Structure−Activity Relationships of 1-Alkyl-5-(3,4-dichlorophenyl)-5-{2-[(3-substituted)-1-azetidinyl]ethyl}-2-piperidones. 1. Selective Antagonists of the Neurokinin-2 Receptor

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The design, synthesis, and pharmacological evaluation of a novel class of neurokinin-2 (NK_2) antagonists 1-alkyl-5-(3,4-dichlorophenyl)-5-{2-[(3-substituted)-1-azetidinyl]ethyl}-2-piperidones (**5**−**44**) are described. These compounds are formally derived from **2** by incorporating the metabolically vulnerable *N*-methylamide function into a more stable six-membered ring lactam **4**, resulting in increased stability in human liver microsome (HLM) preparations relative to **2** ($T_{1/2}$(HLM) of 30 min vs <10 min for **2**). This series was further optimized by replacing the 4,4-disubstituted piperidine functionality found in **4** with simple 3-substituted azetidines. This series, exemplified by 1-benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]-ethyl}-2-piperidone **5**, was found to possess excellent functional potency for the NK_2 receptor in the Rabbit pulmonary artery (RPA) assay ($pA_2 = 9.3$) and increased in vitro metabolic stability ($T_{1/2}$(HLM) = 70 min) relative to **4**. Metabolic route identification studies revealed that *N*-benzyl oxidation was a major route in this relatively lipophilic lead (log $D = 3.2$). Further exploration of the *N*-lactam substituent SAR targeting reduced lipophilicity to attenuate P-450 metabolism revealed that incorporation of a cyclopropylmethyl group in this region of the molecule gave a balance of good potency and high metabolic stability. For example, the significantly less lipophilic analogue **29** (log $D = 2.3$) possessed both good functional potency (RPA, $pA_2 = 8.1$) and high in vitro metabolic stability ($T_{1/2}$(HLM) = 120 min). Optimization in this *N*-cyclopropylmethyllactam series by modification of the nature of the azetidine 3-substituent as a strategy to further increase potency and moderate log *D* led to the identification of sulfamide analogue **33**, which possessed both excellent metabolic stability in vitro ($T_{1/2}$(HLM) >120 min) and high potency in both RPA ($pA_2 = 8.9$) and human bladder smooth muscle ($pK_b = 8.9$) functional assays. In addition, NK_2 antagonist **33** ($IC_{50} = 4$ nM) showed excellent selectivity over both the related human neurokinin receptors h-NK_1 ($IC_{50} = 7.9\ \mu$M) and h-NK_3 ($IC_{50} = 1.8\ \mu$M) in radioligand binding studies.

Introduction

Neurokinin (NK) research has remained an area of sustained activity over the past decade.[1] Three mammalian neurokinin (tachykinin) receptors, classified as neurokinin-1 (NK_1), neurokinin-2 (NK_2), and neurokinin-3 (NK_3), have been cloned and expressed,[2] each possessing an endogenous (tachykinin) ligand that share a common C terminus, "Phe-X-Gly-Leu-Met-NH_2". The three mammalian tachykinins, substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), preferentially activate NK_1, NK_2, and NK_3 receptors, respectively. However, although each of the tachykinins is the preferred ligand at one of the NK receptors, all three are capable of full agonist activity at each of the receptors, albeit with reduced affinity.

Substance P and the other tachykinins are largely located in neurons, principally capsaicin-sensitive primary afferent fibers (C fibers), but are also present in enteric sensory neurons and in a variety of neuronal structures in the central nervous system (CNS). The NK_1 receptor is widely distributed in tissues throughout the periphery and the CNS, while the NK_2 receptor is mainly located in the smooth muscle of the urinary,[3] respiratory,[4] and gastrointestinal tracts, with limited presence in the CNS. In contrast, the NK_3 receptor is primarily expressed in the CNS although it is also found in the GI tract.[5]

Tachykinins and their receptors have been postulated to play a significant role in the pathophysiology of a wide variety of diseases including gastrointestinal disorders,[6] emesis,[7] chronic pain,[8] depression,[9] and asthma,[10] and the search for selective non-peptidic antagonists of these receptors continues, to both further elucidate their role and evaluate their potential as therapeutic targets.

The disclosure of a series of *N*-methyl-*N*-(4,4-disubstituted)piperidinyl)-(3,4-dichlorophenyl)butyl)benzamides[11] as potent non-peptidic NK_2 antagonists, exemplified by (*S*)-**1** (SR-48,968)[12] and **2**,[11] has stimulated

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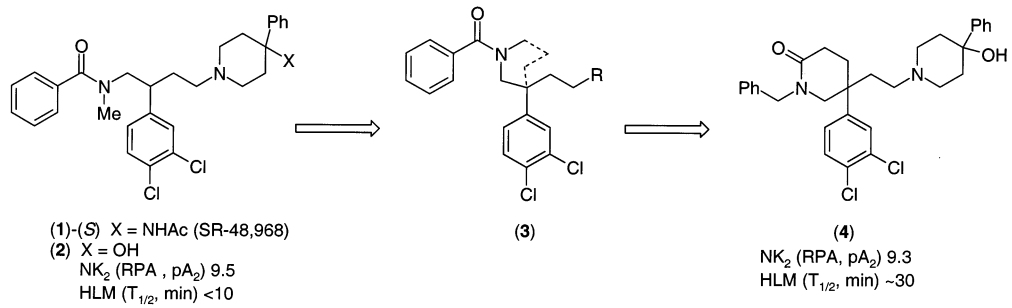
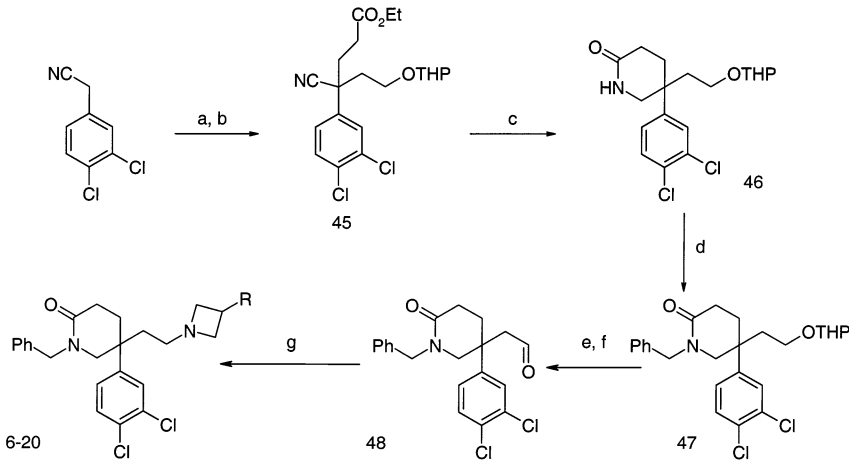


Figure 1. Cyclization strategy to improve metabolic stability in lead series exemplified by **2**.

Scheme 1[a]



[a] Reagents and conditions: (a) 2-bromoethyl tetrahydro-(2*H*)-pyran-2-yl ether, NaH, THF, 0 °C; (b) 3-bromoethyl propionate, LDA, Bu_4NI, THF, −78 °C to room temperature; (c) Raney nickel, H_2, NH_3/MeOH, room temp; (d) benzyl bromide, NaH, DMF, 0 °C; (e) HCl/MeOH, room temp; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to room temp; (g) 3-substituted azetidine, $NaBH(OAc)_3$, AcOH, NEt_3, THF, room temp.

activity both in the clinic[13] and in exploiting this template as a starting point for chemical programs seeking selective NK_2 antagonists.[1]

As part of our long-standing interest in neurokinin antagonists for the treatment of urological disorders,[14] preliminary pharmacological and pharmacokinetic evaluation of **2** (Figure) as a potential lead revealed the compound to be highly potent in both NK_2 binding (pIC_{50} = 8.9) and rabbit pulmonary artery (RPA) functional assays (pA_2 = 9.5). In vitro metabolic stability studies in human liver microsome (HLM) preparations, however, showed the compound to be rapidly turned over in this assay ($T_{1/2}$ < 10 min). Metabolic route identification work revealed that a major pathway in this process was amide N-demethylation to give the essentially inactive secondary amide.[11]

We reasoned that incorporation of this vulnerable methyl group of the amide into a cyclic *N*-acylpiperidine or pyrrolidine **3**[15] or δ-lactam **4**[16] ring system could reduce the potential for metabolism at this site. Though the rate of CYP-450-mediated methylene (CH_2) oxidation is often observed to be more rapid than for methyl, we believed that the reduction in the number of available conformations accessible in this cyclic template, relative to the acyclic form **2**, could result in attenuation of the rate of metabolism. Initial exploration of this strategy revealed that **4** possessed enhanced in vitro metabolic stability relative to **2** (for **4**, $T_{1/2}$ = 30 min; for **2**, $T_{1/2}$ < 10 min) while retaining high potency for the NK_2 receptor (pA_2(RPA) = 8.9). In this paper, we report our preliminary work to identify potent, selective metabolically stable agents from within this δ-lactam template.[17]

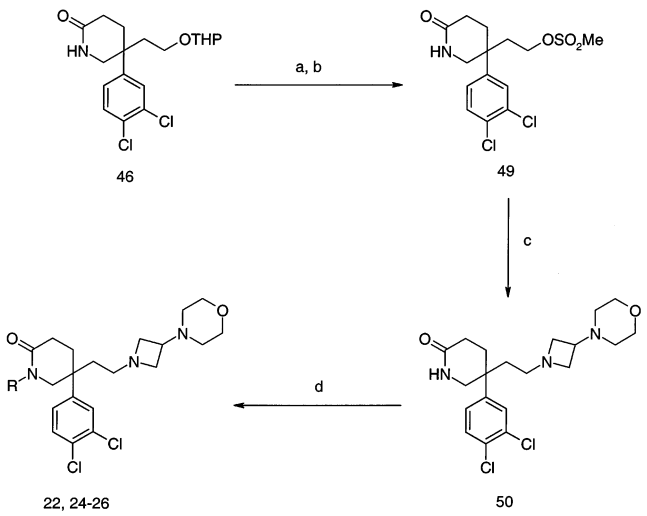
Chemistry

Compounds **6**−**20** were accessed as shown in Scheme 1. 3,4-Dichlorophenylacetonitrile was cleanly alkylated in sequential fashion with 2-bromoethyl tetrahydro-(2*H*)-pyran-2-yl ether followed by 3-bromoethyl propionate in THF to give **45**. Hydrogenation in the presence of Raney nickel at room temperature resulted in a clean reduction of the nitrile to the primary amine followed by in situ lactam cyclization to give the piperidone **46** in 75% yield. Alkylation with benzyl bromide gave **47**, which was deprotected to the primary alcohol using HCl/MeOH and oxidized under Swern conditions[18] to furnish aldehyde **48**. Reductive amination of this aldehyde with the appropriate 3-substituted azetidine,[19] using triacetoxyborohydride as reducing agent, then yielded compounds **6**−**20**.

Compounds **22** and **24**−**26** were accessed as shown in Scheme 2. Acid deprotection of the primary alcohol of lactam **46** using HCl/MeOH and treatment with methanesulfonyl chloride cleanly furnished mesylate **49**. Mesylate displacement using 4-(3-azetidinyl)morpholine hydrochloride in acetonitrile at reflux then gave intermediate piperidone **50**, which was cleanly alkylated with the appropriate alkyl halide, using either KOH in DMSO or NaH in DMF as base, to give compounds **22** and **24**−**26**.

