Drugs of the Future 1998, 23(11): 1176-1189

CCC: 0377-8282/98

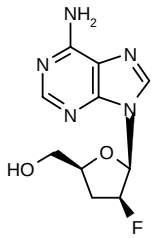
Lodenosine

Prop INN

Anti-HIV
Reverse Transcriptase Inhibitor

DDG-1
FddA
NSC-613792

2',3'-Dideoxy-2'β-fluoroadenosine
9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine
9-(2,3-Dideoxy-2-fluoro-β-D-arabinofuranosyl)adenine



$C_{10}H_{12}FN_5O_2$ Mol wt: 253.2358

CAS: 110143-10-7

EN: 146172

Synthesis

Lodenosine has been obtained by several different ways:

1) The selective tritylation of cordycepin (3'-deoxyadenosine) (I) with trityl chloride in pyridine gives the 5'-*O*-trityl derivative (II), which is then fluorinated with diethylamido sulfur trifluoride in refluxing dichloromethane and deprotected with hot 80% acetic acid (1). Scheme 1.

2) The TLC monitored reaction of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose (III) with 30% HBr in acetic acid gives the bromosugar (IV), which is condensed with 6-chloropurine (V) in refluxing dichloromethane, yielding the chloropurine derivative (VI). The reaction of (VI) with methanolic NH_3 at 100 °C in a steel bomb affords 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (VII), which is selectively silylated with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in DMF, giving the 5'-*O*-silyl derivative (VIII). The reaction of (VIII) with phenyl chlorothioformate by means of dimethylaminopyridine in DMF yields the thiocarbonate (IX), which is reduced with tributyltin hydride and AIBN in hot toluene, affording 9-[2,3-dideoxy-2-fluoro-5-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]adenine (X). Finally, this compound is desilylated with tetrabutylammonium fluoride in THF (2, 3). Scheme 2.

3) The reaction of 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (XI) with HBr in acetic acid gives the bromosugar (XII), which is methylated with methanol/K_2CO_3 in THF, yielding the 1-*O*-methyl glucoside (XIII). The selective benzoylation of (XIII) with benzoyl chloride in pyridine at –30 °C affords the 5-*O*-benzoyl glucoside (XIV), which is treated with CS_2/methyl iodide and NaH in DMF, giving compound (XV). The reduction of (XV) with tributyltin hydride and AIBN in refluxing toluene yields the 3-deoxy glucoside (XVI), which is condensed with 6-chloropurine (V) in refluxing hexamethyldisylazane, affording 9-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)adenine (XVII). Finally, this compound is debenzoylated with methanolic ammonia at 100 °C in a sealed tube (4). Scheme 3.

4) The regioseletive deacetylation of 9-(2,5-diacetoxy-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (XVIII) by means of β-cyclodextrin/$NaHCO_3$ in water or hydrazine monohydrate in ethanol gives 9-(5-acetoxy-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (XIX), which is debrominated by hydrogenation over Pd/C in acetonitrile/water, affording 9-(5-acetoxy-3-deoxy-β-D-xylofuranosyl)adenine (XX). Finally, this compound is fluorinated by means of diethylamido sulfur trifluoride in refluxing dichloromethane (5). Scheme 4.

5) The controlled reaction of 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (XI) with HBr in acetic acid gives the bromosugar (XXII), which is condensed with 6-chloropurine (V) as before, yielding 6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)purine (XXIII). Finally, this compound is treated with ammonia in methanol as before to afford 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (VII) (6). Scheme 5.

6) The selective silylation of 2-deoxy-2-fluoro-1-*O*-methyl-β-D-arabinofuranose (XIII) with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole in DMF gives the 5-*O*-silylated sugar (XXIV), which is treated with

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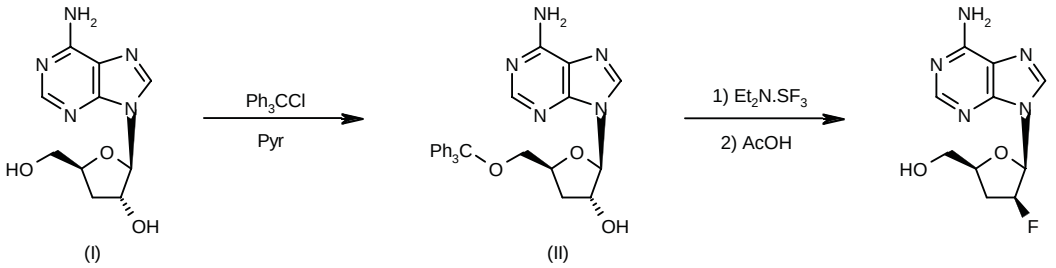
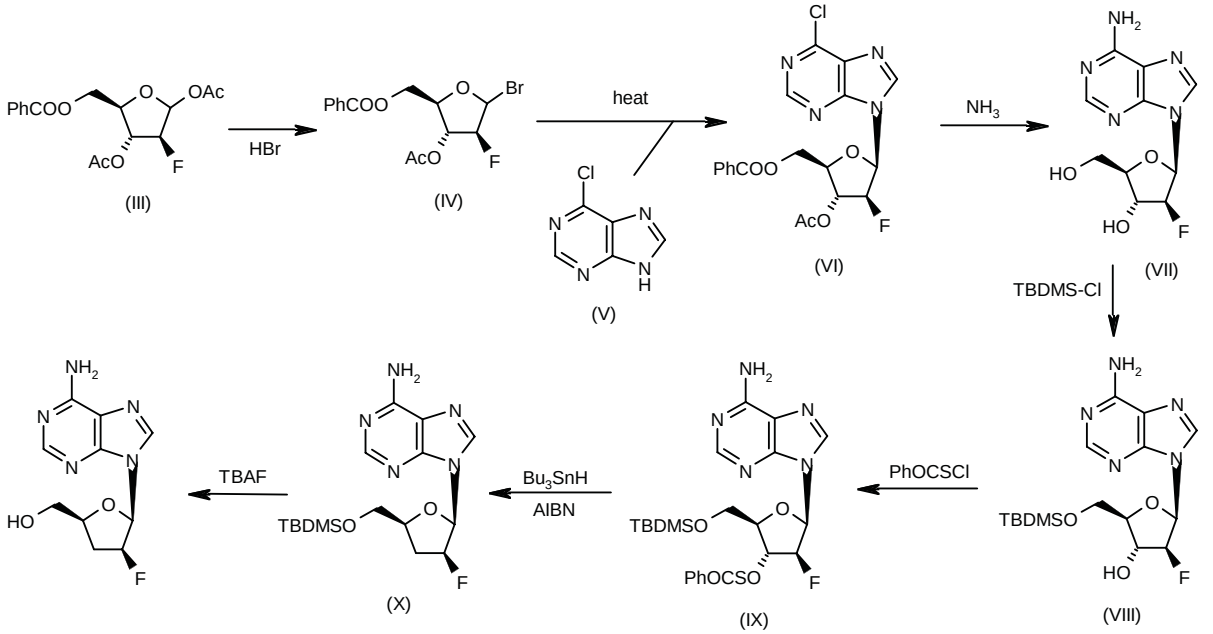
Scheme 1: Synthesis of Lodenosine



