Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 2427–2436

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Anti-HIV Activity of 1,3,4,5-Tetrahydro-2*H*-1,4-benzodiazepin-2-one (TBO) Derivatives. Truncated 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones (TIBO) Analogues

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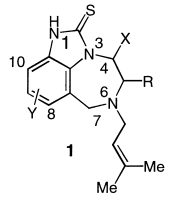
Received 19 February 1999; accepted 20 May 1999

Abstract—4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones (TIBO), **1**, have been shown to significantly inhibit HIV-1 replication, as reported in detail in our prior publications. Since our earlier reports, we have modified the TIBO structures **1** by removing the 5-membered ring of **1**, generating 1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-ones (TBO), **4**, a bicyclic series of compounds. Although compounds **4** possess modest activity when compared to TIBO analogues **1**, they clearly demonstrated significant anti-HIV-1 activity.

Introduction

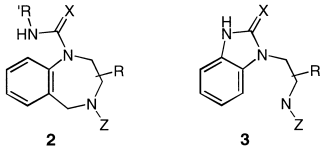
Over a series of publications we have previously reported our detailed studies of a class of 4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-*jk*] benzodiazepin-2-(1*H*)-one compounds (TIBO), **1**. These compounds possess significant inhibitory activity against the human immunodeficiency virus type 1 (HIV-1), the causative infection of acquired immune deficiency syndrome (AIDS).[1–5]

Since our last publications, other groups have explored the possibility of maintaining anti-HIV activity with modified versions of the tricycle **1**. These modifications ranged from extensive examination of the structural requirements of **1**, which resulted in the discovery of the comparatively active PETT series of compounds,[6] to simpler modifications, such as solely opening either the 5- or 7- membered ring of **1**, i.e. **2** and **3**, respectively.[7,8] A group that prepared compounds akin to **2** reported that

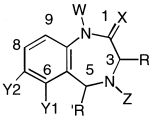


1

1a R=(S)-Me; X=H_2; Y= 8-Cl (**R86183**)
1b R=(S)-Me; X=H_2; Y= 9-Cl (**R82913**)
1c R=(+,-)-Me X=O; Y= 9-Cl (**R84923**)



2 **3**



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Key words: HIV; AIDS; antiviral.
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0968-0896/99/$ - see front matter
PII: S0968-0896(99)00198-4

no anti-HIV activity was detected for their truncated versions of **1**.[7] From the independent study examining disruption of the 7-membered ring of **1**, it was reported that modest anti-HIV activity is maintained (IC_{50} = 4–30 μM) after modification.[8]

This paper will describe our findings related to anti-HIV structure–activity relationships (SAR) of 5-membered ring truncated analogues of **1**, as depicted by generic bicyclic structure **4**, as well as the associated synthetic preparations.

Chemistry

The synthetic routes employed for the preparation of the 30 diversely substituted, final compounds identified in Table 1 are depicted in general Schemes 1 and 2. Specific procedural methods followed for individual final compounds are listed in Table 2, as are related characterization and purification data. Below is a more general description of the chemistry outlined in Schemes 1 and 2, as well as some problematic, unexpected and/or undesired results encountered during the preparation of the final targets.

Table 1. Inhibition of HIV-1 replication in MT-4 cells

No.	R	R′	W	X	Y1	Y2	Z	IC_{50} (μM)[a]	n[b]
1a								0.0034	197
1b								0.034	54
1c								> 50	1
4a	Me	H_2	H	O	H	Cl	*n*-Pr	540	2
4b	H	H_2	H	O	H	Cl	DMA[c]	86.4	8
4c	Me	H_2	H	O	H	Cl	DMA	5.5	8
4d	Me	H_2	H	O	H	Cl	DEA[d]	2.6	7
4e	Me	H_2	H	O	Cl	H	DMA	4.3	7
4f	Me	H_2	H	O	Cl	H	DEA	5.6	6
4g	Me	H_2	H	O	H	H	DMA	29.6	6
4h	Me	H_2	H	O	H	H	CH_2-*c*-Bu	238	5
4i	Me	O	H	O	H	Cl	DMA	> 100	7
4j	Me	H_2	H	S	H	Cl	DMA	1.6	4
4k	Me (S)	H_2	H	O	H	Cl	DMA	4.6	5
4l	Me (S)	H_2	H	O	H	Cl	CH_2-*c*-Pr	> 100	7
4m	Me (S)	H_2	H	O	H	Cl	2-MA[e]	> 100	8
4n	Me (S)	H_2	H	O	H	Cl	-CH_2-Ph	81	6
4o	Me (S)	H_2	H	O	H	Cl	-CH_2-2-Furan	19.7	7
4p	Me (S)	H_2	H	O	H	Cl	-CH_2-2-Pyrrole	> 100	6
4q	Me (S)	H_2	H	O	H	Cl	-CH_2-CO-NH_2	> 934	7
4r	Me (S)	H_2	H	O	H	Cl	-CO-NH-Me	> 713	7
4s	Me (S)	H_2	H	O	H	Cl	-CO-NH-*i*-Pr	> 619	7
4t	*i*-Pr	H_2	H	O	H	Cl	DMA	3.2	7
4u	*i*-Pr	H_2	H	H_2	H	Cl	DMA	> 100	4
4v	*i*-Pr	H_2	H	O	H	Cl	-CH_2-2-Furan	7.7	3
4w	*i*-Pr	H_2	H	O	H	Cl	*t*-BOC	> 100	5
4x	*i*-Pr	H_2	H	S	H	Cl	*t*-BOC	7.9	7
4y	*i*-Pr	H_2	H	S	H	Cl	H	> 100	5
4z	*i*-Pr	H_2	H	S	H	Cl	DMA	5.1	6
4aa	*i*-Pr	H_2	Me	O	H	Cl	*t*-BOC	> 100	5
4bb	*i*-Pr	H_2	Me	O	H	Cl	H	> 100	5
4cc	*i*-Pr	H_2	Me	O	H	Cl	DMA	> 100	6
4dd	Ph	H_2	H	O	H	Cl	DMA	> 100	5
11a	Me	H_2	H	O	H	H	H	> 8.5	1
11b	H	H_2	H	O	H	Cl	H	> 1100	1
11c	Me	H_2	H	O	H	Cl	H	> 1187	3
11d	Me(S)	H_2	H	O	H	Cl	H	> 8.1	1
11e	Me	H_2	H	O	Cl	H	H	—	—
11f	*i*-Pr	H_2	H	O	H	Cl	H	> 1047	9
11g	Ph	H_2	H	O	H	Cl	H	> 48	5

