Communications to the Editor

5-Chloro-3-(phenylsulfonyl)indole-2-carboxamide: A Novel, Non-Nucleoside Inhibitor of HIV-1 Reverse Transcriptase

Theresa M. Williams,* Terrence M. Ciccarone, Suzanne C. MacTough, Clarence S. Rooney, Suresh K. Balani,† Jon H. Condra,‡ Emilio A. Emini,‡ Mark E. Goldman,§,⊥ William J. Greenlee,‖ Laura R. Kauffman,† Julie A. O'Brien,§ Vinod V. Sardana,‡ William A. Schleif,‡ Anthony D. Theoharides,†,# and Paul S. Anderson

Department of Medicinal Chemistry, Department of Drug Metabolism, Department of Virus and Cell Biology, and Department of New Lead Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486-0004, and Department of Exploratory Chemistry, Merck Research Laboratories, Rahway, New Jersey

Received February 16, 1993

Development of effective pharmaceutical interventions in acquired immunodeficiency syndrome (AIDS) is a high priority goal. About 10 million individuals worldwide are estimated to be infected with human immunodeficiency virus (HIV), the causative agent of AIDS, and the number of AIDS-related deaths continues to rise each year. Antiviral therapies which would halt progression of the disease are designed to selectively interfere with the replicative life cycle of the virus.[1] Transcription of virally-encoded genomic RNA to cellular DNA is accomplished by the enzyme HIV reverse transcriptase (RT), and it has been shown that inhibition of this enzyme blocks viral replication.[2] As of this writing, drugs which are approved for the treatment of HIV are the nucleoside analogs 3′-azido-2′,3′-dideoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxycytidine (ddC). Intracellular phosphorylation of these compounds leads to triphosphate nucleoside analogs which serve as alternate RT substrates leading to chain termination.[3] Long-term treatment with nucleoside analogs is clinically limited by side effects which may be due in part to insufficient selectivity between viral and normal cellular polymerases. Side effects accompanying AZT and ddI therapy include bone marrow suppression, peripheral neuropathy, and mitochondrial myopathy.[4-6] Extended therapy has led to the emergence of resistant strains of HIV which are no longer sensitive to AZT or ddI due to specific mutations in the RT.[7] To address the toxicity and resistance problems of nucleoside inhibitors, a major goal in the field of medicinal chemistry has been the discovery and development of non-nucleoside inhibitors. A number of diverse chemical structures have been shown to be potent RT-1 inhibitors: imidazobenzodiazepinethione (TIBO),[8] dipyridodiazepinone, and related compounds;[9] 3-[(arylmethyl)amino]pyridin-2(1*H*)-one;[10] bis(heteroaryl)piperazine (BHAP);[11] and the acyclic nucleoside 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT) and derivatives.[12] The non-nucleoside inhibitors have been shown to interact with the RT at a nonsubstrate binding site.[13] Recent clinical results have demonstrated that resistant strains of HIV-1 RT rapidly emerge in response to treatment with non-nucleoside RT inhibitors and that a number of mutations leading to resistance are similar to those observed in cell culture experiments.[14] Herein we report the discovery and antiviral activity of 5-chloro-3-(phenylsulfonyl)indole-2-carboxamide (1, L-737,126), a novel, highly potent, and selective RT inhibitor which also displays significant activity against two single mutant HIV-1 RTs of current interest.

Chemistry. Reduction of indole-2-carboxylates **2a** and **2b** with LAH followed by reaction with tri-*n*-butylphosphine and diphenyl disulfide led to [(phenylthio)methyl]-indoles **3a** and **3b** in 74% yield (Scheme I). Subsequent reaction with diphenyl disulfide and sodium hydride in DMF[15] gave 55% yields of 3-(phenylthio)-2-[(phenylthio)-methyl]indoles **4a** and **4b**. Oxidation of **4a,b** with 1 equiv of monoperoxyphthalic acid magnesium salt (MMPP) provided [(phenylsulfinyl)methyl]indoles **5a** and **5b**. Further reaction of **5a** with 1 equiv of MMPP led to bis-sulfoxide **6a** as a mixture of diastereomers.

