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Original article

Synthesis, structure–activity relationships, and docking studies of *N*-phenylarylformamide derivatives (PAFAs) as non-nucleoside HIV reverse transcriptase inhibitors

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ABSTRACT

A series of *N*-phenylarylformamide derivatives (PAFAs) with anti-wild-type HIV-1 activity (EC_{50} values) ranging from 0.3 nM to 5.1 nM and therapeutic index (TI) ranging from 10 616 to 271 000 were identified as novel non-nucleoside reverse transcriptase inhibitors. Among them, compound **13g** (EC_{50} = 0.30 nM, TI = 184 578), **13l** (EC_{50} = 0.37 nM, TI = 212 819), **13m** (EC_{50} = 0.32 nM, TI = 260 617) and **13r** (EC_{50} = 0.27 nM, TI = 271 000) displayed the highest activity against this type virus nearly as potent as lead compound GW678248. Moreover, all of them were also active to inhibit the double mutant strain A_{17} (K103N + Y181C) with EC_{50} values of 0.29 μM, 0.14 μM, 0.10 μM and 0.27 μM, respectively. In particular, compound **13m**, which showed broad-spectrum anti-HIV activity, was also effective to inhibit the HIV-2 ROD replication within 4.37 μM concentration.

1. Introduction

Since the identification of the human immunodeficiency virus (HIV) as the causative agent of AIDS [1–4], the search for safe and effective agents for HIV treatments has become a major focus for drug discovery groups worldwide. Although the highly active antiretroviral therapy (HAART) combination regimens such as nevirapine (NVP, **1**, Fig. 1) [5], delavirdine (DLV, **2**, Fig. 1) [6], efavirenz (EFV, **3**, Fig. 1) [7], etravirine (ETV, **4**, Fig. 1) [8] and rilpivirine (RPV, **5**, Fig. 1) [9,10], which have been approved by US FDA as novel HIV-1 NNRTIs, are proving to be effective for AIDS therapy. Unfortunately, the genetic barrier of current NNRTIs is relatively low, and single mutations begin to reduce the susceptibility of virus to drug. Furthermore, cross resistance between the approved NNRTIs is quite common, and patients are generally forced to abandon the approved NNRTIs altogether once they have developed resistance to one of its members [11,12]. Therefore, an urgent need has arisen for more potent NNRTIs that possess both a broad spectrum of antiviral activity against key mutant strains and a high genetic barrier to the selection of new mutant strains.

Benzophenone derivatives (BPs, Fig. 2), originated in a high-throughput screening in 1995 [13], are typical NNRTIs and very efficacious against both wild-type and clinically relevant NNRTI-resistant mutant HIV-1 strains [13–19]. For searching more active BPs as NNRTIs, considerable efforts on the modifications of BPs have been made and led to identify several highly potent inhibitors, such as GW564511 (**7**, Fig. 2) [13] and GW678248 (**8**, Fig. 2) [15,16]. The initial SARs of BPs showed that the keto group between A- and B-rings was important for maintaining their high anti-HIV activity [19,20]. Therefore, few modifications on the keto template were performed in the following structure optimizations. A flexible amido linker between A- and B-rings might not only improve the

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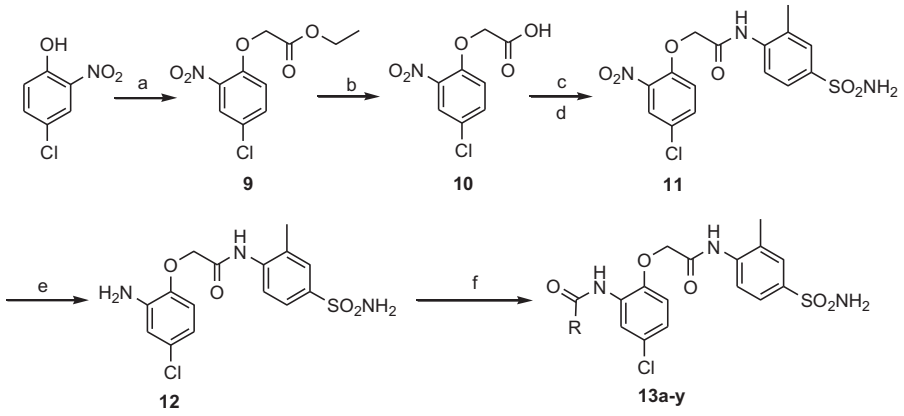

Scheme 1. Synthesis of *N*-phenylarylformamide analogues **13a**–**y**. Reagents and conditions: (a) $BrCH_2COOEt$, K_2CO_3, *n*-Bu_4NBr, acetone, 2 h, 50 °C, 91%; (b) $LiOH{\cdot}H_2O$, THF–H_2O–EtOH, r.t, 2 h, 89%; (c) $SOCl_2$, 80 °C, 1 h; (d) 4-amino-3-methylbenzenesulfonamide, $NaHCO_3$, acetone, 80 °C, 2 h, 85%; (e) Fe, NH_4Cl, acetone-H_2O, 80 °C, 12 h, 82%; (f) RCOCl, $NaHCO_3$, acetone, r.t, 30 min, 70–89%.

adaptation of the inhibitor to RT, but also promote the H-bond bindings with key mutant amino acids Tyr188 or Tyr181. Herein, a series of *N*-phenylarylformamide derivatives (PAFAs) were synthesized and evaluated for their anti-HIV activity. Moreover, their preliminary structure–activity relationships (SARs) and the possible binding modes with RT were also explored in this manuscript.

