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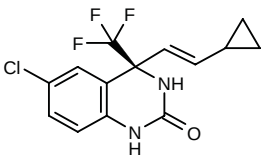
DPC-083

Anti-HIV
Reverse Transcriptase Inhibitor

(*E*)-6-Chloro-4(*S*)-(2-cyclopropylvinyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-quinazolin-2-one



$C_{14}H_{12}ClF_3N_2O$
Mol wt: 316.7088
CAS: 214287-99-7
EN: 282908

Abstract

Infection with HIV-1 remains a global health problem and due to the emergence of drug-resistant HIV variants, there is an ongoing need for new therapeutics for the long-term management of infection. One treatment option includes the NNRTIs, among which only efavirenz, nevirapine and delavirdine mesilate are currently available. However, in vitro and clinical studies have reported the emergence of viruses resistant to these NNRTIs with many of these NNRTI-resistant HIV variants bearing the K103N mutation alone or in combination with other mutations. The search for potent NNRTIs therefore continues. One novel NNRTI currently under development is DPC-083. The antiretroviral activity of DPC-083 has been demonstrated to be more potent than efavirenz. The agent has a good oral bioavailability, a long plasma half-life and acceptable plasma protein binding. Moreover, DPC-083 has been shown to be safe and effective in clinical trials.

Synthesis

DPC-083 is directly obtained by reduction of (–)-6-chloro-4(*S*)-(2-cyclopropylethynyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-quinazolin-2-one (I), DPC-961, with lithium aluminum hydride in 1,2-dichlorobenzene/THF (1-3). Scheme 1.

DPC-961 (I) can be obtained by several different related ways:

1) Condensation of 2'-amino-5'-chloro-2,2,2-trifluoroacetophenone (II) with trimethylsilyl isocyanate in the presence of dimethylaminopyridine in THF, followed by desilylation with tetrabutylammonium fluoride in THF, provides the quinazoline derivative (III), which is dehydrated employing molecular sieves in refluxing toluene to yield the imine (IV). Treatment of compound (IV) with lithium cyclopropylacetylide (V) in THF in the presence of $BF_3.Et_2O$ gives the racemic adduct (VI). Finally, the desired (*S*)-enantiomer (I) is isolated by means of chiral HPLC (1-3). Scheme 2.

2) Condensation of 6-chloro-4-(trifluoromethyl)quinazolin-2(1*H*)-one (IV) with lithium cyclopropylacetylide (V) catalyzed by the chiral auxiliary (X) in toluene/THF gives directly DPC-961. The chiral auxiliary (X) can be synthesized as follows: Epoxidation of (+)-3-carene (VII) with MCPBA in dichloromethane gives the corresponding epoxide (VIII), which is then condensed with morpholine (IX) by means of $MgBr_2$ as catalyst (4). Scheme 2.

3) Condensation of 4-chloro-2-(2,2,2-trifluoro-1,1-dihydroxyethyl)aniline (XI) with (*R*)-1-phenylethyl isocyanate (XII) by means of HCl at low temperature gives a mixture of the urea (XIII) and tetrahydroquinazolinone (XIV). Without isolation, urea (XIII) is cyclized to the tetrahydroquinazolinone (XIV) by heating at 60 °C. Dehydration of (XIV) by means of $SOCl_2$ and Et_3N in toluene affords the quinazolinone (XV), which, without isolation, is condensed with the Grignard reagent bromomagnesium cyclopropylacetylide (XVI) in THF to provide the alkylated tetrahydroquinazolinone (XVII). Finally, compound (XVII) is deprotected from the chiral auxiliary by means of TFA or formic acid (5). Scheme 3.

4) Condensation of 2'-amino-5'-chloro-2,2,2-trifluoroacetophenone (II) with (*R*)-1-phenylethyl isocyanate (XII) by means of either HCl in THF or TMSCl/THF in toluene, followed by heating at 60-65 °C, provides the tetrahydroquinazolinone (XIX). Dehydration of (XIX) with $SOCl_2$ and Et_3N or NMM in toluene affords quinazolinone (XV), which, without isolation, is condensed with the Grignard reagent chloromagnesium cyclopropylacetylide (XX) to give the tetrahydroquinazoline (XVII). Finally, this compound is treated with TFA or formic acid as before (6). Scheme 3.

