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Original article

Chiral resolution, absolute configuration assignment and biological activity of racemic diarylpyrimidine *CH*(*OH*)-DAPY as potent nonnucleoside HIV-1 reverse transcriptase inhibitors

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ABSTRACT

(+)-**3a** and (−)-**3a** were successfully separated from racemate (±)-**3a** by the chiral technique of supercritical fluid chromatography (SCF) with enantiomeric excess (ee%) >99% and purity >99%, and assigned for their absolute configuration as *R* and *S*, respectively, by the experimental electronic circular dichroism (ECD) spectrum and simulated ECD spectra calculated by time-dependent density functional theory (TDDFT) calculations. (+)-(*R*)-**3a** displayed excellent activity with an EC_{50} of 5.3 nM against wild-type HIV-1, which was 12-fold more potent than (−)-(*S*)-**3a**. However, (−)-(*S*)-**3a** showed higher potency than (+)-(*R*)-**3a** against the double HIV-1 RT mutant (K103N + Y181C) as well as HIV-2 strain ROD. The possible reason for the difference of (*R*)- and (*S*)-**3a** in anti-HIV-1 activity was interpreted by molecular docking.

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1. Introduction

The biological properties of different enantiomers often differ greatly due to the stereospecific interactions between an acceptor and a ligand [1,2]. Frequently, one enantiomer is active but the other may be inactive or even toxic [3]. As is well known, nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind to HIV-1 reverse transcriptase (RT), an asymmetric heterodimer [4,5], in a non-competitive manner against the nucleotide substrate, changing the conformation and function of RT and inhibiting its enzymatic activity [6]. The chirality of NNRTIs usually plays an important role in their biological activity [7–10].

Diarylpyrimidine analogs (DAPYs), represented by the excellent anti-HIV-1 drugs etravirine (TMC125) and rilpivirine (TMC278), have been recognized as one of the most successful class of NNRTIs in recent years [11–13]. In the chemical modification of linker between the wing II and central pyrimidine ring, several promising families of DAPYs were identified as NNRTIs [12], among which some families such as compounds **1**–**3** (Fig. 1) possess a chiral center on the linker [14–16]. However, none of their optically pure enantiomers have been evaluated for their anti-HIV activity.

In our previous work [16], *CH(OH)*-DAPYs (Sturcture **3**, Fig. 1), a family of diarylpyrimidines with an hydroxyl methyl linker between wing II and the central pyrimidine, was discovered as a promising family of NNRTIs, among which the most potent compound (±)-**3a** was worth further optimization and development. In this work, we separated racemate (±)-**3a** to get its two optically pure enantiomers (+)-**3a** and (−)-**3a**, which were assigned for their absolute configuration, and evaluated for their anti-HIV activity. Moreover, molecular modeling results for the two enantiomers were also discussed to interpret their significant differences in anti-HIV-1 activity.

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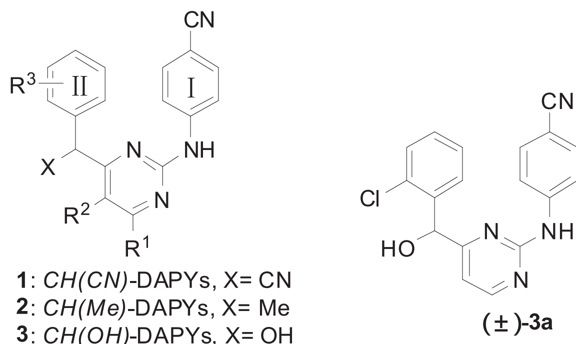

Fig. 1. Chemical structures of DAPYs.

2. Results and discussion

2.1. Chiral resolution

Firstly, we intended to prepare (*R*)-**3a** and (*S*)-**3a** by asymmetric reduction of their prochiral ketone in the presence of chiral BINAL-H [17,18] or chiral oxazaborolidines [19,20]. However, the attempts failed due to low enantiomeric excess (ee) value (<45%), which might be determined by the little bulky difference between the wing II and the central pyrimidine ring. Then we tried to separate the racemate (±)-**3a** by chemical resolution, but regretfully the derivative diastereoisomers were still difficult to separate by routine methods such as column chromatography and recrystallization. In the end, we separated racemate (±)-**3a** with the aid of the chiral technique of supercritical fluid chromatography (SCF) to get optically pure enantiomers (+)-**3a** and (−)-**3a** with ee% >99% and purity >99% (Fig. 2). The resulting enantiomers were analyzed by a Shimadzu LC-10A with a Daicel Chiralcel OD-H (0.46 cm × 25 cm) column using hexane/ethanol/diethylamine 80:20:0.1 (v/v/v) as mobile phase with a flow rate of 1.0 mL/min at a temperature of 35 °C. Moreover, the optical rotations ([α]20D) of (+)-**3a** (Fig. 2b) and (−)-**3a** (Fig. 2c) were determined to be +205.5 ($c = 0.48$, in chloroform) and −206.2 ($c = 0.58$, in chloroform), respectively.

2.2. Absolute configuration assignment

As the high quality monocrystals of (+)-**3a** and (−)-**3a** were difficult to cultivate for direct assigning the absolute configuration (AC) from X-ray data, we relied on the AC assignment by ECD spectroscopy, which was an efficient and widespread method to determine AC [21–24].