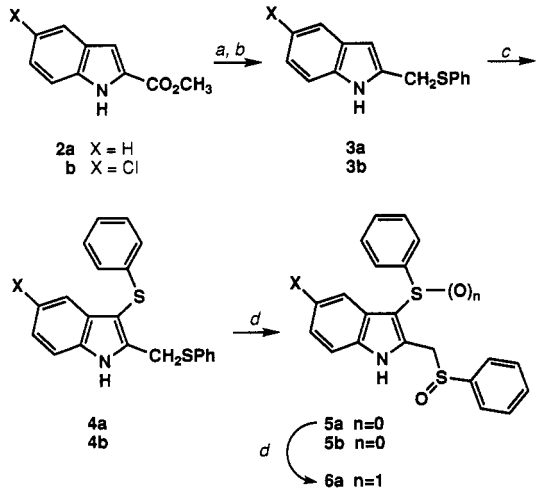
Reaction of indole-2-carboxylic acids **7a** and **7b** with diphenyl disulfide and sodium hydride in DMF gave 60% yields of 3-(phenylthio)indole-2-carboxylic acids **8a** and **8b**, which were converted to the methyl esters **9a,b** with (trimethylsilyl)diazomethane (Scheme II). Conversion of 5-chloro-3-(phenylthio)indole-2-carboxylic acid to the acid chloride by refluxing in chloroform with oxalyl chloride and a catalytic amount of DMF was complicated by loss of the phenylthio substituent. Although the byproduct could be minimized by utilizing short (20 min) reaction times, carboxamide **10** was more conveniently prepared from **8b** with BOP reagent [(benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate] and ammonia in DMF. Compounds **11–13** were also prepared in this fashion. Oxidation of **10** with 1 or 2 equiv of mCPBA or MMPP provided sulfoxide **14** and sulfone **1**, respectively.

Results. Screening of the Merck sample collection identified 2-[(phenylsulfinyl)methyl]-3-(phenylthio)indole **5a** as a potent inhibitor of HIV-1 RT (IC_{50} 63 nM). Further studies demonstrated that **5a** was highly selective for HIV-1 RT vs human DNA polymerases-α, -β, -γ, and -δ, HIV-2 RT, and RNase H, among others. As has been observed with other non-nucleoside RT inhibitors,[8-12] the inhibition potency of **5a** depended upon the identity of the template–primer substrate, indicating that it may be binding to the intact enzyme/template–primer complex. In MT-4 human T-lymphoid cells infected with $HTLV_{IIIb}$, **5a** at a concentration of 400 nM inhibited 95% of viral spread (CIC_{95}) as determined by p24 antigen assay. In rhesus monkeys, **5a** exhibited an iv plasma half-life of 105 min, but oral bioavailability was lacking. Anticipating that oxidation of the sulfide to a sulfoxide would be a primary metabolic route, the bis-sulfoxide **6a** was prepared and found to be 3 orders of magnitude less potent than

† Department of Drug Metabolism, West Point.
‡ Department of Virus and Cell Biology, West Point.
§ Department of New Lead Pharmacology, West Point.
‖ Department of Exploratory Chemistry, Rahway.
⊥ Current address: Ligand Pharmaceuticals, 9393 Towne Centre Drive, San Diego, CA 92121.
Deceased.

