sphere for 2 h, solids were filtered using analytical grade Celite, and the filtrate was concentrated to furnish 1.56 g (86%) of **2** as an amorphous white solid: NMR (D_2O) δ 1.17-1.80 (m, 12 H), 2.11 (s, 3 H), 2.33-2.93 (m, 8 H), 3.15 (t, 4 H, J = 7), 3.33 (s, 3 H), 3.46-3.84 (m, 16 H). Anal. ($C_{27}H_{51}N_5O_{11}$) C, H, N.

11,22,33-Trihydroxy-12,15,23,26,34-pentaoxo-11,16,22,27,33-pentaaza-2,5,8,36,39,42-hexaoxatritetracontane (3). Compound **23** (2.0 g, 1.8 mmol) was debenzylated by the method of **2** to furnish 1.35 g (80%) of **3** as an amorphous solid. A sample of **3** (0.845 g) was passed through Sephadex LH-20 eluting with EtOH to afford an analytical sample (0.766 g) of **3**: NMR (D_2O) δ 1.10-1.78 (m, 12 H), 2.33-2.93 (m, 8 H), 3.15 (t, 4 H, J = 7), 3.33 (s, 6 H), 3.47-3.85 (m, 24 H), 4.38 (s, 2 H). Anal. ($C_{32}H_{61}N_5O_{14}$) C, H, N.

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Registry No. **2**, 135638-91-4; **3**, 135638-92-5; **7**, 129245-21-2; **14**, 135638-82-3; **15**, 135638-83-4; **16**, 135638-84-5; **17**, 135638-85-6; **18**, 135638-86-7; **19**, 135638-87-8; **20**, 135638-88-9; **21**, 135638-89-0; **22**, 135638-90-3; **23**, 135658-21-8; $PhCH_2ONHBOC$, 79722-21-7; succinic anhydride, 108-30-5; 3,6,9-trioxadecyl tosylate, 62921-74-8; 3,6,9-trioxadecanoyl chloride, 63881-16-3; iron, 7439-89-6.

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

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In the first paper of this series a new structure with anti-HIV-1 activity was disclosed and analogues were synthesized to explore the structure-activity relationship of changes in the substituent (R) attached at the N-6 position of **9**. This study describes the syntheses and anti-HIV-1 testing of analogues with variations of the five-membered urea ring of the 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) structures. Although many different rings were synthesized to replace the cyclic urea of TIBO, most were found to be inactive in inhibiting the replication of the HIV-1 virus in MT-4 cells. The exceptions were replacement of the urea oxygen with sulfur or selenium to give the corresponding thio- or selenoureas. These were found to be more active than the oxygen counterparts. A small series of analogues was synthesized and tested which allowed direct comparison of urea and thiourea derivatives. Without exception, the latter were always more active than the former. The most active compound of this series (**8d**) was found to inhibit the HIV-1 virus with an IC_{50} of 0.012 μM which is comparable to that of AZT.

Introduction

In previous publications[1,2] we described the discovery of a new series of compounds, 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one derivatives, that were assigned the acronym TIBO derivatives. The initial lead compounds, represented by structure **9**, were found to specifically inhibit replication of HIV-1 virus, the causative agent for AIDS (acquired immune deficiency syndrome). The first paper in this series[2] described variation of the N-6 substituent and the resultant structure-activity relationships (SAR). Although those compounds had specific and consistent activity against HIV-1 virus, there was a need to find compounds with a higher level of potency. The best compound from the previous paper had activity comparable to DDI (2',3'-dideoxyinosine), which is currently undergoing clinical evaluation, but AZT (Zidovudine), the only approved drug against AIDS, was >2600 times as effective as our best analogue in blocking replication of the HIV-1 virus in the cellular assay used to determine relative potency. This publication describes efforts to systematically alter the 5-ring urea portion of the tricyclic TIBO structure **9** to determine the effects these changes might have on the relative potency of the resultant analogues to block HIV-1 replication.

Chemistry

In addition to the synthetic methods previously described[2] to obtain the basic ring system of the TIBO series, Scheme I illustrates an efficient and versatile synthesis of several analogues and intermediates. Chloroisatoic anhydride (**1**) is treated with alanine methyl ester hydrochloride in pyridine under reflux.[3] Although the *l* isomer is pictured, the scheme has been carried out with both the *d* isomer and racemic material as well. The aromatic chloro substituent in **2** acts as a convenient block to para nitration in the next step, yet can be readily removed (step 8) if desired. Treatment of **2** with cold fuming nitric acid gave a 92% yield of **3**. Reduction of **3** with lithium aluminum hydride (LAH) in refluxing glyme served to reduce both the carbonyls and the nitro functionalities to yield triamine **4**. This material was specifically monoalkylated

† Janssen Research Foundation, Pennsylvania.
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‡ Janssen Research Foundation, Belgium.

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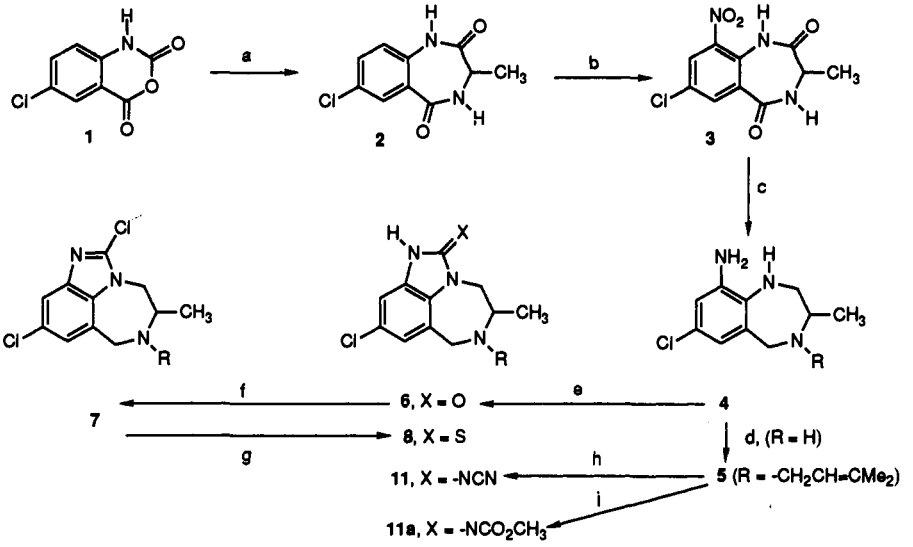
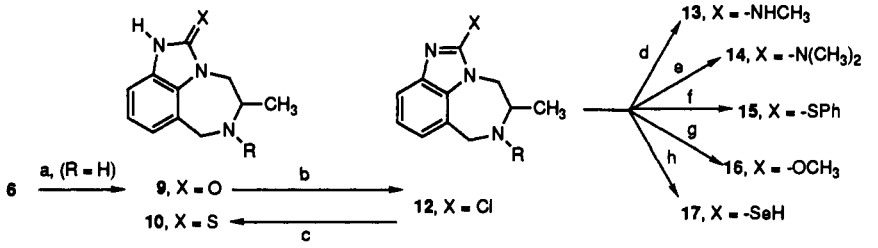
Scheme I[a]



[a] (a) Alanine methyl ester·HCl, pyridine, reflux; (b) fuming nitric acid, 0 °C; (c) LAH, glyme, reflux; (d) $ClCH_2CH{=}CMe_2$, Na_2CO_3, KI, DMF; (e) $Cl_3COCOCl$, N-methyl morpholine, CH_2Cl_2, 0 °C; (f) $POCl_3$, Na_2CO_3, 60–110 °C; (g) thiourea, EtOH, reflux; (h) $(PhO)_2C{=}NCN$, iPrOH; (i) $CH_3OC(=NH)NHCO_2CH_3$, $CHCl_3$/HOAc.

Scheme II[a]



[a] (a) 10% Pd/C, $NH_4^+HCO_2^-$, iPrOH/H_2O; (b) $POCl_3$, Na_2CO_3, 60–110 °C; (c) thiourea, EtOH, reflux; (d) 40% aq H_2NCH_3, MeOH, reflux; (e) 40% aq $HN(CH_3)_2$, MeOH, reflux; (f) PhSH, NaOH, MeOH/H_2O, reflux; (g) Na, MeOH; (h) $H_2NC{=}SeNH_2$, EtOH.

to give **5** by addition of less than 1 equiv of alkylating agent to a cold (0–5 °C) solution of **4** and monitoring the extent of reaction, as well as formation of dialkylated product. As the latter became significant the reaction was halted with the ratio of **4**:**5** ca. 1:2. The product **5** was isolated by column chromatography. By the previously described procedures,[2] **4** and **5** were converted to the corresponding benzimidazolones, **6**. As mentioned above, the chlorine in **6** (R = H) was readily removed by palladium-catalyzed reduction using ammonium formate as the source of hydrogen.[4] Conversion of *ones* (**6** or **9**) to *thiones* (**8** or **10**), when R was not hydrogen, was accomplished in a two-step procedure. Treatment of **6** with phosphorus oxychloride at elevated temperatures gave intermediate **7** in ca. 60% yields. Literature studies[5] of the reaction of benzimidazolone with $POCl_3$ had shown that bubbling HCl through the heated mixture increased the reaction rate. In this case, when R was an allylic side chain, especially 3,3-dimethylallyl, that procedure caused an increase in the amount of side products presumably arising from addition and subsequent elimination of HCl to give isomeric olefin side chains.

Intermediate **5** was treated with diphenyl cyanocarbonimidate[6] to give **11** or with methyl (iminomethoxymethyl)carbamate[7] to obtain guanidine derivative **11a** (Scheme I).

Imino chloride **12**, synthesized by the same method used to obtain **7**, was a useful starting point for analogues **13**–**17** (Scheme II). The displacements to form **13**–**15** all seemed to require the presence of water, since in each case the reactions run under anhydrous conditions were unsuccessful. On the other hand, when **16** was prepared with commercial NaOMe, presumably contaminated with NaOH, a significant amount of hydrolysis product (X = OH) was formed, while freshly prepared reagent did not generate this side product.