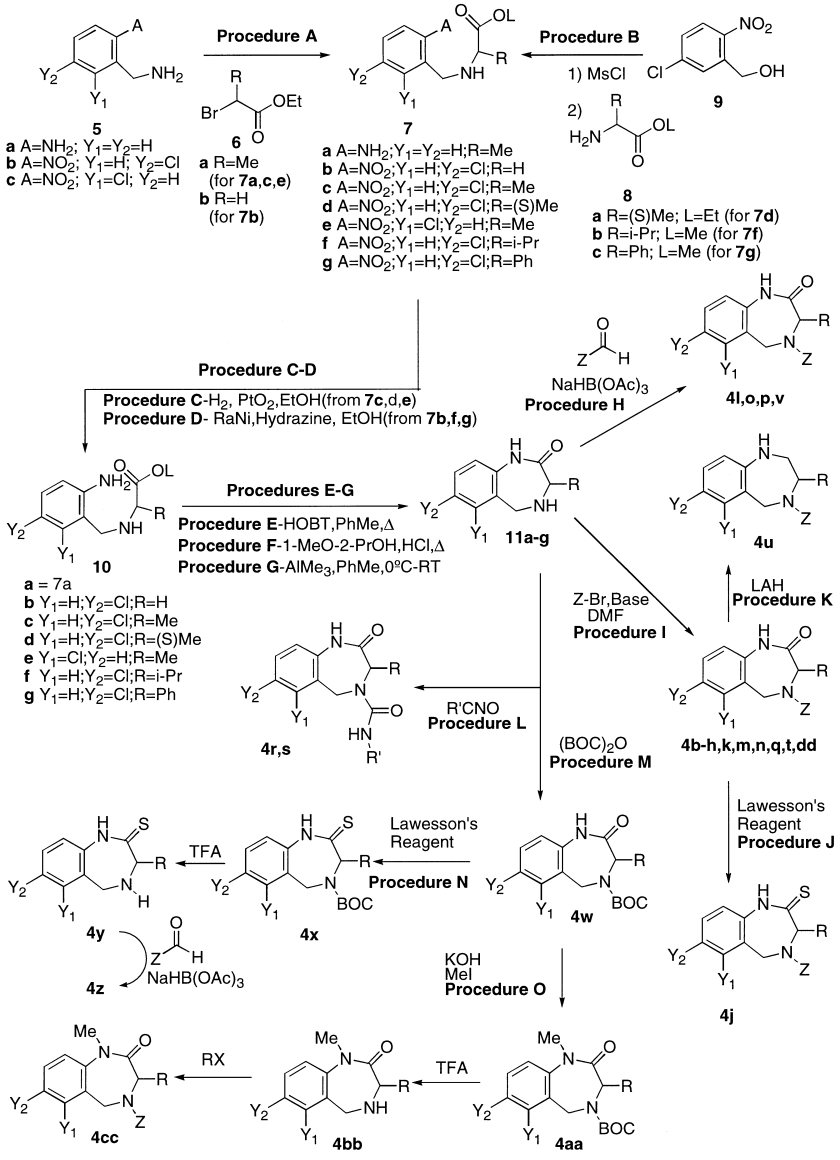
[a] Mean value of effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1.
[b] Number of experiments run for a given compound.
[c] DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl.
[d] DEA = 3,3-diethylallyl or 3-ethyl-2-pentenyl.
[e] 2-MA = 2-methylallyl or 2-methyl-2-propenyl.

The core sequence in Scheme 1 entailed a three step process to reach common intermediates (**11a–g**). Then an additional one to four varied subsequent steps were used to prepare final products **4a–4h** and **4j–dd**. All syntheses in this schematic were initiated from either starting materials **5** or **9**, in either case yielding intermediates **7a–g**. Starting from **9** was generally the reaction of choice when the R group variations of final targets **4** were being examined because of the relative ease of synthesis, i.e. due to the ready availability of various starting material amino acids **8**, both racemic and chiral, as well as the flexibility and advantage of having a stereospecific route, if desired. Thus **7d**, **7f** and **7g** were readily prepared from **8a**, **8b** and **8c**, respectively. Noteworthy, however, was the poor result obtained by this method when glycine ethyl ester (i.e. R = H) was reacted with the mesylate of **9**. Rather than the desired product **7b**, the dibenzylated adduct was the major product isolated, i.e. ethyl *N*,*N*-bis[(5-chloro-2-nitrophenyl)methyl]glycine. Fortunately, **7b** was readily generated by reacting **5** with **6b** in respectable yield. Starting from **5** was also chosen as the method of choice for intermediates **7a, 7c**[4] and **7e** where the Y1 and Y2 groups of final targets **4** were being evaluated. Similar to the above case, this method was employed for these particular compounds because of the ready availability of appropriate starting materials. Thus, starting materials **5b** and **c** were easily prepared from their appropriate commercially available nitrile by following the borane reduction procedure previously reported for **5b**,[9] while diamine **5a** was commercially available.

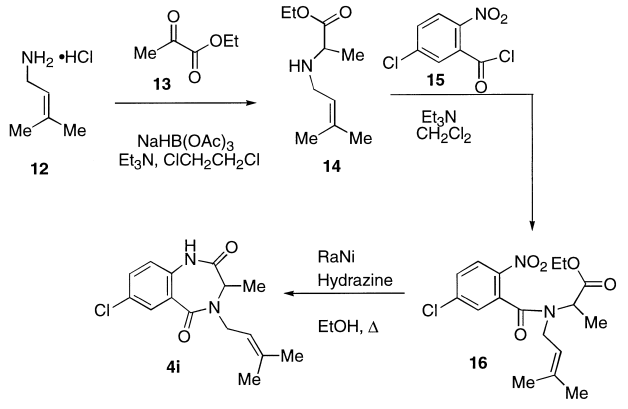
Reductions of **7a–g** to **10a–g** proved straightforward for a couple different reduction conditions explored, however the cyclizations of the various **10**s to their respective **11**s proved somewhat variable, depending mainly on the substituent R.

It was found that when R was H or Me, cyclizations proceeded in modest to good yields by: (1) refluxing **10** in toluene (PhMe) with 1-hydroxybenzotriazole hydrate (HOBT) (**11a**, 7%; **11b**, 20%; **11c**,[4] 38%), or (2) refluxing the HCl salt of **10** in 1-methoxy-2-propanol (**11d**, 89%; **11e**, 73%). However, for **10f**, where R was the bulkier *i*-Pr group, both of these conditions proved unsuccessful, even at extended reaction times, yielding only unreacted starting material or worse, decomposition. This led us to explore various cyclization procedures. We found that $AlMe_3$ facilitated the cyclization of **10f** to cleanly give **11f** in 62% isolated yield after only 4 h at room temperature. In a similar manner, the $AlMe_3$ cyclization reaction proceeded smoothly for **10g**, where R was Ph, to give **11g** in 41% yield.

Alkylation of the resulting secondary amines **11** proceeded uneventfully by pursuing either reductive amination



Scheme 1. Procedures A–O.



Scheme 2. Procedure P.

conditions (**4l**, **4o**, **4p**, **4v**) or alkyl halide substitution conditions (**4b**–**h**, **4k**, **4m**, **4n**, **4q**, **4t**, **4dd**). The availability of starting material aldehyde or halide was generally the determining factor for which method was pursued. Noteworthy is that **4k**, whose synthesis was initiated with enantiomerically pure starting material **8a**, was used as a single case study to examine end product optical purity. It was determined that **4k** was >98% optically pure, based on ^{1}H NMR experiments as described in Experimental. Also readily prepared from amines **11** were ureas **4r** and **4s**, which were prepared under standard isocyanate reaction conditions, as well as carbamate **4w**, which was prepared by reacting amine **11f** with di-*tert*-butyl dicarbonate. Further derivatization of compounds described in this paragraph gave additional final targets **4**.