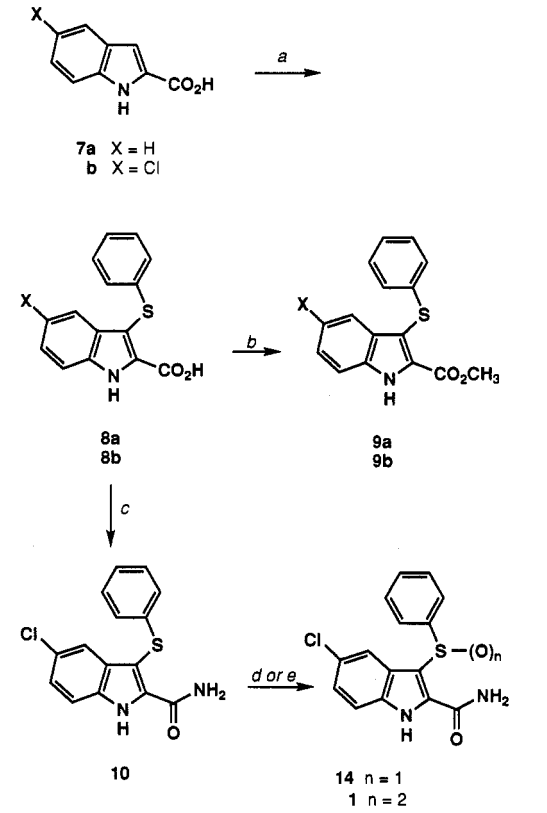
0022-2623/93/1836-1291$04.00/0

Scheme I[a]



[a] (a) $LiAlH_4$, THF, 0 °C, 1 h, 97%; (b) 3 equiv of n-Bu_3P, 3 equiv of PhSSPh, THF, 20 °C, 3 h, 74%; (c) 1.1 equiv of PhSSPh, 1.5 equiv of NaH, DMF, 20 °C, 6 h, 55%; (d) 1 equiv of MMPP, CH_3OH, 0 °C, 0.5 h, 46%.

Scheme II[a]



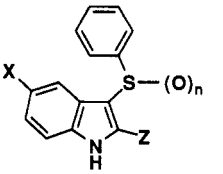
[a] (a) NaH, PhSSPh, DMF, 50 °C, 24 h, 60%; (b) $TMSCHN_2$, 20% CH_3OH–benzene, 20 °C, 100%; (c) BOP reagent, NH_3, DMF, 73%; (d) 1 equiv of MMPP, $CHCl_3/CH_3OH$, 50%; (e) 2.5 equiv of mCPBA, $CHCl_3/CH_3OH$, 20 °C, 6 h, 84%.

5a. An effort was thus initiated to further explore the novel structural class represented by (phenylthio)indole **5a**.

In addition to obtaining orally active compounds, a concomitant goal was to better enzyme inhibition potency to less than 10 nM. We were aware of a number of highly active, non-nucleoside RT inhibitors which incorporate *p*-chloroaniline as a structural element. For example, 8-Cl-TIBO (R86183) is 7-fold more potent than 8-H-TIBO (R82150).[8d] The 5-chloroindole **5b** was therefore synthesized, but to our disappointment **5b** was 2-fold less potent than **5a** (Table I). Of significance, however, was the observation that in related studies, **9b** was 16-fold *more* potent than **9a**. Preparation of amides based on ester **9b** provided additional increases in potency as exemplified by the primary amide **10**. In the MT-4 cell assay, amide **10** inhibited viral spread with a CIC_{95} value of 200 nM. From oral studies in rhesus monkeys and metabolism studies with rat liver microsomes, two active metabolites of **10** were identified as sulfoxide **14** and sulfone **1**.[16] Independent synthesis confirmed the structure and activity of the metabolites. The sulfone **1** was determined to be 5-fold more potent than **10** in the enzyme inhibition assay, while racemic sulfoxide **14** was nearly equipotent with **10**. Sulfone **1** was extremely potent in inhibiting viral spread in MT-4 cells (CIC_{95} 3 nM). In rhesus monkeys, **1** was 45% orally bioavailable with peak plasma levels of 2.0 μM 2 h after a 10 mg/kg dose as a suspension in methocel (HPLC determination).[17]

Sulfone **1** specifically inhibits HIV-1 RT. IC_{50}'s greater than 300 μM were observed for the following enzymes: recombinant human DNA polymerase α, HeLa cell DNA

Table I. Inhibition of HIV-1 RT in Vitro and in Cell Culture



compd	X	*n*	Z	IC_{50} (nM)[a]	CIC_{95} (nM)[b,c]
1	Cl	2	$CONH_2$	3	3
5a	H	0	$CH_2S(O)Ph$	63	400
5b	Cl	0	$CH_2S(O)Ph$	112	800
6a	H	1	$CH_2S(O)Ph$	72800	>3000
9a	H	0	CO_2CH_3	2500	>3000
9b	Cl	0	CO_2CH_3	156	1500
10	Cl	0	$CONH_2$	14	200
11	H	0	$CON(CH_3)_2$	87600	>3000
12	H	0	$CONHCH_3$	746	800
13	Cl	0	$CONHCH_3$	22	200
14	Cl	1	$CONH_2$	23	200
15[d]				36	50
16[e]				311	400
17[f]				101	400
18[g]				1320	3000