Another approach to target structures (Scheme III) was to reduce dilactam **2** to the corresponding benzodiazepine followed by selective acylation of the more basic nitrogen. Nitration followed by chemical reduction of the amide and nitro groups gave **19**, which was used to synthesize analogues **20**–**22**. Use of reactive reagents like sulfuryl chloride or sulfuryl amide chloride failed to give **20** from **19**,

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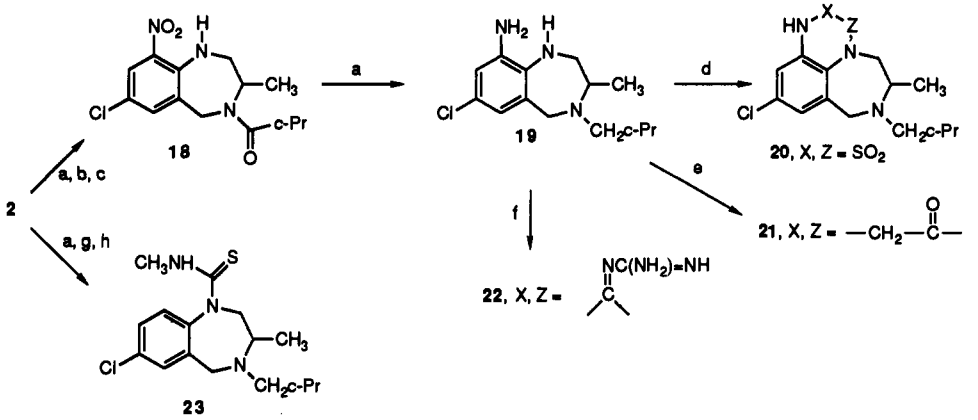
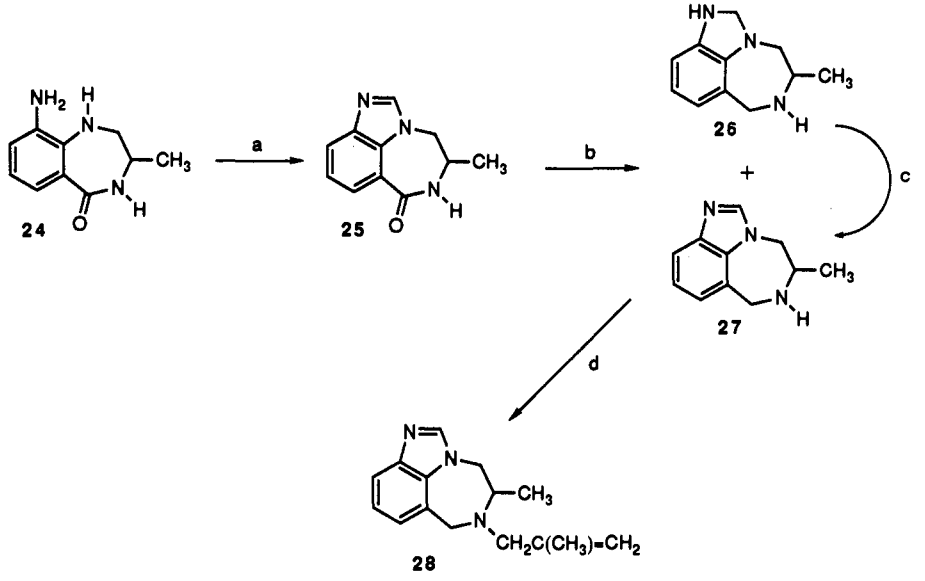
Scheme III[a]



[a] (a) LAH, glyme; (b) c-PrCOCl, Et_3N, CH_2Cl_2; (c) fuming HNO_3; (d) $H_2NSO_2NH_2$, 185 °C; (e) $BrCH_2CO_2H$, CH_2Cl_2; (f) H_2NCN, conc HCl, 90 °C; (g) $BrCH_2c$-Pr, Na_2CO_3, DMF; (h) CH_3NCS, iPrOH.

Scheme IV[a]



[a] (a) Formamidine acetate; (b) LAH, glyme, reflux; (c) air; THF; (d) $ClCH_2C(CH_3)=CH_2$, KI, Na_2CO_3, DMF.

whereas heating **19** neat with sulfamide gave **20**, albeit in low yield. On the other hand, **19** react readily with bromoacetic acid at ambient temperature to give **21**. Interestingly, none of the isomeric material with the carbonyl and methylene interchanged, which would result from alkylation of the ring amine, was detected. Bisguanidine derivative **22** came form reaction of **19** with cyanamide in concentrated hydrochloric acid.

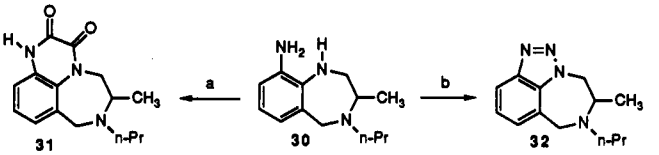
In a three-step procedure (Scheme III), **2** was reduced to the benzodiazepine as before, specifically alkylated at the secondary amine versus the anilino nitrogen, and then reacted with methyl thioisocyanate at the latter amine. This led to acyclic thiourea analogue **23**.

Benzimidazole derivative **28** was obtained from **24**[2] (Scheme IV) by reaction with formamidine acetate. The seven-membered-ring nitrogen of **24** had been rendered nonbasic as a lactam. Subsequent reduction of that carbonyl by LAH also reduced the heterocycle to dihydrobenzimidazole **26**, which was readily air oxidized to **27** by stirring a THF solution in an open flask.

Intermediate **30**, akin to **19**, was reacted with oxalyl chloride or nitrous acid (Scheme V) to form dicarbonyl analogue **31** or triazine **32**, respectively.

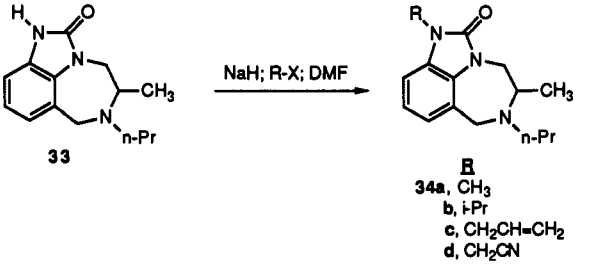
A short series of compounds alkylated on the benzimidazolone nitrogen, **34a–d**, was obtained (Scheme VI)

Scheme V[a]



[a] (a) $(COCl)_2$, $PhCH_3$; (b) $NaNO_2$; HCl.

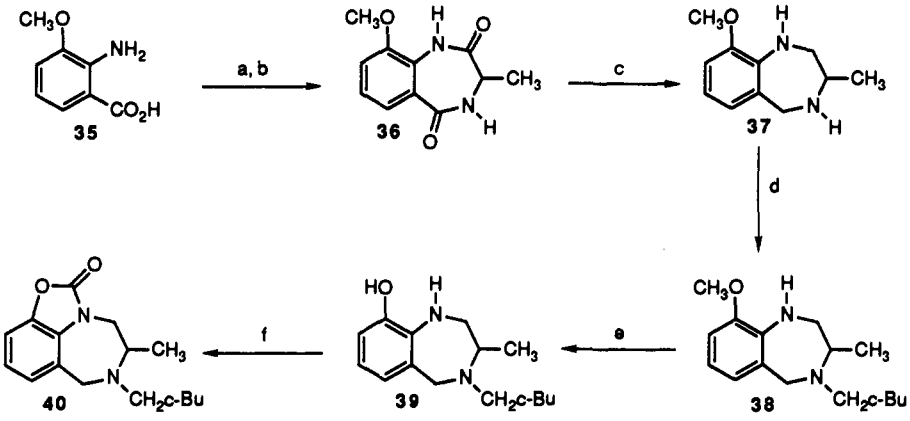
Scheme VI



by deprotonating **33** with sodium hydride in the presence of the appropriate alkylating agent.

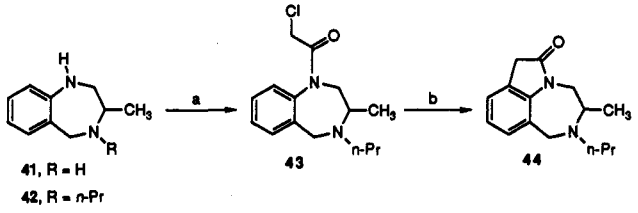
Replacing that same benzimidazolone nitrogen with oxygen was accomplished by the procedure shown in

Scheme VII[a]



[a] (a) Alanine methyl ester, DCC, HBT, NMM; (b) 200 °C, neat; (c) BH_3, THF; (d) $BrCH_2c$-Bu, Na_2CO_3, KI, DMF; (e) BBr_3, CH_2Cl_2; (f) urea, 200 °C.

Scheme VIII[a]



[a] (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2; (b) $AlCl_3$, 175 °C.

Scheme VII. 3-Methoxyanthranilic acid (**35**) was coupled with alanine methyl ester followed by cyclization to give dilactam **36**. Initial attempts to reduce **36** with LAH gave multiple products; the major was from demethylation of the methyl ether to give the phenol analogue of **37**. Attempts to selectively alkylate the benzylic amine of this phenol product or to form the desired benzoxazolone with diphosgene were unsuccessful. Subsequently, reduction of the dilactam **36** to diamine **37** was carried out smoothly with borane. This in turn was selectively alkylated to **38** and converted to phenol **39** with boron tribromide. The final target benzoxazolone **40** was obtained by carbonylating **39** in a melt with urea.

The synthesis of **44** (Scheme VIII), the corresponding carbon replacement of the secondary nitrogen in the five-membered ring of **9**, began with selective alkylation of diamine **41** with *n*-propyl iodide to yield **42**. Compound **42** was acylated with chloroacetyl chloride and the intermediate chloride **43** was cyclized to **44** with aluminum chloride at elevated temperatures.

A series of analogues in which the benzimidazolone tertiary nitrogen of **9** was replaced by carbon is exemplified in Scheme IX. Intermediate **45**, available through a Gassman oxindole synthesis,[8] was alkylated with chloroacetone to yield oxindole **46**. Limited reduction of **46** with zinc dust in acidic media removed the thiomethyl group to give **47**. However, reduction of **46** with Raney nickel in *tert*-butyl alcohol resulted in desulfurization, reduction of the nitrile, and subsequent intramolecular reductive amination of the resultant primary amine with the ketone to furnish the desired ring system **48**. NOE studies indicated that **48** is a single diastereomer with the 3- and 5-position protons of the chiral centers in a cis relationship. Alkylation of **48** was accompanied by epimerization of the oxindole ring to give a 3:1 mixture (^1H NMR) of products **49**. Conversion of **49** to thione **50** was accomplished with Lawesson's reagent and chlorination of **49** with phosphorus oxychloride yielded chloroindole **51**. The stereochemistry of **50** was determined by ^1H NMR to be a 3:2 mixture of diastereomers. Dehalogenation of **51** to indole derivative **52** was accomplished with palladium on carbon. Treatment of **49** with base in the presence of dimethyl sulfoxide resulted in α oxidation to alcohol **53**.