Scheme 2: Synthesis of Lodenosine

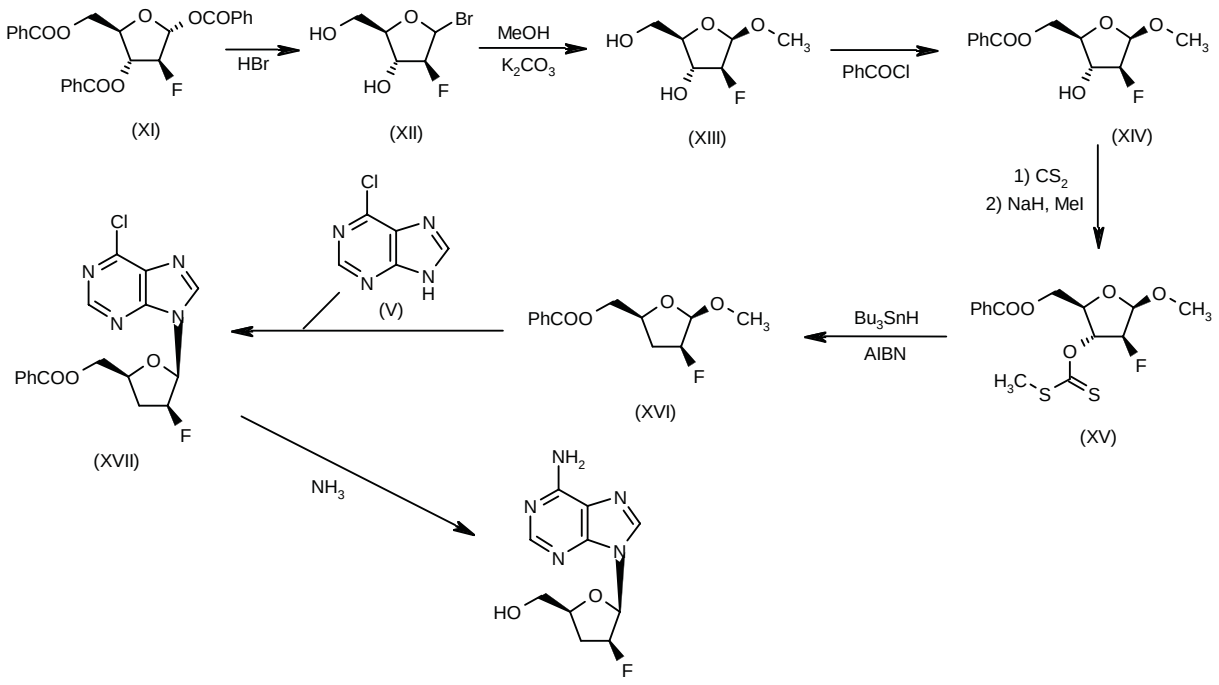


CS_2/NaH/methyl iodide in DMF to yield compound (XXV). The reduction of (XXV) with tributyltin hydride and AIBN in refluxing toluene affords 2,3-dideoxy-2-fluoro-5-*O*-(*tert*-butyldiphenylsilyl)-β-D-arabinofuranose (XXVI), which is treated with HBr in acetic acid to yield the bromosugar (XXVII). The condensation of (XXVII) with 6-chloropurine (V) in hot acetonitrile gives 6-chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(*tert*-butyldiphenylsilyl)-β-D-arabinofuranosyl]-purine (XXVIII), which is desilylated with tetrabutylammonium fluoride in THF, yielding 6-chloro-9-[2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl]purine (XXIX). Finally, this compound is treated with methanolic ammonia at 105 °C as before (7). Scheme 6.

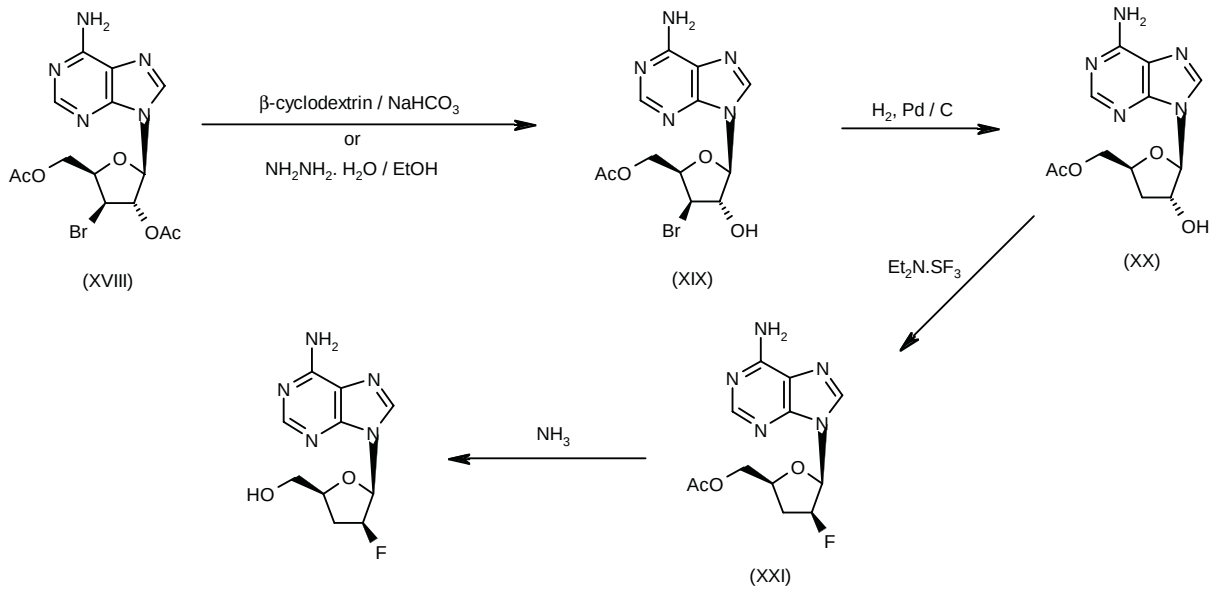
7) The treatment of 2,3-*O*-dimesyl-5-*O*-(4-methoxybenzyl)-1-*O*-methyl-α-D-xylofuranose (XXX) with $NaBH_4$ gives 3-deoxy-5-*O*-(4-methoxybenzyl)-1-*O*-methyl-α-D-xylofuranose (XXXI), which is fluorinated with diethylamido sulfur trifluoride as before, yielding 2,3-dideoxy-2-fluoro-5-*O*-(4-methoxybenzyl)-α-D-arabinofuranose (XXXII). The condensation of (XXXII) with adenine (XXXIII) by means of acetyl bromide affords 9-[2,3-dideoxy-2-fluoro-5-*O*-(4-methoxybenzyl)-β-D-arabinofuraosyl]adenine (XXXIV), which is finally deprotected by hydrogenation over Pd/C in ethanol (8). Scheme 7.

