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Research paper

Structure-based lead optimization to improve antiviral potency and ADMET properties of phenyl-1H-pyrrole-carboxamide entry inhibitors targeted to HIV-1 gp120

Francesca Curreli [a], Dmitry S. Belov [b], Young Do Kwon [c], Ranjith Ramesh [a], Anna M. Furimsky [d], Kathleen O'Loughlin [d], Patricia C. Byrge [d], Lalitha V. Iyer [d], Jon C. Mirsalis [d], Alexander V. Kurkin [b], Andrea Altieri [b], Asim K. Debnath [a, *]

[a] Laboratory of Molecular Modeling & Drug Design, Lindsley F. Kimball Research Institute, New York Blood Center, 310 E 67th Street, New York, NY 10065, USA
[b] EDASA Scientific, Scientific Park, Moscow State University, Leninskie Gory Bld. 75, 77-101b, 119992 Moscow, Russia
[c] Structural Biology Section, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA
[d] SRI International, Biosciences Division, 333 Ravenswood Avenue, Menlo Park, CA 94025, USA

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ABSTRACT

We are continuing our concerted effort to optimize our first lead entry antagonist, NBD-11021, which targets the Phe43 cavity of the HIV-1 envelope glycoprotein gp120, to improve antiviral potency and ADMET properties. In this report, we present a structure-based approach that helped us to generate working hypotheses to modify further a recently reported advanced lead entry antagonist, NBD-14107, which showed significant improvement in antiviral potency when tested in a single-cycle assay against a large panel of Env-pseudotyped viruses. We report here the synthesis of twenty-nine new compounds and evaluation of their antiviral activity in a single-cycle and multi-cycle assay to derive a comprehensive structure-activity relationship (SAR). We have selected three inhibitors with the high selectivity index for testing against a large panel of 55 Env-pseudotyped viruses representing a diverse set of clinical isolates of different subtypes. The antiviral activity of one of these potent inhibitors, **55** (NBD-14189), against some clinical isolates was as low as 63 nM. We determined the sensitivity of CD4-binding site mutated-pseudoviruses to these inhibitors to confirm that they target HIV-1 gp120. Furthermore, we assessed their ADMET properties and compared them to the clinical candidate attachment inhibitor, BMS-626529. The ADMET data indicate that some of these new inhibitors have comparable ADMET properties to BMS-626529 and can be optimized further to potential clinical candidates.

1. Introduction

Advances in available therapeutics, in particular combination antiretroviral therapy (cART), significantly improved the treatment of HIV infection and facilitated the shift from high morbidity and mortality to a manageable chronic disease. Despite this remarkable success, current therapies suffer from several limitations. For example (1) reliance on daily adherence; (2) long-term use resulting in long-term toxicity; (3) limited treatment options due to the development of drug resistance; (4) high cost, and finally, (5) the non-curative nature of current treatments. Further, despite tremendous effort and investment, an effective vaccine or microbicide is not yet available, and significant hurdles must be overcome to achieve a functional cure. Thus, the continued development of small-molecule drugs with high potency against

Abbreviations: HIV-1, Human Immunodeficiency Virus Type 1; Env, Envelope; AIDS, acquired immunodeficiency syndrome; VSV-G, Vesicular stomatitis virus-G; ADMET, absorption distribution metabolism and excretion; SM, starting material; DCM, dichloromethane; DIPEA, N,N-Diisopropylethylamine; HBTU, N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate; TBSCl, tert-Butyldimethylsilyl chloride; TFAA, Trifluoroacetic anhydride.

* Corresponding author.
E-mail address: adebnath@nybc.org (A.K. Debnath).

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novel targets but minimal side effects is imperative. The development of novel therapeutics will aid in increasing the number of new drugs available and will extend the scope of combination therapy. Our group has made significant headway in filling this critical need by developing a new class of HIV-1 entry inhibitors targeted to the Phe43 cavity of HIV-1 gp120, which is distinct from the binding site of the clinical candidate attachment inhibitor from BMS [1].

Viral attachment and fusion to the host cell membrane are critical for HIV-1 to enter host cells and initiate its life-cycle by utilizing host cell machinery [2]. Therefore, viral attachment and fusion (often collectively termed "viral entry") have been targets of new drug discovery for many years [3–6]. There are only two drugs currently on the market that target the entry pathway. FUZEON® (enfuvirtide), a peptide-based drug, targets the envelope glycoprotein gp41 [7,8] and SELZENTRY® (maraviroc), a small molecule drug, targets the host cell receptor CCR5 [9,10].