Results and Discussion

The ability of the compounds reported in this paper to block replication of HIV-1 was determined in MT-4 cells as described previously.[9] The cells were either infected with HIV-1 or mock infected and incubated in the presence of various concentrations of the test compounds. The number of viable cells was then determined 5 days after infection by staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.[10] The reported values shown in Tables I and II 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 virus. 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. In some cases, higher testing concentrations than those shown were precluded because the tested compounds were toxic to the control or mock-infected cells. The IC_{50} determinations or evaluations of activity for each compound reported in the tables were assayed in duplicate and the IC_{50} values are reported as an average of those determinations. 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.

As indicated in Table I, we have made a large range of variations of the five-membered-ring urea portion of the tricyclic TIBO structures. In general, this part of the molecule has proven to be extremely important to the activity of the TIBO series. The majority of these alterations have led to complete loss of activity, although the

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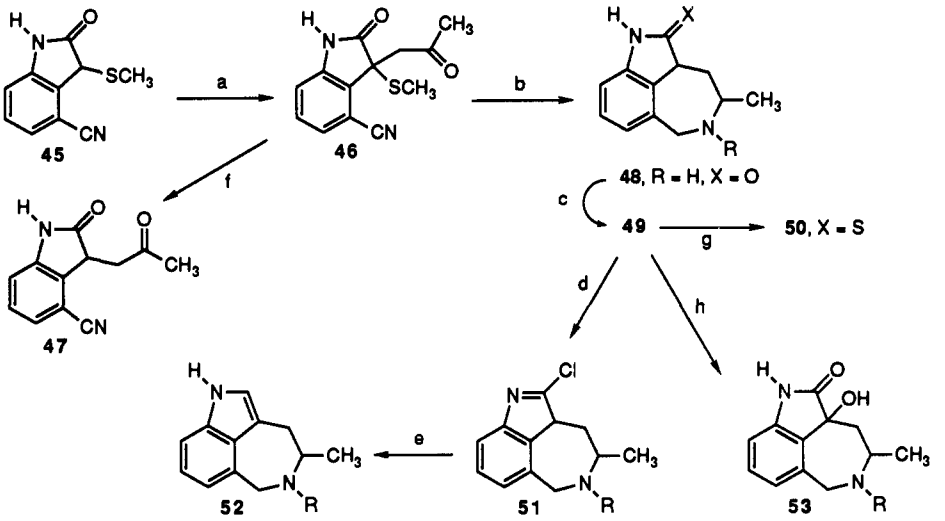
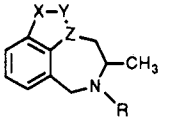
Scheme IX[a]



[a] (a) Chloro acetone, K_2CO_3, KI, DMF; (b) Raney Ni, t-BuOH; (c) R-X, KI, Na_2CO_3, DMF; (d) $POCl_3$, reflux; (e) 10% Pd/C, EtOH, Et_3N; (f) Zn dust, HOAc, THF; (g) Lawesson Reagent, BHT, $PhCH_3$; (h) K_2CO_3, DMSO, H_2O.

Table I. Testing of 5-Ring Variations To Inhibit HIV-1 Replication



no.	X-Y-Z	5-config	arom sub	R	IC_{50},[a] μM
9a	HC-(C=O)-N	±		DMA[b]	9.8
10a	HN-(C=S)-N	±		DMA	0.097
11	HNC(=NCN)-N	*S*	9-Cl	DMA	>250
11a	N=C($NHCO_2CH_3$)-N	*S*(+)	9-Cl	DMA	>10
13	N=C($NHCH_3$)-N	±		DMA	>250
14	N=C(NMe_2)-N	±		DMA	>250
15	N=C(SPh)-N	±		DMA	>50
16	N=C(OCH_3)-N	±		DMA	>250
17	HN-(C=Se)-N	*S*(+)	9-Cl	DMA	0.018
20	HN-SO_2-N	±	9-Cl	CH_2-c-Pr	>10
21	HN-CH_2-(C=O)-N	±	10-Cl	CH_2-c-Pr	>10
22	HN-C=N(C(NH_2)=NH)-N	±	9-Cl	CH_2-c-Pr	>50
23	acyclic (Me-NH-(C=S)-N)	*S*(-)	7-Cl	CH_2-c-Pr	>10
28	N=C-N	±		2-MA[c]	>2
31	HN-(C=O)-(C=O)-N	±		*n*-Pr	>250
32	N=N-N	±		*n*-Pr	>10
34a	Me-N-(C=O)-N	±		*n*-Pr	>250
34b	iPr-N-(C=O)-N	±		*n*-Pr	>250
34c	allyl-N-(C=O)-N	±		*n*-Pr	>50
34d	NCCH_2-N-(C=O)-N	±		*n*-Pr	>250
40	O-(C=O)-N	±		CH_2-c-Bu	>2
44	CH_2-(C=O)-N	±		*n*-Pr	>250
49	HN-(C=O)-CH	±		2-MA	>50
50a	HN-(C=S)-CH	±		2-MA	>10
50b	HN-(C=S)-CH	±		A[d]	>250
51	HN-C(Cl)=C	±		*n*-Pr	>50
52	HN-CH=C	±		*n*-Pr	>250
53	HN-(C=O)-C(OH)	±		2-MA	>250

[a] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 virus or highest concentration tested which did not achieve 50% protection. [b] DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl. [c] 2-MA = 2-methylallyl or 2-methyl-2-propenyl. [d] A = allyl.

replacement of the urea (one) with a thiourea (thione), as indicated in Tables I and II, has yielded much more potent derivatives. In fact, there seems to be a need for the intact ring, since the analogue **23**, which includes all the necessary elements of the most active compounds but in an acyclic array, is inactive. On the other hand, two replacements of the 5-ring with a 6-ring by insertion of a methylene (**21**) or another carbonyl (**31**) also proved to be inactive.

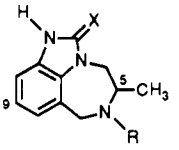
A limited number of changes in the 1-position (X in Table I structures), which included alkylation of the urea nitrogen (**34a–d**) or replacement of the nitrogen with oxygen (**40**) or carbon (**44**), have all led to inactive derivatives. Possibly the NH is necessary for hydrogen bonding either at nitrogen or through tautomerization at the 2-position carbonyl.

Because the 3-position (Z in Table I structures) is a ring juncture, the only logical change was to exchange carbon for nitrogen as indicated in analogues **49–53**. Again, the products of these alterations proved to be inactive compounds, including **49** and **50**, which are the direct carbon analogues of active structures **9** and **10**.

The 2-position (Y in Table I structures) is where the greatest number of variations have been investigated. Analogues with replacements of the carbonyl carbon with nitrogen to give triazine **32** and sulfur dioxide to give sulfonamide **20** or deletion of the oxygen as encompassed in imidazole **28** all failed to protect the test cells from the HIV-1 infection. However, replacement of the carbonyl oxygen with the other group VI elements, sulfur (**10a**) and selenium (**17**), led to compounds with much higher potency. A number of other variations along that theme proved unsuccessful, including cyanamide derivative **11**, which in the histamine H-2 blockers had been a potent isosteric replacement for a thiourea.[11] Additionally, guanidines (**13** and **14**), bisguanidine (**22**), carbamate (**11a**), O-methylated urea (**16**), and S-phenylated thiourea (**15**) were also inactive variations.

These observations give the impression that the heteroatom attached to the 2-position, either oxygen, sulfur, or selenium, is directly involved in the binding of these inhibitors to HIV-1 reverse transcriptase (see below). This is further borne out by the limitations of the heteroatom attached at the 2-position. As previously mentioned, analogues with a nitrogen attachment (**11**, **11a**, **13**, **14**, and **22**) were completely devoid of activity. At this point, it is not clear whether the lack of activity is the result of the electronegativity differences, imparted basicity of nitrogen versus the group VI elements, or the fact that the nitrogen derivatives all have the added bulk of attached substituents.

Table II. Comparison of *One* versus *Thione* Derivatives in Inhibition of HIV-1 Replication



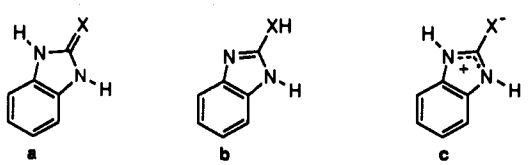
R	5-config	arom sub	X = O no.	X = O IC_{50},[a] μM	X = S no.	X = S IC_{50},[a] μM	ratio (O/S)[b]
DMA[c]	±		**9a**	9.8 (16)	**10a**	0.097 (6)	101
CH_2-c-Pr	*S*(+)		**9b**	10.0 (5)	**10b**	0.06 (5)	167
2-MA[d]	*S*(+)		**9c**	15.2 (17)	**10c**	0.026 (5)	584
n-Pr	±		**9d**	60.0 (15)	**10d**	1.7 (7)	36
CH_2-c-Bu	*S*(+)	9-Cl	**6a**	0.38 (7)	**8a**	0.026 (9)	15
DMA	*S*(+)	9-Cl	**6b**	0.18 (2)	**8b**	0.039 (53)	5
CH_2CH_2-c-Pr	*S*(+)	9-Cl	**6c**	2.2 (3)	**8c**	0.42 (4)	5
DEA[e]	*S*(+)	9-Cl	**6d**	0.029 (7)	**8d**	0.012 (5)	2
DMA	*R*(−)	9-Cl	**6e**	4.2 (6)	**8e**	0.39 (5)	11
AZT						0.004	
DDC						0.137	
DDI						5.5	

[a] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 virus. This is a mean of multiple IC_{50} determinations, the number of which is included in parentheses. [b] Ratio of the IC_{50}s of *one* versus *thione* analogues. [c] DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl. [d] 2-MA = 2-methylallyl or 2-methyl-2-propenyl. [e] DEA = 3,3-diethylallyl or 3-ethyl-2-pentenyl.

