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DIVISION DE NUEVAS CREACIONES
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E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 04-121782- -00003-0000
Fec: 2006-09-27 17:28:05 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 538 PETICION Folios: 2

Trámite : 011
Evento : 379
Actuación: 538

Referencia : Expediente No. 04.121.782
Asunto : Solicitud de patente para **COMPUESTOS NO NUCLEOSIDOS INHIBIDORES DE LA TRANSCRIPTAZA INVERSA, MEDICAMENTOS QUE LOS CONTIENEN Y METODOS TERAPEUTICOS QUE LOS UTILIZAN.**
Solicitante : **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Publicada en : La Gaceta No. 562 Del 31 de marzo de 2006.

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$ 194.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 35582 de 28 de diciembre de 2005.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá,
Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

COLO 09255 841 010 3
JDF/ASG/ID-000539/WPCL9255
Cns M-2006-00010758

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 06 - 65,872
FECHA : AGOSTO 28 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	48872306	28/08/2006	28,856,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	194,000.00
		TOTAL :	\$ 194,000.00

SON: CIENTO NOVENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº _____

06 09255-841-010-3

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04-121782

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **562** DE

FECHA **31** DE **MARZO DE 2006** EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **01** DE **AGOSTO DEL 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO__ _X_ _____

Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 8. 8-Aryloxymethyl- and 8-Arylthiomethyldipyridodiazepinones¹

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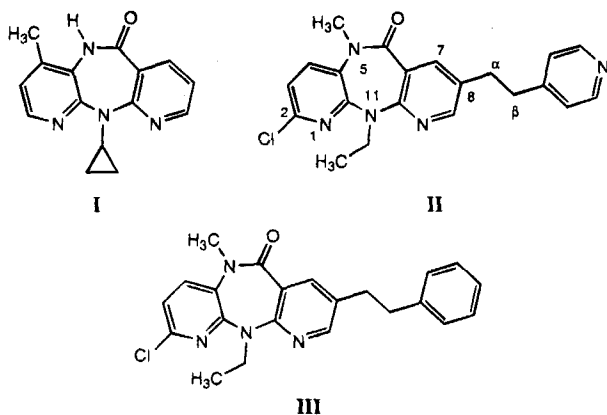
Received October 16, 1997

Nevirapine (**I**) is the first human immunodeficiency virus type 1 (HIV-1) nonnucleoside reverse transcriptase (RT) inhibitor to reach regulatory approval. As a result of a second generation program around the tricyclic core system of nevirapine, 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-(pyridin-4-yl)ethyl)-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**II**)^{1a} and 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-phenylethyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**III**)^{1a} were identified as broad spectrum HIV-1 RT inhibitors. A detailed examination of replacing either of the methylenes of the 8-ethyl linker of **II** or **III** is presented. It was found that 8-aryloxymethyl and 8-arylthiomethyl are the preferred pattern of substitution for potency against RT. The most potent compounds were further evaluated against a panel of clinically significant mutant RT enzymes (K103N, V106A, G190A, P236L) and in cytotoxicity and in vitro metabolism assays. The most potent compound was 2-chloro-8-phenylthiomethyl analogue **37** which displayed sub-100 nM activity against all HIV-1 RT enzymes tested.

Introduction

Nevirapine⁴ (Viramune, **I**) was the first nonnucleoside reverse transcriptase inhibitor (NNRTI) to receive regulatory approval for the treatment of HIV-1 infection and is currently used in combination with nucleoside RT inhibitors such as AZT, 3TC, D4T, and DDI.⁵ It has also been shown to have synergistic effects with the protease inhibitor saquinavir in vitro.⁶ Clinical trials examining combinations of nevirapine and other HIV-protease inhibitors also show great promise.⁷ Although combination therapy has become the standard of care, no single combination has proven completely effective in all patients and there is a need to develop new therapeutics with improved profiles.⁸

changes and rendering the enzyme incompetent.⁹ In the clinic, nevirapine monotherapy results in relatively rapid drug resistance due to mutation of the RT enzyme. Especially significant is the Y181C mutation which is the primary strain of resistant HIV-1 RT found in clinical isolates of patients on nevirapine monotherapy.¹⁰ Here and in the preceding paper^{1a} we present our successful design of a second generation inhibitor which retains nevirapine's favorable properties of wild-type RT potency, metabolic stability, good bioavailability and relatively low toxicity while adding broad spectrum activity against a variety of clinically relevant mutant RT enzymes. We found empirically that activity against wild-type (WT), Y181C, and Y188L enzymes provided good indication of potential potency against a larger number of mutants including those which have been identified in the clinical isolates of patients undergoing NNRTI monotherapy. As reported in the preceding paper, 8-arylalkyl substituents improve potency against several of these clinically significant mutants. The combination of the 8-substituent with a 2-halo substituent such as chlorine or fluorine as exemplified in compounds **II** and **III** was particularly effective. Modifications of the 8-ethyl linker of either of these compounds were not, however, fully explored and it was shown that this linker was a major site of metabolism.^{1a} The major focuses of this report are the modifications of this linker in order to improve potency and determining their effect on metabolic stability. We have found that replacing one of the carbon atoms of the linker with a heteroatom, such as N, O, or S, in combination with changes in the aryl component has a significant impact on the potency of inhibitors and metabolic stability. We have identified several compounds with good activity

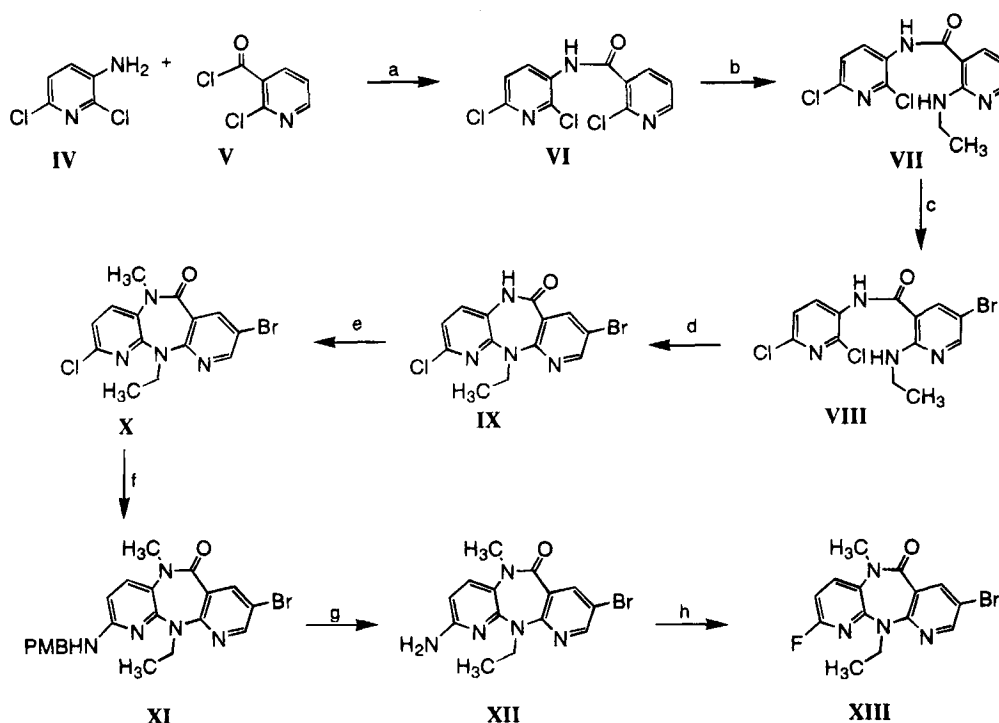


Nevirapine binds to an allosteric site on RT close to the polymerase active site inducing conformational

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Scheme 1. Synthesis of 8-Bromo-2-halo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one Starting Materials^a

^a (a) Pyridine, 1,4-dioxane, cyclohexane, 80%; (b) EtNH₂, xylenes, 165 °C, 60%; (c) Br₂, AcOK, AcOH, 88%; (d) NaHMDS, pyridine, 50 °C, 92%; (e) NaH, MeI, DMF, 50 °C, 88%; (f) *p*-methoxybenzylamine, 1,4-dioxane, 170 °C, 4 days, 47%; (g) TFA, 58%; (h) HF-pyridine, NaNO₂, 87%.

against a panel of competent mutant RT enzymes and improved metabolic stability relative to **II** or **III**.

Chemistry

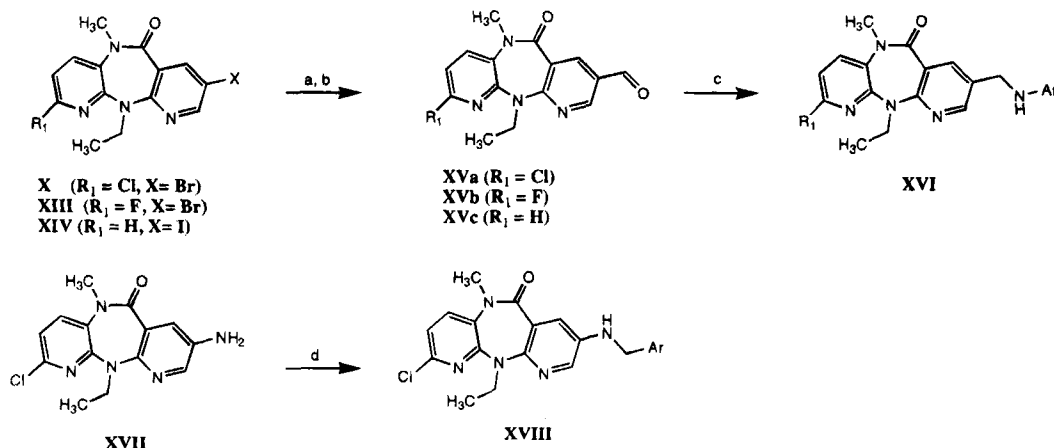
The synthesis of **X**, which was used as the starting material for most analogues reported herein, was accomplished from known 3-amino-2,6-dichloropyridine¹¹ (**IV**) and commercially available 2-chloronicotinic chloride¹² (**V**) as outlined in Scheme 1. Condensation of **IV** and **V** in the presence of pyridine afforded **VI** in good yield. The selective displacement of the 2'-chloro substituent of the pyridinecarboxamide ring with ethylamine produced **VII** which was regioselectively brominated, a result of the newly incorporated amine functionality, to give **VIII**.^{4b,13} This was a significant improvement over the synthesis of the 8-iodo compounds reported in the preceding paper which required the addition of several steps in order to manipulate a 8-nitro group, via diazonium chemistry, to desired iodo species.^{1a} Formation of the diazepinone ring in the presence of sodium hexamethyldisilazane produced **IX**. Use of sodium hydride in this reaction led to debromination as a significant side reaction.¹⁴ Compound **IX** was methylated under standard conditions to give the key 8-bromo intermediate **X**. The 2-fluoro analogue **XIII** was synthesized from **X** by displacement of the chloride with *p*-methoxybenzylamine followed by removal of the amine protecting group to give **XII**. Diazotization of **XII** followed by in situ conversion to the fluoride gave **XIII**.¹⁵ With these intermediates in hand, we turned our attention to the synthesis of our target compounds. All of the modifications of the linker reported herein were

synthetically accessible from the 8-halo compounds **X**, **XIII**, **XIV**,^{1a} or the 8-amino compound **XVII**^{1a} utilizing the methods outlined in Schemes 2–5.

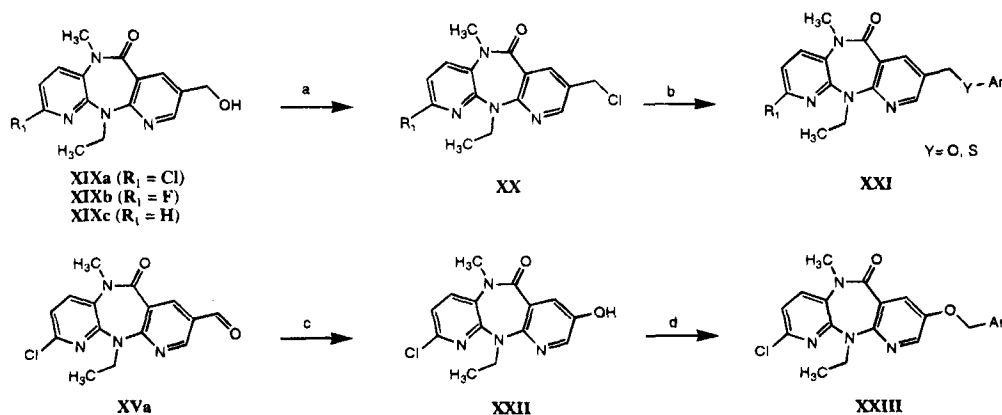
The synthesis of analogues containing the amino linker is shown in Scheme 2. Palladium-mediated cross coupling of **X**, **XIII**, or **XIV** with vinyltributyltin yielded the unstable 8-vinyl compounds, which were immediately subjected to ozonolysis to afford the corresponding aldehyde **XV** in good yields (57–81%). Reductive amination of aldehydes **XV** in methanol with NaCNBH₃ and acetic acid produced the β -nitrogen linked analogues **XVI**.¹⁶ A directly analogous procedure was used to produce the α -nitrogen linked analogues by reacting 8-amino analogue **XVII** with various benzaldehydes to yield compounds **XVIII**.

