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Structural basis for drug resistance mechanisms for non-nucleoside inhibitors of HIV reverse transcriptase

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Abstract

The selection of drug resistant virus is a significant obstacle to the continued successful treatment of HIV infection. Reverse transcriptase is the target for numerous approved anti-HIV drugs including both nucleoside inhibitor (NRTI) and non-nucleosides (NNRTI). The many available crystal structures of RT reveal that, generally, in relation to their binding sites NRTI resistance mutations are generally more distally positioned, whilst for NNRTIs mutations are clustered. Such clustering implies a direct stereochemical basis for NNRTI resistance mechanisms, which is indeed observed in many cases such as the loss of key ring stacking interactions with inhibitors via mutations at Tyr181 and Tyr188. However, there are also indirect resistance mechanisms observed, e.g. V108I (via perturbation of Tyr188 and Tyr181) and K103N (apo-enzyme stabilisation). The resistance mechanism can be NNRTI-dependent as is the case for K101E where either indirect (nevirapine) or direct effects (efavirenz) apply. Structural studies have contributed to the design of newer generation NNRTIs and identified a number of features which may contribute to their much improved resistance profiles. Such factors include reduced interactions with Tyr181, the presence of inhibitor/main-chain H-bonds and ability to undergo conformational flexing and rearrangement within the mutated drug site.

Keywords: HIV; Non-nucleoside inhibitor; NNRTI; Reverse transcriptase; Drug resistance

1. Introduction

The emergence of resistant mutant forms of HIV by selection from a range of quasispecies by drug selective pressure, characterises the problem of maintaining effective therapy of HIV infected individuals. The initial anti-HIV drugs developed acted as inhibitors of reverse transcriptase (RT) and were based on nucleoside analogues (NRTIs) (Mitsuya et al., 1990). Non-nucleoside RT inhibitors (NNRTIs) were subsequently identified as a chemically diverse class of compounds which looked initially promising as potential anti-HIV drugs (Fig. 1); *in vitro* data showed low toxicity combined with high potency (Miyasaka et al., 1989; Pauwels et al., 1990). However, from clinical trials of the prototype NNRTI, nevirapine, as monotherapy to treat HIV infection (Merluzzi et al., 1990), extremely rapid selection of resistant virus meant that the utility of this drug class appeared rather limited (Richman et al., 1994). With the introduction of multi-drug combination therapy an important role for NNRTIs has now been established (De Clercq, 2001). Subsequent efforts have lead to the development of many anti-HIV drugs acting against an expanding range of targets, particularly HIV protease but also now a fusion inhibitor targeting gp41 and a co-receptor antagonist. Based on current progress it is hoped that integrase inhibitors will be the next class of anti-HIV drugs available (Reed and Daar, 2006). However, due to problems of patient compliance related to the chronic nature of HIV infection and the inability of drugs to reach every reservoir of infection in the body, then of course resistance selection inevitably still occurs. In spite of the development of newer HIV inhibitors acting at novel target sites, HIV RT still remains important for the development of further drugs including NNRTIs, with those having improved resistance profiles being a particular objective. Understanding the underlying molecular mechanisms whereby mutations give rise to drug resistance is not only of interest from the basic science standpoint but also of importance in helping the design of novel drugs which are able to combat the plethora of existing mutant HIV forms selected by current drug therapy.

HIV-1 RT consists of a p66/p51 heterodimer, the larger subunit contains both NRTI and NNRTI binding sites (Kohlstaedt et al., 1992; Huang et al., 1998) (Fig. 2). The p66 subunit consists of