Amide-amine **4t** was cleanly converted to diamine **4u** under standard LAH reduction conditions. Unfortunately, conversion of amide-amines of **4** to thioamide-amines proved somewhat more problematic giving modest yields, at best. Under standard Lawesson's conditions, thioamide **4j** (R = Me) was prepared in 19% yield from amide **4e** after laborious chromatography. Similar conditions for amide **4t**, where R was *i*-Pr,

Table 2. Product purification and characterization

No.	Synthesis[a]	Formula[b]	Purification[c]	Yield (%)	mp (°C)
1a	[d]				
1b	[d]				
1c	[d]				
4a	I[d]				
4b	I	$C_{14}H_{17}ClN_2O{\cdot}0.2H_2O$	CH_3CN	24	125–126
4c	I	$C_{15}H_{19}ClN_2O$	CH_3CN	47	119–121
4d	I	$C_{17}H_{23}ClN_2O$	20:1 CH_2Cl_2:MeOH; CH_3CN[e]	24	93–95
4e	I	$C_{15}H_{19}ClN_2O$	25:1 CH_2Cl_2:MeOH[e]	9	116–117
4f	I	$C_{17}H_{23}ClN_2O$	50:1 CH_2Cl_2:MeOH; CN_3CN[e]	7	74–75
4g	I	$C_{15}H_{20}N_2O$	CH_3CN	41	97.5–99
4h	I	$C_{15}H_{20}N_2O$	CH_3CN	25	100–103
4i	P	$C_{15}H_{17}ClN_2O_2$	MeOH	14	172–174
4j	J	$C_{15}H_{19}ClN_2S$	100:1 CH_2Cl_2:MeOH; CH_3CN[e]	19	141–143
4k	I	$C_{15}H_{19}ClN_2O$	CH_3CN	54	109–111
4l	H	$C_{14}H_{17}ClN_2O{\cdot}0.1H_2O$	CH_3CN	80	145–146
4m	I	$C_{14}H_{17}ClN_2O$	CH_3CN	59	84.5–86.5
4n	I	$C_{17}H_{17}ClN_2O$	CH_3CN	44	122–124
4o	H	$C_{15}H_{15}ClN_2O_2$	CH_3CN	74	138.5–140.5
4p	H	$C_{15}H_{16}ClN_3O$	CH_3CN; Et_2O; CH_3CN	21	125.5–127.5
4q	I	$C_{12}H_{14}ClN_3O_2{\cdot}0.15H_2O$	Et_2O	40	205–213
4r	L	$C_{12}H_{14}ClN_3O_2$	H_2O; Et_2O	100	243.5–246
4s	L	$C_{14}H_{18}ClN_3O_2$	H_2O; Et_2O	92	211–214
4t	I	$C_{17}H_{23}ClN_2O$	CH_3CN	77	132.5–135
4u	K	$C_{17}H_{25}ClN_2{\cdot}0.9C_2H_2O_4$	EtOH	51	181–183
4v	H	$C_{17}H_{19}ClN_2O_2$	CH_3CN	98	112–114
4w	M	$C_{17}H_{23}ClN_2O_3$	CH_2Cl_2	94	231–233
4x	N	$C_{17}H_{23}ClN_2O_2S$	100% CH_2Cl_2[e]	54	175–177
4y	N	$C_{12}H_{15}ClN_2S{\cdot}1.3\ C_2HF_3O_2$	CH_2Cl_2	100	220–222
4z	N	$C_{17}H_{23}ClN_2O$	CH_3CN	44	141–143
4aa	O	$C_{18}H_{25}ClN_2O_3$	MeOH	46	154–156
4bb	O	$C_{13}H_{17}ClN_2O{\cdot}0.28C_2HF_3O_2{\cdot}1.0H_2O$[f]	Et_2O	46	132–135
4cc	O	$C_{18}H_{25}ClN_2O{\cdot}HCl$	Et_2O	50	221–223
4dd	I	$C_{20}H_{21}ClN_2O$	CH_3CN	73	163–165
11a	E	$C_{10}H_{12}N_2O{\cdot}0.5C_4H_4O_4$	EtOH	5	228–229
11b	E	$C_9H_9ClN_2O{\cdot}0.4H_2O$	CH_2Cl_2	20	182–183
11c	E[d]	—	—	—	—
11d	F	$C_{10}H_{11}ClN_2O{\cdot}HCl$	1-Methoxy-2-propanol/*i*-Pr_2O	89	286
11e	F	$C_{10}H_{11}ClN_2O{\cdot}HCl$[g]	1-Methoxy-2-propanol/Et_2O	73	ND[h]
11f	G	$C_{12}H_{15}ClN_2O$	Et_2O	62	159–161
11g	G	$C_{15}H_{13}ClN_2O$	Et_2O	41	190–191

[a] Method/reagent used to synthesize the product.
[b] All products analyzed correctly for C, H and N, unless noted.
[c] Products were crystallized and/or recrystallized from listed solvents.
[d] Preparations have been previously described for **1a**[5] and **1b**[3] as well as **1c**, **4a** and **11c**.[4]
[e] Crude material was flash chromatographed on silica gel, eluting with identified solvent system, prior to crystallization with listed solvent.
[f] Intermediate **4bb** was analyzed for C, H, N, F, Cl; H: calcd, 6.42; found, 5.85, Cl: calcd 11.71; found, 11.13; MS (CI) *m/z* 253 ($M^+ + 1$).
[g] No EA was performed on this intermediate.
[h] ND = not determined.

proved more problematic yielding a multitude of unidentified products by thin layer chromatography (TLC). Fortunately, conversion of the related amide-carbamate **4w** proceeded smoothly under the same Lawesson conditions to give thioamide-carbamate **4x** (54%). Thiocarbamate **4x** was easily *tert*-butoxycarbonyl (BOC) deprotected under standard triflouroacetic acid (TFA) conditions to furnish the secondary amine **4y** (100%), which was subjected to reductive amination conditions to obtain desired thioamide-amine **4z** (44%).

Amide carbamate **4w** was also used to prepare disubstitituted amide analogue **4cc**. Compound **4w** was treated with KOH and MeI in acetone to generate **4aa** (46%). Compound **4aa** was BOC deprotected under standard TFA conditions (46%) and the resulting secondary amine subsequently alkylated to give final target **4cc** (50%).

The chemistry outlined in Scheme 2 proceeded uneventfully to yield final product **4i**. The related chemistry on compounds **1a** and **b**, which were used as our biological standards, and **1c** has been reported in our previous publications.[3–5]

Results and Discussion

As discussed in our previous publications, the TIBO series of compounds **1** has shown anti-HIV activity in both primary and secondary screens, as well as shown potential clinical efficacy against the HIV virus.[10] For the entire TIBO series of compounds **1**, as well as for the truncated TIBO analogues **4** described in this paper, the primary screen has supplied the initial results from which we have drawn our basic SAR conclusions. This

primary screen, which has previously been described,[11] involves testing a compound's ability to inhibit the cytopathic effects of HIV-1 in MT-4 cells. These cells are infected with HIV-1 and incubated in the presence of various concentrations of the test compounds. The number of viable cells is then determined 5 days after infection by staining with 3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide.[12] The reported values shown in Table 1 are the concentrations of each compound required to protect 50% (IC_{50}) of the MT-4 cells from cell death brought on by infection with HIV-1. The IC_{50}s reported as greater than a specified value are the highest concentration tested for that particular compound which failed to protect 50% of the MT-4 cells from the cytopathic effect of HIV-1. The reported IC_{50} values are the mean of a varied number of assays (n) for each analogue tested. The nature of the assay makes a determination of the standard deviations tenuous at best, although the values were usually quite consistent within the multiple determinations.

We began our study of the anti-HIV activity relative to the truncated TIBO structures when it was noted that **4a**, prepared as an intermediate in the synthesis of the previously reported TIBO analogue **1c**,[4] showed a trace of anti-HIV activity.

