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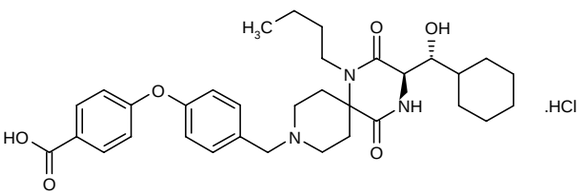
CCC: 0377-8282/2004

GW-873140

Anti-HIV Therapy
HIV Entry Inhibitor
CCR5 Antagonist

AK-602
ONO-4128
873140

4-[4-[1-Butyl-3(*R*)-[1(*R*)-cyclohexyl-1-hydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-ylmethyl]phenoxy]benzoic acid hydrochloride



$C_{33}H_{43}N_3O_6$.HCl
Mol wt: 614.1786
CAS: 461023-63-2
CAS: 461443-59-4 (as free base)
EN: 333200

Abstract

The human immunodeficiency virus (HIV) is a highly mutative virus, representing a challenge for researchers in terms of the development of effective therapeutic strategies against HIV and AIDS. HIV entry inhibitors block the fusion of HIV with host cells and are not compromised by the process of viral resistance, implicit with many anti-HIV therapies. The R5 viral strain is the most prevalent viral type isolated from asymptomatic individuals and its coreceptor CCR5 is blocked by GW-873140 (Ono-4128, AK-602). GW-873140 demonstrated potent activity against a wide spectrum of laboratory and primary HIV R5 isolates, and anti-HIV activity was observed for up to 24 h following binding to CCR5. This was also demonstrated in a phase I study in healthy adult subjects, with prolonged CCR5 receptor occupancy despite plasma levels of GW-873140 at or below the assay detection limit. The drug was well tolerated in this study and is entring phase II testing.

Synthesis

The condensation of (3*R*)-*N*-Boc-3-cyclohexyl-D-serine (I) with 1-benzylpiperidin-4-one (II), benzyl isonitrile (III) and butylamine (IV) in refluxing methanol gives the piperidine derivative (V), whose Boc group is removed by treatment with TFA in dichloromethane, to yield the amino acid (VI). Cyclization of compound (VI) by means of AcOH in hot toluene affords the spiro[piperazine-2,4'-piperidine] derivative (VII), which is hydrogenated in methanol over palladium hydroxide on carbon to cleave the benzyl protecting group and provide the unprotected spiro derivative (VIII). Finally, this compound is reducto-condensed with 4-(4-formylphenoxy)benzoic acid (IX) by means of sodium triacetoxyborohydride in DMF/AcOH (1). Scheme 1.

Introduction

The World Health Organization (WHO) estimates that there are 40 million people living with HIV/AIDS worldwide. The socioeconomic burden of the disease is huge and the development of effective therapeutic interventions has challenged researchers for over a decade. There are a growing number of antiretroviral agents and combinations available for the treatment of HIV/AIDS, but none are capable of eliminating the highly mutative virus. HIV entry inhibitors are a promising focus of development as they block the fusion of HIV with host cells. Their activity and potency therefore depend more directly on host cell factors and are not compromised by the process of viral resistance. Recent studies on the mechanisms of HIV infection have identified several chemokine receptors as potential HIV coreceptors. The CCR5 coreceptor is