8) The reaction of 2,3-*O*-isopropylidene-D-ribofuranose (XXXV) with 4-methylbenzoyl chloride (XXXVI) by means of pyridine in butyl acetate gives 2,3-*O*-isopropylidene-5-*O*-(4-methylbenzoyl)-D-ribofuranose (XXXVII), which is methylated by means of NaH and dimethylsulfate in THF to yield the expected methyl ribofuranoside (XXXVIII). The hydrolysis of the acetonide group of (XXXVIII) with trifluoromethanesulfonic acid in acetonitrile affords 1-*O*-methyl-5-*O*-(4-methylbenzoyl)-α-D-ribofuranose (XXXIX), which is treated with SO_2Cl_2/triethylamine in butyl acetate to give the cyclic sulfate (XL). The reduc-

Scheme 3: Synthesis of Lodenosine

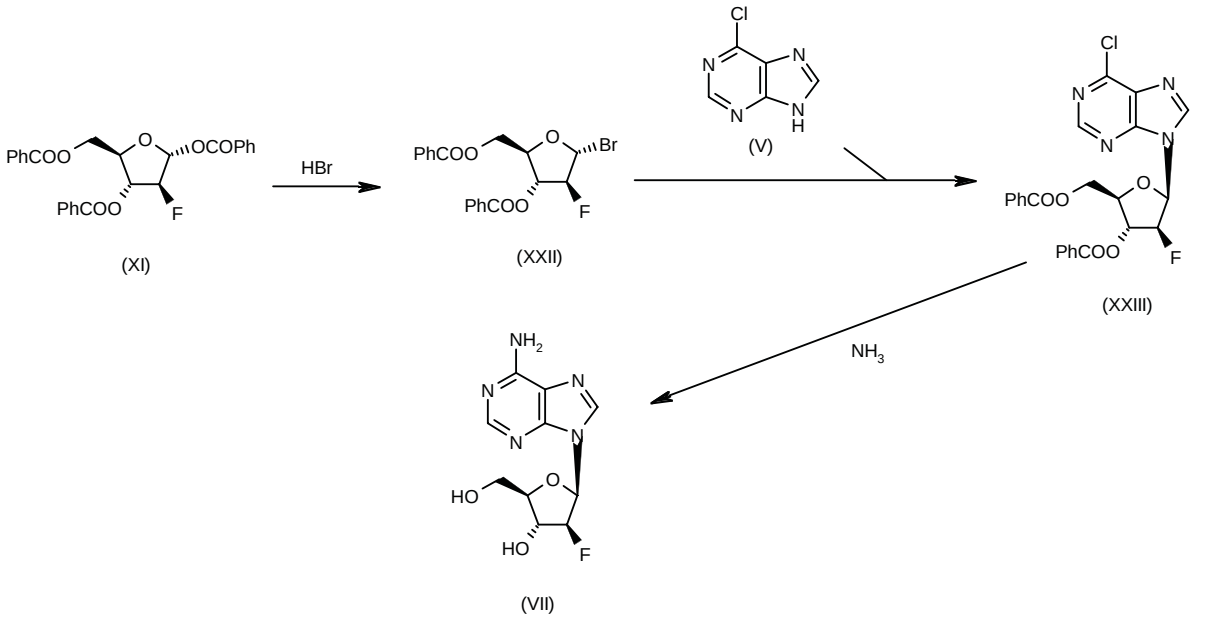


Scheme 4: Synthesis of Lodenosine

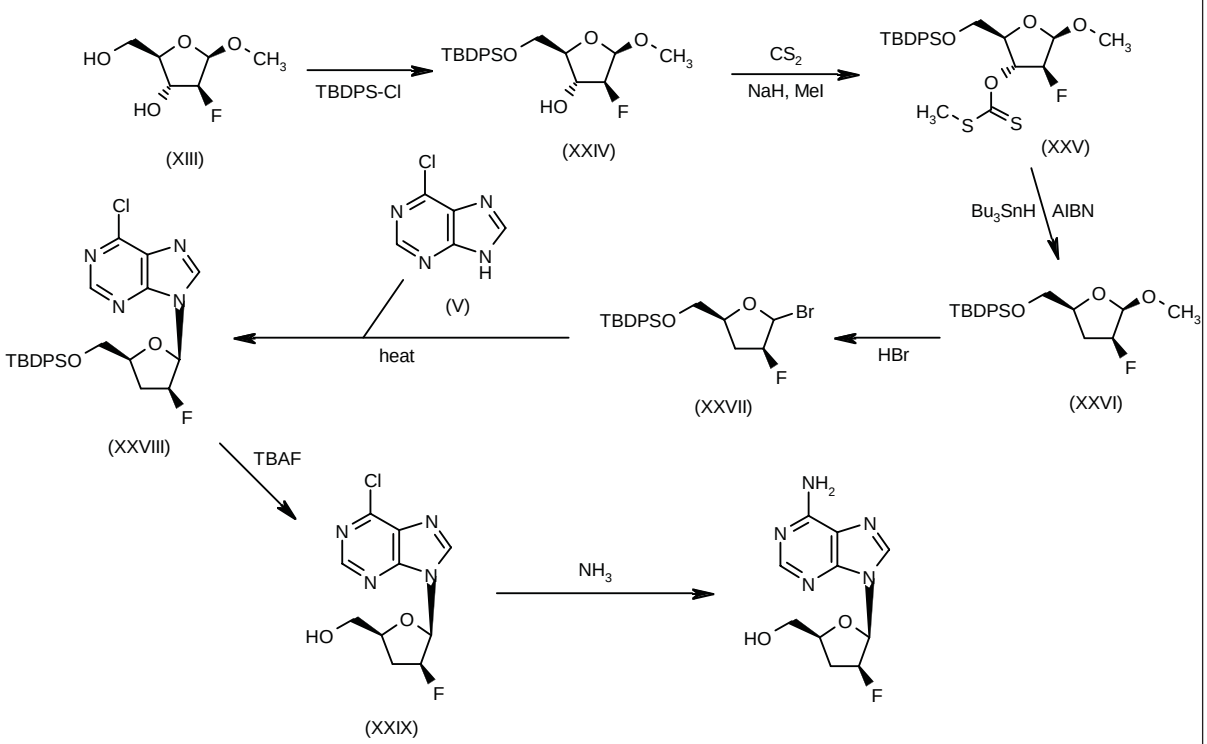


tion of (XL) with $NaBH_4$ in THF yields 3-deoxy-1-*O*-methyl-5-*O*-(4-methylbenzoyl)-α-D-ribofuranose (XLI), which is treated with trifluoromethanesulfonic anhydride and tetrabutylammonium fluoride in dichloromethane/pyridine to afford 2,3-dideoxy-2-fluoro-1-*O*-methyl-α-D-arabinofuranose (XLII). The reaction of (XLII) with HBr in acetic acid as before gives the bromosugar (XLIII), which is condensed with 6-chloro-9-(trimethylsilyl)purine (XLIV) in dichloromethane to yield 6-chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(4-methylbenzoyl)-β-D-arabinofuranosyl]purine