After discovering the weak anti-HIV activity for **4a**, we proceeded to make systematic structural variations to this new class of HIV inhibitory, bicyclic compounds. We began our SAR exploration of these bicycles at the easily modified Z group of **4**. For purposes of direct comparison, generally only the Z group of **4a** was altered to maintain mono-varied analogues of **4a**. The most significant increase in anti-HIV activity was noted by substituting a dimethylallyl group (**4c** and **k**) or diethylallyl group (**4d**) for the simple Pr group of **4a**. Other Z group substituted analogues exhibited less promising anti-HIV activity than these dialkylsubstituted allyl analogues **4c**,**k**, and **f**, although the furan substituted analogues of **4** did show reasonable activity. The relative activities were as follows: -$CH_2C{=}C(CH_2CH_3)_2$ (**4d**) ≥ -$CH_2C{=}C(CH_3)_2$ (**4c** and **k**) > -CH_2-2-furan (**4o**) > -CH_2-Ph (**4n**) > -CH_2-c-Pr (**4l**), -CH_2-$C(CH_3){=}CH_2$ (**4m**), -CH_2-2-pyrrole (**4p**) ≥ -*n*-Pr (**4a**) > -CO-NH-*i*-Pr (**4s**), -CO-NH-Me (**4r**), -CH_2-CO-NH_2 (**4q**), -H (**11c**). Analogues which could not be directly correlated to **4a** because they had two variations relative to **4a** also showed, via alternate extrapolations, that the dialkyl allyl group yielded the most promising HIV inhibitors. These extrapolated comparisons include: -$CH_2C{=}C(CH_3)_2$ (**4g**) > -CH_2-*c*-Bu (**4h**); and also -$CH_2C{=}C(CH_3)_2$ (**4t**) > -*t*-BOC (**4w**). With the dialkyl allyl substitution the most favorable at the Z position of **4**, we proceeded to hold that group constant while exploring a few variations of the R group of **4**.

From our limited examination of various R groups on **4** we found no group that significantly enhanced the HIV inhibitory activity relative to the initial lead compounds (R = Me), except when R was *i*-Pr where comparable or slightly better anti-HIV activity was noted. In brief, the directly comparable, mono-varied analogues of **4**, where only R was changed, indicate: *i*-Pr (**4t**) ≥ Me (**4c**) > H (**4b**), Ph (**4dd**); also *i*-Pr (**4v**) ≥ Me (**4o**). A definitive conclusion as to whether compounds **4** exhibit biological stereospecificity with respect to R cannot be clearly answered based on our studies, since only one enantiomer (S), or racemates, were ever prepared. In the sole directly comparable case of a single enantiomer versus an active racemate, at best a marginal increase in anti-HIV was noted, i.e. where R was (*S*)-Me (**4k**) ≥ racemic Me (**4c**).

Continuing our examination of the SAR of compound **4**, we held R constant as Me or *i*-Pr, based on the above findings, and varied substituents at the X position. We found that for analogues of **4** where X was the sole variable (S, O, or H_2), sulfur had comparable or slightly enhanced anti-HIV activity versus oxygen and the methylene analogue proved inactive, i.e. X = O (**4t**) ≥ X = S (**4z**) >> X = H (**4u**); also X = S (**4x**) > X = O (**4w**); as well as X = S (**4j**) ≥ X = O (**4c**). We also found that a Me for H substitution on the N of the secondary amide of one of the most potent compounds led to complete loss of anti-HIV activity (**4cc** versus **4t**).

Based on the fact that halogen substitution on the phenyl ring of **1** was instrumental to enhancing anti-HIV activity,[2,5] we also explored a couple variable phenyl substitutions on **4**. This exercise yielded the following comparisons: Y1 = Cl, Y2 = H (**4e**)∼Y1 = H, Y2 = Cl (**4c**) > Y1 = Y2 = H (**4g**); and also Y1 = H, Y2 = Cl (**4d**) ≥ Y1 = Cl, Y2 = H (**4e**). Unfortunately, again a clear cut enhancement of anti-HIV activity was not achieved.

Further synthetic work was discontinued upon completion of these cursory, systematic variations of W, X, Y, and Z on **4** since improvement in anti-HIV activity, although marked relative to initial lead **4a**, still proved weak in comparison to the extremely potent parent compounds **1**. Regardless, this limited study clearly demonstrates that, even though less active than **1**, significant anti-HIV activity can be maintained for 5-membered ring disrupted analogues of **1**.

Experimental

All final products **4** included in Table 2, as well as intermediates **11a–d,f,g** were characterized by 360-MHz ^{1}H NMR (Bruker AM 360 WB), mass spectra (Finnegan 3300), and elemental analyses. Reported ^{1}H NMRs of intermediates were also run on the 360-MHz NMR. Representative ^{1}H NMRs for both intermediates and final products are included, or cited from our prior publications, in Experimental. The elemental analyses were carried out by the internal Analytical Research Department of Janssen Research Foundation in Beerse, Belgium. All products identified above were within the 0.4% limit values of the calculated percent values for C, H and N. All final products were also assayed for homogeneity by TLC on Whatman MK6F (1 in×3 in×250 μm) silica gel plates. Melting points (mp) were determined on a Thomas–Hoover Unimelt capillary m.p. apparatus and are uncorrected. All reagents were commercially available

unless otherwise specified and all reactions were run under an inert atmosphere of Ar or N_2 unless otherwise specified. Table 2 also identifies the typical procedure followed to prepare each respective final product. Variance from these typical procedures is outlined below for all compounds where modifications were required.

Typical procedure A

(±)-Ethyl *N*-[(5-chloro-2-nitrophenyl)methyl]alanine (7c). The preparation and spectral characterization of this compound has been previously reported.[4] The reaction conditions described in the cited reference exemplify the standard conditions employed for procedure A of this paper.

(±)-Ethyl *N*-[(2-aminophenyl)methyl]alanine (7a). This material was prepared in a similar manner as **7c**, except diamine **5a** was used in place of a nitro monoamine as for the other examples. Also noteworthy was the fact that no additional purification was done to desired **7a** since the subsequent conversion to desired intermediate noramine **11a** yielded a product which was readily purified.

Ethyl *N*-[(5-chloro-2-nitrophenyl)methyl]glycine (7b). This material was prepared in a similar manner as **7c** except the reaction was run at room temperature for 4 h. Also the crude product was further purified by silica gel column chromatography eluting with straight CH_2Cl_2 to yield 53% of desired **7b** as a solid. A small sample was recrystallized from hexane for analysis purposes, mp 53.5–54.5°C. Anal. ($C_{11}H_{13}ClN_2O_4$) C, H, N.

(±)-Ethyl *N*-[(2-chloro-6-nitrophenyl)methyl]alanine (7e). This material was prepared in a similar manner as **7c** yielding desired product **7e** in 81% crude yield. Starting material amine **5c** used in this reaction was prepared in one step from commercially available 6-chloro-2-nitrobenzonitrile in 77% yield via a reported borane reduction procedure[9] (TLC: 10:1 CH_2Cl_2: MeOH, $R_f = 0.8$; >85% pure).

Typical procedure B

(±)-Methyl 2-[[(5-chloro-2-nitrophenyl)methyl]amino]-3-methylbutanoate (7f). Methanesulfonyl chloride (2.5 mL, 30 mmol) was added to a stirring, cold (0°C) mixture of 5-chloro-2-nitro-benzyl alcohol, **9** (3.8 g, 20 mmol) in toluene (PhMe) (50 mL). Triethylamine (Et_3N) (4.5 mL, 33 mmol) was then slowly added over 15 min while keeping the temperature between 0 and 8°C. After stirring at 5°C for 2 h, water (100 mL) was added to the reaction mixture and the resulting solid filtered off. The resulting solid was dissolved in chloroform ($CHCl_3$), washed with water, and then combined with the toluene filtrate. The combined PhMe:$CHCl_3$ solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 5 g (94%) of mesylated alcohol. Identical results were obtained when this reaction was run on a 1.09 mol scale. Another batch of mesylate (8.49 g, 32 mmol) prepared by this same method was added to a room temperature mixture of D,L valine methyl ester hydrochloride, **8b** (16.07 g, 96 mmol) and Et_3N (16.9 mL, 120 mmol) in tetrahydrofuran (THF) (150 mL). The reaction was then warmed to reflux and heated 3 days. The reaction was then cooled to room temperature, added to water, and the resulting mixture extracted four times with ethyl acetate (EtOAc). The combined organics were washed with brine, dried over $MgSO_4$, filterered, and concentrated under reduced pressure to yield 8.60 g (89%) of desired **7f** as a brown oil, which was used without further purification (TLC: 25% EtOAc:hexane, $R_f = 0.6$; >90% pure).