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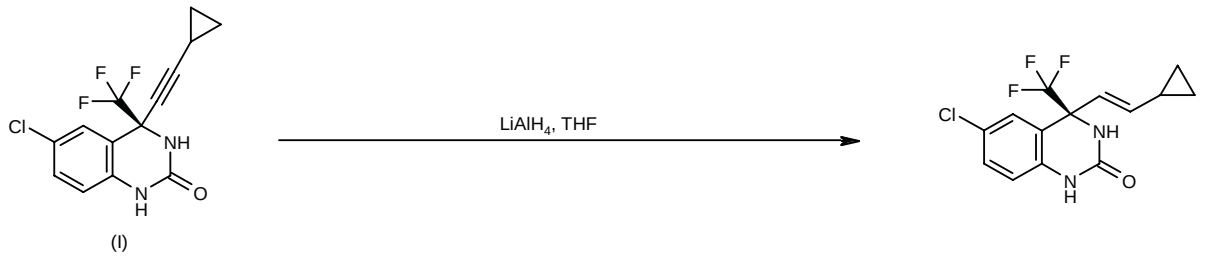
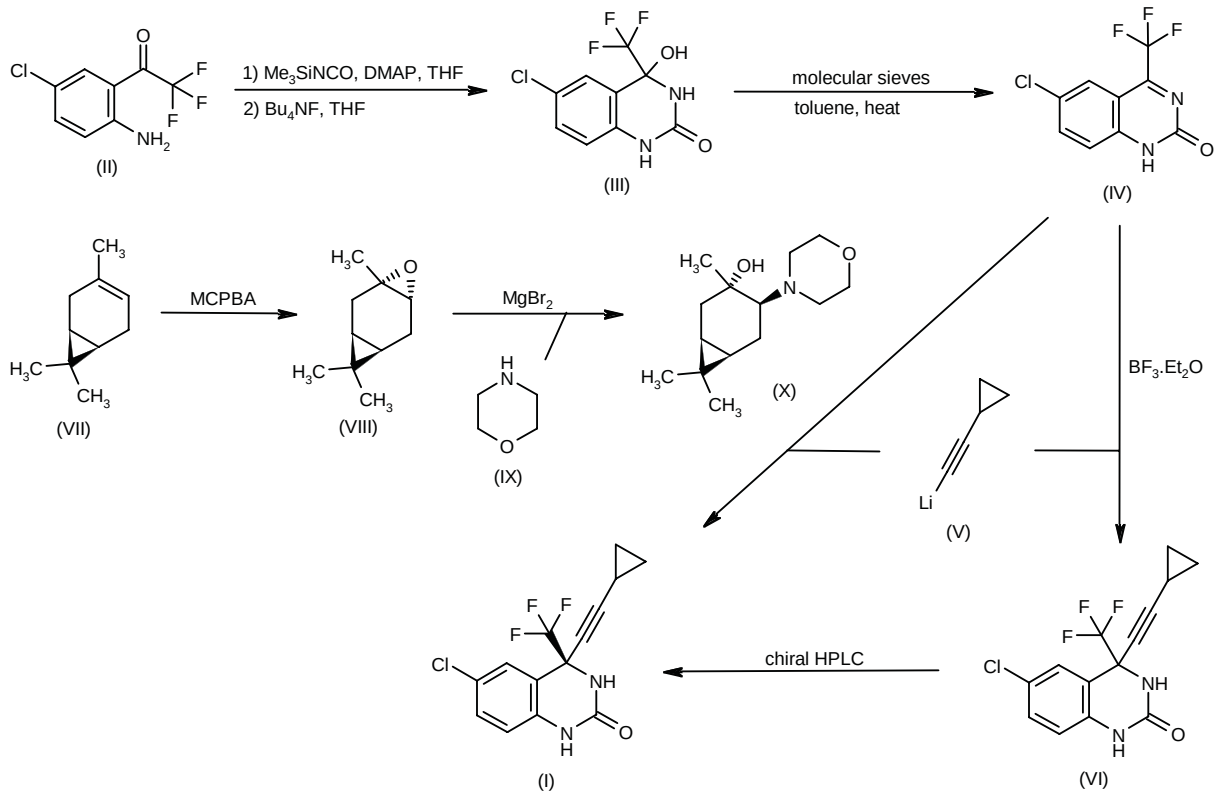
Scheme 1: Synthesis of DPC-083



Scheme 2: Synthesis of Intermediate (I)