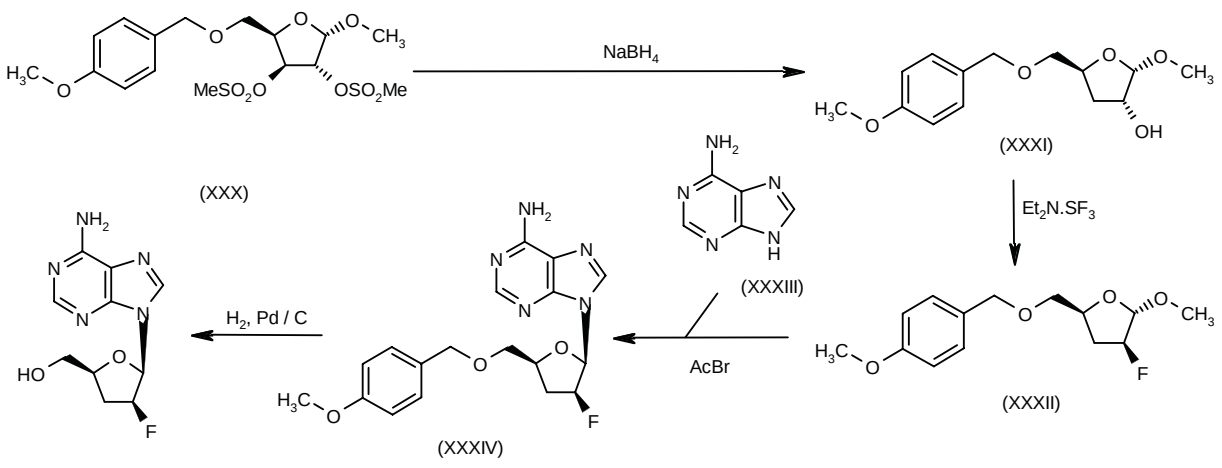
Scheme 5: Synthesis of Intermediate (VII)



Scheme 6: Synthesis of Lodenosine



Scheme 7: Synthesis of Lodenosine



(XLV). Finally, this compound is treated with ammonia in methanol at 90 °C (9). Scheme 8.

Description

Crystals, m.p. 227 °C, $[\alpha]_D^{24}$ +57.8° (c 0.083, H_2O) (2);white solid, m.p. 225-7 °C (4); crystals, m.p. 227 °C (8).

Introduction

The 2',3'-dideoxynucleoside class of antiviral agents are potent inhibitors of the cytopathic effects of the human immunodeficiency virus (HIV). One of the most extensively studied compounds in this class is dideoxyadenosine (ddA). The activated form of the drugs in this class, their 5'-triphosphate form, does not actually eradicate the virus, but rather inhibits its replication. As such, the drugs must be taken on a continual basis in order to maintain their efficacy. A drawback of early examples of this class of anti-HIV compounds was their low stability under the acidic conditions of the gastrointestinal tract. In an attempt to discover new anti-HIV compounds from the same series as ddA but with increased acid stability, more potent antiretroviral activity and less toxicity, scientists at the National Institutes of Health synthesized several fluorine-containing purine dideoxynucleoside compounds with increased resistance to degradation at acidic pH and selected the monofluoro 2'-diasteromer of ddA (FddA) for further evaluation (2, 3). The chemical structures and enzyme inhibitory activities of some of the most extensively studied reverse transcriptase inhibitors are summarized in Tables I and II, respectively.

In 1995, U.S. Bioscience entered into a Cooperative Research and Development Agreement with the NIH to develop FddA (lodenosine) for the treatment of HIV infection, HIV-related infection or HIV-related diseases in humans (10).

Pharmacological Actions

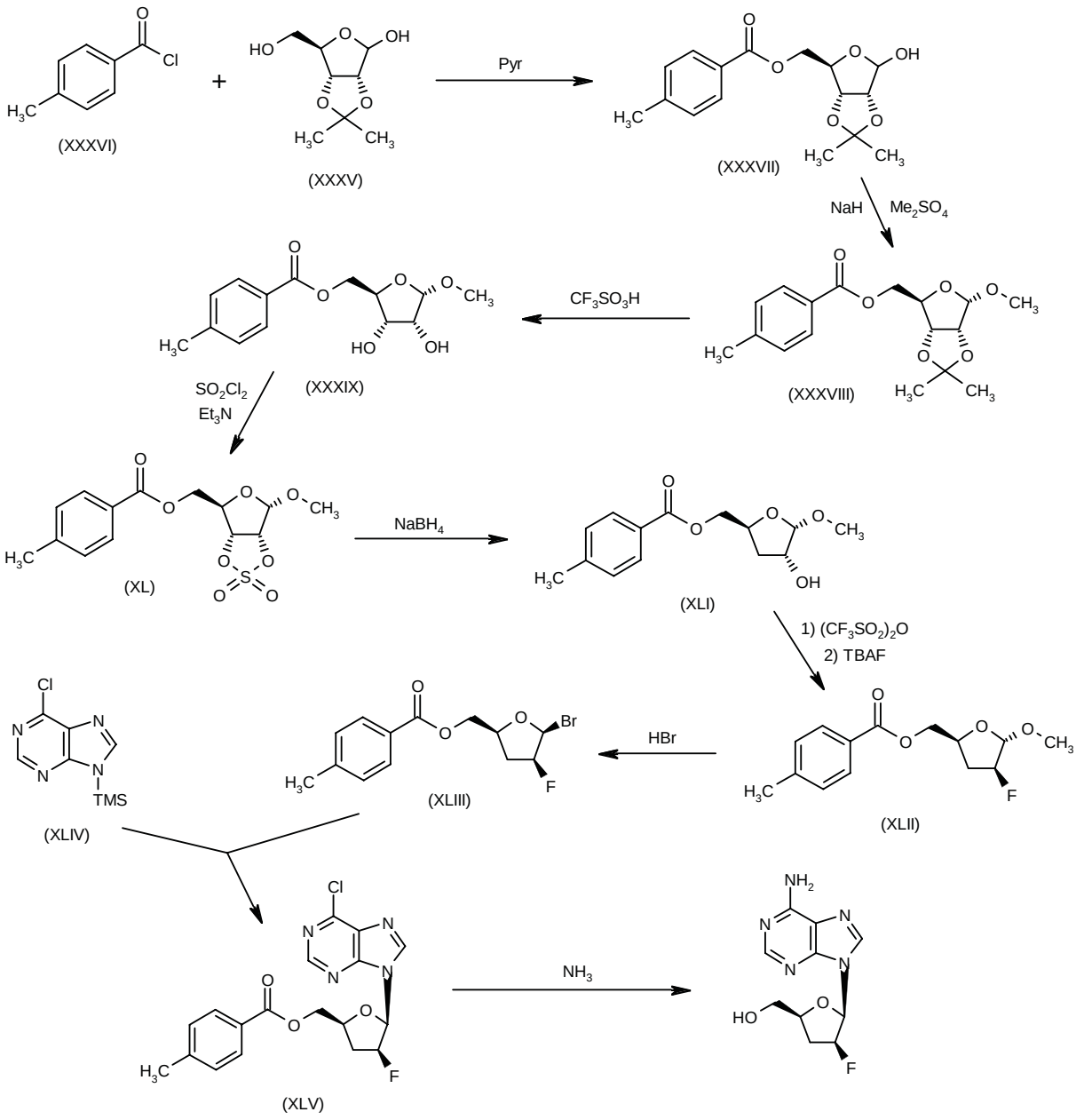
FddA is converted *in vivo* to the metabolite FddI by the enzyme adenosine deaminase (EC 3.5.4.4). Both FddA and FddI are ultimately anabolized to F-ddATP, a potent HIV reverse transcriptase inhibitor and viral DNA chain terminator with a prolonged intracellular half-life (11), as shown in Scheme 9.