(*S*)-Ethyl *N*-[(5-chloro-2-nitrophenyl)methyl]alanine hydrochloride (7d). This material was prepared on a much larger scale which contributed to some variations in the procedures. While maintaining a 20°C reaction temperature, L-alanine ethyl ester hydrochloride, **8a** (122.9 g, 0.8 mol) in tetrahydrofuran (THF) (1 L) was treated with Et_3N (118.3 mL, 0.85 mol). After stirring 2 h the reaction mixture was filtered and the solid rinsed with THF (250 mL). The resulting filtrate was filtered a second time and the refiltered solution combined with the mesylated alcohol of **9** (199.3 g, 0.75 mol) which had been dissolved in THF (1.25 L). Et_3N (118.3 mL, 0.85 mol) was added to the mixture and the reaction was heated at reflux for 16 h. The reaction mixture was then treated with an additional portion of **8a** free base (0.2 mol) and Et_3N (0.25 mol) and warmed at reflux an additional 2 h. The reaction mixture was then concentrated under reduced pressure by removing THF (1.8 L) and then PhMe (1.5 L) was added and the reaction was warmed to 85–90°C for 16 h. The reaction mixture was then cooled and washed with water (3×1.5 L). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in EtOAc (0.5 L) and treated with an HCl/*i*-PrOH solution. The resulting solid precipitate was filtered, rinsed with EtOAc, and dried at 60°C under high vacuum to yield 90 g (37%) of desired **7d** which was used without further purification.

(±)-α-[[(5-Chloro-2-nitrophenyl)methyl]amino]benzeneacetic acid methyl ester (7g). This material was prepared in a similar manner as **7f**, however the crude product was further purified by silica gel column chromatography eluting with 10% EtOAc/hexane to yield 43% of desired **7g** as a yellow oil.

Typical procedure C

(±)-Ethyl *N*-[(2-amino-5-chlorophenyl)methyl]alanine (10c). The preparation of this compound has been previously reported[4] and those reaction conditions exemplify the standard conditions employed for procedure C of this paper.

(*S*)-Ethyl *N*-[(2-amino-5-chlorophenyl)methyl]alanine (10d). This material was prepared in a similar manner to **10c** except the reaction was run on a 86 g scale and was done under H_2 at atmospheric pressure in MeOH, rather than on a Parr hydrogenator under high pressure. Also the catalyst was varied to Pt on C and the catalyst was poisoned with a 1% thiophene to yield desired **10d** in 75% yield.

(±)-Ethyl *N*-[(2-amino-6-chlorophenyl)methyl]alanine (10e). This material was prepared in a similar manner to **10c** to yield desired **10e** in 98% crude yield (TLC: 10:1 CH_2Cl_2:MeOH, $R_f = 0.7$; >85% pure).

Typical procedure D

Ethyl *N*-[(2-amino-5-chlorophenyl)methyl]glycine (10b). Hydrazine hydrate (14.3 mL, 294 mmol) was added slowly over 20 min to a refluxing mixture of **7b** (12.3 g, 45.2 mmol) and RaNi (12.0 g; Fluka) in EtOH (500 mL). After heating an additional 1.5 h the reaction was cooled to room temperature and carefully filtered through Dicalite. The filtrate was concentrated under reduced pressure after which the residue was dissolved in CH_2Cl_2 and washed with water and then brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 8.11 g (74%) of desired **10b** as a brown oil which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.65$).

(±)-Methyl 2-[[(2-amino-5-chlorophenyl)methyl]amino]-3-methylbutanoate (10f). This material was prepared in a similar manner to **10b** except the reaction was run in MeOH rather than EtOH with half the amount of RaNi relative to the **7f** starting material. Also the reaction was run for 4 h rather than 1.5 h to give desired **10f** in 89% yield.

(±)-α-[[(2-Amino-5-chlorophenyl)methyl]amino]benzeneacetic acid methyl ester (10g). This material was prepared in a similar manner as **10b** except the reaction was run in MeOH rather than EtOH to give desired **10g** in quantitative yield (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.85$; >85% pure; minor impurities at R_f 0.5 and 0.55).

Typical procedure E

(±)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (11c). The preparation and spectral characterization of this compound has been previously reported.[4] The reaction conditions described in the cited reference exemplify the standard conditions employed for procedure E of this paper.

(±)-1,3,4,5-Tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (11a). This material was prepared in a similar manner to **11c** except that after work up the crude 47 g of product was dissolved in acetone (60 mL) from which crystallized 3.56 g (7%) of desired **11a** as a white solid. A sample of **11a** (0.176 g, 0.75 mmol) was dissolved in EtOH (4.5 mL) and combined with a solution of fumaric acid (0.12 g, 1.0 mmol) in EtOH (4.5 mL) to yield an analytical sample of the 0.5 molar equivalent fumarate salt of **11a**, mp 228–229°C (TLC: 5:1 CH_2Cl_2:MeOH, $R_f = 0.65$).

7-Chloro-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (11b). This material was prepared in a similar manner to **11c** except that in the work up it was found that the product was water soluble when it was attempted to wash away the HOBT with saturated aqueous $NaHCO_3$. Therefore a continuous extraction with CH_2Cl_2 overnight was employed to yield, after concentration of the organic solution, 20% of desired **11a** as a white solid, mp 182–183°C.

Typical procedure F

(*S*)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (11d). A mixture of **10d**, as its dihydrochloride salt (60 g, 0.182 mol) in 1-methoxy-2-propanol (500 mL) was stirred at reflux for 3 h. The solution was then cooled to room temperature and the resulting solid washed consecutively with 1-methoxy-2-propanol (50 mL) and then diisopropyl ether (4×50 mL). The solid was dried under reduced pressure at 50°C affording 40.2 g (89%) of desired product **11d** as a white solid which was used without further purification.

(±)-6-Chloro-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (11e). This material was prepared in a similar manner as **11d** to yield desired product **11e** in 73% yield (TLC: 10:1 CH_2Cl_2:MeOH, $R_f = 0.4$; ~80% pure; impurities at $R_f = 0.35$ and origin).

Typical procedure G

(±)-7-Chloro-1,3,4,5-tetrahydro-3-(1-methylethyl)-2*H*-1,4-benzodiazepine-2-one (11f). A solution of trimethylaluminum (Me_3Al) (2 M in PhMe; 60 mL, 120 mmol) was added dropwise over 5 min to a 0°C solution of **10f** (8.11 g, 29.95 mmol) in PhMe (150 mL). After stirring an additional 10 min at 0°C the cooling bath was removed and the reaction was warmed to room temperature. After 4 h the reaction mixture was recooled to 0°C and slowly quenched over 30 min with MeOH (125 mL). Upon completion of addition the reaction was rewarmed to room temperature and stirred an additional 0.5 h. The reaction was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. This mixture was filtered and the solid rinsed with a small amount of EtOAc. The biphasic filtrate was separated and the organic phase dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 6.87 g of a brown solid. This material was purified as described in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.3$). **11f**: ^{1}H NMR (DMSO-d_6) δ 0.85–0.9 (d, 6H), 1.9–2.1 (m, 1H), 2.9–3.0 (d, 1H), 3.35 (s, 1H), 3.8 (s, 2H), 6.95–7.05 (d, 1H), 7.25–7.35 (m, 2H), 9.85 (s, 1H).