Table II lists a series of analogues and their IC_{50}s in blockade of HIV-1 replication, which allows comparison of the *one* and *thione* derivatives. The list includes a variety of N-6 substituents,[2] compounds with or without a 9-chloro substituent, and racemic, *R*, or *S* configurations at the 5-position. Looking at this data, a few trends are apparent which warrant mention. Without exception, the *thiones* are more potent than the corresponding *ones* in the MT-4 cell assay, which is exemplified by the ratios (see Table II) being >1 in all cases. However, the ratios are not consistent within the limited series and range from 2 to 584.

There are some obvious differences between the oxygen and sulfur TIBO derivatives which might help to explain the differences in activity. As indicated earlier, the proton of the secondary urea seems to be necessary for activity. The relative pK_as of the urea proton versus the thiourea proton might be an indication of the propensity of the proton to form a hydrogen bond in binding at a receptor. Although we have not measured the pK_as in our compounds, Brown has found[12] that, in the case of the simple thiobenzimidazolone versus benzimidazolone, the acidity of the sulfur analogue (pK_a = 10.24) is significantly higher than that of the oxygen analogue (pK_a = 11.95).

One might speculate that the active form of the TIBO structures that interacts with the reverse transcriptase (see later discussion) is the hydroxy (**54b**) or thiol (**55b**) tautomer of the urea or thiourea, respectively. Although we



54, X = O
55, X = S

a b c

have no experimental determinations within the reported series of *ones* and *thiones*, in either case the tautomerization presumably lies far to the side of the carbonyl (**54a**) or thiocarbonyl (**55a**) with the hydroxy or thiol constituting a minor contribution to the character of the molecules. However, a crystallographic study of thiobenzimidazolone[13] suggests that there is approximately 80% double bond character in the C–S bond, much less than would be expected for the C–O bond in benzimidazolone. Furthermore, measuremnet of the dipole moment of thiobenzimidazolone[14] indicates that there may be a significant contribution of the dipole form **55c**, whereas the oxygen analogue is very close to the calculated value for the double bond tautomer **54a**.

Another obvious difference between the oxygen and sulfur analogues is the size of the atoms and the subsequent length of the C–O versus C–S bonds. The latter is naturally longer and may help to span a distance more efficiently in a binding site.

Another unexplained trend in Table II is that the compounds with a 9-Cl substituent seem, within the limited series, to have smaller ratios of relative potency of the *ones* to *thiones* than the nonhalogenated analogues. In other words, the oxygen and sulfur analogues are much closer in relative potency with the presence of the 9-Cl. Possibly the reasons for the activity differences discussed here will be clearer as we make further analogues in this series.

A discussion of some preliminary studies to ascertain the mechanism by which the TIBO series blocks HIV-1 replication has been published[1] and a more detailed discussion followed.[15] The conclusions of those studies were that these compounds, like AZT and other 2′,3′-dideoxynucleoside analogues, act by inhibiting reverse transcrip-

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(12) Brown, D. Some 2-Substituted Linear Naphthaimidazoles. *J. Chem. Soc.* **1958**, 1974–7.
(13) Form, G.; Raper, E.; Downie, T. The crystal and molecular structure of 2-mercaptobenzimidazole. *Acta Crystallogr.* **1976**, *B32*, 345–8.
(14) Benzimidazoles and Congeneric Tricyclic Compounds. Preston, P., Ed.; An Interscience Publication; New York: John Wiley & Sons, 1981; p 354.
(15) Debyser, Z.; Pauwels, R.; Andries, K.; Desmyter, J.; Kukla, M.; Janssen, P.; De Clercq, E. An antiviral target on reverse transcriptase of human immunodeficiency virus type 1 revealed by tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one and -thione derivatives. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1451–1455.

tase, but unlike the latter, TIBO compounds are specific for HIV-1 and do not interfere with HIV-2 or other viral reverse transcriptases. Additionally, AZT and related compounds, by virtue of their nucleoside structures, are phosphorylated by cellular kinases. The resultant nucleotides are incorporated into the growing DNA chain by the reverse transcriptase during transcription of RNA to DNA by the RNA-dependent DNA polymerase. This leads to chain termination, halt of DNA formation, and consequent inhibition of HIV-1 replication. The compounds of the present series, on the other hand, do not require prior phosphorylation to inhibit reverse transcriptase. The TIBO compounds apparently block HIV-1 reverse transcriptase in a specific and unique manner. The exact nature of the inhibition is currently under study.

Experimental Section

All final products included in the tables were characterized by 360-MHz ^{1}H NMR (Bruker AM 360WB, reported in ppm relative to TMS), IR (Nicolet 60SX), and mass spectra (Finnegan 3300) as well as elemental analyses. The latter were performed by the internal Analytical Research Department of Janssen Research Foundation in Beerse, Belgium. All final products were assayed for homogeneity by thin-layer chromatography on Whatman MK6F (1 × 3 in × 250 μm) silica gel plates. Melting points were determined on a Thomas-Hoover capillary immersion apparatus or a Mel-Temp hot stage and are uncorrected.

(+)-(*S*)-7-Chloro-3,4-dihydro-3-methyl-1*H*-1,4-benzodiazepine-2,5-dione (2). Chloroisatoic anhydride (1; 41.49 g, 0.21 mol) and *l*-alanine methyl ester hydrochloride (31.4 g, 0.225 mol) were combined in 110 mL of pyridine under argon. The mixture was heated under reflux for 10 h, then it was allowed to cool to ambient temperature and stirred another 12 h before it was filtered, and the collected solid was rinsed with water. The solid was rinsed with EtOH and then Et_2O to yield 24.77 g (52%) of white solid (mp 285–287 °C), which was used without further purification.

(+)-(*S*)-7-Chloro-3,4-dihydro-3-methyl-9-nitro-1*H*-1,4-benzodiazepine-2,5-dione (3). Fuming nitric acid (94 mL) was cooled with an ice bath under argon before addition of **2** (24.55 g) over 27 min. The mixture was stirred for 3.5 h at 0 °C and then it was slowly added to 450 g of ice with stirring. The precipitated solid was isolated on a filter and washed with a small amount of water. It was air-dried at room temperature overnight to yield 27.84 g (95%) of yellow solid (mp 240–242 °C), which was used without further purification.

(*S*)-7-Chloro-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepin-9-amine (4) (R = H). To a stirred, cooled (ice bath) suspension of LAH (18.2 g, 0.48 mol) in glyme (300 mL) under nitrogen was added neat **3** over 90 min. The mixture was stirred another 2 h at 0 °C and then slowly brought to reflux and maintained for 40 h. It was then recooled with an ice bath and quenched with careful sequential addition of 18.2 mL of H_2O in 54 mL of THF, 18.2 mL of 15% NaOH, and 54.6 mL of H_2O. The mixture was warmed to ambient temperature and stirred for 1 h before the solid was filtered off. The solid was digested with 200 mL of hot THF and refiltered. The combined filtrates were concentrated under vacuum, and the resultant oil was used without further purification to synthesize **5** (R = $CH_2CH{=}CMe_2$) or **5** (R = H).

7-Chloro-2,3,4,5-tetrahydro-3-methyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepin-9-amine (5) (R = $CH_2CH{=}CMe_2$). To a stirred solution of **4** (R = H) (221.6 g, 1.047 mol) in 3.24 L of DMF under nitrogen were added KI (173.8 g, 1.047 mol) and Na_2CO_3 (163.1 g, 1.539 mol). The reaction was cooled to 0–5 °C, and 1-chloro-3-methyl-2-butene (76.7 g, 0.733 mol) in DMF (850 mL) was added dropwise over 2 h. After 18 h at 0–5 °C another portion of 1-chloro-3-methyl-2-butene (16.4 g, 0.157 mol) in 175 mL of DMF was added over 0.5 h, and finally after 0.5 h, a third portion of 1-chloro-3-methyl-2-butene (16.4 g, 0.157 mol) in 175 mL of DMF was added over 0.25 h. The reaction was monitored by GLC throughout to compare the relative amounts of desired product, starting material, and dialkylated product. The final ratio was 4.3:2.4:1, respectively. The mixture was poured into 3.66 L of CH_2Cl_2 and 2.4 L of H_2O, and the layers were separated. The aqueous was extracted with another 1.25 L of CH_2Cl_2. The combined organics were washed 7 times with a total of 4.8 L of H_2O, dried over Na_2SO_4, and concentrated to yield 217.7 g of crude product. This was column chromatographed on silica gel with toluene/2-propanol (98:2) as eluant to give 89 g of product which was rechromatographed on silica gel with CH_2Cl_2/EtOH/MeOH saturated with NH_3 (95:5:1) as eluant to yield 64.5 g of oil. This was triturated with hexane (130 mL) at room temperature and cooled to 0 °C before the solid product was isolated on a filter and dried under vacuum at 30 °C to yield 54.7 g of **5**.

(*S*)-2,9-Dichloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine (7).