In vitro in peripheral blood mononuclear cells infected by a primary clinical HIV isolate, the IC_{50} of FddA was 3.7 μM, which was similar to that of other nucleosides (3). The anti-HIV-1 activity of the title compound was compared to that of several other dideoxynucleoside analogs (zidovudine, ddI and ddC) in cell strains that were sensitive or resistant to AZT, ddI and nonnucleoside reverse transcriptase inhibitors. FddA was active against all resistant viral isolates, including the ddI-resistant strain (12).

In vitro studies were performed in order to induce, through serial passages, resistance to FddA in the wild-type HIV-1 virus. After 18 passages, three amino acids were found to be changed in the reverse transcriptase-encoding region of the *pol* gene; one of these changes, P119S, was found to be directly responsible for the reduced sensitivity of the virus to FddA. Cross-resistance to nucleoside reverse transcriptase inhibitors, including in strains resistant to more than one dideoxynucleoside, was minimal (13).

In vitro in the presence of the adenosine deaminase inhibitor 2'-deoxycoformycin (2'-dCF), the extracellular

Scheme 8: Synthesis of Lodenosine



deamination of both ddA and ddI was inhibited, resulting in the rapid intracellular uptake of the unchanged compounds and leading to significant increases in the intracellular amounts of the active 5'-triphosphate forms. The antiviral activity of ddA increased by 2.2-fold in the presence of 20 or 50 nM 2'-dCF. The combination of ddA plus 2'-dCF was considered of potential interest due to the possibility of reducing the clinical dosage of the antiviral agent (11). Coadministration with the ribonucleotide reductase inhibitor hydroxyurea was also effective in enhancing the anti-HIV activity of dideoxynucleoside compounds such as FddA *in vitro* in lymphocytes and macrophages of human origin (14). A similar increase in efficacy was observed following coadministration of FddA and the inosine monophosphate (IMP) dehydrogenase inhibitor ribavirin; the anti-HIV potency of the title compound (5 μM) in MOLT-4 cells was approximately doubled in the presence of 5 μM ribavirin (15).

Table I: Chemical structures of nucleoside and nonnucleoside reverse transcriptase inhibitors.

Nucleosides

Launched

1. Didanosine (*Videx*)
   Bristol-Myers Squibb (1991)
2. Lamivudine (3TC; *Epivir*)
   BioChem Pharma; Glaxo Wellcome (1995)
3. Stavudine (*Zerit*)
   Bristol-Myers Squibb (1994)
4. Zalcitabine (*Hivid*)
   Roche (1992)
5. Zidovudine (*Retrovir*)
   Glaxo Wellcome (1987)

Clinical Trials

6. Abacavir sulfate (*Ziagen*)
   Glaxo Wellcome (PR)
7. Adefovir dipivoxil (*Preveon*)
   Bristol-Myers Squibb; Gilead (CT 3)
8. Bis(POC)PMPA
   Gilead (CT 2)
9. (–)-FTC
   Triangle Pharm.; Glaxo Wellcome (CT 2)
10. (R)-PMPA
    Gilead (CT 2)
11. Lodenosine
    NCI; U.S. Bioscience (CT 2)

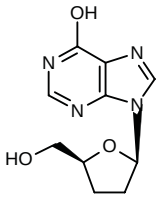
Nonnucleosides

Launched

12. Delavirdine mesilate (*Rescriptor*)
    Pharmacia & Upjohn (1997)
13. Efavirenz (*Sustiva*)
    DuPont Pharm. (1998)
14. Nevirapine (*Viramune*)
    Boehringer Ingelheim (1996)

Clinical Trials

15. MKC-442
    Triangle Pharm. (CT 3)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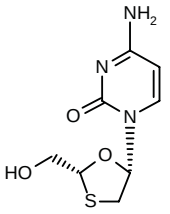
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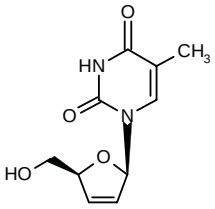
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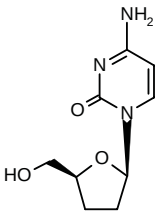
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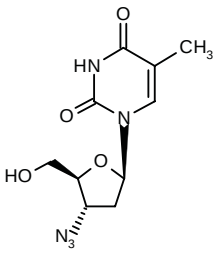
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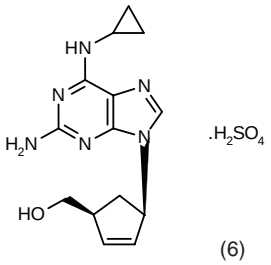
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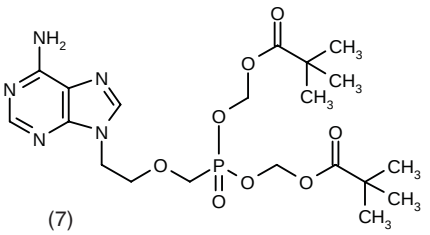
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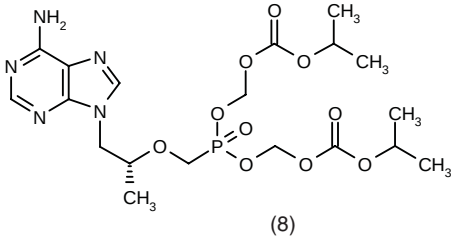
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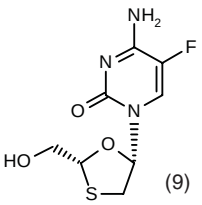
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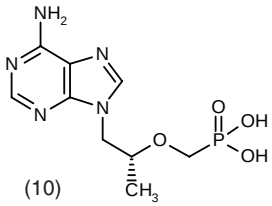
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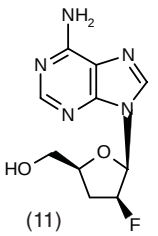
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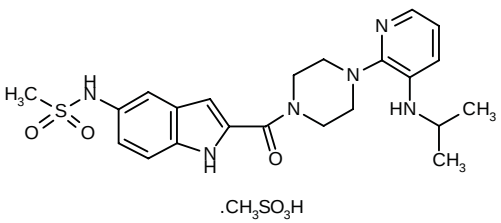
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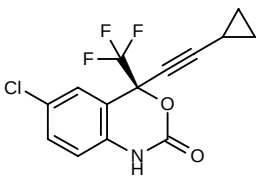
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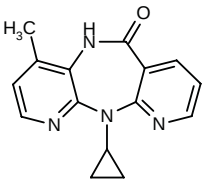
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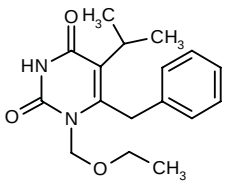

(15)

Source: Prous Science Ensemble database.

