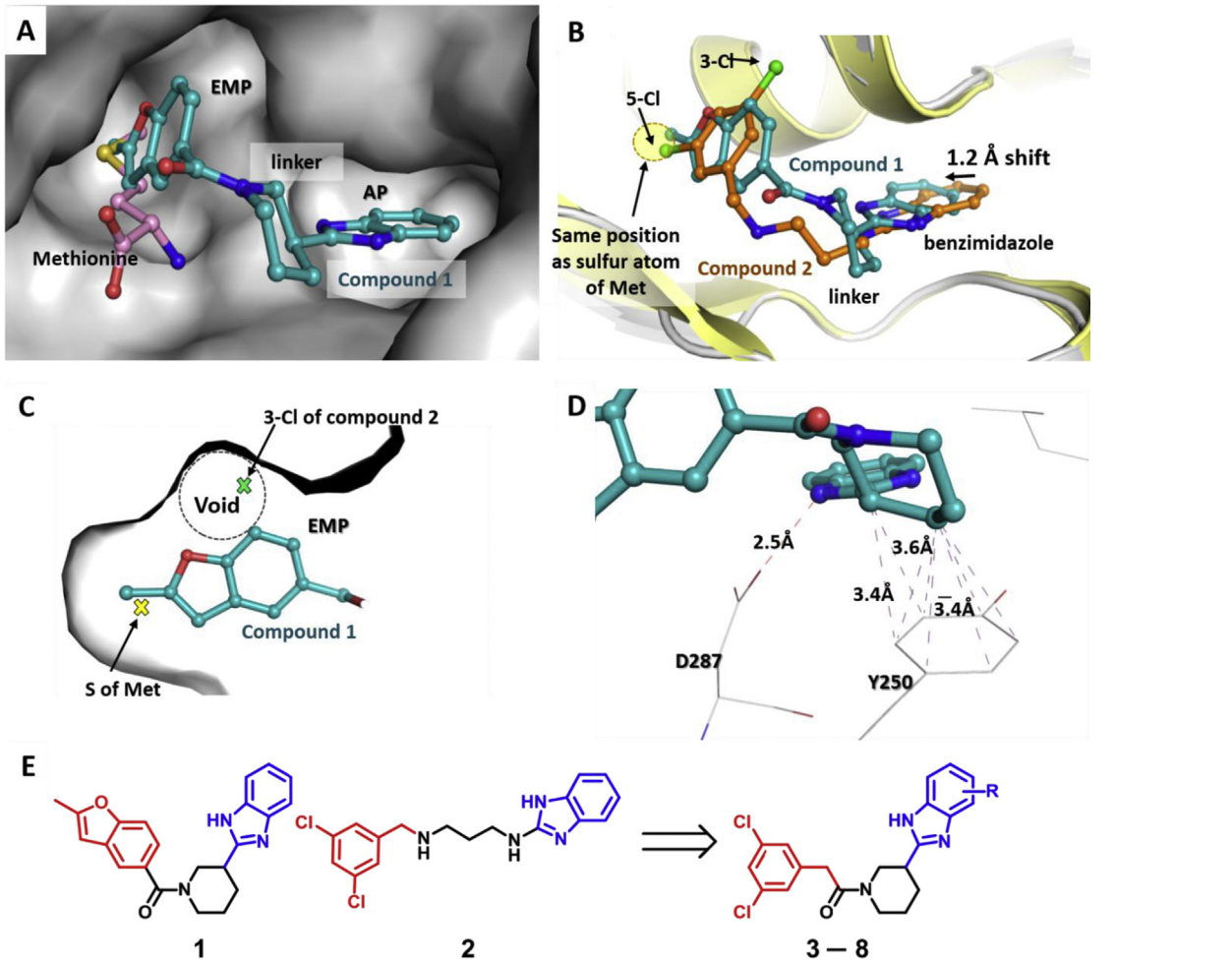

Fig. 1. Crystal structures of compounds **1** and **2** in complex with *Tb*MetRS and the design strategy of new compounds. (A) Compound **1** (cyan carbons) in the *Tb*MetRS active site, bound methionine from a previously determined structure (PDB: 4EG1) is shown as a reference (pink carbons) [13]; (B) Superimposed structures of compounds **1** (cyan) and **2** (orange) in complex with *Tb*MetRS; (C) A void existing in the EMP when the benzofuran group of compound **1** binds; (D) The piperidine ring in the linker of compound **1** interacts with Tyr250; (E) Inhibitor design strategy of combining compounds **1** and **2**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

78% and 20% inhibition in a *Tb*MetRS aminoacylation assay at 10 and 1 μM respectively. Compound **1** can be chemically parsed into three parts: a benzimidazole moiety, a benzofuran moiety, and a linker connecting these two aryl rings. Similarly, compound **2** (Fig. 1E), a potent *Tb*MetRS inhibitor reported previously [12–15], also contains a benzimidazole moiety connected by a linker to an aryl ring (3,5-dichlorophenyl group). The benzimidazole moiety has already been identified as an effective fragment that binds the "auxiliary pocket" (AP) of *Tb*MetRS [14]. The new attachment mode of the benzimidazole group to the other aryl moiety (benzofuran) seen in compound **1** provided opportunities to arrive at *Tb*MetRS inhibitors with alternative linkers.

To aid the design of new inhibitors, a crystal structure of *Tb*MetRS with compound **1** (Fig. 1A) was obtained at 2.7 Å resolution (Table S1). The binding mode of compound **1** was compared to compound **2** bound to *Tb*MetRS and analyzed in detail (Fig. 1B). The benzimidazole group of compound **1** binds similarly to the "auxiliary pocket" (AP) compared to compound **2**. Both compounds interact with the AP by means of hydrophobic interactions with residues His289, Gly290 and Val473. A previously observed hydrogen bond interaction between the catalytic residue Asp287 and the benzimidazole moiety in compound **2** is also formed by compound **1** (Fig. 1D). However, there is a shift of 1.2 Å away from the binding pocket of the benzimidazole moiety of compound **1** with respect to **2** (Fig. 1B). At the other end of compound **1**, the benzofuran moiety occupies the "enlarged methionine pocket" (EMP) (Fig. 1C), which is formed mainly by hydrophobic residues (including the ones engaged in methionine binding) and interacts favorably with residue Phe522. However, compared to compound **2**, the benzofuran binding of compound **1** leaves a void that is filled by the 3-chlorine of the 3,5-dichloro-benzene moiety in compound **2** (Fig. 1C) providing in the latter case favorable hydrophobic interactions especially with residue Trp474. In the linker region, the piperidine ring in compound **1** restricts the conformational freedom of the linker. The piperidine ring is also engaged in hydrophobic interactions with residue Tyr250 (Fig. 1D), adding to the previously described *Tb*MetRS·inhibitor stacking interactions [13].

From comparing the binding modes of compounds **1** and **2**, we hypothesized that hybridizing elements of both compounds would lead to a novel chemotype exploiting the best features of both parental compounds (Fig. 1E). Considering that the 3,5-dichlorophenyl moiety in compound **2** was established as a preferred fragment for the EMP [9,14] and it binds more efficiently (no void) than the benzofuran moiety in compound **1**, we decided to fix it as the fragment to fill the EMP in all the designed compounds reported here. We focused our investigation on varying the

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