[a] The HIV-1 RT assay using rC·dG as template-primer was carried out in a reaction mixture (50 μL) containing 55 mM Tris-HCl (pH 8.2), 30 mM KCl, 30 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 1 mg/mL bovine serum albumin (BSA), 20 μg/mL rC·$dG_{(12-18)}$ (Pharmacia), 50 μM EGTA, 8 μM [^{3}H]dGTP, 0.01% (v:v) Triton X-100, and 0.25 units of recombinant HIV-1 RT (NY5 isolate). The remainder of the procedure was performed as previously described.[10a] The concentration that produced 50% inhibition (IC_{50}) is stated as the mean of at least three determinations. [b] Cell culture inhibitor concentrations (CIC_{95}) are defined as those which inhibited by >95% the spread of HIV-1 infection in suseptible cell culture. [c] The CIC_{95} was determined in MT-4 cells. MT-4 human T-lymphoid cells were maintained in RPMI 1640 medium containing 10% heat-inactivated bovine serum albumin. Cells were infected en masse at low multiplicity (0.01) with use of HIV-1 strain IIIb and were incubated for 24 h. At this time, cells were washed and distributed into 96-well microtiter dishes. Serial 2-fold dilutions of inhibitor were added to the wells and the cultures were maintained for 3 additional days. Virus spread was assessed by HIV-1 p24 core antigen ELISA. Control cultures in the absence of inhibitor were fully infected at 4 days. [d] **15**: 3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (L-697,661). [e] **16**: (+)-(5*S*)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (R82913). [f] **17**: 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (BI-RG-587). [g] **18**: 1-[3-(1-ethylamino)-2-pyridinyl]-4-[(5-methoxy-1*H*-indol-2-yl)carbonyl]piperazine (U-87201E).

Table II. Inhibition of Single Mutant HIV-1 RTs

compd	IC_{50} (nM) K103N[a]	IC_{50} (nM) Y181C[b]
1	116	71
5a	2570	2990
10	1460	1040
14	2760	1390
15	545	25000
16	7320	39500
17	57900	11300
18	33400	70200
1[c]	45	14
AZT-TP[c]	16	23

[a] Unless otherwise noted, the mutant HIV-1 RT assay using rC·dG as template-primer was carried out in a reaction mixture (50 μL) containing 55 mM Tris-HCl (pH 8.2), 30 mM KCl, 30 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 1 mg/mL bovine serum albumin (BSA), 6 μg/mL rC·$dG_{(12-18)}$ (Pharmacia), 50 μM EGTA, 16 μM [^{3}H]dGTP, 0.01% (v:v) Triton X-100, and 0.25 units of recombinant (K103N) HIV-1 RT (1 unit equals 5 pmol of [^{3}H]GMP incorporated in 45 min at 37 °C). The remainder of the procedure was performed as previously described.[10a] The average of at least three determinations is reported. [b] The assay conditions are the same as described in *a* above except 8 μg/mL rC·$dG_{(12-18)}$, 17 μM [^{3}H]dGTP, and 0.25 units of recombinant (Y181C) HIV-1 RT were used. [c] The average of at least three determinations using ribosomal RNA (16S, 23S) annealed to 5′-TAA CCT TGC GGC CGT-3′. The wild-type IC_{50} for 1 under these conditions is 1 nM and for AZT-TP is 53 nM.

polymerases-β, -γ, and -δ, HIV-2 RT, HIV-1 RNase H, Klenow fragment, Moloney murine leukemia virus RT, *Escherichia coli* RNA polymerase, and avian myeloblastosis virus RT. In contrast to the BHAP inhibitors described by Romero et al.[11] (in which one of the aryl groups of the bis-heteroarylpiperazine is 2-indolyl), tertiary amides of 3-(phenylthio)indole-2-carboxylic acid such as **11** were extremely poor RT inhibitors (Table I). In contrast, secondary amide **12** was 2 orders of magnitude more potent than **11**. Introduction of the 5-chloro substituent (**13**) led to a 30-fold increase in potency, similar to the initial observation in the 2-carboxylate series.