Compounds **5, 21**, and **23** were prepared from intermediate **46** as shown in Scheme 3. N-Alkylation using

Scheme 2[a]



[a] Reagents and conditions: (a) HCl/MeOH, room temp; (b) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C; (c) 4-(3-azetidinyl)morpholine hydrochloride, K_2CO_3, NEt_3, CH_3CN, reflux; (d) alkyl halide, KOH, DMSO or alkyl halide, NaH, DMF, room temp.

the appropriate benzylic bromide in DMF gave the benzylated compounds **51**, which were readily converted to their respective mesylates **52**. Treatment with 4-(3-azetidinyl)morpholine hydrochloride in the presence of potassium carbonate furnished the target compounds **5**, **21**, and **23**.

Single enantiomer compounds **27** and **28** were prepared as shown in Scheme 4. Sequential alkylation of 3,4-dichlorophenylacetonitrile with allyl bromide and the sodium salt of bromopropionic acid, in THF using sodium hydride as base, gave **53**, which was converted to the diastereomeric aminooxazolines **54** in two steps via transformation of the acid to the oxazoline with (*S*)-valinol under Dean and Stark conditions[20] and reduction of the nitrile to the amine with lithium aluminum hydride in diethyl ether. The resulting diastereomeric amines were then readily separated by column chromatography.

Conversion of each diastereomer to the single enantiomer compounds (*S*)-**27** and (*R*)-**28**[21] was then achieved in four steps via acid-mediated cyclization to the piperidone **55,** N-alkylation with cyclohexylmethylbromide in DMSO using KOH as base, ozonolysis of the terminal olefin to the aldehyde, and reductive amination using 4-(3-azetidinyl)morpholine hydrochloride in the presence of sodium triacetoxyborohydride.

N-Cyclohexyl-substituted piperidone **30** was prepared from acid **53** in six steps as shown in Scheme 5. Conversion to the homochiral ester-aldehyde **56** was readily achieved via resolution[22] with *R*-(+)-naphthylethylamine, reduction of the nitrile to the aldehyde using diisobutylaluminum hydride in toluene, and conversion of the acid to the methyl ester using MeOH in the presence of hydroxybenzotriazole (HOBT) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI). Treatment of **56** with cyclohexylamine in THF in the presence of triacetoxyborohydride at reflux yielded the cyclized product **57** in 48% yield, which was converted to **30** (49% for two steps) via ozonolysis and subsequent reductive amination using the conditions described above.

Compounds **29** and **31**−**44** were prepared from aldehyde **58** as shown in Scheme 6, using the reductive amination conditions described in Scheme 1.

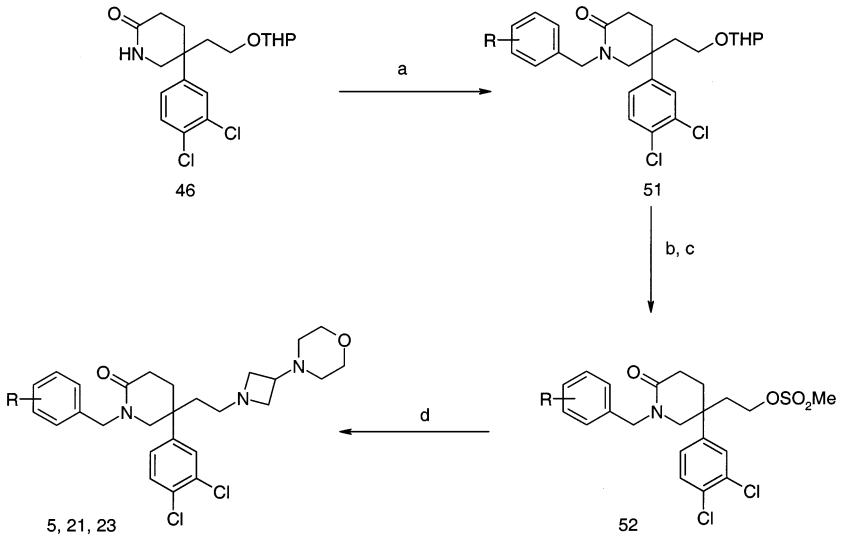
Results and Discussion

SAR studies initially focused on exploring the role of the 4-hydroxy-4-phenylpiperidine moiety in **4** in conferring both potency and metabolic stability in this lactam template. Our aims in this initial phase of the program were to identify an agent that possessed both high functional potency against the NK_2 receptor in the RPA assay ($pA_2 \approx 9$) and high in vitro metabolic stability ($T_{1/2}$ > 120 min) in HLM preparations, to minimize first-pass metabolism in planned in vivo studies. Initial investigations sought to replace the piperidine with the smaller 3-substituted azetidine group, which we reasoned would mimic the general directionality of the 4-substituted piperidine moiety found in **4** (Table 1). Pleasingly, this strategy yielded a series of potent compounds and revealed that the 4-hydroxy-4-phenylpiperidine could be replaced with a range of 3-monosusbstituted azetidines possessing a range of H-bond donor−acceptor functionality with good retention of functional potency. For example, 3-(morpholino)azetidine **5** was found to be equipotent with **4** and possessed improved in vitro metabolic stability ($T_{1/2}$(HLM) = 70 min vs $T_{1/2}$(**4**) = 30 min). Furthermore, this compound was found to be potent in the human bladder functional assay (pK_b = 9.0). Metabolic route profiling revealed that CYP-450-mediated oxidation of the *N*-benzyl group was a major metabolic pathway in this relatively lipophilic (log *D* = 3.2) compound.

The related cyclic ethers, the 1,4-oxazepanyl analogue **6** (pA_2 = 8.7), morpholinone **7** (pA_2 = 8.6), and 2-phenylmorpholine **8** (pA_2 = 8.0), all retained high levels of potency, although they offered no potency advantage over **5**. The introduction of a second basic center (**9** and **10**) to reduce log *D* and to explore the role of further H-bonding potential in this region was also well tolerated, although the tertiary amine **10** was somewhat weaker (pA_2 = 7.8) than **5**. To explore the role of H-bonding potential still further in this region, secondary amine **9** was converted to both the acetamide **11** and sulfonamide **12**, which resulted in a small increase in potency relative to **9**. Interestingly, the thiomorpholine **13** and related sulfoxide **14** and sulfone **15** were essentially equipotent. A range of primary and secondary alcohols (**16**−**20**), as hydrogen-bond donors, were also examined and found to be potent in the RPA functional assay. Acyclic amino alcohol **19** displayed good activity (pA_2 = 8.5), which increased 40-fold in the conformationally constrained 4-hydroxypiperidine analogue **16**, although tropane **20** was found to be weaker than **16**. The directionality of the alcohol function was also found to play a role in conferring potency, the 3-hydroxypiperidine **18** and 3-hydroxypyrrolidine **17** analogues both being >10-fold weaker than **16**.

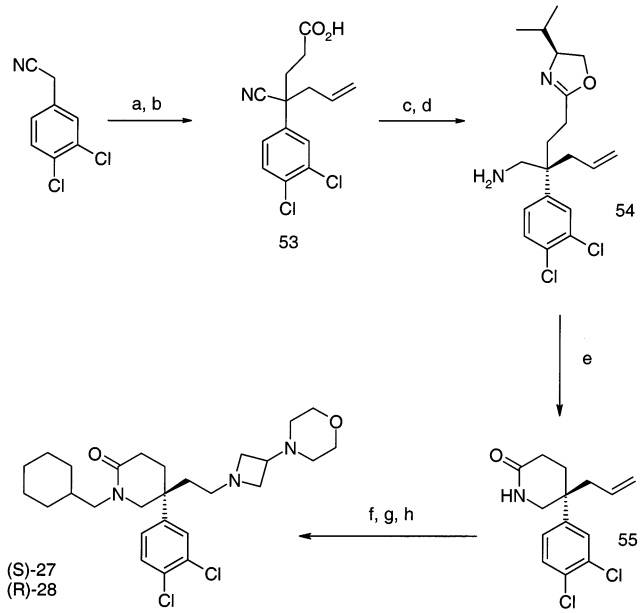
The role of the N-lactam substituent in conferring both potency and in vitro metabolic stability was next explored within a series incorporating the azetidine morpholine moiety identified earlier (Table 2). No substitution at the piperidone 1-position (R = H; **50**) resulted in a dramatic loss of activity (pA_2 < 5). Methyl substitution at the ortho (**21**), meta (**22**), and para (**23**)

Scheme 3[a]



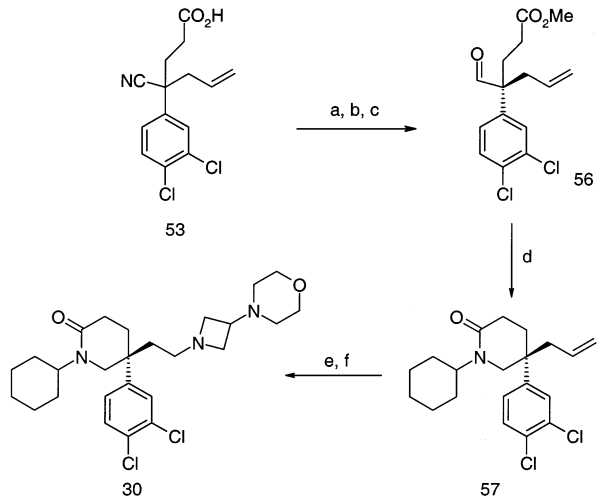
[a] Reagents and conditions: (a) benzylic bromide, NaH, DMF, 0 °C; (b) HCl/MeOH, room temp; (c) $MeSO_2Cl$, NEt_3, CH_2Cl_2, room temp; (d) 4-(3-azetidinyl)morpholine hydrochloride, K_2CO_3, NEt_3, CH_3CN, reflux.

Scheme 4[a]



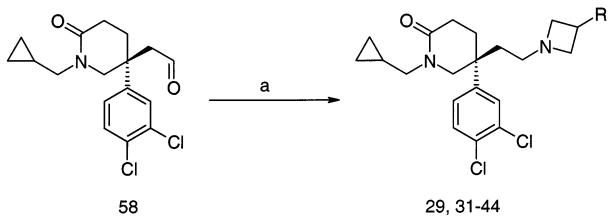
[a] Only the (*S*)-isomer is shown for clarity. Reagents and conditions: (a) allyl bromide, NaH, THF, 0−50 °C; (b) bromopropionic acid sodium salt, NaH, THF, room temp to 70 °C; (c) *s*-valinol, toluene, Dean−Stark, reflux; (d) $LiAlH_4$, Et_2O, 0 °C, separate diastereomers; (e) 8% H_2SO_4 in EtOH, reflux; (f) cyclohexylmethyl bromide, KOH, DMSO, room temp; (g) O_3, dimethyl sulfide, MeOH, −78 °C; (h) 4-(3-azetidinyl)morpholine hydrochloride, $NaBH(OAc)_3$, NEt_3, AcOH, THF, room temp.

Scheme 5[a]



[a] Reagents and conditions: (a) *R*-(+)-naphthylethylamine, EtOAc, recrystallization; (b) DIBAL, toluene, −78 to −40 °C; (c) WSCDI, HOBT, MeOH, CH_2Cl_2, room temp; (d) cyclohexylamine, $NaBH(OAc)_3$, THF, AcOH, reflux; (e) O_3, dimethylsulfide, MeOH, −78 °C; (f) 4-(3-azetidinyl)morpholine hydrochloride, $NaBH(OAc)_3$, NEt_3, AcOH, THF, room temp.