(±)-7-Chloro-1,3,4,5-tetrahydro-3-phenyl-2*H*-1,4-benzodiazepin-2-one (11g). This material was prepared in a similar manner as compound **11f** and subsequently purified as outlined in Table 2.

Typical procedure H

(+)-(*S*)-7-Chloro-4-(cyclopropylmethyl)-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (4l). Sodium triacetoxyborohydride ($NaHB(OAc)_3$) (0.32 g, 1.5 mmol) was added neat to a room temperature mixture of the HCl salt **11d** (0.25 g, 1 mmol), cyclopropanecarboxaldehyde (0.11 mL, 1.4 mmol), and Et_3N (0.20 mL, 1.4 mmol) in 1,2-dichloroethane (7 mL). After stirring 3 days the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, concentrated under reduced pressure

and purified as outlined in Table 2. **4l**: ^{1}H NMR ($CDCl_3$) δ 0.05–0.2 (m, 2H), 0.5–0.6 (d, 2H), 0.8–1.0 (m, 1H), 1.35–1.4 (d, 3H), 2.25–2.4 (dd, 1H), 2.55–2.65 (dd, 1H), 3.6–3.7 (q, 1H), 4.0–4.15 (dd, 2H), 6.8–6.9 (d, 1H), 7.2–7.25 (m, 2H), 7.65 (bs, 1H).

Compounds 4o, 4p, 4v. These materials were prepared in a similar manner as compound **4l** except for variations in reaction times for **4o** and **4p**. The reaction time for **4o** was 24 h and for **4p** 8 h, after which all three analogues were purified as outlined in Table 2.

Typical procedure I

(±)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-4-(3-methyl-2-butenyl)-2*H*-1,4-benzodiazepin-2-one (4c). 4-Bromo-2-methyl-2-butene (0.27 g, 1.8 mmol) was added neat to a 0°C heterogeneous mixture of **11c** (0.31 g, 1.5 mmol) and *N*,*N*-diisopropylethylamine (*i*-Pr_2EtN) (0.26 mL, 1.5 mmol) in DMF (4 mL). After 0.25 h the reaction became homogeneous. The reaction was then warmed to room temperature and stirred an additional 13 h after which it was partitioned between Et_2O and saturated aqueous $NaHCO_3$. The organic phase was washed with water, then brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.26 g of white solid which was purified as outlined in Table 2. **4c**: ^{1}H NMR ($CDCl_3$) δ 1.35–1.4 (d, 3H), 1.55 (s, 3H), 1.75 (s, 3H), 3.1–3.2 (m, 2H), 3.45–3.55 (q, 1H), 3.8–3.95 (dd, 2H), 5.2–5.3 (t, 1H), 6.85–6.9 (d, 1H), 7.15 (s, 1H), 7.2–7.25 (d, 1H), 7.95 (bs, 1H).

Compounds 4b, 4d, 4e, 4f, 4g, 4k, 4n. These materials were prepared in a similar manner as compound **4c** and purified as outlined in Table 2. The optical purity of **4k** was determined to be >98% based on comparison ^{1}H NMR shift reagent studies with its racemate **4c**. The study entailed adding approximately one molar equivalent of Mosher's acid to respective samples of **4k** (S isomer) and **4c** (racemic mixture) in C_6D_6. The following differences were noted: (1) the Me group on the 3-position of the benzodiazepine ring separated out as a set of overlapping doublets for **4c** while for **4k** it remained a clean doublet; (2) the H on the aromatic ring ortho to the lactam moiety of **4** also separated out as a set of overlapping doublets for **4c** while for **4k** it again remained a clean doublet; and finally, (3) the lactam NH proton split into two clean singlets for **4c** while remaining a sole singlet for **4k**.

(±)-4-(Cyclobutylmethyl)-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (4h). This material was prepared in a similar manner as compound **4c** except the reaction was warmed to 83°C for 16 h, after adding 1 equivalent of KI to facilitate the reaction. The compound was purified as outlined in Table 2.

(+)-(*S*)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-4-(2-methyl-2-butenyl)-2*H*-1,4-benzodiazepin-2-one (4m). This material was prepared in a similar manner as compound **4c** except the reaction was treated with one extra equivalent of *i*-Pr_2EtN to free the salt of **11d**, one equivalent of KI, and was warmed to 65°C for 2 h, then stirred at room temperature for 3 days, to facilitate complete conversion. The crude product was then purified as outlined in Table 2.

(+)-(*S*)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-2-oxo-4*H*-1,4-benzodiazepine-4-acetamide (4q). This material was prepared in a similar manner as compound **4c** except the reaction was treated with one extra equivalent of *i*-Pr_2EtN to free the salt of **11d**, one equivalent of KI, and then warmed to reflux for 3 days to facilitate the reaction. The crude product was then purified as outlined in Table 2. **4q**: ^{1}H NMR (DMSO-d_6) δ 1.15–1.2 (d, 3H), 2.7–3.1 (dd, 2H), 3.3–3.4 (m, 1H), 3.85 (s, 2H), 7.0–7.1 (d, 1H), 7.2 (bs, 1H), 7.3–7.4 (m, 3H), 10.05 (s, 1H).

(±)-7-Chloro-1,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-3-(1-methylethyl)-2*H*-1,4-benzodiazepin-2-one (4t). This material was prepared in a similar manner as compound **4c**, except the reaction was treated with two extra equivalents of 4-bromo-2-methyl-2-butene and the reaction was run for 8 days. The reaction was then purified as outlined in Table 2.

(±)-7-Chloro-1,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-3-phenyl-2*H*-1,4-benodiazepin-2-one (4dd). This material was prepared in a similar manner as compound **4c**, except the reaction was treated with Na_2CO_3 as the base rather than *i*-Pr_2EtN and one equivalent of KI was added to facilitate the reaction. The crude product was then purified as outlined in Table 2. **4t:** ^{1}H NMR ($CDCl_3$) δ 0.8–0.85 (d, 3H), 0.85–0.9 (d, 3H), 1.4–1.55 (m, 1H), 1.65 (s, 3H), 1.75 (s, 3H), 2.95–3.05 (d, 1H), 3.15–3.25 (dd, 1H), 3.25–3.35 (dd, 1H), 3.65–3.85 (dd, 2H), 5.2–5.3 (t, 1H), 6.8–6.9 (d, 1H), 7.2–7.3 (m, 2H), 7.55 (s, 1H).

Procedure J

(±)-7-Chloro-1,3,4,5-tetrahydro-3-methyl-4-(3-methyl-2-butenyl)-2*H*-1,4-benzodiazepin-2-thione (4j). Lawesson's reagent (2.02 g, 5 mmol) was added to a room temperature mixture of **4c** (0.56 g, 2 mmol) in THF (40 mL) after which the reaction mixture was warmed to reflux. This material was then concentrated under reduced pressure and the residue purified as outlined in Table 2. **4j**: ^{1}H NMR ($CDCl_3$) δ 1.35–1.4 (d, 3H), 1.65 (s, 3H), 1.75 (s, 3H), 3.15–3.25 (dd, 1H), 3.25–3.35 (dd, 1H), 3.65–3.85 (dd, 2H), 3.95–4.05 (q, 1H), 5.2–5.3 (t, 1H), 6.9–7.0 (d, 1H), 7.25–7.3 (m, 2H), 9.7 (bs, 1H).