The oxygen and sulfur linked analogues were synthesized via complementary routes as shown in Scheme 3. Reduction of **XV** with NaBH₄ afforded **XIX**, which was converted to the corresponding chloride **XX** with SOCl₂ in CHCl₃. Reaction of **XX** with various phenolates or thiophenolates in a nonprotic solvent, such as THF or DMSO, gave the β -oxygen or sulfur compounds **XXI**. Compound **XXII** was produced by Baeyer–Villiger oxidation of **XVa** followed by in situ hydrolysis. The α -oxygen linked compounds **XXIII** were synthesized from pyridinol **XXII** via alkylation with benzyl halides.

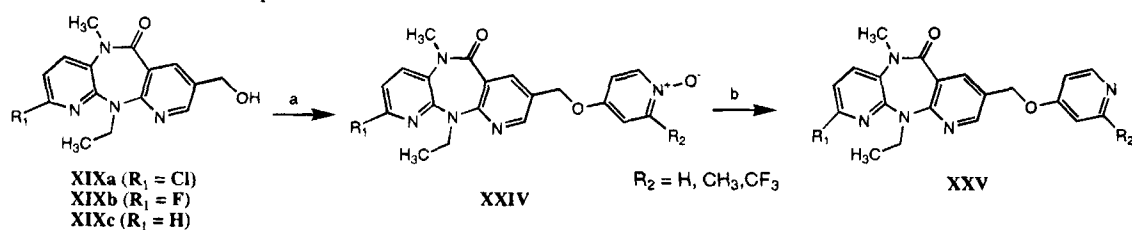
There were difficulties with these methods in certain cases. For instance the key pyridyl analogues **XXV** could not be efficiently produced via alkylation chemistry. The alkylation of **XX** with 4-hydroxypyridine leads predominately to N-substitution, with only trace amounts of the desired O-alkylated product **XXV**. Nu-

Scheme 2. Method A: Reductive Amination^a

^a (a) $\text{CH}_2\text{CHSnBu}_3$, $(\text{Ph}_3\text{P})_4\text{Pd}$, DMF; (b) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ followed by DMS; (c) ArNH_2 , AcOH, then NaCNBH_3 , AcOH; (d) ArCHO , AcOH, NaCNBH_3 , AcOH.

Scheme 3. Method B: Alkylation^a

^a (a) SOCl_2 , CHCl_3 ; (b) ArYH , base (NaH , NaHMDS , $t\text{-BuOK}$, etc.), DMSO or THF; (c) MCPBA, CH_2Cl_2 then MeOH; (d) NaH , ArCH_2Br , THF.

Scheme 4. Method C: Nucleophilic Aromatic Substitution^a

^a (a) KH , THF, then substituted 4-nitropyridine *N*-oxides; (b) PCl_3 , CHCl_3 .

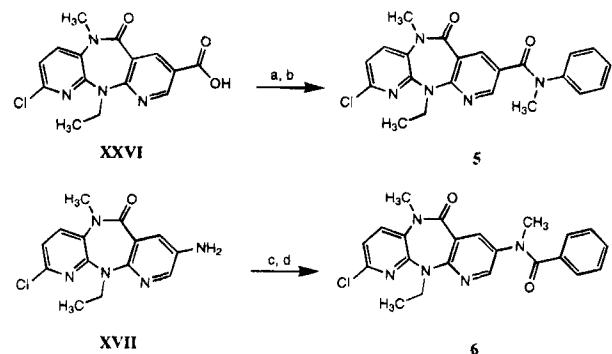
cleophilic aromatic substitution (Scheme 4) provided a successful alternative approach to these important compounds. Thus, reaction of the anion of **XIX** with 4-nitropyridine *N*-oxides provided **XXIV** in good yields. The parent pyridyl analogues **XXV** were produced via reduction with PCl_3 in CHCl_3 of **XXIV** followed by basic workup.

The amide linked analogues were synthesized as described in Scheme 5. Oxidation of **XIXa** with Jones reagent gave the starting acid **XXVI**. Amide **5** was synthesized in two steps from **XXVI** by treatment with oxalyl chloride followed by addition of *N*-methylaniline in 65% overall yield. Amide **6** was produced from **XVII**

via acylation with benzoyl chloride followed by alkylation with MeI.

Biological Results

The results obtained from testing the analogues against wild-type (WT) RT along with Y181C and Y188L mutant RT in a purified enzyme assay are presented in Table 1. Early on it was decided to focus on compounds with the 2-chloro substituent which improved mutant RT enzyme potency profiles in the alkyl linked series. The first question addressed was whether a heteroatom would be tolerated in the linker at the 8-position. It was found that the β -position is the

Scheme 5. Method D: Acylation^a

^a (a) (COCl)₂, CHCl₃; (b) *N*-methylaniline, CH₂Cl₂; (c) PhCOCl, DIPEA, CH₂Cl₂; (d) NaI, MeI, DMF.

preferred site for substitution with heteroatoms on the linker as demonstrated by compounds 1–4 (Table 1). The α -amino compound 1 showed no inhibition of Y188L, and the α -oxygen analogue 3 was a completely ineffective inhibitor at 1 μ M against either of the two mutants tested. The β -oxygen linked analogue 4 showed better potency vs Y188L mutant RT than the β -amino analogue 3. The next question addressed was whether there could be an improvement in the potency of the analogues with nitrogen containing linkers by introducing rigidity either by substitution or by adding oxidation on the linker. Compounds 5–7 were synthesized to answer this question. The *N*-methyl analogue 7 did not show improvement against Y188L RT and was significantly weaker against Y181C. In the preceding paper it was reported that the *cis*-olefin geometry of the two carbon linker was preferred. It was found that secondary amides in the 8-position are very weak inhibitors (<40% inhibition at 1 μ M against all three enzymes of the primary screen).¹⁷ The lack of activity was attributed to these amides adopting a transoid geometry of the aromatic ring at the 8-position relative to the tricyclic nucleus. The tertiary amides 5 and 6 were synthesized in order to bias the amide geometry to mimic the *cis*-olefin linker. Although these compounds were an improvement relative to the secondary amides, none of these amide analogues improved potency against the Y188L mutant relative the β -oxygen analogue 4.

It was clear that β -oxygen analogue 4 was the best of the first group of compounds tested with submicromolar activity against all three enzymes. In fact 4 proved to be slightly more potent against the Y188L mutant (0.64 vs 0.96 μ M) than the analogous phenethyl derivative III.^{1a} We examined the SAR of the phenyl ring of 4. Compounds 10–25 showed trends very similar to those reported for the alkyl linked counterparts. The trend of substitution at the meta position being preferred continued in this series with compounds 10 and 20 having potencies very comparable to that of 4. One notable exception was the *m*-dimethylamino analogue 22. There was a trend in WT-RT activity displayed by substituted phenyloxymethyl groups at the 8-position that suggested an electronic component to the phenyl ring in the pharmacophore of the inhibitor. It was noticed that with electron donating substituents, such as hydroxyl, the preferred position is meta while with

electron withdrawing groups such as fluoro ortho or para substitution is preferred (see compounds 9–14). Inhibitors with a meta hydrogen bond donor, especially nitrogen, display improved potency against Y188L mutant (see compounds 18–20, 24). In the preceding paper the mutant RT activity profile of the phenyl series was paralleled in the pyridyl series. However when pyridyl compound 29 was tested against the Y188L mutant it showed diminished activity relative to that of II. In the previously described alkyl linked series the 2-fluoro substituent improved potency vs the Y188L mutant.^{1a} The 2-fluoro compound 28, however, showed only marginally improved activity against the Y188L mutant. This information clearly showed a divergent SAR of the alkyl linked analogues compared to those reported here. We further investigated the pyridyl series with an emphasis on improving the Y188L activity while maintaining potency against the other RT enzymes. In the alkyl linked series there was a preference for the pyrid-4-yl compound II which was the most potent of the pyridine isomers. The 3-pyridyl analogue 26, however, showed virtually identical activity against the Y181C and Y188L mutants. We were able to improve Y188L mutant RT potency by incorporating electron donating meta substitution as shown with 2-methylpyridyl compound 30. The trifluoromethyl analogue 31 and the *N*-oxides 32–36 displayed reduced potency against Y188L relative to 30, consistent with a preference for an electron rich aromatic ring at the 8-position.

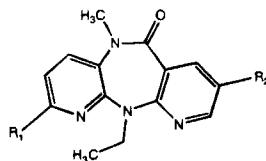
Since there was divergent SAR in the β -oxygen linked series we decided to examine the effect of β -sulfur substitution on the linker of II. Interestingly, the phenylthiomethyl compound 37 proved to be among the most potent nonnucleoside RT inhibitors reported. It displayed IC₅₀'s of ~100 nM or less against all mutants tested. Sulfur oxidation products 38 and 39 showed reduced activity especially against the Y188L mutant. The trend of the phenyl moiety being preferred over the pyridyl ring continued in this series as well with 41 showing weaker activity against the Y188L mutant. Compounds 42 and 43, however, were quite potent against Y188L RT. Both compounds have a nitrogen in the equivalent of the meta position which is consistent with trends of the other series.

Secondary Tests

Compounds with good profiles in the primary screening against the WT, Y181C, and Y188L enzymes were further evaluated for in vitro metabolic stability in human liver microsomes,¹⁸ cytotoxicity,¹⁹ and activity against a panel of mutant RT enzymes.¹⁹ Nevirapine (I) itself has a very slow rate of metabolism in human liver microsomes (2 (pmol/min)/mg of microsomal protein) and low cytotoxicity (>500 μ M).

The in vitro metabolism data for some representative examples are shown in Table 2. Compound II, which served as the benchmark for this work, was metabolized at a rate of 145 (pmol/min)/mg of microsomal protein. It should be noted that II was metabolized significantly faster than nevirapine (I) in this in vitro microsomal assay. However, the rate in this assay was virtually identical to delavirdine (U-90152), the only other approved NNRTI.²⁰ The β -oxygen linked analogues all

