BIOCHEMICAL PHARMACOLOGY 76 (2008) 156–168

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Selective targeting of the HIV-1 reverse transcriptase catalytic complex through interaction with the "primer grip" region by pyrrolobenzoxazepinone non-nucleoside inhibitors correlates with increased activity towards drug-resistant mutants

Samantha Zanoli [a], *Sandra Gemma* [b,e], *Stefania Butini* [b,e], *Margherita Brindisi* [b,e], *Bhupendra P. Joshi* [b,e], *Giuseppe Campiani* [b,e], *Caterina Fattorusso* [c,e,*], *Marco Persico* [c,e], *Emmanuele Crespan* [a], *Reynel Cancio* [a], *Silvio Spadari* [a], *Ulrich Hübscher* [d], *Giovanni Maga* [a,e,**]

[a] *Institute of Molecular Genetics, IGM-CNR, via Abbiategrasso 207, I-27100 Pavia, Italy*
[b] *Dipartimento Farmaco Chimico Tecnologico, Universita' degli Studi di Siena, via Aldo Moro, I-53100 Siena, Italy*
[c] *Dipartimento di Chimica delle Sostanze Naturali, Universita' di Napoli "Federico II", via D. Montesano 49, I-80131 Napoli, Italy*
[d] *Institute of Veterinary Biochemistry and Molecular Biology, University of Zürich-Irchel, CH-8057 Zürich, Switzerland*
[e] *European Research Centre for Drug Discovery and Development, Universita' degli Studi di Siena, I-53100 Siena, Italy*

ARTICLE INFO

Article history:
Received 13 March 2008
Accepted 11 April 2008

Keywords:
HIV-1
Reverse transcriptase
NNRTIs
Kinetics
Drug resistant
Molecular modeling

ABSTRACT

PBO (pyrrolobenzoxazepinone) derivatives are non-nucleoside reverse transcriptase inhibitors (NNRTIs), which display a selective interaction with the catalytic ternary complex of HIV-1 reverse transcriptase (RT) and its substrates. In order to develop novel PBOs with improved resistance profiles, we synthesised additional PBO derivatives, specifically designed to target highly conserved residues in the β12–β13 hairpin, the so-called "primer grip" region of HIV-1 RT. Here, we investigated the biochemical and enzymological mechanism of inhibition of HIV-1 RT wild type and carrying NNRTIs-resistance mutations, by these derivatives. Our kinetic analysis indicates that the ability of PBOs to selectively target the catalytic ternary complex of RT with its substrates directly correlates with greatly reduced sensitivity to NNRTIs-resistance mutations, particularly the K103N substitution. Molecular modeling and docking studies provided an explanation for this correlation at the structural level.

1. Introduction

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric and non-competitive modulators of reverse transcriptase (RT), one of the key enzyme in the life cycle of HIV-1 [1,2]. Because of their generally good tolerability and low toxicity [3], these drugs are essential components of highly active antiretroviral therapy (HAART), with nucleoside reverse

* *Corresponding author at*: Dipartimento di Chimica delle Sostanze Naturali, Universita' di Napoli "Federico II", via D. Montesano 49, I-80131 Napoli, Italy.
** *Corresponding author at*: Institute of Molecular Genetics, IGM-CNR, via Abbiategrasso 207, I-27100 Pavia, Italy. Tel.: +39 0382546354; fax: +39 0382422286.
E-mail addresses: cfattoru@unina.it (C. Fattorusso), maga@igm.cnr.it (G. Maga).
0006-2952/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2008.04.009

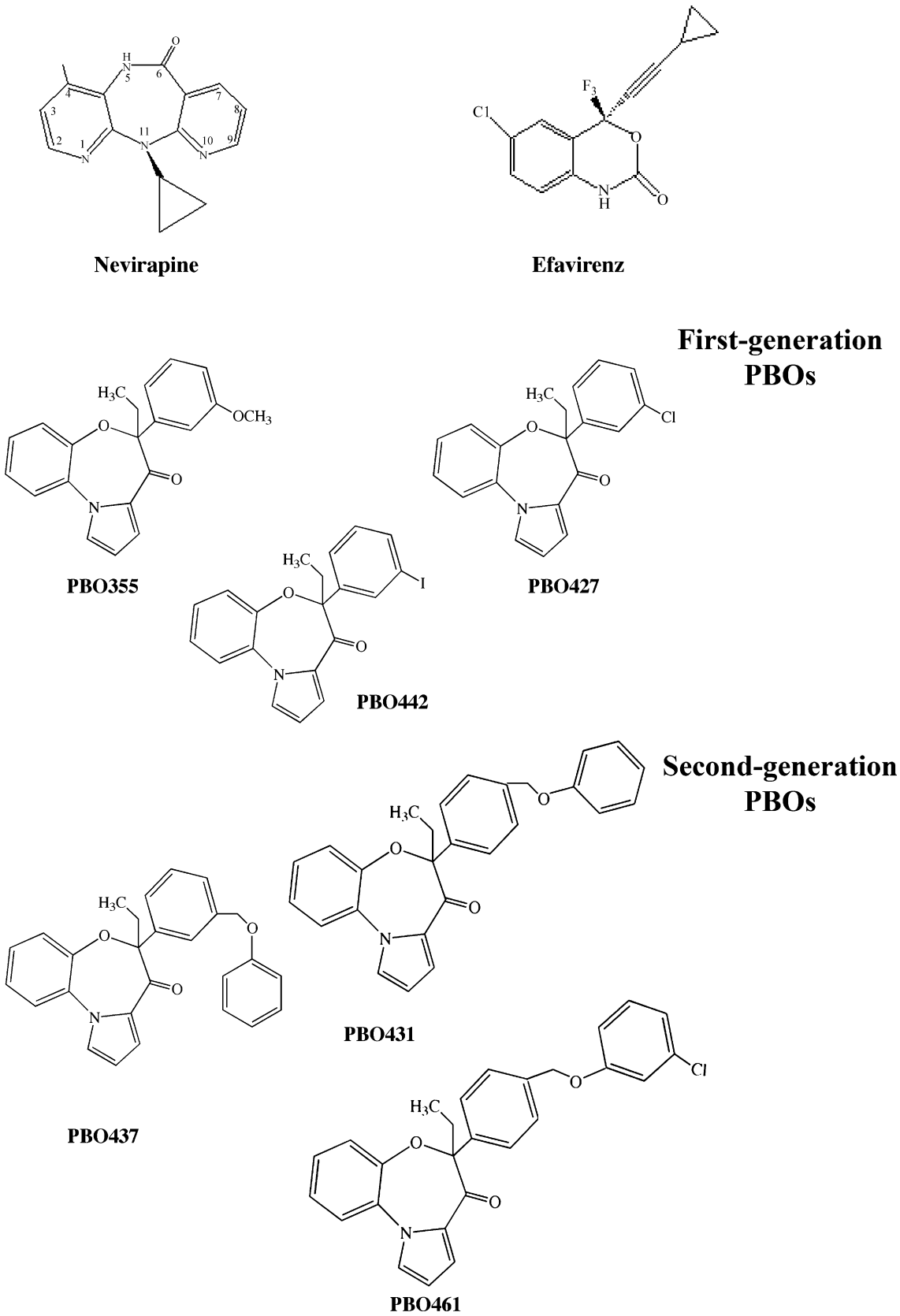

Fig. 1 – Structures of the NNRTIs nevirapine and efavirenz and of the PBO derivatives used in this study.