Table III. Product Purification and Characterization

no.	formula[a]	purification[b]	mp, °C	% yield
6(±)	$C_{11}H_{12}ClN_3O$	CH_3OH	199–200	23
6(*S*)	$C_{11}H_{12}ClN_3O$	CH_3CN	199.5–200	39
6(*R*)	$C_{11}H_{12}ClN_3O$	CH_3CN	199–201	48
6a	$C_{16}H_{20}ClN_3O$	+, CH_3CN	137	64
6b	$C_{16}H_{20}ClN_3O$	CH_3CN	132.5–135	71
6c	$C_{16}H_{20}ClN_3O$	+, CH_3CN	124–127	60
6d	$C_{18}H_{24}ClN_3O{\cdot}HCl$	+, EtOH/Et_2O	237 dec	92
6e	$C_{16}H_{20}ClN_3O$	CH_3CN	132–133.5	45
8a	$C_{16}H_{20}ClN_3S$	+, CH_3CN	205–207	78
8b	$C_{16}H_{20}ClN_3S$	+	178–181.5	11
8c	$C_{16}H_{20}ClN_3S$	+	176–179	81
8d	$C_{18}H_{24}ClN_3S{\cdot}HCl$	+, EtOH/Et_2O	>260	84
8e	$C_{16}H_{20}ClN_3S$	+	183–184	12
9b	$C_{15}H_{19}N_3O$	+	112–114	43
10a	$C_{16}H_{21}N_3S$[c]	+	124.5–126.5	53
10b	$C_{15}H_{19}N_3S$[d]	+	199–202	32
10c	$C_{15}H_{19}N_3S$	+	134–136	24
10d	$C_{14}H_{19}N_3S$[e]	+, CH_3CN	149–151	20
11	$C_{17}H_{20}ClN_5$	CH_3CN	181–184	28
11a	$C_{18}H_{23}ClN_4O_2$	+	140	22
13	$C_{17}H_{24}N_4{\cdot}H_2O$[f]	H_2O/CH_3OH	100–105	45
14	$C_{18}H_{26}N_4{\cdot}1.5C_4H_4O_4$	*i*-PrOH	173.5–175.5	15
15	$C_{22}H_{25}N_3S$	+, CH_3CN	87–90	53
16	$C_{17}H_{23}N_3O{\cdot}1.5C_4H_4O_4$	*i*-PrOH	137–138.5	30
17	$C_{16}H_{20}ClN_3Se$	*i*-PrOH	175 dec	64
20	$C_{14}H_{18}ClN_3SO_2$[g]	+, CH_3CN	204–205.5	11
21	$C_{16}H_{20}ClN_3O$	+	149–152	33
22	$C_{16}H_{21}ClN_6{\cdot}C_4H_4O_4$	EtOH	203.5–205.5	25
23	$C_{16}H_{22}ClN_3S{\cdot}C_4H_4O_4$	EtOH/Et_2O	177–179	75
25	$C_{11}H_{11}N_3O$	*i*-PrOH	253–255	34
27	$C_{11}H_{13}N_3{\cdot}C_4H_4O_4$	EtOH	203–204.5	92
28	$C_{15}H_{19}N_3{\cdot}C_4H_4O_4{\cdot}0.2H_2O$	CH_3CN	130–132	75
31	$C_{15}H_{19}N_3O_2$	+, *i*-PrOH	213.5–215.5	20
32	$C_{13}H_{18}N_4{\cdot}HCl{\cdot}0.2H_2O$	+, EtOH	223–225	48
34a	$C_{15}H_{21}N_3O$	CH_3CN/H_2O	105–6	64
34b	$C_{17}H_{25}N_3O{\cdot}C_{10}H_8O_3S$	DMK/Et_2O	178–180	38
34c	$C_{17}H_{23}N_3O{\cdot}C_{10}H_8O_3S$	*i*-PrOH	185–187	62
34d	$C_{16}H_{20}N_4O$	+, hex	83–85	51
40	$C_{16}H_{20}N_2O_2{\cdot}C_4H_4O_4$	EtOH	147–150	17
44	$C_{15}H_{20}N_2O{\cdot}C_4H_4O_4$	*i*-PrOH	160–162	20
46	$C_{13}H_{12}N_2O_2S$	EtOAc	228–230	52
47	$C_{12}H_{10}N_2O_2$	+, EtOH	178–180	83
48	$C_{12}H_{14}N_2O$	EtOAc	164–166	25
49	$C_{16}H_{20}N_2O$	+, EtOAc	165–167	48
50a	$C_{17}H_{22}N_2S$[h]	+, CH_3OH	120 dec	24
50b	$C_{15}H_{18}N_2S$	+, CH_3OH	122 dec	14
51	$C_{15}H_{19}ClN_2{\cdot}HCl$	*i*-PrOH/CH_3OH	>250	28
52	$C_{15}H_{20}N_2{\cdot}HCl$	+, *i*-PrOH	245–247	57
53	$C_{16}H_{20}N_2O_2{\cdot}HCl{\cdot}C_2H_5OH$	+, EtOH	227–230	40

[a] All compounds were analyzed for C, H, N. [b] Purification method: If a silica gel chromatography was done on the crude product, it is indicated by a "+"; the solvent used for recrystallization follows. [c] C: calcd, 66.86; found, 66.34. [d] C: calcd, 65.90; found, 65.48. [e] C: calcd, 64.33; found, 63.88. [f] C: calcd, 67.52; found, 68.12. [g] C: calcd, 51.29; found, 50.49. [h] C: calcd, 71.29; found, 70.03. [i] H: calcd, 7.74; found, 7.25.

Typical Procedure (R ≠ H). A stirred mixture of **6** (2.0 g, 7 mmol) and Na_2CO_3 (0.75 g, 7 mmol) in $POCl_3$ (30 mL) under nitrogen was heated at 95 °C for 28 h. The mixture was concentrated on a rotary evaporator and the residue treated with 150 mL of saturated $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$ and then brine, dried with $MgSO_4$, and concentrated to yield 1.5 g of dark residue **7** that was used without further purification.

(+)-(*S*)-9-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (8). Typical Procedure (R ≠ H). Crude **7** (1.5 g) was dissolved in 30 mL of EtOH before addition of solid thiourea (1.5 g). The stirred mixture was heated at 95 °C under nitrogen for 24 h. It was concentrated under vacuum; the residue was diluted with saturated $NaHCO_3$ and H_2O and extracted with CH_2Cl_2 (3×). The combined extracts were washed with saturated $NaHCO_3$ and then brine, dried with $MgSO_4$, and concentrated to yield 1.35 g of yellow foam. Flash chromatography on silica gel with 40% EtOAc/hexane as eluant gave 0.67 g of pale yellow solid. This was triturated with a few milliliters of ice-cold CH_3CN to yield 0.56 g of off-white solid **8**. **8b**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.3 (d, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 3.05–3.15 (m, 1 H), 3.15–3.25 (m, 1 H), 3.5–3.6 (m, 1 H), 4.05 (d, 1 H), 4.15 (dd, 1 H), 4.5 (dd, 1 H), 5.2 (t, 1 H), 6.89 (s, 1 H), 7.08 (s, 1 H), 10.1 (s, 1 H).

(+)-(*S*)-4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (9) (R = H). Ammonium formate (5 g) in 15 mL of H_2O and then solid **6** (R = H, 5.0 g) were added to a suspension of 10% Pd/C (1.0 g) in 500 mL of *i*-PrOH under argon. After 20 h the reaction was filtered through Dicalite and the catalyst washed with MeOH. The filtrate was concentrated to a tan solid that was redissolved in 100 mL of H_2O and neutralized with the addition of 50 mL of saturated aqueous $NaHCO_3$ and heated on a steam bath. A white solid (3.7 g, 87%) separated, which was isolated after cooling: mp 200–202 °C.

(−)-(*S*)-[[9-Chloro-1,2,4,5,6,7-hexahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2-ylidene]amino]formonitrile (11). **5** (1.0 g, 3.6 mmol) and diphenyl cyanocarbonimidate (Aldrich; 0.85 g, 3.6 mmol) were combined in *i*-PrOH (50 mL) under nitrogen and heated under reflux for 24 h. The mixture was concentrated on a rotary evaporator and the residue partitioned between H_2O/CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and then brine, dried with $MgSO_4$, and concentrated to a clear oil. This was triturated with a few milliliters of ice-cold CH_3CN. The crystals were collected, washed with cold CH_3CN, and dried to yield 0.33 g (28%): mp 181–184 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.28 (d, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.75 (s, 3 H, CH_3), 3.1 (dd, 1 H), 3.2 (dd, 1 H), 3.48–3.58 (m, 1 H), 3.9 (dd, 1 H), 4.02 (d, 1 H), 4.1 (dd, 1 H), 4.2 (d, 1 H), 5.2 (t, 1 H), 6.85 (s, 1 H), 7.2 (s, 1 H), 12.2 (s, 1 H).

(+)-(*S*)-Methyl [9-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2-yl]carbamate (11a). **5** (2.79 g, 10 mmol), methyl (iminomethoxymethyl)carbamate (2.0 g, 15 mmol), and glacial acetic acid (3 g, 50 mmol) were combined in $CHCl_3$ (70 mL) and heated under reflux. After 17 h an additional portion of methyl (iminomethoxymethyl)carbamate (0.66 g, 5 mmol) was added and reflux continued over a few days. The cooled reaction mixture was washed with H_2O and then dilute NH_4OH, dried with $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (5% $MeOH/CH_2Cl_2$). The pure fractions were concentrated and dissolved in diisopropyl ether before addition of *i*-PrOH/HCl to give a solid HCl salt which was washed with CH_3CN to yield 1.9 g. This material was dissolved in H_2O and the free base liberated with addition of NH_4OH and extracted into CH_2Cl_2. The organic layer was concentrated and the residue chromatographed on silica gel (2% $MeOH/Cl_3CCH_3$). The pure fractions were concentrated, and the solid residue was washed with diisopropyl ether to yield 0.8 g (22%): mp 140 °C.

4,5,6,7-Tetrahydro-*N*,5-dimethyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-*jk*][1,4]benzodiazepin-2-amine (13) (Same Procedure for 14). Crude **12** (0.55 g) was suspended in a mixture of 40% aqueous H_2NCH_3 (Aldrich; 10 mL) and MeOH (5 mL) under N_2 and heated at 85 °C (bath temperature) for 25 h. Another 2 mL of H_2NCH_3 solution was added and heating continued for 7 h. The mixture was allowed to cool and a white solid separated which was collected and recrystallized from H_2O/CH_3OH to yield 0.26 g (45%): mp 100–105 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.32 (d, 3 H, CH_3), 1.4 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.08–3.25 (m, 5 H), 3.57–3.67 (m, 1 H), 4.12 (d, 1 H), 4.25 (d, 1 H), 5.22 (m, 1 H), 6.72 (d, 1 H), 47.02 (t, 1 H), 7.37 (d, 1 H).

(±)-4,5,6,7-Tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-2-(phenylthio)imidazo[4,5,1-*jk*][1,4]benzodiazepine (15). Thiophenol (2 mL), followed by 30 mL of H_2O, and then NaOH (1.0 g, 25 mmol) were added to a solution of crude **12** (1.0 g, 3.5 mmol) in MeOH (70 mL). The mixture was stirred at ambient temperature for 24 h before another portion of thiophenol (1 mL) was added and the mixture heated to 50 °C. After 3 h the mixture was concentrated to remove the MeOH. The aqueous residue was further diluted with H_2O and extracted with CH_2Cl_2 (2×). The organics were washed with H_2O and then brine, dried with $MgSO_4$, and concentrated to 1.6 g of crude product. This was flash chromatographed on silica gel (25% EtOAc/hexane) to yield 0.68 g of solid that was recrystallized from CH_3CN to yield 0.23 g (18%) of white solid: mp 87–90 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.19 (d, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 3.1 (dd, 1 H), 3.2 (dd, 1 H), 3.42–3.52 (m, 1 H), 4.1 (d, 1 H), 4.15 (dd, 1 H), 4.29 (dd, 1 H), 4.34 (d, 1 H), 5.22 (t, 1 H), 6.96 (d, 1 H), 7.15 (t, 1 H), 7.23–7.4 (m, 5 H), 7.6 (d, 1 H).