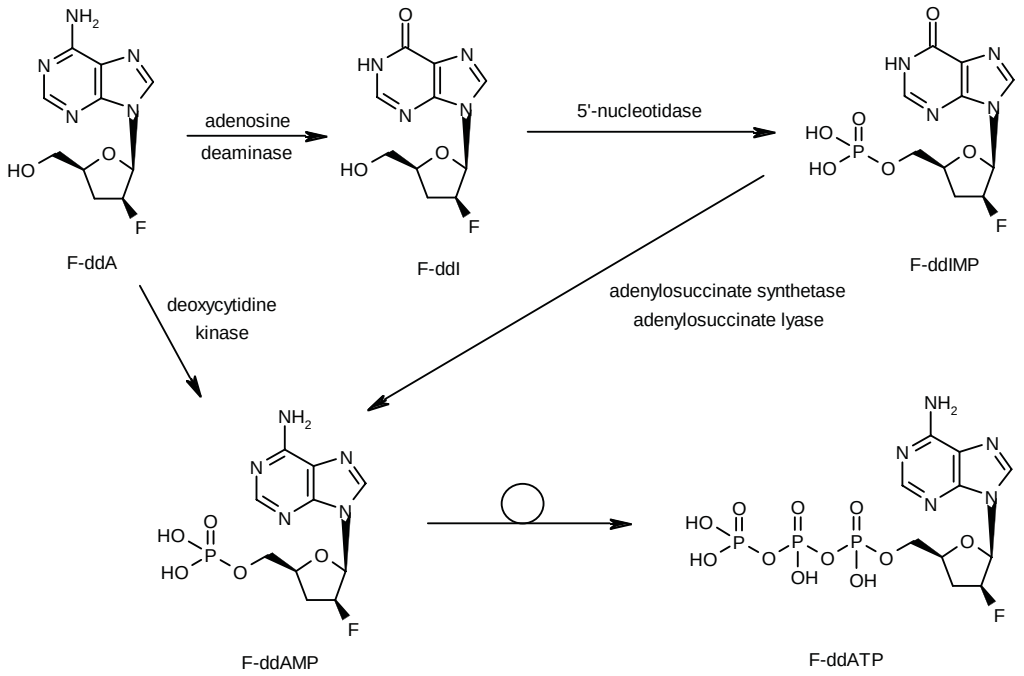
Table II: Inhibitory activity of selected HIV reverse transcriptase inhibitors (data from Prous Science MFLine database).

Compound	Inhibitory Activity (μM)	Template primer-Assay	References
Abacavir*	IC_{50} = 0.03	NR	53
Adefovir	K_i = 0.012	RNA template	34
(PMEA)	K_i = 0.98	DNA template (calf thymus DNA)	34
Delavirdine	IC_{50} = 0.26	poly(rA)oligo (dT)	38
Didanosine	IC_{50} = 0.62	NR	36
	IC_{50} = 0.68	NR	36
Efavirenz	K_i = 0.0029	NR	51
(R)-PMPA	K_i = 0.022	RNA template	34
	K_i = 1.55	DNA template (calf thymus DNA)	34
Lamivudine	IC_{50} = 0.004	NR	36
	IC_{50} = 0.02	NR	36
	IC_{50} = 23.4	DNA template (calf thymus DNA)	43
	K_i = 10.6	poly(rI)oligo(dC)	43
	K_i = 12.4	RNA template	43
Lodenosine	K_i = 1.0	poly(dA-T)	19
	K_i = 3.0	DNA assay	44
	K_i = 150.0	poly(rU)oligo(dA)	44
MKC-442	IC_{50} = 0.012	poly(rA)oligo(dT)	50
	IC_{50} = 0.21	poly(rC)oligo(dG)	50
	K_i = 0.010-0.011	poly(rC)oligo(dG)	50
	K_i = 0.11-0.20	poly(rA)oligo(dT)	50
Nevirapine	IC_{50} = 0.01-2.90	poly(rA)oligo(dT)	37, 38, 50, 52
	IC_{50} = 0.07-0.30	RNA template	37, 52
	IC_{50} = 0.084-0.56	poly(rC)oligo(dG)	42, 50, 52
	K_i = 0.20	NR	42, 48
	K_i = 0.55	poly(rC)oligo(dG)	52
Ribavirin	IC_{50} = 112.0	poly(rA)oligo(dT)	39
Stavudine	K_i = 0.0083-0.032	poly(rA)oligo(dT)	46, 47, 49
	K_i = 70.0	poly(dA)oligo(dT)	47
Talviraline**	IC_{50} = 0.08	NR	45
Zalcitabine	IC_{50} = 0.001	NR	36
	IC_{50} = 0.03	NR	36
	IC_{50} = 1.44	DNA template (calf thymus DNA)	43
	K_i = 0.054-0.33	RNA template	34, 43
	K_i = 0.53	DNA template (calf thymus DNA)	34
	K_i = 1.90	poly(rI)oligo(dC)	43
Zidovudine	IC_{50} = 0.0003	NR	36
	IC_{50} = < 0.002	NR	36
	IC_{50} = 0.006-0.15	poly(rA)oligo(dT)	37, 38, 41, 50, 52
	IC_{50} = 0.02	RNA template	52
	IC_{50} = 0.048	DNA template (calf thymus DNA)	43
	IC_{50} = >2.0->50.0	poly(rC)oligo(dG)	41, 52
	K_i = 0.005-0.04	poly(rA)oligo(dT)	35, 40 43, 46, 47, 49, 52
	K_i = 0.008-0.01	RNA template	34, 35
	K_i = 0.30-0.51	DNA template (calf thymus DNA)	34, 35
	K_i = 84.0	poly(dA)oligo(dT)	47

Inhibitory activity against recombinant wild-type HIV/HIV-1 reverse transcriptase enzyme. Some values refer to the 5'-triphosphate of the compound (*e.g.*, FddA (lodenosine) refers to FddATP; ribavirin refers to ribavirin 5'-triphosphate). *Data referred to carbovir 5'-triphosphate as the active form of abacavir; **Discontinued; NR: not reported.