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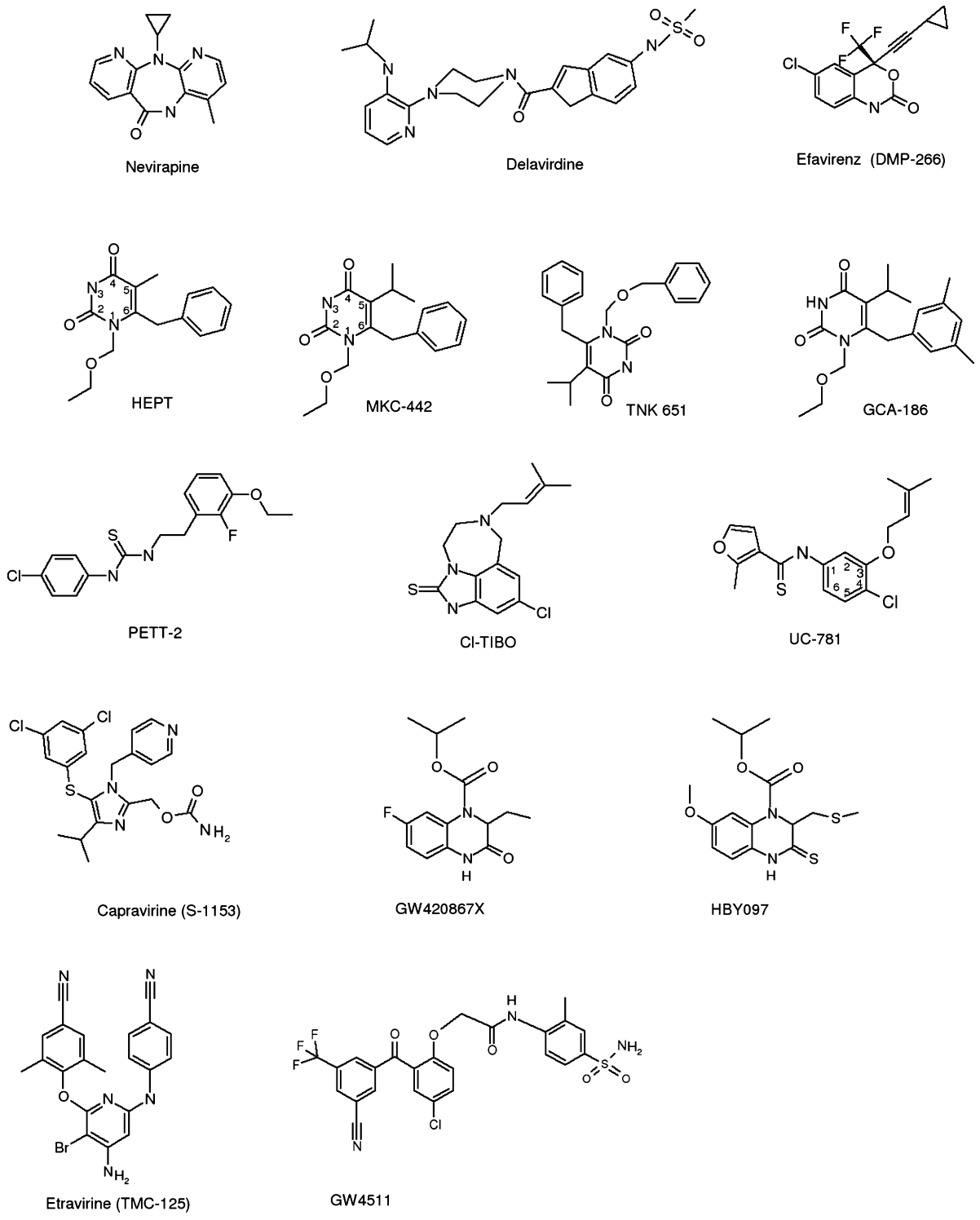

Fig. 1. Structures of some of the NNRTIs referred to in this article.

polymerase and RNase H domains (the latter cleaves RNA from an RNA/DNA heteroduplex). The polymerase domain is composed of four subdomains: fingers, palm, thumb and connection (Kohlstaedt et al., 1992). The NNRTI site is largely associated with the palm subdomain, although Glu138 from p51, located at the edge of the pocket can interact with certain inhibitors. The NNRTI site is distal to the polymerase active site and in contrast to NRTIs, which compete at the active site (Goody et al., 1991), NNRTIs act as non-competitive inhibitors. Mapping many of the known NRTI and NNRTI resistance mutations onto the p66 subunit shows that the latter form more of a cluster, immediately surrounding the drug-binding site (Fig. 2). In contrast, NRTI resistance mutations are in some cases more distally located relative to the dNTP site. Currently, the three FDA-