4,5,6,7-Tetrahydro-2-methoxy-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5-*jk*][1,4]benzodiazepine (*E*)-2-Butenedioate (2:3) (16). Sodium (0.4 g, 17 mmol) was added to cold MeOH (25 mL) under N_2. Crude **12** was added to the cold solution, which was then heated to reflux. After 5.5 h the mixture was concentrated and the residue partitioned between H_2O/CH_2Cl_2 (2×). The organics were washed with H_2O and then brine, dried with $MgSO_4$, and concentrated to an oil (1.1 g) that was flash chromatographed on silica gel (4% EtOAc/hexane) to yield 0.3 g of colorless oil. This oil was dissolved in *i*-PrOH and added to a hot solution of fumaric acid (1.5 equiv) in *i*-PrOH. On cooling of the solution, white crystals separated, collected, and washed with cold CH_3CN and then Et_2O to yield 0.31 g (30%): mp 137–138.5 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.2 (d, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 3.05 (dd, 1 H), 3.19 (dd, 1 H), 3.5–3.6 (m, 1 H), 3.9 (dd, 1 H), 4.0–4.2 (m, 6 H), 5.18 (t, 1 H), 6.77 (d, 1 H), 7.0 (t, 1 H), 7.25 (d, 1 H).

(+)-(*S*)-9-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-selenone (17). This material was synthesized by the same procedure used to make **8** (R = $CH_2CH{=}CMe_2$) except that selenourea was used in place of thiourea. The crude product was recrystallized from *i*-PrOH to yield **17** (64%): mp 175 °C dec.

(±)-7-Chloro-4-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-3-methyl-9-nitro-1*H*-1,4-benzodiazepine (18). At 0 °C under argon a suspension of **2(±)** (22.46 g, 0.1 mol) in 400 mL of glyme was added to a suspension of LAH (9.49 g, 0.25 mol) in 100 mL of glyme. The reaction was heated to reflux for 19 h and then cooled and quenched with the addition of 20.5 mL of 3 N NaOH solution. THF (125 mL) was added and the mixture heated under reflux for 45 min before the solids were filtered off and rinsed thrice with THF. The combined filtrates were evaporated to yield 20.49 g (>100%) of product which was used without further purification. The diamine (20.02 g, 0.102 mol) and Et_3N (14.22 mL, 0.102 mol) were dissolved in 400 mL of CH_2Cl_2 and cooled to 0 °C before dropwise addition of cyclopropanecarbonyl chloride in 150 mL of CH_2Cl_2 over 35 min under argon. The mixture was allowed to warm to ambient temperature. After 72 h the mixture was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to yield 28.59 g (>100%) of amorphous yellow solid which was used without further purification. That material (23.07 g) was added over 30 min to fuming nitric acid (75 mL) cooled to 0 °C. After another 35 min at 0 °C the solution was slowly added to 700 g of ice with stirring. The precipitated solid was filtered and washed with 700 mL of ice water to yield, after drying, 23.57 g (87%) of yellow solid **18**, which was used without purification.

(±)-7-Chloro-4-(cyclopropylmethyl)-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepin-9-amine (19). Solid **18** (18.54 g, 0.06 mol) was added over 45 min to a suspension of LAH (13.7 g, 0.36 mol) in 350 mL of glyme cooled to 0 °C. The reaction was then stirred at ambient temperature for 2 h and heated under

reflux for 17 h before it was quenched with the careful sequential addition of 13.7 mL of H_2O in 41 mL of THF, 13.7 mL of 15% NaOH solution, and 41 mL of H_2O. The solid salts were filtered off and digested with 100 mL of boiling THF for 5 min and refiltered. The combined filtrates were concentrated to yield 14.18 g of brown oil **19** that was used without further purification.

(±)-9-Chloro-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methyl-1*H*-1,2,5-thiadiazolo[4,3,2-*jk*][1,4]benzodiazepine *S*,*S*-Dioxide (20). Sulfuryl diamide (0.46 g, 4.75 mmol) and **19** (1.26 g, 4.75 mmol) were combined under N_2 and immediately placed in an oil bath at 130 °C, which was then heated to 185 °C over 10 min. After 1 h the mixture was cooled and flash chromatographed on silica gel (CH_2Cl_2/MeOH 10:1) to yield 0.17 g (11%) of product which was triturated with CH_3CN to yield 44 mg of **20** as a tan solid: mp 204–205.5 °C. At ambient temperature the ^1H NMR spectrum of **20** was poorly resolved, but when heated to 70 °C the peaks sharpened: ^1H NMR (360 MHz, DMSO-d_6) δ 0.15–0.3 (m, 2 H), 0.5–0.6 (m, 2 H), 0.9–1.05 (m, 1 H), 1.3 (d, 3 H, CH_3), 2.6–2.8 (m, 2 H), 3.45 (dd, 2 H), 3.6 (dd, 2 H), 3.65–3.75 (m, 1 H), 4.1 (d, 1 H), 6.5 (s, 2 H).

(±)-10-Chloro-7-(cyclopropylmethyl)-1,2,5,6,7,8-hexahydro-6-methyl-3*H*-pyrazino[2,3,4-*jk*][1,4]benzodiazepin-3-one (21). Bromoacetic acid (1.06 g, 4 mmol) and **19** (1.06 g, 4 mmol) were combined in CH_2Cl_2 (8 mL) and stirred at ambient temperature for 7 days. Some MeOH was added to bring separated solid back into solution before the mixture was added to saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and concentrated to 0.62 g of brown solid that was flash chromatographed on silica gel (CH_2Cl_2/MeOH 80:3) to yield 0.4 g (33%) of **21** as an off-white solid: mp 149–152 °C; ^1H NMR (360 MHz, $CDCl_3$) δ −0.1 to 0.1 (m, 2 H), 0.4–0.55 (m, 2 H), 0.75–0.9 (m, 1 H), 1.15 (d, 3 H, CH_3), 2.52 (d, 2 H), 3.25–3.4 (m, 1 H), 3.5 (dd, 1 H), 3.75 (d, 1 H), 3.87 (dd, 1 H), 4.35 (d, 2 H), 6.58 (s, 1 H), 6.59 (s, 1 H).

(±)-*N*-[9-Chloro-6-(cyclopropylmethyl)-1,2,4,5,6,7-hexahydro-5-methylimidazo[4,5,1-*jk*]benzodiazepin-2-ylidene]-guanidine (*E*)-2-Butenedioate (1:1) (22). Cyanamide (0.35 g, 8.25 mmol) in 3.5 mL of H_2O was added over 20 s to a mixture of **19** in 1.26 mL of concentrated HCl. The mixture was heated at 90 °C for 2 h, cooled to 0 °C, basified with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated to 1.82 g of black oil that was flash chromatographed on silica gel (CH_2Cl_2/MeOH 7:1) to yield 0.62 g of clear tan oil. The oil was dissolved in 8 mL of EtOH and added to 0.23 g of fumaric acid in 7 mL of EtOH to yield 0.47 g (25% based on cyanamide) of **22** as a white fumarate salt: mp 203–205.5 °C.

(−)-(*S*)-7-Chloro-4-(cyclopropylmethyl)-2,3,4,5-tetrahydro-*N*,3-dimethyl-1*H*-1,4-benzodiazepine-1-carbothioamide (*Z*)-2-Butenedioate (1:1) (23). As previously described (see preparation of **18**), **2(S)** was reduced. The resultant diamine (9.83 g, 50 mmol) and Na_2CO_3 (5.3 g, 50 mmol) were combined in 50 mL of DMF and heated to 90 °C before dropwise addition of cyclopropylbromomethane over 8 min. The mixture was heated another 5 h and then stirred at ambient temperature for 11 h before it was added to 500 mL of H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O (3×) and then brine, dried with $MgSO_4$, and concentrated to yield 11.12 g of tan oil (85% pure by GLC) that was used without further purification. A solution of this material (9.4 g, 37.5 mmol) in 75 mL of *i*-PrOH was heated to 90 °C under argon, while methyl thioisocyanate (Aldrich; 2.84 g, 38.8 mmol) was added dropwise. The reaction was heated at 90 °C for 11 h (an additional 1.0 g (13.7 mmol) of MeNCS was added after 6 h). The reaction was concentrated and the orange gum was flash chromatographed on silica gel (MeOH/CH_2Cl_2 0:100 to 3:97). A 5.36-g sample of purified product was converted to a maleate salt in Et_2O/*i*-PrOH to give 4.9 g which was recrystallized from Et_2O/*i*-PrOH to yield 4.47 g: mp 177–179 °C; ^1H NMR (360 MHz, DMSO-d_6, 78 °C) δ 0.25–0.4 (m, 2 H), 0.57–0.7 (m, 2 H), 1.05–1.2 (m, 1 H), 1.25 (d, 3 H, CH_3), 2.6–2.75 (m, 1 H), 2.75–2.9 (m, 1 H), 2.92 (d, 3 H, CH_3), 3.62–3.77 (m, 1 H), 4.08 (d, 1 H), 3.82–4.15 (m, 1 H), 4.42 (d, 1 H), 4.35–4.7 (m, 1 H), 6.08 (s, 2 H), 7.24 (d, 1 H), 7.3–7.45 (m, 1 H), 7.45–7.55 (m, 1 H), 7.69 (d, 1 H).

(±)-5,6-Dihydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-7(4*H*)-one (25). A mixture of **24**[1] (7.64 g, 0.04 mol) and formamidine acetate (8.32 g, 0.08 mol) was quickly heated to 145 °C and maintained for 1 h before cooling. The resultant solid was triturated with 150 mL of hot CH_3CN, cooled, filtered, and triturated with 150 mL of hot *i*-PrOH to yield 2.7 g (34%) of **25**. A small sample was further purified by recrystallization in *i*-PrOH to yield a light tan solid: mp 253–255 °C.