The anti-HIV activity of FddA was also evaluated *in vivo* in a murine model. Mice with severe combined immunodeficiency reconstituted with human peripheral blood leukocytes (hu-PBL-SCID) were challenged with the HIV virus, resulting in a rate of infection of 93% in untreated controls. Administration of zidovudine lowered the rate of infection to 31%, while treatment with FddA suppressed HIV infection completely (0% infection rate). This anti-HIV activity was confirmed during follow-up, with 18/20 controls and 4/20 FddA-treated animals manifesting signs of viral infection. The compound was found to preserve human $CD4^+$ T cells in the face of HIV infection, as seen by the higher percentage of $CD4^+$ T cells in FddA-treated mice than in controls (10.3% ± 3.4% *vs.*

Scheme 9: Metabolism of Lodenosine



0.27% ± 0.21%). The combined attributes of potent anti-HIV activity *in vivo*, good oral bioavailability, a long intracellular half-life and the capacity to protect $CD4^+$ cells challenged with the HIV virus led the investigators to conclude that clinical testing of FddA was warranted (16).

Toxicity

During the course of clinical testing of the anti-HBV agent FIAU, another member of the 2'-fluoro-containing nucleoside analog class, several cases of unexpected and at times fatal hepatotoxicity were encountered. Given the structural similarities of FIAU and FddA, an evaluation of the potential hepatic toxicity of the title compound was considered relevant. Human MOLT-4 cells were incubated with radiolabeled FddA and FIAU and the incorporation of the compounds into the cellular DNA was compared. FIAU was incorporated in MOLT-4 cell DNA (10 μM) at a level of 35.49 ± 2.37 pmol/1 million cells, while the incorporation of FddA was less than 1% that of FIAU. This difference was attributed to the presence of a 3'-hydroxyl group in FIAU that is lacking in the structure of FddA, making the latter unable to form DNA internucleotide linkages. As such, hepatotoxicity was not predicted to be a problem with this compound (17).

The potential for cardiotoxicity was also evaluated, this time *in vivo* in the rat. FddA and ddA were administered by three different i.v. schedules (2.5-250 mg/kg x 1 day, 125 or 250 mg/kg/day x 5 days or 250 mg/kg b.i.d. for 1 day) and one oral schedule (500 mg/kg b.i.d. x 1 day). The severity of cardiac lesions developing in animals treated with either compound was related to dose and was proportional to plasma concentrations of the undeaminated parent compound. The active deaminated metabolites FddI and ddI were virtually devoid of cardiotoxicity in this study, with only minor cardiac lesions resulting at plasma concentrations in excess of 2 mM. Cardiomyopathy in FddA-treated rats was minimal at all but one dose (250-mg/kg x 1 day), although it was generally greater than that seen with ddA at the same dose. This increase was attributed to the 20-fold slower rate of deamination of FddA, which results in higher plasma concentrations of the title compound. Cardiotoxicity with both compounds was similar with repeat dosing to that seen with single doses, indicating that the toxicity is linked to C_{max} and not to total drug exposure. Cardiotoxicity in this highly sensitive species was encountered only at doses 30- to 50-fold higher than those expected to be used in the clinic (18).

Pharmacokinetics and Metabolism

As indicated above, FddA undergoes a series of transformations in the body following its oral administration (see Scheme 9). The primary route of metabolism of this compound in human T-lymphoblasts is anabolic and

results in the 2'-deoxycytidine kinase-catabolized formation of 2'-fluorodideoxynucleotides. FddA was found in enzymological studies to be deaminated at a rate 10-fold less rapid than ddA. Furthermore, the deaminated product of FddA is resistant to hydrolysis by purine nucleoside phosphorylase, unlike that of ddA. Similar to ddA, FddA is transported into the cell by passive diffusion rather than entering via the purine nucleoside transport carrier system; the title compound, however, enters cells at a rate that is only about half that of ddA. Thus, it is apparent that the metabolic pathway of FddA and its deaminated metabolite are significantly different from those of ddA and its deamination product, ddI (19).

The metabolism of FddA in rats was evaluated in the presence and absence of 2'-deoxycoformycin. FddA was cleared from the plasma in a rapid fashion (Cl = 68.5 ml/kg/min) in rats administered the title compound alone; upon addition of the ADA inhibitor 2'-dCF, clearance dropped to 23.8 ml/min/kg, resulting in a 0.4-fold increase in the steady-state concentration of FddA in plasma. In rats not given 2'-dCF, a full 58% of metabolic clearance was accounted for by conversion of FddA to FddI, with a $t_{1/2}$ for bioconversion of 9.8 ±1.9 min (20).

Uptake of FddA in the central nervous system (brain tissue and CSF) was also increased by coadministration with the ADA inhibitor 2'-dCF. Chronically catheterized rats were administered 2'-dCF (1 mg/kg i.v.) for 0.4, 1, 2 or 5 h, followed by a 30-min infusion of the title compound (66 mg/kg/h). As predicted, the bioconversion of FddA to FddI was inhibited by more than 90% following pretreatment with 2'-cDF. Drug concentrations in the plasma, brain and CSF were approximately 2, 4- and 3-fold higher in pretreated rats than in controls (21). FddA appears to function, at least in part, as a CNS-activated prodrug of FddI (22). Through the effects of ADA localized in the CNS, the compound was converted to FddI with an apparent first-order rate of conversion in brain and CSF of 0.09 ± 0.03 and 0.05 ± 0.02, respectively (23).

The pharmacokinetics in plasma of FddA and FddI were evaluated in chronically catheterized rats. FddA was given by i.v. infusion at a rate of 66 mg/kg/h and the pharmacokinetics of the compound itself were analyzed; pharmacokinetic parameters were analyzed for both FddA and FddI following administration of the compounds at the respective doses of 66 and 48 mg/kg/h i.v. The ADA-catalyzed bioconversion of FddA to FddI in vivo was also studied. Following administration by 120-min infusion, FddA was eliminated rapidly from plasma; clearance was 68.5 ml/kg/min, more than half of which was due to formation of FddI. Mean residence time (MRT) of FddA and FddI was 8.9 and 20.5 min, respectively, and volume of distribution at steady state was 610 and 559 ml/kg, respectively. The apparent first-order rate constant for bioconversion of the compound to FddI was 0.071 ± 0.014 min. Following administration of FddA, the bioavailability of FddI was 58.1%. FddI was administered more slowly after bioconversion, with a total clearance of 27.3 ml/min/kg (24).

A high-performance liquid chromatography assay was developed for determining levels of FddA and its metabolite FddI in plasma and urine of dogs. Compound was administered once daily at doses of 100, 250 or 500 mg/kg p.o. for 14 days. FddI appeared in plasma just 15 min after dosing, and plasma levels of metabolite were greater than those of unchanged FddA. The major route of elimination of FddI appeared to be renal (25). The bioavailability of FddI following oral administration of FddA (50 mg/kg) was 83.2% in a beagle dog (26).