Procedure K

(±)-7-Chloro-2,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-3-(1-methylethyl)-1*H*-1,4-benzodiazepine ethanedioate (1:0.9) (4u). Compound **4t** (0.60 g, 2 mmol) was added neat to a 0°C mixture of lithium aluminum hydride (LAH) (0.223 g, 5.9 mmol) in 1,2 dimethoxyethane (25 mL). The mixture was then stirred at 0°C for 30 min and then warmed to reflux for 16 h. The reaction mixture was then recooled to 0°C and slowly quenched with water (10 mL) and then 3 N NaOH (5 mL). The mixture was then stirred for 1 h after which the salts were filtered off. The filtrate was concentrated under reduced pressure after which the residue was dissolved in CH_2Cl_2 (50 mL), dried over $MgSO_4$, filtered, and

reconcentrated under reduced pressure to give 0.4 g (73%) of faint yellow liquid. A 0.35 g sample of this material was dissolved in EtOH (10 mL) and combined with a solution of oxalic acid (0.215 g, 2.38 mmol) in EtOH (10 mL). The resulting solid was filtered, rinsed with a small amount of EtOH, and then dried under high vacuum at 80°C for 16 h to yield 0.39 g (51%) of the oxalate salt of **4u** as a white solid, mp 181–183°C.

Typical procedure L

(+)-(*S*)-7-Chloro-1,2,3,5-tetrahydro-*N*,3-dimethyl-2-oxo-4*H*-1,4-benzodiazepine-4-carboxamide (4r). Et_3N (0.46 mL, 3.3 mmol) was added neat to a room temperature solution of **11d** (0.74 g, 3 mmol) in MeOH (100 mL). After stirring 15 min methyl isocyanate (0.35 mL, 6 mmol) was added neat to the reaction solution. After 30 min the solution was concentrated under reduced pressure and purified as outlined in Table 2 (TLC: 80:20:5 $CHCl_3$:MeOH:HCOOH, $R_f = 0.75$). **4j**: ^{1}H NMR ($CDCl_3$) δ 1.35–1.45 (d, 3H), 2.5 (d, 3H), 4.3–4.5 (dd, 2H), 5.0–5.1 (q, 1H), 6.5–6.6 (q, 1H), 7.05–7.1 (d, 1H), 7.2–7.25 (dd, 1H), 7.4 (d, 1H), 10.1 (s, 1H).

(+)-(*S*)-7-Chloro-1,2,3,5-tetrahydro-3-methyl-*N*-(1-methylethyl)-2-oxo-4*H*-1,4-benzodiazepine-4-carboxamide (4s). This material was prepared in a similar manner as **4r** and purified as described in Table 2 (TLC: 80:20:5 $CHCl_3$:MeOH:HCOOH, $R_f = 0.8$).

Procedure M

(±)-7-Chloro-1,2,3,5-tetrahydro-3-(1-methylethyl)-2-oxo-4*H*-1,4-benzodiazepin-4-carboxylic acid 1,1-dimethylethyl ester (4w). Di-*tert*-butyl dicarbonate (5.26 g, 24.15 mmol) was added to a room temperature mixture of **11f** (5.47 g, 23 mmol) in CH_3CN (100 mL) and CH_2Cl_2 (200 mL) and immediately warmed to reflux. After 6 h the reaction was cooled to 0°C and the resulting solid filtered and rinsed with a small amount of CH_2Cl_2 to yield, after air drying, 7.35 g (94%) of desired **4w** as a white solid (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.45$). **4w**: ^{1}H NMR (DMSO-d_6) δ 0.8–0.95 (m, 6H), 1.3–1.4 (bs, 9H), 1.7–2.1 (bd, 1H), 4.05–4.25 (bs, 1H), 4.35–4.5 (bd, 2H), 7.05–7.15 (d, 1H), 7.3–7.35 (dd, 1H), 7.4 (bs, 1H), 10.15 (bs, 1H).

Procedure N

(±)-7-Chloro-1,2,3,5-tetrahydro-3-(1-methylethyl)-2-thioxo-4*H*-1,4-benzodiazepin-4-carboxylic acid 1,1-dimethylethyl ester (4x). Lawesson's reagent (6.37 g, 15.75 mmol) was added to a room temperature mixture of **4w** (5.08 g, 15 mmol) in THF (300 mL). The mixture was then warmed to reflux for 1 h and then cooled to room temperature and an additional portion of Lawesson's reagent (6.37 g, 15.75 mmol) was added. The mixture was then rewarmed to reflux and heated an additional 2.5 h. The resulting solution was concentrated under reduced pressure and purified as outlined in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.85$).

(±)-7-Chloro-1,3,4,5-tetrahydro-3-(1-methylethyl)-2*H*-1,4-benzodiazepine-2-thione trifluoroacetate (1:1.3). (**4y**). Compound **4x** (1.42 g, 4 mmol) was slowly added to 0°C trifluoroacetic acid (TFA) (5 mL). Upon completion of addition the reaction was stirred an additional 0.5 h at 0°C and then warmed to room temperature and stirred an additional 0.5 h. The mixture was then concentrated under reduced pressure and the residue partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Between this biphasic mixture a solid precipitated which was filtered and rinsed with a small amount of CH_2Cl_2 to give 1.48 g of desired product **4y** as its TFA salt, mp 220–222°C (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.5$). **4y**: ^{1}H NMR (DMSO-d_6) δ 0.85–0.9 (d, 3H), 0.95–1.0 (d, 3H), 2.5–2.65 (m, 1H), 3.5–3.6 (d, 1H), 3.95–4.3 (dd, 2H), 7.25–7.3 (d, 1H), 7.6 (dd, 1H), 7.6–7.65 (d, 1H), 12.65 (bs, 1H).

(±)-7-Chloro-1,3,4,5-tetrahydro-3-(1-methylethyl)-4-(3-methyl-2-butenyl)-2*H*-1,4-benzodiazepin-2-thione (4z). $NaHB(OAc)_3$ (0.82 g, 3.85 mmol) was added to a room temperature mixture of the TFA salt **4y** (1.01 g, 2.75 mmol) and 3-methyl-2-butenal (0.28 g, 3.3 mmol) in CH_2Cl_2 (100 mL). After stirring 0.4 h, an additional portion of $NaHB(OAc)_3$ (0.82 g, 3.85 mmol) was added. After 0.8 h a third portion of $NaHB(OAc)_3$ (0.82 g, 3.85 mmol) was added. The reaction was then stirred 3 h after which the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.83 g of yellowish solid. This material purified as outlined in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.5$). **4z**: ^{1}H NMR ($CDCl_3$) δ 0.75–0.8 (d, 3H), 0.8–0.85 (d, 3H), 1.15–1.35 (bs, 1H), 1.7 (s, 3H), 1.8 (s, 3H), 3.35–3.4 (d, 2H), 3.45–3.65 (m, 2H), 3.65–3.7 (d, 1H), 5.2–5.3 (t, 1H), 6.9–6.95 (d, 1H), 7.25–7.35 (m, 2H), 9.45 (bs, 1H).

Procedure O

(±)-7-Chloro-1,2,3,5-tetrahydro-1-methyl-3-(1-methylethyl)-2-oxo-4*H*-1,4-benzodiazepin-4-carboxylic acid 1,1-dimethylethyl ester (4aa). Compound **4w** (0.34 g, 1 mmol) was added neat to a stirring, room temperature mixture of powdered KOH (0.27 g, 5 mmol) and MeI (0.62 mL, 10 mmol) in acetone (12 mL). After stirring 4 h the mixture was concentrated under reduced pressure and the residue partitioned between EtOAc and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a white residue. This material purified as outlined in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.7$). **4aa**: ^{1}H NMR ($CDCl_3$) δ 0.65–0.8 (bd, 7H), 1.5 (s, 9H), 3.4 (s, 3H), 4.05–4.2 (bd, 1H), 4.45–4.55 (bs, 1H), 4.75–4.9 (bs, 1H), 7.1–7.15 (d, 1H), 7.35–7.45 (m, 2H).