Despite the fact that HIV-1 gp120 is critical for viral entry and has been the target of prior drug discovery efforts, no drugs that target gp120 have been approved yet by the US FDA. BMS-663068, the most advanced inhibitor in this class, is a prodrug of BMS-626529. The safety and efficacy of BMS-663068 were demonstrated recently in a Phase 2 b clinical trial, and the compound is currently undergoing Phase III clinical trials. In 2015, BMS-663068 received the "B*reakthrough Therapy Designation*" from the US FDA, indicating the importance of gp120 as a target for the development of drugs that prevent viral entry into host cells. This recognition by the FDA confirms that our efforts to develop novel drugs are highly significant, especially for the growing number of treatment-experienced patients with limited treatment options and for use as a combination therapy for the millions of affected individuals worldwide.

Our laboratory had focused on developing novel inhibitors targeted to the Phe43 cavity of gp120 since 2005 when we first reported the discovery of NBD-556, the NBD-series CD4-mimic [11]. Unfortunately, NBD-556 enhanced HIV-1 infection in $CD4^-$-$CCR5^+$ cells and thus behaved as an HIV-1 entry agonist [12,13]. Since this finding, we and others have endeavored to design CD4 mimics with higher potency, lower toxicity, and devoid of this undesirable agonist property [13–21]. However, progress was slow until we determined the crystal structure of HIV-1 gp120 in complex with NBD-556 [22], which guided us the modification of NBD-556 to NBD-11021, an entry antagonist that is a more potent entry inhibitor [15,23]. Since then, we determined the X-ray structures of several new generations of the NBD series HIV-1 entry antagonists in complex with gp120 [13,14,22,24,25]. The structural knowledge provided valuable information for the design of our next generation of inhibitors, which achieved measurable improvements in both potency and selectivity index (SI) against a large panel of >50 Env-pseudotyped viruses representing a diverse set of clinical isolates of different subtypes. Our first entry antagonist NBD-11021, which exhibited ~3-fold higher antiviral activity and ~1.3-fold higher SI compared to the entry agonist, NBD-556. Hence, we optimized our first candidate antagonist lead NBD-11021 and developed several next-generation leads to higher activity and SI (Fig. 1) [13–15,24].

In this report, we describe our concerted effort in optimizing the best lead compounds so far using a structure-based drug design approach. This effort resulted in a new HIV-1 entry antagonist, **55**, which exhibited an extraordinary broad-spectrum activity against a large panel of Tier II HIV-1 clinical isolates and 2 Tier III HIV-1 clinical isolates (NIH #11022 and 11605). The antiviral activity of **55** against some clinical isolates was as low as 63 nM. A comparison of the *in vitro* ADMET data from the best NBD series inhibitors with the attachment inhibitor BMS-626529 indicated that **55** has desirable ADMET profiles as a promising lead for further development [24].

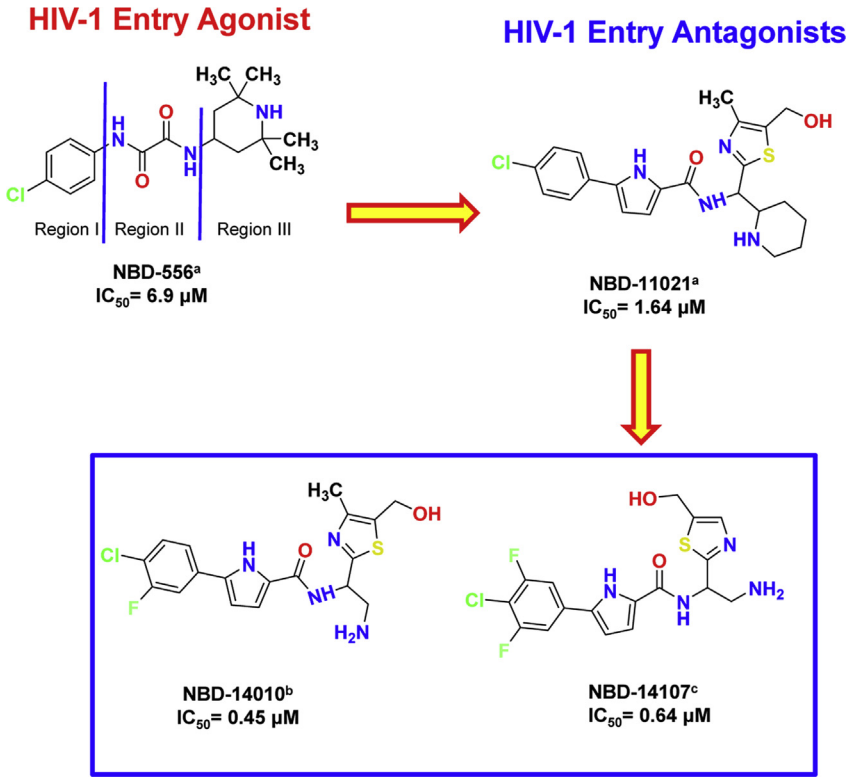

Fig. 1. Structures and a sequential improvement of antiviral activity of NBD series inhibitors. The IC_{50}s were calculated from the data when tested against pseudovirus $HIV\text{-}1_{HXB2}$.