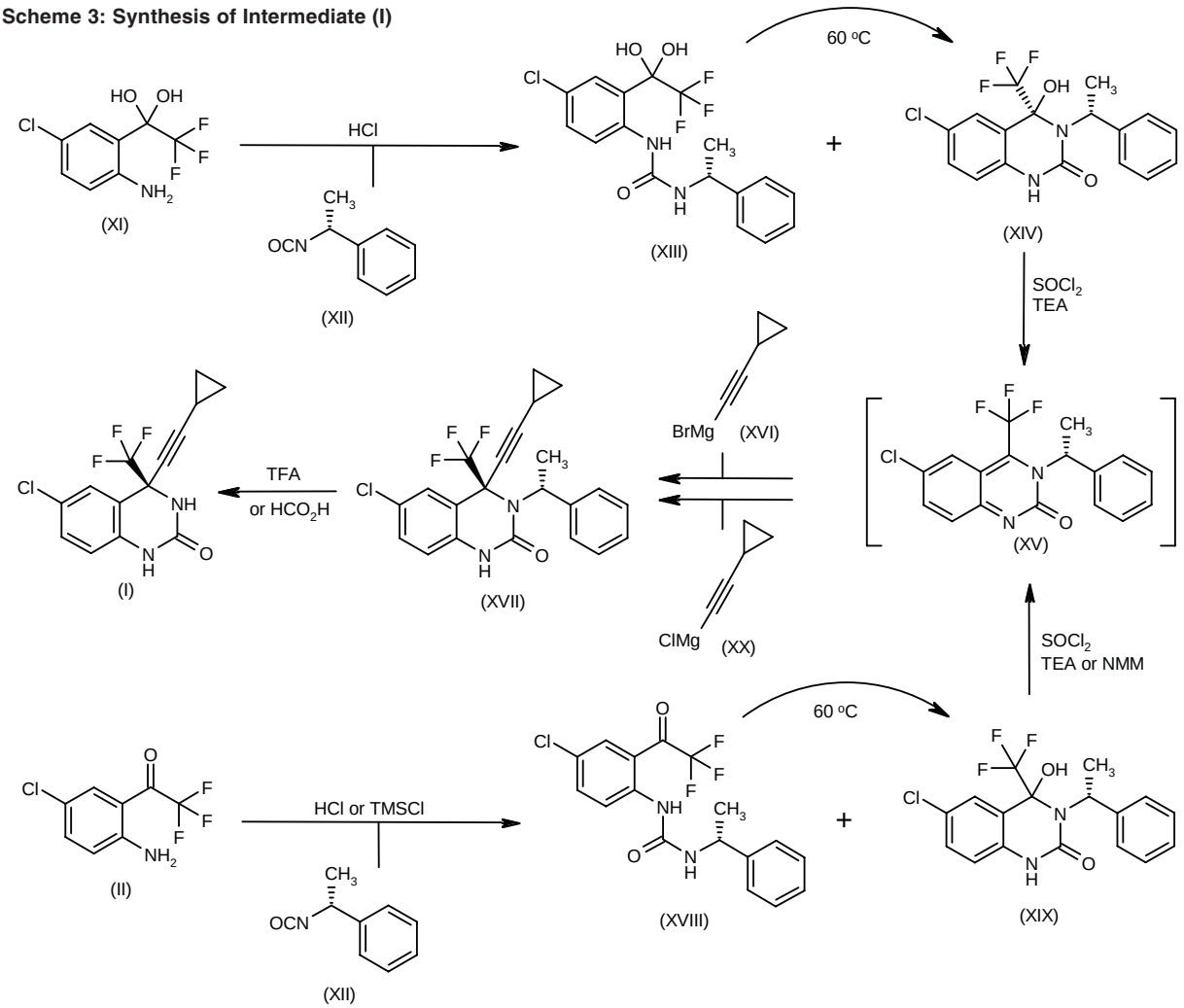


Introduction

Human immunodeficiency virus (HIV) infection is a global health problem with an estimated 16,000 new cases diagnosed each day. There is an ongoing need for new therapeutics for the long-term management of HIV infection since drug-resistance strains emerge in the presence of suboptimal treatment regimens that do not fully inhibit virus replication and for acute HIV infection by drug-resistant strains. Thus, development of new anti-HIV treatments must focus on the ability of regimens to inhibit replication of mutant viruses (7, 8).