Scheme 6[a]

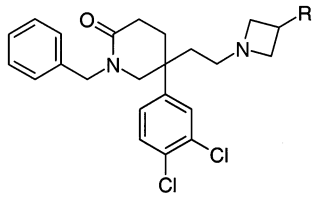


[a] Reagents and conditions: (a) 3-substituted azetidine, $NaBH(OAc)_3$, NEt_3, AcOH, THF, room temp.

positions of the *N*-benzyl ring in **5** was found to be well tolerated with high functional potency generally retained ($pA_2 > 8$). 4-Fluoro-substituted analogue **24** and the 4-pyridylmethyl analogue **25**, however, were found to cause a significant reduction in functional potency. In particular, **25** was found to be 200-fold less potent than the benzyl analogue **5**. *N*-Benzyl substitution was found to routinely retain high potency; however, the lipophilic nature of this group and the previously established vulnerability of this site to metabolism (vide supra) led us to seek alternative and less lipophilic replacements for this group. Saturated cycloalkyl substitution SAR in this region was therefore investigated.

Cyclohexylmethyl substitution (**26**) was found to be equipotent to *N*-benzyl in the RPA functional assay ($pA_2 = 8.9$). In addition, this cycloalkyl analogue retained excellent potency in the human bladder functional assay ($pK_b = 8.5$). Resolution of this analogue to give the enantiomers **27** and **28** revealed that (*S*)-stereoisomer **27** possessed significantly greater potency than (*R*)-

Table 1. NK2 Functional Activity Data of 1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[(3-substituted)-1-azetidinyl]ethyl}-2-piperidones **4**−**20** in Rabbit Pulmonary Artery Assay



compd[a]	R	rabbit pulmonary artery NK_2 (pA_2)[b]
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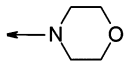
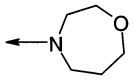
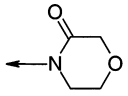
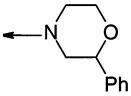
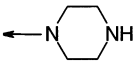
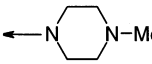
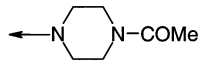
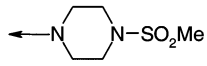
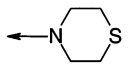
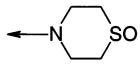
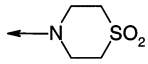
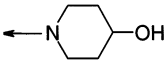
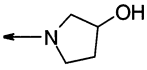
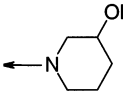
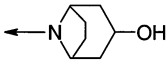
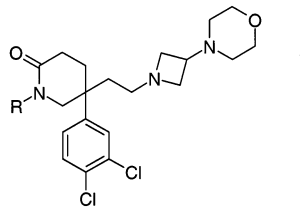
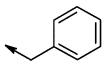
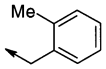
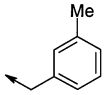
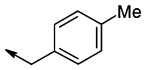
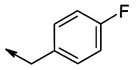
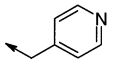
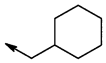
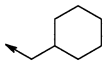
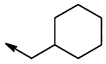
5[d]		9.3
6		8.7
7		8.6
8[e]		8.0
9		8.3
10		7.8
11		8.8
12		9.2
13		9.0
14		9.2
15		8.9
16		10.1
17		8.7
18		8.7
19	-N(Me)$(CH_2)_2$OH	8.5
20		9.2

[a] All compounds are racemates. [b] For all determinations, $n \geq 2$ (each experiment performed in triplicate). [c] Synthesis reported previously. See ref 16. [d] log $D = 3.2$; $T_{1/2}$(HLM) = 70 min. [e] Mixture of diastereomers.

Table 2. RPA Functional Potency and Human in Vitro Microsomal Stability Profiles of 1-Aryl- and 1-Alkyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidones **5** and **21**−**30**



compd	R	Stereochem	rabbit pulmonary artery. NK_2 (pA_2)[a]	Human liver microsomes ($T_{1/2}$, min)[d]
50	H	racemate	<5	NT
5[b]		racemate	9.3	70
21		racemate	9.3	NT
22		racemate	8.6	NT
23		racemate	8.2	NT
24		racemate	7.7	NT
25		racemate	7.0	NT
26		racemate	8.9	70
27		S	9.0	14
28		R	6.2	84
29[c]		S	8.1	120
30		S	9.9	<10

[a] For all determinations, $n \geq 2$ (each experiment performed in triplicate). [b] pK_b(human bladder) = 9.0. [c] pK_b(human bladder) = 8.2. [d] NT: not tested.

enantiomer (**28**) (pA_2 = 9.0 vs 6.2), with the weaker enantiomer possessing the greater in vitro metabolic stability ($T_{1/2}$(HLM) = 84 vs 14 min). Metabolic route identification studies within this cyclohexylmethyl series revealed cycloalkyl ring oxidation as a major pathway. The *N*-cyclohexyl analogue **30**, designed to reduce log *D* relative to that for **27** as a strategy to improve metabolic stability, was found to be very potent (pA_2 = 9.9). Unfortunately, this compound showed no advantage in metabolic stability relative to **27** ($T_{1/2}$ < 10 min). This preliminary SAR suggested to us that the nature of the *N*-lactam substituent played a major role in conferring both potency and metabolic stability in this series and that identifying a suitably stable lipophilic substituent at this position was key to achieving our target of good metabolic stability in this series. To explore this further, a series of saturated *N*-(methylene)-cycloalkyl-substituted lactam analogues possessing a range of lipophilicities were prepared and profiled, seeking to balance potency and metabolic stability. In general, increasing potency was found to correlate with increasing cycloalkyl ring size (3−7), while metabolic

stability generally correlated with decreasing cycloalkyl ring size (i.e., reduced log *D*). From this SAR, cyclopropylmethyl analogue **29** emerged as the compound possessing the best balance of potency and metabolic stability ($pA_2 = 8.1$; $T_{1/2}$(HLM) = 120 min). Furthermore, in the human bladder smooth muscle assay, the compound retained good functional potency ($pK_b = 8.2$), again correlating closely with RPA data ($pA_2 = 8.1$). The greater metabolic stability observed with **29** is noteworthy and may be due to cooperative factors. **29** (log *D* = 2.3) is significantly less lipophilic than **27** (log *D* = 3.3), which may predispose **29** to be intrinsically less susceptible to CYP-450-mediated metabolism.[23] In addition, the electronics of the three-membered cyclopropyl ring are quite distinct from other cycloalkyl ring systems and may contribute to the reduced susceptibility to CYP-450-mediated radical abstraction or α-oxidation.[24]

With the goal of minimizing metabolic turnover at the *N*-lactam substituent achieved in **29**, our attention returned to the nature of the 3-azetidine substituent with the aim of both further increasing potency and optimizing the physical properties while retaining the excellent in vitro metabolic stability seen with **29** (Table 3).

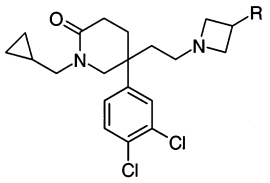
Both hydrogen bond donor and acceptor moieties were well tolerated with 4-substituted piperidine alcohol **41** ($pA_2 = 8.8$), ether **42** ($pA_2 = 8.2$), ketone **44** ($pA_2 = 8.9$), and acid **43** ($pA_2 = 9.4$), all highly potent. Primary amine **37** ($pA_2 = 8.7$) was also highly potent; however, the in vitro metabolic half-life of this dibasic compound was found to be lower than the 3-morpholine azetidinyl analogue **29** ($T_{1/2}$ = 30 vs 120 min). Both acylation to give **38** ($pA_2 = 7.8$) and sulfonylation to give **39** ($pA_2 = 8.0$) resulted in a reduction in potency relative to the primary amine parent **37**. The 4-*N*-acetyl-4-phenyl analogue **40** was somewhat more potent than the *des*-phenyl analogue **38**, although this offered no advantage over **37**. Piperazine **31** ($pA_2 = 7.9$) was found to be weaker than the H-bond acceptor morpholine **29**. Simple methanesulfonylation to give **32** resulted in a 4-fold increase in potency. Unfortunately, this compound was rapidly metabolized in vitro ($T_{1/2}$(HLM) < 10 min) in HLM. Formal replacement of the methyl group of the sulfonamide moiety in **32** with a primary amine to give sulfamide **33** resulted in a drop in log *D* (1.7 vs 2.2 for **32**) and a marked increase in both in vitro metabolic stability ($T_{1/2}$(HLM) > 120 min) and also a 3-fold increase in functional potency. Furthermore, this functional activity was shown to translate well into the human bladder functional assay ($pK_b = 8.9$). Attempts to modulate the H-bonding potential in this sulfamide through either mono-(**34**) or *N*,*N*-dimethylation (**35**) resulted in a progressive drop in potency over the primary sulfamide. Similarly, attempts to replace the sulfamide with the primary urea **36** ($pA_2 = 8.3$) resulted in a 4-fold reduction in potency. NK_2 antagonist **33** (IC_{50} = 4 nM) was also found to possess excellent selectivity over the related human NK_1 (IC_{50} = 7.9 μM) and NK_3 (IC_{50} = 1.8 μM) receptors in radioligand binding studies.

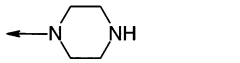
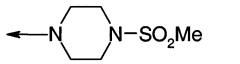
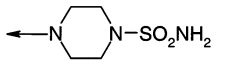
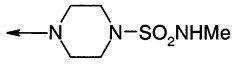
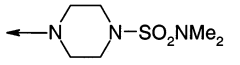
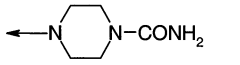
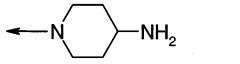
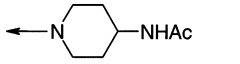
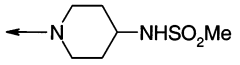
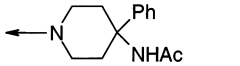
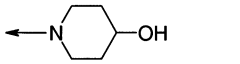
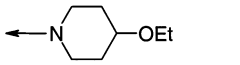
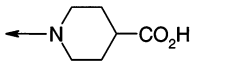
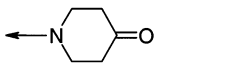
Conclusion

The design of the NK_2 antagonists described above was guided by both in vitro metabolic stability and metabolic route data in HLM preparations to identify major sites of CYP-450 metabolism. These data initially identified amide N-demethylation in lead **2** as a major route of metabolism and were subsequently used in SAR studies to guide selection of piperidone N-substitution in the piperidone series. This work identified the cyclopropylmethyl substituent as a group that possessed low susceptibility to P-450-mediated metabolism while retaining good potency in the RPA and human bladder smooth muscle functional assays.

Furthermore, **33** has also been shown to possess good selectivity over both the related human NK_1 and NK_3

Table 3. NK_2 (RPA) Functional Potency and Human in Vitro Microsomal Stability Data of 1-Cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-{2-[(3-substituted)-1-azetidinyl]ethyl}-2-piperidones **31**−**44**



compd[a]	R	rabbit pulmonary artery NK_2 (pA_2)[b]	Human liver microsomes ($T_{½}$, min)
31		7.9	NT
32		8.5	<10
33[c]		8.9	>120
34		8.5	NT
35		8.0	NT
36		8.3	NT
37		8.7	30
38		7.8	NT
39		8.0	NT
40		8.5	NT
41		8.8	NT
42		8.2	NT
43		9.4	NT
44		8.9	NT

[a] All compounds are single (*S*) enantiomers. [b] For all determinations, $n \geq 2$ (each experiment performed in triplicate). [c] pK_b(human bladder) = 8.9. h-NK_1 binding (IM9 cells) IC_{50} = 7.9 μM; h-binding (CHO cells) IC_{50} = 4 nM; h-NK_3 binding (CHO cells) IC_{50} = 1.8 μM.

receptors in radioligand binding studies. Following further profiling, **33** (UK-224,671) was progressed into clinical development.[25] Our work to further optimize the pharmacokinetic (DMPK) properties of this series[26] will be the subject of further communications from these laboratories.