2. Results and discussion

2.1. Chemistry

As depicted in Scheme 1, alkylation of the staring material 4-chloro-2-nitrophenol with ethyl bromoacetate [21], and subsequent hydrolysis gave the acid derivative **10** [22]. Treatment acid chloride of **10** with 4-amino-3-methylbenzenesulfonamide in basic condition provided the compound **11** [8]. After reducing the nitro-compound **11** in the presence of Fe–NH_4Cl, amino compound **12** was obtained in 82% yield. Finally, coupling **12** with the appropriately substituted of benzoyl chloride was accomplished by mixing with $NaHCO_3$ in the solvent of acetone at room temperature to provide the corresponding target compounds **13a**–**y** in 70–89% yield.

2.2. Biological activity

All title molecules were evaluated for the activity against wild-type HIV-1 strain III_B, the double mutant HIV-1 strain A_{17} (K103N + Y181C) and HIV-2 strain ROD in C8166 cells [23,24]. For comparation, lead compound GW678248 and the FDA-approved drug, zidovudine (AZT) were also tested as reference compounds, and the activity data is interpreted in CC_{50} (cytotoxicity), EC_{50} (anti-HIV activity) and TI (therapeutic index, given by the CC_{50}/EC_{50} ratio).

As illustrated in Tables 1and 2, more than half of the newly synthesized compounds displayed strong potency against the wild-type HIV-1 strain III_B with EC_{50} values ranging from 0.30 nM to 5.10 nM, and therapeutic index values from 10 616 to 271 000. In particular, analogues **13g** (EC_{50} = 0.30 nM, TI = 184 578), **13l** (EC_{50} = 0.37 nM, TI = 212 819), **13m** (EC_{50} = 0.32 nM, TI = 260 617) and **13r** (EC_{50} = 0.27 nM, TI = 271 000) were identified as the maximum inhibitors nearly as potent as GW678248 against this type of virus, indicating that the flexibility of amide linkage might improve the adaptation of inhibitor to RT.

To explore the potential SARs, great efforts on the modifications of the A-ring, which placed in the top hydrophobic pocket lined by the important aromatic residues Tyr181, Tyr188 and Trp229 was carried out [20]. It was found that relatively small changes in structure did prove to have a significant impact on the anti-wild-type potency. In general, placement of a small group at the *meta* position (**13c**) was more favourable than at the *ortho* (analogue **13b**) or at the *para* (analogue **13d**) position, but for the nitro group, the *ortho*-substituted analogue **13g** was 2-fold higher than the *meta*-substituted analogue **13h**. In the case of *meta*-substituted analogues **13b**–**j**, the order of the potency against wild-type virus was NO_2 > Me > Cl > F > CF_3, but the trifluoro-substituted analogue **13i** almost lost 1000-fold activity in particular.

Additionally, several analogues with di-*meta* substitutions at different positions (analogue **13k**–**u**) were also synthesized and

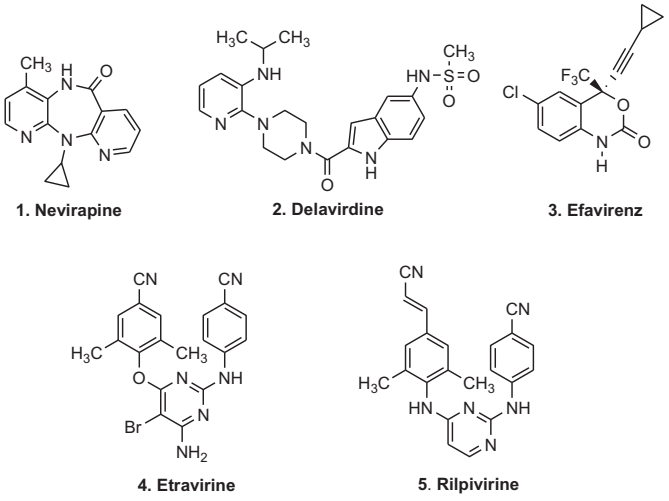

Fig. 1. Structures of currently marketed NNRTIs.

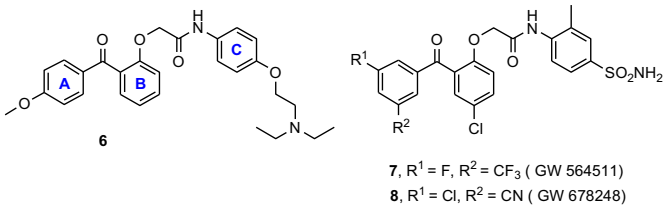

Fig. 2. Structures of potent benzophenones.