Table 1. Inhibition of HIV-1 RT



no.	R ₁	R ₂	method	IC ₅₀ (μM) or % inhibition at 1 μM		
				WT RT	Y181C RT	Y188L RT
II	Cl	CH ₂ CH ₂ (pyrid-4-yl)		0.08	0.12	1.85
III	Cl	CH ₂ CH ₂ Ph		0.05	0.15	0.96
1	Cl	NHCH ₂ Ph	A	0.26	0.39	0%
2	Cl	CH ₂ NHPh	A	0.08	0.37	28%
3	Cl	OCH ₂ Ph	B	20%	0%	0%
4	Cl	CH ₂ OPh	B	0.11	0.06	0.64
5	Cl	C(O)N(CH ₃)Ph	D	15%	20%	46%
6	Cl	N(CH ₃)C(O)Ph	D	0.21	22%	13%
7	Cl	CH ₂ N(CH ₃)Ph	B	0.59	18%	17%
8	Cl	CH ₂ NH(Ph- <i>m</i> -NH ₂)	A	0.06	0.100	19%
9	Cl	CH ₂ O(Ph- <i>o</i> -OH)	B	0.10	0.35	15%
10	Cl	CH ₂ O(Ph- <i>m</i> -OH)	B	0.13	0.25	0.78
11	Cl	CH ₂ O(Ph- <i>p</i> -OH)	B	0.21	27%	21%
12	Cl	CH ₂ O(Ph- <i>o</i> -F)	B	0.17	0.57	13%
13	Cl	CH ₂ O(Ph- <i>m</i> -F)	B	24%	11%	16%
14	Cl	CH ₂ O(Ph- <i>p</i> -F)	B	0.28	1.66	16%
15	Cl	CH ₂ O(Ph- <i>o</i> -CO ₂ Me)	B	25%	2%	2%
16	Cl	CH ₂ O(Ph- <i>m</i> -CO ₂ Me)	B	0.70	23%	11%
17	Cl	CH ₂ O(Ph- <i>p</i> -CO ₂ Me)	B	0.80	33%	0%
18	Cl	CH ₂ O(Ph- <i>m</i> -CO ₂ H)	B ^a	0.09	0.55	20%
19	Cl	CH ₂ O(Ph- <i>m</i> -CONH ₂)	B ^b	0.13	0.28	0.34
20	Cl	CH ₂ O(Ph- <i>m</i> -NH ₂)	B ^c	0.05	0.10	0.37
21	Cl	CH ₂ O(Ph- <i>m</i> -NO ₂)	B	0.17	0.35	0%
22	Cl	CH ₂ O(Ph- <i>m</i> -NMe ₂)	B	0%	0%	7%
23	Cl	CH ₂ O(Ph- <i>m</i> -OMe)	B	0.10	0.28	34%
24	Cl	CH ₂ O(indol-4-yl)	B	0.33	0.71	1.36
25	Cl	CH ₂ O(indol-5-yl)	B	0.31	0.09	28%
26	Cl	CH ₂ O(pyrid-3-yl)	B	0.19	0.26	16%
27	H	CH ₂ O(pyrid-4-yl)	C	0.02	0.14	5.52
28	F	CH ₂ O(pyrid-4-yl)	C	0.05	0.19	30%
29	Cl	CH ₂ O(pyrid-4-yl)	C	0.07	0.26	17%
30	Cl	CH ₂ O(2-methylpyrid-4-yl)	C	0.03	0.03	0.23
31	Cl	CH ₂ O(2-trifluoromethylpyrid-4-yl)	C	0.04	0.07	45%
32	H	CH ₂ O(pyrid-4-yl <i>N</i> -oxide)	C	0.21	1.34	0%
33	F	CH ₂ O(pyrid-4-yl <i>N</i> -oxide)	C	0.03	0.30	31%
34	Cl	CH ₂ O(pyrid-4-yl <i>N</i> -oxide)	C	0.23	39%	0%
35	Cl	CH ₂ O(2-methylpyrid-4-yl <i>N</i> -oxide)	C	0.10	0.21	4.31
36	Cl	CH ₂ O(2-trifluoromethylpyrid-4-yl <i>N</i> -oxide)	C	0.12	0.27	34%
37	Cl	CH ₂ SPh	B	0.02	0.01	0.03
38	Cl	CH ₂ S(O)Ph	B ^d	0.07	0.14	2.42
39	Cl	CH ₂ SO ₂ Ph	B ^d	0.10	0.06	11.0
40	Cl	CH ₂ S(pyrimidin-2-yl)	B	0.03	0.06	30%
41	Cl	CH ₂ S(pyrid-4-yl)	B	0.02	0.05	42%
42	Cl	CH ₂ S(purin-6-yl)	B	0.07	0.09	0.13
43	Cl	CH ₂ S(1- <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-4-yl)	B	0.05	0.07	0.12

^a From **16** by treatment with LiOH. ^b From **18** by treatment with (COCl)₂ followed by NH₃. ^c From **21** by treatment with SnCl₂/HCl. ^d From **37** by treatment with MCPBA.

showed a reduced rate of metabolism relative to the analogous previously reported ethyl linked analogues supporting the initial hypothesis leading to the design of these compounds. The phenoxymethyl compound **4** showed a rate similar to **II** and half that of the phenethyl analogue **III**,^{1a} while displaying a marginal improvement in the enzymatic profile. Major metabolites of **4** were identified as phenyl ring hydroxylated derivatives. The potent *m*-hydroxyphenyl analogue **10** was unfortunately metabolized nearly twice as fast as **4**. The pyridyloxymethyl series, represented by compounds **28** and **29**, showed a marked improvement in their rate of in vitro metabolism. The primary metabolites of **28** and **29** were identified as the *N*-oxides by

LC-MS and comparison to authentic samples. The *N*-oxide **33** was metabolized at a rate approximately 5 times slower than **28**. In contrast to the β -oxygen substitution, the β -sulfur substitution increased the rate of in vitro metabolism relative to **II**. Compound **37** was consumed at rate approximately 3 times faster than **4**. The sulfone **39**, which was identified as a metabolite of **37**, was metabolized at nearly twice the rate relative to **4**. Replacement of the phenyl ring of **37** with heterocycles did not result in a significant improvement in rates of metabolism (compounds **41**–**43** vs compound **37**).

A few compounds were tested for in vivo metabolism in rat. The pyridyloxymethyl compounds **28** and **29**

Table 2. In Vitro Metabolism in Human Liver Microsomes

no.	[(pmol/min)/mg of microsomal protein]	no.	[(pmol/min)/mg of microsomal protein]
I	2	29	53
II	145	30	371
III	288	31	206
4	171	33	9
10	318	37	554
12	264	39	322
19	292	41	372
20	95 ^a	42	591
24	208	43	336
25	177	U-90152	144
28	41		

^a Nonlinear rate.**Table 3.** MTT Toxicity Assay

no.	CC ₃₀ (μM)	no.	CC ₃₀ (μM)
2	>60	27	>256
4	>60	28	160
8	60	29	>120
10	~50	30	>256
18	250	37	>60
19	130	38	45
20	60	42	25
24	>30	43	40

showed a metabolic profile similar to that observed in the in vitro studies with the *N*-oxides of the 8-pyridyl moiety being the predominant metabolite. The bioavailabilities of **28** and **29** were found to be 69 ± 9% and 57 ± 6%, respectively, in this system. The bioavailability of the phenylthiomethyl derivative **37** was below quantitation limits in this assay. The observed drop in bioavailability for **37** could be suggested by rate of in vitro metabolism in rat which was 2831 (pmol/min)/mg of rat microsomal protein which was approximately 10 times faster than either **28** or **29** (224 and 296 (pmol/min)/mg for **28** and **29** respectively).

Due to some observations of toxicity associated with 2-substituted analogues all compounds were screened in an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] cellular assay.^{1b,19} The cytotoxicity of the 8-substituted series in general is relatively low with most displaying CC₃₀'s above 60 μM. Compounds with a *m*-amino or *m*-hydroxy aromatic substituent did exhibit a trend toward increased toxicity (Table 3, compounds **8**, **10**, and **20**), as did the arylthiomethyl series. Compounds **42** and **43** which are two of the more potent compounds were among the most toxic of those reported here. The purinylthiomethyl analogue **42** was the most toxic of the compounds reported herein but still is relatively less toxic than the highly potent but toxic 2-azaindole series reported previously which were approximately 6 μM in the MTT assay.^{1b}

With a goal to develop a broad spectrum RT inhibitor, we further evaluated many compounds against a panel of mutant RT enzymes. Although, in general, the Y188L was the most resistant of the mutant RT enzymes tested, some compounds with relatively weak Y188L activity still displayed good activity against several other clinically significant mutants (see Table 4). Compounds **4** and **37** showed excellent activity against all mutants tested and showed no activity against calf thymus DNA polymerase-α at 50 μg/mL.^{4a,17} The phenylthiomethyl analogue **37** was the most potent compound and showed excellent broad spectrum activ-

Table 4. Mutant HIV-1 RT Panel Data

no.	K103N (μM)	V106A (μM)	G190A (μM)	P236L (μM)
I	1.85	1.48	3.93	0.08
II	0.12	0.55	0.03	0.11
III	0.05	0.84	0.12	0.71
2	0.05	0.51	0.80	0.23
4	0.02	0.21	0.01	0.08
18	0.19	0.16	0.04	0.14
23	0.13	0.22	NT ^a	0.29
27	0.05	0.30	0.01	0.08
28	0.04	0.13	0.05	0.11
29	0.07	0.18	0.12	0.22
37	0.03	0.06	0.04	0.05

^a NT= not tested.**Table 5.** Inhibition of HIV-1_{IIIB} Replication in C8166 Cells

no.	IC ₅₀ (nM) ^a	IC ₉₀ (nM) ^b
4	50	113
20	19	36
29	6	24
37	5	13

^a Inhibitory concentration of compound producing a 50% reductions in the centers of syncytia. ^b Inhibitory concentration of compound producing a 90% reductions in the centers of syncytia. See ref 4a.

ity. The compound was further investigated in the Chow and Hirsch protocol which tests the ability of compounds or mixtures of compounds to eradicate HIV-1 virus from chronically infected peripheral blood mononuclear cell (PBMC) cultures.²¹ Compound **37** alone, at 5 μM, effectively suppressed viral replication and p24 levels from the cell cultures fell to or below background level by the fourth week of treatment. No virus breakthrough was observed during the 6 weeks following drug removal at week 7. Qualitative PCR, which was able to detect 1 copy of HIV gene per approximately 7600 noninfected cells, showed no HIV-1 specific DNA's from these cultures.²²

A select few compounds including **37** were tested for their ability to inhibit syncytia formation in cell cultures infected with wild-type HIV-1_{IIIB} virus (Table 5).^{4a} Activity in cell culture correlated well with the enzyme data, and all compounds tested showed activity in cell culture. Compound **37** was again the most potent among those tested with an IC₉₀ of 13 nM but the 4-pyridyloxymethyl analogue **29** also was quite potent in this assay with an IC₉₀ of 24 nM.

Conclusion

The multidrug or cocktail approach for the treatment of HIV-1 infection has shown great promise.^{4,5} However with the emergence of resistance there will be a continued need for pharmaceuticals with improved profiles for use in the cocktails of the future. We have shown that the 2-halo-8-aryloxymethyl- and the 2-halo-8-arylthiomethyl-5,11-dihydro-11-ethyl-5-methyl-6-*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-ones are effective inhibitors of wild-type and clinically relevant mutant RT enzymes. The 8-aryloxymethyl compounds possess improved activity and metabolic stability relative to the ethyl linked analogues while maintaining low cytotoxicity. These attributes are prerequisites to the development of new therapeutics and progress in this regard will be the subject of future reports.

Experimental Section

General Chemical Methods. Chromatography was performed on silica gel. Melting points were determined on a Fisher-Johns melting point apparatus in celsius (°C) and are uncorrected. ¹H NMR spectra were recorded in CDCl₃ at 270 MHz on a Bruker AC-270 referencing to solvent unless otherwise noted with *J* values reported in hertz. Mass spectra were performed by Oneida Laboratories, Oneida, NY. High-resolution mass spectra were performed by the Department of Analytical Sciences of Boehringer Ingelheim Pharmaceuticals. Elemental analyses were performed by either Midwest Microanalytical Laboratories, Indianapolis, IN, or Quantitative Technologies, Inc., Whitehouse, NJ.

Preparation of 2-Halo-8-bromo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one Derivatives X and XIII. (a) *N*-(2,6-Dichloro-3-pyridinyl)-2-chloro-3-pyridinecarboxamide (VI). 3-Amino-2,6-dichloropyridine¹¹ (IV) (48.9 g, 0.30 mol) was dissolved in 1,4-dioxane (170 mL), and cyclohexane (110 mL) and pyridine (24.3 mL, 0.30 mol) were added. The 2-chloronicotinoyl chloride¹² (V) (52.8 g, 0.3 mol) in 1,4-dioxane (85 mL) was then added dropwise over a 1 h period. The resultant white suspension was stirred for 16 h and filtered. The solid was washed with H₂O, 1:1 hexanes/EtOAc (200 mL each), suspended in 1:1 CH₂Cl₂/H₂O (2 L), stirred for 1 h and refiltered. The CH₂Cl₂ layer was separated and concentrated, and the combined solid was washed with H₂O, EtOAc, and hexanes (150 mL each) and dried in vacuo at 60 °C to afford VI (72.7 g, 80%): mp 197–198; ¹H NMR 8.98 (br s, 1H), 8.90 (d, *J* = 8.5, 1H), 8.58 (dd, *J* = 4.8, 1.9, 1H), 8.31 (dd, *J* = 7.7, 1.9, 1H), 7.46 (dd, *J* = 7.7, 4.8, 1H), 7.36 (d, *J* = 8.5, 1H); CIMS (CH₄) 302 (MH⁺). Anal. (C₁₁H₆Cl₃N₃O) C, H, N.

(b) *N*-(2,6-Dichloro-3-pyridinyl)-2-ethylamino-3-pyridinecarboxamide (VII). A mixture of VI (12.0 g, 39.8 mmol), ethylamine (3.6 g, 80.7 mmol), and 30 mL of xylenes in a sealed vessel was heated at 165 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with H₂O, and the mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated, and the resulting solid was washed with EtOAc and hexanes to give VII (7.4 g, 60%), suitable for use in the next reaction: mp 110–112; ¹H NMR 8.76 (d, *J* = 8.0, 1H), 8.33 (dd, *J* = 4.8, 1.7, 1H), 8.19 (s, 1H), 7.96 (br s, 1H), 7.74 (dd, *J* = 7.8, 1.7, 1H), 7.33 (d, *J* = 8.0, 1H), 6.58 (dd, *J* = 7.8, 4.83, 1H), 3.54 (m, 2H), 1.28 (t, *J* = 7.0, 3H); CIMS (CH₄) 311 (MH⁺). Anal. (C₁₃H₁₂Cl₂N₄O) C, H, N.

