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Original article

Non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 11: Structural modulations of diaryltriazines with potent anti-HIV activity ☆

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Abstract

A series of novel 6-naphthyloxy substituted DATA analogues bearing different substituents on the C-6 position of triazine ring were synthesized and evaluated for their *in vitro* anti-HIV activity in MT-4 cells. The results demonstrated that most of the compounds in this series are potent activity against HIV-1 with moderate to high selectivity. Among these analogues, two compounds exhibited excellent effect in inhibiting HIV-1 replication at nanomolar concentration (for compound **9h**: $IC_{50} = 9.3$ nM, SI = 15,385; for compound **9i**: $IC_{50} = 9.4$ nM, SI = 14,094), which are about 15-fold more active than nevirapine. In addition, several compounds are active against both HIV-1 and HIV-2, whose mechanism may be different from typical NNRTIs.

Keywords: Non-nucleoside HIV-1 reverse transcriptase inhibitors; Diaryltriazine; Anti-HIV activity

1. Introduction

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) is a key target for inhibition of HIV-1 replication, the RT can be inhibited by two classes of drug belonging either to the nucleoside reverse transcriptase inhibitors (NRTIs) or to the non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs have become key components in the combination regiments of cocktail therapy. Within the NNRTI category, diaryltriazine analogues (DATAs) are a class of interesting compounds which are highly effective against wild-type and various mutant strains of HIV-1 [2,3] (Fig. 1).

Our recent 3D-QSAR [4] on the binding mode of DATAs with HIV-1 RT indicated that increasing volume of substituent on C-6 of triazine ring was beneficial for strengthening π–π stacking interaction between inhibitor and Tyr188 or Tyr181 of RT. This background prompted us to further explore novel DATAs bearing α- or β-naphthyloxy group at C-6 position in triazine ring. In this paper, a series of novel DATA analogues were synthesized and evaluated for anti-HIV activity.

2. Results and discussion

2.1. Chemistry

The synthesis of the novel designed compounds is outlined in Scheme 1. The known 4-(4,6-dichloro-1,3,5-triazine-2-yl)aminobenzonitrile (**5**) was easily prepared from

☆ See Ref. [1].

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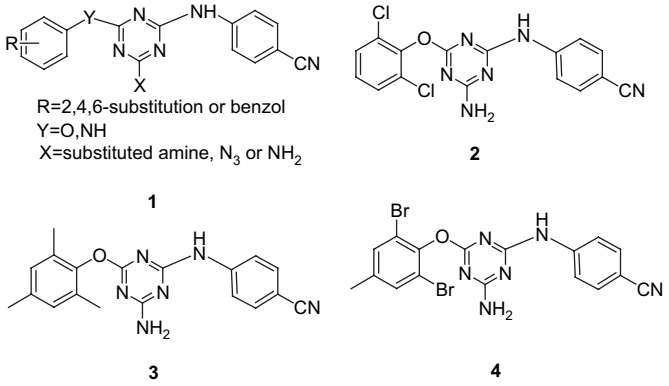


Fig. 1. The structure of DATAs.

the 2,4,6-trichloro-1,3,5-triazine and 4-aminobenzonitrile following the reported method [5,6]. The disubstituted **6a–b** and **7a–e** were obtained in 50–55% upon treatment of the corresponding substituted α- or β-naphthol with **5** in the presence of 60% NaH at 50–60 °C. Condensation of **6a–b** and **7a–e** with appropriate primary amines in 1,4-dioxane at 60–70 °C provided target compounds **8a–g** and **9a–q** in 30–40% yield. Another target compound **9r** was synthesized by reaction of **7c** with NaN_3 in 1,4-dioxane at 90 °C. All the synthesized compounds were well characterized by spectroscopic data as IR, MS, NMR and elemental analysis.

