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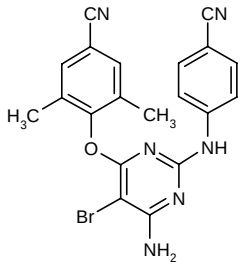
Etravirine

Prop INN; USAN

Anti-HIV Agent
Reverse Transcriptase Inhibitor

R-165335
TMC-125

4-[6-Amino-5-bromo-2-(4-cyanophenylamino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile



$C_{20}H_{15}BrN_6O$

Mol wt: 435.2769

CAS: 269055-15-4

EN: 290137

Abstract

The success of antiretroviral agents such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) is compromised by the rapid emergence of resistant HIV-1 viral strains. A new-generation NNRTI, etravirine (TMC-125), has demonstrated potent activity against wild-type HIV-1 *in vitro*, with significantly greater efficacy and delayed emergence of resistance against HIV-1 strains carrying mutations when compared to other clinically approved NNRTIs. The compound is well tolerated and possesses a good oral pharmacokinetic profile in HIV-1-infected patients. Clinical studies have revealed significant antiviral activity in antiretroviral-naïve patients, with comparable if not higher potency than a 5-drug antiretroviral regimen, as well as in treatment-experienced patients, with rapid and long-term efficacy. Etravirine therefore shows immense promise as a new NNRTI.

Synthesis

Etravirine can be prepared by two different ways:

1) Reaction of 5-bromo-2,4,6-trichloropyrimidine (I) with 4-aminobenzonitrile (II) by means of DIEA in refluxing dioxane gives the diarylamine (III), which is condensed with 4-hydroxy-3,5-dimethylbenzonitrile (IV) by means of NaH in NMP to yield the corresponding adduct (V). Finally, this compound is treated with ammonia in dioxane at 150 °C in a pressure vessel (1). Scheme 1.

2) Cyclization of 4-guanidinobenzonitrile (VI) with diethyl malonate (VII) by means of NaOEt in ethanol gives 4-(4,6-dihydroxypyrimidin-2-ylamino)benzonitrile (VIII), which is treated with $POCl_3$ to yield the corresponding dichloro derivative (IX). Bromination of compound (IX) with Br_2 and $NaHCO_3$ in methanol/water affords 4-(5-bromo-4,6-dichloropyrimidin-2-ylamino)-benzonitrile (III), which is condensed with sodium 4-cyano-2,6-dimethylphenolate (X) and NMP in dioxane to provide the chloro precursor (V). Finally, this compound is treated with ammonia in isopropanol (2). Scheme 2.

Introduction

The human immunodeficiency virus (HIV), a retrovirus belonging to the Retroviridae family, *Lentivirus* genus, causes acquired immune deficiency syndrome, or AIDS, a gradual deterioration of the immune system leading to opportunistic infections and ultimately death. According to UNAIDS, there are currently 39.4 million people living with HIV/AIDS worldwide: 37.2 million adults and 2.2 million children under the age of 15 (figures current as of December 2004) (3).

Highly active antiretroviral therapies (HAARTs) include protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the more novel entry inhibitors and integrase inhibitors. A unique characteristic of retroviruses is the retrotranscription of viral RNA into DNA by the enzyme reverse transcriptase (RT), which is then integrated into the host cell genome. NNRTIs bind directly to the RT enzyme, at the pocket proximal to the polymerase active site, thereby deactivat-