4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine (*E*)-2-Butenedioate (1:1) (27). Neat **25** (2.22 g, 11 mmol) was added to a stirred suspension of LAH (1.68 g, 44 mmol) in 150 mL of glyme at 0 °C under argon. After 2 h at 0 °C the mixture was heated under reflux for 18 h before it was allowed to cool and quenched with careful sequential addition of 1.7 mL of H_2O in 5 mL of THF, 1.7 mL of 15% NaOH solution, and 5.1 mL of H_2O. The salts were filtered and digested with 100 mL of hot THF and refiltered. The combined filtrates were dried over $MgSO_4$ and concentrated to yield 1.91 g of solid which proved to be a 2:1 mixture of **26** and **27**. The former could be separated and purified by recrystallization with CH_3CN. The mixture was converted to pure **27** by stirring a THF solution open to the atmosphere at ambient temperature for 16 h. A small sample of **27** was purified by adding an EtOH solution to 1 equiv of fumaric acid in EtOH to yield a white fumaric acid salt: mp 203–204.5 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.2 (d, 3 H, CH_3), 1.7 (d, 3 H, CH_3), 2.92 (d, 1 H), 3.2 (d, 1 H), 3.53–3.63 (m, 1 H), 4.1 (d, 1 H), 4.15 (d, 1 H), 4.2 (dd, 1 H), 4.42 (dd, 2 H), 4.75 (s, 1 H), 4.85 (s, 1 H), 6.65 (s, 2 H), 6.92 (d, 1 H), 7.1 (t, 1 H), 7.5 (d, 1 H), 8.13 (s, 1 H).

5,6,7,8-Tetrahydro-6-methyl-7-propyl-1*H*-pyrazino[3,2,1-*jk*][1,4]benzodiazepine-2,3-dione (31). A solution of **30** (0.99 g, 4.5 mmol), prepared by methods described in ref 1, in 45 mL of toluene was added to a solution of oxalyl chloride (0.39 mL, 4.5 mmol) in 90 mL of toluene before the reaction was heated to reflux. After 2 h the mixture was cooled, and the solid was filtered and washed with a small amount of toluene followed by Et_2O to yield 1.18 g of brown solid. This was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated. The residue was flash chromatographed on silica gel (CH_2Cl_2/MeOH 20:1) to yield 0.24 g (20%) of off-white solid that was recrystallized from *i*-PrOH to give 130 mg of white solid **31**: mp 213.5–215.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 0.82 (t, 3 H, CH_3), 1.2 (d, 3 H, CH_3), 1.32–1.52 (m, 2 H), 2.4–2.6 (m, 2 H), 3.22–3.32 (m, 1 H), 3.9 (d, 1 H), 4.07–4.28 (m, 1 H), 4.38 (d, 1 H), 4.6 (d, 1 H), 6.95 (d, 1 H), 7.1 (t, 1 H), 7.2 (d, 1 H).

4,5,6,7-Tetrahydro-5-methyl-6-propyl-1,2,3-triazolo[4,5,1-*jk*][1,4]benzodiazepine Monohydrochloride (32). Sodium nitrite (0.24 g, 3.3 mmol) was added over 15 s to a cold (0 °C) solution of **30** (0.66 g, 3 mmol) in 30 mL of 3 N HCl. The mixture was stirred cold for 1 h before it was basified with 3 N NaOH and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated, and the residual oil was flash chromatographed on silica gel (EtOAc/hexane 1:1) to yield 390 mg (49%) of oil. This was dissolved in 5 mL of EtOH and combined with 0.14 mL of concentrated HCl. The white solid HCl salt of **32** was filtered and dried to yield 290 mg: mp 223–225 °C; ^1H NMR (360 MHz, DMSO-d_6/D_2O) δ 0.9 (t, 3 H, CH_3), 1.5 (d, 3 H, CH_3), 1.7–1.88 (m, 2 H), 3.0–3.18 (m, 1 H), 3.18–3.35 (m, 1 H), 4.38–4.53 (m, 1 H), 4.8–4.95 (m, 2 H), 4.95–5.2 (m, 2 H), 7.52 (t, 1 H), 7.6 (d, 1 H), 8.12 (d, 1 H).

4,5,6,7-Tetrahydro-5-methyl-2-oxo-6-propylimidazo[4,5,1-*jk*][1,4]benzodiazepine-1(2*H*)-acetonitrile (34a-d). The procedure is typified by **34d**. Sodium hydride (0.118 g, 3 mmol) and **33** (0.75 g, 3.06 mmol) were combined in 45 mL of DMF under argon at ambient temperature. After 1 h, bromoacetonitrile (0.341 mL, 4.9 mmol) was added and stirring continued another 45 min before the mixture was concentrated. The residue was partitioned between H_2O and CH_2Cl_2. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated to an oil that was flash chromatographed on silica gel (3–5% EtOH/CH_2Cl_2). The solid product was triturated with hexane to yield 0.59 g (51%) of off-white **34d**: mp 83–85 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 0.9 (s, 3 H), 1.38 (d, 3 H, CH_3), 1.4–1.6 (m, 2 H), 2.42–2.6 (m, 2 H), 3.4–3.52 (m, 1 H), 3.83 (dd, 1 H), 4.05 (d, 1 H), 4.1 (dd, 1 H), 4.82 (s, 2 H), 6.9 (d, 1 H), 7.0 (d, 1 H), 7.1 (t, 1 H).

3,4-Dihydro-9-methoxy-3-methyl-1*H*-1,4-benzodiazepine-2,5-dione (36). *N*-Methylmorpholine (11 mL, 0.1 mol) was added to a solution of 2-amino-3-methoxybenzoic acid (16.7 g, 0.1 mol),

(±)-alanine methyl ester hydrochloride (13.9 g, 0.1 mol), and 1-hydroxybenzotriazole (27 g, 0.2 mol) in 400 mL of THF under N_2 at ambient temperature. The mix was cooled to 0 °C before addition of neat liquid dicyclohexylcarbodiimide (20.6 g, 0.1 mol). The reaction was stirred at ambient temperature for 4 days before it was filtered and the filtrate concentrated. The residue was partitioned between EtOAc/saturated aqueous $NaHCO_3$; the organic phase was dried with $MgSO_4$ and concentrated to yield 23.66 g of brown oil. The oil was heated under a Dean–Stark trap (to collect displaced MeOH) in an argon atmosphere at 200 °C for 3 h. It was cooled and triturated with 75 mL of hot *i*-PrOH, cooled, filtered, and washed with cold *i*-PrOH to yield 12.6 g (57%) of off-white **36**, which was used without further purification.

2,3,4,5-Tetrahydro-9-methoxy-3-methyl-1*H*-1,4-benzodiazepine (37). Borane (1 M in THF, 272 mL, 0.27 mol) was added to a cold (0 °C) solution of **36** (12 g, 0.054 mol) in 200 mL of THF. After 5 min the solution was heated to reflux. After 3 days the solution was recooled to 0 °C and quenched with slow addition of 270 mL of 3 N HCl. When the addition was complete, the mixture was heated on a steam bath for 30 min, cooled, and basified with 325 mL of 15% aqueous NaOH. It was then extracted with CH_2Cl_2 (2×), which was then washed with brine, dried with $MgSO_4$, and concentrated to yield 6.53 g (62%) of **37** as a brown oil, which solidified on standing and was used without further purification.

4-(Cyclobutylmethyl)-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepin-9-ol (39). Diamine **37** was monoalkylated to **38** under standard conditions (see ref 1) in 71% yield. The crude **38** (2.6 g, 10 mmol) was dissolved in 225 mL of CH_2Cl_2 before addition of boron tribromide (14.1 mL, 14 mmol) over 1 min, under N_2. After 24 h, MeOH (20 mL) was added carefully to the mixture and it was stirred for 1 h and concentrated. The residue was partitioned between CH_2Cl_2 (2×) and saturated aqueous $NaHCO_3$. The organics were dried with Na_2SO_4 and concentrated to yield 2.51 g (>100%) of **39** as a brown oil which was used directly in the next step.

6-(Cyclobutylmethyl)-4,5,6,7-tetrahydro-5-methyl-2*H*-oxazolo[5,4,3-*jk*][1,4]benzodiazepin-2-one (*E*)-2-Butenedioate (1:1) (40). Urea (0.6 g, 10 mmol) and **39** (1.23 g, 5 mmol) were combined under nitrogen and immediately placed in an oil bath at 155 °C, heated to 200 °C over 20 min, and maintained for another 20 min. The mixture was allowed to cool and partitioned between CH_2Cl_2 (2×) and H_2O. The organics were dried with $MgSO_4$ and concentrated onto silica gel added to the solution. The silica gel was placed atop a flash column and eluted with EtOAc/hexane (15:85) to yield 230 mg (17%) of **40** as a clear yellow oil. A sample was dissolved in EtOH and added to 1 equiv of fumaric acid in EtOH to give, after filtration, the acid addition salt as a white solid: mp 147–150 °C, resolidifies and remelts 173–195 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.17 (d, 3 H, CH_3), 1.47–1.67 (m, 2 H), 1.72–1.9 (m, 2 H), 1.9–2.03 (m, 2 H), 2.4–2.55 (m, 2 H), 2.55–2.7 (m, 1 H), 3.72 (dd, 1 H), 3.89 (dd, 1 H), 4.02 (d, 1 H), 4.1 (d, 1 H), 6.62 (s, 2 H), 6.95 (d, 1 H), 7.03 (t, 1 H), 7.18 (d, 1 H).

1,2,3,4-Tetrahydro-3-methyl-2-propylpyrrolo[3,2,1-*jk*]-[1,4]benzodiazepin-6(7*H*)-one (*E*)-2-Butenedioate (1:1) (44). Diamine **41**[16] was alkylated under standard conditions to give **42** (3.17 g, 15.5 mmol) which was dissolved in 30 mL of CH_2Cl_2 and cooled to 0 °C under argon before addition of chloroacetyl chloride (1.24 mL, 15.5 mmol) in 30 mL of CH_2Cl_2 over 2 min. After 15 min the reaction mixture was washed with saturated aqueous $NaHCO_3$ (2×). The organics were dried with $MgSO_4$ and concentrated to yield 4.63 g (>100%, 4.37 g theoretical) of **43** as an oil used without further purification. The total amount (4.37 g, 15.5 mmol) was placed under argon before addition of solid $AlCl_3$ over 1 min. The mixture was slowly heated to ca. 170 °C over 1 h and maintained for 20 h. It was cooled and the resultant black glass was dissolved by the careful addition of 200 g of ice with swirling. The aqueous solution was basified with 3 N aqueous NaOH and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated to 4.34 g of black oil that was flash chromatographed on silica gel by elution with CH_2Cl_2/MeOH (20:1) to yield 1.15 g. This was rechromatographed to give 0.74 g (19.5%) of **44** as a clear yellow oil. A sample was dissolved in Et_2O and added to 1 equiv of fumaric acid in EtOH. The fumaric salt of **44** was isolated and recrystallized from *i*-PrOH to give a white solid: mp 160–162 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.8 (s, 3 H), 1.08 (d, 3 H, CH_3), 1.32–1.45 (m, 2 H), 2.4 (t, 2 H), 3.05–3.2 (m, 1 H), 3.57 (s, 2 H), 3.65 (dd, 1 H), 3.73 (d, 1 H), 3.98 (dd, 1 H), 4.3 (d, 1 H), 6.62 (s, 2 H), 6.9 (t, 1 H), 7.0 (d, 1 H), 7.1 (d, 1 H).