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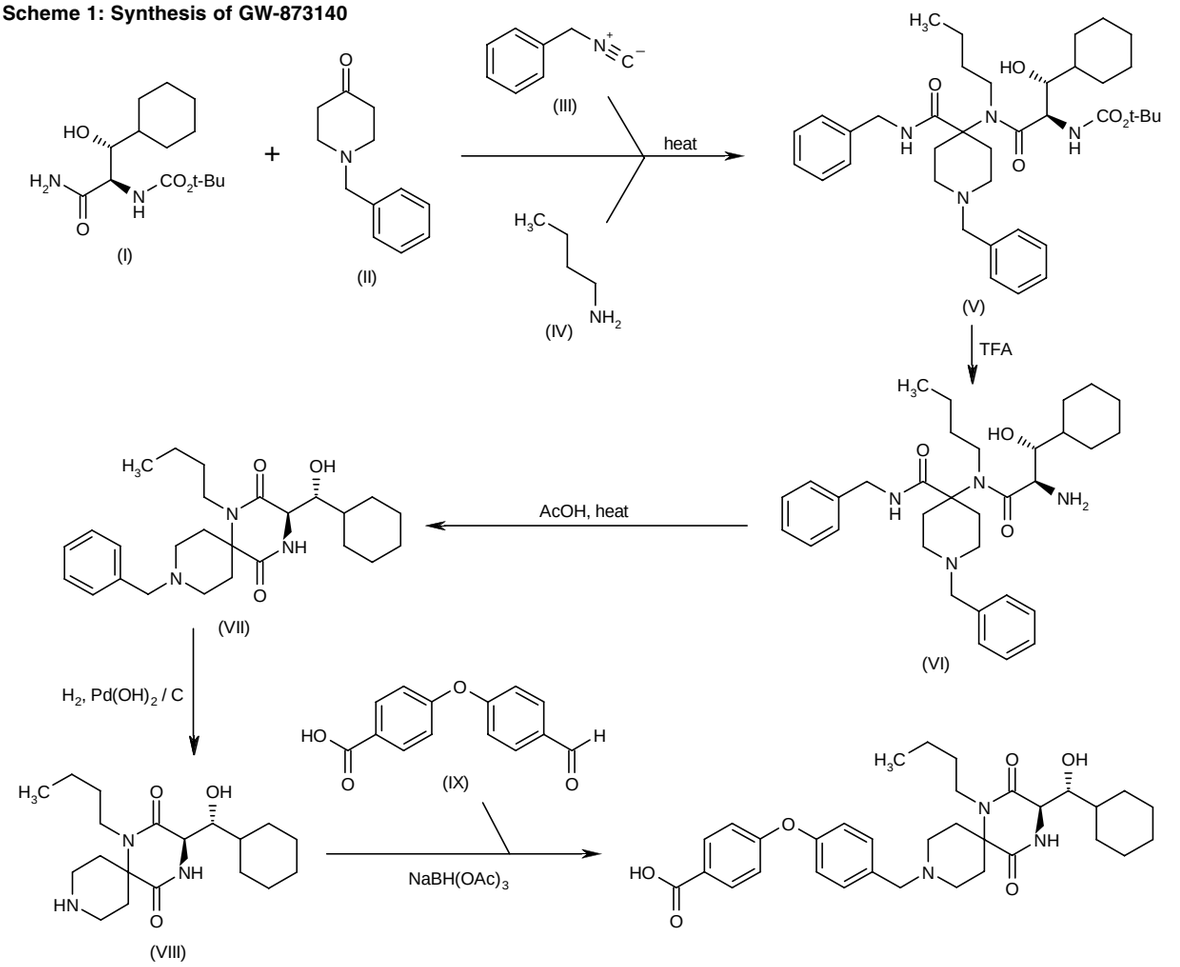
Scheme 1: Synthesis of GW-873140



used by the "primary" R5 virus strain, responsible for viral transmission. This is the prevalent viral type isolated from asymptomatic individuals (2). A novel spirodiketopiperazine chemokine CCR5 receptor antagonist, GW-873140 (Ono-4128, AK-602), is currently in phase II development for the treatment of HIV infection.

Pharmacological Actions

The binding sites of GW-873140 and its interactions with HIV-1 gp120 were evaluated using a variety of mutant CCR5s. GW-873140 demonstrated potent activity against a wide spectrum of laboratory and primary HIV R5 isolates, including multidrug-resistant HIV, at subnanomolar concentrations (IC_{50} = 0.2-0.6 nM). It had high CCR5 receptor binding affinity (K_D = 2.9 nM) and potently inhibited the binding of CCR5 to gp120. GW-873140 completely blocked the binding of an extracellular loop ECL2-specific monoclonal antibody, suggesting that GW-873140 interacts with ECL2. Once bound to $CCR5^+$ cells, GW-873140 remained on the cell surface for more than 9 h after thorough washing, and blocked HIV R5 infection upon delayed exposure. Anti-HIV activity was demonstrated for up to 24 h after removal (3-5).

GW-873140 was administered to human peripheral blood mononuclear cell-transplanted, γ-chain knockout, nonobese diabetic (hu-PBMC-NOD) SCID mice to determine its *in vivo* activity. Human PBMCs were intraperitoneally transplanted into the mice, which were infected 16 days later with HIV R5. GW-873140 was administered twice daily at a dose of 120 mg/kg/day i.p. until the mice were sacrificed on day 16. GW-873140 exerted potent antiviral effects against HIV R5, with significant inhibition of the decrease in $CD4^+$ cells and suppression of serum HIV RNA, intracellular HIV DNA and serum p24 levels. Evidence for oral bioavailability was also obtained in preliminary pharmacokinetic studies (5, 6).

Clinical Studies

A double-blind, randomized, placebo-controlled study was performed to investigate the safety, pharmacokinetics and receptor binding of single and escalating multiple oral doses of GW-873140 in 70 healthy subjects. In the single-dose study, 5 doses between 50 and 1200 mg of GW-873140 were administered. During the multiple-dose phase, GW-873140 was administered as a single dose of 200, 400, 600 or 800 mg on day 1 and then twice daily for 7 days. *In vivo* CCR5 binding analyses showed median receptor occupancy ranging from 68% to 88% 24 h after administration of single doses, and of > 97% at 2 and 12 h after multiple dosing. The prolonged CCR5 occupancy confirmed the findings from pharmacological studies, and supported the possibility of once-daily dosing. GW-873140 was well tolerated; there were no serious adverse events and no grade 3 or 4 adverse events. Abdominal cramping, nausea and diarrhea were reported. Laboratory safety tests, vital sign measurements and ECG revealed no clinically significant trends (7).

Phase II trials are being planned (8).

Sources

GlaxoSmithKline (UK); licensed from Ono Pharmaceutical Co., Ltd. (JP).

References

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