2.2. Anti-HIV activity

All newly synthesized compounds (**8a–g**, **9a–r**) were evaluated as previously described [7] on MT-4 cells for anti-HIV activity and cytotoxicity, in comparison with nevirapine and DDI used as reference drugs, and the results are summarized in Table 1. Among all the newly disclosed DATAs, compounds **9h** and **9i** were the most potent inhibitors of HIV-1 replication of the series ($IC_{50} = 0.0093$ and 0.0094 μM, respectively), coupled with the highest selectivity index (SI = 15,385 and 14,094, respectively). An improvement of the biological profile was obtained by the introduction of halogen substituents (Cl and Br) to the naphthyl ring. The compounds **9h** and **9i** having bromo-substituted on the naphthyl ring are more potent than the corresponding chloro-substituted compounds (**9o** and **9p**). It is noteworthy that decrease in potency was observed when NH_2 group was *N*-alkylated by various alkyl groups (Me, Et, *n*-Pr, *i*-Pr). Further replacement of NH_2 group with N_3 in **8e** converted into compound **9r**, this compound displayed a lower level of cytotoxicity with no effect upon antiviral activity.

Besides the anti-HIV-1 activity, all the compounds were also evaluated activity against HIV-2 ROD in MT-4 cells, it was found that most of the compounds showed less activity against HIV-2 in comparison with that against HIV-1.

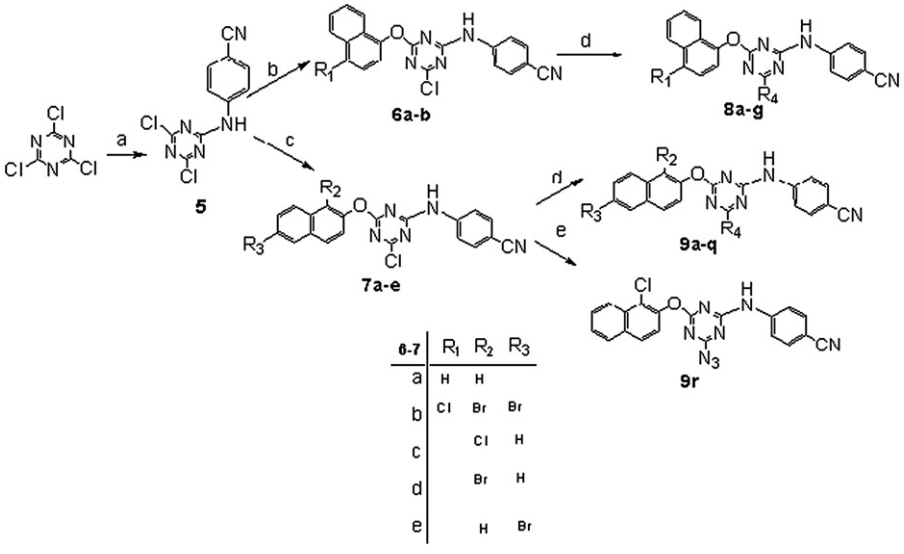
3. Conclusion

In summary, we designed, synthesized and evaluated a series of novel DATA analogues, most of which have potent activities against HIV-1. The results provided useful indicators for guiding further rational design of new inhibitors for the treatment of AIDS. It also afforded information to the deep research on the QSAR and the ongoing investigation of the NNRTI binding site.

4. Experimental protocols

4.1. Chemistry

Melting points were measured on a WRS-1 digital melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a JASCO FT/IR-4200 instrument. ^1H NMR and ^{13}C NMR spectra were measured on a Brucker AV 400 MHz spectrometer in DMSO-d_6. Chemical shifts are expressed in ppm downfield from TMS, which was used as an internal standard.



Scheme 1. Reagents and conditions: (a) *p*-aminobenzonitrile, Et_3N, THF, 0–5 °C; (b) α-naphthol, 60%NaH, anhydrous THF, N_2, 50–60 °C; (c) β-naphthol, 60%NaH, anhydrous THF, N_2, 50–60 °C; (d) NH_3 or RNH_2, 1,4-dioxane, 60–70 °C; and (e) NaN3, 1,4-dioxane, 90 °C.