Experimental Section

Biology. The activity of compound **33** at the tachykinin receptor subtypes NK_1 and NK_3 was assessed in radioligand binding studies using cell membranes prepared from IM9 monocytes (NK_1) and from CHO cells expressing the recombinant human NK_3 receptor.

The NK_2 receptor antagonist activity of compounds **2** and **4**−**44** was determined in vitro by testing their ability to antagonize the contractile effects of the selective NK_2 receptor agonist [β-ala^8]$NKA_{(4-10)}$ in the rabbit pulmonary artery (RPA), using the method of Pataccini and Maggi.[27]

RPA, rather than binding against the human NK_2 receptor stably expressed in the CHO cell line, was chosen as the in vitro surrogate for human bladder based on a series of comparative experiments. In general, the correlation between RPA and human bladder was superior to that observed with data obtained from human the NK_2 binding assay.

Transplant-quality human liver tissue was obtained from the International Institute for the Advancement of Medicine (Exton, PA). Hepatic microsomes were prepared according to the method of Jones et al.[28] Cytochrome P450 (CYP-450) content was determined using the method of Omura and Sato,[29] and the protein concentration was determined using the method of Lowry et al.[30]

Incubations were carried out at 1 μM substrate and 0.5 μM cytochrome P-450 in a total incubation volume of 12 mL. The incubation volume was made up of 50 mM Tris HCl (pH 7.4), 5 mM $MgCl_2$, and 5 μM $MnCl_2$. The reducing equivalents required by cytochrome P-450 were provided by NADPH (1 mM), which was regenerated in situ using an isocitrate/isocitrate dehydrogenase system. All the components were preincubated at 37 °C prior to the addition of the NADPH.

Aliquots (1 mL) were removed from the incubation at 0, 3, 5, 10, 15, 20, 30, 45, and 60 min after the addition of NADPH. The reaction was terminated by addition of the samples to a tube containing 0.2 M sodium borate buffer (pH 10)/*tert*-butyl methyl ether (1:3 v/v) and a suitable internal standard. Samples were mixed and centrifuged, and the ether layer was evaporated to dryness under a stream of nitrogen. Samples were analyzed by HPLC, and the rate of metabolism was determined by log−linear regression of peak height ratio (substrate/internal standard) vs time. The half-life was calculated from 0.693/slope.

Chemistry. Melting points were determined on a Gallenkamp melting point apparatus using glass capillary tubes and are uncorrected. Unless otherwise indicated, all reactions were carried out under a nitrogen atmosphere, using commercially available anhydrous solvents. Thin-layer chromatography was performed on glass-backed precoated Merck silica gel (60 F254) plates, and flash column chromatography was carried out using 40−63 μm silica gel. Proton NMR spectra were measured on a Varian Inova 300 or 400 spectrometer in the solvents specified. Mass spectra were recorded on a Fisons Trio 1000 using thermospray positive (TSP) ionization. Where analyses are indicated only by the symbols of the elements, results obtained are within 0.4% of the theoretical values. In the cases where compounds were analyzed as hydrates, the presence of water was evident in the enhanced peak because of water in the proton NMR spectra. The purity of compounds was carefully assessed using analytical TLC and proton NMR, and the latter technique was used to calculate the amount of solvent in solvated samples. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by proton NMR.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(1,4-oxazepan-4-yl)-1-azetidinyl]ethyl}-2-piperidone (6). (a) To a solution of sodium hydride (60% dispersion in oil) (19.24 g, 481 mmol) in THF (450 mL) cooled in an ice/water bath, was added a solution of 3,4-dichlorophenylacetonitrile (89.5 g, 481 mmol) in THF (450 mL) dropwise over 40 min. After a further 30 min, a solution of 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether (100 g, 481 mmol) in THF (100 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. A 30% aqueous NH_4Cl solution (500 mL) was added, and the mixture was extracted with Et_2O. The organic phase was washed with H_2O (×2), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with Et_2O/hexane to give the alkylated product (51 g, 34%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47−1.66 (4H, m), 1.79 (2H, m), 2.17 (2H, m), 3.34−3.62 (2H, m), 3.88 (2H, m), 4.08 (1H, t), 4.58 (1H, m), 7.21 (1H, d), 7.48 (2H, m).

(b) A solution of the above compound (43.9 g, 138 mmol) in THF (180 mL) was added to a solution of LDA (192 mmol, 1.4 equiv) in THF (80 mL) at −78 °C. The mixture was allowed to warm to room temperature and was cooled again to −78 °C, and a solution of 3-bromoethyl propionate (22.36 mL, 179.5 mmol) in THF (70 mL) was added dropwise. Tetrabutylammonium iodide (50 g) was then added, and the mixture was allowed to stir at room temperature overnight. Water (300 mL) was added, and the solution was concentrated under reduced pressure. The residue was partitioned between EtOAc and brine, the organic phase was washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with Et_2O/hexane to give the ester **45** (35 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, t), 1.39−1.77 (4H, m), 2.03−2.58 (8H, m), 3.39 (2H, m), 3.74 (2H, m), 4.09 (2H, q), 4.46 (1H, m), 7.28 (1H, d), 7.49 (1H, d), 7.57 (1H, s).

(c) To a solution of **45** (14.87 g, 36 mmol) in saturated ammoniacal ethanol (500 mL) was added Raney nickel (1.5 g), and the mixture was stirred under an atmosphere of hydrogen at room temperature for 14 h. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the lactam **46** (10.1 g, 75%). MS *m*/*z*: 372. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39−1.81 (6H, m), 1.90−2.23 (5H, m), 2.40 (1H, m), 3.11 (1H, m), 3.39−3.61 (3H, m), 3.77 (2H, m), 4.38 (1H, d), 6.07 (1H, br, s), 7.18 (1H, d), 7.42 (2H, m).

(d) To a solution of lactam **46** (2.3 g, 6.18 mmol) in DMF (30 mL) was added, with cooling in an ice/water bath, NaH (60% dispersion in oil) (475 mg, 12.3 mmol). The reaction mixture was allowed to warm to room temperature and after 40 min was cooled again in an ice/water bath, and benzylbromide (1.47 mL, 12.3 mmol) was added. After a further 30 min, water was added and the mixture was evaporated to dryness under reduced pressure. The residue was partitioned between H_2O and saturated $NaHCO_3$ and was extracted with EtOAc. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the alkylated product **47** (2.6 g, 91%).

(e) A solution of lactam **47** (2.60 g, 5.63 mmol) in HCl-saturated MeOH (50 mL) was stirred for 2 h. The solvent was removed under reduced pressure, and the residue was partitioned between saturated $NaHCO_3$ and EtOAc. The organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the alcohol (2.07 g), which was used without further purification. MS *m*/*z*: 378 $(MH)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62−2.07 (4H, m), 2.24 (2H, m), 3.02 (2H, m), 3.39 (1H, d), 3.79 (1H, d), 4.27 (1H, t), 4.44 (1H, d), 4.59 (1H, d), 7.16 (1H, d), 7.21−7.40 (6H, m), 7.47 (1H, d).

(f) To a solution of oxalyl chloride (4.95 mL, 57.1 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added DMSO (8.83 mL, 114.2 mmol). After 45 min, a solution of the above alcohol (19.62 g, 51.9 mmol) in CH_2Cl_2 (210 mL) was added and the temperature maintained at −78 °C. After 2 h, NEt_3 (36.1 mL, 259.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction was washed with

saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with EtOAc/hexane to give the aldehyde **48** (9.47 g, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09−2.30 (3H, m), 2.40−2.63 (2H, m), 2.86 (1H, d), 3.39 (1H, d), 3.77 (1H, d), 4.42 (1H, d), 4.81 (1H, d), 6.87 (1H, d), 7.17 (1H, s), 7.22−7.41 (6H, m), 9.40 (1H, s).

(g) To a solution of the aldehyde **48** (427 mg, 1.13 mmol) in THF (9 mL) was added 4-(3-azetidinyl)-1,4-oxazepane bishydrochloride (260 mg, 1.13 mmol) and NEt_3 (0.22 mL, 1.25 mmol). After 1 h, sodium triacetoxyborohydride (305 mg, 1.47 mmol) and AcOH (70 μL, 1.25 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Water was added, and the reaction mixture was made basic with saturated aqueous Na_2CO_3 solution. The mixture was extracted with EtOAc, the organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the title compound **6** (62 mg, 11%). MS *m*/*z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43−1.79 (3H, m), 1.86 (2H, m), 1.92−2.24 (5H, m), 2.43 (4H, t), 2.60 (2H, m), 3.08 (1H, m), 3.28 (1H, d), 3.38 (2H, t), 3.55 (1H, t), 3.69 (2H, dd), 3.79 (2H, t), 4.39 (1H, d), 4.82 (1H, d), 6.80 (1H, d), 7.08 (1H, s), 7.22−7.41 (6H, m).

Compounds **7**−**20** were prepared using the above reductive amination protocol and the appropriate 3-substituted azetidine.

4-(1-{2-[1-Benzyl-3-(3,4-dichlorophenyl)-6-oxo-3-piperidinyl]ethyl}-3-azetidinyl)-3-morpholinone (7). Yield: 11%. MS *m*/*z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (1H, m), 1.70 (1H, m), 2.03 (3H, m), 2.38 (2H, m), 2.46 (1H, m), 2.92 (2H, m), 3.28 (1H, d), 3.39 (4H, m), 3.59 (1H, d), 3.79 (2H, m), 4.14 (2H, s), 4.38 (1H, d), 4.85 (2H, d), 6.80 (1H, d), 7.09 (1H, s), 7.24−7.43 (6H, m). Anal. ($C_{27}H_{31}Cl_2N_3O_3 \cdot {}^1/_3CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(2-phenyl-4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (8). Yield: 9%. MS *m*/*z*: 580 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (1H, m), 1.72 (1H, m), 1.82−2.04 (7H, m), 2.43 (1H, m), 2.60 (1H, d), 2.73 (3H, m), 2.91 (1H, m), 3.23 (1H, d), 3.33 (2H, m), 3.55 (1H, d), 3.79 (1H, t), 4.03 (1H, d), 4.39 (1H, d), 4.52 (1H, d), 4.82 (1H, d), 6.78 (1H, d), 7.08 (1H, s), 7.21−7.40 (11H, m). Anal. ($C_{33}H_{37}Cl_2N_3O_2 \cdot {}^1/_8CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(1-piperazinyl)-1-azetidinyl]ethyl}-2-piperidone (9). (a) To a solution of the aldehyde described in the preparation of compound **4** (342 mg, 0.91 mmol) in THF (8 mL) was added *tert*-butyl 4-(3-azetidinyl)-1-piperazinecarboxylate hydrochloride (278 mg, 1.0 mmol) and NEt_3 (0.14 mL, 1.0 mmol). After 1 h, sodium triacetoxyborohydride (270 mg, 1.27 mmol) and AcOH (60 μL, 1.1 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Water was added, and the reaction mixture was made basic with saturated aqueous Na_2CO_3 solution. The mixture was extracted with EtOAc, the organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the BOC-protected product (101 mg, 18%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (10H, m), 1.50−1.80 (3H, m), 2.01 (3H, m), 2.15 (5H, m), 2.46 (1H, m), 2.65 (2H, m), 2.86 (1H, m), 3.27 (1H, d), 3.38 (1H, m), 3.43 (4H, m), 3.56 (1H, d), 4.39 (1H, d), 5.32 (1H, d), 6.78 (1H, d), 7.08 (1H, s), 7.22−7.40 (6H, m).