(±)-7-Chloro-1,3,4,5-tetrahydro-1-methyl-3-(1-methylethyl)-2*H*-1,4-benodiazepin-2-one trifluoroacetate (2:1) (4bb). This material was prepared in a similar manner as **4y**, after substituting **4aa** for **4x**, to yield desired product **4bb** after purification as outlined in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.4$). **4bb**: ^{1}H NMR (DMSO-d_6) δ 0.7–0.75 (d, 3H), 0.8–0.85 (d, 3H), 1.8–1.95 (m, 1H), 2.6–2.7 (bt, 1H), 2.9–3.0 (bm, 1H), 3.25 (s, 3H), 3.55–3.65 (dd, 1H), 3.7–3.8 (d, 1H), 7.4–7.5 (m, 3H).

(±)-7-Chloro-1,3,4,5-tetrahydro-1-methyl-4-(3-methyl-2-butenyl)-3-(1-methylethyl)-2*H*-1,4-benodiazepin-2-one hydrochloride (1:1) (4cc). This material was prepared following the typical procedure I to yield desired **4cc** after purification as outlined in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.8$). Free Base sample of **4cc**: ^1H NMR ($CDCl_3$) δ 0.65–0.7 (d, 3H), 0.8–0.85 (d, 3H), 1.2–1.3 (m, 1H), 1.7 (s, 3H), 1.75 (s, 3H), 2.9–2.95 (d, 1H), 3.05–3.15 (bdd, 1H), 3.25–3.4 (m, 5H), 3.6–3.65 (d, 1H), 5.2–5.3 (bt, 1H), 7.05–7.1 (d, 1H), 7.3–7.35 (m, 2H).

Procedure P

(±)-Ethyl *N*-(3-methyl-2-butenyl)alanine (14). Et_3N (16.7 mL, 0.12 mol) was added to a room temperature mixture of **12**[13] (12.1 g, 0.10 mol) in DCE (400 mL). After stirring 0.2 h, ethyl pyruvate, **13** (10.95 mL, 0.10 mol) was added and the mixture was stirred an additional 0.4 h. $NaHB(OAc)_3$ (29.67 g, 0.14 mol) was then added to the mixture. After stirring 16 h the mixture was treated with saturated aqueous $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 14.95 g (81%) of desired **14** as an oil which was used without further purification. **14:** ^1H NMR ($CDCl_3$) δ 1.25–1.35 (m, 6H), 1.65 (s, 3H), 1.75 (s, 3H), 3.05–3.15 (dd, 1H), 3.2–3.3 (dd, 1H), 3.3–3.45 (q with broadening underneath, 2H), 4.2–4.3 (q, 2H), 5.2–5.3 (t, 1H).

(±)-Ethyl *N*-(5-chloro-2-nitrobenzoyl)-*N*-(3-methyl-2-butenyl)alanine (16). A solution of **15**[14] (14.24 g, 65 mmol) in CH_2Cl_2 (20 mL) was added to a 0°C solution of **14** (12.02 g, 65 mmol) and Et_3N (9.04 mL, 65 mmol) in CH_2Cl_2 (200 mL). After stirring for 30 min upon completion of addition the mixture was extracted with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 17.94 g (75%) of desired **16** which was used without further purification (TLC: 20:1 CH_2Cl_2: MeOH, $R_f = 0.8$).

(±)-7-Chloro-3,4-dihydro-3-methyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepin-2,5-dione (4i). Hydrazine hydrate (12.1 mL, 0.245 mol) was added over 1 h to a refluxing mixture of **16** (9.2 g, 0.025 mol) and RaNi (3.8 g; Fluka) in EtOH (500 mL). After stirring for 16 h at reflux, the mixture was cooled, filtered over Dicalite, and the resulting filtrate concentrated under reduced pressure to give 7.93 g of residue. This material was purified as outlined in Table 2. **4i:** ^1H NMR ($CDCl_3$) δ 1.15–1.35 (bs, 1.5H), 1.5–1.6 (bs, 1.5H), 1.7–1.85 (bs, 6H), 3.95–4.1 (bd, 0.5H), 4.1–4.3 (q, 1.5H), 4.35–4.5 (bdd, 1H), 5.15–5.3 (bs, 1H), 6.9–6.95 (d, 1H), 7.4–7.45 (dd, 1H), 7.9–8.05 (bs, 1H), 8.15–8.25 (bs, 0.5H), 8.35–8.45 (bs, 0.5H).

Acknowledgments

We appreciate the assistance of John Masucci and William Jones of the R.W. Johnson Pharmaceutical Research Institute for obtaining mass spectra data and Diane Gauthier of the R.W. Johnson Pharmaceutical Research Institute for obtaining NMR data. We also thank Hilda Azijn for technical assistance in the HIV-1 testing, Laurene Latham for information and data retrieval, and James Fortunato for nomenclature assistance.

References

1. Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.; Breslin, H.; Raeymaekers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellenkens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. *Nature* **1990**, *343*, 470.
2. Kukla, M.; Breslin, H.; Pauwels, R.; Fedde, C.; Miranda, M.; Scott, M.; Sherrill, R.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. *J. Med. Chem.* **1991**, *34*, 746.
3. Kukla, M.; Breslin, H.; Diamond, C.; Grous, P.; Ho, C. Y.; Miranda, M.; Rodgers, J.; Sherrill, R.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L.; Janssen, M. A. C.; Janssen, P. *J. Med. Chem.* **1991**, *34*, 3187.
4. Breslin, H.; Kukla, M.; Ludovici, D.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J.; Hitchens, T. K.; Leo, G.; Gauthier, D.; Ho, C.; Scott, M.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. *J. Med. Chem* **1995**, *38*, 771.
5. Ho, W.; Kukla, M.; Breslin, H.; Ludovici, D.; Grous, P.; Diamond, C.; Miranda, M.; Rodgers, J.; Ho, C.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. *J. Med. Chem* **1995**, *38*, 794.
6. Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, A. S.; Clemens, M.; Colacino, J. M.; Deeter, J. B.; Engelhardt, J. A.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kasher, J. S.; Kinnick, M. D.; Lind, P.; Lopez, C.; Morin, J. M., Jr.; Muesing, M. A.; Noreen, R.; Oberg, B.; Paget, C. J.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Rippy, M. K.; Rydergard, C.; Sahlberg, C.; Swanson, S.; Ternansky, R. J.; Unge, T.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. -X. *Antimicrob. Agents Chemother.* **1995**, *39*, 1329.
7. Dodd, R. H.; Liu, J. *J. Heterocyclic Chem.* **1995**, *32*, 523.
8. Townsend, L.; Swayze, E.; Peiris, S.; Kucera, L.; White, E.; Wise, D.; Drach, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 543.
9. Celnik, K.; Jankowske, Z. *Pol. J. Chem.* **1978**, *52*, 947.
10. Pialoux, G.; Youle, B.; DuPont, B.; Gazzard, B.; Cauwenbergh, G.; Stoffels, P.; Davies, S.; De Saint Martin, J.; Janssen, P. *Lancet* **1991**, *338*, 140.
11. Pauwels, R.; De Clercq, E.; Desmyter, J.; Balzarini, J.; Goubau, P.; Herdewijn, P.; Vandeputte, M. *J. Virol. Methods* **1987**, *16*, 171.
12. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 209.
13. Elliott, R.; Montogomery, J. *J. Med. Chem.* **1977**, *20*, 116.
14. Peet, N. P.; Sunder, S. US Patent 4,419,357, *Chem. Abstr.* **1983**, *99*, 194993.