Available therapies involve the targeting of 2 essential HIV enzymes: aspartyl protease and reverse transcriptase (RT). Inhibitors of the HIV RT results in DNA chain termination and reductions in viral replication and viremia. The first HIV RT inhibitors developed were nucleoside substrate analogues which bind to the active ATP-binding pocket where they function as substrate decoys and chain terminators. Many nucleoside RT inhibitors (NRTIs) are currently available and in clinical use. However, these agents have been shown to have limited efficacy in certain combinations because of the emergence of resistance mutations and their association with hematological toxicities. Consequently, a second class of RT inhibitors

Scheme 3: Synthesis of Intermediate (I)

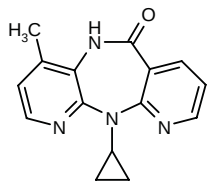


was developed. This class consists of the non-nucleoside RT inhibitors (NNRTIs) which bind to the allosteric site on the HIV-1 enzyme. However, both *in vitro* studies and clinical trials where NNRTIs were administered as monotherapy have reported the emergence of resistant viruses exhibiting decreased susceptibility to the particular NNRTI used (9, 10). The resistant mutations identified include those that are specific for each NNRTI (*e.g.*, Y181C for nevirapine or delavirdine and P236L for delavirdine) and a mutation at amino acid lysine 103 to asparagine which is often detected alone or in combination with other mutations in patients who have failed NNRTI (*e.g.*, efavirenz) treatment. This K103N mutation is referred to as a pan-class resistance mutation (11). Clinical experience in which efavirenz was combined with other highly active antiretroviral agents has resulted in significant antiretroviral activity. However, the K103N mutation was detected in over 90% of the sequences examined from the few patients whose viral load rebounded after an initial response. In addition, the slow emergence of other viruses with multiple mutations after the appearance of K103N was also observed in these patients. These later emerging mutations include the double mutations K103N+V108I or K103N+P225H (12, 13).

Thus, therapeutics with potent activity against mutant viruses carrying the K103N, K103N+V108I or K103N+P225H mutations would be crucial members of combination regimens and important options for salvage therapies and the search for these NNRTI analogues continues. NNRTIs currently available and those under development are shown in Table I (7). One novel NNRTI is DPC-083, which has displayed promising improved activity over efavirenz against mutant HIV variants. DPC-083 with its good oral bioavailability, long plasma half life and acceptable plasma protein binding, has been selected for further development as a treatment for acute and chronic HIV infection (1, 2).

Table I: NNRTIs launched and under development (Prous Science Integrity®).

Drug	Source	Phase
1. Nevirapine (*Viramune*)	Boehringer Ingelheim	L-1996
2. Delavirdine mesilate (*Rescriptor*)	Pharmacia	L-1997
3. Efavirenz (*Sustiva*)	DuPont Pharm.	L-1998
4. Capravirine	Shionogi/Agouron	III
5. DPC-083	DuPont Pharm.	II
6. TMC-120/R-147681	Tibotec-Virco/Janssen	II
7. TMC-125/R-165335	Tibotec-Virco/Janssen	II
8. Calanolide A	Advanced Life Sciences	I/II
9. MIV-150[1]	Medivir	I
10. MV-026048[1]	Medivir/Roche	Preclinical
11. SP-1093V	Supratek	Preclinical
12. UC-781	Biosyn	Preclinical



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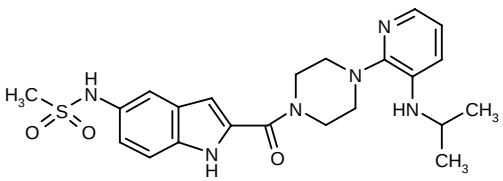
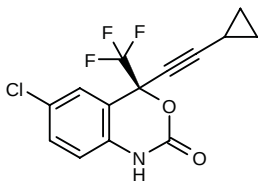


(2) $.CH_3SO_3H$



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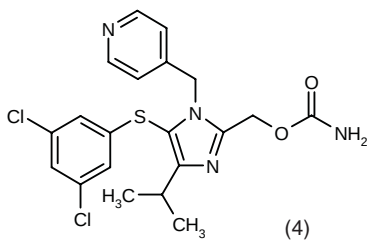

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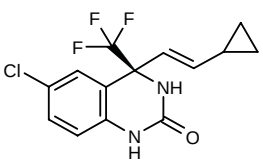