(b) To a solution of the above protected amine (101 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) was added TFA (3.3 mL). After 20 min, the solvent was removed under reduced pressure and the residue was azeotroped with CH_2Cl_2 (×3). The solution was adjusted to about pH 9 using 10% aqueous Na_2CO_3, and the mixture was extracted with EtOAc. The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. CH_2Cl_2 was added, and the solvent was decanted and concentrated under reduced pressure to give the title compound **9** (12 mg, 14%). MS *m*/*z*: 501 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (1H, m), 1.41−1.80 (3H, m), 1.96−2.34 (6H, m), 2.43 (4H, m), 2.77 (2H, m), 2.98 (1H, m), 3.07 (4H, m), 3.24 (1H, d), 3.38 (1H, m), 3.55 (1H, d), 4.39 (1H, d), 4.83 (1H, d), 6.80 (1H, d), 7.08 (1H, s), 7.23−7.41 (6H, m). Anal. ($C_{27}H_{34}Cl_2N_4O \cdot 1.4CH_2Cl_2$) C, H. N: found, 6.84; calcd, 9.03.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-methyl-1-piperazinyl)-1-azetidinyl]ethyl}-2-piperidone (10). Yield: 32%. MS *m*/*z*: 515 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (1H, m), 1.72 (2H, m), 1.92−2.50 (16H, m), 2.65 (2H, m), 2.87 (1H, m), 3.24 (1H, d), 3.32 (2H, m), 3.56 (1H, d), 4.39 (1H, d), 4.84 (1H, d), 6.79 (1H, d), 7.09 (1H, s), 7.24−7.41 (6H, m). Anal. ($C_{28}H_{36}Cl_2N_4O \cdot {}^1/_4CH_2Cl_2$) C, N. H: found, 6.33; calcd, 6.85.

5-{2-[3-(4-Acetyl-1-piperazinyl)-1-azetidinyl]ethyl}-1-benzyl-5-(3,4-dichlorophenyl)-2-piperidone (11). Yield: 19%. MS *m*/*z*: 543 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (1H, m), 1.73 (1H, m), 1.92−2.28 (13H, m), 2.43 (1H, m), 2.66 (1H, m), 2.86 (1H, m), 3.30 (3H, m), 3.43 (2H, t), 3.58 (3H, m), 4.40 (1H, d), 4.83 (1H, d), 6.81 (1H, d), 7.10 (1H, s), 7.24−7.40 (6H, m). Anal. ($C_{29}H_{36}Cl_2N_4O_2 \cdot {}^1/_4CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-(2-{3-[4-(methylsulfonyl)-1-piperazinyl]-1-azetidinyl}ethyl)-2-piperidone (12). Yield: 8%. MS *m*/*z*: 580. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (1H, m), 1.72 (1H, m), 2.01 (3H, m), 2.18 (2H, m), 2.33−2.51 (5H, m), 2.63 (2H, m), 2.75 (3H, s), 2.92 (1H, m), 3.18−3.35 (7H, m), 3.52 (1H, m), 4.40 (1H, d), 4.82 (1H, d), 6.80 (1H, d), 7.11 (1H, d), 7.22−7.40 (6H, m). Anal. ($C_{28}H_{36}Cl_2N_4O_3S \cdot {}^1/_6CH_2Cl_2$) C, H. N: found, 8.98; calcd, 9.43.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-thiomorpholinyl)-1-azetidinyl]ethyl}-2-piperidone (13). Yield: 11%. MS *m*/*z*: 518 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (1H, m), 1.74 (1H, m), 1.94−2.23 (5H, m), 2.46 (5H, m), 2.62 (6H, m), 2.92 (1H, m), 3.23 (1H, d), 3.38 (2H, m), 3.53 (1H, t), 4.40 (1H, d), 4.82 (1H, d), 6.78 (1H, d), 7.08 (1H, s), 7.23−7.40 (6H, m). Anal. ($C_{27}H_{33}Cl_2N_3OS \cdot {}^1/_4CH_2Cl_2$) H, N. C: found, 61.11; calcd, 60.63.

4-(1-{2-[1-Benzyl-3-(3,4-dichlorophenyl)-6-oxo-3-piperidinyl]ethyl}-3-azetidinyl)-1λ^4,4-thiazinan-1-one (14). Yield: 6%. MS *m*/*z*: 534 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, m), 1.70 (1H, m), 2.03 (3H, m), 2.18 (2H, m), 2.48 (3H, m), 2.64 (2H, m), 2.73−2.91 (4H, m), 3.02 (1H, m), 3.24 (1H, d), 3.24 (1H, d), 3.32 (2H, t), 3.54 (1H, d), 4.40 (1H, d), 4.82 (1H, d), 6.80 (1H, d), 7.08 (1H, s), 7.24−7.40 (6H, m). Anal. ($C_{27}H_{33}Cl_2N_3O_2S \cdot {}^3/_8CH_2Cl_2$) C, H, N.

4-(1-{2-[1-Benzyl-3-(3,4-dichlorophenyl)-6-oxo-3-piperidinyl]ethyl}-3-azetidinyl)-1λ^6,4-thiazinan-1,1-dione (15). Yield: 10%. MS *m*/*z*: 550 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45−1.77 (2H, m), 2.00 (3H, m), 2.17 (2H, m), 2.46 (1H, m), 2.62 (2H, q), 2.78 (4H, m), 3.02 (5H, m), 3.24 (1H, d), 3.31 (2H, m), 3.56 (1H, d), 4.41 (1H, d), 4.81 (1H, d), 6.81 (1H, d), 7.09 (1H, s), 7.28−7.40 (6H, m). Anal. ($C_{27}H_{33}Cl_2N_3O_3S \cdot {}^5/_8CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-hydroxy-1-piperidinyl)-1-azetidinyl]ethyl}-2-piperidone (16). Yield: 37%. MS *m*/*z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20−2.23 (17H, m), 2.37−2.74 (3H, m), 2.87 (1H, m), 3.24 (1H, d), 3.39 (1H, m), 3.55 (1H, d), 3.71 (1H, m), 4.38 (1H, d), 4.84 (1H, d), 6.79 (1H, d), 7.08 (1H, s), 7.22−7.41 (6H, m). Anal. ($C_{28}H_{35}Cl_2N_3O_2 \cdot {}^9/_{10}CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(3-hydroxy-1-pyrrolidinyl)-1-azetidinyl]ethyl}-2-piperidone (17). Yield: 70%. MS *m*/*z*: 502 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (1H, m), 1.78 (2H, m), 1.96−2.33 (8H, m), 2.50 (3H, m), 2.81 (3H, m), 3.09 (1H, m), 3.25 (1H, d), 3.34 (2H, m), 3.57 (1H, d), 4.37 (1H, s), 4.39 (1H, d), 4.83 (1H, d), 6.78 (1H, d), 7.08 (1H, s), 7.22−7.41 (6H, m). Anal. ($C_{27}H_{33}Cl_2N_3O_2 \cdot {}^1/_4CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(3-hydroxy-1-piperidinyl)-1-azetidinyl]ethyl}-2-piperidone (18). Yield: 58%. MS *m*/*z*: 516. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42−2.38 (16H, m), 2.48 (1H, m), 2.73 (2H, m), 2.93 (1H, m), 3.23 (1H, d), 3.41 (2H, m), 3.59 (1H, d), 3.81 (1H, d), 4.38 (1H, d), 4.84 (1H, d), 6.79 (1H, d), 7.09 (1H, s), 7.23−7.41 (6H, m). Anal. ($C_{28}H_{35}Cl_2N_3O_2 \cdot {}^{11}/_{16}CH_2Cl_2$) C, H. N: found, 6.81; calcd, 7.30.

1-Benzyl-5-(3,4-dichlorophenyl)-5-(2-{3-[(2-hydroxyethyl)(methyl)amino]-1-azetidinyl}ethyl)-2-piperidone (19). Yield: 34%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (1H, m), 1.76 (1H, m), 1.95−2.24 (9H, m), 2.36 (2H, t), 2.48 (1H, m), 2.66 (2H, m), 3.09 (1H, m), 3.29 (1H, d), 3.42 (2H, m), 3.59 (3H, m), 4.37 (1H, d), 4.88 (1H, d), 6.79 (1H, d), 7.07 (1H, s), 7.24−7.40 (6H, m). Anal. ($C_{26}H_{33}Cl_2N_3O_2 \cdot {}^3/_8CH_2Cl_2$) C, H. N: found, 7.62; calcd, 8.05.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)-1-azetidinyl]ethyl}-2-piperidone (20). (a) To a solution of aldehyde **48** (287 mg, 0.76 mmol) in THF (7 mL) and CH_2Cl_2 (7 mL) was added 8-(3-azetidinyl)-8-azabicyclo[3.2.1]oct-3-yl acetate dihydrochloride (227 mg, 0.76 mmol), NEt_3 (0.1 mL, 0.72 mmol), sodium triacetoxyborohydride (226 mg, 1.06 mmol), and AcOH (48 μL, 0.84 mmol), and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organics were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the acetate (86 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48−2.22 (18H, m), 2.46 (1H, m), 2.66 (2H, m), 3.00 (2H, m), 3.11 (1H, m), 3.29 (3H, m), 3.52 (1H, d), 4.39 (1H, d), 4.83 (1H, d), 4.96 (1H, m), 6.78 (1H, d), 7.08 (1H, s), 7.21−7.40 (6H, m). Anal. ($C_{32}H_{39}Cl_2N_3O_2 \cdot {}^5/_{16}CH_2Cl_2$) C, H, N.

(b) To a solution of the above acetate (78 mg, 0.13 mmol) in MeOH (1.5 mL) was added 6 N aqueous NaOH solution (0.5 mL). After 16 h, the MeOH was evaporated under reduced pressure and H_2O (5 mL) and CH_2Cl_2 (10 mL) were added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure to give the title compound **20** (67 mg, 96%) as a white foam. MS *m*/*z*: 543 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (1H, m), 1.43−2.23 (15H, m), 2.43 (1H, m), 2.61 (2H, m), 3.00 (2H, m), 3.12 (1H, m), 3.26 (3H, m), 3.56 (1H, d), 4.01 (1H, m), 4.40 (1H, d), 4.82 (1H, d), 6.80 (1H, d), 7.08 (1H, s), 7.23−7.40 (6H, m). Anal. ($C_{30}H_{37}Cl_2N_3O_2 \cdot {}^1/_2CH_2Cl_2$) C, N. H: found, 5.95; calcd, 6.55.

Compounds **29** and **31**−**44** were prepared from aldehyde **58** and the appropriate 3-substituted azetidine, using the reductive amination protocol described above.

***(5S)*-1-(Cyclopropylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (29).** Yield: 32%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.33 (2H, m), 0.62 (2H, m), 1.08 (1H, m), 1.63 (2H, m), 1.81 (1H, m), 1.95−2.42 (9H, m), 2.74 (2H, m), 2.93 (1H, m), 3.19 (1H, m), 3.37 (2H, m), 3.44 (2H, m), 3.68 (4H, m), 3.78 (1H, d), 7.16 (1H, d), 7.41 (2H, m). Anal. ($C_{24}H_{33}Cl_2N_3O_2 \cdot {}^1/_2CH_2Cl_2 \cdot {}^1/_5H_2O$) C, H, N.

***(5S)*-1-(Cyclopropylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(1-piperazinyl)-1-azetidinyl]ethyl}-2-piperidone (31).** Yield: 43%. MS *m*/*z*: 465 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (2H, m), 0.61 (2H, m), 1.05 (1H, m), 1.67 (1H, m), 1.75−2.57 (15H, m), 2.78 (1H, m), 2.96 (3H, m), 3.17 (1H, dd), 3.42 (4H, m), 3.78 (1H, d), 7.14 (1H, d), 7.41 (2H, m). Anal. ($C_{24}H_{34}Cl_2N_4O \cdot {}^1/_2CH_2Cl_2 \cdot {}^1/_3H_2O$) C, H, N.