(c) *N*-(2,6-Dichloro-3-pyridinyl)-5-bromo-2-ethylamino-3-pyridinecarboxamide (VIII). To a solution of VII (7.4 g, 24 mmol) and KOAc (2.8 g, 28 mmol) in 90 mL of AcOH was added Br₂ (1.2 mL, 23 mmol). After 15 min, the reaction mixture was diluted with H₂O, and the precipitate was collected by suction filtration to give VIII (8.2 g, 88%), suitable for use in the next reaction: mp 195–196; ¹H NMR 8.69 (d, *J* = 8.5, 1H), 8.33 (d, *J* = 2.3, 1H), 8.09 (br s, 1H), 7.89 (br s, 1H), 7.79 (d, *J* = 2.3, 1H), 7.34 (d, *J* = 8.5, 1H), 3.51 (m, 2H), 1.27 (t, *J* = 7.2, 3H); CIMS (CH₄) 389 (MH⁺). Anal. (C₁₃H₁₁BrCl₂N₄O) C, H, N.

(d) 8-Bromo-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (IX). To a solution of VIII (5.9 g, 15 mmol) in 30 mL of pyridine at 50 °C under argon was added by syringe a 1.0 M solution of sodium hexamethyldisilazide in THF (31.5 mL, 31.5 mmol). After 10 min, the reaction mixture was diluted with ice water and allowed to stir for 2 h. The resultant orange-yellow precipitate was collected by suction filtration and air-dried to give IX (4.9 g, 92%): mp 262–263; ¹H NMR 8.48 (d, *J* = 2.5, 1H), 8.25 (d, *J* = 2.5, 1H), 8.04 (br s, 1H), 7.25 (d, *J* = 8.1, 1H), 7.05 (d, *J* = 8.1, 1H), 4.18 (q, *J* = 7.0, 2H), 1.24 (t, *J* = 7.0, 3H); CIMS (CH₄) 353 (MH⁺). Anal. (C₁₃H₁₀BrClN₄O) C, H, N.

(e) 8-Bromo-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (X). To a solution of IX (4.9 g, 14 mmol) in DMF (140 mL) was added NaH (0.86 g, 18 mmol), and the mixture was heated to 50 °C for 30 min. The mixture was cooled to room temperature and treated with MeI (0.90 mL, 15 mmol). After 1.5 h, the mixture

was carefully diluted with H₂O and filtered, and the solid was washed with petroleum ether and dried to give X (4.45 g, 88%): mp 190–192; ¹H NMR 8.42 (d, *J* = 2.5, 1H), 8.19 (d, *J* = 2.5, 1H), 7.44 (d, *J* = 8.2, 1H), 7.12 (d, *J* = 8.2, 1H), 4.13 (q, *J* = 7.0, 2H), 3.48 (s, 3H), 1.24 (t, *J* = 7.0, 3H); CIMS (CH₄) 367 (MH⁺). Anal. (C₁₄H₁₂BrClN₄O) C, H, N.

(f) 8-Bromo-5,11-dihydro-11-ethyl-2-(((4-methoxyphenyl)methyl)amino)-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XI). A pressure tube was charged with X (3.7 g, 10 mmol), *p*-methoxybenzylamine (3 mL, 23 mmol), and 1,4-dioxane (15 mL), sealed, and heated to 170 °C in a sand bath. An additional 1 mL of the amine was added each day. After 4 days the mixture was cooled, diluted with saturated aqueous NH₄Cl and extracted with EtOAc. The organics were washed with H₂O, saturated aqueous NH₄Cl and brine, then dried over MgSO₄ and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes) followed by recrystallization from EtOAc/hexanes to give XI (2.2 g, 47%): mp 151–154; ¹H NMR 8.36 (d, *J* = 2.3, 1H), 8.15 (d, *J* = 2.3, 1H), 7.26 (d, *J* = 8.6, 2H), 7.24 (d, *J* = 8.7, 1H), 6.87 (d, *J* = 8.6, 2H), 6.17 (d, *J* = 8.7, 1H), 4.78 (t, *J* = 5.5, 1H), 4.41 (d, *J* = 5.5, 1H), 4.04 (q, *J* = 7.0, 1H), 3.80 (s, 3H), 3.41 (s, 3H), 1.20 (t, *J* = 7.0, 3H); CIMS (CH₄) 468 (MH⁺). Anal. (C₂₂H₂₂BrN₅O₂) C, H, N.

(g) 2-Amino-8-bromo-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XII). Compound XI (2.2 g, 4.7 mmol) was dissolved in TFA (25 mL). The mixture turned gradually orange and then red. The excess TFA was removed by rotary evaporation. To the yellow-orange residue was added 3% aqueous NH₄OH, and after 3 h the mixture was extracted with EtOAc and the organic layer was washed with brine, dried over MgSO₄, and concentrated. The resulting solid was recrystallized (EtOAc/hexanes) to afford XII (0.949 g, 58%): mp 204–208; ¹H NMR 8.36 (d, *J* = 2.6, 1H), 8.16 (d, *J* = 2.6, 1H), 7.27 (d, *J* = 8.5, 1H), 6.29 (d, *J* = 8.7, 1H), 4.39 (br s, 2H), 4.04 (q, *J* = 7.0, 1H), 3.43 (s, 3H), 1.22 (t, *J* = 7.0, 3H); CIMS (CH₄) 348 (MH⁺). Anal. (C₁₄H₁₄BrN₅O) C, H, N.

(h) 5,11-Dihydro-11-ethyl-2-fluoro-8-bromo-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XIII). A plastic centrifuge tube was charged with XII (0.50 g, 1.4 mmol). HF-pyridine (10 mL) was added, and the resulting suspension was cooled to 0 °C. NaNO₂ was added in several portions over 10 min to produce a purple solution. The mixture was then capped and stirred for 16 h. The reaction mixture was poured onto ice and 6 N NaOH. EtOAc was added, and the mixture was filtered. The filtrate was separated, and the organic layer was washed with brine, dried over MgSO₄, and concentrated. Purification by flash chromatography (EtOAc/hexanes) and recrystallization (EtOAc/hexanes) afforded XIII (0.44 g, 87%): mp 154–156; ¹H NMR 8.41 (d, *J* = 2.3, 1H), 8.20 (d, *J* = 2.3, 1H), 7.58 (app. t, *J* = 8, 1H), 6.74 (dd, *J* = 8.5, 3.8, 1H), 4.11 (q, *J* = 7.0, 1H), 3.49 (s, 3H), 1.262 (t, *J* = 7.0, 3H); CIMS (CH₄) 351 (MH⁺). Anal. (C₁₄H₁₂BrFN₄O) C, H, N.

Method A. Preparation of 2-Chloro-5,11-dihydro-11-ethyl-8-formyl-5-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XVa, R1 = Cl). A solution of X (R1 = Cl, X = Br) (4.50 g, 12.2 mmol) in DMF (50 mL) was treated with Pd(PPh₃)₄ (0.28 g, 24 mmol) followed by vinyltributyltin (3.8 mL, 12.9 mmol) and heated to 90 °C with stirring. After 2.5 h the mixture was poured into H₂O and extracted with CH₂Cl₂ (4 × 100 mL) and EtOAc (2 × 100 mL). The combined organics were washed with 15% aqueous NH₄OH (2 × 100 mL) and brine (2 × 100 mL), then dried over Na₂SO₄ and concentrated, and the gross impurities were removed by rapid flash chromatography (gradient hexanes to EtOAc) to give the unstable 2-chloro-5,11-dihydro-11-ethyl-5-methyl-8-vinyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (100%) which was dissolved in 1:1 CH₂Cl₂/MeOH (40 mL) and cooled to –78 °C. This solution was then saturated with ozone, and a stream of ozone was bubbled through for 10 min more while stirring. The mixture was warmed to ambient temperatures and quenched with excess dimethyl sulfide. The mixture was then concentrated, and the residue was purified by flash chroma-

tography (gradient of hexanes to 1:1 hexanes/EtOAc) to give **XVa** (1.9 g, 81%); mp 199–201; ^1H NMR 10.00 (s, 1H), 8.84 (d, $J = 2.3$, 1H), 8.56 (d, $J = 2.3$, 1H), 7.48 (d, $J = 8.3$, 1H), 7.18 (d, $J = 8.3$, 1H), 4.29 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.31 (t, $J = 7.0$, 3H); CIMS (CH_4) 317 (MH^+). Anal. ($\text{C}_{15}\text{H}_{13}\text{ClN}_4\text{O}_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-8-formyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XVb, R1 = F). Starting from **XIII** by a procedure analogous to that used for preparation of **XVa**: 72%; mp 133–134; ^1H NMR 10.00 (s, 1H), 8.84 (d, $J = 2.3$, 1H), 8.57 (d, $J = 2.3$, 1H), 7.63 (dd, $J = 8.5$, 7.0, 1H), 6.80 (dd, $J = 8.5$, 3.9, 1H), 4.26 (q, $J = 7.0$, 2H), 3.50 (s, 3H), 1.32 (t, $J = 7.0$, 3H); CIMS (CH_4) 301 (MH^+). Anal. ($\text{C}_{15}\text{H}_{13}\text{FN}_4\text{O}_2$) C, H, N.

Preparation of Compounds XVI. 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylamino)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (2) (R1 = Cl, Ar = Ph). Compound **XVa** (50 mg, 0.16 mmol) was dissolved/suspended in MeOH (2 mL) and treated with NaBH_3CN (30 mg, 0.47 mmol) followed by aniline (43 μL , 4.7 mmol). The mixture was stirred for 5 min, and then AcOH (20 μL , 0.35 mmol) was added. After an additional 3 h at room temperature the mixture was made alkaline with 15% aqueous NaOH, and the white suspension was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organics were washed with brine, dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient) to give **2** (31 mg, 50%); mp 79–80; ^1H NMR 8.40 (d, $J = 2.4$, 1H), 8.09 (d, $J = 2.4$, 1H), 7.41 (d, $J = 8.3$, 1H), 7.15 (dd, $J = 7.7$, 7.5, 2H), 7.08 (d, $J = 8.3$, 1H), 6.72 (t, $J = 7.5$, 1H), 6.59 (d, $J = 7.7$, 2H), 4.31 (s, 2H), 4.16 (q, $J = 7.0$, 2H), 3.47 (s, 3H), 1.57 (br s, 1H), 1.26 (t, $J = 7.0$, 3H); CIMS (CH_4) 394 (MH^+). Anal. ($\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}$) C, H, N.

8-(3-Aminophenylamino)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (8). Compound **XVa** (50 mg, 0.16 mmol) was suspended in MeOH (3 mL) and treated with *m*-phenylenediamine (170 mg, 1.6 mmol). The resulting solution was stirred and treated with NaBH_3CN (50 mg 0.79 mmol) followed by the dropwise addition of AcOH (20 μL , 0.35 mmol). After an additional 2.5 h at room temperature the mixture was made alkaline with 15% aqueous NaOH and extracted with CH_2Cl_2 (4 $\times$ 25 mL). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient), then chromatotron (10 to 50% 2-propanol/hexanes gradient), and finally recrystallization from CH_2Cl_2 /petroleum ether to give **8** (20 mg, 31%); mp 88–90; ^1H NMR 8.39 (d, $J = 2.4$, 1H), 8.08 (d, $J = 2.4$, 1H), 7.41 (d, $J = 8.2$, 1H), 7.09 (d, $J = 8.2$, 1H), 6.93 (t, $J = 8.0$, 1H), 6.09–6.02 (m, 2H), 5.91 (t, $J = 1.6$, 1H), 4.27 (s, 2H), 4.16 (q, $J = 7.1$, 2H), 3.47 (s, 3H), 1.25 (t, $J = 7.1$, 3H); CIMS (CH_4) 409 (MH^+); HRMS (MH^+ , $\text{C}_{21}\text{H}_{22}\text{ClN}_6\text{O}$) calcd 409.1544, found 438.1564. Anal. ($\text{C}_{21}\text{H}_{21}\text{ClN}_6\text{O}$) C, H, N; calcd, 20.55; found 19.44.