2,3-Dihydro-3-(methylthio)-2-oxo-3-(2-oxopropyl)-1*H*-indole-4-carbonitrile (46). A mixture of **45**[17] (80.6 g, 0.395 mol), chloroacetone (31.4 mL, 0.395 mol), potassium carbonate (54.6 g, 0.395 mol), and potassium iodide (65.6 g, 0.395 mol) in 1.5 L of DMF was stirred at ambient temperature for 5 h before it was partitioned between H_2O and EtOAc. The organic layer was washed with H_2O (3×) and then brine, dried with $MgSO_4$, and partially concentrated. Crystallization from solution yielded 53.9 g (52%) of **46**: mp 228–230 °C.

2,3-Dihydro-2-oxo-3-(2-oxopropyl)-1*H*-indole-4-carbonitrile (47). Zinc dust (135 g, 2.0 mol) and **46** (26.7 g, 0.103 mol) in 750 mL of THF and 26 mL of acetic acid were refluxed for 2 h. The mixture was filtered and concentrated to a solid residue that was triturated with *t*-BuOMe (2×) and recrystallized from absolute EtOH to yield 18.3 g (83%) of **47** as a tan solid. A sample was further purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 9:1) followed by recrystallization from EtOAc to give a pale pink powder: mp 178–180 °C.

1,2a,3,4,5,6-Hexahydro-4-methyl-2*H*-azepino[5,4,3-*cd*]indol-2-one (48). Raney nickel (400 g, Fluka) was washed with *t*-BuOH (3×) before it was mixed with **46** (27.8 g, 0.107 mol) in 1 L of *t*-BuOH and refluxed for 1.5 h. The hot solvent was decanted off the nickel which was further washed with hot *t*-BuOH (5×). The combined washes were concentrated to yield 7.62 g of solid that was triturated with EtOAc to yield 5.51 g (25%) of **48** as a pale pink solid. A sample was further purified by recrystallization from EtOAc: mp 164–166 °C.

1,2a,3,4,5,6-Hexahydro-4-methyl-5-(2-methyl-2-propenyl)-2*H*-azepino[5,4,3-*cd*]indol-2-one (49) (R = 2-MA). A mixture of **48** (19.0 g, 60.7 mmol), chloro-2-methyl-2-propene (6.6 mL, 66.8 mmol), KI (11.1 g, 66.8 mmol), and Na_2CO_3 (32 g, 304 mmol) in DMF (200 mL) were stirred at ambient temperature for 2 days before it was partitioned between H_2O/EtOAc. The organic phase was washed with H_2O and then brine, dried with Na_2SO_4, and concentrated to yield 10 g of brown oil. This was flash chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH 95:5:0.1) to yield 7.51 g (48%) of **49** as a yellow solid. A sample was further purified by recrystallization from EtOAc to give a pale yellow solid: mp 165–167 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.2 (s, 3 H), 1.3–1.4 (m, 1 H), 1.65 (s, 3 H, CH_3), 1.82 (d, 1 H), 2.85 (d, 1 H), 3.4–3.5 (m, 1 H), 3.55 (dd, 1 H), 3.68 (d, 1 H), 3.98 (d, 1 H), 4.62 (s, 1 H), 4.78 (s, 1 H), 6.6 (d, 1 H), 6.7 (d, 1 H), 7.07 (t, 1 H), 10.36 (s, 1 H).

1,2a,3,4,5,6-Hexahydro-4-methyl-5-(2-methyl-2-propenyl)-2*H*-azepino[5,4,3-*cd*]indole-2-thione (50) (R = 2-MA). Lawesson's reagent (1.07 g, 2.69 mmol; Aldrich), **49** (R = 2-MA, 0.63 g, 2.23 mmol), and BHT (ca. 2 mg) in 20 mL of toluene were refluxed for 2 h. Filtration gave 1.37 g of brown solid that was flash chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH 93:7:0.1) to give 0.67 g of green glass that was crystallized from MeOH to yield 150 mg (24%) of **50**: mp 120 °C dec.

2-Chloro-3,4,5,6-tetrahydro-4-methyl-5-propyl-1*H*-azepino[5,4,3-*cd*]indole Monohydrochloride (51) (R = *n*-Pr). $POCl_3$ (5 mL) and **49** (R = *n*-Pr, 0.6 g) were heated under reflux for 5 h. The mixture was allowed to cool and added to ice cold saturated aqueous $NaHCO_3$ and CH_2Cl_2. After 0.5 h the organic layer was dried with Na_2SO_4 and concentrated to a green oil that was flash chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH 93:7:0.1) to give 180 mg (28%) of pale yellow solid **51**. This was dissolved in Et_2O, and Et_2O saturated with HCl was added. The precipitated solid was recrystallized from *i*-PrOH/MeOH to yield

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100 mg of white crystalline 51·HCl: mp ca. 250 °C dec.

3,4,5,6-Tetrahydro-4-methyl-5-propyl-1*H*-azepino[5,4,3-*cd*]indole Monohydrochloride (52) (R = *n*-Pr). A mixture of 51 (R = *n*-Pr, 0.15 g), 10% Pd/C (0.15 g), and Et_3N (10 drops) in 20 mL of EtOH was placed on a Parr shaker under 28 psi of hydrogen for 2 h. It was then filtered through Dicalite and concentrated to a yellow glass. Flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 93:7:0.1) gave 80 mg (57%) of 52 as a yellow solid. This was dissolved in EtOAc and ethereal HCl added. The precipitated solid was recrystallized from *i*-PrOH to yield 30 mg of 52·HCl as white crystals: mp 245-247 °C. Protonation of 52 by HCl formed a mixture of diastereomers in a 2:1 ratio as seen in the ^1H NMR. Where protons were separated in the spectrum, the chemical shift of the minor diastereomer is indicated in parentheses, but the proton count of both isomers are combined. ^1H NMR (360 MHz, $CDCl_3$): δ 0.8 (t, 3 H, CH_3), 1.52 (1.42) (d, 3 H, CH_3), 1.65-1.9 (m, 2 H), 2.75-2.9 (2.9-3.02) (m, 1 H), 3.02-3.4 (m, 3 H), 4.05-4.15 (3.87-3.97) (m, 1 H), 4.57-4.82 (m, 2 H), 6.92-7.02 (m, 1 H), 7.02-7.13 (m, 1 H), 7.32 (7.23) (s, 1 H), 7.38 (t, 1 H), 10.34 (s, 1 H), 11.31 (11.18) (s, 1 H).

3,4,5,6-Tetrahydro-2a-hydroxy-4-methyl-5-(2-methyl-2-propenyl)-2a*H*-azepino[5,4,3-*cd*]indol-2(1*H*)-one Monohydrochloride Ethanolate (1:1) (53) (R = 2-MA). A mixture of 49 (R = 2-MA, 0.5 g, 1.95 mmol) and K_2CO_3 (0.54 g, 3.9 mmol) in 9 mL of DMSO and 1 mL of H_2O was stirred overnight at ambient temperature and open to the atmosphere. It was then partitioned between aqueous $NaHSO_3$ solution and CH_2Cl_2. The aqueous phase was saturated with NaCl, basified with 3 N NaOH to pH 10, and repeatedly extracted (7×) with CH_2Cl_2. The combined organics were washed with brine, dried with Na_2SO_4, and concentrated. The residue was flash chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH 93:7:0.1) to give a green oil which was taken up in Et_2O and precipitated with ethereal HCl. Recrystallization from EtOH gave 0.24 g (40%) of 53·HCl·EtOH as pale green crystals: mp 227-230 °C.

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Synthesis and Ocular Antihypertensive Activity of New Imidazolidine Derivatives Containing a β-Blocking Side Chain

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The syntheses of new phenylimidazolidine derivatives (3-6)[1] containing a propanolamine oxime or an oxypropanolamine moiety attached either to the aromatic or to the imidazolidine ring are described. These compounds were evaluated for potential ocular antihypertensive activity in α-chymotrypsin-induced ocular hypertension in rabbits. These compounds represent a unique series of effective ocular antihypertensive agents that despite possessing structural characteristics of β-blockers and of imidazolidine derivatives, exhibit weak α- and β-adrenergic agonist and antagonist activities. These findings may be of significant therapeutic importance in the medical management of glaucoma.

Adrenergic receptors are classified into α- and β-adrenergic receptors[2] and further subdivided into α_1, α_2, β_1 and β_2.[3-6] Most of them have already been found in eye tissue. Physiological and biochemical studies support the importance of α- and β-adrenergic receptors in the regulation of IOP[7,8] (intraocular pressure). Even though the distribution of these receptor subpopulations in eye tissue has not yet been completely delineated, data indicate that the receptors in the ciliary body, which modulate aqueous humor production, are mainly of α_2 and β_2 type.[9-13] α-Adrenergic agonists[14-17] and β-adrenergic antagonists[18] are known to have a favorable effect on the IOP in open-angle glaucoma. β-Adrenoceptor antagonists, widely used in glaucoma therapy, are presumed to lower IOP by decreasing aqueous humor formation, mainly by affecting membrane permeability.[15] α-Agonists and especially clonidine were shown to decrease aqueous humor formation by constriction of afferent ciliary process blood vessels.[9] On another hand, it has been reported that the resistance of aqueous humor outflow was decreased by clonidine.[17,20-22] Prazosin, an antagonist which has a high specificity for the α_1 receptors, lowers IOP in animal models.[23,24] However, prazosin is not a very effective hypotensive agent because it also reduces aqueous humor outflow, thus negating the benefit of reduction of aqueous

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