***(5S)*-1-(Cyclopropylmethyl)-5-(3,4-dichlorophenyl)-5-(2-{3-[4-(methylsulfonyl)-1-piperazinyl]-1-azetidinyl}ethyl)-2-piperidone (32).** Yield: 47%. MS *m*/*z*: 543 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (2H, m), 0.61 (2H, m), 1.07 (1H, m), 1.63 (1H, m), 1.78 (2H, m), 1.94−2.24 (4H, m), 2.38 (5H, m), 2.70 (5H, m), 2.94 (1H, m), 3.19 (5H, m), 3.39 (4H, m), 3.78 (1H, d), 7.15 (1H, d), 7.41 (2H, m). Anal. ($C_{25}H_{36}Cl_2N_4O_3S \cdot {}^2/_3H_2O$) C, H, N.

4-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-1-piperazinesulfonamide (33). Yield: 37%. MS *m*/*z*: 544 $(MH)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26 (2H, m), 0.55 (2H, m), 1.00 (1H, m), 1.58 (1H, m), 1.66 (1H, m), 1.82−2.18 (7H, m), 2.31 (4H, m), 2.65 (2H, m), 2.87 (1H, m), 3.12 (4H, m), 3.25−3.42 (4H, m), 3.72 (1H, d), 4.66 (2H, br, s), 7.08 (1H, d), 7.37 (2H, m). Anal. ($C_{24}H_{35}Cl_2N_5O_3S \cdot H_2O$) C, H, N.

4-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-*N*-methyl-1-piperazinesulfonamide (34). Yield: 79%. MS *m*/*z*: 558 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (2H, m), 0.62 (2H, m), 1.04 (1H, m), 1.83 (1H, m), 1.97−2.41 (9H, m), 2.74 (5H, m), 2.95 (1H, m), 3.10−3.27 (6H, m), 3.41 (5H, m), 3.78 (1H, d), 4.00 (1H, d), 7.15 (1H, d), 7.42 (2H, m). Anal. ($C_{25}H_{37}Cl_2N_5O_3S \cdot {}^1/_{20}H_2O$) C, H, N.

4-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-*N*,*N*-dimethyl-1-piperazinesulfonamide (35). Yield: 16%. MS *m*/*z*: 572. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.28 (2H, m), 0.61 (2H, m), 1.05 (1H, m), 1.62 (1H, m), 1.80 (1H, m), 1.92−2.20 (10H, m), 2.64−2.96 (8H, m), 3.10−3.48 (10H, m), 3.78 (1H, d), 7.15 (1H, d), 7.41 (2H, m). Anal. ($C_{26}H_{39}Cl_2N_5O_3S \cdot {}^1/_2H_2O$) C, H, N.

4-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-1-piperazinecarboxamide (36). Yield: 63%. MS *m*/*z*: 508 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.33 (2H, m), 0.62 (2H, m), 1.07 (1H, m), 1.63 (1H, m), 1.82 (1H, m), 1.98−2.43 (11H, m), 2.74 (2H, m), 2.91 (1H, m), 3.17 (1H, dd), 3.35−3.52 (7H, m), 3.78 (1H, d), 4.40 (2H, s), 7.15 (1H, d), 7.40 (1H, s), 7.42 (1H, d). Anal. ($C_{25}H_{35}Cl_2N_5O_2 \cdot 2H_2O$) C, H, N.

***(5S)*-5-{2-[3-(4-Amino-1-piperidinyl)-1-azetidinyl]ethyl}-1-(cyclopropylmethyl)-5-(3,4-dichlorophenyl)-2-piperidone (37). (a)** To a solution of aldehyde **58** (1.4 g, 4.11 mmol) in THF (60 mL) was added *tert*-butyl 1-(3-azetidinyl)-4-piperidinecarbamate bis-TFA salt (2.2 g, 4.52 mmol) and NEt_3 (1.8 mL, 12.33 mmol). After 90 min, $NaBH(OAc)_3$ (1.2 g, 5.34 mmol) and AcOH (0.64 mL) were added and the reaction mixture was stirred at room temperature for 16 h. Saturated $NaHCO_3$ was then added, the reaction mixture was extracted with EtOAc, the organics were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the BOC-protected product (1.45 g, 61%). MS *m*/*z*: 580. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (2H, m), 0.59 (2H, m), 1.04 (1H, m), 1.42 (10H, m), 1.63 (2H, m), 1.72−2.23 (11H, m), 2.33 (1H, m), 2.54−2.75 (4H, m), 2.86 (1H, m), 3.15 (1H, m), 3.42 (4H, m), 3.75 (1H, d), 4.40 (1H, br s), 7.13 (1H, d), 7.40 (2H, m). Anal. ($C_{30}H_{44}Cl_2N_4O_3 \cdot {}^1/_3CH_2Cl_2$) C, H, N.

(b) To a solution of the above protected amine (1.4 g, 24.2 mmol) in CH_2Cl_2 (20 mL), cooled in an ice/water bath, was added TFA (6.6 mL). The reaction mixture was then warmed to room temperature and was stirred for 1 h. Et_2O was added, and the reaction mixture was allowed to stir overnight. The solid was filtered off and triturated with Et_2O. The solid was filtered off and dried to give the title compound **37** (907 mg, 46%) as a pale-brown solid. MS *m*/*z*: 479 $(MH)^+$. ^{1}H NMR (300 MHz, MeOH-d_4) (selected data): δ 0.40 (2H, m), 0.62 (2H, m), 1.16 (1H, m), 1.72 (2H, m), 1.86−2.22 (8H, m), 2.39 (2H, m), 2.82−3.56 (8H, m), 3.66 (1H, m), 3.97 (3H, m), 7.42 (1H, br, s), 7.64 (2H, m). Anal. ($C_{25}H_{36}Cl_2N_4O \cdot 3TFA \cdot 3H_2O$) C, H, N.

***N*-[1-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichloropehnyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-4-piperidinyl]acetamide (38).** To a solution of amine **37** (300 mg, 0.36 mmol) in CH_2Cl_2 (40 mL) was added NEt_3 (0.255 mL, 1.8 mmol) and acetic anhydride (40 μL, 0.40 mmol). After 16 h, a further amount of 2 equiv of Ac_2O was added and the reaction mixture was allowed to stir for 1 h. The reaction mixture was washed with H_2O and brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. EtOAc (40 mL) was added, and the organic phase was extracted with 2 N HCl. The aqueous phase was made basic with $NaHCO_3$ and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and filtered, the solvent was removed under reduced pressure, and the product was dried over P_2O_5 (53 mg, 28%). MS *m*/*z*: 521 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.30 (2H, m), 0.60 (2H, m), 1.05 (1H, m), 1.38 (2H, m), 1.60 (1H, m), 1.76−2.24 (13H, m), 2.37 (1H, m), 2.63 (4H, m), 2.86 (1H, m), 3.15 (1H, m), 3.41 (4H, m), 3.74 (2H, d), 5.28

(1H, m), 7.12 (1H, d), 7.41 (2H, m). Anal. ($C_{27}H_{38}Cl_2N_4O_2 \cdot CH_2Cl_2 \cdot H_2O$) C, H, N.

***N*-[1-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-4-piperidinyl]methanesulfonamide (39).** To a solution of amine **37** tris-TFA salt (60 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) was added NEt_3 (49 μL, 0.35 mmol), and the reaction mixture was cooled in an ice/water bath. Methanesulfonyl chloride (6.3 μL, 0.88 mmol) was added, and the reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was partitioned between H_2O and CH_2Cl_2, and the organic phase was washed with H_2O. The organic layer was dried ($MgSO_4$) and filtered, the solvent was removed under reduced pressure, and the residue was purified on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 to give the title compound **39** (6 mg, 15%). MS *m/z*: 557 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.33 (2H, m), 0.60 (2H, m), 0.86 (2H, m), 1.08 (1H, m), 1.17−2.40 (14H, m), 2.56−2.78 (3H, m), 2.87 (1H, m), 2.96 (3H, s), 3.18 (1H, m), 3.24−3.50 (4H, m), 3.77 (1H, d), 4.18 (1H, d), 7.15 (1H, d), 7.40 (2H, d).

***N*-[1-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-4-phenyl-4-piperidinyl]acetamide (40).** Yield: 45%. MS *m/z*: 597 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.34 (2H, m), 0.61 (2H, m), 1.04 (1H, m), 1.63 (1H, m), 1.82 (1H, m), 1.99 (3H, s), 2.01−2.27 (9H, m), 2.36 (3H, m), 2.59 (2H, m), 2.74 (2H, m), 2.94 (1H, m), 3.18 (1H, m), 3.42 (4H, m), 3.78 (1H, d), 5.45 (1H, s), 7.12 (1H, d), 7.18−7.43 (7H, m). Anal. ($C_{33}H_{42}Cl_2N_4O_2 \cdot {}^7/_{10}CH_2Cl_2$) C, H, N.

(*5S*)-1-(Cyclopropylmethyl)-5-(3,4-dichloropehnyl)-5-{2-[3-(4-hydroxy-1-piperidinyl)-1-azetidinyl]ethyl}-2-piperidone (41). Yield: 78%. MS *m/z*: 481 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.31 (2H, m), 0.61 (2H, m), 1.04 (1H, m), 1.58 (4H, m), 1.75−2.23 (10H, m), 2.34 (1H, m), 2.57 (2H, m), 2.64 (2H, m), 2.84 (1H, m), 3.17 (1H, m), 3.42 (4H, m), 3.67 (1H, m), 3.79 (1H, d), 7.13 (1H, d), 7.41 (2H, m). Anal. ($C_{25}H_{35}Cl_2N_3O_2 \cdot {}^4/_{10}CH_2Cl_2$) C, H, N.

(*5S*)-1-(Cyclopropylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-ethoxy-1-piperidinyl)-1-azetidinyl]ethyl}-2-piperidone (42). Yield: 64%. MS *m/z*: 508 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.32 (2H, m), 0.60 (2H, m), 1.05 (1H, m), 1.19 (3H, m), 1.60 (4H, m), 1.83 (3H, m), 1.90−2.21 (6H, m), 2.37 (1H, m), 2.53 (2H, m), 2.68 (2H, m), 2.87 (1H, m), 3.13−3.53 (8H, m), 3.78 (1H, d), 7.12 (1H, d), 7.40 (2H, m). Anal. ($C_{27}H_{39}Cl_2N_3O_2 \cdot {}^3/_8CH_2Cl_2$) C, H, N.

1-(1-{2-[(*3S*)-1-(Cyclopropylmethyl)-3-(3,4-dichlorophenyl)-6-oxopiperidinyl]ethyl}-3-azetidinyl)-4-piperidinecarboxylic Acid (43). (a) Aldehyde **58** was reacted with methyl 1-(3-azetidinyl)-4-piperidinecarboxylate dihydrochloride, using the reductive amination conditions described above. Yield: 39%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.29 (2H, m), 0.60 (2H, m), 1.05 (1H, m), 1.62−1.93 (8H, m), 1.96−2.39 (7H, m), 2.62 (2H, m), 2.77 (2H, m), 2.91 (1H, m), 3.17 (1H, m), 3.38−3.56 (4H, m), 3.63 (3H, s), 3.76 (1H, d), 7.15 (1H, d), 7.40 (2H, m). Anal. ($C_{27}H_{37}Cl_2N_3O_3 \cdot {}^1/_{10}CH_2Cl_2 \cdot H_2O$) C, H, N.