Preparation of Compound XVIII. 8-(Phenylmethylamino)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (1). Compound **XVII**^{1a} (27 mg, 0.09 mmol) was suspended in MeOH (2 mL) and AcOH (10 μL , 0.18 mmol), and benzaldehyde (9 μL , 0.09 mmol) was added. The resulting solution was stirred and treated with NaBH_3CN (50 mg, 0.79 mmol) followed by the dropwise addition of AcOH (20 μL , 0.35 mmol). The mixture was stirred and extracted with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (hexanes to 1:1 hexanes/EtOAc gradient) and recrystallization from Et₂O/petroleum ether to give **1** (18 mg, 51%); mp 141; ^1H NMR 7.85 (d, $J = 3.1$, 1H), 7.39–7.26 (m, 2H), 7.03 (d, $J = 8.2$, 1H), 4.32 (d, $J = 5.5$, 2H), 4.10–4.03 (m, 3H), 3.46 (s, 3H), 1.22 (t, $J = 7.0$, 3H); CIMS (CH_4) 394 (MH^+). Anal. ($\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}$) C, H, N.

General Method B. Synthesis of 2-chloro-5,11-dihydro-11-ethyl-8-hydroxy-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XXII). Compound **XVa** (1.02 g, 3.22

mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with MCPBA (80 wt %, 1.04 g, 4.83 mmol). The mixture was stirred for 16 h, then treated with MeOH, and stirred for 8 h more. The mixture was diluted with saturated aqueous NaHCO_3 (20 mL) and extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined organics were washed with saturated aqueous NaHCO_3 (2 $\times$ 20 mL), dried over Na_2SO_4 , and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) to give **XXII** (0.37 g, 38%). The product was recrystallized from hexanes/EtOAc: mp 236–237; ^1H NMR 8.09 (d, $J = 3.1$, 1H), 7.73 (d, $J = 3.1$, 1H), 7.42 (d, $J = 8.3$, 1H), 7.08 (d, $J = 8.3$, 1H), 6.22 (br s, 1H), 4.10 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.23 (t, $J = 7.0$, 3H); CIMS (CH_4) 305 (MH^+). Anal. ($\text{C}_{14}\text{H}_{13}\text{ClN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-phenylmethoxy-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (3). Compound **XXII** (52 mg, 0.17 mmol) was dissolved in THF and treated with excess NaH (60 wt %) followed by benzyl bromide (40 μL , 0.34 mmol). After 24 h of stirring, the mixture was cooled to 0 $^\circ\text{C}$, and the excess NaH was quenched by the dropwise addition of H_2O , and the resulting solution was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organics were dried over MgSO_4 and concentrated, and the residue was purified by chromatography (hexanes to 1:1 hexanes/EtOAc gradient) followed by crystallization from hexanes to give **3** (35 mg, 52%); mp 159–160; ^1H NMR 8.17 (d, $J = 3.1$, 1H), 7.70 (d, $J = 3.1$, 1H), 7.42–7.32 (m, 6H), 7.07 (d, $J = 8.2$, 1H), 5.07 (s, 2H), 4.10 (q, $J = 7.1$, 2H), 3.48 (s, 3H), 1.23 (t, $J = 7.1$, 3H); CIMS (CH_4) 395 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-hydroxymethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one XIXa (R1 = Cl). To a solution of **XVa** (582 mg, 1.84 mmol) in THF (20 mL) was added H_2O (0.1 mL) followed by NaBH_4 (70 mg, 1.84 mmol). The mixture was stirred for 0.5 h, then diluted with brine (20 mL), and extracted with CH_2Cl_2 (3 $\times$ 30 mL). The combined organics were dried and concentrated, and the residue was purified by flash chromatography (gradient hexanes to EtOAc) to yield **XIXa** (R1 = Cl) (520 mg, 89%); mp 166–168; ^1H NMR 8.40 (d, $J = 2.1$, 1H), 8.10 (d, $J = 2.1$, 1H), 7.43 (d, $J = 8.2$, 1H), 7.11 (d, $J = 8.2$, 1H), 4.68 (d, $J = 5.8$, 2H), 4.17 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.78 (t, $J = 5.8$, 1H), 1.26 (t, $J = 7.0$, 3H); CIMS (CH_4) 319 (MH^+). Anal. ($\text{C}_{15}\text{H}_{15}\text{ClN}_4\text{O}_2$) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-8-hydroxymethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XIXb, R1 = F). By a procedure analogous to that reported for **XIXa** from **XVb**: 100%; mp 77–80; ^1H NMR 8.39 (d, $J = 2.4$, 1H), 8.11 (d, $J = 2.4$, 1H), 7.57 (dd, $J = 8.5$, 7.2, 1H), 6.71 (dd, $J = 8.5$, 3.9, 1H), 4.68 (br s, 2H), 4.14 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.84 (br s, 1H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 302 (M^+). Anal. ($\text{C}_{15}\text{H}_{15}\text{FN}_4\text{O}_2$) C, H, N.

5,11-Dihydro-11-ethyl-8-hydroxymethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (XIXc, R1 = H). By a procedure analogous to that reported for **XIXa** from **XVc**: 100%; mp 129–131; ^1H NMR (250 MHz, DMSO) 8.36 (d, $J = 2.0$, 1H), 8.21 (dd, $J = 5.0$, 1.5, 1H), 7.98 (d, $J = 2.0$, 1H), 7.84 (dd, $J = 8.0$, 1.5, 1H), 7.26 (dd, $J = 8.0$, 5.0, 1H), 5.29 (t, $J = 5.7$, 1H), 4.47 (d, $J = 5.7$, 2H), 4.07 (q, $J = 7.0$, 1H), 3.43 (s, 3H), 1.17 (t, $J = 7.0$, 3H); CIMS (CH_4) 285 (MH^+). Anal. ($\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_2$) C, H, N.

2-Chloro-8-chloromethyl-5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one XXa (R1 = Cl). Compound **XIXa** (R1 = Cl) (0.52 g, 1.6 mmol) was dissolved in CHCl_3 (10 mL) and treated with SOCl_2 (0.12 mL, 1.6 mmol) followed by Et₃N (0.23 mL, 1.6 mmol). After 0.5 h of stirring, the mixture was made alkaline with 15% aqueous NaOH and diluted with brine (10 mL), and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 $\times$ 20 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated, and the residue was purified by flash chromatography (gradient hexanes to 1:1 hexanes/EtOAc) to give **XXa** (0.51 g, 93%); mp 133–134; ^1H NMR 8.40 (d, $J = 2.5$, 1H), 8.13 (d, $J = 2.5$, 1H), 7.44 (d, $J = 8.3$, 1H), 7.12 (d, $J = 8.3$, 1H), 4.56 (s, 2H), 4.18 (q, $J = 7.0$,

2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 337 (MH^+). Anal. ($\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenyloxy)-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (4). Phenol (18 mg, 0.19 mmol) in DMSO (4 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.19 mL, 0.19 mmol). After 10 min of stirring at ambient temperature, compound **XXa** (60 mg, 0.18 mmol) was added and the mixture was stirred for an additional hour. The mixture was quenched with brine (5 mL) and made alkaline with 15% aqueous NaOH. The mixture was extracted with CH_2Cl_2 (3×15 mL), the organics were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) to give **4** (55 mg, 78%); mp 140–141; ^1H NMR 8.46 (d, $J = 2.4$, 1H), 8.19 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.2$, 1H), 7.32–7.26 (m, 2H), 7.10 (d, $J = 8.2$, 1H), 6.99–6.92 (m, 3H), 5.02 (s, 2H), 4.19 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 395 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-methylphenylamino)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (7). Compound **XXa** (50 mg, 0.15 mmol) was dissolved in *N*-methylaniline (1 mL) and stirred for 3 days. The mixture was purified by column chromatography (hexanes to EtOAc gradient) to give **7** (25 mg, 41%); mp foam, 55–57; ^1H NMR 8.28 (d, $J = 2.4$, 1H), 7.97 (d, $J = 2.4$, 1H), 7.40 (d, $J = 8.3$, 1H), 7.20 (br t, $J = 8.0$, 2H), 7.08 (d, $J = 8.3$, 1H), 6.74–6.70 (m, 3H), 4.47 (s, 2H), 4.14 (q, $J = 7.0$, 2H), 3.46 (s, 3H), 2.99 (s, 3H), 1.25 (t, $J = 7.0$, 3H); CIMS (CH_4) 408 (MH^+). Anal. ($\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-hydroxyphenyloxy)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (9). Catechol (82 mg, 0.74 mmol) in DMSO (1 mL) was treated with *t*-BuOK (1.0 M in THF, 0.16 mL, 0.16 mmol). The resulting stirred solution was treated with **XXa** (50 mg, 0.14 mmol), and the mixture was stirred an additional 24 h. The mixture was diluted with EtOAc (20 mL) and washed with brine (3×10 mL). The organics were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (hexanes to EtOAc gradient) followed crystallization from hexanes/EtOAc to give **9** (35 mg, 58%); mp 172–173; ^1H NMR 8.46 (d, $J = 2.3$, 1H), 8.18 (d, $J = 2.3$, 1H), 7.45 (d, $J = 8.3$, 1H), 7.12 (d, $J = 8.3$, 1H), 6.95–6.80 (m, 4H), 5.07 (s, 2H), 4.20 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_3$) C, H, N.

Compounds 10–17, 21–26, 40, 42, and 43 were prepared in an analogous fashion from the indicated starting material and **XXa**.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-hydroxyphenyl)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (10): resorcinol; 51%; mp 219–220; ^1H NMR 8.45 (d, $J = 2.3$, 1H), 8.16 (d, $J = 2.3$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.15–7.09 (m, 1H), 7.11 (d, $J = 8.3$, 1H), 6.53–6.43 (m, 3H), 5.21 (s, 1H), 4.97 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.26 (t, $J = 7.0$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-hydroxyphenyloxy)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (11): hydroquinone; 67%; mp 199–200; ^1H NMR 8.44 (d, $J = 2.4$, 1H), 8.16 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.78 (ab, $\Delta\nu = 13.2$, $J = 9.2$, 4H), 6.71 (s, 1H), 4.93 (s, 2H), 4.18 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-fluorophenyloxy)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (12): 2-fluorophenol; 52%; mp 109–110; ^1H NMR 8.47 (d, $J = 2.2$, 1H), 8.19 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.4$, 1H), 7.11 (d, $J = 8.4$, 1H), 7.07–6.89 (m, 4H), 5.08 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($\text{C}_{21}\text{H}_{18}\text{ClFN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-fluorophenyl)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (13): 3-fluorophenol; 70%; mp 104–105; ^1H NMR 8.45 (d, $J = 2.2$, 1H), 8.17 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.3$, 1H),

7.26–7.18 (m, 1H), 7.11 (d, $J = 8.3$, 1H), 6.73–6.63 (m, 3H), 5.00 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($\text{C}_{21}\text{H}_{18}\text{ClFN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-fluorophenyloxy)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (14): 4-fluorophenol; 57%; mp 143–144; ^1H NMR 8.44 (d, $J = 2.2$, 1H), 8.17 (d, $J = 2.2$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.10 (d, $J = 8.3$, 1H), 7.00–6.84 (m, 4H), 4.97 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($\text{C}_{21}\text{H}_{18}\text{ClFN}_4\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-(methoxycarbonyl)phenyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (15): methyl salicylate; 57%; mp 196–197; ^1H NMR 8.53 (d, $J = 2.4$, 1H), 8.25 (d, $J = 2.4$, 1H), 7.83 (dd, $J = 7.7$, 1.7, 1H), 7.49–7.42 (m, 1H), 7.43 (d, $J = 8.3$, 1H), 7.11 (d, $J = 8.3$, 1H), 7.05–6.99 (m, 2H), 5.12 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.91 (s, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-(methoxycarbonyl)phenyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (16): methyl 3-hydroxybenzoate; 90%; mp 163–164; ^1H NMR 8.47 (d, $J = 2.4$, 1H), 8.20 (d, $J = 2.4$, 1H), 7.68–7.61 (m, 2H), 7.44 (d, $J = 8.2$, 1H), 7.35 (t, $J = 7.9$, 1H), 7.15–7.09 (m, 1H), 7.11 (d, $J = 8.2$, 1H), 5.06 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.91 (s, 3H), 3.49 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_4$) C, H, N.