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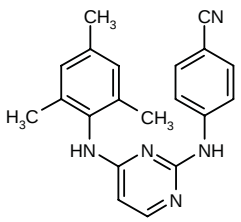
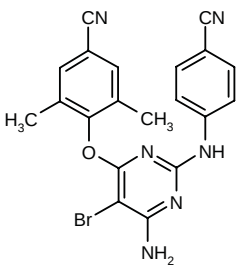


(6)

Formulation of the iron chelate Fe(III)BBNH incorporated into a block copolymer

(11)



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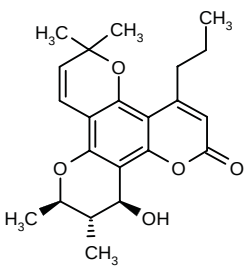

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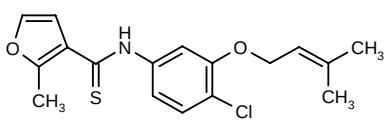

(12)

[1]Structure not yet detected.

Pharmacological Actions

DPC-083 had potent antiviral activity in *in vitro* viral RNA, plaque (*i.e.*, yield of infectious progeny) and viral P24 antigen assays using MT-2 cells or PBMCs infected with laboratory and clinical HIV-1 isolates including zidovudine-resistant isolates; the agent was inactive against HIV-2 (IC_{90} = > 2800 nM). IC_{90} values for the agent were 2.1 ± 0.8 nM (RNA assay) and 1.9 ± 0.9 nM (yield plaque assay) against RF, 0.9 nM against Thai 9466 (a wild-type clinical isolate) and 1.3 ± 0.7 nM against E (zidovudine-resistant clinical isolate with the D67N and K70R mutations). The plasma IC_{90} value for DPC-083 for the RF virus was 40 nM as compared to 92-220 nM for efavirenz. DPC-083 was 2.3-fold more active than efavirenz against the mutant HIV-1 variant carrying the K103N mutation (27 ± 11 *vs.* 64 ± 24 nM) and was more potent than efavirenz against HIV-1 variants bearing the sL100I mutation alone (11 ± 6.8 *vs.* 120 ± 30 nM), the double K103N/V108I mutation (90 ± 6.6 *vs.* 240 ± 68 nM), the double K103N/P225H mutation (140 ± 92 *vs.* 310 ± 130 nM), the double K103N/L100I mutation (1690 ± 160 *vs.* 7300 ± 5000 nM) and the triple sV179D/L100I/Y181C mutation (320 *vs.* 2400 ± 420 nM).

Table II: Antiviral activity (IC_{90}, nM) of NNRTIs launched or under active development (Prous Science Integrity®).

Drug	WT	NNRTI-R	AZT-R
Delavirdine	30-50 (2, 25-27)	1000-5200 (2, 27)	–
DPC-083	0.9-2.1 (1, 2)	11-27 (2)	1.3 (1)
Efavirenz	1.7-8.5 (1, 2, 28)	64-77 (2)	2.8-8.2 (1, 28)
Nevirapine	4.85 (2)	50 (2)	5100 (2)
TMC-120/R-147681	2.60 (29)	–	–
TMC-125/R-165335	2.90 (30)	–	–
Zidovudine[1]	1.2-500 (26, 31, 32)	10* (33-37)	>5000 (31, 32)

*Approximate value derived from IC_{50} values. [1]Zidovudine included for comparative purposes. WT: wild-type isolates; NNRTI-R: isolates resistant to NNRTIs; AZT-R: zidovudine-resistant.

DPC-083 also showed good activity against G190S and Y188L mutant HIV-1 variants and was more potent than efavirenz against variants with K103N/Y181C and K103N/V108I mutations. Similarly, DPC-083 human plasma IC_{90} values were lower than that of efavirenz against K103N (550 *vs.* 3400-8100 nM), sL100I (220 *vs.* 6600-15,700 nM) and sV179D/L100I/Y181C (6000 *vs.* 130,000-309,500 nM) HIV-1 variants and DPC-083 showed an increased free fraction in human plasma (1, 2, 14). The *in vitro* antiviral activity of DPC-083, other NNRTIs and zidovudine is summarized in Table II.

An *in vitro* study using clinical HIV-1 isolates of Group M and O obtained from therapy-naive patients and patients who failed efavirenz combination therapy reported potent antiviral activity of DPC-083. The IC_{50} value of the agent against group M isolates (A-H subtypes) from therapy-naive patients was 0.40 nM. Group O isolates with resistance to nevirapine (> 65 times), delavirdine (95 times) and efavirenz (36 times) were less resistant to DPC-083 (24 times). Those isolates from patients failing efavirenz were less resistant to DPC-083 as compared to efavirenz. The IC_{50} values for DPC-083 *versus* efavirenz against 7 isolates containing the K103N mutation and 16 isolates with multiple NNRTI resistance mutations were 28 *vs.* 43 nM and 100 *vs.* > 190 nM, respectively (15).