(b) To a solution of the above ester (300 mg, 0.57 mmol) in MeOH (10 mL) was added 1 N aqueous NaOH (ca. 2.5 mL), and the reaction mixture was stirred for 16 h. The reaction mixture was acidified to about pH 5 using 2 N HCl, the solvent was removed under reduced pressure, and the residue was triturated with Et_2O. The resulting white solid was filtered off to give the acid **43** (268 mg, 92%). MS *m/z*: 508 $(MH)^+$. ^{1}H NMR (300 MHz, selected data, DMSO-d_6): δ 1.04 (1H, m), 3.49 (1H, d), 3.79 (1H, d), 7.39 (1H, d), 7.62 (2H, m). Anal. ($C_{26}H_{35}Cl_2N_3O_3 \cdot {}^3/_2CH_2Cl_2 \cdot {}^7/_4H_2O$) C, H, N.

(*5S*)-1-(Cyclopropylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-oxo-1-piperidinyl)-1-azetidinyl]ethyl}-2-piperidone (44). Yield: 7%. MS *m/z*: 478 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.33 (2H, m), 0.60 (2H, m), 1.06 (1H, m), 1.73 (1H, m), 1.88 (1H, m), 1.98−2.47 (10H, m), 2.58 (4H, m), 2.87 (2H, m), 3.09 (1H, m), 3.19 (1H, m), 3.48 (4H, m), 3.77 (1H, d), 7.16 (1H, d), 7.42 (2H, m).

5-(3,4-Dichlorophenyl)-1-(4-fluorobenzyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (24). (a) A solution of lactam (**46**) (8.0 g, 21.5 mmol) in HCl-saturated MeOH (100 mL) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, CH_2Cl_2/MeOH was added, and the solution was washed with saturated sodium bicarbonate solution and brine. The organic phase was dried ($MgSO_4$) and filtered, and the residue was purified on silica gel, eluting with MeOH/EtOAc to give the alcohol (3.8 g, 61%) as a white solid. MS *m/z*: 288 $(MH)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64−2.21 (6H, m), 3.09 (2H, m), 3.39 (1H, d), 3.64 (1H, d), 4.35 (1H, d), 7.38 (1H, d), 7.52 (1H, br), 7.63 (2H, m).

(b) To a solution of the above alcohol (3.4 g, 11.8 mmol) in CH_2Cl_2 at room temperature was added NEt_3 (2.5 mL, 17.7 mmol), and the mixture was cooled in an ice/water bath. Methanesulfonyl chloride (1.2 mL, 15.3 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was washed with H_2O (×3), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the mesylate **49** (2.52 g, 58%) as a buff-colored solid. MS *m/z*: 270 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (6H, m), 2.40 (1H, m), 2.90 (1H, s), 3.12 (1H, m), 3.50 (1H, d), 3.80 (1H, m), 3.86−4.08 (2H, m), 6.14 (1H, s), 7.21 (1H, d), 7.42 (1H, s), 7.50 (1H, d).

(c) To a solution of the above mesylate (2.5 g, 6.8 mmol) in CH_3CN (75 mL) was added 4-(3-azetidinyl)morpholine hydrochloride (3.8 g, 20.4 mmol), K_2CO_3 (3.0 g, 20.4 mmol), and NEt_3 (9.3 mL, 68 mmol), and the mixture was heated under reflux for 16 h. The solvent was removed under reduced pressure, water (250 mL) was added, and the mixture was extracted with EtOAc and then 10% MeOH/EtOAc solution. The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the crude product as a white foam that was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the azetidine product **50** (1.25 g, 45%) as a white solid. MS *m/z*: 413 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (1H, m), 1.82 (1H, m), 1.97−2.41 (12H, m), 2.72 (2H, m), 2.92 (1H, m), 3.40 (2H, m), 3.72 (4H, m), 6.17 (1H, br), 7.16 (1H, d), 7.37 (1H, s), 7.42 (1H, d).

(d) Crushed KOH (104 mg, 1.84 mmol) in DMSO (3 mL) was stirred for 5 min, and to this mixture was added a solution of the above lactam (240 mg, 0.46 mmol) in DMSO (5 mL), followed by 4-fluorobenzyl bromide (58 μL, 0.46 mmol). After 50 min, EtOAc was added and the mixture was washed with H_2O (×3), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with EtOAc/MeOH/$NHEt_2$ to give the title compound (**24**) (100 mg, 42%). MS *m/z*: 520 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (1H, m), 1.72 (2H, m), 1.94−2.28 (8H, m), 2.42 (1H, m), 2.67 (2H, m), 2.88 (1H, m), 3.33 (2H, m), 3.49 (2H, m), 3.68 (4H, m), 4.36 (1H, d), 4.82 (1H, d), 6.82 (1H, d), 7.00−7.09 (3H, m), 7.24−7.34 (3H, m). Anal. ($C_{27}H_{32}Cl_2FN_3O_2 \cdot {}^1/_2EtOAc$) C, H, N.

5-(3,4-Dichlorophenyl)-1-(3-methylbenzyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (22). To a solution of lactam **50** (250 mg, 0.6 mmol) in DMF (5 mL) was added NaH (60% dispersion in oil) (22 mg, 0.6 mmol), and the mixture was stirred for 30 min. 3-Methylbenzyl bromide (86 mL, 0.63 mmol) was added, and the reaction mixture was stirred for 75 min. H_2O (1 mL) was added, followed by saturated sodium bicarbonate solution (30 mL). The mixture was extracted with CH_2Cl_2 (×3), and the organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the title compound **22** (60 mg, 20%) as a white foam. MS *m/z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (1H, m), 1.94−2.20 (5H, m), 2.24 (4H, m), 2.36 (3H, s), 2.44 (1H, m), 2.67 (2H, m), 2.88 (1H, m), 3.23 (1H, d), 3.33 (2H, m), 3.56−3.68 (6H, m), 4.34 (1H, d), 4.79 (1H, d), 6.81 (1H, d), 7.04−7.17 (3H, m), 7.23 (3H, m). Anal. ($C_{28}H_{35}Cl_2N_3O_2 \cdot {}^1/_2H_2O$) C, H. N: found, 7.26; calcd, 7.99.

Compounds **25** and **26** were prepared from lactam **50**, employing the alkylation method described for **22** and using the appropriate alkylating agent.

5-(3,4-Dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-1-(4-pyridinylmethyl)-2-piperidone (25). Yield: 80%. MS *m*/*z*: 503 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (1H, m), 1.77 (2H, m), 2.08 (2H, m), 2.15−2.38 (6H, m), 2.48 (1H, m), 2.64 (2H, m), 2.88 (1H, m), 3.32 (3H, m), 3.54 (1H, d), 3.70 (4H, m), 4.50 (1H, d), 4.74 (1H, d), 6.89 (1H, d), 7.12 (1H, s), 7.20 (2H, d), 7.37 (1H, d), 8.61 (2H, d). Anal. ($C_{26}H_{32}Cl_2N_4O_2 \cdot {}^1/_5CH_2Cl_2$) C, H, N.

1-(Cyclohexylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (26). Yield: 10%. MS *m*/*z*: 509 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (2H, m), 1.22 (2H, m), 1.58−1.83 (9H, m), 1.96−2.43 (10H, m), 2.76 (2H, m), 2,92 (1H, m), 3.18 (1H, m), 3.88 (4H, m), 3.57 (1H, m), 3.75 (4H, m), 7.08 (1H, d), 7.32 (1H, s), 7.42 (1H, d). Anal. ($C_{27}H_{39}Cl_2N_3O_2 \cdot {}^1/_5CH_2Cl_2$) C, H, N.

1-Benzyl-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (5). (a) To a solution of the alcohol described in the synthesis of **6** (2.07 g, 5.48 mmol) in CH_2Cl_2 (40 mL) was added NEt_3 (1.14 mL, 8.22 mmol), and the reaction mixture was cooled in an ice/water bath. Methanesulfonyl chloride (0.51 mL, 6.58 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. Saturated NH_4Cl was added, and the mixture was extracted with CH_2Cl_2 (×3). The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the mesylate (2.32 g, 93%), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96−2.24 (5H, m), 2.47 (1H, m), 2.82 (3H, s), 3.37 (1H, d), 3.66 (1H, d), 3.81 (1H, m), 3.90 (1H, m), 4.32 (1H, d), 4.96 (1H, d), 6.69 (1H, d), 7.13 (1H, s), 7.23−7.41 (6H, m).

(b) To a solution of the above mesylate (500 mg, 1.1 mmol) in MeCN (25 mL) was added 4-(3-azetidinyl)morpholine hydrochloride (973 mg, 5.5 mmol), NEt_3 (1.45 mL, 11 mmol), and K_2CO_3 (404 mg, 3.3 mmol), and the reaction mixture was heated at reflux for 6 h. The reaction mixture was cooled to room temperature, water was added, and the MeCN was evaporated under reduced pressure. The aqueous phase was diluted with aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the title compound **5** (260 mg, 47%). MS *m*/*z*: 502 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, m), 1.74 (2H, m), 1.93−2.32 (8H, m), 2.23 (1H, m), 2.68 (2H, m), 2.89 (1H, m), 3.24 (1H, d), 3.35 (2H, m), 3.56 (1H, d), 3.68 (4H, m), 4.39 (1H, d), 4.83 (1H, d), 6.80 (1H, d), 7.08 (1H, s), 7.23−7.42 (6H, m). Anal. ($C_{27}H_{33}Cl_2N_3O_2 \cdot {}^1/_{10}CH_2Cl_2$) C, H, N.

5-(3,4-Dichlorophenyl)-1-(2-methylbenzyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (21). Yield: 11%. Compound **21** was prepared using the method described for **3** using 2-methylbenzyl bromide in the initial alkylation step. MS *m*/*z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (1H, m), 1.71 (1H, m), 2.02 (4H, m), 2.12−2.52 (9H, m), 2.63 (2H, m), 2.84 (1H, m), 3.17 (1H, d), 3.32 (2H, m), 3.53 (1H, d), 3.68 (4H, m), 4.37 (1H, d), 4.98 (1H, d), 6.77 (1H, d), 7.02 (1H, s), 7.16−7.33 (5H, m). Anal. ($C_{28}H_{35}Cl_2N_3O_2 \cdot {}^1/_5H_2O$) C, H, N.

5-(3,4-Dichlorophenyl)-1-(4-methylbenzyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (23). Yield: 32%. Compound **23** was prepared using the method described for **3** using 4-methylbenzyl bromide in the initial alkylation step. MS *m*/*z*: 516 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (1H, m), 1.69 (1H, m), 1.93−2.20 (5H, m), 2.24 (4H, m), 2.38 (3H, s), 2.43 (1H, m), 2.66 (2H, m), 2.86 (1H, m), 3.22 (1H, d), 3.32 (2H, t), 3.53 (1H, d), 3.68 (4H, m), 4.32 (1H, d), 4.81 (1H, d), 6.81 (1H, d), 7.02 (1H, s), 7.19 (3H, m), 7.28 (2H, m). Anal. ($C_{28}H_{35}Cl_2N_3O_2 \cdot 0.2H_2O$) C, H. N: found, 10.19; calcd, 8.08.

***(5S)*-1-(Cyclohexylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (27). (a)** To a suspension of NaH (60% dispersion in oil) (43 g, 1.08 mol) in THF (400 mL) cooled in an ice/water bath was added dropwise a solution of 3,4-dichlorophenylacetonitrile (200 g, 1.08 mol) in THF (400 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 14 h. The reaction was cooled again in an ice/water bath, and allyl bromide (93 mL, 1.08 mol) was added. The reaction mixture was stirred at room temperature for 5 h, then at 50 °C for 4 h. The reaction mixture was cooled, water was added, and the mixture was partitioned between water and Et_2O. The organic phase was evaporated and the residue was purified on silica gel, eluting with Et_2O/hexane to give the alkylated product (104.8 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (2H, dd), 3.87 (1H, t), 5.21 (2H, m), 5.78 (1H, m), 7.19 (1H, d), 7.47 (2H, m).