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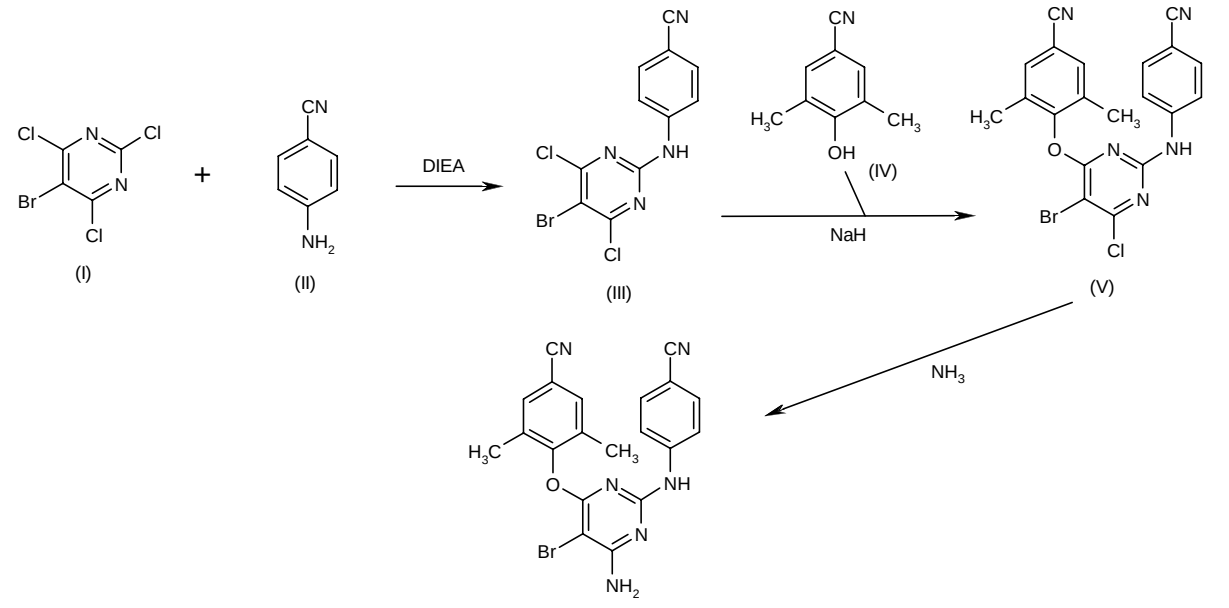
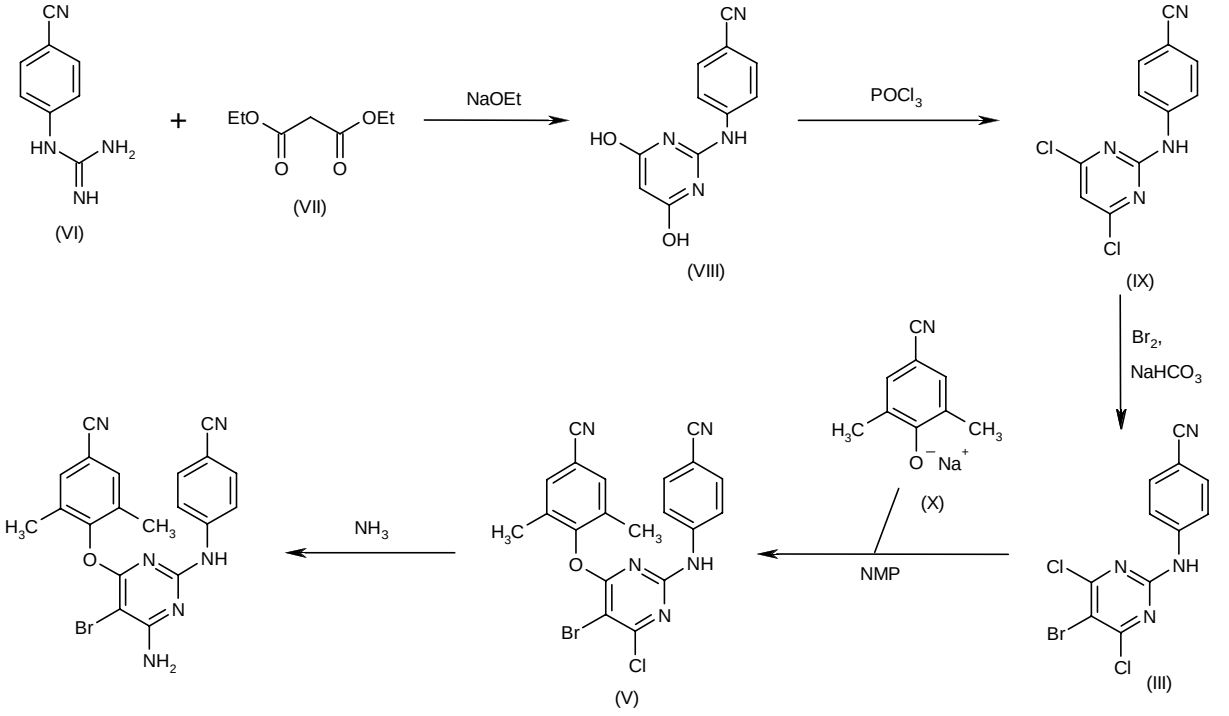
Scheme 1: Synthesis of Etravirine



Scheme 2: Synthesis of Etravirine

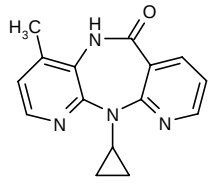


ing it. Several NNRTIs are now available as clinical treatments for HIV-1 infection (3) (Table I).

