proceedings

Abstract

Designing Novel Hydrazinecarbothioamides as Potential HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors †

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Reverse transcriptase (RT), the key enzyme in the HIV life cycle of HIV, is one of the main targets for the antiretroviral chemotherapy. Nonnucleoside reverse transcriptase inhibitors (NNRTIs), including HEPT, DABO, TIBO, DATA, and DAPY, are the main drugs for treating AIDS efficiently. Among them, DAPYs were regarded as one of the most successful NNRTI members including Etravirine (TMC125) as the FDA approved drugs showing the improved potency against many drug resistance mutations. The newly approved Rilpivirine (TMC278) possessed a higher genetic barrier to oppose various clinically relevant RT mutations than Etravirine. However, the rapid emergence of the drug resistance and the serious side effects of the long-term clinical drugs impelled the medicinal chemists to develop the structure diversified NNRTIs. As indicated in the previous papers, our program in NNRTIs led to the modifications on DAPY derivatives with hydroxyl, cyano, chlorine, and hydrazone groups attached to the CH_2-linker between the left benzene ring and the central pyrimidine ring, which showed the excellent activity against HIV-1 replication. Moreover, the docking results show that these groups could fill the Val179-including active binding pocket (Lys101/Glu138/Val179) of HIV-1 RT, which provide some possibilities to generate the suitable electrostatic interactions with the amino acid residues at the wall of the active site. On the other hand, thiosemicarbazone derivatives have been evaluated for their inhibitor activity against antiviral, as well as the effects against human immunodeficiency virus (HIV).

Based on the SAR analysis of these NNRTIs and the structure feature of HIV-1 RT NNIBP, we postulate that introducing a thiosemicarbazone group might be well accommodated in the open position in front of Lys101/Glu138/Val179, which is considered as the entrance channel for the NNRTIs. Therefore, we designed and synthesized a new series of CR_2-DAPYs featuring a thiosemicarbazone group at the CH_2 linker between wing I and the central pyrimidine ring in order to evaluate their biological activities against HIV-1 RT for the further structure–activity relationship (SAR) studies (**1**, Figure 1).

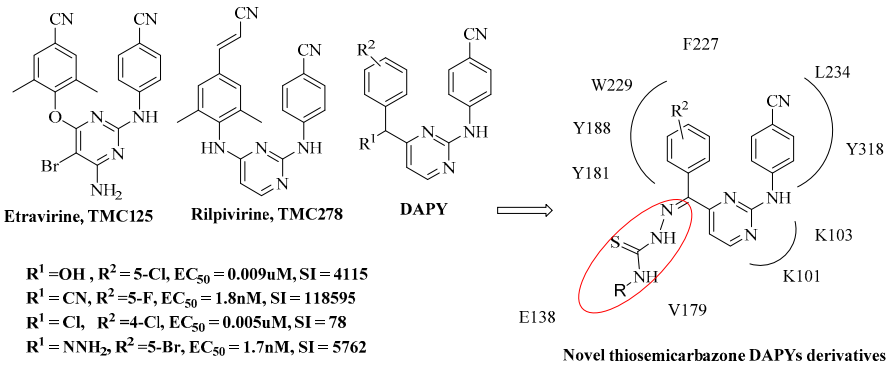

Figure 1. Designing of new DAPY-NNRTIs with the scaffold of thiosemicarbazone.

The HIV-1 reverse transcriptase assay of the synthesized compounds also indicates that the target of these compounds is HIV-1 RT. Most of these target compounds displayed anti-HIV-1 activity at the level of micromolar EC_{50} values in infected MT-4 cells. Compound **1e** exhibited the most potent activity with an EC_{50} value of 0.0047 μM on HIV-1 RT enzymatic assay screening test. However, almost all of the target compounds lost the potency against the mutant type virus and HIV-2, except for compound **1a**, which showed both the potent anti-HIV-1 activity with IC_{50} values of 0.038 μM against wild type and the inhibitory activity with an EC_{50} value of 0.082 μM against the mutant type virus (Y181C). In addition, the molecular docking result revealed that introducing a small thiosemicarbazone group into CH_2 linker occupied the binding space in the hydrophobic cavity lined with Tyr181, Tyr188, Phe227, Trp229 of NNIBP, and the bulky thiosemicarbazone group tailed with phenyl ring was docked in front of the Y181-Val179 binding pocket. Both of the two interaction modes retained the low cellular inhibitory potencies. Further, SAR analysis showed that the thiosemicarbazone moiety played the more important role on enhancing the inhibition potency than other skeleton moiety does. However, as the length of the thiosemicarbazone attaching group increased, the inhibition activity against the mutant type of HIV-1 decreased accordingly.

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