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Design, synthesis, and biological activity of a novel series of 2,5-disubstituted furans/pyrroles as HIV-1 fusion inhibitors targeting gp41

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ABSTRACT

Based on molecular docking analysis of earlier results, we designed a series of 2,5-disubstituted furans/pyrroles (**5a–h**) as HIV-1 entry inhibitors. Compounds were synthesized by Suzuki–Miyaura cross coupling, followed by a Knoevenagel condensation or Wittig reaction. Four of these compounds were found to be effective in inhibiting HIV-1 infection, with the best compounds being **5f** and **5h**, which exhibited significant inhibition on HIV-1_{IIIB} infection at micromolar levels with low cytotoxicity. These compounds are also effective in blocking HIV-1 mediated cell-cell fusion and the gp41 six-helix bundle formation, suggesting that they are also HIV-1 fusion inhibitors targeting gp41 and have potential to be developed as a new class of anti-HIV-1 agents.

Human immunodeficiency virus type 1 (HIV-1) entry into a target cell is initiated by the binding of the viral envelope glycoprotein (Env) surface subunit gp120 to the primary receptor CD4 and a coreceptor CXCR4 or CCR5, which triggers a series of conformational changes in gp41 to expose the inner trimeric coiled-coil formed by three parallel N-terminal heptad repeat (NHR) units of gp41. There is a deep hydrophobic cavity in each of the grooves on the surface of NHR-trimer, which is an attractive target for development of small molecule HIV fusion/entry inhibitors.[1] Binding of the gp41 C-terminal heptad repeat (CHR) units to the NHR-trimer results in formation of a six-helix bundle (6-HB) core, which brings the viral and target cell membranes into close proximity for fusion.[2–4]

We previously identified several series of small molecule HIV-1 fusion inhibitors that were expected to target the gp41 cavity, such as N-substituted pyrrole derivatives **1** and **2** (NB-2 and NB-64),[5] 2-aryl 5-(4-oxo-3-phenethyl-2-thioxothiazolidin-ylidenemethyl) furans (**3a–o**),[6] and 5-((arylfuran/1*H*-pyrrol-2-yl) methylene)-2-thioxo-3-(3-(trifluoromethyl)phenyl)thiazolidin-4-ones (**4a–o**),[7] (Fig. 1). These compounds could effectively inhibit HIV-1 infection, HIV-1 Env-mediated cell–cell fusion and gp41 six-helix bundle formation and have the potential for the development of a new class of anti-HIV drugs.

In order to expand the chemical diversity within the series, we have now designed and synthesized a novel series of 2,5-disubstituted furans/pyrroles **5a–h** (Fig. 2) and tested their biological activity against HIV-1 infection, HIV-1 mediated cell–cell fusion and the gp41 six-helix bundle (6-HB) core formation, including **3d**, one of the most active compounds in the series of 2-aryl 5-(4-oxo-3-phenethyl-2-thioxothiazolidin-ylidenemethyl) furans[6] as a control (Table 1).

2,5-Disubstituted furans/pyrroles (**5a–h**) were synthesized by Suzuki–Miyaura cross couplings and subsequent condensations. The inhibitory activities of **5a–h** on HIV-1_{IIIB} replication in MT-2 cells were assessed using an enzyme-linked immunosorbent assay (ELISA) for p24 measurement as previously described.[6] Two of the compounds, **5f** and **5h** inhibited HIV-1_{IIIB} infection with EC_{50}

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