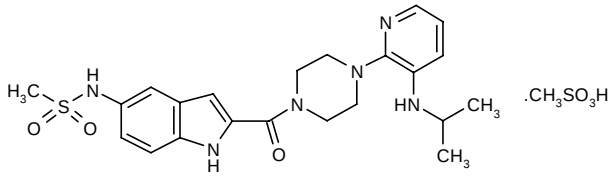
However, the success of NNRTI therapy is compromised by the rapid emergence of resistant viral strains carrying mutations at residues that surround the NNRTI binding pocket. Combination therapy, introduced because of the issue of drug resistance, has also led to the development of adherence problems, reduced antiretroviral

Table I: Non-nucleoside reverse transcriptatse inhibitors (NNRTIs) marketed for the treatment of HIV/AIDS.

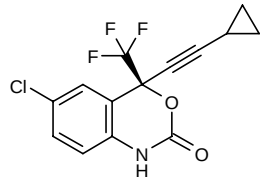
Drug	Source	Phase
1. Nevirapine (Viramune)	Boehringer Ingelheim	L-1996
2. Delavirdine mesilate (Rescriptor)	Pfizer	L-1997
3. Efavirenz (Sustiva, Stocrin)	Bristol-Myers Squibb; Merck & Co.	L-1998



(1)



(2)



(3)

activity and drug toxicity. As a result, there is a need for new antiretroviral agents that can improve treatment with convenience, reduced toxicity and improved antiretroviral activity against both wild-type and drug-resistant HIV. Furthermore, extensive crossresistance among the available NNRTIs has been documented (4-7). Therefore, next-generation NNRTIs that show promise against 'signature' mutations are in development. One such new drug is etravirine (TMC-125, R-165335), a potent diarylpyrimidine derivative discovered during a screening involving comprehensive profiling of antiviral activity against wild-type and mutant NNRTI-resistant HIV-1 strains (2, 8-13) and currently under phase II development at Tibotec (14).

Pharmacological Actions

In vitro, etravirine demonstrated potent activity against wild-type HIV-1 (EC_{50} = 1.4-4.8 nM), comparable to efavirenz, with some activity against HIV-2 (EC_{50} = 3.5 μM) and very low cytotoxicity (CC_{50} > 100 μM in MT-4 cells). It was also significantly more effective than other clinically approved NNRTIs against HIV-1 strains carrying mutations, with EC_{50} values of 1-19 nM against a panel of viruses carrying 1 or 2 amino acid substitutions. Human serum albumin or α_1-acid glycoprotein did not significantly affect its antiviral activity. Etravirine also inhibited 98% of over 2,000 clinical isolates and 97% of approximately 1,000 NNRTI-resistant strains, compared to 77% and 54% of strains, respectively, with efavirenz (2, 8-12). Its inhibitory activity against RT and HIV-1, including NNRTI-resistant strains, and its cytotoxicity in comparison to other RT inhibitors are shown in Table II.

In further studies, etravirine exhibited antiviral activity against 91% of 5,610 clinical samples, with an EC_{50} of < 10 nM, while efavirenz inhibited 67% at 10 nM. In those samples showing resistance to the currently available NNRTIs, etravirine inhibited 76% at 10 nM (15).

Rates of emergence of resistance were monitored in MT-4 cells infected with wild-type HIV-1 at high multiplicities of infection (MOIs). Resistance to the first-generation NNRTIs nevirapine and efavirenz developed rapidly in viruses harboring single mutations in Y181C and G190E, respectively. In contrast, the emergence of HIV-1 resistance to etravirine was delayed, requiring the presence of 2 mutations (L100I + Y181C after 21 days), and in some cases did not occur at all (16-18). Furthermore, etravirine exhibited an EC_{50} of < 10 nM against 63% of recombinant clinical isolates harboring 4 NNRTI resistance mutations. For comparison, an EC_{50} of < 10 nM was recorded for efavirenz against 70% of the samples with only 2 mutations (15).

The sensitivity to etravirine of specific single and multiple mutations observed *in vitro* or associated with decreased susceptibility in clinical isolates was also examined. The drug exhibited potent antiviral activity against the majority of site-directed mutants and decreased susceptibility was only associated with the less prevalent triple mutants (19, 20).

Computer modeling and structural analysis of etravirine has enabled characterization of its interaction with the RT binding pocket, and the effects of pocket mutations on this binding profile. These experiments demonstrated that etravirine benefits from a shape that potentially enables the molecule to bend or flex and reposition, and this may help it retain RT binding despite mutations, which normally push other NNRTIs out of their site of action. These characteristics appear to be crucial for the drug's potency against wild-type and a wide range of drug-resistant mutant HIV-1 RTs (21-23).

Pharmacokinetics and Metabolism

Incubation of etravirine with human liver microsomal fractions suggested good metabolic stability, with 15% drug degradation and a 7% decrease in antiviral activity after 120 min (8-10).