2-chloro-5,11-dihydro-11-ethyl-8-(4-(methoxycarbonyl)phenyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (17): methyl 4-hydroxybenzoate; 45%; mp 196–197; ^1H NMR 8.46 (d, $J = 2.4$, 1H), 8.18 (d, $J = 2.4$, 1H), 7.99 (d, $J = 8.9$, 2H), 7.43 (d, $J = 8.3$, 1H), 7.11 (d, $J = 8.3$, 1H), 6.95 (d, $J = 8.9$, 2H), 5.07 (s, 2H), 4.19 (q, $J = 7.1$, 2H), 3.88 (s, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.1$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(3-nitrophenylamino)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (21): 3-nitrophenol; 95%; mp 171–172; ^1H NMR 8.47 (d, $J = 2.4$, 1H), 8.20 (d, $J = 2.4$, 1H), 7.86 (ddd, $J = 8.1$, 1.9, 0.8, 1H), 7.79 (app t, $J = 2.3$, 1H), 7.45 (t, $J = 8.1$, 1H), 7.45 (d, $J = 8.3$, 1H), 7.26 (ddd, $J = 8.1$, 2.6, 0.8, 1H), 7.12 (d, $J = 8.3$, 1H), 5.09 (s, 2H), 4.20 (q, $J = 7.1$, 2H), 3.50 (s, 3H), 1.28 (t, $J = 7.1$, 3H); CIMS (CH_4) 440 (MH^+). Anal. ($\text{C}_{21}\text{H}_{18}\text{ClN}_5\text{O}_4$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-(*N,N*-dimethylamino)phenyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (22): 3-dimethylaminophenol; 65%; mp 132–133; ^1H NMR 8.46 (d, $J = 2.4$, 1H), 8.19 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.13 (t, $J = 8.4$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.39–6.30 (m, 3H), 5.01 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 2.92 (s, 6H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 438 (MH^+). Anal. ($\text{C}_{23}\text{H}_{24}\text{ClN}_5\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(3-methoxyphenyloxy)-methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (23): 3-methoxyphenol; 54%; mp 95–97; ^1H NMR 8.46 (d, $J = 2.4$, 1H), 8.18 (d, $J = 2.4$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.18 (t, $J = 8.1$, 1H), 7.10 (d, $J = 8.3$, 1H), 6.55–6.48 (m, 3H), 5.00 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.78 (m, 3H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 425 (MH^+). Anal. ($\text{C}_{22}\text{H}_{21}\text{ClN}_4\text{O}_3$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(4-indolyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (24): 4-hydroxyindole; 14%; mp 183–185; ^1H NMR 8.55 (d, $J = 2.4$, 1H), 8.24 (d, $J = 2.4$, 1H), 8.19 (br s, 1H), 7.43 (d, $J = 8.3$, 1H), 7.12–7.02 (m, 3H), 7.10 (d, $J = 8.3$, 1H), 6.65 (t, $J = 2.6$, 1H), 6.56 (dd, $J = 7.1$, 1.2, 1H), 5.18 (s, 2H), 4.17 (q, $J = 7.1$, 2H), 3.49 (s, 3H), 1.28 (t, $J = 7.1$, 3H); CIMS (CH_4) 434 (MH^+). Anal. ($\text{C}_{23}\text{H}_{20}\text{ClN}_5\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(5-indolyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (25): 5-hydroxyindole; 22%; mp 176–178; ^1H NMR 8.49 (d, $J = 2.3$, 1H), 8.21 (d, $J = 2.3$, 1H), 7.42 (d, $J = 8.3$, 1H), 7.28 (d, $J = 8.8$, 1H), 7.18 (t, $J = 2.7$, 1H), 7.14 (d, $J = 2.3$, 1H), 7.09 (d, $J = 8.3$, 1H), 6.88 (dd, $J = 8.8$, 2.3, 1H), 6.47 (d, $J = 2.7$,

1H), 5.06 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 434 (MH^+). Anal. ($\text{C}_{23}\text{H}_{20}\text{ClN}_5\text{O}_2 \cdot 0.25 \text{ EtOAc}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(3-pyridyloxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (26): 3-hydroxypyridine; 72%; mp 183–184; ^1H NMR 8.46 (d, $J = 2.3$, 1H), 8.37 (br s, 1H), 8.27 (br s, 1H), 8.19 (d, $J = 2.3$, 1H), 7.44 (d, $J = 8.3$, 1H), 7.35 (br s, 1H), 7.12 (d, $J = 8.3$, 1H), 5.09 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.49 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 396 (MH^+). Anal. ($\text{C}_{20}\text{H}_{18}\text{ClN}_5\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(2-pyrimidinylthio)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (40): 6-mercaptopyrimidine; 69%; mp 163–164; ^1H NMR 8.51 (d, $J = 4.8$, 2H), 8.48 (d, $J = 2.5$, 1H), 8.16 (d, $J = 2.5$, 1H), 7.40 (d, $J = 8.3$, 1H), 7.07 (d, $J = 8.3$, 1H), 6.96 (t, $J = 4.8$, 1H), 4.32 (s, 2H), 4.13 (q, $J = 7.0$, 2H), 3.46 (s, 3H), 1.24 (t, $J = 7.0$, 3H); CIMS (CH_4) 413 (MH^+). Anal. ($\text{C}_{19}\text{H}_{17}\text{ClN}_6\text{OS}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(purin-6-ylthio)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (42): 6-mercaptopurine; 67%; mp 148–151; ^1H NMR 8.74 (s, 1H), 8.52 (d, $J = 2.5$, 1H), 8.21 (d, $J = 2.5$, 1H), 8.08 (s, 1H), 7.39 (d, $J = 8.2$, 1H), 7.06 (d, $J = 8.2$, 1H), 4.59 (s, 2H), 4.13 (q, $J = 7.1$, 2H), 3.45 (s, 3H), 1.23 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($\text{C}_{20}\text{H}_{17}\text{ClN}_8\text{OS} \cdot 0.25 \text{ EtOAc}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(1H-pyrazolo[3,4-*d*]pyrimidin-4-ylthio)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (43): 3-mercapto-1H-pyrazolo[3,4-*d*]pyrimidine; 75%; mp 128–130; ^1H NMR 8.80 (s, 1H), 8.52 (d, $J = 2.5$, 1H), 8.22 (d, $J = 2.5$, 1H), 8.06 (s, 1H), 7.40 (d, $J = 8.3$, 1H), 7.07 (d, $J = 8.3$, 1H), 4.59 (s, 2H), 4.15 (q, $J = 7.0$, 2H), 3.47 (s, 3H), 1.24 (t, $J = 7.0$, 3H); CIMS (CH_4) 453 (MH^+). Anal. ($\text{C}_{20}\text{H}_{17}\text{ClN}_9\text{OS} \cdot 0.125 \text{ DMSO}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylthio)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (37): A solution of thiophenol (0.16 mL, 1.6 mmol) in DMF (15 mL) was treated with NaH (60 wt %, 62 mg, 1.6 mmol). After 15 min of stirring, compound XXa (0.50 g, 1.5 mmol) was added, and the mixture was stirred for an additional 18 h. The excess thiolate was quenched with MeOH, and the mixture was diluted with aqueous NaHCO_3 and extracted with CH_2Cl_2 . The organics were dried over Na_2SO_4 , filtered, and concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate) and recrystallization from hexanes/EtOAc to give **37** (0.378 g, 62%); mp 92–93; ^1H NMR 8.23 (d, $J = 2.4$, 1H), 8.04 (d, $J = 2.4$, 1H), 7.41 (d, $J = 8.3$, 1H), 7.30–7.18 (m, 5H), 7.08 (d, $J = 8.3$, 1H), 4.14 (q, $J = 7.0$, 2H), 4.04 (s, 2H), 3.46 (s, 3H), 1.23 (t, $J = 7.0$, 3H); CIMS (CH_4) 411 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{OS}$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(pyridinylthio)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (41): By a procedure analogous to that used for the preparation of **37**, and starting from XXa and 4-mercaptopyridine, compound **41** was produced in 79% yield; mp 140–142; ^1H NMR 8.40 (d, $J = 2.5$, 1H), 8.38 (d, $J = 6.2$, 2H), 8.13 (d, $J = 2.5$, 1H), 7.43 (d, $J = 8.2$, 1H), 7.11 (d, $J = 8.2$, 1H), 7.09 (d, $J = 6.2$, 2H), 4.16 (q, $J = 7.0$, 2H), 4.16 (s, 2H), 3.48 (s, 3H), 1.26 (t, $J = 7.0$, 3H); CIMS (CH_4) 412 (MH^+). Anal. ($\text{C}_{20}\text{H}_{18}\text{ClN}_5\text{OS} \cdot 0.50 \text{ H}_2\text{O}$) C, H, N.

Modifications to compounds synthesized by method B: 2-Chloro-5,11-dihydro-11-ethyl-8-(3-(carboxy)phenyloxy)methyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (18): Compound **16** (23 mg, 0.051 mmol) was dissolved in THF (1 mL) and treated with aqueous LiOH (1M, 2 mL, 2 mmol). The reaction was stirred until no starting material was detected by TLC. The mixture was then acidified to pH = 6 with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 ($3 \times 20 \text{ mL}$). The combined organics were dried over Na_2SO_4 and concentrated, and the residue was recrystallized from hexanes/EtOAc to give **18** (15 mg, 67%); mp 181–182; ^1H NMR 8.48 (d, $J = 2.4$, 1H), 8.21 (d, $J = 2.4$, 1H), 7.72 (br d, $J = 7.7$, 1H), 7.66 (d, $J = 2.5$, 1H), 7.44 (d, $J = 8.3$, 1H),

7.39 (t, $J = 7.7$, 1H), 7.18 (dd, $J = 7.7$, 2.5, 1H), 7.11 (d, $J = 8.3$, 1H), 5.07 (s, 2H), 4.19 (q, $J = 7.0$, 2H), 3.50 (s, 3H), 1.28 (t, $J = 7.0$, 3H); CIMS (CH_4) 439 (MH^+). Anal. ($\text{C}_{22}\text{H}_{19}\text{ClN}_4\text{O}_4$) C, H, N.

8-(3-(Aminocarbonyl)phenyloxy)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (19): Compound **16** (33 mg, 0.073 mmol) was dissolved in THF (5 mL) and treated with aqueous LiOH (1.0M, 73 μL , 0.073 mmol). After 16 h the mixture was diluted with saturated aqueous NH_4Cl (15 mL), extracted with EtOAc ($2 \times 20 \text{ mL}$), dried over Na_2SO_4 , and concentrated. The residue was azeotropically dried with benzene (50 mL) and used directly. The residue was dissolved in CH_2Cl_2 (10 mL) and treated with oxalyl chloride (0.063 mL, 0.72 mmol) followed by a catalytic amount of DMF (4 μL). The mixture was stirred for 0.5 h and then concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL), treated with NH_3 (g), and stirred for 5 min more. The mixture was then diluted with EtOAc (15 mL), washed with brine ($2 \times 10 \text{ mL}$), dried over Na_2SO_4 , and concentrated, and the residue was purified by chromatography (hexanes to EtOAc gradient) to give **19** (25 mg, 79%); mp 96–98; ^1H NMR 8.46 (d, $J = 2.3$, 1H), 8.19 (d, $J = 2.3$, 1H), 7.45–7.34 (m, 3H), 7.43 (d, $J = 8.3$, 1H), 7.12–7.09 (m, 1H), 7.11 (d, $J = 8.3$, 1H), 5.07 (s, 2H), 4.19 (q, $J = 6.9$, 2H), 3.49 (s, 3H), 1.27 (t, $J = 6.9$, 3H); CIMS (CH_4) 438 (MH^+). Anal. ($\text{C}_{22}\text{H}_{20}\text{ClN}_5\text{O}_3$) C, H, N.