The ECD spectra of the two enantiomers of a chiral molecule are of equal magnitude and opposite sign: i.e. mirror-image enantiomers give mirror-image ECD spectra. In principle, the AC of a chiral molecule can therefore be determined from its ECD spectrum. In practice, the determination of the AC of a chiral molecule from its experimental ECD spectrum requires a methodology which reliably predicts the ECD spectra of its enantiomers. The ECD calculation using *ab initio* density functional theory in the GAUSSIAN program provides such a reliable methodology. This methodology has been widely used in determining ACs from experimental ECD [25–28]. The ECD spectrum was calculated by time-dependent density functional theory (TDDFT) approach at B3LYP/TZVP level based on the structure optimized at the same level in Gaussian09 program package. Effect of methanol solvent was mimicked by the polarizable continuum model (PCM) at room temperature.

The AC of (+)-**3a** and (−)-**3a** was assigned by comparison of the experimental ECD spectrum with simulated spectra calculated by TDDFT (Fig. 3). Based on the phase consistency between the experimental ECD spectrum of (+)-**3a** (line 3) and the calculated

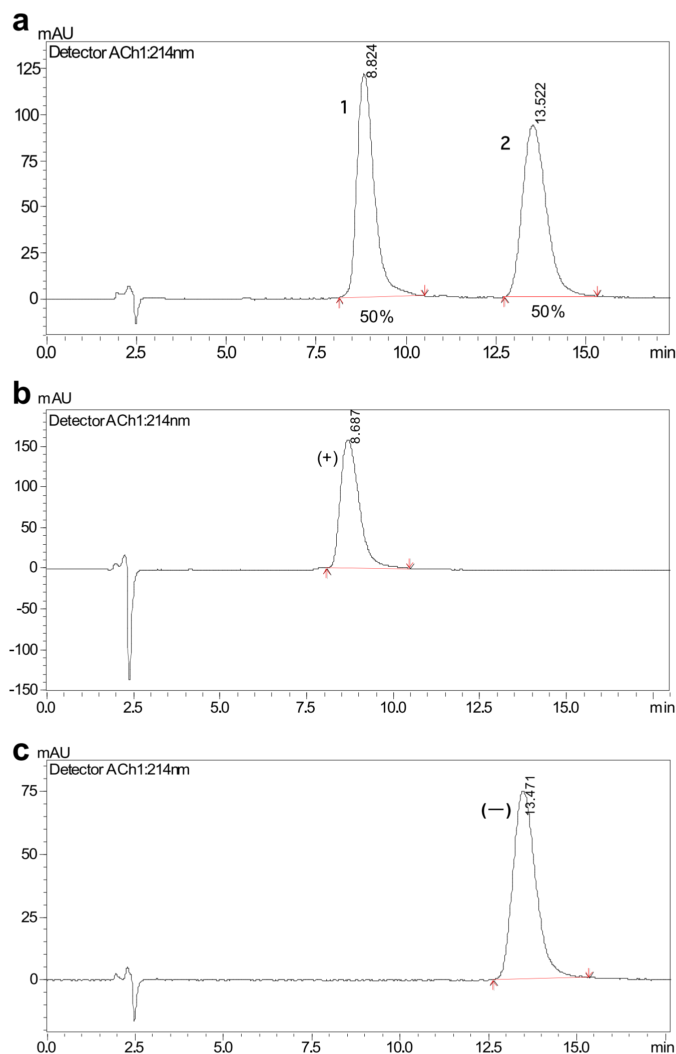

Fig. 2. Chiral HPLC spectrum of the racemate (±)-**3a** and its two enantiomers **a**) Racemate (±)-**3a**; **b**) (+)-**3a**; **c**) (−)-**3a**.

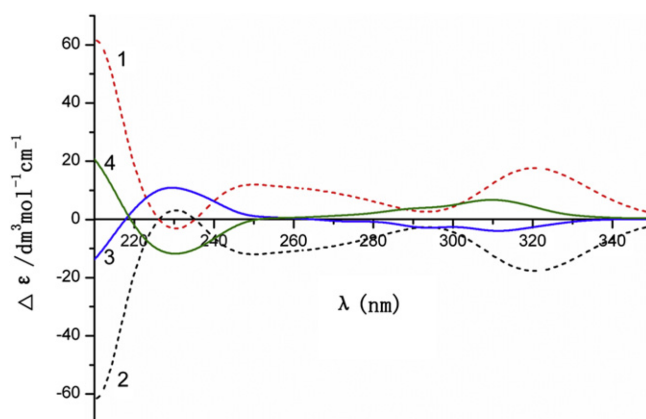

Fig. 3. Experimental and theoretical ECD spectra of **3a**. Experimental spectra (Methanol, $c = 0.79$ mM for (−)-**3a** and 0.5 mM for (+)-**3a**) are shown in dark green full line 4 and blue full line 3, respectively; theoretical result for (*S*)- and (*R*)-**3a** are shown in red dot line 1 and black dot line 2, respectively. Calculated spectra were shifted to lower energy by 0.330 eV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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