A phase I study was carried out to examine the drug interaction profile of etravirine. As the agent induces the cytochrome P-450 (CYP) isozyme CYP3A4, its metabo-

Table II: Pharmacological profile of etravirine compared to other selected RT inibitors launched or currently under active development (from Prous Science Integrity®).

Compound	HIV-1 RT inhibition (IC_{50}, nM)	HIV-1 antiviral activity (IC_{50}, nM)	HIV-1 (NNRTI-resistant) antiviral activity (IC_{50}, nM)	Cytotoxicity (CC_{50}, μM)
Etravirine	38.0	1.56 (1.4-2.0)	1.1 (1.0-1.2)	> 100
Abacavir		865.5 (321-1410)		136
Amdoxobir		3827 (540-10,000)		> 100
BCH-10618		21,075 (2800-43,000)		> 500
BCH-13520		140		> 250
Calanolide A	472.5 (25-1600)	186.7 (53-400)		9.1 (7.0-14.8)
Capravirine	227.7 (5.3-450)	0.70		
Dapivirine	24.0	0.98 (0.9-1.0)	1.0	2.3 (2.2-2.5)
D-D4FC	371.8 (67-1000)			> 206
Delavirdine	254.0 (230-260)	69.4 (14.4-200)	38.0	73
Didanosine	650.0 (620-680)	8500 (530-32,000)	8083 (7150-9800)	368 (59->2000)
Efavirenz	18.2 (0.7-48)	5.9 (0.9-50)	34,616 (2.0-207,000)	57.5 (42-> 100)
Emtricitabine		515 (500-530)		> 100
Foscarnet	200.0	24,533 (16,300-41,000)		223
GW-5634	13.4 (5.7-21)	49.0		
GW-8248	2.80 (1.8-4.7)	1.0		
Lamivudine	284.8 (4.0-600)	1331 (56-4400)		2667
Nevirapine	3774 (0.75-23,000)	1154 (20-38,000)	9617 (638-> 100,000)	329 (75-743)
Rilpivirine		0.40		10
SP-1093V		1000		> 100
Stavudine	545 (80-1010)	1313 (240-2800)		268 (47-564)
Tenofovir	K_i = 22	75,218 (630-500,000)		737 (197-1250)
Tenofovir disoproxil fumarate		5.0 (3.0-7.0)		31.3 (22-50)
UC-781	23.0	10.4		
Zalcitabine	399 (1.0-1440)	716.1 (9.8-3020)	170 (60-280)	335 (4.0-3000)
Zidovudine	79.7 (3.0-480)	63.5 (0.5-2100)	11.6 (1.0-100)	65.5 (0.09-> 500)

HIV-1 antiviral activity and cytotoxicity evaluated in infected and noninfected MT-4 or MT-2 human T-lymphoblastoid cells, respectively. Range in parentheses.

lism can be moderately reduced by pure CYP3A4 inhibitors, such as the PI indinavir, and increased by other CYP3A4 inducers, such as the first-generation NNRTI nevirapine. Ritonavir, which is associated with both inhibition and induction of CYP3A4 and induction of glucuronidation, reduced etravirine exposure (24).

New tablet formulations of etravirine were compared to the reference formulation in an open-label, randomized, crossover study in 45 healthy volunteers. The subjects received single 400-mg doses of each formulation with a standard meal, separated by a washout period of 2 weeks. Rapid absorption was observed after all formulations, but the relative oral bioavailability, as measured by C_{max} and AUC, was significantly greater after administration of the new tablet formulations and intersubject variability was lower (25).

Table III: Clinical studies of etravirine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
HIV infection	Randomized Double-blind	Etravirine, 900 mg p.o. b.i.d. x 7 d (n=12) Placebo (n=7)	19	Etravirine was well tolerated and effective in decreasing the viral load of treatment-naïve patients with HIV-1 infection after only 7 days of treatment	21-23
HIV infection	Pooled/meta-analysis	Etravirine, 900 mg b.i.d. x 7 d (n=12) Zidovudine + Lamivudine + Abacavir + Indinavir + Nevirapine x 7 d (n=13)	25	Etravirine monotherapy given for 7 days was as effective as a combination of 5 antiretroviral drugs in reducing plasma viral levels in patients with HIV-1 infection	24, 25
HIV infection	Open	Etravirine, 900 mg p.o. b.i.d. x 7 d	16	Patients with HIV-1 infection and resistance to current NNRTIs showed a median HIV-1 viral load reduction of 0.89 $\log_{10}$ copies/ml after receiving etravirine for 7 days. Only mild to moderate adverse events were found	26, 27
HIV infection	Open	Etravirine, 800 mg b.i.d. + 3-4 Antiretroviral agents x 48 wks	7	Long-term treatment of patients with HIV infection with etravirine in addition to other antiretroviral therapies was well tolerated and effective	28