8-(3-(Aminophenyloxy)methyl-2-chloro-5,11-dihydro-11-ethyl-5-methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (20): Compound **21** (80 mg, 0.18 mmol) was dissolved in AcOH (5 mL) and treated with a solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (154 mg, 0.68 mmol) in concentrated HCl (2 mL). After 17 h of stirring, for the resulting mixture was made alkaline with 50% aqueous NaOH and extracted with CH_2Cl_2 ($8 \times 20 \text{ mL}$). The combined organics were dried over Na_2SO_4 , and concentrated, and the residue was purified by flash chromatography (hexanes to 1:1 hexanes/EtOAc gradient) to give **20** (46 mg, 62%); mp 148–149; ^1H NMR 8.44 (d, $J = 2.3$, 1H), 8.16 (d, $J = 2.3$, 1H), 7.43 (d, $J = 8.3$, 1H), 7.10 (d, $J = 8.3$, 1H), 7.04 (t, $J = 8.0$, 1H), 6.36–6.25 (d, $J = 8.3$, 3H), 4.97 (s, 2H), 4.18 (q, $J = 7.0$, 2H), 3.65 (br s, 2H), 3.48 (s, 3H), 1.27 (t, $J = 7.0$, 3H); CIMS (CH_4) 410 (MH^+). Anal. ($\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}_2$) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylsulfinyl)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (38) and 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(phenylsulfonyl)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (39): Compound **37** (70 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (2.5 mL), cooled to 0 $^\circ\text{C}$, and treated with MCPBA (60 wt %, 59 mg, 0.21 mmol). After 1 h the mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NaHCO_3 . The organic phase was dried and concentrated, and the resulting residue was purified by preparative TLC to give **38** (8 mg, 11%) and **39** (29 mg, 39%). Data for **38**: mp 96–98; ^1H NMR 7.89 (br s, 1H), 7.79 (br s, 1H), 7.48–7.38 (m, 6H), 7.13 (d, $J = 8.3$, 1H), 4.14 (q, $J = 7.0$, 2H), 4.26 (ab, $\Delta\nu = 45$, $J = 13$, 2H), 3.46 (s, 3H), 1.24 (t, $J = 7.1$, 3H); CIMS (CH_4) 427 (MH^+); HRMS (MH^+ , $\text{C}_{21}\text{H}_{20}\text{ClN}_4\text{O}_2\text{S}$) calcd 427.0995, found 427.1007. Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_2\text{S}$) C, H, N; calcd, 13.12; found, 12.58. Data for **39**: mp 98–100; ^1H NMR 8.05 (d, $J = 2.4$, 1H), 7.95 (d, $J = 2.4$, 1H), 7.72–7.63 (m, 2H), 7.53–7.35 (m, 3H), 7.44 (d, $J = 8.3$, 1H), 7.14 (d, $J = 8.3$, 1H), 4.26 (s, 2H), 4.16 (q, $J = 7.1$, 2H), 3.46 (s, 3H), 1.24 (t, $J = 7.1$, 3H); CIMS (CH_4) 443 (MH^+). Anal. ($\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_3\text{S}$) C, H, N.

Method C. Synthesis of Compounds XXIV. 5,11-Dihydro-11-ethyl-5-methyl-8-((1-oxo-pyridin-4-yl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (32): Compound XIXc (142 mg, 0.499 mmol) was dissolved in THF (5 mL) and was treated with excess KH followed by 4-nitropyridine *N*-oxide (0.105 g, 0.749 mmol). The reaction mixture was stirred for 18 h, then diluted with CH_2Cl_2 (20 mL), and quenched with brine (dropwise). The organic layer was separated, and the aqueous was extracted with CH_2Cl_2 ($3 \times 15 \text{ mL}$). The combined organics were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by

preparative TLC (10% MeOH/CH₂Cl₂), the resulting white foam was stirred vigorously with petroleum ether for 24 h, and the resulting white solid was collected by filtration to give **32** (115 mg, 61%): mp 218–219; ¹H NMR 8.43 (d, *J* = 2.4, 1H), 8.22 (dd, *J* = 4.7, 1.6, 1H), 8.16 (d, *J* = 2.4, 1H), 8.15 (d, *J* = 7.6, 2H), 7.51 (dd, *J* = 8.0, 1.6, 1H), 7.13 (dd, *J* = 8.0, 4.7, 1H), 6.85 (d, *J* = 7.6, 2H), 5.05 (s, 2H), 4.22 (q, *J* = 7.1, 2H), 3.52 (s, 3H), 1.28 (t, *J* = 7.1, 3H); CIMS (CH₄) 378 (MH⁺). Anal. (C₂₀H₁₉N₅O₃) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-5-methyl-8-(1-oxo-4-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (33). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXb** and 4-nitropyridine *N*-oxide, compound **33** was produced in 69% yield: mp 194–196; ¹H NMR 8.43 (d, *J* = 2.4, 1H), 8.16 (d, *J* = 2.4, 1H), 8.12 (br d, *J* = 6.9, 2H), 7.59 (dd, *J* = 8.4, 7.1, 1H), 6.84 (br d, *J* = 6.9, 2H), 6.74 (dd, *J* = 8.4, 3.9, 1H), 5.05 (s, 2H), 4.16 (q, *J* = 7.0, 2H), 3.50 (s, 3H), 1.28 (t, *J* = 7.0, 3H); CIMS (CH₄) 380 (MH⁺ - O). Anal. (C₂₀H₁₈FN₅O₃·0.25H₂O) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(1-oxo-4-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (34). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitropyridine *N*-oxide, compound **34** was produced in 86% yield: mp 208–210; ¹H NMR 8.44 (d, *J* = 2.3, 1H), 8.16 (d, *J* = 2.3, 1H), 8.15 (d, *J* = 7.3, 2H), 7.45 (d, *J* = 8.3, 1H), 7.13 (d, *J* = 8.3, 1H), 6.85 (d, *J* = 7.3, 2H), 5.05 (s, 2H), 4.20 (q, *J* = 7.1, 2H), 3.49 (s, 3H), 1.28 (t, *J* = 7.1, 3H); CIMS (CH₄) 412 (MH⁺), 396 (MH⁺ - O). Anal. (C₂₀H₁₈ClN₅O₃) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((2-methyl-1-oxo-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (35). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-picoline *N*-oxide, compound **35** was produced in 41% yield: mp 190–192; ¹H NMR 8.43 (d, *J* = 2.4, 1H), 8.16 (br s, 1H), 8.15 (d, *J* = 2.4, 1H), 7.45 (d, *J* = 8.3, 1H), 7.13 (d, *J* = 8.3, 1H), 6.84 (br s, 1H), 6.74 (br s, 1H), 5.03 (s, 2H), 4.20 (q, *J* = 7.0, 2H), 3.49 (s, 3H), 2.54 (br s, 3H), 1.26 (t, *J* = 7.0, 3H); CIMS (CH₄) 426 (MH⁺); HRMS (MH⁺, C₂₁H₂₁ClN₅O₃) calcd 426.1328, found 438.1330. Anal. (C₂₁H₂₀ClN₅O₃·0.5H₂O) C, H, N: calcd, 16.10; found, 15.21.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((2-trifluoromethyl-1-oxo-pyridin-4-yl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (36). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-trifluoromethylpyridine *N*-oxide, compound **36** was produced in 36% yield: mp 105–108; ¹H NMR 8.43 (d, *J* = 2.4, 1H), 8.20 (d, *J* = 7.3, 1H), 8.15 (d, *J* = 2.4, 1H), 7.44 (d, *J* = 8.3, 1H), 7.25 (d, *J* = 3.4, 1H), 7.12 (d, *J* = 8.3, 1H), 7.00 (dd, *J* = 7.3, 3.4, 1H), 5.08 (s, 2H), 4.19 (q, *J* = 7.0, 2H), 3.48 (s, 3H), 1.27 (t, *J* = 7.0, 3H); CIMS (CH₄) 480 (MH⁺). Anal. (C₂₁H₁₇ClF₃N₅O₃) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-8-(2-methyl-4-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (30). By a procedure analogous to that used for the preparation of **32**, and starting from **XIXa** and 4-nitro-2-picoline, compound **30** was produced in 69% yield: mp 163–164; ¹H NMR 8.44 (d, *J* = 2.4, 1H), 8.32 (d, *J* = 5.8, 1H), 8.17 (d, *J* = 2.4, 1H), 7.44 (d, *J* = 8.3, 2H), 7.12 (d, *J* = 8.3, 1H), 6.71 (d, *J* = 2.3, 1H), 6.68 (dd, *J* = 5.8, 2.3, 1H), 5.05 (s, 2H), 4.19 (q, *J* = 7.0, 2H), 3.49 (s, 3H), 2.52 (s, 3H), 1.28 (t, *J* = 7.0, 3H); CIMS (CH₄) 410 (MH⁺). Anal. (C₂₁H₂₀ClN₅O₂·0.25H₂O) C, H, N.

5,11-Dihydro-11-ethyl-5-methyl-8-(4-pyridinyloxy)ethyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (27). A solution of **32** (72 mg, 0.190 mmol) in CHCl₃ (5 mL) was treated with PCl₃ (24 μL, 0.28 mmol). After 3 h of stirring at ambient temperature, the mixture was made alkaline with 15% aqueous NaOH and the organic layer was separated. The aqueous layer was then extracted with CH₂Cl₂ (2 × 15 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated, and the residue was purified by preparative TLC (10% MeOH/CH₂Cl₂) and further purified by precipitation from EtOAc solution with hexanes to give **27** (57 mg, 83%): mp

164–165; ¹H NMR 8.44 (br d, *J* = 2.4, 3H overlaps broad s), 8.21 (dd, *J* = 4.7, 1.6, 1H), 8.17 (d, *J* = 2.4, 1H), 7.50 (dd, *J* = 8.0, 1.6, 1H), 7.12 (dd, *J* = 7.9, 4.7, 1H), 6.85 (d, *J* = 6.3, 2H), 5.06 (s, 2H), 4.21 (q, *J* = 7.0, 2H), 3.52 (s, 3H), 1.27 (t, *J* = 7.0, 3H); CIMS (CH₄) 362 (MH⁺). Anal. (C₂₀H₁₉N₅O₂) C, H, N.

5,11-Dihydro-11-ethyl-2-fluoro-5-methyl-8-(4-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (28). By a procedure analogous to that used for the preparation of **27**, and starting from **33**, compound **28** was produced in 81% yield: mp 146–148; ¹H NMR 8.45–8.44 (m, 3H), 8.18 (d, *J* = 2.3, 1H), 7.58 (dd, *J* = 8.5, 7.1, 1H), 6.85 (br d, *J* = 5.0, 2H), 6.73 (dd, *J* = 8.5, 3.9, 1H), 5.07 (s, 2H), 4.16 (q, *J* = 7.0, 2H), 3.50 (s, 3H), 1.28 (t, *J* = 7.0, 3H); CIMS (CH₄) 380 (MH⁺). Anal. (C₂₀H₁₈FN₅O₂·0.25H₂O) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(4-pyridinyl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (29). By a procedure analogous to that used for the preparation of **27**, and starting from **34**, compound **29** was produced in 100% yield: mp 169–170; ¹H NMR 8.45 (d, *J* = 2.5, 1H), 8.45 (br s, 1H), 8.18 (d, *J* = 2.5, 1H), 7.44 (d, *J* = 8.3, 1H), 7.12 (d, *J* = 8.3, 1H), 6.85 (d, *J* = 6.2, 2H), 5.06 (s, 2H), 4.19 (q, *J* = 7.0, 2H), 3.49 (s, 3H), 1.27 (t, *J* = 7.0, 3H); CIMS (CH₄) 396 (MH⁺). Anal. (C₂₀H₁₈ClN₅O₂) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-((2-trifluoromethylpyridin-4-yl)oxy)methyl-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (31). By a procedure analogous to that used for the preparation of **27**, and starting from **36**, compound **31** was produced in 67% yield: mp 170–171; ¹H NMR 8.55 (d, *J* = 5.6, 1H), 8.46 (d, *J* = 2.5, 1H), 8.18 (d, *J* = 2.5, 1H), 7.45 (d, *J* = 8.3, 1H), 7.24 (d, *J* = 2.4, 1H), 7.12 (d, *J* = 8.3, 1H), 6.99 (dd, *J* = 5.6, 2.4, 1H), 5.11 (s, 2H), 4.20 (q, *J* = 7.0, 2H), 3.49 (s, 3H), 1.28 (t, *J* = 7.0, 3H); CIMS (CH₄) 464 (MH⁺). Anal. (C₂₁H₁₇ClF₃N₅O₂) C, H, N.

Method D. 2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-methyl-*N*-phenyl)carboxamido-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (5). Compound **XIXa** (68 mg, 0.22 mmol) was dissolved in acetone (2.5 mL) and was treated with Jones reagent (2.5M, 174 μL, 0.435 mmol). The reaction mixture was stirred for 10 min. Then, 50% aqueous NaOH (2 mL) and saturated aqueous NaHCO₃ (20 mL) were added, and the mixture was extracted with CH₂Cl₂ (2 × 15 mL). The aqueous phase was then acidified to pH = 5 (1.2 M aqueous HCl), extracted with EtOAc (3 × 20 mL), dried over Na₂SO₄, and concentrated to give crude **XXVI**. The resulting residue was dissolved in CH₂Cl₂ (10 mL) and treated with oxalyl chloride (112 μL, 1.28 mmol) followed by a catalytic amount of DMF (5 μL). After 15 min the solvent and excess oxalyl chloride were removed in vacuo. The acid chloride was redissolved in CH₂Cl₂ (9 mL) and treated with *N*-methylaniline (47 μL, 0.43 mmol). After 15 min of stirring, the reaction mixture was quenched with aqueous NaOH and extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na₂SO₄, and concentrated, and the residue was purified by flash chromatography (1:1 hexanes/EtOAc to EtOAc gradient) followed by recrystallization from hexanes to give **5** (59 mg, 65%): mp 165–167; ¹H NMR 8.29 (d, *J* = 2.1, 1H), 8.05 (d, *J* = 2.1, 1H), 7.39 (d, *J* = 8.3, 1H), 7.30–7.06 (m, 6H), 4.11 (q, *J* = 7.0, 2H), 3.48 (s, 3H), 3.41 (s, 3H), 1.18 (t, *J* = 7.1, 3H); CIMS (CH₄) 422 (MH⁺). Anal. (C₂₂H₂₀ClN₅O₂) C, H, N.