Antiviral therapy with non-nucleoside RT inhibitors may be compromised by the appearance of drug-resistant strains of HIV. Mutations in the RT which generate resistance to pyridinone RT inhibitors (e.g. L-697,661, **15**)[10a-c,e] in cell culture have been identified as lysine 103 → asparagine and tyrosine 181 → cysteine.[14] These residues appear to affect the binding of diverse non-nucleoside inhibitors.[18] Compared to the wild-type enzyme, the 103 and 181 mutant enzymes are also less sensitive to 9-Cl-TIBO (R82913, **16**),[8] nevirapine (BI-RG-587, **17**),[9a,b] and BHAP (U-87201E, **18**)[11] (Table II) (see also, ref 19). Improved activity against these mutant enzymes may be beneficial in terms of suppressing the emergence of drug-resistant strains of virus. As with other non-nucleoside inhibitors, (phenylsulfonyl)indole **1** is less active against these mutant enzymes than against the wild-type RT. However, in terms of absolute potency, **1** is 5-fold more potent than **15** against the 103 mutant and 350-fold more active vs the 181 mutant. In this study, a head-to-head comparison of AZT-TP with **1** revealed that they are nearly equipotent against the 103 and 181 mutant enzymes (Table II). Current studies are directed at identifying more potent analogs of **1** with useful activity against a broad spectrum of mutant RTs.

Summary. A series of highly potent, structurally novel, non-nucleoside RT inhibitors has been described. Low nanomolar concentrations of 5-chloro-3-(phenylsulfonyl)-indole-2-carboxamide (**1**) inhibit the HIV-1 RT enzyme in vitro and $HTLV_{IIIb}$ viral spread in MT-4 human T-lymphoid cells. Good oral bioavailability was observed in rhesus monkeys upon oral dosing of **1** as a suspension in methocel. When compared to other non-nucleoside inhibitors (e.g. **15–18**), **1** possesses improved inhibitory potency with respect to the wild-type RT, as well as the K103N and Y181C mutant enzymes. Additional studies within this class of inhibitors are in progress.

Acknowledgment. We thank Mr. John Moreau for elemental analyses, Dr. Harri Ramjit and Mr. Arthur Coddington for mass spectra, and Ms. Jean Kaysen for manuscript preparation.