An *in vitro* study using MT-2 cells infected with laboratory and clinical HIV-1 isolates examined the emergence of viruses resistant to DPC-083. Results demonstrated that multiple passages were needed to produce highly resistant (> 100-fold) virus populations. Significant resistance to DPC-083 required at least 2 or even 4 mutations, with L100I followed by K103N, Y188C and V106I/M/A being most frequently detected in highly resistant populations. Other mutant variants that emerged bore combinations of mutations not commonly seen *in vivo* such as K103N associated with L100I or Y188C. Those mutations (K103N/V108I, K103N/P225H, K103N/Y181C) that are commonly seen in patients failing efavirenz therapy were not observed (16).

Two studies have reported new methods for controlling the purity of DPC-083. A study has evaluated 3 columns for HPLC separation and developed and validated a chiral method to control the enantiomeric purity of NNRTIs including DPC-083. The method is used for routine testing of tablets and drug substances. Another study developed a thin layer chromatography method to detect polymeric impurities (*e.g.*, tartaric acid) in DPC-083 generated during the synthetic process (17, 18).

A study characterized the degradation of DPC-083 in the presence of the excipient sodium lauryl sulfate (SLS) in solid-dose formulations. DPC-083 was degraded when the DPC-083/SLS mixture was stored at 60 °C. However, addition of 5% water stabilized DPC-083 at temperatures of 45-60 °C. DPC-083 was degraded by 67% after 12 weeks of storage with the major degradation products identified as isomers generated from water addition to the rearranged cyclopropylethenyl group. The mixture was also found to be incompatible with a reduced melting point of 100 °C as compared to DPC-083 at 168 °C (19).

Pharmacokinetics

The pharmacokinetics of oral DPC-083 were reported in rhesus monkeys (10 mg/kg) and chimpanzees (2 mg/kg). Plasma DPC-083 concentrations at 24 h postdosing were 6.84 and 7.6 μM for monkeys and chimpanzees, respectively, as compared to 0.36 and 2.7 μM for efavirenz. The $t_{1/2}$ value for DPC-083 (24 h) was consistent with the feasibility of once-daily dosing. The estimated levels of free drug in plasma in chimpanzees were concluded to correlate with significant inhibition of wild-type and mutant variant HIV replication (2).

The pharmacokinetics of multiple oral DPC-083 were examined in male (50, 100, 200, 300 and 400 mg) and female (100 mg) healthy subjects. Subjects were administered 2 doses of the agent on day 1 followed by once-daily dosing for 8 days. Peak plasma DPC-083 concentrations were reached 2.5-4 h postdosing and the terminal $t_{1/2}$ value was > 140 h. Steady state was not achieved after the 10 doses. However, 10 doses of 100 mg or greater resulted in average trough concentrations that were greater than the calculated amount required to inhibit 90% of wild-type, K103N, K103N/P225H, K103N/V108I and K103N/Y181C viruses by > 172-fold, > 11-fold, > 1.9-fold > 2.9-fold and > 1.6-fold, respectively (20).

Box 1: DPC-083 plus two NRTIs in HIV infection (22) [Prous Science Integrity®].

Design	Multicenter, randomized, double-blind clinical study
Population	Patients with HIV infection who had failed an NNRTI-containing regimen and who had plasma HIV RNA levels ≥ 1000 copies/ml (n = 51)
Treatments	DPC-083, 100 mg p.o. o.d. + 2 NRTI (U.S.) DPC-083, 200 mg p.o. o.d. + 2 NRTI (U.S.)/Europe)
Results	Response [<400 copies/ml] rate (%) @ 8 wks: 57 -in patients using no new NRTI: 4/10 (40%) -in patients using one new NRTI: 13/18 (72%) -in patients using two new NRTI: 10/15 (67%) Viral load (log copies/ml) change @ 8 wks: –1.28
Conclusions	DPC 083 was active in patients who had failed marketed NNRTIs and who had NNRTI-resistant mutations, and was well tolerated and more effective in combination with at least one new NRTI

Box 2: DPC-083 compared to efavirenz in HIV infection (23) [Prous Science Integrity®].