(b) To a solution of NaH (60% dispersion in oil) (21.15 g, 505 mmol) in THF (3 L) cooled in an ice/water bath was added a solution of bromopropionic acid (73.7 g, 482 mmol) in THF (400 mL), and the reaction mixture was allowed to stir for 16 h.

To a solution of NaH (60% dispersion in oil) (21.15 g, 505 mmol) in THF (300 mL) cooled in an ice/water bath was added a solution of the above allyl compound (103.8 g, 459 mmol) in THF (300 mL). The reaction mixture was then allowed to warm to room temperature and stirred for 16 h. This solution was then cannulated into the sodium salt solution of bromopropionic acid, stirred at room temperature for 16 h, and then heated to 70 °C for 4 h. The reaction mixture was cooled, water was carefully added, and the reaction mixture was concentrated under reduced pressure (to ∼1 L). The mixture was made basic using $NaHCO_3$ and extracted with Et_2O. The aqueous phase was then acidified (concentrated HCl) and extracted with Et_2O (×3), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with EtOAc/hexane to give the acid **53** (88.6 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (2H, m), 2.39 (1H, m), 2.54 (1H, m), 2.68 (2H, m), 5.18 (2H, m), 5.62 (1H, m), 7.22 (1H, d), 7.49 (2H, m).

(c) To a solution of the above acid (88.6 g, 297 mmol) in toluene (800 mL) was added (*S*)-valinol (30.7 g, 297 mmol), and the reaction mixture was heated under Dean and Stark conditions for 72 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with Et_2O/hexane to give the oxazoline product **54** as a mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (3H, d), 0.96 (3H, d), 1.68 (1H, m), 2.00−2.30 (2H, m), 2.40 (2H, m), 2.68 (2H, m), 3.82 (2H, m), 4.17 (1H, m), 5.18 (2H, m), 5.62 (1H, m), 7.22 (1H, d), 7.42 (1H, s), 7.48 (1H, d).

(d) To a suspension of $LiAlH_4$ (2.32 g, 61.1 mmol) in Et_2O (100 mL) cooled in an ice/water bath was added a solution of the above oxazolines (18.2 g, 61.1 mmol) in Et_2O (100 mL). After 2 h, H_2O (2.5 mL), 2 N NaOH (4 mL), and H_2O (2.5 mL) were then added sequentially, the solid was filtered off, and the solvent was removed under reduced pressure. The residue was partitioned between 2 N HCl and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with CH_2Cl_2/MeOH to give first the (*S*,*S*)-amine (2.55 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (3H, m), 0.97 (3H, m), 1.74 (0.5H, m), 1.84−2.19 (3H, m), 2.33 (1H, m), 2.49 (1.5H, m), 2.8−3.0 (1H, m), 3.09 (0.5H, m), 3.28−3.47 (2H, m), 3.61 (0.5H, m), 3.73 (0.5H, d), 3.84 (0.5H, d), 3.96 (1H, d), 4.95−5.07 (2H, m), 5.34 (1H, m), 7.10 (0.5H, d), 7.21 (0.5H, d), 7.37 (0.5H, s), 7.43 (1.5H, m), 8.90 (0.5H, d), 9.34 (0.5H, d), 9.97 (0.5H, s), 10.12 (0.5H, s). Following this off the column was the (*R*,(*S*)-diastereomer (1.55 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.8−1.0 (8H, m), 1.76−2.70 (7H, m), 3.04−3.13 (1H, m), 3.42−4.04 (5H, m), 5.01 (3H, m), 5.37 (1H, m), 7.12 (1H, d), 7.37 (1H, m), 7.42 (1H, m), 8.65 (0.66H, d), 9.52 (0.33H, d), 9.92 (0.66H, s), 10.23 (0.33H, s).

(e) A solution of the above (*S*,*S*)-isomer (2.54 g, 6.88 mmol) in 8% H_2SO_4 in EtOH (100 mL) was heated under reflux for 5 days. The reaction mixture was cooled, made basic with $NaHCO_3$, and extracted with EtOAc. The organics were dried ($MgSO_4$) and filtered, and the solvent was removed under

reduced pressure. The residue was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the lactam **55** (1.00 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00−2.22 (3H, m), 2.37 (2H, m), 2.58 (1H, m), 3.40 (1H, d), 3.62 (1H, d), 5.02 (2H, m), 5.39 (1H, m), 6.07 (1H, br), 7.17 (1H, d), 7.40 (1H, s), 7.44 (1H, d).

(f) KOH (790 mg, 14.1 mmol) was added to DMSO (20 mL), and the mixture was allowed to stir for 20 min. To this mixture was added a solution of the above lactam (1.00 g, 3.52 mmol) in DMSO (20 mL) followed by cyclohexylmethyl bromide (0.54 mL, 3.87 mmol). After 16 h, H_2O was added and the mixture was extracted with EtOAc (×3). The combined organics were washed with H_2O (×3), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with EtOAc/pentane to give the alkylated product (1.25 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (2H, m), 1.22 (3H, m), 1.57−1.80 (6H, m), 1.97−2.57 (6H, m), 3.20 (1H, m), 3.37 (2H, m), 3.52 (1H, d), 5.01 (2H, m), 5.39 (1H, m), 7.09 (1H, d), 7.32 (1H, s), 7.42 (1H, d).

(g) Ozone was bubbled through a solution of the above olefin (1.25 g, 3.29 mmol) in MeOH (40 mL) at −78 °C until the solution turned blue. After a further 20 min, a solution of Me_2S (2.5 mL, 33 mmol) in MeOH (5 mL) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure, the residue was partitioned between H_2O and EtOAc, and the organic phase was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue was purified on silica gel, eluting with EtOAc/hexane to give the aldehyde (0.98 g, 78%). MS *m*/*z*: 382 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (2H, m), 1.22 (3H, m), 1.55−1.90 (6H, m), 2.20 (3H, m), 2.41 (1H, m), 2.72 (1H, d), 2.97 (1H, d), 3.19 (1H, m), 3.40 (1H, m), 3.49 (1H, d), 3.79 (1H, d), 7.18 (1H, d), 7.42 (2H, m), 9.50 (1H, s).

(h) To a solution of the above aldehyde (0.98 g, 2.57 mmol) in THF (40 mL) was added 4-(3-azetidinyl)morpholine hydrochloride (600 mg, 2.83 mmol) and NEt_3 (0.79 mL, 5.65 mmol), and the reaction mixture was stirred for 1 h. $NaBH(OAc)_3$ (818 mg, 3.86 mmol) was then added followed immediately by AcOH (147 μL, 2.57 mmol). After 5 min, H_2O was added and the mixture was extracted with EtOAc (×3). The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with MeOH/CH_2Cl_2 to give the title compound **27** (771 mg, 58%). MS *m*/*z*: 508 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (2H, m), 1.23 (3H, m), 1.54−1.87 (9H, m), 2.02 (1H, m), 2.08−2.26 (4H, m), 2.29 (4H, m), 2.40 (1H, m), 2.77 (2H, m), 2.93 (1H, m), 3.17 (1H, dd), 3.29−3.44 (3H, m), 3.57 (1H, d), 3.70 (4H, m), 7.08 (1H, d), 7.32 (1H, s), 7.41 (1H, d). Anal. ($C_{27}H_{39}Cl_2N_3O_2 \cdot {}^1/_{10}CH_2Cl_2$) C, H. N: found, 8.55; calcd, 8.13.

The (*R*)-enantiomer **28** was prepared in an identical fashion from the more polar oxazoline-amine diastereomer **54**.

(5*R*)-1-(Cyclohexylmethyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (28). MS *m*/*z*: 508 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): spectral data identical to data for **27**. Anal. ($C_{27}H_{39}Cl_2N_3O_2 \cdot {}^1/_4CH_2Cl_2$) C, H, N.

(5*S*)-1-(Cyclohexyl)-5-(3,4-dichlorophenyl)-5-{2-[3-(4-morpholinyl)-1-azetidinyl]ethyl}-2-piperidone (30). (a) To a solution of racemic acid **53** (100 g, 335 mmol) in EtOAc (∼100 mL) was added a solution of *R*-(+)-naphthylethylamine (24.9 g) in EtOAc (50 mL), and the solvent was removed under reduced pressure. The solid residue was recrystallized three times from EtOAc to give a white solid (20 g). The solid was suspended in CH_2Cl_2 (500 mL), and 1 N HCl (∼300 mL) was added. The aqueous layer was removed, and the organic layer was washed with 1 N HCl, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give the acid as the single (*S*)-enantiomer (>98% ee) (column, Diacel Chiralcel OD, 250 mm × 4.6 mm; mobile phase 70% v/v hexane, 30% v/v IPA + 0.1% v/v TFA; flow = 1.0 mL/min; run time = 30 min, wavelength, results at 220 nM).

(b) To a solution of the above (*S*)-nitrile (2.0 g, 6.71 mmol) in toluene (20 mL) at −78 °C was added DIBAL (13.5 mL, 1.5M solution in toluene) in three aliquots, and the reaction mixture was allowed to warm to −40 °C over 3 h. The reaction mixture was poured into 10% aqueous citric acid solution, and the mixture was stirred for 30 min. The organic layer was separated, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure to give the aldehyde, which was used without further purification.

(c) To a solution of the above aldehyde (1.34 g, 4.45 mmol) in CH_2Cl_2 (50 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI) (1.19 g, 6.23 mmol) and hydroxybenzotriazole (HOBT) (0.68 g, 4.45 mmol). After 10 min, MeOH (0.9 mL, 22.3 mmol) was added and the reaction mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was partitioned between 0.5 N HCl and EtOAc. The organic phase was dried (Na_2SO_4) and filtered and the solvent was removed under reduced pressure to give the ester **56** (1.6 g), which was used without further purification.

(d) To a solution of the above ester (500 mg, 1.59 mmol) in THF (30 mL) was added cyclohexylamine (200 μL, 1.75 mmol). After 10 min, $NaBH(OAc)_3$ (470 mg, 2.23 mmol) and AcOH (91 μL, 1.59 mmol) were added and the reaction mixture was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and made basic with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, the organics were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel, eluting with CH_2Cl_2/MeOH to give the lactam **57** (281 mg, 48%). MS *m*/*z*: 366 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (1H, m), 1.47 (3H, m), 1.70 (4H, m), 1.84 (2H, m), 1.93−2.54 (6H, m), 3.32 (1H, d), 3.48 (1H, d), 4.58 (1H, m), 5.02 (2H, m), 5.40 (1H, m), 7.12 (1H, d), 7.36 (1H, s), 7.44 (1H, d).

(e) The above olefin was converted to the aldehyde using the method described for **27** (98%, crude). MS *m*/*z*: 368 $(MH)^+$. ^{1}H NMR (selected data, 300 MHz, $CDCl_3$): δ 9.52 (aldehyde).

(f) The above aldehyde was converted to **30** using the method described in the preparation of **27** (49%). MS *m*/*z*: 494 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (4H, m), 1.56−1.88 (8H, m), 2.96 (1H, m), 2.03−2.34 (8H, m), 2.40 (1H, m), 2.76 (2H, m), 2.93 (1H, m), 3.21 (1H, d), 3.38 (2H, t), 3.49 (1H, d), 3.66 (4H, m), 4.50 (1H, m), 7.11 (1H, d), 7.34 (1H, s), 7.41 (1H, d). Anal. ($C_{26}H_{37}Cl_2N_3O_2 \cdot {}^1/_4CH_2Cl_2$) C, H, N.

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