References

(1) Mitsuya, M.; Yarchoan, R.; Broder, S. Molecular Targets for AIDS Therapy. *Science* **1990**, *249*, 1533–1544.
(2) De Clercq, E. HIV Inhibitors Targeted at the Reverse Transcriptase. *AIDS Res. Hum. Retrov.* **1992**, *8*, 119–134.
(3) (a) St. Clair, M. H.; Richards, C. A.; Spector, T.; Weinhold, K. J.; Miller, W. H.; Langlois, A. J.; Furman, P. A. 3′-Azido-3′-Deoxythymidine Triphosphate as an Inhibitor and Substrate of Purified Human Immunodeficiency Virus Reverse Transcriptase. *Antimicrob. Agents Chemother.* **1987**, *31*, 1972–1977. (b) Heidenreich, O.; Kruhoffer, M.; Grosse, F.; Eckstein, F. Inhibition of Human Immunodeficiency Virus 1 Reverse Transcriptase by 3′-Azidothymidine Triphosphate. *Eur. J. Biochem.* **1990**, *192*, 621–625.
(4) Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsch, M.; Jackson, G. G.; Durack, D. T.; Nusinoff-Lehrman, S. N. The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. A Double-Blind, Placebo-Controlled Trial. *N. Engl. J. Med.* **1987**, *317*, 192–197.
(5) Dalakas, M. C.; Illa, I.; Pezeshkpour, G. H.; Laukaitis, J. P.; Cohen, B.; Griffin, J. L. Mitochondrial Myopathy Caused by Long-Term Zidovudine Therapy. *N. Engl. J. Med.* **1990**, *322*, 1098–1105.
(6) Lambert, J. S.; Seidlin, M.; Reichman, R. C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. 2′,3′-Dideoxyinosine (ddI) in Patients with Aquired Immunodeficiency Syndrome or AIDS-Related Complex. A Phase 1 Trial. *N. Engl. J. Med.* **1990**, *322*, 1333–1240.
(7) (a) Larder, B. A.; Darby, G.; Richman, D. D. HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy. *Science* **1989**, *243*, 1731–1734. (b) Larder, B. A.; Kemp, S. D. Multiple Mutations in HIV-1 Reverse Transcriptase Confer High-Level Resistance to Zidovudine (AZT). *Science* **1989**, *246*, 1155–1158. (c) Rooke, R.; Tremblay, M.; Soudeyns, H.; DeStephano, L.; Yao, X.-J.; Fanning, M.; Montaner, J. S. G.; O'Shaughnessy, M.; Gelmon, K.; Tsoukas, C.; Gill, J.; Ruedy, J.; Wainberg, M. A. Canadian Zidovudine Multi-Centre Study Group. Isolation of Drug-Resistant Variants of HIV-1 from Patients on Long-Term Zidovudine Therapy. *AIDS* **1989**, *3*, 411–415. (d) Japour, A. J.; Chatis, P. A.; Eigenrauch, H. A.; Crumpacker, C. S. Detection of Human Immunodeficiency Virus Type 1 Clinical Isolates with Reduced Sensitivity to Zidovudine and Dideoxyinosine by RNA-RNA Hybridization. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 3092–3096. (e) St. Clair, M. H.; Martin, J. L.; Tudor-Williams, G.; Bach, M. C.; Vavro, C. L.; King, D. M.; Kellam, P.; Kemp, S. D.; Larder, B. A. Resistance to ddI and Sensitivity to AZT Induced by a Mutation in HIV-1 Reverse Transcriptase. *Science* **1991**, *253*, 1557–1559. (f) Kellam, P.; Boucher, C. A. B.; Larder, B. A. Fifth Mutation in Human Immunodeficiency Virus Type 1 Reverse Transcriptase Contributes to the Development of High-Level Resistance to Zidovudine. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 1934–1938.
(8) (a) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kulka, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Potent and Selective Inhibition of HIV-1 Replication in vitro by a novel series of TIBO Derivatives. *Nature* **1990**, *343*, 470–474. (b) Kukla, M. J.; Breslin, H. J.; Pauwels, R.; Fedde, C. L.; Miranda, M.; Scott, M. K.; Sherrill, R. G.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO). *J. Med. Chem.* **1991**, *34*, 746–751. (c) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) Derivatives. 2. *J. Med. Chem.* **1991**, *34*, 3187–3197. (d) Pauwels, R.; Andries, K.; Debyser, Z.; Kukla, M.; Schols, D.; Desmyter, J.; De Clercq, E.; Janssen, P. A. J. TIBO Derivatives: A New Class of Highly Potent and Specific Inhibitors of HIV-1 Replication. *Biochem. Soc. Trans.* **1992**, *20*, 509–512.

(9) (a) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. Inhibition of HIV-1 Replication by a Nonnucleoside Reverse Transcriptase Inhibitor. *Science* **1990**, *250*, 1411–1413. (b) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones. *J. Med. Chem.* **1991**, *34*, 2231–2241. (c) Klunder, J. M.; Hargrave, K. D.; West, M.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2. Tricyclic Pyridobenzoxazepinones and Dibenzoxazepinones. *J. Med. Chem.* **1992**, *35*, 1887–1897.