2-Chloro-5,11-dihydro-11-ethyl-5-methyl-8-(*N*-benzene-carbonyl-*N*-methylamino-6H-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (6). To a cooled solution of **XVII^a** (41 mg, 0.13 mmol) in CH₂Cl₂ and *N,N*-diisopropylethylamine (35 μL, 0.2 mmol) was added benzoyl chloride (16 μL, 0.14 mmol). After being warmed to ambient temperature, the mixture was diluted with EtOAc and washed with H₂O. The organics were dried over MgSO₄ and concentrated. The residue was dissolved in DMF (2 mL) and treated with NaH (8 mg, 0.17 mmol). After 15 min, MeI (12 μL, 0.19 mmol) was added. The mixture was worked up by quenching with ice and extracting with EtOAc. The organics were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by column chromatography (EtOAc/Hex) and recrystallization (EtOAc/Hex) to afford **6** (24 mg, 43%): mp 166–169; ¹H NMR 8.03 (d,

$J = 2.7, 1\text{H}$), 7.92 (d, $J = 2.7, 1\text{H}$), 7.42 (d, $J = 8.2, 1\text{H}$), 7.33–7.19 (m, 5H), 7.12 (d, $J = 8.2, 1\text{H}$), 4.09 (q, $J = 7.0, 2\text{H}$), 3.46 (s, 3H), 3.45 (s, 3H), 1.19 (t, $J = 7.0, 3\text{H}$); CIMS (CH_4) 422 (MH^+). Anal. ($\text{C}_{22}\text{H}_{20}\text{ClN}_5\text{O}_2$) C, H, N.

General Biological Methods. The procedures for the reverse transcriptase wild-type and mutant enzyme, inhibition of HIV-1_{IIIIB} replication in C8166 cells, and MTT toxicity assays have appeared elsewhere.^{1b,4}

In Vitro Metabolism Assay. Male Sprague–Dawley rats were obtained from either Taconic Farms (Germantown, NY, strain Tac:N(SD)fBR). Human liver was received frozen (-80°C) from the Department of Pharmacology and Toxicology of the Medical College of Wisconsin (Milwaukee, WI) and was collected according to their protocol from organ donors. The tissue was stored frozen at -80°C until the microsomes were prepared.

Preparation of Microsomes. Animal and liver weights were recorded. Subsequently, the livers were processed into microsomes using a modification of the method of Guengerich.^{18b} Modifications included centrifugation at 145 000g at 4°C for 60 min, rather than 100 000g and suspension of the microsomes for storage in 66 mM Tris buffer (pH 7.4, containing 250 mM sucrose and 5.4 mM EDTA). The microsomal suspensions were stored in liquid nitrogen as 1 mL aliquots. Microsomal total protein concentration was determined by the method of Lowry et al.,^{18c} using bovine serum albumin as a standard.

Determination of Rates of Metabolism. Metabolism of test compounds was determined by incubating 30 μM of test compound, 1 or 2 mg of microsomal protein (rat and human, respectively), and 2.5 mM NADPH at 37°C in 66 mM Tris (pH 7.4) for 30 min (1 mL total assay volume). Test compound was added to the incubation mixtures as a methanol solution. Metabolism was initiated by addition of NADPH and terminated by addition of 100 μL of 1 N aqueous NaOH. Test compound and its metabolites were extracted into 5 mL of EtOAc that was subsequently evaporated under a stream of nitrogen at 40°C . The dried residue was taken up into 200 μL of HPLC mobile phase, 100 μL of which was injected onto the HPLC. The HPLC system consisted of a Hewlett-Packard (Wilmington, DE) 1050 pump, 1050 autinjector, and 1040A diode-array detector set to monitor UV absorbance between 200 and 400 nm and record a chromatogram at 240 nm. The HPLC column was a Waters (Milford, MA) NovaPac C18 (300 $\times$ 3.9 mm) that was maintained at 40°C in a column oven. The flow rate was 1.0 mL/min with an isocratic mobile phase of 17/83 acetonitrile/0.05 M phosphate buffer (pH 4.6) containing 0.1% triethylamine (v/v). Test compounds and their metabolites were quantitated with calibration curves that were constructed using authentic standards.

In Vivo Rat Metabolism. Five male rats were fasted for 12–16 h prior to oral or intravenous administrations of test compounds. Two animals received test compound via intravenous injection in a 1.0 mg/mL solution (30% DMA, 0.9% NaCl in H_2O) at 1.0 mg/kg. Three animals received test compounds by gavage as 0.5 mg/mL suspensions (0.5% Methocel, 0.3% Tween 80) at 5 mg/kg. Blood samples were obtained from interdwelling jugular cannulas at 0.08 (iv treatment only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 h after dosing. Plasma was recovered and frozen (-20°C) until analysis.

Assay Procedure. Plasma samples (400 μL) were alkalized with 50 μL of 3.3 N NaOH and were shaken for 20 min with 5 mL of EtOAc. The EtOAc extracts were transferred to 16 $\times$ 100 mm glass tubes and evaporated to dryness under N_2 at 45°C . The residues were dissolved in 200 μL of 40 mM KH_2PO_4 , pH 4.5:AcCN (68:32) and centrifuged at 14 000g. Aliquots (100 μL) of the supernatants were injected onto the following HPLC system: column, C₁₈ MetaChem Intersil 5 μm , 4.6 $\times$ 150 mm; mobile phase, 40 mM KH_2PO_4 , pH 4.5:AcCN (68:32); flow rate, 1.2 mL/min; column temp, 40°C ; detector, UV set to monitor 236 nm. Test compounds and their metabolites were quantitated with calibration curves that were constructed using authentic standards.

Acknowledgment. John R. Proudfoot is gratefully acknowledged for his development of the selective bromination and ring closure conditions utilized in the synthetic scheme leading to the synthesis of **X**. Helga Silverstein, Joseph McDevitt, Bill Adams, and Peter Kinkade are acknowledged for contributions to the in vivo metabolism studies. John L. Sullivan and Frank Brewster of the University of Massachusetts are acknowledged for performing the HIV-1 syncytia assay. The authors thank Walter Davidson for performing the HRMS analyses and Roger Dinallo for mass spectral analysis of metabolites. John Proudfoot, Leah Frye, Daniel McNeil, and Karl Hargrave are acknowledged for very helpful discussions and critical reading of the manuscript. Additionally Julian Adams, Usha Patel, Suresh Kapadia, Terence Kelly, and Vittorio Farina are acknowledged for their critical input as members of the second generation NNRTI chemistry program.

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- (22) Full details of these experiments will be reported in due course.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C., 06/03/2008

Abogado
EMILIO FERRERO
Apoderado

ASUNTO	Radicación	04121782
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	242 ⁶⁷¹⁶

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/CA03/00718		
Fecha de Presentación Internal.	14/05/2003		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 119 a 202
- 1.2. Reivindicaciones: Folios 203 a 212
- 1.3. Prioridad: Fecha: 16/05/2002, país: US, número: 60/380.886

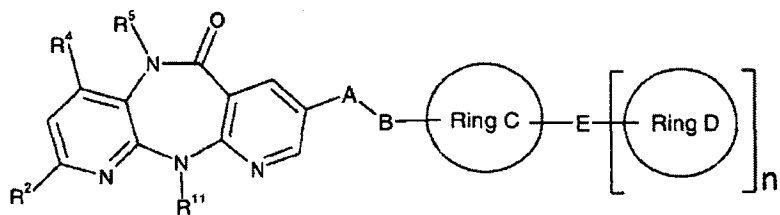
2. Objeto de la invención

- Título de la solicitud: **COMPUESTOS NO NUCLEOSIDOS INHIBIDORES DE LA TRANSCRIPTASA INVERSA, MEDICAMENTOS QUE LOS CONTIENEN Y MÉTODOS TERAPÉUTICOS QUE LOS UTILIZAN.** número de folio: 219

El objeto de la presente solicitud de patente de invención consiste en compuestos de fórmula (I) como inhibidores de transcriptasa inversa de VIH.

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Reivindicaciones 1-13: Compuesto de fórmula (I).



Reivindicación 14: Composición que comprende un compuesto de fórmula (I) o una sal y un vehículo.

Reivindicaciones 15-18: Métodos de tratamiento.

Reivindicación 19: Uso de un compuesto para fabricar un medicamento.

El problema planteado en esta solicitud es la necesidad de compuestos que inhiben las funciones enzimáticas de la transcriptasa inversa de VIH-1 y la replicación de VIH-1 en células infestadas, los cuales son útiles para la prevención y tratamiento de infecciones por VIH-1 en seres humanos.

Para solucionar este problema técnico la solicitud en estudio proporciona nuevos compuestos inhibidores de cepas tipo salvaje dobles mutantes (específicamente K103N/Y181C) de RT y sus sales ya sea solos o en combinación con otros agentes terapéuticos.

Clasificación Internacional de Patentes (IPC.):A61K 31/55

3. De la solicitud de Patente (según el caso)

3.1. Descripción (artículo 28 D. 486)

- Se muestra el nivel de inhibición de cepas de RT de tipo salvaje y mutantes para algunos compuestos (folios 197-202). Pero no se presentan resultados que evidencien las ventajas o el salto tecnológico de los compuestos con respecto al estado de la técnica y/o una mejora en los niveles de actividad.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)) (según causal)

Reivindicaciones 15-18: Se refieren a métodos de tratamiento por lo tanto no se aceptan según la legislación vigente.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Reivindicación 19: Que se refiere al uso de un compuesto para la fabricación de un medicamento, no es patentable según los artículos citados.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2/07/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de
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			241 publicación *
D ₁	XP002181340	NOVEL NONNUCLEOSIDE INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE. 8.8-ARYLOXYMETHYL-AND 8-ARYLTHIOMETHYLDIPYRIDODIAZEPINONES	1998

7. Análisis de patentabilidad (según requisito) (artículo 14 D486)

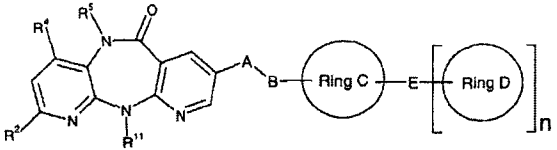
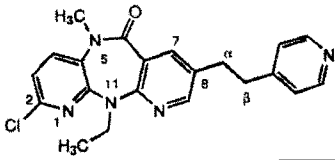
7.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica (de 1 - 13) un compuesto de fórmula general I:

Dicho compuesto se ve afectado por el siguiente documento más cercano del Estado de la Técnica:

D₁ que enseña la Nevirapine como el primer inhibidor de transcriptasa reversa nonucleosido VIH-1. (Ver folios: 226-238).

TABLA 1

SOLICITUD		ANTERIORIDAD (D ₁)		Estado comparativo
(I)		(1)		
R ₂	halo		Cl	Equivalente
R ₄	H		H	Equivalente
R ₅	Me		CH ₃	Equivalente
R ₁₁	Alquilo C ₁ -C ₄		CH ₃	Equivalente
A	Cadena de conexión de alquilo C ₁₋₃		(1)	Equivalente
B	O o S		H	Diferente
	Si n=0 el Anillo C= arilo 6-10o heterociclo 5-6 con heteroátomos como O, N y S		(1)	Equivalente

La única **diferencia con D₁** es que esta solicitud **posee un grupo E** como sustituyente adicional y además un **O o S** como sustituyente B pero esta diferencia no parece conceder un efecto técnico inesperado o una ventaja que otorgue un salto tecnológico ventajoso excepcional.

De esta forma no puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada porque la descripción no presenta datos en tal sentido.

De esta forma el Problema Técnico Objetivo fundamental de la Invención Reivindicada no puede definirse y los compuestos y composiciones reivindicados se consideran tan solo una alternativa, sin algún salto tecnológico que lo haga superior a lo **previamente conocido**.

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Por consiguiente, de acuerdo a las consideraciones expuestas anteriormente, resultaría obvio el diseño de este tipo de compuestos y composiciones para un experto en la materia.

8 Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	XP002181340	1-14	NIVEL INVENTIVO

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
04 JUL 2001

v.º 02/03

CONCEPTO TÉCNICO No. 661	EXAMINADOR TÉCNICO Código No. 202087
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