Another study in healthy subjects examined the pharmacokinetic interaction between etravirine and didanosine. In this open-label, randomized, crossover study, the volunteers received etravirine 800 mg b.i.d. for 7 days followed by a single dose on day 8. After a 14-day washout period, they were administered didanosine 400 mg/day for 16 days and etravirine 800 mg b.i.d. on either days 1-8 or days 9-16. No significant pharmacokinetic interaction was seen between etravirine and didanosine, and therefore no dose adjustment should be necessary when they are used in combination (26).

Clinical Studies

Etravirine advanced to clinical studies within 1 year of its identification. The first study in HIV-1-infected patients was a double-blind, randomized, placebo-controlled trial conducted in Russia to evaluate the antiviral activity of etravirine as monotherapy in antiretroviral-naïve male patients. Twelve patients received etravirine (900 mg b.i.d.) for 7 days and 6 received matching placebo. Baseline characteristics included median $CD4^+$ cell counts of 650 cells/mm^3 and a median viral load of 57,619 copies/ml. Viral load was reduced by a mean of 1.99 $\log_{10}$ copies/ml and 0.06 $\log_{10}$ copies/ml, respectively, after 7 days in the etravirine and placebo groups. Daily plasma viral decline rates of 0.33 $\log_{10}$ copies/ml and 0.02 $\log_{10}$ copies/ml, respectively, were observed in the etravirine and placebo groups. Of 12 etravirine-treated patients, plasma viral load decreased to < 50 copies/ml in 2 and to < 400 copies/ml in 8. No viral rebound was seen and there was no evidence of resistance development. Adverse events were mild, the most common being somnolence (reported in 3 etravirine patients and 1 placebo patient). Steady state was reached in 4-5 days, with mean trough plasma levels (246 ng/ml) well exceeding the *in vitro* EC_{50} (27-29). The results from this and the following clinical studies are summarized in Table III.

The rate of viral decline achieved with etravirine monotherapy (900 mg b.i.d. for 1 week) was compared to a 5-drug antiretroviral regimen (zidovudine, lamivudine, abacavir, indinavir, nevirapine) in 25 antiretroviral-naïve patients. A similar initial rate of decline in plasma HIV-1 RNA was observed, with a median decrease in HIV-1 RNA of 1.92 and 1.55 $\log_{10}$ copies/ml, respectively, and a median increase in $CD4^+$ T-cells of 119 and 60 cells/mm^3, respectively, measured on etravirine and the 5-drug regimen (30, 31).

Etravirine also demonstrated high potency in treatment-experienced patients. The drug was examined for its efficacy in HIV-1-infected patients failing NNRTI (efavirenz or nevirapine) therapy and with confirmed resistance to efavirenz in an open-label phase IIa trial. Sixteen patients receiving an NNRTI-containing antiretroviral regimen with an HIV-1 RNA viral load of > 2,000 copies/ml and phenotypic resistance to NNRTIs received etravirine for 7 days as a substitute for their current NNRTI. Viral loads after treatment showed a median decrease of 0.9 $\log_{10}$ copies/ml from baseline, which continued to decrease following treatment on day 8. Seven patients showed a decrease of > 1 $\log_{10}$ copies/ml. Steady-state drug levels were achieved by day 6, with mean peak plasma concentrations reached at 4 h and a

mean elimination half-life of 36 h. The most significant adverse events were grade 1 diarrhea (31%) and mild headache (25%) (32, 33).

Long-term treatment of patients with HIV-1 infection with etravirine was evaluated in an open phase II trial including 7 patients continuing other antiretroviral therapies. In addition to 3 or 4 other antiretroviral agents, patients received etravirine 800 mg b.i.d. Results were assessed at 48 weeks and all but 2 patients had a viral load below 50 copies/ml; the remaining 2 patients had a viral load below 500 copies/ml. In an exploratory cohort of patients (n=77) with matched treatment history who began a new antiretroviral therapy, the probability of achieving such reductions in viral load was greatly reduced. Etravirine was well tolerated and in treated patients the median decrease from baseline in viral load was 1.4 $\log_{10}$ copies/ml (34).

A long-term phase IIb dose-finding study in treatment-experienced HIV-1-infected patients is currently recruiting subjects in a number of countries in Europe and in Canada (14).

Source

Tibotec (BE, US) (a subsidiary of Johnson & Johnson).

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