(10) (a) Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. Pyridinone Derivatives: Specific Human Immunodeficiency Virus Type 1 Reverse Transcriptase Inhibitors with Antiviral Activity. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6863–6867. (b) Saari, W. S.; Hoffman, J. M.; Wai, J. S.; Fisher, T. E.; Rooney, C. S.; Smith, A. M.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Stern, A. M.; Anderson, P. S. 2-Pyridinone Derivatives: A New Class of Nonnucleoside, HIV-1-Specific Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1991**, *34*, 2922–2925. (c) Wai, J. S.; Goldman, M. E. L-697,661. *Drugs Future* **1992**, *17*, 283–285. (d) Hoffman, J. M.; Wai, J. S.; Thomas, C. M.; Levin, R. B.; O'Brien, J. A.; Goldman, M. E. Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1 Specific Reverse Transcriptase Inhibitors. 1. Phthalimidoalkyl and -alkylamino Analogues. *J. Med. Chem.* **1992**, *35*, 3784–3791. (e) Saari, W. S.; Wai, J. S.; Fisher, T. E.; Thomas, C. M.; Hoffman, J. M.; Rooney, C. S.; Smith, A. M.; Jones, J. H.; Bamberger, D. L.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. S. Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 2. Analogues of 3-Aminopyridin-2(1*H*)-one. *J. Med. Chem.* **1992**, *35*, 3792–3802. (f) Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Emini, E. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Anderson, P. S. Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 3. Pyridyl and Phenyl Analogs of 3-Aminopyridin-2(1*H*)-one. *J. Med. Chem.* **1993**, *36*, 249–255.

(11) Romero, D. L.; Busso, M.; Tan, C.-K.; Reusser, F.; Palmer, J. R.; Poppe, S. M.; Aristoff, P. A.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G. Nonnucleoside Reverse Transcriptase Inhibitors that Potently and Specifically Block Human Immunodeficiency Virus Type 1 Replication. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8806–8810.

(12) (a) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E. A New Lead for Specific Anti-HIV-1 Agents: 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine. *J. Med. Chem.* **1989**, *32*, 2507–2509. (b) Baba, M.; Tanaka, H.; De Clercq, E.; Pauwels, R.; Balzarini, J.; Schols, D.; Nakashima, H.; Parno, C.-F.; Walker, R. T.; Miyasaka, T. Highly Specific Inhibition of Human Immunodeficiency Virus Type 1 By a Novel 6-Substituted Acyclouridine Derivative. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 1375–1381. (c) Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clercq, E. A New Class of HIV-1 Specific 6-Substituted Acyclouridine Derivatives: Synthesis and Anti-HIV-1 Activity of 5- or 6-Substituted Analogues of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymidine (HEPT). *J. Med. Chem.* **1991**, *34*, 349–357.

(13) (a) Franck, K. B.; Noll, G. J.; Connell, E. V.; Sim, I. S. Kinetic Interaction of Human Immunodeficiency Virus Type-1 Reverse Transcriptase with the Antiviral Tetrahydroimidazo[4,5,1-*jk*]-[1,4]-benzodiazepine-2-(1*H*)-thione Compound R82150. *J. Biol. Chem.* **1991**, *266*, 14232–14236. (b) White, E. L.; Buckheit, R. W., Jr.; Ross, L. J.; Germany, J. M.; Andries, K.; Pauwels, R.; Janssen, P. A. J.; Shannon, W. M.; Chirigos, M. A. A TIBO Derivative, R82913, is a Potent Inhibitor of HIV-1 Reverse Transcriptase with Heteropolymer Templates. *Antiviral Res.* **1991**, *16*, 257–266. (c) Wu, J. C.; Warren, T. C.; Adams, J.; Proudfoot, J.; Skiles, J.; Raghaven, P.; Perry, C.; Potocki, I.; Farina, P. R.; Grob, P. M. A Novel Dipyridodiazepinone Inhibitor of HIV-1 Reverse Transcriptase Acts Through a Non-Substrate Binding Site. *Biochemistry* **1991**, *30*, 2022–2026. (d) Grob, P. M.; Wu, J. C.; Cohen, K. A.; Ingraham, R. H.; Shih, C.-K.; Hargrave, K. D.; McTague, T. L.; Merluzzi, V. J. Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase: Nevirapine as a Prototype Drug. *AIDS Res. Hum. Retrov.* **1992**, *8*, 145–152. (e) Dueweke, T. J.; Kezdy, F. J.; Waszak, G. A.; Deibel, M. R., Jr.; Tarpley, W. G. The Binding of a Novel Bisheteroarylpiperazine Mediates Inhibition of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. *J. Biol. Chem.* **1992**, *267*, 27–30. (f) Debyser, Z.; Pauwels, R.; Andries, K.; Desmyter, J.; Engelborghs, Y.; Janssen, P. A. J.; De Clercq, E. Allosteric Inhibition of Human Immunodeficiency Virus Type 1 Reverse Transcriptase by Tetrahydroimidazo[4,5,1-*jk*]-[1,4]-benzodiazepine-2(1*H*)-one and -thione Compounds. *Mol. Pharmacol.* **1992**, *41*, 203–208.