An early reversed-phase HPLC method was developed for detecting FddA and its metabolite in plasma and urine. The method gives a limit of quantitation of 50 ng/ml in both analytes, and was used in preclinical studies in rats and monkeys (27). This method was not appropriate for use in clinical trials, however, because the sample work-up was not compatible with requisite HIV viral decontamination procedures. Thus, another HPLC method with UV detection, this one suitable for use in clinical trials, was subsequently developed for use in determining the levels of FddA and FddI in human plasma. The method was used in phase I trials conducted by the NCI (28).

The pharmacokinetics and oral bioavailability of FddA (lodenosine) were evaluated in symptomatic HIV-positive adults. The first dose of the compound was administered by 90-min i.v. infusion, and dosing was later switched to the oral route for a 12-week course of twice-daily treatment, with doses ranging from 0.2-3.2 mg/kg/dose. Oral liquid and capsule formulations were both used. The steady-state plasma concentration of lodenosine and the maximum plasma concentration of FddI were dose-proportional, with respective values of 2.32 μM and 12.2 μM at the highest dose level. Lodenosine was rapidly metabolized to FddI, with the metabolite accounting for 88 ± 3.5% of plasma lodenosine equivalents over the dose range of 0.8-3.2 mg/kg. The principal route of excretion was renal, with 92 ± 12% of the administered dose (0.8-3.2 mg/kg) excreted in the urine in the 12-h postdosing period. Total plasma drug exposure (total AUC) with lodenosine was nearly 3 times higher than that obtained with an equivalent dose of didanosine. The mean oral bioavailability of lodenosine, administered as a liquid in the fasting state, was 67 ± 21%, and the maximum plasma concentration of the metabolite was about 80% of that seen with i.v. dosing. A capsule formulation of lodenosine was bioequivalent to the liquid form. Measurable levels of FddA and FddI were both detected in the cerebrospinal fluid, indicating that the compound penetrates into the CNS (29) (Box 1).

Clinical Studies

In a phase I efficacy study, 25 subjects with symptomatic HIV infection and CD4 cell counts of <500 cells/mm^3 were treated with lodenosine at doses ranging from 0.2-3.2 mg/kg p.o. b.i.d. for a period of 12 weeks. The oral bioavailabilities of lodenosine in the fasting and

Box 1: Pharmacokinetics and oral bioavailability of lodenosine (29).

Study Design	Phase I trial
Study Population	Adult patients with symptomatic HIV infection
Intervention Groups	Lodenosine, initial dose 0.2-3.2 mg/kg i.v. followed by capsules or liquid formulations, 0.2-3.2 mg/kg p.o. b.i.d. x 12 weeks
Results	I.v. infusion: C_{pss} and C_{pmax} for lodenosine and FddI, 2.32 μM and 12.2 μM, respectively; lodenosine metabolized rapidly to FddI (88 ± 3.5%); 92 ± 12% of administered dose recovered in urine. Oral dose: bioavailability for lodenosine, 67 ± 21%; C_{pmax} for FddI, 80% of that of i.v. dose; capsule formulation was bioequivalent to liquid formulation
Conclusions	Orally administered lodenosine in the fasted and fed states has excellent bioavailability. The greater enzymatic stability and superior bioavailability of lodenosine compared to F-ddI is reflected in a 3-fold greater AUC for equivalent 0.8 and 1.6 mg/kg doses

Source: Prous Science CTLine database.

Box 2: Activity of lodenosine in patients with symptomatic HIV infection (30).

Study Design	Phase I dose-escalating trial
Study Population	Patients with symptomatic HIV infection and CD4 cells/mm^3 <500 (n = 22)
Intervention Groups	Lodenosine 0.2-3.2 mg/kg b.i.d. x 12 weeks
Adverse Events	Asymptomatic transaminase elevations, neutropenia, hyperglycemia, hyperamylasemia
Results	Oral bioavailability, 74.5 ± 5.2% and 64.5 ± 4.5% in fasting and nonfasting states, respectively. At week 6, decrease in HIV viral load and median HIV RNA at 1.6 mg/kg. Median change in HIV RNA of $-0.395\log_{10}$ copies/ml was significant ($p < 0.03$). Downward trend in viral loads at 0.4 and 0.8 mg/kg
Conclusions	Lodenosine has excellent bioavailability and anti-HIV activity on a twice-daily dosing schedule at doses that are well tolerated over 12 weeks, even in heavily pretreated patients

Source: Prous Science CTLine database.

Box 3: Activity of lodenosine in patients with symptomatic HIV infection (31).

Study Design	Phase I dose-escalating trial
Study Population	Patients with symptomatic HIV infection and CD4 cells/mm^3 <500 (n = 25)
Intervention Groups	Lodenosine 0.2-3.2 mg/kg b.i.d. x 12 weeks
Adverse Events	Asymptomatic transaminase elevations, neutropenia, hyperglycemia, hyperamylasemia
Results	Oral bioavailability, 75% and 65% in fasting and nonfasting states, respectively. At week 6, decrease in HIV viral load and median HIV RNA at 1.6 and 3.2 mg/kg. Median change in HIV RNA of $-0.49\log_{10}$ copies/ml was significant ($p < 0.01$). Downward trend in viral loads at 0.4 and 0.8 mg/kg and upward trend in CD4 counts at highest doses
Conclusions	Lodenosine has excellent bioavailability, is well tolerated and has anti-HIV activity on a twice-daily dosing schedule, even in heavily pretreated patients

Source: Prous Science CTLine database.

nonfasting states were 75% and 65%, respectively. Viral HIV RNA load decreased by –0.49 $\log_{10}$ copies/ml in the 8 patients treated with the two highest doses after 6 weeks of therapy. Similar downward trends in viral load were observed with the 0.4- and 0.8-mg/kg doses, while a trend toward an increase in CD4 counts was observed at the highest dose levels. Anti-HIV responses were obtained even in patients who had received extensive prior nucleoside anti-HIV therapy. Twelve patients reported increased energy and 7 patients had weight gain of at least 1.5 kg. Adverse events, none of which were clearly related to the study drug, included asymptomatic increases in transaminases, neutropenia, hyperglycemia and hyperamylasemia. These preliminary results indicate that lodenosine is effective in the treatment of HIV infection on a twice-daily dosing schedule, even in heavily pretreated patients, and that once-daily dosing may be a possibility (30, 31) (Boxes 2 and 3).

The design of this phase I trial was subsequently modified to evaluate the efficacy of once-daily dosing of lodenosine in combination with stavudine and nelfinavir. U.S. Bioscience has received FDA approval for a phase II trial, which recently got under way, evaluating lodenosine in combination with stavudine and indinavir sulfate in previously untreated HIV-infected patients (32, 33).

Manufacturer

Natl. Cancer Inst. (US); U.S. Bioscience (US).

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