Design	Multicenter, comparative, randomized, double-blind, dose-finding, clinical study
Population	Antiretroviral treatment-naive patients with HIV infection with plasma HIV RNA levels ≥ 1000 copies/ml and CD4 cell count >200/mm^3 (n = 134)
Treatments	DPC-083, 50 mg p.o. o.d. + Lamivudine/Zidovudine DPC-083, 100 mg p.o. o.d. + Lamivudine/Zidovudine DPC-083, 200 mg p.o. o.d. + Lamivudine/Zidovudine Efavirenz, 600 mg p.o. o.d. + Lamivudine/Zidovudine
Adverse Events	D50: rash 15%, dizziness 11-18% D100: rash 33%, dizziness 11-18% D200: rash 53%, dizziness 11-18% E: rash 38%, dizziness 32%
Results	Response [<50 copies/ml] rate (%) @ 24 wks: D50 (79) ≥ E (78) ≥ D200 (72) ≥ D100 (67) All doses of D provided median steady-state free plasma trough levels above the IC_{90} for K103N and many double mutations
Conclusions	DPC-083 was highly effective and well tolerated in antiretroviral treatment-naive patients with HIV infection

Since DPC-083 is metabolized by the cytochrome P450 (CYP) enzymes, CYP2B6 and CYP3A4, drug interactions with CYP inducers or inhibitors are a possibility. DPC-083 is a CYP3A4 inducer and therefore may interact with agents metabolized by this enzyme. DPC-083 is also contraindicated with oral contraceptives since reductions in hormonal contraceptive plasma levels have been observed with concomitant administration which consequently may decrease contraceptives effects (21).

Clinical Studies

Phase I clinical studies have reported that the most common adverse events associated with antiviral therapy including DPC-083 are dizziness, skin rashes, paresthesia, euphoric mood, abnormal feelings, feeling drunk, abdominal pain, fatigue, lethargy and vomiting. In addition, reversible liver enzyme elevations and increases in total cholesterol and triglycerides levels have also been seen. (21).

An ongoing, randomized, double-blind, phase II study conducted in 51 patients with 1000 copies/ml or more HIV RNA (mean viral load $\log_{10}$ = 3.85 copies/ml; CD4 cells = 473 cells/mm^3) and who had failed NNRTI-containing regimens (61% failed nevirapine; 39% failed efavirenz) compared once-daily dosing with 100 or 200 mg DPC-083. All patients received 2 NRTIs according to baseline genotype and treatment history. Of the 48 patients from whom baseline genotypic profiles were available, 94% had mutations consistent with failure of NNRTI therapy including mutations at positions 101 (44%), 103 (52%), 181 (17%) and 190 (25%). DPC-083 was generally well tolerated. The on-treatment response rate (*i.e.*, > 400 copies/ml) at 8 weeks was 57% with a mean change in viral load from baseline of -1.28 log. Response rates were higher when DPC-083 was administered together with at least 1 NRTI (response rates: 40% with no new NRTIs, 72% with 1 new NRTI and 67% with 2 new NRTIs). A 16% discontinuation rate due to adverse events was reported (22) (Box 1).

The efficacy and tolerability of DPC-083 (50, 100 and 200 mg once daily) was compared to efavirenz (600 mg once daily) in a multicenter, randomized double-blind study involving 134 HIV antiretroviral-naive patients (mean viral load = 33,113 copies/ml; mean CD4 cells = 367 cells/mm^3) also receiving Combivir (zidovudine/lamivudine). All DPC-083 doses resulted in median steady-state free plasma trough levels greater than the IC_{90} values required for K103N and other double mutations. The intent-to-treat response rates were 79, 67 and 72% for the respective doses of DPC-083 as compared to 78% for efavirenz. No significant differences were detected between any of the treatment groups. Discontinuation rates were similar for all groups (14, 17 and 24%, respectively, for DPC-083 and 22% for efavirenz). Incidence of dizziness was less frequent with DPC-083 (11-18%) as compared to efavirenz (32%) and the frequency of rash observed with DPC-083 was dose dependent (15, 33 and 53%, respectively; 28% with efavirenz). The study is ongoing (23) (Box 2).

DPC-083 is currently in phase II development for the treatment of acute and chronic HIV infection (24).

Source

DuPont Pharmaceuticals Co. (US), now part of Bristol-Myers Squibb Co. (US).

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