(14) (a) Nunberg, J. H.; Schleif, W. A.; Boots, E. J.; O'Brien, J. A.; Quintero, J. C.; Hoffman, J. M.; Emini, E. A.; Goldman, M. E. Viral Resistance to Human Immunodeficiency Virus Type 1-Specific Pyridinone Reverse Transcriptase Inhibitors. *J. Virol.* **1991**, *65*, 4887–4892. (b) Byrnes, V. W.; Sardana, V. V.; Condra, J. H.; Schleif, W. A.; Schneider, C. L.; Waterbury, J. A.; Wolfgang, J. A.; Graham, D. J.; Gotlib, L.; Schlabach, A. J.; Wolanski, B. S.; Long, W. J.; Rhodes, A.; Titus, D. L.; Roth, E.; Blahy, O. M.; Emini, E. A. HIV-1 Reverse Transcriptase Residues That Influence Sensitivity to Nonnucleoside Inhibitors. *J. Cell. Biochem.* **1993**, Supplement 17E, in press.

(15) Atkinson, J. G.; Hamel, P.; Girard, Y. A New Synthesis of 3-Arylthioindoles. *Synthesis* **1988**, 480–481.

(16) Balani, S. K.; Goldman, M. E.; Kauffman, L. R.; Varga, S. L.; O'Brien, J. A.; Smith, S. J.; Olah, T. V.; Ramjit, H. G.; Schorn, T. W.; Pitzenberger, S. M.; Williams, T. M.; Rooney, C. S.; Theoharides, A. D. Biotransformation of 5-Chloro-3-phenylthioindole-2-carboxamide (L-734,005) in Rhesus Monkeys and Rat Liver Microsomes to a Potent HIV-1 Reverse Transcriptase Inhibitor. *Drug Metab. Dispos.* **1993**, in press.

(17) O'Brien, J. A.; Ostovic, D.; Schorn, T. W.; Smith, S. J.; Ruffing, T. L.; Siegl, P. K. S.; Goldman, M. E. A Rapid Bioassay for the Determination of Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitor Plasma Levels. *Life Sci.* **1993**, *52*, 243–249.

(18) (a) Condra, J. H.; Emini, E. A.; Gotlib, L.; Graham, D. J.; Schlabach, A. J.; Wolfgang, J. A.; Colonno, R. J.; Sardana, V. V. Identification of the Human Immunodeficiency Virus Reverse Transcriptase Residues That Contribute to the Activity of Diverse Nonnucleoside Inhibitors. *Antimicrob. Agents Chemother.* **1992**, *36*, 1441–1446. (b) Shaharabany, M.; Hizi, A. The Catalytic Functions of Chimeric Reverse Transcriptases of Human Immunodeficiency Viruses Type 1 and Type 2. *J. Biol. Chem.* **1992**, *267*, 3674–3678. (c) Shih, C.-K.; Rose, J. M.; Hansen, G. L.; Wu, J. C.; Bacolla, A.; Griffin, J. A. Chimeric Human Immunodeficiency Virus Type 1/Type 2 Reverse Transcriptases Display Reversed Sensitivity to Non-Nucleoside Analog Inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 9878–9882.

(19) Sardana, V. V.; Emini, E. A.; Gotlib, L.; Graham, D. J.; Lineberger, D. W.; Long, W. J.; Schlabach, A. J.; Wolfgang, J. A.; Condra, J. H. Functional Analysis of HIV-1 Reverse Transcriptase Amino Acids Involved in Resistance to Multiple Nonnucleoside Inhibitors. *J. Biol. Chem.* **1992**, *267*, 17526–17530.